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Novel Ways to Generate Polypropionates for the Synthesis of Polyketide Natural Products

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Matthew Edward Calder

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Abstract of the Dissertation

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Polyketide natural products are desirable targets due to their interesting biological and pharmacological properties. Polyketides contain synthetically challenging propionate subunits, which are comprised of alternating methyl and hydroxyl stereogenic centers. The synthesis of polypropionate subunits is the central theme of this work.

The first project focused on employing the stereopentad and stereotetrad of the broad-spectrum antibiotic oleandomycin for the total synthesis of the polyketide natural product discodermolide. Our strategy involved a deconstruction/reconstruction process to access the polypropionate fragments that could then be modified to known discodermolide intermediates. Unfortunately, the unavailability of oleandomycin made completing this project difficult.

The second project focused on developing a new methodology employing cyclic hydroboration for the stereoselective synthesis of stereopentad fragments. Cyclic hydroboration has been a little used technique in organic synthesis. However, it has been shown to be an effective method for generating simple acyclic compounds that contain remote stereogenic centers in a single step.

To date, the cyclic hydroboration of 1,5-dienes has not been employed to synthesize stereopentad subunits. Utilizing work done on model systems in our group and literature precedents, we designed and synthesized a series of structurally complex acyclic dienes. Cyclic hydroboration of the complex dienes afforded stereopentads in moderate to high yields and diastereoselectivity. The reaction installs three of the five contiguous stereocenters in a single step. This work demonstrates that cyclic hydroboration can be an effective way to generate stereopentads. The synthesis, optimization and potential application of this methodology for the synthesis of polyketide natural products are discussed.

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9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
acac	acetylacetonyl
AIBN	azoisobutyronitrile
Ar	aryl
aq	aqueous
BAIB	(PIDA) bis(acetoxy) iodobenzene
BHT	butylated hydroxytoluene
BINAL-H	2,2'-dihydroxy-1,1'-binaphthyl lithium aluminum hydride
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2,2'-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
BQ	benzoquinone
BRSM	(b.r.s.m.) based on recovered starting material
BSA	N,O-bis(trimethylsilyl)acetamide
Bu	butyl
Bz	benzoyl
CAN	cerium (IV) ammonium nitrate
CB	catecholborane
Cbz	benzyloxycarbonyl

CDMT	2-Chloro-4,6-dimethoxy-1,3,5-triazine
COD	1,5-cyclooctadiene
cp	cyclopentadienyl
CSA	camphorsulfonic acid
cy	cyclohexyl
d.e.	(de) diastereomeric excess
d.r.	(dr) diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]-octane
Dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]-undec-7ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane, glyme
DMF	*N,N*-dimethylformamide
DMI	1,3-dimethylimidazolidin-2-one

DMP	Dess-Martin periodinane
DMPU	*N,N*-dimethyl propylene urea
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPPA	diphenylphosphoryl azide
dppf	diphenylphosphinoferrocene
DTBP	2,6-*tert*-butylpyridine
e.e. (ee)	enantiomeric excess
e.r. (er)	enantiomeric ratio
EDA	ethyl diazoacetate
Et	ethyl
hfacac	hexafluoroacetylacetonyl
hν	irradiation with light
HMDS	1,1,1,3,3,3-hexamethyldisilazane
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide
NMM	N-methylmorpholine
NMO	N-methylmorpholine oxide
NMP	(MPD) N-methyl-2-pyrrolidinone
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate

Ph	phenyl
PIFA	phenyliodonium bis(trifluoroacetate)
piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium toluenesulfonate
Pr	propyl
PTSA (TsOH)	*p*-toluenesulfonic acid
Rf	retention factor
r.t. (rt)	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBAOH	tetrabutylammonium hydroxide
TBDPS	*tert*-butyl-diphenyl silyl
TBHP	*tert*-butyl hydroperoxide
TBS (TBDMS)	*tert*-butyl-dimethyl silyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFa	trifluoroacetamide
TFAA	trifluoroacetic anhydride
Th	2-thienyl
THF	tetrahydrofuran
TIPS	triisopropyl silyl

TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethyl silyl
TMU	tetramethylurea
TPAP	tetra-*n*-propylammonium perruthenate
Tr	trityl
Ts	*p*-toluenesulfonyl

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CHAPTER 1

Natural Products as Tubulin Interactive Chemotherapeutics and (+)-Discodermolide

1.1 Background

Natural products that disrupt microtubule dynamics during mitosis are attractive anticancer agents because of their ability to prevent cell division, which leads to apoptosis/programmed cell death.[1] The first of these cytotoxic secondary metabolites, Taxol®, was discovered in 1967 by Wall and Wani.[2] Taxol is an anticancer drug that promotes the assembly of microtubules and stabilizes dynamic microtubules from depolymerizing.[3] Since Taxol was classified as an antimitotic agent, several structurally diverse natural products, acting by a similar mechanism have been isolated and characterized.

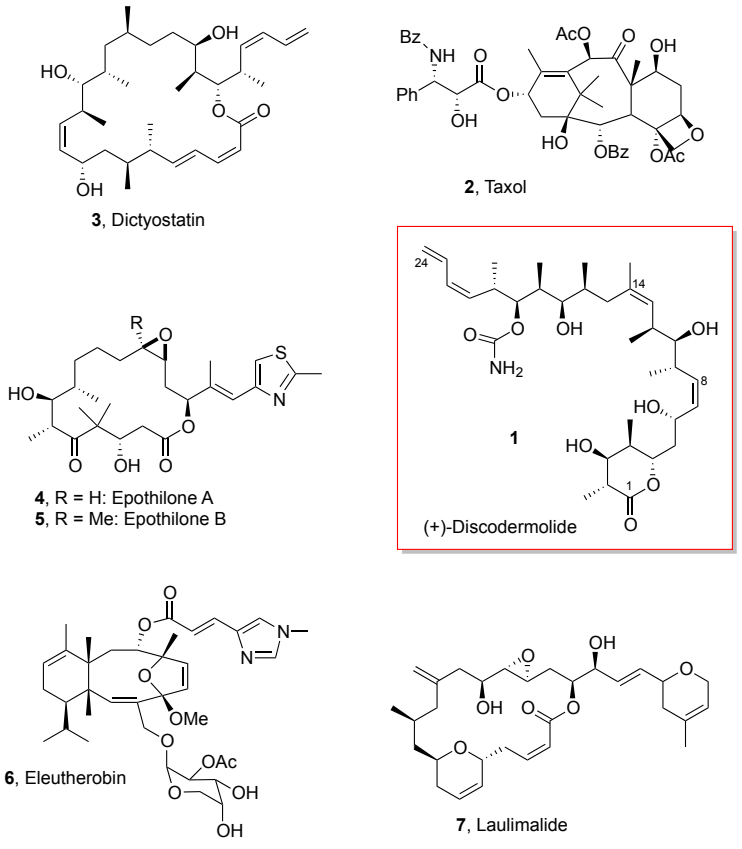


Figure 1.1 Tubulin interactive chemotherapeutics

Along with Taxol, the potential anticancer agents in this class are epothilones A and B,[4] dictyostatin,[5] eleutherobin,[6] laulimalide,[7] and discodermolide (**1**) (Figure 1.1).[8] Of the antimitotics listed, **1** has several structural and biological properties that differentiate it from the rest of the natural products in this class.

Discodermolide was first isolated from the Caribbean marine sponge *Dissolute discoderma* and its structure was elucidated in 1990 by Gunasekera *et. al*. at the Harbor Branch Oceanographic Institute.[8] Discodermolide is a unique polyketide that contains a stereopentad (C_{16}-C_{20}), a stereotriad (C_{10}-C_{12}), and a fully substituted stereotetrad lactone moiety (C_1-C_5). Furthermore, **1** contains three *cis*-olefins (C_8-C_9), including one trisubstituted olefin (C_{13}-C_{14}) and a terminal diene (C_{21}-C_{24}). Interestingly, the stereotetrad and stereopentad of discodermolide contain the same repeating *syn-anti*-stereotriad that is located at C_{10}-C_{12}. Of the 13 stereocenters located on discodermolide, seven bear methyl groups, four bear hydroxyl groups and one bears a carbamate moiety. Also of note, the linear framework of **1** is unique to the class of microtubule stabilizing agents. From a purely synthetic stand point, the structure of discodermolide makes for a challenging endeavor but is not what made **1** the target of many organic laboratories.

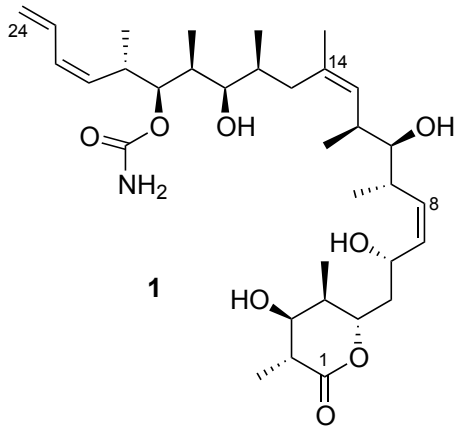


Figure 1.2 Structure of discodermolide

1.2 Biological properties of (+)-discodermolide

When initially discovered, **1** was found to have potent immunosuppressive activity in the nanomolar range.[9] After extensive *in vitro* testing, discodermolide was found to be an antiproliferative agent, halting cell growth at the G2/M phase of the cell cycle by promoting the polymerization and stabilization of microtubules.[10] This antiproliferative activity was soon

correlated to that of taxol (**2**), where discodermolide was not only more potent, but demonstrated activity against MDR resistant and Taxol resistant cell lines.[11a, 11] Unlike taxol, **1** was also found to be effective at polymerizing tubulin under a wide range of polymerizing and depolymerizing conditions.[11a] Competitive binding experiments showed that tubulin bound with **2** did not inhibit the binding of discodermolide.[11] However, tritiated **1** and taxol binding experiments showed discodermolide displaced **2** when binding to tubulin, but not vice versa. These results suggest the binding sites of **1** and **2** are overlapping or shared.[11b] Further studies indicated that discodermolide could be used in a potent synergistic combination with **2**.[12] In addition to the unique biological profile of discodermolide, it was also found to accelerate cell senescence.[13] Senescence typically occurs after a cell has gone through several cell divisions. Discodermolide is the only microtubule-stabilizing agent to demonstrate this type of accelerated aging of cells. To date, **1** is still the most potent promoter of microtubule polymerization discovered.[14] The lack of an accessible natural source, along with the unique combination of biological properties of **1,** makes it a desirable chemotherapeutic and drug target.

1.3 Syntheses of Discodermolide

Since its discovery in 1990, there have been 13 total syntheses of **1** by nine groups in both academia and industry. The first total synthesis was completed in 1993 by the Schreiber group, while the last total synthesis was completed by the Betzer/Ardisson laboratories in 2008. In between, several interesting and impressive total syntheses have been completed. The common retrosynthetic strategy employed, consisted of disconnecting **1** into three fragments of equal complexity. The retrosynthetic analysis of all the total syntheses are shown in Figure 3. Since the same repeating *anti-syn* stereotriad is present in each fragment, it allowed the synthesis of these fragments from advanced common precursors. A few of the total syntheses have been described in detail below.

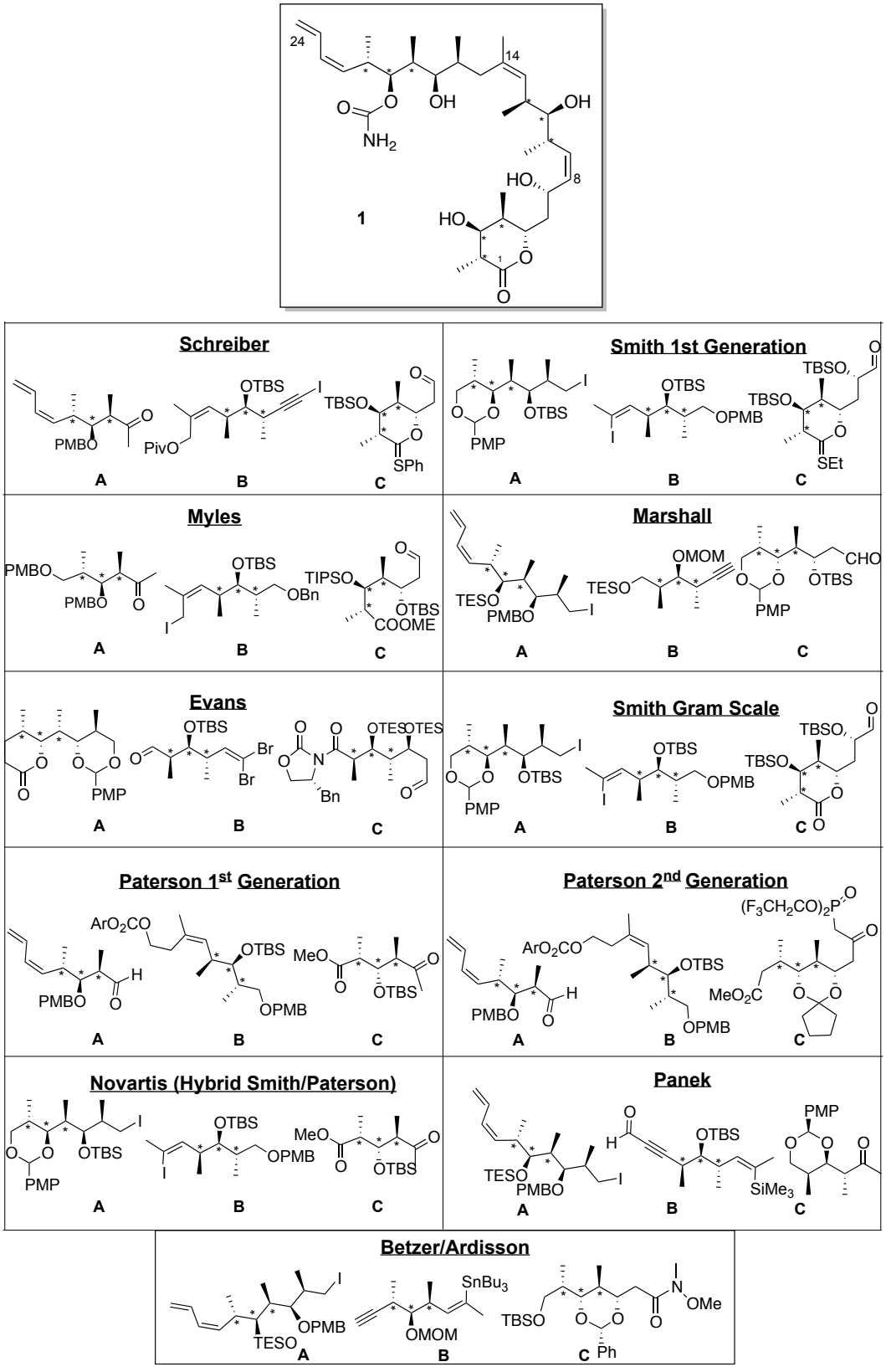


Figure 1.3 Retrosynthetic analyses of 1.[15]

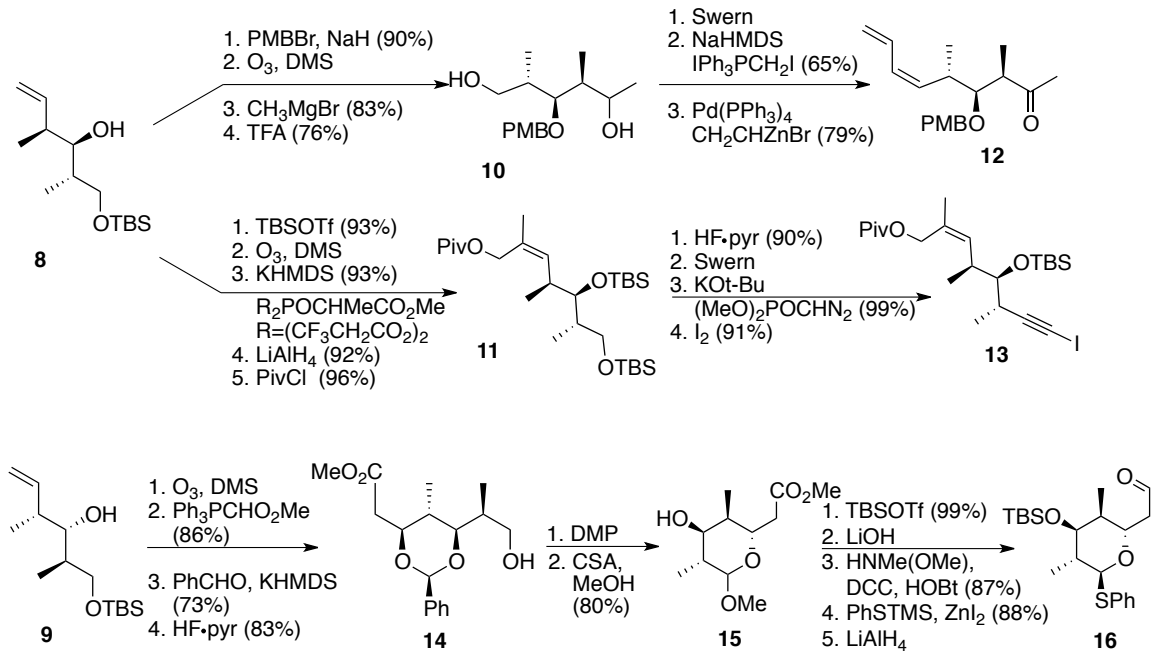
1.3.1 Schreiber synthesis of discodermolide

The Schreiber group was the first to synthesize discodermolide in 1993.[16] Unfortunately, they synthesized the unnatural enantiomer (-)-Discodermolide (*ent*-**1**), which lead to the elucidation of the absolute stereochemistry of **1**. Three years later, the Schreiber group synthesized the natural antipode (+)-discodermolide employing the same route as *ent*-**1** but in the correct enantiomeric series.

As shown in Scheme 1.1, Schreiber began his synthesis from known homoallylic alcohols **8** and **9**,[17] which could easily be synthesized from 3-methyl-2-methylpropionate. Diol **10** was synthesized in 4 steps from alcohol **8**. Alcohol protection, ozonolysis, Grignard addition to the resultant ketone and deprotection of the silyl ether afforded diol **10** in good yields. The left fragment **12** was synthesized in three steps from PMB-ether **10**. Diol **10** was oxidized to the keto-aldehyde, Stork-Zhao iodination[18] afforded vinyl iodide and vinyl iodide was converted to diene **12**[19] in moderate yields.

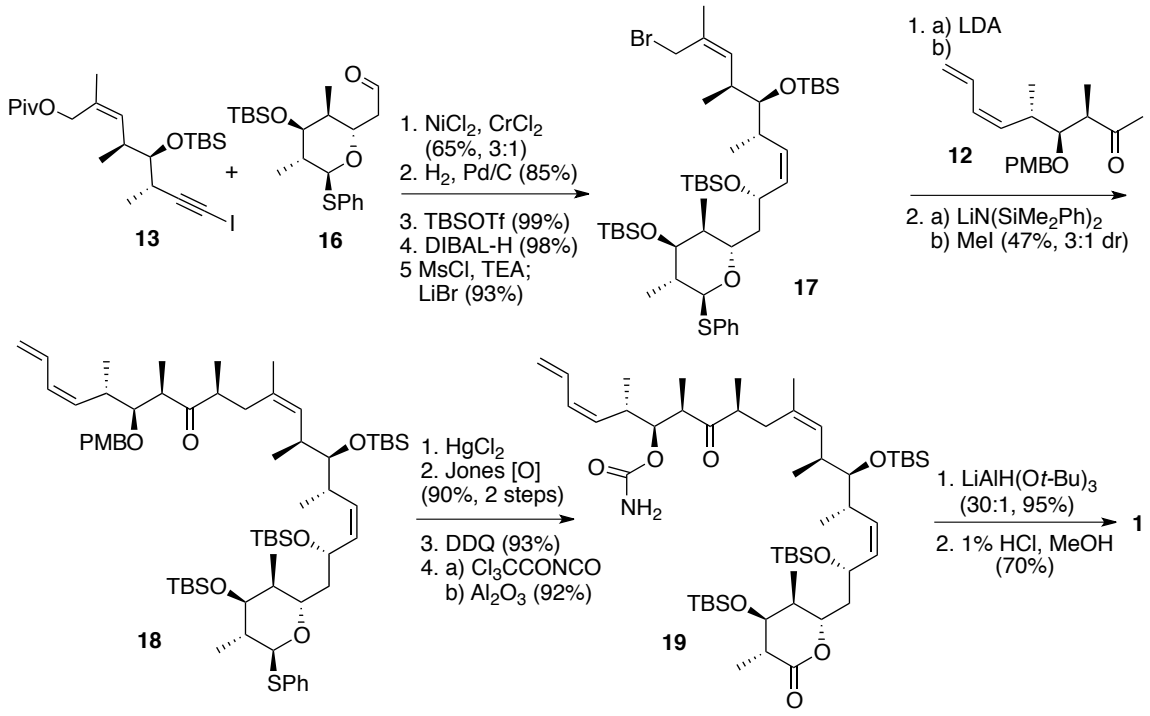
Alkynyl iodide **13** was synthesized in nine steps from common precursor **8**. Alcohol protection with TBSOTf, ozonolyis and subsequent Still-Genari olefination furnished the *cis*-trisubstituted olefin in good yields. Reduction of the enone and protection of the resultant alcohol with pivolyl chloride afforded intermediate **11**. Selective deprotection of the primary alcohol, swern oxidation, homologation to the alkyne and subsequent iodination supplied fragment **13** in good yields.

Access to the fully substituted lactone **16** began from known intermediate **9**. Ozonolysis of the alkene, Wittig olefination, hemi-acetal formation and subsequent 1,4 intramolecular addition of the resultant alkoxide afforded PMP-acetal.[20] Silyl-ether deprotection with HF-pyridine gave the alcohol **11**. Methyl ester **15** was accessed in two steps from **11**, which was converted to desired thiolactone **16** in five steps.



Scheme 1.1. Synthesis of major fragments **12**, **13**, **16**.

As shown in Scheme 1.2, Coupling of **13** and **16** via Nozaki-Hiyama-Kishi conditions[21] and subsequent reduction of the alkyne installed the requisite *cis*-olefin at C8-C9. Protection of the resulting alcohol, cleavage of the pivalate, mesylation and allylic bromide formation gave advanced intermediate **17**. Formation of the discodermolide backbone was realized with the addition of **17** and the enolate derived from **12**. Six additional steps were needed to complete the total synthesis of **1** in 24 linear steps (36 overall) with an overall yield of 4.3%



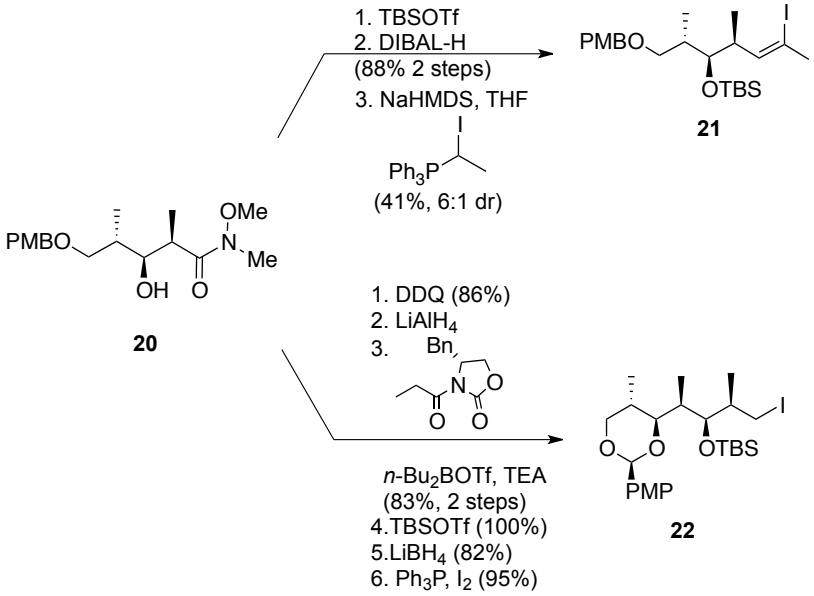
Scheme 1.2. Schreiber total synthesis of discodermolide

1.3.2 Novartis 60 gram synthesis of discodermolide

The impressive preclinical results of discodermolide, made it an attractive target for clinical studies in humans. Unfortunately the amount of material needed for this type of study could not be supplied from its natural source, as the yields of discodermolide when harvesting are poor. The need to chemically synthesize enough material had already started with Smith and Paterson groups attempts to synthesize gram scale quantities of **1**. In 2004, Novartis disclosed that they had scaled up enough material for clinical trials by synthesizing 60 grams of discodermolide.[22] To accomplish this, Novartis utilized a hybrid Smith gram scale[23] /Paterson 1st generation[24] approach where the three major fragments would be synthesized from Smith's common precursor **20**.

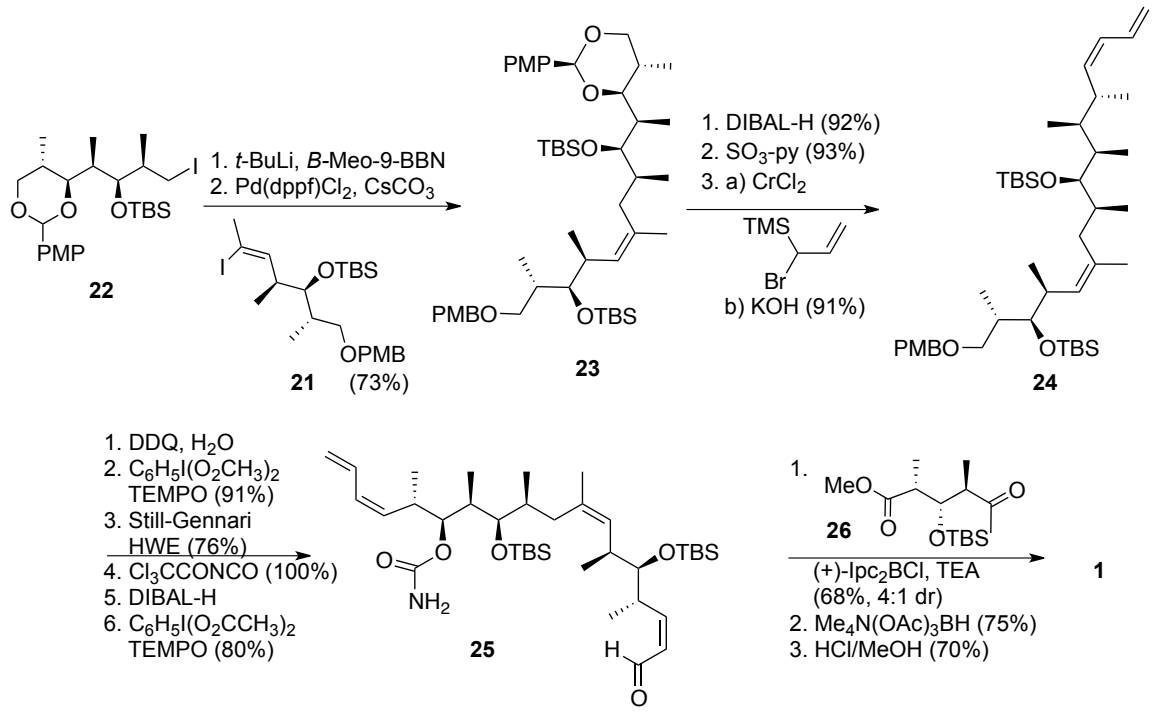
The common precuror **20** was synthesized from commercially available Roche ester. As depicted in Scheme 1.3, fragments **21** and **22** were synthesized three and six steps respectively. Protection of **20** with TBSOTf, reduction and subsequent olefination afforded vinyl iodide **21** in good yields. For **22**, oxidative cleavage of the PMB-ether with DDQ, reduction and Evans aldol

coupling afforded the requisite stereopentad. Protection, reduction and subsequent iodination furnished benzylidene acetal **22** in good yields.



Scheme 1.3. Synthesis of fragments **21** and **22**

As shown in Scheme 1.4 below, advanced interemediate **23** was synthesized from the Suzuki coupling of alkyl boron derived **22** and **21**. The requisite diene in **24** was installed in 3 steps via benzylidine reduction, oxidation, addition and subsequent elimination. At this point, the conversion of **24** to the final coupling of the Paterson endgame required six steps to afford aldehyde **25**. Coupling of the final two fragments was accomplished via boron-mediated aldol addition. Unfortunately, the best conditions found achieved modest yields and low diastereoselectivity to finish the large scale synthesis of **1**. Even with the less than ideal results of the final coupling, Novartis was still able to produce over 60 grams of pure compound. This was enough material to proceed with the clinical studies of discodermolide.



Scheme 1.4. Novartis 60 gram scale synthesis of discodermolide

Unfortunately, in 2004 discodermolide was pulled from clinical trials for being too cytotoxic. Despite this deleterious result, the ability to synthesize complex natural products in a concise, efficient manner will continue to be a major hurdle as more structurally complex bioactive natural products are discovered.

1.4 Conclusions

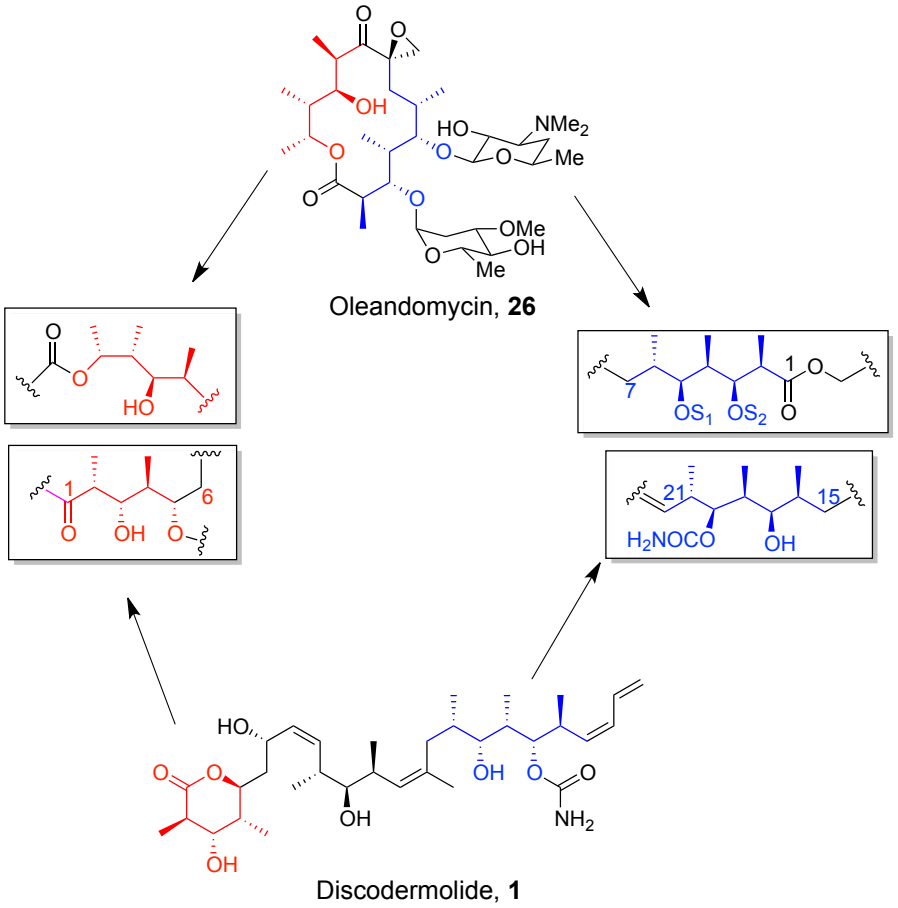
Since its discovery in 1993, discodermolide has received an enormous amount of attention from synthetic laboratories all over the world. The synthetic efforts of Novartis and others demonstrate that it is feasible to synthesize usable quantities of difficult-to-access natural products. Additionally, this type of effort fosters an environment in which new asymmetric methods are developed to continually improve and further the field of natural product synthesis.

1.5 Deconstruction and Reconstruction of Oleandomycin; Accessing key Synthons for the Total Synthesis of Discodermolide.

1.5.1 Initial considerations

To date, nine research laboratories have completed the total synthesis of discodermolide,[25] with several groups having synthesized multiple generations.[26] The amount of available reactions that are called upon to synthesize discodermolide and other similar polypropionate units is admittedly small. In an effort to develop a more efficient synthesis of discodermolide while deviating from this type of chemistry, a new strategy was developed where the complex structure of oleandomycin was deconstructed and then reconstructed into desired synthons of the polyketide discodermolide.

Oleandomycin (**26**) is a commercially available macrolide antibiotic that is used to treat infections caused by gram-positive bacteria. It is a functionalized 14-membered macro-lactone containing two deoxy sugars, desoamine and oleandrose, as well as, two sections of four and five contiguous stereocenters. Through pattern recognition, the C_1-C_7 stretch of oleandomycin contains the same stereopentad structural motif as discodermolide. (Scheme 1.5, blue) The five contiguous stereocenters are located between the lactone moiety and an exocyclic epoxide. These chemical handles can selectively be modified via orthogonal chemical transformations. Furthermore, the stereotetrad located at C_{10}-C_{13} on oleandomycin contains the identical *syn-anti* stereo triad as the lactone in discodermolide (Scheme 1.5, red). The C_{10}-C_{13} fragment could also be accessed and modified from the initial deconstruction process. The chemical handles of the stereotriad-containing fragment could be reconstructed to the fully substituted lactone moiety of discodermolide.

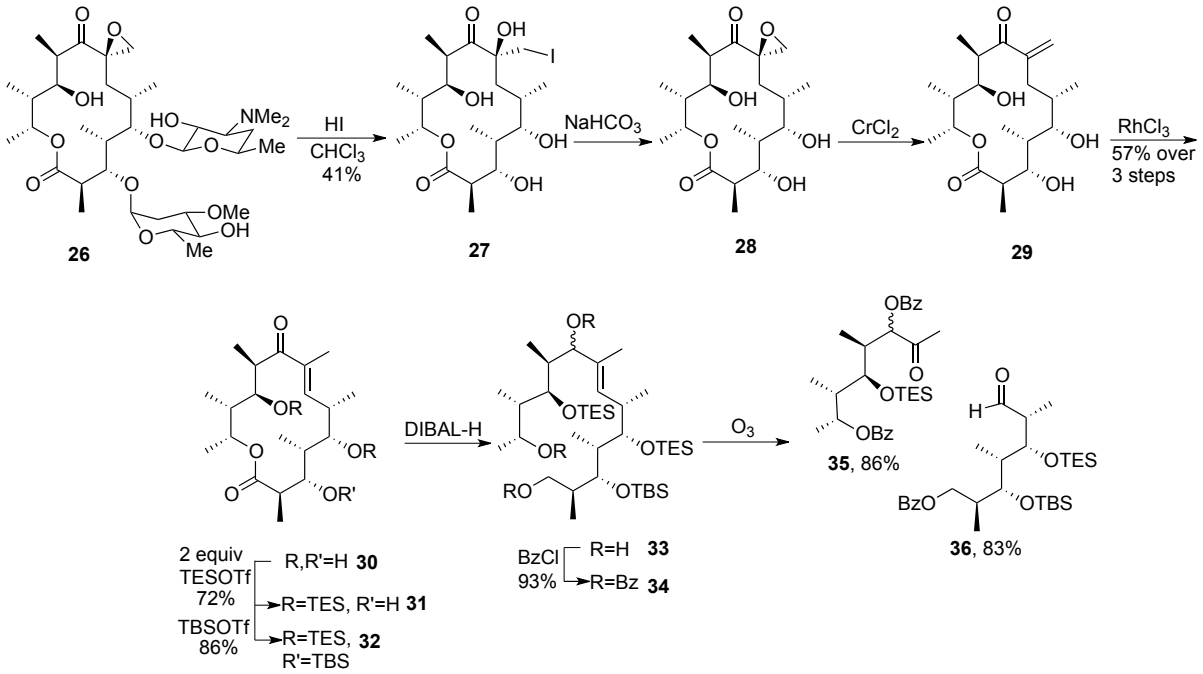


Scheme 1.5. Comparison of discodermolide and oleandomycin

1.5.2 Deconstruction of Oleandomycin and reconstruction to the C_{15}-C_{24} synthon of Discodermolide

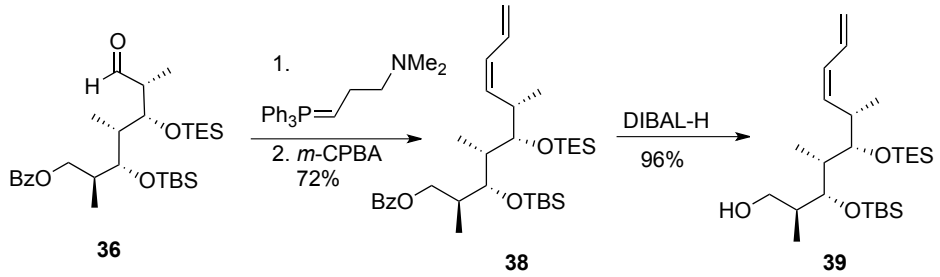
Previous work in the Parker laboratories deconstructed oleandomycin (**26**) to access the stereopentad and reconstruct it to the C_{15}-C_{24} fragment of discodermolide.[27] As depicted in Scheme 1.6, treatment of oleandomycin with HI resulted in cleavage of both sugars and concomitant epoxide opening to yield iodohydrin **27**. Addition of sodium bicarbonate to iodohydrin **27** afforded the known oleandolide **28**.[28] Following Sciavolino's procedure,[29] deoxygenation of the expoxide using freshly prepared $CrCl_2$ furnished enone **29**. Isomerization of the exocyclic olefin into the macrocycle with $RhCl_3$ provided enone **30** (57% from **27**). Selective protection with TESOTf afforded di-TES protected ether **31**. Subsequent protection of C_3 hydroxyl group with TBSOTf gave tri-silyl ether **32**. Reductive cleavage of the lactone and simultaneous reduction of the enone with DIBAL-H produced triol **33**. Protection of **33** with

benzoyl chloride yielded tribenzoate **34**, which upon treatment with ozone, afforded two fragments, ketone (**35**) and aldehyde (**36**) in 86% and 83% yields respectively.



Scheme 1.6. Deconstruction of Oleandomycin

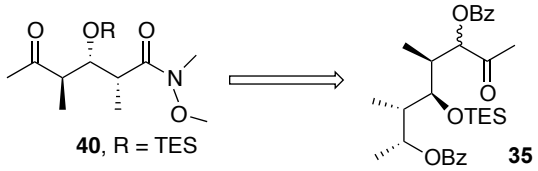
The desired aldehyde fragment (**36**) was subjected to Wittig conditions using [3-(dimethylamino)propylidene]triphenylphosphorane followed by subsequent Cope elimination to afford *cis*-diene **38** in 72% yield over two steps. Deprotection of the benzoate using DIBAL-H gave the desired C_{15}-C_{24} fragment **39** for the synthesis of discodermolide (Scheme 1.7).



Scheme 1.7. Reconstruction to C_{15}-C_{24} fragment of discodermolide

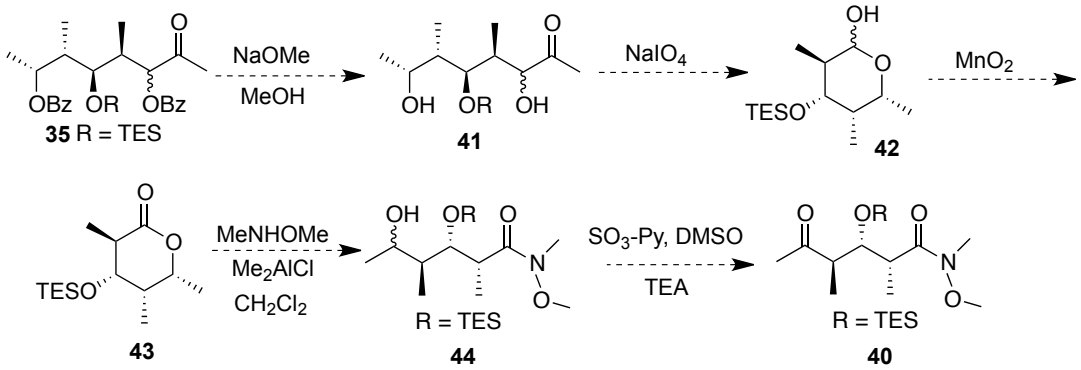
1.5.3 Reconstruction of C_8-C_{13} fragment from Oleandomycin to C_1-C_6 Novartis intermediate

With the C_{15}-C_{24} fragment of discodermolide in hand, we turned our attention to the polyketide ketone (**35**). Ketone fragment (**35**) originates from the C_8-C_{13} stretch of oleandomycin (Scheme 1.5, red), which contains a *syn-anti*-stereotriad. Discodermolide contains the identical repeating *syn-anti* stereotriad in the C_2-C_4 on lactone ring, C_{10}-C_{12}, and C_{18}-C_{20} of the stereopentad. Recognizing the similarities between **35** and the Novartis C_1-C_6 intermediate[30] (**40**) of discodermolide, a new reconstruction strategy was sought (Scheme 1.8).



Scheme 1.8. Retrosynthesis of Novartis intermediate

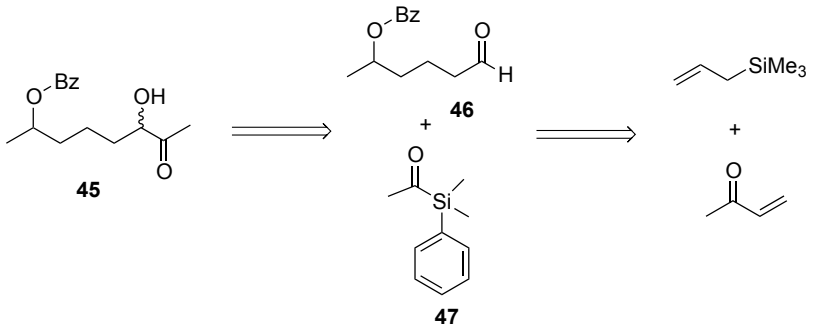
Our proposed synthesis for the reconstruction of ketone **35** is shown in Scheme 1.9. Hydrolysis of the benzoyl-ester would yield α-hydroxy ketone **41**. Treatment of **41** with sodium periodate and subsequent oxidation with manganese oxide would afford known lactone **42**. Lewis acid catalyzed lactone opening with Weinreb amide would furnish a mixture of diastereomers **44**. Oxidation of the mixture with pyridine-sulfate complex would afford known Novartis intermediate **40**.



Scheme 1.9. Proposed reconstruction of ketone **40** to Novartis intermediate

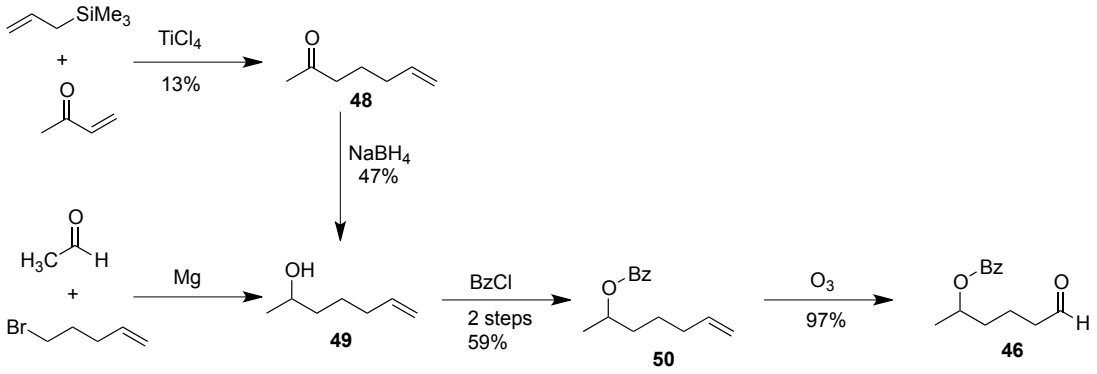
1.5.3.1 Retrosynthesis of model systems

In order to test the validity of our synthesis of the Novartis Weinreb amide **40** from ketone **35**, we designed a simple model shown in Scheme 1.10. The model of advanced intermediate ketone **35** could be synthesized from aldehyde **46** and acyl silane **47** via a benzoin condensation reaction.[31] Aldehyde **46** and acyl silane **47** could be synthesized from commercially available allyltrimethylsilane and methyl vinyl ketone.



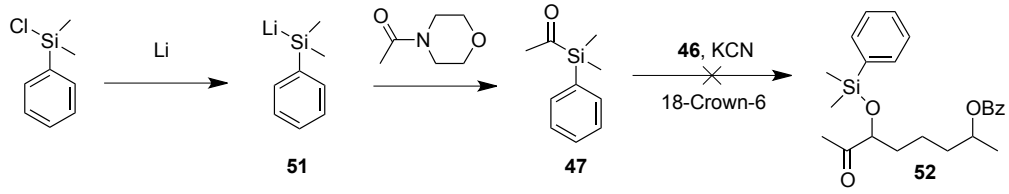
Scheme 1.10. Retrosynthesis of model

Michael addition with allyltrimethylsilane and methyl vinyl ketone afforded ketone **48** in very low yields (Scheme 1.11). Reduction of the ketone with sodium borohydride gave alcohol **49**. The combined poor yield of the Michael addition and subsequent reduction prompted us to revise our approach. Addition of acetaldehyde to a Grignard reagent generated in situ from 5-bromo-1-pentene and magnesium afforded alcohol **49**. Protection with benzoyl chloride gave the benzoate **50** (59% over 2 steps). Ozonolysis of the benzoate furnished aldehyde **46** in high yields. With aldehyde **46** in hand, our attention turned to the synthesis of the other model intermediate, acyl silane **47**.



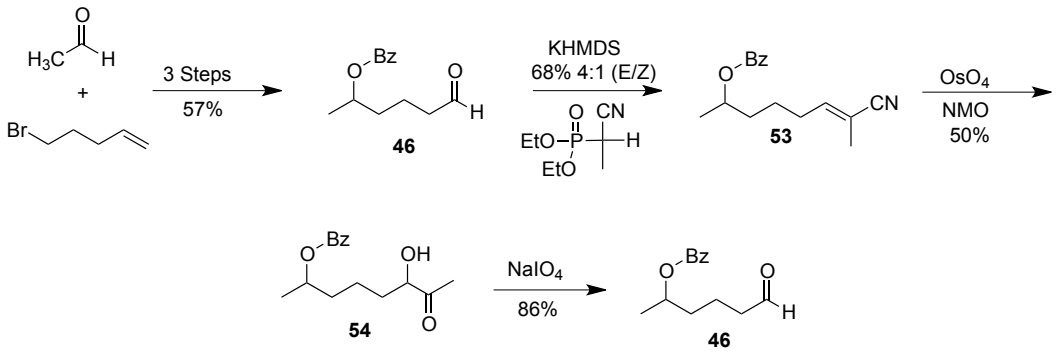
Scheme 1.11. Synthesis of model precursor 46

Dimethylphenylchlorosilane was added to lithium metal to form silyllithium **51**, to which 4-acetylmorpholine was added to afford desired acylsilane **47** (Scheme 1.12). Acyl silane was treated with KCN and 18-crown-6 and upon treatment with aldehyde **46** afforded a complex mixture with very little product.[31] After several failed attempts, the benzoin coupling of **46** and **47** proved to be too unreliable. At this point, we reevaluated our model synthesis to find an alternate route.



Scheme 1.12. Attempts to synthesize **52** via benzoin coupling conditions

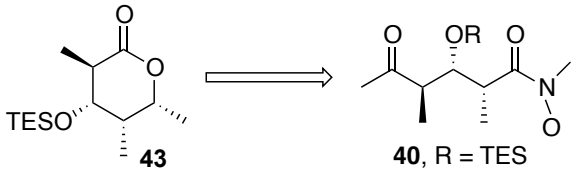
In an effort to preserve the work done on the model synthesis, we revised our model synthesis to incorporate aldehyde **46**. Benzoate **46** was subjected to Horner-Wadsworth-Emmons conditions to afford vinyl cyanide **53**. Oxidation of **53** with OsO_4 and NMO furnished the desired α-hydroxy ketone **54**.[32] Sodium periodate cleavage on α-hydroxy ketone 54, proceeded smoothly to furnish intermediate aldehyde **46** in good yields (Scheme 1.13).[33]



Scheme 1.13. Synthesis of model **28**

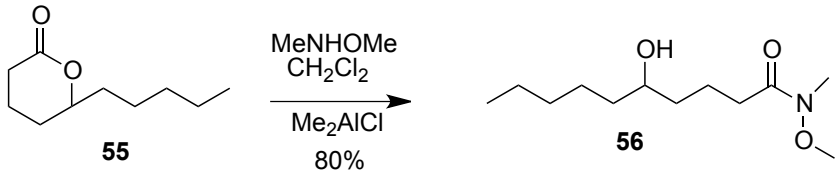
1.5.3.2 Model reaction for Weinreb opening of a lactone

The other potentially problematic reaction in the reconstruction of ketone **35** to the C_1-C_6 stretch discodermolide is the Weinreb amide opening of lactone **43** (Scheme 1.14). To test this reaction, commercially available δ-decalactone was chosen as the model substrate.



Scheme 1.14. Retrosynthesis of Weinreb amide **40** from lactone **43**.

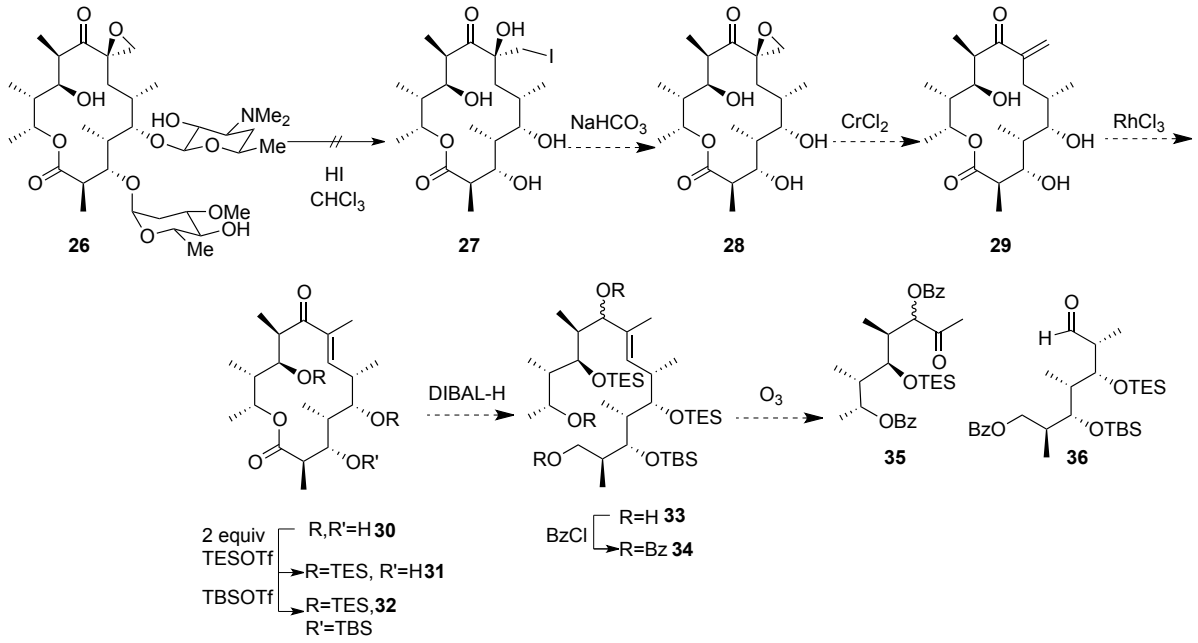
When subjected to lactone **55** was treated with Weinreb amide and Lewis acid, **55** opened cleanly and in good yields to afford Weinreb amide **56** (Scheme 1.15).[34]



Scheme 1.15. Weinreb amide opening of **55**

With both model reactions completed, we set forth to generate enough material to reconstruct the C_1-C_6 synthon of discodermolide. Following work previously reported in our group,[3] we employed the novel 1-step cleavage of the oleandrose and desosamine sugars off of oleandomycin using hydroiodic acid to afford iodohydrin **27**. Unfortunately, our attempts to

reproduce previous results were unsuccessful (Scheme 1.16). An alternative route to access key intermediate (**35**) can be achieved by cleavage off the sugars at a later point in the synthesis.



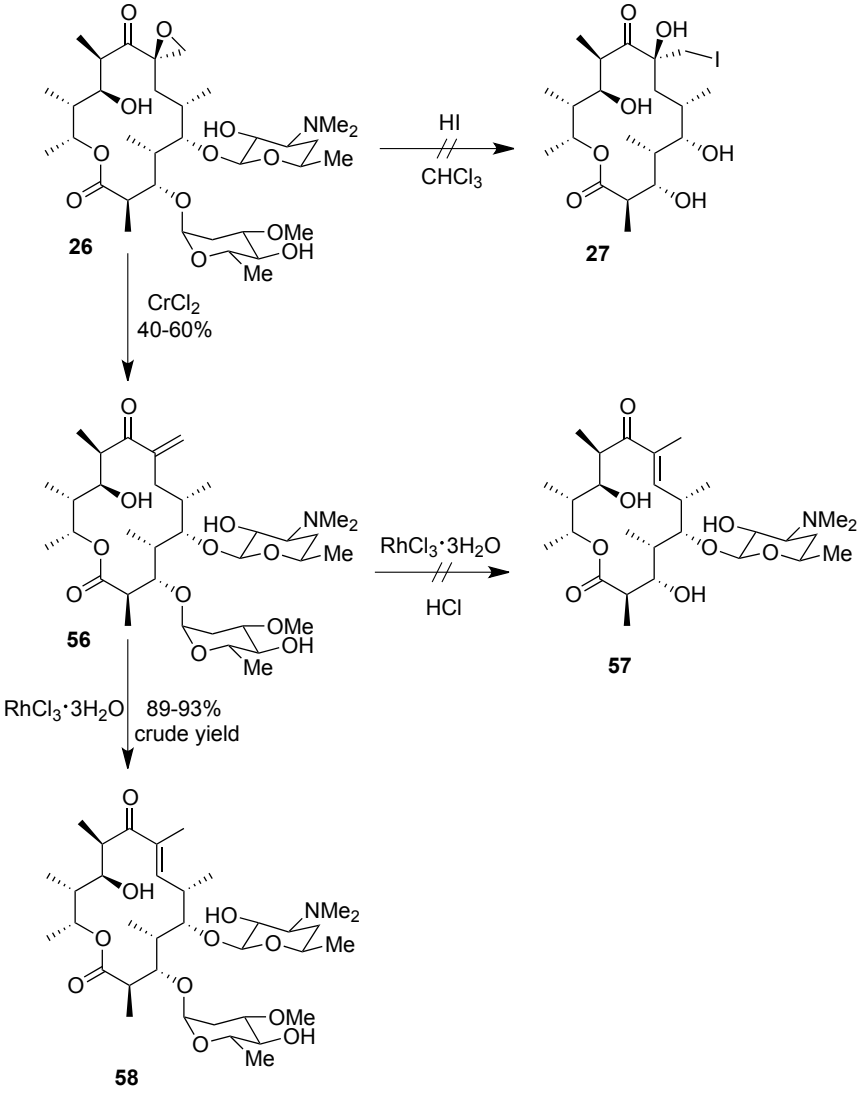
Scheme 1.16. Attempted 1-step sugar cleavage of oleandomycin

1.5.4 Alternative attempts to degrade oleandomycin to access the left half fragment (35)

As described in scheme 1.17, deoxygenation of the epoxide with $CrCl_2$ afforded exocylic olefin (**56**) as a white amorphous solid in 40-60% yield.[3] Previous work by Peng Wang in the Parker laboratories on enone **56**,[35] had shown that the exocylic olefin could be isomerized into the macrocycle with $RhCl_3$, as well as, cleave the more labile oleandrose sugar when a catalytic amount of concentrated HCl was added to the reaction mixture (Scheme 1.17). Attempts to reproduce these results were unsuccessful, usually resulting in either no reaction, decomposition of starting material or very little isomerized product isolated. Additionally, varying the order of addition, concentration and amount of acid added to the reaction had no discernable effect on product formation (Table 1; Entries 1-2,4-7; appendix 1).

With the less than ideal results of the isomerization reaction in the presence of acid (**56** -> **57**), our attention turned to the olefin isomerization without HCl (**56** -> **58**) (Scheme 1.17). An exhaustive optimization of reaction conditions was undertaken to improve the yield of this isomerization step (Table 1; Entries 3, 8-13; appendix 1). The best conditions were achieved

when 20 mol % $RhCl_3$ was added to enone **56** neat, followed by addition of solvent to the solid mixture (Table 1; Entries 13-14; appendix 1). However, even with the optimized conditions, the isomerization of enone **56** to **58** was extremely temperamental and unreliable. With a finite amount of oleandomycin available, we reevaluated our strategy to avoid the inconsistent isomerization reaction in order to ascertain the desired ketone **35**.



Scheme 1.17. Attempted isomerization of olefin into macrocycle

1.5.5 Attempts to locate more oleandomycin and closure

When this project was originally designed, oleandomycin was an inexpensive, readily accessible reagent. At some point in time, oleandomycin became very expensive and difficult to

find. With a finite amount of starting material available, coupled with the slow progress that was being made, it was not in our best interests to pursue this project any further.

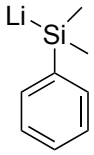
1.6 Experimental Section

1.6.1 Materials and Methods

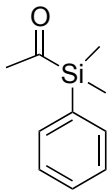
Infrared (IR) Spectra were obtained using a Shimadzu FTIR-8400S. Proton (^{1}H NMR) nuclear magnetic resonance spectra were recorded on a Varian Oxford NMR 300, 400 and 500 and a Bruker NMR 400. Carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Varian Oxford NMR 400 and Bruker NMR 400. For both instruments solvent resonance was used as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from indicated deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. Analytical thin layer chromatography (TLC) was performed on Whatman 250 μm layer aluminum silica gel plates. Visualization was accomplished with UV light and phosphomolybdic acid in ethanol stain followed by heating. Purification of the reaction products was carried out by flash chromatography using Sorbent technologies standard grade 60 Å (270-400 mesh) silica gel and Büchi GKR-51 Kugelrohr distillation apparatus. All reactions were carried out under an atmosphere of inert gas in oven-dried glassware with magnetic stirring unless otherwise stated. Diethyl ether, THF, and CH_2Cl_2 were distilled from Na, Na/benzophenone, and CaH respectively. Anhydrous Pyridine was used as received. 18-Crown-6 was recrystallized from acetonitrile and dried under vacuum overnight. Unless otherwise noted,

reagents were obtained from commercial sources and used without further purification.

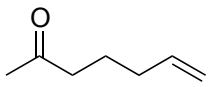
1.6.2 Preparative procedures



Dimethylphenylsilyl lithium (51) - To a solution of lithium wire (0.70 g, 0.10 mol, 4.8 eq) in THF (10 mL) cooled to 0 °C, was added a solution containing chlorodimethylphenyl silane (3.60 g, 0.021 mol, 1 eq) and THF (20 mL) dropwise. The reaction mixture was warmed to room temperature and stirred for 4 h, at which time the solution was filtered and stored in the freezer. The lithium solution can be used up to a month when kept at -20 °C.

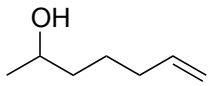


1-(dimethyl(phenyl)silyl)ethanone (47) – The following procedure was used from previously reported literature.[36]

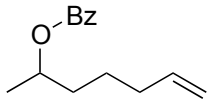


6-Hepten-2-one (48) - To a solution of methyl vinyl ketone (2.59 g, 0.037 mol, 1 eq) in CH_2Cl_2 (45 mL) cooled to -78 °C, was added $TiCl_4$ (8.26 g, 0.044 mol, 1.19 eq) dropwise over 5 min. After 15 min of stirring at -78°C, a solution of allyltrimethyl silane (6.47 g, 0.057 mol, 1.54 eq) in CH_2Cl_2 (20 mL) was added dropwise all at once. The reaction was stirred for 45 min then

quenched with water at -78°C and allowed to warm to room temperature. The hetereogenous mixture was diluted with DCM and the resulting solution was washed with 10% HCl aq. solution, saturated $NaHCO_3$, brine and dried over $MgSO_4$. Purification via kugelrohr distillation afforded ketone (523 mg, 13 % yield) as light yellow oil. ^1H NMR spectrum was in agreement with that described in the literature.[37]

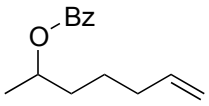


Hept-6-en-2-ol (49) – To a stirred solution of **48** (167 mg, 1.49 mmol, 55.6 M) in MeOH (5 mL) at 0 °C, was added 2 portions of $NaBH_4$ (60 mg, 53 mg; 3.00 mmol total, 2 eq) slowly. After 15 min of stirring at 0 °C, a third portion of $NaBH_4$ (113 mg, 3.00 mmol, 2 eq) was added and the mixture was stirred for 15 additional minutes (30 min total). The reaction was quenched with acetone (5 mL) and the volatiles were evaporated. The crude was taken up in ether and washed saturated NH_4Cl. The heterogeneous mixture was extracted with ether and the resulting solution was washed with water, dried over $MgSO_4$ and concentrated in vacuo to afford alcohol (80 mg, 47 % yield) as light yellow oil ^1H NMR spectrum was in agreement with that described in the literature.[38]



Hept-6-en-2-yl benzoate (50) – To a solution of **49** (82.0 mg, 0.72 mmol, 1 eq) in DCM (2 mL) cooled to 0°C, was added pyridine (1.5 mL) and benzoyl chloride (249 mg, 1.76 mmol, 2.44 eq) consecutively. Upon consumption of starting material (2.5 hr) via TLC analysis, the reaction was quenched with water and the heterogeneous mixture was extracted with ether. The resulting

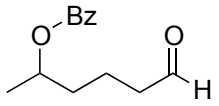
organic solution was washed with 5% HCl aq. solution (x 10), water, saturated $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated in vacuo. Purification via column chromatography (10% EA:H) afforded benzoate (71.5 mg, 45 % yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 5.80 (m, 1H), 5.54 (m, 1H), 4.98 (m, 2H), 2.08 (q, *J* = 7.2 Hz, 2H), 1.60 (m, 4H), 1.33 (d, *J* = 6.0 Hz, 3H), 1H NMR is in agreement with literature values.[39]



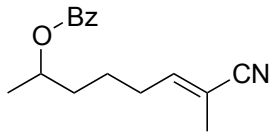
Hept-6-en-2-yl benzoate (50) – To a mixture of Mg (1.1 g, 43.55 mmol, 1.3 eq) and ether (10 ml) was added a portion of 5-bromo-1-pentene (562 mg, 3.77 mmol) at room temperature. The mixture was cooled to -5 °C, at which time a solution of 5-bromo-1-pentene (4.43 g, 29.7 mmol, 33.5 mmol total) in ether (10 mL) and a solution of acetaldehyde (3.1 g, 70.4 mmol, 2.1 eq) and ether (10 mL) was added dropwise via cannula consecutively. The reaction mixture was stirred at -5 °C for 15 min, warmed to room temp and stirred for 30 more minutes. The mixture was filtered and the resulting filtrate was quenched with 30 mL 10% aq. HCl solution. The heterogeneous mixture was extracted with ether and the resulting solution was washed with water, dried with $MgSO_4$, and concentrated in vacuo to afford crude alcohol (3.02 g) that was used as is directly in the next step.

To a solution of crude alcohol (2.90 g, 0.025 mol, 1 eq) in DCM (30 mL) was added pyridine (10 mL, 5 eq) and benzoyl chloride (4.22 g, 0.03 mol, 1.2 eq) consecutively. The mixture was stirred for 1.5 hr, at which time water was added to quench the reaction. The heterogeneous mixture was diluted with ether and the resulting organic solution was washed with 10 % HCl aq. solution

(x 2), water, saturated $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated. Purification via column chromatography with a solvent gradient (5% EA:H) afforded **X** (2.98 g, 54 % yield over two steps) as a colorless oil.

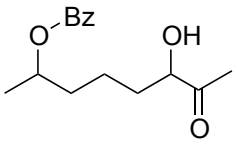


6-oxohexan-2-yl benzoate (46) – To a solution of **50** in CH_2Cl_2 (15 mL) cooled to -78 °C, ozone was bubbled through the solution until reaction was saturated and turned purple (10 min). The mixture was bubbled with argon till the purple color had dissipated (20 min) and Me_2S (68.3 mg, 1.1 mmol, 10 eq) was added and the mixture was stirred overnight. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (10% EA:H) to afford **46** (21.3 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, J = 1.5 Hz, 1H), 8.05 (dd, J = 1.0, 8.3 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 5.20 (sextet, J = 6.8 Hz, 1H), 2.52 (m, 2H), 1.83-1.66 (m, 4H), 1.38 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 166.3, 133.0, 130.8, 129.7, 128.5, 71.2, 43.7, 35.6, 20.2, 18.2; LCMS: Mass calc'd for $C_{13}H_{16}O_3$ $[M+H]^+$, 221.1099. Found 221.1



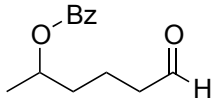
(***E***)**-7-cyanooct-6-en-2-yl benzoate (53**): To a solution of diethyl(1-cyanoethyl)phosphonate (97.5 mg, 0.51 mmol) in toluene (2 mL) cooled to -78 °C, KHMDS (101.7 mg, 0.51 mmol) was added dropwise slowly. The reaction was stirred for 1 hr, at which time a solution of aldehyde **46** (100 mg, 0.46 mmol) and toluene (4 mL) was added dropwise. The reaction was stirred for 5.5 hr at -78 °C, then warmed to room temp and quenched with aqueous NH_4Cl. The

heterogeneous mixture was diluted with ether and the resulting organic solution was washed with water, brine, dried ($MgSO_4$) and concentrated. Purification via column chromatography (10% EA:H) afforded product (**53**, 38 mg, 68% adjusted, *Z/E* = 1/1) as a colorless oil and recovered starting material (52 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.8 Hz, 3H), 8.04 (dq, *J* = 1.1, 6.9 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 6.33 (tq, *J* = 1.1, 7.4 Hz, 0.5H), 6.12 (tq, *J* = 1.1, 7.7 Hz, 0.5H), 5.17 (sextet, *J* = 1.4 Hz, 1H), 2.38 (dq, *J* = 1.1, 7.4 Hz, 1H), 2.21 (q, *J* = 6.9 Hz, 1H), 1.92 (q, *J* = 1.4 Hz, 1.5H), 1.85 (q, *J* = 1.1 Hz, 1.5H), 1.79 – 1.47 (m, 4H), 1.35 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 147.7, 147.6, 132.9, 132.8, 130.6, 130.5, 129.5, 129.4, 128.3, 128.2, 118.0, 109.7, 71.2, 70.9, 35.5, 31.4, 28.1, 24.6, 24.1, 20.1, 20.0, 14.8; IR: 2976.9, 2934.5, 2864.1, 2216.1, 1713.6, 1707.9, 1601.8, 1584.4, 1450.4, 1305.5, 1273.9.

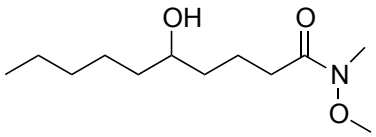


6-hydroxy-7-oxooctan-2-yl benzoate (**54**): To a solution of **53** (20.6 mg, 0.08 mmol), and dry CH_2Cl_2 (1.5 mL), OsO_4 (20.4 mg, 0.08 mmol, 25.2 μL) was added and let stir at room temp for 1 hr. A solution of NMO (93 mg, 0.8 mmol) and dry CH_2Cl_2 (1 mL) was added dropwise, where the color of the reaction turned from colorless to light yellow. The reaction was stirred overnight at room temp and quenched with sodium metabisulfite (1.5 g) at 0 °C. The mixture was stirred for 1 hr at room temp, diluted with ether and filtered through a pad of celite. The filtrate was washed with water, brine, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (HE:EA = 5:1 then 3:1) afforded starting material (2.9 mg) and product (**54**, 9 mg, 50%) as a slight yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.4 Hz,

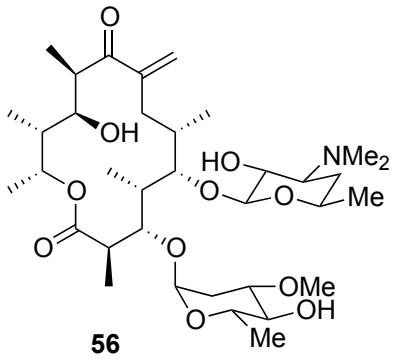
1H), 7.44 (t, *J* =7.7 Hz, 2H), 5.18 (Septet, *J* = 6.2 Hz, 1H), 4.17 (m, 1H), 3.45 (s, 1H), 2.18 (d, *J* = 12.1 Hz, 3H), 1.91-1.53 (m, 6H), 1.35 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 166.4, 133.0, 130.9, 129.7, 128.5, 71.4, 71.2, 35.9, 35.8, 33.5, 33.4, 25.3, 21.1, 20.8, 20.3, 20.2; FTIR (thin film/NaCl): 3484.2, 2949.9, 2932.6, 2867.6, 1720.4, 1703.0, 1698.2, 1694.4, 1601.8, 1584.4, 1450.4, 1355.9, 1314.4, 1276.8, 1112.9, 713.6.



6-oxohexan-2-yl benzoate (46): To a vial containing α-hydroxy ketone **54** (4.9 mg, 0.02 mmol) and a 3:1 mixture of t-butanol : water (200 μL), was added 3 portions of $NaIO_4$ (18 mg total) at 30 min intervals. Let stir at room temp for 3 hr, added water (2 mL) and let stir for an additional 15 min. The reaction was diluted with ether and the organic phase was separated. The aqueous phase was extracted with ether. The organic phase was washed with 10% sodium sulfite, water, and brine, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (HE : EA = 90 : 10) afforded unreacted starting material (1.0 mg) and product (**23**, 2.8 mg, 86% adjusted) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.5 Hz, 1H), 8.05 (dd, *J* = 1.0, 8.3 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 5.20 (Sextet, *J* = 6.8 Hz, 1H), 2.52 (m, 2H), 1.83-1.66 (m, 4H), 1.38 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 166.3, 133.0, 130.8, 129.7, 128.5, 71.2, 43.7, 35.6, 20.2, 18.2; IR: LCMS: Mass calcd for $C_{13}H_{16}O_3$ $[M+H]^+$, 221.1099. Found 221.1



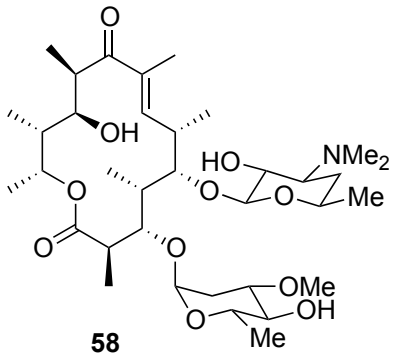
5-hydroxy-N-methoxy-N-methyl-decanamide (**56**): To a solution of Weinreb reagent (998 mg, 0.01 mol) in CH_2Cl_2 (12 mL) cooled to 0 °C, was slowly added $AlMe_2Cl$ (925 mg, 0.01 mol) dropwise due to the evolution of gas upon addition. The mixture was stirred for 1 hr at 0 °C then warmed to room temperature whereupon a solution of delta-decalactone (340 mg, 2 mmol) in CH_2Cl_2 (2 mL) was added via cannula and the reaction was stirred overnight at room temperature. Upon consumption of starting material via TLC analysis, phosphate buffer (20 mL, 100μM, pH = 8) was added to the reaction mixture. The heterogeneous mixture was stirred for 30 min then filtered through a pad of celite. The filtrate was diluted with DCM and the resulting organic solution was washed with water, brine, dried over $MgSO_4$ and concentrated in vacuo. Purification via column chromatography (50% EA:H) afforded product (**56**, 364 mg, 79% actual, 91% adjusted) as a yellow oil and recovered starting material (46 mg). ^{1}H NMR is in agreement with literature precedent.[40]



56

To a stirred solution of oleandomycin (2.5 g, 3.18 mmol) in water (13 mL) was added $CrCl_2$ (2.8M, 10.5 mL, 28 mmol), acetone (10 mL) and $CrCl_2$ (2.8M, 10.5 mL, 28 mmol; Total 21 mL, 56 mmol) successively. The aqueous mixture was stirred for 45 min at room temperature, diluted with DCM and quenched with 3N NaOH. A blue emulsion precipitated out of solution, which was subsequently filtered through a pad of celite. The heterogeneous filtrate was diluted

with DCM and the resulting combined organic solutions were washed with brine and dried over $MgSO_4$ to afford crude enone **56** (1.2 g, 57% yield) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, 0.5H) 5.53 (s, 0.5H), 5.41 (m, 1H), 4.96 (d, *J* = 2.7 Hz, 1H), 4.28 (m, 1H), 3.81-3.34 (m, 11H), 3.15 (m, 2H), 2.82 (m, 2H), 2.61 (m, 2H), 2.50 (s, 5H), 2.34 (m, 2H), 2.24 (m, 1H), 1.68 (m, 3H), 1.50(m, 2H), 1.32-0.89 (m, 30H).



58

To a flask containing enone **56** (243.1 mg, 0.36 mmol) and rhodium chloride (19.1 mg, 0.07 mmol, 20 mol %) was added absolute ethanol (25 mL) and the mixture was refluxed (90°C) for 2.5 hrs. The mixture was cooled to room temperature and diluted with DCM. The homogeneous mixture was quenched with aq. sodium bicarbonate and the resulting organic solutions were washed with brine and dried over $MgSO_4$ to afford crude **58** (202 mg, 83% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (d, *J* = 7.2Hz, 1H), 5.43-5.25 (m, 2H), 4.91 (m, 3H), 4.31 (d, *J* = 6 Hz, 1H), 4.21 (m, 2H), 3.74-3.08 (m, 37H), 2.88 (m, 10H), 2.59-2.33 (m, 18H), 1.32-0.81 (m, 82H).

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Appendix 1: Reaction Conditions for Isomerization of Olefin into Macrolide (56->58)

	Amount (mg) [a]	Acid added (1 drop of 12 N)	Catalyst Amount (mol %)	Solvent	Order of addition (Sol. or Cat.)	Reflux time (hr)	Amount of crude (mg)	Pdt + (overall amount weight) in mg	Yield (%)
1	122.1(*cr)*	Y	50	EtOH	solvent	2	116 (79 [b])	18 (cr)	
2	24 (*cr)*	Y	50	EtOH	solvent	4	17.9	-	decomp
3	22.4 *(cr)*	N	50	1:1 EtOH:$CHCl_3$	solvent	2	25.2	Rec Sm (cr)	No rxn
4	20 *(cr)*	Y *(1 N)*	50	EtOH	solvent	2	23.2	4.2 (12)	
5	20.4 *(cr)*	Y *(6 N)*	50	EtOH	solvent	2	15.5	2.8 (6)	
6	*21 (cr)*	Y	50	EtOH	solvent	2	-	-	No rxn
7	*20 (cr)*	Y	50	EtOH	solvent	2	18.3	2.5 (6.4)	
8	*21.6 (cr)*	N	20	EtOH	solvent	2	-	7.7 (11.8)	
9	*20 (cr)*	N	20	EtOH	solvent	3[d]	-	Rec Sm (cr)	-
10	26.1 *(p)*	N	20	EtOH	solvent	2	6.4 (.7 aq)	-	-
11	56 *(p)*	N	20	EtOH	solvent	2	19.3	-	-
12	20.4 *(p)*	N	20	EtOH	catalyst	2	18.2	Used in next	89(cr)
13	321.9 *(p)*	N	20	EtOH	catalyst	4	300.7	Used in next	93(cr)

a. Crude enone = cr; pure enone = p. b. Column plugged which resulted in losing 37 mg of crude. c. Prep TLC resulted in no pdt or starting material recovered. d. solvent evaporated while refluxing, additional EtOH was added. e. Spilled over half the crude before workup.

CHAPTER TWO

Methods for the Synthesis of Polypropionates

2.1 Background

Polyketides are comprised of a diverse family of natural products with a broad array of biological and pharmacological properties.[1] Currently, polyketides are in commercial use as antibiotics, cytostatics, insecticides, antifungals and anticholestermics.[2] Polyketides have a structural commonality in that they contain smaller subunits of alternating methyl and hydroxyl stereogenic centers of varying lengths (Figure 2.1). These alternating polypropionates are biosynthetically assembled via iterative condensations of propionyl or polyacetate building blocks.[3] This iterative process is responsible for the broad diversity of stereochemical permutations that polypropionate-containing polyketides possess. The challenge for synthetic chemists is to mimic these biosynthetic pathways by taking simple compounds and modifying them into stereochemically complex polypropionates efficiently.

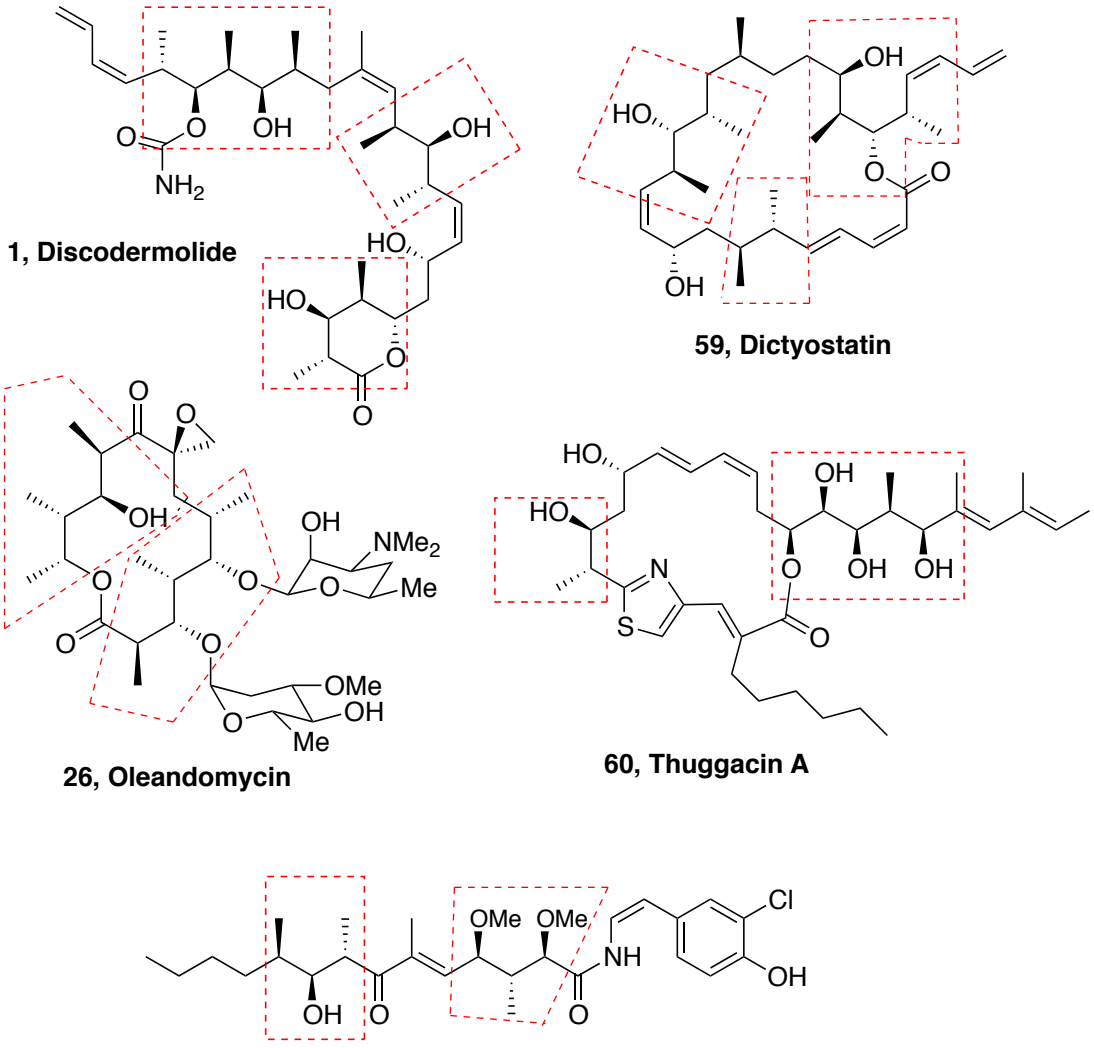


Figure 2.1 Polypropionate containing polyketides. Polypropionate fragments are highlighted in dashed red boxes.

2.2 Current Methodologies

To date, there are several well-established methods, as well as, several newer methodologies for synthesizing various polypropionates (Figure 2.2). Many of these methods have been remarkably efficacious and they enjoy a broad range of applications in the construction of complex polypropionate containing polyketides. Several of these methods are briefly outlined below.

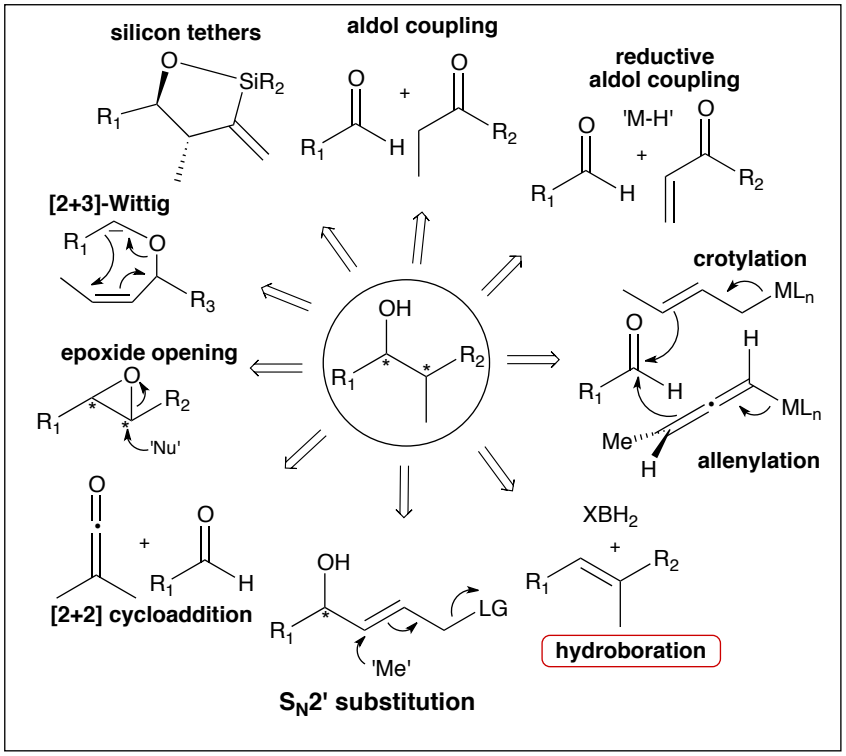
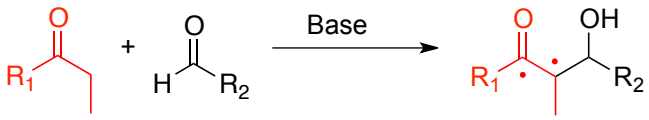


Figure 2.2 Methods to synthesize polypropionates. [4]

2.2.1 Basic Aldol Coupling

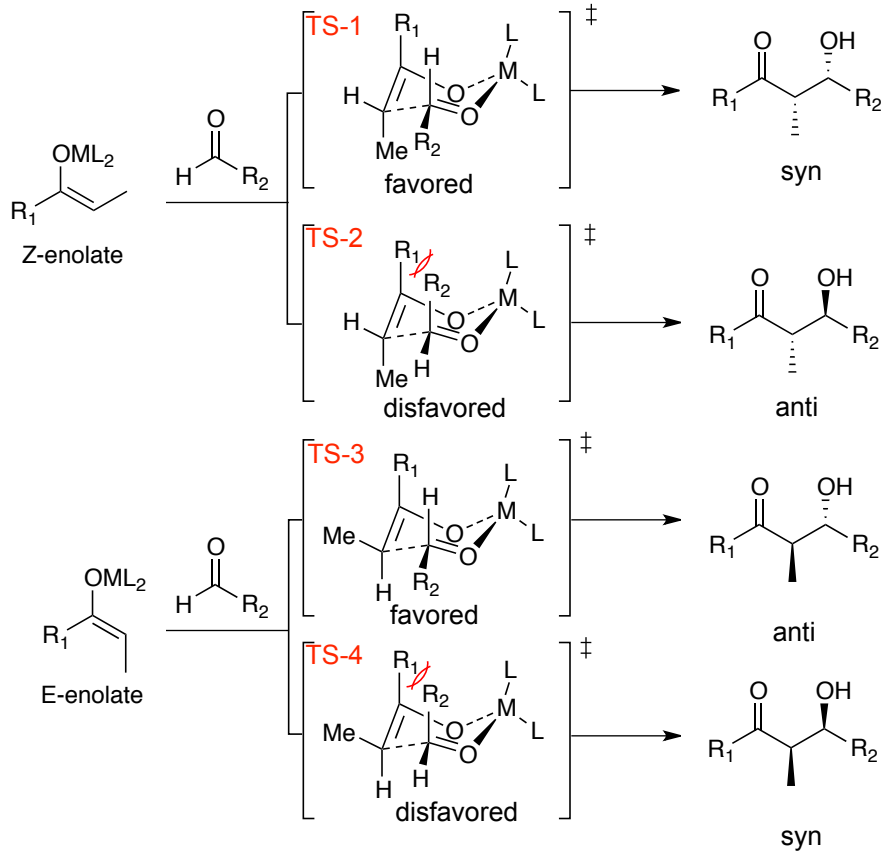
Aldol coupling represents one of the most fundamental and important discoveries in organic chemistry. The aldol reaction and its many variations have been extensively employed both in nature and in the laboratory for the stereoselective assembly of structurally diverse polypropionates.[5] The basic aldol reaction involves the nucleophilic addition of a ketone enolate to an aldehyde and it affords a beta-hydroxy ketone adduct[6] (Scheme 2.1).



