

Progress Toward the Total Synthesis of the Marine Natural Product Amphidinol 3

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Abstract

Timothy James Martin: Progress Toward the Total Synthesis of the Marine Natural Product Amphidinol 3
(Under the direction of Michael T. Crimmins)

A convergent synthesis of the C31-C52 bis-tetrahydropyran core of the natural product amphidinol 3 is reported. A common intermediate was synthesized from D-tartaric acid utilizing an asymmetric glycolate alkylation/ring-closing metathesis sequence to construct the THP rings. Differential elaboration of the common intermediate allowed the synthesis of two distinct coupling partners, which were joined through a modified Horner-Wadsworth-Emmons olefination to provide the bis-tetrahydropyran core. A convergent approach to the C9-C29 fragment has also been achieved, utilizing Julia-Kocienski olefination to unite key fragments. Exploiting the repeating units of the C1-C17 domain of the polyol, stereocenters C2, C6, C10, and C14 have all been introduced via the asymmetric glycolate alkylation reaction. An iterative acetate aldol sequence followed by a propionate aldol provided the carbon skeleton and required stereocenters of the C21-C29 domain. Following completion of the polyol domain, union with the bis-tetrahydropyran core is envisioned to introduce the C1-C52 domain of amphidinol 3.

To Darcie, Thank You.

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List of Abbreviations

9-BBN	9-borabicyclo-[3.3.1]-nonane
Ac	acetyl
<i>t</i> -AmOH	<i>tert</i> -amylalcohol
Bn	benzyl
BOM	benzyloxymethyl
Bu	butyl
Bz	benzoyl
COSY	correlation spectroscopy
CSA	10-camphorsulfonic acid
Cp	cyclopentadienyl
DBU	1,8-diazabicyclo-[5.4.0]-undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	di- <i>iso</i> -propyl azodicarboxylate
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DTBMP	di- <i>tert</i> -butyl-4-methylpyridine
Et	ethyl

G1	Grubbs first generation metathesis catalyst
HG2	Hoveyda-Grubbs second generation metathesis catalyst
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
LiDBB	lithium 4',4'-ditert-butylbiphenylide
Me	methyl
Mes	mesityl
MOM	methyloxymethyl
Ms	methanesulfonyl
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NIS	<i>N</i> -iodosuccinimide
Ph	phenyl
Piv	pivaloyl
PMB	<i>para</i> -methoxylbenzyl
PMP	<i>para</i> -methoxyphenyl
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
PTSA	<i>para</i> -toluenesulfonic acid
PTSH	1-phenyl-1 <i>H</i> -tetrazole-5-thiol
rt	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetrabutylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
TBDPS	<i>t</i> -butyldiphenylsilyl

TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TfO	triflate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl

Chapter 1

Discovery of Amphidinol 3 and Previous Synthetic Efforts

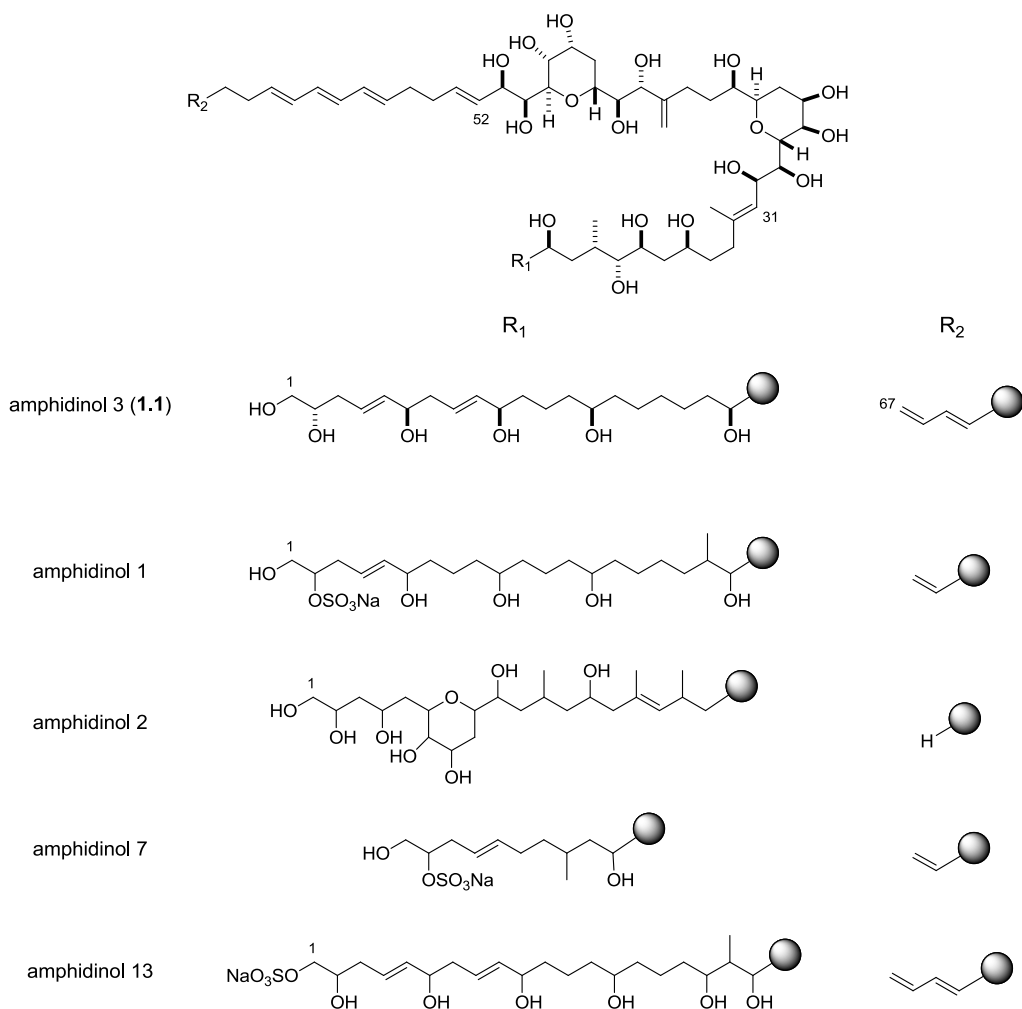
A. Isolation, Structure, and Biological Activity of Amphidinol 3

In 1991, Yasumoto and co-workers isolated a structurally novel compound from the marine dinoflagellate *Amphidinium klebsii* that displayed potent anti-fungal activity.¹ Amphidinol was determined to be the first member of a new class of polyhydroxy-polyene compounds.² To date, fifteen amphidinols have been isolated from *Amphidinium klebsii* and *Amphidinium carterae* off the coasts of Japan and New Zealand respectively. Long carbon chains that include multiple hydroxyl groups and olefins characterize the amphidinol family. While the polyol and polyene regions of the amphidinols, C1-C22 and C53-C67 of **1.1**, may vary between compounds, the bis-tetrahydropyran core is conserved throughout the family (Figure 1.1). The polyol domains vary in number and position of hydroxy groups, and some amphidinols contain a sulfate ester (i.e. amphidinols 1, 7, and 13). Amphidinols that contain a terminal sulfate ester, such as amphidinol 13, are reported to have significantly lower biological activities, indicating the importance of the terminal hydroxyl group.³ It is speculated that *Amphidinium klebsii* produces such toxic secondary metabolites in order to compete for resources with diatoms, which are the dominant microalgae in the coastal waters where the dinoflagellate was isolated.

Amphidinol 3 (**1.1**) was isolated in 1996 by Murata and co-workers and is reported to have the highest anti-fungal activity of the family, and even greater activity than

amphotericin B. Harvested cells from 442 liters of culture led to the isolation of 12 milligrams of amphidinol 3, which was found to display not only anti-fungal activity, but also strong hemolytic, cytotoxic, ichthyotoxic activities, and strong surfactant properties.⁴

Figure 1.1 The amphidinol family.

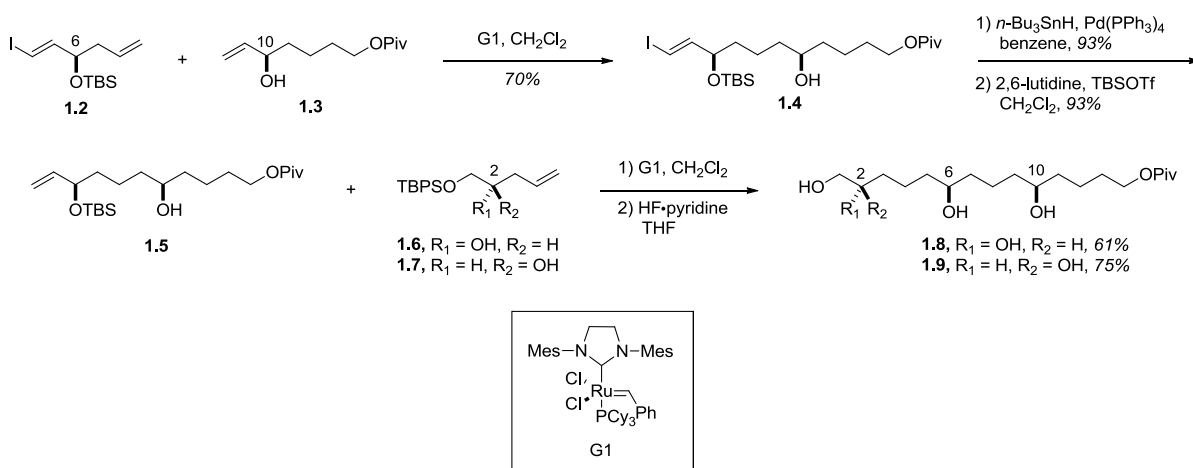


The absolute configuration of amphidinol 3 was determined in 1999 by Murata and co-workers, utilizing a *J-based configuration analysis* developed in their laboratory,⁵ NOE analysis, and the modified Mosher method.⁶ To increase the ease of determination, Murata and co-workers prepared a ¹³C enriched sample of amphidinol 3 from a two-hundred liter culture with 12 mM NaH¹³CO₃. The relative configurations of C20-27 and C32-C52 were

determined utilizing intact **1.1**, whereas the configurations of C2, C6, C10, and C14 were determined by degradation and modified Mosher analysis of the fragments.⁷

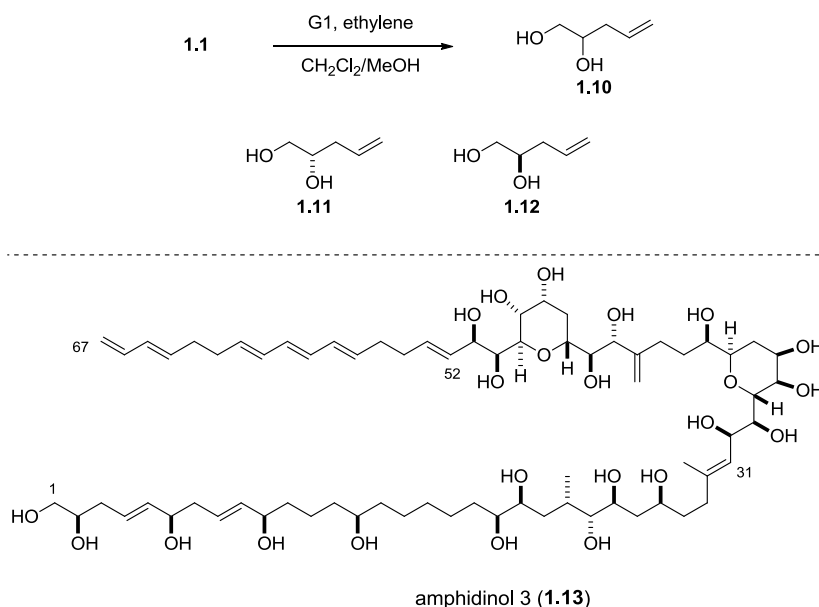
In 2008 Murata and co-workers studied the differences in the polyol and polyene domains and their effect on biological activity. Toward this end, Murata and co-workers synthesized both the 2,6-*anti* isomer **1.8** and 2,6-*syn* isomer **1.9** of the C1-C14 region of amphidinol 3 (Scheme 1.1).⁸ Upon NMR comparison of both fragments to **1.1**, discrepancies

Scheme 1.1 Synthesis of C1-C14 isomers.



were uncovered that led to a reinvestigation of the stereochemistry at C2. While both fragments were very similar or indistinguishable, **1.9** showed smaller deviation from **1.1** at C4 than **1.8**, the presumably correct 2,6-*anti* isomer. Degradation of amphidinol 3 utilizing Grubbs first generation catalyst and ethylene (Scheme 1.2) and comparison of **1.10** to **1.11** and **1.12** utilizing chiral GC-MS revealed that **1.10** was identical to **1.12**, both having retention times of 9.90 minutes. Based on this evidence, Murata revised the absolute configuration at C2 to *R*. Thus, the corrected structure of amphidinol 3 is **1.13**.⁸

Scheme 1.2 Revised structure of amphidinol 3.



Murata hypothesized the structure of membrane bound amphidinol 3 and co-workers in 2008 based on the formation of pores in biological membranes.⁹ In this study, Murata used isotropic small bicelles consisting of dimyristoylphosphatidylcholine (DMPC) and dihexanoylphosphatidylcholine (DHPC) with incorporation of 25 mol % amphidinol 3. The topological orientation of amphidinol 3 in the bicelles was determined utilizing Mn^{2+} as a paramagnetic agent to enhance relaxation of NMR nuclei. Thus, portions of amphidinol 3 exposed to the aqueous exterior of the membrane display a shorter relaxation time T_{1M} . The C66 and C67 vinyl protons of the polyene domain display large T_{1M} values, due to a limited effect of the Mn^{2+} . This indicates that the hydrophobic polyene domain inserts deep into the interior of the lipid bilayer. The bis-tetrahydropyran and polyol regions are located along the membrane/water interface, as evidenced by smaller T_{1M} values for the protons of those domains. Energy minimization calculations indicated that the bis-tetrahydropyran domain adopts a hairpin conformation positioning the hydrophilic polyol domain on the bilayer surface. It is hypothesized that the polyol domain adopts a bent configuration, however

cannot be confirmed due to the high flexibility of the C1-C20 region. The polyol domain then forms ion-permeable pores/lesions across the membrane via interaction with the lipid head groups. It has been determined that amphidinol 3 displays potent hemolytic activity regardless of cell membrane thickness, which supports the hypothesis that the membrane disrupting activity of amphidinol 3 stems from the formation of toroidal, or carpet-type, pores.

B. Previous Synthetic Efforts Toward Amphidinol 3

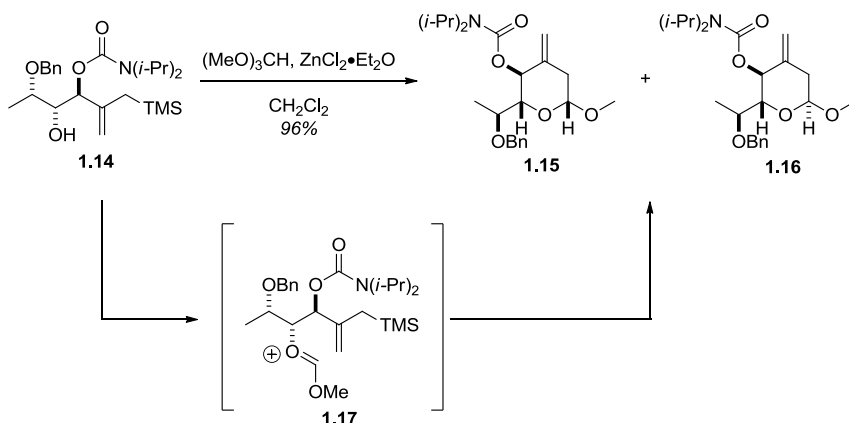
Due to the challenging structures of the amphidinols, they have become interesting targets for the synthetic community. Specifically, amphidinol 3 is an attractive target due to its potent biological activity and scarce natural abundance. Markó¹⁰, Oishi¹¹, Cossy¹², Paquette¹³, Roush¹⁴, and Rychnovsky¹⁵ have synthesized fragments of amphidinol 3, however its total synthesis has yet to be achieved. Many syntheses focus on exploitation of the symmetry of the C34-38 and C45-49 tetrahydropyrans of the bis-tetrahydropyran domain through synthesis of a common precursor for each.^{11,13,14,15} Previous syntheses of the C1-C30 polyol domain generally rely on convergent coupling of fragments utilizing olefination^{12,13} or metathesis reactions^{12,15}.

(i) Marko's Synthesis of a Tetrahydropyran Precursor

In 2005, Marko and co-workers reported an *anti*-allylation/intramolecular Sakurai cyclization sequence that affords highly substituted 2,6-*anti* tetrahydropyrans (Scheme 1.3).¹⁰ Treatment of alcohol **1.14** with zinc dichloride etherate and an orthoester led to the formation of the diastereomeric cyclic acetals **1.15** and **1.16** as a 3:1 ratio in 96% yield, presumably through intermediate **1.17**. Marko then converted **1.15** and **1.16** to tetrahydropyran **1.18** over a three step sequence (Scheme 1.4). To introduce a required stereocenter of the tetrahydropyrans of amphidinol 3, ozonolysis of the alkene followed by

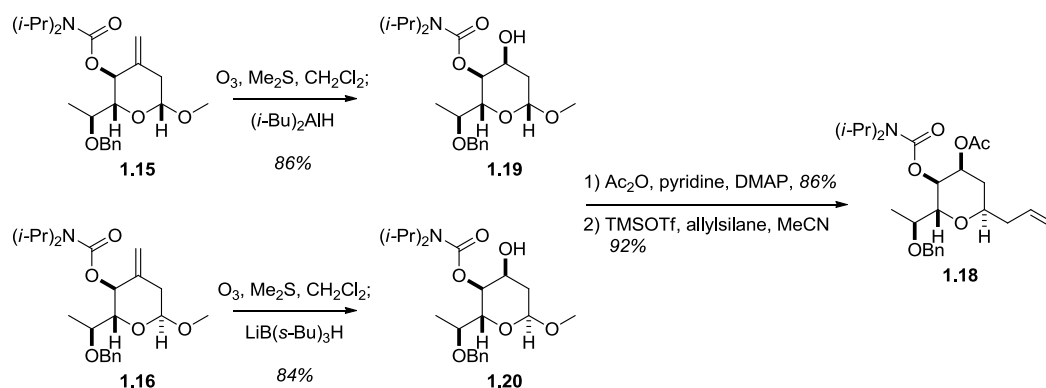
selective reduction afforded the axial products **1.19** and **1.20**. The secondary alcohols were protected and subjected to alkylation with allyltrimethylsilane to afford a single diastereomer

Scheme 1.3 Marko's synthesis of substituted THPs.



of the desired 2,6-*anti*-tetrahydropyran **1.18**. With this, Marko was able to access a tetrahydropyran intermediate in 92% yield. The terminal alkene can serve as a functional group handle for further manipulation on the right-hand side; however, the terminal methyl of the left-hand side poses a challenge to further elaboration to access the tetrahydropyran subunits of amphidinol 3.

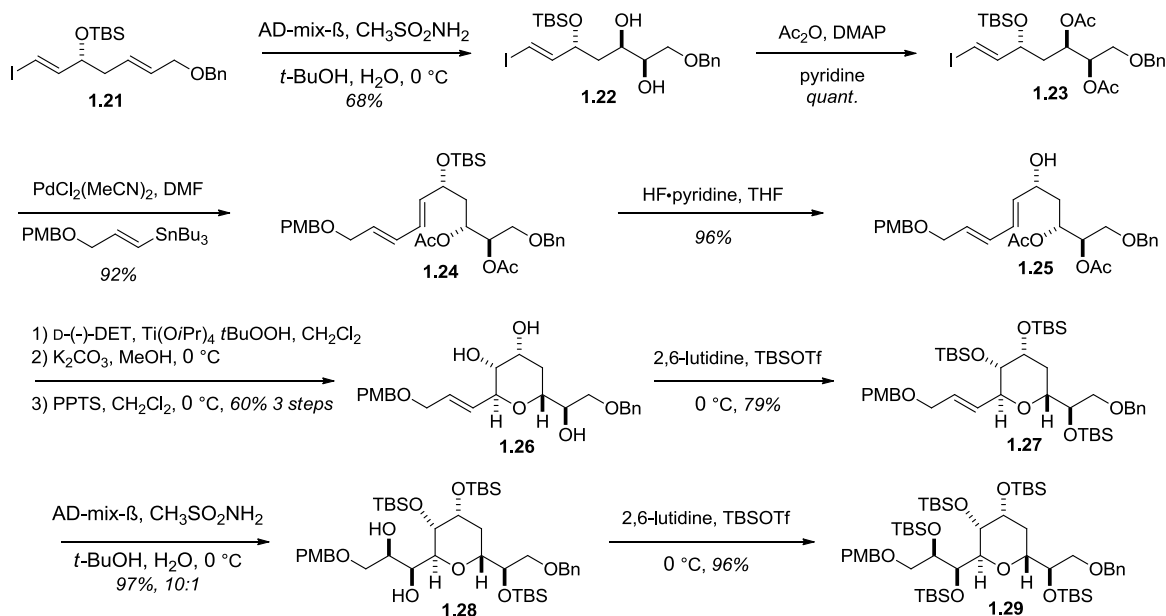
Scheme 1.4 Marko's synthesis of 2,6-*anti*-substituted THPs.



(ii) Oishi's Synthesis of a Tetrahydropyran Precursor

In 2009, Oishi *et al.* reported a synthesis of a tetrahydropyran intermediate that could be utilized to access the C31-C40 or the C43-C52 tetrahydropyrans of amphidinol 3.¹¹ Utilizing a Sharpless asymmetric dihydroxylation and a Katsuki-Sharpless asymmetric epoxidation, Oishi introduced what corresponds to all of the stereocenters of the bis-THP core, except for the C43 stereocenter. The tetrahydropyran ring was closed utilizing a 6-*endo-tet* cyclization. Oishi began with treatment of alkene **1.21** with Sharpless asymmetric dihydroxylation conditions to react with the less hindered, electron-rich olefin to afford the desired isomer **1.22** in 68% yield (Scheme 1.5). Quantitative protection of diol **1.22**, followed by a Migita-Kosugi-Stille coupling reaction¹⁶ provided the *E,E*-diene **1.24** in 92% yield. The secondary

Scheme 1.5 Oishi's synthesis of 2,6-anti-substituted THPs.



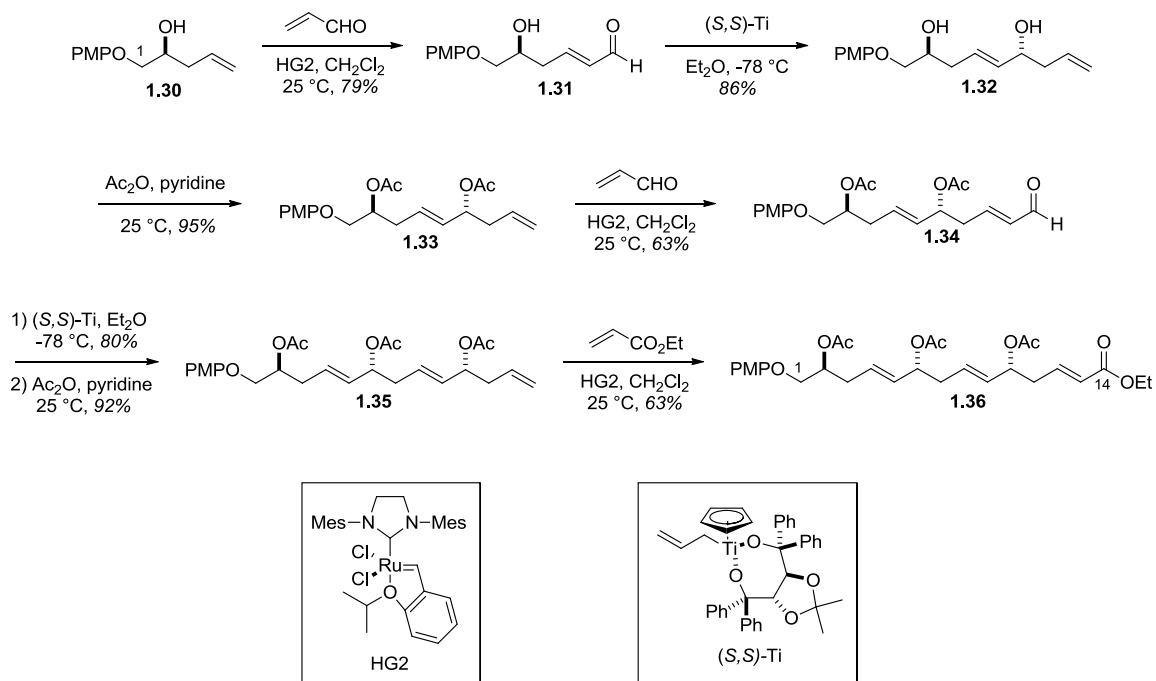
silyl ether was removed to furnish the required allylic alcohol (**1.25**) for selective epoxidation. Allylic alcohol **1.25** underwent Sharpless asymmetric epoxidation, followed by acetate

cleavage, and a 6-*endo-tet* cyclization to introduce the desired tetrahydropyran ring (**1.26**) in 60% yield over three steps. The structure of **1.26** was confirmed by NOE experiments. Triol **1.26** was protected as the tris-TBS ether to afford alkene **1.27** that could then undergo a Sharpless asymmetric dihydroxylation to introduce the final stereocenters of the C31-C40 and C43-C52 tetrahydropyrans of amphidinol 3 in high yield and good selectivity. Protection of the resulting diol (**1.28**) as the bis-TBS ether afforded tetrahydropyran **1.29**, with differentially protected primary alcohols. Theoretically, tetrahydropyran **1.29** can be utilized as a common intermediate for both tetrahydropyrans of the bis-tetrahydropyran core of amphidinol 3.

(iii) Cossy's Synthetic Efforts toward the Polyol and Polyene Domains

In 2001, Cossy reported an iterative sequence utilizing enantioselective allyltitanations and chemoselective cross-metathesis reactions to synthesize the C1-C14 portion of the polyol domain of amphidinol 3.^{12,17} Homoallylic alcohol **1.30**, previously synthesized in enantiomerically pure form by Cossy, was subjected to a cross-metathesis with Hoveyda-Grubbs 2nd generation catalyst¹⁸ to afford aldehyde **1.31** in 79% yield with >50:1 *E:Z* selectivity (Scheme 1.6). Treatment of aldehyde **1.31** with a chiral allyltitanium complex (*S,S*)-Ti led to diol **1.32** in high yield and selectivity. The diol was protected as the diacetate **1.33**, which was then subjected to a second round of selective cross-metathesis followed by highly selective allylation (>95:5) in high yield. Protection of the resultant secondary alcohol provided **1.35**, which was subjected to a final cross-metathesis reaction to access the C1-C14 fragment **1.36**.

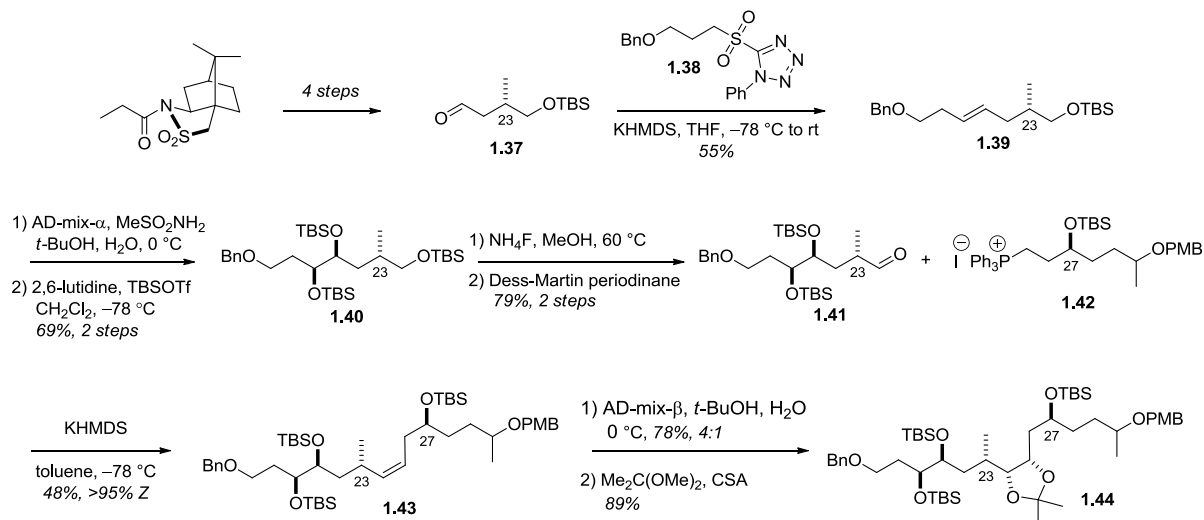
Scheme 1.6 Cossy's synthesis of the C1-C14 fragment.



In 2009, Cossy and Marko collaborated on the synthesis of the C18-C30 fragment of amphotidinol **3** utilizing successive olefination/dihydroxylation reactions (Scheme 1.7). Aldehyde **1.37** was obtained from alkylation of Oppolzer's sultam followed by cleavage of the chiral auxiliary and protection of the secondary alcohol.¹⁹ Julia-Kocienski olefination between aldehyde **1.37** and sulfone **1.38** afforded *E*-alkene **1.39** in 55% yield as a >95:5 ratio of *E/Z* isomers. A Sharpless asymmetric dihydroxylation of alkene **1.39** afforded a 4:1 mixture of diastereomers favoring the desired diol, which was then protected as bis-TBS ether **1.40**. Cleavage of the primary TBS ether followed by oxidation gave access to Wittig olefination partner **1.41**. Aldehyde **1.41** was subjected to Wittig olefination with **1.42** to provide desired *Z*-alkene **1.43**. Phosphonium salt **1.42** was prepared in 11 steps from hex-5-en-2-one with the C27 stereocenter arising from the enantioselective allylation that was successfully used to introduce the C6 and C10 stereocenters in the synthesis of the C1-C14 fragment. *Z*-alkene **1.43** was obtained in modest yield with high *Z* selectivity. Exposure of

1.43 to Sharpless asymmetric dihydroxylation conditions again resulted in a 4:1 ratio of diastereomers favoring the desired diol, which was then protected as the acetonide to provide C18-C30 fragment **1.44**. The completed fragment was obtained in 15 steps and 6.3% yield overall for the longest linear sequence (24 steps total).

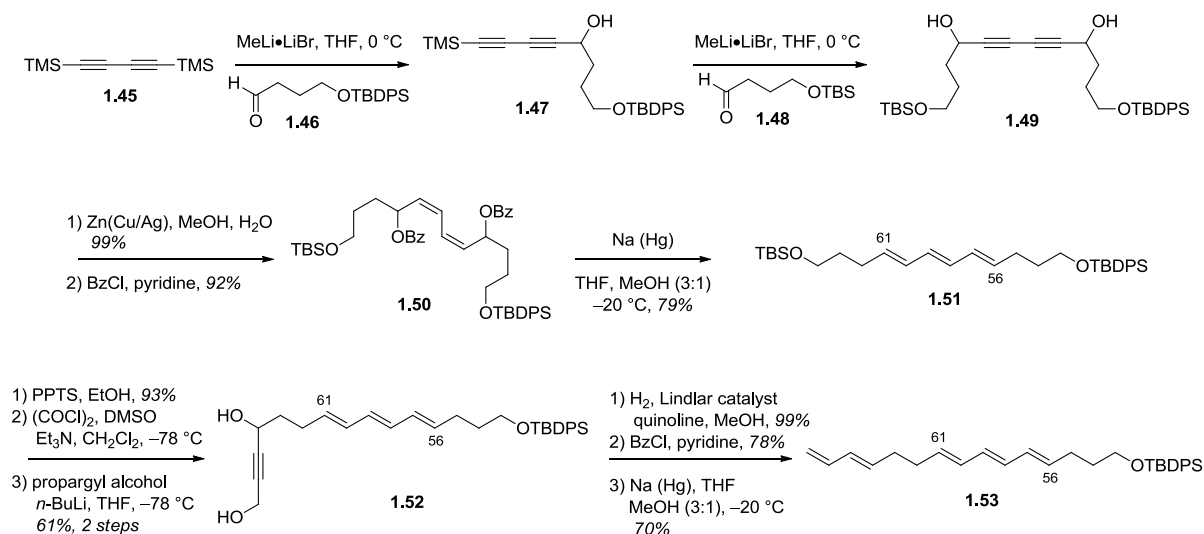
Scheme 1.7 Cossy's synthesis of the C18-C30 fragment.



Cossy and Marko collaborated in 2007 on the synthesis of the C53-C67 polyene fragment of amphidinol 3 utilizing reductive eliminations of allylic benzoates as key steps for provide the *trans* alkenes (Scheme 1.8). The linear approach began from diyne **1.45**, which was subjected to iterative organolithium additions with aldehyde **1.46** to afford alcohol **1.47** then aldehyde **1.48** to afford diol **1.49**. Both aldehyde **1.46** and **1.48** were obtained from 1,4-butanediol in two steps. The required *Z,Z*-diene moiety was obtained following stereoselective reduction of the alkynes and the diol was subsequently protected as the dibenzoate (**1.50**). Reductive elimination of dibenzoate **1.50** with sodium amalgam established the *E,E,E*-triene of the polyene domain. At this stage the C65-C67 portion was added following deprotection of the primary TBS ether, Swern oxidation, and addition of lithiated propargyl alcohol to the resultant aldehyde to complete the C53-C67 backbone **1.52**

of the polyene domain. Propargylic diol **1.52** was converted to diene **1.53** following the same alkyne reduction, benzylation, and reductive elimination sequence utilized to synthesis triene **1.51**. Diene **1.53** was obtained as a single isomer in 16% yield over 11 steps.

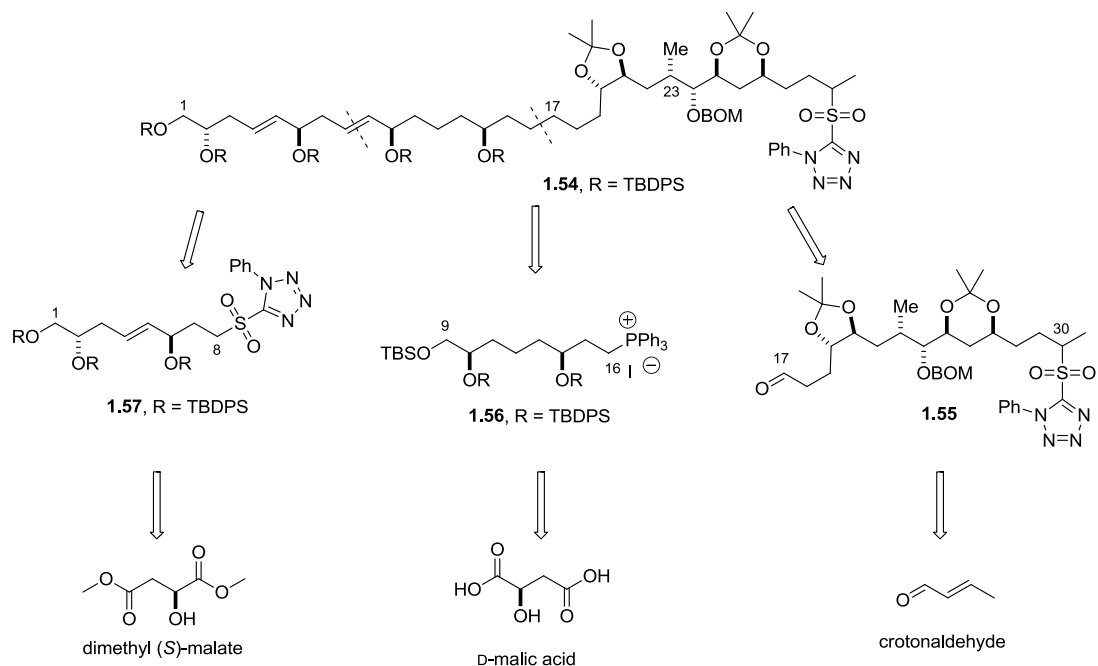
Scheme 1.8 Cossy and Marko's synthesis of the C53-C67 polyene fragment.



(iv) Paquette's Synthesis of the C1-C30, C43-C67, and C31-C52 Domains

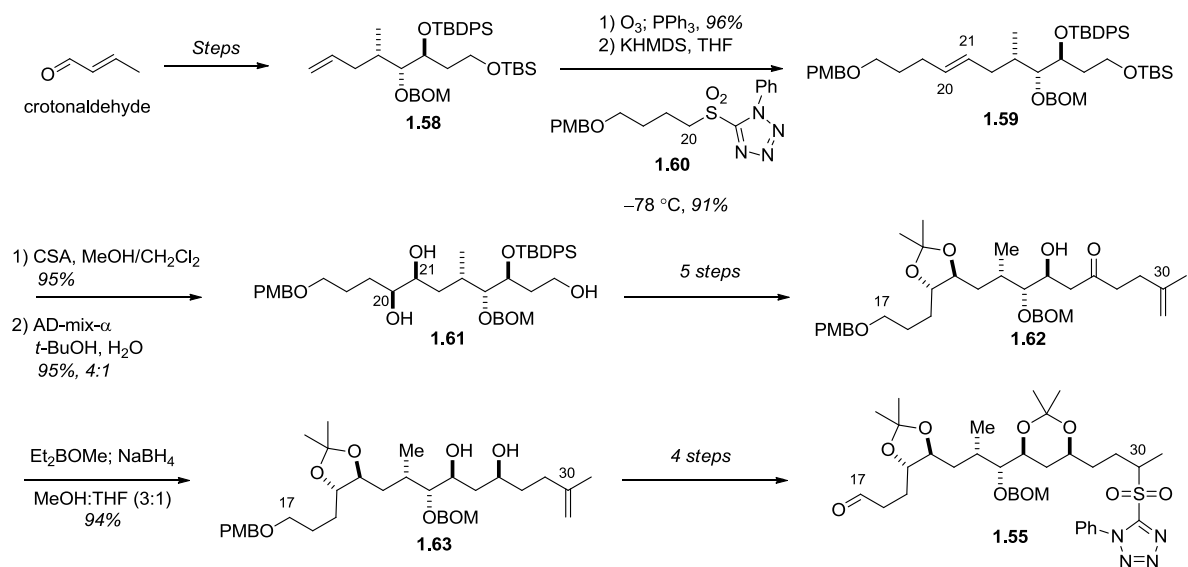
In 2005, Paquette reported a convergent approach to the C1-C30 polyol domain **1.54** of amphidinol 3 utilizing olefinations to couple the C17-C30 (**1.55**), C9-C16 (**1.56**), and C1-C8 (**1.57**) domains (Figure 1.2).¹³ Keto aldehyde **1.55** was derived from crotonaldehyde, phosphonium salt **1.56** was obtained from D-malic acid, and sulfone **1.57** was accessed starting from dimethyl (S)-malate. To access **1.55** from crotonaldehyde, known compound **1.58** was synthesized. Alkene **1.59** was accessed following oxidative cleavage of olefin **1.58** and Julia-Kocienski olefination with sulfone **1.60** using KHMDS as base (Scheme 1.9). Following removal of the primary TBS ether, introduction of the C20-C21 diol was achieved using Sharpless asymmetric dihydroxylation. The triol was obtained in 95% yield as a 4:1 mixture of separable diastereomers favoring **1.61**. After a 5 step sequence β-hydroxy ketone

Figure 1.2 Paquette's retrosynthesis of the C1-C30 domain 1.54.



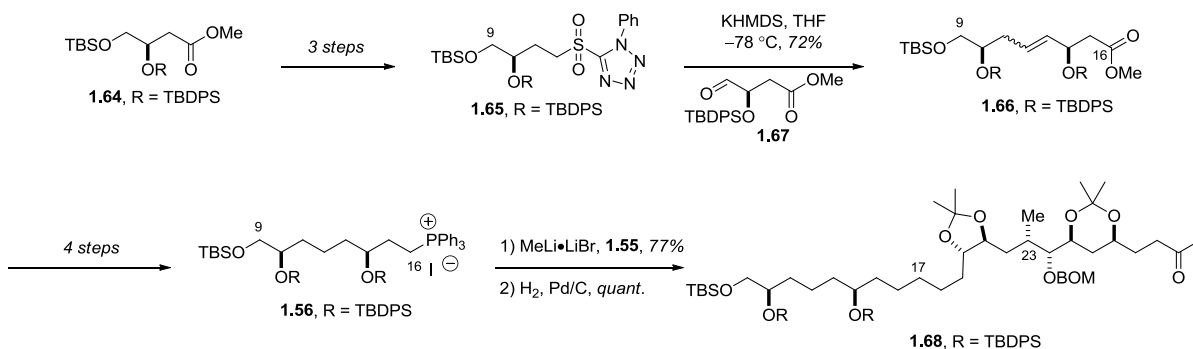
1.62 was accessed, from which the C27 stereocenter was introduced utilizing a diastereoselective 1,3-*syn* reduction. Keto aldehyde **1.55** was accessed after a 4 step sequence of diol protection, removal of the PMB ether, Johnson-Lemieux cleavage of the double bond, and oxidation of the primary alcohol.

Scheme 1.9 Paquette's synthesis of keto aldehyde 1.55.



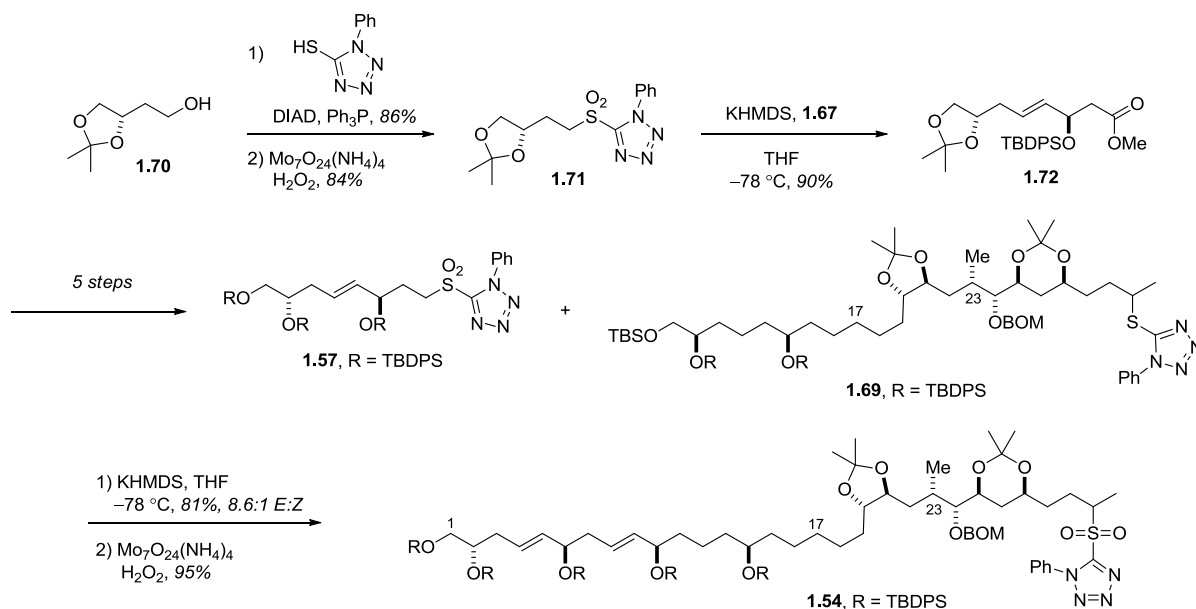
To access phosphonium salt **1.56**, ester **1.64** was synthesized from D-malic acid and then converted to sulfone **1.65** over 3 steps (Scheme 1.10). Alkene **1.66** was obtained after Julia-Kocienski olefination of **1.65** with aldehyde **1.67**, also derived from ester **1.64**. The 4:1 *E/Z* selectivity of the Julia-Kocienski olefination was inconsequential, as the following step was catalytic hydrogenation of the C12-C13 double bond. Subsequent ester reduction and transformation to phosphonium salt provided **1.56** via the iodide occurred smoothly. Phosphonium salt **1.56** underwent Wittig olefination with aldehyde **1.55** and alkene reduction to access the C9-C30 fragment **1.68**.

Scheme 1.10 Paquette's synthesis of the C9-C30 domain.



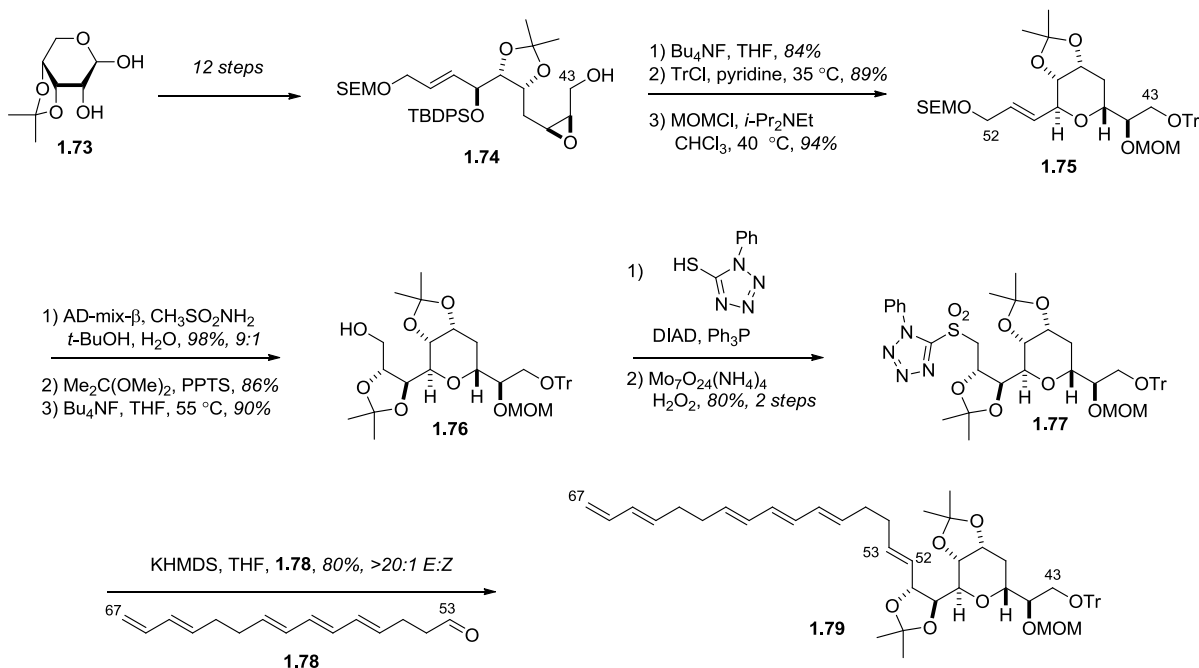
All that remained for the synthesis of **1.54** was development of a route to access sulfone **1.57** and to perform a Julia-Kocienski olefination with aldehyde **1.69**, derived from C9-C30 fragment **1.68** (Scheme 1.11). Alcohol **1.70** was accessed from dimethyl (*S*)-malate following Saito's procedure.²⁰ Conversion of primary alcohol **1.70** to sulfone **1.71** and subsequent Julia-Kocienski olefination with aldehyde **1.67** afforded alkene **1.72** as a 3:1 ratio of *E/Z* isomers. The *E/Z* ratio could be improved to 12:1 upon radical-induced isomerization. Alkene **1.72** was converted to sulfone **1.57** in 5 steps, which following another Julia-Kocienski olefination and oxidation provided the protected C1-C30 fragment **1.54** as a 9:1 mixture of separable *E:Z* isomers.

Scheme 1.11 Paquette's synthesis of the C1-C30 fragment 1.54.



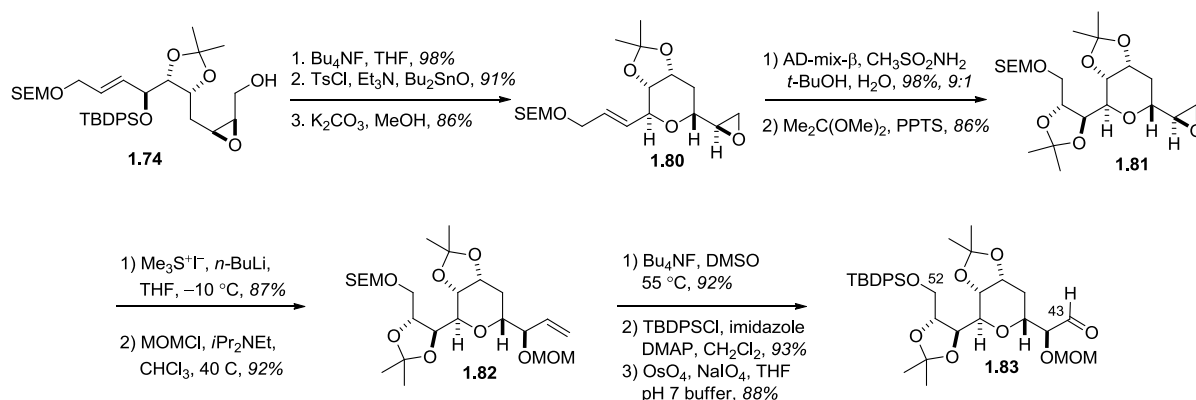
Paquette has accessed the C43-C52 tetrahydropyran unit of amphidinol 3 and demonstrated its successful coupling with the C53-C67 polyene and the C31-C42 tetrahydropyran domains. Epoxide **1.74** was accessed in 12 steps from 3,4-O-isopropylidene- β -D-ribofuranose **1.73**, with the key Sharpless asymmetric epoxidation proceeding in 82% yield to provide 5:1 ratio of diastereomers (Scheme 1.12). Cyclization to afford the desired tetrahydropyran framework of **1.75** was triggered upon deprotection of the TBDPS ether with tetrabutylammonium fluoride (TBAF). The primary alcohol was selectively protected as the trityl ether, and the secondary alcohol was protected as the MOM ether to afford alkene **1.75**. The C50-C51 hydroxy groups of **1.76** were introduced selectively using Sharpless asymmetric dihydroxylation and protected as the acetonide. Cleavage of the SEM ether afforded alcohol **1.76**. Mitsunobu reaction of **1.76** with molybdate-promoted oxidation provided sulfone **1.77**. A Julia-Kocienski olefination between sulfone **1.77** and aldehyde **1.78**, obtained via HWE olefination and subsequent Julia-Lythgoe olefination, gave access to the C43-C67 fragment **1.79** in high yield with excellent *E/Z* selectivity.

Scheme 1.12 Paquette's synthesis of the C43-C76 fragment.



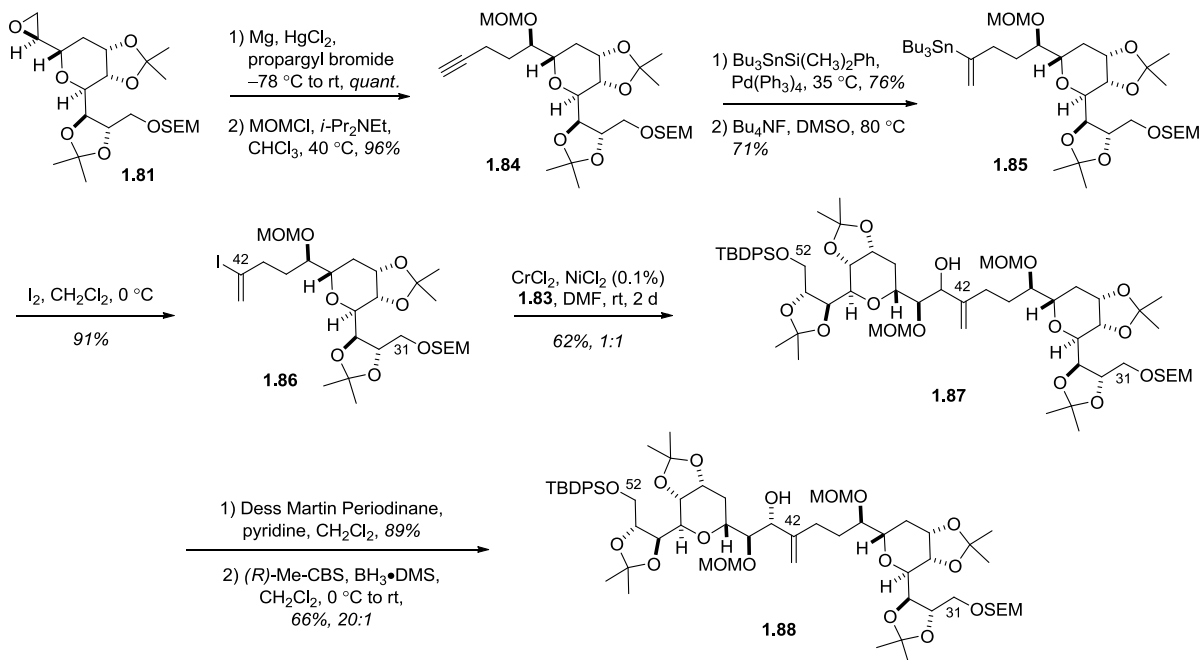
To access the C31-C52 fragment of amphidinol 3, Paquette again began with epoxide **1.74** and obtained the tetrahydropyran upon treatment with TBAF (Scheme 1.13). The primary alcohol was converted to a tosylate which was displaced to form epoxide **1.80**. The C50-C51 hydroxy groups were introduced as before, utilizing Sharpless asymmetric dihydroxylation, and subsequently protected as the acetonide to afford **1.81**. The epoxide of **1.81** was cleaved using trimethylsulfonium iodide and *n*-butyllithium (*n*-BuLi) and the resulting allylic alcohol was protected as the MOM ether **1.82**. To differentially protect the C31 and C52 primary alcohols, the SEM ether was exchanged for a TBDPS ether, and the terminal alkene was cleaved by use of the Johnson-Lemieux oxidation to arrive at aldehyde **1.83**.

Scheme 1.13 Paquette's synthesis of the C43-C52 THP.



The C31-C42 tetrahydropyran was also accessed from epoxide **1.81** (Scheme 1.14). Addition of the Grignard reagent derived from propargyl bromide and subsequent protection of the secondary alcohol as the MOM ether afforded alkyne **1.84**. Palladium catalyzed silylstannation of **1.84** and cleavage of the C-Si bond provided vinyl stannane **1.85**. Tin-iodine exchange provided the C31-C42 coupling partner **1.86**. A Nozaki-Hiyama-Kishi reaction formed the key C42-C43 bond and afforded the C31-C52 carbon skeleton of amphidinol 3 (**1.87**). Unfortunately, the product obtained was a 1:1 mixture of diastereomers, contrary to the expected Felkin-Ahn addition of **1.83**. To obtain the desired stereochemistry at C43, an oxidation/stereoselective reduction sequence was performed, granting the desired allylic alcohol **1.88** in 66% yield and a >20:1 ratio of diastereomers. With that, Paquette has successfully accessed the bis-tetrahydropyran core of amphidinol 3 utilizing a convergent approach from common intermediate **1.81**, derived from known compound 3,4-O-isopropylidene- β -D-ribose **1.73**.

Scheme 1.14 Paquette's synthesis of the bis-THP core.



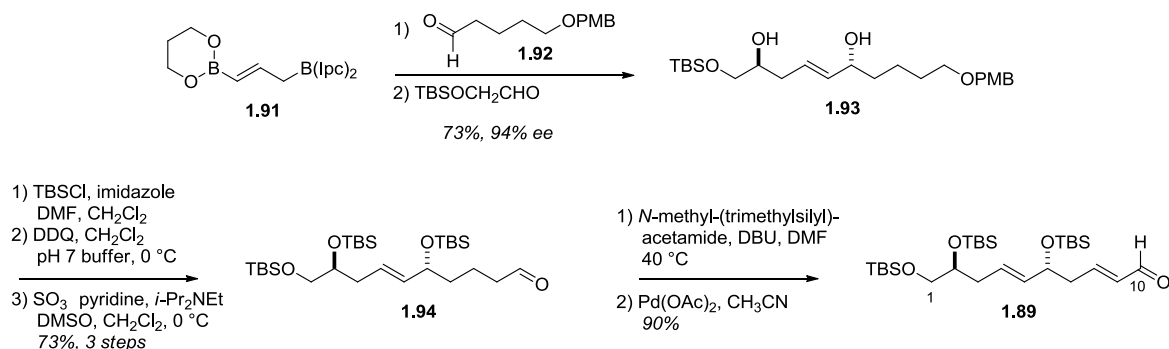
With completion of **1.88**, Paquette has successfully synthesized the C1-C30 and C31-C52 domains of amphidinol 3, as well as the C43-C67 domain **1.79**. The C1-C30 fragment **1.54** was assembled through multiple olefination reactions beginning from chiral pool starting materials, dimethyl (*S*)-malate and D-malic acid. The bis-THP core **1.88** was prepared by exploitation of the symmetry of the two tetrahydropyran rings starting from 3,4-O-isopropylidene-β-D-ribose **1.73**. The ether linkage of the tetrahydropyrans was derived from opening nucleophilic of an epoxide. Finally, the convergent synthesis of the C43-C67 fragment **1.79** was achieved via a Julia-Kocienski olefination of **1.77** and **1.78** to install the C52-C53 *E*-olefin.

(v) Roush's Efforts Toward Amphidinol 3

In 2005, Roush utilized the double allylboration reaction developed in his laboratories to synthesize the C1-C25 polyol domain of amphidinol 3.¹⁴ The double allylboration allowed

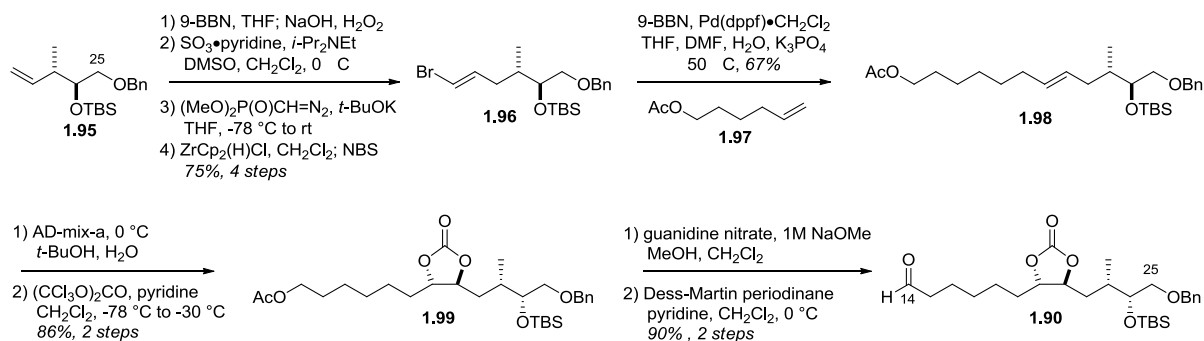
for quick access to the C1-10 aldehyde **1.89** (Scheme 1.15) and facile union with the C14-C25 aldehyde **1.90** (Scheme 1.16). A double allylboration reaction between borane **1.91** generated *in situ*²¹, aldehyde **1.92**²², and α -*t*-butyldimethylsilyloxy acetaldehyde²³ afforded diol **1.93** in 73% yield and 94% ee, introducing the C2 and C6 stereocenters in a one-pot procedure (Scheme 1.15). Protection of the diol as the TBS ether followed by cleavage of the PMB ether and oxidation of the primary alcohol afforded aldehyde **1.94**. Introduction of the C8-C9 olefin was accomplished via formation of the silyl enol ether and oxidation with Pd(OAc)₂ to yield α,β -unsaturated aldehyde **1.89**.

Scheme 1.15 Roush's synthesis of the C1-C10 fragment 1.89.



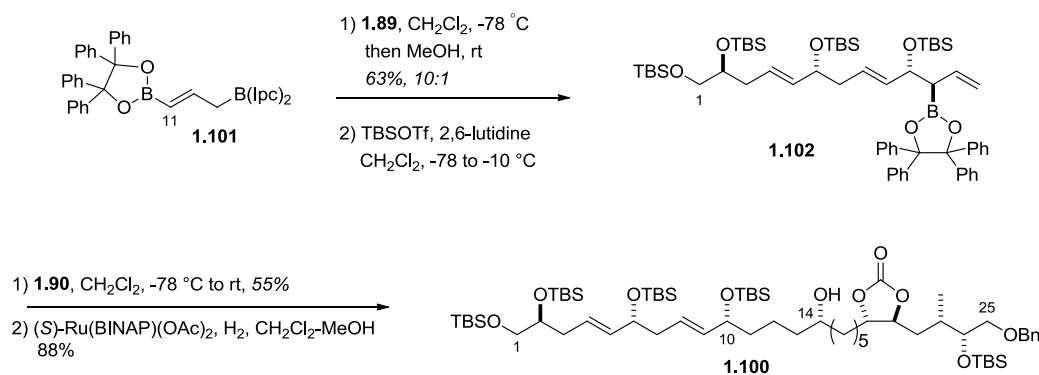
Synthesis of aldehyde **1.90** began with known compound **1.95** (Scheme 1.16).²⁴ A four step sequence effecting one carbon homologation of **1.95** provided vinyl bromide **1.96**, which was subjected to a Suzuki-Miyaura cross coupling²⁵ with alkene **1.97** to afford alkene **1.98**. The C20 and C21 hydroxyl groups were introduced with high stereoselectivity using Sharpless asymmetric dihydroxylation and protection of the resultant diol yielded acetate **1.99**. Deprotection of the primary acetate and oxidation with Dess-Martin periodinane gave access to the C14-C25 coupling partner **1.90**.

Scheme 1.16 Roush's synthesis of aldehyde 1.90.



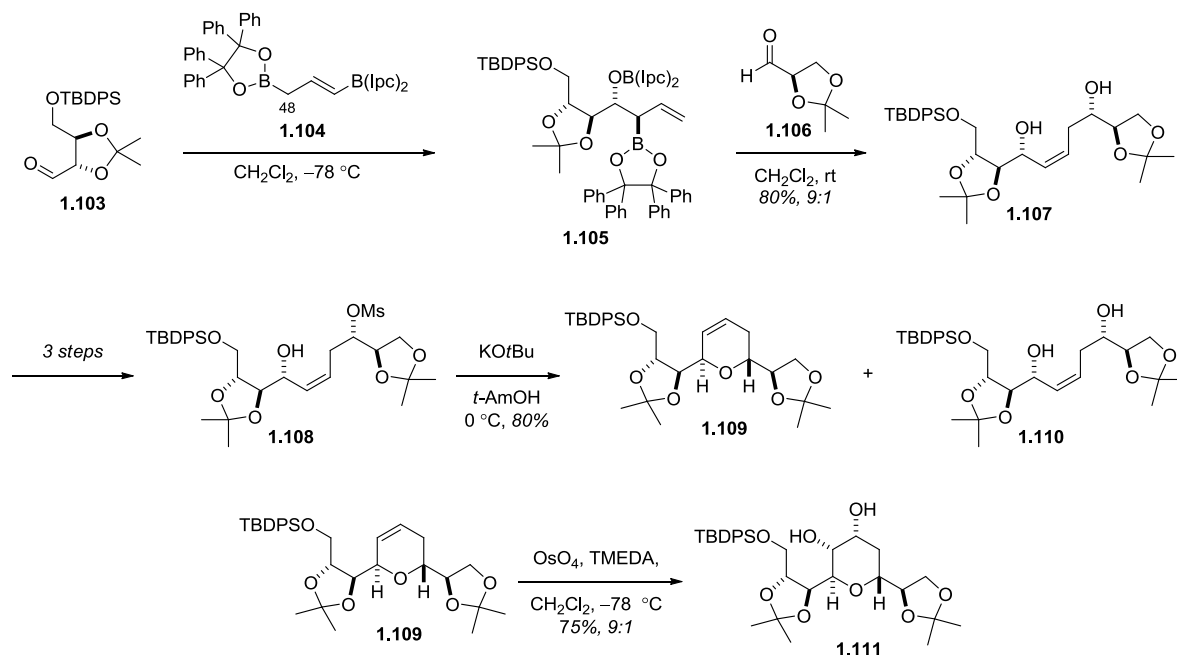
To access the C1-C25 fragment **1.100**, Roush again utilized the double allylboration reaction (Scheme 1.17). To differentiate the two secondary alcohols, the reaction was carried out in an interrupted three-pot process. Treatment of aldehyde **1.89** with borane **1.101** and protection of the intermediate secondary alcohol as the TBS ether afforded allylboronate **1.102**. Treatment of allylboronate **1.102** with aldehyde **1.90** and directed hydrogenation of the homoallylic alcohol yielded the desired C1-C25 fragment **1.100**. The protection of the C10 hydroxyl group as TBS ether **1.102** prior to the second allylboration reaction was required for selective hydrogenation with Noyori's ruthenium catalyst of the undesired homoallylic C11-C12 olefin over the desired C8-C9 olefin.

Scheme 1.17 Roush's union of aldehydes 1.89 and 1.90.



Roush further utilized the double allylboration reaction developed in his laboratories to synthesize the bis-THP core of amphidinol 3. Aldehyde **1.103**, prepared from D-tartaric acid, was subjected to the double allylboration reaction with allylboration reagent **1.101** (Scheme 1.18). Intermediate **1.104** could be isolated, and upon treatment with D-glyceraldehyde acetonide **1.105**, allylic alcohol **1.106** was obtained as a 9:1 ratio of diastereomers. Three steps of protecting group manipulation provided mesylate **1.107**, which was poised to undergo cyclization to form the desired tetrahydropyran ring. Various conditions were tested for the cyclization of **1.107** to form **1.108**, but many were problematic, resulting in competing formation of diene **1.109** as a byproduct. Ultimately potassium *t*-butoxide was discovered as the optimal base, affording dihydropyran **1.109** in 80% yield. Dihydropyran **1.109** could then be subjected to dihydroxylation to provide the desired tetrahydropyran **1.110**, and following protecting group manipulation primary alcohol **1.111**.

Scheme 1.18 Roush's synthesis of the THP common intermediate.



Scheme 1.19 Roush's synthesis of the C26-C42 and C43-67 fragments.



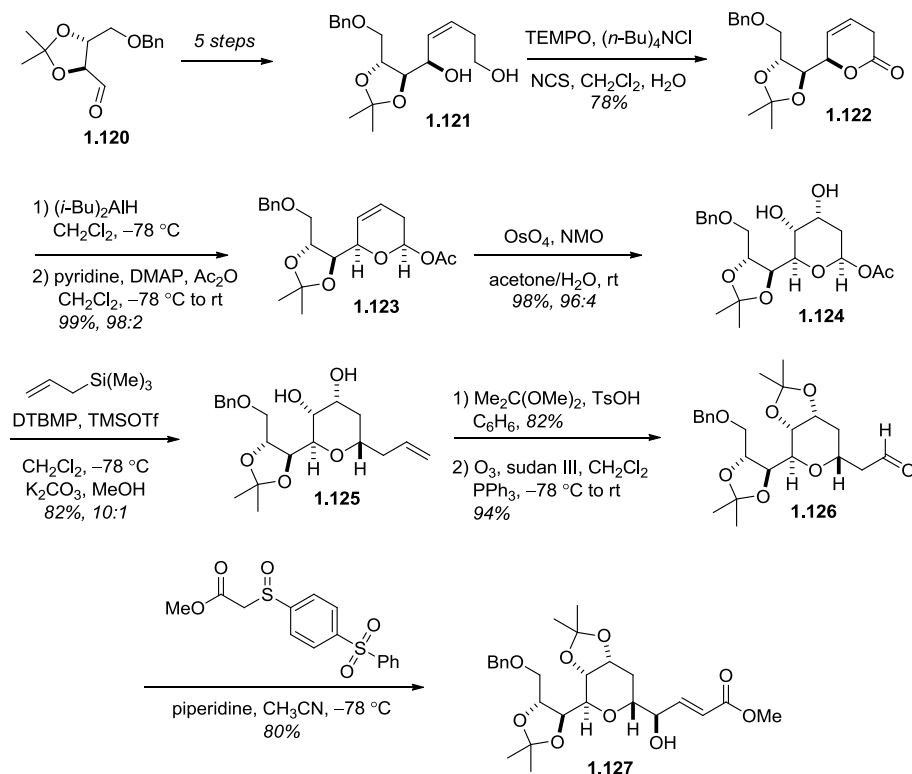
With completion of this work, Roush has been able to report the synthesis of fragments **1.100**, **1.115**, and **1.119**, which comprise the complete unassembled framework of amphidinol 3. The C1-C25 polyol domain **1.100** was quickly assembled utilizing the double allylboration methodology to introduce the 1,5-*syn*-diol moieties, starting from known compounds. Synthesis of the C43-C67 domain **1.115** and the C26-C42 domain **1.119** was achieved in divergent fashion from common intermediate **1.112**, exploiting the symmetry of the tetrahydropyran domains. Tetrahydropyran **1.112** was accessed by again utilizing the double allylboration methodology and nucleophilic displacement to form the key ether bond.

(vi) Rychnovsky's Synthesis of the C1-C52 Fragment of Amphidinol 3

In 2005, Rychnovsky reported a C-glycosidation reaction that was envisioned for the use in the synthesis and coupling of the tetrahydropyran domains of amphidinol 3.¹⁵ Known aldehyde **1.120**, derived from D-tartaric acid, was converted to diol **1.121** over 5 steps (Scheme 1.20).²⁷ The key ether linkage of the tetrahydropyran fragments was introduced by selective oxidation of the primary alcohol with TEMPO, cyclization to the hemiacetal and oxidation to afford lactone **1.122** in 78% yield. Reductive acetylation of lactone **1.222** furnished dihydropyran **1.123** with high yield and diastereoselectivity. Dihydroxylation of **1.123** introduced diol **1.124** in high yield and diastereoselectivity utilizing osmium tetroxide and NMO. Acetate **1.124** was the intended substrate to further explore the desired C-glycosidation reaction, however the observed selectivities were modest and unimproved by substrate variation. Due to the lower selectivities of the planned C-glycosidation, Rychnovsky explored nucleophilic additions to the oxocarbenium ion derived from lactol acetate **1.124** and found tetrahydropyran **1.125** could be obtained in high yield as a 10:1 mixture of separable diastereomers. Protection of the diol and cleavage of the alkene gave aldehyde **1.126**. A [2,3] sulfoxide/sulfenate rearrangement using hydroxylative Knoevenagel

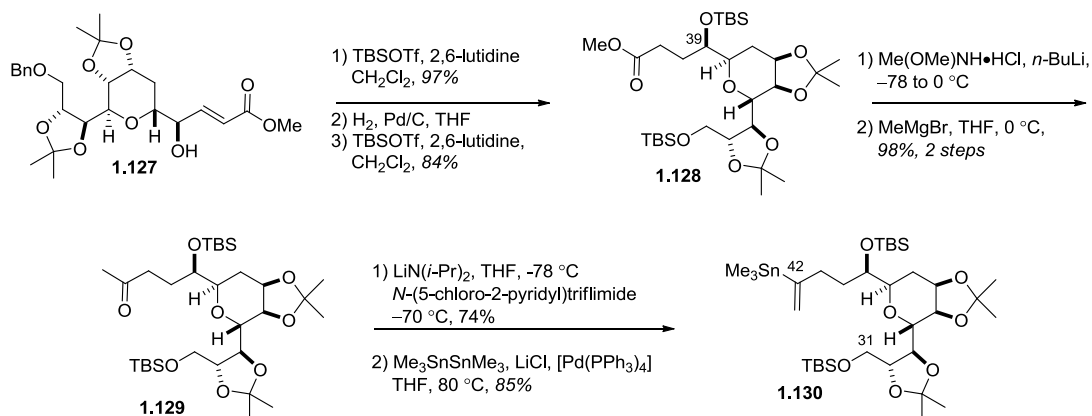
conditions²⁸ provided allylic alcohol **1.127**, introducing the final stereogenic center of the common intermediate as a 6:1 ratio of diastereomers.

Scheme 1.20 Rychnovsky's synthesis of a THP common intermediate.



