Phosphate Tethers in Synthesis: The Total Synthesis of Dolabelide C.

By

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Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements of the degree of Doctor of Philosophy

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Abstract

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The utilization of phosphate tethers in synthesis is the focus of the dissertation research described herein. Specifically, cross metathesis of various olefin partners with a phosphate tether has been demonstrated. These studies established the Type III olefin reactivity of the exocyclic olefin of the triply allylic bicyclic phosphate tether. Cross metathesis between the bicyclic phosphate and complex olefin partners allowed for rapid assembly of advanced polyol subunits. Understanding the reactivity of the bicyclic phosphate allowed for the application of this methodology toward the synthesis of a natural product. The target chosen was dolabelide C, a 24-membered macrolactone possessing cytotoxicity against HeLa-S_3 cervical cancer cells. Retrosynthetic analysis of dolabelide C revealed two subunits that could be accessed by the developed bicyclic phosphate tether methodologies. In the synthesis of the C1-C14 subunit of dolabelide C the bicyclic phosphate tether mediates a selective cross metathesis with the terminal exocyclic olefin, differentiates the endocyclic and exocyclic olefins for selective hydrogenation, and serves as a leaving grouping for a regioselective palladium(0)-catalyzed hydride opening. Upon removal of the phosphate tether, the C1-C14 subunit of dolabelide C was completed in six subsequent steps. Studies toward the C15-C30 subunit of dolabelide C also utilized the bicyclic phosphate tether methodology. Three routes toward this subunit were

realized, each took advantage of the latent leaving group ability of the phosphate tether to set the C23 stereocenter. These sequences supplied the C15-C30 of dolabelide C which was then prepared for pairing with the C1-C14 subunit. Final coupling of the C1-C14 and C15-C30 subunits of dolabelide C was accomplished and five more steps were successfully achieved, culminating in a macrocyclic ring-closing metathesis to completed the total synthesis of dolabelide C. The total synthesis of dolabelide C using our temporary phosphate tether methods was achieved in 24 steps (longest linear sequence from acetylacetone) and 54 total steps. The overall yield for this synthesis was 0.73% with an average yield per chemical step being 81.5%.

To my wife,

Shelli

Acknowlegdements

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The Hanson Group: Alan Whitehead, you have shown me the chemistry skills and that allowed me to progress and succeed during my graduate career. Your guidance during my time here is invaluable and thanks for everything you have done for me. Steve Sieck, you were a great labmate and gave me an outlet for my musing on sporting and world events. Jim, I thank you for all the discussions, chemistry and none chemistry related ,that have made my time at KU more enjoyable. To the rest of the Hanson group, past and present, I thank you for making the group enjoyable and the commodore we all have, which will always accompany the Hanson experience.

To my Family: Mom, Kathy Bowen, I would like to say that I am blessed that you are my mother. You have supported me in everyway I have gone and without

your guiding hand I would not be where I am today. Throughout my life you have shown me that hard work and dedication is what is needed to attain your goals in life. I love you and thank you for all you have done for me. Dad, Gary Waetzig, I thank you for all the support you have given me through my life. Sarah, we have grown up together and you have always been my role model to me. Derek and Hannah are blessings to us all and I thank you for bringing them into my life. Thanks for always being their for me and I know we will continue to grow up together. Pam and Phil, you are some of my greatest supporters and Shelli and I are blessed to have you part as of our lives.

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Abbreviations

Ac	acetyl
Alloc	allyloxycarbonyl
Ar	aryl
BBN	borabicyclononane
BHT	2,6-*di*-*t*-butyl-*p*-cresol
Bn	benzyl
BTAF	benzyltrimethylammonium fluoride
Bu	butyl
cat.	catalytic
CM	cross metathesis
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylidene acetone
DCC	*N,N*-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DDQ	dichlorodicyanoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N*, *N*-dimethylformamide

DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
ent	enantiomer
Et	ethyl
EtOH	ethanol
EWG	electron-withdrawing group
EYRCM	enyne ring closing metathesis
GC	gas chromatography
hυ	irradiation
HeLa-S_3	Human epithelial carcinoma cell line
Het	heteroaryl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric acid
HRMS	high resolution mass spectrometry
IC_{50}	inhibitory concentration at 50%
imid	imidazole
Ipc	(-)-β-chlorodiisopinocampheylborane
*i*Pr	isopropyl
IR	infrared radiation
M	molarity
MAPh	methyl aluminum bis(2,6-diphenylphenoxide)
Me	methyl
MOM	methoxymethyl ether
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
*n*BuLi	*n*-butyl lithium
NMO	*N*-methyl-*N*-morpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement

Np	naphthyl
Nuc	nucleophile
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluene sulfonate
psi	pounds per square inch
pyr	pyridine
RCM	ring-closing metathesis
Red-Al	sodium *bis*(2-methoxyethoxy) aluminum hydride
ROMP	ring-opening metathesis polymerization
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
^{t}BuLi	*tert*-butyl lithium
TES	triethylsilyl
TIPS	triisopropylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl
Tol	toluene
Ts	*para*-toluene sulfonyl

Chapter 1

Temporary Tethers in Total Synthesis

1.1 Introduction

The art of total synthesis requires careful retrosynthetic analysis and planning for the desired natural product to be achieved in a rapid and efficient manner. During the course of a synthesis, problems are often encountered where intermolecular reactions provide low reactivity or selectivity and thus necessitate the development of new methods to achieve the desired transformation. One way to circumvent the problems of intermolecular reactions is to install a temporary tether to change the transformation from an intermolecular reaction to one that is intramolecular.

The inherent advantages of intramolecular reactions as compared to intermolecular reactions are numerous. Intramolecular reactions often benefit from the reactive functionalities being in close proximity, which may lower the entropy of the overall reaction. Also, with the reactive centers being attached, milder reactions conditions can be used, decreasing the amount of unwanted side products. Temporary tethers have been shown to regiocontrol over transformations such as the Diels-Alder, Pauson-Khand, as well as olefin metathesis reactions.

When designing a temporary tether, several factors should be considered. First, temporary tethers must be easily installed and covalently attached to the two reacting species. A good tether should be long enough to allow the transformation to occur, but not so long as to lose all the advantages tethers provide. Tethers should also provide some level of pre-organization within the structure that may increase reactive and selectivity. Finally, once the transformation has been achieved, removal of the tether must also be facile as not to destroy the newly formed molecular

structure. Additionally some temporary tethers, when not immediately removed, can also control the regio- and diastereoselectivity in subsequent reactions and participate in further functionalization during their removal.

Ley and Cox reviewed the use of temporary tethers in synthesis in 2000, where they discussed various uses of temporary tethers in synthetic methods as well as in total synthesis.[1] This review will focus on temporary tethers that have been used in total synthesis or are being applied in total synthetic pathways since that publication and cover additional total synthetic efforts not covered by the previous review. All tethers described herein form covalent bonds with the reacting substrates and are isolable, or have the possibility of being isolated, once the reaction is achieved. Transition metal tethers reacting through closed transition states will not be discussed. The focus of this review will be on the installation, functionalization, and removal of temporary tethers with a brief explanation of the advantages that these temporary tethers provide over standard synthetic pathways.

1.2 Silicon Tethers

Temporary silicon tethers are the most widely used tethers in total synthesis. They are extremely attractive due to their facile installment and protecting group attributes upon installation. Also, a number of simple cleavage pathways such as protodesilylation, oxidation, and cross-coupling pathways are available with a silicon tether. This section will discuss temporary silicon tethers used in cycloadditions, olefin metathesis, and radical mediated processes.

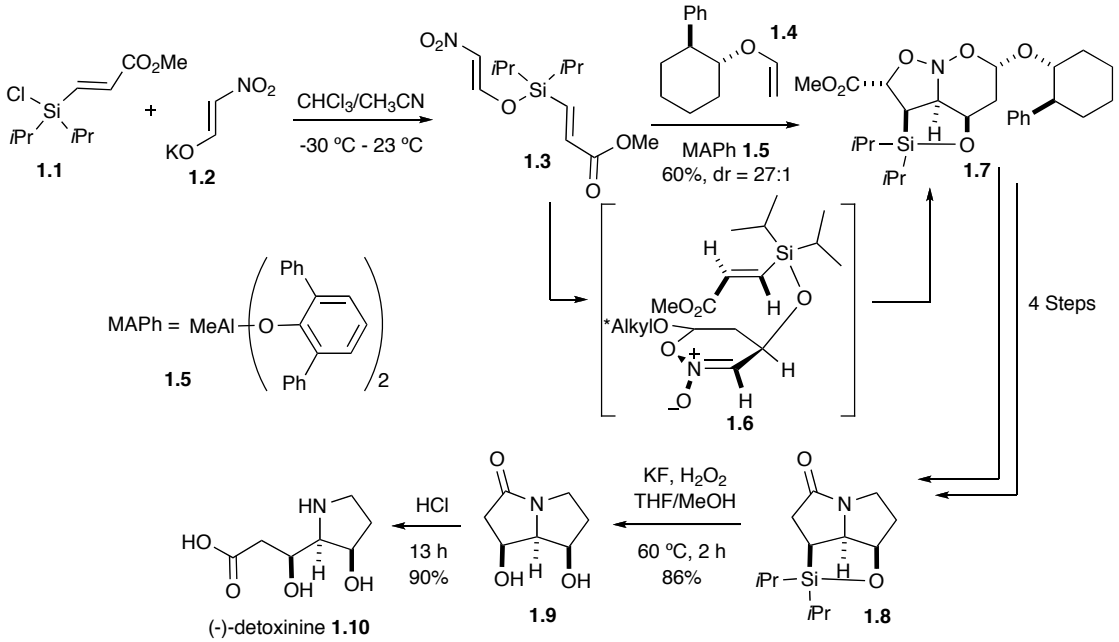
1.2.1 Temporary Silicon Tethers: Cycloadditions

Temporary silicon tethers utilized for cycloadditions provide enhanced levels of stereo- and regiocontrol, as well as increased reaction rates. Denmark and coworkers used a silicon tether mediated cycloaddition strategy in the synthesis of (-)-detoxinine (**1.10**) (Scheme 1).[2] The key step in the synthesis of this target was a tandem [4+2]/[3+2] cycloaddition reaction that is orchestrated by a heteroatom tether. The proper tether choice required that (i) its removal reveal two hydroxy moieties; (ii) two atoms must link the fragments to allow for proper diastereocontrol of the intramolecular cycloadditions; (iii) the tether must tolerate a nitroalkane cycloaddition reaction. Silicon was an ideal choice because of its ability to undergo the Tamao-Fleming oxidation for removal and the possibility for enhanced diastereoselectivity due to the nature of the two-atom tether provided by silicon.

Assembly of the cycloaddition precursor began with the addition of potassium nitroacetaldehyde (**1.2**) to the *E*-configured chlorosilane (**1.1**) to yield vinyl silane **1.3**. Silane **1.3** was immediately subjected to the conditions for cycloaddition without further purification. Addition of chiral vinyl ether **1.4** and Lewis acid **1.5** provided a 60% yield of the tandem [4+2]/[3+2] cycloaddition product **1.7**. This reaction first underwent the [4+2] cycloaddition to generate a zwitterionic species (**1.6**) that reacted with the silicon-tethered dipolarophile in a subsequent [3+2] cycloaddition. The silicon tether was maintained for four steps, when a Tamao-Fleming oxidation cleaved the silicon tether to provide lactam **1.9** in 86% yield. Final acid hydrolysis of the lactam generated (-)-detoxinine (**1.10**) in 90% yield. This total synthesis

showcases how a temporary silicon tether can provide excellent diastereocontrol for a [3+2] cycloaddition and then be removed to reveal two hydroxy stereocenters en route to the total synthesis of (-)-detoxinine.

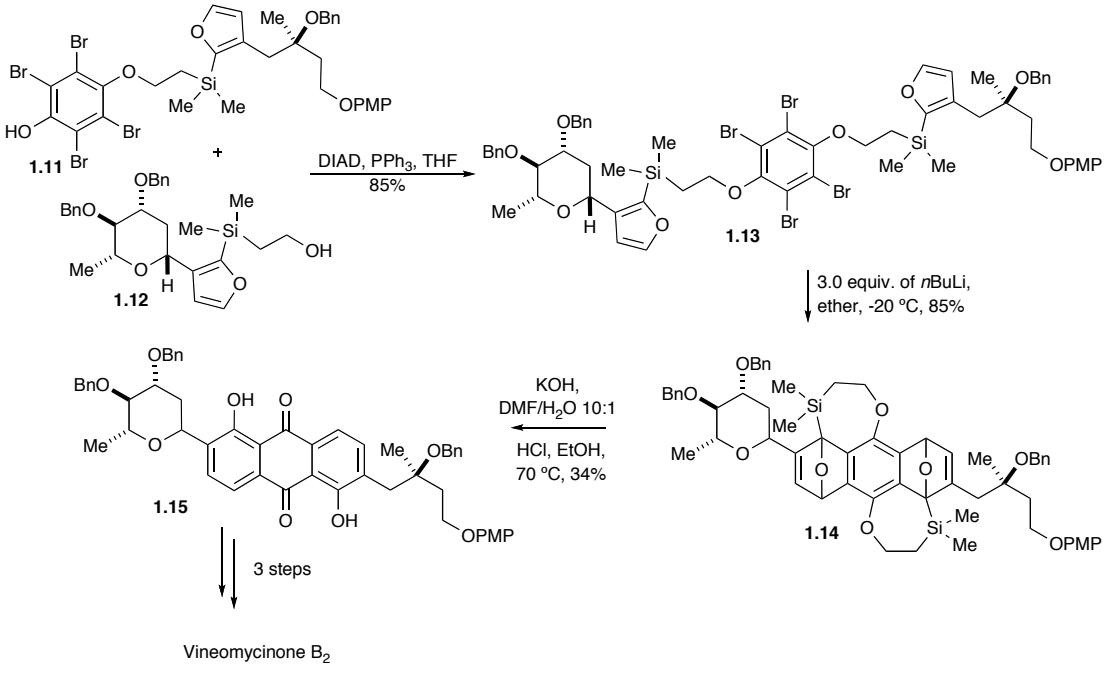
Scheme 1



Martin and coworker have taken advantage of the regiocontrol that silicon-tethered cycloadditions provide in their synthesis of vineomycinone B_2 methyl ester (Scheme 2).[3] The key to the synthesis of vineomycinone B_2 methyl ester was employing a previously developed silicon-tethered benzyne/furan Diels-Alder reaction[4] that would provide regiocontrol and construct the carbohydrate framework of the natural product in a single step. Assembly of the silicon tether began with a Mitsunobu reaction between primary alcohol **1.12** and phenol **1.11** providing Diels-Alder precursor **1.13** in 85% yield. Dropwise addition of *n*BuLi allowed for benzyne formation and subsequent biscycloaddition[5] to occur in 85% yield affording a mixture

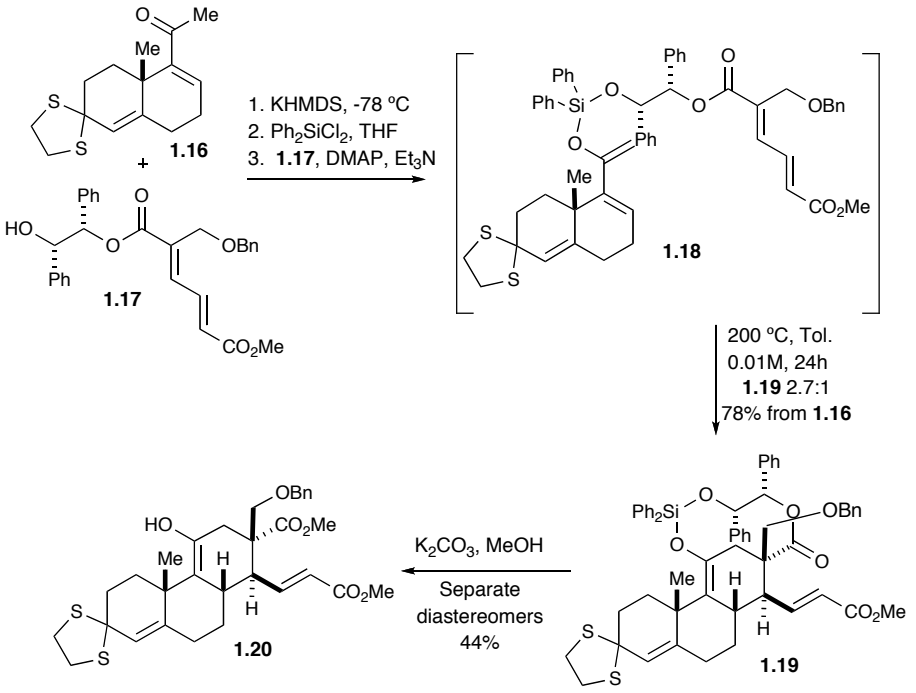
of diastereomers (**1.14**). It was found that both silicon tethers could be efficiently removed using modified Rickborn conditions (KOH in DMF/H_2O).[6] This crude mixture was then subjected to ethanolic HCl that resulted in the regioselective bis-ring-opening followed by air oxidation to provide a 34% yield of quinone **1.15** over two steps. Only three more steps were needed to complete the total synthesis of vineomycinone B_2 methyl ester. Overall, Martin's synthesis of vineomycinone B_2 methyl ester was the first application using silicon tethers to control regioselectivity in a Diels-Alder reaction of substituted benzynes and furans. The successful use of this reaction displayed the ability of temporary silicon tethers to facilitate challenging transformations and rapidly assemble complex targets that might not be possible by intermolecular processes.

Scheme 2



Shea and coworkers utilized a silicon tether in their efforts toward the synthesis of (+)-aldosterone (Scheme 3).[7] The synthetic route envisioned for this target was centered on a chiral silicon-tethered type II intramolecular Diels-Alder reaction. A one pot, three component coupling between **1.16**, **1.17**, and Ph_2SiCl_2 afforded chiral cycloaddition precursor **1.18**. This intermediate was heated to 200 ºC in a sealed tube to provide a 78% yield of cyclized **1.19** as a 2.7:1 mixture of diastereomers. This single reaction set the C8, C10, C13, and C14 stereocenters and validated the use of the proposed Diels-Alder cycloaddition for the enantioselective synthesis of (+)-aldosterone. Facile removal of the tether was achieved with K_2CO_3 in methanol and silica gel separation of the diastereomers provided a 44% yield of **1.20**. The route described is currently being employed to complete the

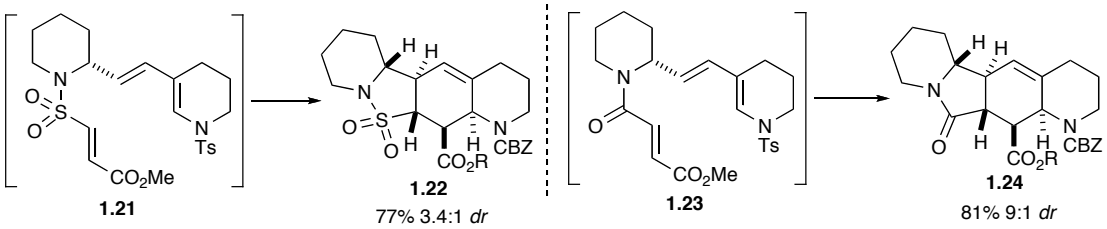
Scheme 3



enantioselective total synthesis of (+)-aldosterone. Given the complexity of this tethered Diels-Alder reaction, it is difficult to imagine a simpler intermolecular reaction that could arrive at the same substrate. This demonstrates how a silicon tether can be used to couple major subunits of natural products and allow stereochemically complex transformations to be achieved.

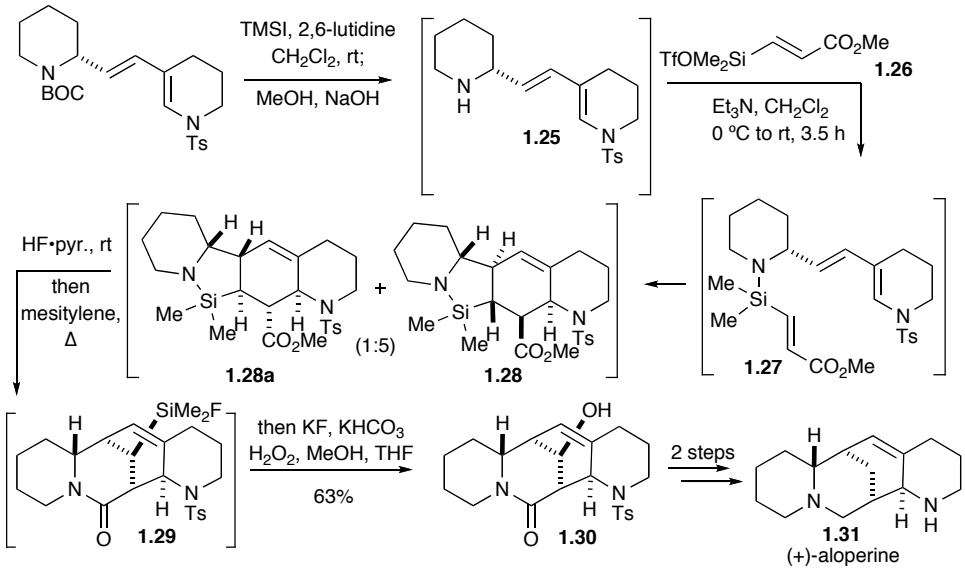
Other heteroatom and carbon tethers have been used to mediate cycloadditions in total synthesis; yet finding a suitable tether to achieve the desired transformation can be its own challenge. In their total synthesis of (+)-aloperine, Overman and coworkers proposed three disposable tethers for an intramolecular Diels-Alder reaction.[8] Investigations began with sulfonyl- and carbonyl-tethered systems due to the electron-withdrawing nature of these groups that were proposed to facilitate the cycloaddition reaction (Scheme 4). Reaction of the sulfonamide-tethered Diels-Alder precursor (**1.21**) provided a 3.4:1 *dr* of the cyclized adduct (**1.22**) in favor of the desired product. Attempts to remove the sulfonamide tether with various reducing conditions were unsuccessful and led to examination of a carbonyl tether. The carbonyl-tethered Diels-Alder precursor **1.23** was cyclized and afforded the tetracyclic core (**1.24**) at 0 ºC as an inseparable mixture of diastereomers. Attempts to remove this tether led to more elaborate synthetic sequences.[9]

Scheme 4



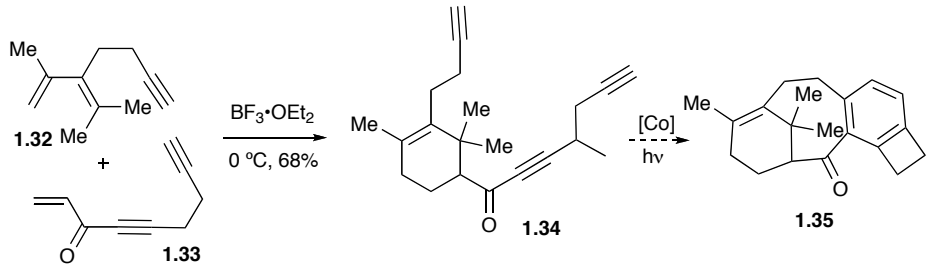
For their final investigation into the tethered Diels-Alder reaction, a silicon tether was attempted. Overman was able to achieve the direct addition of amine **1.25** to silyl triflate **1.26** to provide **1.27** (Scheme 5). Upon cyclization, a 5:1 mixture of diastereomers favoring the product with the desired stereochemistry (**1.28**) was obtained. Interestingly, when this reaction was tried intermolecularly with amine **1.25** and the phenylsilane derivative, no reaction was observed, even when the reaction was heated at 165 ºC. Due to the instability of the silicon tether, silane **1.28** was immediately subjected to HF, cleaving the Si—N bond. After concentrating the reaction and adding mesitylene, the reaction was heated to allow for intramolecular lactamization providing lactam **1.29**. It was found that lactam **1.29** was also unstable to water work-up and thus was taken on directly using the Tamao-Fleming[10] oxidation to furnish alcohol **1.30** in 63% yield. Removal of the alcohol and tosyl deprotection then provided (+)-aloperine (**1.31**). Overall, Overman has shown that a variety of disposable tethers allow for the desired cycloaddition to be achieved, yet not all tethers provide the same results. The tethered systems shown by Overman each gave different diastereoselectivities for the Diels-Alder cyclization and required different conditions for their removal. The silicon-tethered route was chosen because of its facile removal making it the most viable tether for their total synthesis of (+)-aloperine.

Scheme 5



Further, Malacria and coworkers have tested the differences between carbon- and silicon-based tethering strategies in their synthesis of the polycyclic taxane ring system.[11] The approach Malacria envisioned for entry into the taxane ring system was the implementation of a known [4+2] cycloaddition[12] followed by a colbalt-mediated [2+2+2] cyclization that had been developed in his laboratories.[13] Initial efforts were focused on using an intermolecular Diels-Alder reaction to synthesize the A ring and a subsequent [2+2+2] cyclization to construct the B, C and D rings (Scheme 6). The Diels-Alder cyclization occurred in 68% yield (**1.34**) but the

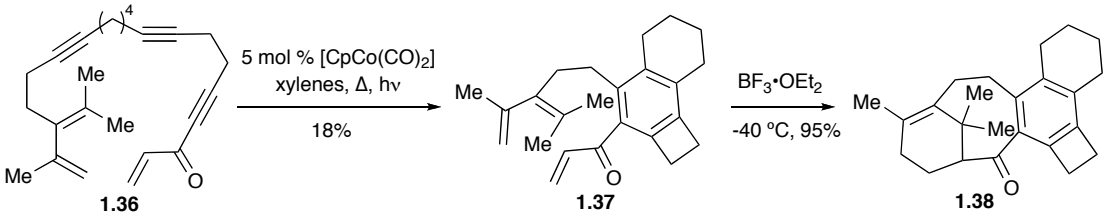
Scheme 6



cyclotrimerization using cobalt and light did not afford the desired compound (**1.35**). However, when the carbonyl was converted to the dimethoxy ketal, the [2+2+2] cyclization did provide tetracyclic **1.35**, albeit in only 15-20% yield.

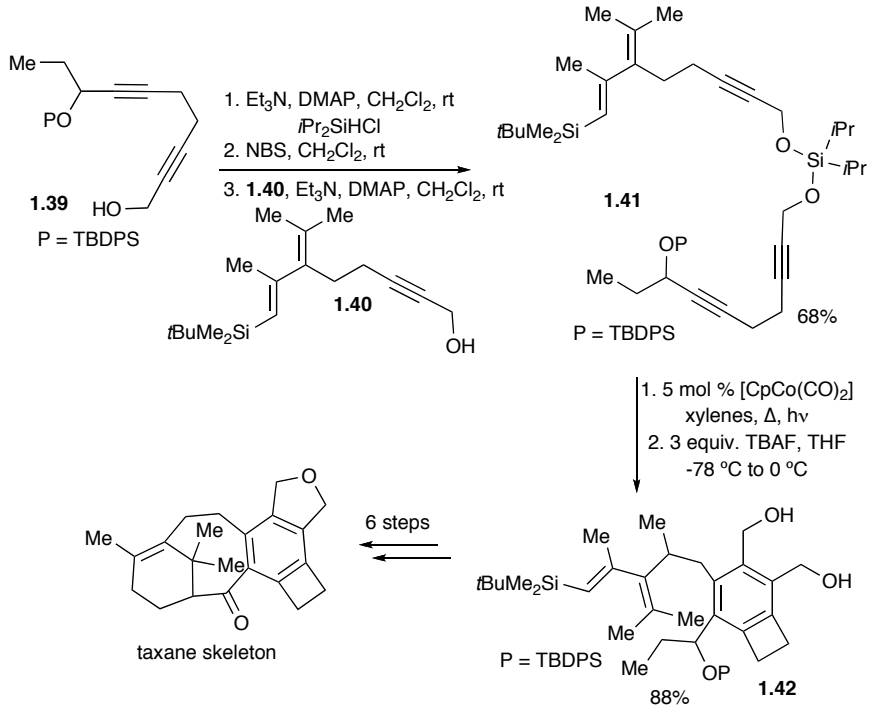
Switching to an alkyl-tethered approach, compound **1.36** was initially subjected to cyclotrimerization conditions forming the C, D and E rings although in only 18% yield (Scheme 7). This cycloadduct then underwent the Diels-Alder reaction to generate taxane skeleton **1.38** in 95% yield.

Scheme 7



Given the limited success with the carbon-based tether, silicon tethers were tested to facilitate both of the proposed reactions (Scheme 8). Construction of silicon tether **1.41** was achieved by the addition of alcohol **1.39** to chlorodiisopropylsilane; this species was then converted to a bromosilane using NBS, and final addition of alcohol **1.40** generated silane **1.41** in 68% yield. Cyclization of triyne **1.41** was promoted by a cobalt catalyst and light and removal of the silicon tether with TBAF then afforded benzocyclobutene **1.42** in 88% over two steps. Benzocyclobutene **1.42** was taken forward in six steps to access the taxane skeleton, in which the [4+2] cycloaddition constructed the A ring in the last step.

Scheme 8

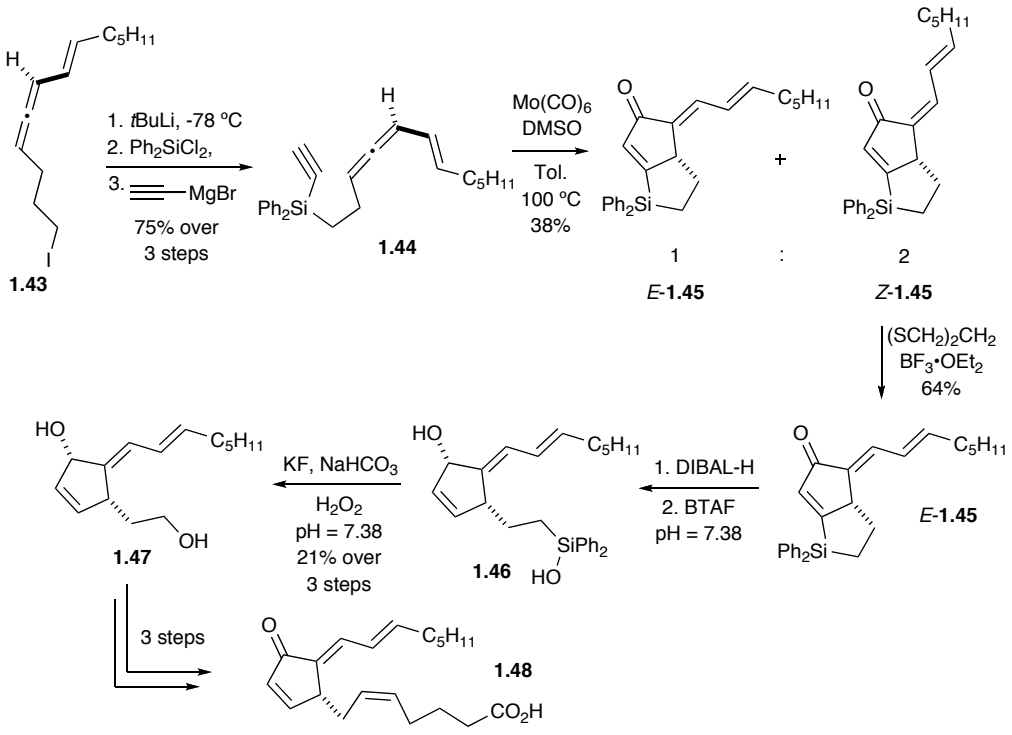


Overall, Malacria has studied various tethers to probe for the best temporary connection and reaction parameters to achieve their desired cyclizations. Although the initial efforts were plagued by side reactions and low yields for the desired transformation, the temporary silicon strategy was successful in providing a high yielding pathway for the taxane skeleton to be accessed.

The intermolecular Pauson-Khand reaction forms a useful cyclopentenone building block, but the reaction is known to have problems with low regioselectivities and yields, limiting its use in synthesis. Intramolecular reactions have shown to be more effective, thus a tethered process has the potential to alleviate these problems. Brummond and coworkers pursued a silicon-tethered allenic [2+2+1],[14] Pauson-Khand-type reaction, to rapidly access the cyclopentanone core of prostaglandins and

address the inherent regiochemical issues in their synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (Scheme 9).[15] Construction of the silicon tether began by converting iodide **1.43** into the lithiate followed by addition of diphenyldichlorosilane. This chlorosilane intermediate was then subjected to ethynylmagnesium bromide to couple the alkyne and allene moieties through silicon providing silane **1.44** in 75% yield over three steps.[16] Then a molybdenum-mediated Pauson-Khand reaction of **1.44** afforded a 1:2 mixture of *E*-**1.45** and *Z*-**1.45** cyclopentenones in 38% yield.[17] Despite the low yield, the undesired *Z*-**1.45** isomer could be readily converted to *E*-**1.45** by addition of propanedithiol and boron trifluoride to yield only *E*-**1.45**.[18] Reduction of the cyclopentenone was achieved using DIBAL-H and then followed by immediate removal of the silicon tether with benzyltrimethylammonium fluoride to yield

Scheme 9



silanol **1.46**. This compound was not purified, but directly subjected to Tamao-Fleming oxidation conditions to provide diol **1.47** in 21% yield over three steps. Three more steps were needed to complete the first total synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (**1.48**). This route displays the utility of a silicon tether to rapidly couple the reacting centers and further functionalize the molecule upon removal of the tether by Tamao-Fleming oxidation. Although the reaction was still low yielding, the restraint the silicon tether imposed to set the regioselectivity for the Pauson-Khand reaction was vital to the total synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2.

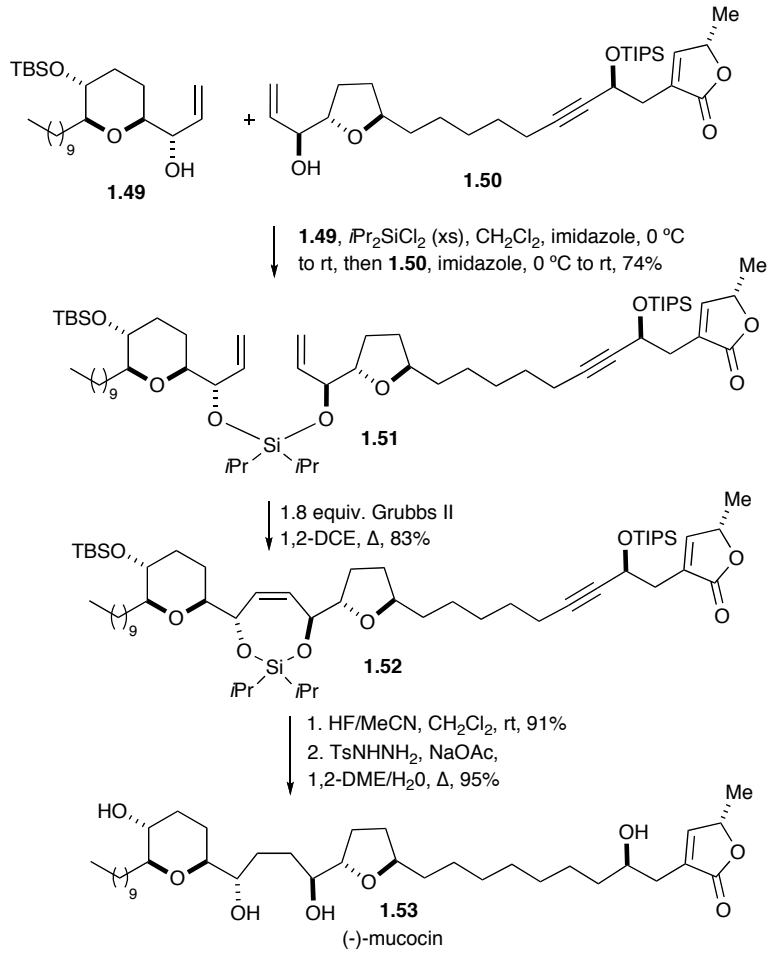
1.2.2 Temporary Silicon Tethers: Olefin Metathesis

Over the past decade new olefin metathesis catalysts have emerged that possess increased activity and functional group tolerance. These catalysts have had a profound impact on tethering strategies toward natural product targets. Ring-closing metathesis (RCM) has mainly been employed due to the cooperative effects of both metathesis and tethers. Again, silicon-tethered RCM is the most commonly used tether in natural product synthesis and described below are the routes which utilizing RCM and a silicon tether.

In the synthesis of (-)-mucocin, P. Andrew Evans and coworker reported a new approach toward 1,4-diols utilizing a temporary silicon tether and RCM (Scheme 10).[19] Their strategy rapidly assembles the silicon tether by coupling allylic alcohols **1.49** and **1.50** with silicon provide silane **1.51** in 74% yield. The metathesis of *trans*-1, 4-diols is known to be an unfavorable process, as shown in a transition state model proposed in early silicon tether metathesis work by Evans.[20] This model reveals that

formation of the *trans*-diol requires one of the allylic R substituents to be placed in an unfavorable pseudo-axial position that imposes increased steric demands on the forming ring as the R becomes larger. The desired RCM in the synthesis of (-)-mucocin (**1.53**) required almost two equivalents of the Grubbs II catalyst to obtain **1.52** in 83% yield. This illustrates that hindered systems, such as this case, may require large amounts of the ruthenium catalyst. Silicon tether removal was achieved with HF and subsequent diimide reduction provided (-)-mucocin (**1.53**) in 91% and

Scheme 10

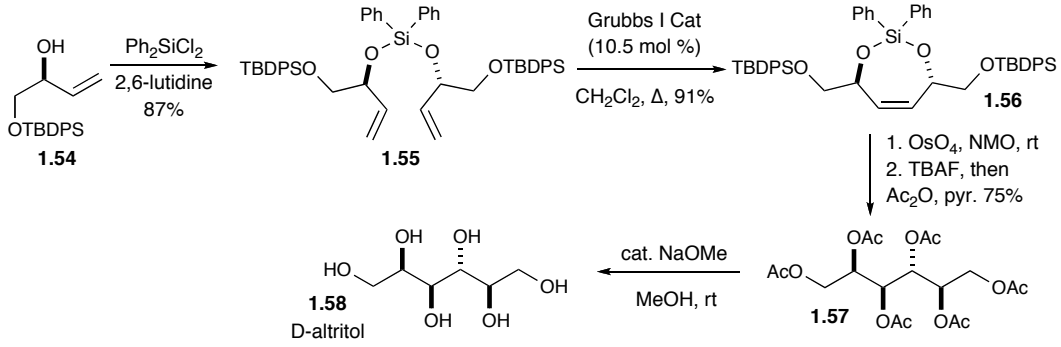


95% yields, respectively. The temporary silicon tether in this total synthesis displays the ability of tethers to rapidly couple advanced subunits of natural products. Once the two olefins are coupled to silicon, RCM provides direct reaction between the olefins, as opposed to CM of these substrates that would lead to both product and homodimerization of these advanced subunits. This report was also the first application of a complex temporary silicon tether RCM as a cross-coupling reaction in total synthesis.

Evans and Murthy were also able to access C_2-symmetric 1,4-diols using a silicon tether/RCM approach. These symmetric 1,4-diols[21] are utilized as asymmetric catalysts,[22] chiral auxiliaries,[23] and as precursors in target-directed synthesis.[24] Evans demonstrated the silicon-tethered/RCM in the total synthesis of D-altritol (Scheme 11).[25] Addition of chiral allylic alcohol **1.54** to diphenyldichlorosilane with 2,6-lutidine afforded bisalkoxysilane **1.55** in 87% yield. **1.55** was then treated with 8 mol % Grubbs I catalyst with an additional 2.5 mol % of catalyst added after 20 h. A 91% yield of silaketal **1.56** was obtained after 32 h. The long reaction times may have been necessary due to the increased sterics of the allylic substituents used in this tethered process.[26] This also displays the difference between the sterics of a symmetric and unsymmetric 1,4-diol. Following dihydroxylation of the olefin, the silicon tether was removed with TBAF. The entire molecule was peracetylated, to aid in isolation, providing **1.57** in 75% yield. Finally, addition of catalytic sodium methoxide afforded D-altritol **1.58** in 88% yield. The silicon-tethered RCM methodology was the highlight in the rapid synthesis of D-altritol obtaining excellent

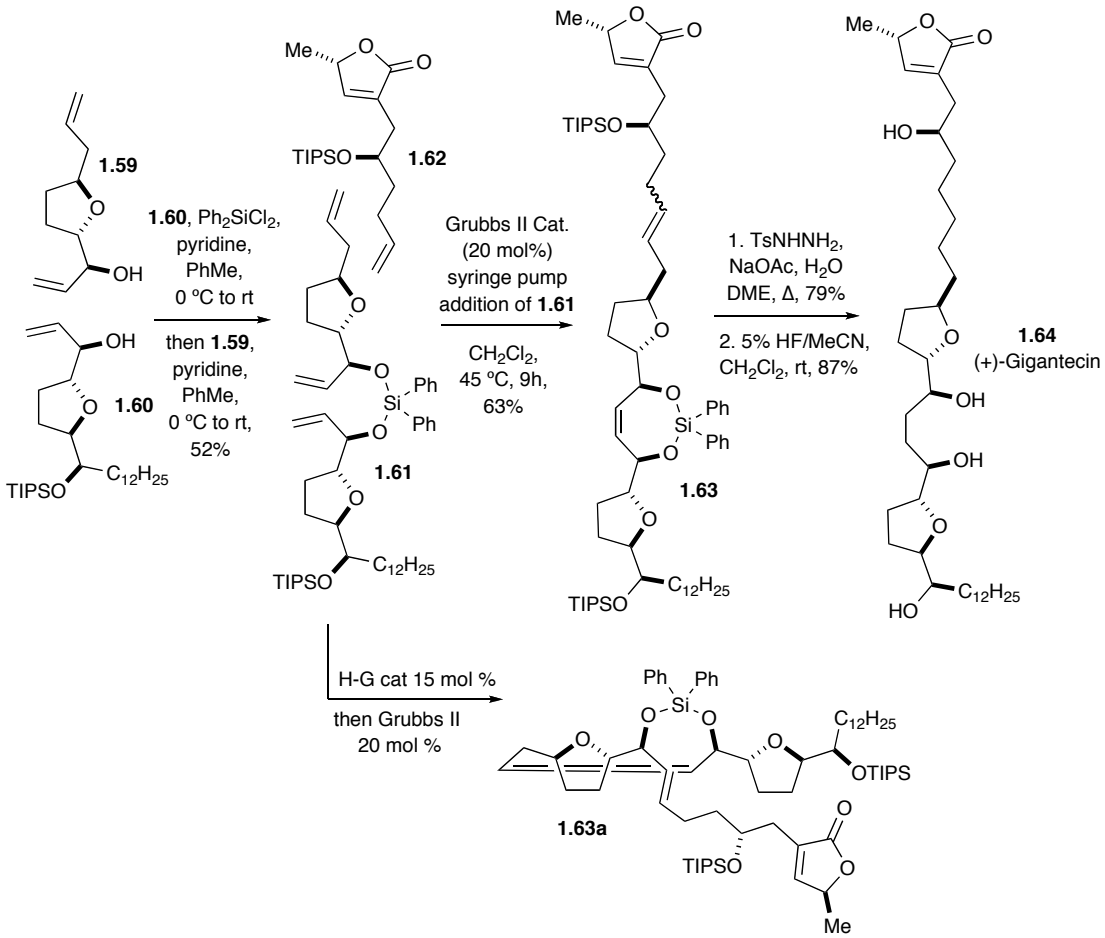
yields for the tethered processes of coupling, metathesis, and removal. This methodology can be applied to a wide range of chiral allylic alcohols and can be used in either target directed synthesis or applied toward other useful intermediates.

Scheme 11



In a related example, Hoye and coworkers were able to combine different modes of metathesis and mixed silicon tethers in their synthesis of (+)-gigantecin (Scheme 12).[27] This synthesis involved the construction of mixed silaketal **1.61** that was obtained by sequential addition of alcohols **1.60** and **1.59** to diphenyldichlorosilane.[28] With silicon tether **1.61** in hand, initial experiments were conducted on triene **1.61** with Hoveyda-Grubbs second generation catalyst[29] to allow for the seven-membered RCM to occur with subsequent CM of **1.62** at the terminal olefin. When this reaction was run and the tether was removed the mass spectrum and the initial ^{1}H NMR suggested that (+)-gigantecin had indeed been synthesized. Upon closer inspection of the ^{1}H NMR spectrum and comparison with the known spectrum, noticeable differences were discovered and the melting point of the final product differed from the reported melting point of the natural product. These differences were validated when the product of the reaction was shown to have

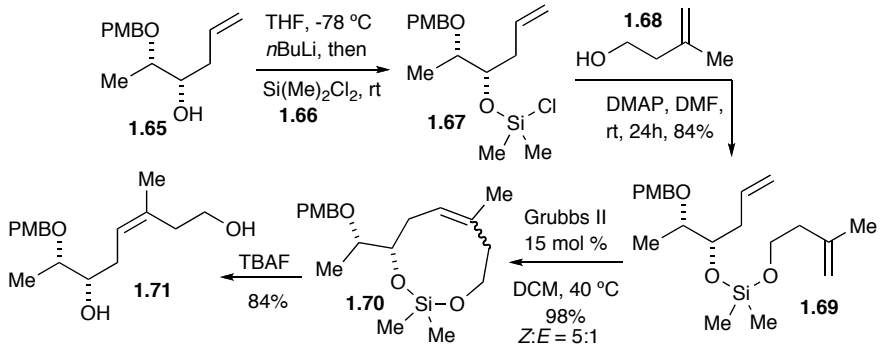
initially undergone an RCM between the terminal olefin and the distal allylic siloxane olefin and then a CM involving the proximal siloxane olefin and terminal olefin **1.62** to yield **1.63a**. To overcome this problem, a site-directed metathesis strategy was adopted in which CM partner **1.62** and Grubbs II catalyst were initially added and then mixed silaketal **1.61** was added over 9 h by syringe pump. This allowed initial CM between the two Type I terminal olefins followed by a slower RCM of the Type II siloxane olefins.[30] The properly metathesized product (**1.63**) was obtained in 63% yield when these conditions were used. Diimide reduction and subsequent **Scheme 12**



global deprotection provided (+)-gigantecin **1.64** in good yield over the two steps. This silicon tether strategy allowed for the rapid coupling of the two major subunits of (+)-gigantecin and demonstrated the control of metathesis initiation, setup by the silicon tether to access the proper carbon framework of (+)-gigantecin.

Mulzer and Gaich took advantage of silicon-tethered metathesis and the inherent *Z*-olefin geometry formation of RCM in the total synthesis of epothilones B and D (Scheme 13).[31] In a one-pot process, alcohol **1.65**[32] was rapidly coupled with $Si(Me)_2Cl_2$ and subsequent addition of alcohol **1.68** provided disiloxane **1.69** in 84% yield. **1.69** was subjected to RCM with 15 mol % of Grubbs II catalyst or Hoveyda-Grubbs II catalyst being added by syringe pump to generate the olefin-containing nine-membered ring **1.70** in 98% yield (*Z*:*E* = 5:1).[28] The silicon tether was then removed with TBAF to provide the *Z*-configured **1.71** in 84% yield. This diol was further functionalized to a common intermediate in their previous total synthesis of epothilones B and D.[33] The incorporation of an ester linkage instead of using silicon as a tether led only to the CM product in 19% yield. The silicon-tethered process was reasoned to be atomically larger and have more distorted bonds allowing for the RCM

Scheme 13

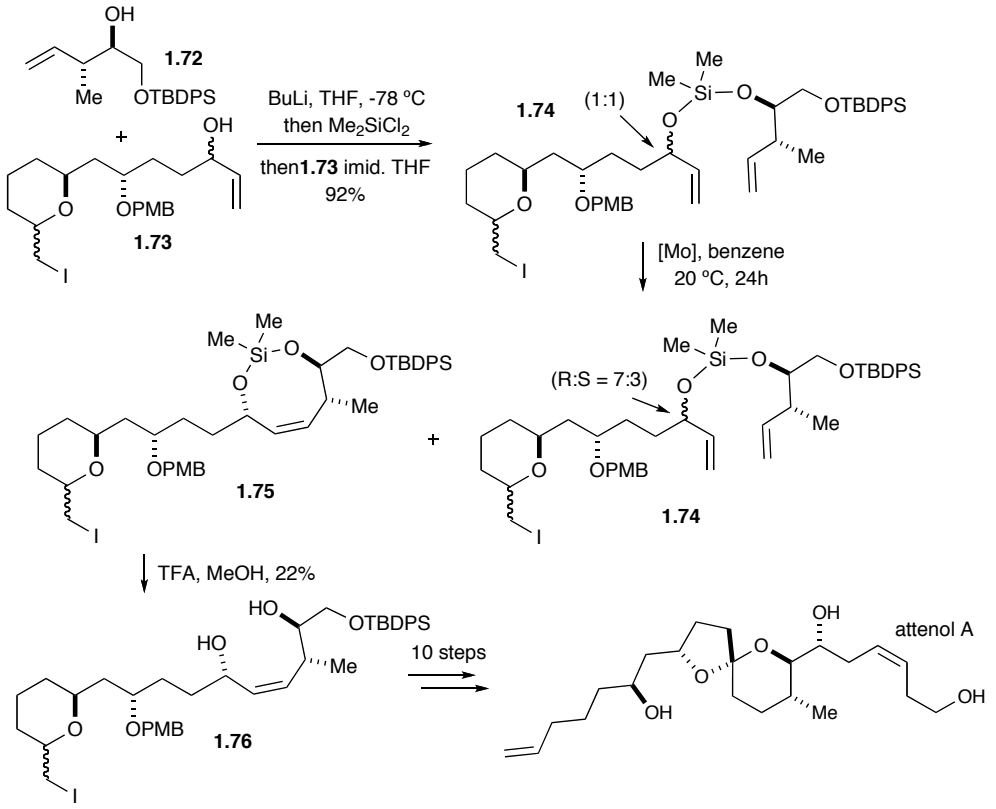


to be achieved due to the decreased ring strain.[34] This shows how heteroatom tethers facilitate transformations that their carbon or carbonyl counterparts are unable to achieve.

Disruptive steric interactions during RCM have been shown to be prevalent in silicon-tethered reactions and Van de Weghe and coworkers were able to support these findings in their total synthesis of attenol A (Scheme 14).[35] Van de Weghe was interested in using silicon to tether two different allylic alcohols and then utilize metathesis to join the two moieties, which they had shown to be a viable process in previous work.[34b] Coupling of the subunits to silicon was achieved by first adding **1.72** and subsequently adding **1.73** to yield bis-siloxane **1.74**. Subjection of **1.74** to metathesis using Schrock's molybdenum catalyst led to partial conversion of cyclized product **1.75**. NOE experiments confirmed the stereochemistry of metathesis product **1.75** and showed that only two of the diastereomers were reactive in the metathesis. In this experiment, the catalyst resolved the diastereomeric allylic alcohol connected to silicon from a 1:1 diastereomeric mixture to a 7:3 mixture of starting material **1.74**. This observation contrasts previous cases where stereochemistry of the substrates did not dictate the outcome of the RCM.[34b] TFA removal of the silicon tether provided **1.76** in 22% yield over two steps. Ten additional steps were required to complete the total synthesis of attenol A. This example demonstrates the limitations associated with the steric demands of the catalyst and those interactions during ring formation. Further studies into sterically hindered RCM are needed to fully understand this synthetic problem. This establishes that successful tethered RCM methods must

account for the steric environment about the reactive olefins for the transformation to be successful.[36]

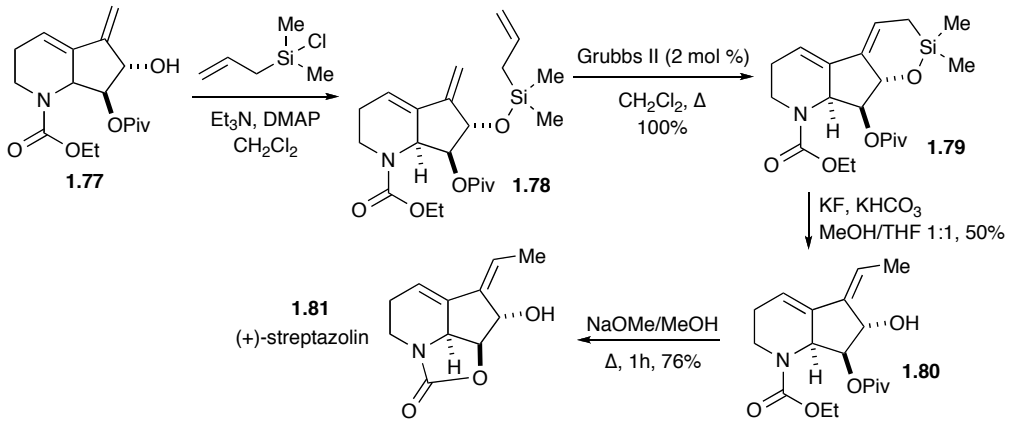
Scheme 14



Silicon-tethered RCM can be used to easily access the *Z*-olefin geometry that may not be as simple to obtain by other methods. Miller and coworkers employed this feature of silicon-tethered RCM in their total synthesis of (+)-streptazoline (Scheme 15).[37] Previous syntheses of (+)-streptazoline (**1.81**) by Kozikowski,[38] Overman,[39] and Miller[40] all utilized a late-stage Wittig olefination to introduce the ethylidene side chain, which provided a 2:1 *E*:*Z* mixture (in favor of the incorrect isomer) of geometric isomers. Miller proposed that, in combination with a heteroatom-tether, the RCM could avoid the stereochemical problem by preferentially

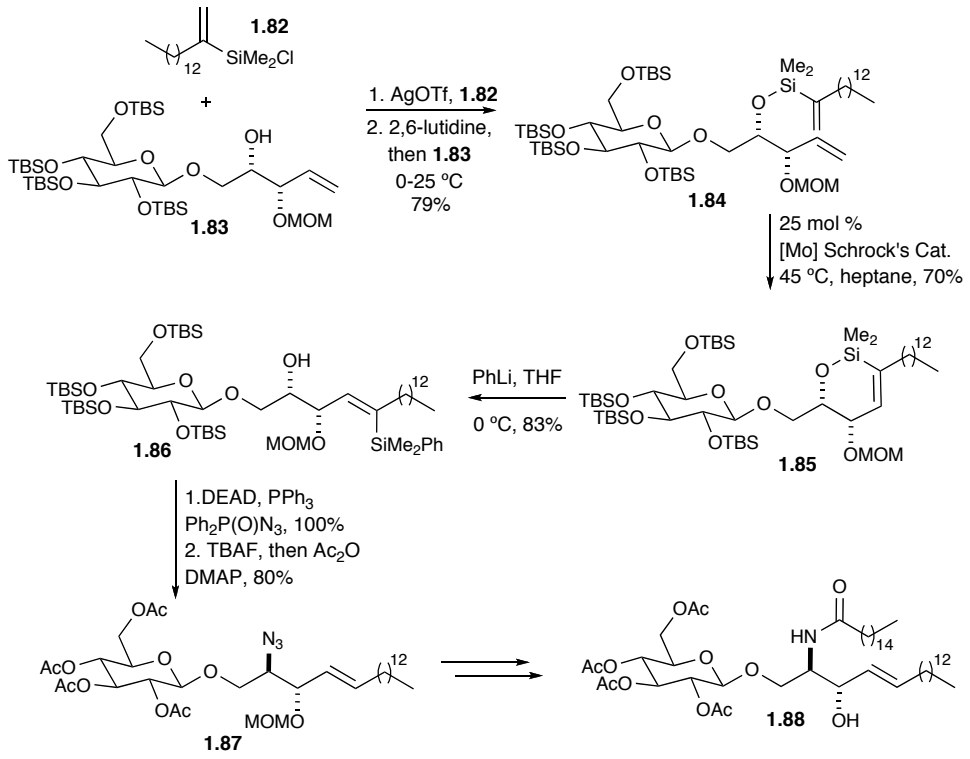
cyclizing to the *Z*-geometry providing a more efficient route to (+)-streptazoline. Silicon was chosen as the tether and was reacted with alcohol **1.77** using commercially available allylchlorodimethylsilane. Subjection of diene **1.78** to Grubbs II generation catalyst allowed for RCM to afford **1.79** quantitatively. Other RCM studies with bis-alkyloxysilanes ($Me_2Si(OR_1)(OR_2)$, $Ph_2Si(OR_1)(OR_2)$, $iPr_2Si(OR_1)(OR_2)$) gave no RCM product, yielding only dimers of the starting material. A less ordered seven-membered transition state was proposed to cause the dimerization, while the six-membered ring was hypothesized to form a tighter transition state, allowing the RCM to proceed. Protodesilation of silane **1.79** afforded alcohol **1.80** in 50% yield and final deprotection/cyclization provided (+)-streptazoline in 76% yield. This silicon tether strategy allowed for exclusive formation of the *Z*-ethylidene side chain in excellent yield and was easily removed to access (+)-streptazoline far surpassing other routes. The differential reactivity between the alkylsilane and the bis- alkyloxysilane provides further evidence that the sterics and electronics of reacting olefins play important roles in the success of RCM.

Scheme 15



Barrett and coworker demonstrated the utility of RCM to define olefin geometry in their synthesis of D,L-glucosylceramide (Scheme 16).[41] Key to this synthesis was the installation of a *trans*-disubstituted double bond that is not easily achieved with high selectivity using conventional methods. To overcome this inherent selectivity problem, Barrett envisioned the use of olefin metathesis to provide the requisite *E*-olefin found in D,L-glucosylceramide. Initial studies focused on cross-metathesis to install the side chain employing either Grubbs I or Schrock's catalysts. All attempts to achieve the desired cross-metathesis product were unsuccessful and an alternative route was needed. RCM using silicon to append the olefins was then attempted; as Barrett[42] and others[26] have shown such silicon-tethered processes to be successful. The silicon tether was constructed by generating a silicon triflate *in situ* with silver triflate and silyl chloride **1.82** followed by the addition of alcohol **1.83** to afford silane **1.84** in 79% yield. RCM using 25 mol % Schrock's catalyst provided the ring-closed product (**1.85**) in 70% yield. **1.85** was treated with phenyl lithium to open the silicon tether and generate silane **1.86** in good yield.[43] A Mitsunobu reaction was used to invert the stereochemistry of the alcohol and install the azide. Subsequent TBAF deprotection removed all protecting groups, including the remaining portion of the silicon tether and upon acetylation, **1.87** was afforded in 80% yield. This species was then taken on to complete the synthesis of D,L-glucosylceramide. Barrett's use of the silicon-tethered RCM overcame the problem of the *trans*-disubstituted double bond in D,L-glucosylceramide, while showing the advantages a silicon-tethered RCM has over the intermolecular CM reaction.

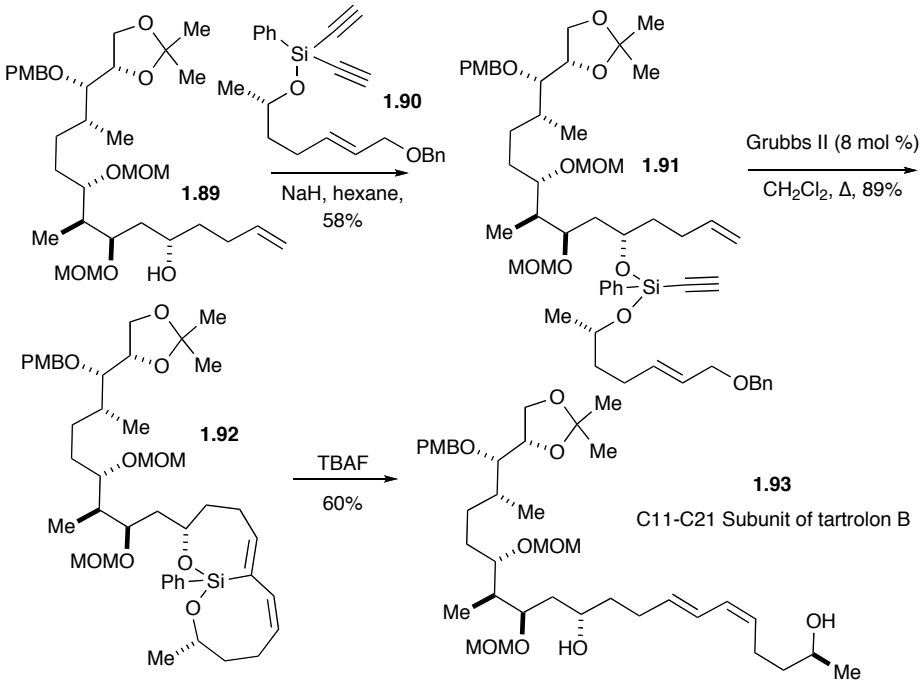
Scheme 16



Enyne RCM (EYRCM) is another type of metathesis reaction that has been exploited in synthetic routes toward natural products. Initial ring-closure for EYRCM begins with reaction at the terminal olefin to yield the terminal ruthenium alkylidiene, which is then poised to react with other olefins to generate a 1,3-diene. EYRCM can be used to form bicyclic compounds in a single synthetic operation. Tartrolon B has a characteristic 1,3-diene motif that Lee and coworkers envisioned to be quickly assembled by a silicon-tethered enyne-metathesis strategy (Scheme 17).[44] To this end, alcohol **1.89** was coupled with silyl ether **1.90** to generate **1.91** in 58% yield. This system was designed to control the initiation site of metathesis[45] by allowing the terminal olefin to react first with the ruthenium catalyst followed by subsequent ring-

closures, by way of the alkyne, to provide the 7,8-ring system. As designed, this metathesis reaction afforded bicyclosilaketal **1.92** in 89% yield using 8 mol % Grubbs II catalyst and then the silicon tether was removed with TBAF to afford **1.93** in 60% yield. The diene system of tartrolon B would be difficult to access by other methods as standard CM does not favor the formation of *Z*-olefins and CM of conjugated dienes has also proven to be difficult. This silicon tether approach rapidly coupled the major subunits contained within tartrolon B and effectively mediated dienyne metathesis to efficiently construct the requisite *E*/*Z*-1,3-diene found in tartrolon B.

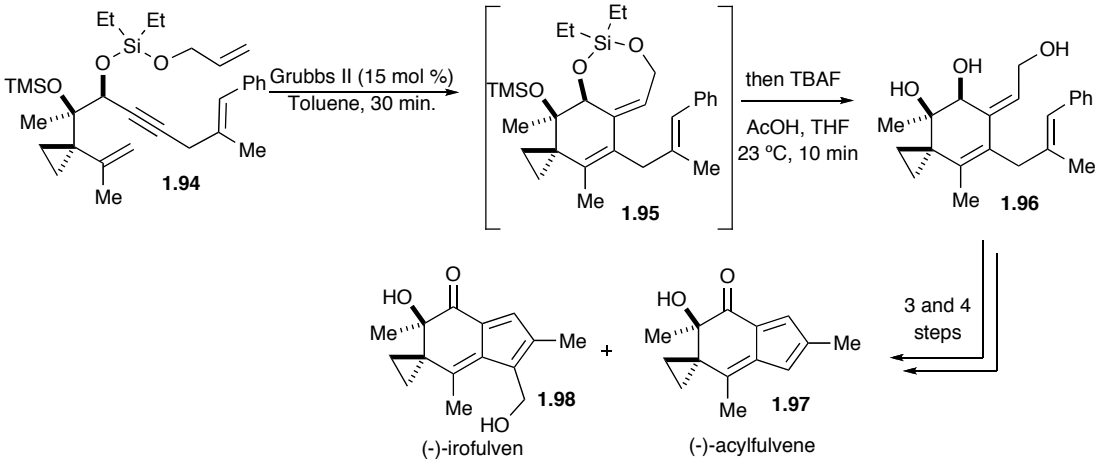
Scheme 17



Movassaghi and coworkers showed the continued utility of silicon tethers and EYRCM in their syntheses of both (-)-acylfulvene and (-)-irofulven (Scheme 18).[46] In their retrosynthetic analysis of the proposed natural products, they envisioned

silicon-mediated EYRCM would not only assemble the AB rings of (-)-acylfulvene and (-)-irofulven but also set the stage for another RCM to complete the total synthesis. Successful construction of bis-siloxane **1.94** set the stage for the proposed tethered EYRCM. Subjection of **1.94** to 15 mol % Grubbs II catalyst at 90 ºC allowed for the formation of the silicon-tethered intermediate **1.95** as observed by ^{1}H NMR spectroscopy. This reaction was presumed to be initiate metathesis at the mono-substituted terminal olefin and sequentially reacted through the alkyne and 1,1-disubstituted olefin to complete the silicon-tethered bicycle (**1.95**). This intermediate was directly converted to triol **1.96** by the addition of TBAF. Earlier attempts to isolate the ring-closed product without the oxygen spacer using allyldimethylsilane, were unsuccessful as the compound decomposed on silica, alumina or when exposed to air. The chosen silyloxy route alleviated the need for isolation of the tethered intermediate due to the facile nature of silicon removal. Three and four subsequent steps were needed to complete the total syntheses of both (-)-acylfulvene and

Scheme 18

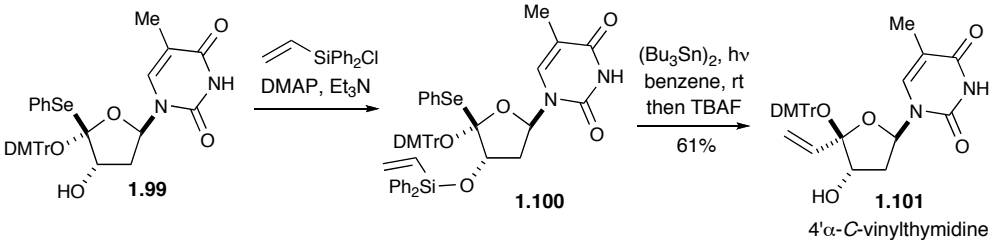


(-)-irofulven, respectively. This route toward (-)-acylfulvene and (-)-irofulven showcases how a tethered EYRCM can access 1,3-diene motifs and how different silicon tethers can affect isolation and removal of the tether.

1.2.3 Temporary Silicon Tethers: Radical Processes

Controlling the regio- and stereoselectivity of intermolecular radical processes is often inefficient. Tethered radical reactions allow for the intramolecular radical cyclization to be more efficient and often times highly regio- and stereoselective.[47] Applications of tethered radical cyclizations in total synthesis have been rarely used over the past decade, but Matsuda and coworkers were able capitalize on a temporary silicon tether radical acceptor in their synthesis of 4'α-*C*-vinylthymidine (Scheme 19).[48] Thymidine derivative **1.99** was prepared and reacted with chlorodiphenylvinylsilane to provide **1.100**. Homolytic cleavage of the Se—C bond was achieved with hν and $(Bu_3Sn)_2$ to allow for the 5-*exo*-trig cyclization to occur. The bicyclic silicon-tethered species was unstable to chromatographic conditions, which necessitated the addition of TBAF to remove the silicon tether and generate **1.101** in 61% yield. The silicon tether used here is an efficient radical acceptor and

Scheme 19

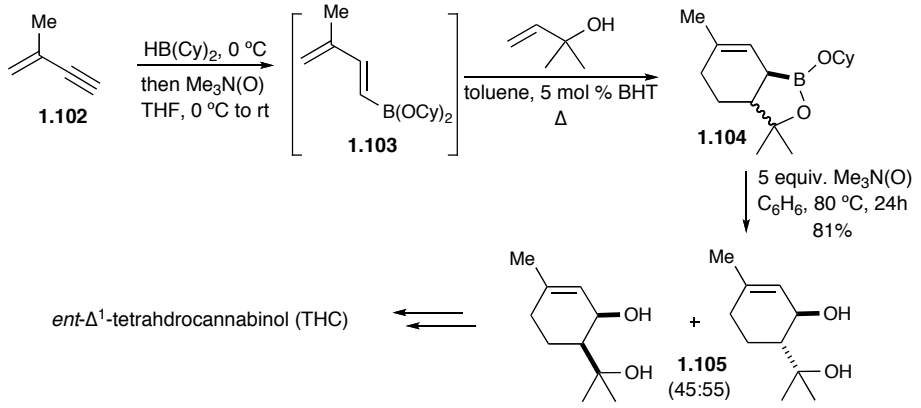


allowed for rapid installation of a vinyl group followed by fluoride elimination to synthesize 4'α-*C*-vinylthymidine.[49]

1.3 Boron Tethers

Boron tethers are rarely used in natural product synthesis likely due to silicon's ease of manipulation relative to boron. Despite this fact, Batey and coworkers have employed a boron-tethered Diels-Alder approach to access cyclohexendiol systems that constructs a common intermediate toward the synthesis of *ent*-Δ^1-tetrahydrocannabinol (THC) (Scheme 20).[50] The boron tether was assembled by an initial hydroboration of enyne **1.102** followed by an oxidation to provide diene boronate **1.103**. Addition of an alcohol allowed for transesterification and a Diels-Alder reaction then occurred to generate boronate **1.104**. The boron tether was easily removed with $Me_3N(O)$ to afford diol **1.105** in 81% yield over the 3 steps. **1.105** was used in the total synthesis of *ent*-Δ^1-tetrahdrocannabinol (THC).[51] Interestingly, changing to O—B—O tethers is not applicable in these cyclization reactions unlike the C—B—O tethers used in this study.[52] Overall, this boron-

Scheme 20



tethered methodology readily assembles the diene and dienophile necessary for the cycloaddition. Accessing the dienes utilized in this study may not be as easy with the silicon tether methodology and demonstrates the utility of boron tethers for these transformations.

1.4 Carbonyl-Based Tethers

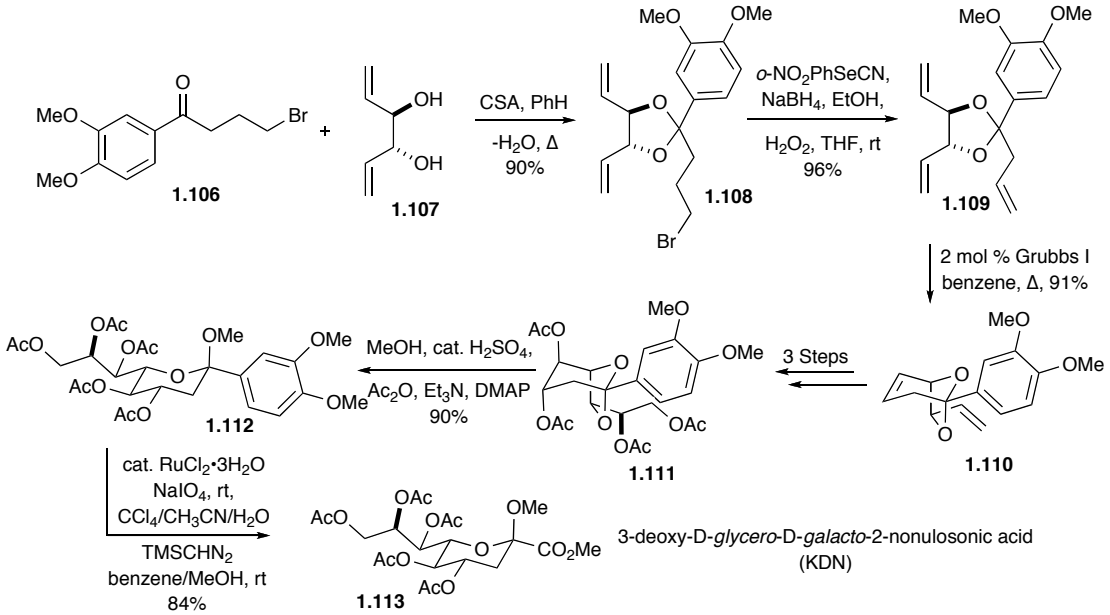
1.4.1 Ketal Tethers

Ketal tethers offer some unique features that distinguish them from their silicon counterparts. The bond lengths of the C—O and Si—O bonds are 1.43Å and 1.64Å, respectively, which provides ketal tethers an increased reactivity due to proximity for Diels-Alder reactions. An inherant problem with shorter C—O bonds and their higher reactivity profile is that the more compact transition state also increases the sterics of the *exo* addition pathways and can reduce the selectivity of the tethered reactions.[53] Ketal tethers, like their silicon counterparts, are also used as a common protecting group in synthesis and thus act in a dual role when they are used in tethering strategies. These known features impact the following examples and can be used in planning other transformations with temporary ketal tethers.

In 2001, Burke and coworkers showcased metathesis on a ketal tether in their synthesis of 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN) (Scheme 21).[54] The ketal tether was constructed by refluxing C_2-symmetric diol **1.107** with alkyl bromide **1.106** to afford ketal **1.108** in 90% yield. Displacement of the bromine was achieved with *o*-NO_2PhSeCN and oxidative elimination of this species provided terminal olefin and metathesis precursor **1.109**. Efforts to make this ketal directly

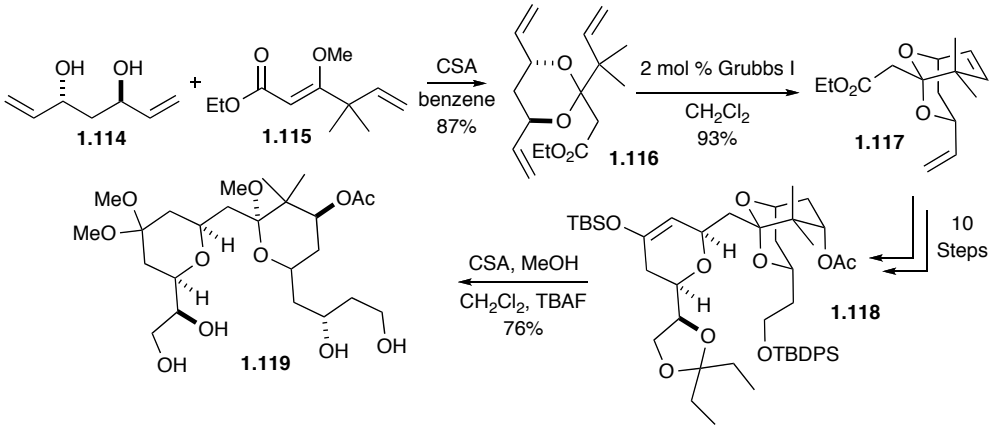
from the corresponding unsaturated ketone led to double bond isomerization to the α,β-unsaturated ketone. Treatment with Grubbs I catalyst allowed for RCM to desymmeterize the C_2-symmetric diol and form bicyclic ketal tether **1.110**. After three steps, the ketal tether was released with H_2SO_4 and MeOH to provide methyl glycoside **1.112** that was subjected to $RuCl_3 \bullet H_2O$ to afford the carboxylic acid and subsequent methylation provided **1.113** (KDN) in 84% yield. Burke displays how a ketal tether can be a tool for desymmeterization by RCM, with further functionalization while the ketal tether is still in place to provide the necessary constraints for selective transformations to be achieved. Intermolecular CM pathways for this desymmeterization would most likely provide a mixture of starting material, CM on both olefins of **1.107**, and the desired product, which highlights the utility of this ketal-tethered RCM.

Scheme 21



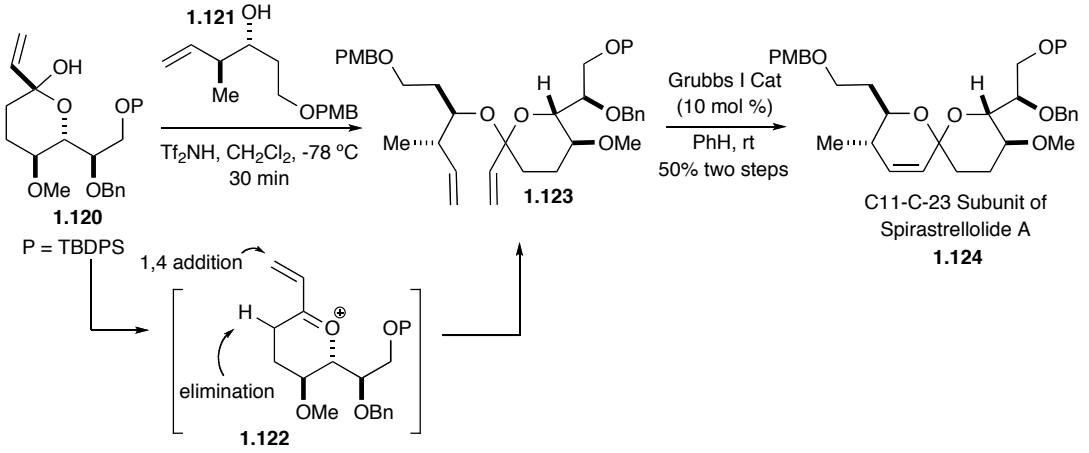
In 2004, Burke and coworkers then explored expanding the scope of their ketal tethers to include C_2-symmetric 1,3-diols for their synthesis of the C1-C16 subunit of bryostatin (Scheme 22).[55] The ketal tether was constructed by addition of CSA to a refluxing solution of diol **1.114** and vinylogous carbonate **1.115** to generate ketal **1.116** in 87% yield. Interestingly, when the equivalent β-keto ester was used, no reaction was observed. The quaternary center adjacent to the carbonyl was believed to impede the ketal formation. Triene **1.116** underwent RCM with 2 mol % Grubbs I catalyst to provide bicyclic ketal **1.117** in excellent yield. This tether was taken forward ten more steps to yield **1.118**. At this point, CSA and MeOH were added to release of the six-membered ring of the ketal tether to generate **1.119** and complete the targeted subunit of bryostatin. Overall, the ketalization/RCM strategy mediates the desymmeterization of a diol, provides steric and conformational constraints for selective functionalization, and serves as a protecting group in their synthesis of the C1-C16 subunit of bryostatin.

Scheme 22



Hsung and coworkers have developed unconventional routes toward spiroketals by developing ketal-tethered reactions such as intramolecular Diels-Alder[56] and RCM[57] approaches to this important substructure (Scheme 23). To display the utility of their methodology they synthesized the C11-C23 subunit of spirastrellolide A, a potent protein phosphatase 2A inhibitor.[58] Formation of a mixed ketal was the first challenge in the implementation of a successful ketal-tethered RCM. Initial additions of simple alcohols into hemiketal **1.120**, activated with various Lewis acids, revealed competing pathways in ketal formation. 1,2- and 1,4-additions, as well as elimination byproducts (**1.122**), were observed upon subjection to acids such as CSA, PPTS, TMSOTf, K-10 clay, and BF_3•OEt_2. Finally, treatment with Tf_2NH[59] at -78 ºC led to exclusive formation of **1.123** as a single diastereomer. RCM of **1.123** proceeded smoothly to give unsaturated spiroketal **1.124** in 50% yield over the two steps. This route towards the C11-C23 subunit of spirastrellolide A highlights the synthetic utility of forming mixed ketal systems and promoting a unique spirocyclization by a ketal-tethered RCM. This spirocycle has been most

Scheme 23



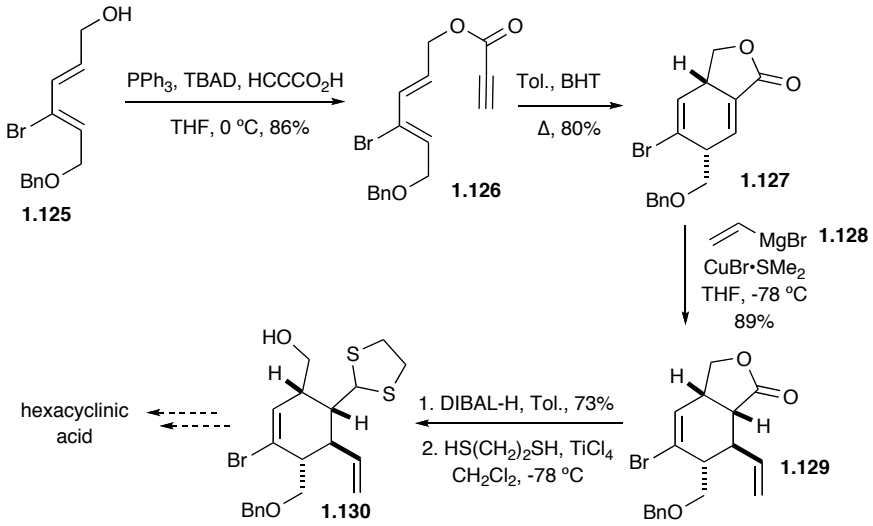
commonly formed by additions of a diol into a ketone, yet this example shows the ease of setting the *Z*-olefin geometry and forming the spirocycle by a tethered intramolecular RCM.

