Multivalent Activation Imparted by Phosphate Tethers:

Metathesis Efforts Towards Fostriecin

By

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B.S. Chem. Loyola University Chicago, 2003

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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July 30, 2009
Date Defended

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Abstract

James P. McParland, Ph. D.

Department of Chemistry, July 2009

The University of Kansas

The utilization and exploration of multifaceted phosphate tethers in synthesis is the focus of the dissertation research described herein. Desymmetrization of a readily derived psuedo-C_2-symmetric monocyclic phosphate via highly diastereoselective *anti*-S_N2' allylic displacement reactions are reported. This method utilizes a wide variety of zinc-derived organocuprates to afford *E*-1,2-*syn*-configured phosphate acid building blocks. Extension of this protocol to unsymmetric monocyclic phosphates exclusively yields 1,2-*anti*-configured products. Within this study stereoelectronic factors coupled with allylic strain ultimately govern regio- and diastereoselective cuprate reactions, thus further substantiating the Corey mechanism for organocuprate additions into allylic esters.

An approach towards fostriecin and fostriecin-like libraries utilizing rapid functionalization via a bicyclic phosphate methodology was investigated. This compact, multifaceted core coupled with an array of selective reactive pathways begged the synthetic queries enacted. Key to unraveling and expanding upon this central core of the molecule was realization of an exocyclic olefin oxidation and a diastereoselective Grignard addition where the source of Grignard used was found to play an important role. Selective cross-metathesis with subsequent attack of lithium thiophenol exploits the orthogonal leaving group ability of the phosphate to reveal the

requisite stereo-tetrad of fostriecin. Not only does this sequence serve as a proof of concept approach for the total synthesis of fostriecin, it also serves as an archetype for the generation of fostriecin-like and phoslactomycin-like libraries.

The explorations of two synthetic approaches towards fostriecin from the bicyclic phosphate were embarked upon simultaneously. Intensive studies found the deactivating nature of the carboxylate oxygen on the alkene of lactone in conjunction with the lethargic protected tertiary allylic alcohol provided unacceptable conversion upon metathesis, despite installation of catalyst delivery vehicles. Attempts to utilize the unprotected bicyclic phosphate variant displayed preferential dimerization in the cross metathesis, while the relay primed analog was frustrated by competing elimination pathways. Analysis of an organometallic addition of the lactone core provided a viable route for future endeavors in the total synthesis.

To my wife,

Crystal

Acknowledgements

The six years I have spent working in pursuit of a Ph. D. could not have been possible, bearable, or educational without a host of talented and unique individuals. If you are not on this very brief list, it is not due to any lack of gratitude or shortsightedness, but rather the physical restrictions of this document. A truly comprehensive list would fill a multi-volume series of books. To all I have had the honor to work, interact, and benefit, my sincerest thanks.

Crystal: My beloved, you have shared trials and tribulations alike with me in these short but wonderful years we have been together. Your support and encouragement continues to see me through. My life is better because you have graced me with your presence. I have no words sufficient to thank you for all that you are and all that you do, so please accept my lifelong adoration and devotion. I love you.

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ylide; I'd be more than happy to remind you. In case you're interested, it happened twice more, once more by the same culprit and another time by a new individual.

Josh Waetzig: I don't think I could have made it through much in graduate school without your camaraderie. All the fun and laughs helped with all the sweat and blood spilled during these graduate years. Thanks for being a great chemist, cool-headed colleague, and a good friend.

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The McParland Family: To my Mom and Dad, you've been my biggest supporters for the longest amount of time. Thank you for the love, and I'll always try to be the best son to and for you. To Paul, your presence here in Lawrence has allowed me to survive and obtain a best friend in you. To Bobby, your demeanor and humor is inspiring. I hope to become best friends with you as well. To Mary, thank you for your abundant love and encouragement. Know I believe in you, too.

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Abbreviations

2,6-lut.	2,6-lutidine
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
Alloc	allyloxycarbonyl
aq	aqueous
Bn	benzyl
Bu	butyl
cat.	catalytic
CM	cross metathesis
Cu	Copper
Cy	cyclohexyl
dba	dibenzylidene acetone
DCE	dichloroethane
DCC	*N*,*N*-dicyclohexylcarbodiimide
DDQ	dichlorodicyanoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
ent	enantiomer
Et	ethyl
EtOAc	ethyl acetate

EtOH	ethanol
FAB	fast atom bombardment
GC	gas chromatography
hν	irradiation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
h	hour
i-Bu	isobutyl
IC_{50}	inhibitory concentration at 50%
$IMes_2$	1,3-dimesityl-4.5-dihydroimidazol-2-ylidene
Imid	imidazole
IR	infrared radiation
Ipc	isopinocampheyl
i-Pr	isopropyl
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
N-	nitrogen-
n-BuLi	*n*-butyl lithium
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nuc	nucleophile

[Ox]	oxidation
P-	phosphorous-
P(III)	phosphorous-(III)
P(V)	phosphorous-(V)
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
pyr.	pyridine
RCM	ring-closing metathesis
Red-Al®	Sodium bis(2-methoxyethoxy)aluminum hydride
rt	room temperature
sat.	saturated
SM	starting material
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethylsilyl triflate
t-Bu	tertiary butyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TIPSCl	triisopropylsilyl chloride

Chapter 1

Total Syntheses of Several Natural Product Phosphatase Inhibitors:
Establishing a Paradigm for the Exploration of Phosphate Tethers

1.1 Introduction

Investigation of phosphatase inhibitors as pharmacologically viable targets is relatively new compared to investigations on kinase inhibitors.[1] While initially phosphatases were regarded as enzymes that "clean-up" after more essential regulatory kinases, a large body of evidence dismisses this misconception in light of the pivotal role of phosphatases in the body.[2] As such, naturally occurring phosphatase inhibitors have arisen as potent probes of the mechanisms of phosphatases as well as therapeutic agents in and of themselves.[1] The following review is designed to cover some of the major total synthetic efforts towards particularly attractive and representative natural product phosphatase inhibitors. Of the phosphatase inhibitors to be discussed (calyculins A and B, dysidiolide, motuporin, tautomycin, phoslactomycin A and B, spirastrellolide A methyl ester, okadaic acid, and fostriecin), the notable omissions of the leustroducsins and cytostatin are due to their more explicit treatment within the remaining chapters of this dissertation, vide infra. Other omissions (Figure 1) are the cladocorans A and B,[3] coscinosulfate,[4] dephostatin,[5] the dinophysistoxins,[6] glucolipsin A,[7] gymnorrhizol,[8] microcystin-LA,[9] pulchellalactam,[10] thyrsiferol and thyrsiferyl 23-acetate,[11] TMC-69 and TMC-69-6*H*;[12] the references provided for these omissions can provide information on these natural product phosphatase inhibitors and their respective syntheses.

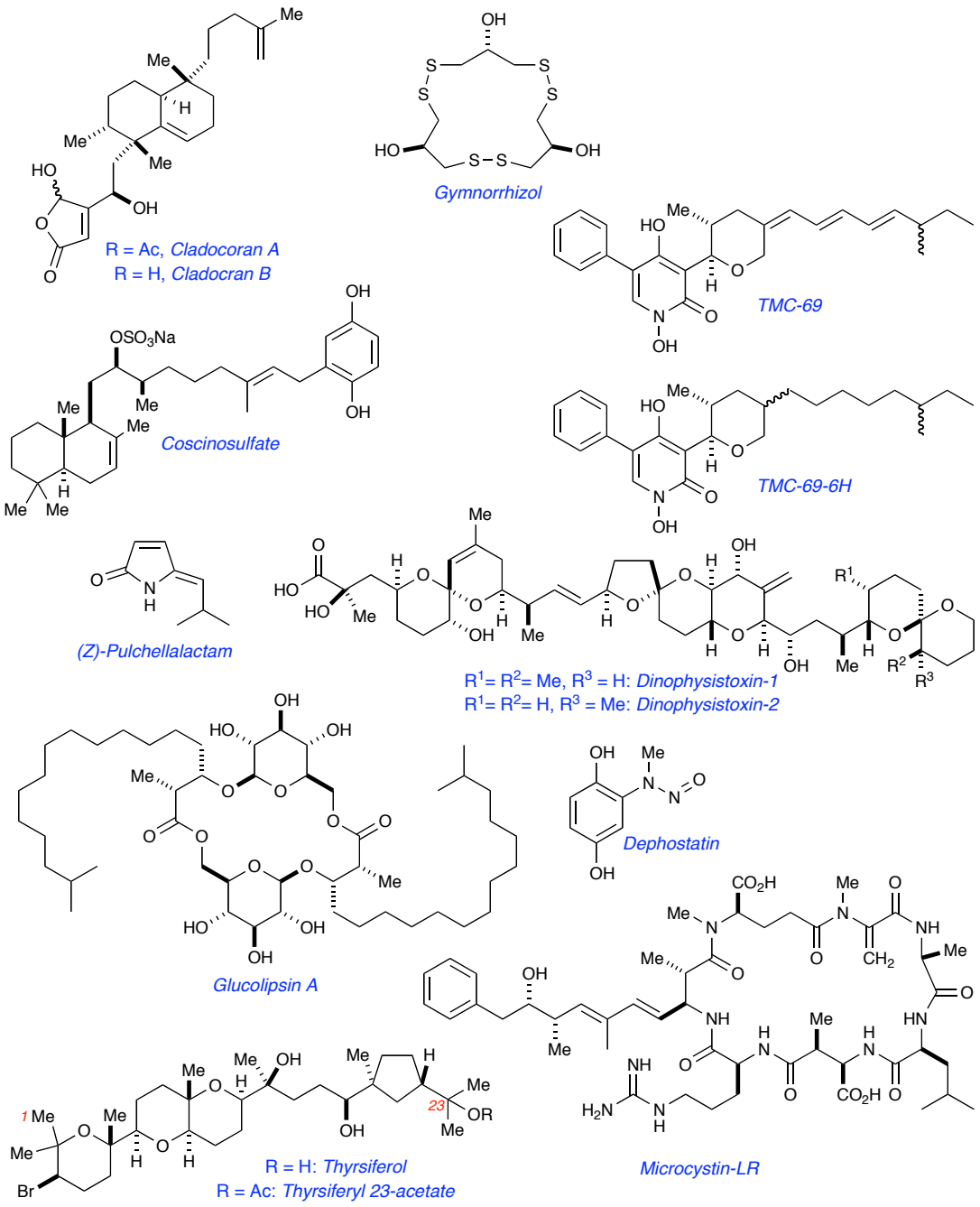


Figure 1 *Several Natural Product Phosphatase Inhibitors*

The purpose of this review is to place into context the utilization of the phosphate ester moiety, often ascribed to be a labile, promiscuous functionality, within synthesis through comparison and reference to previous total syntheses. In

particular the utility, stability, and efficacy of employing otherwise regarded sensitive functionalities in these total synthetic regimes provides a framework within which the following chapters' employment of phosphate tethers can be contemplated.

1.2 Calyculins

Calyculin A was isolated by Fusetani and co-workers from the marine sponge *Discoderma calyx* and its relative stereochemistry was established by subsequent X-ray crystallographic analysis (Figure 2).[13] Further discovery of calyculins B-H, which differ primarily in geometric orientation at Δ^2 and/or Δ^6 and/or an additional methyl group at C32, helped prompt investigation into this class of phosphatase inhibitor.[14] Later, discovery of calyculin J, the caliculinamides A, B, and F, des-*N*-methycalyculin A, and dephosphocalyculin A display the diversity and intriguing activity of this set of molecules.

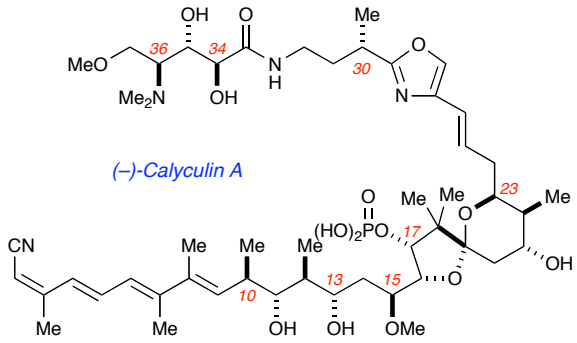
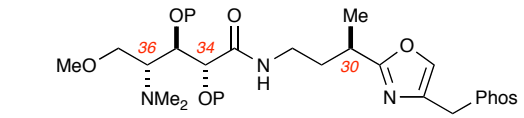


Figure 2 *Calyculin A*

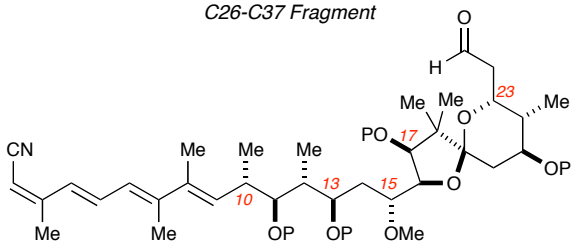
The first total synthesis reported was by the Evan's group in 1992,[15,16] where auxiliary-based reactions (aldol, alkylation, hydroxylation, conjugate addition) would construct 10 of the 15 stereogenic centers (Scheme 1). The phosphate and the tetraene were to be installed late in the synthesis, as the phosphate was deemed a

"liability due to the extra reactivity that such an appendage might confer on the system" and the tetraene posited to be the locus of instability in the natural product.[15] A schism at the C25-C26 olefin provided two fragments that could be joined via a phosphorous-based olefination. Hydroxyl groups to be protected until the conclusion of the synthesis would utilize silicon-based protecting groups, while hydroxyl groups to be manipulated would be masked with appropriate non-silicon based protecting groups in a strategy they termed the 'cumulative silicon strategy'.

Scheme 1



C26-C37 Fragment

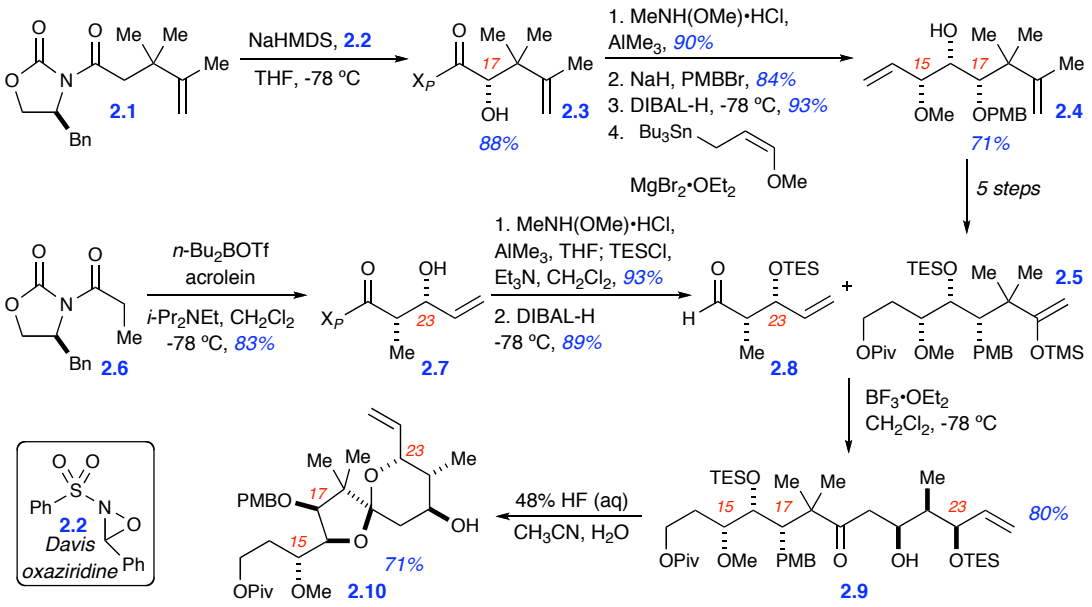


C1-C25 Fragment

Generation of the first stereogenic center of the molecule occurred with application of an auxiliary-controlled asymmetric hydroxylation to form alcohol **2.3** as a single diastereomer (Scheme 2). Conversion to the Wienreb amide, PMB protection of the C17 alcohol and subsequent reduction of the amide to the aldehyde allowed for a diastereoselective (methoxyallyl)stannane addition to generate **2.4** as a 7.5:1 mixture of diastereomers with 71% yield of the desired *syn*,*syn* isomer. Five more steps provided silyl enol ether **2.5** ready for Mukaiyama aldol coupling. The coupling partner was assembled using a chiral auxiliary approach to afford the C22

and C23 centers (**2.7**) followed by a two step conversion to aldehyde **2.8**. The

Scheme 2

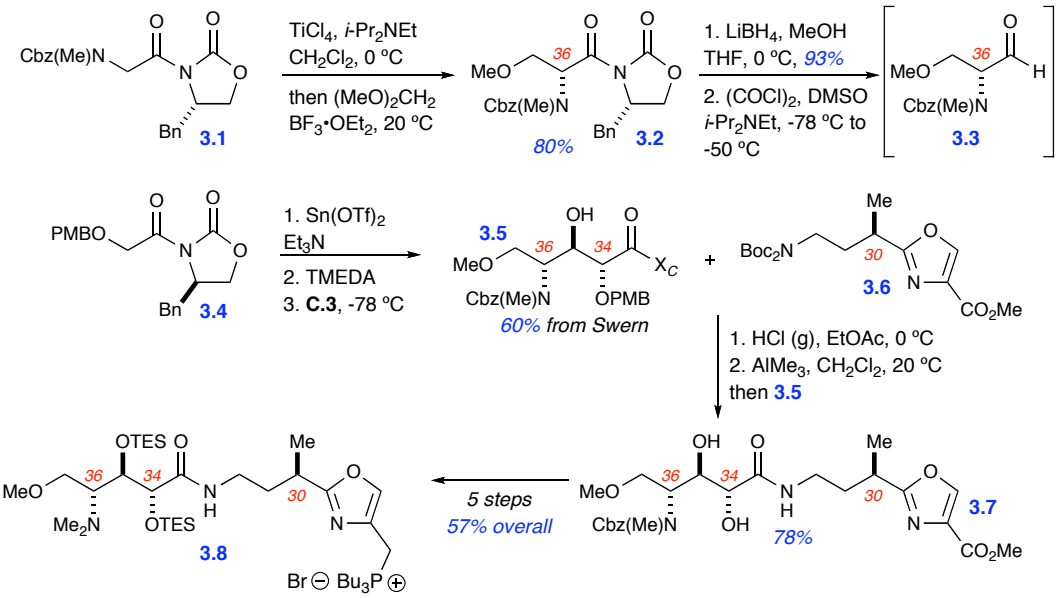


BF_3•OEt_2 mediated addition of silyl enol ether **2.5** with aldehyde **2.8** provided stereohexad **2.9** as a single diastereomer. Subjecting the aldol adduct to a $HF/CH_3CN/H_2O$ mixture provided a 5:1 diastereomeric mixture of spiroketals that could be separated chromatographically to provide the correct spiroketal **2.10** in 71% yield.

Formation of the northern hemisphere of calyculin A proceeded with formation of the C33-C37 γ-amino acid **3.5** (Scheme 3). Two step conversion of sarcosine to (*S*)-phenylalanine-derived oxazolidinone **3.1** allowed for asymmetric alkylation to append a methoxymethyl unit providing **3.2** in good yield and diastereoselectivity. Removal of the chiral auxiliary followed by oxidation to aldehyde **3.3** allowed for addition of the tin (II) enolate of glycolate imide **3.4** to

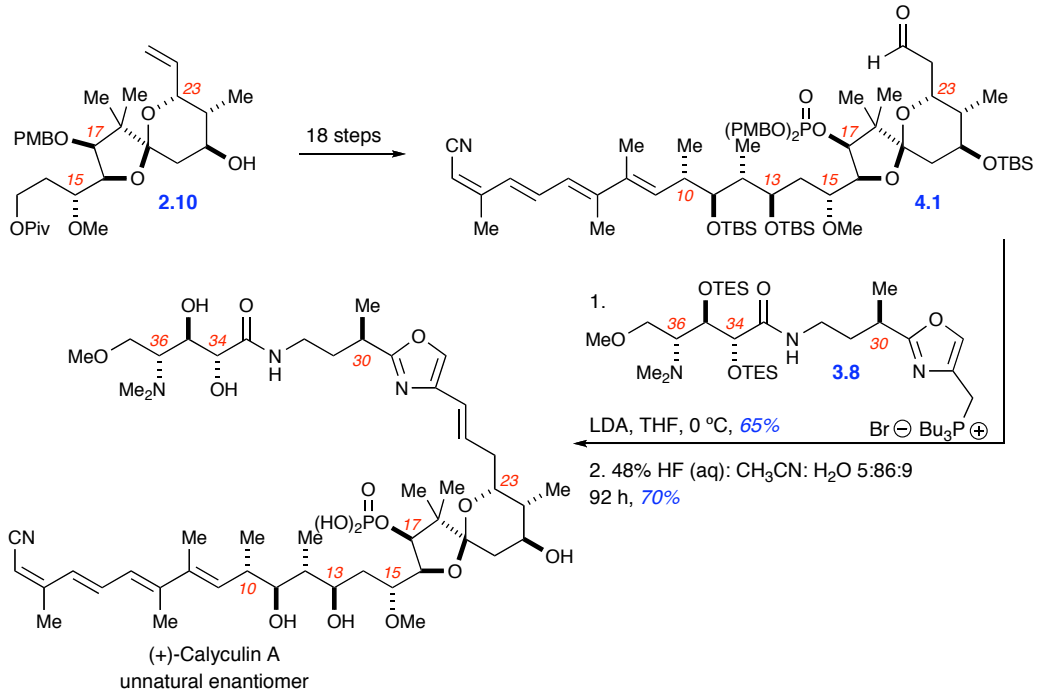
provide *anti*-aldol product **3.5** in 60% yield (excluding other diastereomers). Boc removal from oxazole **3.6** followed by trimethyl aluminum-mediated tandem coupling with amide **3.5**/PMB deprotection generated γ-amino amide **3.7**. A five step sequence provided protected C26-C37 phosphonium subunit **3.8** ready for coupling.

