# Implementation of Catalytic, Asymmetric Technology Toward the Total Synthesis of Apoptolidin C

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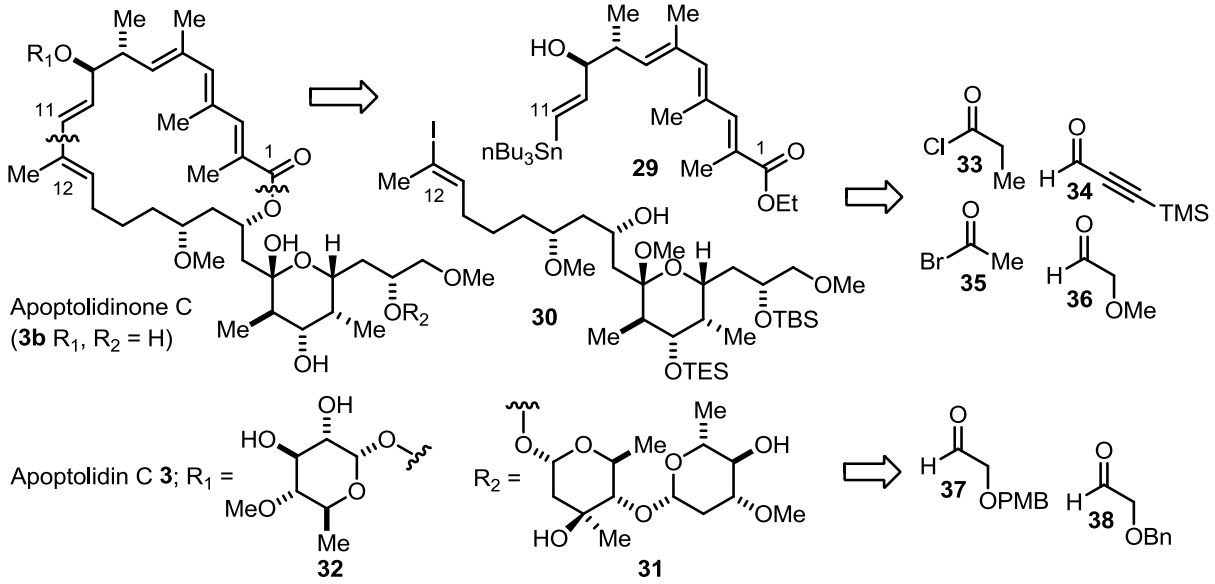
James S. Hale, PhD

University of Pittsburgh, 2012

The total synthesis of apoptolidin C (**3**), a highly selective cytotoxic macrolide, has been under investigation in our lab. Work completed includes the synthesis of the $C_1$-$C_{11}$ fragment **29**, the macrocyclic core **3b**, and the disaccharide subunit **31**. These goals have been realized utilizing catalytic, asymmetric reaction methodology including the acyl halide-aldehyde cyclocondensation (AAC) and proline catalyzed dimerization of simple aldehyde starting materials **33**-**38**.



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## LIST OF ABBREVIATIONS

AIBN……..…Azobisisobutyronitrile

Bpin…….Pinacolborane

BBN……..Borabicyclo[3.3.1]nonane

dba.....…Dibenzylideneacetone

DCE…….1,2-Dichloroethane

DCM……...Dichloromethane

dppf……...1,1`-Bis(diphenylphosphino)ferrocene

DIPEA……...*N*,*N*-Diisopropylethylamine

DMAP……..4-Dimethylaminopyridine

DMF……...*N*,*N*-Dimethylformamide

DMSO……..Dimethylsulfoxide

de……Diastereomeric excess

dr……...Diastereomeric ratio

ee……...Enantiomeric excess

equiv…….Equivalents

EtOAc……Ethyl acetate

imid……Imidazole

HRMS……...High resolution mass spectrum

HWE……Horner-Wadsworth-Emmons

$GI_{50}$……...Growth inhibition 50

LDA…….Lithium diisopropylamide

NaHMDS……...Sodium bis(trimethylsilyl)amide

PCC……Pyridinium chlorochromate

pyr……Pyridine

RT……Room temperature

SM……...Starting material

TBS……...*tert*-Butyldimethylsilyl

TBSCl……*tert*-Butyldimethylsilyl chloride

TBSOTf……*tert*-Butyldimethylsilyl triflate

THF…..Tetrahydrofuran

TLC……Thin-layer chromatography

TMS……Trimethylsilyl

TMSBr……Bromotrimethylsilane

TMSCl……...Trimethylsilyl chloride

Tf……Trifluoromethanesulfonate

Ts……..Tosyl

TsCl……Tosyl chloride

## PREFACE

Thanks to God, without whom nothing is possible or meaningful.

Thanks to Professor Nelson for having me in his lab and for providing a challenging project with valued guidance towards its completion. I would not be nearly the chemist I am without his insistence on excellence and fostering of a positive learning environment. Thanks to my committee members Professor Koide, Wilcox, and Gold as well as my proposal mentor Professor Floreancig for their part in the completion of this degree.

Thanks to Nelson group members, past and present, for camaraderie and advice. The lack of your presence would have made five years seem like fifty. An extra nod goes to Tom Vargo for being a source of aid and commiseration during our united efforts. Thanks to my peers in CSC for all of the same things and additionally for chemicals borrowed.

Thanks to friends and family for their support and understanding, especially my wife, Alison Hale, whom by marrying I performed my only greater accomplishment.

# 1.0 INTRODUCTION

## 1.1 BIOLOGICAL ACTIVITY AND STRUCTURAL FEATURES

Apoptolidin A **(1)** was first discovered by Seto in 1997, isolated from the soil bacteria *Nocardiopsis* sp.[1,2] Structural derivatives apoptolidin B **(2)** and C **(3)** were isolated in 2005 from the same bacteria by Wender (Figure 1).[3] Wender also isolated the most recent addition to this family of natural products, apoptolidin D **(4)**, in 2007.[4] This family of natural products has garnered interest in the scientific community for both its cytotoxic profile and structural complexity. Although a more complete biological profile has been built for apoptolidin A due to its relative ease of isolation, biochemical studies have also focused on B through D as well as other, synthetic derivatives.

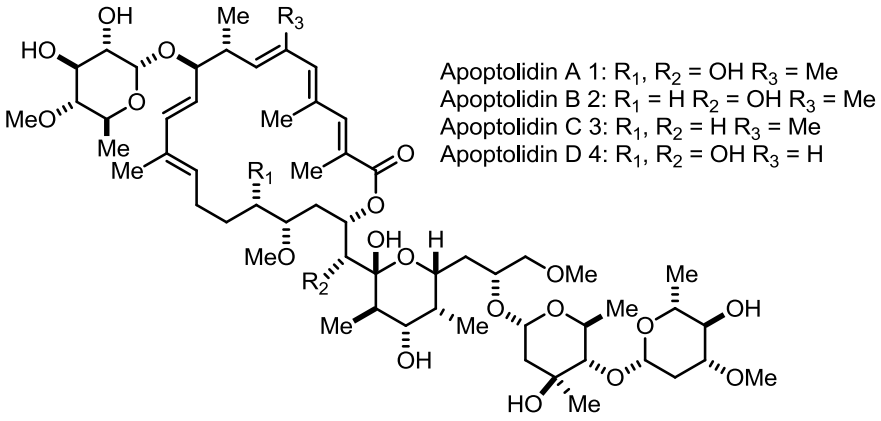


**Figure 1.** Apoptolidin A-D

Cytotoxicity studies have shown the apoptolidins to be highly potent against various resistant cancer cell lines. A $GI_{50}$ of 24 nM has been reported for apoptolidin C in a cell proliferation assay with H292 cancer cells (Table 1).[1] Apoptolidin A displays similar efficiency with apoptolidin C, while data suggest that apoptolidin B is more active. Impressively, apoptolidin A has also been shown to be extremely selective and is detrimental to healthy cells only at high concentrations (>1 μM). This potency and selectivity has caught the attention of many members of the scientific community, causing the formulation of synthetic strategies that allow variability in substrate diversity to be a high priority.

**Table 1.** Growth inhibition assay results with H292 cells

| Apoptolidin | GI50 (μM) |
|---|---|
| A | 0.032 ± 0.003 |
| B | 0.007 ± 0.004 |
| C | 0.024 ± 0.005 |

The work of the Khosla in 2001 was the first documented attempt to elucidate the mechanism of action of the apoptolidins. These data suggested that the cytotoxicity is due to apoptolidin A's inhibition of mitochondrial $F_0F_1$-ATP synthase.[5] This analysis was later applied to a wide range of analogs including apoptolidin C.[6-9] Despite these studies, the structure-activity-relationship responsible for this inhibition remains elusive. These preliminary investigations by Wender suggest that the conformation of the macrocyclic core, as well as variation of the $C_{20}$ and $C_{21}$ functionalization, have a direct and considerable impact on levels of inhibition.

In addition the apoptolidins' impressive biological profile, these natural products are abundant in interesting structural features. This document will focus on the $C_1$-$C_{11}$ fragment of

the macrocycle, the completion of the macrocycle, and the completion of the disaccharide moiety. In total, apoptolidin C contains twenty five stereocenters, five geometrically defined olefins, and a twenty member macrolactone, presenting researchers with a target abundant in opportunities to apply novel, expedient methodology.

## 1.2 PREVIOUS SYNTHESES OF APOPTOLIDIN A

Previous total syntheses of apoptolidin A have been reported by Nicolaou[10-13], Koert[14-17] and Crimmins.[19-22] Sulikowski[23-28] has also reported a synthesis of the aglycone, apoptolidinone. Because the $C_1$-$C_{11}$ fragment of apoptolidin A is identical to that of apoptolidin C, a brief inspection of this derivative's syntheses is useful.

Nicolaou's work on apoptolidin A has been distributed in four reports.[10-13] These works have culminated in the retrosynthetic analysis displayed in Scheme 1, in which the molecule was dissected into four major fragments: the $C_9$ appended sugar **5**, the $C_{27}$ appended hexose **6**, the $C_1$-$C_{11}$ fragment of the aglycone **7**, and the $C_{12}$-$C_{28}$ fragment **8**. Both the sugar **5** and the hexose **6** were joined to their respective fragments prior to the construction of the macrocyclic core. The two major disconnections of this macrocyclic core come from an intermolecular Stille coupling between the organostannane **7** and the vinyl iodide **8** followed by Yamaguchi macrolactonization to complete the macrocyle.

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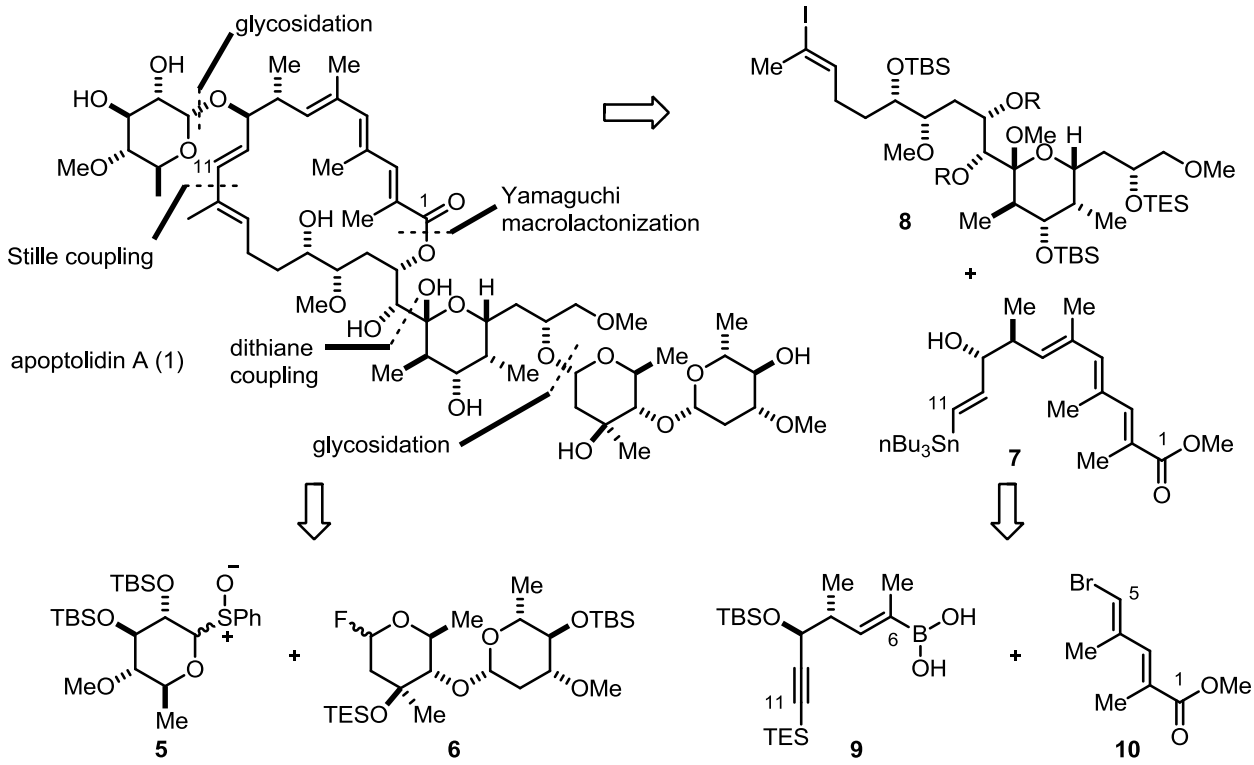
**Scheme 1.** Nicolou's retrosynthetic analysis

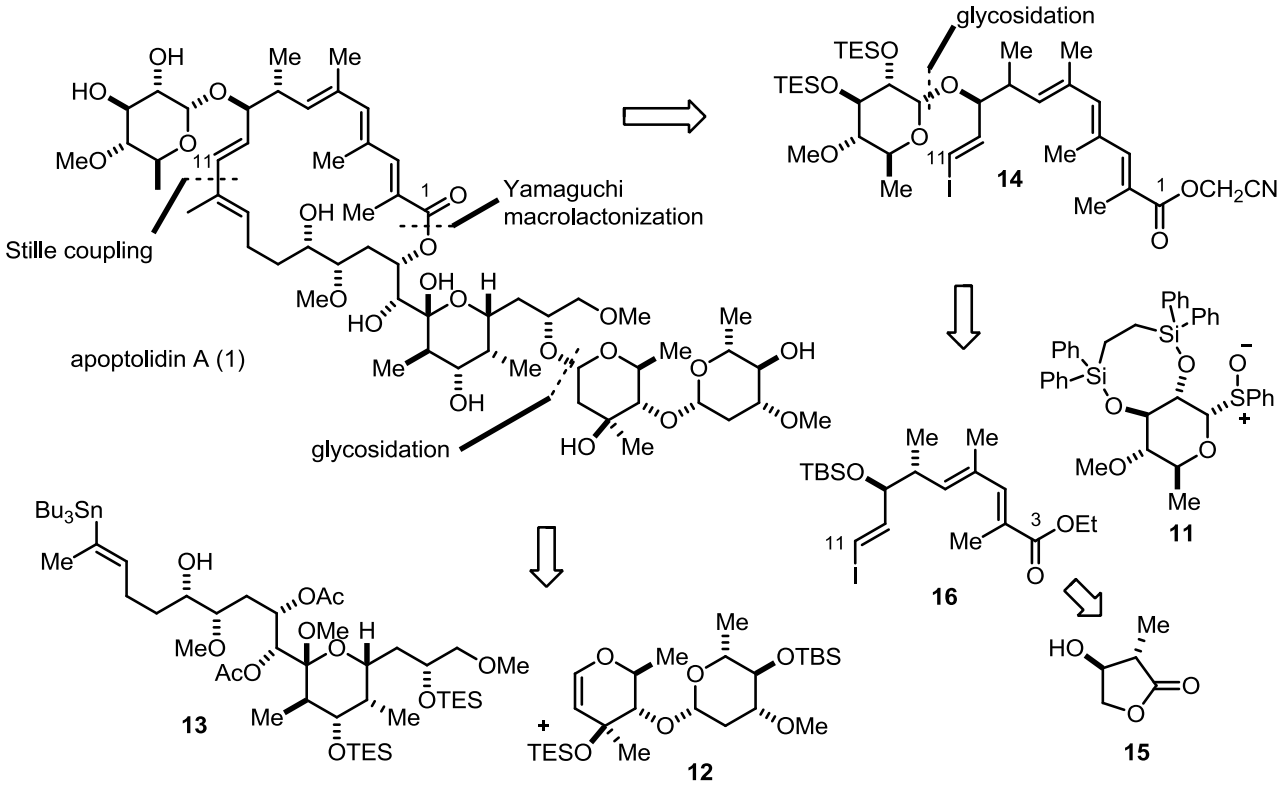



The $C_1$-$C_{11}$ fragment was assembled in two ways. In the pathway preferred by the author, vinyl boronate **9** was joined to diene **10** *via* a Suzuki cross-coupling reaction. The $C_8$ and $C_9$ stereocenters of the vinyl boronate were set utilizing Brown's crotylation method. The boronate was installed from the hydroboration of the alkynyl product of an Ohira-Bestmann homologation. The diene **10** was constructed from a tandem oxidation-Wittig sequence from a known alcohol.

Koert's major disconnections were similar to that of Nicolaou (Scheme 2).[14-17] Similar major building blocks were employed: sugar **11**, hexose **12**, and the same two halves of the aglycone. A Stille cross-coupling reaction was used to couple the two halves together. In this case, however, the organostannane was appended to the $C_{12}$-$C_{28}$ framework **13** and the vinyl

iodide to the $C_1$-$C_{11}$ **14**. Yamaguchi macrolactonization was utilized to complete the macrocycle.

**Scheme 2.** Koert's retrosyntheic analysis

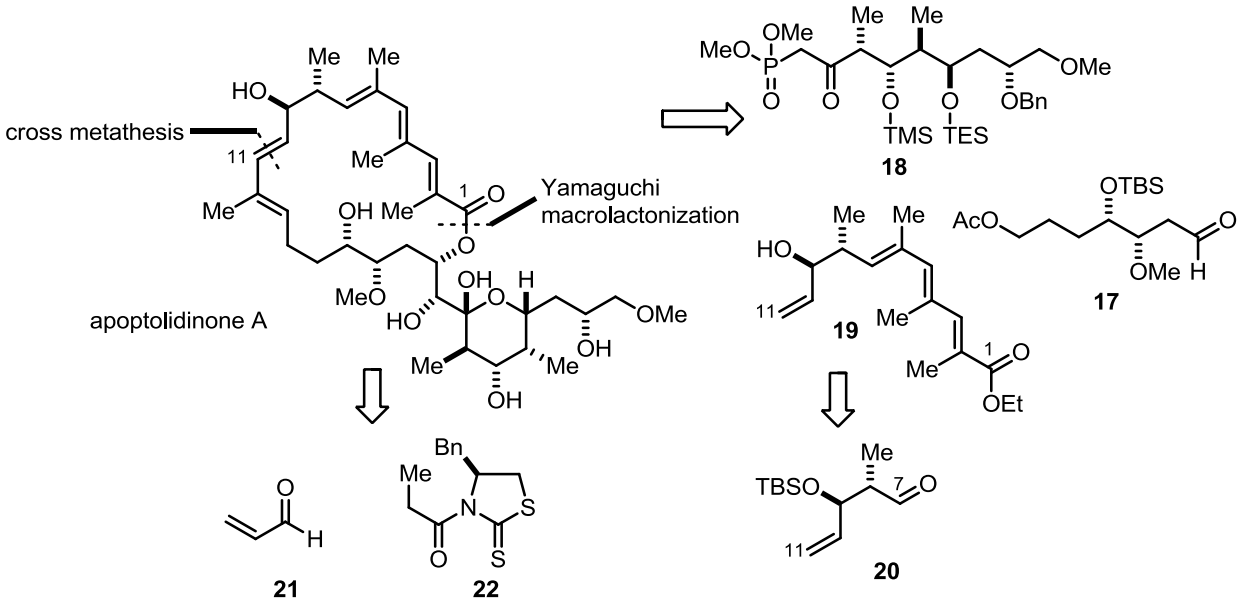



The $C_8$ and $C_9$ stereocenters were set from known β-hydroxylactone **15**, which was easily accessed from a commercially available β-hydroxylactone.[18] The triene moiety of the $C_1$-$C_{11}$ fragments was constructed from a sequence of contiguous Wittig olefinations after consecutive reductive ring opening and oxidation of lactone **15**. The $C_9$ appended sugar **11** was joined to the $C_3$-$C_{11}$ fragment **16** immediately prior to the final olefination.

Crimmins has taken a different approach with respect to the construction of the aglycone (Scheme 3).[19-21] A cross-metathesis reaction was employed to join the two major fragments of the macrocycle instead of opting for the previously discussed cross-coupling reactions.

Macrolactonization under the Yamaguchi conditions was again proven highly efficient. Formation of the $C_{12}$-$C_{28}$ coupling partner was accomplished through a Horner-Wadsworth-Emmons olefination between aldehyde **17** and phosphonate **18**.

**Scheme 3.** Crimmins' retrosynthetic analysis

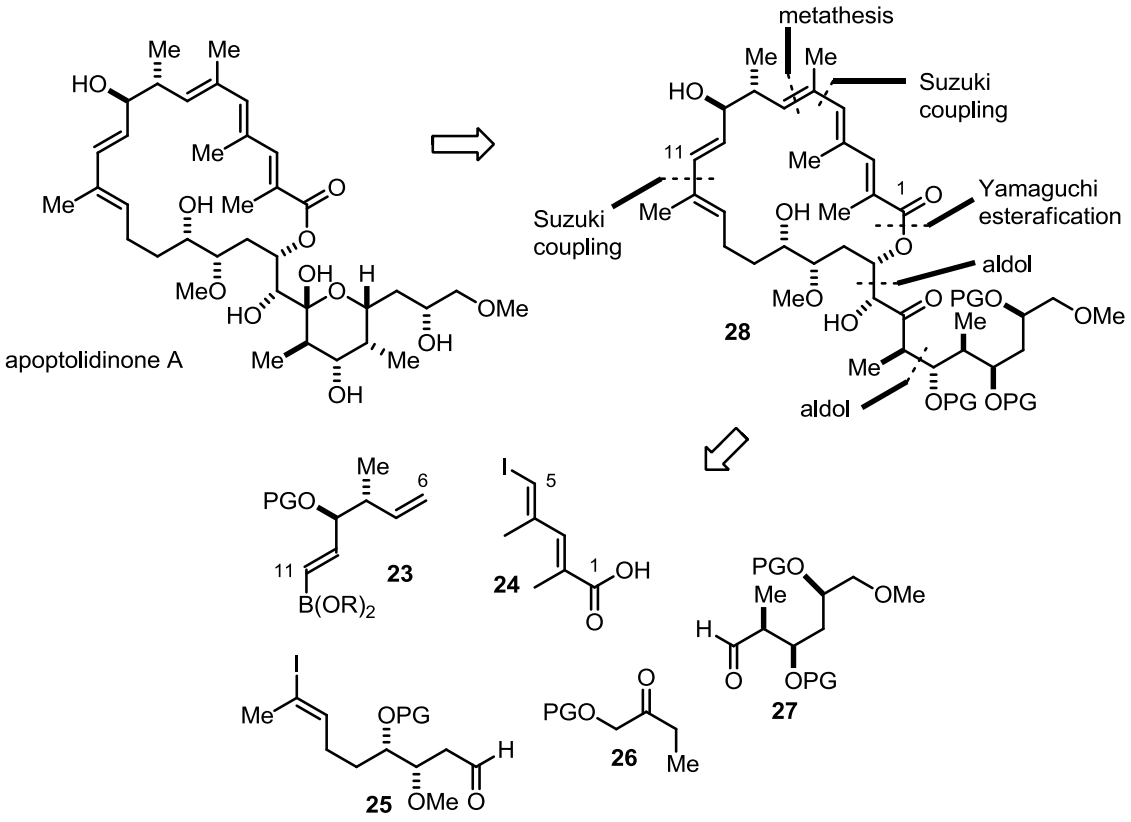



Similar to the synthesis of Koert, the triene fragment **19** was formed *via* three sequential Wittig olefinations from aldehyde **20**. Stereocenters $C_8$ and $C_9$ were installed from methodology developed in the Crimmins group.[22] These transformations involve the titanium mediated cross aldol reaction of aldehyde **21** and the chiral auxiliary appended thiazolidinethione enolate **22**.

Sulikowski has taken a highly convergent approach in the formation of the aglycone (Scheme 4).[23-28] The aglycone was formed from a series of reactions involving vinyl boronate **23**, diene **24** and the product of two consecutive aldol reactions between vinyl iodide **25**, ketone **26**, and aldehyde **27**. The product of these aldol reactions were then joined with vinyl boronate **23** in a Suzuki cross-coupling reaction. Subsequent appendage of diene **24** was accomplished

under Yamaguchi esterification conditions. Ring closure was successfully completed *via* intramolecular Suzuki coupling between the $C_5$ iodide and the $C_6$ boronate, produced from a cross metathesis, hydroboration sequence employed post esterafication.

**Scheme 4.** Sulikowski's retrosynthetic analysis



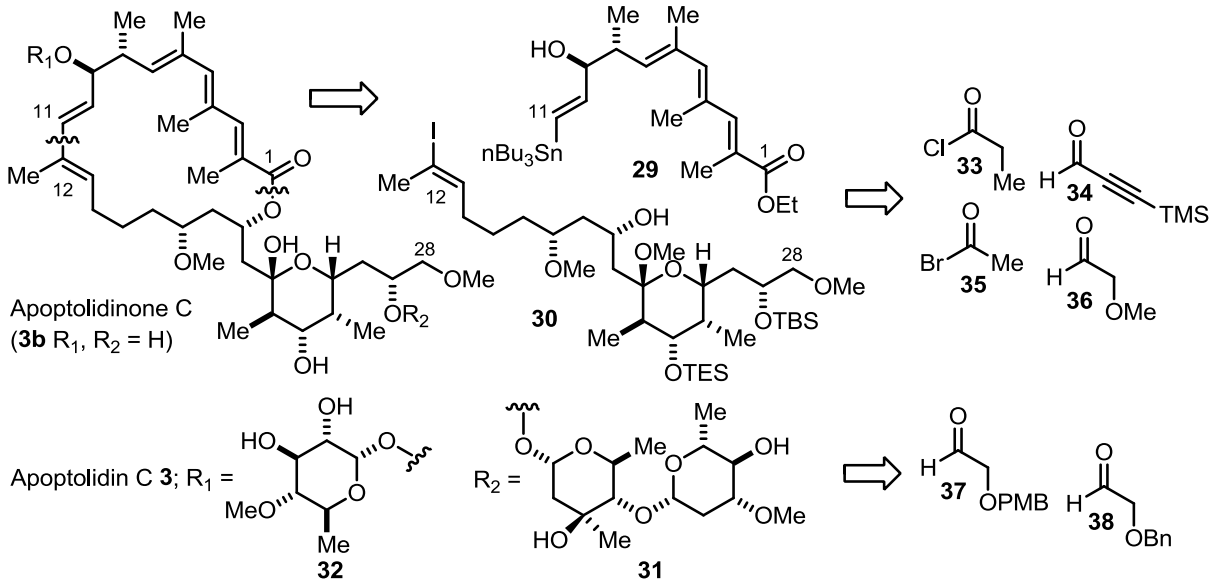

The $C_8$ and $C_9$ stereocenters were set by the implementation of Roush's crotylation protocol[29] utilizing diisopropyl tartrate derived crotylboronates. The crotylation was executed on a known pinacol ester to furnish coupling partner **23**.[30,31] The $C_1$-$C_5$ fragment **24** was produced through an oxidation, Wittig olefination sequence starting with a known alcohol.

In addition to these major syntheses, other investigations into the synthesis of smaller fragments have been reported.[32-39] Many elements of these partial syntheses mirror the aforementioned syntheses.

## 1.3 RETROSYNTHETIC ANALYSIS OF APOPTOLIDIN C

Our retrosynthetic analysis follows literature precedent for reliable major disconnections (Scheme 5). The $C_1$-$C_{11}$ fragment **29** will be joined with $C_{11}$-$C_{28}$ fragment **30** via Stille cross coupling followed by Yamaguchi's macrolactonization conditions to complete the macrocyclic core of apoptolidin C. For a synthesis of the natural product, disaccharide **31** will be coupled via glycosylation to the $C_{12}$-$C_{28}$ fragment **30** followed by Stille cross coupling to the $C_1$-$C_{11}$ fragment **29** and finally glycosylation of sugar subunit **32** prior to macrolactonization to complete the synthesis. The major halves of the macrocycle were constructed from simple achiral acyl halide and aldehyde building blocks **33-36** in acyl halide-aldehyde cyclocondensations (AACs) to set every stereocenter in apoptolidinone C in a catalytic, asymmetric fashion.[40-42] The disaccharide moiety was constructed from proline catalyzed asymmetric aldol dimerizations of simple, protected acetoxyacetaldehydes **37** and **38**.[43,44] This document will focus on the completion of the $C_1$-$C_{11}$ fragment, the macrocyclic core, and the disaccharide moiety.

**Scheme 5.** Our retrosynthetic analysis of apoptolidin C

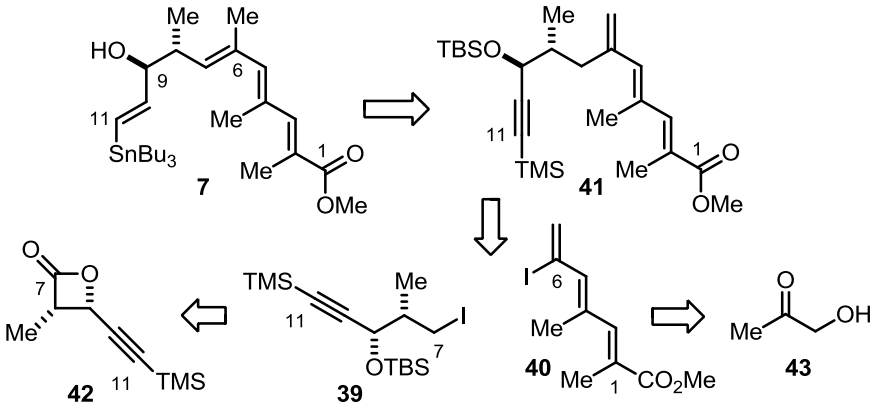


# 2.0 COMPLETION OF THE MACROCYCLE

## 2.1 $C_1$-$C_{11}$ EXPLORATORY SYNTHESES

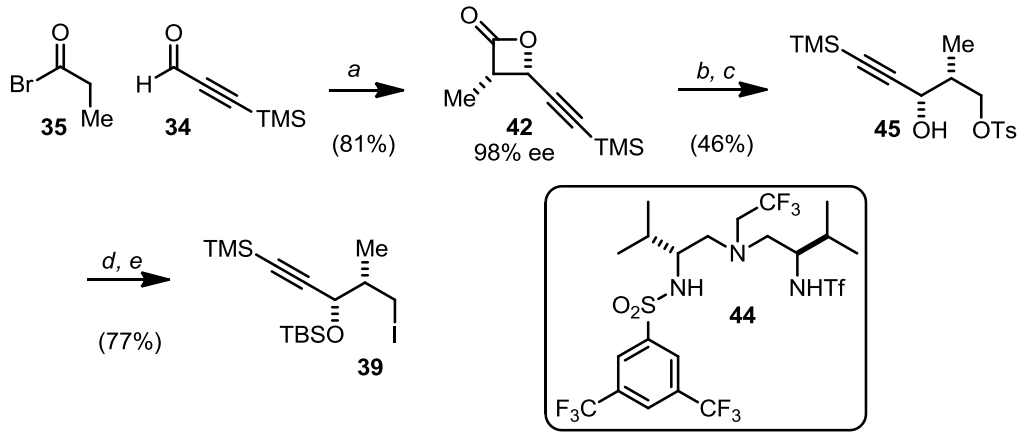
Toward the total synthesis of apoptolidin C, investigations have been completed in our laboratory regarding the construction of the $C_1$-$C_{11}$ fragment **7** of the macrocyclic core. Three major approaches have been attempted, all of which will be covered in this document. Investigations began with exploratory routes that were not incorporated into the final, preferred synthesis. Our primary goals were to set relevant stereocenters from achiral starting materials utilizing catalytic methodology and to generate an efficient, convergent final route. To accomplish this directive, it was decided to set the $C_8$ and $C_9$ stereocenters with acyl halide-aldehyde cyclocondensation (AAC) chemistry,[40-42] laying the foundation for the $C_7$-$C_{11}$ fragment **39** of the molecule. To maximize convergency, it was initially anticipated that the $C_1$-$C_6$ triene **40** would be constructed as one piece and then coupled to the $C_7$-$C_{11}$ fragment (Scheme 6). The final triene **7** would be produced after isomerization of Suzuki cross coupling product **41**. Cross coupling partners **39** and **40** would be constructed from the AAC substrate **42** and acteol (**43**), respectively.

**Scheme 6.** First generation retrosynthetic approach to apoptolidinone C




The first-generation synthesis of the $C_1$-$C_{11}$ fragment began with a triamine **44** catalyzed acyl halide-aldehyde cyclocondensation between propargylic aldehyde **34** and propionyl bromide (**35**) to generate β-lactone **42** in 81% yield, >95:5 dr (93% *ee*, assayed by comparison of $\alpha_D$) (Scheme 7).[45] Reductive ring opening with DIBAl-H followed by selective protection of the crude diol produced the tosylated product **45** in 46% yield over two steps. The modest yield in this sequence is attributed to over-tosylation of the diol, a consequence of the secondary alcohol being propargylic and relatively unhindered. Tosyl-protected product **45** was then converted to the fully protected iodide **39** by silyl ether formation followed by a Finkelstein reaction with NaI to generate the coupling fragment **39** in 77% yield over two steps.

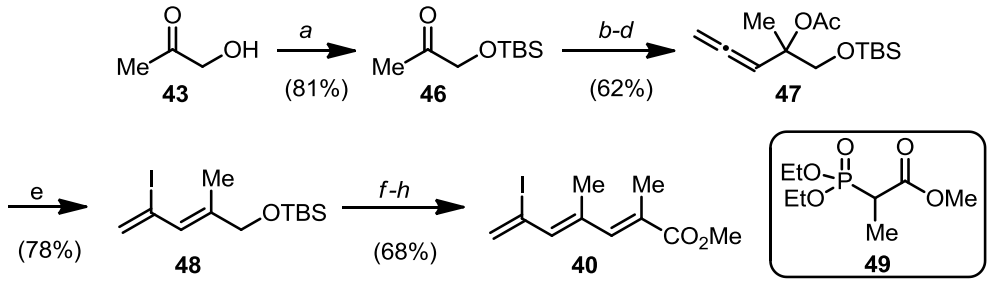
**Scheme 7.** $C_7$-$C_{11}$ fragment synthesis




a) 10 mol% **44**, $AlMe_3$ *i*$Pr_2Net$, $CH_2Cl_2$, –78 ºC. b) *i*$Bu_2AlH$, THF, –78 ºC. c) TsCl, pyr, DMAP, $CH_2Cl_2$. d) TBSCl, imid, DMF. e) NaI, acetone

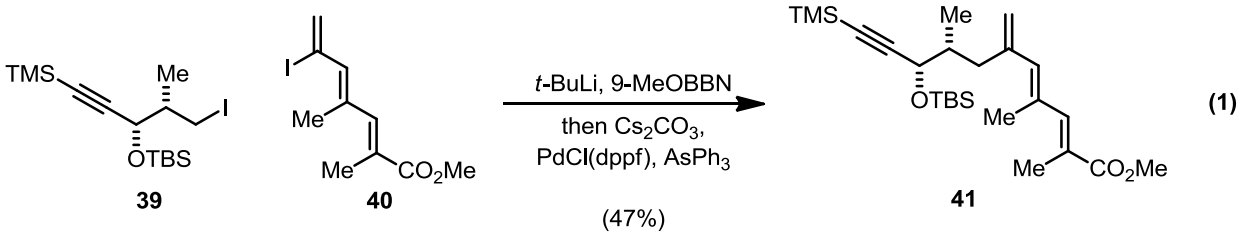
Having completed a synthesis of fragment **39**, silyl protection of acetol (**43**) initiated construction of triene precursor **40**, affording protected product **46** in 81% yield (Scheme 8). Ketone **46** was then converted to allene **47** via addition of ethynylmagnesium bromide, homologation of the alkyne to the allenol with paraformaldehyde, CuBr, and *i*PrNH, and finally acyl protection of the alcohol to produce allene **47** in 62% yield over three steps. An interesting Pd(II)-catalyzed rearrangement[46] of allene **47** produced diene **48** in 78% (9:1 *E*:*Z*) after LiI addition to the π-allyl complex formed from acyl displacement via catalytic $Pd(OAc)_2$. Diene **48** was then homologated to triene **40** after silyl deprotection, Swern oxidation, and HWE olefination with phosphine oxide **49** in 68% (~9:1 *E*:*Z*) over three steps. It is important to note that the polyenes in this final sequence are extremely thermo- and acid-sensitive and must be handled with care. The conjugated aldehyde, for example, decomposed within an hour if left at room temperature and the final triene **40** was prone to olefin isomerization in $CDCl_3$ or upon exposure to light.

**Scheme 8.** $C_1$-$C_6$ fragment synthesis




a) TBSCl, imid, $CH_2Cl_2$. b) ethynylmagnesium bromide, $Et_2O$/THF, –78 ºC. c) $(CH_2O)_n$, CuBr, *i*PrNH, dioxane, Δ. d) $Ac_2O$, pyr, DMAP. e) LiI, Pd(OAc), AcOH, 40 ºC. f) HF•pyr, pyr/THF. g) oxalyl chloride, DMSO, $NEt_3$, –78 ºC to RT. h) **49**, LDA, THF, –78 ºC.

Some optimization was required in formulating conditions for the $sp^2$-$sp^3$ cross coupling reaction (Equation 1). Alkyl iodide **39** was treated with *t*-BuLi and 9-MeOBBN to form the borane coupling partner in situ. This substrate was then subjected to vinyl iodide **40** utilizing $PdCl_2$(dppf) as a precatalyst, $AsPh_3$ for its ligand, and $Cs_2CO_3$ as a base to generate coupling product **41** in 47% yield.[47] While the yield is modest, $sp^3$ coupling reactions are considered difficult because of β-hydride elimination, requiring more active Pd species with large bite angles and electron rich ligands such as $AsPh_3$ to improve reaction rates to make reductive elimination more facile than the competing β-hydride elimination.

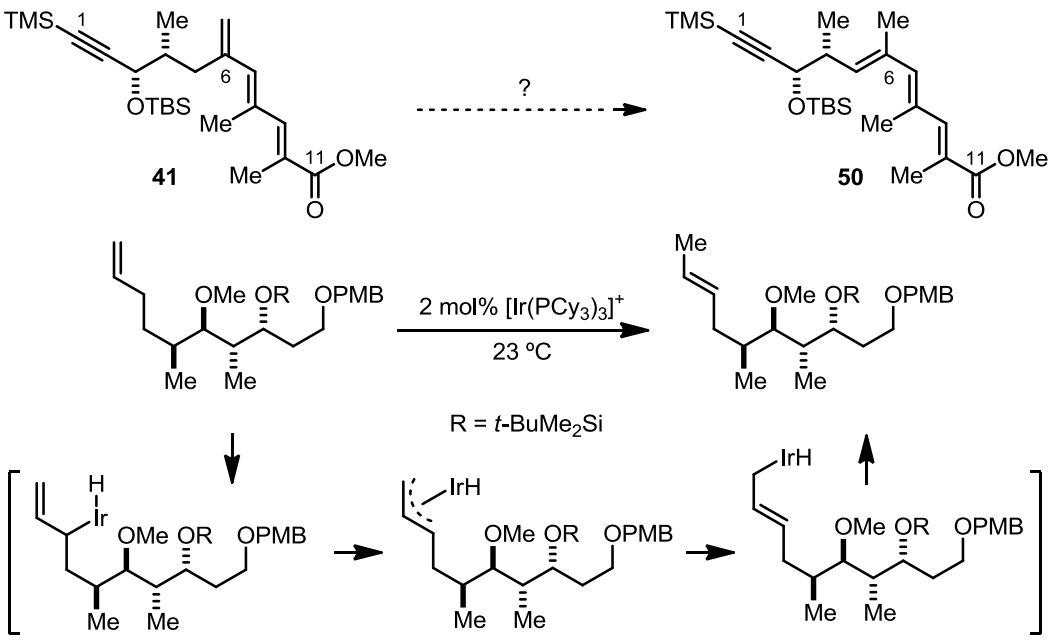



(1)

Having obtained triene **41**, efforts were directed toward performing the requisite isomerization to generate the structural core of the $C_1$-$C_{11}$ fragment (Scheme 9). Our initial efforts focused on cationic iridium-catalyzed isomerization, based on precedent set in similar

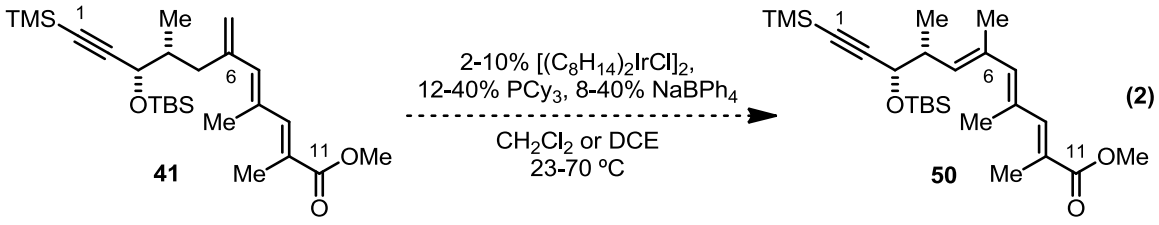
systems.[48] This reaction is known to proceed via Ir(I) insertion into the allylic C-H bond, rearrangement via an $\eta^3$ complex placing Ir-H at the desired carbon, and finally reductive elimination to generate the product. Literature examples do not directly match our system, the least reactive substrates being monosubstituted olefins and 1,1-disubstituted vinyl ethers. It was decided, however, that the mechanism involved should apply to 1,1-disubstituted alkyl systems as well, promoting formation of the more thermodynamically favored trisubstituted alkene **50**.

**Scheme 9.** Desired isomerization and its precedent




Unfortunately, attempts to incorporate this chemistry into the synthesis of apoptolidin C were ultimately unsuccessful (Equation 2). Utilizing a catalyst loading of 2 mol % $[(Cy_3P)_3Ir]^+$ with three equivalents of $PCy_3$ ligand per Ir(I) resulted in no reaction at ambient temperature. In subsequent isomerization attempts, a higher catalyst loading was used (3.6 and 10 mol%) as well as an increase in temperature (40 and 70 °C) using dichloroethane as a solvent. These

modifications resulted in the lack of reactivity seen previously with some decomposition occurring at extended reaction times and higher temperatures. Attempts to use only two equivalents of $PCy_3$ ligand per $Ir^+$ for a more reactive cationic catalyst gave no reaction at low temperatures and decomposition in refluxing dicholoroethane.

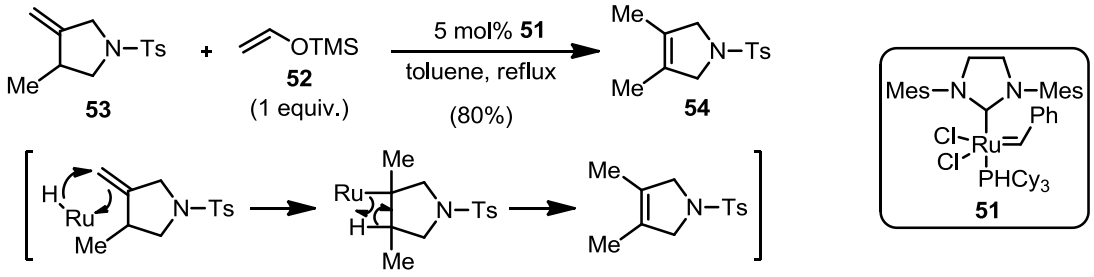



The observed lack of reactivity seen in this system could be attributed to steric hindrance at the vinylogous methylene ($C_7$). As mentioned previously, these cationic metal isomerizations are dependent on initial C-H insertion at $C_7$. The vinylogous carbon in this system is relatively hindered from the α-methyl, β-silyl ether, and triene moieties, especially considering the methyl group from the triene is probably pointing directly at the $-CH_2-$ ($C_7$) in order to maintain orbital alignment and, thus, resonance. Considering the relative bulk of the ligands used in this chemistry ($PCy_3$), it is feasible to conclude that this methylene is too sterically encumbered to allow for the required C-H insertion to occur.