Scheme 2.1. General Aldol coupling reaction.

The geometry of the enolate intermediate determines the stereochemistry of the aldol adduct where Z-enolates and E-enolates afford *syn*-products and *anti*-products

respectively (Scheme 2). This is rationalized with the Zimmerman-Traxler model, in which the transition state of the aldol reaction adopts a 6-membered chair conformation.[7] The stereochemical outcome is dictated by the preference of R_2 (TS 1 and 3) to adopt an equatorial position in the six-membered transition state, minimizing unfavorable 1,3-diaxial interactions. This preference results in high diastereoselectivities.

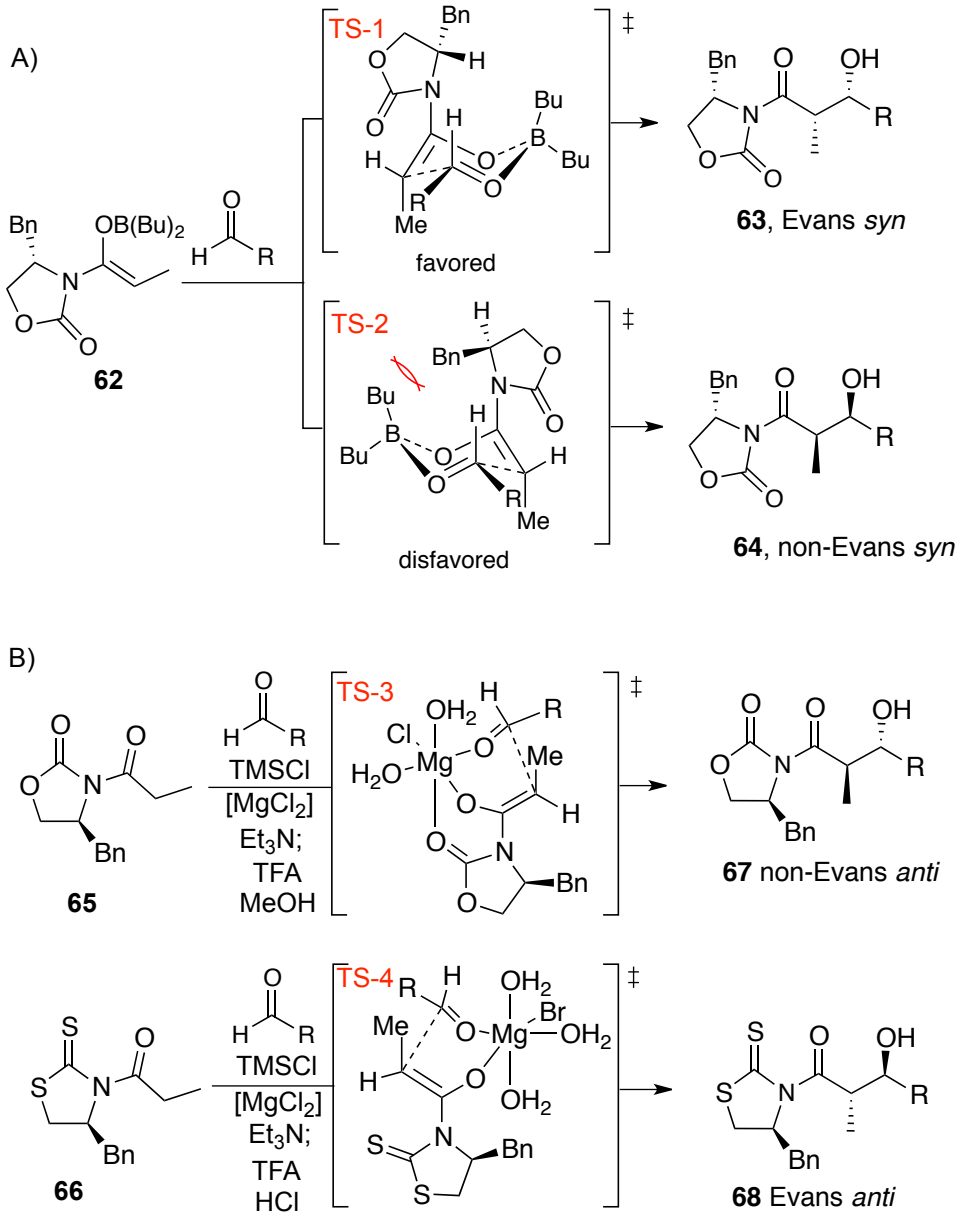


Scheme 2.2. Aldol Transition states based on the Zimmerman-Traxler transition state model.[7]

2.2.2 Aldol variations

Since its inception, extensive work has been done to expand the efficiency and scope of the aldol reaction. One of the more successful variations on the aldol reaction is the boron-mediated auxiliary-based aldol reaction developed by the Evans group.[8] The Evans aldol reaction uses a boron chelated chiral oxazolidinone (**62**) as an auxiliary to achieve high *syn* diastereoselectivity (**63**, Scheme 2.3a). The *syn* selectivity is favored by

minimizing steric interactions between the chiral auxiliary and the chelated boron ligands (**TS-1**).[9] Modifications of the Evans reaction, by Evans[10] and others,[11] allow access to the opposite *anti* diastereoselectivity (**67** & **68**) developed through a chelation controlled process (**TS-3** & **TS-4**) that prevents the formation of a Zimmerman-Traxler transition state (Scheme 2.3B).



Scheme 2.3. a) Evans *syn*-aldol transition states b) Evans *anti*-aldol transition states

Other groups have synthesized chiral N-acyloxazolidinone variants that provide varying degrees of diastereoselectivity and ease of removal (Figure 2.3). One of the downsides to the auxiliary controlled aldol reaction is the added cost (in steps and atom economy) of adding and removing the auxiliary.

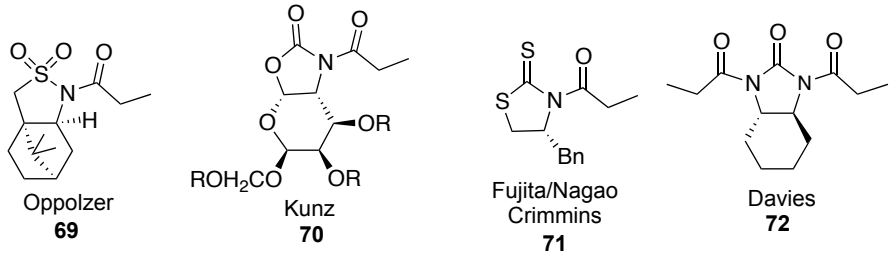


Figure 2.3. N-acyloxazolidinone variants (**69**,[12] **70**,[13] **71**,[14] **72**[15])

Other adaptations on the aldol reaction include, non-oxazolidinone auxiliaries,[16] substrate control,[17] reductive[18] and catalytic aldol coupling.[19] These variations allow access to the characteristic sequences of polypropionate with varying degrees of acyclic stereocontrol and moderate to high yields.

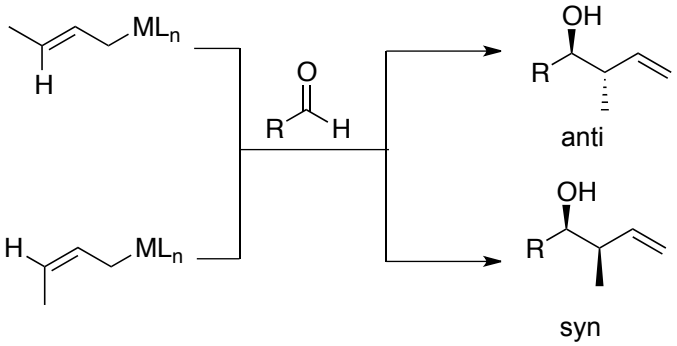
2.2.3 Limitations

Over the past 30 years, aldol reactions have been used as the core fundamental carbon-carbon bond forming reaction for the total syntheses of polyketides. While the aldol reaction has been extremely popular, there are inherent drawbacks. The numerous protection/deprotections that aldol reactions require can be tedious and add multiple steps to a synthesis. In addition, the coupling of larger, more complex fragments remains a difficult endeavor. Therefore, the need to develop more concise, streamlined routes to target polyketides is highly desirable.

2.2.4 Crotylation

Like the aldol reaction, asymmetric crotylations have received a great deal of focus over the last 30 years.[20] In the field of polyketide total synthesis, crotylations have been used extensively in the stereocontrolled formation of polypropionates.[21] These allyl-metal-aldehyde addition reactions result in either *anti* or *syn*-homoallylic alcohol products. They are analagous to metal enolized aldol reactions because the homoallylic

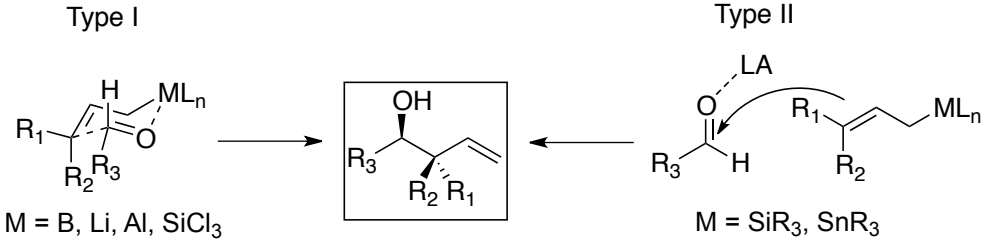
alcohol products can easily be converted to a precursor of the aldol reaction. Generally, diastereoselectivity is dependent upon the olefin geometry of the crotyl reagents (Scheme 2.4).[22] Asymmetric crotylations can achieve high enantioselectivity and high yields while accessing a broad range of permutations depending on the metal employed. Crotylations are classified into two main types of classes: Type I and Type II (Scheme 2.5).



Scheme 2.4. General crotylation reaction.

2.2.4.1 Type I Crotylations

Type I reactions are stoichiometric and proceed through a closed, chair-like transition state.[7] The metal atom activates the carbonyl in an intramolecular fashion via coordination of the carbonyl oxygen. This ordered transition state results in homoallylic products with predictable stereochemistry in which the olefin geometry of the starting crotyl reagents is carried over in the product. For example *(Z)*- and *(E)*-olefins afford *syn*- and *anti*-homoallylic alcohols as products respectively (Scheme 2.4). The most common metal used for type I allylations is boron.[23] Other metals that have successfully been employed include aluminum[24] and crotylsilanes.[25]



Scheme 2.5. Crotylation classes

2.2.4.2 Type II Crotylations

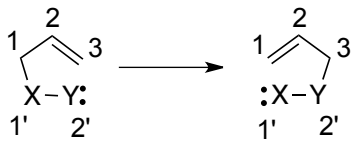
Type II reactions are generally catalytic and proceed through an open transition state in which a Lewis acid is required to activate the aldehyde carbonyl oxygen. Chelating ligands have also been used to catalyze type II reactions.[26] Commonly employed metals for type II allylations are silicon, tin, and, to a lesser extent, boron derivatives.[27] All of these crotylations predominantly afford *syn*-homoallylic alcohols.

2.2.4.3 Limitations

Typically, type I crotylations give better results in both diastereoselectivity and overall yields. This can be attributed to the highly ordered and stable transition state compared to the open transition state associated with type II reactions. In general, type II reactions are limited either by lower reactivity and/or diastereoselectivity. Allylsilane reagents need a very strong Lewis acid for the addition to proceed; this is not compatible with a wide range of functional groups. Furthermore, there is a lack of catalytic systems that can sufficiently overcome the non-ordered transition state of type II reactions to produce practical yields. While type II reactions that employ tin as the metal have shown quite efficacious, the use of tin is a major drawback due to its high toxicity, as well as, difficulties with purification and its deleterious effects on the environment.

2.2.5 2,3-Wittig Rearrangement

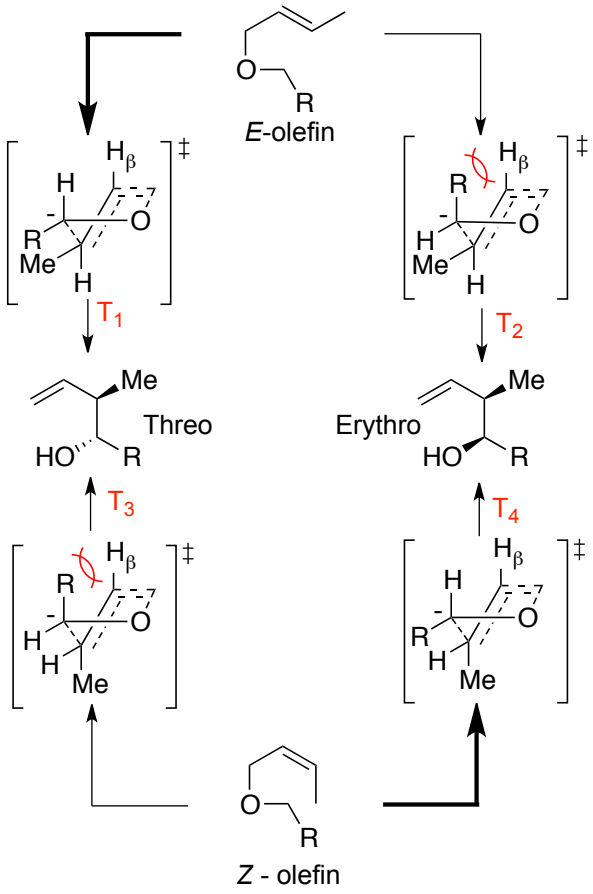
The [2,3]-Wittig rearrangement is a type of sigmatropic bond reorganization that proceeds through a 5-membered 6-electron transition state (Scheme 2.6), where the generated oxycarbanion is the migrating functionality.[28]



Scheme 2.6. Basic [2,3]-rearrangement mechanism

The [2,3]-rearrangement is a very powerful methodology that has been employed in natural product synthesis and in research that requires acyclic stereocontrol.[29] Moreover, the [2,3]-Wittig rearrangement is a versatile reaction that affords predictable stereochemical outcomes generated from retention of olefin geometry and transfer of starting chirality, forming vicinal chiral centers with high diastereoselectivity.

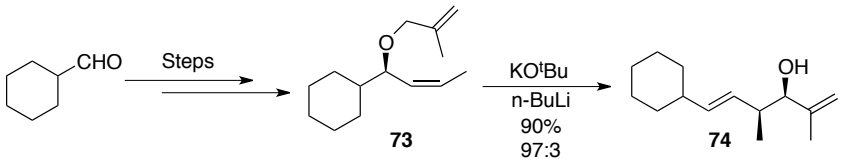
The predictable product formation originates from the olefin geometry of the substrate.[22a] In general, *(E)*- and *(Z)*-olefins give *anti*- (threo) or *syn*- (erythro) products respectively. This stereochemistry can be rationalized through the minimization of 1,3-diaxial interactions with H_β and the R group (Scheme 2.7). The $\mathbf{T_1}$ transition state is favored for *(E)*-olefins while the $\mathbf{T_4}$ transition state is favored for *(Z)*-olefins. The size of the R group in *(E)*-configured substrates needs to be considered because a drop in diastereoselectivity is observed due to the increased gauche interactions with the methyl group ($\mathbf{T_1}$ transition state).



Scheme 2.7 Transition state of [2,3]-Wittig rearrangement

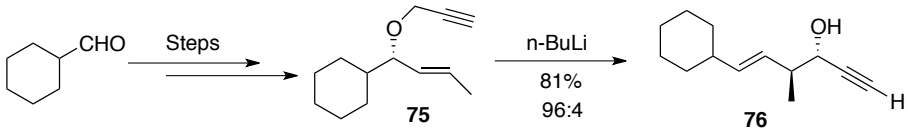
2.2.5.1 Parker Group application of [2,3]-Wittig rearrangement for the synthesis of stereotriad building blocks

Previous work done in the Parker laboratories took advantage of the "Midland sequence" (methallylation, [2,3]-Wittig rearrangement, protection and hydroboration),[30] for synthesis of a major substructure of discodermolide. We employed the [2,3]-Wittig rearrangement to generate both *anti*- and *syn*-stereodiads, demonstrating the versatility of this type of rearrangement. In both the *syn*-[31] and *anti*-[32] cases, we started from inexpensive, commercially available cyclohexane carboxyaldehyde. In the *syn*-[2,3]-Wittig rearrangement, the allylic ether **73** was treacted with Schlosser's base to afford *syn*-product **74** in 90% yield and 97:3 *syn/anti* diastereoselectivity of the desired product (Scheme 2.8).



Scheme 2.8 Synthesis of **74** via [2,3]-Wittig rearrangement

In the *anti*-[2,3]-Wittig rearrangement, propargyl ether **75** was treated with *n*-BuLi to afford *anti*-propargyl alcohol **76** in 81% yield and 96:4 *anti/syn* diastereoselectivity (Scheme 2.9). The predictability of product distribution from the [2,3]-Wittig rearrangement is a valuable and practical synthetic trait of this reaction.



Scheme 2.9. Synthesis of **76** via [2,3]-Wittig rearrangement

2.2.5.2 Limitations

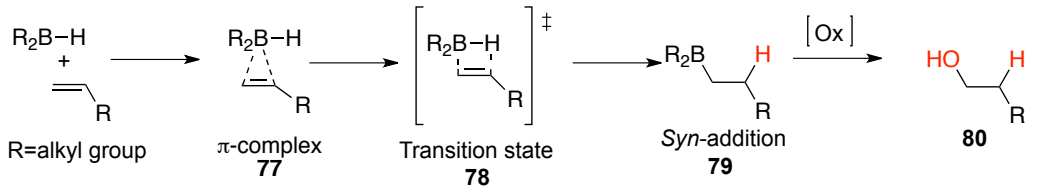
The [2,3]-Wittig rearrangement has shown to be a reliable and valuable synthetic tool, although it does have some limitations. The scope of the rearrangement is limited by the availability of methods for generating carbanions at temperatures low enough to reduce the amount of competing [1,2]-alkyl shifts.[33] Furthermore, substrates containing

multiple allylic positions can potentially lead to regiochemical issues when generating the anionic intermediate. The generation of the carbanion at the wrong allylic position can lead to unwanted [1,2] or [1,4]-alkyl shifts, which detracts from the applicability of the rearrangement.[33]

2.2.6 Hydroboration

Since its discovery by Herbert C. Brown in 1956,[34] hydroboration has become one of the most instrumental organometallic reactions in organic synthesis. In its simplest form, the hydroboration reaction is the addition of a boron-hydrogen bond to an unsaturated carbon-carbon bond via a *syn*-addition process.

Hydroboration of alkenes preferentially adds in an *anti*-Markovnikov manner,[35] i.e. the boron adds to the least substituted carbon of the olefin. This concerted process generates a four-centered transition state (**78**), which consists of the simultaneous formation of a boron-carbon and hydrogen-carbon σ-bond, as well as, the cleavage of a boron-hydrogen σ-bond and a carbon-carbon π-bond, (Scheme 2.10).[36]



Scheme 2.10. Hydroboration of olefins

For smaller, less hindered borane reagents (e.g. BH_3-THF) there is a weak pre-transition state π-complex (**77**) prior to the transition state.[37] The resulting alkylborane is oxidized with alkaline peroxide to afford the alcohol stereospecifically (**80**). The original configuration of boron is retained in the oxidized product, relative to the other substituents on the carbon.

2.2.6.1 Non-catalytic hydroboration

Since its discovery, the number of available organoboranes for the hydroboration of olefins has grown exponentially. A few of the more commonly used boranes are shown below. (Figure 2.4)

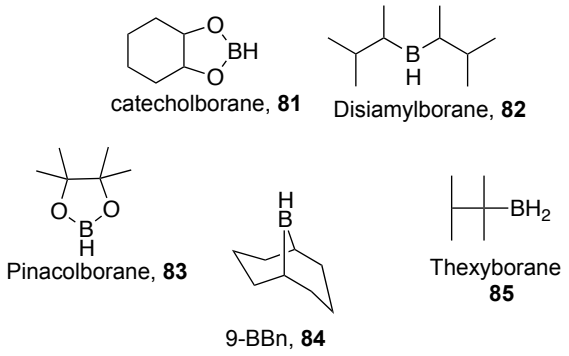
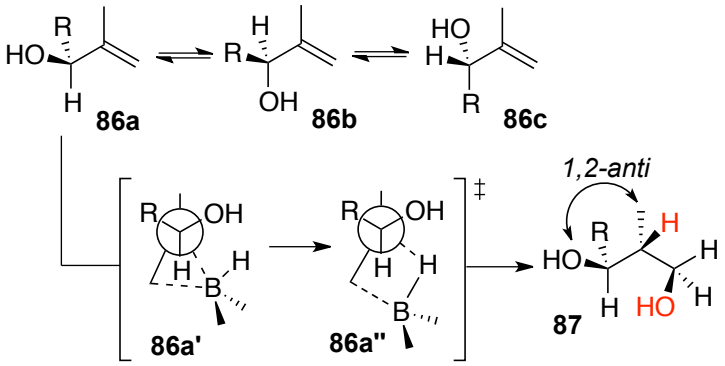


Figure 2.4. Common hydroborating reagents

These sterically demanding organoboranes are very useful when employed for the hydroboration of acyclic, allylic alcohols, a common precursor in polypropionate synthesis. Of the boranes shown, catecholborane (**81**) and pinacolborane (**83**) are particularly unreactive because the boron is directly bonded to electronegative oxygens. This decrease in reactivity can be attributed to the lone pairs on the adjacent oxygens overlapping with the empty orbital on boron, thus lowering boron's Lewis acidity and subsequent ability to complex with olefins.

Still et al. showed that the hydroboration of 1,1-disubstituted allylic alcohols gave 1,2-*anti* products (**87**) in a diastereoselective fashion (Scheme 2.11).[38] This result can be rationalized by looking at the lowest energy conformers of the allylic alcohol. Structure **86a** has the lowest in energy as a result of the smallest substituent (-H) being situated directly over the face of the four-centered transition state (**86a'** or **86a''**). This leads to the α-methyl preferentially adopting an anti position relative to the allylic alcohol. Varying degrees of reactivity and anti diastereoselectivity can be achieved with different organoboranes on allylic alcohols.



Scheme 2.11. Hydroboration of 1,1-disubstituted olefins

The diastereoselectivity is generated in part by the steric influences of the borane. Experimental observations by Still[38] and theoretical studies by Houk,[39] demonstrated that increases in diastereoselectivity could also be achieved by functionalizing the allylic alcohol through steric and/or stereoelectronic factors. In Figure 2.5, the preferential orientations for both electronic and steric demands (a and b respectively) of the substituents are shown.[40] In general, allylic alcohols protected with sterically bulky and/or electrophilic groups enhance the diastereoselectivity of the reaction.

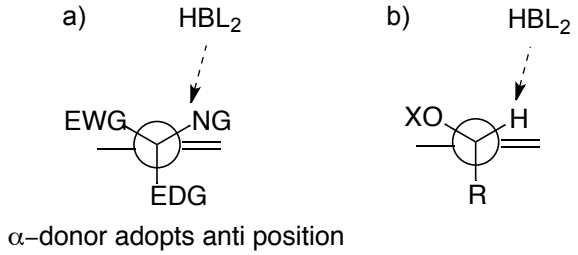
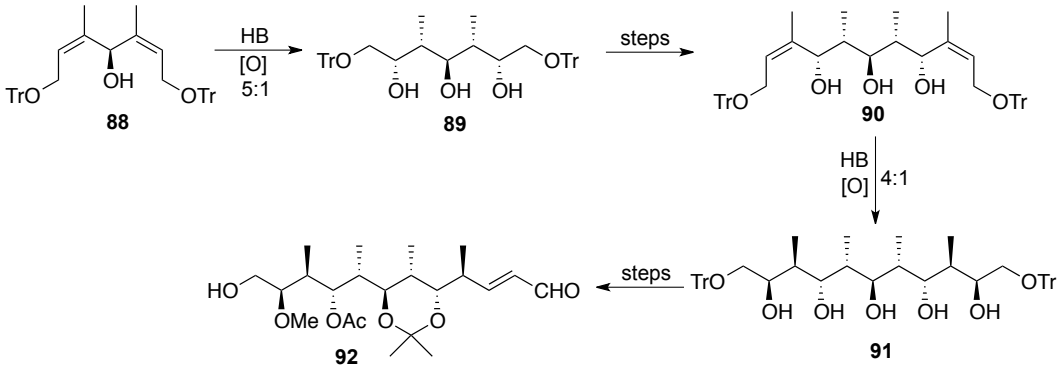


Figure 2.5. Preferential orientation of the olefin during hydroboration a) orientation with electronic demands of substituent b) orientation with steric demands of substituent

The synthetic utility of the hydroboration of allylic alcohols is derived from its predictable threo or *anti*-selectivity, as well as the prevalence of 1,3-diol substructures in polyketide natural products. These substructures are versatile building blocks for constructing carbon frameworks. Still et al. demonstrated the versatility by synthesizing the ansa-bridge of rifamycin with a double chain elongation via hydroboration strategy. After multiple hydroborations, the meso polyol **91** was desymmetrized and subsequently refunctionalized to the ansa bridge **92** in ten steps (Scheme 2.12).[38]



Scheme 2.12. Still et al.[38] synthesis of ansa bridge of rifamycin with hydroboration

2.2.6.2 Limitations

In general, the hydroboration of olefins is a predictable and dependable reaction; however it is not without its limitations. Alkenes that are more hindered can require longer reaction times and have a marked decrease in diastereoselectivity. Also, organoboranes can act as reducing agents for a large number of functional groups (e.g. ketones, amides, carboxylic acids etc).

2.2.6.3 Catalytic hydroboration

In 1985, twenty-five years after Brown discovered hydroboration of olefins, Mannig and Noth found rhodium complexes (e.g. Wilkinsons catalyst) enhanced the rates of hydroborations, especially those of less reactive reagents such as catecholborane. [41] Since their initial discovery, an enormous amount of work has been done to gain a better understanding of the scope of the reaction and to expand the number of viable metal catalysts.[42] Other transition metal complexes that have been studied include Li,[43] Ni,[44] Pd,[45] Ru,[46] Ir,[47] Sm,[48] La,[49] Ti[50] and Zr.[51] However, none has delivered the selectivity and rate enhancement that rhodium catalysts have demonstrated.

While the exact mechanism has not been elucidated, in depth mechanistic studies by Mannig,[41] Evans,[52] Burgess[40] and others, have lead to a better understanding of the catalyzed hydroboration. While the mechanism can change depending on substrate, catalyst, reagent and conditions, the basic catalytic cycle with Wilkinson's catalyst is shown below (Figure 2.6).

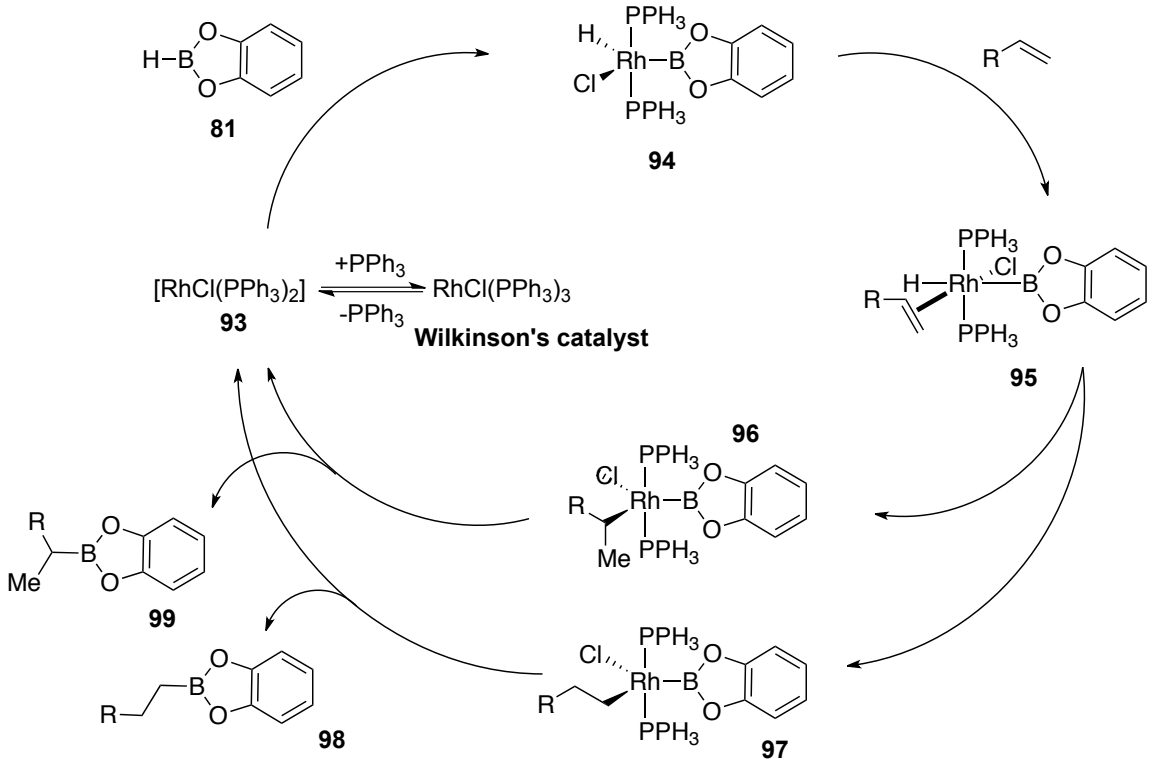


Figure 2.6. Hydroboration catalytic cycle with Wilkinson's catalyst

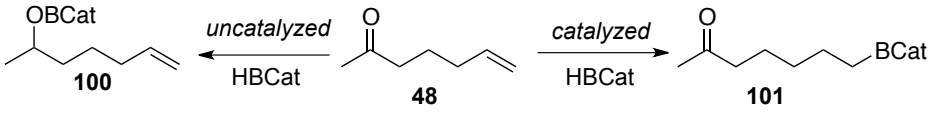
Wilkinson's catalyst dissociates a triphenylphosphine ligand (**93**) to react with stoichiometric amounts of catacholborane (**81**). Coordination of the alkene trans to the chlorine yields a six-coordinate H-Rh-B complex **95**. Migratory insertion of the alkene into the rhodium hydride bond produces either Markovnikov (**96**) or anti-Markovnikov (**97**) alkyl boronate esters. Reductive elimination leads to organoboranes (**98** and **99**), which afford alcohols upon oxidative workup. Degradation of catacholborane can generate hydrogen and diborane, which can lead to hydrogenation and uncatalyzed hydroboration that can compete with the metal catalyzed variant.[53]

2.2.6.4 Chemo-, Stereo, and Regioselectivities of catalyzed hydroborations

Catalytic hydroboration is stereocomplementary to the uncatalyzed congeners. It has been shown to provide enhanced chemo, stereo and regioselectivities as compared to

the uncatalyzed reaction, which increases the applicability for the use in many natural product and drug syntheses.

Catalyzed intramolecular hydroboration is chemoselective, in that it preferentially hydroborates the olefin in the presence of more reactive functional groups (Scheme 2.13).[41] The uncatalyzed variants show no functional group selectivity and will attack the more reactive group first **48**.



Scheme 2.13. Chemoselectivity of catalyzed and uncatalyzed hydroborations

Scheme 2.2.6.5. Chemoselectivity of catalyzed and uncatalyzed hydroboration

Evans showed that when cyclic chiral allylic alcohols were hydroborated (Figure 2.7), the catalyzed reactions gave predominantly 1,3 anti products (**104**), while the uncatalyzed reactions afforded 1,2 anti diols (**103**).[54] Both resulted in high yields and good diastereoselectivities. This simple yet elegant study demonstrated the versatile, regioselective nature of catalyzed hydroborations.

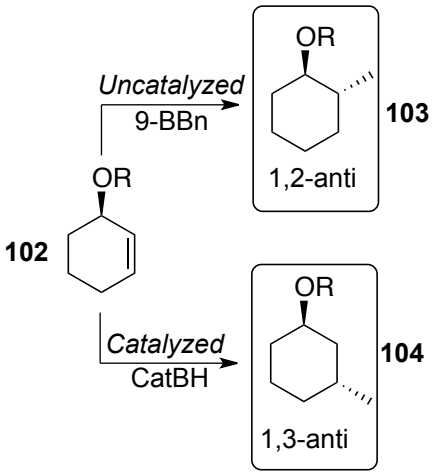


Figure 2.7. Regioselectivity of catalyzed and uncatalyzed hydroboration

Evans,[55] and subsequently Burgess[56], found that catalyzed hydroborations with catacholborane on mono- and disubstituted olefins proceeded at faster rates and under milder conditions than their uncatalyzed counterparts. When reacted with chiral allylic

alcohols, catalyzed hydroborations produced predominantly *syn*-isomers, the opposite result of the uncatalyzed variants. This complementary result is attributed to the addition of the boron-hydrogen bond to the olefin being different when delivered via transition metal versus direct addition. This can be rationalized by the orientation the olefin adopts when complexed with the metal catalyst (Figure 2.8).[40] In instances in which steric interactions are prevalent (Figure 2.8a), the largest group adopts an anti position relative to the olefin. The smallest group (s) will adopt the sterically crowded "inside position." Electronically, the preferential orientation places the electron-withdrawing group in the anti position because this provides the most orbital overlap between the σ*-orbital of the EWG and π*-orbital of the olefin (Figure 2.8b). This secondary orbital interaction lessens the gap in energy between the metal d orbital and the π*-orbital of the uncomplexed alkene.[40] Once again, the smallest group adopts the sterically crowded inside position. The steric and stereoelectronic demands of the protected allylic alcohol affect the diastereoselectivities of catalytic hydroborations similar to the uncatalyzed versions.

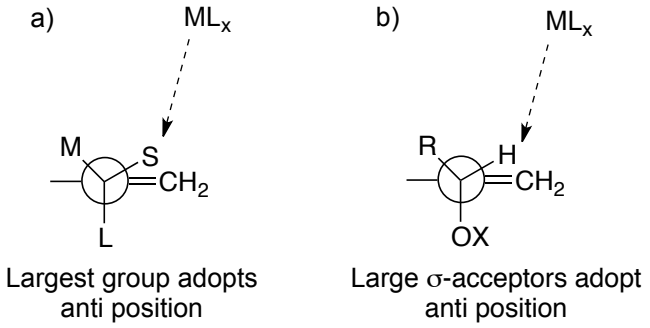
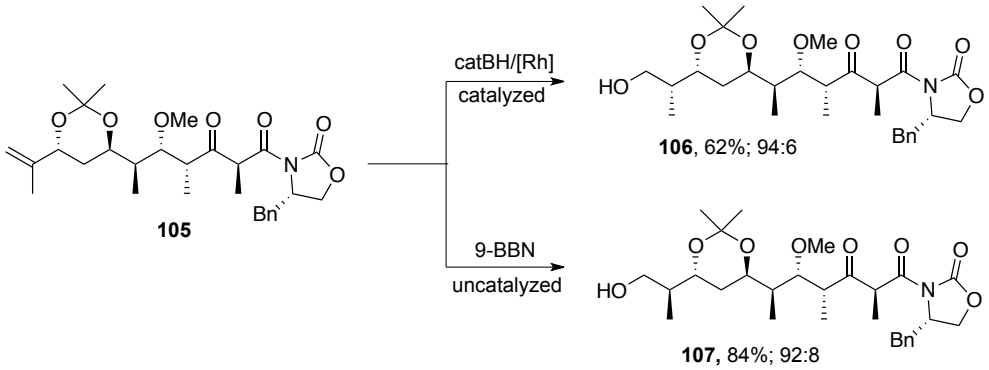


Figure 2.8. Steric and electronic preferential orientations (a and b respectively) on catalytic hydroboration of olefins

The complementary nature of uncatalyzed and catalyzed hydroborations has been shown in model studies for the total synthesis of loncomycin, with either diastereomer accessible in good yields and high diastereoselectivities (Scheme 2.14).[57]



Scheme 2.14. Stereochemical differences between catalyzed vs uncatalyzed hydroboration

2.2.6.6 Limitations

While Mannig and Noth's landmark discovery has paved the way for the development of transition metal catalyzed hydroboration's as an important, powerful class of reactions. Work still needs to done on increasing the catalytic efficiency, as well as, developing a better understanding of the exact mechanism involved. The importance of fine-tuning substrate and transition metal ligand interactions (electronic and steric) remains a hindrance, as a general catalyst has yet to be developed that can tolerate a wide range of substrates.

2.2.6.7 Asymmetric Hydroboration

In 1961, Brown pioneered the reagent controlled asymmetric synthesis when he showed that almost complete asymmetric induction was achieved when diisopinocampheylborane ($(Ipc)_2BH$) reacted with prochiral cis-alkenes (Figure 2.9, **108**).[58] At the time, this was a feat usually reserved for enzymatic processes. Since his discovery, the scope of reagent controlled asymmetric synthesis has increased exponentially.

In the reaction of a prochiral olefin with a chiral organoborane reagent, two major factors, both of which are derived from steric interactions, are involved in the efficiency of asymmetric hydroboration (Figure 2.9). The diastereoselectivity is derived from the two-diastereomeric transition states (*si*- or *re*- face of olefin), where the sterically unhindered transition state is the most favorable. The other factor is the reactivity of the

chiral hydroborating agent with the olefin. The need to tailor the chiral organoborane to the prochiral olefin is essential in achieving a desirable outcome.

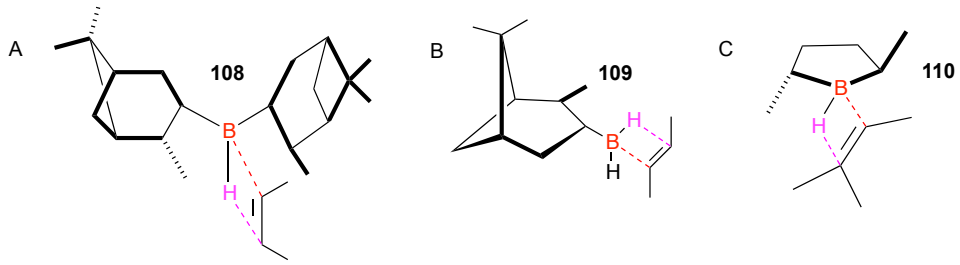


Figure 2.9. Asymmetric hydroboration reagents. A) Brown's $(Ipc)_2BH$ complexed to cis alkene B) Brown's $IpcBH_2$ complexed with trans alkene C) Masasume's DMB complexed with trisubstituted alkene

Several very effective chiral hydroborating agents have been developed, achieving moderate to high levels of asymmetric induction for the four major classes of alkenes: *cis*-, *trans*-, tri- and geminal substituted olefins (Table 1).[59]

	$(Ipc)_2BH_2$	$(Ipc)BH_2$	DMB	Soderquist-Ph	Soderquist-TMS
Olefin type	$)_2BH$ **108**	BH_2 **109**	B H **110**	Ph BH **111**	TMS BH **112**
	14	73	99.5	96	95
	99.1	24	97.6	32	84
	15	53	97.6	74	—
 *i*Pr	32	—	1.5	38	52
 Ph	—	5	—	78	66

Table 1. Chiral hydroboration reagents and their enantioselectivities

2.2.6.8 Brown's chiral boranes

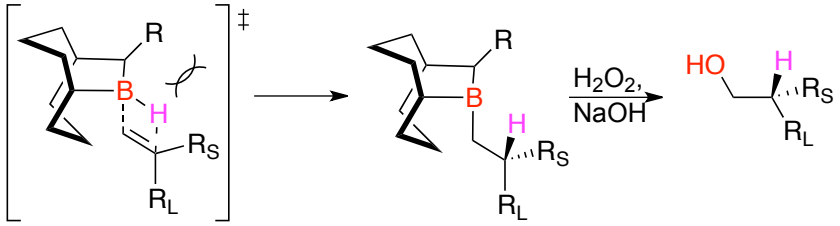
Brown synthesized the chiral dialkylborane, $(Ipc)_2BH$ (**108**), from readily available α-pinene.[60] He found that a high level of asymmetric induction was observed with *cis*-alkenes, but poor enantioselectivity for *trans*- and trisubstituted variants. The enormous steric load of the dialkylborane was perfect for *cis*-olefins but was sterically detrimental too more hindered alkenes. In the latter two cases, hydroboration proceeded with the displacement of pinene by competing dehydroboration. With these results in hand, Brown subsequently synthesized the less hindered monoalkylborane derivative $IpcBH_2$ **109**. As expected, monoisopinocampheylborane increased levels of asymmetric induction for the bulkier *trans*- and trisubstituted olefins but showed considerably less induction for the cis case (73, 53, 24% ee respectively). While $(Ipc)_2BH$ (**108)** and $IpcBH_2$ (**109**) were the first two chiral hydroborating agents reported by Brown, they both are still frequently used today.

2.2.6.8 Masasume's chiral borane

To date, the most sterically unhindered asymmetric hydroborating agent is also the most efficient.[61] Masamunes 2,5-dimethylborolane (DMB) **110** achieves very high levels of asymmetric induction for *cis*-, *trans*-, and trisubstituted olefins. Although it has been shown to be very efficient in converting three out of the four types of prochiral olefins, it is not employed very often because its lengthy synthesis detracts from its practicality.

2.2.6.9 Soderquist's chiral boranes

The most difficult alkene to achieve acceptable levels of induction is 1,1-disubstituted olefin because it is difficult for the chiral borane to differentiate between the two enantiotopic faces.[59] Browns pinene based reagents (**108** & **109**), as well as, Masasume's DMB reagent (**110**) are ineffective in inducing chiral induction. In 2008, Soderquist et al, developed a chiral 9-BBn derivative, 10-substituted-9-borabicyclo[3.3.2]decanes (10-R-9-BBD-H; **111** & **112)** that is uniquely effective at inducing asymmetric induction for 1,1-disubstituted olefins (Table 1, columns 4 and 5).[62]



Scheme 2.15. 10-R-9-BBD-H; **111**: R = Ph, **112**: R = TMS

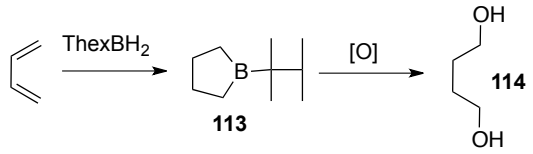
These new chiral reagents have achieved up to 92% ee on 1,1-disubstituted olefins. They also improved enantioselectivities for trans (95%+) and trisubstituted (74%) olefins, though not to the levels that Masasume's reagent exhibits. Soderquist's 10-R-9-BBD-H reagent can easily be prepared in four steps from commercially available *B*-methoxy-9-BBN; this makes it an attractive option for inducing chirality on various sterically encumbered olefins.

2.2.6.10 Limitations of asymmetric hydroboration

The ability to develop easily accessible chiral reagents from cheap and practical sources is key to asymmetric hydroboration. Hard to find chiral sources and/or lengthy syntheses detract from the overall utility of the reaction, as in the case of Masaume's powerful asymmetric reagent. While Soderquist's two chiral reagents are a marked improvement over previous examples, additional improvements in enantioselectivity especially for geminal-substituted olefins still need to be made.

2.2.6.11 Cyclic hydroboration

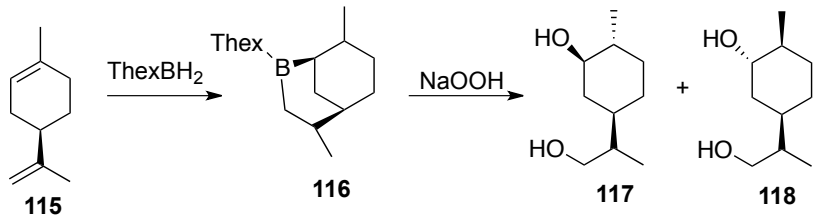
Out of all the hydroboration variations that have evolved from Brown's original discovery, cyclic hydroboration is the least employed and explored. In 1971, Brown found that organoboranes with more than one hydrogen (BH_3-THF, thexylborane, **85**) could convert dienes to cyclic boranes **113**, when oxidized would afford diols **114** (Scheme 2.16).[63]



Scheme 2.16. Cyclic hydroboration of dienes to form boracycles

In exploring the methodology of cyclic hydroboration, Brown found several interesting mechanistic generalizations. Similar to the relative rates of ring closures, 5-membered borocycles are strongly favored in the competitive formation of 5- and 6-membered boracycles. In the competitive formation of 6 or 7 membered borocycles, neither one is favored therefore; standard hydroboration directive effects take over in these cases.

Realizing the potential for stereospecific cyclic hydroboration, Brown chose D-(+)-limonene **115** as a model (Scheme 2.17).



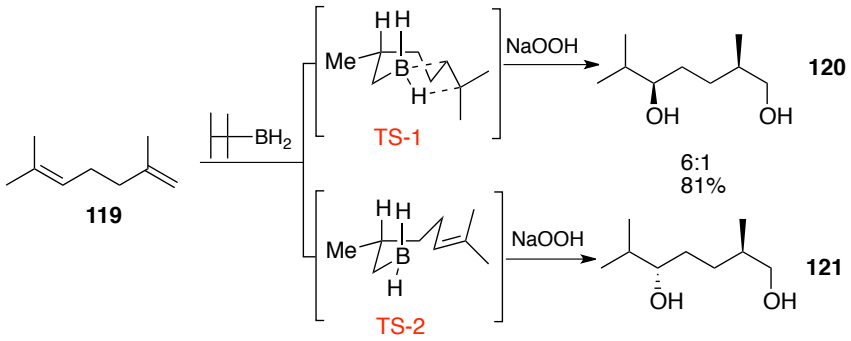
Scheme 2.17. Cyclic hydroboration of D-(+)-limonene

Cyclic hydroboration and subsequent oxidation of **115** gave a mixture of *cis*- (**117**) and *trans*- (**118**) diols (85:15 respectively) in 90% yield. This result showed that cyclic hydroboration could be a powerful synthetic tool for achieving remote stereospecific hydroboration.

2.2.6.12 Still: Remote asymmetric induction with cyclic hydroboration

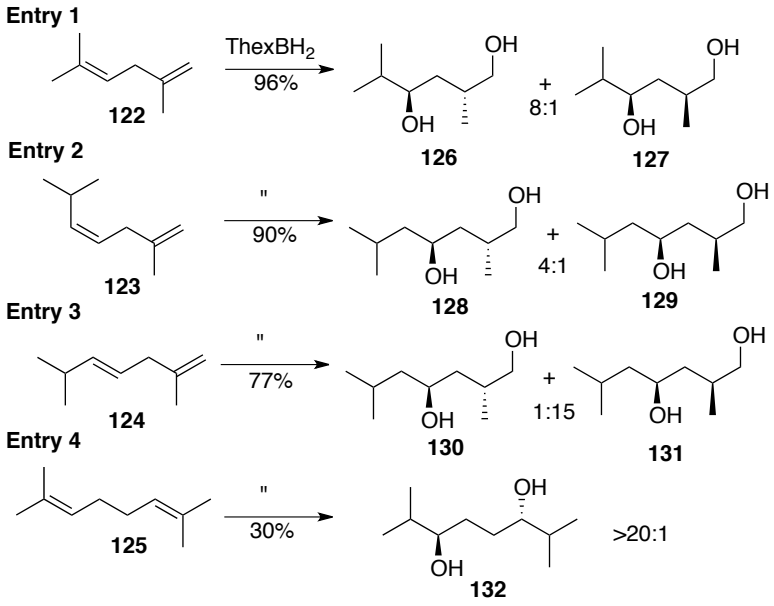
In the early 1970s, remote asymmetric induction of acyclic systems greater than two adjacently linked carbons was a rare and difficult endeavor. Drawing from Brown's previous stereospecific results from the cyclic hydroboration on D-(+)-limonene (**115**), Still looked to establish a more efficient way to synthesize new asymmetric centers remotely from preexisting ones on acyclic substrates.[64]

When 1,5-diene **119**, was treated with BH_3-THF (not shown) no stereochemical control was observed. However, when **119** was reacted with thexylborane, substantial 1,4 asymmetric induction was observed (Scheme 2.18).



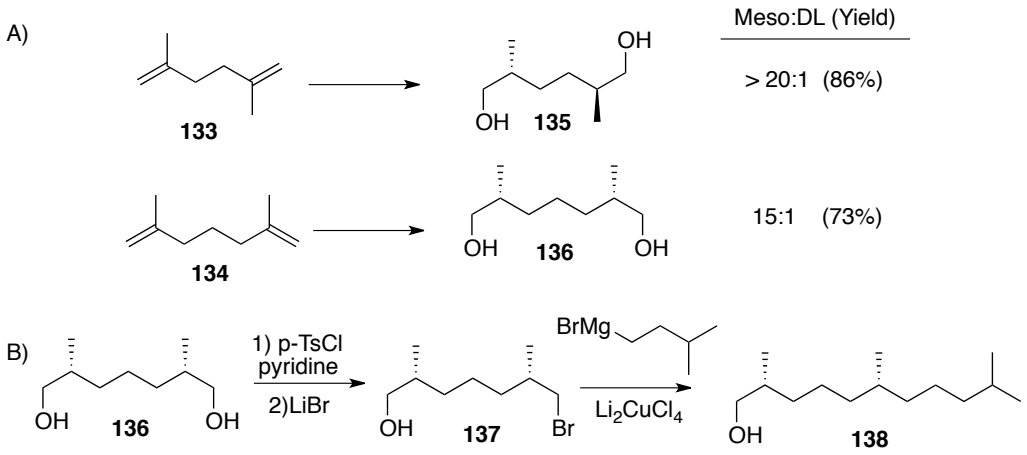
Scheme 2.18. Initial cyclic hydroboration studies

The major product is the result of a stereoelectronic effect, which results from the transition state adopting a boatlike geometry (**TS-1**) and the larger substituents adopting equatorial positions. The boat geometry allows the borane to form the classic four-centered complex (**TS-1**), while the chairlike geometry precludes this complex (**TS-2**). Still expanded the methodology on related 1,3- and 1,4-dienes that all showed impressive degrees of remote asymmetric induction (Scheme 2.19). Entry 2 exhibited lower asymmetric induction because of a competing intermolecular hydroboration of the disubstituted *cis*-olefin.



Scheme 2.19. Scope of cyclic hydroboration with 1,3- and 1,4-dienes

Still also applied intramolecular hydroboration to symmetrical 1,5-dienes to form 7 and 8 membered borocycles, obtaining meso products with high asymmetric induction (Scheme 2.20a). Attempts to expand the reaction to 1,6-dienes were unsuccessful. Further modification of **136** to the vitamin E sidechain **138** in two steps demonstrates the direct application of this methodology (Scheme 2.20b)

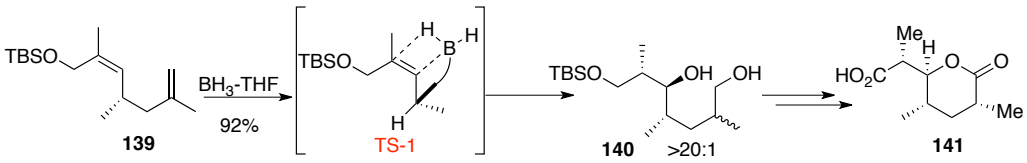


Scheme 2.20. a) meso b) synthesis of Vitamin E sidechain

With his pioneering work, Still developed and demonstrated the utility of cyclic hydroboration of acyclic dienes. Stereochemical control of the intramolecular hydroboration with the remote preexisting chiral center is a powerful tool for synthetic chemists.

2.2.6.13 Cyclic hydroboration of dienes for the synthesis of Prelog-Djerassi lactonic acid

Two independent research groups, Still[65] and Morgan,[66] demonstrated the value of cyclic hydroboration by synthesizing the Prelog-Djerassi lactonic acid **141** (Scheme 2.21) and lactone concurrently. Cyclic hydroboration of **139** with BH_3-THF afforded stereotriad **140** in high yields and diastereoselectivity (>20:1).



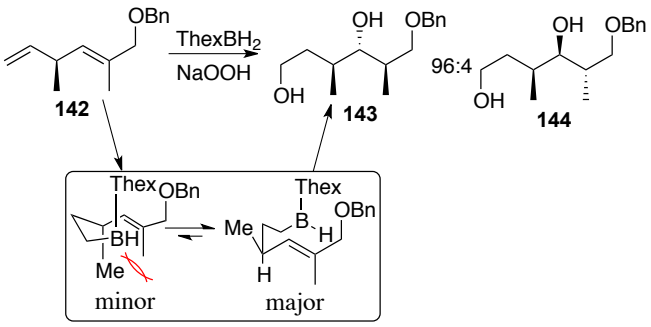
Scheme 2.21. Still et al. synthesis of Prelog-Djerassi lactonic acid via cyclic hydroboration

Still and Morgan both predicted that preferential attack from the *re*-face would lead to the major product shown (**TS-1,** Scheme 2.21). The observed diastereoselectivity originates from allylic 1,3-strain.[67] In $A_{(1,3)}$-strain, the stereocenter α- to the olefin adopts an orientation that places the smallest substituent in the same plane as the olefin (**TS-1,** Scheme 2.21). This minimizes unfavorable steric interactions between the substituents on the olefin and allylic carbon and positions the alkylborane on the *re*-face of the olefin, leading to the observed diastereoselectivity.

2.2.6.14 Yokoyama's allylic strain induced cyclic hydroboration

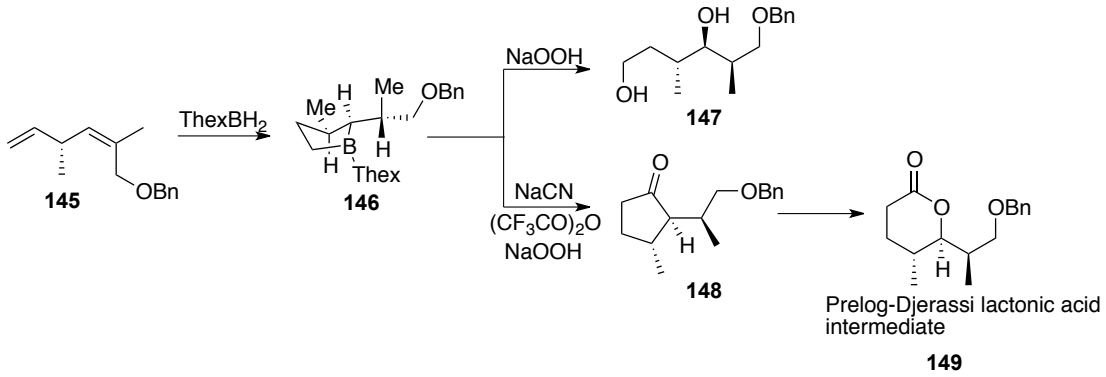
Previous work on $A_{(1,3)}$-strain-controlled cyclic hydroborations had only focused on 1,5-dienes (Still and Morgans). In 1990, Yokoyama extended this methodology to include 1,4-dienes.[68] As expected, the 1,4-isomers afforded 1,4-diols in good yields (75%) and excellent stereoselectivity (Scheme 2.22). The transition state is dictated by

$A_{(1,3)}$-strain and the major product (**143**) is the result of the smallest substituent (H-) adopting the axial position relative to the olefin (Scheme 2.22).[69]



Scheme 2.22. Cyclic hydroboration of 1,4-dienes to form stereotriads[69]

Like Still and Morgans before him, Yokoyama applied this methodology for the formal synthesis of Prelog-Djerossi lactonic acid (Scheme 2.23). Starting from 1,4-diene, **145**, cyclic hydroboration with thexylborane afforded boracycle (**146**). Instead of the usual oxidative workup, Yokoyama employed the previously reported synthesis of ketones via trialkylcyanoborates,[70] where treatment of the boracycle with sodium cyanide, trifluoroacetic anhydride and then alkaline peroxide afforded cyclopentanone **148** in 78% yield. Oxidation of **148** afforded known Prelog-Djerossi lactonic acid intermediate[71](**149**) in good yields.



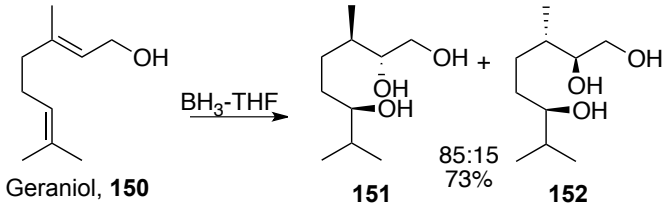
Scheme 2.23 Synthesis of **149** from diene **145**.

2.2.6.15 Whitney's cyclic hydroboration of geraniol derivatives

In 1985, there were enough precedents in the literature to show that hydroboration of 1,4- and 1,5-dienes proceeded with moderate to high levels of asymmetric induction

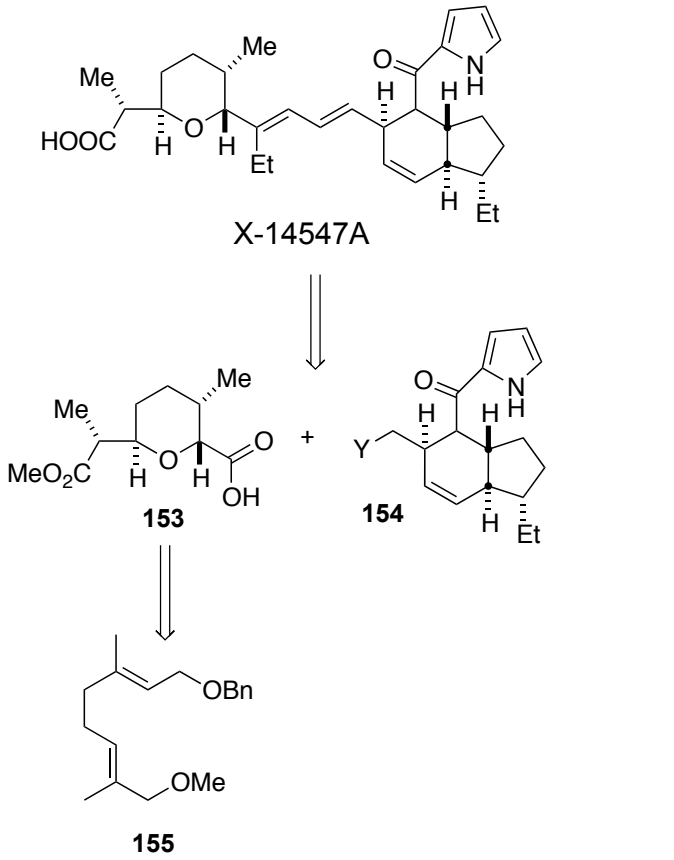
on achiral substrates. Whitney recognized that geraniol (**150**) was an inexpensive and commercially available 1,5-diene that would be a good model system for cyclic hydroboration.[72]

Cyclic hydroboration of **150** with borane-tetrahydrofuran complex resulted in a mixture of **151** and **152** (85:15 respectively) in 73% yield.



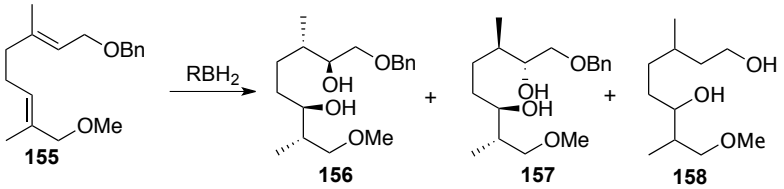
Scheme 2.24. Cyclic hydroboration on geraniol

The major product, **151**, is the result of the isopropyl group adopting the anti position in the transition state, leading to an endocyclic intramolecular hydroboration. With the model results in hand, Whitney turned to applying this methodology for the synthesis of a natural product. He recognized that the left portion of X-14547A, a tetrahydropyran ring, when deconstructed, had a functionalized backbone similar to that of geraniol (**155**) (Scheme2.25)



Scheme 2.25. Retrosynthesis of X-14547A

Cyclic hydroboration of the geraniol derivative, **155** with BH_3-THF afforded a 1:1 mixture of **156** and **157** (Scheme 2.26). When thexylborane was used, diastereoselectivity increased dramatically; however, a substantial amount of β-elimination product **158** was generated from a competing pathway. Attempts to increase the yield and decrease β-elimination rehydroboration were unsuccessful.

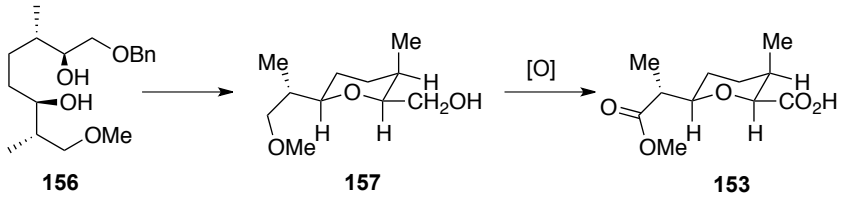


Borane	156:157	Yield
BH_3-THF	1:1	—
$ThexBH_2$	88:12	31%[a]

a) Substantial amount of β-elimination product isolated

Scheme 2.26 Cyclic hydroboration of **155**

The differences in stereoselectivities between geraniol derivatives (**150** and **155**) can be rationalized in terms of the regioselectivity of the initial intermolecular hydroboration. In **150**, the initial hydroboration preferentially reacts with the trisubstituted olefin with carbon substituents, which subsequently leads to an endocyclic intramolecular hydroboration. This is due to the electron withdrawing allylic alcohol decreasing the reactivity of the olefin to hydroboration.[73] In **155**, the regioselectivity is reversed, with the initial hydroboration occurring at the olefin containing the allylic methoxy group. This reversal can be attributed to allylic heteroatom substituent effects. The rate of addition of boron to an alkene is slower when the carbon that is coordinating to boron is γ rather than β to the allylic heteroatom via induction and hyperconjugation.



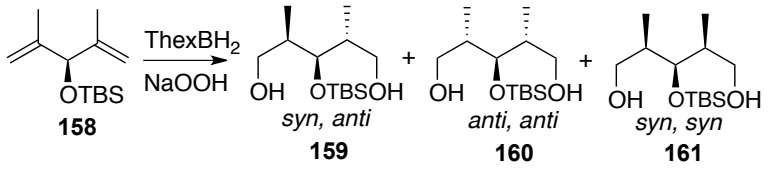
156 **157** **153**

Scheme 2.27. Derivatization of product

Derivatization of **156** to the tetrahydropyran **157** was required to confirm the observed stereochemistry. Additionally, **157** was also the intermediate for the synthesis of the left hand portion of X-14547A (Scheme 2.25). Tetrahydropyran **157** was easily oxidized to afford **153**, the left-hand fragment of X-14547A in a concise manner. This was the first published result of cyclic hydroboration generating a racemic mixture of four stereocenters in a single step from an achiral substrate.

2.2.6.16 Oku's synthesis of symmetrical stereotriads and stereotetrads

In 1990, Oku et al, showed that synthesizing contiguous stereocenters on sterically bulky acyclic systems with cyclic hydroboration was possible.[74] His substrate was the sterically encumbered, symmetrical dialkenyl carbinol **158** (Scheme 2.28). Cyclic hydroboration on the **158** yielded the *syn*-, *anti*- product **159** in high yields and excellent diastereoselectivity (91%, 15:1:1, respectively).



Scheme 2.28. Synthesis of stereotriads via cyclic hydroboration

The initial hydroboration affords *anti*-selectivity with respect to the preexisting stereocenter (-OTBS), while the second, intramolecular hydroboration was found to give *syn*-diastereoselectivity. The *syn*-stereoselectivity was the opposite found in Still's pioneering work. The results of Still et al., were controlled by stereoelectronic factors, where the -OX, alkyl and hydrogen substituents adopt outside, anti and inside positions, respectively (Figure 2.9a).[38,39] The transition state is stabilized when an electron-donating group (i.e alkyl) is affixed to the anti position. The results of Oku et al., were controlled by sterics from the pseudo equatorial orientation of the alkyl substituent in a cyclic transition state (Figure 2.9b). The -OX and hydrogen substituents adopt outside and anti positions, while the alkylborane adopts the inside (pseudoequatorial) position.

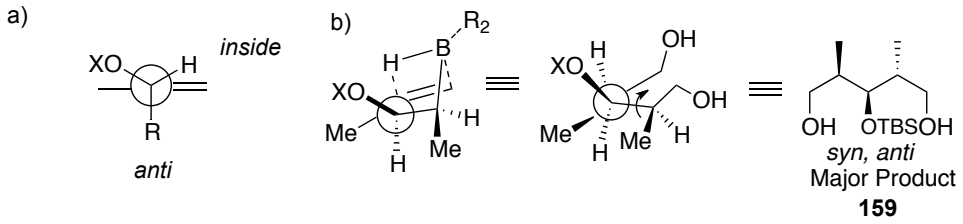
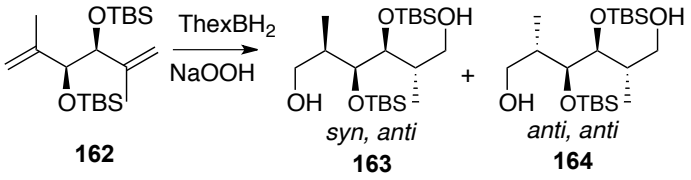


Figure 2.10. a) Stereoelectronic preferential orientation of hydroboration of olefin. b)

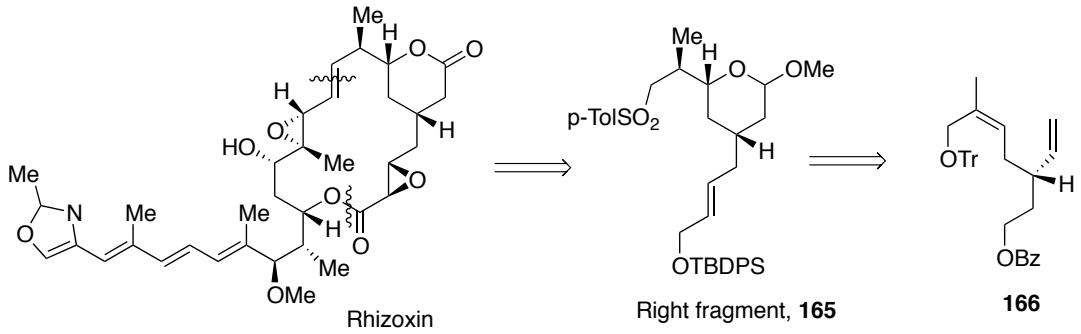
Oku showed the utility of cyclic hydroboration by synthesizing stereotetrads in a concise manner (Scheme 2.29). Like the stereotriad variant, the *syn, anti*-product was obtained in a stereoselective fashion in moderate yields (24:1, 62%). This was the first reported application of synthesizing stereotetrads via cyclic hydroboration. Previous work employing cyclic hydroboration had only synthesized three contiguous or remote stereocenters.



Scheme 2.29. Synthesis of stereotetrads via cyclic hydroboration

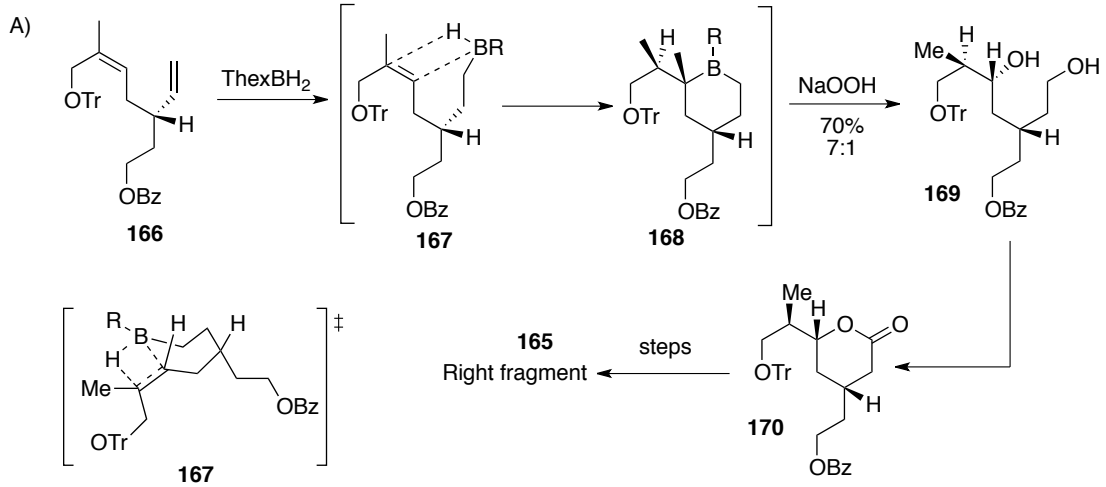
2.2.6.17 Kobayashi's synthesis of fragment for total synthesis of rhizoxin

More recently, Kobayashi employed cyclic hydroboration as a key step in the synthesis of the right half of the natural product, rhizoxin (Scheme 2.30).[75]



Scheme 2.30. Retrosynthesis of Rhizoxin

Cyclic hydroboration of **166** gave diol **169** in good yield and diastereoselectivity (70%, 7:1 respectively). Intramolecular hydroboration (**167 ->168**) of the internal trisubstituted olefin from the *si*-face furnishes two new remote stereocenters with moderate stereocontrol (Scheme 2.31).



Scheme 2.31. Synthesis of right fragment via cyclic hydroboration

The proposed transition state (Figure 2.31b, **167**) shows the boracycle adopting a boat conformation with the large alkyl benzoyl substituent orientated in an equatorial position. This conformation allows for favorable boron-hydrogen and olefin π-bond eclipsing interactions leading to the known four centered transition state.

2.3 Concluding remarks

For practical, environmental and economic reasons it is desirable to reduce numbers of chemical operations to a minimum. Despite many well-established reactions of acylic stereocontrol used for the synthesis of polypropionates, several aspects of these processes, however, can detract from their utility and efficiency. These include multiple protections and deprotections, cleavage of auxiliary groups and the use of expensive or toxic metals. There exists a need to develop new methodologies for more direct and sequential approaches for the synthesis of polypropionates.

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CHAPTER 3

New Methodologies for the Synthesis of Polypropionate via Cyclic Hydroboration of Complex Dienes

3.1 Initial considerations

Hydroboration of olefins has been used in the synthesis of countless polyketide natural products for its predictable regio- and stereoselectivity.[1,2] However, there is a limited number of examples employing cyclic hydroboration in the literature. In general, cyclic hydroboration has been employed as a method to effectively generate remote centers of asymmetry, while the synthesis of compounds containing contiguous stereocenters has received little attention. The laboratories of Oku and Yokoyama have shown the utility of cyclic hydroboration to generate novel compounds with contiguous stereocenters, although these compounds were relatively simple (<3 stereocenters) and/or symmetrical. We realized the potential of cyclic hydroboration to generate larger chain polypropionates (>4 stereocenters) with remote asymmetric induction.

Initially, we were unsure if this type of chemistry would still be effective when applied to more complex systems. In searching for a suitable model system to test the validity of cyclic hydroboration on more complex systems, we turned to two compounds that have been previously synthesized in our group (Figure 3.1). Both *syn*- and *anti*-models (**74** and **171** respectively) have been employed in the Parker laboratories for the synthesis of polyketides and are easily synthesized from commercially available cyclohexane carboxyaldehyde. Cyclic hydroboration of these model compounds would afford stereotetrad polypropionate fragments, which have not previously been reported. Furthermore, we felt these models would give us insight into the cyclic hydroboration of more complex substrates.

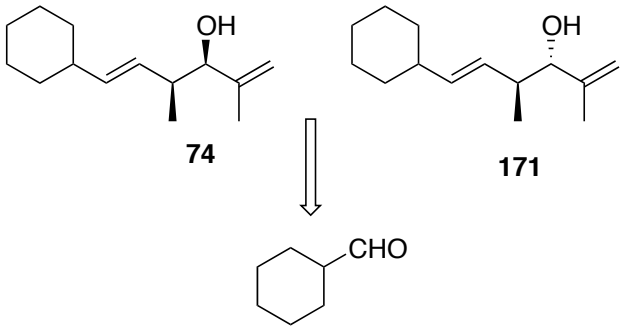
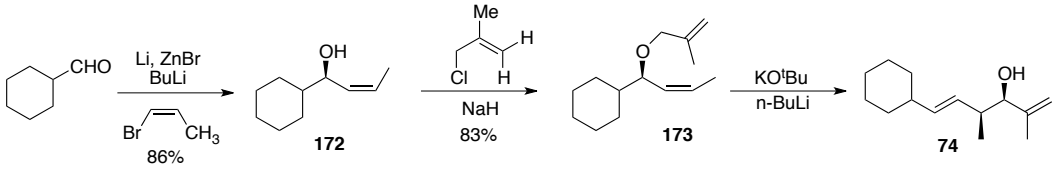


Figure 3.1. Retrosynthetic analysis for cyclic hydroboration study on *syn* and *anti*-model systems

3.2 Synthesis of Models

3.2.1 Synthesis of *syn*-model, 74

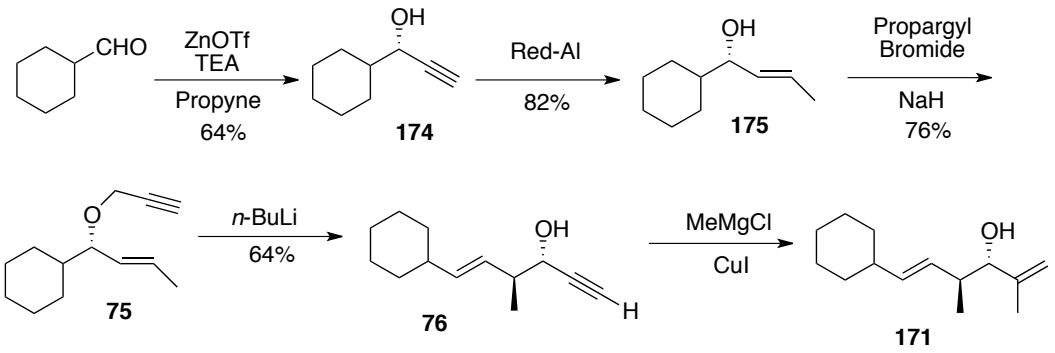
Following the previously reported synthesis of **74** in the Parker laboratories[3] (Scheme 3.1), commercially available cyclochexane carboxyaldehyde was treated with Z-propenylzinc bromide complex to afford racemic allylic alcohol **172**. Alkylation of **172** with 3-chloro-2-methylpropene afforded double allylic ether **173**, which, when treated with Schlosser's base, underwent a [2,3]-Wittig rearrangement to afford **74**.



Scheme 3.1. Synthesis of syn-model system

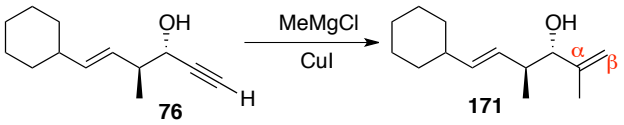
3.2.2 Synthesis of *anti*-model 171

The *anti*-model **171** was also synthesized following previously reported work in the Parker laboratories (Scheme 3.2).[4] In this case, cyclohexane carboxyaldehyde was treated with a mixture of zinc triflate, TEA and propyne to afford racemic propargyl alcohol **174**. Alkyne **174** was reduced with Red-Al to afford *trans*-allylic alcohol **175**. Alkylation of **175** with propargyl bromide furnished ether **75**, which when treated with base, underwent [2,3]-Wittig rearrangement to afford propargyl alcohol **76**.



Scheme 3.2. Synthesis of anti-model system

Carbometallation of **76** gave extremely low yields of the desired α-product (Table 3.1, Entry 1; Scheme 3.3). The same conditions were employed again with more attention paid to regulating the temperature of the reaction leading to a modest increase in yield (Entry 2). While purification of CuI[5] increased the yields further (Entry 3), the best yield was observed when purified CuI was used in conjunction with monitoring the internal temperature of the reaction (Entry 4). In my hands, this was the best that could be achieved. Although the yields were roughly half of that reported in our group, this result provided enough material to conduct the model cyclic hydroboration study.



Scheme 3.3. Carbometallation of **76**

Entry	CuI	α-product (%)	β-product (%)	Rec'd starting material (%)
1	Commercial	11%	2%	12%
2	Commercial	23.5%	7%	11%
3	Repurified	27%	8%	16%
4[a]	**Repurified**	**41%**	**16%**	**2.5%**

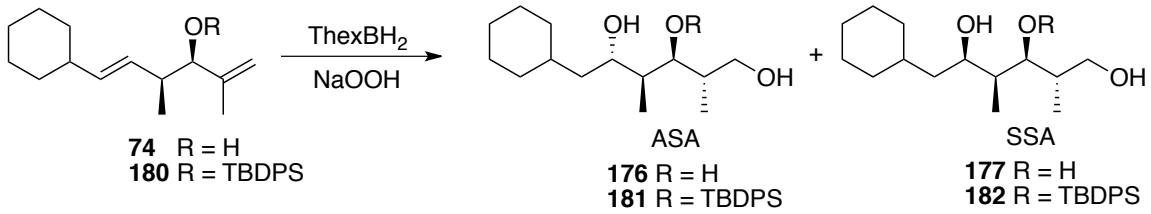
a. Internal reaction temperature was monitored

Table 3.1. Conditions for carbometallation of **76**.

3.3 Cyclic hydroboration on model systems

3.3.1 Cyclic hydroboration on *syn*-model, 74

With *syn*-model in hand, treatment of **74** with thexylborane at -78°C and oxidative workup afforded two major diastereomers, **176** and **177,** that were separable by column chromatography (Scheme 3.3). The results are summarized in Table 3.2.



Scheme 3.4. Cyclic hydroboration of 74

Cyclic hydroboration on **74** (Entries 1-3) showed almost no diastereoselectivity and proceeded in poor yields. We observed a slight preference for the *anti-syn-anti* isomer **176** in all three cases. In all three experiments, an inseparable mixture of two compounds was also isolated.

Entry	-OR	Equivalents	Yield (%)[a]	ASA:SSA
1	H	2.0	28	2.1:1[b]
2	H	2.0	20	1.8:1[b]
3	H	1.3	29	1.5:1[b]
4	TBDPS	2.4	31	>20:1[c]
5	TBDPS	2.0	30	>20:1[c]

[a.] Isolated diastereomers. [b]A mixture of two compounds (**178** & **179**) also isolated are believed to be the minor products generated from the first hydroboration [c]The SSA diastereomer **182** was not seen in ^{1}H-NMR and was not isolated through column chromatography.

Table 3.2. Cyclic hydroboration of *syn*-model **74**.

These are believed to be the other minor diastereomers of the initial hydroboration (Figure 3.2). When combined with the major products, the total yield averaged 50% for all three experiments. Varying the amount of thexylborane used, as well as the concentration of substrate appeared to have no discernable effect on the efficiency of intramolecular hydroboration.

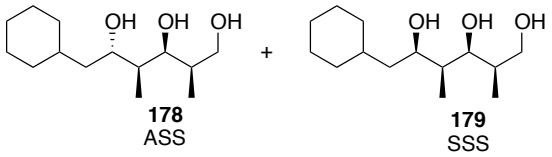
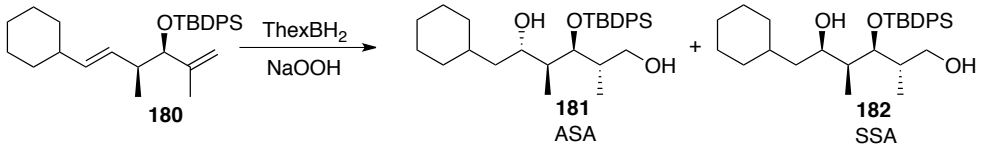


Figure 3.2 Minor hydroboration products

Since no diastereoselectivity was observed in the hydroboration experiments on **47** via stereoelectronic factors, we hypothesized that we may be able to achieve diastereoselection through steric interactions (e.g. Protection of the alcohol with a bulky electron withdrawing group). This was indeed the case when cyclic hydroboration of **180**, afforded excellent stereoselectivity (Entries 4 and 5). In both TBDPS experiments, only the *anti-syn-anti* isomer **181** was isolated.



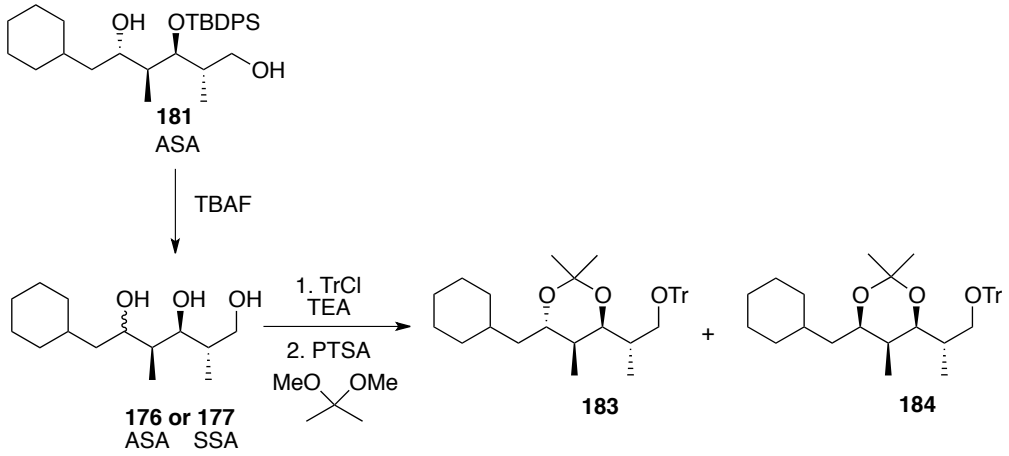
Scheme 3.5. Steric cyclic hydroboration study

However, the yields could not be improved upon from the cyclic hydroboration of the unprotected model systems.

Due to the structural complexity of **74**, we thought that the sterically demanding thexylborane could be the reason for our poor diastereoselectivity and low yields. To test this hypothesis, cyclic hydroboration of **74** and **180** with the less hindered borane-tetrahydrofuran complex were completed. In both cases, no cyclic hydroboration products were observed with complete decomposition of starting material.

3.3.2 Derivatization of *syn*-model 47 and 180 products

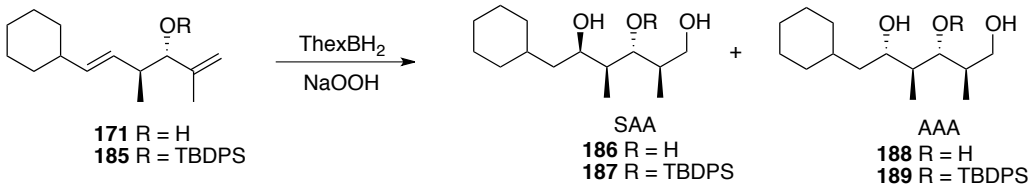
The relative stereochemistry of the diastereomers was determined by tritylation of the primary alcohol **176** and subsequent acetonide formation of the 1,3-diol **183** and **184** (Scheme 3.6). The silyl-protected products were treated with TBAF to afford triol **176**, which were then derivatized as previously described. The acetonide geminal methyls were analyzed via ^{13}C NMR spectroscopy to assign the relative stereochemistry of the 1,3-diols.[6] In the *anti-syn-anti* isomer (**183**), the methyls are affixed in a pseudo-equatorial position because the newly formed 6-membered ring adopts a twist conformation to avoid unfavorable 1,3-diaxial interactions, while the *syn-syn-anti* isomer (**184**) adopts a well-defined chair conformation. The acetonide methyls show a distinct pattern in ^{13}C NMR spectroscopy where **183** has 2 peaks at 25 ppm, while **184** has an axial methyl peak at 19 ppm and an equatorial methyl peak at 30 ppm.



Scheme 3.6. Standard procedure for the derivatization of **176/177** diastereomers

3.3.3 Cyclic hydroboration of *anti*-model 171

A series of cyclic hydroboration reactions on the *anti*-models **171** and **185** were run with thexylborane (Scheme 3.7). The results are shown below in Table 3.3.



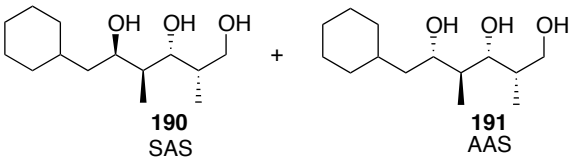
Scheme 3.7. Cyclic hydroboration of *anti*-model **171** and **185**

Entry	-OR	Equivalents	Yield (%)	AAA:SAA
1	OH	3	21	1:1[a,b]
2	OH	3	37	1:1[a,b]
3	OH	2	36	1.5:1[a,b]
4	TBDPS	1.7	31	1:2.1[c]

[a.] Inseparable [b.] Mixture of two accessible from initial intermolecular hydroboration. [c.] Only the SAA isomer **187** was isolated cleanly. The other products isolated were a complex mixture

Table 3.3. Results of cyclic hydroboration on *anti*-model systems

While the yields were slightly improved over the *syn*-model system, the intramolecular hydroboration of the **171** proceeded with no stereoinduction and afforded a 1:1 mixture of triols **186** and **188**. Similar to **47**, a small amount of an inseparable mixture of compounds was isolated (Table 3.3, Entries 1-3; Scheme 3.8). We believe these to be the diastereomers derived from the initial hydroboration. When combined with the major products, the yields increased to 55%. These results mirror the *syn*-model systems in that no stereoselectivity was observed.