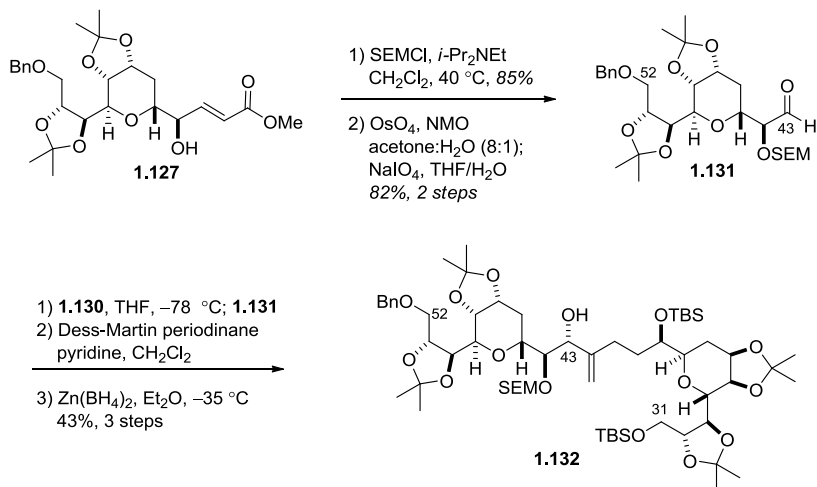
The C31-C42 domain was accessed from **1.127** in 7 steps (Scheme 1.21). Protection of the allylic alcohol as the TBS ether, simultaneous reduction of the C40-C41 olefin and cleavage of the benzyl ether, and protection of the resulting primary alcohol as the TBS ether afforded ester **1.128**. Upon synthesis of **1.128**, the C39 diastereomers that resulted from the hydroxylative Knoevenagel reaction were separable. Conversion of methyl ester **1.128** to methyl ketone **1.129** via the Weinreb amide proceeded in high yield. Methyl ketone **1.129** was converted to the enol triflate which underwent a Stille cross-coupling with hexamethylditin to furnish the desired coupling partner **1.130**.

Scheme 1.21 Rychnovsky's synthesis of the C31-C42 THP.



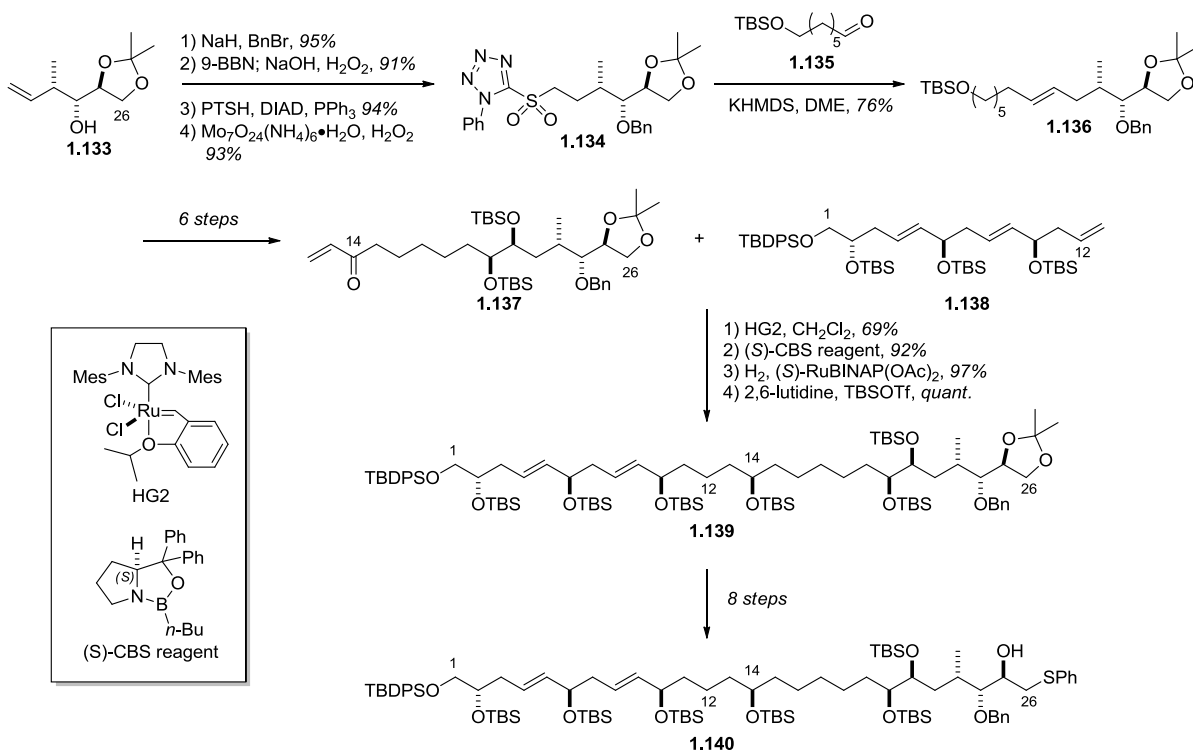
With access to the nucleophilic coupling partner, synthesis of the C43-C52 tetrahydropyran from **1.127** commenced (Scheme 1.22). Protection of the allylic alcohol as a SEM ether allowed for separation of the C44 diastereomers from the hydroxylative Knoevenagel reaction. The SEM ether also proved crucial for its ability to participate in chelation when attempting to introduce the C43 stereogenic center. A Johnson-Lemieux oxidation provided coupling partner **1.131** in 82% yield. Treatment of **1.130** with *n*-butyllithium provided a nucleophilic vinyl lithium species that was added to aldehyde **1.131**. This provided the carbon skeleton of the C31-C52 domain, however the addition was non-selective. Oxidation with Dess-Martin periodinane and subsequent chelate-controlled reduction of the ketone with zinc borohydride provided **1.132** in 43% over 3 steps as a single diastereomer.

Scheme 1.22 Rychnovsky's synthesis of the bis-THP core.



Rychnovsky assembled the C1-C26 domain of amphidinol 3 in a convergent fashion utilizing a cross metathesis reaction (Scheme 1.23). Upon protection of the secondary alcohol of **1.133**, synthesized following Roush's protocol²⁹, as a benzyl ether the terminal alkene was converted to the sulfone to provide **1.134**. A Julia-Kocienski olefination between **1.134** and **1.135** yielded alkene **1.136**. Over six steps including Sharpless asymmetric dihydroxylation to introduce the C20-C21 stereocenters and conversion of the primary hydroxyl group to the requisite enone, the C13-C26 fragment **1.137** was obtained in high yield. Alkene **1.138**, accessed following Cossy's procedure^{12a}, was subjected to a cross-metathesis reaction with enone **1.137** to unite the C1-C26 carbon skeleton **1.139**. Subsequent manipulations of enone **1.139** afforded the desired C1-C26 fragment **1.140** for coupling with the bis-THP core. The C14 stereocenter of the polyol domain was introduced by selective reduction of the enone with the (S)-CBS reagent.

Scheme 1.23 Rychnovsky's synthesis of the polyol fragment.

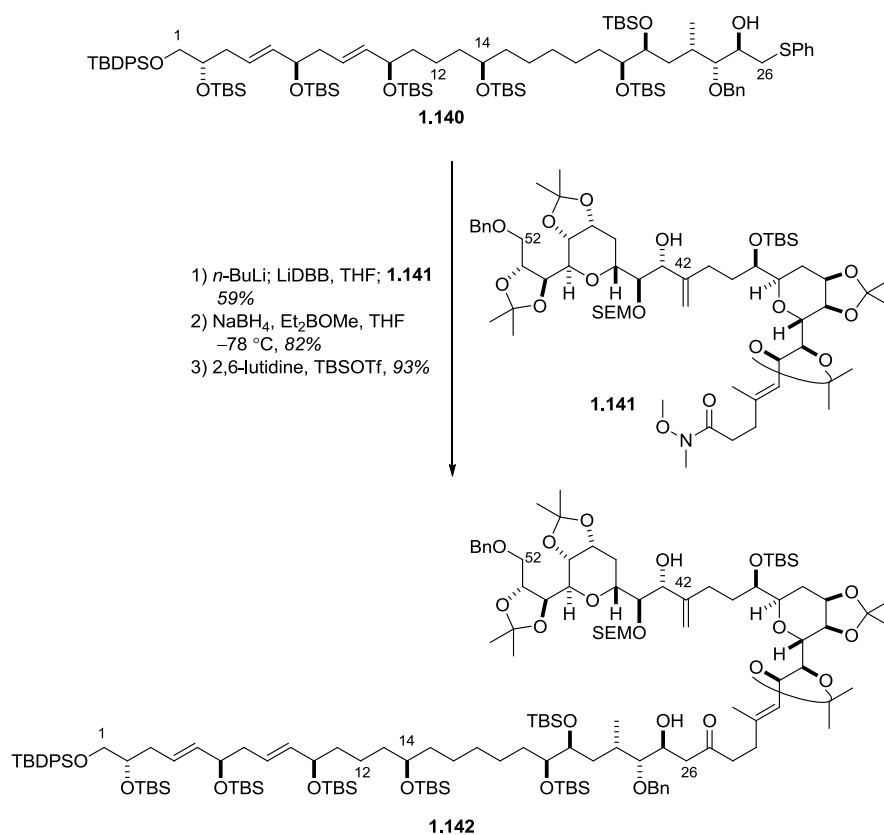


Rychnovsky united the C1-C26 and C27-C52 fragments **1.140** and **1.132** by first converting bis-THP core **1.132** to Weinreb amide **1.141** over 7 steps. The C30-C31 *E* olefin was introduced via an Ireland-ester Claisen rearrangement.^{24,25} Reductive lithiation of thioether **1.140** afforded an intermediate alkylolithium species that was reacted with Weinreb amide **1.141** to afford the desired C1-C52 framework in 59% yield (Scheme 1.24). The C25 hydroxyl group was deprotonated with *n*-butyllithium prior to reductive lithiation to avoid elimination. A hydroxyl directed reduction of the ketone under Prasad's conditions²⁶ introduced the C27 stereocenter and the resultant secondary alcohol was protected as the TBS ether to afford the protected C1-C52 fragment **1.142**.

Rychnovsky's completion of C1-C52 fragment **1.142** marks synthesis of the largest fragment of amphidinol 3 to date. The synthesis was achieved in a convergent manner, focusing on the assembly of the C1-C52 fragment via an alkylolithium addition of **1.140** to

1.141. Synthesis of the bis-THP core was achieved through vinyl lithium addition of **1.130** to aldehyde **1.131**. Exploiting the symmetry of the tetrahydropyran units, both fragments were accessed from common intermediate **1.127**, which was ultimately synthesized from chiral starting material D-tartaric acid. The C1-C26 fragment **1.140** was also accessed in a convergent manner, from cross metathesis of enone **1.137** and alkene **1.138**.

Scheme 1.24 Rychnovsky's synthesis of the C1-C52 fragment.



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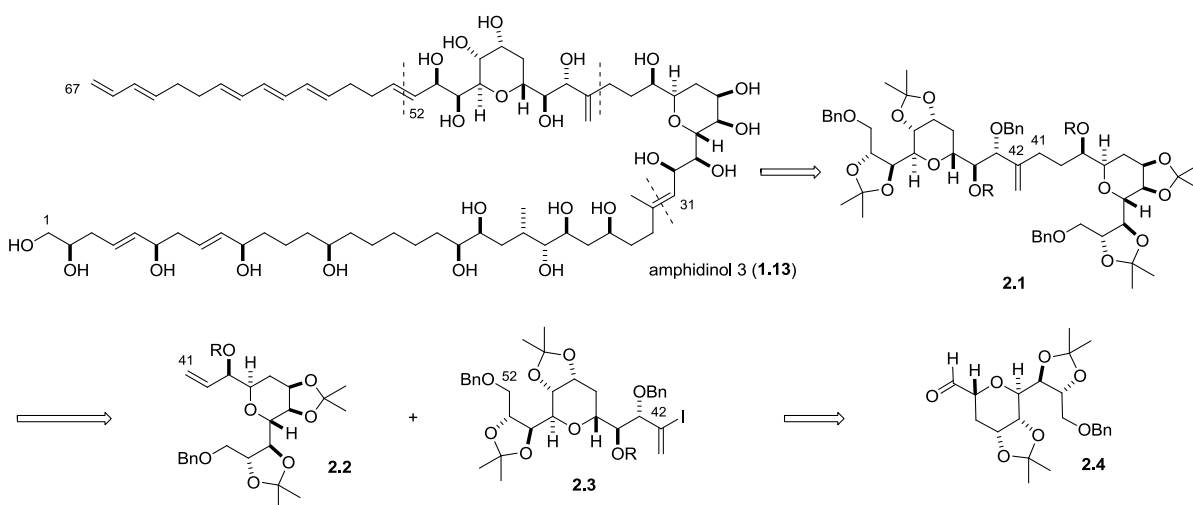
Chapter 2

Synthesis of the bis-Tetrahydropyran Core of Amphidinol 3

A. Original Retrosynthetic Analysis

To approach the synthesis of amphidinol 3 (**1.13**), our strategy was to first synthesize the C31-C52 bis-tetrahydropyran (THP) core of the molecule, and then introduce the C1-C30 polyol and C53-C67 polyene domains via a convergent coupling strategy. Our initial retrosynthetic analysis, developed by Dr. Theodore Martinot, focused on exploitation of the symmetry of the C31-C39 and C44-C52 THP moieties to access the core bis-THP unit (Figure 2.1).³² A Suzuki-Miyaura cross coupling reaction between alkene **2.2** and vinyl iodide

Figure 2. 1 Original retrosynthetic analysis of amphidinol 3.

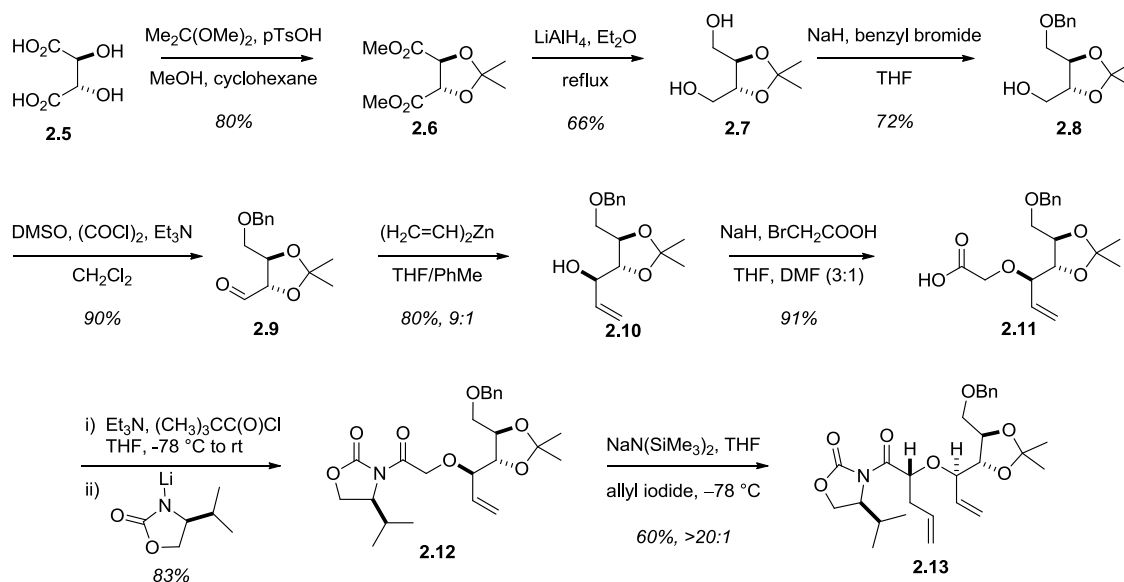


2.3 would introduce the key C41-C42 bond of the bis-THP core of amphidinol 3 (**1.13**) directly. As the C31-C38 and C45-C52 domains of amphidinol 3 (**1.13**) are identical, both tetrahydropyran **2.2** and tetrahydropyran **2.3** could be derived from common intermediate **2.4**. A selective vinyl addition to aldehyde **2.4** was envisioned to introduce the C39 stereocenter and provide alkene **2.2**. A glycolate *anti* aldol reaction with aldehyde **2.4** would introduce the C43-C44 stereocenters and provide a carbonyl that could be converted to C42 vinyl iodide. Dr. Martinot successfully developed a route to access tetrahydropyran **2.4** utilizing the glycolate alkylation-ring closing metathesis strategy developed previously in the Crimmins laboratory.³³

B. Synthesis of the Aldehyde Common Intermediate

Known aldehyde **2.9** was accessed via D-tartaric acid **2.5**, following a four step protocol (Scheme 2.1).³⁴ Several conditions for the vinyl addition to aldehyde **2.9** were

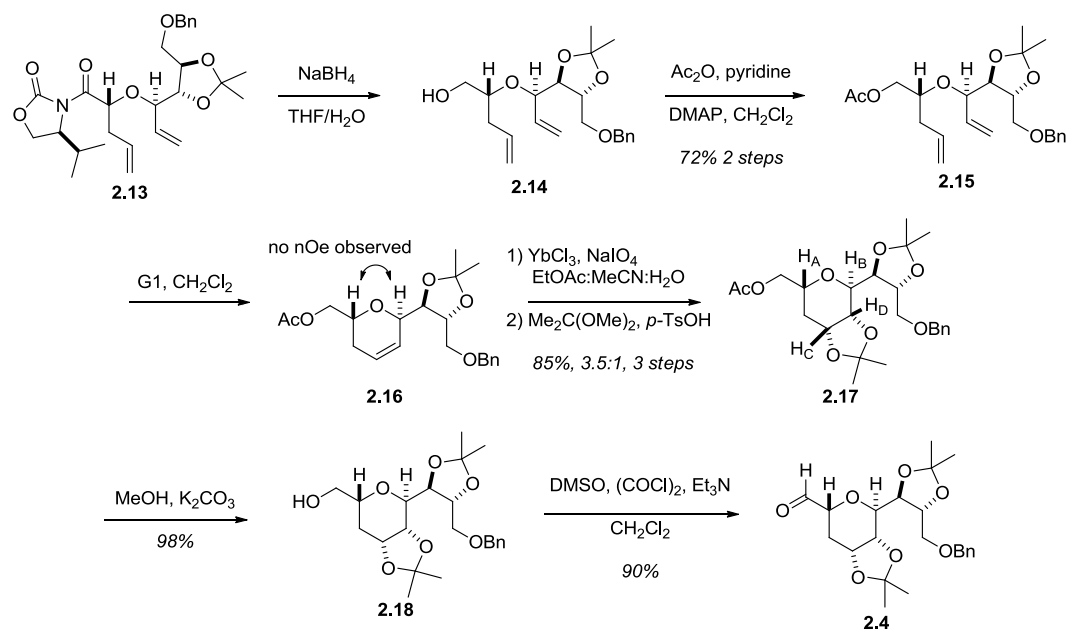
Scheme 2.1 Synthesis of the diene precursor to aldehyde 2.4.



tested, and ultimately Felkin-Ahn controlled divinyl zinc addition was determined to deliver allylic alcohol **2.10** as a 9:1 ratio of inseparable diastereomers in 80% yield. Alkylation of alcohol **2.10** with bromoacetic acid afforded acid **2.11**, which could be coupled with a valine-derived oxazolidinone to afford *N*-glycolyl oxazolidinone **2.12**. At this point the two diastereomers could be readily separated by chromatography. Alkylation of the sodium enolate of **2.12** with allyl iodide yielded diene **2.13**, introducing a key stereocenter with excellent diastereoselectivity (>20:1).^{33a}

Reductive removal of the auxiliary followed by protection of the resultant alcohol afforded diene **2.15** (Scheme 2.2). The alkylation could be performed on 20 gram scale and carried forward without purification to diene **2.15**. From diene **2.15**, a ring closing metathesis³⁵ followed by a dihydroxylation³⁶ provided the requisite functionality of common intermediate **2.4**. 2D NMR analysis of dihydropyran **2.16** showed the substituents adjacent to the ring oxygen in the tetrahydropyran to be *trans*. Protection of the diol as an acetonide afforded tetrahydropyran **2.17**. The presence of an nOe between H_A and H_C/H_D and lack of an interaction between H_B and H_C/H_D of **2.17** provided evidence for the desired stereochemistry of the tetrahydropyran domains. Methanolysis of the acetate protecting group unmasked primary alcohol **2.18** which could then be oxidized under Swern conditions³⁷ to access the desired common intermediate **2.4** in 90% yield.

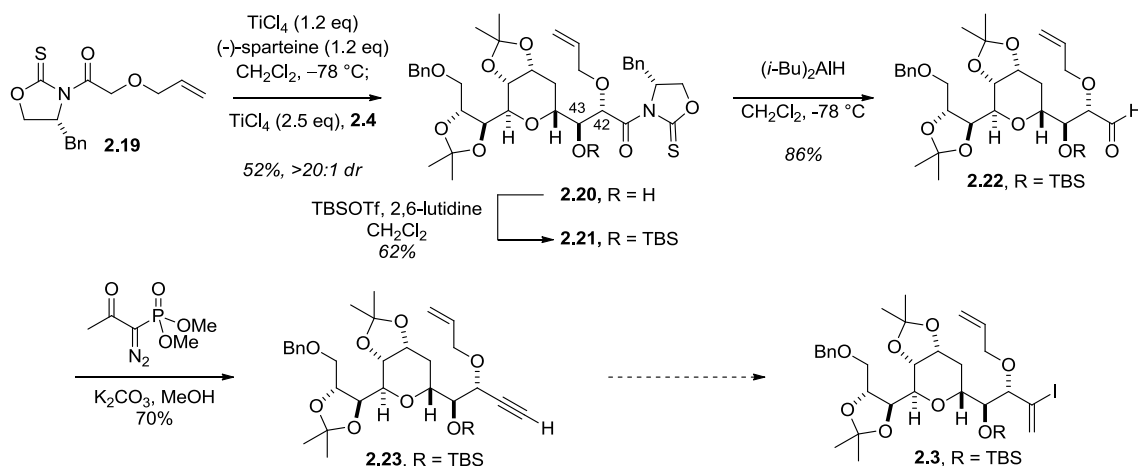
Scheme 2.2 Synthesis of common intermediate 2.4.



C. Elaboration of Common Intermediate 2.4 to the C42-C52 Tetrahydropyran

With common intermediate **2.4** in hand, we first sought to synthesize vinyl iodide **2.3** (Scheme 2.3). A titanium mediated glycolate *anti* aldol reaction between **2.19** and aldehyde **2.4** introduced the C43 and C44 stereocenters with high diastereoselectivity and moderate yield.³⁸ Following protection of the secondary alcohol as the TBS ether **2.21**, reductive cleavage of the auxiliary afforded aldehyde **2.22**. Treatment of aldehyde **2.22** with the Ohira-Bestmann reagent³⁹ provided access to alkyne **2.23**, our intended precursor to vinyl iodide **2.3**. Unfortunately, attempts at introducing the vinyl iodide through an intermediate vinyl stannane were unsuccessful (Scheme 2.4).⁴⁰ The reaction conditions were successful in

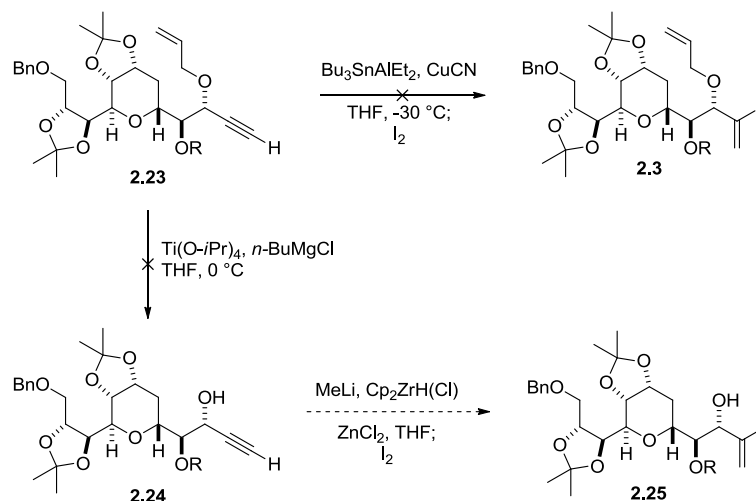
Scheme 2.3 Planned synthesis of vinyl iodide 2.3.



facilitating the desired reaction on a similar substrate; however there was no substitution at the C43 or C44 carbons.⁴¹ It is possible this additional steric influence resulted in the observed prolonged reaction times and decomposition. Another possible complication was the presence of the terminal alkene of the allyl protecting group from the glycolate *anti* aldol reaction. The alkene may have reacted with the iodine and resulted in byproduct formation and degradation of starting material.

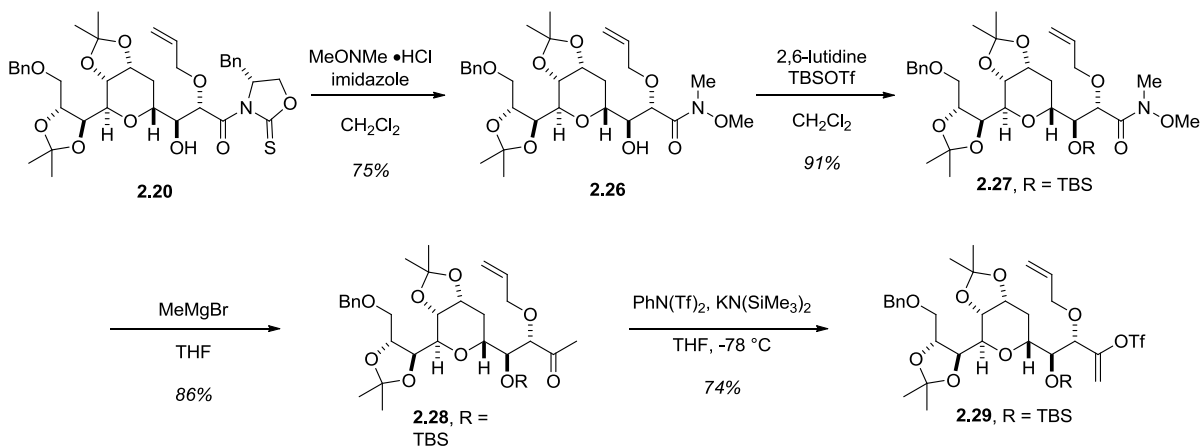
To avoid these potential complications, we theorized that propargylic alcohol **2.24** could be subjected to directed hydrozirconation⁴² to provide vinyl iodide **2.25** (Scheme 2.4). In 2007, Ready reported a directed hydrozirconation of propargylic alcohols using methyl lithium, $\text{Cp}_2\text{ZrH}(\text{Cl})$, and zinc chloride. An intermediate alkoxide is formed which directs hydrozirconation to the internal site of the alkyne, resulting in formation of 1,1-disubstituted alkenes upon treatment with an electrophile such as iodine. This would be ideal for our system, so we attempted to remove the allyl ether utilizing the Kulinkovich protocol⁴³ to access **2.24**. However the reaction was problematic, resulting in decomposition of the starting material and no isolation of desired product.

Scheme 2.4 Attempts at vinyl iodide synthesis.



In light of the problems with accessing the vinyl iodide, we revised our strategy to utilize a vinyl triflate for the desired fragment coupling. Despite the lower reactivity of vinyl triflates in the Suzuki-Miyaura cross-coupling reaction, there are several examples of their successful use in such reactions.⁴⁴ With this in mind, we sought to introduce the vinyl triflate from the glycolate *anti* aldol adduct **2.20** (Scheme 2.5). Direct displacement of the chiral auxiliary with *N,O*-dimethylhydroxylamine hydrochloride afforded the Weinreb amide **2.26** in 75% yield. The unprotected secondary alcohol was required for conversion to the Weinreb amide and was subsequently protected under standard conditions to afford TBS ether **2.27**. The Weinreb amide was then converted to the desired vinyl triflate **2.29** through a two step sequence via methyl ketone **2.28**.

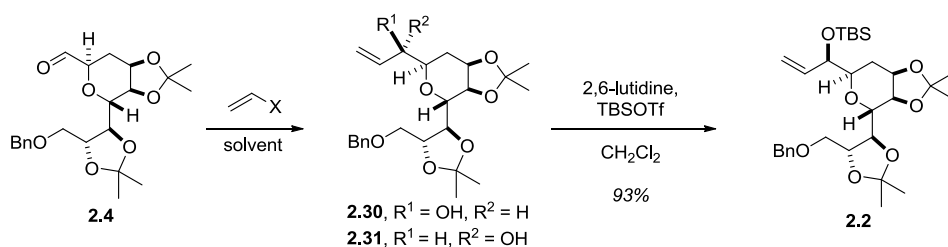
Scheme 2.5 Synthesis of vinyl triflate 2.29.



D. Elaboration of Common Intermediate 2.4 to the C31-C41 Tetrahydropyran

Having synthesized the C42-C52 tetrahydropyran coupling partner, our next task was the synthesis of the C31-C41 tetrahydropyran. From common intermediate **2.4**, we envisioned a vinyl addition to introduce the requisite alkene for coupling partner **2.2** (Scheme 2.6). The desired stereochemistry at C39 would arise from a chelate controlled

Scheme 2.6 Planned synthesis of alkene 2.2.



vinyl addition to aldehyde **2.4**. Despite testing various conditions to introduce the C39 stereocenter, a stereoselective vinyl addition remained elusive (Table 2.1). Addition of divinyl zinc was unselective even at low temperatures. Vinyl magnesiumbromide was also

Table 2.1 Vinyl addition to aldehyde 2.4.

Entry	Nucleophile	Temp (°C)	Solvent	Yield	Ratio (2.30:2.31)
1	divinyl zinc	-78 to 23	PhMe	61%	2:1
2	vinyl magnesiumbromide	-78 to 23	Et ₂ O	43%	2:1
3	vinyl magnesiumbromide	-78 to 23	THF	86%	1.4:1
4	vinyl magnesiumbromide	-78 to 23	PhMe	59%	3:1
5	vinyl magnesiumbromide	-78 to 23	CH ₂ Cl ₂	52%	3:1

tested, and while the use of THF as solvent afforded 86% yield the selectivity remained low. Diethyl ether which is less coordinating to metal counter ions as compared to THF was tested, however the yields and selectivities obtained were poor. In order to facilitate a chelated transition state, use of non-coordinating solvents such as toluene and methylene chloride was investigated. Unfortunately, only a marginal increase in selectivity, yielding at best a 3:1 mixture of diastereomers, was observed. Addition of nucleophiles to similar aldehydes has been previously reported with comparable results.⁴⁵

In light of this challenge, we pursued an oxidation/stereoselective reduction to introduce the desired *R* configuration (Scheme 2.7). Addition of vinyl magnesium bromide to aldehyde **2.4** afforded a mixture diastereomers **2.30** and **2.31** which were subsequently oxidized to enone **2.32** utilizing Dess-Martin periodinane.⁴⁶ Several reagents were tested for Felkin-Ahn delivery of the hydride to enone **2.32** including di-*iso*-butylaluminum hydride (Entry 1), Luche conditions⁴⁷ (Entries 2,3), and “naked” hydride⁴⁸ (Entry 4); however only the use of the Corey-Bakshi-Shibata reagent⁴⁹ afforded high selectivity of the desired allylic alcohol (Table 2.2). Synthesis of both the *R* and *S* Mosher esters of allylic alcohol **2.30** and analysis of their chemical shifts by ¹H NMR following the advanced Mosher ester analysis

determined that treatment of **2.32** with the *R*-Me-CBS reagent indeed resulted in the desired *R* configuration of the allylic alcohol.⁵⁰ Protection of **2.30** as the TBS ether afforded the carbon framework of the C31-C41 tetrahydropyran coupling partner **2.2**.

Scheme 2.7 Synthesis of alkene 2.2 via oxidation/stereoselective reduction.

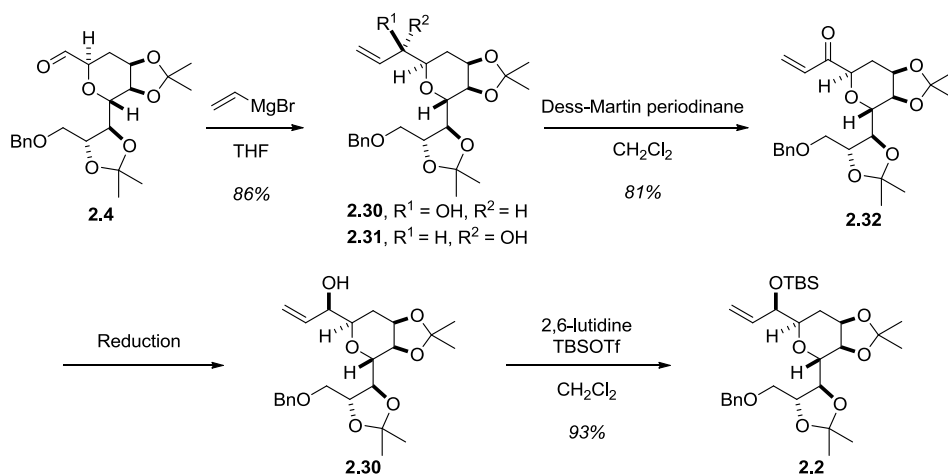


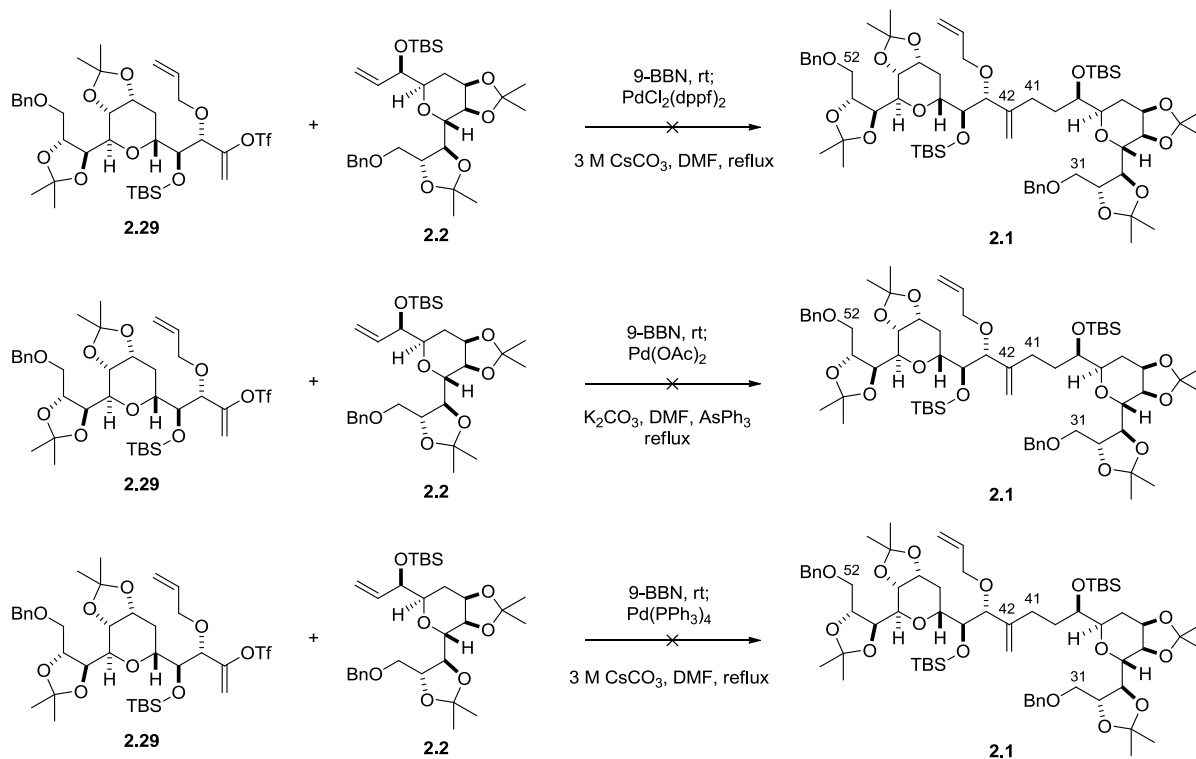
Table 2.2 Conditions for selective reduction of enone 2.32.

Entry	Conditions	Temp (°C)	Yield	Ratio
1	(<i>i</i> -Bu) ₂ AlH, CH ₂ Cl ₂ ,	-78	43%	1.7:1
2	NaBH ₄ , CeCl ₃ , MeOH	-78	74%	3.5:1
3	NaBH ₄ , CeCl ₃ , MeOH	23	--	1.7:1
4	PhMe ₂ SiH, <i>n</i> -Bu ₄ N ⁺ F ⁻ , HMPA	-78	20%	5:1
5	S-Me-CBS, BH ₃ •SMe ₂ , CH ₂ Cl ₂	0 to 23	92%	2:1
6	R-Me-CBS, BH ₃ •SMe ₂ , CH ₂ Cl ₂	0 to 23	72%	>20:1

E. Attempted Suzuki-Miyaura Cross Couplings

With both coupling partners in hand, a Suzuki-Miyaura cross coupling was explored to form the C41-C42 bond of the bis-THP while introducing the 1,1-disubstituted alkene at C42 and the alkyl linker of C40 and C41 (Scheme 2.8).^{44,51} Treatment of alkene **2.2** with 9-BBN was envisioned to provide an intermediate alkyl borane that would then be combined with vinyl triflate **2.29**, a palladium (0) catalyst, and base to effect the desired reaction. $\text{PdCl}_2(\text{dppf})_2$, $\text{Pd}(\text{OAc})_2$, and $\text{Pd}(\text{PPh}_3)_4$ were all tested, however the desired product could not be isolated. $\text{PdCl}_2(\text{dppf})_2$ resulted in recovery of starting material, while $\text{Pd}(\text{OAc})_2$ and $\text{Pd}(\text{PPh}_3)_4$ resulted in cleavage of the allyl protecting group of vinyl triflate **2.29**, and isolation of a mixture of unidentified byproducts. Separation of compounds from the reactions also proved difficult, due to the similar polarities of vinyl triflate **2.29**, alkene **2.2**, and unidentified byproducts. The proton NMR spectra of recovered material revealed complex mixtures of alkene containing compounds.

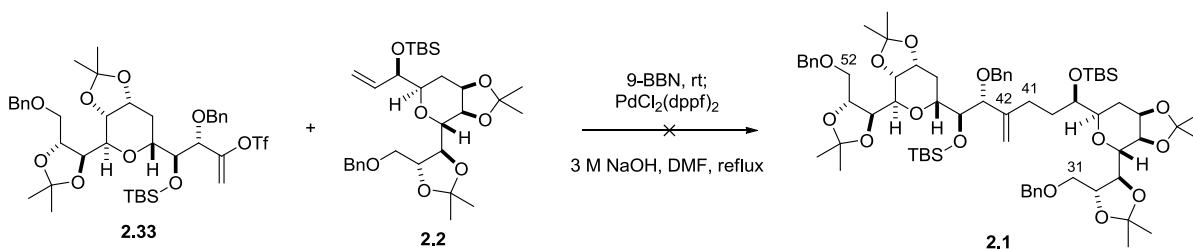
Scheme 2.8 Attempted Suzuki-Miyaura cross-couplings.



Utilizing model systems to test the Suzuki-Miyaura coupling reaction, we determined that the reaction conditions could indeed effect the desired reaction in our hands, and sought to modify our system. We believed that the allyl-protecting group of the C43 hydroxyl was interfering with the reaction and providing a degradation pathway of vinyl triflate **2.29**, potentially resulting in decreased efficiency of the palladium catalyst. To avoid this, the allyloxy glycolate **2.19** was replaced with the analogous benzyloxy glycolate for the glycolate *anti* aldol reaction and carried forward to access vinyl triflate **2.33** following the reactions outlined in Schemes 2.3 and 2.5. A consequence of this substitution was reduction of the yield of the glycolate *anti* aldol reaction to 44% with a 10:1 ratio of diastereomers, still favoring the desired *anti* aldol adduct analogous to **2.20** (Scheme 2.3).

Altered vinyl triflate **2.33** was then utilized in the Suzuki-Miyaura cross coupling (Scheme 2.9). Sodium hydroxide was utilized as the base for the reaction to better activate the intermediate alkyl borane. Again we met little success in these endeavors, even when

Scheme 2.9 Vinyl triflate 2.33 in attempted Suzuki-Miyaura cross-couplings.

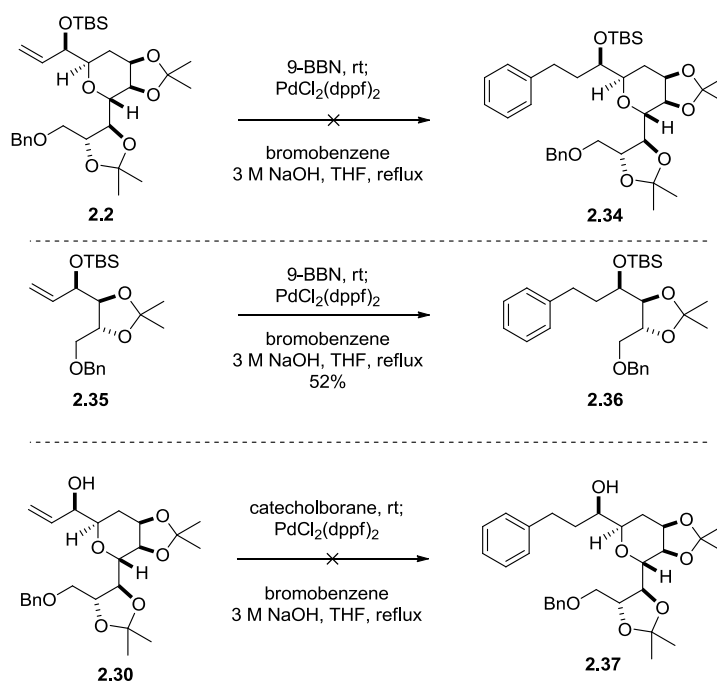


utilizing a microwave to facilitate the reaction. In some cases the vinyl triflate was consumed, however no coupled product **2.1** was observed. One challenge of the reaction became monitoring the formation of the intermediate alkyl borane. Recovery of alkene **2.2** was observed in some reactions, with as great as 70% recovery in one case. This led to the hypothesis that hydroboration of alkene **2.2** was slow, and possibly incomplete, leading to non-productive side reactions. To increase the speed of hydroboration, we subjected alkene **2.2** and 9-BBN to sonication for several hours before treatment with vinyl triflate **2.33** and the palladium catalyst, although no productive reaction was observed.

Subsequently, we further investigated hydroboration of alkene **2.2** (Scheme 2.10). Treatment of alkene **2.2** with standard Suzuki conditions and bromobenzene failed to provide the coupled product **2.34**. Variations in catalyst and base also failed to provide desired product **2.34**. At this time, we questioned if the TBS ether was too sterically bulky to allow a successful hydroboration of allylic alcohol **2.2**, despite previous reports of the use of bulky alkenes in the literature.^{44b} To test this, we performed a Suzuki coupling between bromobenzene and alkene **2.35** and found the reaction proceeded in 52% yield. We also attempted the Suzuki coupling utilizing allylic alcohol **2.30**, however even without the TBS

ether, no reaction was observed. Utilization of Wilkinson's catalyst to increase the rate of hydroboration⁵² with 9-BBN or catecholborane also failed to effect hydroboration. Treatment of **2.30** with Wilkinson's catalyst and catecholborane may have resulted in competing isomerization of the terminal alkene, as an increase in vinyl signals was observed. In light of the many difficulties we encountered with the Suzuki-Miyaura cross-coupling, we revised our retrosynthetic analysis to unite the two fragments in a different manner.

Scheme 2.10 Investigation of the hydroboration of alkene 2.2.

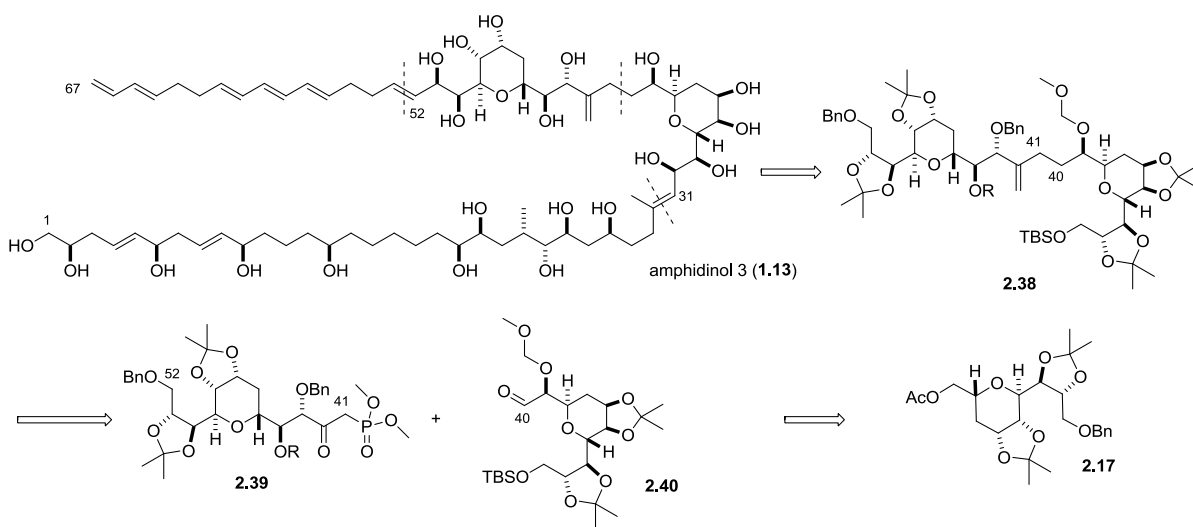


F. Coupling Strategy Utilizing a Horner-Wadsworth-Emmons Olefination

It was envisioned that a Horner-Wadsworth-Emmons (HWE) olefination⁵³ could be used to introduce the desired C40-41 bond as an enone and the complete C31-C52 skeleton of the bis-THP, which could be further elaborated to the desired bis-THP core **2.38** (Figure 2.2). β -ketophosphonate **2.39** would be obtained after a glycolate *anti* aldol reaction to introduce the C43 and C44 stereocenters. Aldehyde **2.40** would be accessed in a similar

manner to aldehyde **2.4**, again utilizing the CBS reagent to set the stereocenter at C39. As a consequence of utilizing a common intermediate for the synthesis of both coupling partners, the two primary alcohols at C32 and C52 were both protected as benzyl ethers. However, differential protection of the two primary alcohols is required for the selective introduction of the polyene and polyol domains of amphidinol 3 (**1.13**). We sought to address this in our revised retrosynthetic analysis by utilizing acetate **2.17** (Schemes 2.1 and 2.2) as the common precursor for the coupling partners.

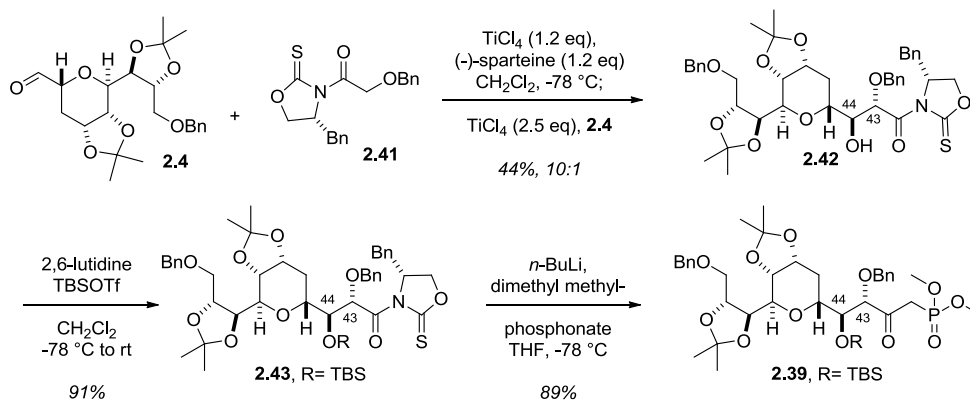
Figure 2.2 Revised retrosynthesis of amphidinol 3.



From common intermediate **2.17**, synthesis of the C41-C52 tetrahydropyran coupling partner **2.39** was initiated by methanolysis of the acetate followed by Swern oxidation to access aldehyde **2.4** (Scheme 2.2). A glycolate *anti* aldol reaction between aldehyde **2.4** and *N*-glycolyl oxazolidinethione **2.41** introduced the C43 and C44 stereocenters as a 10:1 ratio of separable diastereomers in 44% yield (Scheme 2.11). Varying the amount of Lewis acid used in the reaction in an attempt to increase the yield resulted in decomposition or decreased selectivity. Simple conversion of aldol adduct **2.42** to the desired coupling partner, β-ketophosphonate **2.39**, was effected by protection of the alcohol as the TBS ether

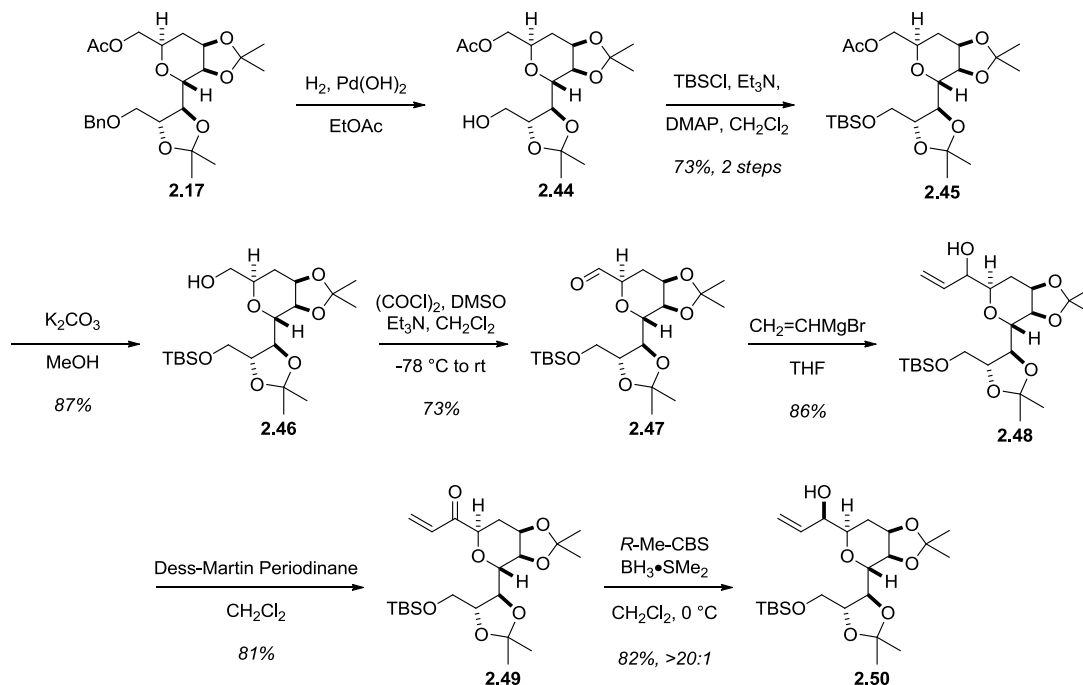
and direct displacement of the auxiliary with lithiated dimethyl methylphosphonate in 89% yield.

Scheme 2.11 Synthesis of phosphonate 2.39.



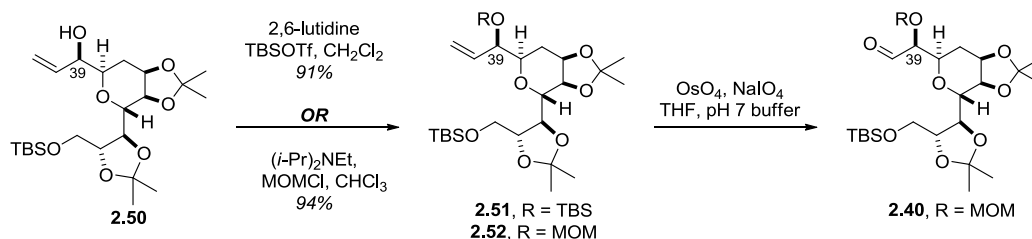
To access aldehyde **2.40** from common intermediate **2.17**, the benzyl ether was cleaved and the resulting primary alcohol **2.44** was protected with TBSCl to afford silyl ether **2.45** (Scheme 2.12). Methanolysis of the acetate protecting group afforded alcohol **2.46**, which was oxidized under Swern conditions to aldehyde **2.47**, the TBS protected analog of aldehyde **2.4** from our original retrosynthetic analysis (Scheme 2.1). As with aldehyde **2.4**, aldehyde **2.47** was subjected to a non-selective vinyl addition, and oxidized to enone **2.49**. Treatment of enone **2.49** with the CBS reagent afforded the desired allylic alcohol **2.50**, again in high yield as well as excellent diastereoselectivity.

Scheme 2.12 Protecting group exchange and synthesis of alcohol 2.50.



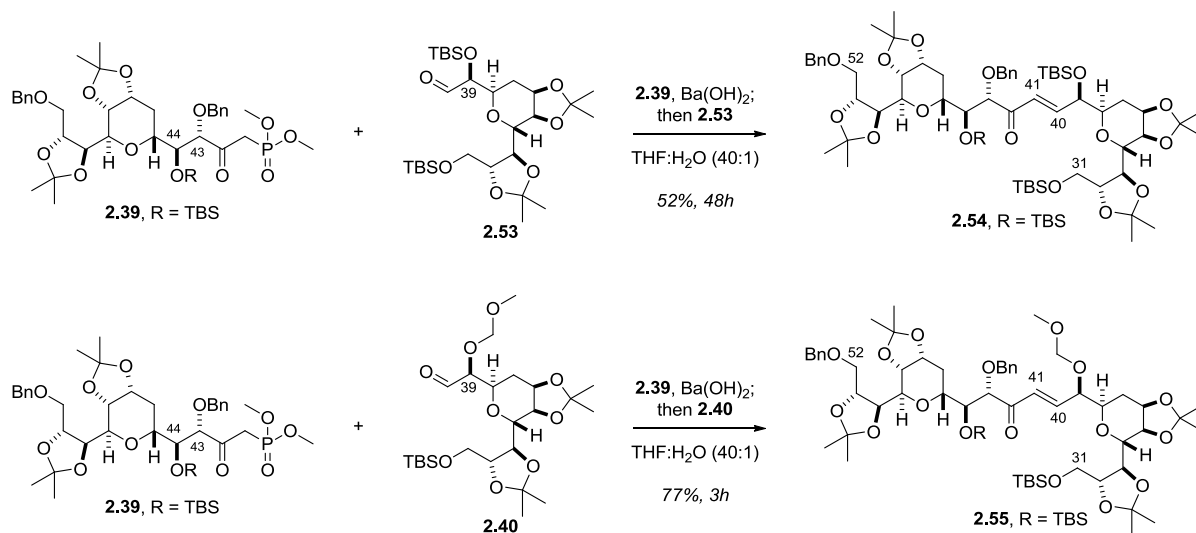
Alcohol **2.50** was then protected as the TBS ether to afford alkene **2.51** (Scheme 2.13). Initially we sought to access aldehyde **2.53** via oxidative cleavage with ruthenium chloride and sodium periodate, however, only 47% of the desired product was obtained. Treatment with osmium tetroxide followed by sodium periodate afforded a similarly low yield. Ozonolysis also provided poor yield of the desired product. Despite these lower yields, we were able to obtain enough of aldehyde **2.53** to test the key Horner-Wadsworth-Emmons olefination reaction (Scheme 2.14). Treatment of β -ketophosphonate **2.39** with barium hydroxide followed by addition of aldehyde **2.53** yielded the desired C31-C52 bis-THP **2.54** in 52% yield as an inconsequential mixture of *E:Z* isomers only after reaction for 48 hours at room temperature.^{32,53} The prolonged reaction times and moderate yields of the HWE olefination as well as the lower yields of the oxidative cleavage of alkene **2.51** caused us to investigate use of a less bulky protecting group for the C39 hydroxyl.

Scheme 2.13 Synthesis of aldehyde 2.40.



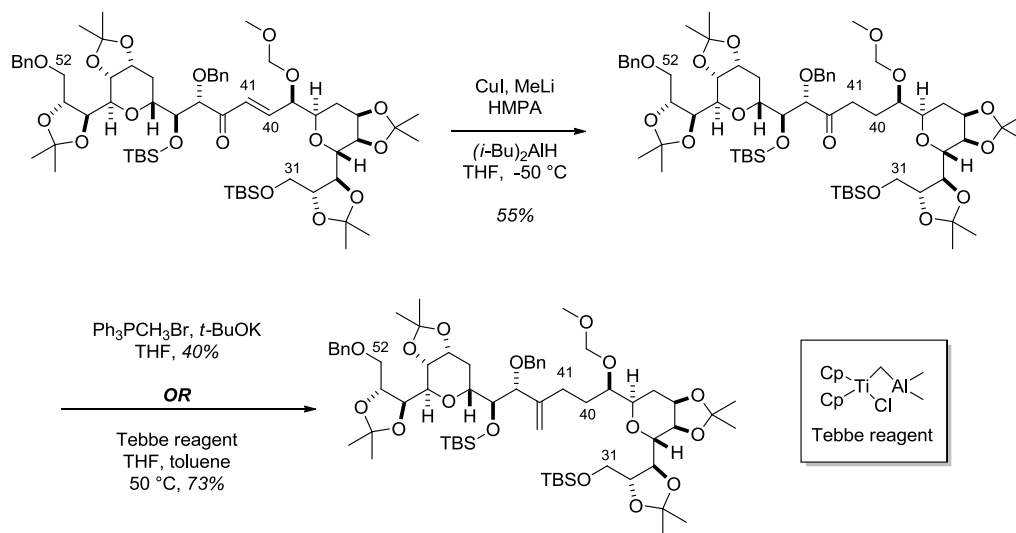
A methoxymethyl (MOM) ether would provide a protecting group that could be removed under acidic conditions that would also allow for concomitant cleavage of the acetal protecting groups. A MOM ether was also used to protect the C39 hydroxyl of amphidinol 3 (**1.13**) in a fragment synthesis by Paquette.^{45a} To this end, alcohol **2.50** was treated with di-*iso*-propylethylamine and methoxymethyl chloride to introduce the MOM ether and obtain alkene **2.52** in excellent yield (Scheme 2.14). We also explored conditions utilized by Paquette for the oxidative cleavage of the C40 alkene to access aldehyde **2.40**.^{45a} Subjection of alkene **2.52** to Johnson-Lemieux oxidation afforded aldehyde **2.40** in higher yield than the previously tested oxidations.⁵⁴ Use of aldehyde **2.40** in place of aldehyde **2.53** in the HWE olefination resulted in a decrease in reaction time to 3h, as well as an increase in yield to 77% of the desired enone **2.55**. Confirmation of successful olefination was obtained upon examination of the proton NMR which showed the presence of two vinyl protons at 6.83 and 6.78 ppm. Due to the improved yields and reaction times, we opted to utilize the MOM ether over the TBS ether to protect the C39 hydroxyl.

Scheme 2.14 Horner-Wadsworth-Emmons olefinations.



With a route to access the carbon skeleton of the C31-C52 fragment, we set out to reduce the C40-41 alkene and introduce the 1,1-disubstituted alkene at C42 of the natural product. A conjugate reduction utilizing methyl copper and di-*iso*-butylaluminum hydride was performed on enone **2.55**, introducing the alkyl linker and providing ketone **2.56** (Scheme 2.15).⁵⁵ We then attempted a methylene Wittig reaction to introduce the 1,1-disubstituted alkene at C42, but the desired alkene **2.38** could only be obtained at best in 40% yield.⁵⁶ Poor recovery of starting material and the presence of unidentifiable impurities in the proton NMR spectra seemed to indicate a significant amount of decomposition was occurring during the course of the reaction. To eliminate the potential presence of base, “salt-free” conditions for the methylene Wittig were also tested, unfortunately without success.⁵⁷ To ensure there was no water present in the phosphonium salt, the methyltriphenylphosphonium bromide was dried in a drying pistol for 72h and used only under an inert atmosphere prior to ylide formation. Despite these precautions, the yield of the reaction remained inconsistent with a large amount of decomposition.

Scheme 2.15 Elaboration of the bis-THP core.



Facing problems with the methylene Wittig reaction, we explored other conditions for olefination. The Tebbe reagent has been utilized on numerous systems for introduction of alkenes.⁵⁸ Treatment of ketone **2.56** with the Tebbe reagent at room temperature did not result in the formation of the desired product, even at prolonged reaction times. Fortunately, heating of the reaction mixture to 50 degrees Celsius afforded the desired 1,1-disubstituted alkene **2.38** in 73% yield. The presence of the 1,1-disubstituted alkene was confirmed by two distinct vinyl signals at 5.10 and 5.02 ppm in the proton NMR of **2.38**.

G. Summary

In summary we have achieved a convergent synthesis of the C31-C52 bis-tetrahydropyran core **2.38** of amphidinol 3 **1.13** utilizing common intermediate **2.17**. Tetrahydropyran **2.17** contains all of the stereocenters required for the C32-C38 and C45-C51 domains of the bis-THP core, and was obtained in 14 steps from D-tartaric acid utilizing the glycolate alkylation-ring closing metathesis strategy. β -ketophosphonate **2.39** was

obtained from common intermediate **2.17** following a 5 step sequence, including a glycolate *anti* aldol reaction to introduce the C43-C44 stereocenters. Aldehyde **2.40** was derived from common intermediate **2.17** in 9 steps with introduction of the C39 stereocenter by CBS reduction. Union of the C31-C40 and C41-C52 fragments was achieved through HWE olefination in 77% yield, and the protected bis-THP core **2.38** was accessed following conjugate reduction and Tebbe olefination to introduce the C42 1,1-disubstituted alkene.

H. References

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Chapter 3

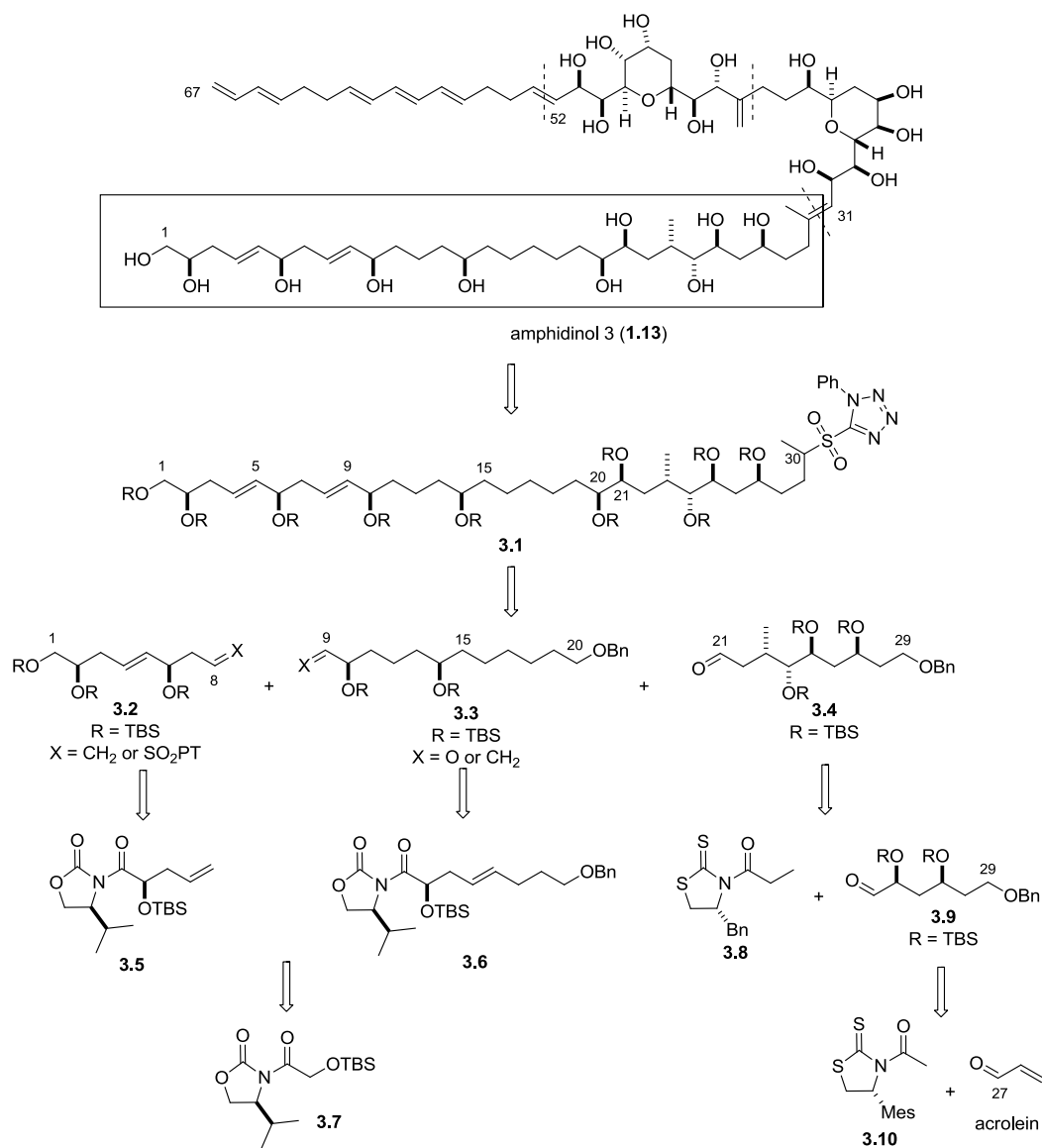
Efforts Toward the C1-C30 Polyol Domain and Planned Fragment Coupling

A. Retrosynthetic Analysis of the C1-C30 Polyol Domain

Upon completion of the bis-THP core of amphidinol 3, we turned our attention to the synthesis of the C1-C30 domain of the molecule. Multiple hydroxyl groups characterize the C1-C30 fragment, which contains ten stereocenters of the natural product. The C2-C17 domain contains a repeating four-carbon unit varying only in the presence of an olefin at the C4-C5 and C8-C9 units. As with the bis-THP core, we sought to exploit similarities in the molecule to expedite the synthesis of advanced intermediates.

We focused on a convergent route to access sulfone **3.1** via fragments **3.2**, **3.3**, and aldehyde **3.4** (Figure 3.1). A Julia-Kocienski olefination would unite the C9-C20 and C21-C29 fragments **3.3** and **3.4**.⁵⁹ A Sharpless asymmetric dihydroxylation of the resultant C20-C21 olefin would then introduce the required C20-C21 stereocenters.⁶⁰ A cross-metathesis or olefination reaction could then append the C1-C8 unit completing sulfone **3.1**. We believed that the glycolate alkylation reaction could be utilized to synthesize the 1,5-*syn*-diol moieties of the polyol domain. To this end, alkene **3.2** would be accessed utilizing known glycolate alkylation product **3.5** as the source of both the C1-C4 and C5-C8 units.⁶¹ The C4-C5 olefin would be introduced by cross-metathesis or olefination. We also sought to access the C9-C17 domain utilizing the glycolate alkylation reaction, again relying on alkylation product **3.5**

Figure 3.1 Retrosynthetic analysis of the C1-C30 domain of amphidinol 3.



as the source for the C9-C12 segment. It was envisioned that the C13-C20 fragment would be accessible from alkene **3.6**.

The C21-C29 fragment **3.4** would be accessed utilizing aldol methodology previously developed in the Crimmins laboratory. A propionate aldol between **3.8** and aldehyde **3.9** would provide the C21-C29 fragment with the desired stereochemistry.⁶² Aldehyde **3.9** would be accessed following an iterative acetate aldol sequence starting with

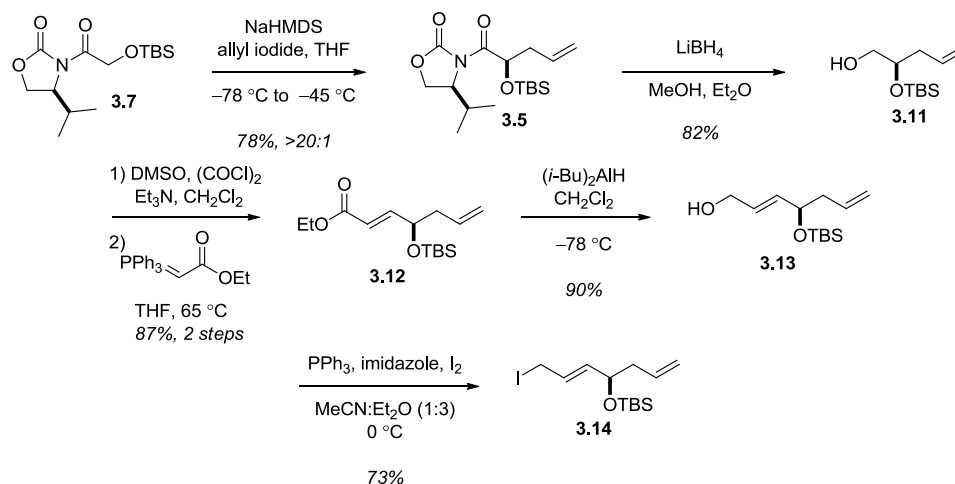
thiazolidinethione **3.10** and acrolein.⁶³ Following this planned route, all of the stereocenters except the C21-C22 diol would be introduced using aldol or alkylation chemistry developed in the Crimmins laboratory.

B. Synthesis of the C9-C20 Fragment Utilizing the Glycolate Alkylation

(i) Attempted Iterative Glycolate Alkylations

To quickly access alkenes **3.2** and **3.3**, we hoped to utilize an iterative glycolate alkylation procedure (Scheme 3.1). Treatment of **3.7** with sodium hexamethyldisilazide (NaHMDS) and allyl iodide effected alkylation of the sodium enolate of **3.7** to provide **3.5** in good yield with excellent selectivity (>20:1). Reductive cleavage of the chiral auxiliary afforded alcohol **3.11**. A Swern oxidation of **3.11** followed by Wittig olefination provided ester **3.12** in 87% yield over two steps. Reduction of ester **3.12** with DIBAL proceeded smoothly to yield allylic alcohol **3.13**. Treatment of allylic alcohol **3.13** with triphenylphosphine, imidazole, and iodine afforded the allylic iodide **3.14** required to test the iterative glycolate alkylation sequence.

Scheme 3.1 Synthesis of the iterative glycolate alkylation precursor.



With allylic iodide **3.14** in hand, we attempted to use it as the electrophile in the glycolate alkylation reaction (Scheme 3.2). Unfortunately, reaction of glycolate **3.7**, NaHMDS, and allylic iodide **3.14** under standard glycolate alkylation conditions proceeded in very poor yield, with only 4% of the desired product **3.15** isolated. While only 4% of the desired product could be isolated, we were able to recover 51% of allylic iodide **3.14** and 68% of glycolate **3.7**. Based on these findings, we presumed the reaction was slow and attempted optimize the reaction conditions to facilitate the desired transformation (Table 3.1).

Scheme 3.2 Attempted iterative glycolate alkylations.

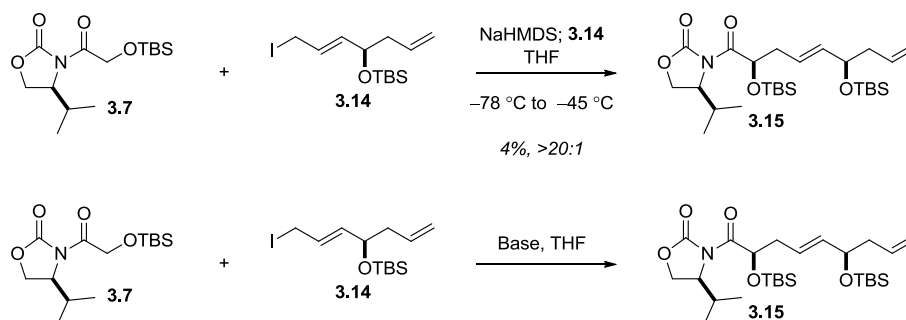


Table 3.1 Conditions for the iterative glycolate alkylation.

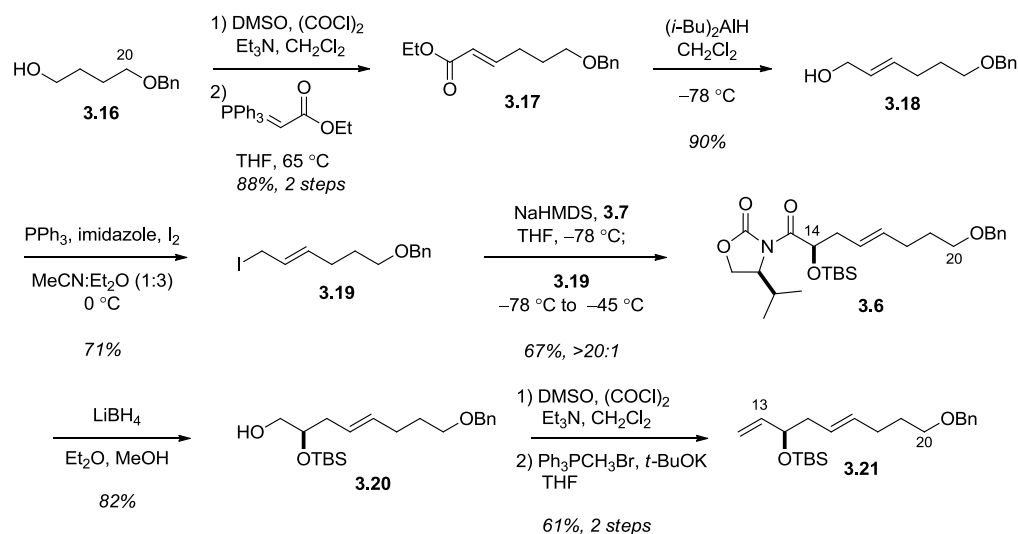
Entry	Equivalents 3.7	Equivalents 3.14	Base	Temp (°C)	Time (h)	Result
1	1	1	NaHMDS	-78 to -45	17	Glycolate decomposition; Partial recovery of 3.14
2	3	1	NaHMDS	-78 to -45	3	No reaction
3	3	1	NaHMDS	-78 to -45	17	Glycolate decomposition; Decomposition of 3.14
4	1.1	1	KHMDS	-78 to -45	4	No reaction
5	5	1	NaHMDS	-78 to -45	3	Partial recovery of 3.7 ; Decomposition of 3.14
6	5	1	KHMDS	-78 to -45	17	16% of an unidentified product; Mostly decomposition

Prolonged reaction of **3.7**, NaHMDS, and **3.14** resulted in decomposition of the glycolate and only partial recovery of the allylic iodide (Entry 1). Use of excess **3.7** and NaHMDS also failed to provide the desired product **3.15**, even after prolonged reaction times at -45 °C (Entries 2, 3). Due to the known higher reactivity of the potassium enolate derived from **3.7**, KHMDS was investigated as a base for the reaction (Entries 4, 6). Unfortunately, as with NaHMDS, no desired product could be isolated and large amounts of decomposition were observed.