1.4.2 Ester Tethers

A variety of transformations have been mediated by temporary ester tethers to afford increased levels of regioselectivity for the desired reactions. Clarke and Cridland utilized an ester-tethered Diels-Alder strategy in their studies toward the synthesis of hexacyclinic acid (Scheme 24).[60] Ester tethers have been problematic in Diels-Alder reactions due to the harsh reaction conditions and an unfavorable equilibrium for the reactive s-cis diene conformer. Despite their dependence on chain length and problems with polymerization,[61] Clarke and Cridland found an efficient use of an ester tether. First, the ester tether was constructed by a Mitsunobu esterification between alcohol **1.125** and propiolic acid that proceeded in 86% yield. Refluxing ester **1.126** in toluene allowed the intramolecular [4+2] cycloaddition to occur in 80% yield. A copper-mediated vinyl conjugate addition on **1.127** was achieved with complete selectivity to provide γ-unsaturated lactone **1.129**.[62] At this point the relative stereochemistry was conformed by ^{1}H NMR coupling constants and gradient NOE experiments. Reduction of the ester tether with DIBAL-H and subsequent formation of the dithiolane provided **1.130** in good yields. Efforts toward completing hexacyclinic acid are currently in progress. This report of a stereocontrolled ester-tethered Diels-Alder reaction showcases the controlled

construction of the desired tethered moiety, the conformation and electronic bias an ester tether can provide, and the ease at which an ester tether can be removed.

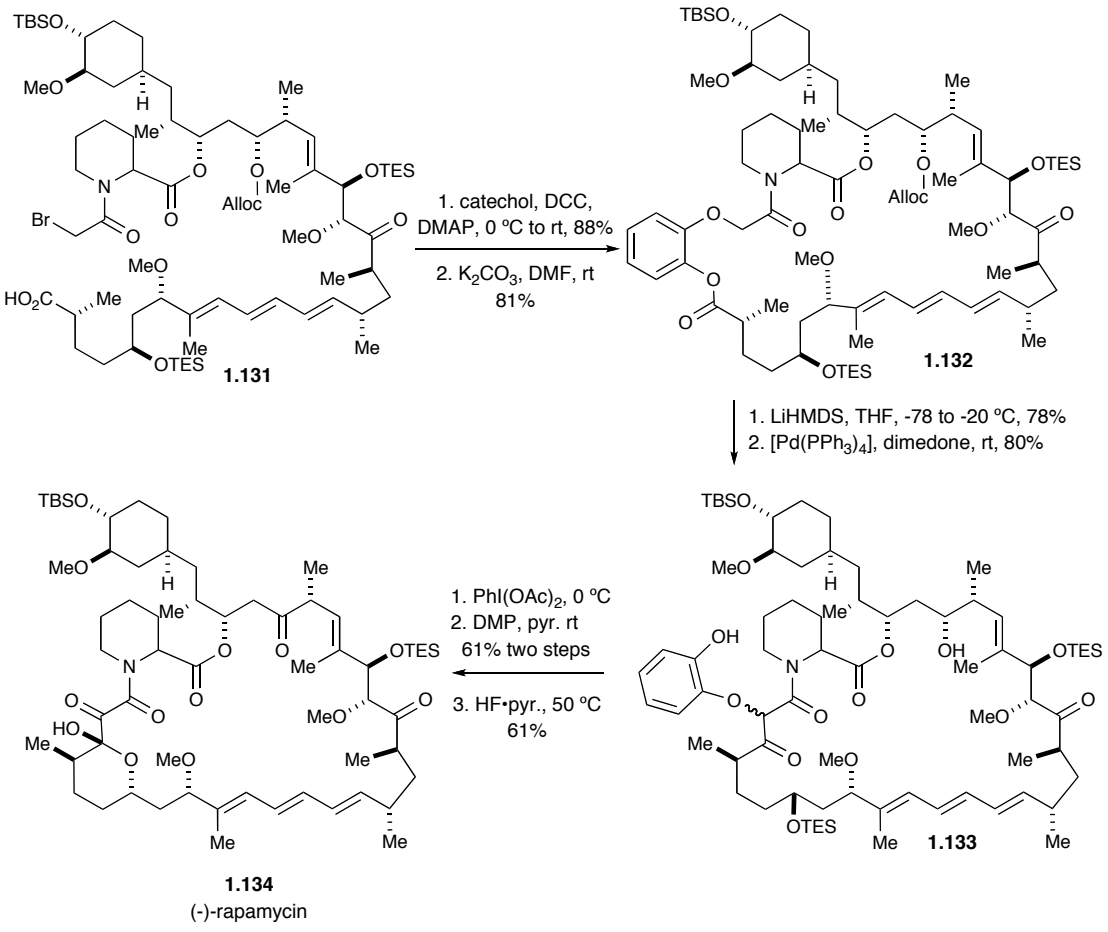
Scheme 24



Tethering strategies have been employed as a tool for macrocyclization. Ley and coworkers, in their total synthesis of (-)-rapamycin, showcased a transannular catechol-templated Dieckmann-like reaction for the formation of the macrocycle contained within (-)-rapamycin (Scheme 25).[63] Synthesis of the tether began with a DCC-coupling between carboxylic acid **1.131** and catechol, followed by the intramolecular alkylative ring closure with K_2CO_3 to provide **1.132** in 71% overall yield. Subsequent ring contraction with LiHMDS constructed the necessary C9-C10 bond in 78% yield. The success of this reaction was due to the Dieckmann-like condensation that proceeds through a six-membered transition state and not through a larger macrocycle, allowing for a successful ring-contracting pathway. This same tethering strategy was also successfully employed by Ley in the synthesis of antascomcin B.[64] Allyloxycarbonyl (Alloc) deprotection with palladium provided

1.133 and set the stage for tether removal. Using $PhI(OAc)_2$, the catechol tether was cleaved from the molecule allowing for the final oxidation and global deprotection to yield (-)-rapamycin **1.134**. This catechol tether strategy provided an efficient route for macrocyclization by a simple six-membered ring contraction. This elegant pathway to the formidable core contained within (-)-rapamycin provides one synthetic answer to problems associated with cyclization of large ring systems.

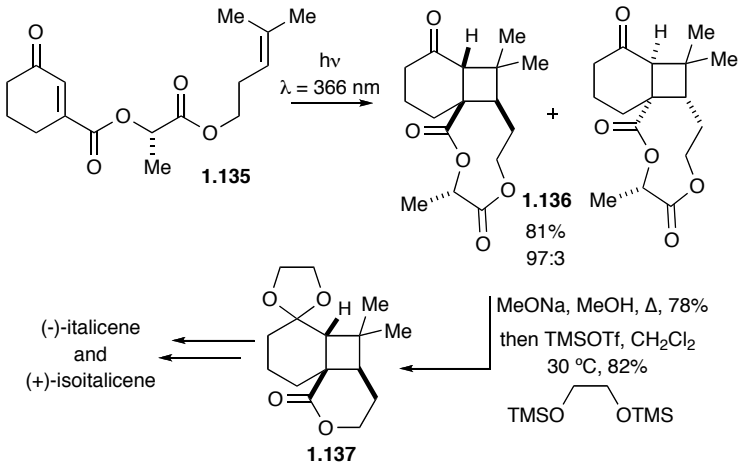
Scheme 25



Piva and Faure, in the synthesis of both (-)-italicene and (-)-isoitalicene, applied a chiral, temporary ester-tethering strategy to mediate an intramolecular [2+2]

photocycloaddition (Scheme 26).[65] (*S*)-lactic acid was a chiral tether[66] between the requisite alcohol and the known oxoacid.[67] **1.135** was subjected to 366 nm light in CH_2Cl_2 to generate cycloadducts **1.136** in 81% yield with complete regioselectivity and excellent diastereoselectivity (97:3). The ester tether was opened by NaOMe and heat followed by slightly acidic conditions to provide lactone **1.137**. **1.137** is a synthetic intermediate *en route* toward both (-)-italicene and (-)-isoitalicene, which are currently being completed in the Piva laboratories. This temporary ester tether demonstrates the ability of a chiral ester tether to couple major subunits of natural products though photochemical reactions and control the regio-, enantio-, and diastereoselectivity of a desired intramolecular transformation.

Scheme 26

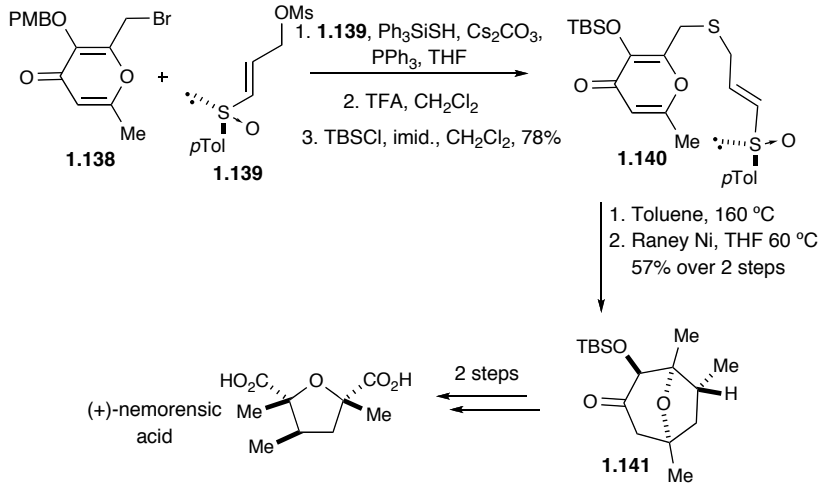


1.5 Sulfur Tethers

Sulfur tethers have been used in synthesis due to their ease in preparation and high reactivity toward cycloaddition reactions. Mascareñas and coworkers utilized a sulfide tether and a homochiral *p*-tolylsulfinyl group to provide a regio- and

diastereoselective thermal [5+2] intramolecular pyrone-alkene cycloaddition in a concise total synthesis of (+)-nemorensic acid (Scheme 27). Intramolecular [5+2] cycloadditions have been difficult to achieve intermolecularly, providing either poor selectivity or no reaction. Mascareñas envisioned that a sulfide-mediated [5+2] cycloaddition where the sulfur could be easily removed would provide a pathway to (+)-nemorensic acid. The formation of thioether **1.140** was achieved by addition of a thiol to mesylate **1.139** with subsequent addition of bromide **1.138** to yield the PMB-protected thiol ether. This thioether was taken on, without purification, to remove the PMB protecting group with TFA and reprotected with TBS to generate **1.140**. **1.140** was then heated in a sealed tube at 160 ºC for 12 h to provide the cycloadduct in 82% yield and 93:7 diastereoselectivity. Treatment of this thioether with Raney nickel allowed for desulfenation of the entire compound and yielded ketone **1.141**. TBS-removal and oxidative cleavage of the seven-membered carbocycle provided (+)-nemorensic acid. Earlier studies had shown that tethered olefins, without the vinyl sulfinyl group, did react but required higher temperatures and longer reaction times. The increased rate of this reaction is attributed to the electron-withdrawing nature of the vinyl sulfinyl, which promotes the thermal [5+2] intramolecular cycloaddition. Interestingly, carbon-tethered analogues of this reaction have increased reaction rates and provide the product in similar yields and selectivities. The sulfide tether was ideal for its ease of installation and ability to mediate difficult [5+2] cycloaddition as well as its ability to be removed from the molecule in a traceless manner, which cannot be as readily achieved for the carbon-based counterparts.

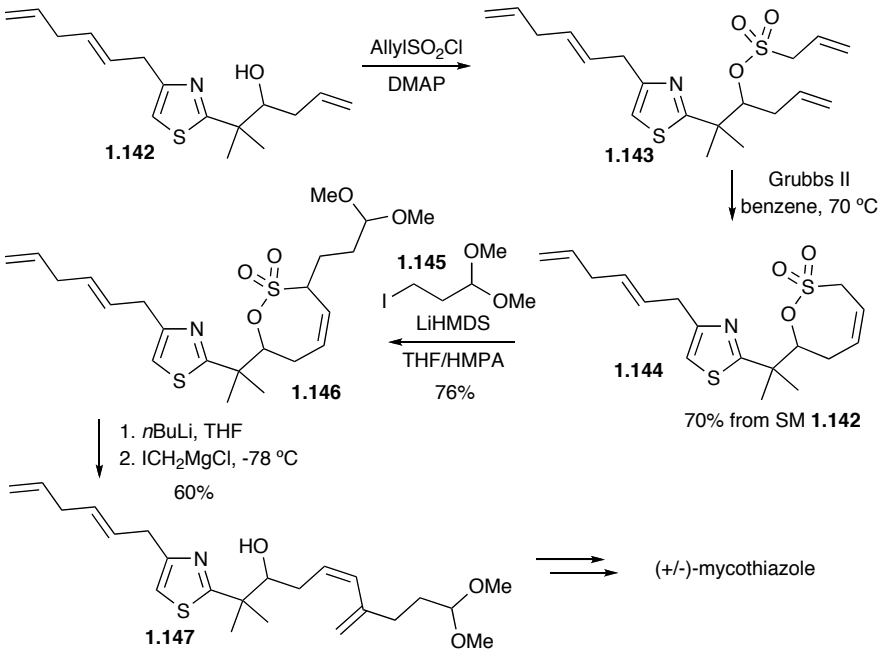
Scheme 27



Sulfone tethers have been used by Cossy and coworkers in their in total synthesis of (±)-mycothiazole (Scheme 28).[68] Previously, the Cossy groups had demonstrated that homoallylic alcohols and allylsulfonyl chloride could be readily coupled and undergo RCM to give various sulfone precursors.[69] These sulfones were then elaborated with sequential deprotonation/alkylation pathways. Removal of the sulfone-tether was achieved by addition of a carbenoid ICH_2MgCl[70] to alkylate the sulfone and subsequent β-hydride elimination resulted in loss of sulfur dioxide and removal of the tether. To test this strategy in total synthesis, alcohol **1.142** was coupled with allylsulfonyl chloride and the crude product was subjected to Grubbs II catalyst to generate cyclic unsaturated sulfone **1.144** in 70% yield. **1.144** was then monoalkylated with iodide **1.145**[71] to give **1.146**. The sulfone tether was then removed by α-deprotonation followed by addition of carbenoid ICH_2MgCl to provide **1.147** in 60% yield. Following this, just four more steps were needed to complete the total synthesis of (±)-mycothiazole. In retrospect, the sulfone tether was used to set

the *Z*-olefin geometry through metathesis, couple the major subunits of the molecule, and was then eliminated to afford the necessary terminal olefin. Cossy has provided an excellent example of temporary tethers, not only to couple subunits of a molecule but also reveal new functionality as they are removed.

Scheme 28



1.6 Summary

This review demonstrates the utility of temporary tethers in the total synthesis of natural products over the past decade. The cornerstone of these reactions that has allowed them to gain prominence and overcome synthetic problems is their ability to convert a difficult intermolecular reaction to an intramolecular transformation. Other benefits of tethers continue to be showcased by their ability to control the regio-, enantio-, and diastereoselectivities of reactions, act as protecting group, provide steric constraint after being installed, and reveal new and different functionality upon their

removal. As new methods are reported, even more elaborate and imaginative uses of these temporary connections will be demonstrated and tethering strategies will continue to be a simplifying tactic in total synthesis.

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Chapter 2

Cross Metathesis in Synthesis: Applications to Phosphate Tethers

2.1 Introduction

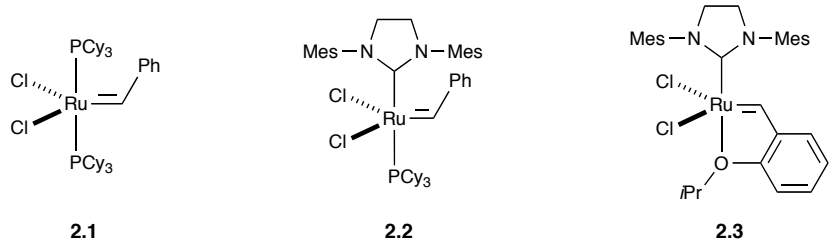
Over the past decade, olefin metathesis has revolutionized transition metal mediated C—C bond formation to become one of the most powerful synthetic tools available in organic synthesis. The advent of new, well-defined metathesis catalysts, possessing immense functional-group compatibility, has permitted the rapid, mild, and selective construction of rings via ring-closing metathesis (RCM).[1a] Additionally, polymers can be synthesized by ring-opening metathesis polymerization (ROMP),[1b] and cross metathesis (CM) can rapidly functionalize olefins.[1c] Compared to its metathesis counterparts, CM is relatively underrepresented owing to a lack of predictability of olefinic reaction partners as well as poorly defined stereochemical outcome of the ensuing product. Ongoing development in the field of CM has lead to a greater understanding of viable olefin partners for selective CM and has provided opportunities for stereoselective synthesis of interesting targets.

Identifying the differential reactivity of olefins is a synthetic challenge encountered when utilizing CM chemistry.[2] Effective synthetic routes may be altered to allow for the most precious substrate to undergo a CM in which its only operative pathway is productive CM and not deleterious homodimerization. The current methodology and total synthetic efforts highlighted herein showcase the successful use of selective CM.

2.1.1 Examples of Selective Cross Metathesis

For selective CM to occur, a suitable catalyst must be chosen that accounts for the steric and electronic nature of the reacting olefin partners. Common catalysts used

for these CM are Grubbs first (**2.1**)[3a,b] and second (**2.2**)[3c] generation catalysts in addition to Hoveyda-Grubbs catalyst (**2.3**)[3d] (Figure 1). In 2003, Grubbs and coworkers put forth a general model for selectivity in olefin cross metathesis reactions.[2] Olefins were categorized by their relative rates of homodimerization correlating to the metathesis catalyst being used for CM. The classes ranged from Type I olefins, which were characterized by rapid, reversible homodimerization to Type IV olefins, which were classified as spectators to CM. The pairing of different olefin types allows for varying product ratios to be attained; reacting two Type I olefins yields a statistical mixture of CM product to homodimers of each olefin. In contrast, a reaction between a Type I and a Type III olefin generates a selective, high yielding CM. Therefore olefin partners possessing disparate reactivity are optimal for CM to proceed selectively and efficiently.



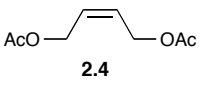
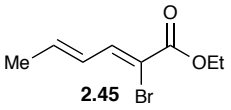
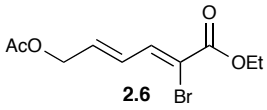
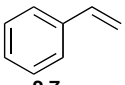
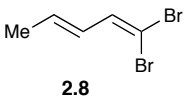
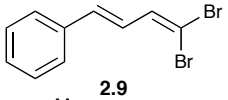
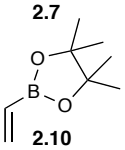
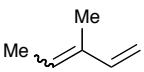
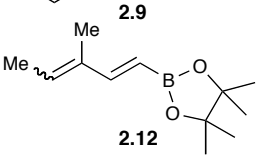
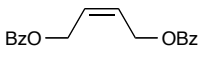
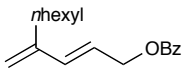
2.1 **2.2** **2.3**

Figure 1. Structure of the metathesis catalysts.

Building on the established model for olefin CM, further research is expanding the array of olefin partners and leading to a greater understanding of their reactivity. An example of this development was the construction of functionalized dienes utilizing CM. This area has not been studied as in depth due to the chemo- and stereoselectivity issues encountered in the CM of conjugated systems. To overcome

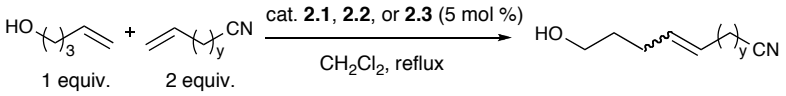
these issues, Grubbs and coworkers adjusted the electronics and sterics of conjugated dienes to deactivate just one of the double bonds.[4,5] Placing electron-withdrawing groups on the α-carbon of the diene sufficiently reduced the electron density of the α,β-unsaturated double bond such that efficient CM was achieved to yield conjugated dienes **2.6** and **2.9** (Table 1, entries 1 and 2). Steric differentiation of conjugated double bonds was also accomplished using 3-methyl-1,3-pentadiene (**2.11**) to shield one of the olefins to allow for the vinyl boronate (**2.10**) to react with the sterically unencumbered olefin yielding boronate **2.12**. Again, steric deactivation of one olefin was accomplished by placing substituents at the 2-position of butadiene (**2.14**) permitting CM at the more reactive olefin providing diene **2.15**. This method further illustrates the importance of disparate olefin reactivity in CM, which Grubbs was able to employ via steric and electronic demands in diene systems to enable chemoselective construction of functionalized conjugated dienes.

Table 1. CM with Functionalized Dienes.

entry	olefin	conjugated diene	product	yield (%) E/Z ratio
1	 **2.4**	 **2.45**	 **2.6**	70 7.5:1
2	 **2.7**	 **2.8**	 **2.9**	60 20:1
3	 **2.10**	 **2.11**	 **2.12**	80 >99:1
4	 **2.13**	 **2.14**	 **2.15**	73 >99:1

Hoveyda and coworkers investigated CM reactivity patterns in their efforts to synthesize unsaturated amino alcohols.[6] The authors proposed using Type III and Type I cyanide olefin partners and reacting these with various unsaturated alcohols. Subsequent reduction of the CM products rapidly produced the corresponding amino alcohols. When submitting acrylonitrile[7] (**2.17a**), a Type III olefin, to CM conditions with pent-4-en-1-ol (**2.16**), a Type I olefin, the reaction proceeded with catalysts **2.2** and **2.3** to yield the desired products (Table 2). This reaction was presumed to be selective because electron deficient **2.17a** exhibits a slow rate of homodimerization, which allows for selective CM. Additional reactions of allyl cyanide[8] (**2.17b**) and homoallyl cyanide (**2.17c**) with **2.16** revealed that these proposed Type I CM partners did undergo selective CM reactions at optimal reaction concentrations. This may be due to decreased reactivity of olefins **2.17b** and **2.17c** as a result of the inductively withdrawing nature of the cyanide group. As illustrated in Table 2 (entries 4-10), adjustment of the reaction concentration with respect to the catalyst allows for products **2.18b** and **2.18c** to be formed in good yields and *E/Z* selectivities. Hoveyda's examples of CM between **2.17b** and **2.17c** with Type I olefins emphasizes that considerations for these reactions must not only focus on the number of equivalents of olefin used, but also rely on proper choice of catalyst with regard to reaction concentration, thus affording the most efficient CM.

Table 2. CM patterns of various unsaturated cyanides.



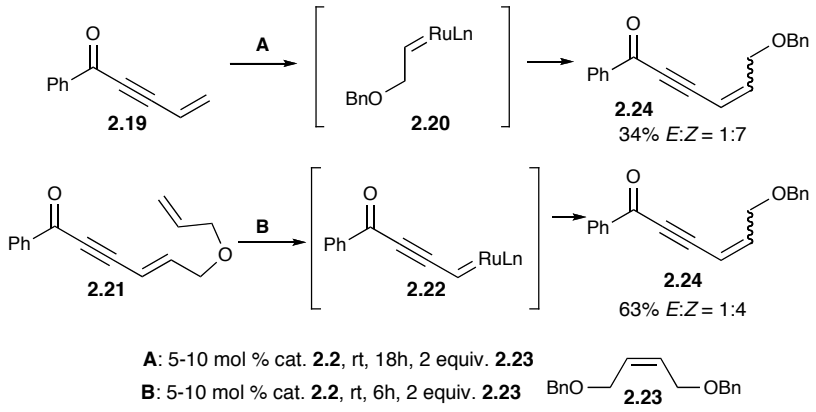
1 equiv. **2.16** | 2 equiv. **2.17a** (y=0), **2.17b** (y=1), **2.17c** (y=2) | **2.18a** (y=0), **2.18b** (y=1), **2.18c** (y=2)

entry	Ru complex	reaction concentration (M)	product	yield (%), *E*/*Z* ratio
1	**2.2**	0.5	**2.18a**	35, 1:2
2	**2.3**	0.07	**2.18a**	74, 1:2.5
3	**2.3**	0.24	**2.18a**	60, 1:2
4	**2.1**	1.2	**2.18b**	2, 3.5:1
5	**2.2**	0.05	**2.18b**	38, 6:1
6	**2.2**	0.5	**2.18b**	81, 6:1
7	**2.3**	0.05	**2.18b**	72, 2:1
8	**2.3**	0.5	**2.18b**	65, 6:1
9	**2.2**	0.5	**2.18c**	72, 5:1
10	**2.3**	0.05	**2.18c**	48, 4:1

A new approach in the CM of less reactive olefin partners was shown in the synthesis of enynes and related structures as disclosed by Hansen and Lee.[9] Critical to this process was the generation of alkynyl Ru-alkylidene **2.22** to understand its reactivity toward both alkenes and alkynes (Scheme 1).[10] Initial attempts employed catalyst **2.2** and terminal enyne **2.19**. Surprisingly, a 34% yield of predominately the *Z*-isomer of **2.24** was obtained despite the electron-deficient nature of **2.19** with a Type I olefin partner **2.23**. Due to the low reactivity of the enyne olefin partner an alternate delivery system was required. Synthesis of compound **2.21** and treatment with catalyst **2.2** revealed that metathesis was initiated at the terminal allyl of the conjugated enyne system and subsequently generates alkynyl alkylidiene **2.22**. Further, CM with **2.23** yields **2.24** in better yield albeit with slightly lower selectivity for the *Z*-isomer. Generating of the Ru-alkylidene complex on a previously unreactive olefin metathesis converts a low yielding process into a viable synthetic

route for relay construction of these enyne systems. Implementation of this novel catalyst delivery and subsequent CM displays an approach that may be applied to other challenging systems.

Scheme 1.



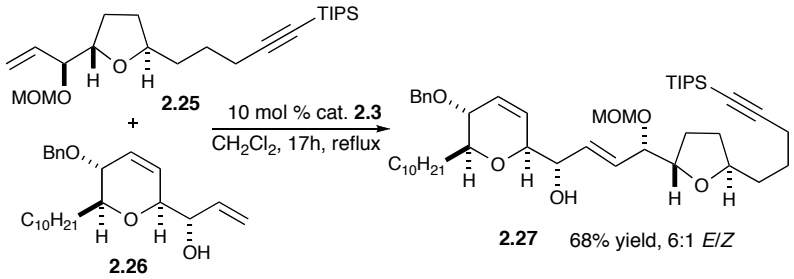
2.1.2 Cross Metathesis in Total Synthesis

Establishing effective CM models and expanding methodologies surrounding reactive olefin partners is allowing CM to gain greater prominence in total synthetic efforts. Vital to developing successful synthetic CM pathways is the appropriate design of olefin partners possessing differential reactivity. This is optimal when the precious component displays either Type I reactivity patterns, where homodimerization is not a deleterious pathway, or Type III reactivity when the homodimerization pathway is non-operative.[2] Utilizing these techniques allows for the implementation of selective CM in total synthetic routes.

The total synthesis of (-)-mucocin illustrates the use of disparate olefin reactivity for a selective CM in a key step of the synthesis.[11] Exploiting asymmetric glycolate Aldol additions and RCM methods, Crimmins efficiently constructed CM

precursors **2.25** and **2.26** (Scheme 2). Modifying **2.25** to bear a MOM group allowed for differential reactivity between the otherwise similar allylic alcohols in the CM. Mixing a 1:1 ratio of **2.25** and **2.26** with catalyst **2.3** yields the desired cross-coupled product **2.27** in 68% (6:1 *E/Z*). Changing the protecting group on allyl alcohol **2.25** to a TES-group rendered the olefin unreactive, but reacting this system with catalyst **2.2** under the same conditions yielded 58% of the desired product.[12] Overall, the synthesis of (-)-mucocin displays a selective CM without use of excess ratios of either substrate, ideal for natural product synthesis.

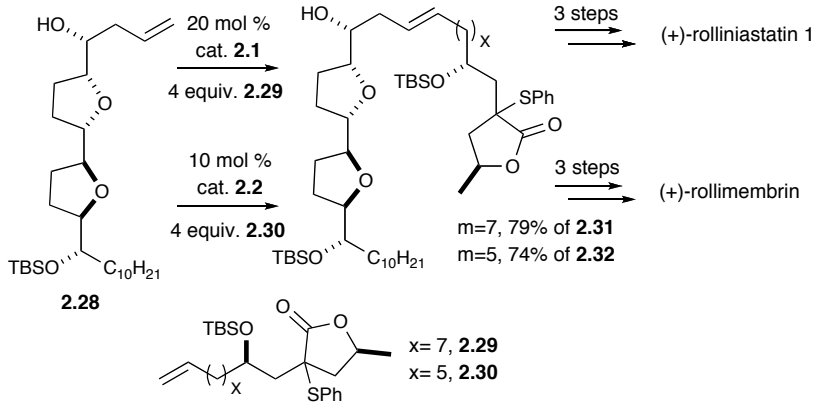
Scheme 2



Conversely, when both olefins possess Type I reactivity, an excess of one CM partner is necessary to achieve the heterocoupled product. In the total synthesis of (+)-rolliniastatin 1 and (+)-rollimembrin by Lee and coworkers, a pivotal CM between fragment **2.28** and compound **2.29** or **2.30** coupled large fragments of these molecules (Scheme 3).[13] Using four equivalents of **2.29** and 20 mol % catalyst **2.1**, CM product 2.31 was achieved for the synthesis of (+)-rolliniastatin 1 in 79% yield. Again, four equivalents of **2.30** were used to obtain **2.32** in 74% yield, a precursor of (+)-rollimembrin, using only 10 mol % catalyst **2.2**. When using just one equivalent of **2.30**, a 46% yield of **2.32** was obtained along with 28% yield of the homodimer of

2.30. This synthesis displays that CM between two olefins of similar reactivity requires an excess of one olefin to achieve the desired product in good yield. If one of the CM partners is easily synthesized, as in this case, this does not present a problem in obtaining the CM product. Lee has shown in his syntheses of (+)-rolliniastatin 1 and (+)-rollimembrin the power of CM to rapidly access a variety of natural product targets.

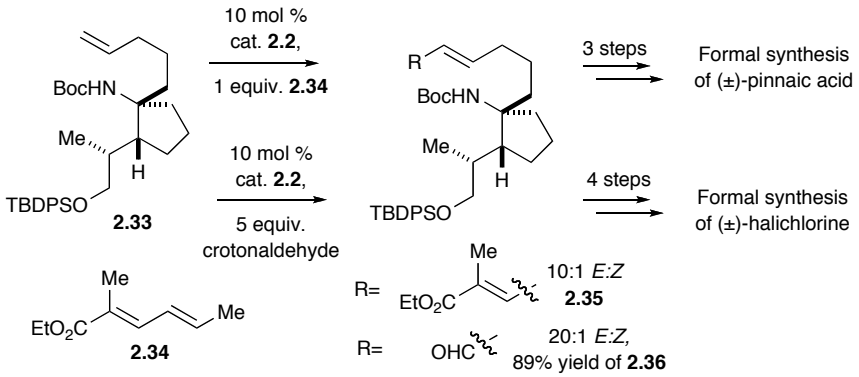
Scheme 3.



The total synthesis of both (±)-pinnaic acid and (±)-halichlorine was accomplished by CM methodology with terminal olefin **2.33** to achieve advanced subunits *en route* to the natural product targets (Scheme 4).[14] Martin and coworkers showcased a selective CM between **2.34**, sterically and electronically biased,[4] and electron rich **2.33** to obtain intermediate **2.35**. Similarly, Type I olefin **2.33** was reacted with Type II olefin crotonaldehyde to achieve **2.36** in 89% yield with excellent *E:Z* selectivity. When using a more common CM partner acrolein, 30-35% yields were consistently obtained with a large amount of unreacted **2.33**, displaying that the stability, electronics, or sterics of acrolein are not ideal for this C—C bond

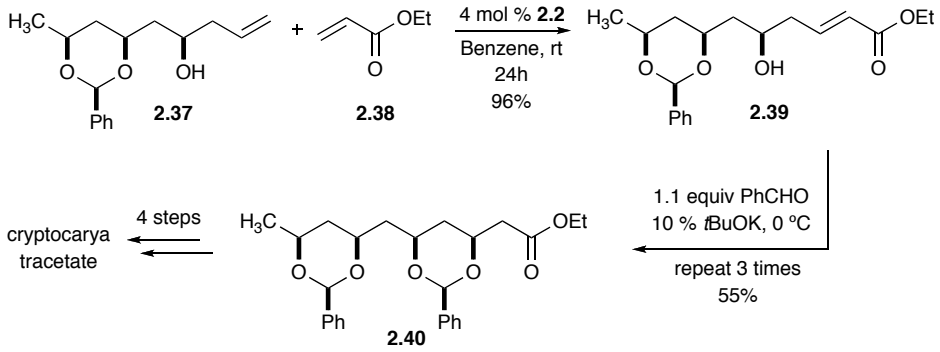
construction. This methodology highlights the utility of CM in natural product synthesis where a common subunit may be functionalized by CM to quickly obtain advanced intermediates required for the synthesis of multiple targets.

Scheme 4



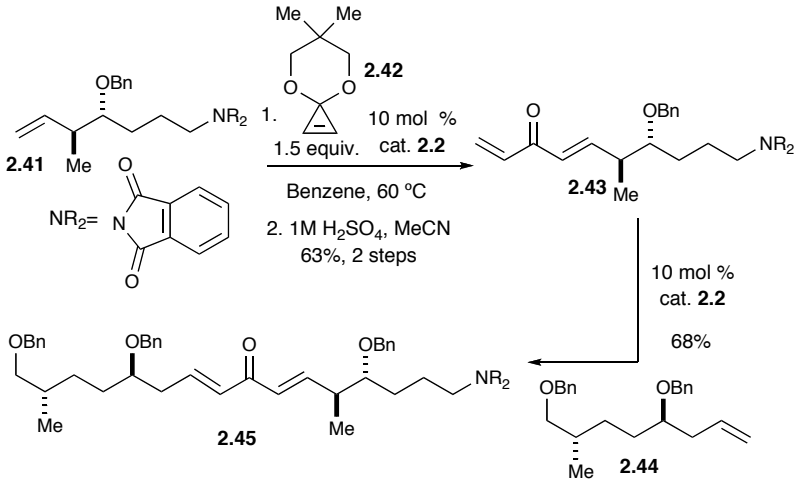
O'Doherty and coworker in their synthesis of cryptocarya triacetate, cryptocaryolone, and cryptocarylolone diacetate showcase a simple and effective use of CM.[15] Their route to these natural products hinged on a CM between homoallylic alcohol **2.37**, a Type I olefin, and 2 equiv. of Type II CM partner ethyl acrylate (Scheme 5). Previously, a three-step protection/oxidative cleavage/Wittig reaction protocol was used to obtain **2.40** from **2.37**, yet the envisioned CM would provide the desired product in a single step. Selective cross coupling occurred between **2.37** and ethyl acrylate with catalyst **2.2** in 96% yield after 24 hours with a *E*:*Z* ratio of 20:1. Exposure of **2.39** to benzaldehyde and a catalytic amount of *t*BuOK installed the final stereocenter of cryptocarya triacetate in 55% yield. This procedure showed how CM could react two olefins without the need for additional functionalization to achieve a shorter and more facile route to tetraol **2.40** by CM.

Scheme 5.



Kozmin and coworkers synthesized advanced intermediates by CM in their route toward bistramide A (Scheme 6).[16] A tandem ring opening/CM sequence between cyclopropene **2.42** and alkene **2.41** yields **2.43** upon acidic deprotection of the ketal in 63% yield with 2:3 *E:Z* selectivity. Using two equivalents of dienone 52, a Type II olefin, and 1 equiv. of compound **2.44**, a Type I olefin, afforded the desired product (**2.45**) in 68% yield. Subsequent hydrogenation of **2.45** allowed for the formation of a single spiroketal fragment found in bistramide A. Sequential selective

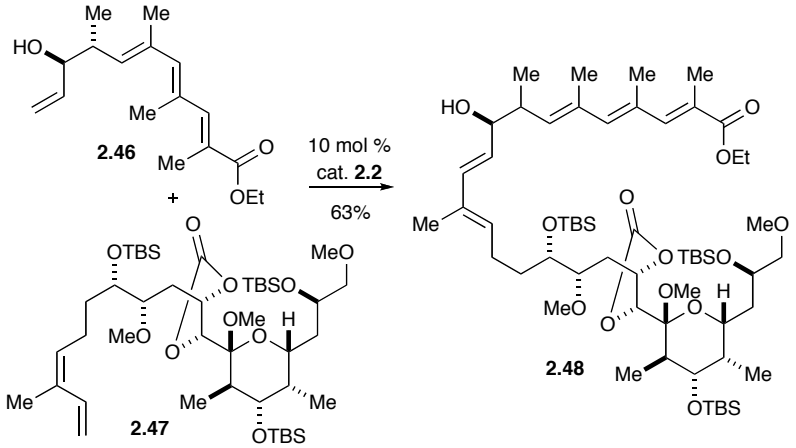
Scheme 6



CM revealed by Kozmin demonstrates the power of this methodology to construct complex targets.

The application of CM in the final stages of the enantioselective synthesis of apoptolidinone by Crimmins and coworkers showcases a regio- and stereoselective use of CM methodology (Scheme 7).[17] Construction of **2.46** and **2.47** set the stage for the key CM between the Type II and Type III olefins, respectively. Relying on the unreactive nature of the trisubstituted and conjugated olefins in **2.46**, and the terminally biased reactivity of the diene in **2.47**, the proposed CM was expected to be selective for the terminal olefins of each molecule. With two equivalents of **2.46** and 10 mol % catalyst **2.2**, a 63% yield of **2.48** in 95:5 *E:Z* selectivity was achieved along with 31% yield recovered **2.47**. Both the recovered starting material and homocoupled **2.46** could be recycled in this process. When compound **2.46** was protected as a TBS ether instead of the free alcohol the CM proceeded in poor yields (~20%) which is most likely attributed to the additional steric congestion imposed on the Type II olefin partner, rendering it less reactive with a Type III olefin partner.

Scheme 7.



This synthesis validates that a well-designed CM can be utilized, even in the presences of numerous olefins, in synthesis.

2.2 Results and Discussion

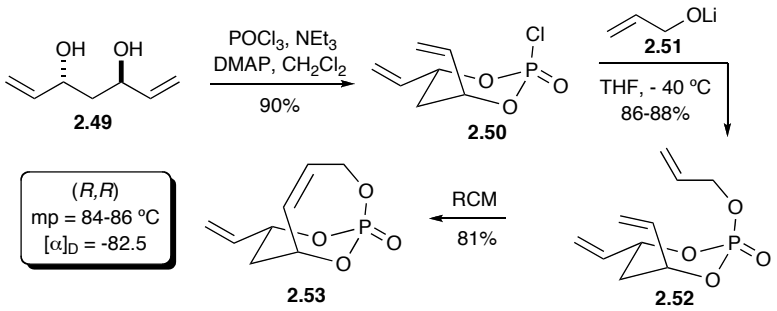
2.2.1 Cross Metathesis with Temporary Phosphate Tethers

Exploiting temporary tethers[18] as a tactic to join complex synthetic building blocks has emerged as a versatile approach to rapidly access biologically relevant targets. As previously discussed, the use of temporary tethers in synthesis has centered largely on silicon.[18] We have reported the use of phosphinamide, phosphonamide, phosphonamidate,[19] and phosphate tethers (*P*-tethers),[20] each possessing a number of salient features that can be exploited in synthesis. In particular, we have demonstrated that phosphate tethers not only provide orthogonal protective attributes, but also multifaceted activation of the corresponding phosphate ester appendages by providing innate leaving group ability within the tether. Employing a phosphate tether, we constructed the unique *P*-chiral bicyclo[4.3.1]phosphate triester **2.53** (Scheme 8) and demonstrated its utility in a myriad of regio-, chemo- and stereoselective transformations.[20] In light of this advancement, we then reported an extension of the phosphate tether methodology in which additional functionalization via highly selective cross metathesis (CM) of **2.53** allows for the facile assembly of a diverse array of complex polyol subunits.

Bearing in mind the features of CM, we set out to explore the scope and utility of CM reactions between the terminal olefin of **2.53** and other olefinic partners. Construction of *P*-chiral bicyclic[4.3.1]-phosphate triester **2.53** began with coupling

of C_2-symmetric diene 1,3-diol **2.49**[21] and phosphoryl trichloride producing the pseudo-C_2-symmetric compound **2.50** possessing interchangeable, homotopic Cl and P=O groups. Concurrent addition of lithium allyloxide **2.51** into phosphoryl monochloride **2.50** yields phosphate triene **2.52**. Ring-closing metathesis (RCM) using Grubbs second-generation catalyst **2.2**[3c] afforded desired phosphate **2.53** in good yield.

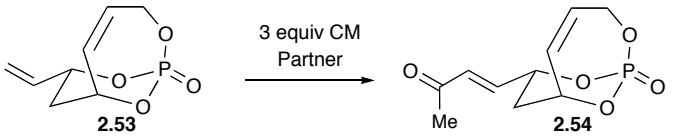
Scheme 8



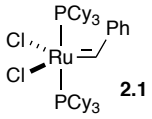
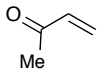
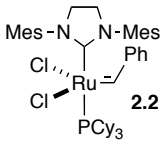
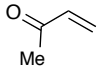
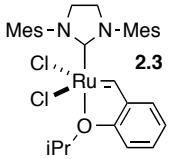
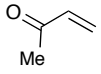
This project was started by screening metathesis catalysts **2.1**, **2.2**, and **2.3** for viability in CM between **2.53** and suitable olefinic partners (Table 3). Reaction of phosphate **2.53** with methyl vinyl ketone under refluxing CH_2Cl_2 was employed as a standard system for preliminary proof-of-concept experiments. Various catalyst loadings and reaction concentrations produced disappointingly low conversions, < 5% and 26%, when using both Grubbs first and second generation catalysts **2.1**[3] and **2.2**, respectively. We next studied use of Hoveyda-Grubbs second-generation catalyst **2.3**,[22] which Blechert and coworkers employed in successful CM with electron-deficient systems.[23] Using Blechert's conditions, we produced a selective CM between **2.53** and methyl vinyl ketone yielding **2.54** (75%) with excellent olefin

selectivity (*E*:*Z* = 44:1). Increasing the concentration to 0.1 M (relative to the substrate) provided similar yields but *E*:*Z* ratio decreased to 15:1.

Table 3. CM studies with bicyclic phosphate **2.53**.



2.53 **2.54**

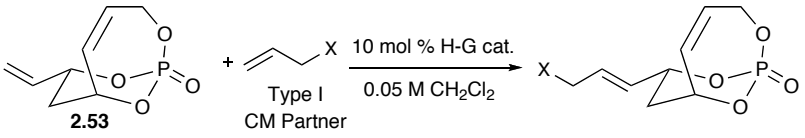
entry	10% catalyst	CM partner	conc./ solvent	% yield
1	 **2.1**		0.05 M/ CH_2Cl_2	<5[a]
2	 **2.2**		0.05 M/ CH_2Cl_2	25[a]
3			0.1 M/ CH_2Cl_2	26[a]
4	 **2.3**		0.05 M/ CH_2Cl_2	75[b]
5			0.1 M/ CH_2Cl_2	71[b,c]

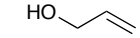
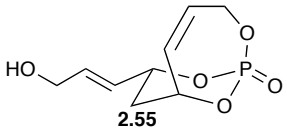
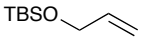
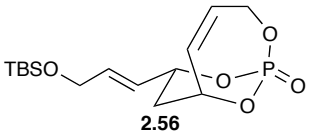
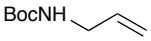
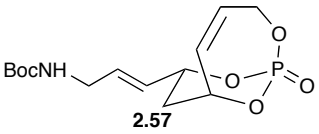
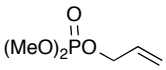
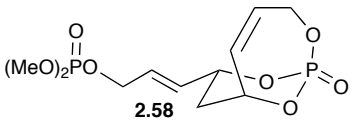
[a] Yields determined by ^{31}P NMR. [b] Yields determined by isolated, purified products. [c] Used 4.0 equiv of MVK.

With this result in hand, other CM partners were studied. Beginning with Type I olefins (Table 4), CM of **2.53** with allyl alcohol and TBS-protected allyl alcohol proceeded smoothly with excellent yield and selectivity (86% and 87% yields, >99:1 *E*:*Z* selectivity) using 10 mol % of Hoveyda-Grubbs catalyst **2.3** in refluxing CH_2Cl_2 over a 3-6 hour period. When the CM partner was switched to a Boc-protected allyl amine, the yield of the corresponding protected amino phosphate triester **2.57** decreased, but selectivity was maintained (>99:1). Coupling allyloxy dimethoxyphosphate with bicyclic phosphate **2.53** produced **2.58** in good yield, albeit

with low *E*:*Z* selectivity (2:1). Again, when **2.1** and **2.2** were used in these CM reactions with Type I olefin partners, yields were considerably lower.

Table 4. CM with Type I olefins.

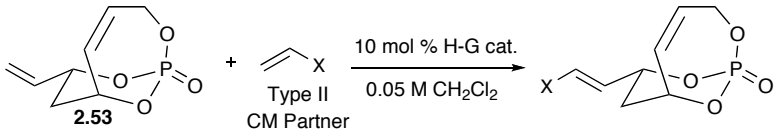


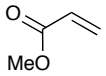
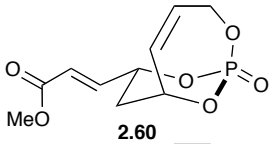
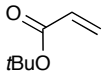
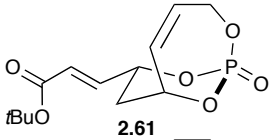
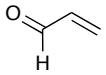
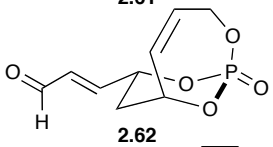
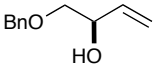
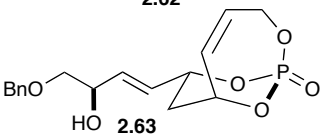
entry	CM partner	product	% yield	*E*:*Z*
1		 **2.55**	86	>99:1
2		 **2.56**	87	>99:1
3		 **2.57**	69	>99:1
4		 **2.58**	80	2:1

Given the success of Type I olefins, we next turned toward screening CM reactions between Type II olefin coupling partners and **2.53** (Table 5). With electron deficient Type II olefins, 4-5 equivalents of the CM partner were needed to obtain the highest yields. Optimized conditions were found to occur with 10-12 mol % Hoveyda-Grubbs catalyst **2.3**. Having achieved CM with methyl vinyl ketone, other electron deficient olefins were employed. Treatment of **2.53** with methyl acrylate occurred in good yield and selectivity (78% yield, *E*:*Z* = 8:1) (Table 5, entry 1). Interestingly, when *t*butyl acrylate was used the yield dropped to 60% and the *E*:*Z*

ratio decreased to 5:1 (Table 5, entry 2). When acrolein was used, CM proceeded smoothly to afford 16 in good yield and with excellent selectivity (Table 5, entry 3).

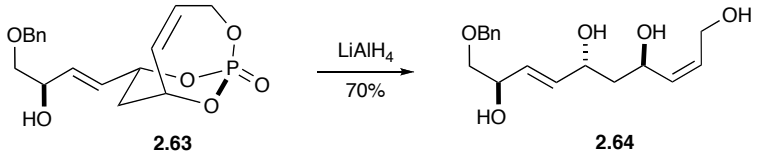
Table 5. CM with Type II olefins.



entry	CM partner	product	% yield	*E*:*Z*
1		 **2.60**	78	8:1
2		 **2.61**	60	5:1
3		 **2.62**	78	>99:1
4	 **2.59**	 **2.63**	72	>99:1

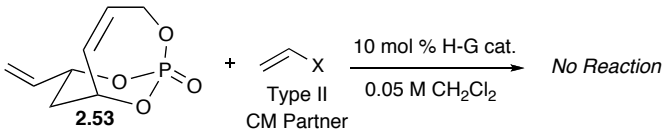
Use of more elaborate coupling partners provides an attractive extension of this chemistry. Thus, treatment of 5 with readily prepared (*R*)-1-(benzyloxy)but-3-en-2-ol **2.59**[24] (Table 5, entry 4) gave phosphate **2.63** in 72% yield and *E*:*Z* = 99:1. Furthermore, convenient removal of the tether in **2.63** was realized with $LiAlH_4$[25] affording the advanced polyol subunit **2.64** in 70% yield (Scheme 9). Overall, stereochemically rich **2.64** is readily derived from **2.49** in a concise five-step sequence.

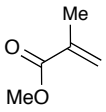
Scheme 9



To fill out the reactivity profile of **2.53**, Type III olefins were surveyed as CM partners. After treating with methyl methacrylate for 12 h, **2.53** was unreacted and could be cleanly recovered (Table 6, entry 1). Using isobutylene afforded only trace amounts of product even when the reaction was run neat (Table 6, entries 2 and 3). CM between bicyclic phosphate **2.53** and electron deficient acrylonitrile[6] also yielded no product (Table 6, entry 4). Attempted homo-dimerization of bicyclic phosphate **2.53**, produced no observable product after 24 h under the aforementioned CM

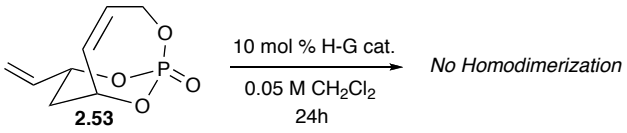
Table 6. CM with Type III olefins.



entry	CM partner	equivalents	% yield
1		4.0	<5
2		4.0	<5
3		Neat	<5
4		4.0	N.R.

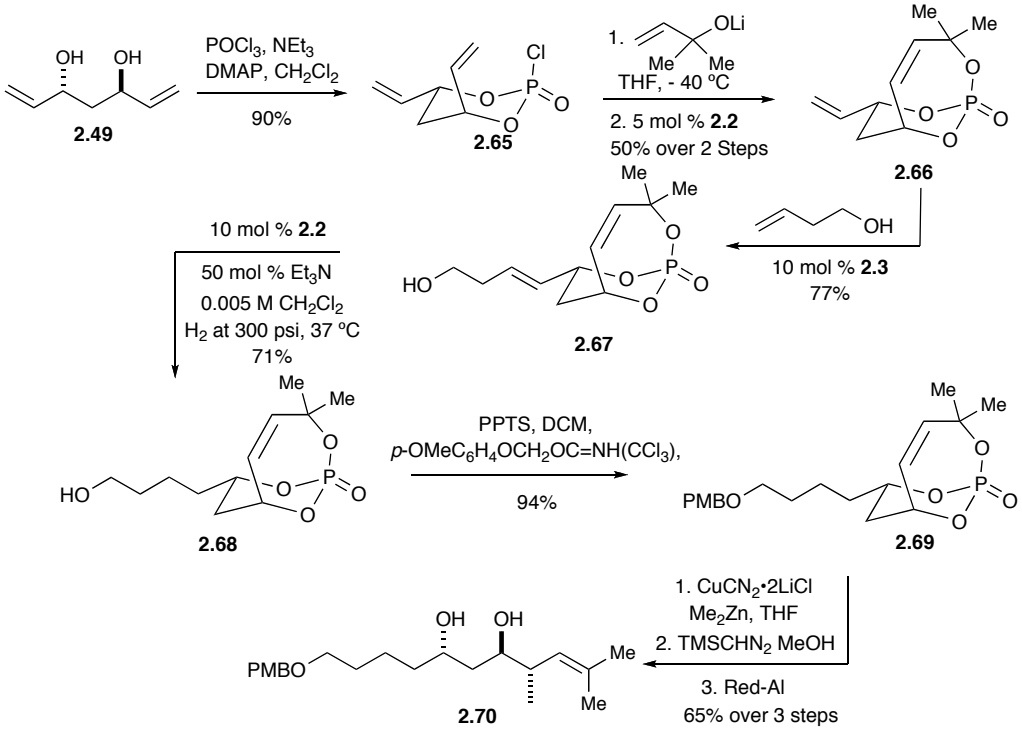
conditions (Scheme 10). This result, when taken with the data compiled in Table III, suggests the external olefin of phosphate **2.53** possess Type III character.

Scheme 10



To display the utility of this CM methodology, we were able to construct complex polyketide fragment **2.70** (Scheme 11) possessing a key stereotriad found in a number of natural products,[26] including dolabelides A and B.[27] We envisioned that a selective hydrogenation would be possible at the external olefin of phosphate **2.53** if we imposed additional steric constraints by incorporation of a geminal dimethyl group in **2.67**. Thus, utilizing the lithium alkoxide of 2-methylbut-3-en-2-ol as a coupling partner with diol **2.49** and $POCl_3$, provided a phosphate triene that undergoes smooth RCM to afford **2.66**. CM of phosphate **2.66** with homoallyl alcohol using Hoveyda-Grubbs catalyst **2.3** generated functionalized phosphate **2.67**. Subjection of **2.67** to 10 mol % of Grubbs catalyst **2.2**, in the presence of 0.5 equivalents of triethylamine[28] at 300 psi H_2, achieved selective hydrogenation of the external olefin in good yield. PMB-protection of alcohol **2.68** using a PMB-imidate produced **2.69** in 94% yield. Final diversification of this substrate using a highly regio- and diastereoselective methyl cuprate addition,[20] followed by phosphate removal, produced the differentiated polyol fragment **2.70** as the sole product in 65% yield over three steps.

Scheme 11



This study demonstrated the utility of CM in bicyclic phosphates **2.53** and **2.66** with application to rapid assembly of advanced polyol subunits. Moreover, we have determined a Type III olefinic character with respect to CM for the exocyclic olefin in both **2.53** and **2.66**. This empirical observation illustrates deficiencies in our knowledge of cross metathesis in complex molecules and suggests that additional studies are necessary to fully understand these systems.

2.3 Summary

Advances in CM methodology have led to a greater understanding and increased application of CM in synthetic pathways. Despite being underrepresented in the field of metathesis, CM is becoming an indispensable tool for organic chemistry and complex natural product synthesis.

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Chapter 3

Phosphate Tethers in Synthesis:

Total Synthesis of Dolabelide C

3.1 Introduction

3.1.1 Overview of the Dolabelide Family

In 1995, the isolation and structural characterization of two new 22-membered macrolides, dolabelides A and B,[1] from the sea hare *Dolabella auricularia* was reported. Isolation of dolabelides C and D (**3.1**),[2] 24-membered macrolides, was achieved shortly after from the same source in 1997. Cytotoxicity studies of dolabelides A-D revealed activity of these macrolactones against cervical cancer HeLa-S_3 cells with IC_{50} values of 6.3, 1.3, 1.9, and 1.5 μg/mL, respectively. Although the mechanism of action of these compounds remains unknown, synthetic studies toward various subunits of dolabelide have recently been reported[3] with Leighton and coworkers completing the only total synthesis of dolabelide D in 2006.[4]

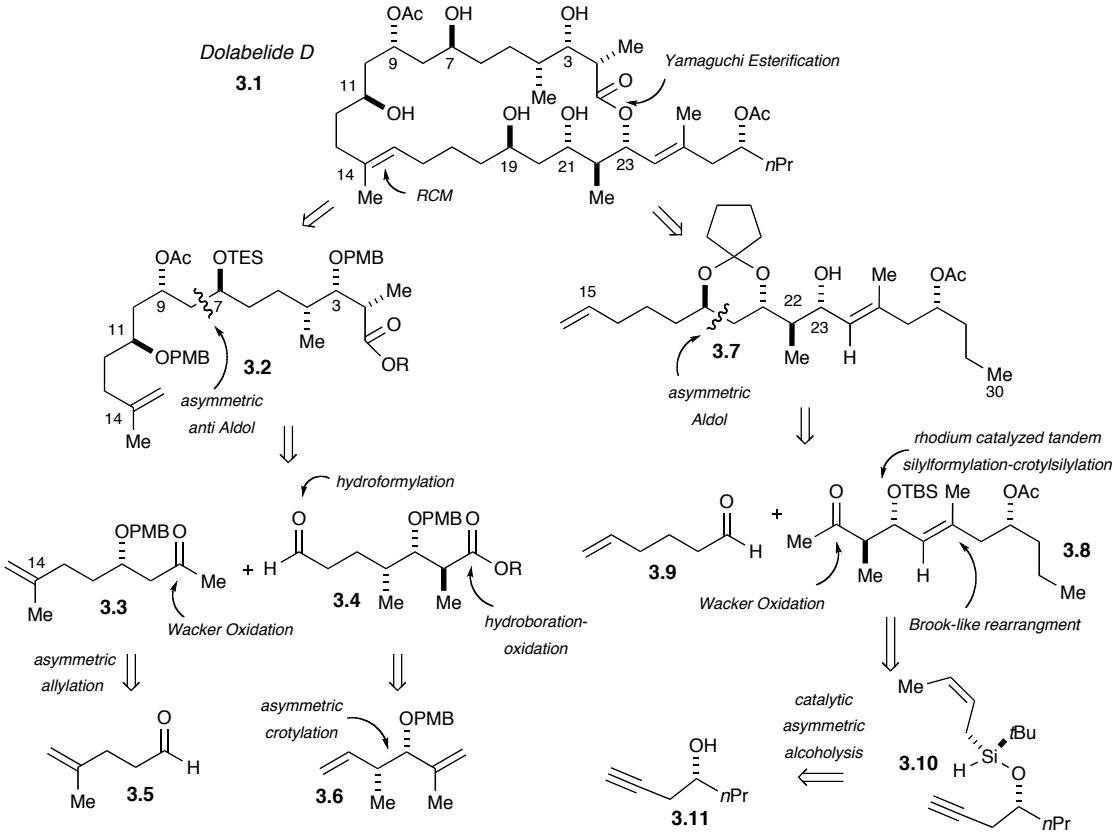
3.1.2 Leighton's Synthesis of Dolabelide D

Leighton's synthesis of dolabelide D (**3.1**) began with disconnections at the lactone between C1-C23 and at the C14-C15 olefin (Scheme 1). The two subunits of dolabelide D generated by this analysis were C1-C14 **3.2** and C15-C30 **3.7**. Carboxylic **3.2** and alcohol **3.7** were coupled by a Yamaguchi esterification with a subsequent RCM to afford the trisubstituted C14/C15 olefin and complete the macrocycle. The C1-C14 (**3.2**) subunit was constructed by an asymmetric *anti*-Aldol[5] reaction to make the C9/C10 C—C bond by reacting ketone **3.3** and aldehyde **3.4**. Subsequent reduction of the C9 ketone with L-selectride set the requisite stereochemistry for the formation of C1-C14 subunit **3.2**. Ketone **3.3** was achieved by Wacker oxidation of a terminal olefin, which was preceded by an asymmetric

allylation of aldehyde **3.5** using Leighton's strained silacycle technology.[6] Aldehyde **3.4** was generated by a hydroformylation of diene **3.6** in the presence of 2,2-methoxypropane to afford the requisite acetal, which was subjected to a hydroboration[7]-oxidation-oxidation-deprotection sequence to provide aldehyde **3.4**. Diene **3.5** was obtained using an asymmetric crotylation reagent, developed by Leighton, and methacrolien.[8]

The C15-C30 subunit of dolabelide D, **3.7**, was initially disconnected between the C19-C20 bond, which was achieved by an asymmetric Aldol addition[9] of ketone **3.8** with aldehyde **3.9** followed by an Evan's *anti* reduction of the C21 ketone.[10]

Scheme 1



Assembly of ketone **3.8** was achieved by Wacker oxidation of a terminal olefin, which was preceded by a tandem rhodium-catalyzed silylformylation-crotylsilylation of silyl ether **3.10**[11] and a Brook-type rearrangement[12] of the vinyl silane. This sequence installed the C24-C25 trisubstituted olefin and set the C22 and C23 stereocenters. Leighton utilized their catalytic asymmetric alcoholysis methodology for construction of silyl ether **3.10** from homopropargylic alcohol **3.11** and *t*butyl-*cis*-crotylsilane.[13] Overall, Leighton's synthesis of dolabelide D showcased his strained silacycle methodologies to rapidly assemble this complex natural product in 17 steps (longest linear sequence) from methacrolien.

3.2 Results and Discussion

3.2.1 Phosphate Tether Approach to Dolabelide C.

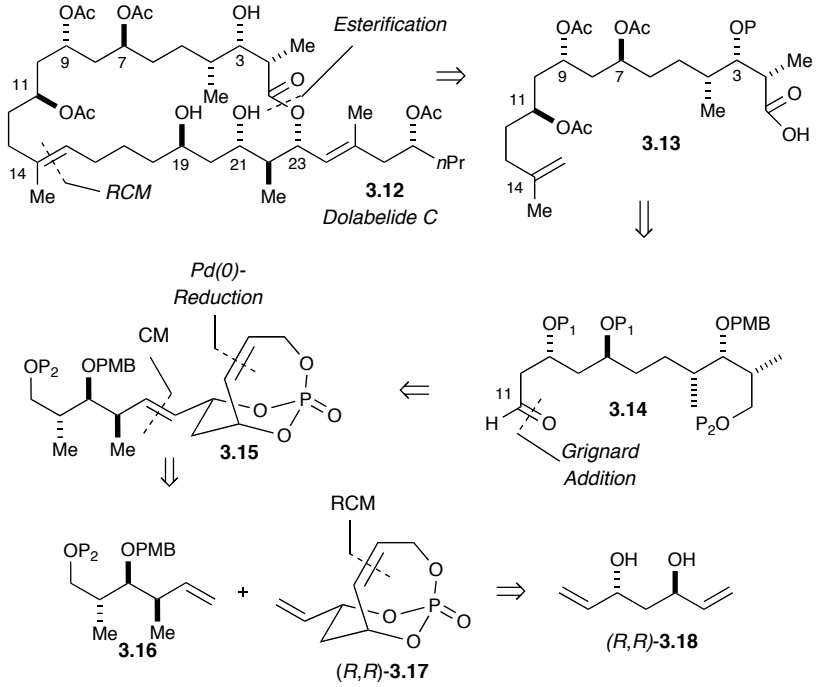
The cornerstone for our synthetic approach to dolabelide C (**3.12**) employs our recent studies that have revealed a functionally active phosphate tether[14] within the *P*-chiral bicyclic phosphate **3.17** (Scheme 2).[15] These studies revealed selective cleavage through displacement reactions at carbon (S_N2, S_N2') and phosphorus, ultimately affording multi-positional activation, which extends throughout the bicyclic framework. Using this tether approach it was envisioned that access to advanced polyol synthons could be attained, providing the impetus for this total synthesis.[11]

3.2.2 Retrosynthetic Analysis of the C1-C14 Subunit of Dolabelide C

Common features among the dolabelide family are eleven-stereogenic centers, eight of which bear oxygen, and two *E*-configured trisubstituted olefins. Other

attributes possessed by this family of macrolactones include 1,3-*anti*-diol fragments found at C7/C9 and C19/C21, along with an accompanying 1,3-*syn*-diol at C9/C11 and polypropionate fragments at C1/C4 and C22/23. The endgame strategy for ring closure was planned to hinge on a key RCM of the C14/C15 trisubstituted olefin following precedent set by Leighton and coworkers.[4a] Preceding this macrocyclization is a simple esterification connecting the C1 carboxylic acid and C23 alcohol, thus coupling the C1-C14 (**3.12**) and C15-C30 subunits of dolabelide C. Retrosynthetic analysis shows that assembly of the C1-C14 (**3.12**) portion can be achieved via a Grignard addition into C11 aldehyde **3.14**, which is accessed by regioselective hydride opening of the advanced phosphate intermediate **3.15**. Regioselective CM between bicyclic phosphate (*R*,*R*)- **3.17** and terminal olefin **3.16**

Scheme 2

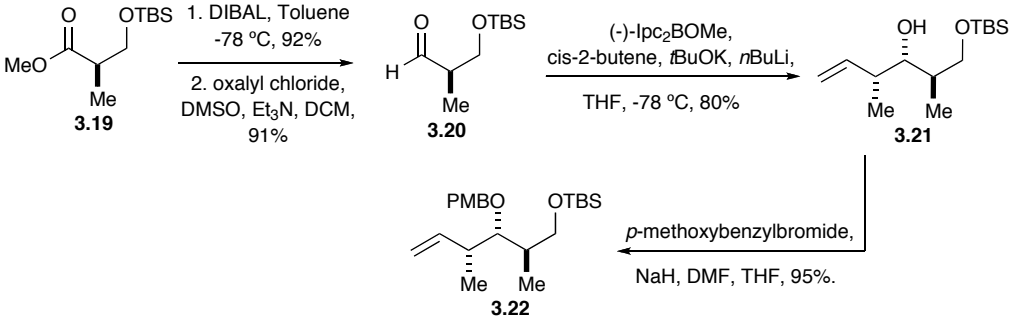


generates the C5-C6 alkene and brings together five of the six stereocenters found within the C1-C14 subunit of dolabelide. Bicyclic phosphate tether (*R*,*R*)- **3.17** is readily constructed from the proper enantiomeric, C_2-symmetric 1,3-*anti*-diol, (*R*,*R*)- **3.18** via a *P*-tether-mediated diastereotopic differentiation using RCM.

3.2.3 Synthesis of the C1-C14 Subunit of Dolabelide C

Our synthesis of the C1-C14 subunit of dolableide C began with the construction of CM partner **3.22** (Scheme 3). Terminal olefin **3.22** was achieved through initial reduction of TBS-protected Roche ester **3.19**, followed by subsequent Swern oxidation of the alcohol providing the necessary aldehyde **3.20**.[16] Reaction of the formed aldehyde with the *Z*-crotyl (-)-Ipc-borane generated enantiopure homoallylic alcohol **3.21** in 80% yield.[17] PMB-protection of alcohol **3.21** was achieved using *p*-methoxybenzyl bromide and sodium hydride to afford **3.22** in 95% yield.[18]

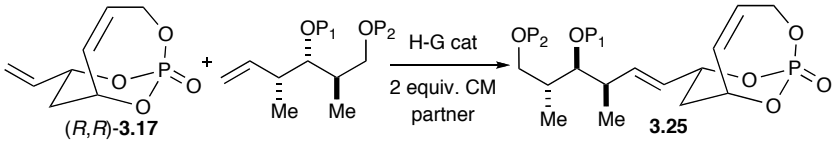
Scheme 3

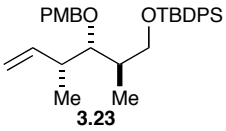
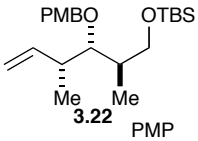
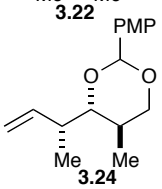


A key component of the proposed synthesis of dolabelide C was the selective CM between bicyclic phosphate (*R*,*R*)-**3.17**[11a] and synthesized homoallylic alcohol **3.22**. Previous studies of CM with bicyclic phosphate (*R*,*R*)- **3.17**[19] had shown that

the exocyclic olefin possessed Type III olefin behavior, implying that no detrimental homodimerization pathways would be operative.[19,20] Other protected derivatives of **3.22** (TBDPS (**3.23**)[21a] and PMP acetal (**3.24**)[21b]) were synthesized to determine the most viable substrate to undergo the necessary CM reaction. Using TBDPS as a protecting group (**3.23**) gave low reactivity and low yields during CM (Table 1, Entries 1-3). CM was then attempted between (*R*,*R*)- **3.17** and **3.22** under the conditions previously reported (6 mol % Hoveyda-Grubbs cat., DCM, 45 ºC),[19] but incomplete consumption of the starting phosphate was observed after six hours (Entry 4). Optimizing the reaction conditions with various solvents revealed that use of toluene (90 ºC), with the same catalyst loading, gave essentially the same results (Table 1, Entry 5). However, an improved yield of 60% was obtained (Table 1, Entry 6) when 12 mol % catalyst was added to the CM reaction. Switching to DCE (90 ºC), and adding only 6 mol % Hoveyda-Grubbs catalyst, gave the optimum results with **3.22** providing 72% yield of CM product **3.25** after two hours. When removing the silyl protecting group altogether, **3.24** furnished similar results to **3.22** . It should be noted that in all cases excess **3.22**, **3.23**, and **3.24**, Type II CM partners, could be recovered in near quantitative yield and recycled in future CM events. This differential reactivity pattern of protected alcohol substrates demonstrates that both proximal and distal steric interactions play vital roles in the success of selective CM reactions.[22]

Table 1. CM Studies with (*R*,*R*)-**3.17**.



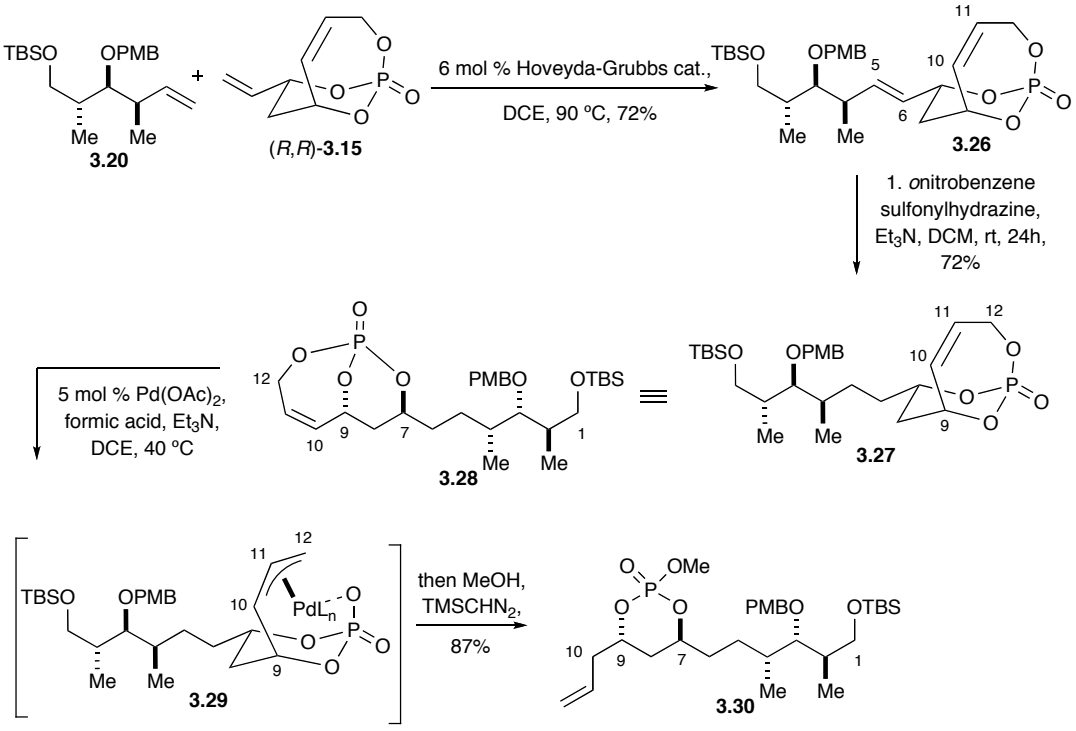
CM partner	entry	H-G cat.	solvent	temp. (°C)	yield (%)
	1	6 mol %	Toluene	60	N.A.
	2	6 mol %	Toluene	90	28
	3	12 mol %	Toluene	90	31
	4	6 mol %	CH_2Cl_2	50	42
	5	6 mol %	Toluene	90	45
	6	12 mol %	Toluene	90	60
	7	6 mol %	DCE	90	72
	8	6 mol %	CH_2Cl_2	50	32
	9	6 mol %	Toluene	90	63
	10	6 mol %	DCE	90	73

Having identified optimal CM conditions, **3.22** was chosen over **3.24** owing to the facile removal of the silyl protecting group in the late stages of the synthesis. The CM between (*R*,*R*)-**3.17** and **3.22** provided phosphate **3.26** in 72% yield on multigram scale (Scheme 3). Regioselective hydrogenation of the exocyclic C5-C6 olefin in the presence of the C10-C11 internal olefin was paramount to allow for subsequent regioselective opening of the bicyclic system. Upon investigating several hydrogenation conditions, (Wilkinson's catalyst, Crabtree's catalyst, Pd/C) it was found that an *in situ* generated diimide reduction under mild conditions (*o*-nitrobenzenesulfonyl-hydrazine,[23] Et_3N, DCM) provided the necessary regioselective hydrogenated phosphate **3.27** with near complete selectivity for the exocyclic olefin.

Other diimide conditions (tosylhydrazine, NaOAc, H_2O, DCE, 90 ºC) gave drastically lower yields, likely due to the bicyclic phosphate's instability under basic medium.

With phosphate **3.27** in hand, efforts were directed to making further use of the tether in a potential regioselective olefin transposition to the desired terminal olefin. Initial attempts focused on the use of allylic hydride addition employing various reagents (Stryker's reagent, CuCN•LiCl/$PhSiH_3$, $CeCl_3$•$7H_2O$/$NaBH_4$). To our dismay, however, all conditions probed provided unreacted starting material or total decomposition of the reaction mixture. Various palladium-catalyzed formate reductions were then investigated for generation of the requisite terminal olefin.[24] Employing 1.5 equivalents of formic acid and 5 mol % palladium acetate at 40 ºC in DCE selectively opened phosphate **3.27** to provide the desired terminal olefin.

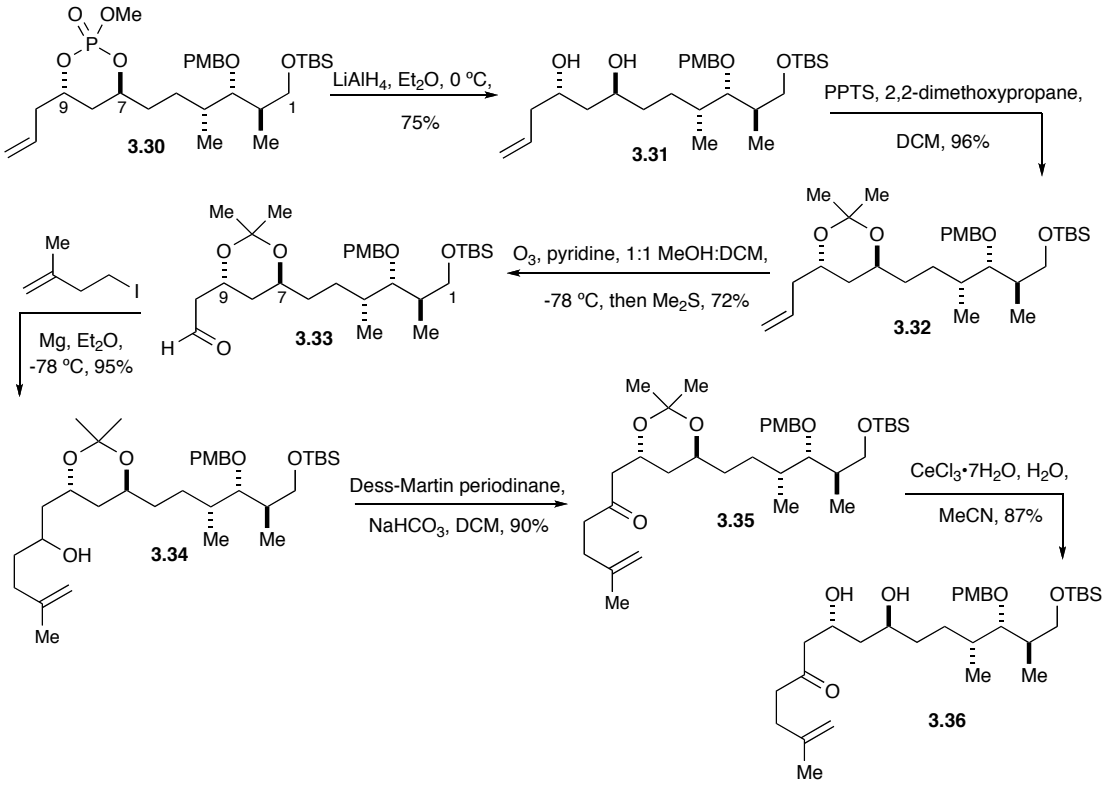
Scheme 3



Methylation of the phosphate acid intermediate showed that a highly regioselective process was operative (37:1 ratio of regioisomers as evident by ^{31}P NMR analysis). Purification provided phosphate **3.30** in 87% yield. The remarkable regioselectivity reveals another feature of the phosphate tether, whereby orthogonal orbital alignment[11] within **3.27** allows for selective Pd(0)-catalyzed allylic phosphate ionization at C12 over C9.

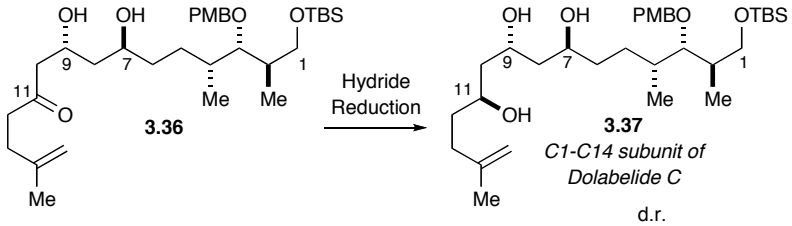
Installation of the C11-C14 fragment began with cleavage of the phosphate **3.30** using $LiAlH_4$, which generated a diol (**3.31**) that was subsequently protected as the acetonide (PPTS, 2,2-methoxypropane, DCM) to yield **3.32** in 96% (Scheme 4). Ozonolysis (O_3, pyridine, DCM:MeOH 1:1, Me_2S) of the terminal olefin produced the intended aldehyde (**3.33**), which was subjected to the Grignard generated from 1-iodo-3-methyl-3-butene[25] affording **3.34** in 95% yield. Dess-Martin periodinane (DMP, $NaHCO_3$, DCM) oxidation of the free alcohol in **3.34** generated the requisite ketone (**3.35**) in 90% yield. Attempts to selectively reduce the acetonide protected ketone, using an assortment of reducing agents, resulted in a 1:1 mixture at C11.[26] This problem seemed likely to be circumvented by deprotection of the acetonide and subsequent *syn* reduction taking advantage of the C9 free alcohol for chelation. Removal of the acetonide was achieved by the addition of $CeCl_3 \bullet 7H_2O$ and water,[27] which efficiently cleaved the acetonide protecting group without loss of the primary TBS group and provided diol **3.36** in 86% yield.

Scheme 4



To complete the synthesis of the C1-C14 subunit of dolabelide, a 1,3-*syn* reduction at the C11 position was needed. Attempts with DIBAL and $LiAlH_4/LiI$[28] did not provide the desired 1,3-*syn* selectivity, obtaining only 1:1 and 1.6:1 mixtures, respectively (Table 2). However, utilizing different chelating groups did allow for the selective 1,3-*syn* reduction to be achieved. The addition of $ZnCl_2$ and $NaBH_4$ provided a 3.2:1 *syn*:*anti* ratio, while $Et_3B/NaBH_4$ afforded a 5.3:1 *syn*:*anti* mixture in 71% yield.[29] Lastly, ketone **3.36** was reduced using Et_2BOMe and $NaBH_4$ to afford triol **3.37** in 60% yield (95%, based on recovered starting material) with excellent diastereoselectivity (*dr* = >20:1)[30] completing the desired C1-C14 subunit of dolabelide.

