Asymmetric Synthesis of 1,3-*anti*-Diol-Containing Subunits using Phosphorus-Based Tethers: Application in the Total Synthesis of Dolabelide C

By

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B.S. Northwest Missouri State University, 2005

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

Christopher D. Thomas

Department of Chemistry, November 2010

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The focus of this dissertation is the desymmetrization of C_2-symmetric 1,3-*anti*-diols through the construction of pseudo-C_2-symmetric phosphorus heterocycles, bearing a chirotopic, non-stereogenic center at phosphorus. Diastereotopic differentiation is achieved through cyclization via ring-closing metathesis (RCM), affording a chiral, non-racemic bicyclic *P*-heterocycle, which is stereogenic at phosphorus. This strategy is central to building skeletally diverse polyol subunits, which are commonly seen in polyketide-based natural products. Terminus differentiation and chain elongation through selective transformations on the previously reported bicyclo[4.3.1]phosphate (both antipodes), e.g. cross-metathesis, regioselective olefin reduction and regio- and diastereoselective allylic phosphate displacements, provide a rapid protocol to accessing the aforementioned motifs. The development of this methodology advanced into an application toward the total synthesis of dolabelide C (bearing two separate 1,3-*anti*-diol containing fragments), which exhibits cytotoxicity against cervical cancer HeLa-S_3 cells with an IC_{50} value of 1.9 μg/mL. A route to this target was devised, where the final step was amending the 24-membered marcocycle through RCM. The result provided a diastereomeric mixture of *E* and *Z* isomers, which proved to be difficult to separate during initial efforts. However, LC-MS analysis of the mixture showed the contaminants were by-

products arising from isomerization events occurring prior to RCM. Other reports coincide with this observation, mainly in the synthesis of medium to larger sized rings. Scale-up was required after this initial study to provide ample material for final characterization and the re-synthesis provided a copious amount of the RCM precursor. The large amount of material allowed for optimization studies and finally resulted in 14 mgs of analytically pure dolabelide C and 10 mgs of the non-natural *Z*-isomer, which to the best of our knowledge is the first synthesis of both compounds and the most synthetic material available of each to date.

To the most important person in my life,

My wife and best friend, Morgan

Acknowledgements

I can honestly say I never expected to be in the position I'm in now. Five years ago I came in knowing little about what kind of career I wanted in chemistry and five years before that, I was a journalism major as a freshman at Northwest Missouri State University. The moral here is, you never know what life will bring. I wish I could write an entire book on persons I'd like to thank during my life, but I will try to be as concise as possible.

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Richard Toomey, Ph.D.: No one pushed me harder in my undergraduate than you and I'm glad to have worked for you as a T.A. as also to be your student. I still feel your impact has been tremendous in carrying myself not only as a chemist, but also as a professional. I still remember the times I sat in your office and said "I don't get it," still you kept welcoming in your office for help.

Paul: One thing that I've learned in being in your lab is "grab the low hanging fruit." I've tended to make things too complicated instead of building off of simpler concepts and results. I can honestly say I feel much more prepared for the next stage of my career every year I've been in your group. You've provided me a lot of opportunities and now I find myself in a good opportunity because of that.

Lab (Former Members): Alan Whitehead, I'll always remember how enthusiastic you seemed about your research, I try to mimic that as much as possible. Josh, you taught me a lot while working with me on dolabelide C. I'm glad to have gotten that experience with you and Morgan and I hope our paths cross again soon. Steve, you were the first to train me up in the group. It only took me until reaction two to blow up something (water + acetyl chlorides = bad). Jim, it's probably been the hardest transition for me when you left. I'll always remember our jam sessions to the

Toadies, Smashing Pumpkins and Underground by Ben Folds. You were the closet friend I had in the Hanson lab and I hope we continue that friendship for a long time.

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Friends: Dave, you've been my closet friend during my time at KU. I'm glad you decided to take an interest in Kansas City sports, because Morgan doesn't share the same enthusiasm. Or maybe I just have enough for both of us. I wish you, Carrie and Sandy the best and I hope we stay in touch. Brad, you might think you first got me started as a chemist, however I think I may have been scared away from it after being your lab partner. Good thing I came back to it.

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Asymmetric Synthesis of 1,3-*anti*-Diol-Containing Subunits using Phosphorus-Based Tethers: Application in the Total Synthesis of Dolabelide C

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Abbreviations

Ac	acetyl
Aq	aqueous
BBN	borabicyclononane
Bn	benzyl
Bu	butyl
c	concentration
cat.	catalytic
CBS	Corey-Bakshi-Shibata cataylst
CM	cross metathesis
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	day
DCE	dichloroethane
DDQ	dichlorodicyanoquinone
DEPT	distortionless enhancement by polarization transfer
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
ds	diastereoselectivity
Et	ethyl
GC	gas chromatography
HeLa-S_3	Human epithelial carcinoma cell line
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric acid
HRMS	high resolution mass spectrometry

IC_{50}	inhibitory concentration at 50%
i-Pr	isopropyl
IR	infrared radiation
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
M	molarity
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl ether
MVK	methyl vinyl ketone
n-BuLi	*n*-butyllithium
NMO	*N*-methyl-*N*-morpholine-*N*-oxide
NMR	nuclear magnetic resonance
Nuc	nucleophile
o-NBSH	*ortho*-nitrobenzenesulfonyl hydrazide
Ph	phenyl
PMB	*para*-methoxybenzyl
Piv	pivalate
ppm	parts per million
PPTS	pyridinium *para*-toluene sulfonate
psi	pounds per square inch
RCM	ring-closing metathesis
Red-Al	sodium *bis*(2-methoxyethoxy) aluminum hydride
rs	regioselectivity
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
TIPS	triisopropylsilyl

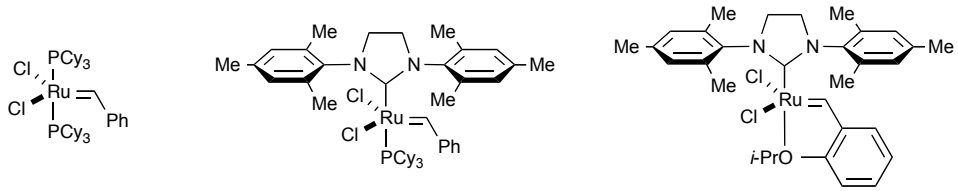
Tf	triflate
TIC	total ion chromatogram
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluene sulfonyl
V-ATPase	vacuolar-type H^+-ATPase
2,2-DMP	2,2-dimethoxypropane

Chapter 1

Phosphorus and Sulfur Heterocycles *via* Ring-Closing Metathesis: Applications in Total Synthesis

1.1 Introduction

The development of new synthetic strategies allowing for the efficient asymmetric syntheses of complex biologically active targets, with minimal protecting group manipulations and chemical steps, is an enormous challenge in natural product synthesis. An effective way of addressing this challenge is through the use of convergent methodologies employing the temporary tethering of two advanced intermediates. Historically, silicon has been the most widely used temporary tether due to its facile installation/cleavage attributes as well as its innate protecting group properties.[1] Moreover, the ability of silicon tethers to undergo myriad of functional group transformations positions them as ideal tethers in the realm of total synthesis.[2] Phosphorus and sulfur, namely phosphates and sultones, possess alternative properties as tethers in that they can serve as leaving groups mediating a variety of nucleophilic substitution reactions while retaining orthogonal stability. Both tethers can also serve as the central linchpin in the formation of the corresponding heterocycle *via* ring-closing metathesis (RCM) catalyzed by the well-defined olefin-metathesis First (cat-**A**) and Second (cat-**B**) Generation Grubbs[3] and Hoveyda-Grubbs[4] (cat-**C**) catalysts (Figure 1), which have also served an important role as an effective transformation in the total synthesis of natural products.[5]



cat-**A** cat-**B** cat-**C**

Figure 1

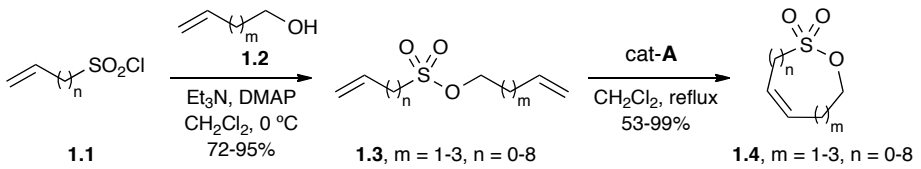
In addition, their facile cleavage resulted in by-products that are easily removed through aqueous workup (phosphine oxide)[6] or extrusion (SO_2).[7,8] Rapid access to complex, functionalized intermediates have allowed these methodologies to emerge in the realm of natural product synthesis.[8,9]

1.2 Sulfur Heterocycles

1.2.1 Synthesis and Reactivity of Sultones Derived from RCM

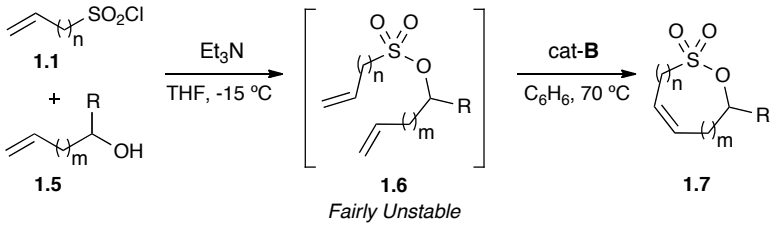
In 2002, Metz *et al.* reported the first synthesis of an unsaturated sultone **1.4** resulting in a method producing a variety of ring sizes.[10] These heterocycles were achieved in a two-step protocol starting from a variety of olefinic sulfonyl chlorides **1.1** and alkenols **1.2** (Scheme 1).

Scheme 1



In 2003, Cossy and coworkers demonstrated the ability to construct sultones from secondary alkenols, thus augmenting previous work by Metz with primary alkenols.[7] The unsaturated sulfonates derived from secondary alkenols (**1.5**, Scheme 2) were more difficult to construct and exhibited reduced stability. This problem was circumvented by subjecting the crude sulfonates **1.6** to catalyst cat-**B** (C_6H_6, 70 ºC) thus affording a variety of substituted unsaturated sultones **1.7** in good yields (Scheme 2).

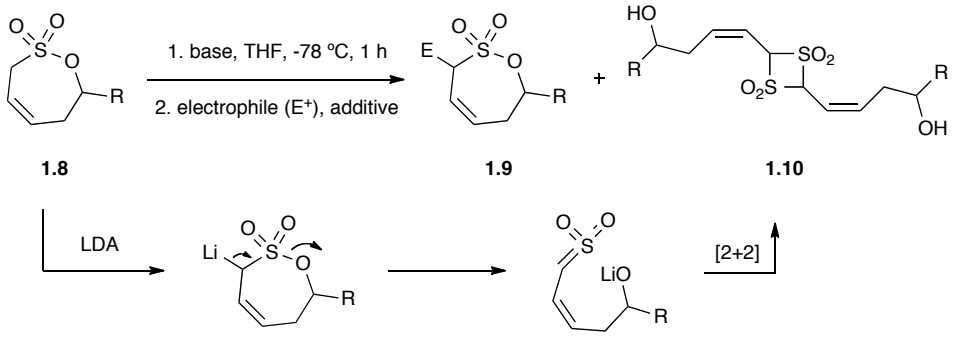
Scheme 2



m	n	R	Yield of **1.7**
0	1	$(CH_2)_3OBn$	76%
0	1	CO_2Et	54%
1	0	CH_2OPiv	74%
1	0	$CH_2OTBDPS$	65%
1	1	$(CH_2)_3OBn$	65%

The aforementioned heterocyclic building blocks possess the potential for exploring numerous reaction pathways.[11] Hence, Cossy and coworkers highlighted α-alkylation of various sultones **1.8** in the presence of *n*-butyllithium followed by the addition of different alkyl halides (Scheme 3).[8] The choice of base was also found to be crucial, as the use of LDA resulted in formation of a sulfene intermediate, which rapidly dimerized to product **1.10** through a [2+2]-cycloaddition.

Scheme 3



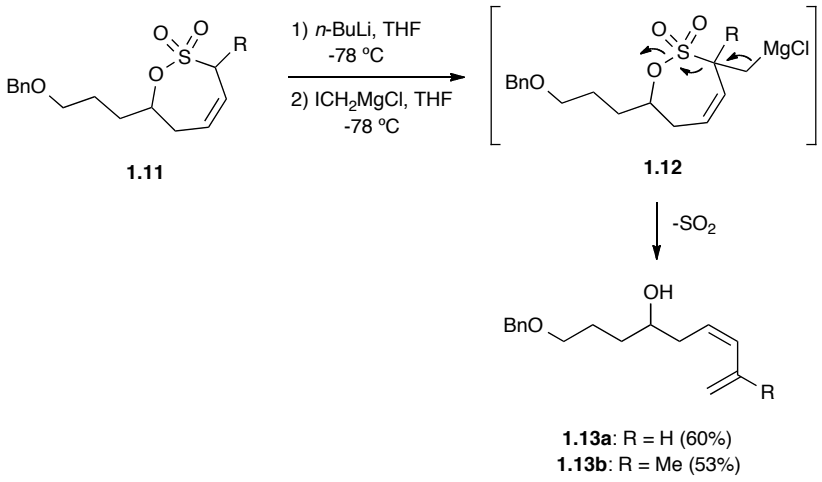
R	E^+	Base	Additive	Yield of **1.9**	Yield of **1.10**
H	MeI	*n*-BuLi (1 eq)	none	99%	0%
$(CH_2)_3OBn$	MeI	*n*-BuLi (1 eq)	none	85%	0%
$(CH_2)_3OBn$	$Br(CH_2)_3OBn$	*n*-BuLi (1 eq)	HMPA	84%	0%
$(CH_2)_3OBn$	none	LDA (3 eq)	none	0%	55%[a]

[a]60:40 mixture of *trans*/*cis* diastereomers

The leaving group ability of the sultone was exploited in an innovative alkylation/elimination sequence. The removal of the tether is facilitated by metallation of **1.11** (*n*-BuLi) and treatment with iodomethylmagnesium chloride (from CH_2I_2, *i*-PrMgCl, THF, -78 ºC) to produce the reactive Grignard species **1.12**. This species undergoes subsequent β-elimination resulting in loss of SO_2 to afford

homoallylic alcohols bearing 1,3-dienes with an internal *Z*-disubstituted olefin and a terminal or α,α-disubstituted alkene, **1.13a**/**1.13b**, respectively (Scheme 4).[8]

Scheme 4



A number of bioactive natural products possess a similar homoallylic conjugated *Z*-dienol which can be produced from a sultone heterocycle (Figure 2).[12] The approach of Cossy et al. to this synthon is unique compared to previous methodologies that do not utilize olefin metathesis to afford the internal *Z*-olefin of the 1,3-dienol.[13]

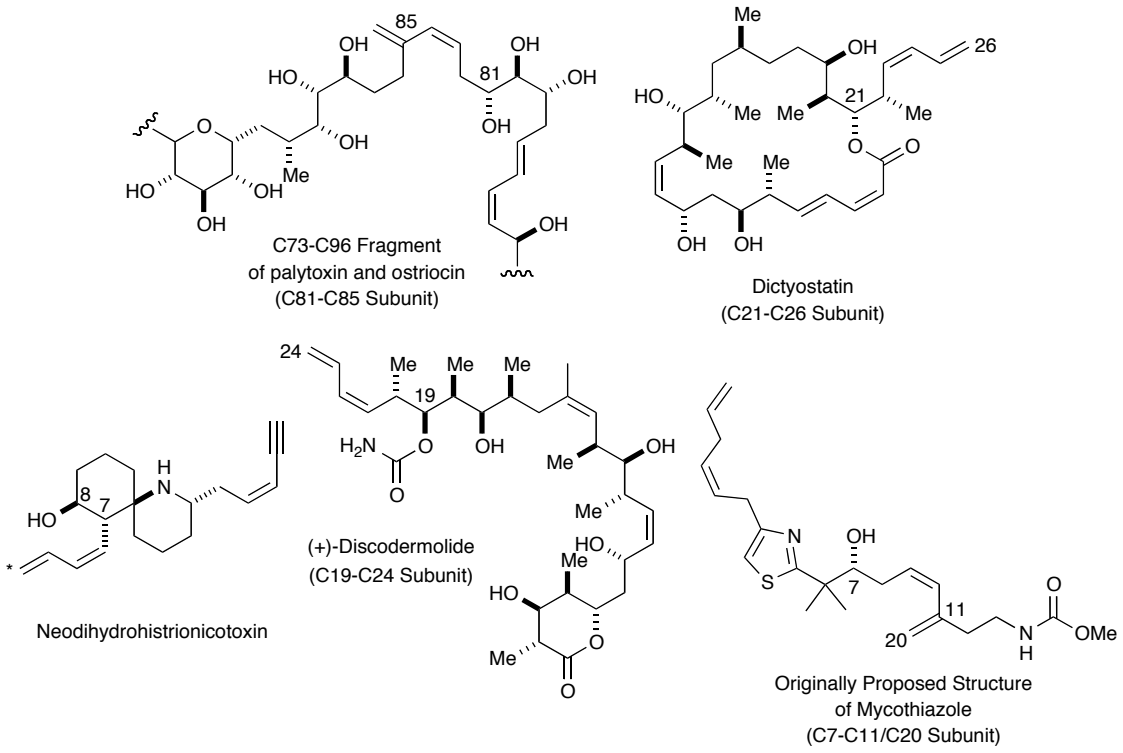


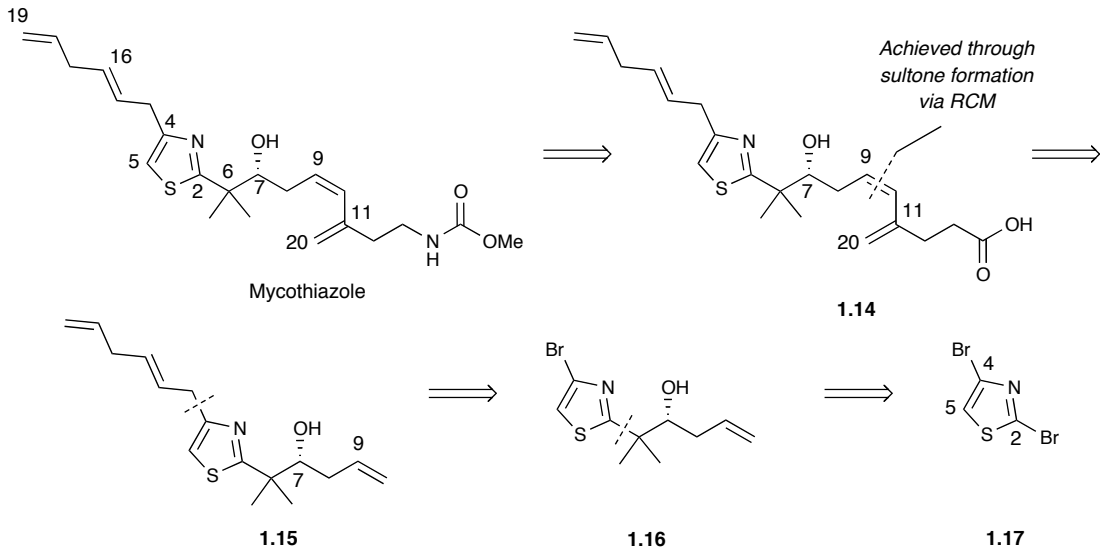
Figure 2

1.2.2 Total Synthesis of (±)-Mycothiazole (The Originally Proposed Structure)

The development of a method towards constructing conjugated *Z*-dienols led Cossy and coworkers to pursue the total synthesis of (±)-mycothiazole,[8] with the originally proposed structure[14] outlined in Scheme 5. The synthesis was designed for the C7-C11/C20 subunit to be accessed through formation of a sultone tether from homoallylic alcohol **1.15** through sulfonylation and RCM (Scheme 5). Subsequent alkylation of the α-position to the sulfonyl would afford requisite functionalization to append the C12-C13 side chain. Overall, the retrosynthetic approach started from

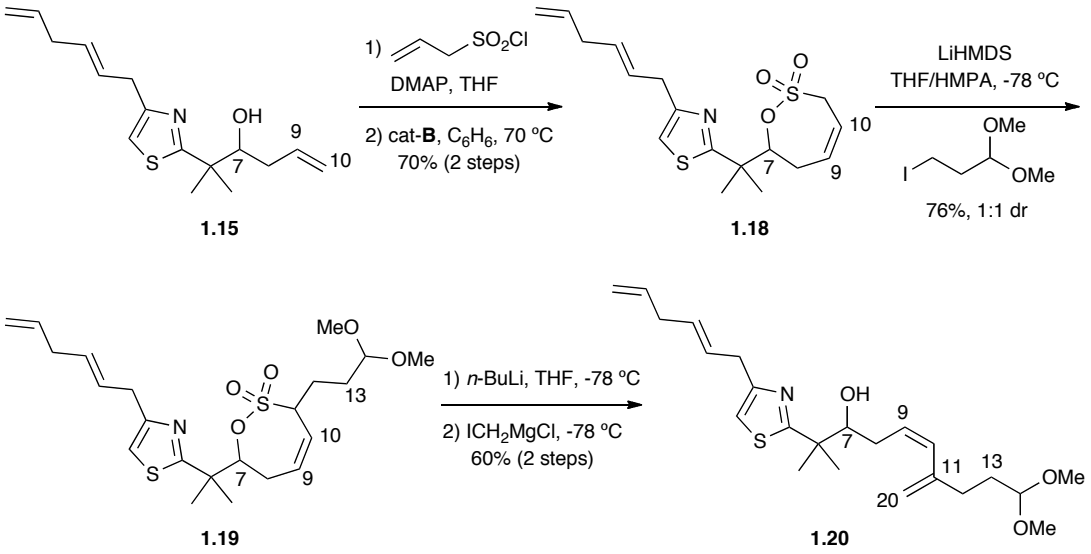
readily available 2,4-dibromothiazole (**1.17**),[8] which established the necessary connectivity for the uniquely substituted thiazole ring.

Scheme 5



The key sequence began with the formation of the sultone derived from the advanced homoallylic alcohol **1.15**, where sulfonation and subsequent RCM with cat-**B** afforded sultone **1.18**, bearing the necessary C9-C10 *Z*-olefin, as a single diastereomer in 70% yield over two steps (Scheme 6). Subsequent alkylation of the sultone with 1,1-dimethoxy-3-iodopropane, furnished sultone **1.19** as a 1:1 mixture of diastereomers at C11. Construction of the dienol commenced *via* deprotonation of **1.19** with *n*-BuLi followed by addition of ICH_2MgCl (supplying the C20 terminal methylene group), yielding the desired *Z*-dienol **1.20** in 60% yield.[8]

Scheme 6

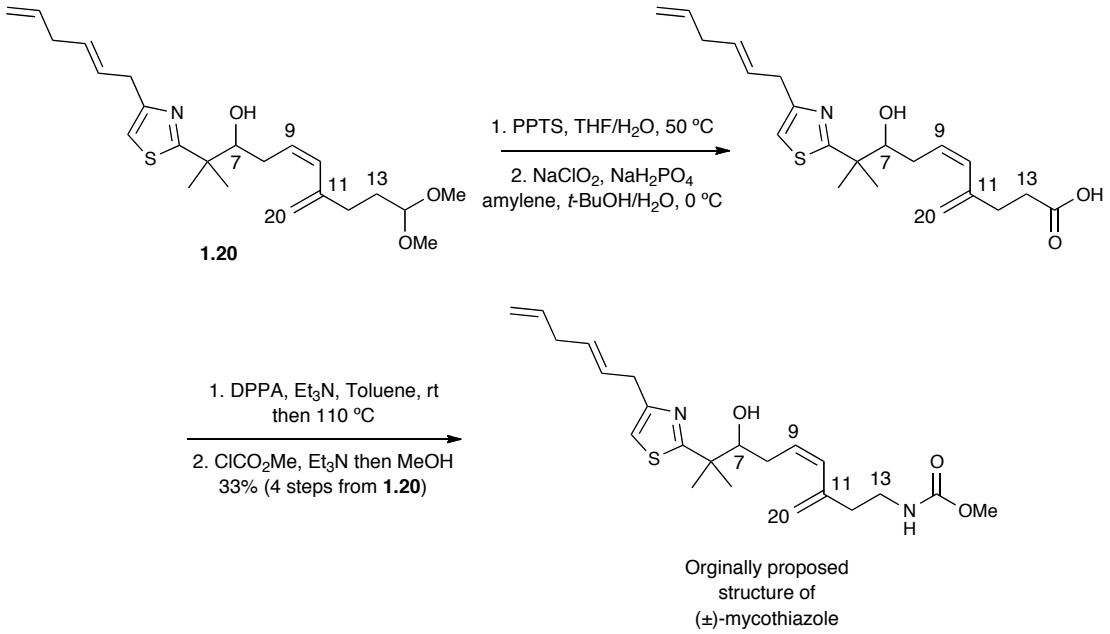


Following assembly of the key C9-C11/C20 subunit, conjugated *Z*-dienol, dimethyl acetal **1.20** was converted to the required carbamate in 33% yield over four steps, achieving a racemic synthesis of the originally proposed structure of mycothiazole in 5% overall yield and 18 steps from 2,4-dibromothiazole **1.17** (Scheme 7).[8] This was the first example of utilization of a sulfur-mediated tether in the context of the total synthesis of a biologically active natural product.

Overall, the construction of sultones *via* sulfonation/RCM from the corresponding allylic alcohol fulfills the requirements of an effective temporary tether in synthesis. The sultone functionality provides sufficient reactivity under basic conditions to afford complex *Z*-substituted 1,3-dienols after the facile removal of the sulfonyl through the extrusion of SO_2. The prospect of utilizing additional selective

reaction pathways has the potential to generate new synthons furnishing a variety of pathways to biologically active natural products.[7,8]

Scheme 7



1.3 Phosphorus Heterocycles

1.3.1 Synthesis and Reactivity of Phosphates from RCM

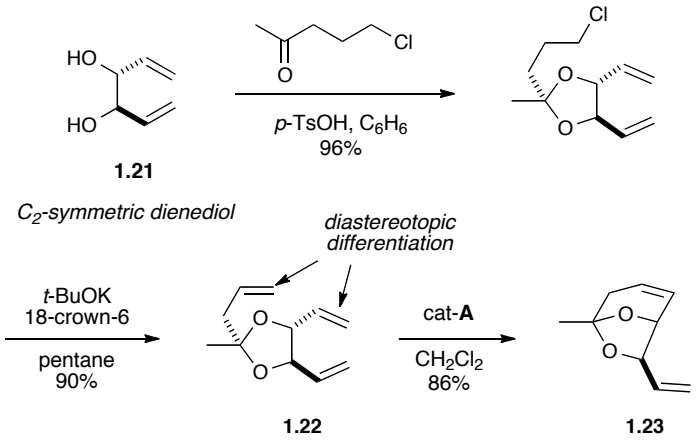
Despite enormous research on organophosphorus compounds, the general use of phosphate triesters in synthesis has been relatively limited until recently. Phosphorus has inherent properties that make it an attractive tether candidate, including the ability to mediate di- and tripodal coupling, provide orthogonal

protection and serve as a leaving group. Irrespective of these attributes, the application of phosphates in synthesis is largely centered on monovalent activation of a single phosphate ester appendage. Such classical use of phosphates in complex synthesis focus on nucleophilic displacement reactions of allylic phosphates,[15] cross-coupling/reduction reactions with enol-phosphates,[16] and more recent applications employing direct displacements of phosphates in cyclization protocols.[17] Additional uses of phosphate triesters in iodophosphonylation procedures[18] and their role in oligonucleotide synthesis[19] further highlight both nucleophilic properties and facile coupling characteristics innate to phosphates. These reaction processes utilize the leaving group ability of a phosphate monoanion, where a single ester moiety is activated (monovalent activation) and the remaining ester positions serve as ancillary substituents.

In 2005, Hanson and coworkers investigated the possibility of exploiting both multipodal coupling and multivalent activation attributes within phosphate triesters, which by their nature presented opportunities to investigate selective processes. This study resulted in a new method that embodied several underdeveloped areas of phosphate chemistry, namely their use as removable, functionally active tethers capable of multipodal coupling and multivalent activation and their subsequent role as latent leaving groups in a number of unprecedented selective cleavage reactions. In addition, stereoelectronic effects within the bicyclic framework lend orthogonal protecting group stability. In 2005, Hanson and coworkers implemented this protocol for constructing cyclic phosphates from allylic alcohols[6c] and 1,5-diene-2,4-diols[6a] to

yield unique mono- and bicyclic heterocycles that undergo several selective transformations while imparting orthogonal stability. The utilization of a tether to desymmetrize a C_2-symmetric diol was inspired by the work of Burke et al., who demonstrated that ketalization of 1,5-diene-3,4-diol **1.21** with 5-chloropentan-2-one and subsequent elimination of the primary chloride with *tert*-butoxide could generate triene **1.22** (Scheme 8).[20] After undergoing cyclization in presence of cat-**A**, RCM afforded chiral, non-racemic bicycle **1.23** in 86% yield. Diastereotopic differentiation of the pseudo-C_2-symmetric ketal **1.22** using RCM was facilitated by the proximity of the newly installed allyl group, which allowed the differentiation of the previously homotopic terminal vinyl groups.

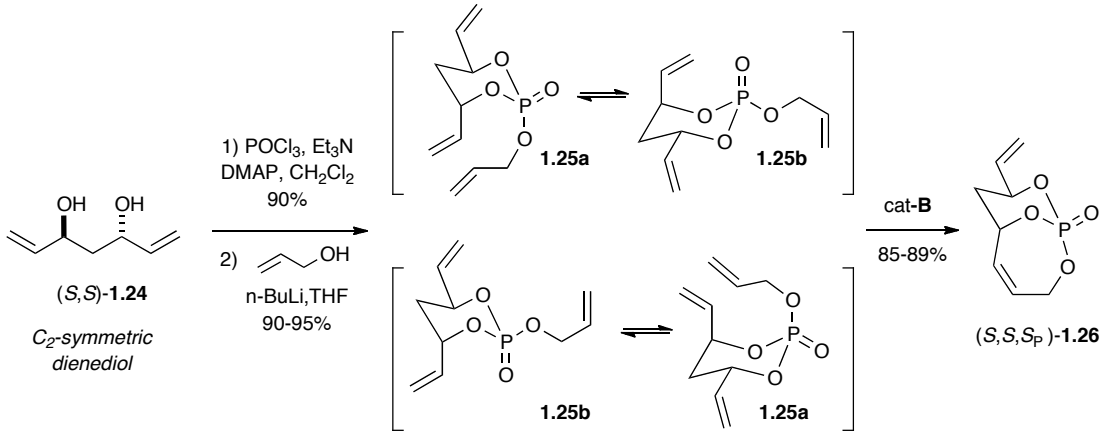
Scheme 8



In 2005, Hanson and coworkers utilized this concept with a phosphate tether in the desymmetrization of C_2-symmetric (3*S*,5*S*)-1,6-diene-diol (*S,S*)-**1.24** (Scheme 9).[6a] After coupling with $POCl_3$, allyl alcohol was added to the phosphoryl chloride

species, yielding phosphate triene (*S,S*)-**1.25**. In the presence of cat-**B** (Figure 1), the proximity of the two 1,3-diaxial terminal olefins in ring conformer **1.25a** allowed for facile RCM affording the *P*-chiral, nonracemic bicyclo[4.3.1]phosphate scaffold (S,S,S_P)-**1.26**.

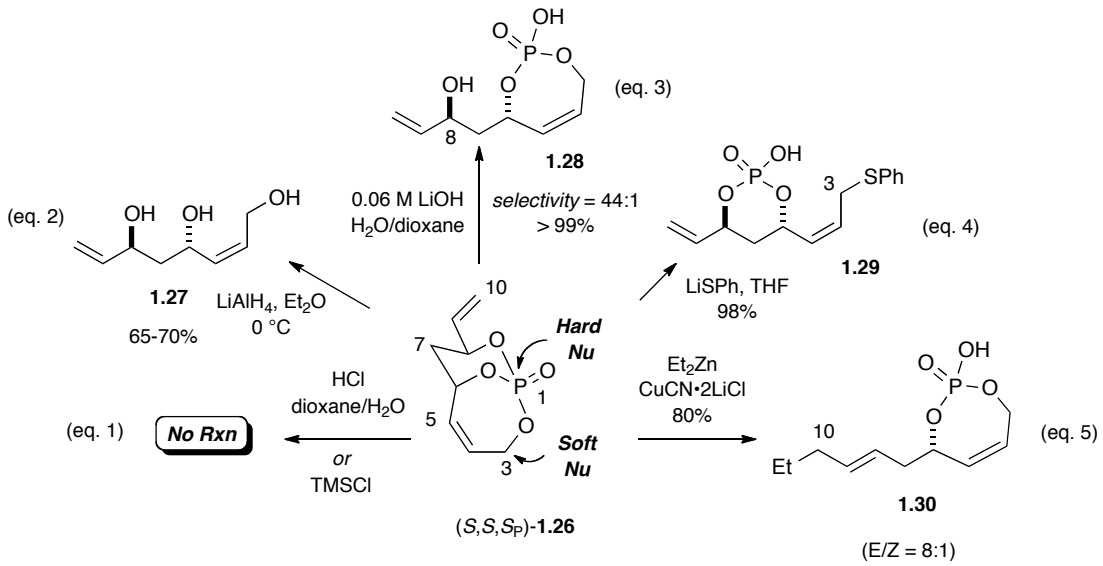
Scheme 9



The nature of bicyclo[4.3.1]phosphate (S,S,S_P)-**1.26**, showed promise in pursuing selective transformations, whereby the tripodal phosphate tether imparts multivalent activation of the three carbinols en route to differentiated polyol fragments.[6a] Consistent with previous reports of cyclic phosphines and phosphates, it was shown that in acidic media, **1.26** exhibited excellent stability due to the decrease in proton affinity (basicity) of the phosphonyl oxygen (eq. 1, Scheme 10), thus hindering activation pathways.[21] Different nucleophiles were shown to yield selective reaction pathways through their hard/soft characteristics.[22] First, addition of $LiAlH_4$ resulted in hydride addition to phosphorus resulting in facile removal of the

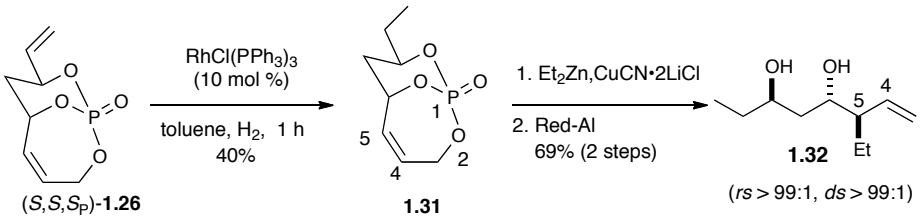
phosphate thus affording triol **1.27** (eq. 2, Scheme 10). This result supports the ability of the phosphate to be utilized as a temporary tether in coupling diol **1.24** with allyl alcohol through a phosphate-mediated sequence.[6a] Basic hydrolysis (eq. 3, Scheme 10) also resulted in attack at phosphorus, however due to the characteristics of the phosphate mono-anion,[23] an excess of LiOH only displaced one of the three P-O bonds, yielding phosphate acid **1.28**. Variation from an oxygen nucleophile to a softer sulfur nucleophile such as LiSPh (eq. 4, Scheme 10) demonstrated the preference for addition onto the most sterically accessible C3 carbinol position, furnishing phosphate acid **1.29**. Lastly, cuprate addition resulted in allylic displacement of the more sterically accessible olefin (eq. 5, Scheme 10), resulting in phosphate acid **1.30**, along with preferential formation of the *E*-isomer, which is consistent with previous reports in the field of cuprate additions to allylic phosphates.[24]

Scheme 10



The preference of cuprate nucleophiles to add into the more sterically accessible olefin of **1.26** led into examining the possible functionalization of the endocyclic olefin.[6a] After regioselective hydrogenation of the exocyclic olefin in the presence of Wilkinson's catalyst, cuprate addition to phosphate **1.31** preferentially occurred at the C5 position with high regioselectivity (Scheme 11). Removal of the phosphate acid with Red-Al produced diol **1.32** bearing an 1,3,4-*anti*,*anti*-stereotriad, as a single diastereomer over the three-step sequence from (*S*,*S*,S_P)-**1.26**.

Scheme 11



The remarkable regioselectivity in this transformation is attributed to inherent stereoelectronic effects of the C4-C5 olefin and P-O bond of the corresponding allylic phosphate. For addition into the C5 position (path A, Figure 3, X-ray of structure **1.26**), orthogonal alignment of the π* orbital of the C=C bond and σ* orbital of the P-O provide proper electronics for the allylic displacement to occur. However, in a potential C4 addition (path B, Figure 3), S_N2' addition does not take place due to coplanar alignment of the aforementioned π* orbital of the C=C bond to the P-O σ* orbital.[6a]

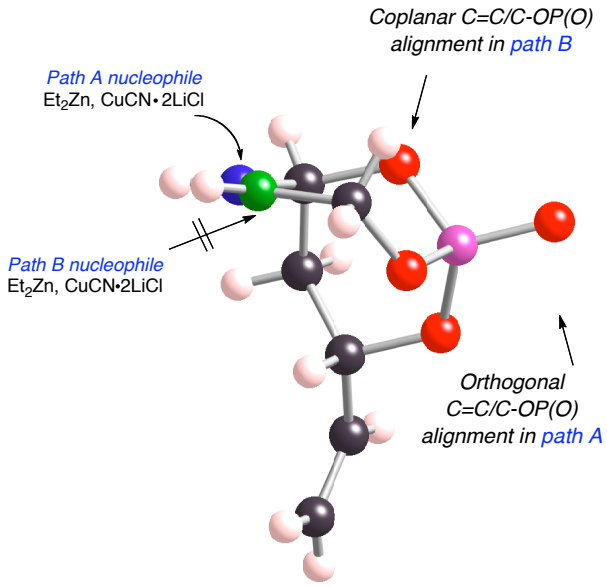


Figure 3

Facial selectivity was attributed to the overall geometry of the bicyclic skeleton of **1.26**, whereby the bicyclo[4.3.1]phosphate system, hinders approach of the cuprate from the concave face (Figure 4, X-ray of structure **1.26**).[6a]

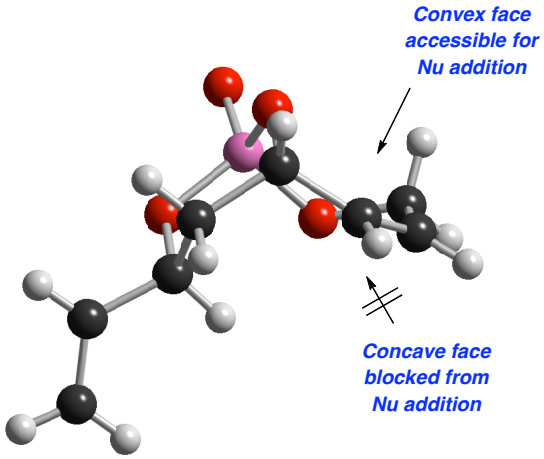
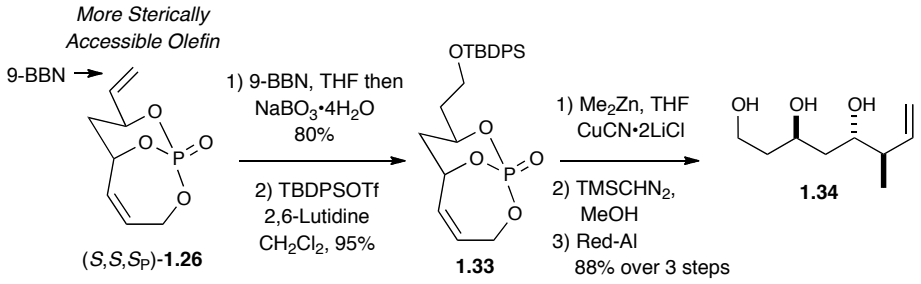


Figure 4

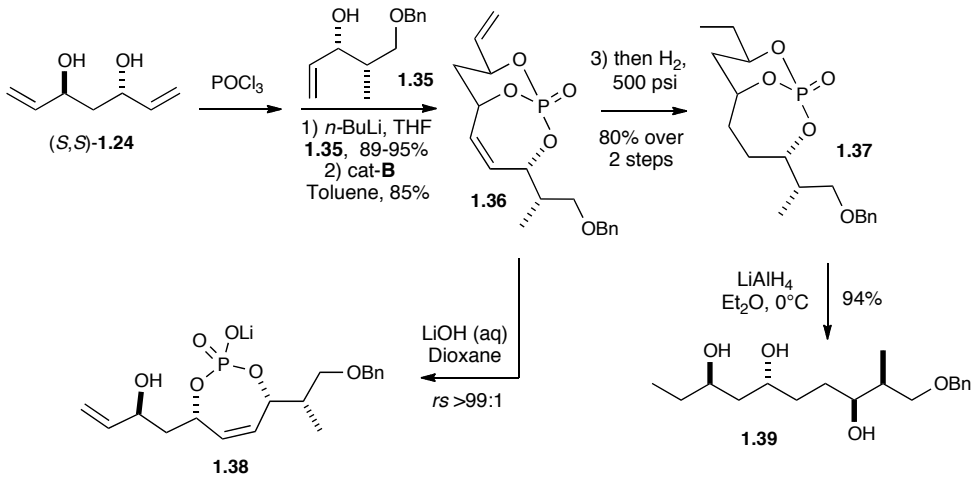
Another highlight of selective functionalization of (*S*,*S*,S_P)-**1.26** was seen in hydroboration (Scheme 12).[6a] Addition of 9-BBN across the exocyclic olefin, followed by mild oxidation of the corresponding borane ($NaBO_3$•$4H_2O$)[25] furnished a primary alcohol,[26] which was protected with TBDPSOTf to give silyl ether **1.33** in good yield. Further conversion to triol **1.34**[27] was accomplished first by cuprate addition and methylation of the resulting phosphate acid to a more convenient phosphate ester for handling and reductive removal (Red-Al) (Scheme 12).[6a]

Scheme 12



The utility of the phosphate tether for the rapid generation of advanced polyol subunits is highlighted in Scheme 13. After coupling diol (*S*,*S*)-**1.24** with chiral allylic alcohol **1.35**, successful RCM gave the complex phosphate **1.36**. Hydrolysis of the phosphate yielded **1.38** as the phosphate lithio-salt in 3 steps from **1.24**. Exhaustive hydrogenation[28] of both olefins (H_2, 500 psi) and quantitative phosphate cleavage ($LiAlH_4$) afforded the polyol subunit **1.39** in an efficient 4-step protocol from **1.24**.[6a]

Scheme 13



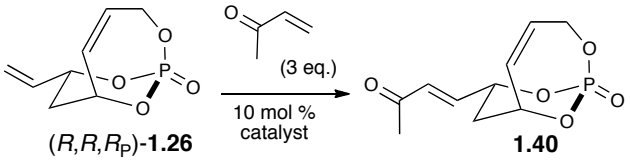
Overall, a number of selective nucleophilic additions to (S,S,S_P)-**1.26** have been demonstrated. These observations highlight the ability of multivalent activation in phosphate triesters to rapidly access complex, differentiated polyol subunits, which are applicable to natural product synthesis.

1.3.2 Reactivity of Phosphate 1.26 in Cross-Metathesis

Cross-metathesis (CM) studies were explored with (R,R,R_P)-**1.26**, with the aim of observing a regioselective of the exocyclic olefin and also determining the reactivity of **1.26**,[29] allowing insight to its compatibility with a variety of cross-partners. First, the reactivity was probed in subjecting (R,R,R_P)-**1.26** with methyl-vinyl ketone (MVK) with three different methathesis catalysts (Table 1).[6b] Results showed excellent regioselectivity, yielding **1.40**, in all of the conditions screened

along with the optimal parameters utilizing cat-**C** and a slight increase of MVK (entry 5) in comparison to entries 1-4.

Table 1



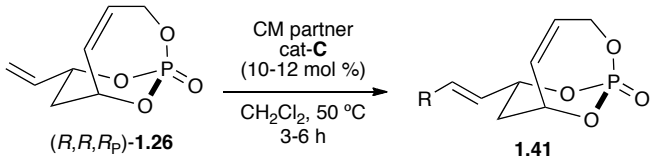
(R,R,R_P)-**1.26** **1.40**

entry	catalyst	conc./ solvent	% yield
1	cat-**A**	0.05 M/ CH_2Cl_2	<5[a]
2	cat-**B**	0.05 M/ CH_2Cl_2	25[a]
3	cat-**B**	0.1 M/ CH_2Cl_2	26[a]
4	cat-**C**	0.05 M/ CH_2Cl_2	75[b]
5	cat-**C**	0.1 M/ CH_2Cl_2	71[b,c]

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

With the ideal conditions in hand, a variety of cross-partners were screened. Observations revealed that **1.26** was reactive with type I (rapid homodimerization) and type II (slow homodimerization)[29] olefins, providing good yields and good to excellent *E*:*Z* ratios (Table 2). When attempting to undergo CM with type III partners, very poor yields were observed. In accordance with Grubbs classification of CM partners, type III olefins do not undergo homodimerization, and are therefore ideal hetero-partners with substrates bearing type I and II olefins and unreactive with substrates possessing type III olefins.[29] Based on these results and the fact that **1.26** did not undergo homodimerization, the exocyclic olefin in **1.26** (also assumed for the (S,S,S_P)-antipode) was deemed to be type III.[6b]

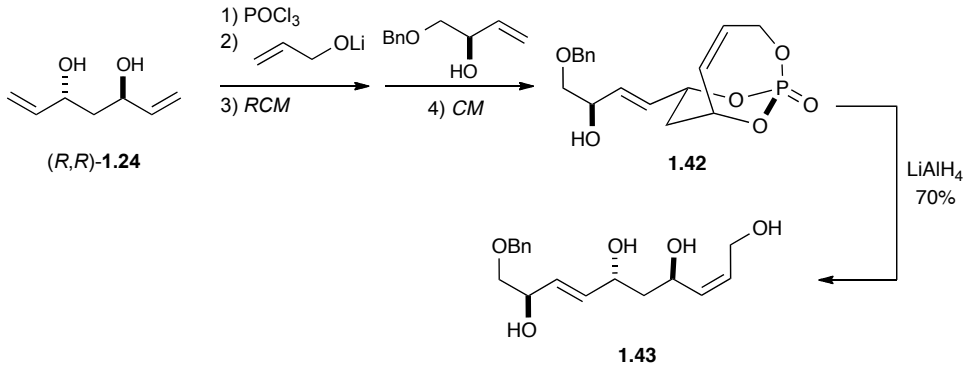
Table 2



CM partner	% yield	*E/Z*	Type	CM partner	% yield	*E/Z*	Type
HO	86	>99:1	I	O, H	78	>99:1	II
TBSO	87	>99:1	I	BnO, HO	72	>99:1	II
BocNH	69	>99:1	I	O, MeO	**<5**	**n/a**	III
O, $(MeO)_2PO$	80	2:1	I		**<5**	**n/a**	III
O, MeO	78	8:1	II	NC	**N.R.**	**n/a**	III
O, t-BuO	60	5:1	II	***none***	**N.R.**	**n/a**	

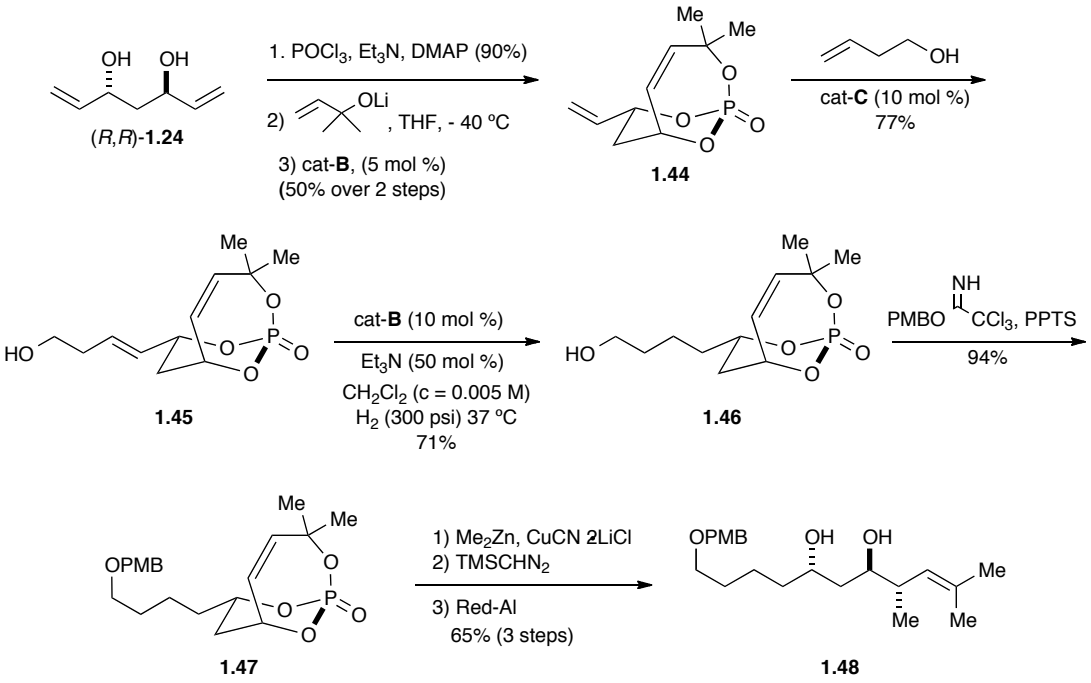
The key result from this study is the ability to use metathesis as a rapid means to desymmetrizing C_2-symmetric diol (*R*,*R*)-**1.24** (Scheme 14). It can be seen that each of the homotopic termini of **1.24** is selectively differentiated through the construction of tetrol **1.43** after reductive removal ($LiAlH_4$) of the phosphate tether.[6b] A wide array of cross-partners can also be utilized via this approach, since the type III reactivity of the exocyclic olefin of **1.26** allows for high selectivity with type I and II olefins, especially cross-partners bearing higher levels of complexity (vide infra).

Scheme 14



By combining the cross-metathesis and cuprate methodologies, an advanced intermediate **1.48** containing key aspects of the dolabelide family was constructed (Scheme 15).[30a] Hence, phosphate-mediated coupling of (*R*,*R*)-**1.24** with 1,1-dimethylallyl alcohol afforded the bicyclic phosphate **1.44** over a three-step sequence. Cross-metathesis of the latter with but-3-en-1-ol in the presence of cat-**C** and subsequent hydrogenation of the exocyclic olefin of **1.45** furnished an extended side-chain (**1.46**) bearing the C15-C19 structure of dolabelide. After benzylation of the primary alcohol in **1.46** with *p*-methoxybenzyl trichloroacetimidate, addition of a methyl cuprate, methylation of the phosphate acid ($TMSCHN_2$) and removal of the phosphate ester (Red-Al) yielded advanced intermediate **1.48**, a key synthon toward the synthesis of dolabelide C.[6b]

Scheme 15



The differentiated 1,3,4-*anti,anti*-stereotriad seen in **1.48** is also present in a number of biologically active natural products, including dolabelides C, bitungolide E, (+)-discodermolide, dictyostatin and salicylihalamide A (Figure 5).[30]

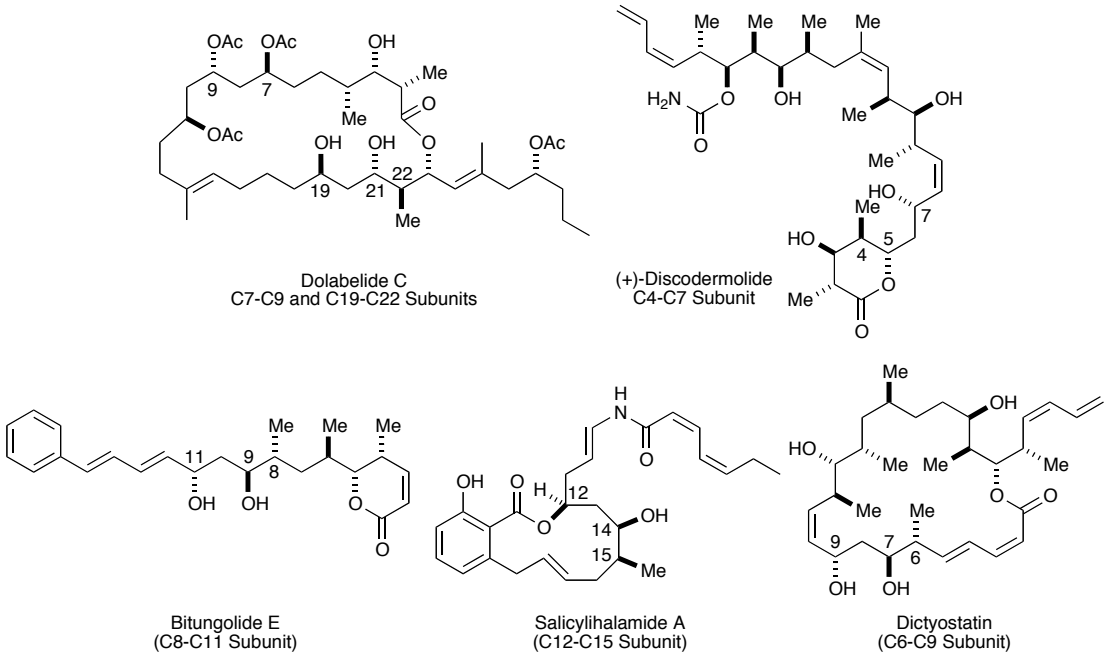
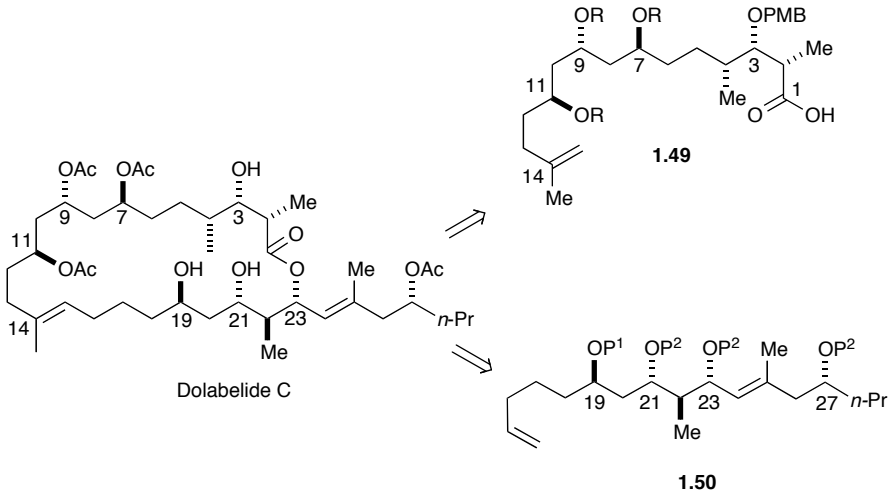


Figure 5

1.3.3 Efforts Toward the Synthesis of Dolabelide C

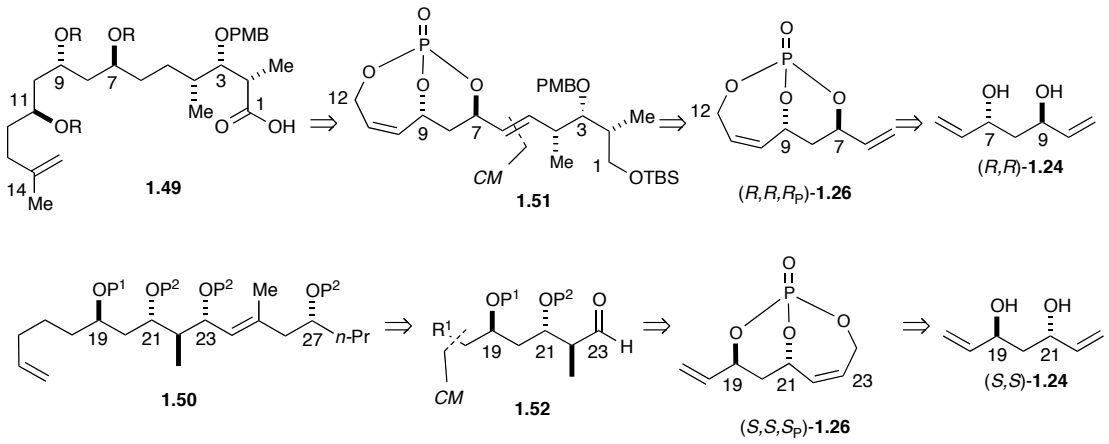
Dolabelides A-D were isolated from a sea hare, *dolabella auricularia*.[30a] To date, Leighton's total synthesis of Dolabelide D stands as the lone synthesis of any member in this family.[31] In 2008, Hanson and coworkers reported the synthesis of two key subunits of dolabelide C, possessing the 1,3-*anti*-diol motif observed at the C7/C9 positions and the 1,3,4-*anti*,*anti*-diol subunit at the C19/C21-C22 positions. Retrosynthetic analysis segmented the 24-membered macrolide into a C1-C14 subunit **1.49** and C15-C30 subunit **1.50** from disconnecting the lactone bond and C14-C15 olefin (Scheme 16).[9]

Scheme 16



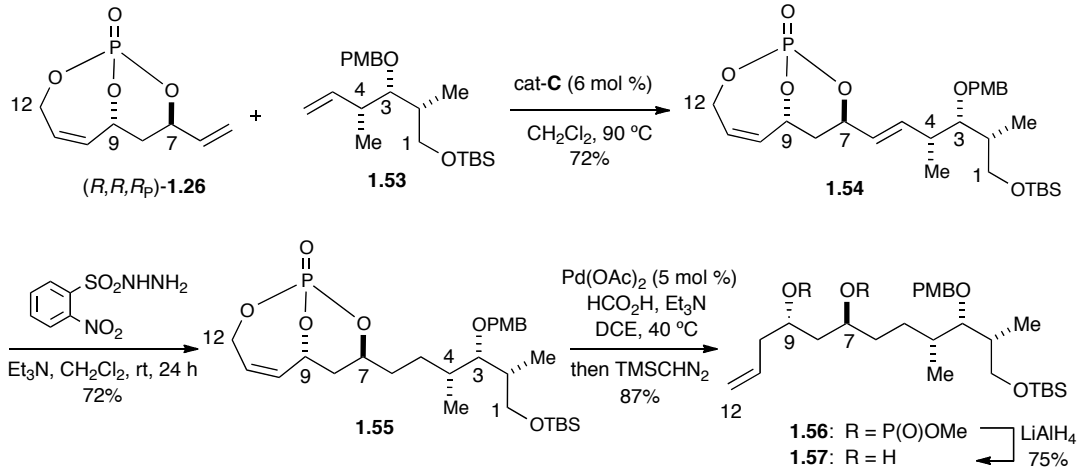
Each subunit was constructed by a phosphate-mediated desymmetrization of **1.24**, followed by the aforementioned CM and allylic phosphate displacements. The C1-C14 subunit was envisioned to have the C1-C6 side chain appended *via* CM to yield advanced intermediate **1.51** from (R,R,R_P)-**1.26**. Subsequent regioselective hydrogenation of the C5-C6 olefin and regioselective Pd(0)-mediated allylic hydride addition (to C11) would afford a terminal olefin armed for oxidation and subsequent installation of the C11 carbinol center (Scheme 17).[9a] The C15-C30 subunit largely depended on the CM/cuprate approach and the advanced intermediate **1.52** would be synthesized from (S,S,S_P)-**1.26**.[9b]

Scheme 17



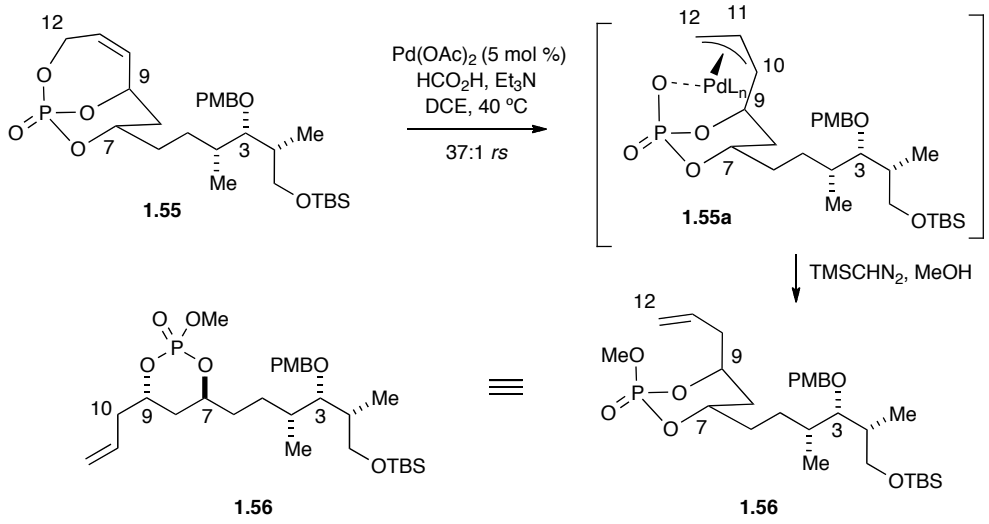
The synthesis of the C1-C14 subunit was initiated from readily available (*R*,*R*,*R*$_P$)-**1.26**, which was coupled with olefin **1.53**, possessing the necessary C2-C4 stereochemistry, by CM in the presence of cat-**C** (Scheme 18). Regioselective hydrogenation of the external olefin in **1.54** was accomplished using *in situ* formation of diimide from *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH)[32] and Et_3N to provide partially reduced phosphate **1.55**. This was followed by another regioselective ring-opening, and a Pd(0)-mediated reduction of allylic phosphate **1.55** *via* formation of hydride from formic acid and Et_3N.[33] Overall, this transformation resulted in an allylic displacement of the endocyclic phosphate with hydride, which after methylation with $TMSCHN_2$ yielded phosphate ester **1.56**. Removal of the phosphate ester with $LiAlH_4$ produced advanced intermediate **1.57**, bearing the C1-C10 framework.[9a]

Scheme 18



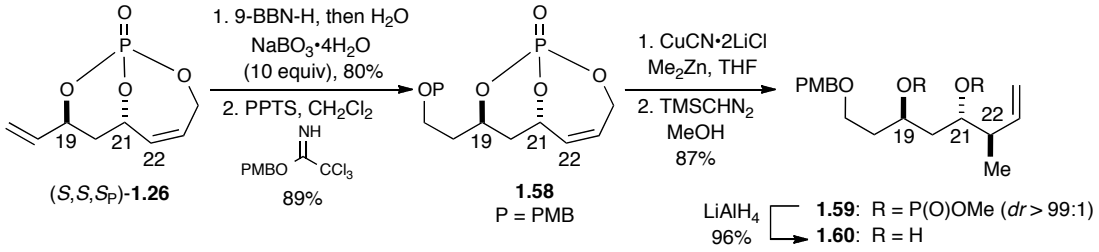
Introducing Pd(0) to phosphate **1.55** gave rise to π-allyl complex **1.55a** (Scheme 17). The Pd(0)-mediated allylic hydride addition[9a] to phosphate **1.55** gave the desired regioselectivity of hydride addition at the internal position (C10) of **1.55a** (regioselectivity C10/C12 = 37:1), similar to the previous cuprate additions to **1.26**. Both examples are illustrative of the preference in regioselectivity of allylic phosphate displacements with the endocyclic π-bond.