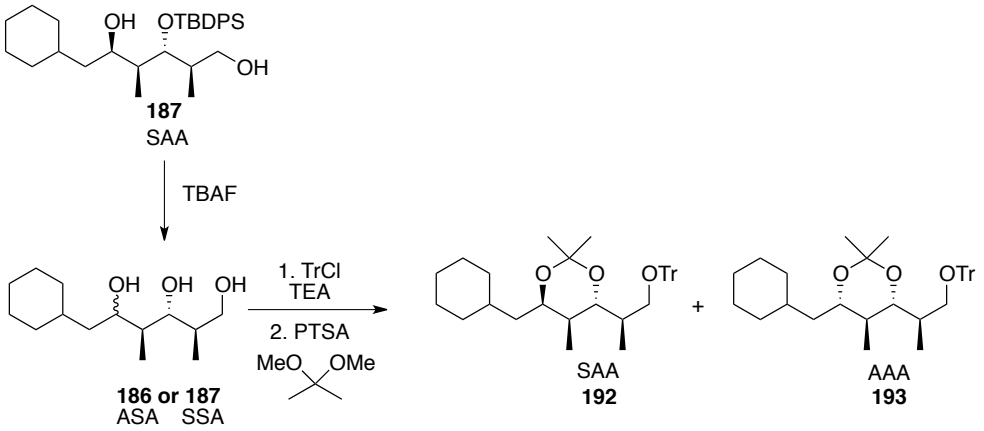


Scheme 3.8. Minor diastereomers from the initial hydroboration of **171**

Following the same thought process as the *syn*-model, we protected **171** with the sterically encumbered TBDPS group (**185**) to achieve an increase in stereoselection through steric factors (Table 3.3, Entry 4). Indeed, a marginal increase in diastereoselectivity for the *syn-anti-anti* product **187** was observed. Unfortunately, the yield was once again in the 30% range. When the products were isolated, only the major product could be cleanly isolated and characterized.

3.3.4. Derivatization of *anti*-model

Derivatization was done in the same fashion as the *syn*-model experiments (Scheme 3.9). Cyclic hydroboration product **187** was treated with TBAF to afford deprotected triol **186** or **187**. The primary alcohol was protected with trityl chloride and the resulting 1,3-diol was protected to form acetonide **192** or **193**. Analysis of the acetonide by ^{13}C NMR spectroscopy indicated the presence of two methyls at 25 ppm, representative of an *anti*-1,3-diol **193**. The relative stereochemistry of the major product in entry 4 was determined to be the *syn-anti-anti* isomer **192**.



Scheme 3.9. General procedure for the derivatization of the *anti*-model system

3.3.5 General observations from model study

Even though the results of the model study were relatively poor, they did provide some insights that could be applied for the synthesis of future substrates. In the case of free alcohol **74** and **171**, the common appearance of an inseparable mixture of diastereomers from the initial hydroboration suggests, at the very least, a moderately sized protecting group needs to be present to provide high *anti*-diastereoselectivities. This was realized when no diastereomeric mixtures were isolated in the protected alcohol examples (**180** and **185**).

In an overly simplified system, intramolecular hydroboration is driven primarily by two factors. The first factor is the size of the boracycle ring that is formed. A 5-membered ring will preferentially form over a 6-membered ring. When 6- and 7-

membered cycles are involved, there is no dominating preference between the two rings.[7] The second factor is the usual directive effects of boron itself, where boron will coordinate to the least substituted carbon of the carbon-carbon double bond. In more complicated systems, steric forces are introduced that can either positively or negatively affect the yields and/or stereochemical outcomes.

In all free alcohol cases (**74** and **171**), many minor, undesired side products were observed. Individually they did not amount to much in terms of yield, but collectively they accounted for a large portion of the poor yields observed. A part of this is from the substitution pattern of the internal olefin. The trans-olefin has an sp^3-hybridized carbon adjacent to each side of the carbon-carbon double bond. There is nothing differentiating either carbon of the double bond, allowing hydroboration to occur at either side without preference. This is an important factor in the efficiency of the intramolecular hydroboration, especially when dealing with intermediates with 6- and 7-membered boracycle rings, like those in our model. After the initial hydroboration, there was no dominant force directing the boron to react in a regiospecific manner. When the sterically bulky and σ-accepting silyl-protecting group was introduced, we saw a rather dramatic increase in diastereoselectivity. Through steric and stereoelectronic interactions derived from the silyl-protecting group, the diastereoselectivity was improved substantially. From these insights, we can design a substrate that would be better suited for the generation of polypropionate fragments with four or more contiguous stereocenters.

3.4 Designing a suitable substrate

3.4.1 Initial considerations

Drawing from our model study results, as well as literature precedent, we set out to develop more suitable substrates for synthesis of stereopentads via cyclic hydroboration. The basic model structure is broken into two segments shown in Figure 3.4. The left half (**A**) will remain as is because the stereochemistry of the initial intermolecular hydroboration will always be anti to the allylic alcohol. This provides three of the five stereocenters. However, the right half (**B**) would need to be modified to

differentiate the internal olefin carbons. By making the internal olefin trisubstituted, we should be able to induce the boron to target the less hindered carbon. Olefin isomers would allow for an increase in the number of stereopentad polypropionate fragments available for synthesis. The cyclohexane moiety would be replaced with a more easily modifiable (i.e. ester, allylic alcohol) functional group completing the design of our new substrate.

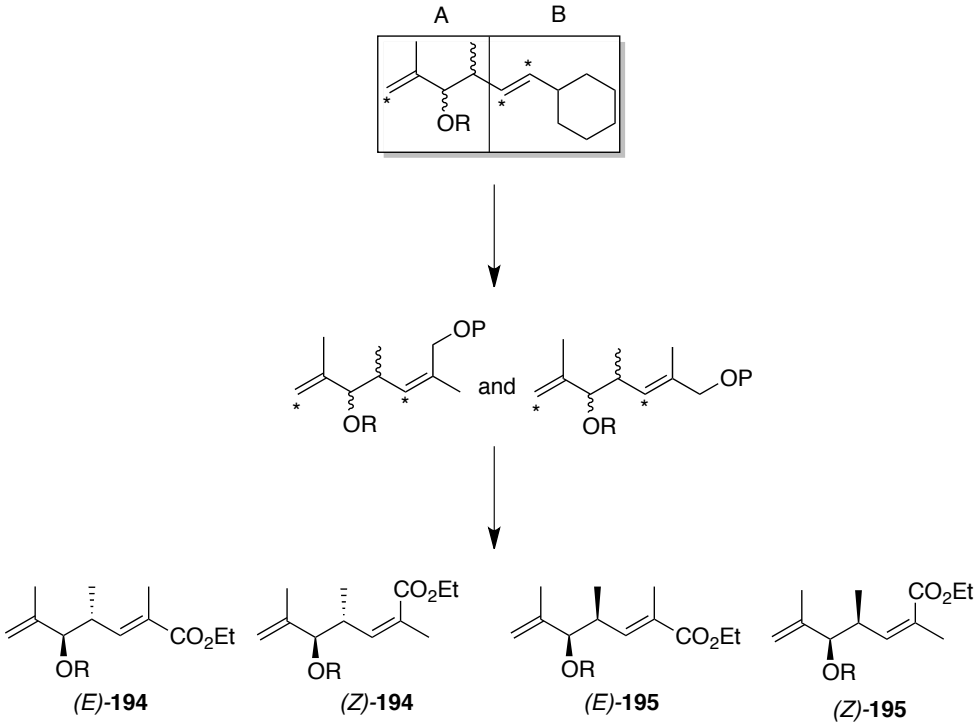
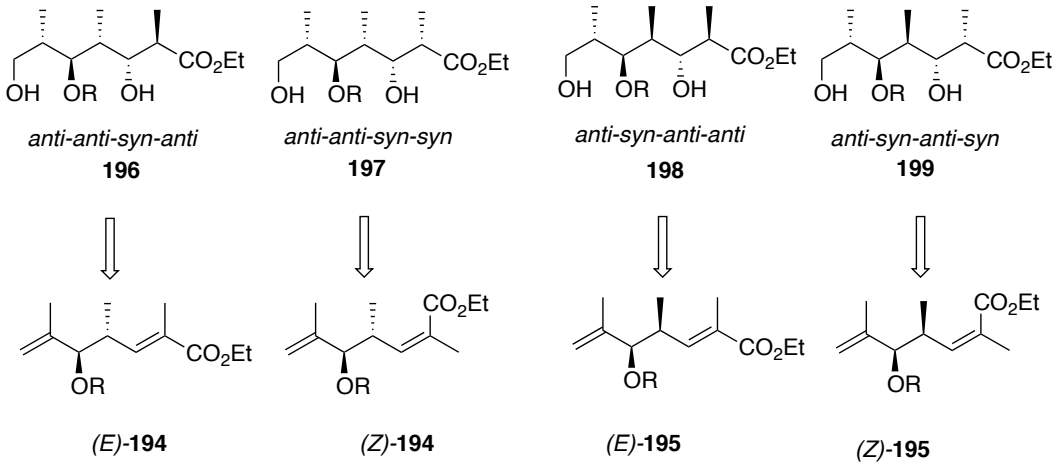


Figure 3.4. Designing new substrates

3.4.2 Potentially accessible stereopentads and their application for the synthesis of relevant natural products

The potentially accessible stereopentads are outlined below in scheme 3.10. In order to demonstrate the potential utility of this methodology, we set out to find polyketides that contained these stereopentad combinations.



Scheme 3.10. Accessible stereopentads from substrates

As shown in Figure 3.5, the stereopentads (**196**, **197**, **198**, **199**) available from our four substrates allow us to access a broad range of natural products with interesting structures and biological properties, including the well-known Rifamycin A. In the case of **199**, the *anti-syn-anti-syn* stereopentad is prevalent in a broad range of polyketides.

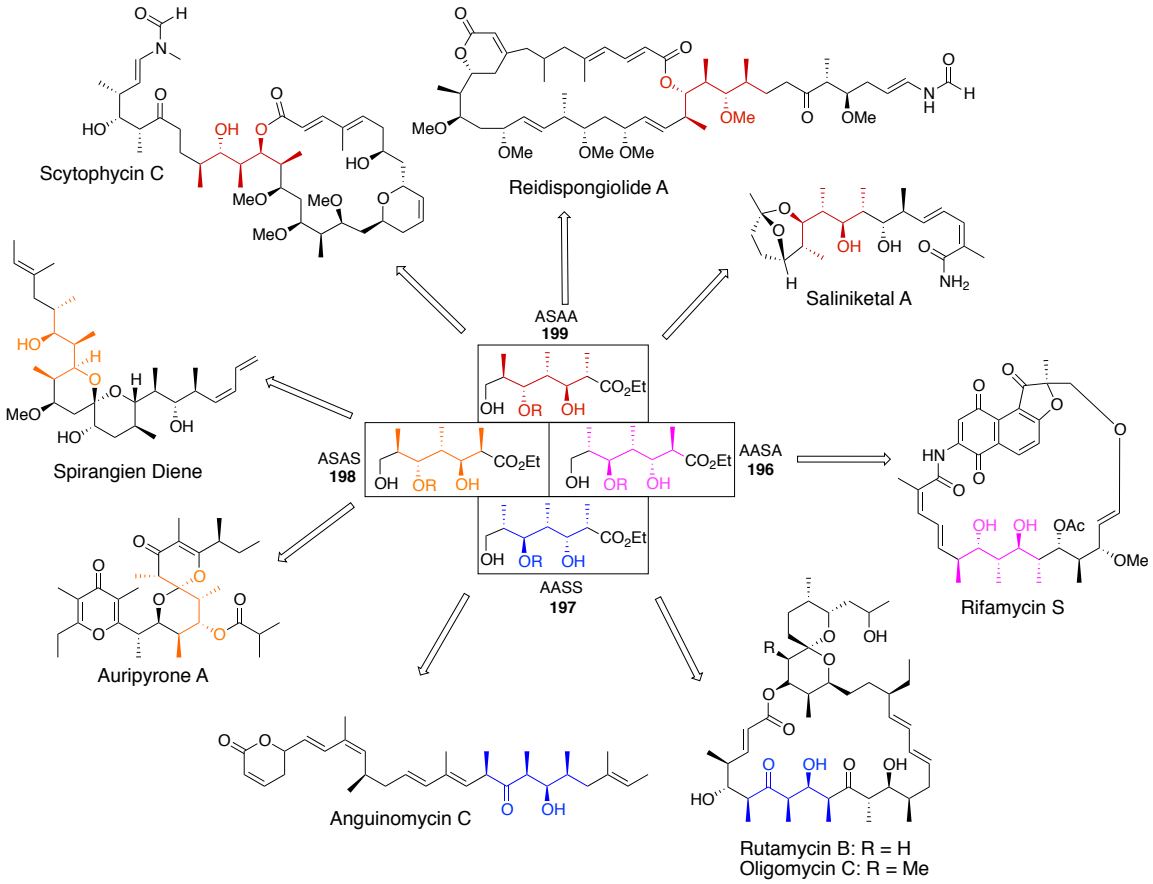
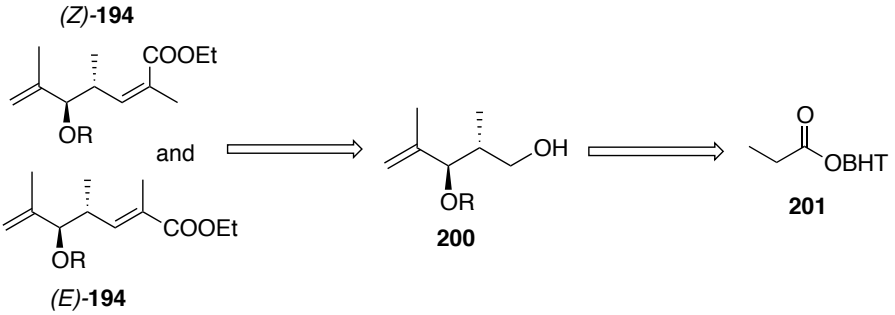


Figure 3.5. Natural products accessible from substrates **196**, **197**, **198**, **199**

3.5 Retrosynthetic analysis of anti-substrate (*E*)-194 and (*Z*)-194

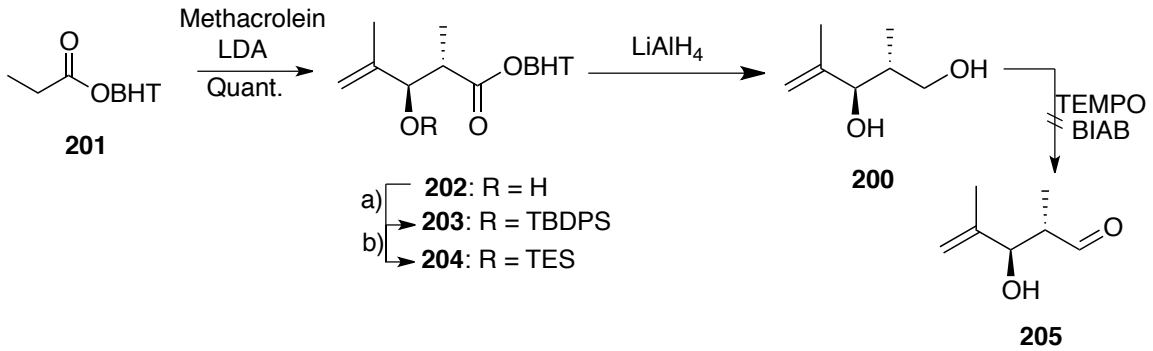
As outlined in scheme 3.11, our strategy to synthesize the (*E*)-**194** and (*Z*)-**194** regioisomers relies on a highly convergent synthesis. Both regioisomers would be accessed in the latter stages of the synthesis from a late stage common precursor. Our desired substrates would be synthesized from diol **200**, which would be readily synthesized from BHT-ester **201** under standard aldol conditions.



Scheme 3.11. Retrosynthetic analysis of anti-substrate

3.5.1 Synthesis of (*E*)-194 and (*Z*)-194

Starting from known BHT-ester **201**,[8] aldol condensation with methacrolein and LDA afforded allylic alcohol **202** in quantitative yields (Scheme 3.12). Analysis via ^{13}C NMR spectroscopy showed the presence of only one diastereomer. Reduction of aldol product **202** with lithium aluminum hydride afforded diol **200** in 60% yield. Unfortunately, attempts to protect alcohol **202** prior to the reduction of BHT-ester resulted in either total decomposition or the isolation of the unprotected diol **200** (Scheme 3.12).



Conditions: a) TBDPS-Cl, DBU, $AgNO_3$, 50%; b) TESOTf, TEA, DCM, 97%

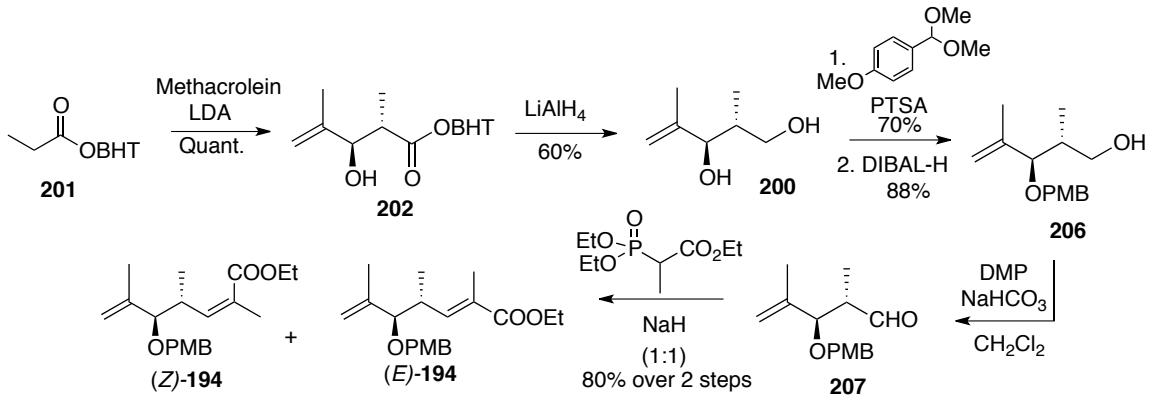
Entry	Compound (PG)	Product	Yield
1	**202**(None)	**200**	60%
2	**203** (TBDPS)	Decomposition	-
3	**204** (TES)	**200**	48%

Scheme 3.12. Initial attempts to reduce BHT-ester in the presence of a protected alcohol

With diol **200** in hand, we attempted to selectively oxidize the primary alcohol with the radical oxidizer TEMPO. Unfortunately, only a complex mixture of side products was

isolated, with no trace of starting material **200** or oxidized product **205**. As a result, we were forced to find an alternate route to synthesize our targets.

In reaching our target substrates (*E*)-**194** and (*Z*)-**194**, we wanted to avoid a costly (in steps) linear protection/deprotection synthesis to isolate aldehyde **205** in a concise manner. To that end, we felt that a diol protection and subsequent selective deprotection strategy could be used to circumvent our problem (Scheme 3.13). This was indeed the case, where benzylidine acetal formation with *p*-anisaldehyde dimethyl acetal and protecting group migration with DIBAL-H afforded PMB-ether **206** cleanly. Oxidation of the primary alcohol with Dess-Martin periodinane and subsequent Horner-Wadsworth-Emmons olefination afforded a 1:1 mixture of separable (*Z*)-**194** and (*E*)-**194** isomers in high yield over 2 steps.

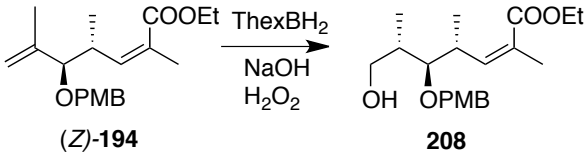


Scheme 3.13. Synthesis of (*E*)-**194** and (*Z*)-**194**

3.6 Cyclic hydroboration on *anti*-isomers (*Z*)-194 and (*E*)-194

3.6.1 Initial cyclic hydroboration of enone (*Z*)-194

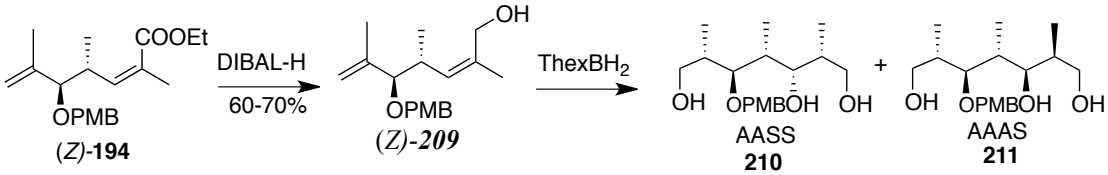
With both (*Z*)-**194** and (*E*)-**194** isolated, this set the stage for our first attempt at cyclic hydroboration on these newly designed substrates. When *cis*-enone (*Z*)-**194** was treated with freshly prepared thexylborane, no cyclic hydroboration occurred and monohydroborated product was isolated exclusively (Scheme 3.14). We suspect that the conjugated olefin is extremely unreactive to hydroboration so only the initial intermolecular hydroboration takes place.



Scheme 3.14. First attempt of cyclic hydroboration on enone (*Z*)-**194**

As a result, enones (*Z*)-**194** and (*E*)-**194** were subsequently reduced with DIBAL-H to afford allylic alcohol (*Z*)-**209** and (*E*)-**209** in good yields. Cyclic hydroboration of the newly created allylic alcohols afforded cyclic hydroborated products. The results are summarized below in Scheme 3.15.

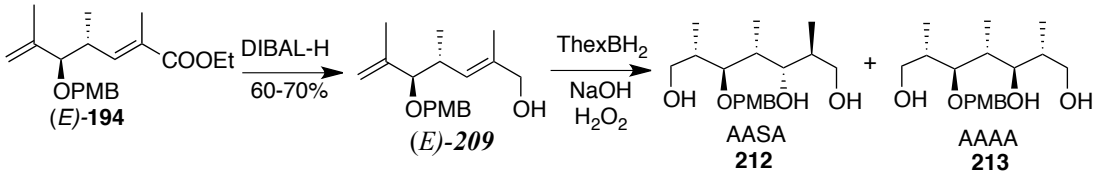
A)



Entry	Substrate	Major Product	**210**:**211**[b]	Yield[c]
1[a]	(*Z*)-**209**	AASS (**210**)	7:1	70%
2	(*Z*)-**209**	AASS (**210**)	13:1	89%

a) Thexylborane was one week old b) Determined by ^{1}H NMR c) isolated yields

B)



Entry	Substrate	Major Product	**212**:**213**	Yield[b]
1	(*E*)-**209**	AASA (**212**)	5:1	30%[c]

a) Determined by ^{1}H NMR b) isolated yields c) a large amount of nonpolar side products were also isolated, including anisaldehyde

Scheme 3.15. Reduction of A) (*Z*)-**194** and B) (*E*)-**194** and subsequent cyclic hydroboration.

Our first attempt to cyclic hydroborate (*Z*)-**209** yielded a 7:1 mixture of **210** and **211** respectively (Entry 1, Scheme 3.15A). We were pleased to see that the yields had also increased substantially relative to our model systems. When the same reaction was run again, excellent diastereoselectivity and yield were observed (Entry 2). While the

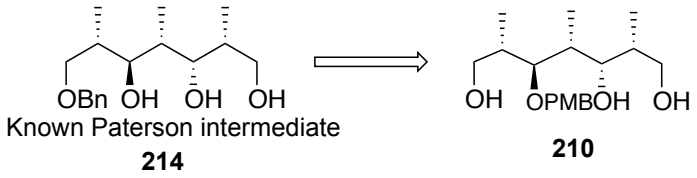
dramatic increases in selectivity and yields from Entry 1 to Entry 2 was a pleasant surprise, we were perplexed at what would cause such a dramatic change in the same reaction. Upon closer inspection, we found that the only difference between the two reactions was the age of the thexylborane. In entry one, the thexylborane was a week old while the thexylborane in entry 2 was prepared and used the same day. Since thexylborane is not commercially available, it needs to be prepared fresh from borane-tetrahydrofuran complex and 2,3-dimethyl-2-butene. Still reports that thexylborane should be used within a week or yields and diastereoselectivity decrease substantially.[9] As a result, all subsequent cyclic hydroborations were run with freshly prepared thexylborane.

With the cyclic hydroboration of (*Z*)-**209** completed, our attention turned to (*E*)-**209**. When (*E*)-**209** was reacted with thexylborane, stereopentad **212** was the major product but with a decrease in yield and diastereoselectivity (Entry 1, Scheme 3.15B). A small amount of anisaldehyde and various non-polar side products were also isolated upon purification. The presence of anisaldehyde suggests an oxidative cleavage of the PMB-ether is occurring during workup. We suspect that a combination of oxidative conditions to work up hydroboration reactions, along with the inherent Lewis acidity of boron is the culprit for this disproportion-like reaction. Under these conditions, it is possible for the boron to abstract a hydride at the benzyl position of the ether, which leaves a stable benzyl cation. The presence of hydroxide leads to the formation of a hemiacetal, which is oxidatively cleaved to the resultant anisaldehyde. Interestingly, this deleterious side reaction only occurs on (*E*)-**209**.

3.6.2 Derivatization and elucidation of relative stereochemistry: Attempts to obtain crystal for X-ray crystal analysis

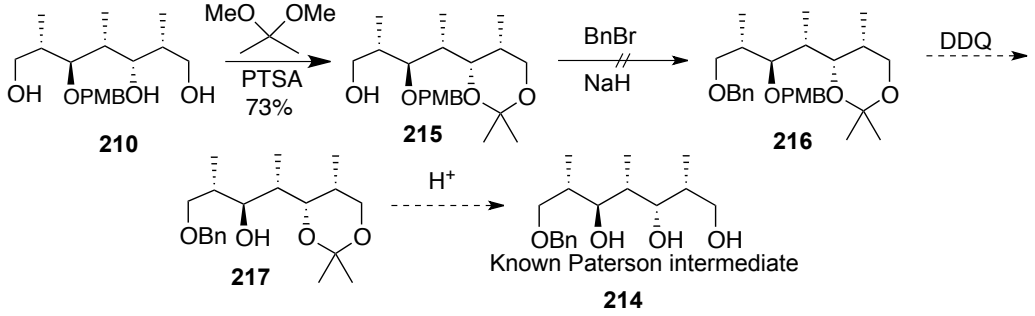
In order to confirm the relative stereochemistry of our newly synthesized stereopentads, we searched the literature for compounds with the same *anti-anti-syn-syn* stereochemistry as our product **210**. Paterson et al. had made a series of 16 stereochemical possible stereopentad permutations with either a TBDPS or benzyl-

protecting group on one of the two primary alcohols. The stereopentad corresponding to our product **210** is shown below in scheme 3.16.



Scheme 3.16. Retrosynthesis of PMB-ether **210** to Paterson intermediate

In order to modify **210** to Paterson's reported stereopentad **214**, we needed to subject **210** to a series of protections and deprotections shown below in Scheme 3.17. Initially, stereopentad **210** was treated with 2,2-Dimethoxypropane to form acetonide **215**. Subsequent attempts to protect the primary alcohol in **215** with benzyl bromide proved unsuccessful.

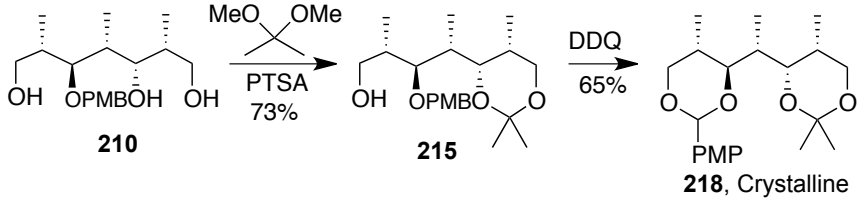


Scheme 3.17. Confirmation of stereochemistry of **210** via derivatization to known Paterson stereopentad

With the problematic protection of **215** to **216** and the overall number of steps to reach the Paterson intermediate, we reevaluated our approach to derivatizing triol **210** in a more concise manner. As a result, we sought out to derivatize **210** into a crystalline solid, with hopes that a crystal could be isolated and a crystal structure determined via single crystal X-ray spectroscopy.

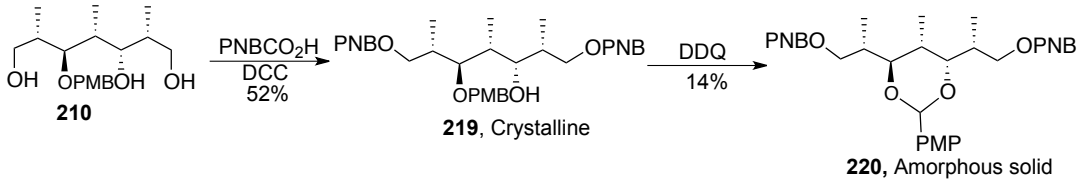
Our first attempt for a crystalline derivative involved acetal formation of the free 1,3-diol to form acetonide **215** (Scheme 3.18). Subsequent benzylidine acetal formation

with DDQ afforded crystalline **218**. Unfortunately, upon visualization under a microscope, the crystalline solid that had formed was fibrous in nature. Recrystallization with hot hexanes produced a more uniform crystalline solid that could be mounted and examined in the X-ray diffractometer. Unfortunately, the quality of the crystal was not sufficient to defract well and the structure could not be deduced.



Scheme 3.18. First attempt to obtain a crystalline derivative

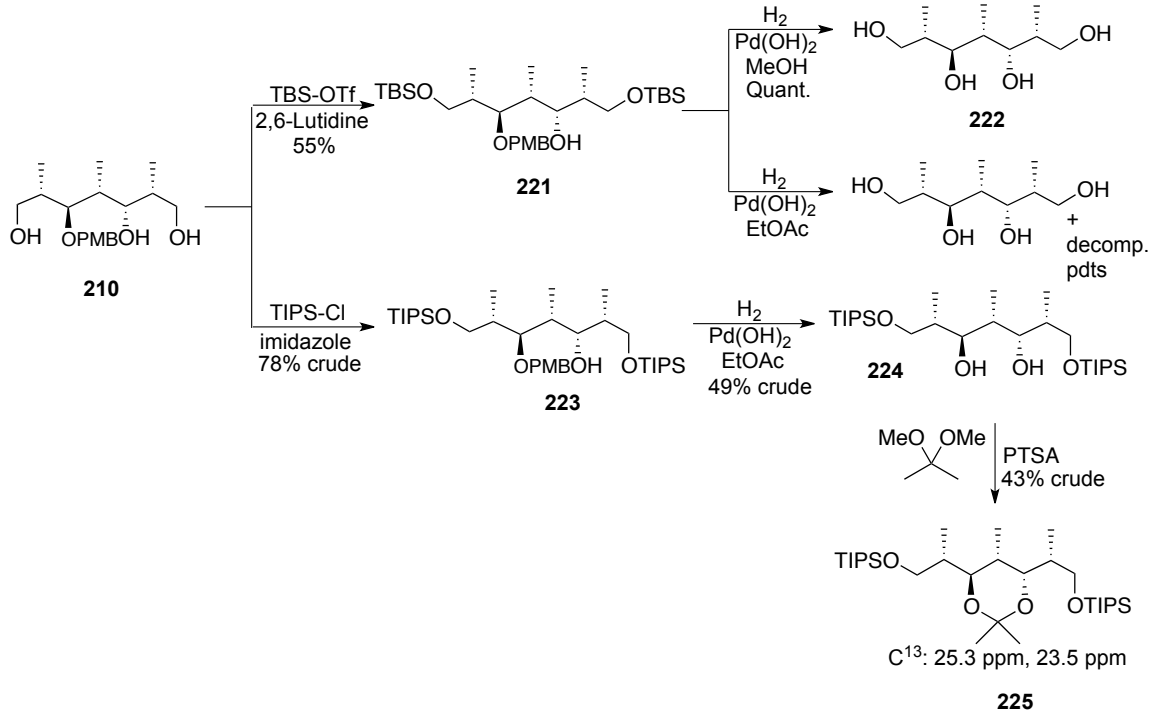
Our second attempt to synthesize a crystalline derivative involved selective esterification of the primary alcohols to afford di-*p*-nitrobenzoyl ester **219** (Scheme 3.19). Unfortunately, PNB-ester **219** appeared to be an amorphous solid. Treatment of **219** with DDQ furnished benzylidine acetal (**220**) in low yields, along with some recovered starting material. As was the case for **219**, benzylidine **220** was also an amorphous solid. At this time, the recovered PMB-ether (**219->200**) in 20% ethyl acetate:hexanes was set aside and left to slowly evaporate. Fortunately, after several days, the solvent mixture had evaporated and a crystalline solid had developed. The crystalline material was carefully extracted and examined under a microscope to reveal several well-defined crystals. A crystal was prepared for X-ray crystallography. However, the experiment has not been run at this time.



Scheme 3.19. Second attempt to obtain a crystalline derivative

3.6.3 Elucidation through chemical means

In order to confirm the relative stereochemistry of **210**, we set out to chemically derive PMB-ether **210**, which is shown below in Scheme 3.20. Our first attempt involved the selective protection of **210** with TBS-OTf to afford silyl-ether **221**. Unfortunately, treatment of **221** under standard hydrogenation conditions in methanol, globally deprotected tetrol **222** was isolated. A quick search in the literature revealed that TBS-ethers are labile under hydrogenation conditions when methanol is used but quite stable in other solvents. As a result, we employed the same hydrogenation conditions but with dry ethyl acetate instead. Regrettably, the deprotected tetrol was isolated again. We suspect that the inherent water content of $Pd(OH)_2$ (60% H_2O) is the source of this deleterious result.



Scheme 3.20. Derivatization of stereopentad **210**.

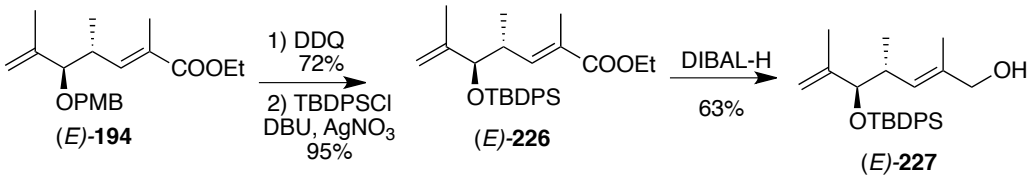
3.6.4 Reevaluation of derivatization and subsequent relative conformation analysis

After the derivatization attempts with the TBS protecting group, we focused our attention on a more robust silyl group that could withstand the hydrogenation conditions needed to remove the PMB-ether. Selective protection of **210** with TIPS-Cl afforded an inseparable mixture of the desired TIPS-ether **223** and TIPS-OH. The crude mixture was

stirred under hydrogenation conditions to afford diol **224**, which was subsequently treated with 2,2-Dimethoxypropane to afford acetonide **225** in 43% yield. The relative *anti*-configuration of the hydroxy groups at C3 and C5 was confirmed by the analysis of the ^{13}C NMR spectrum (δ 23.5, 25.3 ppm for Me_2C). This outcome confirmed the stereochemistry of the C5 position was a result of high 1,4-asymmetric induction. Furthermore, the confirmation of the relative stereochemistry of **225** provided us with insight into how the other substrates will behave with respect to the newly created stereocenter at C5, thus eliminating the need to derivitize every major product of a cyclic hydroboration reaction.

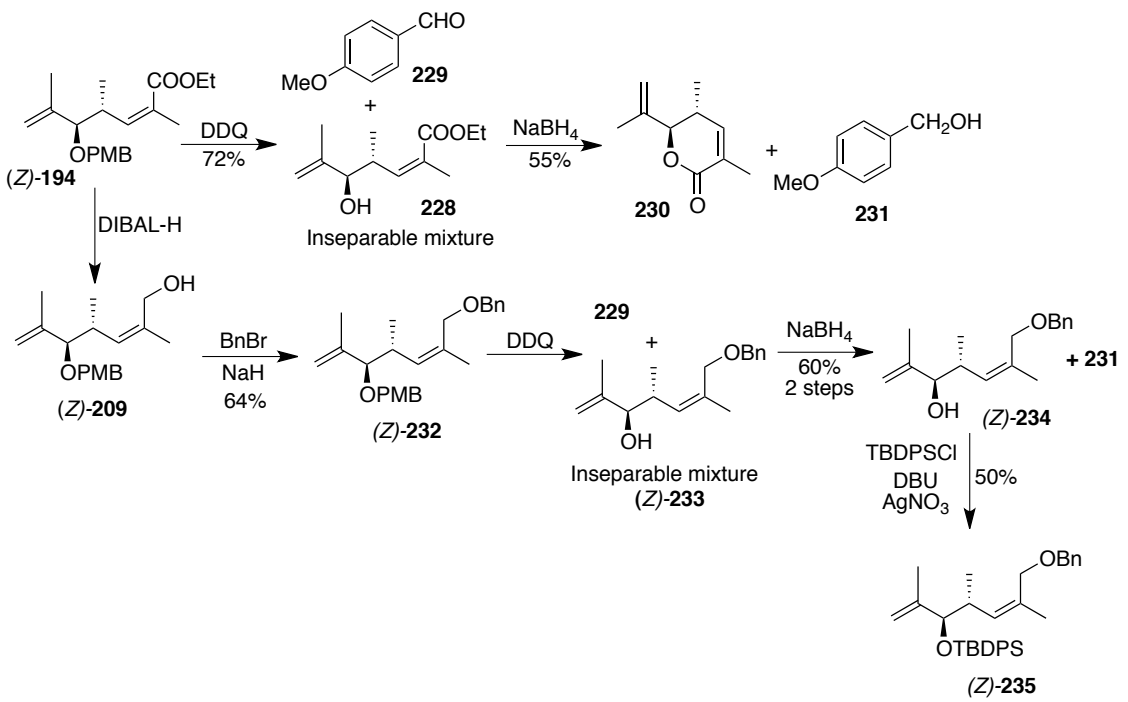
3.7 Steric interaction study on (*Z*)-209 and (*E*)-209

We were interested to see if steric interactions would increase the selectivity of the intramolecular hydroboration, similar to what was observed in our previous model studies. For consistency, we chose the TBDPS protecting group, for its steric and electronic properties. As shown in Scheme 3.21, silyl-ether (*E*)-**227** was synthesized in three steps from enone (*E*)-**194**. Oxidative cleavage of the PMB-ether with DDQ and subsequent protection with TBDPS-Cl afforded silyl-ether (*E*)-**226** in good yields. Reduction of the enone with DIBAL-H furnished the target diene (*E*)-**227** in 63% yield.



Scheme 3.21. TBDPS protection of (*E*)-**194**

Employing the same protocol with (*Z*)-**194**, treatment with DDQ lead to an inseparable mixture of allylic alcohol **228** and anisaldehyde **229** (Scheme 3.22). Attempts to separate the mixture with a sodium bisulfite wash lead to a complex mixture of products. However, when the mixture was treated with sodium borohydride, the resulting mixture was easily separated via column chromatography. Unfortunately, we did not isolate any of our desired enone **228**.

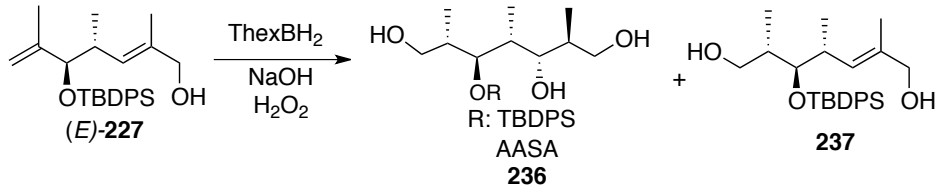


Scheme 3.22. Synthesis of silyl-ether (*Z*)-**235**

Instead, we isolated lactone (**230**) and the reduced benzyl alcohol as the exclusive products. To circumvent this problem, enone (*Z*)-**194** was reduced with DIBAL-H to afford allylic alcohol (*Z*)-**209**. Treatment of alcohol (*Z*)-**209** with benzyl bromide afforded benzyl ether in 64% yield. Subsequent oxidative cleavage of the PMB-ether afforded an inseparable mixture of alcohol (*Z*)-**233** and anisaldehyde **229**. The mixture was subjected to reductive conditions using sodium borohydride to afford a separable mixture of desired alcohol (*Z*)-**234** and benzyl *p*-methoxybenzyl alcohol **231**. Allylic alcohol (*Z*)-**234** was treated with TBDPS-Cl to afford silyl-ether (*Z*)-**235** in 99% yield (adjusted for recovered starting material).

With both TBDPS protected substrates, (*E*)-**227** and (*Z*)-**235** in hand, we treated each with thexylborane at -78°C. The results are shown below in scheme **3.23**.

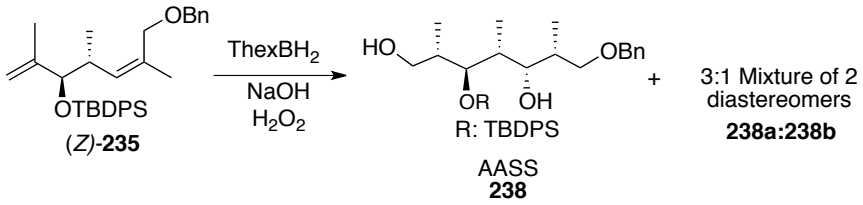
a)



Entry	Substrate	Desired product	**236**:**237**	Yield[a]
1	(*E*)-**227**	**236**	1:3	12%

a)17% yield of monohydroborated product **237** was isolated. b) reactions were not clean and produced a myriad of side products

b)



Entry	Substrate	Major product	**238**:**238a:238b**	Yield[a]
1	(*Z*)-**235**	AASS (**238**)	1.5:1:0.4	44%[b]
2	(*Z*)-**235**	AASS (**238**)	1.7:1:0.3	67%

a) Reactions were not clean and produced a myriad of side products b) Yield is adjusted after recovery of (*Z*)-**235**.

Scheme 3.23. Results of cyclic hydroboration of sterically hindered substrates a) (*E*)-**227** and b) (*Z*)-**235**

Cyclic hydroboration of (*E*)-**227** afforded a complex mixture of products with **236** being the only stereopentad isolated (Scheme 3.23a). However, the desired stereopentad was not the major product. Instead the major product isolated was the monohydroborated compound **237**. Regrettably, the yields and diastereoselectivity could not be improved upon from the PMB-protected congenor.

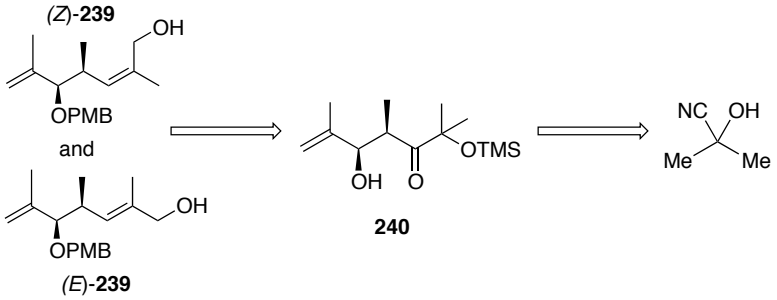
When (*Z*)-**235** was treated with thexylborane, the major stereopentad isolated was AASS stereopentad **238** (Scheme 2.38b). Unfortunately, a 3:1 mixture of two other stereopentads was also isolated. All together, almost no diastereoselectivity was observed with a 1.7:1:0.3 mixture of the three isolated stereopentads. The inseparable mixture will be derivatized to confirm the relative stereochemistry in due course. While

the steric bulk of the TBDPS-protecting group increased the selectivity of our model systems, it negatively affected our designed substrates substantially.

The silyl-protected substrates did not cyclize as smoothly as the PMB variants. In several of the hydroboration runs, starting material or monohydroborated products were recovered. This is the result from the steric encumberance of the TBDPS-protecting group being too large and prevents the second intramolecular hydroboration from occurring smoothly.

3.8 Retrosynthetic analysis for syn substrate

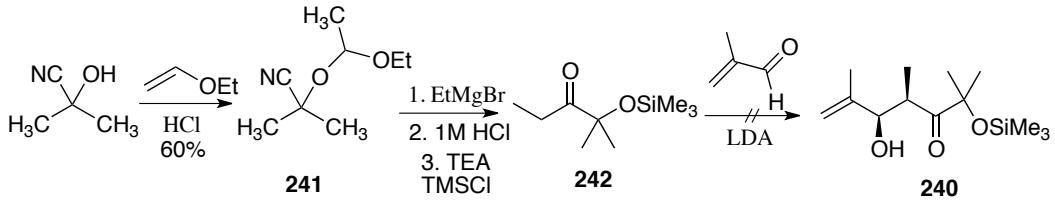
As outlined in scheme 3.24, our strategy was to synthesize (*Z*)-**239** and (*E*)-**239** in a highly convergent process. Following a similar synthesis to that of (*Z*)-**209** and (*Z*)-**209**, isomeric (*Z*)-**239** and (*E*)-**239** would be synthesized from the *syn*-aldol adduct **240**. Aldol product **240** would be accessed from inexpensive, commercially available acetone cyanohydrin.



Scheme 3.24. Retrosynthesis of syn substrate (*Z*)-**239** and (*E*)-**239**

3.8.1. Synthesis of aldol intermediate 240.

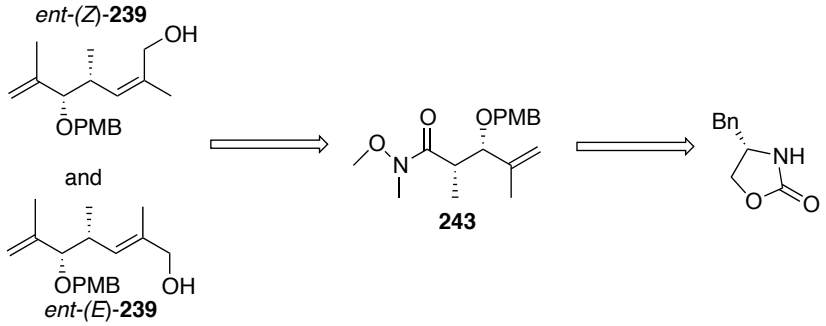
Following Heathcock's syn-aldol procedure,[8] acetone cyanohydrin was alklyated with ethyl vinyl ether to furnish protected cyanohydrin **241**. α-Siloxyketone **242** was synthesized cleanly in 3 steps from protected cyanohydrin (**241**->**242**). Aldol condensation of siloxyketone **242** with methacrolein afforded a complex mixture with poor diastereoselectivity. Disappointed with the observed diastereoselectivy, we considered alternative routes to synthesize (*Z*)-**239** and (*E*)-**239**.



Scheme 3.25. Synthesis of aldol adduct **240**

3.9.1 Revised retrosynthetic analysis for *syn*-substrates *ent*-(*Z*)-239 and *ent*-(*E*)-239

Our search eventually lead to a report by Evans et al., on the Total Synthesis of (+)-Calyculin A.[10] In this report, Evans synthesized unprotected Weinreb amide **243** via chiral auxillary Evan's aldol condensation. Weinreb amide **243** could easily be modified to generate chiral *ent*-(*Z*)-**239** and *ent*-(*E*)-**239**, as a result, we decided to revise our retrosynthetic strategy to take advantage of this new method. *Ent*-(*Z*)-**239** and *ent*-(*E*)-**239** could be isolated from Weinreb amide **243** in 3 steps (oxidation, olefination and reduction), while previously made amide **243** could be synthesized from a chiral aldol reaction employing commercially available (S)-(+)-4-Phenyl-2-oxazolidinone.

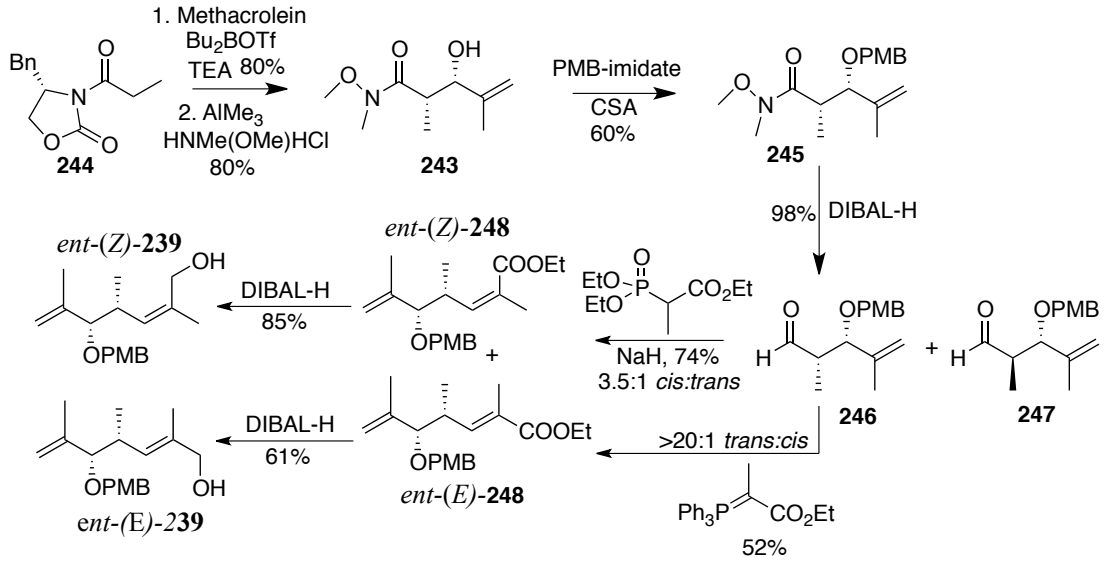


Scheme 3.26. Revised retrosynthetic scheme for *ent*-(*Z*)-**239** and *ent*-(*E*)-**239**

3.9.2 Synthesis of *syn* substrates *ent*-(*Z*)-239 and *ent*-(*E*)-239

In accord with our strategy outlined in Scheme 3.26, addition of methacrolein to the boron enolate, derived from carboximide **244**, afforded diastereomerically pure aldol adduct after purification via column chromatography. Subsequent transamination of the aldol adduct afforded Weinreb amide **245** and the cleaved auxiliary in good yields. Alcohol protection with PMB-imidate and CSA afforded PMB-ether **245**, which upon

treatment with DIBAL-H at -78°C afforded aldehyde **246** in good yields. A small amount (<10%) of C_2-epimerized aldehyde was also isolated **247**. Attempts to reduce the amount of epimerization product proved unsuccessful. Surprisingly, when aldehyde **246** was reacted with triethyl 2-phosphonopropionate and NaH, a 3.5:1 mixture of *ent*-(*Z*)-**248** and *ent*-(*E*)-**248** favoring the *cis*-isomer was isolated. In order to access more of *ent*-(*E*)-**248**, aldehyde **246** was treated with (carbethoxyethylidene) triphenylphosphorane to afford essentially *ent*-(*E*)-**248**. Reduction of enones *ent*-(*Z*)-**248** and *ent*-(*E*)-**248** furnished allylic alcohols *ent*-(*Z*)-**239** and *ent*-(*E*)-**239** in 85 and 61% yields respectively.

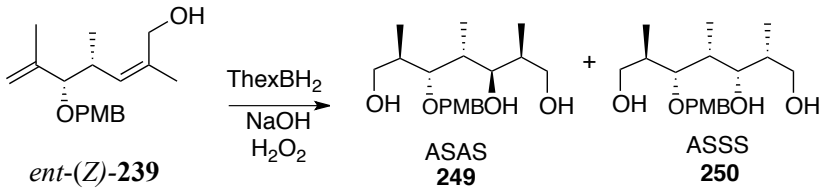


Scheme 3.27. Synthesis of *ent*-(*Z*)-**239** and *ent*-(*E*)-**239**

3.10 Cyclic hydroboration of *ent*-(*Z*)-239 and *ent*-(*E*)-239

As shown in Scheme 3.28a, cyclic hydroboration of *ent*-(*Z*)-**239** provided stereopentad **249** as the major product. The hydroboration of *ent*-(*Z*)-**239** proceeded cleanly in high yields and diastereoselectivity (80% and 10:1 respectively). This was consistent with the hydroboration results observed with diastereomer (*Z*)-**209.** When *ent*-(*E*)-**239** was treated with thexylborane, only one diastereomer was isolated (Scheme 3.28b). While this result was an improvement over *anti*-variant (*E*)-**209**, a myriad of nonpolar side products including anisaldehyde were also isolated, which led to a poor overall yield.

a)

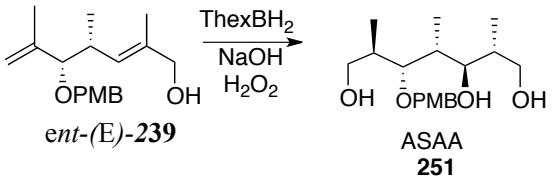


ent-(*Z*)-**239**

Entry	Substrate	Major Product	**249:250**	Yield[a]
1	*ent*-(*Z*)-**239**	AASS (**249**)	10:1	80%

a) Isolated yields

b)



ent-(E)-**239**

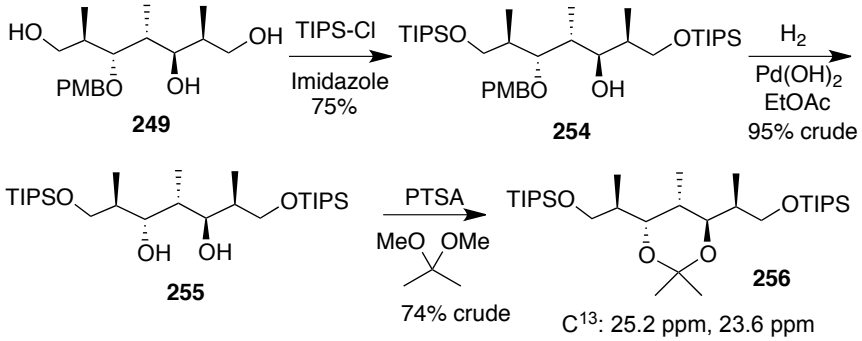
Entry	Substrate	Major Product	**251**	Yield[a,b]
1	*ent*-(*E*)-**239**	AASA (**251**)	>20:1	24%

a) Isolated yields b) anisaldehyde and other non-polar decomposition products were isolated and could not be characterized

Scheme 3.28. Results of cyclic hydroboration on a) *ent*-(*Z*)-**239** and b) *ent*-(*E*)-**239** substrates

3.11 Derivatization of *syn*-substrate results

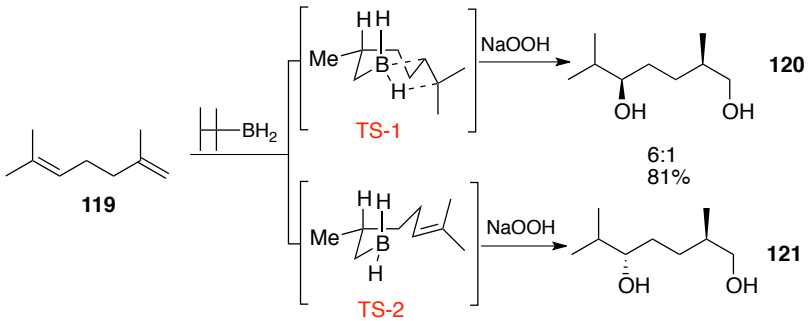
As shown in Scheme 3.29, the relative stereochemistry of the *syn*-substrate hydroboration product **249** was determined after transformation to the corresponding acetonide **256**. Selective protection of the primary alcohols to the TIPS-ethers (**254**) and subsequent cleavage of the PMB-ether under hydrogenation conditions gave diol **255**. Protection of crude diol **255** with 2,2-dimethoxypropane in the presence of CSA afforded acetonide **256**. The relative stereochemistry of the 1,4 asymmetric induction product **249** was confirmed by analyzing the ^{13}C NMR chemical shift (δ = 25.3, 23.5 for Me_2C) of the acetonide methyls on **256**.



Scheme 3.29 Derivatization of *syn*-substrates series

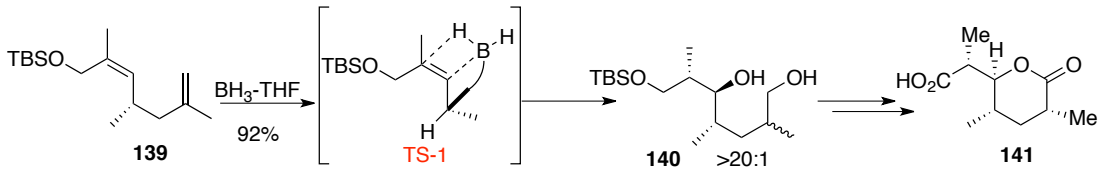
3.12 Proposed mechanistic rationale of reaction outcome

In an attempt to rationalize the product distribution and yields of our cyclic hydroboration methodology, we examined the possible mechanistic pathways involved by reviewing the literature on related systems. Precedents in the literature have shown there are two main mechanisms that can account for asymmetric induction occurring in cyclic hydroborations. The first was exemplified in the pioneering work of Still et al.,[11] with the cyclic hydroboration of simple dienes, as shown in Scheme 3.29. When diene **119** was treated with thexylborane, a considerable stereoelectronic effect was observed to afford **120** as the major product. The two possible transition states show that the non-hydrogen substituents preferentially adopt equatorial positions on the ring, while the diastereoselectivity is generated from the orientation of the alkylborane. The major product is the result of the boron-hydrogen bond eclipsing the olefin in **TS-1**, while it does not in **TS-2** (Scheme 3.30). These stereoelectronic factors dictate the preference of one diastereomer over the other.



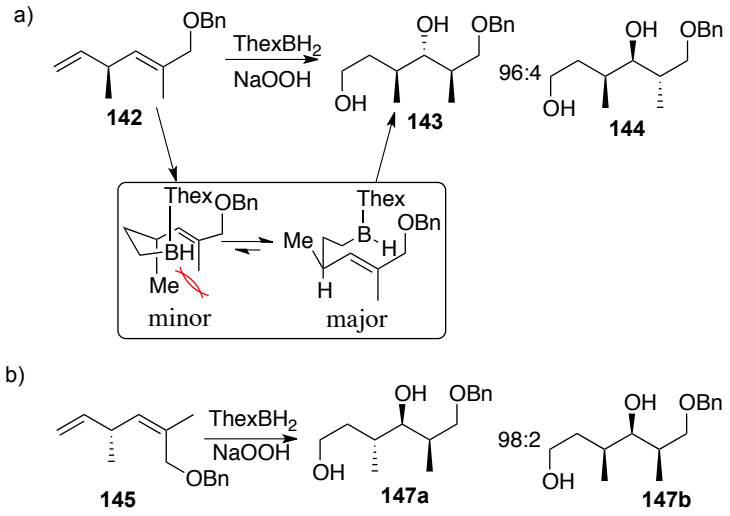
Scheme 3.30. Stereoelectronic effects account for observed remote stereoselection in Still's models.

The second was evidenced by Yokoyama et al.[12] as well as by Still et al.[13] in their work associated with Prelog-Djerossi lactonic acid **141**. In both cases, the remotely formed stereocenters can be explained by allylic strain.[14] As shown in Scheme 3.30 below, after the initial intermolecular hydroboration, the alkyl boron can attack from either *re*- or *si*-face of the olefin (Scheme 3.31, **TS-1**). However, the *cis*-orientation of the trisubstituted olefin generates a large amount of allylic strain, especially when the allylic methyl is *anti*/eclipsed with the *cis*-substituent (-OTBS). The conformational preference of the substrate to minimize allylic strain dictates the stereochemistry of the newly formed stereocenters. The smallest substituent (-H) will adopt the eclipsed or *anti* position, which forces the alkyl boron to preferentially attack from the *re*-face of the olefin with high asymmetric stereoselection (**140**, >20:1).



Scheme 3.31. Still's allylic strain directed cyclic hydroboration[13]

The work done by Yokohama demonstrates the same principle on a more condensed system. In Scheme 3.32, the proposed transition state demonstrates the relief of allylic strain when the methyl adopts the equatorial position (Scheme 3.32a). This results in excellent and predictable diastereoselectivities in the synthesis of stereotriads.



Scheme 3.32. Work done by Yokoyama on allylic strain directed cyclic hydroboration

It is worth noting that cyclic hydroboration of **145** afforded essentially one diastereomer (**147a**) as the major product (Scheme 3.32b). The orientation of the *cis*-olefin is more constrained and congested, which leads to a greater increase in selectivity. The ability of the olefin to relieve this strain is the major driving force for the smallest substituent to adopt an axial position with respect to the olefin. As a result, the unfavorable steric interactions associated with allylic strain are minimized.

In accord with our product distributions and subsequent derivatizations, we observed 1,4 asymmetric induction with respect to the newly created stereocenters. In order to attain a better understanding as to why this induction was occurring, we initially needed to focus on the intermolecular hydroboration first. We knew from literature precedent that intermolecular hydroborations would furnish a new stereocenter *anti* to an adjacent asymmetric center (Figure 3.6a). The largest and/or electron-donating group preferentially adopts the *anti*-position relative to the olefin, which allows the least hindered path of the alkyl borane to the internal olefin. This is consistent with the accepted mechanistic explanation for the hydroboration of olefins. After the addition of boron to the external olefin, the origins of the asymmetric induction become clear (Figures 3.6b and c). In both substrates, (*Z*)-**209** and *ent*-(*Z*)-**239**, the resultant alkyl boranes position the smallest substituent eclipsed with the backbone of the molecule. This preferential orientation situates the alkylborane on the *si*- and *re*-face of the internal

olefin, leading to the four-centered transition boracycles (*Z*)-**252** and *ent*-(*Z*)-**253** respectively (Figure 3.6b and c). This is the case for all four alkyl borane intermediates produced, so only the *cis*-compounds are shown for clarity. In Figure 3.6b, transition state (*Z*)-**252** adopts a twist-boat conformation, where the substituents are positioned in a pseudoequatorial orientation. In Figure 3.6c, transition state *ent*-(*Z*)-**253** adopts a traditional boat conformation, where the substituents are positioned in an energetically favorable equatorial orientation.

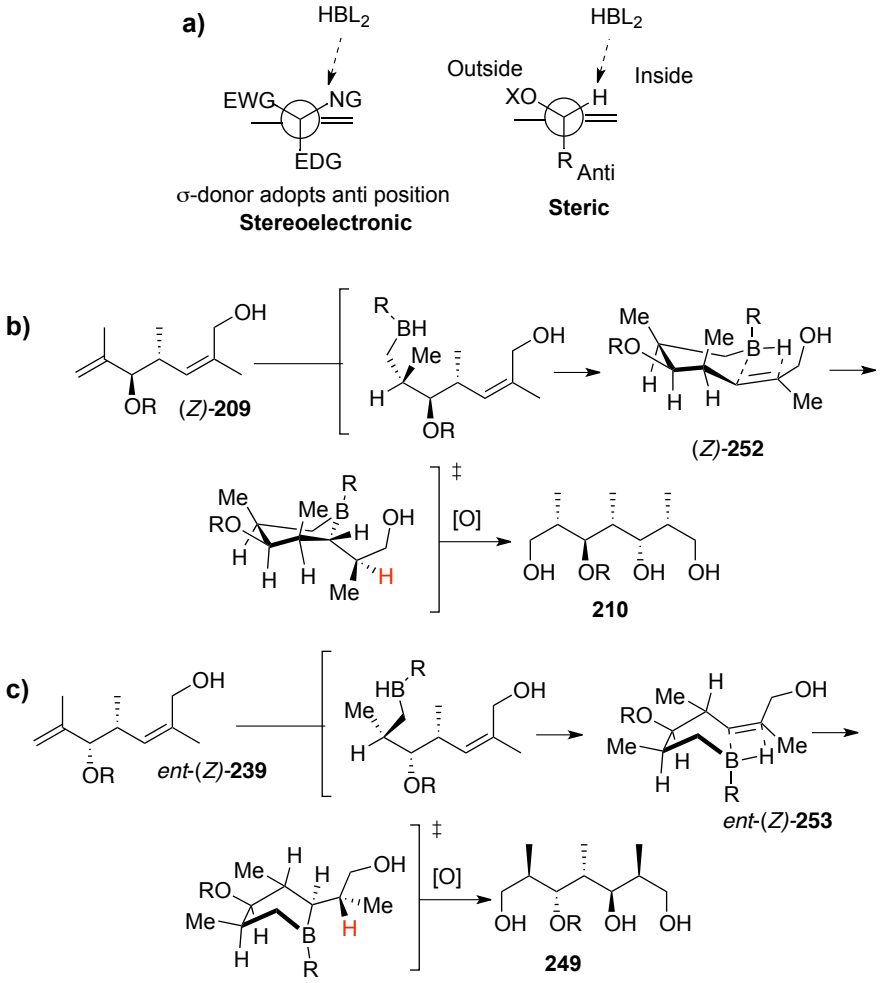


Figure 3.6. a) General hydroboration mechanism b) Cyclic hydroboration of (*Z*)-**209** mechanism c) Cyclic hydroboration of *ent*-(*Z*)-**239** mechanism

However, this mechanistic rationale only explains the 1,4 asymmetric induction that we observed. It does not explain the stark differences between the overall efficiency

of the cyclic hydroboration of the *cis*- and *trans*-isomers. In the previously reported cyclic hydroborations involving allylic strain, they lacked an allylic alcohol in their systems. The absence of a bulky electron-donating group allows for only allylic strain to direct the stereoselection of their cyclic hydroboration systems. However, our substrates contain a trisubstituted olefin, as well as, a protected allylic alcohol. Thus the previously described stereoelectronic factors, as well as, allylic strain will be present and need to be accounted for in our experiments.

Taking allylic strain into account, the proposed transition states for the four substrates are shown below in Figure 3.7. In the (*Z*)-**252** and (*E*)-**252** transition states (Figure 3.7a), a twist-chair conformation is formed, with all 3 substituents adopting equatorial (-OR) or pseudoequatorial conformations (-Me). The only difference between the two transition states is the isomeric orientation of the olefin. We suspect that the differences in allylic strain between (*Z*)-**252** and (*E*)-**252** accounts for the experimental results we observed. The relief of allylic strain in *cis*-olefins is greater than the *trans*-isomers, which coincides favorably with the results of our methodology. In the *ent*-(*Z*)-**239** and *ent*-(*E*)-**239** transition states, a boat-like conformation is formed with all three substituents taking up equatorial positions on the ring. Furthermore, the smallest allylic substituent (-H) is orientated in the axial position to minimize the 1,3-allylic strain. Preliminary transition state modeling studies[15] confirms this minimized allylic strain orientation.

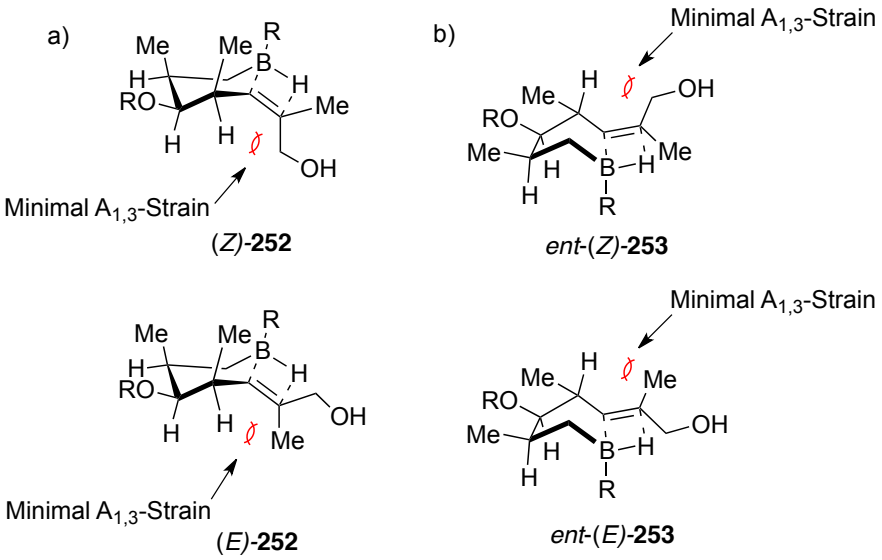


Figure 3.7. Transition states of substrates minimizing allylic strain. a) *anti*-transition states b) *syn*-transition states

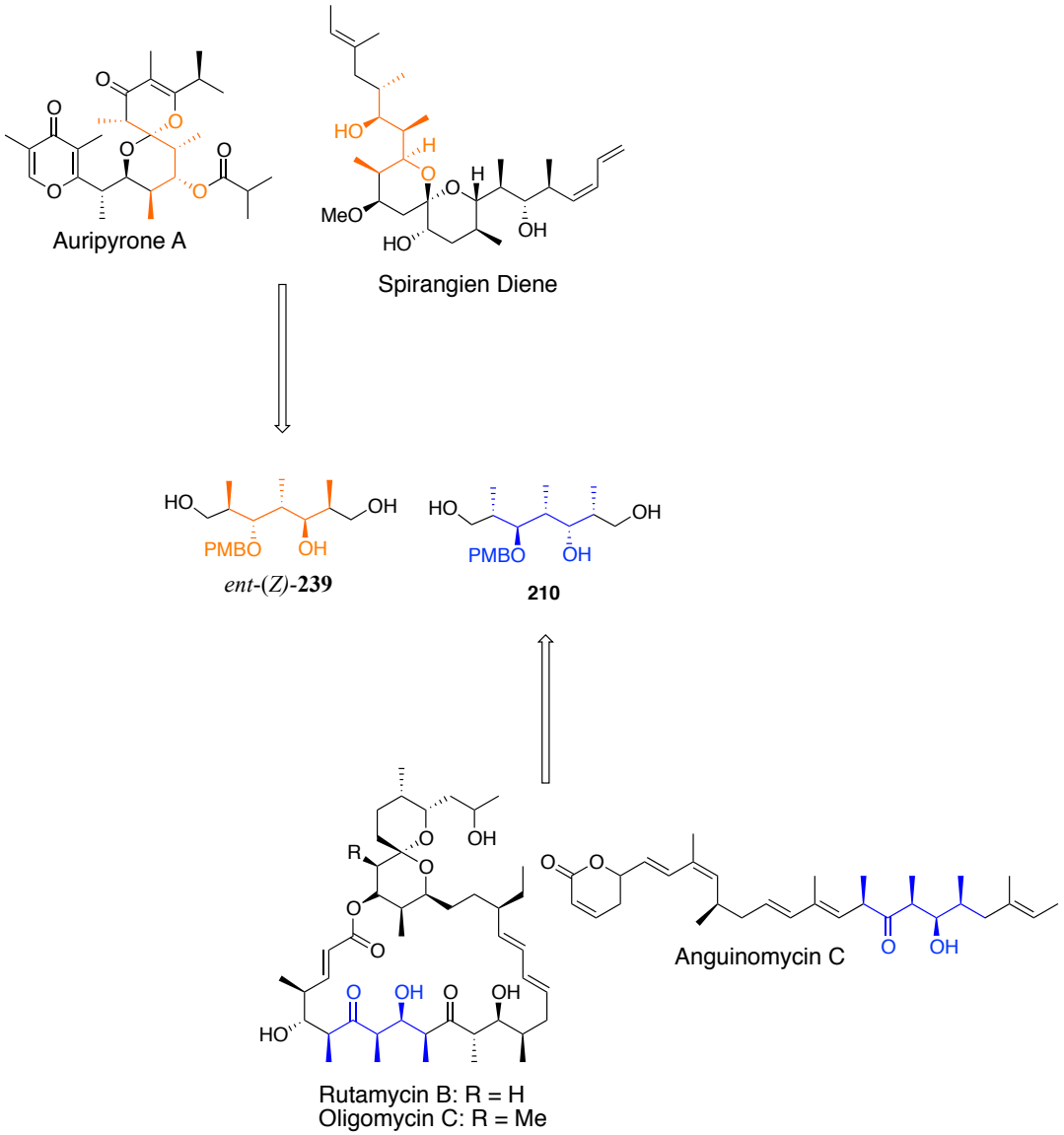
Interestingly, when the alcohol-protecting group was changed to the much more sterically demanding TBDPS group, both yields and stereoselectivity decreased substantially. We believe that the TBDPS group is too encumbered for this system, as the appearance of starting material and monohydroborated product suggests that the substrates had difficulty cyclizing to the internal olefin.

Preliminary transition state modeling studies suggests that once the alkyl borane has complexed with the internal olefin, there is very little difference in the resultant boracycle of the *cis* and *trans*-substrates. The differences in the two reactions must originate prior to the formation of the intermediate boracycle. The overall efficiency in diastereoselectivity and yields of the *cis*-isomers (*Z*)-**209** and *ent*-(*E*)-**239** suggests that a distinct preferential pathway is occurring. On the other hand, the *trans*-isomers (*Z*)-**209** and *ent*-(*E*)-**239** appear to proceed through multiple pathways that are similar in energy that precludes the possibility of high acylic asymmetric induction. While we are achieving a moderate amount of diastereoselection in the *trans*-isomers, the lack of preponderance for a distinct pathway leads to the poor yields and multiple side products observed, thus distracting from the overall utility and practicality of cyclic hydroboration of those substrates.

3.13 Conclusions and future directions

In summary, we rationally designed, developed and carried out a new methodology for the synthesis of stereopentads via cyclic hydroboration. These results demonstrate that cyclic hydroboration is a viable method for the generation of select stereopentads. The highlight of this methodology involves the acylic installation of three new stereocenters (two remotely) to generate stereopentads with moderate to excellent diastereoselectivity and yields in a single step. To our knowledge, this was the first application of cyclic hydroboration to synthesize stereopentads which can be further modified for the synthesis of relevent polyketide natural products.

The next phase will consist of demonstrating the utility of this methodology by synthesizing several of the viable polyketide targets shown in Scheme 3.33.



Scheme 3.33 Natural products targets

Also of interest is expanding the overall scope of this methodology in terms of effects of various protecting groups and different boranes. For instance, employing a bulky, chiral cyclic hydroborating agent, like monoisopinocampheylborane, Ipc-BH_2, could be effective in increasing the diastereoselectivity of these reactions. In addition, catalyzing the cyclic hydroboration with Wilkinson's catalyst could potentially increase the amount of accessible stereopentad permutations available for the synthesis of even more polyketide natural products. However, as with all iterations of olefin hydroboration, the borane needs to be complementary to the substrate and vice versa for optimal results.

3.14 Experimental Section

3.14.1 Materials and methods

Infrared (IR) Spectra were obtained using a Shimadzu FTIR-8400S. Proton (^{1}H NMR) nuclear magnetic resonance spectra were recorded on a Varian Oxford NMR 300, 400 and 500 and a Bruker NMR 400. Carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Varian Oxford NMR 400 and Bruker NMR 400. For both instruments solvent resonance was used as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from indicated deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. Analytical thin layer chromatography (TLC) was performed on Whatman 250 μm layer aluminum silica gel plates. Visualization was accomplished with UV light and phosphomolybdic acid in ethanol stain followed by heating. Electrospray ionization HRMS was preformed at the University of Illinois at Champagne Urbana mass spectrometry facility. Purification of the reaction products was carried out by flash chromatography using Sorbent technologies standard grade 60 Å (270-400 mesh) silica gel and Büchi GKR-51 Kugelrohr distillation apparatus. All reactions were carried out under an atmosphere of inert gas in oven-dried glassware with magnetic stirring unless otherwise stated. Diethyl ether, THF, and CH_2Cl_2 were distilled from Na, Na/benzophenone, and CaH respectively. Anhydrous Pyridine was used as received. 18-

Crown-6 was recrystallized from acetonitrile and dried under vacuum overnight. Unless otherwise noted, reagents were obtained from commercial sources and used without further purification.

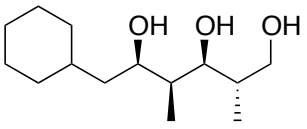
3.14.2 Preparative procedures

Preparation 0.5 M Thexylborane[16]

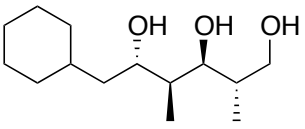
To a 3-neck RBF fitted with a thermometer, an addition funnel, and an argon inlet, was added BH_3-THF (1M, 10 mL). The flask was placed in a salt water ice bath so that the internal temperature was below 0°C. 2,3-Dimethyl-2-butene (1M, 10 mL) was placed in the addition funnel and slowly added to the borane as to keep the internal temperature below 0°C. After addition, the reaction was stirred for 1 hour at <0°C. A small amount of the newly formed thexylborane was placed in a small RBF and slowly quenched with 3M NaOH. A vigorous exotherm should be released. If an exotherm was present, the freshly prepared thexylborane was used immediately. A decrease in diastereoselectivity and yield was noticed when older thexylborane was used.

Representative example of cyclic hydroboration of dienes

To a solution of diene in THF cooled to -78°C was added a freshly prepared solution of thexylborane (0.5 M) all at once. The reaction was slowly warmed to room temperature and stirred overnight. The homogeneous mixture was slowly quenched with 3N NaOH (vigorous gas evolution), 35% H_2O_2 and stirred for 1-2 hrs at room temperature. The heterogeneous mixture was diluted and extracted with ethyl acetate. The organic solutions were combined and the resulting solution was washed with brine and dried over $MgSO_4$.