Having attempted a number of reaction conditions within the $Ir^+$ system, alternate reaction pathways were considered involving a variety of metals and reagents. Multiple conditions attempted involved a RuH or RhH catalyst. Incorporation of both premade and in situ generated catalysts were was attempted (Scheme 10). These systems were thought to succeed where Ir(I) had proven insufficient, considering the mechanism involves insertion across the alkene itself followed by β-hydride elimination to regenerate the catalyst. The π-bond involved

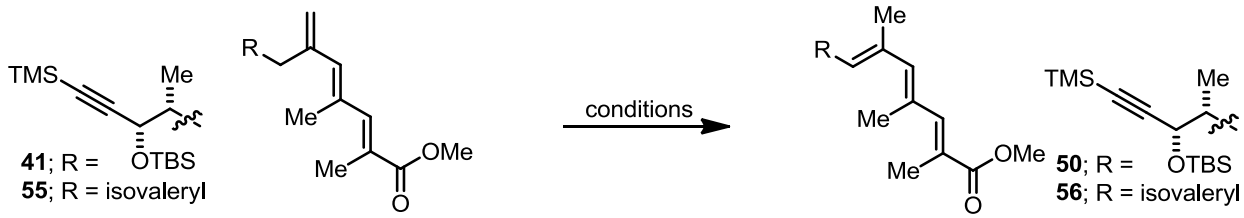
in the first step of this reaction sequence was thought to be less sterically hindered than the methylene. The RuH catalyst generated from Grubbs II (**51**) and vinyl TMS ether **52** is known to isomerize 1,1-disubstituted olefin **53** to fully substituted olefin **54**.[49]

**Scheme 10.** Literature example of olefin isomerization




A number of conditions were attempted, some of which on a test substrate where R = isovaleryl to convert test substrate **55** to isomerized product **56**. All conditions attempted resulted in recovery of starting material or decomposition to unisolable materials under harsher reaction conditions (Table 2). Subjecting the triene to RuH generated in situ (vinyloxytrimethylsilane, Grubbs II) led to recovery of starting material at lower temperatures and decomposition at higher temperatures. Considering that a more aggressive catalyst may be useful, the triene was reacted with RhH formed from refluxing $RhCl_3$ in EtOH[50] to less successful results, rapidly decomposing the starting material. Preformed RhH[51] and RuH hydride catalysts ($RhH(CO)(PPh_3)_3$) were not effective and led to recovery of starting material; similar results were obtained from attempts at base catalyzed isomerization (NaHMDS).

**Table 2.** Attempted isomerization conditions




| Entry | Conditions | Result |
|---|---|---|
| 1 | 10 equiv. vinyloxytrimethylsilane, 5 mol % Grubbs II, $CH_2Cl_2$, DCE, or toluene 40, 83, or 110 °C | SM, decomposition at higher temperature |
| 2 | $RhCl_3$, reflux in EtOH | Decomposition |
| 3 | $RhH(CO)(PPh_3)_3$, toluene, 70 or 110 °C | Majority SM after 2.5 hrs |
| 4 | NaHMDS, THF, –78 °C | No reaction |

The lack of reactivity seen in all these metal isomerizations could be attributed to the large steric bulk presented by these catalysts (Figure 2). Inability to access the vinyl C-H bond for C-H insertion explains the observed lack of reactivity in the case of the iridium catalyzed isomerizations. While the alkene is not as sterically hindered as the vinylogous methylene, the $C_6$ olefin in this triene system is fairly sterically hindered, contributing to lack of M-H insertion into the π-bond. Deactivation of the alkene via resonance with the triene/ether system should also be taken into account as a less electron-rich olefin would be less susceptible to react with the electron-deficient RuH and RhH species. The results of these studies have shown that bulky, metal based isomerization catalysts are even more susceptible to deactivation via steric hindrance and electronic deactivation than initially anticipated.

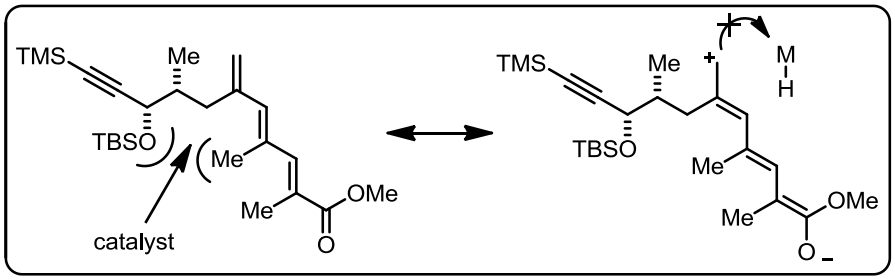



**Figure 2.** 1,1-Disubstituted olefin stability towards isomerization

Unwilling to completely abandon this synthetic route, efforts were focused on implementing a slightly altered key intermediate that would allow for adjustment in the key isomerization step while retaining a considerable amount of the synthesis. Investigations into diazene rearrangement of allylic diazenes (Figure 3) suggested that this type of reaction could be integrated into the synthesis of apoptolidinone C.[52]

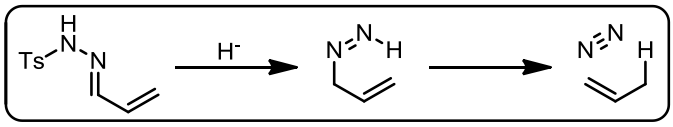
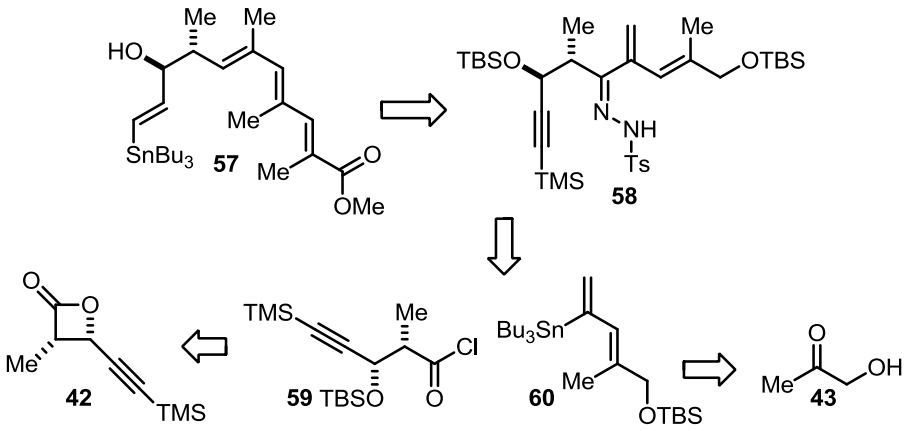



**Figure 3.** *N*-Tosyl hydrazine diazine rearrangement

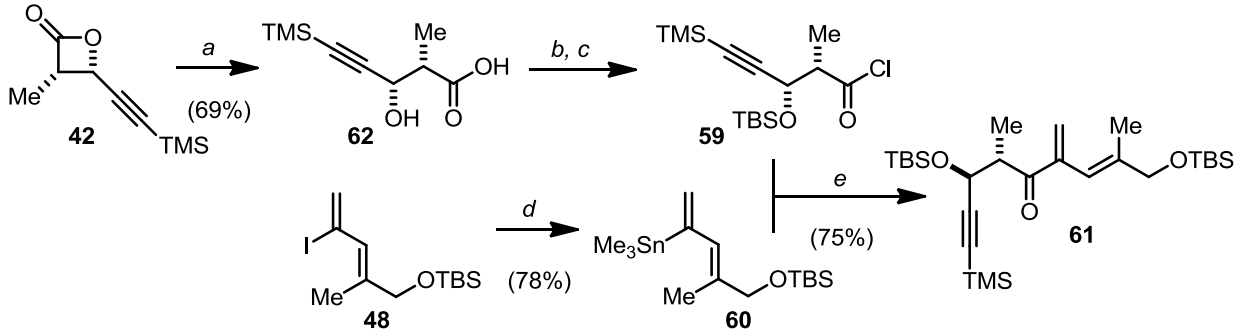
This diazene rearrangement to final triene **57** would require access to vinylogous *N*-tosyl hydrazone intermediate **58**, necessitating adjustments to the synthetic scheme (Scheme 11). Hydrazone intermediate **58** would be constructed from the ketone product of Stille cross coupling between acid chloride **59** and vinyl stannane **60**. The coupling partners will be accessed from β-lactone **42** and acetol (**43**), starting materials used in the previous approach.

**Scheme 11.** $C_1$-$C_{11}$ second aproach retrosynthesis




Construction of ketone **61** began with ring opening of β-lactone **42** with lithium peroxide and subsequent reduction to the carboxylic acid **62** in 69% yield (Scheme 12). Direct ring opening with various hydroxides resulted in TMS deprotection while the peroxide nucleophile was soft enough to promote ring opening while leaving the silane intact. Protecting the secondary alcohol as the TBS ether followed by acid chloride formation with oxalyl chloride gave coupling partner **59** that was used crude in the coupling sequence. Generating the stannane coupling partner **60** was accomplished by metal-halide exchange, treating vinyl iodide **48** with $Sn_2Me_6$ and catalytic $Pd(PPh_3)_4$ (78%). Coupling of stannane **60** and acid chloride **59** with $Pd_2(dba)_3$ as the palladium source proceeded in good yield (75% over 3 steps) to produce ketone intermate **61**.

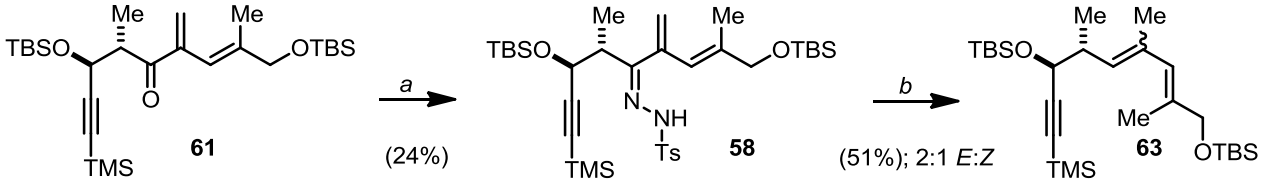
**Scheme 12.** $C_1$-$C_{11}$ second approach forward synthesis




a) LiOH, $H_2O_2$, then $Na_2SO_3$, THF/$H_2O$, 0 ºC to RT. b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, –78 ºC. c) oxalyl chloride, benzene. d) $Sn_2Me_6$, $Pd(PPh_3)_4$, DIPEA, benzene, 80 ºC to RT. e) $Pd_2(dba)_3$, DIPEA, Benzene.

Ketone **61** was then subjected to hydrazone formation conditions with little initial success towards formation of rearrangement precursor **58**. Preliminary attempts to aminate the ketone (EtOH, Δ; AcOH; EtOH, HCl) resulted in either no reaction or decomposition (Scheme 13). The terminal unsaturated enone was found to be considerably unstable. Somewhat counter-intuitively, harsher conditions for a shorter period of time were found to be most effective. TFA catalysis was found to generate hydrazone **58** at an acceptable level of efficiency (23%) to then test the key rearrangement. Subjecting hydrazone **58** to catecholborane and then NaOAc buffer and heat[52] lead to formation of the rearrangement product **63** in moderate yield and *E*:*Z* selectivity (51%; 2:1 *E*:*Z*).

**Scheme 13.** Hydrazone formation and rearrangement




a) $H_2NNHTs$, TFA, $CH_2Cl_2$. b) catecholborane, $SiO_2$, $CHCl_3$, then $NaOAc•3H_2O$, Δ; 2:1 (*E*:*Z*).

The result of moderate *E*:*Z* selectivity was unexpected considering an analysis of the transition state (Figure 4). After reduction of the hydrazone to the diazene, the retroene reaction may occur from one of two transition states, one in which the two large alkyl groups (R, $R_L$) are eclipsing one another and one in which they are anti. Reaction from the enthalpically lower transition state would be expected, producing the desired olefin geometry as the major product. Unfortunately, experimental evidence disproves this analysis, likely due to the high degree of planarity in these large R groups with $sp^2$ and *sp* centers alpha and beta to the reactive sites. The discovery that this rearrangement generated less than optimal results coupled with the low yields from working with sensitive intermediates leading up to the rearrangement, it was decided that another approach to this fragment may be appropriate.

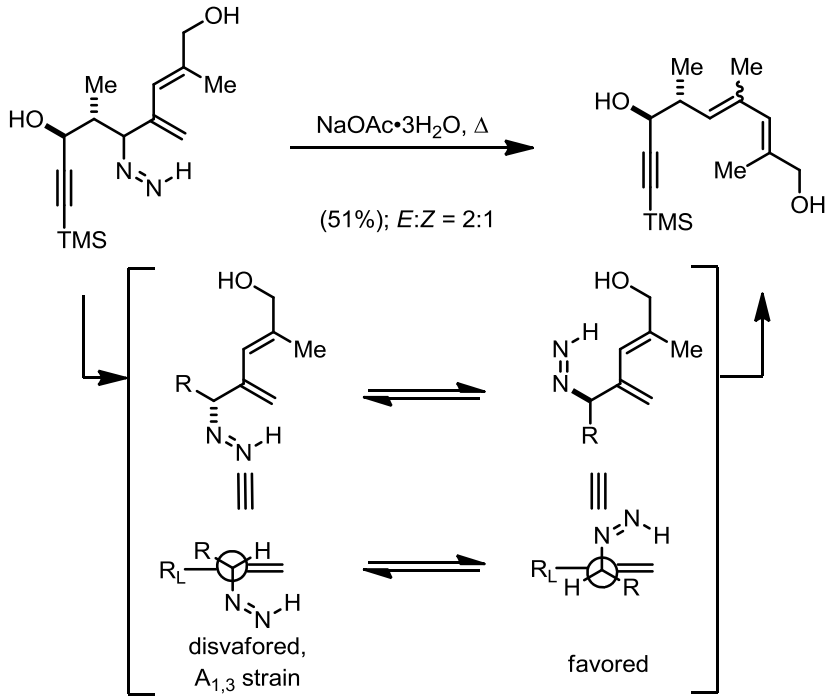
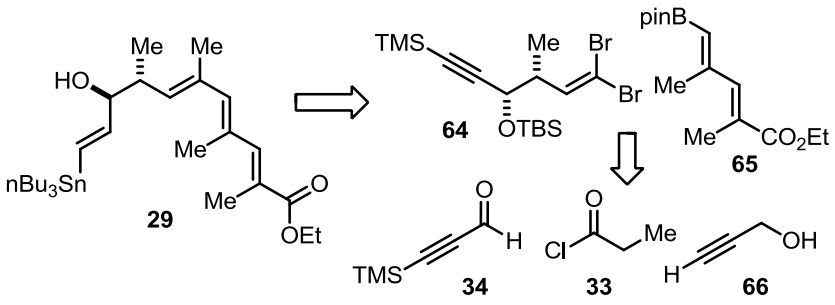



**Figure 4.** Analysis of retroene transition state

## 2.2 $C_1$-$C_{11}$ FINALIZED ROUTE

Having attempted to implement isomerization of a $C_6$ terminal olefin to the desired isomer in two different routes, our thoughts shifted to the possibility of incorporating a synthesis of the $C_1$-$C_{11}$ fragment **29** in which the $C_6$ olefin was already in the correct position prior to coupling (Scheme 14). A convergent retrosynthetic analysis was devised in which dibromide **64** and vinyl borane **65** would be joined via regioselective Suzuki cross coupling, placing the $C_6$ olefin in the correct orientation. Dibromide coupling partner **64** would be constructed from a Corey-Fuchs reaction after setting the requisite stereocenters utilizing an AAC reaction involving aldehyde **34** and propionyl chloride (**33**). The vinyl borane coupling partner **65** would be generated from propargyl alcohol (**66**) after carboalumination and an oxidation, Wittig reaction sequence.

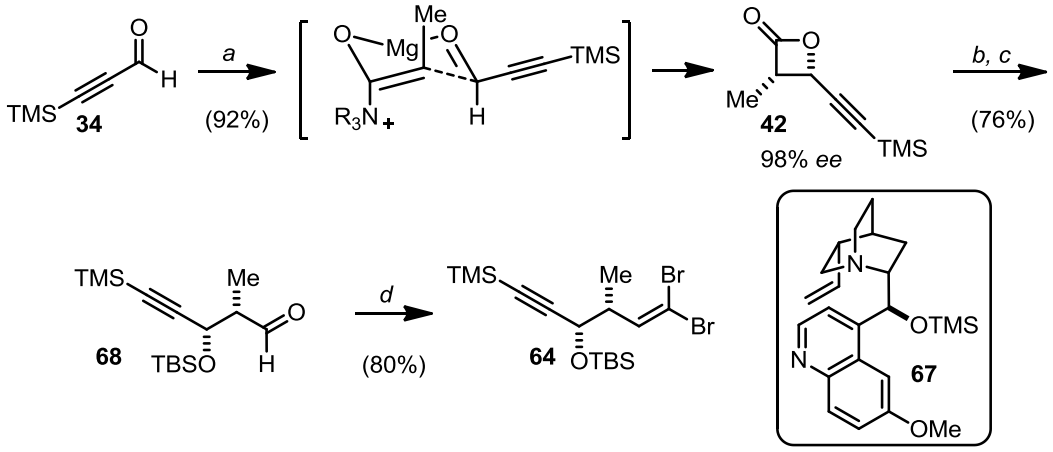
**Scheme 14.** Final $C_1$-$C_{11}$ retrosynthetic analysis.




Synthesis of dibromide fragment **64** commenced with a cinchona alkaloid catalyzed AAC reaction between aldehyde **34** and propionyl chloride (**33**) (Scheme 15). Upon reaction of these cycloaddition partners with cinchona alkaloid catalyst **67**, $MgCl_2$ and $i$Pr$_2$NEt, β-lactone **42** was obtained in 92% yield (98% *ee*). In previous routes, this reaction was completed with the triamine Lewis acidic catalyst. Propargylic aldehydes are often not compatible with the cinchona

alkaloid procedure due to their rapid reactivity and lack of steric bias in the transition state, promoting poor diastereoselectivity. It was assumed that the use of the less reactive $MgCl_2$ as a Lewis acidic additive rather than the more traditional LiI used in these reactions would allow for shorter coordinative bond lengths in the transition state and a slower rate of reaction allowing for the use of propargylic aldehydes. The β-lactone **42** ring was then opened and the resulting alcohol protected in an efficient one-pot procedure. KHMDS catalyzed the nucleophilic attack of ethane thiol that was followed by in situ silyl trapping of the free alcohol (TBSOTf, 2,6-lutidine) to give the crude thioester. The thioester was then reduced to aldehyde **68** (76%, 2 steps) with *i*$Bu_2AlH$ and subjected to the ylide formed from $CBr_4$ and $PPh_3$, converting the aldehyde to dibromide **64** in 80% yield.

**Scheme 15.** $C_1$-$C_6$ Fragment synthesis

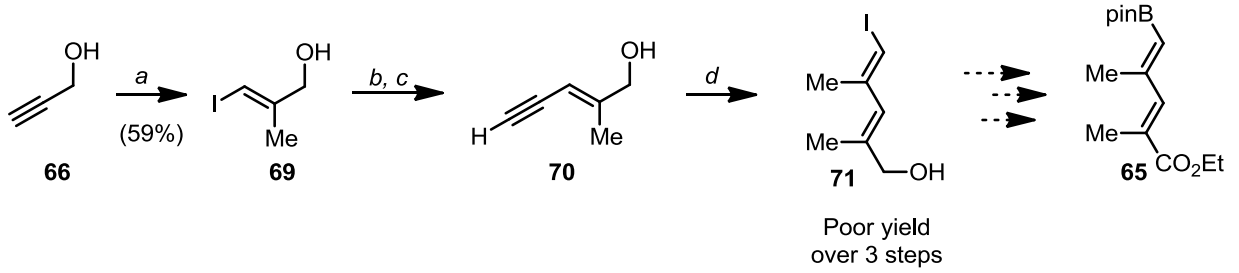



a) 10 mol% **67**, EtCOCl, $MgCl_2$, *i*$Pr_2NEt$, –78 °C. b) 10 mol% KHMDS, EtSH, THF then TBSOTf, 2,6-lutidine. c) *i*$Bu_2AlH$, THF, –78 °C. d) $CBr_4$, $PPh_3$, $CH_2Cl_2$. KHMDS = potassium hexamethyldisilazide.

Integration of dibromide **64** into the $C_1$-$C_{11}$ portion of the molecule required a synthesis of Suzuki coupling partner vinyl borane **65** beginning with commercially available propargyl alcohol (**66**) (Scheme 16). The alkyne was halogenated in a modification of a known

carboalumination procedure[53] ($Cp_2ZrCl_2$, $AlMe_3$, $H_2O$ then $I_2$) to afford vinyl iodide **69** (59%). The water additive in this reaction was not used in literature procedures and the 20% increase in yield is attributed to increased basicity of the aluminum methoxide. A more basic aluminum species allowed the propargyl alcohol to be fully deprotonated prior to formation of a proton-sensitive carboaluminum intermediate. Vinyl iodide **69** was then converted to alkynol **70** via $Pd[(PPh)_3]_4$-catalyzed cross coupling with 1-(trimethylsilyl)-alkyne followed by TBAF deprotection to liberate alkyne **70**. Attempts to incorporate another carboalumination into the synthesis to generate diene **71** at this point led to mediocre results and poor yields. The unsatisfactory results were attributed to formation of sensitive intermediates related to the reactive alkyne being in conjugation with an olefin.

**Scheme 16.** Attempted borane construction

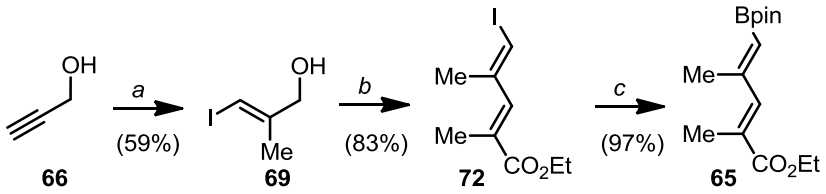



a) $Cp_2ZrCl_2$, $AlMe_3$, $H_2O$, $C_2H_4Cl_2$, then THF, $I_2$. b) 1-(Trimethylsilyl)-alkyne, $i$Pr$_2$NH, CuI, $Pd(PPh_3)_4$. c) TBAF, THF, 0 °C to RT. d) $Cp_2ZrCl_2$, $AlMe_3$, $H_2O$, $C_2H_4Cl_2$.

To avoid the second, low yielding carboalumination, the route to vinyl borane **65** was slightly modified to generate diene **72** directly from carboaluminated propargyl alcohol (**66**) (Scheme 17). A one-pot oxidation, Wittig reaction was carried out on the carboalumination product **69** with $MnO_2$ as the oxidant and the appropriate triphenylphosphine ylide to give homologated diene **72** in 83% yield.[54] Performing these reactions sequentially resulted in a slightly improved yield over two steps (89%) but the convenience of the one pot procedure

secured its position as the reaction of choice for material throughput. To complete the Suzuki coupling partner, vinyl borane **65** was obtained via metal-halogen exchange of the iodide (bis(pinacolato)diboron, [Pd(dppf)$Cl_2$], KOAc; 97%).[55]

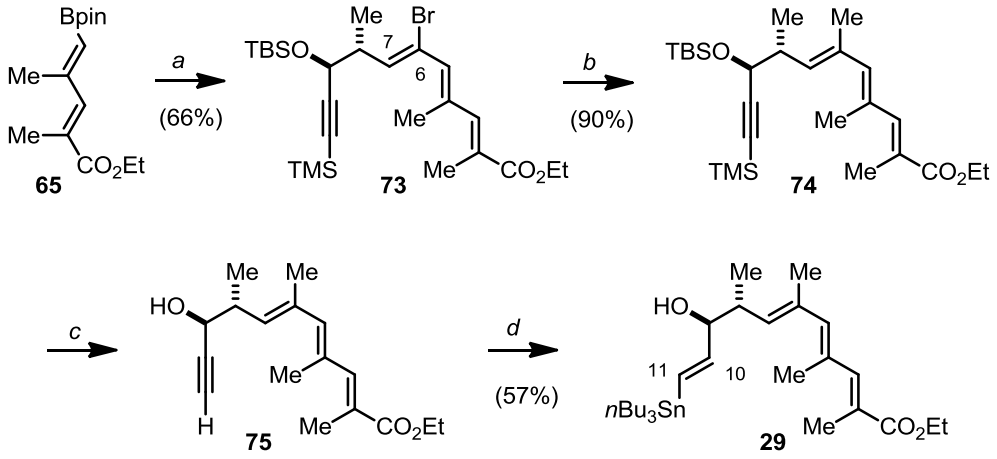
**Scheme 17.** Completion of the $C_1$-$C_{11}$ fragment




a) $Cp_2ZrCl_2$, $AlMe_3$, $H_2O$, $C_2H_4Cl_2$, then THF, $I_2$. b) $MnO_2$, $PPh_3C(CH_3)CO_2Et$, $CH_2Cl_2$. c) $(pinB)_2$, 3 mol% [Pd(dppf)$Cl_2$], KOAc, DMSO, 85°C. Dppf = 1,1`-bis(diphenylphosphino)ferrocenyl, pin = pinacol ($C_6H_4O_2$).

Regioselective coupling of borane **65** and dibromide **64** proceeded smoothly by reaction at the less sterically hindered bromine to generate the "all-*E*" triene fragment **73** in 66% yield (Scheme 18). This coupling reaction was optimized when using TlOEt and catalytic [Pd($PPh_3$)$_4$];[56] the use of bases lacking Thallium's halide affinity lead to slow reaction times, incomplete conversion and poor regioselectivity. Methylation at $C_6$ required some optimization; attempts to append the methyl group via Suzuki coupling with various methyl boranes such as trimethylboroxine and 9-MeBBN produced decomposition or no reaction. Implementing a fairly exotic palladium catalyst with a large bite angle, [Pd(P*t*$Bu_3$)$_2$], in a Negishi coupling with $ZnMe_2$ resulted in 90% yield of triene **74** product (6.6:1 *E*:*Z*).[57] The modest *E*:*Z* selectivity is attributed to residual [Pd($PPh_3$)$_4$] from the previous step; [Pd($PPh_3$)$_4$] is known to give the *Z* olefin under these conditions.[58] Triene **74** was then functionalized appropriately for Stille coupling by silyl removal (TBAF) to furnish alcohol **75** and hydrostannation[59] (*n*$Bu_3SnH$, 3 mol% [$PdCl_2(PPh_3)_2$]) of the terminal alkyne (57%, 2 steps) to complete the $C_1$-$C_{11}$ fragment **29** of the aglycone.

**Scheme 18.** Completion of the $C_1$-$C_{11}$ fragment

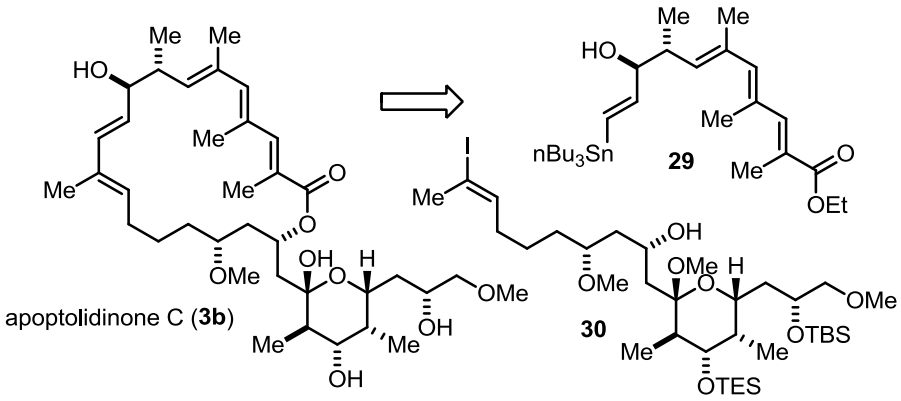



a) **64**, 10 mol% $[Pd(PPh_3)_4]$, TlOEt, aq THF. b) $ZnMe_2$, 7 mol% $[Pd(PtBu_3)_2]$, THF; $C_6$-$C_7$ *E*:*Z* = 6.6:1. c) $nBu_4NF$, THF. d) $nBu_3SnH$, 3 mol% $[PdCl_2(PPh_3)_2]$, THF; $C_{10}$-$C_{11}$ *E*:*Z* = 3.4:1.

## 2.3 MACROCYCLE SYNTHESIS

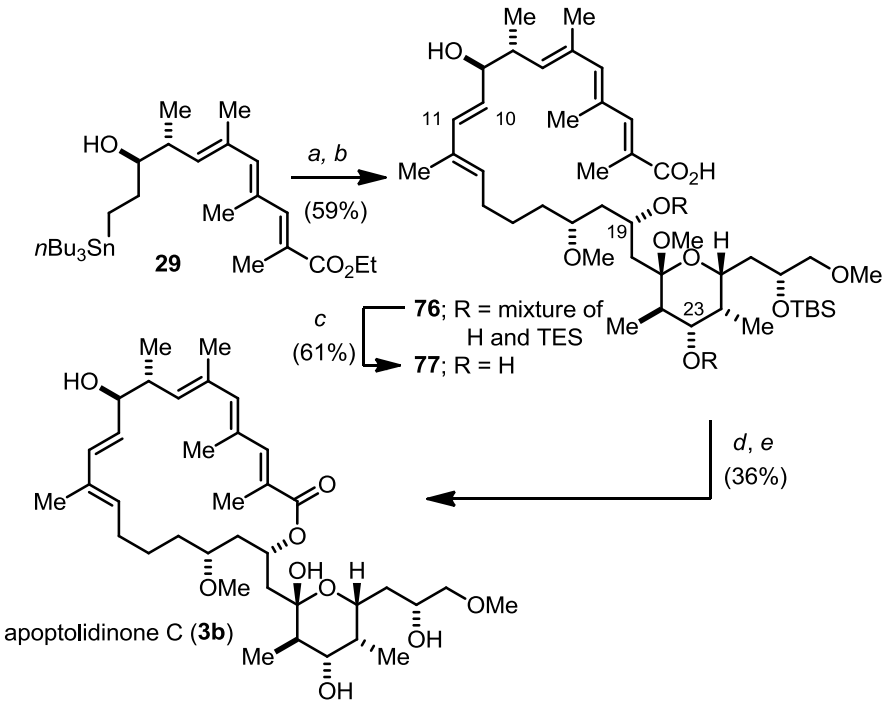
Following completion of the $C_1$-$C_{11}$ fragment **29**, our attention was turned to completion of the macrocyclic core of apoptolidin C (Scheme 19). The two major fragments would be joined in a Stille cross coupling reaction to construct the $C_{11}$-$C_{12}$ bond, generating an intermediate that could be saponified to the seco-acid. The seco-acid would then be closed to the macrocycle via lactonizating followed by global deprotection to give the final product.

**Scheme 19.** Retrosynthesis of apoptolidinone C



We initially anticipated implementing cross coupling conditions from previous syntheses of apoptolidin A to complete the aglycone synthesis (Scheme 20).[10-13] Our particular system, however, required further optimization than was present in the literature. After extensive experimentation, treating the coupling partners **29** and **30** with $[PdCl_2(MeCN)_2]$ and phosphine salt $Ph_2PO_2N(nBu)_4$[60] was found to consistently produce the coupling product in 75% yield with 12:1 (*E*:*Z*) enantiopurity across the $C_{10}$-$C_{11}$ bond. Without the phosphine additive, complex mixtures (~1:1; *E*:*Z*) of olefin isomers were obtained; other palladium sources produced similar results.[61] $Ph_2PO_2N(n\text{-}Bu)_4$ is thought to maintain olefin geometry by scavenging tin halide byproducts that could otherwise isomerize weak π-bonds via a metathesis pathway.

**Scheme 20.** Synthesis of apoptolidinone C




a) 0.25 equiv **30,** 10 mol% $PdCl_2(MeCN)_2$, 5 equiv $Ph_2PO_2N(n\text{-}Bu)_4$, DMF; $C_{10}$-$C_{11}$ *E*:*Z* = 12:1. b) LiOH, THF:MeOH:$H_2O$ (6:2:1). c) 1 equiv TFA, $CH_2Cl_2$:MeOH, –15 °C. d) $NEt_3$, DMAP, 2,4,6-trichlorobenzoyl chloride, THF:Toluene. e) $H_2SiF_6$ (aq), MeCN, –35 °C. TFA = Trifluoroacetic acid, DMAP = 4-Dimethylaminopyridine.

Saponification of the ethyl ester under basic conditions (LiOH) lead to conversion of the ester moiety to the carboxylic acid along with non-selective partial TES removal at the $C_{19}$ and $C_{23}$ alcohols to afford a complex mixture of products **76** (~78% of the mixture). The mixture of partially deprotected compounds **76** was treated with TFA in MeOH to selectively remove the remaining TES groups while leaving the TBS ether intact to generate seco-acid **77** (61%). It was anticipated that macrolaconization would occur preferentially at the desired proximal ($C_{19}$) alcohol rather than at the more remote position ($C_{23}$). Yamaguchi's conditions[62] generated the protected aglycone, with the majority of lactonization occurring on the $C_{19}$ alcohol (~10:1). The rigidity of the highly unsaturated $C_1$-$C_{13}$ framework was thought to play a major role in this regioselectivity.[63] Deprotection of the anomeric methoxy and TBS ether was not trivial. Various conditions including HF•pyridine, TBAF followed by aqueous acid, and TASF either failed to remove the protecting groups or lead to decomposition. Concomitant silyl deprotection/anomeric hydrolysis was ultimately achieved using aqueous $H_2SiF_6$ in acetonitrile at –35 °C, completing the synthesis of apoptolidinone C (**3b**) (36%, 2 steps).[14-17] The lower yield in this step is attributed to some decomposition at necessarily elevated reaction temperature; lower temperatures lead to incomplete conversion while higher temperatures lead to decomposition.

This synthesis of apoptolidinone C displays the efficacy of the acyl halide-aldehyde cyclocondensation (AAC) as well as a highly efficient, convergent route to the $C_1$-$C_{11}$ triene portion of the molecule. The derivation of 10 of 10 stereocenters catalytically, 8 directly 2 indirectly, illustrates the reality that asymmetric synthesis of complex targets does not necessitate stoichiometric and/or auxiliary based methodology. To expand upon our success in catalytic,

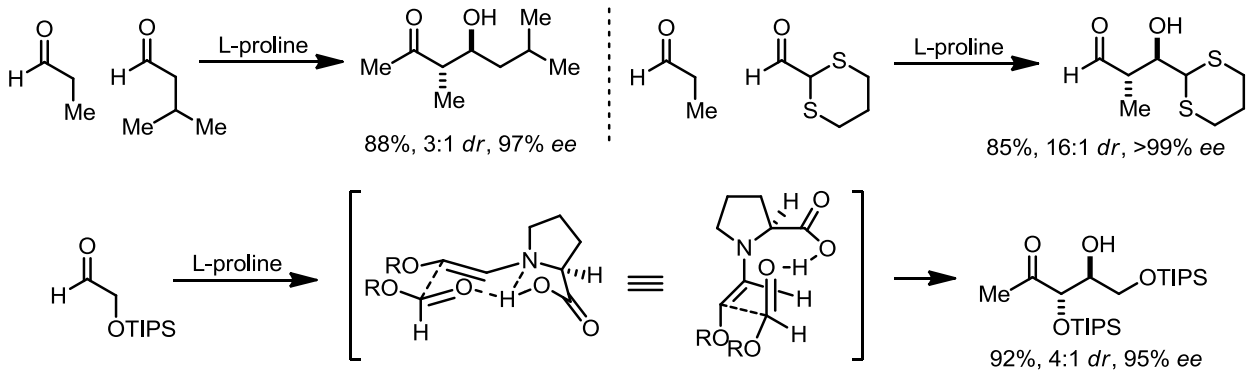
asymmetric synthesis, a route to the disaccharide portion of the natural product has been developed, heavily utilizing organocatalysis.

# 3.0 COMPLETION OF THE DISACCHARIDE

## 3.1 DISACCHARIDE EXPLORATORY ROUTES

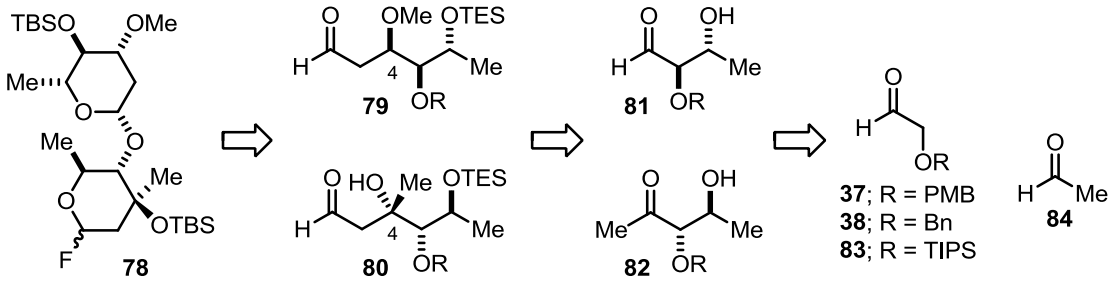
Upon completing the aglycone, our efforts were focused on devising a synthetic route for the disaccharide moiety of the molecule, to be integrated into the total synthesis of apoptolidin C. Similar to our fragment synthesis for the aglycone, our goal in the disaccharide synthesis was to provide an expedient route to each sugar subunit utilizing interesting and efficient catalytic methods to set requisite stereocenters. Toward that goal, it was decided that the increasingly prolific work on organocatalyzed aldol products could potentially be assimilated into the synthesis of the apoptolidin disaccharide (Scheme 21). Of particular interest were these cross-aldol reactions being performed by a number of laboratories, giving high yields of enantioenriched polyols, polyethers, and polypropionate subunits.[64,65]

**Scheme 21.** Recent breakthroughs in organocatalyzed aldol reactions



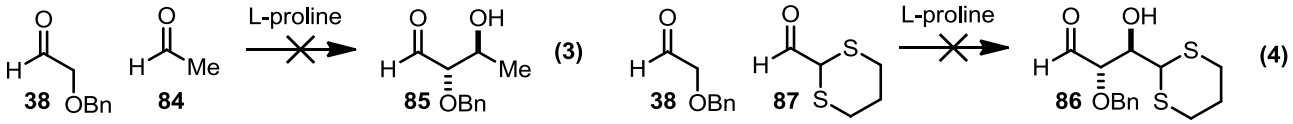
With this chemistry in mind, our retrosynthetic analysis from disaccharide **78** began with glycosidic bond formation between the sugars derived from cyclization of aldol products **79** and **80** (Scheme 22). The cyclization precursors are being built from a Mukaiyama aldol onto organocatalyzed cross-aldol products **81** and **82**. The core of our initial analysis of this synthesis was the formation of these cross-aldol products, thought to be obtainable through proline catalysis between simple aldehyde starting materials **37**, **38**, **83** and **84**.

**Scheme 22.** Initial disaccharide retrosynthetic analysis



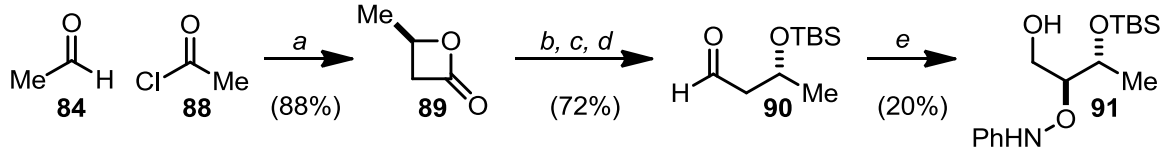

Preliminary studies focusing on utilization of L-proline met with little success (Scheme 23-3, 23-4). Our ambition was to incorporate acetoxyacetaldehyde-based nucleophile **38** and electrophile **84** into cross-aldol systems in the absence of literature examples.[64,65] It was discovered that application of proline catalysis resulted in a complex mixture of products, with no desired product **85** found (3). Very low yields of product **86** were obtained (15%) when using nucleophile **38** and non-enolizable aldehyde **87** (4). The inductive effects of the benzyl ether moiety results in excellent electrophilicity at the aldehyde position and poor enolate nucleophilicty, making this compound a poor candidate as a nucleophile in cross-aldol additions.

**Scheme 23.** Attempts at proline catalyzed cross aldol chemistry




Maintaining a desire to incorporate proline catalysis into the dissacharide synthesis, a potential opportunity presented itself in the α-oxidation of aldehydes[66] that could be made from our group's AAC chemistry (Scheme 24). Cinchona alkaloid-catalyzed cyclocondensation between acetaldehyde **84** and acetyl chloride **88** resulted in β-lactone **89** followed by a ring opening (Weinreb amine), protection (TBSOTf), reduction sequence ($i$Pr$_2$AlH) to generate aldehyde **90**. α-Oxidation of the aldehyde with proline and nitrosobenzene resulted in only 48% conversion and 20% isolated yield of the oxidized product **91**. Realizing that the literature substrate scope of this reaction is limited to unsubstituted propionate aldehydes, it is likely that bulky β-substitution of the TBS ether prevents an efficient rate of conversion.

**Scheme 24.** Proline catalyzed α-oxidation of aldehydes

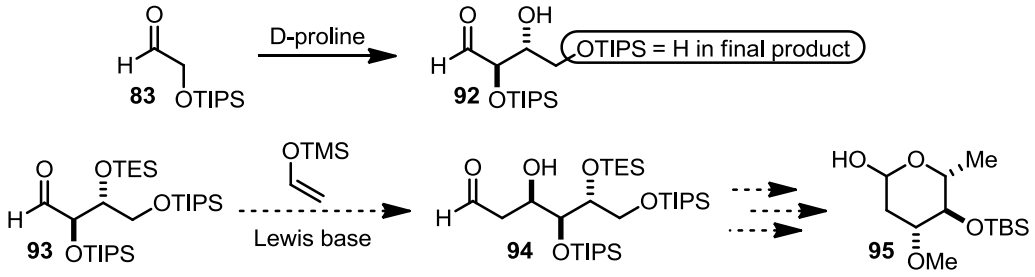



a) $LiClO_4$, TMSQd, DIPEA, $Et_2O$, $CH_2Cl_2$, –78 °C. b) $Me_2AlCl$, $CH_2Cl_2$, –45 °C. c) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, –78 °C. d) $i$Pr$_2$AlH, THF, –78 °C. e) PhNO, L-proline, DMSO, then $NaBH_4$, EtOH.

With setbacks in attempting to make innovations in cross-aldol chemistry and other organocatalyzed considerations, it seemed prudent to consider more analogous literature examples going forward. Proline-catalyzed dimerization of the acetoxyacetaldehyde ethers we had been working with are known,[43,44] the drawback in this chemistry being that the methyl

group of the electrophilic aldehyde is one oxidation state too high for direct incorporation into our sugar synthesis (Scheme 25). The dimerization chemistry is, however, sufficiently efficient to allow for the necessary additional steps involved in deoxygenating the methyl group. After formation of dimer **92** and protection to silyl ether **93**, aldehyde **94** could be obtained via a Lewis base catalyzed substrate controlled Mukaiyama aldol that has been implemented in other syntheses in our labs.[67] From aldehyde **94**, cyclization and functional group manipulations would provide access to sugar **95**.

**Scheme 25.** Proline catalyzed dimerization and incorporation into synthesis




Before continuing with the forward synthesis, an analysis of the Lewis base catalyzed Mukaiyama aldol's transition state made us wary of the potential diastereoselective outcome of this reaction (Figure 5). In previous applications of this chemistry, the OTIPS group was replaced with the much smaller, electron donating methyl group. Under these conditions, addition occurred Felkin with respect to the alkyl group being $R_L$, providing the correct, desired product for the synthesis of the apoptolidin sugars. In our example, however, there was a recognized possibility that the OTIPS group is sufficiently large and electron withdrawing enough to occupy the $R_L$ position in the Felkin model, leading to the undesired diastereomer.

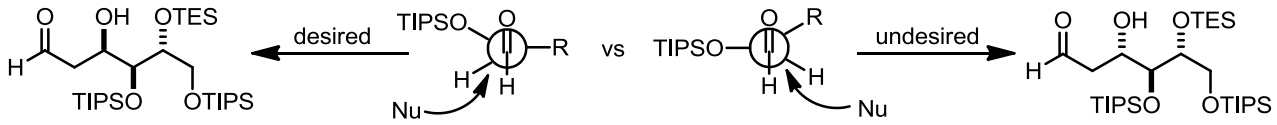
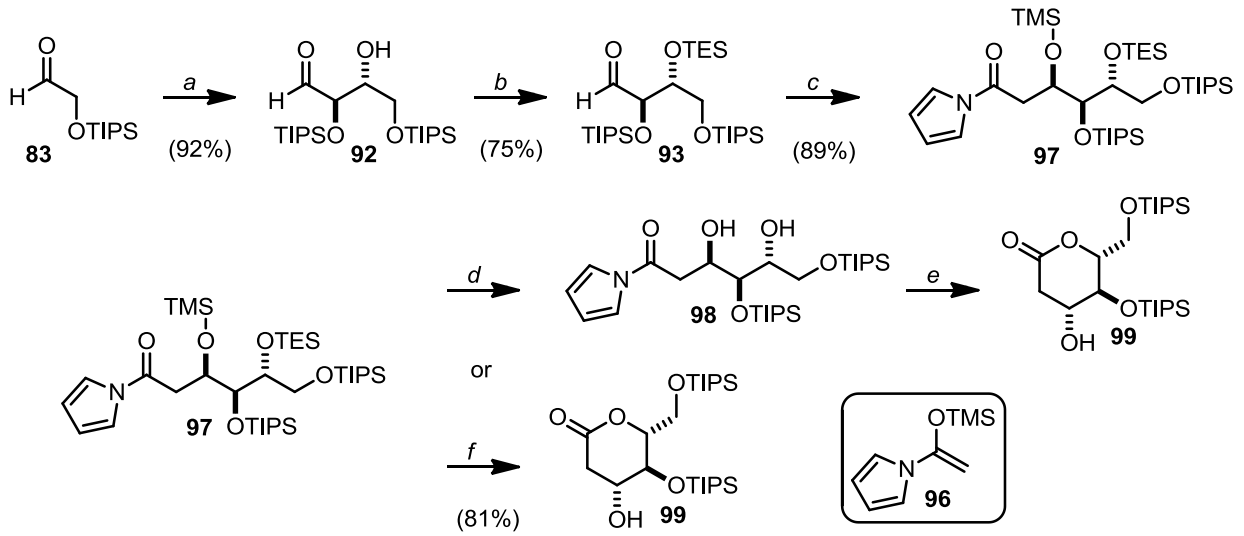



**Figure 5.** Stereochemical outcome of Mukaiyama aldol

With aldehyde **92** only a few steps from a known enantiopure material,[19] the most expedient way to deduce relative stereochemistry was to construct the known material. Dimerization of TIPS-protected acetoxyacetaldehyde **83** to dimer **92** followed by silyl protection (TESOTf, 2,6-lutidine) gave fully silated triol **93** in 58% yield over two steps (Scheme 26). Achiral Lewis base tetra-*n*-butylammonium *p*-nitrophenoxide-catalyzed Mukaiyama aldol addition of enol silane **96** to aldehyde **93** gave amide **97** as a single diastereomer in 89% yield,[67] relative stereochemistry currently unknown but represented as the desired isomer in this scheme. Attempts to cyclize the resulting straight chain to produce the sugar core was more problematic than anticipated. Direct acidic cyclization failed to produce the cyclization product when reacting the amide or the aminol resulting from reduction with catalytic acid. During the course of these attempts it was found that the TES and TMS groups could be deprotected with 1 M HCl and from intermediate diol **98** and the cyclization to lactone **99** would occur under basic conditions. Ultimately a one pot procedure in which simultaneous acidic cleavage of both the TMS and TES silanes followed by in situ base promoted cyclization was devised to generate the 6-membered lactone **99** in good yield (81%).