Table 2. Synthesis of C1-C14 Subunit of dolabelide C (**3.37**).



Conditions	Yield (%)	d.r. C9/C11-*syn* : C9/C11-*anti*
DIBAL-H, -78 ºC	75	1:1
$LiAlH_4$, LiI	90	1.6:1
$ZnCl_2$, $NaBH_4$	64	3.2:1
Et_3B, $NaBH_4$, THF, MeOH -78 ºC	60	20:1
Et_2BOMe, $NaBH_4$, THF, MeOH -78 ºC	82	4:1

The completion of the stereoselective reduction marked the successful synthesis of the C1-C14 subunit of dolabelides A-D using phosphate tether methodology has been achieved. Overall, the phosphate tether serves a multifaceted role by (i) mediating the initial desymmeterization event leading to (*R,R*)-**3.17**, (ii) providing a selective Type III CM to couple two major complex fragments in the C1-C14 subunit of dolabelides, (iii) differentiating olefin reactivity within the bicyclic system **3.26** allowing for a selective hydrogenation, and finally (iv) serving as an excellent leaving group in a regioselective Pd(0)-catalyzed formate reduction. The route outlined above takes advantage of orthogonal protecting and leaving group properties innate to phosphate esters.

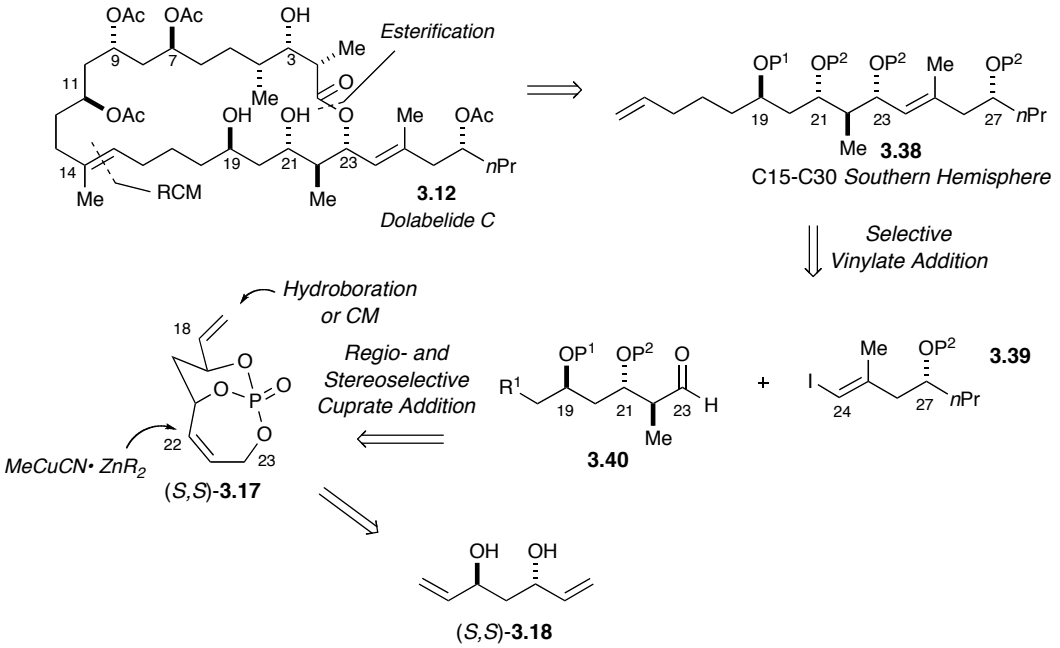
3.2.4 Retrosynthetic Analysis of the C15-C30 Subunit of Dolabelide C.

Several synthetic studies[3] have recently been reported for the dolabelide family, including the aforementioned total synthesis of dolabelide D by Leighton and coworkers in 2006.[4] Among these efforts, two reports toward the C15-C30 fragment

have been presented, with Leighton and coworkers publishing the only complete C15-C30 fragment bearing the requisite stereochemistry.[3d]

As previously mentioned, retrosynthetic analysis reveals a logical disconnection at C1-C14 and C15-C30 (**3.38**, Scheme 5) for the entire family of dolabelides. Convergent assembly of the C15-C30 subunit by the C23-C24 bond is envisioned to occur through a coupling of metallated **3.39** with aldehyde **3.40**. A regio- and diastereoselective cuprate addition into a functionalized bicyclic phosphate (by terminal olefin oxidation or CM/hydrogenation) was expected to provide the requisite stereotriad found in the C19-C22 subunit of dolabelide. The 1,3-*anti* diol moiety contained within subunit **3.38** (C19 and C21) can be derived from phosphate triester building block (*S*,*S*)- **3.17**,[15,19] assembled via phosphate tether mediated desymmeterization of C_2-symmetric *anti*-diol (*S*,*S*)- **3.18**.

Scheme 5

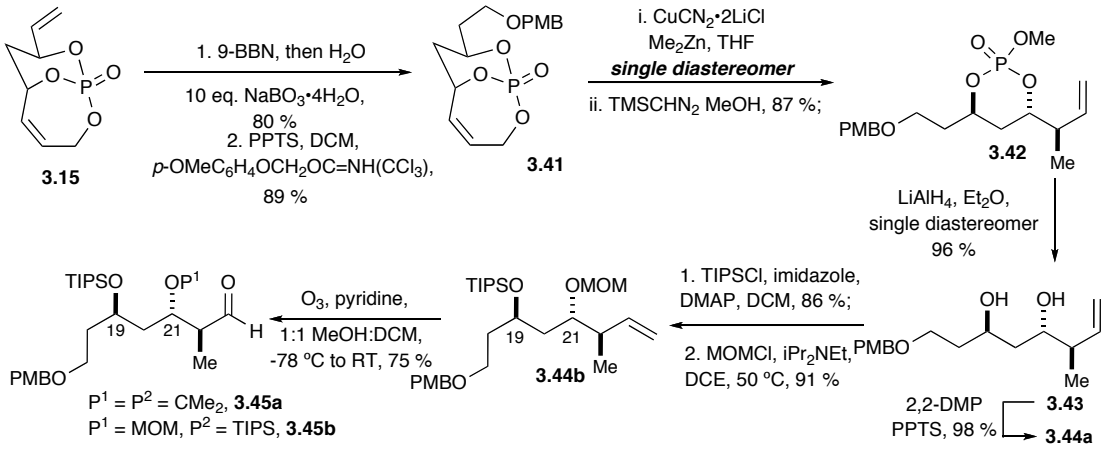


3.2.5 Synthesis of the C15-C30 Subunit of Dolabelide C.

Initial efforts toward the construction of the C15-C30 subunit of dolabelide began with the enantiomeric bicyclic phosphate (*S*,*S*)-**3.17** of that used for the C1-C14 subunit (Scheme 6). Chemoselective hydroboration of the exocyclic olefin of (*S*,*S*)-**3.17**, followed by a perborate oxidation protocol developed by Burke and coworkers[31] that was optimized for bicyclic phosphate **3.17**. The yields obtained for these reactions were highly dependent on the amount of oxidant, equivalents of H_2O, and reaction time. Subsequent PMB ether formation using *p*-methoxybenzyl trichloroacetimidate produced **3.41** in good yields and highlights the stability of bicyclic phosphate (*S*,*S*)-**3.17** under acidic conditions. A regio- and diastereoselective cuprate addition[15] to **3.41** (CuCN•2LiCl, $ZnMe_2$, THF, -30 ºC to rt) generated the S_N2' displaced phosphate acid exclusively (*dr* = >95:5). Subsequent methylation ($TMSCHN_2$ and MeOH) afforded cyclic phosphate ester **3.42** in excellent yield (87%). The unique orbital alignment within bicyclic phosphate **3.41**, in synergy with its concave nature, dictates the high selectivity in this S_N2' cuprate reaction.[32]

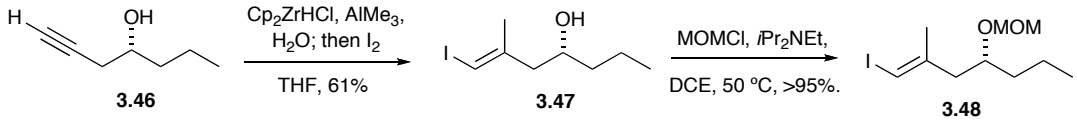
The remaining steps to aldehyde **3.45** were non-problematic and involved an initial reductive cleavage of the monocyclic phosphate ester with $LiAlH_4$ in Et_2O to provide diol **3.43** as a single diastereomer in excellent yield (96%). Near quantitative acetonide formation and subsequent ozonolysis afforded **3.45a** in good yield. Alternatively, diol **3.43** was also selectively mono-TIPS protected (TIPSCl, imidazole, rt)[33] followed by a MOM protection (**3.44b**) and ozonolysis to produce **3.45b** in good yield over three steps.

Scheme 6



Construction of the C24-C30 vinyl iodide fragment **3.48** was achieved in two steps from known **3.46** (Scheme 7).[3d] Alkyne **3.46** was produced from commercially available *R*-(-)-epichlorohydrin, employing a Yamaguchi protocol for oxirane alkynylation.[34] Subsequent zirconocene-promoted carboalumination, utilizing Wipf's water-accelerated procedure[35] and iodine quench, provided trisubstituted vinyl iodide **3.47** in 61% yield. MOM protection ultimately afforded **3.48** in >95% yield.

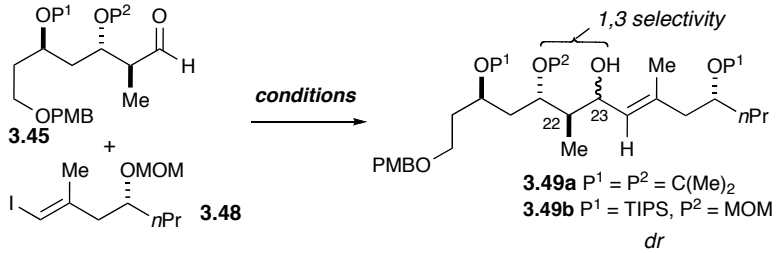
Scheme 7



With **3.45a**/**3.45b** and vinyl iodide **3.48** in hand, methods for the construction of both the C23-C24 C—C bond and installation of the C23 stereochemistry were investigated (Table 3). To this end, reaction of acetonide-protected **3.45a** with lithiate **3.48** (*t*BuLi, -78 ºC to rt) or the vinyl Grignard of **3.48** (*t*BuLi, -78 ºC, $MgBr_2$•Et_2O) provided Felkin 22,23-*syn* selectivity for the undesired C21-C23 1,3-

anti product **3.49a** in modest diastereoselectivity (2-4:1 dr). Selectivity for the undesired C23 carbinol was the highest when employing an Oshima protocol[36] using vinyl magnesiate formation in the presence of $MgBr_2 \bullet Et_2O$, where selectivities of ~8:1 were observed in favor of 1,3-*anti*-**3.49a**.[37] To circumvent this selectivity issue we employed a reagent controlled asymmetric addition using Oppolzer's zinc vinylate-lithium alkoxy *N*-methylephedrine complex[38] recently described by Marshall[39] and coworkers for vinylate additions with chiral aldehydes. Under these conditions, **3.49b** was formed in an 11:1 ratio of diastereomers favoring the desired C21-C23-*syn* product in moderate yield.

Table 3. Additions to aldehyde **3.45**.

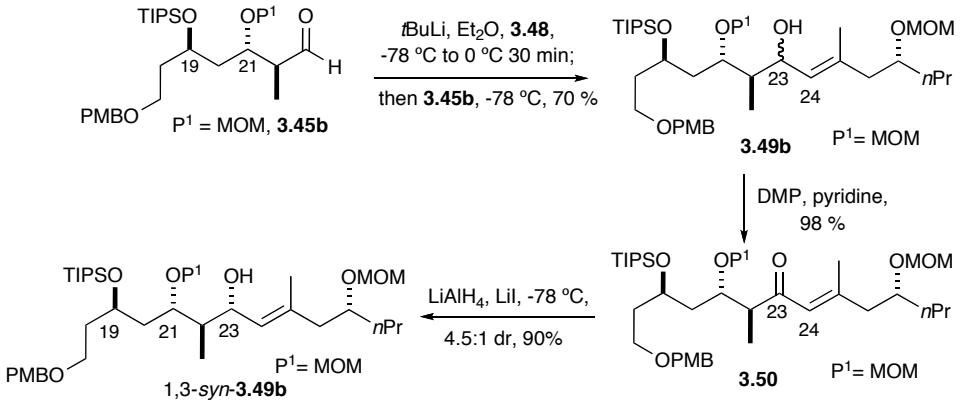


Conditions	Yield	dr 1,3-syn : 1,3-anti
3.45a $P^1 = P^2 = C(Me)_2$		
*t*BuLi, -78 ºC	78%	1:2
*t*BuLi, $MgBr_2 \bullet Et_2O$, -78 ºC	78%	1:4
*s*BuLi, *i*PrMgCl; $MgBr_2 \bullet Et_2O$, -78 ºC	68%	1:6-8
3.45b P^1 = TIPS, P^2 = MOM		
*t*BuLi, -78 ºC	70%	1:1
*t*BuLi, $ZnBr_2$; *n*BuLi, (*R,S*)-*NME*	55%	11:1

Despite this success, difficulties in reaction reproducibility (also recently noted by Marshall)[40] and low product yields prompted the investigation of an alternative oxidation/hydride reduction sequence for the formation of the requisite 1,3-*syn* diol within **3.49b** (Scheme 8). Thus, Dess-Martin periodinane oxidation of

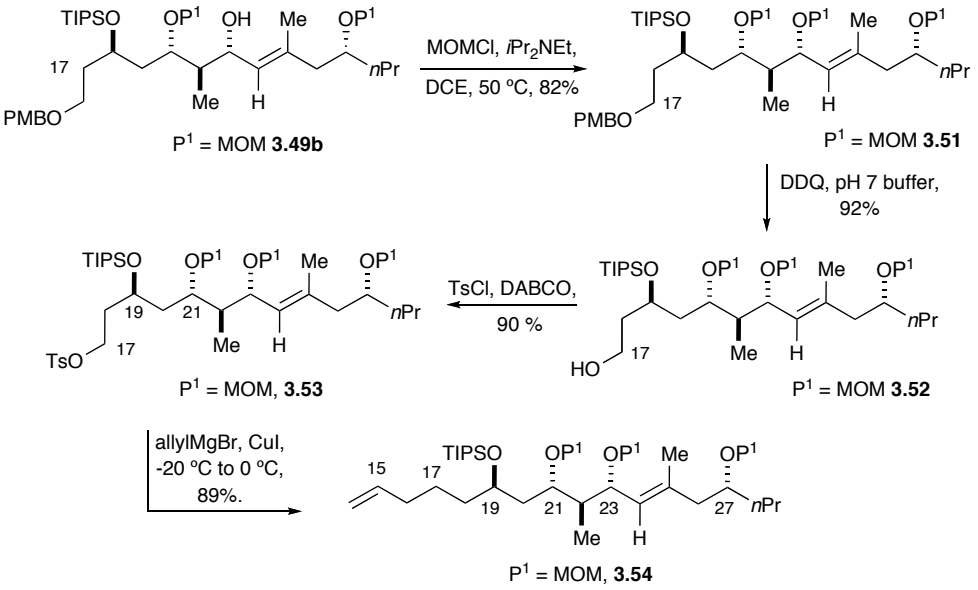
the C23 epimers of **3.49b**, followed by reduction of the resulting ketone (**3.50**) using Suzuki's 1,3-*syn* selective, chelation-controlled reduction conditions ($LiAlH_4$, LiI)[28] afforded a 4.3:1 mixture of diastereomers the desired 1,3-*syn* diol (**3.49b**) in 90% yield.[41]

Scheme 8



With **3.49b** in place, only the installation of the C14-C15 terminal olefin was needed to complete the C15-C30 subunit of dolabelide C. Following MOM-protection of the C23 alcohol (**3.51**), DDQ removal of the PMB ether proceeded in good yield to afford alcohol **3.52** (Scheme 9). Tosylation of the primary alcohol provided **3.53** in 90% yield. Treatment of **3.53** with an allyl Grignard in the presence of stoichiometric CuI led to the formation of allylated product **3.54** in 89% yield. Overall, this sequence represents a 12-step synthesis to **3.54** from **3.17**, bearing the requisite stereochemistry for the C15-C30 subunit of dolabelide C.

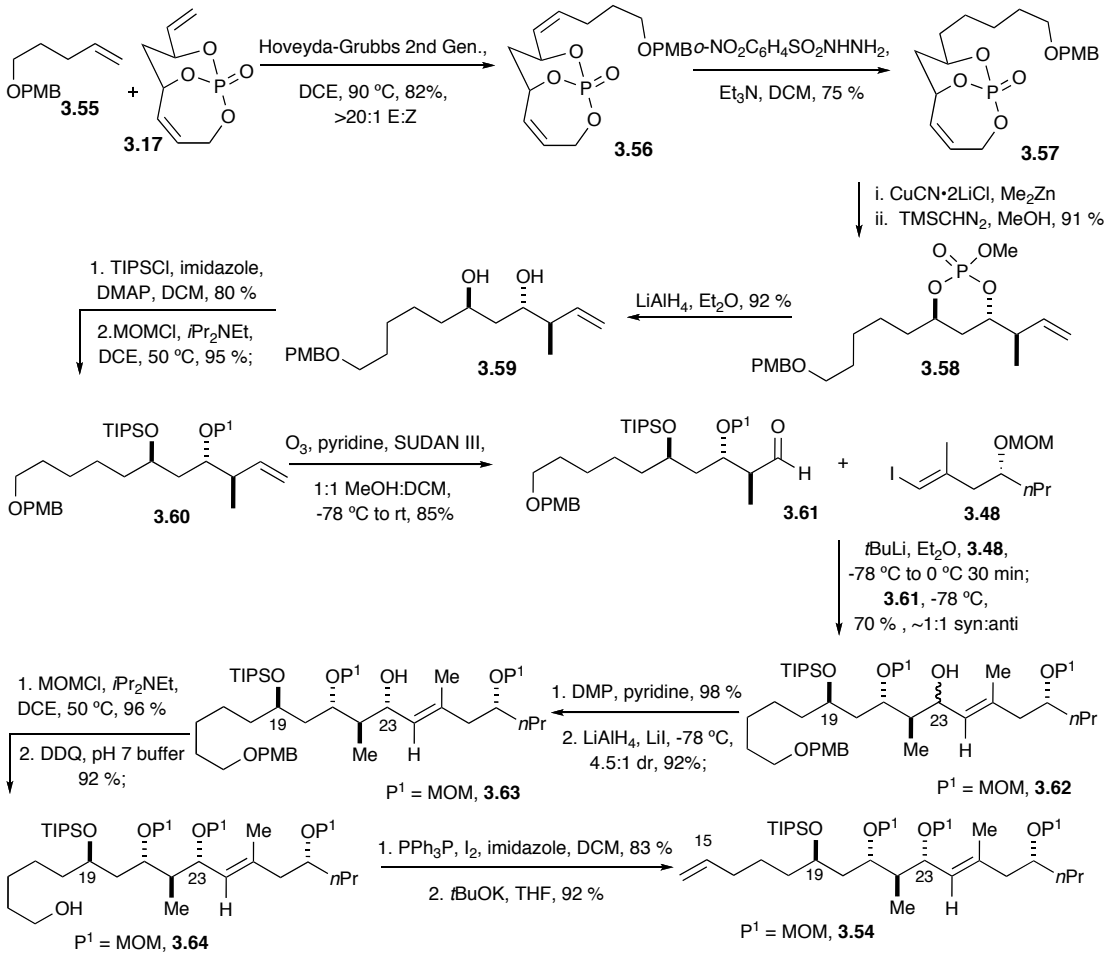
Scheme 9



An alternative approach to the C15-C30 side chain was investigated to show the flexibility of our phosphate tether as well as our previously established cross metathesis methodology (Scheme 10).[19] As anticipated, **3.17** underwent CM with **3.55** in the presence of 6 mol % H-G catalyst[42] in DCE (90 ºC) providing *E*-configured **3.56** in 82% yield (>95:5, E:Z).[19] Selective reduction of the external olefin was achieved with *o*nitrobenzenesulfonylhydrazine,[23] which provided **3.57** in (>95:5) regioselectivity and 75% yield.[43] Regio- and diastereoselective methyl cuprate addition into **3.57**, under the aforementioned conditions, and subsequent phosphate cleavage afforded diol **3.59** in good yield. Aldehyde **3.61** was rapidly accessed using a three-step TIPS-MOM-ozonolysis sequence (Scheme 10). Lithiate addition into aldehyde **3.61** produced **3.48** as a 1:1 mixture of C23 epimers in 70% yield. Subsequent employment of the aforementioned Suzuki oxidation/reduction conditions ($LiAlH_4$/LiI) afforded the desired diastereomer of **3.63** in 92% yield (*dr* = 4.5:1 at

C23).[28] Substrate **3.63** was MOM-protected and the PMB-ether removed using DDQ to produce primary alcohol **3.64**. Iodination of the C14 primary alcohol occurred in 83% yield, followed by facile E2 elimination of the primary iodide in the presence of *t*BuOK (THF, 30 min, rt) afforded **3.54**, in 92% yield. Due to the success, and convenience of the alternative elimination approach to the C15 olefin, we are currently investigating selective vinylate addition with **3.48** for stereocontrolled formation of C23 within **3.62**.

Scheme 10

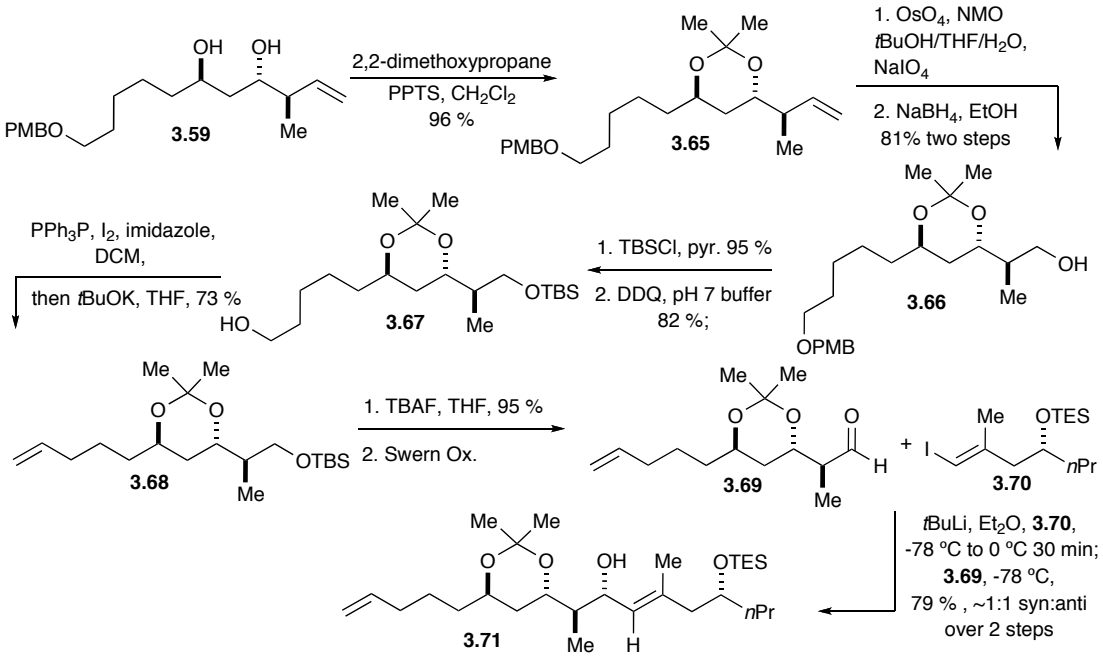


The C15-C30 subunit **3.54** bearing three MOM-protecting groups proved to be problematic when attempting to remove these groups. To our dismay, all conditions tested for cleavage of these groups in the presence of the more labile TIPS-protecting groups provided unreacted starting material or total decomposition of the substrate. The difficulty in removing these protecting groups prompted a reevaluation of protecting groups to access a suitable C15-C30 subunit of dolabelide.

We embarked on a route that utilized the CM/diimide reduction sequence to obtain diol **3.59**. Acetonide protection of diol **3.59** with PPTS and 2,2-dimethoxypropane provided acetonide **3.65** in 96% yield (Scheme 11). The terminal olefin was then converted into a primary alcohol (**3.66**) by a dihydroxylation/ oxidation/reduction sequence, which occurred in good yields. TBS-protection of alcohol **3.66** proceeded in 86% yield and was followed by removal of the PMB-ether with DDQ to provide the corresponding primary alcohol **3.67**. Iodination of alcohol **3.67** allowed for the formation of the primary iodide that was immediately taken onto the next reaction without further purification. Elimination was achieved with *t*BuOK to afford terminal olefin **3.68** in excellent yield over the two step sequence. TBAF removal of the TBS protecting group and Swern oxidation provided aldehyde **3.69** necessary for the addition of the C24-C30 fragment. Vinyl iodide **3.70** was converted to the lithiate with 2 equivalents of *t*BuLi followed by the addition of aldehyde **3.69** to afford a 1:1 mixture of C23 epimers of alcohol **3.71** in 70% yield. The two diastereoisomers of **3.71** were easily separated by column chromatography allowing

for the isolation of the correct stereoisomer of alcohol **3.71** that was taken forward to couple with the C1-C14 subunit of dolabelide C.

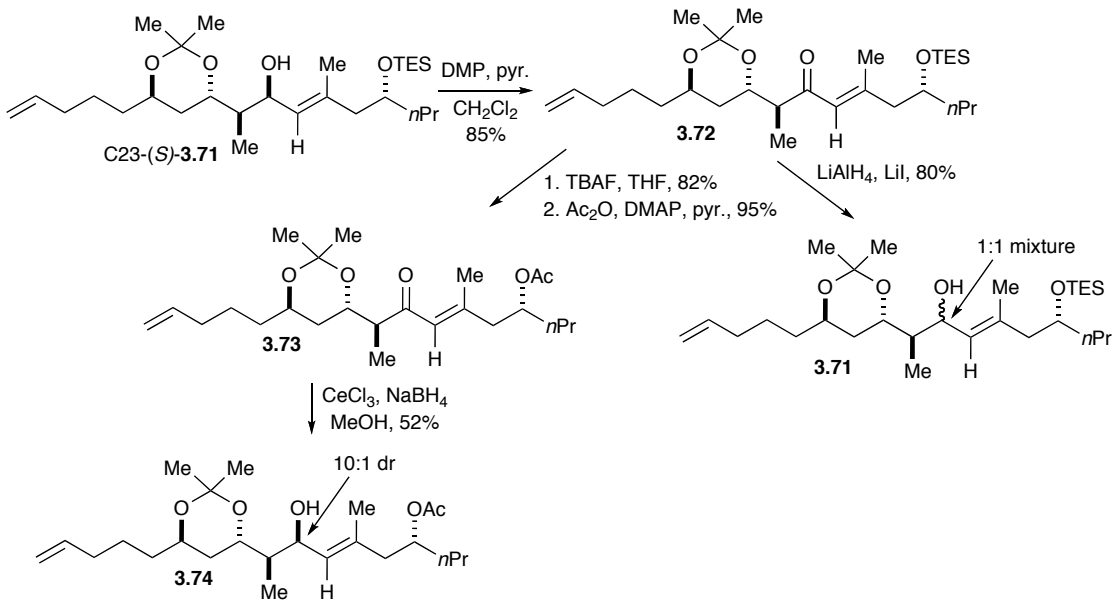
Scheme 14



The low diastereoselectivity prompted us to find a reaction that provided increased diastereoselectivity of alcohol **3.71**. Therefore **3.71** was oxidized to ketone **3.72** and subjected to various reducing conditions to obtain a reaction that favored the desired isomer of alcohol **3.71** (Scheme 12). Initial reduction utilizing Mori's condition ($LiAlH_4$, LiI)[28] generated only a 1:1 mixture diastereomers. Other reductants such as DIBAL-H and $NaBH_4$ provided the undesired isomer in a greater then 1:1 diastereomeric ratio. Further, it was tested whether removal of the silyl group prior to the reduction of ketone **3.73** could be beneficial. To this end, deprotection of ketone **3.72** with TBAF and acetylation with acetic anhydride occurred in good yield to afford acetate **3.73**. Upon subjection of acetate **3.73** to

Luche's conditions[44] with $CeCl_3$ and $NaBH_4$ we were disappointed at the observation of a 10:1 mixture of isomers in favor of undesired alcohol **3.74**. Currently, studies are being directed toward reducing ketone **3.72** using a CBS-reduction to provide the desired diastereomer of alcohol **3.71** as the major product of the reaction. Overall, this alternative route to **3.71** is a 13-step synthesis from phosphate **3.17**, and provides a route with protecting groups that allow for coupling of the C15-C30 subunit with the C1-C14 subunit of dolabelide C.

Scheme 12

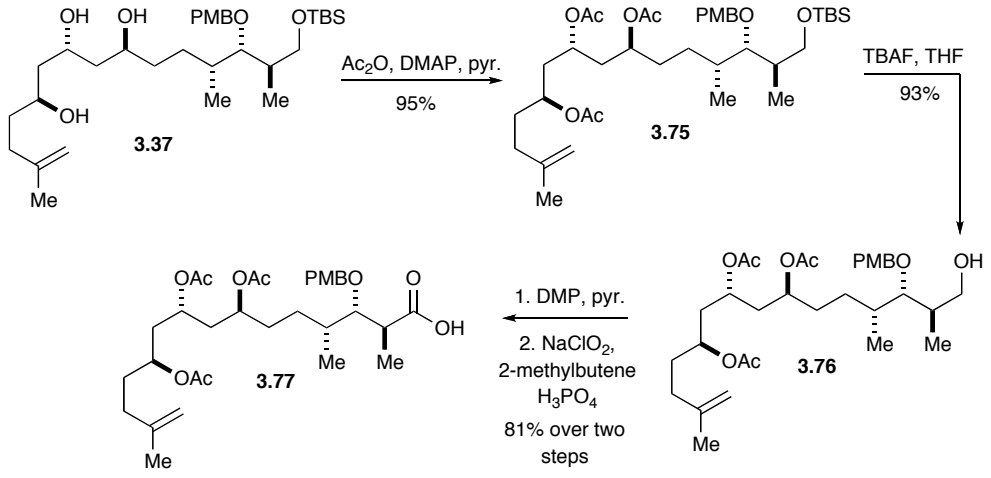


To date, we have successfully completed the synthesis of the C15-C30 subunit of dolabelides A-D using different strategies that all rely on the temporary phosphate tether methodologies developed in our laboratories. These pathways make use of the orthogonal protecting- and leaving group properties innate to phosphate esters and showcase the utility of phosphate tethers in synthesis.

3.2.6 Endgame: Total Synthesis of Dolabelide C.

With both subunits of dolabelide C successfully synthesized, we began studies toward the completion of dolabelide C. This process began with the complete acetylation of triol **3.37** to install the proper acetylation pattern for C1-C14 subunit of dolabelide C (Scheme 13). This was accomplished by adding acetic anhydride and pyridine to triol **3.37** that afforded triacetyl **3.75** in excellent yield. Deprotection of the TBS protecting group was then achieved with TBAF to provide alcohol **3.76** in 93% yield. It was found that Swern oxidation of alcohol **3.76** generated the desired aldehyde that was prone to epimerization and was taken on without purification. Further oxidation of the aldehyde provided carboxylic acid **3.77** in 81% yield over the two-step sequence. Carboxylic acid **3.77** was the properly acetylated C1-C14 subunit of dolabelide C for coupling with the C15-C30 subunit.

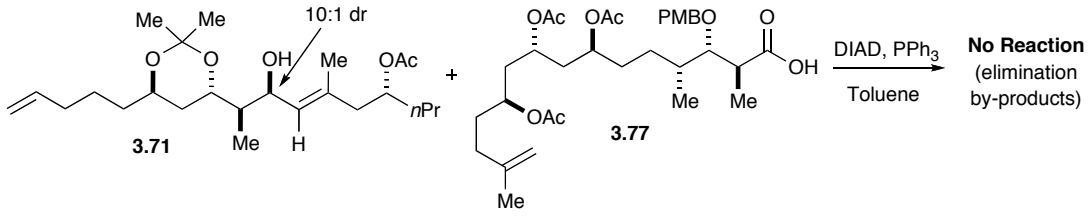
Scheme 13



Previous studies on the coupling the C1-C14 and C15-C30 subunits of dolabelide B and D used Yamaguchi's esterification conditions to join these

subunits.[13,45] Other esterification protocols were attempted [$(PhO)_2P(O)Cl$, DCC, and Mukaiyama reagent] with only starting material recovered and no observation of the desired coupled product.[45] In the course of these studies it was demonstrated that Yamaguchi conditions at 0 ºC caused epimerization at the C2 position of carboxylic acid **3.2** when using extended reaction times.[45] Knowing this, and having sufficient quantities of **3.71**, we investigated a Mitsunobu reaction to invert the C23 carbinol and join the two subunits (Scheme 14). Unfortunately, this reaction provided no coupled product but observation of the reaction mixture by ^1H NMR spectroscopy demonstrated that elimination by-products of the C15-C30 subunit were formed. This could be attributed to the steric congestion about the C23 carbinol position of **3.71** and activation of triphenylphosphine causing elimination to be more favorable than S_N2 displacement.

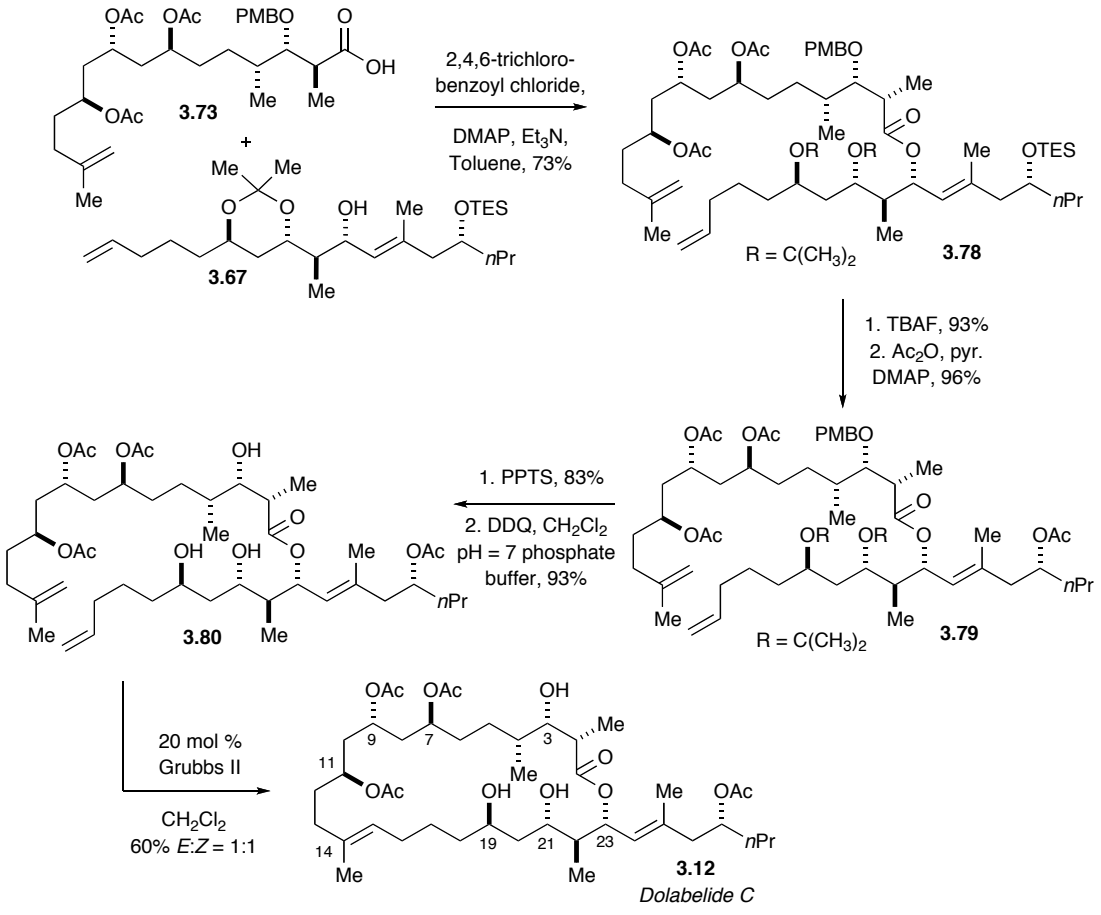
Scheme 14



The final coupling of the C1-C14 carboxylic acid, **3.77**, and the C15-C30 alcohol, **3.71**, was achieved using the Yamaguchi conditions as previously describe by Leighton and coworkers (Scheme 15).[4] The addition of 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, and DMAP at -78 ºC for 21 hours avoided epimerization at C2 and afforded the desired coupled **3.78** in 73% yield. With the C1-C14 subunit coupled with the C23 alcohol, deprotection of the C27 TES protecting group was

achieved with TBAF in 93% yield. This alcohol was then acetylated to afford **3.79** in 96% yield. The final two protecting groups were removed with the addition of PPTS in MeOH and DDQ to provide metathesis precursor **3.80** in excellent yield over two steps. Efforts to close the ring were attempted prior to PMB ether removal and provided the RCM product as observed by high resolution mass spectrometry. Unfortunately, observation of the reaction by TLC poor reaction conversion and further investigations focused on the RCM of deprotected triol **3.80**. Addition of Grubbs II catalyst to triol **3.80** afforded dolabelide C (**3.12**) in a 60%

Scheme 15



yield as a 1:1 mixture of *E*:*Z* isomers. These isomers were sparingly separable by column chromatography and were able to isolated as a 4:1 *E*:*Z* mixture for spectroscopic identification of dolabelide C. The total synthesis of dolabelide C using our temporary phosphate tether methods was achieved in 24 steps (longest linear sequence from acetylacetone) and 54 total steps. The overall yield for this synthesis was 0.73% with an average yield per chemical step being 81.5%.

3.3 Summary

In conclusion, we have successfully completed the total synthesis of dolabelide C. The synthesis used a temporary phosphate tether methodology developed in our laboratories, which includes selective CM with the exocyclic olefin, regioselective olefin hydrogenation, regioselective Pd(0)-catalyzed opening of the bicyclic phosphate, a selective terminal olefin oxidation, and a highly regio- and diastereoselective cuprate addition. Collectively, these methods allowed for the first total synthesis using temporary phosphate tethers for the construction of dolabelide C. Ongoing efforts will continue to expand and develop new temporary phosphate tether methodologies to allow for the synthesis of new bioactive natural products.

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(39) Marshall, J. A.; Eidam, P., "Diastereoselective Additions of Chiral Vinylzinc Reagents to α-Chiral Aldehydes." *Org. Lett.* **2004,** *6*, 445-448.

(40) Marshall and coworkers reported protonolysis products under Oppolzer conditions with similar homoallylic protected vinyl iodides, which we witnessed in unsuccessful reactions, along with decomposed aldehyde, see: Marshall, J. A.; Eidam, P. M., "A Formal Synthesis of the Callipeltoside Aglycone." *Org. Lett.* **2008**, *10*, 93-96.

(41) Additional reductions using a variety of reducing agents (DIBAL-H, $LiAlH_4$, $Zn(BH_4)_2$, $NaBH_4$) failed to generate the desired C23 stereochemistry (a) Evans, D. A.; Ng, H. P.; Rieger, D. L., "Total synthesis of the macrolide antibiotic rutamycin B." *J. Am. Chem. Soc.* **1993**, *115*, 11446-11459. (b) Oishi, T.; Nakata, T., "An introduction of chiral centers into acyclic systems based on stereoselective ketone reduction." *Acc. Chem. Res.* **1984**, *17*, 338-344. (c) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J., "General Strategies toward the Syntheses of Macrolide Antibiotics. The Total Syntheses of 6-Deoxyerythronolide B and Oleandolide." *J. Am. Chem. Soc.* **1998**, *120*, 5921-5942.

(42) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H., "Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts." *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.

(43) For example of diimide reduction in synthesis see: Haukaas, M. H.; O'Doherty, G. A., "Enantioselective Synthesis of 2-Deoxy- and 2,3-Dideoxyhexoses." *Org. Lett.* **2002,** *4*, 1771-1774.

(44) Luche, J. L., "Lanthanides in organic chemistry. 1. Selective 1,2 reductions of conjugated ketones." *J. Am. Chem. Soc.* **1978,** *100*, 2226-2227.

(45) O'Malley, S. J., Tandem alkyne silylformylation-allylsilylation reactions and studies toward a total synthesis of dolabelide B. Ph.D., Columbia University, United States -- New York, 2004.

Chapter 4

Experimental Data: Chapters 2 and 3

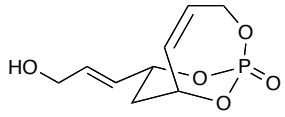
4.1 General Experimental Methods

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gastight syringes, cannulas, and septa. Stirring was achieved with oven-dried magnetic stir bars. Et_2O, toluene, THF and CH_2Cl_2 were purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520). Et_3N was purified by passage over basic alumina and stored over KOH. *n*Butyl Lithium (2.5M in THF) was purchased from Aldrich and titrated prior to use. Grubbs first and second-generation, as well as the Hoveyda-Grubbs olefin metathesis catalysts, were acquired from Materia and used without further purification. Glycidol ether was acquired from Daiso Co., Ltd., Fine Chemical Department and used without further purification. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 um). Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz, 100 MHz, and 162 MHz respectively; or a Bruker Advance operating at 500 MHz and 125 MHz respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained on a VG Instrument ZAB double-focusing mass spectrometer.

4.2 Experimental Data: Chapter 2

General Procedure for Cross Metathesis of Type I Olefins: A flask or pressure tube containing **2.53** (20 mg, 0.099 mmol) was charged with CH_2Cl_2 (2 mL) that had been degassed 15 minutes with argon. The Type I olefin partner (1.1 equiv. relative to compound **2.53**) followed by Hoveyda-Grubbs II catalyst (**2.3**) (6.2 mg, 0.009 mmol) were added and the reaction mixture was refluxed for 3-6 h. Upon completion (monitored by TLC) the reaction was cooled to rt and concentrated under reduced pressure.

(2*E*)-Propen-1-ol, 3-[(1*R*, 6*R*, 8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]: 2.55



Purification via flash chromatography (9:1 EtOAc/MeOH) supplied 19 mg (86% yield) of **2.55** as a viscous oil.

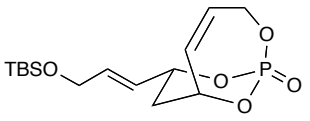
[∝]$_D$ -78.8 (*c* = 0.60, CH_2Cl_2);

IR (neat) 3402, 2923, 2358, 1286, 1064, 973 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92-6.03 (m, 2H), 5.72 (ddd, J_{HH} = 15.5, 3.8, 1.5 Hz, 1H), 5.55 (ddd, J_{HH} = 11.8, 3.6, 2.7 Hz, 1H), 5.10-5.19 (m, 1H), 5.01 (dd, J_{HH} = 11.8, 5.6 Hz, 1H), 4.91-4.98 (m, 1H), 4.38 (ddd, *J* = 27.8, 14.8, 6.7 Hz, 1H), 4.14 (d, J_{HH} = 4.3 Hz, 2H), 2.20 (ddd, J_{HH} = 18.3, 12.2, 6.2 Hz, 1H), 1.73 (d, J_{HH} = 14.7 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.6, 130.1, 128.5, 127.2 (d, J_{CP} = 10.3 Hz), 77.6, 76.4 (d, J_{CP} = 6.1 Hz), 63.5 (d, J_{CP} = 6.4 Hz), 62.5, 35.6 (d, J_{CP} = 5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.70; Exact Mass: calculate for $C_9H_{13}O_5P$ $(M+Na)^+$ 255.0398; found 255.0403 (ESI)

(1*R*, 6*R*, 8*R*)- 2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene, 8-[(1*E*)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-propenyl]-, 1-oxide: 2.56



Purification via flash chromatography (1:1 Hexane/EtOAc) supplied 29 mg (87% yield) of **2.56** as a oil.

[∝]$_D$ -44.2 (*c* = 0.24, CH_2Cl_2);

IR (neat) 2954, 2927, 2856, 2348, 1299, 1068 cm^{-1};

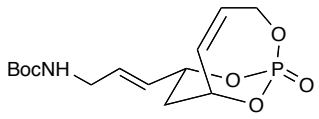
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (dddd, J_{HH} = 12.0, 6.6, 2.8, 2.8 Hz, 1H), 5.88 (dddd, J_{HH} = 15.5, 8.2, 4.1, 1.6 Hz, 1H), 5.67-5.71 (m, 1H), 5.63 (ddd, J_{HH} = 11.8, 3.8, 2.8 Hz, 1H), 5.18-5.25 (m, 1H), 5.00 (dd, J_{HH} = 11.5, 5.4 Hz, 1H), 4.95 (m, 1H), 4.37 (ddd, *J* = 27.7, 14.8, 6.7 Hz, 1H), 4.13 (t, J_{HH} = 1.9 Hz, 2H), 2.19 (ddd, J_{HH} = 18.2, 12.1, 6.2 Hz, 1H), 1.70-1.74 (m, 1H), 0.84 (s, 9H), 0.00 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.1, 129.7, 128.4, 125.8 (d, J_{CP} = 10.0 Hz), 76.0 (d, J_{CP} = 6.3 Hz), 63.0 (d, J_{CP} = 6.4 Hz), 62.5, 35.3 (d, J_{CP} = 6.3 Hz), 25.9, 18.4, -5.31, -5.29;

^{31}P NMR (162 MHz, $CDCl_3$) δ -2.75;

HRMS Exact Mass: calculate for $C_{15}H_{27}O_5PSi$ $(M+Na)^+$ 369.1263; found 369.1263 (ESI)

Carbamic acid, [(2*E*)-3-[(1*R*, 6*R*, 8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]-2-propenyl]-, 1,1-dimethylethyl ester: 2.57



Purification via flash chromatography (1:1 Hexane/EtOAc) supplied 22 mg (69% yield) of **2.57** as a oil.

[∝]$_D$ -49.4 (*c* = 0.16, CH_2Cl_2);

IR (neat) 3330, 2962, 2358, 1712, 1515, 1292 cm^{-1};

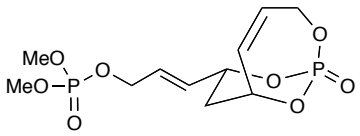
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98-6.02 (m, 1H), 5.81 (app dt, J_{HH} = 15.3, 5.3 Hz, 1H), 5.59 (dd, J_{HH} = 15.5, 5.1 Hz, 1H), 5.53 (app dt, J_{HH} = 10.9, 3.2 Hz, 1H), 5.13 (app d, *J* = 24.5 Hz, 1H), 4.90-5.01 (m, 2H), 4.40 (ddd, *J* = 28.8, 14.8, 6.7 Hz, 1H), 3.71 (s, 2H), 2.17 (ddd, J_{HH} = 18.41, 12.32, 6.26 Hz, 1H), 1.71 (d, J_{HH} = 14.53, 1H) 1.46 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 130.9, 129.6, 128.2, 127.9 (d, J_{CP} = 9.6 Hz), 76.9, 75.8 (d, J_{CP} = 6.1 Hz), 63.0 (d, J_{CP} = 6.3 Hz), 41.6, 35.1 (d, J_{CP} = 6.0 Hz), 29.7, 28.4;

^{31}P NMR (162 MHz, $CDCl_3$) δ -2.96;

HRMS Exact Mass: calculate for $C_{14}H_{22}NO_6P$ $(M+H)^+$ 332.1263; found 332.1277 (ESI)

Phosphoric acid, dimethyl (2*E*)-3-[(1*S*, 6*R*, 8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]-2-propenyl ester: 2.58



Purification via flash chromatography (9:1 EtOAc/MeOH) supplied 27 mg (80% yield) of **2.58** as a oil.

[∝]$_D$ -48.3 (*c* = 0.48, CH_2Cl_2);

IR (neat) 2956, 2358, 1296 1037, 955 cm^{-1};

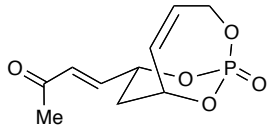
^{1}H NMR (500 MHz, $CDCl_3$) trans isomer δ 5.98-6.03 (m, 1H), 5.94 (app dt, J_{HH} = 15.5, 5.3 Hz, 1H), 5.78 (dd, J_{HH} = 15.5, 3.5 Hz, 1H), 5.55 (app dt, J_{HH} = 11.8, 3.7 Hz, 1H), 5.15 (d, J_{HH} = 24.3 Hz, 1H), 5.00-5.06 (m, 1H), 4.91-4.99 (m, 1H), 4.51 (dd, *J* = 7.8, 4.7 Hz, 2H), 4.33 (ddd, *J* = 27.7, 14.8, 6.7 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 2.17 (app ddd, J_{HH} = 18.3, 12.4, 6.1 Hz, 1H), 1.75 (app d, J_{HH} = 14.2 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) trans isomer δ 130.0 (d, J_{CP} = 10.3 Hz), 129.5, 128.3, 127.4 (d, J_{CP} = 6.6 Hz), 77.0, 76.9, 75.1 (d, J_{CP} = 6.0 Hz), 66.5 (d, J_{CP} = 5.2 Hz), 54.5, 54.4, 35.0 (d, J_{CP} = 5.8 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) trans isomer δ 2.66, -3.04; cis isomer δ 2.74, 2.89; **HRMS** Exact Mass: calculate for $C_{11}H_{18}O_8P_2$ $(M+Na)^+$ 363.0375; found 363.0386 (ESI)

General Procedure for Cross Metathesis of Type II Olefins: A flask or pressure tube containing **2.53** (20 mg, 0.099 mmol) was charged with CH_2Cl_2 (2 mL) that had been degassed 15 minutes with argon. The Type II olefin partner (4-5 equiv. relative to compound **2.53**) followed by Hoveyda-Grubbs II catalyst (**2.3**) (6.2 mg, 0.009 mmol) were added and the reaction mixture was refluxed for 3-6 h. Upon completion (monitored by TLC) the reaction was cooled to rt and concentrated under reduced pressure.

(3*E*)-Buten-2-one, 4-[(1*S*, 6*R*, 8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]: 2.54



Purification via flash chromatography (9:1 EtOAc/MeOH) supplied 18 mg (75% yield) of **2.54** as an oil.

[∝]$_D$ -56.7 (*c* = 0.33, CH_2Cl_2);

IR (neat) 2958, 2362, 1701, 1677, 1275, 973 cm^{-1};

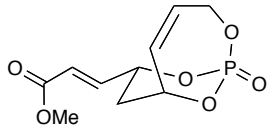
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (app dt, J_{HH} = 20.3, 3.5 Hz, 1H), 6.50 (dd, J_{HH} = 15.7, 1.7 Hz, 1H), 6.12 (ddd, J_{HH} = 11.9, 3.8, 2.8 Hz, 1H), 5.57 (dddd, J_{HH} = 11.8, 6.6, 2.8, 2.4 Hz, 1H), 5.20-5.24 (m, 1H), 5.14-5.19 (m, 1H), 4.94-5.00 (m, 1H), 4.35 (ddd, *J* = 28.0, 14.9, 6.7 Hz, 1H), 2.22 (s, 3H), 2.13-2.23 (m, 1H), 1.82 (app dd, J_{HH} = 14.6, 1.5 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 140.4 (d, J_{CP} = 10.4 Hz), 129.9, 129.2, 128.7, 76.9 (d, J_{CP} = 5.7 Hz), 74.2 (d, J_{CP} = 5.9 Hz), 63.2 (d, J_{CP} = 6.3 Hz), 34.5 (d, J_{CP} = 6.0 Hz), 28.67;

^{31}P NMR (162 MHz, $CDCl_3$) δ -3.39;

HRMS Exact Mass: calculate for $C_{10}H_{13}O_5P$ $(M+Na)^+$ 267.0398; found 267.0409 (ESI)

(2*E*)-Propenoic acid, 3-[(1*S*, 6*R*, 8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]-, methyl ester: 2.60



Purification via flash chromatography (1:2 Hexane/EtOAc) supplied 20 mg (78% yield) of **2.60** as a oil.

[∝]$_D$ -42.8 (*c* = 0.40, CH_2Cl_2);

IR (neat) 2954, 2852, 1724, 1300, 973 cm^{-1};

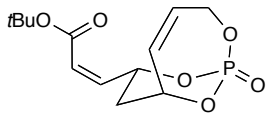
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (app dt, J_{HH} = 15.6, 3.7 Hz, 1H), 6.27 (dd, J_{HH} = 15.5, 1.9 Hz, 1H), 6.12 (dddd, J_{HH} = 11.9, 6.6, 2.8, 2.4 Hz, 1H), 5.66 (ddd, J_{HH} = 11.9, 3.8, 2.7 Hz, 1H), 5.28-5.32 (m, 1H), 5.22-5.28 (m, 1H), 5.03-5.09 (m, 1H), 4.44 (ddd, *J* = 27.9, 14.8, 6.7 Hz, 1H), 3.79 (s, 3H), 2.25 (ddd, J_{HH} = 18.4, 12.3, 6.2 Hz, 1H), 1.90 (app dd, J_{HH} = 14.7, 1.3 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 142.6 (d, J_{CP} = 10.3 Hz), 129.2, 128.7, 122.1, 76.8, 74.1 (d, J_{CP} = 5.8 Hz), 52.0, 34.4 (d, J_{CP} = 5.9 Hz) 29.7;

^{31}P NMR (162 MHz, $CDCl_3$) δ -3.36;

HRMS Exact Mass: calculate for $C_{10}H_{13}O_6P$ $(M+H)^+$ 261.0528; found 261.0533 (ESI)

(2*Z*)-Propenoic acid, 3-[(1*S*, 6*R*, 8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]-, 1,1-dimethylethyl ester: 2.61



Purification via flash chromatography (1.5:1 Hexane/EtOAc) supplied 3 mg of the minor *cis*-**2.61** isomer of methyl acrylate derived bicyclic phosphate as a oil. The *trans* isomer was inseparable from starting material (5:1 *E/Z)*.

[∝]$_D$ -65.5 (*c* = 0.20, CH_2Cl_2);

IR (neat) 3010, 2923, 1710, 1301, 1242, 1159, 973 cm^{-1};

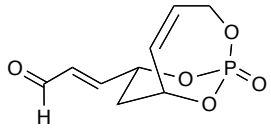
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (dd, J_{HH} = 11.7, 6.7 Hz, 1H), 6.04-4.14 (m, 2H), 5.77 (dd, J_{HH} = 11.7, 1.1 Hz, 1H), 5.72 (ddd, J_{HH} = 11.9, 3.9, 2.7 Hz, 1H), 5.16-5.27 (m, 1H), 4.98-5.08 (m, 1H), 4.44 (ddd, *J* = 28.0, 14.6, 6.7 Hz, 1H), 2.14-2.24 (m, 1H), 2.06 (ddd, J_{HH} = 14.4, 3.9, 2.4 Hz, 1H), 1.48 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 144.5 (d, J_{CP} = 12.5 Hz), 129.8, 128.0, 122.7, 81.2, 74.3 (d, J_{CP} = 5.0 Hz), 63.1, 33.4 (d, J_{CP} = 6.3 Hz) 29.7, 28.1;

^{31}P NMR (162 MHz, $CDCl_3$) δ -3.33 *trans*, -3.29 *cis*;

HRMS Exact Mass: calculate for $C_{13}H_{19}O_6P$ $(M+Na)^+$ 325.0817; found 325.0825 (ESI)

(2*E*)-Propenal, 3-[(1*S*, 6*R*, 8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]: 2.62



Purification via flash chromatography (9:1 EtOAc/MeOH) supplied 18 mg (78% yield) of **2.62** as a oil.

[∝]$_D$ -34.4 (*c* = 0.45, CH_2Cl_2);

IR (neat) 3150, 2930, 1698, 1300, 975 cm^{-1};

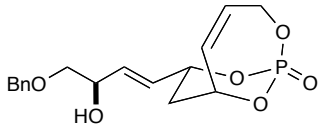
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (d, J_{HH} = 7.4 Hz, 1H), 6.76 (ddd, J_{HH} = 15.7, 3.9, 3.1 Hz, 1H), 6.47 (ddd, J_{HH} = 16.3, 7.4, 1.6 Hz, 1H), 6.12-6.18 (m, 1H), 5.68 (ddd, J_{HH} = 11.9, 3.9, 2.7 Hz, 1H), 5.36 (ddd, *J* = 12.3, 3.8, 1.8 Hz, 1H), 5.26-5.33 (m, 1H), 5.04-5.11 (m, 1H), 4.46 (ddd, *J* = 28.0, 14.9, 6.7 Hz, 1H), 2.33 (ddd, J_{HH} = 18.4, 12.2, 2.1 Hz, 1H), 1.95 (ddd, J_{HH} = 14.5, 3.4, 2.1 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 149.8 (d, J_{CP} = 10.8 Hz), 132.1, 129.1, 128.9, 76.7, 74.0 (d, J_{CP} = 5.7 Hz), 63.2 (d, J_{CP} = 6.3 Hz), 34.2 (d, J_{CP} = 6.0 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ -3.65;

HRMS Exact Mass: calculate for $C_9H_{11}O_5P$ $(M+H)^+$ 231.0422; found 231.0447 (ESI)

(2*R*, 3*E*)-Buten-2-ol, 4-[(1*S*, 6*R*, 8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]-1-(phenylmethoxy): 2.63



Purification via flash chromatography (1:2 Hexane/EtOAc) supplied 25 mg (72% yield) of **2.63** as a oil.

[∝]$_D$ -45.0 (*c* = 0.60, CH_2Cl_2);

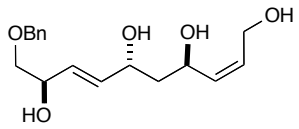
IR (neat) 3404, 2923, 2854, 1272, 1114 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.33 (m, 5H), 5.94-6.01 (m, 1H), 5.75-5.85 (m, 2H), 5.53 (ddd, J_{HH} = 11.9, 3.8, 2.6 Hz, 1H), 5.13 (app d, *J* = 24.5 Hz, 1H), 4.91-5.02 (m, 2H), 4.50 (s, 2H), 4.33 (m, 1H), 4.31 (ddd, *J* = 27.8, 14.8, 6.7 Hz, 1H), 3.48 (dd, J_{HH} = 9.6, 3.3 Hz, 1H), 3.27 (dd, J_{HH} = 9.6, 8.0 Hz, 1H), 2.47 (s, 1H), 2.16 (ddd, J_{HH} = 18.2, 12.1, 6.2 Hz, 1H), 1.72 (dd, J_{HH} = 14.7, 1.2 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 131.6, 129.6, 128.5, 128.3 (d, J_{CP} = 10.1 Hz), 128.2, 128.0, 127.9, 77.0, 75.6 (d, J_{CP} = 6.1 Hz), 73.7, 73.5, 70.2, 63.0 (d, J_{CP} = 6.3 Hz), 35.2 (d, J_{CP} = 5.7 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ -2.88

(2*Z*,4*R*,6*R*,7*E*,9*R*)-10-(benzyloxy)deca-2,7-diene-1,4,6,9-tetraol: 2.64



2.63 (0.033 g, 0.090 mmol) was taken up in THF (2.0 mL) and lowered to 0 ºC. $LiAlH_4$ (17 mg, 0.45 mmol) was slowly added. Upon complete addition of $LiAlH_4$, the reaction was warmed to rt and stirred for one hour. The reaction was quenched under non-aqueous conditions (0.017 mL H_2O slowly, 0.017 mL 15% NaOH slowly, and 0.051 mL H_2O). Salts were filtered and washed (5x with ether) and reaction was concentrated. The concentrated reaction mixture was purified by flash chromatography (9:1 EtOAc) to supply 23 mg of **2.64** (70% yield) as an oil.

$[\alpha]_D$ -24.28 (*c* = 0.034, CH_2Cl_2);

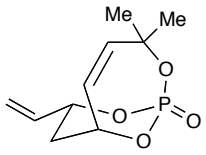
IR (neat) 3404, 2923, 2856, 1452, 1272, 1110 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.39 (m, 5H), 5.85 (dd, J_{HH} = 15.3, 5.2 Hz, 1H), 5.54-5.76 (m, 3H), 4.68-4.77 (m, 1H), 4.56 (s, 2H), 4.33-4.44 (m, 2H), 4.24 (dd, J_{HH} = 12.5, 6.6 Hz, 1H), 4.02-4.10 (m, 1H), 3.51 (dd, J_{HH} = 9.5, 3.2 Hz, 1H), 3.38 (app t, J_{HH} = 8.0 Hz, 1H), 3.13-3.33 (broad s, 4H), 1.75-1.85 (m, 1H), 1.68-1.71 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 134.6, 134.6, 130.2, 128.9, 128.5, 128.0, 127.9, 74.0, 73.4, 70.7, 69.8, 65.7, 58.7, 42.6;

HRMS Exact Mass: calculate for $C_{17}H_{24}O_5$ $(M+NH_4)^+$ 326.1968; found 326.1942 (FAB)

(1*R*, 6*R*, 8*R*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene, 8-ethenyl-3,3-dimethyl-, 1-oxide,: 2.66



A flask was charged with diol **2.49** (0.60 g, 4.69 mmol), NEt_3 (1.444 g, 14.3 mmol), and DMAP (0.057 g, 0.47 mmol) in DCM (23 mL). The solution was cooled to 0 ºC, and freshly distilled $POCl_3$ (0.789 g, 5.16 mmol) was added dropwise. After 25 minutes stirring in the ice bath, 20 mL of ether was added, and the salts filtered off. The concentrated reaction mixture was purified by flash chromatography (1:1 Hexane/EtOAc) to supply 0.682 g (70% yield) of the (3*R*,5*R*)-phosphate monochloride as a clear oil. A solution of 2-methylbut-3-en-2-ol (0.310 g, 3.60 mmol) in THF (18.0 mL) was cooled to -30 ºC. BuLi (2.47 M, 3.60 mmol) was slowly added, followed by one hour of stirring. A solution of phosphate monochloride (0.682 g, 3.27 mmol) in THF (6.0 mL) was slowly cannulated into the reaction vessel containing the alkoxide. The reaction was stirred at rt for 24 h and was quenched with 1 mL of NH_4Cl (sat'd aq) and diluted with 20 ml distilled water. The separated aqueous layer was extracted EtOAc (3x), and the combined organic layers were washed with $NaHCO_3$ (sat'd aq.), brine, and dried (Na_2SO_4). A flask containing triene phosphate was charged with CH_2Cl_2 (360 mL) that had been degassed 15 minutes with argon. Grubbs Second Generation catalyst was added (122 mg, 0.144 mmol) and the reaction mixture was refluxed for 3-3.5 h. Upon completion (monitored by TLC) the reaction was cooled to rt and concentrated under reduced pressure. Purification

via flash chromatography (1:1 Hexanes/EtOAc) supplied 377 mg (50% yield over two steps) of the **2.66**.

[∝]$_D$ -93.2 (*c* = 0.72, CH_2Cl_2);

IR (neat) 3197, 2933, 2383, 1384, 1299, 999 cm^{-1};

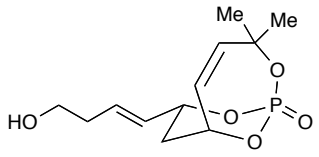
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83-5.94 (m, 1H), 5.87 (dd, J_{HH} = 12.2, 1.4 Hz, 1H), 5.45 (d, J_{HH} = 16.5 Hz, 1H), 5.42 (dd, J_{HH} = 12.3, 4.7 Hz, 1H), 5.27 (d, J_{HH} = 10.6 Hz, 1H), 5.14 (ddd, *J* = 24.6, 5.9, 4.6 Hz, 1H), 4.99 (ddd, *J* = 11.9, 3.4, 1.5 Hz, 1H), 2.20 (ddd, J_{HH} = 18.2, 12.1, 6.2 Hz, 1H), 1.84 (s, 3H), 1.79 (app dd, J_{HH} = 14.6, 1.2 Hz, 1H), 1.52 (d, J_{HP} = 2.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 135.0 (d, J_{CP} = 10.4 Hz), 125.6, 117.1 (d, J_{CP} = 1.1 Hz), 80.9 (d, J_{CP} = 7.6 Hz), 75.9 (d, J_{CP} = 6.5 Hz), 75.8 (d, J_{CP} = 6.0 Hz), 34.6 (d, J_{CP} = 5.8 Hz), 31.5 (d, J_{CP} = 12.2 Hz), 28.7;

^{31}P NMR (162 MHz, $CDCl_3$) δ -6.86;

HRMS Exact Mass: calculate for $C_{10}H_{15}O_4P$ $(M+H)^+$ 231.0786; found 231.0793 (ESI)

(3*E*)-Buten-1-ol, 4-[(1*R*, 6*R*, 8*R*)-3,3-dimethyl-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]-: 2.67



A flask or pressure tube containing **2.66** (20 mg, 0.087 mmol) was charged with CH_2Cl_2 (2 mL) that had been degassed 15 minutes with argon. Homo-allyl alcohol (12.5 mg, 0.173 mmol) followed by Hoveyda-Grubbs II catalyst (**2.3**) (6.2 mg, 0.009 mmol) was added and the reaction mixture was refluxed for 3-6 h. Upon completion (monitored by TLC) the reaction was cooled to rt and concentrated under reduced pressure. Purification via flash chromatography (9:1 EtOAc/MeOH) supplied 17 mg (71% yield) of **2.67** as an oil.

[∝]$_D$ -99.3 (*c* = 0.30, CH_2Cl_2);

IR (neat) 3404, 2923, 1384, 1288, 1271, 1002 cm^{-1};

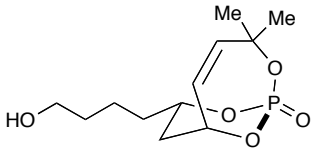
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (dd, J_{HH} = 15.1, 6.9 Hz, 1H), 5.77 (dd, J_{HH} = 12.3, 1.6 Hz, 1H), 5.56 (ddd, J_{HH} = 15.1, 5.7, 0.6 Hz, 1H), 5.32 (dd, J_{HH} = 12.3, 4.6 Hz, 1H), 4.98-5.08 (m, 1H), 4.90 (q, *J* = 11.7, 5.7 Hz, 1H), 3.63 (t, J_{HH} = 6.9 Hz, 2H), 2.27 (q, J_{HH} = 12.6, 6.2 Hz, 2H), 2.17 (ddd, J_{HH} = 19.0, 12.0, 6.3 Hz, 1H), 1.75 (s, 3H), 1.68 (ddd, J_{HH} = 14.5, 3.2, 2.2 Hz, 1H), 1.44 (d, J_{HP} = 2.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 130.5, 129.8 (d, J_{CP} = 10.1 Hz), 125.6, 80.9 (d, J_{CP} = 7.7 Hz), 75.9 (d, J_{CP} = 6.4 Hz), 75.8 (d, J_{CP} = 5.9 Hz), 61.6, 35.4, 34.9 (d, J_{CP} = 5.8 Hz), 31.5 (d, J_{CP} = 12.3 Hz), 28.7;

^{31}P NMR (162 MHz, $CDCl_3$) δ -6.89;

HRMS Exact Mass: calculate for $C_{12}H_{19}O_5P$ $(M+H)^+$ 275.1048; found 275.1059 (ESI)

(1*R*, 6*R*, 8*S*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-8-butanol, 3,3-dimethyl-, 1-oxide: 2.68



CH_2Cl_2 (14 mL) was added to a flask containing the **2.67** (0.019 g, 0.069 mmol). Grubbs second generation catalyst (0.06 g, 0.007 mmol) was added along with Et_3N (0.004 g, 0.03 mmol). The solution was then canulated into a H_2 Parr bomb apparatus. The solution was purged with H_2 and the bomb sealed. The mixture was heated at 37 ºC and 300 psi H_2 for 2 h. Concentration under reduced pressure and purification of the mixture via flash chromatography (9:1 EtOAc/MeOH) supplied 15 mg of the **2.68** (76% yield) as a oil.

$[\propto]_D$ -68.9 (*c* = 0.14, CH_2Cl_2);

IR (neat) 3407, 2927, 2854, 1384, 1290, 1271, 1095, 1002 cm^{-1};

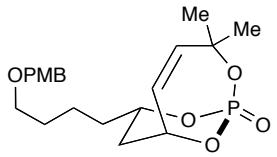
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (dd, J_{HH} = 10.3, 1.9 Hz, 1H), 5.28 (dd, J_{HH} = 12.3, 4.7 Hz, 1H), 4.96-5.02 (m, 1H), 4.38-4.45 (m, 1H), 3.57 (t, J_{HH} = 6.3, 2H), 2.08 (ddd, J_{HH} = 18.0, 12.0, 6.0 Hz, 1H), 1.73 (s, 3H), 1.40-173 (m, 7H), 1.41 (d, J_{HP} = 2.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 125.5, 80.4 (d, J_{CP} = 7.5 Hz), 75.9 (d, J_{CP} = 3.8 Hz), 75.8 (d, J_{CP} = 3.8 Hz), 62.3, 35.1 (d, J_{CP} = 8.8 Hz), 34.0 (d, J_{CP} = 6.3 Hz), 31.9, 31.2 (d, J_{CP} = 12.5 Hz), 28.3, 20.7;

^{31}P NMR (162 MHz, $CDCl_3$) δ -6.37;

HRMS Exact Mass: calculate for $C_{12}H_{21}O_5P$ $(M+H)^+$ 277.1205; found 277.1213 (ESI)

(1*R*,6*R*,8*S*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene, 8-[4-[(4-methoxyphenyl)methoxy]butyl]-3,3-dimethyl-, 1-oxide: 2.69



The PMB-imidate was prepared via previous method (Organ, M. G.; Wang, J. *J. Org. Chem.* **2002**, *67*, 7847-7851). The crude PMB-imidate (86 mg, 0.306 mmol) was dissolved in CH_2Cl_2 (1.0 mL) at rt and **2.68** (28 mg, 0.102 mmol) and PPTS (3 mg, 0.0119 mmol) were added. The mixture was stirred for 22 h during which time a white solid formed. After washing with saturated $NaHCO_3$ and brine, the solution was dried over anhydrous Na_2SO_4 and subsequently filtered. Concentration under reduced pressure and purification of the mixture via flash chromatography (1:1 EtOAc/MeOH) supplied 37 mg of the **2.69** (94% yield) as an oil.

[∝]$_D$ -65.7 (*c* = 0.525, CH_2Cl_2);

IR (neat) 2931, 2858, 1612, 1512 1367, 1290, 1271, 1095, 1000 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (app d, J_{HH} = 6.50 Hz, 2H), δ 6.87 (app d, J_{HH} = 8.6 Hz, 2H), δ 5.81 (dd, J_{HH} = 12.3, 1.7 Hz, 1H), 5.35 (dd, J_{HH} = 12.3, 4.5 Hz, 1H), 5.08 (app dt, *J* = 24.6, 5.6 Hz, 1H), 4.45-4.53 (m, 1H), 4.42 (s, 2H), 3.81 (s, 3H), 3.43 (t, J_{HH} = 6.2 Hz, 2H), 2.13 (ddd, J_{HH} = 18.1, 11.9, 6.3 Hz, 1H), 1.81 (s, 3H), 1.45-179 (m, 7H), 1.49 (d, J_{HP} = 6.0 Hz, 3H);

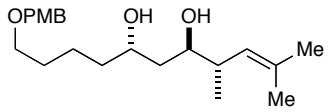
^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 136.6, 129.5, 128.3, 124.8, 112.8, 79.7 (d, J_{CP} = 7.7 Hz), 75.2 (d, J_{CP} = 3.1 Hz), 75.1 (d, J_{CP} = 2.7 Hz), 71.6, 68.7, 54.3, 34.5 (d, J_{CP}

= 9.3 Hz), 33.3 (d, J_{CP} = 5.9 Hz), 30.5 (d, J_{CP} = 12.1 Hz), 28.3, 27.6, 20.4;

^{31}P NMR (162 MHz, $CDCl_3$) δ -6.34;

HRMS Exact Mass: calculate for $C_{20}H_{29}O_6P$ $(M+H)^+$ 397.1780; found 397.1782 (ESI)

(4*S*,5*R*,7*S*)-11-(4-methoxybenzyloxy)-2,4-dimethylundec-2-ene-5,7-diol: 2.70



A thoroughly dried flask was charged with a solution of CuCN•2LiCl in THF (0.342 mL, 1.0 M solution) and lowered to –30 ºC. Me_2Zn in THF (0.171 mL, 2.0 M solution) was slowly added. Upon addition, the mixture was stirred for 30 minutes at –30 ºC (mossy green color). A solution of **2.69** (27 mg, 0.069 mmol) in THF (0.069 mL) was cannulated slowly into the cuprate solution (at –30 ºC). The reaction was stirred for 3 hrs and quenched with 10% HCl (5 mL, the reaction was stirred until copper solids dissolved). The two layers were separated, and the aqueous layer was washed with CH_2Cl_2 (4x). The combined organic layers were washed with H_2O (1x) and concentrated under reduced pressure to provide the crude phosphonic acid (one product peak by ^{31}P analysis) as an oil. The acid was taken up in methanol and $TMSCHN_2$ was added at rt until the yellow solution persisted. A drop of acetic acid was added and the solution was evaporated under reduced pressure. The phosphate was taken up in toluene (0.685 mL) and cooled to 0 ºC. Red-Al (0.083 mL of 65% solution in toluene) was slowly added. Upon addition of Red-Al, the flask was warmed to rt and stirred for 3 hrs. The reaction was quenched with 3 mL of NH_4Cl (sat'd, aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (1:1 EtOAc/hexane) provided 15 mg of **2.70** (65% yield over three steps).

[∝]$_D$ -13.7 (*c* = 0.510, CH_2Cl_2);

IR (neat) 3392, 2927, 2856, 1612, 1512 1363, 1247, 1209, 1097, 1035 cm^{-1};

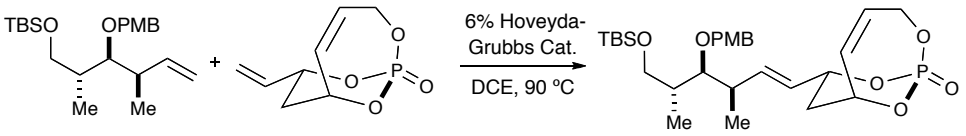
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (app d, J_{HH} = 8.4 Hz, 2H), δ 6.87 (app d, J_{HH} = 8.5 Hz, 2H), δ 4.97 (d, J_{HH} = 9.8 Hz, 1H), 4.42 (s, 2H), 3.90-3.96 (m, 1H), 3.81 (s, 3H), 3.58 (ddd, J_{HH} = 7.9, 7.9, 3.0 Hz, 1H), 3.44 (t, J_{HH} = 6.5 Hz, 2H), 2.80 (broad s, 2H), 2.44-2.51 (m, 1H), 1.76 (s, 3H), 1.67-173 (m, 1H), 1.66 (s, 3H), 1.35-1.65 (m, 9H), 0.92 (d, J_{HH} = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 135.2, 130.7, 129.3, 126.7, 113.8, 73.4, 72.6, 70.0, 69.1, 55.3, 39.0, 38.9, 37.2, 29.8, 26.1, 22.6, 18.4, 17.0;

HRMS Exact Mass: calculate for $C_{21}H_{34}O_4$ $(M+H)^+$ 351.2535; found 351.2538 (ESI)

4.3 Experimental Data: Chapter 3

TBS-PMB Protected Phosphate: 3.26



To a stirring solution of olefin **3.22** (3.22g, 8.51 mmol) and degassed DCE (85 mL) were added bicyclic phosphate **3.17** (870 mg, 4.26 mmol) and Hoveyda-Grubbs II catalyst (213 mg, 0.27 mmol). The solution was equipped with a reflux condenser and placed into an oil bath at 90 ºC, at which time a stream of Ar was bubble through the solution for 1.5 h (until disappearance of phosphate **3.17** by TLC). The solution was allowed to cool to room temperature before being concentrated under vacuum pressure. Purification via flash chromatography (2:1 EtOAc/Hexane) supplied 1.71 g (72% yield) of **3.26** as a viscous oil.

$[\alpha]_D$ -57.5 (*c* = 0.80, CH_2Cl_2);

FTIR (neat) 2954, 2927, 2883, 1514, 1463, 1249 cm^{-1};

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 7.23 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 6.04 (dddd, *J* = 11.8, 6.5, 2.9, 2.8 Hz, 1 H), 5.90 (dd, *J* = 15.5, 7.5 Hz, 1 H), 5.59 (ddd, *J* = 11.8, 3.7, 2.6 Hz, 1 H), 5.53 (dd, *J* = 15.5, 6.5 Hz, 1 H), 5.11-5.20 (m, 1 H), 4.97 (m, 1 H), 4.95 (dd, *J* = 12.9, 7.8 Hz, 1 H), 4.49 (d, *J* = 11.0 Hz, 1 H), 4.41 (d, *J* = 11.0 Hz, 1 H), 4.37 (ddd, J_{HP} = 27.7, J_{HH} = 14.8, 6.7 Hz, 1 H), 3.80 (s, 3 H), 3.59-3.67 (m, 1 H), 3.63 (dd, *J* = 8.1, 5.5 Hz, 1 H), 3.29 (dd, *J* = 7.7, 4.0 Hz, 1 H), 2.43-2.50 (m, 1 H), 2.17 (ddd, *J* = 14.7, 12.1, 6.2 Hz, 1 H), 1.78-1.86 (m, 1 H), 1.63 (d, *J* =

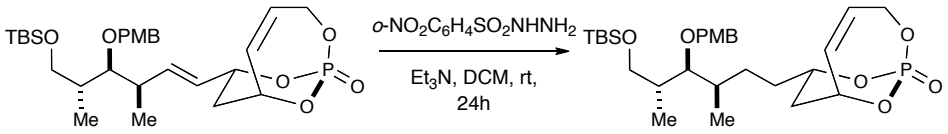
13.8 Hz, 1 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.04 (s, 6 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 159.1, 139.3, 131.2, 129.7, 129.2, 128.1, 126.0 (J_{CP} = 10.1 Hz), 113.7, 83.7, 76.8 (J_{CP} = 6.4 Hz), 76.81, 74.2, 62.9 (J_{CP} = 6.2 Hz), 55.3, 38.6, 38.5, 35.3 (J_{CP} = 5.5 Hz), 29.7, 26.0, 18.3, 14.5, 13.8, -5.3, -5.4;

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -3.57;

HRMS Exact Mass: calculate for $C_{28}H_{49}NO_7PSi$ $(M+NH_4)^+$ 570.3016; found 570.3002 (ESI).

Partially Hydrogenated TBS-PMB Protected Phosphate: 3.27



The cross-metathesized phosphate intermediate (**3.26**) (1.53 g, 2.76 mmol) was taken up in CH_2Cl_2 (35 mL) followed by the addition of Et_3N (12 mL, ~2 mL/gram of NBS-H), and NBS-H (6.00 g, 27.60 mmol). After the reaction was stirred for 12 h, EtOAc (100 mL) was added, and the reaction extracted with $NaHCO_3$ (sat'd aq, 2x). The aq layer was re-extracted with EtOAc (1x). The combined organic layers were dried (anhydrous Na_2SO_4) and concentrated. The material was then re-subjected to the same conditions before being purified. Flash chromatography (2:1 Hex:EtOAc) afforded **3.27** (1.11 g, 72%) as a clear oil and 150 mg of starting material.