Scheme 19



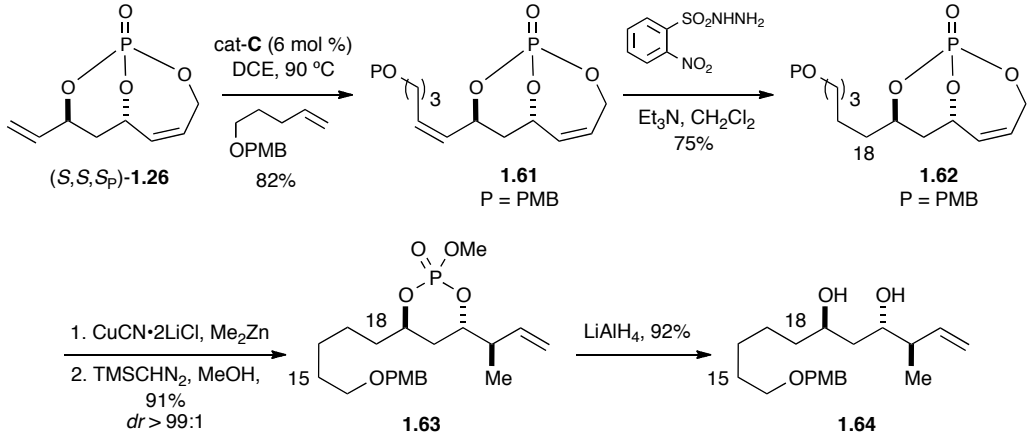
The C15-C30 subunit was synthesized by means of two approaches. Initially, regioselective hydroboration[25] of the exocyclic olefin in (*S*,*S*,*S*P)-**1.26**, followed by PMB-protection of the primary alcohol provided **1.58** (Scheme 20).[9b] Allylic displacement using a methyl cuprate derived from Me_2Zn and CuCN•2LiCl furnished the aforementioned 1,3,4-*anti*,*anti*-stereotriad of the C19/C21-C22 subunit as a single diastereomer. Methylation of the phosphate acid and cleavage of the resulting phosphate ester **1.59** with $LiAlH_4$ afforded 1,3-diol **1.60** over the five-step sequence from bicyclic phosphate **1.26**.[9b]

Scheme 20



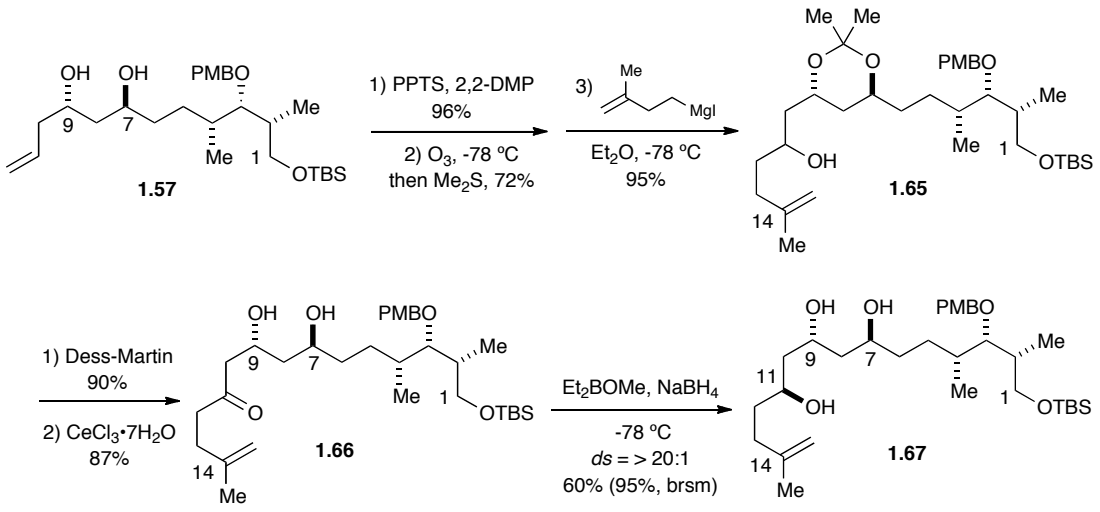
An alternative route utilized cross-metathesis of (*S*,*S*,S_P)-**1.26** and PMB-protected pent-4-en-1-ol to give phosphate **1.61** (Scheme 21). Selective hydrogenation of the exocyclic olefin gave **1.62**, which possesses the C15-C18 side chain of the C15-C30 subunit. Again, allylic displacement with a methyl cuprate derived from Me_2Zn and CuCN•2LiCl occurred regioselectively and gave phosphate **1.63** (after methylation with $TMSCHN_2$). Phosphate cleavage with $LiAlH_4$ afforded 1,3-diol **1.64** in a five-step protocol from **1.26** in higher overall yields than the previous route, providing the C15-C18 framework intact.[9b]

Scheme 21



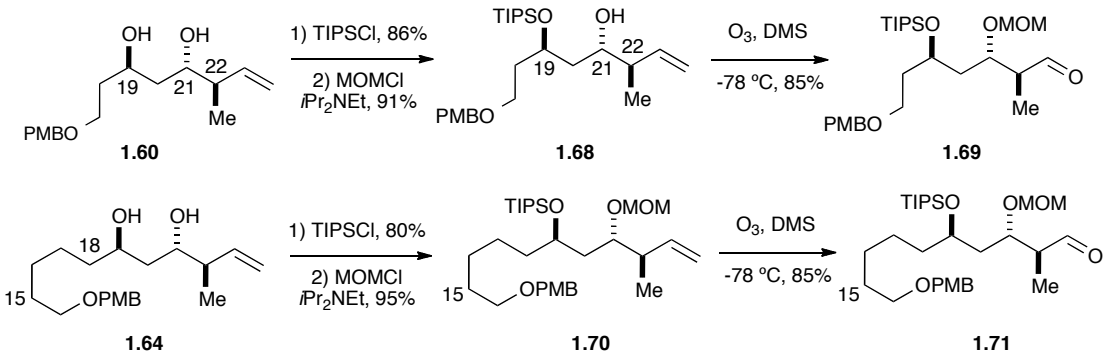
Final steps to completing the C1-C14 framework included acetonide protection, followed by ozonolysis of the terminal C11-C12 olefin and Grignard addition (derived from 1-iodo-3-methyl-3-butene) to produce **1.65** (Scheme 22). Oxidation of the C11 carbinol (Dess-Martin periodinane) and removal of the acetonide using $CeCl_3 \bullet 7H_2O$ set the stage for a stereoselective reduction of **1.66** using Evan's *syn*-reduction[34] conditions (20:1 *ds* of desired C11 epimer), affording all of the necessary stereocenters (**1.67**) in 13 steps from phosphate (S,S,S_P)-**1.26**.[9a]

Scheme 22



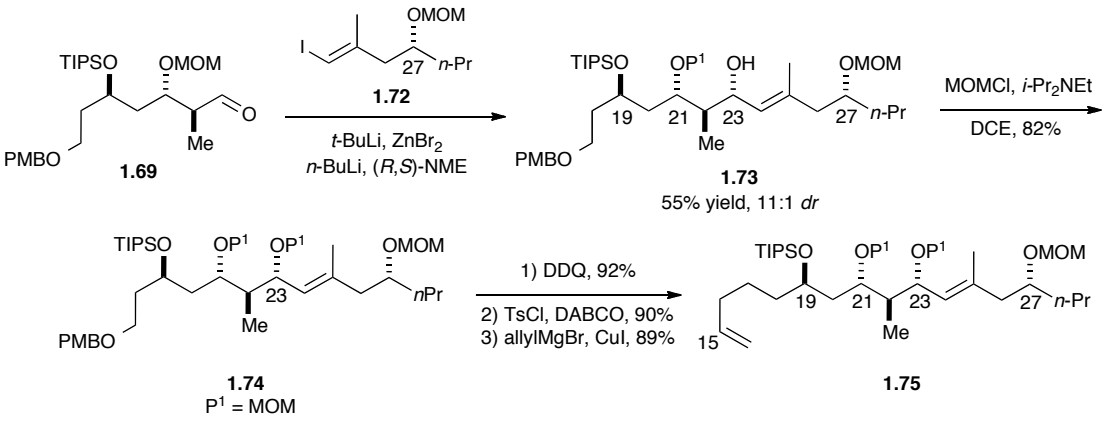
Efforts toward completing the carbon framework of the C15-C30 subunit were investigated using both 1,3,4-*anti*, *anti* diols, **1.60** and **1.64**, which were both orthogonally protected and their olefins (**1.68** and **1.70**) oxidized to their respective aldehydes, **1.69** and **1.71** (Scheme 23).[9b]

Scheme 23



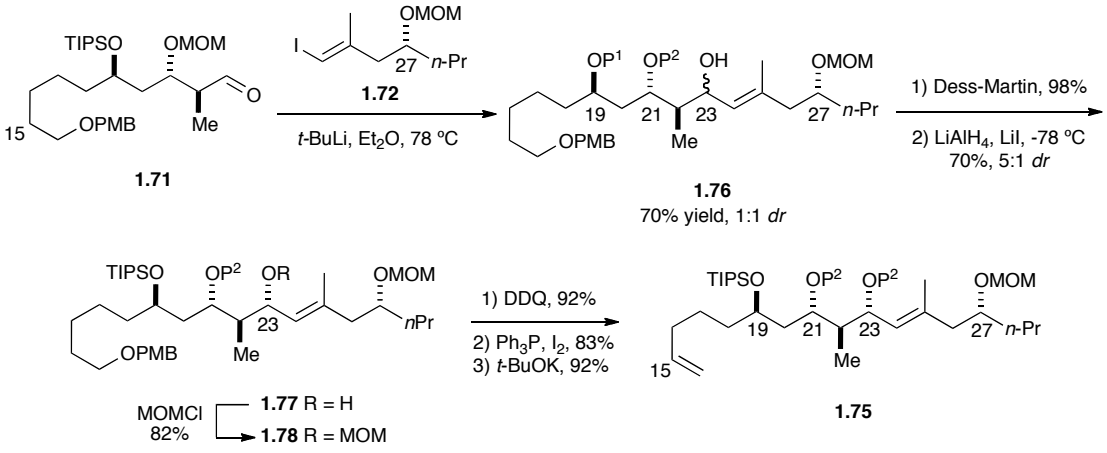
Final steps toward the C15-C30 fragment were completed via two different stereoselective generation of the C23 carbinol and the construction of the terminal C15 olefin. Diastereoselective vinylate addition (generated from **1.72**) yielded the desired epimer of **1.73** in 11:1 *dr* from the reagent-controlled step.[35] After protecting the newly formed C23 carbinol (MOMCl), the primary carbinol of **1.75** was debenzylated (DDQ), tosylated and substituted with a allyl-based cuprate yielding the C15-C30 subunit (**1.76**) of dolabelide C.

Scheme 24



A conformationally controlled oxidation/reduction protocol also achieved good levels of stereoselectivity, where vinylate addition (generated from **1.72**) into **1.71** gave a 1:1 mixture of epimers at C23 (Scheme 25).[9b] The undesired epimer was separable and recycled through oxidation (Dess-Martin periodinane) and a 1,3-*syn*-hydride reduction with LiI[36] provided a 5:1 *dr* favoring the desired C23 epimer. After protecting the newly formed C23 carbinol (MOMCl), the primary carbinol of **1.78** was debenylzated (DDQ), iodinated and eliminated with *t*-BuOK to yield the C15-C30 subunit (**1.76**), where both routes provided a 13-step synthesis from phosphate **1.26**.[9b]

Scheme 25

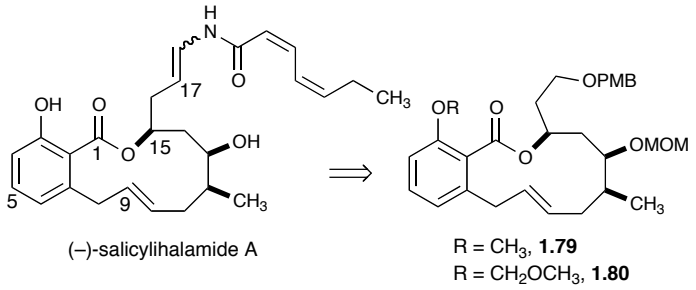


1.3.4 Formal Synthesis of (–)-Salicyhalimide A

(–)-Salicylihalamide A, a potent inhibitor of melanoma cell lines and mammalian V-ATPase,[37] was targeted by the Hanson group utilizing their phosphate-mediated approach to constructing a similar 1,3,4-*anti*,*anti*-stereotriad observed in

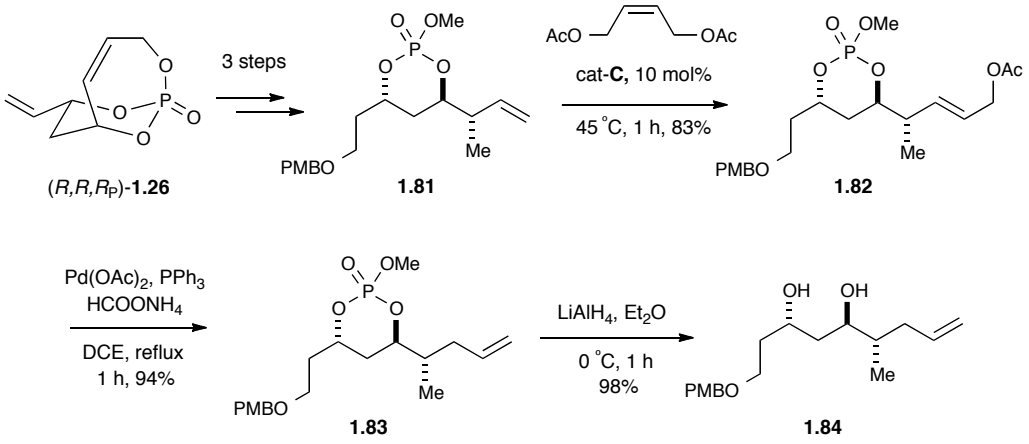
dolabelide C.[38] The synthetic strategy gave rise to two potential common intermediates (**1.79** and **1.80**) previously reported in the literature.[39,40]

Scheme 26



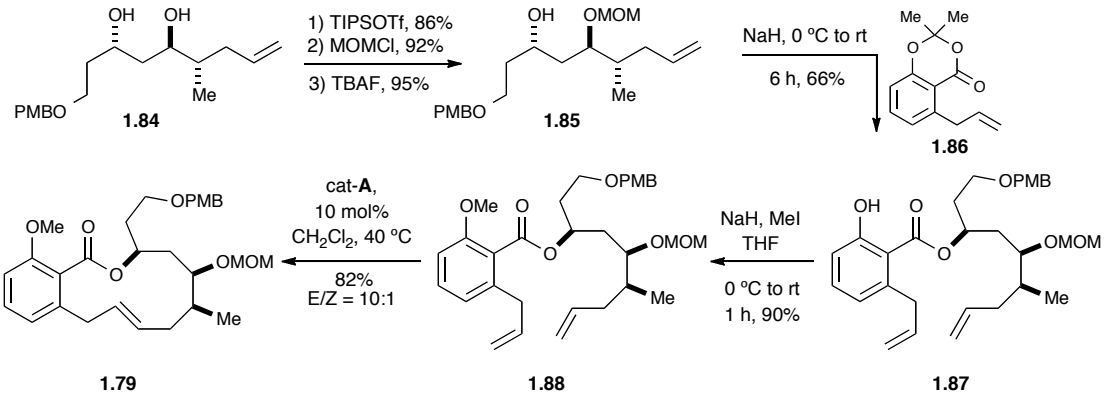
From phosphate **1.81** (3 steps from (*R*,*R*,R_P)-**1.26**) 1,3-*anti*-diol **1.84** was synthesized first from cross-metathesis with cat-**C** and *cis*-1,4-butene-diacetate, providing **1.82**. Pd(0)-formate reduction[33] and reductive phosphate removal yielded **1.86**, which was a pivotal intermediate for accessing **1.79** and **1.80** (Scheme 27).

Scheme 27



Advancing diol **1.84** through orthogonal protection and subsequent deprotection furnished intermediate **1.85** over 3 steps (Scheme 28). Esterification under basic conditions with dioxinone **1.86** gave ester **1.87** in 66% yield. Methylation of the resultant phenol gave ether **1.88**, which was refluxed with cat-**A** to initiate an RCM yielding known macrocycle **1.79**[39] and giving a 12-step protocol from (*R*,*R*,R_P)-**1.26**.

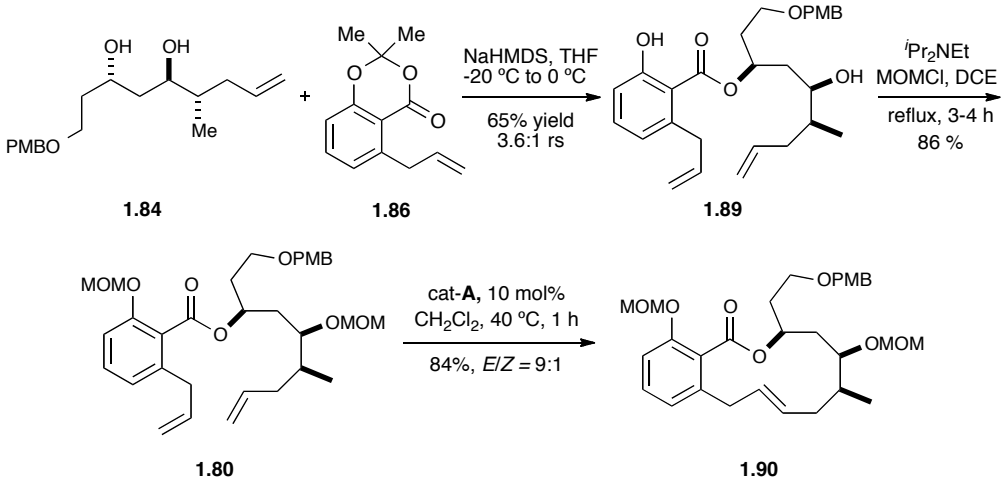
Scheme 28



Alternatively, this synthesis was streamlined by performing the esterification on diol **1.84** (Scheme 29). Treating **1.84** with NaHMDS and addition into dioxinone **1.86** gave ester **1.89** in 65% combined yield with its regioisomer in a 3.6:1 ratio (undesired regioisomer could be recycled through transesterification). Bis-etherificaton of the resulting diol with MOMCl and RCM reduced the number of steps significantly (12-step to 8-step protocol) yielding known intermediate **1.80**.[40] Utilizing a similar fragment from the protocol to construct polyols bearing the 1,3,4-

anti,*anti*-stereotriad, a concise formal synthesis of salicylihalamide A was realized using a phosphate-mediated process.

Scheme 29

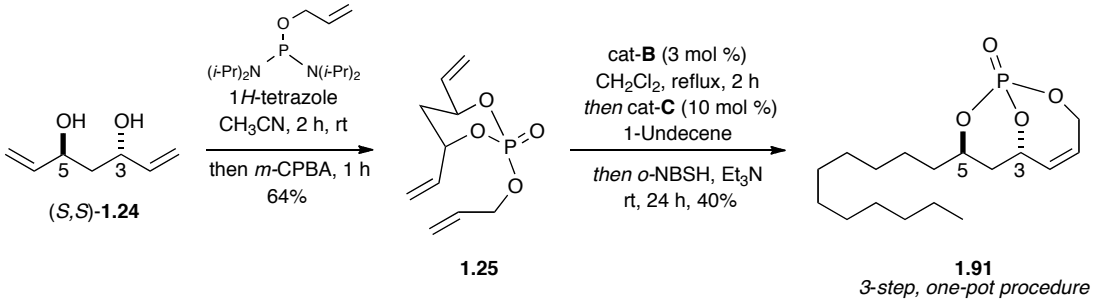


1.3.5 Total Synthesis of (–)-Tetrahydrolipstatin

The natural product-based antiobesity drug, (–)-tetrahydrolipstatin,[41] was synthesized via the Hanson group's phosphate-mediated methodology.[42] While there were several total syntheses existing in the literature,[43] this approach is the most streamlined to date of this target. Efficiency was gained through a tandem RCM/CM/H_2 from **1.25** to **1.91**, reducing the amount of linear steps significantly (Scheme 30). The generation of **1.91** was achieved using this one-pot procedure first from **1.25**, which was synthesized from (*S*,*S*)-**1.24** via an alterative method through a two-step, one-pot phosphorylation with allyl tetraisopropylphosphoramidite and subsequent oxidation with *m*-CPBA.[42] Under refluxing conditions in CH_2Cl_2, first

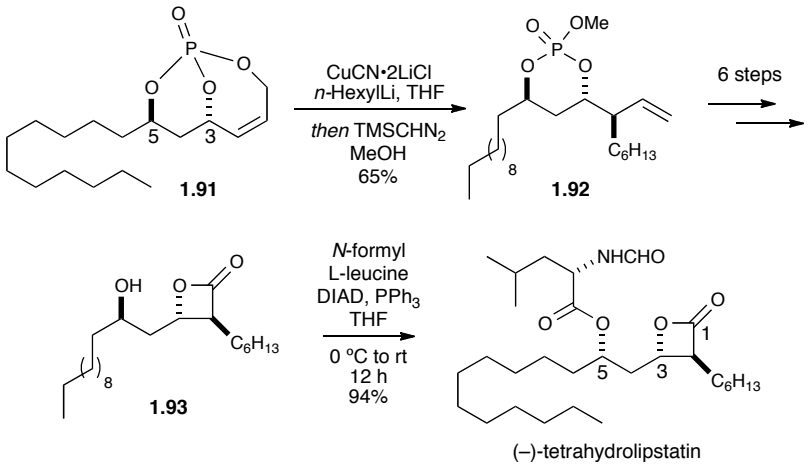
RCM was accomplished with 3 mol % of cat-**B** followed by the addition of 1-undecene and 10 mol % of cat-**C**. The reaction was then cooled to room temperature and sequential addition of Et_3N and *o*-NBSH furnished phosphate **1.91** in 40% overall yield (~74% yield per step) over the multi-step procedure.

Scheme 30



With phosphate **1.91** in hand, cuprate addition, derived from *n*-hexyllithium, provided the 1,3,4-*anti,anti*-stereotriad (**1.92**) seen previously (Scheme 32). Phosphate **1.92** was carried through 6 synthetic steps leading to alcohol **1.93**, which was primed for Mitsunobu inversion[44] through a previously reported protocol[43a] finished the construction of (–)-tetrahydrolipstatin in an 8-step linear synthesis from (*S*,*S*)-**1.24**.

Scheme 31



1.4 Conclusion

The use of temporary tethers in synthesis represents a powerful approach to the coupling of two advanced structures en route to more advanced synthons. Ring-closing metathesis plays a key role in the construction of sultone and phosphate heterocycles providing effective methods where both sulfur and phosphorus serve as temporary tethers mediating several selective transformations. The use of sultones to construct 1,3-dienols possessing an internal *Z*-olefin has been utilized in the synthesis of the originally proposed structure of (±)-mycothiazole and has the potential of expanding to other biologically active natural products. Phosphate tethers have served a central role in the construction of asymmetric 1,3-*anti*-diol subunits, which have been demonstrated in the construction of both the C1-C14 and C15-C30 subunits of dolabelide C, a formal synthesis of (–)-salicylohalamide A and a total

synthesis of (–)-tetrahydrolipstatin. Additional uses of these versatile heterocycles are in order and will be reported in future studies.

1.5 References

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Chapter 2

Asymmetric Synthesis of 1,3-*anti*-Diol-Containing Subunits using Phosphorus-Based Tethers

2.1 Introduction

2.1.1 Terminus Differentiation and Chain Elongation

Polyols are essential building blocks in Nature's construction of an array of polyketide-derived natural products.[1] One challenge for the synthetic chemist is replicating the exquisite selectivity displayed by the enzymatic processes to piece together structures of high skeletal diversity. The 1,3-*anti*-diol subunit is prevalent in several natural products bearing a wide array of biological activities.[1] Common approaches to these building blocks are through stereoselective aldol reactions, reduction of 1,3-hydroxyketones and 1,3-diketones, and addition reactions to 1,3-hydroxyaldehydes (e.g. alkylation, allylation and crotylation).[1c] Another common approach to rapidly accessing complex 1,3-*anti*-diol intermediates is through desymmetrization through chain elongation of a readily accessible 1,3-*anti*-diol building block.[2] Schreiber describes four strategies for the synthesis for acyclic chains, which can be applied for short chains that are either a racemate or enantiomerically pure (Figure 1).[2b]

The first case entailed in Figure 1 is the differentiation of meso or achiral chains (eq 1).[2] Requirements to achieving terminus differentiation are through the use of substrate-controlled reactions. Using chiral, non-racemic reagents for this goal must be added sequentially in order to obtain a chiral, non-racemic product.

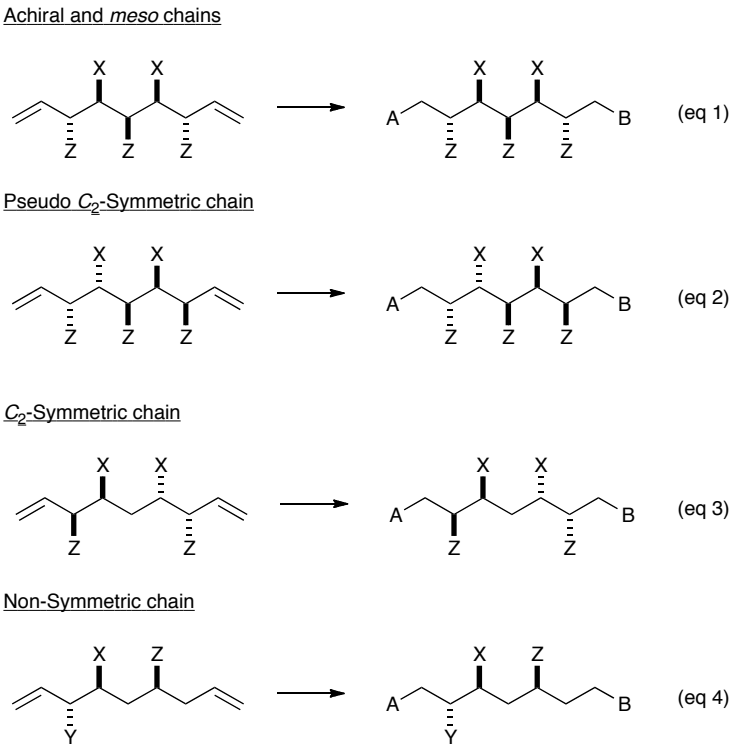


Figure 1

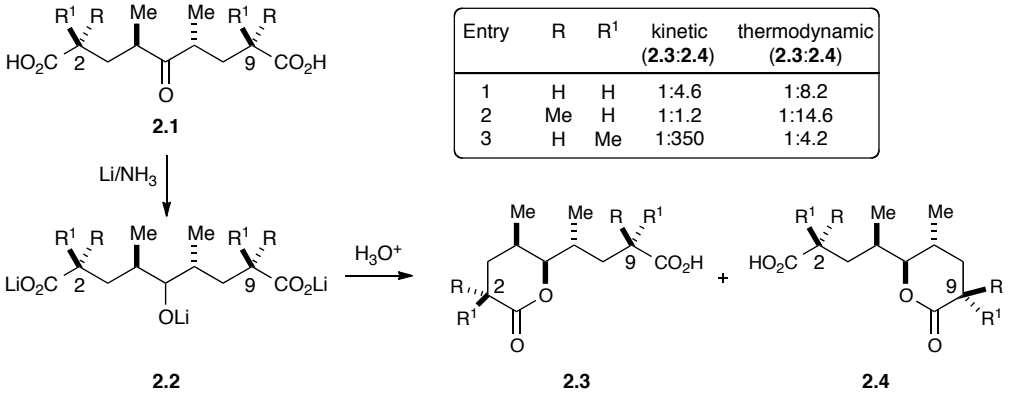
C_2-symmetric chains (eq 2) contain homotopically equivalent groups that can be differentiated without selective functionalization. Psuedo-C_2-symmetric substrates (eq 3) are termed "pseudo," because without the central carbon center the chain would be C_2-symmetric. However, the central center is not stereogenic, but is chirotopic, non-stereogenic, because both faces are homotopic. However, because of the prochiral nature of the central carbon, the termini are now diastereotopic and can be differentiated through a group selective transformation that will also simultaneously convert the central carbon into a stereogenic center. Lastly, non-symmetric chains (eq 4) are accessed through double addition of chiral or achiral reagents to racemic or

non-racemic chains. Differentiation is achieved through selectively functionalizing between two different chemical environments.

2.1.2 Desymmetrization Thru Pseudo-C_2-Symmetric Intermediates

This research is concentrated on the C_2-desymmetrization of chiral, non-racemic diol substrates through synthesizing pseudo-C_2-symmetric intermediates. One of the earlier examples of this type of terminus differentiation was by Hoye and coworkers[3] where C_2-symmetric keto-diacid **2.1** was reduced with Li/NH_3 to generate pseudo-C_2-symmetric lithiate **2.2** (Scheme 1). Acidification of the **2.2** under pH ~3 (kinetic control) and pH ~1 (thermodynamic control) led to mixtures of *cis*- and *trans*-lactones **2.3** and **2.4** respectively.

Scheme 1

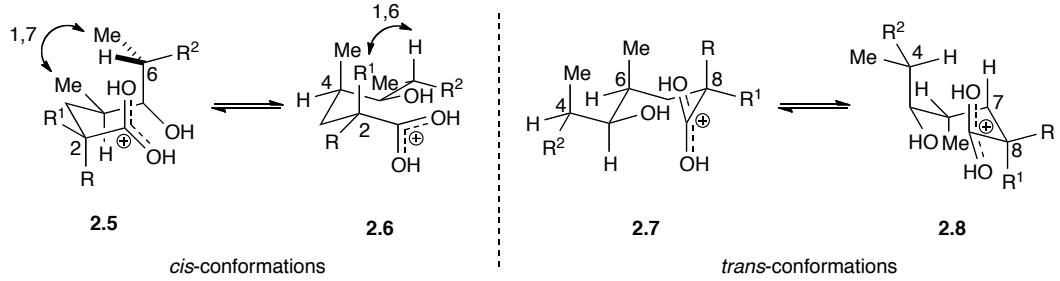


Entry	R	R^1	kinetic (**2.3**:**2.4**)	thermodynamic (**2.3**:**2.4**)
1	H	H	1:4.6	1:8.2
2	Me	H	1:1.2	1:14.6
3	H	Me	1:350	1:4.2

The selectivity shown in Scheme 1, where the *trans*-lactone is predominant, is attributed to 1,7-[4] (shown in **2.5**) and 1,6-interactions (shown in **2.6**) building up in the chair-like conformations (R^2 = $CH_2C(Me)CO_2H$) formed in attack of the free

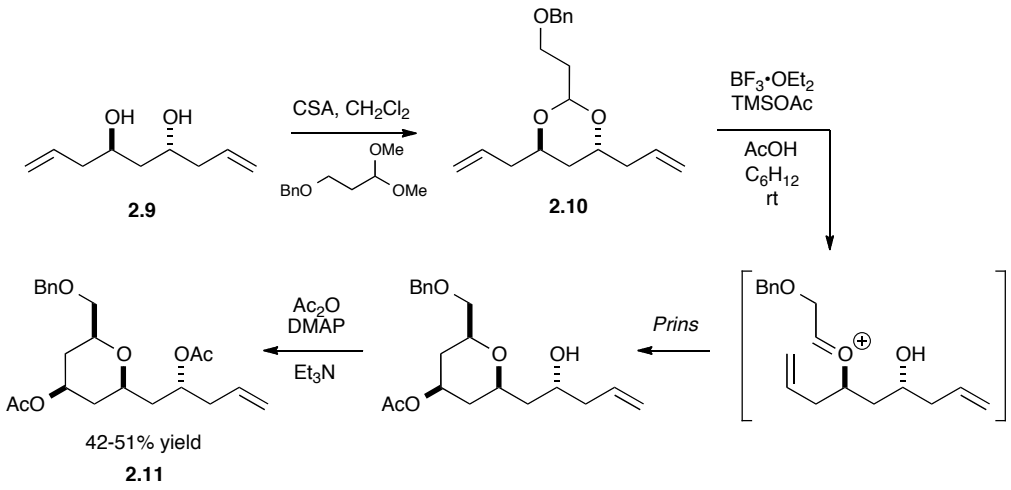
hydroxyl on the carboxylic acid (Scheme 2). As steric bulk increases from R and R^1 = H to both R and R^1 = Me, the *trans*-conformer becomes predominant (1:350, entry 1, Scheme 1). This study developed an effective method to desymmetrizing a symmetric chain by use of a functional group that resides on a symmetry element.[3]

Scheme 2



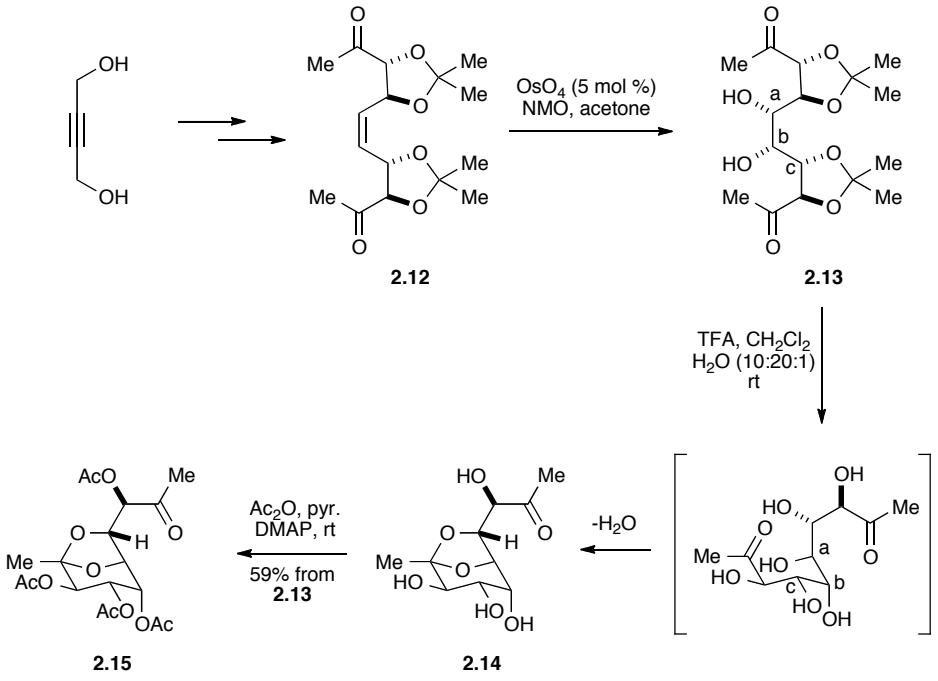
In their synthesis of 17-deoxyroflamycoin, Rychnovsky and coworkers employed a Prins cyclization strategy to desymmetrize C_2-symmetric diol **2.9** (Scheme 3).[5] By generating pseudo-C_2-symmetric acetal **2.10**, subjection to Lewis acidic conditions (BF_3•Et_2O) and acyl trapping[6] with acetic anhydride, afforded the *trans*-tetrahydropyran **2.11** in 42-51% yield over 2 steps. This advanced intermediate was crucial in synthesizing the macrocyclic 17-deoxyroflamycoin (derived from roflamycoin),[7] which contains numerous 1,3-diol subunits within its structure.

Scheme 3



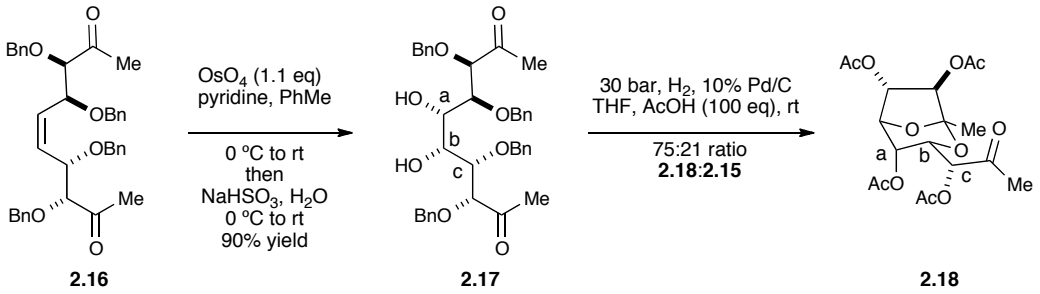
One of the more recent examples of this approach is by the Metz group, by constructing C_2-symmetric dione **2.12** from a multistep synthesis starting with 2-butyne-1,4-diol (Scheme 4).[8] Dihydroxylation afford pseudo-C_2-symmetric diol **2.13** that was differentiated through intramolecular acetalization furnishing **2.14**, which was peracetalated with acetic anhydride to yield **2.15** in 59% yield over 2 steps. The conformational preference is based toward ketalization of carbinol a (from structure **2.13**) where carbinol b is locked in an axial conformation and cannot cyclize with the other diastereotopic methyl ketone. The subsequent ketalization is also differentiated by the fact carbinol c, in its equatorial position, is also not at a favorable position, thus resulting in ketal **2.14** as a single stereoisomer.

Scheme 4



An interesting result was obtained from changing the carbinol protecting groups from acetonide to benzyl, where using a similar synthetic route from 2-butyne-1,4-diol to C_2-symmetric dione **2.16** and dihydroxylation provided pseudo-C_2-symmetric diol **2.17** (Scheme 5). Hydrogenation or acidification gave epimer **2.18** as the major product after peracetylation of each resulting tetrol.[8] The key to achieving the different carbinol ketalization (carbinol b over a) was the rate of debenzylation was crucial in selectivity. Compound **2.15** was also converted to **2.18** by subjection to a high concentration of HCl at low temperature. This model study provided crucial insight to Metz and coworkers efforts toward the zaragozic acids/squalestatins, in which the heterocyclic core of these bioactive species was achieved through this method.[9]

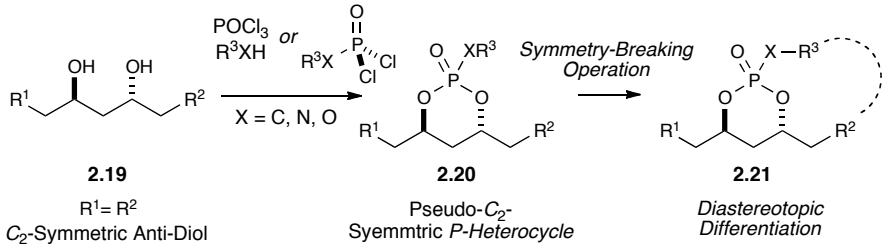
Scheme 5



2.1.3 Diastereotopic Differentiation Strategy Through P-Heterocycles

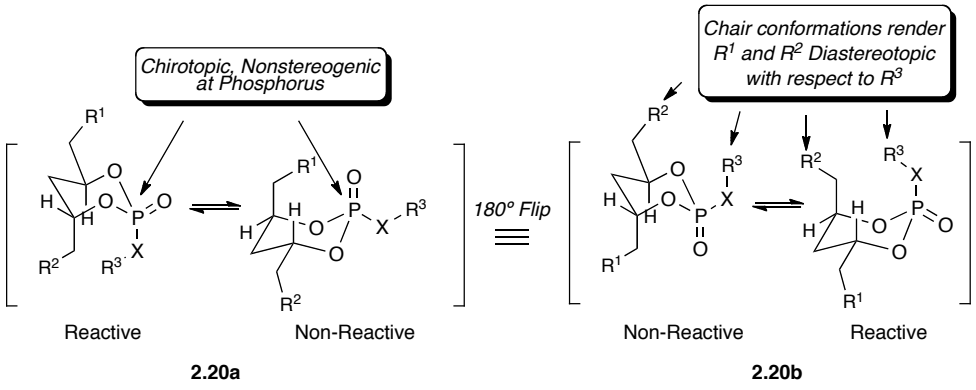
The strategy developed was desymmetrization of a C_2-symmetric diol **2.19** through construction of pseudo-C_2-symmetric heterocycle **2.20** from tripodal coupling of **2.19** with $POCl_3$ and an alcohol or amine (R^3XH, X = N, O) or a dichlorophosponate (X = C) to provide a conformationally controlled system (Scheme 6). This system would render the previously homotopic R^1 and R^2 groups diastereotopic through a symmetry-breaking cyclization event generating a chiral, non-racemic bicyclic species. Accoringly with our group's work[10] and the Gouverneur group[11] the synthesis of a *P*-chiral species from a prochiral *P*-heterocycle is a well-established approach.

Scheme 6



Since phosphorus is chirotopic and non-stereogenic, the construction of **2.20** is empirically observed as a single diastereomer from **2.19** (Scheme 7). Both possible approaches (**2.20a** and **2.20b**) yield two possible chair conformations, where R^1 is rendered unreactive with R^3 in all four possibilities. R^2 is only reactive if it is in a diaxial conformation with R^3 through a cyclization event similar to the examples discussed in section 2.2.1. However, it is important to notice that both reactive conformers of **2.20a** and **2.20b** will give the same chiral, non-racemic bicyclic *P*-heterocycle.

Scheme 7



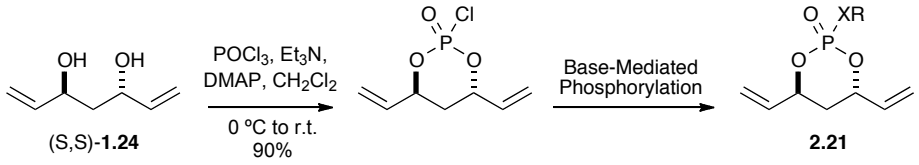
2.2 Results and Discussion

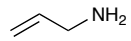
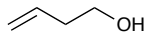
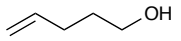
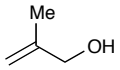
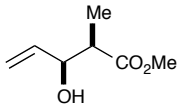
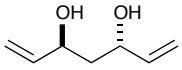
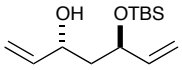
2.2.1 Synthesis of Pseudo-C_2-Symmetric Heterocycles

While this diastereoselective differentiation has been effectively displayed to generate [4.3.1]-bicyclic phosphate **1.26** (Scheme **9**, Chapter 1),[10g] a scope of different R^3X coupling groups was investigated to determine if this differentiation strategy could be general. Tripodal coupling with $POCl_3$ and dienediol (*S*,*S*)-**1.24** provided a pseudo-C_2-symmetric phosphoryl chloride, which had been previously reported by our group.[10g] Various coupling partners successfully generated pseudo-C_2-symmetric phosphoramidate **2.21a** and a variety of phosphates **2.21b-g** (Table 1).

Base-mediated addition of each example proved to be the highest yielding method. Neutral conditions proved to lead to incomplete conversion for every example except for phosphonate **2.21a**, which could be synthesized using DMAP and Et_3N (68% yield) or in a one-pot procedure from (*S*,*S*)-**1.24** (38% yield). Interestingly, phosphates **2.21c** and **2.21g** could not survive ambient temperature, due to over addition side-products arising. This also resulted in incomplete conversion as well when using a 1:1 stoichiometric ratio of the phosphoryl chloride and the allylic alcohol.

Table 1

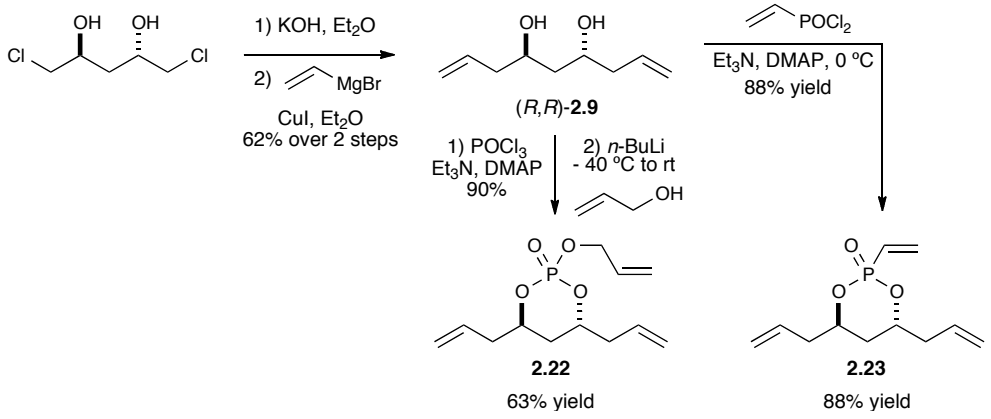


Entry	XR	Conditions	Yield
2.21a		*n*-BuLi, THF -40 ºC to rt	88%
2.21b		*n*-BuLi, THF - 40 ºC to rt	75%
2.21c		*n*-BuLi, THF - 40 º to 0 ºC	81%[a]
2.21d		*n*-BuLi, THF - 40 ºC to rt	81%
2.21e		NaHMDS THF, -78 ºC to rt	62%
2.21f		*n*-BuLi, THF - 40 ºC to rt	30%[b]
2.21g		*n*-BuLi, THF - 40 º to 0 ºC	41%[a,c]

[a]Antipode of **2.21** synthesized from (*R*,*R*)-**1.24**. [b]Statistical mixture obtained. [c]Unoptimized result.

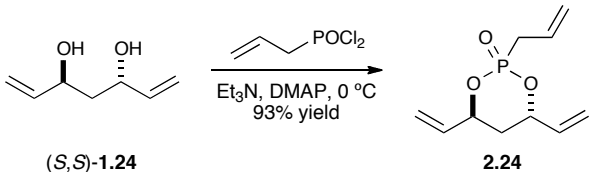
P-heterocycles were also constructed from known diol (*R*,*R*)-**2.9**, which was prepared in a two-step procedure without any purification from (2*S*,4*S*)-1,5-dichloro-2,4-petanediol (Scheme 8).[6,12] Tripodal coupling with $POCl_3$ followed by base-mediated addition of allyl alcohol provided phosphate **2.22**. Phosphonate **2.23** was constructed in one step from vinylphosphonic dichloride[13] in good yield.

Scheme 8



Lastly, from the (*S*,*S*)-**1.24** building block, phosphonate **2.24** was synthesized by coupling with allylphosphonic dichloride in good yield (Scheme 9). Overall, an array of pseudo-C_2-symmetric *P*-heterocycles were constructed utilizing a similar protocol previously reported in our group[10g-j] through direct and formal tripodal coupling with various coupling partners.

Scheme 9

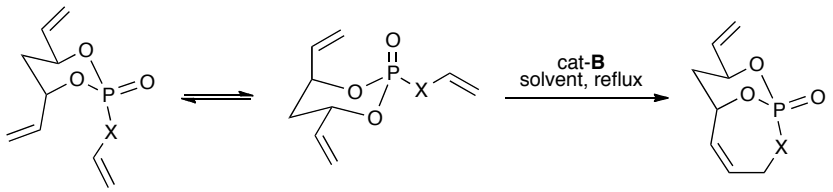


2.2.2 Synthesis of Chiral Non-Racemic Bicyclic P-Heterocycles

All of the pseudo-C_2-symmetric substrates were introduced to Grubbs' second-generation catalyst (cat-**B**)[14] under refluxing solvent. As discussed previously,

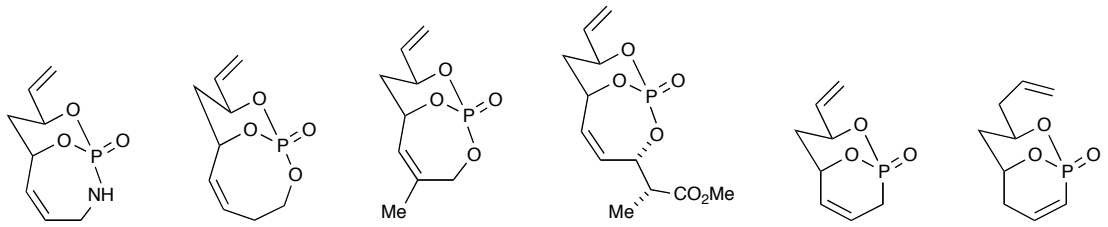
diastereotopic differentiation is achieved from conformational constraints, where the *cis*-conformation **2.25a** is reactive and the *trans*-conformer **2.25b** is not due to inadequate distance between the respective olefins (Scheme 10).

Scheme 10



2.25a *Reactive* **2.25b** *Unreactive* **2.26**

Most of the *P*-heterocycles smoothly converted to their respective chiral, non-racemic, *P*-stereogenic bicyclic products (Figure 2). Phosphonate (S,S,S_P)-**2.26a**[15] proved to be the highest yielding out of all the examples. Phosphates (S,S,S_P)-**2.26b** and (S,S,S_P)-**2.26c** required harsher cyclization conditions due to larger ring size ((S,S,S_P)-**2.26b**) and higher substition (10 hours of reflux for (S,S,S_P)-**2.26c**) to access those respective products. Benzene proved to be the most effective solvent in obtaining (S,S,S_P)-**2.26d** and (S,S,S_P)-**2.26e**,[15] contrary to the chlorinated solvents used in all of the other examples. The most interesting RCM was the reaction obtaining phosphonate (S,S,S_P)-**2.26f** (constructed from **2.23**).[16] This cyclization was the most rapid (less than 15 minutes), however longer reaction times lead to a sharp decrease in yield (45% yield after stirring for ~1 hour), so immediate water quenching to terminate catalyst activity was required to obtain formidable yields for this system.



(*S*,*S*,*S*P)-**2.26a**
2 mol %
CH_2Cl_2, 40 ºC
94% yield

(*S*,*S*,*S*P)-**2.26b**
5 mol %
DCE, 90 ºC
71% yield

(*S*,*S*,*S*P)-**2.26c**
5 mol %
DCE, 90 ºC
80% yield

(*S*,*S*,*S*P)-**2.26d**
5 mol %
PhH, 80 ºC
79% yield

(*S*,*S*,*S*P)-**2.26e**
3 mol %
PhH, 80 ºC
88% yield

(*S*,*S*,*S*P)-**2.26f**
2 mol %
CH_2Cl_2, 40 ºC
71% yield

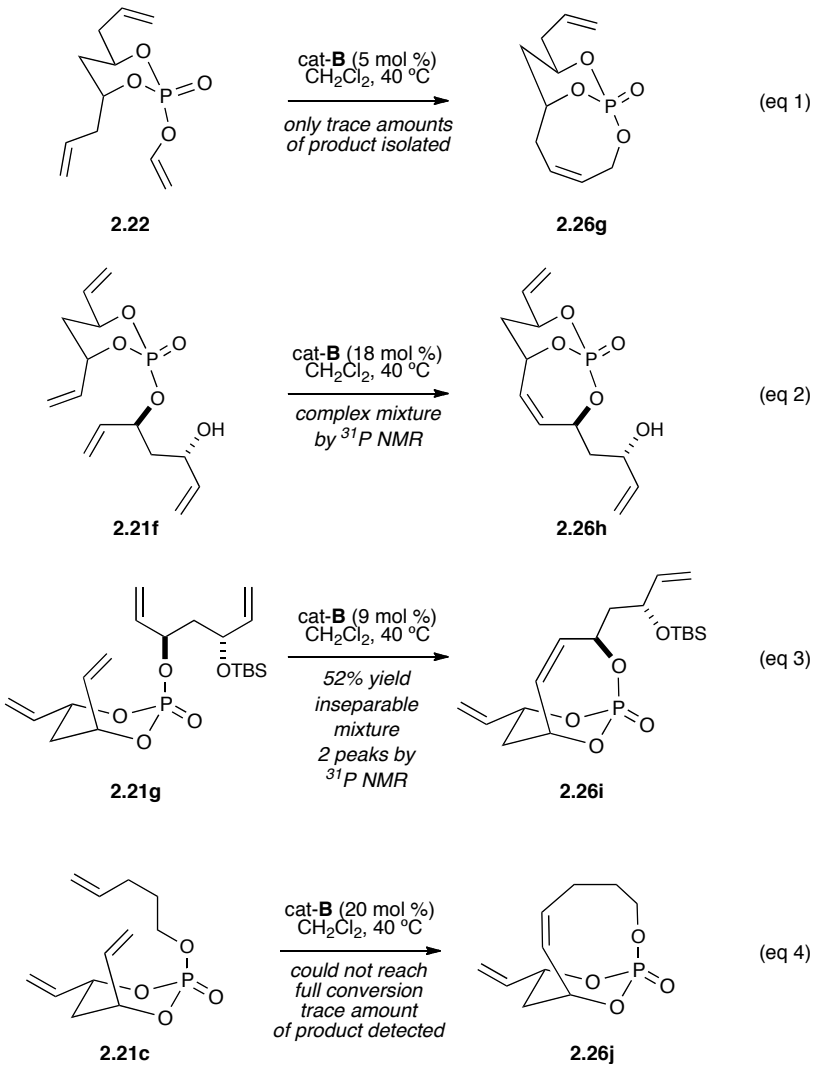
Figure 2

As stated before, not every pseudo-C_2-symmetric *P*-heterocycle converted efficiently to its respective bicycle. Triene **2.21c** was observed to undergo complete conversion by TLC after 1 hour, however isolation of bicycle **2.26g** was difficult resulting in only a trace amount of product (Scheme 11, eq 1). Phosphate **2.21f**, derived from two equivalents of (*S*,*S*)-**1.24**, required much higher catalyst loading to furnish **2.26h**, presumably due to the free alcohol. After isolating what appeared to be a single product by TLC showed a complex mixture after ^{31}P NMR, which could be the result of promiscuous CM pathways and the alternate 9-membered ring formation (eq 2).