Scheme 3



Spiroketal **2.10** required an 18-step procedure to generate the southern segment **4.1** (Scheme 4), involving auxiliary controlled formation of the C12, C13 centers and appending the cyanotetraene through Horner-Emmons and Stille bond constructions. Wittig olefination of aldehyde **4.1** with the ylide of **3.8** provided fully protected calyculin A as a single observable olefin isomer, with subsequent deprotection affording (+)-calyculin A. This product was equal to the natural product in all respects except in the sign of the optical rotation, thus confirming the absolute configuration calyculin A to be the enantiomer of (+)-calyculin A.[17,18]

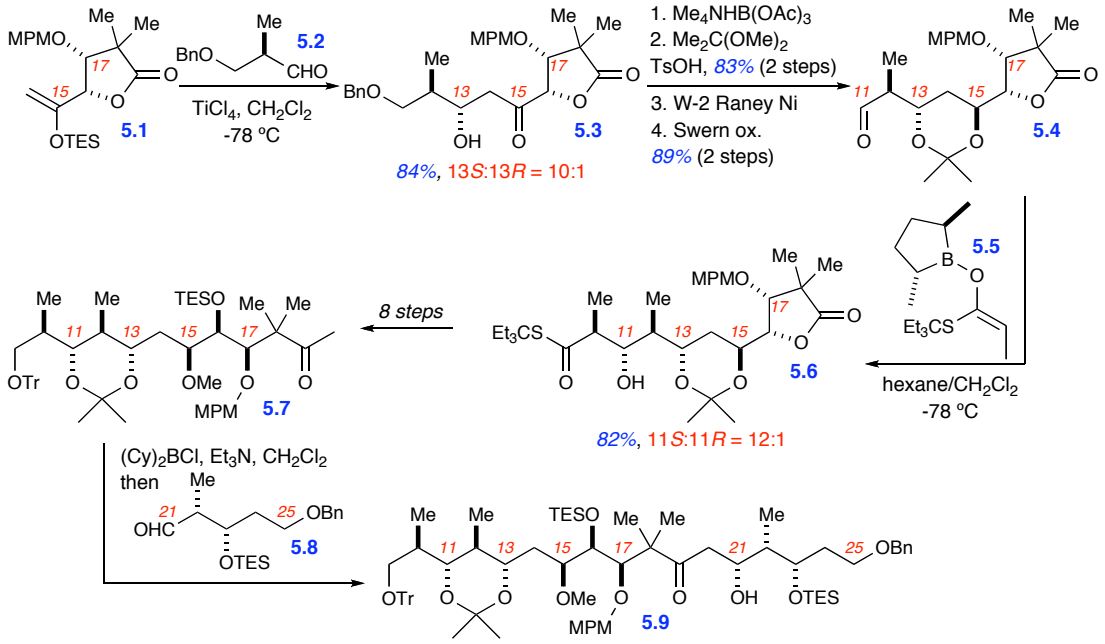
Scheme 4



The total synthesis of naturally occurring (–)-calyculin A was reported in 1994 by the Masamune group.[19] Utilizing chiral, non-racemic starting materials, rather than chiral auxiliaries, the Masamune group hoped to explore the stereoselective coupling of chiral fragments via aldol reactions towards forming the southern spiroketal-containing fragment. Scheme 5 illustrates a chelation-controlled Mukaiyama-type aldol of silyl-enol ether **5.1** with aldehyde **5.2** providing aldol adduct **5.3** in good yield with 10:1 diastereoselection. Conversion to **5.4** allowed for investigations into the C10,11,12,13 *anti*,*anti*,*anti* stereoisomer **5.6**. Adduct **5.6** was the 'worst' mismatched pair possible for the aldol product, and achiral addition provided a 1:4 distribution of diastereomers with isomer **5.6** as the minor component. Overriding substrate control by employing *E*(O)-enolate **5.5** allowed for isomer **5.6**

to be provided in good yield and with 12:1 diastereoselection. Similarly, construction of the carbon skeleton of the southern hemisphere **5.9** relied on coupling ketone **5.7** with aldehyde **5.8** to selectively generate the C21 stereogenic center. Surveying a variety of achiral boron reagents provided the insight that increasing size of the boron ligands enhanced diastereoselectivity, thus utilizing dicyclohexyl boron chloride yielded **5.9** as the exclusive isomer.

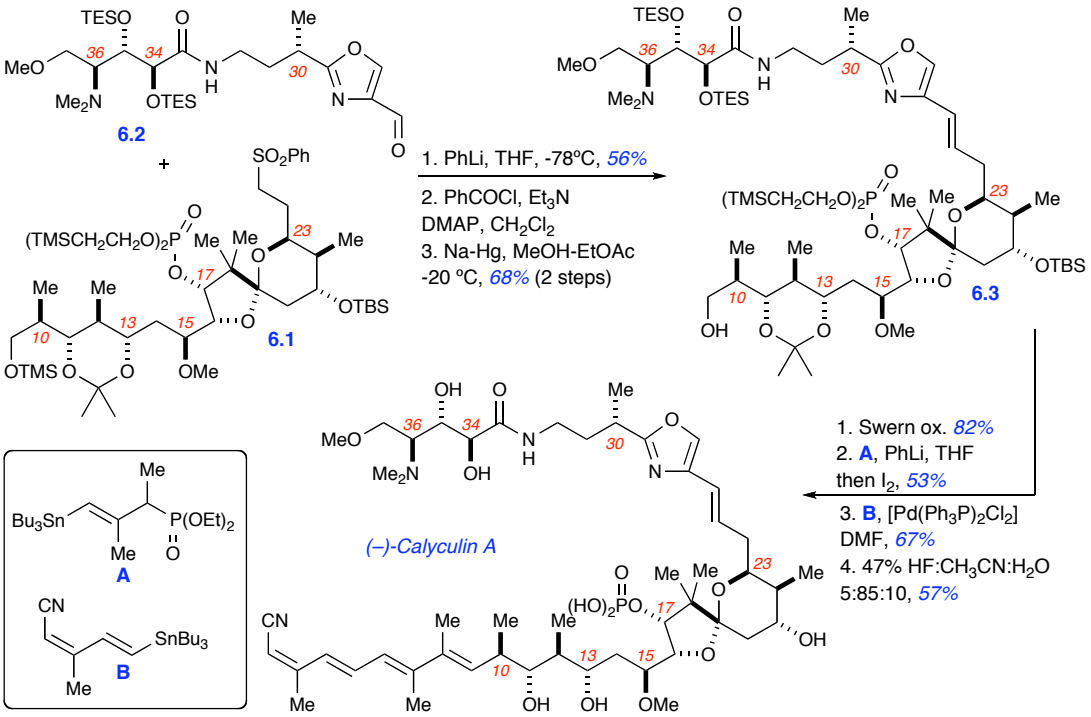
Scheme 5



Coupling of the northern and southern fragments is noteworthy, as it proceeded via a Julia-Lythgoe olefination in the presence of the protected phosphate (Scheme 6). The total synthesis of Evans group beforehand and the total syntheses appearing after the Masamune group report rely on Wittig or Horner-Emmons type couplings in the presence of the phosphate. Utilizing the spiroketal generated from **5.9**, sulfone **6.1** was deprotonated by phenyllithium to subsequently react with

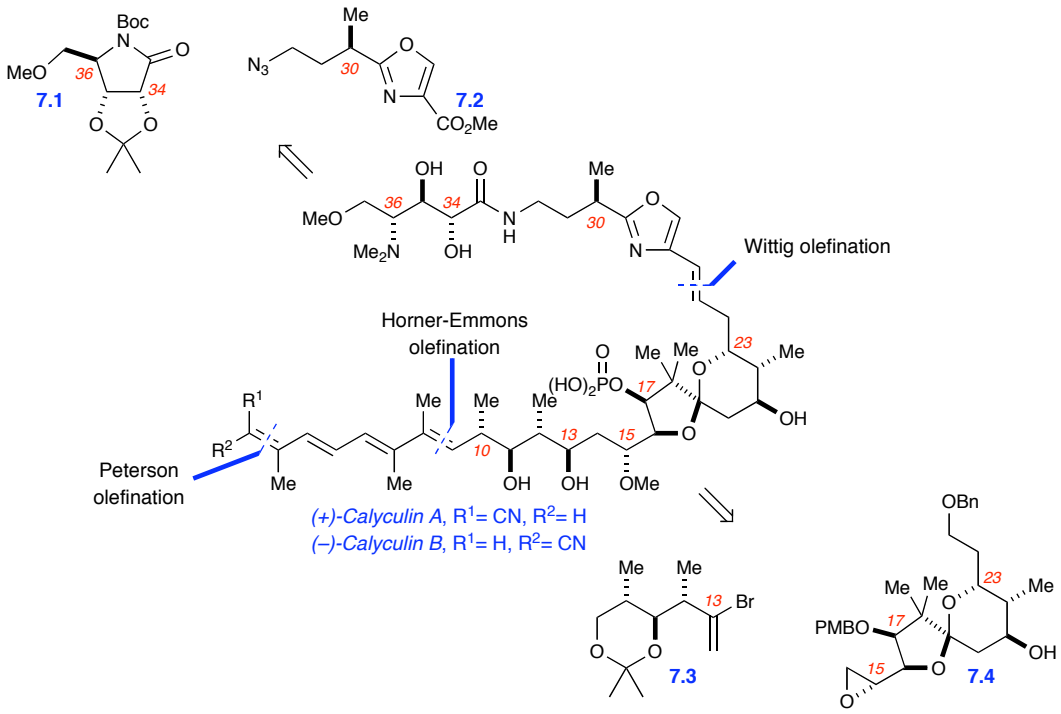
oxazole **6.2**[20] (in the presence of the unprotected amide and the phosphate), followed by benzoylation and sodium amalgam mediated reductive elimination to provide *E*-olefin **6.3** as the major product. (–)-Calyculin A was provided in 4 more steps to yield the first total synthesis of the naturally occurring inhibitor.

Scheme 6



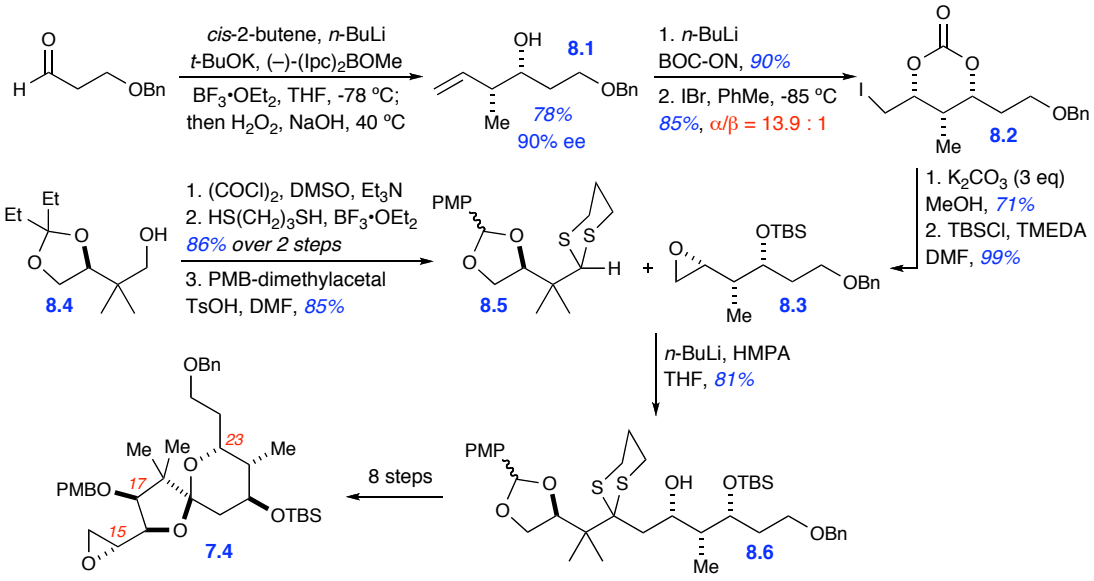
In 1998[21] and 1999,[22] the Smith group reported their approach to (+)-calyculin A as well as the total synthesis of (–)-calyculin B. The similar splitting of the molecule into a northern and southern hemisphere was noted, with the exception that the cyanotetraene would be produced in the last two bond forming steps of the synthesis (Scheme 7).

Scheme 7



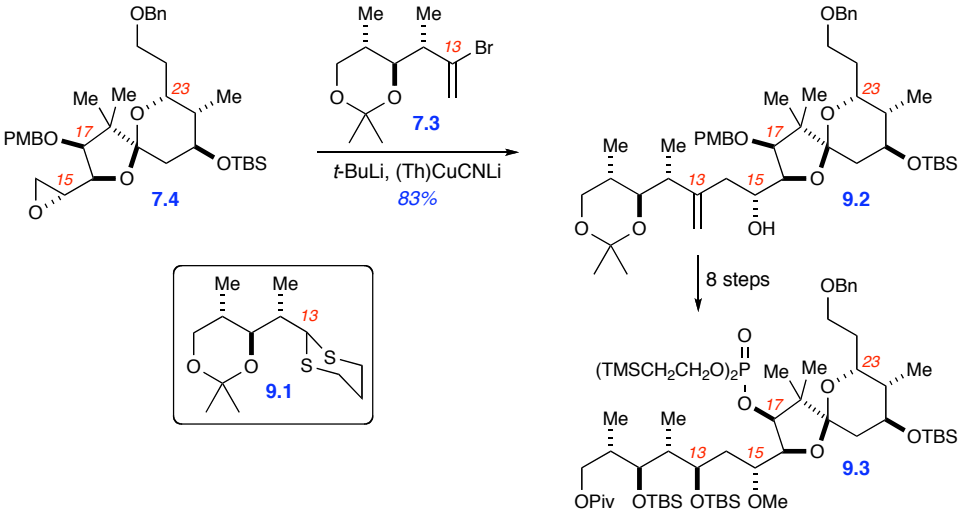
The Smith group approach centered on the efficient and large scale production of four key advanced synthons, with generation of the spiroketal **7.4** initiating from Brown allylboration of 3-benyloxypropanal to yield alcohol **8.1** (Scheme 8). Protection as the *tert*-butyl carbonate followed by IBr-induced diastereoselective cyclization produced the desired sterotriad **8.2**, which was converted in two steps to epoxide **8.3**. (*S*)-Malic acid derived alcohol **8.4** provided dithiane **8.5** in two steps, where coupling of the anion of dithiane **8.5** with epoxide **8.3** provided masked aldol product **8.6** to afford 120 g in a single experiment. Subsequent manipulations provided spiroketal epoxide **7.4**.

Scheme 8



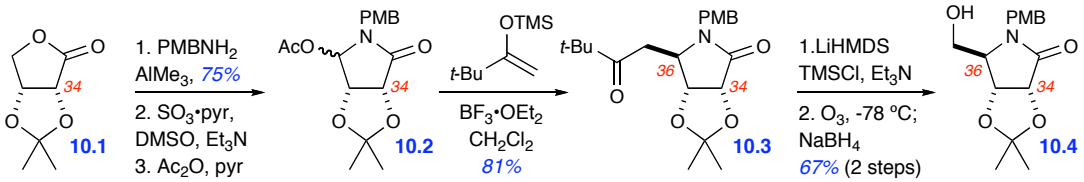
Hoping to complete the southern hemisphere, attempts to couple dithiane **9.1** with epoxide **7.4** suffered from lack of reactivity, despite multiple studies indicating the feasibility of the attempt. Utilizing a vinyl cuprate addition of bromide **7.3** with epoxide **7.4**, however, produced alcohol **9.2** in 83% yield on ~2 g scale. The southern hemisphere was completed in 8 more steps to provide **9.3**.

Scheme 9



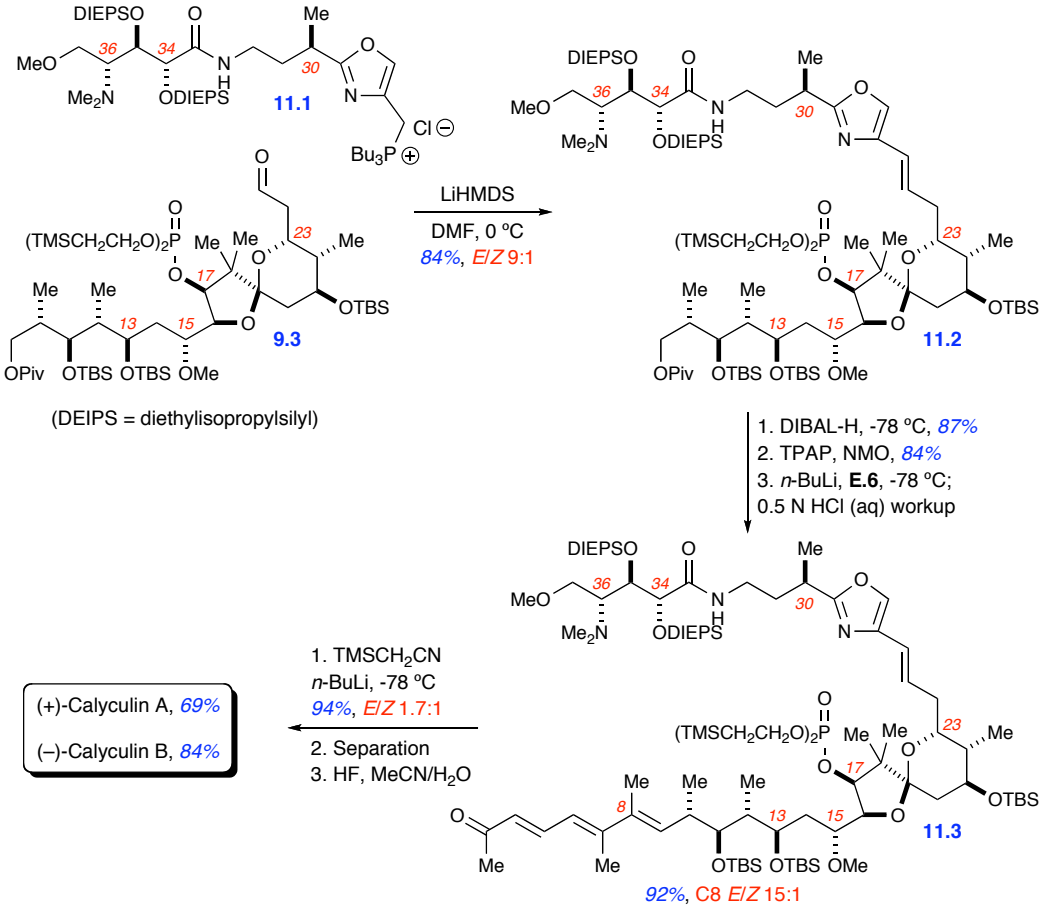
Construction of the northern hemisphere engaged upon a short synthesis of the γ-amino subunit **7.1**, where commercially available isopropylidene-D-erythronolactone **10.1** was converted into lactam **10.2** (Scheme 10). The silyl enol ether of pinacolone was added to lactam **10.2** to efficiently and selectively generate **10.3**, followed by enolization and ozonolysis to yield alcohol **10.4** in over 4 g.

Scheme 10



The requisite subunit **7.1** was provided in three more steps, which was eventually coupled with the oxazole subunit **7.2** to generate the northern hemisphere. The northern and southern hemispheres were joined via Wittig coupling to yield **11.2**, which was converted in three steps to ketone **11.3**. Peterson olefination provided a 1.7:1 *E*/*Z* mixture, with radial chromatography separating fully protected (–)-calyculin B and fully protected (+)-calyculin A, respectively. Global deprotection provided (+)-calyculin A and (–)-calyculin B, where analysis of (–)-calyculin B confirmed it to be the enantiomer of the natural occurring phosphatase.

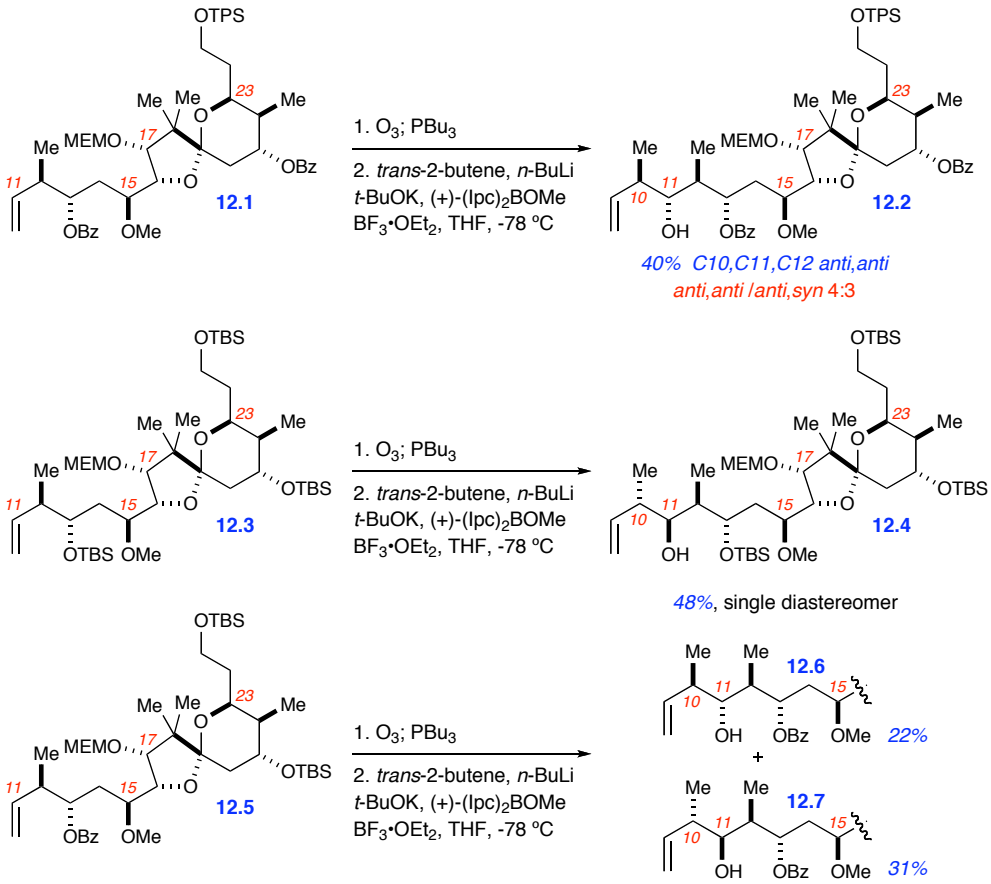
Scheme 11



The Armstrong group reported the total synthesis of naturally occurring calyculin C in 1998, where their investigations provided interesting insight into remote protecting group effects on the diastereoselectivity of Brown crotylborations.[23] In previous studies, it was found that ozonolysis followed by Brown crotylboration of **12.1** (Scheme 12) provided the desired C10, C11, C12 *anti-anti* diastereomer **12.2** in 40% isolated yield, separable from a 4:3 mixture of *anti-anti*: *anti-syn*. Employing this protocol with TBS-protected **12.3**, however, provided adduct **12.4** as the single, undesired *anti-syn* diastereomer. Inferring that this was due to the protecting group change at C13, replacement of the C13 as a benzoyl protected

alcohol while keeping the synthetically more tenable silyl protecting groups at C21 and C25 allowed for crotylboration of **12.5**. While the effect of the β-alkoxy protecting group on stereoselectivity was evident as formation of the desired product **12.6** occurred, it was the minor component of the product distribution, the major being undesired *anti-syn* adduct **12.7**.