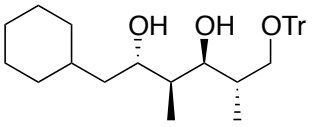
177 and



176

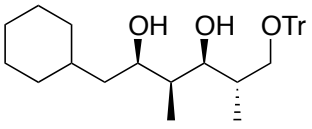
(2*S*,3*S*,4*S*,5*R*)-6-cyclohexyl-2,4-dimethylhexane-1,3,5-triol and **(2*S*,3*S*,4*S*,5*S*)-6-cyclohexyl-2,4-dimethylhexane-1,3,5-triol** – To a RBF containing allylic alcohol (**74**, 213.4 mg, 1.02 mmol) and 1.3 mL of THF cooled to -78°C, was added thexylborane (0.5 M, 3.9 mL) drop wise. The reaction was slowly warmed to room temperature and stirred overnight for 24 hrs. Sodium peroxide (10 mL; 5 mL 3M NaOH + 5 mL 30% hydrogen peroxide) was added to the reaction at 0°C and stirred for 30 min. The heterogeneous mixture was diluted with ether and resulting organic solution was washed organics with brine and dried over $MgSO_4$. Purification via flash chromatography (50% EA to 80% EA:H) afforded 2 diastereomers, *syn* and *anti* (22.7 mg and 47.2 mg respectively, 28% overall yield), as colorless oils. The first diastereomer to elute was the **177**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (dq, *J* = 4.4 Hz, 1.5 Hz, 1H), 3.75 (d, *J* = 9.3 Hz, 1H), 3.67 (m, 2H), 3.19 (s, 3H), 1.87 (m, 1H), 1.80 (m, 1H), 1.71-1.63 (m, 4H), 1.56-1.45 (m, 2H), 1.38-1.34 (m, 1H), 1.28-1.11 (m, 5H), 0.98-0.93(m, 1H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.5, 74.8, 69.2, 43.3, 38.3, 37.3, 34.1, 33.0, 26.5, 26.3, 26.1, 13.2, 4.1; IR: 3350.0, 2962.3, 2922.7, 2850.9, 1448.2, 1386.0, 1336.7, 1261.4, 1179.3, 1149.5, 1101.3, 1064.7, 1030.4, 968.3; The second to elute was **176**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (dd, *J* = 9.8 Hz, 1.5 Hz, 1H), 3.74 (m, 1H), 3.65 (m, 2H), 3.54 (s, 3H), 1.88-1.83 (m, 1H), 1.77 (m, 1H), 1.67-1.62 (m, 4H), 1.56-1.49 (m, 2H), 1.44-1.38 (m, 1H), 1.32-1.13 (m, 4H), 1.01 (d, *J* = 7.3 Hz, 3H), 1.00-0.80 (m, 2H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.2, 74.0, 69.1, 43.3, 38.6, 37.0, 34.3, 34.2, 32.8, 26.5, 26.3, 26.1, 13.1, 10.7; IR: 3339.1, 2966.1, 2922.7, 2851.1, 1448.0,

1381.9, 1338.1, 1278.5, 1103.1, 1030.3, 971.6, 909.5, 734.2; HRMS-ESI *m/z* calcd. for C14H28O3 245.2117; found 245.2118 $[M+Na]^+$



176a

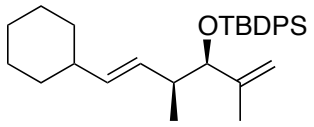
(2*S*,3*S*,4*S*,5*S*)-1-cyclohexyl-3,5-dimethyl-6-(trityloxy)hexane-2,4-diol - To a RBF containing triol (**176**, 18mg, 0.05 mmol) and CH_2Cl_2 (1 mL) was added TEA (27 µL, 0.20 mmol, 2.9 eq) at room temperature. Trityl chloride (27.9 mg, 0.10 mmol, 1.4 eq) was added and the mixture was stirred overnight at room temperature. The reaction was diluted with ether and the resulting organic solution was washed with brine and dried over $MgSO_4$. Flash chromatography (10% EA:H) afforded tritylated product (24mg, 70.5 % yield) as a white amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 6H), 7.35-7.25 (m, 9H), 3.94 (s, 1H), 3.83 (d, *J* = 8.8 Hz, 1H), 3.68 (s, 1H), 3.38 (dd, *J* = 9.3 Hz, 3.9 Hz, 1H), 3.14 (t, *J* = 8.8 Hz, 1H), 3.01 (d, *J* = 6.8 Hz, 1H), 1.92 (m, 1H), 1.83 (m, 1H), 1.71-1.65 (m, 4H), 1.51-1.48 (m, 3H), 1.29-1.12 (m, 5H), 1.02 (d, *J* = 7.3 Hz, 3H), 0.88-0.82 (m, 1H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 128.6, 127.9, 127.2, 87.7, 75.9, 73.2, 69.7, 43.7, 38.7, 36.1, 34.4, 32.9, 26.6, 26.4, 26.2, 13.2, 10.4; IR: 3446.5, 3090.9, 3058.7, 3032.6, 2963.7, 2922.1, 2850.7, 1489.9, 1448.2, 1418.8, 1386.6, 1319.3, 1261.1, 1222.1, 1153.3, 1088.3, 1051.1, 1030.5, 973.0, 908.9, 802.3; HRMS-ESI *m/z* calcd. for C33H42O3Na 509.3032; found 509.3041 $[M+Na]^+$



177a

(2*R*,3*S*,4*S*,5*S*)-1-cyclohexyl-3,5-dimethyl-6-(trityloxy)hexane-2,4-diol - To a solution of **177** (32.5 mg, 0.13 mmol) in dry CH_2CH_2 (3 mL) was added TEA (54 µL, 39.4 mg,

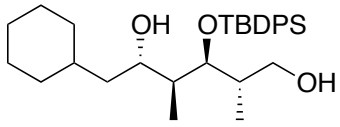
0.39 mmol, 3 eq) dropwise at room temperature. Trityl chloride (72.4 mg, 0.26 mmol, 2 eq) was added and the reaction was stirred overnight. The mixture was diluted with ether and the resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via combiflash (hexane to 50% EA:H) afforded tritylated product (63.2 mg, 66% yield) as a white amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 6H), 7.31-7.21 (m, 9H), 4.06 (s, 1H), 3.93-3.90 (q, *J* = 4.4 Hz, 1H), 3.61 (m, 2H), 3.32 (dd, *J* = 9.4 Hz, 3.8 Hz, 1H), 3.05 (t, *J* = 8.8 Hz, 1H), 1.92-1.87 (m, 1H), 1.81-1.78 (m, 1H), 1.67-1.60 (m, 4H), 1.51-1.37 (m, 3H), 1.27-1.06 (m, 4H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 128.5, 127.9, 127.1, 87.7, 82.2, 73.7, 69.5, 42.9, 38.5, 36.2, 34.2, 34.1, 33.0, 26.6, 26.3, 26.2, 13.3, 4.2; FTIR (thin film/NaCl): 3454.7, 3086.8, 3058.4, 3027.0, 2967.3, 2922.6, 2850.3, 1490.2, 1448.3, 1387.3, 1318.2, 1269.4, 122.1, 1181.2, 1153.8, 1122.8, 1087.5, 1068.5, 1051.8, 1030.5, 969.8, 908.9;



180

***tert*-butyl(((3*R*,4*S*,*E*)-6-cyclohexyl-2,4-dimethylhexa-1,5-dien-3-yl)oxy)diphenylsilane** - To a solution of alcohol **74** (175.6 mg, 0.84 mmol) in CH_2CH_2 (6 mL) was added a solution of imidazole (111.4 mg, 1.63 mmol, 1.9 eq) in CH_2CH_2 (2 mL). The reaction was cooled to 0°C, at which time TBDPS-Cl (565 μL, 599 mg, 2.18 mmol, 2.5 eq) was added dropwise slowly. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water, extracted with ether and the resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via flash chromatography (hexanes to 15% EA:H) afforded silyl ether (218.7 mg, 58% yield) as a

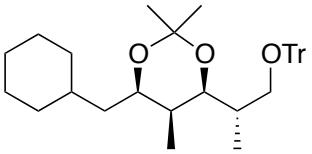
colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77-7.70 (m, 4H), 7.48-7.37 (m, 6H), 5.35-5.22 (dq, *J* = 7.3 Hz, 6.4 HZ, 2H), 4.72 (s, 1H), 4.67 (s, 1H), 3.98 (d, *J* = 6.4 Hz, 1H), 2.31 (m, 1H), 1.88-1.83 (m, 1H), 1.75-1.69 (m, 7H), 1.34-1.17 (m, 3H), 1.15 (s, 9H), 1.08-1.00 (m, 2H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 136.2, 136.1, 135.4, 134.5, 134.1, 129.9, 129.3, 127.2, 112.7, 82.0, 41.6, 40.6, 33.0, 27.1, 26.2, 26.0, 19.6, 18.4, 18.3, 16.7; FTIR (thin film/NaCl): 3135.0, 3071.3, 3048.5, 3014.1, 2958.9, 2925.3, 2853.9, 2738.1, 2709.9, 2667.1, 1956.9, 1887.9, 1820.2, 1651.9, 1589.8, 1567.8, 1472.0, 1448.4, 1427.5, 1390.2, 1370.4, 1260.7, 1190.8, 111.2, 1066.3, 1006.9, 967.6, 937.8, 897.4, 849.8, 821.3, 738.7; HRMS-ESI *m/z* calcd. for C30H42ONaSi 469.2898; found 469.2903 $[M+Na]^+$



181

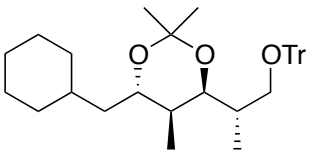
(2*S*,3*S*,4*S*,5*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-6-cyclohexyl-2,4-dimethylhexane-1,5-diol - See representative cyclic hydroboration procedure: Purification via combiflash (20% EA to 50% EA:H) afforded **181** (37.7 mg, 31% yield) as the only isolated diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74-7.70 (m, 4H), 7.45-7.37 (m, 6H), 4.22 (dd, *J* = 5.5 Hz, 1.4 Hz, 1H), 3.45-3.35 (dq, *J* = 11.4 Hz, 7.1 Hz, 2H), 3.24 (t, *J* = 9.0 Hz, 1H), 2.00-1.94 (m, 1H), 1.83 (s, 2H), 1.69-1.51 (m, 6H), 1.34-1.11 (m, 5H), 1.09 (s, 9H), 0.96-0.88 (m, 1H), 0.85 (d, *J* = 7.1 Hz, 3H), 0.82 (d, *J* = 7.1 Hz, 3H), 0.72-0.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 134.1, 134.0, 129.7, 127.5, 73.9, 71.1, 65.2, 42.8, 41.0, 40.6, 34.7, 33.6, 32.2, 27.2, 26.5, 26.4, 26.0, 19.7, 12.7, 12.0; FTIR (thin film/NaCl): 3575.9, 3372.7, 3070.5, 3048.8, 2925.9, 2854.2, 1472.2, 1460.9, 1447.8,

1427.2, 1390.1, 1359.1, 1329.2, 1307.5, 1110.1, 1060.1, 1040.1, 1021.8, 938.9, 908.2, 842.5, 821.3; HRMS-ESI *m/z* calcd. for C30H46O3Si 483.3294; found 483.3292



183

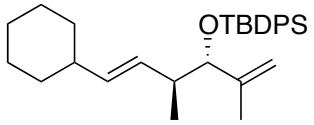
(4*R*,5*S*,6*S*)-4-(cyclohexylmethyl)-2,2,5-trimethyl-6-((*S*)-1-(trityloxy)propan-2-yl)-1,3-dioxane - To a solution of **177a** (35.3 mg, 0.072 mmol) in 2,2-dimethoxypropane (5 mL) was added a catalytic amount of PTSA. Upon consumption of diol (2 hrs) via TLC analysis, the reaction was diluted with CH_2Cl_2 and the resulting solution was washed with sat'd $NaHCO_3$, brine and dried over $MgSO_4$. Purification via column chromatography (hexanes) afforded acetonide (18.1 mg, 48% yield) as a white amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.3 Hz, 6H), 7.30-7.20 (m, 9H), 4.01-3.98 (m, 1H), 3.90 (d, *J* = 9.8 Hz, 1H), 3.24 (dd, *J* = 8.3 Hz, 4.3 Hz 1H), 3.06 (dd, *J* = 8.3 Hz, 2.5 Hz 1H), 1.77-1.64 (m, 7H), 1.50-1.37 (m, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.23-1.12 (m, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.96-0.82 (m, 2H), 0.79 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 128.8, 127.5, 126.6, 98.5, 85.8, 73.7, 70.7, 63.8, 40.6, 35.3, 33.9, 33.6, 33.2, **32.9**, 29.9, 26.6, 26.2, **19.5**, 13.0, 4.5; FTIR (thin film/NaCl): 3089.8, 3058.4, 3024.4, 2986.2, 2964.4, 2923.5, 2851.3, 1489.6, 1448.3, 1385.2, 1377.4, 1353.6, 1261.8, 1199.7, 1157.7, 1105.0, 1086.0, 1070.3, 1027.9, 1009.2, 963.6, 909.3, 743.8, 701.5



184

(4*S*,5*S*,6*S*)-4-(cyclohexylmethyl)-2,2,5-trimethyl-6-((*S*)-1-(trityloxy)propan-2-yl)-1,3-dioxane - To a vial containing **176a** (17 mg, 0.034 mmol) and 3 mL 2,2-

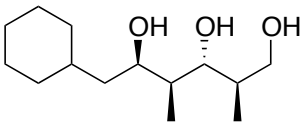
Dimethoxypropane, a catalytic amount of PTSA was added at room temperature. After 4 hours, TLC showed the consumption of starting material. The reaction was diluted with CH_2Cl_2 and the resulting organic solution was washed with $NaHCO_3$, brine and dried over $MgSO_4$. The volitiles were evaporated in vacuo which afforded fully protected acetonide (16.1 mg, 90.4% yield) as a white amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.3 Hz, 6H), 7.30-7.21 (m, 9H), 3.72-3.69 (dd, *J* = 10.7 Hz, 4.4 Hz, 1H), 3.30-3.25 (m, 2H), 3.08 (t, *J* = 5.8 Hz, 1H), 1.79-1.59 (m, 7H), 1.55-1.41 (m, 2H), 1.30-1.21 (m, 3H), 1.19 (s, 3H), 1.07 (s, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.98-0.90 (m, 1H), 0.83 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 128.9, 127.5, 126.7, 100.4, 86.1, 72.5, 69.8, 64.6, 42.7, 38.8, 34.3, 33.9, 32.3, 26.6, 26.2, **25.0**, **23.6**, 13.8, 11.4; FTIR (thin film/NaCl): 3081.4, 3059.6, 3027.1, 2983.6, 2921.4, 2850.9, 1596.9, 1489.9, 1448.28, 1378.5, 1315.6, 1225.5, 1182.5, 1150.7, 1130.9, 1103.8, 1073.9, 1021.7, 997.1; HRMS-ESI *m/z* calcd. for C36H46O3 549.3345; found 549.3350



185

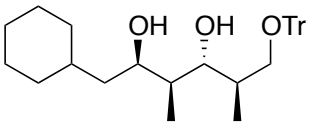
***tert*-butyl(((3*S*,4*S*,*E*)-6-cyclohexyl-2,4-dimethylhexa-1,5-dien-3-yl)oxy)diphenylsilane** - To a solution of alcohol (250.4 mg, 1.20 mmol) in 2.5 mL dry CH_2CH_2 cooled to 0°C, was treated with imidazole (318 mg, 4.7 mmol, 3.9 eq) and TBDPSCl (808 μL, 857 mg, 3.1 mmol, 2.6 eq). The mixture was warmed to room temperature and stirred overnight. The reaction was diluted with water and extracted with CH_2CH_2 and the organic solution was washed with brine, dried over $MgSO_4$. After filtration and concentration, purification via flash chromatography afforded silyl-ether (310 mg, 58 % yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76-7.68 (m, 4H), 7.47-7.34 (m, 6H), 5.92

(m, 2H), 4.73 (m, 2H), 3.97 (d, *J* = 6.7 Hz, 1H), 2.30 (m, 1H), 1.86-1.61 (m, 5H), 1.36-1.17 (m, 5H), 1.13 (s, 9H), 1.06-0.90 (m, 4H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 136.2, 136.1, 135.9, 134.5, 134.2, 130.6, 129.4, 129.3, 127.2, 127.1, 112.9, 81.9, 77.2, 41.5, 40.6, 32.9, 27.1, 26.3, 26.2, 26.1, 19.5, 18.2, 16.3; FTIR (thin film/NaCl): 3071.3, 3048.2, 2960.2, 2926.1, 2854.2, 1472.3, 1448.6, 1427.4, 1111.6, 1072.5, 700.6; HRMS-ESI *m/z* calcd. for C30H42ONaSi 469.2898; found 469.2886 $[M+Na]^+$



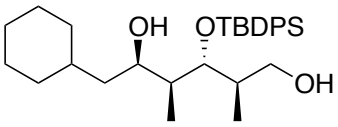
186

(2*R*,3*R*,4*S*,5*R*)-6-cyclohexyl-2,4-dimethylhexane-1,3,5-triol - To a solution of **171** (87.6 mg, 0.18 mmol) in 4 mL THF, was added TBAF (360 μL, 0.36 mmol, 1M in THF, 2 eq) dropwise at room temperature. Upon consumption of starting material (2.5 hrs) via TLC, the reaction was quenched with sat'd ammonium chloride. The heterogeneous mixture was extracted with ethyl acetate and the resulting solution was washed with brine and dried over $MgSO_4$. Flash chromatography (2:1 H:EA) afforded triol (25.7 mg, 58% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (bs, 1H), 4.14 (m, 1H), 3.79 (m, 2H), 3.62 (t, *J* = 8.0, 1H), 3.57 (m, 1H), 3.47 (s, 1H), 1.98 (m, 1H), 1.87 (s, 1H), 1.79-1.63 (m, 7H), 1.49-1.28 (m, 7H), 1.00 (d, *J* = 7.0, 3H), 0.94 (m, 2H), 0.83 (d, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 132.4, 132.3, 129.9, 127.9, 127.8, 82.6, 69.7, 68.3, 42.3 38.3, 36.9, 34.2, 34.1, 33.2, 26.7, 26.6, 26.3, 26.2, 18.9, 13.4, 11.2; FTIR (thin film/NaCl): 3346.6, 2962.0, 2923.2, 2851.0, 1448.1, 1031.3, 970.2; HRMS-ESI *m/z* calcd. for C14H28O3 245.2117; found 245.2120



186a

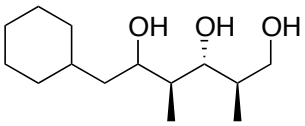
(2*R*,3*S*,4*R*,5*R*)-1-cyclohexyl-3,5-dimethyl-6-(trityloxy)hexane-2,4-diol - To a solution of **186** (18 mg, 0.07 mmol) in 4 mL CH_2CH_2 was added TEA (19.4 μL, 14.1 mg, 0.14 mmol, 2 eq) dropwise at room temperature. The reaction was stirred for 10 min then trityl chloride (22.3 mg, 0.08 mmol, 1.1 eq) was added all at once. The mixture was stirred overnight at room temperature, at which time the reaction was diluted with ether and the resulting solution was washed with brine and dried over $MgSO_4$. Column chromatography (5% EA:H) afforded tritylated product (18.8 mg, 55% yield) as an amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.20 (m, 15H), 4.33 (d, J = 2 Hz, 1H), 4.05 (m, 1H), 3.64(s, 1H), 3.44 (m, 1H), 3.36 (dd, J = 9.4, 3.6 Hz, 1H), 3.08 (t, J = 8.7 Hz, 1H), 2.06 (m, 1H), 1.82 (m, 1H), 1.67 (m, 4H), 1.52-1.04 (m, 8H), 0.94 (d, J = 7.0 Hz, 3H), 0.93-0.82 (m, 2H), 0.77 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 128.4, 128.0, 127.2, 87.8, 82.3, 69.0, 68.1, 42.4, 38.1, 35.8, 34.3, 34.1, 33.2, 26.6, 26.3, 26.2, 14.0, 11.1; FTIR (thin film/NaCl): 3428.1, 2969.5, 2923.4, 2850.7, 1136.4, 1448.2; HRMS-ESI *m/z* calcd. for C33H42O3Na 509.3032; found 509.3036 $[M+Na]^+$



187

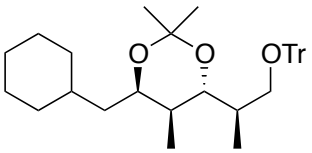
(2*R*,3*R*,4*S*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-6-cyclohexyl-2,4-dimethylhexane-1,5-diol - See representative cyclic hydroboration procedure. Purification via column chromatography (5% EA:H) afforded diol (92.5 mg, 31% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.40 (m, 10H), 4.68 (s, 1H), 4.14 (m, 1H), 3.82 (m, 2H), 3.65 (m, 2H), 2.07 (m, 1H), 1.85-1.10 (m, 14H), 1.06 (s, 9H), 1.03 (d, *J* = 7.3 Hz, 3H), 0.93-0.87 (m, 2H), 0.77 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 132.4, 132.3, 129.9, 127.9, 127.8, 82.6, 69.7, 68.3, 42.3, 38.3, 36.9, 34.2, 34.1, 33.2, 26.7, 26.6, 26.3, 26.2, 18.9, 13.4, 11.2; FTIR (thin film/NaCl): 3419.7, 3071.2, 3049.4, 2962.2, 2926.2, 2926.3, 2854.8, 1471.8, 1448.0, 1427.7, 1112.4, 1078.1; HRMS-ESI *m/z* calcd. for C30H46O3Si 483.3294; found 483.3288



1:1 mix of **186** and **188**

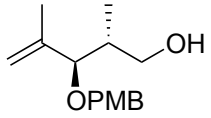
(2*R*,3*R*,4*S*)-6-cyclohexyl-2,4-dimethylhexane-1,3,5-triol - See representative cyclic hydroboration procedure. Purification via column chromatography (2:1 H:EA) afforded an inseparable mixture of triols (70.2 mg, 36% yield). A small amount of the major diastereomer was isolated and fully characterized: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (s, 1H), 3.96 (dd, *J* = 10.7, 2.4 Hz, 1H), 3.74 (t, *J* = 8.0 Hz, 1H), 3.58 (m, 2H), 3.27 (s, 1H), 3.05 (s, 1H), 1.90-1.83 (m, 2H), 1.75-1.63 (m, 7H), 1.51-1.19 (m, 6H), 1.14 (d, *J* = 7.1, 3H), 0.98 (m, 2H), 0.80 (d, *J* = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.6, 74.5, 65.1, 43.2, 42.1, 35.8, 34.8, 33.6, 32.3, 26.6, 26.4, 26.1, 15.2, 14.0; FTIR (thin film/NaCl): 3339.4, 2922.8, 2850.5, 1447.9, 1377.0, 1030.6, 978.2



192

(4*R*,5*S*,6*R*)-4-(cyclohexylmethyl)-2,2,5-trimethyl-6-((*R*)-1-(trityloxy)propan-2-yl)-1,3-dioxane - To a vial containing **186a** (17.6 mg, 0.036 mmol) in 3 mL 2,2-

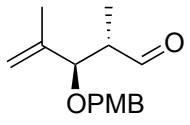
Dimethoxypropane was added a catalytic amount of PTSA at room temperature. After stirring for 3.5 hrs, the reaction was completed via TLC analysis. The reaction was diluted with CH_2CH_2 and quenched with sat'd $NaHCO_3$. The heterogeneous mixture was extracted with CH_2CH_2 and the resulting organic solution was washed with brine and dried over $MgSO_4$. Flash chromatography (hexanes) afforded acetonide (9.9 mg, 53% yield) as a white amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.21 (m, 15H), 3.81 (m, 1H), 3.28 (dd, *J* = 6.8, 5.8 Hz, 1H), 3.13-3.07 (dq, *J* = 9.3, 5.8 Hz, 2H), 3.06 (s, 1H), 1.87 (m, 1H), 1.74-1.62 (m, 6 H), 1.34 (m, 4H), 1.25 (s, 3H), 1.21 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 143.9, 128.8, 128.7, 127.7, 127.5, 126.8, 126.7, 100.0, 86.3, 76.4, 66.3, 64.7, 38.2, 36.9, 34.1, 33.8, 33.1, 26.6, 26.3, **26.2**, **25.5**, 23.6, 14.4, 12.6; FTIR (thin film/NaCl): 3086.8, 3058.2, 3032.2, 2981.5, 2924.8, 2850.6, 1490.0, 1448.4, 1377.9, 1224.1, 1173.8, 1074.5; HRMS-ESI *m/z* calcd. for C36H46O3Na 549.3345; found 549.3339 $[M+Na]^+$



206

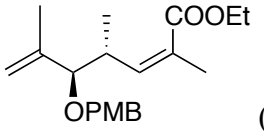
(2*R*,3*R*)-3-((4-methoxybenzyl)oxy)-2,4-dimethylpent-4-en-1-ol -To a RBF containing benzylidine acetal **200a** (103 mg, 0.42 mmol) and 3 mL dry toluene cooled to 0°C, was added DIBAL-H (1M in heptane, 1.24 mL, 1.24 mmol, 3 eq). Upon consumption of starting material (3.5 hr), the reaction was cooled to 0°C, quenched slowly with MeOH, 10% Rochelle's salt and stirred vigorously for 30 min while warming to room temperature. The heterogeneous mixture was extracted with ether and the resulting solution was washed with brine and dried over $MgSO_4$. Alcohol **206** (91.4 mg, 88% yield) was pure by ^{1}H NMR and used directly in the next step without further

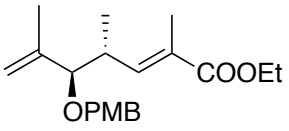
purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.06 (s, 1H), 4.92 (s, 1H), 4.45-4.16 (abq, *J* = 11.2 Hz, 10.7 Hz, 2H), 3.78 (s, 3H), 3.58 (m, 3H), 3.23 (s, 1H), 1.94 (m, 1H), 1.71 (s, 3H), 0.72 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 142.4, 129.9, 129.4, 115.8, 113.7, 89.2, 69.4, 67.9, 55.0, 36.8, 16.1, 13.5; FTIR (thin film/NaCl): 3287.3, 2961.9, 2867.5, 2836.7, 1650.8, 1612.8, 1586.2, 1514.0, 1455.7, 1375.1, 1301.9, 1247.4; HRMS-ESI *m/z* calcd. for C15H22O3 251.1647; found 251.1654



207

(2*S*,3*R*)-3-((4-methoxybenzyl)oxy)-2,4-dimethylpent-4-enal - A 100 mL RBF containing Dess-Martin periodinane (14 g, 33.15 mmol, 1.7 eq), sodium bicarbonate (4.91 g, 58.5 mmol, 3 eq) and 45 mL dry CH_2Cl_2 was cooled to 0°C. A solution of **206** (4.9 g, 19.5 mmol) in CH_2Cl_2 (5 mL +1 mL wash) was added dropwise to the slurry and the resulting mixture was allowed to stir for 1 hr at 0°C. The mixture was warmed to room temperature and stirred for 7 hrs. Upon consumption of starting material indicated by TLC, the reaction was cooled to 0°C, quenched with sat'd $NaHC0_3$ and sat'd sodium thiosulfate successively. The heterogeneous mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. The resulting aldehyde (3.8 g crude) contained minor impurities and was used as such in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (d, *J* = 2.9 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.12 (s, 1H), 4.99 (s, 1H), 4.46-4.16 (abq, *J* = 11.7 Hz, 11.7 Hz, 2H), 3.85 (d, *J* = 9.7 Hz, 1H), 3.77 (s, 1H), 2.58 (m, 1H), 1.71 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); FTIR (thin film/NaCl): 3073.8, 3034.1, 2971.2, 2936.2, 2860.3, 2837.1, 2716.8, 1727.9, 1612.4, 1514.1, 1455.7, 1388.0, 1374.1, 1302.2.



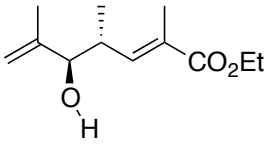
(*Z*)-**194** and


(*E*)-**194**

(4*R*,5*R*,*Z*)-ethyl 5-((4-methoxybenzyl)oxy)-2,4,6-trimethylhepta-2,6-dienoate and **(4*R*,5*R*,*E*)-ethyl 5-((4-methoxybenzyl)oxy)-2,4,6-trimethylhepta-2,6-dienoate** - To a 500 mL round-bottom flask containing triethyl-2-phosphonopropionate (7.28 g, 30.6 mmol, 6.5 mL, 2 eq) and 300 mL dry THF cooled to 0°C, was added 95% NaH (1.15 g, 45.9 mmol, 3 eq). The mixture was stirred for 5 min then a solution of aldehyde in THF (40 mL) was added dropwise via addition funnel. Upon consumption of starting material via TLC analysis (14 hr), the reaction was quenched with water and extracted with ether. The organic solutions were combined and the resulting solution was washed with brine and dried over $MgSO_4$. Purification via flash chromatography (15% EA:H) afforded enones (*E*)-**194** and (*Z*)-**194** (4.42 g as a ~1:1 mixture of *cis* and *trans* isomers, 87% combined yield over 2 steps) as a colorless oil. The first isomer to elute was (*Z*)-**194**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.76 (dd, *J* = 9.1, 1.4 Hz, 1H), 5.02 (s, 1H), 4.89 (s, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.15 (m, 3H), 3.80 (s, 3H), 3.43 (m, 2H), 1.90 (s, 3H), 1.68 (s 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 167.8, 158.9, 146.4, 143.0, 130.7, 129.3, 126.6, 114.9, 113.5, 86.9, 69.3, 59.8, 55.1, 35.8, 20.7, 16.9, 14.1; FTIR (thin film/NaCl): 3071.1, 2977.5, 2962.2, 2869.9, 1712.8, 1650.9, 1612.6, 1513.9, 1455.7, 1371.9, 1301.7, 1247.7; HRMS-ESI *m/z* calcd. for C20H28O4 333.2066; found 333.2074.

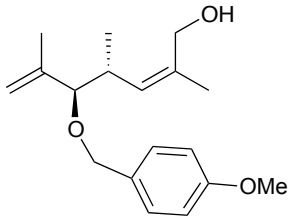
The second isomer to elute was (*E*)-**194**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.64 (dd, *J* = 9.5, 1.3 Hz, 1H), 5.05 (s, 1H), 4.91 (s, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.24-4.17 (m, 2H), 4.15 (d, *J* = 11.8 Hz, 1H), 3.78 (s, 3H),

3.50 (d, *J* = 8.7 Hz, 1H), 2.70 (m, 1H), 1.86 (s, 3H), 1.70 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 168.2, 158.8, 145.4, 142.6, 130.5, 129.1, 127.6, 115.7, 113.4, 86.6, 69.3, 60.1, 55.1, 35.7, 16.5, 16.1, 14.2, 12.6; FTIR (thin film/NaCl): 3071.5, 2977.2, 2932.6, 2870.7, 2837.0, 1708.8, 1651.1, 1612.7, 1586.1, 1513.8, 1454.6, 1387.9, 1367.1, 1296.2, 1247.5; HRMS-ESI *m/z* calcd. for C20H28O4Na 355.1885; found 355.1888 $[M+Na]^+$



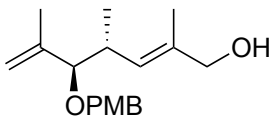
(*E*)-**194a**

(4*R*,5*R*,*E*)-ethyl 5-hydroxy-2,4,6-trimethylhepta-2,6-dienoate - To a solution of (*E*)-**194** (84 mg, 0.25 mmol) in 8 mL (8:1 mix of CH_2Cl_2:pH = 7.2 buffer) was added DDQ (85 mg, 0.375 mmol, 1.5 eq) at room temperature. The color of the reaction immediately changed to dark green/black upon addition. The heterogeneous mixture was stirred at room temperature until starting material was consumed as indicated by TLC (2 hr). The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organics were combined and the resulting solution was washed with brine and dried over $MgSO_4$. Purification via column chromatography (15% EA:H) afforded alcohol (38.4 mg, 72 % yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (dd, *J* = 9.9, 1.2 Hz, 1H), 4.93 (s, 1H), 4.91 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.88 (d, *J* = 7.9 Hz, 1H) 2.73-2.63 (m, 1H), 1.87 (s, 3H), 1.79 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 168.0, 145.1, 143.8, 128.9, 113.5, 80.1, 77.3, 76.9, 76.6, 60.4, 37.0, 16.9, 16.4, 14.1, 12.6; FTIR (thin film/NaCl): 3485.6, 3075.5, 2977.8, 2931.1, 2873.3, 1708.2, 1650.6, 1449.9, 1389.7, 1368.4, 1269.4.



(*Z*)-**209**

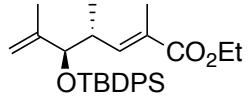
(4*R*,5*R*,*Z*)-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylhepta-2,6-dien-1-ol - To a solution of (*Z*)-**194** (1.12 g, 3.3 mmol) in CH_2Cl_2 (20 mL) cooled to -78°C was added DIBAL-H (1M in heptane, 7.7 mL, 7.7 mmol, 2.3 eq) dropwise slowly. Upon consumption of starting material via TLC analysis (45 min), the mixture was quenched with MeOH and 10% Rochelle's salt then allowed to stir for 1 hr at room temperature. The heterogeneous mixture was extracted with CH_2Cl_2 and the resulting organic solutions were washed with brine and dried over $MgSO_4$. Purification via flash chromatography (20% EA:H) afforded alcohol (606 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 5.06 (s, 1H), 4.95 (d, *J* = 9.7 Hz, 1H), 4.88 (s, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 4.12 (d, *J* = 11.2 Hz, 1H), 3.78 (s, 3H), 3.63 (t, *J* = 9.7 Hz, 1H), 3.24 (d, *J* = 9.7 Hz, 1H), 3.01 (d, *J* = 8.2 Hz, 1H), 2.66 (m, 1H), 1.82 (s, 3H), 1.71 (s, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 159.1, 142.5, 136.3, 131.7, 129.6, 129.5, 116.3, 113.6, 86.3, 69.4, 61.7, 55.0, 54.3, 22.6, 17.2, 16.0; FTIR (thin film/NaCl): 3435.7, 3071.1, 3035.6, 2964.7, 2870.3, 1648.6, 1613.1, 1586.1, 1514.2, 1455.1, 1374.4, 1247.1; HRMS-ESI *m/z* calcd. for C18H26O3 291.1960; found 291.1961



(*E*)-**209**

(4*R*,5*R*,*E*)-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylhepta-2,6-dien-1-ol - To a solution of (*E*)-**194** (672 mg, 2.02 mmol) in 15 mL dry CH_2Cl_2 cooled to -78°C, was

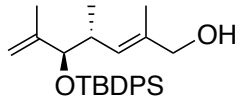
added DIBAL-H (1M in heptane, 4.6 mL, 4.6 mmol, 2.3 eq) dropwise slowly. Upon consumption of starting material via TLC analysis (45 min), the mixture was quenched with MeOH and 10% Rochelle's salt then allowed to stir for 1 hr at room temperature. The heterogeneous mixture was extracted with CH_2Cl_2 and the resulting organic solutions were washed with brine and dried over $MgSO_4$. Purification via flash chromatography (15% EA:H) afforded alcohol (424 mg, 72%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.24 (d, *J* = 8.9 Hz, 1H), 5.02 (s, 1H), 4.89 (s, 1H), 4.46(d, *J* = 11.8 Hz, 2H) 4.12 (d, *J* = 11.8 Hz, 2H), 3.96 (s, 2H), 3.77 (s, 3H), 3.42 (d, *J* = 8.4 Hz, 1H), 2.61 (m, 1H), 2.24 (s, 1H), 1.70 (s, 3H), 1.67 (s, 3H), 0.82 (d, *J* = 6.8, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 158.7, 143.0, 134.7 130.6, 129.4, 129.0, 114.9, 113.3 87.0, 69.2, 68.6, 54.9, 34.4 17.1, 16.6, 13.8; FTIR (thin film/NaCl): 3358.0, 3070.2, 2959.3, 2926.0, 2862.0, 2862.8, 1648.5, 1612.6, 1586.1, 1513.5; HRMS-ESI *m/z* calcd. for C18H26O3Na 313.1780; found 313.1781 $[M+Na]^+$



(*E*)-**226**

(4*R*,5*R*,*E*)-ethyl 5-((*tert*-butyldiphenylsilyl)oxy)-2,4,6-trimethylhepta-2,6-dienoate - To a solution of (*E*)-**194a** (131 mg, 0.62 mmol) in THF (10 mL) cooled to 0°C, was added DBU (557 μL, 563 mg, 3.7 mmol, 5 eq), silver nitrate (210 mg, 1.24 mmol, 2 eq) and *tert*-butyldiphenylchlorosilane (777 μL, 824 mg, 3.0 mmol, 5 eq) successively. The reaction flask was fitted with a reflux condenser, heated to ~85 °C and refluxed for 2.5 days. The mixture was cooled to room temperature, diluted with water, extracted with ether and the resulting solution was washed with brine and dried over $MgSO_4$. Purification via flash chromatography (5% EA:H -> 20% EA:H) afforded silyl-ether (127 mg, 95% adjusted yield) and recovered starting material (68.3 mg). ^{1}H NMR (500 MHz,

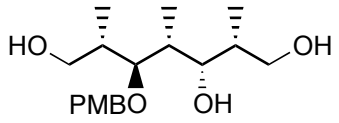
$CDCl_3$) δ 7.65-7.22 (m, 11H), 6.56 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.71 (s, 1H), 4.61 (s, 1H), 4.11 (dq, *J* = 7.3, 1.0 Hz, 2H), 3.91 (d, *J* = 7.3 Hz, 1H), 2.71 (m, 1H), 1.80 (s, 3H), 1.67(s, 3H), 1.25 (t, *J* = 7.3, 3H), 1.03 (s, 9H), 0.77 (d, *J* = 6.8, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 168.0, 145.4, 144.5, 136.2, 136.1, 135.6, 135.5, 133.9, 133.8, 133.7, 129.5, 129.4, 127.5, 127.2, 113.9, 81.5, 60.2, 38.2, 27.0, 19.4, 17.5, 15.9, 14.2, 12.5; FTIR (thin film/NaCl): 3071.9, 2961.1, 2931.3, 2892.3, 2857.8, 1710.4, 1472.3, 1427.7, 1390.3, 1365.8, 1289.2, 1265.5, 1226.8, 1112.1



(*E*)-**227**

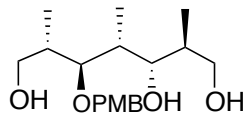
(4*R*,5*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-2,4,6-trimethylhepta-2,6-dien-1-ol - To a solution of (*E*)-**226** (332 mg, 0.74 mmol) in 15 mL dry CH_2Cl_2 cooled to -78°C, was added DIBAL-H (1M in heptane, 1.8 mL, 1.8 mmol, 2.5 eq) dropwise. The reaction was stirred for 2.5 hrs whereupon TLC analysis indicated the reaction of complete. The reaction was quenched with MeOH at -78°C, let warm to 0°C and added 10% Rochelle's salt. The mixture was stirred vigorously at room temperature overnight. The heterogeneous mixture was extracted with diethyl ether and the resulting solution was washed organics with brine and dried over $MgSO_4$. Purification via flash chromatography (15% EA:H) afforded alcohol (190.3 mg, 63% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.67 (m, 4H), 7.46-7.36 (m, 6H), 4.98 (d, *J* = 9.7 Hz, 1H), 4.80 (s, 1H), 4.70 (s, 1H), 3.93 (d, *J* = 8.2 Hz, 1H), 3.79 (s, 2H), 2.64 (m, 1H), 1.78 (s, 3H), 1.61 (s, 3H), 1.07 (s, 9H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 145.2, 136.1, 135.9, 134.5, 134.1, 133.7, 130.1, 129.4, 129.3, 127.2, 127.1113.3, 82.0,

68.8, 65.7, 36.8, 26.9, 19.3, 17.3, 16.7, 15.1, 13.6; FTIR (thin film/NaCl): 3336.0, 3071.4, 3049.1, 3013.2, 2960.5, 2930.3, 2857.5, 1649.2, 1589,5, 1472.3, 1427.6, 1389.7, 1373.1



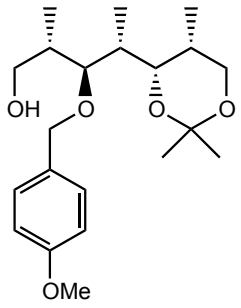
210

(2*R*,3*S*,4*R*,5*S*,6*S*)-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptane-1,3,7-triol - To a solution of (*Z*)-**194** (350 mg, 1.2 mmol) and 6 mL dry THF, cooled to -78°C was added freshly prepared thexylborane (0.5 M, 5.3 mL, 2.6 mmol, 2.2 eq) all at once. The reaction was slowly warmed to room temperature and stirred overnight. The mixture was quenched with 8 mL each of 3N NaOH followed by 35% H_2O_2 and let stir for 2 hrs. The heterogenous mixture was extracted with ethyl acetate and the resulting solution was washed with brine and dried over $MgSO_4$. Purification by flash chromatography (2:1 EA:H) afforded triol (354 mg, 90%, 13:1 diastereoselectivity) as a colorless, viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.56 (dd, *J* = 10.4, 3.4 Hz, 2H), 3.84 (d, *J* = 6.4 Hz, 1H), 3.76 (s, 3H), 3.66 (m, 2H), 3.51 (dq, *J* = 5.0, 5.0 Hz, 2H), 3.43 (dd, *J* = 5.3, 3.0 Hz, 1H), 3.32 (bs, 1H), 2.63 (bs, 1H), 2.48 (bs, 1H), 1.96 (m, 2H), 1.75 (m, 1H), 1.09 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 159.3, 129.7, 129.5, 113.9, 88.5, 75.6, 72.5, 65.6, 65.4, 55.1, 38.5, 37.8, 36.1, 14.7, 13.4, 12.2; FTIR (thin film/NaCl): 3394.1, 2964.6, 2930.7, 2878.0, 1612.6, 1586.0, 1514.6, 1462.8, 1346.9, 1249.5; HRMS-ESI *m/z* calcd. for C18H30O5 327.2171; found 327.2170



212

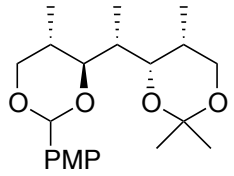
(2*S*,3*S*,4*R*,5*S*,6*S*)-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptane-1,3,7-triol. See representative cyclic hydroboration procedure. Purification via column chromatography (2:1 EA:H) afforded triol (23 mg, 23% yield, 5.8:1 dr) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.58 (m, 2H), 3.84 (d, *J* = 8.9 Hz, 1H), 3.77 (s, 3H), 3.74 (m, 1H), 3.68 (dd, *J* = 10.7, 4.5 Hz, 1H), 3.60 (m, 2H), 3.49 (dd, *J* = 8.8, 2.6 Hz, 1H), 2.00 (m, 1H), 1.85 (m, 2H), 1.10 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 159.4, 129.6, 129.5, 113.9, 88.2, 76.7, 76.0, 68.9, 65.2, 55.1, 37.8, 37.1, 35.4, 14.6, 13.2, 11.5; FTIR (thin film/NaCl): 3404.2, 2964.7, 2933.5, 2875.4, 1691.2, 1612.6, 1586.0, 1514.5, 1463.1, 1420.7, 1251.1, 1174.1, 1034.5; HRMS-ESI *m/z* calcd. for C18H30O5 327.2171; found 327.2174



215

(2*S*,3*S*,4*S*)-3-((4-methoxybenzyl)oxy)-2-methyl-4-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl)pentan-1-ol - To a solution of **210** (87 mg, 0.26 mmol) in 2,2-dimethoxypropane (3.5 mL, neat) was added a catalytic amount of PTSA. The mixture was stirred at room temperature for 1.5 hrs, diluted with CH_2Cl_2 and quenched with sat'd $NaHCO_3$. The heterogeneous mixture was extracted with CH_2Cl_2 and the resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via column chromatography (20% EA:H) afforded acetonide (62.5 mg, 65% yield) a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.61 (d, *J*

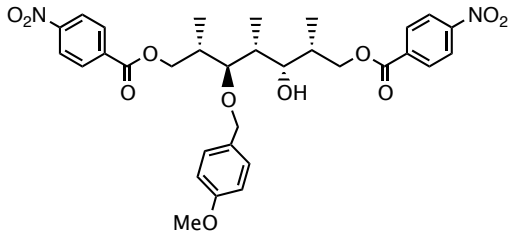
= 10.7 Hz, 1H), 4.36 (d, *J* = 10.7 Hz, 1H), 4.04 (dd, *J* = 11.2, 2.4 Hz, 1H), 3.86 (dd, *J* = 8.7, 2.2 Hz, 1H), 3.79 (s, 3H), 3.72 (m, 1H), 3.56 (m, 2H), 3.37 (m, 1H), 2.90 (s, 1H), 2.08 (m, 1H), 1.88 (m, 1H), 1.50 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.14 (d, *J* = 6.8, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 159.3, 129.9, 129.2, 113.8, 98.7, 84.7, 72.7, 72.3, 67.0, 66.7, 55.1, 37.1, 36.3, 31.3, **29.6**, **18.9**, 16.2, 11.8, 11.0; FTIR (thin film/NaCl): 3459.4, 2990.7, 2963.4, 2933.5, 2876.5, 1612.9, 1586.3, 1514.3, 1463.1, 1379.0, 1247.6



218

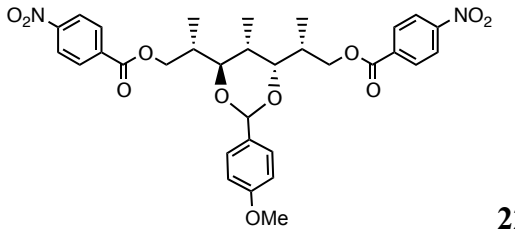
(4*S*,5*R*)-4-((1*S*)-1-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethyl)-2,2,5-trimethyl-1,3-dioxane - To a vial containing **215** (29 mg, 0.079 mmol) in CH_2Cl_2:pH = 7 phosphate buffer (4.0:0.5 mL respectively), was added DDQ (26.9 mg, 0.12 mmol, 1.5 eq). Upon consumption of starting material (2.5 hrs) via TLC analysis, the reaction was quenched with sat'd $NaHCO_3$. The heterogeneous mixture was diluted with CH_2Cl_2 and the resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via flash chromatography (20% to 70% EA:H) afforded PMP-acetal (18.5 mg, 64% yield) as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.39 (s, 1H), 4.07 (m, 2H), 3.96 (d, *J* = 9.2 Hz, 1H), 3.80 (s, 3H), 3.58 (d, *J* = 11.2 Hz, 1H), 3.41 (m, 2H), 2.05 (m, 1H), 1.99 (m, 1H), 1.74 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.3, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 159.8 131.3, 127.3, 113.5, 101.3, 98.9, 85.1, 73.2, 72.9, 67.1, 55.3, 37.7, 31.7, 31.0, 29.8, 19.0, 14.3, 12.7, 10.9;

FTIR (thin film/NaCl): 2988.7, 2962.7, 2935.4, 2876.1, 2837.5, 1615.6, 1518.5, 1461.5, 1381.9, 1248.5, 1115.5



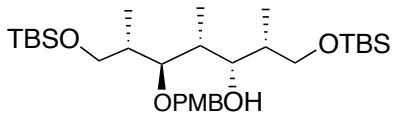
219

(2*R*,3*S*,4*R*,5*S*,6*S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptane-1,7-diyl bis(4-nitrobenzoate) - To a solution of **210** (58 mg, 0.18 mmol) in CH_2Cl_2 (3.5 mL) cooled to 0°C, was added pyridine (356 µL, 35 mg, 0.44 mmol, 2.5 eq), DMAP (6.1 mg, 0.05 mmol, 0.3 eq), 4-nitrobenzoic acid (65.2 mg, 0.39 mmol, 2.2 eq) and DCC (80.5 mg, 0.39 mmol, 2.2 eq) consecutively. The reaction as warmed to room temperature and stirred for 4 hrs. Upon consumption of starting material via TLC analysis, the mixture was diluted with ether and filtered. The organic solution was washed with sat'd $NaHCO_3$, brine and dried over $MgSO_4$. Purification via flash chromatography (5% EA:H) afforded di-PNB ether (60.6 mg, 52% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27-8.13 (m, 8H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 4.60 (d, *J* = 10.7, 1H), 4.52 (m, 2H), 4.40 (dd, *J* = 10.7, 6.0 Hz, 1H), 4.33 (dd, *J* = 11.2, 4.3 Hz, 1H), 4.20 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.91 (d, *J* = 8.7, 1H), 3.76 (s, 3H), 3.50 (dd, *J* = 8.2, 3.4 Hz, 1H), 3.29 (s, 1H), 2.33 (m, 1H), 2.11 (m, 1H), 2.01 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H), 1.18 (d, *J* = 6.8, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 164.6 164.5, 150.5, 135.4, 135.3, 130.6, 130.5, 129.4, 123.6, 123.5, 113.9, 86.2, 75.9, 71.6, 67.8, 67.6, 55.1, 49.0, 36.1, 35.9, 35.7, 15.0, 14.5, 11.8; FTIR (thin film/NaCl): 3473.7, 3110.1, 3079.3, 2967.3, 2932.0, 1723.8, 1610.1, 1529.5, 1463.9, 1349.3, 1276.5, 1103.1, 719.8



220

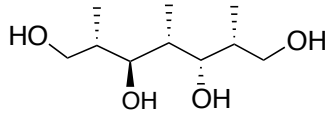
(2*R*,3*S*,4*R*,5*S*,6*S*)-3,5-((4-methoxybenzylidine)-2,4,6-trimethylheptane-1,7-diyl bis(4-nitrobenzoate) - To a solution of **219** (55 mg, 0.083 mmol) in CH_2Cl_2 (1.5 mL) was added $NaSO_4$ (55 mg, 0.083 mmol, 1 eq) and stirred for 20 min at room temperature. DDQ (21 mg, 0.093 mmol, 1.1 eq) was added whereupon the mixture turned black immediately. The reaction was stirred for 6 hrs then diluted with ether. The resulting organic solution was washed with sat'd $NaHCO_3$ (3x) and dried over $MgSO_4$. Purification via column chromatography (20% EA:H) afforded PMP-ether (7.5 mg, 14% yield) as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.14 (m, 8H), 7.38 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.3, 2H), 5.75 (s, 1H), 4.56 (dd, *J* = 10.7, 4.8 Hz, 1H), 4.39 (m, 2H), 4.17 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.86 (dd, *J* = 10.0, 3.4 Hz, 1H), 3.80 (s, 3H), 3.46 (t, *J* = 6.0 Hz, 1H), 2.28-2.19 (m, 3H), 1.18 (d, *J* = 6.8 Hz, 6H), 1.13 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 164.6, 159.7, 150.5, 135.5, 135.3, 132.0, 130.6, 130.5, 127.1, 123.6, 123.5, 113.4, 97.9, 82.5, 77.1, 71.0, 67.4, 67.1, 55.2, 37.0, 35.6, 33.3, 14.8, 14.1, 13.9; FTIR (thin film/NaCl): 2967.7, 2935.2, 1724.1, 1609.8, 1527.5, 1348.7, 1275.2, 1102.3



221

(6*R*,7*S*,8*R*,9*S*,10*S*)-9-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,10,13,13,14,14-undecamethyl-4,12-dioxa-3,13-disilapentadecan-7-ol - To a solution of **210** (51 mg, 0.156 mmol) in DCM (6 mL) was added 2,6-Lutidine (45 μL, 41.7 mg, 0.39 mmol, 2.5

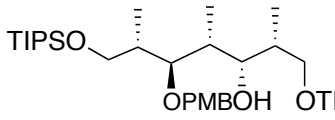
eq) at room temperature. The mixture was cooled to -78°C and a solution of TBS-OTf in DCM (0.5 mL) was added dropwise slowly. Upon consumption of starting material (1 hr) via TLC, the reaction was quenched with sat'd $NaHCO_3$ and allowed to warm to room temperature slowly. The heterogeneous mixture was diluted with DCM and the resulting organic solution was washed with 10% citric acid, sat'd $NaHCO_3$, brine and dried over $MgSO_4$. Purification via a pad of silica (5% EA:H) afforded disilyl ether X (48 mg, 55% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.55 (abq, *J* = 19.5, 7.4 Hz, 2H), 3.81 (m, 2H), 3.78 (s, 3H), 3.62 (dd, *J* = 9.7, 3.0 Hz, 1H), 3.53-3.44 (m, 3H), 2.05-1.93 (m, 2H), 1.70 (m, 1H), 1.10 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.92 (m, 12H), 0.87 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 130.5, 129.3, 113.8, 86.8, 75.5, 72.5, 65.6, 64.7, 55.2, 38.6, 38.4, 34.9, 26.0, 25.9, 18.3, 18.2, 14.7, 14.2, 12.3, -5.30, -5.43, -5.46, -5.50.



222

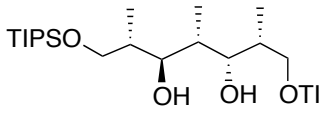
(2*R*,3*S*,4*R*,5*S*,6*S*)-2,4,6-trimethylheptane-1,3,5,7-tetraol - A 3-neck flask containing a solution of **221** (44 mg, 0.08 mmol), Pd(OH)/C (16.8 mg, 0.024, 0.3 eq) in MeOH (5 mL) was evacuated under vacuum and then filled with hydrogen gas via balloon. The flask was evacuated and filled in this manner three times and stirred overnight at room temperature. Upon consumption of starting material (16 hr) via TLC analysis, the mixture was filtered through a pad of celite and concentrated in vacuo to afford crude tetrol (15.4 mg, Quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (d, *J* = 7.5 Hz, 1H), 3.80 (dd, *J* = 10.7, 3.3 Hz, 1H), 3.61 (m, 4H), 2.01 (m, 3H), 1.83 (m, 2H), 1.10 (d, *J* = 7.1

Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 84.0, 73.3, 69.1, 65.9, 38.6, 37.4 35.4, 29.7, 13.5, 13.3, 11.5



223

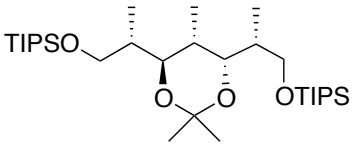
(6*R*,7*S*,8*R*,9*S*,10*S*)-3,3,13,13-tetraisopropyl-9-((4-methoxybenzyl)oxy)-2,6,8,10,14-pentamethyl-4,12-dioxa-3,13-disilapentadecan-7-ol - To a solution of **210** (85 mg, 0.26 mmol) in DCM (2 mL) was added imidazole (53 mg, 0.78 mmol) and TIPS-Cl (106 mg, 0.55 mmol, 117 μL, 2.1 eq) successively. Upon consumption of starting material (12 hr) via TLC analysis, the mixture was diluted with water and extracted with DCM. The resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via column chromatography (20%EA:H) afforded an inseparable mixture of TIPS-ether and TIPS-OH (129 mg, 77% yield) as a colorless oil. The presence of the TIPS-OH did not affect the subsequent transformation and was used as such. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.54 (d, *J* = 2.7 Hz, 2H), 3.81 (d, *J* = 5.0 Hz, 2H), 3.78 (s, 3H), 3.57 (m, 2H), 3.45 (dd, *J* = 9.0, 1.9 Hz, 1H), 2.05 (m, 3H), 1.75 (m, 2H), 1.11 (d, *J* = 7.1 Hz, 3H), 1.04 (m, 95H), 0.96 (d, *J* = 9.2 Hz, 3H); FTIR (thin film/NaCl): 3448.2, 2942.4, 2863.7, 1613.8, 1514.9, 1465.1, 1383.1, 1249.9, 1067.0



224

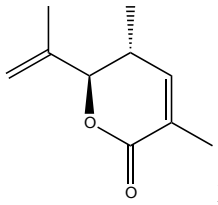
(6*R*,7*S*,8*R*,9*S*,10*S*)-3,3,13,13-tetraisopropyl-2,6,8,10,14-pentamethyl-4,12-dioxa-3,13-disilapentadecane-7,9-diol - A flask containing crude **223** (52 mg, 0.08 mmol), $Pd(OH)_2$/C (28.5 mg, 0.04 mmol, 0.5 eq) in dry ethyl acetate (4 mL), was evacuated under vacuum and subsequently filled with hydrogen gas from a balloon. The flask was

evacuated and filled in this manner three times at room temperature. Upon consumption of starting material (1 hr) via TLC analysis, the mixture was filtered through a pad of celite and concentrated in vacuo. Purification via column chromatography (20% EA:H → 50% EA:H) to afford a mixture diol (20.4 mg, 44% yield) and TIPS-OH. The crude mixture was used as such in the following reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (m, 2H), 3.69-3.59 (m, 4H), 2.08 (m, 1H), 1.96 (m, 1H), 1.79 (m, 1H), 1.07 (m, 93H), 0.77 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.0, 73.0, 66.3, 39.1, 37.2, 35.7, 18.0, 17.9, 17.7, 14.2, 13.9, 12.2, 11.9, 11.6, 11.5



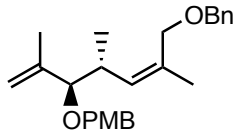
225

(6*R*,7*S*,8*R*,9*S*,10*S*)-3,3,13,13-tetraisopropyl-2,6,8,10,14-pentamethyl-4,12-dioxa-3,13-disilapentadecane-3,5-acetonide - To a solution of crude **224** (20.4 mg, 0.035 mmol) in 2,2-dimethoxypropane (4 mL) was added a catalytic amount of PTSA. The mixture was stirred overnight at room temperature, whereupon TLC analysis confirmed the consumption of starting material. The mixture was diluted with DCM and the resulting organic solution was washed with sat'd $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated in vacuo to afford crude acetonide (9.4 mg, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.64-3.53 (m, 3H), 3.48 (s, 0.5H), 3.32 (s, 1H), 3.29 (m, 1H), 1.90 (m, 1H), 1.76 (m, 2H), 1.41 (m, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.04 (m, 54H), 0.95 (d, *J* = 6.8, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.3, 75.8, 71.1, 64.7, 40.6, 35.6, 35.1, **25.3**, **23.5**, 18.0, 17.7, 14.5, 13.3, 13.0, 12.2, 12.0, 11.9



230

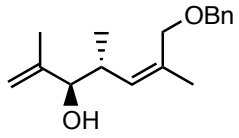
(5*R*,6*R*)-3,5-dimethyl-6-(prop-1-en-2-yl)-5,6-dihydro-2*H*-pyran-2-one - To a crude mixture of **228** and **229** (807 mg, 3.8 mmol) in 20 mL MeOH cooled to 0°C, was added $NaBH_4$ (287 mg, 7.6 mmol, 2 eq) in one portion slowly. The mixture was slowly warmed to room temperature and stirred overnight. Upon consumption of starting material via TLC analysis, the mixture was quenched with acetone and the volitiles were evaporated. Purification via flash chromatography (10% EA:H) afforded lactone (226.4 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.97 (s, 1H), 4.94 (s, 1H), 4.34(d, *J* = 10.9 Hz, 1H), 2.58 (m, 1H), 1.84 (s, 3H), 1.72 (s, 3H), 0.94 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 165.4, 145.6, 140.1, 126.9, 116.6, 87.9, 31.0, 16.9, 16.6, 15.7; FTIR (thin film/NaCl): 3081.1, 2975.5, 2927.1, 2888.5, 1712.9, 1653.3, 1453.5, 1362.3, 1223.9, 1131.5



(*Z*)-**232**

1-((((3*R*,4*R*,*Z*)-7-(benzyloxy)-2,4,6-trimethylhepta-1,5-dien-3-yl)oxy)methyl)-4-methoxybenzene -To a solution of (*Z*)-**209** (181.7 mg, 0.63 mmol) in dry THF (3 mL) cooled to 0°C was added 95% NaH (47 mg, 1.89 mmol, 3 eq). The mixture was stirred for 5 min then BnBr (186 μL, 266.8 mg, 1.56 mmol, 2.5 eq) was added and the reaction was stirred overnight at room temperature. Upon consumption of starting material via TLC analysis, water was added and the reaction was extracted with ethyl ether. The organic solutions were combined and washed with brine and dried over $MgSO_4$.

Purification via a pad of silica (hexanes) afforded slightly crude benzyl ether (154 mg, 64% yield) as a colorless oil. This material was used as such in following reactions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 5H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.7, 2H), 5.27 (d, *J* = 9.7 Hz, 1H), 5.08 (s, 1H), 4.94 (s, 1H), 4.50 (s, 2H), 4.47 (s, 1H), 4.20 (m, 2H), 4.05 (d, *J* = 11.7 Hz, 1H), 3.83 (s, 3H), 3.41 (d, *J* = 8.2 Hz, 1H), 2.68 (m, 1H), 1.90 (s, 3H), 1.73 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 158.8, 143.3, 138.8, 133.2, 132.0, 131.0, 129.0, 128.1, 127.7, 127.3, 115.1, 113.4, 87.2, 71.2, 69.4, 68.9, 55.1, 34.6, 21.5, 17.8, 16.7; FTIR (thin film/NaCl): 3066.0, 3031.1, 2965.7, 2931.4, 2859.6, 1612.4, 1586.0, 1513.5, 1453.6, 1373.7, 1247.8 1070.8

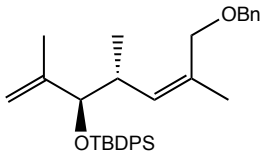


(*Z*)-**234**

(3*R*,4*R*,*Z*)-7-(benzyloxy)-2,4,6-trimethylhepta-1,5-dien-3-ol - To a solution of (*Z*)-**232** (683 mg, 1.79 mmol) in an 8:1 mixture of CH_2Cl_2:pH = 7.2 Buffer (40:5 mL respectively) at room temperature, was added DDQ (611 mg, 2.7 mmol, 1.5 eq). Upon consumption of starting material (2 hrs) via TLC analysis, the mixture was quenched sat'd $NaHCO_3$. The heterogeneous mixture was diluted with CH_2Cl_2 and the resulting organic solution was washed with brine and dried over $MgSO_4$. The isolated crude (661 mg) was a mixture of the deprotected alcohol and anisaldehyde as an inseparable mixture that was carried through to the next step and characterized.

To a solution of crude alcohol/anisaldehyde mixture (661 mg, 2.54 mmol) in MeOH (15 mL) cooled to 0°C, was added $NaBH_4$ (100 mg, 2.64 mmol, 1.05 eq) in 3 portions. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with acetone and the volatiles were evaporated. The crude was diluted with

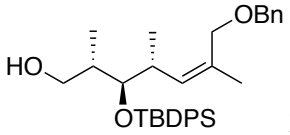
ethyl acetate, washed with water, brine and dried over $MgSO_4$. Purification via flash chromatography (10% EA:H) afforded alcohol (277.9 mg, 60% yield, <4% anisaldehyde present) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 5.23 (d, *J* = 10.2 Hz, 1H), 4.89 (m, 2H), 4.52 (s, 2H), 4.07 (d, *J* = 10.7 Hz, 1H), 3.91 (d, *J* = 10.7 Hz, 1H), 3.62 (dd, *J* = 9.0, 2.7 Hz, 1H), 2.54-2.48 (m, 2H), 1.85 (d, *J* = 1.0 Hz, 3H), 1.67 (s, 3H), 0.84 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 145.1, 137.9, 134.5, 132.5, 128.3, 127.8, 127.6, 113.8, 80.1, 72.4, 68.8, 36.3, 22.6, 17.6, 16.3; FTIR (thin film/NaCl): 3446.1, 3067.1, 3030.8, 2969.2, 2925.9, 2868.9, 1453.7, 1373.9, 1069.5



(*Z*)-**235**

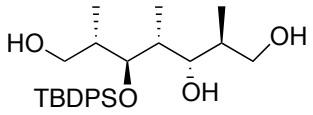
(((3*R*,4*R*,*Z*)-7-(benzyloxy)-2,4,6-trimethylhepta-1,5-dien-3-yl)oxy)(*tert*-butyl)diphenylsilane - To a solution of (*Z*)-**235** (275 mg, 1.05 mmol) in THF (10 mL) cooled to 0°C was added DBU (384mg, 3.15 mmol, 381 µL, 3 eq), silver nitrate (356 mg, 2.1 mmol) and TBDPS-Cl (989.4 mg, 2.6 mmol, 933 µL, 2.5 eq) successively. The mixture was refluxed at 80°C for 2 days then allowed to cool before water was added to quench the reaction. The heterogeneous mixture was diluted with ethyl acetate and the resulting organic solution was washed with 10% NaOH, brine and dried over $MgSO_4$. Purification via column chromatography afforded silyl ether (258.7 mg, 99% adjusted) as a colorless oil and recovered starting material (139.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 5H), 7.36 (m, 10H), 5.01 (d, *J* = 9.8 Hz, 1H), 4.68 (s, 1H), 4.58 (s, 1H), 4.38 (dd, *J* = 11.8, 5.9 Hz, 2H), 4.02 (d, *J* = 11.5 Hz, 1H), 3.82 (d, *J* = 7.4 Hz, 1H), 3.78 (d, *J* = 11.5 Hz, 1H), 2.56 (m, 1H), 1.67 (s, 3H), 1.62 (s, 3H), 1.02 (s, 9H), 0.72 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 145.0, 138.7, 136.2, 136.1, 134.3, 134.1, 133.6,

131.7, 129.4, 128.3, 127.6, 127.4, 127.3, 127.2, 113.5, 81.7, 71.4, 68.9, 37.0, 27.0, 21.6, 19.4, 17.8, 17.4; FTIR (thin film/NaCl): 3070.9, 3048.5, 2959.9, 2930.8, 2856.9, 1472.0, 1454.0, 1427.7, 1373.4, 1260.9, 1111.5, 1065.1, 700.5



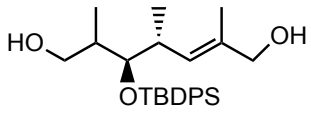
235a

(2*S*,3*R*,4*R*,*Z*)-7-(benzyloxy)-3-((*tert*-butyldiphenylsilyl)oxy)-2,4,6-trimethylhept-5-en-1-ol - See representative cyclic hydroboration procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.35 (m, 11H), 5.29 (d, *J* = 6.4 Hz, 1H), 4.24 (abq, 24.4, 12.0 Hz, 2H), 3.65 (m, 3H), 3.54 (dq, *J* = 11.1, 5.2 Hz, 2H), 2.58 (m, 1H), 2.16 (s, 2H), 1.85 (m, 1H), 1.67 (s, 4H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); FTIR (thin film/NaCl): 3431.7, 3070.2, 3046.1, 3026.9, 2961.4, 2930.6, 2856.9, 1472.3, 1453.75, 1427.4, 1110.4, 1026.8, 702.4



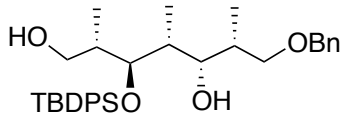
236

(2*S*,3*S*,4*R*,5*S*,6*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-2,4,6-trimethylheptane-1,3,7-triol - The second to elute was cyclic hydroboration product (25.3 mg, 12% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.63 (m, 4H), 7.45-7.32 (m, 6H), 4.35 (dd, *J* = 3.4, 1.9 Hz, 1H), 3.57 (dd, *J* = 11.1, 3.0 Hz, 1H), 3.34 (m, 3H), 3.13 (t, *J* = 9.8 Hz, 1H), 1.95-1.85 (m, 2H), 1.60 (m, 1H), 1.10 (s, 9H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 136.2, 136.1, 134.7, 134.6, 129.8, 129.7, 127.5, 78.9, 77.2, 72.5 66.7, 64.4, 42.4, 36.1, 34.9, 27.2, 19.6, 15.7, 12.8, 11.4; FTIR (thin film/NaCl): 3357.7, 3071.3, 3048.8, 2961.8, 2931.5, 2857.7, 1472.3, 1427.4, 1389.6, 1110.8, 1037.9, 821.4, 740.1, 702.9



237

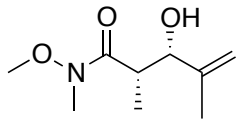
(4*R*,5*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-2,4,6-trimethylhept-2-ene-1,7-diol - See representative cyclic hydroboration procedure. Purification via column chromatography (25% EA:H) afforded two major compounds. The first to elute was monohydroborated product (35.1 mg, 17 % yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.69 (m, 4H), 7.45-7.37 (m, 6H), 5.22 (dd, *J* = 9.2, 1.0 Hz, 1H), 3.75 (s, 2H), 3.71 (t, *J* = 4.6 Hz, 1H), 3.64 (m, 2H), 2.59 (m, 1H), 1.88 (m, 1H), 1.38 (d, *J* = 0.9 Hz, 3H), 1.05 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 136.1, 136.0, 134.4, 133.9, 133.2, 129.8, 129.5, 129.1, 127.6, 127.3, 80.8, 77.1, 68.7, 65.3, 38.4, 36.6, 27.1, 19.8, 17.3, 15.5, 13.5; FTIR (thin film/NaCl): 3373.5, 3071.4, 3048.9, 2961.3, 2931.1, 2857.8, 1472.5, 1461.8, 1427.4, 1389.3, 1110.4, 1025.6, 821.3, 740.2, 703.1



238

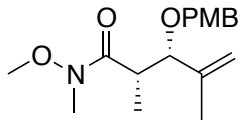
(2*S*,3*S*,4*R*,5*S*,6*R*)-7-(benzyloxy)-3-((*tert*-butyldiphenylsilyl)oxy)-2,4,6-trimethylheptane-1,5-diol - See representative cyclic hydroboration procedure. Purification via column chromatography (15% EA:H) afforded diol (35.4 mg, 32% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.41-7.28 (m, 11H), 4.91 (s, 1H), 4.45(abq, *J* = 12.0, 6.6 Hz, 2H), 4.12 (s, 1H), 3.90 (d, *J* = 8.7 Hz, 1H), 3.76 (dd, 10.2, 4.0 Hz, 1H), 3.65 (m, 2H), 3.38 (d, *J* = 4.8 Hz, 2H), 2.12 (m, 1H), 1.92 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 0.63 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 138.4, 135.5, 132.4, 132.2, 130.1, 130.0, 128.2, 127.9, 127.8, 127.5, 127.4, 83.7, 73.3, 73.2, 73.0, 70.7, 37.2, 37.0, 35.3, 26.7, 19.0, 14.8, 12.8,

11.3; FTIR (thin film/NaCl): 3427.3, 3068.2, 3047.8, 2961.2, 2930.9, 2857.7, 1471.5, 1454.8, 1427.8, 1390.5, 1361.7, 1112.3, 1070.2



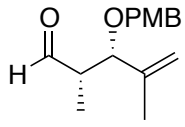
243

(2*S*,3*S*)-3-hydroxy-*N*-methoxy-*N*,2,4-trimethylpent-4-enamide - To a solution of Weinreb amide reagent (563 mg, 5.77 mmol, 2 eq) in DCM (10 mL) cooled to <0°C (ice/brine), was added trimethylaluminum (2M in toluene, 2.88 mL, 5.77 mmol, 2 eq) very slowly. A vigorous exotherm was observed and the mixture was stirred for 30 min at room temperature. The mixture was subsequently cooled down to <0°C and a solution of oxazolidinone **244a** (875 mg, 2.8 mmol) in DCM (5 mL + 2 mL rinse) was added dropwise slowly. The mixture was stirred overnight and subsequently transferred via cannula to a flask containing 1M tartaric acid (15 mL). The heterogeneous mixture was stirred for 1 hr, diluted with DCM and the resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via flash chromatography (2:1 H:EA) afforded Weinreb amide (416 mg, 80% yield) as a white crystalline solid. This compound is in agreement with literature precedent.[17] $[\alpha]^{22} = +13.5$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.79 (s, 1H), 4.15 (s, 1H), 4.02 (s, 1H), 3.58 (s, 3H), 3.06 (s, 3H), 2.94 (bs, 1H), 1.57 (s, 3H), 0.96 (dd, J = 6.8, 2.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 143.2, 111.3, 73.9, 61.1, 36.4, 31.5, 29.2, 18.9, 9.9; FTIR (thin film/NaCl): 3354.6 2998.4, 2980.5, 2935.9, 2917.6, 2871.4, 1132.6, 1466.6, 1372.4, 1311



245

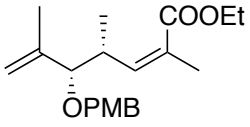
(2*S*,3*S*)-*N*-methoxy-3-((4-methoxybenzyl)oxy)-*N*,2,4-trimethylpent-4-enamide - To a solution of **243** (70 mg, 0.37 mmol) in DCM (2.2 mL) was added PMB-imidate (209 mg, 0.74 mmol, 154 μL, 2 eq) and CSA (21 mg, 0.09 mmol, 0.25 eq) successively. Upon consumption of starting material (12 hrs) via TLC analysis, 10% NaOH was added to quench the mixture. The heterogeneous mixture was diluted with water and extracted with DCM. The resulting organic solutions were combined and washed with 10% NaOH (x2) then concentrated in vacuo. Purification via column chromatography (20% EA:H) afforded PMB-ether (65.4 mg, 58% yield) as a colorless oil. PMB-ether is known and is agreement with literature precedent.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.00 (d. *J* = 4.6 Hz, 2H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.20 (d, *J* = 11.1 Hz, 1H), 3.91 (d, *J* = 9.5 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.27 (s, 1H), 3.12 (s, 3H), 1.74 (s, 3H), 1.27 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 159.0, 142.7, 130.4, 129.4, 115.5, 113.6, 84.1, 69.9, 61.3, 55.1, 38.9 32.0, 17.0, 14.8



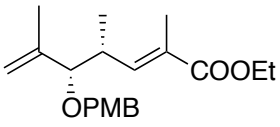
246

(2*S*,3*S*)-3-((4-methoxybenzyl)oxy)-2,4-dimethylpent-4-enal - To a solution of **245** (62 mg, 0.20 mmol) in THF (1 mL) cooled to -78°C was added DIBAL-H (1M in hexane, 300 μL, 0.30 mmol, 1.5 eq) dropwise slowly. Upon consumption of starting material (1.5 hrs) via TLC analysis, the reaction was quenched with MeOH slowly at -78°C. The mixture was warmed to 0°C, whereupon 10% Rochelle's salt was added and stirred vigorously for 1 hr. The heterogeneous mixture was extracted with ether and the resultant organic solutions were washed with brine and dried over $MgSO_4$. Purification via flash chromatography (50% DCM:Hexanes) to afford a mixture of desired aldehyde

(50.9 mg, 88%) and C2 epimerized aldehyde (10%) as a colorless oil. The epimerized diastereomer was removed in the subsequent step. Aldehyde **246** has been previously made and is in agreement with literature precedent.[18] $[\alpha]^{D,23}$ = -29.1 (*c* = 0.22 in DCM) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 1.8 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.05 (abq, *J* = 37.0, 16.6 Hz, 2H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.20 (d, *J* = 11.4 Hz, 1H), 4.01 (d, *J* = 6.3 Hz, 1H), 3.80 (s, 3H), 2.56 (m, 1H), 1.72 (s, 3H), 1.10 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ (minor isomer in parenthesis) (204.4), 203.6, 159.1, 141.6, (130.0), 129.3, 114.8, 113.7, (83.7), 81.4, 69.8, (69.5), 55.2, 49.0, (48.0), 18.0, (16.1), (10.7), 9.19; FTIR (thin film/NaCl): 3073.4, 2973.4, 2937.0, 2867.4, 2837.3, 1727.5, 1612.5, 1514.3, 1456.4, 1248.8, 1066.6



ent-(*Z*)-**248 and**

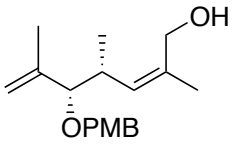


ent-(*E*)-**248**

(4*R*,5*S*,*Z*)-ethyl 5-((4-methoxybenzyl)oxy)-2,4,6-trimethylhepta-2,6-dienoate and **(4*R*,5*S*,*E*)-ethyl 5-((4-methoxybenzyl)oxy)-2,4,6-trimethylhepta-2,6-dienoate -** To a solution of triethyl-2-phosphonopropionate (638 mg, 2.67 mmol, 2 eq) in THF (50 mL) cooled to 0°C, was added 95% NaH (84.5 mg, 3.35 mmol, 2.5 eq) slowly. The mixture was removed from the ice bath and a solution of **246** (372 mg, 1.34 mmol) in THF (5 mL) was added dropwise slowly. Upon consumption of starting material via TLC analysis (0.5 hr), water was added to quench the mixture. The heterogeneous mixture was extracted with ether, washed with brine and dried over $MgSO_4$. Purification via column chromatography (5% EA:H) afforded enones *ent*-(*Z*)-**248** and *ent*-(*E*)-**248** (330 mg as a 3.6:1 mixture of *cis* and *trans* isomers, 74% combined yield) as a colorless oil. The first isomer to elute was *ent*-(*Z*)-**248**. $[\alpha]^{D,20}$ = -62.8 (*c* = 0.21 in DCM); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.64 (dd, *J* = 10.2, 1.3 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.19 (m, 3H), 3.82 (s, 3H), 3.47 (m, 1H), 1.86 (d, *J* = 1.2 Hz, 3H), 1.66 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 168.1, 159.0, 143.8, 143.6, 130.8, 129.3, 126.2, 114.0, 113.6, 86.5, 69.8, 60.1, 55.2, 36.1, 20.8, 17.2, 16.6, 14.2; FTIR (thin film/NaCl): 3067.8, 2979.6, 2929.1, 2868.1, 2836.6, 1713.0, 1651.1, 1612.0, 1514.1, 1455.9, 1372.1, 1248.6, 1217.4, 1172.5, 1095.8, 1035.7; HRMS-ESI *m/z* calcd. for C20H28O4 333.2066; found 333.2060

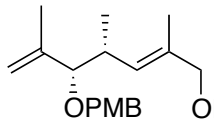
The second enone to elute was *ent*-(*E*)-**248**. $[\alpha]^{D,20}$ = -40.6 (*c* = 0.053 in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 10.3 Hz, 1H), 4.97 (s, 1H), 4.91 (s, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 4.15 (m, 3H), 3.79 (s, 3H), 3.51 (d, *J* = 8.5 Hz, 1H), 2.72 (m, 1H), 1.80 (s, 3H), 1.62 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 168.2, 159.1, 143.6, 143.0, 130.5, 129.4, 126.8, 115.1, 113.7, 86.3, 69.7, 60.4 55.2, 36.4, 16.9, 16.5, 14.2, 12.3; FTIR (thin film/NaCl): 2980.1, 2932.7, 2868.9, 1709.2, 1651.2, 1612.7, 1514.2, 1455.9, 1248.2, 1172.6, 1076.6; HRMS-ESI *m/z* calcd. for C20H28O4 333.2066; found 333.2076



ent-(*Z*)-**239**

(4*R*,5*S*,*Z*)-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylhepta-2,6-dien-1-ol - To a solution of *ent*-(*Z*)-**248** (209 mg, 0.63 mmol) in CH_2Cl_2 (20 mL) cooled to -78°C was added DIBAL-H (1M in hexane, 1.57 mL, 1.57 mmol, 2.5 eq) dropwise slowly. Upon consumption of starting material (1 hr) via TLC analysis, the mixture was quenched with MeOH and 10% Rochelle's salt then allowed to stir for 1 hr at room temperature. The

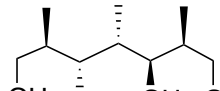
heterogeneous mixture was extracted with CH_2Cl_2 and the resulting organic solutions were washed with brine and dried over $MgSO_4$. Purification via Flash chromatography (15% EA:H) afforded alcohol (155 mg, 85% yield) as a colorless oil. $[\alpha]^{D,20}$ = -32.4 (*c* = 0.158 in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.02 (s, 1H), 4.98 (d, *J* = 10.1 Hz, 1H), 4.87 (s, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.17 (d, *J* = 11.3 Hz, 2H), 3.84 (d, *J* = 11.7 Hz, 1H), 3.79 (s, 3H), 3.50 (d, *J* = 7.0 Hz, 1H), 2.73 (m, 1H), 1.82 (s, 1H), 1.76 (s, 3H), 1.66 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 159.1, 143.1, 134.9, 130.5, 130.2, 129.6, 115.2, 113.7, 86.7, 69.9, 61.7, 55.2, 35.8, 21.9, 18.3, 18.1; FTIR (thin film/NaCl): 3396.5, 3070.7, 3034.1, 2965.8, 2867.5, 1612.8, 1586.2, 1514.1, 1455.1, 1372.9, 1302.0, 1247.6, 1173.1, 1036.1; HRMS-ESI *m/z* calcd. for C18H27O3 291.1960; found 291.1972



ent-(*E*)-**239**

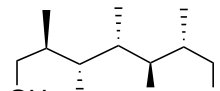
(4*R*,5*S*,*E*)-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylhepta-2,6-dien-1-ol - To a solution of *ent*-(*E*)-**248** (166 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) cooled to -78°C was added DIBAL-H (1M in hexane, 1.24 mL, 1.24 mmol, 2.5 eq) dropwise slowly. Upon consumption of starting material (1.5 hr) via TLC analysis, the mixture was quenched with MeOH and 10% Rochelle's salt then allowed to stir for 1 hr at room temperature. The heterogeneous mixture was extracted with CH_2Cl_2 and the resulting organic solutions were washed with brine and dried over $MgSO_4$. Flash chromatography (15% EA:H) afforded alcohol (89 mg, 61% yield) as a colorless oil. $[\alpha]^{D,21}$ = -76.4 (*c* = 0.088 in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.11 (dd, *J* = 9.8, 1.0 Hz, 1H), 4.95 (s, 1H), 4.85 (s, 1H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.15

(d, *J* = 11.4 Hz, 1H), 3.91 (s, 2H), 3.79 (s, 3H), 3.42 (d, *J* = 8.6 Hz, 1H), 2.60 (m, 1H), 1.63 (s, 6H), 1.03 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 159.0, 143.7, 134.1, 130.8, 129.4, 128.4, 114.6, 113.7, 867.2, 69.7, 68.7, 55.2, 35.1, 17.5, 17.0, 13.6; FTIR (thin film/NaCl): 3385.4, 3070.5, 2957.8, 2926.5, 2865.7, 1612.7, 1586.2, 1514.0, 1455.4, 1370.7, 1248.3, 1172.9, 1072.7, 1036.2, 821.5; HRMS-ESI *m/z* calcd. for C18H27O3 291.1960; found 291.1966



249

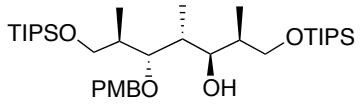
(2*S*,3*R*,4*R*,5*R*,6*R*)-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptane-1,3,7-triol - See representative cyclic hydroboration procedure. Purification via column chromatography (2:1 EA:H) afforded **245**(140 mg, 80%, 10:1 dr via NMR analysis) as a colorless oil. $[\alpha]^{D,21}$ = +4.18 (*c* = 0.11 in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.64 (d, *J* = 10.9 Hz, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 3.83-3.79 (m, 2H), 3.78 (s, 3H), 3.74 (m, 1H), 3.68 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.57 (dd, *J* = 11.0, 4.1 Hz, 1H), 2.94 (s, 3H), 1.98 (m, 1H), 1.78 (m, 2H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 159.3, 130.5, 129.5, 113.9, 82.9, 75.3, 73.8, 68.0, 66.7, 55.2, 37.9, 37.8, 35.8, 14.7, 10.8, 8.3; FTIR (thin film/NaCl): 3381.6, 2968.3, 2935.0, 2879.1, 2832.8, 1612.9, 1585.0, 1514.5, 1463.8, 1248.6, 1034.1; HRMS-ESI *m/z* calcd. for C18H31O5 327.2171; found 327.2180



251

(2*R*,3*R*,4*R*,5*R*,6*R*)-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptane-1,3,7-triol - See representative cyclic hydroboration procedure. Purification via column chromatography

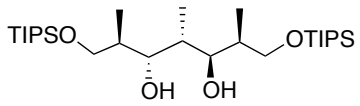
(2:1 EA:H) afforded triol (23 mg, 23% yield, >20:1 dr) as a colorless oil. $[\alpha]^{D,21}$ = -10.8 (*c* = 0.02 in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.5 Hz, 2H), 6.88 (d, *J* = 7.5 Hz, 2H), 4.62 (s, 2H), 3.87 (t, *J* = 8.5 Hz, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.50 (t, *J* = 6.0 Hz, 1H), 2.94 (bs, 3H), 2.00-1.94 (m, 3H), 1.00 (m, 6H), 0.93 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 159.4, 130.0, 129.6, 113.9, 82.4, 80.7, 73.5, 66.4, 66.0, 55.2, 38.1, 37.4, 36.3, 14.8, 14.6, 11.6; FTIR (thin film/NaCl): 3401.2, 2966.6, 2934.2, 2879.1, 1639.0, 1613.3, 1514.6, 1463.2, 1249.1, 1032.2; HRMS-ESI *m/z* calcd. for C18H31O5 327.2171; found 327.2173



254

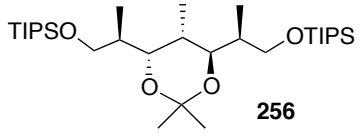
(6*S*,7*R*,8*R*,9*R*,10*R*)-3,3,13,13-tetraisopropyl-9-((4-methoxybenzyl)oxy)-2,6,8,10,14-pentamethyl-4,12-dioxa-3,13-disilapentadecan-7-ol - To a solution of **249** (50 mg, 0.153 mmol) in DCM (1 mL) was added imidazole (31.2 mg, 0.46 mmol, 3 eq) and TIPS-Cl (70.9 mg, 0.367 mmol, 78.7 μL, 2.4 eq) successively. Upon consumption of starting material (12 hr) via TLC analysis, the mixture was diluted with water and extracted with DCM. The resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via column chromatography (2% EA:H) afforded a slightly crude TIPS-ether **254** (73.6 mg, 75% yield) as a colorless oil. The slightly crude tips-ether was used as such in the following reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.67 (d, *J* = 11 Hz, 1H), 4.52 (d, *J* = 11 Hz, 1H), 3.89 (m, 3H), 3.83 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.79 (s, 3H), 3.74 (d, *J* = 9.8 Hz, 1H), 3.56 (dd, *J* = 9.2, 7.5 Hz, 1H), 1.89 (m, 1H), 1.77 (m, 2H), 1.05 (m, 41H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 158.9, 131.8,

129.3, 113.6, 79.2, 75.1, 74.1, 70.1, 66.2, 55.2, 39.5, 37.8, 35.7, 18.1, 18.0, 17.9, 14.2, 12.0, 11.8, 9.5, 8.9; FTIR (thin film/NaCl): 3501.1, 2941.9, 2865.6, 1613.8, 1514.2, 1463.3, 1384.0, 1247.5, 1066.1, 882.3.



255

(6*R*,7*R*,8*R*,9*R*,10*S*)-3,3,13,13-tetraisopropyl-2,6,8,10,14-pentamethyl-4,12-dioxa-3,13-disilapentadecane-7,9-diol - A flask containing crude **254** (59 mg, 0.09 mmol), $Pd(OH)_2/C$ (32 mg, 0.23 mmol, 0.5 eq) in dry ethyl acetate (5 mL), was evacuated under vacuum and subsequently filled with hydrogen gas from a balloon. The flask was evacuated and filled in this manner three times at room temperature. Upon consumption of starting material (1.5 hr) via TLC analysis, the mixture was filtered through a pad of celite and concentrated in vacuo to afford crude diol (44.3 mg, 85% crude yield) as a colorless oil. The crude mixture was used as such in the following reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97-3.73 (m, 6H), 1.89 (m, 1H), 1.80 (m, 1H), 1.71 (m, 1H), 1.07 (m, 39H), 0.89 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 76.0, 75.8, 70.6, 69.1, 37.5, 37.3, 37.0, 18.0, 17.9, 17.7, 12.7, 11.9, 11.8, 11.7, 10.3, 9.42; FTIR (thin film/NaCl): 3424.2, 2945.6, 2864.6, 1463.1, 1383.8, 1337.9, 1258.9, 1100.2, 882.1, 788.0.

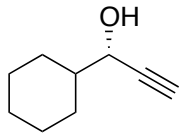


256

(6*R*,7*R*,8*R*,9*R*,10*S*)-3,3,13,13-tetraisopropyl-2,6,8,10,14-pentamethyl-4,12-dioxa-3,13-disilapentadecane-7,9-acetonide – To a solution of **255** (44 mg, 0.076 mmol) in 2,2-dimethoxypropane (4 mL) was added a catalytic amount of PTSA. The mixture was

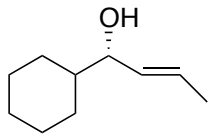
stirred overnight at room temperature. Upon consumption of starting material via TLC analysis, the mixture was diluted with DCM and washed with saturated $NaHCO_3$. The resulting organics were combined and washed with brine, dried over $MgSO_4$ and concentrated to afford crude acetonide (35 mg, 74% crude yield) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (dd, *J* = 7.5, 2.4 Hz, 1H), 3.65-3.48 (m, 5H), 1.83 (m, 1H), 1.69 (m, 2H), 1.28 (s, 3H), 1.26 (s, 3H), 1.05 (m, 39 H), 0.92 (d, *J* = 5.4 Hz, 3H), 0.88 (d, *J* = 5.5 Hz, 3H), 0.85 (d, *J* = 5.3 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 100.3, 73.6, 65.3, 65.0, 39.6, 35.8, 34.9, **25.2**, **23.6**, 18.1, 18.0, 13.1, 12.1, 12.0, 11.8, 10.7.

Experimentals of known compounds



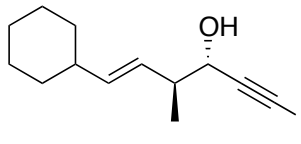
174

(*S*)-1-cyclohexylprop-2-yn-1-ol - To a 2L pressure vessel containing a solution of zinc triflate (71.3 g, 0.196 mol, 1.1 eq) in toluene (1.5 L), was added TEA (62 mL, 45 g, 0.445 mol, 2.5 eq) at room temperature and stirred for 1 hr. A solution of cyclohexane carboxyaldehyde (100 mL toluene) was added to the vessel and cooled to -78°C, at which time propyne (10.6 g, 0.267 mol, 1.5 eq) was added. The reaction was warmed to room temperature slowly and stirred overnight. The vessel was opened slowly and sat'd NH_4Cl was added. Purification via high vacuum distillation afforded propargyl alcohol (16.8 g, 62% yield) as a yellow oil. All compounds listed herein have been previously in our lab and are in agreement with published data.[19]



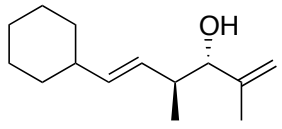
175

(*S*,*E*)-1-cyclohexylbut-2-en-1-ol - To a solution of propargyl alcohol **174** (10.1 g, 0.066 mol) in THF (350 mL) cooled to 0°C, was added Red-Al (75 mL, 0.26 mol, 3.5 M in toluene, 4 eq) slowly. The reaction was warmed to room temperature then refluxed overnight. Upon consumption of alcohol via TLC analysis, the mixture was transferred to a large Erlenmeyer flask, cooled to 0°C and quenched with sat'd NH_4Cl. The heterogeneous mixture was extracted with ether and the resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via flash chromatography (10% EA:H) afforded allylic alcohol (8.40 g, 82% yield) as a yellow oil.[19]



76

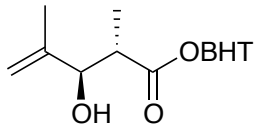
(3*S*,4*S*,*E*)-6-cyclohexyl-4-methylhex-5-en-1-yn-3-ol - To a solution of **75** (588 mg, 3.06 mmol) in THF (11 mL) cooled to -78°C, was added n-BuLi (2.5 M in hexanes, 3.67 mL, 9.18 mmol, 3 eq). The mixture was stirred at -78°C for 1 h, allowed to warm to room temperature and stirred overnight. The reaction was quenched with sat'd NH_4Cl and diluted with ether. The heterogeneous mixture was extracted with ether and the resulting solution was dried over $MgSO_4$. Purification via column chromatography (10% EA:H) afforded propargyl alcohol (378 mg, 64% yield) as a colorless oil.[19]



74

(3*S*,4*S*,*E*)-6-cyclohexyl-2,4-dimethylhexa-1,5-dien-3-ol - To a solution of freshly purified CuI (297 mg, 1.56 mmol, 2 eq) in THF (4 mL) cooled to -30°C, was added MeMgCl (3 M in THF, 1.04 mL, 372 mg, 3.12 mmol, 4 eq) slowly. The mixture was stirred for 30 min whereupon a solution of propargyl alcohol **76** (150 mg, 0.78 mmol) in THF (2 mL) was added dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with water, extracted with ether and the resulting organic solution was filtered through a pad of celite and dried over $MgSO_4$. Purification via flash chromatography (5% EA:H) afforded desired alcohol (43.4 mg, 31% adjusted yield) and recovered propargyl alcohol (24.2 mg).[19]

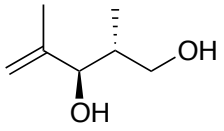
The experimentals listed herein are known compounds from the literature[20]



202

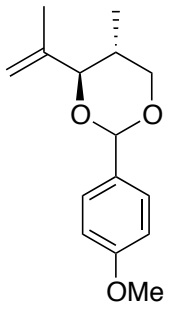
(2*S*,3*R*)-2,6-di-*tert*-butyl-4-methoxyphenyl 3-hydroxy-2,4-dimethylpent-4-enoate - To a solution of *n*BuLi (1.6 M in hexane, 67 mL, 0.11 mol, 1.5 eq) in THF (100 mL) cooled to 0°C, was added diisopropylamine (16.3 mL, 11.7 g, 115.8 mmol, 1.6 eq) dropwise slowly. The reaction was stirred for 1 hr then cooled to -78°C, whereupon a solution of BHT ester **201** (20g, 72.3 mmol) in THF (30 mL) was added dropwise via addition funnel. The reaction was stirred for 1 hr then added methacrolein (8.9 mL, 7.6 g, 108.4 mmol, 1.5 eq) dropwise. The mixture was stirred for 20 min the sat'd NH_4Cl was added all at once and warmed to room temperature. The heterogeneous mixture was extracted with ether and the resultant organic solution was dried over $MgSO_4$ and concentrated. The crude was isolated as a red/orange solid (25.0 g, Quantitative) as one isomer by C^{13} NMR. There were minor impurities in the crude and was used as such. ^1H NMR (500

MHz, $CDCl_3$) δ 7.14 (d, *J* = 5.8 Hz, 2H), 5.02 (s, 1H), 4.99 (s, 1H), 4.31 (dd, *J* = 9.3, 2.4 Hz, 1H), 2.86 (m, 1H), 2.32 (s, 3H), 1.79 (s, 3H), 1.35 (m, 21H)



200

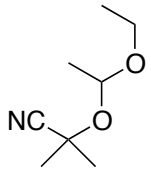
(2*R*,3*R*)-2,4-dimethylpent-4-ene-1,3-diol -To a stirred solution of $LiAlH_4$ (21 g, 0.55 mol, 5 eq) in 850 mL of THF cooled to 0°C was added a solution of **202** in THF (150 mL; 50 mL wash) dropwise via addition funnel. The mixture was refluxed for 6 hrs, at which time 100 mL of ethyl acetate was added. The mixture was transferred to a large Erlenmeyer flask cooled to 0°C and worked up using conventional Feiser and Feiser conditions. The heterogeneous mixture was filtered through a pad of celite, and the filtrate was washed extracted with ethyl acetate. The resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via a pad of silica under vacuum (20% EA:H) afforded diol (7.6 g, 60% yield) as a colorless oil. This material contained minor impurities and was used as such. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.86 (s, 1H), 3.92 (d, *J* = 8.7 Hz, 1H), 3.70 (dd, *J* =10.7, 3.9 Hz, 1H), 3.61 (dd, *J* = 10.7, 7.2 Hz, 1H), 3.36 (bs, 2H), 1.86 (m, 1H), 1.70 (s, 3H), 0.75 (d, *J* = 6.8 Hz, 3H)



200a

(4*R*,5*R*)-2-(4-methoxyphenyl)-5-methyl-4-(prop-1-en-2-yl)-1,3-dioxane - To a solution of **200** (7.6 g, 65.4 mmol) in CH_2CH_2 (90 mL) cooled to 0°C, was added *p*-anisaldehyde

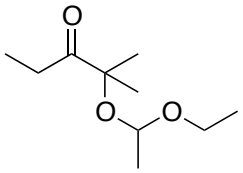
dimethyl acetal (14.9 g, 14 mL, 81.7 mmol, 1.3 eq) all at once. A catalytic amount of PTSA (3.7 g, 19.6 mmol, 0.3 eq) was added and the reaction was stirred for 3 hours. Upon consumption of starting material via TLC analysis, the reaction was diluted with CH_2CH_2 and quenched with sat'd $NaHCO_3$. The heterogeneous mixture was extracted with ether and the resulting organic solution was washed with brine and dried over $MgSO_4$. Purification via column chromatography (10% EA:H) afforded benzylidene acetal (11.3 g, 70% yield) as a colorless oil. Benzylidene **200a** has been previously made and in agreement with literature precedent.[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.51 (s, 1H), 4.99 (d, *J* = 8.3 Hz, 2H), 4.17 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.86 (d, *J* = 10.2 Hz, 1H), 3.79 (s, 3H), 3.54 (t, *J* = 10.9 Hz, 1H), 2.05 (m, 1H), 1.82 (s, 3H), 0.72 (d, *J* = 6.8 Hz, 3H).