To attempt to lower catalyst loadings and also increase the efficiency of the phosphorylation to **2.21g**, TBS-protection of the alcohol was performed (eq 3).[17] The concomitant RCM proved to decrease catalyst loadings, however after isolating what appeared to be a single spot by TLC revealed two compounds by ^{31}P NMR analysis. LC-MS analysis revealed one product with the desired m/z ratio of 386, but could not

be confirmed to be the correct isomer since the 9-membered cyclization was also possible.

Scheme 11



Nine-membered formation may have been negligible since phosphate **2.21c** was subjected to very high catalyst loadings and long reaction time (>8 hours). When attempting at higher temperature (90 ºC in DCE) no improvements were made and

starting material was observed along with a second product by TLC of higher polarity. Isolation of the second product was achieved, however only a trace amount of what appeared to be the 9-membered cyclization was obtainable.[18] It seems from these studies that obtaining larger ring sizes than 8 could prove to be the threshold for constructing these chiral, non-racemic bicyclic *P*-heterocycles.

2.3 Conclusions

A general protcol was established by expanding from the reported chiral, non-racemic bicylic *P*-heterocycles.[10] The diastereotopic differentiation of C_2-symmetric, 1,3-*anti*-diol builing blocks, both antipodes of **1.24** and (*R*,*R*)-**2.9**, is the key step in developing a terminus differention, chain elongation strategy.[2] Future directions of this project would entail the study of potential reactivity patterns shown from phosphates (R,R,R_P)- and (S,S,S_P)-**1.26**, (S,S,S_P)-**1.36**,[10g] and (R,R,R_P)-**1.44**[10i] in olefin metathesis and regioselective transformations (e.g. hydroboration, olefin reduction, etc.) of the variety of systems made (Figure 3). Ideally, this study will expand the scope of polyol subunits synthesized via *P*-heterocyclic templates to apply toward the facile construction biologically active natural products.

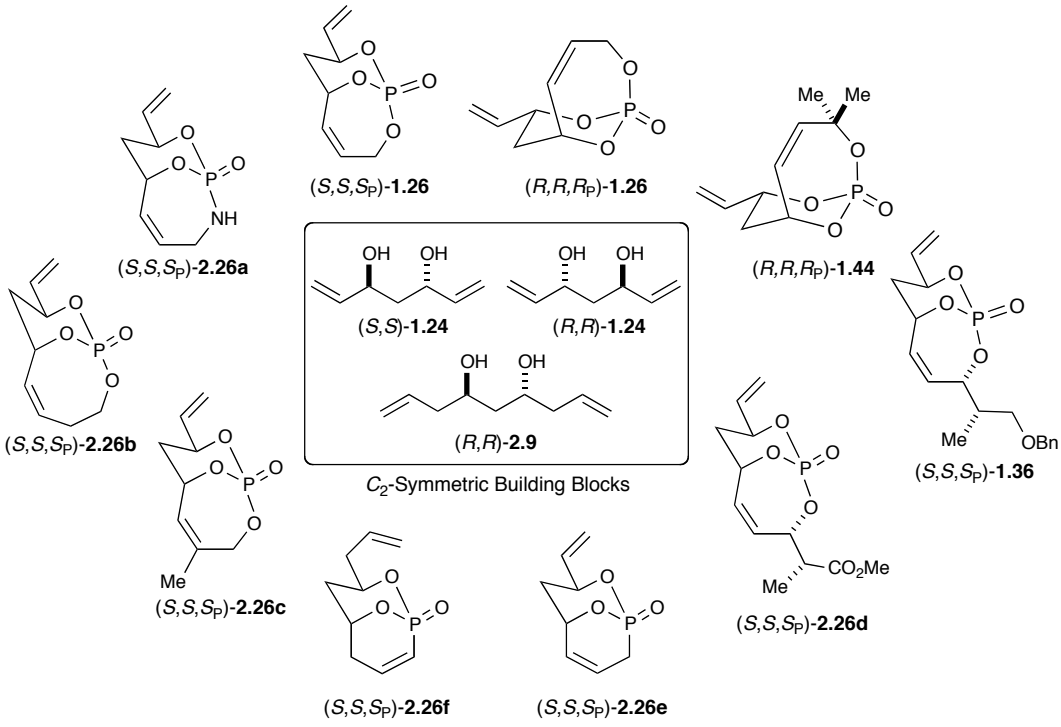


Figure 3

2.4 References

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Chapter 3

Phosphate Mediated Construction of the C15-C30

Subunit and Total Synthesis of Dolabelide C

3.1. Introduction

3.1.1 Isolation and Bioactivity of Dolabelide C

In 1995, the isolation and structural characterization of two new 22-membered macrolides, dolabelides A and B, from the sea hare *Dolabella auricularia* was reported (Figure 1).[1] These compounds exhibited cytotoxicity against cervical cancer HeLa-S_3 cells with IC_{50} values of 6.3 and 1.3 μg/mL, respectively. Two years later, dolabelides C and D,[2] 24-membered macrolides, were isolated from the same source and were found to possess cytotoxicity toward HeLa-S_3 cells with IC_{50} values of 1.9, and 1.5 μg/mL, respectively. To the best of our knowledge, the mechanism of action of these compounds remains unknown to date.

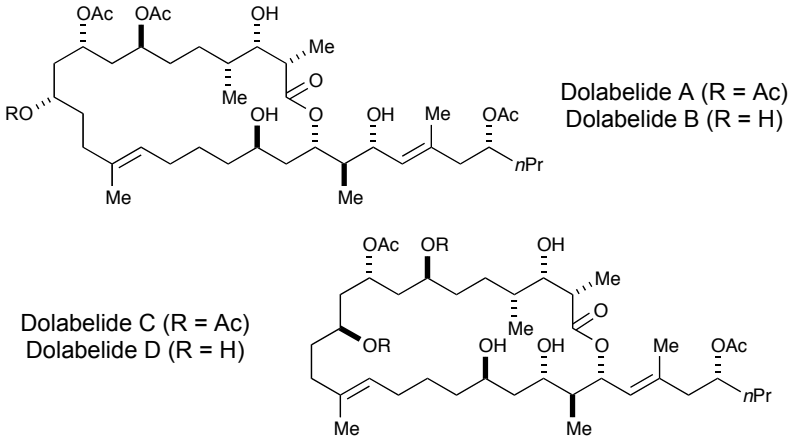


Figure 1

Common features among the dolabelide family are 11 stereogenic centers, 8 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 C21/C23. The stereochemical complexity and biological profile of this class of compounds has attracted synthetic interest from several groups[3] and in 2006, the total synthesis of dolabelide D was reported by Leighton and coworkers.[4]

3.1.2 Synthetic Approaches Toward Dolabelide Family

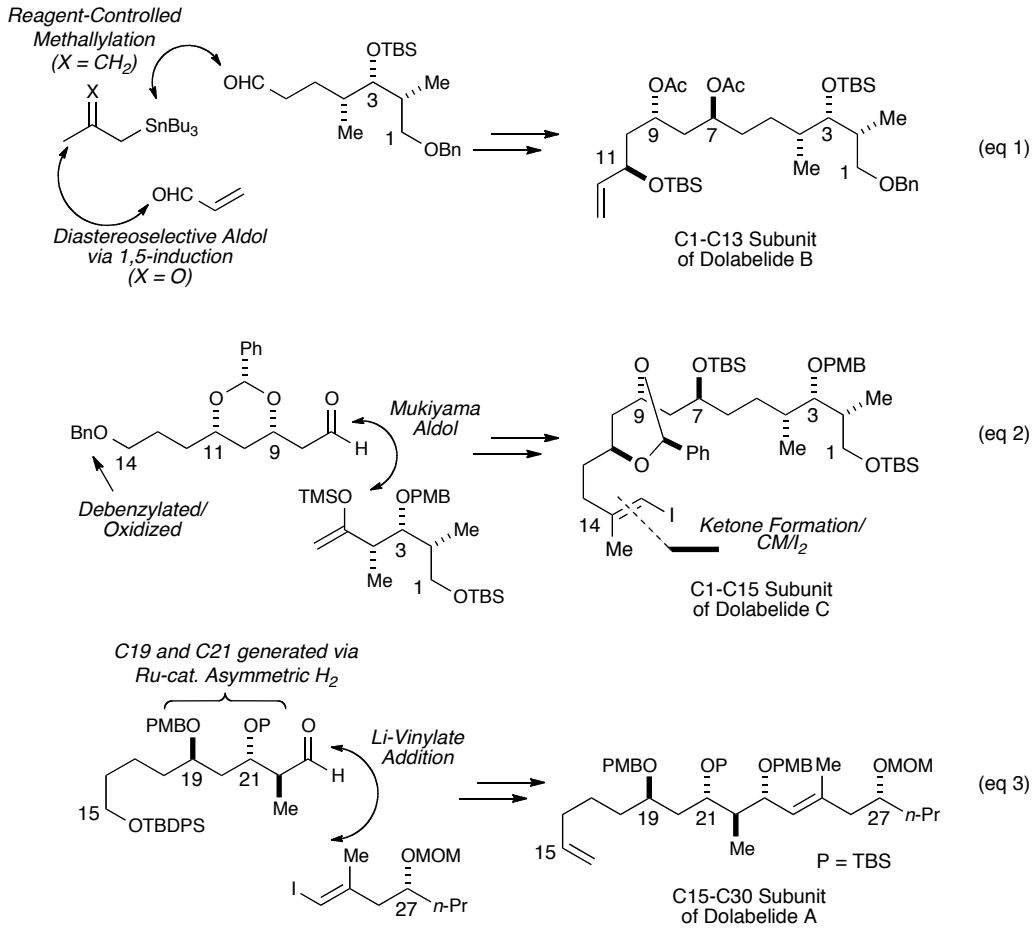


Figure 2

Along with the Leighton group, there have been other efforts concentrated toward the dolabelide family (Figure 2). Keck and McLaws synthesized the C1-C13 subunit first starting from a fragment bearing the C1/C3/C4 stereochemistry (derived from benzyl-protected Roche's ester).[5] The C7 stereocenter was generated through a reagent-controlled methallylation with tributylmethallylstannane, followed by manipulation to a ketone, which was reacted with acryolein providing 1,5-stereoinduction[6] from the C7 center setting the C11 carbinol (Figure 2, eq 1). Finally, the C9 center was set through a stereoselective 1,3-*anti*-reduction[7] giving the C1-C13 subunit.

Prunet and coworkers devised a synthesis of the C1-C15 subunit of dolabelide C where the C9 and C11 stereocenters were constructed through a conjugate addition giving a benzylidene acetal, which was converted to an aldehyde bearing the requisite C8-C14 framework (Figure 2, eq 2). A Mukiyama aldol,[8] which a silyl enol ether bearing the necessary C2-C4 stereochemistry furnishing the C1-C14 fragment.[9] The C14 benzyl ether was then converted to a ketone, which was homologated and converted to a *Z*-substituted vinyl-iodide via CM and iodination.

A route to the C15-C30 subunit of dolabelide A was realized by Phansavath, Genet and coworkers (Figure 2, eq 3), where sequential Ru-mediated hydrogenation of β-keto esters was employed to generate the required stereochemistry of the C19 and C21 stereocenters.[10] A lithium-vinylate addition completed the C15-C30 framework, where an oxidation/reduction sequence was required to stereoselectively generate the C23 carbinol.

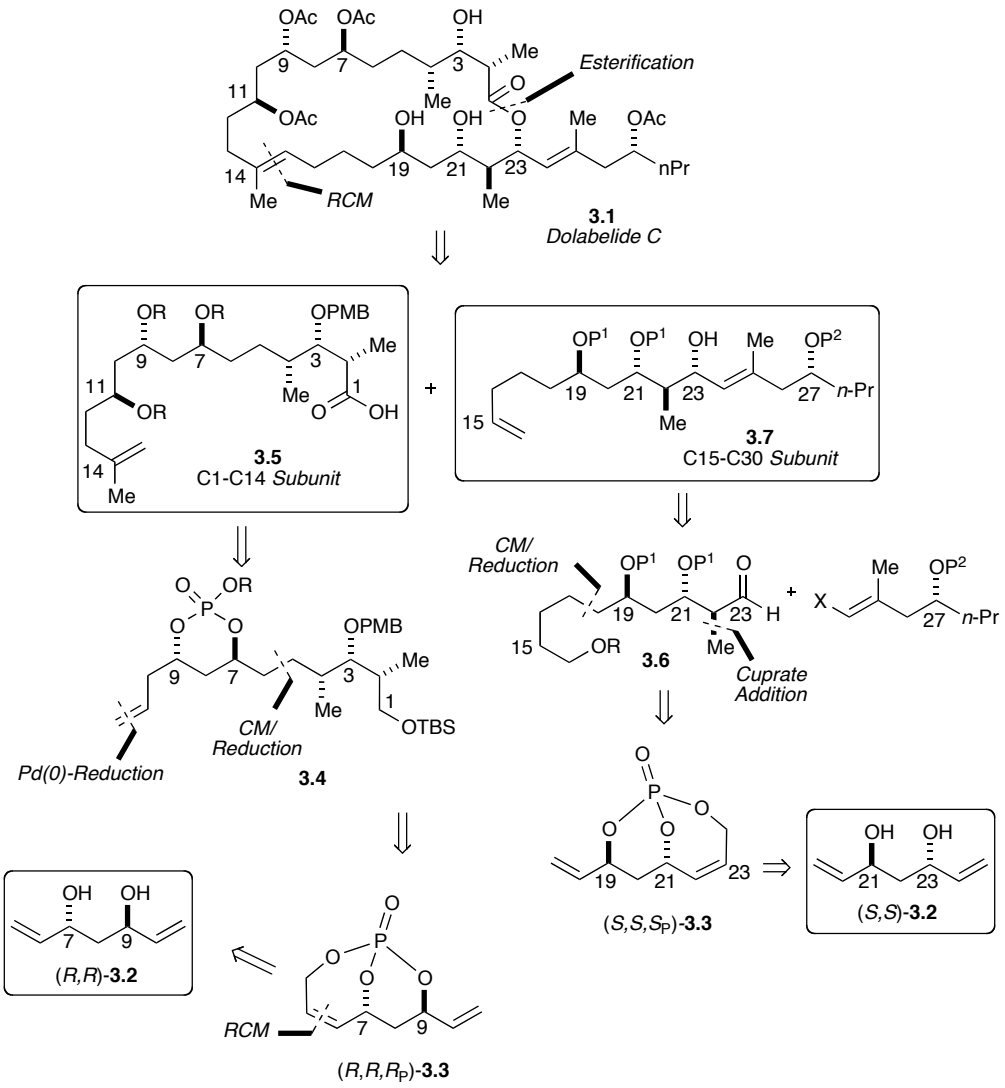
3.2 Results and Discussion

3.2.1 Retrosynthetic Analysis of Dolabelide C

From a synthetic perspective, dolabelide C (**3.1**) can be retrosynthetically disconnected into C1-C14 and C15-C30 subunits, **3.5** and **3.7**, respectively (Scheme 1).[11] The endgame for this approach is similar to Leighton's strategy towards dolabelide D,[4] employing a macrocyclization sequence to install the C14/C15 trisubstituted olefin through a late stage ring-closing metathesis (RCM) reaction. Macrocyclization is preceded by Yamaguchi coupling between the C1 carboxylic acid and the C23 carbinol center contained within the advanced subunits **3.5** and **3.7**, respectively. Central to our synthetic approach are the 1,3 anti-diol motifs at the 7,9 and 19,21 carbinol carbons assembled and functionalized from bicyclic phosphates (R,R,R_P) and (S,S,S_P)-**3.3**.

The development of a formal diastereotopic differentiation strategy of C_2-symmetric diols (R,R) and (S,S)-**3.2** through phosphate tethers allowed us to envision access to both **3.5** and **3.7**.[12] Using the salient features of both antipodes of bicyclic phosphate **3.3**, the utilization of regioselective cross-metathesis and olefin reduction would allow significant elaboration to appending the C1-C6 and C15-C18 segments of **3.5** and **3.7**. Our progress on S_N2' displacements of cyclic allylic phosphates[13] persuaded us to envisage a Pd(0)-mediatied formate reduction of **3.3** to facilitate the generation of the C11-C14 portion of **3.5** and a cuprate addition to install the C22 methyl group of aldehyde **3.6**, which could furnish **3.7** by a vinyl-metallate coupling and subsequent transformation to construct the C15 terminal olefin.

Scheme 1

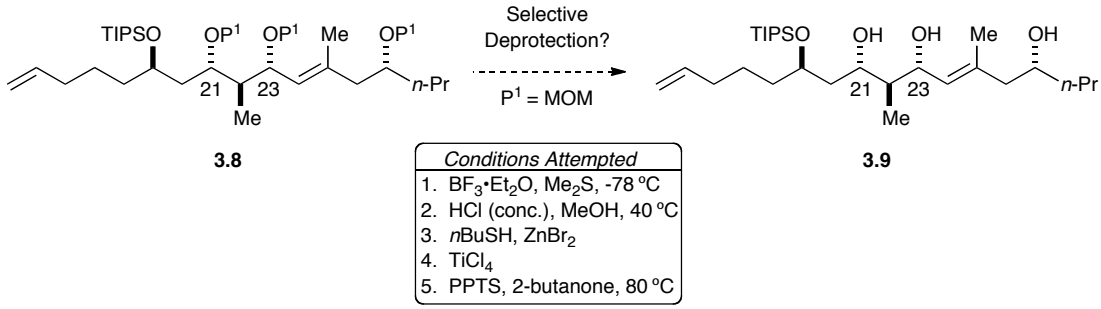


3.2.2 Modification to Synthesis of C15-C30 Subunit

Previous reports showed the possibility of a phosphate-mediated route toward **3.1**, where the carbon framework of both **3.5** and **3.7** were realized (as shown in Chapter 1).[14,15] While the phosphate methodology proved to be a viable proof of

concept, attempts to remove one, two, or all three MOM-protecting groups from **3.8** proved problematic as 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 (Scheme 2). The difficulty in removing these protecting groups to reveal either the C21 carbinol (access to dolabelide A) or C23 carbinol (access to dolabelide C) prompted a reevaluation of protecting groups to access a suitable C15-C30 subunit of dolabelide.

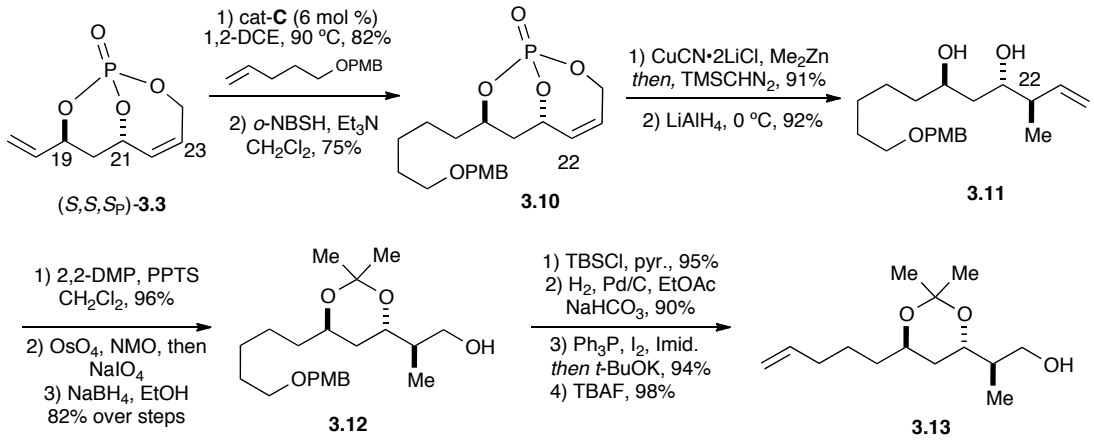
Scheme 2



The new approach sought to introduce the C23 carbinol in a late stage vinylate addition, where the terminal C15 olefin would already be intact. Also, a new protecting scheme was crucial for deprotection manipulation at the end of the total synthesis of dolabelide C. This route commenced from (*S*,*S*,S_P)-**3.3**, employing similar chemistry previously shown to diol **3.11** (also shown in Chapter 1).[15] With the established 1,3,4-*anti*,*anti*-stereotetrad installed, acetonide protection, oxidative cleavage and hydride reduction of the newly formed aldehyde to its resultant primary alcohol (**3.12**) was performed over 3 steps (Scheme 3). Silylation (TBSCl), debenzylation under hydrogenation conditions and iodination/elimination of the

concomitant primary alcohol to its respective terminal olefin was finally desilylated to give intermediate **3.13**.

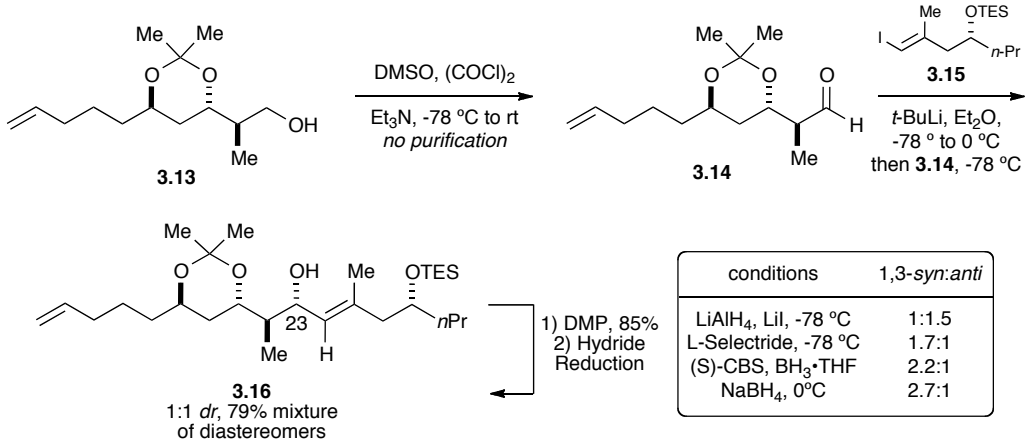
Scheme 3



With alcohol **3.13** in hand, Swern oxidation[16] provided aldehyde **3.14**, which was subjected to vinylate addition from vinyl iodide **3.15**, bearing a TES protecting group instead of the previously utilized MOM group (see Chapter 1). The addition resulted in a separable mixture of epimers in a 1:1 *dr* in 79% yield (Scheme 4).[17] The undesired epimer was recycled through an oxidation/reduction protocol first with Dess-Martin periodinane (85% yield) and hydride reduction (see Table in Scheme 4). Using the previously reported conditions by Mori ($LiAlH_4$, LiI)[18] resulted in a generation of the undesired epimer as the major product (1:1.5 *dr*). However, other reagents, L-selectride, (*S*)-CBS[19] and $NaBH_4$ all gave favorable ratios for the desired epimer, affording a suitable protocol for recycling the undesired epimer. This route

yielded a fragment suitable for acid coupling with the C1-C14 subunit, with the C23 carbinol available.

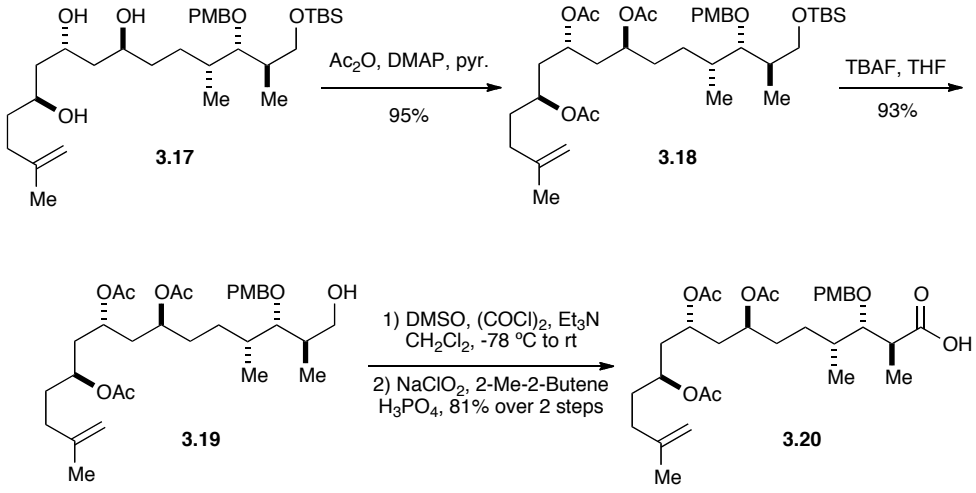
Scheme 4



3.2.3 Final Stages to Total Synthesis of Dolabelide C

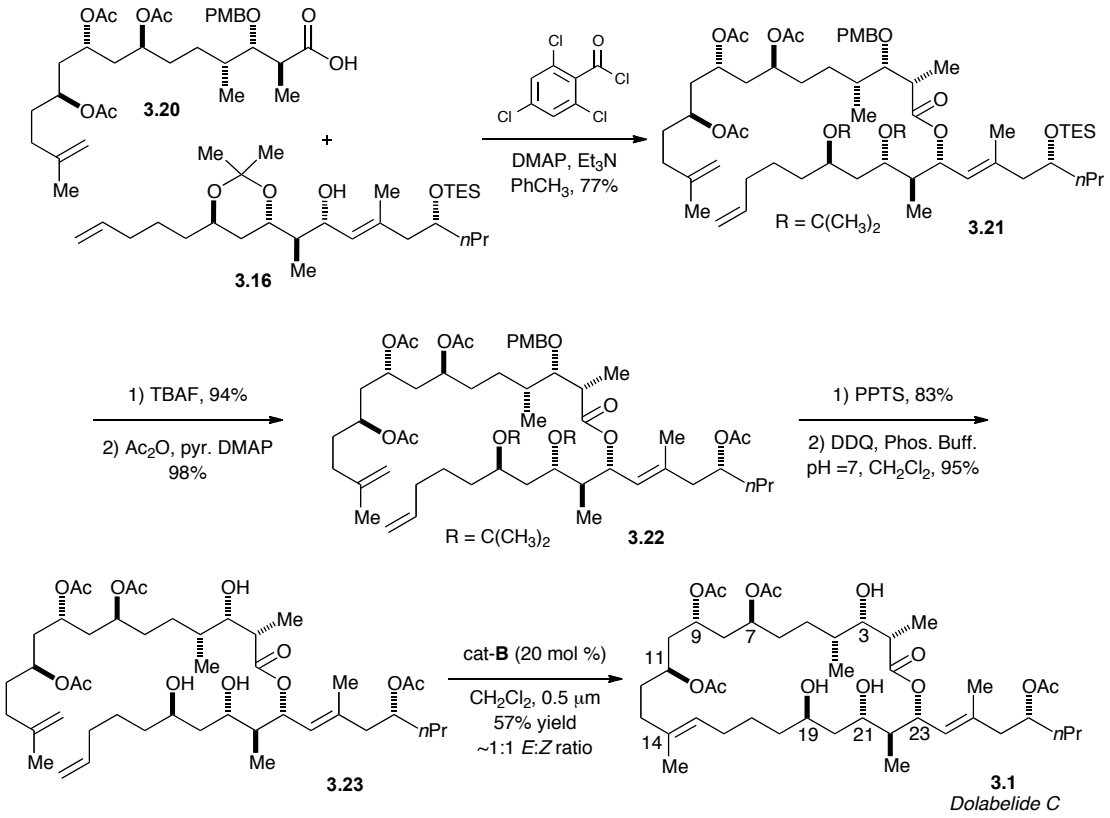
With both subunits of dolabelide C successfully synthesized, studies toward the completion of dolabelide C began (Scheme 5). This process commenced with the complete acetylation of previously reported triol **3.17**[14] to install the proper acetylation pattern for C1-C14 subunit of dolabelide C (Scheme 5). This was accomplished by adding acetic anhydride and pyridine to triol **3.17** to afford triacetate **3.18** in excellent yield. Deprotection of the TBS protecting group provided alcohol **3.19** in 93% yield. Swern oxidation of **3.19** generated the desired aldehyde that was prone to epimerization and was taken on without purification. Pinnick oxidation of the aldehyde provided carboxylic acid **3.20** in 81% yield over the two-step sequence, which was ready for coupling with the C15-C30 subunit.

Scheme 5



Final coupling of the C1-C14 carboxylic acid **3.20** and the C15-C30 alcohol **3.16** was achieved using Yamaguchi conditions,[20] as previously described by Leighton and coworkers (Scheme 6).[4] The addition of 2,4,6-trichlorobenzoyl chloride, Et_3N, and DMAP at -78 ºC for 21 hours avoided epimerization at C2 and yielded the desired coupled **3.21** in 77% yield. Deprotection of the C27-TES protecting group was achieved with TBAF in 94% yield. Subsequent acylation provided **3.22** in 98% yield. The final two protecting groups were removed using PPTS in MeOH, followed by treatment with DDQ to provide metathesis precursor **3.23** in excellent yield over two steps. Efforts to close the ring were attempted prior to PMB ether removal and provided the desired RCM product as observed by HRMS, albeit in poor overall conversion. As a result, subsequent investigations focused on RCM of the deprotected triol **3.23**. Portion-wise addition of 20 mol % of cat-**B**[l] to triol **3.23** afforded approximately a 1:1 *E*/*Z* mixture of dolabelide C **3.1** in a 57% yield.

Scheme 6



3.3 Conclusions

The total synthesis of dolabelide C was completed in 0.73% overall yield from 2,4-pentanedione utilizing a phosphate-mediated approach toward the two 1,3-*anti*-diol subunits embedded within the 24-membered macrocycle's construct. To the best of our knowledge this is the first total synthesis of a natural product utilizing a temporary phosphate tether. While first efforts toward the C15-C30 subunit encountered difficulty with the protecting group strategy, a solution was found by introducing the C23 carbinol in the last step of the sequence via vinylate addition.

Both subunits were obtained in 13-step routes starting from their respective antipodes of phosphate **3.3** and the longest linear sequence from commercially available material, 2,4-pentanedione,[21] was 27 steps and the total synthetic steps required from both antipodes of the readily available 1,5-dichloro-2,4-petanediol were 51.[22]

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Chapter 4

Study of Isomerization/Ring-Closing Metathesis

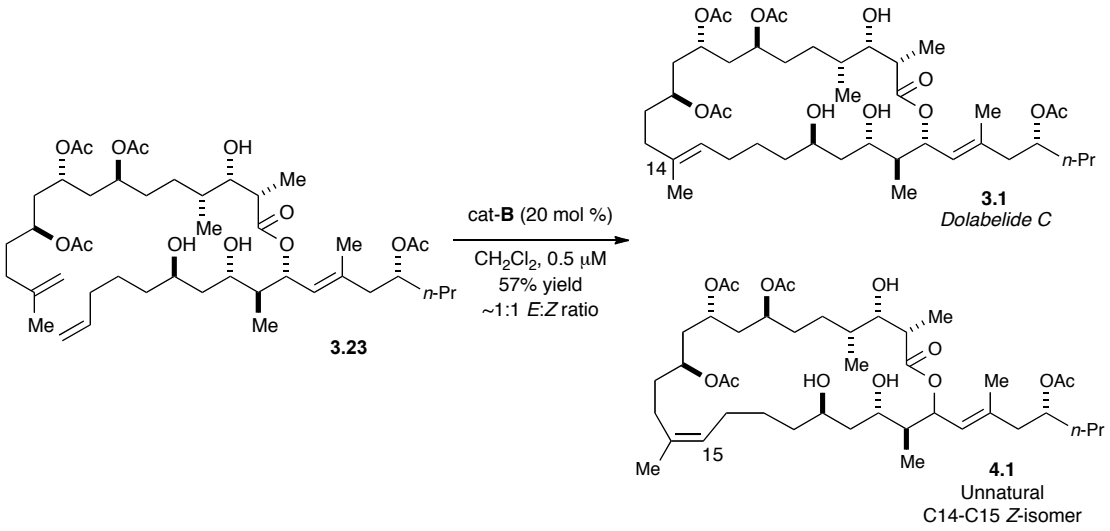
Side Reaction and Scale Up of Dolabelide C

4.1 Introduction

4.1.1 Purification Attempts of Final Mixture of E:Z Diastereomers

After constructing the 24-membered lactone of dolabelide C by RCM, flash chromatography was performed on the final mixture of *E*:*Z* diastereomers to obtain a pure sample of the naturally occurring *E*-isomer (Scheme 1). Based on the premise of the Leighton group's reported protocol to obtain a pure sample for NMR analysis of their 1.3:1 mixture of *E*:*Z* diastereomers,[1] multiple successive attempts of employing normal-phase flash column chromatography from what was a 3.0 mg mixture did not afford a pure enough sample for suitable ^{1}H and ^{13}C NMR analysis.

Scheme 1



What was perplexing was the fact that the *Z*-isomer appeared to be completely separated from the original mixture (see TLC plate in Figure 1). After spotting the isolated *Z*-isomer (left side of the TLC plate) against the *E*-isomer, it appeared they were separating cleanly from one another. The other concern at this stage was the amount of material available through the numerous attempts at purification, which could have led to insufficient material for ample resolution in the NMR experiements.

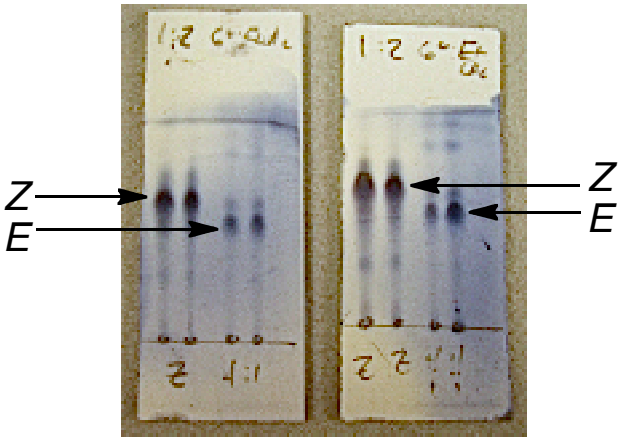


Figure 1. TLC analysis after separating *E*:*Z* diastereomers of **3.1** from flash chromatography. Left side of both plates indicate the *Z*-diastereomer and the right side of each plate the assumed pure *E*-isomer (dolabelide C).

While there was still a significant amount of impurity, the resonances from the isolation paper of dolabelide C[2] were identifiable in the ^{1}H NMR spectrum (Figure 2). Based on peak assignments in the data shown and also HRMS evidence the natural isomer exists within this mixture, an analytical approach was taken to identify a proper means of purifying the end product.

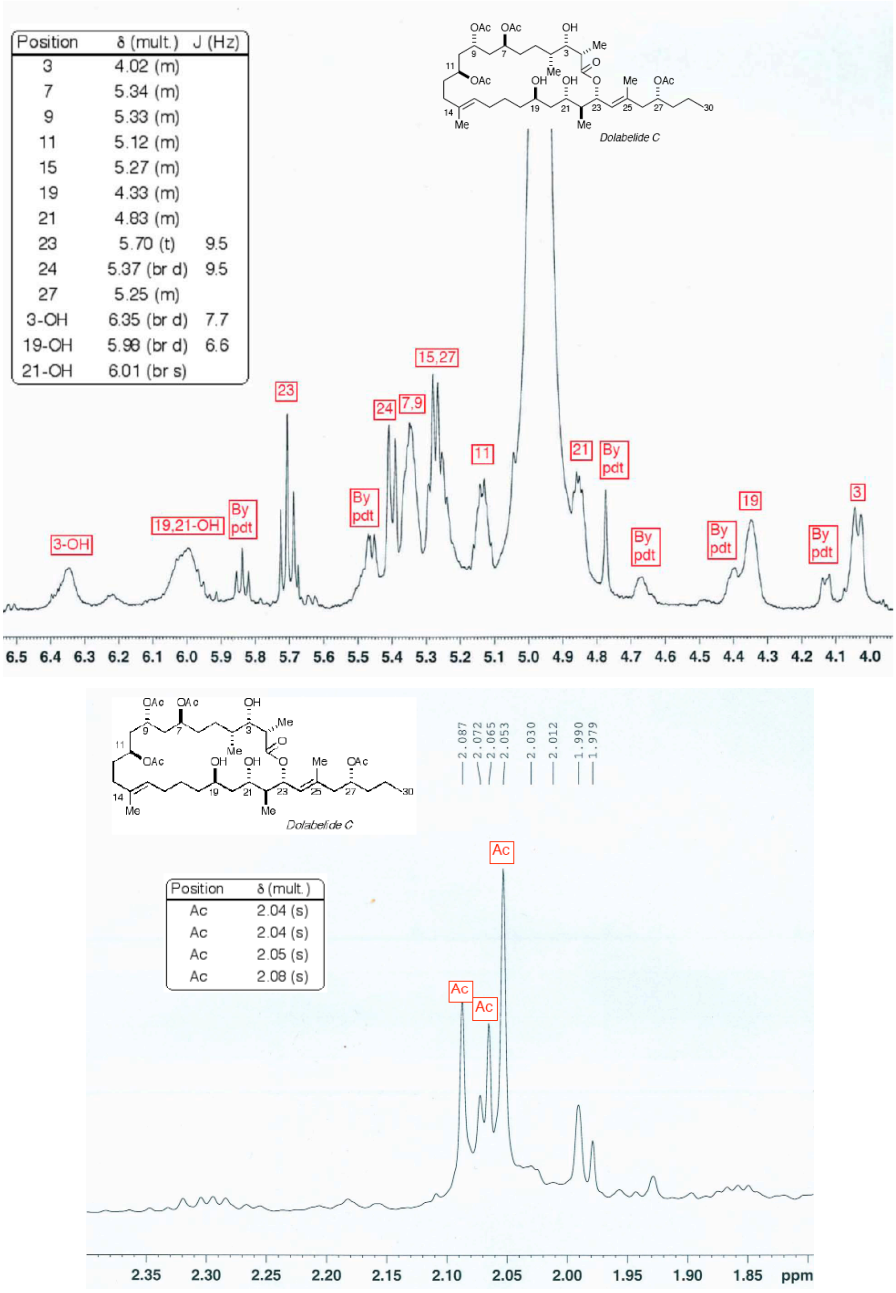


Figure 2. NMR analysis of *E*-isomer with all assigned resonances correlating with the 1997 isolation paper.[2] The top spectrum shows the whole region and bottom the acetate region.

Analytical runs of the mixture on LC-MS analysis[3] sought to achieve an acceptable method to separate the unwanted by-product(s), which was mainly presumed to be the C14-C15 *Z*-diastereomer. However, after obtaining the total-ion chromatograph (TIC) from developing exquisite separation of the components existing in the mixture, the major by-product was not the presumed *Z*-diastereomer (Figure 3). Fortunately the major peak of in the TIC was assumed to be the natural *E*-isomer (*m/z* 797.5 $(+H)^+$) the second most abundant peak was 14 *m/z* units or a methylene group ($-CH_2-$) away from dolabelide C.

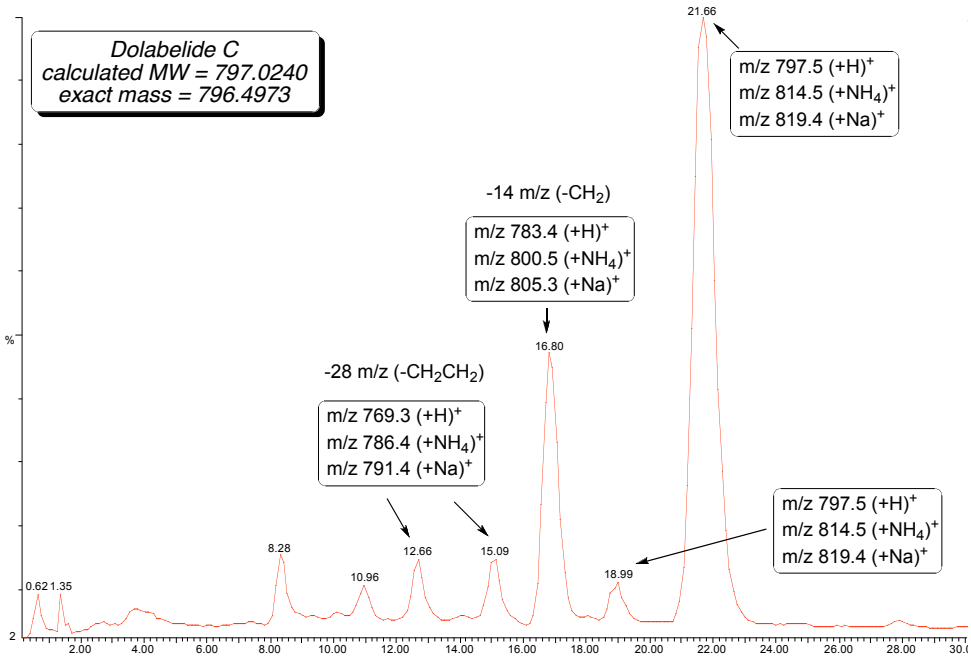


Figure 3. LC-MS analysis of mixture obtained after successive flash chromatography of **3.1**. Peak at 21.66 matches with **3.1** however other major peaks are 22- and 23-membered macrolides contaminating the final product.

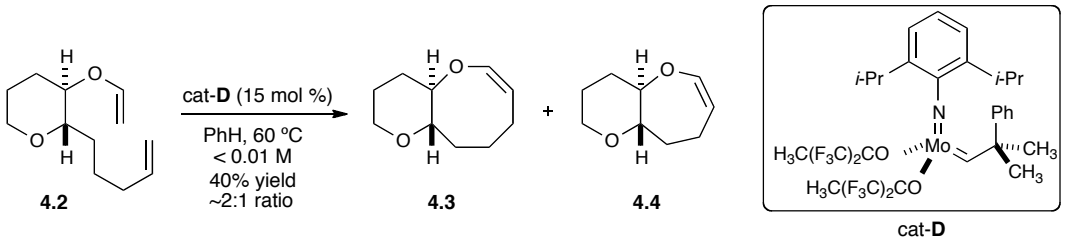
Two additional abundant peaks in the mixture were 28 *m/z* units or two methylene units away (-C_2H_6-) from the desired *E*-isomer. While it was not clear at the time, what these products were and their respective side-reactions, it was confirmed that one of the olefinic diastereomers, which we presumed to be the *Z*-isomer, was being removed effectively by normal-phase flash chromatography.

4.2 Isomerization/Ring-Closing Metathesis

4.2.1 Isomerization/RCM Side Reaction in Synthesis of Medium-Sized Rings

To determine the cause of the side products from the RCM of the 24-membered lactone, reports of the synthesis of medium and large ring sizes were surveyed. In 1997, Clark and Kettle observed in their intentions to constructing 6,8-bicycle **4.3** from pyran **4.2**, a considerable amount of 6,7-bicycle **4.4** was produced in a 2:1 ratio using Schrock's catalyst,[4] cat-**D** (Scheme 2).[5]

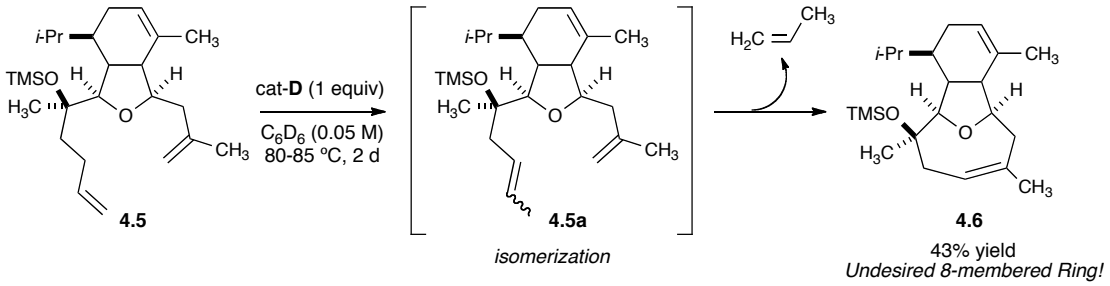
Scheme 2



In the same year, Overman and Joe encountered a similar problem, where compound **4.5** was subjected to 1 equiv. of cat-**D** in dilute conditions (C_6D_6 at 0.05

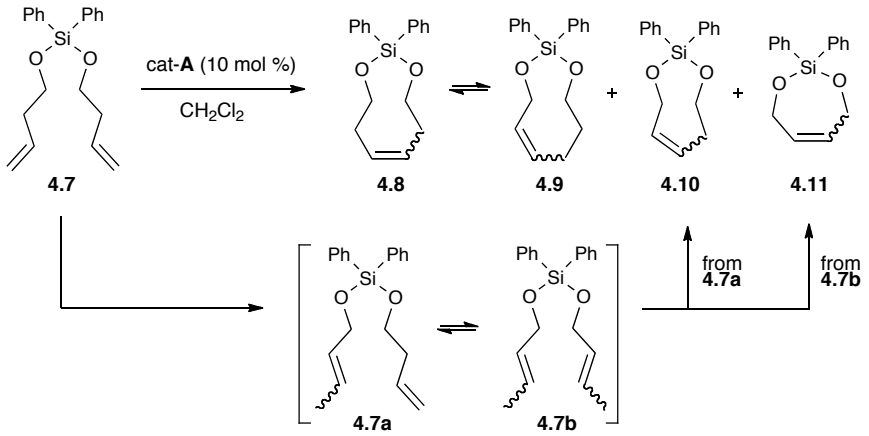
M) providing **4.6**, which lost a methylene group from their desired 9-membered ring (Scheme 3).[6] It was presumed **4.5** was going through an isomerization event prior to ring closure, resulting in a net loss of an extra methylene unit.

Scheme 3



This side process was first reported with Grubb's catalyst by Hoye and Promo in their studies of metathesizing silicon-tethered alkenols (Scheme 4).[7] Silaketal **4.7** was introduced to a catalytic amount of cat-**A** (10 mol %) where aliquots were taken out after 50% conversion (determined by GC-MS).

Scheme 4

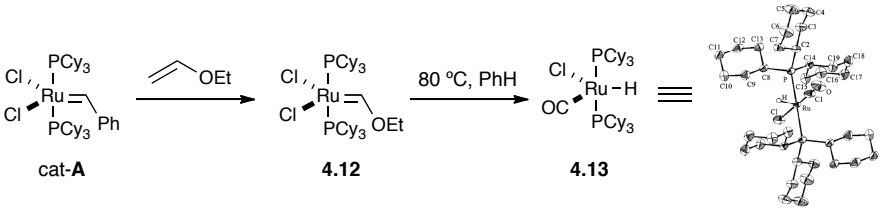


Analysis showed the appearance of expected cyclic silaketal **4.8**, along with heterocycles **4.10** and **4.11**, which were one and two methylene units away, respectively. What is also key to note from this result is the isomerization of **4.8** to **4.9** after RCM. It was suggested a ruthenium hydride species could be the culprit of these deleterious side reactions.[7]

4.2.2 Evidence of Ru-Hydride Species from Grubbs' Complexes

In 2002, Grubbs and Louie isolated the first Ru-hydride species as a decomposition product from generating a Ru Fischer-type carbene **4.12** by reacting cat-**A** with ethyl vinyl ether (Scheme 5).[8] By heating carbene **4.12** to 80 ºC in benzene, evidence of Ru-H bond was determined by NMR analysis and X-Ray crystallography later confirmed this to be complex **4.13**.

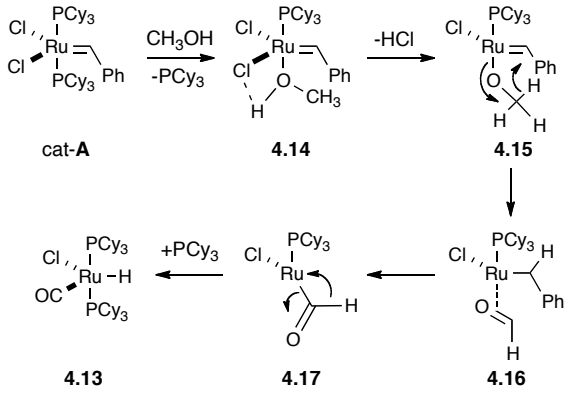
Scheme 5



It was later shown that heating cat-**A** various primary alcohols also induced decomposition to Ru-hydride **4.13**.[9] Dinger and Mol proposed a mechanism of degradation first through dissociation of one of the phosphine ligands followed by coordination of the methanol to ruthenium (**4.14**) (Scheme 6). Elimination of

chloride would have a methoxy-ruthenium species (**4.15**) that would first deliver a hydride to the Ru-carbene (**4.16**) and then eliminate toluene to Ru-formate **4.17**. Ru-hydride formation then occurs through a final hydride delivery from the formyl ligand and phosphine ligation to **4.13**. This phenomenon has also been observed with Grubbs' second-generation catalyst (cat-**B**) by metathesizing ethyl vinyl ether to form the ensuing Ru-alkylidene.[10]

Scheme 6

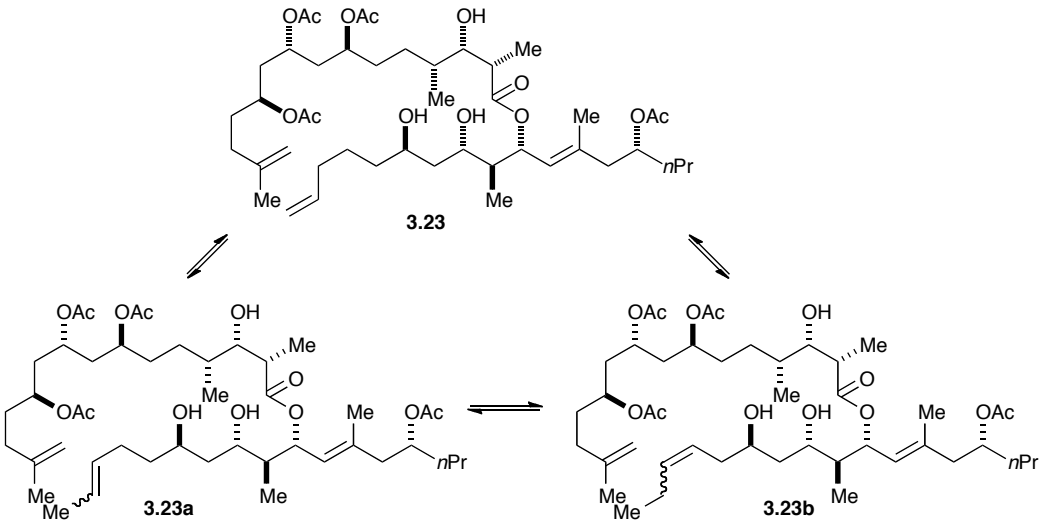


4.3 Results and Discussion

4.3.1 Identification of Isomerization/RCM By-Products

Based on the literature reports of isomerization/RCM side products and LC-MS analysis, it was concluded this side process was the cause for the complex mixture from the final step in the synthesis of dolabelide C (Scheme 7). In light of these facts, intermediates **3.23a** and **3.24b** would be likely candidates for the by-products containing one and two less methylene units, respectively.

Scheme 7



The other by-product (**4.18**) mirroring the *m/z* ratio (Figure 4) is presumed to arise from an isomerization event occurring after RCM, since the *Z*-isomer was removed via flash chromatography.[11] Other macrocycles formed in the reaction mixture are potentially **4.19** (occurring from **3.23a**), **4.20** (occurring from **3.23b**) and **4.21**. Another potential isomerization/RCM could occur from the tri-substituted olefin, forming a 1,1-dimethyl substituted olefin. However, to the best of our knowledge, an RCM under identical conditions has not been reported, therefore this pathway is not being proposed.[12]

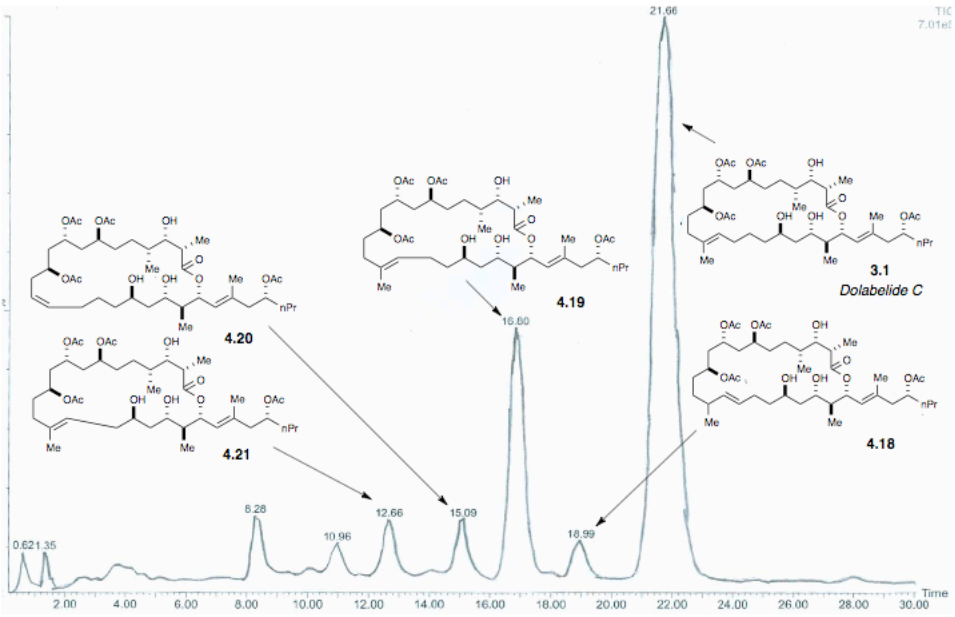


Figure 4. LC-MS peak assignments of major by-products observed from final RCM mixture.

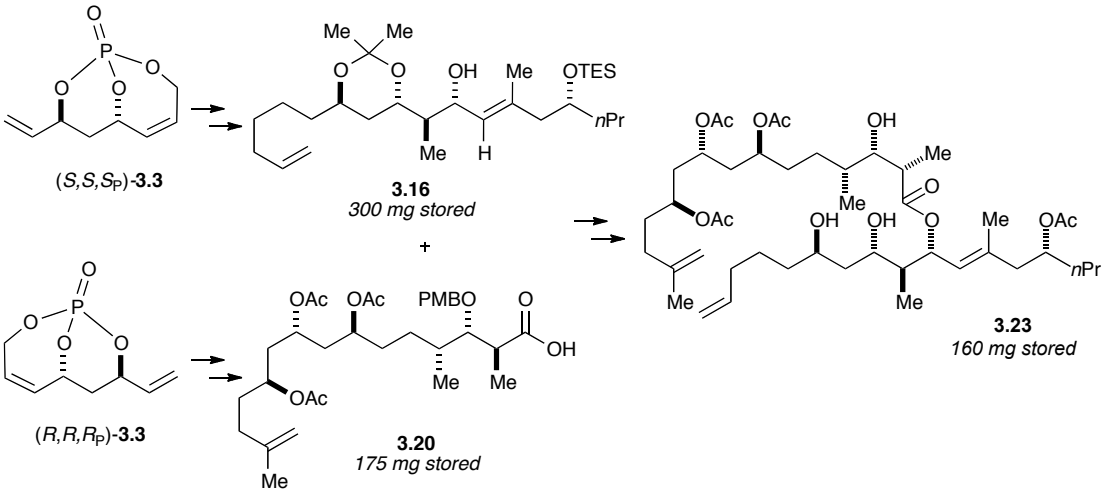
4.3.2 Scale Up Efforts of Developed Route to Dolabelide C

Given the excellent separation shown from the TIC in Figure 4, semi-preparative LC-MS was performed to isolate the peak representing dolabelide C (**3.1**). However, the small amount of material available from the beginning of the purification did not provide ample material for a well resolved ^{1}H NMR. Therefore, a scale up of the route developed in Chapter 3 was performed to provide more of dolabelide C for full characterization.[13]

Both syntheses to each subunit proved to be scalable, providing 300 mg of **3.16** (from (*S*,*S*,*S*$_P$)-**3.3**) and 175 mg of **3.20** (from (*R*,*R*,*R*$_P$)-**3.3**). This material was

carried through the same endgame steps (Scheme 8) affording 160 mg of RCM precursor **3.23** to apply towards the goal of optimizing the C14/15 *E*:*Z* ratio and minimizing the amount of deleterious side reactions occurring in the final RCM step.

Scheme 8

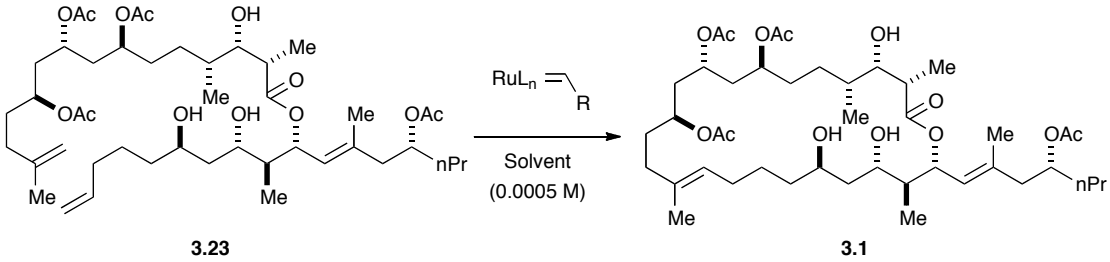


4.3.3 Optimization Studies on Final RCM Step

The copious amount of **3.23** available allowed for a thorough evalulation for the optimization of the final RCM step. It was first studied on microgram scale by preparing solutions of metathesis catalysts and adding them to a refluxing mixture of **3.23**. First the conditions used in the reported final step were attempted to be reproduced, however conversion drastically decreased by using the catalyst in a solution of its respective solvent (entries 1-3 in Table 1). However, by scaling up to milligram scale and adding in neat cat-**B** (entry 4) complete conversion was achieved, reproducing the earlier result. Trying to use Hoveyda-Grubbs second geneation (cat-

C) catalyst on this system proved ineffective for using it as a solution (entry 5) and also neat in milligram scale (entry 6).

Table 1



Entry	Catalyst	Conc. of Cat. Solution	Solvent	Time	Conversion	Total Loading
1	cat-**B**	0.3 mg/mL	CH_2Cl_2	> 12 h	10%	25 mol %
2	cat-**B**	0.3 mg/mL	$PhCH_3$	> 12 h	0%	25 mol %
3	cat-**B**	0.6 mg/mL	CH_2Cl_2	> 12 h	5%	25 mol %
4	cat-**B**	neat	CH_2Cl_2	6 h	100%	25 mol %
5	cat-**C**	0.3 mg/mL	CH_2Cl_2	>12 h	0%	25 mol %
6	cat-**C**	neat	CH_2Cl_2	>12 h	0%	25 mol %

Now that the original conditions were reproduced, a screening of different metathesis catalysts bearing phosphine and NHC ligands[14] was done (since cat-**C** was ineffective, only phosphine-bearing catalysts were desired in this study). These catalysts were presumed to exhibit higher activity than cat-**B** and were shown to metathesize *N*,*N*-diallylbenzenesulfonamide at room temperature.