$[\alpha]_D$ 20.0 (*c* = 0.46, CH_2Cl_2);

FTIR (neat) 2954, 2929, 2883, 1514, 1461, 1249 1072 cm^{-1};

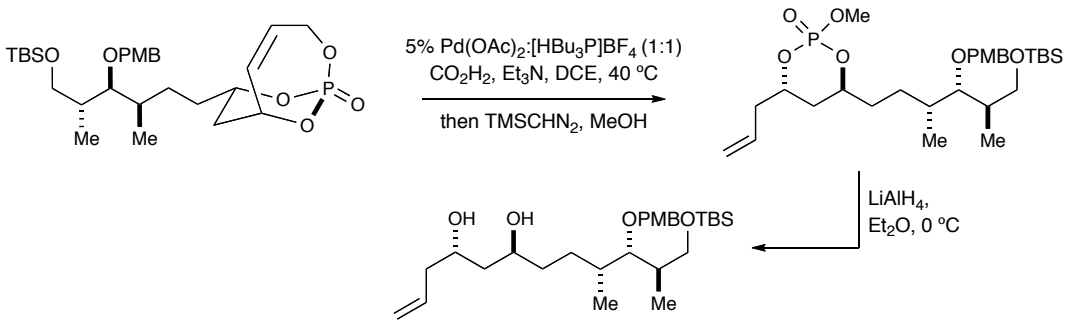
^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 7.27 (d, *J* = 7.6 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.04 (dddd, *J* = 11.8, 6.5, 2.8, 2.6 Hz, 1 H), 5.59 (ddd, *J* = 11.8, 4.0, 2.5 Hz, 1 H), 5.11 – 5.21 (m, 1 H), 5.01 (dddd, *J* = 11.8, 8.6, 5.2, 2.8 Hz, 1 H), 4.57 (d, *J* = 11.4 Hz, 1 H), 4.44 – 4.51 (m, 1 H), 4.46 (d, *J* = 11.0 Hz, 1 H), 4.37 (ddd, J_{HP} = 27.7, J_{HP} = 14.8, 6.6 Hz, 1 H), 3.81 (s, 3 H), 3.74 (dd, *J* = 9.8, 5.0 Hz, 1 H), 3.63 (dd, *J* = 9.8, 3.5 Hz, 1 H), 3.26 (dd, *J* = 8.8, 2.5 Hz, 1 H), 2.09 (ddd, *J* = 14.5, 12.0, 6.3 Hz, 1 H), 1.71-1.86 (m, 2 H), 1.55- 1.70 (m, 3 H), 1.34 – 1.54 (m, 2 H), 0.92 (s, 9 H), 0.90 (d, *J* = 4.1 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.06 (s, 3H), 0.06 (s, 3H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 159.0, 131.5, 129.9, 129.4, 129.2, 127.9, 113.7, 83.0, 77.3, 76.9, 74.1, 64.9, 62.9, 55.3, 38.5, 34.9, 34.6, 33.8, 26.0, 18.3, 14.73, 13.4, -5.3, -5.4;

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -3.12;

HRMS Exact Mass: calculate for $C_{28}H_{51}NO_7PSi$ $(M+NH_4)^+$ 572.3172; found 572.3163 (ESI).

(4*S*,6*S*,9*R*,10*S*,11*R*)-12-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)-9,11-dimethyldodec-1-ene-4,6-diol: 3.31



Phosphate **3.27** (1.84 g, 3.30 mmol) was taken up in 90 mL of DCE and stirred at room temperature. In a different reaction vessel 5 mol % $Pd(OAc)_2$ (47 mg, 0.21 mmol) and $[HBu_3P]BF_4$ (60 mg, 0.21 mmol) and were taken up in 7 mL of DCE. At this time, Et_3N (2.068 mL, 14.87 mmol) and CO_2H_2 (0.280 mL, 7.40 mmol) were added to the reaction vessel containing phosphate **3.27** and the 1:1 mixture of $Pd(OAc)_2$ and $[HBu_3P]BF_4$ was also quickly cannulated into the reaction containing phosphate **3.27**. The reaction was heated to a temperature of 40 ºC. The reaction was stirred at this temperature until the color of the reaction turned black (~1 h) as well as disappearance of starting material by TLC analysis. The reaction was cooled to room temperature, diluted with 50 mL CH_2Cl_2 and 40 mL of 10 % aqueous HCl was added. The layers separated and the aqueous layer was re-extracted (2x) with CH_2Cl_2. The organic layer was then concentrated to ~50 mL under reduced pressure. MeOH (2 mL) followed by $TMSCHN_2$ (2.0 mL, 2.0M in diethyl ether) were added to the stirring solution, which caused the reaction to bubble vigorously. The reaction was allowed to stir for 5 min. and was monitored for disappearance of the phosphate acid.

Upon completion of the reaction a drop of glacial acetic acid was added and the mixture was extracted with CH_2Cl_2 and a saturated solution of $NaHCO_3$. The aqueous layer was re-extracted (2x) with CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (2:1 Hexane:EtOAc) provided 1.67 g of **3.30** (~1:1 diastereomeric mixture at phosphate) in 87% yield as a clear oil.

The 1:1 diastereomeric phosphate mixture (1.67 g, 2.91 mmol) was taken up in Et_2O (103 mL) and cooled to 0 ºC. $LiAlH_4$ (0.222 g, 5.83 mmol) was slowly added in ~ 0.1 g increments. Upon completion of the addition, the reaction was stirred at 0 ºC for 1 h, and quenched via slow sequential addition of H_2O (222 μl), 10% NaOH (222 μl), and H_2O (666 μL), and removal from the bath. After stirring for 1h, white salts had formed and were filtered through a pad of celite washing Et_2O and was concentrated under reduced pressure. The resulting clear oil was pushed through a short plug of silica (2:1 Hexane:EtOAc) to afford 1.09 g of **3.31** (76% yield) as a clear oil.

$[\alpha]_D$ 2.00 (*c* = 0.35, CH_2Cl_2);

FTIR (neat) 3344, 3074, 2954, 2929, 2856, 1247, 1082 cm^{-1};

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 7.28 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.78-5.88 (m, 1 H), 5.16-5.19 (m, 1 H), 5.13-5.15 (m, 1 H), 4.56 (d, *J* = 11.0 Hz, 1 H), 4.49 (d, *J* = 11.0 Hz, 1 H), 3.94 (ddd, *J* = 12.5, 7.1, 5.4 Hz, 1 H), 3.86-3.92 (m, 1 H), 3.81 (s, 3 H), 3.72 (dd, *J* = 9.6, 5.2 Hz, 1 H), 3.65 (dd, *J* = 9.7, 3.4 Hz, 1 H), 3.29 (dd, *J* = 8.6, 2.8 Hz, 1 H), 2.23-2.33 (m, 3 H), 1.79-1.89 (m, 1 H), 1.57-1.66 (m,

5 H), 1.38-1.48 (m, 3 H), 0.92 (s, 9 H), 0.91 (d, J = 0.16 Hz, 3 H), 0.90 (d, J = 4.49 Hz, 3 H), 0.06 (s, 3 H), 0.06 (s, 3 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 159.0, 134.6, 131.6, 129.2, 118.3, 113.7, 83.3, 74.3, 69.5, 68.2, 65.0, 55.3, 42.0, 41.9, 38.6, 35.6, 35.2, 30.9, 26.0, 18.3, 14.8, 13.6, -5.3, -5.4;

HRMS Exact Mass: calculate for $C_{28}H_{50}NaO_5Si$ $(M+Na)^+$ 517.3325; found 517.3315 (ESI).

((2*R*,3*S*,4*R*)-6-((4*S*,6*S*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)-3-(4-methoxybenzyloxy)-2,4-dimethylhexyloxy)(*tert*-butyl)dimethylsilane: 3.32

The diol (1.07 g, 2.16 mmol) was dissolved in CH_2Cl_2 (4 mL) followed by the addition of 2,2-DMP (4 mL), and PPTS (54 mg, 0..216 mmol). Upon completion (~15 min, monitored by TLC) the reaction was diluted with CH_2Cl_2 and quenched with $NaHCO_3$ (sat'd aq., 2 mL), dried (Na_2SO_4) and filtered. Flash chromatograph (10:1 Hexane:EtOAc) provided acetonide **3.32** (1.10 g, 96%).

$[\alpha]_D$ -4.33 (*c* = 0.30, CH_2Cl_2);

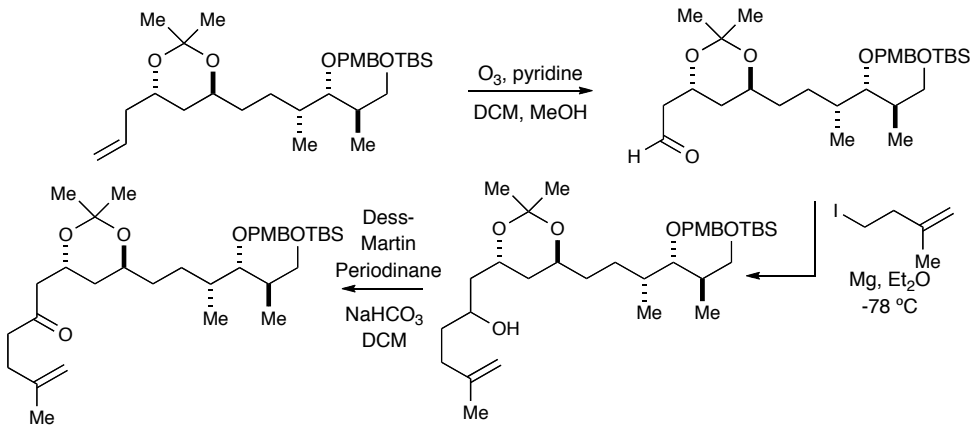
FTIR (neat) 3074, 2954, 2929, 2856, 1514, 1247, 1039 cm^{-1};

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.27 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.82 (dddd, *J* = 13.7, 10.6, 10.2, 7.1 Hz, 1 H), 5.08 (dd, *J* = 17.2, 1.8 Hz, 1 H), 5.04-5.08 (m, 1 H), 4.55 (d, *J* = 10.9 Hz, 1 H), 4.48 (d, *J* = 10.9 Hz, 1 H), 3.82-3.90 (m, 1 H), 3.81 (s, 3 H), 3.75 – 3.78 (m, 2 H), 3.65 (dd, *J* = 9.6, 3.4 Hz, 1 H), 3.26 (dd, *J* = 8.4, 2.6 Hz, 1 H), 2.27-2.36 (m, 1 H), 2.16 – 2.22 (m, 1 H), 1.79-1.87 (m, 1 H), 1.52-1.61 (m, 4 H), 1.38-1.45 (m, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 0.92 (s, 9 H), 0.90 (d, *J* = 3.6 Hz, 3 H), 0.89 (d, *J* = 5.4 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 159.0, 134.5, 131.6, 129.2, 116.8, 113.7, 100.2, 83.2, 74.4, 66.7, 66.2, 65.0, 55.3, 40.2, 38.6, 38.2, 35.0, 33.9, 30.4, 26.0, 24.8, 24.8, 18.3, 14.7, 13.5, -5.3, -5.4;

HRMS Exact Mass: calculate for $C_{31}H_{54}O_5Si$ $(M+H)^+$ 535.3819; found 535.3817 (ESI).

1-((4*R*,6*S*)-6-((3*R*,4*S*,5*R*)-6-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-3,5-dimethylhexyl)-2,2-dimethyl-1,3-dioxan-4-yl)-5-methylhex-5-en-2-one: 3.35



The olefin (0.913 g, 1.71 mmol) was taken up in CH_2Cl_2:MeOH 1:1 (29 mL) followed by the addition of pyridine (1.352 g, 17.10 mmol) and SUDAN III (indicator, ~1 mg) at rt under argon. The solution was cooled to -78 ºC, and a stream of O_3 was lightly bubbled through the solution until a light yellow color persisted. The stream of O_3 was removed when the SM was consumed (monitored by TLC). The flask was flushed with Ar, and Me_2S (5.1 mL) was slowly added. The reaction was slowly warmed to rt over a 4 h period. After stirring for 1 h. at rt, Et_2O (50 mL) was added and extracted with sat'd $CuSO_4$ (2x 15 mL), and brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). Flash chromatography (9:1 Hexane: EtOAc) afforded the aldehyde (0.657 g, 72 %) as an oil.

To a solution of iodide (1.6 g, 8.0 mmol) in Et_2O, with a cold finger condenser (dry ice, acetone), (8.9 mL, 0.9M solution) at rt was added freshly prepared magnesium chips (150 mg, 6.24 mmol). At which time the reaction refluxed (metal

gray color) and was stirred under Ar until the solution had re-cooled to room temperature. A separate reaction flask of aldehyde (641 mg, 1.20 mmol) in Et_2O (6 mL) was cooled to -78 ºC, then 6.64 mL of MgI solution was added dropwise. The bath was removed after 5 min. of stirring and the reaction was warmed to rt. The reaction was quenched with aqueous 5 mL of NH_4Cl (sat'd aq) after the disappearance of starting material. The layers were separated and aqueous layer was extracted with Et_2O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (10:1 Hex:EtOAc) afforded a 1:1 mixture of **3.34** (ratio determined by ^1H NMR analysis of crude reaction mixture, 700 mg, combine yield of diastereomers 96%).

The alcohol (0.171 g, 0.281 mmol) was taken up in CH_2Cl_2 (9.3 mL) followed by the addition of $NaHCO_3$ (0.236 g, 2.81 mmol) and Dess-Martin periodinane (0.261 g, 0.618 mmol) at rt under argon. Upon completion (monitored by TLC), Et_2O (15 mL) was added, and the solution extracted with $NaHCO_3$ (sat'd aq., 2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (10:1 Hex:EtOAc) to give the **3.34** (0.154 g, 90%) as a clear oil.

$[\alpha]_D$ 17.7 (*c* = 1.65, CH_2Cl_2);

FTIR (neat) 2954, 2933, 2856, 1718, 1458, 1247, 1037 cm^{-1};

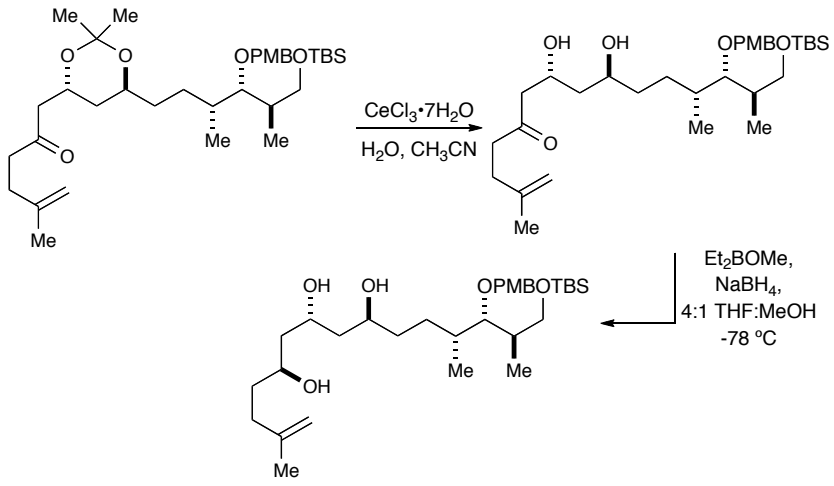
^1H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.28 (d, *J* = 7.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 4.75 (s, 1 H), 4.67 (s, 1 H), 4.58 (d, *J* = 10.7 Hz, 1 H), 4.49 (d, *J* = 10.7 Hz, 1 H),

4.30 (ddd, *J* = 14.4, 9.3, 5.4 Hz, 1 H), 3.82 (s, 3 H), 3.73 (dd, *J* = 9.9, 5.3 Hz, 2 H), 3.64 (dd, *J* = 9.9, 3.3 Hz, 1 H), 3.28 (dd, *J* = 9.1, 2.88 Hz, 1 H), 2.68 (dd, *J* = 15.9, 8.3 Hz, 1 H), 2.62 (dd, *J* = 7.3, 1.5 Hz, 1 H), 2.60 (d, *J* = 6.3 Hz, 1 H), 2.48 (dd, *J* = 15.9, 4.8 Hz, 1 H), 2.29 (dd, *J* = 8.1, 7.3 Hz, 2 H), 1.78-1.87 (m, 1 H), 1.75 (s, 3 H), 1.48-1.73 (m, 7 H), 1.36 (s, 3 H), 1.33 (s, 3 H), 0.93 (s, 9 H), 0.92 (d, *J* = 4.8 Hz, 3 H), 0.90 (d, *J* = 4.6 Hz, 3 H), 0.07 (d, *J* = 2.0 Hz, 6 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 208.3, 159.0, 144.5, 131.6, 129.2, 113.6, 110.0, 100.4, 83.4, 74.5, 66.9, 65.0, 63.2, 55.3, 48.7, 41.7, 38.6, 38.4, 35.2, 34.0, 31.1, 30.6, 26.0, 24.7, 24.5, 22.7, 18.3, 14.7, 13.4, -5.3, -5.4;

HRMS Exact Mass: calculate for $C_{35}H_{60}NaO_6Si$ $(M+H)^+$ 627.4057; found 627.4038 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-15-(*tert*-butyldimethylsilyloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethylpentadec-1-ene-5,7,9-triol 3.37



A solution of ketone **3.35** (0.050 g, 0.083 mmol) in CH_3CN (1.38 mL) was added H_2O (198 μl) followed by $CeCl_3 \bullet 7H_2O$ (93 mg, 0.250 mmol). The reaction was stirred until the disappearance of starting material (~5h). The reaction was diluted with Et_2O, quenched with $NaHCO_3$ (sat'd aq.), and the aqueous layer was re-extracted with Et_2O (2x). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (3:1 Hexane:EtOAc) provided 40 mg of **3.36** in 87% yield as a clear oil.

Reduction with Et_2BOMe, $NaBH_4$: To a solution of **3.36** (0.090 g, 0.159 mmol) in 4:1 THF:MeOH (0.353 mL) was added Et_2BOMe (1M in THF, 0.043 mL) at -78 ºC and stirred for 15 minutes. $NaBH_4$ (0.014 g, 0.368 mmol) was added and stirred at -78 ºC for 1 h. Then the reaction flask was warmed to rt and stirred for an additional hour. The reaction was quenched at -20 ºC with 10% aqueous NaOH, 35% H_2O_2, and stirred for 12 h at rt. The layers were separated, and the aq. layer extracted with Et_2O

(2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a silica column (2:1 Hex:EtOAc) to afford the title compound as a >20:1 mixture (determined by ^{1}H NMR of crude reaction) of **3.37** (0.054 g, 60%, 95% brsm) as a clear oil as well as 32 mg of starting ketone.

Reduction with DIBAL-H: To a solution of the ketone (0.010 g, 0.0176 mmol) in toluene (0.200 mL) was slowly added DIBAL-H (1.0M in toluene, 0.040 mL) at -78 ºC. After two hours of stirring at -78 °C, the reaction was quenched with NH_4Cl (sat'd, aq.), and the reaction warmed to rt while stirring. The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (2:1 Hex:EtOAc) to afford the title compound as a 1:1 mixture (determined by ^{1}H NMR of crude reaction) of **3.37** (0.0075 g, 75%) as a clear oil.

Reduction with $LiAlH_4$/LiI: To a solution of the ketone (0.020 g, 0.035 mmol) in Et_2O (0.440 mL) was added LiI (0.047 g, 0.350 mmol) at 0 °C (solution turns reddish-brown color). Once the LiI is completely dissolved (< 5 min), the reaction was cooled to -78 °C and a solution of $LiAl_4H$ (2.0 M in Et_2O, 0.175 mL) was slowly added. After twenty minutes, the reaction was quenched with sodium-potassium tartrate (sat'd, aq.), and the reaction warmed to rt while stirring. The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated

(rotary evaporator). The mixture was pushed through a short plug of silica (2:1 Hex:EtOAc) to afford the title compound as a 1.6:1 mixture (determined by ^{1}H NMR of crude reaction) of **3.37** (0.018 g, 90%) as a clear oil.

Reduction with Et_3B, $NaBH_4$: To a solution of the ketone (0.020 g, 0.035 mmol) in 4:1 THF:MeOH (0.353 mL) was added Et_3B (1.0M in THF 0.056 mL) at rt stirred for 15 minutes. The reaction was then cooled to -78 ºC and $NaBH_4$ (0.003 g, 0.071 mmol) was added and stirred at that temperature for 3h. The reaction was quenched at -78 ºC with 10% aqueous NaOH, 35% H_2O_2, and the reaction was stirred for 12 h at rt. The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (2:1 Hex:EtOAc) to afford the title compound as a 5.3:1 mixture (determined by ^{1}H NMR of crude reaction) of **3.37** (0.014 g, 70%) as a clear oil.

Reduction with $ZnCl_2$, $NaBH_4$: To a solution of the ketone (0.010 g, 0.0175 mmol) in CH_2Cl_2 (0.175 mL) was added $ZnCl_2$ (1M in THF, 0.0175 mL) at rt and stirred for 15 minutes. $NaBH_4$ (0.0015 mg, 0.0012 mmol) was then added and the reaction was stirred for 12 h. The reaction was quenched with 10% aqueous NaOH, 35% H_2O_2, and the reaction was stirred for 12 h at rt. The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (2:1 Hex:EtOAc) to afford the title

compound as a 3.3:1 mixture (determined by ^{1}H NMR of crude reaction) of **3.37** (0.006 g, 64%) as a clear oil.

$[\alpha]_D$ 7.26 (*c* = 1.35, CH_2Cl_2);

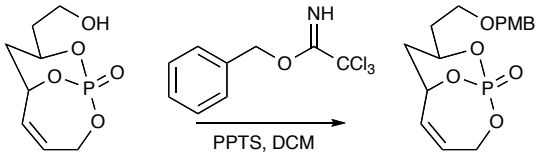
FTIR (neat) 3371, 2933, 2883, 2856, 1612, 1514, 1461 cm^{-1};

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.27 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 4.74 (d, *J* = 1.3 Hz, 1 H), 4.73 (s, 1 H), 4.56 (d, *J* = 10.9 Hz, 1 H), 4.49 (d, *J* = 10.9 Hz, 1 H), 4.18-4.26 (m, 1 H), 3.85-3.97 (m, 2 H), 3.80 (s, 3 H), 3.73 (dd, *J* = 9.6, 5.3 Hz, 1 H), 3.63 (dd, *J* = 9.6, 3.3 Hz, 1 H), 3.30 (dd, *J* = 8.8, 2.5 Hz, 1 H), 2.14 (dddd, 2 H), 1.78-1.86 (m, 1 H), 1.75 (s, 3 H), 1.58-1.73 (m, 8 H), 1.46-1.57 (m, 4 H), 1.27 (m, 3 H), 0.92 (s, 9 H), 0.91 (d, *J* = 2.3 Hz, 3 H), 0.89 (d, *J* = 2.3 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 159.0, 145.7, 131.61, 129.2, 113.7, 110.3, 83.3, 77.3, 74.3, 73.2, 70.9, 69.8, 65.0, 55.3, 42.5, 38.6, 35.9, 35.7, 35.3, 33.8, 31.1, 26.0, 22.4, 18.3, 14.7, 13.4, -5.3, -5.4;

HRMS Exact Mass: calculate for $C_{32}H_{58}NaO_6Si$ $(M+Na)^+$ 589.3900; found 589.3890 (ESI).

PMB protected hydroxyl bicyclic phosphate: 3.41



To a solution of NaH (38 mg, 0.955 mmol) in Et_2O (5 mL) was slowly cannulated a solution of PMBOH (5.28 g , 38.2 mmol) in Et_2O (19 mL) at rt. After stirring for 40 min. the solution was cooled to 0 ºC and Cl_3CCN (5.52 g, 38.2 mmol) was slowly added via dropwise addition. After 5-10 min., the solution was removed from the bath and stirred for an additional hour. The reaction was quenched with 10 mL of $NaHCO_3$ (sat'd aq), and the layers separated. The aqueous layer was further extracted with Et_2O (3x), the combined organic layers were dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The crude mixture was then cannulated with CH_2Cl_2 (96 mL) to a flask containing the phosphate (2.1 g, 9.55 mmol), followed by the addition of PPTS (239 mg, 0.96 mmol). After stirring for 16 h the reaction was quenched with 50 mL of NH_4Cl (sat'd aq), and the layers separated. The aq. layer was extracted with CH_2Cl_2 (3x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (EtOAc) provided 2.89 g (89% yield) of **3.41** as a viscous, light yellow oil.

$\mathbf{[\alpha]_D^{20}}$ = +63.8 (*c* = 3.1, CH_2Cl_2);

FTIR (neat) 2934, 1730, 1612, 1514, 1299, 1091 cm^{-1};

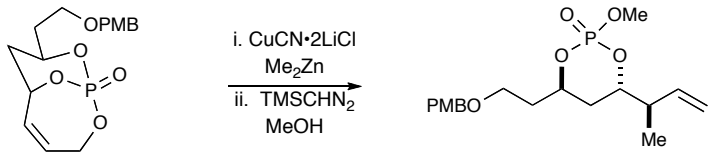
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23, (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.98-6.05 (m, 1H), 5.56 (ddd, 11.9, 3.8, 2.6 Hz, 1H), 5.16 (d, J = 24.4 Hz, 1H), 4.95-5.04 (m, 1H), 4.76-4.84 (m, 1H), 4.42 (s, 2H), 4.30-4.46 (m, 1H), 3.82 (s, 3H), 3.52-3.65 (m, 2H), 2.13-2.24 (m, 1H), 1.83-2.00 (m, 2H), 1.74 (d, J = 14.4 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 130.1, 129.8, 129.2, 127.7, 113.7, 77.2 (d, J_{CP} = 6.5 Hz), 74.0 (d, J_{CP} = 6.7 Hz), 72.7, 64.7, 62.9, 55.2, 35.8 (d, J_{CP} = 9.5 Hz), 34.8 (d, J_{CP} = 6.0 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ -2.29;

HRMS calculated for $C_{16}H_{21}O_6P$ $(M+Na)^+$ 369.0973; found 369.0984 (FAB).

Monocyclic PMB-Protected Phosphate Ester: 3.42



Within a drybox, CuCN (3.28 g, 36.6 mmol, dried overnight in a vacuum oven at 60 ^{o}C/0.3 mmHg and stored in a drybox), and LiCl (3.10 g, 73.3 mmol, dried overnight in a vacuum oven at 60 ºC/0.3 mmHg and stored in a drybox) were added to a round bottom flask and sealed with a septa. The flask was removed from the drybox and placed under a balloon of argon. THF (37 mL) was added and the mixture was stirred for 20 minutes at rt, then cooled to -30 ºC. A solution of Me_2Zn (33.3 mL, 1.2 M in toluene) was then added fast drop wise and the solution stirred for 30 minutes at -30 ºC (solution turns deep green). After 30 minutes, the phosphate (2.5 g, 7.33 mmol) in THF (7.3 mL) was cannulated fast dropwise (0.5 mL rinse), and the solution immediately removed from the bath and stirred at rt for 2 h. Upon completion (monitored by TLC, baseline spot in EtOAc), the reaction was cooled to 0 ºC and slowly quenched with 10% HCl (4 mL) followed by water (8 mL), and stirred at rt for 10 min (pepper colored salts form). The solution was filtered through a pad of celite and rinsed thoroughly with EtOAc. To the resulting bilayer solution was added 10% HCl (5 mL), and the layers separated. The aq layer was extracted with EtOAc (2x), and the combined organic layers were concentrated via a rotary evaporator. The resulting oil was taken up in MeOH (~20 mL), followed by the dropwise addition of $TMSCHN_2$ (2 M in Et_2O, ~10 mL), resulting in a deep yellow solution. Excess

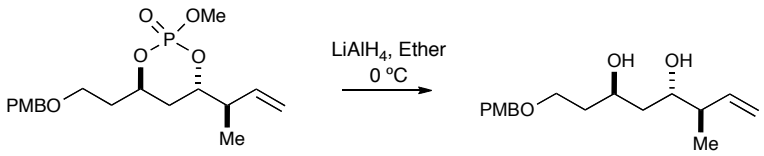
$TMSCHN_2$ was quenched via slow dropwise addition of glacial acetic acid (3-4 drops), and the solution dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). Flash chromatography (2:1 EtOAc) provided 2.37 g (87% yield) of **3.42** as a clear oil, and as a ~1:1 mixture of diastereomers at phosphorus.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J_{HH} = 8.6 Hz, 2H), 6.87 (d, J_{HH} = 8.6 Hz, 2H), 5.80 (dddd, J = 17.4, 10.4, 7.6, 1.7, 1H), 5.06-5.13 (m, 2H), 4.67-4.80 (m, 1H), 4.30-4.48 (m, 3H), 3.81 (s, 3H), 3.77 (d, 7.24 (d, J_{HP} = 5.4 Hz, 1.5H), 3.74 (d, J_{HP} = 5.4 Hz, 1.5H), 3.54-3.68 (m, 2H), 2.37-2.55 (m, 1H), 2.06-2.22 (m, 2H), 1.67-1.98 (m, 2H), 1.09 (d, J_{HH} = 6.9 Hz, 1.5H), 1.05 (d, J_{HH} = 6.9 Hz, 1.5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.2, 137.7, 130.0, 129.9, 129.2, 116.6, 116.3, 113.7, 79.8 (d, J_{CP} = 6.4 Hz), 78.8 (d, J_P = 7.0 Hz), 76.3 (d, J_{CP} = 7.2 Hz), 74.3 (d, J_{CP} = 6.2 Hz), 72.7, 65.6, 65.2, 55.1, 54.2 (d, J_{CP} = 6.1 Hz), 53.7 (d, J_{CP} = 5.7 Hz), 42.3 (d, J_{CP} = 7.9 Hz), 41.6 (d, J_{CP} = 5.2 Hz), 35.4 (d, J_{CP} = 6.1 Hz), 34.1, 32.8 (d, J_{CP} = 7.2 Hz), 32.0 (d, J_{CP} = 7.9 Hz), 15.7, 15.3,

^{31}P NMR (162 MHz, $CDCl_3$) δ -4.17, -4.50.

(3*R*,5*S*,6*R*)-1-(4-methoxybenzyloxy)-6-methyloct-7-ene-3,5-diol: 3.43



The 1:1 diastereomeric phosphate mixture (2.27 g, 6.19 mmol) was taken up in Et_2O (103 mL) and cooled to 0 ºC. $LiAlH_4$ (0.464 g, 12.2 mmol) was slowly added in ~ 0.1 g increments. Upon complete addition, the reaction was stirred at 0 ºC for 2.5 h, and quenched via slow sequential addition of H_2O (464 mL), 10% NaOH (464 mL), and H_2O (1.4 mL), and removal from the bath. After stirring for 30 minutes, 15 mL of 10% HCl was added and the layers separated. The aq layer was extracted with Et_2O (3x), and the combined organic layers rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The resulting clear oil was pushed through a short plug of silica (1:1 EtOAc:Hex) to afford 1.76 g of **3.43** (96% yield) as a clear oil.

$[\alpha]_D^{20} = -6.8$ ($c = 6.4$, CH_2Cl_2);

FTIR (neat) 3407, 2916, 1612, 1514, 1247, 1091, 1035 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.71-5.80 (m, 1H), 5.08 (s, 1H), 5.04 (d, J = 2.2, 1H), 4.43 (s, 2H), 4.06-4.13 (m, 1H), 3.72 (s, 3H), 3.71-3.77 (m, 1H), 3.55-3.68 (m, 2H), 3.53 (bs, 2H), 2.15-2.24 (m, 1H), 1.78-1.89 (m, 1H), 1.64-1.73 (m, 1H), 1.51-1.59 (m, 2H), 0.99 (d, J = 6.9, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 140.4, 129.9, 129.2, 115.5, 113.7, 72.7, 71.35, 68.5, 68.4, 55.1, 44.0, 39.9, 36.3, 15.8;

(4*S*,6*R*)-4-((*R*)-but-3-en-2-yl)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane: 3.44a

The diol (0.079 g, 0.269 mmol) was dissolved in DCM (1 mL) followed by the addition of 2,2-DMP (1 mL), and PPTS (3.3 mg, 0.013 mmol). Upon completion (~15 min, monitored by TLC) the reaction was quenched with $NaHCO_3$ (sat'd aq., 20 mL), and anhydrous Na_2SO_4 was added, filtered through a short plug of silica (EtOAc), and concentrated (rotary evaporator), to provide acetonide **3.44a** (0.088 g, 98%) that was used without further purification.

$[\alpha]_D^{20}$ = -17.3 (*c* = 2.8, CH_2Cl_2);

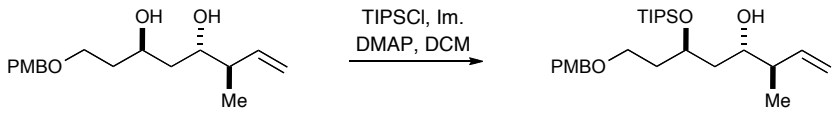
FTIR (neat) 2983, 1612, 1514, 1379, 1247 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.85 (ddd, *J* = 17.6, 10.6, 7.2 Hz, 1H), 5.06 (d, *J* = 6.7 Hz, 1H), 5.02 (d, *J* = 0.8 Hz, 1H), 4.44 (s, 2H), 3.91-3.99 (m, 1H), 3.83 (s, 3H), 3.67 (ddd, *J* = 12.6, 6.3, 3.2 Hz, 1H), 3.50-3.58 (m, 2H), 2.21-2.29 (m, 1H), 1.79 (d, *J* = 4.3 Hz, 1H), 1.76 (d, *J* = 6.4 Hz, 1H), 1.71 (ddd, *J* = 15.5, 9.6, 6.0 Hz, 1H), 1.43-1.55 (m, 2H), 1.35 (s, 6H), 1.01 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.1, 140.8, 130.5, 129.3, 114.4, 113.7, 100.3, 72.7, 69.9, 66.3, 63.3, 63.9, 55.3, 42.0, 36.0, 35.9, 24.6, 24.3, 15.2;

HRMS calculated for $C_{20}H_{30}O_4$ $(M+Na)^+$ 357.2042; found 357.2046 (FAB).

(3R,4S,6R)-8-(4-methoxybenzyloxy)-3-methyl-6-(triisopropylsilyloxy)oct-1-en-4-ol: SI1



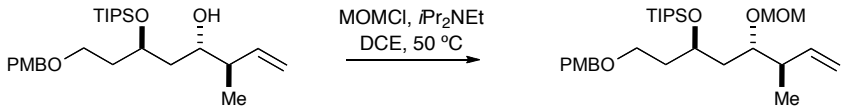
The diol (1.76 g, 5.98 mmol) was dissolved in CH_2Cl_2 (40 mL) followed by the addition of imidazole (2.44 g, 35.88 mmol), and DMAP (73 mg, 0.598 mmol). TIPSCl (3.80 mL, 17.94 mmol) was then added dropwise over several minutes. The reaction was stirred at rt overnight. The reaction was diluted with Et_2O (100 mL) followed by 10% HCl (30 mL), and the layers separated. The aq layer was extracted with Et_2O (1x), and the combined organic layers rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). Flash chromatography (9:1 Hex:Et_2O to remove excess silane, then 5:1 Hex:EtOAc) yielded monosilylated **SI1** (2.31g, 86%) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.24 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.73-5.84 (m, 1H), 5.04 (s, 1H), 5.01 (d, J = 2.3 Hz, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 4.27-4.32 (m, 1H), 3.79-3.85 (m, 1H), 3.80 (s, 3H), 3.56 (bs, 1H), 3.41-3.56 (m, 2H), 2.13-2.22 (m, 1H), 1.91-2.08 (m, 2H), 1.70 (ddd, J = 14.8, 10.6, 4.3 Hz, 1H), 1.53 (ddd, J = 14.6, 4.0, 1.8 Hz, 1H), 1.04-1.09 (m, 21H), 1.00 (d, J = 6.9 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.1, 140.6, 136.3, 129.2, 114.8, 113.7, 72.6, 71.5, 69.9, 66.3, 55.2, 44.1, 37.7, 35.8, 18.1, 18.0, 15.3, 12.4;

HRMS calculated for $C_{26}H_{46}O_4Si$ $(M+Na)^+$ 473.3063; found 473.3029 (FAB).

(5S,7R)-5-((R)-but-3-en-2-yl)-9,9-diisopropyl-7-(2-(4-methoxybenzyloxy)ethyl)-10-methyl-2,4,8-trioxa-9-silaundecane: 3.44b



The secondary alcohol (0.700 g, 1.55 mmol) was dissolved in DCE (5.2 mL) followed by the addition of Et_2*i*PrN (2.00 g, 15.6 mmol) and MOMCl (0.624 g, 7.75 mmol) at rt under argon. The flask was fitted with a reflux condenser under argon, and the reaction was heated to 50 ºC for 3-4 h. Upon completion (monitored by TLC), the reaction was cooled to rt and Et_2O (20 mL) was added followed by slow addition of 10% HCl (2 mL). The layers are separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (3:1 Hex:EtOAc) to afford **3.44b** (0.699 g, 91%) as a clear oil.

$[\alpha]_D^{20}$ = + 3.0 (*c* = 3.74, CH_2Cl_2);

FTIR (neat) 3072, 2943, 1612, 1514, 1247, 1097, 1039 cm^{-1};

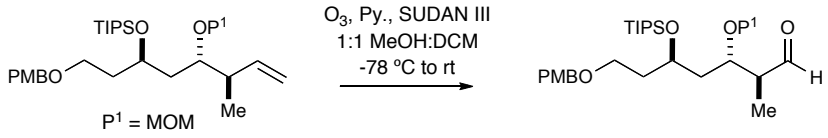
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.74-5.84 (m, 1H), 5.06 (dd, *J* = 2.0, 1.1 Hz, 1H), 5.03 (dd, *J* = 1.7, 1.3 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.9, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 11.6, 1H), 4.05-4.11 (m, 1H), 3.80 (s, 3H), 3.65-3.69 (m, 1H), 3.53-3.57

(m, 2H), 3.37 (s, 3H), 2.46-2.56 (m, 1H), 1.81-1.89 (m, 2H), 1.64 (ddd, J = 14.1, 6.9, 4.4 Hz, 1H), 1.56 (ddd, J = 14.6, 7.0, 5.0 Hz, 1H), 1.04-1.07 (m, 24H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.0, 140.1, 130.7, 129.1, 114.9, 113.6, 96.5, 79.5, 72.6, 68.0, 66.4, 55.6, 55.2, 41.2, 39.1, 37.7, 18.2, 14.4, 12.8;

HRMS calculated for $C_{28}H_{50}O_5Si$ $(M+Na)^+$ 517.3325; found 517.3300 (FAB).

(2S,3S,5R)-7-(4-methoxybenzyloxy)-3-(methoxymethoxy)-2-methyl-5-(triisopropylsilyloxy)heptanal: 3.45b

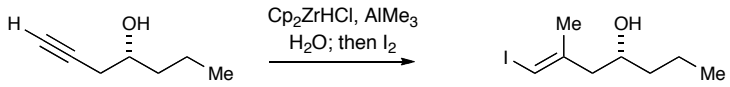


The olefin (0.450 g, 0.910 mmol) was taken up in CH_2Cl_2:MeOH 1:1 (15 mL) followed by the addition of pyridine (0.720 g, 9.10 mmol) and SUDAN III (indicator, ~1 mg) at rt under argon. The solution was cooled to -78 ºC, and a stream of O_3 was lightly bubbled through the solution until a light yellow color persisted. The stream of O_3 was removed and the reaction was stirred until the SM was consumed (monitored by TLC). The flask was flushed with Ar, and Me_2S (3.3 mL) was slowly added. The reaction was slowly warmed to over to rt over a 4 h period. After stirring for 1 h. at rt, Et_2O (40 mL) was added and extracted with sat'd $CuSO_4$ (2x 10 mL), and brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). Flash chromatography (7:2:1 Hex:Et_2O:EtOAc) afforded **3.45b** (0.339 g, 75 %) as an off-white oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.71 (d, J = 1.3 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.71 (d, J = 7.0 Hz, 1H), 4.63 (d, J = 7.0 Hz, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.38 (d, J = 11.6, 1H), 4.09-4.15 (m, 2H), 3.79 (s, 3H), 3.49 (t, J = 6.6 Hz, 2H), 3.34 (s, 3H), 2.72-2.79 (m, 1H), 1.85-1.94 (m, 1H), 1.76-1.84 (m, 2H), 1.47 (ddd, J = 14.1, 7.7, 3.5 Hz, 1H), 1.11 (d, J = 7.0, 3H), 1.03-1.07 (m, 21H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 203.3, 159.0, 130.5, 129.1, 113.6, 96.8, 76.3, 72.6, 67.8, 66.2, 55.7, 55.1, 50.9, 40.3, 37.9, 18.1, 12.8, 9.2.

(*R*,*E*)-1-iodo-2-methylhept-1-en-4-ol: 3.47



Cp_2ZrHCl (3.93 g, 13.40 mmol) was taken up in CH_2Cl_2 (223 mL) followed by the addition of Me_3Al (2.0 M solution in toluene, 41.5 mL, 83.02 mmol) at rt under argon. The solution was cooled to 0 ºC, and H_2O (0.482 mL, 26.78 mmol) was added over 10 min. After an additional 20 minutes of stirring, the alkyne (3.0 g, 26.78 mmol) was cannulated in CH_2Cl_2 (14 mL) and the reaction warmed to rt and stirred for 12 h. The reaction was cooled to -30 ºC, and quenched via cannulation of I_2 (13.6 g, 53.56 mmol) in THF (100 mL). The reaction was warmed to rt and stirred for an additional 20 min., followed by the slow addition of sat'd K_2CO_3 (2 mL) and 30 minutes of stirring (white salts form). Anhydrous Na_2SO_4 is added and the reaction filtered through a pad of Celite, and concentrated (rotary evaporator). Flash chromatography (4:1 Hex:EtOAc) afforded **3.47** (4.2 g, 61 %) as a light yellow oil.

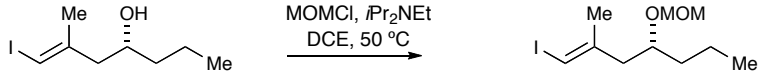
$\mathbf{[\alpha]_D^{20}}$ = –13.6 (*c* 2.7, CH_2Cl_2);

FTIR (neat) 3382, 3056, 2996, 1614, 1273 cm^{-1},

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H), 3.71-3.78 (m, 1H), 2.37 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.30 (dd, *J* = 13.7, 8.5 Hz, 1H), 1.88 (s, 3H), 1.55 (bs, 1H), 1.33-1.51 (m, 4H), 0.94 (t, *J* = 7.0, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 77.2, 68.7, 47.7, 39.1, 24.1, 18.8, 14.0.

(*R*,*E*)-1-iodo-4-(methoxymethoxy)-2-methylhept-1-ene: 3.48



The alcohol (1.56 g, 6.2 mmol) was dissolved in DCE (31 mL) followed by the addition of iPr$_2$NEt (8.0 g, 61.9 mmol) and MOMCl (2.49 g, 31.0 mmol) at rt under argon. The flask was fitted with a reflux condenser under argon, and the reaction was heated to 50 ºC for 3-4 h. Upon completion (monitored by TLC), the reaction was cooled to rt and Et_2O (20 mL) was added followed by slow addition of 10% HCl (10 mL). The layers are separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (4:1 Hex:EtOAc) to **3.48** (1.76 g, 95%) as a clear oil.

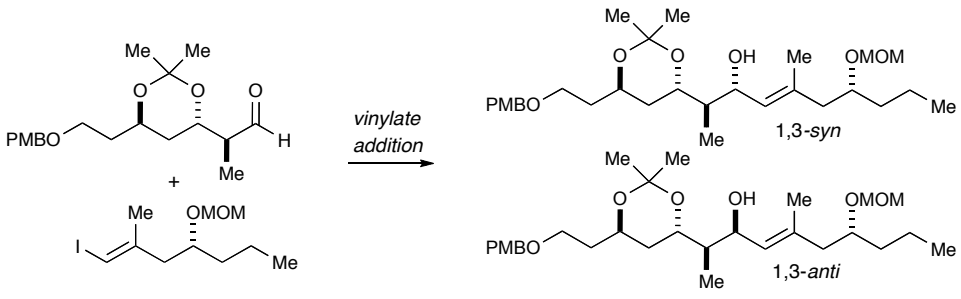
$[\alpha]_D^{20}$ = + 1.2 (*c* 12.8, CH_2Cl_2);

FTIR (neat) 3058, 2956, 2931, 1377, 1274, 1149 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H), 4.63 (d, *J* = 7.1 Hz, 1H), 4.59 (d, *J* = 7.1 Hz, 1H), 3.65-3.72 (m, 1H), 3.33 (s, 3H), 2.43 (dd, *J* = 13.8, 7.3 Hz, 1H), 2.32 (dd, *J* = 13.7, 5.3 Hz, 1H), 1.85 (s, 3H), 1.26-1.49 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H),

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 95.3, 77.1, 74.7, 55.6, 44.8, 36.7, 24.4, 18.5, 14.1.

(2*R*,3*R*,7*R*,*E*)-2-((4*S*,6*R*)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-7-(methoxymethoxy)-5-methyldec-4-en-3-ol (*syn*-3.49a and *anti*-3.49a)



Procedure for vinyl lithiate addition: To a solution of the vinyl iodide (0.036 mg, 0.119 mmol) in Et_2O (0.265 mL) at – 78 ºC was *t*BuLi (1.7 M in pentane, 0.140 mL, 0.231 mmol), and the reaction was immediately warmed to 0 ºC for 25 min. The reaction was recooled to - 78 ºC, and the aldehyde (0.020 g, 0.059 mmol) was slowly added via syringe in Et_2O (0.180 mL, 20 mL rinse). After 1 h, the reaction was quenched at - 78 ºC with NH_4Cl (sat'd, aq), warmed to rt, and the layers separated. The aq. layer was extracted with Et_2O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (3:1 Hex:EtOAc) afforded a 2:1 mixture of 1,3 *anti:syn* (ratio determined by ^1H NMR analysis of crude reaction mixture, 21 mg, combine yield of diastereomers 68%).

Procedure for vinyl Grignard addition: To a solution of the vinyl iodide (0.080 mg, 0.269 mmol) in Et_2O (0.331 mL) at - 78 ºC was added *t*BuLi (1.65 M in pentane, 0.154 mL, 0.253 mmol), and the reaction (pale yellow color) stirred for 15 minutes.

A $MgBr_2$•Et_2O solution (0.3 M in THF, 0.993 mL, 0.298 mmol) was added and the reaction was warmed to 0 ºC and stirred for 15 minutes (white precipitates form). After 15 minutes, the aldehyde (0.050 mg, 0.149 mmol) is cannulated in Et_2O (0.82 mL, 0.100 mL rinse) and the reaction stirred at temperature for 3 h. The reaction was quenched with 4 mL of NH_4Cl (sat'd aq), and the layers separated. The aq. layer was extracted with Et_2O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (3:1 Hex:EtOAc) afforded a 4:1 mixture of 1,3 *anti:syn* (ratio determined by ^1H NMR analysis of crude reaction mixture, 54 mg, combine yield of diastereomers 73%).

Procedure for vinyl magnesiate addition: To a solution of *i*PrMgCl (2.0 M in THF, 0.316 mL, 0.600 mmol) at 0 ºC was added *s*BuLi (1.4 M in cyclohexane, 0.920 mL, 1.20 mmol) and the reaction (light yellow color) stirred for 10 minutes. The vinyl iodide (0.178 mg, 0.600 mmol) in THF (1.0 mL) was cannulated slowly, and the reaction stirred for 30 min at which point it was cooled - 78 ºC. The aldehyde (0.100 g, 0.300 mmol), which was stirred for 20 minutes with $MgBr_2$•Et_2O solution (0.3 M in THF, 2 mL, 0.60 mmol, light heating was used to insure the mixture remained homogenous), was then cannulated to the vinyl magnesiate and stirred for 2 h at - 78 ºC. The reaction was quenched with 5 mL of NH_4Cl (sat'd aq), and the layers separated. The aqueous layer was extracted with Et_2O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (3:1 Hex:EtOAc) afforded a 8:1 mixture

of 1,3 *anti:syn* (ratio determined by ^{1}H NMR analysis of crude reaction mixture, 103 mg, combine yield of diastereomers 68%).

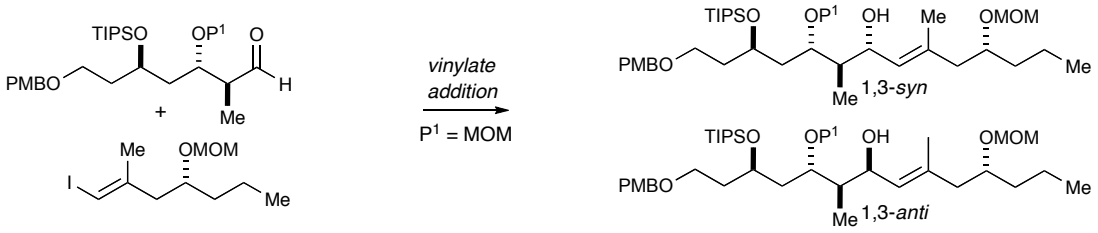
$[\alpha]_D^{20}$ = -4.0 , (*c* , 0.3 CH_2Cl_2);

FTIR (neat) 3448, 2954, 1610, 1512, 1247, 1097 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.5, 2H), 5.34 (*J* = 8.9, 2H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.43-4.46 (m, 1H), 4.41 (s, 2H), 3.98-4.03 (m, 1H), 3.84-3.89 (m, 1H), 3.82 (s, 3H), 3.69-3.75 (m, 1H), 3.48-3.57 (m, 2H), 3.38 (s, 3H), 2.32 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.17 (dd, *J* = 13.7, 6.1 Hz, 1H), 1.81-1.86 (m, 1H), 1.74-1.81 (m, 1H), 1.72 (s, 3H), 1.56-1.71 (m, 2H), 1.43-1.51 (m, 3H), 1.41 (s, 3H), 1.35-1.41 (m, 1H), 1.34 (s, 3H), 0.93-0.96 (m, 3H), 0.83 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.2, 135.1, 130.5, 129.3, 127.9, 113.8, 100.7, 95.4, 75.5, 72.8, 70.9, 70.1, 66.2, 63.8, 55.5, 55.3, 45.3, 44.1, 37.6, 36.7, 35.8, 24.7, 24.5, 18.7, 17.2, 14.2, 11.8.

(5*R*,9*R*,10*R*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(2-(4-methoxybenzyloxy)ethyl)-11-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-9-ol (1,3-*syn*-3.49b and 1,3-*anti*-3.49b)



Procedure for asymmetric zincate addition: The vinyl iodide (0.691 g, 2.32 mmol) was dissolved in Et_2O (3.8 mL) and cooled to -78 ºC followed by the fast dropwise addition of *t*BuLi (1.7 M in pentane, 2.67 mL, 4.54 mmol). The solution was stirred for 40 min. at -78 ºC, followed by the addition of $ZnBr_2$ (0.87 M in Et_2O, 2.87 mL, 2.50 mmol) and transfer to a 0 ºC bath. After 40 minutes, a solution of (1*R,*2*S*)-LiNME [prepared from (*R,S*)-NME (0.416 g, 2.32 mmol) in 11.6 mL toluene at 0 ºC was added *n*BuLi (2.5 M in hexane, 0.928 mL, 2.32 mmol) and stirred for 20 minutes] was slowly cannulated to the flask containing the zincate and stirred for 1 h at 0 ºC. After 1 h, the aldehyde (0.460 g, 0.926 mmol) was cannulated as a solution in toluene (2.81 mL) and stirred for 1.5 h at 0 ºC. The reaction was quenched with 20 mL of NH_4Cl (sat'd aq), and the layers separated. The aqueous layer was extracted with Et_2O (3x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (2:1 Hex:EtOAc) afforded *syn*-**3.49b** as the major diastereomer (11:1 dr , 368 mg, 65 %) as a clear oil.

$[\alpha]_D^{20}$ = +1.1, (*c* , 5.6 CH_2Cl_2);

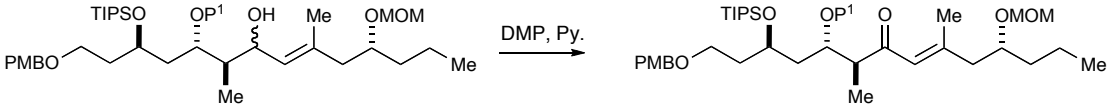
FTIR (neat) 3469, 3103, 2939, 1612, 1514, 1463, 1097, 1040 cm^{-1},

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6, 2H), 5.24 (*J* = 8.6, 1H), 4.55-4.71 (m, 5H), 4.42 (s, 2H), 4.10-4.17 (m, 2H), 4.03-4.07 (m, 1H), 3.81 (s, 3H), 3.67-3.74 (m, 1H), 3.54 (t, *J* = 6.4, 2H), 3.37 (s, 3H), 3.36 (s, 3H), 2.31 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.15 (dd, *J* = 13.3, 7.3 Hz, 1H), 1.84-1.98 (m, 3H), 1.69 (s, 3H), 1.64-1.73 (m, 2H), 1.31-1.51 (m, 4H), 1.01-1.18 (m, 21H), 0.87-0.94 (m, 3H), 0.79 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.1, 135.8, 130.7, 130.0, 129.2, 113.7, 96.6, 95.4, 75.4, 72.6, 70.2, 68.6, 66.7, 55.7, 55.5, 55.2, 45.2, 43.1, 38.7, 38.1, 36.6, 18.4, 18.3, 17.1, 14.2, 12.9, 10.9;

HRMS calculated for $C_{37}H_{68}O_8$ $(M+Na)^+$ 691.4581; found 691.4598 (FAB).

(5*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(2-(4-methoxybenzyloxy)ethyl)-11-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-9-one: 3.50



The alcohol (0.050 g, 0.074 mmol) was taken up in DCM (2.5 mL) followed by the addition of pyridine (0.046 g, 0.590 mmol) and Dess-Martin periodinane (0.063 g, 0.149 mmol) at rt under argon. Upon completion (monitored by TLC), Et_2O (15 mL) was added, and the solution extracted with $NaHCO_3$ (sat'd aq., 2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (1:1 Hex:EtOAc) to give **3.50** (0.049 g, 98%) as a clear oil.

$[\alpha]_D^{20}$ = +24.1 (*c* = 2.1, CH_2Cl_2);

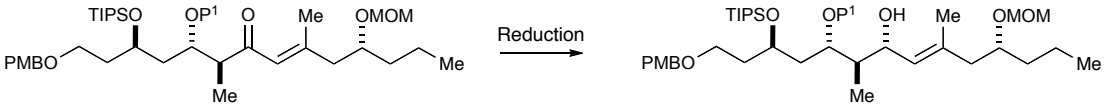
FTIR (neat) 1680, 1612, 1512, 1099, 1037 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.24 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.19 (s, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.66 (d, *J* = 7.0, 1H), 4.63 (s, 2H), 4.39 (d, *J* = 1.8 Hz, 2H), 4.02-4.13 (m, 2H), 3.80 (s, 3H), 3.72-3.79 (m, 1H), 3.46-3.53 (m, 2H), 3.35 (s, 6H), 2.98 (dq, *J* = 6.9, 1.7 Hz, 1H), 2.39 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.23 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.14 (s, 3H), 1.76-1.94 (m, 2H), 1.59-1.68 (m, 1H), 1.31-1.49 (m, 4H), 0.97-1.10 (m, 24H), 0.92 (t, *J* = 6.9, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 201.6, 159.0, 156.0, 130.7, 129.2, 125.3, 113.7, 97.0, 95.4, 75.4, 72.6, 67.8, 66.5, 55.8, 55.5, 55.2, 51.8, 46.9, 39.2, 38.1, 36.8, 19.9, 18.5, 18.2, 14.1, 12.9, 10.4;

HRMS calculated for $C_{37}H_{66}O_8$ $(M+Na)^+$ 689.4425; found 689.4425 (FAB).

(5*R*,9*R*,10*R*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(2-(4-methoxybenzyloxy)ethyl)-11-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-9-ol: 3.49b

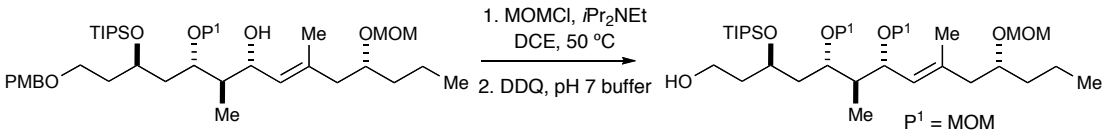


Reduction with DIBAL-H: To a solution of the ketone (0.050 g, 0.0746 mmol) in toluene (0.746 mL) was slowly added DIBAL-H (1.0M in toluene, 0.149 mL) at -78 ºC. After two hours of stirring at -78 ºC, the reaction was quenched with NH_4Cl (sat'd, aq.), and the reaction warmed to rt while stirring. The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (2:1 Hex:EtOAc) to afford the title compound as a 5:1 mixture (determined by ^1H NMR of crude reaction) of 1,3 *anti:syn* (0.040 g, 80%) as a clear oil.

Reduction with $LiAlH_4$/LiI: To a solution of the ketone (0.030 g, 0.045 mmol) in Et_2O (0.563 mL) was added LiI (0.06 g, 0.45 mmol) at 0 ºC (solution turns reddish-brown color). Once the LiI is completely dissolved (< 5 min), the reaction was cooled to -78 ºC and a solution of $LiAl_4H$ (1.0 M in Et_2O, 0.450 mL) was slowly added. After twenty minutes, the reaction was quenched with sodium-potassium tartrate (sat'd, aq.), and the reaction warmed to rt while stirring. The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated

(rotary evaporator). The mixture was pushed through a short plug of silica (2:1 Hex:EtOAc) to afford the title compound as a 4.3:1 mixture (determined by ^{1}H NMR of crude reaction) of 1,3 *syn:anti* **3.49b** (0.028 g, 90%) as a clear oil.

(3*R*,5*S*,6*S*,7*R*,11*R*,*E*)-5,7,11-tris(methoxymethoxy)-6,9-dimethyl-3-(triisopropylsilyloxy)tetradec-8-en-1-ol: 3.52



The secondary alcohol (0.05 g, 0.074 mmol) was dissolved in DCE (300 mL) followed by the addition of *i*Pr_2NEt (0.096 g, 0.740 mmol) and MOMCl (0.030 g, 0.372 mmol) at rt under argon. The flask was fitted with a reflux condenser under argon, and the reaction was heated to 50 ºC for 3-4 h. Upon completion (monitored by TLC), the reaction was cooled to rt and Et_2O (2 mL) was added followed by slow addition of 10% HCl (1 mL). The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (1:1 Hex:EtOAc) to the MOM-protected ether (0.044 g, 82%) as a clear oil. The MOM- protected PMB ether (0.05 g, 0.070 mmol) was taken up in CH_2Cl_2 (1.4 mL) followed by the addition of pH buffer solution (0.07 mL) and DDQ (0.032 g, 0.139 mmol) at rt. Upon completion (~1 h, monitored by TLC), Et_2O (2 mL) was added followed by $NaHCO_3$ (sat'd aq, 1 mL). The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). Flash chromatography (2:1 Hex:EtOAc) afforded **3.52** (0.038 g, 92%) as a clear oil.

$[\alpha]_D^{20}$ = –26.0 (*c* = 0.77, CH_2Cl_2);

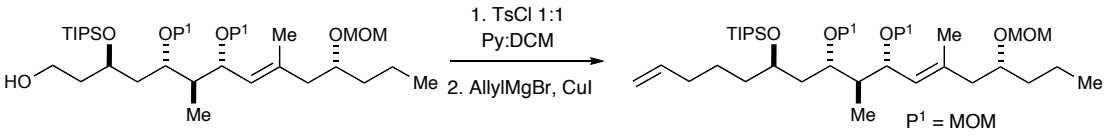
FTIR (neat) 3507, 2941, 2359, 2341, 1097, 1037 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.02 (d, *J* = 9.4, 1H), 4.61-4.68 (m, 6H), 4.38 (d, *J* = 6.5 Hz, 1H), 4.21-4.24 (m, 1H), 4.13 (dd, *J* = 9.2, 9.1, 1H), 4.00-4.03 (m, 1H), 3.85-3.90 (m, 1H), 3.75-3.81 (m, 1H), 3.68-3.73 (m, 1H), 3.39-3.51 (m, 9H), 2.52 (bs, 1H), 2.34 (dd, *J* = 13.3, 5.8 Hz, 1H), 2.17 (dd, *J* = 13.3, 5.4 Hz, 1H), 2.05-2.11 (m, 1H), 1.92-1.98 (m, 1H), 1.84-1.90 (m, 1H), 1.75-1.79 (m, 2H), 1.70 (d, *J* = 1.5 Hz, 3H), 1.42-1.48 (m, 3H), 1.33-1.37 (m, 1H), 1.07-1.10 (m, 21H), 0.90 (t, *J* = 6.9, 3H), 0.83 (d, *J* = 8.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.1, 126.9, 96.7, 95.4, 93.2, 77.1, 75.5, 73.2, 70.0, 59.6, 56.0, 55.7, 55.5, 45.1, 41.4, 39.1, 36.7, 36.5, 18.4, 18.2, 17.1, 14.1, 12.7, 10.5;

HRMS calculated for $C_{31}H_{64}O_8Si$ $(M+Na)^+$ 615.4268; found 615.4222 (FAB).

(5*R*,9*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-9,11-bis(methoxymethoxy)-7,10,16-trimethyl-13-(pent-4-enyl)-5-propyl-2,4,14-trioxa-15-silaheptadec-7-ene: 3.54



The primary alcohol (0.045 g, 0.076 mmol) was taken up in CH_2Cl_2 (0.365 mL) and pyridine (0.365 mL), and TsCl was added (0.029 g, 0.152 mmol). The reaction was stirred until starting material was no longer being consumed (monitored by TLC). The reaction was quenched (aq NH_4Cl), the layers separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (3:1 Hex:EtOAc) to afford the tosylate (0.030 g, 53 %) as a clear oil, which was immediately used. The tosylate (0.030 g, 0.025 mmol) was taken up in THF (0.500 mL) and CuI (0.013 g, 0.06 mmol) was added. The solution was cooled to – 50 ºC and allylMgBr (1.0 M in Et_2O, 0.240 mL) was added. The reaction was warmed to rt and stirred for 3 h, at which time it was quenched with NH_4Cl (sat'd, aq), layers separated, and the aqueous layer extracted with Et_2O (2 x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). Flash chromatography (2:1 Hex:EtOAc) afforded **3.54** (0.024 g, 80%, ~1:1 ratio with SM) as a clear oil.

$[\alpha]_D^{20} = -18.4$ ($c = 0.3$, CH_2Cl_2);

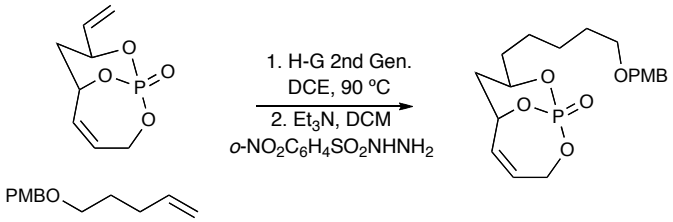
FTIR (neat) 3082, 2939, 2866, 1464, 1151, 1097, 1040 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.76-5.8 (m, 1H), 4.98-5.04 (m, 2H), 4.93-4.97 (m, 1H), 4.73 (d, *J* = 6.7 Hz, 1H), 4.64-4.69 (m, 3H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.38 (d, *J* = 6.7 Hz, 1H), 4.15-4.19 (m, 1H), 4.12 (dd, *J* = 9.4, 9.3 Hz, 1H), 4.02-4.07 (m, 1H), 3.68-3.73 (m, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 2.35 (dd, *J* = 13.4, 5.6 Hz, 1H), 2.17 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.12-2.17 (m, 1H), 2.03-2.08 (m, 2H), 1.71 (d, *J* = 0.90 Hz, 3H), 1.42-1.65 (m, 14H), 1.04-1.09 (m, 21H), 0.88-1.92 (m, 3H), 0.82 (d, *J* = 7.0 Hz, 3H),

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 139.1, 138.3, 127.4, 114.7, 97.8, 95.7, 93.1, 77.3, 75.8, 73.1, 69.9, 56.2, 56.0, 55.8, 45.3, 41.9, 38.4, 36.8, 36.5, 34.3, 24.4, 18.7, 18.6, 18.5, 17.4, 14.4, 13.2, 10.6.

HRMS calculated for $C_{34}H_{68}O_8Si$ $(M+Na)^+$ 639.4632; found 639.4641 (FAB).

Partially Hydrogenated PMB-Protected derived Bicyclic Phosphate: 3.56



The bicyclic phosphate (1.36 g, 6.67 mmol) was taken up in DCE (degassed 10 min. with Ar, 133.4 mL) followed by the addition of the PMB-ether protected terminal olefin (1.92 g, 10.0 mmol), and Hoveyda-Grubbs 2nd generation catalyst (0.208, 0.333 mmol) under argon at rt. The flask was fitted with a reflux condenser under argon, and lowered into a preheated 90 ºC bath for 2 h. Upon completion (monitored by ^{31}P NMR analysis of aliquots of the reaction), the reaction was concentrated (rotary evaporator). Flash chromatography (1:2 Hex:EtOAc) afforded the cross-metathesis product (2.01 g, 82%, >20:1 *E*:*Z*) as a light brown oil. The cross-metathesized phosphate intermediate (1.5 g, 4.10 mmol) was taken up in CH_2Cl_2 (82 mL) followed by the addition of Et_3N (18 mL, ~2 mL per gram of NBS-H), and NBS-H (8.90 g, 41.0 mmol). After the reaction was stirred for 12 h, EtOAc (150 mL) was added, and the reaction extracted with $NaHCO_3$ (sat'd aq, 2x). The aq layer was reextracted with EtOAc (1x). The combined organic layers were dried (anhydrous Na_2SO_4) and concentrated. Flash chromatography (1:2 Hex:EtOAc) afforded **3.56** (1.13 g, 75%) as a clear oil and 300 mg of starting material.

$\mathbf{[\alpha]_D^{20}}$ = +50.3 (*c* = 5.4, CH_2Cl_2);

FTIR (neat) 2936, 1612, 1512, 1300, 1247, cm^{-1};

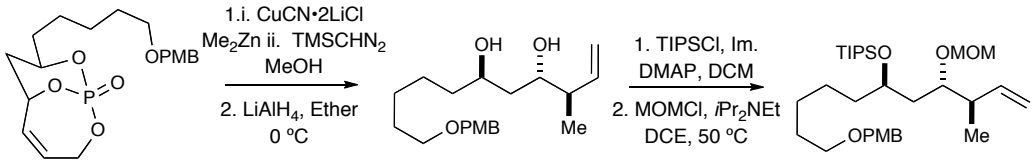
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.28, (d, J = 8.6, 2H), 6.98 (d, J = 8.7, 2H), 6.03 (dddd, J = 11.9, 6.7, 3.0, 2.1 Hz, 1H), 5.59 (ddd, 11.8, 3.8, 2.5 Hz, 1H), 5.18 (d, J = 24.3 Hz, 1H), 4.98-5.05 (m, 1H), 4.55-4.61 (m, 1H), 4.45 (s, 2H), 4.37 (ddd, J = 27.6, 14.7, 6.7 Hz, 1H), 3.82 (s, 3H), 3.45 (t, J = 6.5 Hz, 2H), 2.18 (ddd, J = 14.6, 11.9, 6.3 Hz, 1H), 1.68-1.81 (m, 2H), 1.35-1.80 (m, 7H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 158.9, 130.5, 129.7, 129.0, 127.7, 113.5, 77.13 (d, J_{CP} = 6.6 Hz), 76.6 (d, J_{CP} = 6.7 Hz), 72.3, 69.6, 62.7 (d, J_{CP} = 6.4 Hz), 55.1, 35.4 (d, J_{CP} = 9.4 Hz), 34.6 (d, J_{CP} = 5.9 Hz), 29.3, 25.6, 24.2;

^{31}P NMR (162 MHz, $CDCl_3$) δ -2.96;

HRMS calculated for $C_{19}H_{27}O_6P$ $(M+Na)^+$ 405.1443; found 405.1427 (FAB).

(5*S*,7*R*)-5-((*R*)-but-3-en-2-yl)-9,9-diisopropyl-7-(5-(4-methoxybenzyloxy)pentyl)-10-methyl-2,4,8-trioxa-9-silaundecane: 3.60



Following cuprate addition protocol, CuCN (2.11 g, 23.56 mmol) and LiCl (2.0 g, 47.12 mmol) were stirred in THF (24 mL) for 20 min at rt, then cooled to -30 ºC. A solution of Me_2Zn (1.2 M in toluene, 19.6 mL, 23.6 mmol) was added (stirred for 30 minutes), followed by phosphate addition (2.08 g, 5.62 mmol) in THF (6 mL, 0.4 mL rinse), and the solution immediately removed from the bath and stirred at rt for 2 h. Reaction workup, methylation, and flash chromatography (1:1 Hex:EtOAc) provided the monocyclic phosphate (2.05 g, 91 % yield) as a clear oil, and as a ~1:1 mixture of diastereomers at phosphorus. Following phosphate cleavage protocol, to the 1:1 diastereomeric phosphates (2.05 g, 5.13 mmol) in Et_2O (86 mL) was added $LiAlH_4$ (0.486 g, 12.8 mmol) at 0 ºC. Reaction workup and flash chromatography (1:1 Hex:EtOAc) provided the diol (1.59 g, 92% yield) as a clear oil. Following monosilylation protocol, the diol (1.39 g, 4.13 mmol) in CH_2Cl_2 (28 mL) was added imidazole (1.69 g, 24.8 mmol) and DMAP (50 mg, 0.413 mmol), followed by TIPSCl (2.39 g, 12.4 mmol). Reaction workup and flash chromatography (9:1 Hex:Et_2O, then 5:1 Hex:EtOAc) provided monosilylated product (1.36 g, 80%) as a clear oil. Following MOM protection protocol, to the secondary alcohol (0.830g, 1.68 mmol) in DCE (4.2 mL) and Et_2iPrN (2.17 g, 16.8 mmol) was added MOMCl (0.678 g, 8.42

mmol). After heating at 50 ºC for 3-4 h, reaction workup and flash chromatography (2:1 Hex:EtOAc) provided **3.60** (0.860 mg, 95%) as a clear oil.

$[\alpha]_D^{20} = -4.2$ ($c = 3.3$, CH_2Cl_2);

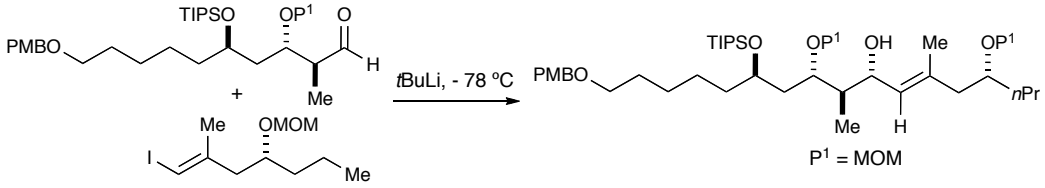
FTIR (neat) 3072, 2939, 1514, 1464, 1245, 1097, 1040 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.26 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.77-5.86 (m, 1H), 5.09 (dd, J = 4.1, 1.4 Hz, 1H), 5.05 (d, J = 1.1 Hz, 1H), 4.71 (d, J = 6.8 Hz, 1H), 4.68 (d, J = 6.8, 1H), 4.45 (s, 2H), 3.92-3.99 (m, 1H), 3.82 (s, 3H), 3.68-3.73 (m, 1H), 3.49 (t, J = 6.5 Hz, 2H), 3.39 (s, 3H), 2.51-2.57 (m, 1H), 1.34-1.64 (m, 10H), 1.02-1.16 (m, 24H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.1, 140.2, 130.7, 129.1, 114.8, 113.7, 96.7, 79.7, 72.5, 70.1, 70.1, 55.6, 55.1, 41.4, 38.5, 37.9, 29.7, 26.5, 24.5, 18.2, 18.2, 14.3, 12.9;

HRMS calculated for $C_{31}H_{56}O_5Si$ $(M+Na)^+$ 559.3795; found 559.3749 (FAB).

(5*R*,9*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(5-(4-methoxybenzyloxy)pentyl)-9-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-11-ol: 3.62



To a solution of vinyl iodide (0.140 mg, 0.469 mmol) in Et_2O (1.42 mL) at -78 ºC was added *t*BuLi (1.7 M in pentane, 0.529 mL, 0.901 mmol), and the reaction was immediately warmed to 0 ºC for 25 min. The reaction was recooled to -78 ºC, and the aldehyde (0.101 g, 0.188 mmol) was slowly added via syringe in Et_2O (0.312 mL, 30 mL rinse). After 1 h, the reaction was quenched at -78 ºC with NH_4Cl (sat'd, aq), warmed to rt, and the layers separated. The aqueous layer was extracted with Et_2O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (3:1 Hex:EtOAc) afforded a 1:1 mixture of **3.62** (ratio determined by ^{1}H NMR analysis of crude reaction mixture, 94 mg, combine yield of diastereomers 70 %). Separation of diastereomers was achieved using a Horizon Biotage flash chromatography system (Biotage Si 12M column, 5-10 % EtOAc gradient in hexanes). Compound data for 1,3-*syn* **3.62**.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6, 2H), 5.28 (J = 8.7, 2H), 4.63-4.73 (m, 4H), 4.43 (s, 2H), 4.18 (dd, J = 9.2, 9.0 Hz, 1H),

4.05-4.10 (m, 1H), 3.98-4.03 (m, 1H), 3.85 (s, 3H), 3.70-3.75 (m, 1H), 3.45 (t, J = 6.5, 2H), 3.35-3.43 (m, 6H), 2.34 (dd, J = 13.2, 5.8 Hz, 1H), 2.19 (dd, J = 13.3, 7.4 Hz, 1H), 1.73 (s, 3H), 1.31-1.69 (m, 14 H), 1.04-1.12 (m, 21 H), 0.89-0.98 (m, 3H), 0.80 (d, J = 6.9 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.1, 135.8, 130.7, 129.9, 129.2, 113.7, 96.7, 95.4, 77.8, 75.4, 72.5, 70.6, 70.3, 70.1, 55.7, 55.5, 45.2, 43.1, 38.3, 38.3, 36.6, 29.8, 26.6, 24.9, 18.4, 17.1, 14.1, 13.0, 12.9, 10.9;

HRMS calculated for $C_{40}H_{74}O_8Si$ $(M+Na)^+$ 733.5051; found 733.5031 (FAB).

(5*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(5-(4-methoxybenzyloxy)pentyl)-11-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-9-one: SI2

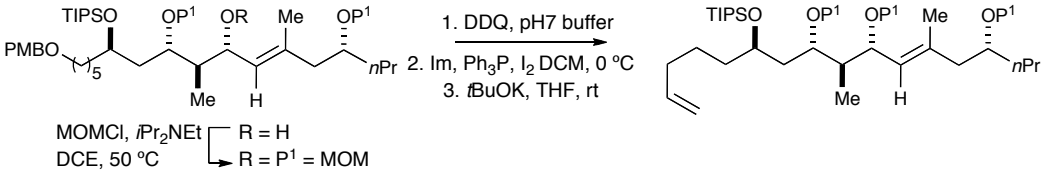
To a solution of allylic alcohol (0.057 mg, 0.080 mmol) in CH_2Cl_2 (2.7 mL) at rt was added pyridine (53 μL, 0.656 mmol) followed by DMP (0.075 mg, 0.176 mmol). The reaction was allowed to stir until the disappearance of starting material (via TLC, ~1h). The reaction was then diluted with Et_2O and washed with $NaHCO_3$ (2X) and the layers separated. The aq. layer was extracted with Et_2O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (5:1 Hex:EtOAc) afforded 51 mg of the desired ketone in 90% yield as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.6, 2H), 6.21 (s, 1H), 4.70 (q, J = 12.2, 6.9 Hz, 2H), 4.64 (s, 2H), 4.44 (s, 2H), 4.06-4.12 (m, 1H), 3.92-4.00 (m, 1H), 3.82 (s, 3H), 3.74-3.80 (m, 1H), 3.45 (t, J = 6.6, 2H), 3.37 (d, J = 2.3, 6H), 2.96-3.05 (m, 1H), 2.42 (dd, J = 13.4, 6.4 Hz, 1H), 2.25 (dd, J = 15.3, 8.6 Hz, 1H), 2.15 (s, 3H), 1.31-1.69 (m, 14 H), 1.09 (d, J = 6.9 Hz, 3H), 1.04-1.09 (m, 21 H), 0.89-0.98 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 201.7, 159.1, 156.0, 130.7, 129.2, 125.4, 113.7, 97.2, 95.4, 77.3, 75.4, 72.5, 70.1, 69.8, 60.4, 55.8, 55.6, 55.2, 52.0, 46.9, 38.7, 38.3, 36.7, 29.8, 26.6, 24.8, 19.9, 18.5, 18.3, 18.3, 14.2, 14.1, 13.0;

HRMS calculated for $C_{40}H_{72}O_8Si$ $(M+NH_4)^+$ 726.5340; found 726.5358 (FAB).

(5*R*,9*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-9,11-bis(methoxymethoxy)-7,10,16-trimethyl-13-(pent-4-enyl)-5-propyl-2,4,14-trioxa-15-silaheptadec-7-ene: 3.54



Reduction with $LiAlH_4$/LiI: To a solution of the ketone (0.030 g, 0.045 mmol) in Et_2O (0.563 mL) was added LiI (0.06 g, 0.45 mmol) at 0 ºC (solution turns reddish-brown color). Once the LiI is completely dissolved (< 5 min), the reaction was cooled to -78 ºC and a solution of $LiAl_4H$ (1.0 M in Et_2O, 0.450 mL) was slowly added. After twenty minutes, the reaction was quenched with sodium-potassium tartrate (sat'd, aq.), and the reaction warmed to rt while stirring. The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (2:1 Hex:EtOAc) to afford the title compound as a 4.5:1 mixture (determined by ^{1}H NMR of crude reaction) of alcohol (0.028 g, 90%) as a clear oil. Following the same procedure for MOM protection, the alcohol (0.032 g, 0.045 mmol) was dissolved in DCE (0.225 mL) followed by the addition of *i*Pr_2NEt (0.061 g, 0.468 mmol) and MOMCl (0.019 g, 0.234 mmol) at rt under argon. Reaction workup and flash chromatography (4:1 Hex:EtOAc) afforded the MOM-protected ether (0.031 g, 95%). Following the same procedure of PMB removal, tri-MOM protected PMB ether (0.031 g, 0.041 mmol) was taken up in CH_2Cl_2 (0.820 mL) followed by the addition

of pH 7 phosphate buffer solution (0.043 mL) and DDQ (0.019 g, 0.082 mmol) at rt. Reaction workup and flash chromatography (2:1 Hex:EtOAc) afforded the primary alcohol (0.024 g, 92%) as a clear oil. The primary alcohol was taken up in CH_2Cl_2 (0.139 mL), followed by the addition of imidazole (0.003 mg, 0.0417 mmol), Ph_3P (0.011 mg, 0.042 mmol). The reaction was cooled to 0 ^oC and I_2 (0.007 mg, 0.0278 mmol) was added. Upon completion (reaction monitored by TLC, ~30 minutes), the reaction was concentrated and subjected to flash chromatography (3:1 Hex:EtOAc) to afford the primary iodide (8.8 mg, 84 %). The iodide was subsequently taken up in THF (0.140 mL) and a solution of *t*BuOK (1.0 M in THF, 0.018 mL) at rt. Upon completion (reaction monitored by TLC, ~30 min.), the reaction was concentrated and subjected to flash chromatography (3:1 Hex:EtOAc) to afford **3.54** (0.007 mg, 94%).