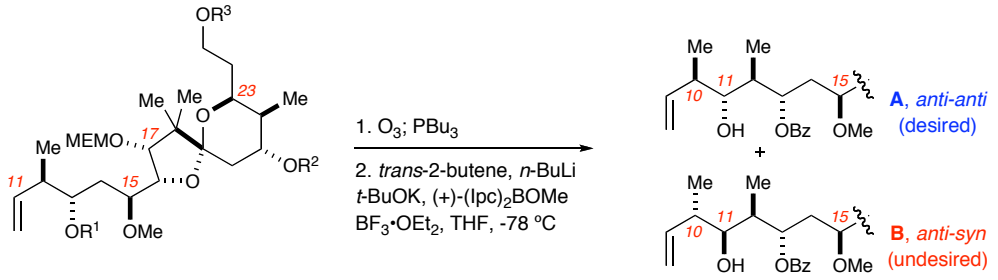
Scheme 12



This discrepancy between the diastereomeric ratios of generated from **12.1** and **12.5** suggested to the Armstrong group that remote effects of the protecting groups at C21 and C25 could be at play. One further experiment illustrated this hypothesis, that in which a simple replacement of the C25 TPS group of **12.1** was

replaced with a TBS group to generate **13.1**. The two-step ozonolysis/Brown crotylboration protocol produced a 35:39 ratio of desired to undesired diastereomers; the seemingly simple change of a TPS group to a TBS group at the remote C25 position changed the product distribution to favor the undesired *anti-syn* product. All *anti-anti* diastereomers were taken on to the completion of the molecule, which verified the absolute structure of calyculin C.

Scheme 13



	R^1	R^2	R^3	yield of A:B
12.3	TBS	TBS	TBS	0:48
12.5	Bz	TBS	TBS	22:31
12.1	Bz	Bz	TPS	40:30
13.1	Bz	Bz	TBS	35:39

1.3 Dysidiolide

Dysidiolide is a *neo*-isolabdanoid sesterterpene isolated from the marine sponge *Dysidea etheria* de Laubenfels collected off the Bahamian islands (Figure 3).[24] It was the first known natural inhibitor of the dual specificity phosphatase enzyme Cdc25A (IC_{50} 9.4 μM), inhibiting the growth of A-549 human lung carcinoma (IC_{50} 4.7 μM) and P388 murine leukemia cells (IC_{50} 1.5 μM).[24] While Blanchard and co-workers suggested the inhibition to be caused by an unidentified component in the crude extract,[25] Shirai and co-workers confirmed the inhibitory

activity against Cdc25A (recording IC_{50} 35 μM) and found dysidiolide additionally inhibits Cdc25B (IC_{50} 87 μM).[26] Given the structural novelty and promising anti-mitotic properties of dysidiolide, it is not surprising that the first three total syntheses were reported almost concurrently, vide infra.

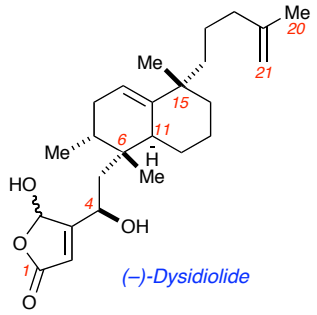
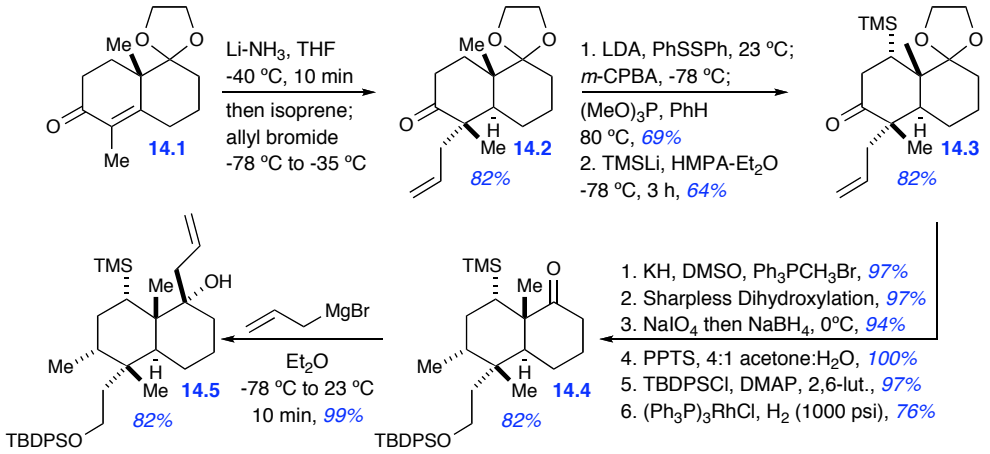


Figure 3 *(–)-Dysidiolide*

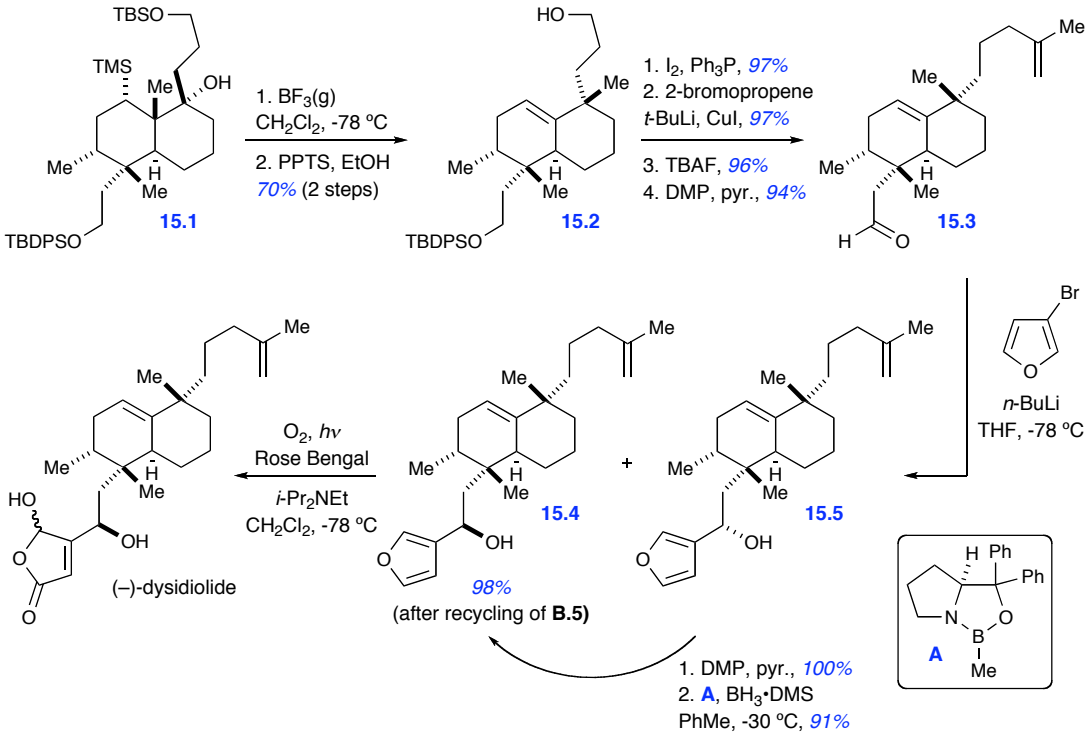
Corey's group reported the first enantioselective total synthesis of the natural product in 1997.[27] The synthesis initiated from readily available **14.1** (Scheme 14), where selective reduction of the α,β-enone forms an enolate that is trapped by allyl bromide to provide the geminal methyl allyl ketone **14.2**. The C7-C8 unsaturated ketone is then formed followed by axial addition of TMSLi to provide β-TMS ketone **14.3**, a moiety the proved essential in forming the natural product. A methylenation/position selective Sharpless hydroxylation protocol followed by periodate mediated glycol cleavage, reduction, TBDPS protection, and diastereoselective hydrogenation afforded ketone **14.4**. In generating tertiary alcohol **14.5**, attempts to add the requisite 4-methyl-4-pentenyl group by organolithium, magnesium, and cerium reagents returned starting material. Addition of allylmagnesium bromide, however, afforded 99% yield of the axial tertiary alcohol **14.5**.

Scheme 14



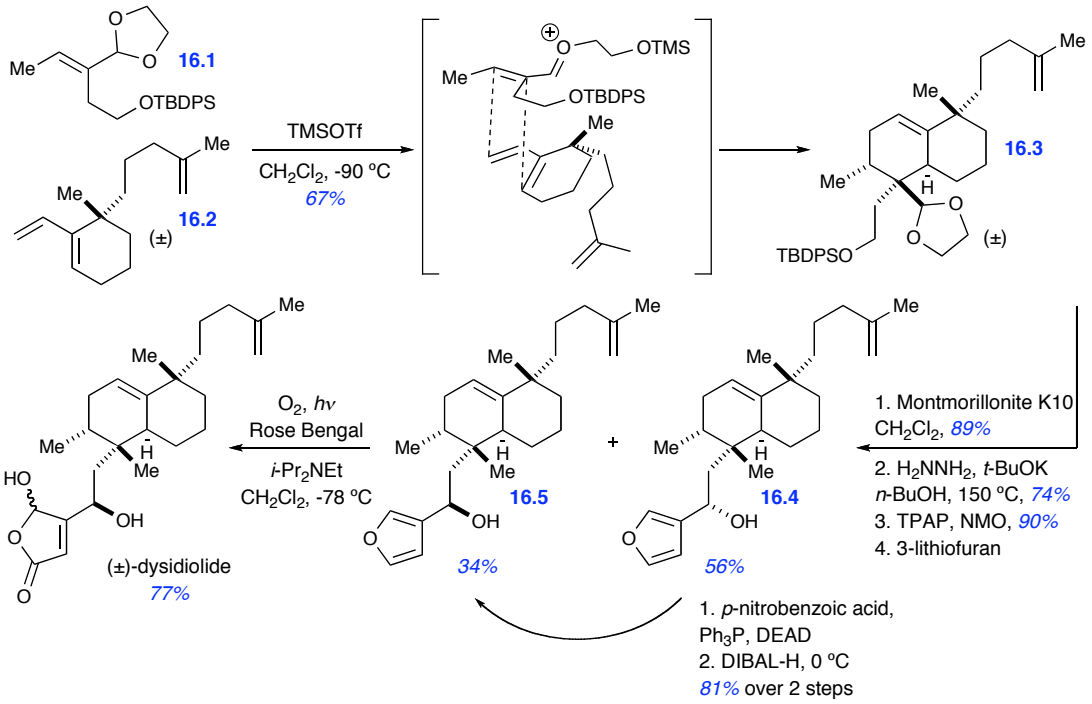
The necessity of the C8 TMS group is revealed upon conversion of tertiary alcohol **15.1** to the fully substituted bicyclic core **15.2** (Scheme 15). Utilization of analogues with a hydrogen or $Ph(Me)_2Si$ group instead of TMS provided little, if any, desired rearrangement product under myriad conditions. The $BF_3(g)$ mediated rearrangement of **15.1** provided rearranged adduct **15.2** in 70% yield, where the β-silicon group in addition to specific double bond generation facilitates the reaction. Elaborating **15.2** to aldehyde **15.3** allows for 3-lithiofuran addition to provide epimeric secondary alcohols **15.4** and **15.5** as a 1:1 mixture. Facile separation allowed for conversion of **15.5** to **15.4** via an oxidation/CBS reduction protocol, noting that attempts to invert via Mitsunobu conditions only progressed partially and attempts at diastereoselective reduction with L-Selectride, $NaBH_4$, and $LiBH_4$ provided **15.5** as the major product. Singlet oxygen addition to furan **15.4** provided (–)-dysidiolide in 98% yield as a white solid and established the absolute stereochemistry.

Scheme 15



The Danishefsky group reported the racemic total synthesis two months later in 1998,[28,29] where a Diels-Alder between dioxolenium activated dienophile **16.1** and racemic diene **16.2** was the key step (Scheme 16). TMSOTf catalyzed the reaction to afford 67% of the endo-dioxolane product **16.3** along with 5% of an undetermined stereoisomer. Attempts at performing the same reaction utilizing trisubstituted ester analogues, rather than acetal, were ineffective in the Diels-Alder reaction. Elaboration of the C4 silyl protected alcohol **16.3** to the racemic natural product occurred in five steps to present a 12 step total synthesis of (±)-dysidiolide. Further testing of the racemate showed growth arrest on four cancer cell lines, with PC3, TSU-Pr1, and DU145 exhibiting massive apoptosis concurrent with growth arrest.

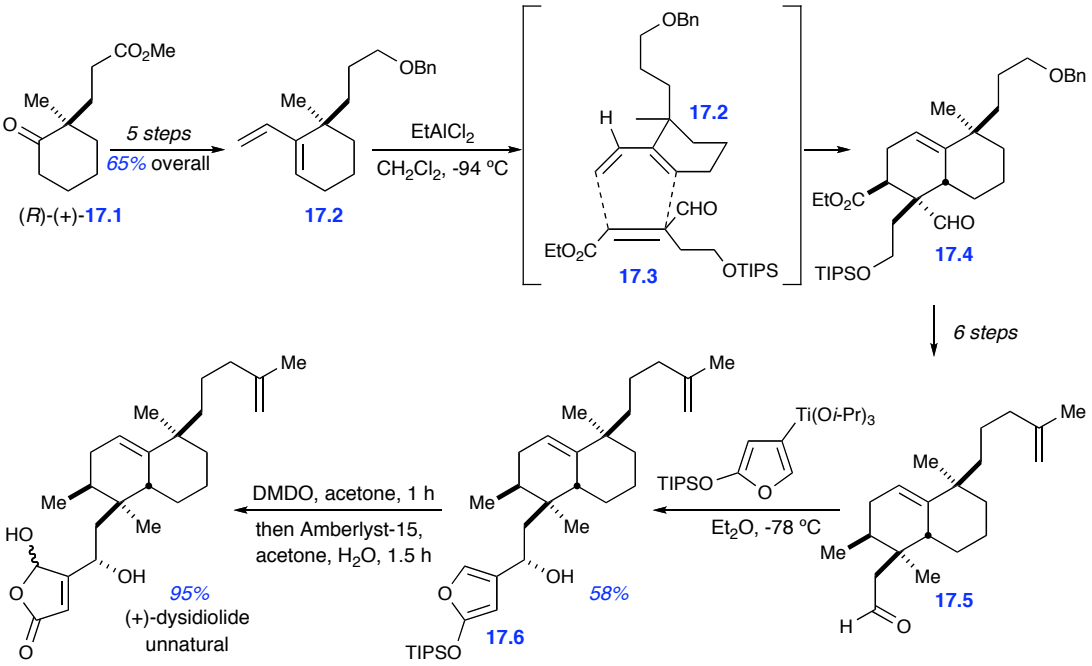
Scheme 16



Seven days after submission of Danishefsky's racemic synthesis, the Boukouvalas group submitted their total synthesis of (+)-dysidiolide (published 1998).[30] Similarly, the key step in the Boukouvalas group sequence was a Diels-Alder between chiral, non-racemic diene **17.2** and doubly activated dienophile **17.3** (Scheme 17). Diene **17.3** was itself available from commercially available ketoester **17.1**, which can be obtained as either antipode. Utilizing (+)-ketoester **17.1** allowed for quick generation of **17.2**, which upon cycloaddition with dienophile **17.3** provides two (out of a possible eight) diastereomeric adducts with the major being adduct **17.4**. Subsequent modification to aldehyde **17.5** allowed for a siloxyfuranyl addition, reminiscent of the Corey and Danishefsky approaches with the notable exception that addition would occur via the titanium reagent. This (siloxyfuranyl)titanium reagent provided a 2.2:1 desired: undesired mixture of epimeric alcohols, although isolation

provided 58% yield of desired **17.6** and 14% yield of the epimer. Dimethyldioxirane oxidation followed by treatment with Amberlyst-15[31] provided (+)-dysidiolide in a total of 15 linear steps and 5.26% overall yield. At the time of writing, this established the absolute stereochemistry of naturally occurring dysidiolide as the enantiomer of (+)-dysidiolide, however, the Corey group's paper published sixteen days after the Boukouvalas report was submitted provided this information.

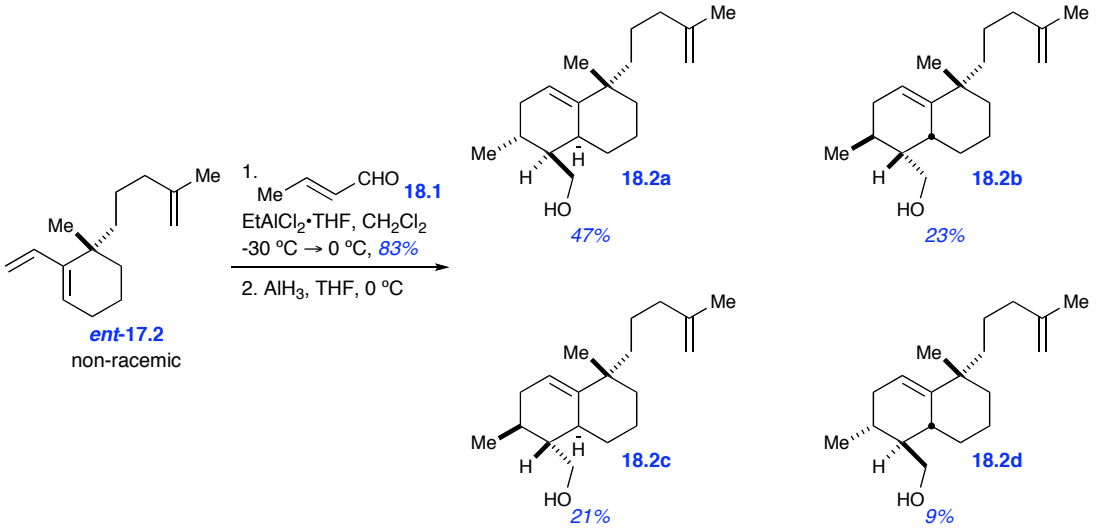
Scheme 17



The Hashimoto-Shirai group's total synthesis of (–)-dysidiolide in 2000 explored the Diels-Alder approach towards generating analogs for structure-activity relationship inquiries.[32] Utilizing ketoester (*S*)-(–)-**17.1**, the group synthesized chiral, non-racemic diene *ent*-**17.2** (Scheme 18) which was combined with crotonaldehyde (**18.1**) to produce four inseparable adducts in 83% yield, where subsequent reduction allowed for identification of the isomeric products **18.2a-d**. Isomer **18.2a** was taken

on to synthesize (–)-dysidiolide in 8 more steps, with isomers **18.2b-d** illustrating the method's flexibility towards analog development.

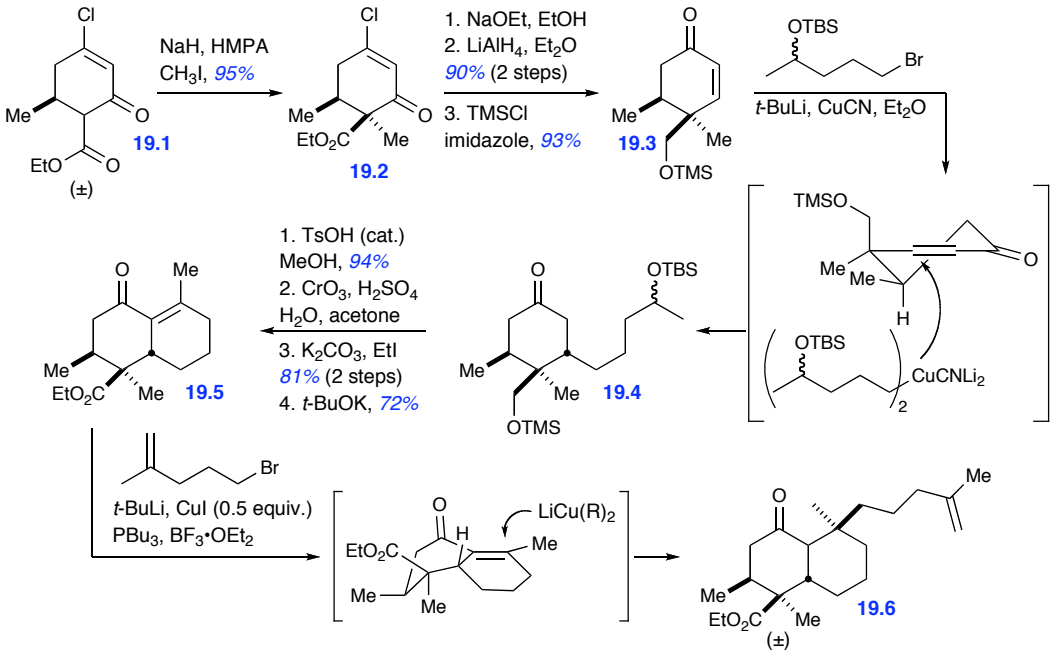
Scheme 18



The Forsyth group provided a total synthesis of racemic dysidiolide in 2000 that relied on highly diastereoselective sequential transfer of stereochemical information to install the core stereogenic centers of the bicyclic natural product. [33,34] Starting with racemic vinylogous acyl chloride **19.1**, selective methylation *anti* to the C7 methyl group provided ketoester **19.2** (Scheme 19). Addition of sodium ethoxide to provide the vinylogous ester prior to lithium aluminum hydride reduction allows for acid catalyzed rearrangement to form enone **19.3**. TMS protection of the primary alcohol allows for cyanocuprate addition to effect a conjugate addition *anti* to silyl protected oxymethyl group at C6 to yield ketone **19.4**. Ketone **19.4** underwent a global deprotection followed by Jones oxidation and esterification, allowing for annulation to afford bicyclic enone **19.5**. The β,β-disubstituted bicyclic enone **19.5** underwent an exquisitely stereoselective 1,4-addition by the Gilman cuprate formed

from 5-bromo-2-methylpentene, delivering the bicyclic core of dysidiolide (**19.6**). Racemic dysidiolide was then synthesized in 9 more steps.