(ii) Attempted Synthesis of 3.3 utilizing Glycolate Alkylation and Cross-Metathesis

Due to the problems we encountered while attempting an iterative glycolate alkylation sequence, we planned to perform a single glycolate alkylation followed by a cross-metathesis in order to access **3.2** and **3.3**. First, we explored the synthesis of the C9-C20 fragment **3.3** via alkylation product **3.6** (Scheme 3.3). Synthesis of **3.6** began with primary alcohol **3.16**,⁶⁴ which was subjected to oxidation under Swern conditions and Wittig

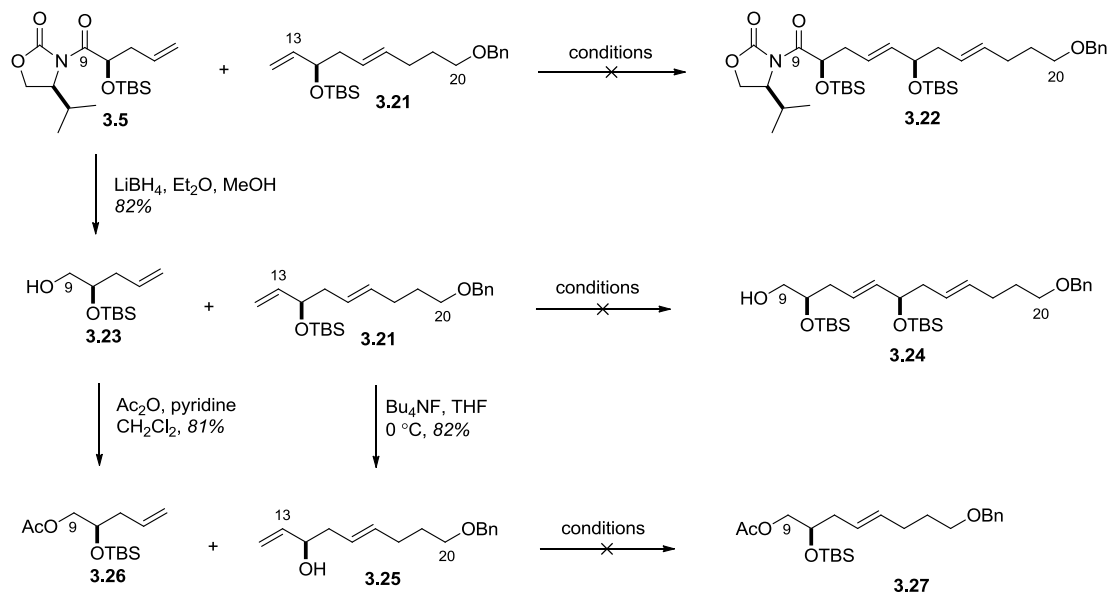
Scheme 3.3 Synthesis of the C13-C20 fragment.



olefination to afford ester **3.17**. Reduction of the ester with DIBAL afforded allylic alcohol **3.18** in high yield. The allylic alcohol was then converted to allylic iodide **3.19** using the previously discovered conditions (Scheme 3.1). Glycolate alkylation between **3.7** and allylic iodide **3.19** afforded alkene **3.6** in 67% yield with excellent diastereoselectivity (>20:1). The use of 5 equivalents of allylic iodide **3.19** was required for a successful reaction. The chiral auxiliary was reductively cleaved to provide alcohol **3.20**, which was then converted to alkene **3.21** following oxidation and olefination.

With the C13-C20 fragment **3.21** in hand; efforts were focused on homologation to access the C10-C20 fragment. We planned to achieve this via a cross-metathesis reaction between alkene **3.21** and alkylation product **3.5** (Scheme 3.4).⁶⁵ We began our investigations

Scheme 3.4 Attempted cross metatheses to access the C9-C20 fragment.



of a cross-metathesis reaction between terminal alkene **3.5** and protected allylic alcohol **3.21** utilizing Grubbs second-generation metathesis catalyst (G2)⁶⁶ at room temperature. However, we found the reaction afforded no desired product **3.22** and resulted in formation of a mixture of byproducts (Table 3.2, Entry 1). Upon heating, similar results were observed (Table 3.2, Entry 2). The Hoveyda-Grubbs second-generation metathesis catalyst (HG2) was also tested, with similar results.⁶⁷ Recovery of the starting materials was possible, albeit not quantitative, and identification of isolated byproducts was difficult due to the presence of multiple alkene signals in the ¹H NMR spectra. One potential, but unconfirmed byproduct, was cleavage of the C16-C17 alkene of **3.21** and unproductive cross metathesis with either **3.5** or a second molecule of **3.21**. Attempted dimerization of **3.5** proved sluggish, which prompted us to explore use of the primary alcohol **3.23** instead of the bulkier glycolate **3.5**. We hoped this would allow for faster cross-metathesis and decrease byproduct formation.

Table 3.2 Cross metatheses attempted to synthesize the C9-C20 fragment.

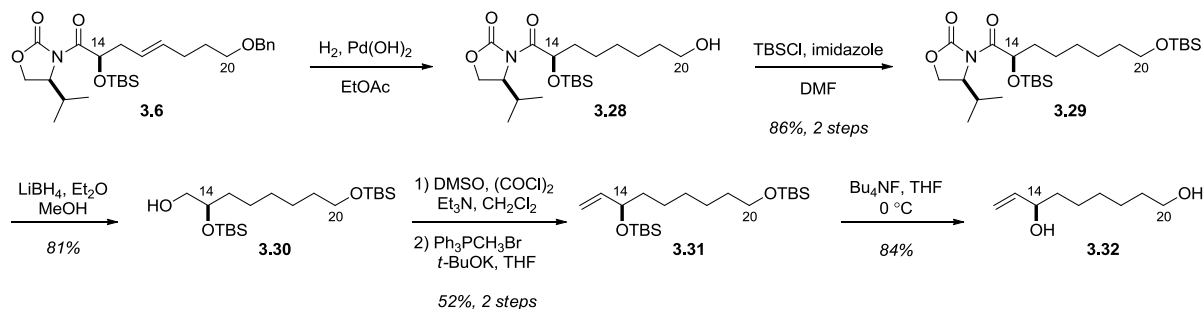
Entry	C9-C12 alkene (eq)	C13-C20 alkene (eq)	Catalyst/ Solvent	Temp (°C)	Time (h)	Method	Result
1	3.5 (1.2)	3.21 (1.0)	G2 CH ₂ Cl ₂	20	9	Combine 3.5 and 3.21 , degas, add G2	Several byproducts formed; poor recovery of 3.5 and 3.21 ; no formation of 3.22 by ¹ H NMR
2	3.5 (1.2)	3.21 (1.0)	G2 CH ₂ Cl ₂	35	15	Combine 3.5 and 3.21 , degas, add G2, reflux O/N	Recover 50% of 3.5 and 3.21 ; unidentified byproduct formation; no formation of 3.22
3	3.5 (1.0)	3.21 (1.0)	HG2 CH ₂ Cl ₂	20	3	Combine 3.5 and 3.21 , degas, add HG2	Several byproducts formed; poor recovery of 3.5 and 3.21 ; no formation of 3.22 by ¹ H NMR
4	3.23 (1.0)	3.21 (1.0)	G2 CH ₂ Cl ₂	20	15	Slow addition of 3.23 to 3.21 and G2	Dimerization of 3.23 ; poor recovery of 3.21
5	3.23 (1.0)	3.25 (1.0)	G2 CH ₂ Cl	20	15	Combine 3.23 and 3.25 , degas, add G2	Dimerization of 3.23 ; poor recovery of 3.25
6	3.26 (1.0)	3.25 (1.0)	G2 CH ₂ Cl	20	3	Combine 3.26 and 3.25 , degas, add G2	Dimerization of 3.26 ; poor recovery of 3.25
7	3.26 (1.0)	3.25 (1.0)	G2 CH ₂ Cl	35	3	Combine 3.26 and 3.25 , degas, add G2	Dimerization of 3.26 ; poor recovery of 3.25
8	3.26 (3.0)	3.21 (1.0)	G2 CH ₂ Cl	20	3	Combine 3.26 and 3.25 , degas, add G2	Dimerization of 3.26 ; 38% of 3.27

Thus, treatment of **3.5** with lithium borohydride provided primary alcohol **3.23** cleanly in high yield (Scheme 3.4). Dimerization of **3.23** occurred quickly upon treatment with G2, and no cross-metathesis could be observed when **3.23** and **3.21** were combined before addition of catalyst. To avoid competing dimerization of **3.23**, we tested slow addition of the terminal alkene to a mixture of **3.21** and G2 (Table 3.2, Entry 4). However, we found this did not alleviate dimerization of **3.23**, and isolated no desired product **3.24**. Furthermore, we were only able to recover 50% of alkene **3.21**, supporting the belief that cleavage of the C16-C17 bond was occurring over reaction with the C12-C13 olefin. At this time, we thought that the bulky TBS protecting group of the allylic alcohol was blocking the C12-C13 olefin

from participating in the cross-metathesis, resulting in reaction of the C16-C17 olefin and dimerization of the C9-C12 coupling partner. The TBS ether of **3.21** was cleaved with TBAF to afford allylic alcohol **3.25**. Cross metathesis of terminal alkene **3.23** and allylic alcohol **3.25** proved fruitless, as combination of the two alkenes in the presence of G2 again resulted in dimerization of **3.23** and partial recovery of allylic alcohol **3.25** (Table 3.2, Entry 5). We also tested the cross-metathesis of terminal alkene **3.26** and allylic alcohol **3.25**, but the acetate protected C9-C13 partner proved no better than **3.5** or **3.23** (Table 3.2, Entries 6, 7). However, with this reaction, we were able to isolate what appeared by proton NMR to be alkene **3.27** (Scheme 3.4). This provided some evidence that the C16-C17 olefin was interfering with the reaction.

As the C16-C17 olefin is not present in the natural product, we explored its reduction at this earlier stage to explore the impact on cross-metathesis (Scheme 3.5). Hydrogenation of **3.6** with palladium (II) hydroxide afforded primary alcohol **3.28**, which was then protected as a TBS ether to provide **3.29**. Reductive cleavage of the chiral auxiliary yielded primary alcohol **3.30**. Primary alcohol **3.30** could be converted to alkene **3.31** in 52% over two steps. Cleavage of the TBS ethers of alkene **3.31** afforded allylic alcohol **3.32**. Both **3.31** and **3.32** were tested in the cross metathesis reaction with the C9-C13 partner (Scheme 3.6).

Scheme 3. 5 Modification of the C13-C20 fragment.



Conditions that were previously used for attempted cross-metathesis of the C9-C12 and C13-C20 fragments were revisited with the modified C13-C20 fragments **3.31** and **3.32**

(Table 3.3). Initially, the reaction of terminal alkene **3.23** and protected allylic alcohol **3.31** in the presence of G2 seemed promising. The desired C9-C20 fragment **3.33** was obtained in 25% yield after prolonged reaction at room temperature (Table 3.3, Entry 1). Dimerization of the C9-C12 fragment **3.23** remained a competing reaction, despite slow addition of **3.23** to **3.31** and catalyst. To alleviate this, we hoped to facilitate faster reaction of **3.31** with the terminal alkene. Varying solvent and reaction temperature as well as use of the more reactive metathesis catalyst HG2 failed to increase the rate of the desired cross-metathesis. (Table 3.3, Entries 2, 3). The use of allylic alcohol **3.32** as the C13-C20 fragment also proved problematic. Cross-metathesis of **3.31** with terminal alkene **3.26** resulted in no formation of desired product **3.34** (Scheme 3.6). While allylic alcohol **3.32** was consumed, the dimer of terminal alkene **3.26** was isolated, indicating that **3.32** was being consumed in a competing, undesired reaction (Table 3.3, Entries 4, 5, 6). Despite prolonged reaction and heating, the desired product could not be obtained. Due to the complications encountered with the cross-metathesis reaction, we began exploring different methods to unite the C9-C12 and C13-C20 fragments.

Scheme 3.6 Additional attempted cross-metatheses.

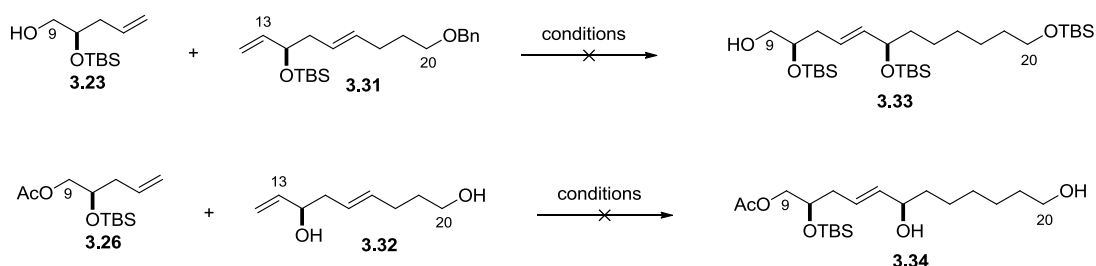


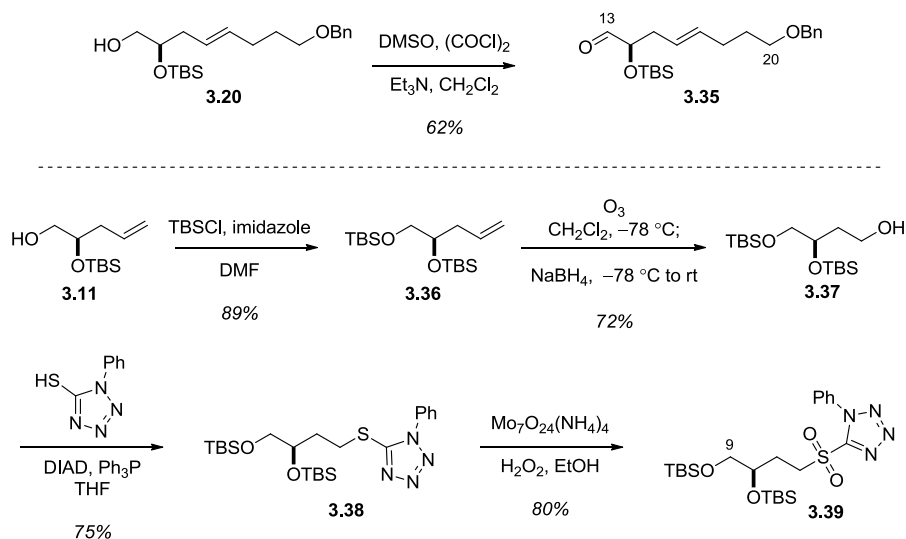
Table 3.3 Addition attempts to access the C9-C20 fragment via cross metathesis.

Entry	C9-C12 alkene (eq)	C13-C20 alkene (eq)	Catalyst/ Solvent	Temp (°C)	Time (h)	Method	Result
1	3.23 (1.0)	3.31 (1.0)	G2 CH ₂ Cl ₂	rt	24	Slow addition of 3.23 to 3.31 and G2	25% yield of 3.33 , Dimerization of 3.23
2	3.23 (1.0)	3.31 (1.0)	G2 toluene	80	3	Slow addition of 3.23 to 3.31 and G2	Dimerization of 3.23 , Recovered 3.31
3	3.23 (1.0)	3.31 (1.0)	HG2 CH ₂ Cl ₂	20	3	Slow addition of 3.23 to 3.31 and HG2	Dimerization of 3.23 , Recovered 3.31
4	3.26 (1.0)	3.32 (1.0)	G2 CH ₂ Cl ₂	20	3	Slow addition of 3.26 to 3.31 and G2	Consumption of 3.32 , Dimerization and poor recovery of 3.26
5	3.26 (1.0)	3.32 (1.0)	G2 CH ₂ Cl ₂	20	20	Combine 3.26 and 3.32 , degas, add G2	Consumption of 3.32 , Dimerization and poor recovery of 3.26
6	3.26 (1.0)	3.32 (1.0)	G2 CH ₂ Cl ₂	35	3	Combine 3.26 and 3.32 , degas, add G2	Consumption of 3.32 , Complete dimerization 3.26

(iii) Synthesis of the C9-C30 Fragment utilizing Glycolate Alkylation and Olefination

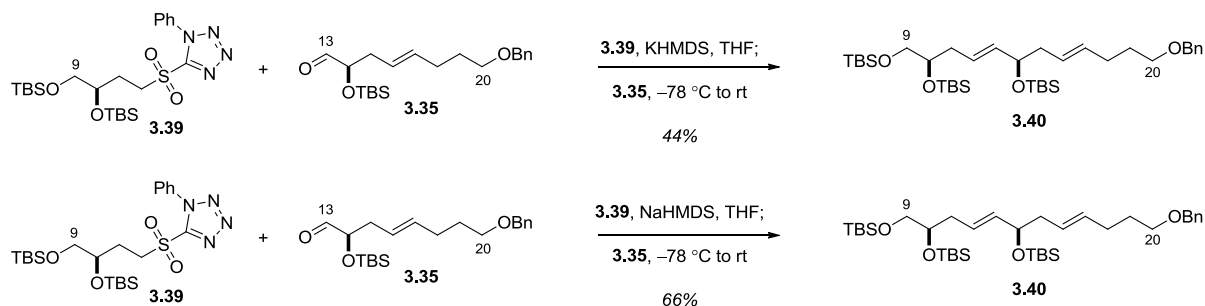
As we planned to utilize a Julia-Kocienski olefination to merge fragments **3.3** and **3.4** of the C9-C30 domain, we thought the reaction could also be useful for union of the C9-C12 and C13-C20 fragments.⁵⁹ To this end, primary alcohol **3.20** was oxidized to give aldehyde **3.35**, the desired C13-C20 coupling partner (Scheme 3.7). To access the C9-C12 fragment, primary alcohol **3.11** was protected as TBS ether **3.36**. Ozonolysis of **3.36** with a reductive

Scheme 3.7 Synthesis of coupling partners for Julia-Kocienski olefination.



quench afforded primary alcohol **3.37**. Alcohol **3.37** was treated with 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions to yield thioether **3.38**. Oxidation of thioether **3.38** granted access to sulfone **3.39**, the desired C8-C12 coupling partner. Treatment of sulfone **3.39** with KHMDS followed by addition of aldehyde **3.35** provided C9-C20 fragment **3.40** in 44% yield as an inconsequential mixture of *E:Z* isomers. The yield could be improved to 66% with use of NaHMDS as base (Scheme 3.8).

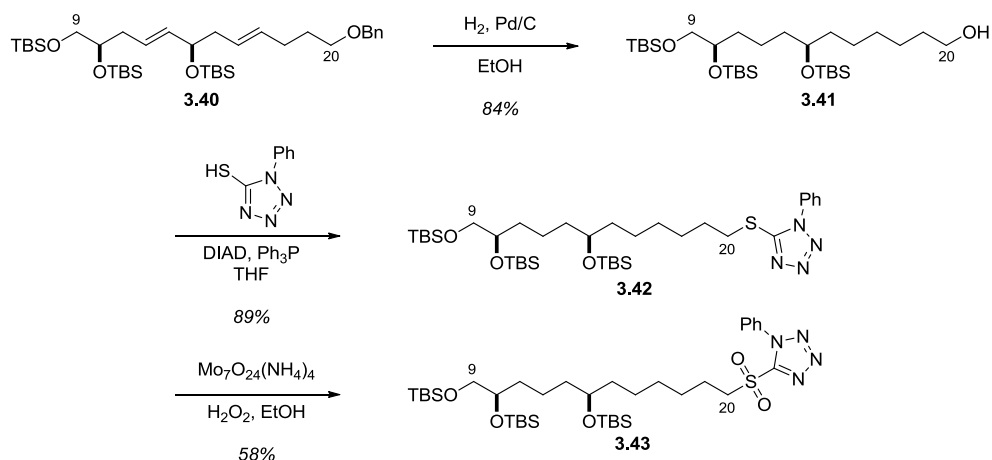
Scheme 3.8 Synthesis of the C9-C20 fragment via Julia-Kocienski olefination.



To access the desired C9-C20 fragment for coupling with the C21-C30 fragment, further manipulation was required (Scheme 3.9). Hydrogenation of **3.40** reduced both the

C12-C13 and C16-C17 olefins as well as cleaved the benzyl ether. Primary alcohol **3.41** could be obtained cleanly in 84% yield following filtration through a celite plug. Sulfone **3.43** was obtained following the previously described method (Scheme 3.7). Oxidation of thioether **3.42** to sulfone **3.43** proceeded in lower yield, presumably due to loss of the TBS protecting group of the C8 hydroxyl. With synthesis of sulfone **3.43**, we have been able to access the desired C9-C20 coupling partner of the polyol domain of amphidinol 3. Also, due to the repeated 1,5-*syn*-diols of the polyol domain of amphidinol 3, sulfone **3.39** can serve as the C1-C4 and the C5-C8 fragments of amphidinol 3.

Scheme 3.9 Elaboration of the C9-C20 fragment.

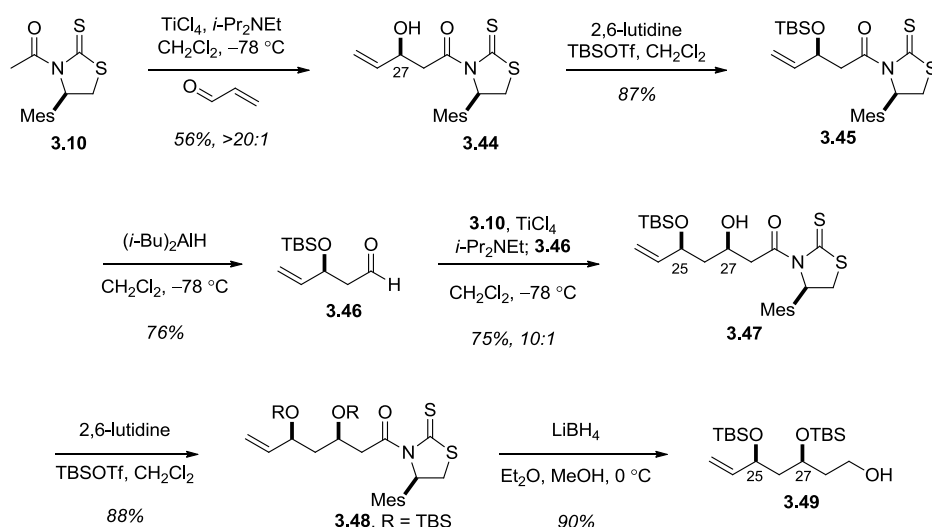


C. Synthesis of the C21-C30 Fragment

To access the C21-C30 fragment, we envisioned a route utilizing the acetate aldol and propionate aldol to introduce the majority of the requisite stereocenters. We began with an iterative acetate aldol sequence to introduce the C25 and C27 stereocenters.⁶³ Known acetate **3.10** was treated with titanium (IV) chloride, di-*iso*-propylethylamine (DIEA), and acrolein, providing aldol adduct **3.44** in 56% yield as a single diastereomer (Scheme 3.10). Protection of the secondary alcohol as the TBS ether **3.45** and reductive cleavage of the

chiral auxiliary to provide aldehyde **3.46** yielded the aldehyde to be used in the second acetate aldol reaction. Subjecting aldehyde **3.46** to the same titanium enolate derived from **3.10** provided aldol adduct **3.47** in good yield and high selectivity (10:1). Protection of the secondary alcohol as the TBS ether gave **3.48**. Reductive cleavage of the chiral auxiliary using sodium borohydride resulted in moderate yields (~60%); however treatment with lithium borohydride yielded the desired primary alcohol **3.49** in high yield.

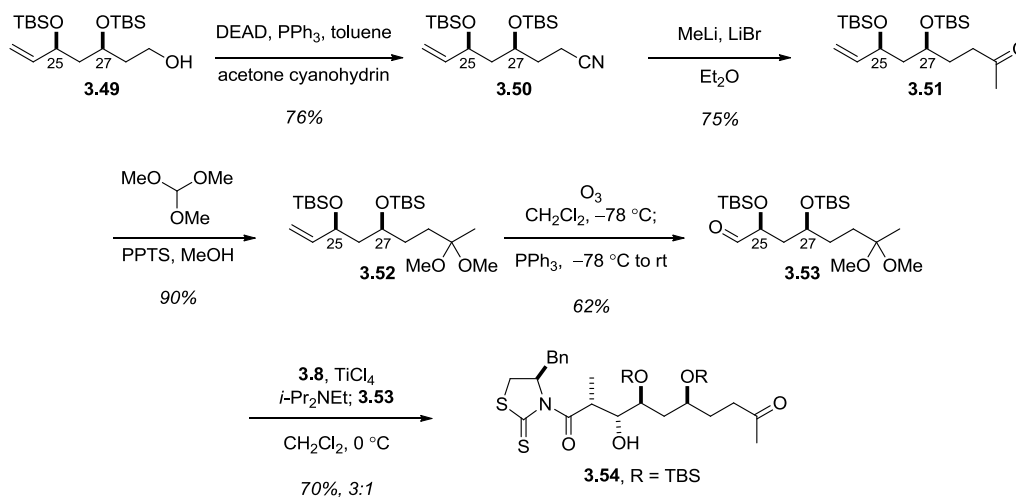
Scheme 3.10 Iterative acetate aldol sequence to access the C21-C29 fragment.



Having completed the iterative aldol sequence, the next task was introduction of C30 by one-carbon homologation followed by oxidative cleavage of the olefin to unmask an aldehyde for the propionate aldol. Primary alcohol **3.49** was converted to nitrile **3.50** in 76% yield utilizing Mitsunobu conditions (Scheme 3.11).⁶⁸ Addition of methyllithium to nitrile **3.50** proved problematic, with low yields and decomposition. Use of lithium bromide in the reaction improved the yield to 75%, furnishing methyl ketone **3.51**.⁶⁹ Protection of methyl ketone **3.51** as the dimethyl ketal **3.52** and oxidative cleavage of the olefin afforded desired aldehyde **3.53**. The propionate aldol reaction between **3.8** and aldehyde **3.53** was envisioned to introduce the C23 and C24 stereocenters in high diastereoselectivity.⁶²

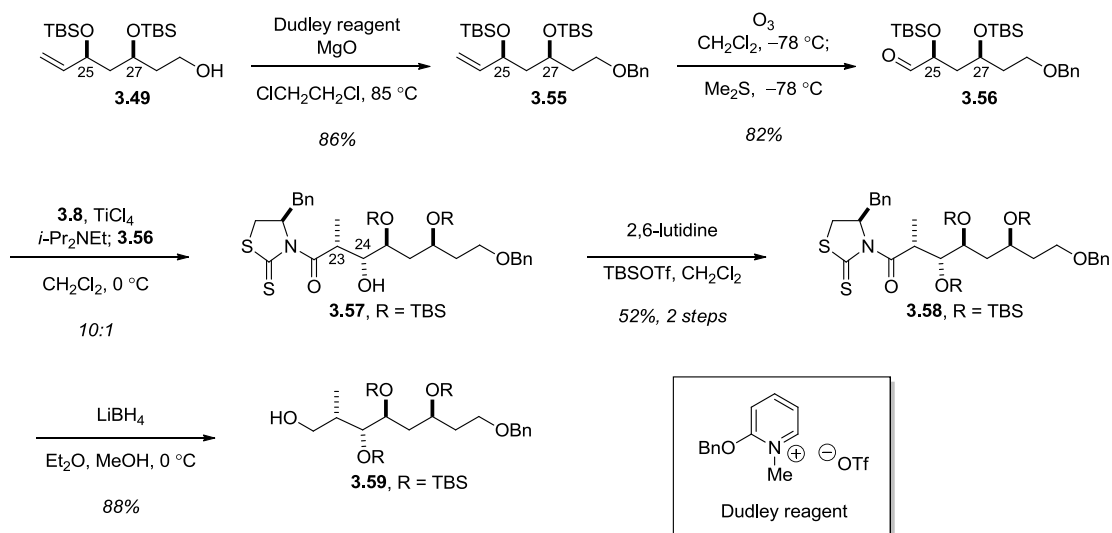
Unfortunately, under standard propionate aldol conditions the ketone was unmasked and poor diastereoselectivity was obtained. We tested use of excess **3.8** and di-*iso*-propylethylamine in the reaction and found that the methyl ketone was still unmasked, providing **3.54** instead of the desired aldol adduct.⁷⁰ Although the reaction seemed to proceed in moderate yield, the diastereoselectivity was low (3:1).

Scheme 3.11 One carbon homologation and propionate aldol.



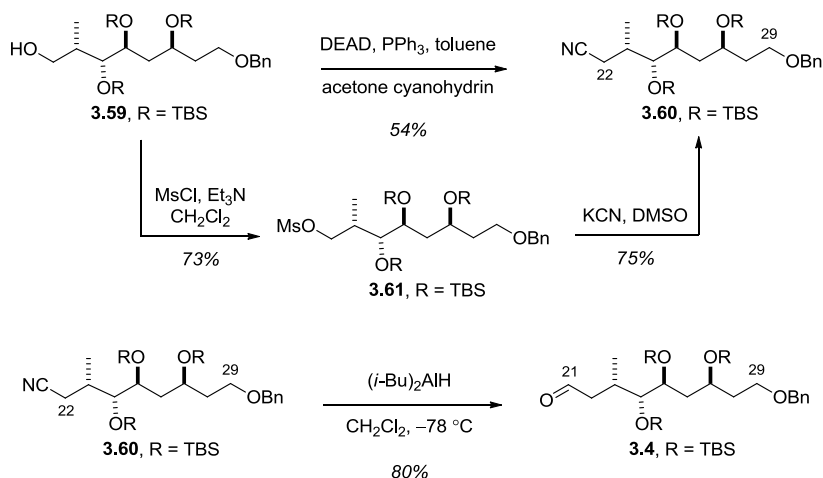
Facing complications caused by early homologation to introduce C30, we changed the order of steps to perform the propionate aldol and access aldehyde **3.4** for coupling with the C9-C20 fragment before introduction of C30 to eliminate the problems with the dimethyl ketal. Straightforward protection of primary alcohol **3.49** with sodium hydride and benzyl bromide yielded benzyl ether **3.55** in only 36% yield. The addition of tetrabutylammonium iodide (TBAI) to speed up the desired reaction did little to improve the yield. It is believed that migration of the C27 TBS ether to the C29 hydroxyl group prevented productive formation of **3.55**. To avoid this, neutral conditions for benzyl protection were attempted. Use of the Dudley reagent provided the desired benzyl ether **3.55** in good yield (Scheme 3.12).⁷¹ Oxidative cleavage of olefin **3.55** afforded aldehyde **3.56**. Standard conditions for

the propionate aldol provided aldol adduct **3.57**. Proton NMR of the crude reaction mixture indicated a 10:1 ratio of diastereomers. Alcohol **3.57** could not be separated from propionate **3.8**, so the mixture was subjected to 2,6-lutidine and TBSOTf after which **3.58** could be obtained in 60% yield over 2 steps. Reductive removal of the chiral auxiliary gave primary alcohol **3.59**.



Direct conversion of alcohol **3.59** to nitrile **3.60** under Mitsunobu conditions proceeded in 54% yield, however was not reproducible on repeated attempts. A two-step sequence for conversion of alcohol **3.59** to nitrile **3.60** via mesylate **3.61** provided access to the one carbon homologated product. Aldehyde **3.4** was accessed following treatment of nitrile **3.60** with DIBAL and potassium sodium tartrate. Aldehyde **3.4**, represents the C21-C29 coupling partner with functional group handles for further manipulation, including olefination with the C9-C20 fragment and homologation to introduce C30.

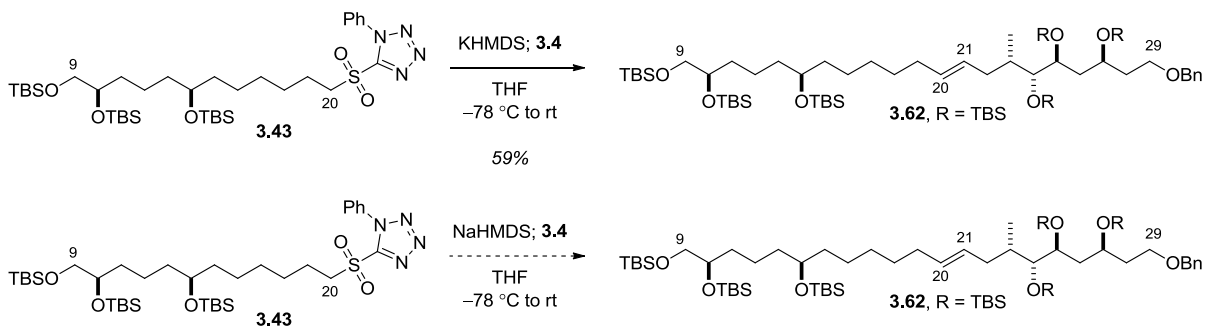
Scheme 3.13 Synthesis of aldehyde 3.4.



D. Union of the C9-C20 and C21-C29 Fragments and Planned Completion of 3.1

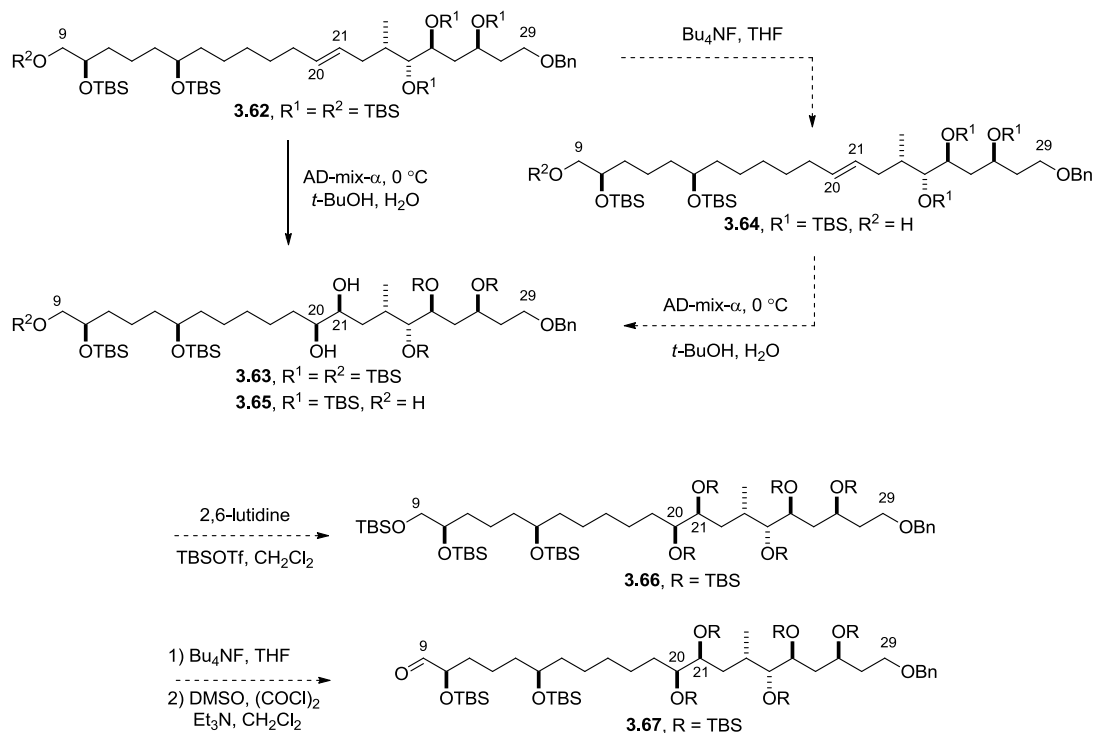
With C9-C20 fragment **3.43** and C21-C29 fragment **3.4** in hand, we were poised to test Julia-Kocienski olefination conditions for their coupling. Deprotonation of **3.43** with KHMDS and subsequent addition of aldehyde **3.4** at -78 °C followed by warming to room temperature afforded the desired olefin **3.62** in 43% yield (Scheme 3.14). Proton NMR of **3.62** indicates the reaction proceeded with high *E* selectivity (>20:1). The yield was further increased to 59% by addition of KHMDS to a premixed solution of sulfone **3.43** and aldehyde **3.4**. It has been shown that while KHMDS leads to higher *E* selectivity, NaHMDS proceeds with comparable selectivity and higher yields.⁵⁹ It may be possible to further optimize the reaction utilizing NaHMDS as base to afford desired olefin **3.62** in higher yield, and will be explored.

Scheme 3.14 Union of the C9-C20 and C21-C29 fragments.



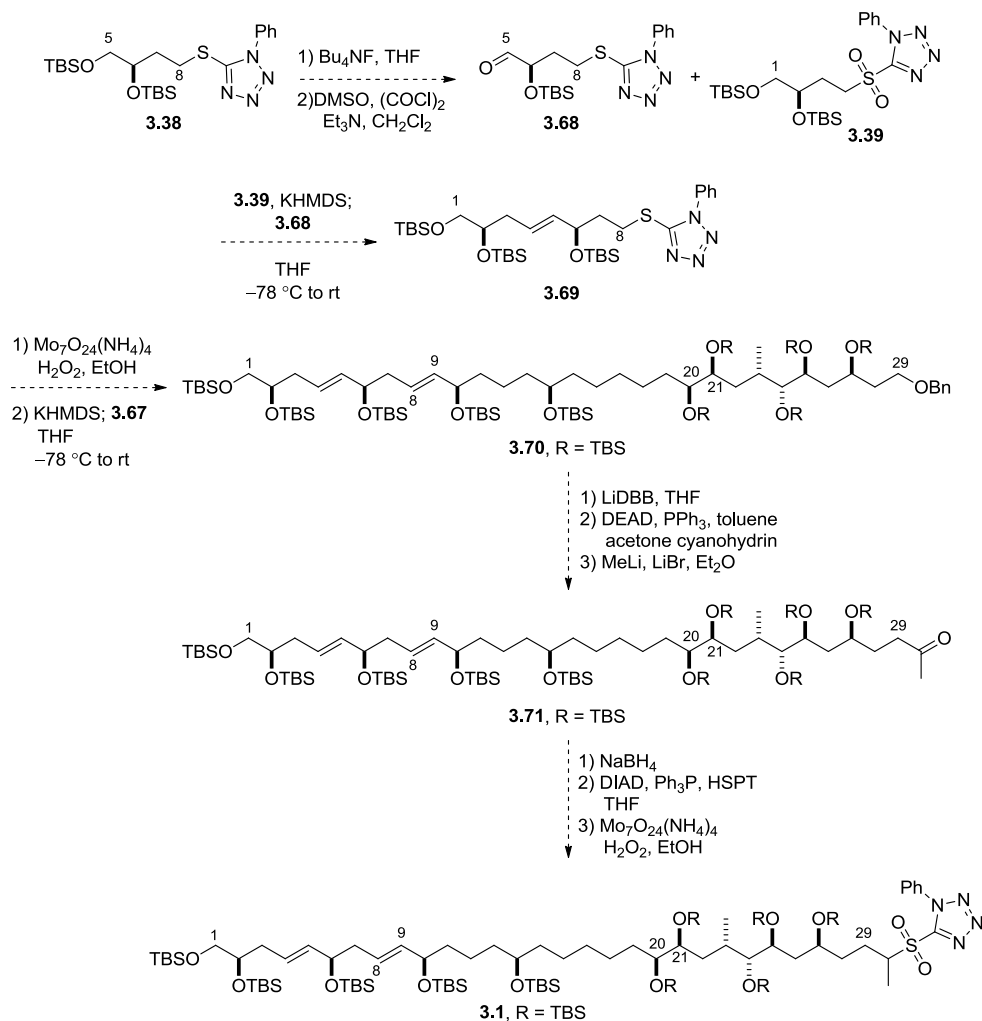
Further elaboration of the C9-C29 fragment **3.62** will include a Sharpless asymmetric dihydroxylation to introduce the C20 and C21 stereocenters (Scheme 3.15).⁶⁰ Initial attempts at dihydroxylation of **3.62** have yet to provide the desired diol. Treatment of olefin **3.62** with AD-mix- α at $0\text{ }^{\circ}\text{C}$ and at room temperature for prolonged times has resulted only in recovery of starting material. Addition of the individual reagents for asymmetric dihydroxylation instead of use of the pre-combined AD-mix- α may provide the desired diol **3.63** and will be investigated. It is also a possibility that the hydrophobic nature of **3.62** significantly decreases its solubility in the reaction media of *t*-butanol and water. A possible solution to this challenge may be the use of different solvent systems, even though the selectivity of the reaction has been reported to decrease upon varying solvent. A solution that should not interfere with the selectivity of the reaction could lie in cleavage of the primary TBS ether to reveal **3.64** with the C9 hydroxyl unmasked. The free alcohol should increase the solubility of **3.64** in *t*-butanol and water and allow access to triol **3.65**. Once conditions for dihydroxylation are found, protection of the C20 and C21 hydroxyl groups as TBS ethers will provide **3.66**. Selective cleavage of the C9 TBS ether with TBAF and oxidation of the primary alcohol will grant access to aldehyde **3.67**. Aldehyde **3.67** can then be coupled with the C1-C8 fragment of the polyol domain.

Scheme 3.15 Planned elaboration of the C9-C29 fragment.



In light of the previously described challenges with the use of cross-metathesis for the synthesis of the C9-C20 domain, the C1-C9 fragment will be synthesized utilizing the Julia-Kocienski olefination. Conversion of thioether **3.38** to aldehyde **3.68** is planned via selective cleavage of the primary TBS ether and oxidation under Swern conditions (Scheme 3.16). It is anticipated that a Julia-Kocienski olefination between sulfone **3.39** and aldehyde **3.68** would deliver the desired C1-C8 fragment with good selectivity for the *E* olefin. Oxidation of thioether **3.69** and another Julia-Kocienski olefination, this time with the C9-C29 aldehyde fragment **3.67**, is envisioned to unite the C1-C8 and C9-C29 fragments by formation of the C8-C9 olefin with good *E* selectivity. Reductive debenzoylation of **3.70** using

Scheme 3.16 Planned synthesis of the C1-C30 polyol domain.

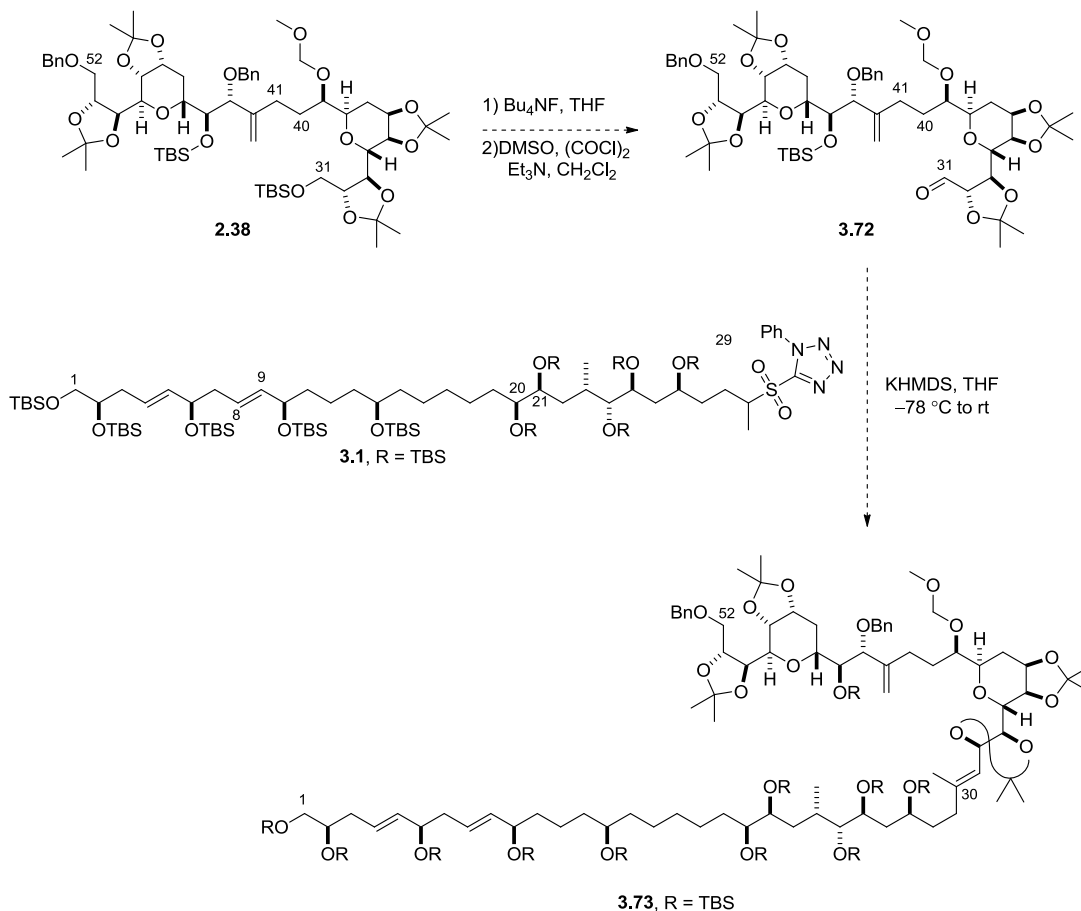


lithium di-*t*-butylbiphenylide and one carbon homologation to introduce C30 following previously utilized conditions will afford methyl ketone **3.71**. Reduction of ketone **3.71** to afford a secondary alcohol and conversion to the requisite sulfone for Julia-Kocienski olefination would provide the desired C1-C30 coupling partner **3.1**.

E. Planned Completion of the C1-C52 domain of amphidinol 3

Upon completion of the C1-C30 fragment **3.1** of amphidinol 3, coupling with the C31-C52 bis-THP core will be undertaken. Selective cleavage of the primary TBS ether of **2.38** followed by oxidation will provide aldehyde **3.72** (Scheme 3.17). It is believed union of the

Scheme 3.17 Planned synthesis of the C1-C52 domain of amphidinol 3.



C1-C30 fragment **3.1** and the C31-C52 fragment **3.72** can be achieved utilizing Julia-Kocienski olefination to introduce the required C30-C31 olefin. Initially, KHMDS will be utilized as base due to the reported high *E* selectivity that can be obtained with its use. If the key coupling proves low yielding, NaHMDS may also be explored as a base for the reaction.

Successful union of **3.1** and **3.72** would represent synthesis of the C1-C52 domain of amphidinol 3, as well as introduction of all 25 stereocenters of the natural product.

F. Summary

In conclusion, we have developed a convergent synthesis to access the C9-C29 fragment of the polyol domain of amphidinol 3. Alkene **3.62** was obtained from Julia-Kocienski olefination of C9-C20 fragment **3.43** and C21-C29 fragment **3.4**. While optimization of the olefination remains, this poses a viable route to access the C9-C29 fragment **3.62**. Further elaboration of alkene **3.62** to aldehyde **3.67** and subsequent coupling with the C1-C8 fragment offers a pathway to access the assembled polyol domain **3.1** of amphidinol 3. Sulfone **3.43** was accessed in convergent fashion, utilizing the glycolate alkylation reaction and subsequent olefination with **3.39**. Exploiting the repeating units of the C1-C17 domain of the polyol, stereocenters C2, C6, C10, and C14 have all been introduced via the asymmetric glycolate alkylation reaction developed in the Crimmins laboratory. Aldehyde **3.4** was obtained from acrolein utilizing an iterative acetate aldol sequence followed by a propionate aldol. Applying this sequence, the C23, C24, C25, and C27 stereocenters were all introduced utilizing aldol chemistry developed in the Crimmins laboratory.

G. References

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Chapter 4

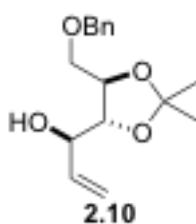
Experimental Information and NMR Spectra for Chapters 2 and 3

A. Methods and Materials

Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Nuclear magnetic resonance (^1H , ^{13}C , COSY, NOESY) spectra were recorded on Bruker model Avance 400 (^1H at 400 MHz; ^{13}C at 100 MHz) and Bruker model Avance 500 (^1H at 500 MHz; ^{13}C at 125 MHz) instruments. Chemical shifts are reported relative to chloroform (δ 7.26 for ^1H NMR spectra and δ 77.0 for ^{13}C spectra). ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Optical rotations were determined using a Jasco P1010 polarimeter. Mass spectra were obtained using a Bruker BioTOF II mass spectrometer with electrospray ionization (ESI). Thin layer chromatography (TLC) was conducted on silica gel F254 TLC plates purchased from EMD Chemicals Inc. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating unless otherwise noted. Flash column chromatography was carried out using Ultra Pure Silica Gel Silia-P (40 to 63 μm) purchased from SiliCycle Inc. Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were dried by passage through a column of neutral alumina under argon immediately prior to use. All alkylamines were distilled from calcium hydride immediately prior to use. Dess-Martin periodinane was prepared according to literature procedures and stored at $-20\text{ }^\circ\text{C}$. All other

reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were performed in flasks flame dried under positive flow of argon and conducted under an argon atmosphere. Yield refers to isolated yield of analytically pure material unless otherwise noted.

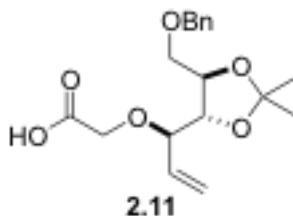
B. Procedures



Allylic Alcohol 2.10: Preparation of the vinylzinc reagent: A dry 1 L three-neck round-bottomed flask equipped with a pressure equalizing addition funnel (150 mL), cold-finger condenser, and septum, was charged with magnesium (9.87 g, 406 mmol, flame dried), iodine (spatula tip, catalytic), and THF (120 mL). The mixture was stirred at room temperature as a solution of vinyl bromide (29 mL, 411 mmol) in THF (50 mL) was added dropwise. An initial induction phase was followed by a violent reflux after approx. 5 mL of solution was added. The remaining vinyl bromide solution was added dropwise over 80 min maintaining a light reflux. Upon completion of the addition, the solution was diluted further with THF (100 mL). To the light brown solution was added a solution of zinc chloride (30.0 g, 220 mmol; fused under high vacuum, then dissolved in THF (150 mL) with sonication for 2 hours) portion wise via cannula (the addition is exothermic), affording a black solution.

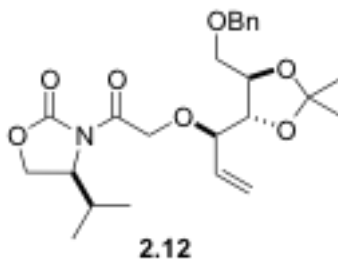
To a stirred solution of known aldehyde **2.9** (20.7g, 82 mmol) in toluene (1.6 L) at -78 °C was added the solution of divinyl zinc via cannula. The reaction mixture was stirred at -78 °C and allowed to warm to rt over 12 h. The reaction mixture was then quenched with

water (500 mL), and the resultant inorganic salts were removed by filtration with a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x 500 mL). The combined organic layers were washed with brine (400 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to yield allylic alcohol **2.10** (19.1g, 68.6 mmol, 80% yield, 9:1 mixture of diastereomers) as a viscous yellow oil: R_f = 0.43 (silica gel, 70:30 hexanes:EtOAc); IR (film) ν 3458, 3087, 3064, 3030, 2986, 2868, 1454, 1371, 1250, 1214, 1166, 1132, 1084, 996, 925, 738, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.30 (m, 5H), 5.86 (m, 1H), 5.39 (d, J = 17.2 Hz, 1 H), 5.22 (d, J = 10.4 Hz, 1H), 4.60 (d, J = 4 Hz, 2H), 4.26 (dd, J = 5.2, 5.2 Hz, 1 H), 4.16-4.12 (m, 1H), 3.84 (dd, J = 5.6 Hz, 5.2 Hz, 1H), 3.62 (dd, J = 4.4, 4.4 Hz, 2H), 2.72 (s, 1H), 1.44 (s, 3H), 1.43 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 137.6, 136.0, 128.42, 127.8, 116.7, 109.3, 80.9, 73.6, 72.3, 70.7, 26.9 ppm; ESI-MS $\text{C}_{16}\text{H}_{22}\text{O}_4$ $[\text{M}+\text{H}^+]$ calc. 278.16, found 278.20.



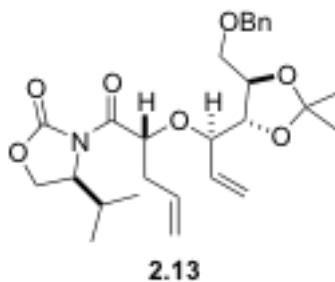
Acid 2.11: A 250 mL round bottom flask was charged with sodium hydride (60% on mineral oil, 8.23g, 206 mmol) and washed with pentanes to remove the mineral oil. The sodium hydride was then dried under a stream of argon for 10 minutes, dissolved in THF (45 mL) and DMF (21 mL), and cooled to 0 °C. Bromoacetic acid (10.5g, 75.5 mmol) in THF (15 mL) was added dropwise via an addition funnel over 10 min with evolution of hydrogen gas. Allylic alcohol **2.10** (19.1g, 68.6 mmol) was added dropwise in THF (23 mL) and the reaction mixture was warmed to rt and stirred overnight. The cloudy reaction mixture was quenched slowly with of 10% aqueous HCl at 0 °C until a clear biphasic mixture appeared (~50 mL).

The organic layer was separated and the aqueous layer was extracted with EtOAc (3x 400 mL). The combined organic layers were washed with brine (400 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 70:30 hexanes:EtOAc) to yield glycolic acid **2.11** (21.4g, 63.6 mmol, 93% yield) as an orange oil: $R_f = 0.25$ (70:30 hexanes:EtOAc); $[\alpha]_D^{20.3} - 4.4^\circ$ ($c = 2.70$, CH₂Cl₂); IR (film) ν 3169 (broad), 3082, 3065, 3031, 2987, 2934, 2914, 2875, 2658, 2573, 1958, 1880, 1759, 1734, 1454, 1426, 1372, 1250, 1215, 1168, 1115, 1027, 990, 935, 856, 740, 699 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 11.25 (s, 1H), 7.3 (m, 5H), 5.67 (ddd, $J = 7.2, 10.4, 17.2$ Hz, 1H), 5.31 (d, $J = 10.4, 17.2$ Hz, 2H), 4.35 (s, 2H), 4.17 (m, 2H), 3.92 (m, 3H), 3.61 (dd, $J = 4.0, 10.4$ Hz, 1H), 3.55 (dd, $J = 4.0, 10.4$ Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 173.9, 137.7, 132.9, 128.3, 127.7, 127.6, 120.8, 109.8, 82.0, 79.0, 77.4, 73.4, 70.5, 65.5, 26.9, 26.6, 20.7 ppm; ESI-MS C₁₈H₂₄O₆ [M+H]⁺ calc. 337.16, found 337.20.



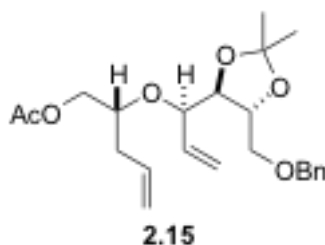
N-glycolyl oxazolidinone 2.12. To a 2 L three-neck round bottom flask, equipped with a mechanical stirrer, was added glycolic acid **2.11** (21.39g, 63.6 mmol), THF (600 mL), and triethylamine (10.6 mL, 76.3 mmol). The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and trimethylacetyl chloride (9.0 mL, 73.1 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 1 h, after which time the solution was again cooled to $-78\text{ }^{\circ}\text{C}$. Concomitantly, a 1 L round bottom flask was charged with (S)-4-isopropylloxazolidin-2-one (10.6 g, 70.0 mmol), and THF (650 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. A 2.5M solution *n*-butyl lithium (70.0 mmol, 33 mL) was added dropwise, forming a thick slurry. The mixture was

stirred vigorously at $-78\text{ }^{\circ}\text{C}$ for 1 h, and then transferred via cannula to the flask containing the mixed anhydride, formed *in situ*, at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 3 h, slowly warming to rt, and then quenched with H_2O (400 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x 400 mL). The combined organic layers were washed with brine (400 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 70:30 hexanes:EtOAc) to afford desired *N*-glycolyl oxazolidinone **2.12** (20.9 g, 46.7 mmol, 73% yield, single diastereomer) as a yellow oil: $R_f = 0.40$ (70:30 hexanes:EtOAc); $[\alpha]_D^{23.3} + 36.8^{\circ}$ ($c = 2.8$, CH_2Cl_2); IR (film) ν 3087, 3065, 3031, 2983, 2965, 2931, 2875, 1781, 1715, 1487, 1456, 1389, 1369, 1305, 1259, 1211, 1167, 1121, 1054, 1017, 993, 967, 859, 777, 742, 699 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.20 (m, 5H), 5.81 (ddd, $J = 7.6, 10.4, 14\text{ Hz}$, 1H), 5.39 (dd, $J = 1.2, 10.4\text{ Hz}$, 1H), 5.36 (dd, $J = 1.2, 14\text{ Hz}$, 1H), 4.68 (ab, $J = 28\text{ Hz}$, 2H), 4.62 (s, 2 H), 4.39-4.43 (m, 1 H), 4.32 (m, 2H), 4.27 (dd, $J = 3.2, 7.2\text{ Hz}$, 1H), 3.94-4.0 (m, 2H), 3.75 (dd, $J = 3.2, 10.4\text{ Hz}$, 1 H), 3.65 (dd, $J = 6.0, 10.4\text{ Hz}$, 1H), 2.34-2.44 (m, 1H), 1.43 (s, 3 H), 1.42 (s, 3H), 0.92 (d, $J = 7.2\text{ Hz}$, 3H), 0.87 (d, $J = 6.8\text{ Hz}$, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.9, 153.9, 138.2, 134.0, 128.2, 127.6, 127.5, 127.4, 120.9, 109.7, 82.3, 79.0, 78.3, 73.3, 71.0, 67.6, 64.3, 58.1, 28.2, 27.0, 26.8, 17.8, 14.5 ppm; ESI-MS $\text{C}_{24}\text{H}_{33}\text{NO}_7$ $[\text{M}+\text{H}^+]$ calc. 448.23, found 448.20.



Alkylated N-glycolyl oxazolidinone 2.13. A flame-dried 1 L three-neck flask, equipped

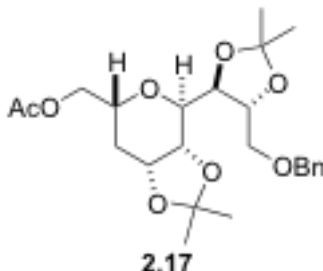
with an addition funnel and internal thermometer was charged with 0.762 M sodium hexamethyldisilazide (80 mL, 60.7 mmol) and 240 mL THF. The solution was cooled to -78°C and *N*-glycolyl oxazolidinone **2.12** (20.9g, 46.7 mmol) in THF (200 mL) was added dropwise via addition funnel. Maintaining an internal temperature below -70°C during the addition was crucial to avoid decomposition. After addition, the bright yellow solution was stirred at -78°C for 1 h, after which time allyl iodide (55% in pentanes, 38 mL, 234 mmol) was added dropwise. The solution was stirred for 2 h and allowed to warm slowly to -65°C . Saturated ammonium chloride (200 mL) was added and the biphasic mixture was warmed to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x 400 mL). The combined organic layers were washed with brine (400 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to afford desired alkylated *N*-glycolyl oxazolidinone **2.13** (14.1 g, 28.9 mmol, 62% yield, >20:1 ratio of diastereomers) as a bright yellow oil: $R_f = 0.42$ (60:40 hexanes:EtOAc); $[\alpha]_D^{21.9} + 62.6^{\circ}$ ($c = 1.9$, CH_2Cl_2); IR (neat) ν 3079, 3031, 2982, 2966, 1936, 285, 1779, 1713, 1388, 1374, 1301, 1245, 1207, 1171, 1097, 1058, 1019, 992, 926, 853, 738, 699 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.30 (m, 5 H), 5.84 (m, 1H), 5.75 (ddd, $J = 8.0, 10.0, 17.6$ Hz, 1H), 5.27 (m, 3H), 5.11 (d, $J = 8.0$ Hz, 1H), 5.09 (d, $J = 10.0$ Hz, 1H), 4.60 (ab, $J = 13.2$ Hz, 2H), 4.43 (ddd, $J = 3.6, 7.6, 11.6$ Hz, 1H), 4.24 (ab, $J = 12$ Hz, 2H), 4.21 (m, 1H), 3.87 (m, 2H), 3.74 (dd, $J = 3.2, 10.4$ Hz, 1H), 3.57 (dd, $J = 6.4, 10.4$ Hz, 1H), 2.52 (ddd, $J = 5.2, 6.4, 14.4$ Hz, 1H), 2.41 (ddd, $J = 6.8, 7.2, 14.0$ Hz, 1H), 2.27 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.7, 153.6, 138.1, 135.7, 132.7, 128.3, 127.7, 127.5, 119.8, 118.4, 109.8, 83.8, 78.62, 78.60, 75.8, 73.4, 71.3, 64.0, 58.2, 37.6, 28.4, 27.0, 26.9, 17.8, 14.8 ppm; ESI-MS $\text{C}_{27}\text{H}_{37}\text{NO}_7$ $[\text{M}+\text{Na}^+]$ calc. 510.24, found 510.20, $[\text{M}+\text{NH}_4^+]$ calc. 505.29, found 505.30, $[\text{M}+\text{H}^+]$ calc. 488.59, found 488.20.



Diene 2.15. Sodium borohydride (2.5 g, 64.1 mmol) in water (50 mL) was added dropwise to a solution of alkylated glycolate **2.13** (10.4 g, 21.4 mmol) in THF (200 mL) at 0 °C. The reaction mixture was stirred vigorously for 5 h and then carefully quenched with 10% aqueous HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x 300 mL). The combined organic layers were washed with brine (400 mL), dried (Na₂SO₄), and concentrated. It was found the alcohol could be carried on without further purification.

To the crude primary alcohol in CH₂Cl₂ (150 mL) was added pyridine (9.7 mL, 120 mmol), a catalytic amount of DMAP, and acetic anhydride (6.9 mL, 73.0 mmol). The reaction mixture was stirred 2 h at rt and quenched with 10% aqueous HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x 200 mL). The combined organic layers were washed with brine (400 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to afford desired acetate **2.15** (6.25 g, 15.5 mmol, 72% yield) as a clear oil: $R_f = 0.61$ (60:40 hexanes:EtOAc); $[\alpha]_D^{20.6} - 3.6^\circ$ (c = 1.4, CH₂Cl₂); IR (film) ν 3074, 3031, 2985, 2934, 2910, 2866, 1742, 1642, 1495, 1454, 1370, 1237, 1171, 1088, 1045, 995, 925, 857, 738, 698, 604 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.5 (m, 5 H), 5.74 (m, 2 H), 5.30 (m, 2 H), 5.07 (m, 2 H), 4.60 (ab, 2 H), 4.6 (m, 1 H), 4.05 (m, 1 H), 3.94 (m, 2 H), 3.80 (dd, $J = 2.2, 7.8$ Hz, 1 H), 3.67 (m, 2 H), 3.55 (dd, $J = 7.8, 14.2$ Hz, 1 H), 2.27 (m, 2 H), 2.04 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 170.8, 138.1, 135.5, 133.4, 128.3, 127.7,

127.6, 119.3, 118.1, 109.7, 80.6, 79.1, 78.3, 74.3, 73.4, 71.2, 65.8, 35.6, 27.1, 26.9, 20.9 ppm; ESI-MS $C_{23}H_{32}O_6$ $[M+Na^+]$ calc. 427.21, found 427.30, $[M+H^+]$ calc. 405.23, found 405.30.

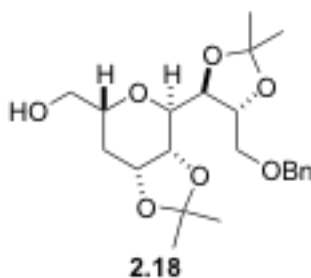


Tetrahydropyran 2.17. In a dry 1 L flask, acetate **2.15** (6.9 g, 17.0 mmol) was dissolved in CH_2Cl_2 (600 mL) and the solution was degassed for 1 h under an argon atmosphere. Grubbs 1st generation catalyst (0.29 g, 0.35 mmol) was added and the reaction mixture was refluxed for 4 h. Upon consumption of starting material, the reaction was opened to air and the catalyst was quenched. The crude mixture was concentrated under vacuum, and used without purification for the next step.

The crude ring-closed product and ruthenium catalyst were dissolved in acetonitrile (300 mL) and EtOAc (300 mL) and cooled to 0 °C. Ytterbium chloride hexahydrate (0.90 g, 2.32 mmol) was added, followed by sodium periodate (5.47 g, 25.6 mmol) in water (100 mL). The biphasic mixture was stirred vigorously for 2 h and then quenched with a saturated solution of sodium bisulfite (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x 300 mL). The combined organic layers were washed with brine (400 mL), dried (Na_2SO_4), and concentrated.

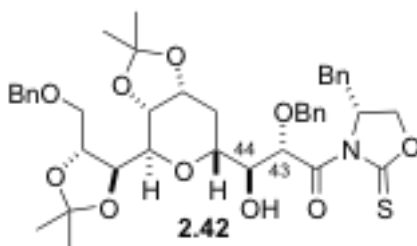
The crude diol was then dissolved in CH_2Cl_2 (20 mL) and 2,2-dimethoxypropane (10 mL). A catalytic amount of *p*-toluenesulfonic acid was added and the reaction mixture was stirred for 2 h at rt. The reaction was partitioned between EtOAc (200 mL) and cold 10% aqueous sodium hydroxide (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with

brine (100 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to afford desired tetrahydropyran **2.17** (5.6 g, 12.4 mmol, 73% yield, 5:1 ratio of diastereomers, 4.5 g, 10.0 mmol, 59% desired diastereomer) as a clear oil: $R_f = 0.31$ (80:20 hexanes:EtOAc); $[\alpha]_D^{25.7} +0.7^\circ$ ($c = 4.3$, CH_2Cl_2); IR (film) ν 3088, 3094, 3031, 2985, 2935, 2878, 1742 (strong) 1496, 1455, 1370, 1240, 1166, 1140, 1053, 861 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.29 (m, 5H), 4.54 (s, 2H), 4.32 (dd, $J = 6.0, 5.6$ Hz, 1H), 4.23 (dd, $J = 7.6, 11.6$ Hz, 1H), 4.18 (m, 1H), 4.12 (dd, $J = 5.6, 5.6$ Hz, 1H), 3.98 (dd, $J = 4.8, 8.0$ Hz, 1H), 3.90 (d, $J = 3.6$ Hz, 1H), 3.85 (dd, $J = 5.2, 10.4$ Hz, 2H), 3.66 (dd, $J = 3.6, 10.8$ Hz, 1H), 3.58 (dd, $J = 5.6, 10.8$ Hz, 1H), 1.98 (s, 3H), 1.91 (ddd, $J = 4.8, 4.8, 18.4$ Hz, 1H), 1.56 (ddd, $J = 8.8, 8.8, 13.6$ Hz, 1H), 1.40 (s, 3H), 1.34 (s, 6H), 1.27 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.6, 138.0, 128.3, 127.5, 122.1, 109.8, 108.7, 79.0, 76.7, 73.4, 71.8, 71.2, 70.9, 70.4, 68.7, 64.9, 28.8, 27.9, 27.1, 26.8, 25.7, 20.7 ppm; ESI-MS $\text{C}_{24}\text{H}_{34}\text{O}_8$ $[\text{M}+\text{Na}^+]$ calc. 473.22, found 473.30, $[\text{M}+\text{H}^+]$ calc. 451.23, found 451.30.



Primary Alcohol 2.18: To tetrahydropyran **2.17** (4.50 g, 9.99 mmol) in methanol (100 mL) was added a catalytic amount of potassium carbonate. The reaction mixture was stirred at rt for 1 h and then quenched with saturated ammonium chloride (50 mL). The mixture was partitioned between EtOAc (100 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (3x 200 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography

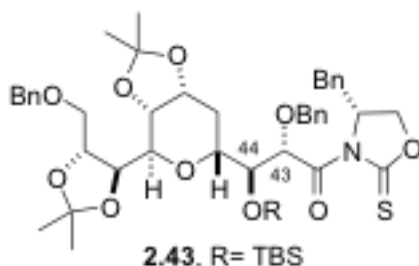
(silica gel, 60:40 hexanes:EtOAc) to afford desired alcohol **2.18** (3.92 g, 9.59 mmol, 87% yield) as a clear oil: $R_f = 0.15$ (60:40 hexanes:EtOAc); $[\alpha]_D^{23.5} +3.76^\circ$ ($c = 3.3$, CH_2Cl_2); IR (film) ν 3474, 3088, 3063, 3030, 2985, 2934, 2875, 1636, 1496, 1455, 1371, 1245, 1216, 1166, 1133, 1061, 863, 736 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.31 (m, 5H), 4.57, (s, 2H), 4.31 (m, 1H), 4.23 (m, 2H), 4.08 (dd, $J = 3.6, 8.4$ Hz, 1H), 3.90 (dd, $J = 3.6, 5.2$ Hz, 1H), 3.78 (m, 1H), 3.61 (m, 3H), 3.49 (m, 1H), 2.10 (dd, $J = 4.4, 7.6$ Hz, 1H), 1.88 (m, 1H), 1.62 (m, 1H), 1.43 (s, 3H), 1.40 (s, 6H), 1.31 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) 137.9, 128.4, 127.7, 109.8, 108.6, 79.3, 76.8, 73.5, 72.5, 71.4, 71.2, 71.1, 70.6, 64.7, 29.0, 27.9, 27.1, 26.9, 25.7 δ ppm; ESI-MS $\text{C}_{22}\text{H}_{32}\text{O}_7$ $[\text{M}+\text{Na}^+]$ calc. 431.24, found 431.30, $[\text{M}+\text{H}^+]$ calc. 409.22, found 409.3.



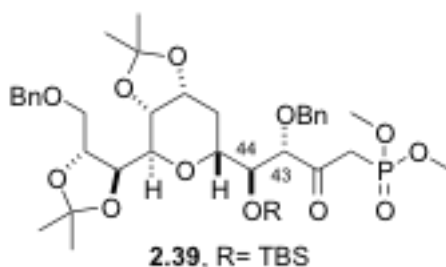
Anti aldol adduct 2.42: Aldehyde **2.4**: Oxalyl chloride (98%, 0.59 mL, 6.85 mmol) was dissolved in CH_2Cl_2 (70 mL) and cooled to -78°C . Dimethylsulfoxide (0.92 mL, 13.02 mmol) in CH_2Cl_2 (11 mL) was added dropwise via addition funnel, and the reaction mixture was stirred for 15 min at -78°C . The primary alcohol (1.4 g, 3.43 mmol) in CH_2Cl_2 (30 mL) was added dropwise via addition funnel and the reaction mixture was stirred for an additional 30 min at -78°C . Triethyl amine (3.72 mL, 26.75 mmol) was added dropwise via addition funnel and the reaction mixture was stirred for 10 min at -78°C before slow warming to rt over 1 h. The reaction mixture was quenched with 10 % aqueous HCl (20 mL), the organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with sodium bicarbonate (saturated aqueous, 50

mL), brine (100 mL), dried (Na_2SO_4), and concentrated. Filtration through a silica plug (70:30 hexanes:EtOAc) afforded desired aldehyde **2.4** (1.29 g, 3.17 mmol, 93% yield) as a clear oil, which was used directly for the *anti* aldol reaction.