241

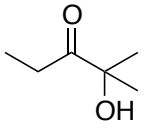
2-(1-ethoxyethoxy)-2-methylpropanenitrile - Following Heathcocks procedure: To a solution of acetone cyanohydrin (5 g, 58 mmol) and 1 drop concentrated HCl, was added ethyl vinyl ether (4.1 g, 58 mmol, 5.6 mL, 1 eq) was added slowly (exothermic) dropwise, keeping the temperature below 50°C. The flask was fitted with a distillation apparatus and the solution was heated to 90°C for 2 hrs. Purification via fractional distillation under reduced pressure afforded a 50:50 mixture of ether and starting material. The mixture was stirred with aqueous potassium carbonate overnight to afford ether (5.09 g) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (q, *J* = 5.4 Hz, 1H),

3.58 (m, 1H), 3.48 (m, 1H), 1.53 (s, 6H), 1.29 (d, J = 5.4 Hz, 3H), 1.15 (t, J = 7.3 Hz, 3H)



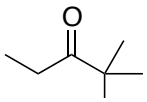
241a

2-(1-ethoxyethoxy)-2-methylpentan-3-one - Following Heathcocks procedure: To a solution of ethylmagnesium bromide (1M, 56 mL, 56 mmol, 3.5 eq) in THF (90 mL) was added a solution of protected cyanohydrin **241** (2.5 g, 16.0 mmol) in THF (25 mL) via addition funnel at 0°C. The reaction was refluxed at 80°C for 1 day, allowed to cool to room temperature and quenched with saturated ammonium chloride. The heterogeneous mixture was extracted with ether and dried over $MgSO_4$. Purification via flash chromatography (5% EA:H) afforded ketone (2.28 g) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (q, J = 4.8 Hz, 1H), 3.29 (m, 2H), 2.74 (m, 1H), 2.37 (m, 1H), 1.19 (m, 9H), 1.00 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H)



241b

2-hydroxy-2-methylpentan-3-one - To a solution of keto-ether **241a** (878.9 mg, 4.66 mmol) in THF (10 mL) was added 1N HCl (10 mL) and stirred overnight at room temperature. Upon consumption of starting material (TLC analysis), the heterogeneous mixture was extracted with ether, washed with sat'd sodium bicarbonate, brine and dried over $MgSO_4$ to afford alcohol (407.8 mg, 75% yield) as a yellow oil. α-hydroxy ketone is known and is agreement with literature precedent ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (bs, 1H), 2.49 (q, J = 7.2 Hz, 2H), 1.26 (s, 6H), 0.99 (t, J = 7.2 Hz, 3H).



242

2-methyl-2-((trimethylsilyl)oxy)pentan-3-one - To a solution of **241b** (180 mg, 1.55 mmol) in DCM (3 mL) was added triethylamine (861 µL, 626 mg, 6.2 mmol, 4 eq) and TMS-Cl (396 µL, 336 mg, 3.1 mmol, 2 eq) successively. The mixture was stirred overnight at room temperature, whereupon TLC analysis showed the consumption of starting material. The mixture was quenched with water, diluted with ether and the resultant organics were washed with brine and dried over $MgSO_4$. Purification via kugelrohr distillation afforded silyl ether (198 mg, 67% yield as a yellow oil. Silyl ether is known and is agreement with literature precedent. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (q, J = 7.3 Hz, 2H), 1.31 (s, 6H), 1.01 (t, J = 7.3 Hz, 3 H), 0.13 (s, 9H)

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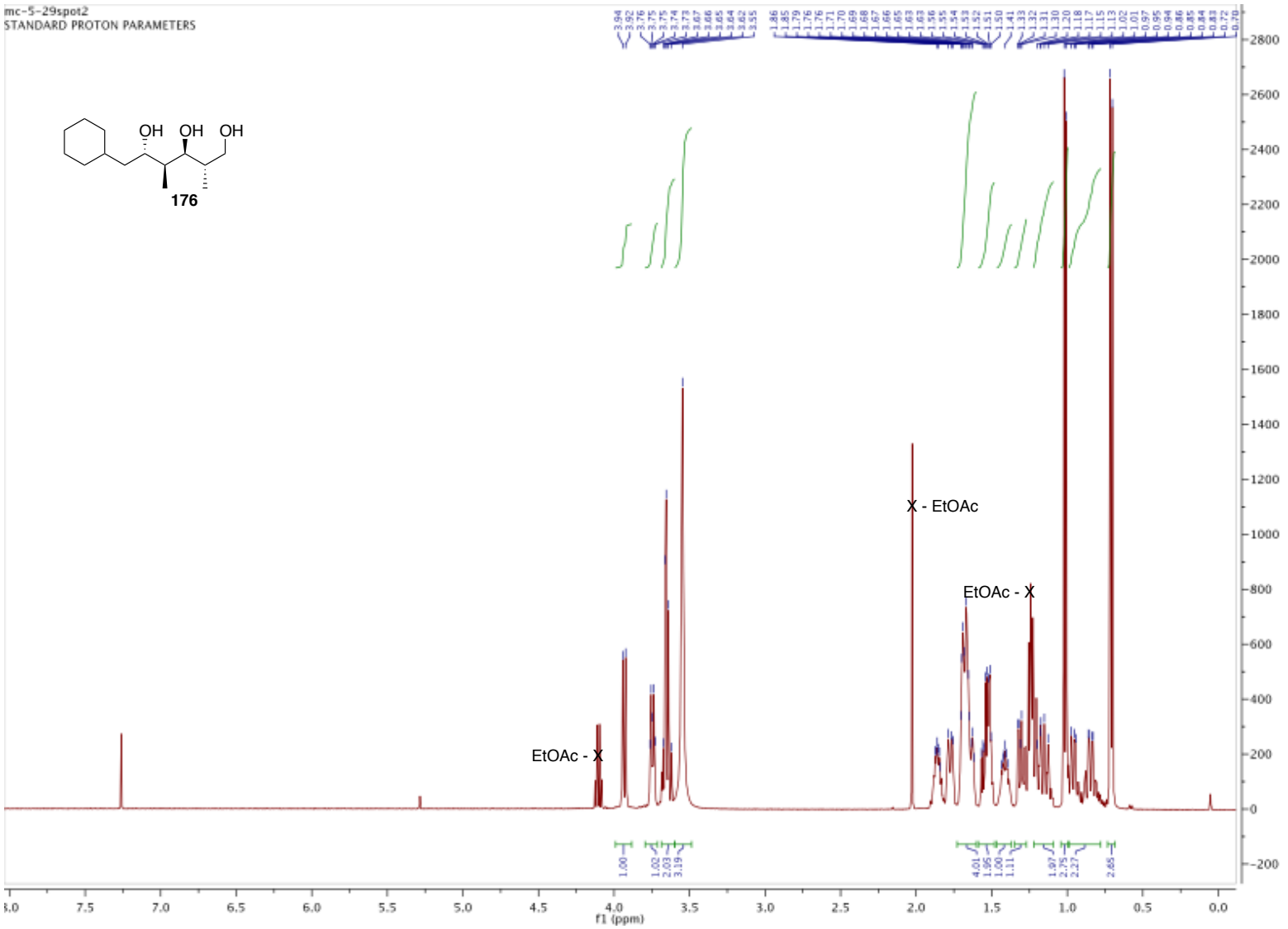
Appendix II: Relevant Spectra for Chapter 3

Compounds **Page**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OH
176
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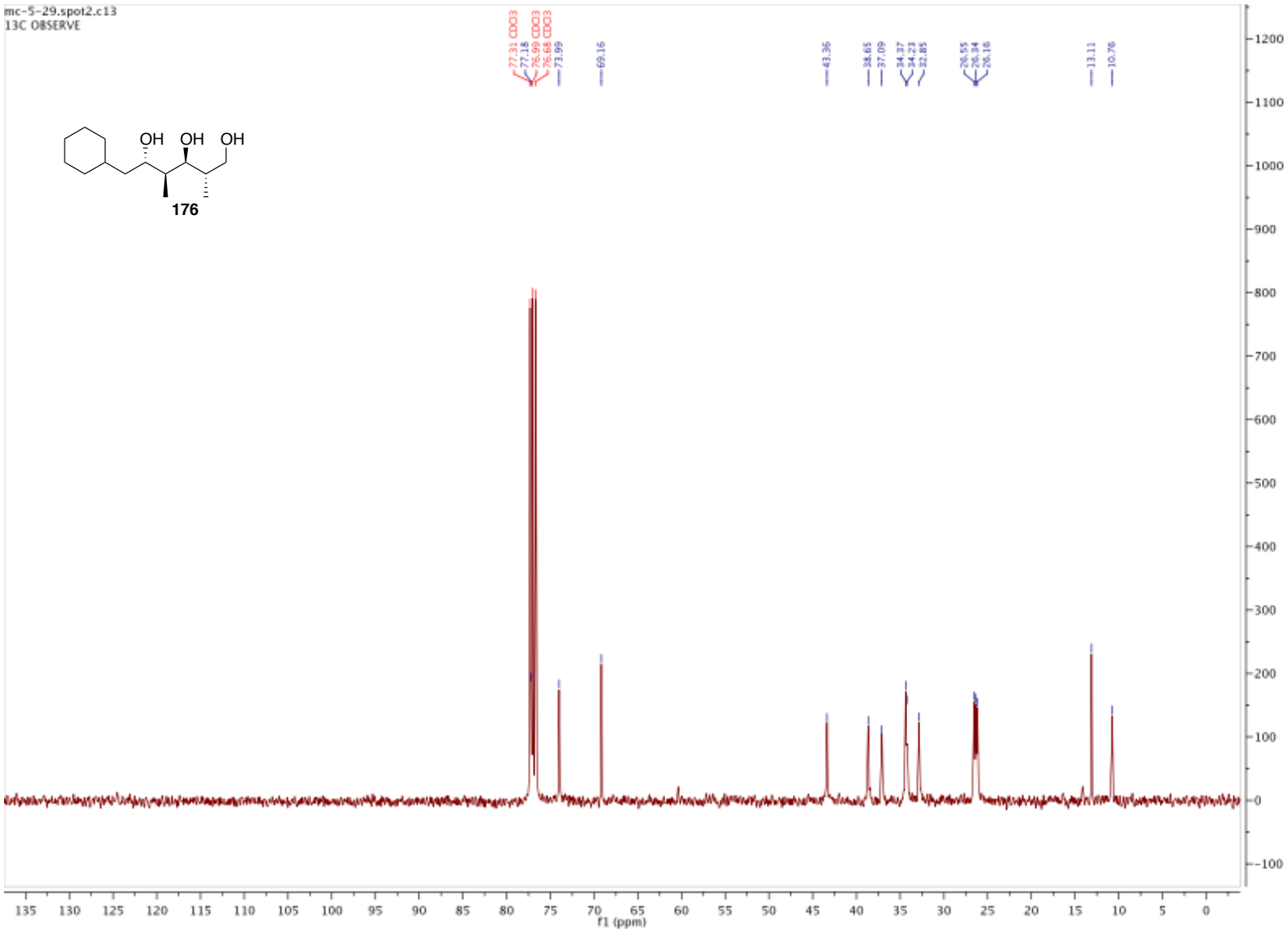
EtOAc - X
EtOAc - X
f1 (ppm)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OH
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77.18
77.05 CDCl3
76.68 CDCl3
73.99
69.16
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26.34
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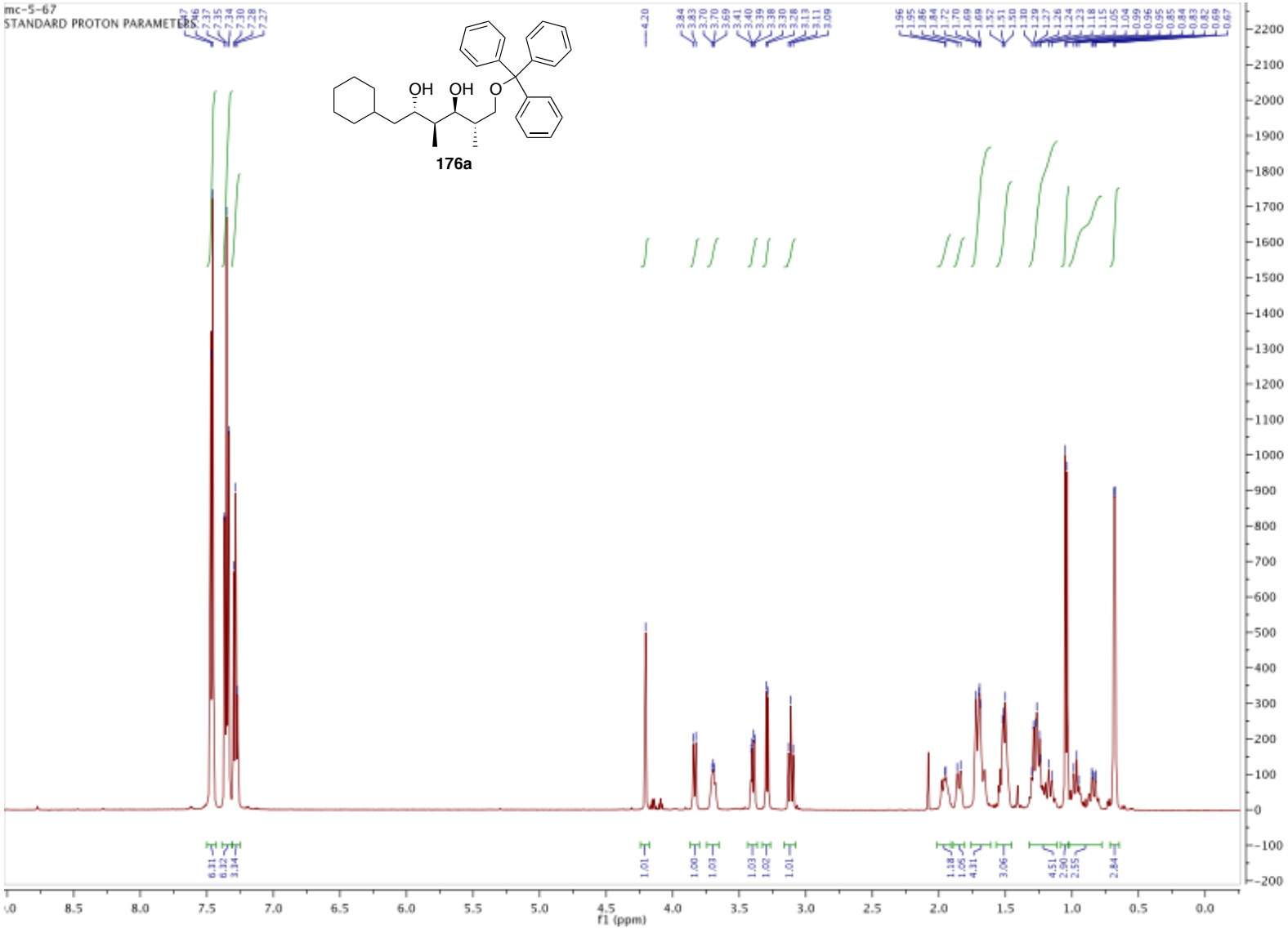
10.76
f1 (ppm)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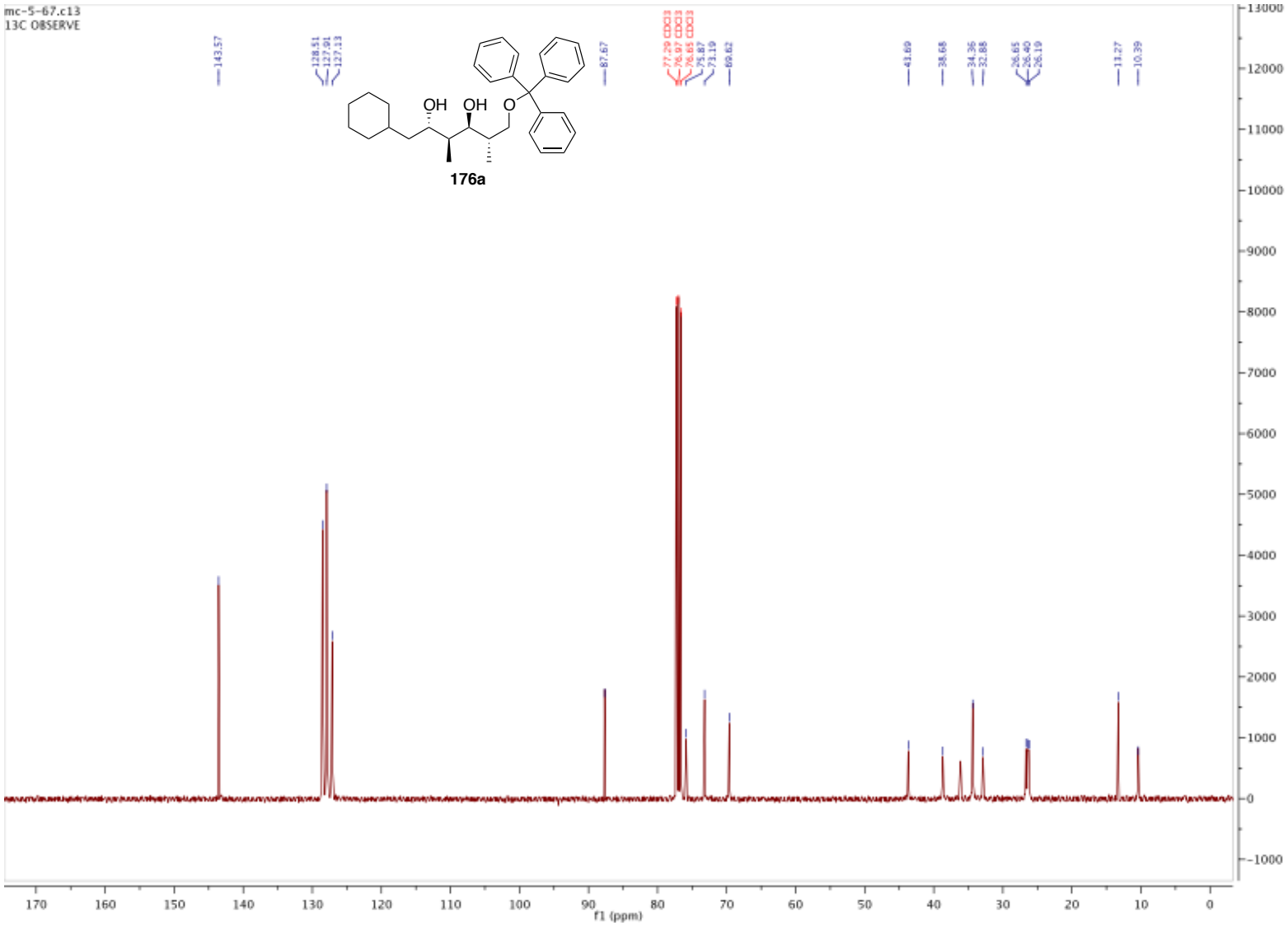
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75.87
73.19
69.62
41.69
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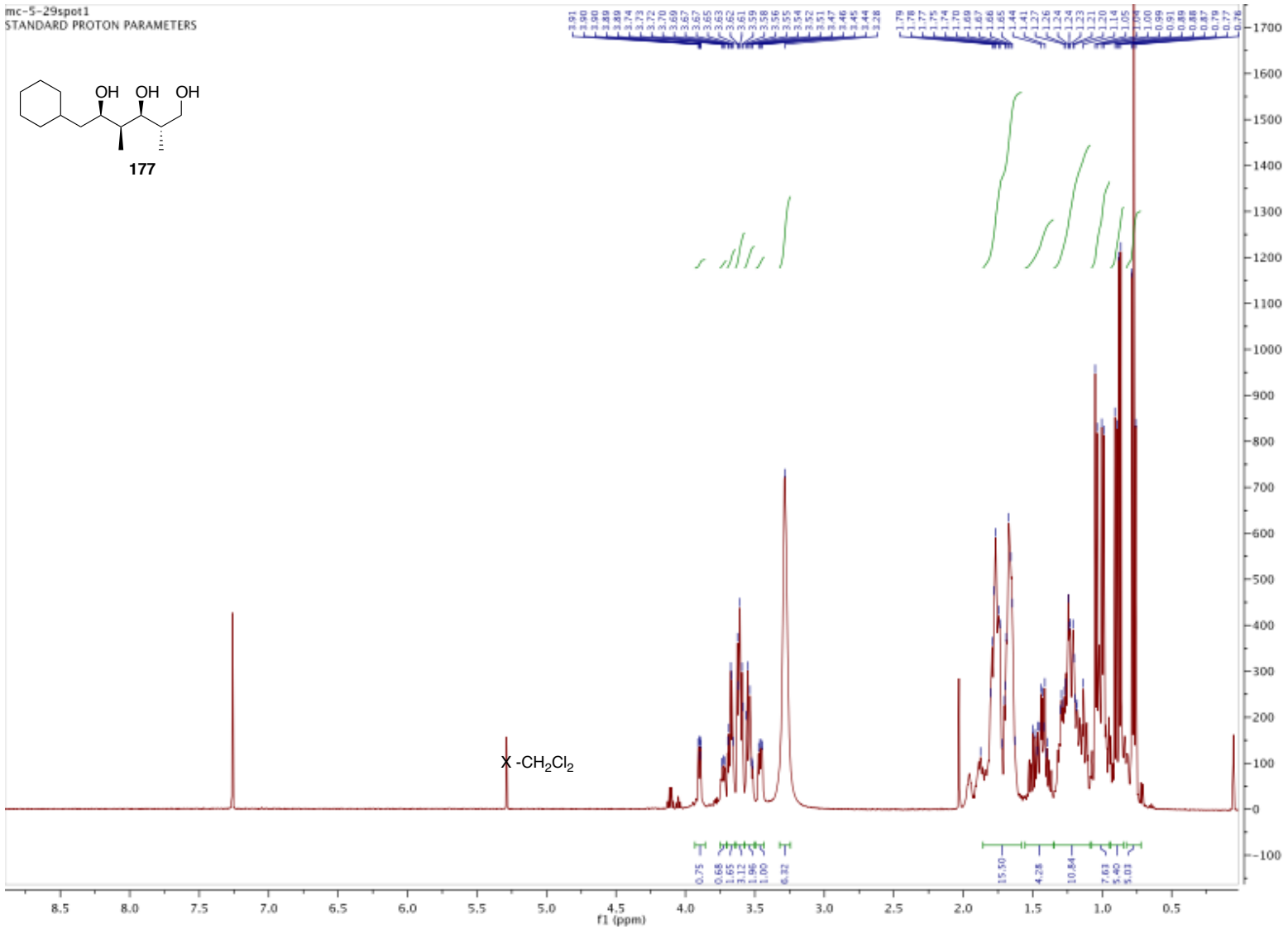
O
176a
f1 (ppm)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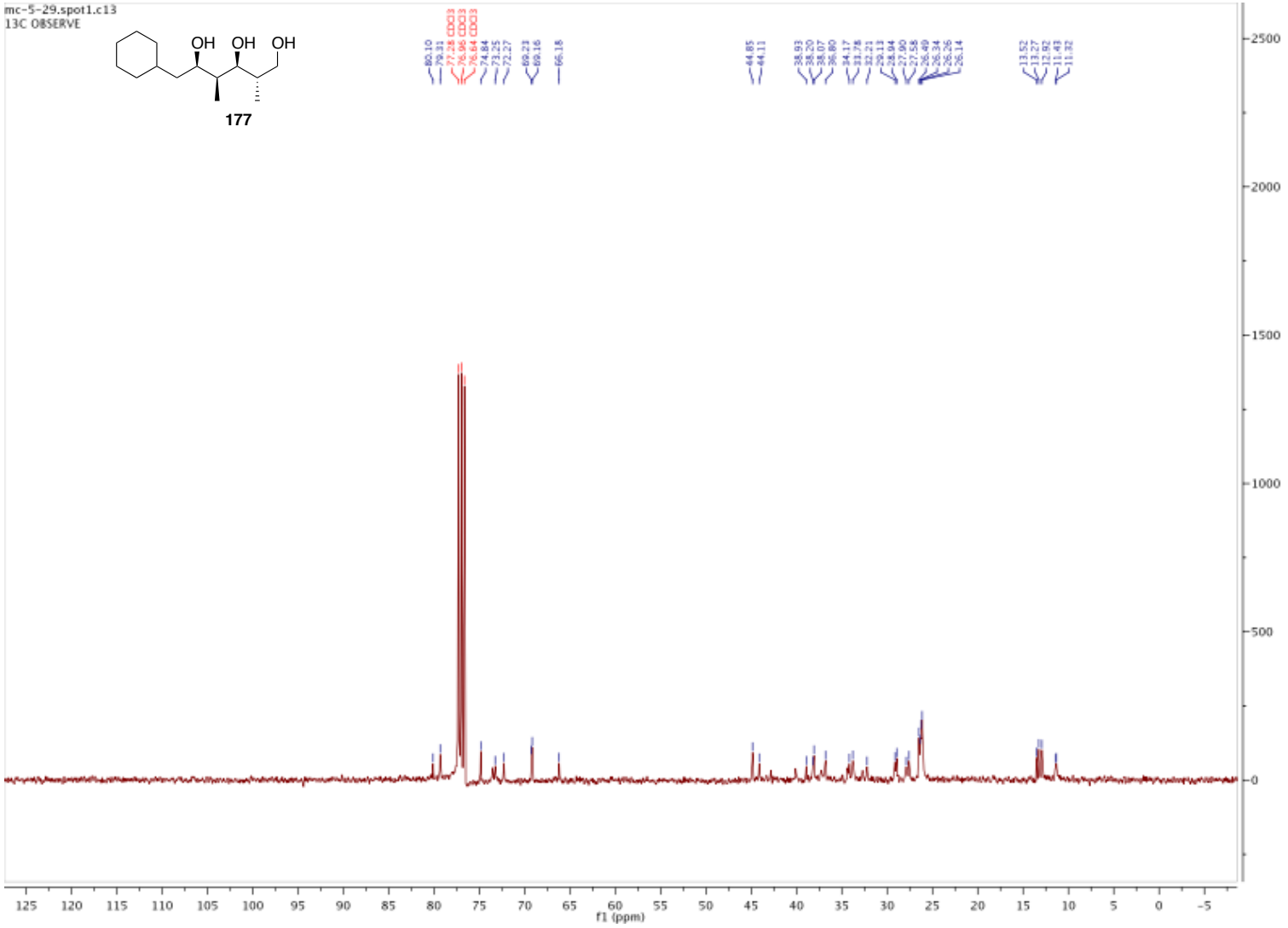
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76.64 CDCl3
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72.27
69.23
69.16
66.18
44.85
44.11
38.93
38.20
38.07
36.80
34.17
33.78
32.21
29.13
28.04
27.90
27.58
26.49
26.34
26.26
26.14
13.52
13.27
12.92
11.43
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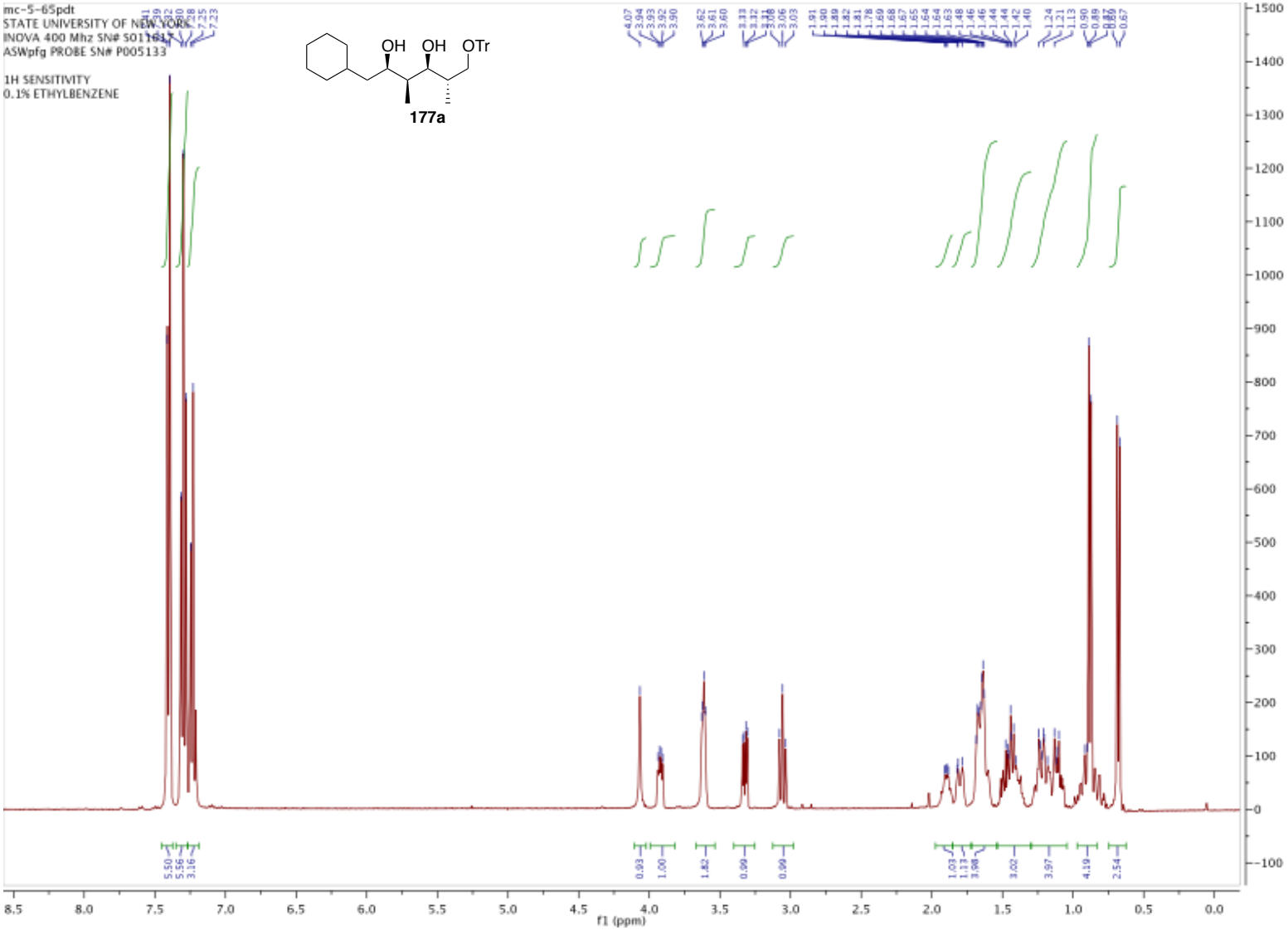
f1 (ppm)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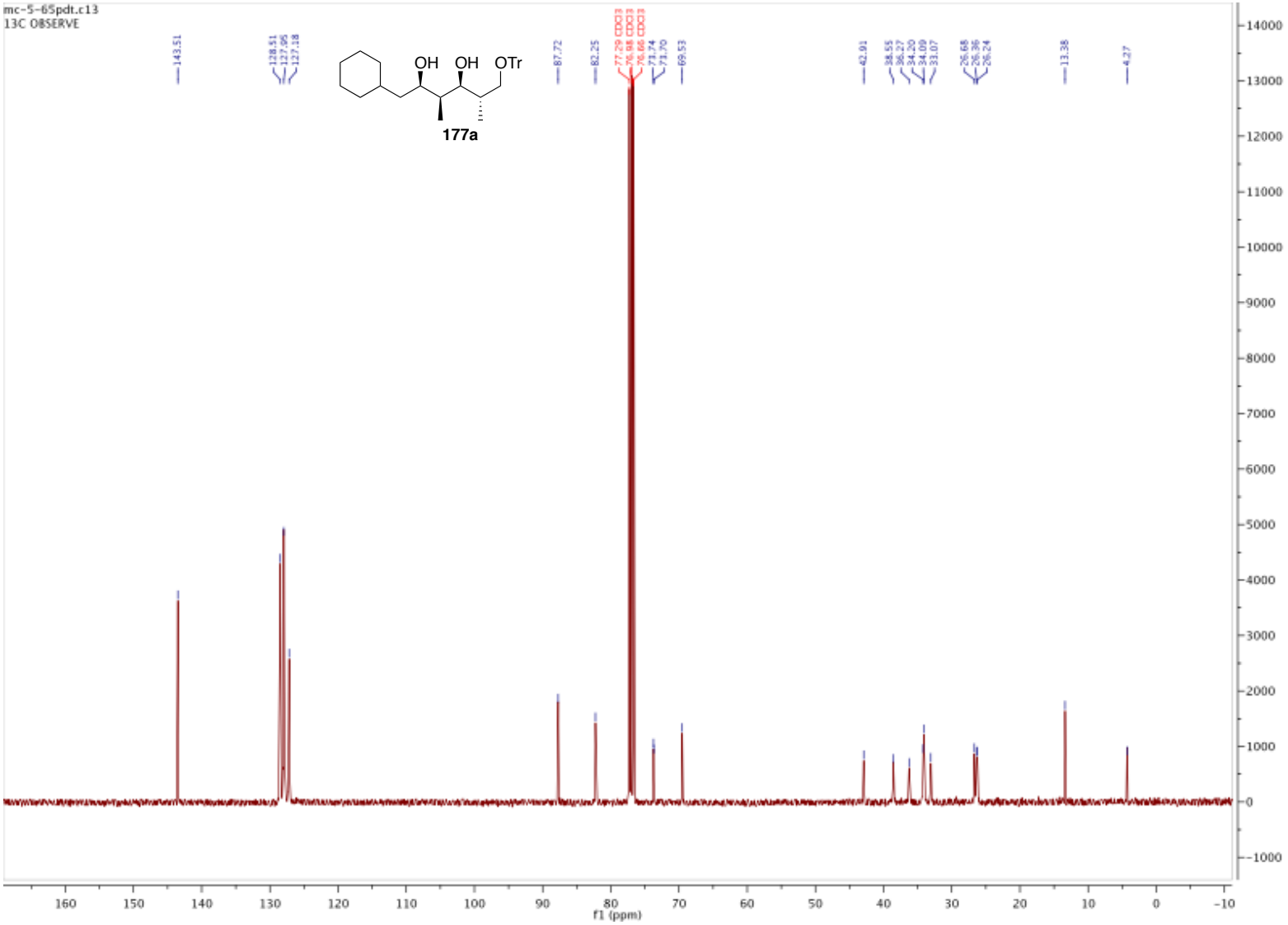
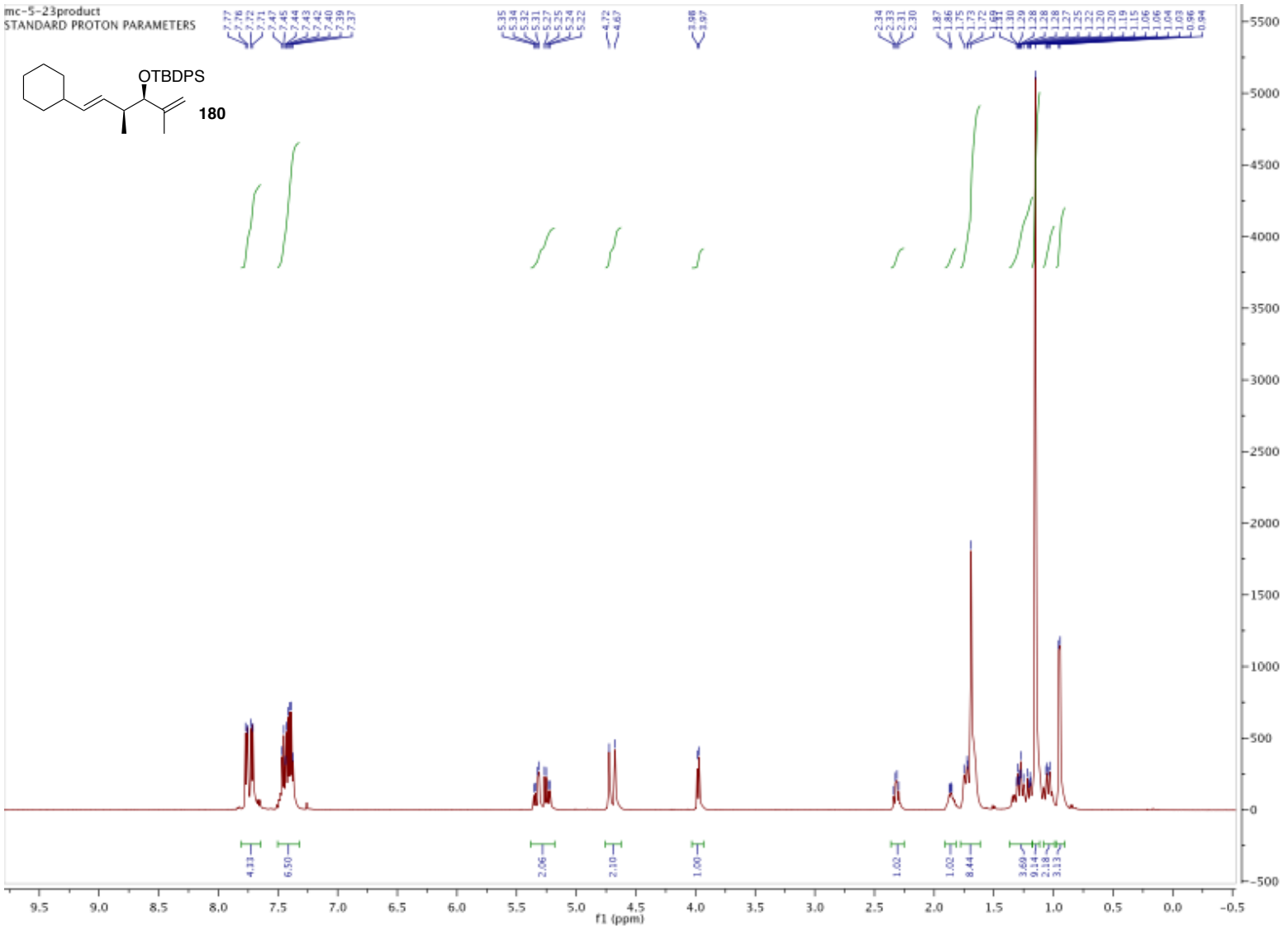
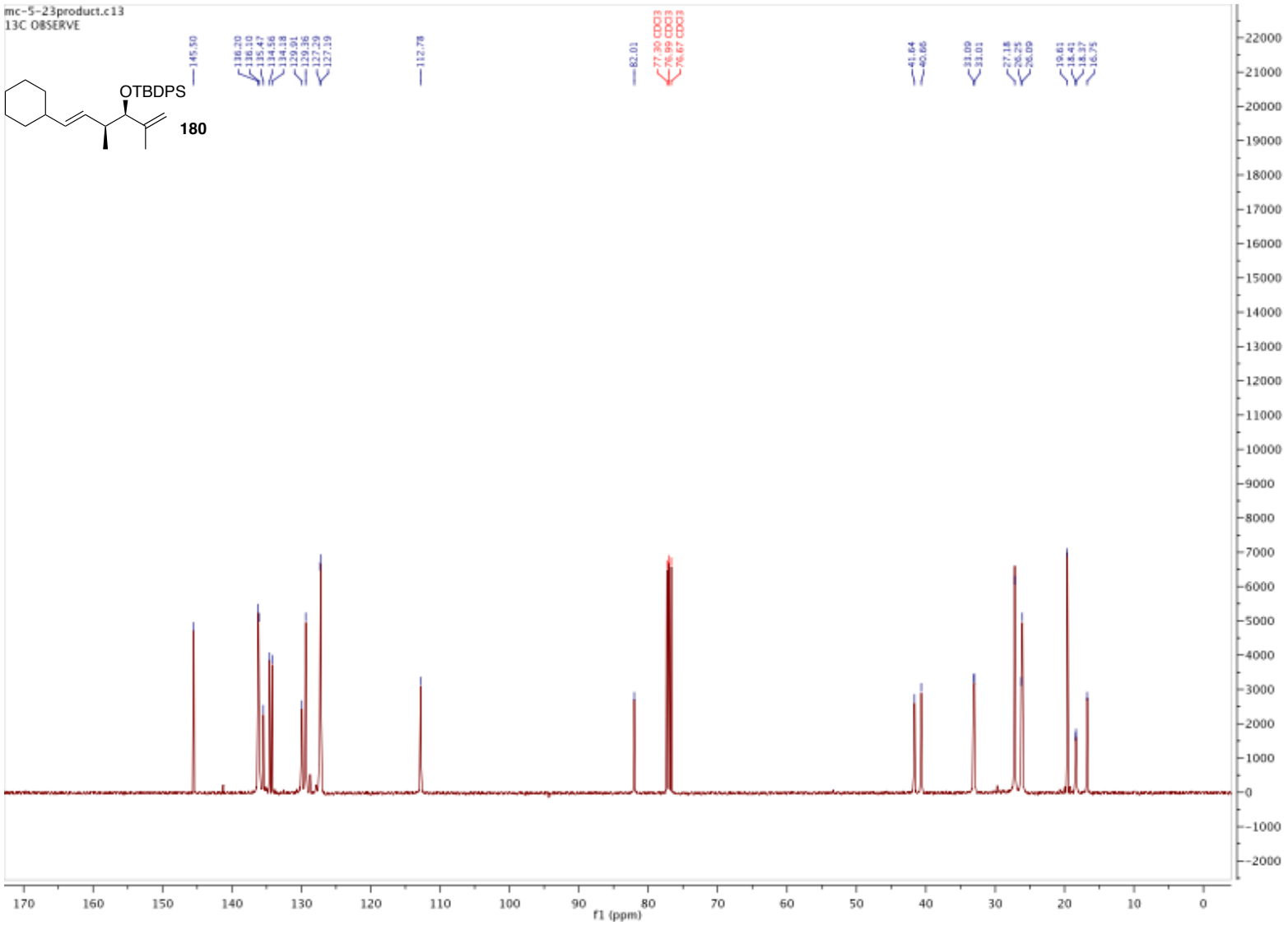
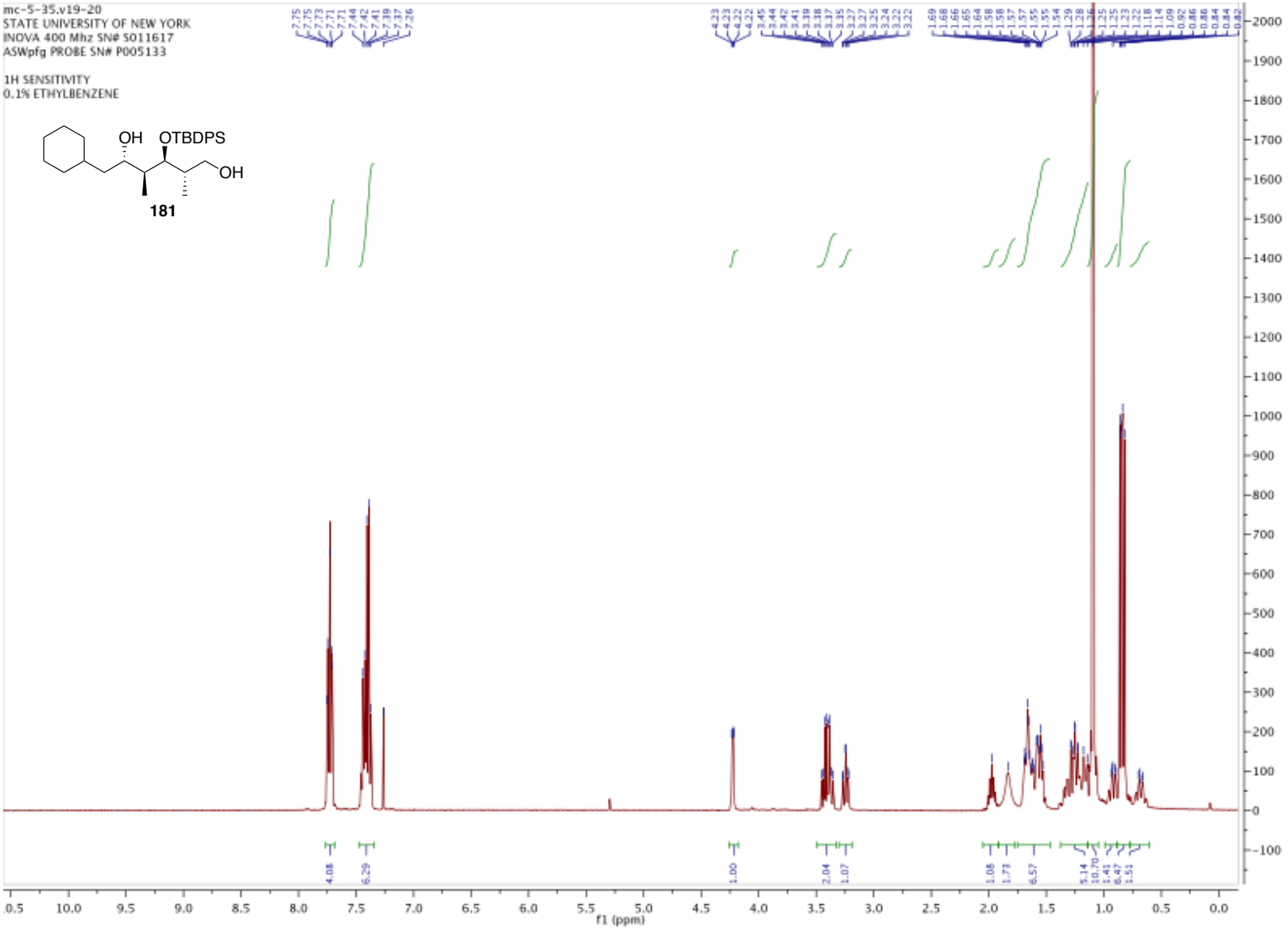
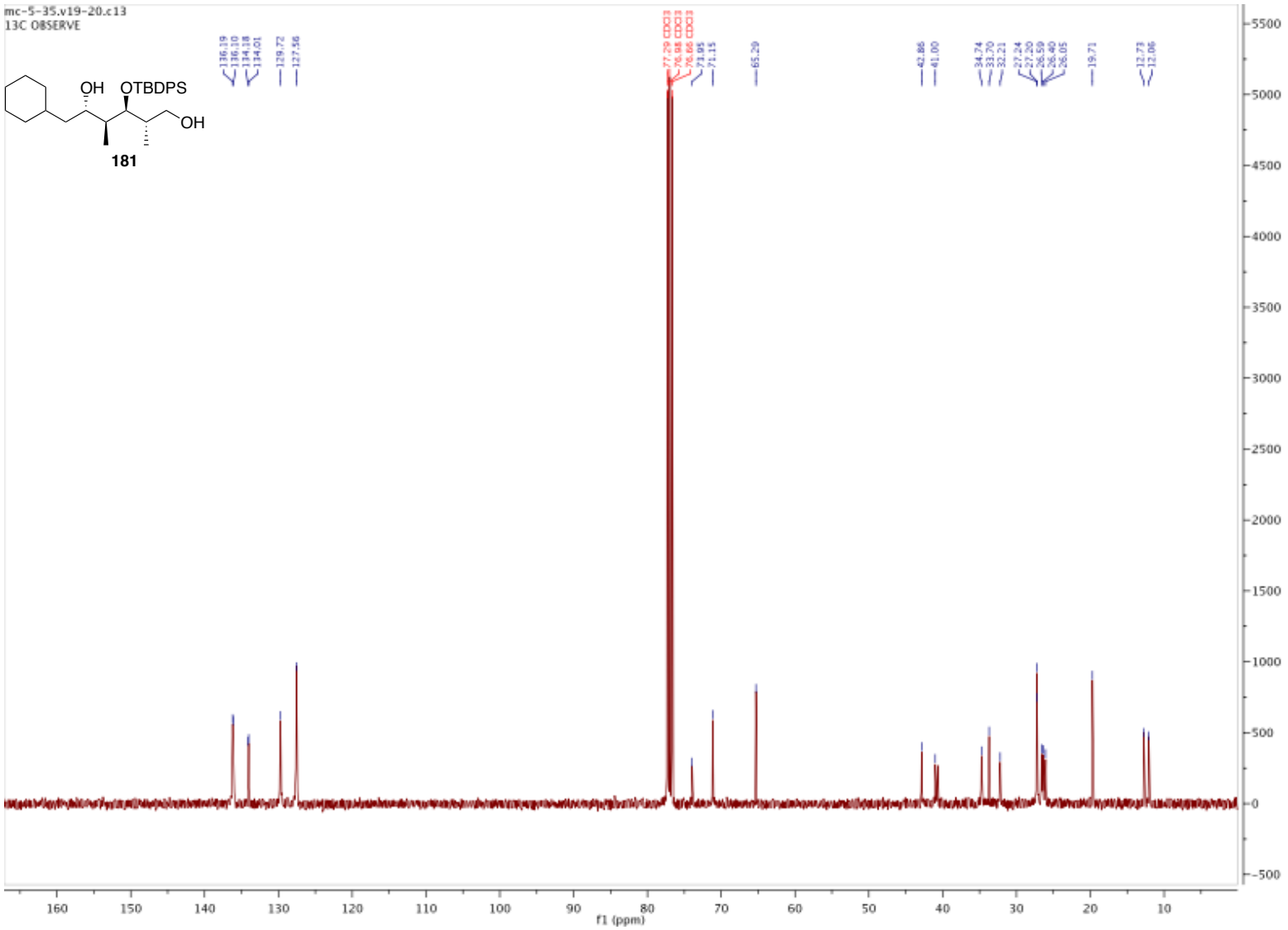
OH
OH
OTr
177a
f1 (ppm)

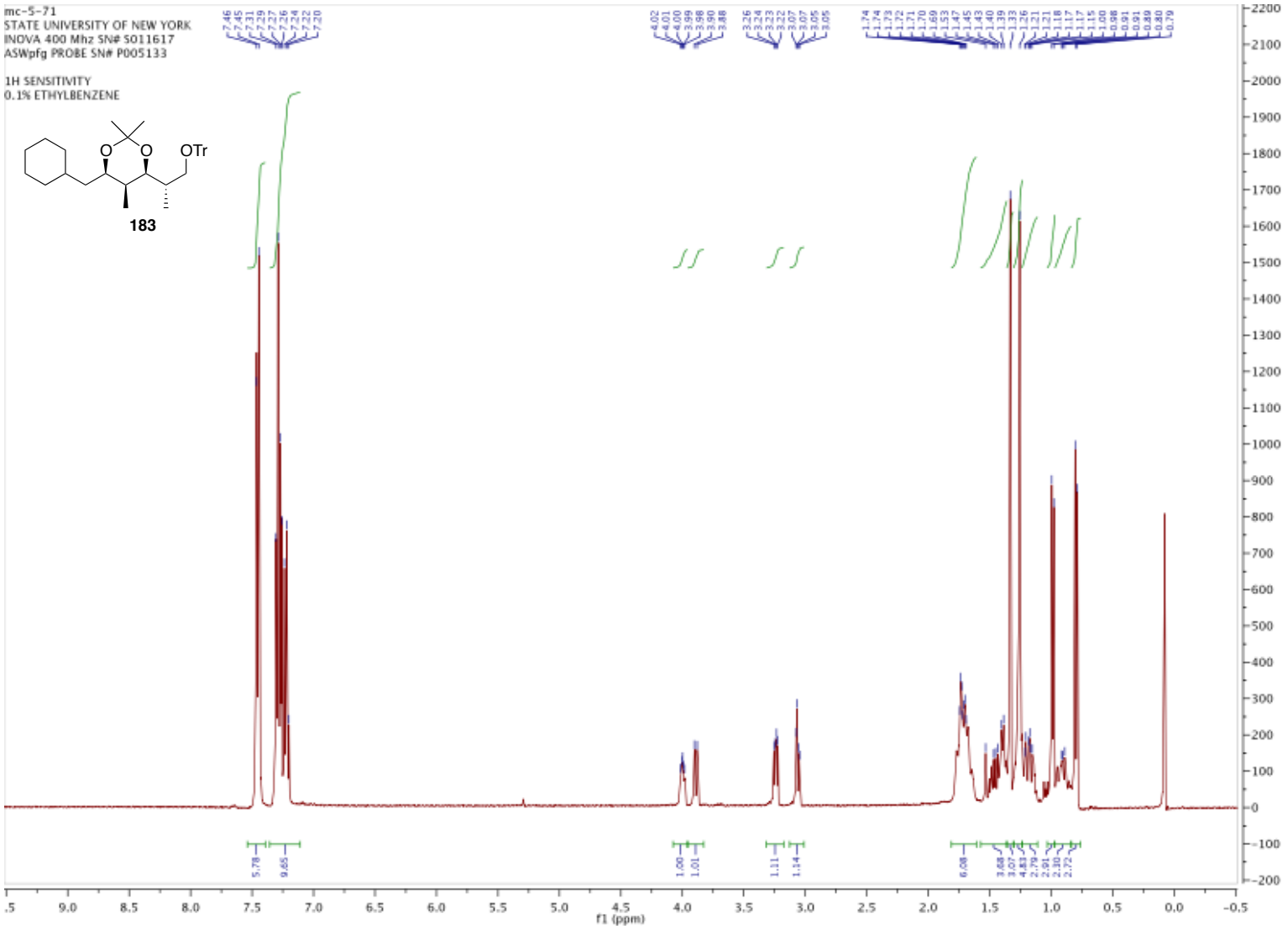

mc-5-65pdt.c13
13C OBSERVE
143.51
128.51
127.95
127.18
87.72
82.25
77.29 CDCl3
76.98 CDCl3
76.66 CDCl3
73.74
73.70
69.53
42.91
38.55
36.27
34.20
34.09
33.07
26.68
26.36
26.24
13.38
4.27
OH
OH
OTr
177a
f1 (ppm)

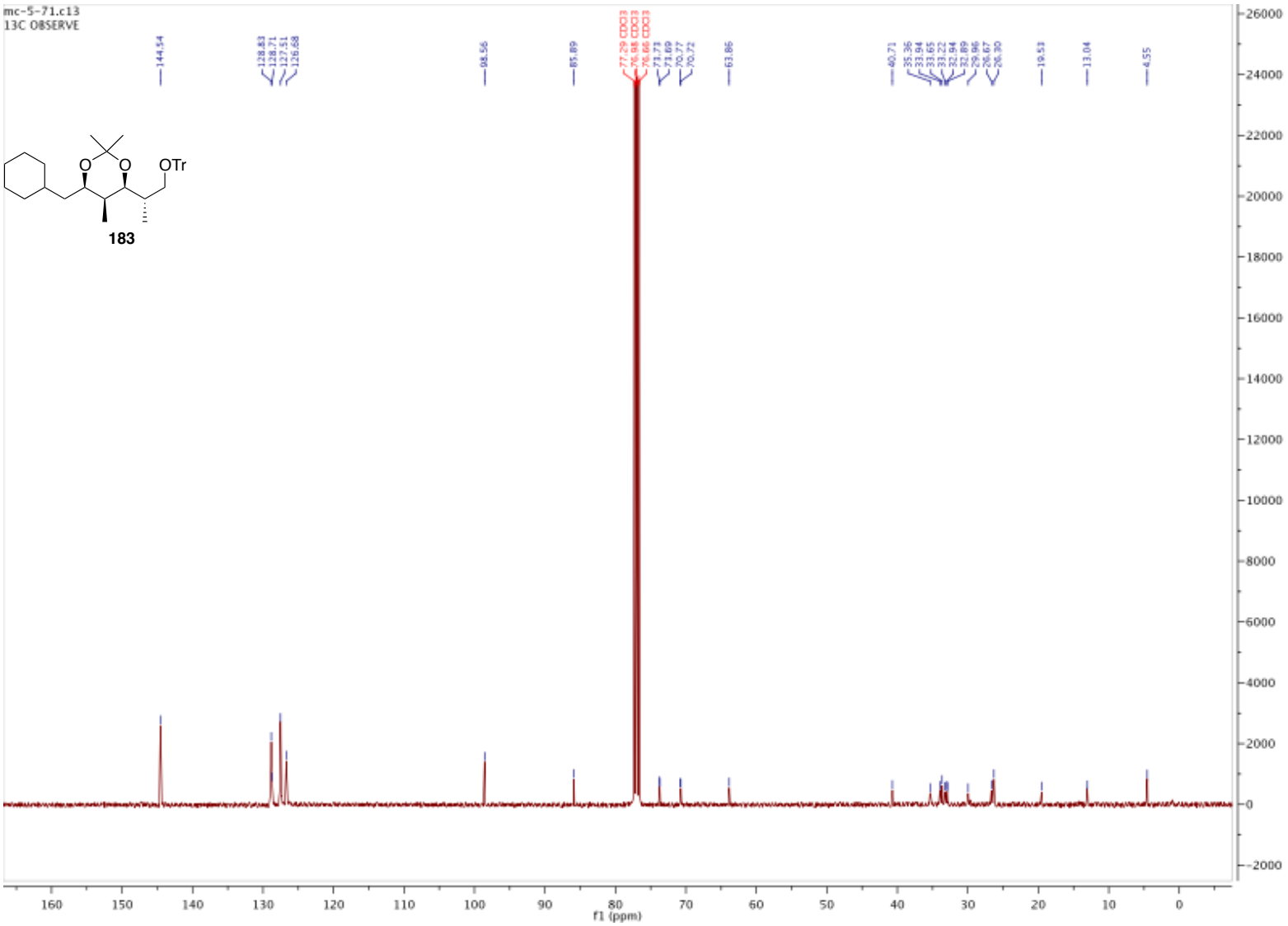

mc-5-23product
STANDARD PROTON PARAMETERS
OTBDPS
180
f1 (ppm)

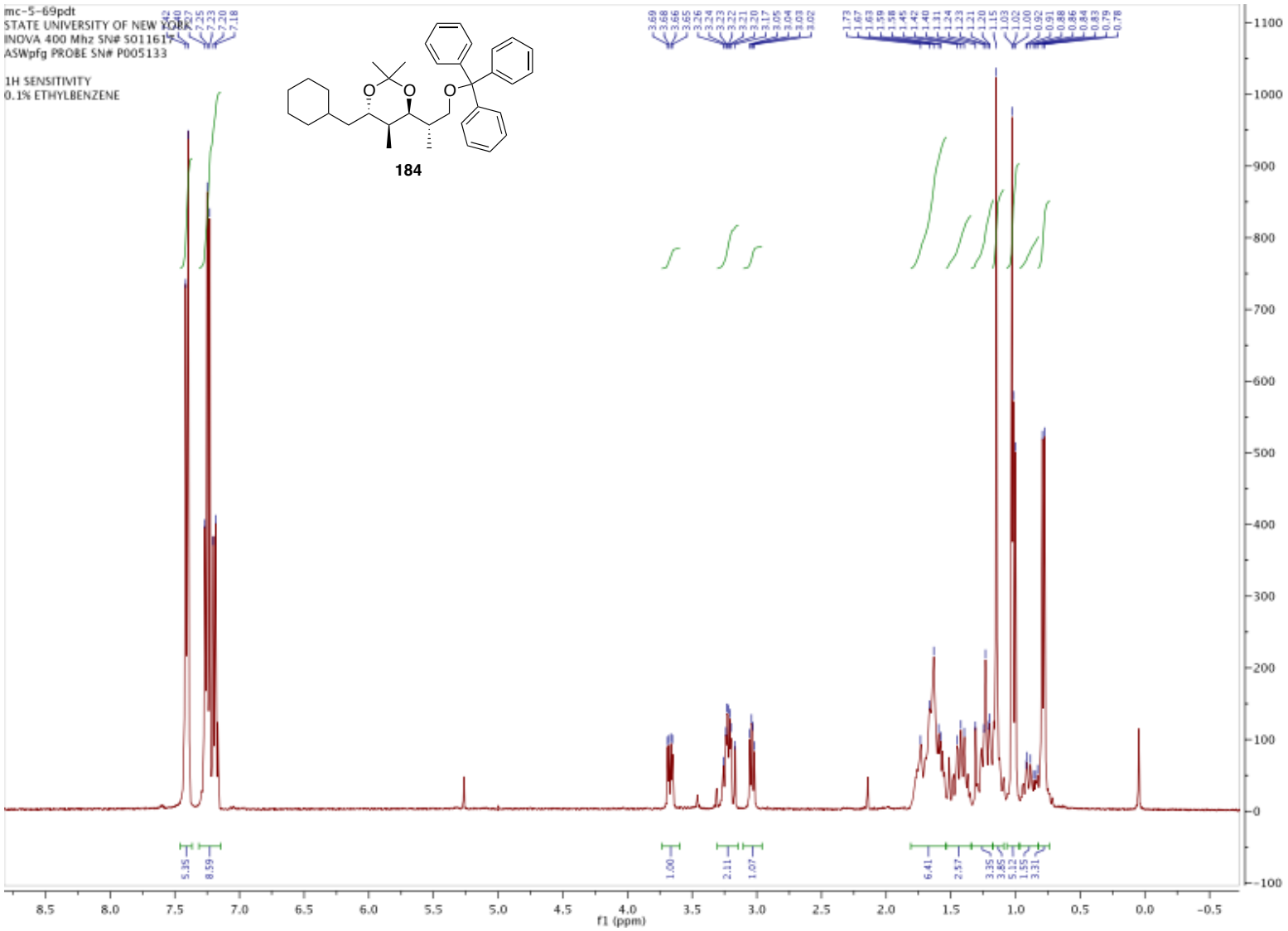

mc-5-23product.c13
13C OBSERVE
OTBDPS
180
145.50
136.20
136.10
135.47
134.56
134.18
129.91
129.36
127.29
127.19
112.78
82.01
77.30 CDCl3
76.99 CDCl3
76.67 CDCl3
41.64
40.66
31.09
31.01
27.18
26.25
26.09
19.61
18.41
18.37
16.75
f1 (ppm)

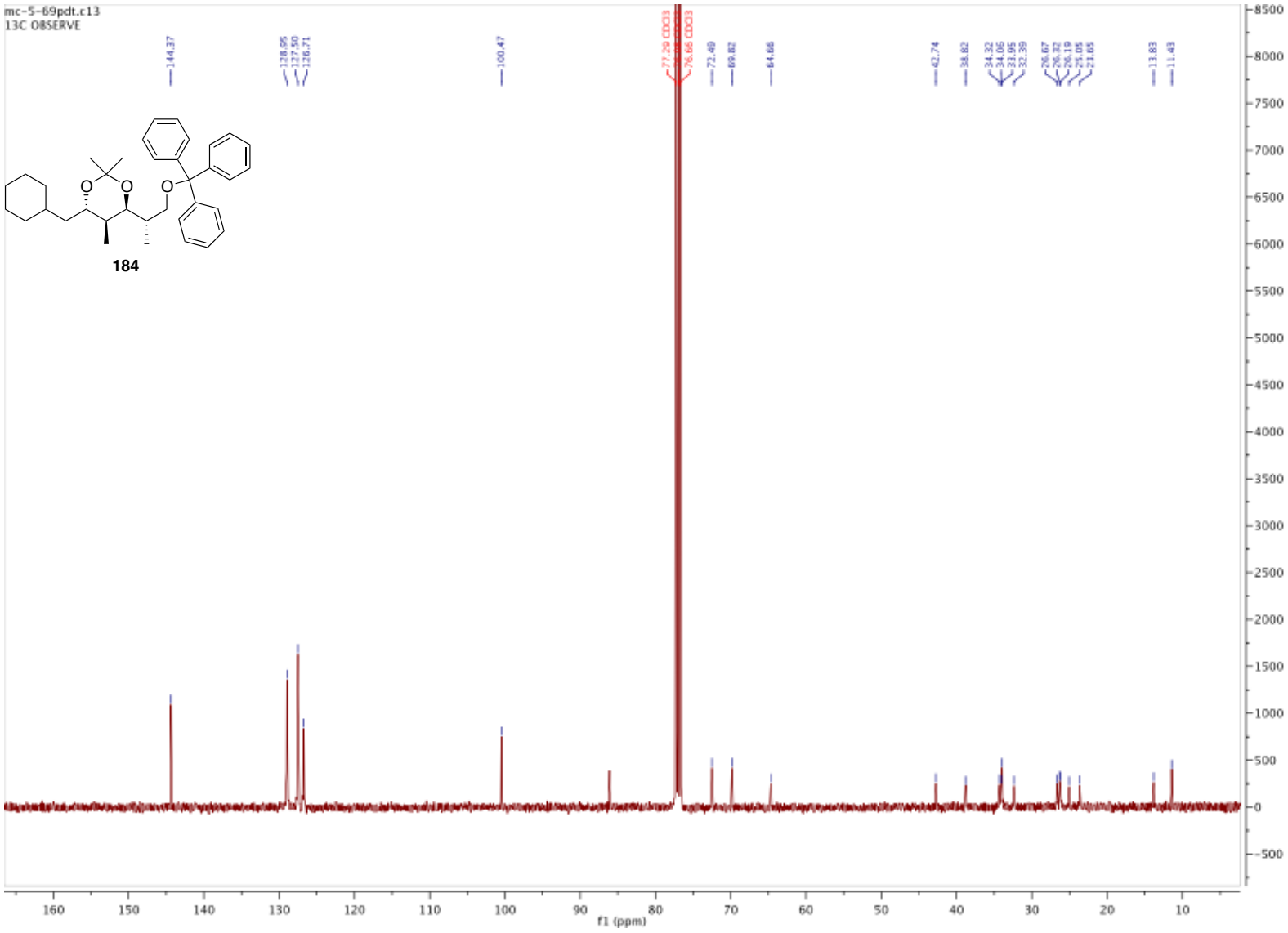

mc-5-35.v19-20
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
OH
OTBDPS
OH
181
f1 (ppm)

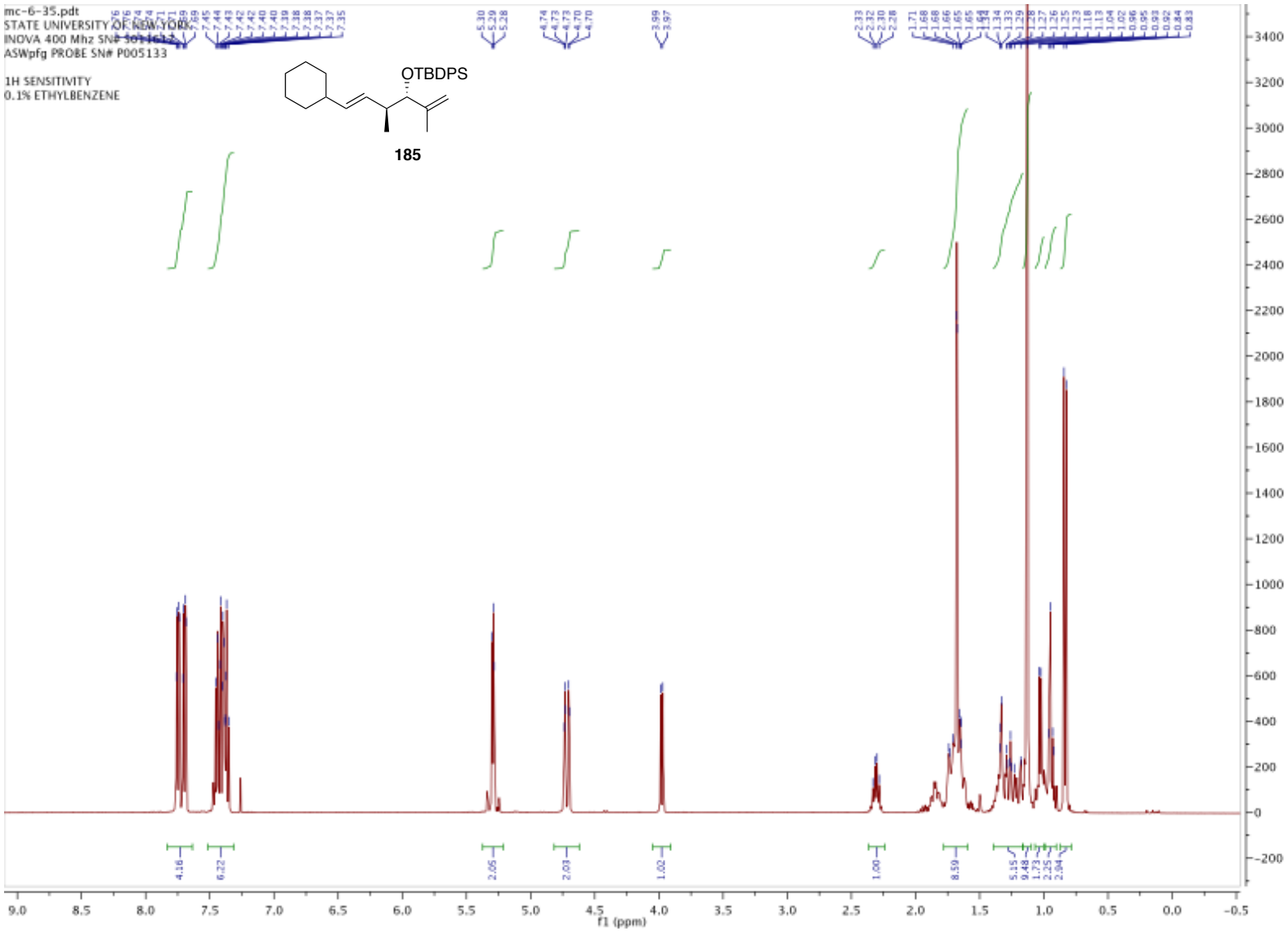

mc-5-35.v19-20.c13
13C OBSERVE
OH
OTBDPS
OH
181
136.19
136.10
134.38
134.01
129.72
127.56
77.29 CDCl3
76.98 CDCl3
76.66 CDCl3
74.95
71.15
65.29
42.86
41.00
34.74
33.70
32.21
27.24
27.20
26.59
26.40
26.05
19.71
12.73
12.06
f1 (ppm)

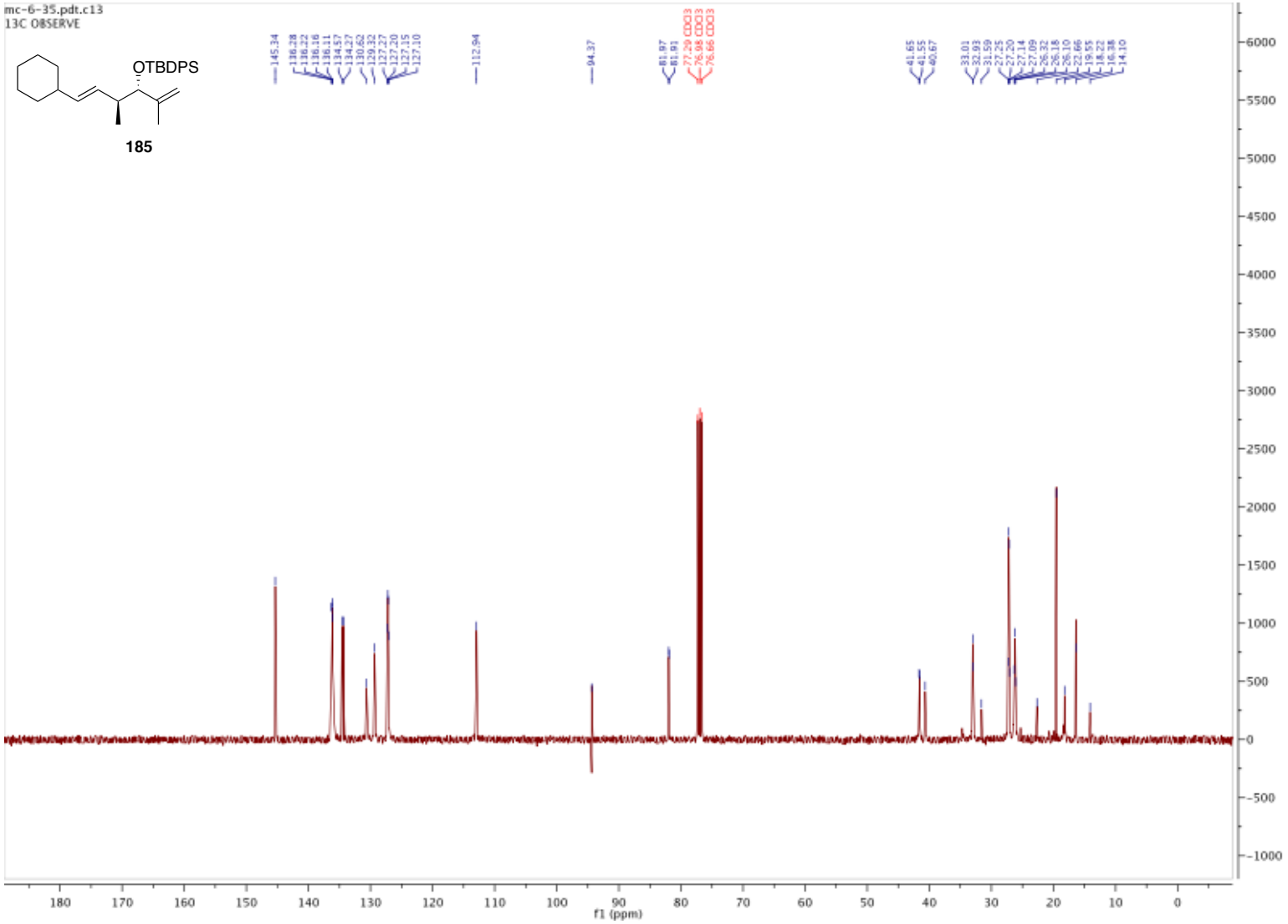

mc-5-71
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
OTr
183
f1 (ppm)

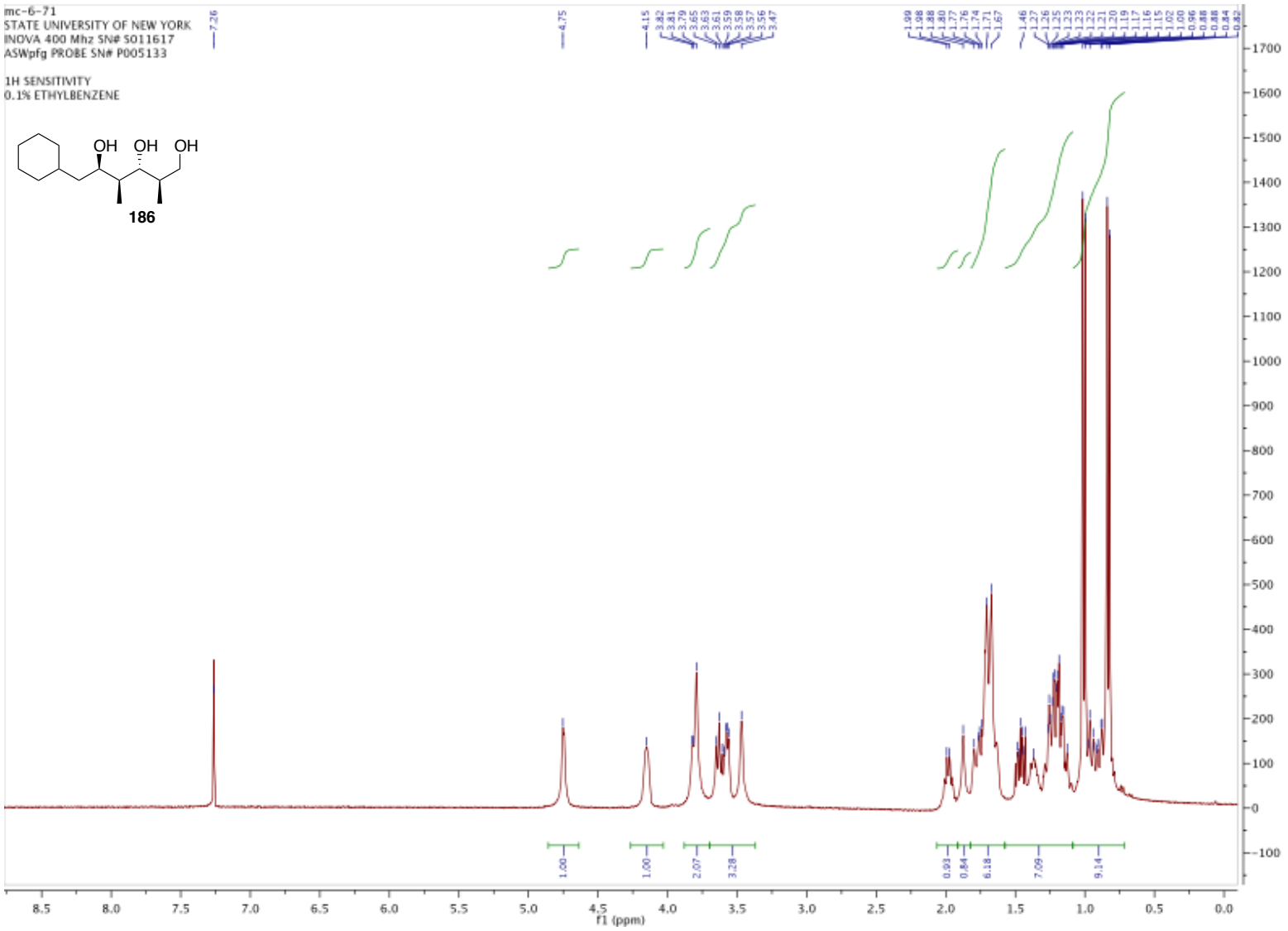

mc-5-71.c13
13C OBSERVE
144.54
128.83
128.71
127.51
126.68
98.56
85.89
77.29 CDCl3
76.98 CDCl3
76.66 CDCl3
73.73
71.69
70.77
70.72
63.86
40.71
35.36
33.94
33.65
33.22
32.94
32.89
29.96
26.67
26.30
19.53
13.04
4.55
O
O
OTr
183
f1 (ppm)

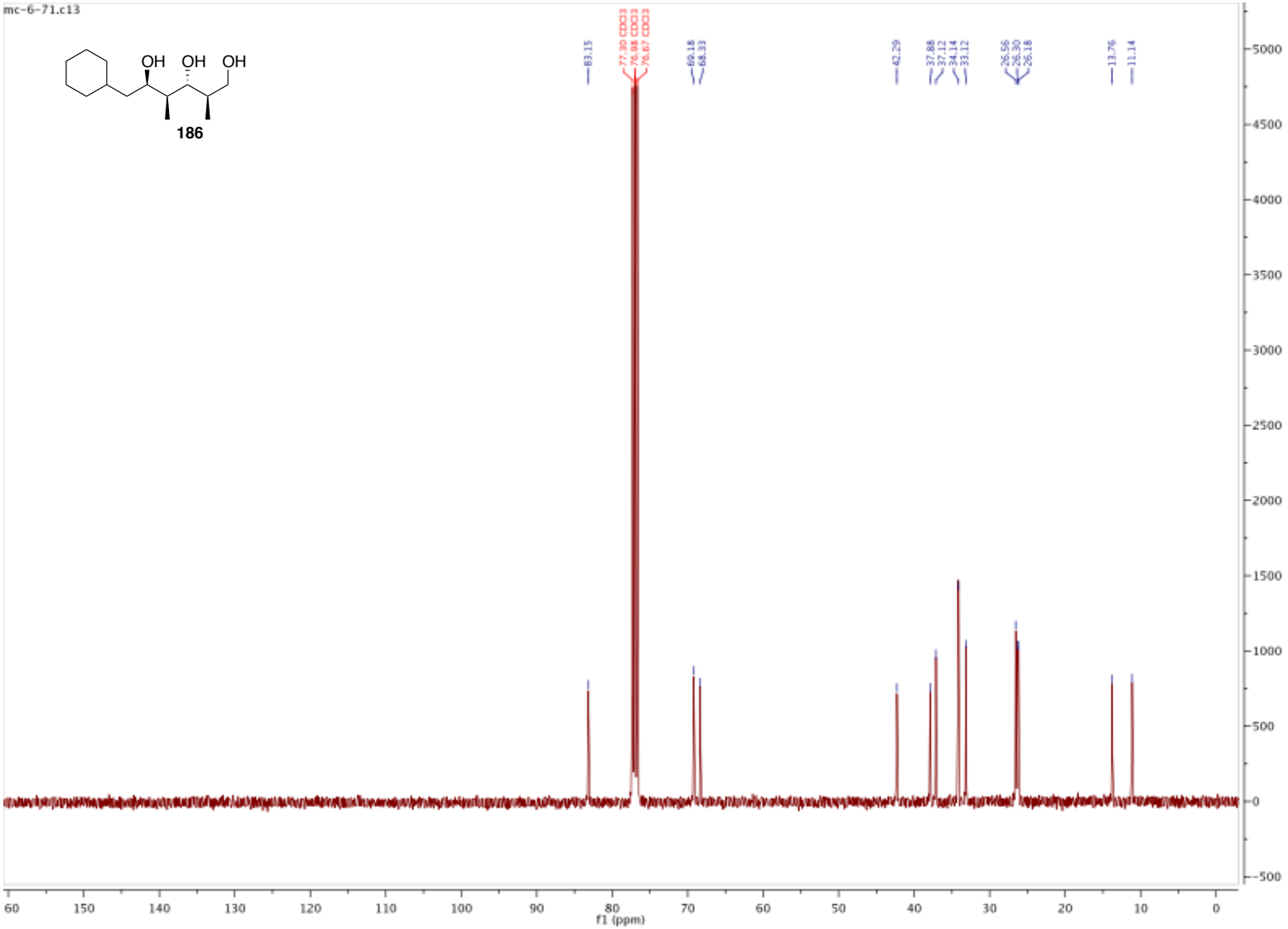

mc-5-69pdt
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617-1
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
184
f1 (ppm)