$[\alpha]_D^{20} = -18.4$ ($c = 0.3$, CH_2Cl_2);

FTIR (neat) 3082, 2939, 2866, 1464, 1151, 1097, 1040 cm^{-1};

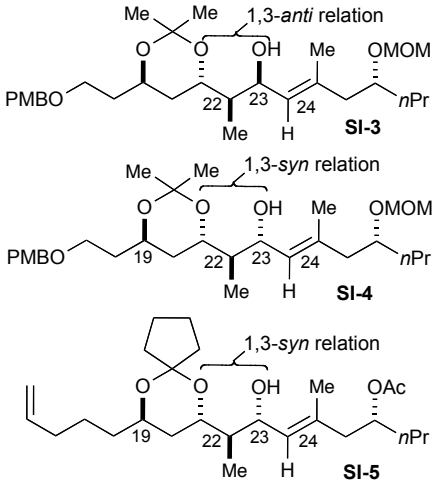
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.76-5.8 (m, 1H), 4.98-5.04 (m, 2H), 4.93-4.97 (m, 1H), 4.73 (d, J = 6.7 Hz, 1H), 4.64-4.69 (m, 3H), 4.62 (d, J = 6.8 Hz, 1H), 4.38 (d, J = 6.7 Hz, 1H), 4.15-4.19 (m, 1H), 4.12 (dd, J = 9.4, 9.3 Hz, 1H), 4.02-4.07 (m, 1H), 3.68-3.73 (m, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 2.35 (dd, J = 13.4, 5.6 Hz, 1H), 2.17 (dd, J = 13.3, 7.3 Hz, 1H), 2.12-2.17 (m, 1H), 2.03-2.08 (m, 2H), 1.71 (d, J = 0.90 Hz, 3H), 1.42-1.65 (m, 14H), 1.04-1.09 (m, 21H), 0.88-1.92 (m, 3H), 0.82 (d, J = 7.0 Hz, 3H),

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 139.1, 138.3, 127.4, 114.7, 97.8, 95.7, 93.1, 77.3, 75.8, 73.1, 69.9, 56.2, 56.0, 55.8, 45.3, 41.9, 38.4, 36.8, 36.5, 34.3, 24.4, 18.7, 18.6, 18.5, 17.4, 14.4, 13.2, 10.6.

HRMS calculated for $C_{34}H_{68}O_8Si$ $(M+Na)^+$ 639.4632; found 639.4641 (FAB).

Stereochemical Analysis of the C23 Carbinol Position.

The stereochemical assignment for the C23 carbinol center was based on vicinal ^{1}H coupling constant analysis of 1,3-syn and 1,3-anti isomers **SI3** and **SI4** respectively, with the structurally similar C15-C30 fragment reported by Leighton and coworkers (**SI5**, Figure SI-1). Key markers include the C22 methyl substituent, C23 proton, and C24 vinylic proton. Proton-proton interactions and coupling patterns were confirmed by 2D-COSY analysis. Good correlation was found between *syn*- **SI3** and Leighton's **SI5**, with both C22-Me and C24-H chemical shifts being in close agreement. Most notably however are the identical shifts (4.26 to 4.27 ppm) and coupling constants (8.7 to 8.6 Hz) for the C23-H of **SI3** and **SI5**.



	C22-Me	C23-H	C24-H
***Anti*-Fragment SI3**	δ = 0.82 ppm *J* = 7.1 Hz	δ = 4.47 ppm *J* = nd	δ = 5.34 *J* = 8.9 Hz
***Syn*-Fragment SI4**	δ = 0.72 ppm *J* = 6.9 Hz	δ = 4.27 ppm *J* = 8.6, 8.6 Hz	δ = 5.22 ppm *J* = 9.1 Hz
Literature Values Fragment SI5	δ = 0.68 ppm *J* = 6.9 Hz	δ = 4.26 ppm *J* = 8.7, 8.7 Hz	δ = 5.15 ppm *J* = 9.0 Hz

Figure SI-2: C23 stereochemical assignment.

These coupling constants are in accord with the analysis of Weldman, Boger, and others, who have proposed both rigid twisted-boat (not shown) and chair confirmation H-bonding models (**SI6**) to elucidate the C10-C11 relative

stereochemistry in cytostatin (Figure SI-2).[1] **SI6** shows that the largely *anti*-periplanar relationship between H_{10} and H_{11} results in larger coupling constants of 8-10 Hz. Analogously, fragment **SI6** similarly could be imagined as existing in a chair conformation (**SI7**) favoring the all-equatorial arrangement of C21-R, C22-Me, and C23-vinyl groups. The preferred conformation of the C23-vinyl group would further explain the identical coupling constants observed between the H23-H22 and H23-H24 protons of **SI3**.

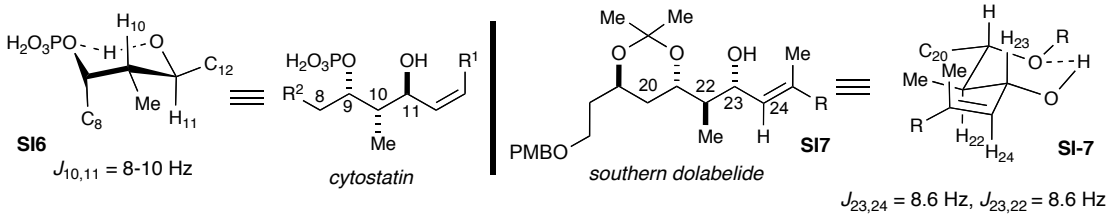
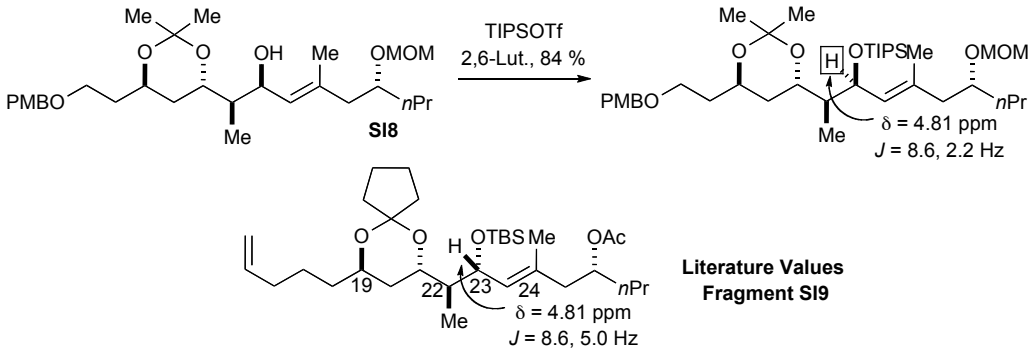


Figure SI-2: H-Bonding Chair Model

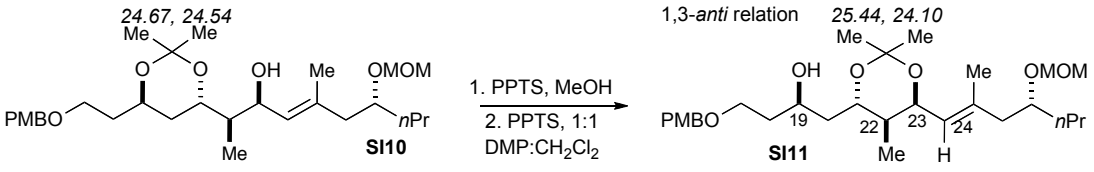
While the coupling constant of the *syn*-relation of C23-H could not be extrapolated from **SI8**, TIPS protection (84 %) cleanly afforded an autonomous C23-H signal for ^{1}H analysis. The silylated C23 carbinol position with 1,3-anti 3.44 has an 8.6 Hz coupling with the adjacent vinylic proton, and an anticipated smaller coupling of 2.2 Hz with the syn-C22 proton. This correlates well with Leighton and coworkers reported TBS protected 1,3-syn **SI9**, in which the C22-H had the same chemical shift as the C22-H of 3.21 (4.81 ppm), but with a larger 5.0 Hz coupling constant with the adjacent C22 proton.

Scheme SI-1:



Finally, removal of the ketal, followed by acetonide formation provided a mixture of starting material and regioisomeric acetonide **SI11** (Scheme SI-2). In accordance with Rychnovsky-Evans acetonide analysis,[2] ^{13}C analysis of the 1,3-anti isomer **SI11** contained acetonide peaks at 25.44 ppm and 24.10 ppm, indicative of the newly formed 1,3-anti acetonide. The difference in chemical shifts of 25.44 ppm and 24.10 ppm (D = 1.34 ppm) for **SI10** compared with that of 24.67 ppm and 24.54 ppm (D = 0.33 ppm) for 3.46 is consistent with previous reports for larger methyl acetonide shifts with 1,3-anti acetonides for polyketide fragments, in which a methyl group is contained within the acetonide ring.

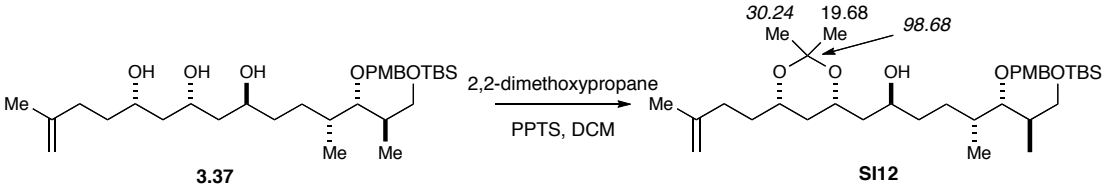
Scheme SI-2



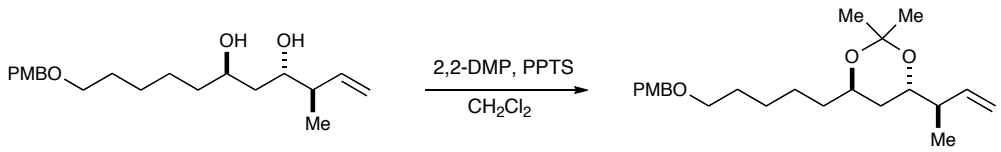
Stereochemical Analysis of the C11 Carbinol Position.

Finally, isolation of the major diastereomer of the reduction, followed by acetonide formation provided a mixture of **3.37** and regioisomeric acetonide (Scheme SI-1). In accordance with Rychnovsky-Evans acetonide analysis,[2] ^{13}C analysis of the **SI12** contained acetonide peaks at 30.24 ppm, 19.68 ppm, and 98.68, indicative of the newly formed 1,3-*syn* acetonide.

Scheme SI-3



(4*S*,6*R*)-4-((*R*)-but-3-en-2-yl)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxane: 3.65



Diol **3.59** (391 mg, 1.09 mmol) was taken up in CH_2Cl_2 (4 mL) at room temperature. 2,2-Dimethoxypropane (4 mL) and pyridinium *p*toluenesulfonate (28 mg, 0.10 mmol) were added respectively and clear solution was stirred until completion. Reaction was quenched with $NaHCO_3$ and diluted with Et_2O. Aqueous layer was extracted three times with Et_2O (5 mL portions) and organics were washed once with brine (5 mL). The collected organic layer was dried with Na_2SO_4 and concentrated in vacuo. **3.65** was isolated using flash chromatography (19:1, Hexanes:Ethyl Acetate) as a clear oil in 98% yield (408 mg, 1.08 mmol).

$[\alpha]_D$ -36.3 (*c* = 0.4, CH_2Cl_2);

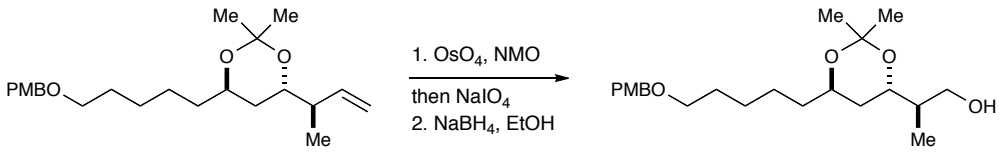
FTIR (neat) 2983, 2935, 2856, 1612, 1512, 819 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.25 (d, *J* =8.4, 2H), 6.87 (d, *J* =8.6, 2H), 5.83 (ddd, *J* =17.4, 10.5, 7.3, 1H), 5.03 (ddd, *J* =17.5, 11.0, 2.6, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.66-3.74 (m, 1H), 3.63 (ddd, *J* =9.7, 6.3, 1H), 3.45 (t, *J* =6.6, 2H), 2.18-2.26 (m, 1H), 1.64-1.71 (m, 1H), 1.53-1.63 (m, 2H), 1.55-1.35 (m, 7H), 1.32 (s, 6H), 1.30-1.24 (m, 2H), 0.98 (d, *J* =6.9, 3H);

^{13}C NMR ($CDCl_3$, 500 MHz) δ ppm 159.1, 140.9, 130.7, 129.3, 114.4, 113.7, 100.3, 72.5, 70.1, 70.0, 66.8, 55.3, 42.1, 36.3, 35.9, 29.7, 26.2, 25.3, 24.7, 24.4, 15.3.

HRMS calculated for $C_{23}H_{36}O_4$ (M+Na) 319.0198; found 320.1426 (ESI).

(*R*)-2-((4*S*,6*R*)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-1-ol: 3.66



Olefin was taken up in *t*BuOH:THF:H_2O (10:2:1, 3.5 mL) at room temperature. *N*-methyl morpholine oxide (112 mg, 0.96 mmol) and OsO_4 (0.19 mL, 0.03 mmol, 4% aq. in H_2O) and stirred for approximately 12 h until olefin was completely consumed. The mixture was then diluted with phosphate buffer pH 7 (2x's the volume of *t*BuOH) and sodium periodinate was added (911 mg, 4.26 mmol). The reaction was stirred vigorously for approximately 2 h when diol was completely consumed. The milky white solution was partitioned with 1:1 Et_2O:H_2O and aqueous layer was extracted three times with Et_2O (5 mL portions). Collected organics were washed once with brine (5 mL portion) was then dried with Na_2SO_4. After concentrating in vacuo, product was isolated using flash chromatography (5:1, Hexanes:Ethyl Acetate). The title compound was a gold oil.

The resultant aldehyde was taken up in ethanol (3.5 mL) and cooled to 0 °C. Sodium borohydride (65 mg, 1.71 mmol) was added and the reaction was slowly brought back to room temperature. Upon completion (~45 min), the solution was partitioned with 2:1, Et_2O:H_2O. The aqueous layer was extracted three times with Et_2O (5 mL portions) and collected organics were washed once with brine (5 mL). After drying the organics with $MgSO_4$, **3.66** (290 mg, 0.77 mmol) was isolated using

flash chromatography (1:2, Hexanes:Ethyl Acetate) as clear oil in 81% yield over two steps.

$[\alpha]_D$ -0.26 (*c* 0.18, CH_2Cl_2);

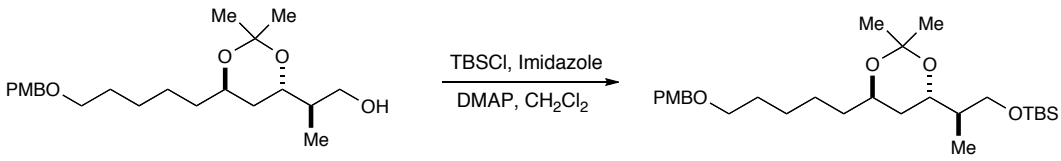
FTIR (neat 3442, 2933, 2856, 1612, 1512, 819 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.25 (d, *J* = 8.5, 2H), 6.87 (d, *J* = 8.6, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.79-3.73 (m, 1H), 3.68 (ddd, *J* = 9.2, 6.3, 1H), 3.58 (d, *J* = 5.1, 2H), 3.43 (t, *J* = 6.6, 2H), 3.08 (s, 1H), 1.80-1.20 (m, 11H), 1.38 (s, 3H), 1.33 (s, 3H), 0.82 (d, *J* = 7.0, 3H);

^{13}C NMR ($CDCl_3$, 500 MHz) δ ppm 159.1, 130.8, 129.2, 113.7, 100.5, 73.1, 72.5, 70.1, 68.3, 66.6, 55.3, 40.6, 37.9, 35.8, 29.7, 26.2, 25.2, 24.6, 24.6, 12.7.

HRMS calculated for $C_{22}H_{36}O_5$ (M+Na) 403.2460; found 403.2413 (ESI).

***tert*-butyl((*R*)-2-((4*S*,6*R*)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxan-4-yl)propoxy)dimethylsilane: SI13**



Alcohol **3.66** (290 mg, 0.77 mmol) was taken up in CH_2Cl_2 (5.1 mL) at room temperature. Imidazole (79 mg, 1.16 mmol), DMAP (10 mg, 0.08 mmol) and TBSCl (138 mg, 0.92 mmol) were added respectively and reaction was run until completion (about 90 min). Reaction was quenched with NH_4Cl and diluted with Et_2O. Aqueous layer was extracted Et_2O three times (5 mL) and organics were washed once with brine (5 mL). Collected organics were dried with Na_2SO_4 and concentrated in vacuo. **SI13** was isolated using flash chromatography (20:1, hexanes:ethyl acetate) as a gold colored oil in 95% yield (358 mg, 0.72 mmol).

$[\alpha]_D$ -16.6 (*c* 0.35, CH_2Cl_2);

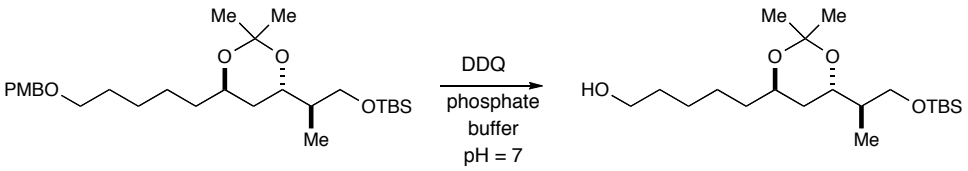
FTIR neat 2933, 2856, 2881, 1247, 835 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.26 (d, *J* = 8.4, 2H), 6.88 (d, *J* = 8.6, 2H), 4.24 (s, 2H), 3.80 (s, 3H), 3.66-3.74 (m, 2H), 3.56 (d, *J* = 4.4, 2H), 3.44 (t, *J* = 6.6, 2H), 1.37-1.67 (m, 11H), 1.31 (s, 6H), 0.89 (s, 9H), 0.85 (d, *J* = 6.8, 3H), 0.02 (s, 6H);

^{13}C NMR ($CDCl_3$, 500 MHz) δ ppm 159.0, 130.7, 129.2, 113.7, 100.1, 72.5, 70.1, 67.0, 66.8, 64.1, 55.2, 40.5, 36.6, 35.9, 29.7, 26.1, 25.9, 25.3, 24.6, 24.5, 18.2, 12.2, -5.5, -5.5.

HRMS calculated for $C_{28}H_{50}O_5Si$ (M+Na) 517.3325; found 517.3334 (ESI).

5-((4*R*,6*S*)-6-((*R*)-1-(*tert*-butyldimethylsilyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)pentan-1-ol: 3.67



PMB Ether (614 mg, 1.25 mmol) was taken up in CH_2Cl_2 (11.9 mL) and pH 7 phosphate butter (0.6 mL) at room temperature. DDQ (340 mg, 1.50 mmol) was added and solution immediately turned a green color. After reaction was complete (~1 hrs, solution color light orange), saturated, aqueous $NaHCO_3$ (1 mL) was added. Aqueous layer was extracted three times with Et_2O (5 mL portions) and organics were washed once with brine (5 mL). After drying with Na_2SO_4, **3.67** was isolated using flash chromatography (10:1 Hexanes:Ethyl Acetate) as a clear oil (390 mg, 1.04 mmol) in 82% yield.

$[\alpha]_D$ -0.11 (*c* 0.4, CH_2Cl_2);

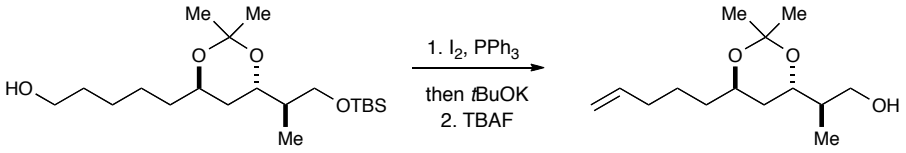
FTIR (neat) 3357, 2933, 2858, 1379, 1251, 1224, 835, 775 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 3.72 (dd, *J* = 14.5, 2H) 3.67-3.60 (m, 2H), 3.58-3.52 (d, *J* = 4.8, 2H), 1.70-1.38 (m, 10H), 1.33 (s, 6H), 1.28-1.22 (m, 2H), 0.90-0.88 (s, 9H), 0.85-0.83 (d, *J* = 6.9, 3H), 0.05-0.02 (s, 6H);

^{13}C NMR ($CDCl_3$, 500 MHz) δ ppm 100.2, 67.1, 66.8, 64.1, 63.0, 40.5, 36.6, 35.9, 32.7, 25.9, 25.7, 25.3, 24.6, 24.5, 18.2, 12.2, -5.5, -5.5;

HRMS calculated for $C_{20}H_{42}O_4Si$ (M+Na) 397.2750, found 397.2773 (ESI).

(*R*)-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)propan-1-ol: SI14



Alcohol (300 mg, 0.80 mmol) was taken up in THF (8 mL) at room temperature. Triphenylphosphine (252 mg, 0.96 mmol) and imidazole (120 mg, 1.76 mmol) were added respectively and cooled to 0 ºC. I_2 (242 mg, 0.96 mmol) was added and stirred for approximately 30 minutes (followed by TLC). Diluted with hexanes and filtered through a pad of silica, while washing with hexanes, and concentrated in vacuo. Crude product was taken onto next step.

Iodo compound was taken up in THF (10 mL) at room temperature and a solution of *t*BuOK in THF (2.14 mL, 1.0 M in THF) was added. Reaction was stirred for about 30 minutes and was then quenched with H_2O. The aqueous layer was extracted three times with ethyl acetate (5 mL portions) and collected organics were washed once with brine (5 mL). Ethyl acetate layer was dried with Na_2SO_4 and concentrated in vacuo. **3.68** (209 mg, 0.59 mmol) was isolated by flash chromatography (20:1, hexanes:EtOAc) as a clear oil in 73% yield.

The resultant silyl ether (203 mg, 0.57 mmol) was then taken up in THF (2.8 mL) and cooled to 0 ºC. A solution of TBAF in THF (0.85 mL, 1.0 M in THF) was added dropwise. The reaction stirred at 0 ºC until completion (approximately 45 minutes). Reaction was quenched with NH_4Cl and the aqueous layer was extracted three times with Et_2O (5 mL portions). Collected organics were washed once with brine (5 mL) and dried with Na_2SO_4. After concentrating in vacuo, **SI14** was isolated

by flash chromatography (10:1, hexanes:EtOAc) as a clear oil (132 mg, 0.55 mmol, 95% yield).

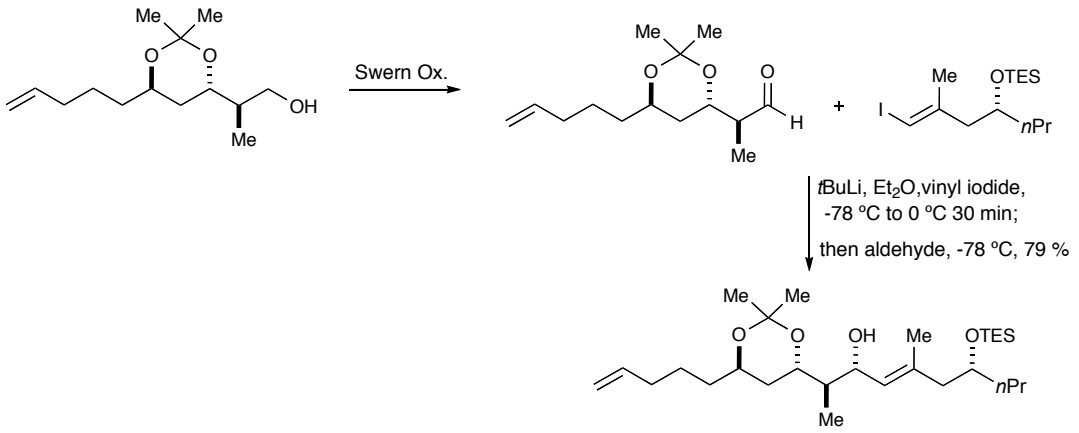
$[\alpha]_D$ -78.6 (*c* 0.5, CH_2Cl_2);

FTIR (neat) 3446, 2983, 2935, 2879, 1379, 1224, 908 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.86-5.75 (m, 1H), 5.07-4.93 (m, 2H), 3.82-3.76 (m, 1H), 3.73-3.66 (ddd, *J* = 9.2, 6.2, 1H), 3.61-3.55 (m, 2H), 3.12-3.05 (s, 1H), 2.06 (dd, *J* = 14.1, 7.1, 2H), 1.40-180 (m, 8H), 1.38 (s, 3H), 1.33 (s, 3H), 0.83-0.80 (d, *J* = 7.0, 3H);

^{13}C NMR ($CDCl_3$, 500 MHz) δ ppm 138.7, 114.7, 100.5, 73.0, 68.2, 66.6, 40.6, 37.8, 35.3, 33.6, 24.7, 24.6, 12.6.

(2*R*,3*R*,7*R*,*Z*)-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-5-methyl-7-(triethylsilyloxy)dec-4-en-3-ol: 3.71



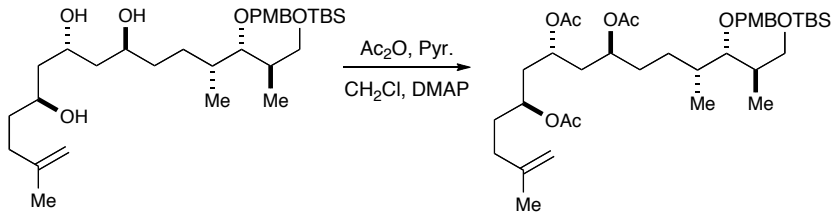
A solution of oxalyl chloride **(**0.06 mL, 0.70 mmol) in CH_2Cl_2 **(**2.1 mL) was cooled to -78 ºC and dimethyl sulfoxide **(**0.102 mL, 1.45 mmol) was added slowly by syringe (gas evolution). After stirring for 10 minutes a solution of alcohol **SI14 (**130 mg, 0.537 mmol) in CH_2Cl_2 (1.34 mL) was added by cannula and rinsed twice with 0.2 mL of CH_2Cl_2. The cloudly mixture was stirred at -78 ºC was 15 minutes at which time triethylamine **(**0.225 mL, 1.61 mmol) was added dropwise. The reaction mixture was then stirred for 1 h at -78 ºC. The reaction was quenched cold with $NaHCO_3$ (2 mL) and was allowed to warm to room temperature. The reaction was diluted with CH_2Cl_2, and the layers were separated. The aqueous layer was re-extracted with CH_2Cl_2 (3x). The organic layer was dried (Na_2SO_4), filtered through a silica plug and rinse (3 x 10 mL) with a 1:1 EtOAc:CH_2Cl_2. The filtrate was then concentrated under reduced pressure to give aldehyde **3.69** as a yellow oil. The crude aldehyde was taken immediately to the next reaction with further purification.

To a solution of the vinyl iodide (456 mg, 1.25 mmol) in Et_2O (4.16 mL) at –78 ºC was *t*BuLi (1.7 M in pentane, 1.47 mL, 2.50 mmol), and the reaction was immediately warmed to 0 ºC for 25 min. The reaction was recooled to - 78 ºC, and the aldehyde was slowly added via syringe in Et_2O (1.0 mL, 0.25 mL rinse). After 1 h, the reaction was quenched at - 78 ºC with NH_4Cl (sat'd, aq), warmed to rt, and the layers separated. The aq. layer was extracted with Et_2O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (10:1 Hex:EtOAc) afforded a 1:1 mixture of 1,3 *anti:syn* **3.71** (ratio determined by ^{1}H NMR analysis of crude reaction mixture, 195 mg, 0.42 mmol, combine yield of diastereomers 79% over two steps).

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.82 (dddd, *J* = 16.9, 10.1, 6.7, 6.7 Hz, 1 H), 5.16 (d, *J* = 9.1 Hz, 1 H), 5.01 (ddd, *J* = 17.1, 3.4, 1.5 Hz, 1 H), 4.95 (d, *J* = 10.2 Hz, 1 H), 4.27 (t, *J* = 8.7 Hz, 1 H), 3.99 (s, 1H), 3.84-3.74 (m, 3H), 2.27 (dd, *J* =14.1, 4.3, 1H), 2.16 (dd, *J* =8.7, 3.0, 1H), 2.06 (q, *J* = 7.0, 2H), 1.70 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.72-1.20 (m, 11H), 0.96 (t, *J* = 8.2 Hz, 9H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H), 0.59 (q, *J* = 8.2 Hz, 6H);

^{13}C NMR ($CDCl_3$, 500 MHz) δ ppm 138.6, 136.0, 128.8, 114.6, 100.6, 72.9, 72.4, 70.7, 66.6, 48.5, 44.1, 38.7, 38.0, 35.2, 33.6, 31.6, 24.7, 24.6, 24.5, 18.4, 17.3, 14.2, 11.6, 7.0, 5.0;

(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-15-(*tert*-butyldimethylsilyloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethylpentadec-1-ene-5,7,9-triyl triacetate: 3.75



A solution of triol **3.37 (**60 mg, 0.107 mmol) in CH_2Cl_2 (1.5 mL) was added DMAP (2 mg, 0.016 mmol), pyridine (0.345 mL, 4.28 mmol), and acetic anhydride (0.203 mL, 2.15 mmol). The reaction was stirred until disappearance of starting material at rt (~2h). The reaction was diluted with EtOAc, quenched with NH_4Cl (sat'd aq.), and the aqueous layer was re-extracted with EtOAc (3x). The organic layer was then washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (5:1 Hexane:EtOAc) provided of **3.75 (**70 mg, 0.102 mmol) in 95% yield as a clear oil.

$[\alpha]_D$ 12.4 (*c* = 0.50, CH_2Cl_2);

FTIR (neat) 2956, 2929, 2883, 2856, 1739, 1514, 1461, 1247 cm^{-1};

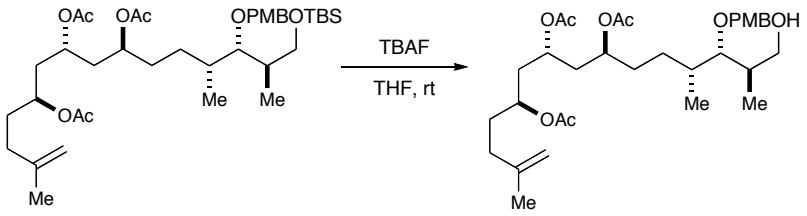
^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.26 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 4.97 (dddd, *J* = 9.5, 6.2, 6.2, 3.1 Hz, 1 H), 4.89 (m, 2 H), 4.71 (s, 1H), 4.66 (s, 1H), 4.53 (d, *J* = 10.9 Hz, 1 H), 4.46 (d, *J* = 10.9 Hz, 1 H), 3.80 (s, 3 H), 3.71 (dd, *J* = 9.7, 5.3 Hz, 1 H), 3.63 (dd, *J* = 9.7, 3.3 Hz, 1 H), 3.25 (dd, *J* = 8.7, 2.4 Hz, 1 H), 1.99-2.07 (m, 2 H), 2.05 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.92 (dddd, *J* = 18.7, 10.2, 4.4, 4.4 Hz, 1 H), 1.68-1.84 (m, 6H), 1.71 (s, 3 H), 1.54-1.64 (m, 3 H), 1.38-1.46 (m, 1 H),

1.22-1.34 (m, 1 H), 0.92 (s, 9 H), 0.90 (d, *J* = 2.3 Hz, 3 H), 0.88 (d, *J* = 2.3 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 170.8, 170.7, 170.6, 159.1, 144.9, 131.7, 129.3, 113.9, 110.5, 83.3, 74.6, 70.9, 70.3, 67.5, 65.1, 55.4, 39.2, 38.7, 38.6, 35.4, 33.5, 33.1, 32.3, 30.5, 29.9, 26.1, 22.6, 21.3, 21.3, 21.2, 18.5, 14.8, 13.6, -5.2, -5.2;

HRMS Exact Mass: calculate for $C_{38}H_{64}NaO_9Si$ $(M+Na)^+$ 715.4217; found 715.4213 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-15-hydroxy-13-(4-methoxybenzyloxy)-2,12,14-trimethylpentadec-1-ene-5,7,9-triyl triacetate: 3.76



A solution of **3.75** (65 mg, 0.094 mmol) in THF (1 mL) was added TBAF (0.283 mL, 1.0M in THF). The reaction was stirred until disappearance of starting material at rt (~3h). The reaction was diluted with EtOAc, quenched with NH_4Cl (sat'd aq.), and the aqueous layer was re-extracted with EtOAc (2x). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (2:1 Hexane:EtOAc) provided of **3.76** (50 mg, 0.087 mmol) in 93% yield as a clear oil.

$[\alpha]_D$ 13.1 (c = 2.35, CH_2Cl_2);

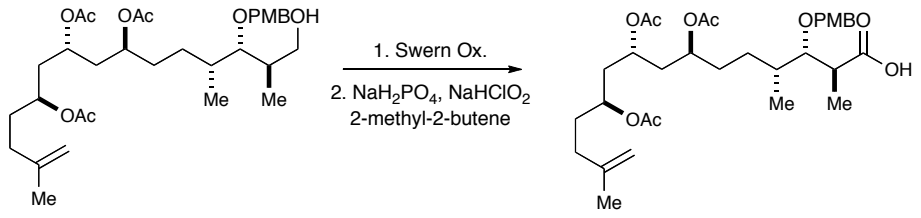
FTIR (neat) 3502, 3072, 2964, 2935, 2875, 1737, 1514, 1454, 1245 cm^{-1};

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.28 (d, J = 8.5 Hz, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 4.98 (dddd, J = 9.6, 6.3, 6.3, 3.3 Hz, 1 H), 4.91 (m, 2 H), 4.73 (s, 1H), 4.67 (s, 1H), 4.58 (d, J = 10.6 Hz, 1 H), 4.51 (d, J = 10.6 Hz, 1 H), 3.81 (s, 3 H), 3.64 (m, 2 H), 3.25 (dd, J = 7.6, 3.3 Hz, 1 H), 2.71 (s, 1 H), 1.99-2.07 (m, 2 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.86-1.95 (m, 2 H) 1.68-1.84 (m, 6 H), 1.72 (s, 3 H), 1.56-1.64 (m, 2 H), 1.44-1.54 (m, 1 H), 1.22-1.34 (m, 1 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 7.1 Hz, 3 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 170.7, 170.6, 170.5, 159.3, 144.7, 130.4, 129.4, 113.9, 110.4, 87.6, 74.8, 70.6, 70.0, 67.3, 66.5, 55.3, 39.0, 38.4, 37.7, 36.1, 33.3, 32.8, 32.2, 30.0, 22.4, 21.2, 21.1, 21.1, 15.4, 14.3;

HRMS Exact Mass: calculate for $C_{32}H_{50}NaO_9$ $(M+Na)^+$ 601.3353; found 601.3354 (ESI).

(2*S*,3*S*,4*R*,7*S*,9*R*,11*S*)-7,9,11-triacetoxy-3-(4-methoxybenzyloxy)-2,4,14-trimethylpentadec-14-enoic acid: 3.77



A solution of oxalyl chloride (0.017 mL, 0.190 mmol) in CH_2Cl_2 (0.562 mL) was cooled to -78 ºC and dimethyl sulfoxide (0.032 mL, 0.447 mmol) was added slowly by syringe (gas evolution). After stirring for 10 minutes a solution of alcohol **3.76** (42 mg, 0.075 mmol) in CH_2Cl_2 (0.680 mL) was added by cannula and rinsed twice with 0.05 mL of CH_2Cl_2. The cloudy mixture was stirred at -78 ºC was 15 minutes at which time triethylamine (0.075 mL, 0.535 mmol) was added dropwise. The reaction mixture was then stirred for 2 h at -78 ºC. The reaction was quenched cold with $NaHCO_3$ (1 mL) and was allowed to warm to room temperature. The reaction was diluted with CH_2Cl_2, and the layers were separated. The aqueous layer was re-extracted with CH_2Cl_2 (3x). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give aldehyde **SI15** as a yellow oil. The crude aldehyde was taken immediately to the next reaction with further purification.

To a solution of crude aldehyde **SI15** was added *t*butanol (1.5 mL) and 2-methyl-2-butene (0.5 mL). A solution of sodium chlorite (135 mg, 1.500 mmol) and sodium dihydrogen phosphate (125 mg, 1.042 mmol) in H_2O (0.743 mL) was prepared and added to the reaction mixture by syringe. The yellow solution was

stirred vigorously for 2 h at room temperature. The reaction was then diluted with Et_2O (5 mL) and pour into H_2O (3 mL), the layers were separated and the aqueous phase was extracted with Et_2O (3x). The combine organic layers were dried with (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (1:1 Hexane:EtOAc) provided **3.77 (**34 mg, 0.059) in 81% yield (over two steps) as a clear oil.

$[\alpha]_D$ 8.13 (*c* = 0.16, CH_2Cl_2);

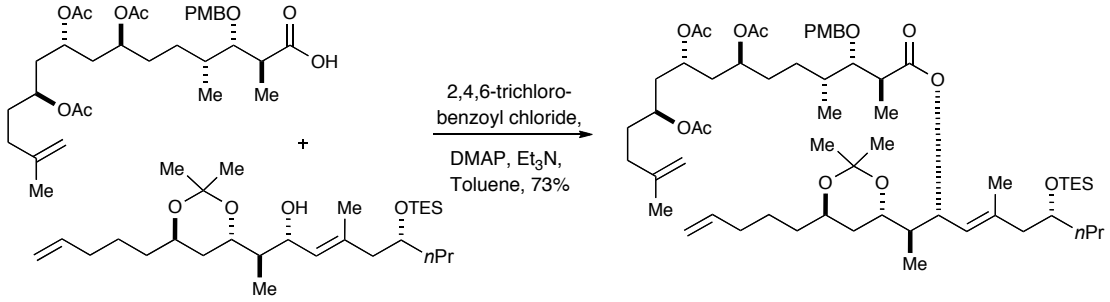
FTIR (neat) 3251, 3076, 2964, 2923, 2854, 1737, 1714, 1512, 1454, 1245 cm^{-1};

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.24 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 4.85-5.10 (m, 3 H), 4.73 (s, 1H), 4.67 (s, 1H), 4.56 (d, *J* = 10.7 Hz, 1 H), 4.50 (d, *J* = 10.6 Hz, 1 H), 3.79 (s, 3 H), 3.57 (dd, *J* = 7.2, 3.5 Hz, 1 H), 2.78 (dddd, *J* = 14.33, 7.1, 7.1, 7.1 Hz, 1 H), 1.99-2.07 (m, 2 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.86-1.95 (m, 1 H) 1.64-1.84 (m, 5 H), 1.72 (s, 3 H), 1.40-1.64 (m, 3 H), 1.20-1.39 (m, 2 H), 1.17 (d, *J* = 7.1 Hz, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 177.3, 170.8, 170.7, 170.5, 159.4, 144.7, 130.0, 129.5, 113.9, 110.3, 84.2, 74.4, 70.8, 69.9, 67.3, 55.3, 42.3, 39.0, 38.1, 35.6, 33.3, 32.5, 32.3, 28.9, 22.4, 21.2, 21.1, 21.1, 14.7, 14.4;

HRMS Exact Mass: calculate for $C_{32}H_{48}NaO_{10}$ $(M+Na)^+$ 615.3145; found 615.3131 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((2*S*,3*R*,7*R*,*Z*)-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-5-methyl-7-(triethylsilyloxy)dec-4-en-3-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: 3.78



A solution of alcohol **3.71 (**17 mg, 0.035 mmol), carboxylic acid **3.77 (**23 mg, 0.039 mmol), and 4-dimethylaminopyridine **(**215 mg, 1.766 mmol) in toluene (6.93 mL) at -78 ºC was added triethylamine **(**0.111 mL, 0.798 mmol) dropwise followed by the slow addition of 2,4,6-trichlorobenzoyl chloride **(**0.124 mL, 0.7911 mmol). This caused the white solution to thicken and the mixture was stirred for 21h at -78 ºC ensuring that the bath temperature did not rise above -65 ºC. The reaction flask was then moved to a dry ice/acetonitrile bath and stirred for 2.5h maintaining the temperature between -30 ºC to -42 ºC. At the end of the 2.5h the solution was slowly allowed to warm to rt in the bath over 1h. The flask was then placed in an ice bath for 2h while being stirred. The reaction was quenched by the addition of $NaHCO_3$ (3 mL). The layers were separated and the aqueous layer was back extracted with Et_2O (6 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduce pressure. Purification by flash chromatography (5:1

hexane:EtOAc) provided ester **3.78** (27.3 mg, 0.025 mmol) in 73% yield as a colorless oil.

$[\alpha]_D$ 3.63 (*c* = 0.275, CH_2Cl_2);

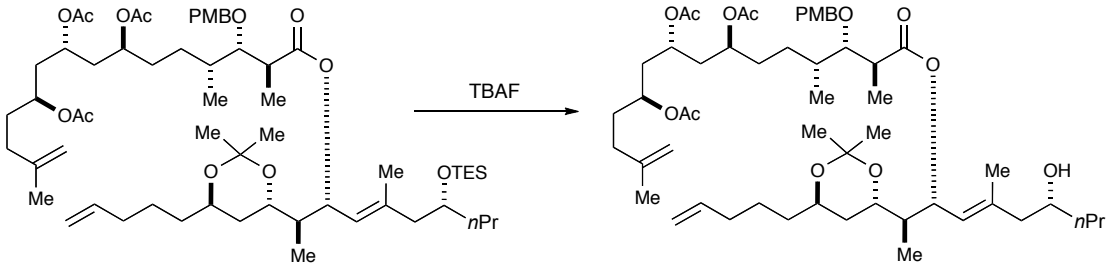
FTIR (neat) 3076, 2954, 2935, 2875, 1739, 1515, 1442, 1244 cm^{-1};

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.19 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 5.82 (dddd, *J* = 17.0, 10.2, 6.8, 6.8 Hz, 1 H), 5.68 (dd, *J* = 9.9, 5.7 Hz, 1 H), 5.17 (d, *J* = 9.8 Hz, 1 H), 5.02 (ddd, *J* = 17.1, 3.2, 1.6 Hz, 1 H), 4.93-5.00 (m, 3 H), 4.85-4.94 (m, 2 H), 4.74 (s, 1 H), 4.67 (s, 1 H), 4.51 (d, *J* = 10.8 Hz, 1 H), 4.34 (d, *J* = 10.8 Hz, 1 H), 3.79 (s, 3 H), 3.70-3.80 (m, 2 H), 3.60-3.69 (m, 3 H), 2.69 (dt, *J* = 14.2, 7.1 Hz, 1 H), 1.89-2.20 (m, 8 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 2.00 (s, 3 H), 1.76 (s, 3 H), 1.73 (s, 3 H), 1.34 (s, 3 H), 1.29 (s, 3 H), 1.20-1.80 (m, 20 H), 1.08 (d, *J* = 7.1 Hz, 3 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 0.84-0.93 (m, 9 H) 0.58 (q, *J* = 7.9 Hz, 6 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 175.3, 170.6, 170.6, 170.5, 158.9, 144.7, 139.6, 138.8, 131.2, 129.0, 122.7, 114.6, 113.6, 110.3, 100.1, 83.1, 73.9, 71.4, 70.7, 70.2, 70.0, 67.3, 67.1, 66.5, 55.2, 53.5, 48.8, 43.5, 42.1, 39.1, 38.5, 38.5, 35.4, 34.7, 33.7, 33.3, 32.1, 30.3, 29.9, 29.7, 24.9, 24.9, 24.8, 22.4, 21.2, 21.1, 21.1, 18.3, 17.6, 15.3, 14.8, 13.2, 9.8, 7.0, 5.0;

HRMS Exact Mass: calculate for $C_{60}H_{100}NaO_{13}Si$ $(M+Na)^+$ 1079.6831; found 1079.7115 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((2*S*,3*R*,7*R*,*Z*)-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-7-hydroxy-5-methyldec-4-en-3-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: SI16



The ester (27.3 mg, 0.025 mmol) was then taken up in THF (0.100 mL) and cooled to 0 ºC. A solution of TBAF in THF (0.038 mL, 1.0 M in THF) was added dropwise. The reaction stirred at 0ºC until completion (approximately 45 minutes). Reaction was quenched with NH_4Cl and the aqueous layer was extracted three times with Et_2O (5 mL portions). Collected organics were washed once with brine (5 mL), dried with Na_2SO_4, filter, and concentrated under reduced pressure. Purification by flash chromatography (2:1, hexanes:EtOAc) afforded **SI16** (22.7 mg, 0.024 mmol) as a clear oil in 93% yield.

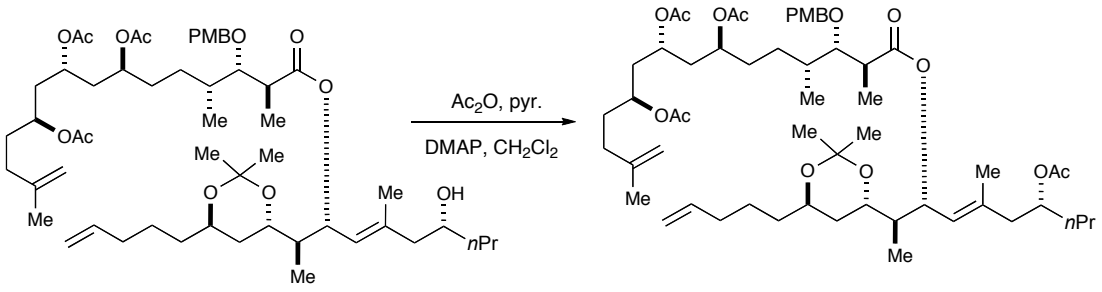
^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.22 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 5.81 (dddd, *J* = 17.0, 10.2, 6.7, 6.7 Hz, 1 H), 5.64 (dd, *J* = 9.9, 5.2 Hz, 1 H), 5.20 (d, *J* = 9.6 Hz, 1 H), 5.01 (ddd, *J* = 17.1, 3.4, 1.6 Hz, 1 H), 4.93-5.00 (m, 2 H), 4.85-4.93 (m, 2 H), 4.72 (s, 1 H), 4.67 (s, 1H), 4.53 (d, *J* = 10.7 Hz, 1H), 4.38 (d, *J* = 10.7 Hz, 1 H), 3.79 (s, 3 H), 3.69-3.76 (m, 1 H), 3.59-3.66 (m, 1 H), 3.60-3.54 (m, 1 H), 3.53 (dd, *J* = 8.4, 3.0 Hz, 1 H), 2.70 (dt, *J* = 15.2, 7.2 Hz, 1 H), 1.87-2.15 (m, 8 H),

2.06 (s, 3 H), 2.04 (s, 3 H), 2.00 (s, 3 H), 1.20-1.80 (m, 23 H), 1.76 (s, 3 H), 1.73 (s, 3 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.10 (d, J = 7.1 Hz, 3H), 0.84-0.93 (m, 9 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 175.3, 170.7, 170.6, 170.5, 158.9, 144.7, 139.6, 138.7, 131.2, 128.8, 123.1, 114.6, 113.5, 110.3, 100.2, 83.7, 73.8, 71.8, 70.7, 70.0, 68.4, 67.3, 66.4, 55.2, 53.5, 48.1, 43.4, 42.1, 39.2, 39.1, 38.5, 36.3, 35.4, 35.1, 33.7, 33.3, 32.8, 32.2, 29.8, 29.7, 24.8, 24.6, 22.4, 21.2, 21.1, 21.0, 18.9, 17.5, 14.8, 14.2, 13.6, 9.9;

HRMS Exact Mass: calculate for $C_{54}H_{86}NaO_{13}$ $(M+Na)^+$ 965.5966; found 965.5897 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((2*S*,3*R*,7*R*,*Z*)-7-acetoxy-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-5-methyldec-4-en-3-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: 3.79



A solution of triol **SI16 (**10 mg, 0.0106 mmol) in CH_2Cl_2 (0.5 mL) was added DMAP (1 crystal), pyridine (0.034 mL, 0.424 mmol), and acetic anhydride (0.020 mL, 0.212 mmol). The reaction was stirred until disappearance of starting material at rt (~2h). The reaction was diluted with EtOAc, quenched with NH_4Cl (sat'd aq.), and the aqueous layer was re-extracted with EtOAc (3x). The organic layer was then washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (1.5:1 Hexane:EtOAc) provided **3.79** (10 mg, 0.0102 mmol) in 96% yield as a clear oil.

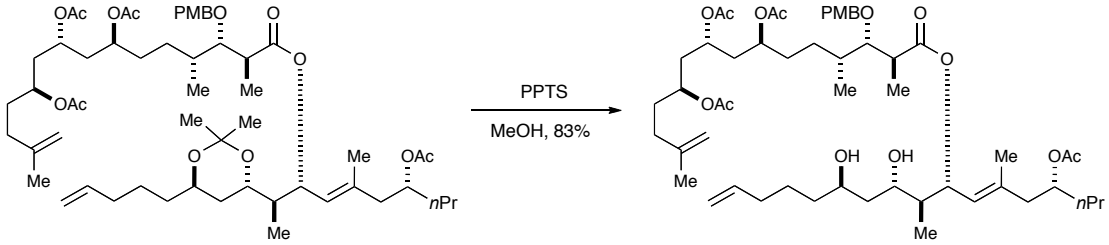
^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.18 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 5.80 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1 H), 5.67 (dd, *J* = 9.9, 5.6 Hz, 1 H), 5.16 (d, *J* = 9.7 Hz, 1 H), 5.00 (ddd, *J* = 17.1, 3.4, 1.6 Hz, 1 H), 4.92-5.00 (m, 3 H), 4.84-4.92 (m, 2 H), 4.73 (s, 1 H), 4.66 (s, 1 H), 4.50 (d, *J* = 10.9 Hz, 1 H), 4.35 (d, *J* = 10.9 Hz, 1 H), 3.79 (s, 3 H), 3.68-3.75 (m, 1 H), 3.55-3.62 (m, 2 H), 2.68 (dt, *J* = 16.0, 6.9,

1 H), 1.87-2.15 (m, 8 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.20-1.80 (m, 20 H), 1.77 (s, 3 H), 1.73 (s, 3 H), 1.33 (s, 3 H), 1.27 (s, 3 H), 1.06 (d, J = 7.1 Hz, 3 H), 0.84-0.93 (m, 9 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 175.1, 170.6, 170.6, 170.6, 170.5, 158.9, 144.7, 138.7, 138.6, 131.3, 128.8, 122.5, 114.6, 113.5, 110.3, 100.2, 83.2, 73.8, 72.1, 71.2, 70.7, 70.0, 67.3, 66.4, 55.2, 53.5, 44.2, 42.1, 39.2, 39.1, 35.9, 35.4, 33.7, 33.3, 32.2, 31.9, 31.6, 29.9, 24.8, 24.8, 22.7, 21.3, 21.2, 21.1, 21.0, 18.4, 17.8, 14.7, 14.2, 14.2, 14.0, 13.2, 9.7;

HRMS Exact Mass: calculate for $C_{56}H_{88}NaO_{14}$ $(M+Na)^+$ 1007.6072; found 1007.6210 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((4*R*,8*R*,9*S*,10*S*,12*R*,*Z*)-4-acetoxy-10,12-dihydroxy-6,9-dimethylheptadeca-6,16-dien-8-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: SI17



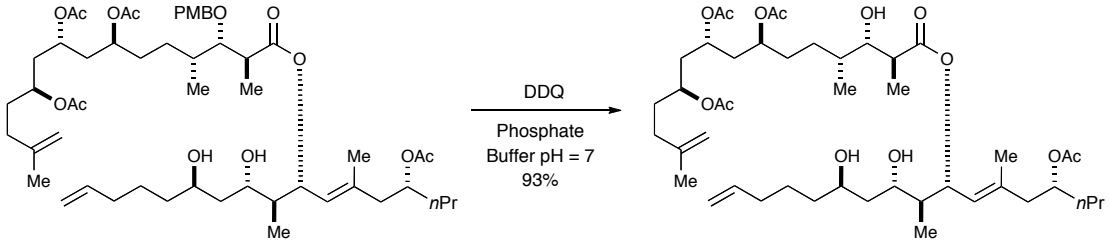
A solution of tetraacetate **3.79 (**20 mg, 0.0203 mmol) in MeOH (2 mL) was added PPTS (0.800 mg, 0.0305 mmol). The reaction was stirred until disappearance of starting material at rt (~4h). The reaction was diluted with EtOAc, quenched with $NaHCO_3$ (sat'd aq.), and the aqueous layer was re-extracted with EtOAc (3x). The organic layer was then washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (1.5:1 Hexane:EtOAc) provided **SI17** (15.7 mg, 0.017 mmol) in 83% yield as a clear oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 7.21 (d, *J* = 8.3 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 5.82 (dddd, *J* = 15.8, 12.1, 5.4, 5.4 Hz, 1 H), 5.69 (dd, *J* = 9.7, 6.0 Hz, 1 H), 5.18 (d, *J* = 9.8 Hz, 1 H), 4.85-5.05 (m, 6 H), 4.73 (s, 1 H), 4.67 (s, 1 H), 4.51 (d, *J* = 10.9 Hz, 1 H), 4.34 (d, *J* = 11.0 Hz, 1 H), 3.86-3.92 (m, 1 H), 3.80 (s, 3 H), 3.71 (m, 1 H), 3.58 (dd, *J* = 8.4, 2.0 Hz, 1 H), 2.73 (dddd, *J* = 14.2, 6.8, 6.8, 6.8 Hz, 1 H), 1.19-2.50 (m, 28 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.82 (s, 3 H), 1.72 (s, 3 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.89 (t, *J* = 7.3 Hz, 3 H), 0.81-0.86 (m, 9 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 175.1, 170.7, 170.6, 170.6, 170.5, 158.9, 144.7, 138.7, 138.6, 131.1, 128.4, 123.4, 114.7, 113.7, 110.3, 83.5, 73.8, 73.5, 72.5, 70.7, 70.1, 68.8, 67.3, 60.4, 55.2, 44.3, 43.4, 43.0, 39.5, 39.1, 38.5, 37.1, 36.3, 34.9, 33.7, 33.3, 32.2, 31.6, 29.8, 25.1, 22.7, 21.3, 21.2, 21.1, 21.1, 18.4, 17.8, 14.2, 14.0, 13.6, 10.8;

HRMS Exact Mass: calculate for $C_{53}H_{84}NaO_{14}$ $(M+Na)^+$ 967.5759; found 967.5789 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((4*R*,8*R*,9*S*,10*S*,12*R*,*Z*)-4-acetoxy-10,12-dihydroxy-6,9-dimethylheptadeca-6,16-dien-8-yloxy)-13-hydroxy-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: 3.80



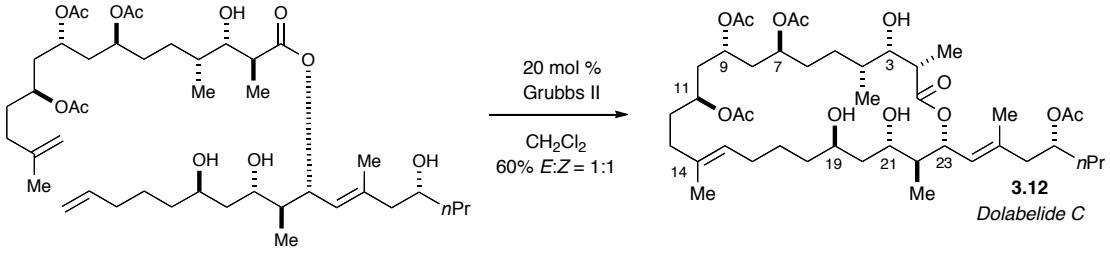
The ester **SI17** (0.016 mg, 0.0169 mmol) was taken up in CH_2Cl_2 (1.0 mL) followed by the addition of pH buffer solution (1.0 mL) and DDQ (8 mg, 0.0338 mmol) at rt. Upon completion (~0.5 h, monitored by TLC), CH_2Cl_2 (2 mL) was added followed by $NaHCO_3$ (sat'd aq, 1 mL). The layers were separated, and the aq. layer extracted with CH_2Cl_2 (3x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). Flash chromatography (2:1 Hex:EtOAc) afforded **3.80** (12.9 mg, 0.0157 mmol, 93%) as a clear oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 5.79 (dddd, *J* = 17.0, 10.2, 6.7, 6.7 Hz, 1 H), 5.19 (dd, *J* = 9.7, 9.5 Hz, 1 H), 4.87-5.07 (m, 6 H), 4.73 (s, 1 H), 4.66 (s, 1 H), 4.09-4.15 (m, 2 H), 3.89-3.96 (m, 1 H), 3.71 (dd, *J* = 9.9, 1.2 Hz, 1 H), 2.54 (dddd, *J* = 14.1, 7.0, 7.0, 7.0 Hz, 1 H), 1.19-2.17 (m, 28 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.82 (s, 3 H), 1.72 (s, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 0.89 (t, *J* = 7.3 Hz, 3 H), 0.81-0.86 (m, 9 H);

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 174.0, 172.4, 170.8, 170.8, 170.6, 144.6, 138.7, 138.0, 125.3, 114.6, 110.4, 72.6, 72.6, 72.4, 71.9, 70.7, 68.1, 67.1, 66.9, 45.3, 44.2, 42.7, 39.0, 37.6, 37.3, 36.9, 36.0, 33.7, 33.6, 33.3, 32.3, 31.5, 29.0, 25.3, 22.4, 21.4, 21.3, 21.2, 21.1, 18.5, 17.8, 13.9, 13.6, 12.5, 9.5;

HRMS Exact Mass: calculate for $C_{45}H_{76}NaO_{13}$ $(M+Na)^+$ 847.5184; found 847.5183 (ESI).

(3*S*,4*S*,5*R*,8*S*,10*R*,12*S*,20*R*,22*S*,23*S*,24*R*,*E*)-24-((*R*,*E*)-4-acetoxy-2-methylhept-1-enyl)-4,20,22-trihydroxy-3,5,15,23-tetramethyl-2-oxooxacyclotetracos-15-ene-8,10,12-triyl triacetate, Dolabelide C: 3.12



To a refluxing solution of ester **3.80** (5.4 mg, 0.0065 mmol) in degassed CH_2Cl_2 (13.5 mL) was added Grubbs II catalyst (0.620 mg, 0.73 μmol). The reaction was refluxed 6 h with the addition of Grubbs II catalyst (0.310 mg, 0.37 μmol) at 2 h intervals. The solution was allowed to cool to room temperature before being concentrated under vacuum pressure. Purification via flash chromatography (8:1 CH_2Cl_2/acetone) supplied **3.12**, (3.1 mg, 0.0039 mmol) as a 1:1 *E*/*Z* mixture, as a viscous oil in 60% yield. Repeat purification in by flash chromatography (8:1 CH_2Cl_2/acetone) afforded a **3.12** as a 4:1 *E*/*Z* mixture.

^{1}H NMR (500 MHz, pyridine-d_5) δ 6.30-6.40 (br s, 1H), 5.90-6.10 (br m, 2H), 5.70 (t, *J* = 9.3 Hz, 1H), 5.40 (d, *J* = 9.5 Hz, 1H), 5.31-5.38 (m, 2H), 5.23-5.30 (m, 2H), 5.10-5.16 (m, 1H), 4.82-4.88 (m, 1H), 4.32-4.37 (m, 1H), 4.03 (br d, *J* =9.1 Hz, 1H), 2.85-2.93 (m, 1H), 2.48-2.52 (m, 1H), 2.32 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.28 (dd, *J* = 13.9, 5.4 Hz, 1H), 2.15-2.21 (m, 1H), 2.00-2.11 (m, 6H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.92-1.96 (m, 2H), 1.80-1.90 (m, 4H), 1.58-1.79 (m, 7H), 1.59 (s, 3H), 1.49-1.53 (m, 3H), 1.28-1.32 (m, 2H), 1.19 (d, *J* = 7.3 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (126 MHz, pyridine-d_5) δ ppm 173.9, 170.6, 170.5, 170.4, 170.3, 136.7, 132.6, 127.3, 127.2, 74.3, 73.5, 71.8, 69.9, 69.9, 68.0, 67.9, 67.3, 46.4, 44.5, 43.7, 38.8, 38.5, 38.0, 37.2, 36.3, 35.2, 34.1, 31.8, 31.6, 29.3, 28.0, 27.0, 21.1, 21.0, 20.9, 20.9, 18.8, 17.6, 15.2, 14.0, 13.8, 12.6, 11.0;

HRMS Exact Mass: calculate for $C_{43}H_{72}NaO_{13}$ $(M+Na)^+$ 819.4871; found 819.4858 (ESI).

4.4 References

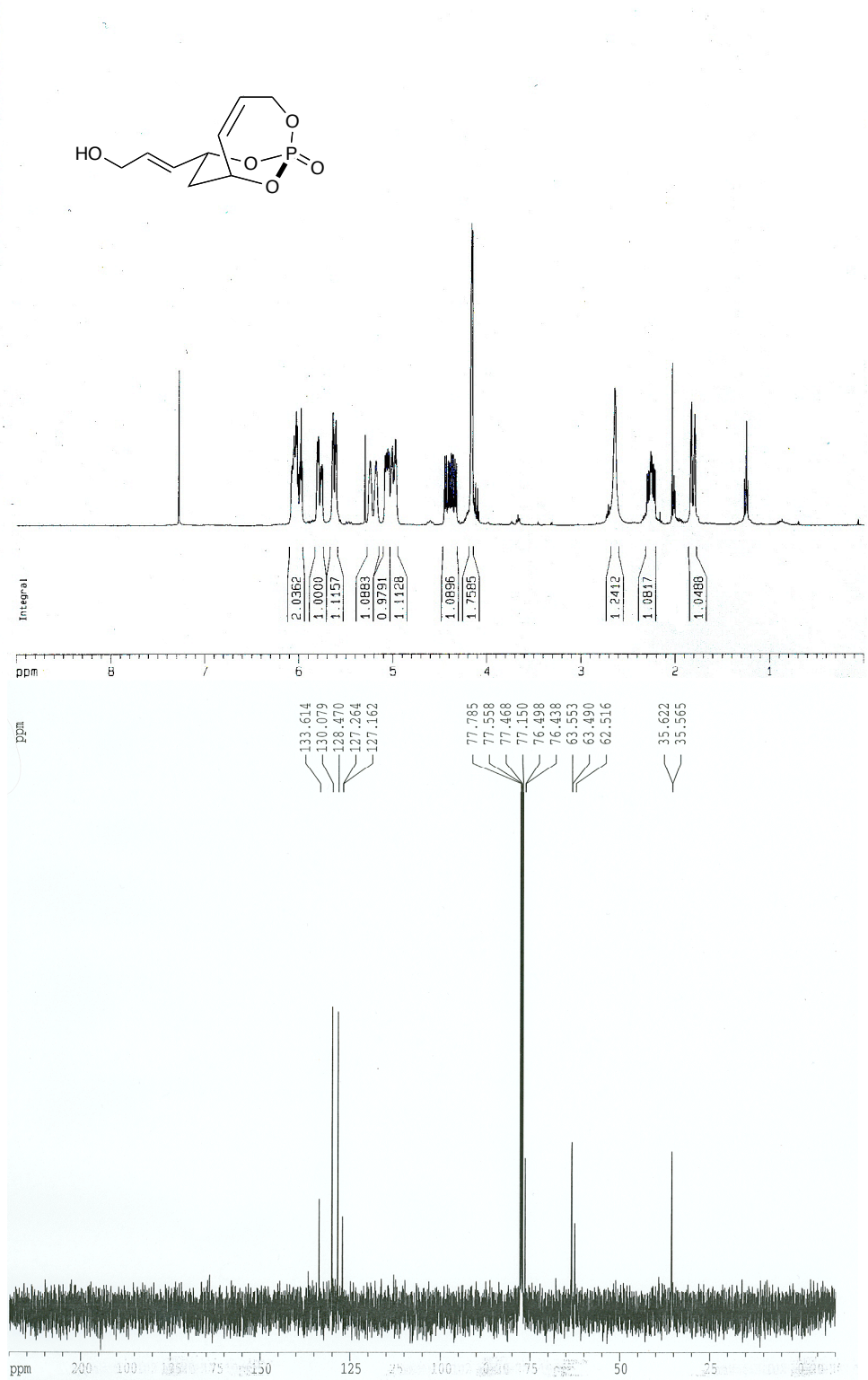
(1) Bialy, L.; Waldmann, H., "Total synthesis and biological evaluation of the protein phosphatase 2A inhibitor cytostatin and analogues." *Chem.- Eur. J.* **2004**, *10*, 2759-2780 and references therein.

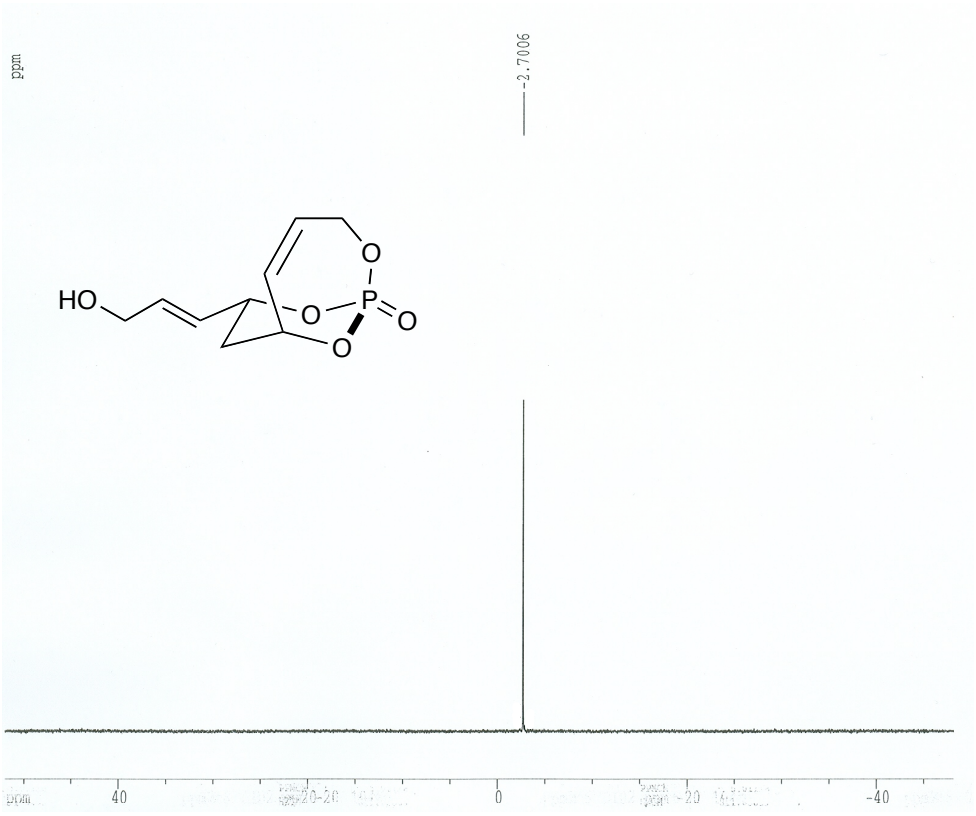
(2) (a) Rychnovsky, S. D.; Skalitzky, D. J., "Stereochemistry of alternating polyol chains: NMR analysis of 1,3-diol acetonides." *Tetrahedron Lett.* **1990**, *31*, 945-8. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R., "Carbon-13 NMR chemical shift correlations in 1,3-diol acetonides. Implications for the stereochemical assignment of propionate-derived polyols." *Tetrahedron Lett.* **1990**, *31*, 7099-100

Appendix A

NMR Spectra: Chapters 2 and 3

Allyl Alcohol derived Bicyclo[4.3.1]phosphate Triester: 2.55

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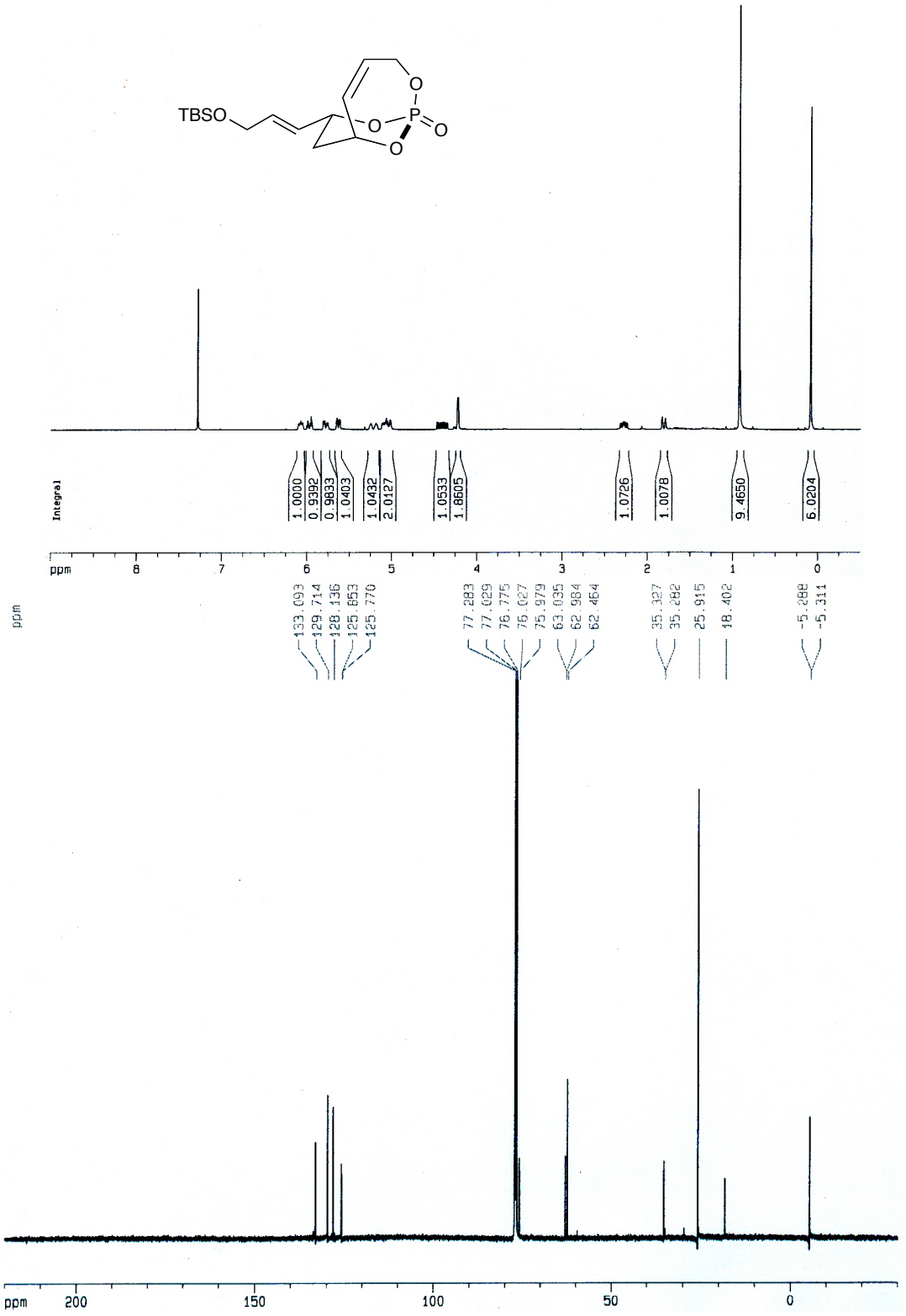
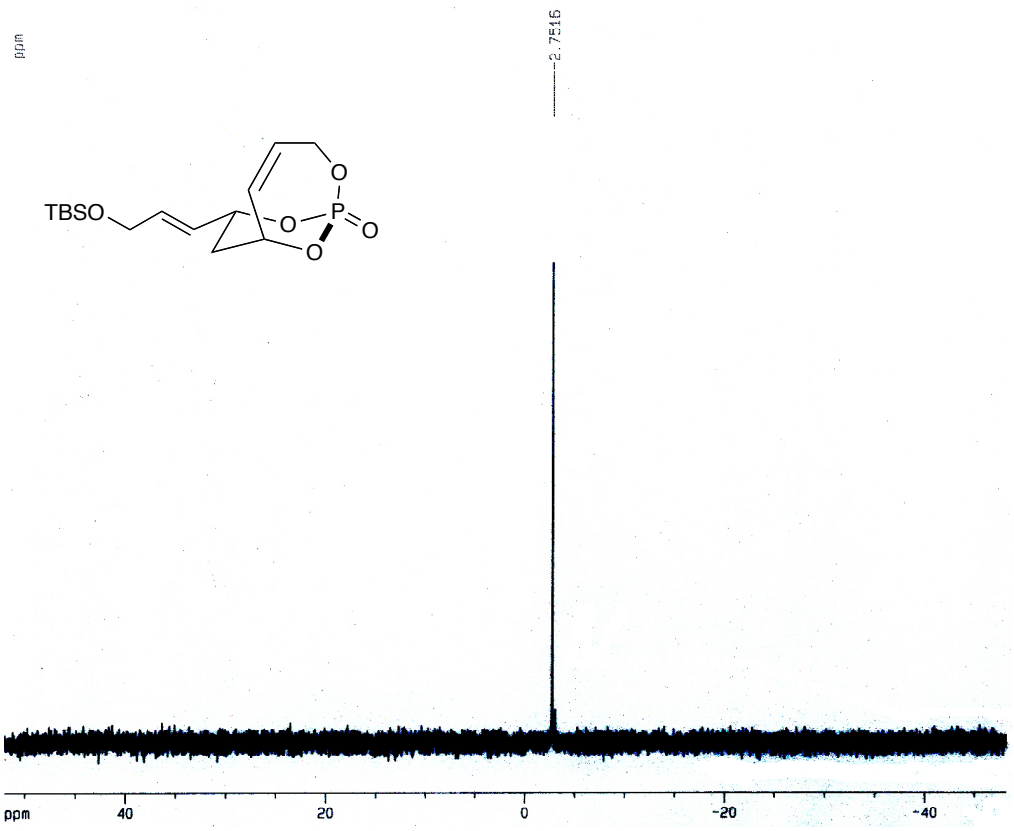
HO
O
O
P
O
O
40
20
0
-20
-40

TBS-Protected Allyl Alcohol derived Bicyclo[4.3.1]phosphate Triester: 2.56

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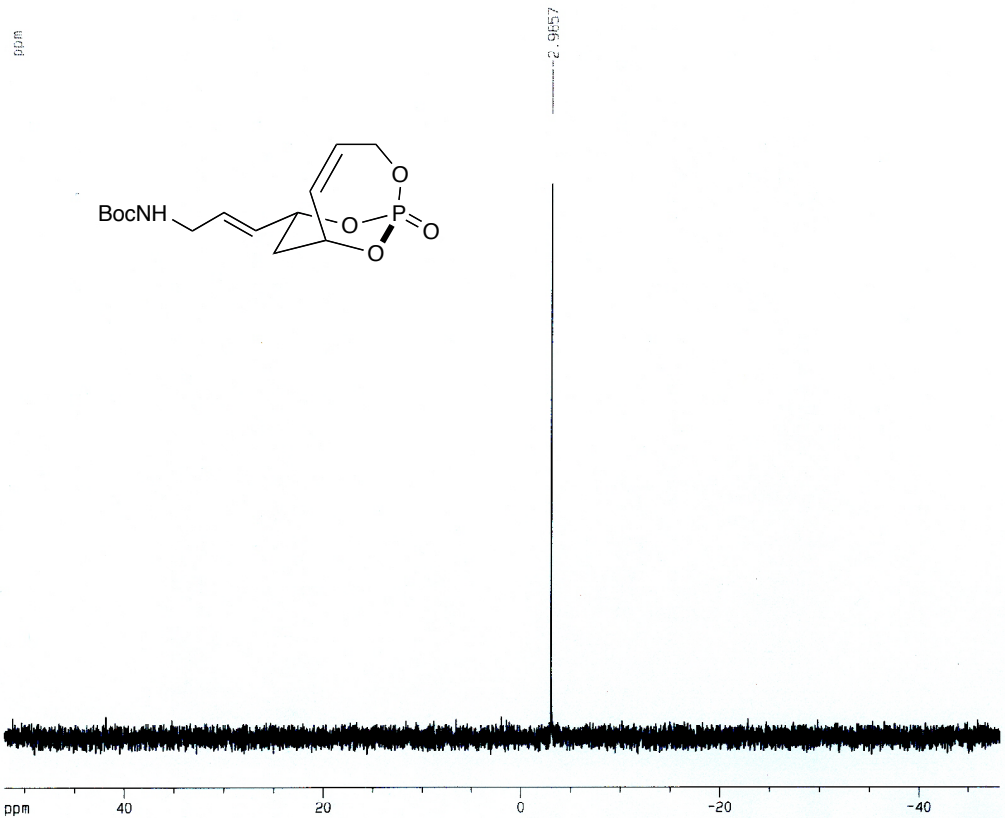
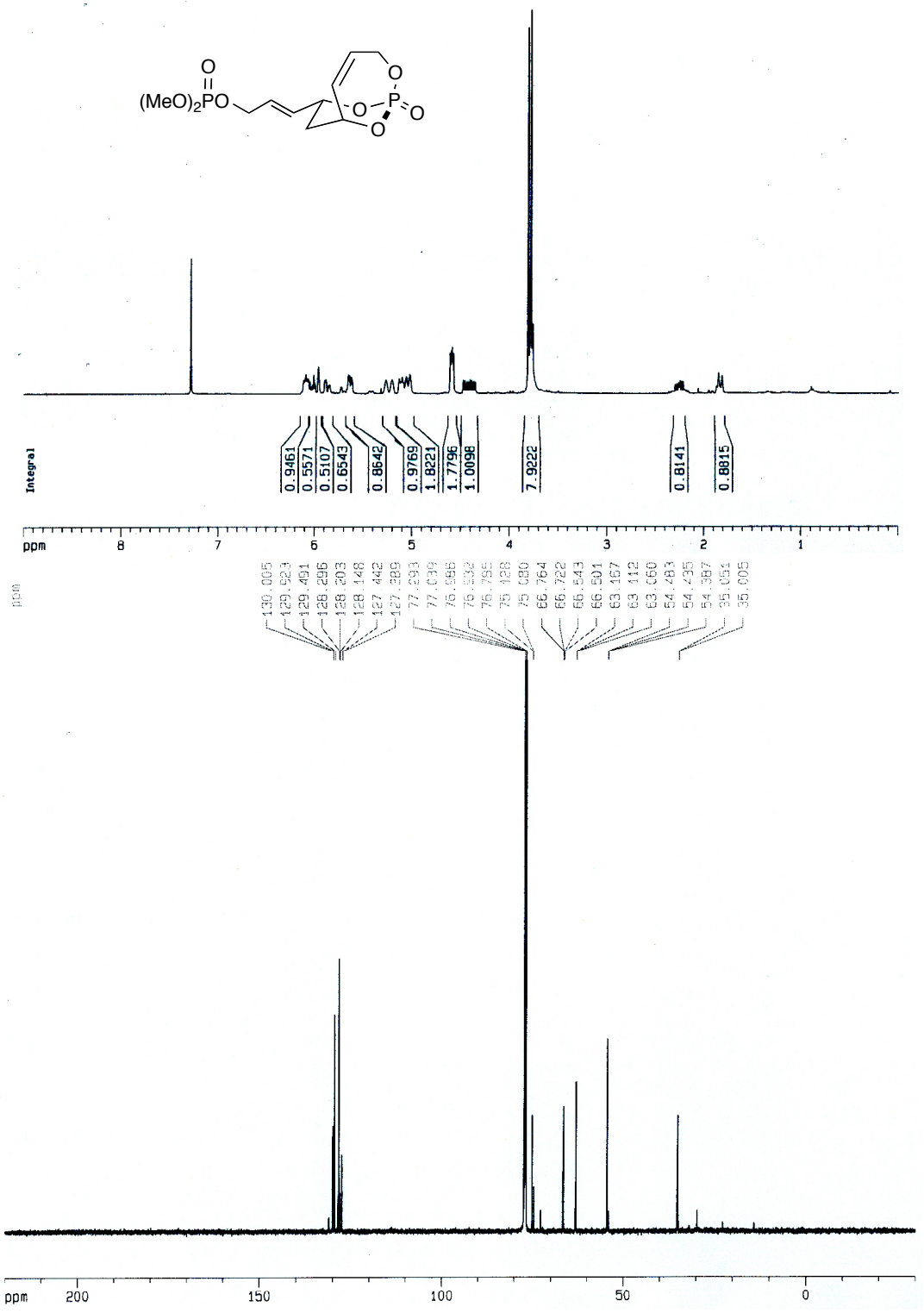
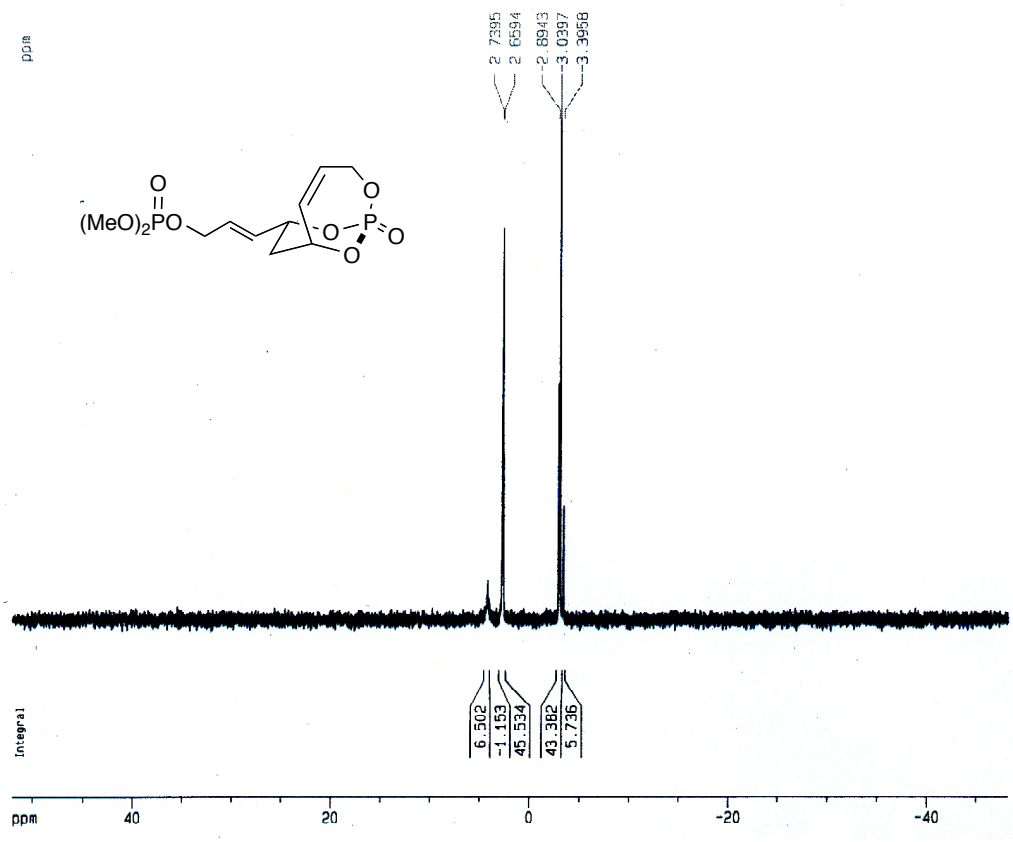
2.7516
TBSO
O
O
P
O
O
ppm
40
20
0
-20
-40