Titanium tetrachloride (0.19 mL, 1.73 mmol) was added dropwise to *N*-glycolyloxazolidinethione glycolate **2.41** (493 mg, 1.44 mmol) in CH_2Cl_2 (36 mL) at -78°C . The bright yellow solution was stirred for 15 min and then (–)-sparteine (0.4 mL, 1.73 mmol) in CH_2Cl_2 (0.7 mL) was added dropwise. The dark purple solution was stirred for 45 min at -78°C , at which time excess titanium tetrachloride (0.38 mL, 3.47 mmol) was added at once followed immediately by aldehyde **2.4** (587 mg, 1.44 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred for 30 min and then quenched with pH 7 phosphate buffer. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2x 50 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 70:30 hexanes:EtOAc) to afford *anti* aldol adduct **2.42** (474 mg, 0.63 mmol, 44%, 10:1 ratio of diastereomers, 41% desired product) as a yellow oil: $R_f = 0.44$ (60:40 hexanes:EtOAc); $[\alpha]_D^{22.9} -60.54^\circ$ ($c = 0.22$, CH_2Cl_2); IR (film) ν 3418, 3062, 3029, 2984, 2931, 2358, 1703, 1496, 1455, 1369, 1206, 1164, 1067, 736, 700 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.30 (m, 15H), 6.43 (d, $J = 9.2$ Hz, 1H), 4.72 (d, $J = 11.6$ Hz, 1H), 4.59 (s, 2H), 4.39 (m, 3H), 4.31 (dd, $J = 6.0, 6.0$ Hz, 1H), 4.20 (m, 4H), 4.12 (d, $J = 5.6$ Hz, 1H), 3.93 (dd, $J = 8.4, 8.4$ Hz, 1H), 3.74 (dd, $J = 10.0, 10.4$ Hz, 1H), 3.63 (m, 2H), 3.40 (d, $J = 10.6$ Hz, 1H), 3.10 (dd, $J = 2.8, 13.6$ Hz, 1H), 2.70 (dd, 9.6, 14.0 Hz, 1H), 2.05 (m, 1H), 1.93 (m, 1H), 1.46 (s, 6H), 1.41 (s, 3H), 1.33 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 185.7, 174.2, 137.8, 137.0, 134.8, 129.3, 128.9, 128.7, 128.1, 128.0, 127.9, 127.4, 127.3, 127.1, 109.7, 108.5, 80.5, 74.1, 73.5, 73.3, 72.0, 70.8, 70.5, 69.0, 60.0, 37.0, 29.2, 27.5, 26.8, 26.7, 25.3 ppm; ESI-MS $\text{C}_{41}\text{H}_{49}\text{NO}_{10}\text{S}$ $[\text{M}+\text{Na}^+]$ calc. 770.31, found 770.18, $[\text{M}+\text{Cs}^+]$ calc. 880.21, found 880.08.

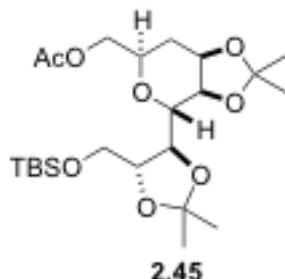


TBS ether 2.43: Secondary alcohol **2.42** (700 mg, 0.938 mmol) in CH₂Cl₂ (10 mL) was cooled to –78 °C. 2,6-Lutidine (0.44 mL, 3.75 mmol) was added dropwise followed by TBSOTf (0.43 mL, 1.88 mmol). The reaction mixture was stirred for 4 h warming to 0 °C before addition of saturated sodium bicarbonate (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to afford desired TBS ether **2.43** (700 mg, 0.812 mmol, 87% yield) as a yellow oil: R_f = 0.65 (60:40 hexanes:EtOAc); $[\alpha]_D^{23.8}$ –26.78° (c = 4.85, CH₂Cl₂); IR (film) ν 3063, 3030, 2984, 2931, 2857, 1702, 1644, 1496, 1455, 1370, 1323, 1251, 1197, 1159, 1092, 835, 738, 699 cm^{–1}; ¹H NMR (CDCl₃, 400 MHz) δ 7.31 (m, 15H), 6.36 (d, J = 6.8 Hz, 1H), 4.75 9d, J = 10.0 Hz, 1H), 4.61 (d, J = 10.0 Hz, 1H), 4.52 (dd, J = 3.2, 10.0 Hz, 2H), 4.36 (m, 3H), 4.27 (m, 1H), 4.26 (dd, J = 2.4, 5.6 Hz, 1H), 4.13 (m, 2H), 4.02 (m, 2H), 3.66 (d, J = 6.4, 6.4 Hz, 1H), 3.59 (m, 2H), 3.36 (dd, J = 2.4, 10.4 Hz, 1H), 2.49 (dd, J = 5.6, 5.6 Hz, 1H), 2.01 (m, 2H), 1.46 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 0.81 (s, 9H), 0.07 (s, 3H), –0.002 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 184.8, 172.9, 138.2, 138.0, 135.5, 129.3, 129.0, 128.4, 128.2, 128.1, 127.6, 110.0, 108.7, 79.6, 74.8, 74.0, 73.4, 73.3, 72.8, 71.9, 71.4, 70.6, 70.4, 60.8, 37.6, 28.8, 27.5, 27.2, 26.9, 26.1, 25.6, 25.3, 21.1, 18.2, –3.9, –4.2 ppm; ESI-MS C₄₇H₆₃NO₁₀SSi [M+Cs⁺] calc. 994.30, found 994.20, [M+Na⁺] calc. 884.38, found 884.30.



β-ketophosphonate 2.39: *n*-BuLi (2.5 M, 2.7 mL, 6.69 mmol) was added to a jacketed addition funnel and cooled to $-78\text{ }^{\circ}\text{C}$ and then added dropwise to a solution of dimethyl methylphosphonate (0.72 mL, 6.73 mmol) in THF (10 mL) at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$ during which time the solution turned a cloudy white. Oxazolidinethione **2.43** (725 mg, 0.841 mmol) in THF (3 mL) was added dropwise via jacketed addition funnel at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred for 2 h at $-78\text{ }^{\circ}\text{C}$, after which time saturated ammonium chloride (10 mL) was added and the biphasic mixture was warmed to rt. The organic layer was separated and the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 to 40:60 hexanes:EtOAc) to afford desired β-ketophosphonate **2.39** (591 mg, 0.746 mmol, 89% yield) as a yellow oil: $R_f = 0.16$ (60:40 hexanes:EtOAc); $[\alpha]_D^{24.9} +18.36^{\circ}$ ($c = 0.35$, CH_2Cl_2); IR (film) ν 3088, 3063, 3030, 2985, 2953, 2932, 2894, 2857, 1760, 1720 (strong), 1497, 1471, 1455, 1379, 1371, 1252, 1215, 1056, 836, 779, 738, 699 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.30 (m, 10H), 4.62 (m, 4H), 4.27 (m, 2H), 4.19 (ddd, $J = 4.8, 9.2, 4.8$ Hz, 1H), 4.13 (d, $J = 2.8$ Hz, 1H), 4.07 (m, 2H), 3.89 (m, 1H), 3.81 (ddd, $J = 3.6, 5.6, 12.0$ Hz, 1H), 3.78 (m, 6H), 3.60 (d, $J = 4.0$ Hz, 2H), 3.58 (dd, $J = 14.8, 20.0$ Hz, 1H), 3.12 (dd, $J = 15.2, 22.4$ Hz, 1H), 2.00 (m, 1H), 1.80 (m, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 1.34 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 202.3, 138.0, 137.4, 128.3, 128.0, 127.5, 109.8, 108.5, 85.9, 85.8, 79.1, 75.6, 73.4, 73.3, 72.7, 72.4, 72.0, 70.8, 70.3, 53.0, 52.9, 52.7, 52.6, 38.5, 37.5, 28.9, 27.6, 27.0, 26.8, 25.8, 25.5, 18.1, -4.5 , -4.9 ppm; ESI-MS $\text{C}_{40}\text{H}_{61}\text{O}_{12}\text{P}$

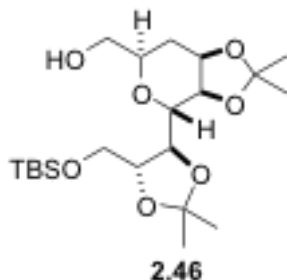
[2M+Na⁺] calc. 1607.72, found 1608.53, [M+Cs⁺] calc. 927.27, found 925.18, [M+Na⁺] calc. 815.36, found 815.28.



Acetate 2.45: Tetrahydropyran **2.17** (1.1 g, 2.53 mmol) in EtOAc (15 mL) was sparged with a stream of argon for 10 min. Palladium hydroxide (20% on carbon, 0.72 g, 0.51 mmol) was added to the degassed solution. The argon was removed under reduced pressure, and the flask was backfilled with hydrogen. The reaction mixture was stirred for 2 h, after which time the solution was filtered through a pad of celite with EtOAc (100 mL), dried (Na₂SO₄), concentrated, and used without purification in the next step.

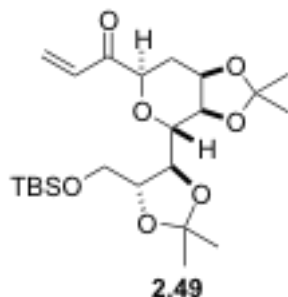
Triethylamine (0.7 mL, 5.06 mmole), DMAP (30 mg, 0.25 mmol), and TBSCl (570 mg, 3.8 mmol) were added to the crude primary alcohol in CH₂Cl₂ (10 mL). The mixture was stirred at rt overnight and was then quenched with saturated sodium bicarbonate (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 100:0 to 75:25 hexanes:EtOAc) to afford desired acetate **2.45** (875 mg, 1.84 mmol, 73% yield) as a yellow oil: *R*_f = 0.76 (60:40 hexanes:EtOAc); [α]_D^{23.3} +2.18° (c = 0.64 CH₂Cl₂); IR (film) ν 2986, 2933, 2857, 1745, 1644, 1461, 1370, 1241, 1166, 1142, 1054, 837, 778 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.30 (m, 3H), 4.13 (m, 2H), 4.01 (m, 2H), 3.88 (dd, *J* = 2.8, 6.0 Hz, 1H), 3.76 (m, 2H), 2.05 (s, 3H), 1.99 (m, 1H), 1.65 (m, 1H), 1.47 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 170.8,

109.5, 108.7, 79.1, 77.8, 72.0, 71.3, 70.8, 68.7, 65.2, 63.5, 29.0, 27.9, 27.2, 26.9, 25.9, 25.7, 20.8, 18.3, -5.4, -5.5 ppm; ESI-MS $C_{23}H_{42}O_8Si$ $[2M+Na^+]$ calc. 971.52, found 971.49, $[M+Cs^+]$ calc. 607.17, found 607.14, $[M+Na^+]$ calc. 497.25, found 497.23.



Alcohol 2.46: To acetate **2.45** (385 mg, 0.81 mmol) in methanol (5 mL) was added a catalytic amount of potassium carbonate. The reaction mixture was stirred at rt for 1 h and then quenched with saturated ammonium chloride (10 mL). The mixture was partitioned between EtOAc (100 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (3x 50 mL) and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 60:40 hexanes:EtOAc) to afford desired alcohol **2.46** (303 mg, 0.70 mmol, 87% yield) as a clear oil: $R_f = 0.43$ (60:40 hexanes:EtOAc); $[\alpha]_D^{24.0} -0.32^\circ$ ($c = 1.0$, CH_2Cl_2); IR (film) ν 3443, 2986, 2933, 2857, 2093, 1644, 1472, 1462, 1371, 1251, 1217, 1165, 1138, 1064, 836, 779 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 4.32 (m 1H), 4.25 (dd, $J = 4.8, 9.2$ Hz, 1H), 4.15 (dd, $J = 2.0, 6.4$ Hz, 1H), 4.06 (m, 1H), 3.93 (dd, $J = 2.0, 4.4$ Hz, 1H), 3.85 (m, 1H), 3.78 (dd, $J = 3.2, 8.8$ Hz, 1H), 3.7 (dd, $J = 4.4, 8.8$ Hz, 1H), 3.62 (ddd, $J = 3.2, 5.6, 9.2$ Hz, 1H), 3.52 (m, 1H), 2.13 (dd, $J = 3.2, 6.4$ Hz, 1H), 1.89 (m, 1H), 1.59 (m, 1H), 1.44 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.5, 108.6, 79.5, 77.5, 72.3, 71.4, 71.2, 70.9, 64.7, 63.7, 29.0, 27.9, 27.1, 26.9, 25.9, 25.6, 18.3, -5.4, -5.5 ppm; ESI-MS $C_{21}H_{40}O_7Si$ $[2M+Na^+]$ calc. 887.49, found 887.46,

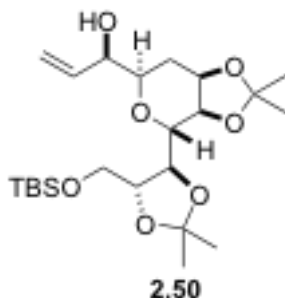
[M+Cs⁺] calc. 565.16, found 565.14, [M+Na⁺] calc. 455.24, found 455.22.



Enone 2.49: Oxalyl chloride (98%, 0.13 mL, 1.53 mmol) was dissolved in CH₂Cl₂ (15 mL) and cooled to –78 °C. Dimethylsulfoxide (0.21 mL, 2.91 mmol) in CH₂Cl₂ (2 mL) was added dropwise, and the reaction mixture was stirred for 10 min at –78 °C. Primary alcohol **2.46** (331 mg, 0.77 mmol) in CH₂Cl₂ (8 mL) was added dropwise and the reaction mixture was stirred for 20 min at –78 °C. Triethyl amine (0.80 mL, 6.0 mmol) was added dropwise and the reaction mixture was stirred for 10 min at –78 °C before slowly warming to rt over 1 h. 10 % aqueous HCl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were washed with saturated sodium bicarbonate (25 mL), brine (25 mL), dried (Na₂SO₄), and concentrated. The oil was then dissolved in EtOAc (50 mL) and filtered through a pad of celite. The crude aldehyde **18** was carried forward without further purification.

Freshly prepared vinyl magnesium bromide in THF (~0.91 M, 3.0 mL, 2.73 mmol) was added dropwise to aldehyde **2.47** in THF (5 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h, then saturated ammonium chloride (10 mL) was added dropwise to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (100 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (silica gel, 70:30 hexanes:EtOAc) afforded an inseparable mixture of diastereomers.

Dess Martin periodinane (360 mg, 0.80 mmol) was added at once to the mixture of diastereomers **2.48** in CH₂Cl₂ (5 mL). The reaction mixture was stirred at rt for 3 h, after which time a 5:1 mixture of saturated NaHCO₃: saturated Na₂SO₃ (10 mL) was added. The biphasic mixture was stirred vigorously until two distinct layers were formed (~15 min). Following extraction with CH₂Cl₂ (3x 25 mL), the combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to afford desired enone **2.49** (168 mg, 0.37 mmol, 50% yield) as a clear oil: $R_f = 0.67$ (60:40 hexanes:EtOAc); $[\alpha]_D^{23.3} +8.22^\circ$ ($c = 0.18$, CH₂Cl₂); IR (film) ν 2986, 2933, 2896, 2857, 2359, 1702, 1613, 1472, 1461, 1402, 1380, 1371, 1251, 1216, 1165, 1142, 1066, 1005, 837, 779 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.83 (dd, $J = 10.8, 17.6$ Hz, 1H), 6.39 (dd, $J = 1.6, 17.6$ Hz, 1H), 5.76 (dd, $J = 1.6, 10.4$ Hz, 1H), 4.32 (m, 3H), 4.24 (dd, $J = 2.4, 8.4$ Hz, 1H), 4.15 (m, 1H), 3.92 (dd, $J = 2.4, 6.4$ Hz, 1H), 3.73 (m 2H), 2.18 (m, 1H), 2.07 (m, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 0.87 (s, 9H), 0.05 (s, 6H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 198.9, 131.2, 129.6, 109.6, 109.2, 79.4, 75.3, 73.3, 71.4, 70.6, 63.6, 28.3, 27.7, 27.2, 26.9, 26.1, 25.9, 25.7, 18.4, -5.4, -5.5 ppm; ESI-MS C₂₃H₄₀O₇Si [2M+Na⁺] calc. 935.49, found 935.46, [M+Cs⁺] calc. 589.16, found 589.13, [M+Na⁺] calc. 479.24, found 479.22.

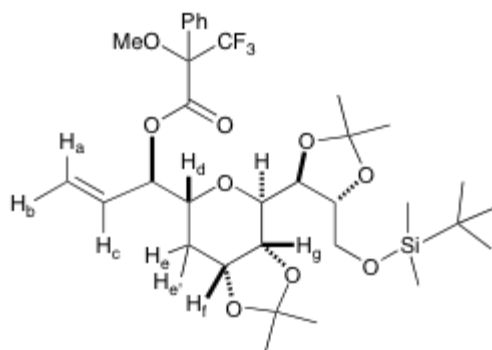


Allylic Alcohol (CBS) 2.50: Borane dimethyl sulfide complex (0.08 mL, 0.82 mmol) was added to a solution of enone **2.49** (315 mg, 0.69 mmol) and (*R*)-(+)-2-methyl-CBS-

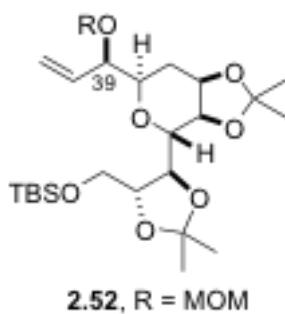
oxazaborolidine (1 M, 0.82 mL, 0.82 mmol) in CH₂Cl₂ (7 mL) at 0 °C. The reaction mixture was stirred for 1.5 h and then quenched with methanol (1 mL) and saturated sodium bicarbonate (3 mL). Following extraction with CH₂Cl₂ (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 75:25 hexanes:EtOAc) to afford desired allylic alcohol **2.50** (261 mg, 0.57 mmol, 82% yield) as a clear oil: $R_f = 0.50$ (60:40 hexanes:EtOAc); $[\alpha]_D^{24.6} +7.61^\circ$ ($c = 0.91$, CH₂Cl₂); IR (film) ν 3443, 2986, 2955, 2933, 2857, 2084, 1644, 1461, 1371, 1251, 1215, 1165, 1141, 1063, 835, 778 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.75 (ddd, $J = 6.8, 10.4, 17.2$ Hz, 1H), 5.36 (d, $J = 17.2$ Hz, 1H), 5.23 (d, $J = 10.4$ Hz, 1H), 4.30 (m, 2H), 4.17 (dd, $J = 2.4, 8.4$ Hz, 1H), 4.11 (m, 2H), 3.94 (dd, $J = 2.4, 6.0$ Hz, 1H), 3.81 (dd, $J = 4.0, 10.8$ Hz, 1H), 3.72 (dd, $J = 5.6, 10.4$ Hz, 1H), 3.60 (m, 1H), 2.71 (s, 1H), 1.97 (m, 1H), 1.63 (m, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 136.0, 118.1, 109.6, 108.8, 79.8, 74.6, 74.0, 72.4, 71.8, 71.0, 63.9, 28.9, 27.8, 27.2, 26.9, 25.9, 25.5, 18.4, -5.4, -5.5 ppm; ESI-MS C₂₃H₄₂O₇Si [2M+Na⁺] calc. 940.31, found 939.49, [M+Cs⁺] calc. 591.57, found 591.15, [M+Na⁺] calc. 481.65, found 481.23.

Mosher's Ester Analysis of C39:

Preparation of *R* and *S* Mosher Esters: The Mosher esters were prepared following the protocol of Hoyer. In a dry 5 mL vial, allylic alcohol **2.50** (10 mg, 0.22 mmol) was dissolved in CH₂Cl₂. The *R* or *S* MTPA acid (15.3 mg, 0.065 mmol) was added followed by DCC (14 mg, 0.065 mmol). The reaction mixture was stirred for 24 h, over which time a white precipitate formed. The reaction mixture was filtered, concentrated, and purified by flash chromatography to provide the diastereomeric Mosher ester.

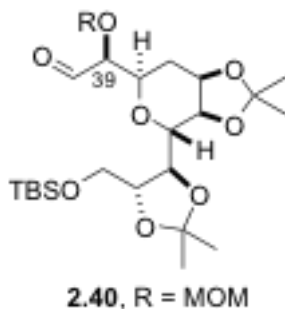


Proton	δ S-ester	δ R-ester	$\Delta \delta^{SR} (= \delta_S - \delta_R)$
H _a	5.428	5.321	+0.107
H _b	5.338	5.275	+0.063
H _c	5.812	5.674	+0.138
H _d	3.819	3.914	-0.095
H _e	1.845	1.971	-0.126
H _{e'}	1.561	1.662	-0.101
H _f	4.296	4.313	-0.017



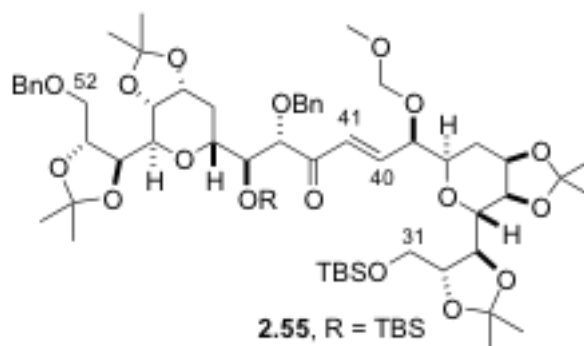
Alkene 2.52: Methoxymethyl chloride (0.9 mL, 11.6 mmol) was added dropwise to a solution of allylic alcohol **20** (243 mg, 0.53 mmol) and diisopropylethylamine (5.0 mL, 29.0 mmol) in chloroform (3 mL). The reaction mixture was stirred at 40 °C for 24 h, and then quenched with H₂O. The organic layer was separated and the aqueous layer was extracted with

CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 70:30 hexanes:EtOAc) to afford desired ether **2.52** (252 mg, 0.50 mmol, 94% yield) as a yellow oil: *R*_f = 0.64 (60:40 hexanes:EtOAc); [α]_D^{23.7} –13.2° (*c* = 0.30, CH₂Cl₂); IR (film) ν 2986, 2932, 2857, 1644, 1462, 1379, 1370, 1251, 1215, 1149, 1098, 1038, 921, 836, 778 cm^{–1}; ¹H NMR (CDCl₃, 400 MHz) δ 5.72 (ddd, *J* = 7.6, 10.4, 17.6 Hz, 1H), 5.28 (m, 2H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.30 (m, 2H), 4.16 (dd, *J* = 2.8, 8.4 Hz, 1H), 4.10 (m, 2H), 3.90 (dd, *J* = 2.8, 5.2 Hz, 1H), 3.75 (m, 3H), 3.33 (s, 3H), 1.90 (m, 1H), 1.72 (m, 1H), 1.44 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 0.87 (s, 9H), –0.04 (m, 6H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 134.5, 119.3, 109.4, 108.6, 94.2, 79.1, 78.6, 77.7, 72.9, 72.1, 71.3, 63.5, 55.5, 28.9, 27.8, 27.2, 27.0, 25.9, 25.5, 18.4, –5.4, –5.5 ppm; ESI-MS C₂₅H₄₆O₈Si [M+Na⁺] calc. 525.29, found 525.27.



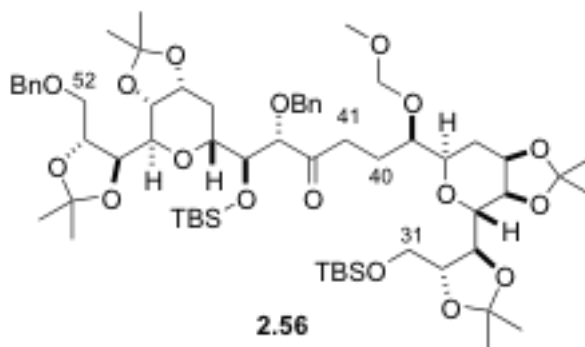
Aldehyde 2.40: Sodium periodate (250 mg, 1.18 mmol) was added to a solution of alkene **21** (252 mg, 0.59 mmol) and OsO₄ (20mg/mL, 0.75 mL, 0.06 mmol) in THF (3.0 mL) and pH 7.0 phosphate buffer (3.0 mL) at rt. The reaction mixture was stirred vigorously for 4 h before being quenched with saturated NaHCO₃ and NaS₂O₃(1:1, 5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 70:30

hexanes:EtOAc) to afford desired aldehyde **2.40** (187 mg, 0.037 mmol, 66% yield) as a clear oil: $R_f = 0.50$ (60:40 hexanes:EtOAc); $[\alpha]_D^{24.2} -39.5^\circ$ ($c = 0.33$, CH_2Cl_2); IR (film) ν 2986, 2933, 2857, 2359, 2341, 2113, 1735, 1644, 1462, 1379, 1252, 1215, 1153, 1061, 837, 779 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.70 (s, 1H), 4.76 (d, $J = 7.0$ Hz, 1H), 4.69 (d, $J = 5.6$ Hz, 1H), 4.33, (m, 1H), 4.22 (m, 2H), 4.10 (dd, $J = 2.0, 8.5$ Hz, 1H), 4.04 (dd, $J = 2.0, 5.5$ Hz, 1H), 4.01 (m, 1H), 3.89 (d, $J = 2.0$ Hz, 1H), 3.74 (ddd, $J = 4.0, 10.5, 21.5$ Hz, 2H), 3.93 (s, 3H), 1.92 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 202.2, 109.7, 108.7, 97.1, 83.6, 79.9, 77.6, 73.9, 71.8, 71.1, 70.9, 63.6, 56.2, 29.0, 27.8, 27.1, 26.9, 25.9, 25.5, 18.4, -5.4 , -5.5 ppm; ESI-MS $\text{C}_{24}\text{H}_{44}\text{O}_9\text{Si}$ $[\text{M}+\text{MeOH}+\text{Na}^+]$ calc. 559.29, found 559.26.



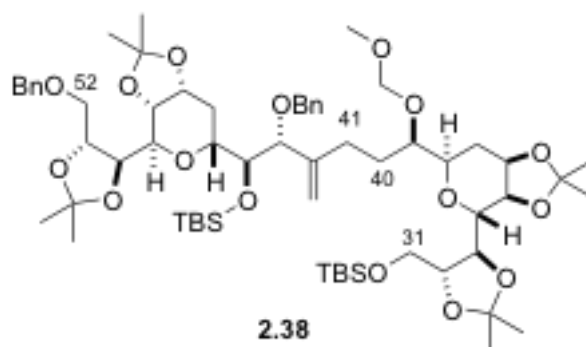
Enone 2.55: To β -ketophosphonate **2.39** (342 mg, 0.41 mmol) in THF (0.4 mL) was added anhydrous barium hydroxide (51 mg, 0.30 mmol). The mixture was stirred 30 min at rt. Aldehyde **2.40** (187 mg, 0.37 mmol) was added in 40:1 THF:H₂O (0.2 mL) and the viscous, yellow mixture was vigorously stirred 2 h at room temperature. Saturated ammonium chloride (1 mL) was added and the mixture was diluted with EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to afford desired enone **2.55** (320 mg, 0.27 mmol, 74% yield based on

aldehyde **2.40**) as a yellow oil: $R_f = 0.69$ (60:40 hexanes:EtOAc); $[\alpha]_D^{23.3} +5.57^\circ$ ($c = 5.1$, CH_2Cl_2); IR (film) ν 3065, 3031, 2985, 2932, 2887, 2857, 2359, 2341, 1694, 1630, 1497, 1471, 1455, 1379, 1370, 1251, 1215, 1097, 918, 836, 810, 778, 736 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 7.30 (m, 10H), 6.83 (s, 1H), 6.78 (d, $J = 4.8$ Hz, 1H), 4.57 (m, 4H), 4.48 (s, 2H), 4.35 (dd, $J = 4.4, 4.4$ Hz, 1H), 4.28 (m, 4H), 4.29 (m, 1H), 4.17 (dd, $J = 2.4, 7.6$ Hz, 1H), 4.10 (m, 1H), 4.04 (m, 2H), 3.99 (dd, $J = 4.0, 4.0$ Hz, 1H), 3.89 (m, 3H), 3.81 (m, 1H), 3.75 (m, 2H), 3.56 (m, 2H), 3.31 (s, 3H), 1.95 (m, 1H), 1.85 (m, 1H), 1.64 (m, 2H), 1.41 (m, 18H), 1.30 (s, 6H), 0.88 (s, 9H), 0.81 (m, 9H), 0.05 (s, 6H), 0.01 (s, 3H), -0.04 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 199.0, 142.3, 138.0, 137.3, 128.4, 127.9, 127.5, 109.8, 109.5, 108.7, 108.6, 95.1, 84.7, 79.3, 77.5, 76.5, 75.6, 73.4, 72.9, 72.8, 72.7, 72.6, 72.3, 72.0, 71.7, 71.2, 70.8, 70.5, 68.0, 63.4, 55.8, 29.1, 28.8, 27.8, 27.6, 27.1, 27.0, 26.9, 26.8, 25.9, 25.5, 25.4, 18.4, 18.2, -4.2 , -4.6 , -5.3 , -5.4 ppm; ESI-MS $\text{C}_{62}\text{H}_{98}\text{O}_{17}\text{Si}_2$ $[\text{M}+\text{Na}^+]$ calc. 1193.62, found 1193.56.



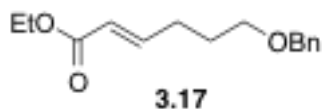
Ketone 2.56: A dry 25 mL round-bottom flask, under argon, was charged with CuI (20 mg, 0.10 mmol) and THF (2 mL). The solution was cooled to -50°C and MeLi (1.6 M, 0.07 mL, 0.11 mmol) was added dropwise. The yellow suspension was stirred 5 min, then freshly distilled HMPA (0.40 mL) was added, followed by DIBAL (1.0 M, 1.27 mL, 1.27 mmol). The mixture was stirred 30 min at -50°C , at which point an aliquot (0.6 mL) was added to enone

2.55 (102 mg, 0.087 mmol) in THF (0.4 mL). The reaction mixture was stirred 1 h at $-50\text{ }^{\circ}\text{C}$. The dry ice bath was removed and 10% aqueous HCl (5 mL) was added. The mixture was diluted with Et₂O (25 mL) and allowed to stir for 5 min. The layers were separated and the organic layer was washed with 10% aqueous HCl (2x 10 mL), then with H₂O (3x 10 mL). The organic layer was washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to afford desired ketone **2.56** (56 mg, 0.048 mmol, 55% yield) as a clear oil: $R_f = 0.69$ (60:40 hexanes:EtOAc); $[\alpha]_D^{23.8} +14.3^{\circ}$ ($c = 0.10$, CH₂Cl₂); IR (film) ν 2986, 2954, 2931, 2857, 2359, 2115, 1644, 1497, 1471, 1455, 1379, 1371, 1251, 1215, 1164, 1096, 1061, 835, 777, 736, 698 cm^{-1} ; ¹H NMR (CDCl₃, 500 MHz) δ 7.30 (m, 10H), 4.65 (d, $J = 5.2$ Hz, 1H), 4.57 (m, 4H), 4.47 (d, $J = 9.2$ Hz, 1H), 4.27 (m, 4H), 4.19 (m, 1H), 4.13 (dd, $J = 2.0, 6.4$ Hz, 1H), 4.04 (m, 3H), 3.92 (d, $J = 2.8$ Hz, 2H), 3.84 (m, 2H), 3.73 (m, 3H), 3.57 (m, 2H), 3.46 (m, 1H), 3.25 (s, 3H), 2.76 (m, 1H), 2.64 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.74 (m, 1H), 1.65 (m, 3H), 1.44 (s, 3H), 1.38 (m, 15H), 1.31 (s, 3H), 1.29 (s, 3H), 0.87 (s, 9H), 0.82 (s, 9H), 0.04 (m, 12H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 210.6, 138.0, 137.5, 128.4, 128.3, 127.8, 127.5, 109.8, 109.5, 108.57, 108.55, 97.2, 85.6, 79.5, 79.3, 78.7, 77.6, 76.3, 75.4, 73.4, 73.1, 73.0, 72.9, 72.5, 72.3, 72.2, 72.1, 71.1, 70.9, 70.4, 63.6, 55.8, 36.5, 29.2, 29.0, 27.8, 27.7, 27.1, 27.0, 26.9, 26.8, 25.9, 25.8, 25.5, 25.4, 23.8, 18.4, 18.2, -4.4 , -4.7 , -5.4 , -5.5 ppm; ESI-MS C₆₂H₁₀₀O₁₇Si₂ [M+Na⁺] calc. 1195.64, found 1195.58.



Protected bis-tetrahydropyran core 2.38: To ketone **2.56** (21.2 mg, 0.018 mmol) in THF

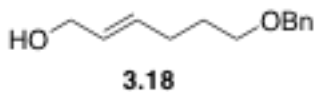
(0.06 mL) was added the Tebbe reagent (0.5 M in toluene, 0.2 mL, 0.09 mmol) at rt. The reaction mixture was heated to 50 °C, and stirred for 5 h. After consumption of starting material, the reaction was quenched with 15% aqueous NaOH (1 mL), diluted with Et₂O (25 mL), and filtered through a small pad of celite. The organic layer was dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to afford desired bis-tetrahydropyran core **2.38** (15 mg, 0.013 mmol, 73% yield) as a clear oil: *R*_f = 0.48 (80:20 hexanes:EtOAc); [α]_D^{24.4} +2.18° (*c* = 1.56, CH₂Cl₂); IR (film) ν 3064, 3030, 2985, 2932, 2887, 2857, 2359, 1644, 1496, 1472, 1455, 1379, 1370, 1164, 1146, 1065, 917, 836, 811, 777 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.30 (m, 10H), 5.10 (s, 1H), 5.02 (s, 1H), 4.64 (d, *J* = 5.6 Hz, 1H), 4.59 (d, *J* = 5.6 Hz, 1H), 4.56 (d, *J* = 10.0 Hz, 1H), 4.50 (d, *J* = 10.0 Hz, 1H), 4.37 (d, *J* = 9.2 Hz, 1H), 4.25 (m, 6H), 4.13 (dd, *J* = 2.0, 7.2 Hz, 1H), 4.07 (m, 1H), 3.97 (m, 2H), 3.92 (m, 2H), 3.89 (d, *J* = 6.0 Hz, 1H), 3.74 (m, 3H), 3.65 (dd, *J* = 2.0, 5.6 Hz, 1H), 3.50 (m, 3H), 3.29 (s, 3H), 2.25 (m, 1H), 2.00 (m, 1H), 1.80 (m, 4H), 1.65 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 1.38 (m, 9H), 1.30 (m, 9H), 0.87 (s, 9H), 0.82 (m, 9H), 0.04 (s, 6H), 0.01 (s, 3H), -0.06 (s, 3H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 145.9, 138.4, 128.3, 128.2, 127.6, 127.5, 115.1, 110.0, 109.5, 108.5, 97.0, 83.5, 79.8, 79.5, 79.4, 77.6, 75.3, 73.4, 73.3, 73.0, 72.7, 72.5, 72.1, 70.9, 70.3, 63.6, 55.8, 29.5, 29.1, 27.9, 27.8, 27.5, 27.1, 26.93, 26.90, 26.7, 26.1, 25.9, 25.5, 25.3, 18.4, 18.3, -3.8, -4.2, -5.37, -5.44 ppm; ESI-MS C₆₂H₁₀₂O₁₇Si₂ [M+Na⁺] calc. 1193.66, found 1193.60.



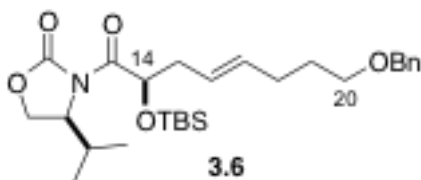
Ester 3.17: Oxalyl chloride (98%, 0.98 mL, 11.1 mmol) was dissolved in CH₂Cl₂ (55 mL) and cooled to -78 °C. Dimethylsulfoxide (1.5 mL, 21.6 mmol) in CH₂Cl₂ (18 mL) was added dropwise via addition funnel, and the reaction mixture was stirred for 15 min at -78 °C.

Primary alcohol **3.16** (1.0 g, 5.55 mmol) in CH₂Cl₂ (18 mL) was added dropwise via addition funnel and the reaction mixture was stirred for an additional 30 min at –78 °C. Triethyl amine (6.0 mL, 43.3 mmol) was added dropwise via addition funnel and the reaction mixture was stirred for 10 min at –78 °C before slow warming to rt over 1 h. The reaction mixture was quenched with 10 % aqueous HCl (50 mL), the organic layer was separated, and the aqueous layer extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with sodium bicarbonate (saturated aqueous, 50 mL), brine (100 mL), dried (Na₂SO₄), and concentrated. Filtration through a silica plug (70:30 hexanes:EtOAc) afforded an aldehyde that was used without further purification for the next step.

The aldehyde (5.55 mmol) was dissolved in THF (55 mL) and carboethoxy methylenetriphenyl phosphene (2.9 g, 8.33 mmol) was added at once. The reaction mixture has heated to reflux for 15 h. The reaction mixture was then cooled to rt, concentrated, and the residue was purified by column chromatography (90:10 hexanes:EtOAc) to afford ester **3.17** (1.34 g, 5.39 mmol, 97%, 2 steps) as a colorless oil: R_f = 0.61 (80:20 hexanes:EtOAc); IR (film) ν 3030, 2980, 2938, 2857, 1719, 1654, 1454, 1391, 1367, 1267, 1204, 1171, 1044, 980, 737, 698 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (m, 5H), 6.94 (ddd, J = 6.8, 14.0, 6.8 Hz, 1H), 5.80 (d, J = 16.8 Hz, 1H), 4.47 (s, 2H), 4.15 (dd, J = 7.2, 14.4 Hz, 2H), 3.46 (dd, J = 6.4, 6.4 Hz, 2H), 2.30 (m, 2H), 1.75 (ddd, J = 6.4, 14.0, 6.4 Hz, 2H), 1.26 (dd, J = 7.2, 7.2 Hz, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 166.6, 148.5, 138.3, 128.3, 127.6, 127.5, 121.6, 72.9, 69.2, 60.1, 28.9, 28.1, 14.2 ppm; ESI-MS C₁₅H₂₀O₃ [M+Na⁺] calc. 271.13, found 271.13.



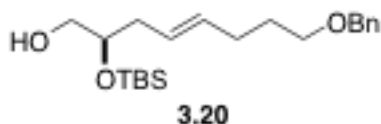
Allylic alcohol 3.18: Ester **3.17** (1.34 g, 5.39 mmol) was dissolved in CH₂Cl₂ and cooled to –78 °C. Di-*iso*-butylaluminum hydride (1.0 M in CH₂Cl₂ 16.2 mL, 16.2 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h, upon which time potassium sodium tartrate (25 mL) was added. The mixture was warmed to rt with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x 50 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 hexanes:EtOAc) to afford desired alcohol **3.18** (1.04 g, 5.07 mmol, 93% yield) as a clear oil: *R*_f = 0.18 (80:20 hexanes:EtOAc); IR (film) ν 3390, 3087, 3063, 3029, 2963, 2857, 1495, 1454, 1364, 1308, 1099, 1026, 1000, 970, 736, 698 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (m, 5H), 5.64 (m, 2H), 4.48 (s, 2H), 4.05 (s, 2H), 3.46 (dd, *J* = 6.4, 6.4 Hz, 2H), 2.12 (dd, *J* = 6.4, 14.4 Hz, 2H), 1.69 (ddd, 6.8, 14.4, 6.8 Hz, 2H), 1.37 (bs, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 138.5, 132.4, 129.3, 128.3, 127.6, 127.5, 72.8, 69.5, 63.6, 29.1, 28.8 ppm; ESI-MS C₁₃H₁₈O₂ [M+Na⁺] calc. 229.12, found 229.12.



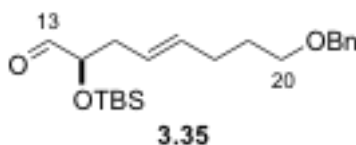
Alkylated N-glycolyl oxazolidinone 3.6: **Allylic iodide 3.19:** Triphenylphosphine (18.5 g, 70.5 mmol) and imidazole (5.28 g, 70.6 mmol) were dissolved in Et₂O (96 mL) and acetonitrile (32 mL). The mixture was cooled to 0 °C and iodine (18.0 g, 70.5 mmol) was added portionwise. The resulting viscous yellow solution was stirred vigorously for 1 h at 0 °C. A solution of allylic alcohol **3.18** (4.82 g, 23.5 mmol) in Et₂O (20 mL) was added dropwise to the mixture. The reaction was stirred for 30 min at which time a 1:6 mixture of Et₂O:hexanes was added. The solution was filtered and concentrated. Flash

chromatography (silica gel, 96:4 hexanes:Et₂O) afforded desired allylic iodide **3.19** (5.23 g, 16.6 mmol, 71% yield) as a yellow oil, which was used immediately for the glycolate alkylation reaction.

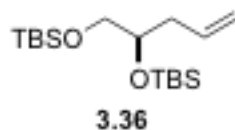
A flame-dried 50 mL flask, was charged with 0.75 M sodium hexamethyldisilazide (4.6 mL, 3.45 mmol) and THF (7 mL). The solution was cooled to –78 °C and *N*-glycolyl oxazolidinone **3.7** (745 mg, 2.47 mmol) in THF (4 mL) was added dropwise. Maintaining an internal temperature below –70 °C during the addition was crucial to avoid decomposition. After addition, the bright yellow solution was stirred at –78 °C for 30 min, after which time allylic iodide **3.19** (3.5 g, 11.1 mmol) in THF (3 mL) was added dropwise. The solution was slowly warmed to –45 °C and stirred for 3 h. Saturated ammonium chloride (20 mL) was added and the biphasic mixture was warmed to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 to 85:15 hexanes:EtOAc) to afford desired alkylated *N*-glycolyl oxazolidinone **3.6** (813 mg, 1.66 mmol, 67% yield, >20:1 ratio of diastereomers) as a bright yellow oil *R*_f = 0.39 (80:20 hexanes:EtOAc); [α]_D^{19.4} +38.1° (*c* = 0.64, CH₂Cl₂); IR (film) ν 2959, 2931, 2856, 1779, 1714, 1644, 1463, 1388, 1362, 1301, 1248, 1206, 1105 cm^{–1}; ¹H NMR (CDCl₃, 600 MHz) δ 7.31 (s, 4H), 7.26 (m, 1H), 5.51 (m, 2H), 5.33 (dd, *J* = 3.6, 7.2 Hz, 1H), 4.48 (m, 3H), 4.31 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.21 (dd, *J* = 3.6, 4.8 Hz, 1H), 3.45 (m, 2H), 2.51 (m, 1H), 2.29 (m, 2H), 2.07 (m, 2H), 1.65 (ddd, *J* = 6.6, 13.8 Hz, 2H), 0.88 (s, 12H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H) ppm; ¹³C NMR (CDCl₃, 150 MHz) δ 173.8, 153.7, 138.7, 133.5, 128.4, 127.7, 127.5, 125.4, 72.9, 71.5, 69.9, 63.9, 58.2, 38.9, 29.4, 29.2, 28.3, 25.7, 18.4, 17.9, 14.7, –4.85, –5.10 ppm; ESI-MS C₂₇H₄₃NO₅Si [M+Na⁺] calc. 512.28, found 512.27.



Primary alcohol 3.20: Lithium borohydride (0.94 mL, 1.89 mmole) was added dropwise to a solution of alkylated *N*-glycolyl oxazolidinone **3.6** (842 mg, 1.72 mmol) and methanol (0.07 mL, 1.72 mL) in Et₂O (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h after which time saturated sodium bicarbonate (10 mL) was added slowly and the biphasic mixture was warmed to rt. The organic layer was separated and the aqueous layer was extracted with Et₂O (3x 20 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 85:15 hexanes:EtOAc) to afford desired alcohol **3.20** (525 mg, 1.44 mmol, 84% yield) as a colorless oil: *R*_f = 0.39 (80:20 hexanes:EtOAc); [α]_D^{19.7} –5.85° (*c* = 1.6, CH₂Cl₂); IR (film) ν 3442, 3031, 2952, 2929, 2883, 2856, 1644, 1471, 1361, 1254, 1105, 971, 835, 776 cm^{–1}; ¹H NMR (CDCl₃, 600 MHz) δ 7.32 (s, 4H), 7.26 (m, 1H), 5.45 (ddd, *J* = 6.6, 14.4, 6.6 Hz, 1H), 5.35 (ddd, *J* = 6.6, 14.4, 6.6 Hz, 1H), 4.47 (s, 2H), 3.70 (m, 1H), 3.51 (ddd, *J* = 4.2, 6.6, 10.8 Hz, 1H), 3.43 (m, 3H), 2.17 (m, 2H), 2.07 (dd, *J* = 7.2, 14.4 Hz, 2H), 1.82 (dd, *J* = 6.6, 6.6 Hz, 1H), 1.66 (ddd, *J* = 6.6, 13.8, 6.6 Hz, 2H), 0.88 (s, 9H), 0.06 (s, 6H) ppm; ¹³C NMR (CDCl₃, 150 MHz) δ 138.6, 132.7, 128.3, 127.6, 127.5, 126.0, 72.8, 72.7, 69.7, 65.9, 37.4, 29.4, 29.2, 25.8, 18.1, –4.44, –4.68 ppm; ESI-MS C₂₁H₃₆O₃Si [M+Na⁺] calc. 387.23, found 387.23.



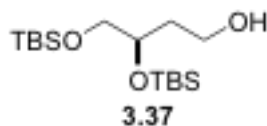
Aldehyde 3.35: Oxalyl chloride (98%, 0.15 mL, 1.72 mmol) was dissolved in CH₂Cl₂ (8.6 mL) and cooled to –78 °C. Dimethylsulfoxide (0.24 mL, 3.35 mmol) in CH₂Cl₂ (1.1 mL) was added dropwise, and the reaction mixture was stirred for 15 min at –78 °C. Primary alcohol **3.20** (314 mg, 0.86 mmol) in CH₂Cl₂ (3 mL) was added dropwise and the reaction mixture was stirred for an additional 30 min at –78 °C. Triethyl amine (0.94 mL, 6.74 mmol) was added dropwise and the reaction mixture was stirred for 10 min at –78 °C before slow warming to rt over 1 h. The reaction mixture was quenched with 10 % aqueous HCl (10 mL), the organic layer was separated, and the aqueous layer extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were washed with saturated sodium bicarbonate (10 mL), brine (10 mL), dried (Na₂SO₄), and concentrated. Filtration of the residue through a silica plug (80:20 hexanes:EtOAc) afforded desired aldehyde **3.35** (205 mg, 0.57 mmol, 66% yield) as a clear oil: *R*_f = 0.66 (80:20 hexanes:EtOAc); [α]_D^{22.0} +12.98° (c = 0.21, CH₂Cl₂); IR (film) ν 3064, 3030, 2951, 2930, 2884, 2856, 2796, 1737, 1471, 1462, 1454, 1362, 1253, 1110, 970, 836, 779, 735, 697 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 9.56 (s, 1H), 7.32 (s, 5H), 5.49 (ddd, *J* = 6.6, 15, 6.6 Hz, 1H), 5.38 (m, 1H), 4.47 (s, 2H), 3.95 (ddd, *J* = 1.2, 6.6, 4.8 Hz, 1H), 3.44 (dd, 6.6, 6.6 Hz, 2H), 2.35 (ddd, 5.4, 13.2, 5.4 Hz, 1H), 2.28 (ddd, *J* = 7.2, 14.4, 7.2 Hz, 1H), 2.08 (dd, *J* = 6.6, 14.4 Hz, 2H), 1.65 (ddd, *J* = 6.6, 13.2, 6.6 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H) ppm; ¹³C NMR (CDCl₃, 150 MHz) δ 203.9, 138.6, 133.8, 128.3, 127.6, 127.5, 124.5, 77.7, 72.8, 69.6, 36.2, 29.3, 29.2, 26.0, 25.8, 25.7, 18.2, –4.7, –4.9 ppm; ESI-MS C₂₁H₃₄O₃Si [M⁺] calc. 362.23, found 362.23.



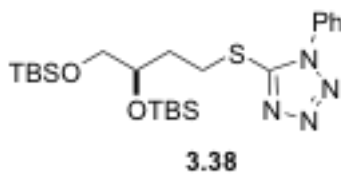
Alkene 3.36: Primary Alcohol 3.11: Lithium borohydride (2.0 M in Et₂O, 3.90 mL, 7.73 mmol) was added dropwise to a solution of alkylated *N*-glycolyl oxazolidinone **3.5** (2.40 g,

7.03 mmol) and methanol (0.30 mL, 7.03 mmol) in Et₂O (55 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h after which time saturated sodium bicarbonate (25 mL) was added slowly and the biphasic mixture was warmed to rt. The organic layer was separated and the aqueous layer was extracted with Et₂O (3x 50 mL). The combined organic layers were washed with brine (25 mL), dried (MgSO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 85:15 hexanes:EtOAc) afforded desired alcohol **3.11** (1.24 g, 5.73 mmol, 82% yield) as a colorless oil, which was used immediately in the subsequent reaction.

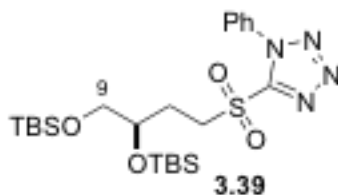
Primary alcohol **3.11** (600 mg, 2.77 mmol) was dissolved in DMF (5 mL). Imidazole (340 mg, 5.0 mmol) and *t*-butyldimethylsilyl chloride (500 mg, 3.3 mmol) were added and the reaction mixture was stirred at rt for 2 h. The reaction was quenched by addition of saturated sodium bicarbonate (5 mL). Et₂O (50 mL) was added and the organic layer was separated. The organic layer was washed with water (2x 10 mL), brine (10 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 hexanes:EtOAc) to afford desired alkene **3.36** (818 mg, 2.47 mmol, 89% yield) as a colorless oil: $R_f = 0.78$ (80:20 hexanes:EtOAc); $[\alpha]_D^{21.6} +3.45^\circ$ ($c = 1.43$, CH₂Cl₂); IR (film) ν 2955, 2929, 2857, 1643, 1472, 1463, 1361, 1255, 1113, 1004, 913, 835, 776 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.82 (ddd, $J = 7.2, 16.8, 16.8$ Hz, 1H), 5.02 (dd, $J = 17.4, 17.4$ Hz, 2H), 3.69 (ddd, $J = 5.4, 11.4, 5.4$ Hz, 1H), 3.48 (d, $J = 5.4, 10.2$ Hz, 1H), 3.40 (dd, $J = 6.6, 9.0$ Hz, 1H), 2.32 (ddd, $J = 5.4, 13.2, 5.4$ Hz, 1H), 2.14 (ddd, $J = 6.6, 13.8, 6.6$ Hz, 1H), 0.87 (s, 9H), 0.86 (s, 9H), 0.03 (s, 6H), 0.2 (s, 6H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 135.2, 116.8, 72.9, 66.9, 39.0, 26.0, 25.9, 18.4, 18.2, -4.36, -4.66, -5.30, -5.36 ppm; ESI-MS C₁₇H₃₈O₂Si₂ [M+Na⁺] calc. 353.23, found 353.23.



Primary alcohol 3.37: Alkene **3.36** (963 mg, 2.91 mmol) was dissolved in methanol (30 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. Ozone was bubbled through the solution until a blue color was observed, at which time oxygen was bubbled through the solution to removed excess ozone and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min. The reaction mixture was then warmed to $0\text{ }^{\circ}\text{C}$ and sodium borohydride (550 mg, 14.6 mmol) was added. The reaction mixture was slowly warmed over 2 h and then quenched with 10% HCl (15 mL). Ethyl acetate (50 mL) was added and the organic layer was separated. The aqueous layer was washed with EtOAc (2x 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (silica gel, 80:20 hexanes:EtOAc) to afford desired alcohol **3.37** (705 mg, 2.11 mmol, 72% yield) as a clear oil: $R_f = 0.54$ (80:20 hexanes:EtOAc); $[\alpha]_D^{23.8} +15.3^{\circ}$ ($c = 1.3$, CH_2Cl_2); IR (film) ν 3432, 2955, 2929, 2885, 2857, 1643, 1472, 1463, 1388, 1361, 1255, 1094, 1024, 835, 776 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 3.85 (ddd, $J = 4.8, 11.4, 4.8\text{ Hz}$, 1H), 3.73 (m, 2H), 3.57 (dd, $J = 4.8, 10.2\text{ Hz}$, 1H), 3.47 (dd, $J = 7.2, 9.6\text{ Hz}$, 1H), 2.72 (bs, 1H), 1.85 (m, 1H), 1.71 (m, 1H) 0.86 (s, 18H), 0.04 (s, 12H) ppm; ^{13}C NMR (CDCl_3 , 150 MHz) δ 72.3, 66.8, 59.7, 36.7, 26.0, 25.9, 25.8, 25.7, 18.3, 18.0, -4.47 , -4.96 , -5.41 , -5.45 ppm ; ESI-MS $\text{C}_{16}\text{H}_{38}\text{O}_3\text{Si}_2$ $[\text{M}+\text{H}^+]$ calc. 335.24, found 335.23.

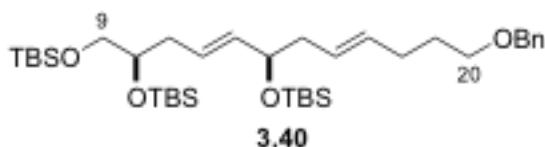


Thioether 3.38: Di-*iso*-propyl azodicarboxylate (0.33 mL, 1.68 mmol) was added to a mixture of primary alcohol **3.37** (550 mg, 1.64 mmol), triphenylphosphine (517 mg, 1.97 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (351 mg, 1.97 mmol) in THF (6.5 mL) at 0 °C. The reaction mixture was stirred for 15 h with slow warming to rt, after which time saturated ammonium chloride was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x 25 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (silica gel, 95:5 hexanes:EtOAc) to afford desired thioether **3.38** (609 mg, 1.23 mmol, 75% yield) as a clear oil: R_f = 0.63 (80:20 hexanes:EtOAc); $[\alpha]_D^{2318} +17.6^\circ$ (c = 0.26, CH₂Cl₂); IR (film) ν 2954, 2929, 2857, 1644, 1500, 1471, 1387, 1361, 1251, 1120, 1084, 835, 797 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.52 (m, 5H), 3.78 (m, 1H), 3.54 (d, J = 5.4, 10.2 Hz, 1H), 3.50 (m, 1H), 3.40 (m, 2H), 2.10 (m, 1H), 1.89 (ddd, J = 7.2, 13.8, 13.8 Hz, 1H), 0.85 (s, 9H), 0.85 (s, 9H), 0.03 (s, 6H), 0.01 (s, 6H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 154.4, 133.7, 130.0, 129.7, 123.8, 71.5, 66.7, 33.5, 29.4, 25.8, 25.85, 25.82, 25.79, 18.2, 18.0, -4.33, -4.83, -5.43, -5.45 ppm; ESI-MS C₂₃H₄₂N₄O₂SSi₂ [M+Na⁺] calc. 517.25, found 517.21.



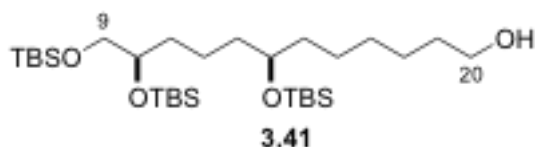
Sulfone 3.39: Thioether **3.38** (609 mg, 1.23 mmol) was dissolved in ethanol (12 mL) and cooled to 0 °C. A solution of ammonium molybdate tetrahydrate (306 mg, 0.25 mmol) in hydrogen peroxide (30%, 1.25 mL) was added dropwise to the solution of thioether **3.38**. The resultant bright yellow solution was stirred for 18 h, upon which time water (10 mL) was added. Ethyl acetate (20 mL) was added and the organic layer was separated. The aqueous

layer was washed with EtOAc (2x 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (silica gel, 95:5 hexanes:EtOAc) to afford desired sulfone **3.39** (517 mg, 0.98 mmol, 80% yield) as a colorless oil: $R_f = 0.63$ (80:20 hexanes:EtOAc); $[\alpha]_D^{25.3} 11.7^\circ$ ($c = 1.1$, CH₂Cl₂); IR (film) ν 2954, 2929, 2885, 2857, 1644, 1498, 1471, 1462, 1443, 1344, 1255, 1121, 1077, 835 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 7.67 (m, 2H), 7.60 (m, 3H), 3.84 (m, 3H), 3.57 (dd, $J = 4.8, 10.2$ Hz, 1H), 3.82 (dd, $J = 7.2, 10.2$ Hz, 1H), 2.20 (m, 1H), 2.09 (m, 1H), 0.87 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ¹³C NMR (CDCl₃, 150 MHz) δ 153.4, 133.1, 131.4, 129.7, 125.1, 70.5, 68.0, 66.3, 52.3, 26.5, 25.8, 25.7, 25.6, 18.2, 18.0, -4.45, -4.88, -5.45, -5.46 ppm; ESI-MS C₂₃H₄₂N₄O₄SSi₂ [M+Na⁺] calc. 549.24, found 549.19.



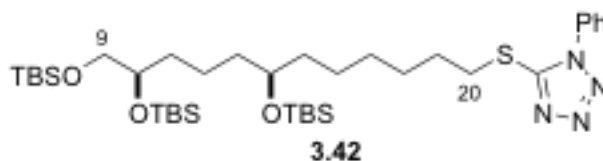
Benzyl ether 3.40: NaHMDS (0.75 M in THF, 0.33 mL, 0.237 mmol) was added dropwise to sulfone **3.39** (125 mg, 0.237 mmol) in THF (1.4 mL) at -78 °C. The resulting yellow solution was stirred at -78 °C for 30 min. A solution of aldehyde **3.35** (90 mg, 0.249 mmol) in THF was then added dropwise, and the reaction mixture was stirred for 3 h at -78 °C, followed by slow warming to rt and stirring for 12 h. Upon consumption of the starting materials, the reaction was quenched with H₂O (2 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (silica gel, 95:5 hexanes:EtOAc) to afford desired alkene **3.40** (101 mg, 0.152 mmol, 64% yield) as a colorless oil: $R_f = 0.72$ (80:20 hexanes:EtOAc); $[\alpha]_D^{25.3} -2.77^\circ$

($c = 0.32$, CH_2Cl_2); IR (film) ν 2954, 2929, 2895, 2857, 1645, 1472, 1406, 1360, 1254, 1103, 970, 835, 776 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 7.31 (m, 4H), 7.25 (m, 1H), 5.56 (ddd, $J = 6.6, 7.2, 6.6\text{ Hz}$, 1H), 5.42 (m, 3H), 4.47 (s, 2H), 4.00 (dd, $J = 6.6, 12.6\text{ Hz}$, 1H), 3.67 (ddd, $J = 5.4, 11.4, 5.4\text{ Hz}$, 1H), 3.44 (m, 4H), 2.23 (m, 1H), 2.14 (m, 3H), 2.07 (m, 2H), 1.66 (ddd, $J = 6.6, 13.2\text{ Hz}, 6.6\text{ Hz}$, 2H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 138.6, 135.6, 135.1, 131.9, 131.8, 128.3, 127.6, 127.4, 127.1, 126.9, 125.9, 73.7, 73.0, 72.8, 69.9, 66.7, 41.9, 37.1, 29.5, 29.3, 26.0, 25.89, 25.87, 25.84, 18.3, 18.2, 18.1, $-4.28, -4.35, -4.43, -4.72, -5.31, -5.37$ ppm.

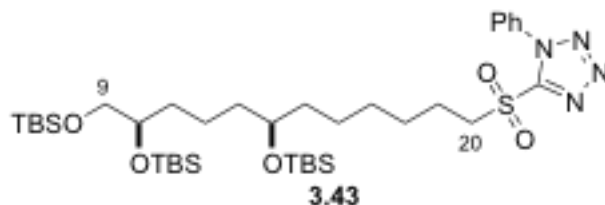


Primary alcohol 3.41: Benzyl ether **3.40** (150 mg, 0.226 mmol) was dissolved in ethanol (3 mL) and the solution was purged with argon. Palladium, 5% on activated carbon (100 mg) was added to the solution. The flask was placed under vacuum and backfilled with H_2 . This process was repeated and the solution was allowed to stir at rt under a hydrogen atmosphere for 18 h. Upon consumption of the starting material, the solution was filtered through a celite plug. Primary alcohol **3.41** (110 mg, 0.191 mmol, 84% yield) was obtained as a colorless oil and used without further purification. $R_f = 0.57$ (80:20 hexanes:EtOAc); $[\alpha]_D^{22.0} +7.15^\circ$ ($c = 0.38$, CH_2Cl_2); IR (film) ν 3338, 2930, 2857, 2738, 2709, 1078, 1472, 1462, 1405, 1388, 1361, 1254, 1109, 1078, 1005, 939, 835, 775 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 3.61 (m, 4H), 3.48 (dd, $J = 6.0, 10.2\text{ Hz}$, 1H), 3.37 (dd, $J = 6.6, 8.4\text{ Hz}$, 1H), 1.52 (m, 4H), 1.34 (m, 14H), 0.85 (s, 27H), 0.03 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H), 0.004 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 150 MHz) δ 73.2, 72.2, 67.4, 63.0, 37.4, 37.0, 34.6, 32.8, 29.7, 26.0,

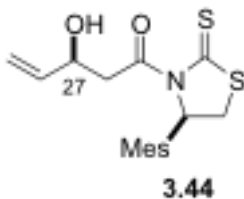
25.9, 25.91, 25.83, 25.75, 25.3, 20.8, 18.4, 18.14, 18.12, -4.3, -4.41, -4.44, -4.7, -5.3, -5.4 ppm; ESI-MS $C_{30}H_{68}O_4Si_3$ $[M+Na]^+$ calc. 599.43, found 599.49.



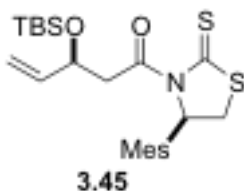
Thioether 3.42: Diisopropyl azodicarboxylate (0.06 mL, 0.294 mmol) was added to a mixture of primary alcohol **3.41** (166 mg, 0.288 mmol), triphenylphosphine (91 mg, 0.35 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (61 mg, 0.35 mmol) in THF (2.0 mL) at 0 °C. The reaction mixture was stirred for 15 h with slow warming to rt, after which time saturated ammonium chloride was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (silica gel, 95:5 hexanes:EtOAc) to afford desired thioether **3.42** (190 mg, 0.26 mmol, 89% yield) as a colorless oil: R_f = 0.43 (80:20 hexanes:EtOAc); $[\alpha]_D^{22.3} +7.22^\circ$ (c = 0.78, CH_2Cl_2); IR (film) ν 2952, 2929, 2857, 1598, 1500, 1471, 1462, 1408, 1387, 1253, 1105, 1005, 939, 835, 810, 775 cm^{-1} ; 1H NMR ($CDCl_3$, 600 MHz) δ 7.55 (m, 5H), 3.60 (m, 2H), 3.48 (dd, J = 5.4, 9.6 Hz, 1H), 3.38 (dd, J = 6.6, 6.6 Hz, 3H), 1.80 (ddd, J = 7.2, 14.4, 7.2 Hz, 2H), 1.50 (m, 1H), 1.39 (m, 8H), 1.29 (m, 7H), 0.85 (s, 28H), 0.03 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H), 0.004 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.5, 133.8, 130.1, 129.8, 123.9, 73.2, 72.2, 67.4, 37.4, 36.9, 34.6, 33.4, 29.3, 29.1, 28.7, 26.02, 25.96, 25.94, 25.87, 25.1, 20.9, 18.4, 18.18, 18.15, -4.2, -4.37, -4.41, -4.67, -5.27, -5.34 ppm; ESI-MS $C_{37}H_{72}N_4O_3SSi_3$ $[M]^+$ calc. 736.46, found 736.53.



Sulfone 3.43: Thioether **3.42** (223 mg, 0.301 mmol) was dissolved in ethanol (3.0 mL) and cooled to 0 °C. A solution of ammonium molybdate tetrahydrate (75 mg, 0.06 mmol) in hydrogen peroxide (30%, 0.3 mL) was added dropwise to the solution of **3.42**. The resultant bright yellow solution was stirred for 18 h, upon which time water (5 mL) was added. Ethyl acetate (20 mL) was added and the organic layer was separated. The aqueous layer was washed with EtOAc (2x 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (silica gel, 95:5 hexanes:EtOAc) to afford desired sulfone **3.43** (133 mg, 0.175 mmol, 58% yield) as a colorless oil: $R_f = 0.43$ (80:20 hexanes:EtOAc); $[\alpha]_D^{22.4} +4.69^\circ$ ($c = 0.30$, CH₂Cl₂); IR (film) ν 2952, 2929, 2857, 1498, 1462, 1343, 1254, 1153, 1106, 835, 775 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 7.67 (m, 2H), 7.59 (m, 3H), 3.71 (dd, $J = 7.6, 7.6$ Hz, 2H), 3.61 (ddd, $J = 6.0, 12.0, 6.0$ Hz, 2H), 3.48 (dd, $J = 5.4, 9.6$ Hz, 1H), 3.37 (dd, $J = 6.0, 9.6$ Hz, 1H), 1.93 (m, 2H), 1.48 (m, 3H), 1.38 (m, 5H), 1.31 (m, 4H), 1.25 (m, 2H), 0.85 (s, 27H), 0.02 (s, 18H) ppm; ¹³C NMR (CDCl₃, 150 MHz) δ 153.5, 133.0, 131.4, 129.7, 125.0, 37.4, 37.0, 34.6, 29.2, 28.2, 25.98, 25.90, 24.9, 22.0, 20.8, 18.4, 18.14, 18.10, -4.25, -4.40, -4.45, -4.70, -5.31, -5.38 ppm; ESI-MS C₃₇H₇₂N₄O₅SSi₃ [M⁺] calc. 768.45, found 768.54.

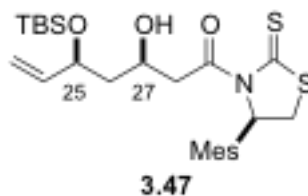


Aldol adduct 3.44: Titanium tetrachloride (0.56 mL, 5.14 mmol) was added dropwise to a solution of thiazolidinethione **3.10** (1.20 g, 4.28 mmol) in CH₂Cl₂ (20 mL) at –78 °C. The resulting orange solution was stirred 10 min, upon which time di-*iso*-propylethyl amine (0.90 mL, 5.14 mmol) was added dropwise. The purple solution was stirred for 45 min at –78 °C, after which time acrolein (0.58 mL, 8.56 mmol, distilled over calcium hydride) was added dropwise. The reaction mixture was stirred for 3 h at –78 °C, and then ½ saturated ammonium chloride (20 mL) was added and the mixture warmed to rt. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (silica gel, 85:15 hexanes:EtOAc) to afford desired alcohol **3.44** (800 mg, 2.39 mmol, 56% yield) as a yellow oil. Physical data obtained for **3.44** agreed with the data of the known compound prepared using the same procedure.



S,S- 3.45: A solution of secondary alcohol **3.44** (800 mg, 2.38 mmol) in CH₂Cl₂ (24 mL) was cooled to 0 °C. 2,6-Lutidine (0.83 mL, 7.15 mmol) was added dropwise to the solution followed by TBSOTf (0.82 mL, 3.58 mmol). The reaction mixture was stirred for 2 h at 0 °C before addition of saturated sodium bicarbonate (20 mL). The organic layer was separated

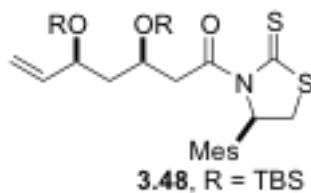
and the aqueous layer was extracted with CH₂Cl₂ (3x 30 mL). The combined organic layers were washed with brine (25 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 hexanes:EtOAc) to afford desired TBS ether **3.45** (930 mg, 2.06 mmol, 87% yield) as a yellow oil: *R*_f = 0.62 (80:20 hexanes:EtOAc); [α]_D^{24.0} −37.2° (c = 1.6, CH₂Cl₂); IR (film) ν 3434, 2954, 2856, 2360, 1707, 1644, 1461, 1370, 1256, 1183, 1121, 851, 836 cm^{−1}; ¹H NMR (CDCl₃, 600 MHz) δ 6.81 (s, 2H), 6.31 (dd, *J* = 9.6, 19.6 Hz, 1H), 5.41 (ddd, *J* = 5.4, 10.2, 16.6 Hz, 1H), 4.97 (d, *J* = 16.6 Hz, 1H), 4.77 (d, *J* = 10.2 Hz, 1H), 4.55 (dd, *J* = 6.0, 13.2 Hz, 1H), 3.62 (dd, *J* = 5.4, 17.4 Hz, 1H), 3.53 (dd, *J* = 11.4, 11.4 Hz, 1H), 3.33 (dd, *J* = 10.6, 10.6 Hz, 1H), 3.09 (dd, *J* = 8.4, 16.6 Hz, 1H), 2.34 (s, 6H), 2.23 (s, 3H), 0.83 (s, 9H), −0.01 (s, 3H), −0.03 (s, 3H) ppm; ¹³C NMR (CDCl₃, 150 MHz) δ 200.8, 172.8, 139.3, 137.9, 137.8, 132.4, 129.0, 128.2, 125.3, 114.4, 70.1, 67.9, 48.5, 32.7, 25.8, 21.4, 20.8, 20.3, 18.1, −4.66, −5.04 ppm; ESI-MS C₂₃H₃₅NO₂S₂Si [M+Na⁺] calc. 472.18, found 472.14.



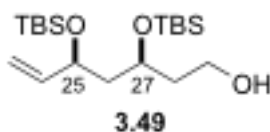
Iterative aldol adduct 3.47: Aldehyde **3.46**: Thiomide **3.45** (930 mg, 2.06 mmol) was dissolved in CH₂Cl₂ (20 mL) and the resulting yellow solution was cooled to −78 °C. Di-*iso*-butylaluminum hydride (1.0 M, 4.5 mL, 4.5 mmol) was added dropwise until the yellow color disappeared. Saturated potassium sodium tartrate (15 mL) was immediately added and the biphasic mixture was warmed to rt and stirred vigorously until two layers had formed (~2 h). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2x 20 mL). The combined organic layers were washed with brine (25 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10

hexanes:EtOAc) to afford desired aldehyde **3.46** (355 mg, 1.55 mmol, 75% yield) as a clear liquid which was used immediately for the iterative acetate aldol.

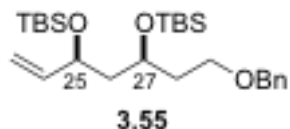
Titanium tetrachloride (0.24 mL, 2.21 mmol) was added dropwise to a solution of thiazolidinethione **3.10** (620 mg, 2.21 mmol) in CH₂Cl₂ (22 mL) at –78 °C. The resulting orange solution was stirred 10 min, upon which time di-*iso*-propylethyl amine (0.38 mL, 2.21 mmol) was added dropwise. The purple solution was stirred for 45 min at –78 °C, after which time aldehyde **3.46** (460 mg, 2.01 mmol) was added dropwise in CH₂Cl₂ (2 mL). The mixture was stirred for 1.5 h at –78 °C, and then ½ saturated ammonium chloride (20 mL) was added and the mixture was warmed to rt. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 hexanes:EtOAc) to afford desired alcohol **3.47** (760 mg, 1.51 mmol, 75% yield, >20:1) as yellow needle-like crystals: R_f = 0.38 (80:20 hexanes:EtOAc); $[\alpha]_D^{23.8}$ –120.6° (c = 0.10, CH₂Cl₂); IR (film) ν 2955, 2928, 2856, 2088, 1644, 1371, 1325, 1257, 1176, 1128, 1078, 922, 835 cm^{–1}; ¹H NMR (CDCl₃, 600 MHz) δ 6.80 (bs, 2H), 6.35 (dd, J = 10.2, 10.2 Hz, 1H), 5.68 (ddd, J = 6.6, 10.2, 16.6 Hz, 1H), 5.06 (d, J = 16.6 Hz, 1H), 5.00 (d, J = 10.2 Hz, 1H), 4.24 (dd, J = 6.6, 12.6 Hz, 1H), 4.06 (m, 1H), 3.55 (m, 2H), 1.62 (m, 1H), 1.35 (ddd, J = 3.0, 5.4, 8.4 Hz, 1H), 0.84 (s, 9H), 0.02 (s, 3H), –0.002 (s, 3H) ppm; ¹³C NMR (CDCl₃, 150 MHz) δ 201.3, 174.0, 140.7, 137.7, 132.6, 114.6, 73.2, 68.0, 66.7, 60.34, 47.1, 43.6, 34.6, 32.5, 31.5, 25.8, 22.6, 20.7, 18.0, 14.1, –4.16, –4.94 ppm.