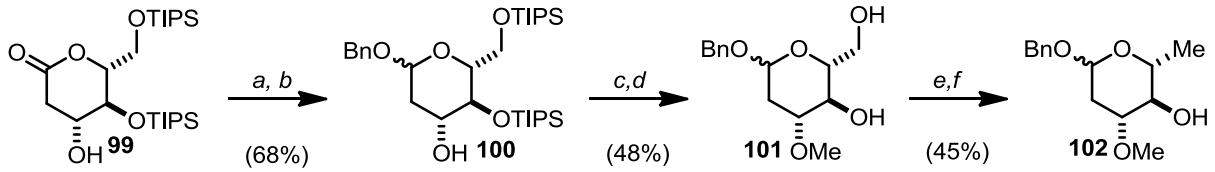
**Scheme 26.** Disaccharide forward synthesis




a) D-proline, DMF. b) TESOTf, 2,6-lutidine, $CH_2Cl_2$, –78 °C. c) 20 mol% $NO_2C_6H_4ONBu_4$, **96**, THF, –70 °C. d) 1 M HCl, MeOH. e) NaOMe, MeOH, 0 °C f) $CF_3CO_2H$, $CH_2Cl_2$/MeOH, 0 °C then NaOMe.

The cyclization product **99** was then reduced to the lactol with *i*$Pr_2AlH$ and subsequently benzyl protected at the anomeric center with benzyl alcohol and catalytic PPTS to afford benzyl ether **100** in moderate yield over 2 steps (68%) (Scheme 27). Alcohol **100** was then methylated (MeI, NaH) prior to silyl ether deprotection (TBAF) to yield diol **101** (48%). Interestingly, attempts to methylate or desilate lactone **99** directly lead to decomposition suggesting that this intermediate is base sensitive, probably due to retroaldol tendencies. Barton deoxygenation of diol **101** proceeded in moederate yield (45%) through selective formation of the primary *o*-phenylthionoformate and subsequent radical initiation with catalytic AIBN in the presence of $Bu_3SnH$.[68] Enough material was obtained at this stage to compare the product to a known literature sample of **102**.

**Scheme 27.** Disaccharide forward synthesis




a) *i*$Pr_2AlH$, $CH_2Cl_2$, −78 °C. b) PPTS, BnOH, $CH_2Cl_2$. c) MeI, NaH, THF, 0 °C to RT. d) TBAF, THF, 0 °C to RT. e) PhOCSCl, pyr, $CH_2Cl_2$. f) AIBN, $Bu_3SnH$, toluene, Δ.

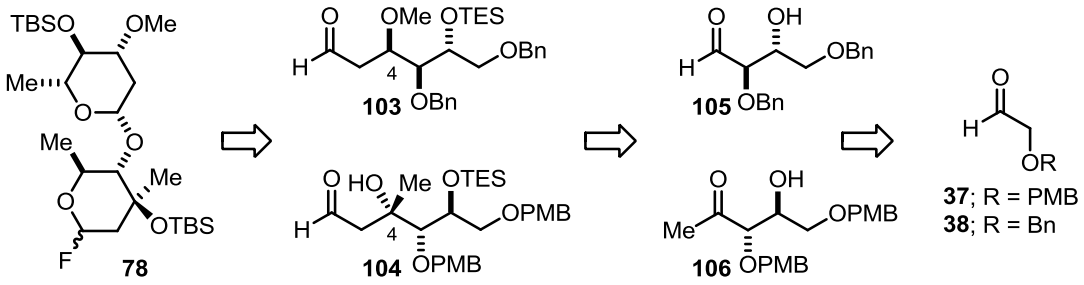
Unfortunately, our sample's spectra showed enough incongruence between the $^1H$ and $^{13}C$-NMR of the literature sample[19] to suggest that we had obtained the wrong diastereomer. All chemical shifts were accounted for, with major alteration in the position of the proton and carbon formed in the Mukaiyama aldol addition. 2D experimentation also supported the probability of having generated the incorrect isomer. With this data in hand it was necessary to develop some alterations in the route while maintaining as much of the core synthesis as possible.

## 3.2 DISACCHARIDE FINAL ROUTE

Advancement of the disaccharide synthesis required some alteration in our approach in order to incorporate an appropriate substrate controlled addition to the dimer product (Scheme 28). The disaccharide **78** would still be accessed via the glycosidation of cyclized, deoxygenated precursors **103** and **104**. The $C_4$ stereocenter in aldehydes **103** and **104** would be set in a chelate controlled allylation of dimers **105** and **106** rather than the Lewis base catalyzed Mukaiyama aldol attempted previously, which proceeded via an open transition state. Utilizing substrate controlled chelation required incorporation of a different dimerizing aldehyde, **37** or **38**, so that the α-center would contain a coordinating group for the transition state. This scheme allows all

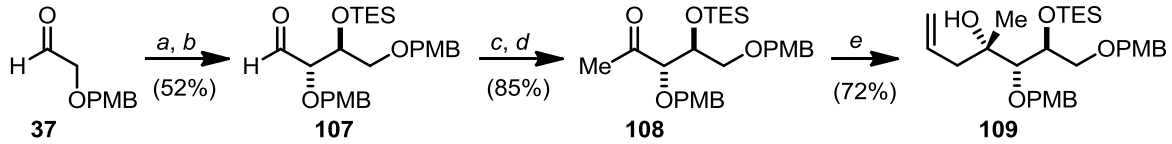
6 fixed stereocenters to be derived from a single reaction in which commercially available proline (100 g, $63.50; Sigma-Aldrich) is the only additional reagent.

**Scheme 28.** Disaccharide retrosynthesis




Application of the proline catalyzed aldol dimerization on **37** yielded the PMB dimer **106** (4:1 *anti*:*syn*, 98% *ee*)[43,44] that was protected as the TES silyl ether **107** (TESOTf, 2,6-lutidine; 52% 2 steps) (Scheme 29). This silyl protection was less trivial than anticipated; decomposition related to Lewis acid induced retroaldol was found to be a major contributor to the reported modest yield. The reaction necessitated the use of TESOTf in lieu of TBSOTf and higher reaction temperatures so that the hydroxyl group was protected immediately upon addition of the silating reagent, restricting the possibility of undesired decomposition pathways. Aldehyde **107** was then alkylated (MeMgBr) and directly oxidized (DMP) to generate ketone **108** in 85% yield over 2 steps. Chelate controlled allylation of the ketone ($n$Bu$_3$SnAllyl, MgBr$_2$·Et$_2$O) gave alcohol product **109** in 72% yield (> 95:5 dr).[69]

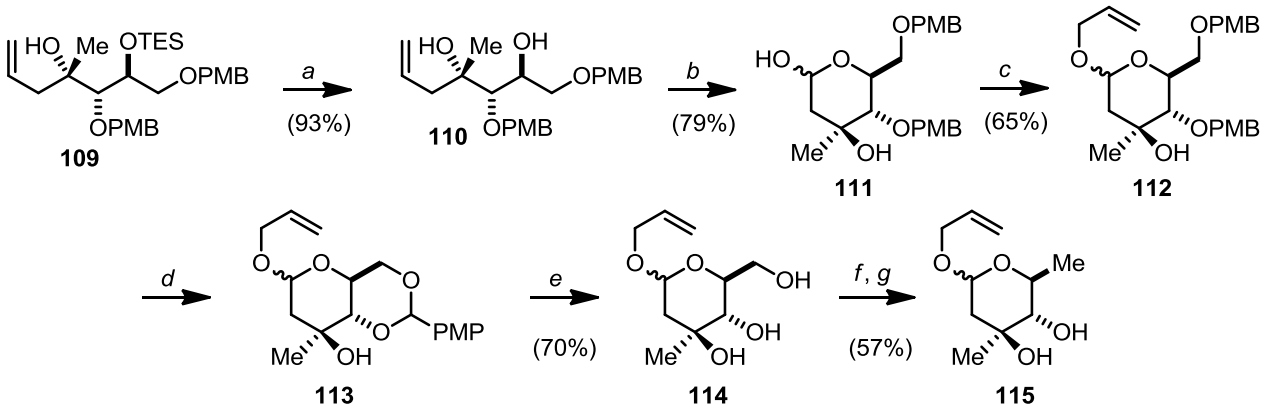
**Scheme 29.** L-Proline derived sugar forward synthesis




a) 10 mol% L-proline, DMF; 4:1 (*anti*:*syn*), 98% *ee*. b) TESOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C; 2.8:1. c) MeMgBr, $Et_2O$, –78 °C. d) DMP, $NaHCO_3$, $CH_2Cl_2$; >95:5 dr. e) *n*$Bu_3SnAllyl$, $MgBr_2 \cdot Et_2O$, $CH_2Cl_2$, –78 °C-RT. DMP = Des-Martin periodinane.

Continuing from silyl ether **109**, Basic fluoride conditions effected silyl ether cleavage to give diol **110** in 93% yield (Scheme 30). Cyclization of alkene **110** to pyran core **111** was accomplished using a one pot dihydroxylation/oxidative cleavage/cyclization ($OsO_4$, $NaIO_4$) in the presence of 2,6-lutidine, acting as a buffer for potential carboxylic acids/peroxides that may be formed during oxidative cleavage.[70] Allyl protection of the resulting anomeric alcohol of **111** ($Ag_2O$, allyl bromide; 48%, 2 steps) generated the fully protected pyran core **112**.[71] Attempts to directly deprotect bisPMB ether **112** lead to formation of the PMP acetal or decomposition under more aggressive reaction conditions (CAN). A compromise in which **112** was transformed into the PMP acetal **113** under oxidizing conditions (DDQ) followed by hydrolysis to the triol (aq AcOH) furnished **114** in good yield (70%, 2 steps). It is also noted that this substrate was also constructed with benzyl protecting groups in exchange for PMB. Various methods failed to successfully deprotect the benzyl ethers with acceptable efficiency (LiDBB; Na Naphthalenide; $ClO_2SNCO$). Selective formation of the primary xanthate (pyridine, phenyl chlorothionoformate) followed by radical deoxygenation ($Bu_3SnH$, AIBN) completed the synthesis of the appropriately functionalized glycosyl donor **115** (57%, 2 steps).

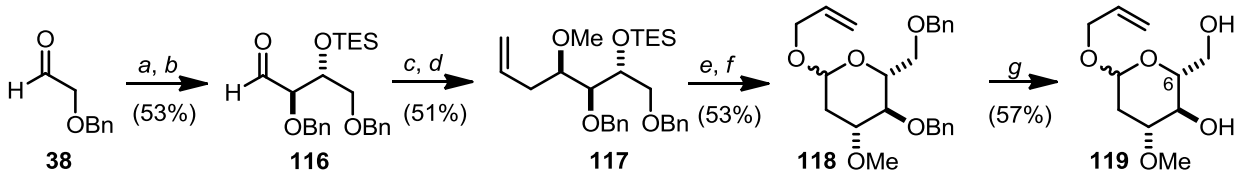
**Scheme 30.** L-Proline derived sugar forward synthesis




a) TBAF, THF, 0 °C; 1:1 (α:β). b) $OsO_4$, $NaIO_4$, 2,6-lutidine, dioxane:$H_2O$ (3:1). c) AllylBr, $Ag_2O$, DMF; > 95:5 (α:β). d) DDQ, $CH_2Cl_2$:pH 7 buffer. e) 80% AcOH. f) pyridine, phenyl chlorothionoformate, $CH_2Cl_2$. g) $n$$Bu_3SnH$, AIBN, toluene, Δ. TBAF = tetra-*n*-butylammonium fluoride.

Opting for benzyl protecting groups in the synthesis of the D-Proline derived sugar, dimerization[43,44] of benzyl protected acetoxyacetaldehyde **38** followed by silyl ether formation afforded the TES protected dimer **116** in 53% yield (Scheme 31). The $C_4$ stereocenter was set under the same chelate controlled allylation conditions[69] seen previously ($n$$Bu_3SnAllyl$, $MgBr_2 \cdot Et_2O$) and methylation ($Me_3OBF_4$, proton sponge) of the resulting alcohol, avoiding a hard alkoxide and TES migration, yielded alkene **117** in 51% over 2 steps. Replication of the oxidative cleavage conditions[70] on alkene **117** followed by simultaneous silyl ether cleavage/cyclization/anomeric allyl protection under acidic conditions (PPTS, allyl alcohol) furnished the cyclized product **118** (53% 2 steps). Reductive deprotection of dibenzyl ether **118** with LiDBB afforded diol **119** in moderate yield (57%).

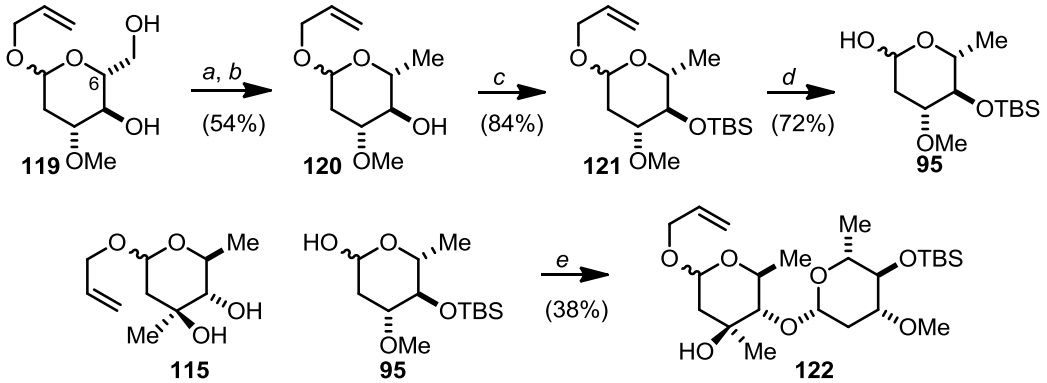
**Scheme 31.** D-Proline derived sugar and disaccharide synthesis




a) 10 mol% D-proline, DMF; 4:1 (*anti*:*syn*), 98% *ee*. b) TESOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C; 2.8:1. c) $n$$Bu_3SnAllyl$, $MgBr_2 \cdot Et_2O$, $CH_2Cl_2$, −78 °C-RT. d) $Me_3OBF_4$, proton sponge, $CH_2Cl_2$. e) $OsO_4$, $NaIO_4$, 2,6-lutidine, dioxane:$H_2O$ (3:1). f) $HOCH_2C_2H_3$, PPTS, 55 °C. g) LiDBB, THF, −78 °C. PPTS = pyridinium *p*-toluenesulfonate, LiDBB = lithium 4,4`-ditertbutylbiphenylide.

To continue the synthesis, the $C_6$ position of **119** was then deoxygenated under Barton's conditions to generate alcohol **120** (54% 2 steps; Scheme 32). TBS protection (2,6-lutidine, TBSOTf) to **121** (84%) followed by nucleophilic allyl deprotection mediated by a ruthenium species generated from $[CpRu(MeCN)_3]PF_6$ and quinaldic acid gave the glycoside accepter precursor **95** (72%; 80% conv).[72] Formation of disaccharide **122** was ultimately accomplished by conversion of anomeric alcohol **95** to the bromide followed by treatment with alcohol **115** and lewis acidic activation via $Ag_2O$-$SiO_2$[73,74] (38%) with a nontrivial quantity of glycosidation occurring at the tertiary alcohol (18%).[19]

**Scheme 32.** D-Proline derived sugar and disaccharide synthesis

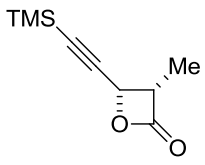



a) pyridine, phenyl chlorothionoformate, $CH_2Cl_2$. b) $n$$Bu_3SnH$, AIBN, toluene, Δ. c) TBSOTf, 2,6-lutidine, $CH_2Cl_2$. d) $[CpRu(MeCN)_3]PF_6$, quinaldic acid, MeOH. e) TMSBr, $C_6H_6$ then **115**, $Ag_2O$–$SiO_2$, $CH_2Cl_2$, −78 °C. AIBN = azobisisobutyronitrile, TMSBr = bromotrimethylsilane.

Implementation of the proline-catalyzed dimerization into the synthesis of the apoptolidin C sugar substructures has been realized. All 6 non-anomeric stereocenters present in the disaccharide have been set by a single catalytic reaction. With completion of the sugar moieties and aglycone, future work involves their mergence into the natural product synthesis. Integration of these substructures into the preexisting aglycone synthesis would involve glycosidation of the $C_1$-$C_{11}$ and $C_{12}$-$C_{29}$ fragment prior to coupling. It is anticipated that the end-game synthesis of the natural product will be closely related to that of the aglycone.

# 4.0 EXPERIMENTAL

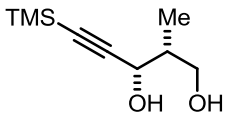
**General Information:** Optical rotations were measured in chloroform obtained directly from a bottle purchased from Sigma-Aldrich and measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (*c* g/100mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance-300 (300 MHz) spectrometer with chemical shifts reported relative to residual $CHCl_3$ (7.26 ppm) for $^1H$, $CHCl_3$ (77.00 ppm) for $^{13}C$ NMR, $CH_2Cl_2$ (5.30 ppm) for $^1H$, and $CH_2Cl_2$ (53.52 ppm) for $^{13}C$ spectra. Unless otherwise stated, all reactions were carried out in dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous solvents ($CH_2Cl_2$, THF, DMF, diethyl ether, pentane and toluene) were obtained by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. *N*,*N*-Diisopropylethylamine, *N*,*N*-diisopropylamine and triethylamine were distilled under nitrogen from $CaH_2$. Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh).




**3-(*S*)-Methyl-4-(*S*)-(trimethylsilylethynyl)oxetan-2-one (42):**[45]

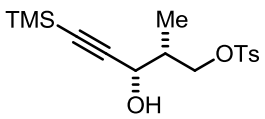
Dimethylaluminum chloride (0.79 mL, 0.79 mmol, 1 M) was added to a solution of triamine **44** (0.48 g, 0.79 mmol) in 20 mL of $CH_2Cl_2$ at ambient

temperature and stirred for 2 h. The reaction was cooled to −50 °C and DIPEA (2.74 mL, 15.8 mmol) and propionyl bromide (1.40 mL, 15.8 mmol) was added in succession. The reaction was stirred 3 min prior to the addition of aldehyde **34** (1.0 g, 7.9 mmol). The reaction stirred for 12 h at −50 °C and was quenched at that temperature with 40 mL saturated aqueous $NH_4Cl$. The mixture was allowed to come to ambient temperature and the aqueous and organic portions were separated. The aqueous portion was extracted with $CH_2Cl_2$ (3x 40 mL) and the organics were combined, dried ($MgSO_4$), filtered, and concentrated. 1.16 g (81%) of the title compound was isolated after purification of the crude oil *via* flash chromatography (5-15% $Et_2O$/hexanes). $[\alpha]_D$ +12.6 (*c* 1.02, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.12 (d, J = 6.6 Hz, 1H), 3.91-3.81 (dq, J = 6.6, 7.8 Hz, 1H), 1.43 (d, J = 7.5, 3H), 0.21 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 171.3, 98.9, 97.1, 64.8, 49.9, 10.6, −0.2; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_9H_{14}O_2Si$: 167.0530; found: 167.0528.



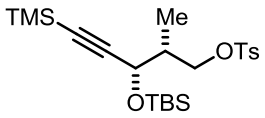

**(2*R*,3*S*)-2-Methyl-5-(trimethylsilyl)pent-4-yne-1,3-diol (42b):** Diisobutylaluminum hydride (11 mL, 11 mmol, 1 M) was added to a −50 °C solution of β-lactone **42** (0.644 g, 3.54 mmol) in 25 mL of THF over 30 min. The resulting reaction mixture was stirred for 30 min at −50 °C, was removed from the cold bath and was stirred an additional 30 min prior to being quenched with 30 mL saturated aqueous Rochelle's salt. The mixture was stirred for 2 h and was then extracted with $Et_2O$ (3x 30 mL) and the combined organics were dried ($MgSO_4$) and concentrated. The resulting crude product was routinely used crude in the next step; a small sample was further purified *via* column chromatography (20% EtOAc/hexanes) for characterization purposes. $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.50 (d, J = 3.9 Hz, 1H), 3.87 (dd, J = 8.4, 10.5 Hz, 1H), 3.70 (dd, J = 4.2, 10.8 Hz,

1H), 2.24 (s, 1H), 2.17-2.07 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.18 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 104.6, 91.3, 67.1, 65.9, 40.2, 12.4, −0.1; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_9H_{18}O_2Si$: 168.0970; found: 168.0965.



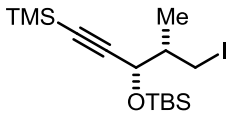

**(2*R*,3*S*)-3-Hydroxy-2-methyl-5-(trimethylsilyl)pent-4-ynyl 4-methylbenzenesulfonate (45):**

Pyridine (0.71 mL, 8.7 mmol), DMAP (0.084 g, 0.77 mmol), and TsCl (0.985 g, 5.22 mmol) were added successively a solution of diol **42b** (0.644 g, 3.48 mmol) in 19 mL of $CH_2Cl_2$ at ambient temperature. The resulting reaction mixture was allowed to stir for 20 h and was quenched with saturated aqueous $NH_4Cl$ (20 mL) and the organic and aqueous portions were separated. The aqueous portion was washed with $CH_2Cl_2$ (3x 20 mL) and the combined organics were dried ($MgSO_4$), concentrated, and the resulting crude product was purified *via* column chromatography (10-20% EtOAc/hexanes) to afford 0.554 g (46% over 2 steps) of the title compound. $[\alpha]_D$ +8.2 (*c* 1.03, $CHCl_3$); IR (thin film): 3524, 2962, 1598, 1361, 1176 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.42 (d, J = 4.2 Hz, 1H), 4.14 (dd, J = 7.2, 9.6 Hz, 1H), 3.95 (dd, J = 6, 9.6 Hz, 1H), 2.45 (s, 3H), 2.08-2.16 (m, 1H), 0.99 (d, J = 6.9, 3H), 0.14 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 145.0, 133.1, 130.1, 128.2, 104.2, 91.5, 71.7, 63.4, 39.2, 21.9, 11.0, 0.0; HRMS (*Q-Tof*) *m/z* calcd for ($M^+$ + Na) $C_{16}H_{24}O_4SiSNa$: 363.1062; found: 363.1041.




**(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-(trimethylsilyl)pent-4-ynyl 4-methylbenzenesulfonate (45b):**

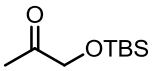
Imidazole (0.016 g, 0.24 mmol) was added to a mixture of alcohol **45** (0.042 g, 0.12 mmol) and TBSCl (0.027 g, 0.18 mmol) in 0.5 mL of DMF and the resulting solution was allowed to stir for 24 h at ambient temperature. The crude reaction mixture was passed through a plug of silica gel eluting with $CH_2Cl_2$. The mixture was concentrated and was left under reduced pressure for about 12 h to yield 0.055 g (99%) of the title compound as a crude oil. Sample purified further *via* flash chromatography (5% $Et_2O$/hexanes) for characterization purposes. $[\alpha]_D$ +37.4 (*c* 1.02, $CHCl_3$); IR (thin film): 2957, 2858, 2175, 1599, 1468, 1252cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1, 2H), 4.36 (d, J = 4.2 Hz, 1H), 4.08 (dd, J = 6.6, 9.6 Hz, 1H), 3.92 (dd, J = 6.9, 9.6 Hz, 1H), 2.4 (s, 3H), 1.98-2.07 (m, 1H), 0.97 (d, J = 6.9 Hz, 3H), 0.83 (s, 9H), 0.13 (s, 6H), 0.10 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 144.9, 133.3, 130.0, 128.2, 105.3, 90.6, 71.9, 63.7, 40.1, 31.8, 25.9, 21.8, 18.3, 11.77, –0.1, –4.3, –5.0; HRMS (*Q-Tof*) *m/z* calcd for ($M^+$ + Na) $C_{22}H_{38}O_4Si_2SNa$: 477.1927; found: 477.1902.




***tert*-Butyl((3*S*,4*S*)-5-iodo-4-methyl-1-(trimethylsilyl)pent-1-yn-3-yloxy)dimethylsilane (39):**

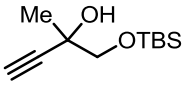
A solution of tosylate **45b** (0.623 g, 1.37 mmol) and NaI (0.282 g, 1.88 mmol) was refluxed in 3 mL dry acetone for 10 h. The resulting reaction mixture was cooled to ambient temperature and passed through a plug of silica gel eluting with $Et_2O$. The volatiles were removed and the resulting crude product mixture was purified *via* column chromatography (1-5% EtOAc/hexanes) to yield 0.436 g (78%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 4.42 (d, J = 4.5 Hz, 1H), 3.35 (dd, J = 6.3, 6.6 Hz, 1H), 3.15 (dd, J = 6.6, 9.6 Hz), 1.84-1.92 (m, 1H), 1.11 (d, J =

6.6 Hz, 3H), 0.90 (s, 9H), 0.16 (s, 6H), 0.153 (s, 3H), 0.13 (s, 3H); HRMS (*EI*) *m/z* calcd for ($M^+$) $C_{15}H_{31}O_1ISi_2$: 410.0958; found: 410.0957.



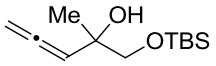

**1-(*tert*-Butyldimethylsilyloxy)propan-2-one (46):**

Acetol (10.0 g, 0.135 mol) was added to a mixture of TBSCl (22.4 g, 0.149 mol) and imidazole (18.0 g, 0.270 mol) in 250 mL of $CH_2Cl_2$ at 0 °C and the resulting reaction mixture was allowed to come to ambient temperature and stirred for 1 h. The resulting crude mixture was passed through a plug of silica gel eluting with $CH_2Cl_2$. The volatiles were removed and the resulting crude oil was purified *via* column chromatography (5%-10% EtOAc/hexanes) to yield 20.4 g (81%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 4.15 (s, 2H), 2.17 (s, 2H), 0.92 (s, 9H), 0.09 (s, 6H).



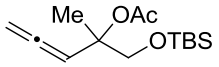

**1-(*tert*-Butyldimethylsilyloxy)-2-methylbut-3-yn-2-ol (46b):**

Ethynylmagnesium bromide (58.3 mL, 28.2 mmol, 0.5 M in THF) was added dropwise to a −78 °C solution of silyloxypropanone **46** (4.86 g, 25.8 mmol) in 145 mL of THF:$Et_2O$ (2:1). The resulting mixture stirred at −78 °C for 30 min, then was allowed to warm to ambient temperature and was stirred an additional 2 h prior to being quenched with 1 M citric acid (250 mL). The resulting aqueous and organic portions were separated. The aqueous layer was extracted with EtOAc (2x 250 mL) and the combined organics were dried ($MgSO_4$), concentrated, and the resulting crude product was used in the next step without further purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 3.68 (d, J = 9.6 Hz, 1H), 3.51 (d, J = 9.3 Hz, 1H), 2.95 (s, 1H), 2.37 (s, 1H), 1.43 (s, 3H), 0.92 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H).




**1-(*tert*-Butyldimethylsilyloxy)-2-methylpenta-3,4-dien-2-ol (46c):**

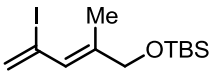
Dry dioxane (157 mL) was added to a mixture of CuBr (1.66 g, 11.7 mmol) and paraformaldehyde (1.08 g, 37.2 mmol) in a 250 mL 3-neck round bottom flask equipped with a reflux condenser. DIPA (3.92 mL, 27.4 mmol) and alkyne **46b** (5.00 g, 23.5 mmol) were added successively to the mixture and the resulting suspension was heated at reflux for 14 h. The mixture was allowed to cool to ambient temperature and was diluted with $H_2O$ (150 mL) and extracted with $Et_2O$ (3 x 150 mL). The combined organics were washed with cold 10% aqueous NaCl (5 x 150 mL). The organic portion was dried ($MgSO_4$), concentrated and the resulting crude mixture was used in the next step without further purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 5.27 (t, J = 6.6 Hz, 1H), 4.86 (d, J = 6.6 Hz, 2H), 3.52 (d, J = 9.3 Hz, 1H), 3.45 (d, J = 9.3 Hz, 1H), 1.27 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H).




**(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-methylpenta-3,4-dien-2-yl acetate (47):**

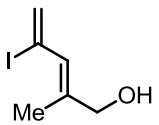
Allenol **46c** (5.00 g, 21.8 mmol) was heated in a solution of acetic anhydride (4.50 mL, 47.5 mmol), DMAP (0.288 g, 21.8 mmol), and pyridine (1.78 mL, 22.4 mmol) at 40 °C for about 12 h. The crude reaction mixture was cooled to ambient temperature and loaded directly onto a flash column. The column was eluted (10% $Et_2O$/hexanes) and the volatiles were removed to yield 3.7 g (62% over 3 steps) of the title compound as a translucent oil. IR (thin film): 2955, 2858, 1958, 1741, 1250 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 5.55 (t, J = 6.9, 1H), 4.89 (dd, J = 6.9, 11.1 Hz, 1H), 4.84 (dd, J = 6.6, 11.1 Hz), 3.83 (d, J = 10.2, 1H), 3.67 (d, J = 10.2, 1H), 1.99 (s, 3H), 1.51 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 207.5, 171.7,

170.1, 93.4, 81.1, 77.8, 68.0, 25.8, 25.5, 22.1, 21.2, 18.2, 17.5, –5.0, –5.4; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_{14}H_{26}O_3Si$: 270.1651; found: 270.1650.




**(*E*)-*tert*-Butyl(4-iodo-2-methylpenta-2,4-dienyloxy)dimethylsilane (48):**

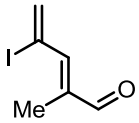
Allenic ester **47** (3.50 g, 13.0 mmol) was added to a mixture of LiI (3.92 g, 29.5 mmol) and palladium acetate (0.042 g, 0.19 mmol) in 120 mL of acetic acid and the resulting reaction mixture was allowed to stir at 40 °C for about 8 h. Pentane and $H_2O$ were added to the solution and the resulting aqueous and organic portions separated. The aqueous portion was extracted with pentane (3x) and the combined organic extracts were washed with $H_2O$ (1x), $NaHCO_3$ (2x), and brine (1x). The organic solution was dried ($MgSO_4$), concentrated and the resulting crude oil was purified by flash chromatography (1-3% $Et_2O$/hexanes) to yield 3.42g (78%) of the title compound as a yellow oil. IR (thin film): 2930, 2857, 1723, 1468, 1255cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 6.16 (s, 1H), 5.97 (t, J = 1.2 Hz, 1H), 5.95 (d, J = .6 Hz, 1H), 4.07 (d, J = .9 Hz, 2H), 1.74 (t, J = .6 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 139.2, 131.1, 128.3, 128.0, 103.2, 67.1, 26.1, 18.6, 14.8, –5.1; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_{12}H_{23}OSiI$: 338.0563; found: 338.0562.




**(*E*)-4-Iodo-2-methylpenta-2,4-dien-1-ol (48b):**

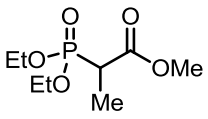
HF·pyr (2.15 mL, 70:30) was added to a solution of TBS ether **48** (0.650 g, 2.15 mmol) in 50 mL THF/pyr (2:1) at ambient temperature and the reaction mixture was allowed to stir for 20 h before being quenched with 1 M NaOH (50 mL). The aqueous portion was extracted with $Et_2O$ (3x 50 mL) and the combined organics were washed with saturated aqueous $NH_4Cl$ (50 mL) followed by brine (50 mL), dried ($Na_2SO_4$), and concentrated. Purification of

the resulting crude oil *via* column chromatography (20% EtOAc/hexanes) yielded 0.420 g (98%) of the title compound as a pale yellow oil. IR (thin film): 3315, 2913, 2854, 1646, 1067 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.16 (d, J = 0.6 Hz, 1H), 6.00 (t, J = 1.5 Hz, 1H), 5.98 (d, J = 0.6 Hz, 1H), 4.09 (s, 2H), 1.81 (d, J = 1.2 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 139.3, 129.1, 128.5, 67.3, 15.0; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_6H_9OI$: 223.9698; found: 223.9694.




**(*E*)-4-Iodo-2-methylpenta-2,4-dienal (48c):**

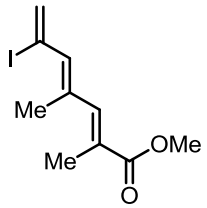
Oxalyl chloride (0.030 mL, 0.33 mmol) was added dropwise to a −78 °C solution of DMSO (0.050 mL, 0.69 mmol) in 3 mL of $CH_2Cl_2$ in a 10 mL round bottom flask wrapped in aluminum foil. The reaction mixture was stirred for 30 min and a solution of dienol **48b** (0.050 g, 0.21 mmol) in 2.5 mL of DCM was added. The reaction mixture was stirred at −78 °C for 1.5 h before the addition of $NEt_3$ (0.10 mL, 0.69 mmol) and the resulting mixture was allowed to warm to ambient temperature and stirred an additional 25 min before being quenched with 3 mL saturated aqueous $NH_4Cl$. The resulting aqueous and organic portions were separated. The aqueous portion was extracted with $CH_2Cl_2$ (3x mL) and the combined organics were washed with brine, dried ($Na_2SO_4$), and concentrated. The resulting crude dark yellow oil was immediately dissolved in THF and carried on to the next step.




**Methyl 2-(diethoxyphosphoryl)propanoate (49):**[51]

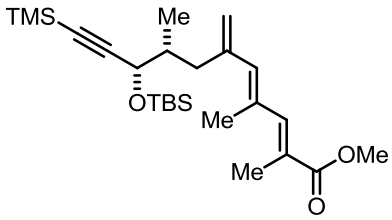
A mixture of 2-bromomethylpropionate (6.7 mL, 66 mmol) and triethyl phosphite were heated at 140 °C for 48 h and the undesired byproduct bromoethane was removed under reduced pressure. The resulting crude mixture was distilled under reduced pressure (95 °C, 1.0 mm Hg) to yield 7.69 g (52%) of the title compound. $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.10-4.20

(m, 4H), 3.75 (s, 3H), 3.05 (dq, J = 7.5, 23.4 Hz, 1H) 1.44 (dd, J = 7.2, 16.5 Hz, 3H), 1.31-1.36 (m, 6H).



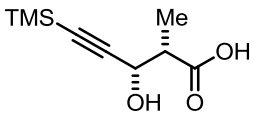

**(2*E*,4*E*)-Methyl 6-iodo-2,4-dimethylhepta-2,4,6-trienoate (40):**

*n*-BuLi (0.80 mL, 1.2 mmol, 1.6 M in hexanes) was added to a solution of phosphonate ester **49** (0.280 g, 1.20 mmol) in 6 mL of THF at 0 °C in a 10 mL round bottom flask wrapped in aluminum foil. The solution stirred for 15 min and was then cooled to −78 °C before adding aldehyde **48c** (0.100 g, 0.450 mmol) as a solution in 5 mL of THF. The mixture was stirred for 3 h, then was warmed to ambient temperature and was stirred an additional 30 min before being quenched with 6 mL saturated aqueous $NaHCO_3$. The resulting solution was extracted with $Et_2O$ (3x 6 mL) and the combined organics were washed with brine, dried ($Na_2SO_4$), and concentrated. The crude product was purified *via* flash chromatography (10% $Et_2O$/Hexanes) to yield 0.078 mg (69%) of the title compound as a yellow oil. IR (thin film): 2950, 1714, 1435, 1256, 1211, 1119 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 0.33H), 7.05 (s, 0.66H), 6.17 (s, 0.66H), 6.17 (q, J = 1.5 Hz, 0.33H), 6.07 (t, J = 1.5 Hz, 0.66H), 6.03-6.04 (m, 0.66H), 5.95 (t, J = 1.5 Hz, 0.33H), 5.90 (d, J = 1.5 Hz, 0.33H), 3.71 (s, 3H), 2.00 (d, J = 1.5 Hz, 2H), 1.97 (d, J = 1.2 Hz, 2H), 1.94 (d, J = 1.5 Hz, 1H), 1.88 (d, J = 1.5 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 140.5, 137.3, 137.1, 135.4, 135.3, 129.6, 129.1, 51.9, 22.7, 17.5, 14.3, 13.9.




**(2*E*,4*E*,8*R*,9*S*)-Methyl 9-(tert-butyldimethylsilyloxy)-2,4,8-trimethyl-6-methylene-11-(trimethylsilyl)undeca-2,4-dien-10-ynoate (41):**

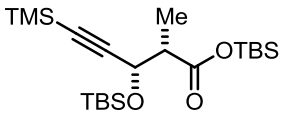
*tert*-Butyllithium (0.70 mL, 1.1 mmol, 1.5 M in hexanes) was added to a −78 °C solution of alkyl iodide **39** (0.21 g, 0.50 mmol) in 7.5 mL of $Et_2O$. The reaction was stirred for 5 min before adding 9-MeOBBN (1.2 mL, 1.2 mmol, 1 M in hexanes) and 7.5 mL of THF. The resulting mixture was stirred for 10 min, then allowed to warm to ambient temperature and stirred for an additional 1 h. A solution of $Cs_2CO_3$ (0.50 g, 1.6 mmol) in 0.4 mL of $H_2O$ was added to the reaction followed by triene **40** (0.088 g, 0.30 mmol) as a solution in 7.5 mL of DMF. $Pd(dppf)Cl_2$ (0.024 g, 0.030 mmol) was added to the reaction followed by $AsPh_3$ (0.014 g, 0.036 mmol) and the reaction mixture was allowed to stir for 18 h before being diluted with 15 mL $H_2O$ and extracted with $Et_2O$ (3x 15 mL). The combined organic extracts were dried ($Na_2SO_4$), concentrated, and the resulting crude product mixture was purified *via* column chromatography (1%-6% EtOAc/hexanes) to yield 0.063 g (47%) of the title compound. $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 0.2H), 7.10-7.13 (m, 0.8H), 5.91-5.98 (m, 1H), 5.13 (s, 0.8H), 5.02 (s, 0.2H), 4.99 (s, 0.8H), 4.86 (s, 0.2H), 4.2 (d, J = 4.8 Hz, 1H), 3.70-3.71 (m, 3H), 2.45 (dd, J = 5.1, 13.5 Hz, 1H), 1.90-2.0 (m, 7H), 1.15 (d, J = 6.9 Hz, 0.6H), 0.88-0.91 (m, 11.4H), 0.08-0.13 (m, 15H).




**(2*S*,3*S*)-3-Hydroxy-2-methyl-5-(trimethylsilyl)pent-4-ynoic acid (62):**

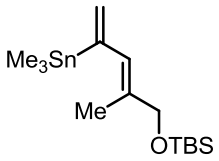
A premixed solution of 0.2N LiOH (2.3 mL) and 30% $H_2O_2$ (4.6 mL) was added to a solution of β-lactone **42** (0.050 g, 0.28 mmol) in 17 mL of THF at 0 °C and the resulting reaction mixture was allowed to warm to ambient temperature and was stirred for 1.5 h.

The reaction was then cooled to 0 °C before quenching with 2 M $Na_2SO_3$ (15 mL) dropwise and the mixture stirred for 30 min before adjustment to a pH of 3 with 1 M HCl. The resulting solution was extracted with $Et_2O$ (5x, 20 mL) and the combined organics were dried ($MgSO_4$). Removal of the volatiles yielded 0.039 g (69%) of the title compound as a crude product that was used in the next step without further purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 4.68 (d, J = 3.9 Hz, 1H), 2.82 (dq, J = 3.9, 7.2 Hz, 1H), 1.43 (s, 1H), 1.34 (d, J = 7.2 Hz, 3H), 0.17 (s, 9H).




**(2*S*,3*S*)-*tert*-Butyldimethylsilyl 3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-(trimethylsilyl)pent-4-ynoate (62b):**

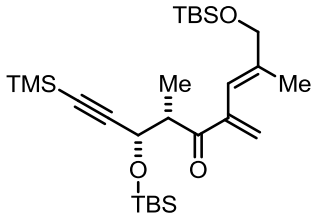
A mixture of 2,6-lutidine (2.2 mL, 19 mmol) and carboxylic acid **62** (0.656 g, 3.28 mmol) in 2 mL $CH_2Cl_2$ was cooled to −78 °C. TBSOTf (1.9 mL, 8.3 mmol) was added dropwise to the reaction mixture and the reaction was stirred for 3 h. The mixture was quenched at −78 °C with saturated aqueous $NaHCO_3$ and the resulting solution was allowed to warm to ambient temperature prior to separation of the aqueous and organic portions. The aqueous portion was extracted with $CH_2Cl_2$ (3x) and the combined organics were washed with 1 M $NaHSO_4$. The organics were then dried ($MgSO_4$), concentrated, and purification of the crude oil by column chromatography (20% EtOAc/hexanes) yielded 0.660 g (47%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 4.71 (d, J = 5.4 Hz, 1H), 2.58-2.67 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.94 (s, 9H), 0.88 (s, 9H), 0.26 (m, 6H), 0.15-0.16 (m, 9H), 0.10 (s, 3H).




**(*E*)-*tert*-Butyldimethyl(2-methyl-4-(trimethylstannyl)penta-2,4-dienyloxy)silane (60):**

*N*,*N*-Diisopropylethylamine (0.010 mL, 0.058 mmol), hexamethylditin (0.17

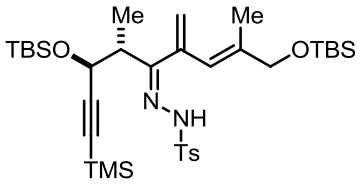
mL, 0.82 mmol), and $Pd(PPh_3)_4$ (0.017 g, 0.014 mmol) were added successively to a solution of diene **48** (0.100 g, 0.290 mmol) in 3 mL of benzene. The reaction was heated for 1 h at 80 °C, then was allowed to cool to ambient temperature and was stirred an additional 2 h. The reaction mixture was quenched with 3 mL saturated aqueous $CuSO_4$ and the resulting aqueous and organic portions were separated. The aqueous portion was extracted with hexanes (1x 3 mL) and the combined organics were dried ($Na_2SO_4$) and passed through a plug of Celite eluting with EtOAc. The volatiles were removed and purification of the resulting crude oil *via* column chromatography (1:5:100-1:0:25 EtOAc/toluene/hexanes) yielded 0.083 g (78%) of the title compound. IR (thin film): 3038, 2930, 2857, 1463, 1078 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.14 (dd, J = 1.2, 2.7 Hz, 1H), 5.68 (dd, J = 1.8, 3.3 Hz, 1H), 5.36 (dd, J = 1.2, 3.3 Hz, 1H), 4.07 (s, 2H), 1.66 (s, 3H), 0.92 (s, 9H), 0.15 (s, 9H), 0.07 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 151.3, 134.1, 128.8, 127.3, 68.6, 26.2, 18.6, 14.8, −5.0, −8.8; HRMS (*EI*) *m/z* calcd for ($M-CH_3^+$) $C_{14}H_{29}OSiSn$: 361.1010; found: 361.0994.