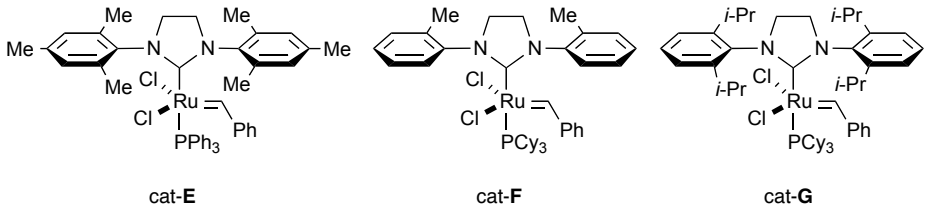


Figure 5

Through the developed method on LC-MS, the results in Table 2 were determined by integrating underneath the peak areas from the TIC. One important modification to the RCM protocol for this screening was the preparation of solvent. Each reaction was run in non-stabilized CH_2Cl_2 that was passed through a purification system employing activated Al_2O_3,[15] then distilled over CaH_2 and finally degassed utilizing the freeze-thaw technique with a Schlenk system. This protocol was used in the conditions reported in Chapter 3 (entry 1, Table 2) giving nearly complete conversion, a 1:1 *E*:*Z* ratio of diastereomers and about 8% of the overall mixture consisted of by-products arising from Ru-hydride side reactions.

Table 2

Entry	Catalyst	Conversion[b]	*E*:*Z*[b]	*E*:*Z*:By-Pdts[b]
1	cat-**B**	>99%	1:1	1:1:0.17
2[a]	cat-**B**	87%	1.2:1	1.2:1:0.26
3	cat-**E**	100%	1:1	1:1:0.80
4	cat-**F**	100%	1:1.1	1:1.1:0.45
5	cat-**G**	87%	1.2:1	1.2:1:0.61

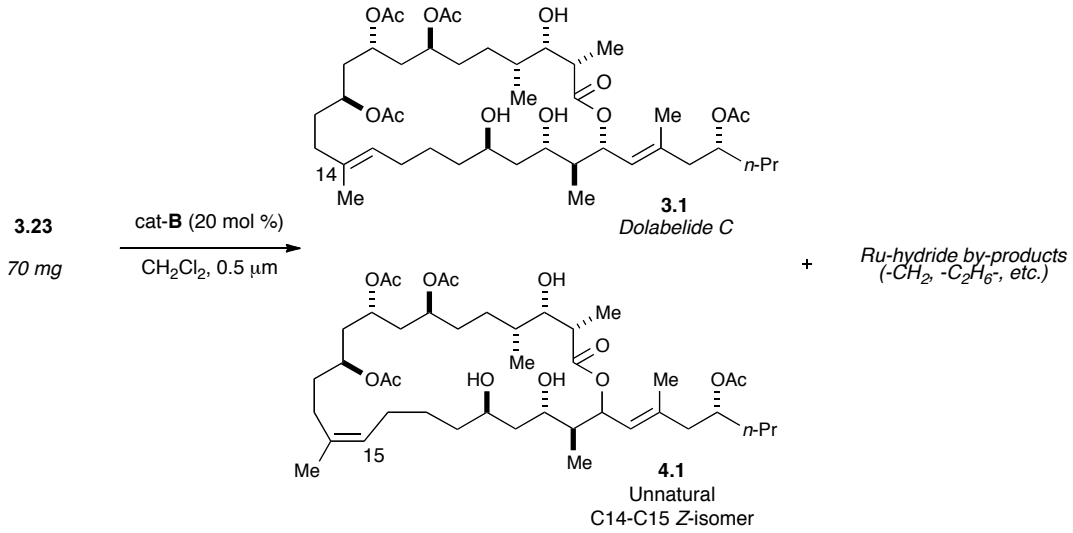
[a]Purified newly purchased catalyst through SiO_2 plug in 10:1 hexanes:ethyl acetate.
[b]Conversion and product ratios were determined from crude LC-MS analysis.

Eluding cat-**B** through a short plug of SiO_2 in hexanes:ethyl acetate (10:1 ratio) gave a slight increase in *E*:*Z* ratio, but provided a decrease in conversion and delivered a higher percentage of by-products (entry 2). In screening the new catalysts, cat-**E** (entry 3) and cat-**F** (entry 4) gave complete conversion of starting material, but also provided a higher percentage of by-products. Lastly, cat-**G** proved inefficient in comparision to cat-**B** as well, yielding a significantly higher percentage[16] of by-products along with incomplete conversion (entry 5).

4.3.4 Scale Up of Final RCM and Isolation of Natural and Non-Natural Isomers

Even though the optimization study did not provide a better candidate for reaction scale up of the final RCM step, the ability to scale the overall process to yield 160 mg of RCM precursor **3.23** was a great proof of concept that this synthesis can provide ample quantities for purification with the knowledge gained of Ru-hydride by-products. The last step was run on 70 mg scale furnishing another mixture of *E*:*Z* diastereomers and Ru-hydride by-products (Scheme 9).

Scheme 9



After screening potential solvent systems to isolate both the natural isomer **3.1** and the non-natural isomer **4.1**, it was determined running the mixture through two successive normal-phase, flash columns (one through CH_2Cl_2:acetone 8:1, and the second through pentane:ethyl acetate 5:1) could provide both isomers analytically

pure. Gratifyingly, the developed protocol provided 14 mg of analytically pure dolablide C (Figure 6).

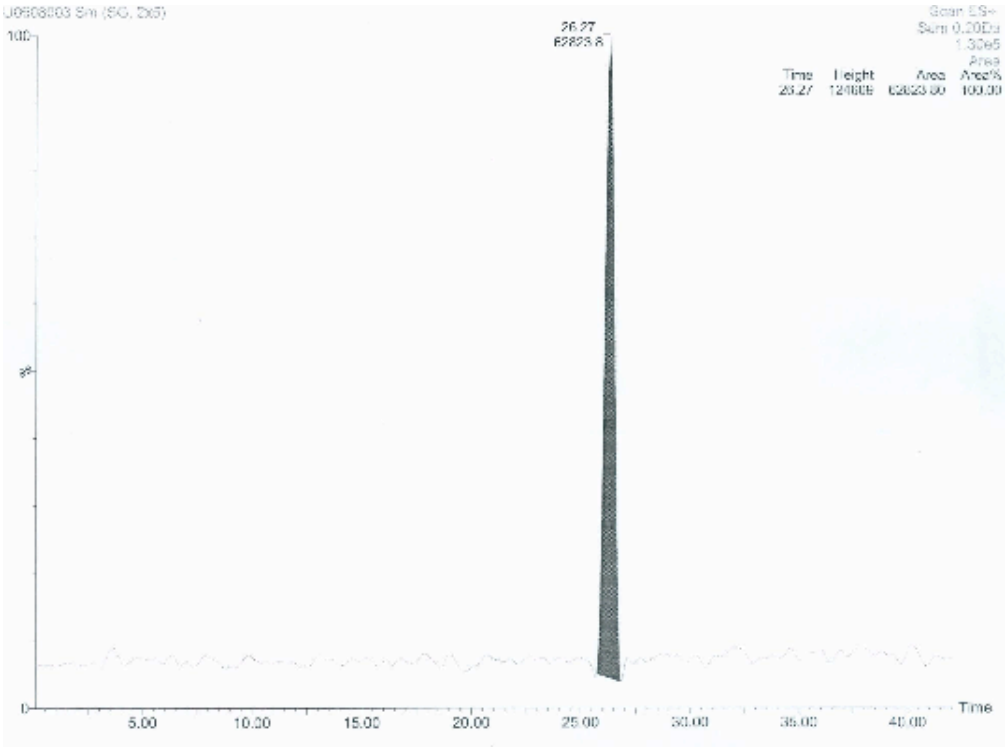


Figure 6. Analytically pure sample of dolablide C (**3.1**) from LC-MS analysis.

Accordingly, the sample was submitted for ^{1}H NMR analysis, which showed all of the resonances reported in the isolation paper[2] and no significant amount of by-products (Figure 7). Overall, this reaction gave a 24% yield from the final scale up of the synthesis and also gave 10 mg of the non-natural *Z*-isomer, which was also fully characterized.[13] These compounds will be submitted to the National Cancer Institute for 60-cell testing of each compound and also a head-to-head comparison of the two isomers.[17]

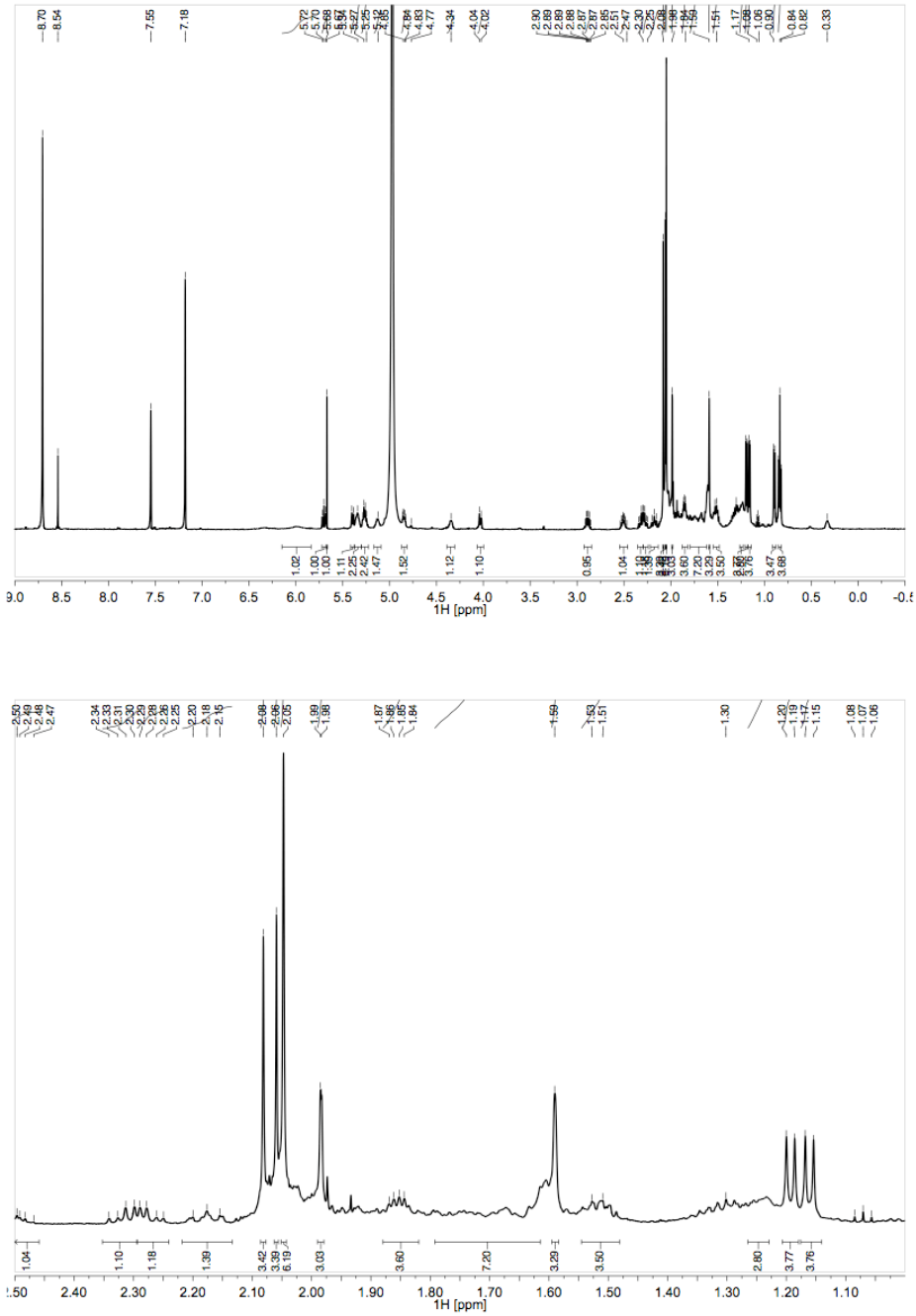


Figure 7. Top spectrum shows NMR analysis of an analytically pure sample of dolabelide C in pyridine-d_5 and the bottom spectrum is an expanded view from δ 1.0-2.5.

4.4 Conclusion

Dolabelide C and its non-natural C14-C15 *Z*-diastereomer were produced and isolated from a scalable phosphate-mediated synthesis. A complex mixture was generated in the final RCM step resulting in by-products, which arose from a net loss of CH_2 and C_2H_6, that proved to be inseparable through repeated flash chromatography (8:1 CH_2Cl_2:acetone). Since the material produced at the end of the first synthesis of **3.1** was sparse, a re-synthesis provided 175 mg of the C1-C14 subunit (**3.20**), 300 mg of the C15-C30 subunit (**3.16**) and 160 mg of RCM precursor **3.23**. This allowed a detailed optimization study through a screening of various metathesis catalysts, concluding with the originally developed conditions in Chapter 3 provided the optimum results. Overall, 14 mg of dolabelide C and 10 mg of the *Z*-isomer (**4.1**) were produced and their biological activities will be further evaluated by the National Cancer Institute for 60-cell testing of each compound and also a head-to-head comparison of the two isomers.[17]

4.5 References

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(3) HPLC-MS analysis was developed with a Waters 2695 HPLC system on a SiliChromTM XDB C18 reverse phase column (4.6 mm I.D. x 200 mm) and detected on an AUTOSPEC-Q tandem mass spectrometer.

(4) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. "Synthesis of Molybdenum Imido Alkylidene Complexes and Some Reactions Involving Acyclic Olefins." *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886.

(5) Clark, J. S.; Kettle, J. G. "Synthesis of Brevetoxin Sub-units by Sequential Ring-Closing Metathesis and Hydrogenation." *Tetrahedron Lett.* **1997**, *38*, 123-126.

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(8) Louie, J.; Grubbs, R. H. "Metathesis of Electron-Rich Olefins: Strucuture and Reactivity of Electron-Rich Carbene Complexes." *Organometallics* **2002**, *21*, 2153-3164.

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(11) *Z*-isomer was isolated and analyzed via LC-MS analysis, using identical conditions (see reference 3). The retention time was different than that of the 18.99 min shown in Figure 4.

(12) There are examples of Ru-alkylidene species metathesizing with 1,1-dimethyl substituted olefins in tandem enyne metathesis: (a) Boyer, F.-D.; Hanna, I.; Ricard, L. "Formal Synthesis of (±)-Guanacastepene A: A Tandem Ring-Closing Metathesis Approach." *Org. Lett.* **2004**, *6*, 1817-1820. (b) Kim, M.; Lee, D. "Boron-Directed Regio- and Stereoselective Enyne Cross Metathesis: Efficient Synthesis of Vinyl Boronate Containing 1,3-Dienes." *Org. Lett.* **2005**, *7*, 1865-1868. (c) Park, S.; Kim, M.; Lee, D. "Tandem Sequence of Cross Metathesis–Ring-Closing Metathesis Reaction of Alkynyl Silyloxy-Tethered Enynes." *J. Am. Chem. Soc.* **2005**, *127*, 9410-9415. (d) Kim, M.; Miller, R. L.; Lee, D. "Cross and Ring-Closing Metathesis of 1,3-Diynes: Metallotropic [1,3]-Shift of Ruthenium Carbenes." *J. Am. Chem. Soc.* **2005**, *127*, 12818-12819. (e) Boyer, F.-D.; Hanna, I. "Substituent Effects in Tandem Ring-Closing Metathesis Reactions of Dienynes." *Eur. J. Chem. Org.* **2006**, 471-482.

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(14) Catalysts cat-**E**, **F** and **G** were obtained from Materia, Inc.
(15) Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. "Safe and Convenient Procedure for Solvent Purification." *Organometallics* **1996**, *15*, 1518-1520.
(16) Peak integrations and ratios were determined using Waters MassLynx version 4.1.
(17) Collaboration with John A. Beutler, Ph.D. at the National Cancer Institute has been established for screening.

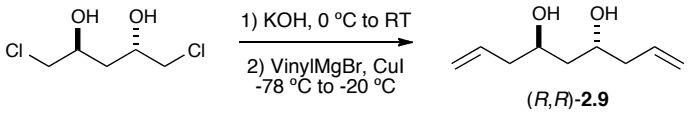
Chapter 5

Experimentals and Spectra for Chapters 2-4

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, canellas, and septa. Stirring was achieved with oven-dried, magnetic stir bars. Et_2O, toluene, THF and CH_2Cl_2 were purified by passage through a 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. Flash column chromatography was performed with SiO_2 (Silica Gel 60Å, 40-63 um) and thin layer chromatography was performed on silica gel 60F254 plates (both purchased from Sorbent Technologies). ^1H were collected at resonance frequencies of 400 MHz, 100 MHz, and 162 MHz and ^{13}C NMR spectra at 500 MHz and 125 MHz respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained on a double-focusing mass spectrometer. HPLC-MS analysis was developed with a Waters 2695 HPLC system on a SiliChrom™ XDB C18 reverse phase column (4.6 mm I.D. x 200 mm) and detected on an AUTOSPEC-Q tandem mass spectrometer.

(4*R*,6*R*)-nona-1,8-diene-4,6-diol: 2.9



(2*S*,4*S*)-1,5-dichloro-2,4-pentanediol[1] (1.2 g, 6.9 mmol) was taken up in Et_2O (69 mL) and cooled to 0 ºC. Crushed KOH was added in portions to the cold solution over 5 minutes. The reaction was allowed to warm back to RT. After 3 hours (disappearance of SM observed by GC analysis) the clear solution was filtered through $MgSO_4$ and rinsed with a minimal amount of dry Et_2O. This solution was then placed under an argon atmosphere. CuI (533 mg, 2.8 mmol) was added and the solution was stirred at RT for about 10 minutes. After cooled to -78 ºC, a freshly prepared 1.0 M of vinylmagnesium bromide in THF (28 mL, 28 mmol) was added dropwise over 10 minutes. The resulting brown colored solution was allowed to warm slowly to -20 ºC in the cold bath. After 2.5 hours, the solution was quenched slowly with NH_4Cl (25 mL) at -20 ºC and was allowed to warm to RT. The resulting suspension was filtered through celite to remove any solids forming from the quenching process. The layers were partitioned with H_2O and Et_2O and the aqueous layer was extracted with Et_2O (3 x 50 mL). The collected organics were washed with brine (25 mL), dried with Na_2SO_4 and filtered. The filtrate was concentrated providing (*R*,*R*)-**2.9** as a yellow oil (674 mg, 62% yield over 2 steps).

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

FTIR (neat) 3352.05, 3076.25, 3002.96, 2977.89, 2935.46, 1976.90, 1641.31, 1433.01, 1326.93, 1220.86, 1135.99, 1049.20, 995.20, 914.20, 871.76, 831.26 cm^{-1};

[1] Readily available from 2,4-pentanediol: Rychnovsky, S. D.; Griesgraber, G.; Powers, J. P. *Org. Syn.* **2000**, *77*, 1-6.

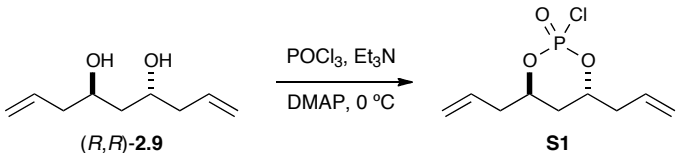
^{1}H NMR ($CDCl_3$, 500 MHz)[2] δ ppm 5.87-5.77 (m, 2H), 5.19-5.12 (m, 4H), 4.03-3.97 (m, 2H), 2.45-2.35 (m, 2H), 2.32-2.22 (m, 4H), 1.65 (t, J = 6.2 Hz, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 134.6 (2), 118.3 (2), 68.1 (2), 42.0 (2), 41.5;

HRMS calculated for $C_9H_{16}O_2$ $(M+NH_4)^+$ 174.1494; found 174.1466 (ESI).

[2] Peak at δ 2.04 is presumed to be a H_2O peak, which was difficult to remove.

(4*R*,6*R*)-4,6-diallyl-2-chloro-1,3,2-dioxaphosphinane 2-oxide: S1



(*R*,*R*)-**2.9** **S1**

Diol **2.9** (98 mg, 0.627 mmol) was taken up in CH_2Cl_2 (3.14 mL) at RT. Triethylamine (0.393 mL, 2.82 mmol) and DMAP (7.66 mg, 0.0627 mmol) were added sequentially. After cooling the mixture to 0 ºC, freshly distilled $POCl_3$ (0.088 mL, 0.941 mmol) was added dropwise resulting in a white suspension (from formation of amine salts). After 10 minutes, **2.9** was consumed (determined by TLC analysis) and the suspension was diluted with Et_2O (5 mL) to crash out remaining amine salts. The mixture was filtered through a fritted funnel and rinsed thoroughly with Et_2O (20 mL). The filtrate was concentrated under reduced pressure and purified through a plug of SiO_2 in 2:1, hexanes:EtOAc. The collected fractions were concentrated under reduced pressure affording a yellow oil (133 mg, 90% yield).

$[\alpha]_D$ +39.1 (*c* = 0.45, CH_2Cl_2);

FTIR (neat) 3080.11, 2923.88, 2491.86, 2453.29, 1641.31, 1303.79, 1087.78, 1027.99, 981.70, 921.91 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.70-5.82 (m, 2H), 5.17-5.23 (m, 4H), 4.68-4.82 (m, 2H), 2.78-2.85 (m, 1H), 2.41-2.62 (m, 3H), 2.15 (ddd, *J* = 14.9, 9.1, 5.3 Hz, 1H), 2.02 (ddd, *J* = 15.0, 5.9, 3.6 Hz, 1H[3]);

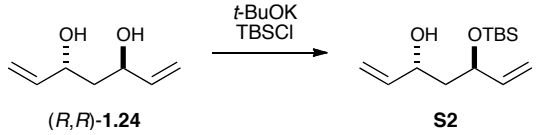
^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 131.7, 131.2, 119.7, 119.6, 81.0 (d, $J_{C\text{-}P}$ = 9.0 Hz), 77.1 (d, $J_{C\text{-}P}$ = 7.8 Hz), 39.7 (d, $J_{C\text{-}P}$ = 9.3 Hz), 38.1 (d, $J_{C\text{-}P}$ = 2.2 Hz), 32.2 (d, $J_{C\text{-}P}$ = 8.1 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -3.84;

[3] Water peak at δ 2.04 zeroed out to give a ddd, 1H signal.

HRMS calculated for $C_9H_{14}ClO_3P$ $(M+Na)^+$ 259.0267; found 259.0274 (ESI).

(3*R*, 5*R*)-5-((*tert*-butyldimethylsilyl)oxy)hepta-1,6-dien-3-ol: S2



(*R*,*R*)-**1.24** **S2**

To a suspension of *t*-BuOK (57 mg, 0.504 mmol) in THF (1.01 mL) was added a solution of diol (*R*,*R*)-**1.24** (61 mg, 0.480 mmol) in THF (0.240 mL), dropwise. After stirring 45 minutes at RT, TBSCl (76 mg, 0.504 mmol) was added portion-wise. The reaction was stirred for 16 hours at RT and quenched with about 5-10 drops of 10% aq. K_2CO_3 (until suspension broke up). Anhydrous Na_2SO_4 was added directly to the mixture and filtered. The filtrate was concentrated under reduced pressure and purified via flash chromatography in 20:1, hexanes:EtOAc. Product **S2** was obtained as a yellow oil (60 mg, 52% yield) along with recovered starting material (12 mg, 65% BRSM).

$[\alpha]_D$ -13.5 (*c* = 0.20, CH_2Cl_2);

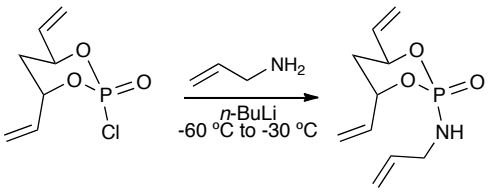
FTIR (neat) 3421.48, 2954.74, 2927.74, 2856.38, 2358.78, 2341.42, 1652.88, 1253.64, 1072.35, 837.05, 777.26 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.86 (dtd, *J* = 17.1, 10.3, 5.6 Hz, 2H), 5.25 (dtd, *J* = 17.2, 4.8, 1.6 Hz, 2H), 5.11 (ddt, *J* = 25.5, 10.5, 1.5 Hz, 2H), 4.48-4.52 (m, 1H), 4.40 (br s, 1H), 3.28 (s, 1H), 1.66-1.78 (m, 2H), 0.92 (s, 9H), 0.08 (d, *J* = 17.2 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 140.9, 140.1, 114.7, 113.9, 72.3, 69.6, 43.1, 25.8 (3), 18.1, -4.5, -5.1;

HRMS calculated for $C_{13}H_{26}O_2Si$ $(M+Na)^+$ 265.1600; found 265.1592 (ESI).

(4*S*,6*S*)-2-(allylamino)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21a



2.21a

Allylamine (0.13 mL, 0.176 mmol) was taken up in THF (0.881 mL) and cooled to -60 ºC. Dropwise addition of *n*-butyllithium (0.70 mL, 2.4 M solution in hexanes) afforded a yellow solution that was stirred for about 10 minutes at -60 ºC. A solution of (4*S*,6*S*)-2-chloro-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide[4] (35 mg, 0.168 mmol) in THF (0.336 mL) was delivered dropwise via cannulation. The reaction was allowed to warm slowly in the cold bath to -30 ºC. After 35 minutes, TLC analysis showed consumption of the starting material. The solution was quenched at -30 ºC with NH_4Cl (1 mL) and was warmed to RT. After partitioning with H_2O (5 mL) and EtOAc (5 mL), the aqueous layer was extracted with EtOAc (3 x 5 mL). The collected organics were washed once with brine (5 mL), dried with Na_2SO_4 and filtered. Filtrate was concentrated under reduced pressure and purified using flash chromatography (2:1, hexanes:EtOAc). Concentration of the collected fractions under reduced pressure provided **2.21a** as a yellow oil (34 mg, 88% yield).

$[\alpha]_D$ +67.4 (*c* = 0.38, CH_2Cl_2);

FTIR (neat) 3207.40, 2985.60, 2931.60, 2856.38, 1645.17, 1614.31, 1514.02, 1442.66, 1377.08, 1245.93, 1224.71, 1110.92, 1027.99, 995.20, 927.70 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.12 (ddd, *J* = 16.7, 10.7, 5.8 Hz, 1H), 5.87 (ddddd, *J* = 17.3, 10.7, 5.3, 3.1, 1.7 Hz, 2H), 5.20-5.50 (m, 5H), 5.07-5.13 (m, 2H), 4.90-4.97 (m, 1H), 3.52-3.59 (m, 2H), 2.93-3.00 (m, 1H), 2.08-2.15 (m, 1H), 1.98-2.07 (m, 1H);

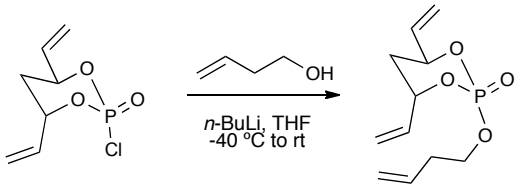
[4] Synthesis reported in earlier publication: Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375-3378.

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 135.8 (d, J_{C-P} = 1.9 Hz), 135.8, 135.7 (d, J_{C-P} = 2.1 Hz), 117.9, 116.9, 115.7, 77.4 (d, J_{C-P} = 6.1 Hz), 73.8 (d, J_{C-P} = 4.9 Hz), 44.0, 35.3 (d, J_{C-P} = 7.5 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm 3.58;

HRMS calculated for $C_{10}H_{16}NO_3P$ $(M+Na)^+$ 252.0766; found 252.0739 (ESI).

(4*S*,6*S*)-2-(but-3-en-1-yloxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21b



2.21b

A solution of 3-buten-1-ol (0.049 mL, 0.564 mmol) in THF (2.82 mL) was cooled to -40 ºC. Dropwise addition of a 2.4 M *n*-butyllithium in hexanes (0.224 mL, 0.537 mmol) resulted in a yellow colored solution that was stirred for about 10 minutes. (4*S*,6*S*)-2-chloro-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (56 mg, 0.268 mmol) was delivered as a solution in THF (0.536 mL) dropwise, via cannulation. The cold bath was dropped and the reaction was allowed to warm back to RT. After 80 minutes, the SM was completely consumed (determined by TLC analysis) and quenched with NH_4Cl (1 mL). The mixture was partitioned with EtOAc (5 mL) and H_2O (5 mL). Aqueous layer extracted three times with EtOAc (5 mL portions) and the collected organics were washed once with brine (5 mL), dried with Na_2SO_4 and filtered. Filtrate was concentrated under reduced pressure and purified via flash chromatography in 2:1, hexanes:EtOAc, yielding **2.21b** as a yellow oil (49 mg, 75% yield).

$[\alpha]_D$ +99.0 (*c* = 0.20, CH_2Cl_2);

FTIR (neat) 3080.11, 2916.17, 2848.67, 2360.71, 1647.10, 1641.31, 1280.65, 1265.22, 1012.56, 989.41, 736.76 cm^{-1};

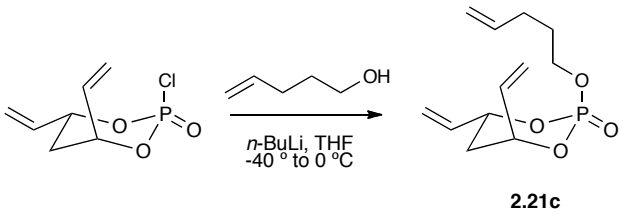
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.04 (ddd, *J* = 17.2, 10.6, 6.1 Hz, 1H), 5.91 (dddd, *J* = 17.3, 10.7, 5.2, 1.7 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.49-5.36 (m, 2H), 5.28-5.33 (m, 2H), 5.15 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1H), 5.10 (ddd, *J* = 10.3, 2.8, 1.2 Hz, 1H), 4.95-5.08 (m, 2H), 4.10-4.20 (m, 2H), 2.46 (q, *J* = 6.6 Hz, 2H), 2.17 (dddd, *J* = 14.7, 8.2, 4.9, 1.5 Hz, 1H), 2.05 (dddd, *J* = 14.7, 5.3, 3.6, 1.9 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 135.1 (d, J_{C-P} = 4.2 Hz), 135.0, 133.5, 118.2, 117.6 (d, J_{C-P} = 33.5 Hz), 77.8 (d, J_{C-P} = 6.8 Hz), 76.1 (d, J_{C-P} = 6.1 Hz), 66.9 (d, J_{C-P} = 5.9 Hz), 35.2 (d, J_{C-P} = 7.7 Hz), 34.7 (d, J_{C-P} = 6.6 Hz), 29.7;

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -7.01;

HRMS calculated for $C_{11}H_{17}NaO_4P$ $(M+Na)^+$ 267.0762; found 267.0732 (ESI).

(4*R*,6*R*)-2-(pent-4-en-1-yloxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21c



2.21c

A solution of 4-penten-1-ol (0.037 mL, 0.357 mmol) in THF (1.79 mL) was cooled to -40 ºC. Dropwise addition of *n*-butyllithium (0.142 mL, 0.340 mmol, 2.4 M in hexanes) resulted in a yellow colored solution, which was stirred at -40 ºC for about 10 minutes. (4*R*,6*R*)-2-chloro-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (0.071 mg, 0.357 mmol) in THF (0.680 mL) was added dropwise through cannulation. After consumption of SM (2 hours by TLC analysis), the reaction was quenched with NH_4Cl (1 mL) at 0 ºC and the mixture was allowed to warm to RT. Mixture was partitioned with EtOAc (5 mL) and H_2O (5 mL) and the aqueous layer was extracted with EtOAc (3x5mL). Collected organics were washed once with brine (5 mL), dried with anhydrous Na_2SO_4 and filtered. Filtrate was concentrated under reduced pressure and purified via flash chromatography in 2:1, hexanes:EtOAc. Phosphate **2.21c** was obtained as a yellow oil (67 mg, 81% yield).

$[\alpha]_D$ -69.1 (*c* = 0.33, CH_2Cl_2);

FTIR (neat) 3080.11, 2960.53, 2923.88, 2360.71, 2341.42, 2331.78, 1733.89, 1718.46, 1637.45, 1429.15, 1280.65, 1118.64, 1010.63, 968.20, 925.77 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.03 (ddd, *J* = 17.2, 10.6, 6.0 Hz, 1H), 5.92 (dddd, *J* = 17.3, 10.6, 5.2, 1.6 Hz, 1H), 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.47 (ddd, *J* = 17.1, 1.5, 0.9 Hz, 1H), 5.38 (ddd, *J* = 17.2, 1.4, 1.0 Hz, 1H), 5.29-5.33 (m, 2H), 4.95-5.08 (m, 4H), 4.09-4.14 (m,

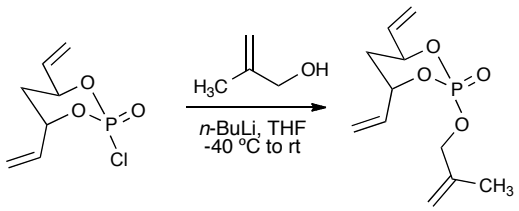
2H), 2.13-2.18 (m, 2H), 2.05 (dddd, J = 14.7, 5.4, 3.6, 1.8 Hz, 1H), 1.76-1.83 (m, 2H), 1.61 (s, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 137.2, 135.1 (d, $J_{C\text{-}P}$ = 1.4 Hz), 135.0 (d, $J_{C\text{-}P}$ = 2.5 Hz), 118.1, 117.5, 115.5, 77.6 (d, $J_{C\text{-}P}$ = 6.7 Hz), 76.1 (d, $J_{C\text{-}P}$ = 6.1 Hz), 67.3 (d, $J_{C\text{-}P}$ = 5.9 Hz), 35.2 (d, $J_{C\text{-}P}$ = 7.6 Hz), 29.6, 29.4 (d, $J_{C\text{-}P}$ = 6.8 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -6.91;

HRMS calculated for $C_{12}H_{19}O_4P$ $(M+Na)^+$ 281.0919; found 281.0886 (ESI).

(4*S*,6*S*)-2-((2-methylallyl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21d



2.21d

Alcohol (0.032 mL, 0.385 mmol) was taken up in THF (1.93 mL) and cooled to -40 ºC. Dropwise addition of a 2.4 M *n*-butyllithium solution in hexanes (0.160 mL, 0.385 mmol) provided a yellow colored solution, which was stirred for 10 minutes. Dropwise addition of a solution of (4*S*,6*S*)-2-chloro-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (73 mg, 0.350 mmol) in THF (0.700 mL) via cannulation provided no color change. The cold bath was dropped after addition and the reaction was stirred to RT for about 70 minutes. Consumption of SM was determined by TLC analysis and the reaction was quenched with NH_4Cl (1 mL) and partitioned with CH_2Cl_2 (5 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). Collected organics were washed once with brine (5 mL), dried with Na_2SO_4 and filtered. Filtrate was concentrated under reduced pressure and purified via flash chromatography in 3:2, hexanes:EtOAc. Collected fractions were concentrated under reduced pressure resulting in a yellow oil (69 mg, 81% yield).

$[\alpha]_D$ +59.6 (*c* = 0.55, CH_2Cl_2);

FTIR (neat) 3083.96, 2920.03, 2538.78, 2339.49, 1649.02, 1452.30, 1431.08, 1411.80, 1282.57, 1006.77, 925.77, 877.55 cm^{-1};

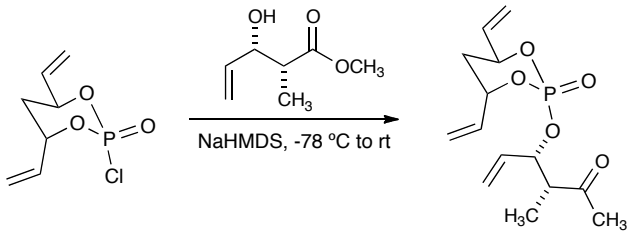
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.04 (ddd, *J* = 17.2, 10.6, 5.9 Hz, 1H), 5.91 (dddd, *J* = 17.3, 10.6, 5.2, 1.7 Hz, 1H), 5.36-5.49 (m, 2H), 5.28-5.34 (m, 2H), 4.94-5.09 (m, 4H), 4.50 (d, *J* = 7.2 Hz, 2H), 2.18 (dddd, *J* = 14.7, 8.1, 4.9, 1.5 Hz, 1H), 2.06 (dddd, *J* = 14.8, 5.3, 3.7, 1.9 Hz, 1H), 1.78 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 140.0 (d, J_{C-P} = 7.4 Hz), 135.0 (d, J_{C-P} = 3.0 Hz), 134.9 (d, J_{C-P} = 1.0 Hz), 118.2, 117.5, 113.4, 77.8 (d, J_{C-P} = 6.8 Hz), 76.2 (d, J_{C-P} = 6.1 Hz), 71.0 (d, J_{C-P} = 5.5 Hz), 35.1 (d, J_{C-P} = 7.7 Hz), 19.04;

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -7.02;

HRMS calculated for $C_{11}H_{17}O_4P$ $(M+Na)^+$ 267.0762; found 267.0744 (ESI).

(3*R*,4*S*)-3-methyl-4-(((4*S*,6*S*)-2-oxido-4,6-divinyl-1,3,2-dioxaphosphinan-2-yl)oxy)hex-5-en-2-one: 2.21e



2.21e

Alcohol (93 mg, 0.644 mmol) was taken up in THF (3.22 mL) and cooled to -78 ºC. A freshly prepared 1.0 M NaHMDS (0.644 mL, 0.644 mmol) in THF was added on dropwise and stirred for about 15 minutes. (4*S*,6*S*)-2-chloro-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (112 mg, 0.537 mmol) was delivered dropwise as a solution in THF (1.07 mL) via cannulation, in which the resulting yellow colored solution was allowed to warm to RT in the cold bath. After stirring for about 16.5 hours, the reaction was quenched with NH_4Cl (1 mL) and partitioned with H_2O (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). Collected organics were washed once with brine (5 mL), dried with Na_2SO_4 and filtered. Filtrate was concentrated under reduced pressure and purified via flash chromatography in 2:1, hexanes:EtOAc. After collecting the fractions of the major TLC spot, concentrating them under reduced pressure provided a yellow oil (73 mg, 43% yield).

$[\alpha]_D$ +59.6 (*c* =, CH_2Cl_2);

FTIR (neat) 2950.89, 2925.81, 2362.64, 2343.35, 1733.89, 1301.86, 1205.43, 1124.42, 1087.78, 997.13, 966.27, 877.55 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.05 (ddd, *J* = 17.2, 10.6, 6.0 Hz, 1H), 5.84-5.94 (m, 2H), 5.33-5.50 (m, 3H), 5.29 (dd, *J* = 10.6, 1.2 Hz, 3H), 5.22 (ddd, *J* =8.3, 6.2, 4.9, Hz, 1H), 4.95-5.08

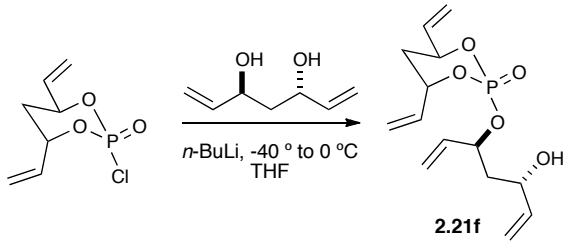
(m, 2H), 3.68 (s, 3H), 2.73-2.82 (m, 1H), 2.12-2.19 (m, 1H), 2.04 (dddd, J = 14.8, 5.5, 3.8, 1.9 Hz, 1H), 1.20 (d, J = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 173.3, 135.1 (d, J_{C-P} = 5.7 Hz), 135.1, 134.1 (d, J_{C-P} = 2.8 Hz), 118.6, 118.0, 117.5, 80.3 (d, J_{C-P} = 5.6 Hz), 78.0 (d, J_{C-P} = 7.0 Hz), 76.1 (d, J_{C-P} = 6.2 Hz), 52.0, 44.5 (d, J_{C-P} = 6.6 Hz), 35.1 (d, J_{C-P} = 7.7 Hz), 11.2;

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -7.96;

HRMS calculated for $C_{14}H_{21}O_6P$ $(M+Na)^+$ 339.0973; found 339.0944 (ESI).

(4*S*,6*S*)-2-(((3*S*,5*S*)-5-hydroxyhepta-1,6-dien-3-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21f



2.21f

(*S*,*S*)-diol **1.24** (37 mg, 0.292 mmol) was dissolved in THF (1.45 mL) and cooled to -40 ºC. Dropwise addition of *n*-butyllithium (0.123 mL, 0.292 mmol, 2.4 M in hexanes) gave a yellow colored solution, which was stirred at -40 ºC for about 10 minutes. A solution of (4*S*,6*S*)-2-chloro-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (58 mg, 0.278 mmol) in THF (0.556 mL) was delivered dropwise via cannulation. Reaction was quenched after 2.5 hours with saturated aq. NH_4Cl (1 mL) and partitioned with EtOAc (5 mL) and H_2O (5 mL). Aqueous layer was extracted with EtOAc (3 x 5mL). Collected organics were washed once with brine (5 mL), dried with anhydrous Na_2SO_4 and filtered. Filtrated was concentrated and purified via flash chromatography in 2:1, hexanes:EtOAc providing phosphate (25 mg, 30% yield) as a yellow oil.

$[\alpha]_D$ +32.0 (*c* = 0.35, CH_2Cl_2);

FTIR (neat) 3352.05, 3085.89, 2358.78, 2341.42, 1716.53, 1699.17, 1521.73, 1265.22, 1118.64, 1056.92, 989.41, 927.70, 873.69 cm^{-1};

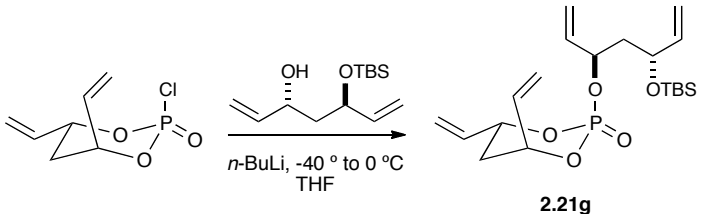
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.05 (ddd, *J* = 16.7, 10.7, 5.9 Hz, 1H), 5.82-5.96 (m, 3H), 5.27-5.45 (m, 6H), 5.20 (ddd, *J* = 10.4, 1.0 Hz, 1H), 5.05-5.15 (m, 3H), 4.91-4.96 (m, 1H), 4.42 (br s, 1H), 4.07-4.24 (br m, 1H), 2.20 (dddd, *J* = 14.9, 8.6, 5.0, 1.4, 1H), 2.05 (dddd, *J* = 14.8, 5.2, 3.3, 1.9 Hz, 1H), 1.83 (ddd, *J* = 14.0, 11.0, 2.7 Hz, 1H), 1.64-1.73 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 139.9, 136.6 (d, $J_{C\text{-}P}$ = 4.7 Hz), 134.8 (d, $J_{C\text{-}P}$ = 2.6 Hz), 134.7 (s, $J_{C\text{-}P}$ = 8.2 Hz), 118.3, 117.7, 117.2, 114.2, 78.7 (d, $J_{C\text{-}P}$ = 6.8 Hz), 76.6 (d, $J_{C\text{-}P}$ = 5.2 Hz), 75.9 (d, $J_{C\text{-}P}$ = 5.9 Hz), 67.0, 43.5 (d, $J_{C\text{-}P}$ = 3.9 Hz), 35.1 (d, $J_{C\text{-}P}$ = 7.5 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -5.32;

HRMS calculated for $C_{14}H_{21}O_5P$ $(M+Na)^+$ 323.1024; found 323.1011 (ESI).

(4*R*,6*R*)-2-(((3*R*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)hepta-1,6-dien-3-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21g



2.21g

Alcohol **S2** (119 mg, 0.501 mmol) was dissolved in THF (2.5 mL) and cooled to -40 ºC. Dropwise addition of *n*-butyllithium (0.190 mL, 0.455 mmol, 2.4 M solution in hexanes) gave a yellow colored solution, which was stirred at -40 ºC for about 10 minutes. A solution of (4*R*,6*R*)-2-chloro-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (95 mg, 0.455 mmol) dissolved in THF (0.910 mL) was added dropwise via cannlae. The resultant solution was allowed to warm slowly to 0 ºC. After 3 hours, saturated aq. NH_4Cl (1 mL) was added slowly at 0 ºC and the mixture was allowed to warm to RT. The mixture was partitioned with EtOAc (5 mL) and H_2O (5 mL) and the aqueous layer was extracted with EtOAc (3x5 mL). Collected organics were washed once with brine (5 mL), dried with Na_2SO_4 and filtered. Filtrate was concentrated under reduced pressure and purified via flash chromatography in 4:1, hexanes:EtOAc. The collected product was a yellow oil (77 mg, 41% yield).

$[\alpha]_D$ -49.2 (*c* = 0.12, CH_2Cl_2);

FTIR (neat) 2954.74, 2927.74, 2358.78, 2341.42, 1716.53, 1558.38, 1521.73, 1506.30, 1284.50, 1259.43, 1083.92, 991.34, 835.12, 777.26 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz)[5] δ ppm 6.02 (ddd, *J* = 17.2, 10.6, 5.2 Hz, 1H), 5.85-5.95 (m, 2H), 5.80 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.31-5.46 (m, 3H), 5.29 (dd, *J* = 10.6, 5.3 Hz, 2H), 5.22

[5] Peak at δ 1.57 is presumed to be a H_2O peak, which was difficult to remove.

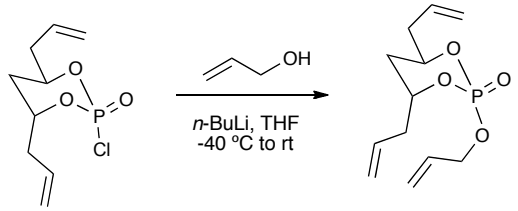
(dt, J = 10.4, 0.9 Hz, 1H), 5.15 (dt, J = 17.2, 1.3 Hz, 1H), 5.01-5.08 (m, 2H), 4.91-4.98 (m, 2H), 4.22-4.27 (m, 1H), 2.15 (dddd, J = 14.5, 7.7, 4.7, 1.4 Hz, 1H), 2.04 (dddd, J = 14.6, 5.6, 3.8, 1.8 Hz, 1H), 1.93 (ddd, J = 14.0, 8.1, 4.8 Hz, 1H), 1.75-1.82 (m, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 141.3, 136.9 (d, $J_{C\text{-}P}$ = 2.3 Hz), 135.3 (d, $J_{C\text{-}P}$ = 3.8 Hz), 135.2, 135.1, 117.8, 117.7, 117.4, 114.6, 77.8 (d, $J_{C\text{-}P}$ = 6.0 Hz), 77.4, 75.9, 75.8, 70.5, 44.7 (d, $J_{C\text{-}P}$ = 7.3 Hz), 35.3 (d, $J_{C\text{-}P}$ = 7.5 Hz), 25.9 (3), 18.1;

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -7.90;

HRMS calculated for $C_{20}H_{35}O_5PSi$ $(M+Na)^+$ 437.1889; found 437.1860 (ESI).

(4*R*,6*R*)-4,6-diallyl-2-(allyloxy)-1,3,2-dioxaphosphinane 2-oxide: 2.22



S1 **2.22**

Allyl alcohol (0.013 mL, 0.195 mmol) was dissolved in THF (0.975 mL) and cooled to -40 ºC. Dropwise addition of *n*-butyllithium (0.074 mL, 0.177 mmol, 2.4 M solution in hexanes) provided a yellow colored solution, which was stirred for about 10 minutes. Phosphoryl chloride **S1** (0.042 mg, 0.177 mmol) was added as a solution in THF (0.354 mL) dropwise via cannulation. Reaction was allowed back to RT and stirred for about 90 minutes (**S1** consumed by TLC analysis), at which saturated aqueous NH_4Cl (1 mL) was added. Mixture was partitioned with H_2O (5 mL) and EtOAc (5 mL) and the aqueous layer was extracted with EtOAc (3x5 mL). Collected organics were washed once with brine (5 mL), dried with anhydrous Na_2SO_4 and filtered. Filtrate was concentrated under reduced pressure and purified via flash chromatography in 2:1, hexanes:EtOAc. Phosphate **2.22** was isolated as a yellow oil (29 mg, 63% yield).

$[\alpha]_D$ +29.1 (*c* = 0.33, CH_2Cl_2);

FTIR (neat) 3076.25, 2927.74, 2538.78, 2341.42, 1645.17, 1286.43, 1095.49, 1016.42, 975.91, 919.98 cm^{-1};

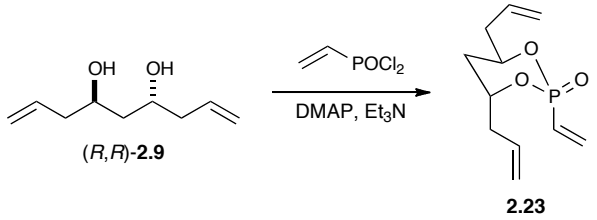
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.96 (ddd, *J* = 22.6, 10.9, 5.6 Hz, 1H), 5.72-5.84 (m, 2H), 5.37 (ddd, *J* = 17.1, 3.0, 1.5 Hz, 1H), 5.26 (ddd, *J* = 10.4, 2.4, 1.2 Hz, 1H), 5.12-5.18 (m, 4H), 4.49-4.67 (m, 4H), 2.63-2.70 (m, 1H), 2.56 (dtd, *J* = 14.3, 6.6, 1.2 Hz, 1H), 2.35-2.44 (m, 2H), 1.99-2.07 (m, 1H), 1.88 (dddd, *J* = 14.7, 5.3, 3.6, 1.9 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 132.6 (d, J_{C-P} = 7.0 Hz), 132.5, 132.2, 119.0, 118.8, 118.3, 77.3 (d, J_{C-P} = 7.1 Hz), 75.5 (d, J_{C-P} = 6.7 Hz), 68.1 (d, J_{C-P} = 5.3 Hz), 39.9 (d, J_{C-P} = 7.6 Hz), 38.8 (d, J_{C-P} = 3.0 Hz), 33.0 (d, J_{C-P} = 6.9 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -6.21;

HRMS calculated for $C_{12}H_{19}O_4P$ $(M+H)^+$ 259.1099; found 259.1069 (ESI).

(4*R*,6*R*)-4,6-diallyl-2-vinyl-1,3,2-dioxaphosphinane 2-oxide: 2.23



(*R*,*R*)-diol **2.9** (34 mg, 0.218 mmol) was taken up in CH_2Cl_2 (1.09 mL) at RT. DMAP (2.67 mg, 0.0218 mmol) and Et_3N (0.136 mL, 0.979 mmol) were added and the solution was cooled to 0 ºC. Freshly prepared vinylphosphonyl dichloride[6] (0.034 mL, 0.326 mmol) was added dropwise, resulting in a white suspension. After 20 min, **2.9** was consumed (verified by TLC analysis) and the suspension was diluted with Et_2O (5 mL) to crash out amine salts. Salts were filtered from the liquid through a fritted funnel and rinsed thoroughly with Et_2O (20 mL). The filtrate was concentrated under reduced pressure and purified through a plug of SiO_2 in 1:2, hexanes:EtOAc. Collected fractions were concentrated under reduced pressure to give a yellow colored oil (44 mg, 88% yield).

$[\alpha]_D$ +60.5 (*c* = 0.40, CH_2Cl_2);

FTIR (neat) 3083.96, 2880.24, 2358.78, 2341.42, 2331.78, 1701.10, 1670.24, 1280.65, 1118.64, 1006.77, 991.34, 931.55 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.24-6.35 (m, 1H), 6.05-6.18 (m, 2H), 5.72-5.82 (m, 2H), 5.12-5.20 (m, 3H), 4.71 (tdd, *J* = 11.7, 6.5, 5.0 Hz, 1H), 4.33-4.42 (m, 1H), 2.63-2.70 (m, 1H), 2.33-2.55 (m, 3H), 2.04 (dddd, *J* = 14.5, 6.2, 4.5, 1.5 Hz, 1H), 1.89-1.96 (m, 1H);

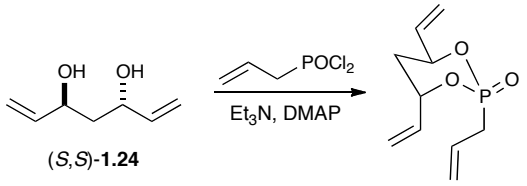
[6] Synthesis of vinylphosphonyl dichloride: Herpel, R. H.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *Tetrahedron Lett.* **2006**, *47,* 6429-6432.

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 135.6 (d, J_{C-P} = 1.8 Hz), 132.5, 132.1, 126.8, 125.3, 118.9 (d, J_{C-P} = 9.9 Hz), 75.2 (d, J_{C-P} = 6.7 Hz), 73.2 (d, J_{C-P} = 6.5 Hz), 40.1 (d, J_{C-P} = 3.9 Hz), 40.0 (d, J_{C-P} = 2.1 Hz), 33.9 (d, J_{C-P} = 6.7 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm 12.57;

HRMS calculated for $C_{11}H_{17}O_3P$ $(M+Na)^+$ 251.0813; found 251.0837 (ESI).

(4*S*,6*S*)-2-allyl-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.24



(*S*,*S*)-**1.24** **2.24**

(*S*,*S*)-diol **1.24** (82 mg, 0.640 mmol) was taken up in toluene (5.0 mL) at RT. After addition of Et_3N (0.223 mL, 1.60 mmol) and DMAP (8 mg, 0.0640 mmol), the reaction flask was cooled to -40 ºC. A solution of allylphosphonic dichloride[7] (0.115 mL, 0.960 mmol) in toluene (1 mL) was added dropwise over 30 minutes. The reaction was allowed to warm slowly in the cold bath to RT. After the SM was consumed (determined by TLC analysis), the solution was concentrated under reduced pressure and the resulting residue was purified on flash chromatography (1:2, hexanes:EtOAc). Collected fractions from the column were concentrated under reduced pressure to give a clear oil (127 mg, 93% yield).

$[\alpha]_D$ +82.9 (*c* = 0.35, CH_2Cl_2);

FTIR (neat) 3083.96, 2923.88, 2358.78, 2331.78, 1652.88, 1637.45, 1419.51, 1263.29, 1118.64, 1026.06, 925.77 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.00 (ddd, *J* = 17.0, 10.7, 5.3 Hz, 1H), 5.75-5.90 (m, 2H), 5.53 (ddd, 17.1, 1.5, 0.9 Hz, 1H), 5.20-5.40 (m, 5H), 5.04-5.10 (m, 1H), 4.85-4.95 (m, 1H), 2.73 (ddt, *J* = 22.3, 7.4, 1.2 Hz, 2H), 2.03-2.17 (m, 2H);

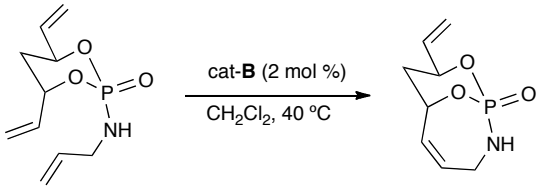
^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 135.6 (d, $J_{C\text{-}P}$ = 7.0 Hz), 135.4 (d, $J_{C\text{-}P}$ = 3.0 Hz), 127.3 (d, $J_{C\text{-}P}$ = 12.1 Hz), 120.2 (d, $J_{C\text{-}P}$ = 15.0 Hz), 117.9, 117.1, 76.5 (d, $J_{C\text{-}P}$ = 7.6 Hz), 73.1 (d, $J_{C\text{-}P}$ = 6.7 Hz), 35.6 (d, $J_{C\text{-}P}$ = 7.7 Hz), 32.8 (d, $J_{C\text{-}P}$ = 140.2 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm 21.69;

[7] Allylphosphonic dichloride was purchased from Acros Organics.

HRMS calculated for $C_{10}H_{15}O_3P$ $(M+Na)^+$ 237.0657; found 237.0648 (ESI).

(1*S*,6*S*,8*S*)-8-vinyl-9,10-dioxa-2-aza-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide: 2.26a



2.21a **2.26a**

Phosphoramidate **2.21a** (20 mg, 0.0873 mmol) was taken up in dry and degassed (with Ar for 15 minutes) CH_2Cl_2 (6.0 mL) and heated to 40 ºC. Cat-**B** (1.5 mg, 0.0017 mmol) was added and the solution turned a brown color. After refluxing for 6 hours, SM material was completely consumed (by TLC analysis). The reaction was allowed to cool to RT and the solution was concentrated under reduced pressure. The resulting residue was purified via flash chromatography in EtOAc. After collecting fractions and concentrating them under reduced pressure a white solid was obtained (17 mg, 94% yield).

$[\alpha]_D$ +61.5 (*c* = 0.33, CH_2Cl_2);

FTIR (neat) 3257.55, 3240.19, 2956.67, 2923.88, 2852.52, 2358.78, 2331.78, 1677.95, 1612.38, 1247.86, 1122.49, 1087.78, 1035.70, 1000.99, 966.27, 943.13, 921.91, 873.69 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.00-6.05 (m, 1H), 5.88 (dddd, *J* = 17.3, 10.6, 5.3, 1.8 Hz, 1H), 5.47 (ddd, *J* = 11.9, 3.7, 2.7 Hz, 1H), 5.41 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.23 (dt, *J* = 10.6, 1.2 Hz, 1H), 5.16 (d, *J* = 21.1 Hz, 1H), 5.03-5.07 (m, 1H), 4.01-4.08 (m, 1H), 3.33-3.46 (m, 1H), 3.09 (s, 1H), 2.21 (ddd, *J* = 14.5, 11.9, 6.0 Hz, 1H), 1.73 (ddd, *J* = 14.5, 3.5, 2.1 Hz, 1H);

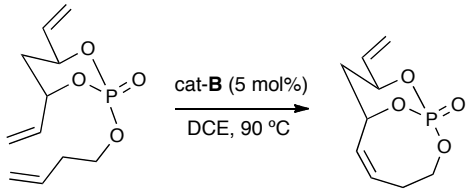
^{13}C NMR ($CDCl_3$, 125 MHz)[8] δ ppm 135.5 (d, $J_{C\text{-}P}$ = 10.1 Hz) 130.2, 128.1, 116.8, 76.8 (d, $J_{C\text{-}P}$ = 6.6 Hz) 74.9 (d, $J_{C\text{-}P}$ = 6.1 Hz) 38.9, 35.4 (d, $J_{C\text{-}P}$ = 6.0 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -5.63;

HRMS calculated for $C_8H_{12}NO_3P$ $(M+Na)^+$ 224.0452; found 224.0421 (ESI).