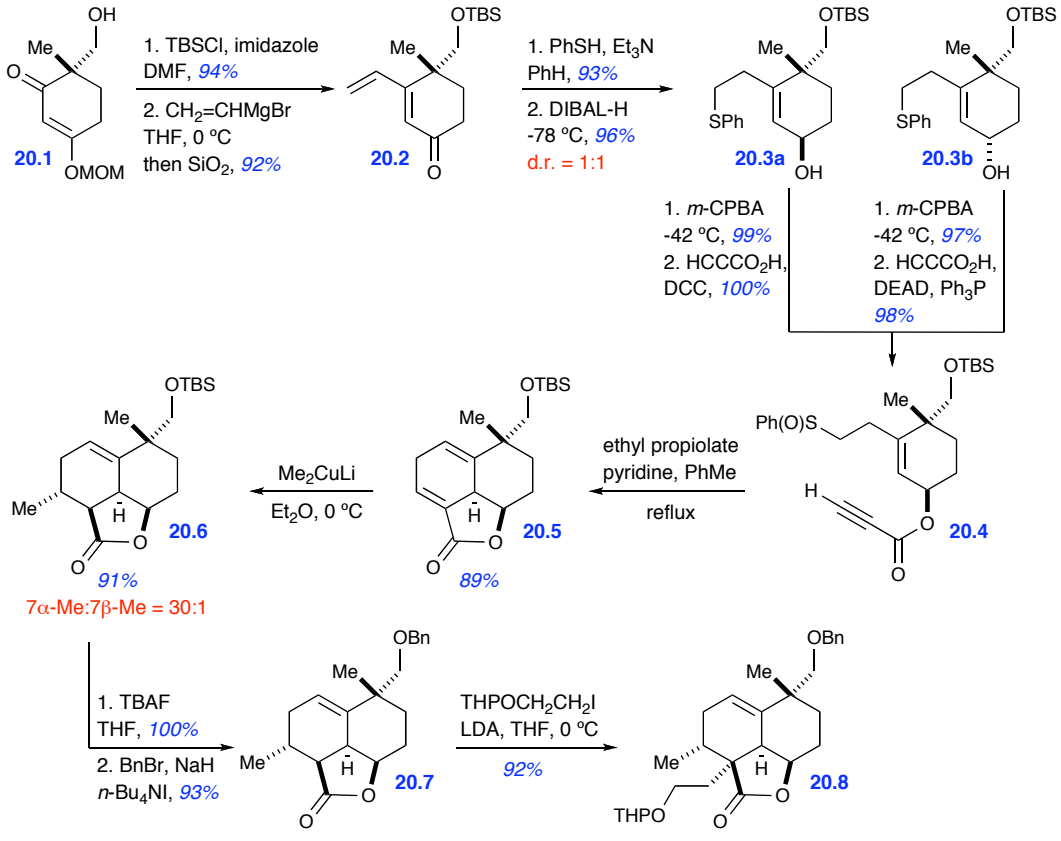
Scheme 19



In 2001 Yamada's group presented the total synthesis of (–)-dysidiolide utilizing an *intramolecular* Diels-Alder reaction to construct the bicyclic core.[35,36] Chiral, non-racemic enone **20.1**[37] was converted to dienone **20.2** in two steps (Scheme 20), followed by conjugate addition of thiophenol and DIBAL reduction to afford epimeric alcohols **20.3a** and **20.3b**. Attempting to acylate the alcohol with the diene intact provided a 4:17 mixture of tandem acylation/Diels-Alder adduct **20.5** with S_N2' adduct, thus necessitating thiophenol masking of the diene functionality. The readily separated epimers were each oxidized to the sulfoxide, where the correct C12 epimer **20.3a** was directly acylated with propiolic acid to generate **20.4**, while the undesired **20.3b** was converted to the requisite propionate ester **20.4** via

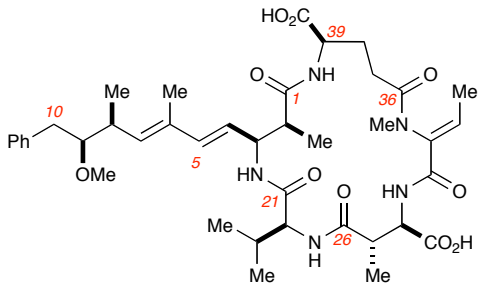
Mitsunobu inversion. Refluxing sulfoxide **20.4** in toluene with the presence of ethyl propiolate and pyridine unmasked the diene moiety in situ and provided intramolecular Diels-Alder adduct **20.5**. Subsequent stereoselective methylation with Me_2CuLi provided tricycle **20.6** in 91% yield with a 30:1 C7α:C7β ratio. This rigid tricycle set the stage for selective generation of the C6 quaternary stereogenic center by deprotonation of **20.7** and alkylation with THP protected 2-iodoethanol to provide **20.8** in 92% yield as the sole product. Subsequent elaboration of the fully functionalized core yielded a 27 step synthesis of naturally occurring dysidiolide in 9.7% overall yield from **20.1**.

Scheme 20



1.4 Motuporin/Nodularin V

Motuporin (nodularin-V) is a cyclic pentapeptide isolated in 1992 from the marine sponge *Theonella swinhoei* Gray (Figure 4).[38] In addition to containing the unusual β-amino acid Adda, motuporin is one of the most potent PP1 inhibitors known (IC_{50} < 1.0 nM) and shows strong cytotoxicity against a variety of human cancer cells.[38] As motuporin is available from a much less readily accessible source than other members of its class (okadaic acid class), much of the information on it has been extrapolated from data on nodularin and the microcystins. While sharing similar biological properties, important functional differences exist between the microcystins and nodularins (motuporin included) such as microcystin covalent bonding to PP1 and PP2A.[39] As such, motuporin became an attractive target for total synthesis.



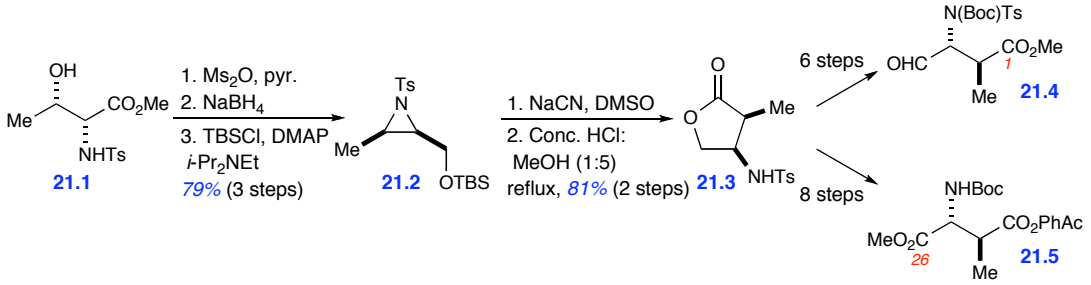
(–)-Motuporin

Figure 4 *Motuporin*

The first total synthesis of (–)-motuporin was unveiled in 1995 by the Schreiber group where all the stereocenters arrived from common amino acids or D-mandelic acid.[40] Key to the route was realizing the generation of the C_{20} amino acid (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda)[41] and D-*erythro*-β-methylaspartate (β-MeAsp),[42] which the group chose to access via a novel route from D-threonine towards a common intermediate. To

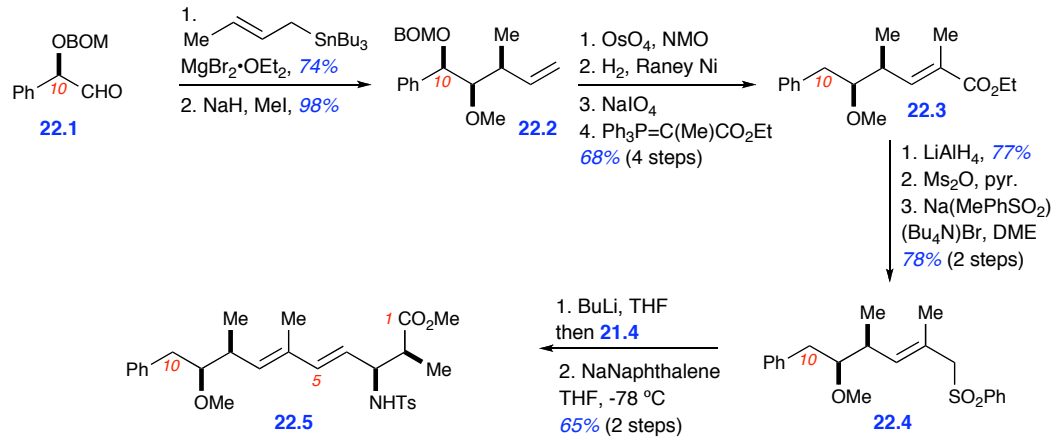
achieve this, protected D-threonine **21.1** (Scheme 21) was converted to tosylaziridine **21.2**, followed by cyanide addition and methanolysis to afford γ-lactone **21.3**. This proved to be the common intermediate for formation of the C1-C4 backbone of Adda **21.4** and for generation of the differentially protected β-MeAsp derivative **21.5**.

Scheme 21



The key generation of protected Adda continued with conversion of mandelaldehyde **22.1** (Scheme 22) through Lewis acid promoted crotylstannane addition to produce the C8 and C9 stereogenic centers followed by methylation to provide alkene **22.2**. Elaboration to the α,β-unsaturated ester **22.3** allowed for conversion to sulfone **22.4**.

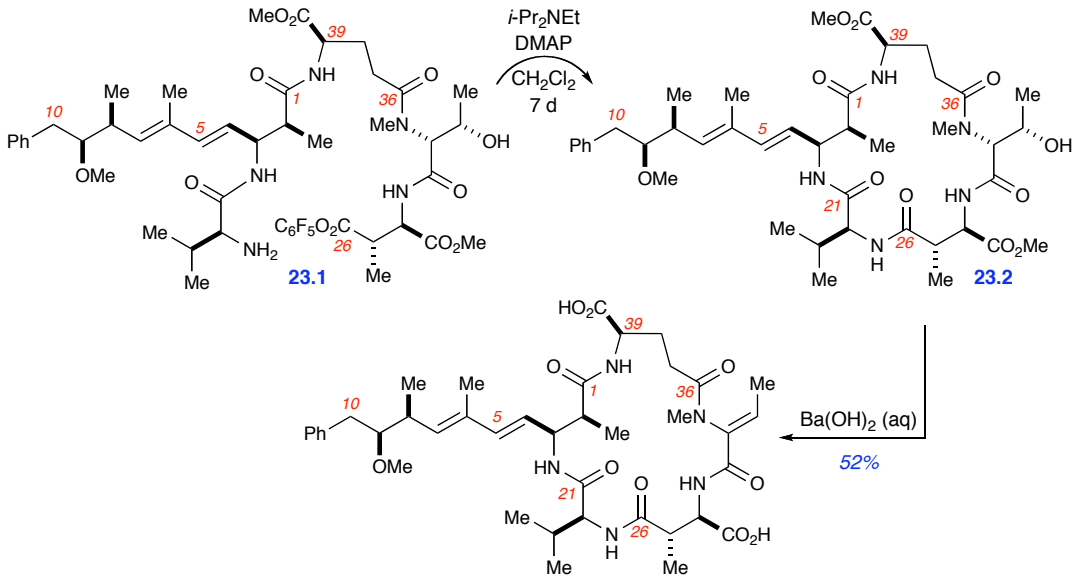
Scheme 22



Sulfone **22.4** underwent a stereoselective diene-forming addition with aldehyde **21.4** by utilizing a modified Julia olefination to provide protected Adda **22.5** as the only detectable diene isomer.

Given the presence of several amino acid linkages lacking α-amino substituents, convergent coupling of the fragments was performed without troublesome epimerization. As such, the linear precursor to the desired natural product, **23.1**, was quickly in hand (Scheme 23). Neutralization of an acidic solution of **23.1** by Hünig's base allowed for macrolactamization to yield the desired macrocycle **23.2**. The methyl esters of **23.2** were deprotected with aqueous $Ba(OH)_2$ with the unexpected complete dehydration of the *N*-methyl-D-threonine subunit to produce (–)-motuporin in 52% yield.

Scheme 23



The Toogood laboratory provided the second total synthesis of (–)-motuporin in 1999 along with synthesis of 5-[L-Ala]-motuporin (Figure 5) to investigate the

contribution of the *N*-methyldehyrobutyrine residue, a moiety the authors suggested was inessential to activity since it did not undergo covalent modification unlike the dehydroalanine in microcystin-LR.[43] In these efforts, the Toogood group developed another synthesis of Adda they deemed suitable for larger scale generation and provided insight into the macrolactamization step.

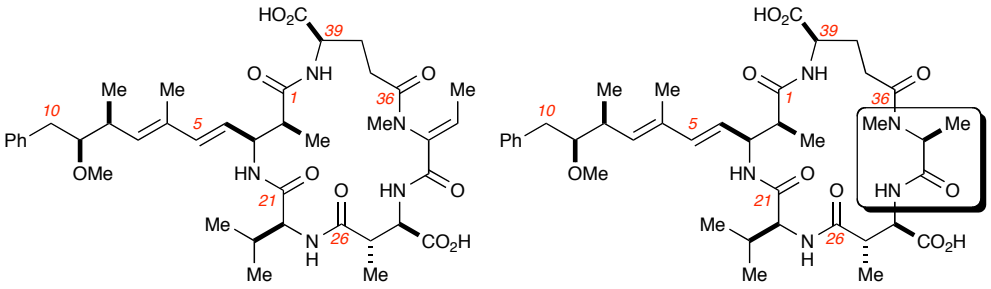
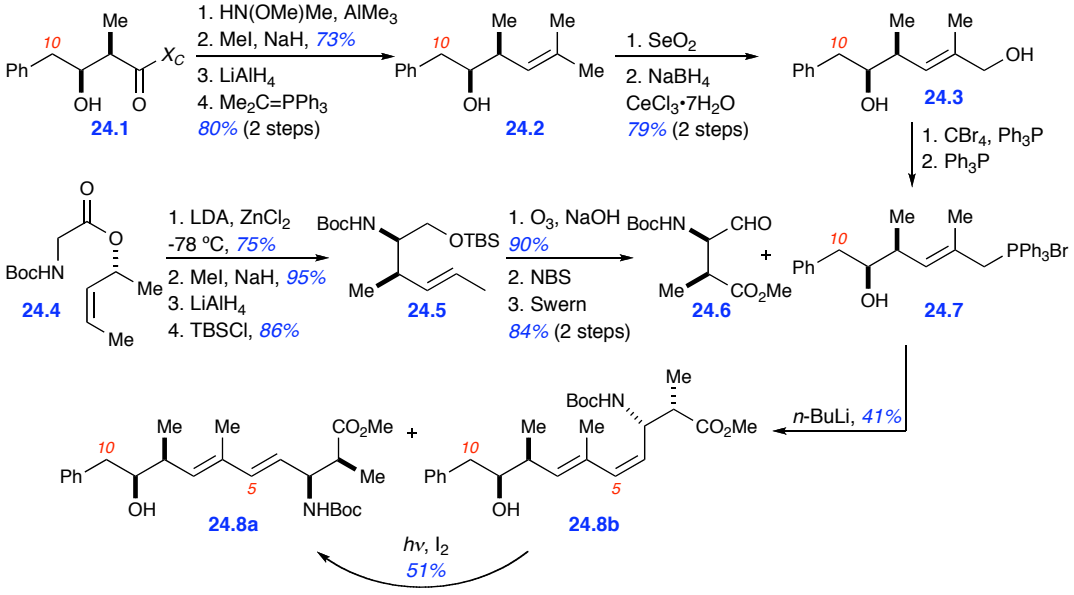


Figure 5 *(–)-Motuporin and the 5-[L-Ala] analogue*

In forming amino acid Adda, Evans aldol adduct **24.1** was converted to trisubstituted alkene **24.2** (Scheme 24). Gem-dimethyl alkene **24.2** was regioselectively oxidized to alcohol **24.3** by SeO_2, with a Luche reduction of the crude mixture to convert minor overoxidized product from SeO_2 into alcohol **24.3**. The C1-C4 fragment originated from (*R*)-3-pentyn-2-ol, where three chemical steps provide **24.4** poised for a highly diastereoselective Claisen rearrangement, followed by methylation of the acid, reduction to the alcohol, and subsequent protection to afford **24.5**. Conversion of the alkene to the methyl ester followed Marshall's procedure,[44] followed by selective silyl deprotection with NBS according to Taylor's method[45] and oxidation to aldehyde **24.6**. Despite numerous attempts to circumvent the poor *E*-olefin selectivity of the triphenylphosphonium ylide of **24.7** with aldehyde

24.6, the described conditions provided the best results to yield a 2:1 *E*:*Z* mixture with 41% yield of the desired *E*-olefin. Fortunately, the Toogood group found the undesired isomer could be converted to *E*-isomer **24.8a**, thus completing the synthesis of protected Abba.

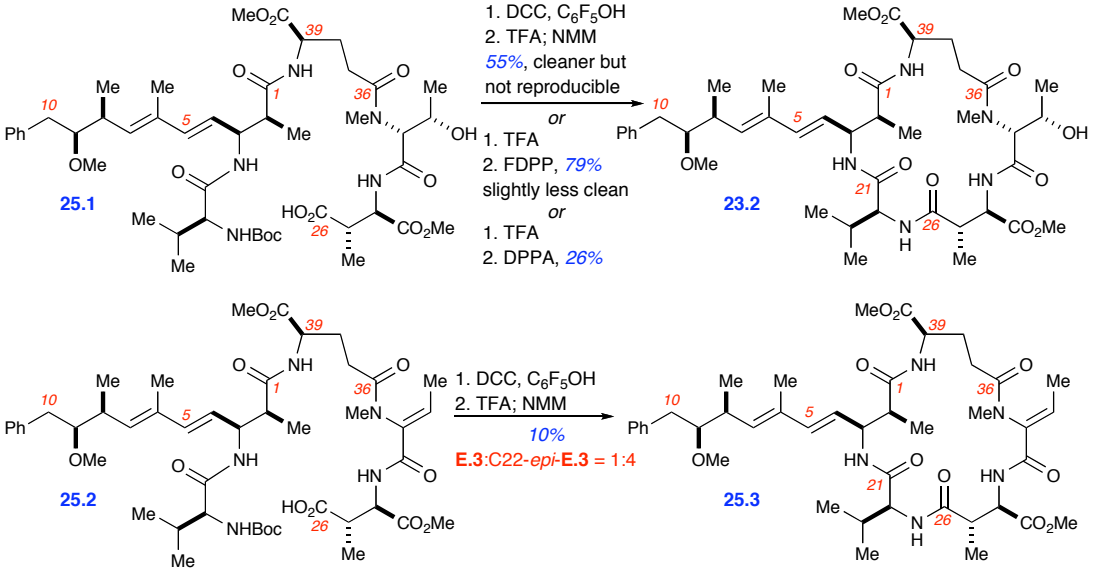
Scheme 24



Achieving the necessary macrolactamization for completing the phosphatase inhibitor proved to be fraught with complications. Utilizing Schreiber's cyclization conditions provided the cleanest product, by a small degree, but was not reproducible (Scheme 25). Cyclization with pentafluorophenyl diphenylphosphinate (FDPP) proceeded smoothly and consistently, while utilizing diphenylphosphoryl azide (DPPA)[46] provided yields of only 26%. Investigation of the *N*-methyldehyrobutyrine residue containing variant **25.2** was expected to provide a higher yield of cyclized product due to additional conformational constraint enforced by the olefin, yet cyclization provided a 1:4 mixture of desired product **25.3** to the C22 epimer. Similar

results were obtained in synthesizing 5-[L-Ala]-motuporin. Noting additional epimerization during saponification to the natural product, the authors suggest that future endeavors employ acid labile carboxyl protecting groups. Subsequent assays showed that 5-[L-Ala]-motuporin was a slightly weaker inhibitor of PPA compared to (–)-motuporin, indication diastereomers of motuporin and motuporin analogues may be effective PP1 inhibitors.

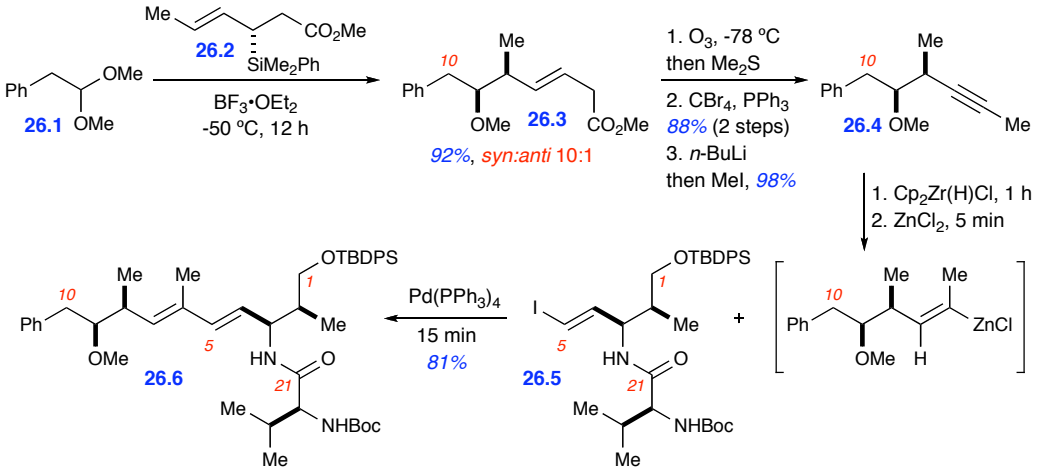
Scheme 25



Just sixteen days after the publication of the Toogood investigations, the Panek group report was revealed to the scientific community,[47] with a further publication in 2002[48] providing the synthesis in greater detail with improved macrocyclization conditions. Panek's report featured introducing six of the eight stereogenic centers through asymmetric crotylsilane bond constructions, yet another approach to constructing Abba, and a method for late stage introduction of the diene within the valine-Abba dipeptide. The valine-Abba dipeptide synthesis initiated with

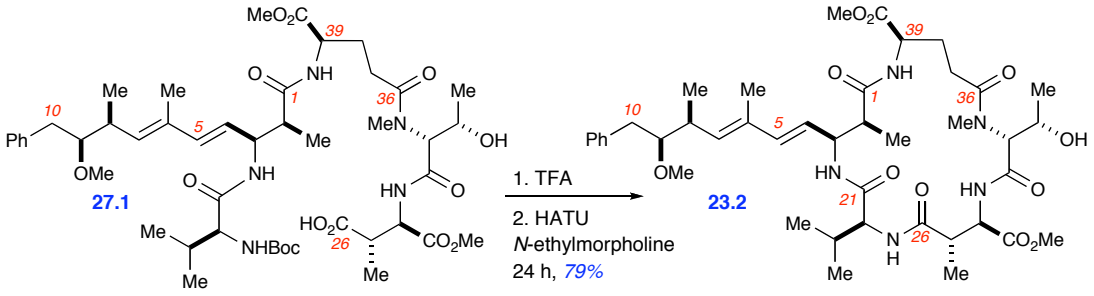
acetal **26.1** (Scheme 26), where BF_3•OEt_2 promoted addition of (*S*)-chiral silane **26.2** to afford homoallylic ether **26.3** in 92% yield with 10:1 *syn*/*anti* diastereoselectivity. Ozonolysis followed by a dibromo-olefination and a subsequent Corey-Fuchs reaction, where the acetylenic anion is trapped by MeI to provide acetylene **26.4**. The acetylene was then transformed into dipeptide **26.6** by a hydrozirconation/Negishi coupling strategy with iodide **26.5** to generate valine-Abba dipeptide **26.6** in 81% yield with exquisite selectivity for the desired diene isomer. The success of the cross-coupling was nested in the double transmetallation of a low kinetic barrier (Zr→Zn→Pd) versus a single transmetallation (Zr→Pd) of high activation energy.