TBS ether 3.48: Secondary alcohol **3.47** (760 mg, 1.49 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C. 2,6-Lutidine (0.52 mL, 4.48 mmol) was added dropwise followed by TBSOTf (0.48 mL, 2.10 mmol). The reaction mixture was stirred for 2 h at 0 °C before addition of saturated sodium bicarbonate (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x 30 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 hexanes:EtOAc) to afford desired TBS ether **3.48** (800 mg, 1.32 mmol, 88% yield) as a yellow oil: $R_f = 0.63$ (80:20 hexanes:EtOAc); $[\alpha]_D^{24.1} -49.1^\circ$ ($c = 0.74$, CH_2Cl_2); IR (film) ν 2954, 2928, 2856, 1712, 1611, 1471, 1370, 1256, 1175, 1099, 835, 776 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 6.80 (s, 2H), 6.31 (dd, $J = 9.6, 19.6$ Hz, 1H), 5.47 (ddd, $J = 6.6, 10.2, 16.6$ Hz, 1H), 4.99 (d, $J = 16.6$ Hz, 1H), 4.93 (d, $J = 10.2$ Hz, 1H), 4.07 (m, 2H), 3.60 (dd, $J = 4.6, 16.6$ Hz, 1H), 3.53 (dd, $J = 10.6$ Hz, 1H), 3.34 (dd, $J = 10.6$ Hz, 1H), 3.08 (dd, $J = 7.6, 17.4$ Hz, 1H), 2.34 (s, 6H), 2.21 (s, 3H), 1.48 (ddd, $J = 5.4, 7.6, 13.6$ Hz, 1H), 1.14 (ddd, $J = 4.6, 7.6, 13.2$ Hz, 1H), 0.84 (s, 9H), 0.82 (s, 9H), -0.004 (s, 3H), -0.017 (s, 3H), -0.037 (s, 3H), -0.044 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 150 MHz) δ 200.8, 173.1, 140.8, 137.9, 132.2, 114.3, 70.7, 67.9, 66.4, 48.1, 45.2, 32.6, 25.84, 25.79, 20.7, 20.3, 18.1, 17.9, -4.32 , -4.48 , -4.65 , -4.89 ppm; ESI-MS $\text{C}_{31}\text{H}_{53}\text{NO}_3\text{S}_2\text{Si}_2$ $[\text{M}+\text{Na}^+]$ calc. 630.29, found 630.24.

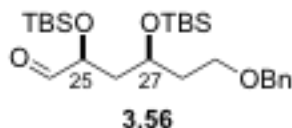


Primary alcohol 3.49: Lithium borohydride (0.70 mL, 1.40 mmol) was added dropwise to a solution of **3.48** (775 mg, 1.28 mmol) and methanol (0.05 mL, 1.28 mmol) in Et₂O (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h after which time saturated sodium bicarbonate (10 mL) was added slowly and the biphasic mixture was warmed to rt. The organic layer was separated and the aqueous layer was extracted with Et₂O (3x 50 mL). The combined organic layers were washed with brine (25 mL), dried (MgSO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 85:15 hexanes:EtOAc) to afford desired alcohol **3.39** (431 mg, 1.15 mmol, 90% yield) as a colorless oil: $R_f = 0.67$ (80:20 hexanes:EtOAc); $[\alpha]_D^{23.2} -20.8^\circ$ ($c = 0.4$, CH₂Cl₂); IR (film) ν 3374, 3079, 2952, 2886, 2857, 2738, 2709, 1644, 1472, 1462, 1419, 1406, 1387, 1361, 1255, 1080, 1005, 937, 924, 836, 775 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 5.76 (ddd, $J = 6.0, 10.2, 23.4$ Hz, 1H), 5.12 (d, $J = 17.4$ Hz, 1H), 5.02 (d, $J = 10.6$ Hz, 1H), 4.09 (m, 1H) ppm, 4.07 (m, 1H), 3.82 (m, 1H), 3.70 (ddd, $J = 5.4, 10.6, 16.0$ Hz, 1H), 2.52 (dd, $J = 4.8, 4.8$ Hz, 1H), 1.88 (m, 1H), 1.77 (ddd, $J = 4.8, 8.4, 13.2$ Hz, 1H), 1.66 (ddd, $J = 4.8, 8.4, 13.2$ Hz, 2H), 0.86 (s, 18H), 0.07 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 141.4, 114.05, 71.2, 69.1, 60.1, 45.0, 37.4, 25.8, 18.1, 17.8, -4.2, -4.5, -4.74, -4.94 ppm; ESI-MS C₁₉H₄₂O₃Si₂ [M+Na⁺] calc. 397.25, found 397.25.



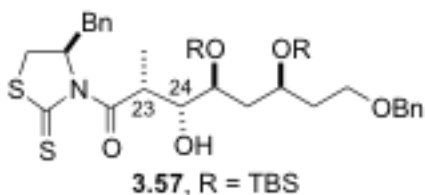
Benzyl ether 3.55: Primary alcohol **3.49** (673 mg, 1.79 mmol), the Dudley reagent (1.30 g, 3.73 mmol), and magnesium oxide (151 mg, 3.73 mmol) were dissolved in dichloroethane (10 mL) in a 50 mL round bottom flask equipped with a reflux condensor. The reaction mixture was heated to 85 °C and stirred for 20 h. The reaction mixture was then cooled to rt, filtered, and concentrated. The residue was purified by flash column chromatography (silica

gel, 90:10 hexanes:EtOAc) to afford desired benzyl ether **3.55** (722 mg, 1.55 mmol, 86% yield) as a colorless oil: $R_f = 0.85$ (80:20 hexanes:EtOAc); $[\alpha]_D^{23.2} -4.35^\circ$ ($c = 1.7$, CH_2Cl_2); IR (film) ν 3066, 3030, 2954, 2929, 2885, 2857, 1472, 1462, 1387, 1360, 1254, 1095, 1028, 1005, 924, 836, 775 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 7.31 (m, 5H), 5.77 (ddd, $J = 6.0$, 10.2, 16.6 Hz, 1H), 5.11 (d, $J = 16.6$ Hz, 1H), 5.00 (d, $J = 10.2$ Hz, 1H), 4.46 (dd, $J = 12.0$, 21.0 Hz, 2H), 4.17 (dd, $J = 6.6$, 12.6 Hz, 1H), 3.91 (dd, $J = 6.0$, 6.0 Hz, 1H), 3.52 (m, 2H), 1.85 (m, 1H), 1.72 (ddd, $J = 5.4$, 7.2, 13.2 Hz, 2H), 1.55 (m, 1H), 0.86 (s, 18H), 0.02 (s, 12H) ppm; ^{13}C NMR (CDCl_3 , 150 MHz) δ 141.6, 138.6, 128.3, 127.58, 127.55, 127.4, 113.8, 72.9, 71.8, 71.1, 66.9, 66.7, 46.2, 37.0, 25.88, 25.85, 18.1, 18.0, -4.23 , -4.36 , -4.41 , -4.53 , -4.86 ppm; ESI-MS $\text{C}_{26}\text{H}_{48}\text{O}_3\text{Si}_2$ $[\text{M}+\text{Na}^+]$ calc. 487.30, found 487.29.

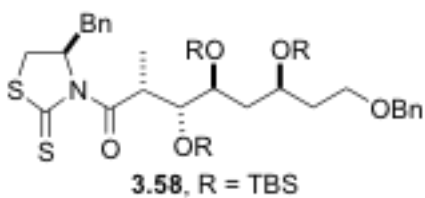


Aldehyde 3.56: Alkene **3.55** (1.75 g, 3.76 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to -78°C . Ozone was bubbled through the solution until a blue color was observed, at which time oxygen was bubbled through the solution to removed excess ozone and the reaction mixture was stirred at -78°C for 15 min. Dimethyl sulfide was added dropwise to the mixture at -78°C . The reaction mixture was slowly warmed for 2 h and then concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 hexanes:EtOAc) to afford desired aldehyde **3.56** (1.45 g, 3.11 mmol, 82% yield) as a colorless oil: $R_f = 0.66$ (80:20 hexanes:EtOAc); $[\alpha]_D^{22.5} -2.13^\circ$ ($c = 0.98$, CH_2Cl_2); IR (film) ν 3065, 3031, 2954, 2929, 2885, 2857, 1734, 1472, 1462, 1361, 1114, 1049, 1005, 939, 837, 808, 777 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 9.56 (s, 1H), 7.30 (m, 5H), 4.45 (dd, $J = 4.2$, 7.2 Hz, 2H), 4.07 (m, 2H), 3.51 (m, 2H), 1.80 (m, 4H), 0.88 (s, 9H), 0.85 (s, 9H), 0.03 (s, 12H)

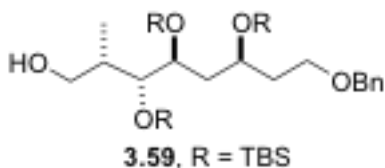
ppm; ^{13}C NMR (CDCl_3 , 150 MHz) δ 203.7, 128.3, 127.6, 127.5, 74.9, 73.0, 66.5, 65.7, 40.6, 36.9, 25.8, 25.7, 25.6, 18.1, 17.9, -4.39 , -4.60 , -4.63 , -5.01 ppm; ESI-MS $\text{C}_{25}\text{H}_{46}\text{O}_4\text{Si}_2$ [M^+] calc.466.29, found 466.32.



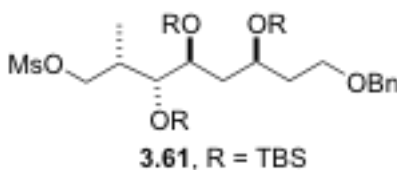
Propionate aldol adduct 3.57: Titanium tetrachloride (0.097 mL, 0.881 mmol) was added dropwise to a solution of thiazolidinethione **3.8** (194 mg, 0.731 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The resulting orange solution was stirred 10 min, upon which time di-*iso*-propylethyl amine (0.15 mL, 0.881 mmol) and *N*-methyl pyrrolidinone (0.085 mL, 0.881 mmol) were added dropwise. The dark red solution was stirred for 45 min at -78 °C, after which time aldehyde **3.56** (252 mg, 0.541 mmol) was added dropwise in CH_2Cl_2 (3 mL). The reaction mixture was slowly warmed to 0 °C over 3 h. The reaction was quenched with $\frac{1}{2}$ saturated ammonium chloride (5 mL) and warmed to rt. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 hexanes:EtOAc) to provide an inseparable mixture of desired alcohol **3.47** and thioimide **3.8** as a yellow semi-solid. The product was carried forward without further purification.



TBS ether 3.58: A solution of crude secondary alcohol **3.57** in CH₂Cl₂ (10 mL) was cooled to 0 °C. 2,6-Lutidine (0.21 mL, 1.79 mmol) was added dropwise to the solution followed by TBSOTf (0.21 mL, 0.89 mmol). The reaction mixture was stirred for 2 h at 0 °C before addition of saturated sodium bicarbonate (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 90:10 hexanes:EtOAc) to afford desired TBS ether **3.58** (290 mg, 0.29 mmol, 52% yield, 2 steps) as yellow needle-like crystals: $R_f = 0.53$ (80:20 hexanes:EtOAc); $[\alpha]_D^{22.6} -135.8^\circ$ ($c = 0.89$, CH₂Cl₂); IR (film) ν 3064, 3028, 2955, 2929, 2886, 2856, 1686, 1496, 1472, 1461, 1362, 1340, 1251, 1191, 1130, 1106, 1052, 1029, 941, 835, 775, 741, 699 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 7.28 (m, 10H), 5.22 (m, 1H), 4.43 (dd, $J = 11.4, 18.0$ Hz, 2H), 4.26 (dd, $J = 7.2, 9.6$ Hz, 1H), 4.05 (d, $J = 9.6$ Hz, 1H), 3.94 (dd, $J = 10.2, 10.2$ Hz, 1H), 3.54 (m, 2H), 3.40 (d, $J = 10.2$ Hz, 1H), 3.36 (dd, $J = 6.6, 11.4$ Hz, 1H), 3.22 (dd, $J = 3.6, 13.2$ Hz, 1H), 3.02 (dd, $J = 10.8, 13.2$ Hz, 1H), 1.83 (ddd, $J = 3.0, 10.8, 13.6$ Hz, 1H), 1.71 (m, 1H), 1.58 (m, 1H), 1.43 (dd, $J = 11.4, 13.6$ Hz, 1H), 1.32 (d, $J = 6.6$ Hz, 3H), 0.94 (s, 9H), 0.90 (s, 9H), 0.86 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.13 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H), 0.003 (s, 3H) ppm; ¹³C NMR (CDCl₃, 150 MHz) δ 200.7, 177.0, 138.6, 136.6, 129.5, 129.0, 128.2, 127.7, 127.4, 127.2, 80.2, 73.6, 73.0, 68.9, 67.3, 66.6, 42.3, 41.1, 36.6, 36.4, 31.8, 26.2, 26.1, 26.0, 25.9, 25.8, 18.5, 18.1, 18.0, 15.9, -3.18, -3.19, -4.18, -4.80, -4.86, -5.00 ppm; ESI-MS C₄₄H₇₅NO₅S₂Si₃ [M+Na⁺] calc. 868.43, found 868.36.

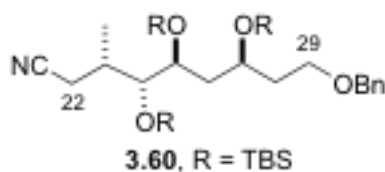


Primary alcohol 3.59: Lithium borohydride (0.19 mL, 0.38 mmol) was added dropwise to a solution of **3.58** (291 mg, 0.34 mmol) and methanol (0.02 mL, 0.34 mmol) in Et₂O (3.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h after which time saturated sodium bicarbonate (5 mL) was added slowly and the biphasic mixture was warmed to rt. The organic layer was separated and the aqueous layer was extracted with Et₂O (3x 15 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 85:15 hexanes:EtOAc) to afford desired alcohol **3.59** (194 mg, 0.30 mmol, 88% yield) as a colorless oil: $R_f = 0.55$ (80:20 hexanes:EtOAc); $[\alpha]_D^{24.1} -17.9^\circ$ ($c = 1.2$, CH₂Cl₂); IR (film) ν 3447, 2955, 2929, 2889, 2859, 1472, 1387, 1360, 1254, 1095, 1042, 938, 869, 835, 774 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 7.30 (m, 4H), 7.25 (m, 1H), 4.45 (dd, $J = 11.4, 20.4$ Hz, 2H), 3.95 (dd, $J = 10.2, 10.2$ Hz, 1H), 3.76 (d, $J = 10.2$ Hz, 1H), 3.67 (d, $J = 4.8$ Hz, 1H), 3.60 (dd, $J = 7.8, 15$ Hz, 1H), 3.52 (dd, $J = 7.2, 15.6$ Hz, 1H), 3.44 (m, 1H), 3.38 (m, 1H), 2.09 (dd, $J = 5.4, 5.4$ Hz, 1H), 1.87 (m, 1H), 1.81 (m, 1H), 1.73 (ddd, $J = 6.6, 12.6, 6.6$ Hz, 1H), 1.60 (m, 2H), 0.88 (s, 9H), 0.87 (s, 9H), 0.84 (s, 12H), 0.11 (s, 3H), 0.05 (s, 3H), 0.03 (s, 9H), -0.01 (s, 3H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 138.4, 128.3, 127.9, 127.5, 79.6, 73.2, 73.0, 67.1, 67.0, 65.6, 41.6, 40.2, 36.0, 26.06, 26.02, 25.8, 18.3, 18.04, 18.00, 13.3, -3.46, -4.26, -4.69, -4.80, -5.10 ppm; ESI-MS C₃₄H₆₈O₅Si₃ [M+Na⁺] calc. 663.43, found 663.38.



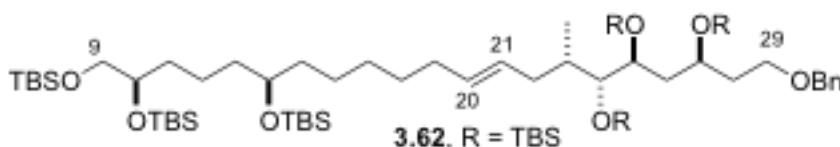
Mesylate 3.61: A solution of alcohol **3.59** (134 mg, .209 mmol) in CH₂Cl₂ (2.0 mL) was cooled to 0 °C. Triethyl amine (0.035 mL, 0.251 mmol) was added dropwise to the solution, followed by the addition of mesyl chloride (0.02 mL, 0.251 mmol). The mixture was stirred

for 1 h at 0 °C, after which time saturated ammonium chloride (5 mL) was added. The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (2x 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 85:15 hexanes:EtOAc) to afford desired mesylate **3.61** (110 mg, 0.153 mmol, 73% yield) as a colorless oil: *R*_f = 0.55 (80:20 hexanes:EtOAc); [α]_D^{23.8} –10.7° (*c* = 0.10, CH₂Cl₂); IR (film) ν 2955, 2929, 2894, 1644, 1472, 1360, 1252, 1178, 1096, 1045, 949, 835 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 7.30 (s, 4H), 7.25 (m, 1H), 4.45 (dd, *J* = 11.4, 22.2 Hz, 2H), 4.05 (dd, *J* = 9.6, 9.6 Hz, 1H), 4.00 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.95 (m, 1H), 3.70 (d, *J* = 3.6 Hz, 1H), 3.64 (m, 1H), 3.56 (m, 1H), 3.52 (dd, *J* = 7.2, 15.0 Hz, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.77 (ddd, *J* = 3.0, 5.4, 13.8 Hz, 1H), 1.54 (m, 2H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H), 0.00 (s, 3H) ppm; ¹³C NMR (CDCl₃, 150 MHz) δ 138.5, 128.2, 127.8, 127.4, 73.5, 73.1, 71.8, 67.0, 66.8, 41.9, 37.6, 37.3, 36.2, 26.0, 25.97, 25.8, 25.6, 18.3, 18.0, 11.9, –3.32, –3.58, –3.62, –4.27, –4.68, –4.81, –5.15, ppm.



Nitrile 3.60: Mesylate **3.61** (110 mg, 0.153 mmol) and potassium cyanide (12 mg, 0.184 mmol) were dissolved in DMSO (1 mL). The mixture was heated to 50 °C and stirred for 4 h after which time the reaction was cooled to rt and water (5 mL) and diethyl ether (25 mL) were added. The organic layer was separated and the aqueous layer was washed with diethyl ether (2x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column

chromatography (silica gel, 90:10 hexanes:EtOAc) to afford desired nitrile **3.60** (75 mg, 0.115 mmol, 75% yield) as a clear oil: $R_f = 0.75$ (80:20 hexanes:EtOAc); $[\alpha]_D^{23.8} -19.6^\circ$ ($c = 1.3$, CH_2Cl_2); IR (film) ν 2955, 2929, 2886, 2857, 2366, 2341, 1644, 1496, 1472, 1462, 1387, 1360, 1255, 1096, 939, 867, 835, 775 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 7.30 (m, 4H), 7.25 (m, 1H), 4.45 (dd, $J = 11.4, 22.6$ Hz, 2H), 3.95 (m, 1H), 3.60 (m, 2H), 3.57 (dd, $J = 6.6, 6.6$ Hz, 1H), 3.51 (dd, $J = 7.2, 15.6$ Hz, 1H), 2.29 (dd, $J = 6.0, 16.8$ Hz, 1H), 2.16 (dd, $J = 7.8, 16.8$ Hz, 1H), 1.93 (m, 1H), 1.85 (m, 1H), 1.75 (dd, $J = 10.6, 10.6$ Hz, 1H), 1.57 (m, 2H), 1.00 (d, $J = 6.6$ Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H), -0.01 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 138.4, 128.2, 127.8, 127.5, 119.0, 79.1, 73.12, 73.10, 66.9, 66.7, 41.9, 36.1, 35.1, 26.0, 25.8, 22.2, 18.3, 18.0, 17.9, 15.2, -3.34 , -3.52 , -4.31 , -4.67 , -4.84 , -5.03 ppm.



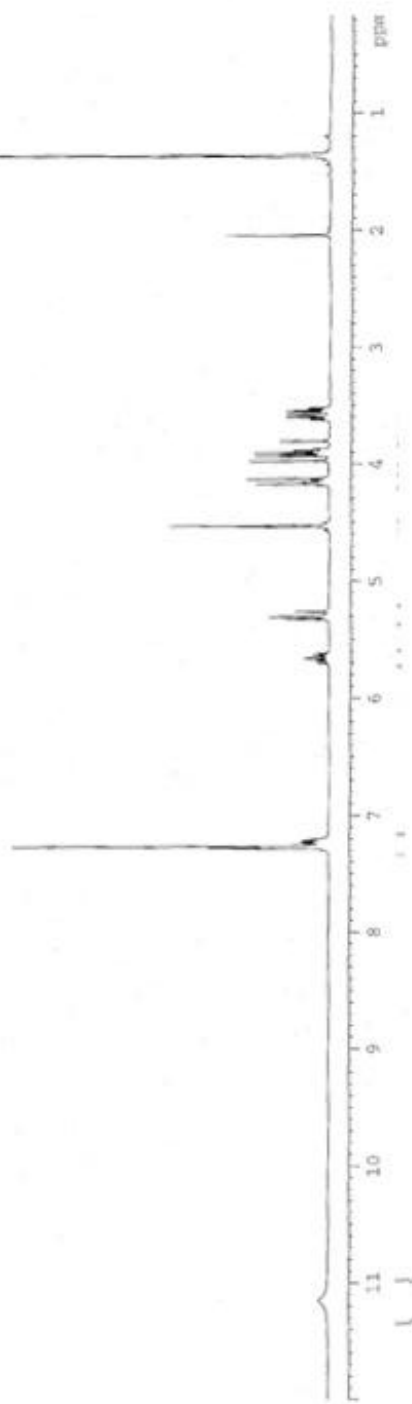
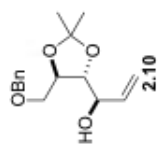
Alkene 3.62: **Aldehyde 3.4:** Di-*iso*-butylaluminum hydride (1.0 M in CH_2Cl_2 , 0.3 mL, 0.30 mmol) was added dropwise to a solution of nitrile **3.60** (75 mg, 0.115 mmol) in CH_2Cl_2 (1.1 mL) at -78°C . The reaction mixture was stirred for 1 h at -78°C at which time saturated potassium sodium tartrate (5 mL) was added. The mixture was warmed to rt and stirred for 3 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (90:10, silica plug) to yield desired aldehyde **3.4** which was used immediately for the Julia-Kocienski olefination.

KHMDS (0.50 M, 0.14 mL, 0.069 mmol) was added dropwise to a solution of sulfone **3.43** (55 mg, 0.069 mmol) and aldehyde **3.4** (45 mg, 0.069 mmol) in THF (0.35 mL) at -78°C .

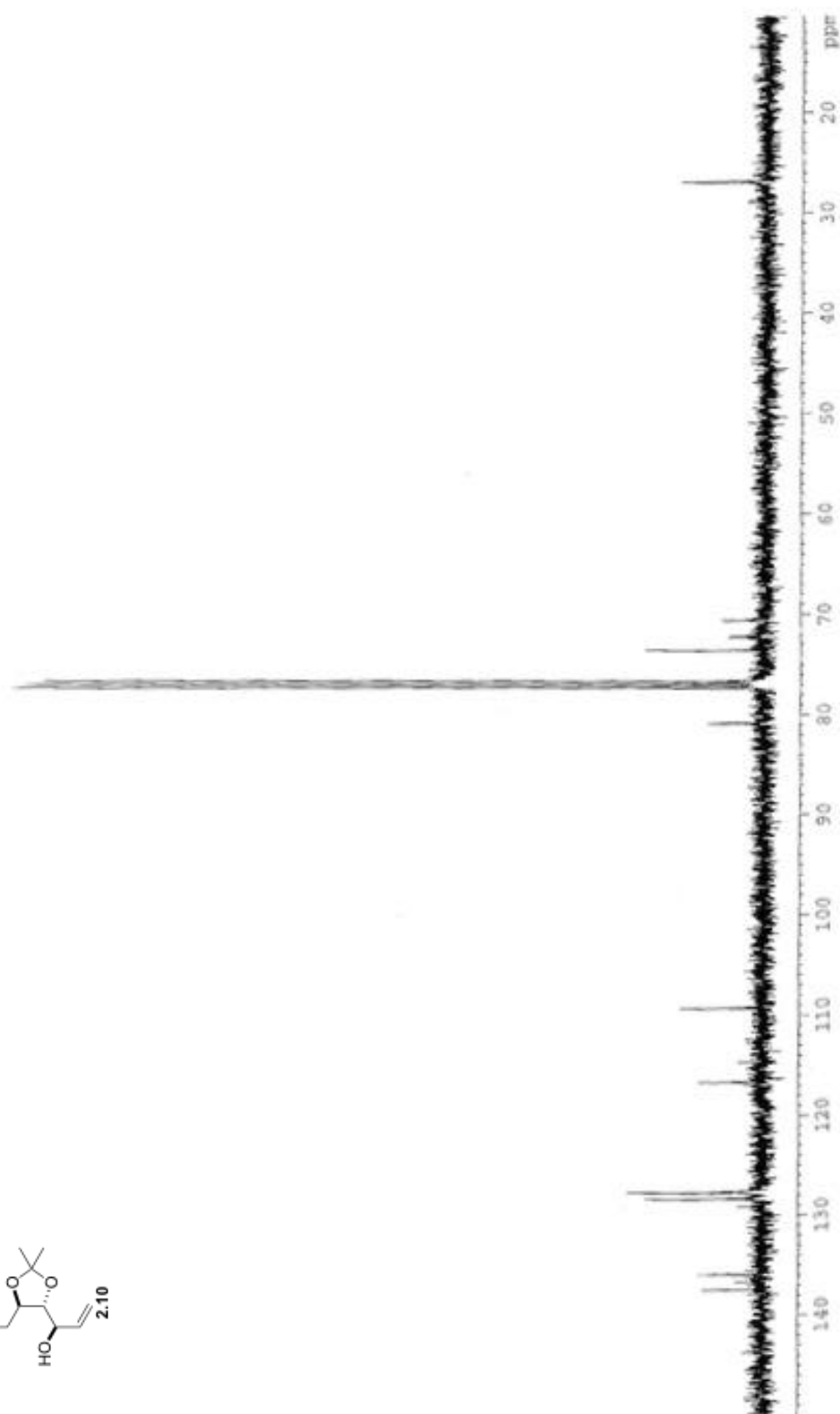
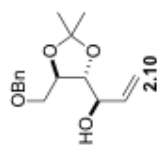
°C. The resulting yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h, and then slowly warmed to rt and stirred for 12 h. Upon consumption of the starting materials, H_2O (2 mL) was added to the cloudy white solution and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (silica gel, 95:5 hexanes:EtOAc) to afford desired alkene **3.62** (46 mg, 0.043 mmol, 62% yield) as a colorless oil: $R_f = 0.87$ (80:20 hexanes:EtOAc); $[\alpha]_D^{22.4} -9.7^{\circ}$ ($c = 0.85$, CH_2Cl_2); IR (film) ν 2954, 2929, 2857, 1472, 1462, 1360, 1254, 1101, 1004, 968, 939, 835, 808, 774, 732, 696 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 7.31 (s, 5H), 5.37 (ddd, $J = 6.6, 15.0, 6.6\text{ Hz}$, 1H), 5.27 (ddd, $J = 7.2, 13.6, 7.2\text{ Hz}$, 1H), 4.45 (dd, $J = 12.0, 22.6\text{ Hz}$, 2H), 3.93 (m, 1H), 3.47-3.63 (m, 7H), 3.38 (dd, $J = 6.0, 10.2\text{ Hz}$, 1H), 2.09 (m, 1H), 1.95 (dd, $J = 6.6, 13.6\text{ Hz}$, 2H), 1.89 (m, 1H), 1.79 (ddd, $J = 3.0, 10.2, 13.6\text{ Hz}$, 1H), 1.70 (m, 1H), 1.53-1.23 (m, 20H), 0.86 (s, 54H), 0.09 (s, 3H), 0.01 (s, 33H) ppm; ^{13}C NMR (CDCl_3 , 150 MHz) δ 138.5, 132.2, 128.5, 127.7, 127.4, 80.9, 73.1, 73.0, 72.9, 72.2, 67.4, 67.3, 67.0, 41.3, 38.2, 37.3, 37.0, 36.3, 34.6, 32.7, 29.6, 29.4, 26.1, 26.0, 25.99, 25.93, 25.90, 25.8, 25.2, 20.9, 18.4, 18.2, 18.1, 18.0, 15.3, -3.27 , -3.39 , -4.25 , -4.42 , -4.43 , -4.58 , -4.73 , -4.84 , -5.29 , -5.38 ppm; ESI-MS $\text{C}_{65}\text{H}_{134}\text{O}_7\text{Si}_6$ $[\text{M}+\text{H}^+]$ calc. 1195.88, found 1195.79.

C. Selected ^1H and ^{13}C Spectra

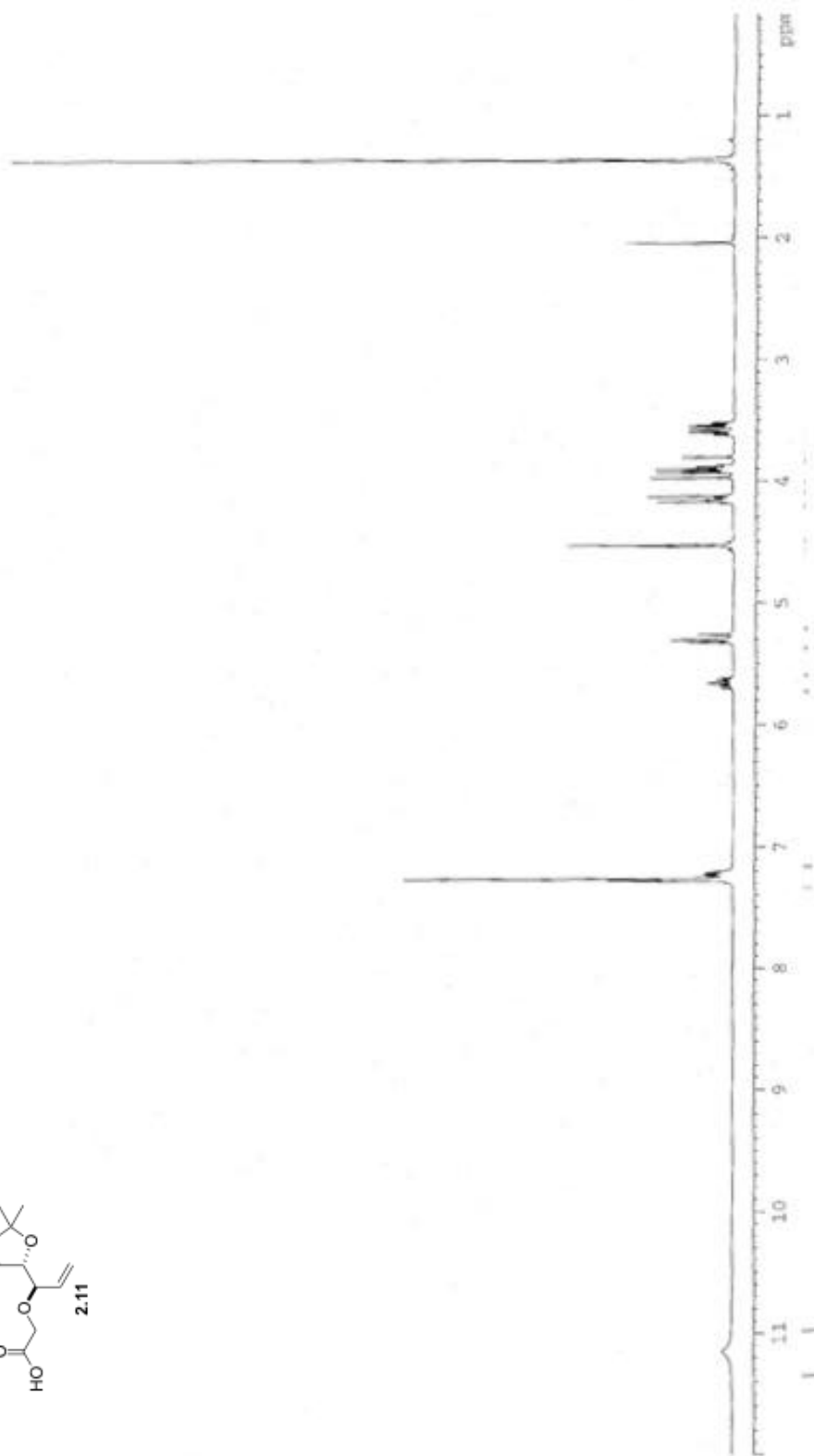
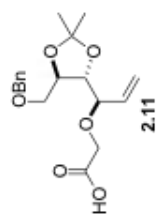
^1H NMR (400 MHz) of acid **2.11** (in CDCl_3)



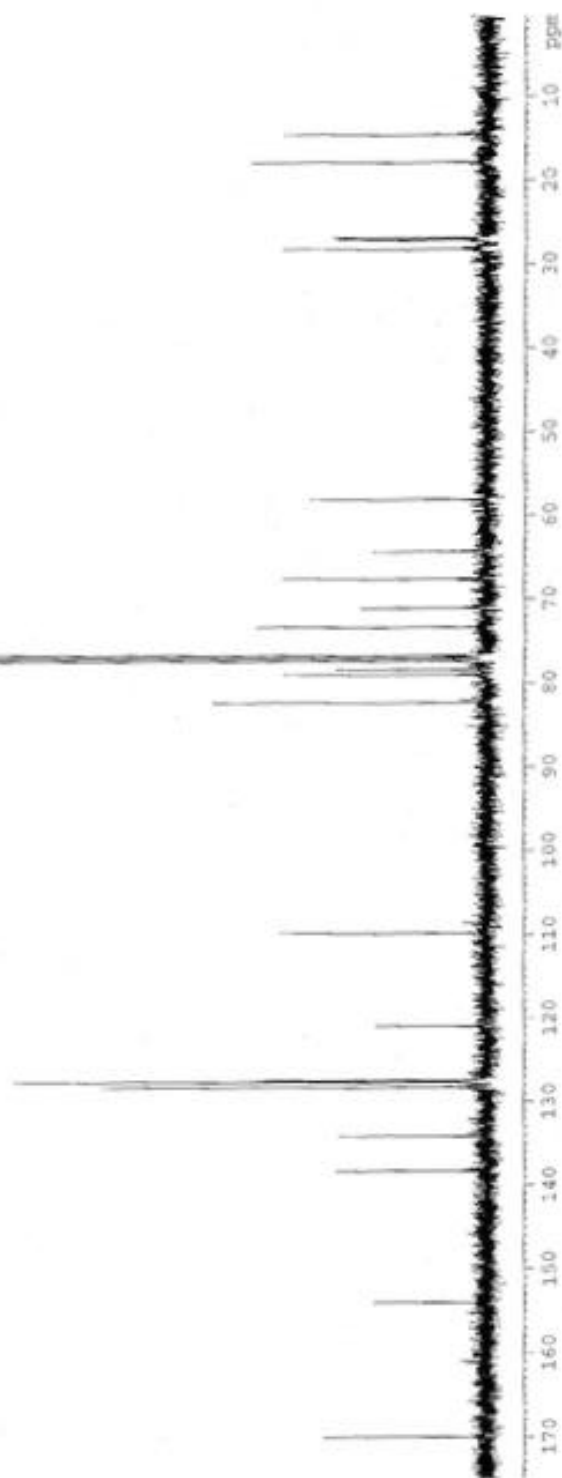
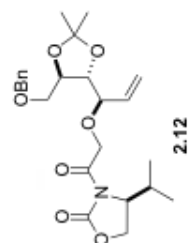
^{13}C NMR (100 MHz) of alcohol **2.10** (in CDCl_3)



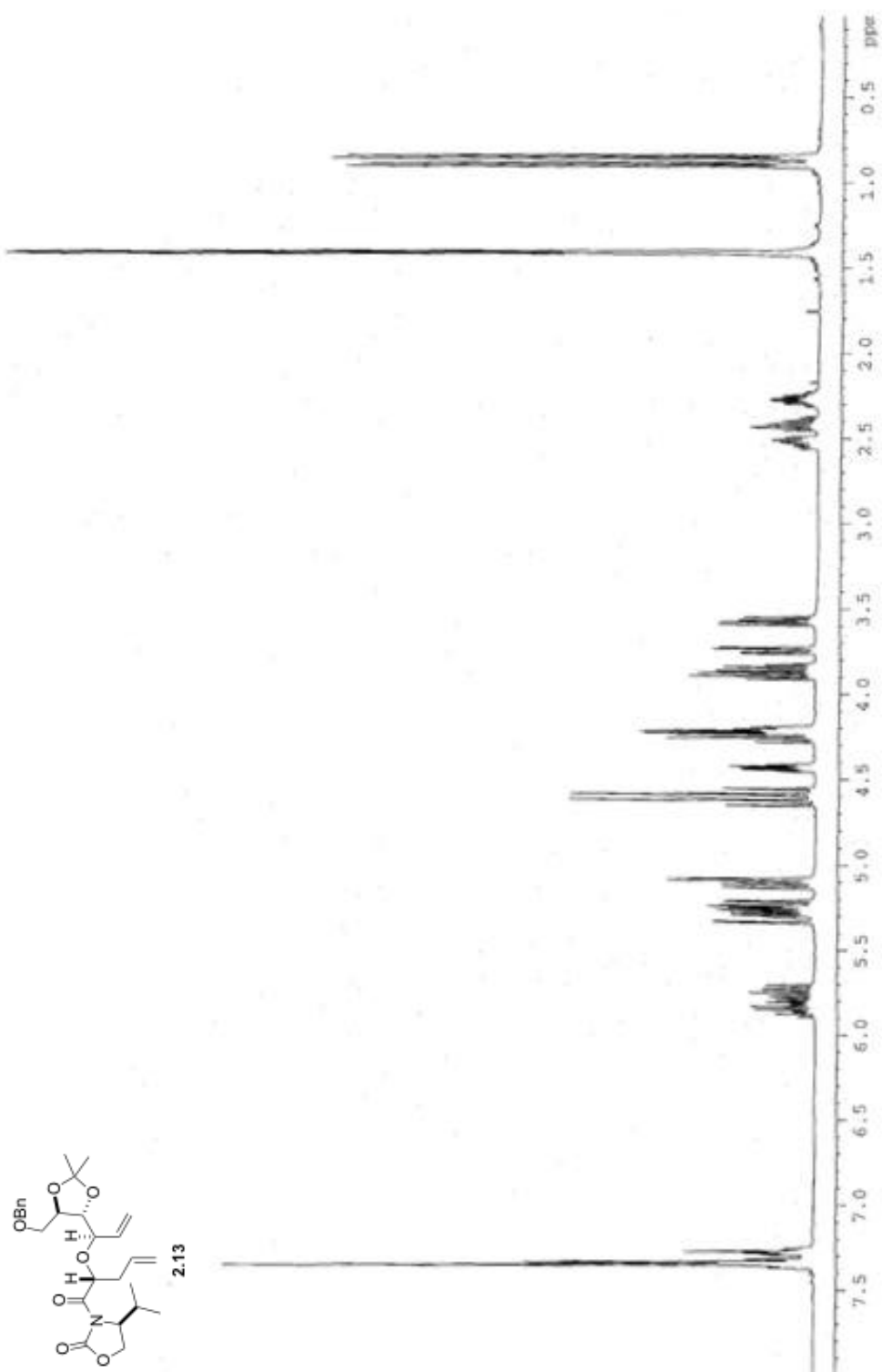
^1H NMR (400 MHz) of acid **2.11** (in CDCl_3)



^{13}C NMR (100 MHz) of glycolate **2.12** (in CDCl_3)



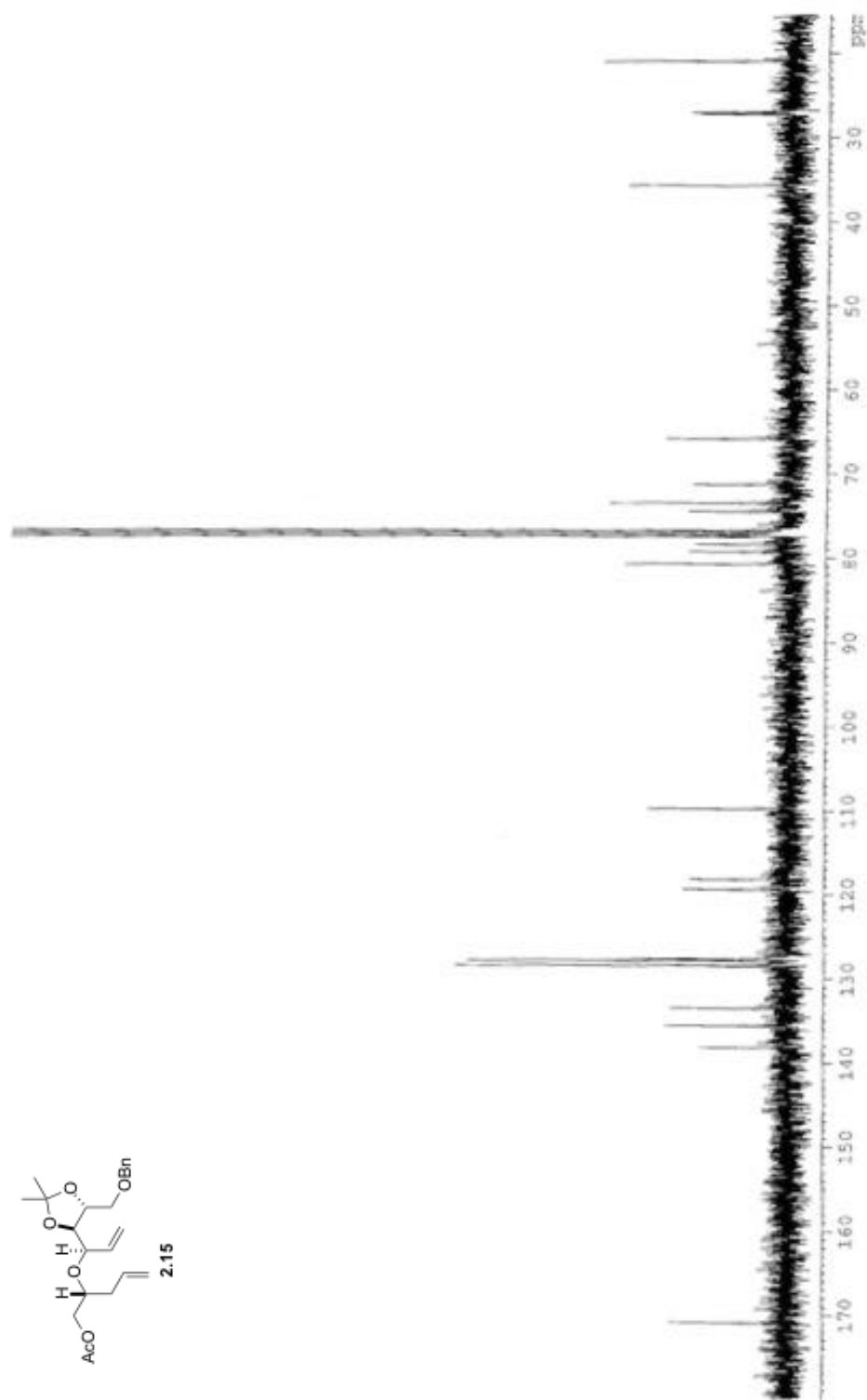
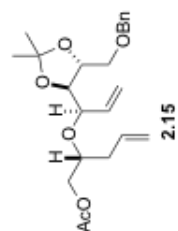
^1H NMR (400 MHz) of alkylation product **2.13** (in CDCl_3)



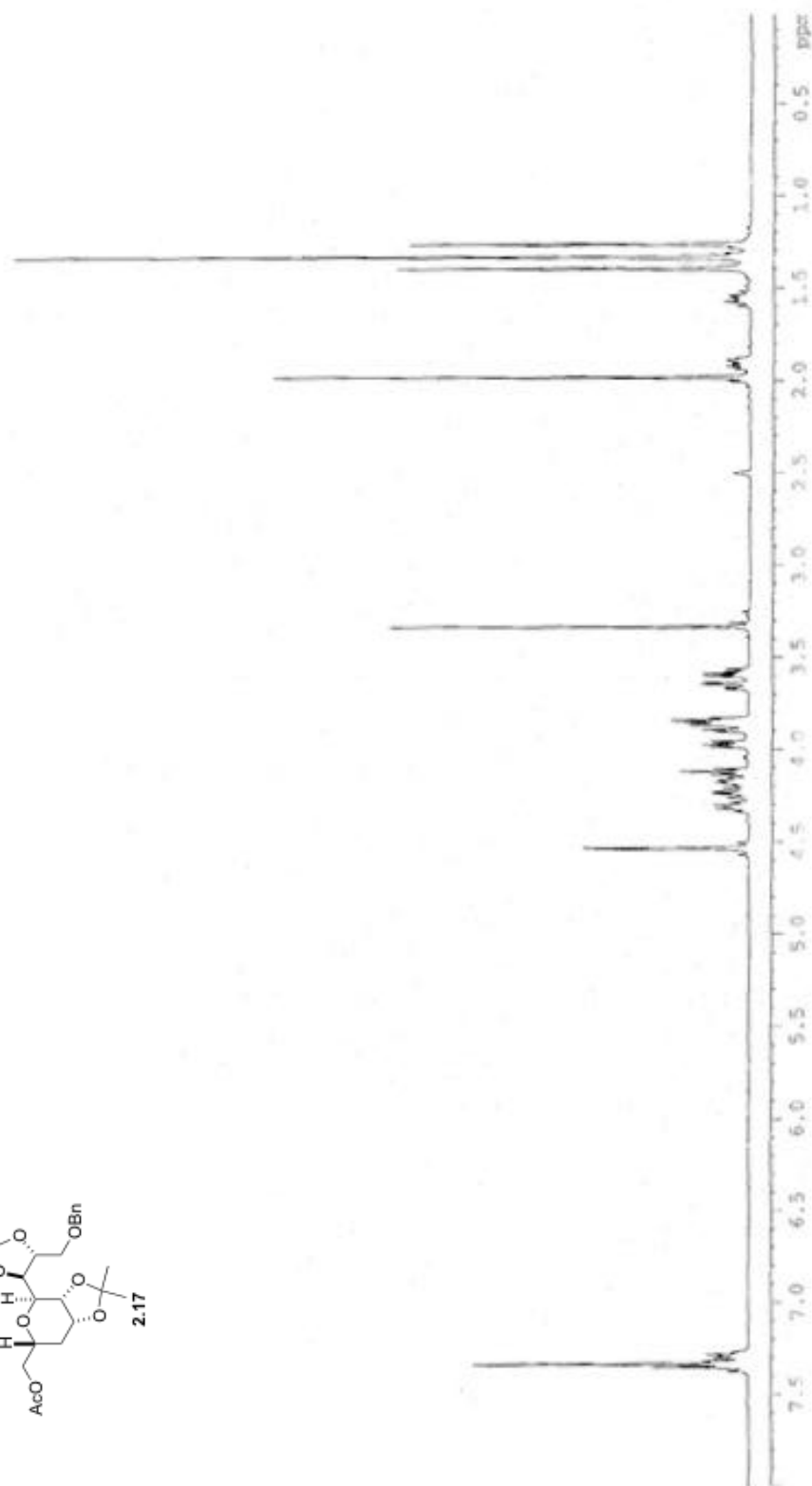
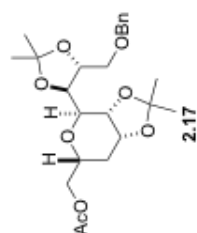
^{13}C NMR (100 MHz) of alkylation product **2.13** (in CDCl_3)



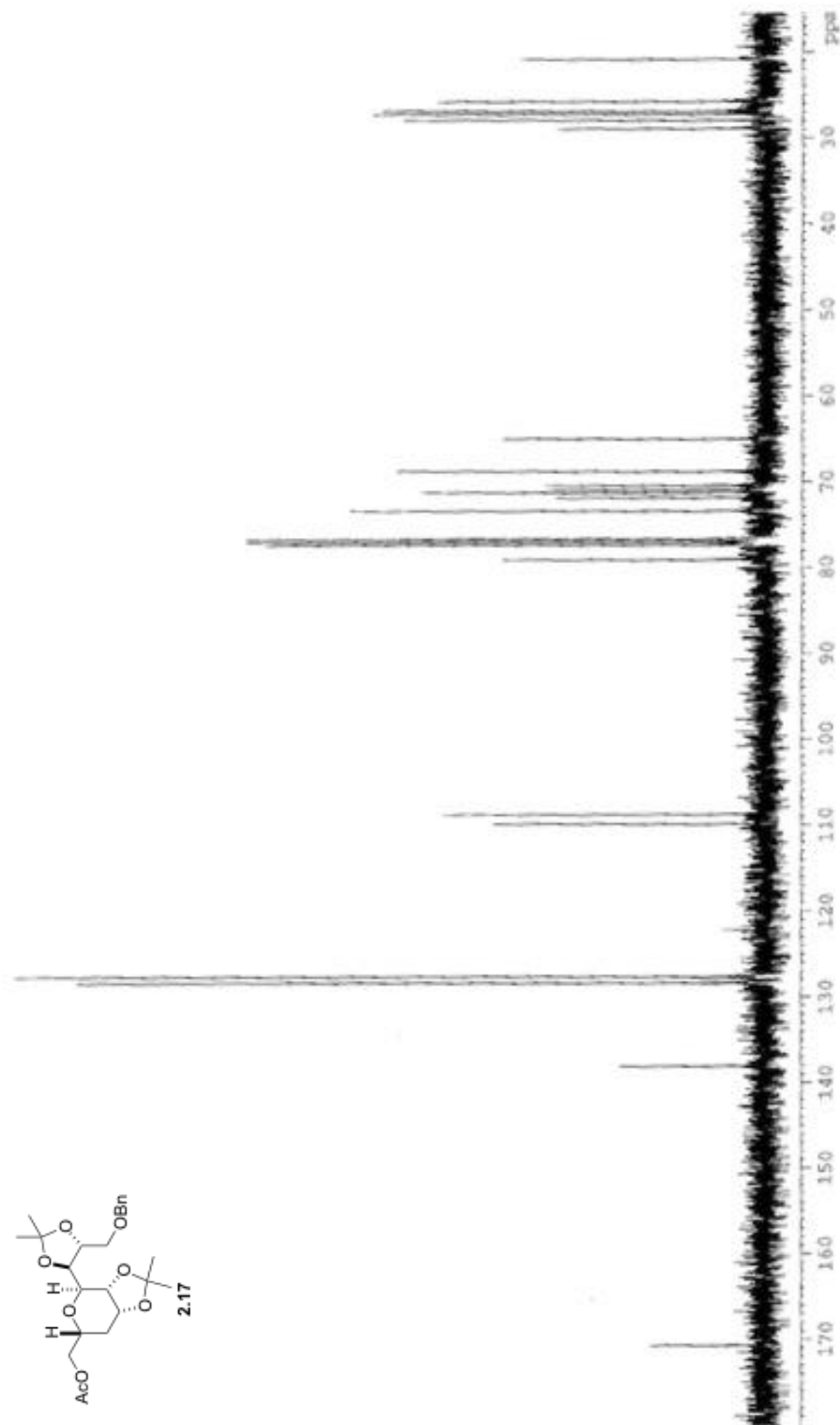
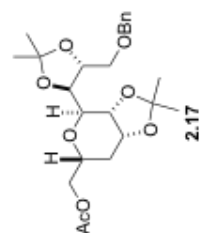
^{13}C NMR (100 MHz) of diene **2.15** (in CDCl_3)



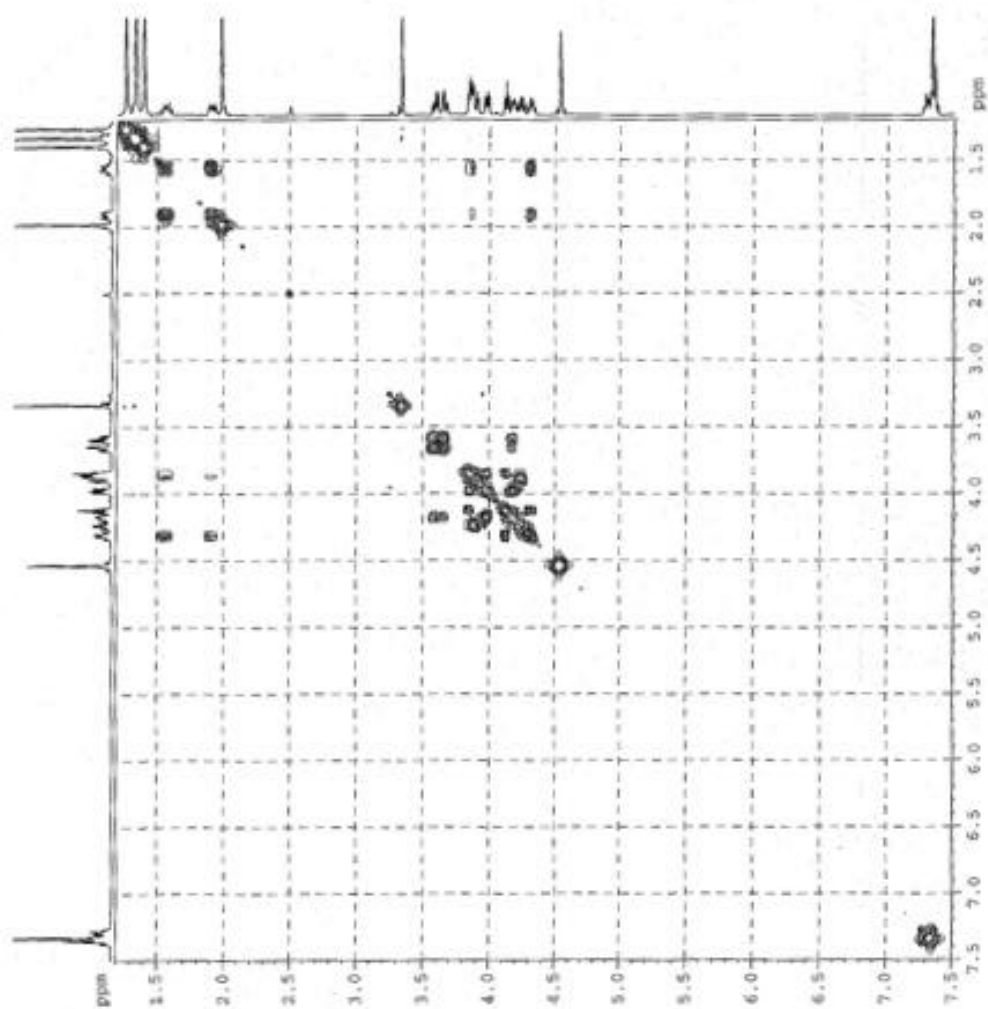
¹H NMR (400 MHz) of THP **2.17** (in DMSO)



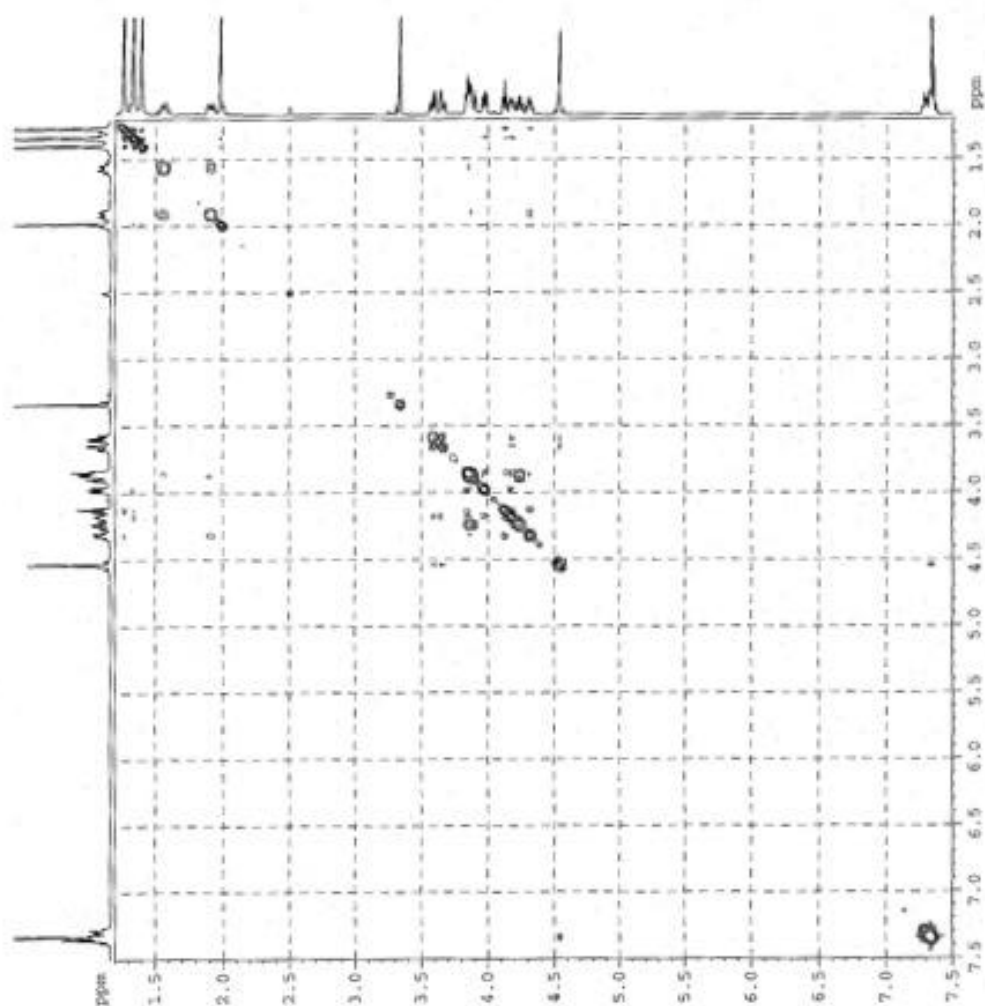
^{13}C NMR (100 MHz) of THP **2.17** (in CDCl_3)



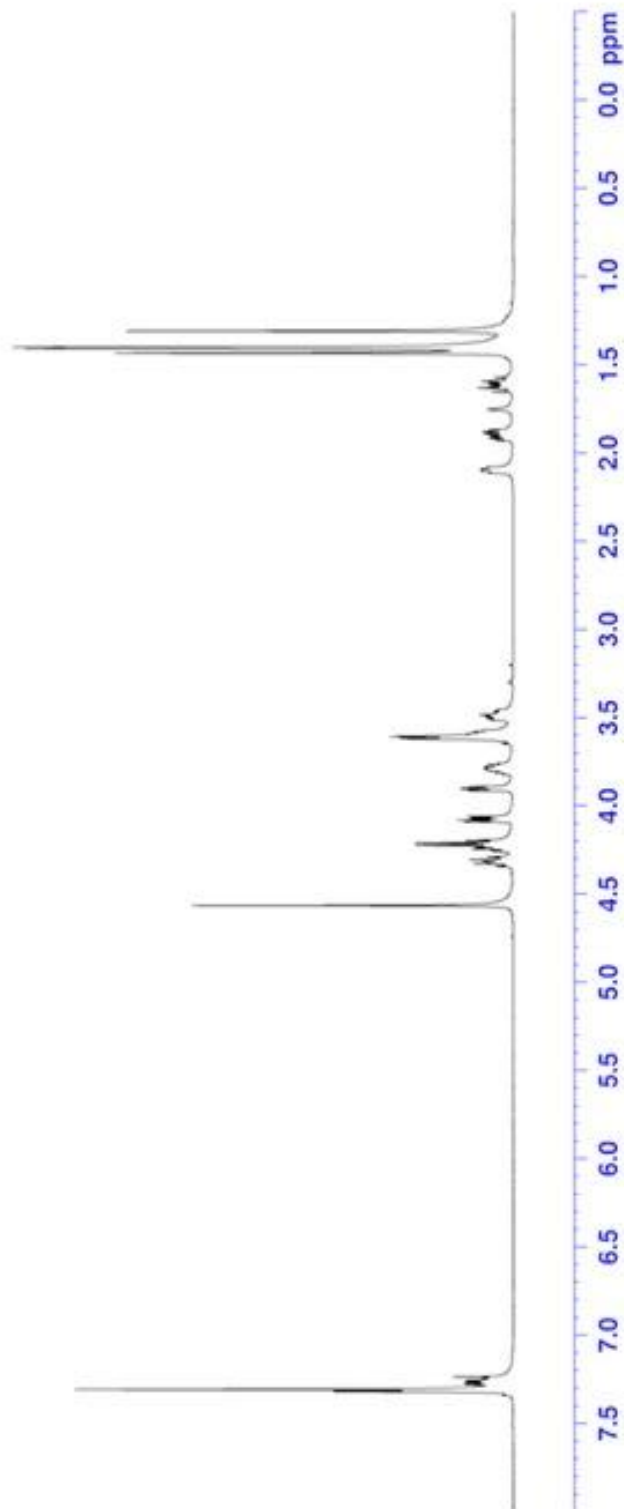
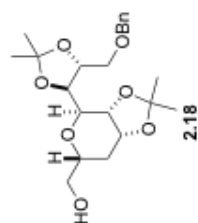
COSY (400 MHz) of THP 2.17 (in DMSO)



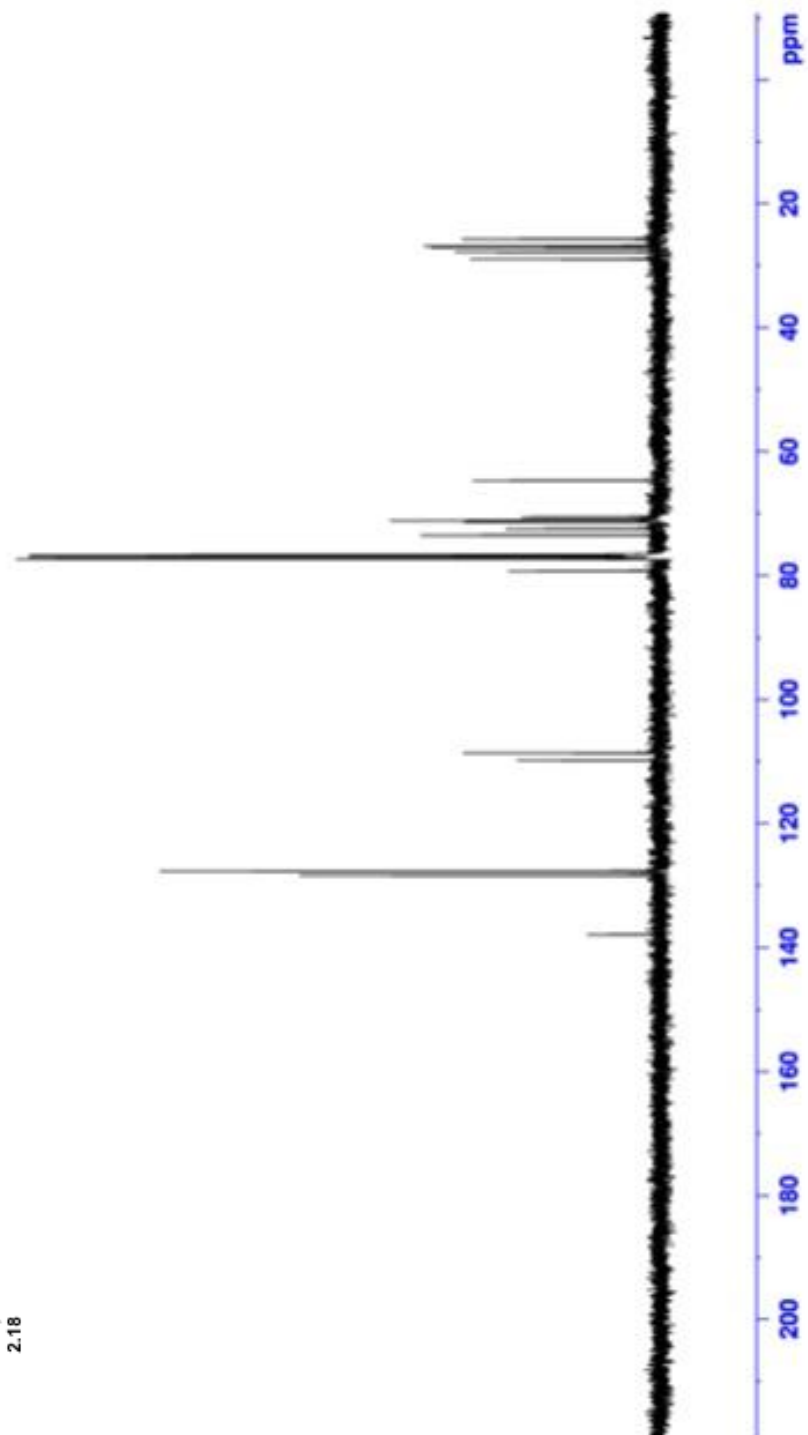
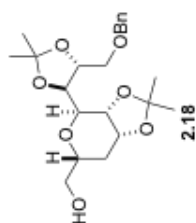
NOESY (400 MHz) of THP **2.17** (in DMSO)



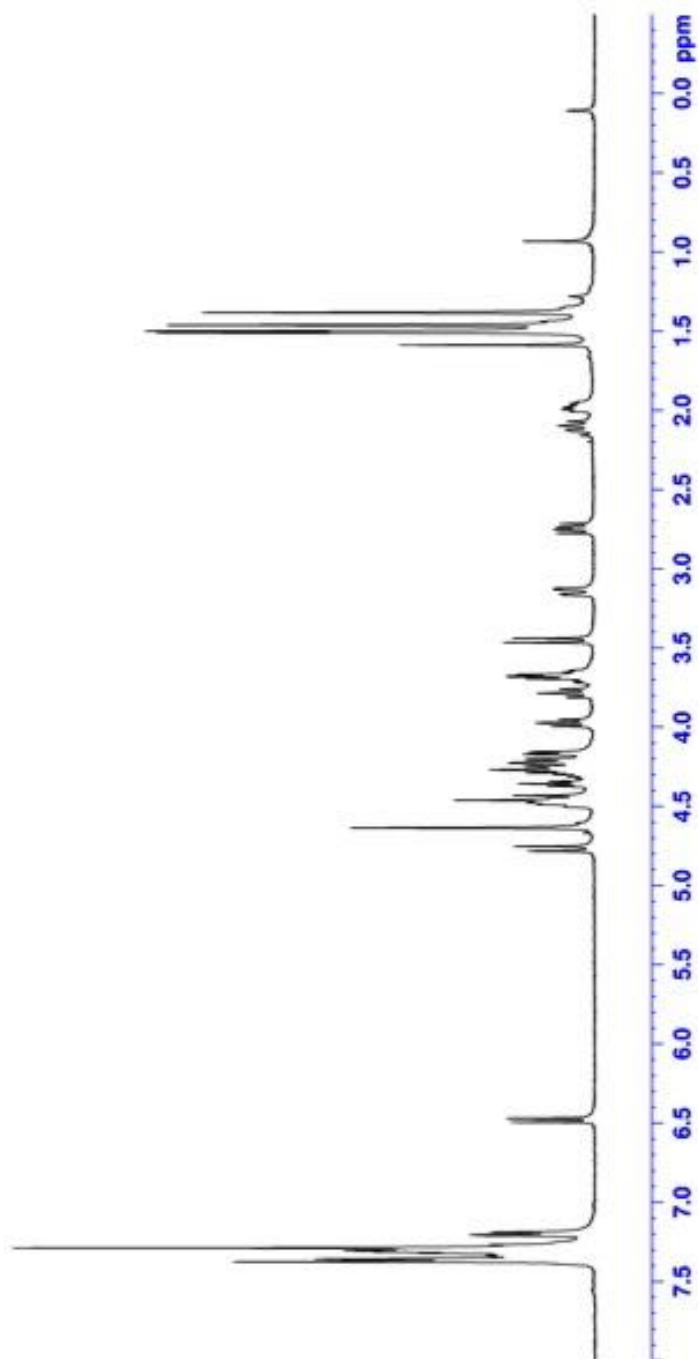
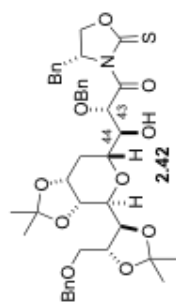
^1H NMR (400 MHz) of primary alcohol **2.18** (in CDCl_3)



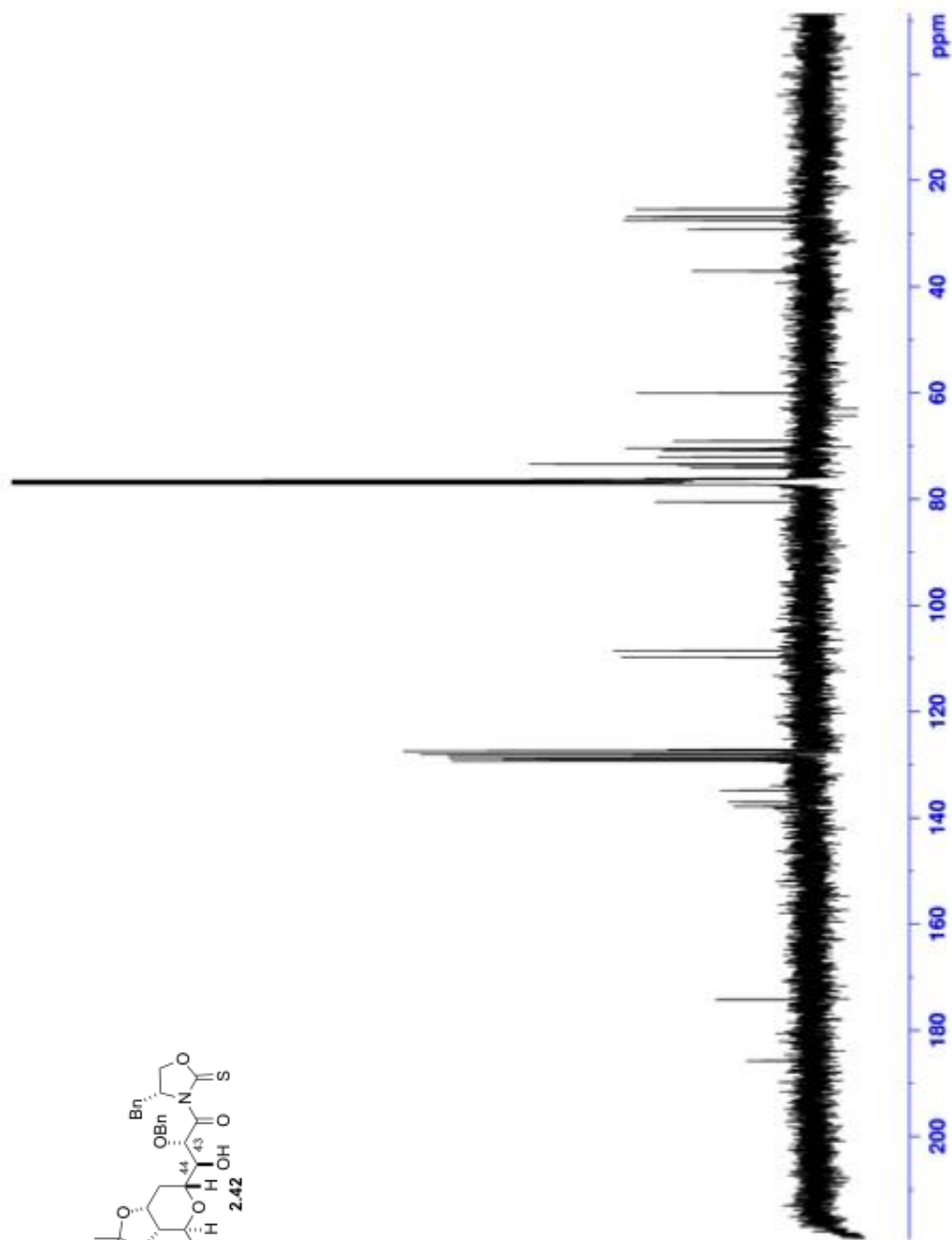
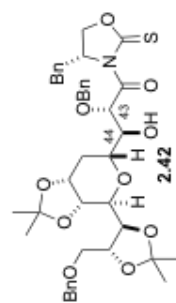
^{13}C NMR (100 MHz) of primary alcohol **2.18** (in CDCl_3)