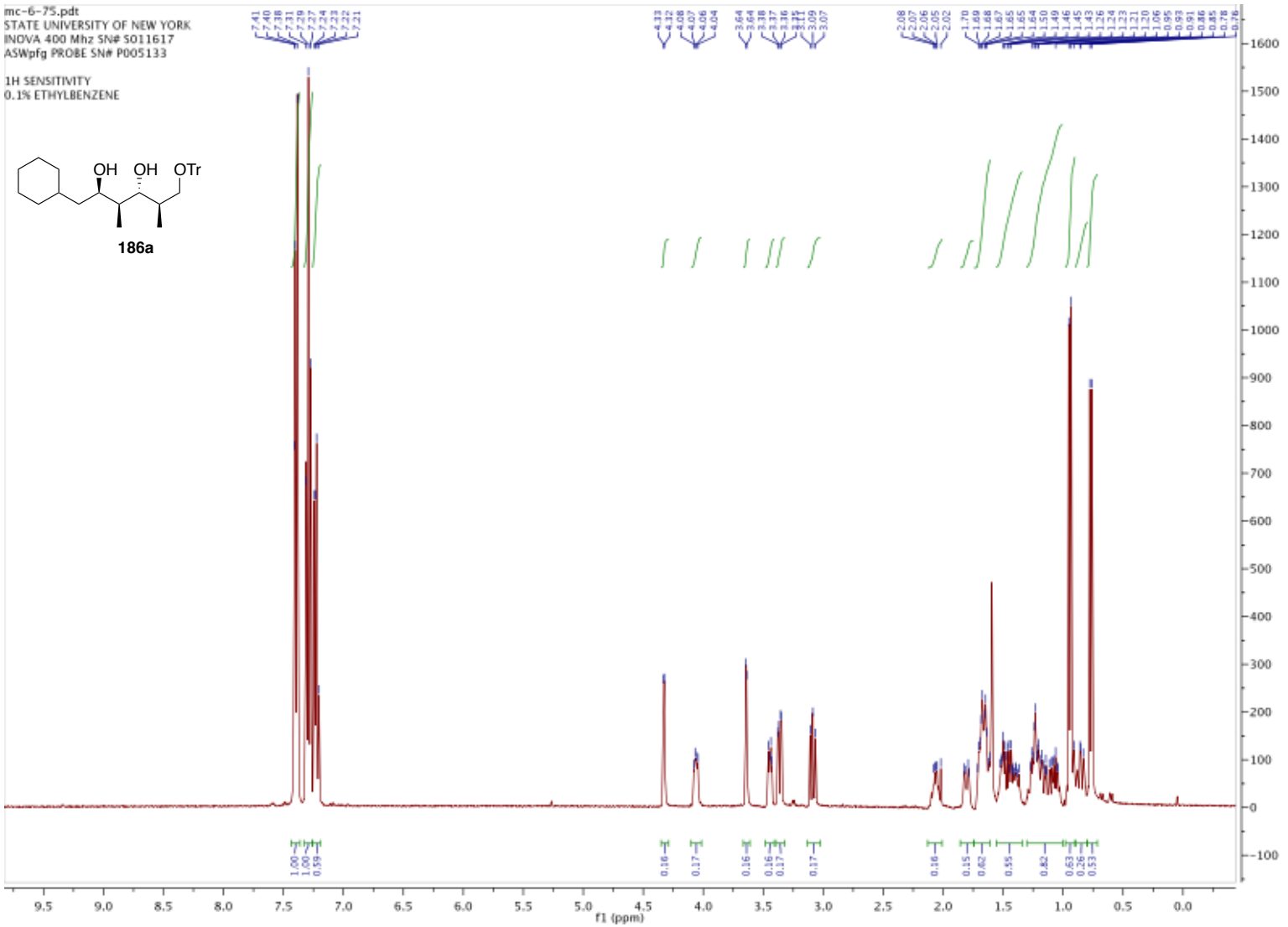

mc-5-69pdt.c13
13C OBSERVE
144.37
128.95
127.50
126.71
100.47
77.29 CDCl3
76.66 CDCl3
72.49
69.82
64.66
42.74
38.82
34.32
34.06
33.95
32.39
26.67
26.32
26.19
25.05
23.65
13.83
11.43
184
f1 (ppm)

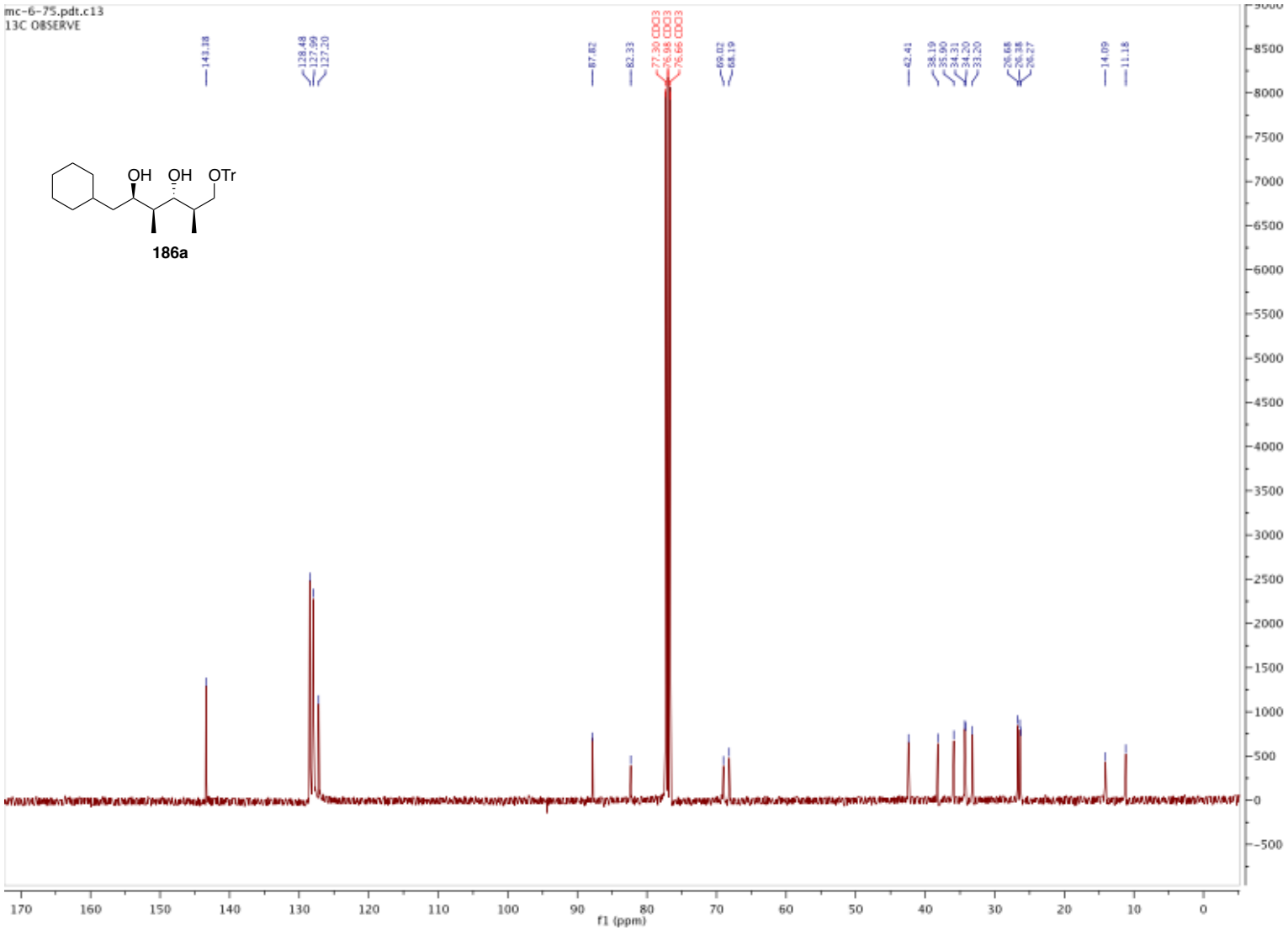

mc-6-35.pdt
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# 501 IC13
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
OTBDPS
185
f1 (ppm)

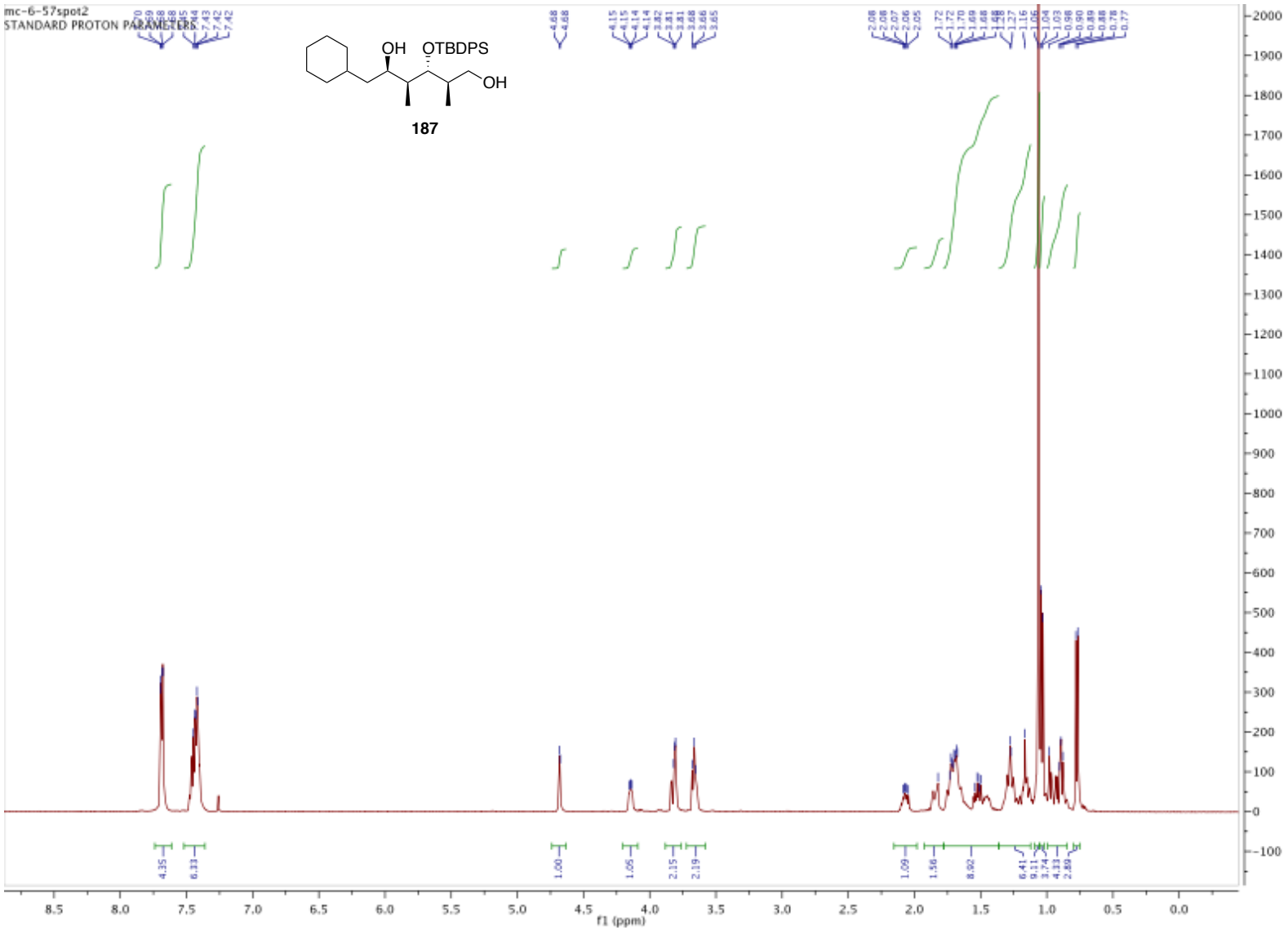

mc-6-35.pdt.c13
13C OBSERVE
OTBDPS
185
f1 (ppm)

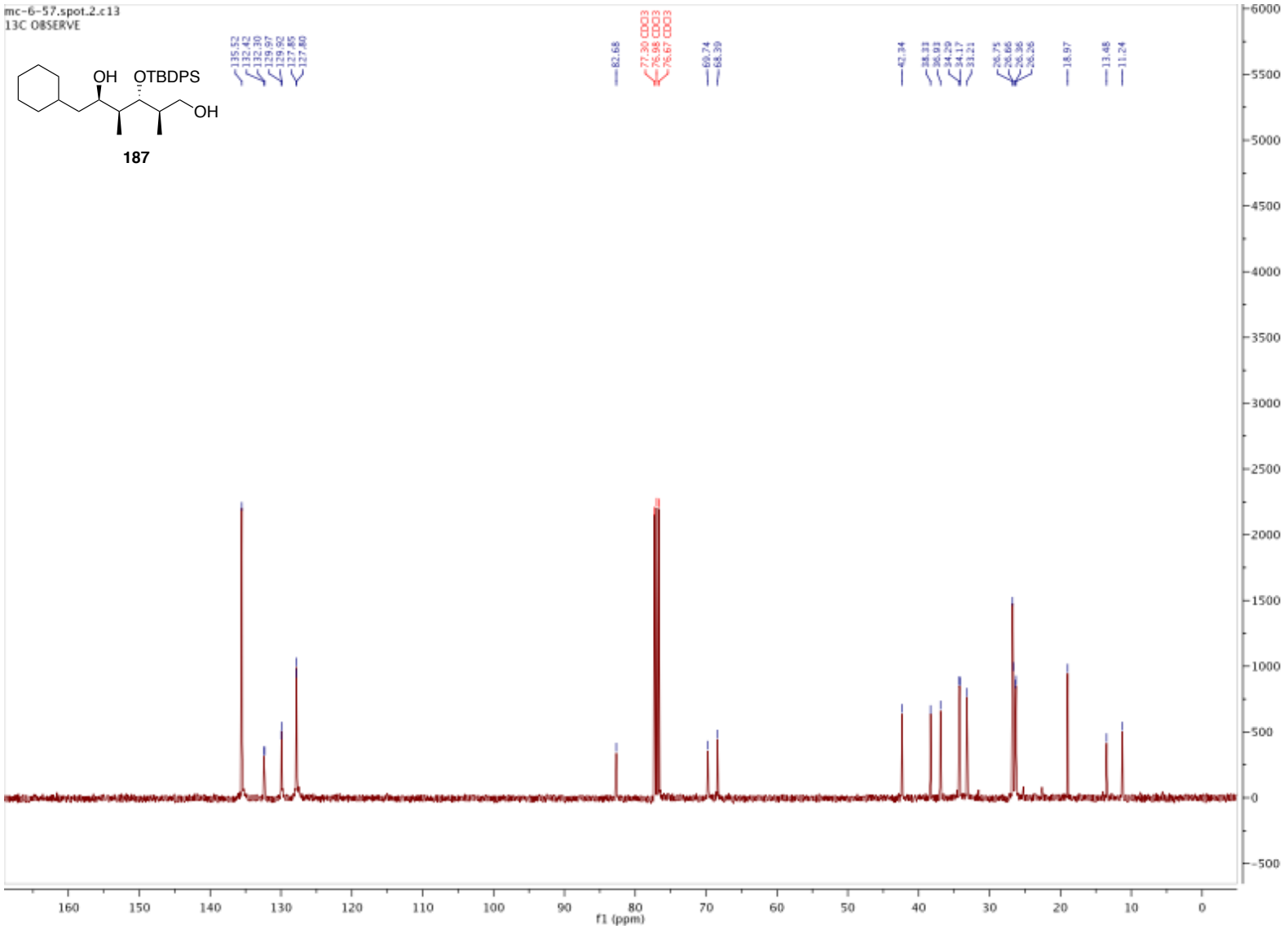

mc-6-71
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
OH
OH
OH
186
f1 (ppm)

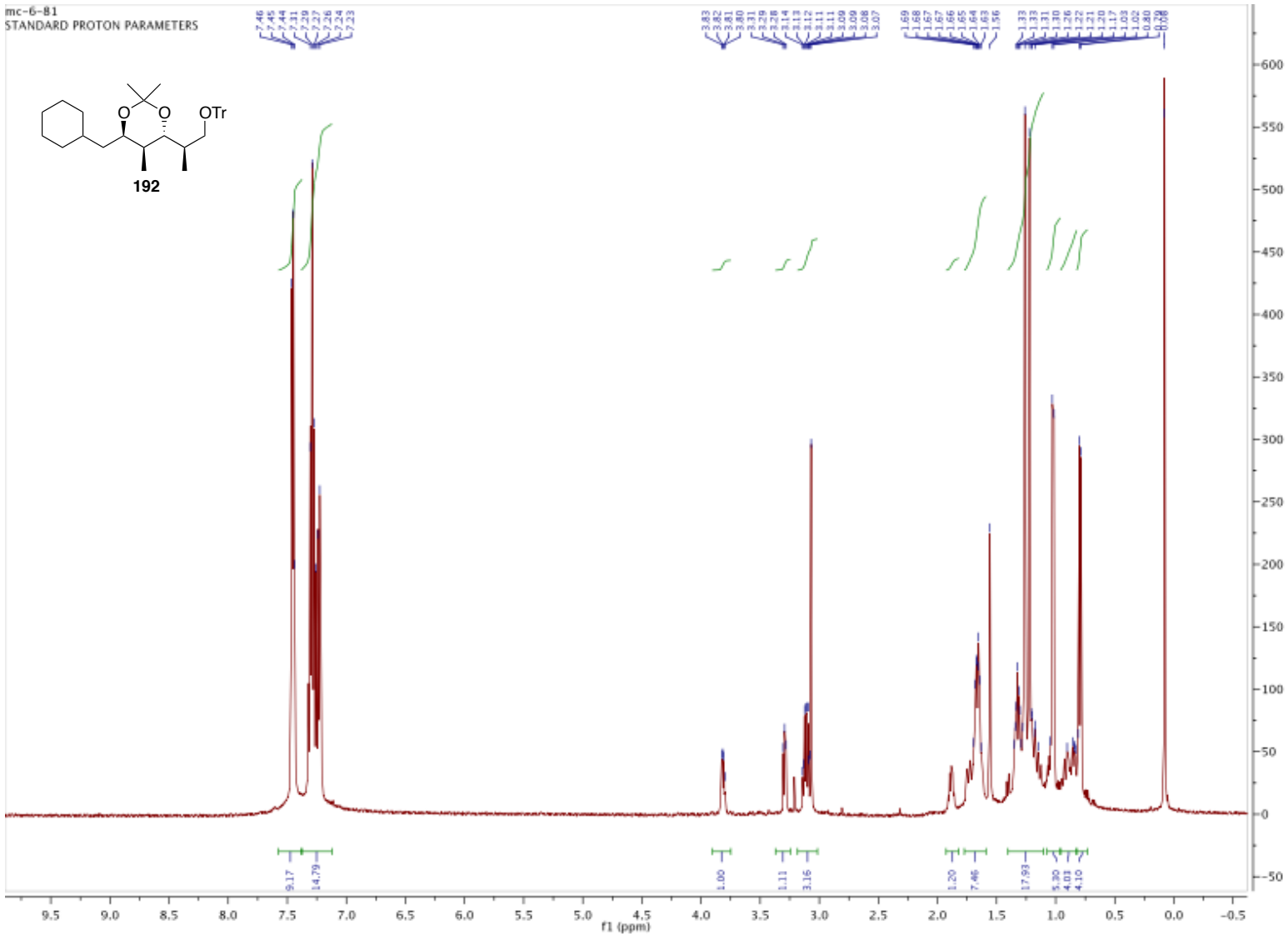

mc-6-71.c13
OH
OH
OH
186
83.15
77.30 CDCl3
76.98 CDCl3
76.67 CDCl3
69.18
68.33
42.29
37.88
37.12
34.14
33.12
26.56
26.30
26.18
13.76
11.14
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
60
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

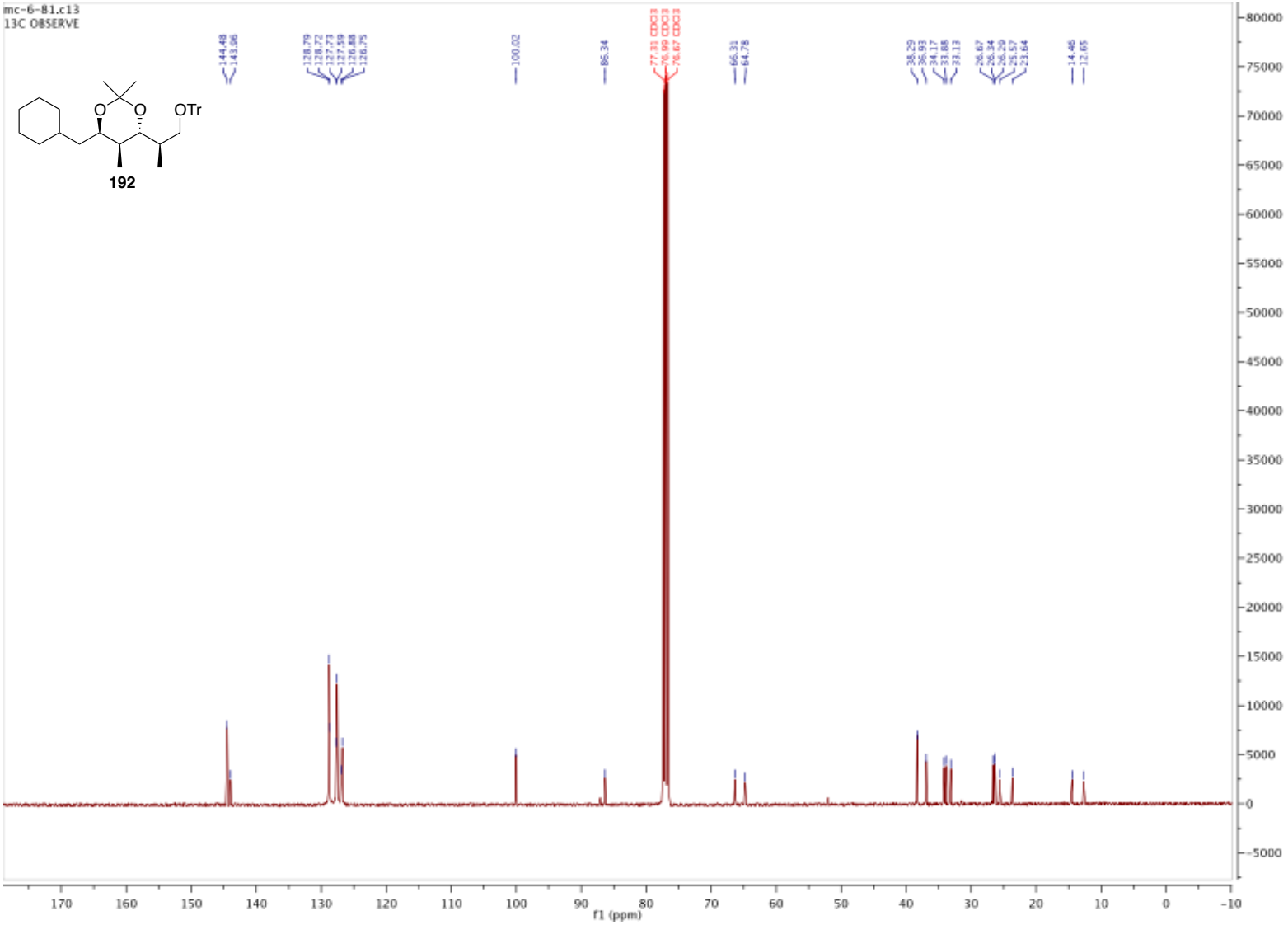

mc-6-75.pdt
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
OH
OH
OTr
186a
f1 (ppm)

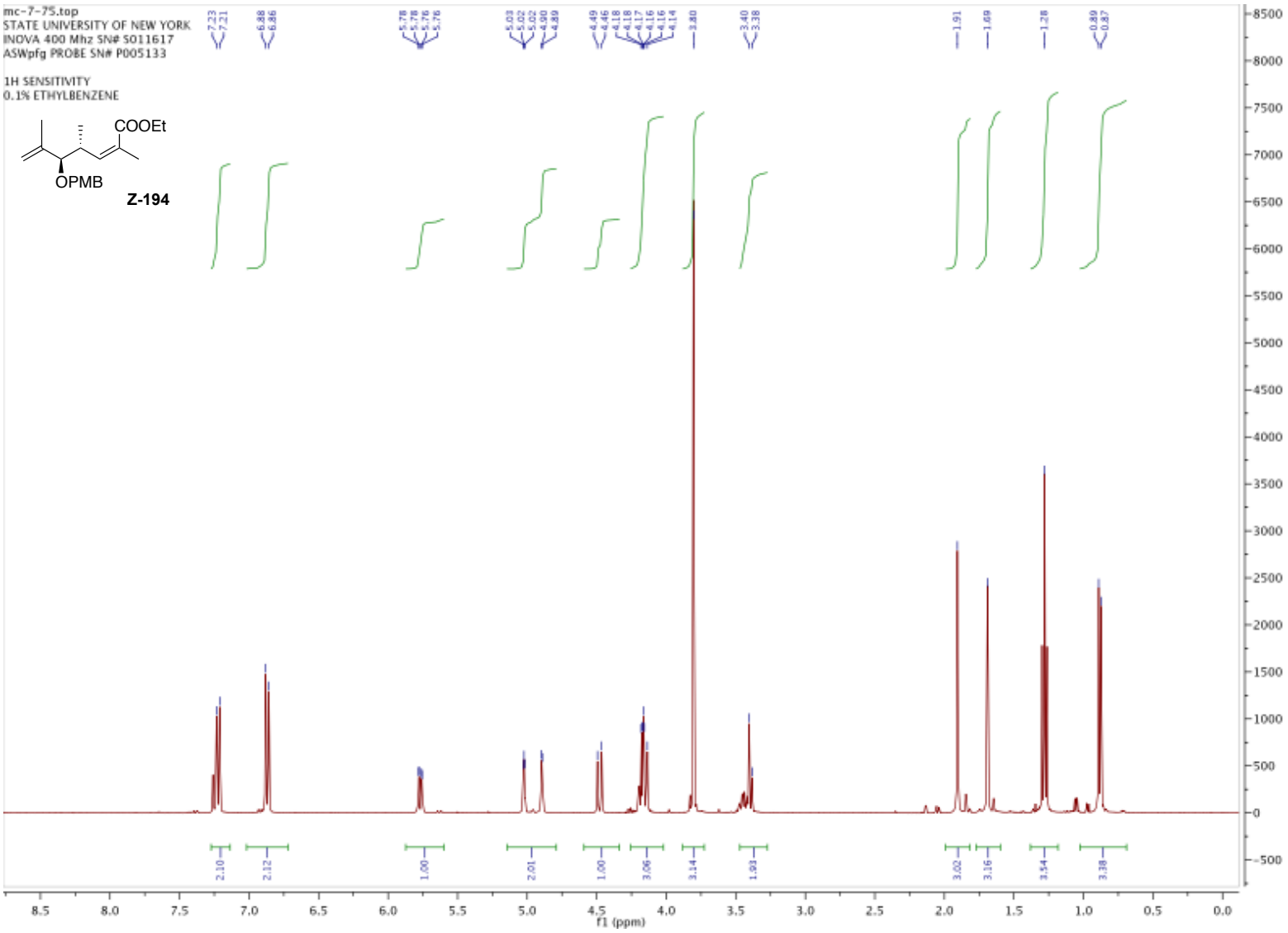

mc-6-75.pdt.c13
13C OBSERVE
OH
OH
OTr
186a
f1 (ppm)

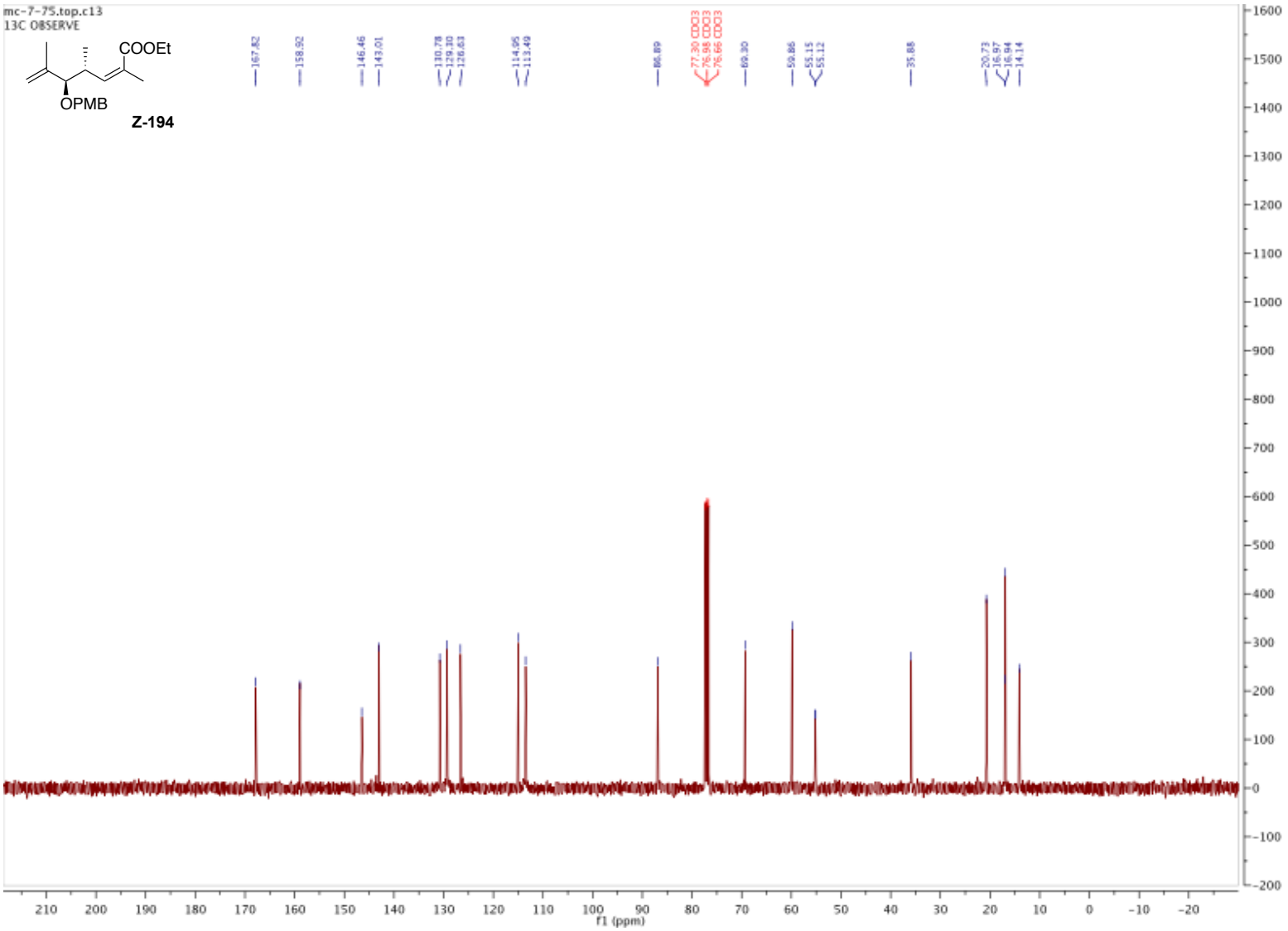

mc-6-57spot2
STANDARD PROTON PARAMETERS
OH
OTBDPS
OH
187
f1 (ppm)

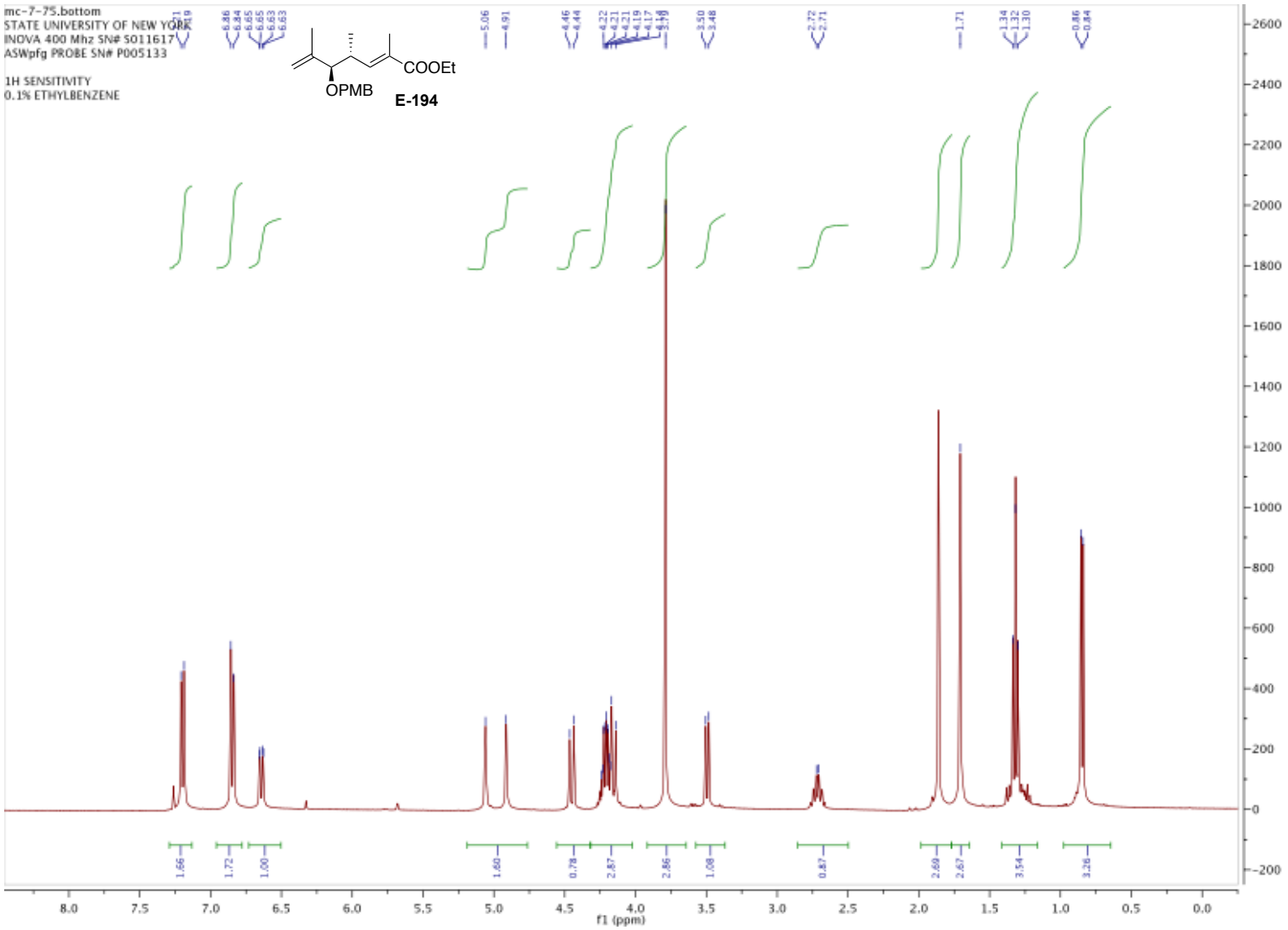

mc-6-57.spot.2.c13
13C OBSERVE
OH
OTBDPS
OH
187
135.52
132.42
132.30
129.97
129.92
127.85
127.80
82.68
77.39 CDCl3
76.98 CDCl3
76.67 CDCl3
69.74
68.39
42.34
38.33
36.93
34.29
34.17
31.21
26.75
26.66
26.36
26.26
18.97
13.48
11.24
f1 (ppm)

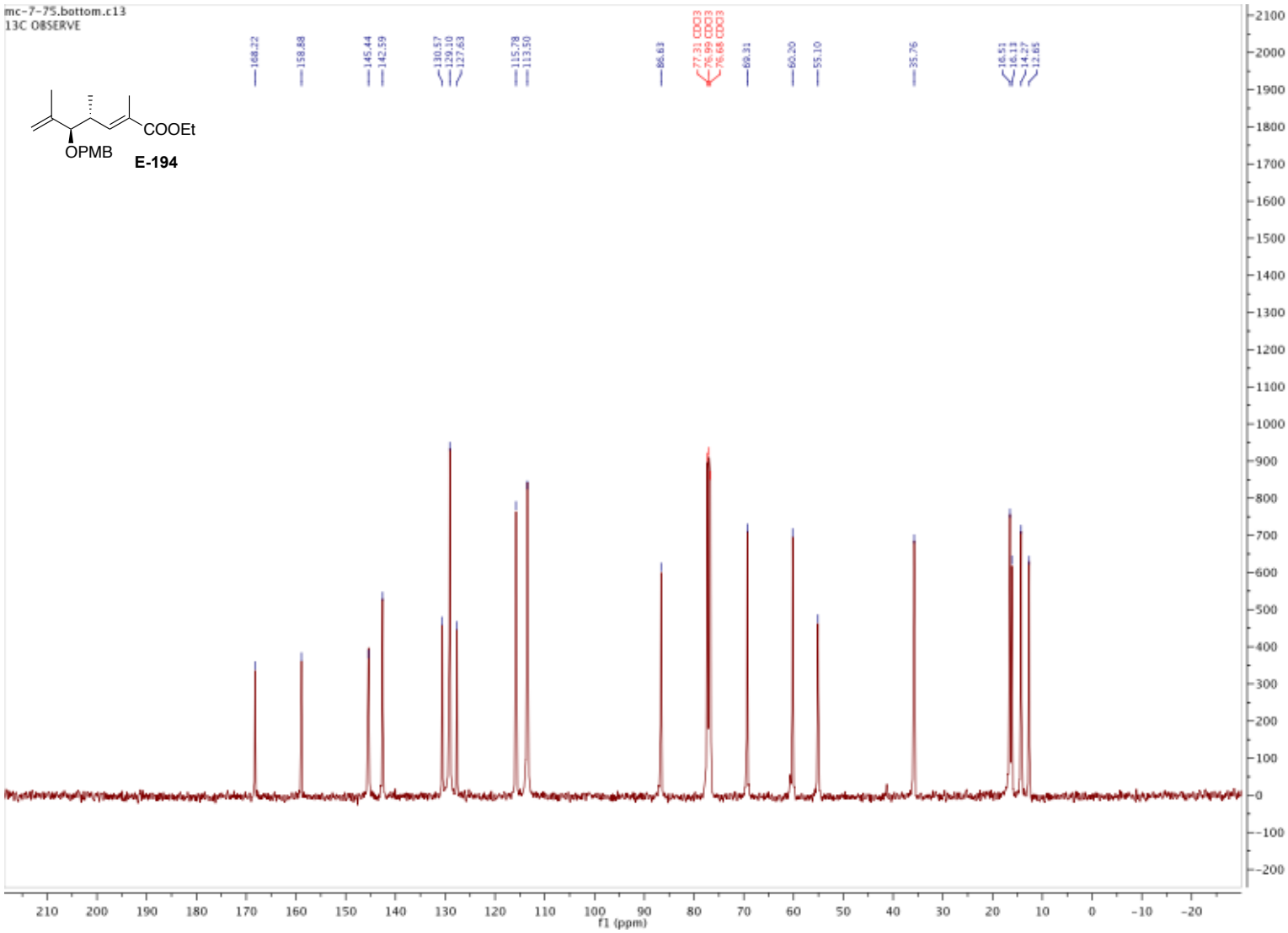

mc-6-81
STANDARD PROTON PARAMETERS
O
O
OTr
192
f1 (ppm)

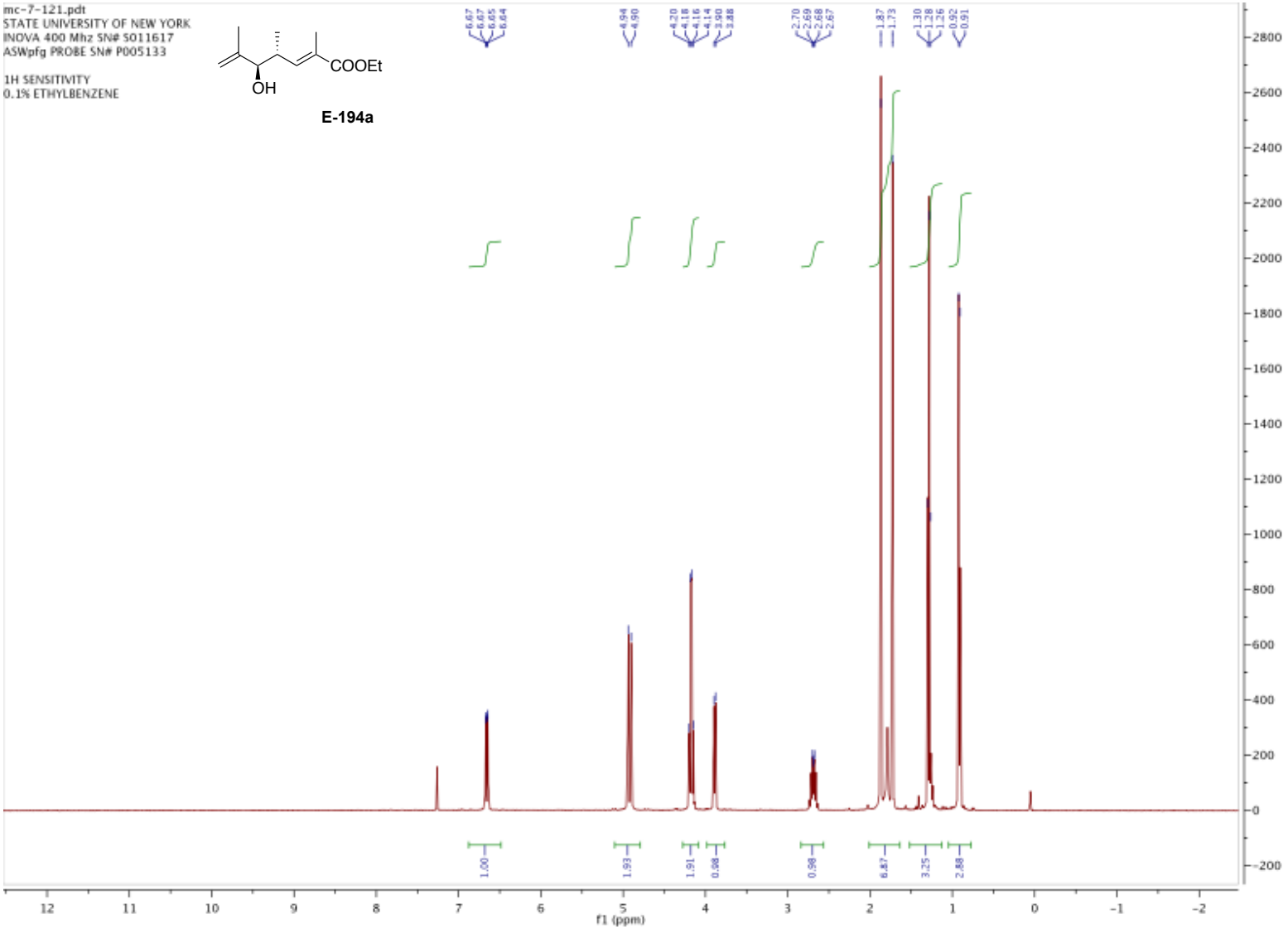

mc-6-81.c13
13C OBSERVE
144.48
143.96
128.79
128.72
127.73
127.59
126.88
126.75
100.02
86.34
77.31 CDCl3
76.99 CDCl3
76.67 CDCl3
66.31
64.78
38.29
36.93
34.17
33.68
33.13
26.67
26.34
26.29
25.57
23.64
14.46
12.65
O
O
OTr
192
f1 (ppm)

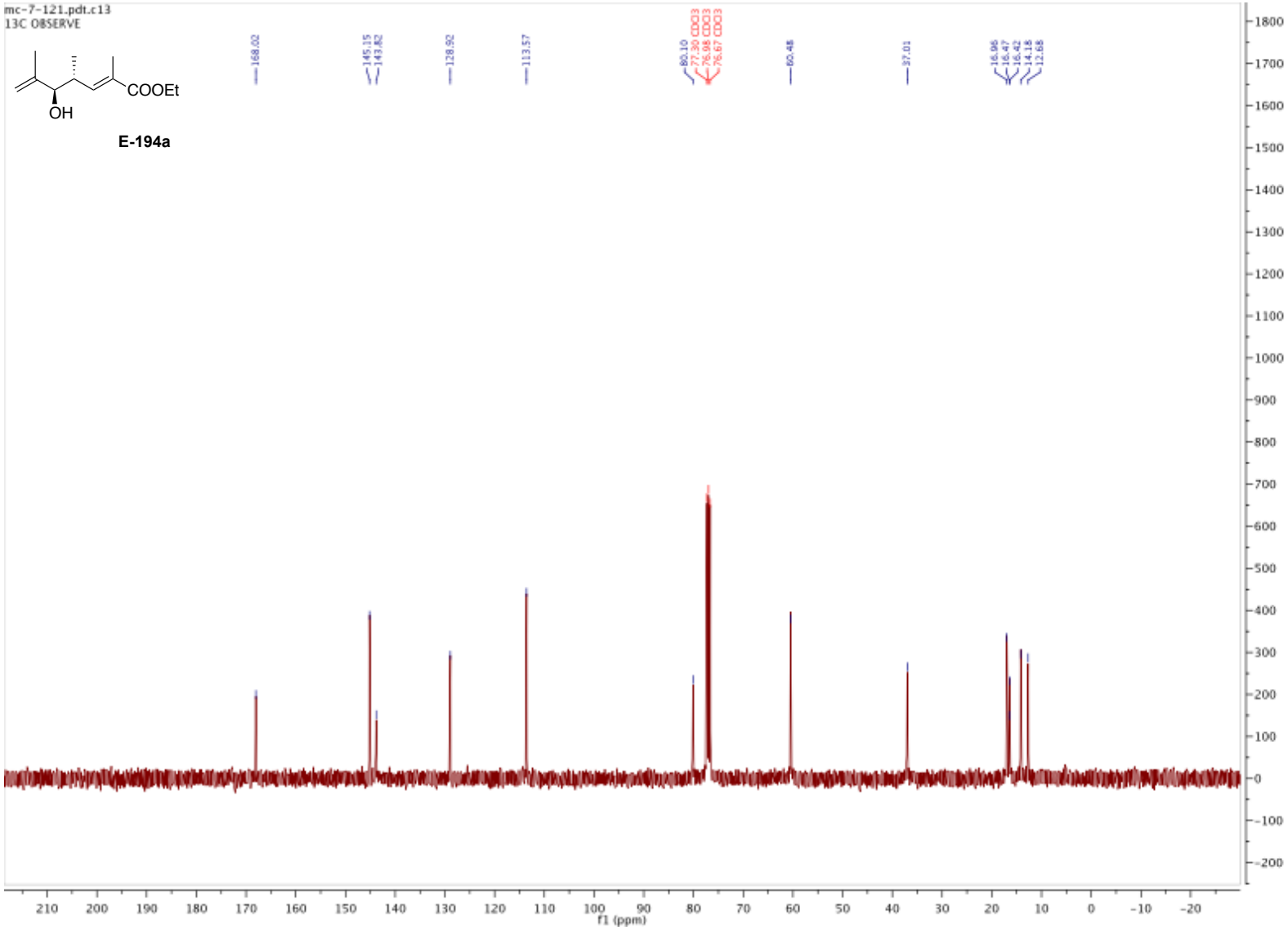

mc-7-75.top
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
COOEt
OPMB
Z-194
f1 (ppm)

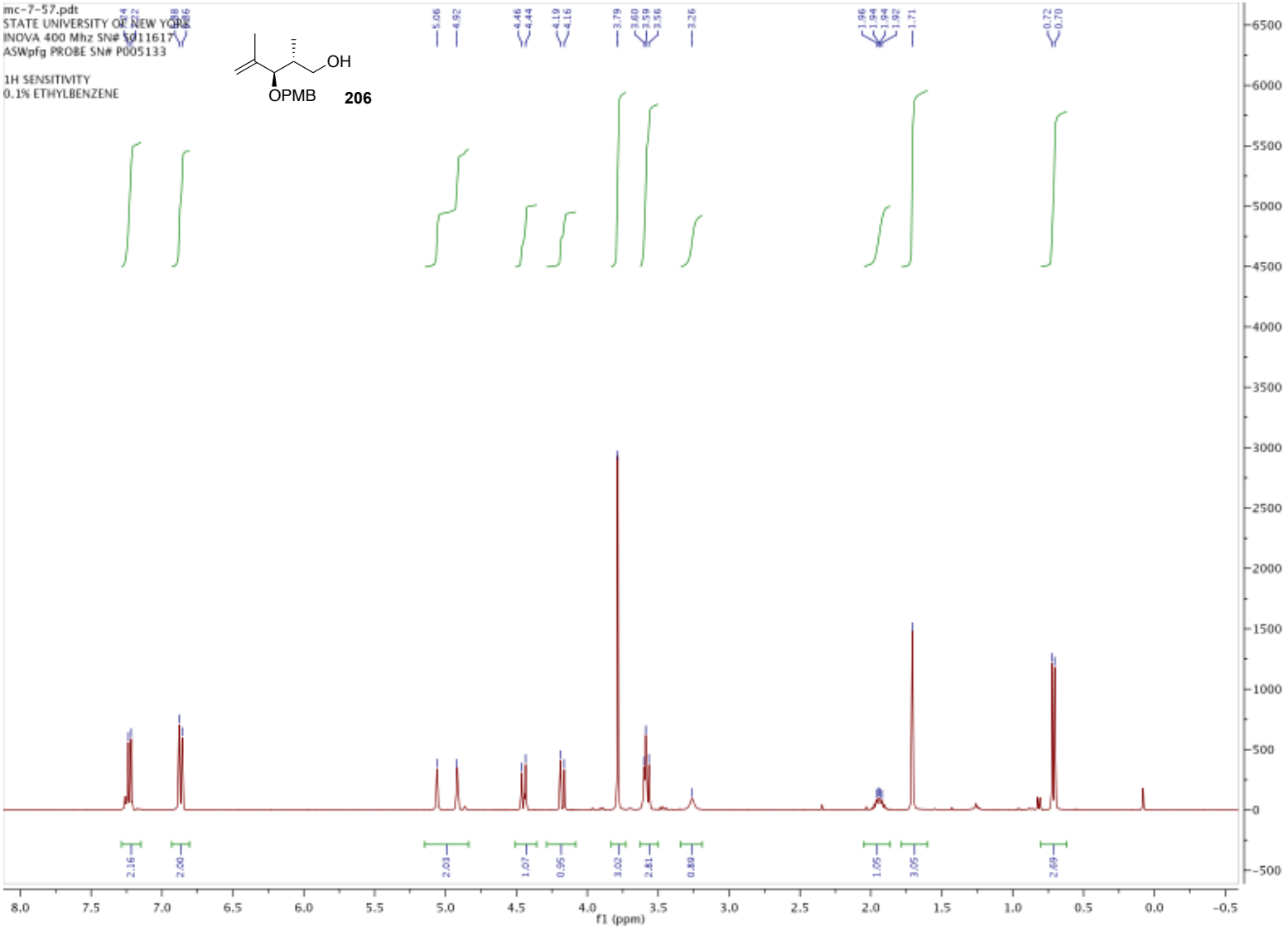

mc-7-75.top.c13
13C OBSERVE
COOEt
OPMB
Z-194
167.82
158.92
146.46
143.01
130.78
129.30
126.63
114.95
113.49
86.89
77.39 CDCl3
76.98 CDCl3
76.66 CDCl3
69.30
59.86
55.15
55.12
35.88
20.73
16.97
16.94
14.14
f1 (ppm)

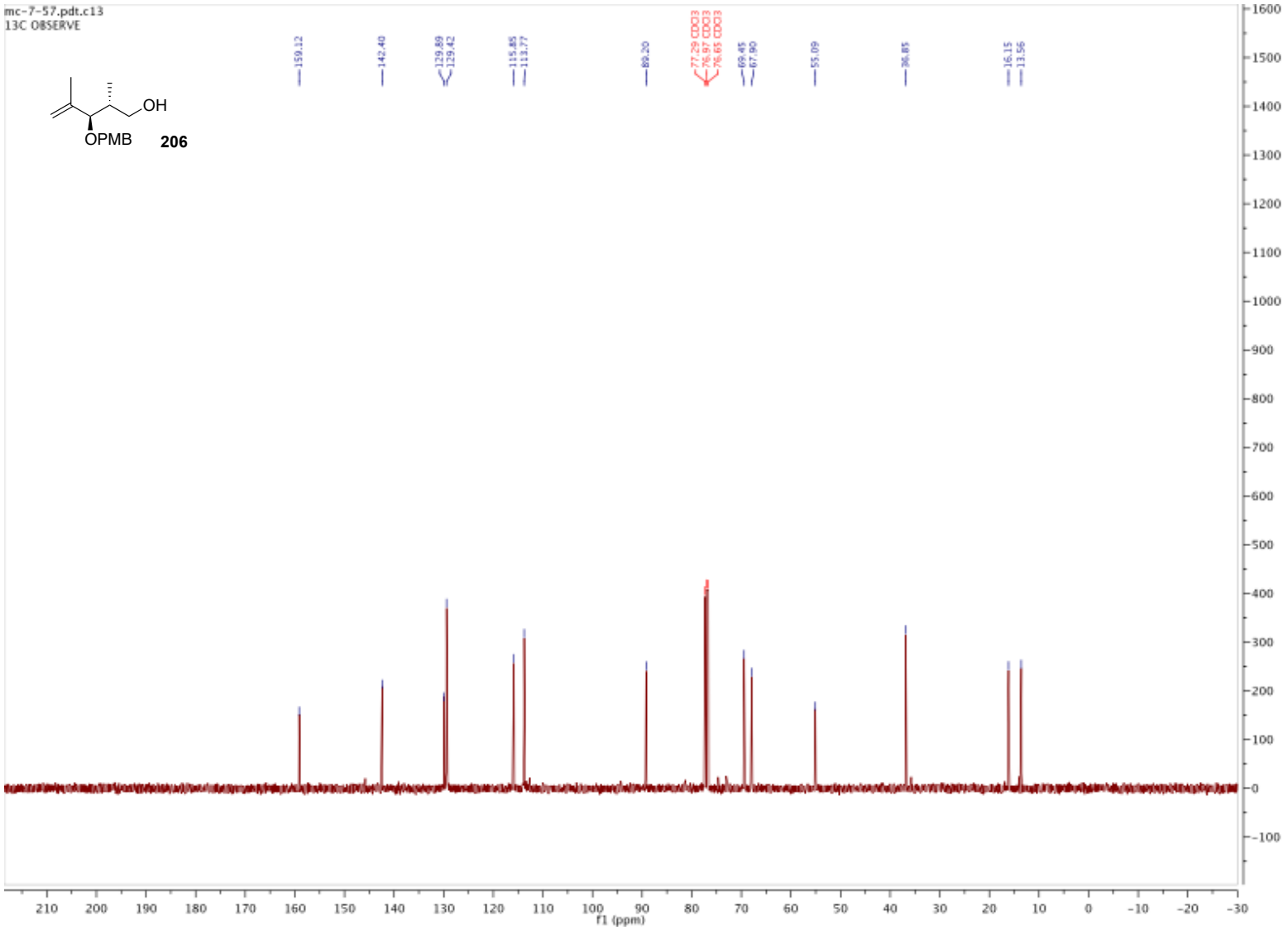

mc-7-75.bottom
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
OPMB
COOEt
E-194
f1 (ppm)

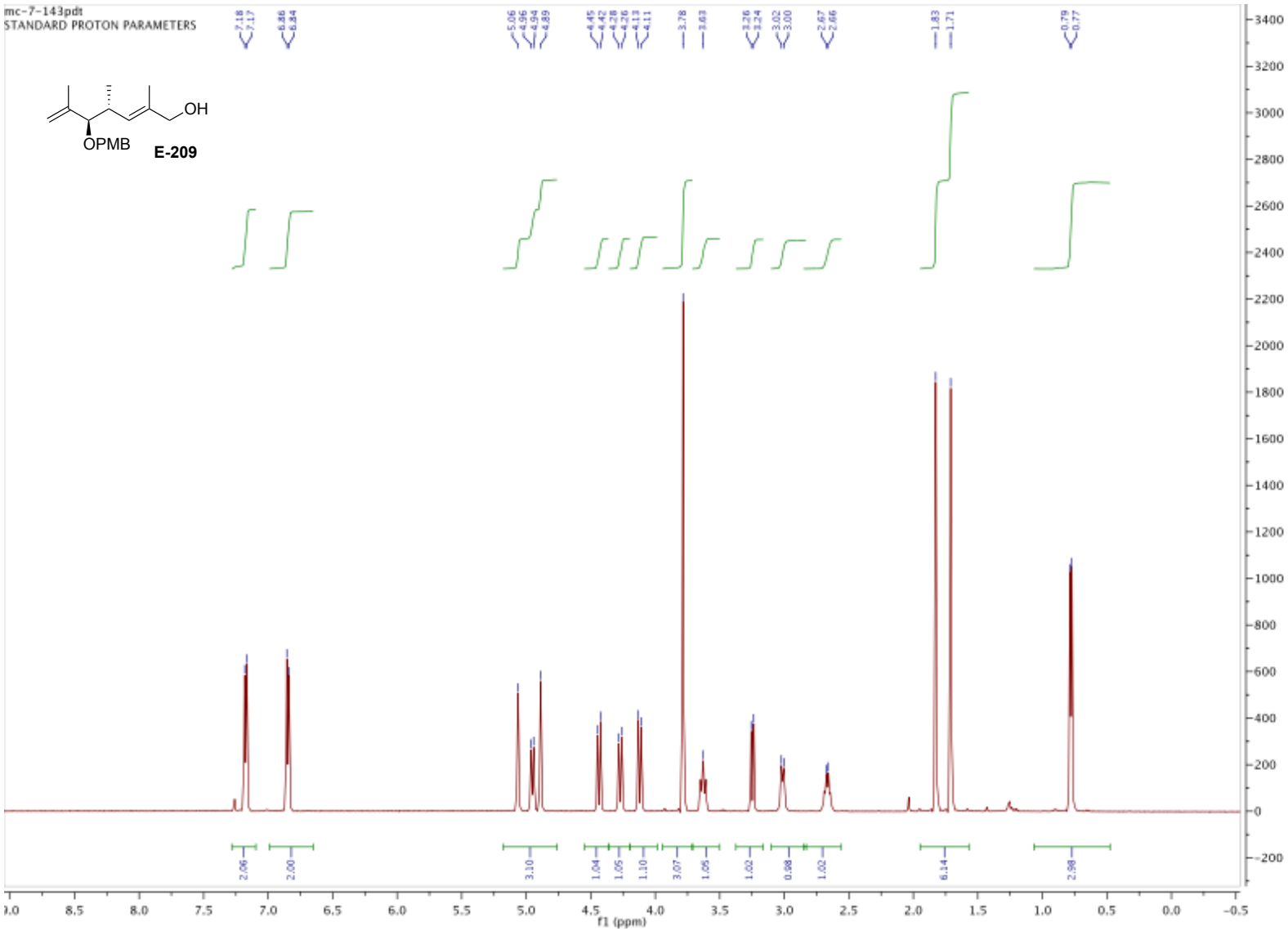

mc-7-75.bottom.c13
13C OBSERVE
168.22
158.88
145.44
142.59
130.67
129.10
127.83
115.78
113.50
86.63
77.31 CDCl3
76.99 CDCl3
76.68 CDCl3
69.31
60.20
55.10
35.76
16.51
16.11
14.27
12.65
COOEt
OPMB
E-194
f1 (ppm)

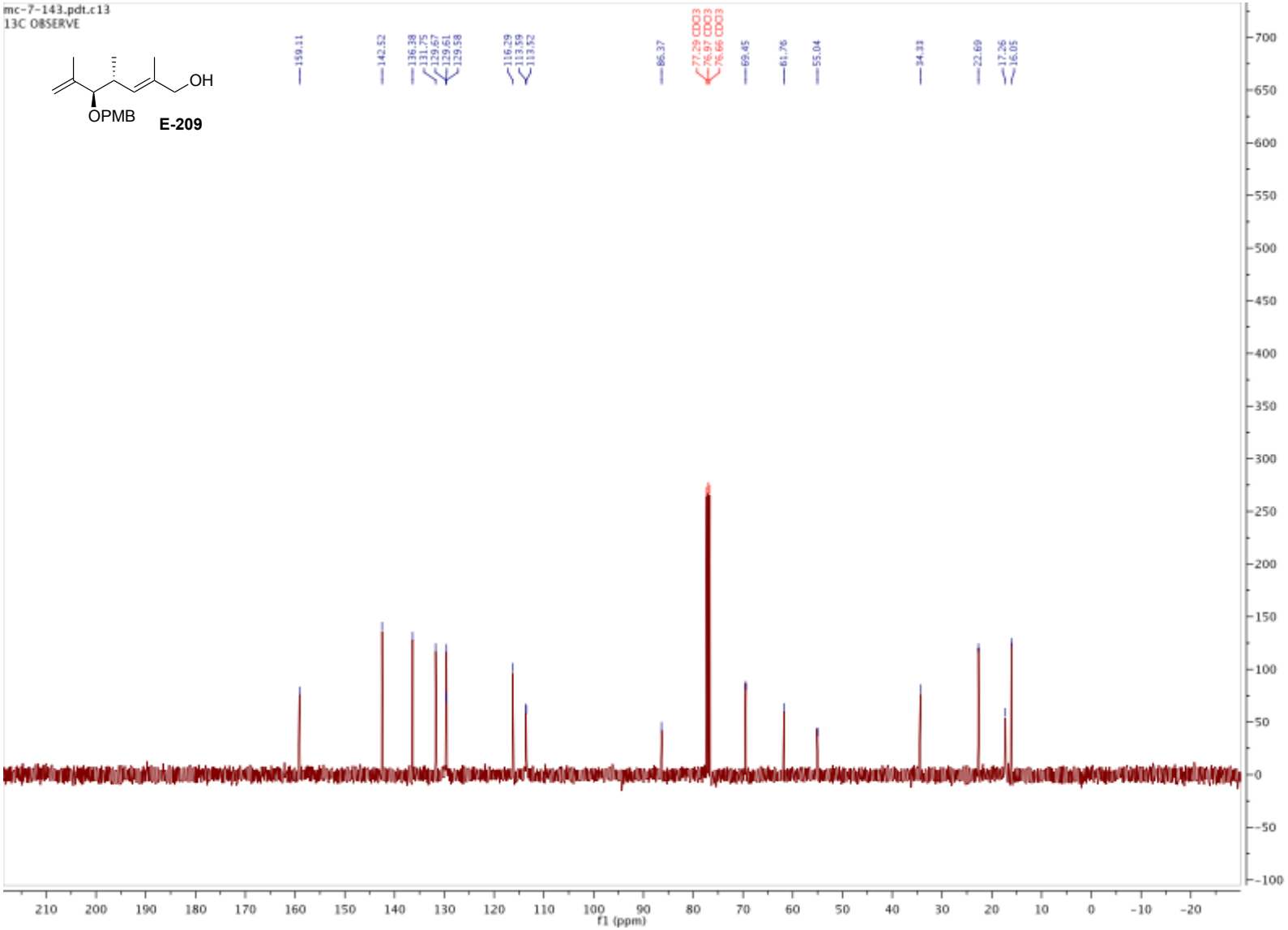

mc-7-121.pdt
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
COOEt
OH
E-194a
f1 (ppm)

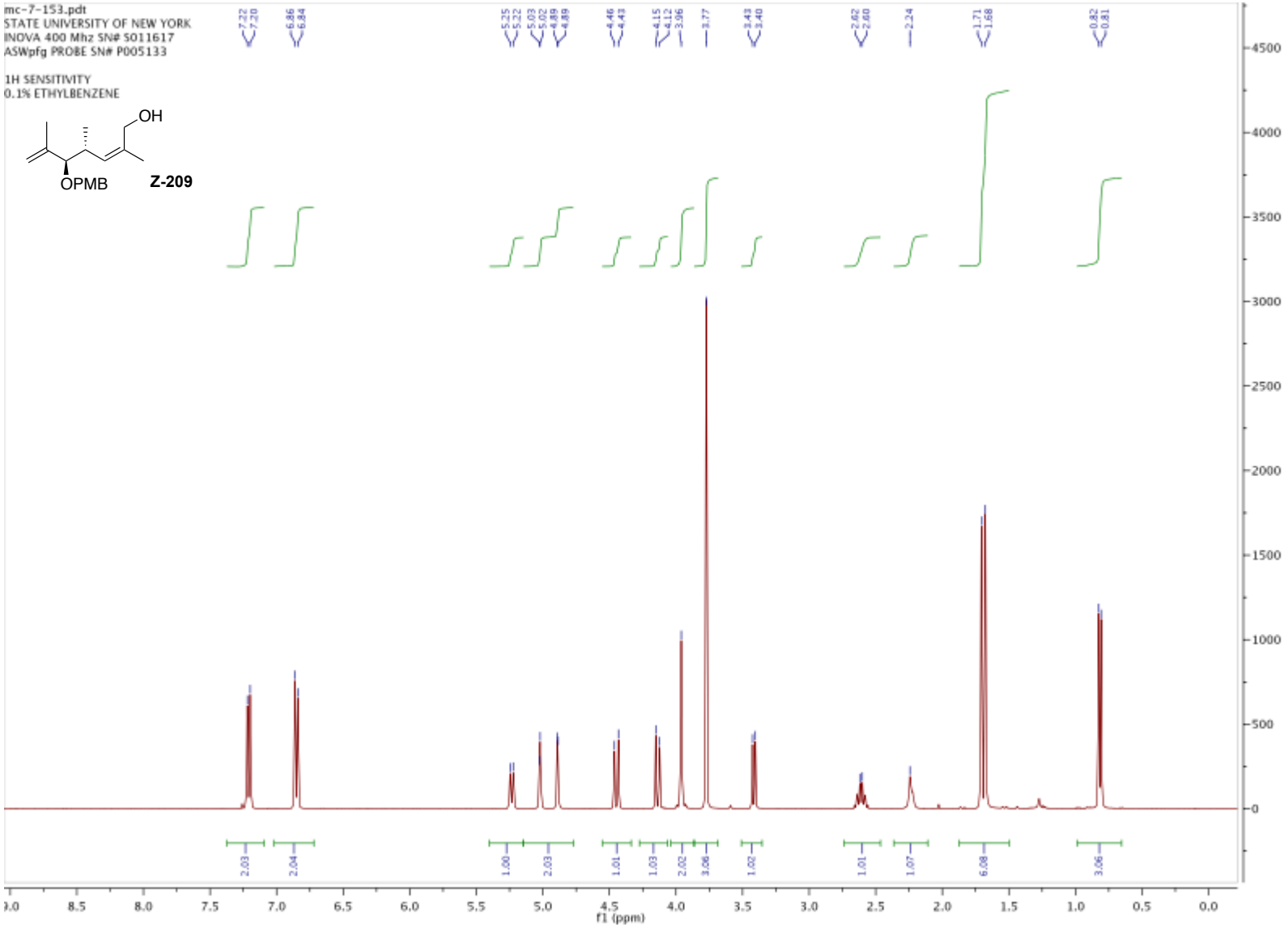

mc-7-121.pdt.c13
13C OBSERVE
OH
COOEt
E-194a
168.02
145.15
143.82
128.92
113.57
80.10
77.30 CDCl3
76.98 CDCl3
76.67 CDCl3
60.48
37.01
16.96
16.47
16.42
14.18
12.68
f1 (ppm)

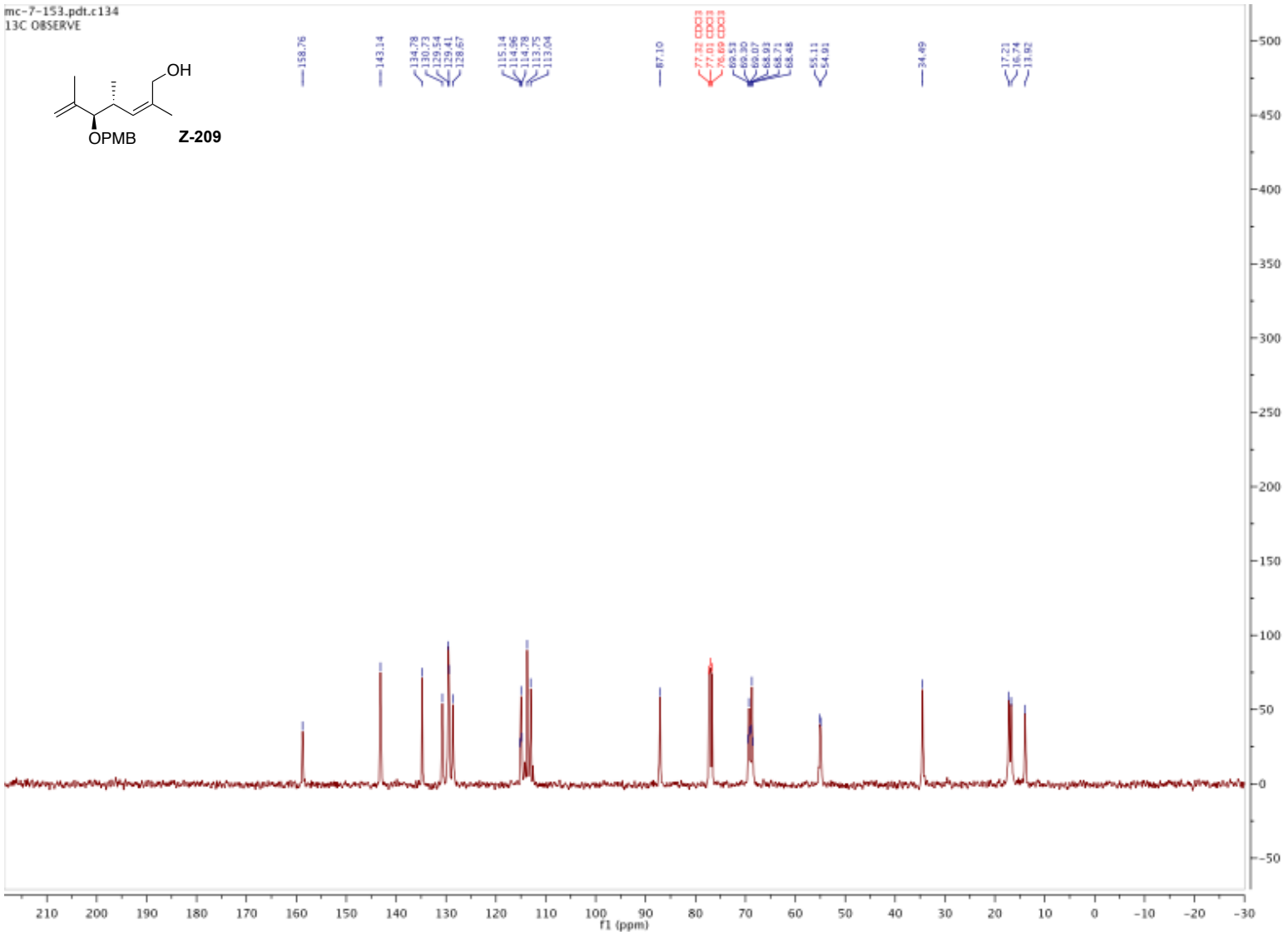

mc-7-57.pdt
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# sd11617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
OH
OPMB
206
f1 (ppm)

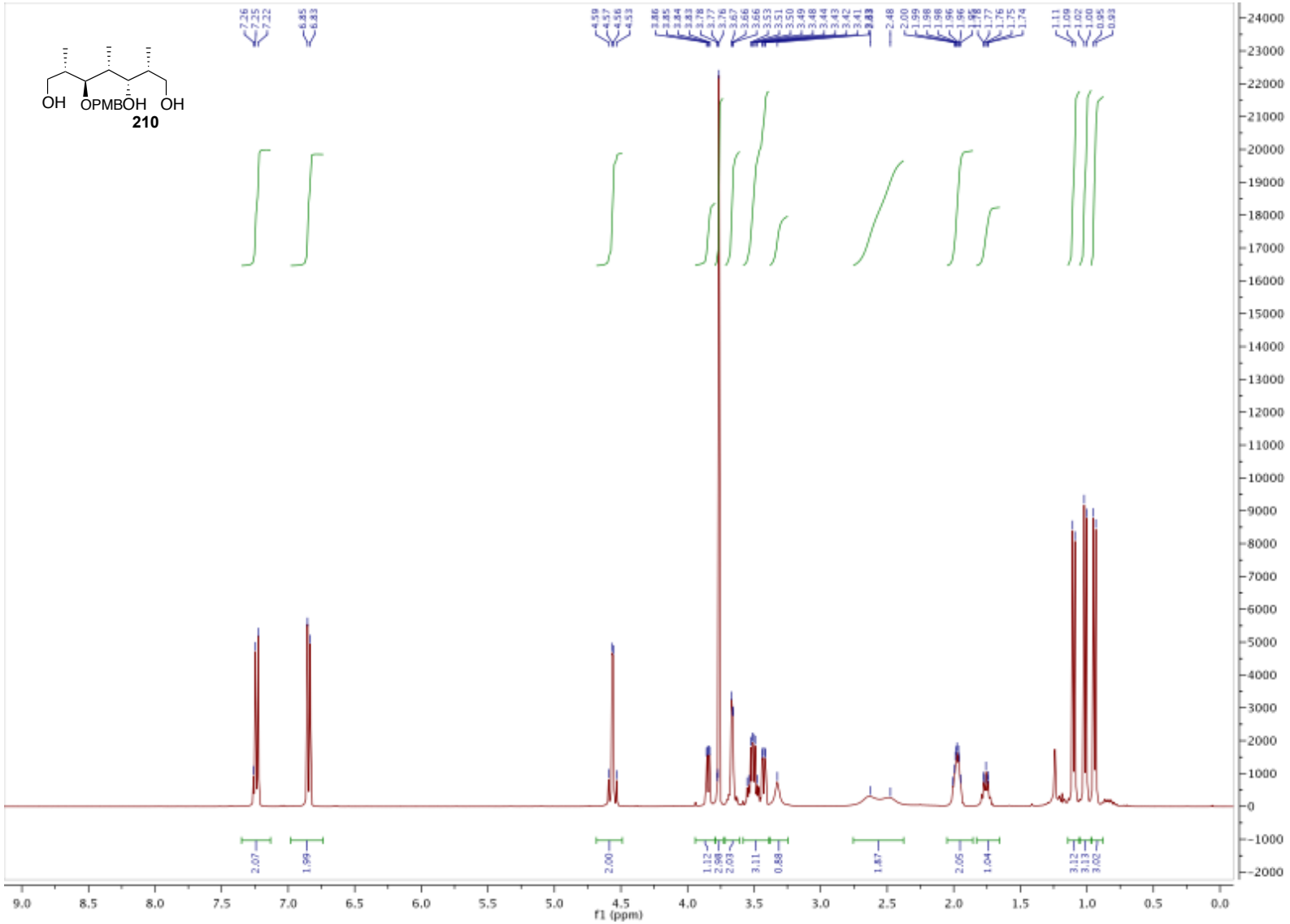

mc-7-57.pdt.c13
13C OBSERVE
OH
OPMB
206
159.12
142.40
129.89
129.42
115.85
113.77
89.20
77.29 CDCl3
76.97 CDCl3
76.65 CDCl3
69.45
67.90
55.09
36.85
16.15
13.56
f1 (ppm)

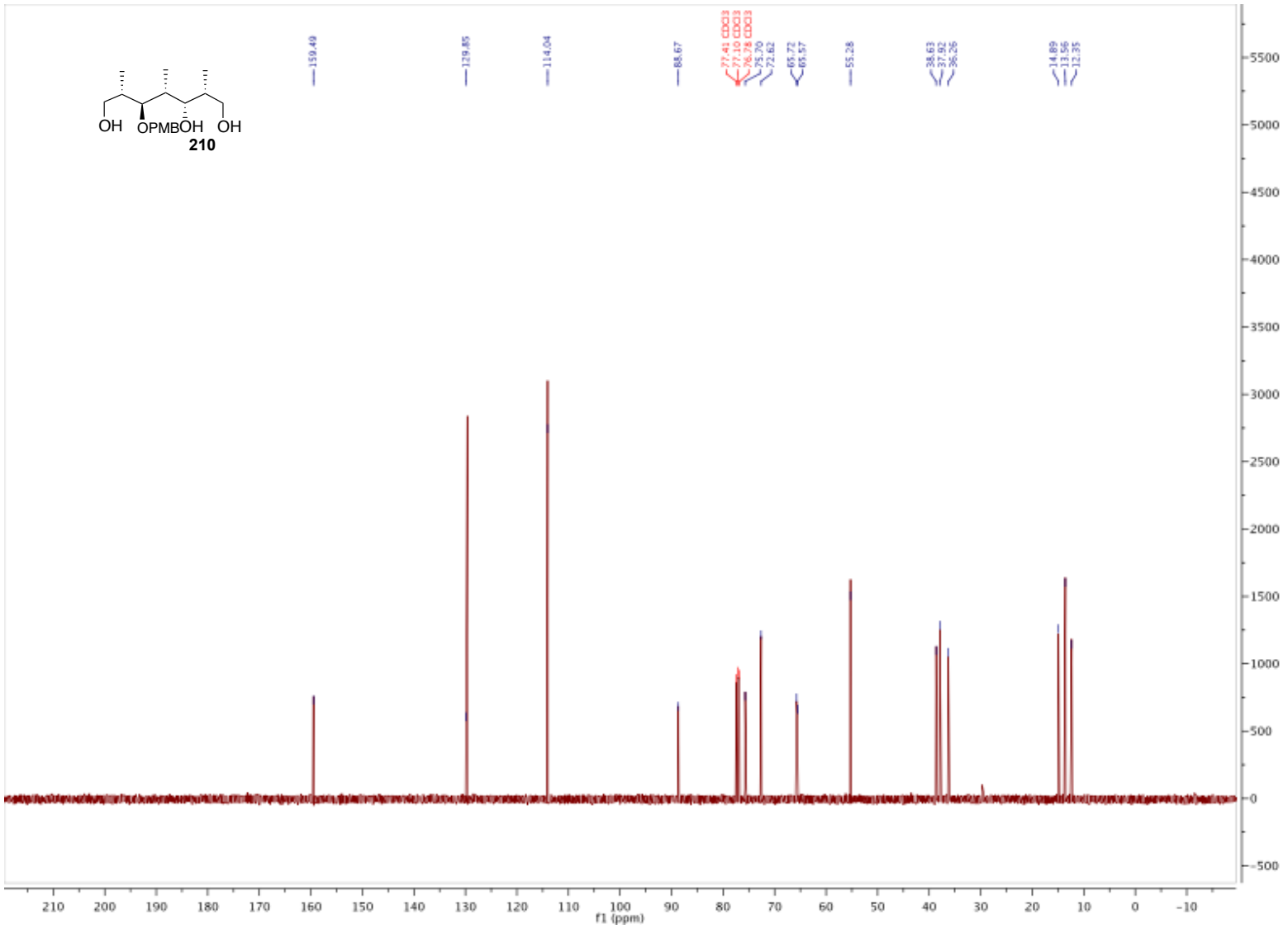

mc-7-143pdt
STANDARD PROTON PARAMETERS
OH
OPMB
E-209
f1 (ppm)

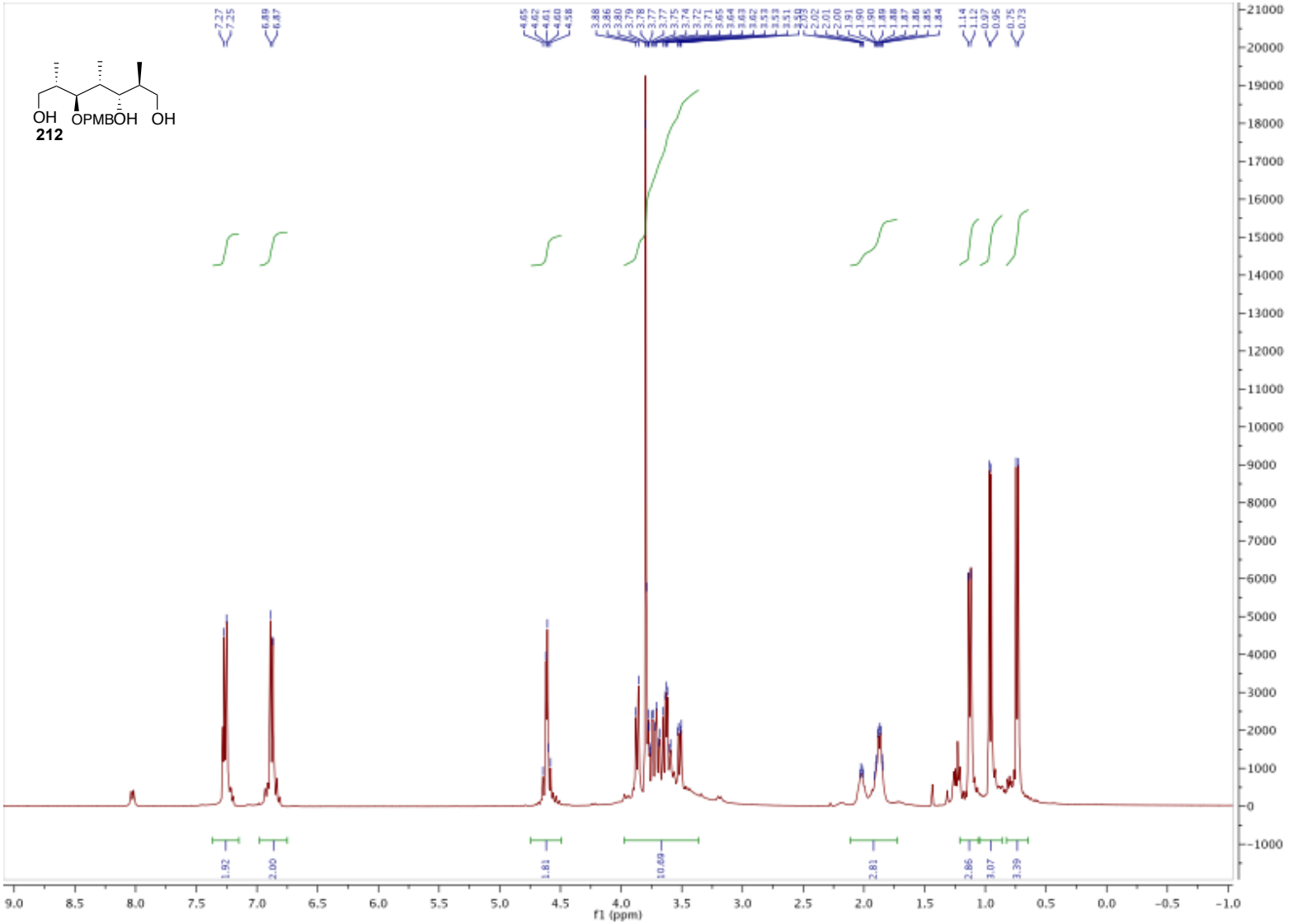

mc-7-143.pdt.c13
13C OBSERVE
OH
OPMB
E-209
159.11
142.52
136.38
131.75
129.67
129.61
129.58
116.29
113.59
113.52
86.37
77.29 CDCl3
76.97 CDCl3
76.66 CDCl3
69.45
61.76
55.04
34.33
22.69
17.26
16.05
f1 (ppm)

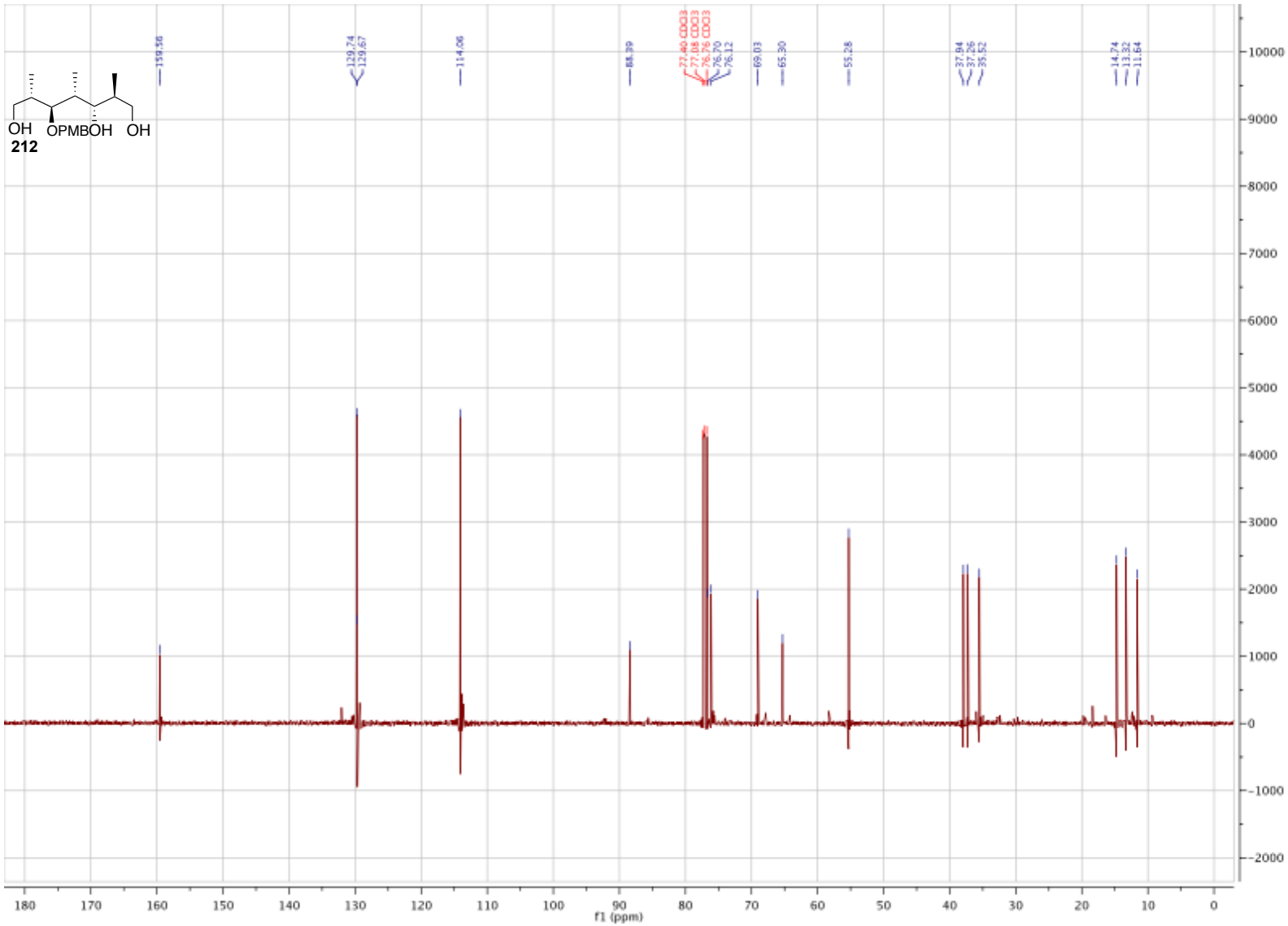

mc-7-153.pdt
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
OH
OPMB
Z-209
f1 (ppm)