**(5*S*,6*S*,*E*)-2,2,3,3,6,10,13,13,14,14-Decamethyl-8-methylene-5-((trimethylsilyl)ethynyl)-4,12-dioxa-3,13-disilapentadec-9-en-7-one (61):**

Oxalyl chloride (0.27 mL, 3.2 mmol) was added to a solution of TBS ester **62b** (0.695 g, 1.62 mmol) in 15 mL benzene at ambient temperature. A catalytic amount of DMF (15 μL) was added to the reaction and the reaction mixture was stirred for 24 h and the volatiles were removed. The resulting crude oil was azeotroped with benzene (3x, 15 mL) and the resulting crude acid chloride was left under reduced pressure for 4 h. The acid chloride was then dissolved in 15 mL benzene and to the resulting solution was added $Pd_2(dba)_3$ (0.077 g, 0.084

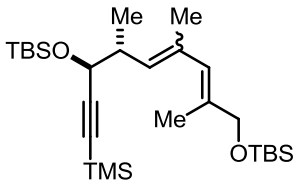
mmol), DIPEA (0.090 mL, 0.45 mmol), and organostannne **60** (0.714 g, 1.89 mmol), successively. The reaction stirred at ambient temperature for 30 min before the addition of another portion of $Pd_2(dba)_3$ (0.077 g, 0.084 mmol). The reaction stirred an additional 1 h before passing the crude reaction mixture through a plug of silica gel eluting with EtOAc and the volatiles were removed. Purification of the crude oil *via* column chromatography (0.5%-2.5% $Et_2O$/hexanes) yielded 0.622 g (75%) of the title compound. IR (thin film): 2931, 2858, 1680, 1463, 1252 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.24 (t, J = 1.2 Hz, 1H), 6.17 (s, 1H), 5.68 (s, 1H), 4.50 (d, J = 7.8 Hz, 1H), 4.12 (s, 2H), 3.41 (quintet, J = 6.9 Hz, 1H), 1.70 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.09-0.13 (m, 18H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 203.3, 144.7, 140.5, 125.4, 119.5, 106.3, 68.3, 66.1, 65.0, 48.7, 26.2, 26.0, 18.6, 18.5, 15.5, 15.4, 13.8, −0.1, −4.3, −4.9, −5.1; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_{27}H_{52}O_3Si_3$: 508.3224; found: 508.3226.




**(*Z*)-*N*'-((3*S*,4*R*,*E*)-3,9-Dihydroxy-4,8-dimethyl-6-methylene-1-(trimethylsilyl)non-7-en-1-yn-5-ylidene)-4-methylbenzenesulfonohydrazide (58):**

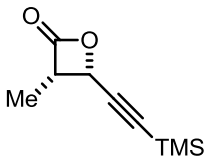
Trifluoroacetic acid (14.3 μL, 0.186 mmol) was added to a solution of ketone **61** (0.358 g, 0.690 mmol) and hydrazide (0.158 g, 0.840 mmol) and the resulting reaction mixture was allowed to stir for 1.5 h before quenching with $H_2O$. The organic phase was separated, dried ($MgSO_4$) and the crude product was purified via flash column chromatography (5% EtOAc/hexanes) to yield 110 mg (23.5%) of the title compound. 1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 6.9 Hz, 2H), 5.90 (s, 1H), 5.36 (s, 1H), 5.04 (s, 1H), 4.46 (d, J = 5.1 Hz, 1H), 3.98 (s,

2H), 2.65-2.54 (m, 1H), 2.41 (s, 3H), 1.15 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.79 (s, 9H), 0.10 (s, 6H), 0.09-0.07 (m, 12H).




**(2*E*,4*E*,6*R*,7*S*)-2,4,6-Trimethyl-9-(trimethylsilyl)nona-2,4-dien-8-yne-1,7-diol (63):**

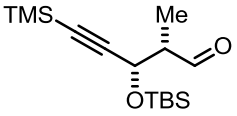
Catecholborane (0.042 mL, 0.148 mmol) was added to a solution of hydrazone **58** (0.050 mg, 0.074 mmol) in 1 mL $CHCl_3$ at 0 °C and the resulting solution stirred for 2 h. $NaOAc•3H_2O$ (0.150 mg, 0.740 mmol) and 1 mL $CHCl_3$ was added and the resulting suspension was refluxed for 14 h before being passed through a plug of $SiO_2$ eluting with $Et_2O$ (20 mL). The volatiles were removed in vacuo and the crude product was purified via flash column chromatography (5% EtOAc/hexanes) to yield 18 mg (51.0%) of the title compound. 1H NMR (300 MHz, $CDCl_3$) *mixture of* E:Z *isomers (~2:1)* δ 5.94 (s, 1H), 5.86 (s, 1H), 5.20-5.17 (m, 2H), 4.15-4.13 (m, 2H), 4.06-4.05 (m, 4H), 2.73-2.47 (m, 2H), 1.79 (s, 3H), 1.75 (s, 3H), 1.61 (s, 3H), 1.25 (s, 3H), 1.03 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.92-0.90 (m, 36H), 0.15-0.05 (m, 42H).




**(3*S*,4*S*)-3-Methyl-4-((trimethylsilyl)ethynyl)oxetan-2-one (42):**

Magnesium(II) chloride (1.90 g, 20.0 mmol) and TMS*Qd* (0.800 g, 2.00 mmol) were stirred in 20 mL $Et_2O$ for 5 min prior to the addition of 50 mL $CH_2Cl_2$ and the resulting suspension was cooled to −78 °C. To this suspension was added sequentially *i*$Pr_2Net$ (8.96 mL, 51.6 mmol), aldehyde **34** (2.52 g, 20.0 mmol) and propionyl chloride (3.44 mL, 39.2 mmol) dissolved in 10 mL of $CH_2Cl_2$ dropwise over 1 h via syringe pump. The reaction mixture was allowed to stir for 10 h before dilution with $Et_2O$ (60 mL) and

the entire reaction contents were passed through a plug of $SiO_2$ eluting with $Et_2O$. The volatiles were removed in vacuo and the crude product was purified via flash column chromatography (5-15% $Et_2O$/hexanes) to yield 3.35 g (92.0%) of the title compound. $[\alpha]_D$ +12.2 (*c* 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.12 (d, J = 6.6 Hz, 1H), 3.91-3.81 (dq, J = 6.6, 7.8 Hz, 1H), 1.43 (d, J = 7.5, 3H), 0.21 (s, 1H).

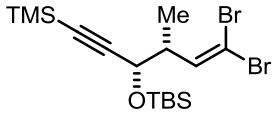



**(2*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-(trimethylsilyl)pent-4-ynal (68):**

KHMDS (0.11 mL, 0.060 mmol) was added to ethanethiol (50.2 μL, 0.660 mmol) in 5.5 mL of THF at 0 °C and was stirred for 5 min prior to the addition of β-lactone **42** (100 mg, 0.550 mmol). The reaction was warmed to ambient temperature and was stirred for 2 h before being cooled to −78 °C. 2,6-Lutidine (0.130 mL, 1.10 mmol) was added to the reaction mixture followed by TBSOTf (0.22 mL, 0.94 mmol) and the reaction was stirred for 1 h before being quenched with $H_2O$ (4 mL). The emulsion was warmed to ambient temperature and the mixture was extracted with $Et_2O$ (3x 5 mL). The organic portions were combined and washed with 1 M $NaHSO_4$ (aq), dried ($MgSO_4$), and the volatiles were removed *in vacuo* to yield 194 mg of the intermediate thioester **xx** that was used without further purification in the subsequent reaction.

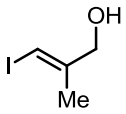
(*i*-Bu)$_2$AlH (1.1 mL, 1.1 mmol, 1 M in THF) was added to the crude thioester (197 mg, 0.550 mmol) in $CH_2Cl_2$ at −78 °C over 30 min and the resulting solution was stirred an additional 30 min. The reaction mixture was quenched with excess MeOH (6.5 mL) dropwise over 15 min prior to the addition of $H_2O$ (10 mL). The mixture was extracted with $CH_2Cl_2$ (3x 10 mL) and the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* flash chromatography (2% EtOAc/hexanes) yielded 123 mg (76% over 2 steps) of the title

compound. $[\alpha]_D$ −45.6 (*c* 1.10, $CHCl_3$); IR (thin film): 2958, 2933, 2896, 2712, 2175, 1730, 1463, 1252, 1143, 1086, 1031 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.77 (d, J = 1.2 Hz, 1H), 4.70 (d, J = 4.5 Hz, 1H), 2.48-2.55 (m, 1H), 1.18 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.16 (s, 6H), 0.15 (s, 3H), 0.11 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 203.7, 104.7, 91.8, 63.8, 52.6, 25.9, 19.0, 9.3, −0.1, −4.2, −4.9; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_{15}H_{30}O_2Si_2$: 298.1784; found: 298.1770.



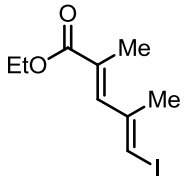

**(3*S*,4*R*)-6,6-Dibromo-3-*tert*-butyldimethylsilyloxy-4-methyl-1-(trimethylsilyl)hex-5-en-1-yne (64):**

Triphenylphosphine (12.1 g, 46.3 mmol) was added at 0 °C to a solution of carbontetrabromide (7.65 g, 23.2 mmol) in 42 mL of $CH_2Cl_2$. Aldehyde **68** (3.51 g, 11.6 mmol) as a solution in 116 mL $CH_2Cl_2$ was added to the resulting reaction mixture. The reaction mixture was warmed to room temperature and stirred for 20 min before being quenched with $H_20$ (350 mL). The organic and aqueous portions were separated and the aqueous portion was extracted with $CH_2Cl_2$ (2x 350 mL). The organics were combined, dried ($MgSO_4$), and the volatiles were removed *in vacuo*. Purification *via* flash chromatography (4% EtOAc/hexanes) afforded 4.22 g (80%) of the title compound. $[\alpha]_D$ −39.6 (*c* 1.00, $CHCl_3$); IR (thin film): 2957, 2931, 2897, 2858, 2174, 1722, 1621, 1462, 1252, 1142, 1103, 1026 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.36 (d, J = 9.3 Hz, 1H), 4.30 (d, J = 5.1 Hz, 1H), 2.70 (ddq, J = 5.1, 6.0, 9.6 Hz, 1H), 1.09 (d, J = 6.6 Hz, 3H), 0.91 (s, 9H), 0.17 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 140.5, 105.4, 90.8, 89.1, 66.0, 45.4, 26.0, 18.5, 14.3, −0.0, −4.3, −4.8; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_{15}H_{27}O_1Si_2Br_2$: 436.9967; found: 436.9965.



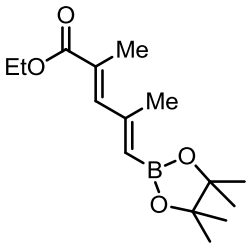
**(*E*)-3-Iodo-2-methylprop-2-en-1-ol (69):**

Trimethylaluminum (77.4 mL, 154 mmol, 2 M in hexanes) was added to $Cp_2ZrCl_2$ in 100 mL dichloroethane at 0 °C and propargyl alcohol (3.00 mL, 51.5 mmol) was added to the resulting solution. The reaction mixture was stirred for 7 h at ambient temperature before cooling to −42 °C and addition of iodine (19.62 g, 77.40 mmol) dissolved in THF (50 mL). The reaction mixture stirred for 20 min prior to quenching with 80 mL saturated aqueous $K_2CO_3$ and 120 mL saturated aqueous Rochelle's salt and the emulsion was allowed to stir vigorously overnight before extracting with $Et_2O$ (3x 200 mL). The organic portions were combined, dried ($MgSO_4$) and the crude product was purified via flash column chromatography (30% EtOAc/hexanes) to yield 5.58 g (55.0%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.28 (s, 1H), 4.12 (s, 2H), 1.84 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 147.4, 77.6, 67.4, 21.6.



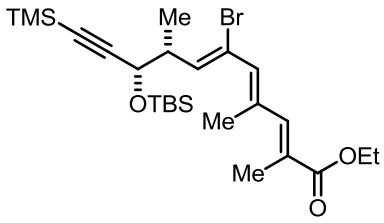
**(2*E*,4*E*)-Ethyl-5-iodo-2,4-dimethylpenta-2,4-dienoate (72):**

(Carbethoxyethylidene)triphenylphosphorane (11.7 g, 32.2 mmol) was added to a suspension of alcohol **69** (5.27 g, 26.6 mmol) and $MnO_2$ (23.5 g, 268 mmol) in 526 mL $CH_2Cl_2$ at ambient temperature. The resulting heterogeneous mixture was stirred for 24 h before being passed through a plug of $SiO_2$ eluting with EtOAc/hexanes (1:5, 300 mL). Purification *via* flash chromatography (10% EtOAc/hexanes) afforded 6.18 g (83%) of the title compound as a yellow oil. IR (thin film): 3065, 2980, 1709, 1244, 1114, 1030 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.40 (s, 1H), 4.22 (q, J = 6.9 Hz, 2H), 2.01 (s, 3H), 1.95 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.4, 143.9, 138.8, 128.5, 85.5, 61.2, 24.8, 14.5, 14.4; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_9H_{13}O_2I$: 279.9960; found: 279.9954.



**(2*E*,4*E*)-Ethyl 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate (65):**

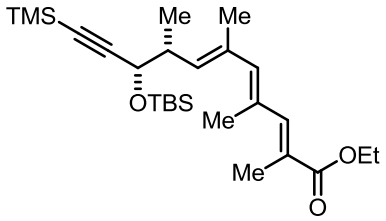
Vinyl iodide **72** (6.30 g, 22.7 mmol) as a solution in 77 mL DMSO was added to a nitrogen flushed flask containing $(Bpin)_2$ (16.2 g, 68.0 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (548 mg, 0.630 mmol), and KOAc (6.65 g, 68.0 mmol). The resulting suspension was warmed to 85 °C and was stirred at that temperature for 20 min. The mixture was cooled to ambient temperature, diluted with $Et_2O$ (500 mL), and the organic solution was washed with $H_2O$ (2x 500 mL). The organics were dried ($MgSO_4$) and the volatiles were removed *in vacuo*. Purification *via* flash chromatrography (10% EtOAc/hexanes) afforded 6.1 g (97%) of the title compound as a yellow oil. IR (thin film): 2979, 2934, 1708, 1623, 1595, 1443, 1327, 1242, 1143, 1034, 968 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 1H), 5.38 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.12 (s, 3H), 1.98 (s, 3H), 1.28-1.32 (m, 15H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 169.0, 154.9, 143.2, 128.4, 83.3, 61.1, 25.1, 21.5, 14.5, 14.3; HRMS (*EI*) *m/z* calcd for ($M^+$) $C_{15}H_{25}BO_4$: 280.1846; found: 280.1838.



**(2*E*,4*E*,6*Z*,8*R*,9*S*)-Ethyl 6-bromo-9-(tert-butyldimethylsilyloxy)-2,4,8-trimethyl-11-(trimethylsilyl)undeca-2,4,6-trien-10-ynoate (73):**

$Pd(PPh_3)_4$ (880 mg, 0.760 mmol) was added to a solution of dibromide **64** (3.45 g, 7.60 mmol) and vinyl borane **65** (6.41 g, 22.9 mmol) in 39 mL THF/$H_2O$ (3:1) at ambient temperature. The suspension stirred for 5 min, TlOEt (1.00 mL, 13.5 mmol) was added, and the suspension was stirred an additional 40 min. The mixture was diluted with $Et_2O$ (~75 mL) and quenched with 1 M $NaHSO_4$ (~60 mL) before being passed through a plug of celite. The resulting eluent was

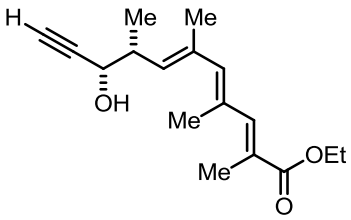
then washed with brine (60 mL), the organics were dried ($MgSO_4$), and the volatiles were removed *in vacuo*. Purification of the crude product *via* flash chromatography (10:1:89 toluene/EtOAc/hexanes to 5% EtOAc/Hexanes) yielded 2.65 g (66.3%) of the title compound as a single regioisomer by $^1$H-NMR. $[\alpha]_D$ −22.2 (*c* 1.03, $CHCl_3$); IR (thin film): 2958, 2931, 2899, 2858, 2173, 1711, 1630, 1462, 1366, 1252, 1107, 1022, 934 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.09 (d, J = 0.9 Hz, 1H), 5.81 (dd, J = 1.2, 9 Hz, 1H), 4.32 (d, J = 5.1 Hz, 1H), 4.21 (q, J = 6.9 Hz, 2H), 2.93 (ddq, J = 5.4, 6.6, 9 Hz, 1H), 2.03 (d, J = 1.2 Hz, 3H), 2.01 (d, J = 1.2, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.1 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.15 (s, 6H), 0.14 (s, 3H), 0.11 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.9, 141.4, 135.8, 135.5, 133.9, 129.8, 128.5, 120.7, 106.6, 90.5, 66.8, 61.1, 44.3, 26.0, 18.5, 15.2, 14.5, 14.4, 0.0, −4.2, −4.8; HRMS (*EI*) *m/z* calcd for $(M-CH_3)^+$ $C_{24}H_{40}O_3Si_2Br$: 511.1699; found: 511.1690.




**(2*E*,4*E*,6*E*,8*R*,9*S*)-Ethyl 9-(*tert*-butyldimethylsilyloxy)-2,4,6,8-tetramethyl-11-(trimethylsilyl)undeca-2,4,6-trien-10-ynoate (74):**

Dimethyl zinc (2.27 mL, 4.54 mmol, 2 M in toluene) was added to a solution of palladium bistributylphosphine (138 mg, 0.270 mmol) in 15 mL THF at 0 °C and the resulting mixture was stirred for 5 min. Triene **73** (1.91 g, 3.63 mmol) as a solution in 8 mL THF was added to the reaction mixture at 0 °C and the resulting solution was warmed to ambient temperature and stirred for 45 min. The reaction was then quenched with $H_2O$ (40 mL) and the resulting emulsion was extracted with $Et_2O$ (3x 40 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (40 mL) followed by brine (40 mL), dried ($MgSO_4$), and the volatiles were removed *in vacuo*. The crude product was purified *via* flash chromatography

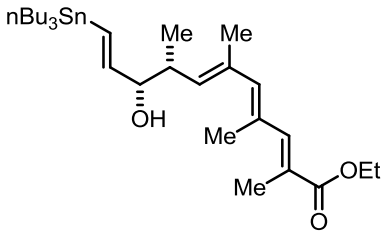
(10% EtOAc/Hexanes) to yield 1.5 g (90%) of the title compound as a ~6.6:1 mixture of olefin isomers as detected by $^1$H-NMR (calculated from δ 1.79 to 1.86). $[\alpha]_D$ +91.2 (*c* 1.01, $CHCl_3$); IR (thin film): 2958, 2931, 2857, 2172, 1708, 1614, 1462, 1388, 1366, 1251, 1208, 1112, 1023, 939, 842 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.01 (s, 1H), 5.32 (d, J = 9.9 Hz, 1H), 4.26-4.16 (m, 3H), 2.76-2.68 (m, 1H), 2.07 (d, J = 1.2 Hz, 3H), 2.03 (d, J = 1.5 Hz, 3H), 1.79 (d, J = 0.9 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 12H), 0.12 (s, 3H); *resonances for the minor diastereomers were observable at:* δ 6.41 (s, 0.15H), 5.81 (dd, J = 1.2, 9 Hz, 0.14H), 4.35-4.32 (m, 0.28H), 2.55-2.60 (m, 0.13H), 2.07 (d, J = 1.2 Hz, 0.54H), 1.86 (s, 3H), 1.12 (d, J = 6.9 Hz, 0.40H), 0.97 (d, J = 6.9 Hz, 0.69H), 0.19 (s, 0.94H), 0.16 (s, 0.62H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.4, 144.0, 139.1, 133.7, 132.9, 132.1, 126.1, 107.0, 89.6, 67.8, 60.8, 40.1, 26.0, 18.6, 18.5, 17.7, 16.7, 14.6, 14.3, 0.0, −4.2, −4.8; HRMS (*Q-TOF*) *m/z* calcd for $(M+Na)^+$ $C_{26}H_{46}O_3NaSi_2$: 485.2883; found: 485.2836.




**(2*E*,4*E*,6*E*,8*R*,9*S*)-Ethyl 9-hydroxy-2,4,6,8-tetramethylundeca-2,4,6-trien-10-ynoate (75):**

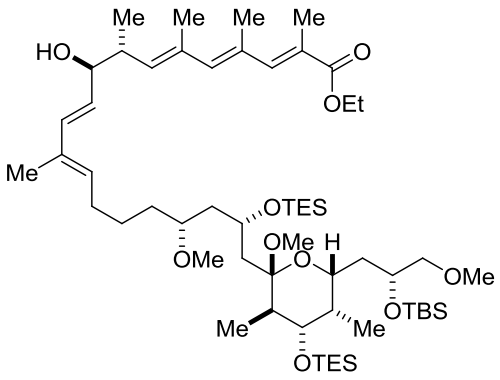
TBAF (0.86 mL, 0.86 mmol, 1 M in THF) was added to a solution of triene **74** (0.100 g, 0.220 mmol) in 4.3 mL THF at 0 °C and the resulting reaction mixture was stirred for 60 min at that temperature. The reaction mixture was allowed to come to ambient temperature and was stirred an additional 20 min before being quenched with a saturated aqueous $NH_4Cl$ solution (10 mL). The resulting emulsion was extracted with $Et_2O$ (3x 10 mL) and the organic portions were combined and dried ($MgSO_4$). The crude product was purified *via* flash chromatography (15-20% EtOAc/Hexanes) to yield 0.873 g (83%) of the title compound. $[\alpha]_D$ +40.8 (*c* 1.00, $CHCl_3$); IR (thin film): 3455, 3300, 2977, 1700, 1610, 1448, 1369, 1254,

1115, 1029 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.03 (s, 1H), 5.42 (dd, J = 9.9, 1.2 Hz, 1H), 4.3 (broad s, 1H), 4.21 (q, J = 7.2, 2H), 2.85 (ddq, J = Hz, 1H), 2.46 (d, J = 2.1 Hz, 1H), 2.03 (d, J = 1.5 Hz, 3H), 2.01 (d, J = 1.2 Hz, 3H), 1.96 (d, J = 6.9 Hz, 1H), 1.83 (d, J = 1.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 169.3, 143.7, 136.1, 135.1, 132.9, 131.9, 126.4, 88.6, 74.2, 66.8, 60.9, 38.3, 18.6, 17.7, 16.3, 14.5, 14.4; HRMS (*Q-TOF*) *m/z* calcd for $(M+Na)^+$ $C_{17}H_{24}O_3Na$: 299.1623; found: 299.1601.




**(2*E*,4*E*,6*E*,8*R*,9*S*,10*E*)-Ethyl 9-hydroxy-2,4,6,8-tetramethyl-11-(tributylstannyl)undeca-2,4,6,10-tetraenoate (29):** Tributyltin hydride (0.680 mL, 2.54 mmol) was added to a solution of alkyne **75** (248 mg, 0.899 mmol) and $PdCl_2(PPh_3)_2$ (22 mg, 0.029 mmol) dissolved in 2.95 mL of THF at 0 °C. The resulting reaction solution was allowed to come to ambient temperature and was stirred for 30 min. The volatiles were removed and the crude reaction product was loaded directly onto a flash column and eluted (10% EtOAc/Hexanes) to yield 0.346 g (68%) of the title compound and 0.101 g (20%) of the undesired regioisomer (3.4:1). $[\alpha]_D$ +73.6 (*c* 1.03, $CHCl_3$); IR (thin film): 3479, 2957, 2926, 2871, 1705, 1705, 1609, 1459, 1370, 1253, 1208, 1174, 1114, 1019 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.18 (dd, J = 1.2, 19.2 Hz, 1H), 6.05 (dd, J = 4.8, 19.8 Hz, 1H), 6.01 (s, 1H), 5.28 (d, J = 10.2 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.97 (app q, J = 6.0 Hz, 1H), 2.72-2.619 (m, 1H), 2.03 (s, 3H), 1.98 (s, 3H), 1.80 (s, 3H), 1.61 (d, J = 5.4 Hz, 1H), 1.51-1.45 (m, 6H), 1.32-1.28 (m, 12H), 1.05 (d, J = 7.2 Hz, 3H), 0.88 (m, 12H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 168.3, 148.9, 143.9, 139.0, 134.0, 133.1, 132.0, 129.0, 126.2, 60.8, 39.4, 29.3, 27.5, 18.6, 17.5,

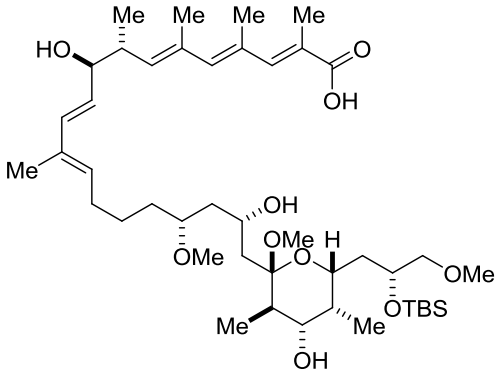
16.7, 14.5, 14.3, 13.7, 8.7; HRMS (*Q-TOF*) *m/z* calcd for $(M+Na)^+$ $C_{29}H_{52}O_3NaSn$: 591.2836; found: 591.2813.




**(2*E*,4*E*,6*E*,8*R*,9*R*,10*E*,12*E*,17*R*,19*S*)-ethyl 20-((2*S*,3*R*,4*S*,5*S*,6*R*)-6-((*R*)-2-(*tert*-butyldimethylsilyloxy)-3-methoxypropyl)-2-methoxy-3,5-dimethyl-4-(triethylsilyloxy)tetrahydro-2H-pyran-2-yl)-9-hydroxy-17-methoxy-2,4,6,8,12-pentamethyl-19-(triethylsilyloxy)icosa-2,4,6,10,12-pentaenoate**

**(29b):** To a flame dried vessel was added 0.151 g of vinyl stannane **29** (0.266 mmol, 4 equiv), and 0.060 g of vinyl iodide **30** (0.066 mmol, 1.0 equiv). The mixture was subjected to high vacuum for one hour before refilling the vessel with $N_{2(g)}$. To this was added 1.3 mL of degassed DMF at ambient temperature, before adding 0.152 g of $Ph_2PO_2NBu_4$ (0.332 mmol, 5 equiv). The vessel was opened to atmosphere momentarily to add 1.7 mg of $Pd_2Cl_2(MeCN)_2$ (0.0066 mmol, 0.1 equiv). The reaction mixture immediately turned black. The reaction was covered in foil and stirred at ambient temperature for 15 hours before being quenched with 13.0 mL of a 1:1 solution of $Et_2O$ to hexanes. This heterogeneous mixture was passed through a plug of celite, rinsing with more of the same 1:1 solution. The yellowish organic eluent was washed with brine (3 x 20 mL) before being dried ($Na_2SO_4$), and concentrated. The crude yellow oil was purified by flash chromatography (10 % EtOAc/Hex) affording 48 mg (75%) of the title compound as a 12:1 mixture of isomers as assayed by 500 MHz $^1$H NMR. $[\alpha]_D^{22}$ +54.7 (*c* 0.19, $CHCl_3$). IR (thin film): 2925, 1705, 1460, 1376, 1250, 1068, 1004 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.22 (d, J = 15.5 Hz, 1H), 6.01 (s, 1H), 5.57 (dd, J = 15.5, 7.0 Hz, 1H), 5.47 (t, J = 7.0

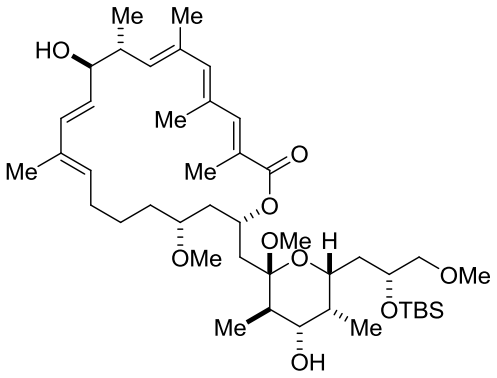
Hz, 1H), 5.27 (d, J = 10.0 Hz, 1H), 4.18 (q, J = 5.0 Hz, 2H), 4.05-4.02 (m, 1H), 3.98-3.94 (m, 1H), 3.93-3.88 (m, 1H), 3.83-3.77 (m, 2H), 3.38-3.29 (m, 5H), 3.26-3.22 (m, 4H), 3.10 (s, 3H), 2.70-2.65 (m, 1H), 2.16-2.10 (m, 2H), 2.02 (s, 3H), 1.96 (s, 3H), 1.92-1.86 (m, 1H), 1.79 (s, 3H), 1.76-1.70 (m, 4H), 1.66-1.61 (m, 3H), 1.50-1.44 (m, 2H), 1.42-1.32 (m, 4H), 1.31-1.24 (m, 5H), 1.05 (d, J = 6.5 Hz, 3H), 0.98-0.90 (m, 21H), 0.88 (s, 9H), 0.86 (d, J = 7.0 Hz, 3H), 0.63-0.57 (m, 12H), 0.06 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.3, 143.6, 138.9, 136.5, 133.7, 133.4, 132.9 (2C), 131.8, 136.9, 125.9, 101.7, 77.8, 73.0, 70.2, 68.2, 66.7, 60.6, 58.7, 55.6, 47.0, 43.0, 40.0, 39.4, 36.9, 32.8, 28.4, 27.8, 26.8, 25.9 (3C), 24.5, 18.2, 17.5, 17.3, 16.5, 14.3, 14.1, 13.6, 12.5, 12.3, 7.0 (3C), 6.9 (3C), 5.4, 5.31 (3C), 5.3 (3C), −3.8, −4.7; HRMS (ES) *m/z* calcd for $C_{58}H_{110}O_{10}NaSi_3$ $(M + Na)^+$: 1073.7305; found: 1073.7268.




**(2*E*,4*E*,6*E*,8*R*,9*R*,10*E*,12*E*,17*R*,19*S*)-20-((2*S*,3*R*,4*S*,5*R*,6*R*)-6-((*R*)-2-(*tert*-butyldimethylsilyloxy)-3-methoxypropyl)-4-hydroxy-2-methoxy-3,5-dimethyltetrahydro-2H-pyran-2-yl)-9,19-dihydroxy-17-methoxy-2,4,6,8,12-pentamethylicosa-2,4,6,10,12-pentaenoic acid (77):** Lithium hydroxide monohydrate (36.8 mg, 0.876 mmol) was added to a solution of ethyl ester **29b** (91.9 mg, 0.087 mmol) in 1.7 mL THF:MeOH:$H_2O$ (6:2:1) and the resulting heterogeneous mixture was stirred for 48 h at ambient temperature. The reaction was quenched with 2 mL saturated aqueous $NH_4Cl$ and the resulting emulsion was extracted with EtOAc (5x 5 mL). The resulting organic portions were combined, dried ($MgSO_4$), and the volatiles removed *in vacuo*. Purification *via* flash chromatography (5-8% MeOH/$CH_2Cl_2$) yielded 7 mg (10%) of the title

compound and 52 mg (~68%) of a mixture of variously $SiEt_3$ protected products that was carried on to the title compound in the following reaction.

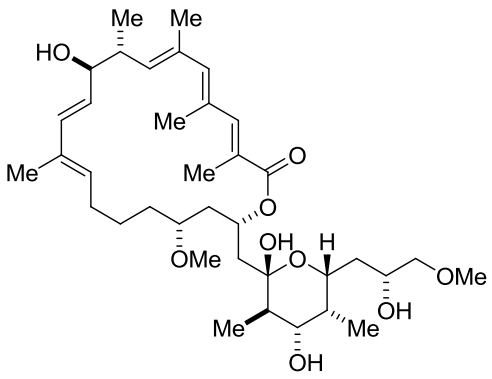
**Deprotection**: The mixture of protected seco-acid (52 mg, 0.0572 mmol, 1.0 equiv) was added to 8.34 mL of a 1:1 mixture of MeOH and $CH_2Cl_2$. The solution was cooled to −15° C in a MeOH and ice bath. 4.3µL (0.0572 mmol, 1.0 equiv) of $CF_3CO_2H$ dissolved in 0.6 mL of $CH_2Cl_2$ and added dropwise. The solution was maintained at −15° C for 30 minutes before being quenched with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), the combined organic layers were dried over $Na_2SO_4$, concentrated, and purified by flash column (5% MeOH/$CH_2Cl_2$), to yield 26.5 mg (58%) of the seco-acid which was combined with the purified material from the previous step, giving an overall yield of 33.5 mg (48% over two steps). $[\alpha]_D$ +58.8 (*c* 0.82, $CHCl_3$); IR (thin film): 3420, 2928, 1683, 1459, 1250, 1067, 834, 776; $^1$H NMR (600 MHz, $CDCl_3$) δ 6.22 (d, J = 15.6 Hz, 1H), 6.07 (s, 1H), 5.57 (dd, J = 6.6, 15 Hz, 1H), 5.47 (t, J = 7.2 Hz, 1H), 5.27 (d, J = 9.6 Hz, 1H), 4.13 (m, 1H), 4.04 (t, J = 6.6 Hz, 1H), 3.94-3.88 (m, 2H), 3.81 (dd, J = 4.2, 10.8 Hz, 1H), 3.48-3.44 (m, 1H), 3.35 (s, 3H), 3.3 (s, 3H), 3.17 (s, 3H), 2.71-2.67 (m, 1H), 2.12-2.15 (m, 2H), 1.98 (s, 3H), 1.93-1.87 (m, 3H), 1.86-1.83 (m, 2H), 1.82 (s, 3H), 1.72 (s, 3H), 1.65-1.60 (m, 4H), 1.50-1.41 (m, 4H), 1.37-1.32 (m, 2H), 1.31-1.27 (m, 2H), 1.06 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H), 0.93-0.90 (m, 3H), 0.89-0.88 (m, 9H), 0.06 (s, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 173.1, 145.9, 140.2, 136.5, 134.3, 133.1, 133.0, 132.9, 131.8, 127.2, 124.6, 102.2, 78.8, 77.6, 72.4, 69.8, 68.4, 66.0, 58.8, 56.8, 47.9, 42.2, 40.8, 39.5, 39.4, 39.3, 38.9, 38.5, 32.9, 28.3, 27.8, 27.0, 26.8, 25.2, 18.2, 18.2, 17.5, 17.3, 16.4, 16.6, 13.9, 13.7, 13.6, 12.5, 11.5, 6.7, 5.1, 5.0, −3.9, −4.7; HRMS (*Q-TOF*) *m/z* calcd for $(M+Na)^+$ $C_{44}H_{78}O_{10}NaSi$: 817.5262; found: 817.5232.



**(3*E*,5*E*,7*E*,9*R*,10*R*,11*E*,13*E*,18*R*,20*S*)-20-(((2*S*,3*R*,4*S*,5*R*,6*R*)-6-((*R*)-2-(*tert*-butyldimethylsilyloxy)-3-methoxypropyl)-4-hydroxy-2-methoxy-3,5-dimethyltetrahydro-2H-pyran-2-yl)methyl)-10-hydroxy-18-methoxy-3,5,7,9,13-pentamethyloxacycloicosa-3,5,7,11,13-pentaen-2-one**

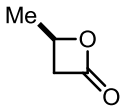
**(77b):** To an ambient temperature solution of 25.0 mg of seco-acid **77** (0.0314 mmol, 1.0 equiv) in 7.44 mL of THF was added 0.174 mL of $NEt_3$ (1.25 mmol, 4.0 equiv), followed by 19.5 µL of 2,4,6-trichlorobenzoyl chloride (0.125 mmol, 40.0 equiv) dropwise. The reaction was stirred in a foil-covered flask at ambient temperature for 15 hours, whereupon it was diluted with 7.44 mL of toluene, and added to 930 mL of toluene containing 0.767 g of DMAP (6.28 mmol, 200 equiv). The addition took place via syringe pump over 1 hour [followed by two rinses of toluene (1.0 and 0.5 mL) added over 20 and 10 minutes respectively]. The reaction was then allowed to stir at ambient temperature for 24 hours, covered in foil, before being concentrated to approximately 200 mL via rotovap. The toluene solution was then quenched with $NH_4Cl$ (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried with $Na_2SO_4$, filtered, and concentrated. The crude mixture was purified by flash column chromatography on IATRO beads with 2% MeOH in $CH_2Cl_2$ yielding 13.9 mg (57%) of the desired lactone based on HMQC, HMBC, and cosy correlations. The reaction also yielded 2.0 mg (8%) of a minor product believed to be macrolactonization on the pyran oxygen. $[\alpha]_D^{21}$ +10.2 (*c* 0.23, $CHCl_3$). IR (thin film): 3409, 2925, 1693, 1460, 1384, 1248, 1096 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 4.2 Hz, 1H), 7.11 (s, 1H), 6.08 (app. d, J = 15 Hz, 1H), 6.07 (app. s, 1H), 5.51 (app. t, J = 7.2 Hz, 1H), 5.34 (dd, J = 15.6, 8.4 Hz, 1H), 5.13 (d, J = 9.6 Hz, 1H), 5.04

(app. t, J = 10.2 Hz, 1H), 3.95-3.89 (m, 2H), 3.86-3.81 (m, 2H), 3.37 (dd, J = 10.2, 4.2 Hz, 1H), 3.35 (s, 3H), 3.33-3.28 (m, 1H), 3.27 (s, 3H), 3.12 (s, 3H), 2.92 (br. q, J = 7.2 Hz, 1H), 2.55-2.50 (m, 1H), 2.27-2.21 (m, 1H), 2.12 (s, 3H), 2.10 (app. d, J = 5.4 Hz, 1H), 2.07 (s, 3H), 2.10-1.90 (m, 3H), 1.88 (s, 3H), 1.86-1.80 (m, 2H), 1.78-1.72 (m, 2H), 1.67-1.63 (m, 4H), 1.46 (ddd, J = 14.4, 7.2, 3.6 Hz, 2H), 1.39 (app. d, J = 5.4 Hz, 1H), 1.35-1.25 (m, 2H), 1.14 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.7, 145.1, 144.5, 140.3, 137.3, 133.0, 132.8, 132.1, 131.8, 128.3, 128.2, 127.1, 123.8, 101.5, 79.7, 79.0, 77.8, 72.4, 70.6, 70.0, 68.5, 58.8, 57.3, 47.2, 41.3, 39.5, 38.9, 38.4, 37.0, 33.5, 29.7, 28.0, 26.7, 25.9 (3C), 18.2, 17.5, 17.3, 16.3, 13.7, 12.0, 11.3, 4.9, −3.8, −4.7; HRMS (ES) *m/z* calcd for $C_{44}H_{76}O_9SiNa$ $(M + Na)^+$: 799.5156; found: 799.5152.




**(3*E*,5*E*,7*E*,9*R*,10*R*,11*E*,13*E*,18*R*,20*S*)-20-(((2*S*,3*R*,4*S*,5*R*,6*R*)-2,4-dihydroxy-6-((*R*)-2-hydroxy-3-methoxypropyl)-3,5-dimethyltetrahydro-2H-pyran-2-yl)methyl)-10-hydroxy-18-methoxy-3,5,7,9,13-pentamethyloxacycloicosa-3,5,7,11,13-pentaen-2-one (3b):** Protected aglycone **77b** (7.5 mg; 0.00965 mmol, 1.0 equiv) was dissolved in 1.37 mL of acetonitrile and cooled to −35° C in a refrigerator. To this solution was added ~34.7 mg of $H_2SiF_6$ (~154 mg of a 20-25% solution in $H_2O$; 0.2413 mmol, 25 equiv.; measured as 10 drops from a 20 gauge needle). The solution remained in the refrigerator for 46 hours before being quenched at −35 °C with 0.200 mL of $NEt_3$. The resulting mixture was allowed to sit for 30 minutes at −35° C before quenching with sat. aq. $NaHCO_3$ (3 mL) and extracting with EtOAc (5 x 5.0 mL). The organic layer was combined and dried over

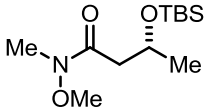
$Na_2SO_4$, before being purified by flash chromatography (5% MeOH/$CH_2Cl_2$ on IATRO beads), yielding 4.0 mg (64%) of the aglycone as a white solid in 90.6% purity as determined by HPLC analysis (20% isopropanol/hexane, 1ml/min). $[\alpha]_D^{19}$ + 56.1 (*c* 0.15, $CHCl_3$). IR (thin film): 3385, 2924, 1670, 1457, 1250, 1095 $cm^{-1}$; $^1H$ NMR (700 MHz, MeOD) δ 7.16 (s, 1H), 6.10-6.08 (m, 2H), 5.54 (dd, J = 9.1, 5.6 Hz, 1H), 5.31 (dd, J = 16.1, 9.1 Hz, 1H), 5.18-5.15 (m, 2H), 4.18 (broad d, J = 10.5 Hz, 1H), 3.84-3.81 (m, 1H), 3.78-3.75 (m, 2H), 3.38-3.34 (m, 5H), 3.29-3.25 (m, 4H), 2.91 (broad q, J = 7.0 Hz, 1H), 2.48-2.43 (m, 1H), 2.33-2.28 (m, 1H), 2.13 (s, 3H), 2.12-2.09 (m, 1H), 2.06 (s, 3H), 1.98-1.93 (m, 2H), 1.88 (s, 3H), 1.82-1.74 (m, 5H), 1.73-1.68 (m, 2H), 1.65 (s, 3H), 1.62-1.57 (m, 1H), 1.38-1.31 (m, 5H), 1.13 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H); $^{13}C$ NMR (175 MHz, MeOD) δ 170.9, 147.1, 146.0, 142.5, 137.9, 134.4, 133.4, 133.0, 132.9, 129.4, 124.7, 100.2, 80.9, 80.4, 78.6, 73.6, 71.3, 68.4, 68.3, 59.3, 57.4, 46.0, 43.0, 41.0, 40.8, 38.6, 38.1, 34.3, 28.8, 28.0, 17.9, 17.8, 16.7, 14.1, 12.4, 12.2, 5.6; HRMS (ES) *m/z* calcd for $C_{37}H_{60}O_9Na$ $(M + Na)^+$: 671.4135; found: 671.4108.




**(*R*)-4-methyloxetan-2-one (89):**

Trimethylsilyl quinidine (0.500 g, 1.26 mmol) dissolved in 25 mL $CH_2Cl_2$ was added to $LiClO_4$ (0.400 g, 3.77 mmol) in 12.5 $Et_2O$ and the resulting suspension was cooled to −78 °C before sequential addition of *i*$Pr_2Net$ (5.50 mL, 31.6 mmol) and acetaldehyde (0.950 g, 17.0 mmol). To the solution was added acetyl chloride (1.78 mL, 25.2 mmol) dissolved in 6.25 mL $CH_2Cl_2$ dropwise over 3 h via syringe pump and the resulting reaction mixture was stirred for 14 h before dilution with $Et_2O$ (10 mL) and the entire contents was passed through a plug of $SiO_2$ eluting with $Et_2O$ to yield 2.95 g (88%) of the crude title compound, used in the next step

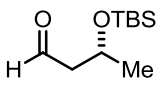
without further purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 4.69 (app q, J = 5.7 Hz, 1H), 3.57 (dd, J = 5.7, 16.2 Hz, 1H), 3.06 (dd, J = 4.2, 16.2 Hz, 1H), 1.57 (d, J = 6.0 Hz, 3H).




**(*R*)-3-Hydroxy-*N*-methoxy-*N*-methylbutanamide (89b):**

Dimethylaluminum chloride (33.9 mL, 33.9 mmol, 1 M in hexanes) was added to *N*,*O*-dimethylhydroxylamine hydrochloride (3.39 g, 34.9 mmol) in 121 mL $CH_2Cl_2$ and the resulting mixture was stirred for 30 min before cooling to −45 °C. Crude β-lactone **89** (1.46 g, 17.0 mmol) was added and the resulting reaction mixture was allowed to stir for ~14h before quenching with Rochelle's salt (150 mL) and extracting with $CH_2Cl_2$ (3x 150 mL). The combined organic portions were dried ($MgSO_4$) and the volatiles removed to obtain 2.50 g of the crude alcohol, used in the next step without further purification.

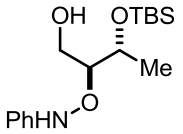
To a −78 °C solution of 2,6-lutidine (5.40 mL, 46.4 mmol) and the crude alcohol (2.30 g, 15.64 mmol) in 32 mL $CH_2Cl_2$ was added TBSOTf (4.70 mL, 20.5 mmol) and the resulting reaction mixture was allowed to stir for 3 h before quenching with saturated aqueous $NaHCO_3$ (30 mL) and extracting with $CH_2Cl_2$ (3x 30 mL). The combined organic portions were washed with 1 M aqueous $NaHSO_4$ (90 mL), dried ($MgSO_4$), and the resulting crude product purified via flash column chromatography (30% EtOAc/hexanes) to yield 2.95 g (66% over 3 steps) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 4.35 (app sextet, J = 6.3 Hz, 1H), 3.70 (s, 3H), 3.17 (s, 3H), 2.76 (dd, J = 6.9, 14.1 Hz, 1H), 2.35 (dd, J = 5.4, 14.7 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).




**(*R*)-3-((tert-Butyldimethylsilyl)oxy)butanal (90):**

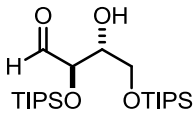
To a −78 °C solution of weinreb amide **89b** (2.95 g, 11.3 mmol) was added

*i*$Pr_2AlH$ (13.6 mL, 13.6 mmol, 1 M in hexanes) and the resulting reaction mixture was allowed to stir for 20 min before quenching with saturated aqueous Rochelle's salt (100 mL). The emulsion was allowed to stir vigorously over 2 h and the resulting mixture was extracted with $Et_2O$ (3x 100 mL). The combined organic portions were died ($MgSO_4$) and the crude product was purified via flash column chromatography ($NEt_3$ treated $SiO_2$, 5% EtOAc/hexanes) to yield 2.02 g (88%) of the title compound. $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.80 (dd, J = 2.1, 2.7 Hz, 1H), 4.35 (app sextet, J = 6.3 Hz, 1H), 2.55 (ddd, J = 3.0, 6.9, 15.6 Hz, 1H), 2.46 (ddd, J = 2.1, 4.8, 15.6 Hz, 1H), 1.23 (d, J = 6.0 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).