[8] Broad singlet at δ 1.65 is presumed to result from water.

(1*S*,7*S*,9*S*,*Z*)-9-vinyl-2,10,11-trioxa-1-phosphabicyclo[5.3.1]undec-5-ene 1-oxide: 2.26b



2.21b **2.26b**

Phosphate **2.21b** (19 mg, 0.0778 mmol) was dissolved in dry (passed through basic Al_2O_3) and degassed (with Ar for 15 minutes) 1,2-dichloroethane (5.2 mL) and heated to 90 ºC. Cat-B (3.3 mg, 0.00389 mmol) was added resulting in an immediate color change from red to brown. After stirring for about 90 minutes, the reaction was cooled to RT. The solution was concentrated under reduced pressure and the resulting residue was purified via flash chromatography in 1:2, hexanes:EtOAc. Collected fractions were concentrated under reduced pressure providing a white solid (12 mg, 71% yield).

$[\alpha]_D$ +94.0 (*c* = 0.45, CH_2Cl_2);

FTIR (neat) 3477.42, 2927.74, 2358.78, 2341.42, 2331.78, 1647.10, 1618.17, 1286.43, 1022.20, 1000.99, 966.27 cm^{-1};

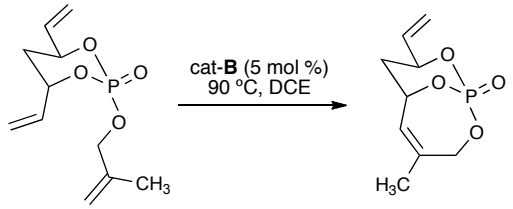
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.78-5.88 (m, 2H), 5.53 (d, *J* = 11.7 Hz, 1H), 5.41 (d, *J* = 17.5 Hz, 1H), 5.31 (br s, 1H), 5.22-5.28 (m, 1H), 5.06 (dd, *J* = 11.9, 5.3 Hz, 1H), 4.46 (ddd, *J* = 10.7, 6.7, 1.7 Hz, 1H), 3.78 (dddd, *J* = 29.2, 15.1, 11.1, 4.1 Hz, 1H), 3.29-3.39 (m, 1H), 2.19 (ddd, *J* = 14.6, 12.1, 6.0 Hz, 1H), 2.13 (ddd, *J* = 13.4, 8.7, 4.0 Hz, 1H), 1.81 (dd, *J* = 14.6, 1.6 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 135.0 (d, $J_{C\text{-}P}$ = 10.0 Hz ppm), 131.2, 126.4, 117.3 (d, $J_{C\text{-}P}$ = 1.2 Hz), 78.2 (d, $J_{C\text{-}P}$ = 7.2 Hz), 77.1 (d, $J_{C\text{-}P}$ = 6.1 Hz), 63.0 (d, $J_{C\text{-}P}$ = 5.2 Hz), 36.2 (d, $J_{C\text{-}P}$ = 6.6 Hz), 26.8;

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -7.43;

HRMS calculated for $C_9H_{13}O_4P$ $(M+Na)^+$ 239.0449; found 239.0437 (ESI).

(1*S*,6*S*,8*S*)-4-methyl-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide: 2.26c



2.21d **2.26c**

Phosphate **2.21d** (23 mg, 0.0942 mmol) was dissolved in dry 1,2-dichloroethane (6.3 mL), which was degassed by bubbling with argon for ~15 min. After heating the solution to 90 ºC, cat-**B** (4.0 mg, 0.00471 mmol) was added and kept at reflux for 10 hours. Upon completion, the mixture was cooled to RT and concentrated under reduced pressure. Residue was purified via flash chromatography in 1:2, hexanes:EtOAc providing a brown oil (16 mg, 80% yield).

$[\alpha]_D$ +19.5 (c = 0.60, CH_2Cl_2);

FTIR (neat) 2923.88, 2358.78, 2341.42, 1699.17, 1558.38, 1299.93, 1134.07, 1114.78, 1056.92, 1020.27, 999.06, 966.27, 904.55, 873.69, 831.26, 802.33 cm^{-1};

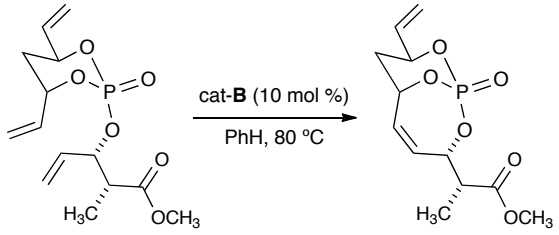
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.86 (dddd, J = 17.2, 10.6, 5.4, 2.0 Hz, 1H), 5.42 (dt, J = 17.2, 1.2 Hz, 1H), 5.30-5.32 (m, 1H), 5.26 (dt, J = 10.6, 1.1 Hz, 1H), 5.14 (br d, J = 24.6 Hz, 1H), 5.00-5.06 (m, 2H), 4.17 (dd, J = 27.3, 14.5 Hz, 1H), 2.20 (ddd, J = 14.5, 12.1, 6.0 Hz, 1H), 1.85 (d, J = 0.6 Hz, 3H), 1.77 (ddd, J = 14.6, 3.6, 2.3 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 136.5, 134.8 (d, $J_{C\text{-}P}$ = 10.4 Hz), 123.1, 117.4, 76.4, (d, $J_{C\text{-}P}$ = 6.1 Hz), 66.9 (d $J_{C\text{-}P}$ = 6.3 Hz), 35.4 (d, $J_{C\text{-}P}$ = 6.0 Hz), 29.7, 23.1;

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -3.61;

HRMS calculated for $C_9H_{13}O_4P$ $(M+Na)^+$ 239.0449; found 239.0425 (ESI).

(*R*)-3-((1*S*,3*S*,6*S*,8*S*)-1-oxido-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-3-yl)butan-2-one: 2.26d



2.21e **2.26d**

Phosphate **2.21e** (26 mg, 0.0822 mmol) was taken up in dry (passed through plug of basic Al_2O_3) and degassed (with Ar for 15 minutes) benzene (8.22 mL) and heated to 80 ºC. Cat-**B** (3.5 mg, 0.00411 mmol) was added and the solution immediately turned to a brown color. After about 2 hours, a second portion of cat-B (3.5 mg) was added to the refluxing solution. TLC analysis showed after 4.5 hours complete consumption of SM and the reaction was allowed to cool to RT. The solution was concentrated under reduced pressure and the resulting residue was purified via flash chromatography in 1:2, hexanes:EtOAc. After concentrating the collected fractions under reduced pressure, a white solid was obtained (19 mg, 79% yield).

$[\alpha]_D$ +37.5 (*c* = 0.16, CH_2Cl_2);

FTIR (neat) 2921.96, 2358.78, 2341.42, 1733.89, 1699.17, 1301.86, 1124.42, 1087.78, 966.27 cm^{-1};

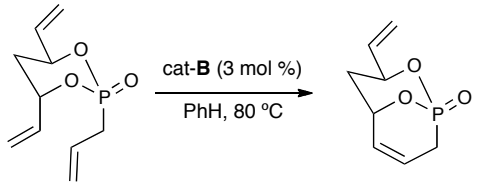
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.92 (ddd, *J* = 11.9, 3.0, 2.1 Hz, 1H), 5.85 (dddd, *J* = 13.9, 10.7, 5.3, 3.2 Hz, 1H), 5.58 (ddd, *J* = 11.9, 3.9, 2.4 Hz, 1H), 5.36-5.45 (m, 2H), 5.25-5.28 (m, 1H), 5.15-5.24 (m, 1H), 4.96-5.02 (m, 1H), 3.74 (s, 3H), 2.76-2.83 (p, *J* = 7.0 Hz, 1H), 2.21 (ddd, *J* = 14.7, 12.1, 6.2 Hz, 1H), 1.79 (ddd, *J* = 14.7, 3.6, 2.3 Hz, 1H), 1.32 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 173.0, 134.6 (d, J_{C-P} = 10.4 Hz), 130.7, 129.6, 117.4 (d, J_{C-P} = 1.1 Hz), 76.9, 76.3 (d, J_{C-P} = 6.2 Hz), 74.2 (d, J_{C-P} = 5.7 Hz), 52.2, 44.5 (d, J_{C-P} = 10.4 Hz), 34.9 (d, J_{C-P} = 6.0 Hz), 12.6;

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -5.21;

HRMS calculated for $C_{12}H_{17}O_6P$ $(M+Na)^+$ 311.0660; found 311.0637 (ESI).

(1*S*,3*S*,5*S*)-3-vinyl-2,9-dioxa-1-phosphabicyclo[3.3.1]non-6-ene 1-oxide: 2.26e



2.24 **2.26e**

Phosphonate **2.24** (25 mg, 0.117 mmol) was taken up in dry benzene (12 mL), which was not degassed. After addition of cat-**B** (3.0 mg, 0.0035 mmol), the reaction was brought to reflux. After 3 hours, the reaction was cooled to RT (SM consumed by TLC) and the solution was concentrated under reduced pressure. Flash chromatography (EtOAc) provided a colorless oil (19.1 mg, 88% yield).

$[\alpha]_D$ +58.7 (*c* = 0.55, CH_2Cl_2);

FTIR (neat) 3442.70, 2956.67, 2925.81, 1649.02, 1598.88, 1298.00, 1249.79, 1074.28, 1016.42, 941.20, 981.41, 784.97 cm^{-1};

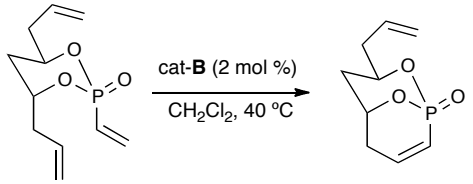
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.08-5.97 (dddd, *J* = 34.0, 10.2, 5.0, 3.2 Hz, 1H), 5.83-5.88 (m, 2H), 5.39 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.27-5.33 (m, 1H), 5.21 (d, *J* = 10.6 Hz, 1H), 4.98-5.05 (m, 1H), 2.70-2.83 (m, 1H), 2.45-2.57 (m, 1H), 2.25 (ddd, *J* = 14.6, 11.8, 4.4 Hz, 1H), 1.74 (ddd, *J* = 14.5, 5.1, 2.1 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 135.4 (d, $J_{C\text{-}P}$ = 7.7 Hz), 127.2 (d, $J_{C\text{-}P}$ = 13.7 Hz), 125.7 (d, $J_{C\text{-}P}$ = 8.9 Hz), 117.0, 78.2 (d, $J_{C\text{-}P}$ = 6.2 Hz), 76.7 (d, $J_{C\text{-}P}$ = 6.4 Hz), 34.3 (d, $J_{C\text{-}P}$ = 6.5 Hz), 24.5 (d, $J_{C\text{-}P}$ = 124.9 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm 15.84;

HRMS calculated for $C_8H_{11}O_3P$ $(M+Na)^+$ 209.0344; found 209.0323 (ESI).

(1*R*,3*R*,5*R*)-3-allyl-2,9-dioxa-1-phosphabicyclo[3.3.1]non-7-ene 1-oxide: 2.26f



2.23 **2.26f**

Phosphonate **2.23** (19 mg, 0.0833 mmol) was taken up in CH_2Cl_2 (8.3 mL) that had been degassed for 15 min by bubbling through with Ar. After heating the solution to 40 ºC, cat-**B** (1.4 mg, 0.00167 mmol) was added. The reaction was complete in less than 15 minutes (determined by TLC analysis) and was quenched with 2-3 drops of H_2O. The mixture was cooled to RT and then concentrated. Purification via flash chromatography (1:2, hexanes:EtOAc) yielded a white solid (12 mg, 71% yield).

$[\alpha]_D$ -25.0 (*c* = 0.20, CH_2Cl_2);

FTIR (neat) 2918.10, 2358.78, 2341.42, 1608.52, 1276.79, 1091.63, 1039.56, 945.05, 802.33 cm^{-1};

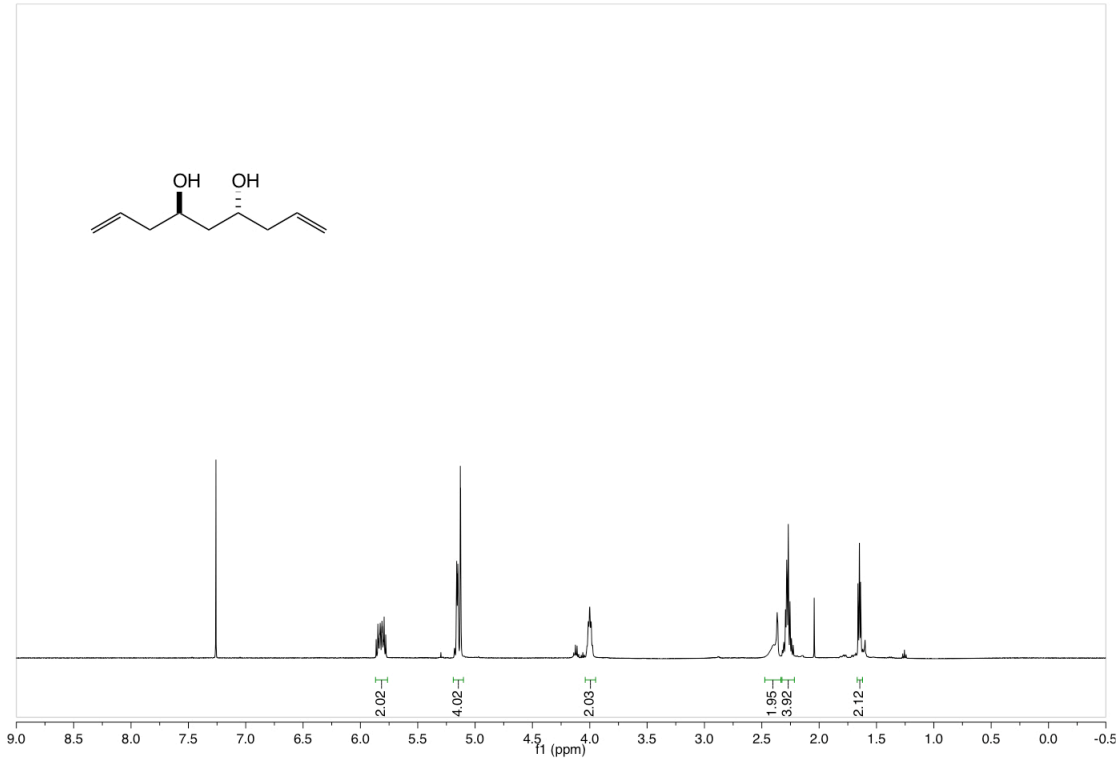
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 6.85 (ddddd, *J* = 44.5, 12.8, 4.3, 2.8, 1.2 Hz, 1H), 5.95 (dddd, *J* = 18.6, 12.8, 2.7, 1.9, 1H), 5.75-5.84 (m, 1H), 5.13-5.16 (m, 1H), 5.12 (t, *J* = 1.1 Hz, 1H), 5.01 (ddd, *J* = 16.9, 6.9, 5.7 Hz, 1H), 4.44 (dtd, *J* = 8.4, 6.1, 2.3 Hz, 1H), 2.96-3.05 (m, 1H), 2.46-2.53 (m, 1H), 2.33-2.41 (m, 1H), 2.18-2.29 (m, 2H), 1.67 (ddd, *J* = 14.6, 4.3, 2.2 Hz, 1H) ppm;

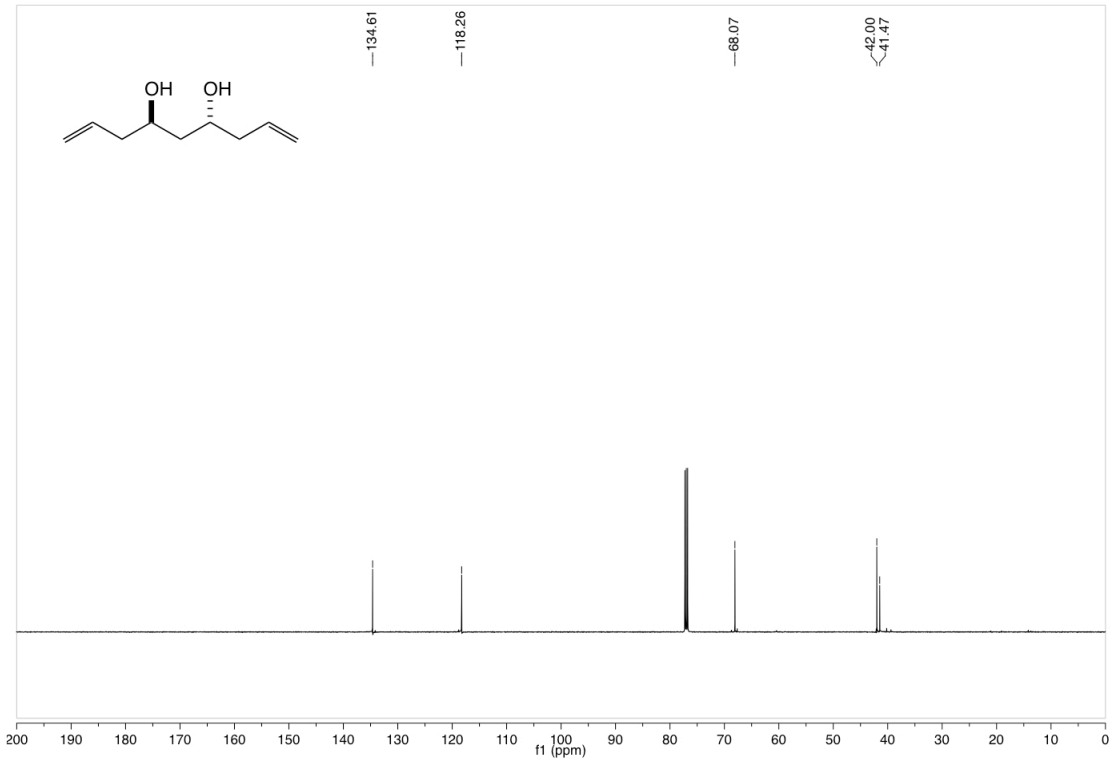
^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 147.7 (d, $J_{C\text{-}P}$ = 0.9 Hz), 132.2, 118.9, 117.1 (d, $J_{C\text{-}P}$ = 161.4 Hz), 76.4 (d, $J_{C\text{-}P}$ = 6.0 Hz), 76.0 (d, $J_{C\text{-}P}$ = 5.6 Hz), 40.5 (d, $J_{C\text{-}P}$ = 8.5 Hz), 36.7 (d, $J_{C\text{-}P}$ = 7.2 Hz), 31.7 (d, $J_{C\text{-}P}$ = 13.2 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -6.13;

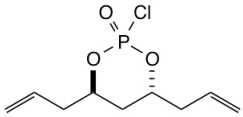
HRMS calculated for $C_9H_{13}O_3P$ $(M+Na)^+$ 223.0500; found 223.0482 (ESI).

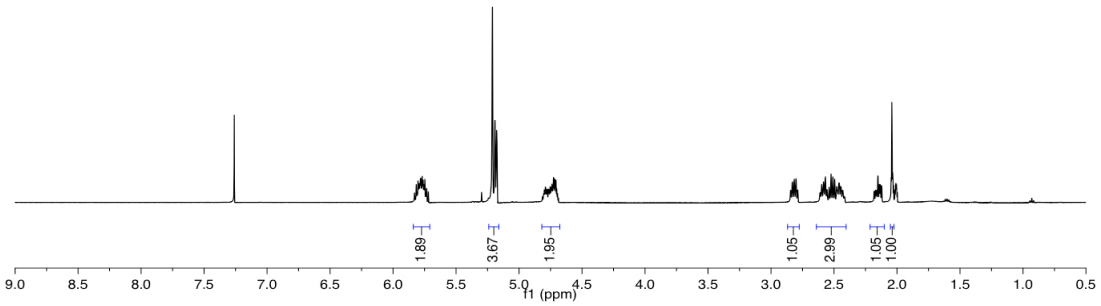
(4*R*,6*R*)-nona-1,8-diene-4,6-diol: 2.9

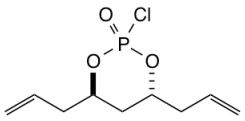


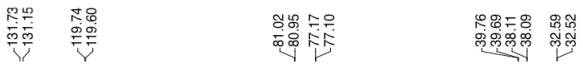


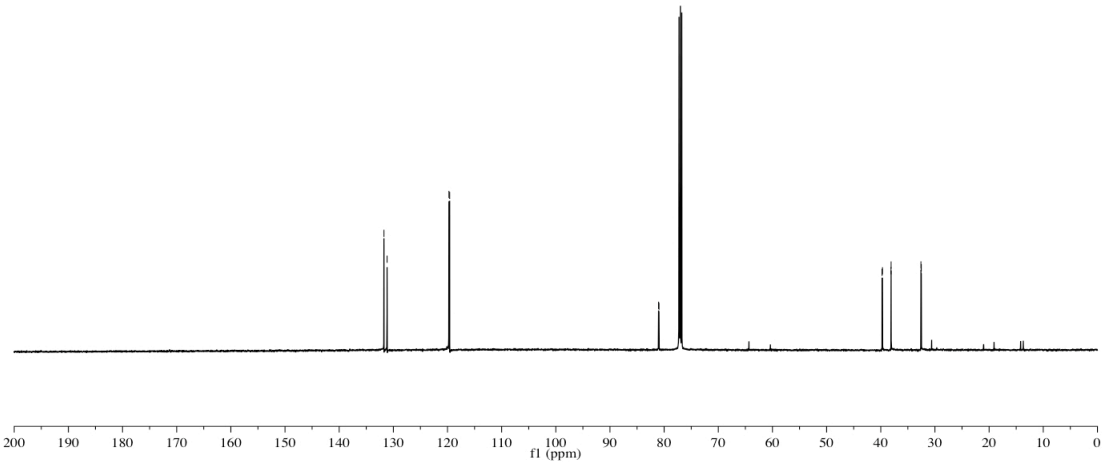
(4*R*,6*R*)-4,6-diallyl-2-chloro-1,3,2-dioxaphosphinane 2-oxide: S1

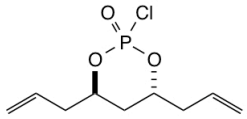











O
Cl
P
O
O

-3.84
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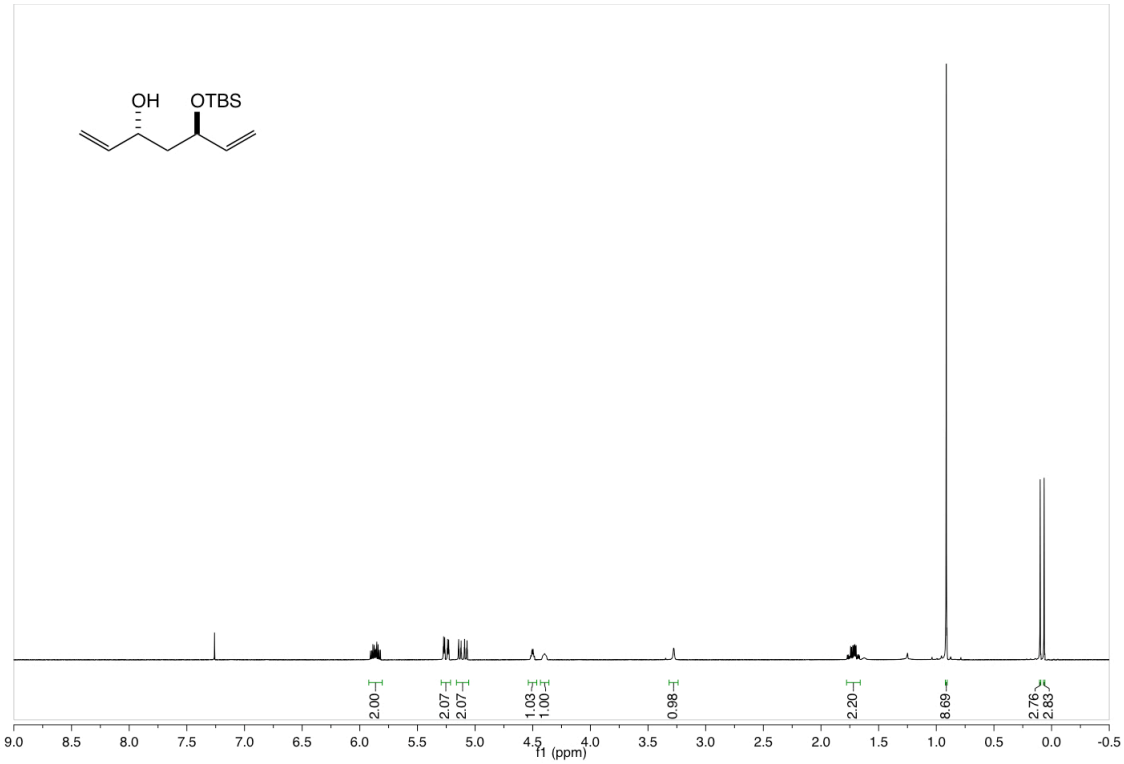
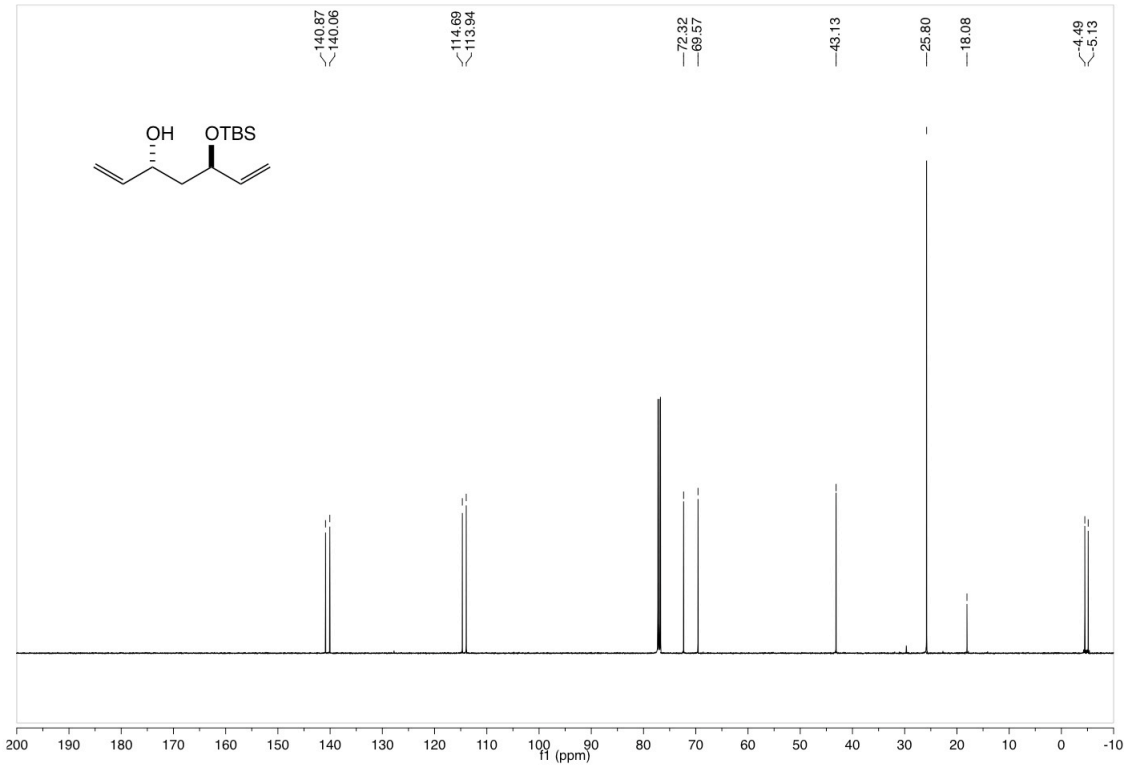
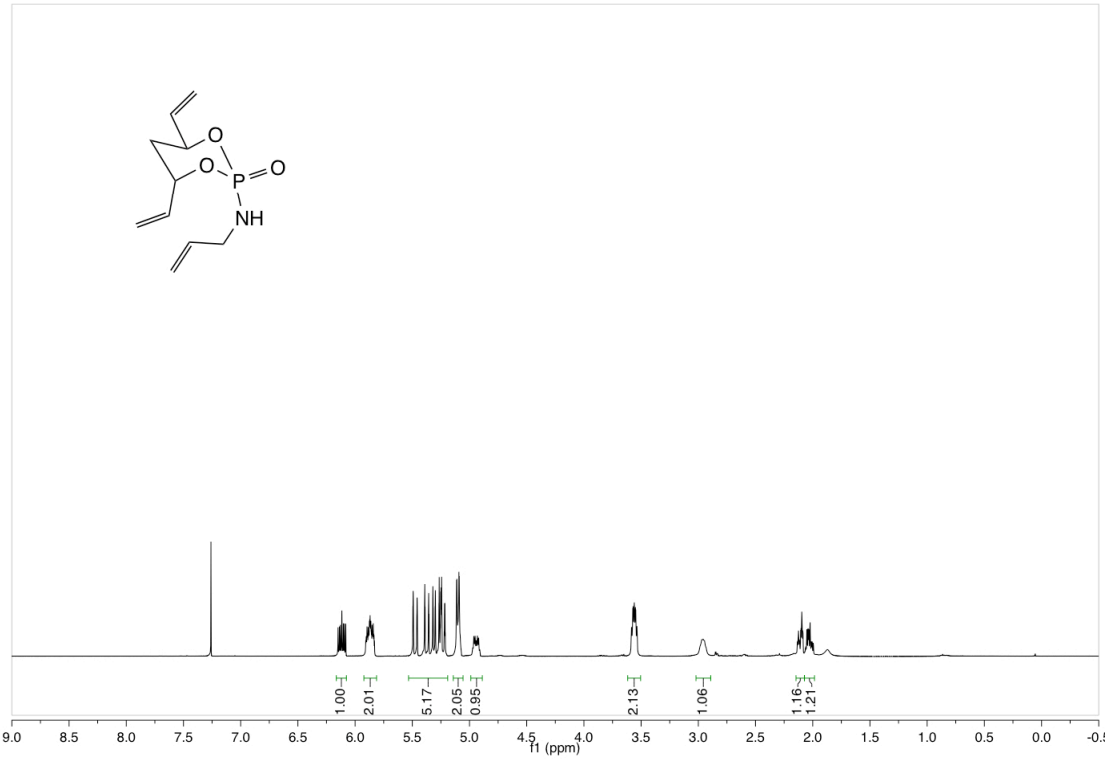
45
40
35
30
25
20
15
10
5
0
f1 (ppm)
-5
-10
-15
-20
-25
-30
-35
-40
-45

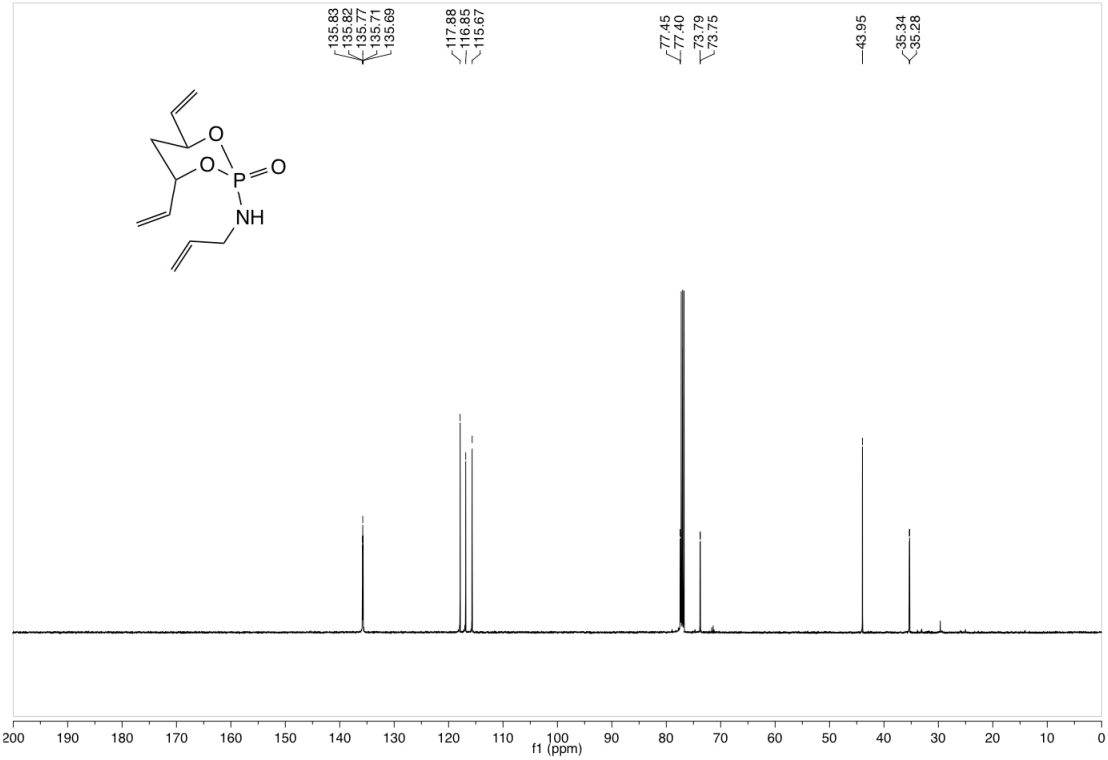
(3*R*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)hepta-1,6-dien-3-ol: S2

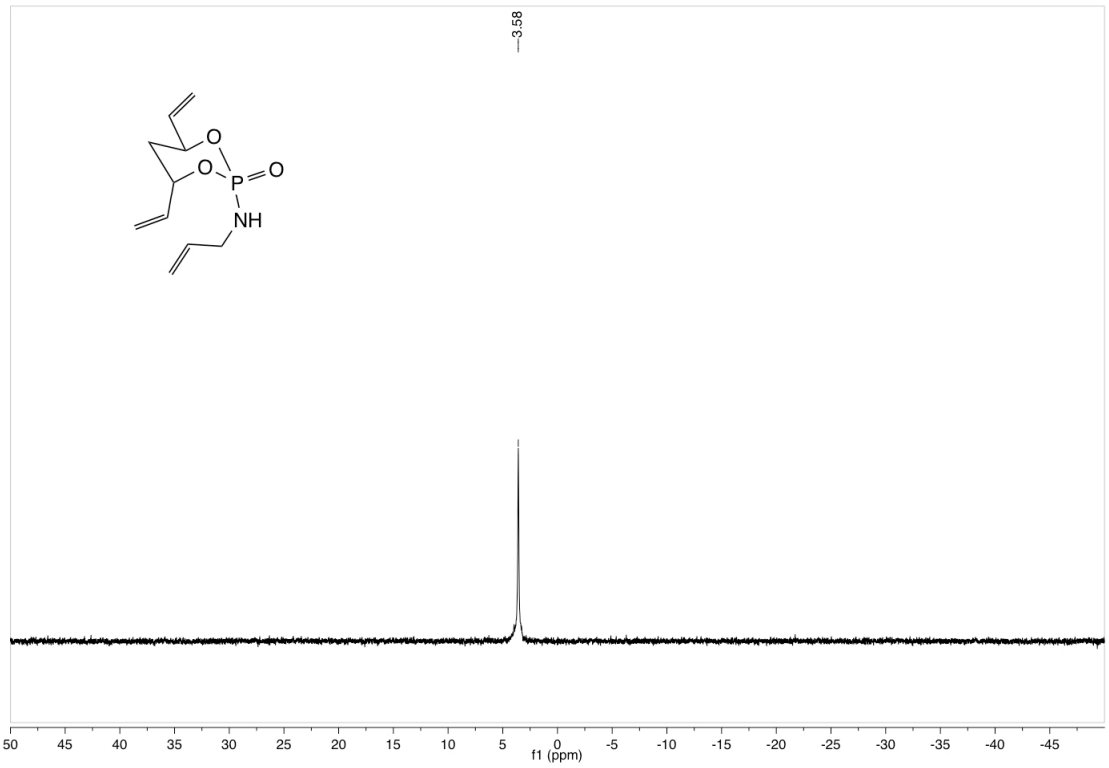




(4*S*,6*S*)-2-(allylamino)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21a






3.58
O
O
P
O
NH
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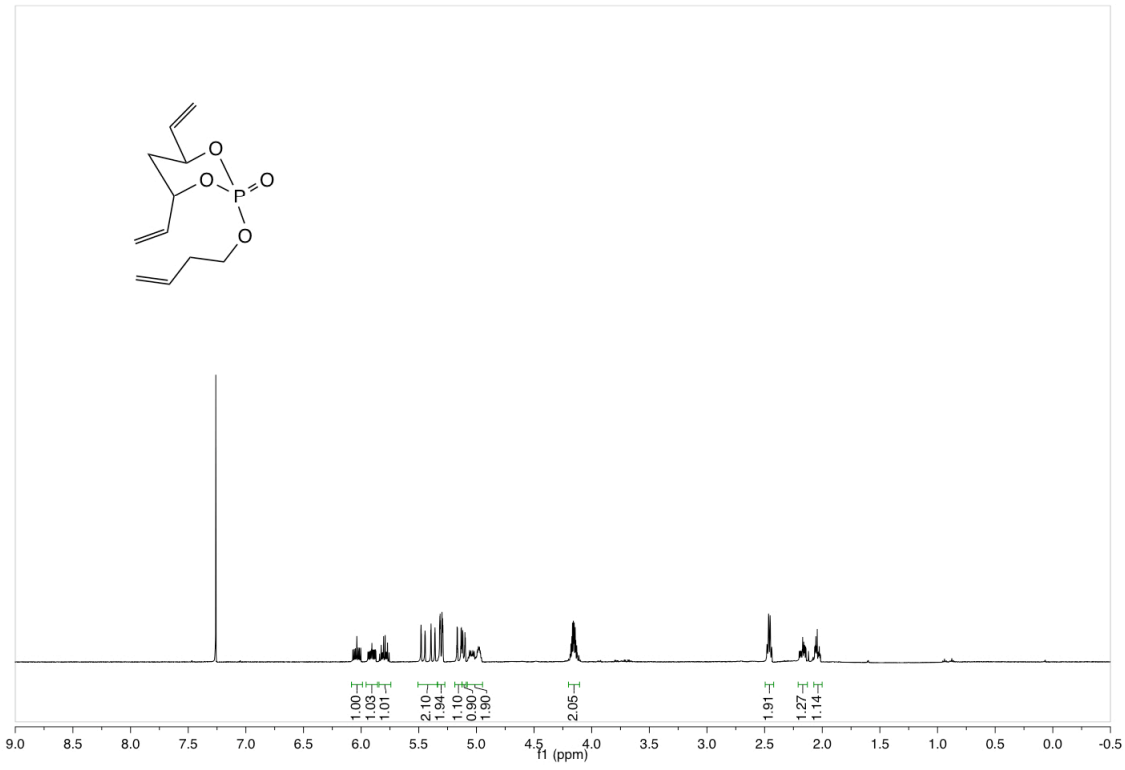
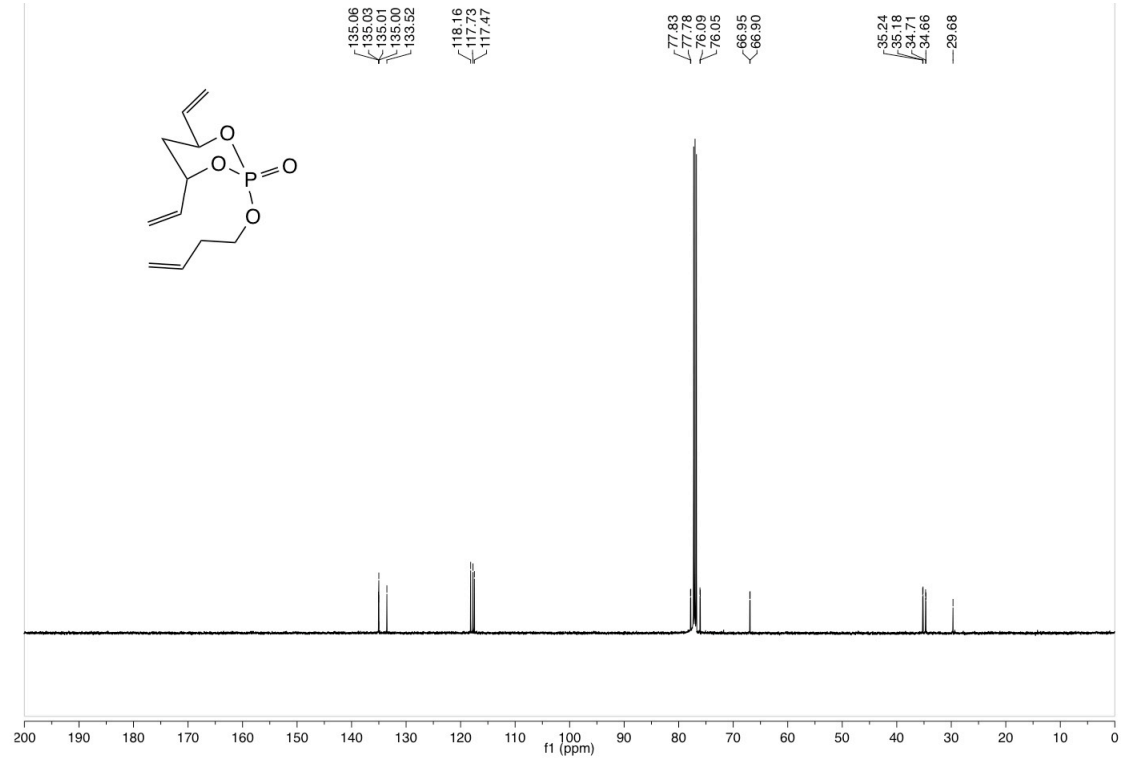
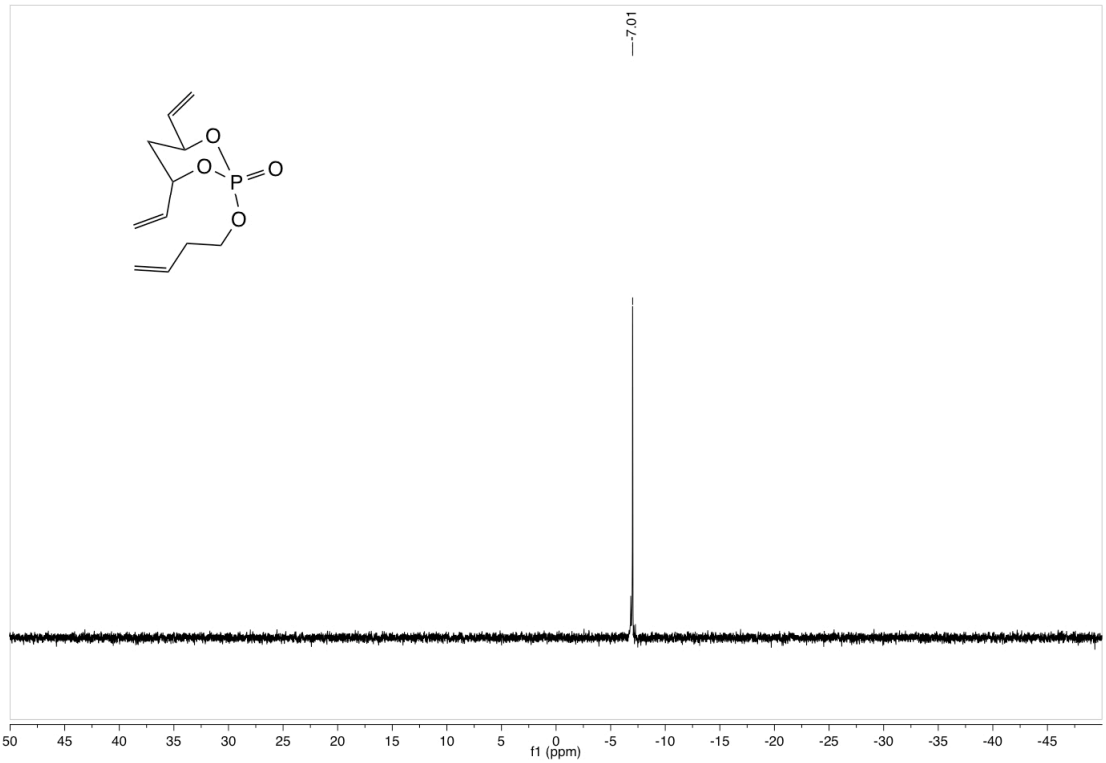
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

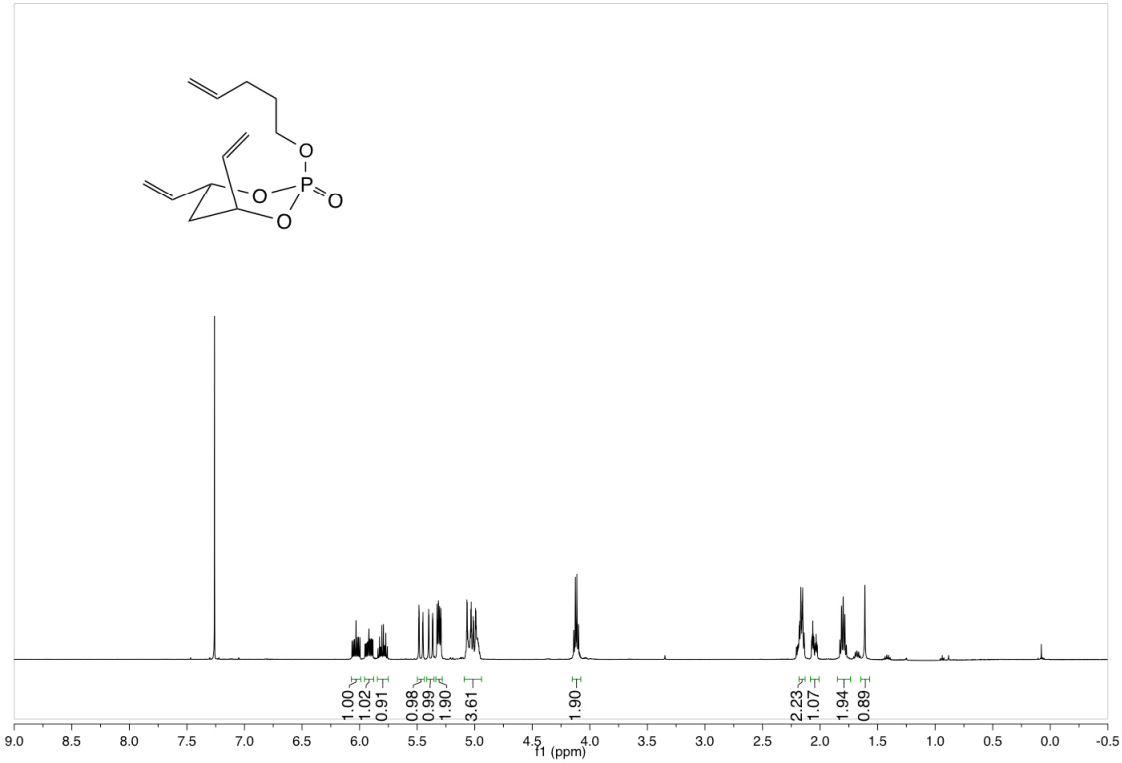
(4*S*,6*S*)-2-(but-3-en-1-yloxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21b

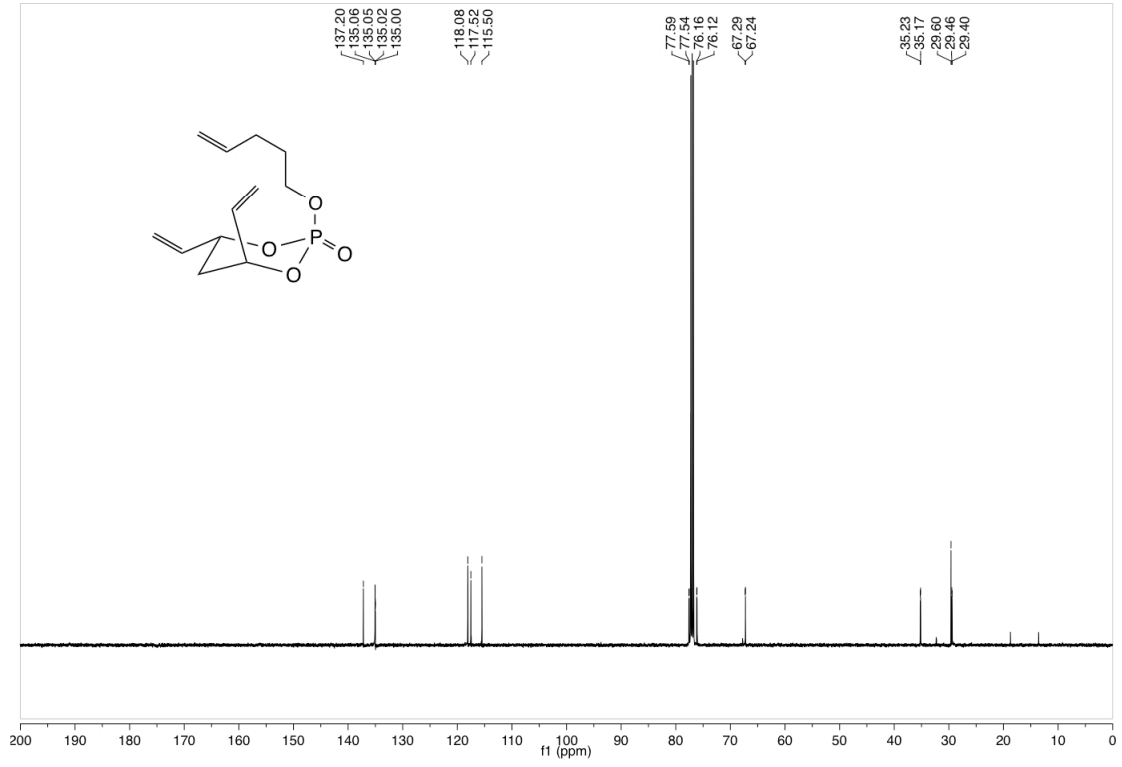


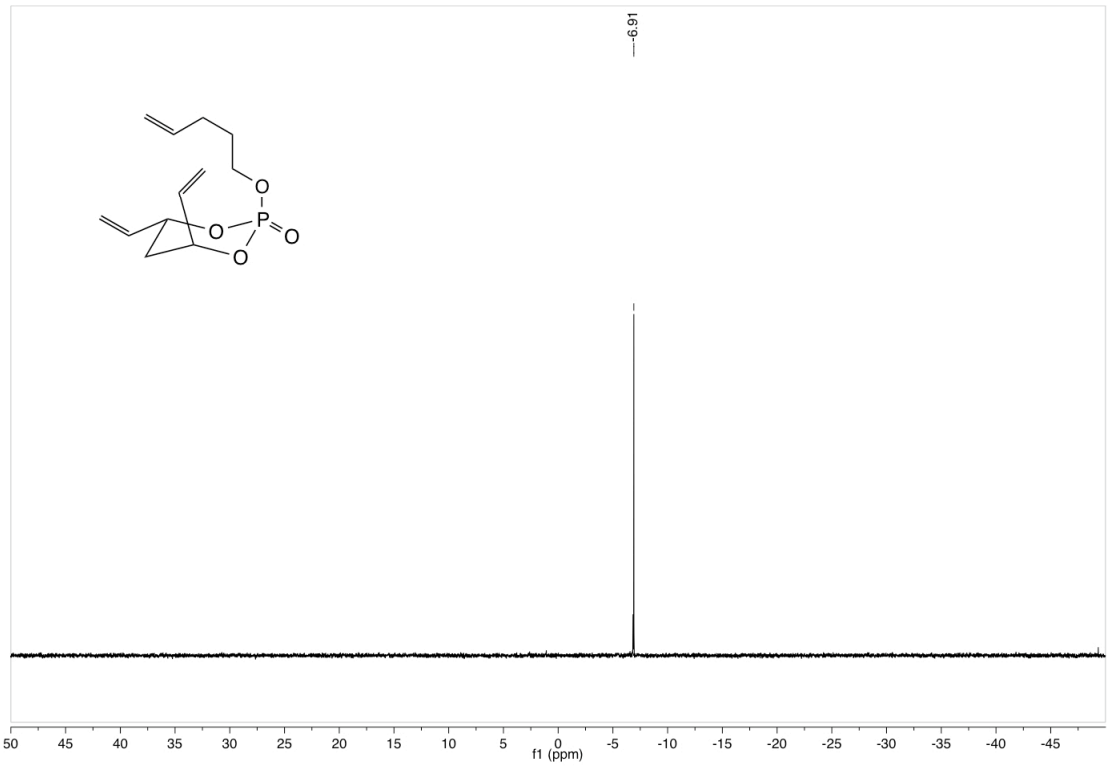



-7.01
O
O
P
O
O
50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45
f1 (ppm)

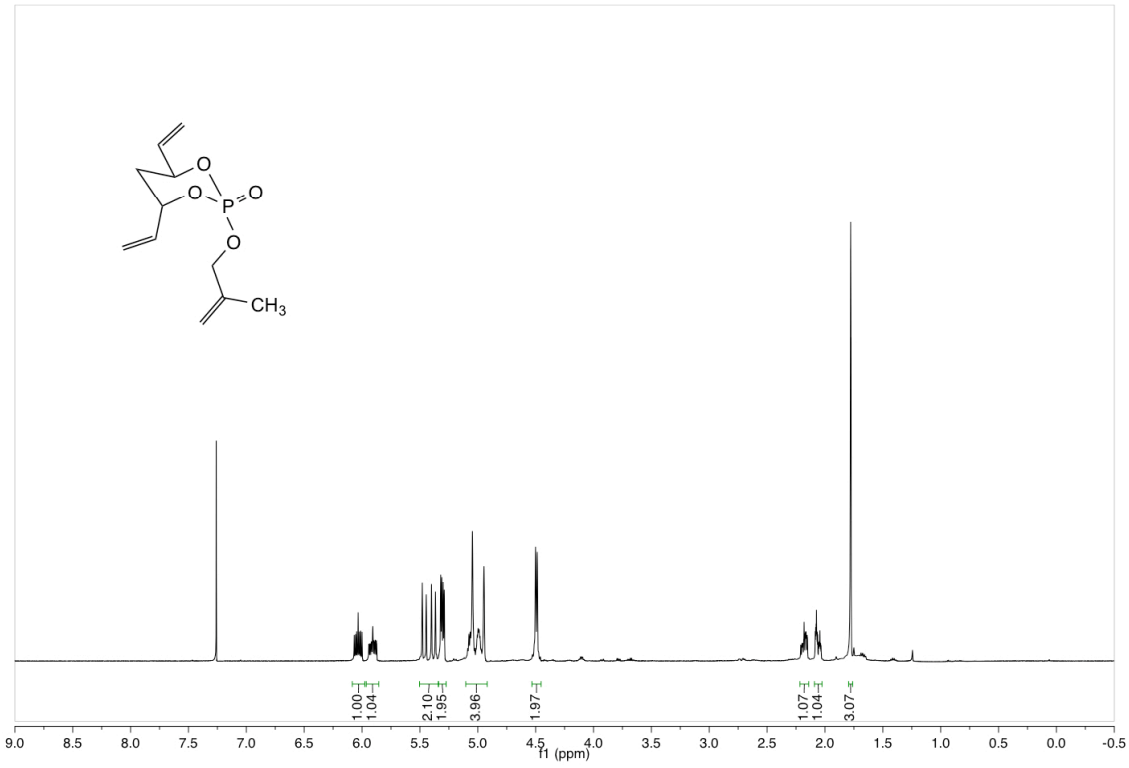
(4*R*,6*R*)-2-(pent-4-en-1-yloxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21c