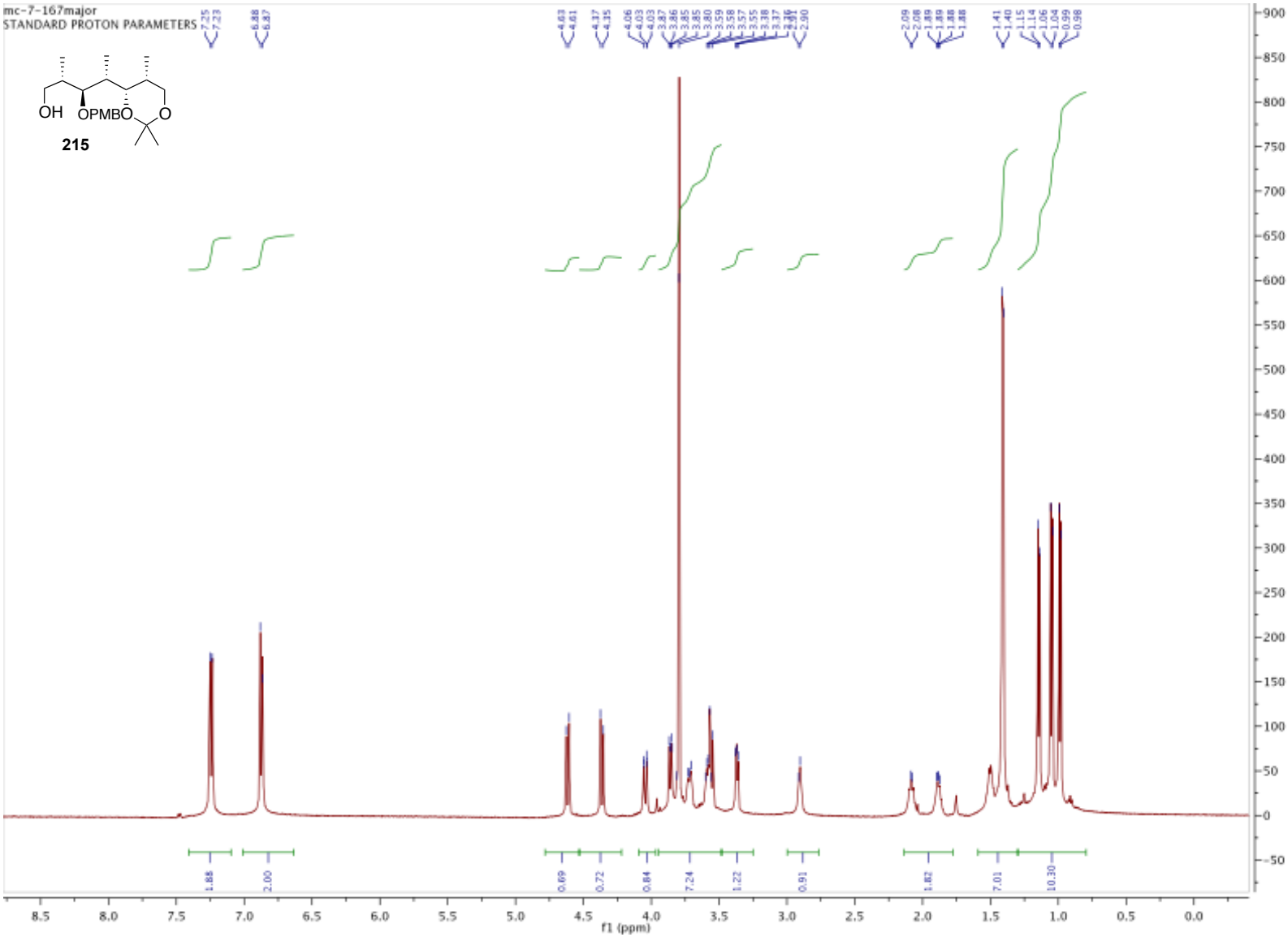

mc-7-153.pdt.c134
13C OBSERVE
OH
OPMB
Z-209
158.76
143.14
134.78
130.73
129.54
129.41
128.67
115.14
114.96
114.78
113.75
113.04
87.10
77.32 CDCl3
77.01 CDCl3
76.69 CDCl3
69.53
69.30
69.07
68.93
68.71
68.48
55.11
54.91
34.49
17.21
16.74
13.92
f1 (ppm)

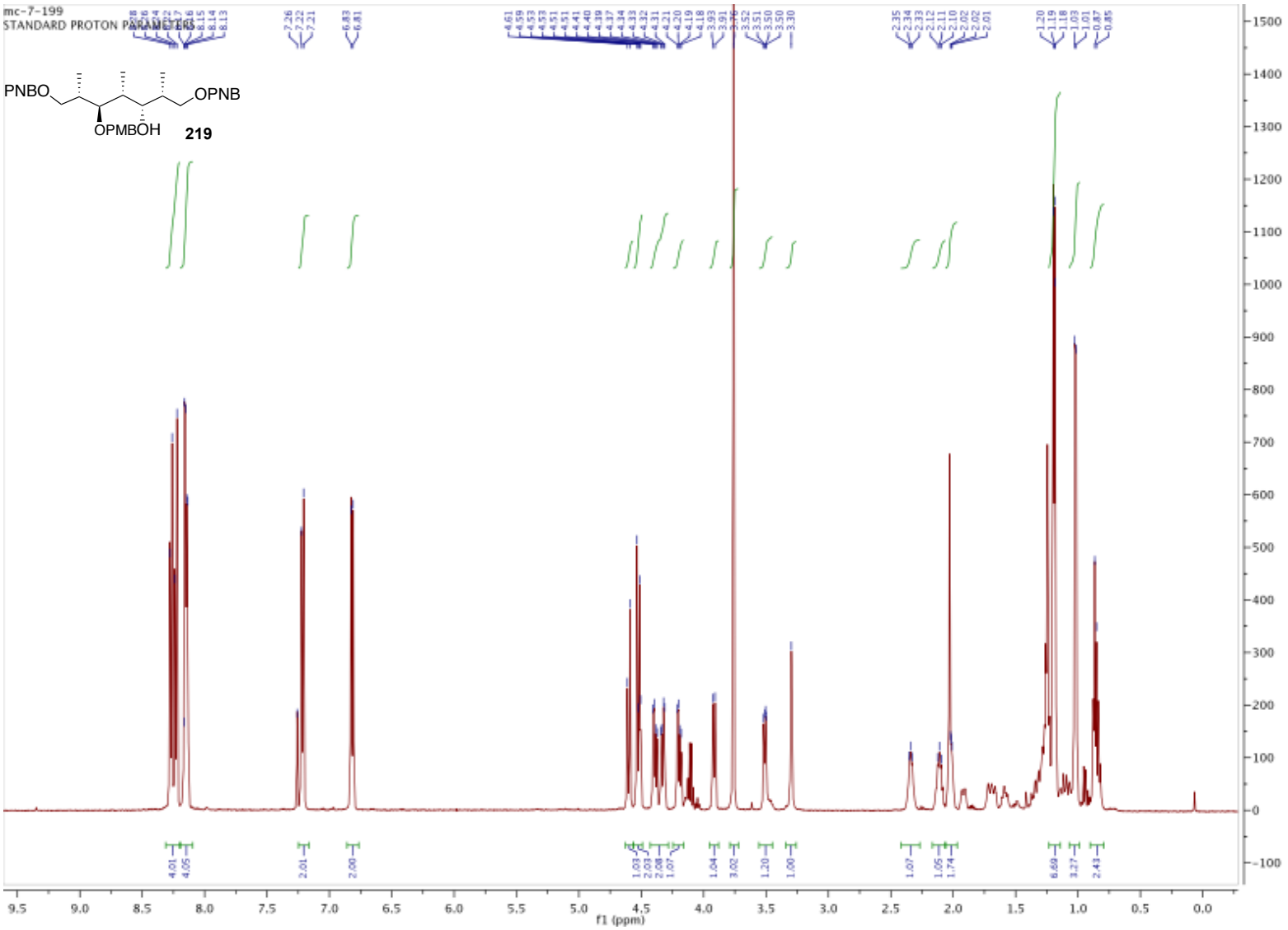

OH
OPMB
OH
OH
210
f1 (ppm)

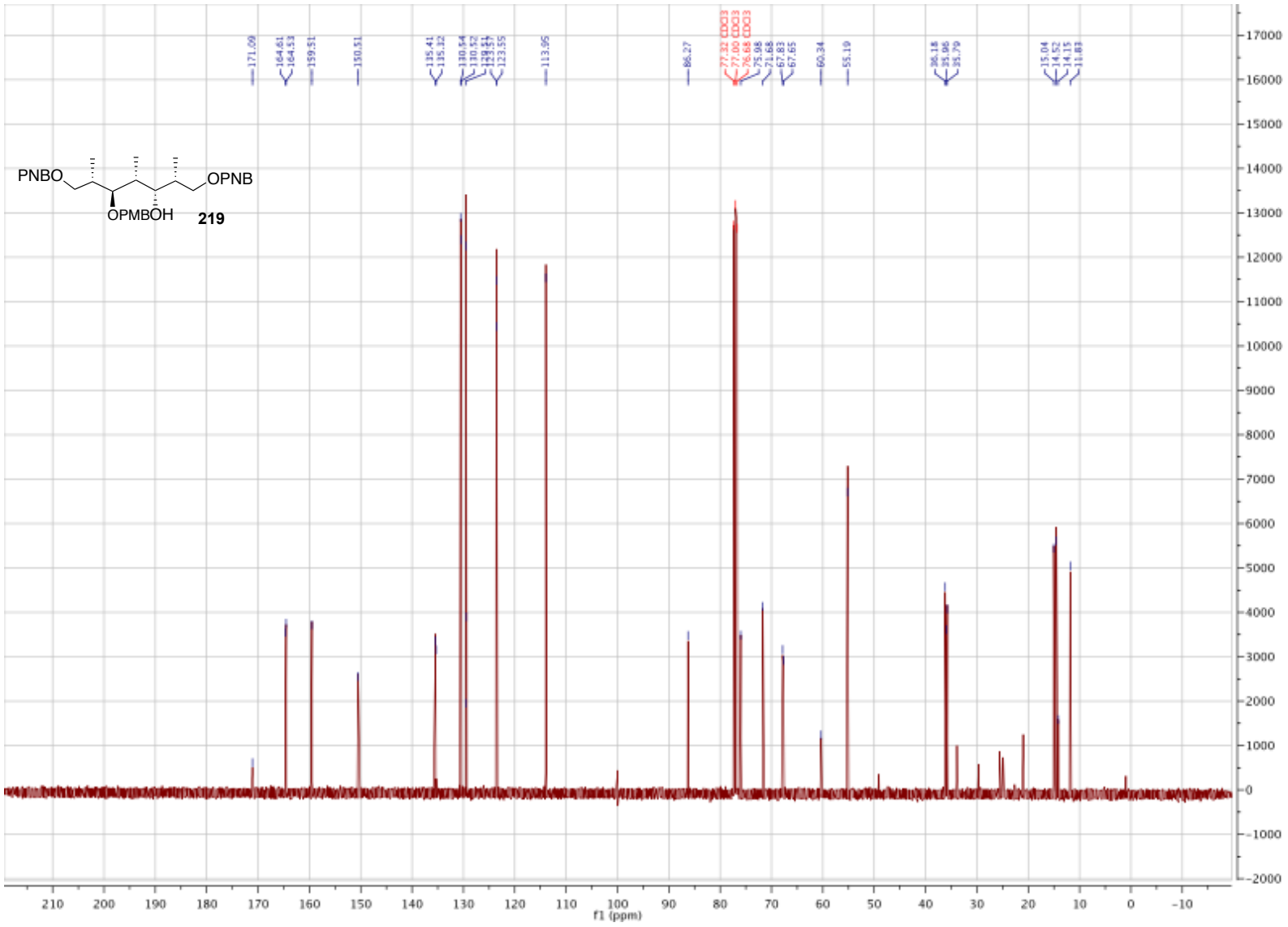

OH
OPMB
OH
OH
210
159.49
129.85
114.04
88.67
77.41 CDCl3
77.10 CDCl3
76.78 CDCl3
75.70
72.62
65.72
65.57
55.28
38.63
37.92
36.26
14.89
13.56
12.35
f1 (ppm)

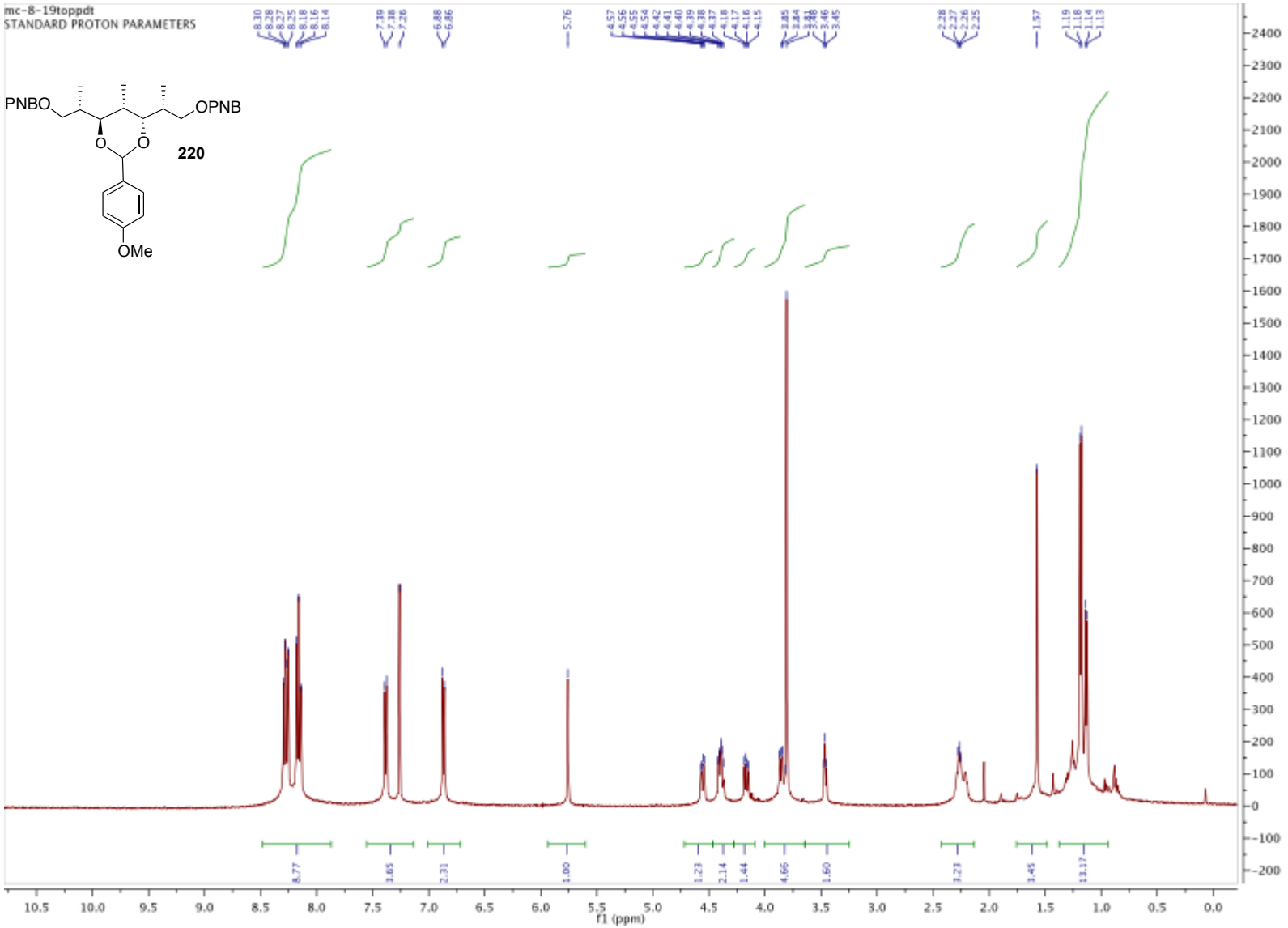

OH OPMBOH OH
212
f1 (ppm)

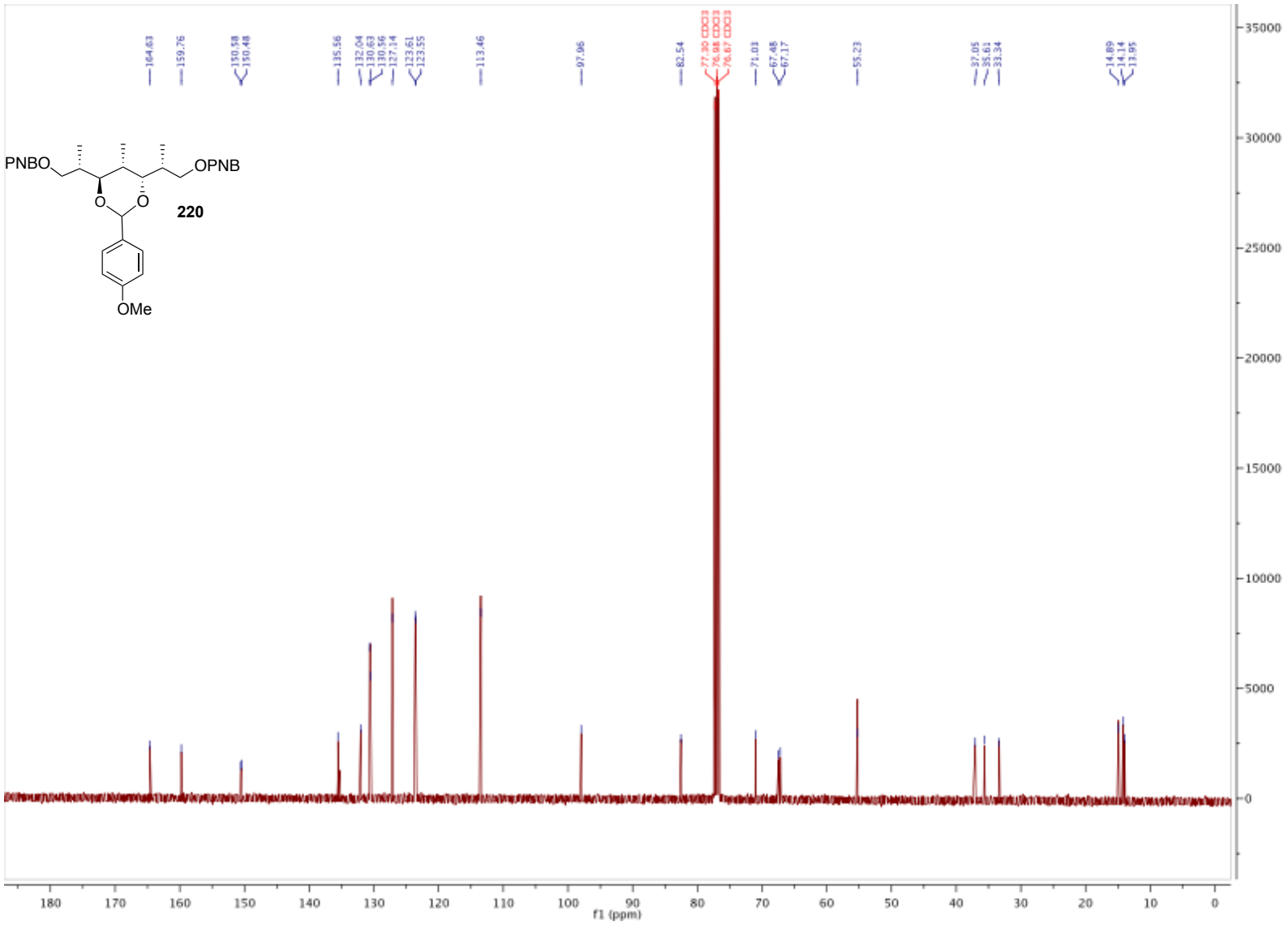

OH
OPMB
OH
OH
212
159.56
129.74
129.67
114.06
88.39
77.40 CDCl3
77.08 CDCl3
76.76 CDCl3
76.70
76.12
69.03
65.30
55.28
37.94
37.26
33.52
14.74
13.32
11.64
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

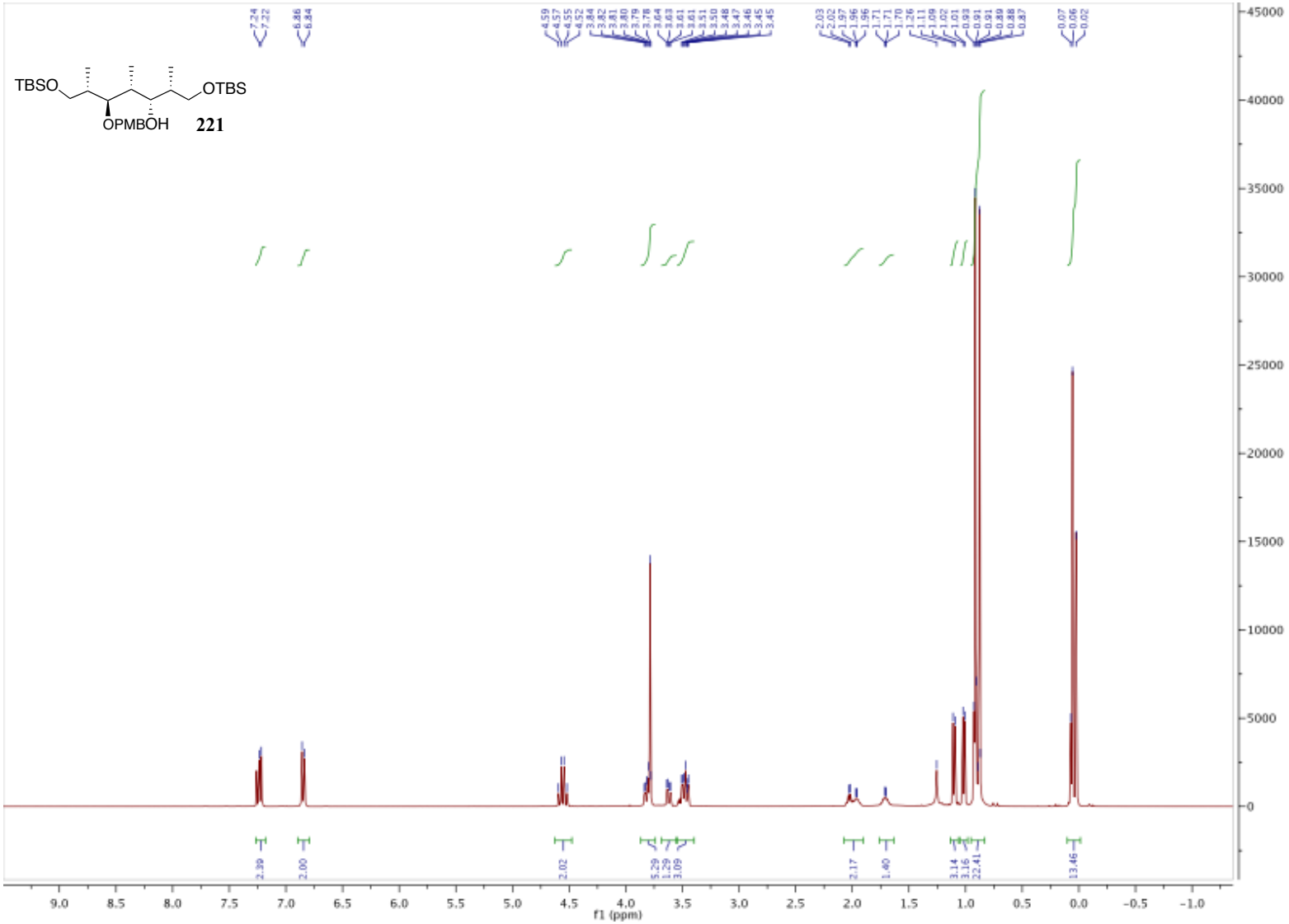

mc-7-167major
STANDARD PROTON PARAMETERS
OH
OPMBO
O
215
f1 (ppm)

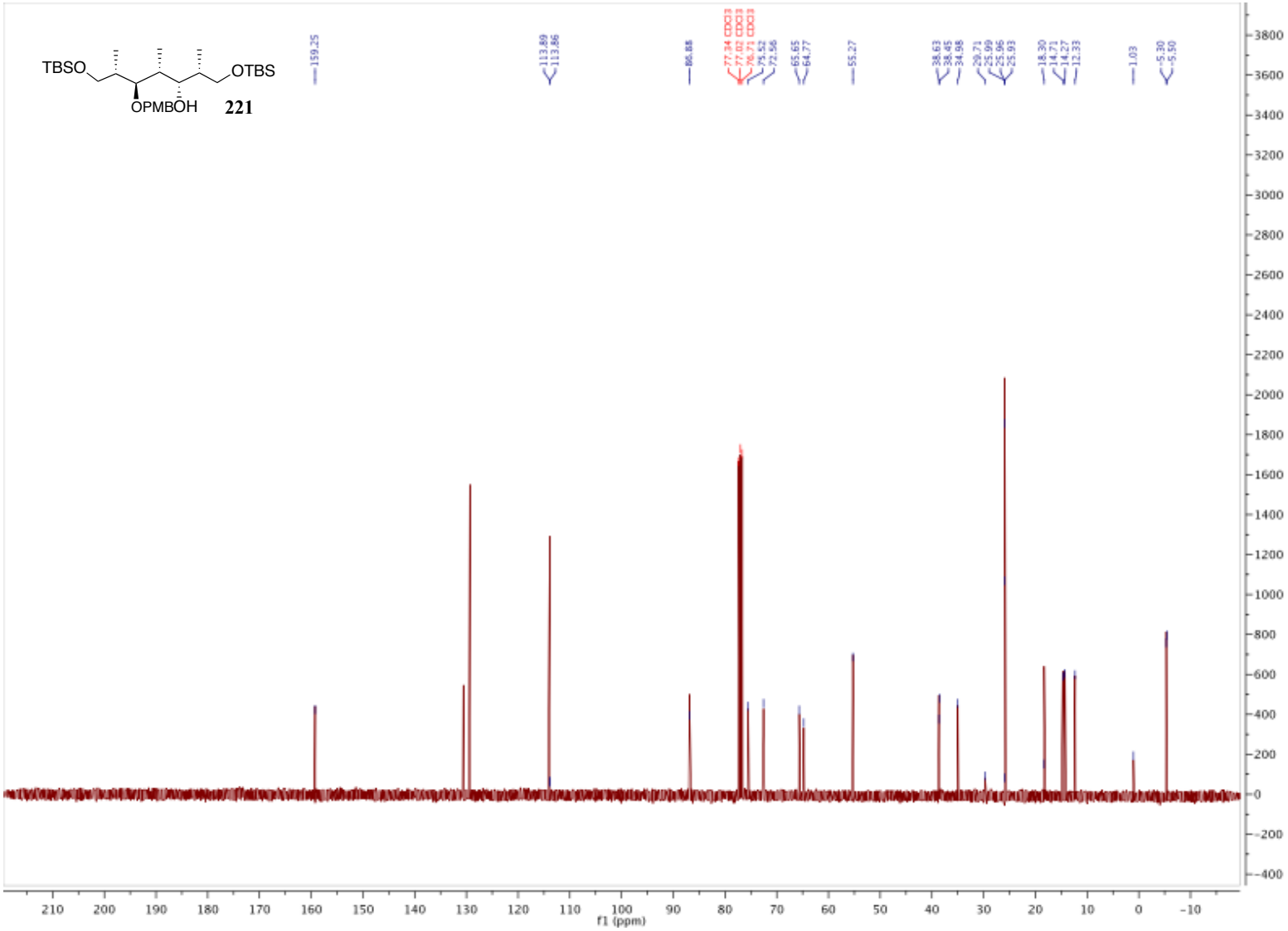

mc-7-199
STANDARD PROTON PARAMETERS
PNBO
OPNB
OPMBOH
219
f1 (ppm)

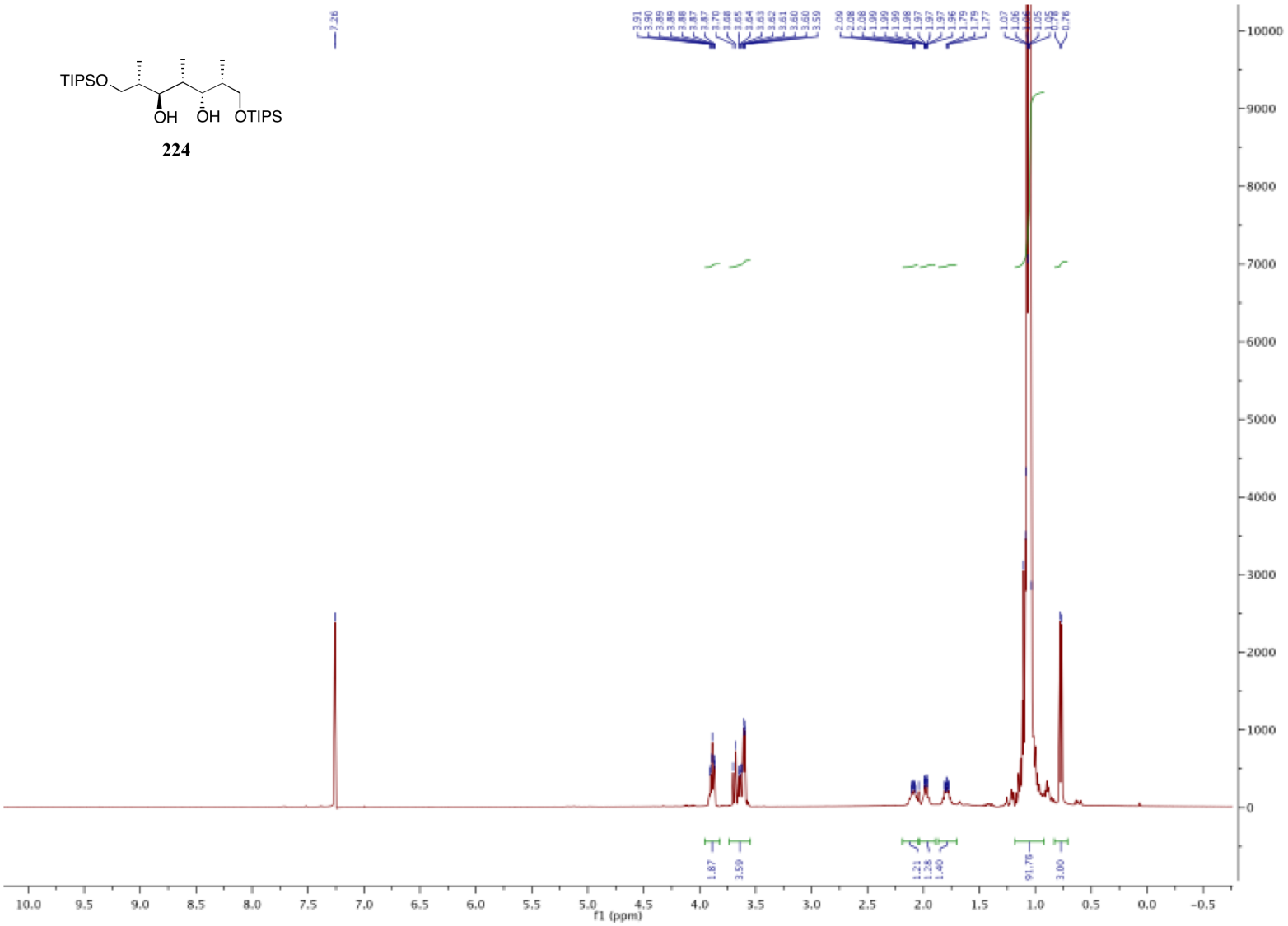

PNBO
OPNB
OPMBOH
219
f1 (ppm)

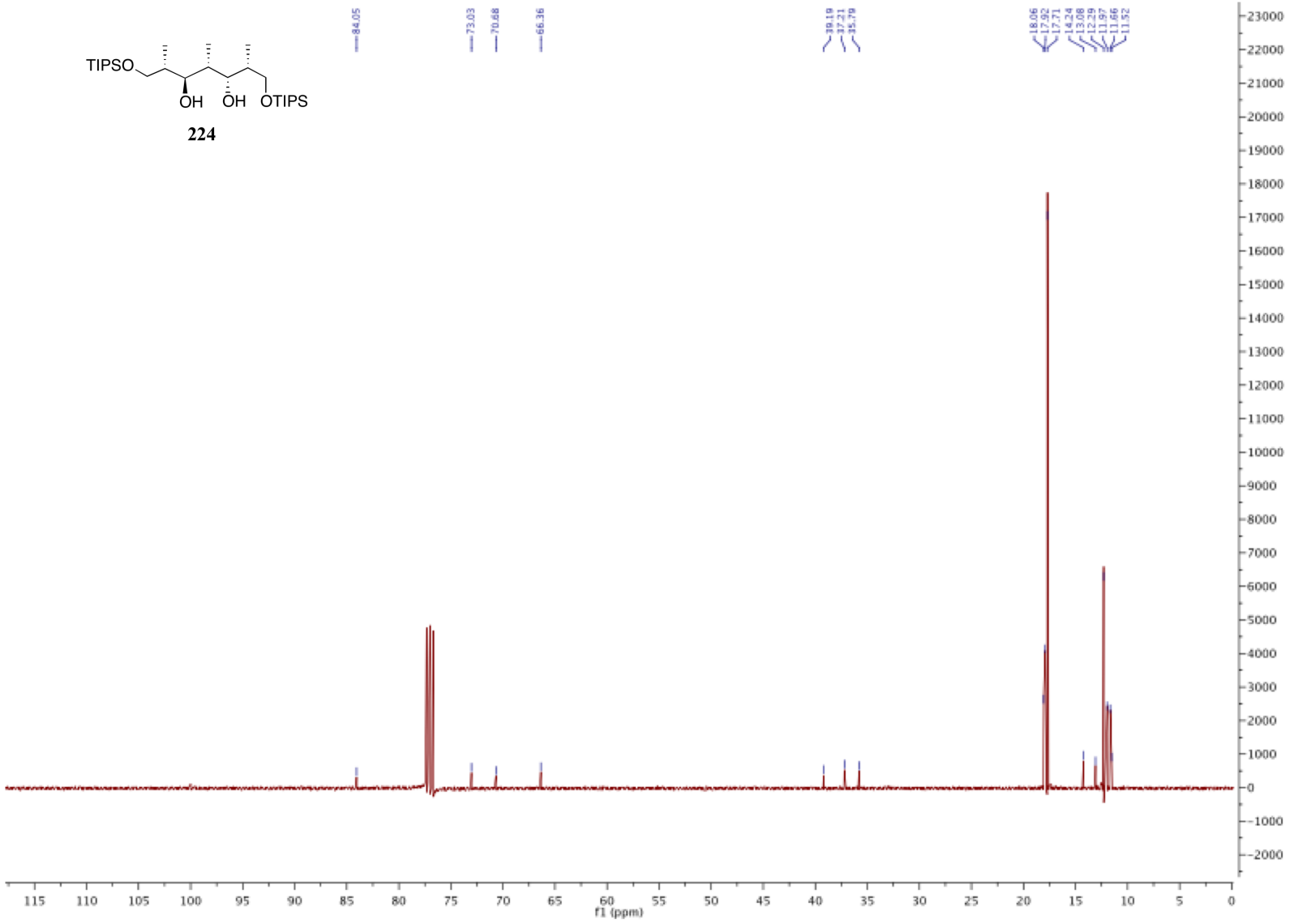

mc-8-19toppdt
STANDARD PROTON PARAMETERS
PNBO
OPNB
O
O
220
OMe
f1 (ppm)

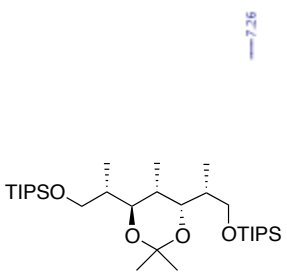

PNBO
OPNB
O
O
220
OMe
164.63
159.76
150.58
150.48
135.56
132.04
130.63
130.56
127.34
123.61
123.55
113.46
97.96
82.54
77.30 CDCl3
76.98 CDCl3
76.67 CDCl3
71.03
67.48
67.17
55.23
37.05
35.61
33.34
14.89
14.14
13.95
35000
30000
25000
20000
15000
10000
5000
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


TBSO
OTBS
OPMBOH
221
f1 (ppm)


TBSO
OTBS
OPMBOH
221
f1 (ppm)

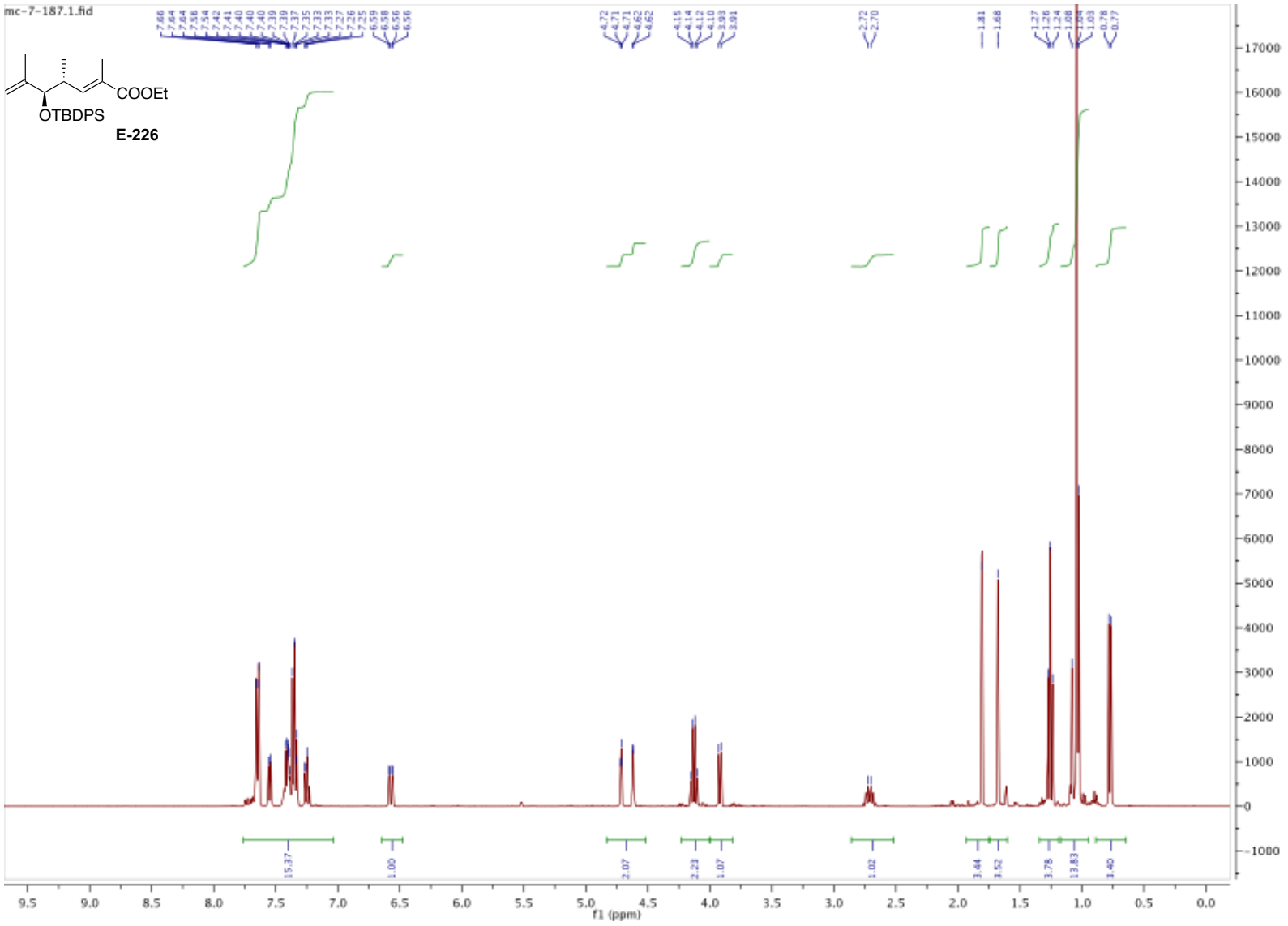

TIPSO
OH
OH
OTIPS
224
f1 (ppm)

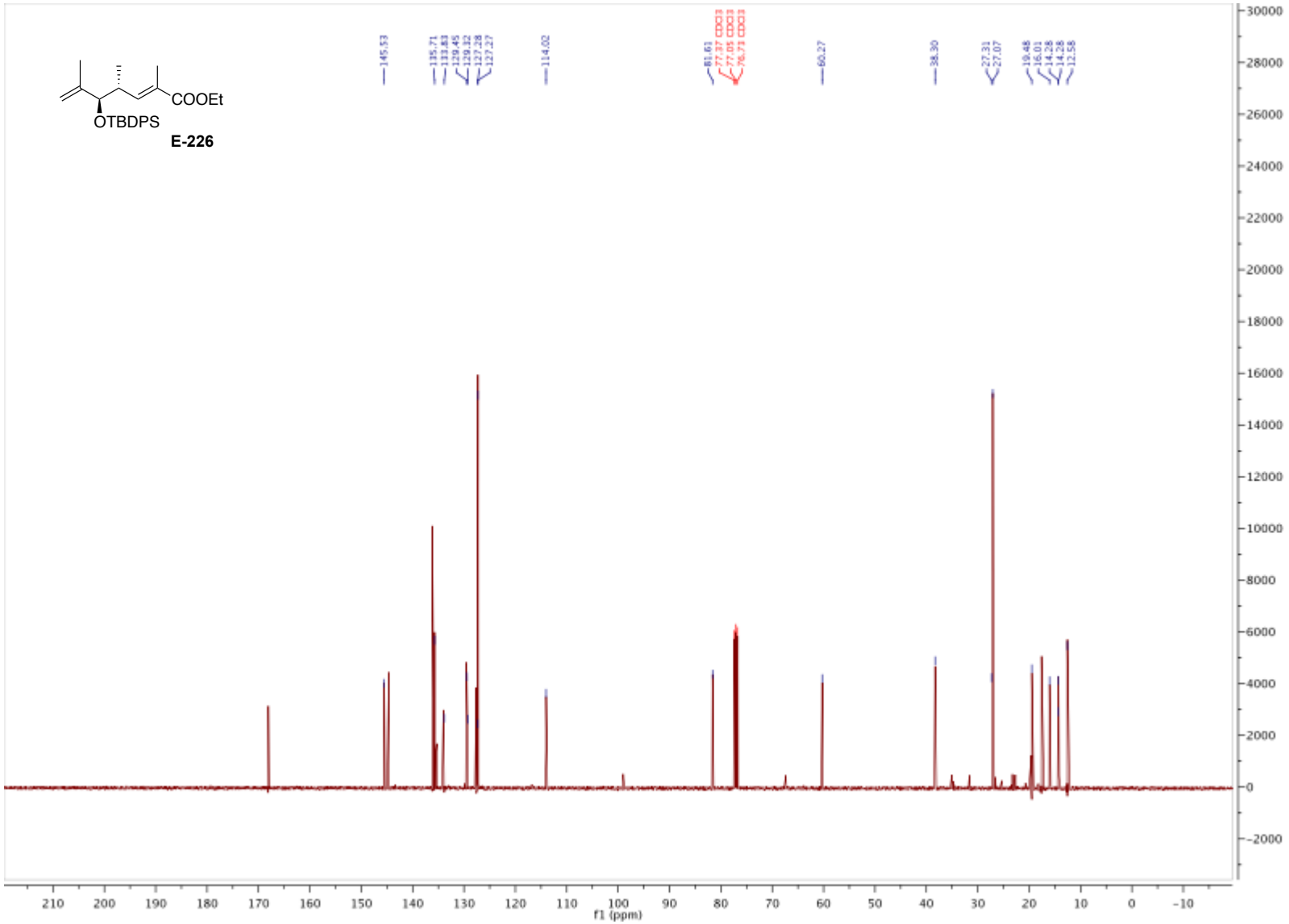

TIPSO
OH
OH
OTIPS
224
84.05
73.03
70.68
66.36
39.19
37.21
35.79
18.06
17.92
17.71
14.24
13.08
12.29
11.97
11.66
11.52
f1 (ppm)

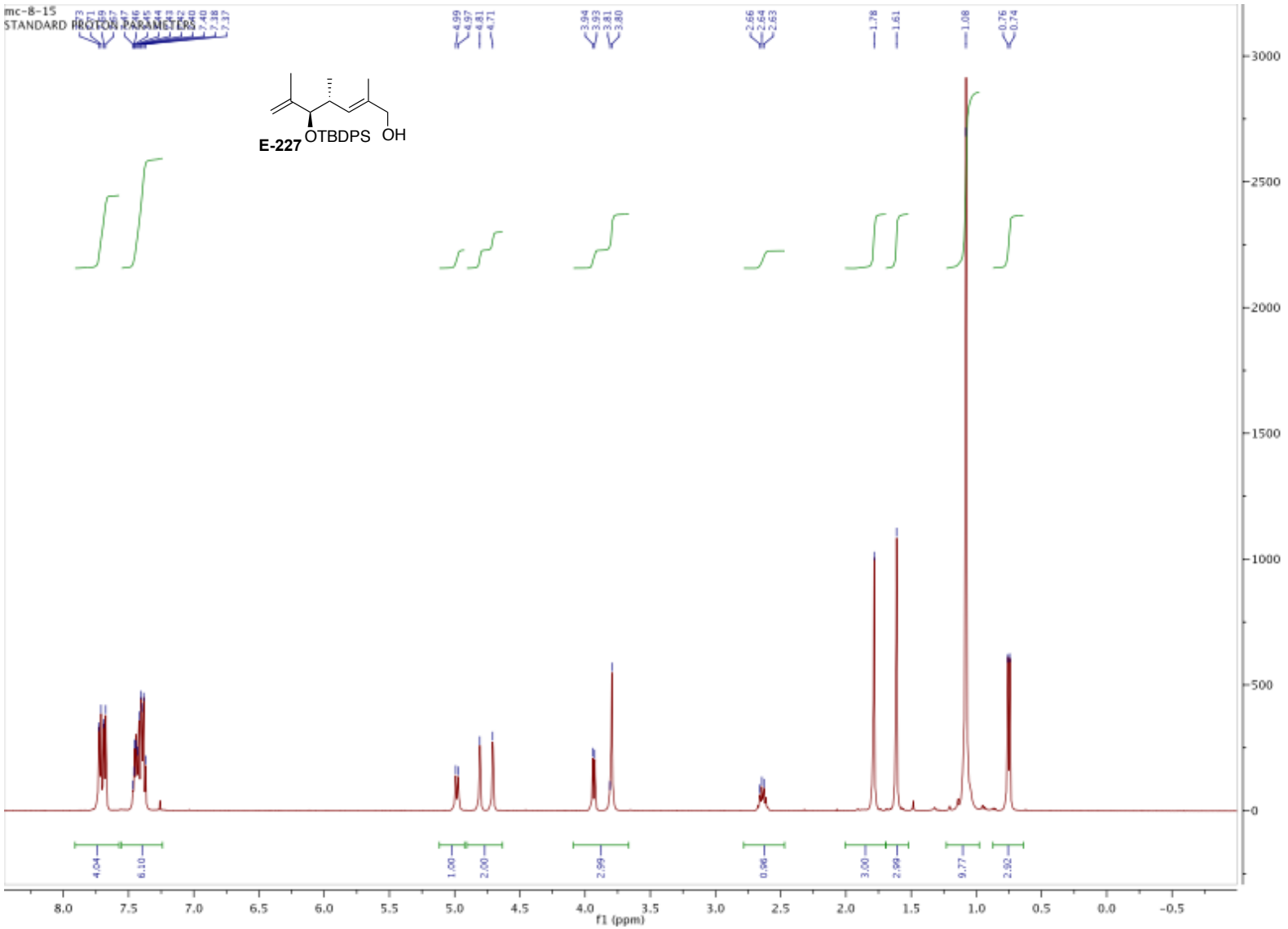


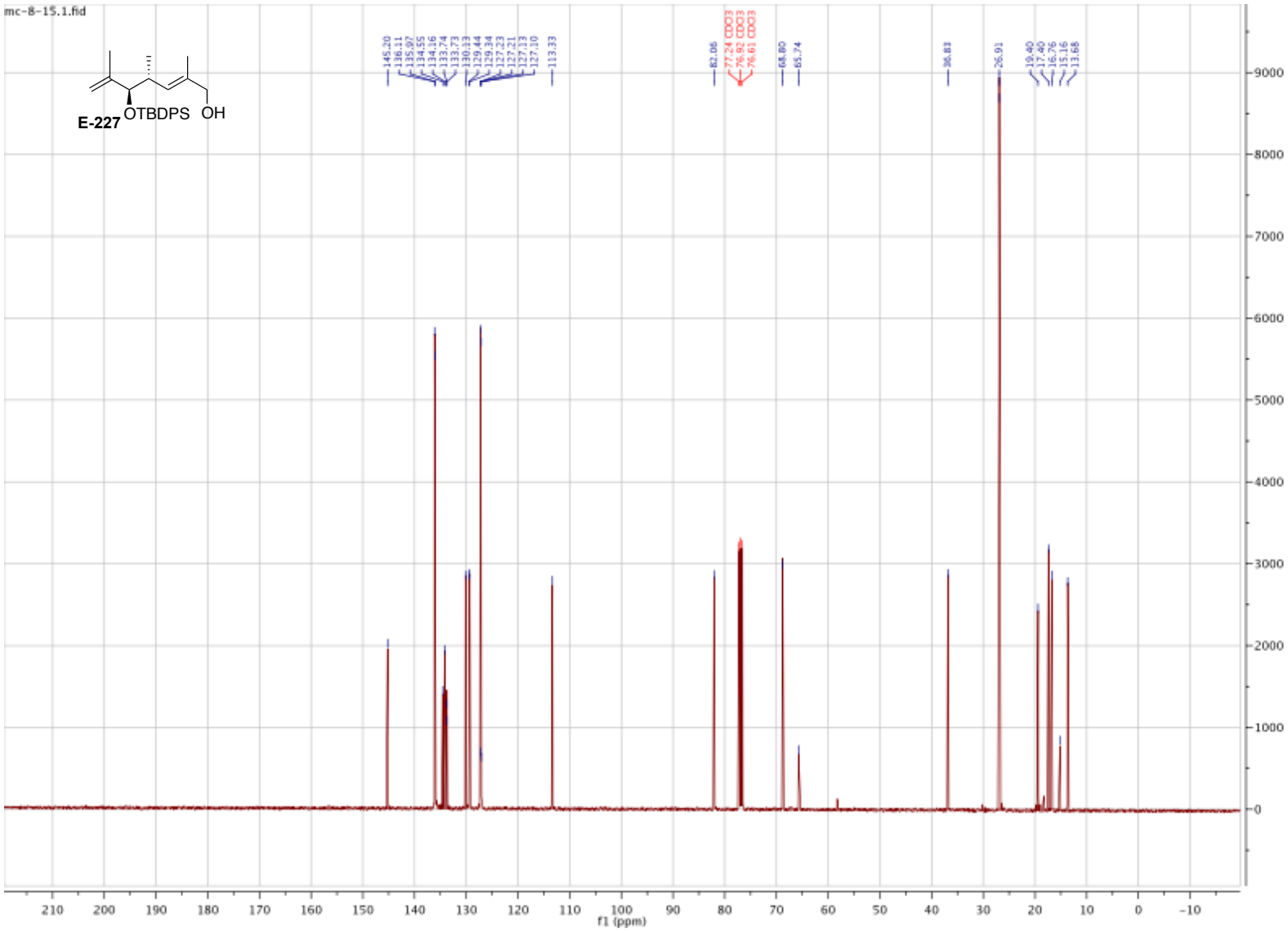
225

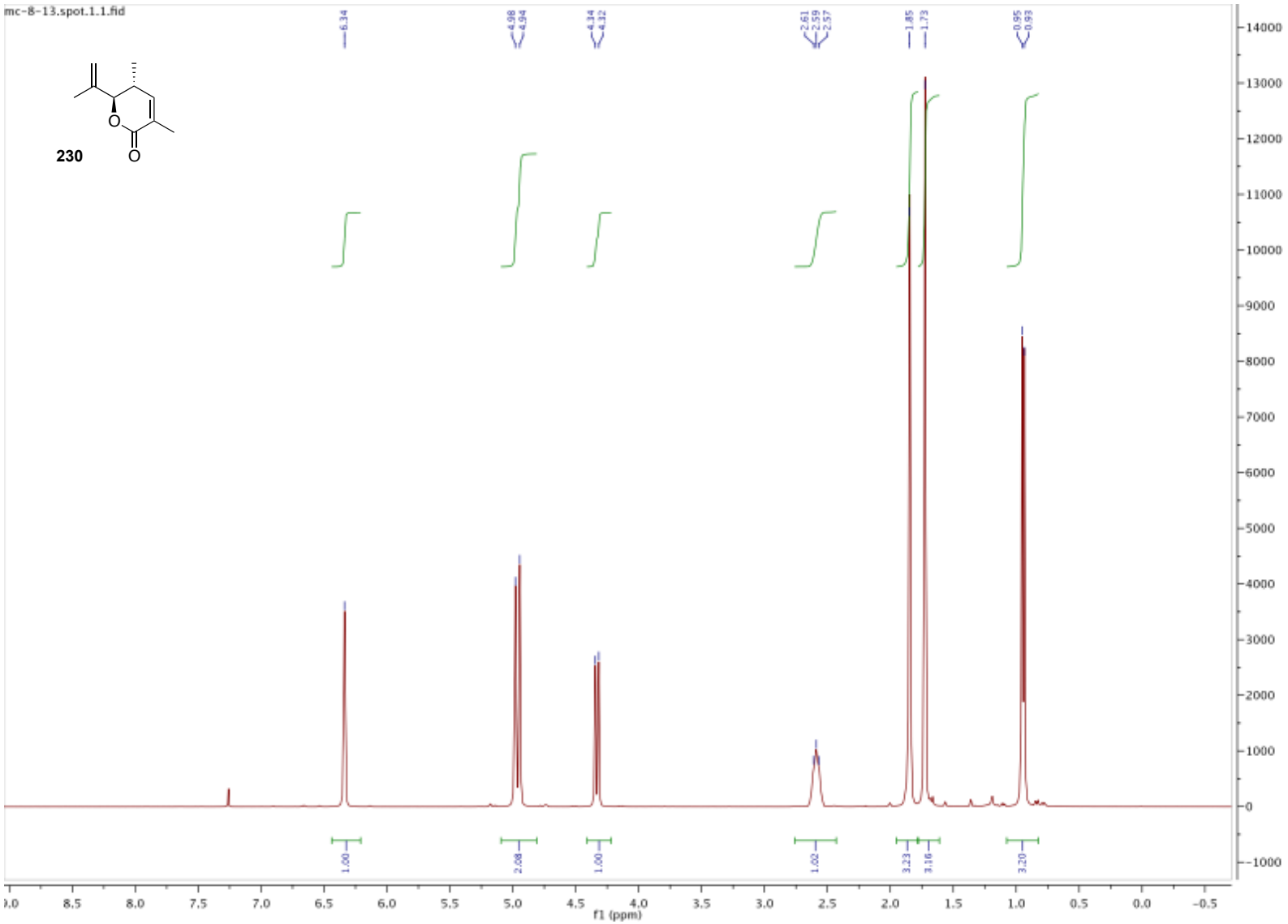

TIPSO
O
O
OTIPS
225
100.34
75.88
71.17
65.11
64.78
40.63
35.64
35.17
25.85
23.59
18.06
17.70
14.54
13.31
13.04
12.29
12.01
11.99
f1 (ppm)

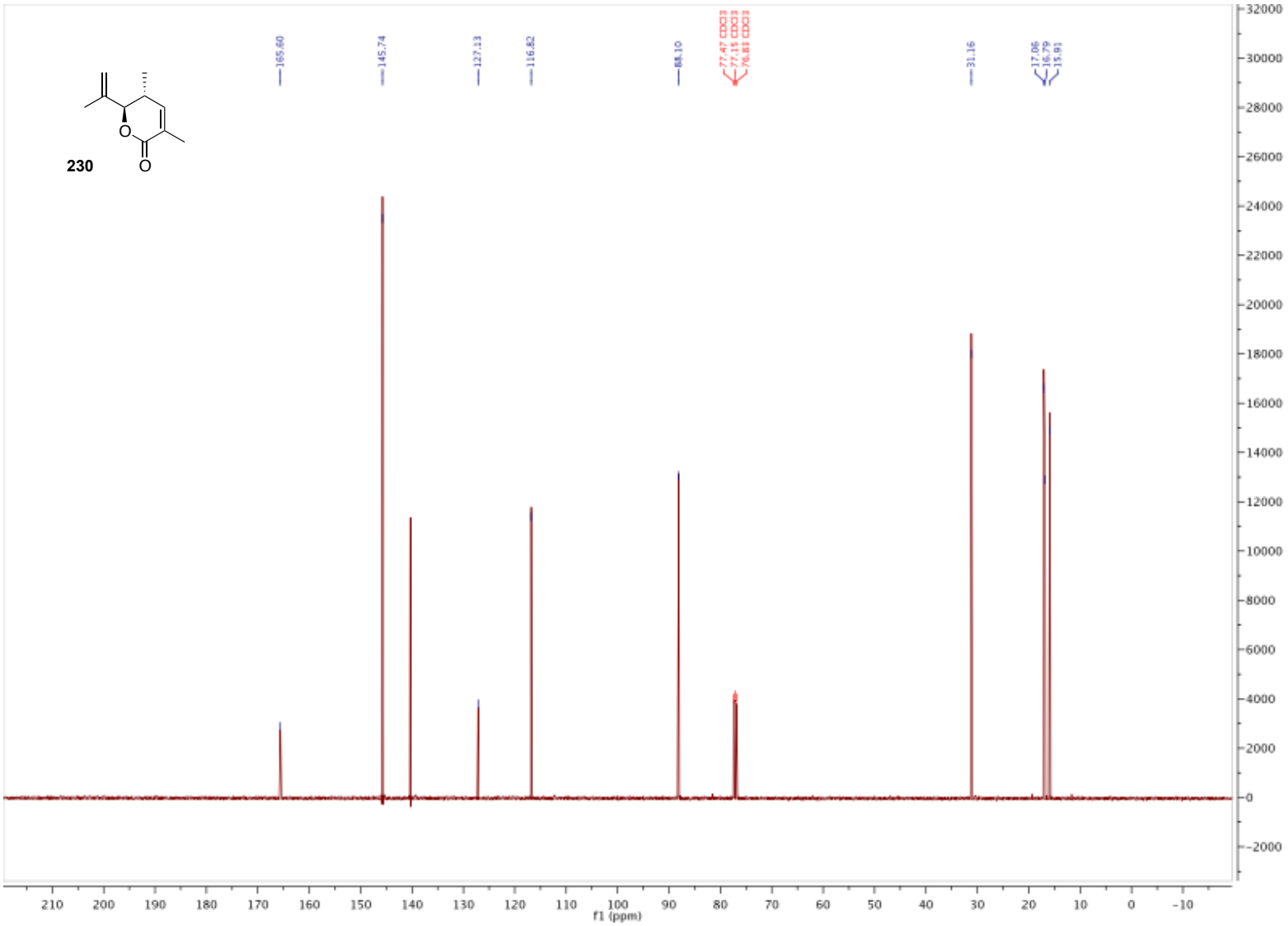

mc-7-187.1.fid
COOEt
OTBDPS
E-226
f1 (ppm)

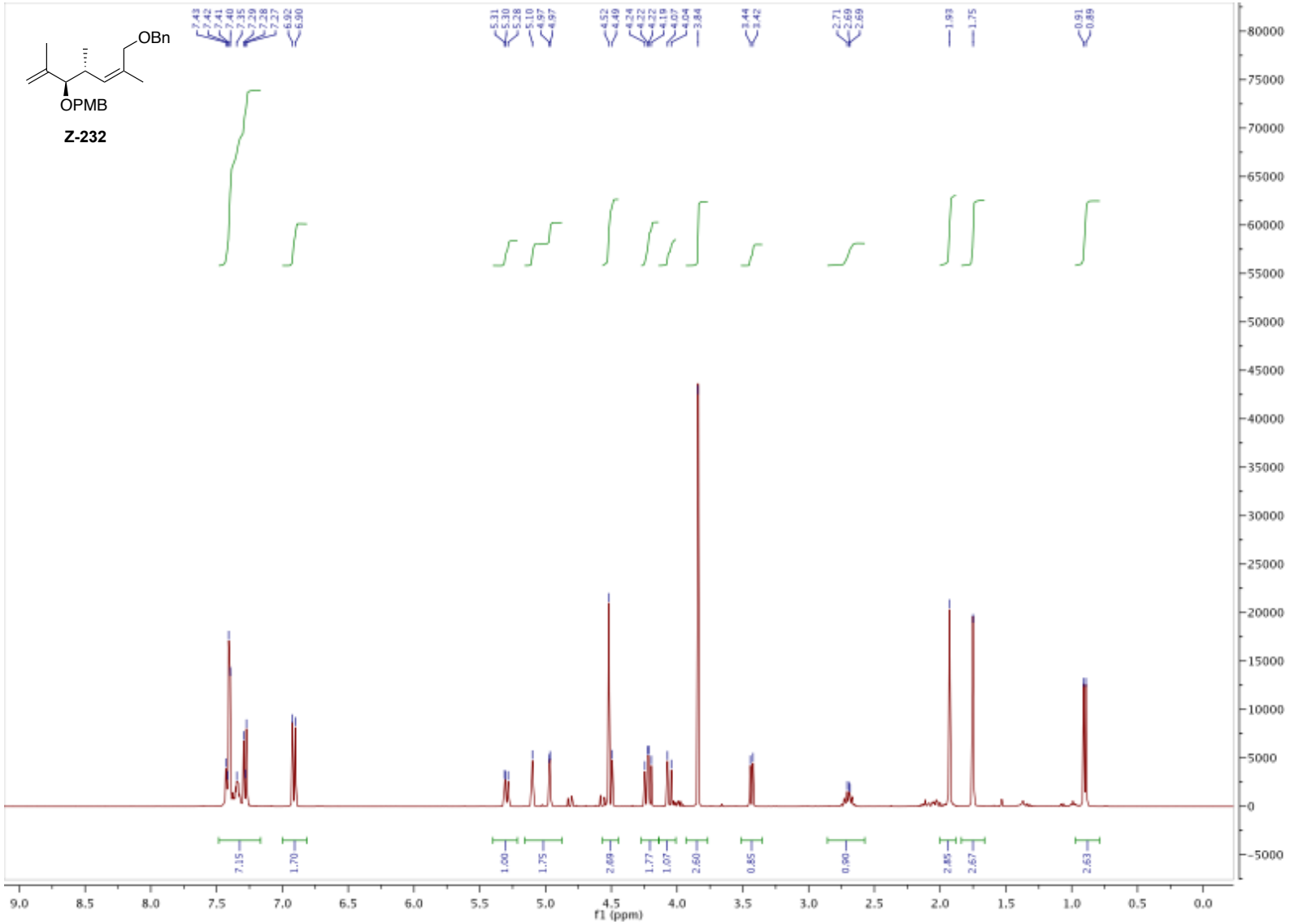

COOEt
OTBDPS
E-226
145.53
135.71
133.83
129.45
129.22
127.28
127.27
114.02
81.61
77.37 CDCl3
77.05 CDCl3
76.73 CDCl3
60.27
38.30
27.31
27.07
19.48
16.01
14.28
14.28
12.58
f1 (ppm)

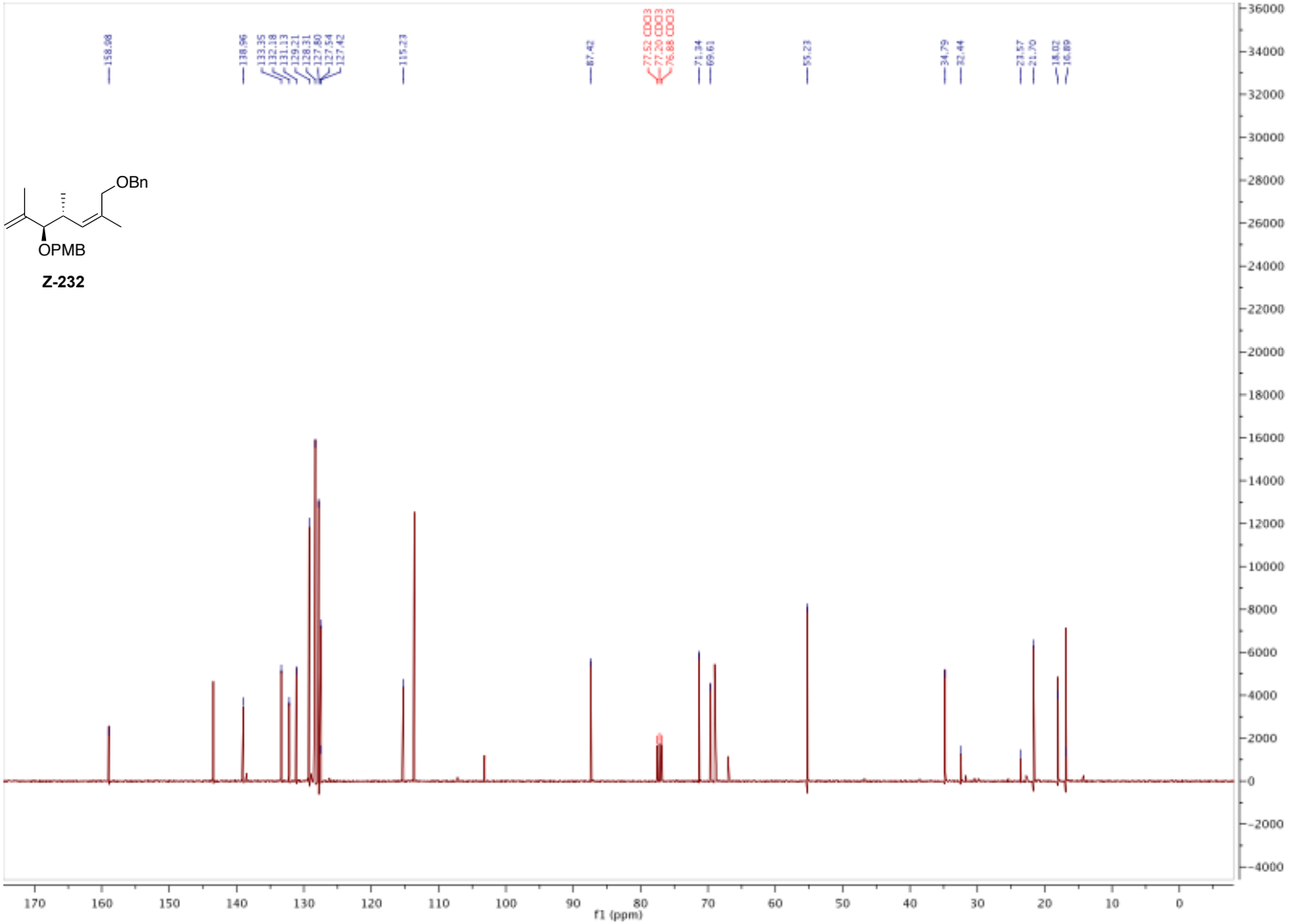

mc-8-15
STANDARD PROTON PARAMETERS
E-227
OTBDPS
OH
f1 (ppm)

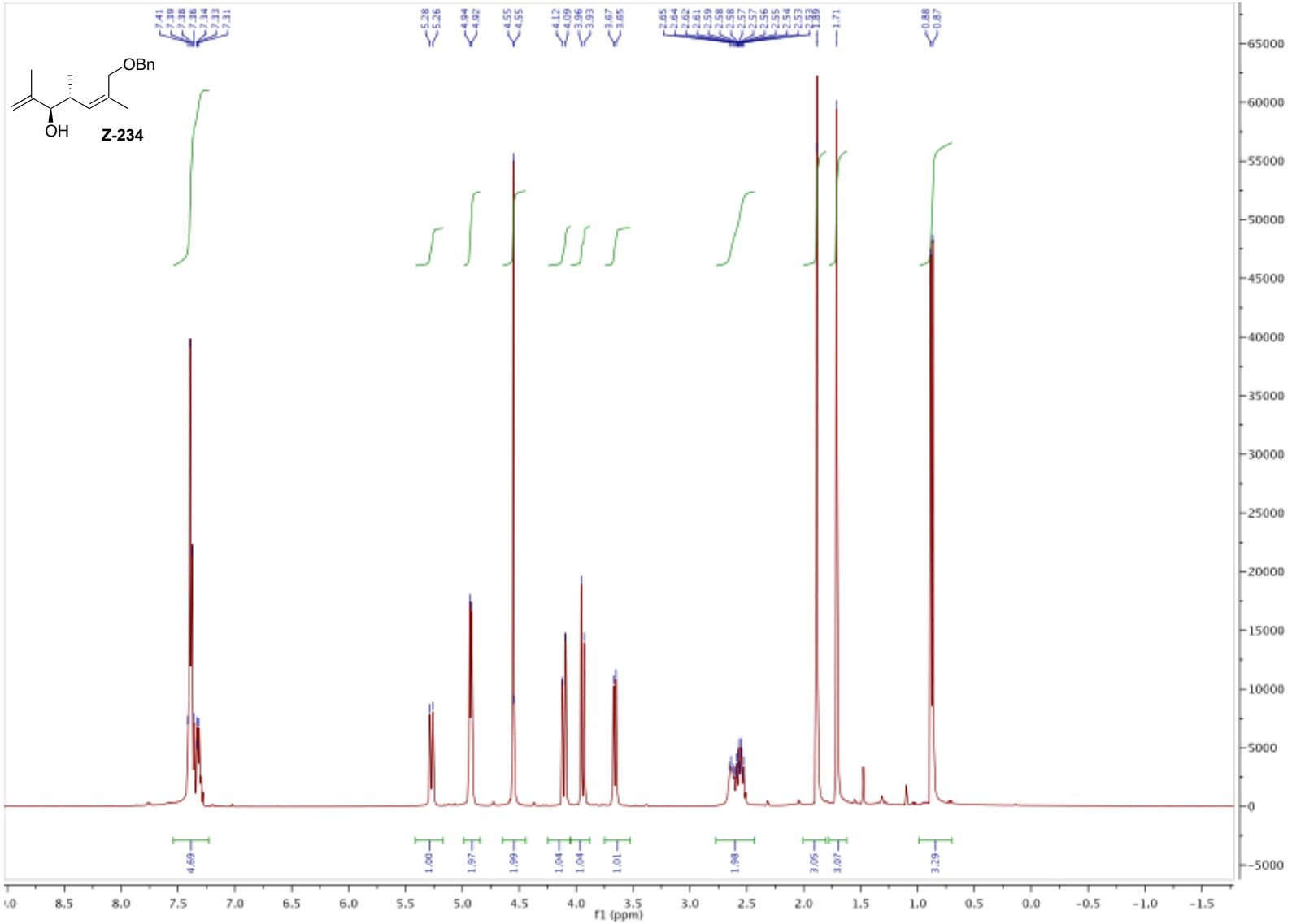

mc-8-15.1.fid
E-227
OTBDPS
OH
145.20
136.11
135.97
134.65
134.16
133.74
133.73
130.13
129.44
129.34
127.23
127.21
127.13
127.10
113.33
82.06
77.24 CDCl3
76.92 CDCl3
76.61 CDCl3
68.89
65.74
36.83
26.91
19.40
17.40
16.76
15.16
13.68
f1 (ppm)

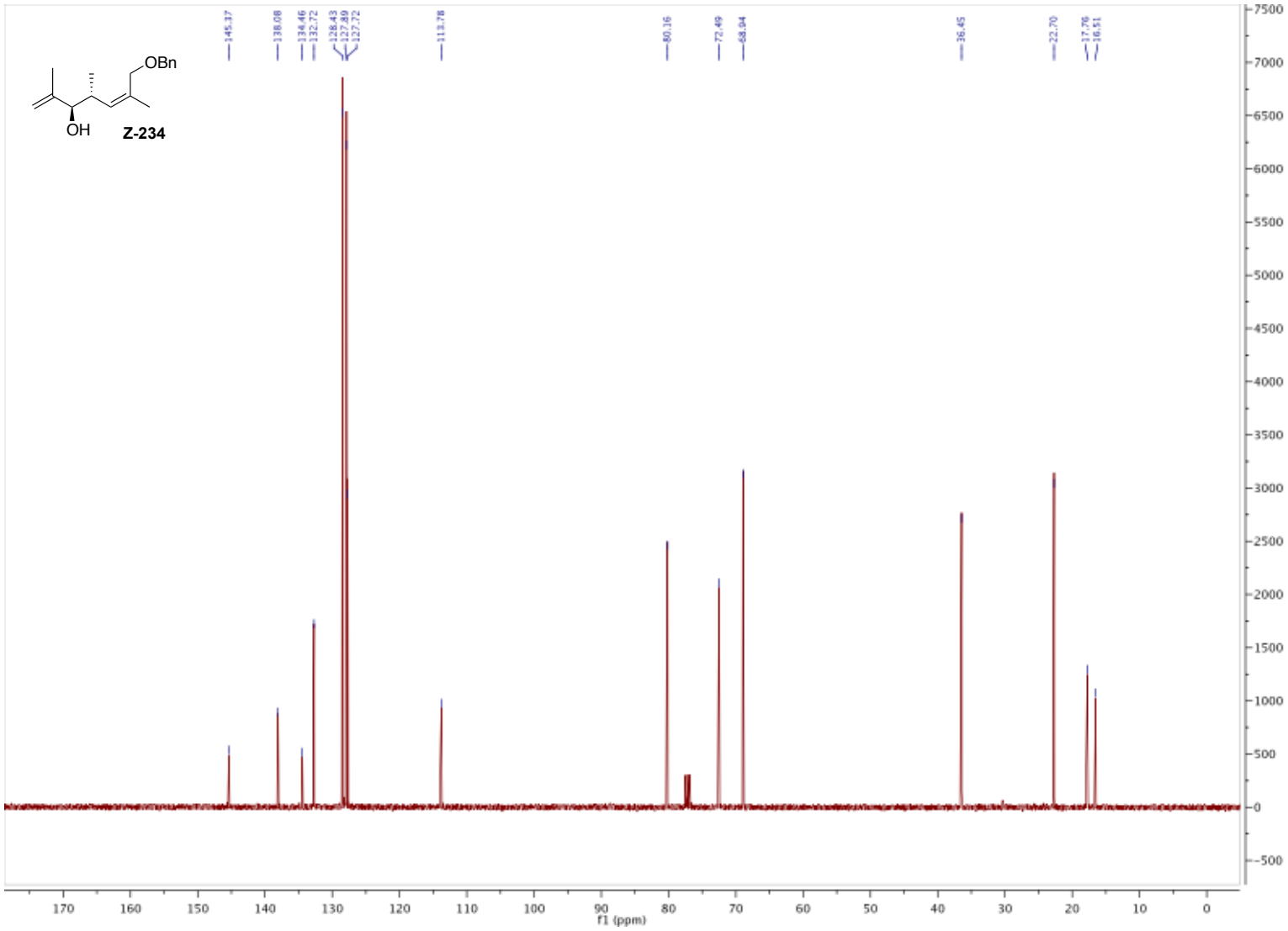

mc-8-13.spot.1.1.fid
230
6.34
4.98
4.94
4.34
4.32
2.61
2.59
2.57
1.85
1.73
0.95
0.93
1.00
2.08
1.00
1.02
3.23
3.16
3.20
f1 (ppm)

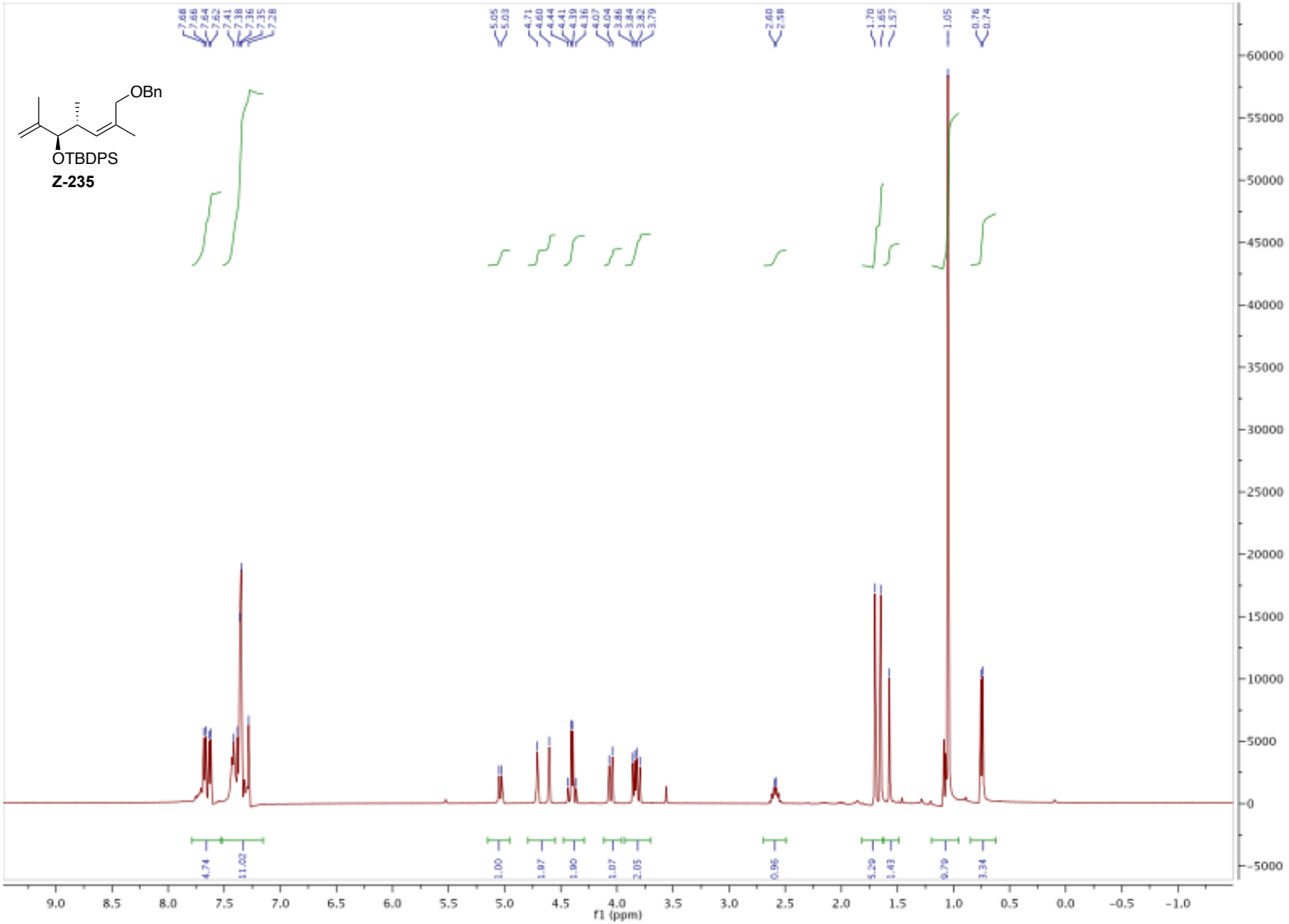

230
165.60
145.74
127.13
116.82
88.10
77.47 CDCl3
77.15 CDCl3
76.83 CDCl3
31.16
17.06
16.79
15.91
f1 (ppm)

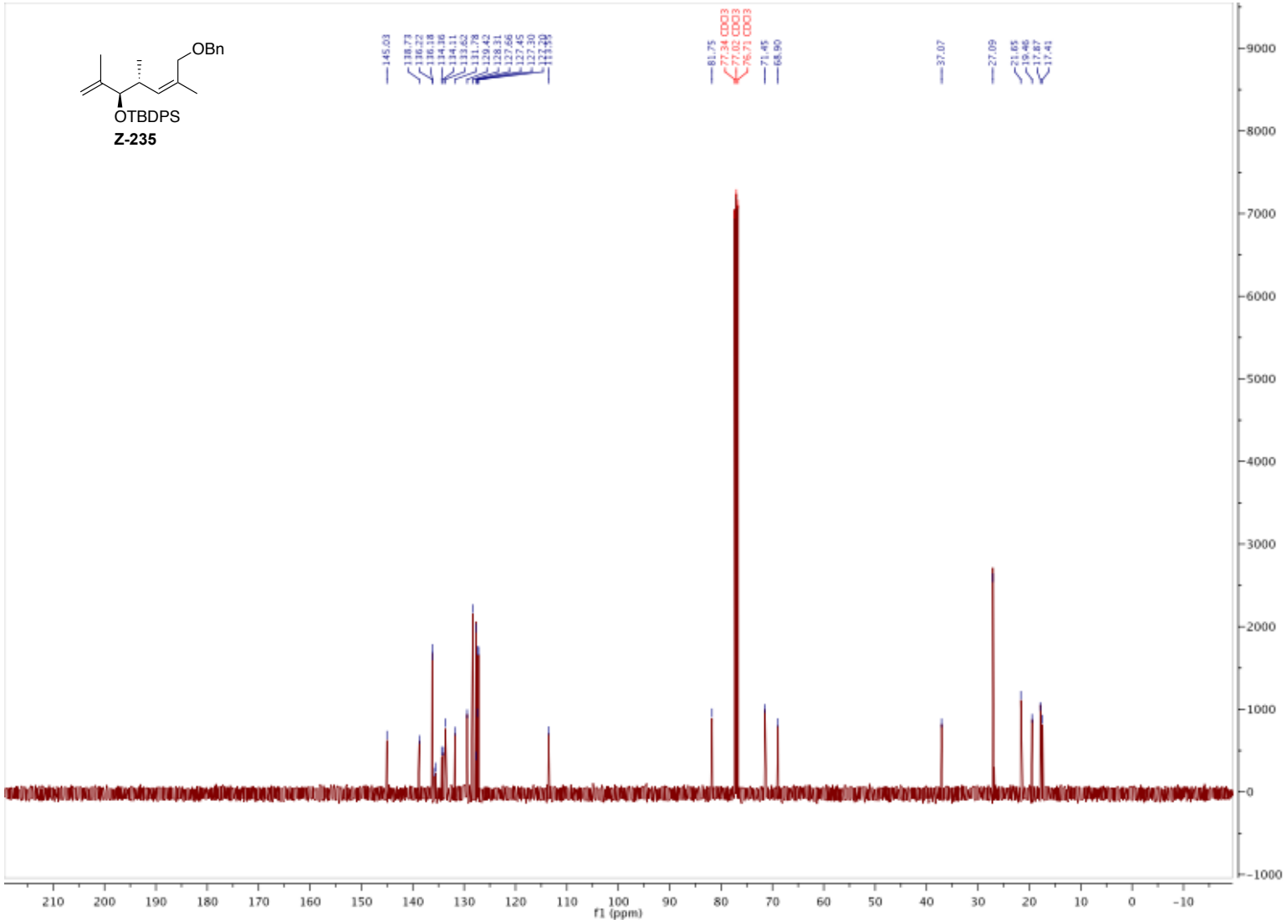

OBn
OPMB
Z-232
f1 (ppm)