Boc-Protected Allyl Amine derived Bicyclo[4.3.1]phosphate Triester: 2.57

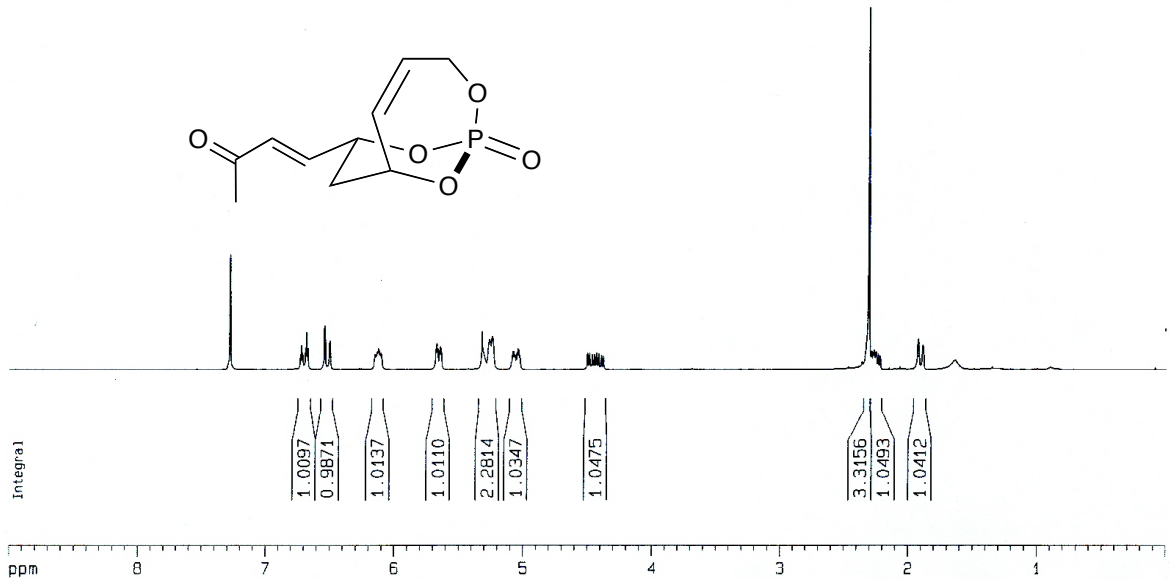

ppm
2.9557
BocNH
O
O
P
O
O
ppm
40
20
0
-20
-40

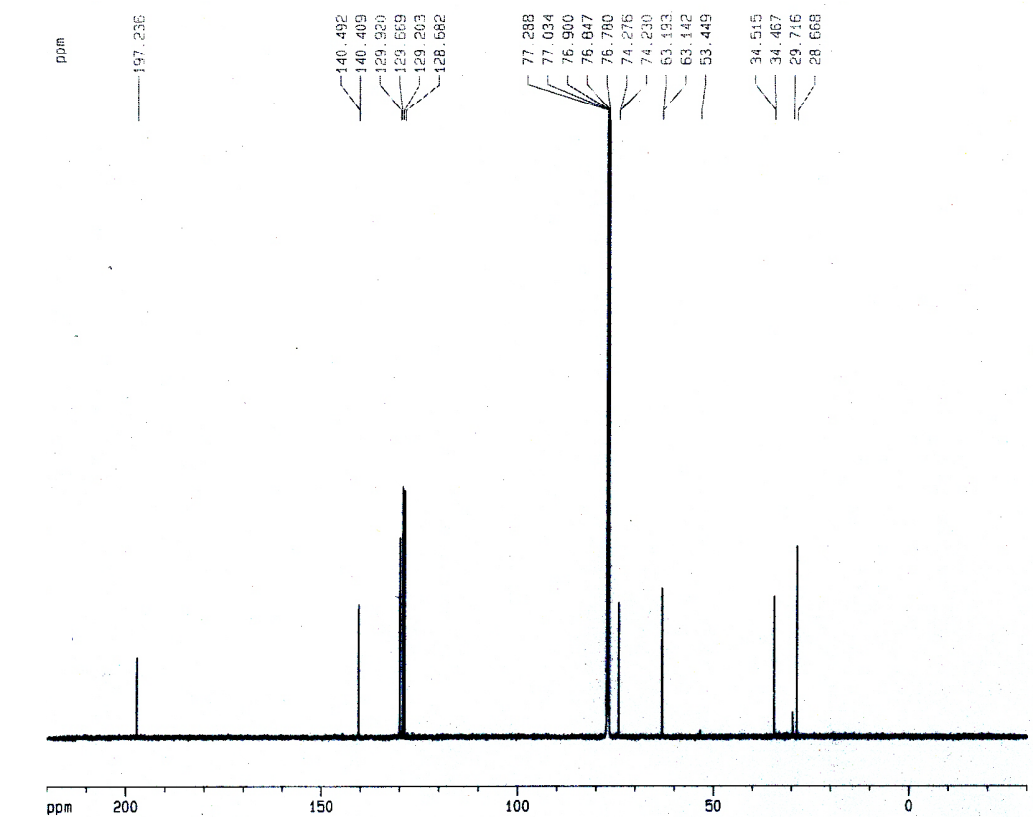
Allyl Phosphate derived Bicyclo[4.3.1]phosphate Triester: 2.58

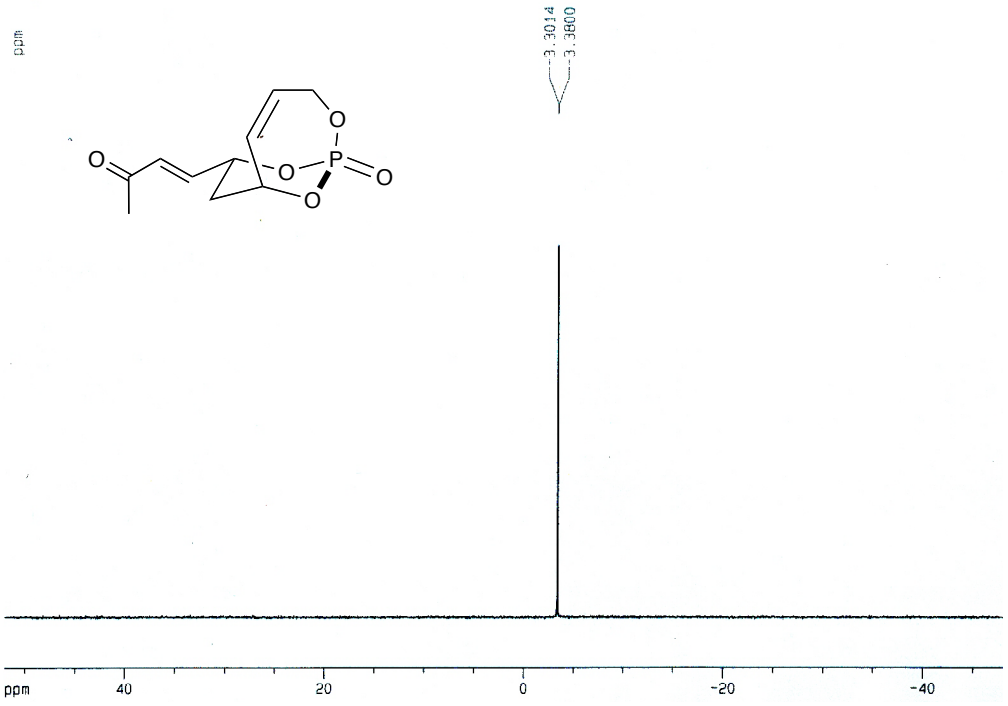



ppm
2.7395
2.6594
2.8943
3.0397
3.3958
O
(MeO)2PO
O
O
P
O
O
Integral
6.502
-1.153
45.534
43.382
5.736
ppm
40
20
0
-20
-40

Methyl Vinyl Ketone derived Bicyclo[4.3.1]phosphate Triester: 2.54






ppm
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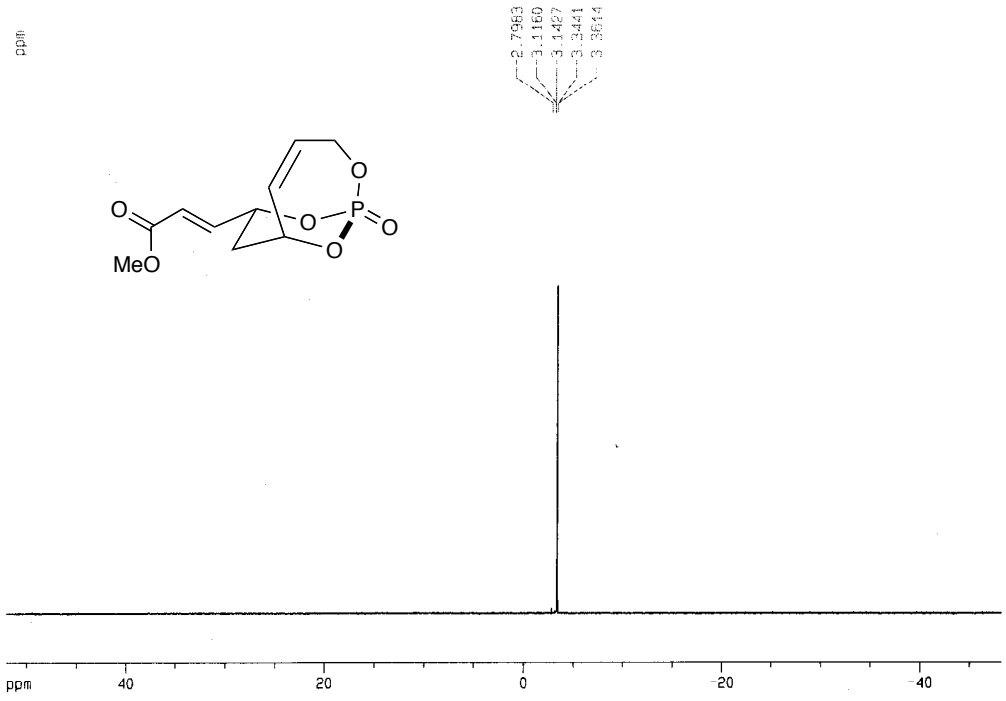
3.3860
O
O
P
O
O
O
ppm
40
20
0
-20
-40

Methyl acrylate derived Bicyclo[4.3.1]phosphate Triester: 2.60


ppm
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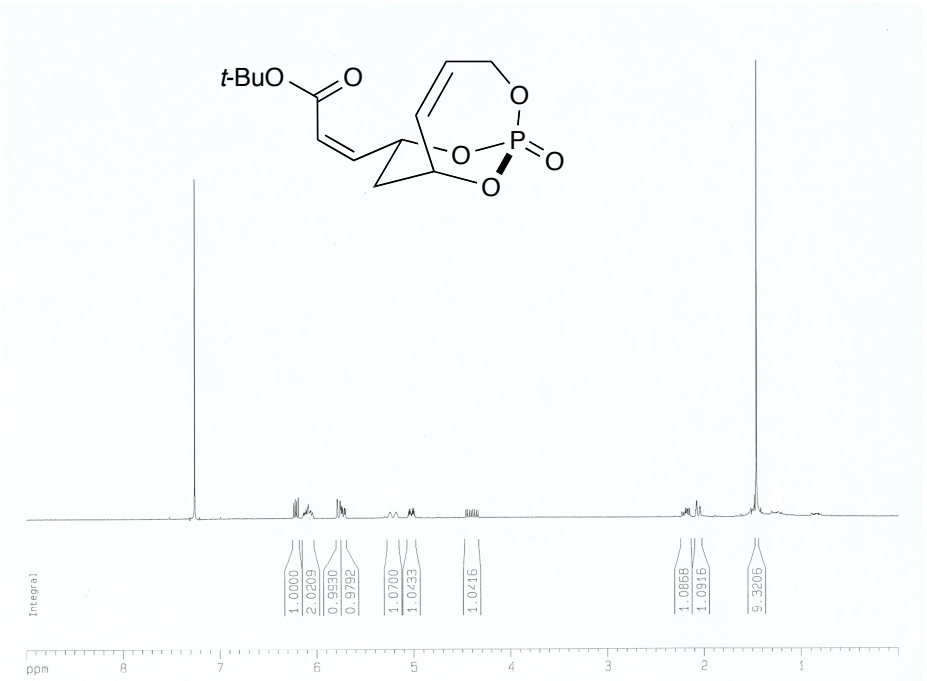
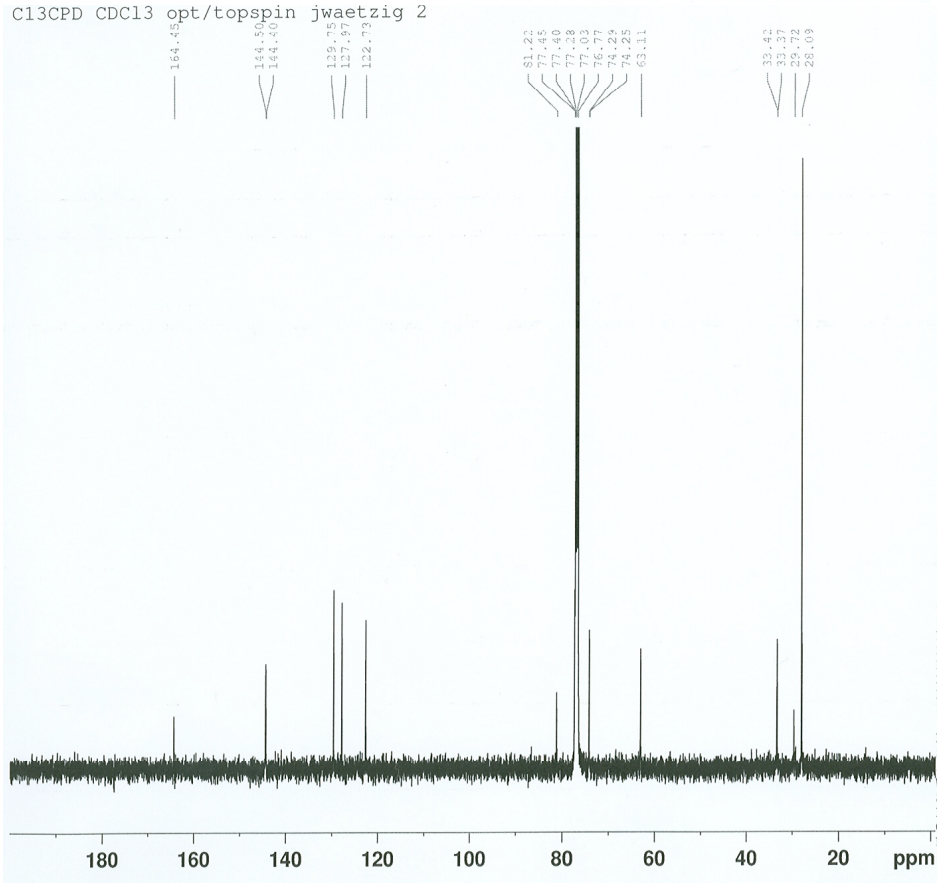
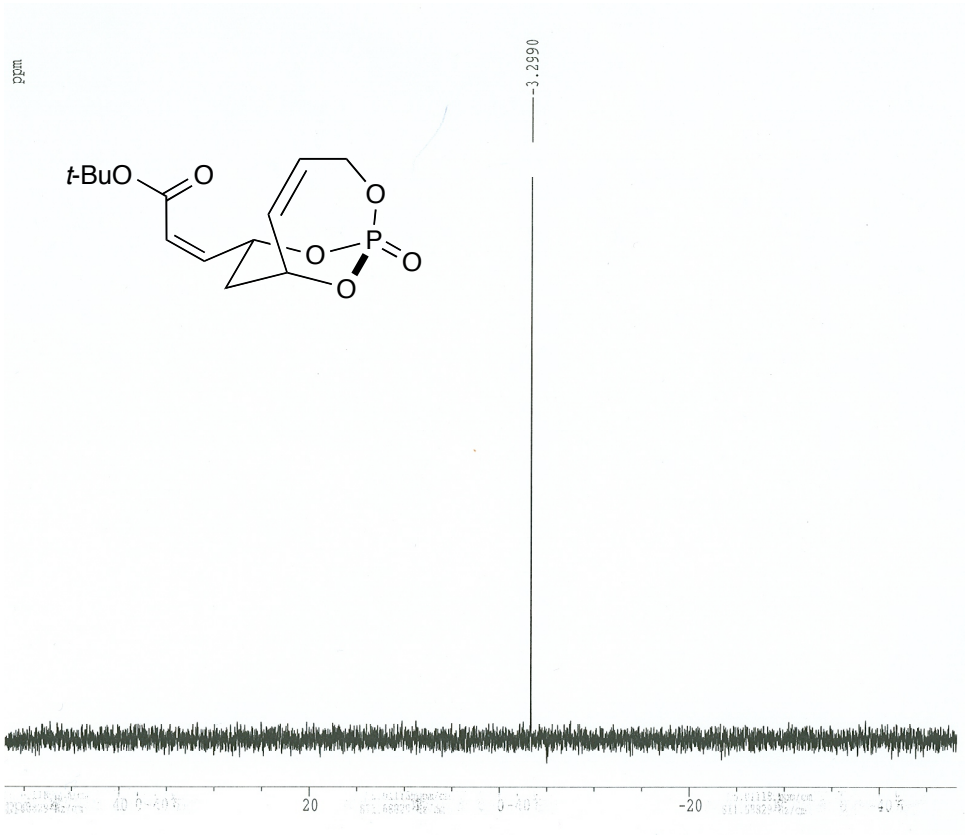
3.1166
3.1427
3.3441
3.3614
O
O
O
P
O
O
MeO
ppm
40
20
0
-20
-40

_t_-Butyl acrylate derived Bicyclo[4.3.1]phosphate Triester: 2.61



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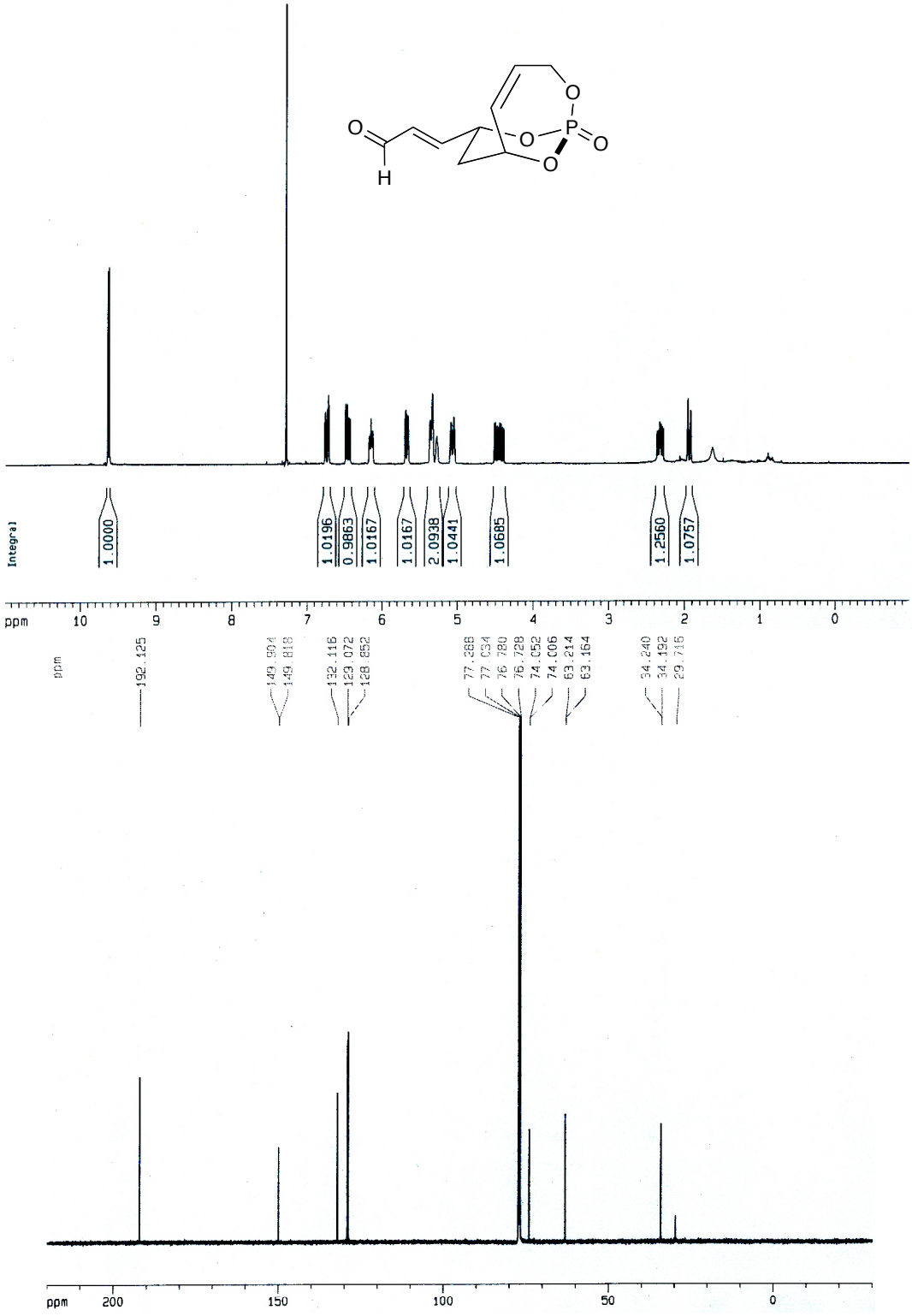
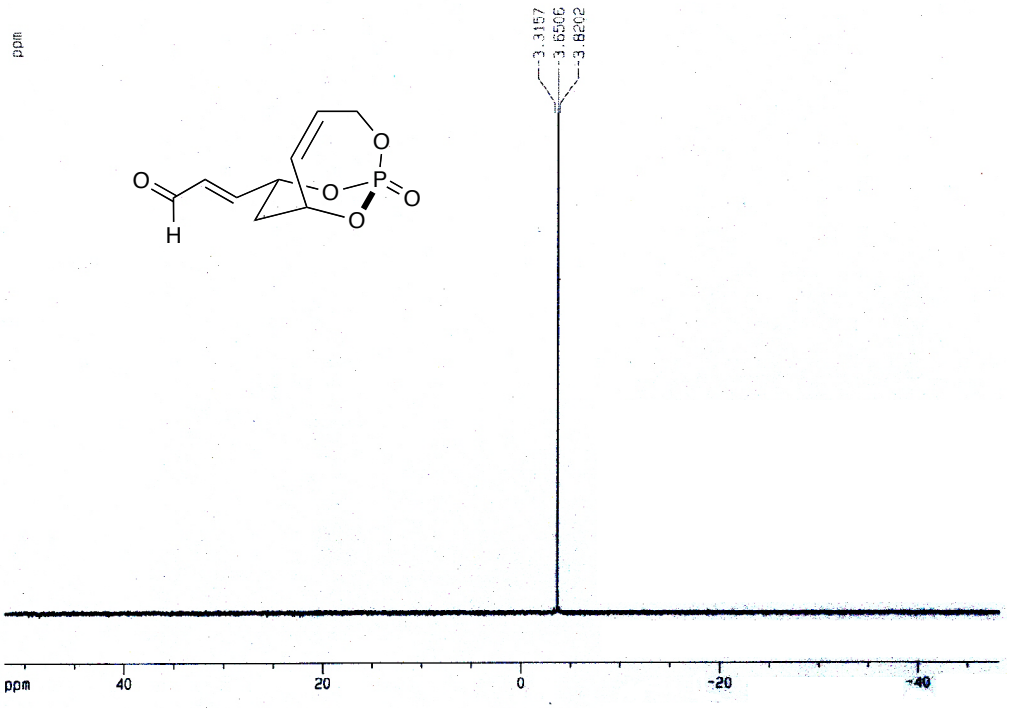
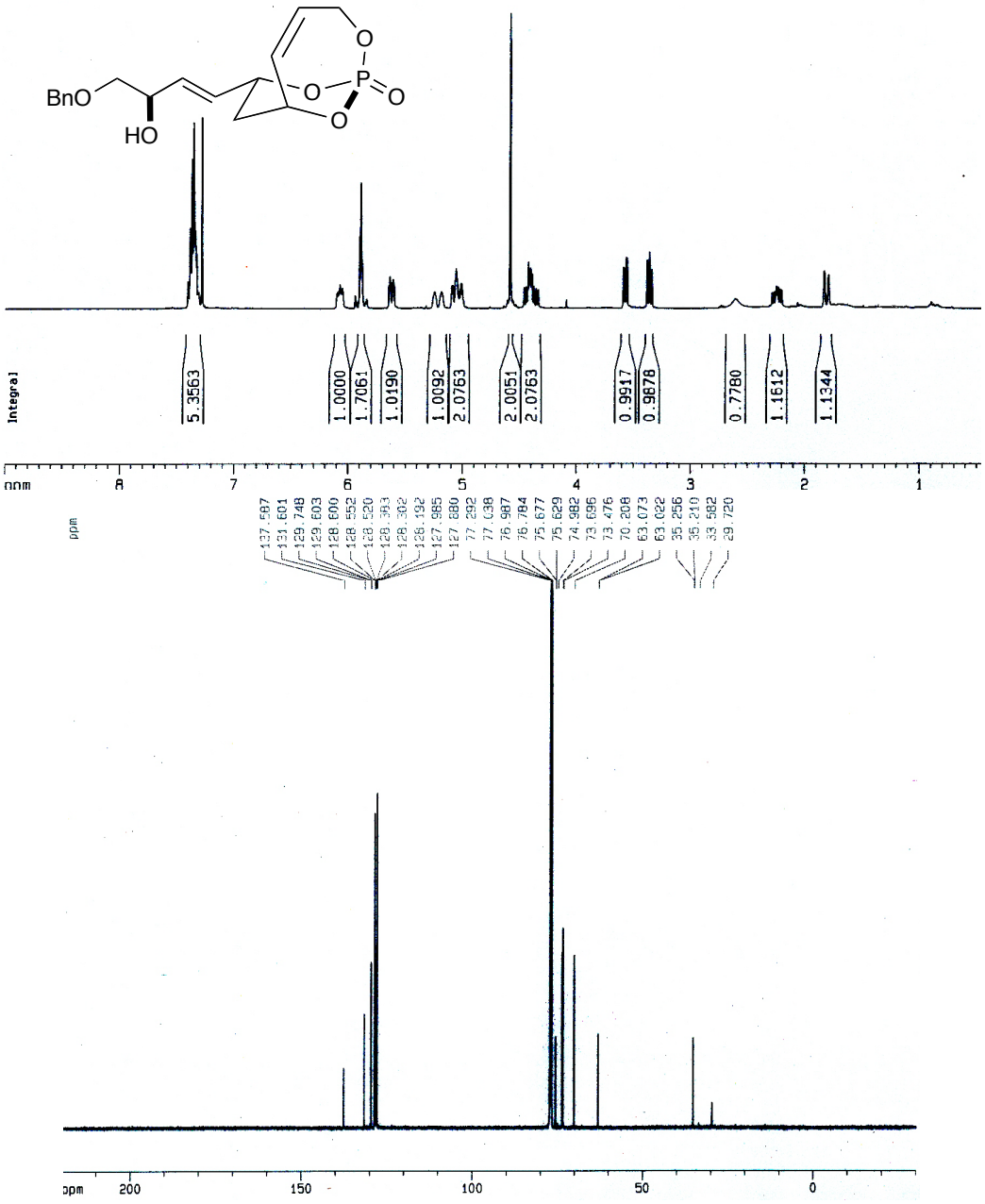
t-BuO
O
O
O
P
O
O
20
-20

Acrolein derived Bicyclo[4.3.1]phosphate Triester: 2.62

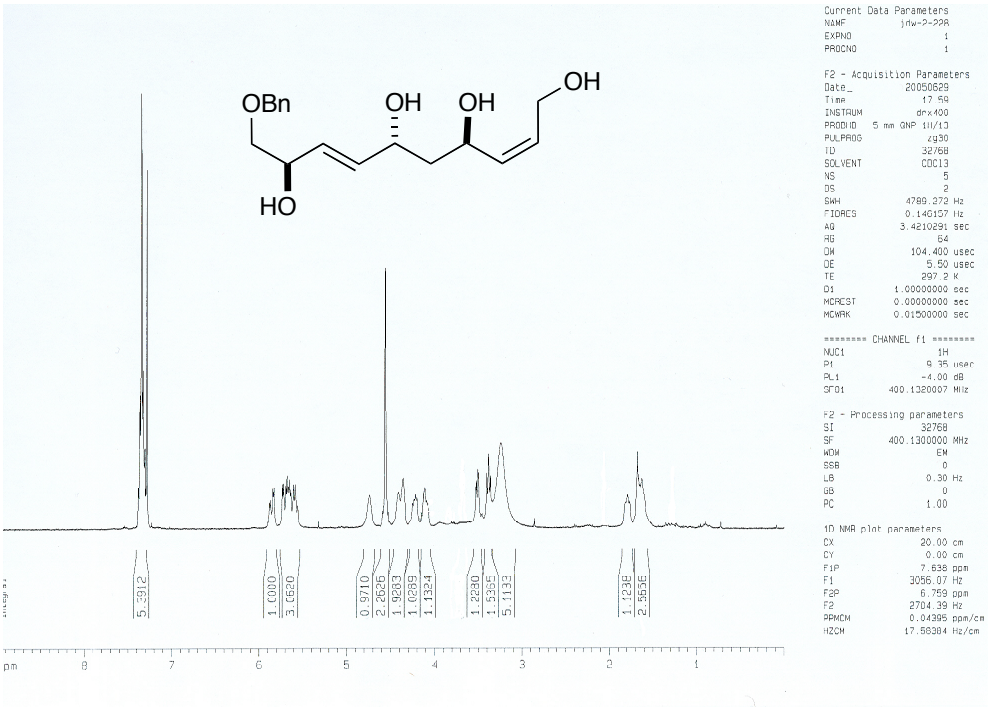


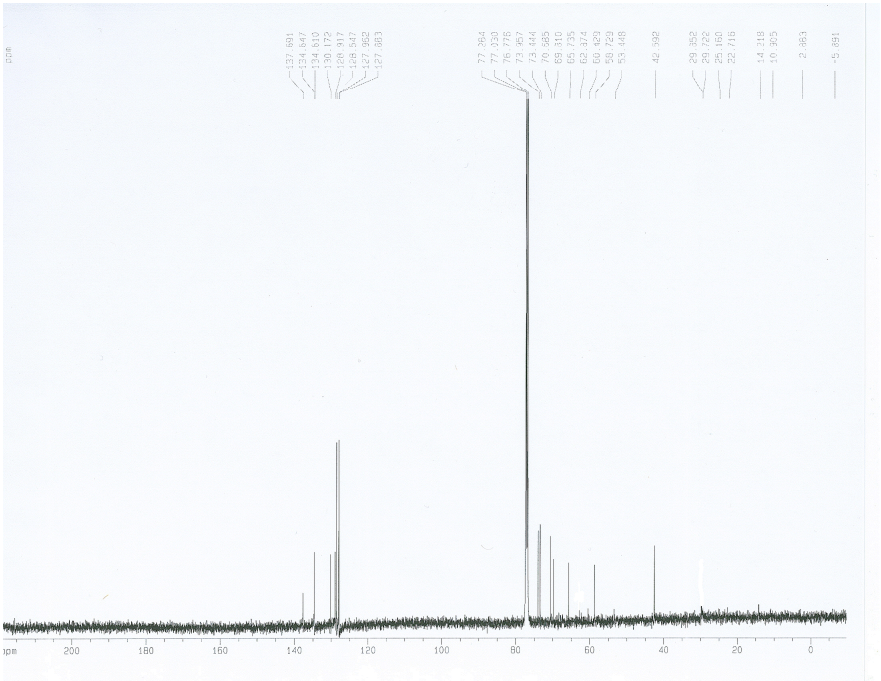

ppm
3.3157
3.6506
3.8202
O
O
P
O
O
O
H
ppm
40
20
0
-20
-40

(*R*)-1-(Benzyloxy)buten-2-ol derived Bicyclo[4.3.1]phosphate Triester: 2.63

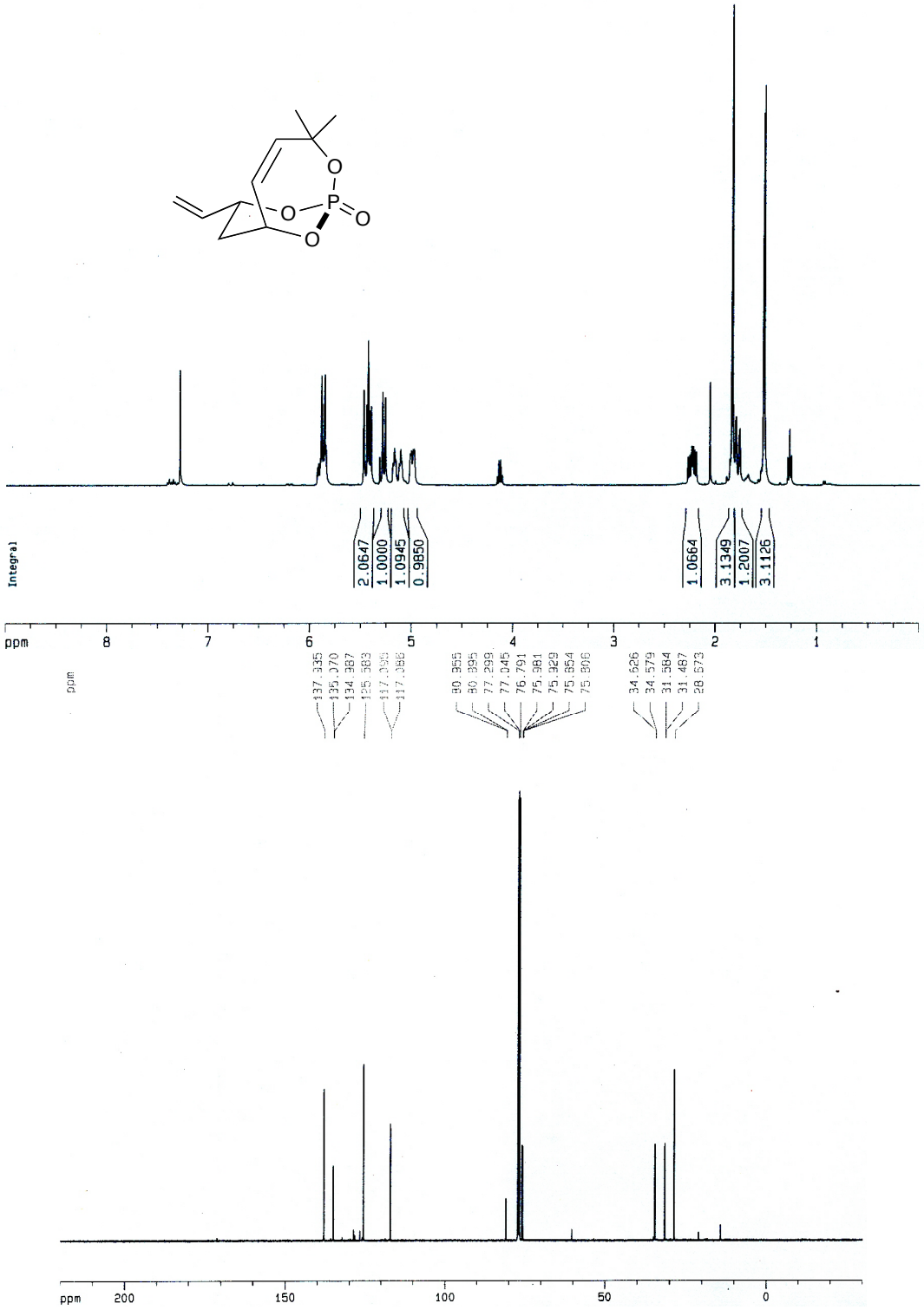


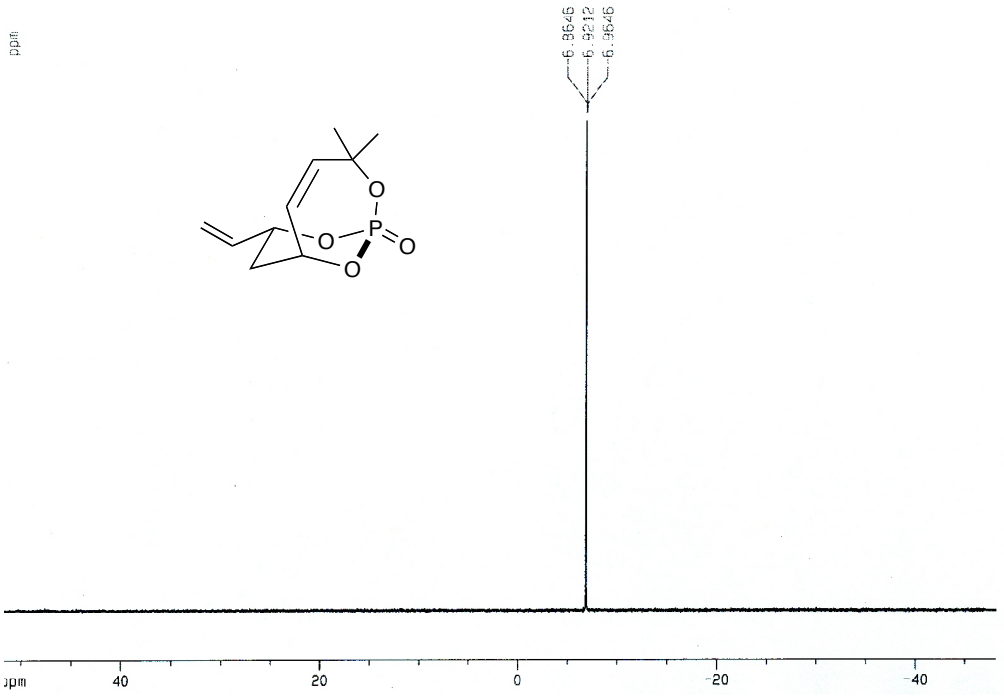
(2*Z*,4*R*,6*R*,7*E*,9*R*)-10-(benzyloxy)deca-2,7-diene-1,4,6,9-tetraol: 2.64



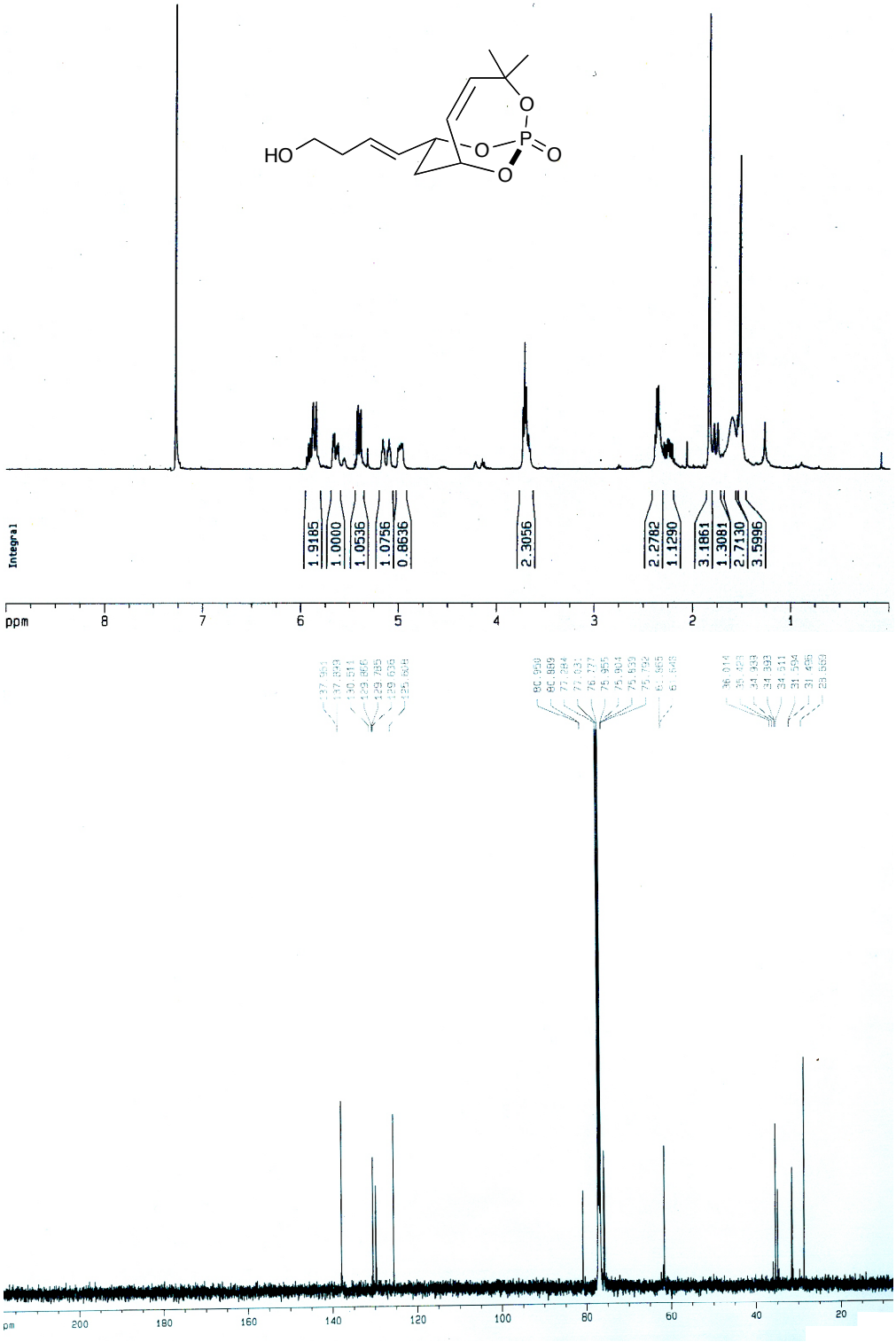


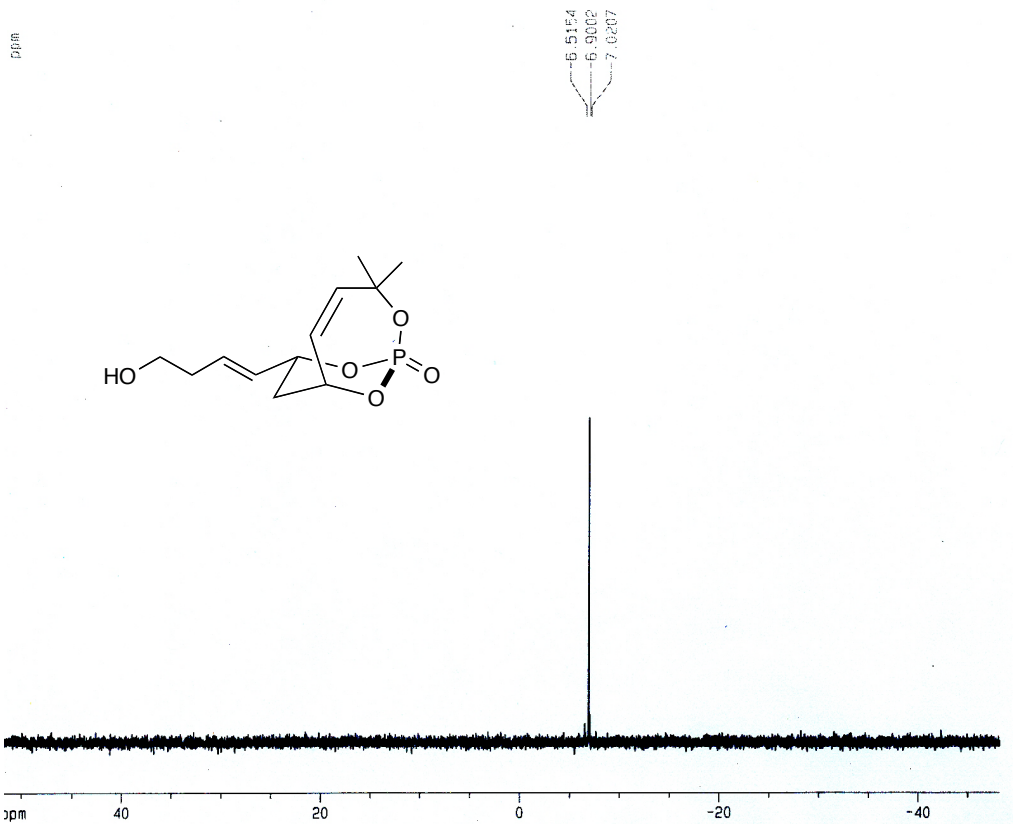
Second Generation Bicyclic Phosphate: 2.66



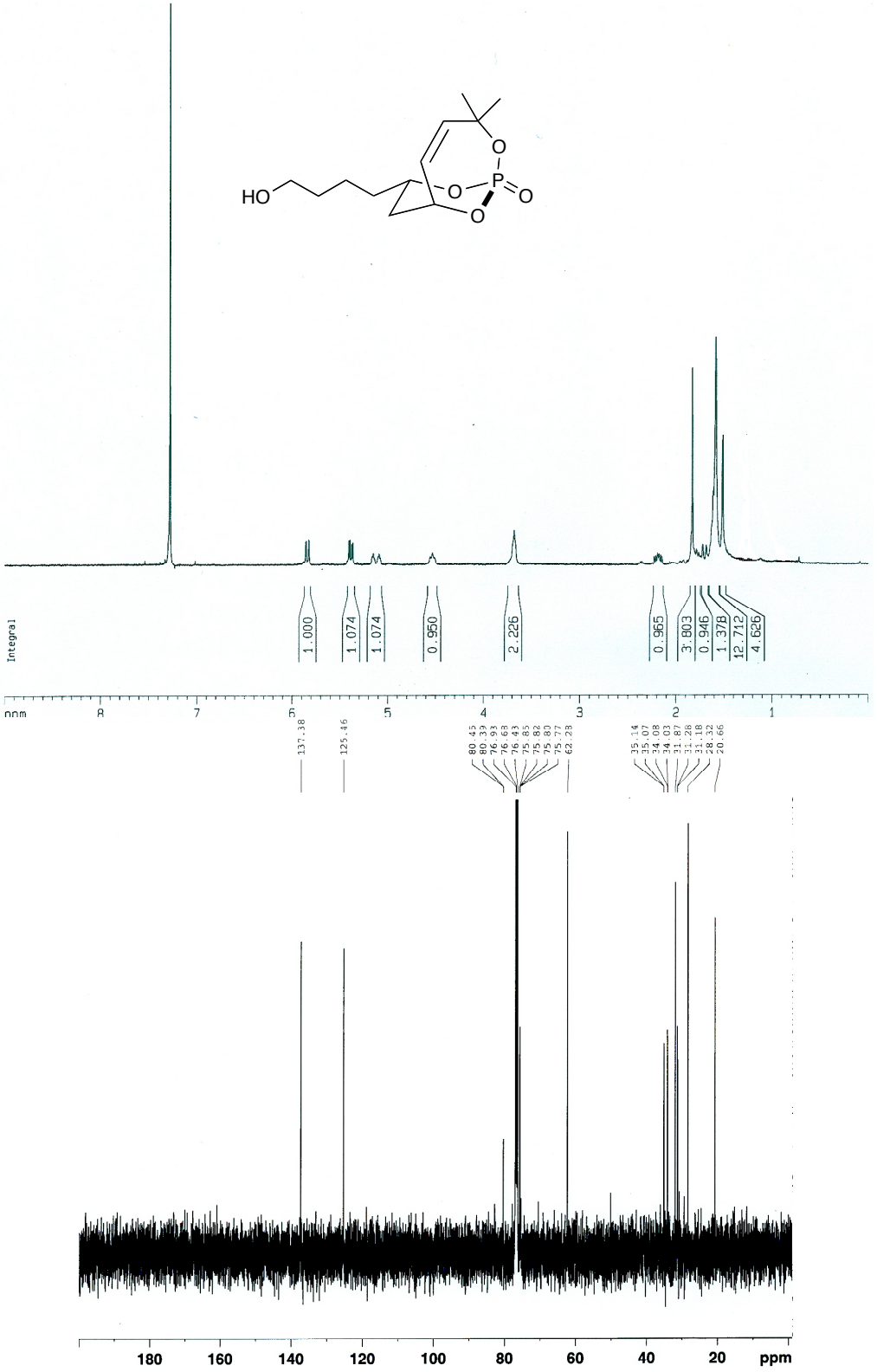

ppm
6.9645
6.9212
6.9646
O
O
P
O
O
O
ppm
40
20
0
-20
-40

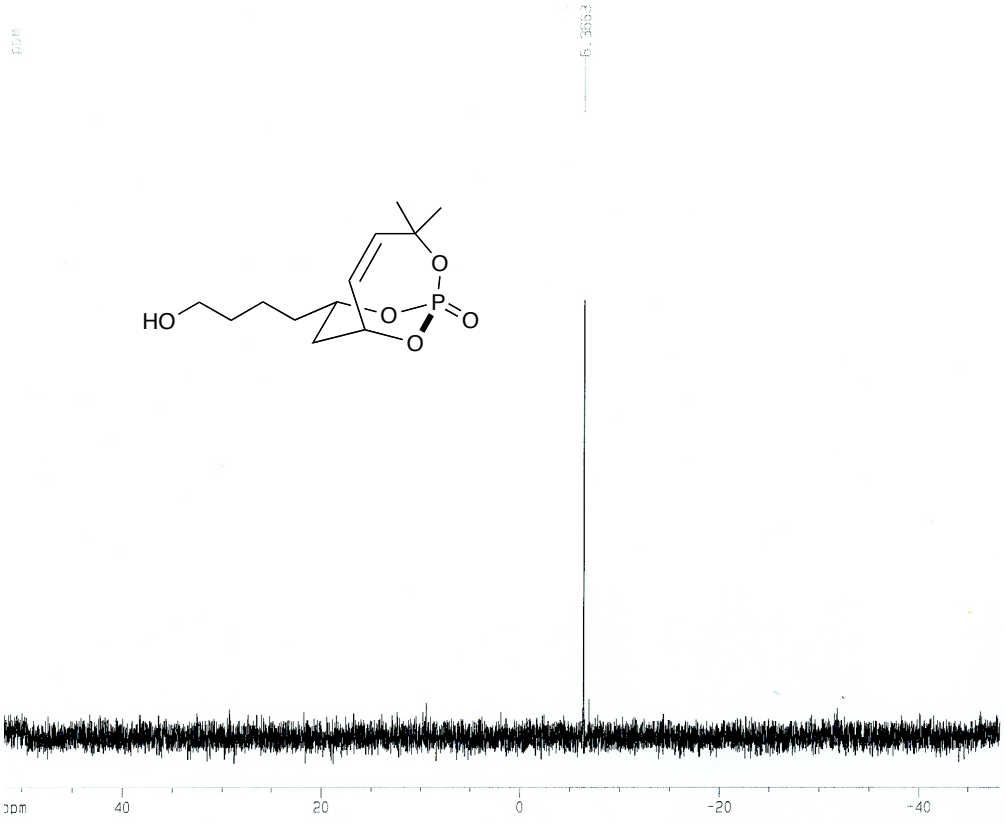
Allyl Alcohol Derive Second Generation Bicyclic Phosphate: 2.67



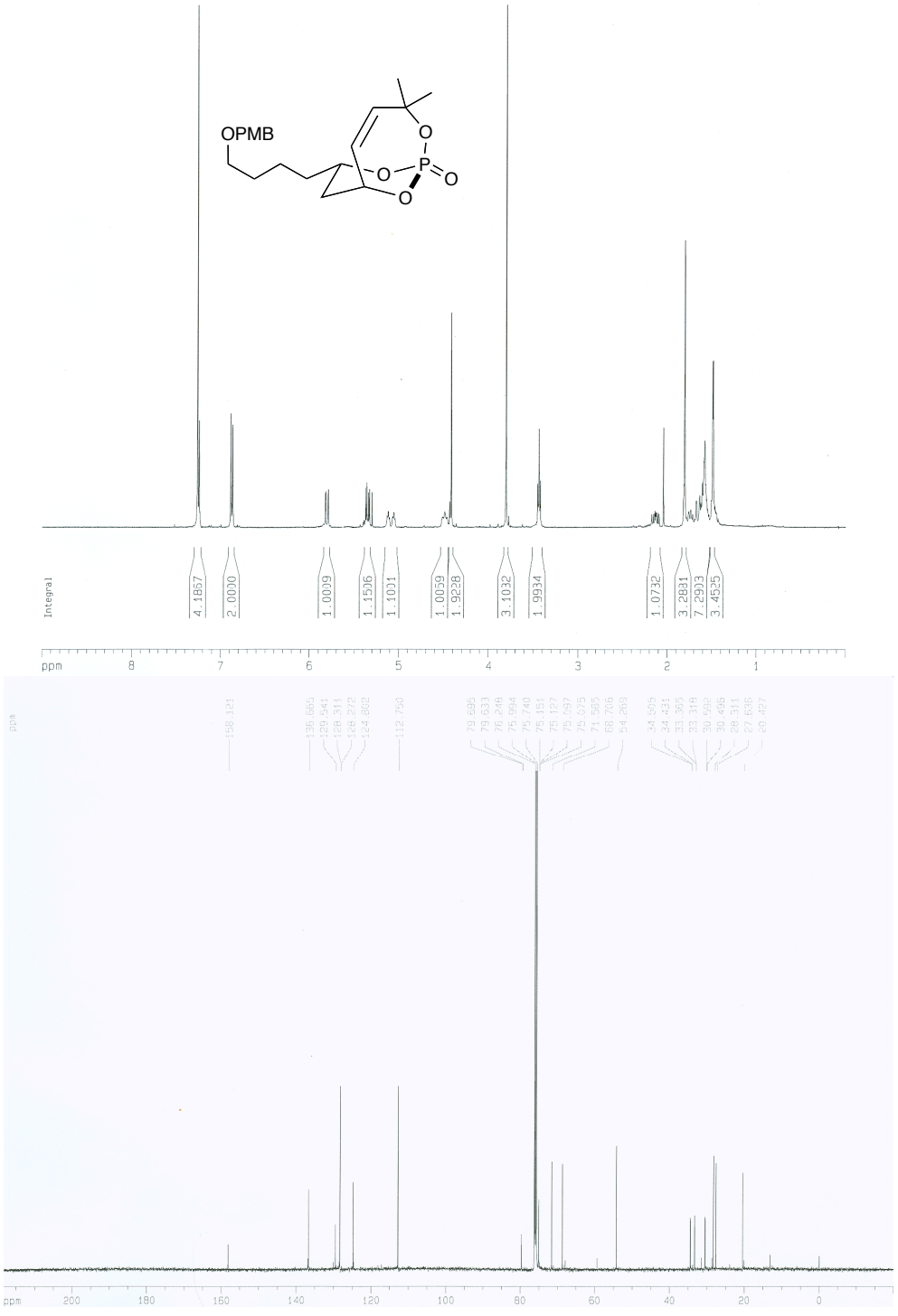

6.5154
6.9002
7.0207
HO
O
O
P
O
O
ppm
40
20
0
-20
-40

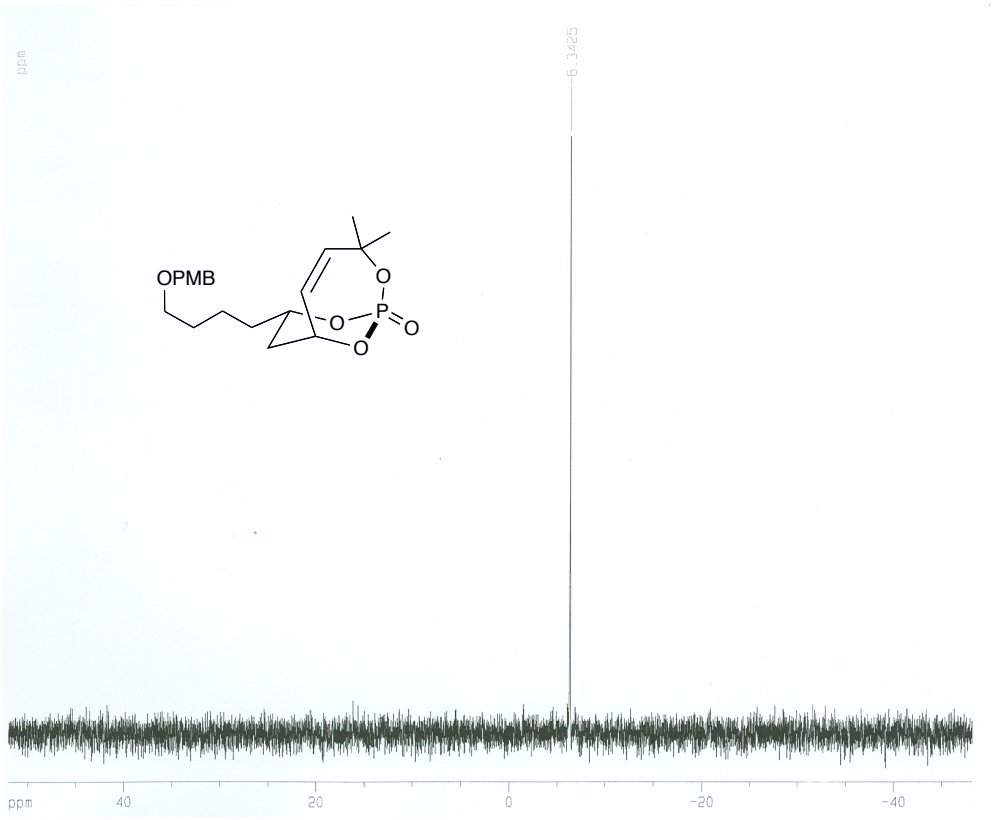
Partially Hydrogenation Alcohol derive Second Generation Phosphate: 2.68



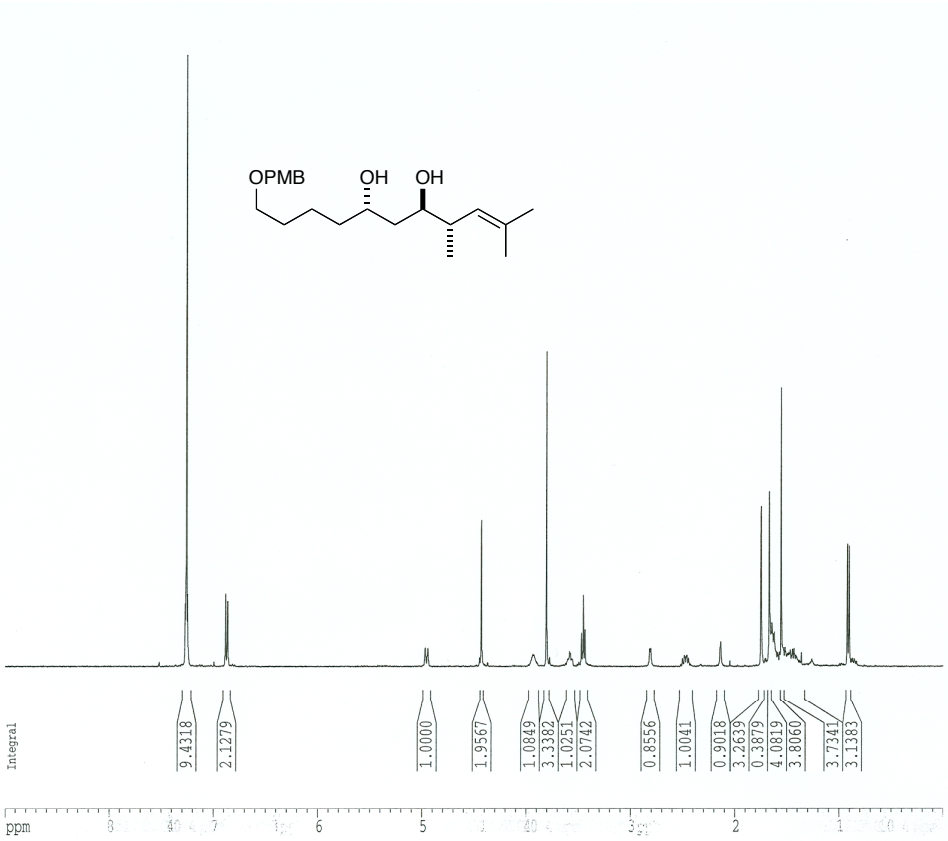

HO
O
P
O
O
O
ppm
40
20
0
-20
-40

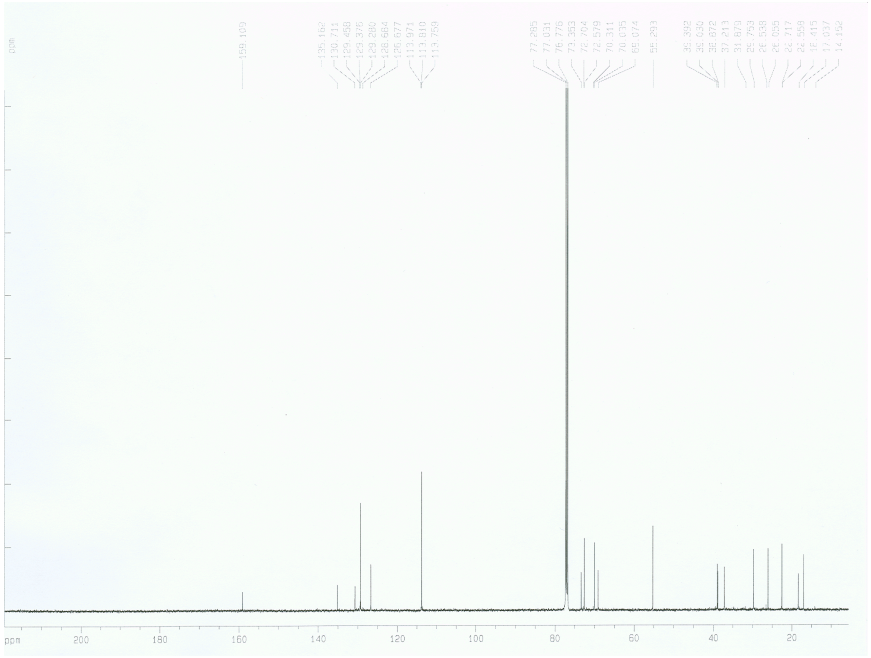
PMB-Protected Hydrogenated Second Generation Phosphate: 2.69



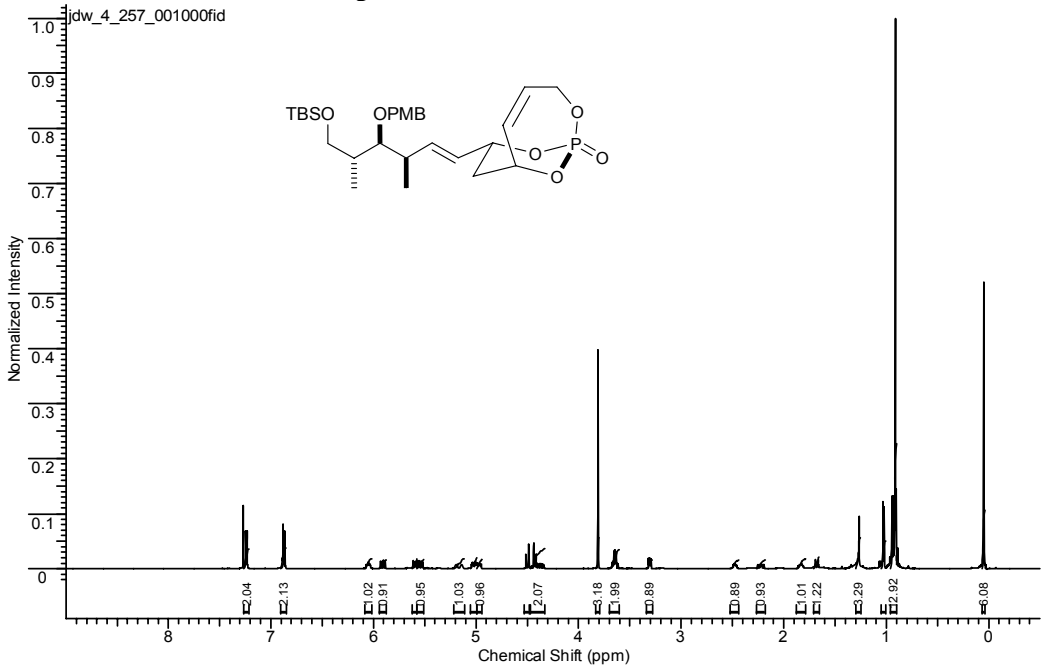

ppm
6.3425
OPMB
O
O
P
O
O
ppm
40
20
0
-20
-40

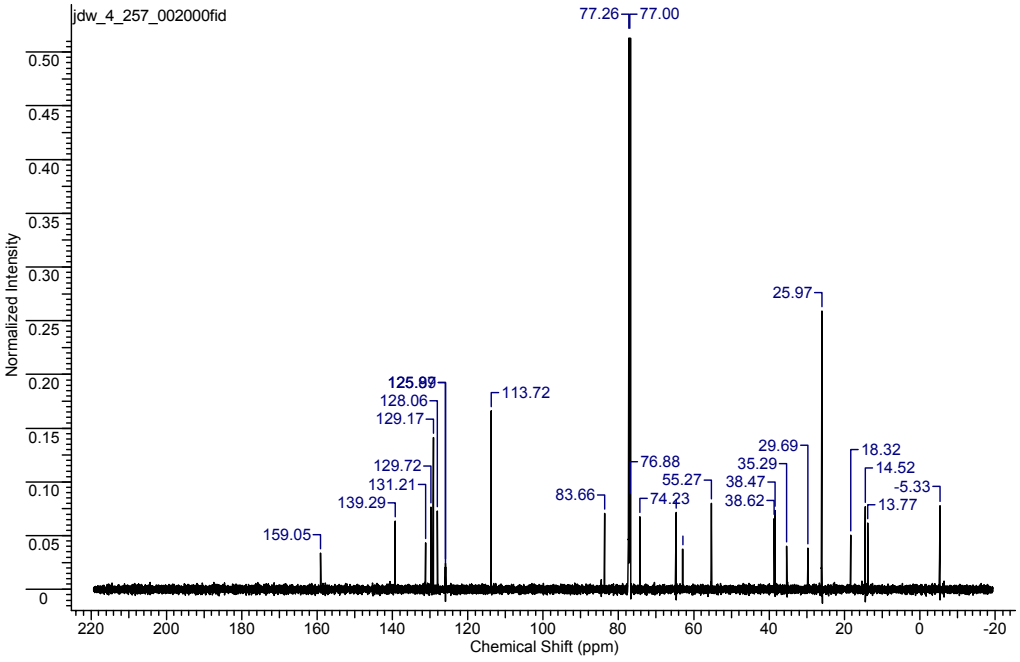
(4*S*,5*R*,7*S*)-11-(4-methoxybenzyloxy)-2,4-dimethylundec-2-ene-5,7-diol: 2.70

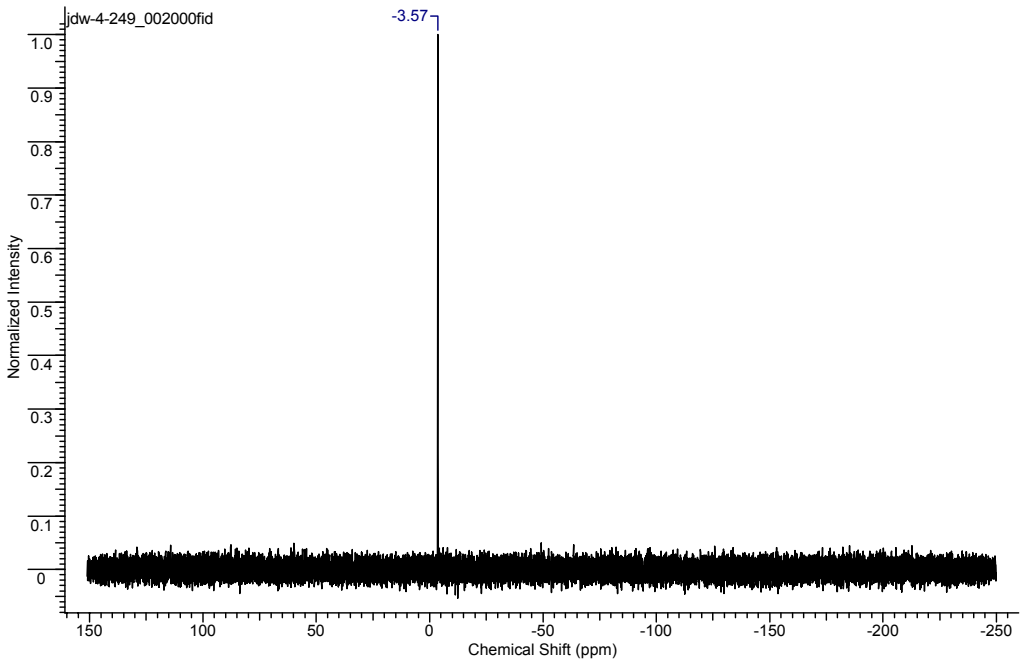




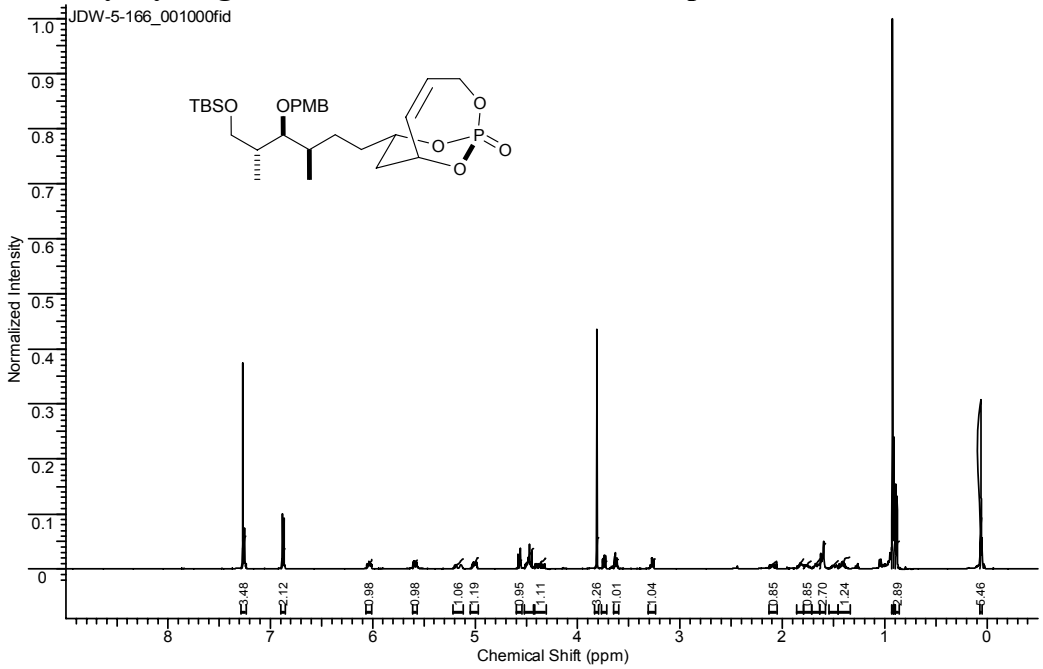
TBS-PMB Protected Phosphate: 3.26

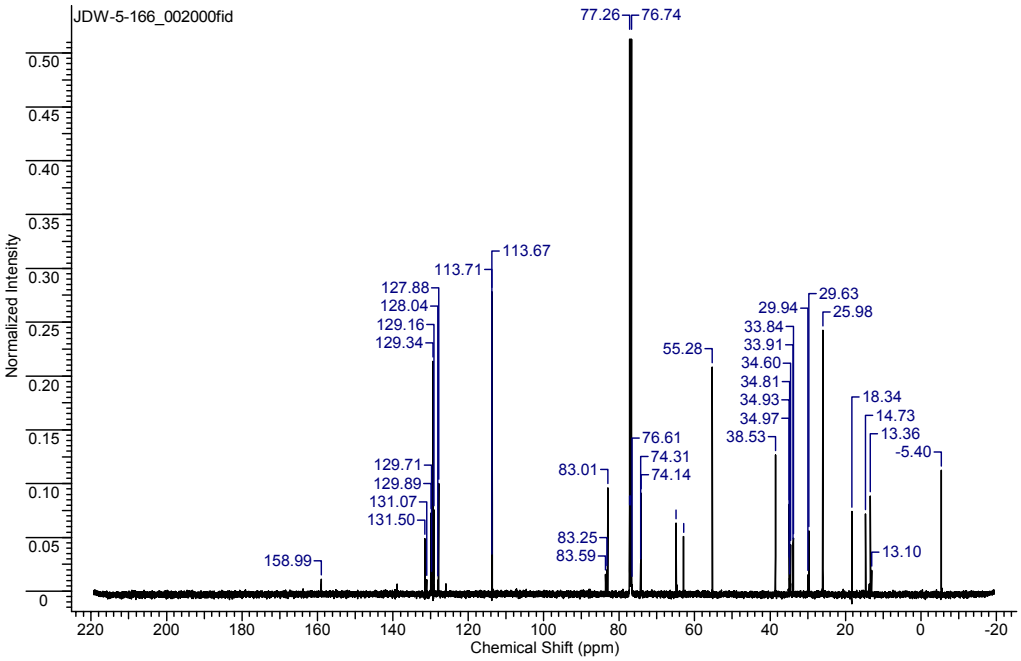


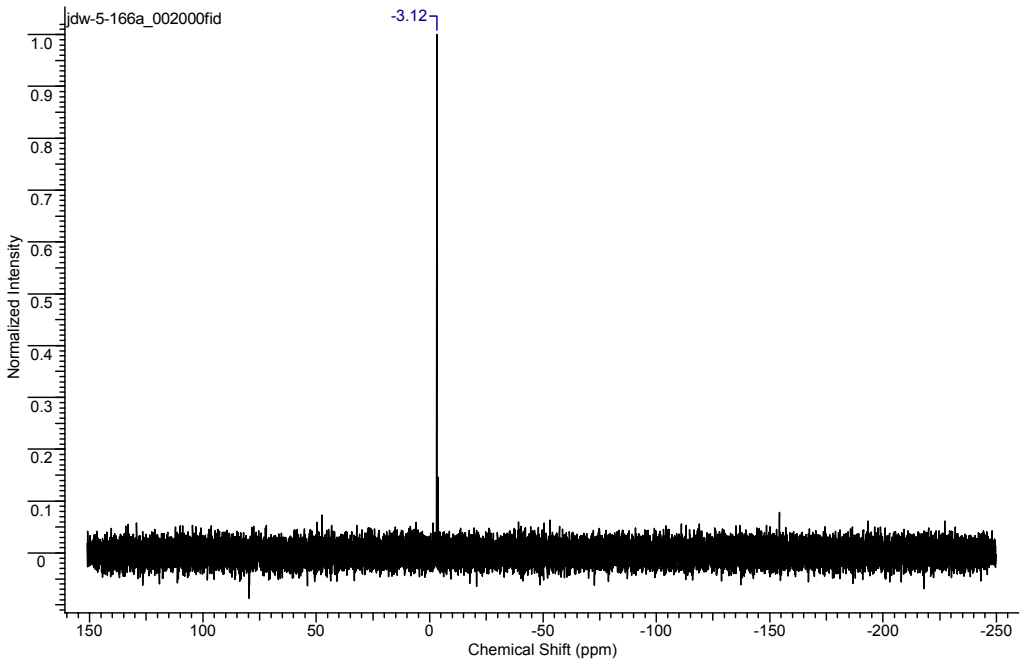



jdw-4-249_002000fid
-3.57
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
150
100
50
0
-50
-100
-150
-200
-250
Chemical Shift (ppm)