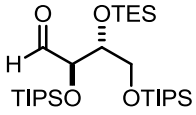

**(2*S*,3*R*)-3-((tert-Butyldimethylsilyl)oxy)-2-((phenylamino)oxy)butan-1-ol (91):**

L-Proline (4.83 mg, 0.042 mmol) was added to a solution of aldehyde **90** (0.05 g, 0.25 mmol) and nitrosobenzene (22.5 mg, 0.21 mol) in 0.42 mL DMSO and the resulting green reaction mixture stirred until the color changed to orange whereupon the reaction mixture was pipeted into a solution of $NaBH_4$ (31.5 mg, 0.830 mmol) in 0.21 mL EtOH. The resulting reaction mixture was stirred for 1 h before quenching with saturated aqueous $NaHCO_3$ (2 mL) and extracting with $CH_2Cl_2$ (3x 3 mL). The organic portions were combined, dried ($MgSO_4$), and the crude product was purified via flash column chromatography (20% EtOAc/hexanes) to yield 16.0 mg (20%; 72% BRSM) of the title compound. $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.39-7.33 (m, 2H), 7.12-7.04 (m, 3H), 4.31-4.25 (m, 1H), 4.07-4.06 (m, 2H), 3.80 (dd, J = 3.6, 7.5 Hz, 1H), 3.05 (t, J = 5.4 Hz, 1H), 1.37 (d, J = 6.3 Hz, 3H), 1.01 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H).



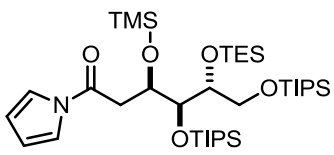
**(2*R*,3*R*)-3-Hydroxy-2,4-bis((triisopropylsilyl)oxy)butanal (92):**

Aldehyde **83** (0.790 g, 3.66 mmol) and L-proline (41.3 mg, 0.359 mmol) were stirred in 15.6 mL DMF for 36 h before dilution with EtOAc (50 mL) and quenching with $H_2O$ (30 mL). The separated organic portion was washed with brine (30 mL), dried ($MgSO_4$), and the crude product was purified via flash column chromatography (2.5% $Et_2O$/hexanes) to yield 574 mg (72%) of the title compound as a 3:1 mixture of diastereomers. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, J = 0.9 Hz, 1H), 9.69 (d, J = 2.1 Hz, 1H), 4.29-4.24 (m, 2H), 4.01-3.95 (m, 2H), 3.87-3.75 (m, 4H), 2.75 (d, J = 9.6 Hz, 1H), 2.38 (d, J = 5.7 Hz, 1H), 1.08-1.05 (m, 84 H).



**(2*R*,3*R*)-3-((Triethylsilyl)oxy)-2,4-bis((triisopropylsilyl)oxy)butanal (93):**

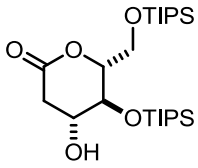
To a −78 °C solution of 2,6-lutidine (0.540 mL, 4.67 mmol) and alcohol **92** (0.500 g, 1.15 mmol) in 3.9 mL $CH_2Cl_2$ was added TBSOTf (0.390 mL, 1.73 mmol) and the resulting reaction mixture was allowed to stir for 2.5 h before quenching with saturated aqueous $NaHCO_3$ (10 mL) and extracting with $CH_2Cl_2$ (3x 10 mL). The combined organic portions were washed with 1 M aqueous $NaHSO_4$ (30 mL), dried ($MgSO_4$), and the resulting crude product was purified via flash column chromatography (30% EtOAc/hexanes) to yield 0.469 mg (74.7%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, J = 1.8 Hz, 1H), 4.23 (t, J = 1.8 Hz, 1H), 4.01 (ddd, J = 1.5, 4.8, 9.9 Hz, 1H), 3.87 (t, J = 9.0 Hz, 1H), 3.52 (dd, J = 4.8, 9.0 Hz, 1H), 1.13-1.04 (m, 42H), 0.97 (t, J = 8.1 Hz, 9H), 0.61 (q, J = 7.5 Hz, 6H).



**(3*R*,4*S*,5*R*)-5-((Triethylsilyl)oxy)-4,6-bis((triisopropylsilyl)oxy)-3-((trimethylsilyl)oxy)hexanal (97):**

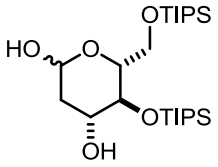
To a −70 °C solution of silyl enol ether **96** (1.15 g, 6.35 mmol) and

aldehyde **93** (0.538 g, 0.980 mmol) in 6.46 mL THF was added $NO_2C_6H_4ONBu_4$ (0.52 mL, 0.26 mmol, 0.5 M in DMF) and the resulting reaction mixture was stirred for 15 h before dilution with $Et_2O$ (20 mL). The entire reaction contents were then passed through a plug of $SiO_2$ eluting with $Et_2O$ and the crude product was purified via flash column chromatography (1% EtOAc/hexanes) to yield 0.636 g (89%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 2H), 6.27 (t, J = 2.1 Hz, 2H), 4.54 (d, J = 8.4, 1H), 4.17 (s, 1H), 3.91 (dt, J = 1.2, 5.7 Hz, 1H), 3.68 (dd, J = 10.2, 21.3 Hz, 1H), 3.66 (dd, J = 10.2, 19.2 Hz, 1H), 3.40 (dd, J = 1.8, 15.6 Hz, 1H), 3.10 (dd, J = 8.7, 15.6 Hz, 1H), 1.16-1.07 (m, 42H), 0.92 (t, J = 7.8 Hz, 9H), 0.57 (q, J = 7.8, 6H), −0.02 (s, 6H).



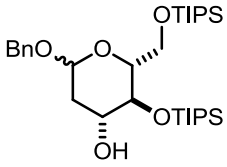

**(4*R*,5*S*,6*R*)-4-Hydroxy-5-((triisopropylsilyl)oxy)-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-2-one (99):**

Trifluoroacetic acid (30.0 μL, 0.392 mmol) was added to amide **97** (0.288 g, 0.313 mmol) in 8 mL $CH_2Cl_2$:MeOH (1:1) and the resulting reaction mixture was stirred for 3.5 h before adding an additional aliquot of trifluoroacetic acid (15.0 μL, 0.196 mmol). The reaction mixture stirred for 30 min before addition of MeONa (0.222 g, 4.10 mmol) in four aliquots over 3 h. The reaction was quenched with pH 7 phosphate buffer (12 mL), extracted with EtOAc (3x 12 mL), and the combined organic portions were washed with brine and dried ($Na_2SO_4$). The crude product was purified via flash column chromatography (10-20% EtOAc/hexanes) to yield 120 mg (81%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, J = 5.7 Hz, 1H), 4.37 (d, J = 8.4 HZ, 1h), 3.86 (dd, J = 3.9, 9.9 Hz, 1H), 3.81 (dd, J = 4.5, 9.9 Hz, 1H), 3.48-3.42 (m, 1H), 2.82 (dd, J = 6.0, 18.0 Hz, 1H), 2.46 (d, J = 17.7 Hz, 1H), 1.12-1.03 (m, 42H).




**(4*R*,5*S*,6*R*)-5-((Triisopropylsilyl)oxy)-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-2,4-diol (99b):**

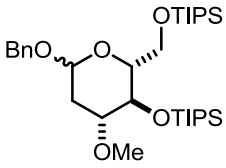
To a −78 °C solution of lactone **99** (0.089 g, 0.163 mmol) in 1.9 mL $CH_2Cl_2$ was added *i*$Pr_2AlH$ (0.465 mL, 0.465 mmol, 1 M in heptanes) and the resulting reaction mixture was allowed to stir for 2 h before quenching with Rochelle's salt (3 mL). The resulting emulsion was allowed to stir for an additional 2 h before extracting with $CH_2Cl_2$ (3x 3 mL). The organic portions were combined, dried ($MgSO_4$) and the crude product was purified via flash column chromatography (10-15% EtOAc/hexanes) to yield 88 mg (76%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 5.4 (bs, 1H), 4.53 (dd, J = 1.5, 3.3 Hz, 1H), 4.29 (d, J = 5.7 Hz, 1H), 3.78 (dd, J = 4.8, 10.2 Hz, 2H), 3.60 (dd, J = 6.0, 10.5 Hz, 1H), 3.49 (dd, J = 6.0, 10.5 Hz, 1H), 3.49 (dd, J = 5.7, 10.5 Hz, 1H), 2.04-2.03 (m, 2H), 1.09-1.05 (m, 42H), −0.10 (s, 9H).




**(2*R*,3*S*,4*R*)-6-(Benzyloxy)-3-((triisopropylsilyl)oxy)-2-(((triisopropylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-4-ol (100):**

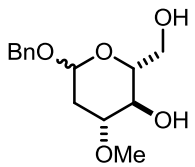
Pyridinium *p*-toluenesulfonate (27.0 mg, 0.108 mmol) was added to a solution of diol **99b** (330 mg, 0.693 mmol) and benzyl alcohol (0.326 mL, 3.16 mmol) in 5.4 mL $CH_2Cl_2$ and the resulting reaction mixture was stirred for 48 h before passing the entire reaction contents through a plug of $SiO_2$ eluting with 20% EtOAc/hexanes. The volatiles were removed and the crude product was purified via flash column chromatography (5-10% EtOAc/hexanes) to yield 348 mg (86%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$), *mixture of α:β anomers (~2:1 )*, δ 7.35-7.28 (m, 10H), 5.39 (dd, J = 4.2, 5.4 Hz, 1H), 5.22 (dd, J = 1.5, 5.7 Hz, 1H), 4.79 (d, J = 12.3 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 4.58 (dt, J = 3.3, 6.9 Hz, 1H), 4.49 (d, J = 12.0, 1H), 4.49 (d, J = 12.3, 1H), 4.02 (d, J = 6.6 Hz, 1H), 4.01 (d, J = 6.9, 1H), 3.84-3.79

(m, 4H), 3.59-3.52 (m, 2H), 2.79 (d, J = 6.0 Hz, 1H), 2.63 (d, J = 5.1 Hz, 1H), 2.32-2.19 (m, 2H), 2.04 (dq, J = 1.5, 13.8 Hz, 1H), 1.08-1.05 (m, 84H).




**(((2*R*,3*S*,4*R*)-6-(Benzyloxy)-4-methoxy-2-(((triisopropylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-3-yl)oxy)triisopropylsilane (100b):**

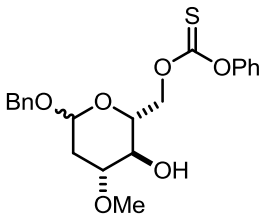
Sodium hydride (20.8 mg, 0.518, 60% in mineral oil) was added to a solution of alcohol **100** (118 mg, 0.208 mmol) in 0.78 mL THF at 0 °C and the solution was warmed to ambient temperature and stirred for 1 h. The solution was cooled to 0 °C, MeI (64.7 μL, 1.04 mmol) was added and the resulting reaction mixture was stirred for 2 h at ambient temperature before quenching with saturated aqueous $NH_4Cl$ (2 mL) and extracting with $Et_2O$ (3x 2 mL). The organic portions were combined, dried ($Na_2SO_4$) and the crude product was purified via flash column chromatography (2-4% EtOAc/hexanes) to yield 85 mg (72%) of the title compound. $^1H$ NMR (300 MHz, $CDCl_3$), *mixture of α:β anomers (~4:1 ) only major anomer tabulated*, δ 7.38-7.29 (m, 5H), 5.25 (dd, J = 1.5, 5.7 Hz, 1H), 4.82 (d, J = 12.3 Hz, 1H), 4.51-4.45 (m, 2H), 4.12 (t, J = 3.6 Hz, 1H), 3.83 (dd, J = 4.8, 10.8 Hz, 1H), 3.77 (dd, J = 6.0, 10.5 Hz, 1H), 3.48 (s, 3H), 3.40 (dd, J = 4.5, 6.0 Hz, 1H), 2.29 (ddd, J = 6.0, 7.5, 13.5 Hz, 1H), 2.00 (dt, J = 2.7, 13.5 Hz, 1H), 1.07-1.05 (m, 42H).




**(2*R*,3*S*,4*R*)-6-(Benzyloxy)-2-(hydroxymethyl)-4-methoxytetrahydro-2*H*-pyran-3-ol (101):**

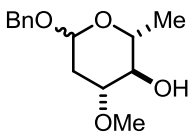
tetra-*n*-Butylammonium fluoride (3.88 mL, 3.88 mmol, 1 M in THF) was added to a 0 °C solution of silyl ether **100b** (564 mg, 0.970 mmol) in 9.7 mL THF and the resulting

reaction mixture was allowed to stir for 2 h before quenching with saturated aqueous $NH_4Cl$ (20 mL) and extracting with $CH_2Cl_2$ (3x 30 mL). The organics were combined, dried ($MgSO_4$) and the crude product was purified via flash column chromatography (85% EtOAc/hexanes) to yield 241 mg (93%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$), *mixture of α:β anomers (~1:1 )* δ 7.38-7.29 (m, 10H), 5.27 (d, J = 4.5 Hz, 1H), 5.24 (d, J = 5.4 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 11.7 Hz, 1H), 4.60 (dd, J = 7.2, 13.5 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.28 (bs, 1H), 4.11-4.09 (m, 1H), 3.93 (dd, J = 3.6, 12.0 Hz, 1H), 3.87 (d, J = 6.6 Hz, 1H), 3.82 (dd, J = 6.0, 14.1 Hz, 1H), 3.73-3.68 (m, 2H), 3.49 (s, 3H), 3.47 (s, 3H), 3.34-3.26 (m, 2H), 2.34 (dd, J = 6.9, 13.2 Hz, 1H), 2.26-2.07 (m, 4H).



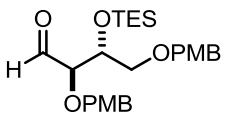

**_O_-(((2_R_,3_S_,4_R_)-6-(Benzyloxy)-3-hydroxy-4-methoxytetrahydro-2_H_-pyran-2-yl)methyl) _O_-phenyl carbonothioate (101b):**

*o*-Phenyl chlorothionoformate (132 μL, 0.900 mmol) was added to a solution of diol **101** (241 mg, 0.900 mmol) in 1.8 mL $CH_2Cl_2$ and the resulting solution was allowed to stir for 30 min before the addition of pyridine (90 μL, 1.13 mmol). The reaction mixture was allowed to stir ~14 h before quenching with $H_2O$ (10 mL), extracting with $CH_2Cl_2$ (3x 10 mL), and washing with brine (10 mL). The combined organic portions were dried ($Na_2SO_4$) and the crude product was purified via flash column chromatography (20-25% EtOAc/hexanes) to yield 227 mg (62%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.45-7.27 (m, 8H), 7.14-7.11 (m, 2H), 5.31 (d, J = 4.2 Hz, 1H), 4.79 (d, J = 11.7 Hz, 1H), 4.76 (dd, J = 4.8, 11.7 Hz, 1H), 4.59 (dd, J = 5.7, 11.7 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.43-4.29 (m, 1H), 4.18 (dd, J = 2.1, 5.4 Hz, 1H), 3.56-3.51 (m, 1H), 3.50 (s, 3H), 2.84 (d, J = 9.9 Hz, 1H), 2.20 (ddd, J = 4.8, 6.3, 13.8 Hz, 1H), 2.09 (d, J = 13.2 Hz, 1H).




**(2*R*,3*R*,4*R*)-6-(Benzyloxy)-4-methoxy-2-methyltetrahydro-2*H*-pyran-3-ol (102):**

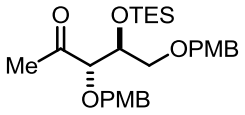
Tributyltin hydride (0.451 mL, 1.68 mmol) was added to a solution of thionoformate **101b** (227 mg, 0.560 mmol) and AIBN (26.2 mg, 0.160 mmol) in 33 mL toluene and the resulting reaction mixture was heated to ~115 °C and was stirred at that temperature for 3 h. The volatiles were removed and the crude product was purified via flash column chromatography (0-20-30% EtOAc/hexanes) to yield 102 mg (72%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 5.30 (d, J = 4.2 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.19 (ddt, J = 2.1, 6.6, 10.2 Hz, 1H), 3.99 (dd, J = 2.1, 4.5 Hz, 1H), 3.37 (dd, J = 4.2, 6.3 Hz, 1H), 3.35 (s, 3H), 2.81 (d, J = 10.2 Hz, 1H), 2.13 (ddd, J = 4.8, 6.3, 13.8 Hz, 1H), 2.04 (dd, J = 0.9, 13.5 Hz, 1H), 1.19 (d, J = 6.6 Hz, 3H).




**(2*S*,3*S*)-2,4-Bis((4-methoxybenzyl)oxy)-3-((triethylsilyl)oxy)butanal (107):**

Triethylsilyltrifluoromethane sulfonate (1.91 mL, 8.46 mmol) was added to a solution of diol **106** (2.6 g, 7.2 mmol) and 2,6-lutidine (2.49 mL, 25.1 mmol) in 14.3 mL $CH_2Cl_2$ at 0 °C. The reaction mixture was stirred for 30 min before quenching with saturated aqueous $NaHCO_3$ (20 mL) and extracting with $CH_2Cl_2$ (3x 20 mL). The combined organic portions were then washed with 1 M $NaHSO_4$ (60 mL), dried ($MgSO_4$) and purified via flash column chromatography (5-15% EtOAc/hexanes) to yield 2.75 g (81%) of the title compound. $[\alpha]_D$ +3 (*c* 1.04, $CHCl_3$); IR (thin film): 2999, 2954, 2875, 2836, 1732, 1613, 1586, 1514, 1463, 1442, 1415, 1364, 1302, 1248, 1174, 1105, 1036, 821, 744 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J = 1.6 Hz, 1H), 7.22 (dd, J = 8.8, 16.8 Hz, 4H), 6.87-6.84 (m, 4H), 4.61 (s, 2H), 4.41 (s, 2H), 4.18 (ddd, J = 3.6,

5.2, 2.4 Hz, 1H), 3.81 (dd, J = 3.6, 2.4 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.60 (dd, J = 7.6, 9.6 Hz, 1H), 3.44 (dd, J = 5.2, 9.6 Hz, 1H), 0.92 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 7.6 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 202.8, 159.6, 159.4, 130.2, 129.9, 129.8, 129.5, 114.0, 113.9, 84.8, 77.4, 73.2, 73.2, 73.0, 55.5, 7.0, 4.9; HRMS (ES) *m/z* calcd for $C_{26}H_{38}O_6Si$ $(M + Na)^+$: 497.2329; found: 497.2335.

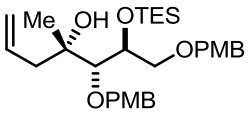



**(3*S*,4*S*)-3,5-Bis((4-methoxybenzyl)oxy)-4-((triethylsilyl)oxy)pentan-2-one (108):**

Methylmagnesium bromide (1.26 mL, 3.78 mmol, 3 M in $Et_2O$) was added to aldehyde **107** (0.895 g, 1.89 mmol) in 35.2 mL $Et_2O$ at −78 °C. The reaction mixture was stirred for 45 min before quenching with saturated aqueous $NH_4Cl$ (40 mL) and extracting with $Et_2O$ (3x 40 mL). The combined organic portions were dried ($Na_2SO_4$) and the solvents were removed in vacuo to yield 0.926 g of a crude alcohol that was used in the following reaction without further purification.

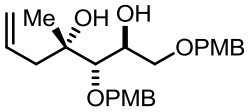
Solid sodium bicarbonate (0.317 g, 3.77 mmol) followed by DMP (1.22 g, 2.88 mmol) was added to the crude alcohol (0.926 g, 1.89 mmol) in 11.7 mL $CH_2Cl_2$. The reaction mixture was stirred for 4 h before diluting with $CH_2Cl_2$ (30 mL), quenching with $H_2O$ (40 mL) and extracting with $CH_2Cl_2$ (3x 40 mL). The combined organic portions were dried ($MgSO_4$) and purified via flash column chromatography (5-15% EtOAc/hexanes) to yield 0.778 g (85%) of the title compound. $[\alpha]_D$ −3.0 (*c* 1.04, $CHCl_3$); IR (thin film): 2999, 2954, 2837, 1715, 1613, 1586, 1514, 1462, 1417, 1353, 1302, 1249, 1175, 1096, 1036, 822, 743 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 5.6, 8.4 Hz, 4H), 6.86 (dd, J = 2.8, 8.8 Hz, 4H), 4.52 (d, J = 2 Hz, 2H), 4.4 (d, J = 4 Hz, 2H), 4.19 (m, 1H), 3.88 (d, J = 4.4 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.56

(dd, J = 6.4, 9.6 Hz, 1H), 3.40 (dd, J = 5.2, 10 Hz, 1H), 2.15 (s, 3H), 0.92 (t, J = 8.4 Hz, 9H, 0.58 (q, J = 7.6 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 210.5, 159.5, 159.3, 130.4, 130.0, 129.7, 129.5, 114.0, 113.9, 85.6, 73.3, 73.1, 73.0, 70.7, 55.5, 55.5, 28.1, 7.0, 5.0; HRMS (ES) *m/z* calcd for $C_{27}H_{40}O_6Si$ $(M + Na)^+$: 511.2492; found: 511.2479.



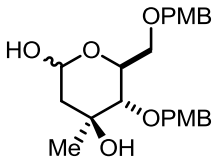

**(4*S*,5*S*,6*S*)-5,7-Bis((4-methoxybenzyl)oxy)-4-methyl-6-((triethylsilyl)oxy)hept-1-en-4-ol (109):**

Ketone **108** (1.52 g, 3.16 mmol) as a solution in 3.12 mL $CH_2Cl_2$ was added to a solution of $MgBr_2$•$Et_2O$ (1.26 g, 4.88 mmol) in 7.02 mL $CH_2Cl_2$ at 0 °C. The suspension was stirred for 5 min before being cooled to −78 °C and allyltributylstannane (0.975 mL, 3.63 mmol) was added. The dry ice/acetone bath was allowed to slowly dissipate (over ~6 h) and the reaction stirred an additional 34 h before quenching with $H_2O$ (20 mL) and extracting with $CH_2Cl_2$ (3x 20 mL). The combined organic portions were dried ($MgSO_4$) and purified via flash column chromatography (6-10% EtOAc/hexanes) to yield 1.2 g (72%) of the title compound. $[\alpha]_D$ −11.0 (*c* 1.0, $CHCl_3$); IR (thin film): 3476, 2954, 2911, 2876, 1613, 1514, 1462, 1302, 1249, 1174, 1085, 1036, 1007 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.24-7.20 (m, 2H), 7.14 (d, J = 8.8 Hz, 2H), 6.82 (app t, J = 8.4 Hz, 4H), 5.89-5.79 (m, 1H), 5.06-5.00 (m, 2H), 4.58 (d, J = 10.8 Hz, 1H), 4.51 (d, J = 10.8 Hz, 1H), 4.45 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 4.10 (app q, J = 5.2 Hz, 1H), 3.77 (s, 3H), 3.77 (s, 3H), 3.71 (dd, J = 4, 10 Hz, 1H), 3.68 (s, 1H), 3.48 (dd, J = 5.6, 10 Hz, 1H), 3.40 (d, J = 5.2 Hz, 1H), 2.32-2.30 (m, 2H), 1.16 (s, 3H), 0.93 (t, J = 8 Hz, 9H), 0.61 (q, J = 7.6, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.2, 159.2, 134.5, 130.5, 129.9, 129.5, 129.5, 129.3, 117.6, 113.7, 113.7, 84.3, 74.5, 74.1, 73.6, 72.9, 71.4, 55.2, 55.2, 43.0, 24.2, 6.8, 5.0; HRMS (ES) *m/z* calcd for $C_{30}H_{47}O_6Si$ $(M + Na)^+$: 531.3142; found: 531.3132.




**(2*S*,3*S*,4*S*)-1,3-Bis((4-methoxybenzyl)oxy)-4-methylhept-6-ene-2,4-diol (110):**

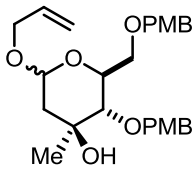
Tetrabutylammonium fluoride (4.5 mL, 4.5 mmol, 1 M in THF) was added to a solution of silyl ether **109** (1.20 g, 2.26 mmol) in 22.6 mL THF at 0 °C and the reaction mixture was stirred for 45 min before quenching with saturated aqueous $NH_4Cl$ (25 mL) and extracting with EtOAc (3x 25 mL). The combined organic portions were dried ($MgSO_4$) and the crude product was purified via flash column chromatography (40-50% EtOAc/hexanes) to yield 0.876 g (93%) of the title compound. $[\alpha]_D$ −27.5 (*c* 1.0, $CHCl_3$); IR (thin film): 3582, 3430, 2912, 1612, 1514, 1462, 1302, 1249, 1175, 1078, 1034 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.17-7.14 (m, 2H), 6.90-6.85 (m, 4H), 5.95-5.86 (m, 1H), 5.12-5.06 (m, 2H), 4.58-4.45 (m, 4H), 4.04-4.00 (m, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.70 (dd, J = 3.2, 9.6 Hz, 1H), 3.61 (dd, J = 6.0, 9.6 Hz, 1H), 3.41 (d, J = 7.2 Hz, 1H), 3.16 (s, 1H), 3.04 (d, J = 4.4 Hz, 1H), 2.38 (d, J = 6.8 Hz, 2H), 2.05 (s, 1H), 1.22 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 159.4, 159.2, 134.2, 130.2, 129.8, 129.6, 129.4, 117.9, 113.9, 113.8, 83.2, 74.9, 74.8, 73.1, 71.5, 70.8, 55.2, 42.5, 24.0; HRMS (ES) *m/z* calcd for $C_{24}H_{32}O_6$ $(M + Na)^+$: 439.2097; found: 439.2113.




**(4*S*,5*S*,6*S*)-5-((4-Methoxybenzyl)oxy)-6-(((4-methoxybenzyl)oxy)methyl)-4-methyltetrahydro-2*H*-pyran-2,4-diol (111):**

2,6-lutidine (0.51 mL, 4.4 mmol), $OsO_4$ (0.431 g, 0.043 mmol, 2.5 wt. % in *t*BuOH), and $NaIO_4$ (1.83 g, 8.58 mmol) were added to a solution of enol **110** (0.876 g, 2.11 mmol) in 20.8 mL dioxane/$H_2O$ (3:1) and the resulting reaction mixture was stirred for 2 h before quenching with $H_2O$ (20 mL) and extracting with $CH_2Cl_2$ (4x 40 mL). The combined organic portions were dried ($MgSO_4$) and the product was purified via flash column

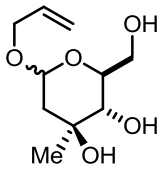
chromatography (60-80% EtOAc/Hexanes) to yield 0.697 g (79%) of the title compound as a yellow oil. $[\alpha]_D$ −21.8 (*c* 1.0, $CHCl_3$); IR (thin film): 3582, 3407, 2918, 1612, 1514, 1461, 1249, 1096, 1034 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$), *mixture of α:β anomers (~1:1 )*, δ 7.27-7.25 (m, 4H), 7.17-7.12 (m, 4H), 6.86-6.82 (m, 8H), 5.33 (s, 1H), 4.75 (t, J = 6.8 Hz, 1H), 4.62 (d, J = 11.2, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.55-4.43 (m, 6H), 4.30 (d, J = 6.8, 1H), 3.96-3.92 (m, 1H), 3.79 (s, 6H), 3.78 (s, 6H), 3.67 (dd, J = 2.0, 10 Hz, 1H), 3.64-3.59 (m, 4H), 3.44 (ddd, J = 2.0, 4.8, 10 Hz, 1H), 3.40 (d, J = 3.2 Hz, 1H), 3.38 (d, J = 3.2 Hz, 1H), 1.95 (dd, J = 2.0, 7.6 Hz, 1H), 1.91 (dd, J = 2.0, 8.4 Hz, 1H), 1.87 (s, 1H), 1.82 (dd, J = 3.6, 13.6 Hz, 1H), 1.68 (dd, J = 9.6, 12.4 Hz, 1H), 1.44 (s, 3H), 1.23 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 159.2, 130.5, 130.4, 129.7, 129.7, 129.5, 129.4, 113.8, 113.7, 93.6, 91.6, 81.3, 80.7, 74.5, 74.3, 74.3, 73.0, 72.5, 72.3, 70.0, 69.3, 69.3, 55.2, 55.2, 46.1, 42.9, 23.5, 21.4; HRMS (ES) *m/z* calcd for $C_{23}H_{30}O_7$ (M + $Na)^+$: 441.1889; found: 441.1879.




**(2*S*,3*S*,4*S*)-6-(Allyloxy)-3-((4-methoxybenzyl)oxy)-2-(((4-methoxybenzyl)oxy)methyl)-4-methyltetrahydro-2*H*-pyran-4-ol (112):**

Silver (I) oxide (0.348 g, 1.50 mmol) and allyl bromide (119 μL, 1.30 mmol) were added to a solution of diol **111** (0.210 g, 0.500 mmol) in 3.48 mL DMF and the resulting reaxtion mixture was stirred for 36 h before being passed through a plug of $SiO_2$ eluting with EtOAc. The product was purified via flash column chromatography (20-40% EtOAc/Hexanes) to yield 0.148 g (65%) of the title compound. IR (thin film): 3465, 2934, 2867, 1612, 1513, 1462, 1399, 1372, 1302, 1248, 1174, 1090, 1034, 930, 821 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 6.89-6.84 (m, 4H) 5.97-5.87 (m, 1H), 5.27 (dd, J = 1.6, 17.6 Hz, 1H), 5.18 (dd, J = 1.6, 10.4 Hz, 1H), 4.61-4.49 (m, 5H), 4.36 (ddt, J = 1.2, 4.8,

12.8 Hz, 1H), 4.04 (dd, J = 6.0, 12.8 Hz, 1H), 3.80 (m, 6H), 3.71 (dd, J = 2.4, 10.4 Hz, 1H), 3.67 (dd, J = 4.8, 10.8 Hz, 1H), 3.48 (ddd, J = 2.4, 4.4, 14.8 Hz, 1H), 3.43 (d, J = 8.8 Hz, 1H), 1.98 (dd, J = 2.4, 13.2 Hz, 1H), 1.85 (s, 1H), 1.77 (dd, J = 8.8, 13.2 Hz), 1.28 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.2, 134.1, 130.5, 130.3, 129.5, 129.5, 117.2, 113.9, 113.7, 98.4, 80.9, 74.7, 74.2, 73.1, 72.3, 69.6, 69.5, 55.2, 44.2, 22.1; HRMS (ES) *m/z* calcd for $C_{26}H_{34}O_7$ (M + Na)$^+$: 481.2202; found: 481.2224.

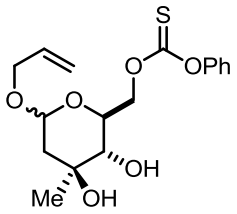



**(2*S*,3*S*,4*S*)-6-(Allyloxy)-2-(hydroxymethyl)-4-methyltetrahydro-2H-pyran-3,4-diol (114):**

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.138 g, 0.608 mmol) was added to a solution of PMB ester **112** (0.90 g, 0.20 mmol) in 5.9 mL $CH_2Cl_2$/pH 7 phosphate buffer (2:1) at 0 °C and the resulting reaction mixture stirred for 1 h before being warmed to ambient temperature and stirred for an additional 2.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL), extracted with $CH_2Cl_2$ (4x 2 mL), and the combined organic portions were dried ($MgSO_4$) and used crude in the next reaction without further purification.

2.25 mL Acetic acid/water (4:1) were added to crude PMP acetal **113** from the previous reaction and the resulting mixture was stirred for 24 h. Approximately ½ the reaction volume was removed at reduced pressure and the resulting solution was loaded directly onto a flash column and eluted (0-10% MeOH/$CH_2Cl_2$) to yield 0.031 g (70%) of the title compound as a white solid. $[\alpha]_D$ +58.6 (*c* 1.0, $CHCl_3$); IR (thin film): 3416, 2933, 1455, 1385, 1199, 1102, 1039, 990 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) *mixture of α:β anomers (~10:1) major anomer tabulated* δ 5.92-5.84 (m, 1H), 5.27 (dd, J = 1.5, 7.0 Hz, 1H), 5.17 (dd, J = 1.0, 10.5 Hz, 1H), 4.56 (dd, J = 1.5, 10 Hz, 2H), 4.32 (dd, J = 5.0, 13 Hz, 1H), 4.03 (dd, J = 6.0, 13 Hz, 1H), 3.90-

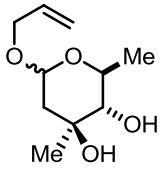
3.80 (m, 3H), 3.62 (d, J = 18 Hz, 1H), 3.23 (d, J = 10 Hz, 1H), 2.00-1.98 (m, 1H), 1.76 (dd, J = 10, 12.5 Hz, 1H), 1.25 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 134.2, 133.9, 117.5, 116.5, 98.9, 98.8, 96.8, 75.0, 73.0, 70.8, 69.9, 67.9, 61.9, 44.7, 42.7, 21.7, 20.0; HRMS (ES) *m/z* calcd for $C_{10}H_{18}O_5Na$ $(M + Na)^+$: 241.1052; found: 241.1055.



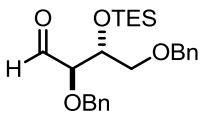

**_O_-(((2_S_,3_S_,4_S_)-6-(Allyloxy)-3,4-dihydroxy-4-methyltetrahydro-2H-pyran-2-yl)methyl) _O_-phenyl carbonothioate (114b):**

*O*-Phenyl chlorothionoformate (180 μL, 1.34 mmol) was added to a solution of triol **114** (270 mg, 1.34 mmol) in 2.5 mL $CH_2Cl_2$ at 0 °C and the resulting reaction mixture was stirred at ambient temperature for 30 min. The reaction mixture was cooled to 0 °C, pyridine (124 μL, 1.54 mmol) was added and the reaction mixture was stirred for 18 h at ambient temperature before quenching with $H_2O$ (5 mL) and extracting with $CH_2Cl_2$ (3x 5 mL). The combined organic portions were dried ($MgSO_4$) and the product was purified via flash column chromatography (40-60% EtOAc/hexanes) to yield 0.276 g (61%) of the title compound as a white foam. $[\alpha]_D$ +37.3 (*c* 1.0, $CHCl_3$); IR (thin film): 3426, 1644, 1291, 1204, 1075 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *mixture of α:β anomers (~2:1 )*, δ 7.44-7.37 (m, 4H), 7.31-7.23 (m, 2H), 7.20-7.11 (m, 4H), 5.96-5.87 (m, 2H), 7.12 (d, J = 8.0 Hz, 1H), 6.0-5.88 (m, 2H), 5.33-5.30 (m, 2H), 5.23-5.20 (m, 2H), 4.84 (dd, J = 2.0, 11.6 Hz, 1H), 4.74 (dd, J = 5.6, 11.6 Hz, 1H), 4.64-4.62 (m, 2H), 4.55 (s, 1H), 4.53 (d, J = 4.0 Hz, 1H), 4.40-4.35 (m, 2H), 4.09-4.04 (m, 2H), 4.07-4.04 (m, 2H), 3.65 (ddd, J = 2.0, 5.2, 9.6 Hz, 1H), 3.60-3.53 (m, 2H), 3.11 (bs, 1H), 3.0 (bs, 1H), 2.53 (bs, 1H), 2.06 (dd, J = 2.0, 13.2 Hz, 1H), 2.05 (dd, J = 2.0, 12.8 Hz, 1H), 1.84-1.78 (m, 2H), 1.32 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 195.3, 154.2, 153.3, 151.0, 133.8, 133.8, 129.5, 129.5, 126.6, 126.2, 121.9, 121.0, 117.7, 117.7, 73.7, 73.6, 73.0, 72.8, 72.0, 71.9,

69.8, 69.8, 68.2, 53.4, 44.4, 20.4, 20.4; HRMS (ES) *m/z* calcd for $C_{17}H_{22}O_6S$ $(M + Cl)^-$: 389.0826; found: 389.0863.

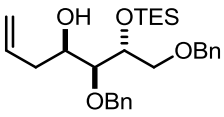



**(2*S*,3*S*,4*S*)-6-(Allyloxy)-2,4-dimethyltetrahydro-2H-pyran-3,4-diol (115):** Azobisisobutyronitrile (36.7 mg, 0.224 mmol) then $n$Bu$_3$SnH (0.63 mL, 2.3 mmol) were added to a solution of thionoformate **114b** (276 mg, 0.817 mmol) in 46 mL toluene and the resulting reaction mixture was stirred for 3 h at 110-120 °C. The volatiles were removed under reduced pressure and the product was purified via flash column chromatography (50-70% EtOAc/hexanes) to yield 0.140 g (93%) of the title compound as a yellow oil. $[\alpha]_D$ +23.8 (*c* 1.0, $CHCl_3$); IR (thin film): 3411, 2978, 2933, 1647, 1453, 1380, 1313, 1118, 1072, 998 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *mixture of α:β anomers only major anomer tabulated (~10:1 )*, δ 5.94-5.83 (m, 1H), 5.27 (dd, J = 1.6, 14.8 Hz, 1H), 5.18 (dd, J = 0.8, 10.4 Hz, 1H), 4.52 (dd, J = 2.0, 10.0 Hz, 1H), 4.33 (dd, J = 5.2, 12.8 Hz, 1H), 4.02, (dd, J = 6.4, 12.8 Hz, 1H), 3.36-3.29 (m, 1H), 3.22 (d, J = 9.6 Hz, 1H), 1.99 (dd, J = 2.0, 12.8 Hz, 1H), 1.74 (dd, J = 10.0, 12.0 Hz, 1H), 1.30 (d, J = 6.0 Hz, 3H), 1.25 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 134.3, 133.9, 117.5, 116.5, 98.3, 96.4, 79.5, 79.2, 72.1, 71.8, 71.0, 69.7, 67.8, 66.7, 45.0, 43.0, 29.6, 22.0, 20.3, 18.3, 18.0; HRMS (ES) *m/z* calcd for $C_{10}H_{18}O_4$ $(M + Na)^+$: 225.1103; found: 225.1076.



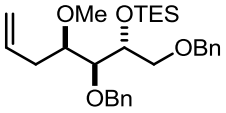

**(2*R*,3*R*)-2,4-Bis(benzyloxy)-3-((triethylsilyl)oxy)butanal (116):** Triethylsilyltrifluoromethane sulfonate (0.178 mL, 0.788 mmol) was added to a solution of diol **105** (0.200 g, 0.670 mmol) and 2,6-lutidine (0.230 mL, 1.99 mmol) in 1.32 mL of $CH_2Cl_2$ at 0 °C. The reaction mixture was stirred for 30 min before quenching with saturated

aqueous $NaHCO_3$ (2 mL mL) and extracting with $CH_2Cl_2$ (3x 2 mL). The combined organic portions were then washed with 1 M $NaHSO_4$ (8 mL), dried ($MgSO_4$) and purified via flash column chromatography to yield 171 g (72%) of the title compound as a 2.8:1 mixture of diastereomers. $[\alpha]_D$ +3.8 (*c* 1.0, $CHCl_3$); IR (thin film): 3031, 2954, 2912, 2876, 1733, 1455, 1105, 735 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) *mixture of diastereomers (~2.8:1 )*, δ 9.74 (d, J = 1.2 Hz, 1H), 9.64 (d, J = 1.5 Hz, 1H), 7.34-7.26 (m, 20H), 4.75 (d, J = 12.0 Hz, 1H), 4.70 (s, 2H), 4.57 (d, J = 11.7 Hz, 1H), 4.49 (s, 2H), 4.47 (d, J = 8.4 Hz, 2H), 4.25-4.11 (m, 2H), 3.92 (dd, J = 1.5, 3.3 Hz, 1H), 3.87 (dd, J = 0.9, 3.9 Hz, 1H), 3.65 (dd, J = 7.5, 9.6 Hz, 1H), 3.60 (dd, J = 6.0, 9.6 Hz, 1H), 3.51 (dd, J = 4.8, 8.1 Hz, 1H), 3.47 (dd, J = 5.1, 9.6 Hz, 1H), 0.99-0.87 (m, 16H), 0.65-0.51 (m, 12H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 195.9, 195.3, 130.9, 130.5, 130.4, 121.4, 121.4, 121.3, 121.2, 121.0, 120.9, 120.9, 120.6, 120.6, 78.0, 77.0, 66.3, 66.2, 66.0, 65.3, 63.4, 63.2, −0.3, −2.3; HRMS (ES) *m/z* calcd for $C_{24}H_{34}O_4Si$ $(M + Na)^+$: 4372124; found: 437.2172.




**(4*R*,5*S*,6*R*)-5,7-Bis(benzyloxy)-6-((triethylsilyl)oxy)hept-1-en-4-ol (116b):** Aldehyde **116** (0.171 g, 0.413 mmol) as a solution in 0.41 mL $CH_2Cl_2$ was added to a solution of $MgBr_2$•$Et_2O$ (0.167 g, 0.647 mmol) in 0.94 mL $CH_2Cl_2$ at 0 °C. The suspension was stirred for 5 min before being cooled to −78 °C and allyltributylstannane (0.130 mL, 0.419 mmol) was added. The dry ice/acetone bath was allowed to slowly dissipate (over ~6 h) and the reaction stirred an additional 17 h before quenching with $H_2O$ (3 mL) and extracting with $CH_2Cl_2$ (3x 3 mL). The combined organic portions were dried ($Na_2SO_4$) and purified via flash column chromatography (3-7% EtOAc/hexanes) to yield 0.106 g (87%) of the title compound. $[\alpha]_D$ −3.0 (*c* 1.17, $CHCl_3$); IR (thin film): 3502, 3066, 3031, 2953, 2911, 2876,

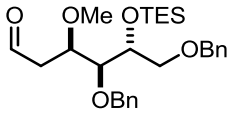
1496, 1455, 1414, 1365, 1324, 1239, 1208, 1100, 1007, 915, 780, 738 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 10H), 5.80 (ddt, J = 7.2, 8.4, 16.4 Hz, 1H), 5.07 (s, 1H), 5.03 (d, J = 5.6 Hz, 1H), 4.71 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 12.8 Hz, 1H), 4.52 (s, J = 2H), 4.11 (q, J = 4.8 Hz, 1H), 3.89-3.84 (m, 1H), 3.59 (ddd, J = 4.8, 10, 16.8 Hz, 1H), 3.49 (dd, J = 2.4, 5.2 Hz, 1H), 2.38-2.24 (m, 2H), 0.95 (t, J = 8.0 Hz, 1H), 0.63 (q, J = 7.6 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 138.1, 137.8, 135.2, 128.3, 128.1, 127.9, 127.7, 127.7, 117.1, 80.0, 73.6, 73.4, 72.3, 71.4, 70.4, 38.6, 6.8, 4.8; HRMS (ES) *m/z* calcd for $C_{27}H_{40}O_4Si$ $(M + Na)^+$: 479.2594; found: 479.2578.




**(((2*R*,3*S*,4*R*)-1,3-Bis(benzyloxy)-4-methoxyhept-6-en-2-yl)oxy)triethylsilane (117):**

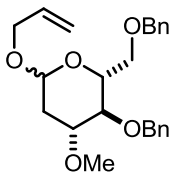
Proton sponge (14.7 g, 68.5 mmol) followed by $Me_3OBF_4$ (9.09 g, 61.4 mmol) were added to alcohol **116b** (7.05, 15.4 mmol) in 153 mL $CH_2Cl_2$. The resulting reaction mixture was stirred for 48 h before loading the entire contents onto a flash column and eluting (5% EtOAc/hexanes) to yield 5.6 g (58% based on pure material present) of ~75% pure product that was inseparable from the 25% impurity. $[\alpha]_D$ −32.4 (*c* 1.0, $CHCl_3$); IR (thin film): 3458, 3066, 3031, 2954, 2911, 2876, 1641, 1496, 1455, 1414, 1362, 1239, 1207, 1097, 1006, 914, 735 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.32-7.23 (m, 10H), 5.81-5.69 (m, 1H), 5.05-5.03 (m, 1H), 5.01-5.00 (m, 1H), 4.60 (q, J = 11.6 Hz, 1H), 4.48 (s, 1H), 3.99-3.92 (m, 1H), 3.69-3.64 (m, 1H), 3.52-3.43 (m, 1H), 3.36 (s, 1H), 2.40-2.30 (m, 2H), 0.94 (app q, J = 8.4 Hz, 1H), 0.60 (t, J = 7.6 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 139.0, 138.4, 138.4, 135.3, 134.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 117.5, 117.4, 82.1, 81.6, 80.9, 80.6, 77.4, 74.9, 73.6, 73.1, 72.4, 72.2,

72.1, 71.2, 58.3, 38.1, 34.8, 7.2, 7.0, 5.3, 5.0; HRMS (ES) *m/z* calcd for $C_{28}H_{42}O_4Si$ $(M + Na)^+$: 493.2750; found: 493.2717.