Scheme 26



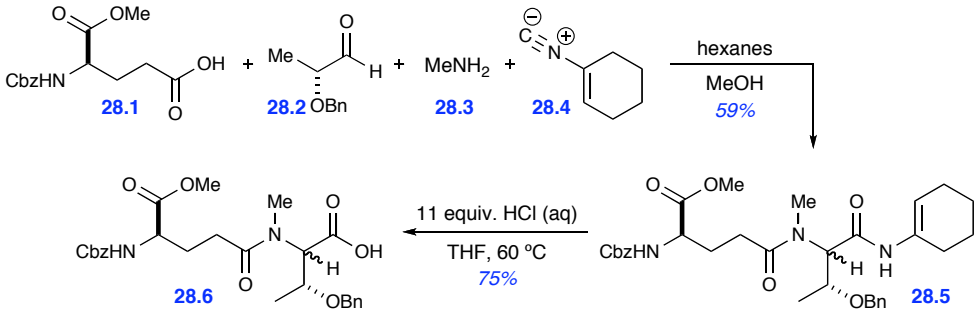
Also notable was the Panek group's approach to the penultimate macrolactamization. TFA deprotection of the amine Boc group of acyclic **27.1** provides an amine ready for HATU coupling with the C26 carboxylic acid, yielding adduct **23.2** in 79% yield. Further treatment with 2 N $Ba(OH)_2$ provided the natural product in 52% yield, constituting a 16 linear step synthesis (from chiral crotylsilane reagents) with an overall yield of 15.8%.

Scheme 27



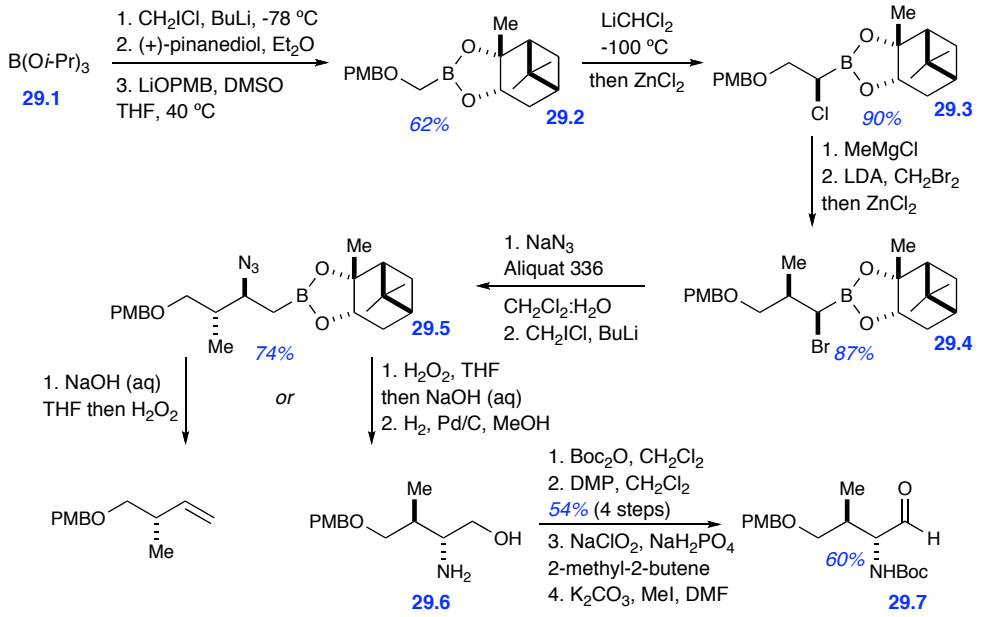
The Armstrong group reported an Ugi four-component coupling reaction to synthesize the 2-(*N*)-methylaminobutenyl residue and a Matteson dihalo-methyllithium insertion methodology[49] for constructing the C26-C29 3-methylaspartyl residue in their 1999 total synthesis.[50] Use of the Ugi technology was postulated to overcome the difficult coupling of a secondary amine and a carboxylic acid using standard peptide coupling methods. Combining protected acid **28.1** (Scheme 28), aldehyde **28.2**, methylamine (**28.3**), and cyclohexenyl isocyanide (**28.4**) provided cyclohexenamide dipeptide **28.5** as a mixture of separable diastereomers, which upon treatment with preheated aqueous hydrochloric acid provided free carboxylic acid **28.6** (47% over 2 steps). The diastereomers were taken through the synthesis as elimination in the latter part of the synthesis renders the mixture inconsequential. Compared to the traditional route, which afforded diastereomerically pure **28.6** in 21% overall yield in 4 steps, the authors noted the significant improvement the Ugi route provided.

Scheme 28



Synthesis of the C26-C29 3-methylaspartyl residue began with triisopropyl borate **29.1** which was subsequently transformed into protected alcohol **29.2** (Scheme 29). Chain extension was affected with dichloromethyllithium followed by subsequent $ZnCl_2$ addition to instigate rearrangement of the ate-complex to provide α-chloroborate ester **29.3**. Stereospecific chloride displacement generates the α-methyl borate, followed by homologation to α-bromoborate **29.4**. Conversion to the azide **29.5** occurred under phase transfer catalyst conditions, notably the only step utilizing this methodology that yielded any detectable amount of diastereomer (in accord with Matteson's observations). Final homologation followed by oxidative removal of boron (where order of addition of the NaOH and H_2O_2 proved to be nontrivial) provided the C26-C29 3-methylaspartyl residue **29.6**, which after differential protection and two step oxidation yielded aldehyde **29.7**.

Scheme 29



1.5 Tautomycin

Tautomycin was reported in 1987 by Isono and co-workers as an isolate from soil bacteria *Streptomyces spiroverticillatus* that exhibited potent antifungal activity against *Sclerotinia sclerotiolum* (Figure 5).[51] Later, it was reported that tautomycin induced a morphological change in human leukemia cells K562[52] and inhibited PP1 and PP2A with IC_{50} of 22-32 with a weak preference for PP1.[53] It was found that the anhydride moiety along with the C18-C26 region was crucial for activity, with the C1-C17 spiroketal bearing region varying affinity between PP1 and PP2A.[54] Since differentiation of the roles of PP1 and PP2A require specific inhibitors of each, and specific inhibitors of PP1 are scarce,[54] efforts towards to total synthesis of tautomycin were greatly desired.

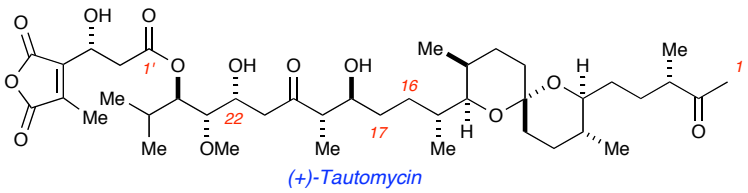
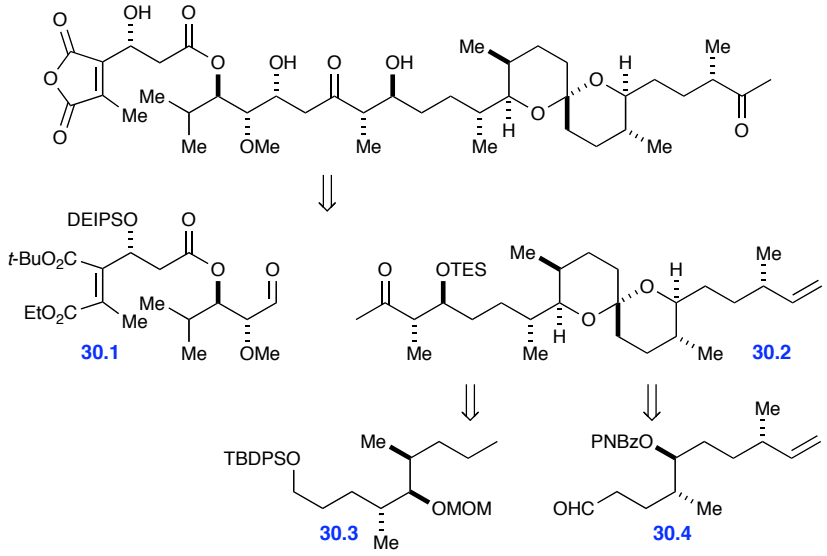


Figure 5 *Tautomycin*

The first total synthesis was reported in 1994 by Oikawa and Ichihara's group,[55] where derivatizations and degradations of the natural product provided insight into the synthetic route they implemented.[56] Key to the synthesis was the coupling of two large subunits, the western aldehyde **30.1** and the eastern ketone **30.2** (Scheme 30). Synthesis of the eastern spiroketal was to be afforded by spiroketal templated synthesis of the C1-C10 portion **30.4** of the molecule.

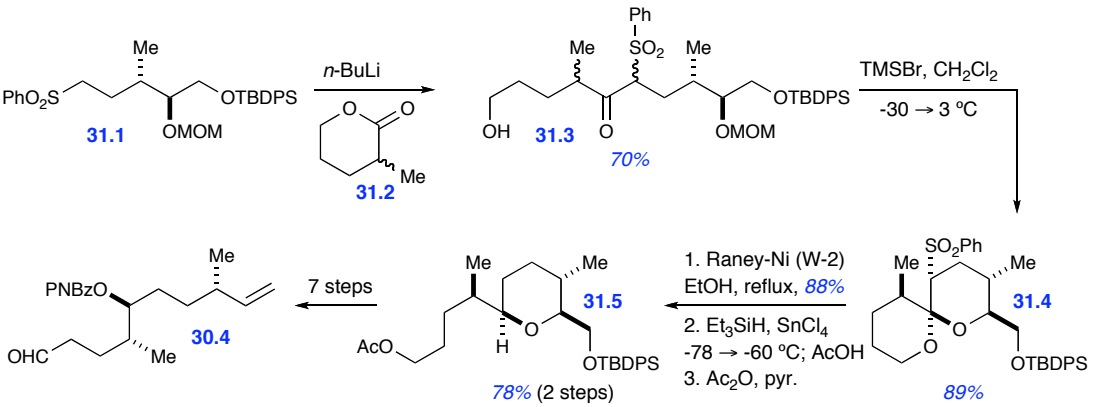
Scheme 30



Synthesis of the C1-C10 fragment reached a crucial juncture upon coupling sulfone **31.1** (Scheme 31) with 2-methyl-δ-valerolactone (**31.2**) to yield ketone **31.3** as a mixture of four isomers. MOM deprotection and concomitant spiroketalization occurred with TMSBr, followed by warming to 0 ºC to provided crystalline

thermodynamically favored spiroketal **31.4** as a single diastereomer. Desulfurization and subsequent acetal reduction provided tetrahydropyran **31.5** with high regio- and stereoselection. Further elaboration including Mitsunobu inversion of the C6 carbinol provided the C1-C10 fragment **30.4**, illustrating the utility of the spiroketal templated remote stereocontrol process.

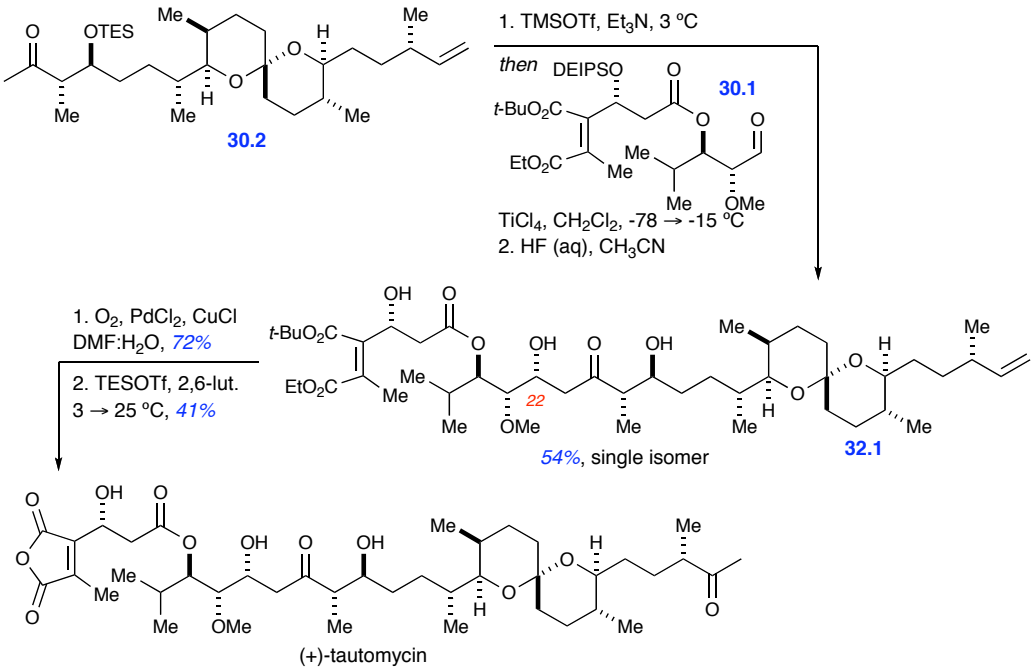
Scheme 31



Coupling of the C1-C10 fragment **30.4** with the C11-C18 fragment **30.3** provided western ketone **30.2** after some additional linear modifications. The essential coupling the western ketone **30.2** with the eastern aldehyde **30.1** was then investigated (Scheme 32), with the authors noting that the desired product necessitated an anti-Felkin aldol to achieve the requisite diastereomer. Utilizing LiHMDS to generate a lithium enolate provided a the undesired C22-(*S*) epimer preferentially, and using Evans' chlorotitanium enolate method provided only 15% desired C22-(*R*) epimer **32.1** along with 48% of the undesired epimer. While the epimers could be easily separated, the authors extensively explored more efficient conditions. Highly selective coupling was attained by utilizing Mukaiyama aldol conditions, where ketone **30.2** is converted to the silyl enol ether followed by

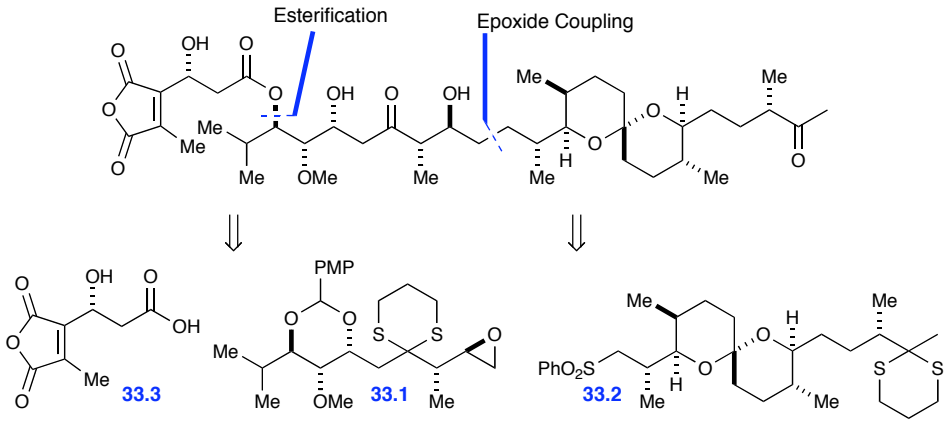
treatment with aldehyde **30.1** in the presence of $TiCl_4$ afforded the desired C22-(*R*) **32.1** as the sole isomer. The authors posit that the high diastereoselection arrived from chelation of the Lewis acid with the α-ether oxygen versus the β-acyl oxygen. Subsequent Wacker oxidation of the C1-C2 olefin followed by optimized TESOTf mediated anhydride formation provided (+)-tautomycin, confirming the relative and absolute stereochemistry of the phosphatase inhibitor.

Scheme 32



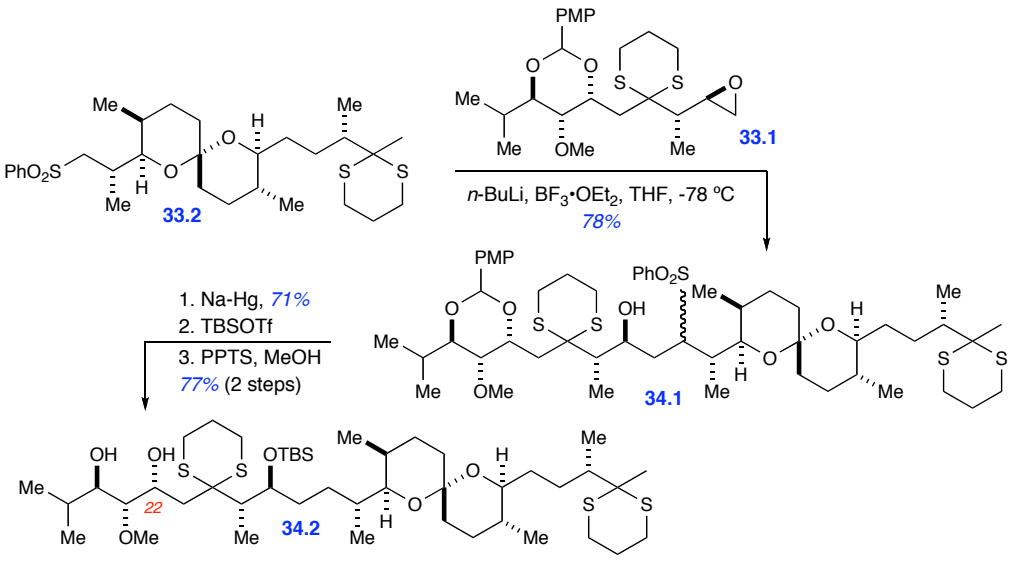
The Isobe group was next to publish their total synthesis of (+)-tautomycin the next year,[57] with a full report subsequently detailing their efforts.[58] The Isobe group divided the molecule into 3 major fragments to facilitate a convergent total synthesis. Two key steps stood out towards realizing the total synthesis (Scheme 33): 1. the coupling of C17-C26 epoxide **33.1** with C1-C16 sulfone **33.2**, and 2. the esterification of acid **33.3** with the western portion of the molecule.

Scheme 33



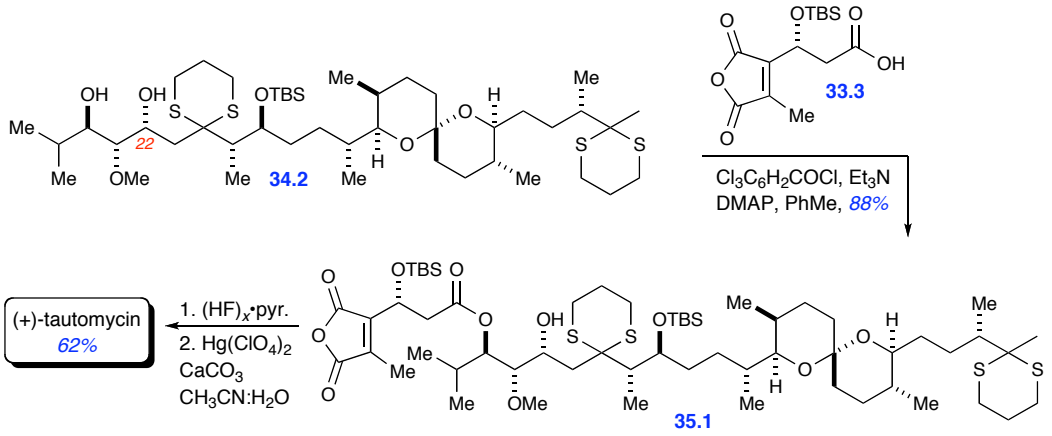
The two key events were performed within 3 steps of each other. First, coupling of the sulfone fragment **33.2** with epoxide **33.1** occurred by generating the anion of **33.2** with subsequent addition of BF_3•OEt_2 activated epoxide **33.1**. This provided the western carbon skeleton **34.1** in 78% yield as a mixture of epimers at the C16 sulfone. Subsequent desulfonlylation followed by protecting group manipulation provided diol **34.2** poised for esterification.

Scheme 34



The esterification had been extensively studied with particularly fruitful observations. One was that TBS protection of the C22 alcohol of **34.2** caused a serious steric interaction that hampered esterification (28% yield). Noting that selective esterification of model diols proceeded smoothly, the selective esterification of diol **34.2** with fully elaborated anhydride acid **33.1** was attempted under Yamaguchi conditions (Scheme 35). Gratifyingly, protected tautomycin **35.1** was formed in 88% yield and upon silyl and thioketal deprotection provided (+)-tautomycin.