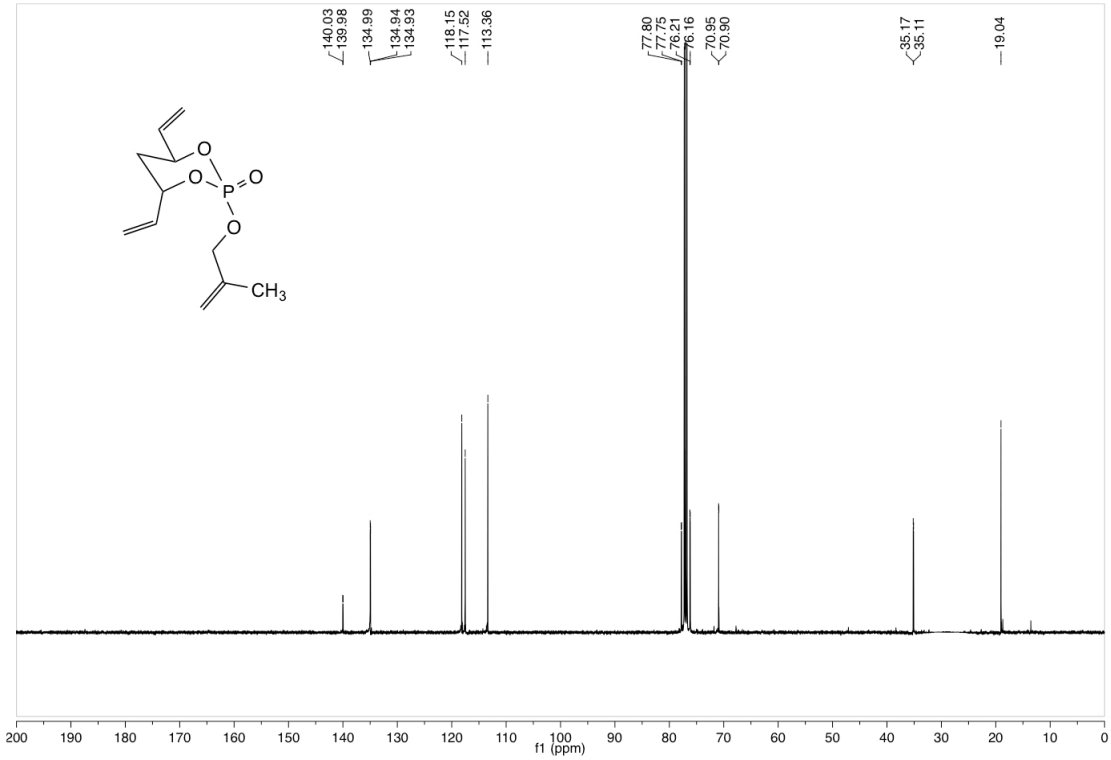


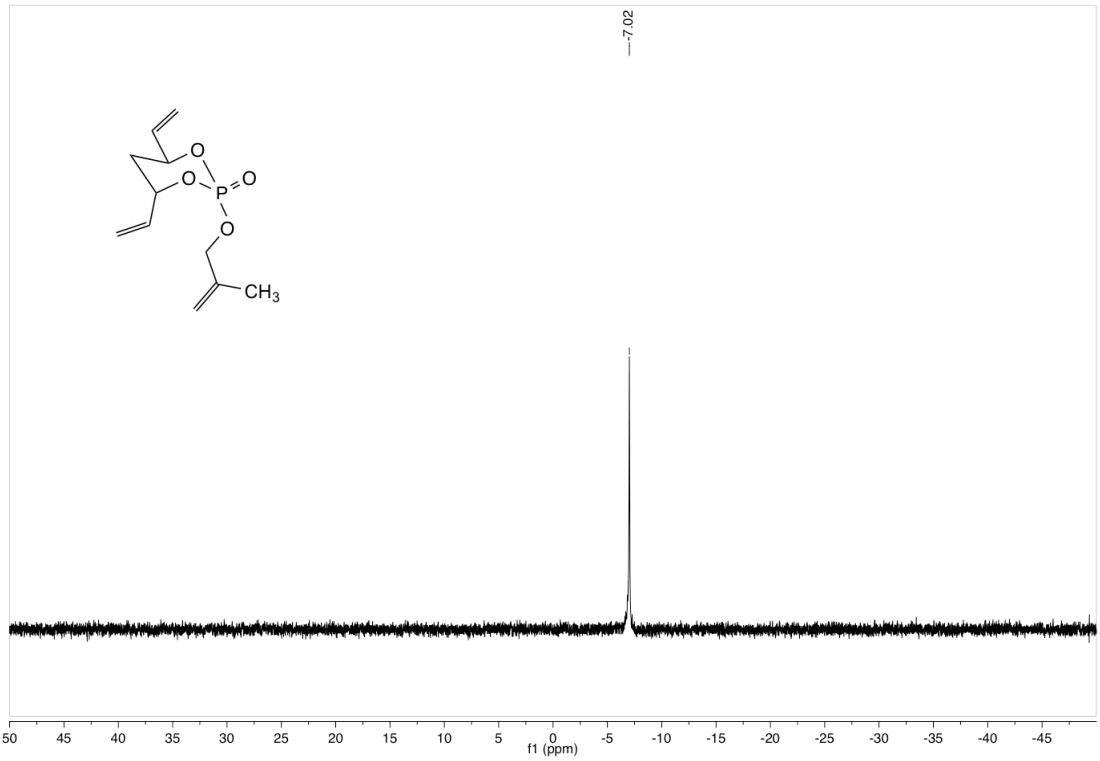



-6.91
O
P
O
O
O
50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45
f1 (ppm)

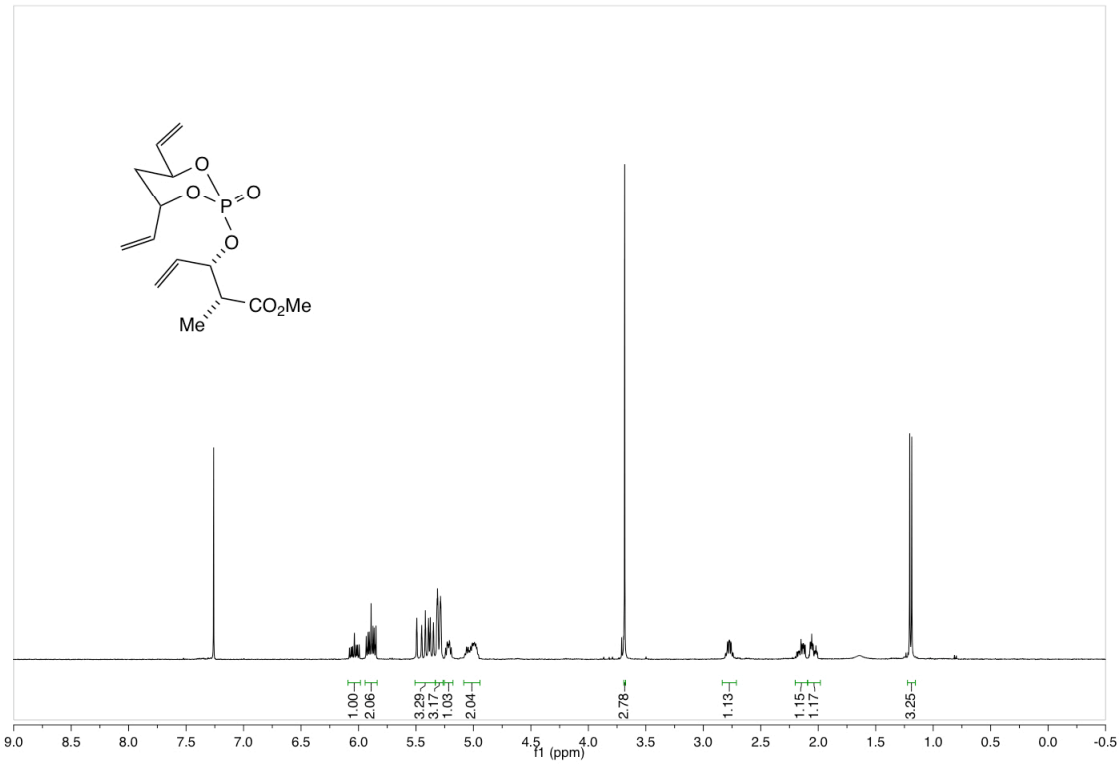
(4*S*,6*S*)-2-((2-methylallyl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21d

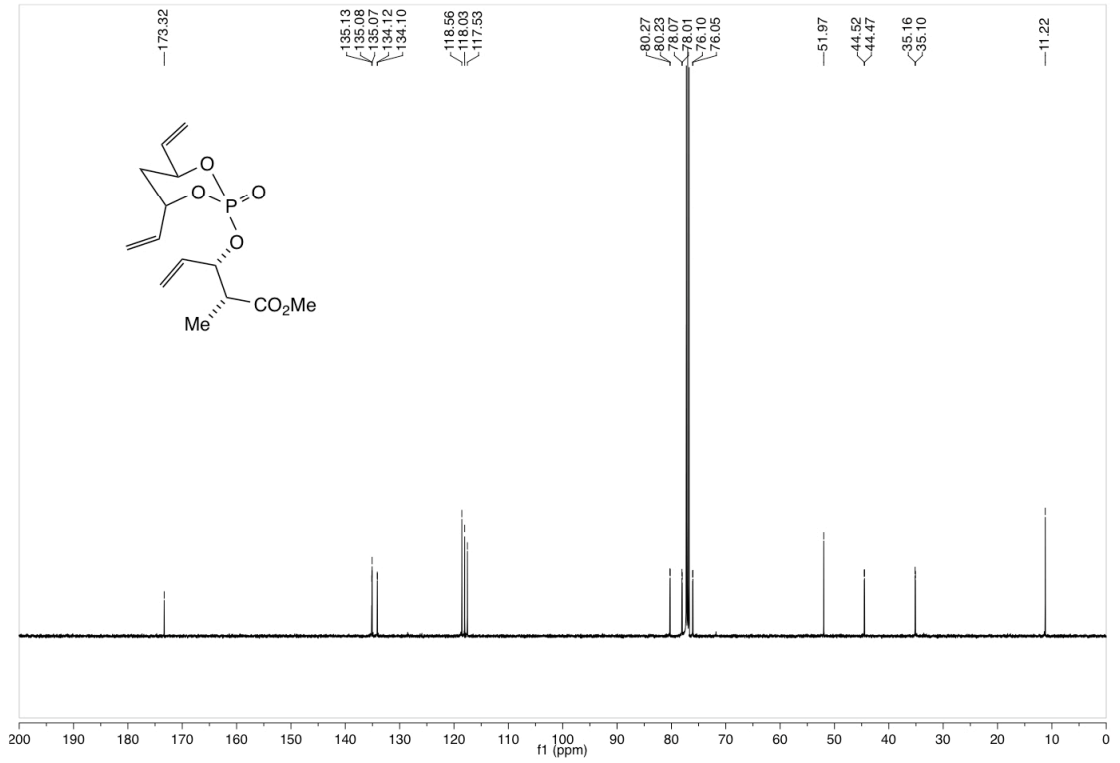


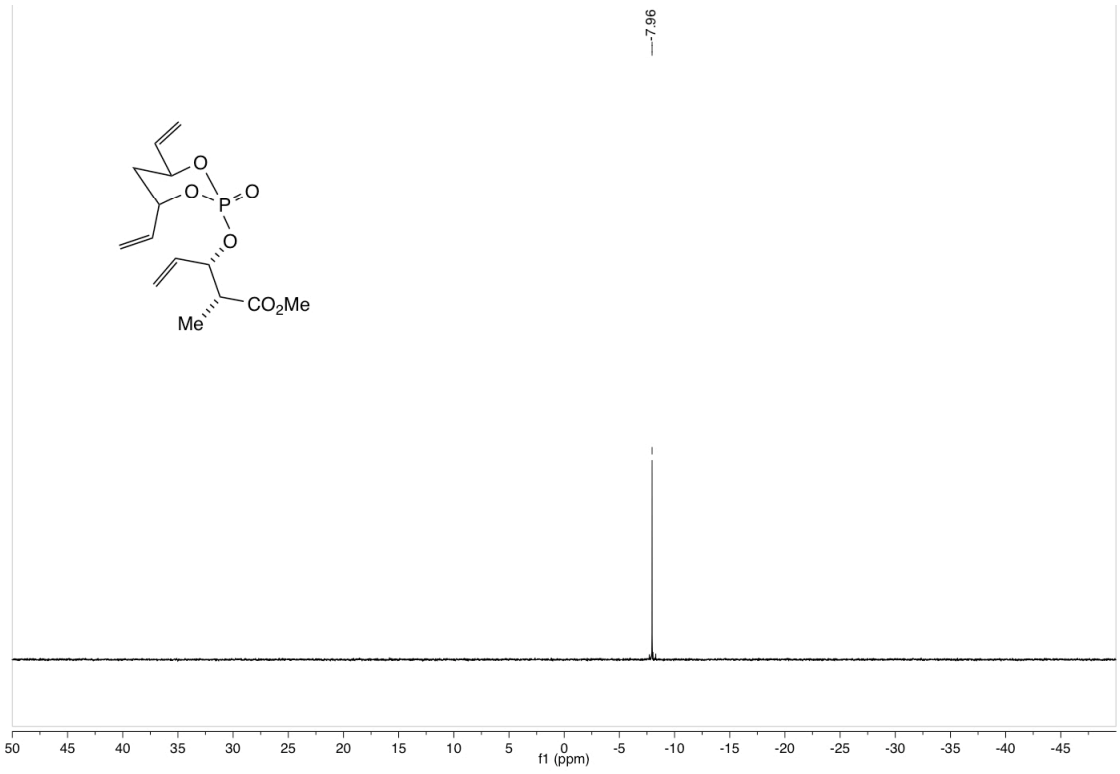



-7.02
O
O
P
O
O
CH3
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

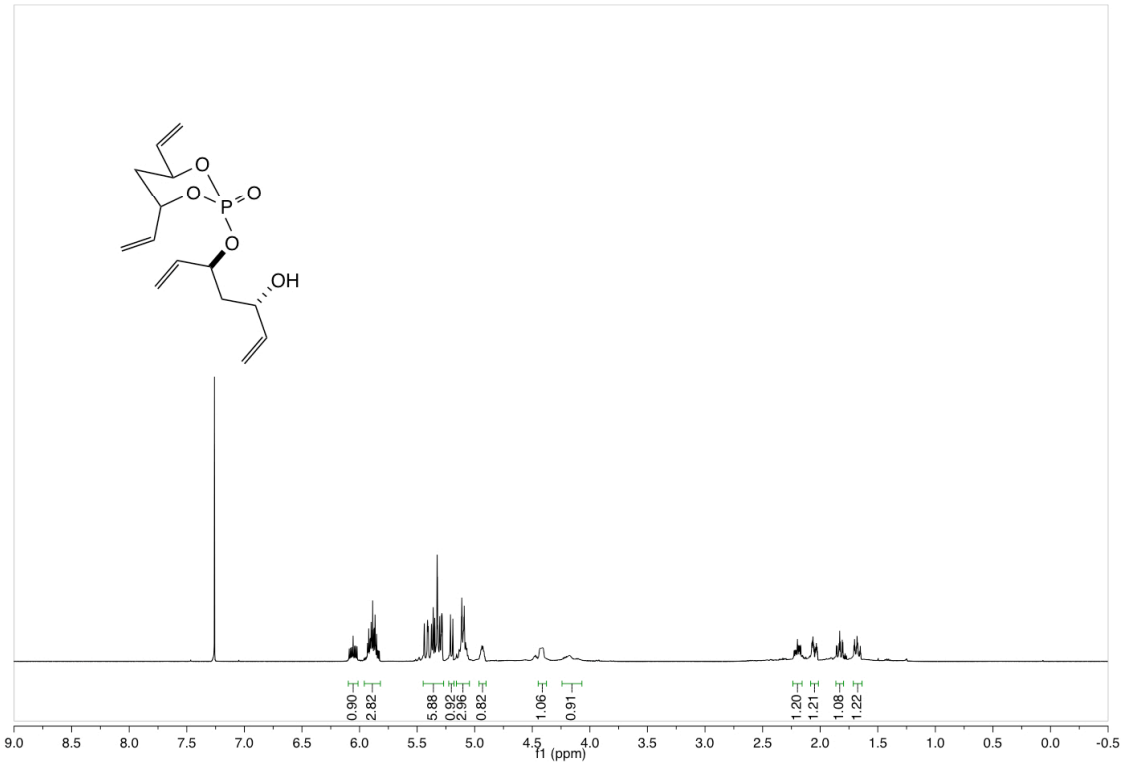
(3*R*,4*S*)-3-methyl-4-(((4*S*,6*S*)-2-oxido-4,6-divinyl-1,3,2-dioxaphosphinan-2-yl)oxy)hex-5-en-2-one: 2.21e

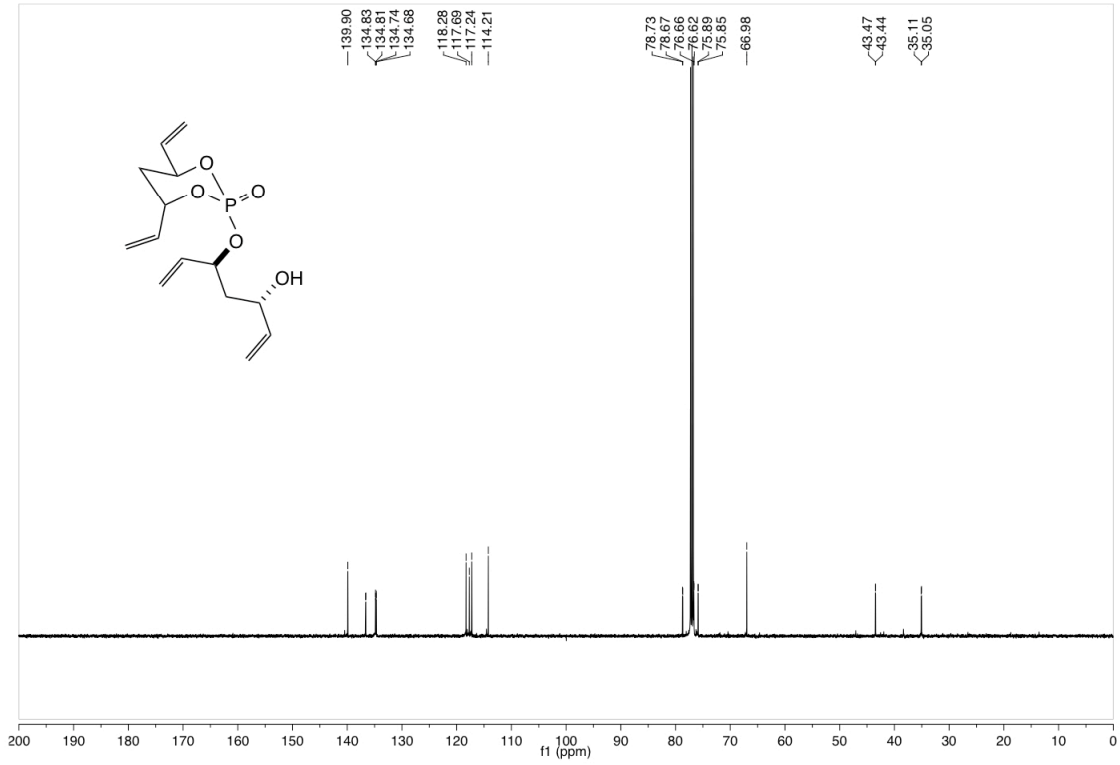


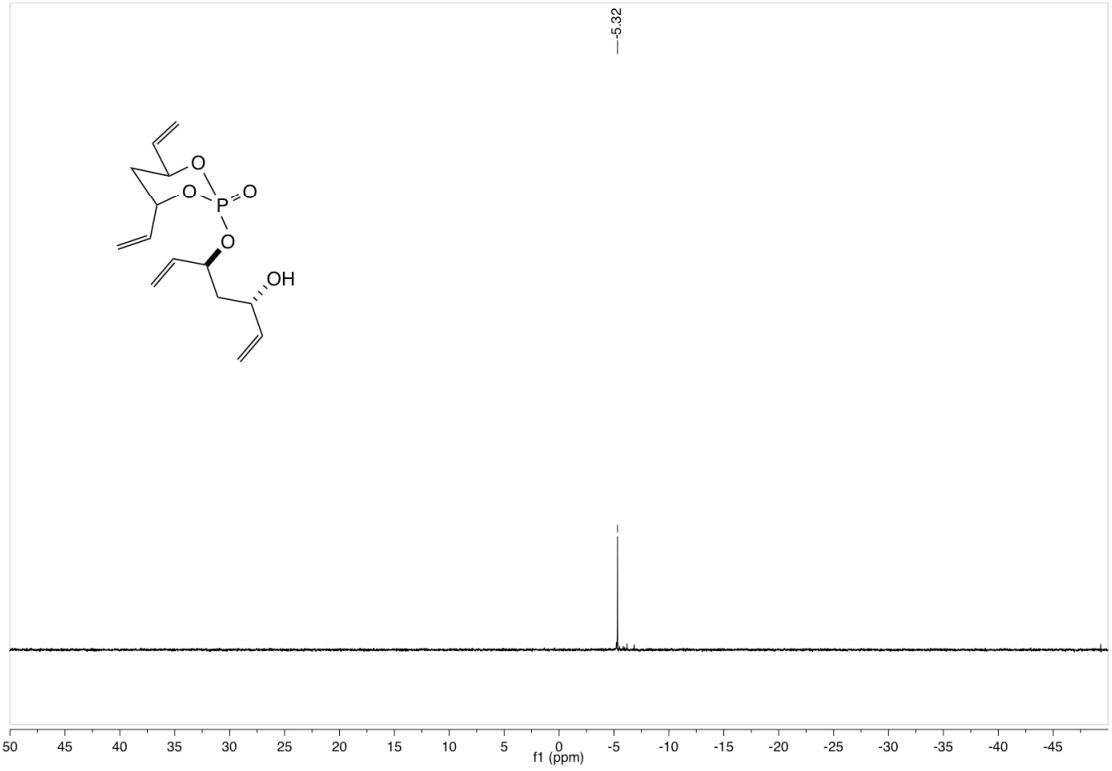



-7.96
O
O
P
O
O
CO2Me
Me
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

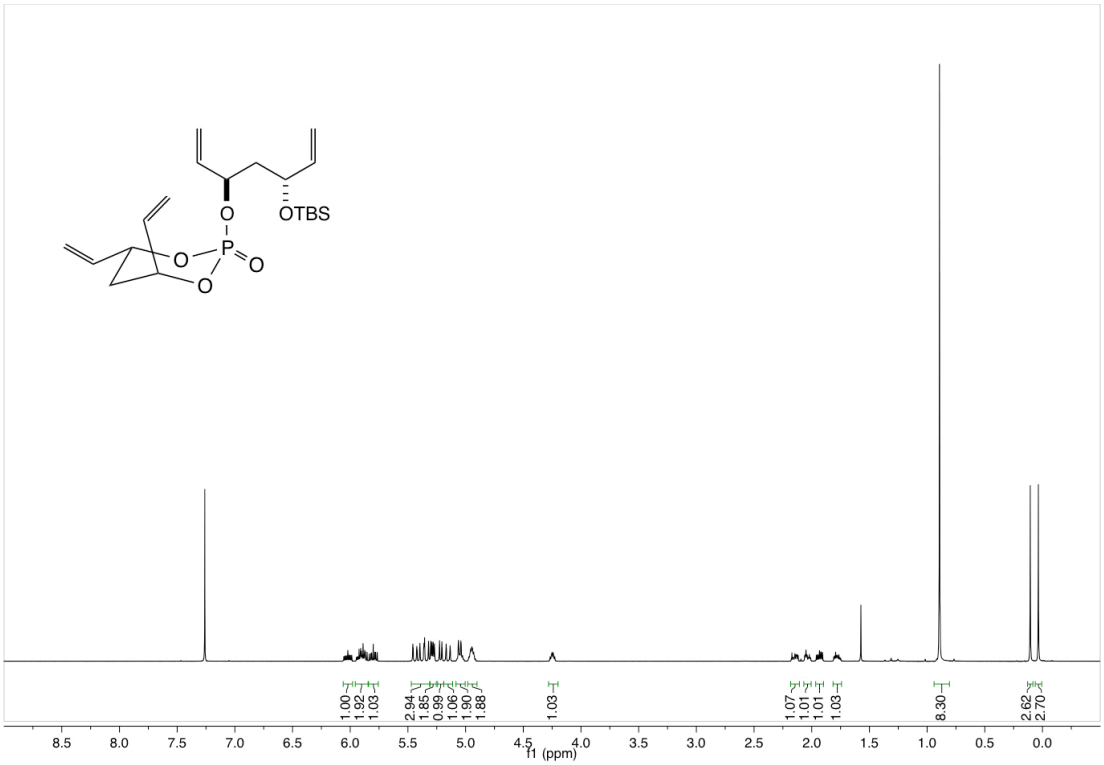
(4*S*,6*S*)-2-(((3*S*,5*S*)-5-hydroxyhepta-1,6-dien-3-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinne 2-oxide: 2.21f

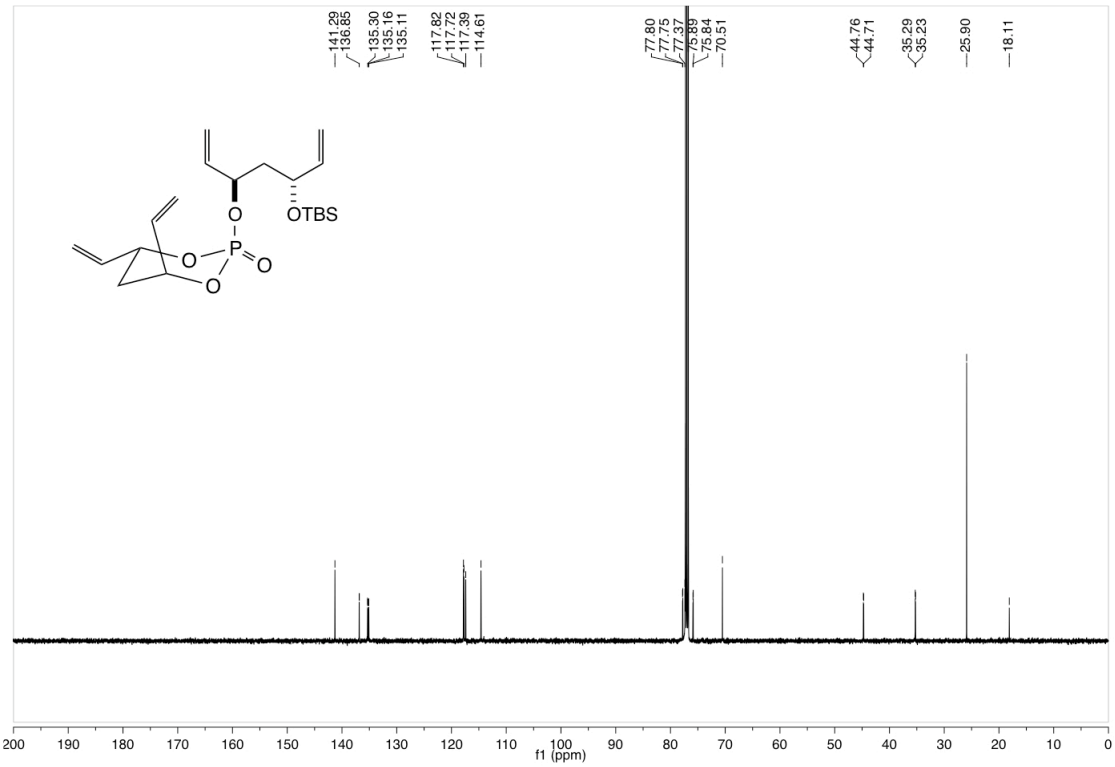


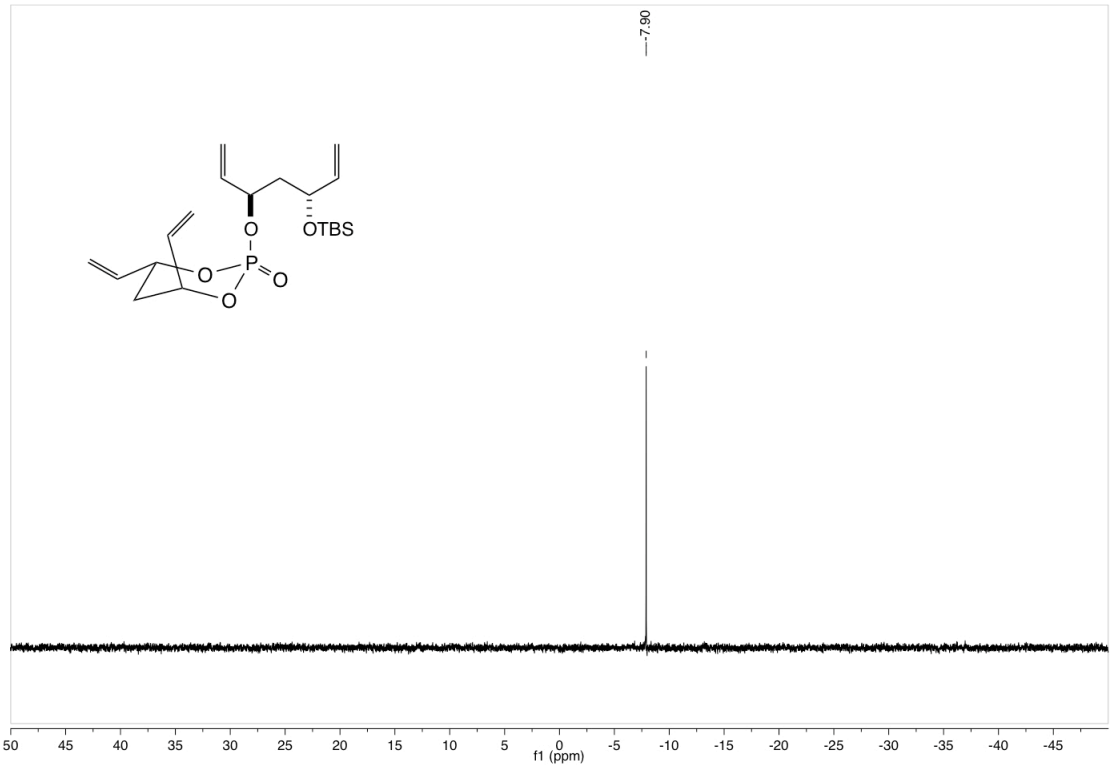



-5.32
O
O
P
O
O
OH
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

(4*R*,6*R*)-2-(((3*R*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)hepta-1,6-dien-3-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.21g






-7.90
OTBS
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P
O
O
O
50
45
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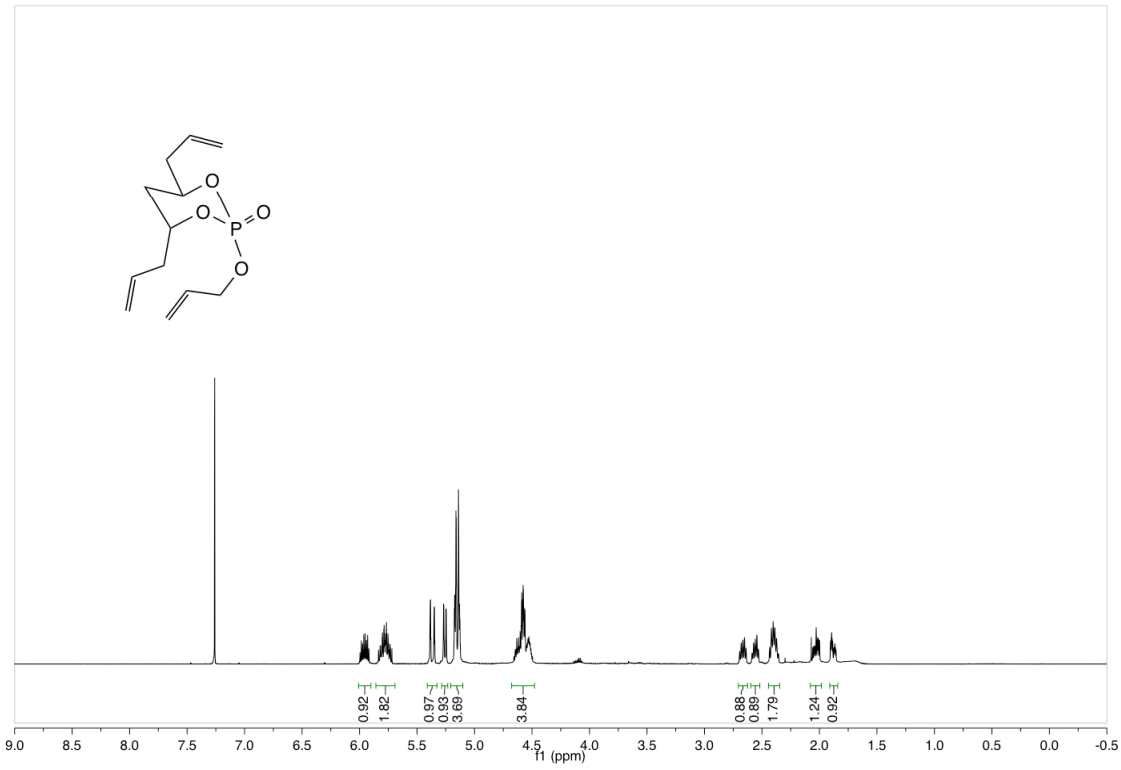
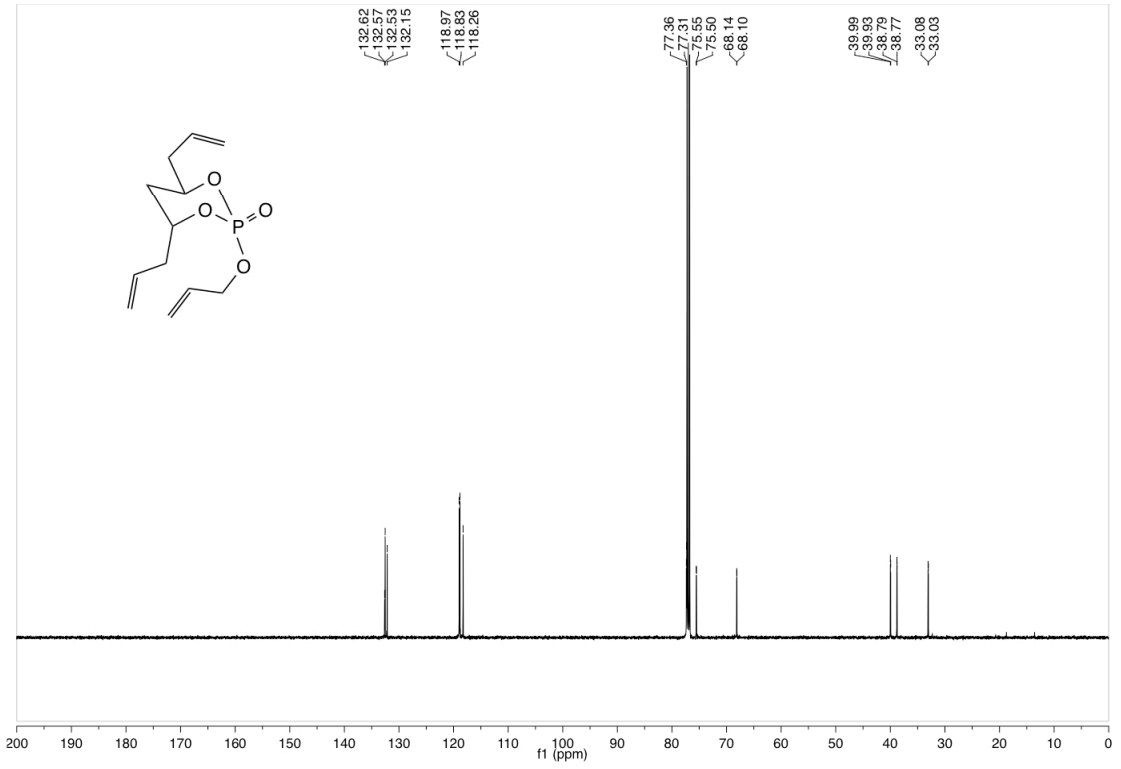
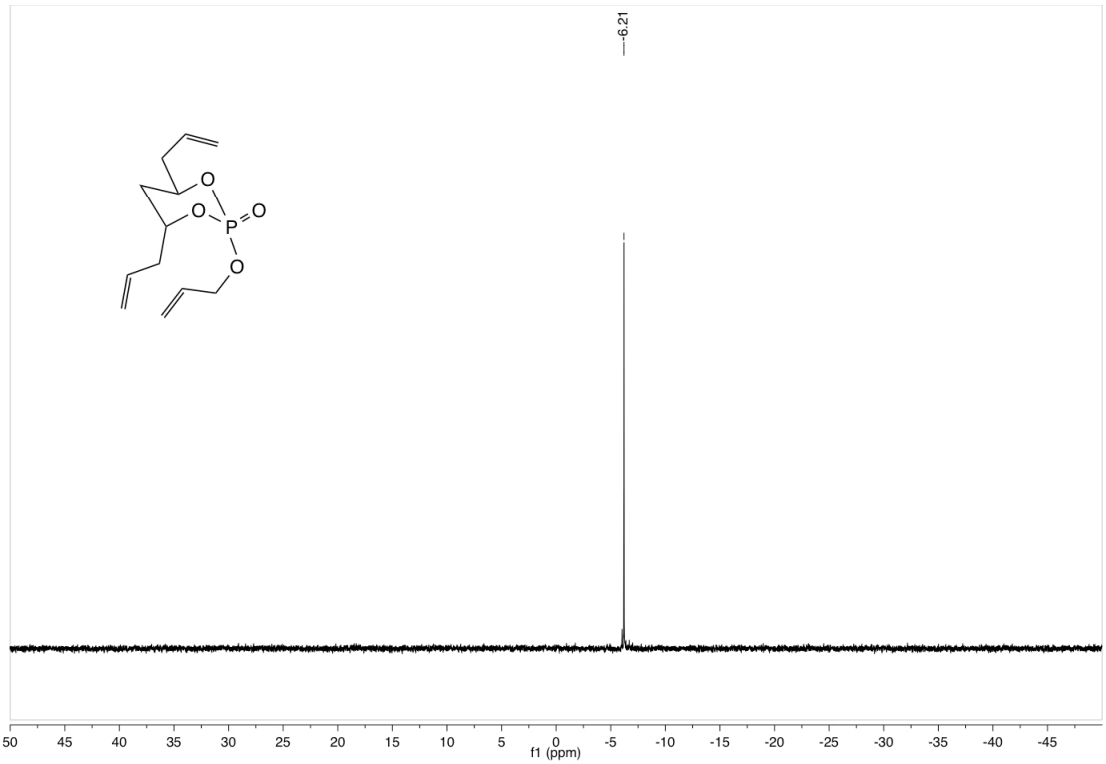
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

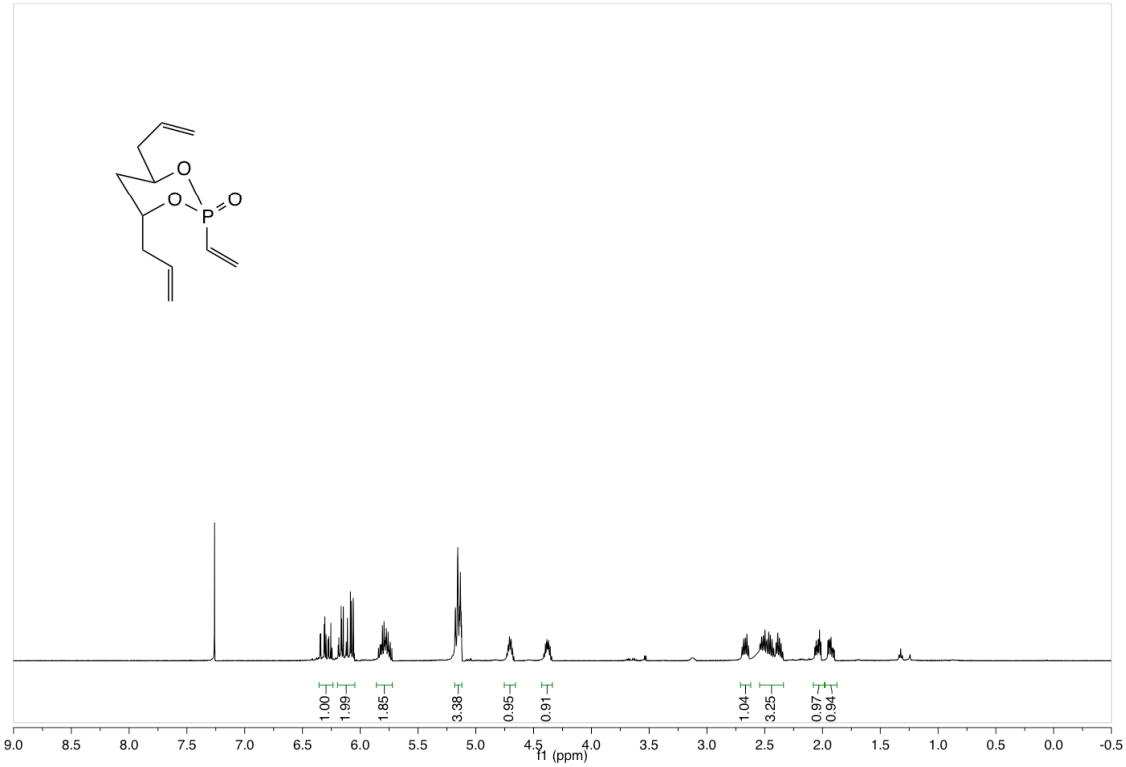
(4*R*,6*R*)-4,6-diallyl-2-(allyloxy)-1,3,2-dioxaphosphinane 2-oxide: 2.22

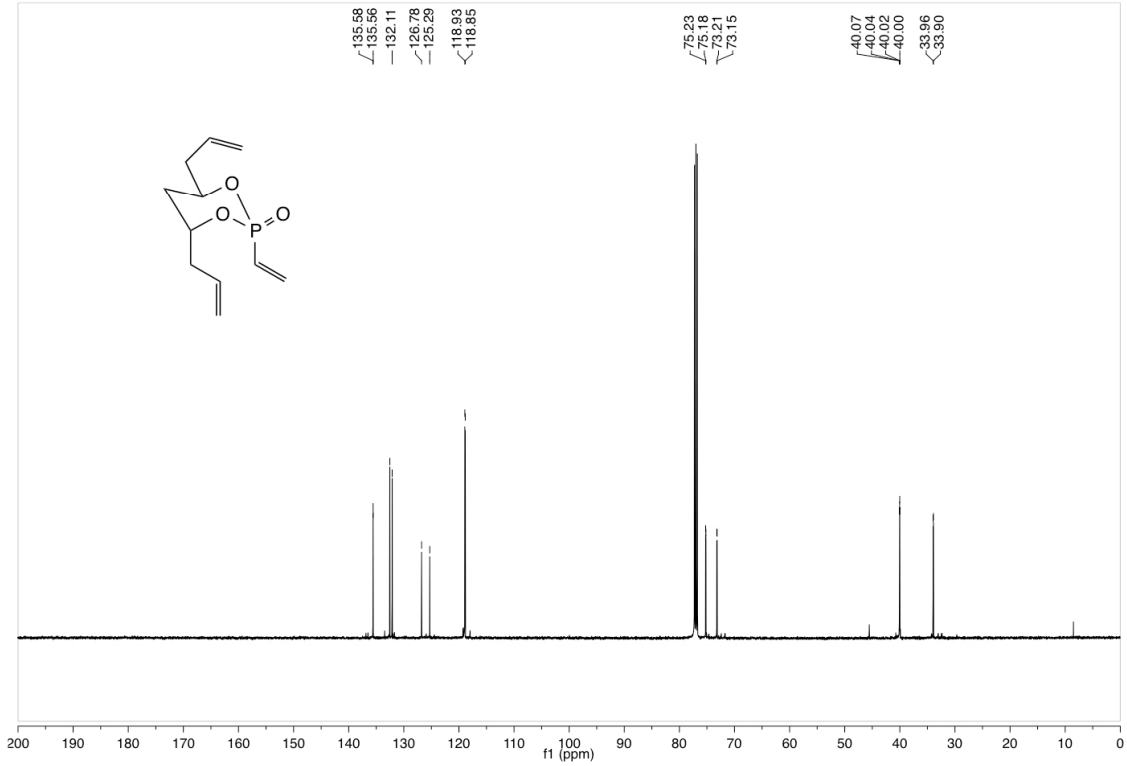


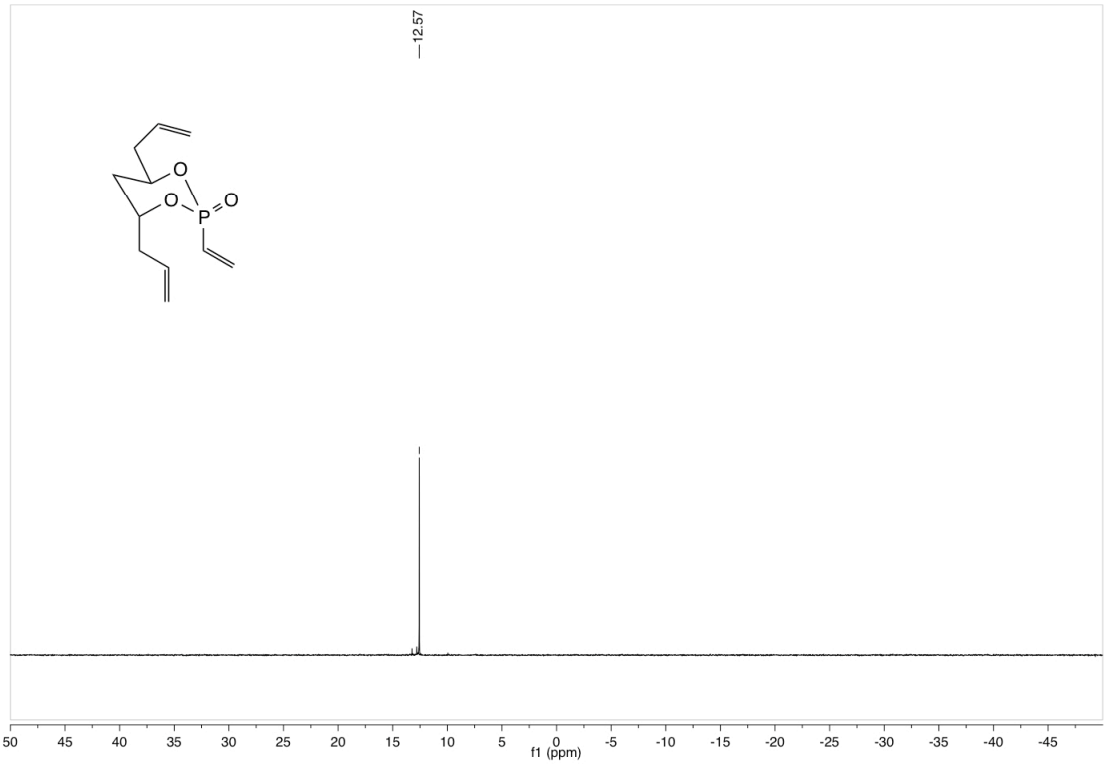



-6.21
O
O
P
O
O
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

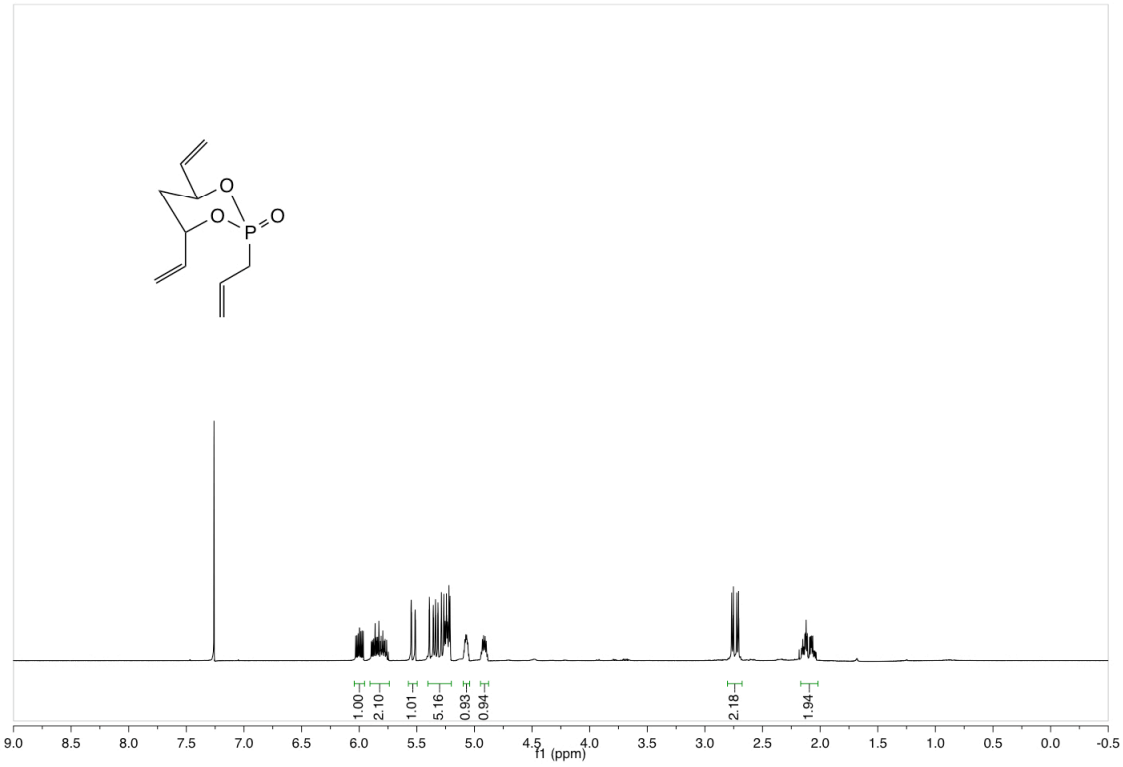
(4*R*,6*R*)-4,6-diallyl-2-vinyl-1,3,2-dioxaphosphinane 2-oxide: 2.23

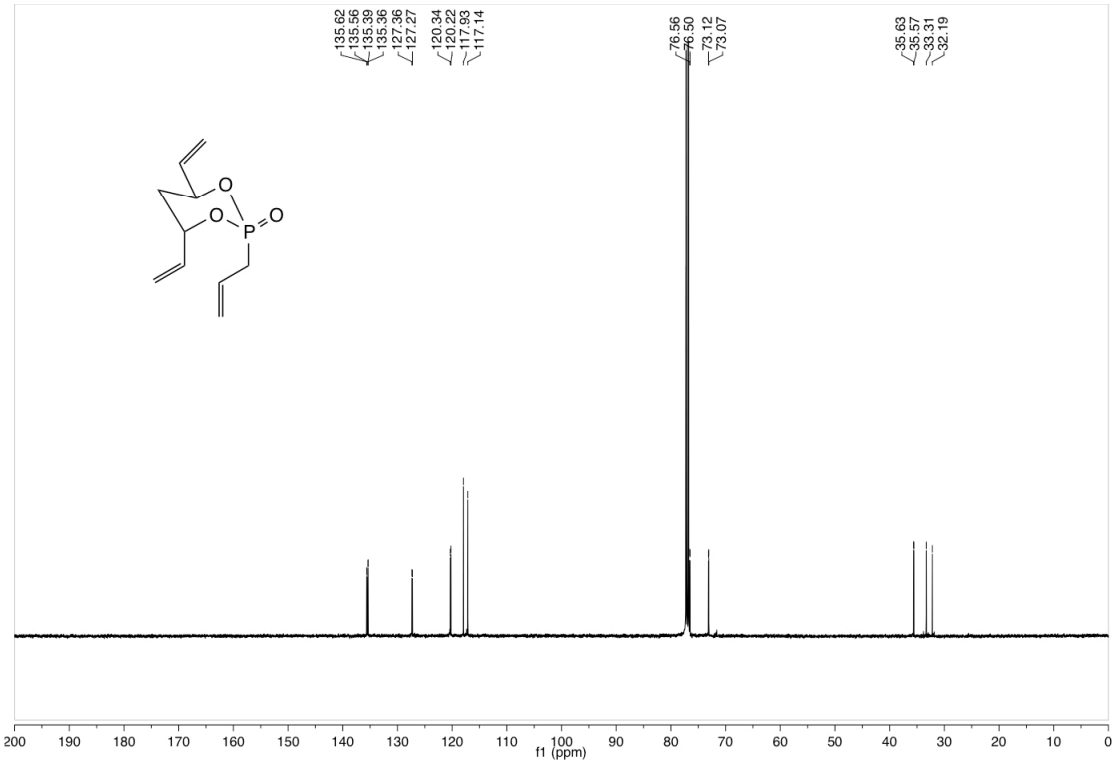


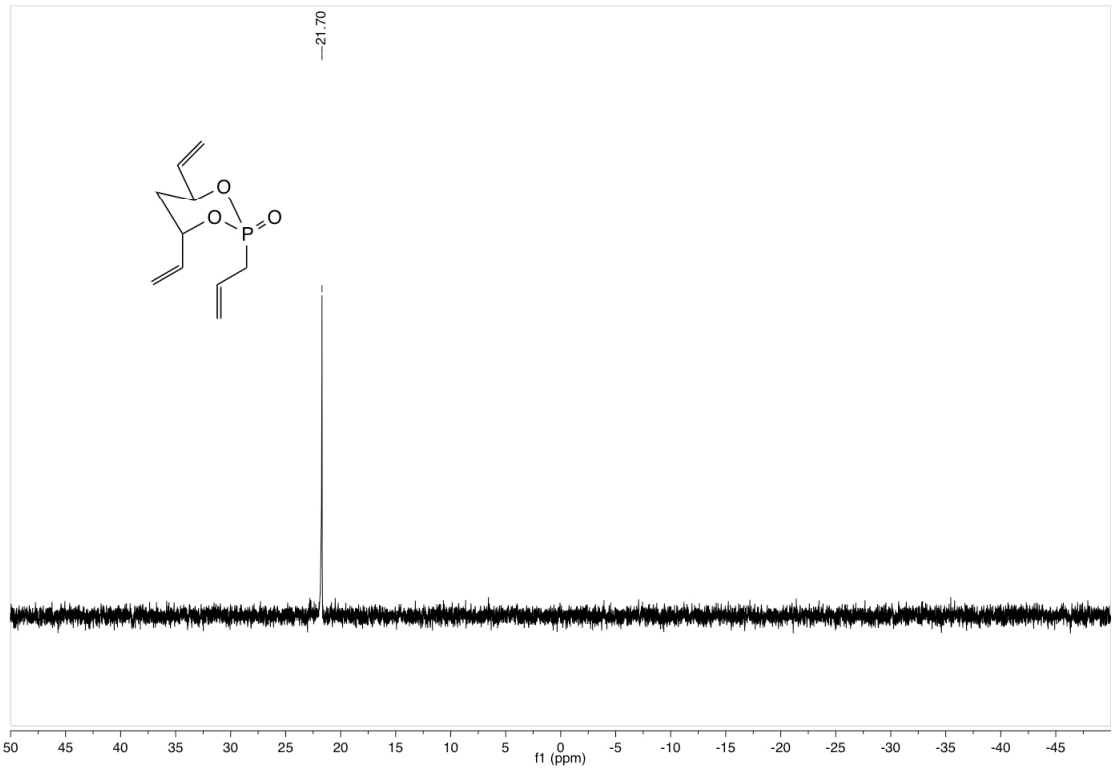



12.57
O
O
P
O
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

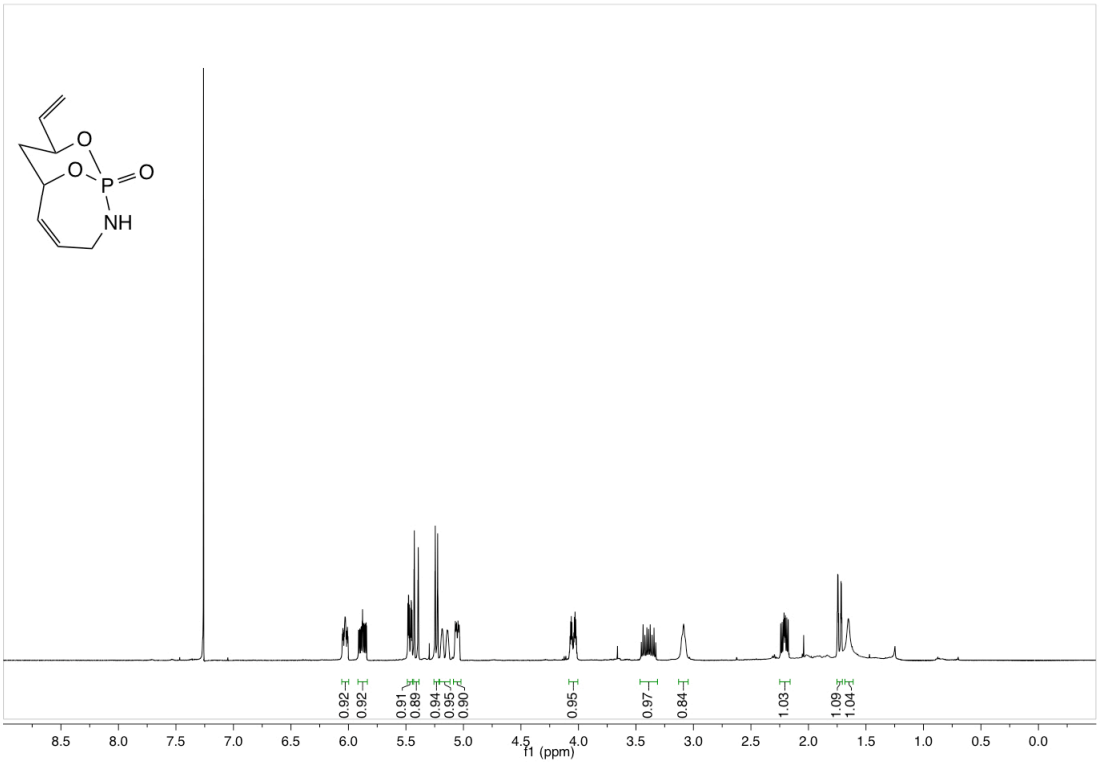
(4*S*,6*S*)-2-allyl-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide: 2.24