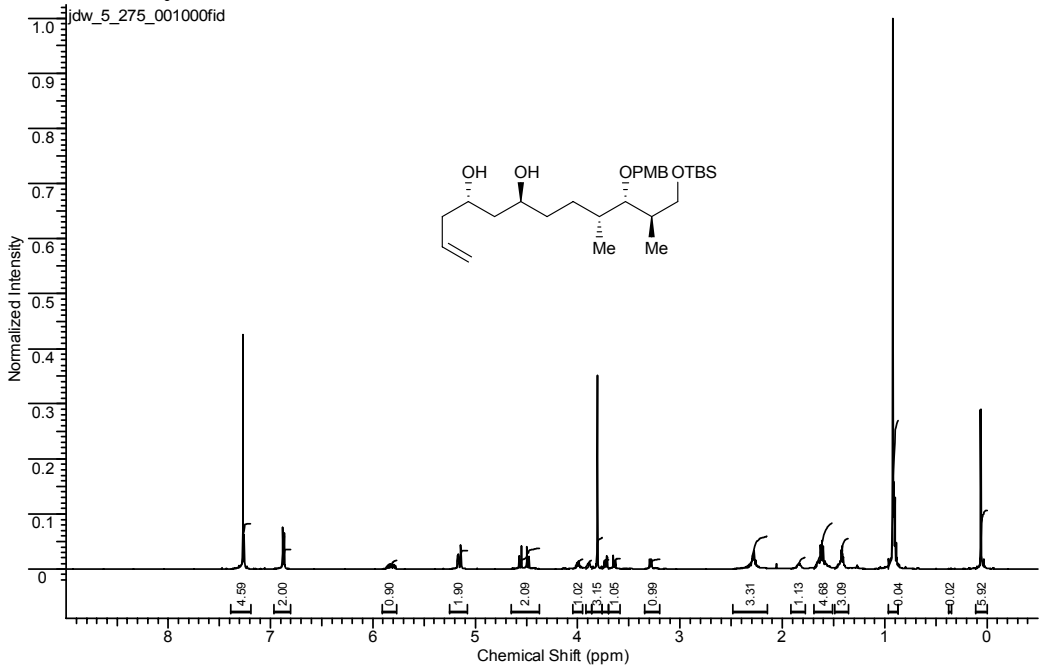
Partially Hydrogenated TBS-PMB Protected Phosphate: 3.27

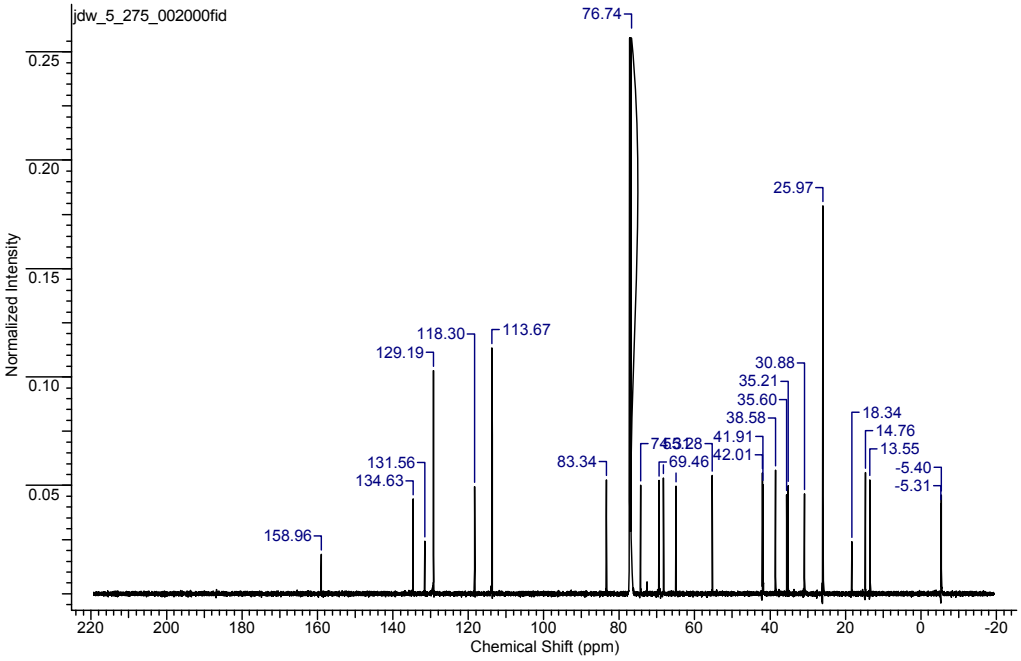




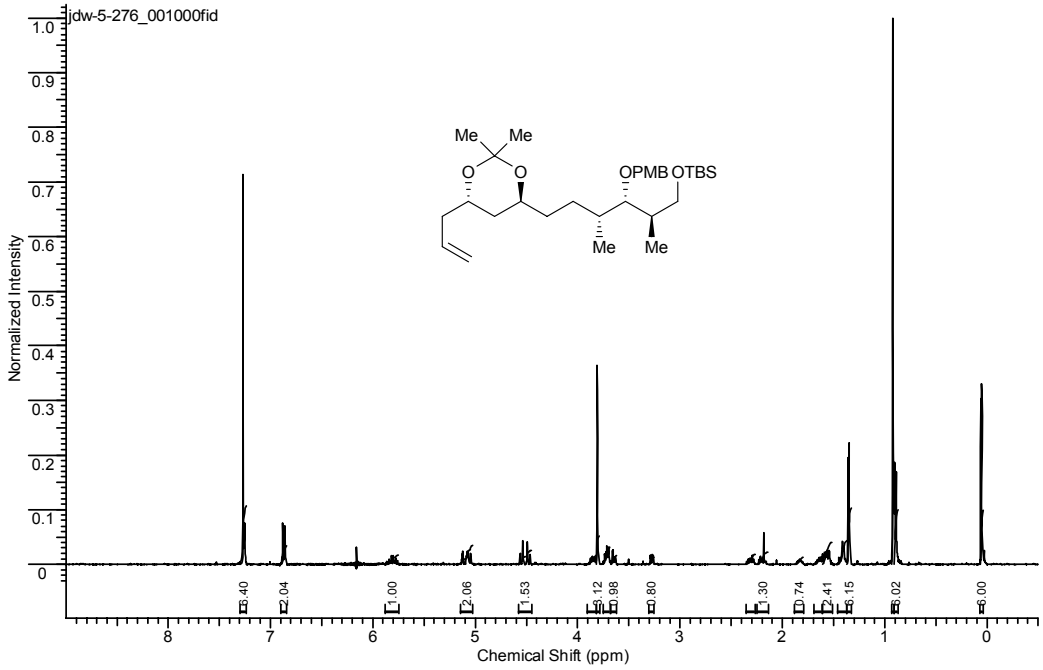

jdw-5-166a_002000fid
-3.12
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
150
100
50
0
-50
-100
-150
-200
-250
Chemical Shift (ppm)

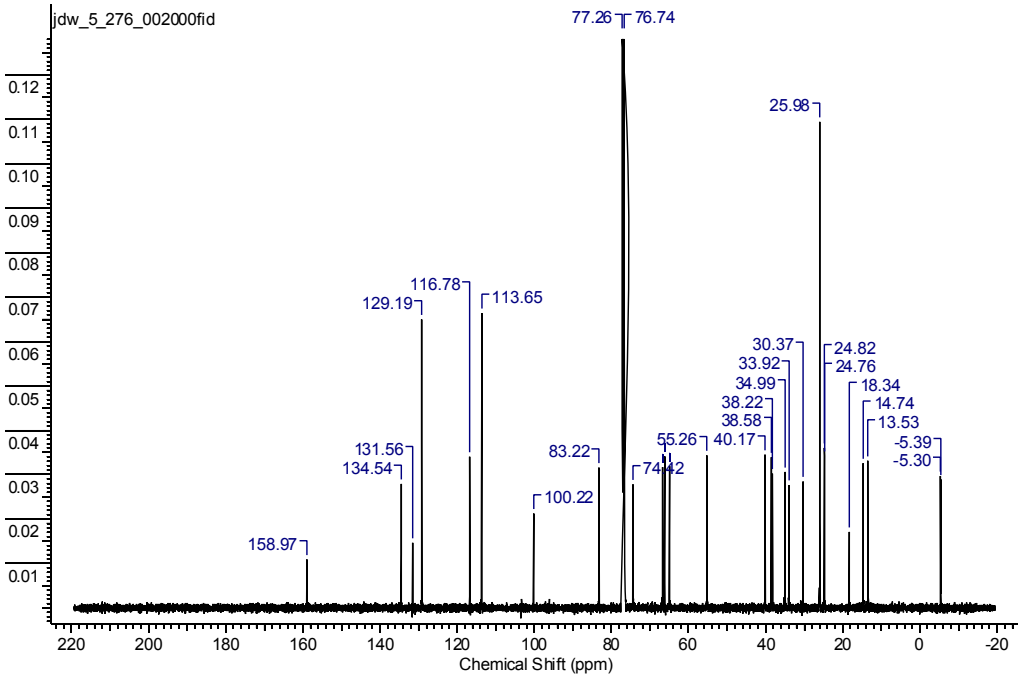
(4*S*,6*S*,9*R*,10*S*,11*R*)-12-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)-9,11-dimethyldodec-1-ene-4,6-diol: 3.31



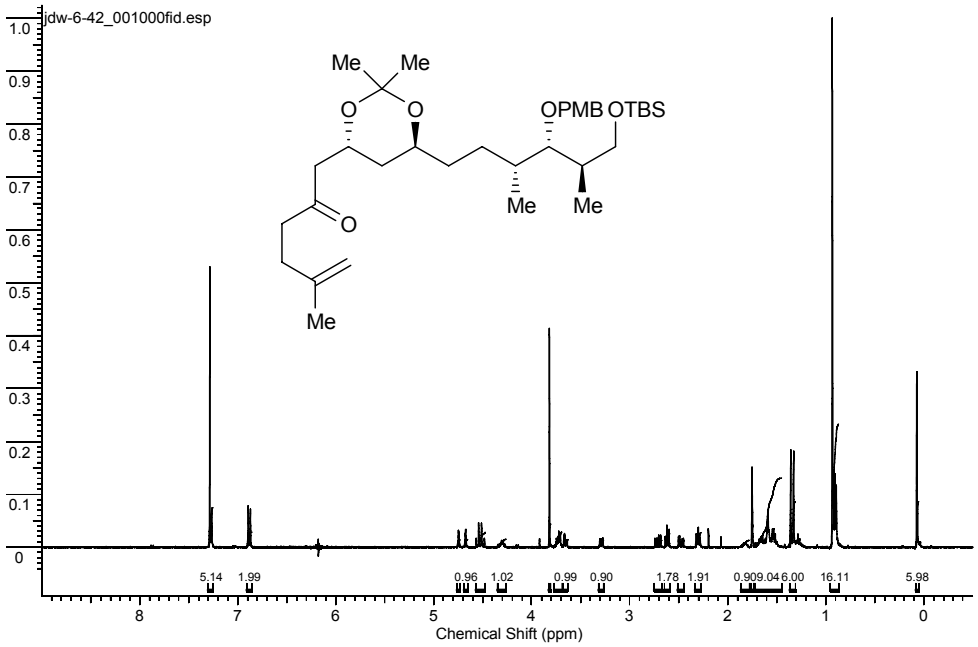


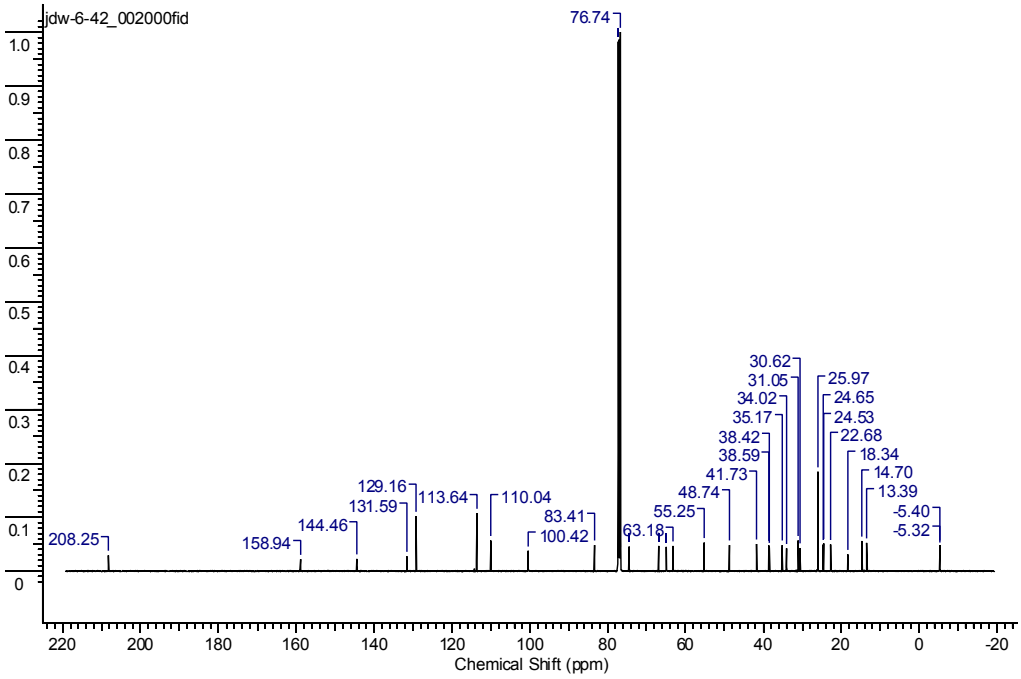
((2*R*,3*S*,4*R*)-6-((4*S*,6*S*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)-3-(4-methoxybenzyloxy)-2,4-dimethylhexyloxy)(*tert*-butyl)dimethylsilane: 3.32



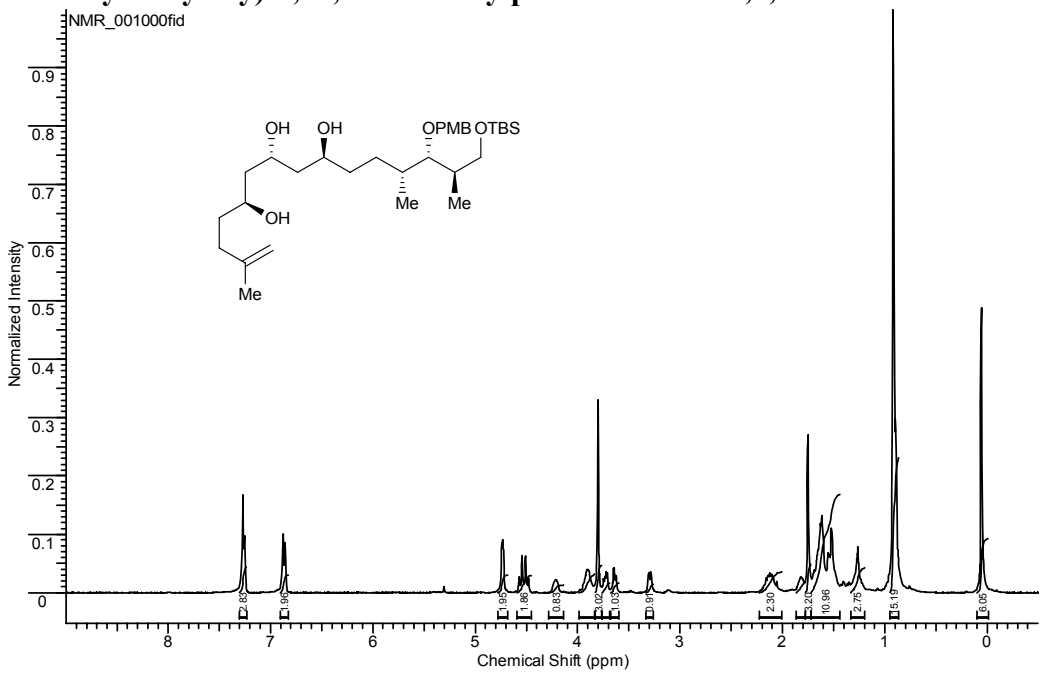


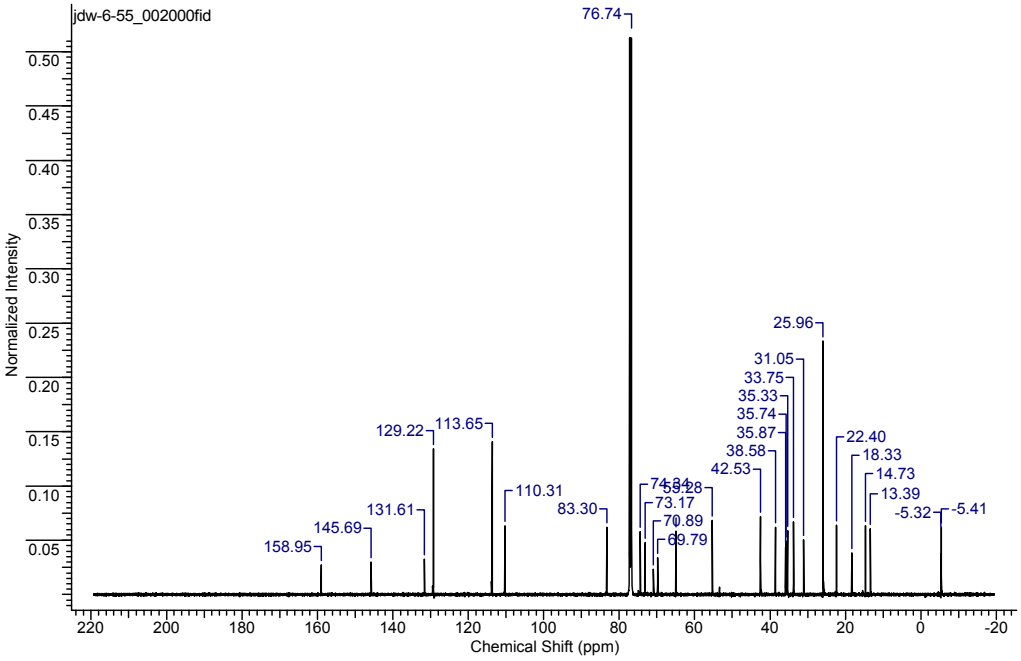
1-((4*R*,6*S*)-6-((3*R*,4*S*,5*R*)-6-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-3,5-dimethylhexyl)-2,2-dimethyl-1,3-dioxan-4-yl)-5-methylhex-5-en-2-one: 3.35



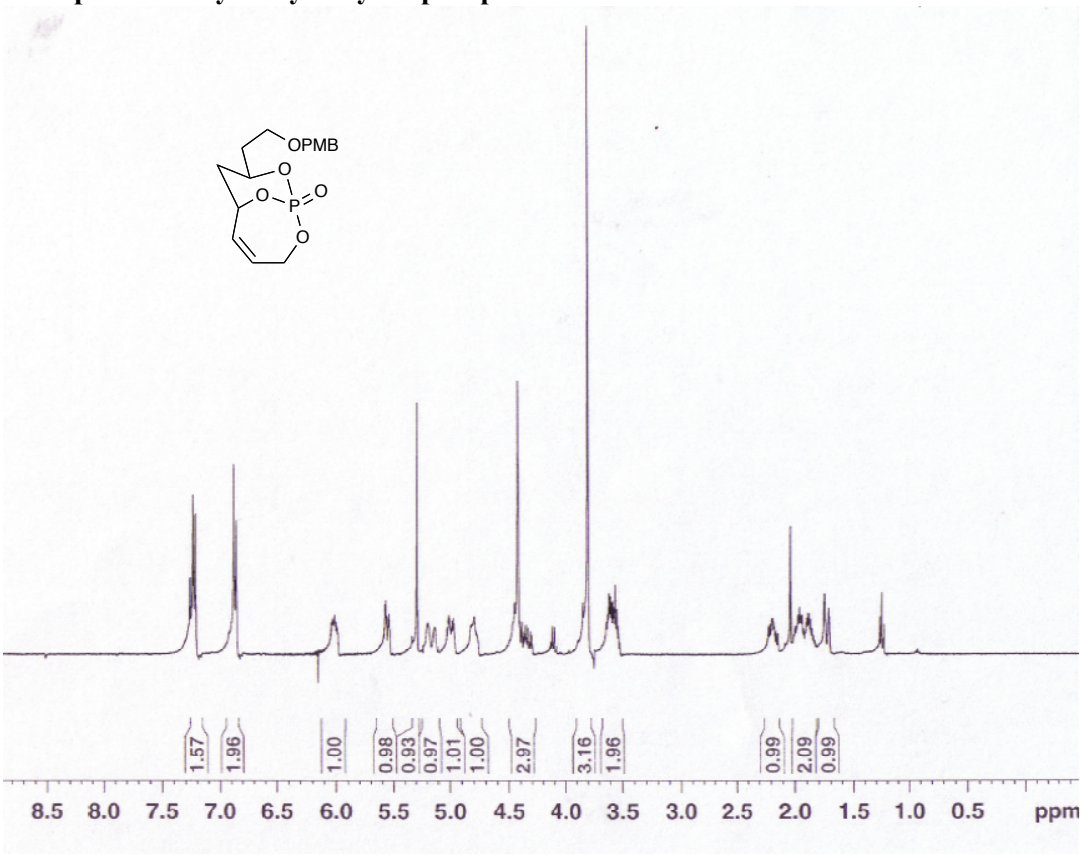


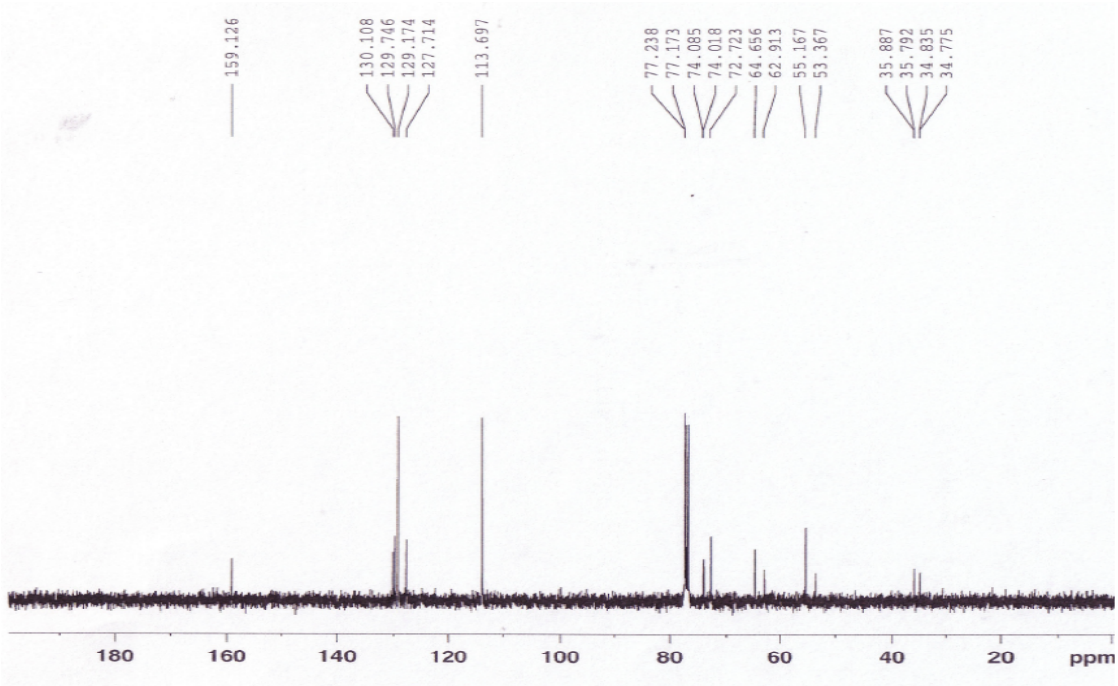
(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-15-(*tert*-butyldimethylsilyloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethylpentadec-1-ene-5,7,9-triol 3.37

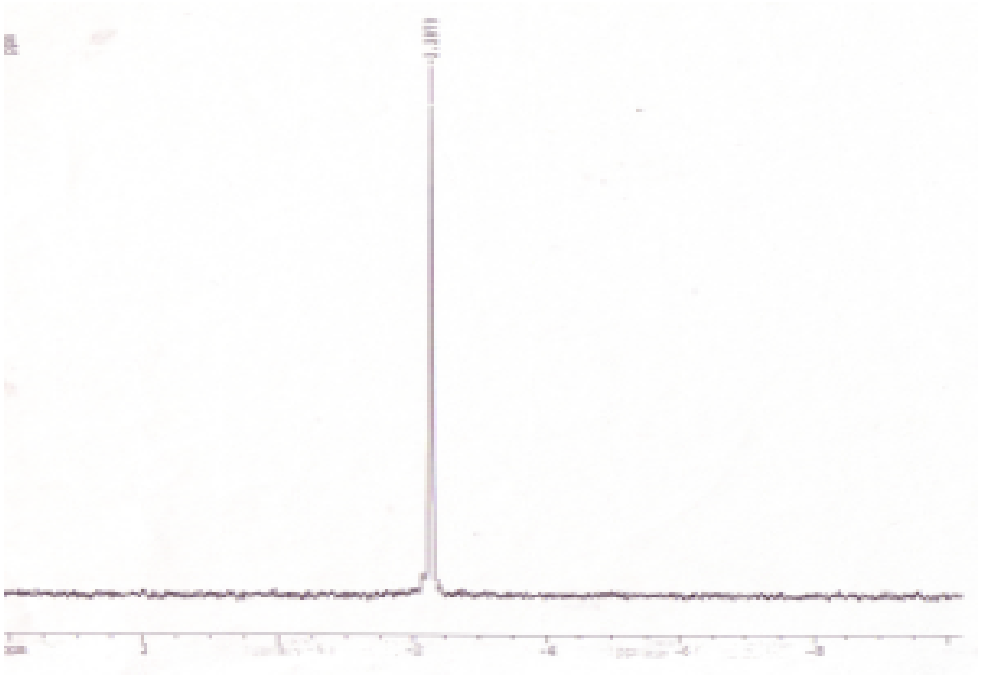




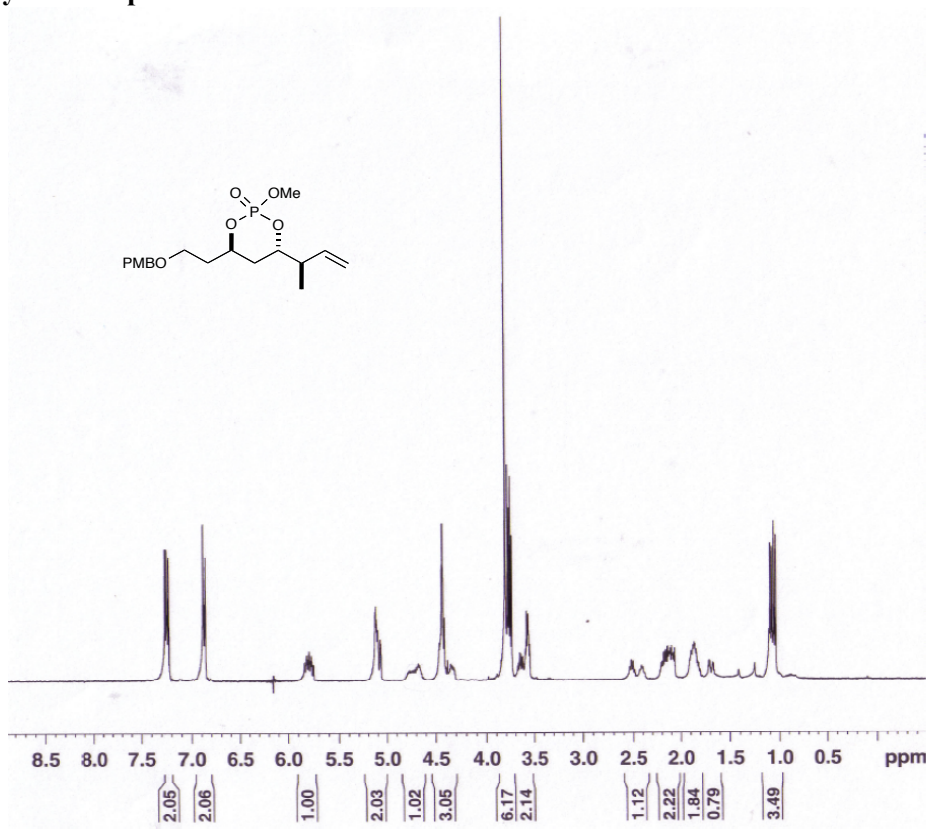
PMB protected hydroxyl bicyclic phosphate: 3.41

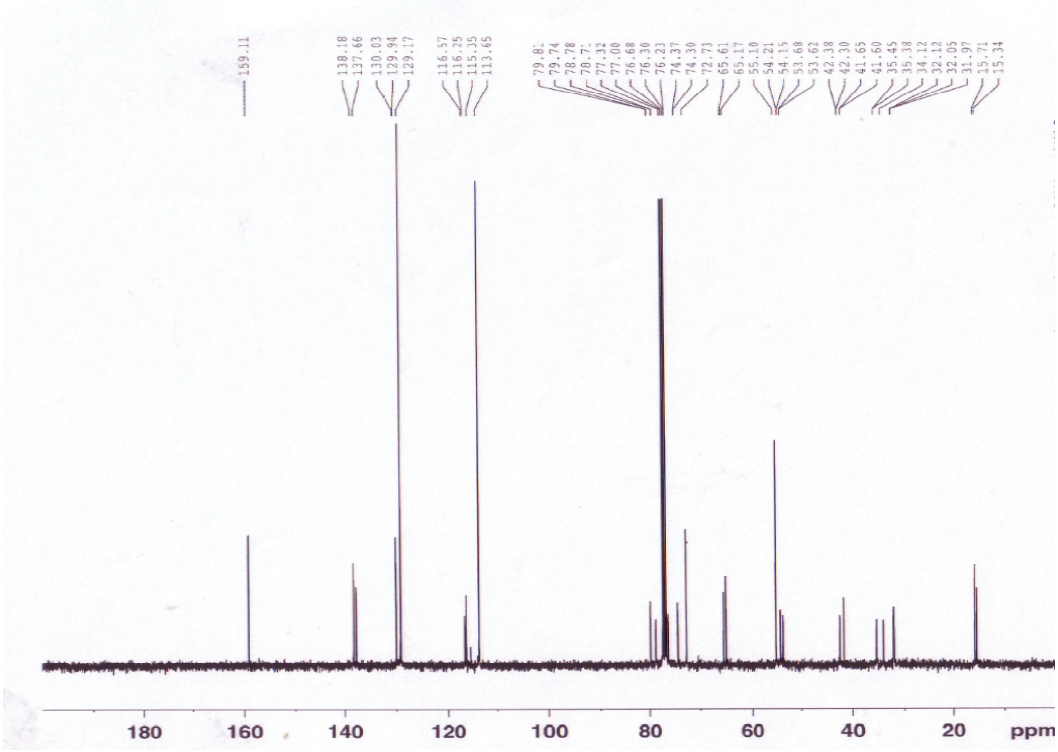


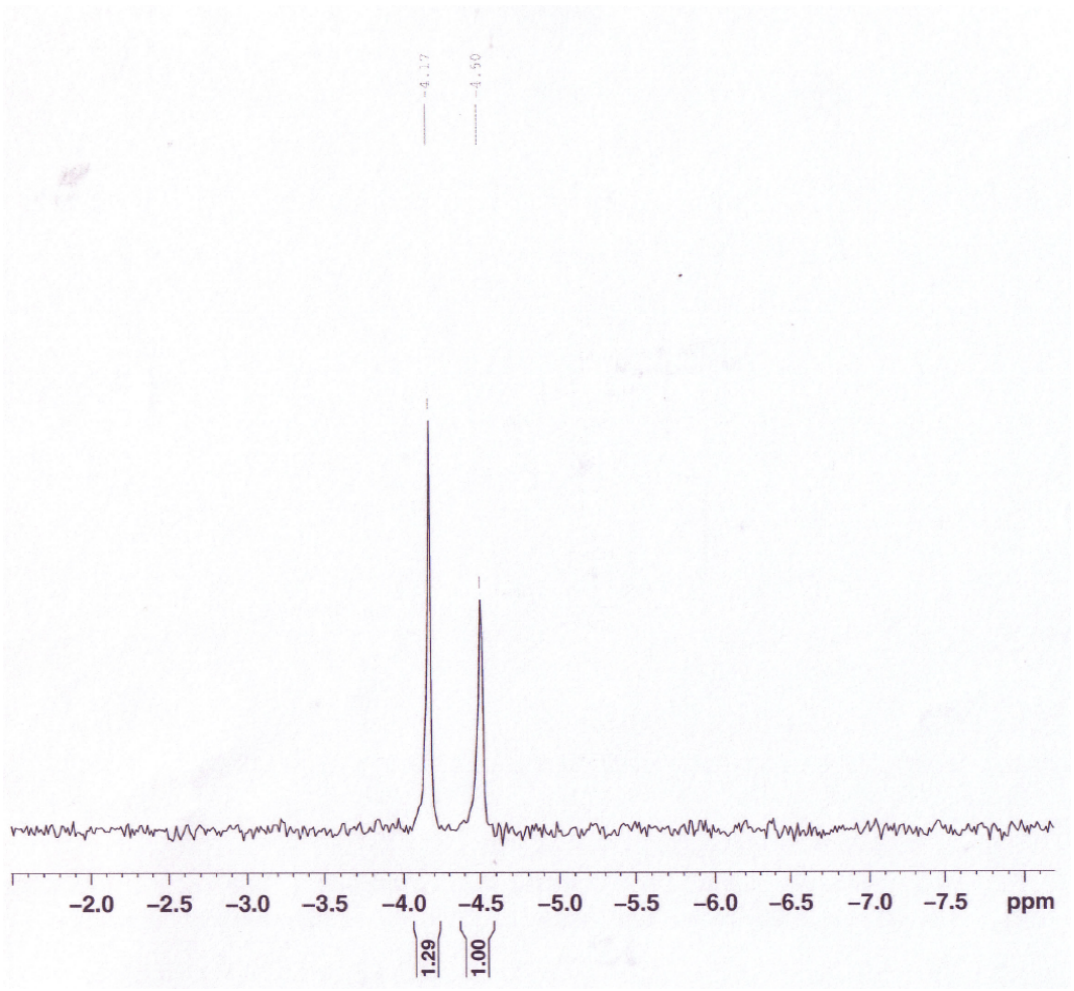




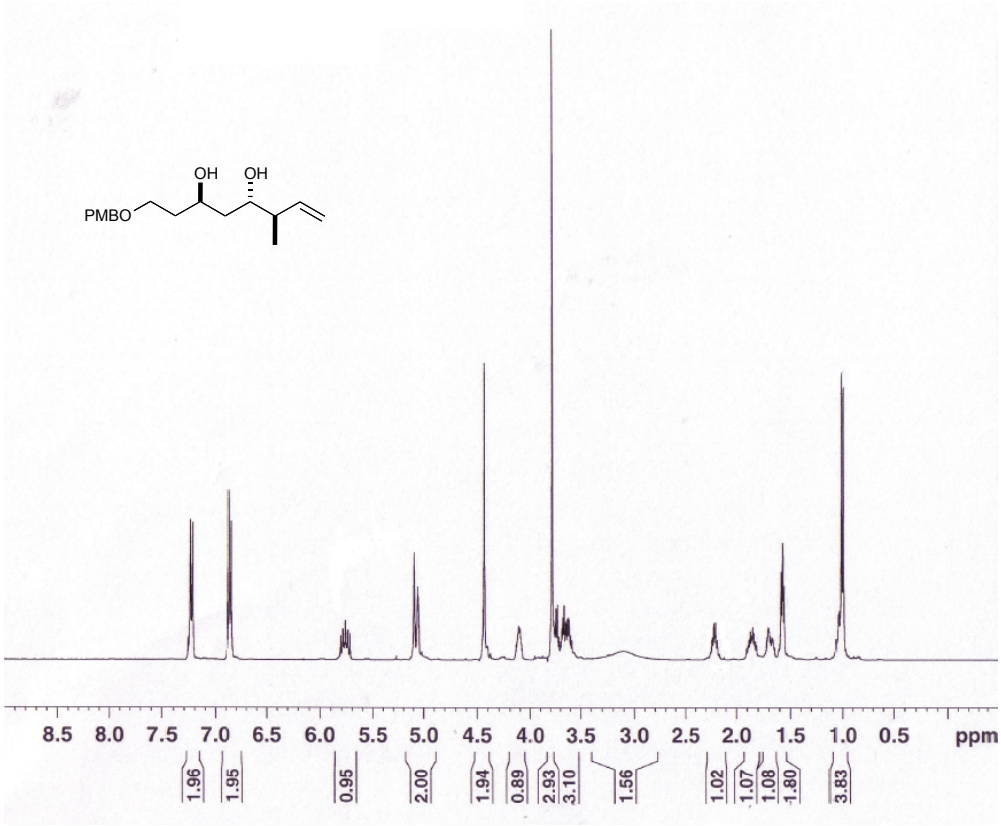
Monocyclic Phosphate Ester: 3.42

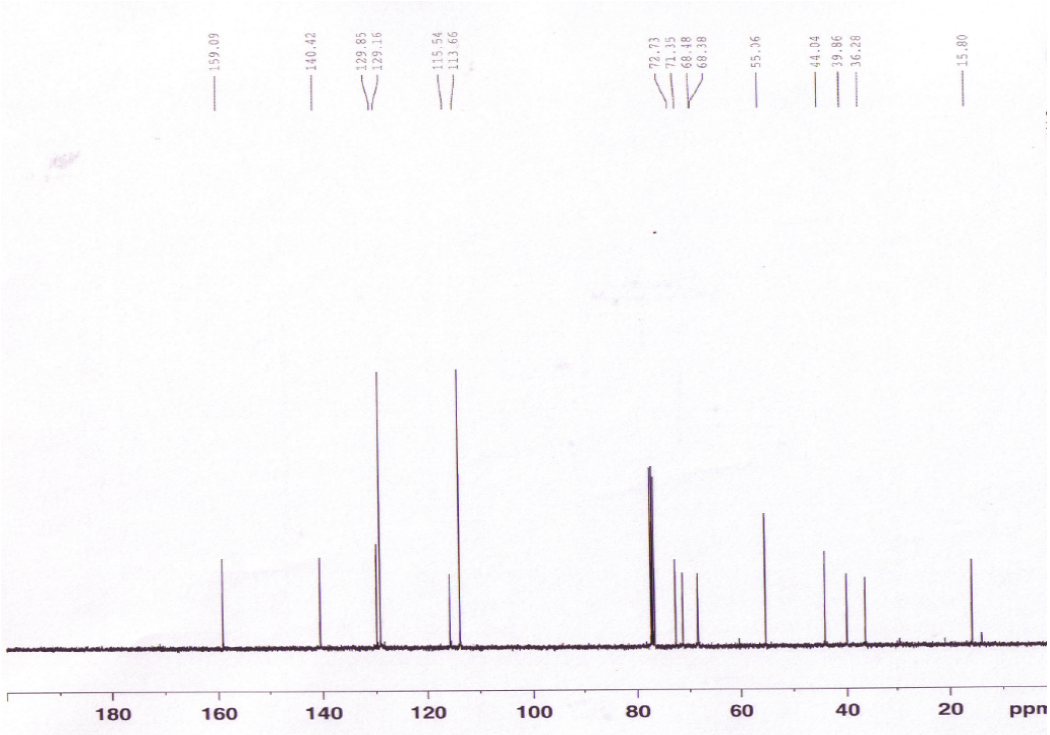




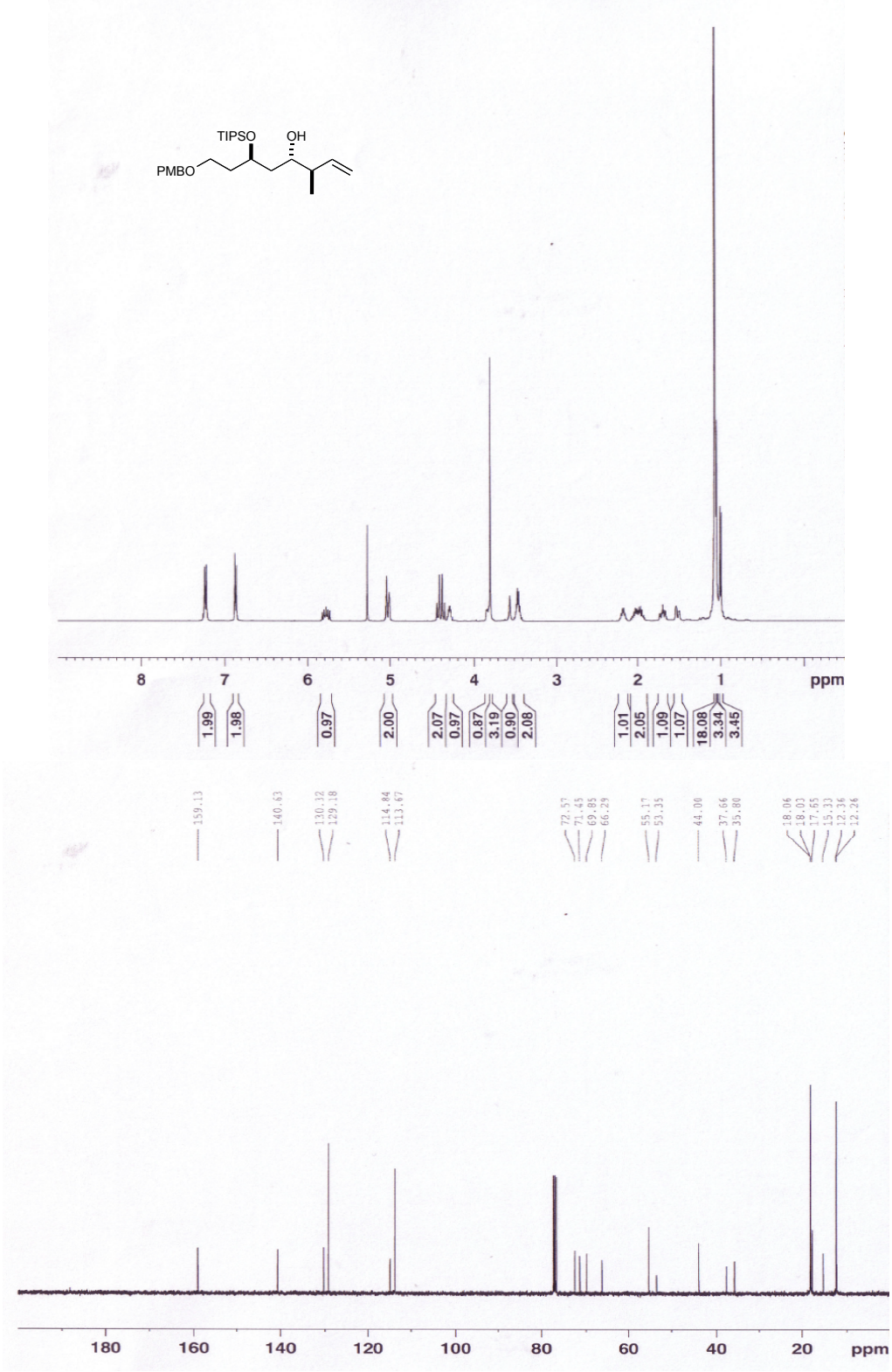

-4.17
-4.50
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-6.5
-7.0
-7.5
ppm
1.29
1.00

(3*R*,5*S*,6*R*)-1-(4-methoxybenzyloxy)-6-methyloct-7-ene-3,5-diol: 3.43

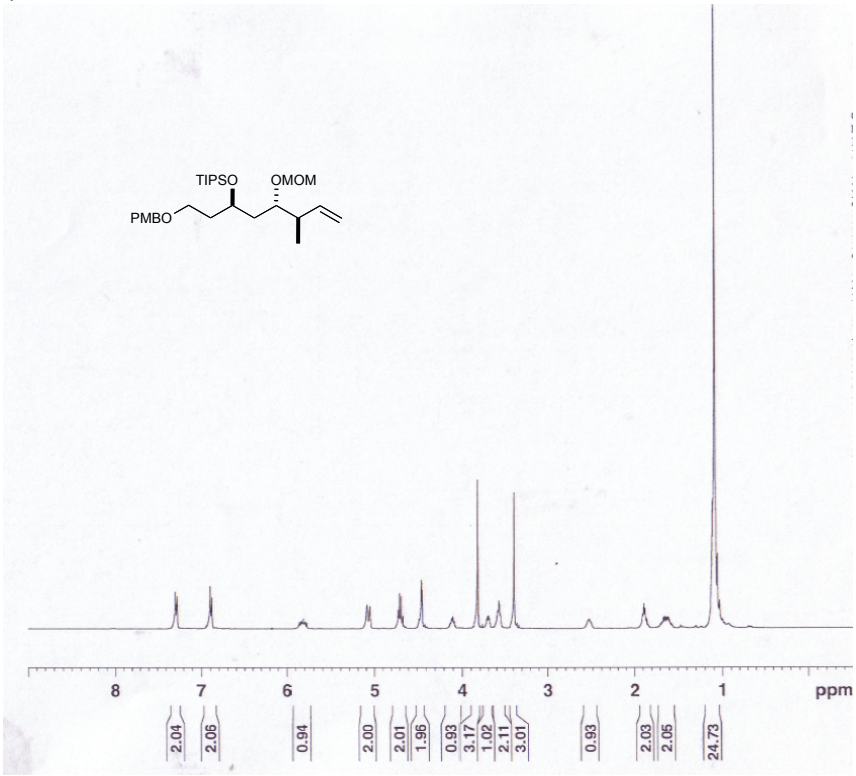


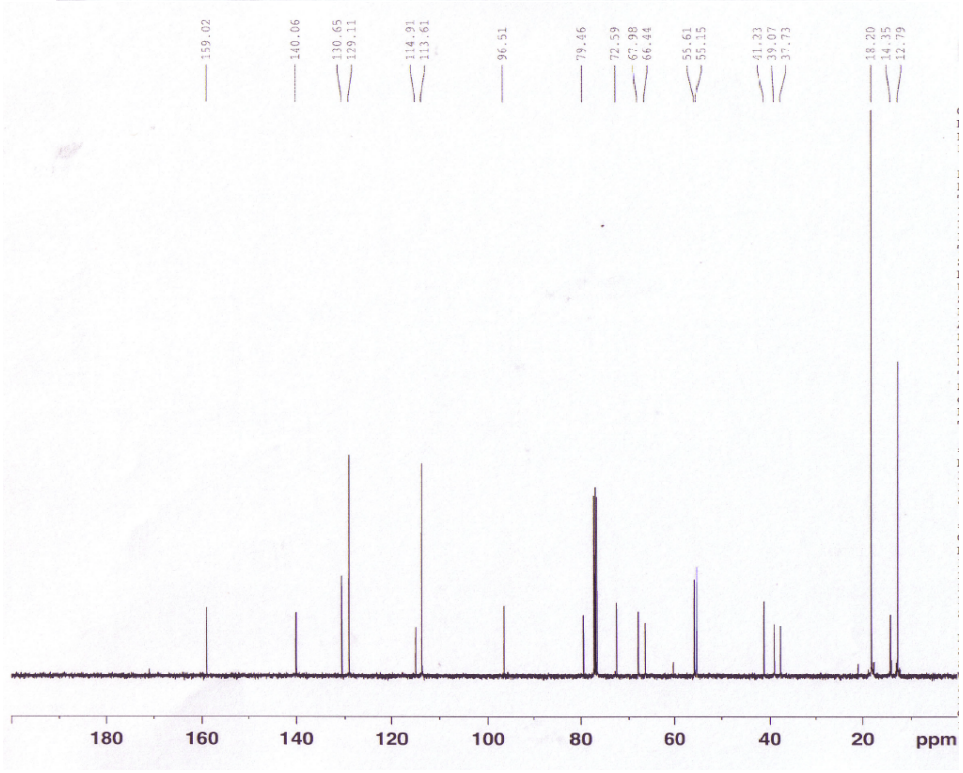


(3R,4S,6R)-8-(4-methoxybenzyloxy)-3-methyl-6-(triisopropylsilyloxy)oct-1-en-4-ol: SI1

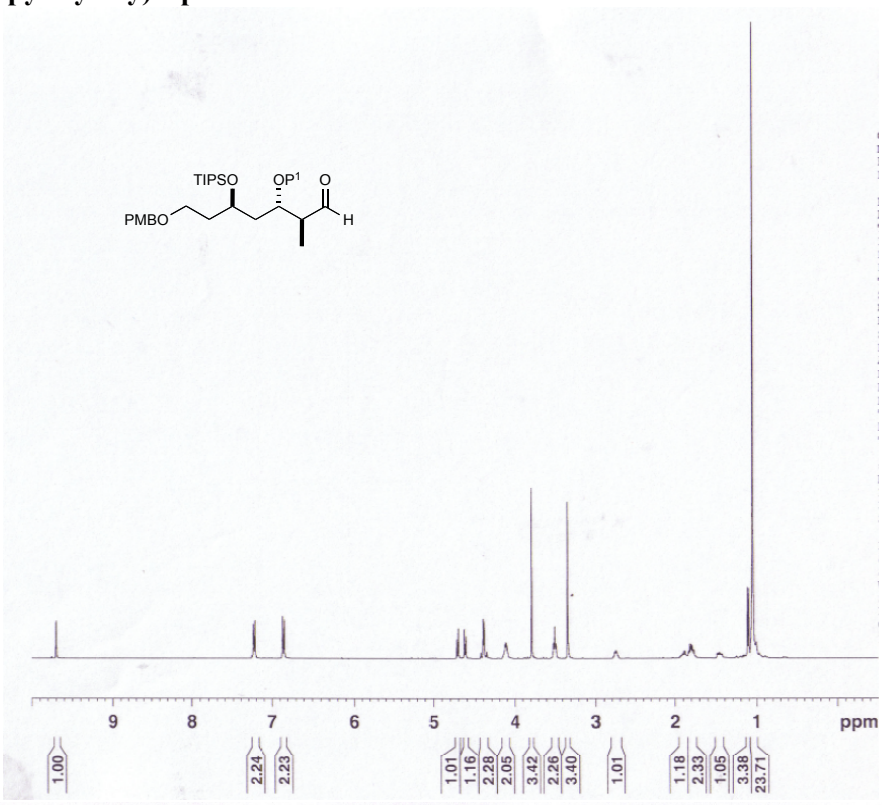


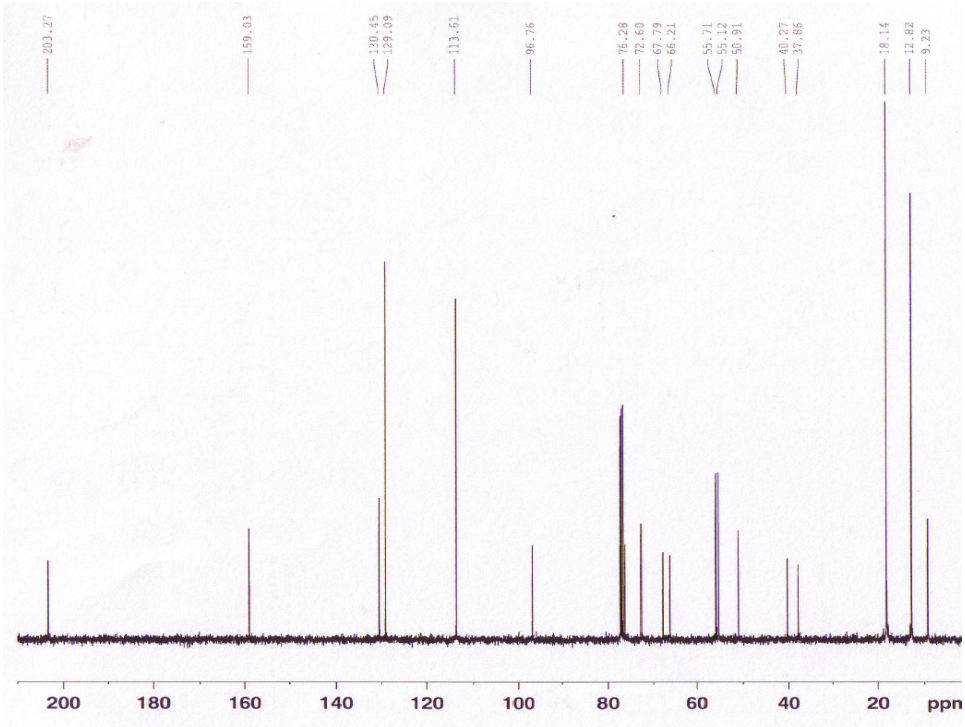
(5S,7R)-5-((R)-but-3-en-2-yl)-9,9-diisopropyl-7-(2-(4-methoxybenzyloxy)ethyl)-10-methyl-2,4,8-trioxa-9-silaundecane: 3.44b



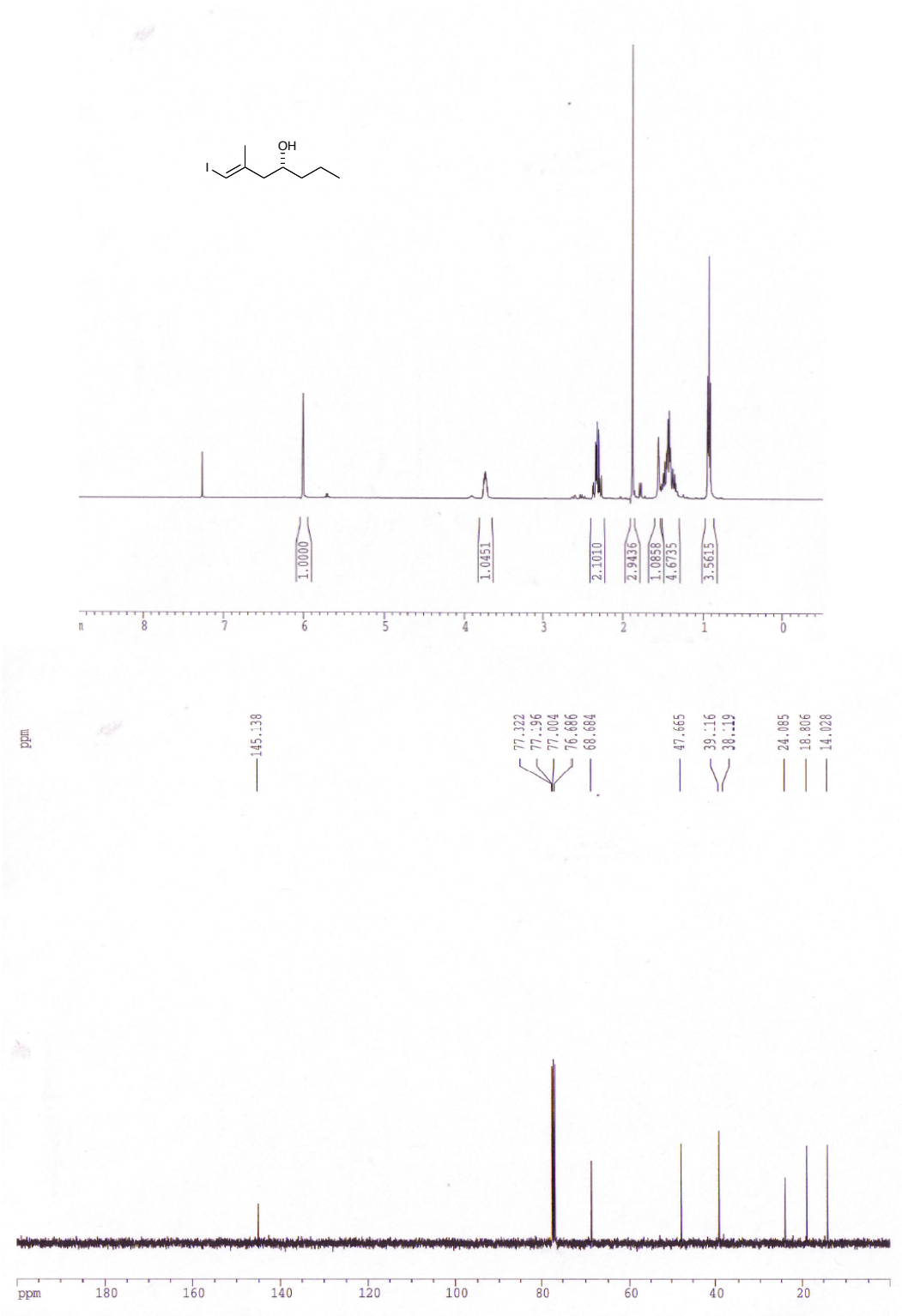


(2S,3S,5R)-7-(4-methoxybenzyloxy)-3-(methoxymethoxy)-2-methyl-5-(triisopropylsilyloxy)heptanal: 3.45b

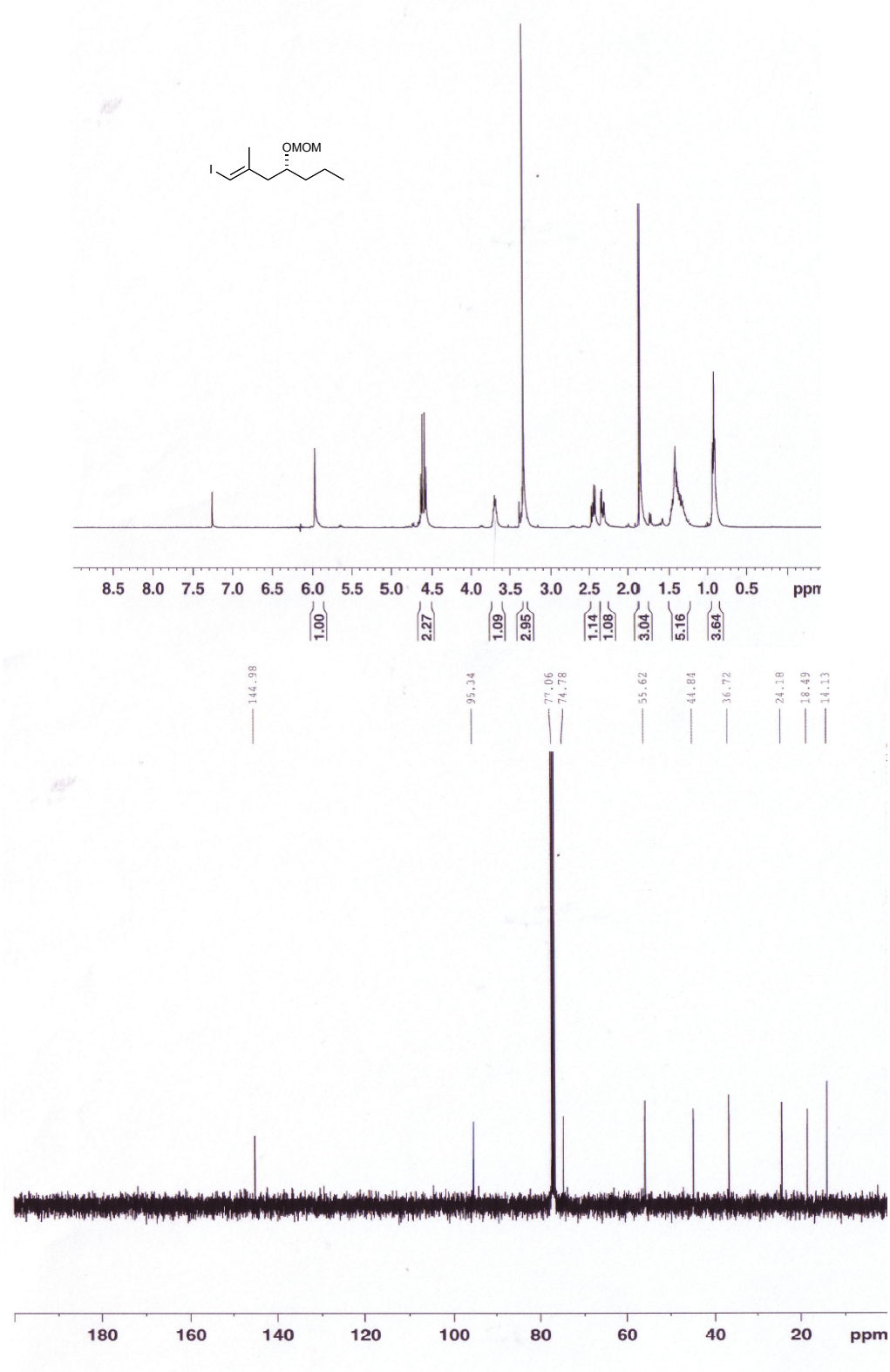




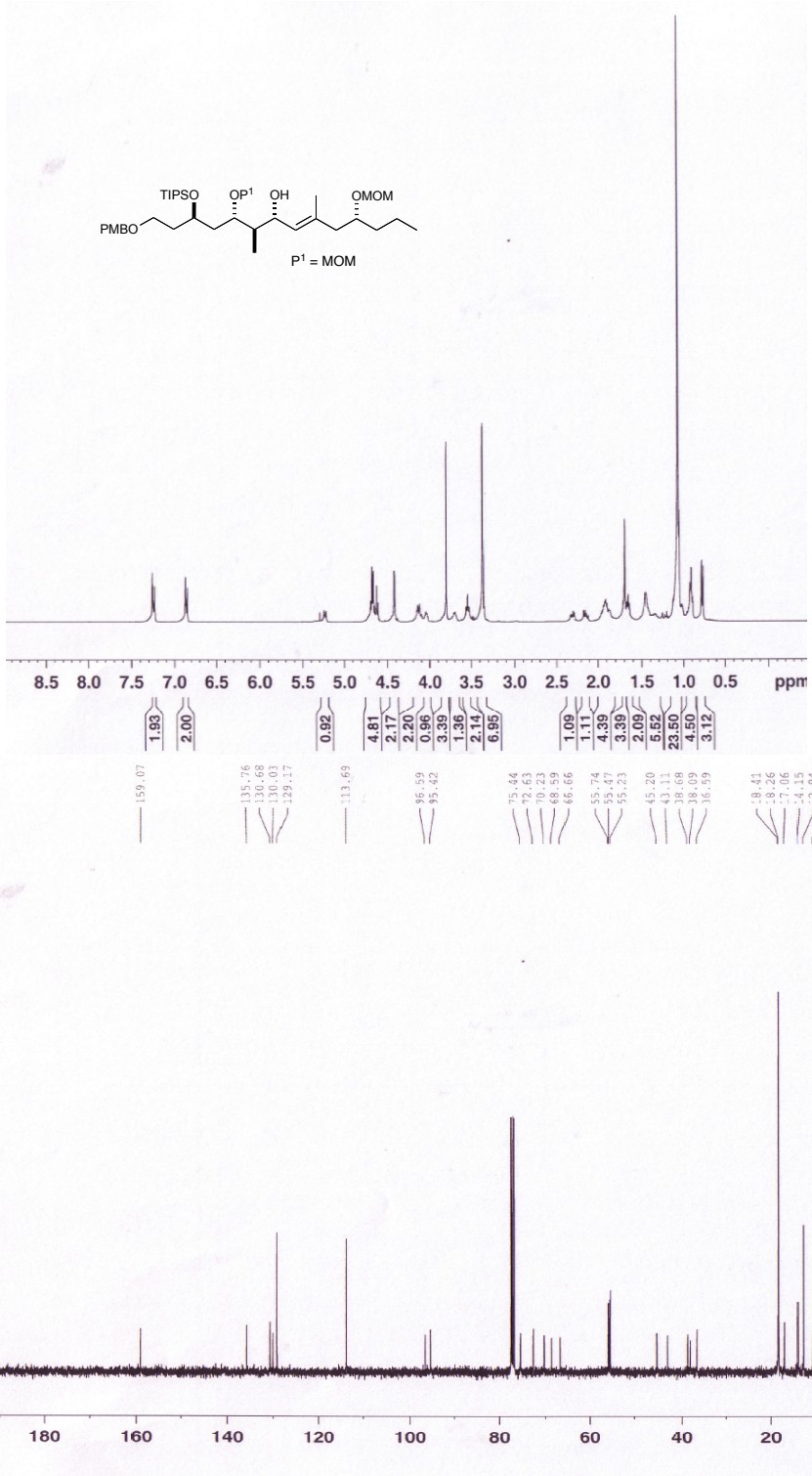
(*R*,*E*)-1-iodo-2-methylhept-1-en-4-ol: 3.47



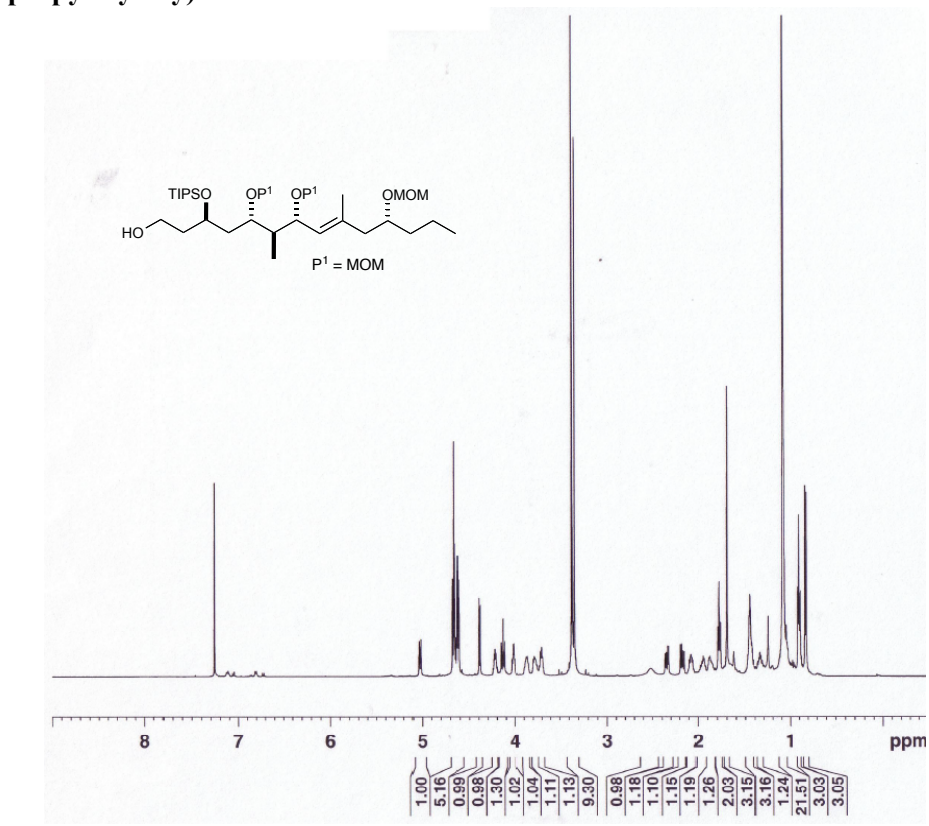
(*R*,*E*)-1-iodo-4-(methoxymethoxy)-2-methylhept-1-ene: 3.48

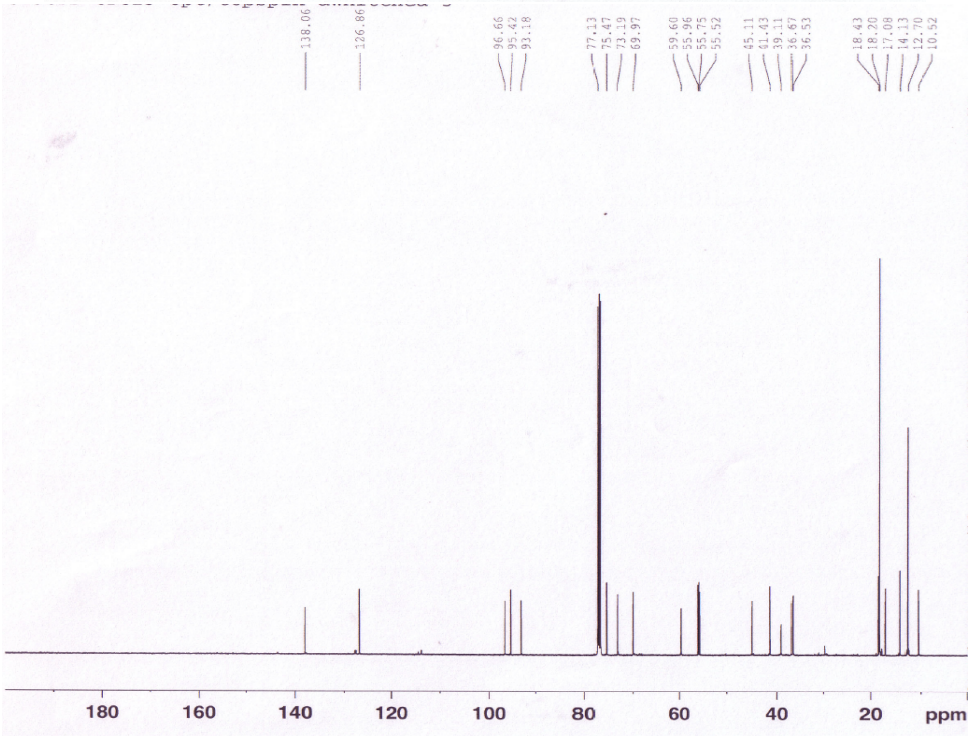


(5*R*,9*R*,10*R*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(2-(4-methoxybenzyloxy)ethyl)-11-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-9-ol: 1,3-*syn*-3.49b

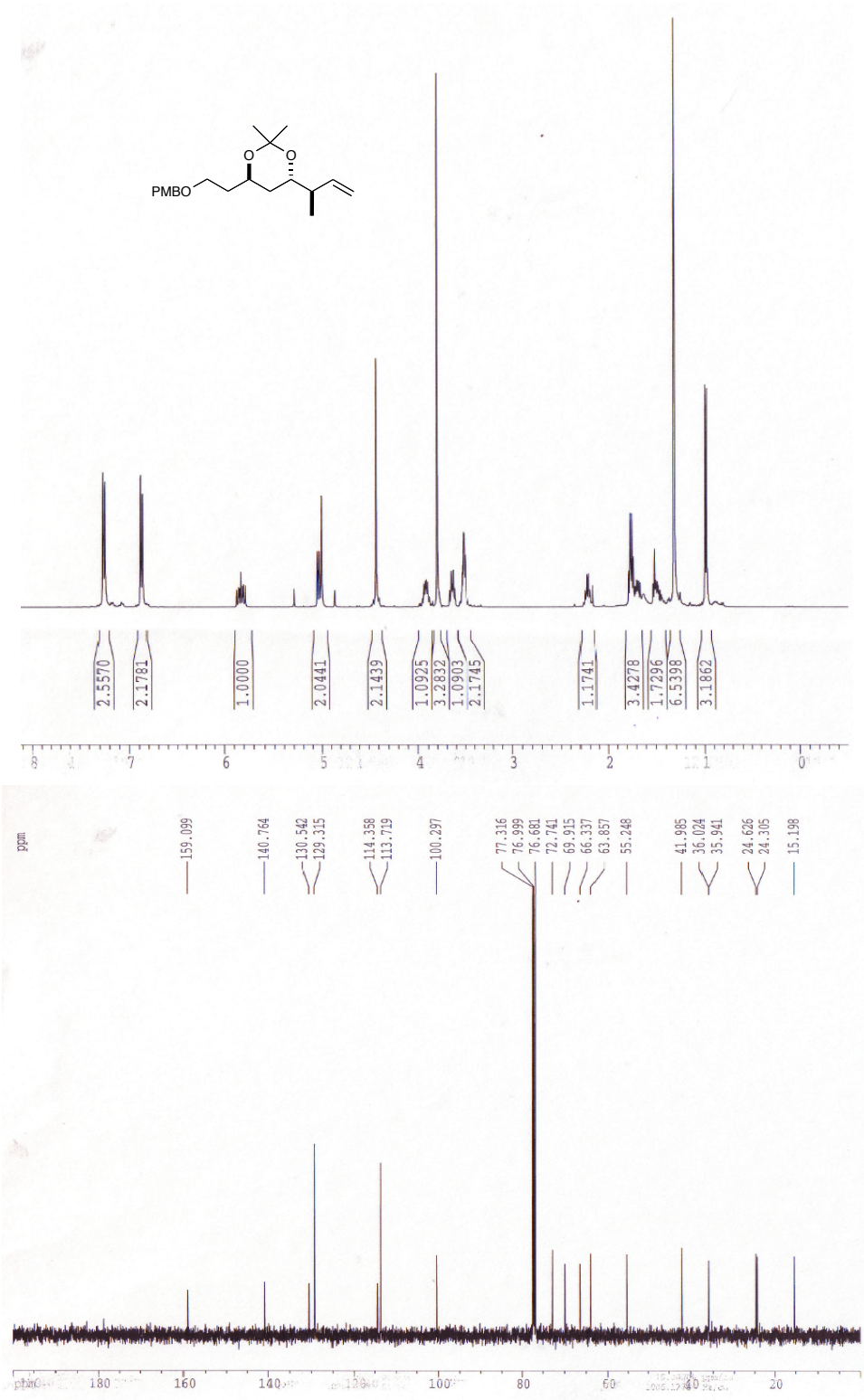


(3*R*,5*S*,6*S*,7*R*,11*R*,*E*)-5,7,11-tris(methoxymethoxy)-6,9-dimethyl-3-(triisopropylsilyloxy)tetradec-8-en-1-ol: 3.52

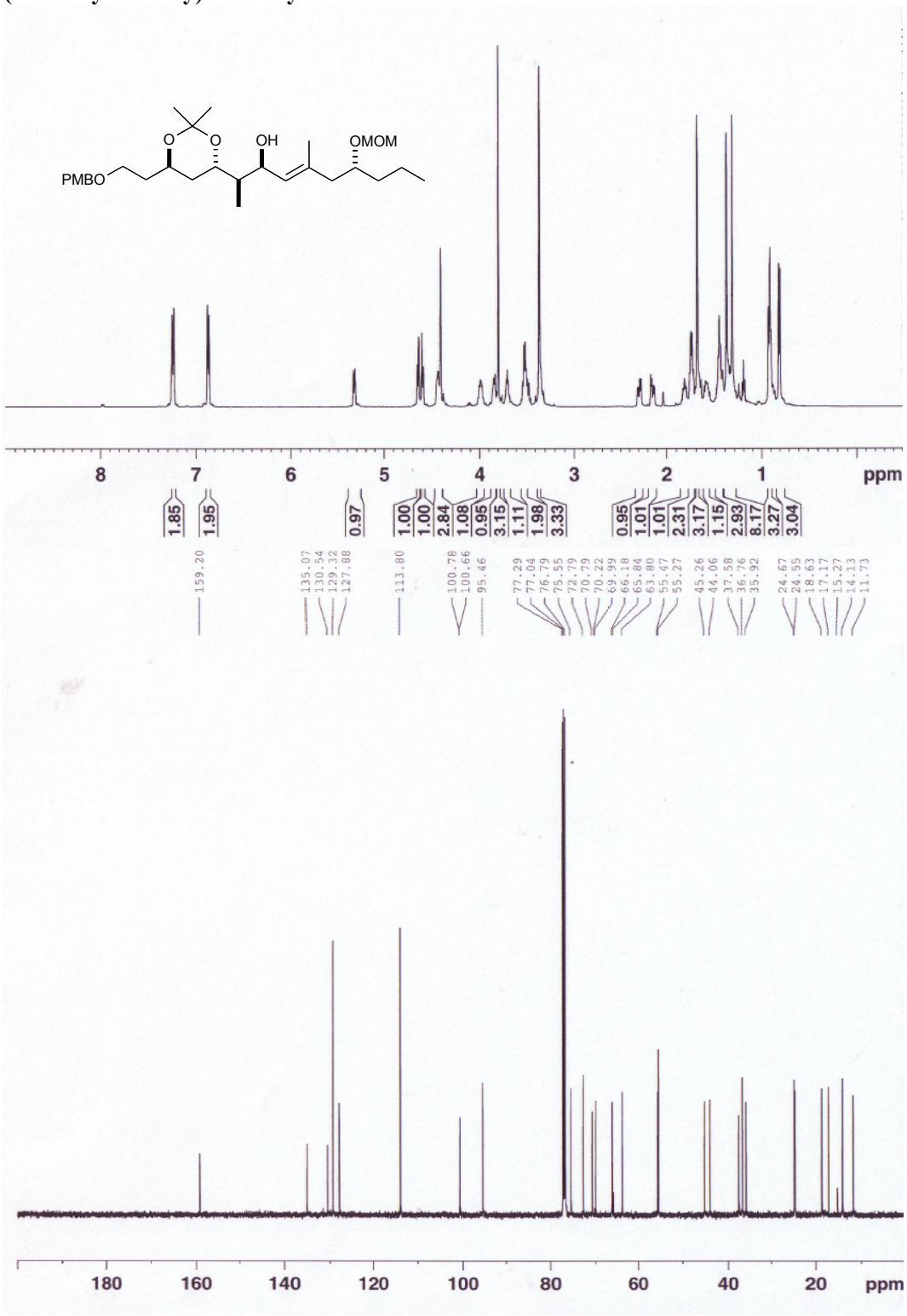




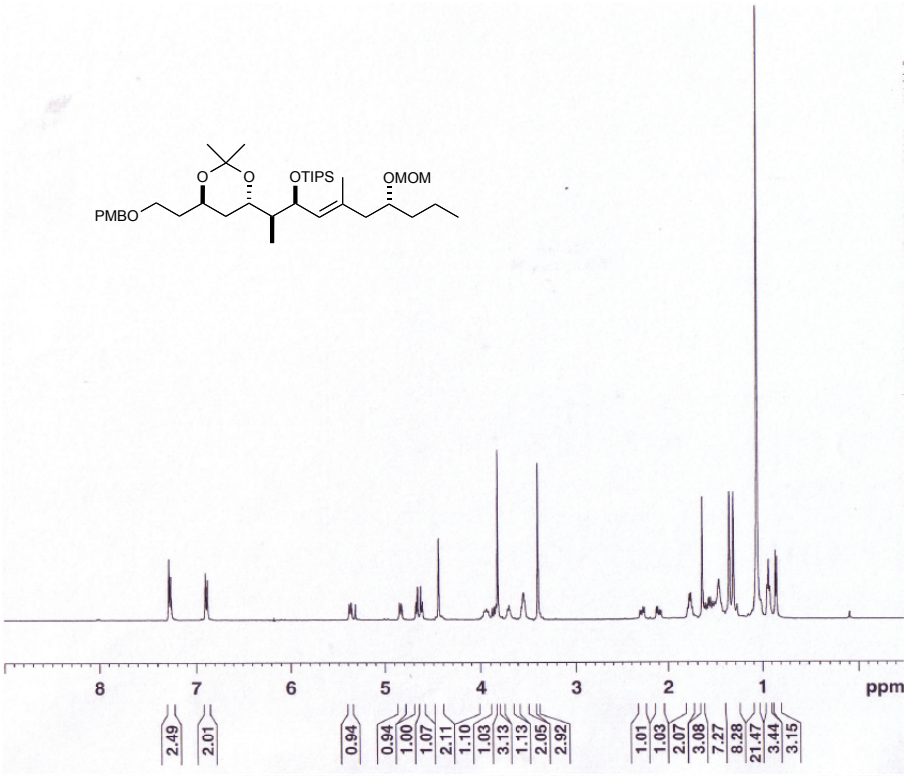
(4*S*,6*R*)-4-((*R*)-but-3-en-2-yl)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane: 3.44a