**(3*R*,4*S*,5*R*)-4,6-Bis(benzyloxy)-3-hydroxy-5-((triethylsilyl)oxy)hexanal (117b):**

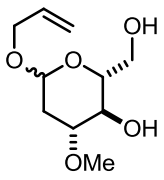
2,6-lutidine (1.1 mL, 9.5 mmol), $OsO_4$ (0.957 g, 0.09 mmol, 2.5 wt% in *t*BuOH), and $NaIO_4$ (4.05 g, 18.9 mmol) were added to a solution of enol **117** (2.20 g, 4.68 mmol, 66% pure) in 46 mL dioxane/$H_2O$ (3:1) and the resulting reaction mixture was stirred for 14 h before quenching with $H_2O$ (25 mL) and extracting with $CH_2Cl_2$ (4x 75 mL). The combined organic portions were dried ($MgSO_4$) and the product was purified via flash column chromatography (5-20% EtOAc/Hexanes) to yield 1.0 g (66%) of the title compound as a yellow oil. $[\alpha]_D$ +13.8 (*c* 1.0, $CHCl_3$); IR (thin film): 3437, 2998, 1642, 1454, 1095 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 9.66 (dd, J = 1.6, 2.8 Hz, 1H), 7.31-7.20 (m, 10H), 4.60 (d, J = 11.2 Hz, 1H), 4.49 (s, 1H), 4.48 (d, J = 10.8 Hz, 1H), 4.08-4.04 (m, 1H), 3.97 (dt, J = 3.6, 9.6 Hz, 1H), 3.66 (dd, J = 3.2, 10.0 Hz, 1H), 3.59 (dd, J = 4.4, 10.0 Hz, 1H), 3.54 (dd, J = 3.6, 6.4 Hz, 1H), 3.35 (s, 3H), 2.62 (ddd, J = 1.2, 5.2, 16.4 Hz, 1H), 2.55 (ddd, J = 2.8, 6.0, 16.4 Hz, 1H), 0.93 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 7.6 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 201.1, 138.0, 137.9, 128.3, 128.3, 128.0, 127.7, 127.7, 81.6, 76.0, 74.1, 73.4, 71.9, 71.6, 58.1, 45.0, 6.9, 5.1; HRMS (ES) *m/z* calcd for $C_{27}H_{40}O_5Si$ $(M + Na)^+$: 495.2543; found: 495.2536.




**(2*R*,3*S*,4*R*)-6-(Allyloxy)-3-(benzyloxy)-2-((benzyloxy)methyl)-4-methoxytetrahydro-2H-pyran (118):**

Pyridinium *p*-toluenesulfonate (62.6 mg, 0.249 mmol) was added to a solution of

aldehyde **117b** (0.596 g, 1.26 mmol) in 11.3 mL allyl alcohol and stirred for 48 h at 55-60 °C before being passed through a plug of $SiO_2$ eluting with 20% EtOAc/hexanes. The volatiles (allyl alcohol) were removed under reduced pressure and the product was purified via flash column chromatography (6-10% EtOAc/hexanes) to yield 0.400 g (80%) of the title compound. $[\alpha]_D$ +43.8 (*c* 1.0, $CHCl_3$); IR (thin film): 3063, 3030, 2932, 1496, 1454, 1367, 1305, 1268, 1202, 1029, 925, 738 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *mixture of α:β anomers (~2:1 )*, δ 7.39-7.23 (m, 20H), 5.32 (dd, J = 1.2, 9.2, 1H), 5.28 (dd, J = 1.2, 9.2 Hz, 1H), 5.23-5.17 (m, 2H), 5.03 (d, J = 2.8 Hz, 1H), 4.87 (d, J = 10.8 Hz, 2H), 4.67 (d, J = 12.4, 1H), 4.65 (d, J = 12.4 Hz, 1H), 4.60-4.50 (m, 6H), 4.41 (dd, J = 4.8, 12.4 Hz, 1H), 4.15 (dd, J = 5.2, 12.8 Hz, 1H), 4.09 (dd, J = 6.0, 12.4 Hz, 1H), 3.95 (dd, J = 6.4, 13.2 Hz, 1H), 3.80-3.67 (m, 6H), 3.55 (t, J = 9.2 Hz, 1H), 3.47 (s, 3H), 3.45 (s, 3H), 3.4 (m, 1H), 2.40-2.36 (m, 1H), 2.30 (dd, J = 4.8, 12.8 Hz, 1H), 1.72-1.56 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 138.2, 138.1, 134.0, 128.3, 128.2, 127.8, 127.8, 127.8, 127.7, 127.5, 127.5, 117.3, 117.1, 98.8, 96.6, 81.4, 79.0, 78.1, 77.8, 75.0, 74.7, 74.7, 73.4, 70.6, 69.6, 69.3, 68.7, 67.6, 57.2, 56.8, 35.9, 34.7; HRMS (ES) *m/z* calcd for $C_{24}H_{30}O_5$ $(M + Na)^+$: 421.1991; found: 421.1990.

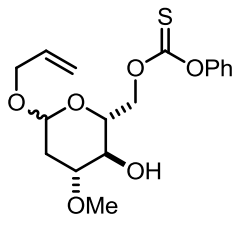



**(2*R*,3*S*,4*R*)-6-(Allyloxy)-2-(hydroxymethyl)-4-methoxytetrahydro-2H-pyran-3-ol (119):**

Lithium-4,4'-di-*t*-butylbiphenylide (1.1 mL, 1.1 mmol, 1 M in THF) was added via cannula to a solution of benzyl ether **118** (0.015 g, 0.038 mmol) in 1.57 mL freshly distilled, degassed THF at −78 °C and the resulting solution was stirred for 90 min. *NOTE: If the dark green/blue color of the reaction mixture faded to red/brown during the course of the reaction, additional LiDBB was added until the dark green/blue color persisted*. The reaction mixture was

quenched with saturated aqueous $NH_4Cl$ (2 mL) and extracted with EtOAc (3x 2 mL). The combined organic portions were dried ($Na_2SO_4$) and the product was purified via flash column chromatography (0-5% MeOH/$CH_2Cl_2$) to yield 4 mg (57%) of the title compound.

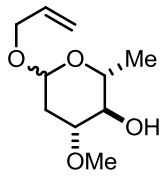
1 M LiDBB was prepared as follows: 4,4'-di-*tert*-Butylbiphenyl (12.7 g, 47.6 mmol) then piecemeal, polished Li Metal (0.297 g, 42.4 mmol) was added to 47.6 mL recently distilled, degassed THF and the resulting suspension was sonicated without allowing the temperature to rise above 25 °C until the Li metal had fully dissolved (~3-4 h). $[\alpha]_D$ +15.0 (*c* 1.0, $CHCl_3$); IR (thin film): 3465, 2934, 2867, 1612, 1513, 1461, 1399, 1372, 1302, 1248, 1174, 1090, 1034, 930, 821 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *isolated in ~80% purity mixture of α:β anomers only major anomer tabulated (~10:1 )* δ 5.93-5.83 (m, 1H), 5.26 (dd, J = 1.6, 17.2 Hz, 1H), 5.17 (dd, J = 1.2, 10 Hz, 1H), 4.96 (d, J = 3.2 Hz, 1H), 4.11 (ddt, J = 1.6, 5.2, 13.2 Hz, 1H), 3.91 (dd, J = 6.0, 12.8 Hz, 1H), 3.81-3.80 (m, 2H), 3.64-3.47 (m, 3H), 3.39 (s, 3H), 2.72 (t, J = 6.4 Hz, 1H), 2.26 (ddd, J = 0.8, 4.4, 12.8 Hz, 1H), 1.49 (ddd, J = 3.6, 11.2, 12.8, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 133.9, 133.8, 117.5, 117.3, 99.1, 96.7, 80.5, 78.2, 75.3, 71.5, 70.8, 70.5, 69.9, 67.8, 62.5, 62.3, 56.6, 56.4, 35.0, 33.8; HRMS (ES) *m/z* calcd for $C_{10}H_{17}O_5$ $(M - H)^-$: 217.1076; found: 217.1083.




**_O_-(((2_R_,3_S_,4_R_)-6-(Allyloxy)-3-hydroxy-4-methoxytetrahydro-2H-pyran-2-yl)methyl) _O_-phenyl carbonothioate (119b):**

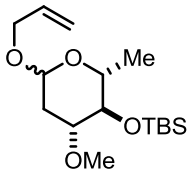
*O*-Phenyl chlorothionoformate (0.295 mL, 2.13 mmol) was added to a solution of diol **119** (0.440 g, 2.02 mmol) in 4.1 mL $CH_2Cl_2$ at 0 °C and the resulting reaction mixture was stirred at ambient temperature for 30 min. The reaction mixture was cooled to 0 °C, pyridine (0.204 mL, 2.54 mmol) was added and the reaction mixture was stirred for 14 h at

ambient temperature before quenching with $H_2O$ (8 mL) and extracting with $CH_2Cl_2$ (3x 12 mL). The combined organic portions were dried ($Na_2SO_4$) and the product was purified via flash column chromatography (20-30% EtOAc/hexanes) to yield 0.480 g (67%) of the title compound as a white foam. $[\alpha]_D$ +24.0 (*c* 1.0, $CHCl_3$); IR (thin film): 3443, 3076, 2936, 2360, 1763, 1591, 1490, 1455, 1385, 1334, 1291, 1204, 1102, 1043, 1004, 969, 930, 878, 848, 826, 773, 734 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *mixture of α:β anomers only major anomer tabulated (~5:1 )* δ 7.43-7.39 (m, 2H), 7.29 (tt, J = 1.2, 7.2 Hz, 1H), 7.13-7.11 (m, 2H), 5.97-5.87 (m, 1H), 5.31 (ddd, J = 2.0, 3.6, 17.2 Hz, 1H), 5.22 (ddd, J = 1.2, 2.8, 10.4 Hz, 1H), 5.04 (d, J = 2.8 Hz, 1H), 4.79 (dd, J = 2.4, 11.6 Hz, 1H), 4.74 (dd, J = 5.2, 12.0 Hz, 1H), 4.16 (ddt, J = 1.6, 5.2, 12.8 Hz, 1H), 4.00-3.94 (m, 2H), 3.66-3.45 (m, 2H), 3.42 (s, 3H), 2.74 (d, J = 2.0 Hz, 1H), 2.32 (ddd, J = 1.2, 4.4, 12.8 Hz, 1H), 1.57 (ddd, J = 3.6, 11.2, 12.8 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 195.2, 153.4, 133.8, 133.8, 129.5, 129.4, 126.5, 121.9, 121.0, 117.7, 117.5, 99.0, 96.8, 80.5, 78.2, 77.3, 73.1, 70.5, 69.3, 67.9, 56.6, 56.4, 34.8, 33.6; HRMS (ES) *m/z* calcd for $C_{17}H_{22}O_6SNa$ $(M + Na)^+$: 377.1035; found: 377.1032.




**(2*R*,3*R*,4*R*)-6-(Allyloxy)-4-methoxy-2-methyltetrahydro-2H-pyran-3-ol (120):** Azobisisobutyronitrile (13.3 mg, 0.081 mmol) then $n$$Bu_3SnH$ (0.23 mL, 0.86 mmol) were added to a solution of thionoformate **119b** (0.103 g, 0.291 mmol) in 16.8 mL toluene and the resulting reaction mixture was stirred for 3 h at 110-120 °C. The volatiles were removed under reduced pressure and the product was purified via flash column chromatography (20-40% EtOAc/hexanes) to yield 48 mg (82%) of the title compound as a yellow oil. $[\alpha]_D$ +62.2 (*c* 1.0, $CHCl_3$); IR (thin film): 3457, 3081, 2971, 2934, 2902, 1741, 1647, 1452, 1384, 1349, 1300, 1242, 1200, 1107, 1050, 986, 921, 869, 830, 767, 734 $cm^{-1}$; $^1H$ NMR

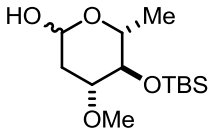
(400 MHz, $CDCl_3$) δ 5.96-5.86 (m, 1H), 5.29 (ddd, J = 2.0, 3.6, 17.3 Hz, 1H), 5.19 (dd, J = 1.2, 10.0 Hz, 1H), 4.93 (d, J = 3.2 Hz, 1H), 4.14 (ddt, J = 1.6, 5.2, 12.0 Hz, 1H), 3.94 (ddt, J = 1.2, 6.0, 12.8 Hz, 1H), 3.70 (ddd, J = 6.0, 9.2, 12.4 Hz, 1H), 3.54 (ddd, J = 4.8, 8.8, 11.2 Hz, 1H), 3.39 (s, 3H), 3.17 (dt, J = 1.6, 9.2 Hz, 1H), 2.45 (d, J = 2.0 Hz, 1H), 2.29 (ddd, J = 1.2, 4.8, 12.8 Hz, 1H), 1.51 (ddd, J = 3.6, 11.4, 12.6 Hz, 1H), 1.29 (d, J = 6.4 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 134.2, 117.1, 96.6, 78.3, 76.2, 67.7, 67.6, 56.4, 33.9, 17.8; HRMS (ES) *m/z* calcd for $C_{11}H_{20}O_4$ $(M + Na)^+$: 239.1259; found: 239.1240.




**(((2*R*,3*R*,4*R*)-6-(Allyloxy)-4-methoxy-2-methyltetrahydro-2H-pyran-3-yl)oxy)(*tert*-butyl)dimethylsilane (121):**

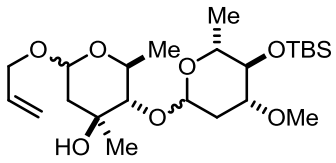
2,6-Lutidine (73 μL, 0.63 mmol) then TBSOTf (73 μL, 0.32 mmol) was added to a solution of alcohol **120** in 2.1 mL $CH_2Cl_2$ at 0 °C and the resulting reaction mixture was stirred for 2h before quenching with saturated aqueous $NaHCO_3$ (2 mL) and extracting with $CH_2Cl_2$ (4x 3 mL). The combined organic portions were dried ($Na_2SO_4$) and the product was purified via flash column chromatography (5% EtOAc/hexanes) to yield 0.052 g (78%) of the title compound as a yellow oil. $[\alpha]_D$ +70.8 (*c* 1.0, $CHCl_3$); IR (thin film): 2957, 2932, 2897, 2857, 1463, 1388, 1251, 1104, 1077, 1040, 987, 922, 893, 837, 777 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *mixture of α:β anomers only major anomer tabulated (~10:1 )* δ 5.95-5.86 (m, 1H), 5.28 (ddd, J = 1.6, 3.2, 17.2, 1H), 5.17 (ddd, J = 1.2, 2.8, 10.4 Hz, 1H), 4.87 (d, J = 2.8, 1H), 4.11 (ddt, J = 1.2, 5.2, 12.8 Hz, 1H), 3.91 (ddd, J = 1.2, 6.0, 12.8 Hz, 1H), 3.43-3.36 (m, 1H), 3.30 (s, 3H), 3.13 (t, J = 8.8 Hz, 1H), 2.28 (ddd, J = 1.6, 5.2, 13.2 Hz, 1H), 1.47 (ddd, J = 3.6, 11.2, 12.8 Hz, 1H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 134.3, 117.4,

117.1, 98.6, 96.4, 81.0, 78.5, 77.1, 76.6, 72.7, 69.6, 68.4, 67.7, 56.3, 56.1, 34.4, 26.0, 18.4, 18.3, −4.0, −4.8; HRMS (ES) *m/z* calcd for $C_{16}H_{32}O_4Si$ $(M + Na)^+$: 339.1968; found: 339.2020.




**(4*R*,5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methoxy-6-methyltetrahydro-2H-pyran-2-ol (95):**

Quinaldic acid (3.00 mg, 0.017 mmol) as a solution in 0.5 mL MeOH was added to a suspension of $[CpRu(MeCN)_3]PF_6$ (7.40 mg, 0.017 mmol) in 0.5 mL MeOH and the resulting reaction mixture was stirred for 30 min before addition of allyl ether **121** (0.052 g, 0.165 mmol) as a solution in 0.2 mL $CH_2Cl_2$. The resulting reaction mixture was stirred for 6 h before being diluted with $Et_2O$ and passed through a plug of florasil eluting with $Et_2O$. The product was purified via flash column chromatography (5-20% EtOAc/hexanes) to yield 0.032 g (70%) of the title compound. $[\alpha]_D$ +29.8 (*c* 1.0, $CHCl_3$); IR (thin film): 3409, 2956, 2932, 2891, 2857, 1463, 1388, 1252, 1150, 1107, 993, 893, 837, 777 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *mixture of α:β anomers (~2:1 )* δ 5.33 (d, J = 2.8 Hz, 1H), 4.78 (d, J = 9.6 Hz, 1H), 3.87 (ddd, J = 6.4, 12.8, 15.6 Hz, 1H), 3.74 (bs, 1H), 3.45 (ddd, J = 5.2, 8.8, 11.6 Hz, 1H), 3.31 (s, 3H), 3.31 (s, 3H), 3.13 (t, J = 8.8 Hz, 1H), 3.12 (t, J = 5.2 Hz, 1H), 3.06 (bs, 1H), 2.41 (ddd, J = 2.0, 4.4, 12.8 Hz, 1H), 2.29 (ddd, J = 1.2, 4.8, 13.2 Hz, 1H), 1.50-1.31 (m, 2H), 1.26 (d, J = 10.4 Hz, 3H), 1.22 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.09-0.07 (m, 12H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 94.0, 92.0, 80.8, 78.1, 77.2, 76.3, 72.9, 68.6, 56.4, 56.2, 37.0, 34.3, 26.0, 26.0, 18.5, 18.4, 18.3, 18.3, −4.0, −4.8, −4.8; HRMS (ES) *m/z* calcd for $C_{13}H_{29}O_4Si$ $(M + Na)^+$: 277.1835; found: 277.1865.



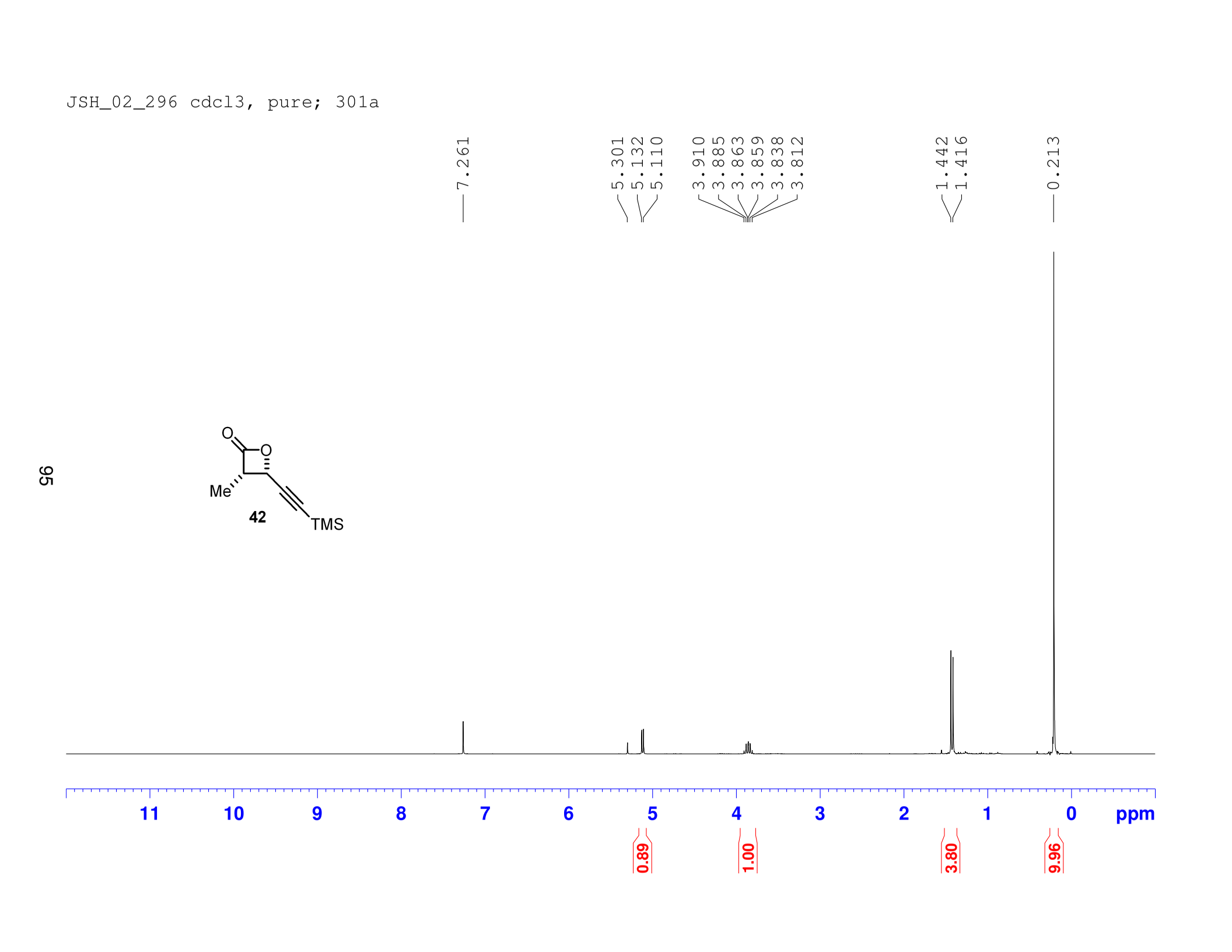

**(2*S*,3*S*,4*S*)-6-(Allyloxy)-3-(((4*R*,5*R*,6*R*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2,4-dimethyltetrahydro-2H-pyran-4-ol (122):**

Bromotrimethylsilane (25.0 μL, 0.190 mmol) was added to a solution of alcohol **95** (41.0 mg, 0.149 mmol) in 0.50 mL of benzene and the reaction mixture was allowed to stir for 5 min before removing the volatiles. The resulting crude anomeric bromide was dissolved in 0.5 mL $CH_2Cl_2$ and added to a suspension of diol **115** (82.0 mg, 0.406 mmol), 4 Å MS (50 mg) and $Ag_2O$-$SiO_2$[74, 75] (250 mg, 0.856 mmol) in 1.5 mL $CH_2Cl_2$ at 0 °C and the resulting reaction mixture was allowed to stir for 30 min before quenching with $NEt_3$. The quenched reaction mixture was loaded directly onto a flash column and eluted (20% EtOAc/Hexanes) to give 26.2 mg (38%) of the title compound and 12.4 mg (18%) of what is believed to be alkylation at the tertiary alcohol. $[\alpha]_D$ +86.6 (*c* 1.0, $CHCl_3$); IR (thin film): 3437, 2932, 2858, 1462, 1387, 1103, 1074, 990 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) *mixture of 4 diastereomers from α:β anomers only major anomer tabulated* δ 5.96-5.88 (m, 1H), 5.27 (d, J = 1.5, 17 Hz, 1H), 5.24 (d, J = 3.0 Hz, 1H), 5.20-5.16 (m, 1H), 4.56 (dd, J = 2.0, 10.0 Hz, 1H), 4.35 (ddd, J = 1.5, 3.5, 13.0 Hz, 1H), 4.13 (s, 1H), 4.04 (dd, J = 6.0, 13.0 Hz, 1H), 3.85-3.79 (m, 1H), 3.39-3.32 (m, 3H), 3.3 (s, 3H), 3.19 (d, J = 9.5 Hz, 1H), 3.13 (t, J = 8.5 Hz, 1H), 2.17 (dd, J = 8.0Hz, 1H), 1.99 (dd, J = 1.5, 8.0 Hz, 1H), 1.78 (t, J = 10.5 Hz, 1H), 1.33 (d, J = 6.0 Hz, 3H), 1.29 (s, 3H), 1.22 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); *mixture of 4 diastereomers from α:β anomers* $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 134.3, 134.1, 134.1, 134.0, 117.4, 117.4, 117.0, 98.5, 98.4, 98.3, 98.1, 93.9, 92.5, 91.7, 90.8, 81.0, 79.6, 78.9, 78.3, 78.1, 78.0, 75.1, 72.8, 70.9, 70.8, 70.4, 70.4, 70.3, 70.2, 70.2, 69.8, 69.7, 69.7, 69.4, 68.6, 56.4, 56.3, 56.2, 45.1, 43.8, 41.6, 36.3, 35.3, 34.4, 31.9, 26.0, 26.0, 20.5, 19.8,

18.6, 18.6, 18.6, 18.5, 18.5, 18.3, 18.3, 18.2, 18.2, 16.0, −4.0, −4.8; HRMS (ES) *m/z* calcd for $C_{23}H_{44}O_7Si$ $(M + Na)^+$: 483.2754; found: 483.2760.

# APPENDIX: SPECTRA

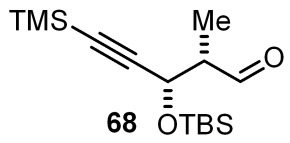
JSH_02_296 cdcl3, pure; 301a



JSH_02_212 300

9.775
9.771
7.261
4.716
4.701
2.547
2.542
2.532
2.527
2.523
2.519
2.508
2.504
2.496
2.485
2.481
1.194
1.171
0.875
0.159
0.153
0.113

96

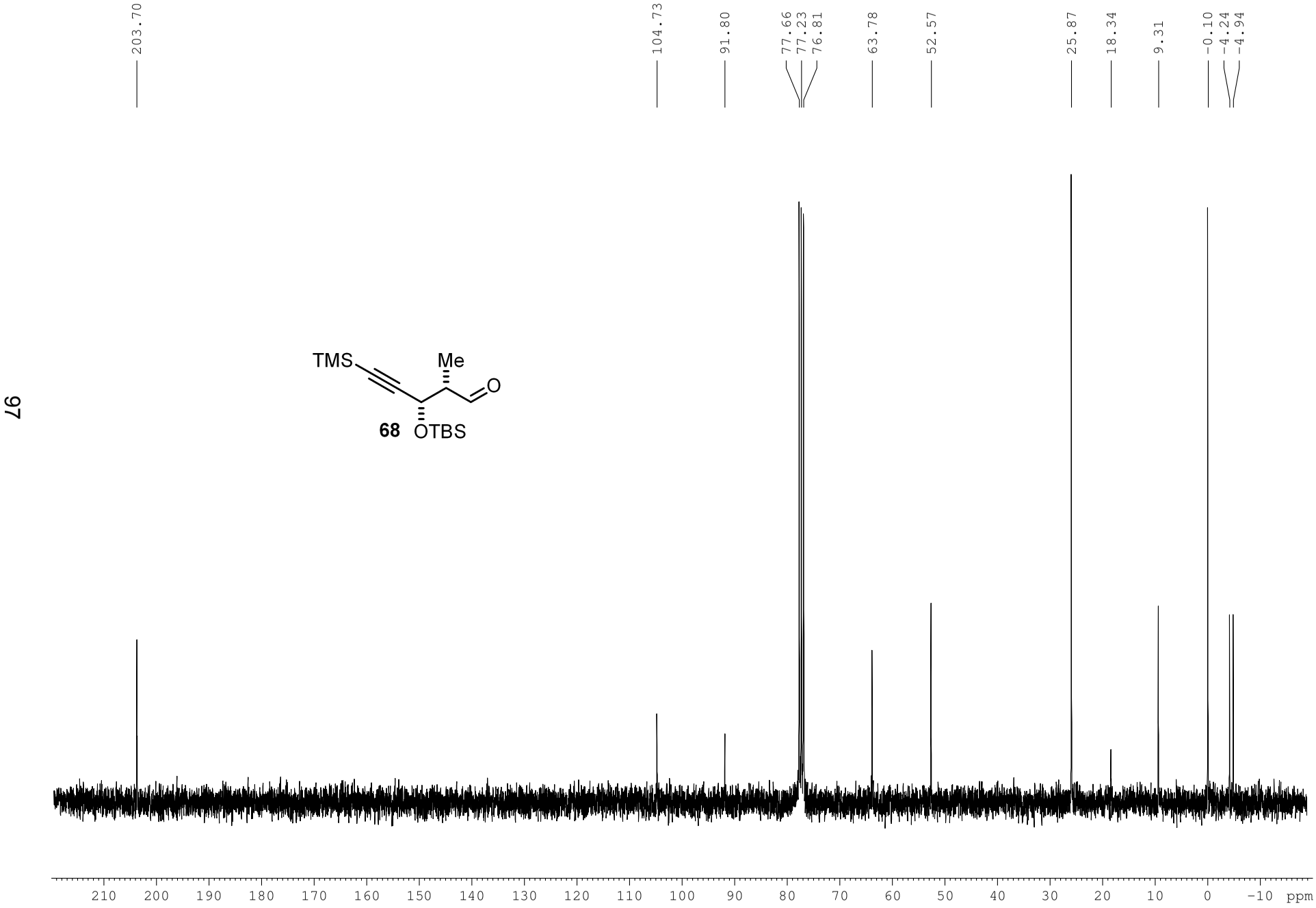



**68**

11 10 9 8 7 6 5 4 3 2 1 0 ppm

1.00 1.10 1.19 4.31 12.24 18.42

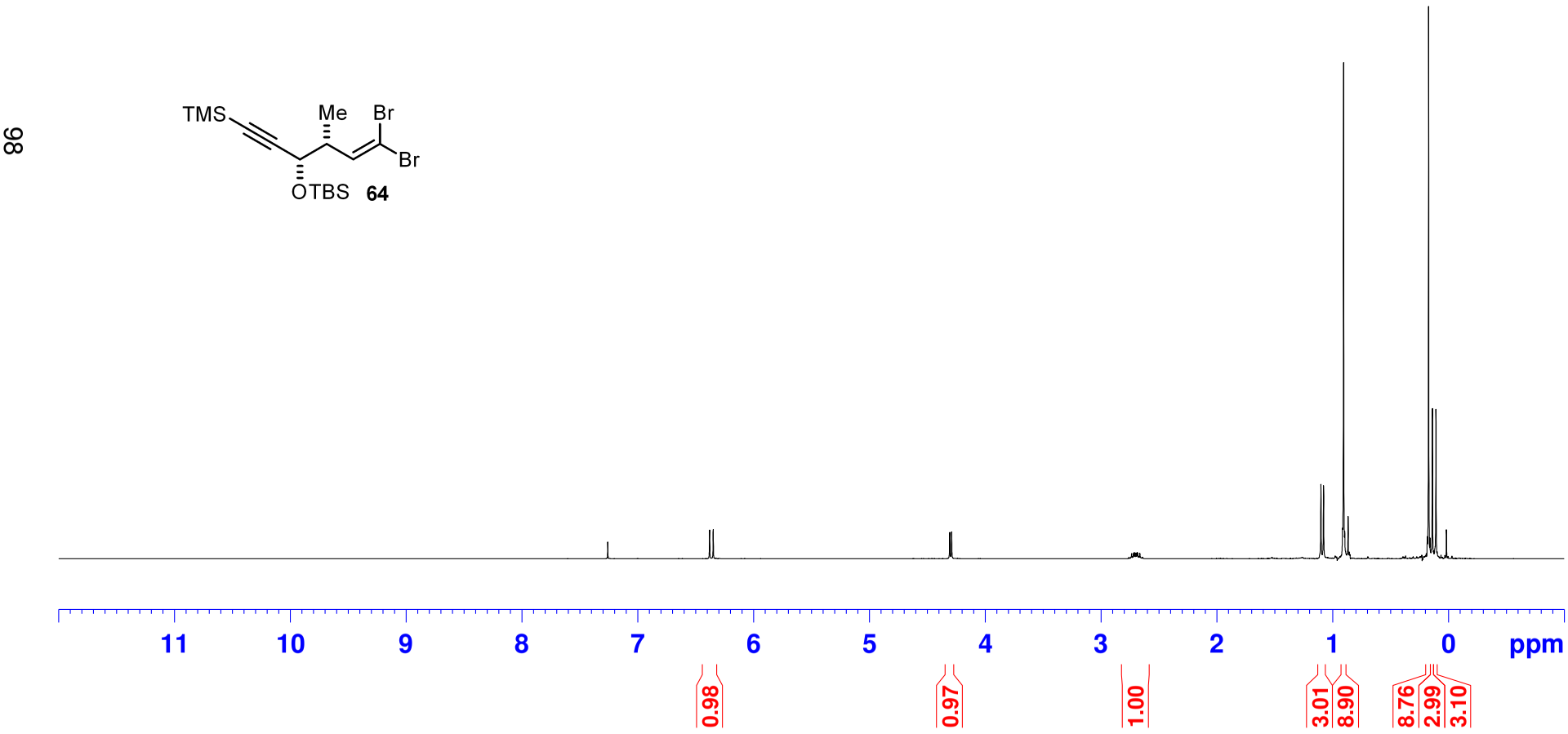
JSH_02_212 300



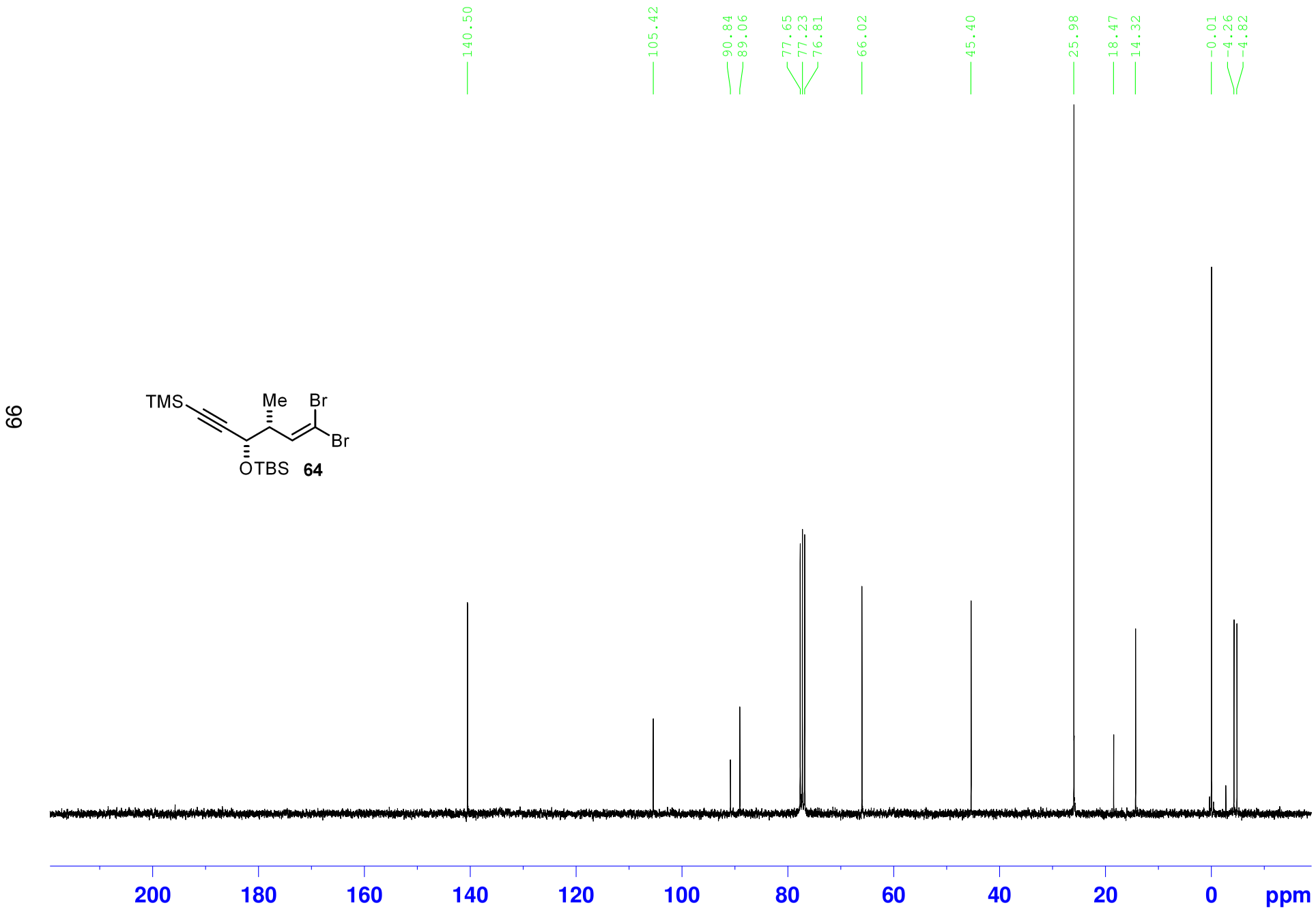
JSH_02_219 301

6.380
6.349

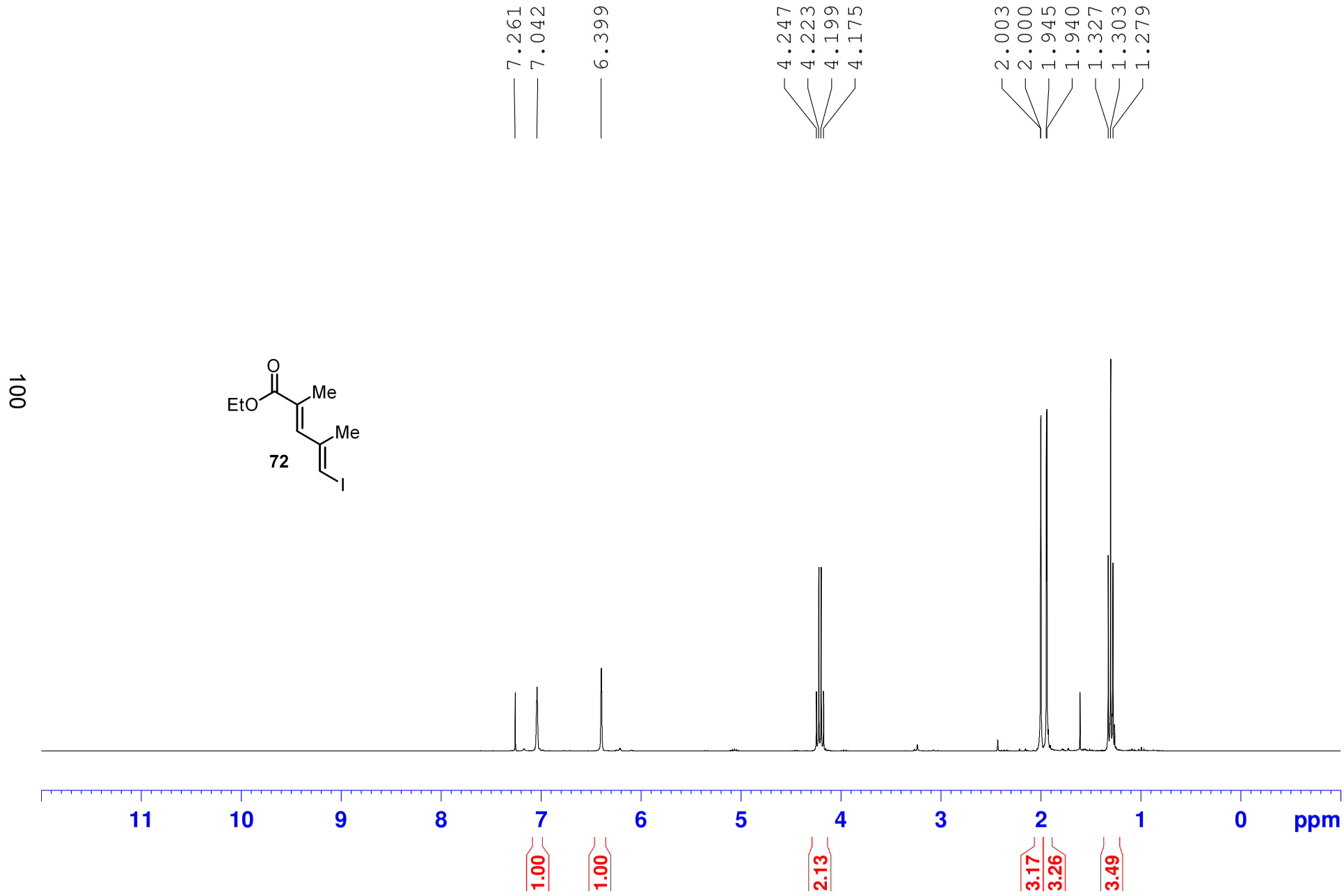
4.307
4.290
2.759
2.742
2.736
2.727
2.720
2.713
2.705
2.697
2.688
2.682
2.674
2.666
2.659
2.643
1.101
1.079
0.906
0.172
0.139
0.108



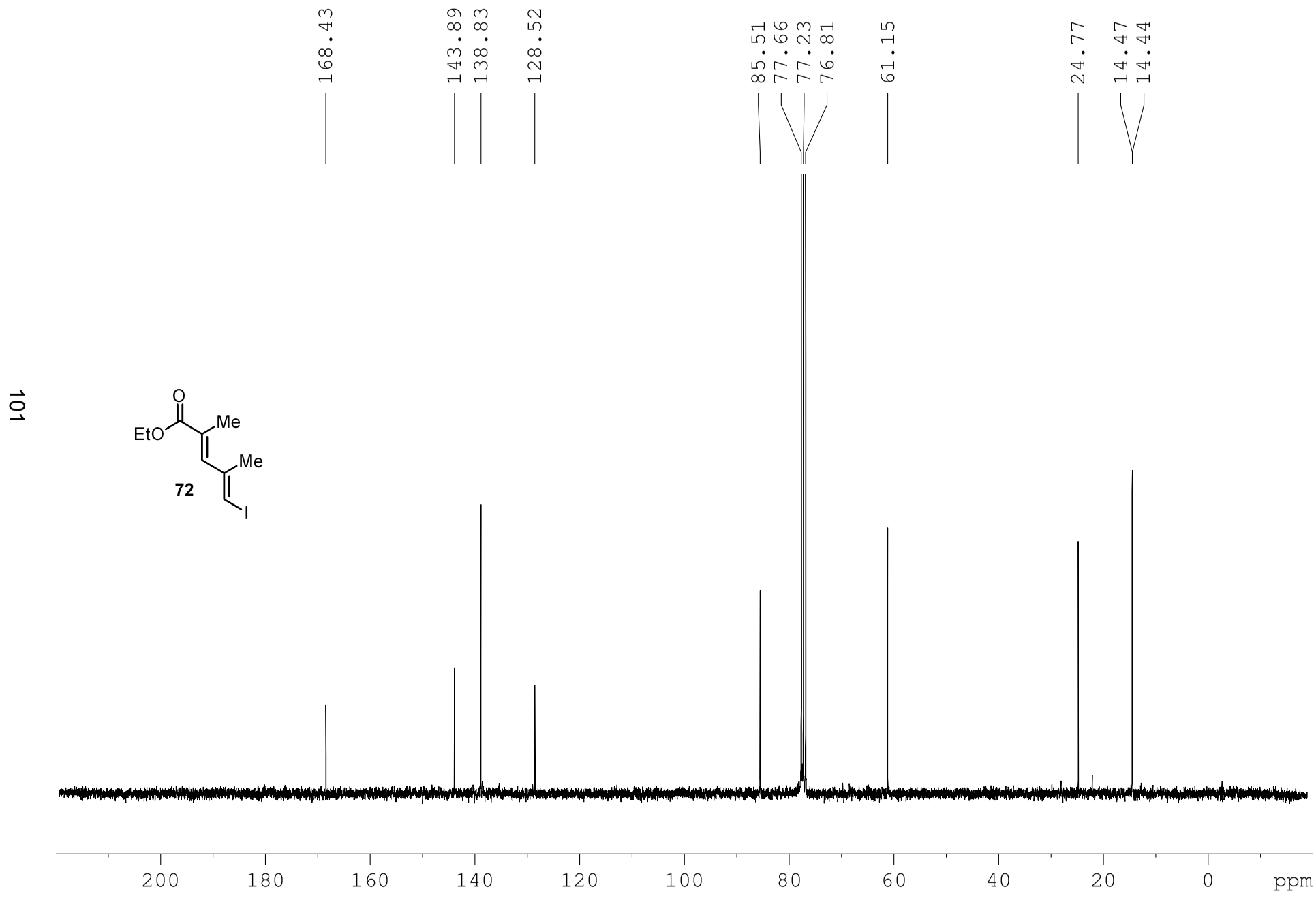
JSH_02_219 301



JSH_02_204 301

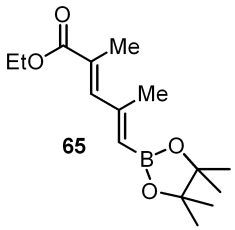


JSH_02_204 301



JSH_02_223 301

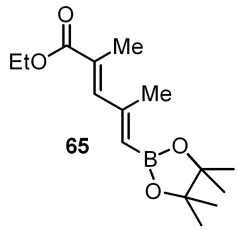
7.260
7.121
5.378
4.239
4.237
4.215
4.213
4.191
4.189
4.168
4.166
2.119
1.984
1.321
1.319
1.298
1.295
1.282
1.280




102

JSH_02_223 301

168.97
154.94
143.23
128.43
83.28
77.66
77.23
76.81
60.96
25.07
21.49
14.47
14.31

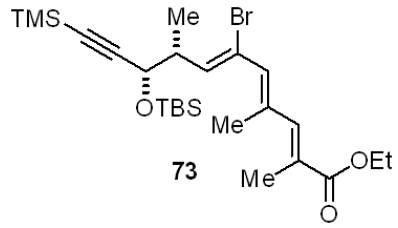



103

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_02_201

7.260
7.183
7.125
6.091
6.087
5.824
5.821
5.794
5.790
4.330
4.313
4.252
4.228
4.204
4.180
2.969
2.951
2.946
2.939
2.929
2.922
2.916
2.898
2.352
2.037
2.032
2.024
2.013
2.008
1.938
1.603
1.344
1.332
1.309
1.290
1.285
1.269
1.127
1.104
0.903
0.894
0.884
0.866
0.817
0.351
0.184
0.164
0.153
0.137
0.127
0.113
0.104
0.094
0.076
-0.049