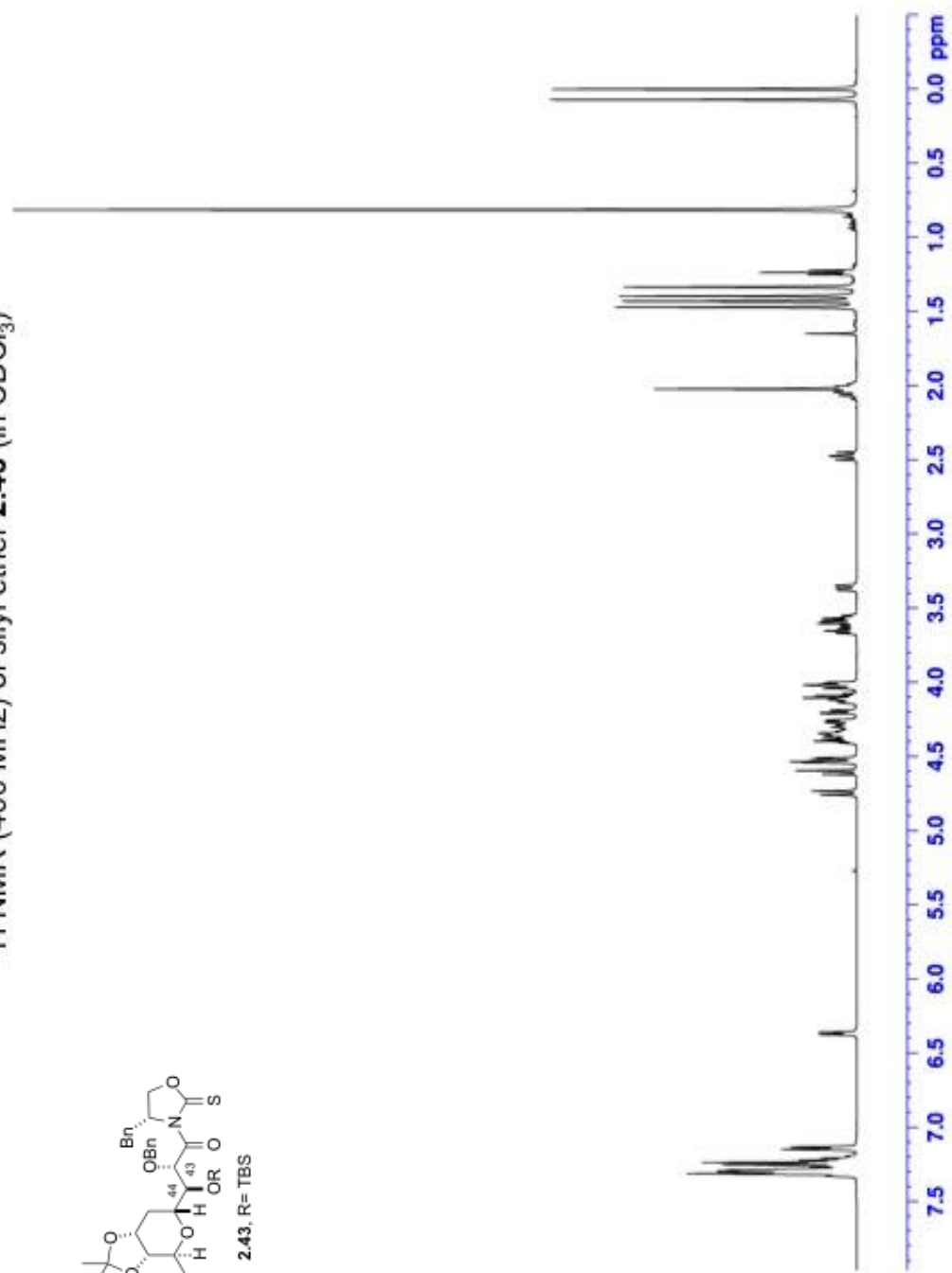
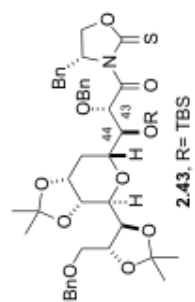
^1H NMR (400 MHz) of *anti* aldol adduct **2.42** (in CDCl_3)



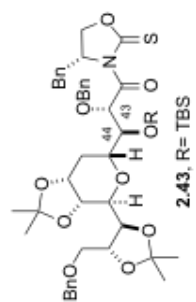
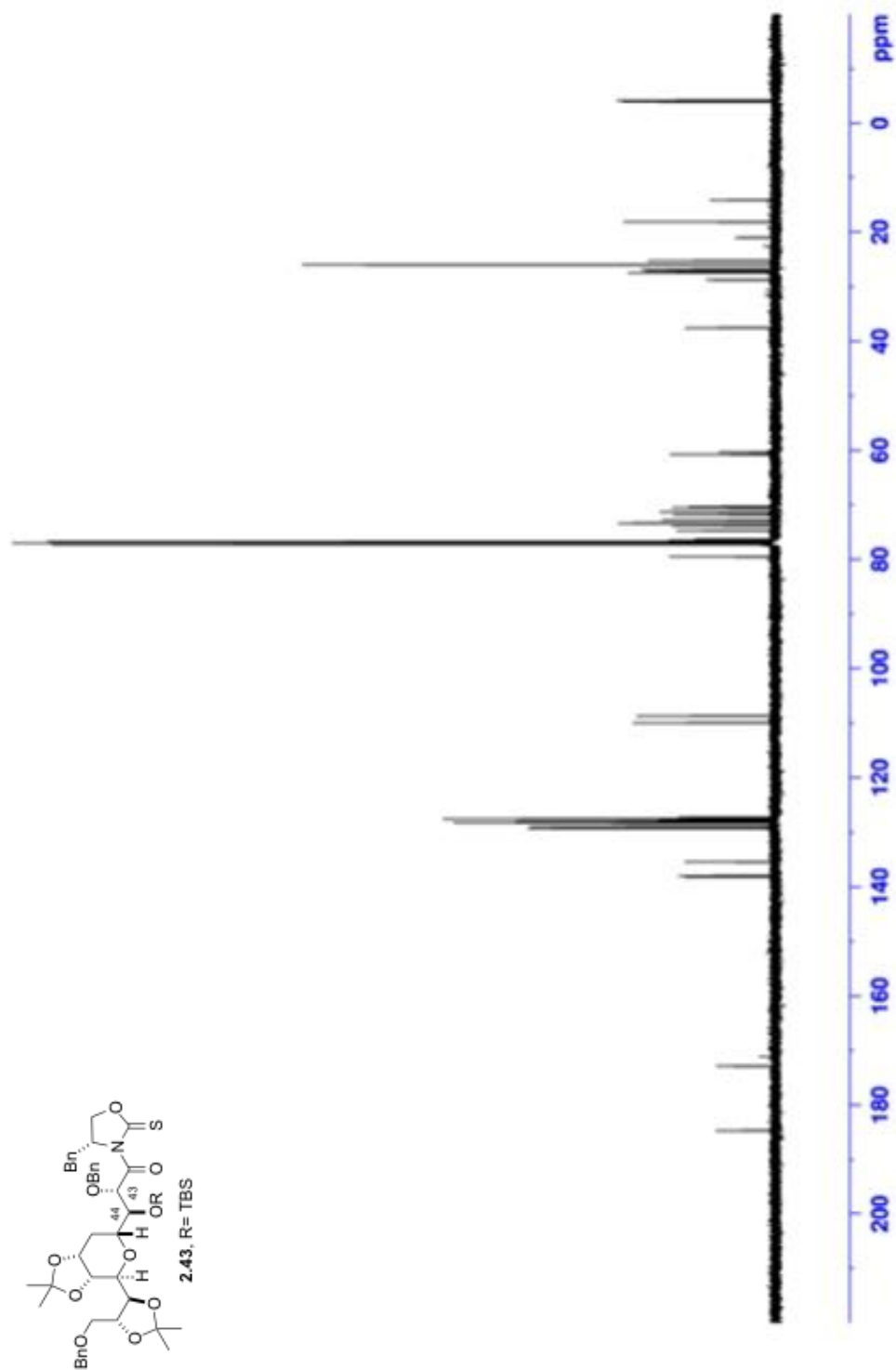
^{13}C NMR (100 MHz) of *anti* aldol adduct **2.42** (in CDCl_3)



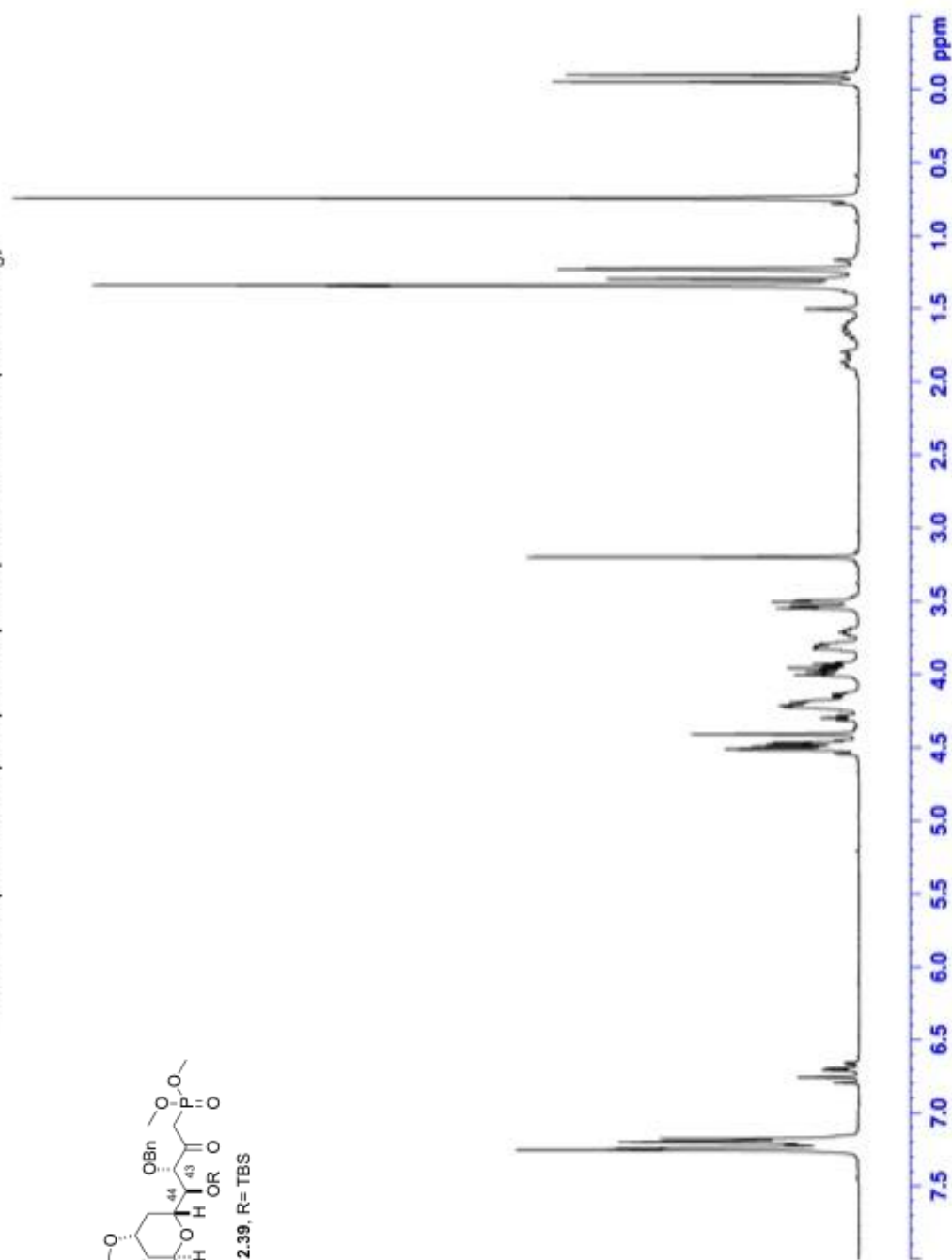
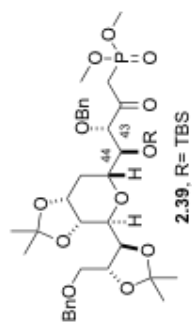
^1H NMR (400 MHz) of silyl ether **2.43** (in CDCl_3)



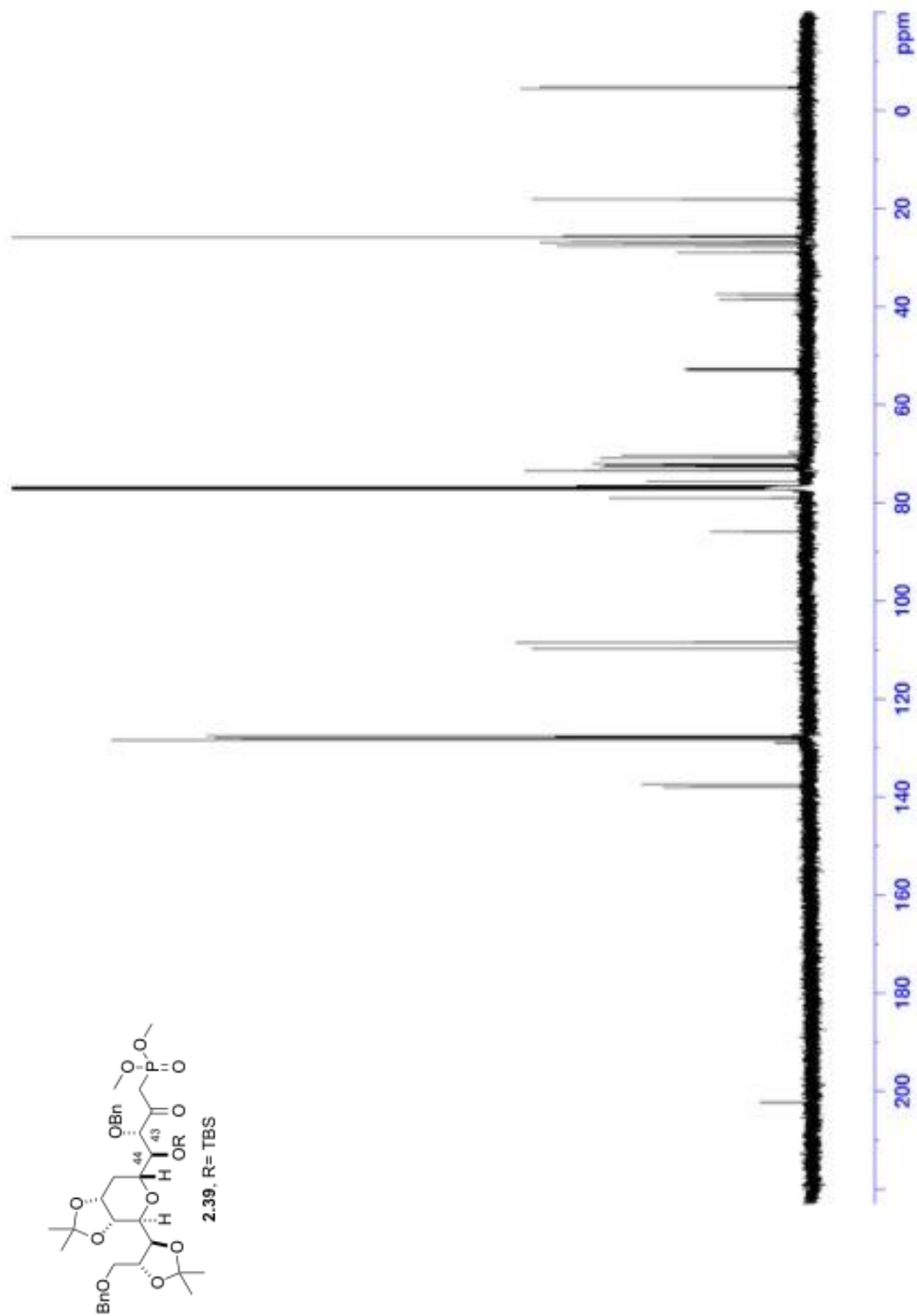
^{13}C NMR (100 MHz) of silyl ether **2.43** (in CDCl_3)



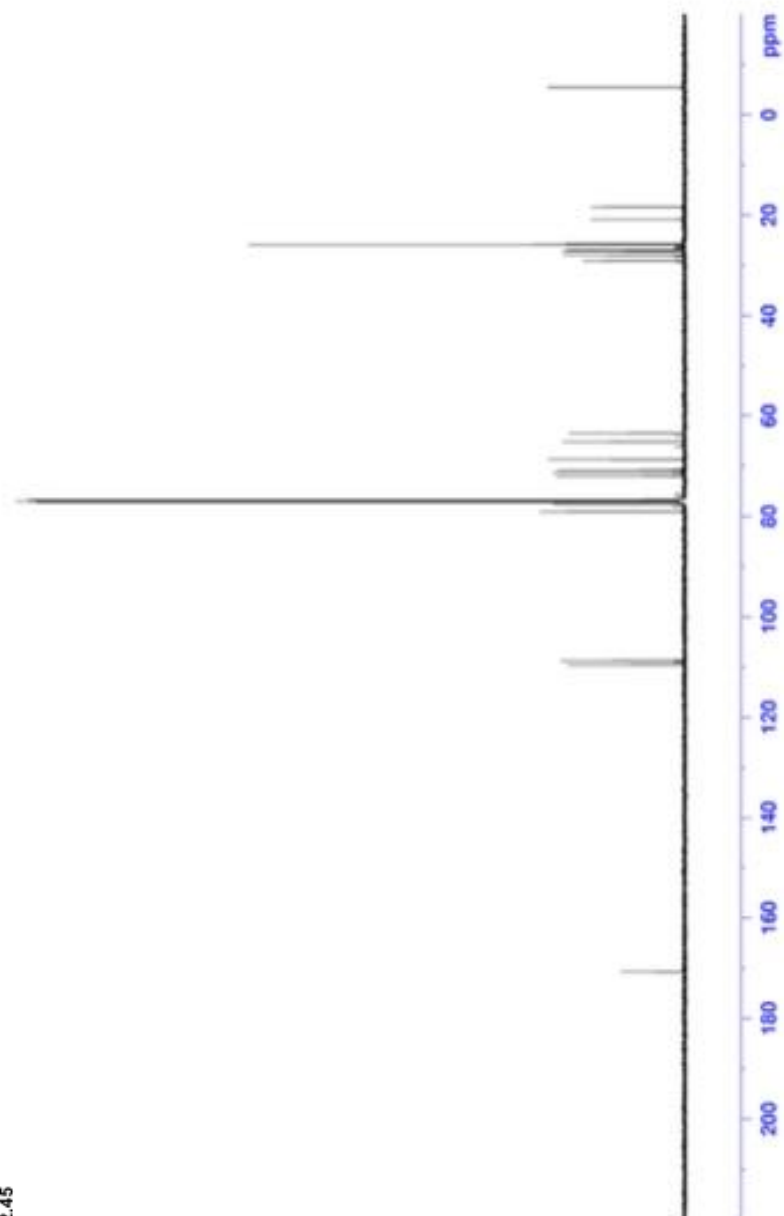
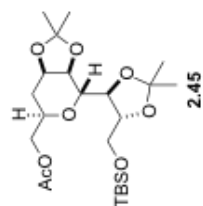
^1H NMR (400 MHz) of β -ketophosphonate **2.39** (in CDCl_3)



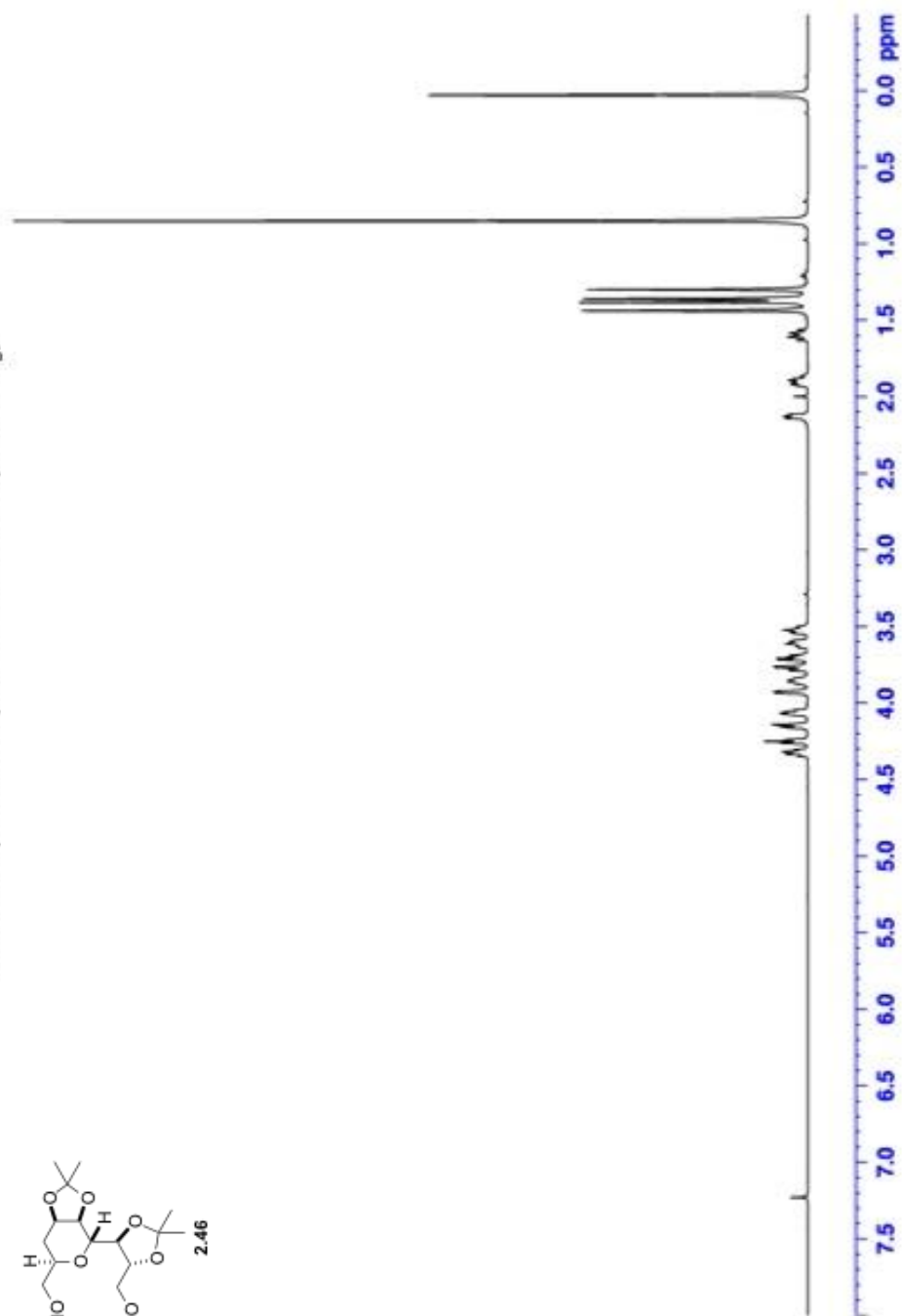
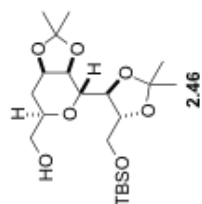
^{13}C NMR (125 MHz) of β -ketophosphonate **2.39** (in CDCl_3)



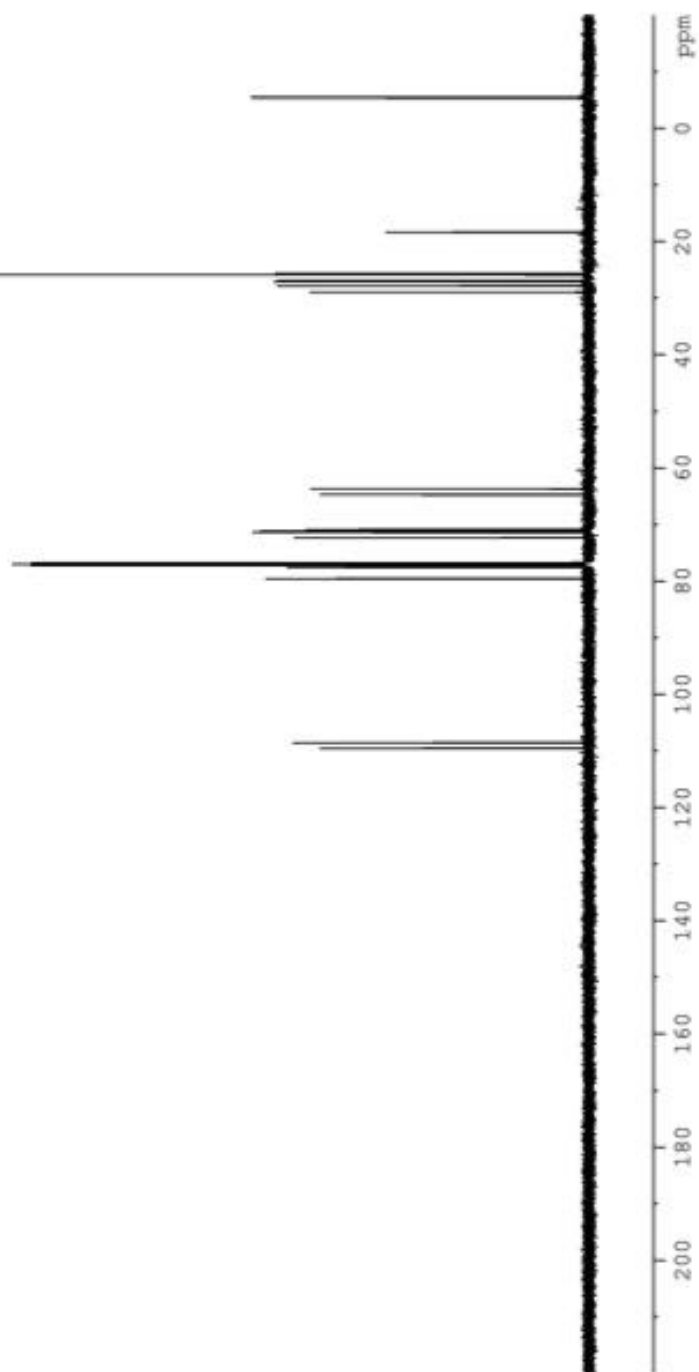
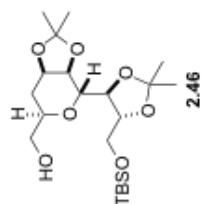
^{13}C NMR (500 MHz) of acetate **2.45** (in CDCl_3)



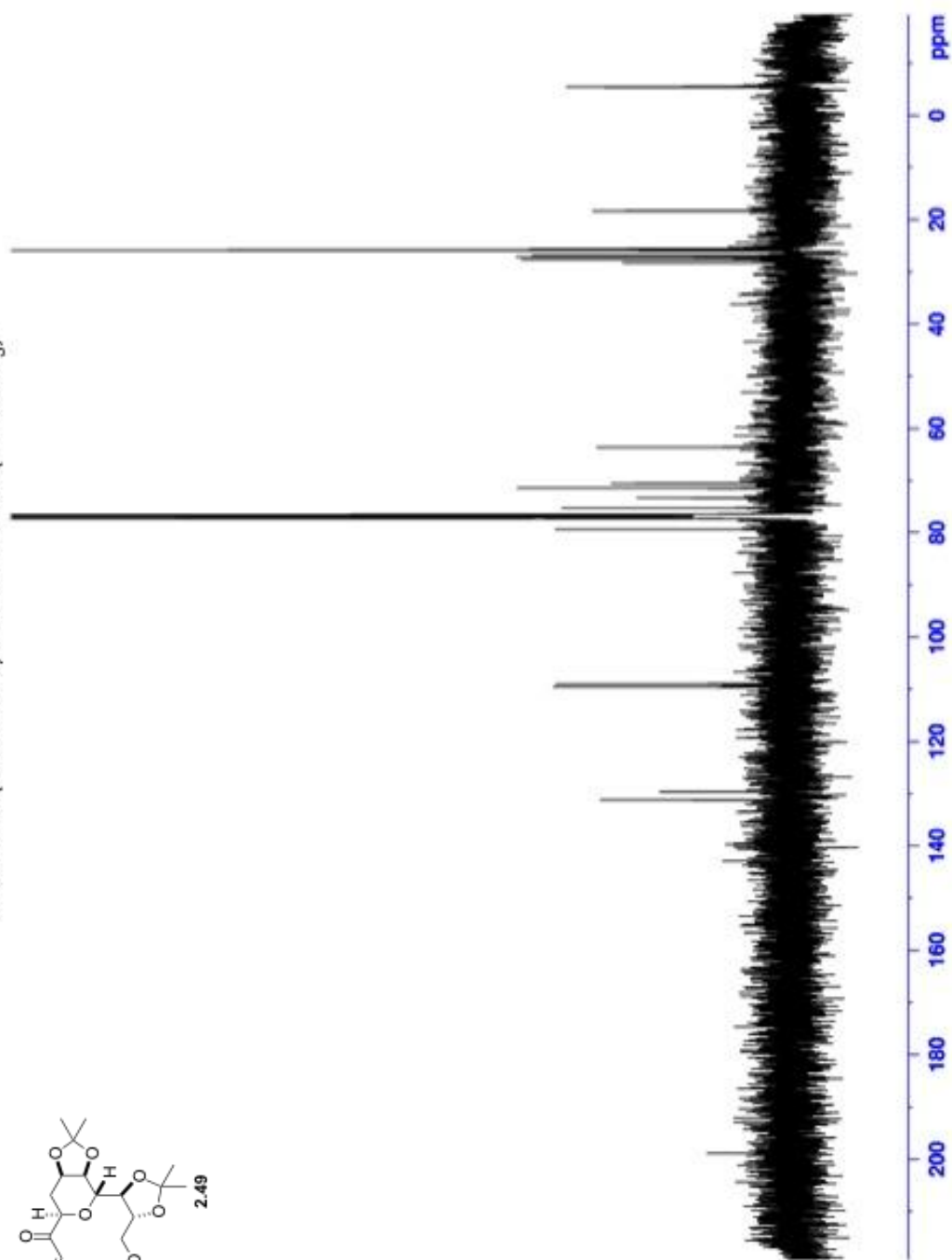
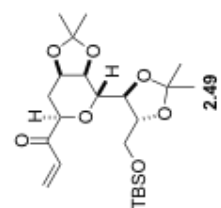
^1H NMR (400 MHz) of alcohol **2.46** (in CDCl_3)



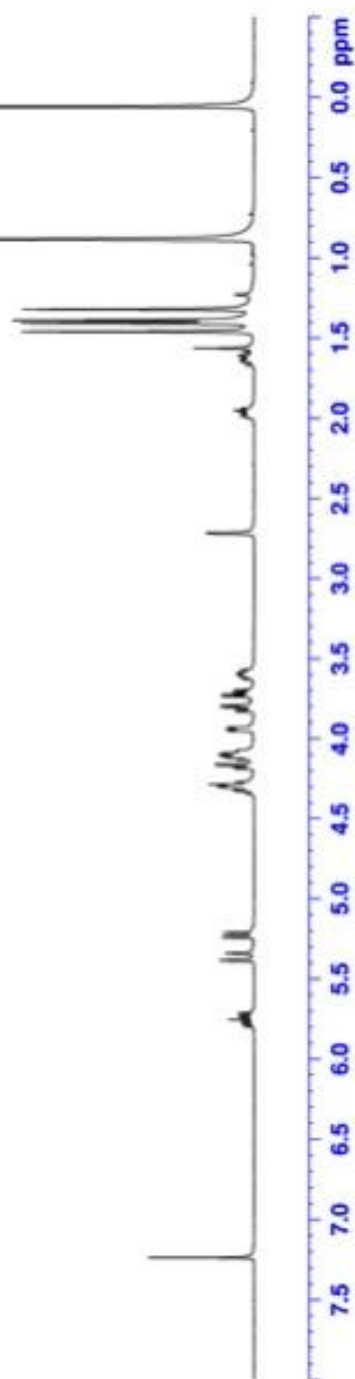
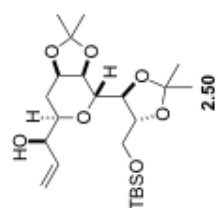
^{13}C NMR (100 MHz) of alcohol **2.46** (in CDCl_3)



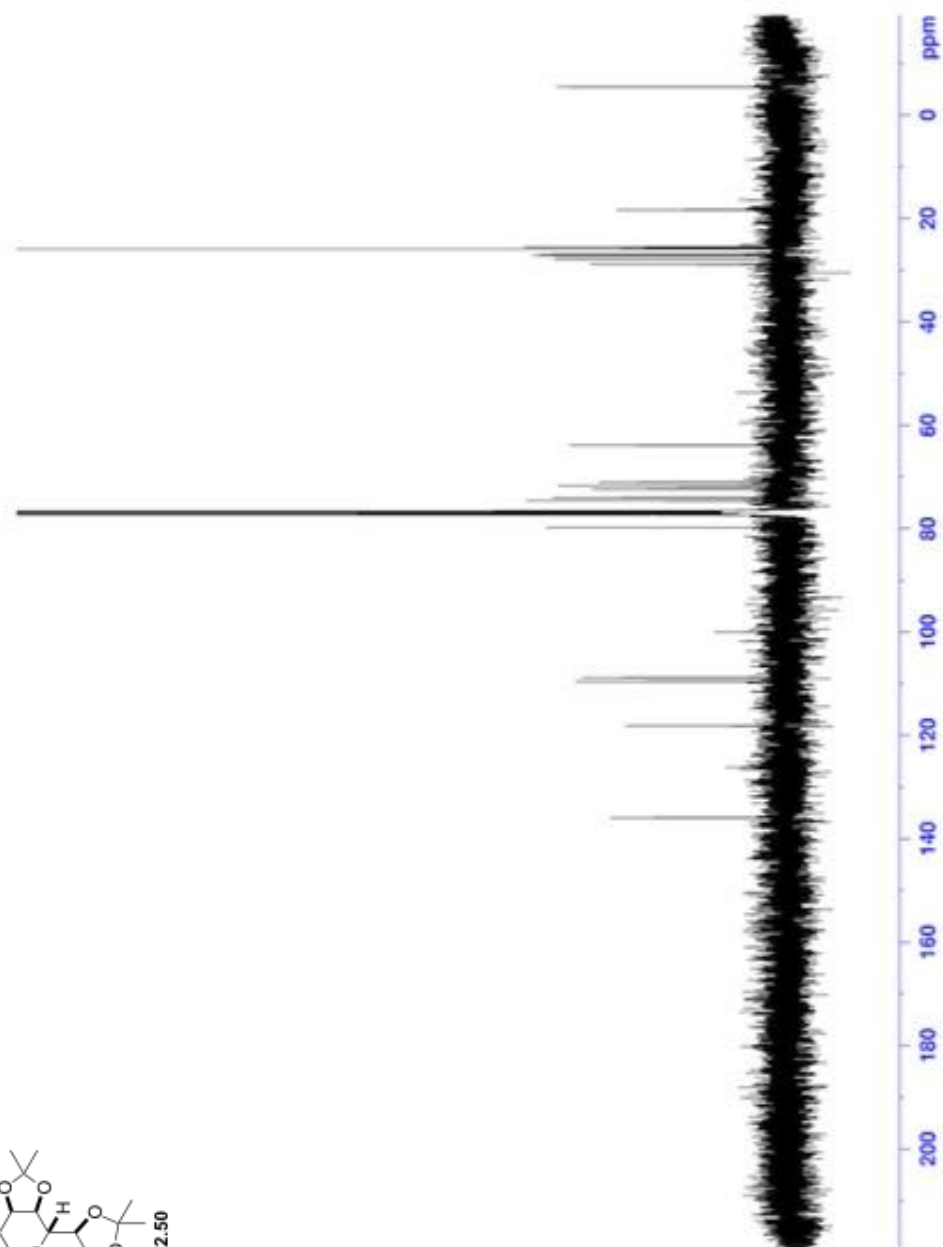
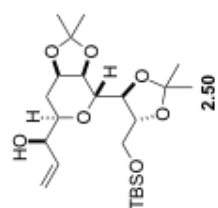
^{13}C NMR (100 MHz) of enone **19** (in CDCl_3)



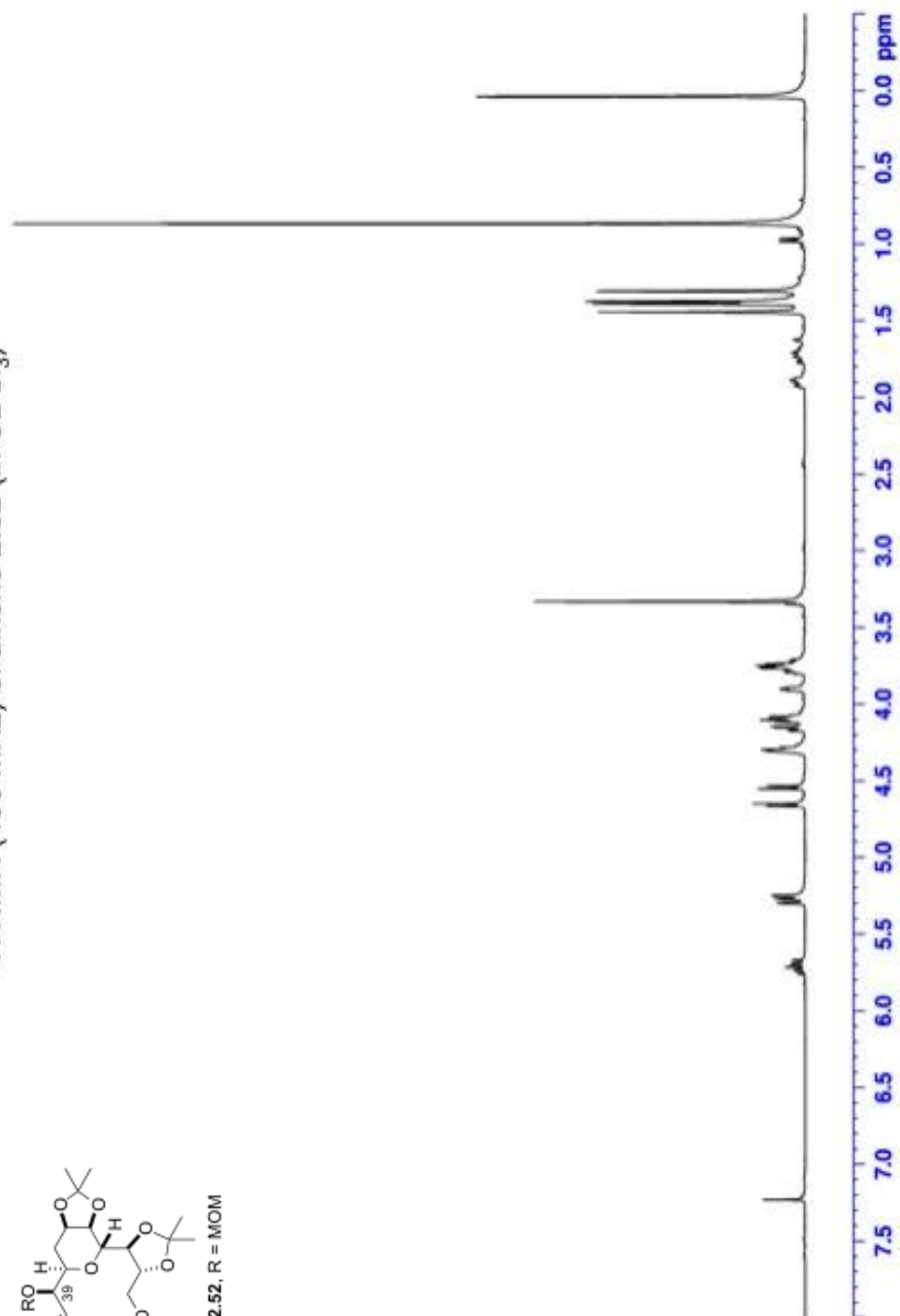
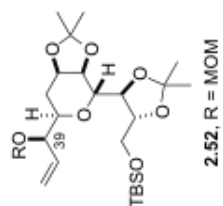
^1H NMR (400 MHz) of allylic alcohol **2.50** (in CDCl_3)



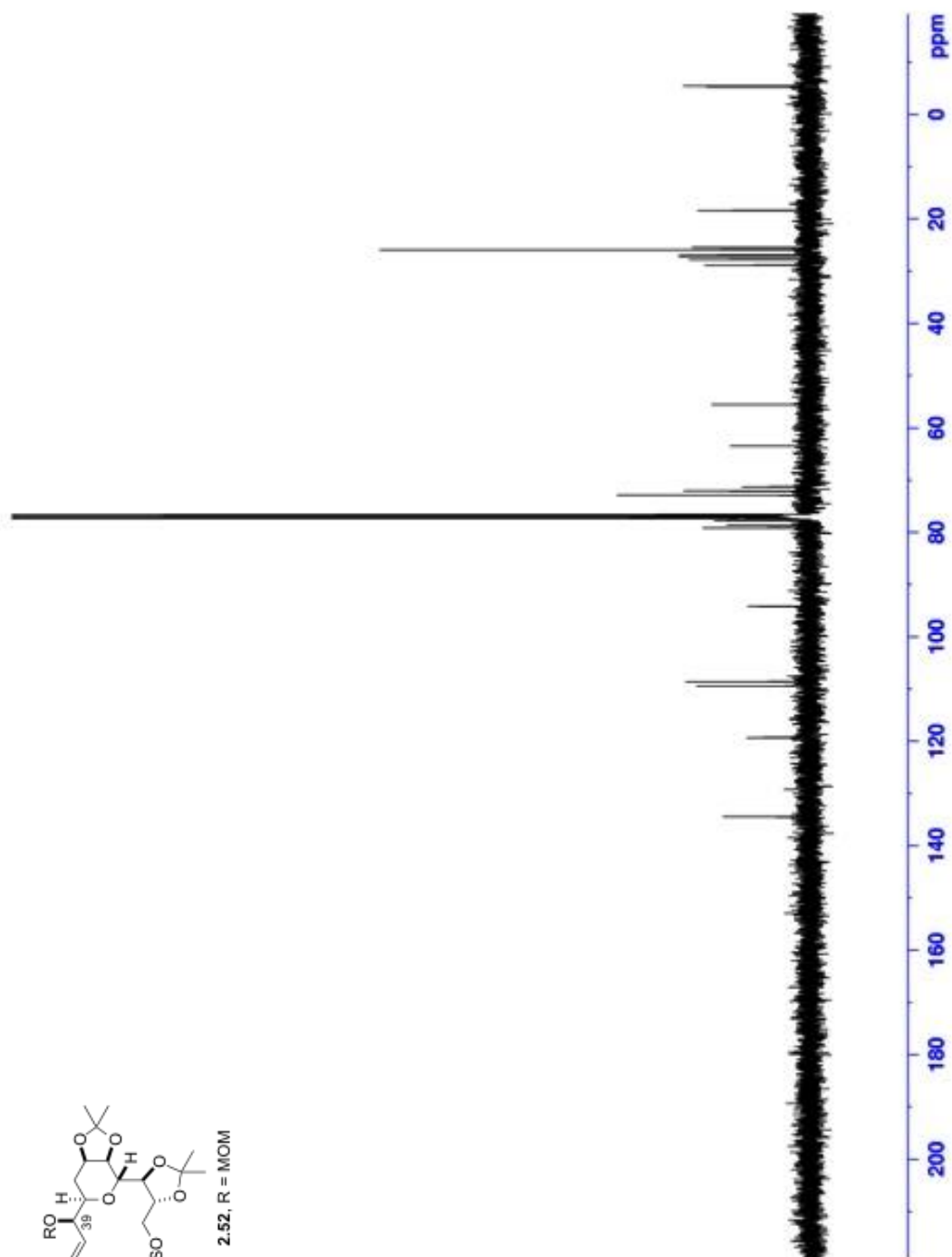
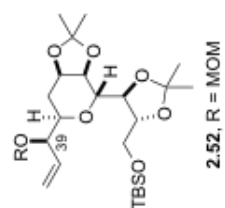
^{13}C NMR (100 MHz) of allylic alcohol **2.50** (in CDCl_3)



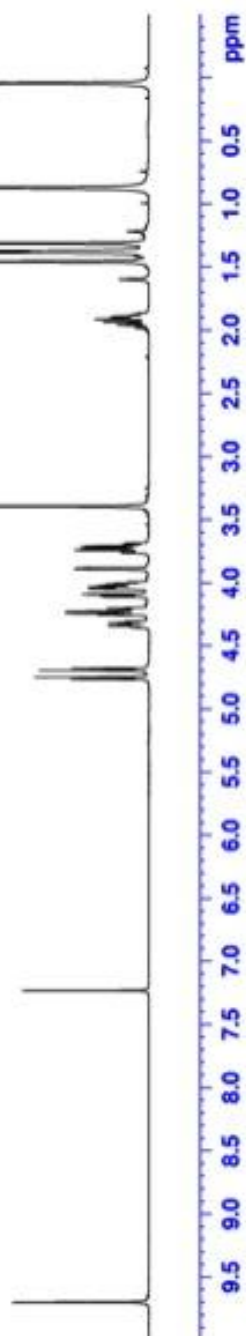
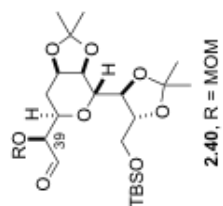
^1H NMR (400 MHz) of alkene **2.52** (in CDCl_3)



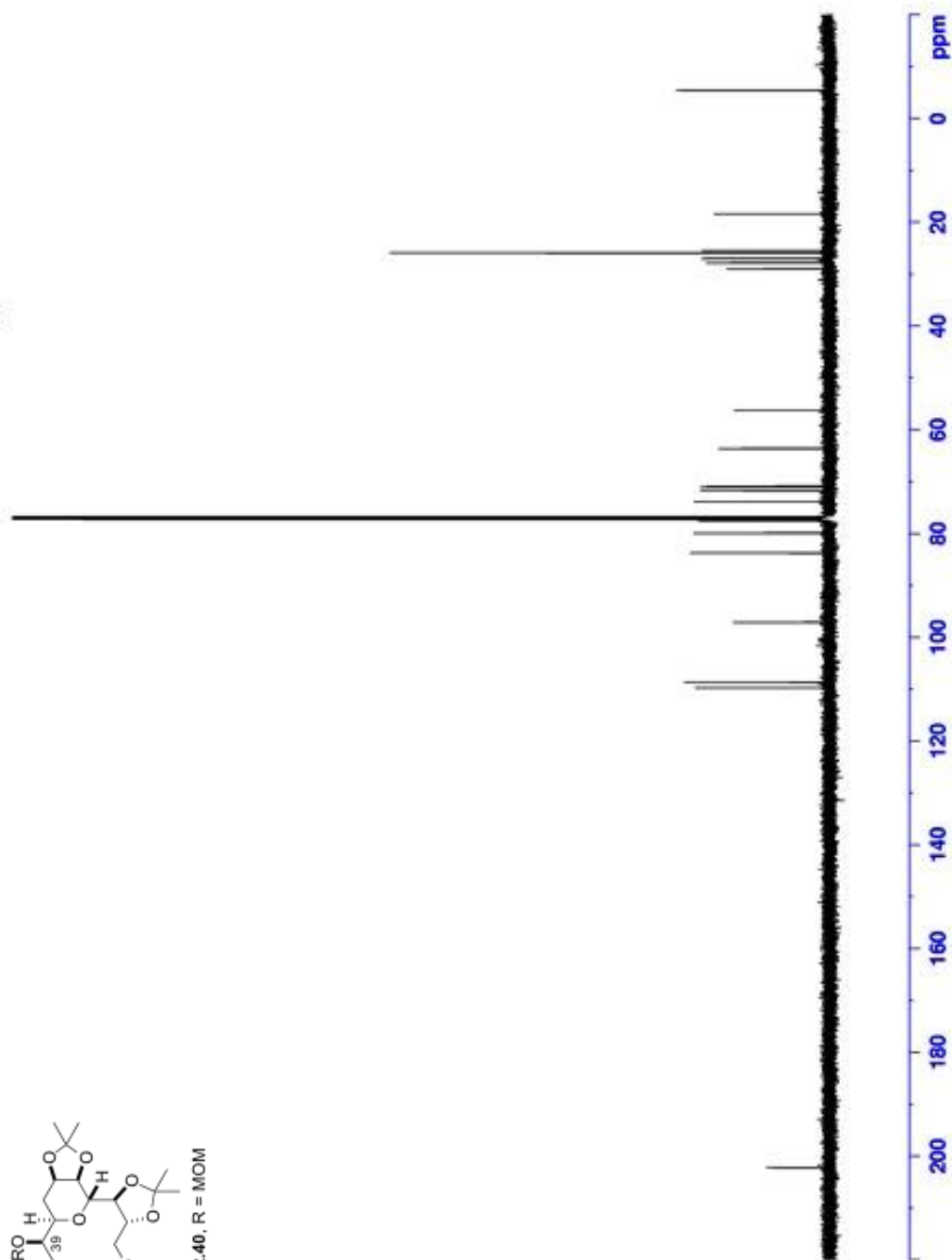
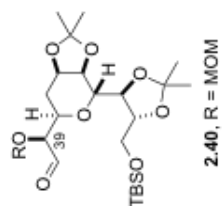
^{13}C NMR (100 MHz) of alkene **2.52** (in CDCl_3)



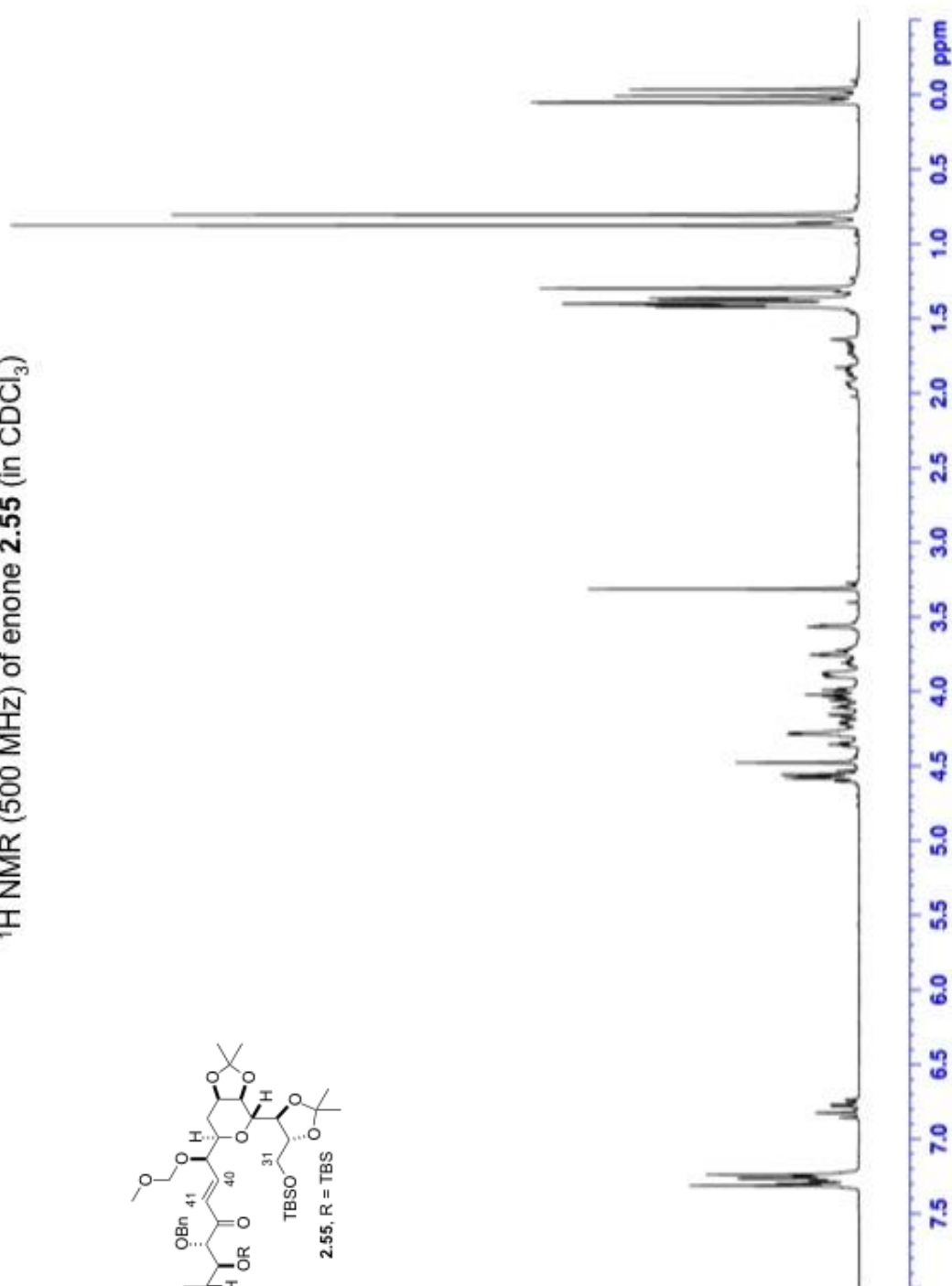
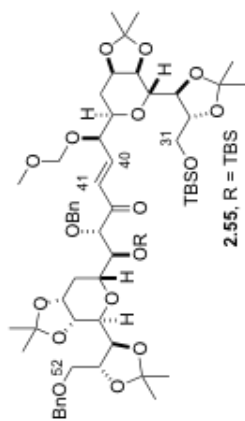
^1H NMR (500 MHz) of aldehyde **2.40** (in CDCl_3)



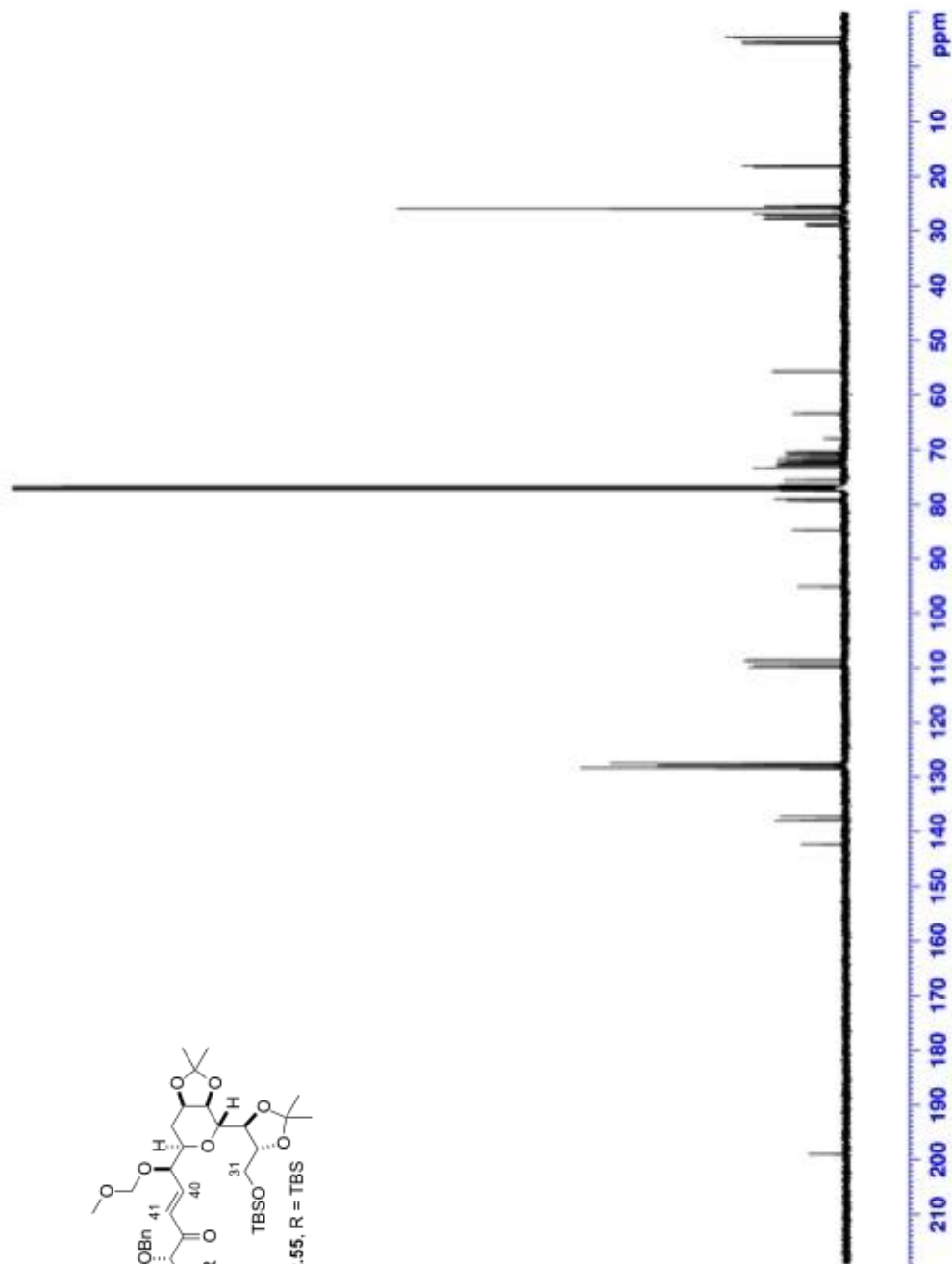
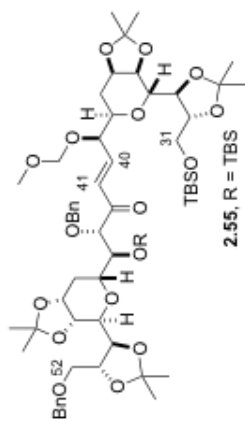
^{13}C NMR (125 MHz) of aldehyde **2.40** (in CDCl_3)

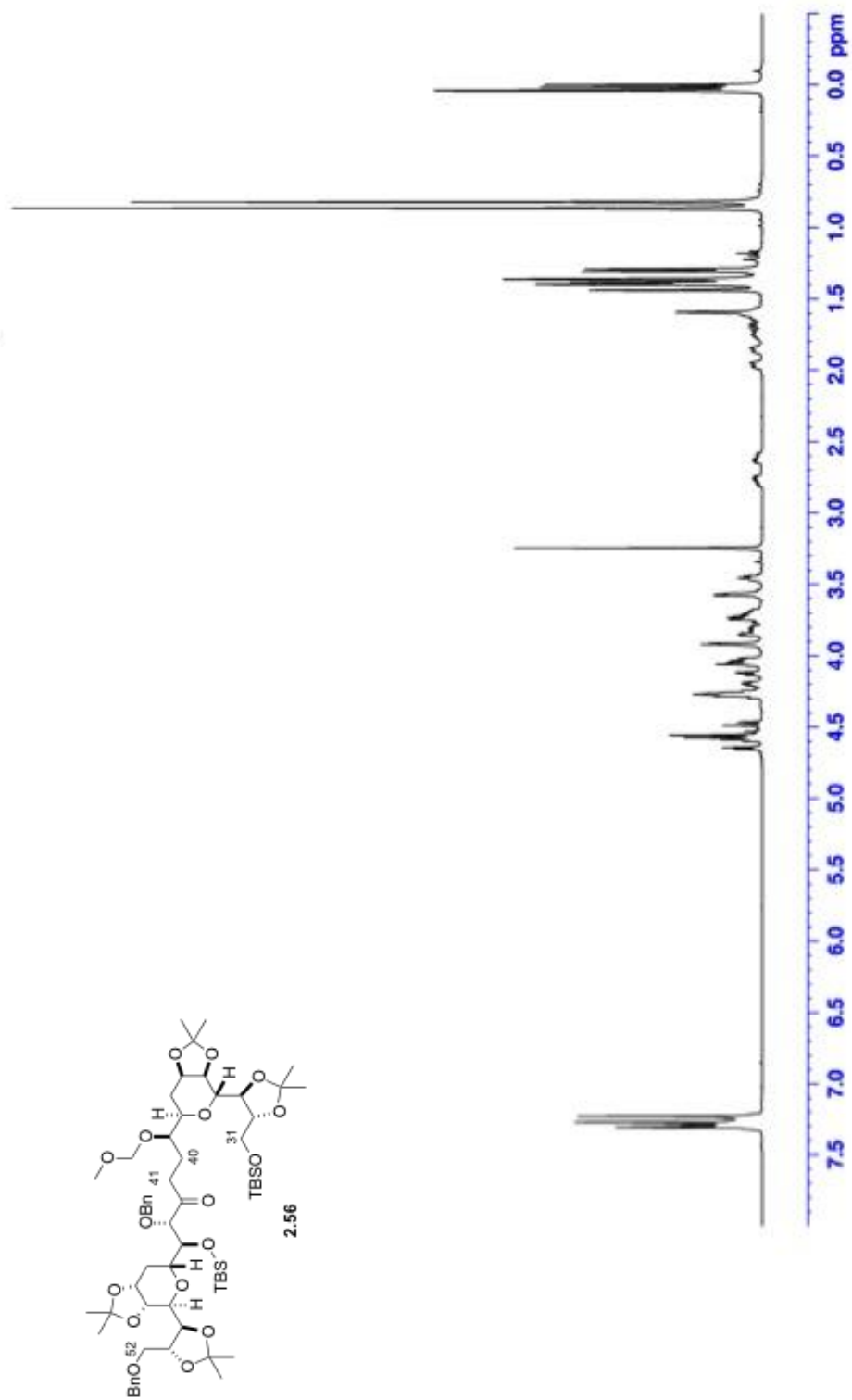


^1H NMR (500 MHz) of enone **2.55** (in CDCl_3)

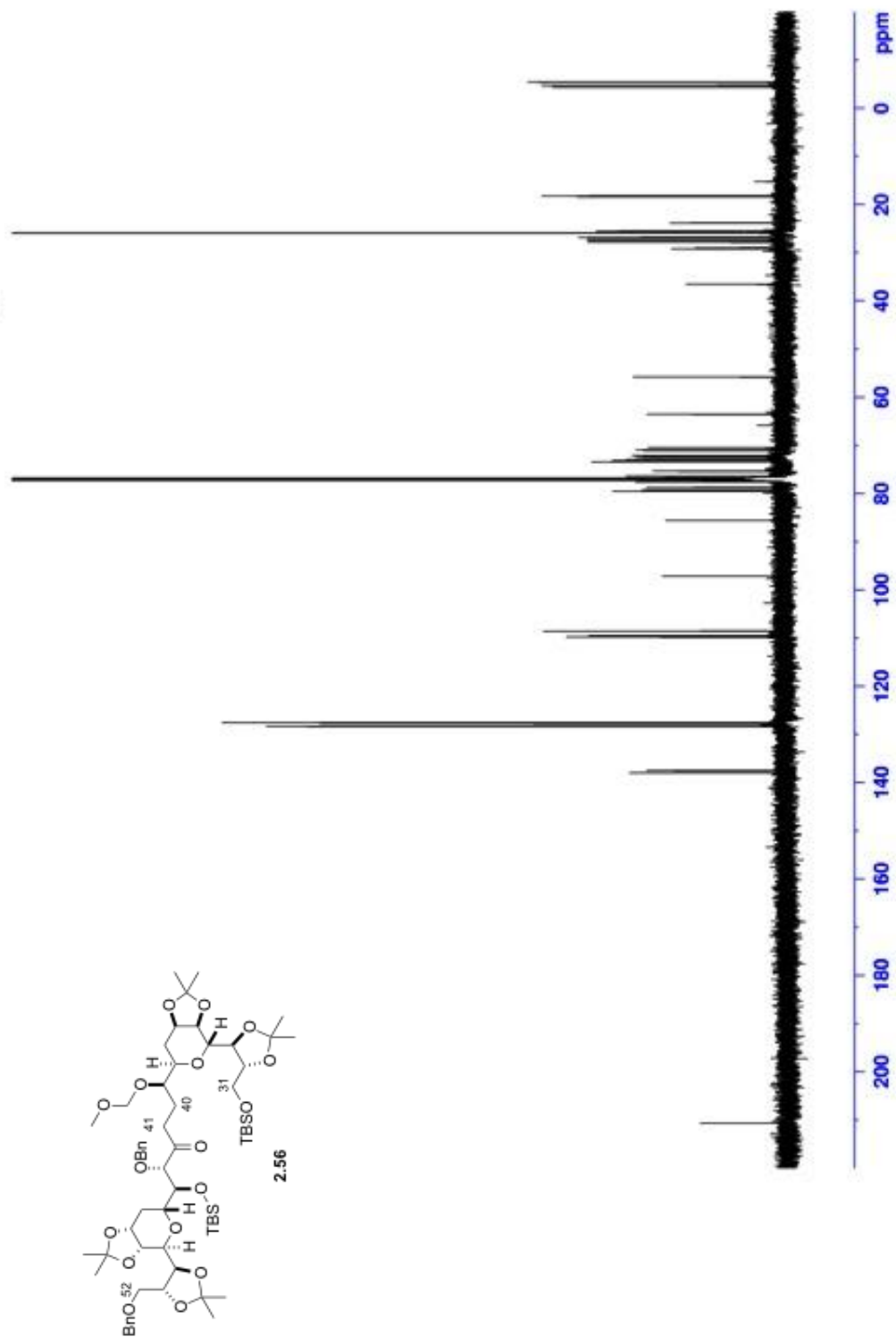


^{13}C NMR (125 MHz) of enone **2.55** (in CDCl_3)

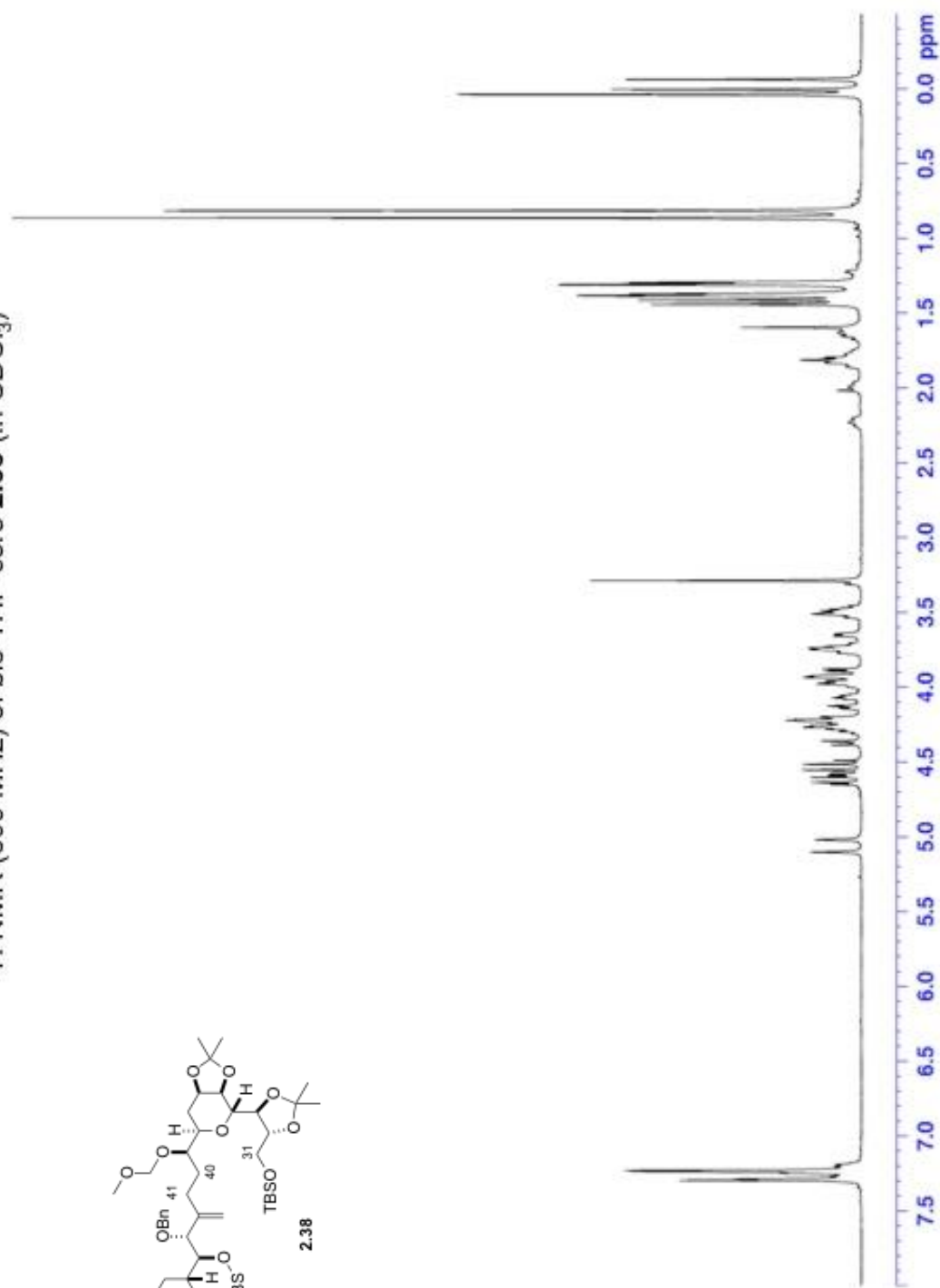
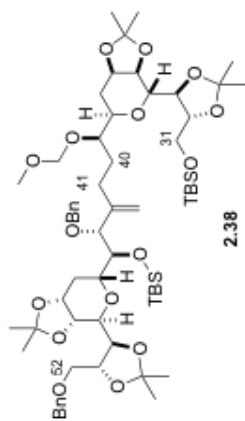


¹H NMR (500 MHz) of ketone **2.56** (in CDCl₃)

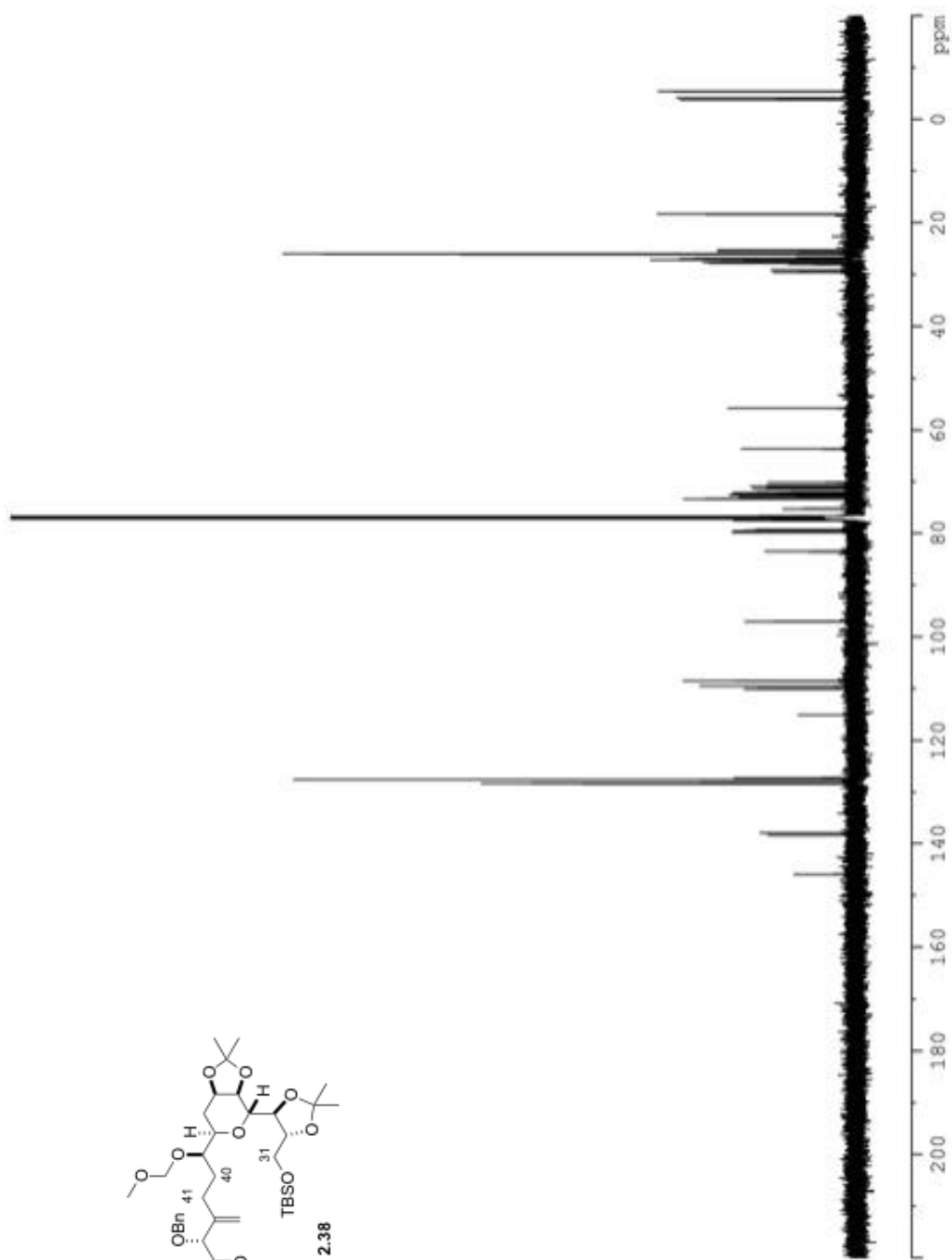
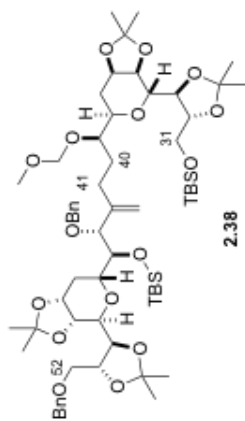
^{13}C NMR (125 MHz) of ketone **2.56** (in CDCl_3)