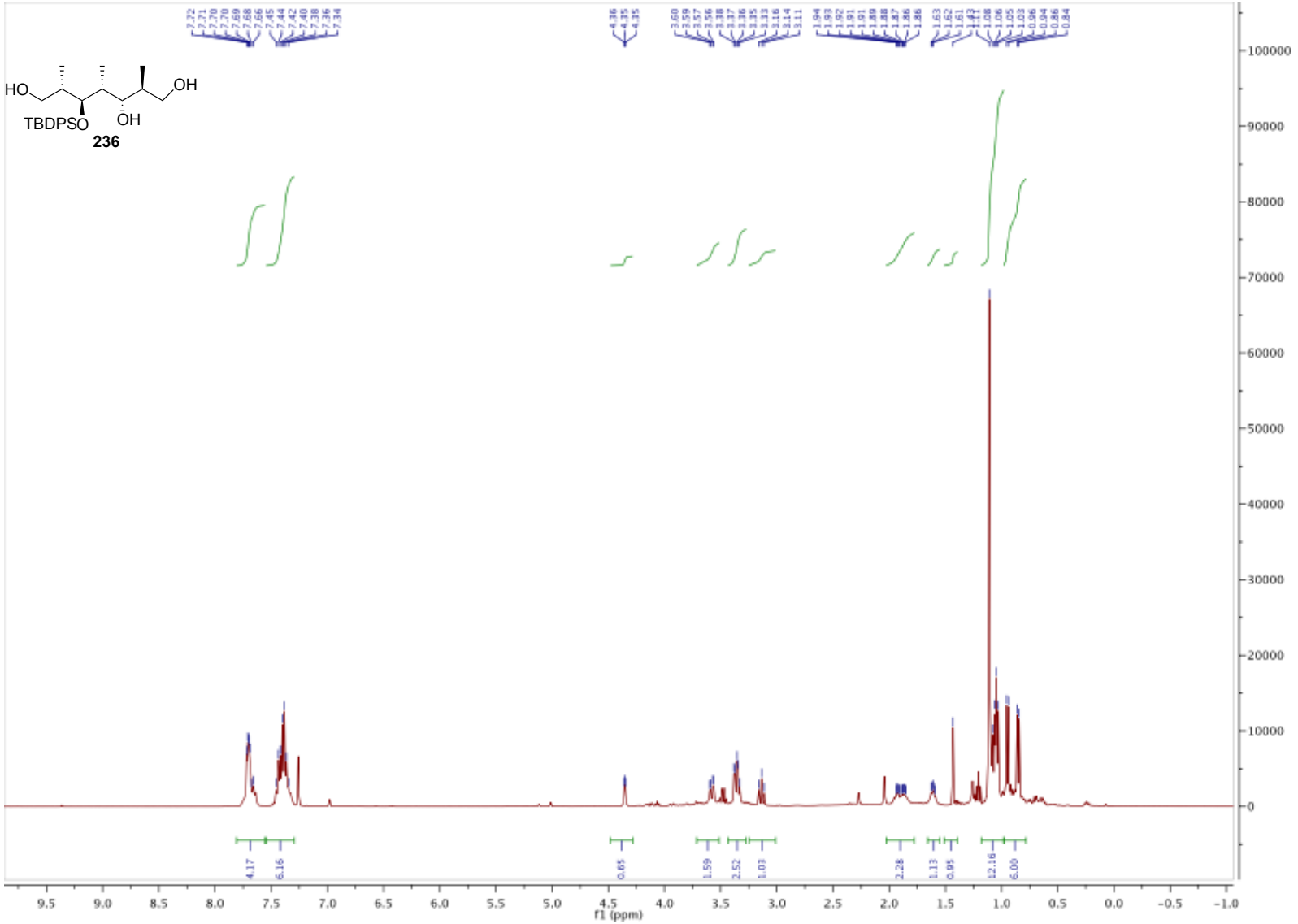

OBn
OPMB
Z-232
158.08
138.96
133.35
132.18
131.13
129.21
128.31
127.80
127.54
127.42
115.23
87.42
77.52 CDCl3
77.20 CDCl3
76.88 CDCl3
71.34
69.61
55.23
34.79
32.44
23.57
21.70
18.02
16.89
f1 (ppm)

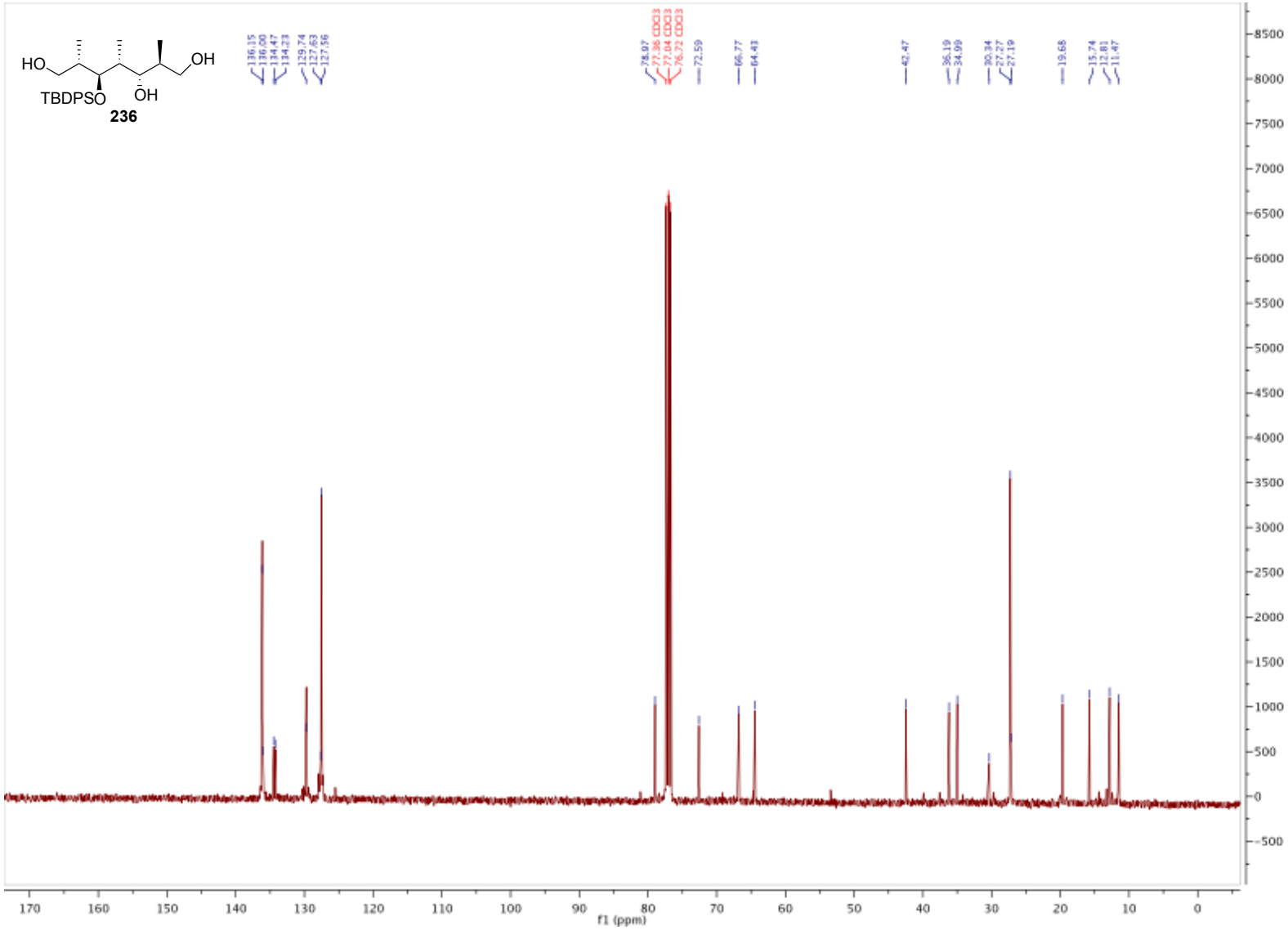

OBn
OH
Z-234
f1 (ppm)

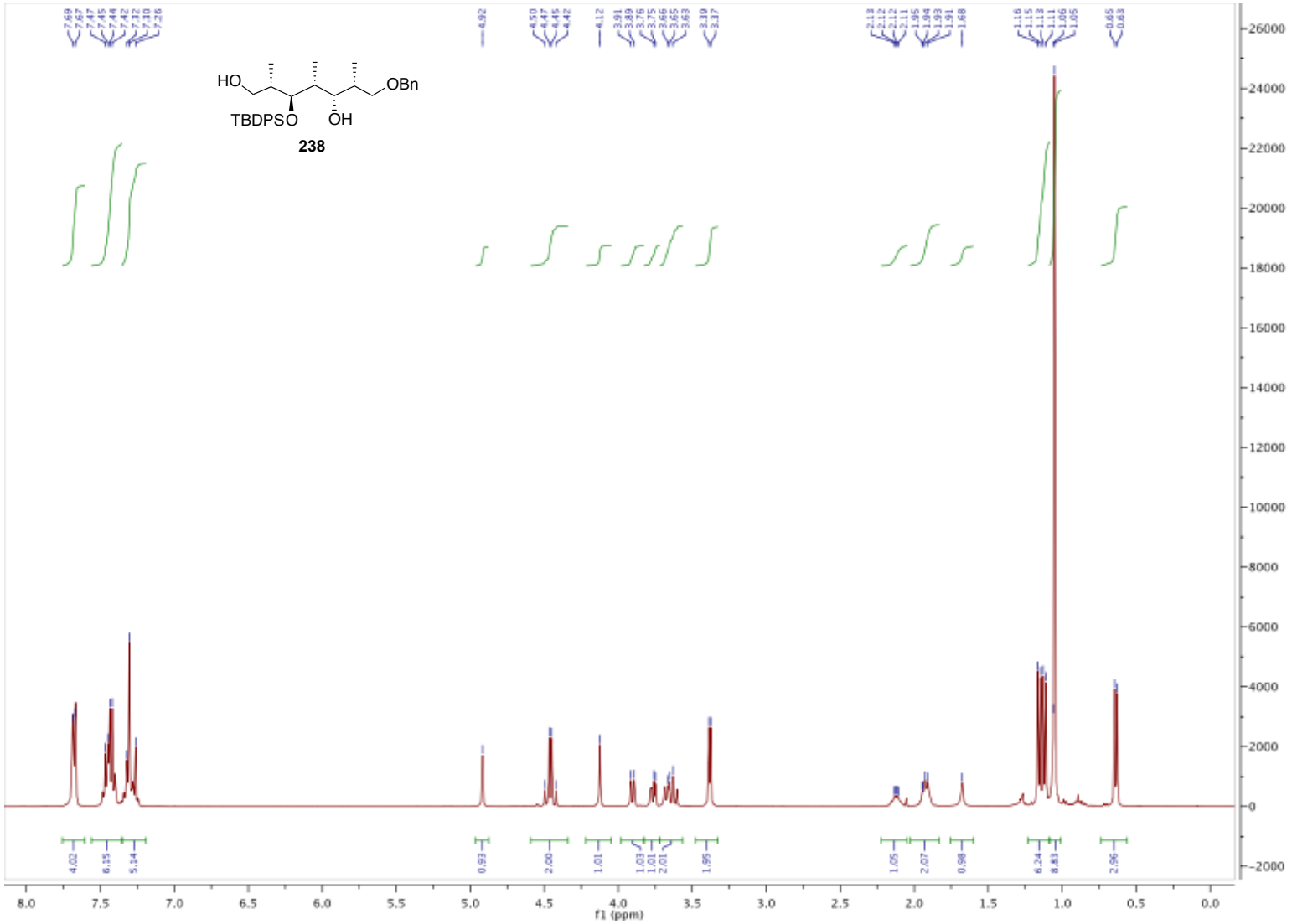

OBn
OH
Z-234
145.37
138.08
134.46
132.72
128.43
127.89
127.72
113.78
80.16
72.49
68.04
36.45
22.70
17.76
16.51
f1 (ppm)

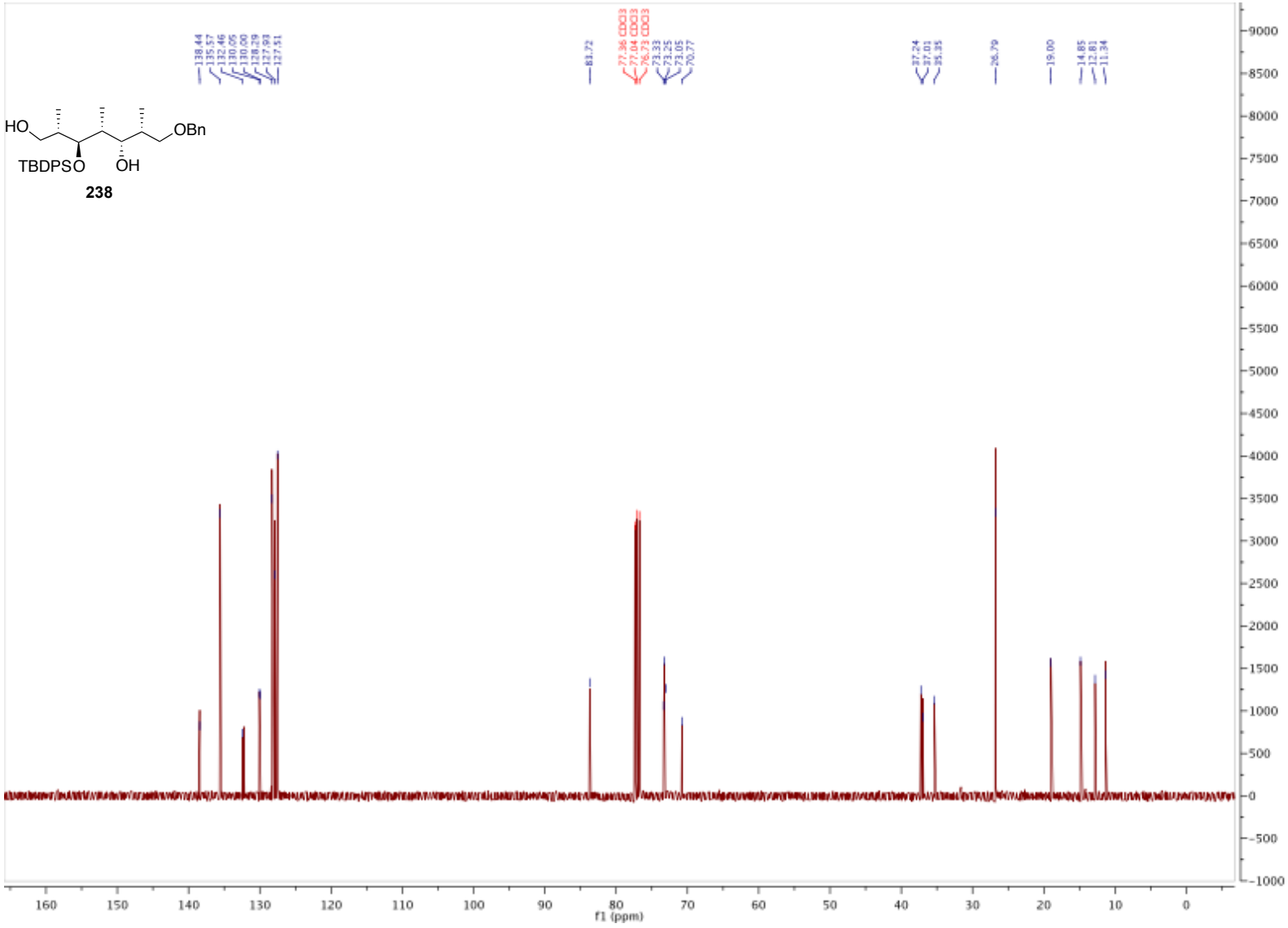

OBn
OTBDPS
Z-235
f1 (ppm)

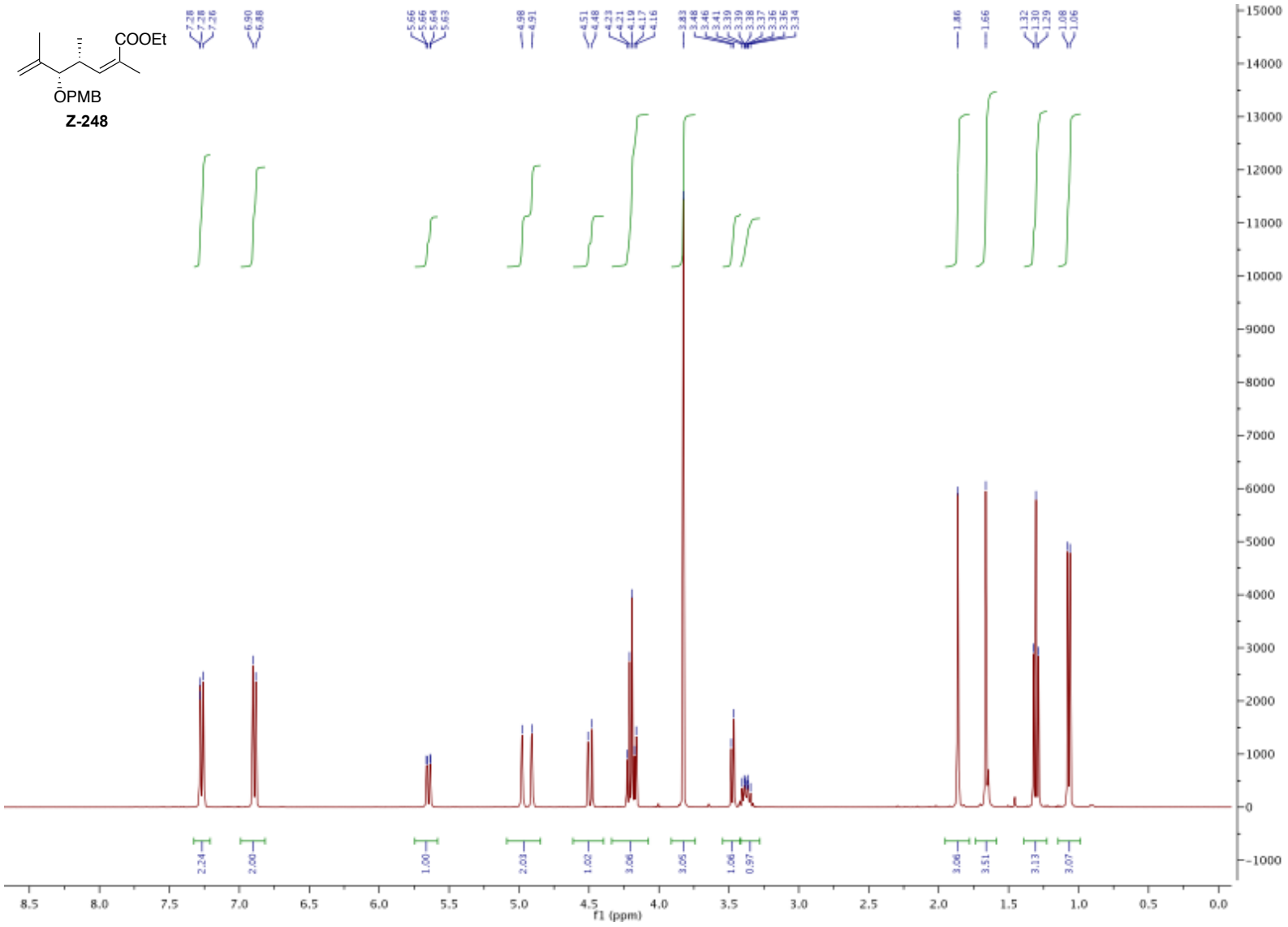

OBn
OTBDPS
Z-235
145.03
138.73
136.22
136.18
134.36
134.11
133.62
131.78
129.42
128.31
127.66
127.45
127.30
81.75
77.34 CDCl3
77.02 CDCl3
76.71 CDCl3
71.45
68.90
37.07
27.09
21.65
19.46
17.87
17.41
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

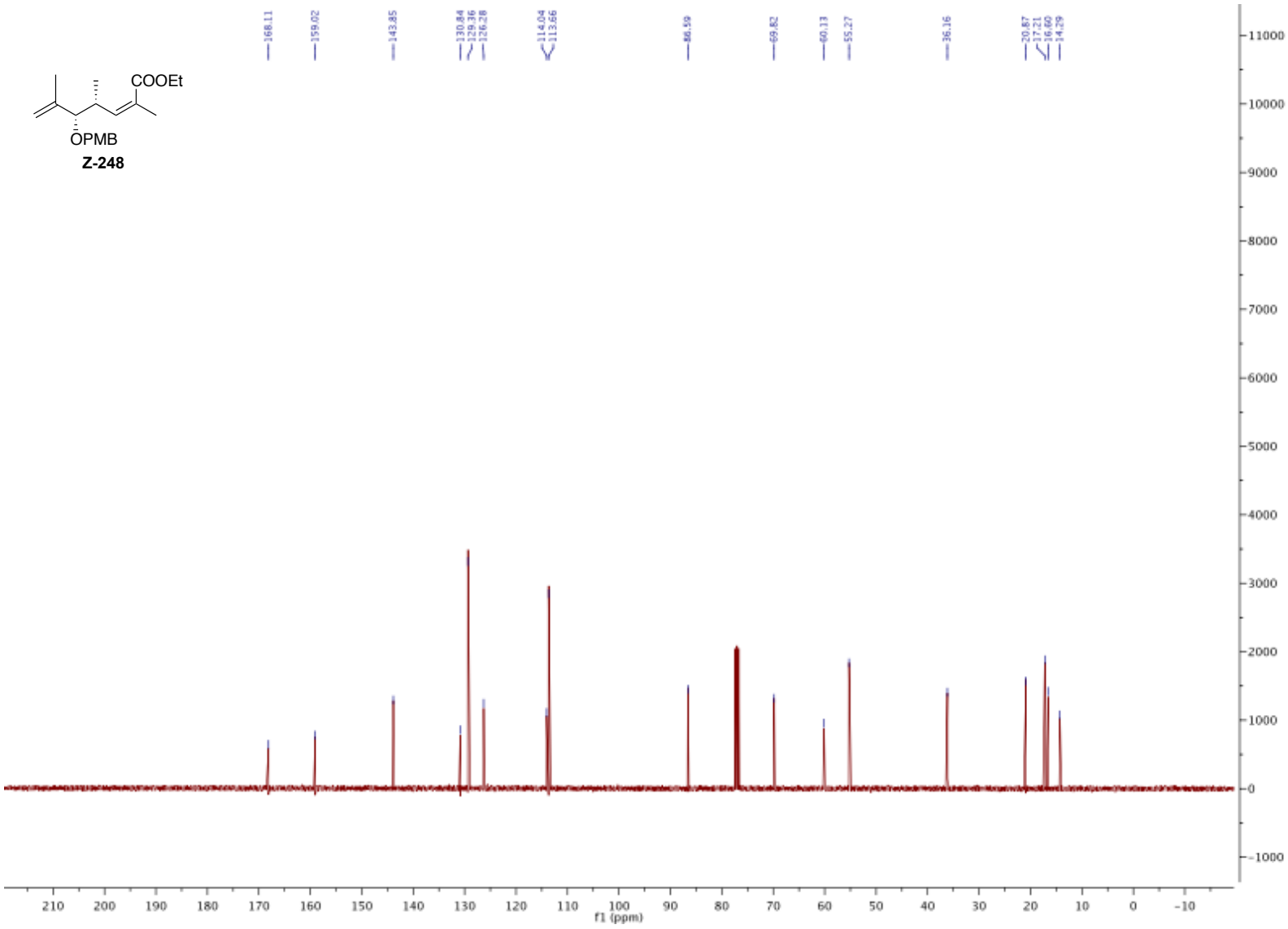

HO
OH
TBDPSO
OH
236
f1 (ppm)

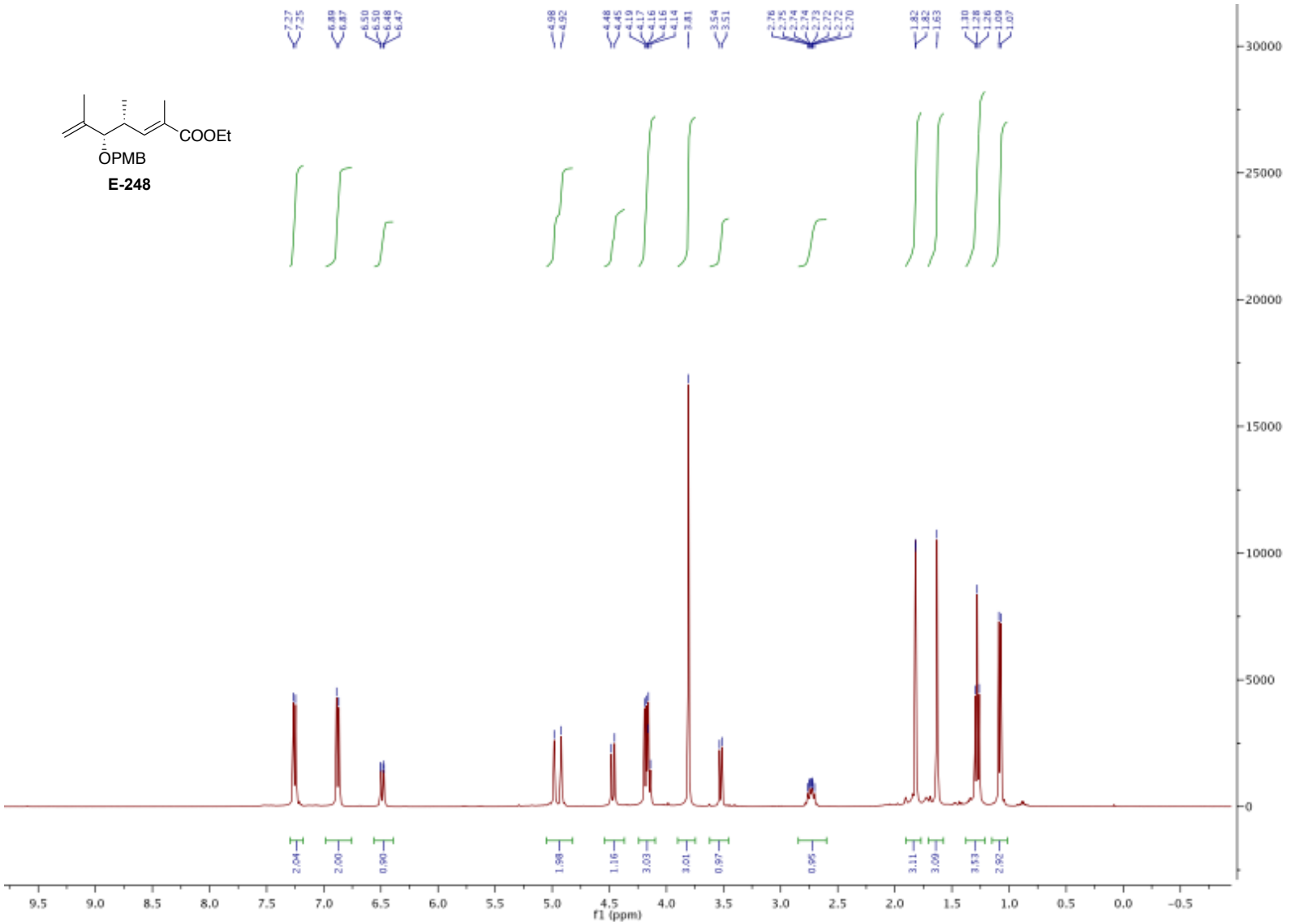

HO
OH
TBDPSO
OH
236
136.15
136.00
134.47
134.23
129.74
127.63
127.56
78.97
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
72.59
66.77
64.43
42.47
36.19
34.99
30.34
27.27
27.19
19.68
15.74
12.81
11.47
f1 (ppm)

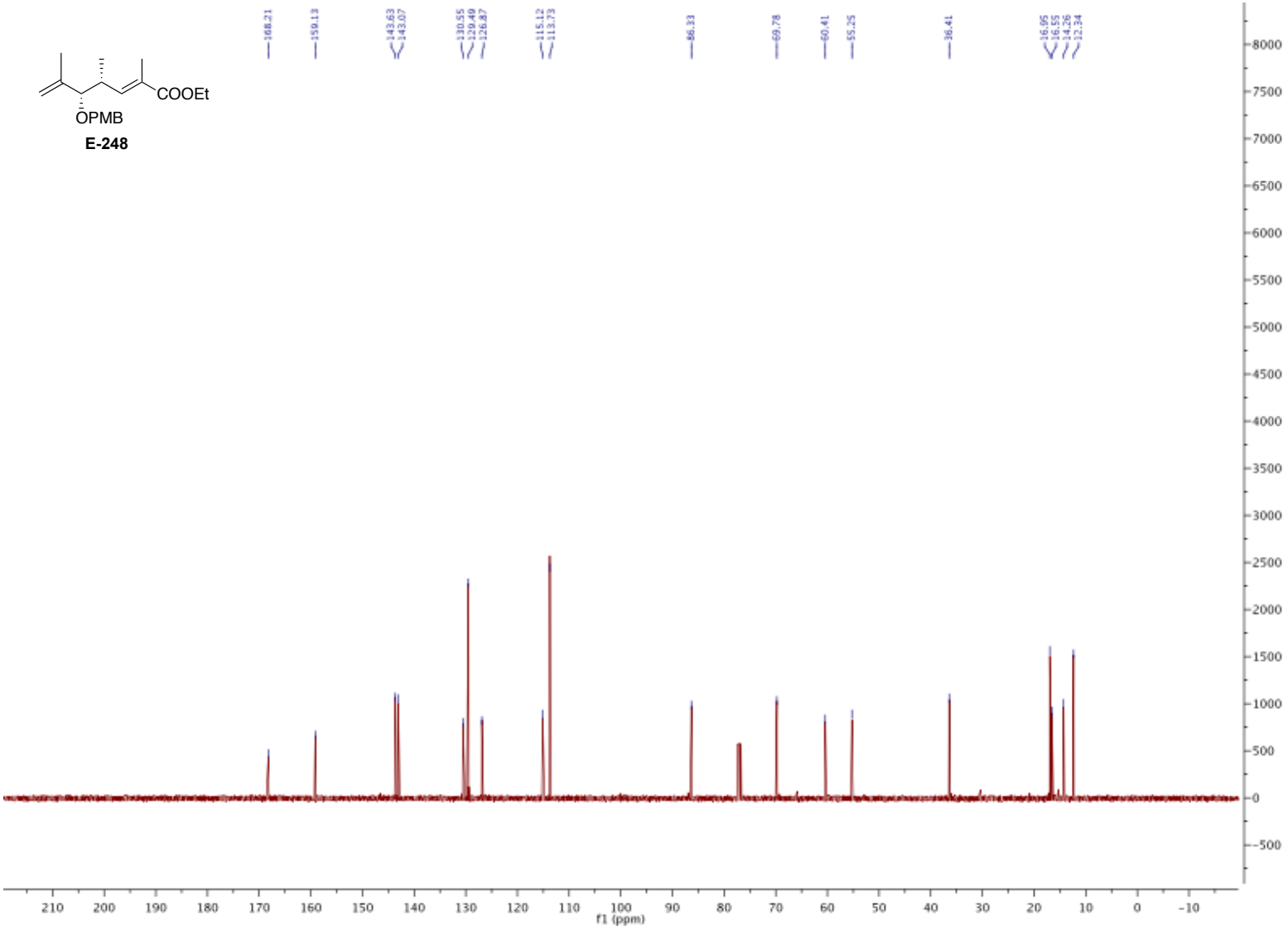

HO
OBn
TBDPSO
OH
238
f1 (ppm)

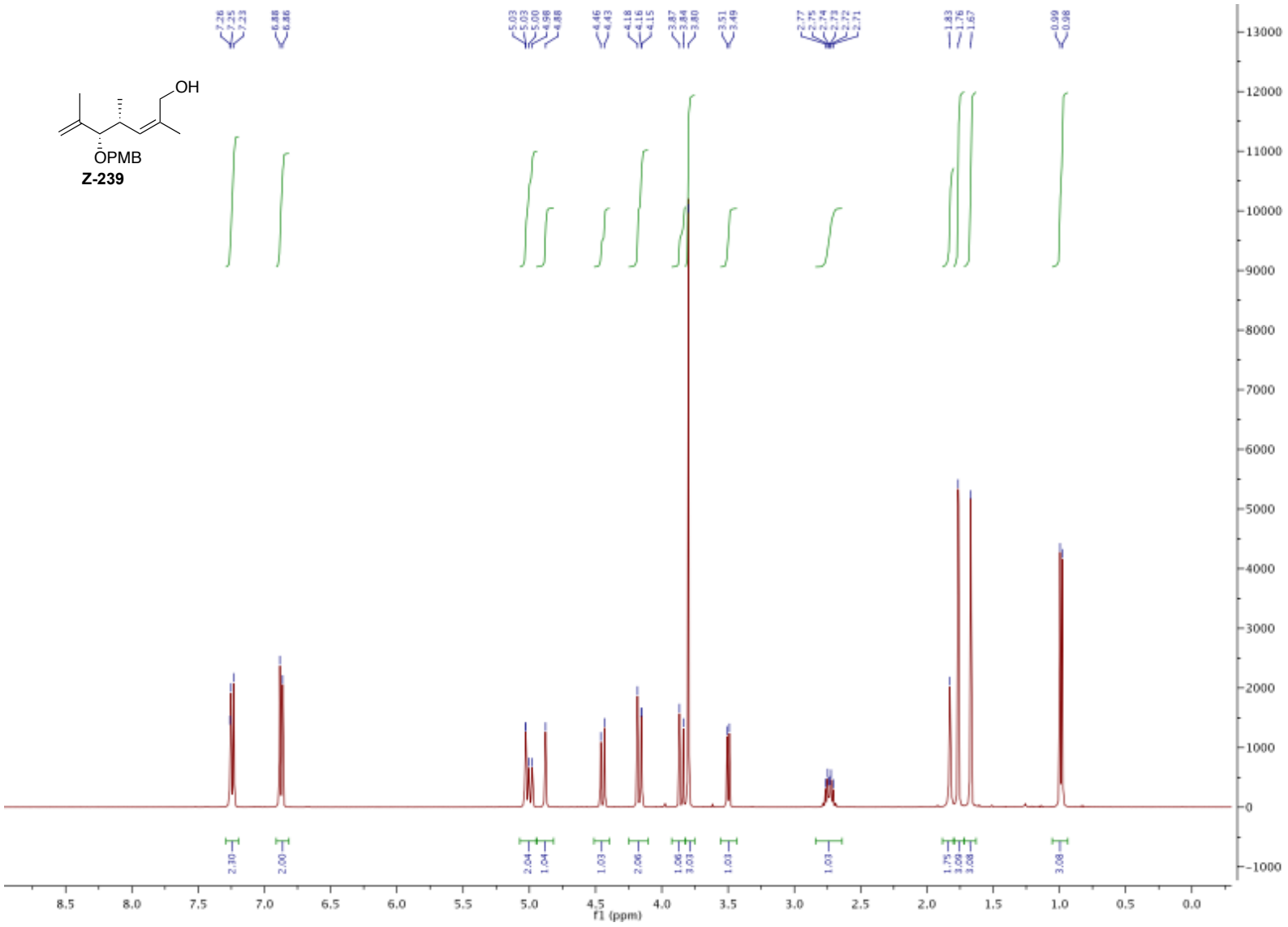

HO
OBn
TBDPSO
OH
238
f1 (ppm)

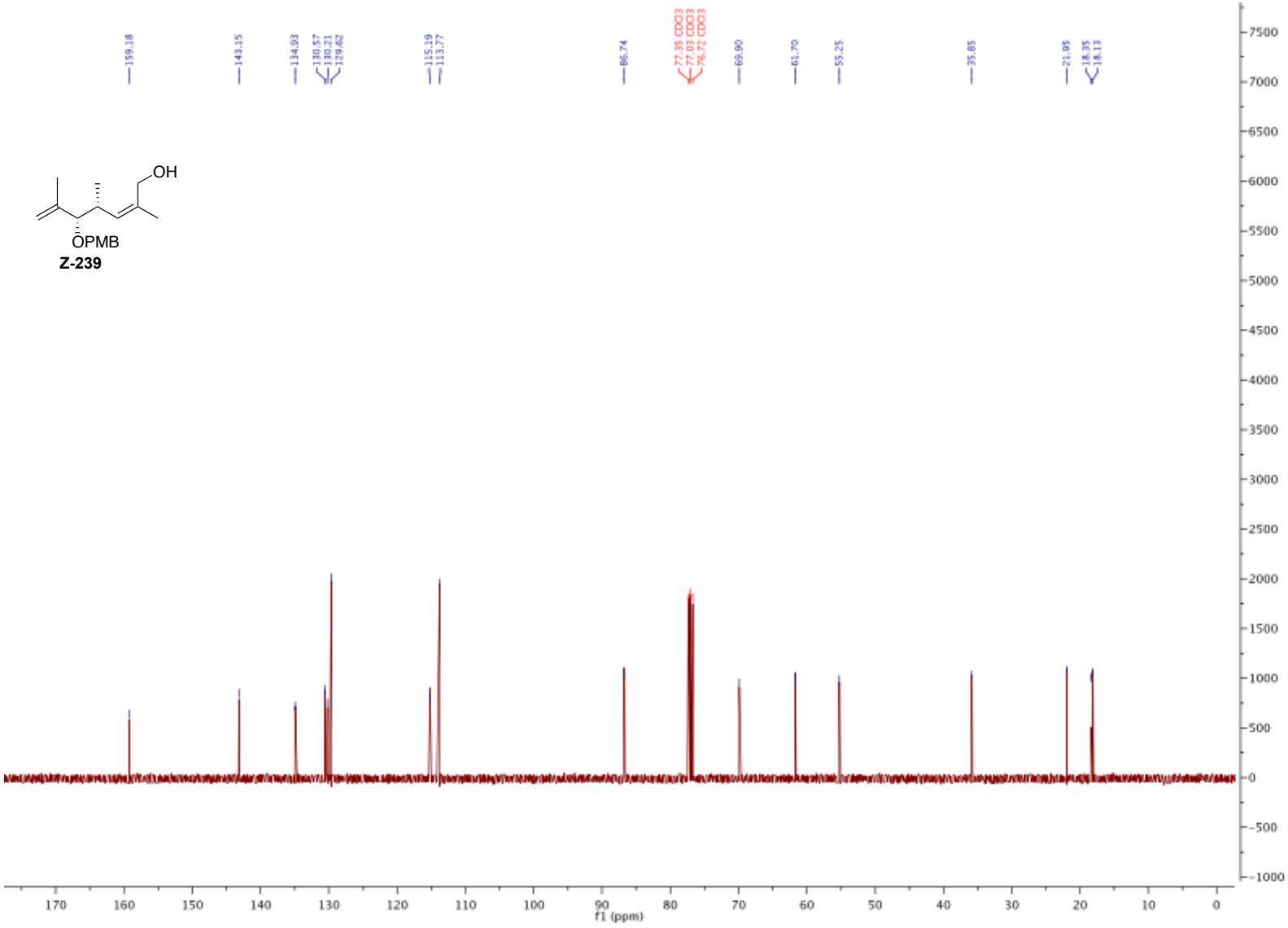

COOEt
OPMB
Z-248
f1 (ppm)

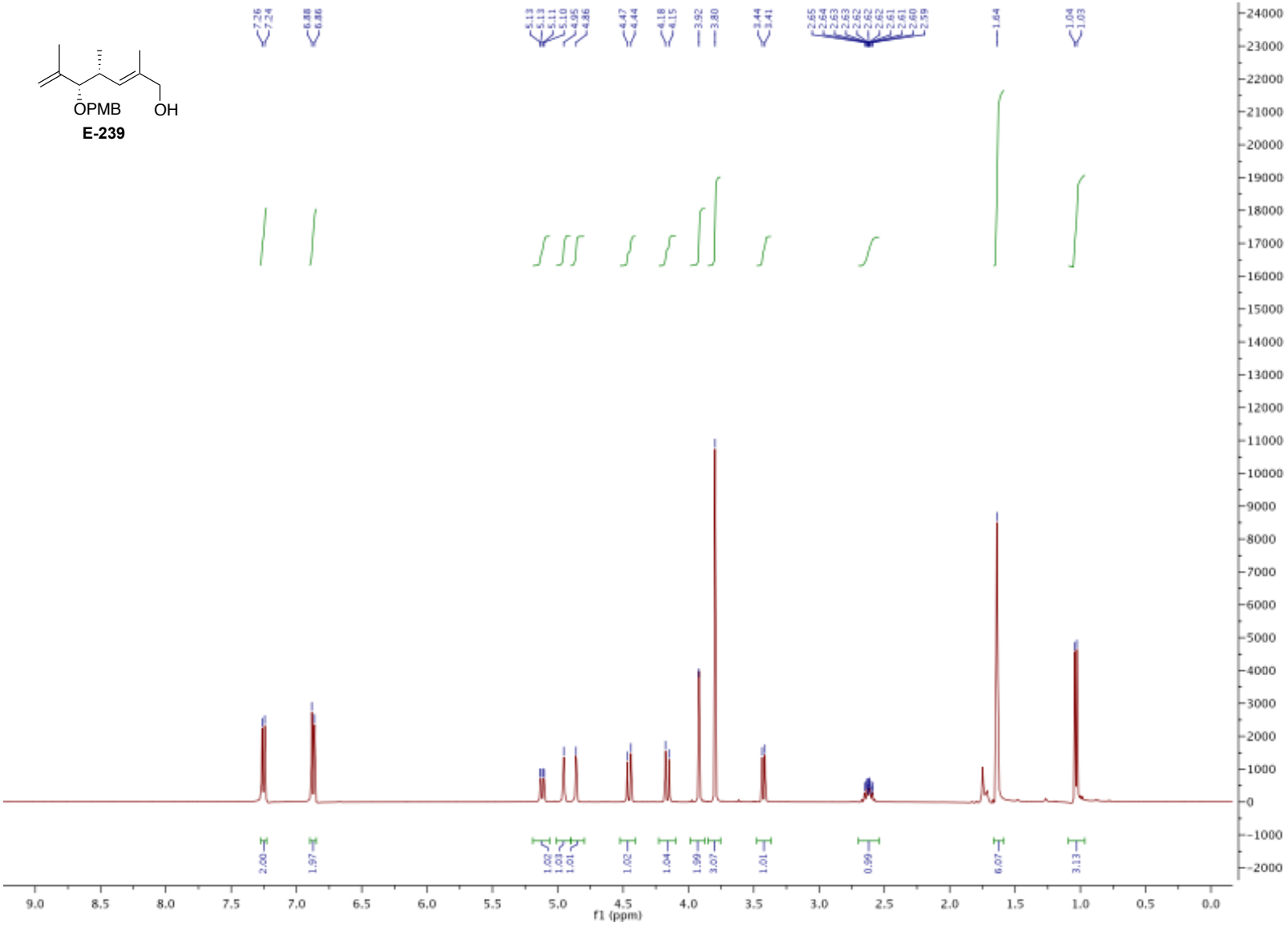

COOEt
OPMB
Z-248
168.11
159.02
143.85
130.84
129.36
126.28
114.04
113.66
86.59
69.82
60.13
55.27
36.16
20.87
17.21
16.60
14.29
f1 (ppm)

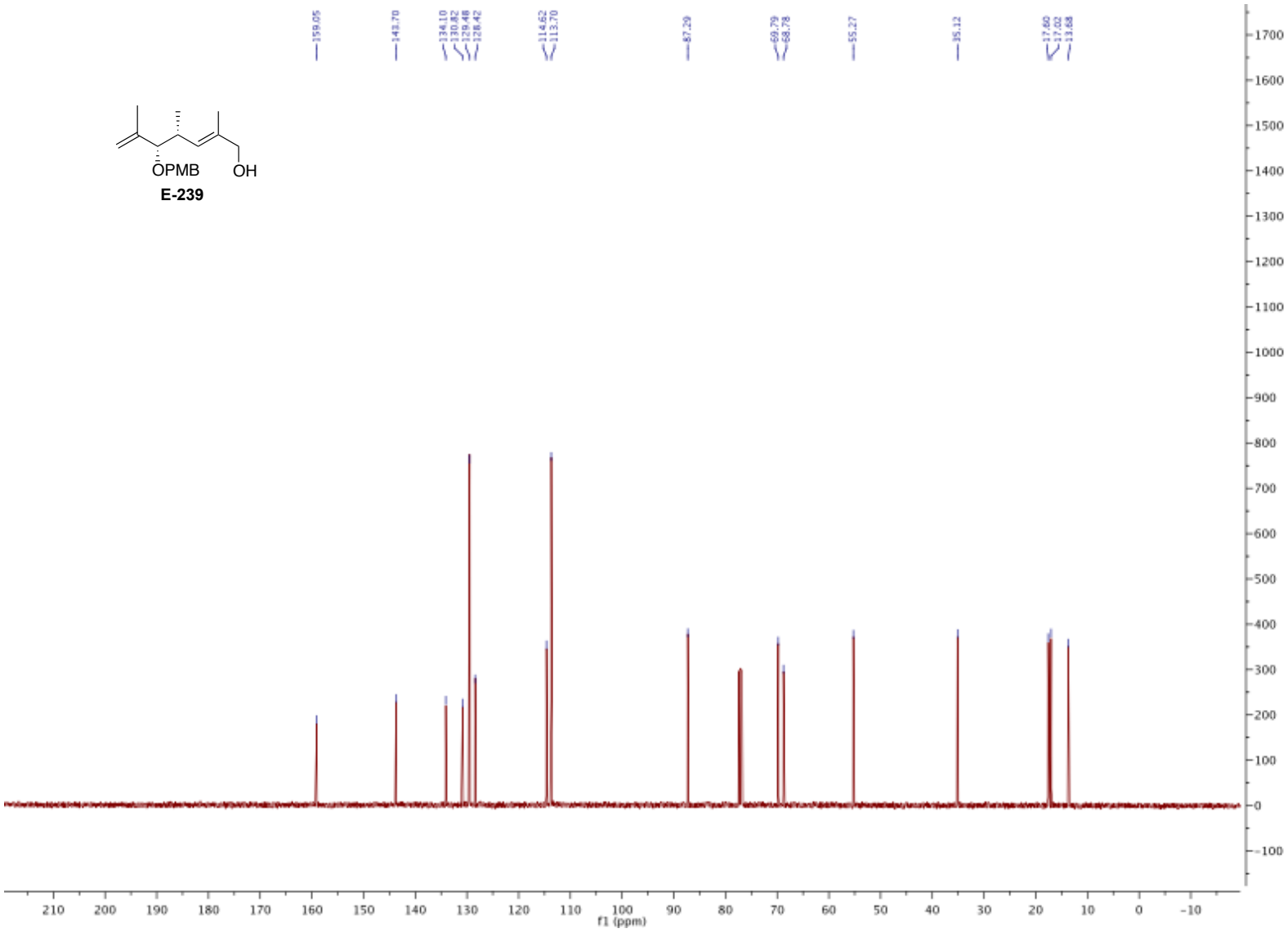

COOEt
OPMB
E-248
f1 (ppm)

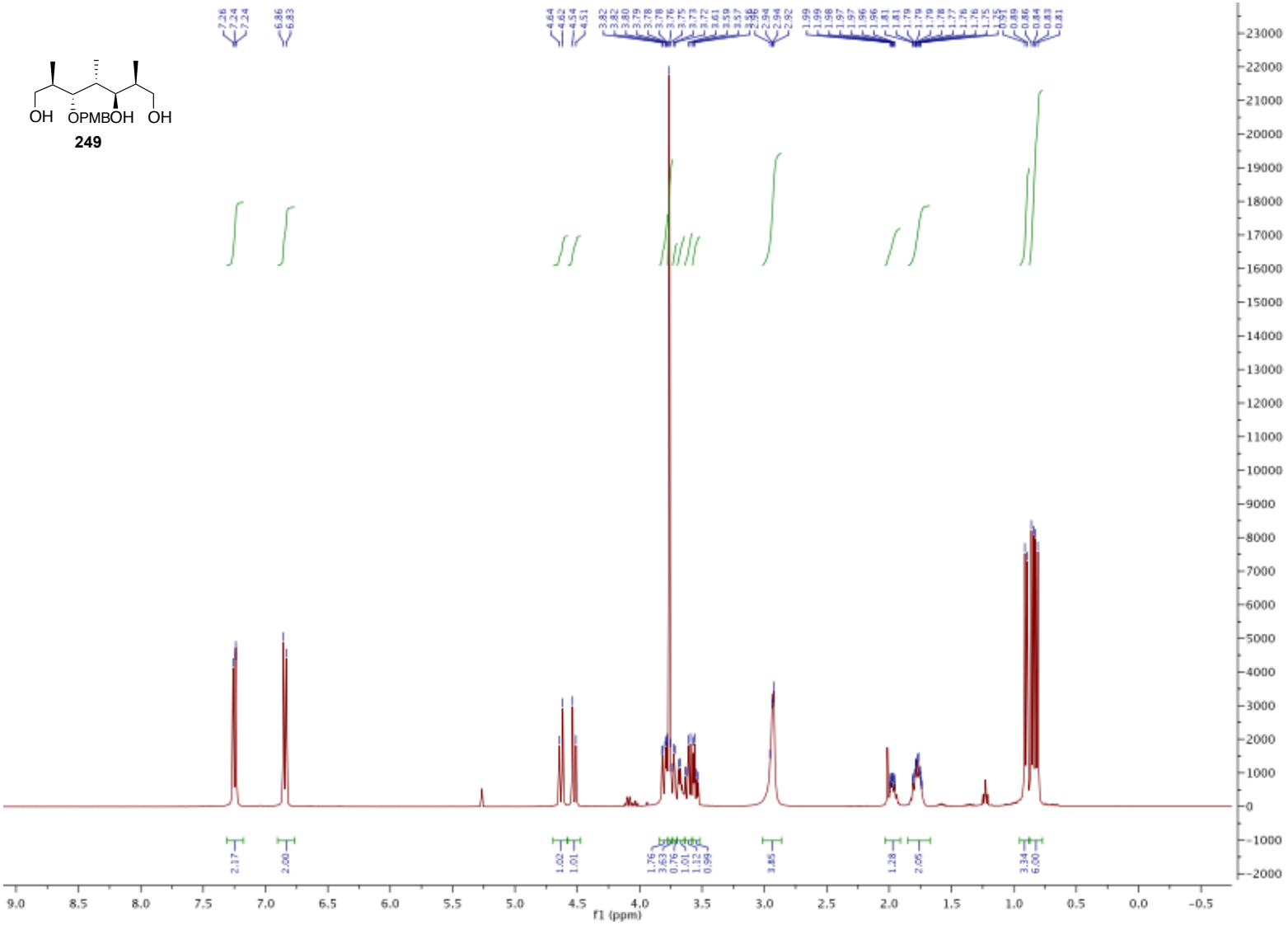

COOEt
OPMB
E-248
168.21
159.13
143.63
143.07
130.55
129.49
126.87
115.12
113.73
86.33
69.78
60.41
55.25
36.41
16.95
16.55
14.26
12.34
f1 (ppm)

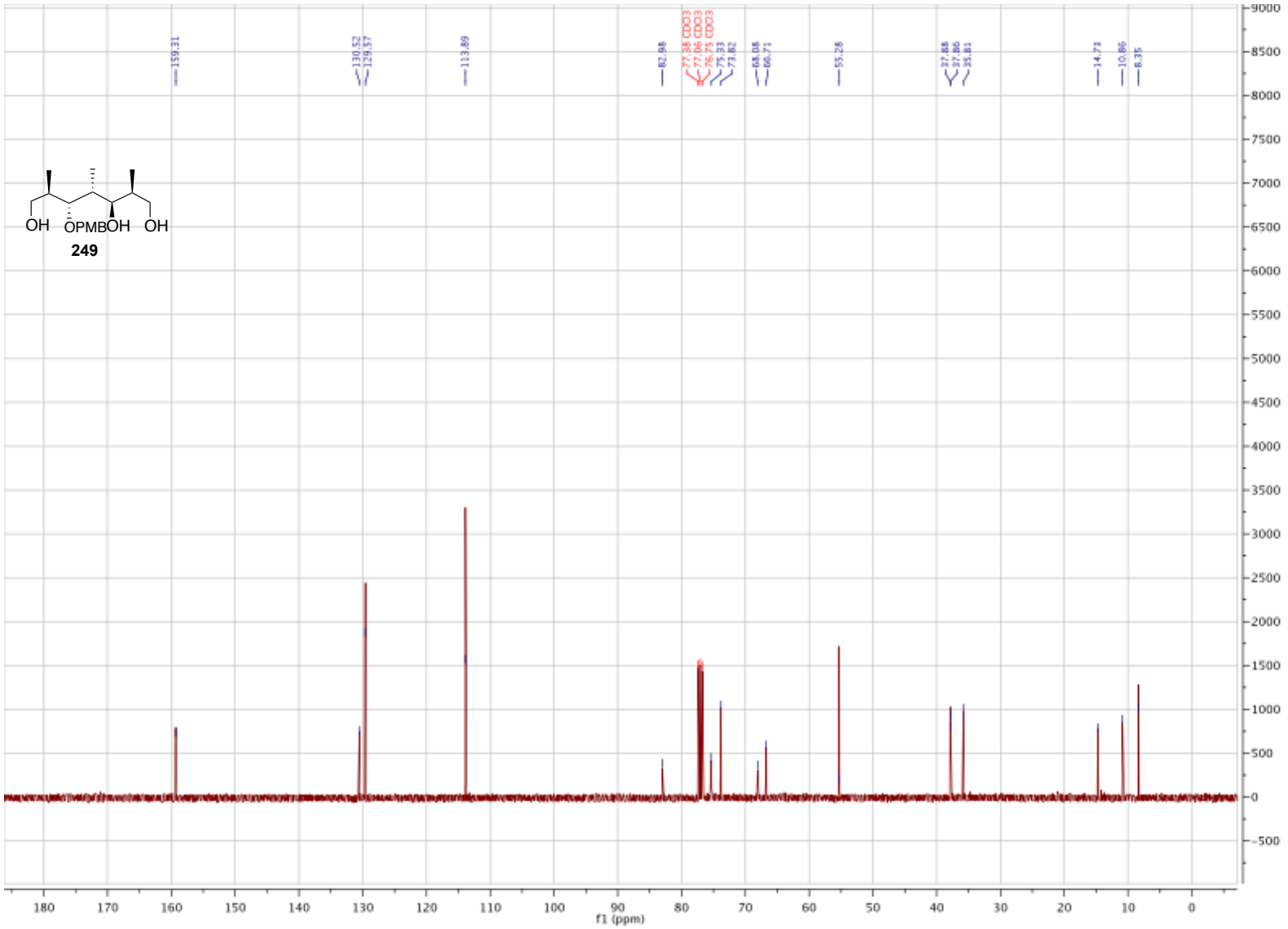

OH
OPMB
Z-239
f1 (ppm)

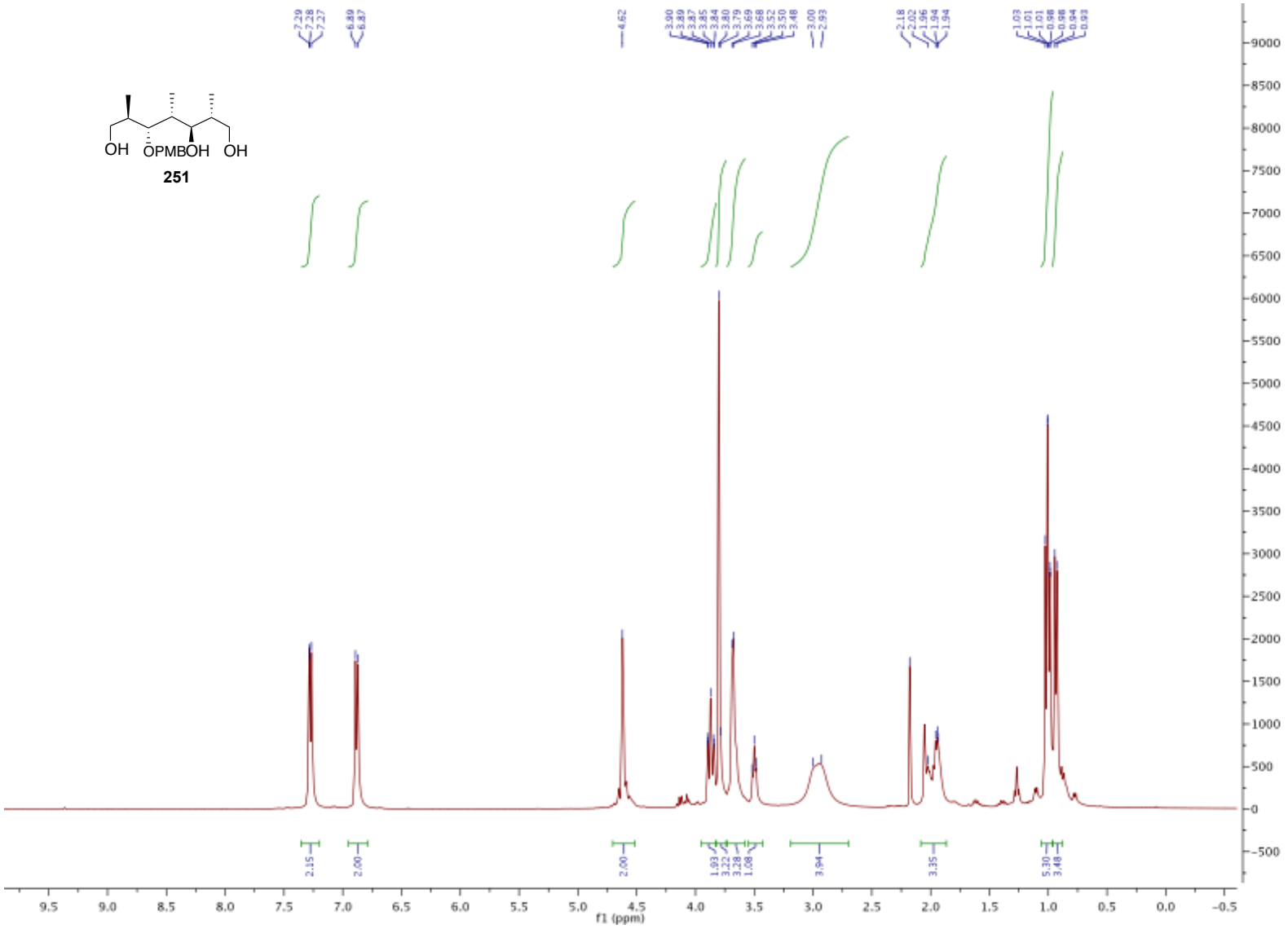

159.38
143.15
134.93
130.57
130.21
129.62
115.19
113.77
86.74
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
69.90
61.70
55.25
35.85
21.95
18.35
18.13
OH
OPMB
Z-239
f1 (ppm)

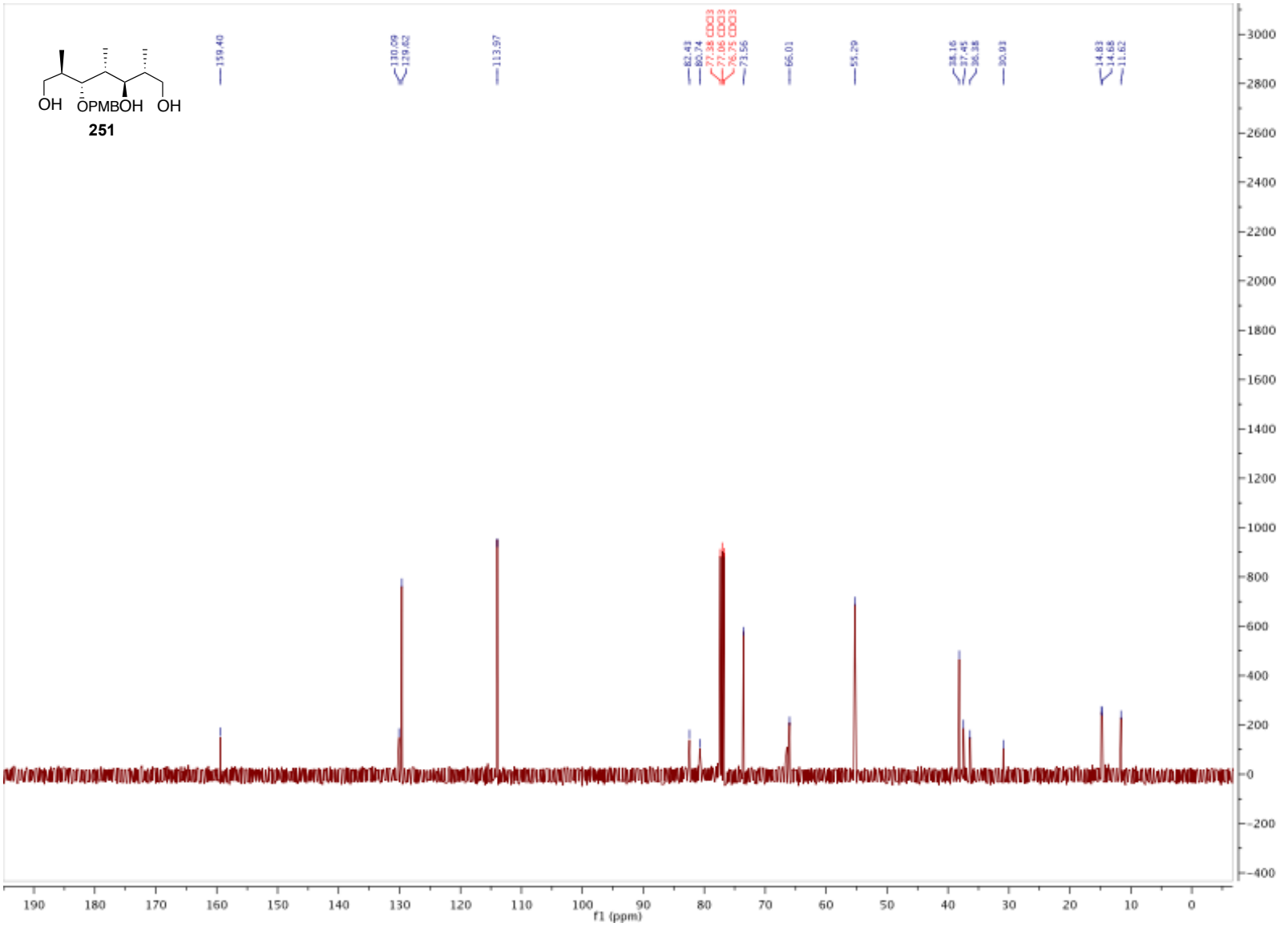

OPMB
OH
E-239
f1 (ppm)

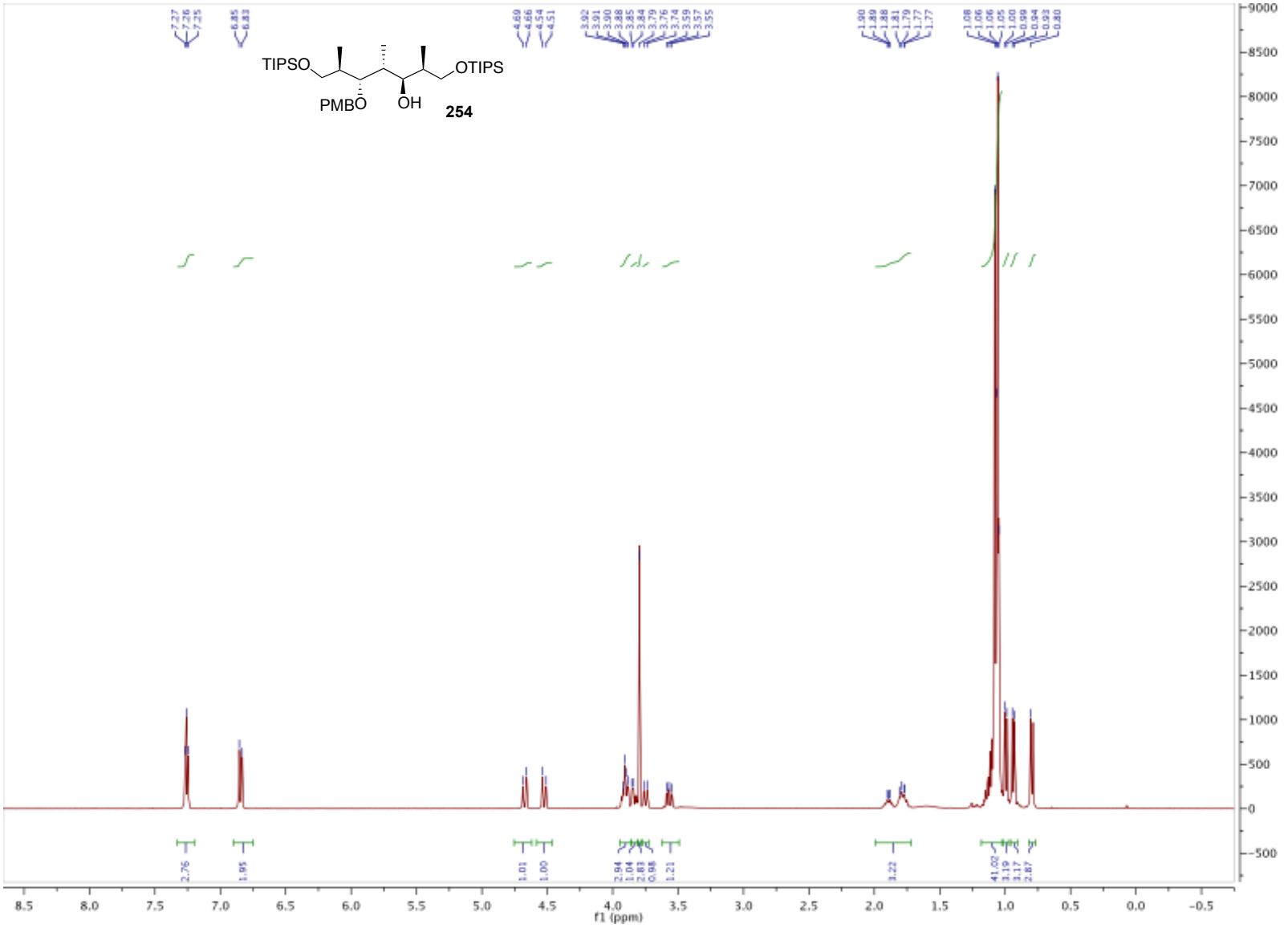

OPMB
OH
E-239
159.05
143.70
134.10
130.82
129.48
128.42
114.62
113.70
87.29
69.79
68.78
55.27
35.12
17.60
17.02
13.68
f1 (ppm)

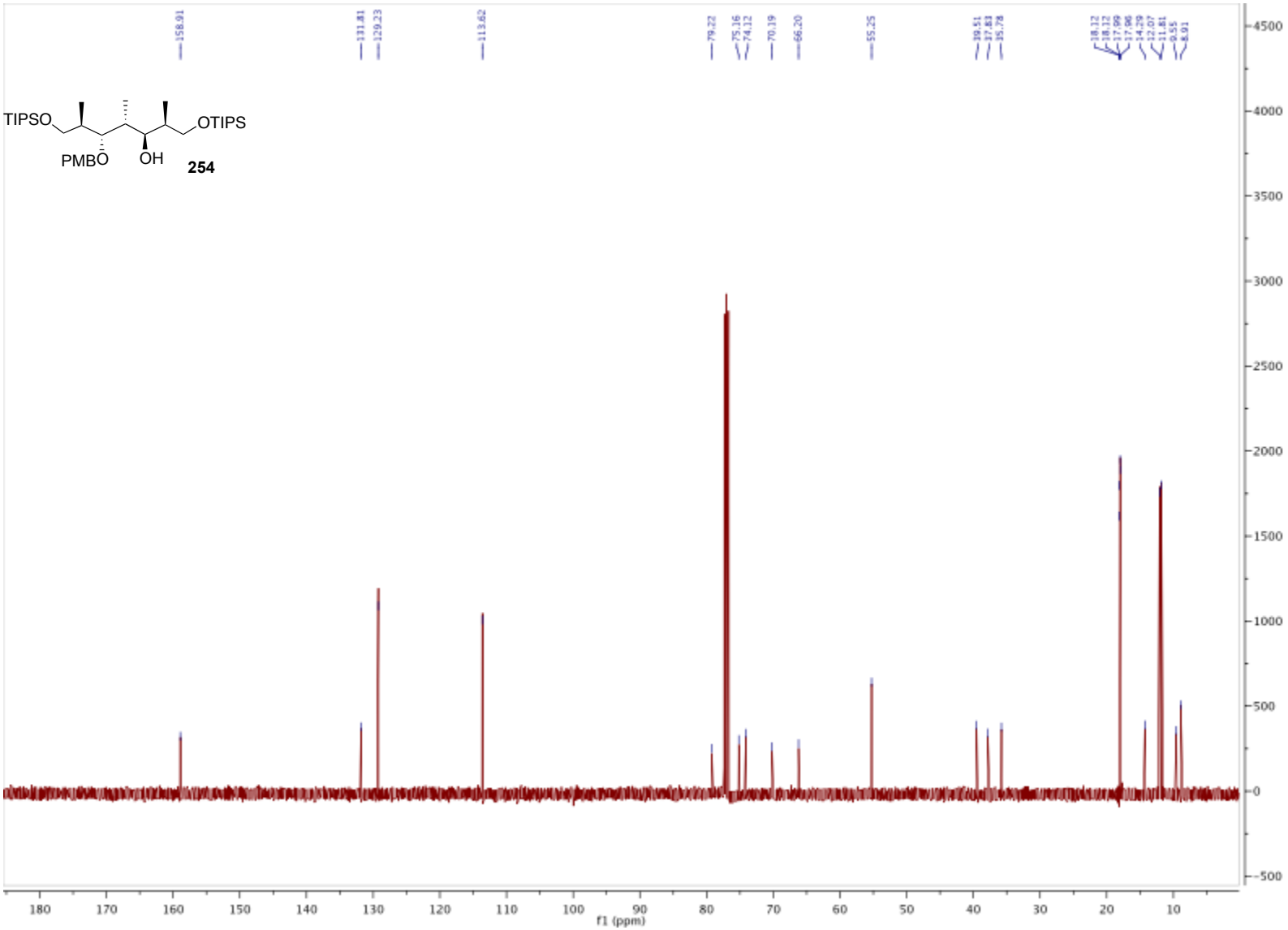

OH OPMB OH OH
249
f1 (ppm)

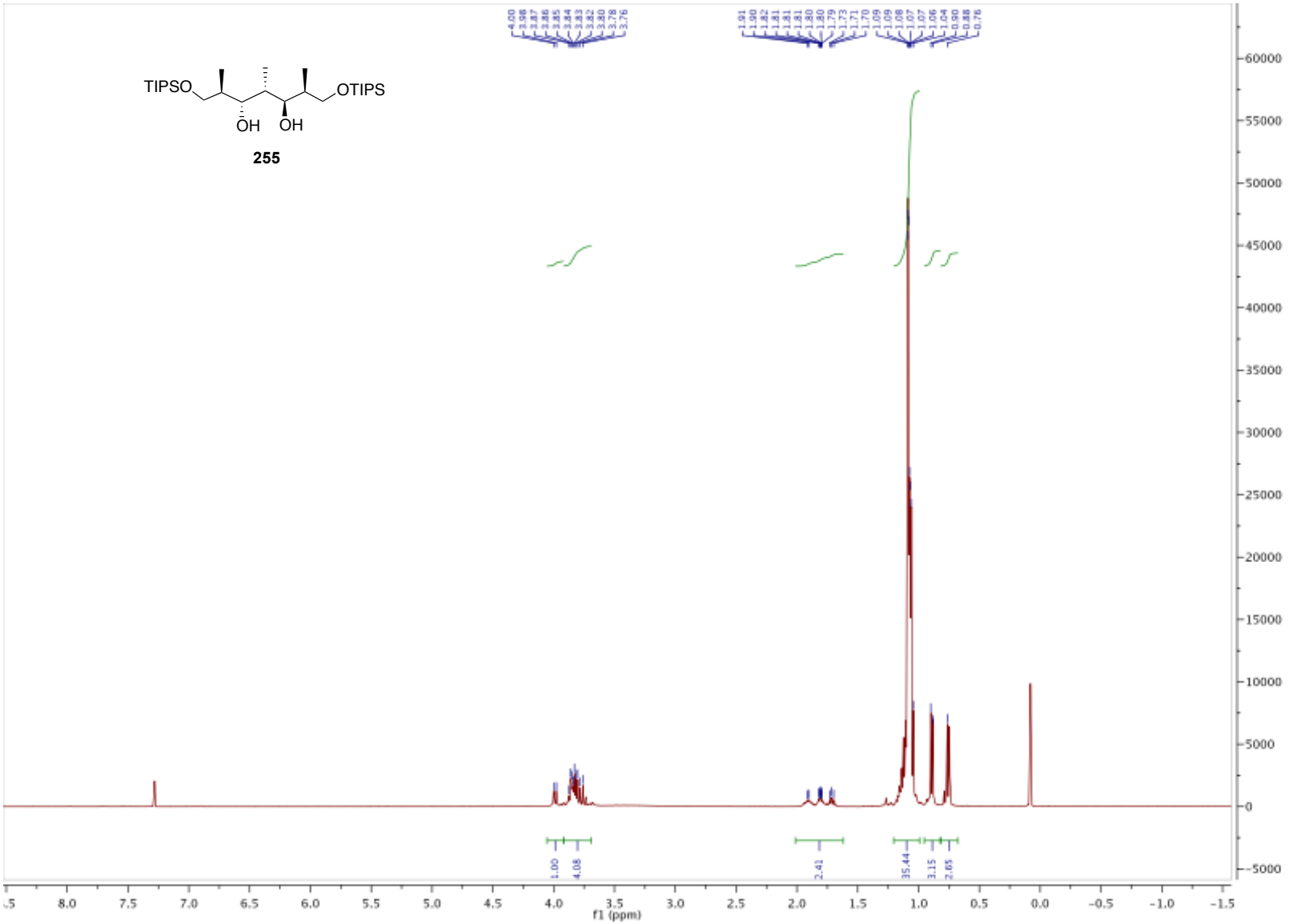

OH
OPMB
OH
OH
249
159.31
130.52
129.57
113.89
82.98
77.38 CDCl3
77.06 CDCl3
76.75 CDCl3
75.33
73.82
68.08
66.71
55.28
37.88
37.86
35.81
14.73
10.86
6.35
f1 (ppm)

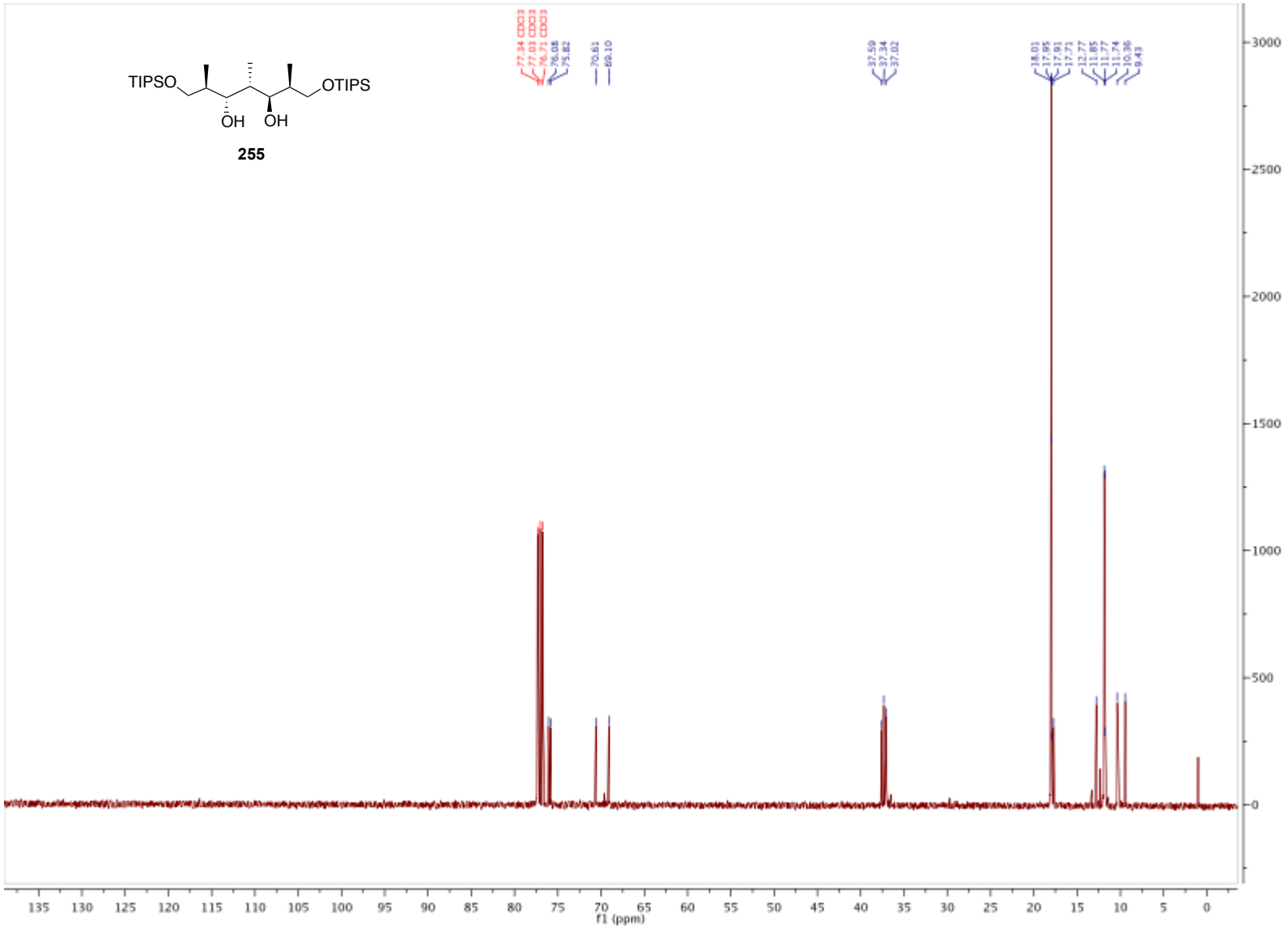

OH
OPMB
OH
OH
251
f1 (ppm)

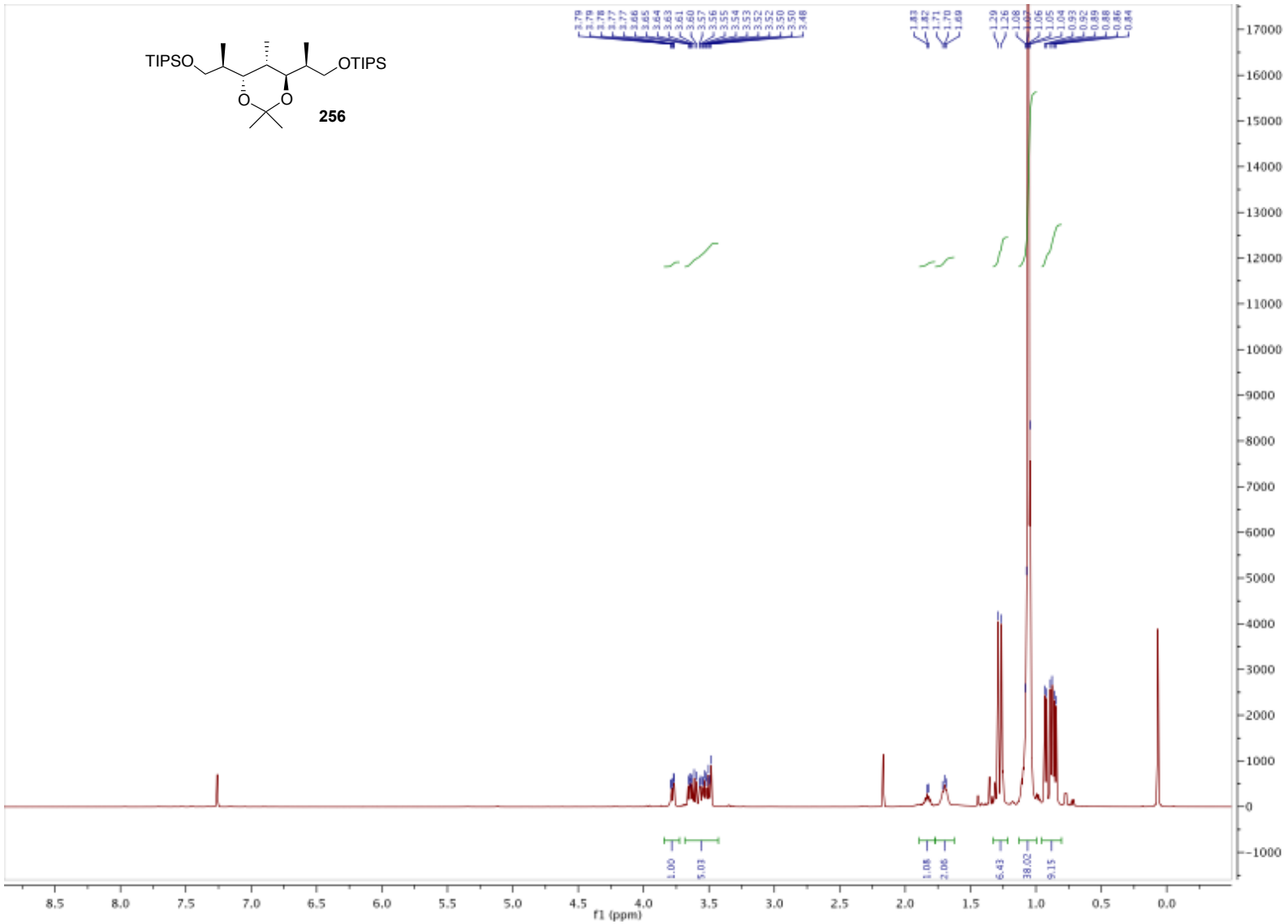

OH
OPMB
OH
OH
251
159.40
130.09
129.62
113.97
82.43
80.74
77.38 CDCl3
77.06 CDCl3
76.75 CDCl3
73.56
66.01
55.29
38.16
37.45
36.38
30.93
14.83
14.68
11.62
f1 (ppm)

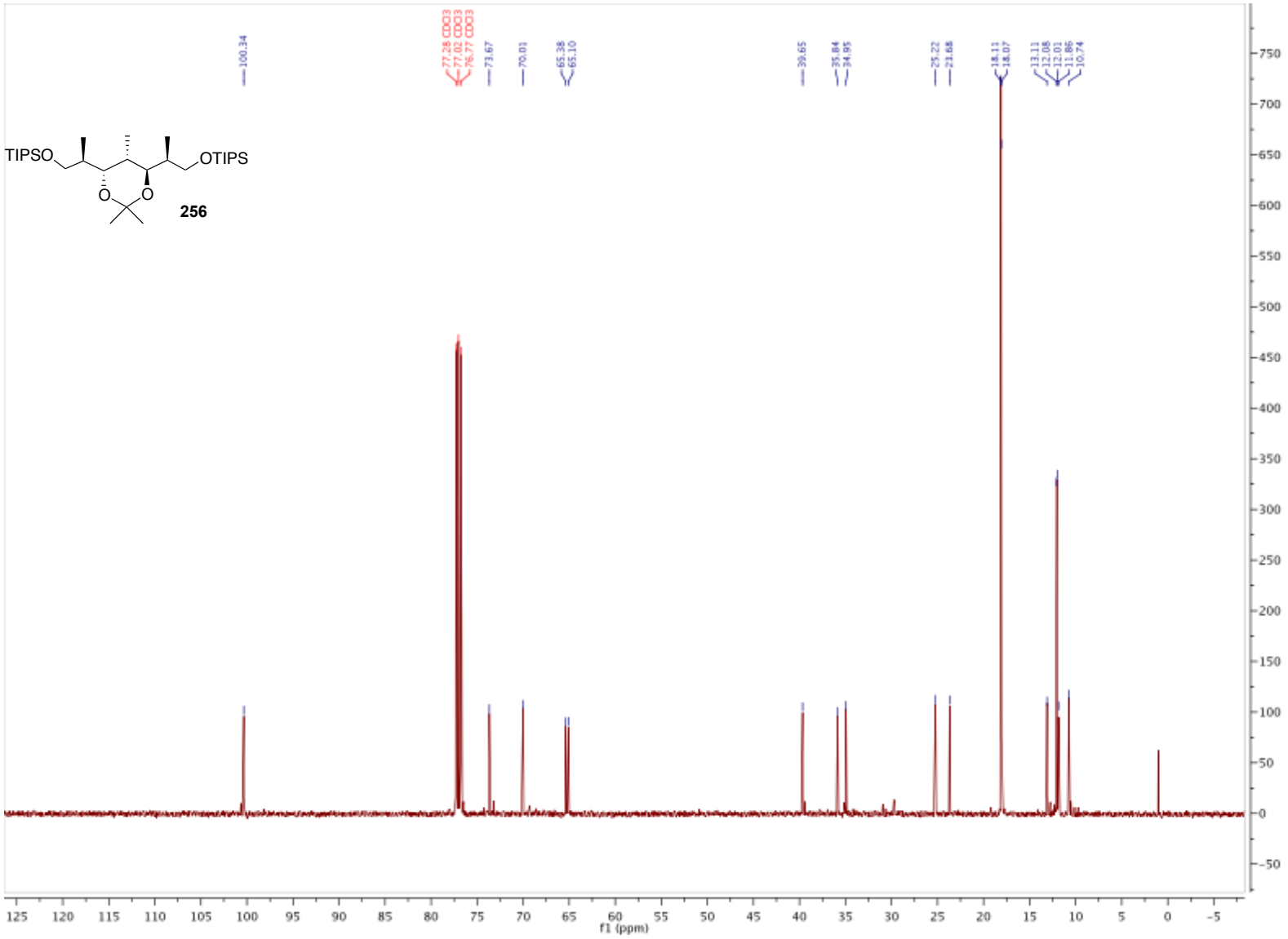

TIPSO
OTIPS
PMBO
OH
254
f1 (ppm)


TIPSO
OTIPS
PMBO
OH
254
158.91
131.41
129.23
113.62
79.22
75.16
74.12
70.19
66.20
55.25
39.51
37.83
35.78
18.12
18.12
17.99
17.96
14.29
12.07
11.81
9.55
8.91
f1 (ppm)


TIPSO
OTIPS
OH
OH
255
f1 (ppm)


TIPSO
OTIPS
OH
OH
255
77.34 CDCl3
77.03 CDCl3
76.71 CDCl3
76.08
75.82
70.61
69.10
37.59
37.34
37.02
18.01
17.95
17.91
17.71
12.77
11.85
11.77
11.74
10.36
9.43
3000
2500
2000
1500
1000
500
0
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)


TIPSO
OTIPS
O
O
256
f1 (ppm)


TIPSO
OTIPS
O
O
256
100.34
77.26 CDCl3
77.02 CDCl3
76.77 CDCl3
73.67
70.01
65.38
65.10
39.65
35.84
34.95
25.22
23.68
18.11
18.07
13.11
12.08
12.01
11.86
10.74
f1 (ppm)