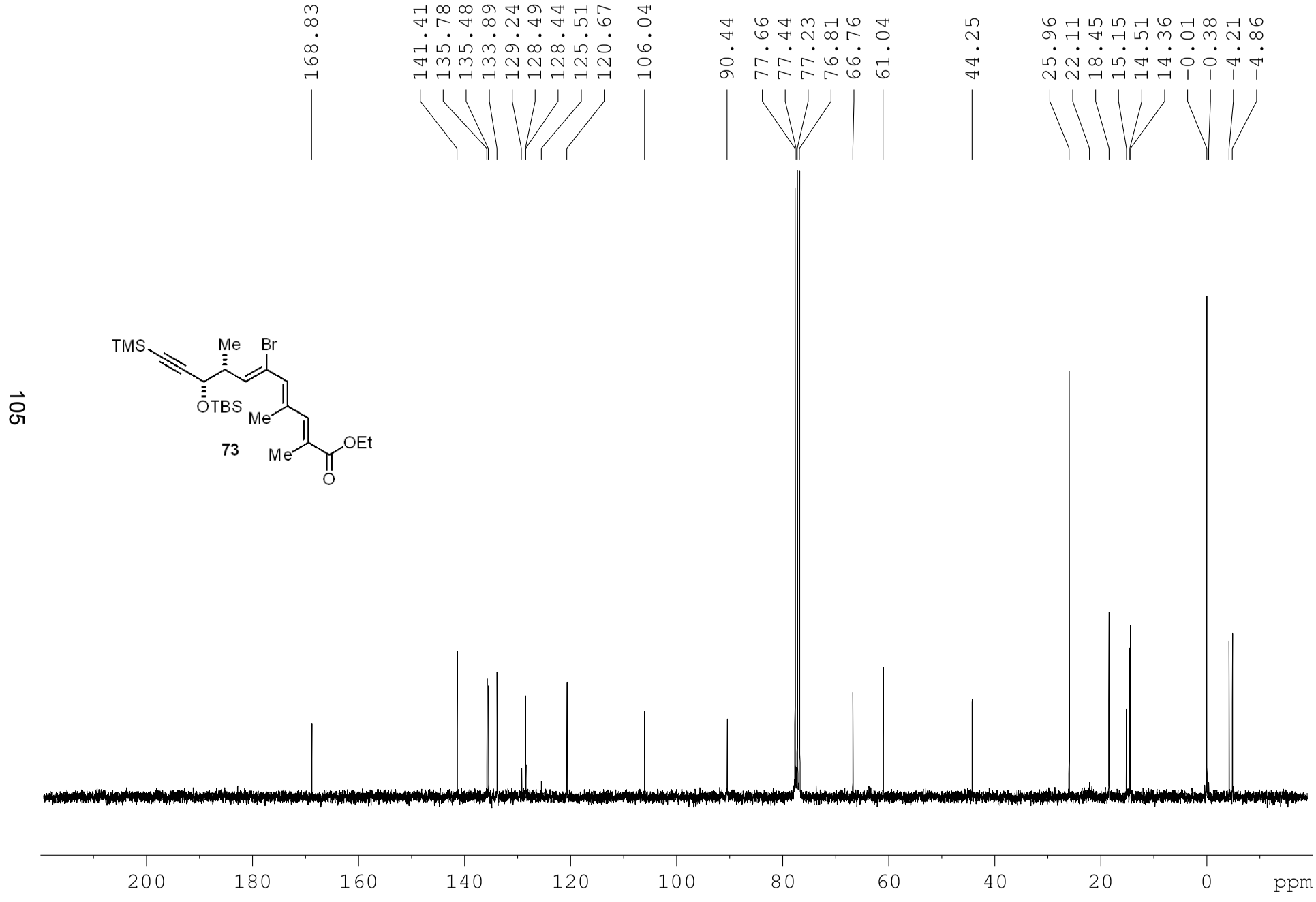

73

104

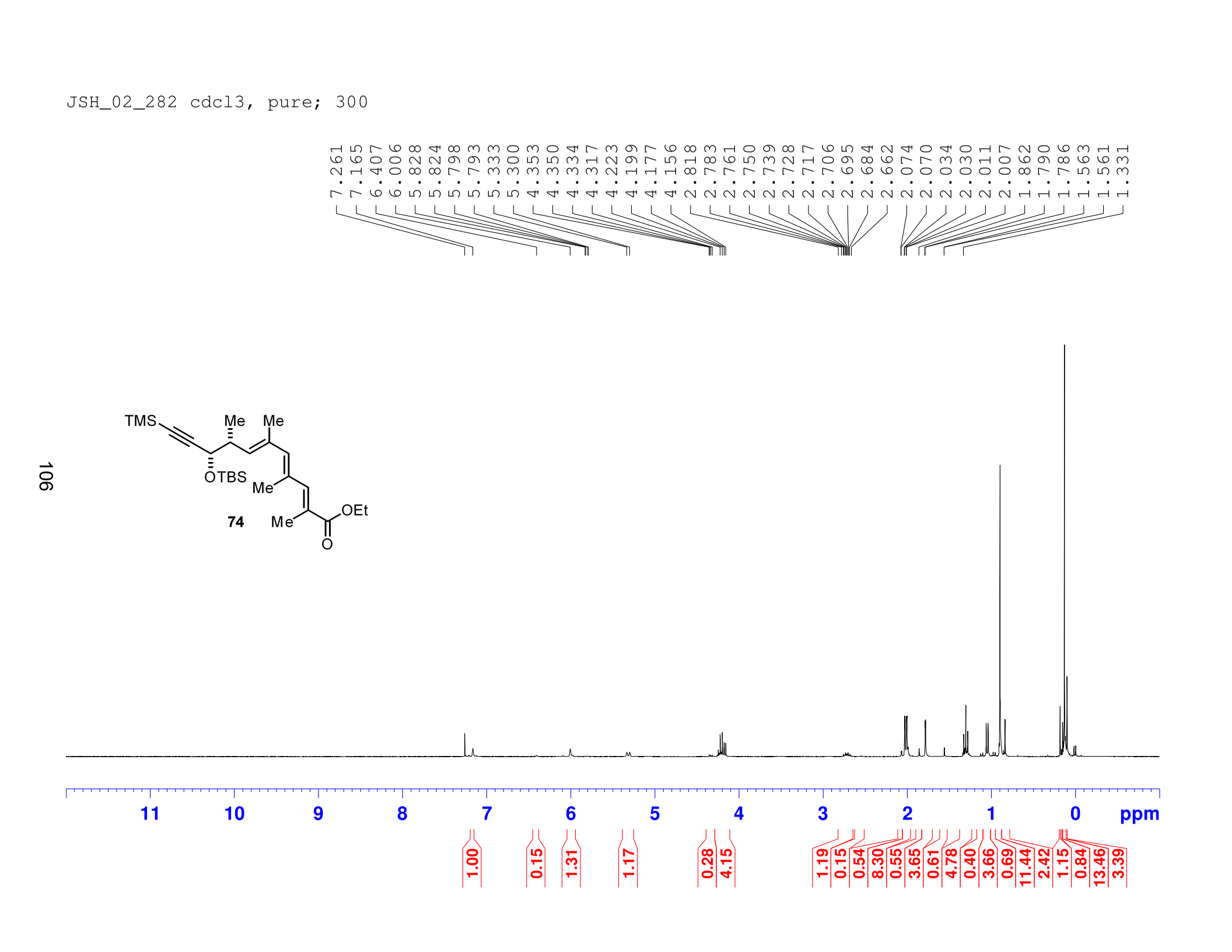
11 10 9 8 7 6 5 4 3 2 1 0 ppm

1.00 1.03 1.04 1.06 2.21 1.07 2.91 3.52 3.49 3.25 9.74 8.25 3.01 2.57

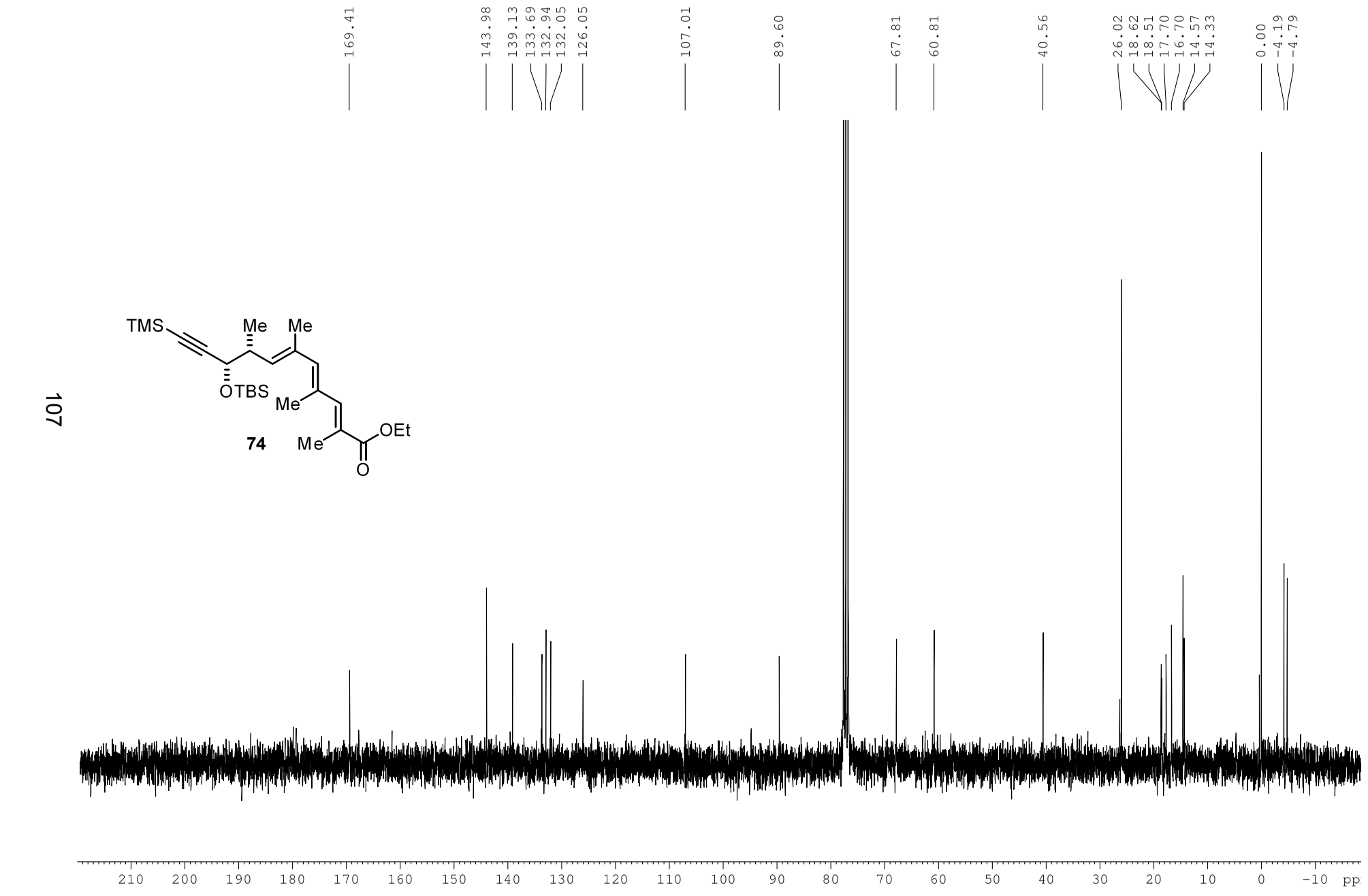
JSH_02_201 301



JSH_02_282 cdcl3, pure; 300

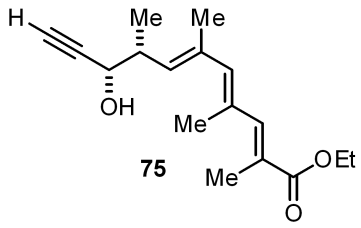


JSH_02_282 cdcl3, pure; 300



JSH_02_284 pure, cdcl3; 300

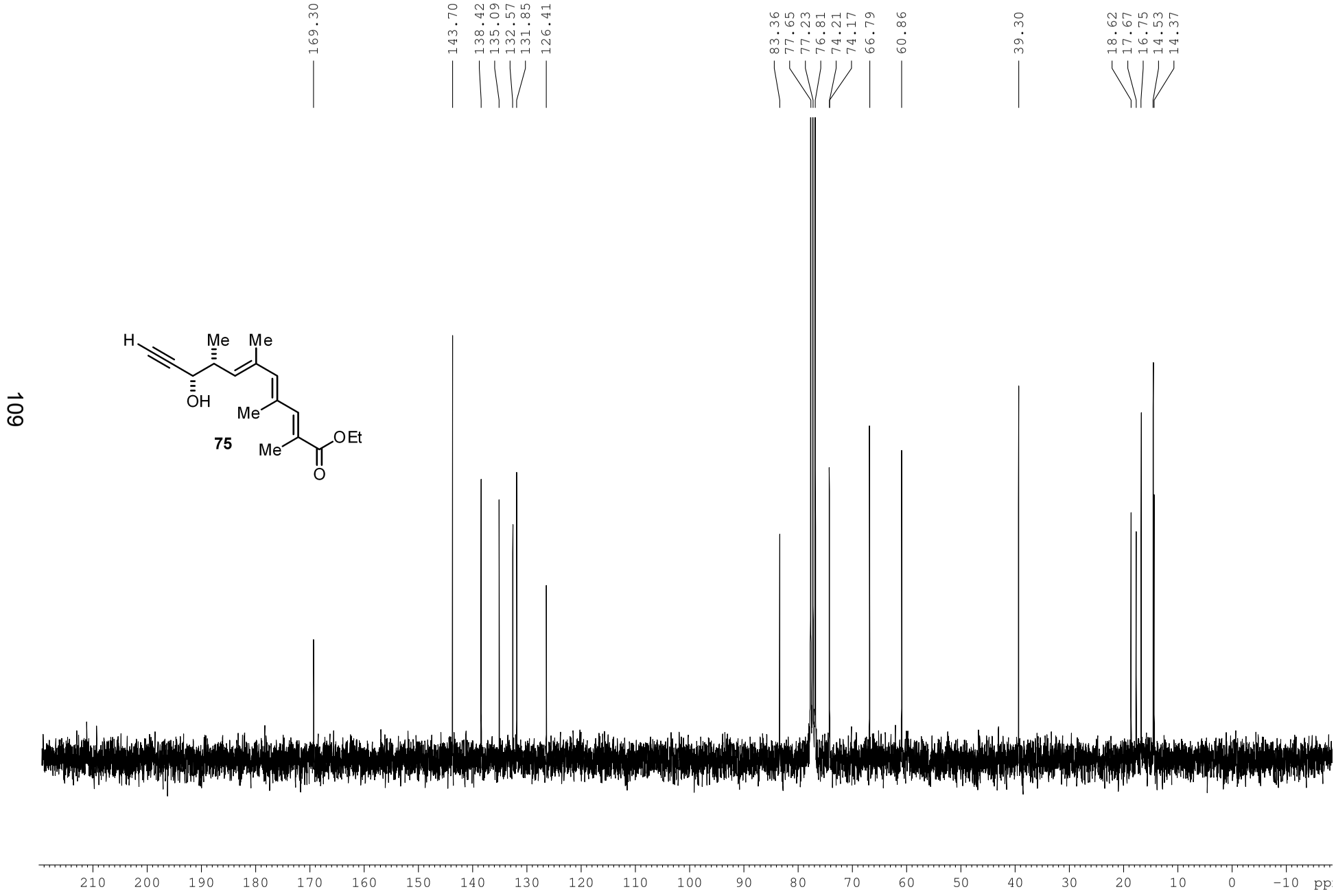
7.261
7.155
6.030
5.436
5.432
5.403
5.399
4.303
4.244
4.220
4.197
4.173
2.908
2.890
2.886
2.875
2.868
2.863
2.858
2.853
2.845
2.840
2.835
2.830
2.823
2.812
2.808
2.790
2.464
2.457
2.034
2.029
2.011
2.007
1.971
1.948
1.828
1.824




75

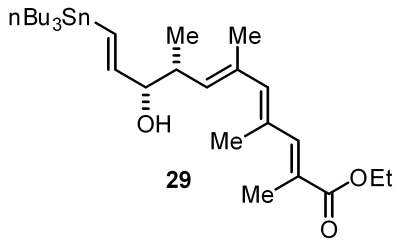
108

JSH_02_284 pure, cdcl3; 300



JSH_02_259 pure, cdcl3; 600

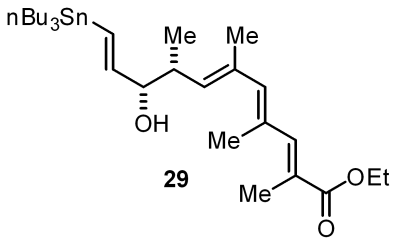
7.262 7.260 7.152 6.191 6.159 6.157 6.068 6.067 6.060 6.058 6.005 5.285 5.268 4.226 4.216 4.214 4.204 4.202 4.192 4.191 3.987 3.977 2.026 2.025 1.981 1.799 1.612 1.603 1.565 1.563 1.505 1.494 1.492 1.479 1.474 1.466 1.453 1.320 1.318 1.312 1.309 1.307 1.300 1.297 1.295 1.288 1.275 1.056 1.044 0.892 0.890 0.879 0.878 0.867 0.865




29

JSH_02_274 cdcl3, pure; 300

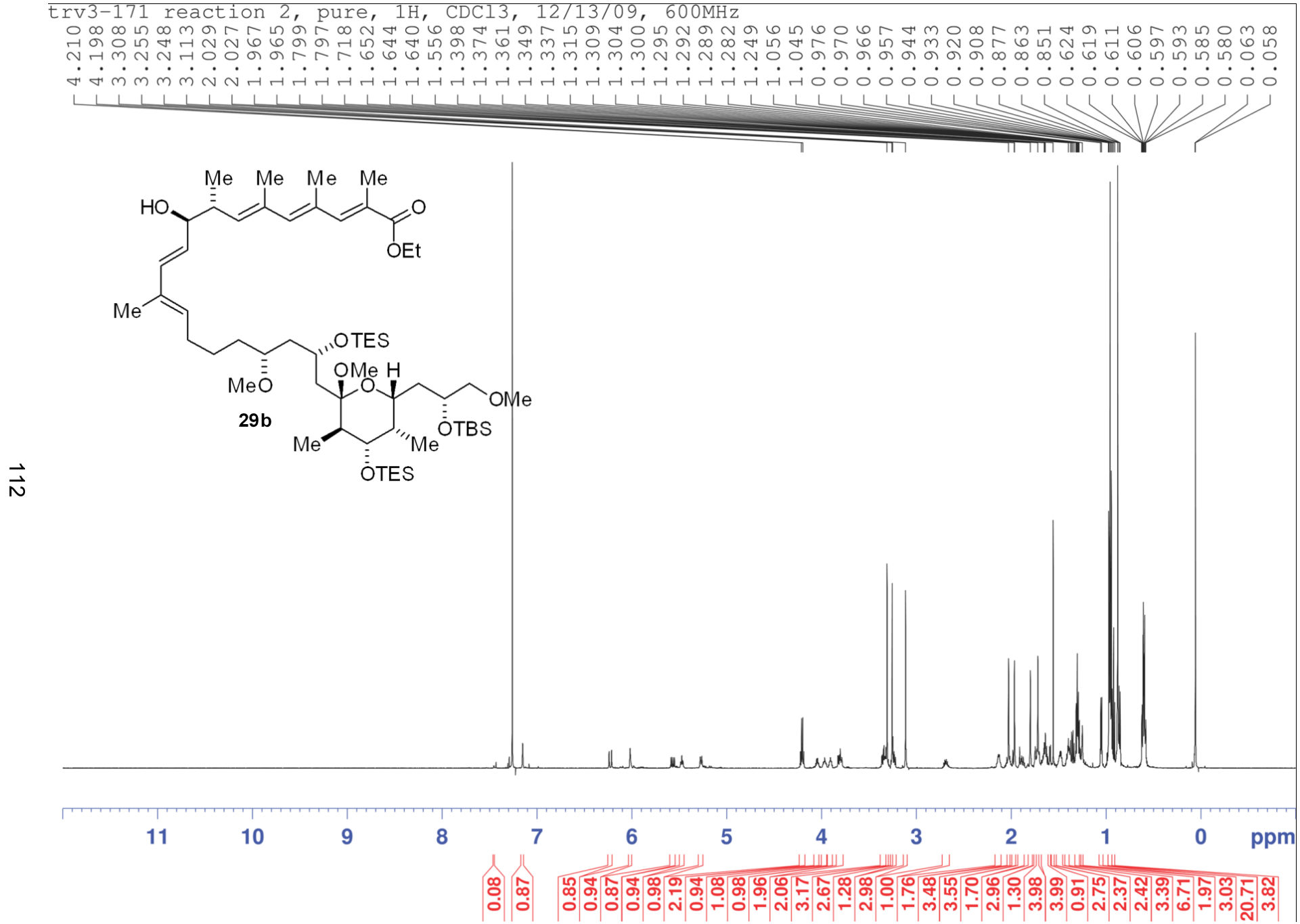
169.34
148.92
143.87
138.96
134.04
133.12
131.97
129.03
126.11
79.22
77.66
77.24
76.81
60.82
39.36
29.29
27.48
18.63
17.54
16.74
14.53
14.33
13.89
9.70

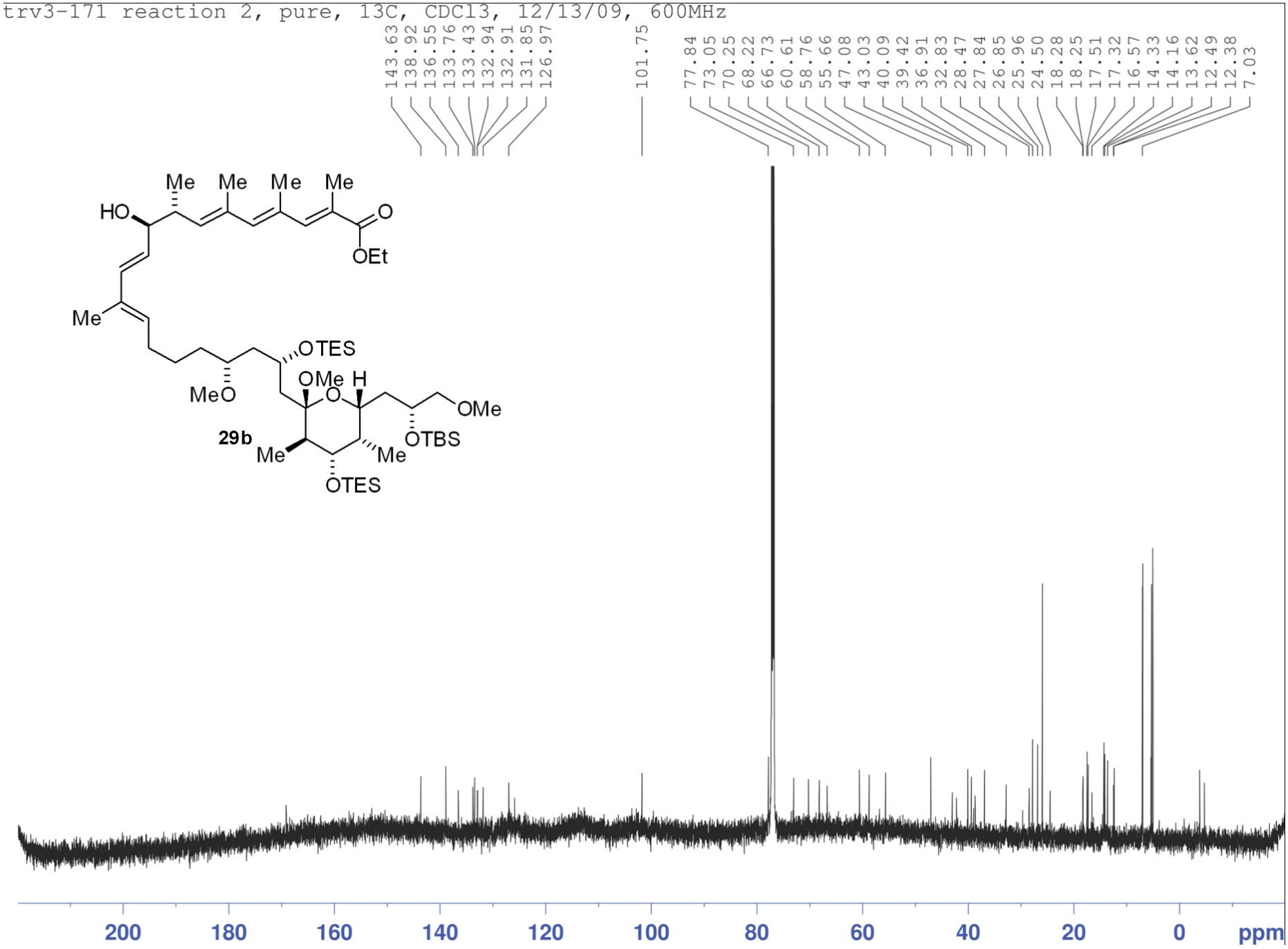



29



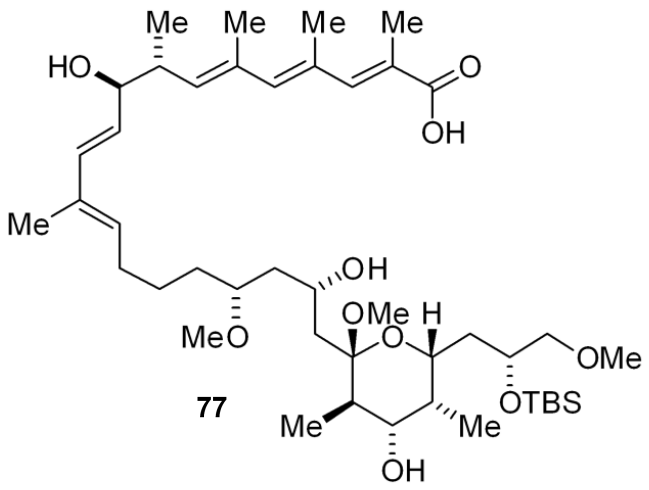
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

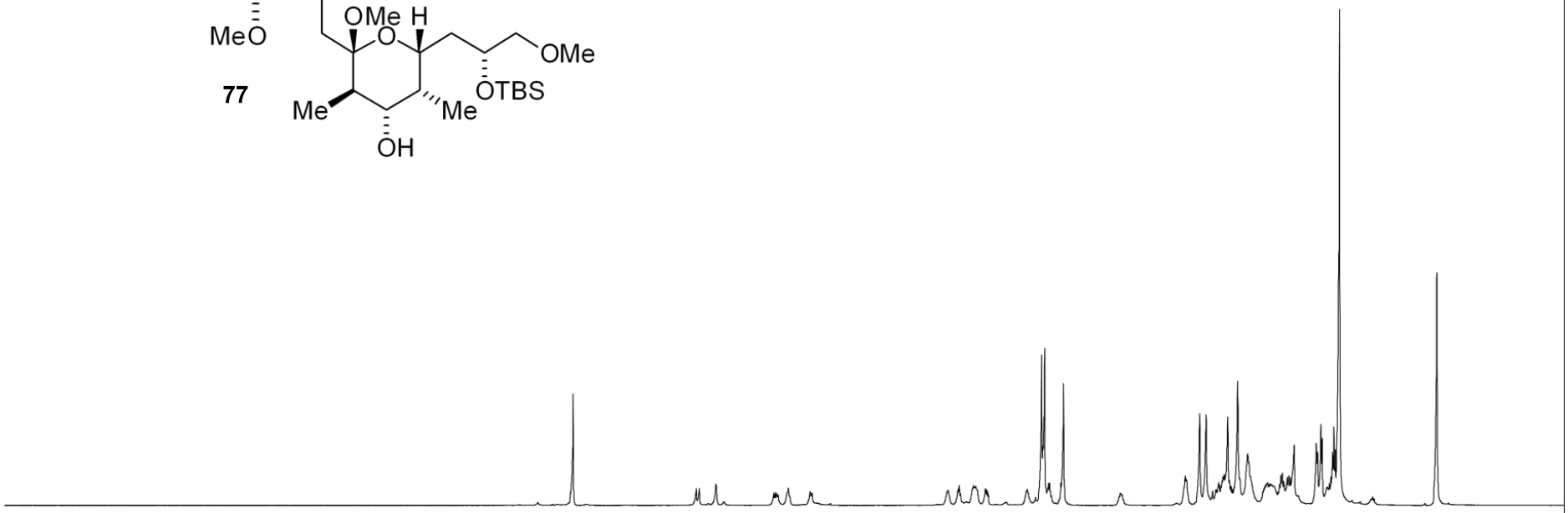

trv3-171 reaction 2, pure, 1H, CDCl3, 12/13/09, 600MHz
4.210 4.198 3.308 3.255 3.248 3.113 2.029 2.027 1.967 1.965 1.799 1.797 1.718 1.652 1.644 1.640 1.556 1.398 1.374 1.361 1.349 1.337 1.315 1.309 1.304 1.300 1.295 1.292 1.289 1.282 1.249 1.056 1.045 0.976 0.970 0.966 0.957 0.944 0.933 0.920 0.908 0.877 0.863 0.851 0.624 0.619 0.611 0.606 0.597 0.593 0.585 0.580 0.063 0.058
Me Me Me Me
HO
O
OEt
Me
OTES
MeO
OMe H
O
OMe
29b
OTBS
Me
Me
OTES
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.08 0.87 0.85 0.94 0.87 0.94 0.98 2.19 0.94 1.08 0.98 1.96 2.06 3.17 2.67 1.28 2.98 1.00 1.76 3.48 3.55 1.70 2.96 1.30 3.98 3.99 0.91 2.75 2.37 2.42 3.39 6.71 1.97 3.03 20.71 3.82


trv3-171 reaction 2, pure, 13C, CDCl3, 12/13/09, 600MHz
143.63
138.92
136.55
133.76
133.43
132.94
132.91
131.85
126.97
101.75
77.84
73.05
70.25
68.22
66.73
60.61
58.76
55.66
47.08
43.03
40.09
39.42
36.91
32.83
28.47
27.84
26.85
25.96
24.50
18.28
18.25
17.51
17.32
16.57
14.33
14.16
13.62
12.49
12.38
7.03
Me
Me
Me
Me
HO
O
OEt
Me
OTES
MeO
OMe
H
O
OMe
29b
OTBS
Me
Me
OTES
200
180
160
140
120
100
80
60
40
20
0
ppm

JSH_03_010 seco acid, cdcl3; 600

7.260 6.068 4.041 3.354 3.344 3.335 3.329 3.297 3.287 3.194 3.172 3.166 3.158 2.147 2.036 1.983 1.879 1.873 1.849 1.843 1.832 1.803 1.788 1.720 1.706 1.700 1.638 1.626 1.612 1.487 1.480 1.475 1.471 1.461 1.450 1.440 1.430 1.372 1.359 1.347 1.335 1.308 1.294 1.281 1.248 1.065 1.054 1.026 1.016 0.930 0.919 0.906 0.872 0.061



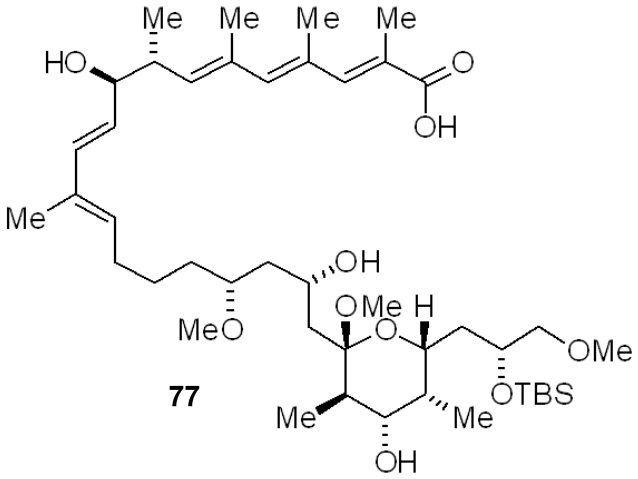



11 10 9 8 7 6 5 4 3 2 1 0 ppm

1.00 0.88 1.14 1.09 0.96 1.13 1.21 2.30 1.11 1.23 3.50 3.95 1.37 3.35 0.98 2.07 3.04 3.46 1.88 2.02 3.91 5.29 5.65 4.75 2.40 2.23 3.02 2.82 3.17 5.07 14.02 0.71

JSH_03_010 seco acid, cdcl3; 600

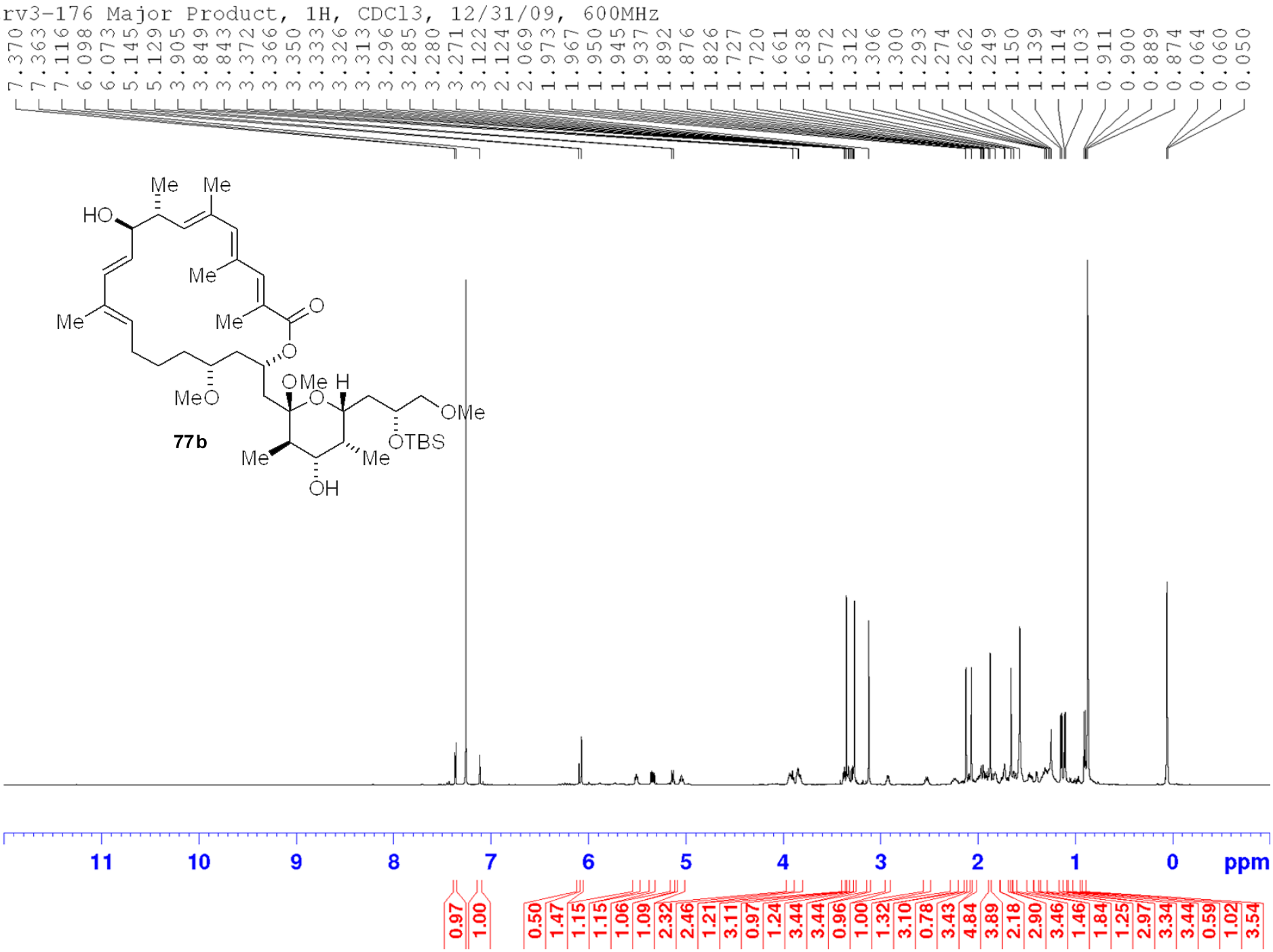
173.11
145.85
140.17
136.49
134.29
133.12
133.02
132.85
131.78
127.15
124.62
102.19
78.82
77.57
72.44
69.82
68.40
65.97
58.83
56.80
47.94
42.17
40.76
39.54
39.44
39.29
38.89
38.49
32.92
29.69
28.32
27.83
27.02
26.84
25.93
25.18
18.21
18.17
17.51
17.25
16.63
16.44
13.88
13.68
13.61
12.50
11.47
6.95
5.11




77

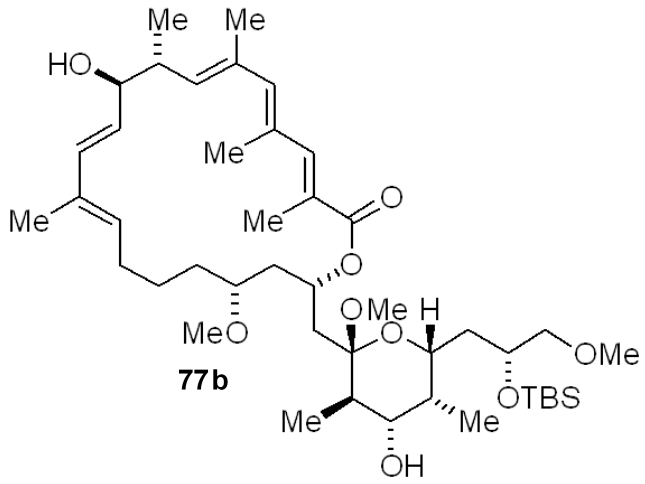
115

200 180 160 140 120 100 80 60 40 20 0 ppm

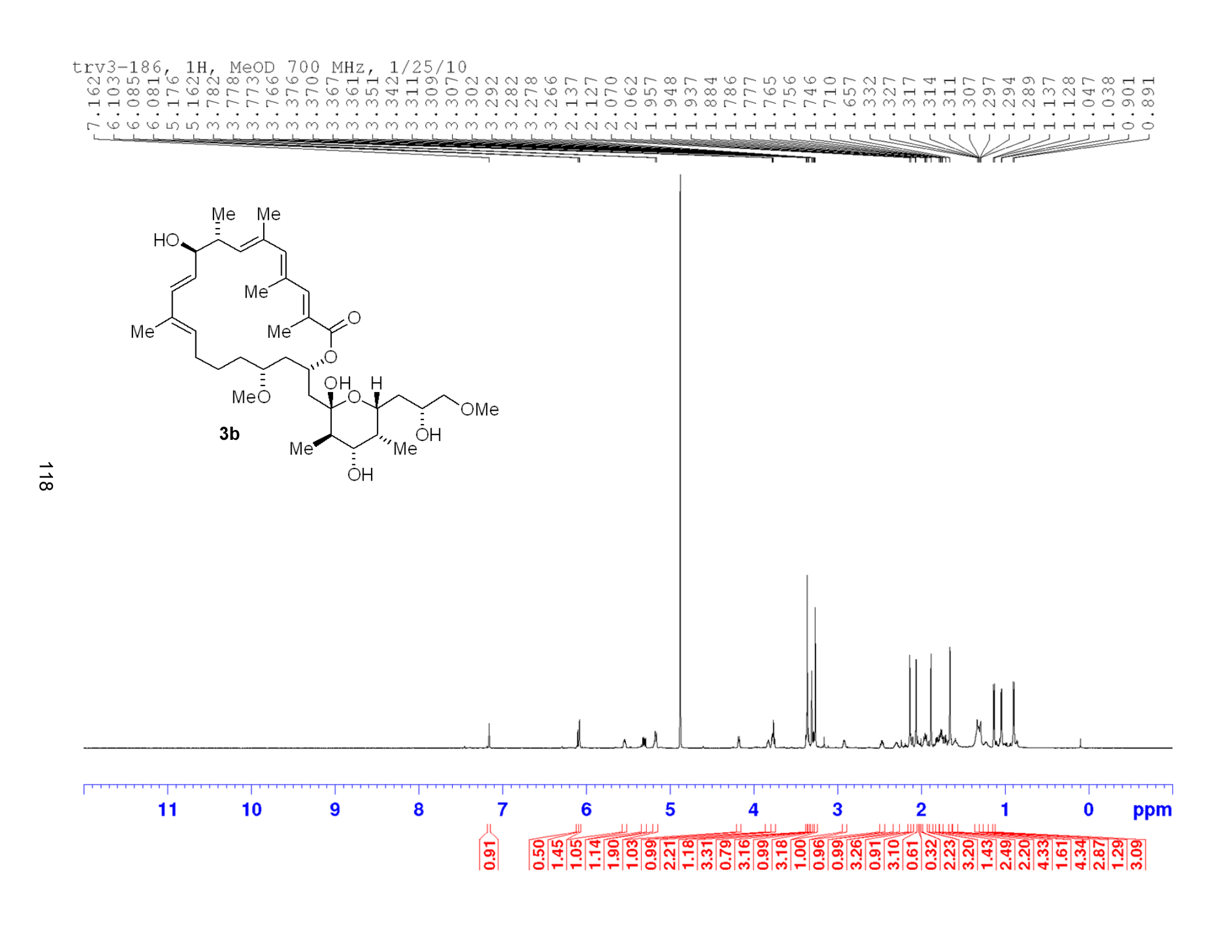

trv3-176 Major Product, 1H, CDCl3, 12/31/09, 600MHz
7.370 7.363 7.116 6.098 6.073 5.145 5.129 3.905 3.849 3.843 3.372 3.366 3.350 3.333 3.326 3.313 3.296 3.285 3.280 3.271 3.122 2.124 2.069 1.973 1.967 1.950 1.945 1.937 1.892 1.876 1.826 1.727 1.720 1.661 1.638 1.572 1.312 1.306 1.300 1.293 1.274 1.262 1.249 1.150 1.139 1.114 1.103 0.911 0.900 0.889 0.874 0.064 0.060 0.050
HO
Me
Me
Me
Me
Me
O
O
MeO
OMe
H
O
OMe
OTBS
Me
Me
OH
77b
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.97 1.00 0.50 1.47 1.15 1.15 1.06 1.09 2.32 2.46 1.21 3.11 0.97 1.24 3.44 3.44 0.96 1.00 1.32 3.10 0.78 3.43 4.84 3.89 2.18 2.90 3.46 1.46 1.84 1.25 2.97 3.34 3.44 0.59 1.02 3.54

trv3-176 Major Product, 13C, CDCl3, 12/31/09, 600MHz

168.72
145.17
144.58
140.32
137.33
133.07
132.82
132.16
131.87
128.33
128.23
127.13
123.79
101.54
79.77
79.02
77.79
72.43
70.60
70.03
68.49
58.83
57.34
47.20
41.37
39.54
38.93
38.42
37.04
33.50
29.70
28.00
26.71
25.95
18.24
17.56
17.30
16.29
13.75
12.00
11.36
4.92
-3.84
-4.69

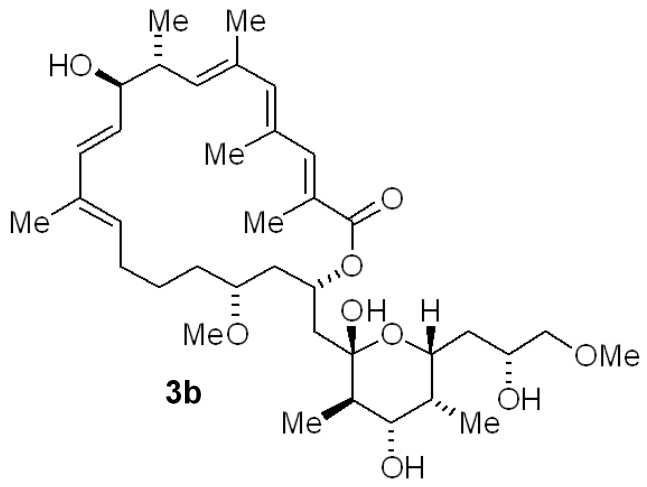



**77b**


trv3-186, 1H, MeOD 700 MHz, 1/25/10
7.162 6.103 6.085 6.081 5.176 5.162 3.782 3.778 3.773 3.766 3.376 3.370 3.367 3.361 3.351 3.342 3.311 3.309 3.307 3.302 3.292 3.282 3.278 3.266 2.137 2.127 2.070 2.062 1.957 1.948 1.937 1.884 1.786 1.777 1.765 1.756 1.746 1.710 1.657 1.332 1.327 1.317 1.314 1.311 1.307 1.297 1.294 1.289 1.137 1.128 1.047 1.038 0.901 0.891
HO
Me
Me
Me
Me
Me
O
O
MeO
OH
H
O
OMe
OH
Me
Me
OH
3b
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.91 0.50 1.45 1.05 1.14 1.90 1.03 0.99 2.21 1.18 3.31 0.79 3.16 0.99 3.18 1.00 0.96 0.99 3.26 0.91 3.10 0.61 0.32 2.23 3.20 1.43 2.49 2.20 4.33 1.61 4.34 2.87 1.29 3.09

trv3-186, 13C, MeOD 700 MHz, 1/25/10

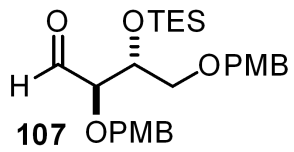
170.95
147.12
146.01
142.50
137.93
134.47
133.48
132.99
132.92
129.42
124.72
100.27
80.91
80.41
78.69
73.58
71.31
68.46
68.35
59.39
57.47
46.06
43.08
41.08
40.89
38.67
38.13
34.38
28.84
28.05
17.97
17.84
16.72
14.10
12.43
12.22
5.69