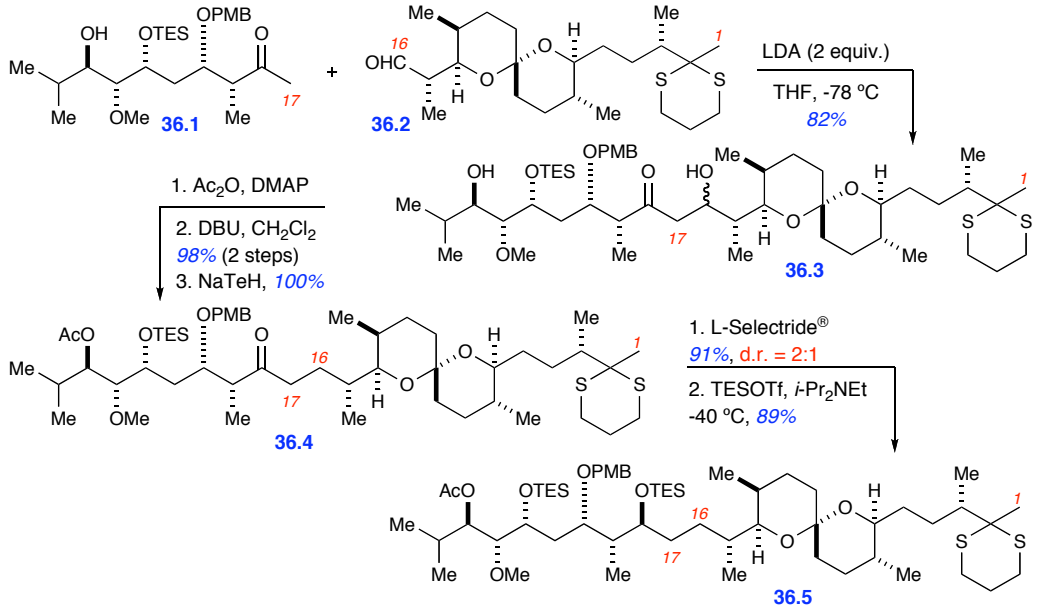
Scheme 35



Shibasaki's group published their approach to the natural product in 1996.[59] Their approach to the coupling the C16-C17 bond was envisioned to proceed through an aldol reaction[60] rather than an epoxide addition as Isobe's report detailed. Also explored was a similar Yamaguchi esterification to append the maleic anhydride fragment, with insight as to an appropriate species to employ issuing from the investigations. Generation of the necessary fragments for providing the aldol substrates occurred from 2-deoxyglucose to afford C17-C26 fragment **36.1** (Scheme

36) and from (+)-diethyl tartrate to provide C1-C16 spiroketal aldehyde **36.2**. The essential aldol condensation was accomplished by generating the dianion of keto-alcohol **36.1**, allowing for addition into aldehyde **36.2** to afford the adduct **36.3** as a diastereomeric mixture in 82% yield. Bis-acylation of the diol **36.3** followed by DBU promoted elimination at C16-C17 provided the enone. While hydrogenation with Wilkinson's catalyst failed, mild conjugate reduction using NaTeH afforded saturated ketone **36.4** quantitatively. Subsequent diastereoselective reduction with L-Selectride® provided the final stereogenic center at C18 in a 2:1 ratio of desired *S* to undesired *R*, an inseparable mixture until TES protection to afford **36.5**.

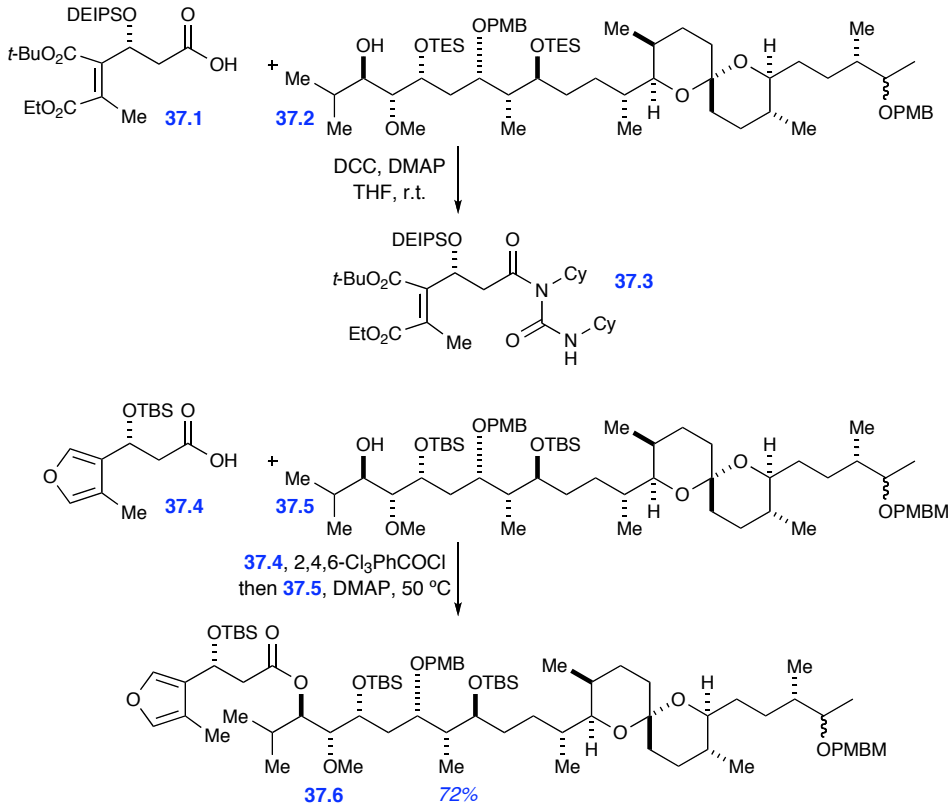
Scheme 36



Rigorous investigation of the key unifying esterification highlighted the sensitivity of the reaction to remote steric interactions. Attempting to couple western diester acid **37.1** with eastern spiroketal **37.2** (Scheme 37) was deemed plausible based on model studies with acid **37.1** under a variety of coupling conditions, all of

which proceeded in good yield. On the actual spiroketal alcohol **37.2**, however, attempting to couple utilizing DCC in THF provided no product and instead yielded dicyclohexylurea adduct **37.3**. Utilizing Keck's method (DCC, PhMe) with DMAP•HCl yielded no DCC adduct **37.3**, but also no desired coupling product. When three other methods failed to provide any product, the authors reevaluated the synthesis and produced furanyl acid **37.4** to circumvent the severe steric interactions

Scheme 37

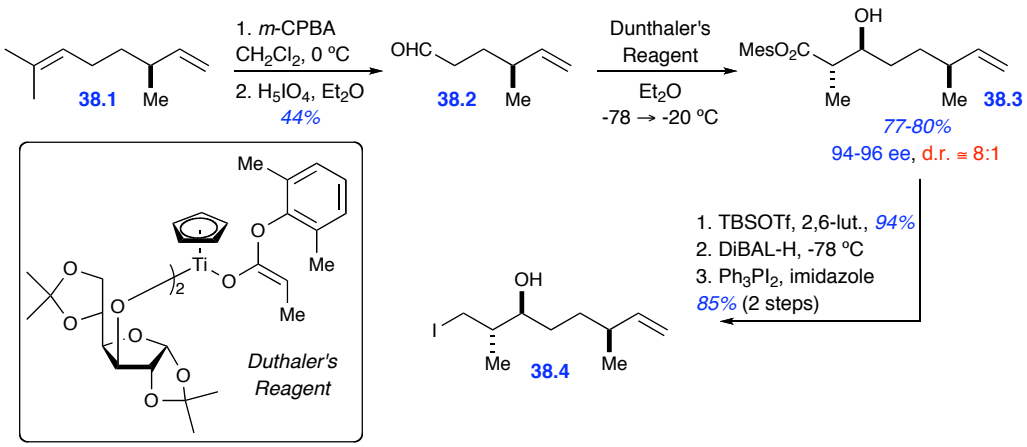


implicated in the recalcitrant esterification. Coupling furanyl acid **37.4** with alcohol **37.5** (only slightly modified from **37.2** to circumvent an unexpected acyl migration during TES deprotection) under modified Yamauchi conditions utilizing a large

excess of DMAP provided ester **37.6**. Six additional functional group manipulations yielded the natural product.

Chamberlin and co-workers expounded upon a different approach to (+)-tautomycin in 1997.[61] Production of the natural product was to originate with (*S*)-citronellene and (2*R*,3*S*)-geraniol epoxide to form the C1-C21 segment of the phosphatase. In this vein, synthesis of the C1-C8 fragment began with selective oxidative cleavage of (*S*)-citronellene (**38.1**, Scheme 38) via a two step Ireland procedure.[62] Attempts to convert aldehyde **38.2** to the *anti* aldol adduct **38.3** surveyed several types of enantioselective routes, with the authors choosing the Duthaler reagent[63] due to its excellent enantioselectivity, convenient scalability, and consistency. Silylation of the C6 hydroxyl, DIBAL reduction of the ester, and functional transposition of the primary alcohol to the iodide generated C1-C8 fragment **38.4**.

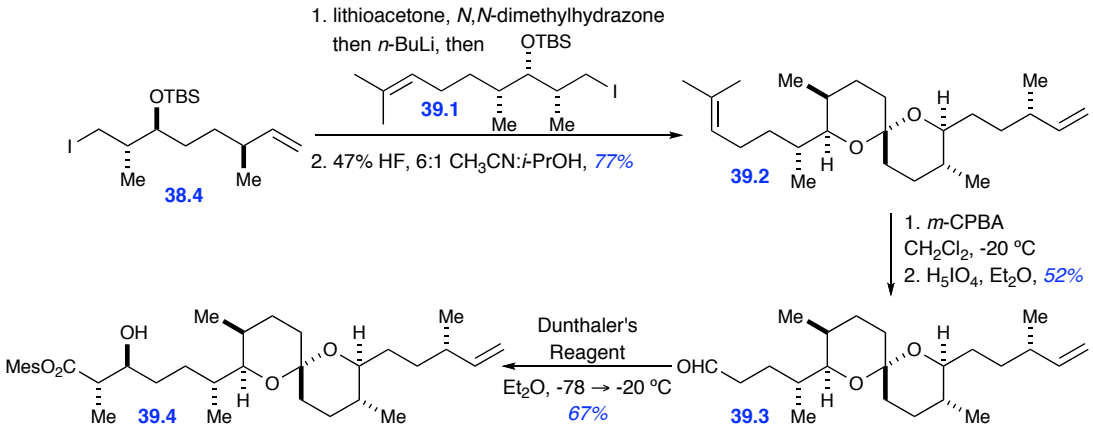
Scheme 38



The C1-C8 iodide **38.4** was joined to acetone and C12-C18 iodide **39.1** (Scheme 39) via a three step, one pot double alkylation procedure to afford the

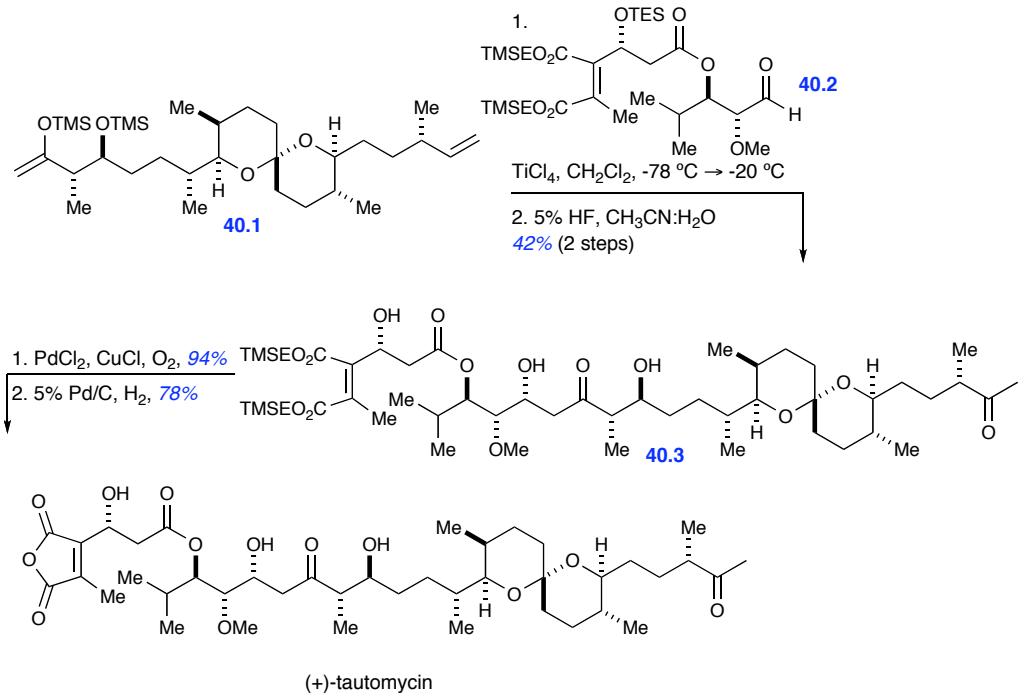
hydrazone, followed by concomitant silyl deprotection and spiroketalization to provide ketal **39.2** as a single isomer in 77% overall yield. While oxidative cleavage provided disappointing yields of aldehyde **39.3** (52%) on large scale, the ready abundance of **39.2** prevented the step from being insurmountable. Utilizing the Dunthaler reagent once more provided a 7:1 mixture of inseparable isomers, favoring adduct **39.4**, in 67% yield. Subsequent saponification (without detectable epimerization), Wienreb amide formation and methylation provided the methyl ketone homologue of **39.4** that was readily separable from the minor isomer.

Scheme 39



To complete the synthesis, anti-Felkin chelation controlled Mukaiyama aldol coupling cleanly combined the C1-C21 segment **40.1** with the western ester **40.2** to provide a single aldol diastereomer **40.3** after silyl deprotection. Wacker oxidation provided the C1-C2 methyl ketone without notable epimerization, allowing for hydrogenolysis to complete the synthesis of the natural product. In summary, the Chamberlin group total synthesis of (+)-tautomycin proceeded in 19 linear steps from (2*R*,3*S*)-geraniol in 1.5% overall yield.

Scheme 40



1.6 Phoslactomycins

Phoslactomycins A-F and I are a class of polyketide natural products bearing a phosphate that exhibit antitumor, antiviral, antibiotic and antifungal properties.[64] The inhibitory activity selective for human protein phosphatase 2A (PP2A)[65] has prompted intensive investigations into this class of molecules. Such investigations have yielded the binding site that interacts with the crucial phosphate group,[66] the cloning and sequencing of the biosynthetic gene cluster,[67] and the origin of the biosynthetically unusual *cis* olefins in the natural product.[68]

The first total synthesis of phoslactomycin B was reported by Kobayashi and co-workers in 2006,[69,70] where the authors initially sought to construct the molecule in an analogous manner to the synthetic route utilized for fostriecin. After investigation, however, it was found that certain key transformations such as the

RCM of the lactone ring were inefficient in application towards phoslactomycin B, as illustrated in Figure 6.

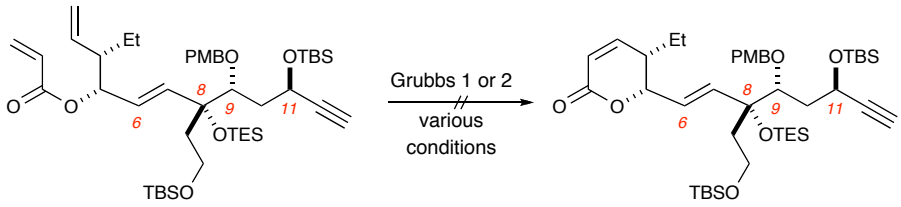


Figure 6 *Attempted Ring-Closing Metathesis by Kobayashi and co-workers*

This observation led to a synthesis where the lactone ring would be afforded by Lewis acid lactonization of the acyclic γ-hydroxy ester (Figure 7). Installation of the C8 stereocenter would occur by chelation controlled diastereoselective Grignard addition governed by the C9 stereocenter. The key *Z,Z*-diene would proceed from reduction of the enyne, which itself would be formed from a Sonogashira coupling.

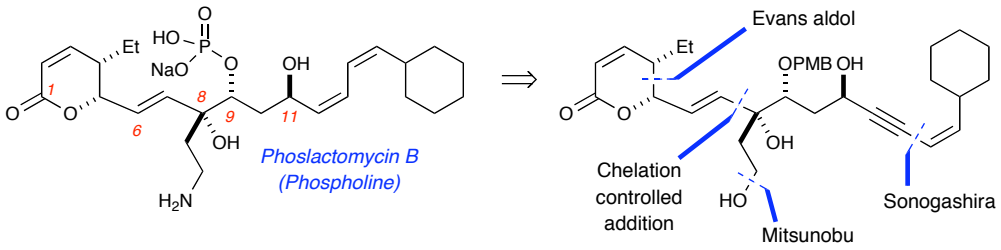
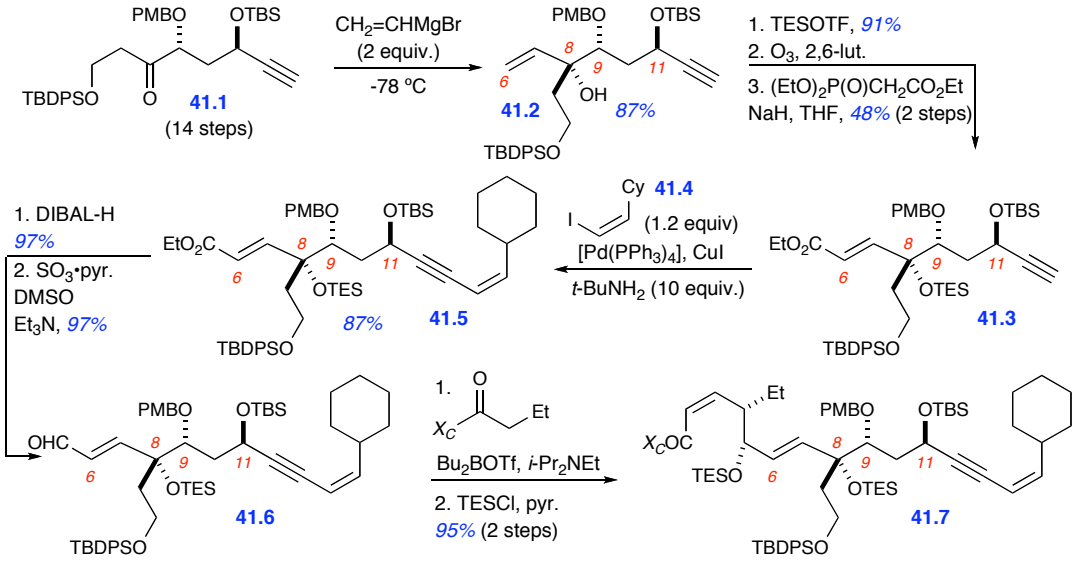


Figure 7 *Kobayashi's Retrosynthesis*

The initial C9 stereocenter was provided by kinetic resolution of racemic (*E*)-ethyl 3-hydroxyhex-4-enoate by Sharpless asymmetric epoxidation. Another 14 steps provides ketone **41.1** (Scheme 41), where a diastereoselective vinylmagnesium bromide addition provided the C8 stereocenter of **41.2** as a single diastereomer, ultimately proven to be the desired configuration upon completion of the molecule. Protection of the C8 alcohol followed by ozonolysis and Horner-Wadsworth-Emmons olefination produced ester **41.3**, setting the stage for completion of the carbon

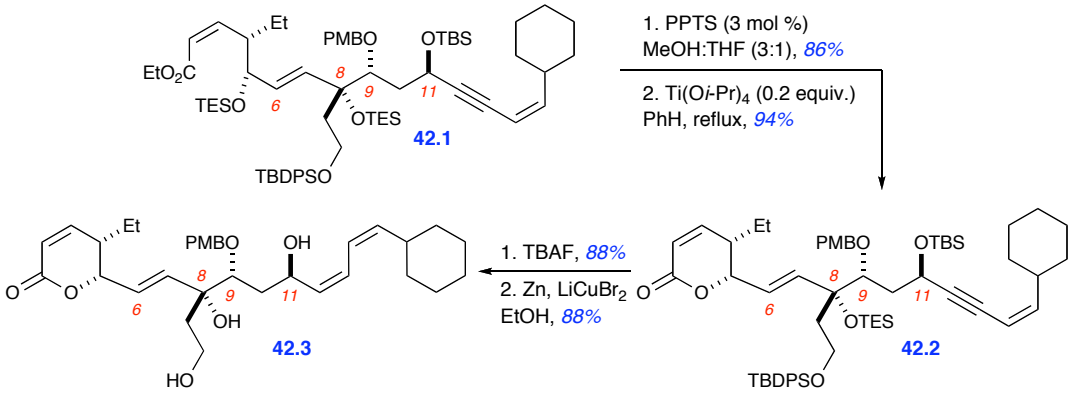
skeleton on the natural product. Enyne **41.5** was afforded through Sonogashira coupling of the acetlyenic carbon with *Z*-vinyl iodide **41.4**. Installation of the lactone occurred through an Evans aldol reaction of aldehyde **41.6** to afford C4-C5 *syn* adduct **41.7**.

Scheme 41



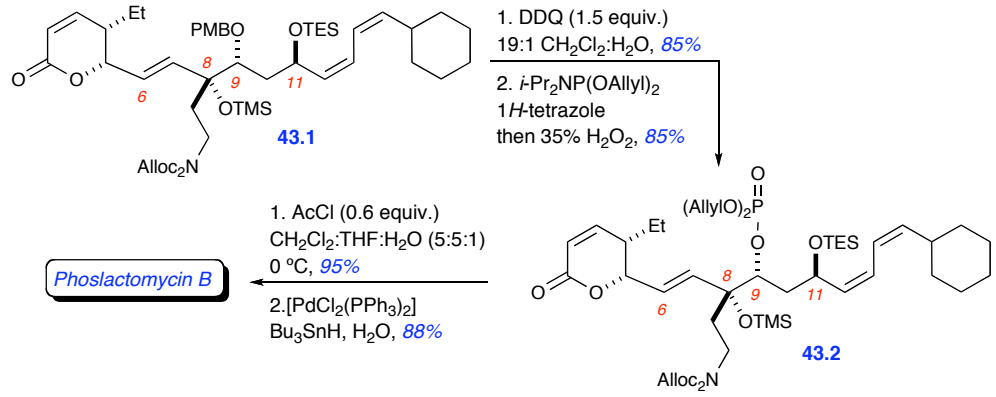
Cleavage of the oxazolidinone followed by aldehyde formation and olefination provided the acyclic lactone precursor **42.1** (Scheme 42). Removal of the C8 TES group allowed for titanium(IV) isopropoxide mediated transesterification to afford lactone **42.2**, again noting that attempts to generate the lactone by RCM to fuse the C2-C3 olefin were fruitless. Generation of the *Z*,*Z*-diene then commenced by global silyl deprotection and zinc reduction to afford diene **42.3** with exquisite *cis* selectivity.

Scheme 42



Completion of the synthesis occurred after Mitsunobu introduction of the amine, where deprotection of the C9 PMB group of **43.1** (Scheme 43) in the presence of the *Z*,*Z*-diene afforded the alcohol in good yield. Phosphate introduction by the phosphoramidite and subsequent oxidation provided fully protected inhibitor **43.2**, which after acidic deprotection of the silyl groups and palladium mediated deallylation yielded (+)-phoslactomycin B. The total synthesis thus proceeded in 38 steps from racemic (*E*)-ethyl 3-hydroxyhex-4-enoate in 0.9% overall yield.