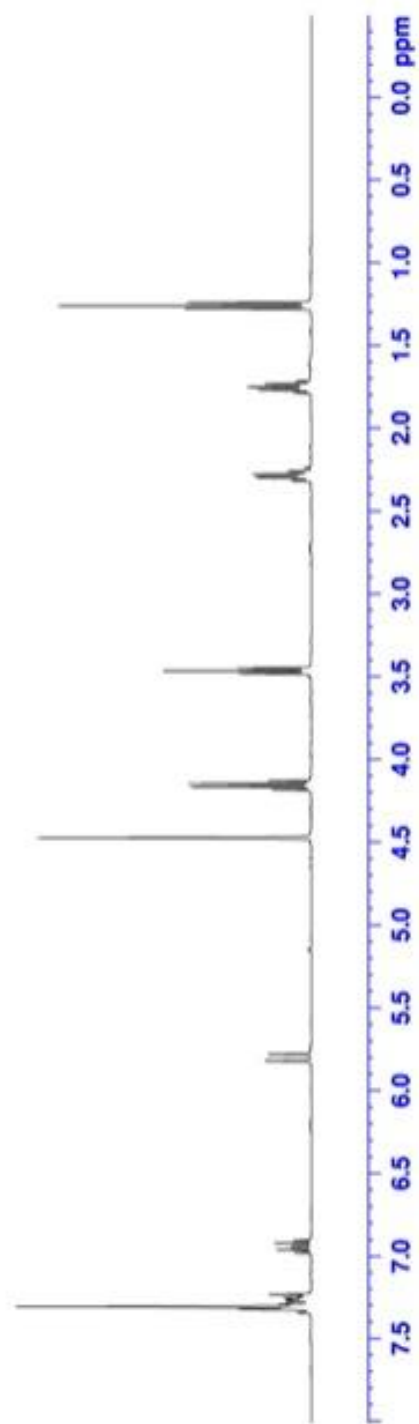
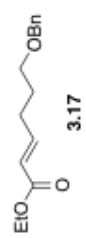
^1H NMR (500 MHz) of bis-THP core **2.38** (in CDCl_3)



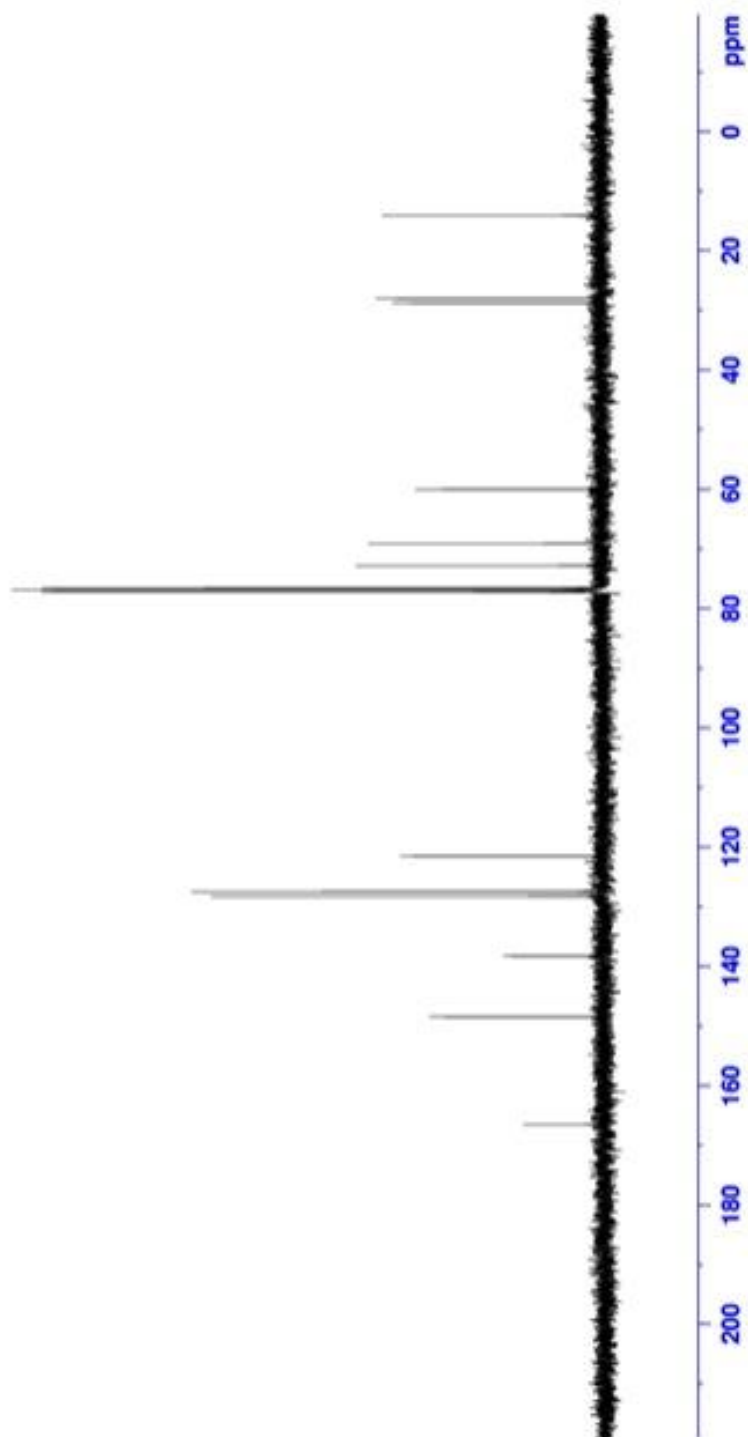
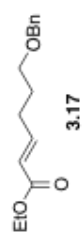
^{13}C NMR (125 MHz) of bis-THP core **2.38** (in CDCl_3)



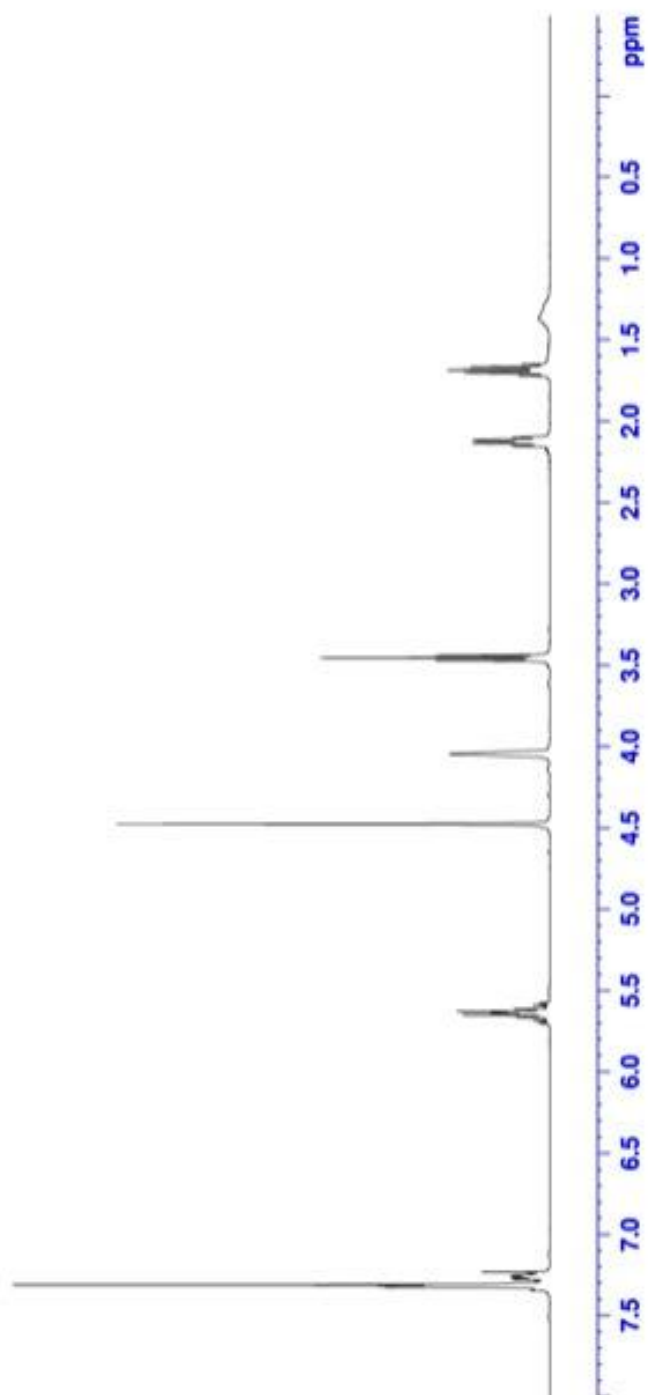
^1H NMR (400 MHz) of ester **3.17** (in CDCl_3)



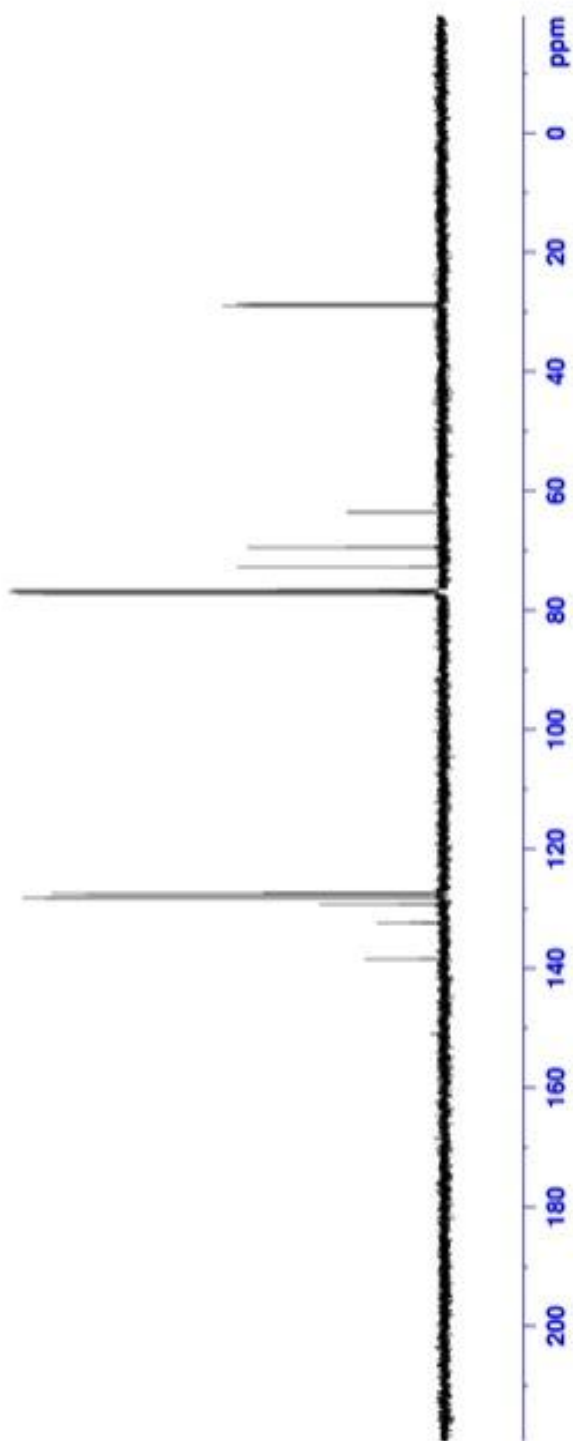
^{13}C NMR (100 MHz) of ester **3.17** (in CDCl_3)



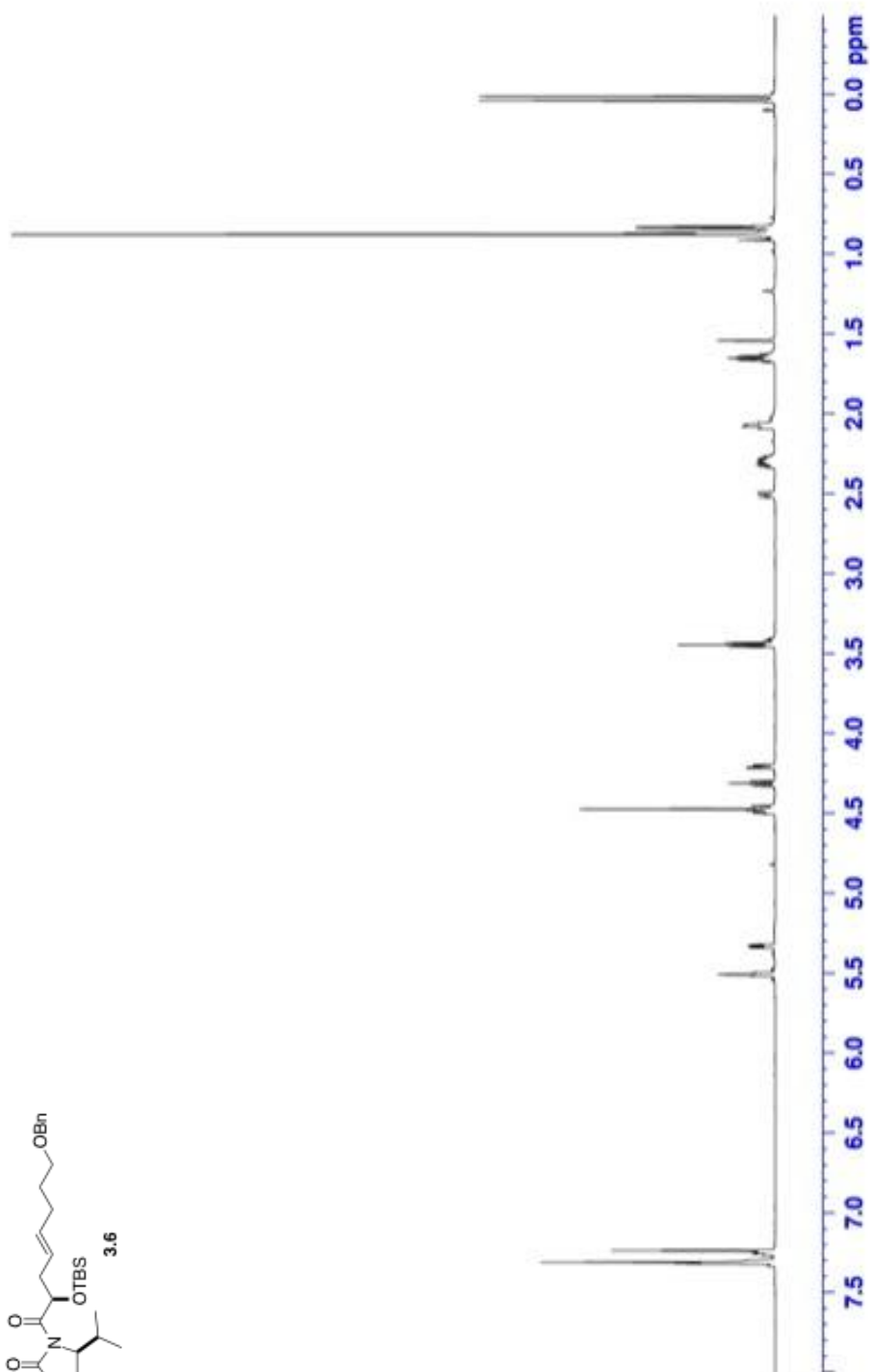
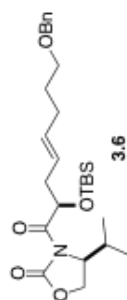
^1H NMR (400 MHz) of allylic alcohol **3.18** (in CDCl_3)



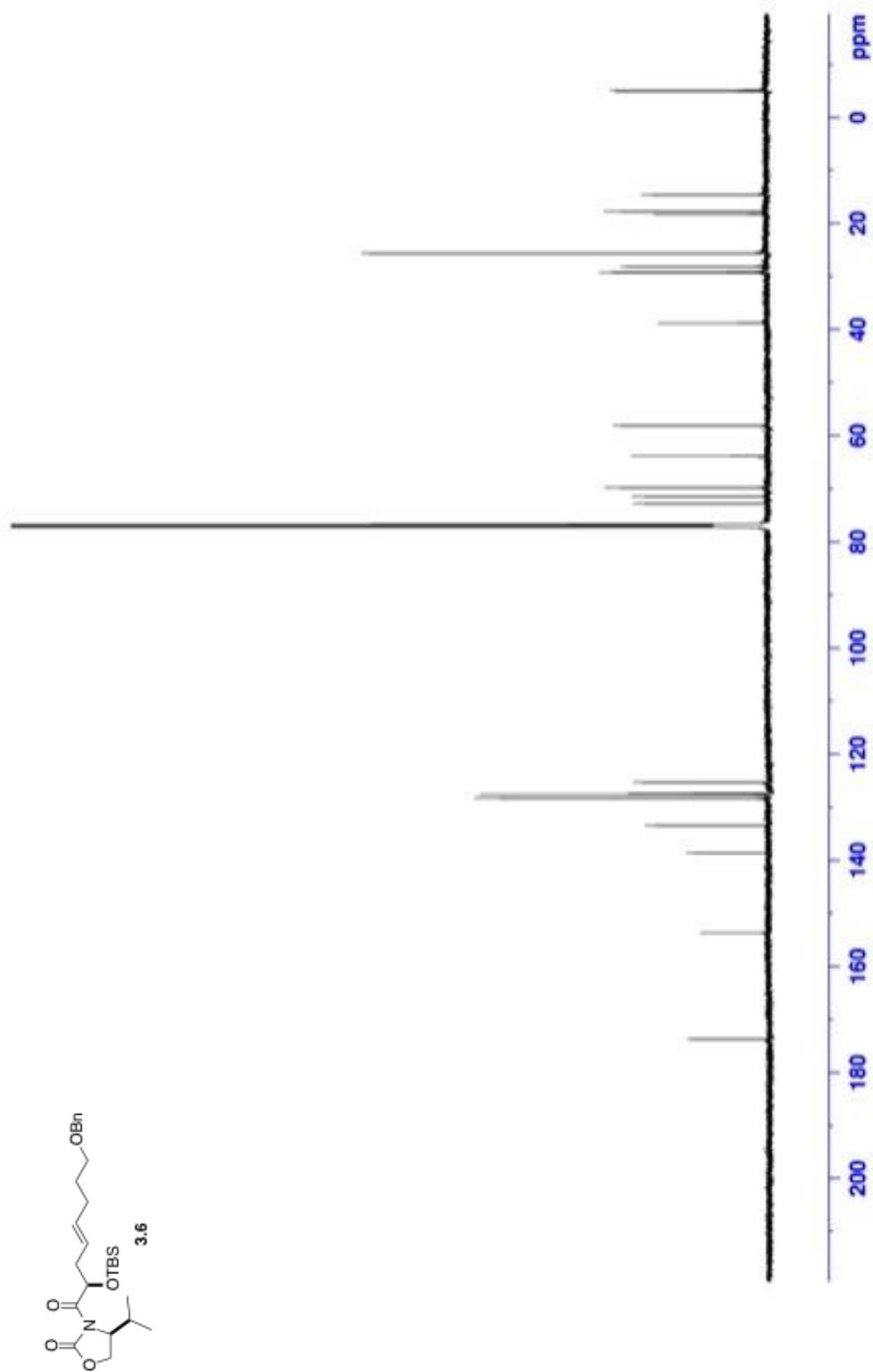
^{13}C NMR (100 MHz) of allylic alcohol **3.18** (in CDCl_3)



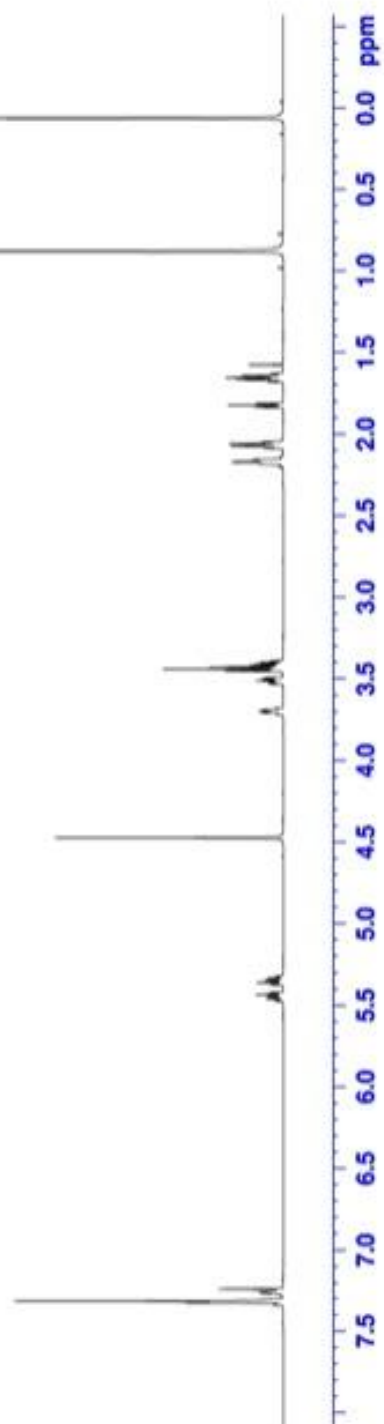
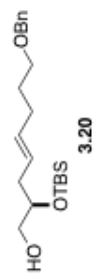
^1H NMR (600 MHz) of alkylation product **3.6** (in CDCl_3)



^{13}C NMR (150 MHz) of alkylation product **3.6** (in CDCl_3)



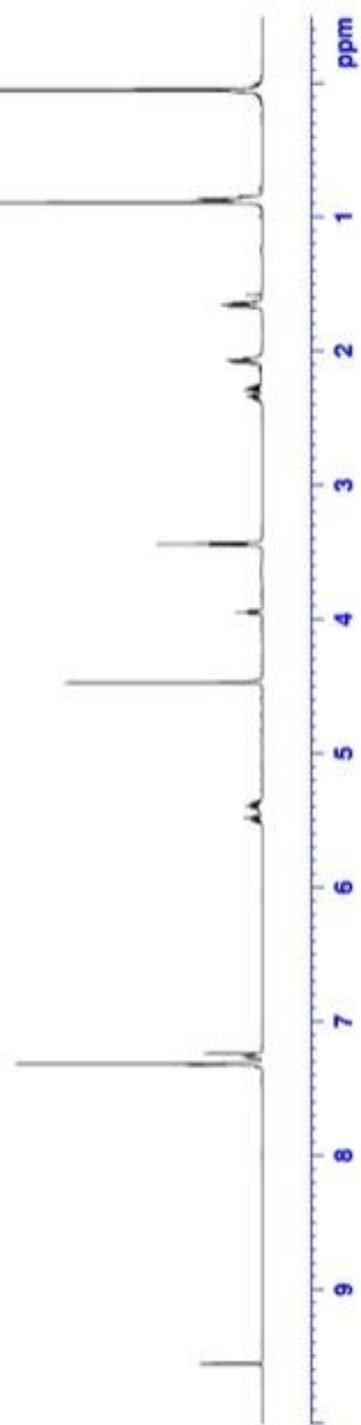
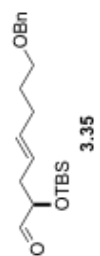
^1H NMR (600 MHz) of alcohol **3.20** (in CDCl_3)



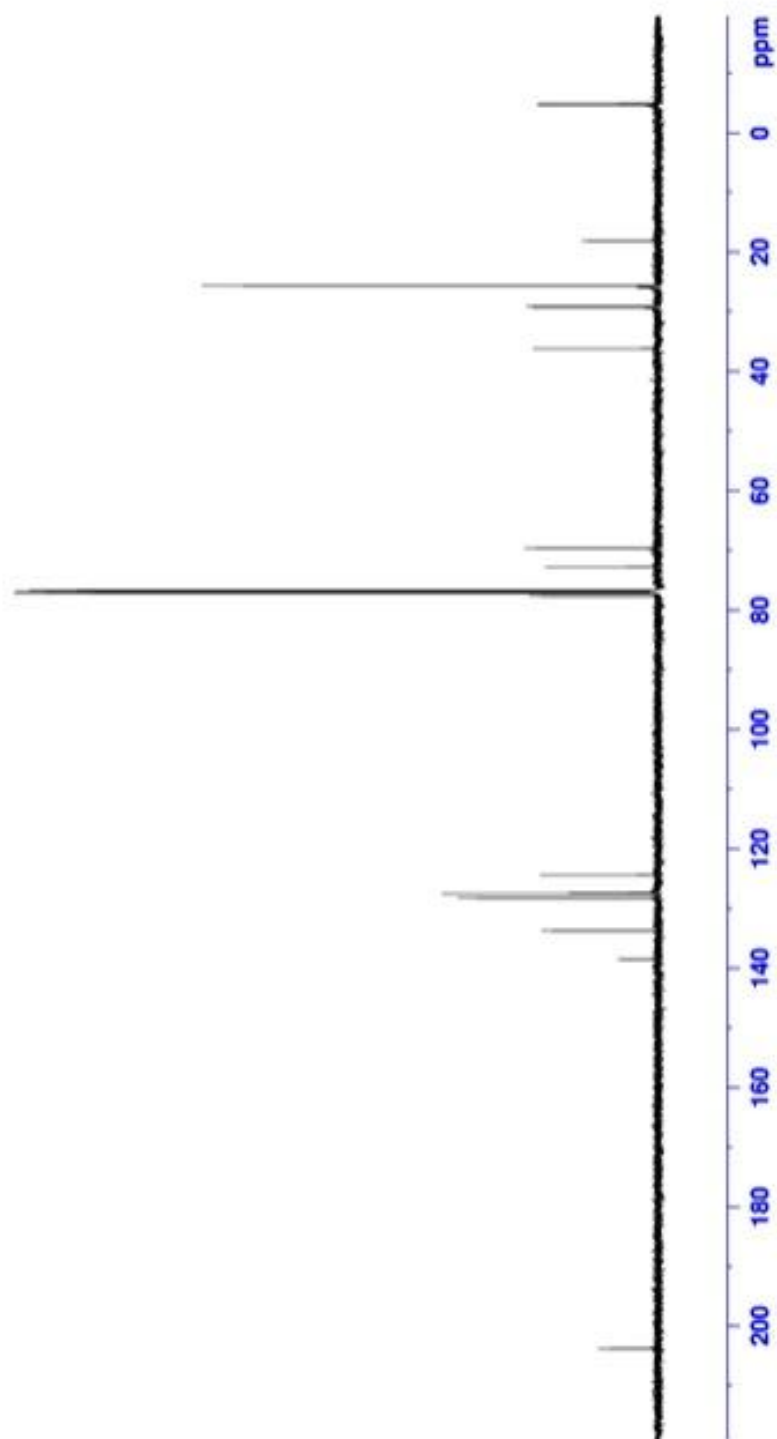
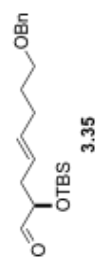
^{13}C NMR (100 MHz) of alcohol **3.20** (in CDCl_3)



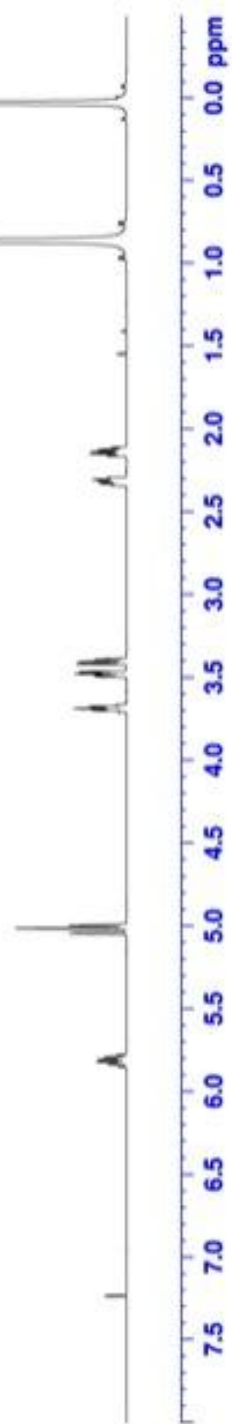
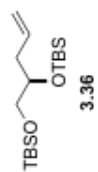
^1H NMR (600 MHz) of aldehyde **3.35** (in CDCl_3)



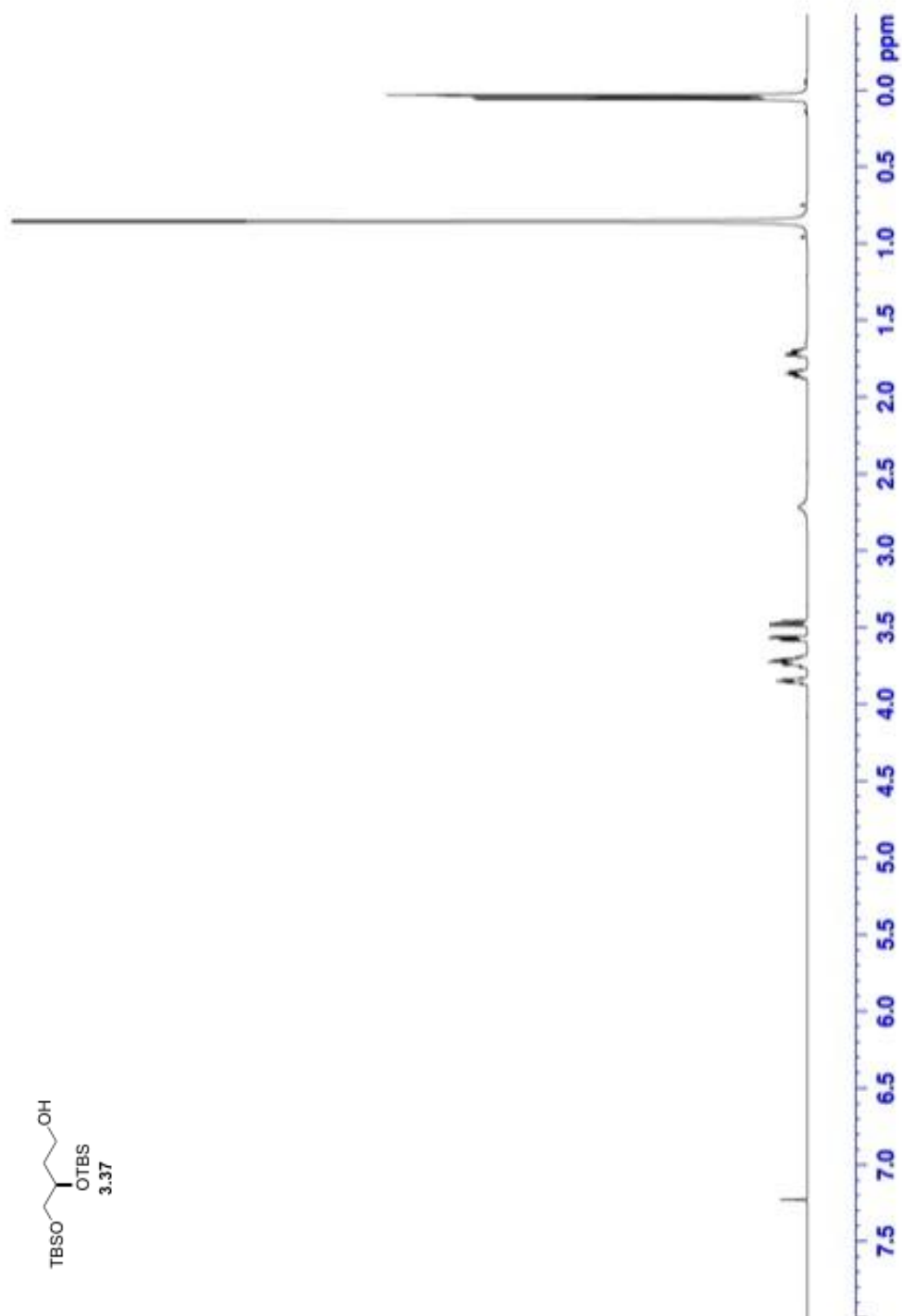
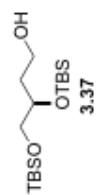
^{13}C NMR (150 MHz) of aldehyde **3.35** (in CDCl_3)



¹H NMR (600 MHz) of alkene **3.36** (in CDCl₃)

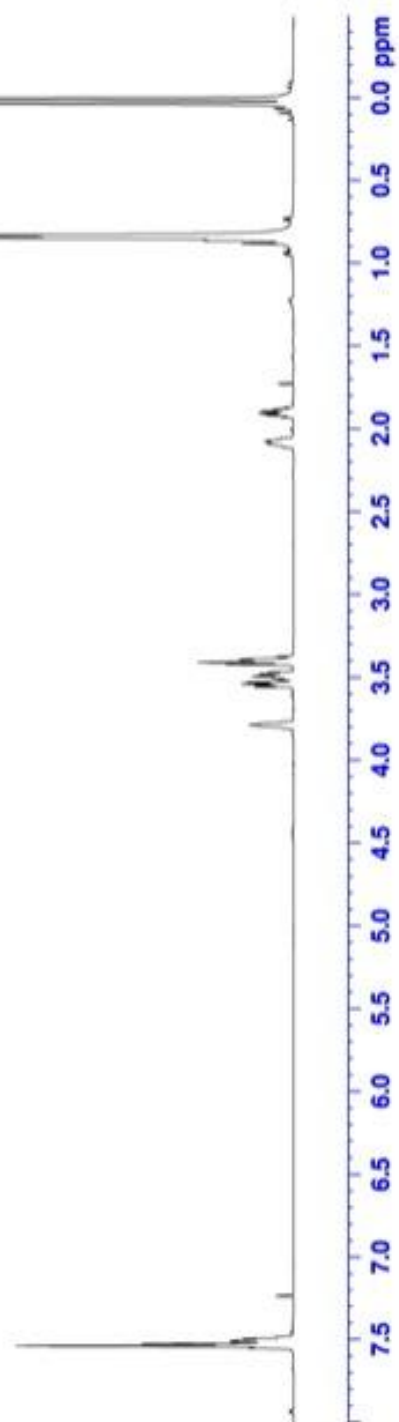
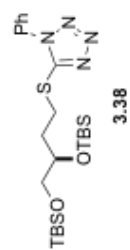


^1H NMR (600 MHz) of alcohol **3.37** (in CDCl_3)

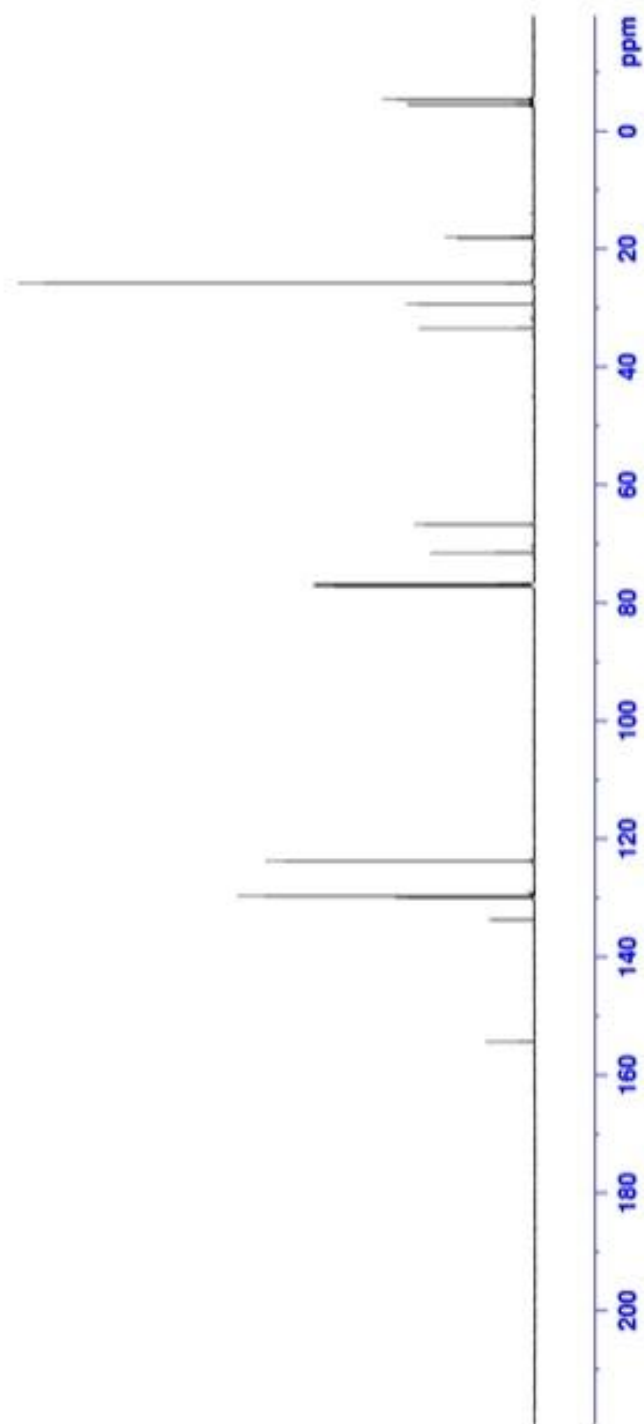
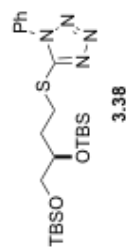




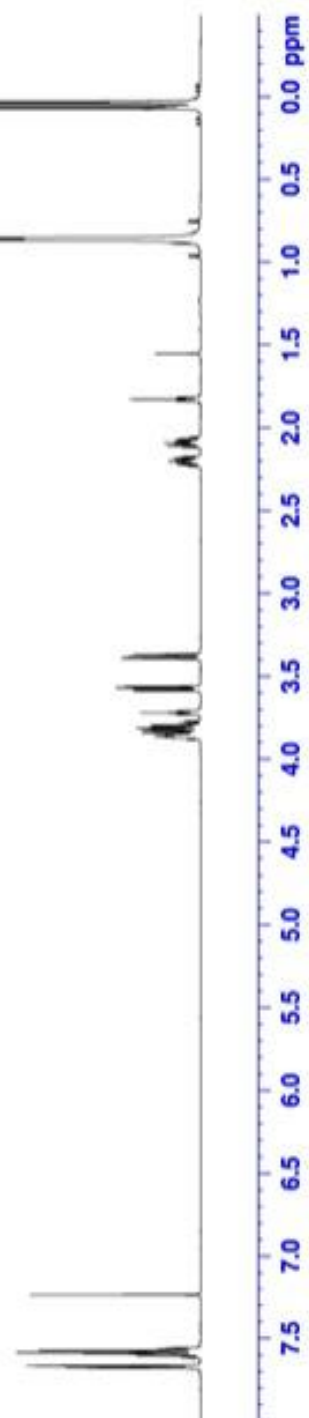
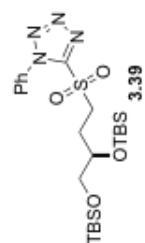
¹H NMR (600 MHz) of thioether **3.38** (in CDCl₃)



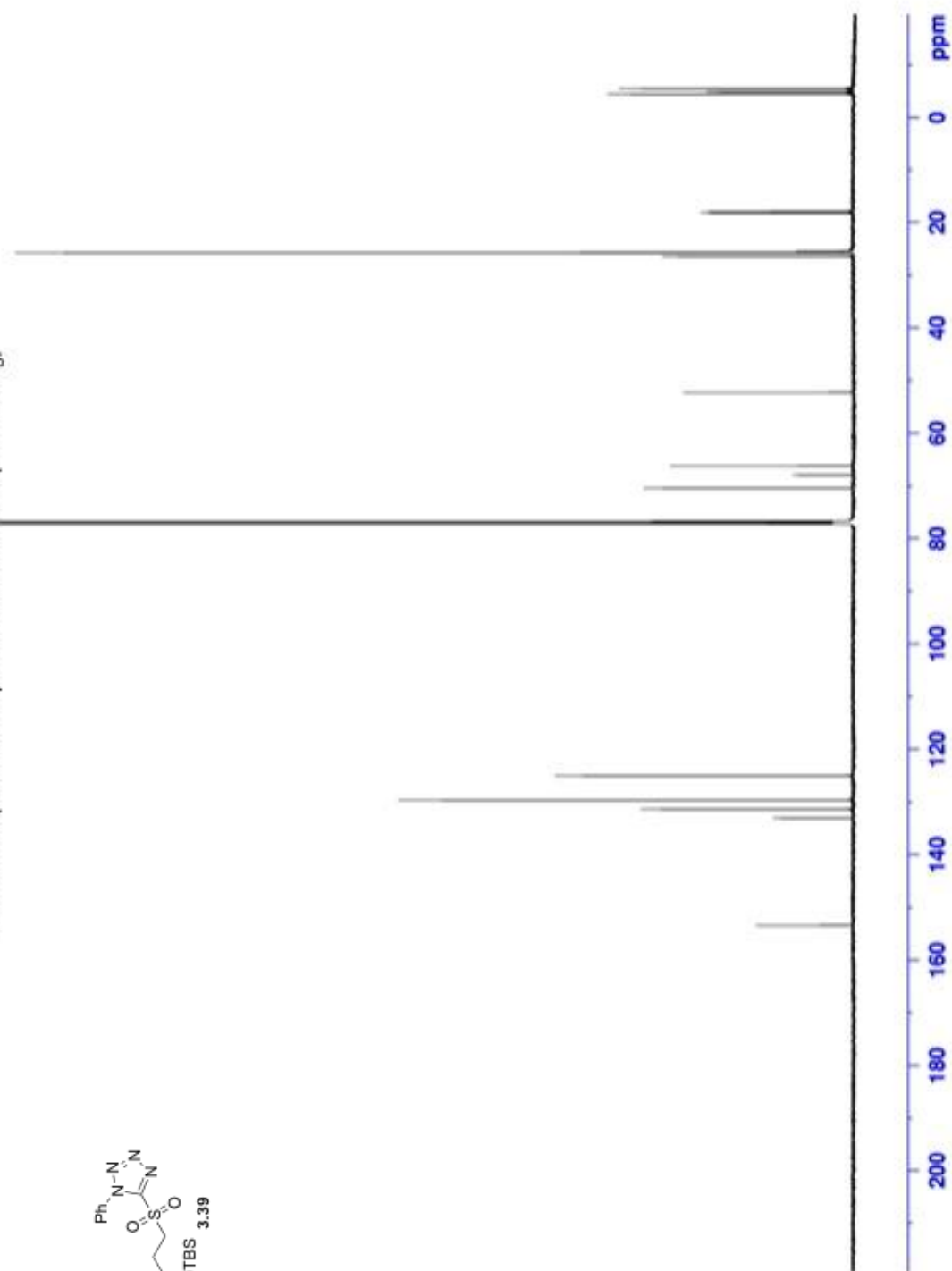
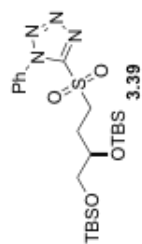
^{13}C NMR (150 MHz) of thioether **3.38** (in CDCl_3)



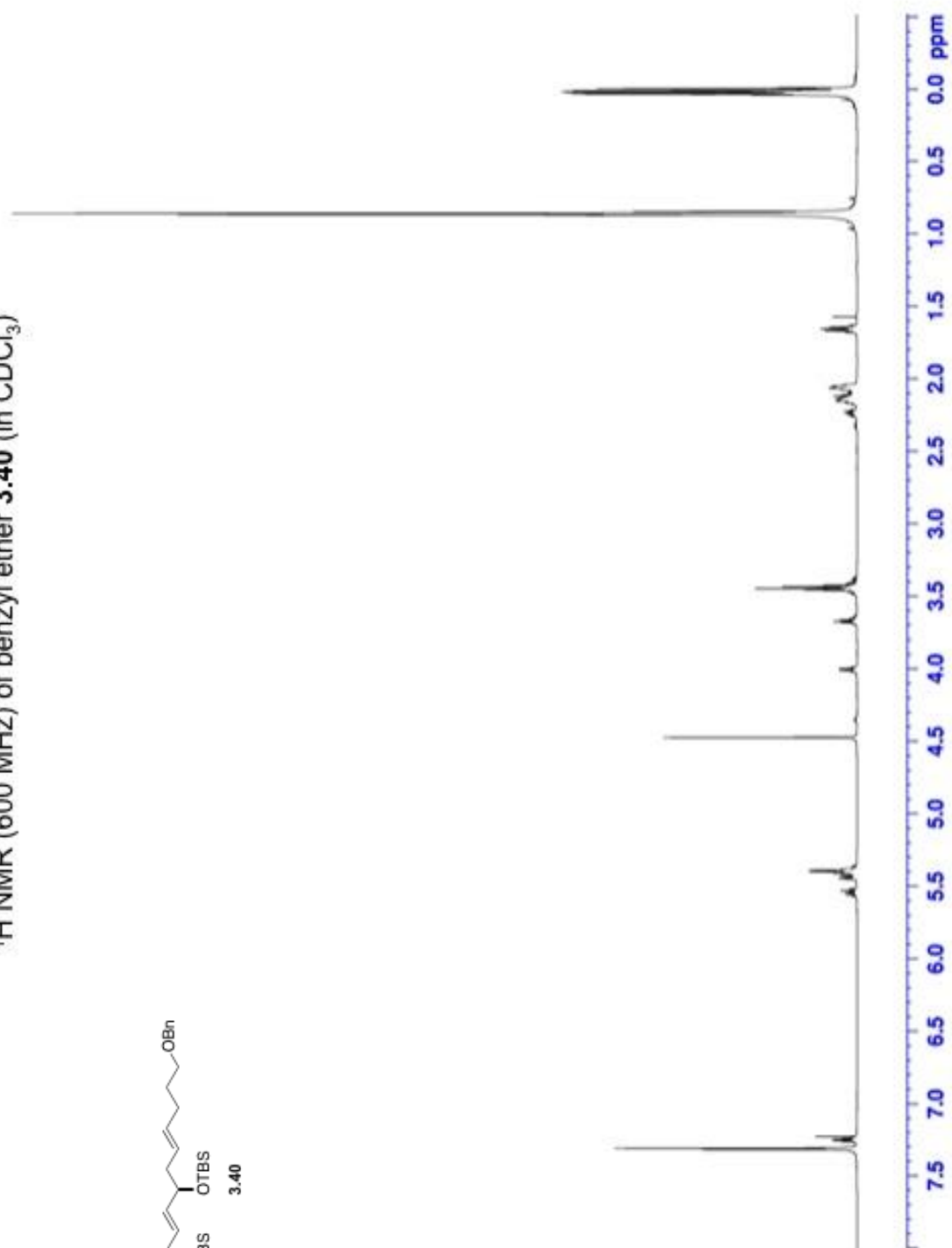
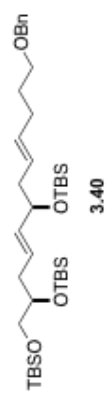
^1H NMR (600 MHz) of sulfone **3.39** (in CDCl_3)



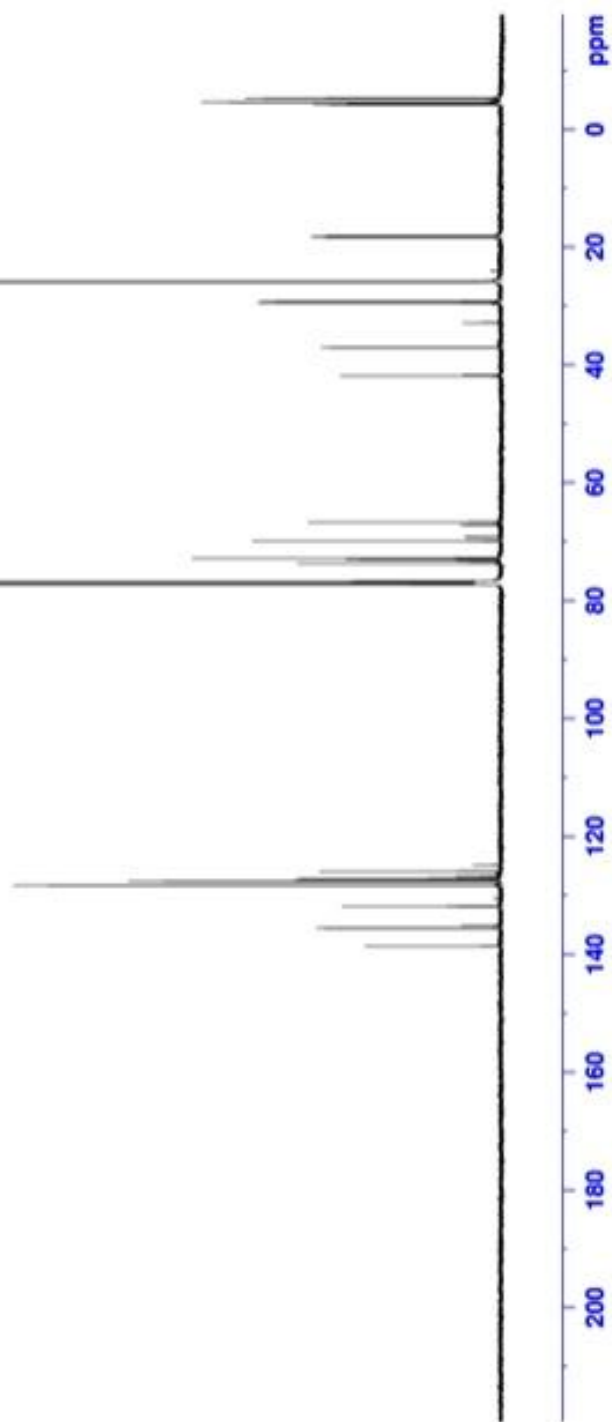
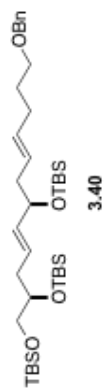
^{13}C NMR (150 MHz) of sulfone **3.39** (in CDCl_3)



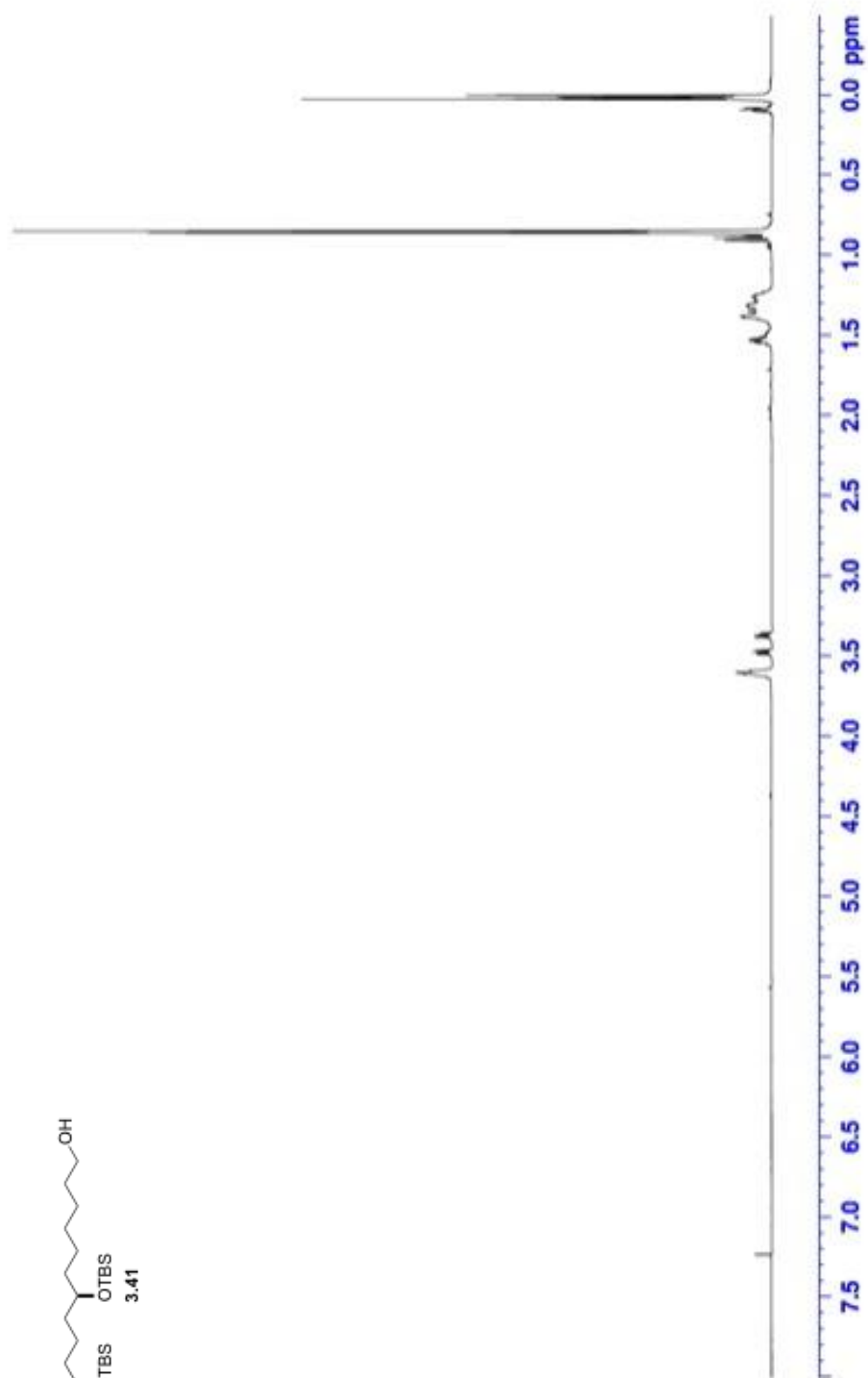
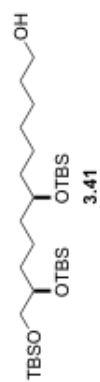
^1H NMR (600 MHz) of benzyl ether **3.40** (in CDCl_3)



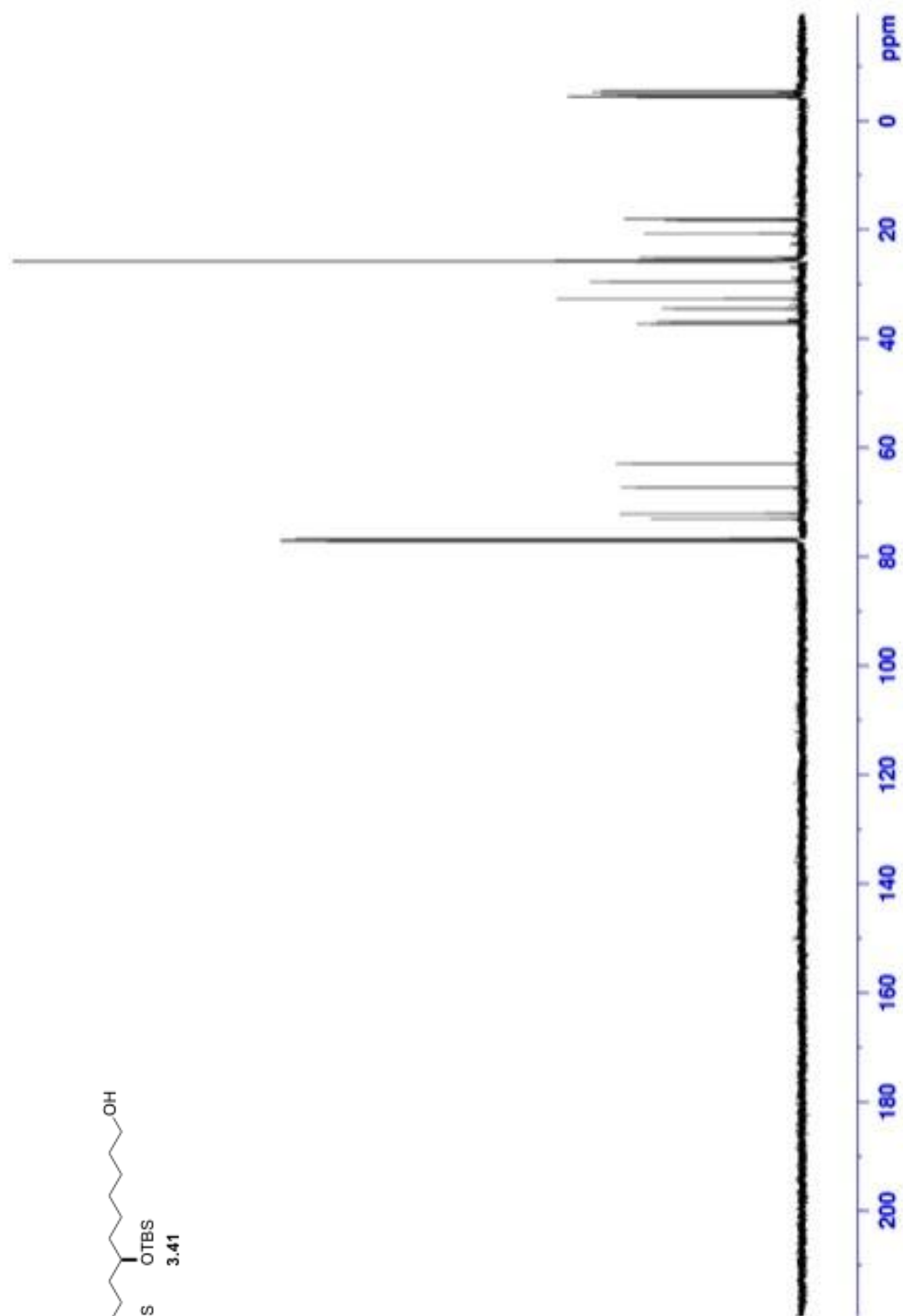
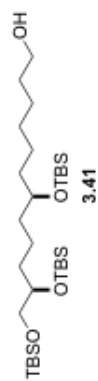
^{13}C NMR (150 MHz) of benzyl ether **3.40** (in CDCl_3)



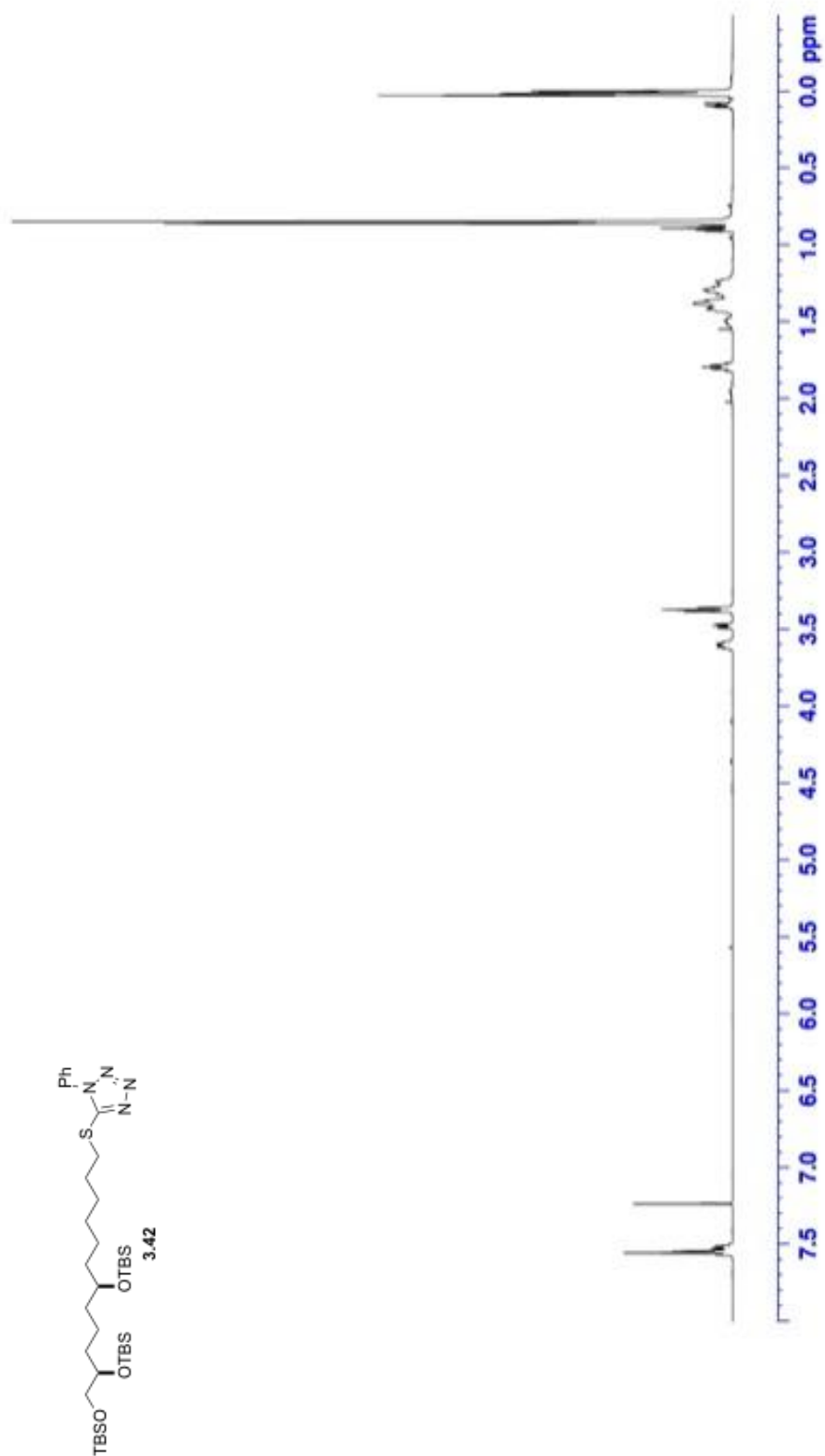
^1H NMR (600 MHz) of alcohol **3.41** (in CDCl_3)



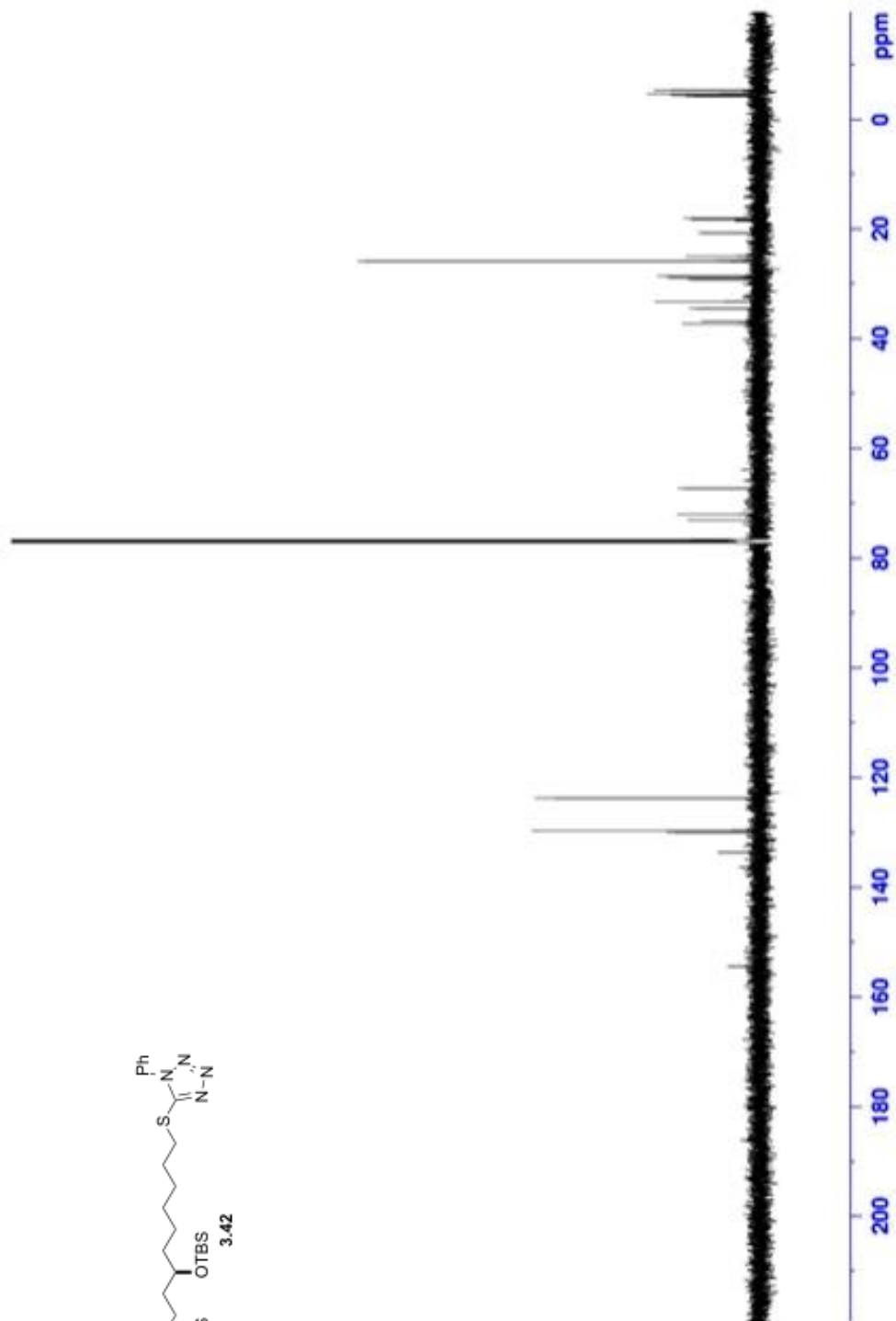
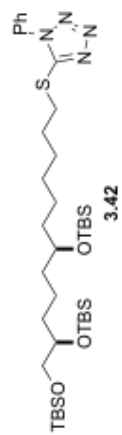
^{13}C NMR (150 MHz) of alcohol **3.41** (in CDCl_3)



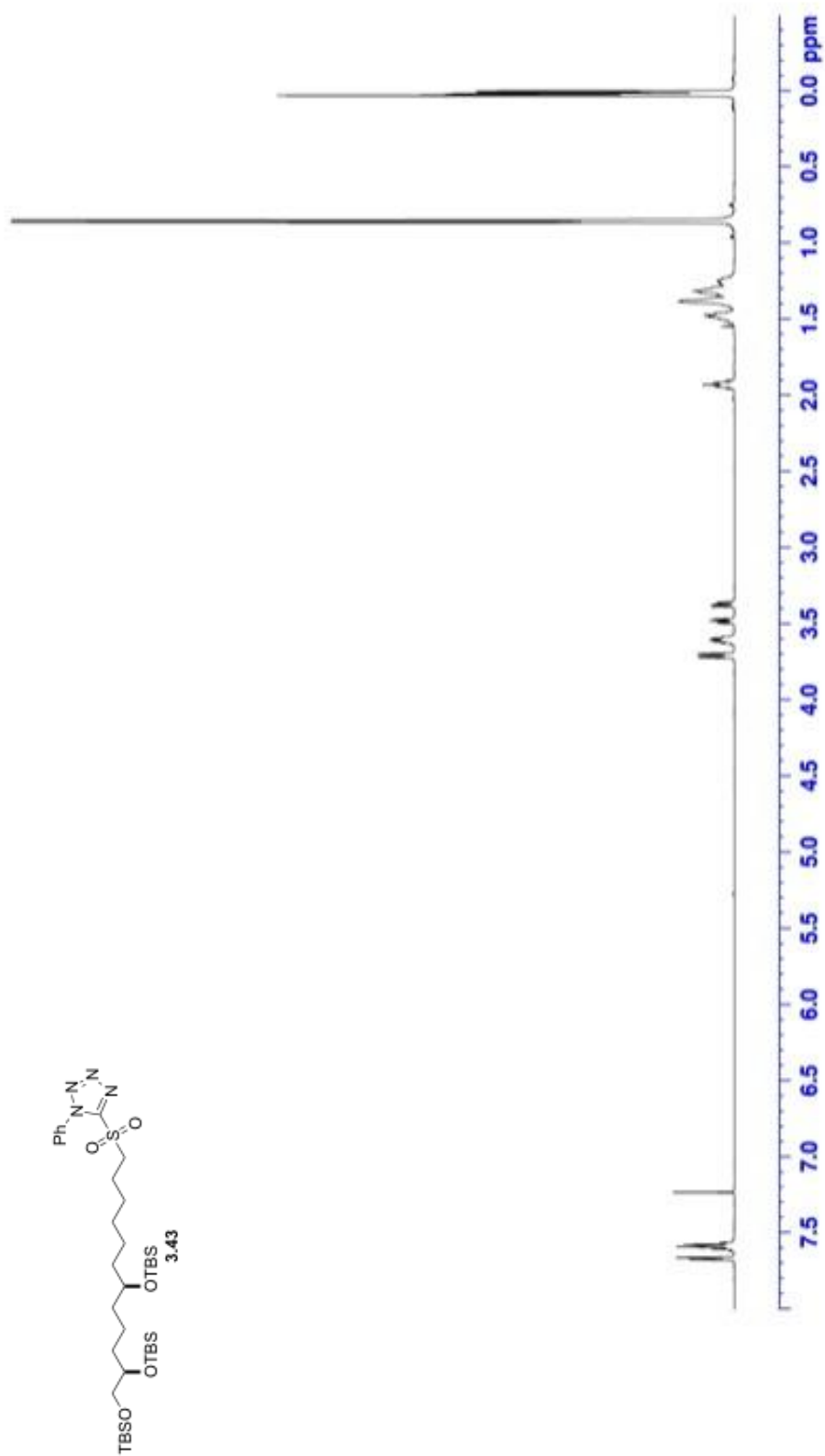
¹H NMR (600 MHz) of thioether **3.42** (in CDCl₃)



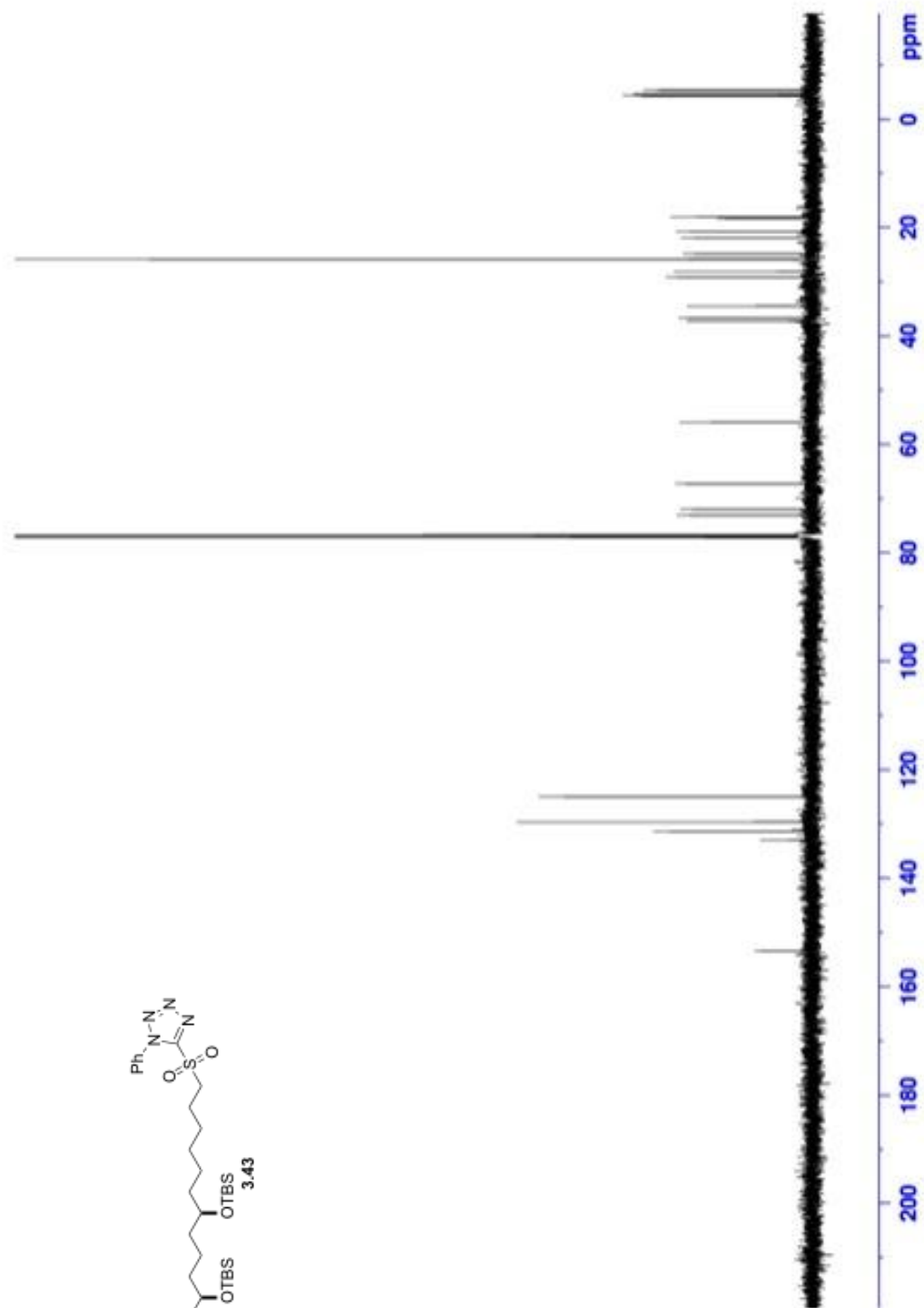
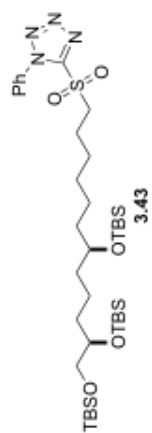
^{13}C NMR (150 MHz) of thioether **3.42** (in CDCl_3)