**3b**

JSH_04_111 cdcl3; 400b

9.593 9.589 7.260 7.255 7.233 7.226 7.213 7.192 6.874 6.869 6.865 6.859 6.853 6.848 6.843 4.612 4.408 4.388 4.378 4.197 4.188 4.184 4.178 4.176 4.169 4.166 4.157 3.888 3.884 3.880 3.876 3.814 3.804 3.798 3.787 3.777 3.773 3.766 3.757 3.625 3.606 3.601 3.582 3.455 3.442 3.431 3.418 0.941 0.921 0.901




**107**

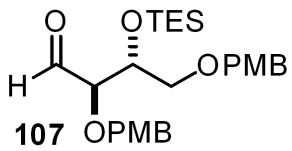
120

11 10 9 8 7 6 5 4 3 2 1 0 ppm

0.77 4.37 4.00 1.83 2.14 0.97 0.78 6.22 1.10 1.04 10.27 6.87

JSH_04_111 cdcl3; 400b

202.77
159.59
159.38
130.19
129.86
129.81
129.51
114.01
113.91
84.75
77.55
77.43
77.23
76.91
73.21
73.15
73.04
70.01
55.45
6.95
4.91

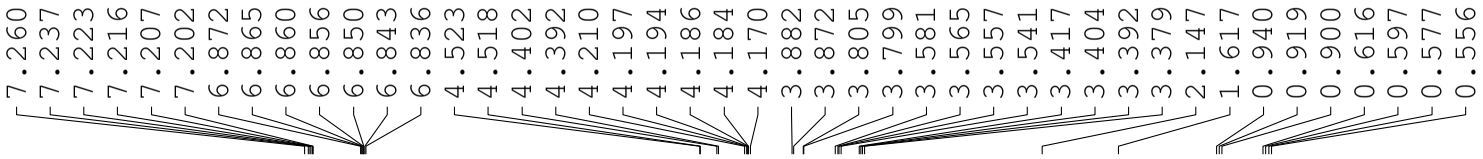



**107**

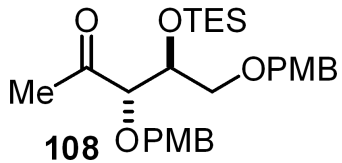
121

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_113 cdcl3; 400b



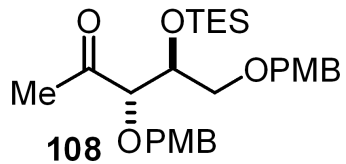

122




**108**

JSH_04_113 cdcl3; 400b

210.45
159.50
159.32
130.39
130.01
129.70
129.52
113.95
113.85
85.60
77.55
77.23
76.91
73.28
73.07
72.95
70.69
55.46
55.45
28.08
6.98
5.01



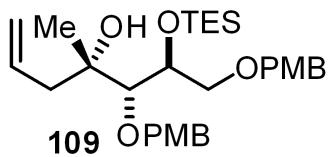

**108**

123

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_117 cdcl3; 400b

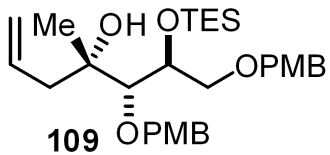
7.237 7.226 7.215 7.208 7.203 7.199 7.150 7.128 6.845 6.824 6.803 5.848 5.829 5.805 5.060 5.055 5.035 4.995 4.598 4.571 4.517 4.490 4.468 4.439 4.402 4.373 4.105 4.095 3.769 3.767 3.726 3.716 3.701 3.692 3.677 3.502 3.488 3.477 3.464 3.403 3.390 2.322 2.315 2.301 1.157 0.949 0.929 0.910 0.904 0.639 0.620 0.602 0.599 0.582 0.578




**109**

JSH_04_117 cdcl3; 400b

159.19
159.15
134.52
130.53
129.85
129.53
129.49
129.34
117.57
113.69
113.65
84.33
77.31
77.00
76.68
74.54
74.14
73.63
72.90
71.42
55.23
55.21
42.96
24.22
6.84
5.00



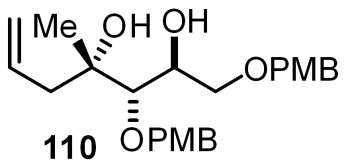

**109**

125

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_118 cdcl3; 400b

7.279 7.274 7.260 7.258 7.251 7.165 7.160 7.148 7.143 6.899 6.894 6.886 6.882 6.877 6.866 6.861 6.850 6.845 5.119 5.107 5.101 5.098 5.096 5.093 5.064 4.550 4.533 4.522 4.506 4.475 4.447 3.805 3.717 3.709 3.693 3.685 3.624 3.609 3.600 3.585 3.425 3.407 3.156 3.042 3.031 2.391 2.390 2.373 2.046 1.706 1.260 1.248 1.243 1.221

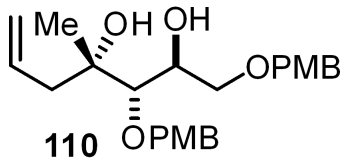



**110**

126

JSH_04_118 cdcl3; 400b

159.37
159.24
134.19
130.21
129.75
129.63
129.37
117.94
113.86
113.75
83.21
77.32
77.00
76.69
74.85
74.79
73.06
71.50
70.78
55.24
42.53
24.01



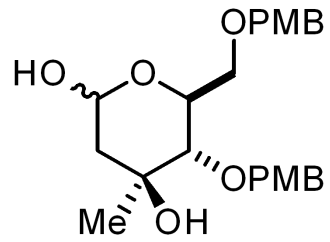

**110**

127

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_121 cdcl3; 400b

7.271 7.260 7.252 7.249 7.166 7.161 7.145 7.129 7.125 6.863 6.855 6.847 6.844 6.842 6.833 6.826 4.639 4.635 4.611 4.607 4.536 4.523 4.516 4.507 4.494 4.468 4.463 4.439 4.433 3.790 3.786 3.776 3.664 3.658 3.639 3.632 3.626 3.624 3.612 3.605 3.601 3.403 3.395 3.379 3.371 2.042 1.930 1.925 1.909 1.906 1.868 1.444 1.255 1.237 1.229




**111**

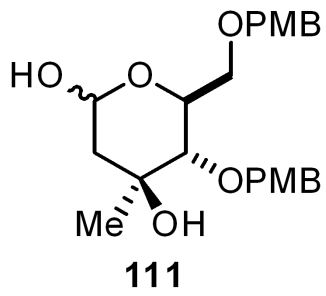
128

11 10 9 8 7 6 5 4 3 2 1 0 ppm

4.95 4.54 9.39 1.00 1.33 2.30 0.71 1.35 1.90 2.09 0.78 1.36 0.44 1.16 13.90 1.58 1.00 3.39 1.39 1.38 0.87 0.68 1.93 2.32 2.10 1.33 3.09 4.57

JSH_04_121 cdcl3; 400b

159.19
130.54
130.42
129.73
129.72
129.47
129.42
113.79
113.69
93.56
91.64
81.26
80.72
77.32
77.00
76.69
74.46
74.34
74.28
73.04
72.45
72.25
69.98
69.32
69.28
55.17
55.15
46.13
42.87
23.47
21.42



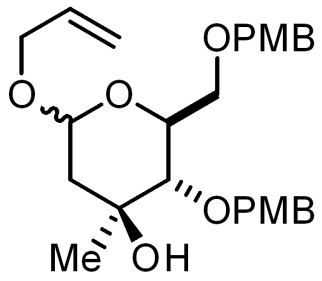

**111**

129

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_040 36-48, cdcl3; 400a 24
PROTON CDCl3 C:\Bruker\TOPSPIN nelson 16

7.297 7.276 7.260 7.180 7.158 6.881 6.876 6.864 6.859 6.853 6.841 6.836 5.297 5.293 5.253 5.250 5.194 5.190 5.168 5.164 4.608 4.599 4.581 4.575 4.570 4.556 4.522 4.493 4.130 4.112 4.064 3.799 3.796 3.789 3.707 3.700 3.691 3.680 3.478 3.472 3.467 3.442 3.420 2.046 2.000 1.994 1.967 1.962 1.853 1.803 1.781 1.552 1.275 1.259 1.242




**112**

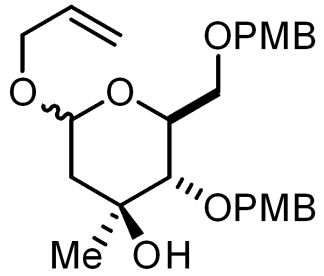
130

11 10 9 8 7 6 5 4 3 2 1 0 ppm

5.95 2.08 4.19 1.00 1.06 1.03 5.33 1.09 0.76 1.04 6.44 2.26 2.05 1.02 1.10 1.01 1.04 1.97 4.31

JSH_04_122 cdcl3; 400b

159.27
159.15
134.14
130.50
130.28
129.54
129.49
117.21
113.86
113.70
98.41
80.93
77.31
77.00
76.68
74.77
74.21
73.12
72.27
69.59
69.48
55.22
44.17
22.14



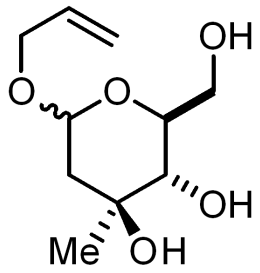

**112**

131

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_126 cdcl3; 500

7.260 5.919 5.908 5.898 5.887 5.886 5.875 5.874 5.863 5.853 5.841 5.277 5.274 5.263 5.242 5.239 5.185 5.183 5.164 5.162 4.576 4.573 4.556 4.553 4.341 4.331 4.315 4.305 4.087 4.047 4.035 4.021 4.009 3.895 3.884 3.869 3.850 3.846 3.821 3.801 3.796 3.654 3.638 3.618 3.243 3.223 2.003 1.981 1.978 1.779 1.759 1.754 1.733 1.400 1.251




**114**

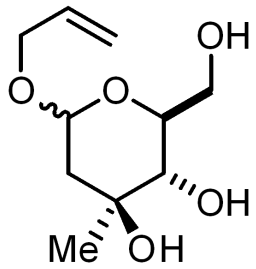
132

11 10 9 8 7 6 5 4 3 2 1 0 ppm

1.00 1.02 1.04 0.11 1.77 1.06 0.52 0.38 1.28 2.83 0.26 1.18 0.21 0.95 1.09 0.13 0.92 0.35 2.76

JSH_04_126 cdcl3; 500

134.20
133.89
117.48
116.49
98.85
98.77
96.80
77.25
77.00
76.74
74.98
72.97
72.04
70.81
69.87
67.89
61.90
44.68
42.71
21.74
20.02



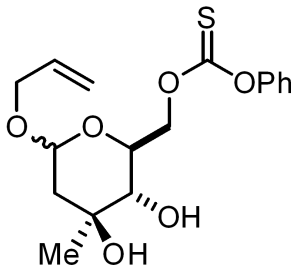

**114**

133

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_135 cdcl3; 400b

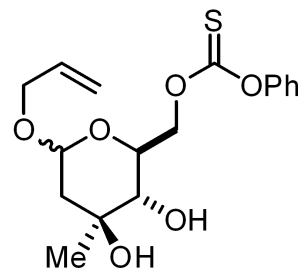
7.436 7.417 7.405 7.401 7.397 7.386 7.365 7.311 7.292 7.260 7.196 7.193 7.175 7.172 7.133 7.130 7.125 7.112 7.110 5.324 5.321 5.316 5.293 5.282 5.277 5.225 5.222 5.218 5.199 5.196 4.854 4.830 4.825 4.763 4.749 4.647 4.642 4.624 4.619 4.354 4.072 3.641 3.633 3.627 3.604 3.579 3.546 2.079 2.074 2.046 2.041 1.813 1.807 1.321 1.310




**114b**

JSH_04_135 cdcl3; 400b

195.27
154.15
153.34
150.96
133.81
133.77
129.53
129.50
126.60
126.16
121.86
120.97
117.69
117.65
98.52
73.65
73.60
73.02
72.77
71.95
71.87
69.83
69.80
68.17
53.41
44.37
20.41
20.38



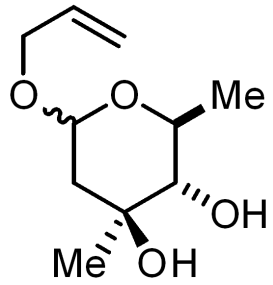

**114b**

135

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_139 cdcl3; 400b

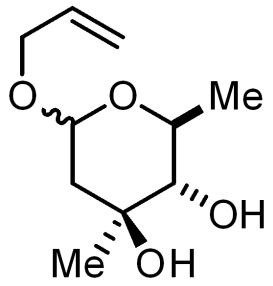
7.260 5.944 5.930 5.917 5.902 5.888 5.874 5.861 5.846 5.289 5.285 5.246 5.242 5.189 5.187 5.163 5.161 4.539 4.534 4.514 4.510 4.349 4.336 4.317 4.305 4.110 4.045 4.029 4.013 3.997 3.358 3.342 3.333 3.328 3.319 3.304 3.289 3.252 3.231 3.207 2.029 2.007 2.002 1.975 1.971 1.762 1.737 1.732 1.706 1.312 1.297 1.267 1.250 1.240 1.237




**115**

JSH_04_139 cdcl3; 400b

134.26
133.93
117.49
116.45
98.27
96.35
79.47
79.19
77.31
77.20
77.00
76.68
72.12
71.79
70.97
69.69
67.76
66.71
44.98
43.04
29.63
22.02
20.33
18.32
18.04



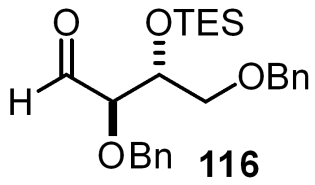

**115**

137

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_163 cdcl3; 301 4th floor

9.759 9.755 9.657 9.652 7.360 7.357 7.352 7.343 7.335 7.329 7.316 7.301 7.291 7.285 7.279 7.260 4.791 4.751 4.711 4.602 4.500 4.473 4.247 4.239 4.236 4.228 4.222 4.211 3.939 3.934 3.928 3.923 3.697 3.672 3.665 3.640 3.517 3.500 3.485 3.468 1.607 0.965 0.949 0.938 0.912 0.883 0.646 0.622 0.606 0.595 0.580 0.569 0.567 0.553 0.529




**116**

138

11 10 9 8 7 6 5 4 3 2 1 0 ppm

0.33 0.97 15.70 0.46 2.09 0.55 2.01 1.08 1.48 1.00 0.39 1.15 0.53 1.49 13.83 9.07

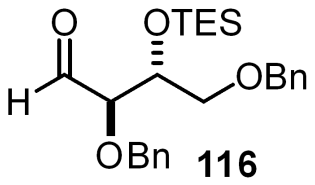
JSH_04_163 cdcl3; 301 4th floor

195.90
195.32

130.92
130.88
130.54
130.35
121.44
121.40
121.32
121.18
121.04
120.91
120.87
120.64
120.61

77.97
76.98
70.43
70.21
70.01
69.58
66.32
66.17
66.05
65.34
63.41
63.15

-0.30
-1.89
-2.28
-2.68



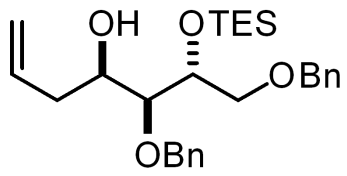

**116**

139

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_107 cdcl3; 400b

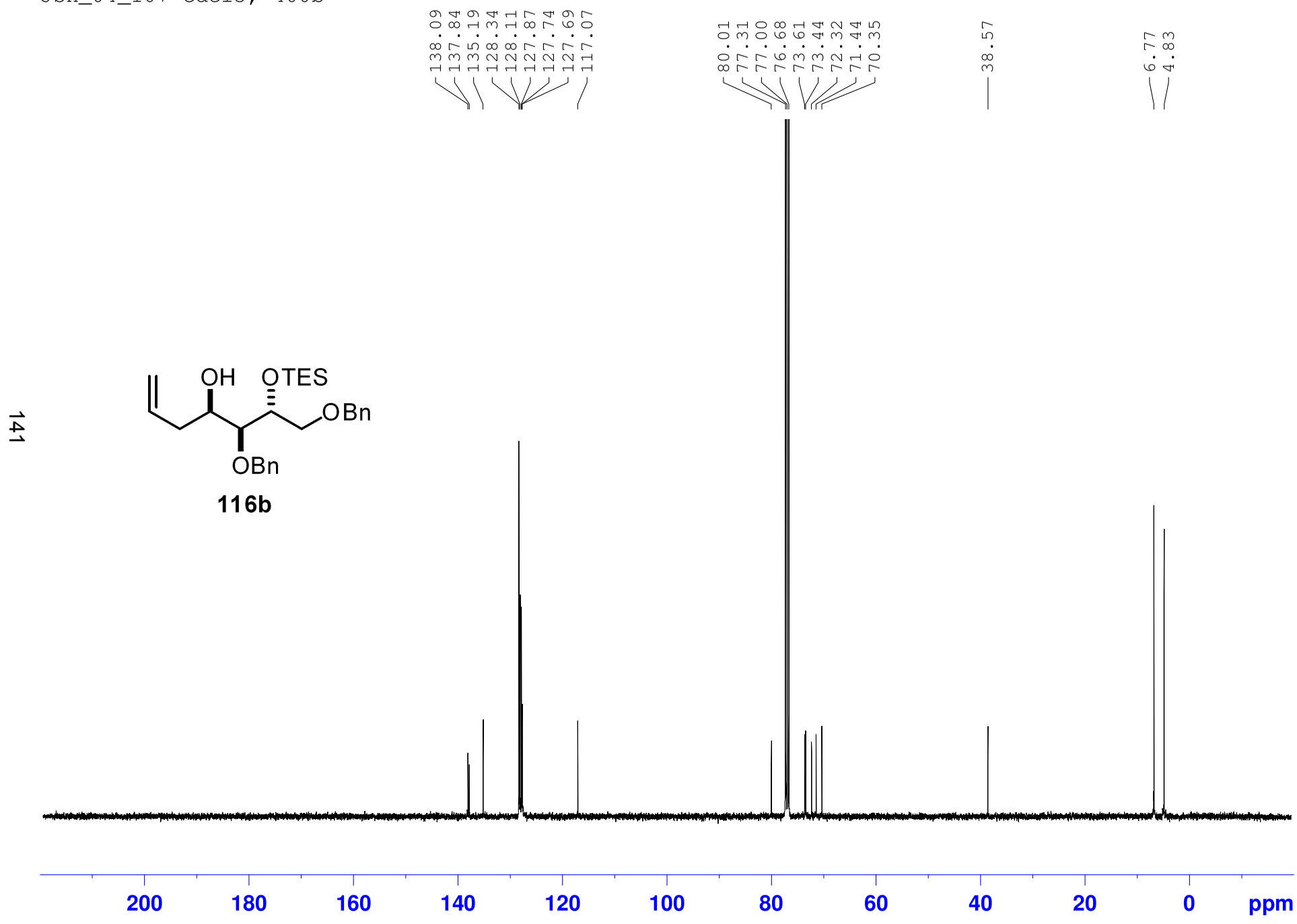
7.344 7.342 7.328 7.316 7.305 7.297 7.292 7.276 7.260 5.795 5.767 5.066 5.039 5.025 5.021 4.727 4.699 4.555 4.523 4.114 4.102 4.090 3.880 3.874 3.866 3.861 3.855 3.627 3.615 3.602 3.590 3.585 3.573 3.560 3.548 3.504 3.498 3.491 3.485 3.015 3.001 2.348 2.330 2.312 2.296 2.293 2.278 1.617 0.971 0.951 0.931 0.662 0.643 0.623 0.602




**116b**

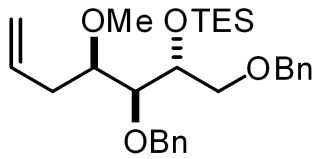
140

JSH_04_107 cdcl3; 400b



JSH_04_116 cdcl3; 400b

7.324 7.317 7.311 7.309 7.301 7.294 7.289 7.274 7.268 7.260 7.250 7.244 7.238 7.234 7.226 5.045 5.028 5.006 5.003 5.000 4.760 4.730 4.612 4.589 4.475 4.471 4.441 4.252 4.239 3.955 3.941 3.932 3.672 3.663 3.649 3.494 3.491 3.481 3.355 1.561 0.967 0.946 0.933 0.925 0.913 0.905 0.638 0.627 0.619 0.608 0.603 0.600 0.589 0.583 0.580



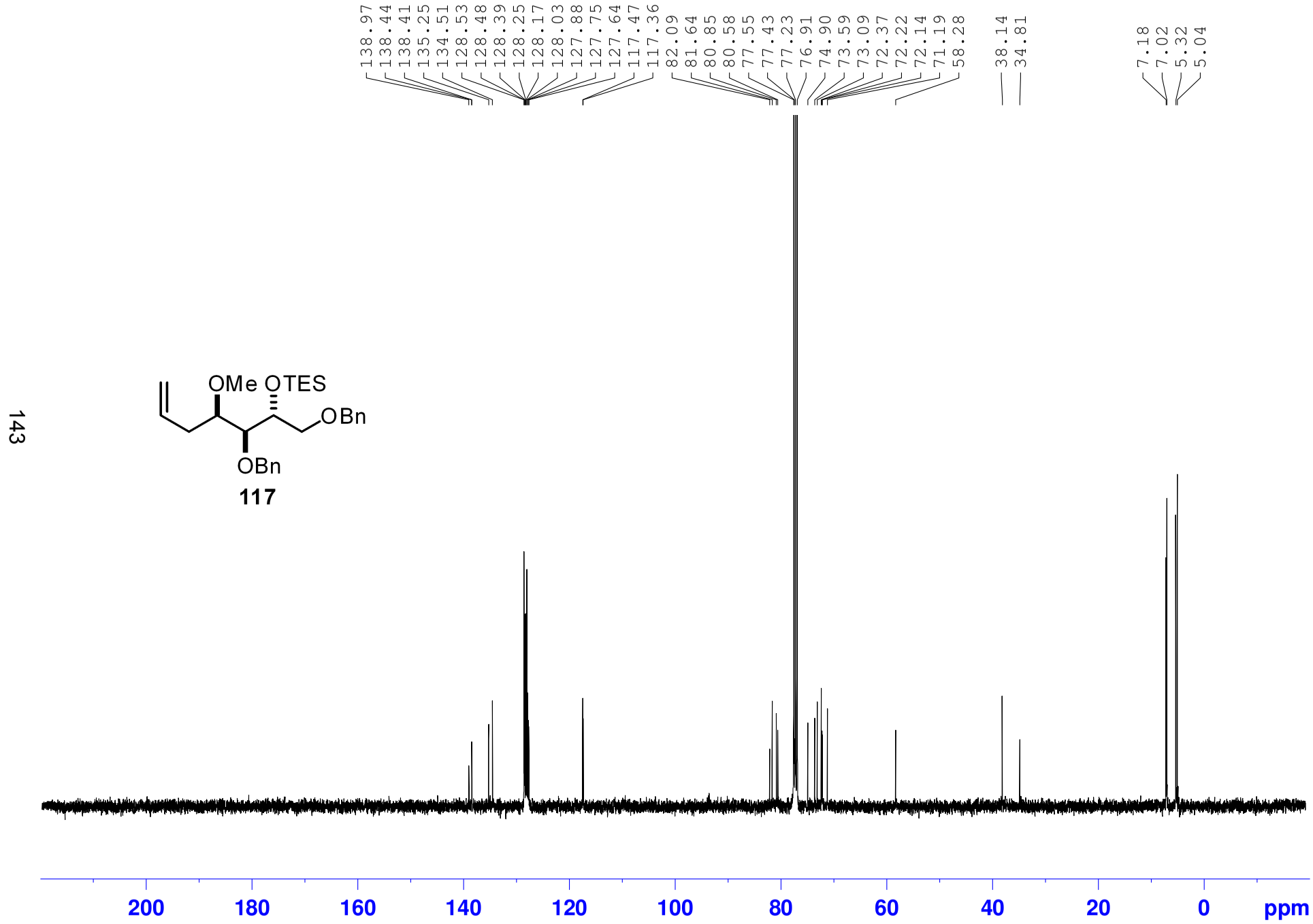

**117**

142

11 10 9 8 7 6 5 4 3 2 1 0 ppm

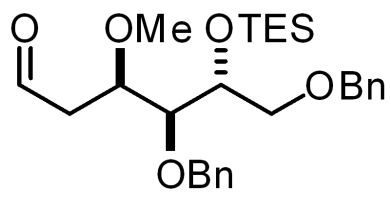
8.06 1.00 1.02 0.93 0.51 0.92 1.08 0.53 0.42 1.12 0.96 0.52 1.53 1.31 1.52 0.52 0.89 9.08 6.11

JSH_04_116 cdcl3; 400b



JSH_04_119 cdcl3; 400b

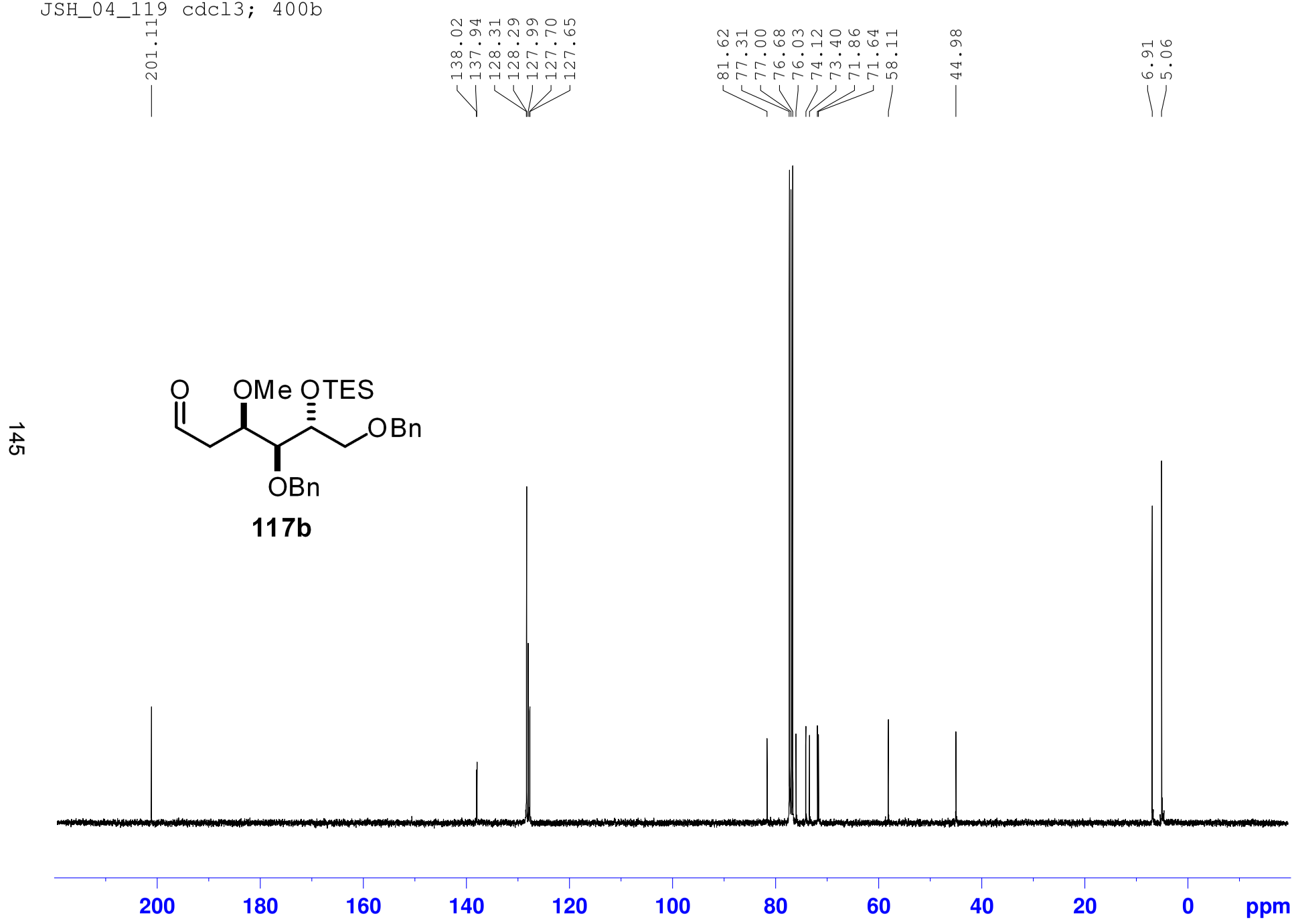
9.669 9.665 9.662 9.658 7.306 7.295 7.284 7.277 7.274 7.269 7.260 7.257 7.256 7.251 7.250 7.246 7.240 7.236 7.225 7.222 7.210 7.207 7.203 4.614 4.586 4.487 4.460 3.653 3.644 3.612 3.601 3.556 3.547 3.540 3.531 3.348 3.321 3.275 2.606 2.592 1.575 0.950 0.930 0.919 0.911 0.905 0.899 0.631 0.629 0.612 0.609 0.593 0.589 0.573 0.568




**117b**

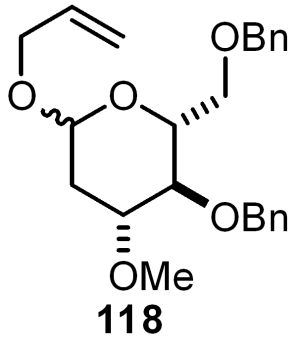
144

JSH_04_119 cdcl3; 400b



JSH_04_120 cdcl3; 400b

7.385 7.382 7.365 7.361 7.341 7.337 7.318 7.305 7.300 7.290 7.286 7.273 7.267 7.260 7.246 7.226 5.949 5.921 5.907 5.314 5.311 5.271 5.268 5.228 5.200 5.174 5.171 5.030 5.023 4.888 4.861 4.684 4.653 4.636 4.598 4.565 4.547 4.532 4.516 4.504 4.130 3.964 3.798 3.786 3.774 3.764 3.736 3.702 3.695 3.674 3.568 3.545 3.468 3.450 3.434




**118**

146

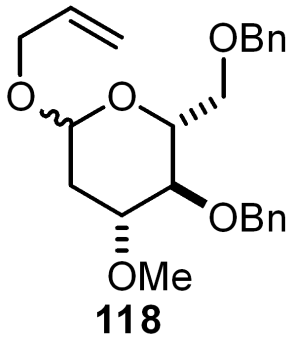


11 10 9 8 7 6 5 4 3 2 1 0 ppm

17.90 1.74 1.72 1.85 1.00 1.72 1.75 3.81 0.84 1.85 1.10 4.16 1.45 1.20 7.35 0.64 1.10 1.97

JSH_04_120 cdcl3; 400b

138.54
138.40
138.24
138.06
134.04
128.25
128.22
127.84
127.80
127.78
127.68
127.53
127.47
117.31
117.08
98.81
96.57
81.38
79.03
78.10
77.84
77.31
77.00
76.68
75.03
74.73
74.70
73.35
70.57
69.63
69.26
68.73
67.63
57.20
56.82
35.91
34.72



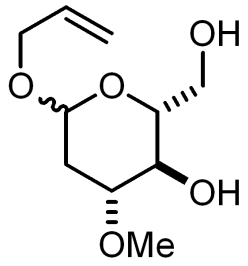

**118**

147

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_123 cdcl3; 400b

7.260 5.886 5.872 5.870 5.289 5.285 5.246 5.242 5.184 5.181 5.159 5.155 4.963 4.955 4.106 4.093 3.936 3.921 3.904 3.889 3.806 3.796 3.629 3.614 3.605 3.600 3.596 3.591 3.578 3.562 3.551 3.528 3.522 3.499 3.493 3.474 3.467 3.420 3.416 3.387 2.737 2.721 2.288 2.286 2.277 2.274 2.256 2.244 2.242 1.517 1.498 1.494 1.489 1.485 1.466

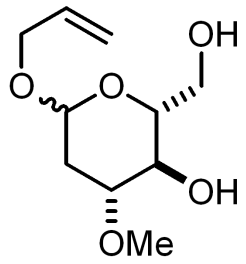



**119**

148

JSH_04_123 cdcl3; 400b

133.92
133.83
128.30
127.91
127.61
117.51
117.26
99.08
96.68
80.50
78.19
77.31
77.00
76.68
75.34
71.49
70.79
70.53
69.85
67.76
62.45
62.25
56.63
56.44
35.02
33.80

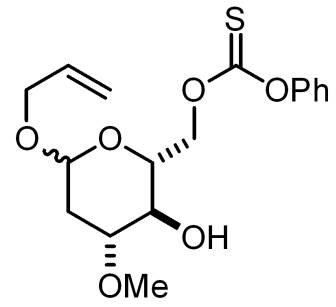



**119**

149

JSH_04_127 cdcl3; 400b

7.432 7.427 7.413 7.397 7.392 7.306 7.303 7.300 7.289 7.285 7.266 7.260 7.132 7.129 7.126 7.121 7.110 7.107 7.105 5.335 5.331 5.293 5.288 5.236 5.233 5.229 5.207 5.203 5.042 5.035 4.778 4.771 4.764 4.751 4.149 4.136 3.989 3.985 3.977 3.973 3.966 3.960 3.957 3.953 3.630 3.613 3.538 3.533 3.471 3.418 2.744 2.739 1.610 1.578 1.573




**119b**

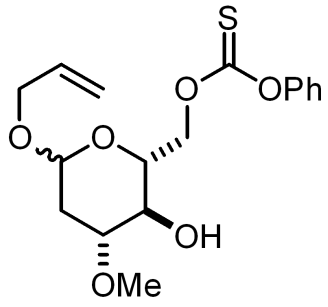
150

11 10 9 8 7 6 5 4 3 2 1 0 ppm

2.02 1.04 1.95 1.00 1.02 1.07 0.87 0.16 0.17 0.59 0.69 0.30 0.18 0.14 0.18 0.38 0.51 0.25 1.66 1.07 0.96 0.52 3.10 0.20 0.19 0.82 0.21 0.90 0.35 1.18 0.18

JSH_04_127 cdcl3; 400b

195.16
153.39
133.83
133.77
129.49
129.43
126.53
121.89
120.99
117.74
117.54
98.96
96.75
80.54
78.16
77.32
77.21
77.00
76.69
73.09
70.48
69.33
67.94
56.63
56.42
34.79
33.60



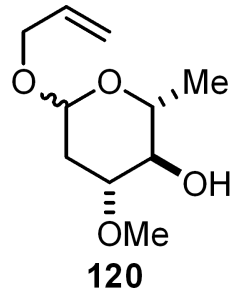

**119b**

151

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_170 cdcl3; 500

5.905 5.893 5.882 5.297 5.294 5.262 5.260 5.187 5.166 4.918 4.912 4.143 4.133 4.117 4.109 4.107 3.946 3.934 3.920 3.908 3.701 3.689 3.683 3.670 3.551 3.541 3.533 3.528 3.523 3.519 3.510 3.502 3.416 3.399 3.381 3.169 3.151 3.133 2.623 2.296 2.287 2.271 2.261 2.029 1.537 1.530 1.514 1.512 1.507 1.489 1.482 1.286 1.274 1.259 1.245

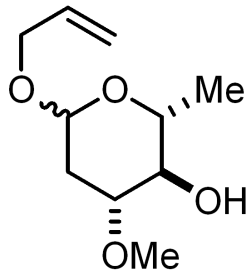



**120**

152

JSH_04_170 cdcl3; 500

134.20
117.06
96.55
78.30
77.25
77.00
76.75
76.15
67.67
67.55
56.42
33.92
17.79



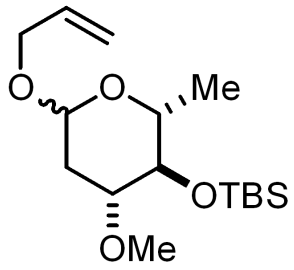

**120**

153

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_171 cdcl3; 500

5.943
5.933
5.921
5.909
5.898
5.888
5.305
5.271
5.194
5.174
4.891
4.885
4.138
4.128
4.112
4.102
3.941
3.929
3.915
3.903
3.648
3.644
3.636
3.630
3.618
3.442
3.430
3.420
3.413
3.407
3.403
3.398
3.390
3.380
3.306
3.154
3.136
3.118
2.308
2.298
2.282
2.272
1.590
1.510
1.503
1.484
1.480
1.477
1.461
1.454
1.240
1.228
0.889
0.087
0.073



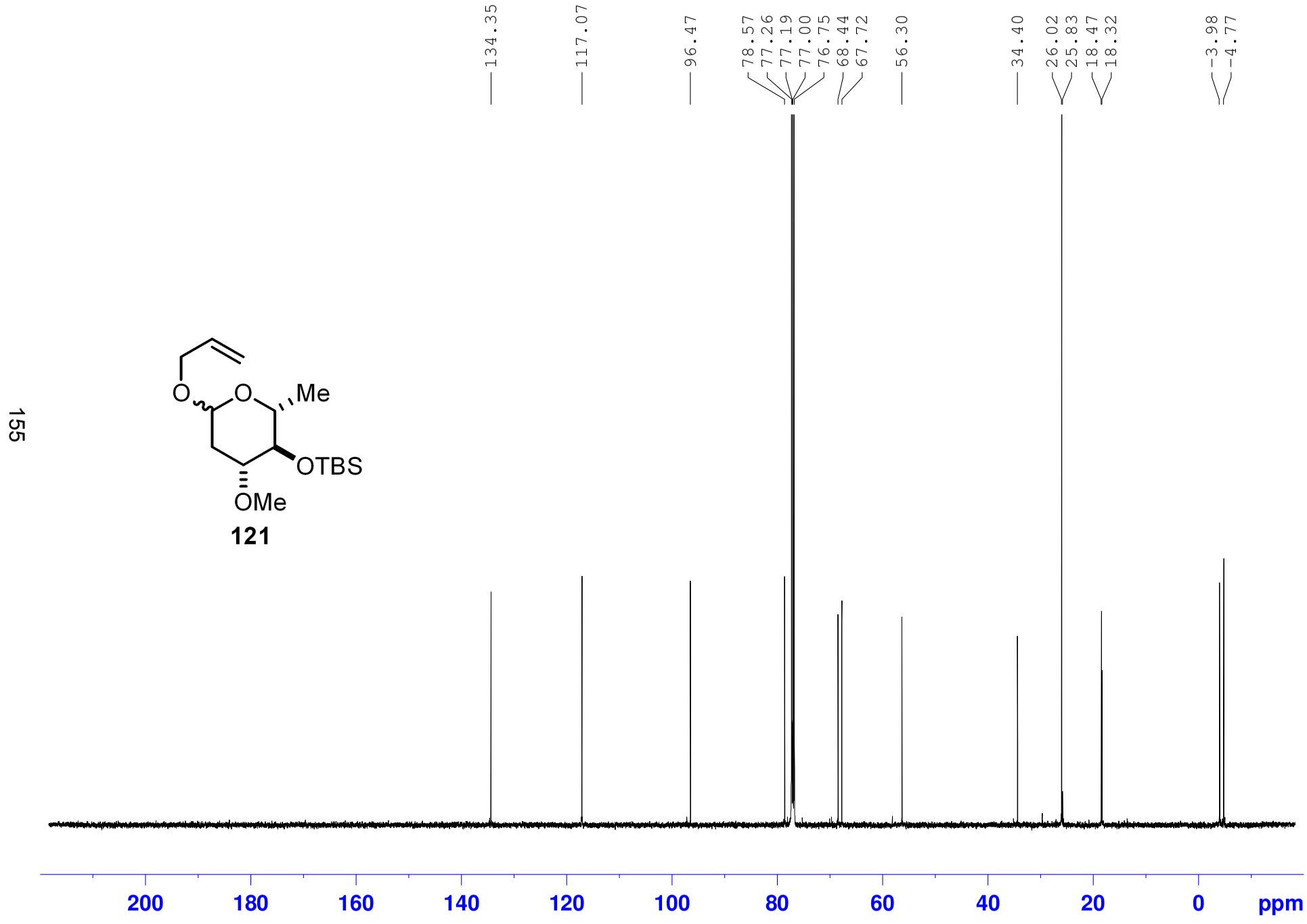

**121**

154

11 10 9 8 7 6 5 4 3 2 1 0 ppm

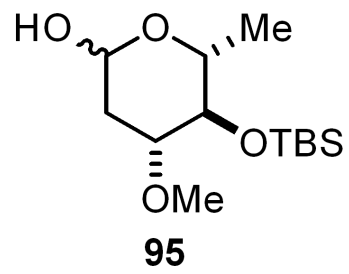
1.00 1.06 1.04 1.02 1.03 1.03 1.02 1.30 3.11 1.03 1.05 1.05 3.62 10.19 6.46

JSH_04_171 cdcl3; 500



JSH_04_141 cdcl3; 400b

5.327 5.320 3.888 3.872 3.865 3.850 3.477 3.464 3.455 3.448 3.443 3.436 3.427 3.415 3.325 3.312 3.310 3.288 3.152 3.130 3.121 3.114 3.108 3.093 3.055 2.427 2.422 2.400 2.397 2.316 2.313 2.304 2.301 2.283 2.280 2.271 2.268 1.499 1.490 1.470 1.466 1.462 1.458 1.438 1.429 1.370 1.286 1.270 1.232 1.216 0.883 0.873 0.086 0.078 0.067




**95**

156

11 10 9 8 7 6 5 4 3 2 1 0 ppm

1.00 0.64 0.99 0.60 1.04 5.63 2.29 0.95 0.63 1.00 0.95 0.61 1.89 3.15 14.87 9.87

JSH_04_141 cdcl3; 400b

93.97
91.98
80.75
78.08
77.31
77.15
77.00
76.68
76.34
72.87
68.59
56.36
56.17
36.99
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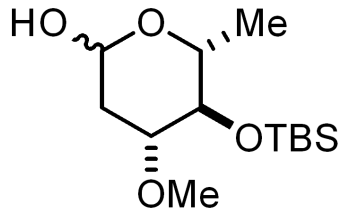
25.98
25.96
18.49
18.44
18.28
18.25
-3.99
-4.80
-4.83



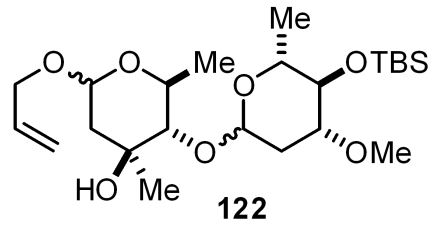

**95**

157

200 180 160 140 120 100 80 60 40 20 0 ppm

JSH_04_144 11-13, cdcl3; 400a
PROTON CDCl3 C:\Bruker\TOPSPIN nelson 22

7.260 5.305 5.302 5.262 5.259 5.241 5.233 5.186 5.160 4.578 4.574 4.553 4.549 4.347 4.334 4.130 4.062 4.047 4.031 4.015 3.816 3.370 3.349 3.337 3.326 3.321 3.299 3.275 3.204 3.180 3.152 3.130 3.116 3.108 2.041 1.994 1.989 1.961 1.957 1.783 1.621 1.349 1.335 1.321 1.299 1.284 1.253 1.238 1.227 1.211 0.891 0.874 0.087 0.068 0.056




122

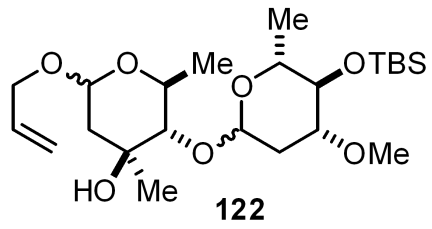
158

11 10 9 8 7 6 5 4 3 2 1 0 ppm

1.00 1.71 1.01 0.12 0.25 0.88 1.02 0.85 0.99 0.82 1.68 3.51 0.82 1.55 0.87 0.78 0.39 0.91 1.17 0.82 0.50 2.65 3.77 2.25 2.85 7.33 3.93 6.65

JSH_04_144 cdcl3; 600

134.27
134.13
134.07
134.04
117.38
117.35
117.00
98.45
98.35
98.30
98.07
92.48
92.04
90.83
81.03
79.55
78.89
78.27
78.07
78.04
77.21
77.00
76.79
75.13
72.76
71.89
70.88
70.80
70.42
70.36
70.20
70.18
69.88
69.75
69.70
69.65
69.45
69.44
68.59
56.38
56.34
56.18
45.09
43.83
41.58
36.34
35.27
34.37
29.64
25.98
25.95
20.49
19.82
18.61
18.57
18.55
18.53
18.46
18.28
18.26
18.18
18.15
16.04
14.10
-3.99
-4.80




**122**

159

200 180 160 140 120 100 80 60 40 20 0 ppm

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