Scheme 43



The second reported total synthesis came from Hatakeyama's group in 2008.[71] The authors dissected the molecule as presented in Figure 8 where a Stille-type coupling would append the vinylcyclohexyl group onto the carbon skeleton. RCM

would generate the lactone from the acyclic diene, while the amine bearing chain from C8 would be incorporated via a Suzuki-Miyaura coupling with a Sharpless asymmetric dihydroxylation providing the C8 and C9 stereocenters. The group wished to install the C4 and C5 stereogenic centers through an asymmetric pentenylation in a Brown or Roush asymmetric crotylation fashion, a feat that was described as unprecedented.

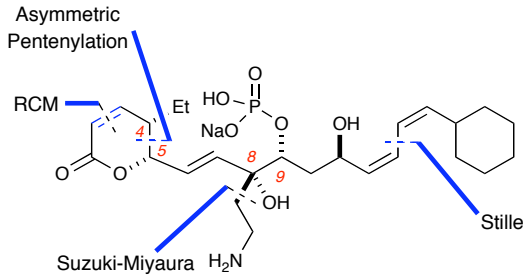
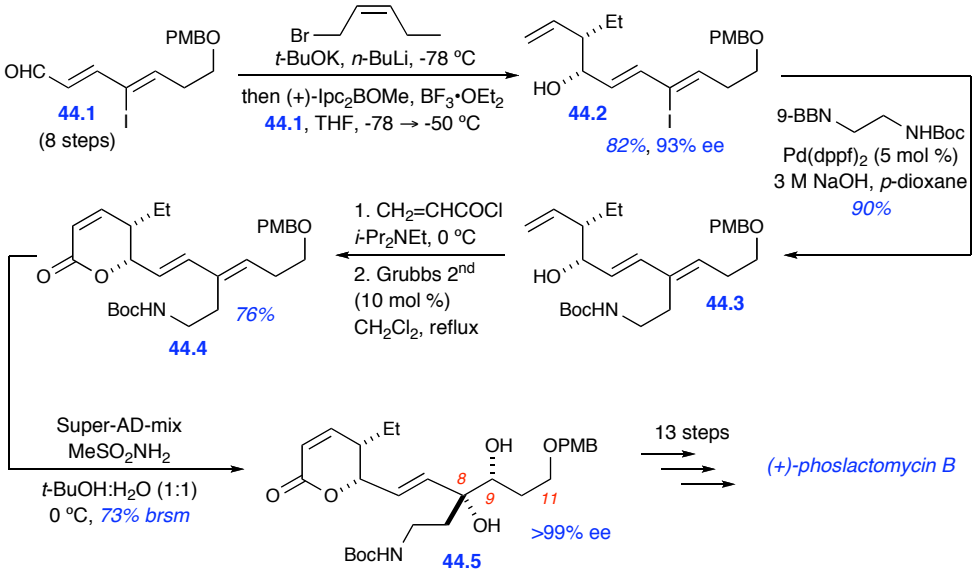


Figure 8 *Hatakeyama's Retrosynthetic Dissection*

The risky asymmetric pentenylation of aldehyde **44.1** was first attempted with Brown conditions (Scheme 44). Initially, the pentenyl borane reagent was prepared from 2-pentenylmagnesium bromide and (+)-Ipc_2BOMe to provide a 98% yield of a 1:3 desired *syn* to undesired *anti* mixture. The authors deduced that a partial isomerization was occurring when preparing the Grignard from (*Z*)-2-pentenyl bromide, and thus opted to use 2-pentenylpotassium. The Brown reagent prepared from 2-pentenylpotassium yielded highly diastereo- and enantioselective pentenylation to provide the *syn* isomer **44.2** in 82% yield as a sole diastereomer in 93% ee. This set the stage for the Suzuki-Miyaura coupling step, where the C8-aminoethyl group was appended smoothly to provide alcohol **44.3**. Acryloylation of alcohol **44.3** allowed for ring-closing metathesis of the resulting acrylate to cleanly

cyclize to lactone **44.4** in 76% yield. This interesting result contrasts with the Kobayashi group's investigations, vide supra. The C8 and C9 stereocenters were then set by utilizing Super-AD-mix with $(DHQD)_2$-PHAL as a chiral ligand to afford a 87:13 mixture of the C8-C9 dihydroxylated product **44.5** with the minor C6-C7 dihydroxy isomer. It was also found that diol **44.5** was generated as an exclusive enantiomer, suggesting a concomitant kinetic resolution of **44.4** during the reaction. Taking 13 more steps to provide (+)-phoslactomycin B, the total synthesis proceeded in 26 steps in 1.3% overall yield.

Scheme 44



The only (as of this writing) synthesis of phoslactomycin A, depicted in Figure 9, that has been reported is that of the Koert group in 2009.[72] The group utilized transformations similar to those described for the phoslactomycin B syntheses (vide supra) as well as for the synthesis of leustroducsin B,[73,74] with key contributions

in the synthesis of the C14-C21 cyclic fragment and the coupling of the C13-C14 bond in the presence of the protected phosphate.

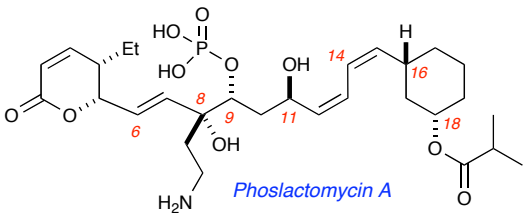
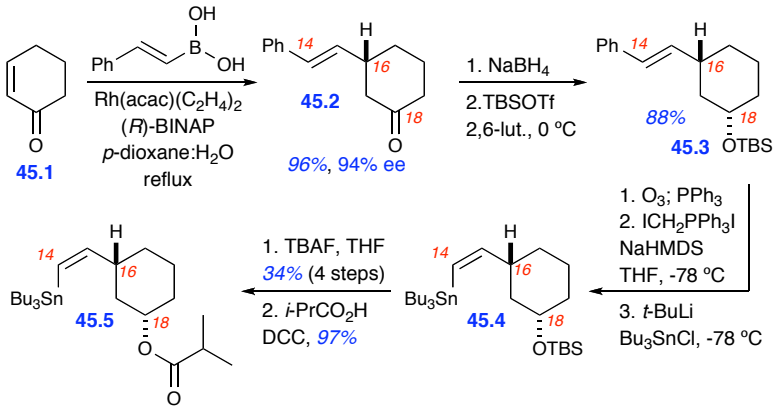


Figure 9 *Phoslactomycin A*

Synthesis of the C14-C21 fragment began with conjugate asymmetric addition of *E*-styrylboronic acid to cyclohexenone (**45.1**) mediated by Hayashi's catalytic conditions[75] to afford ketone **45.2** in 96% yield with 94% ee (Scheme 45). Sodium borohydride reduction and subsequent TBS protection provided alkene **45.3**, followed by ozonolysis, Stork-Zhou olefination, and stannylation to give vinyl stannane **45.4**. Deprotection followed by esterification provided the C14-C21 fragment **45.5**.

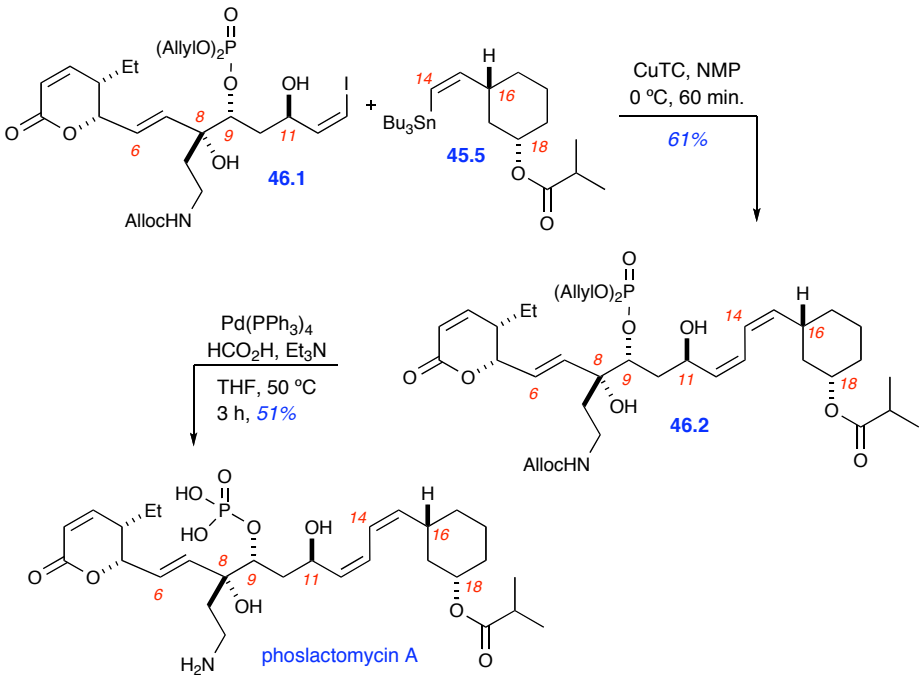
Scheme 45



The final union of the C14-C21 fragment **45.5** to the C1-C14 subunit **46.1** was carefully examined (Scheme 46). While a Pd-catalyzed Stille reaction would be suitable for alkenyl iodide couplings with alkenyl stannanes, the presence of the C9 allyl protected phosphate gives pause to palladium mediated couplings. Utilizing Cu-

mediated Liebeskind coupling[76] prevents side reactions, and copper(I) thiophene carboxylate (CuTC) proved to provided the desired coupling to afford the protected inhibitor **46.2** in 61% yield. The advantage of this method is clear as only a protecting group removal remained in the total synthesis, which was enacted with $Pd(PPh_3)_4/HCO_2H$ to reveal phoslactomycin A.

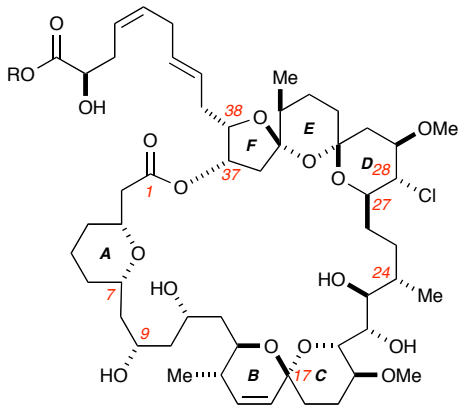
Scheme 46



1.7 Spirastrellolide A Methyl Ester

The isolation of spirastrellolide A and spirastrellolide A methyl ester (Figure 10) from *Spirastrella coccinea* was reported in 2003 by Andersen and co-workers, drawn to discover the inhibitor responsible for mitotic arrest in their cell-based assays.[77] More, although not complete, stereochemical detail was provided in 2004, but of interest was the fact that spirastrellolide A was a potent inhibitor of PP2A (IC_{50}

= 1 nM) that did not effect tubulin polymerization as did other antimitotic sponge macrolides.[78] Instead, it accelerates the entry of cells into mitosis from other stages of the cell cycle then induces arrest, similar to the okadaic acid class of molecules.[78] The 47 carbon backbone of the molecule contains 21 stereocenters, three cyclic ether subunits including the unique DEF chlorosubstituted 5,6,6-trioxadispiroketal, and an exocyclic non-conjugated *Z*,*E*-diene. Given the small amount of spirastrellolide which was isolated coupled with the unique architecture and biological activity, with the added complication of several unresolved stereochemical issues, earnest motivation towards completion of the total synthesis was well founded.[79]



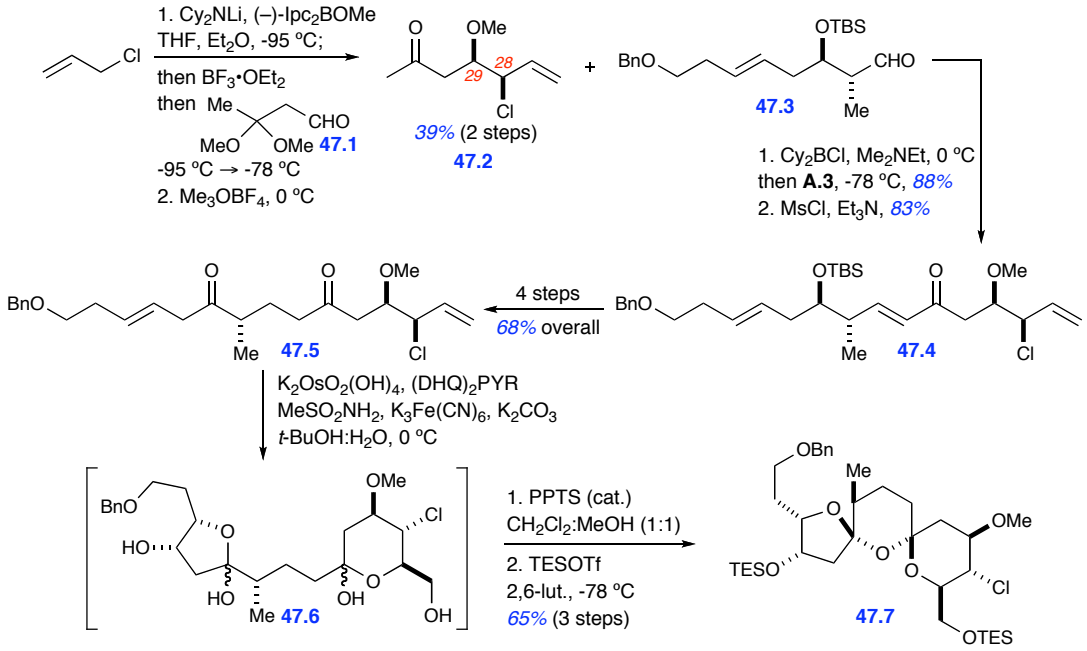
R = H, *Spirastrellolide A*
R = Me, *Spirastellolide A Methyl Ester*

Figure 10 *Spirastrellolide A and spirastrellolide A methyl ester*

The first and, as of this writing, only total synthesis of the spirastrellolide family was reported in back to back publications by Paterson and co-workers in 2008 on their work synthesizing spirastrellolide A methyl ester.[80] Key to their efforts was the efficient and improved synthesis of the C25-C40 bisspiroketal fragment **47.7**, which had been previously reported (Scheme 47).[81] Oehlschlager-Brown chloroallylation[82] of aldehyde **47.1** followed by methylation enantioselectively

provided ketone **47.2** in good yield with excellent diastereoselectivity. Formation of the boron enolate of **47.2** allowed addition to aldehyde **47.3** which, after elimination, provided triene **47.4** on 10 gram scale. Conversion of triene **47.4** to diene dione **47.5** allowed for the pivotal tandem double-Sharpless asymmetric dihydroxylation/spiroketalization tactic, where subsequent TES protection provided the C25-C40 DEF domain **47.7**.

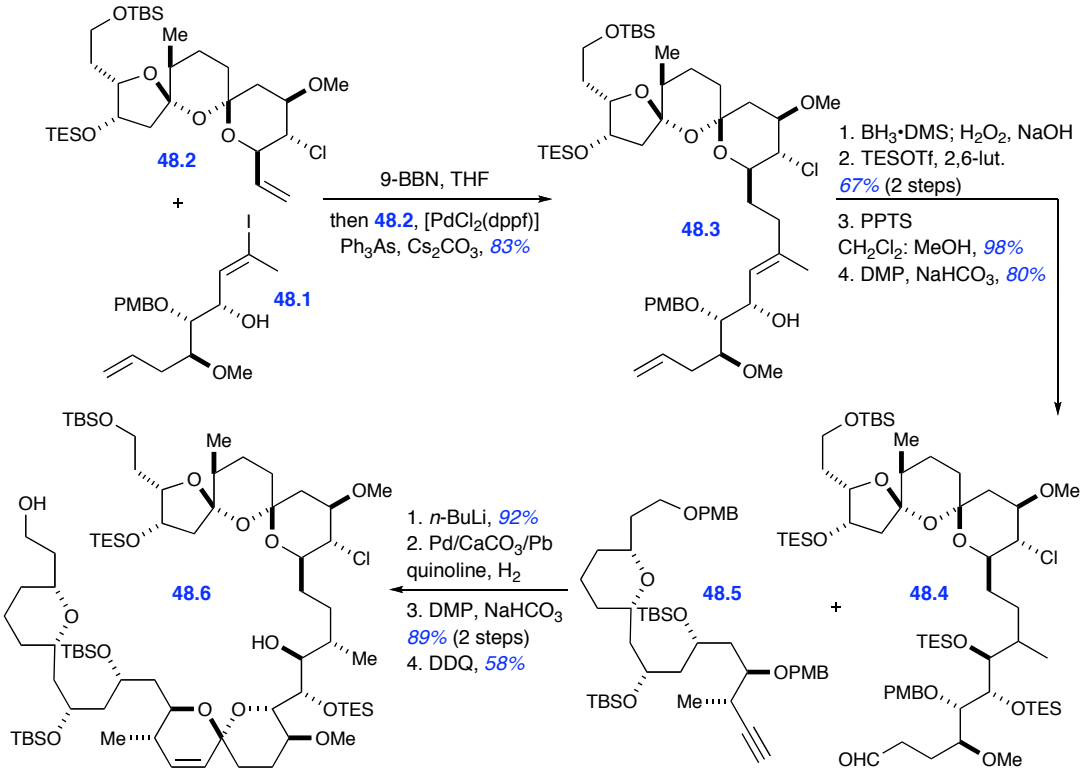
Scheme 47



The crucial coupling of the C17-C24 subunit with the DEF subunit **47.7** could be afforded through a modified Julia olefination, however it was rather lengthy and faced disappointing yields. This led the Paterson group to explore an ambitious sp^2-sp^3 coupling of iodide **48.1** with hydroborated alkene **48.2** (Scheme 48), which afforded the trisubstituted olefin **48.3** in 83% yield. Substrate controlled bis-hydroboration of alcohol **48.3** provided the C23 stereocenter, followed by protection

and formation of the C17 aldehyde **48.4**. Addition of the lithium anion of C1-C16 bearing alkyne **48.5** to aldehyde **48.4** provided a mixture of epimeric alcohols, rendered inconsequential by the subsequent Lindlar reduction and oxidation of the epimeric alcohols to the enone. All three PMB ethers were cleaved with DDQ (with the unexpected TES deprotection at C23) to achieve stereoselective BC spiroacetalization affording hexacyclic diol **48.6** and a mere two step oxidation removed from the crucial macrolactonization event.

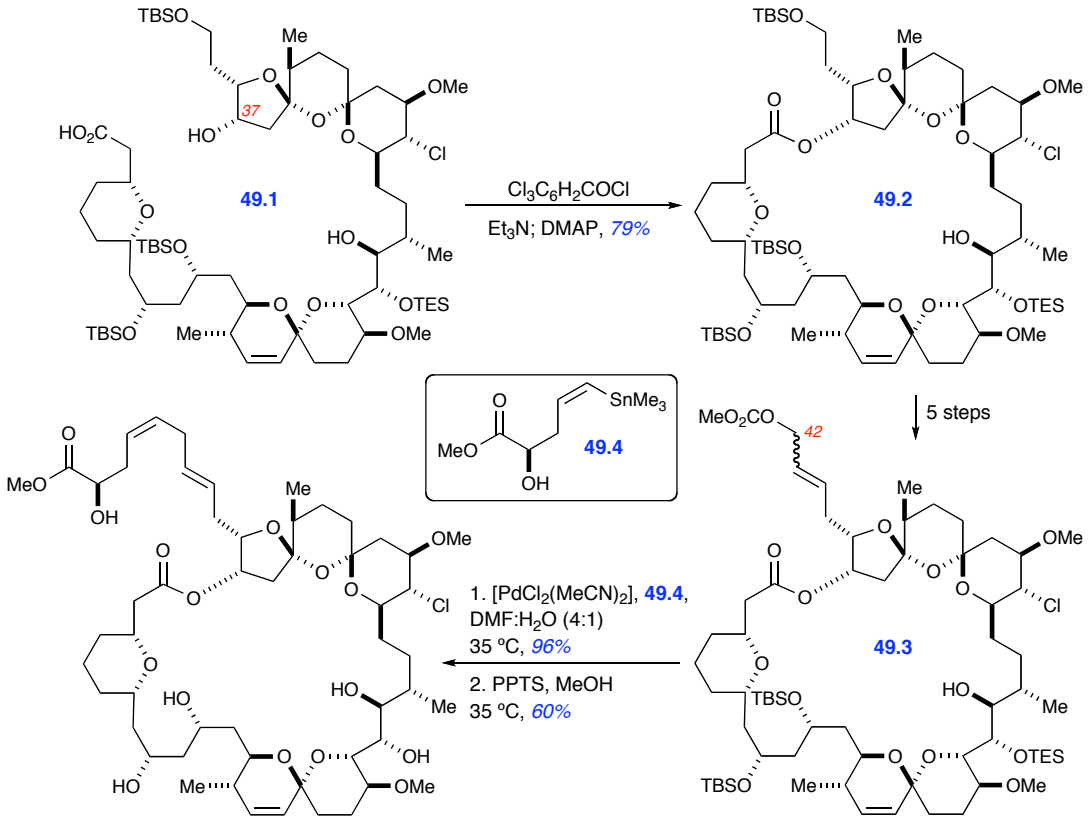
Scheme 48



The critical macrocyclization of seco acid **49.1** (Scheme 49) was found to occur quite readily via the Yamaguchi protocol to rapidly yield the corresponding macrolide **49.2**. What seemed to be a simple selective deprotection of the primary C40 TBS group turned out to be fraught with difficulty, however, necessitating global

deprotection and reprotection followed by transformation to the olefin and a gentle cross-metathesis (which did not degrade starting material) to provide allylic carbonate **49.3**. A crucial π-allyl Stille cross-coupling performed extremely well to append stannane **49.4** to provide the desired 40*E*,43*Z* diene, where cleavage of the acetonide groups yielded (+)-spirastrellolide A methyl ester. In total, the pioneering synthesis comprised 36 linear steps to afford the natural product phosphatase inhibitor.

Scheme 49



1.8 Okadaic Acid

Okadaic acid (Figure 11) was first isolated as a potent antitumor agent from Pacific and Caribbean marine sponges *Halichondria okadai* and *Halichondria*

melanodocia (respectively) during a search for chemotherapies.[83] The isolation group elucidated the structure via X-ray crystallography. In 1982, Yasumoto and co-workers identified okadaic acid as the major diarrhetic shellfish toxin in *Mytilus edulis* and concluded the natural product was accumulated from a dinoflagellate, *Dinophysis fortii*, as the original producer.[84] It was found that okadaic acid is a potent inhibitor of PP1 and PP2A,[85] and is the most widely used tool for probing the roles of these phosphatases.[86] Comprehensive and definitive studies to determine the structural basis of inhibition, however, have been limited by lack of designed structural variants.[87] Combined with the exquisite architecture of the molecule, these attributes have provided much impetus in the rational design of synthetic pathways to the natural product and analogues thereof.