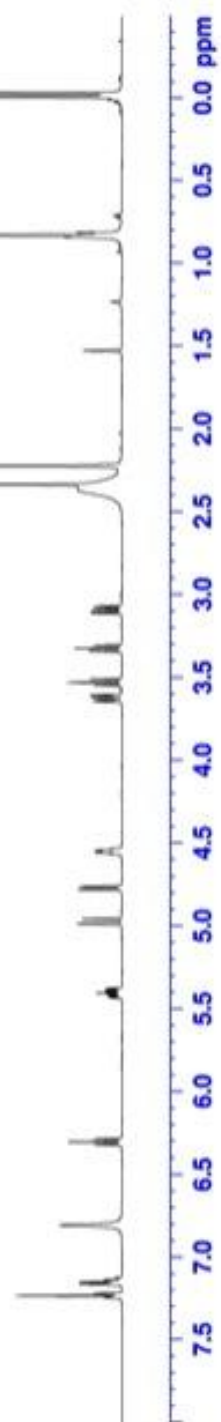
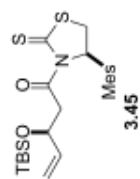
^1H NMR (600 MHz) of sulfone **3.43** (in CDCl_3)



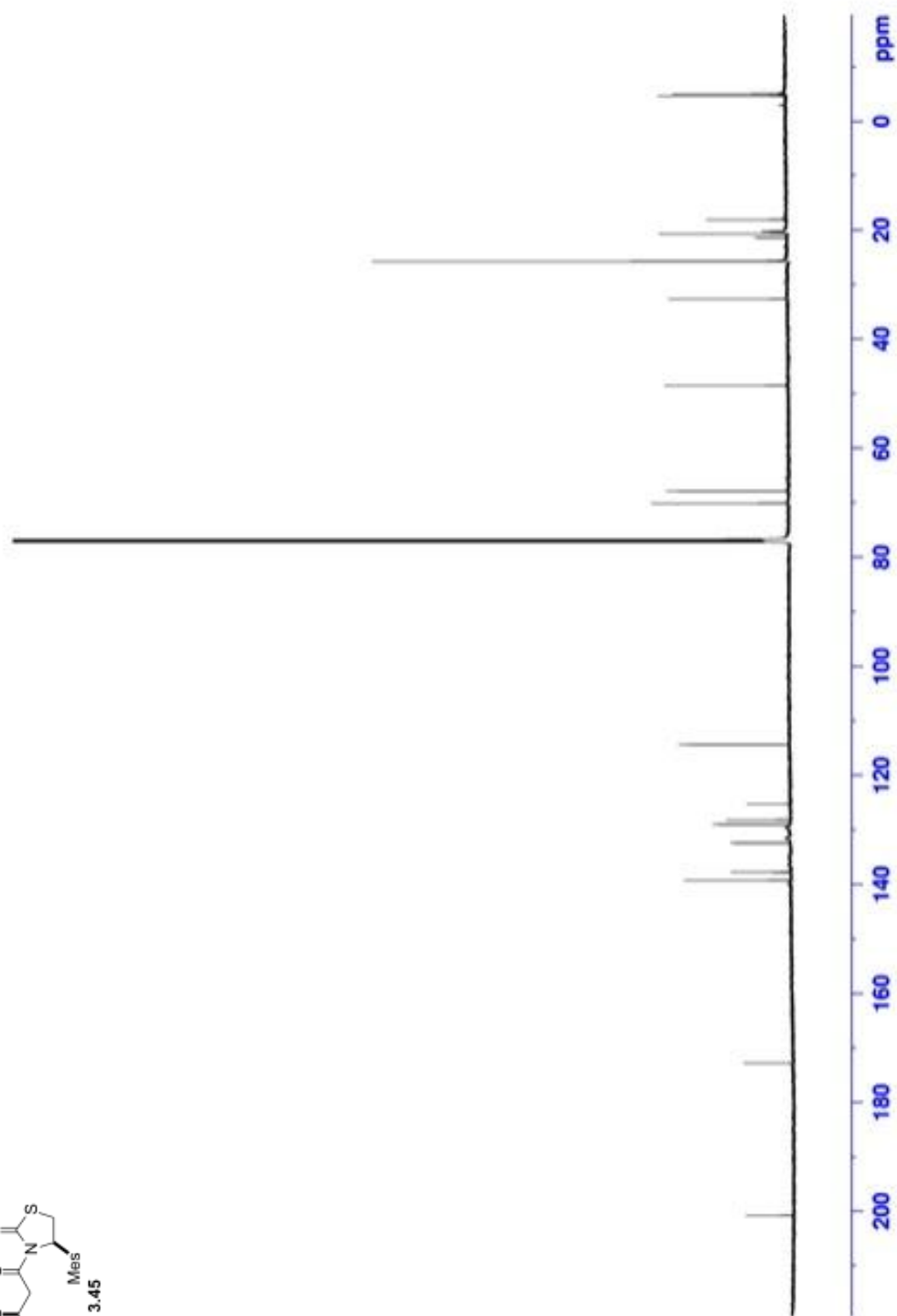
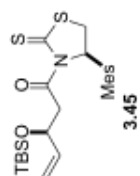
^{13}C NMR (150 MHz) of sulfone **3.43** (in CDCl_3)



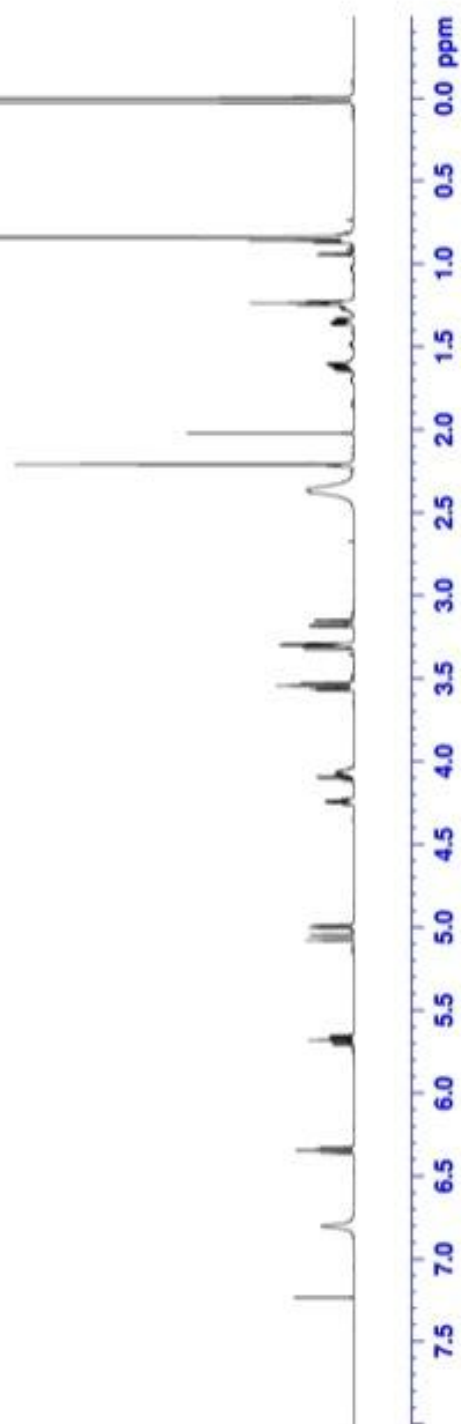
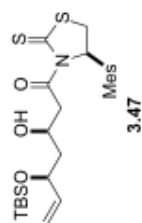
^1H NMR (600 MHz) of TBS ether **3.45** (in CDCl_3)



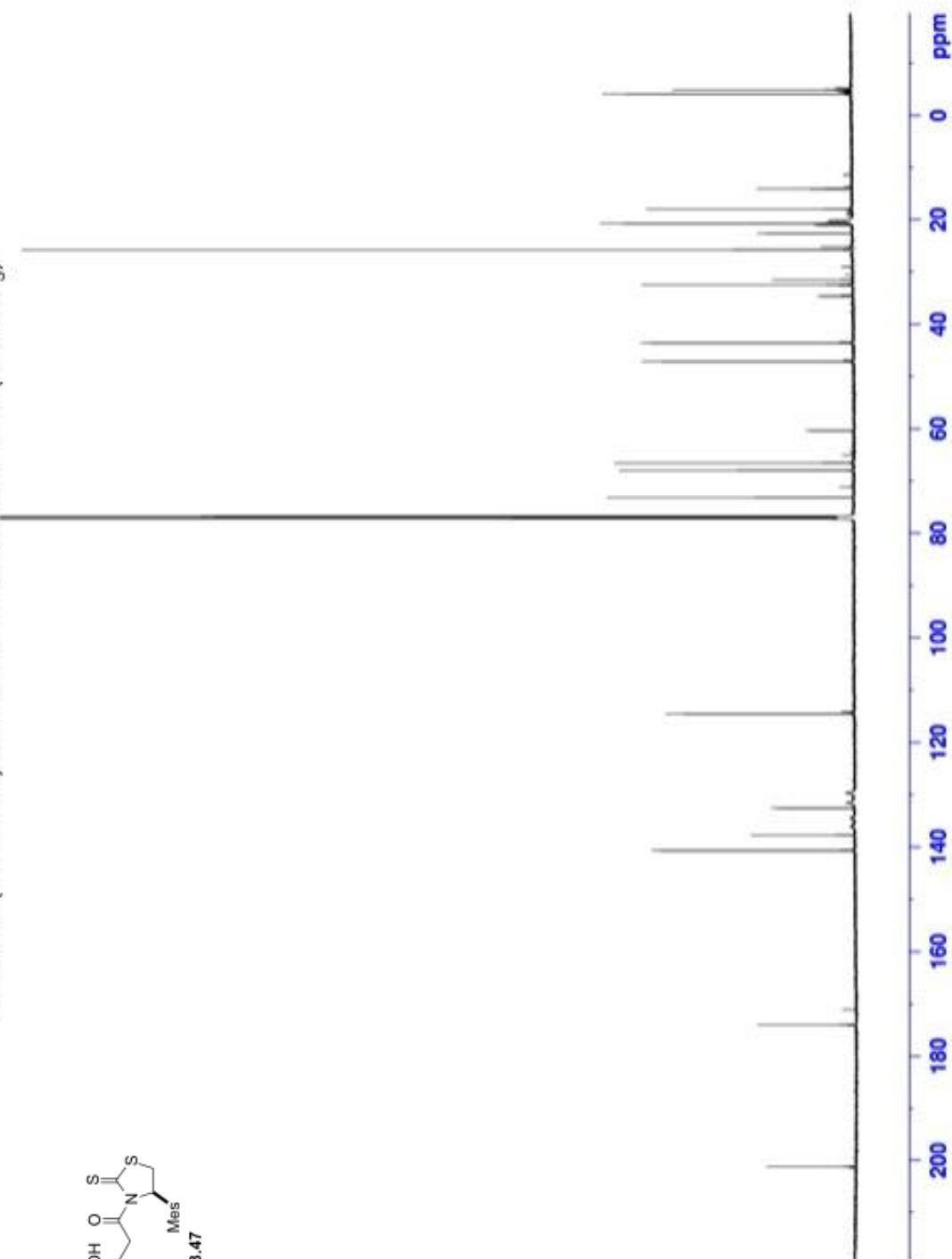
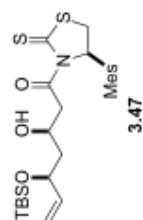
^{13}C NMR (150 MHz) of TBS ether **3.45** (in CDCl_3)



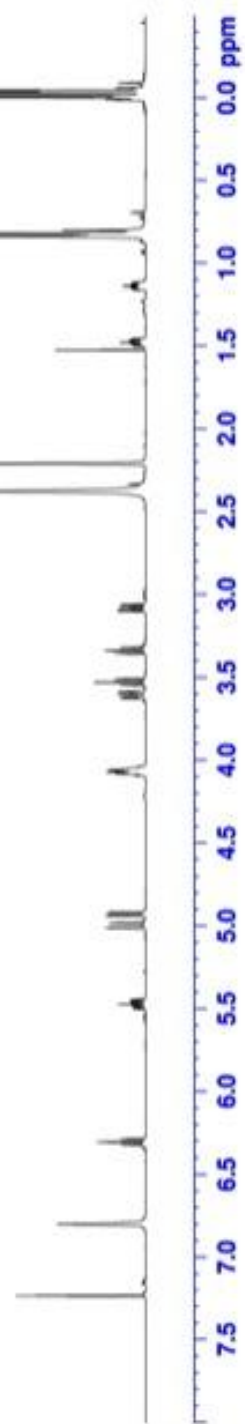
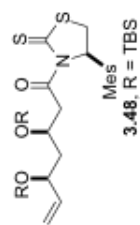
^1H NMR (600 MHz) of iterative aldol adduct **3.47** (in CDCl_3)



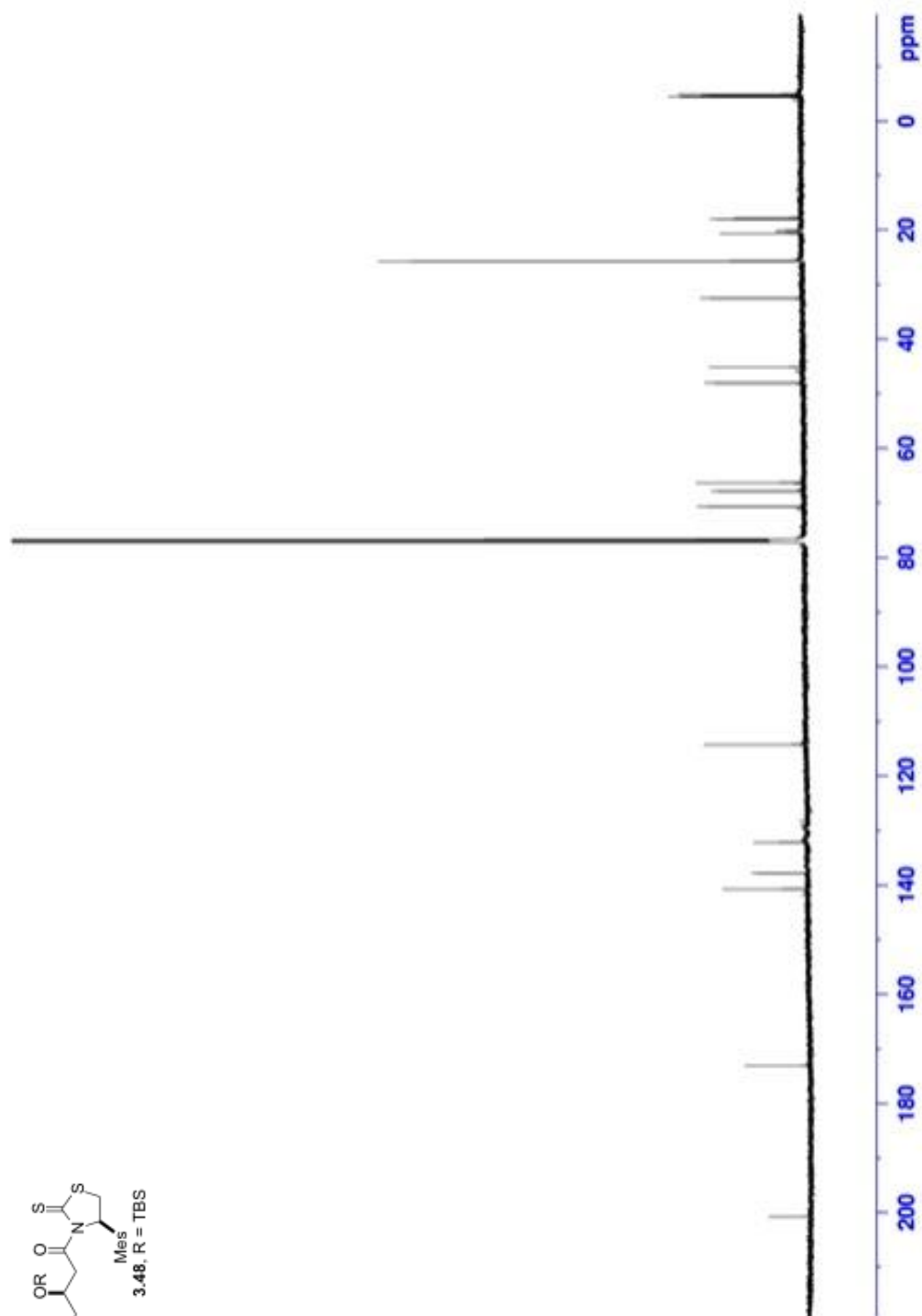
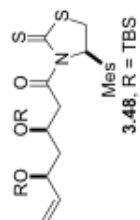
^{13}C NMR (150 MHz) of iterative aldol adduct **3.47** (in CDCl_3)



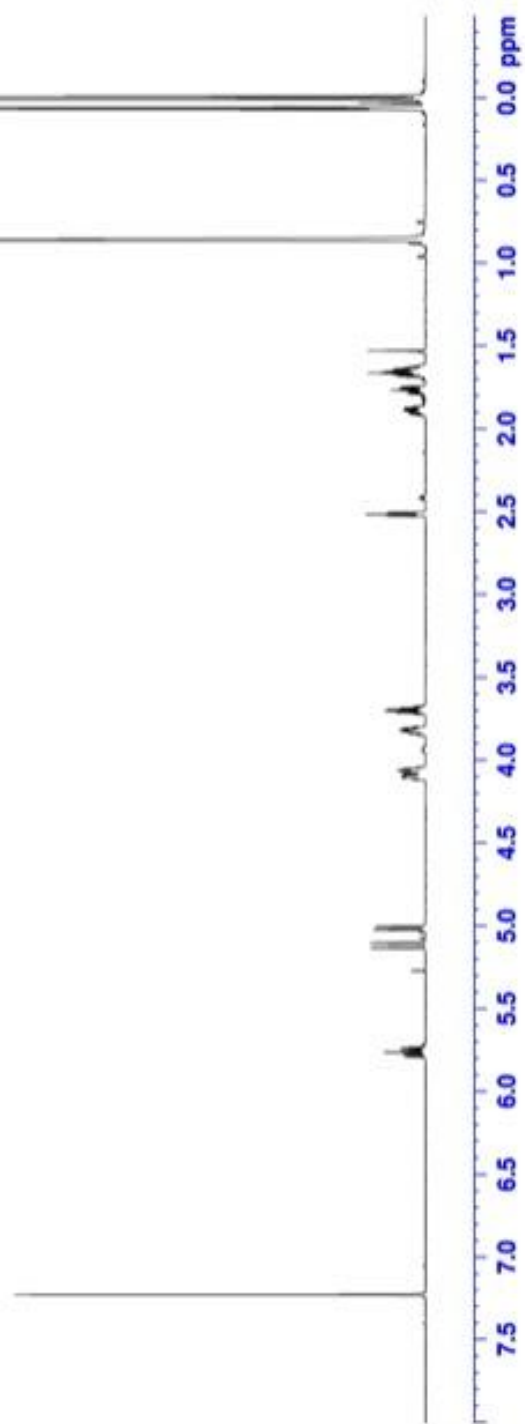
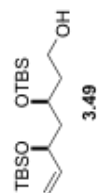
^1H NMR (600 MHz) of TBS ether **3.48** (in CDCl_3)



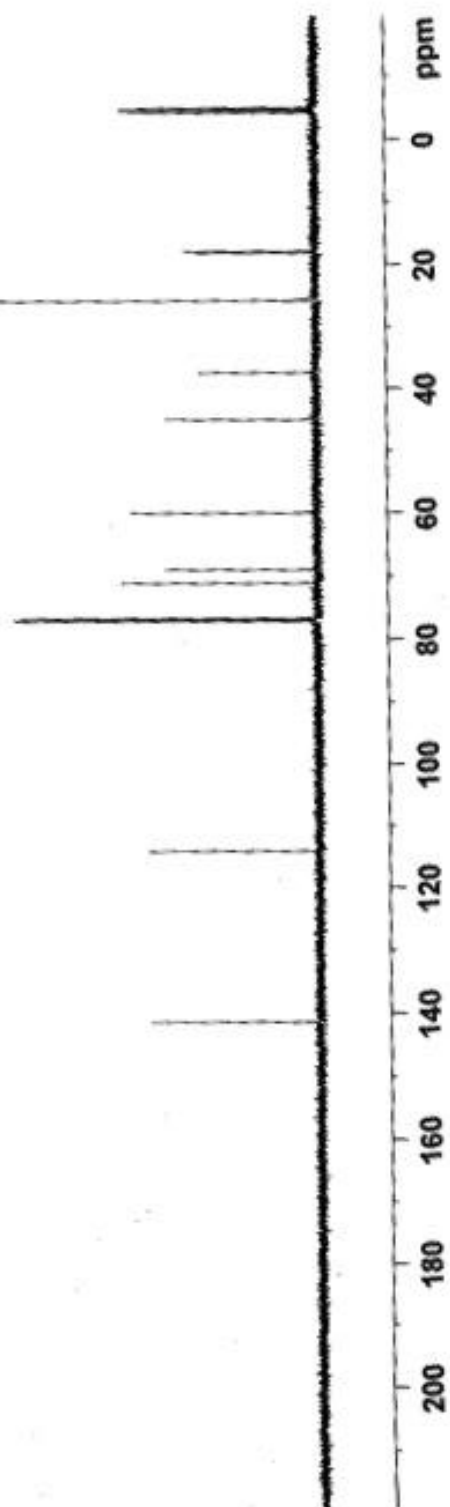
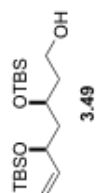
^{13}C NMR (150 MHz) of TBS ether **3.48** (in CDCl_3)



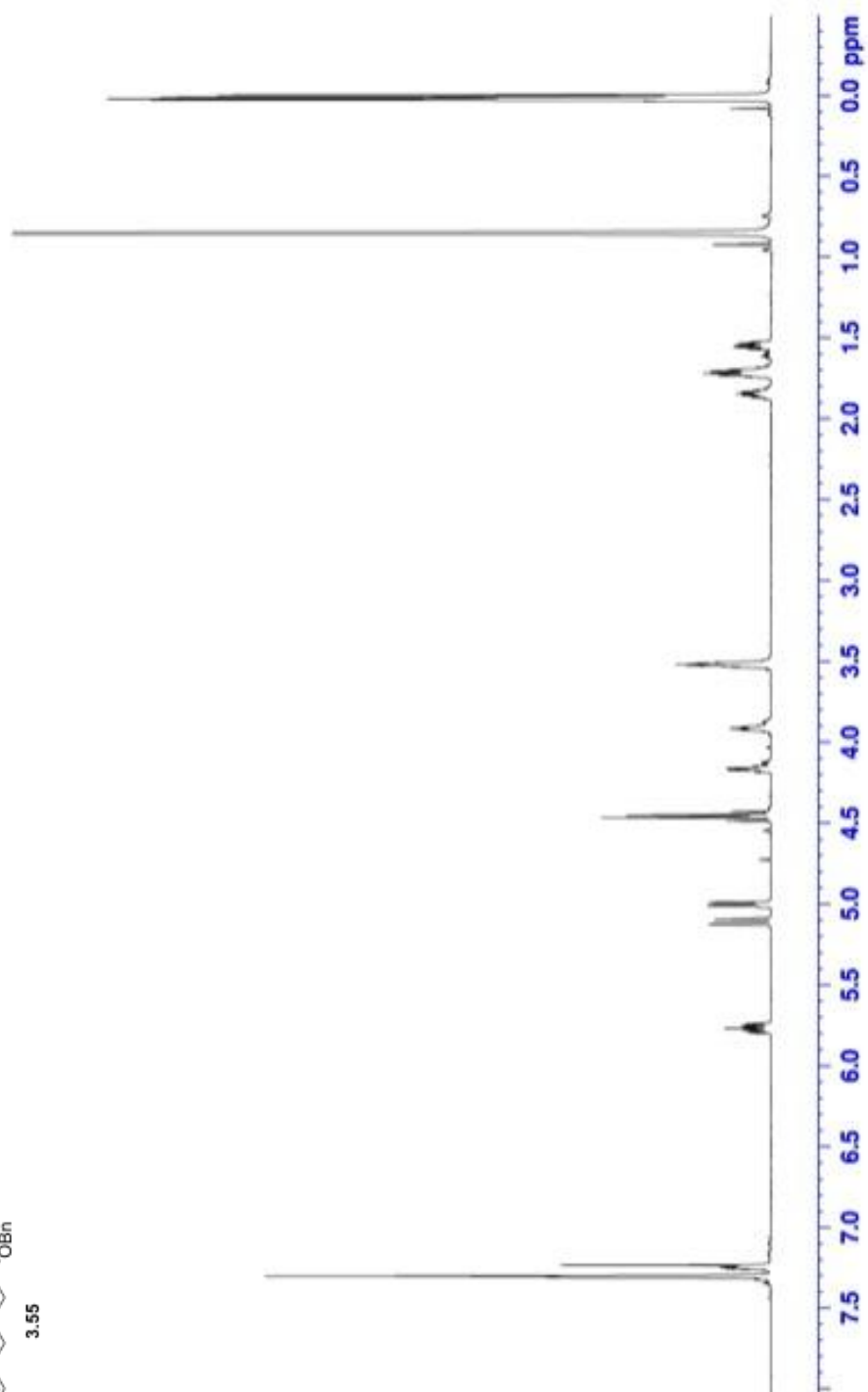
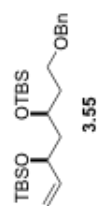
^1H NMR (600 MHz) of primary alcohol **3.49** (in CDCl_3)



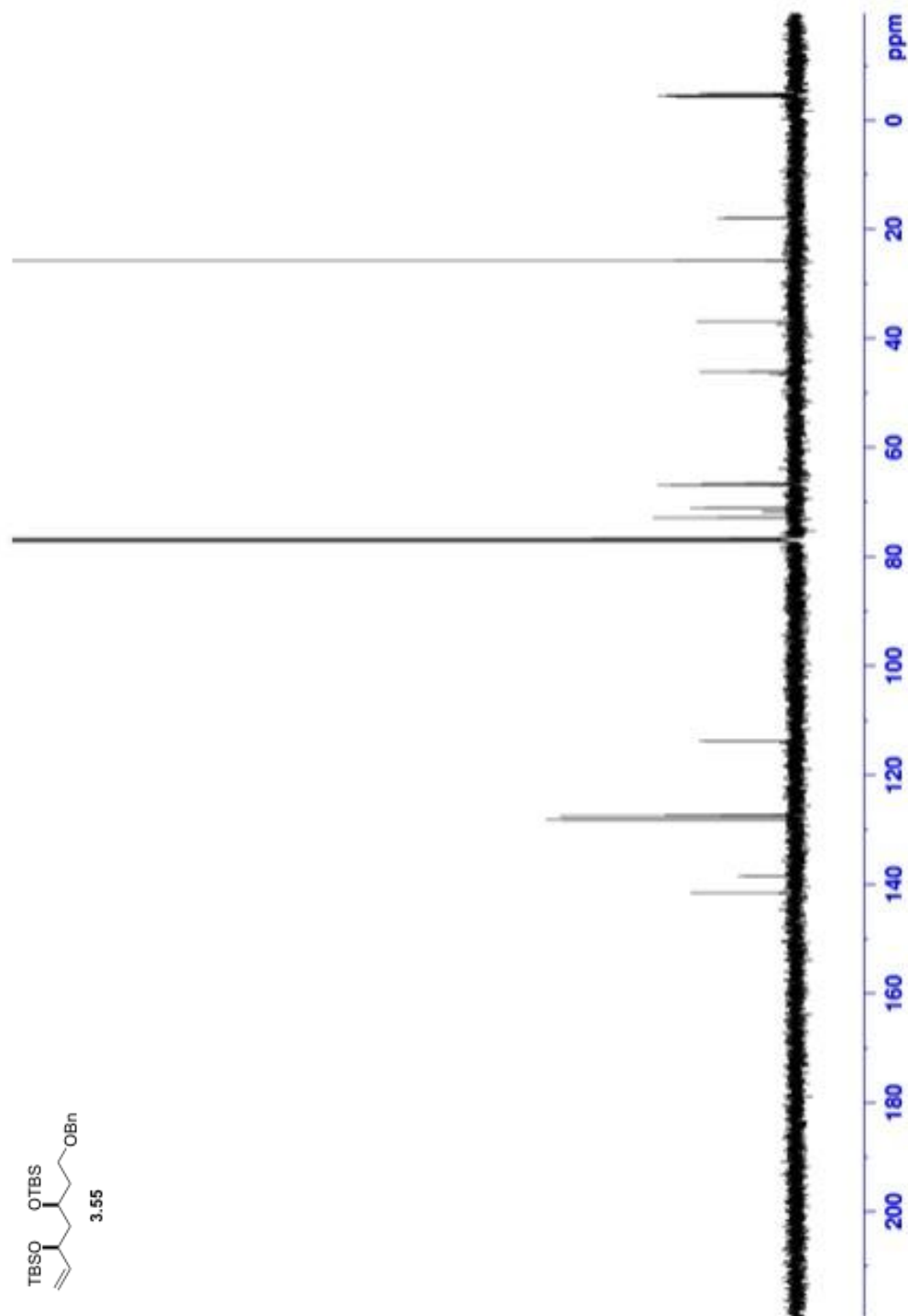
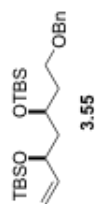
^{13}C NMR (150 MHz) of primary alcohol **3.49** (in CDCl_3)



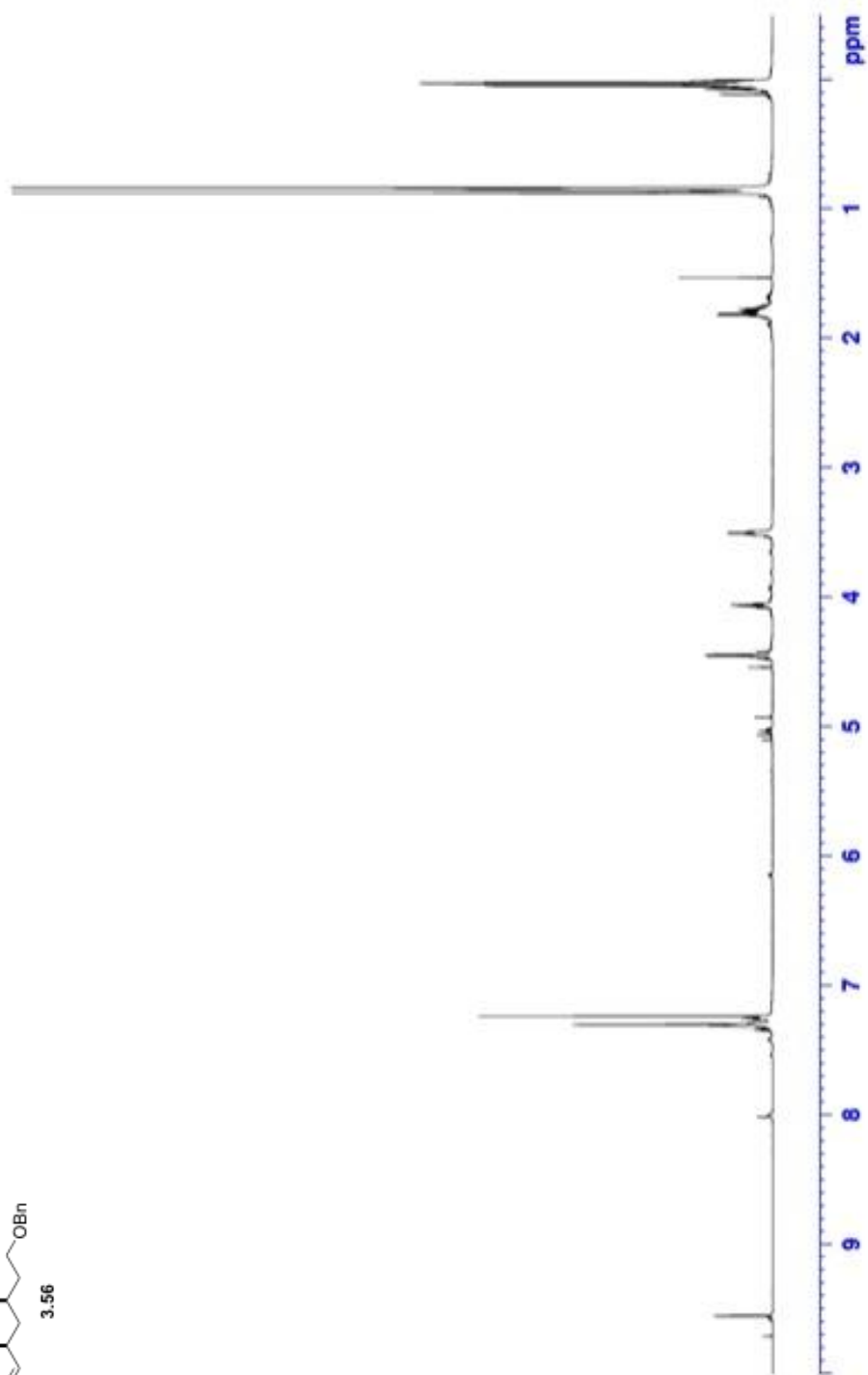
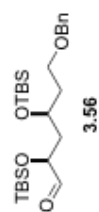
^1H NMR (600 MHz) of benzyl ether **3.55** (in CDCl_3)



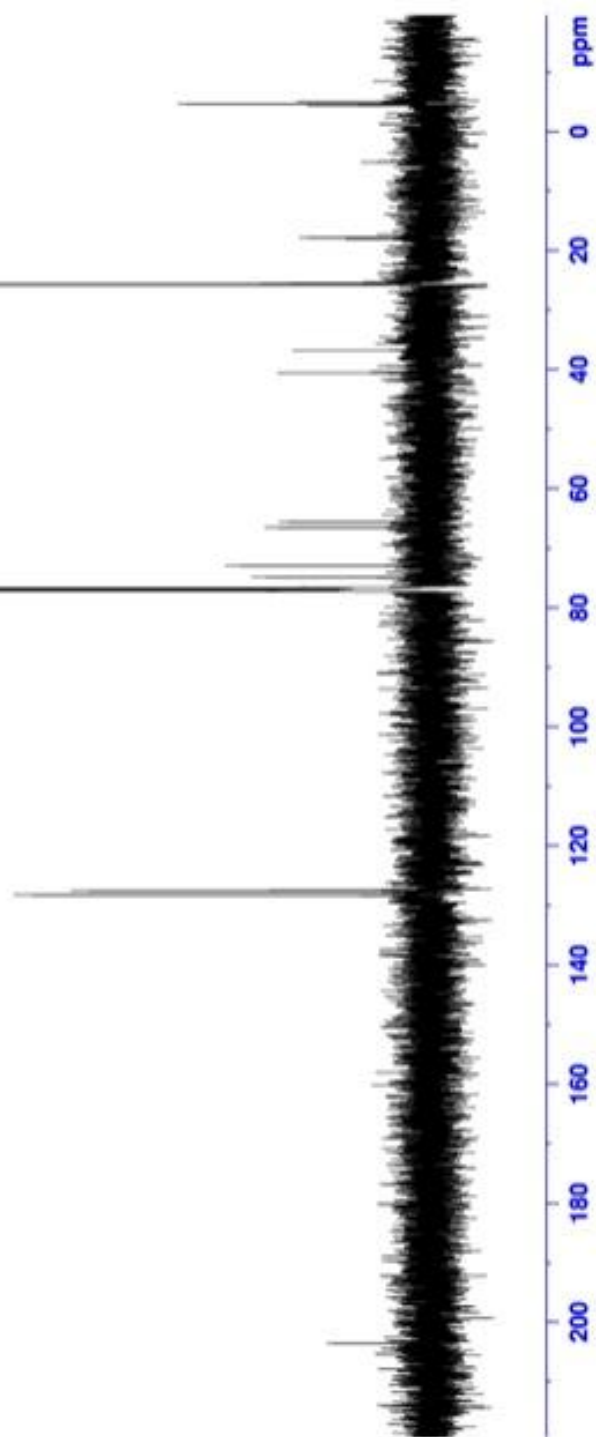
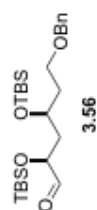
^{13}C NMR (150 MHz) of benzyl ether **3.55** (in CDCl_3)



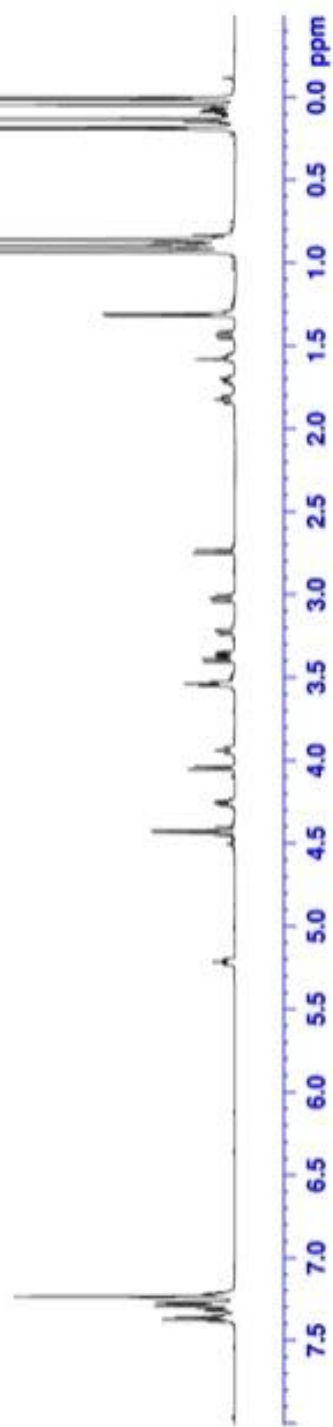
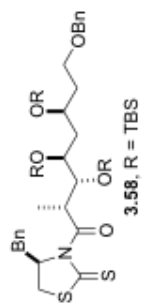
^1H NMR (600 MHz) of aldehyde **3.56** (in CDCl_3)



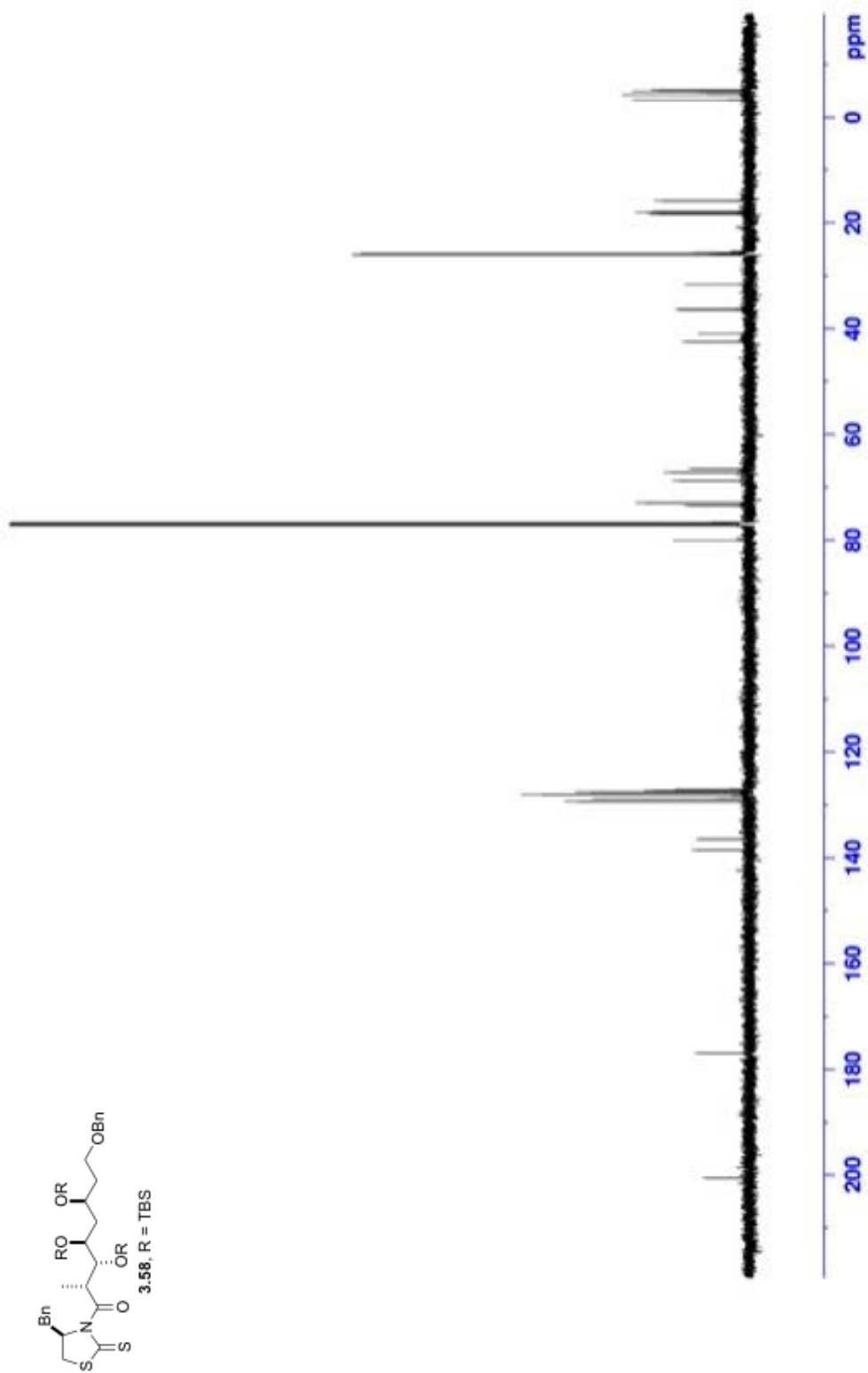
^{13}C NMR (150 MHz) of aldehyde **3.56** (in CDCl_3)



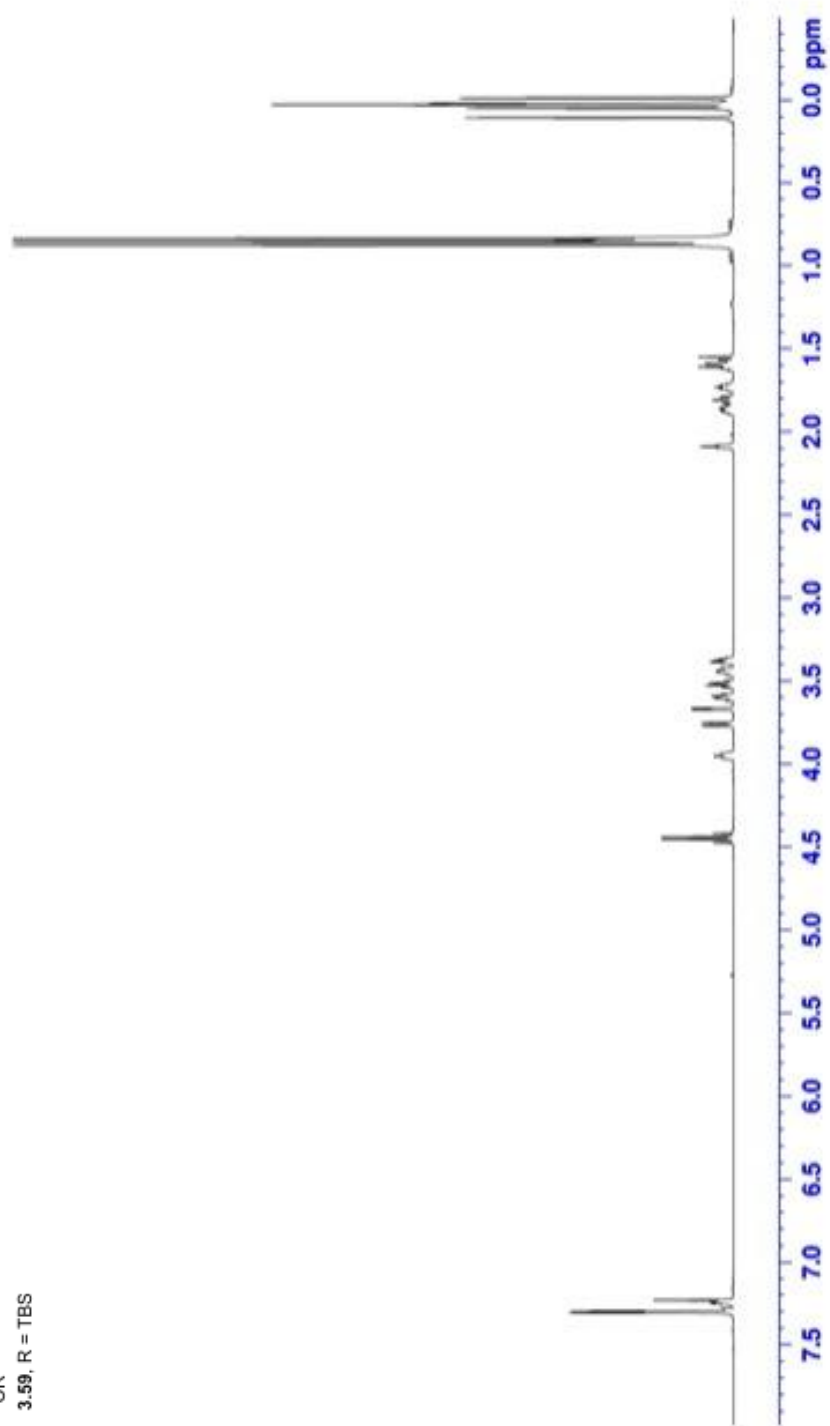
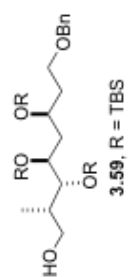
^1H NMR (600 MHz) of TBS ether **3.58** (in CDCl_3)



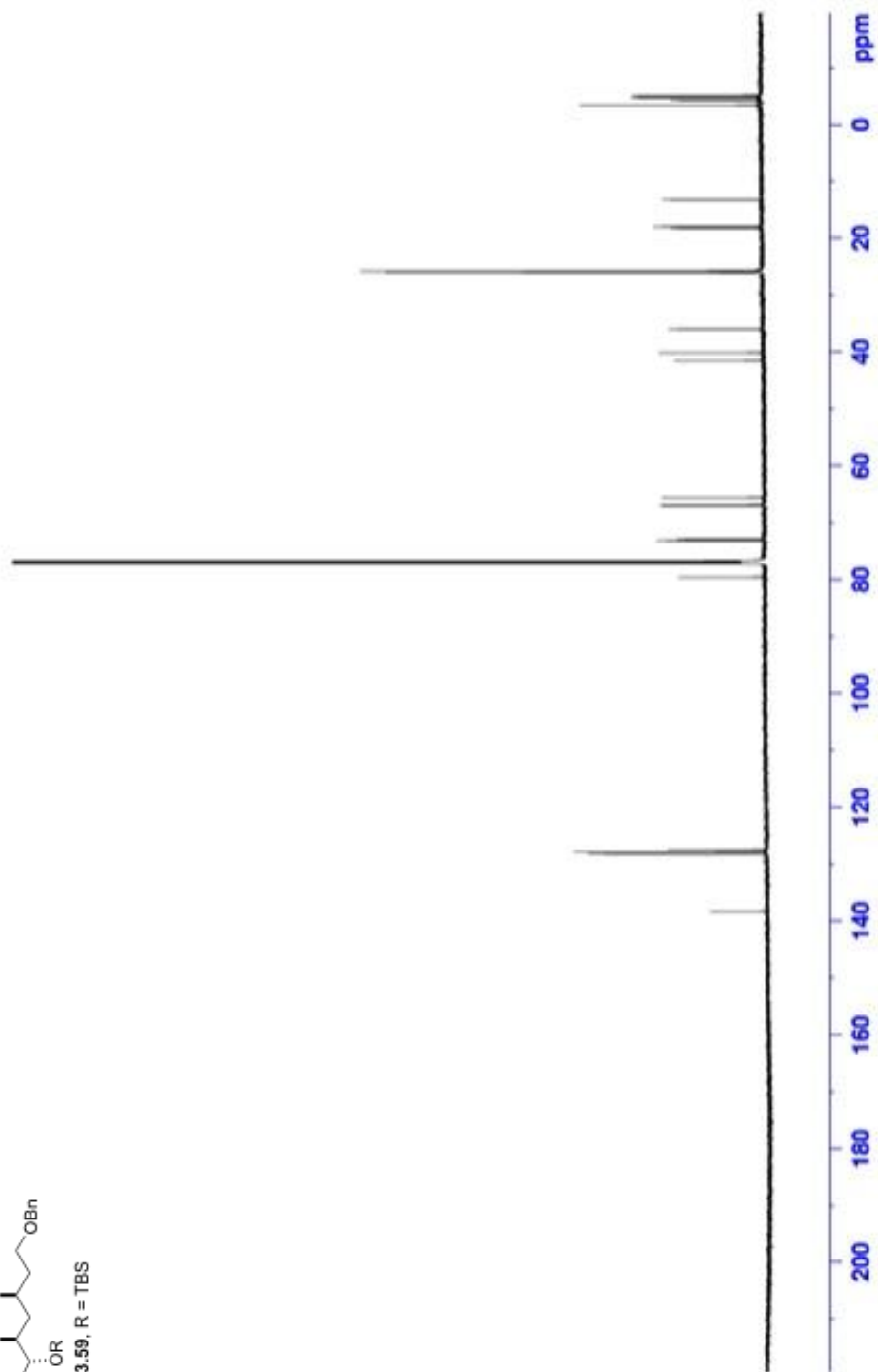
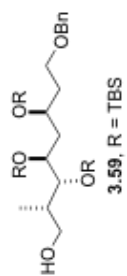
^{13}C NMR (150 MHz) of TBS ether **3.58** (in CDCl_3)



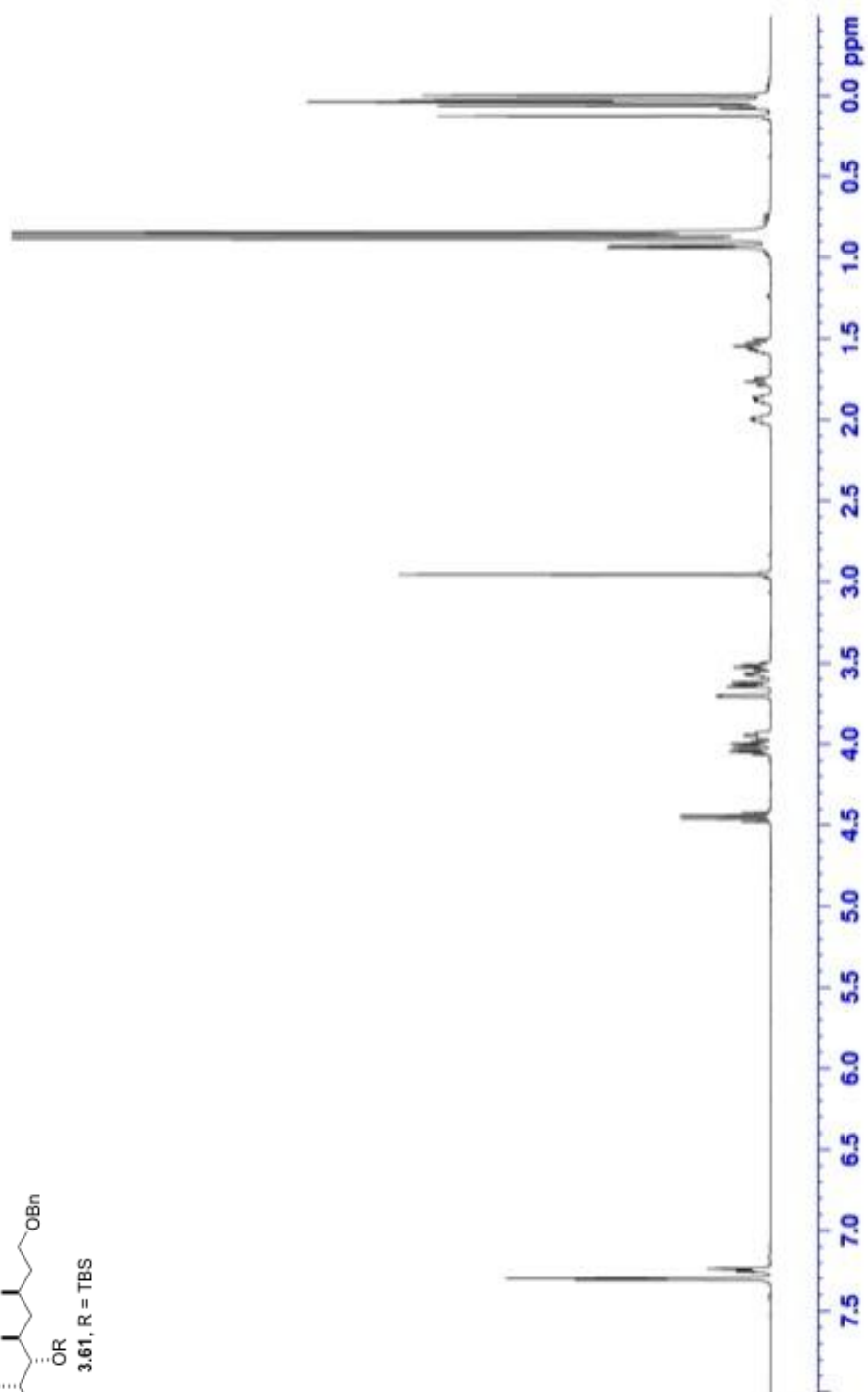
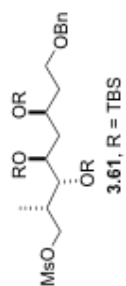
^1H NMR (600 MHz) of primary alcohol **3.59** (in CDCl_3)



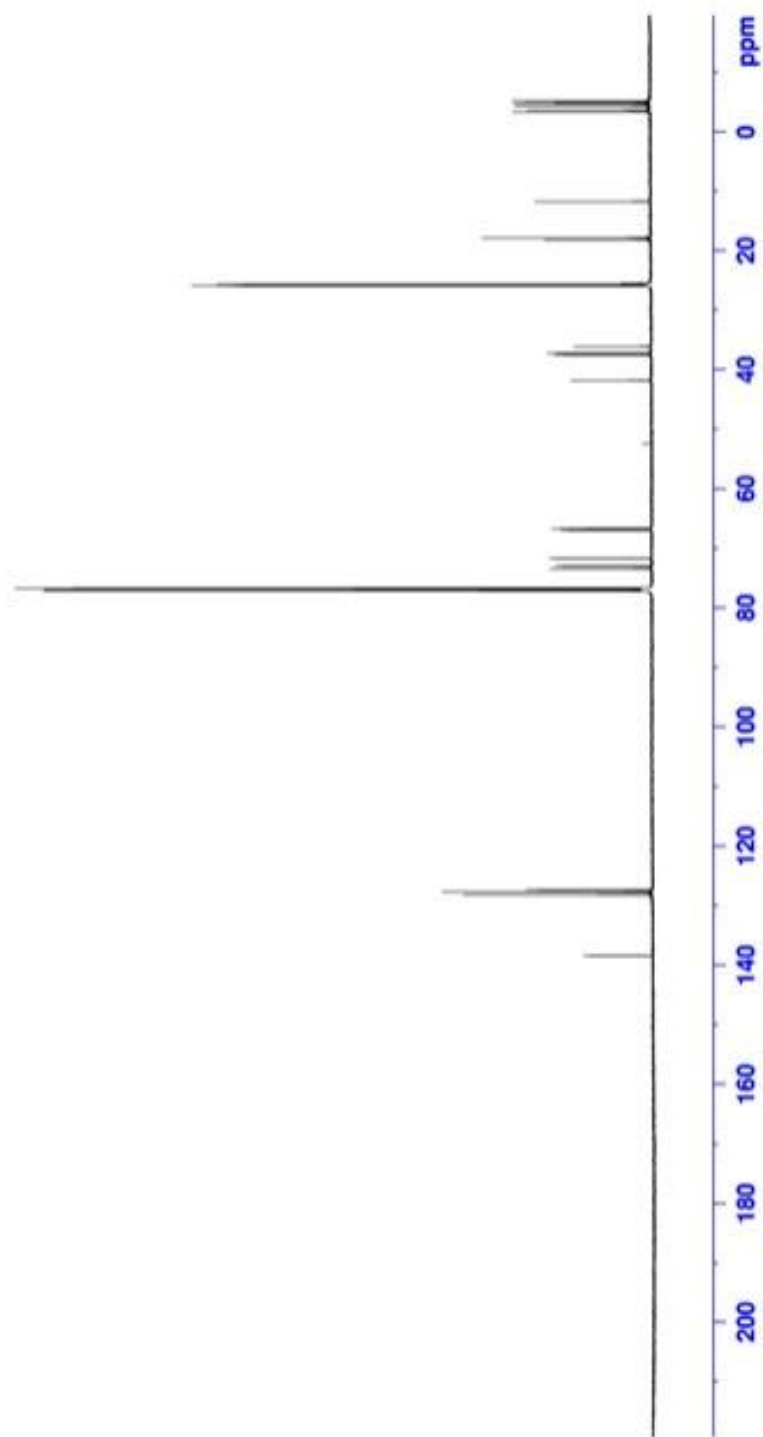
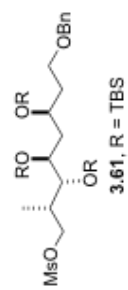
^{13}C NMR (150 MHz) of primary alcohol **3.59** (in CDCl_3)



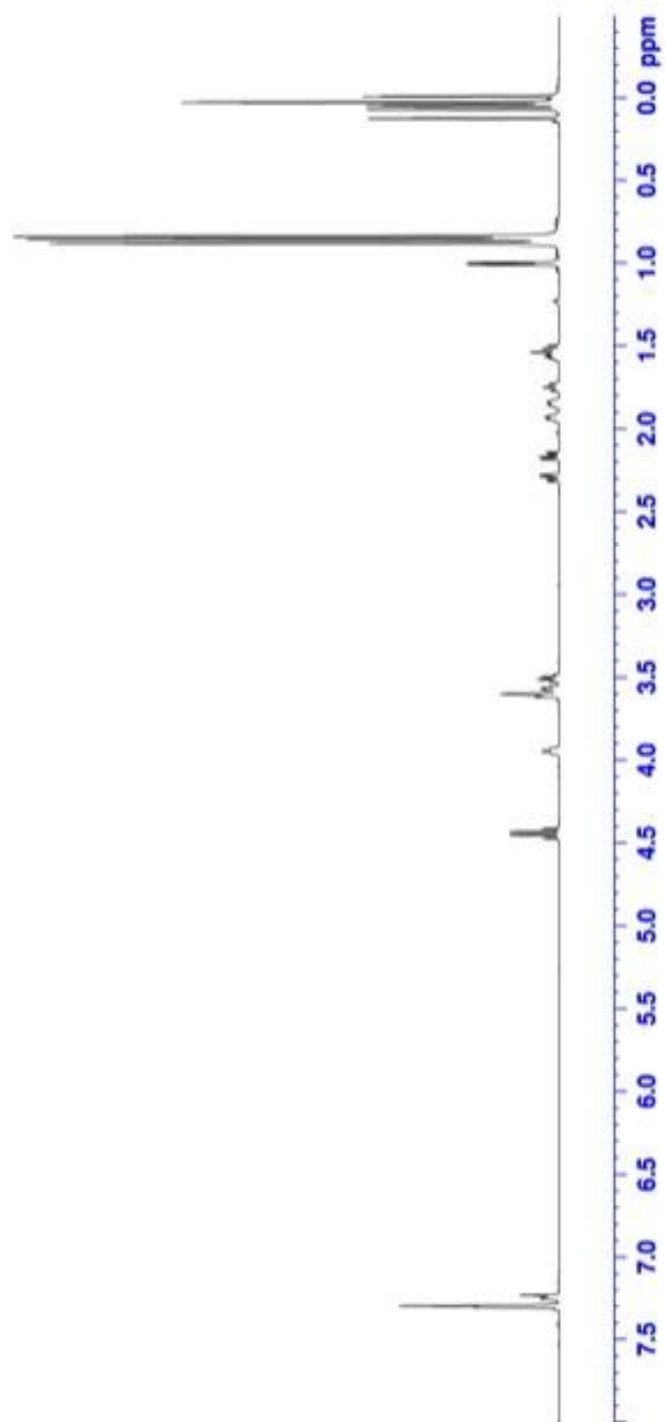
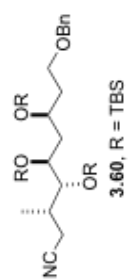
¹H NMR (600 MHz) of mesylate **3.61** (in CDCl₃)



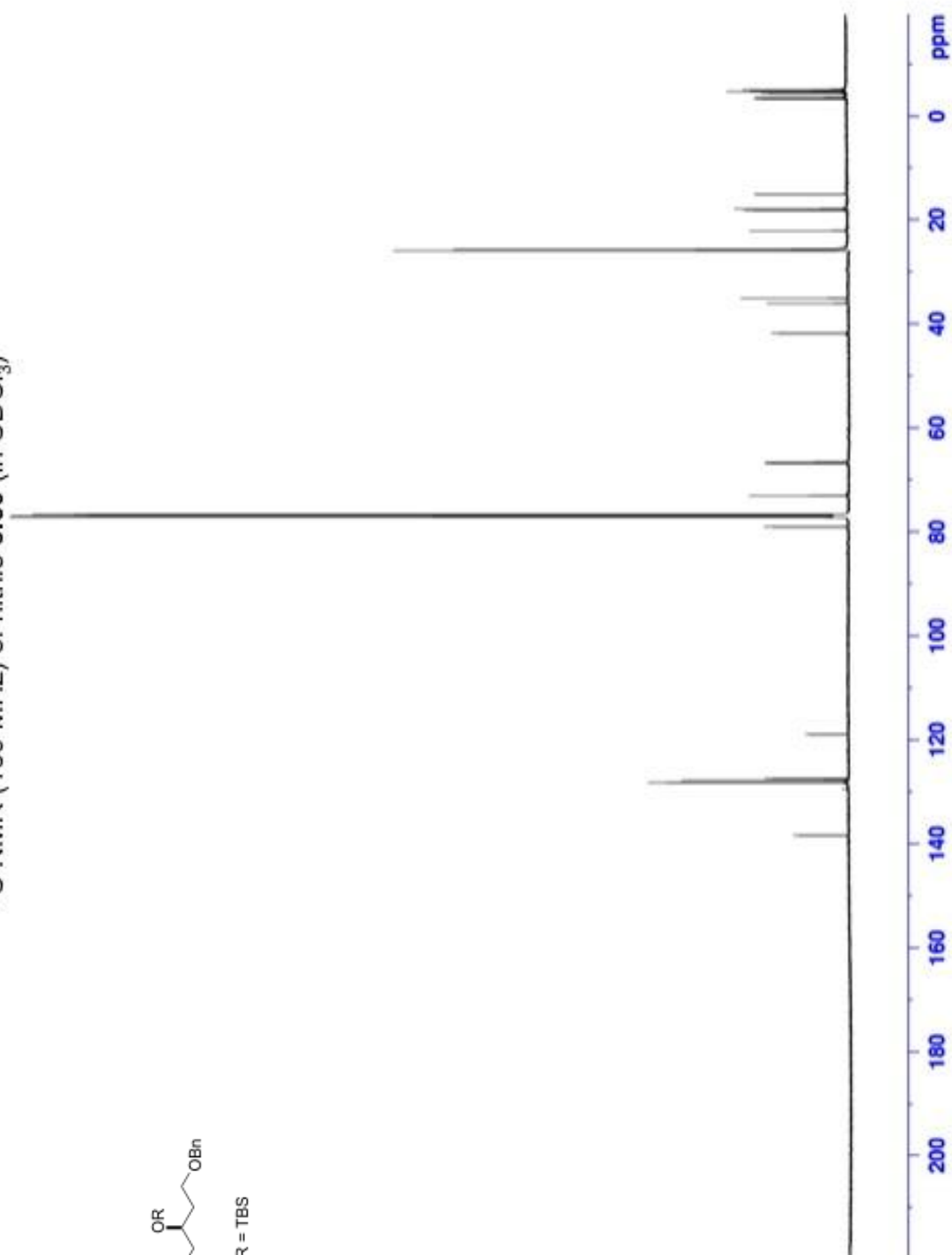
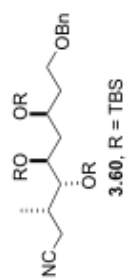
^{13}C NMR (150 MHz) of mesylate **3.61** (in CDCl_3)



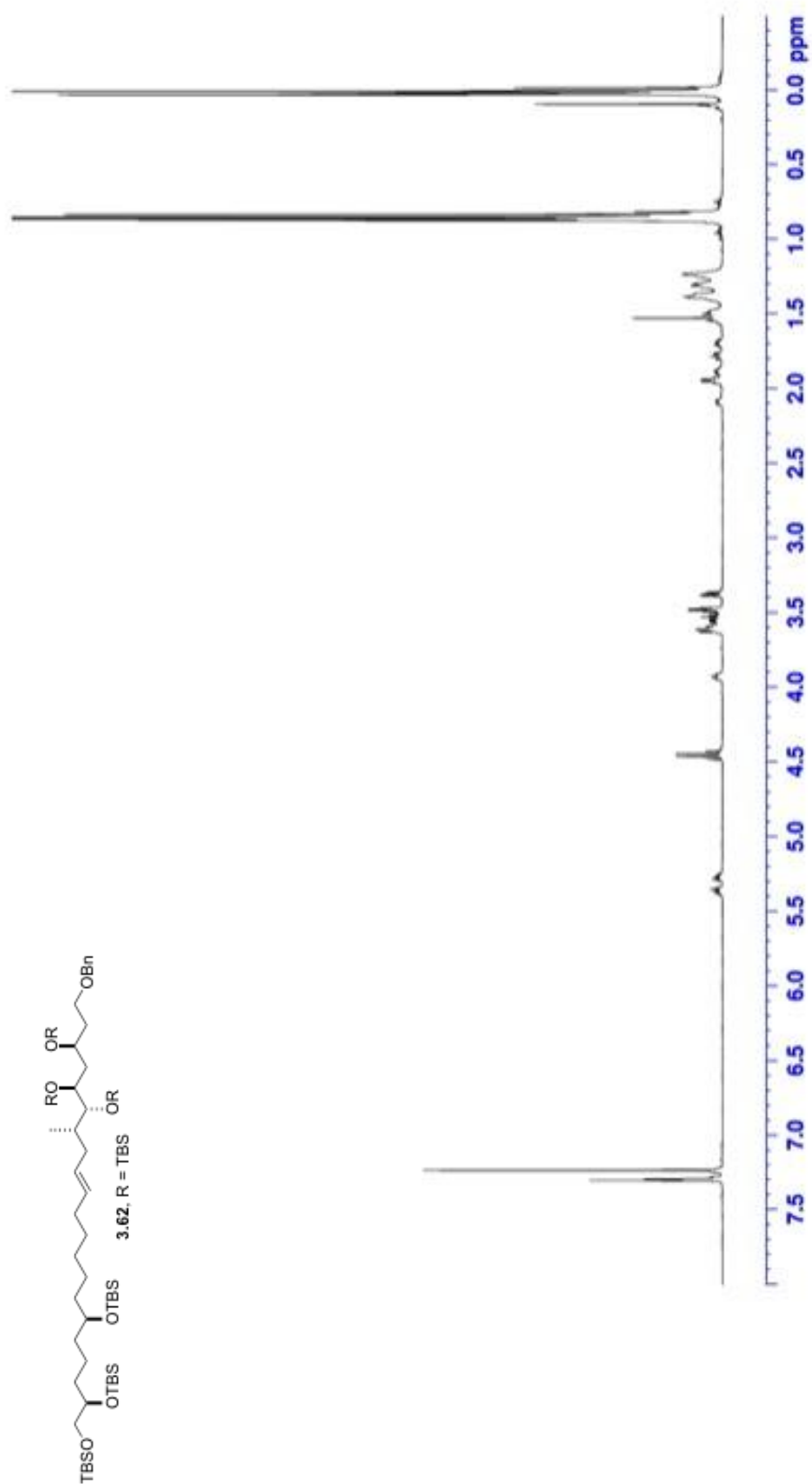
^1H NMR (600 MHz) of nitrile **3.60** (in CDCl_3)



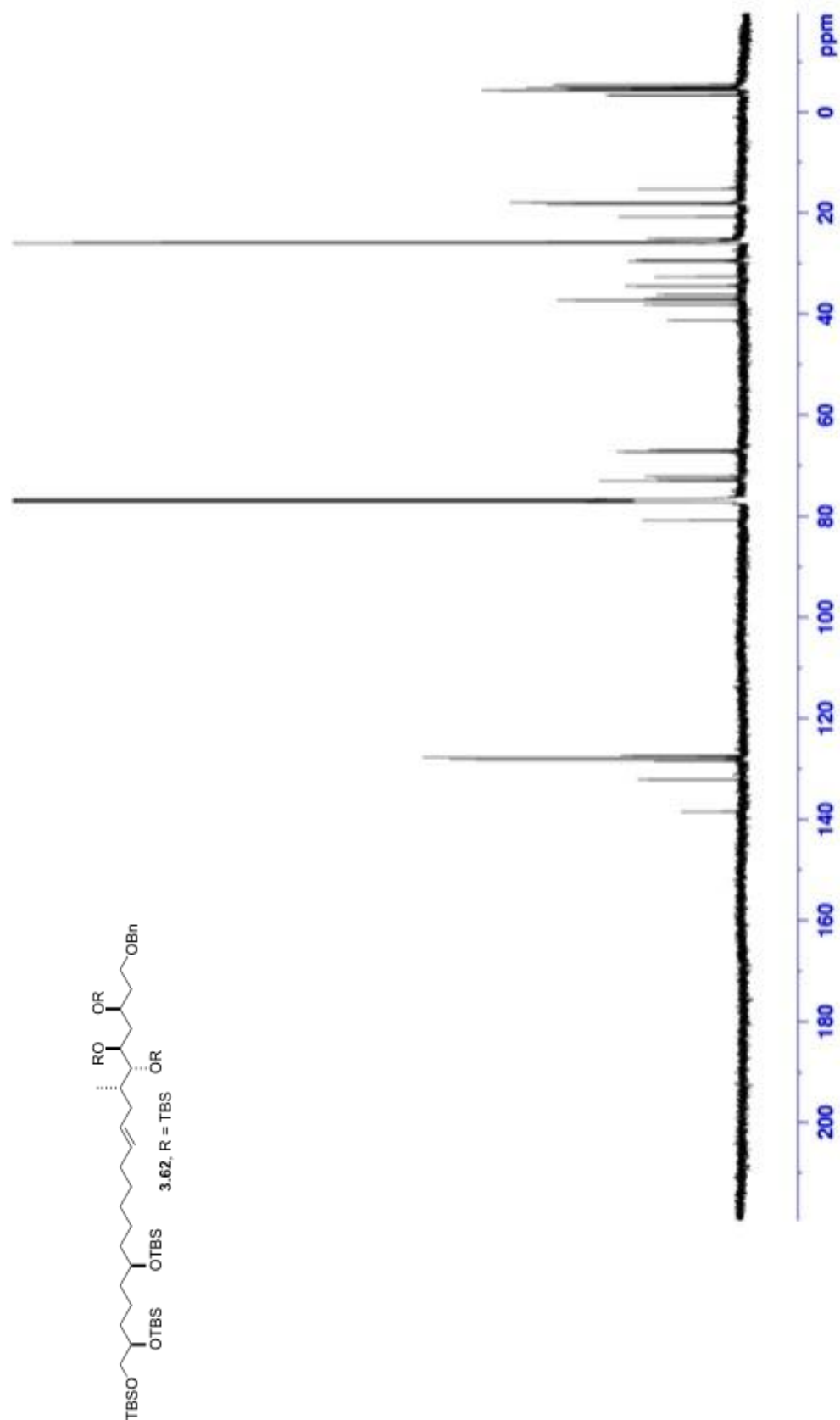
^{13}C NMR (150 MHz) of nitrile **3.60** (in CDCl_3)



^1H NMR (600 MHz) of alkene **3.62** (in CDCl_3)



^{13}C NMR (150 MHz) of alkene **3.62** (in CDCl_3)



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