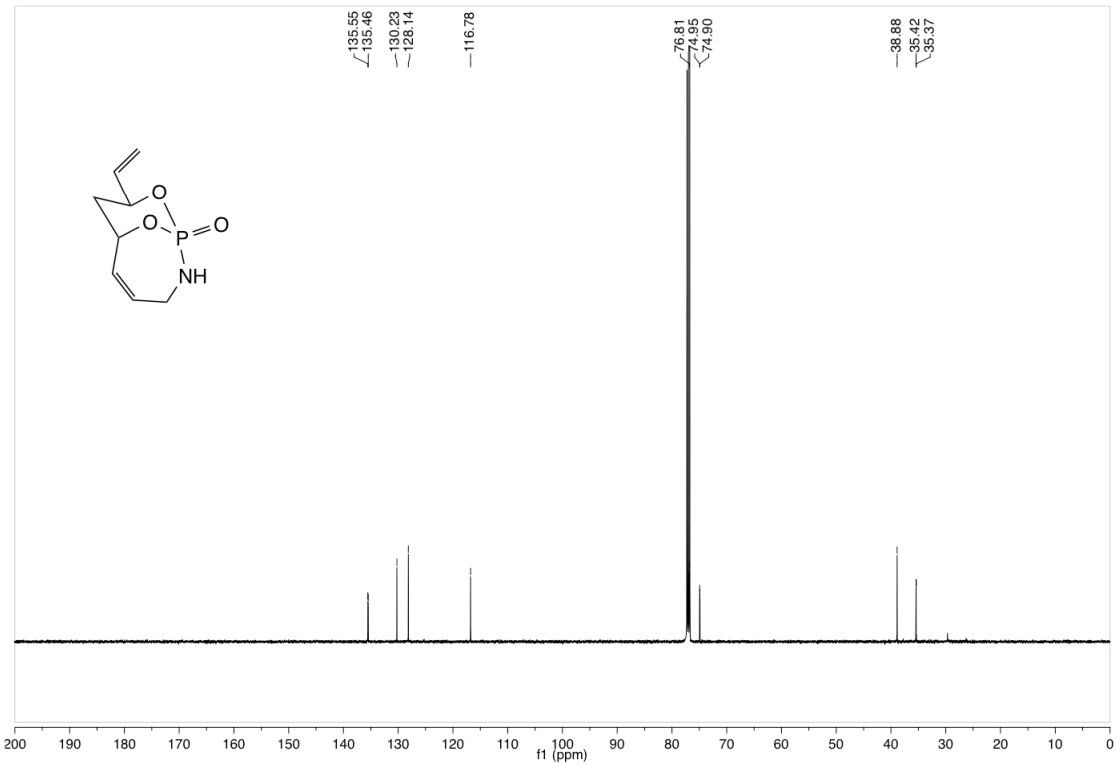


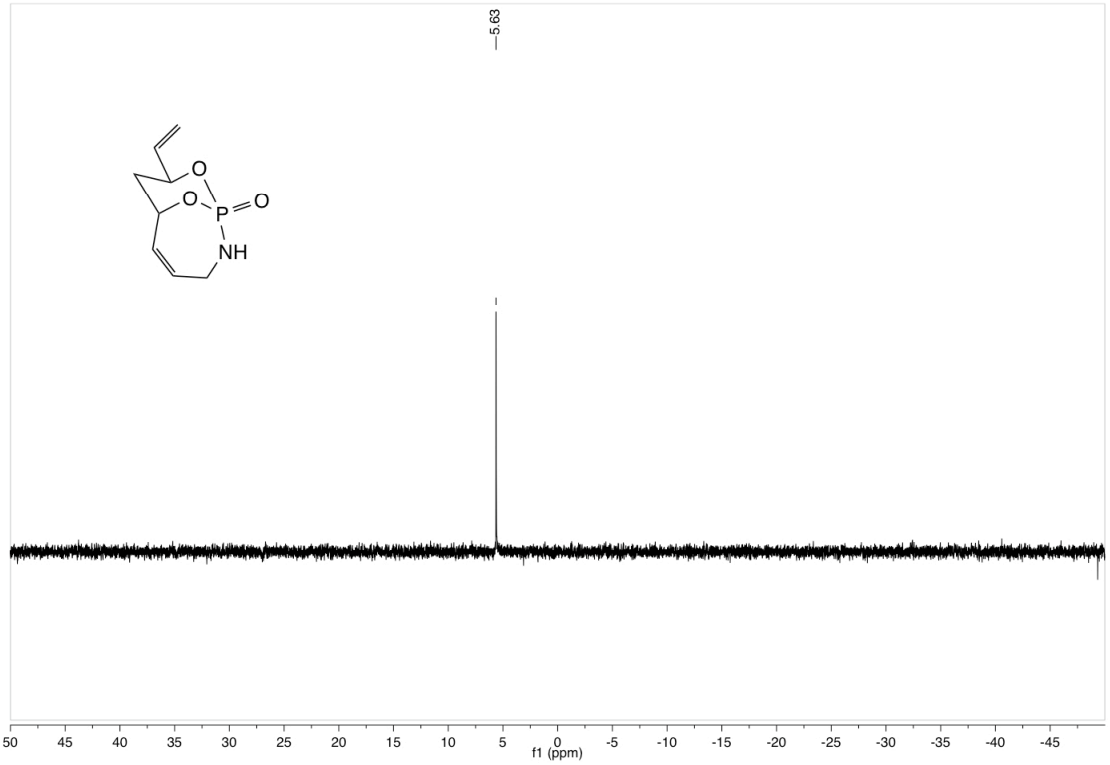



21.70
O
O
P
O
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

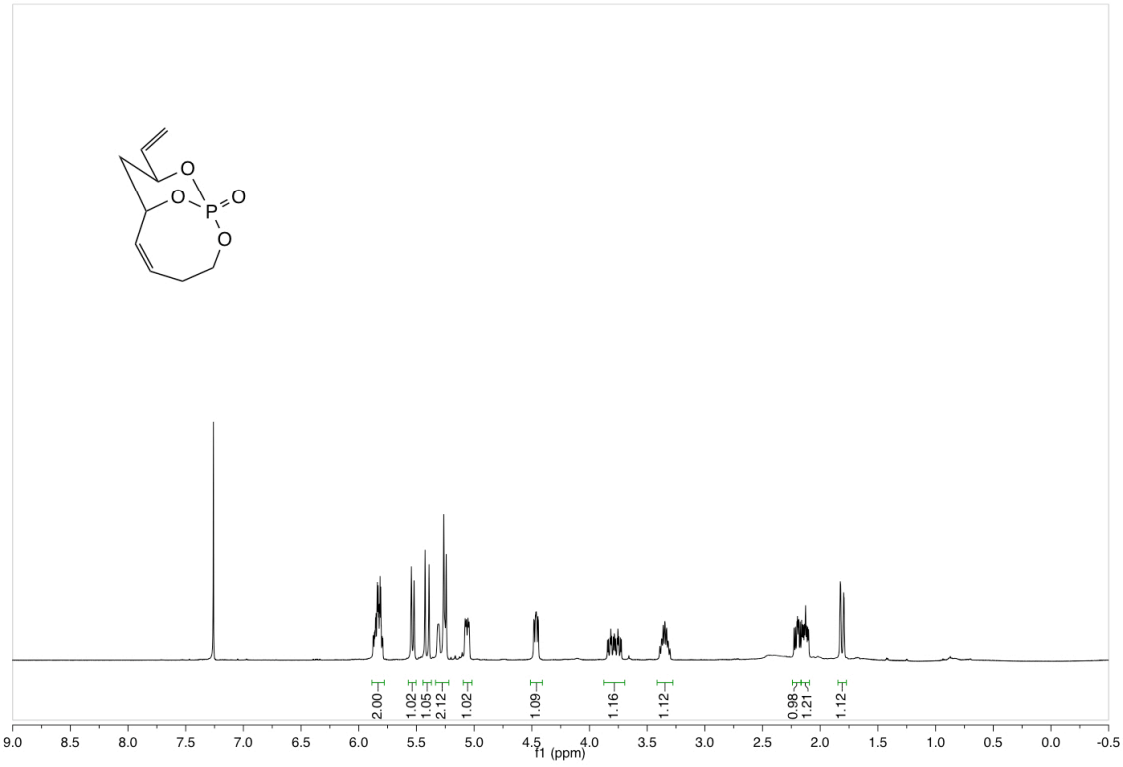
(1*S*,6*S*,8*S*)-8-vinyl-9,10-dioxa-2-aza-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide: 2.26a

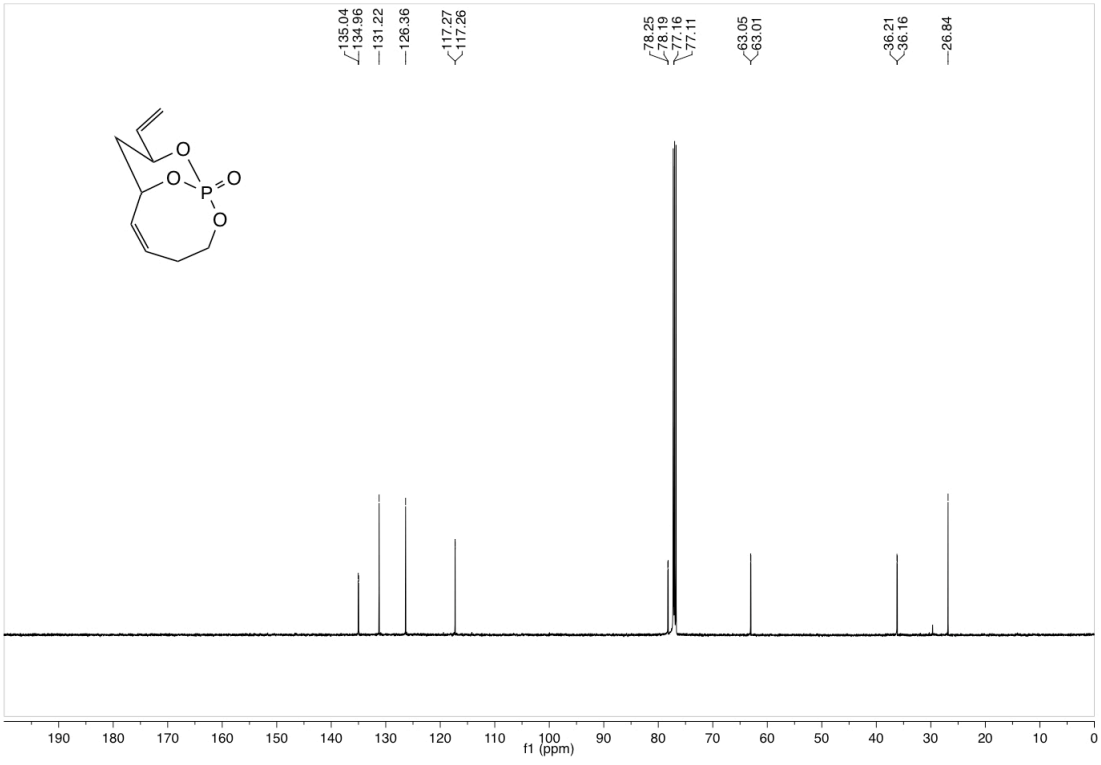


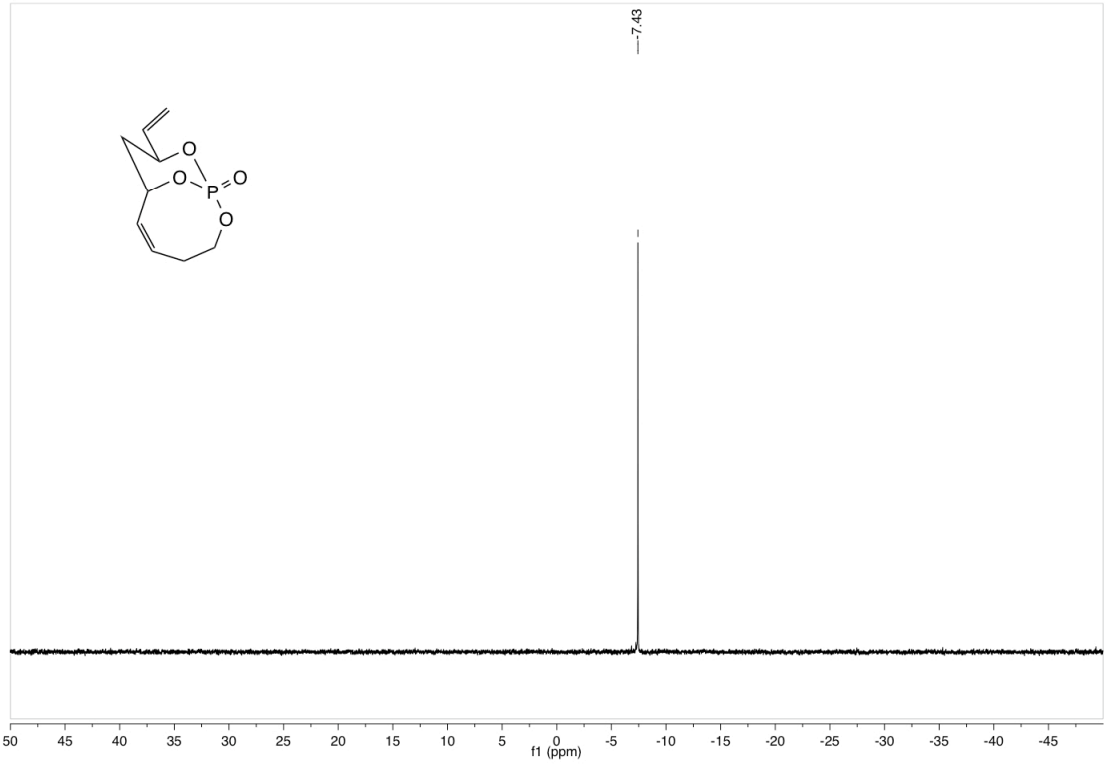



5.63
O
O
P
O
NH
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

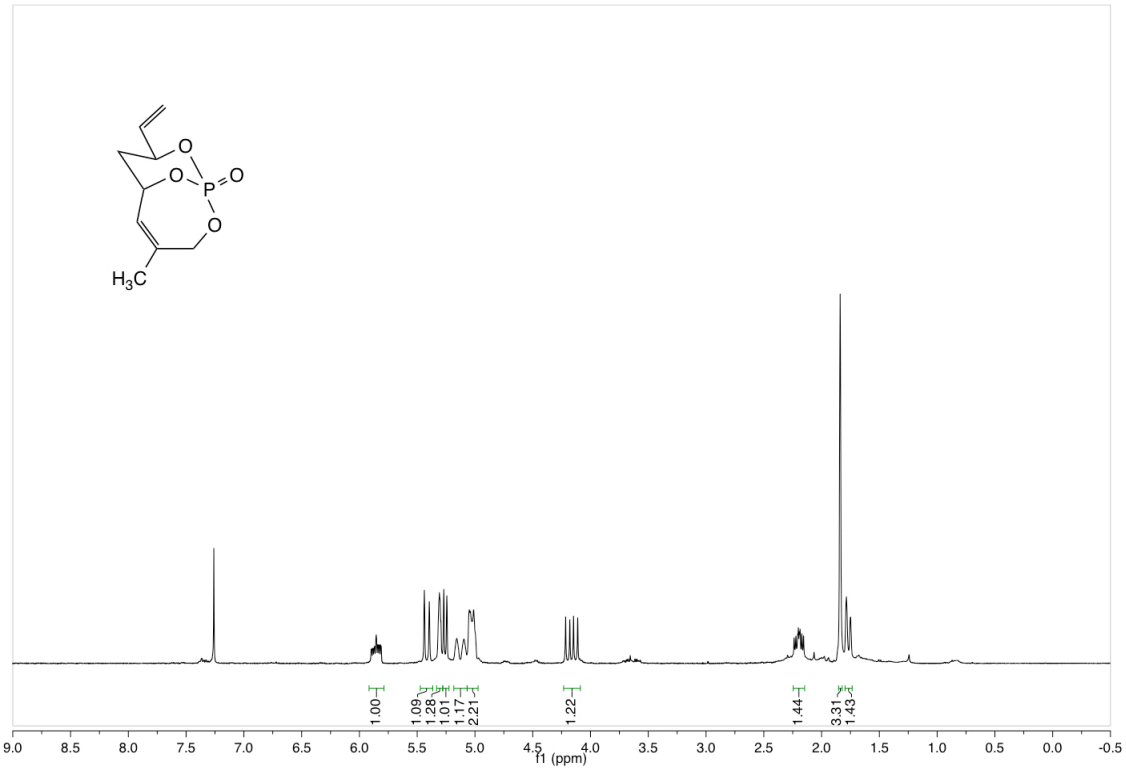
(1*S*,7*S*,9*S*,*Z*)-9-vinyl-2,10,11-trioxa-1-phosphabicyclo[5.3.1]undec-5-ene 1-oxide: 2.26b

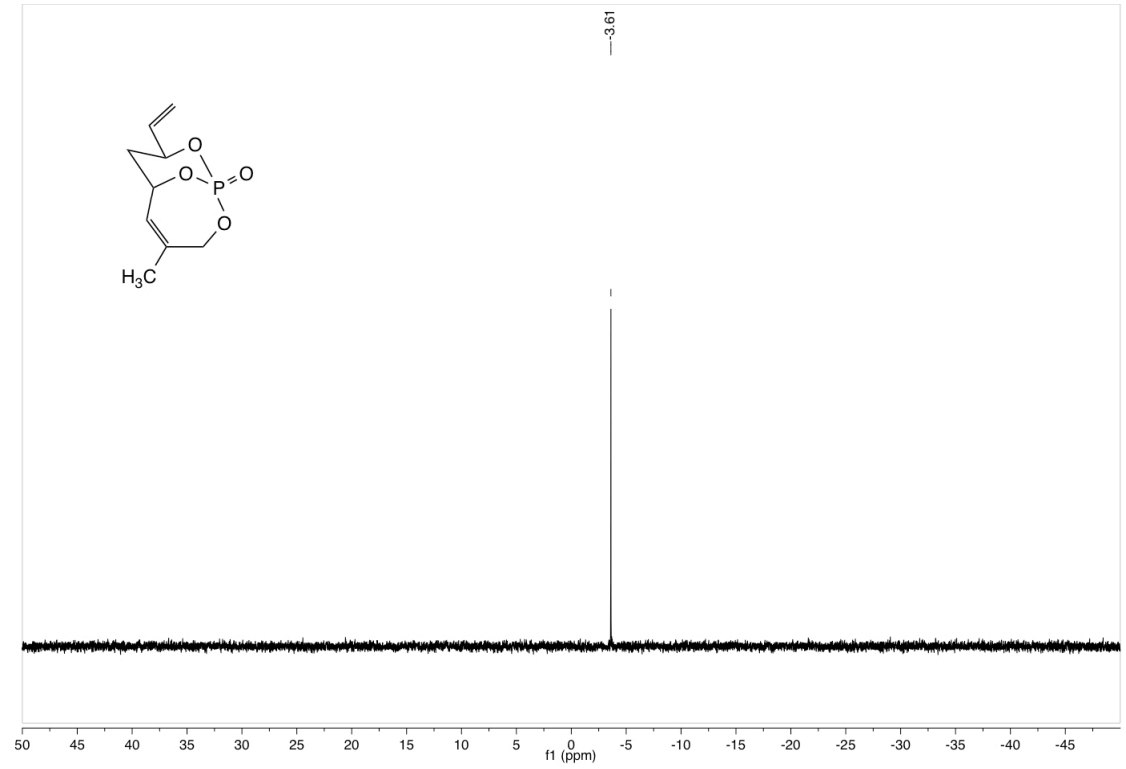


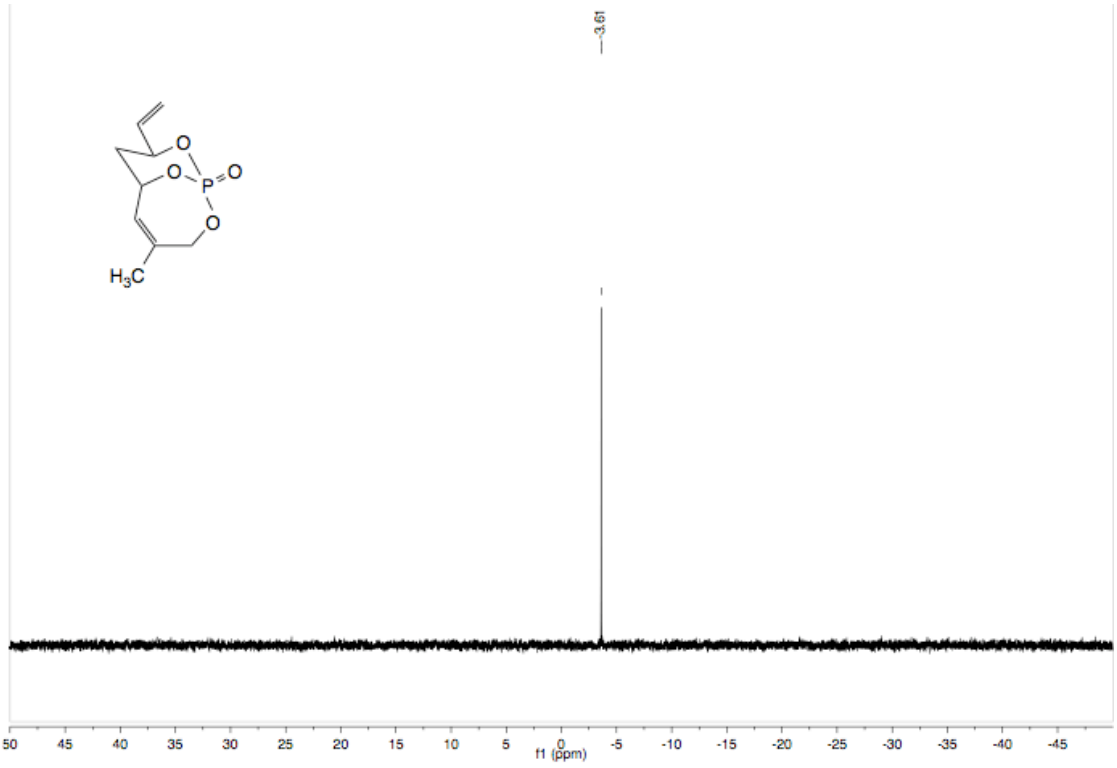



7.43
O
O
P
O
O
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

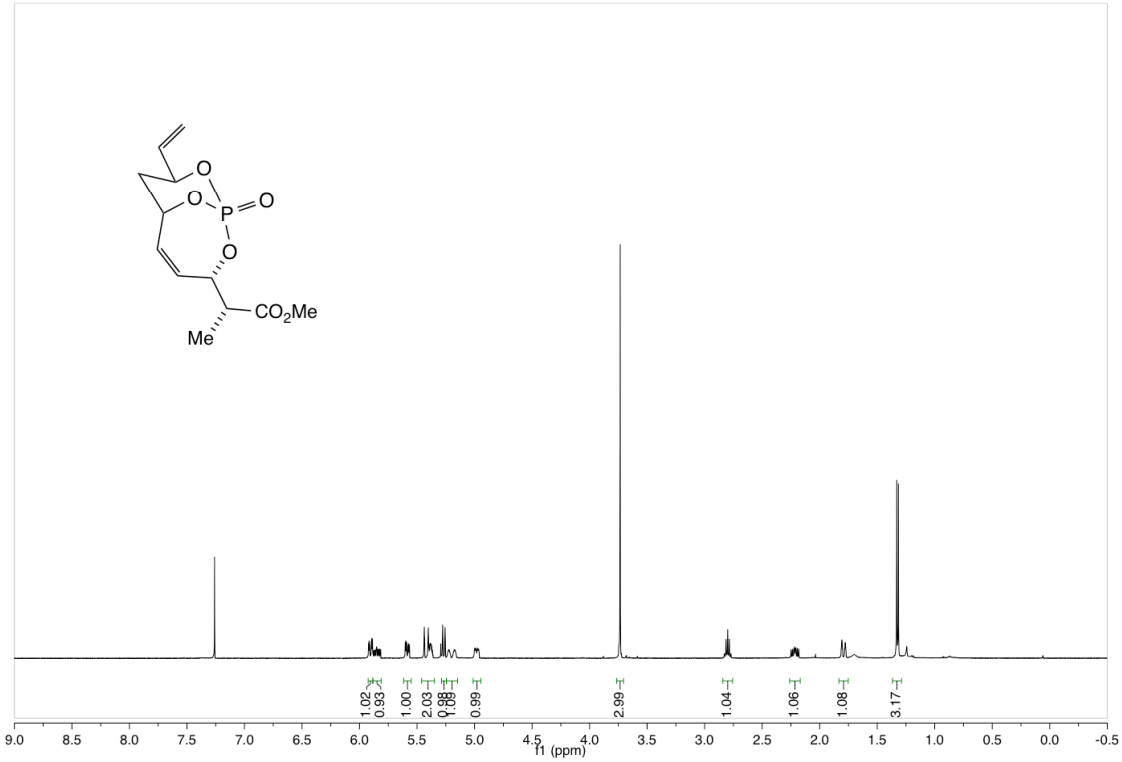
(1*S*,6*S*,8*S*)-4-methyl-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide: 2.26c

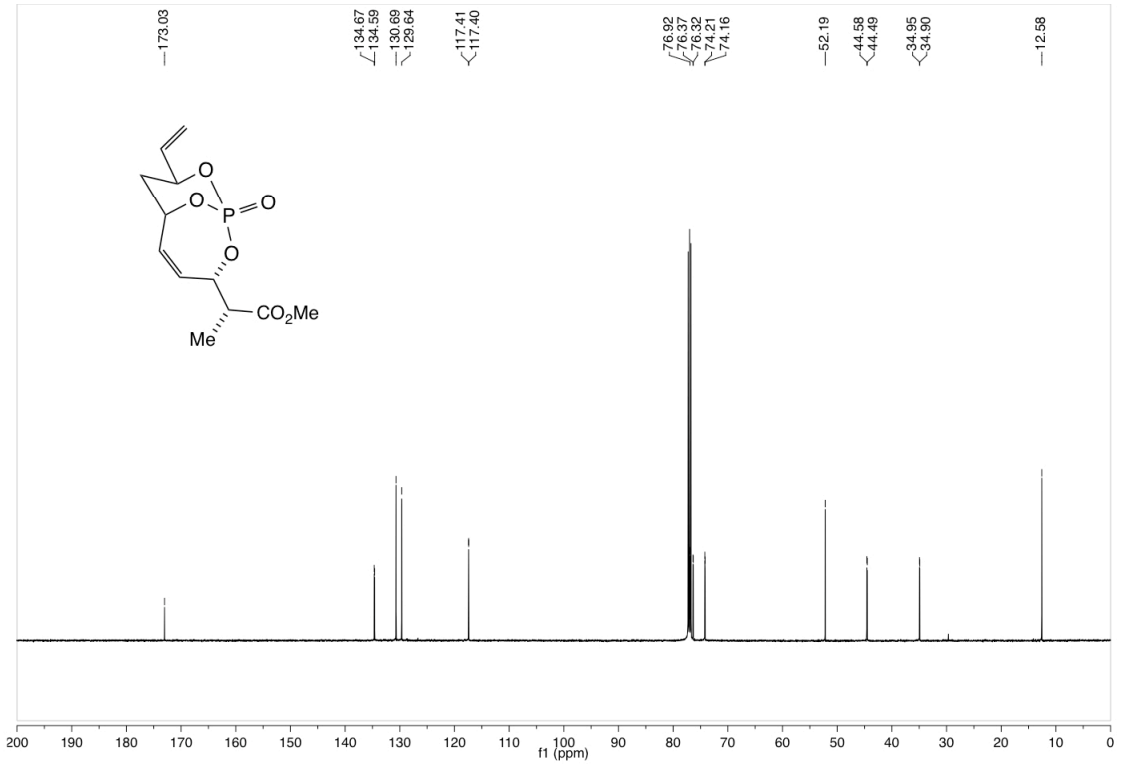


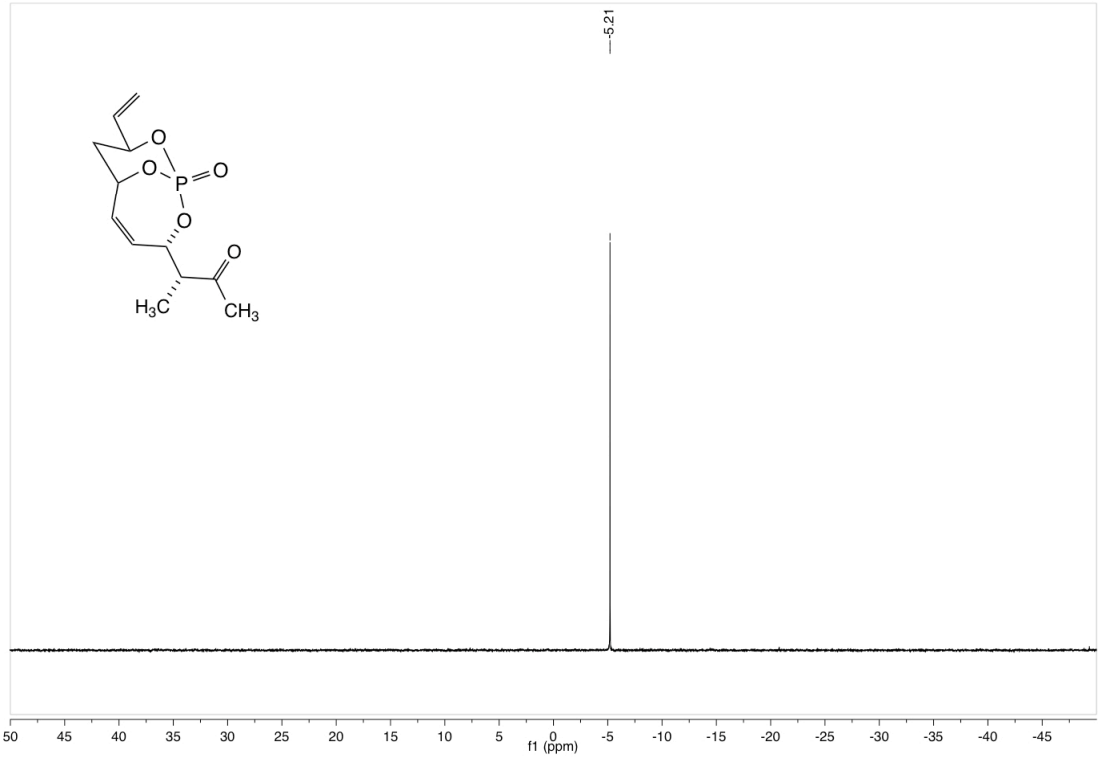



-3.61
O
O
P
O
O
H3C
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

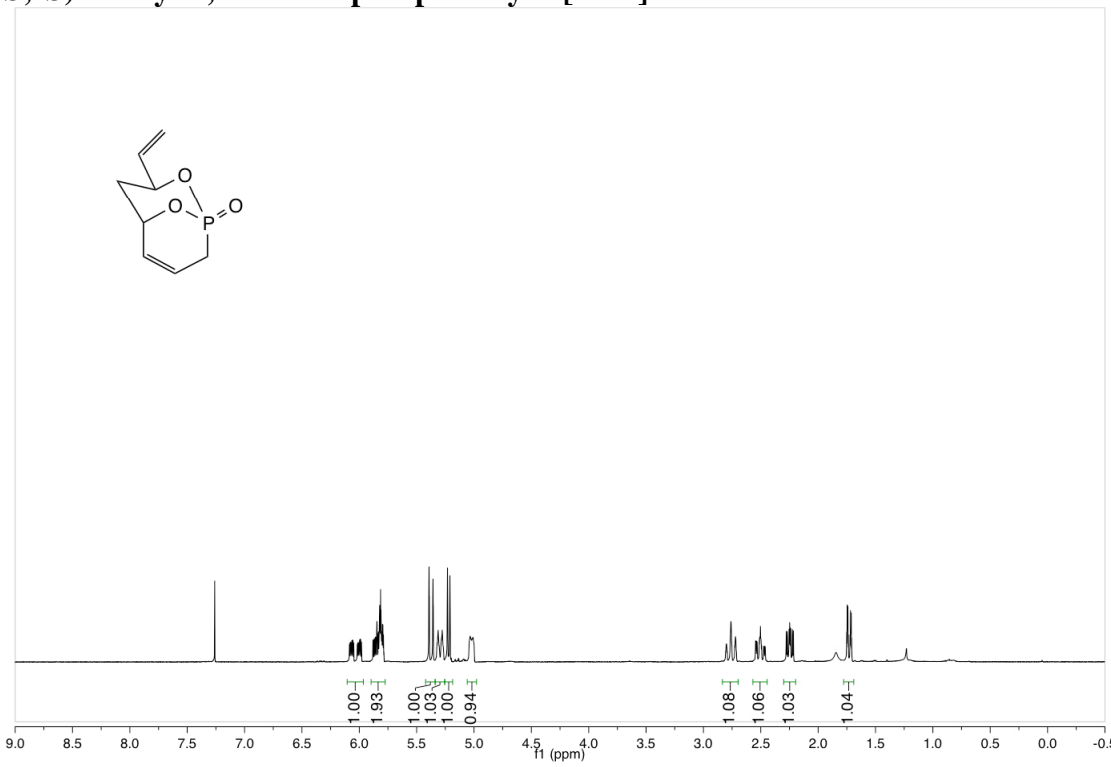
(*R*)-3-((1*S*,3*S*,6*S*,8*S*)-1-oxido-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-3-yl)butan-2-one: 2.26d

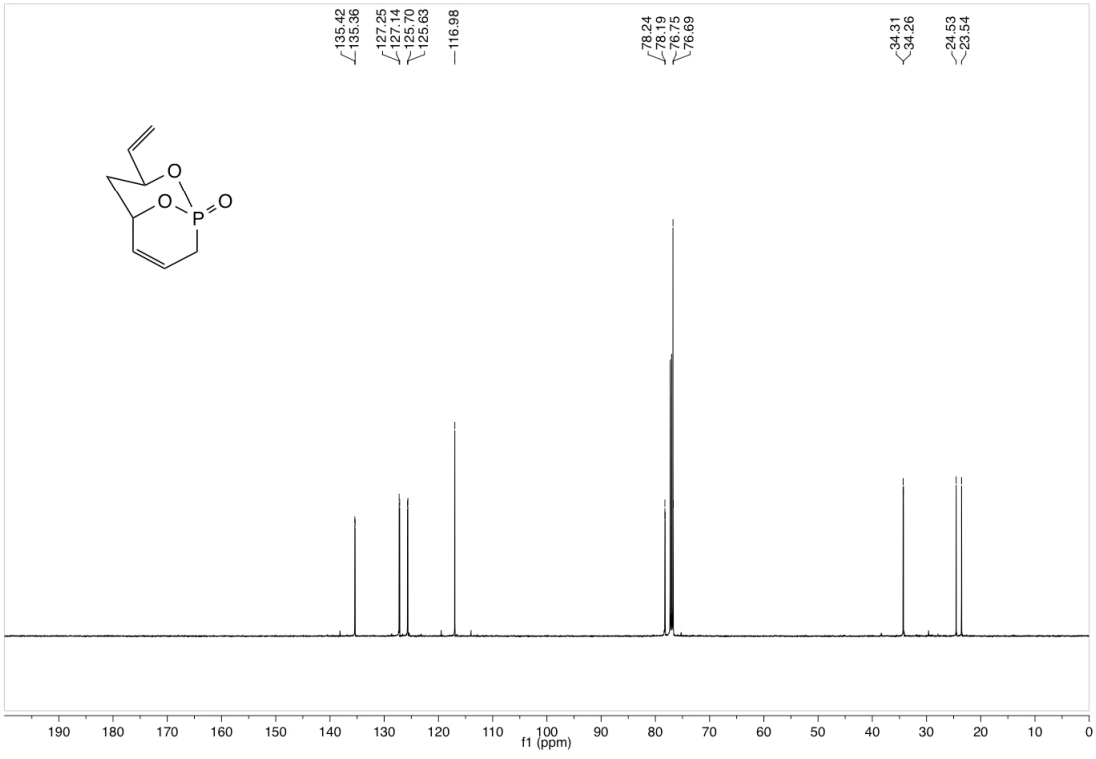


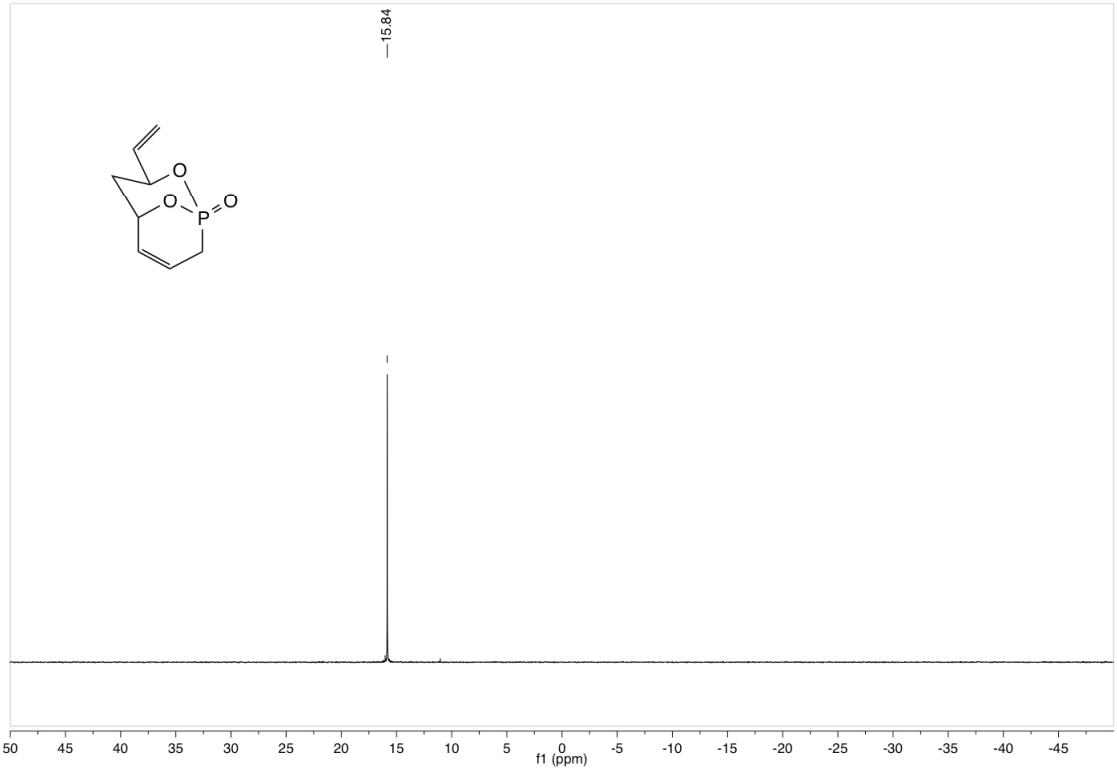



-5.21
O
O
P
O
O
O
H3C
CH3
50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45
f1 (ppm)

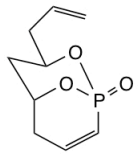
(1*S*,3*S*,5*S*)-3-vinyl-2,9-dioxa-1-phosphabicyclo[3.3.1]non-6-ene 1-oxide: 2.26e

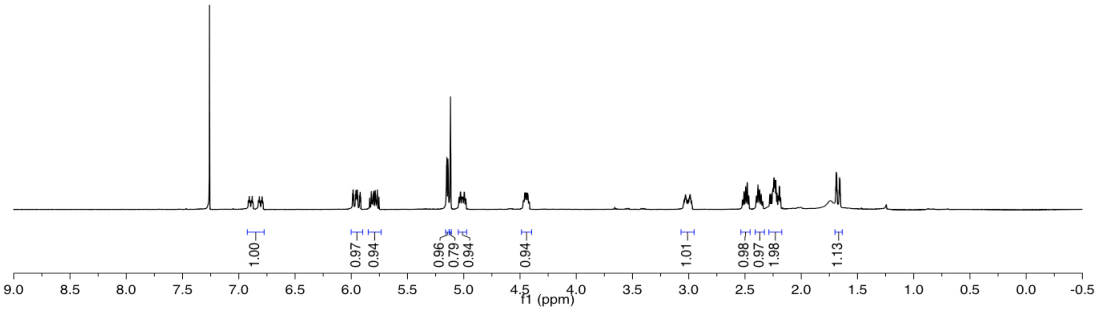


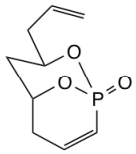


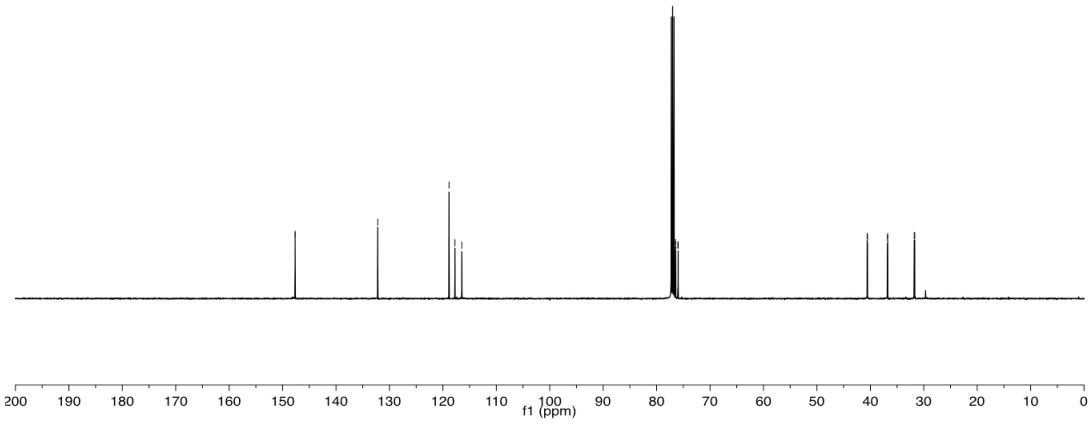

15.84
O
O
P
O
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

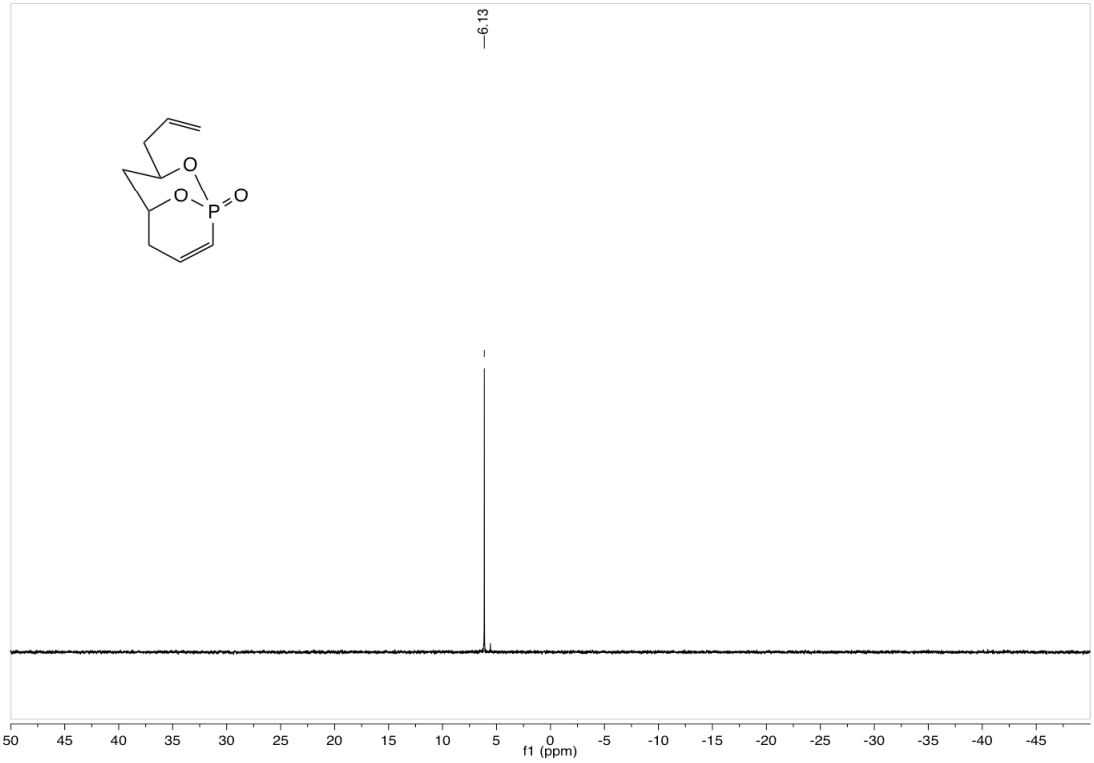
(1*R*,3*R*,5*R*)-3-allyl-2,9-dioxa-1-phosphabicyclo[3.3.1]non-7-ene 1-oxide: 2.26f



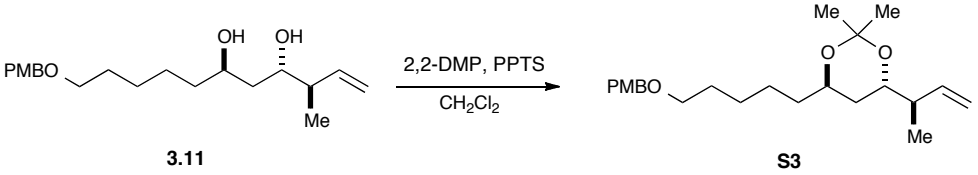







6.13
O
O
P
O
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
f1 (ppm)

(4*S*,6*R*)-4-((*R*)-but-3-en-2-yl)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxane: S3[9]



3.11 **S3**

Diol **3.11** (2.00 g, 5.95 mmol) was taken up in CH_2Cl_2 (8 mL) at RT. 2,2-Dimethoxypropane (8 mL) and PPTS (150 mg, 0.595 mmol) were added respectively and the clear solution was stirred until completion. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were washed once with brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Compound **S3** was isolated using flash chromatography (19:1, hexanes:EtOAc) as a clear oil in 98% yield (2.18 g).

$[\alpha]_D$ -36.3 (*c* = 0.40, CH_2Cl_2);

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

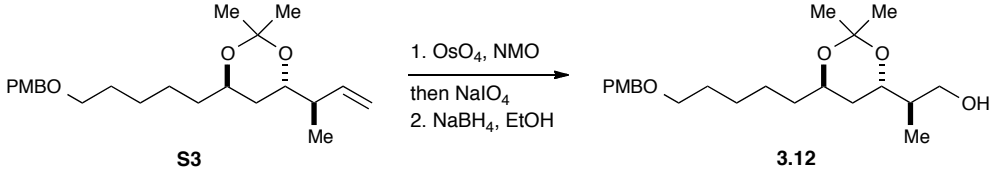
^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.83 (ddd, *J* =17.4, 10.5, 7.3 Hz, 1H), 5.03 (ddd, *J* = 17.5, 11.0, 2.6 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.66-3.74 (m, 1H), 3.63 (ddd, *J* =9.7, 6.3 Hz, 1H), 3.45 (t, *J* =6.6 Hz, 2H), 2.18-2.26 (m, 1H),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

^{13}C NMR ($CDCl_3$, 125 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 $C_{23}H_{36}NaO_4$ $(M+Na)^+$ 319.0198; found 319.0187 (ESI).

[9] Spectra for compounds on pages 70-94 have been shown in Joshua D. Waetzig's dissertation (2008).

(*R*)-2-((4*S*,6*R*)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-1-ol: 3.12



Olefin **S3** (1.50 g, 3.99 mmol) was taken up in a 9:1 mixture of acetone:water (20 mL) at room temperature. *N*-methyl morpholine oxide (933 mg, 7.98 mmol) and OsO_4 (0.19 mL, 0.08 mmol, 4% aq.) were added and the reaction was 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 $NaIO_4$ was added (3.41 mg, 16.0 mmol). The reaction was stirred vigorously for approximately 2 h when until the diol was completely consumed. The reaction was quenched with solid Na_2SO_3 (2.0 g). Acetone was removed under reduced pressure. The residue was partitioned with EtOAc (20 mL) and H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The collected organics were washed once with brine (20 mL portion) and dried with Na_2SO_4. After concentrating under reduced pressure, the product was purified using flash chromatography (5:1, hexanes:EtOAc) to generate the corresponding aldehyde (yield assumed quantitative) as a yellow oil.

The resultant aldehyde was taken up in EtOH (16 mL) and cooled to 0 °C. $NaBH_4$ (303 mg, 7.98 mmol) was added and the reaction was slowly brought back to RT. Upon completion (~45 min), the solution was partitioned with 2:1, Et_2O:H_2O (40 mL). The aqueous layer was extracted with Et_2O (3x5 mL) and the organic layers were combined, washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification with flash chromatography (1:2, hexanes:EtOAc) afforded **3.12** (1.35 g) as a clear oil in 88% yield over two steps.

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

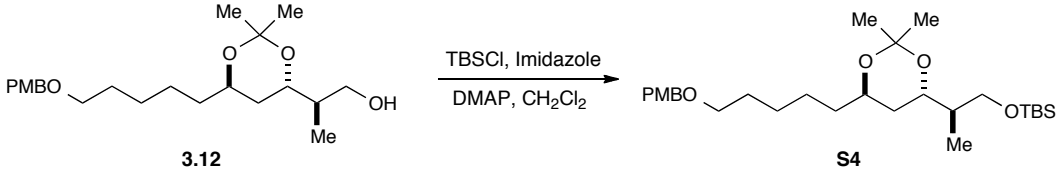
FTIR (neat) 3442, 2933, 2856, 1612, 1512, 819 cm^{-1};

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

^{13}C NMR ($CDCl_3$, 125 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 $C_{22}H_{36}NaO_5$ $(M+Na)^+$ 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: S4**



Alcohol **3.12** (1.34 mg, 3.53 mmol) was taken up in CH_2Cl_2 (23 mL) at RT. Imidazole (720 mg, 10.6 mmol), DMAP (10 mg, 0.08 mmol) and TBSCl (800 mg, 5.29 mmol) were added, respectively. The reaction was quenched upon completion (~90 min) with sat. aq. NH_4Cl and diluted with Et_2O (50 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL) and the organic layers were washed with brine (25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification with flash chromatography (20:1, hexanes:EtOAc) produced **S4** as a yellow oil in 97% yield (1.70 g).

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

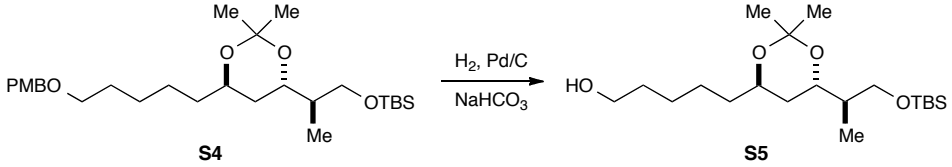
FTIR neat 2933, 2856, 2881, 1247, 835 cm^{-1};

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

^{13}C NMR ($CDCl_3$, 125 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 $C_{28}H_{50}NaO_5Si$ $(M+Na)^+$ 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: S5



PMB ether **S4** (1.65 g, 3.34 mmol) was taken up in EtOAc (16 mL) at RT. A catalytic amount of 10% Pd/C (50 mg) and $NaHCO_3$ (280 mg, 3.34 mmol) were added sequentially and the flask was pressurized with a H_2 balloon. After 10 hours the mixture was filtered through Celite® and rinsed thoroughly with EtOAc. The filtrate was concentrated under reduced pressure and purified with flash chromatography (10:1, hexanes:EtOAc) to yield **S5** as a clear oil (1.12 g, 90% yield).

$[\alpha]_D$ -0.11 (*c* = 0.40, CH_2Cl_2);

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

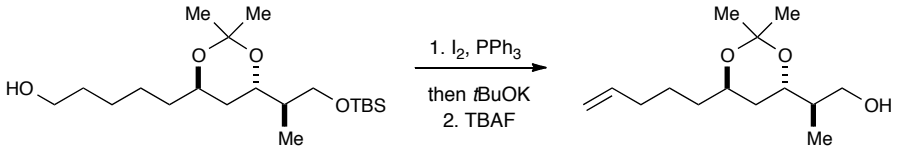
^{1}H NMR ($CDCl_3$, 500 MHz)[10] δ ppm 3.72 (dd, *J* = 14.5 Hz, 2H) 3.60-3.67 (m, 2H), 3.55 (d, *J* = 4.8 Hz, 2H), 1.38-1.70 (m, 10H), 1.33 (s, 6H), 1.22-1.28 (m, 1H), 0.89 (s, 9H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.04 (s, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 100.2, 67.1, 66.8, 64.1, 63.0, 40.5, 36.6, 35.9, 32.7, 25.9 (3), 25.7, 25.3, 24.6, 24.5, 18.2, 12.2, -5.5, -5.5;

HRMS calculated for $C_{20}H_{42}NaO_4Si$ $(M+Na)^+$ 397.2750, found 397.2773 (ESI).

[10] Spectrum integrated to 41 total H, where the unassigned H was presumed to be an O-H peak undergoing H-D exchange.

(*R*)-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)propan-1-ol: 3.13



S5 **3.13**

Alcohol **S5** (1.12 g, 2.99 mmol) was taken up in THF (30 mL) at RT. Triphenylphosphine (941 mg, 3.59 mmol) and imidazole (477 mg, 6.59 mmol) were added, respectively, and the solution was cooled to 0 ºC. I_2 (912 mg, 3.59 mmol) was added and the reaction was stirred for approximately 30 minutes (monitored by TLC). The solution was diluted with hexane and filtered through a pad of silica, while washing with hexane, and concentrated under reduced pressure. The crude product was taken onto the next step.

The iodo compound was dissolved in THF (35 mL) at RT followed by stepwise addition of *t*-BuOK (1.0 g, 8.98 mmol). The reaction was stirred for ~30 minutes and was quenched with H_2O. The aqueous layer was extracted with EtOAc (3 x 20 mL portions) and the organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification with flash chromatography (20:1, hexanes:EtOAc) yielded the resultant terminal olefin (1.00 g) as a clear oil in 94% yield.

The resultant silyl ether (1.00 g, 2.81 mmol) was dissolved in THF (10 mL) and cooled to 0 ºC. A solution of TBAF in THF (8.5 mL, 1.0 M in THF) was added dropwise. The reaction was stirred at 0 ºC until completion (approximately 45 minutes). The reaction was quenched with NH_4Cl and the aqueous layer was extracted with Et_2O (3x20 mL portions). The organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification using flash chromatography (10:1, hexanes:EtOAc) afforded **3.13** as a clear oil (670 mg) in 98% yield.

$[\alpha]_D$ -78.6 (*c* = 0.50, CH_2Cl_2);

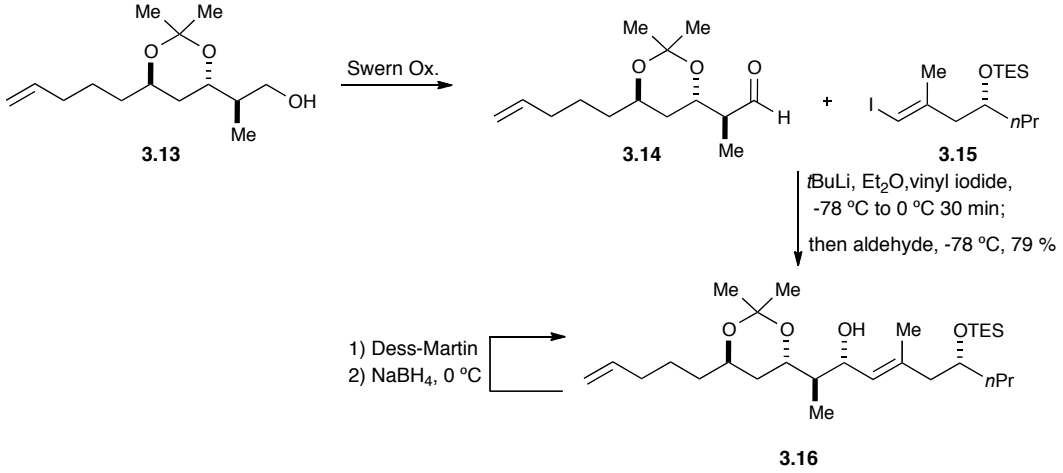
FTIR (neat) 3446, 2983, 2935, 2879, 1379, 1224, 908 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.75-5.86 (m, 1 H), 4.93-5.07 (m, 2 H), 3.76-3.82 (m, 1 H), 3.69 (ddd, *J* = 9.2, 6.2 Hz, 1H), 3.55-3.61 (m, 2H), 3.08 (s, 1H), 2.06 (dd, *J* = 14.1, 7.1 Hz, 2H), 1.40-1.80 (m, 7H), 1.38 (s, 3H), 1.33 (s, 3H), 0.81 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 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, 24.6, 12.6;

HRMS calculated for $C_{14}H_{27}O_3$ $(M+H)^+$ 243.1960, found 243.2895 (ESI).

(2*R*,3*R*,7*R*,*E*)-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: 3.16



A solution of oxalyl chloride **(**0.158 mL, 1.86 mmol) in CH_2Cl_2 **(**4.8 mL) was cooled to -78 ºC and DMSO **(**0.220 mL, 3.01 mmol) was added slowly by syringe (gas evolution). After stirring for 10 minutes, a solution of alcohol **3.13 (**300 mg, 1.24 mmol) in CH_2Cl_2 (3.0 mL) was added by cannula and rinsed with CH_2Cl_2 (2 x 0.5 mL). The cloudy mixture was stirred at -78 ºC for 15 minutes at which time Et_3N **(**0.700 mL, 4.96 mmol) was added dropwise. The reaction mixture was stirred for 1 h at -78 ºC, quenched cold with sat. aq. $NaHCO_3$ (5 mL) and allowed to warm to RT. After diluting with CH_2Cl_2, the layers were separated and the aqueous layer was re-extracted with CH_2Cl_2 (3 x 12 mL). The organic layer was dried (Na_2SO_4), filtered through a silica plug and rinsed (3 x 25 mL) with a 1:1 EtOAc:CH_2Cl_2. The filtrate was concentrated under reduced pressure to give aldehyde **15** as a yellow oil. The crude aldehyde **3.14** was taken immediately to the next reaction without further purification.

To a solution of vinyl iodide **3.15** (1.01 mg, 2.75 mmol) in Et_2O (10 mL) at –78 ºC was added *t*-BuLi (1.7 M in pentane, 3.40 mL, 5.75 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 (2.5 mL, 0.60 mL rinse). After 1 h, the reaction was

quenched at -78 ºC with NH_4Cl (sat'd, aq), warmed to RT, and the layers were separated. The aq. layer was extracted with Et_2O (2x10 mL), and the combined organic layers washed with brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (10:1, hexanes:EtOAc) afforded a 1:1 mixture of 1,3-*syn* and 1,3-*anti* **3.16** (ratio determined by ^1H NMR analysis of crude reaction mixture, 464 mg, combined yield of diastereomers 77% over two steps).

Oxidation/Reduction Sequence:

The 1,3-*anti* diastereomer (65 mg, 0.135 mmol) of **3.16** was dissolved in CH_2Cl_2 (2.6 mL) at RT. Dess-Martin periodinane (115 mg, 0.270 mmol) was added to the stirring solution, where upon completion (monitored by TLC), the reaction was diluted with Et_2O (5 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 x 5 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure and the residual oil was purified through a short plug of SiO_2 (1:1, hexanes:EtOAc) providing a clear oil (40 mg, 85% yield).

The ketone (6 mg, 0.0125 mmol) was dissolved in MeOH and cooled to 0 ºC. $NaBH_4$ (11 mg, 0.035 mmol) was added slowly and the mixture was stirred until the ketone was completely consumed (monitored by TLC). The mixture was partitioned with H_2O:Et_2O (1:1 ratio, 10 mL) and the resultant aqueous layer was extracted with Et_2O (3x5 mL). The collected organic layers were washed with brine (5 mL) and dried (Na_2SO_4). The epimeric ratio of the crude material was determined by ^1H NMR analysis after filtration and removal of solvent under reduced pressure, (~2.7:1). Flash chromatography (5:1 hexanes:EtOAc) provided a clear oil (4 mg, 89**%** yield).