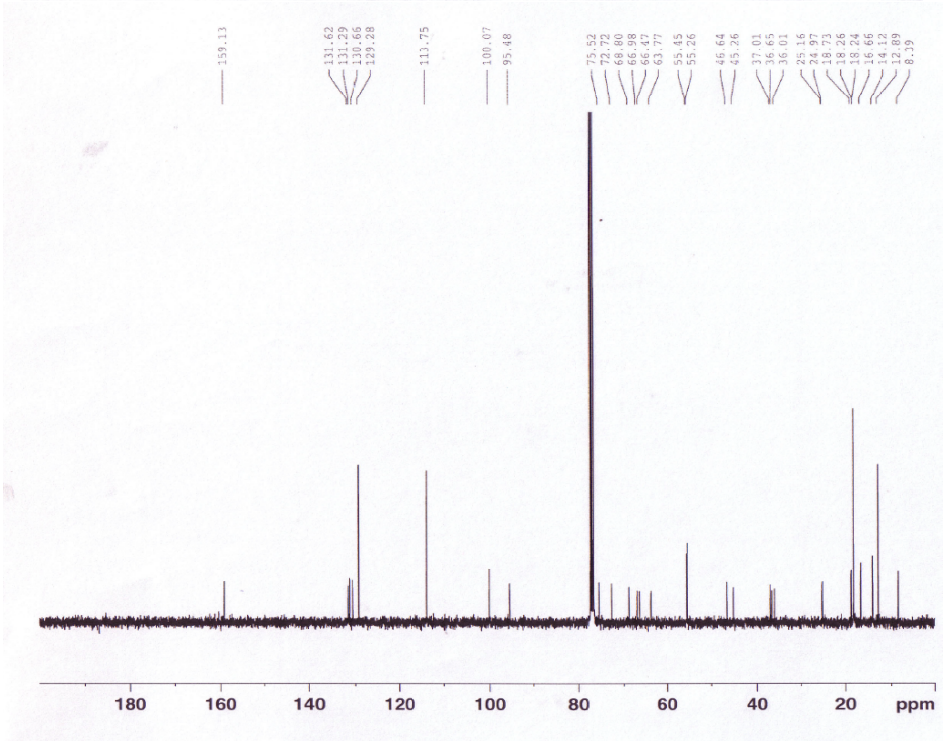


(2*R*,3*R*,7*R*,*E*)-2-((4*S*,6*R*)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-7-(methoxymethoxy)-5-methyldec-4-en-3-ol: *anti*-3.49a

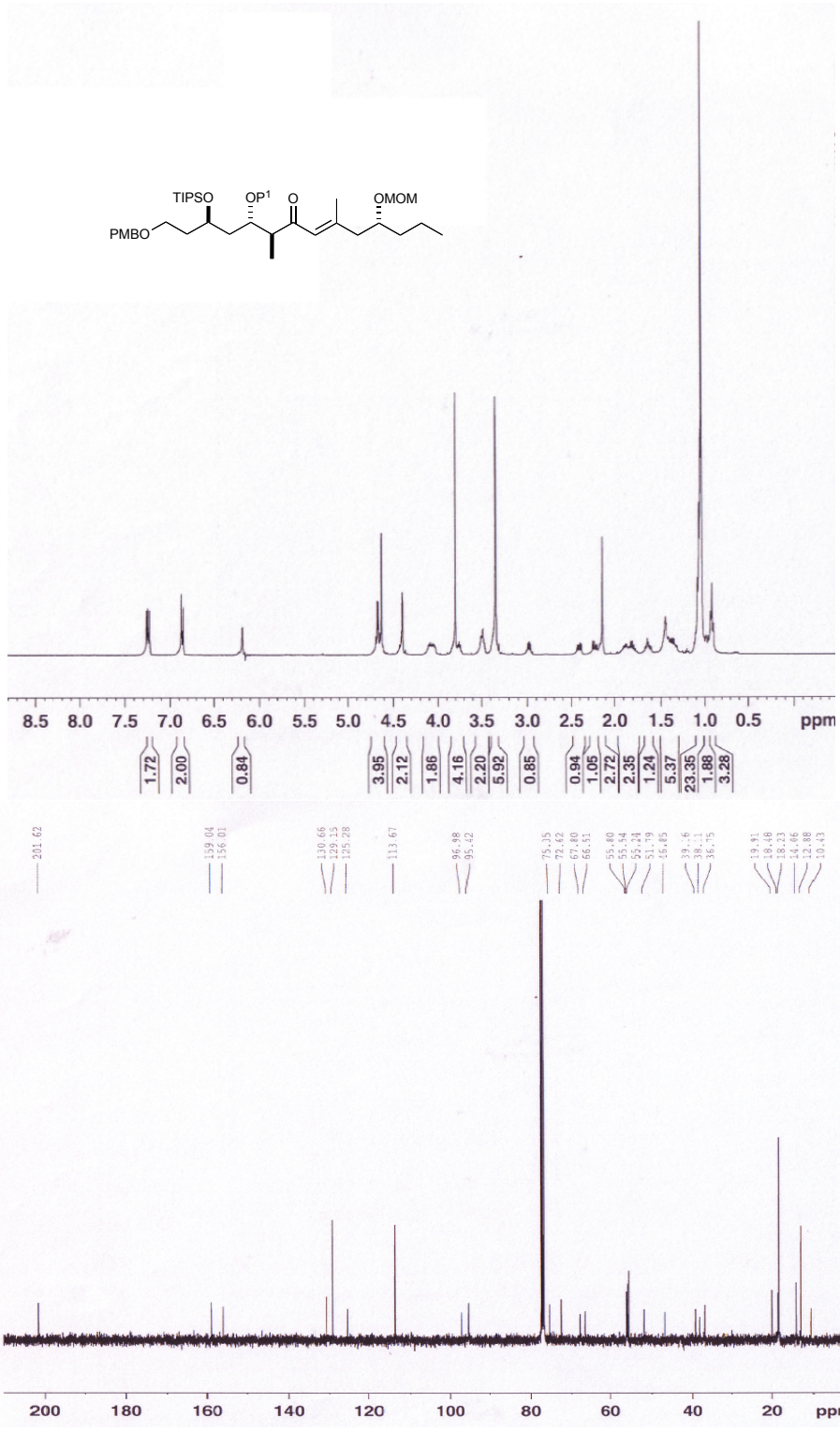


(5*R*,9*S*,*E*)-11,11-diisopropyl-9-((*S*)-1-((4*S*,6*R*)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-7,12-dimethyl-5-propyl-2,4,10-trioxa-11-silatridec-7-ene

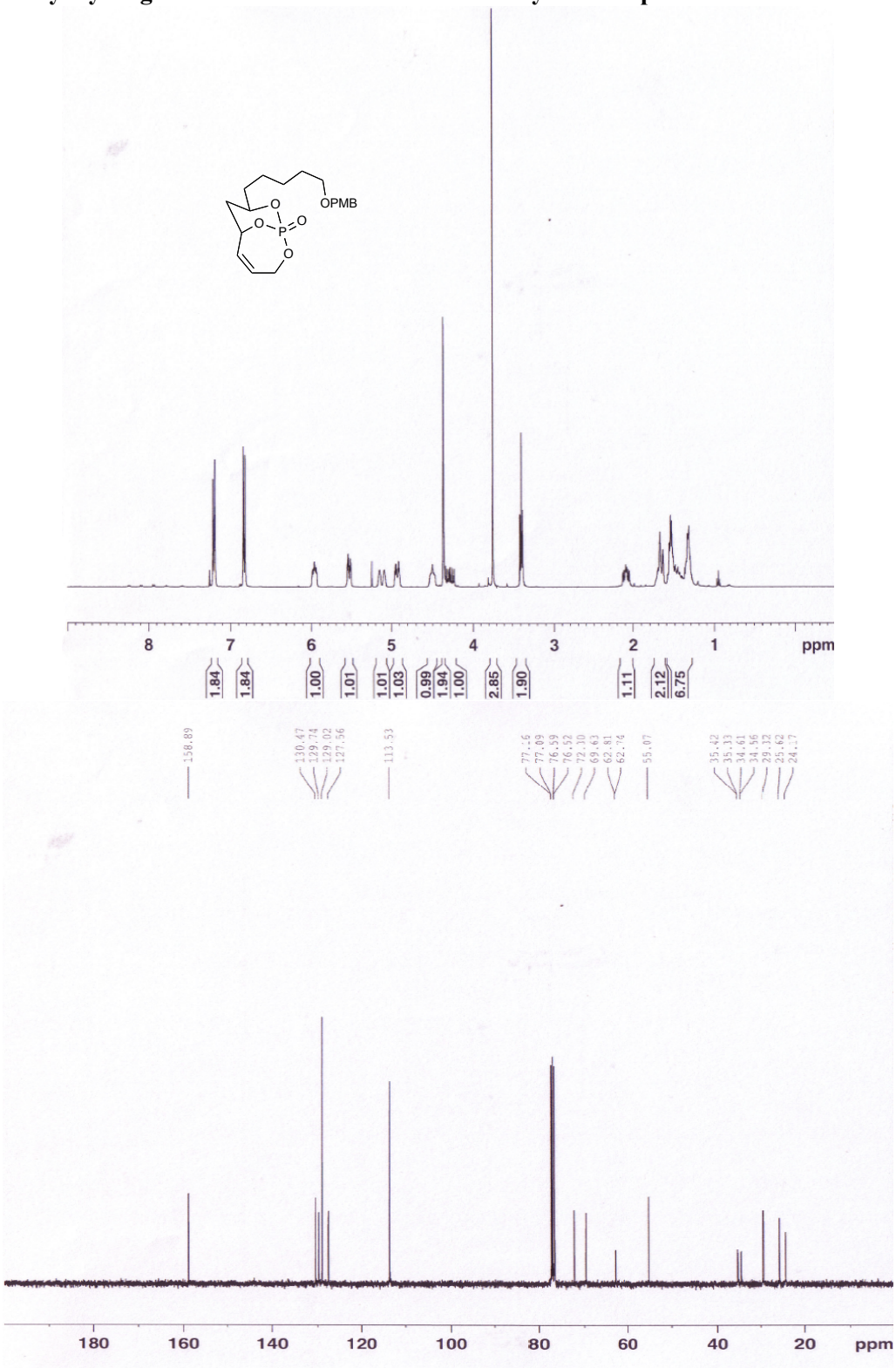


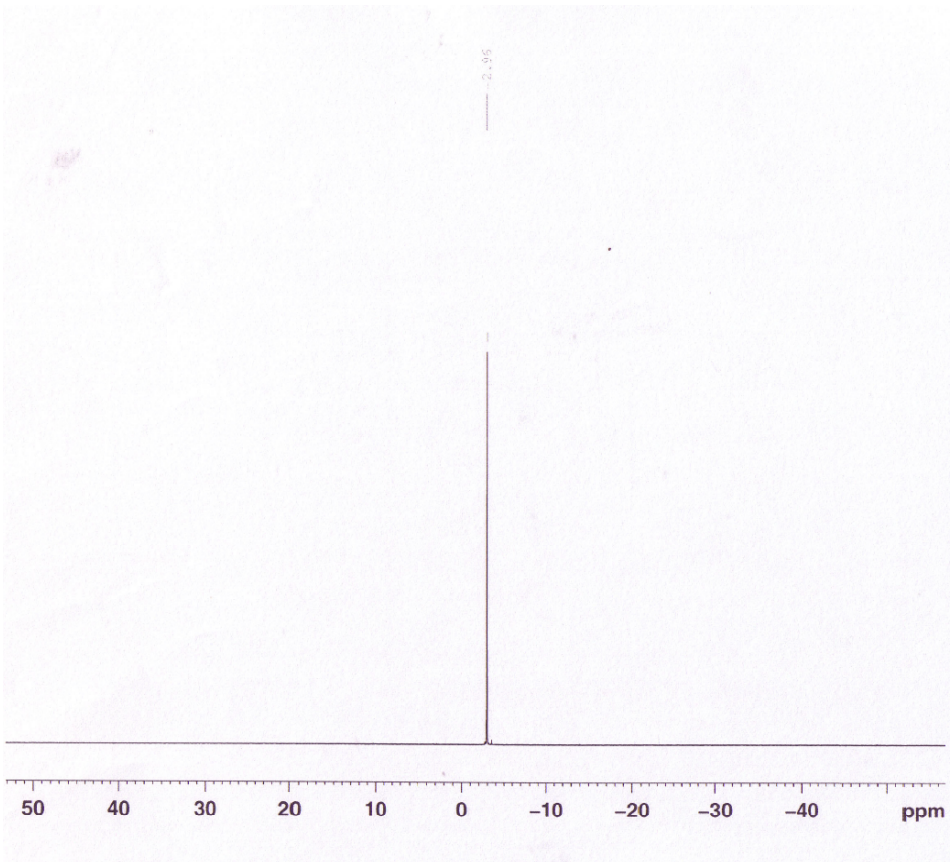


(5*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(2-(4-methoxybenzyloxy)ethyl)-11-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-9-one: 3.50

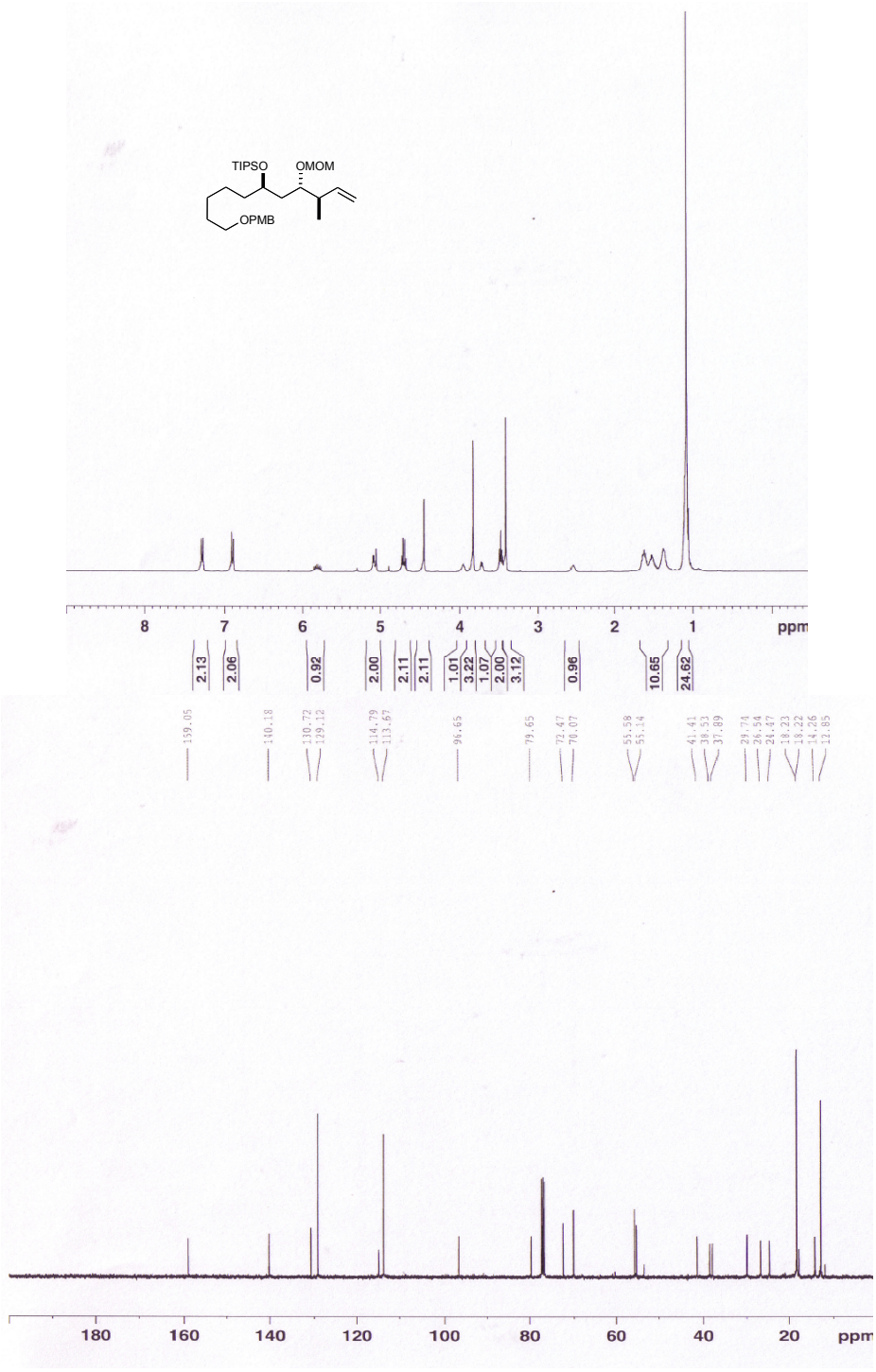


Partially Hydrogenated PMB-Protected derived Bicyclic Phosphate: 3.56

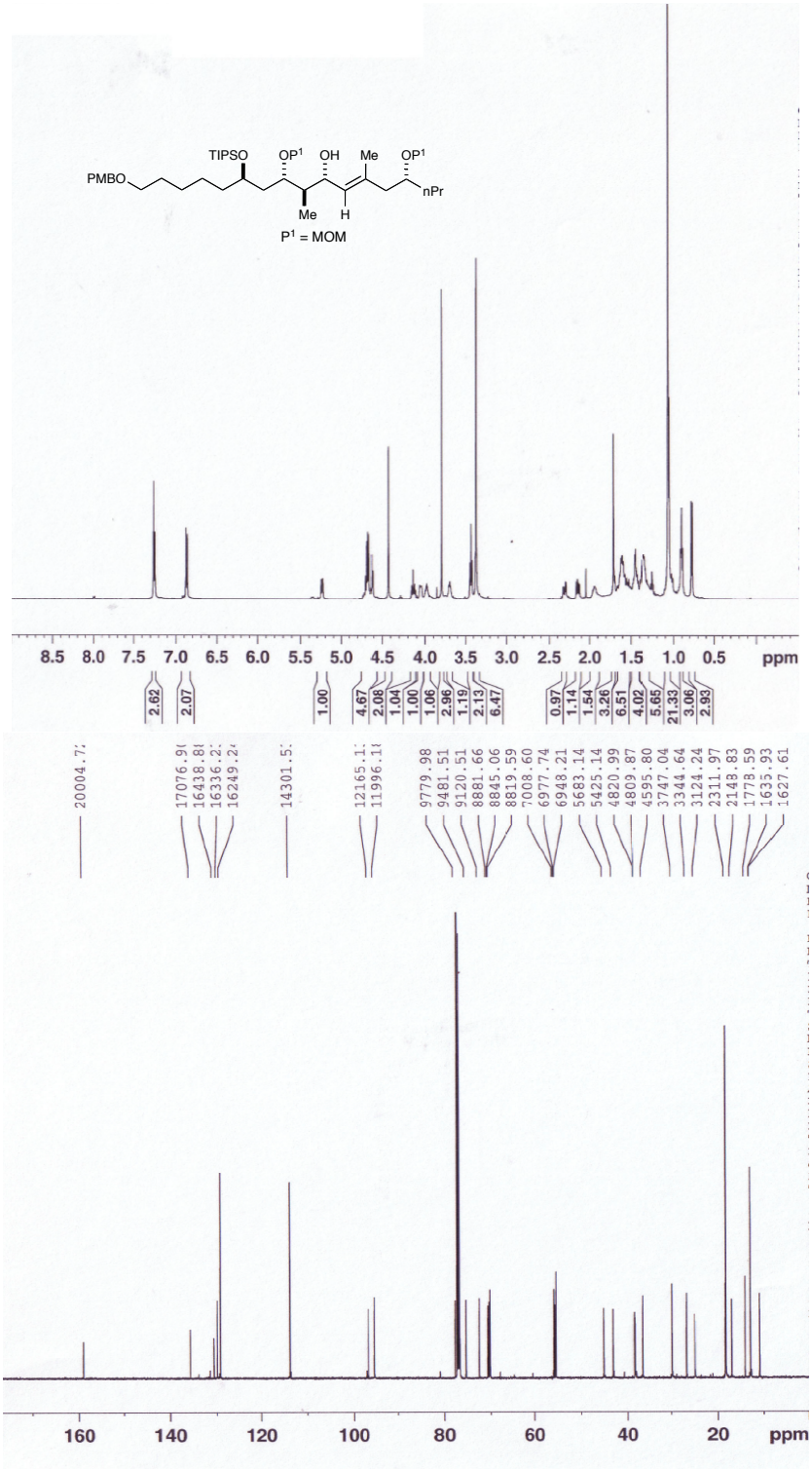



2.95
50
40
30
20
10
0
−10
−20
−30
−40
ppm

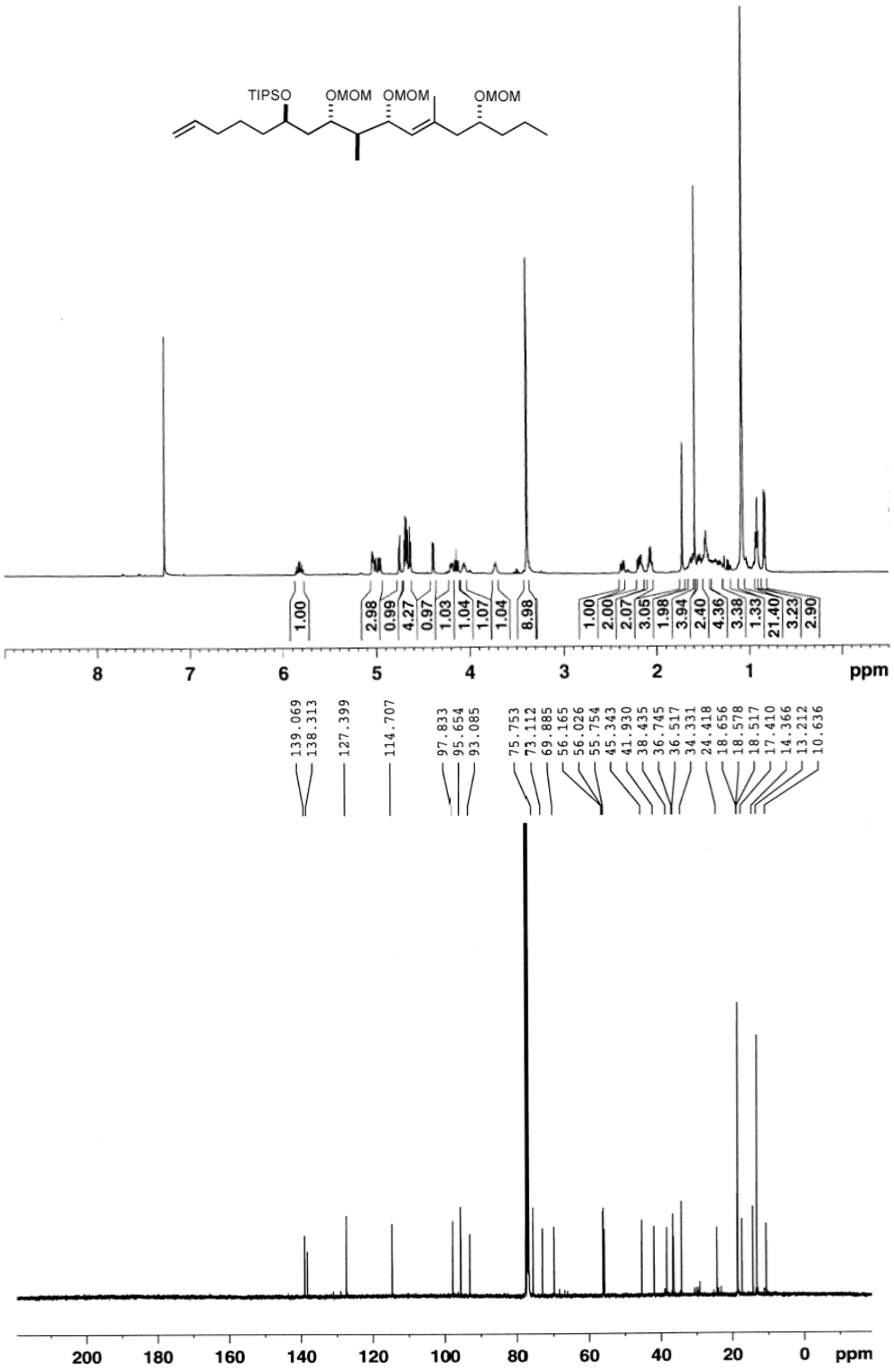
(5*S*,7*R*)-5-((*R*)-but-3-en-2-yl)-9,9-diisopropyl-7-(5-(4-methoxybenzyloxy)pentyl)-10-methyl-2,4,8-trioxa-9-silaundecane: 3.60



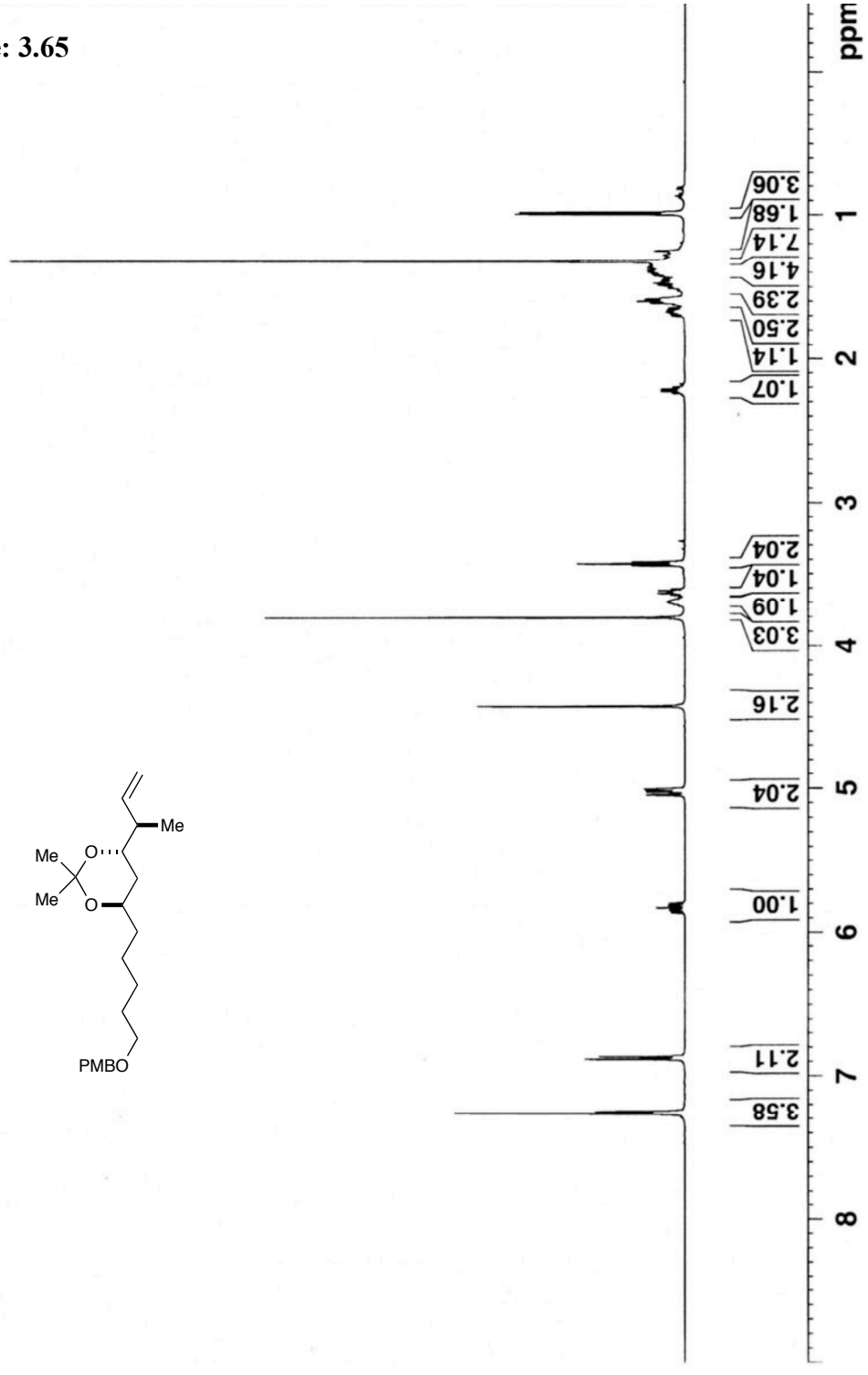
(5*R*,9*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(5-(4-methoxybenzyloxy)pentyl)-9-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-11-ol: 3.62



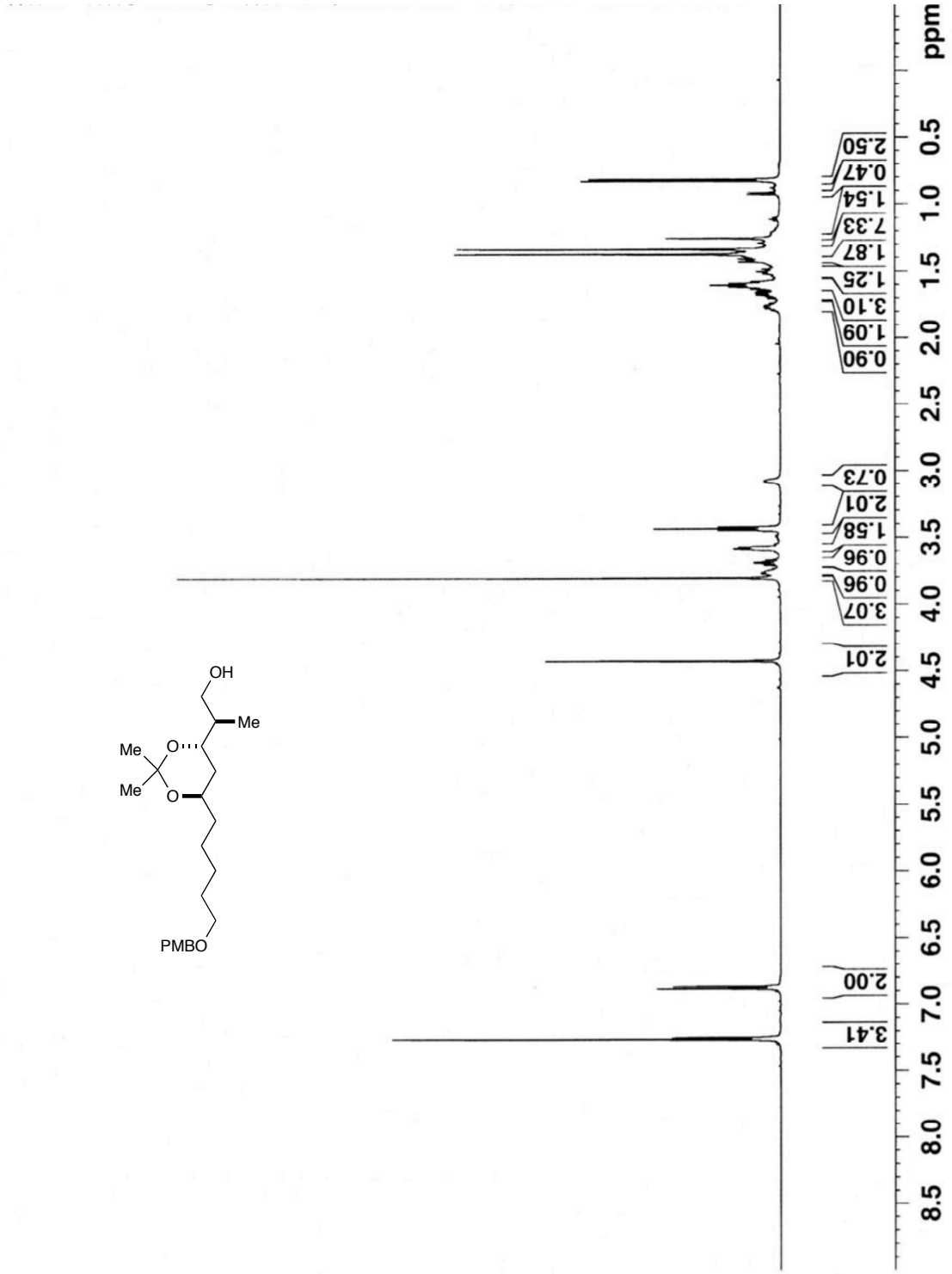
(5*R*,9*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-9,11-bis(methoxymethoxy)-7,10,16-trimethyl-13-(pent-4-enyl)-5-propyl-2,4,14-trioxa-15-silaheptadec-7-ene: 3.54



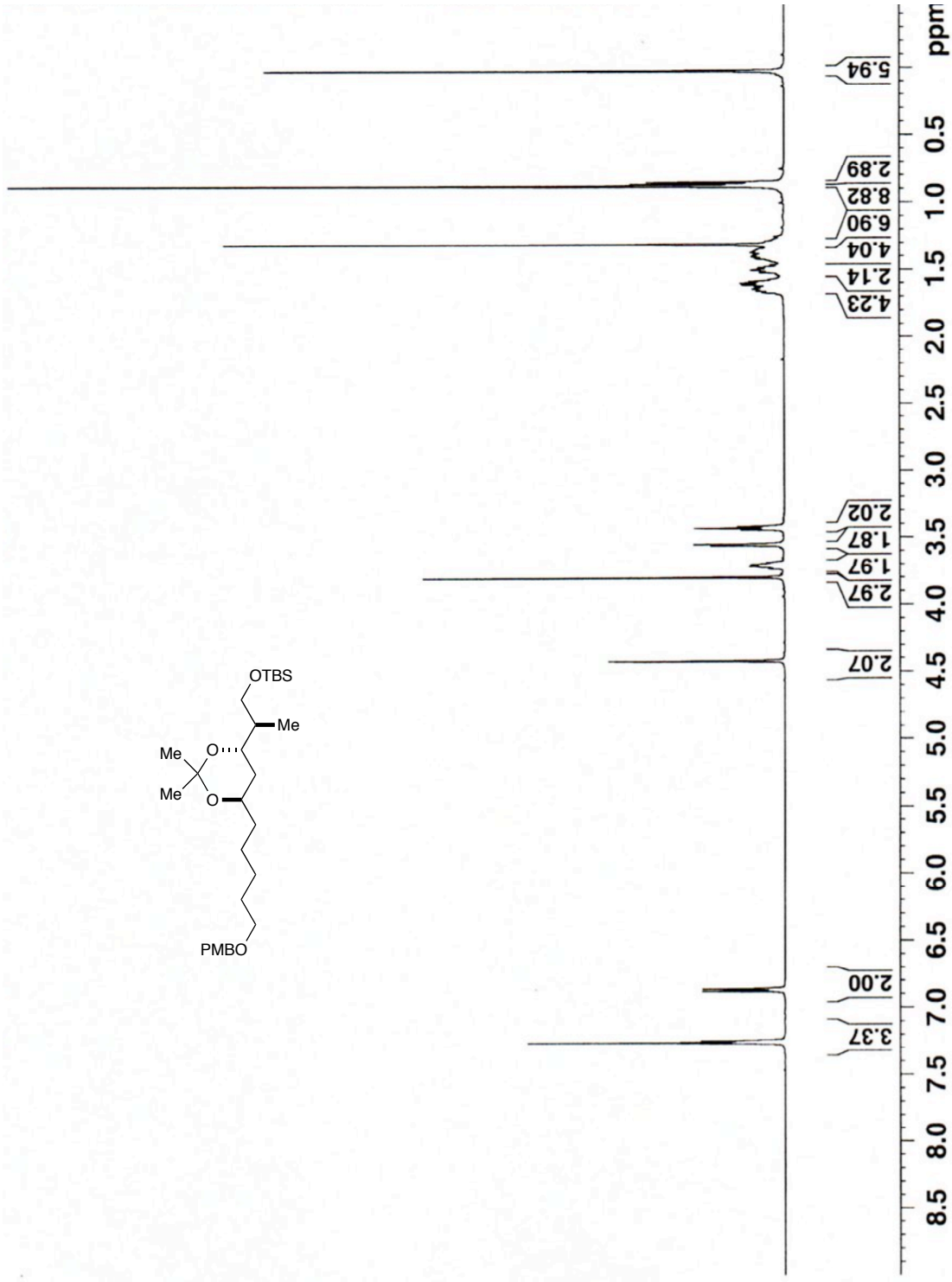
(4*S*,6*R*)-4-((*R*)-but-3-en-2-yl)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxane: 3.65



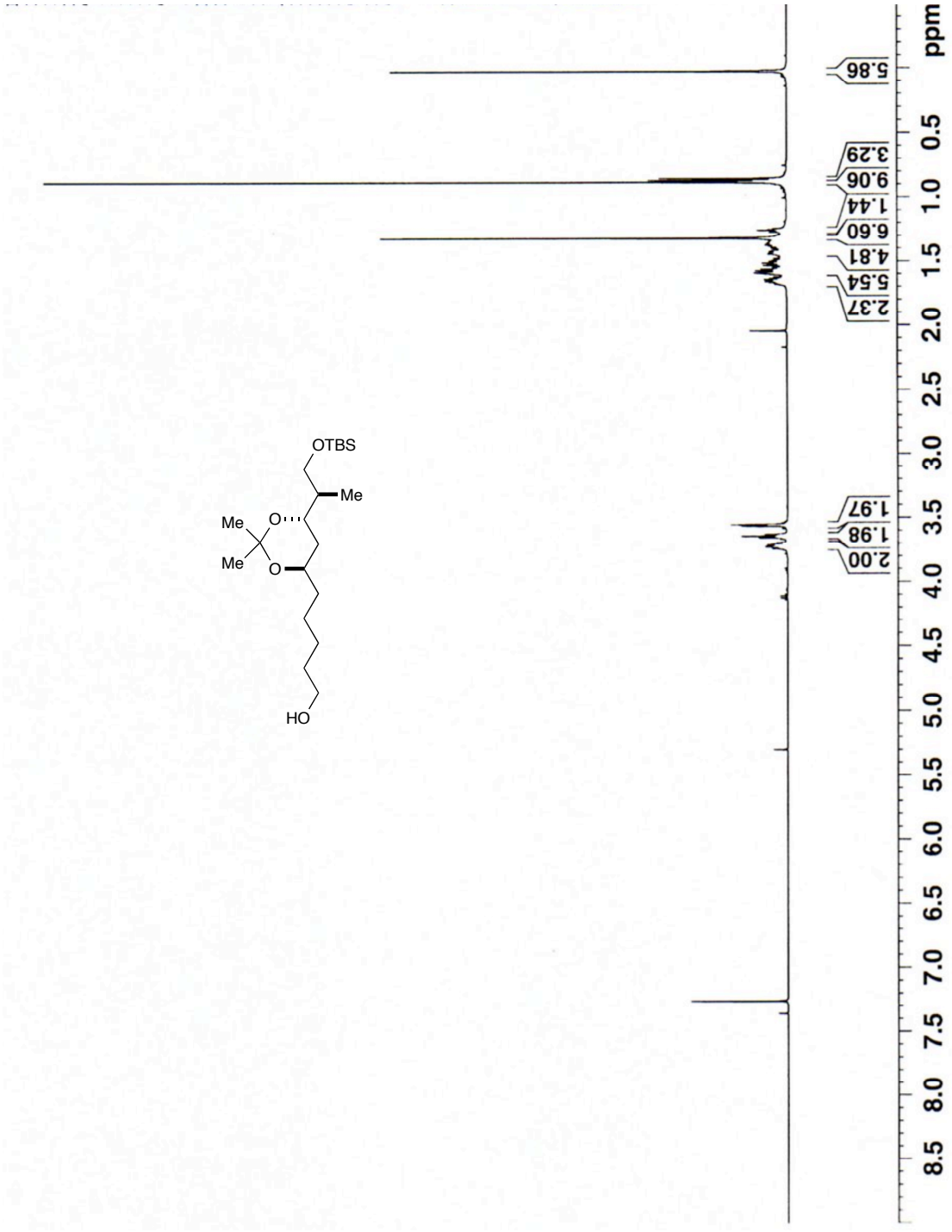
(*R*)-2-((4*S*,6*R*)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-1-ol: 3.66



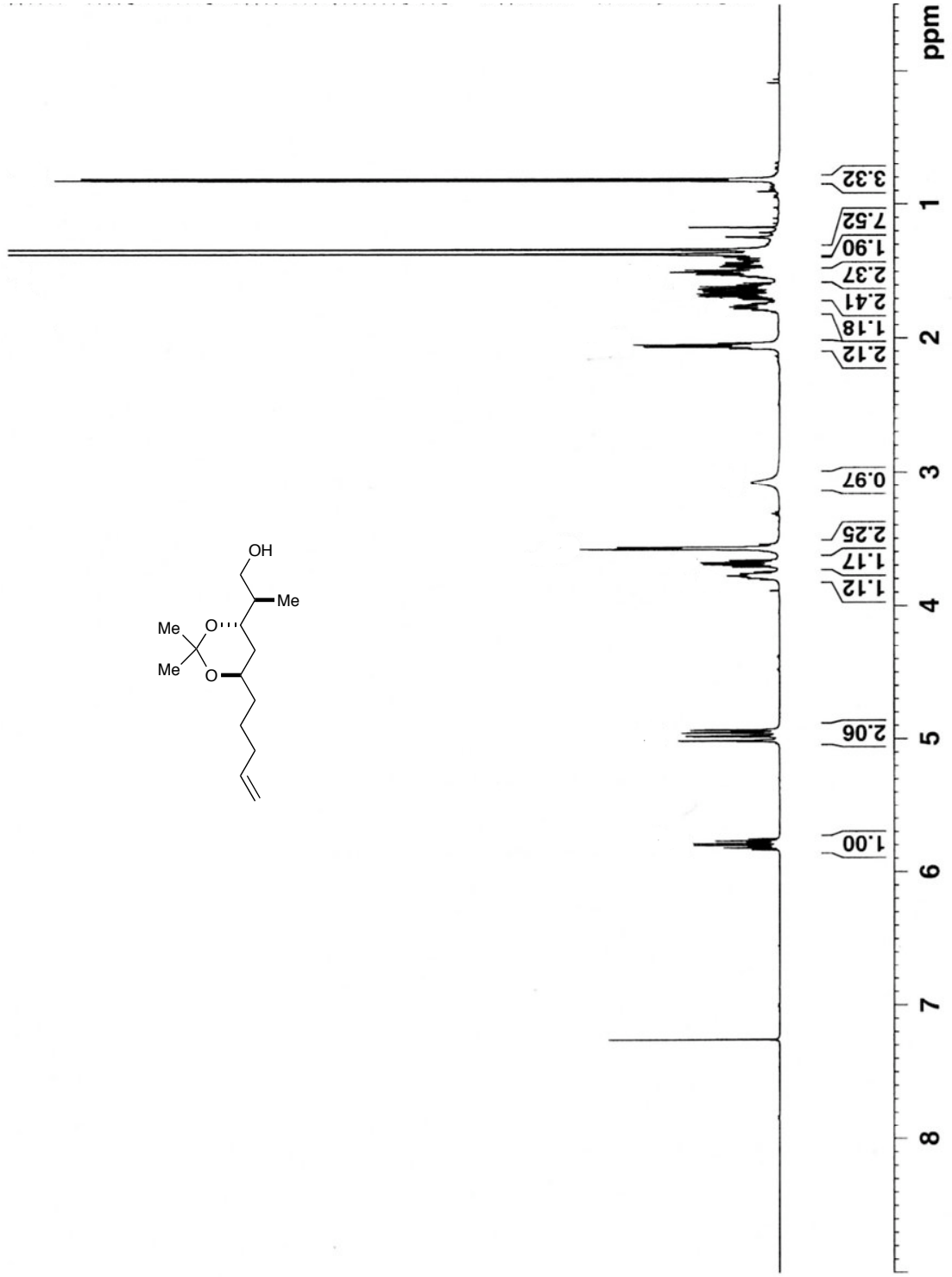
***tert*-butyl((*R*)-2-((4*S*,6*R*)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxan-4-yl)propoxy)dimethylsilane: SI13**



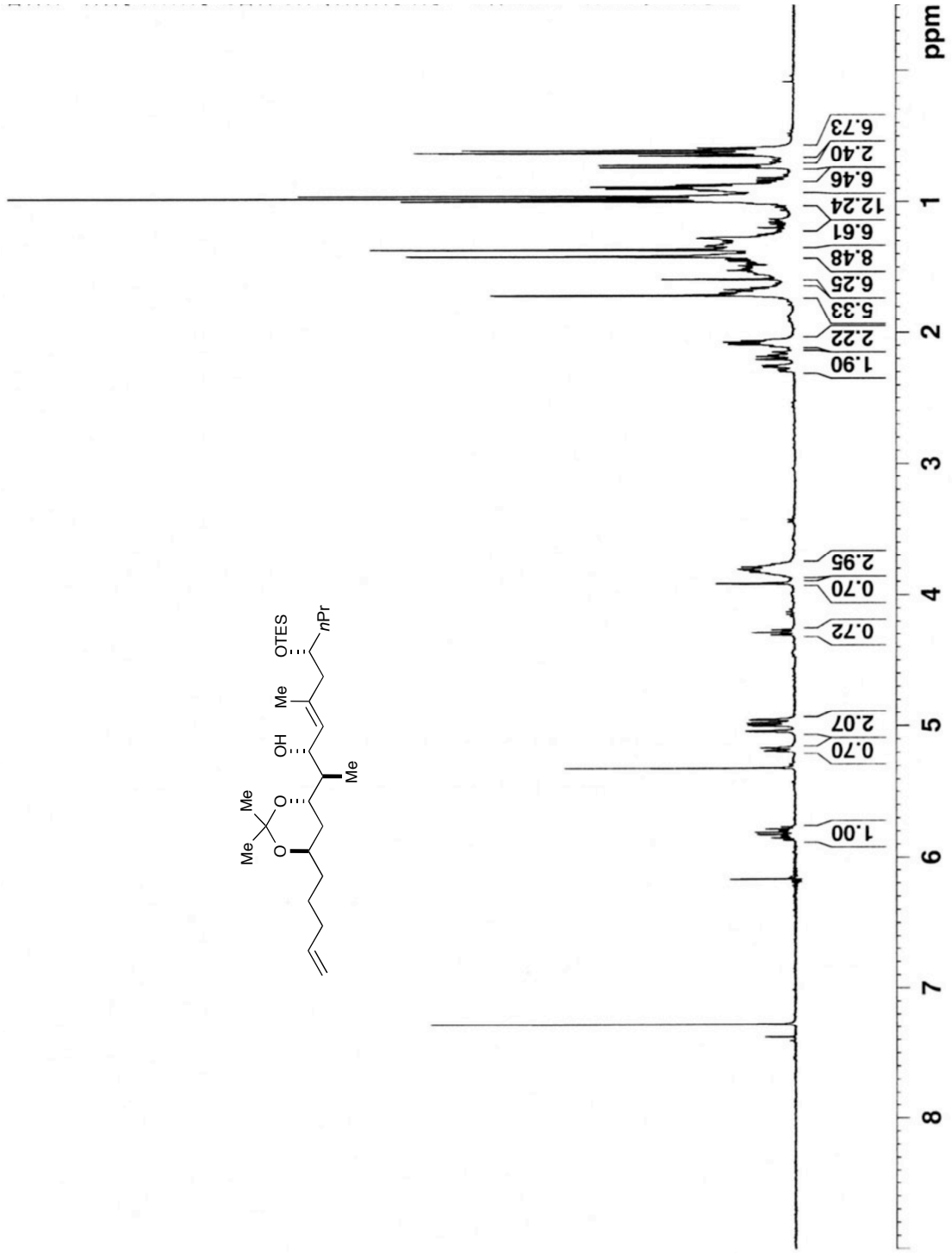
5-((4*R*,6*S*)-6-((*R*)-1-(*tert*-butyldimethylsilyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)pentan-1-ol: 3.67



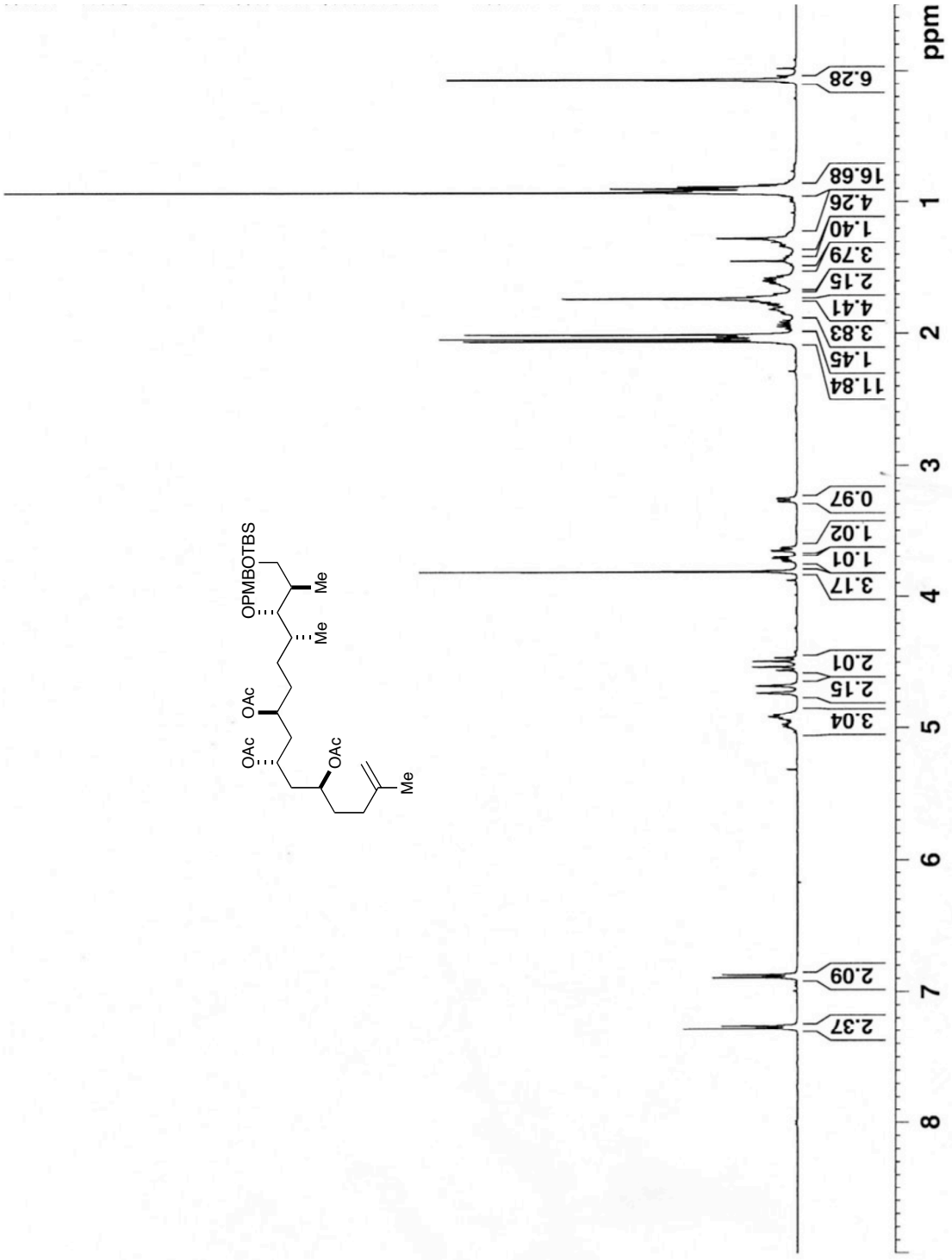
(*R*)-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)propan-1-ol: SI14



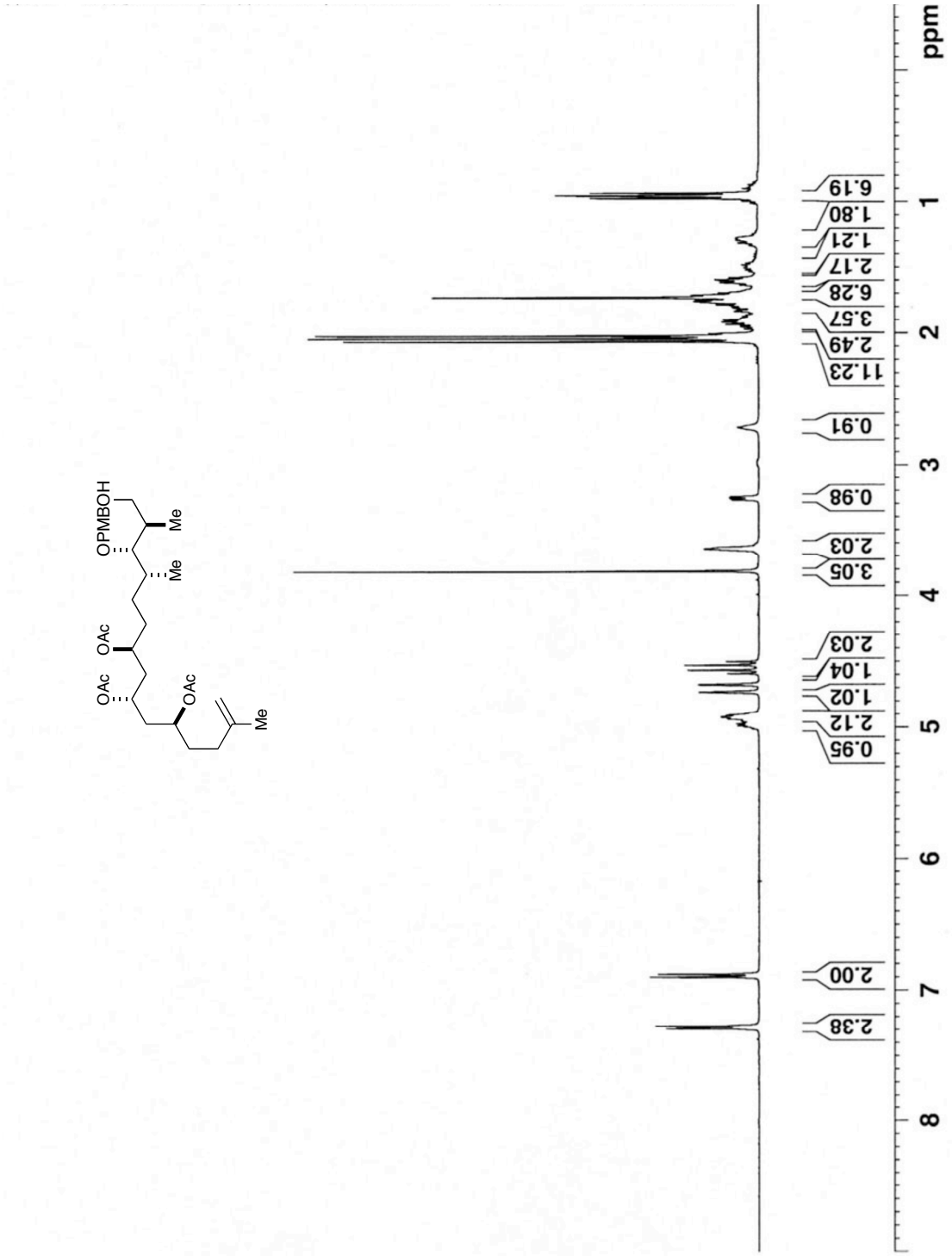
(2*R*,3*R*,7*R*,*Z*)-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-5-methyl-7-(triethylsilyloxy)dec-4-en-3-ol: 3.71



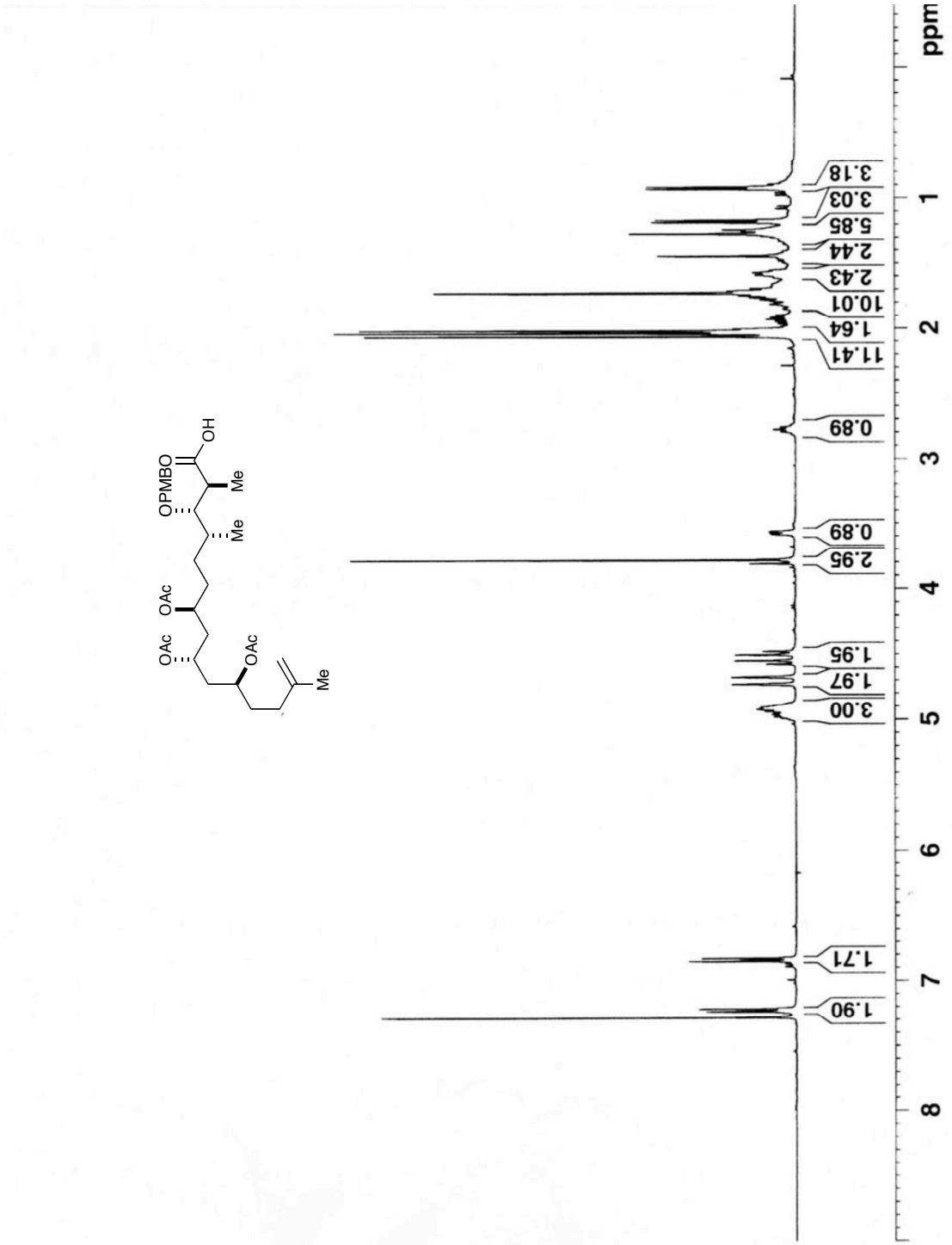
(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-15-(*tert*-butyldimethylsilyloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethylpentadec-1-ene-5,7,9-triyl triacetate: 3.75



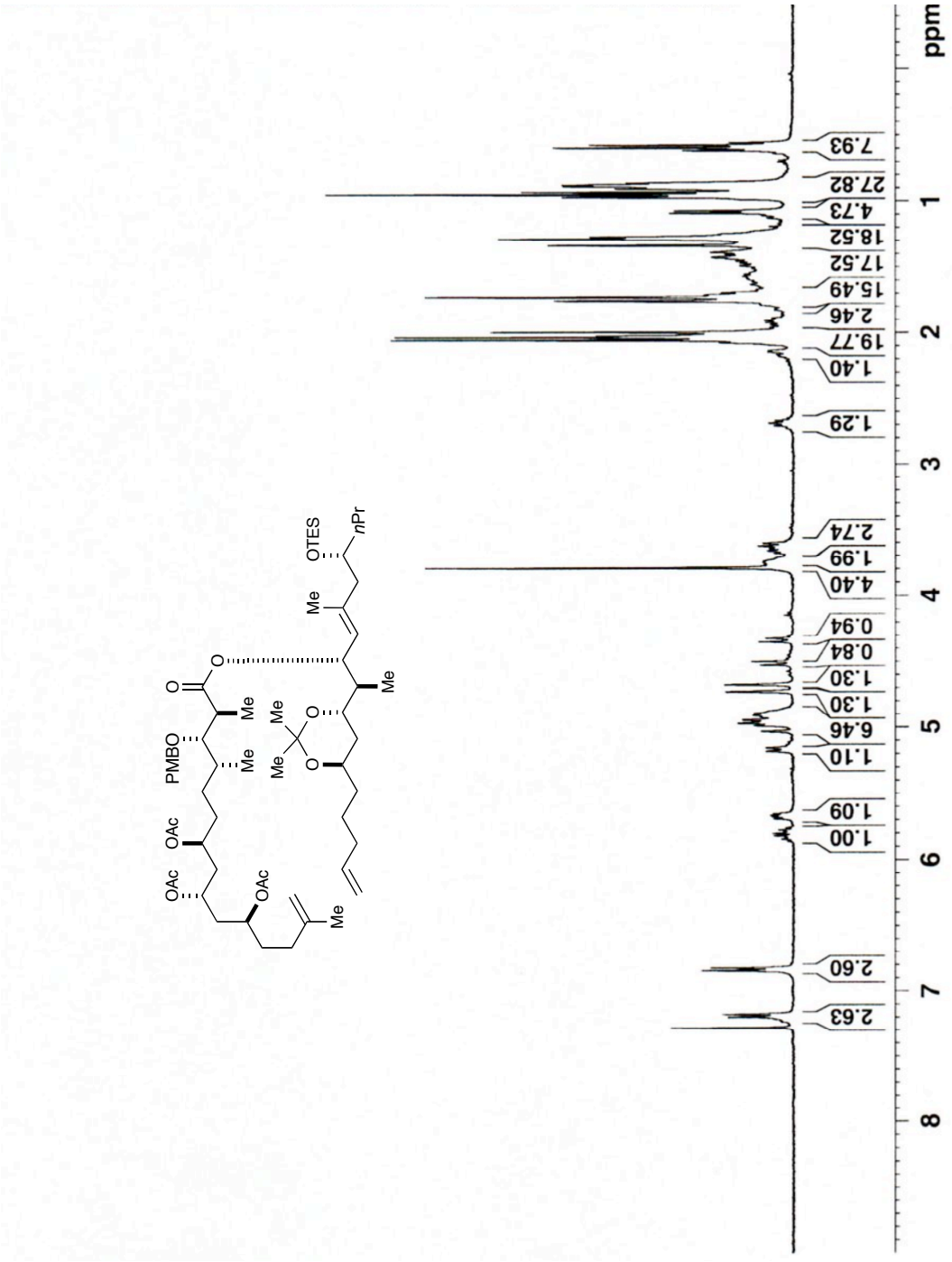
(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-15-hydroxy-13-(4-methoxybenzyloxy)-2,12,14-trimethylpentadec-1-ene-5,7,9-triyl triacetate: 3.76



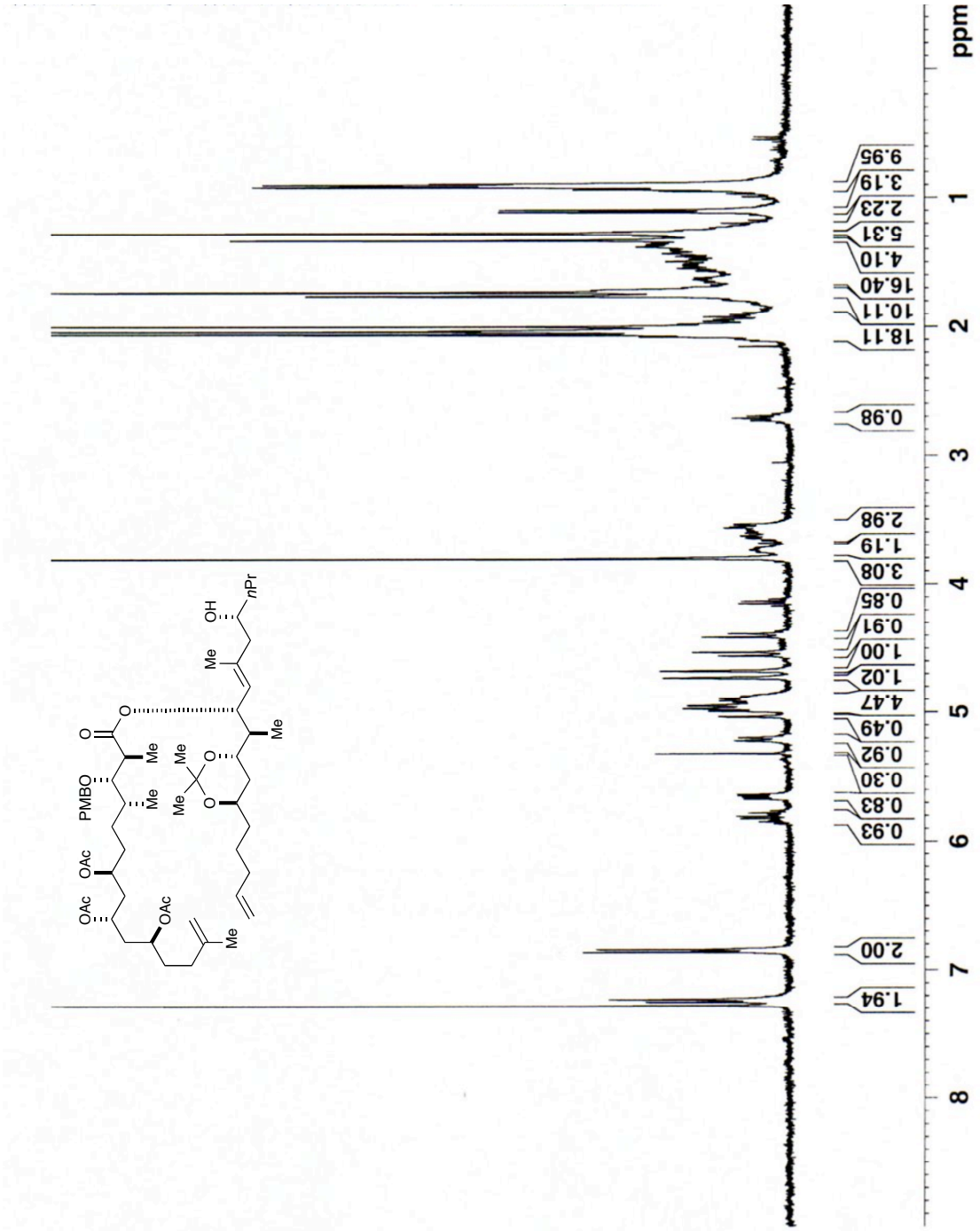
(2*S*,3*S*,4*R*,7*S*,9*R*,11*S*)-7,9,11-triacetoxy-3-(4-methoxybenzyloxy)-2,4,14-trimethylpentadec-14-enoic acid: 3.77



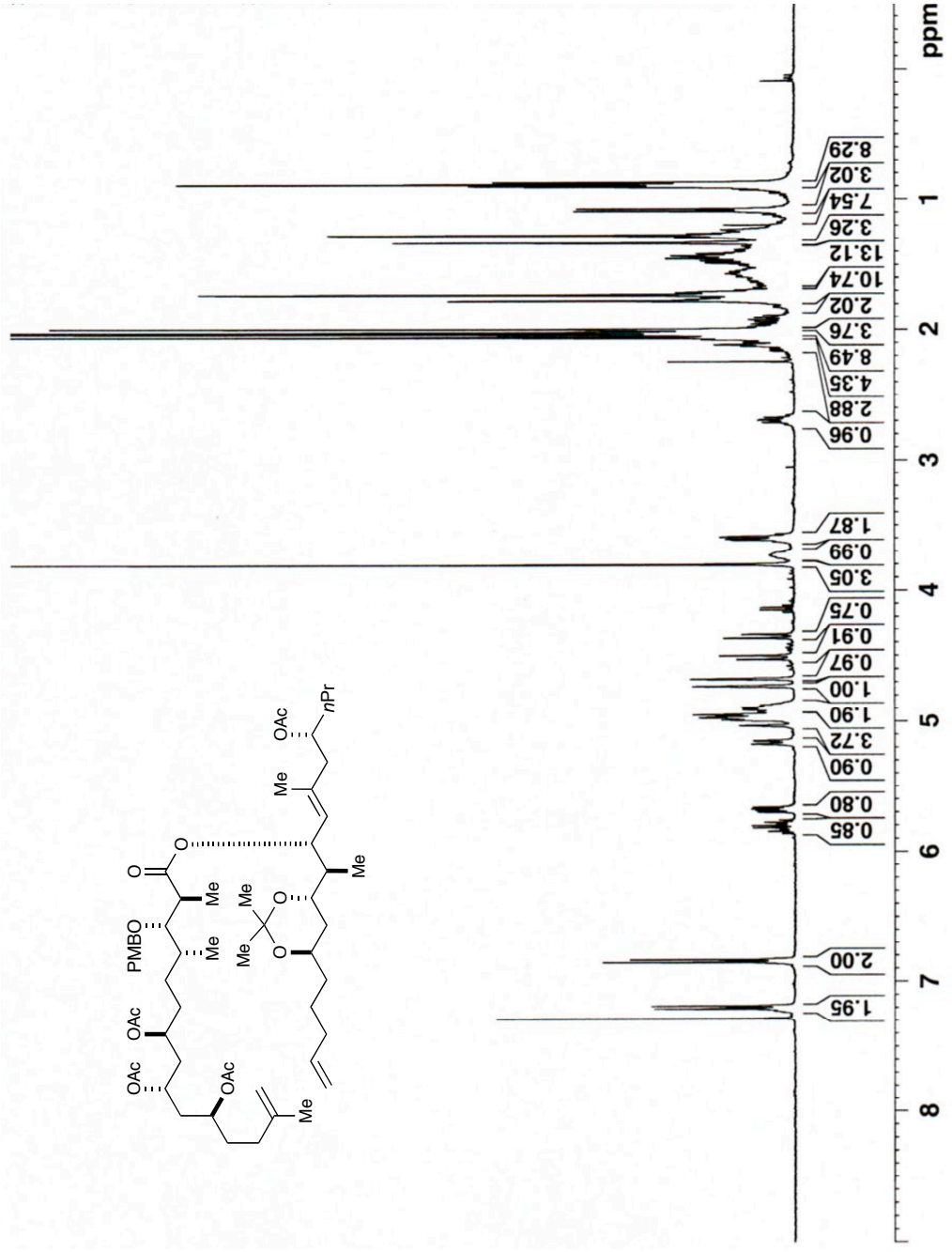
(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((2*S*,3*R*,7*R*,*Z*)-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-5-methyl-7-(triethylsilyloxy)dec-4-en-3-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: 3.78



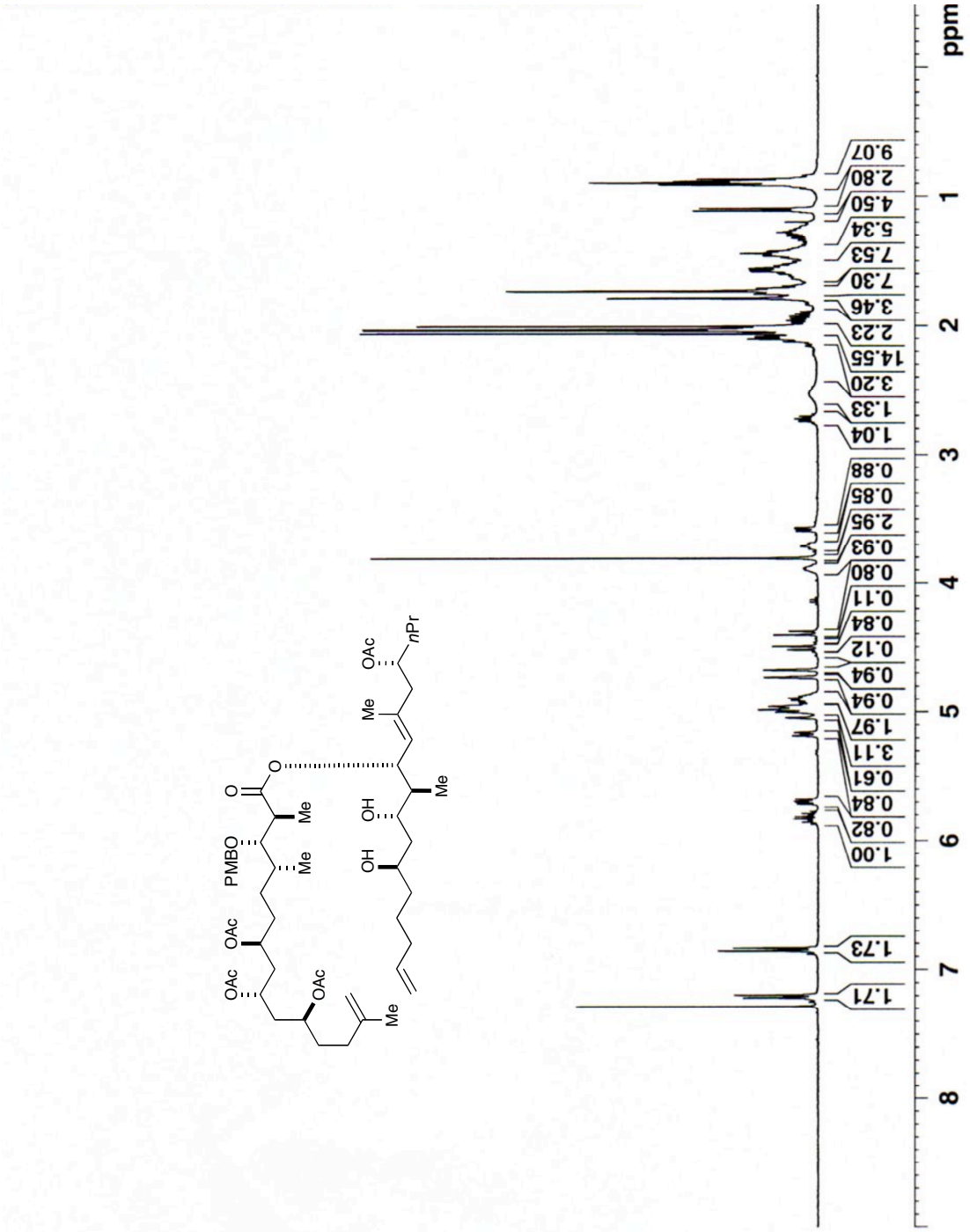
(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((2*S*,3*R*,7*R*,*Z*)-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-7-hydroxy-5-methyldec-4-en-3-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: SI16



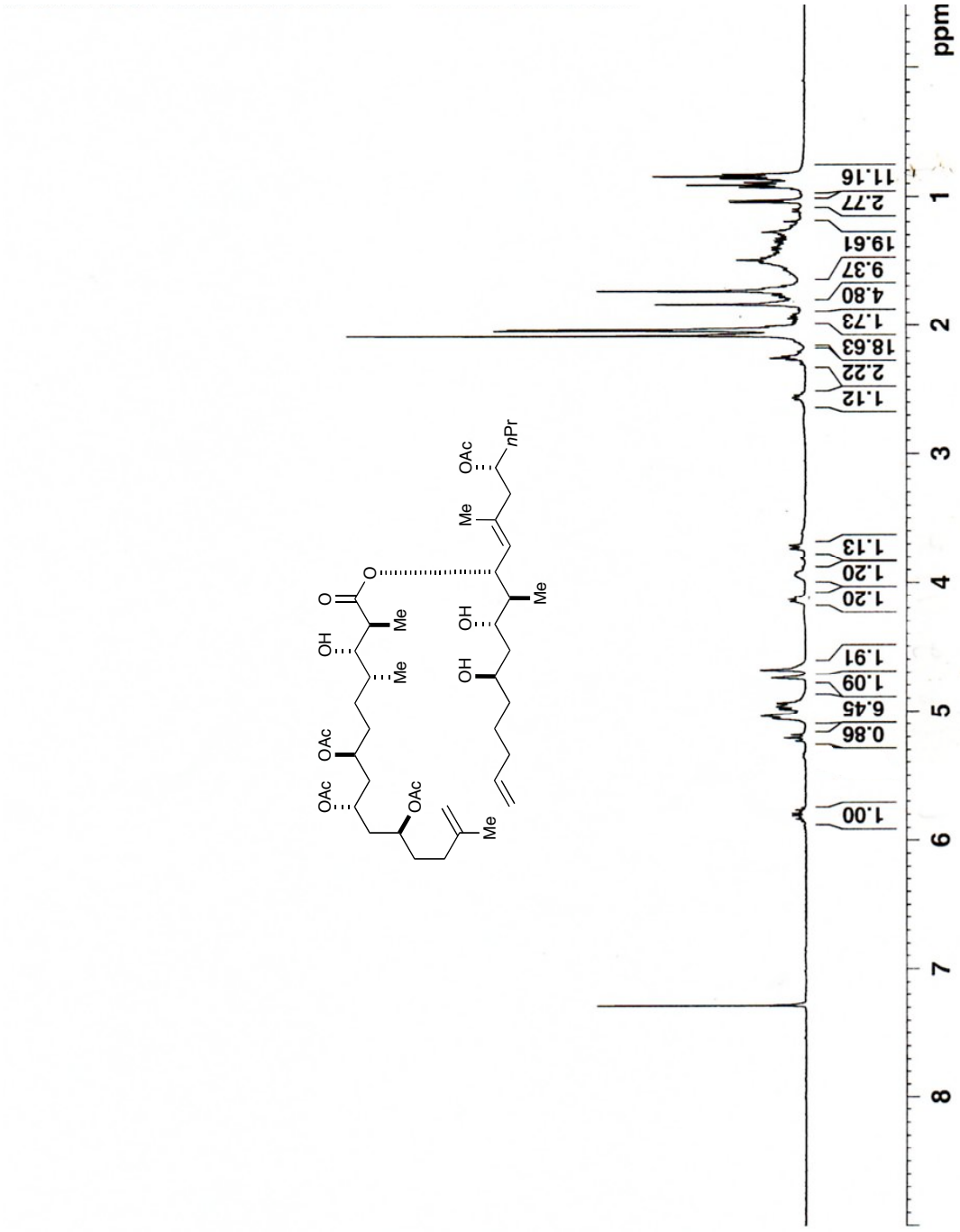
(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((2*S*,3*R*,7*R*,*Z*)-7-acetoxy-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-5-methyldec-4-en-3-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: 3.79



(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((4*R*,8*R*,9*S*,10*S*,12*R*,*Z*)-4-acetoxy-10,12-dihydroxy-6,9-dimethylheptadeca-6,16-dien-8-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: SI17



(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((4*R*,8*R*,9*S*,10*S*,12*R*,*Z*)-4-acetoxy-10,12-dihydroxy-6,9-dimethylheptadeca-6,16-dien-8-yloxy)-13-hydroxy-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate: 3.80



(3*S*,4*S*,5*R*,8*S*,10*R*,12*S*,20*R*,22*S*,23*S*,24*R*,*E*)-24-((*R*,*E*)-4-acetoxy-2-methylhept-1-enyl)-4,20,22-trihydroxy-3,5,15,23-tetramethyl-2-oxooxacyclotetracos-15-ene-8,10,12-triyl triacetate, Dolabelide C: 3.12