$[\alpha]_D$ -8.1 (*c* = 1.3, CH_2Cl_2);

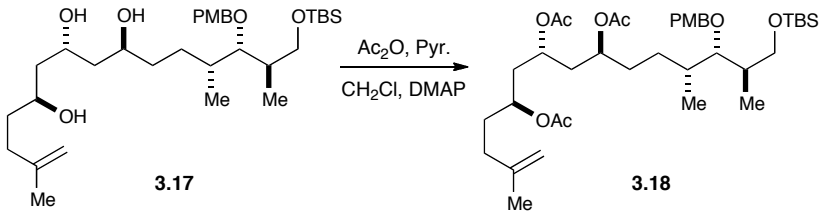
FTIR (neat) 3456, 2954, 2935, 2875, 1458, 1379, 1224, 908 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 5.82 (dddd, *J* = 16.9, 10.1, 6.7, 6.7 Hz, 1H), 5.16 (d, *J* = 9.1 Hz, 1H), 5.01 (ddd, *J* = 17.1, 3.4, 1.5 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 4.27 (t, *J* = 8.7 Hz, 1H), 3.99 (s, 1H), 3.74-3.84 (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 ($CDCl_3$, 125 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, 24.7, 24.6, 24.5, 18.4, 17.3, 14.2, 11.6, 7.0, 5.0;

HRMS Exact Mass calculated for $C_{28}H_{54}NaO_4Si$ $(M+Na)^+$ 505.3689; found 505.3674 (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-triyl triacetate: 3.18



To a solution of triol **3.17** (132 mg, 0.232 mmol) in CH_2Cl_2 (3.3 mL) was added DMAP (3 mg, 0.023 mmol), pyridine (0.750 mL, 9.30 mmol), and acetic anhydride (0.450 mL, 4.65 mmol). The reaction was stirred until disappearance of starting material at RT (~2 h). The reaction was diluted with EtOAc, quenched with NH_4Cl (sat'd aq.), and the aqueous layer was re-extracted with EtOAc (3 x 10 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (5:1 hexanes:EtOAc) provided **3.18** (151 mg) in 94% yield as a clear oil.

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

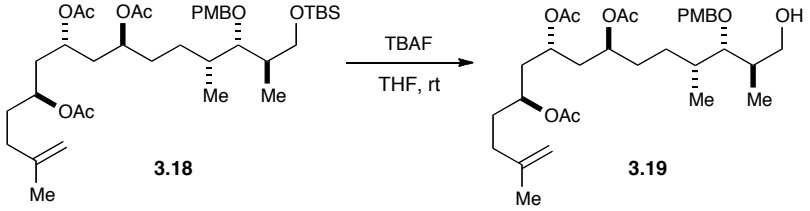
FTIR (neat) 2956, 2929, 2883, 2856, 1739, 1514, 1461, 1247 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.97 (dddd, *J* = 9.5, 6.2, 6.2, 3.1 Hz, 1H), 4.89 (m, 2H), 4.71 (s, 1H), 4.66 (s, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.46 (d, *J* = 10.9 Hz, 1H), 3.80 (s, 3H), 3.71 (dd, *J* = 9.7, 5.3 Hz, 1H), 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, 5H), 1.71 (s, 3H), 1.54-1.64 (m, 4H), 1.38-1.46 (m, 1H), 1.22-1.34 (m, 1H), 0.92 (s, 9H), 0.90 (d, *J* = 2.3 Hz, 3H), 0.88 (d, *J* = 2.3 Hz, 3H), 0.06 (s, 6H);

^{13}C NMR (126 MHz, $CDCl_3$) 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, 26.1, 22.6, 21.3, 21.3, 21.2, 18.5, 14.8, 13.6, -5.2, -5.2;

HRMS Exact Mass calculated 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: 3.19



To a solution of **3.18 (**150 mg, 0.216 mmol) in THF (2.3 mL) was added TBAF (0.70 mL, 1.0 M in THF). The reaction was stirred until disappearance of starting material at RT (~3 h). The reaction was diluted with EtOAc (3 mL), quenched with NH_4Cl (sat'd aq.), and the aqueous layer was re-extracted with EtOAc (2x5 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (2:1, hexanes:EtOAc) provided **3.19 (**118 mg) in 94% yield as a clear oil.

$[\alpha]_D$ +13.1 (*c* = 2.4, CH_2Cl_2);

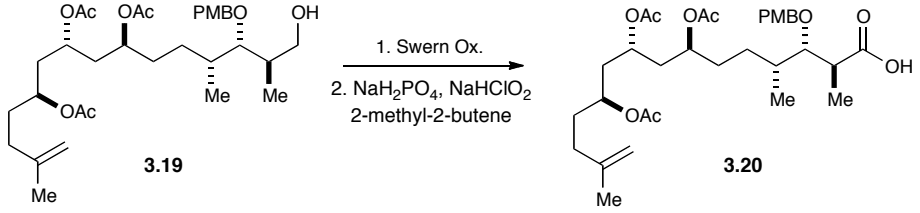
FTIR (neat) 3502, 3072, 2964, 2935, 2875, 1737, 1514, 1454, 1245 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.98 (dddd, *J* = 9.6, 6.3, 6.3, 3.3 Hz, 1H), 4.85-4.99 (m, 2H), 4.73 (s, 1H), 4.67 (s, 1H), 4.58 (d, *J* = 10.6 Hz, 1H), 4.51 (d, *J* = 10.6 Hz, 1H), 3.81 (s, 3H), 3.62-3.67 (m, 2H), 3.25 (dd, *J* = 7.6, 3.3 Hz, 1H), 2.71 (s, 1H), 1.99-2.07 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.86-1.95 (m, 2H) 1.68-1.84 (m, 6H), 1.72 (s, 3H), 1.56-1.64 (m, 2H), 1.44-1.54 (m, 1H), 1.22-1.34 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.7, 170.6, 170.5, 159.3, 144.7, 130.4, 129.4 (2), 113.9 (2), 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 calculated 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: 3.20



A solution of oxalyl chloride (0.046 mL, 0.539 mmol) in CH_2Cl_2 (1.67 mL) was cooled to -78 ºC and DMSO (0.077 mL, 1.08 mmol) was added slowly by syringe (gas evolution). After stirring for 10 minutes a solution of alcohol **3.19** (125 mg, 0.215 mmol) in CH_2Cl_2 (2.00 mL) was added by cannula and rinsed with CH_2Cl_2 (2 x 0.20 mL). The cloudy mixture was stirred at -78 ºC for 15 minutes at which time Et_3N (0.180 mL, 1.29 mmol) was added dropwise. The reaction mixture was stirred for 2 h at -78 ºC. The reaction was quenched at -78 ºC with sat. aq. $NaHCO_3$ (3 mL) and allowed to warm to RT. The reaction was diluted with CH_2Cl_2, and the layers were separated. The aqueous layer was re-extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give aldehyde **S6** as a yellow oil. The crude aldehyde was taken immediately to the next reaction with further purification.

To a solution of crude aldehyde **S6** was added *t*-butanol (4.5 mL) and 2-methyl-2-butene (1.5 mL). A solution of $NaClO_2$ (390 mg, 4.30 mmol) and sodium dihydrogen phosphate (470 mg, 3.01 mmol) in H_2O (2.00 mL) was prepared and added to the reaction mixture by syringe. The yellow solution was stirred vigorously for 2 h at RT, diluted with Et_2O (15 mL) and poured into H_2O (9 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3x10 mL). The combine organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (1:1 hexanes:EtOAc) provided **3.20** (104 mg) in 81% yield (over two steps) as a clear oil.

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

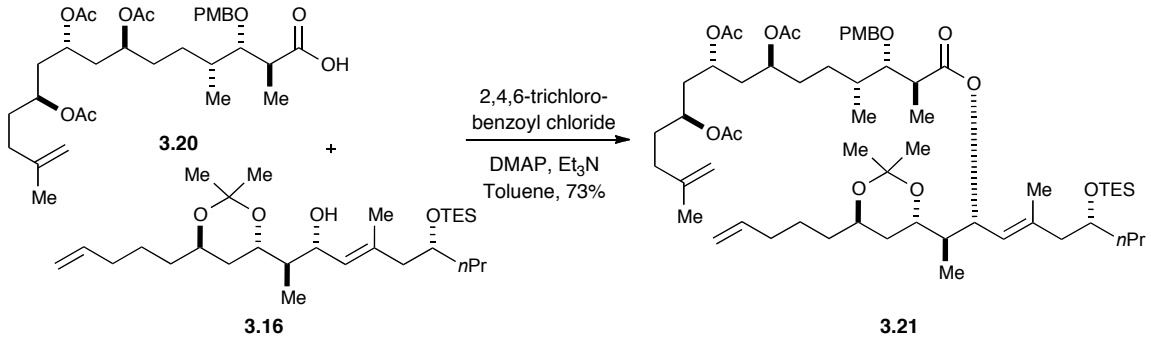
FTIR (neat) 3251, 3076, 2964, 2923, 2854, 1737, 1714, 1512, 1454, 1245 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.24 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.85-5.10 (m, 3H), 4.73 (s, 1H), 4.67 (s, 1H), 4.56 (d, *J* = 10.7 Hz, 1H), 4.50 (d, *J* = 10.6 Hz, 1H), 3.79 (s, 3H), 3.57 (dd, *J* = 7.2, 3.5 Hz, 1H), 2.78 (dddd, *J* = 14.33, 7.1, 7.1, 7.1 Hz, 1H), 1.99-2.07 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.86-1.95 (m, 2H) 1.64-1.84 (m, 5H), 1.72 (s, 3H), 1.40-1.64 (m, 3H), 1.20-1.39 (m, 2H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 177.3, 170.8, 170.7, 170.5, 159.4, 144.7, 130.0, 129.5 (2), 113.9 (2), 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 calculated 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*,*E*)-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: 3.21



To a solution of alcohol **3.16** (77 mg, 0.159 mmol), carboxylic acid **3.20** (106 mg, 0.175 mmol), and DMAP (975 mg, 7.98 mmol) in toluene (32 mL) at -78 ºC was added Et_3N (0.503 mL, 3.61 mmol) dropwise followed by the slow addition of 2,4,6-trichlorobenzoyl chloride (0.560 mL, 3.58 mmol), which caused the white solution to thicken. The mixture was stirred for 21 h at -78 ºC ensuring that the bath temperature did not rise above -65 ºC. The reaction flask was then moved to a dry ice/CH_3CN bath and stirred for 2.5 h maintaining the temperature between -30 ºC to -42 ºC. At the end of the 2.5 h the solution was slowly allowed to warm to RT in the bath over 1 h. The flask was placed in an ice bath for 2 h while being stirred. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer was back extracted with Et_2O (25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduce pressure. Purification by flash chromatography (5:1, hexanes:EtOAc) provided ester **3.21** (130 mg) in 77% yield as a colorless oil.

$[\alpha]_D$ +3.63 (*c* = 0.28, CH_2Cl_2);

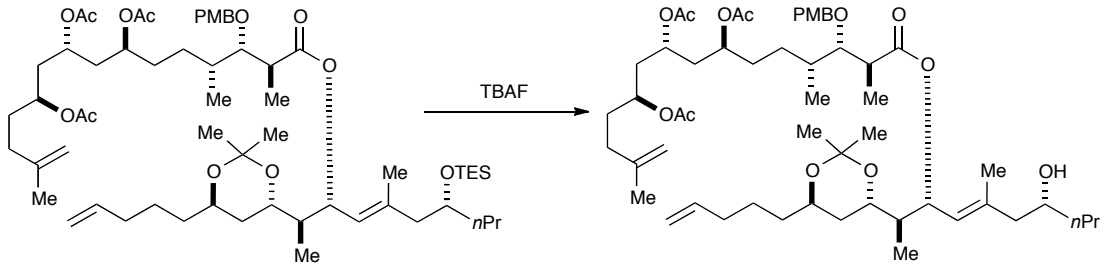
FTIR (neat) 3076, 2954, 2935, 2875, 1739, 1515, 1442, 1244 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.19 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.82 (dddd, *J* = 17.0, 10.2, 6.8, 6.8 Hz, 1H), 5.68 (dd, *J* = 9.9, 5.7 Hz, 1H), 5.17 (d, *J* = 9.8 Hz, 1H), 5.02 (ddd, *J* = 17.1, 3.2, 1.6 Hz, 1H), 4.93-5.00 (m, 3H), 4.85-4.94 (m, 2H), 4.74 (s, 1H), 4.67 (s, 1H), 4.51 (d, *J* = 10.8 Hz, 1H), 4.34 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 3.70-3.80 (m, 2H), 3.60-3.69 (m, 3H), 2.69 (dt, *J* = 14.2, 7.1 Hz, 1H), 1.89-2.20 (m, 8H), 2.06 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.76 (s, 3H), 1.73 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.20-1.80 (m, 18H), 1.08 (d, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.84-0.93 (m, 9H) 0.58 (q, *J* = 7.9 Hz, 6H);

^{13}C NMR (126 MHz, $CDCl_3$) 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, 14.2, 13.2, 9.8, 7.0 (3), 5.0 (3);

HRMS Exact Mass calculated 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*,*E*)-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: S7



3.21 **S7**

Ester **3.21** (75 mg, 0.071 mmol) was dissolved in THF (1 mL) and cooled to 0 ºC. A solution of TBAF in THF (0.214 mL, 1.0 M in THF) was added dropwise. The reaction stirred at 0 ºC until completion (approximately 45 minutes). The reaction was quenched with sat. aq. NH_4Cl and the aqueous layer was extracted with EtOAc (3 x 10 mL portions). The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash chromatography (2:1, hexanes:EtOAc) afforded **S7** (63 mg) as a clear oil in 94% yield.

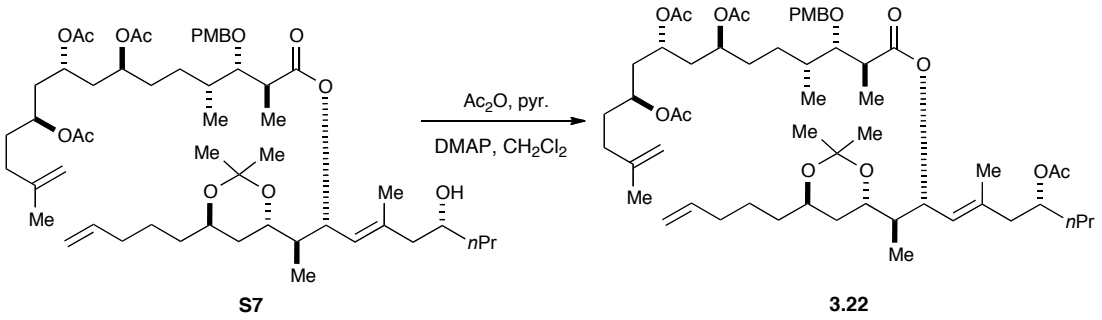
$[\alpha]_D$ -11.4 (*c* = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.22 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.81 (dddd, *J* = 17.0, 10.2, 6.7, 6.7 Hz, 1H), 5.64 (dd, *J* = 9.9, 5.2 Hz, 1H), 5.20 (d, *J* = 9.6 Hz, 1H), 5.01 (ddd, *J* = 17.1, 3.4, 1.6 Hz, 1H), 4.93-5.00 (m, 2H), 4.85-4.93 (m, 2H), 4.72 (s, 1H), 4.67 (s, 1H), 4.53 (d, *J* = 10.7 Hz, 1H), 4.38 (d, *J* = 10.7 Hz, 1H), 3.79 (s, 3H), 3.69-3.76 (m, 1H), 3.59-3.66 (m, 1H), 3.60-3.54 (m, 1H), 3.53 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.70 (dt, *J* = 15.2, 7.2 Hz, 1H), 1.87-2.15 (m, 8H), 2.06 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.20-1.80 (m, 21H), 1.76 (s, 3H), 1.73 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 1.10 (d, *J* = 7.1 Hz, 3H), 0.84-0.93 (m, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) 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 calculated 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*,*E*)-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: 3.22



S7 **3.22**

To a solution of **S7** (58 mg, 0.0616 mmol) in CH_2Cl_2 (3.0 mL) was added DMAP (1 crystal), pyridine (0.200 mL, 2.46 mmol) and acetic anhydride (0.117 mL, 1.23 mmol). The reaction was stirred at RT until disappearance of starting material (~2 h). The reaction was diluted with EtOAc, quenched with NH_4Cl (sat'd aq.) and the aqueous layer was re-extracted with EtOAc (3 x 5 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (1.5:1, hexanes:EtOAc) provided **3.22** (60 mg) in 98% yield as a clear oil.

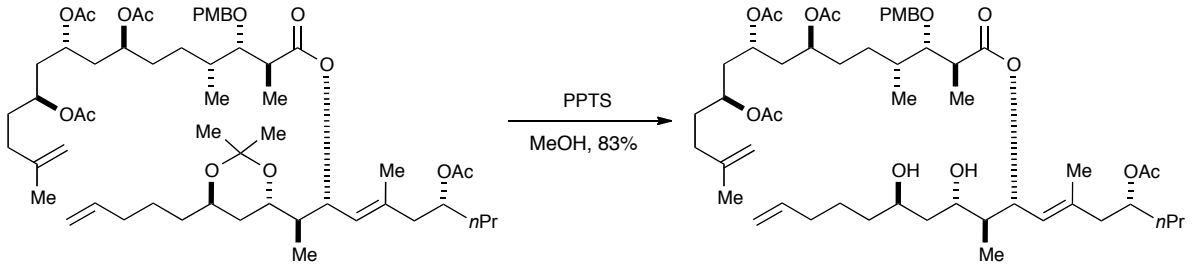
$[\alpha]_D$ +2.2 (*c* = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.18 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.80 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H), 5.67 (dd, *J* = 9.9, 5.6 Hz, 1H), 5.16 (d, *J* = 9.7 Hz, 1H), 5.00 (ddd, *J* = 17.1, 3.4, 1.6 Hz, 1H), 4.92-5.00 (m, 3H), 4.84-4.92 (m, 2H), 4.73 (s, 1H), 4.66 (s, 1H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.35 (d, *J* = 10.9 Hz, 1H), 3.79 (s, 3H), 3.68-3.75 (m, 1H), 3.55-3.62 (m, 2H), 2.68 (dt, *J* = 16.0, 6.9, 1H), 1.87-2.15 (m, 8H), 2.06 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.20-1.80 (m, 20H), 1.77 (s, 3H), 1.73 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.84-0.93 (m, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) 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 calculated 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*,*E*)-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: S8



To a solution of tetraacetate **3.22** (60 mg, 0.0609 mmol) in MeOH (6 mL) was added PPTS (2.5 mg, 0.0305 mmol). The reaction was stirred until disappearance of starting material at RT (~ 4 h). The reaction was diluted with EtOAc, quenched with $NaHCO_3$ (sat'd aq.) and the aqueous layer was re-extracted with EtOAc (3 x 10 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (1.5:1, hexanes:EtOAc) provided **S8** (47 mg) in 82% yield as a clear oil.

$[\alpha]_D$ +8.97 (*c* = 1.7, $CHCl_3$);

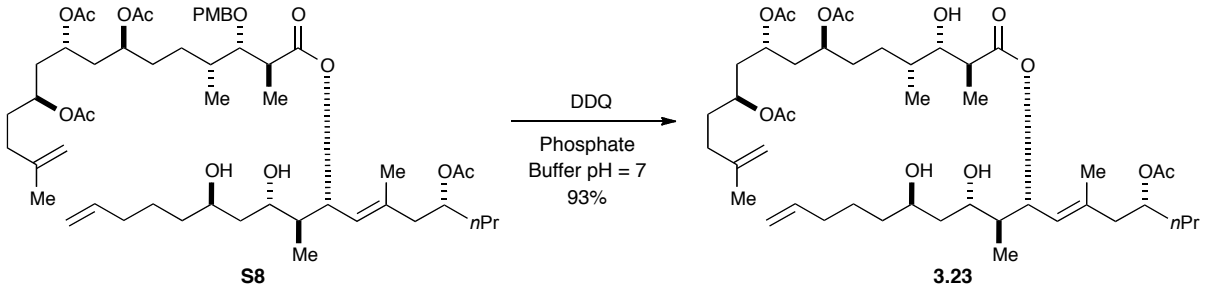
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.21 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.82 (dddd, *J* = 15.8, 12.1, 5.4, 5.4 Hz, 1H), 5.69 (dd, *J* = 9.7, 6.0 Hz, 1H), 5.18 (d, *J* = 9.8 Hz, 1H), 4.85-5.05 (m, 6H), 4.73 (s, 1H), 4.67 (s, 1H), 4.51 (d, *J* = 10.9 Hz, 1H), 4.34 (d, *J* = 11.0 Hz, 1H), 3.86-3.92 (m, 1H), 3.80 (s, 3H), 3.71 (m, 1H), 3.58 (dd, *J* = 8.4, 2.0 Hz, 1H), 2.73 (dddd, *J* = 14.2, 6.8, 6.8, 6.8 Hz, 1H), 1.19-2.50 (m, 28H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.82 (s, 3H), 1.72 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.81-0.86 (m, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) 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 calculated 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*,*E*)-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: 3.23



Ester **S8** (105 mg, 0.112 mmol) was taken up in CH_2Cl_2 (5.0 mL) followed by the addition of pH = 7 buffer solution (5.0 mL) and DDQ (51 mg, 0.224 mmol) at RT. Upon completion (~0.5 h, monitored by TLC), CH_2Cl_2 (13 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 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (2:1, hexanes:EtOAc) afforded **3.23** (89 mg) in 97% yield as a clear oil.

$[\alpha]_D$ +4.4 (*c* = 0.50, $CHCl_3$);

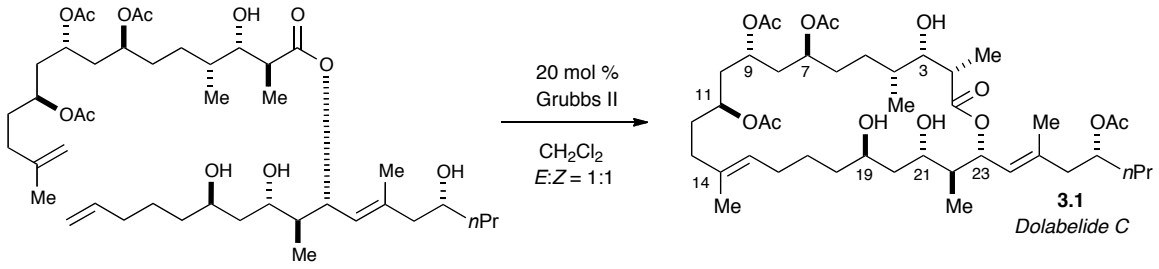
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.79 (dddd, *J* = 17.0, 10.2, 6.7, 6.7 Hz, 1H), 5.19 (dd, *J* = 9.7, 9.5 Hz, 1H), 4.87-5.07 (m, 6H), 4.73 (s, 1H), 4.66 (s, 1H), 4.09-4.15 (m, 2H), 3.89-3.96 (m, 1H), 3.71 (dd, *J* = 9.9, 1.2 Hz, 1H), 2.54 (dddd, *J* = 14.1, 7.0, 7.0, 7.0 Hz, 1H), 1.19-2.17 (m, 28H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.82 (s, 3H), 1.72 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.81-0.86 (m, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) 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 calculated 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: 3.1



To a refluxing solution of ester **3.23** (70 mg, 0.0849 mmol) in degassed CH_2Cl_2 (175 mL) was added Grubbs II catalyst (8.0 mg, 0.00849 mmol). The reaction was refluxed 2 h with the addition of more catalyst (4.0 mg, 0.00425 μmol) after 2 h. A third portion of catalyst (4.0 mg, 0.00425) was had after 2 more hours, the reaction was refluxed for 6 hours (monitored by TLC and LC-MS). The solution was cooled to RT and concentrated under reduced pressure. The resultant residue was purified via flash chromatography through two sequential columns (8:1 CH_2Cl_2/acetone) and (5:1, pentane/EtOAc) delivered **3.1**, (14.0 mg, 21% yield) as an analytically pure sample and its C14-C15 *Z*-configured diastereomer (10 mg, 15% yield) (vide infra).

$[\alpha]_D$ +2.9 (*c* = 0.63, $CHCl_3$);

^{1}H NMR (500 MHz, pyridine-d_5)[11] δ ppm 5.90-6.10 (br m, 1H), 5.70 (t, *J* = 9.3 Hz, 1H), 5.67 (s, 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,

[11] Spectrum integrated to 71 total H, where the unassigned H was presumed to be an O-H peak undergoing H-D exchange. Only the O-H peaks did not match exactly to the reported data.

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;

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.35 (t, J = 9.1 Hz, 1H), 5.05-5.10 (m, 2H), 5.00-5.04 (m, 1H), 4.92-4.98 (m, 1H), 4.82-4.88 (m, 2H), 4.08 (s, 1H), 3.93 (s, 1H), 3.57 (s, 1H), 3.24 (s, 1H), 2.54-2.60 (m, 1H), 2.47-2.54 (m, 1H), 2.25 (dd, J = 7.1, 13.8 Hz, 1H), 2.21 (dd, J = 5.7, 14.1 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.83-1.90 (m, 2H), 1.81 (s, 3H), 1.64-1.78 (m, 3H), 1.62-1.64 (m, 4H), 1.58 (s, 3H), 1.44-1.56 (m, 9H), 1.20-1.43 (m, 9H), 1.07 (d, J = 7.1 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.84 (m, 6H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 171.2, 171.0, 170.7, 170.4, 137.9, 133.1, 126.1, 125.0, 74.6, 73.1, 72.2, 69.8, 69.2, 68.7, 68.1, 67.7, 45.1, 44.3, 42.7, 39.1, 36.8, 36.1, 35.1, 34.6, 31.9, 31.7, 29.7, 28.3, 26.7, 25.0, 21.2, 21.2, 21.2, 21.1, 18.5, 17.7, 15.2, 13.9, 13.6, 12.6, 10.6;

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

*Spectral Data for C14-C15 Z-Diastereomer **4.1***

^{1}H NMR (500 MHz, pyridine-d_5)[12] δ 6.28 (br s , 1 H), 6.05-6.20 (br m, 1 H), 5.85 (t, J = 9.4 Hz, 1 H), 5.51 (d, J = 8.8 Hz, 1 H), 5.40-5.48 (m, 2 H), 5.40-5.48 (m, 2 H), 5.29-5.38 (m, 2 H), 5.18-5.27 (m, 1 H), 4.84-4.88 (m, 1 H), 4.46-4.53 (m, 1 H), 4.14 (br d, J = 7.4 Hz, 1 H), 2.97-3.03 (m, 1 H), 2.56-2.64 (m, 1 H), 2.43 (dd, J = 7.5, 13.8 Hz, 1 H), 2.37 (dd, J = 5.3, 13.1 Hz, 1 H), 2.23-2.34 (m, 3 H), 2.19-2.22 (m, 1 H), 2.14-2.18 (m, 12 H),[13] 2.12-2.13 (m, 1 H), 2.08 (s, 3 H), 2.02-2.06 (m, 1 H), 2.00-2.02 (m, 1 H), 1.95-1.99 (m, 2 H), 1.91-1.95 (m, 1 H), 1.86-1.91 (m, 2 H), 1.79-1.81 (m, 1 H), 1.77 (s, 3 H), 1.66-1.75 (m, 3 H), 1.58-1.64 (m, 2 H); 1.31-1.49 (m, 4 H), 1.21-1.31 (m, 6 H), 1.04 (d, J = 6.6 Hz, 2 H), 0.94 (t, J = 7.3 Hz, 3 H);

^{13}C NMR (126 MHz, pyridine-d_5) δ ppm 174.2, 170.9, 170.9, 170.7, 170.6, 137.2, 134.3, 127.3, 126.9, 75.2, 73.6, 72.2, 71.8, 70.1, 68.3, 68.2, 68.1, 46.6, 44.8, 44.3, 39.9, 39.2, 39.0, 37.6, 36.7, 34.4, 32.8, 32.0, 29.3, 28.4, 27.9, 27.5, 23.3, 21.4, 21.4, 21.3, 21.3, 19.1, 17.9, 14.3, 14.3, 13.0, 11.4;

^{1}H NMR (500 MHz, $CDCl_3$)[14] δ ppm 5.07-5.13 (m, 2H), 4.97-5.03 (m, 3H), 4.91-4.96 (m, 1H), 4.85-4.90 (m, 1H), 4.27 (s, 1H), 4.01-4.05 (m, 1H), 3.68 (d, J = 9.7 Hz, 1H), 2.54 (tt, J = 7.0 Hz, 1H), 2.20-2.31 (m, 4H), 2.13-2.11 (m, 1H), 2.08-2.11 (m, 1H), 2.04-2.06 (m, 2H), 2.03-2.04 (m, 6H), 2.02 (s, 3H), 2.01 (s, 3H), 1.97-2.00 (m, 1H), 1.95-1.97 (m, 1H), 1.82 (s, 3H), 1.76-1.81 (m, 2H), 1.74-1.76 (m, 1H), 1.74-1.71 (m, 1H), 1.66 (s, 3H), 1.61 (s, 1H), 1.58-1.56 (m, 1H), 1.46-1.48 (m, 2H), 1.43-1.45 (m, 2H), 1.39-1.42 (m, 2H), 1.25-1.38 (m, 6H), 1.01 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 173.6, 171.6, 171.3, 170.7, 170.4, 137.6, 133.9, 125.9, 125.8, 74.0, 72.8, 72.3, 71.3, 70.8, 68.0, 67.0, 66.6, 45.7, 44.1, 42.9, 38.0, 37.4, 37.0, 35.9, 34.9, 33.6, 32.2,

[12] Spectrum integrated to 69 total H, where the unassigned H resonances were presumed to be an O-H peaks undergoing H-D exchange.
[13] Spectrum shown integrates to 11H. An integration from δ 2.23-2.07 resulted in a 19H multiplet, where the known signals were subtracted around δ 2.22–2.19 resulting in a 12H signal.
[14] Spectrum integrated to 69 total H, where the unassigned H's were presumed to be O-H peaks undergoing H-D exchange.

31.1, 28.2, 26.7, 25.9, 22.8, 21.4, 21.2, 21.2, 21.2, 21.2, 18.5, 17.8, 13.9, 13.4, 11.5, 9.36;

$[\alpha]_D$ +10.0 (*c* = 0.30, $CHCl_3$);

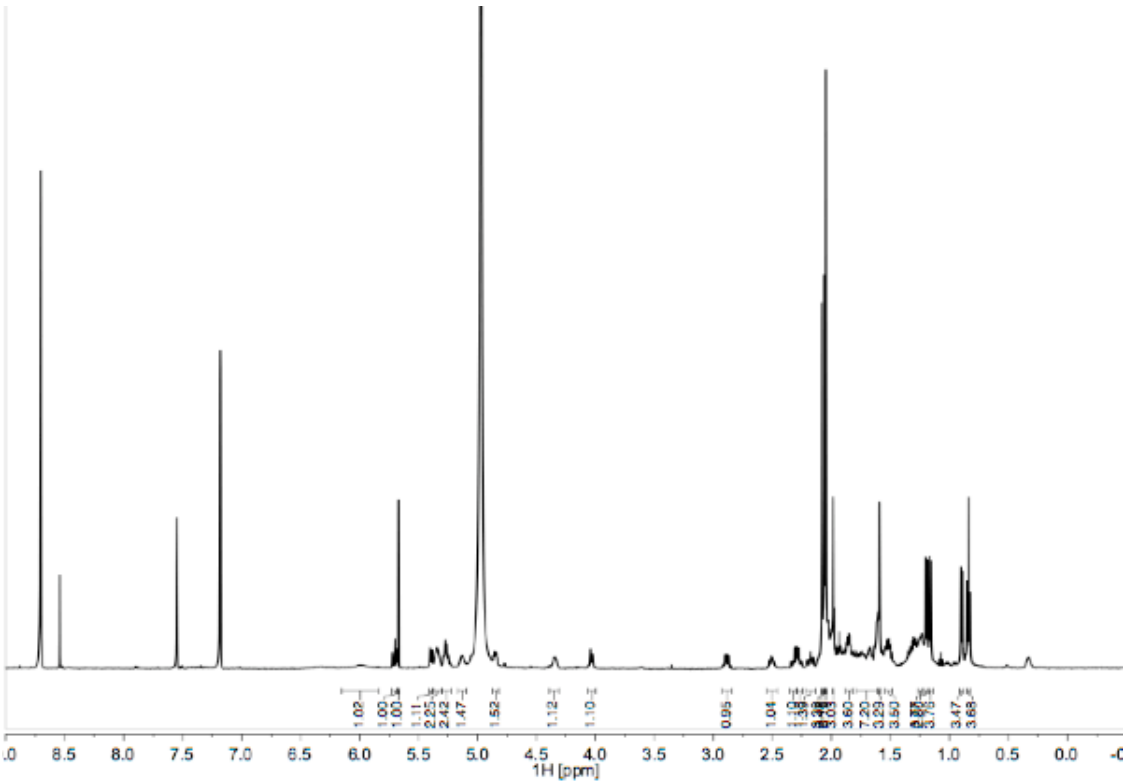
HRMS Exact Mass calculated for $C_{43}H_{72}NaO_{13}$ $(M+Na)^+$ 819.4871; found 819.4877 (ESI).

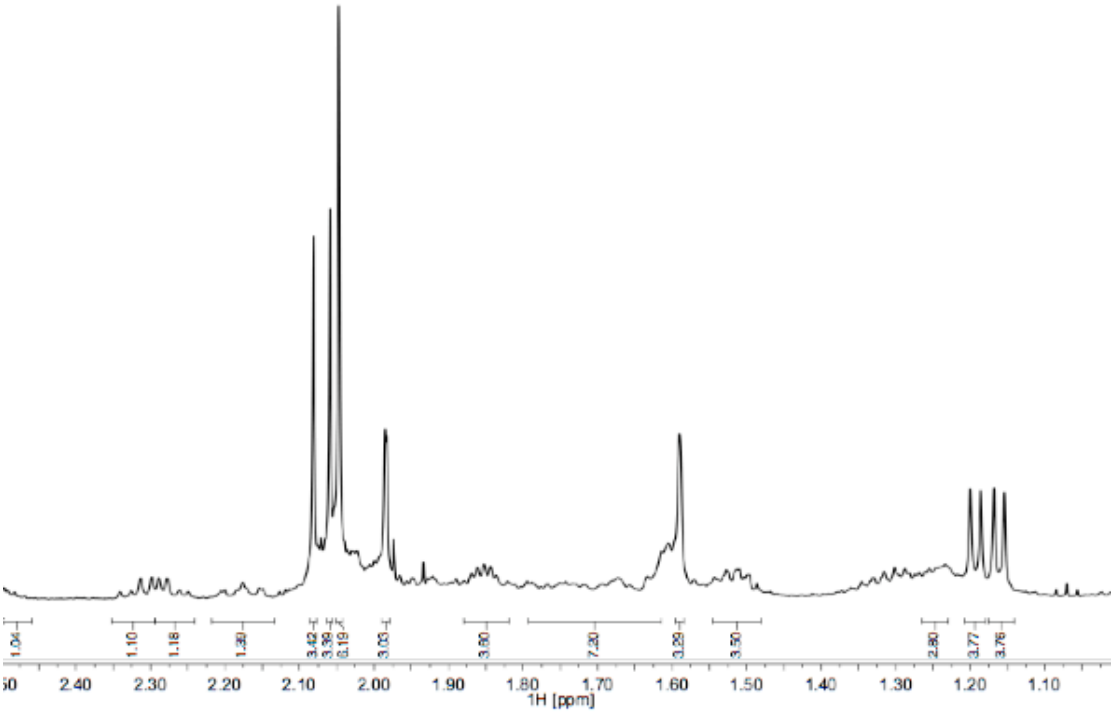
*HPLC-MS Analysis of **3.1***

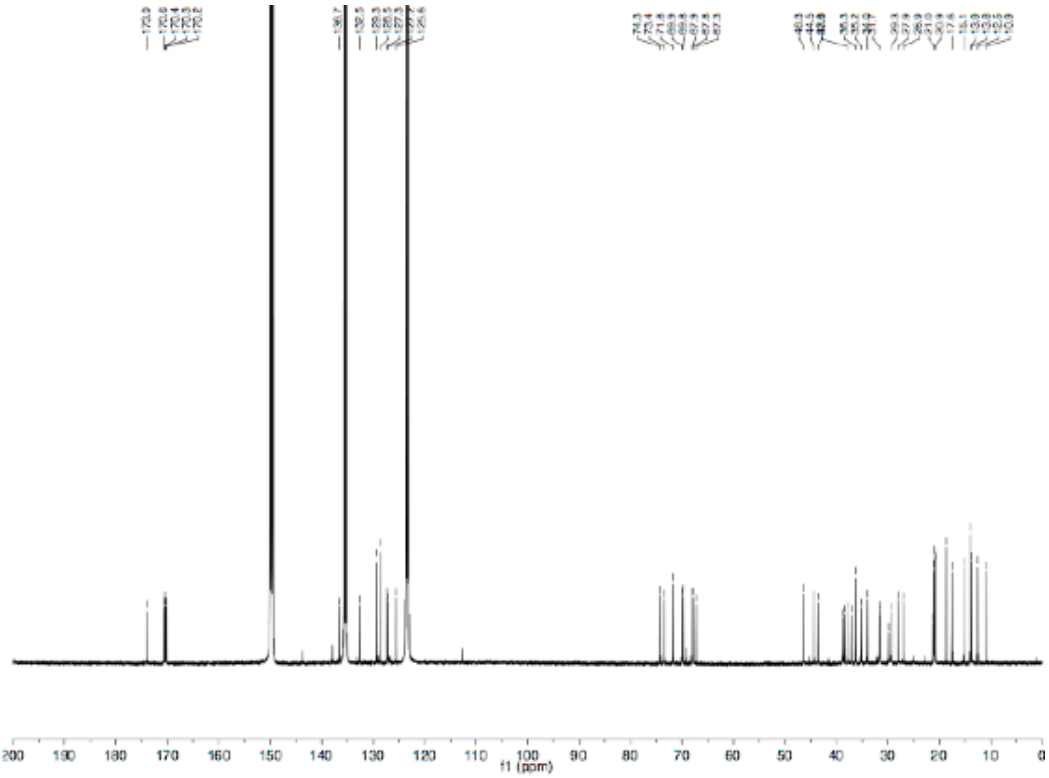
HPLC data was collected using the following gradient over 35 minutes:

Time (min)	A% (99:1 H_2O:MeCN)	B% (99:1 MeCN: H_2O)	Flow Rate (mL/min)
0.00	95.0	5.0	1.000
1.00	40.0	60.0	1.000
31.00	30.0	70.0	1.000

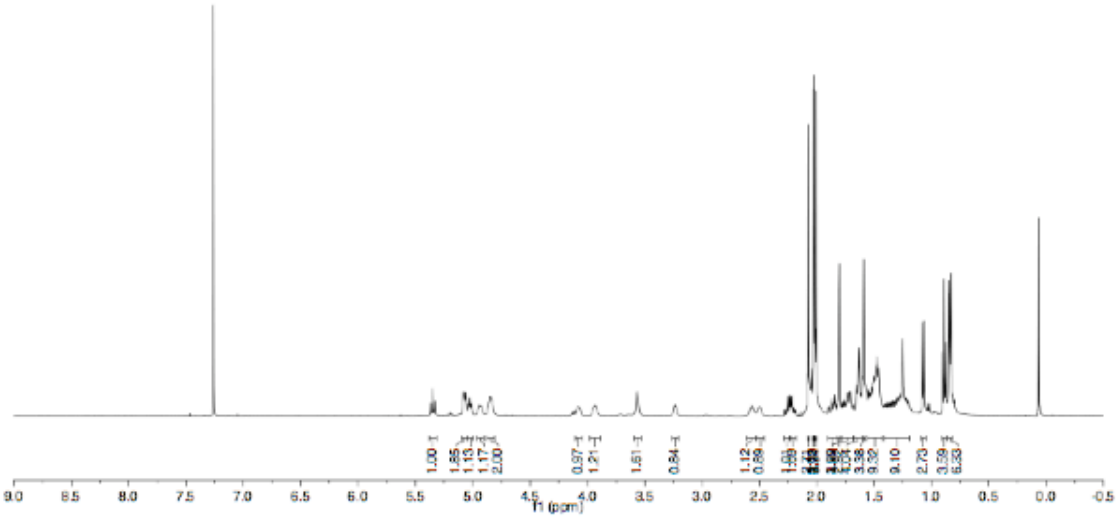
Dolabelide C (3.1), *E*-Isomer in pyridine-D_5

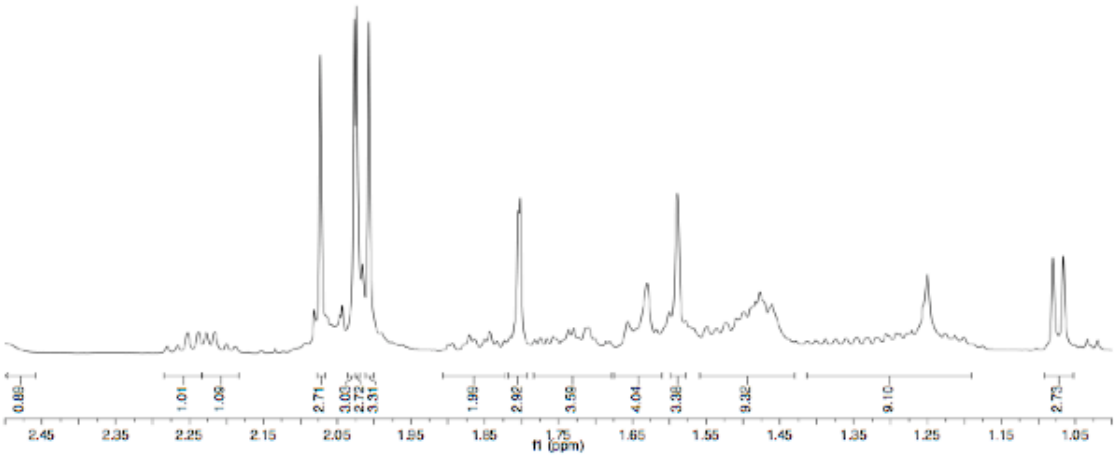


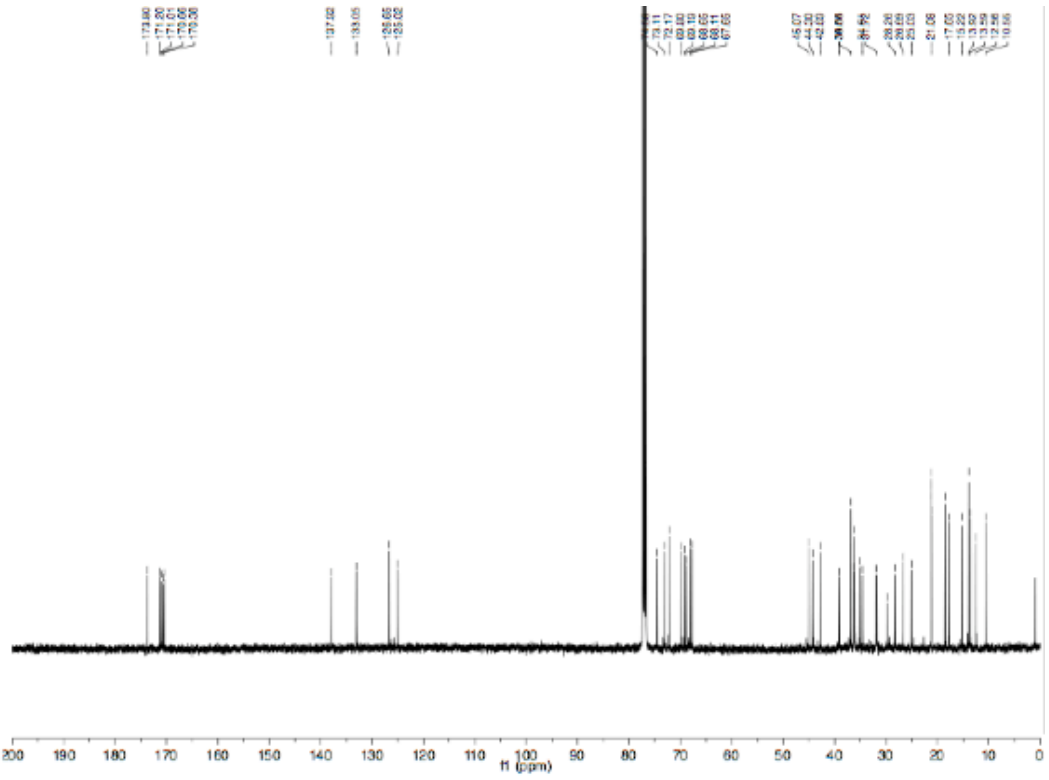



f1 (ppm)

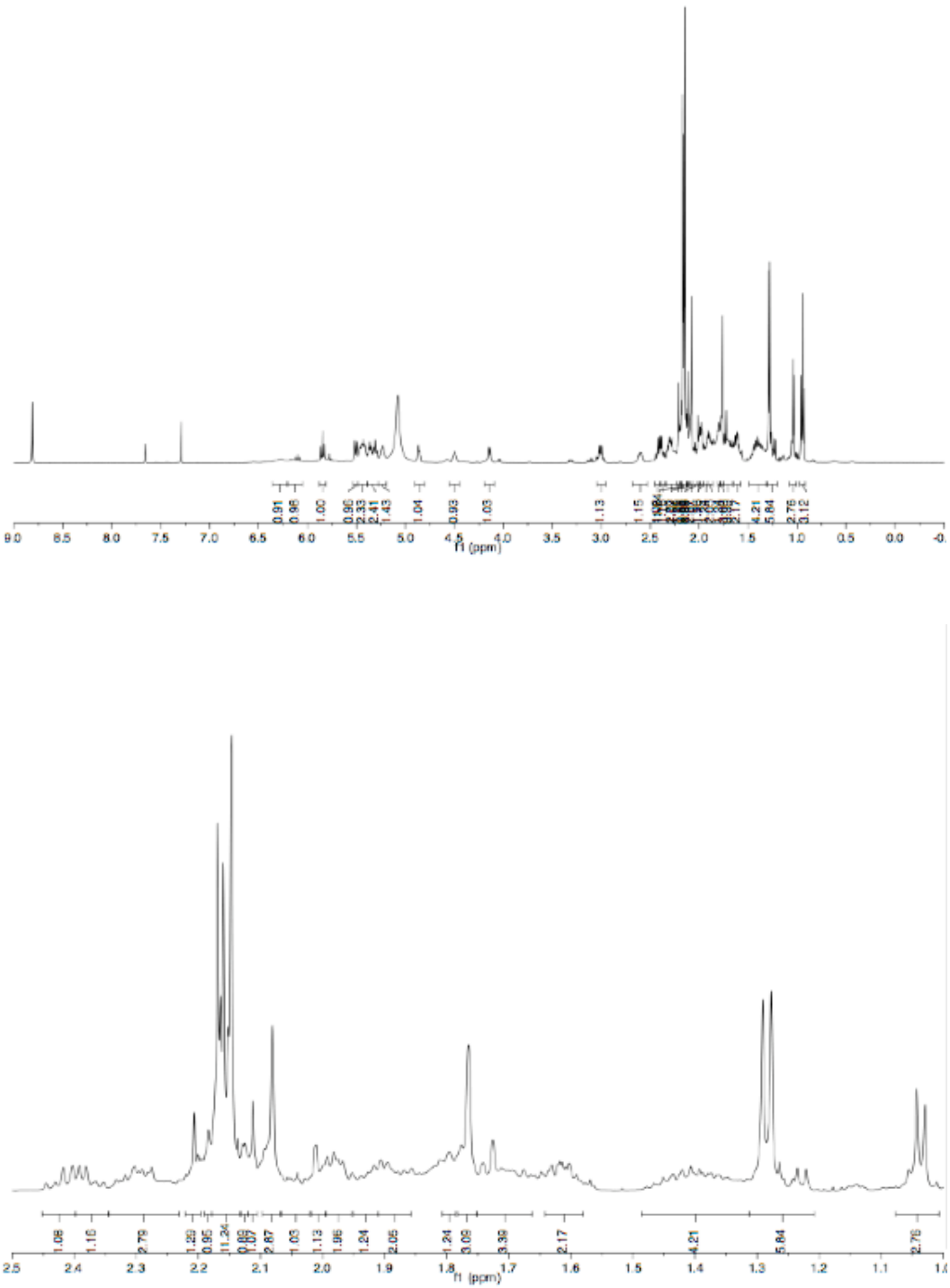
Dolabelide C (3.1), *E*-Isomer in $CDCl_3$

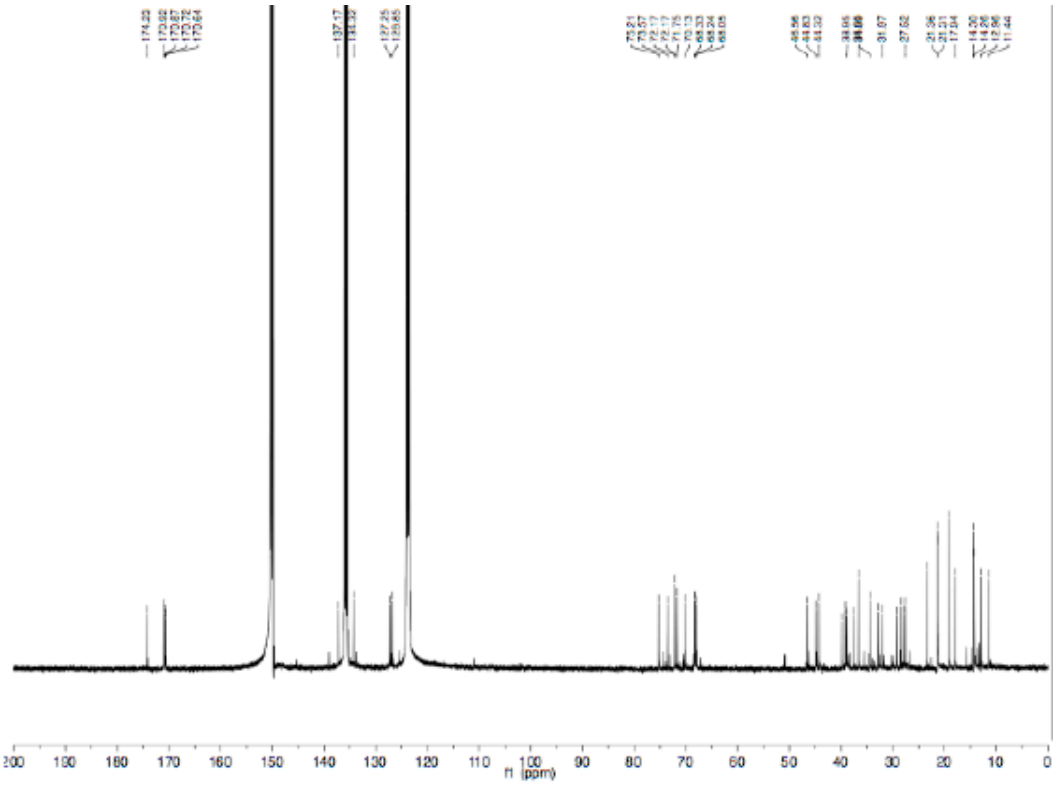




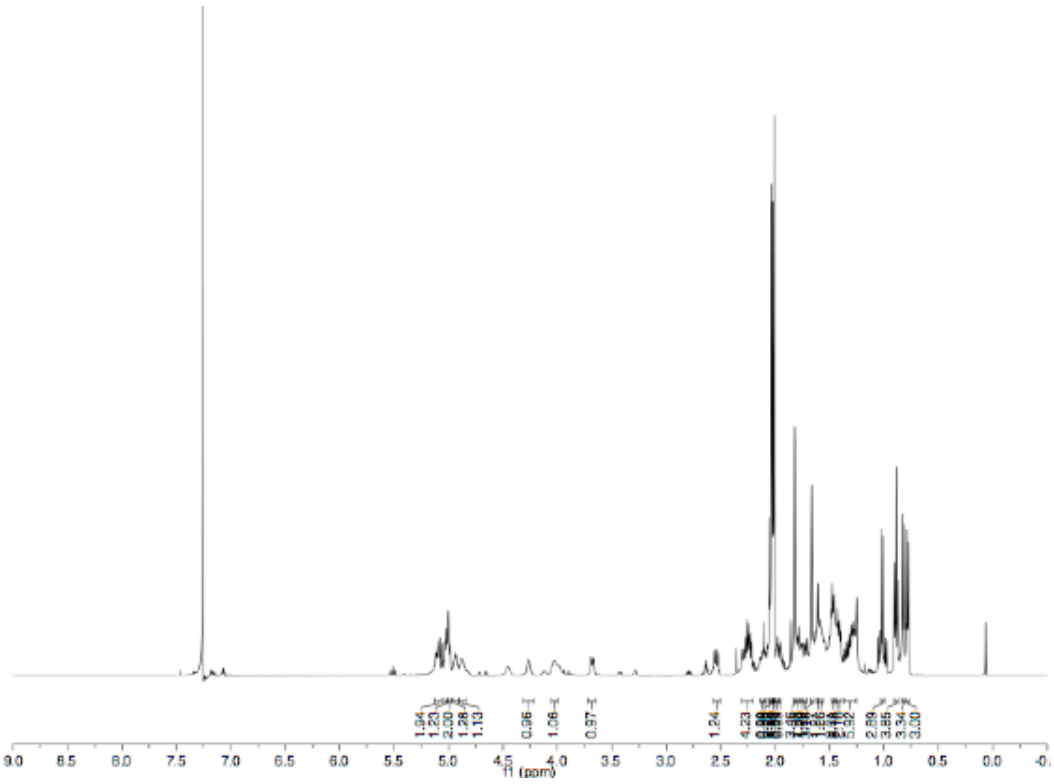

f1 (ppm)

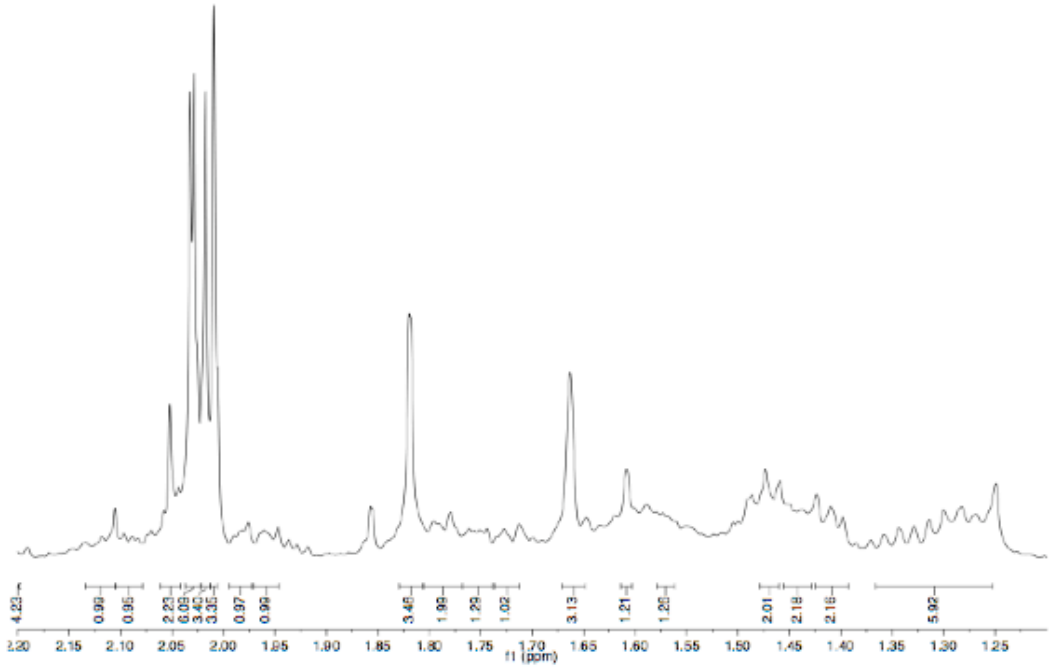
Dolabelide C, *Z*-Isomer (4.1) in pyridine-D_5

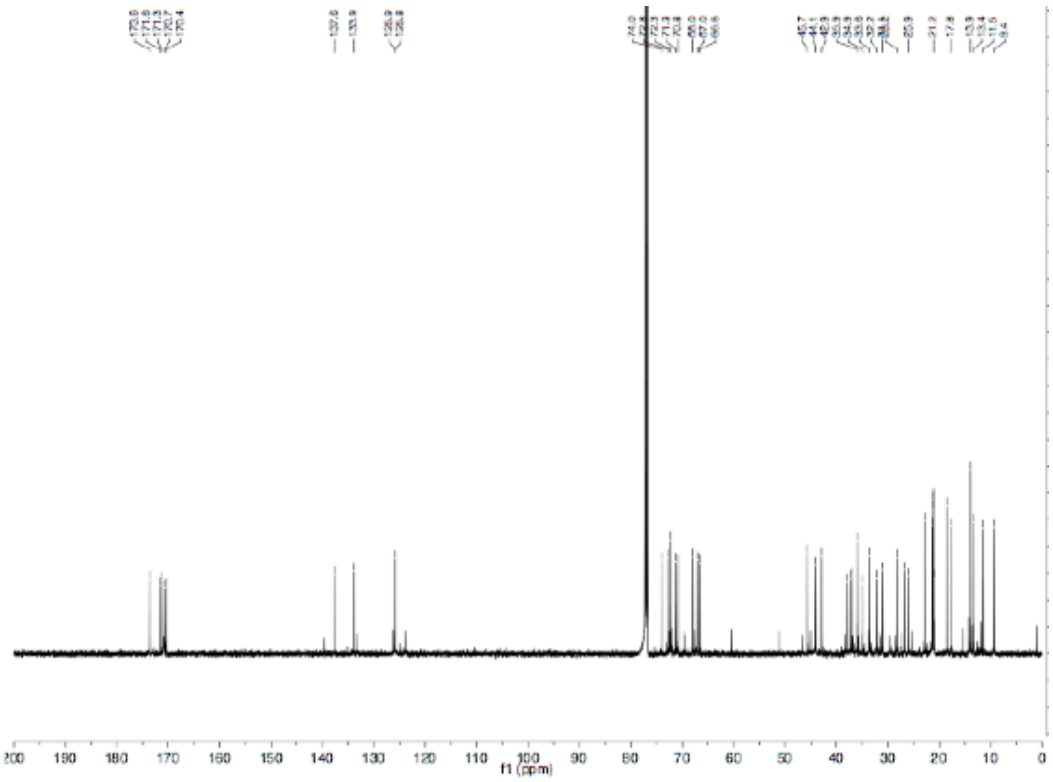



f1 (ppm)

Dolabelide C, *Z*-Isomer (4.1) in $CDCl_3$






f1 (ppm)