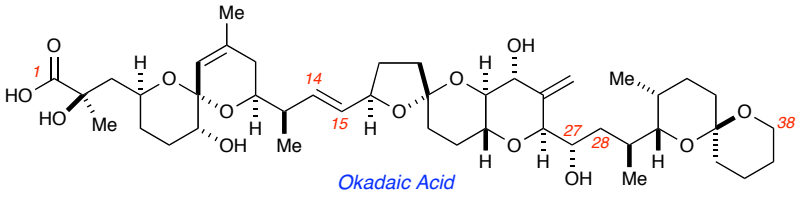
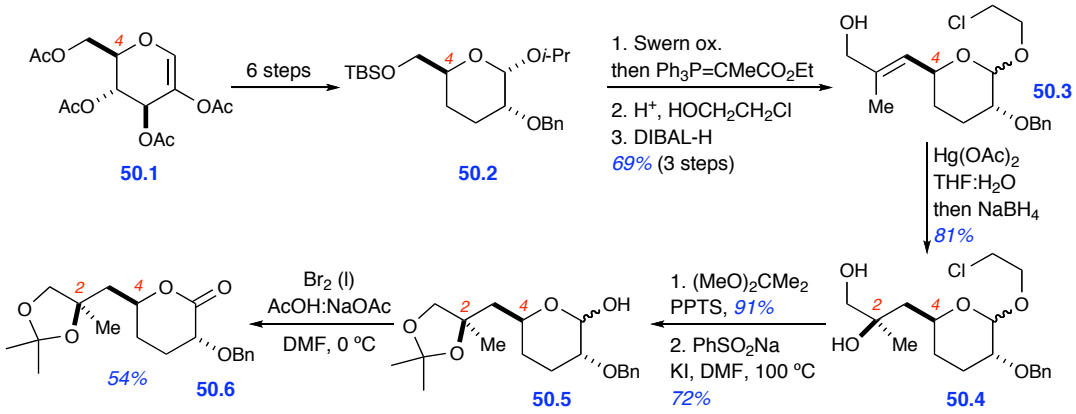


Figure 11 *Okadaic acid*

Isobe and co-workers reported the first synthesis of okadaic acid in 1986.[88,89] The group divided the molecule into three segments: the C1-C14 containing segment A, C15-C27 dispiroketal segment B, and C28-C38 segment C. Segment A was to be synthesized from two glucose derivatives, initiating with 2-acetoxy glucal **50.1** (Scheme 50). Generation of **50.2** allowed for deprotection and oxidation of C1 followed by Wittig olefination, formation of epimeric chloroethylglycosides and ester reduction to yield allylic alcohol **50.3**. The key acyclic C2 hydroxyl group was introduced through selective oxymercuration/demercuration to provided diol **50.4**.

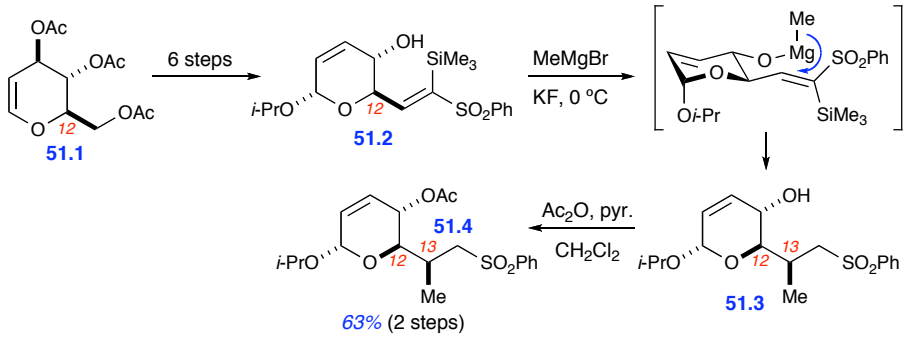
Acetonide protection of the diol masked the C2 hydroxyl group until the final stages of the synthesis, while the chloroethyl glycoside was cleaved with sodium sulfinate to provide lactol **50.5**, where oxidation to the lactone **50.6** by molecular bromine in a buffered media allowed for completion of the C1-C8 fragment of segment A.

Scheme 50



The C9-C14 fragment of segment A relied on a substrate directed approach to introduce the C13 stereogenic center. Formation of heteroolefin **51.2** from D-glucose derivative **51.1** (Scheme 51) occurred in six steps and allowed for application of a previously developed methodology.[90] Thus, β-chelation control of the

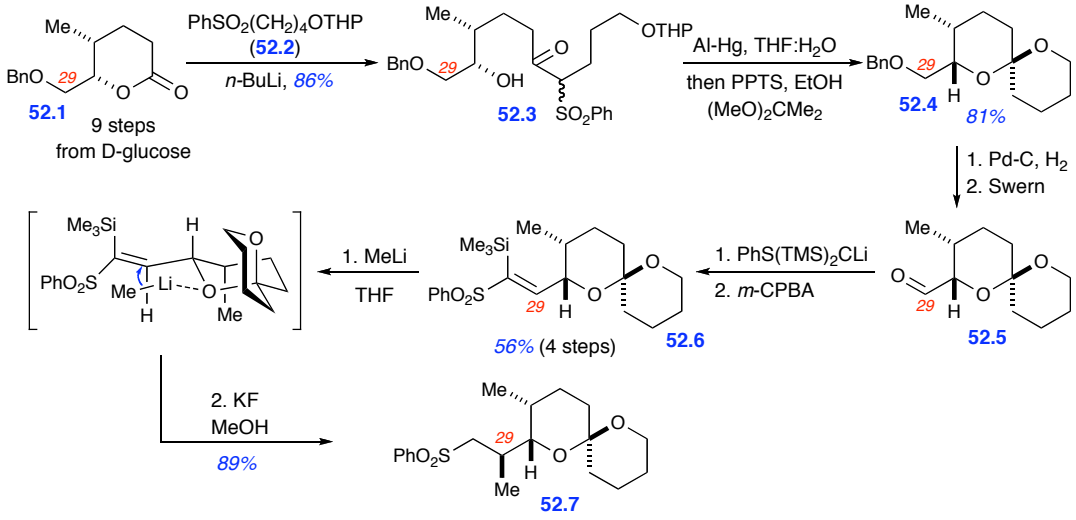
Scheme 51



heteroconjugate addition of methylmagnesium bromide stereoselectively installed the C13 methyl group in alcohol **51.3**. Subsequent acylation provided protected lactol **51.4** as the necessary precursor for generating segment A.

The group approached segment C from lactone **52.1**, available in nine steps from D-glucose (Scheme 52). Opening of the lactone by the anion of protected butyl sulfone **52.2** provided α-sufinyl ketone **52.3**. Reduction followed by immediate treatment with PPTS in refluxing ethanol with 2,2-dimethoxypropane as a dehydrating agent provided spiroether **52.4** in 81% yield. Benzyl deprotection and oxidation of the unmasked alcohol produced aldehyde **52.5**, which after Peterson olefination with $PhS(TMS)_2CLi$ and oxidation of the sulfide produced **52.6**. Chelation controlled heteroconjugate addition afforded the C29 methyl group stereoselectively to complete segment C as sulfone **52.7**, ready for coupling.

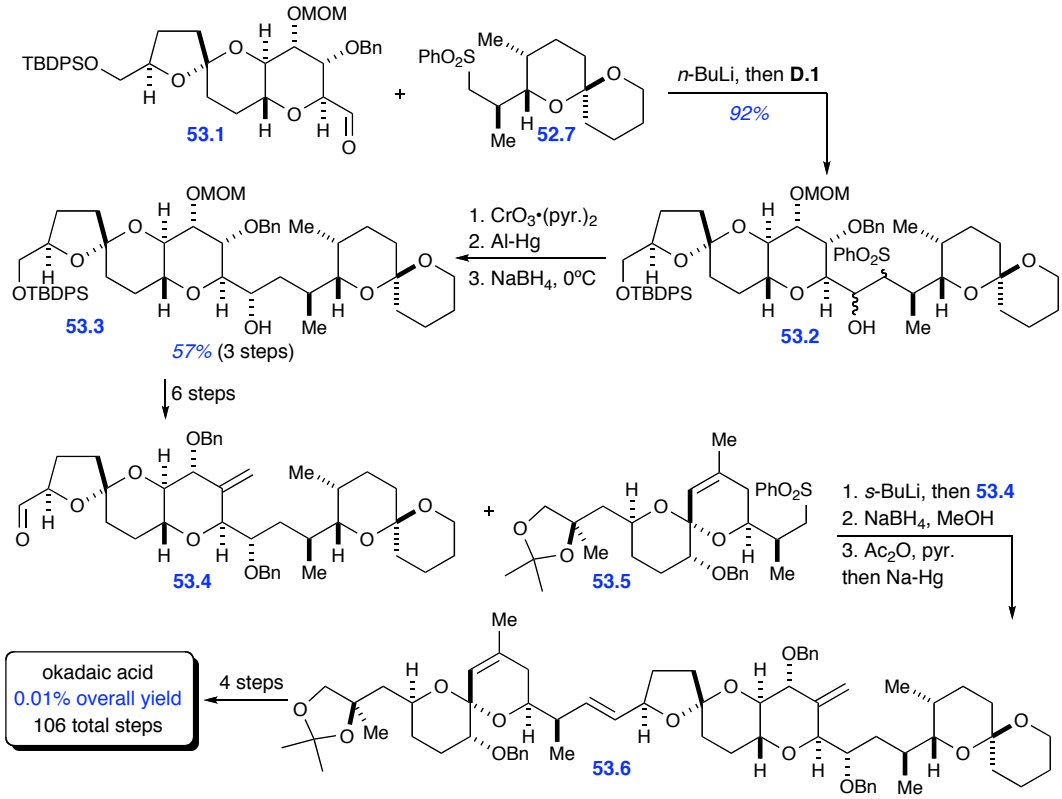
Scheme 52



Final elaboration of the molecule was set into motion by the coupling of segment C sulfone **52.7** with segment B aldehyde **53.1** to afford sulfonate alcohol

53.2 (Scheme 53). Subsequent oxidation of the C27 alcohol followed by desulfurization and sodium borohydride reduction produced BC alcohol **53.3** as a single C27 isomer. Six further modifications allowed for union of the A segment **53.5** with BC aldehyde **53.4**, which after elimination provided the unified molecule **53.6**. Acetonide deprotection, two step oxidation to the C1 carboxylic acid, and benzyl deprotection provided the first totally synthetic okadaic acid, a feat that required 106 total steps and proceeded in 0.01% overall yield.

Scheme 53

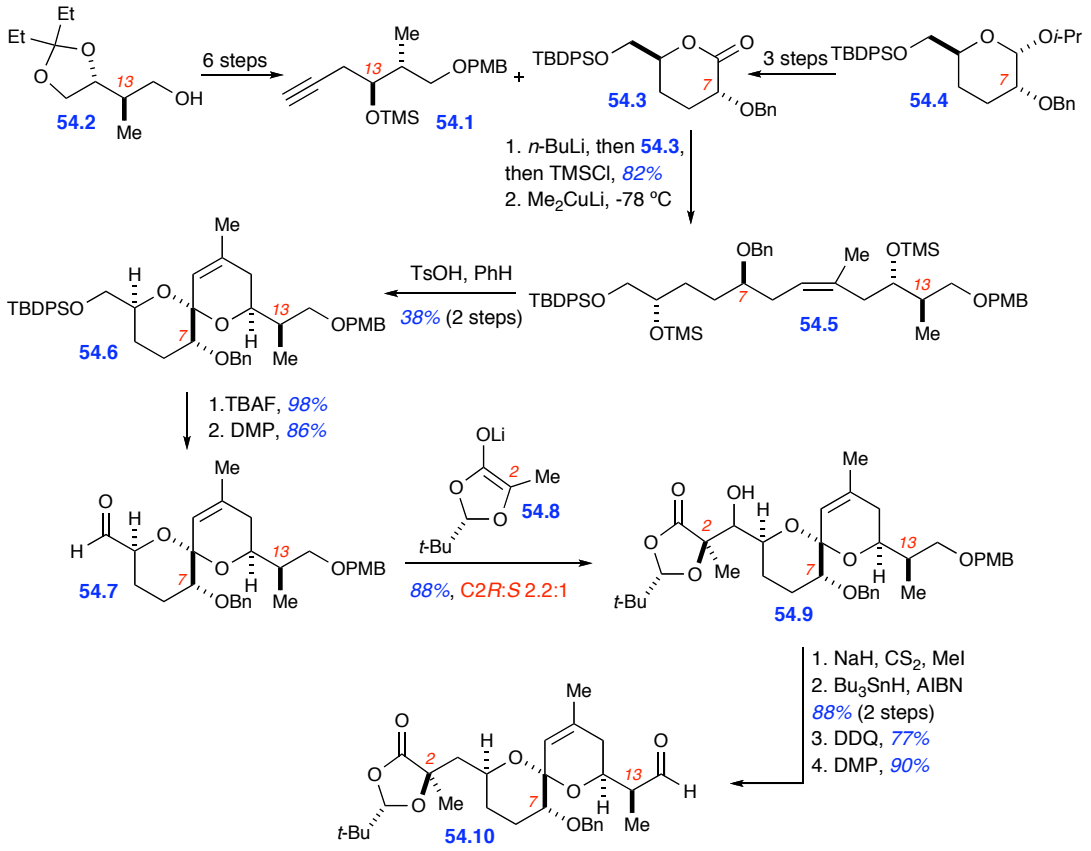


It was eleven years until the next reported total synthesis of okadaic acid. The Forsyth group synthesis of okadaic acid was published in 1997,[91] with additional details provided in 1998.[87,92] While the authors note the disconnections in their

synthesis are similar to Isobe's work, the authors caution that their route relies upon incorporating maximum functionality in each fragment. These highly functionalized fragments were then to be utilized in direct and chemoselective coupling methods to minimize post-coupling transformations.

The C1-C14 fragment was assembled from alkyne **54.1** (Scheme 54), generated from known pentylidene protected triol **54.2**, and lactone **54.3** which arises from Isobe's isopropyl glycoside **54.4**. Addition of the lithium acetylide derived from **54.1** to lactone **54.3** provided the crude ynone that was immediately silylated. Subsequent conjugate addition of dimethylcuprate provided β-methyl enone **54.5**, which upon treatment of the crude enone with TsOH•H_2O promoted spiroketalization to give **54.6**, analogous to Isobe's work. Investigations into incorporating the α-hydroxyl, α-methyl carboxylate at this early stage initially sought to add lactate pivalidene enolate **54.8** to C3 through halide or sulfonate displacement, but numerous attempts proved unsuccessful, potentially due to the crowded steric environment. Addition of enolate **54.8** to the C3 aldehyde **54.7**, however, was successful, albeit in much lower than anticipated facial selectivity in forming the C2 stereocenter of **54.9**. The authors reason this may be due to unfavorable double diastereoselection between the mismatched pair, where the secondary steric interactions erode the facial selectivity based on the *t*-butyl substituent. Subsequent deoxygenation of C3 and deprotection/oxidation of C14 of **54.9** formed C1-C14 aldehyde **54.10**, primed for coupling. This provided an 11 step synthesis of C1-C14 fragment **54.10** from lactone **54.3** in ~20% overall yield.

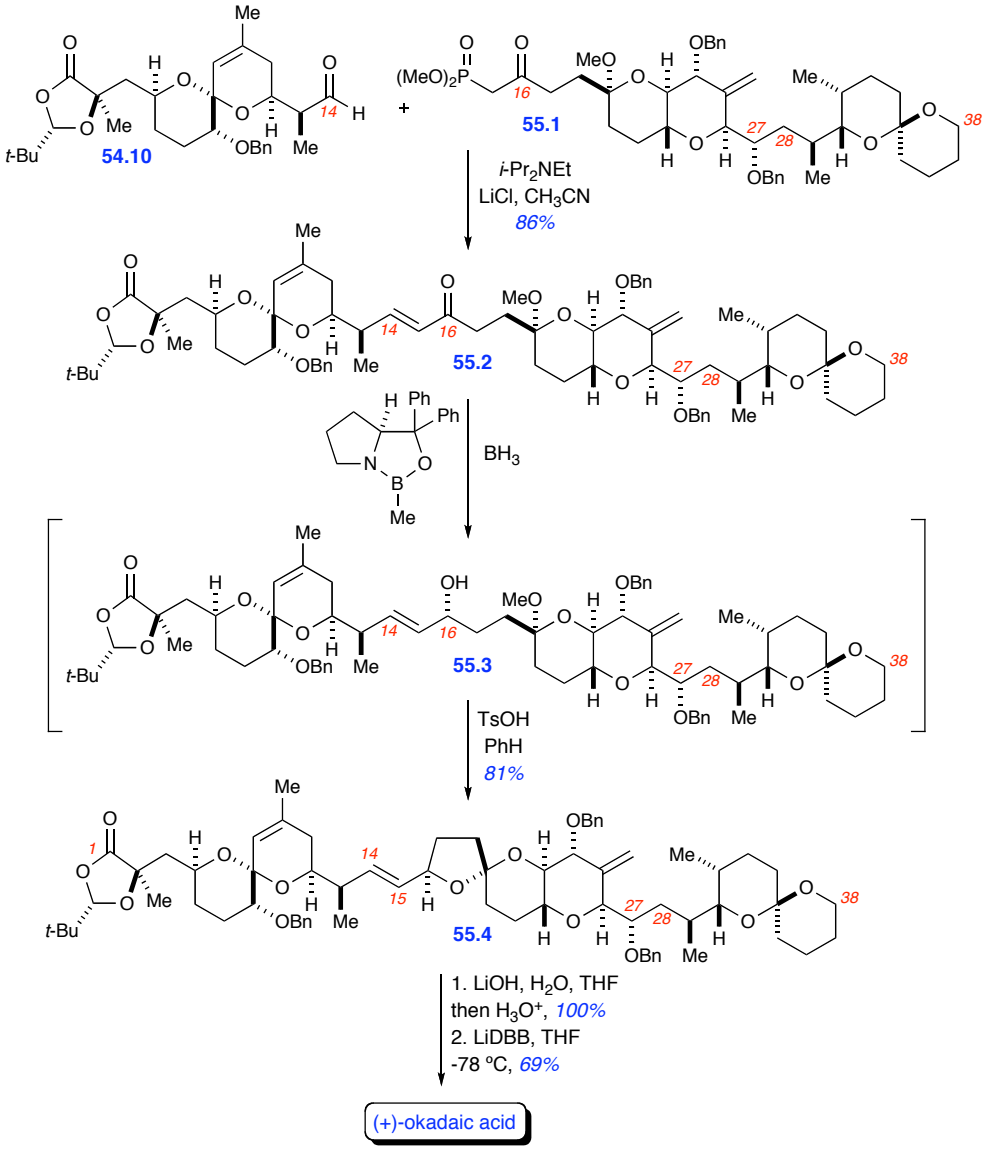
Scheme 54



Realization of the total synthesis relied upon coupling aldehyde **54.10** with advanced intermediate **55.1** in order to unify the carbon skeleton (Scheme 55). The Horner-Wadsworth-Emmons reaction was performed under the mildly basic Masamune-Roush conditions to fuse the two fragments, providing enone **55.2** as a single olefin isomer. Regio- and stereoselective reduction of enone **55.2** was accomplished with (*S*)-CBS and BH_3 to yield the (*R*)-allylic alcohol **55.3**. Since alcohol **55.3** was partially cyclized following acidic workup of the CBS reduction, the crude product mixture was directly subjected to acid-catalyzed spiroketalization to yield protected okadaic acid **55.4**. A two step deprotection completed the total

synthesis of the phosphatase inhibitor as a 26 linear step synthesis with ~2% overall yield.

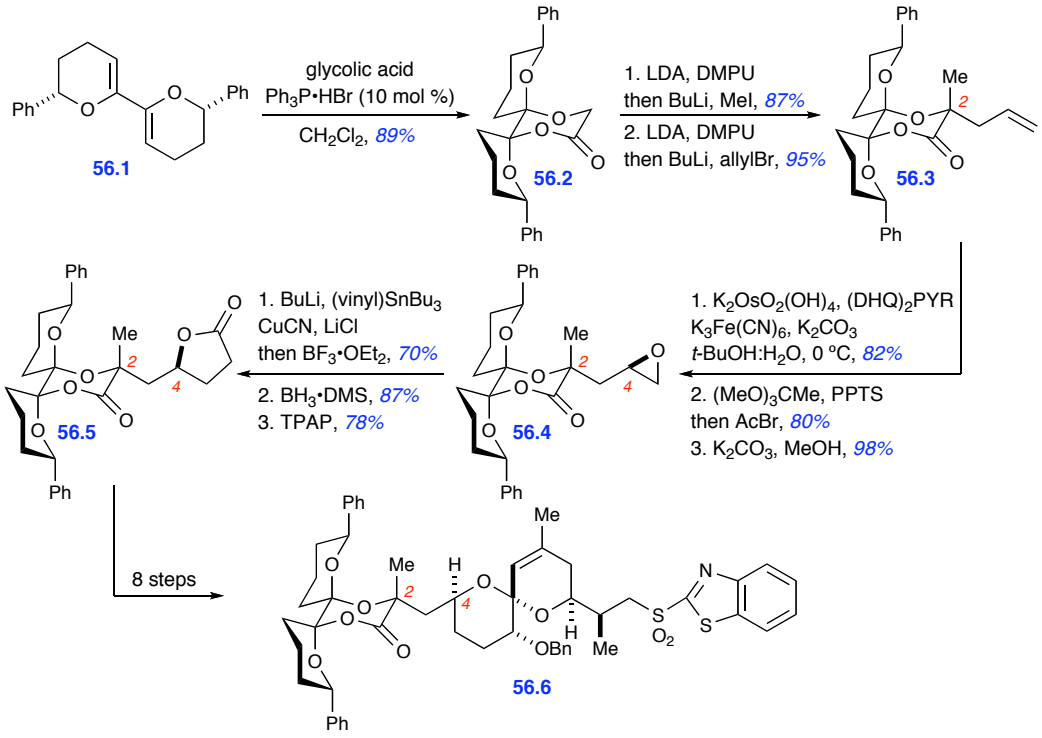
Scheme 55



Ley and co-workers reported their approach to the total synthesis of the inhibitor in 1998,[93] where the authors intended to provide a route to the natural product by chemical methods developed in their laboratories. In producing the C1-C14 fragment, the group chose to employ chemistry specifically developed for the

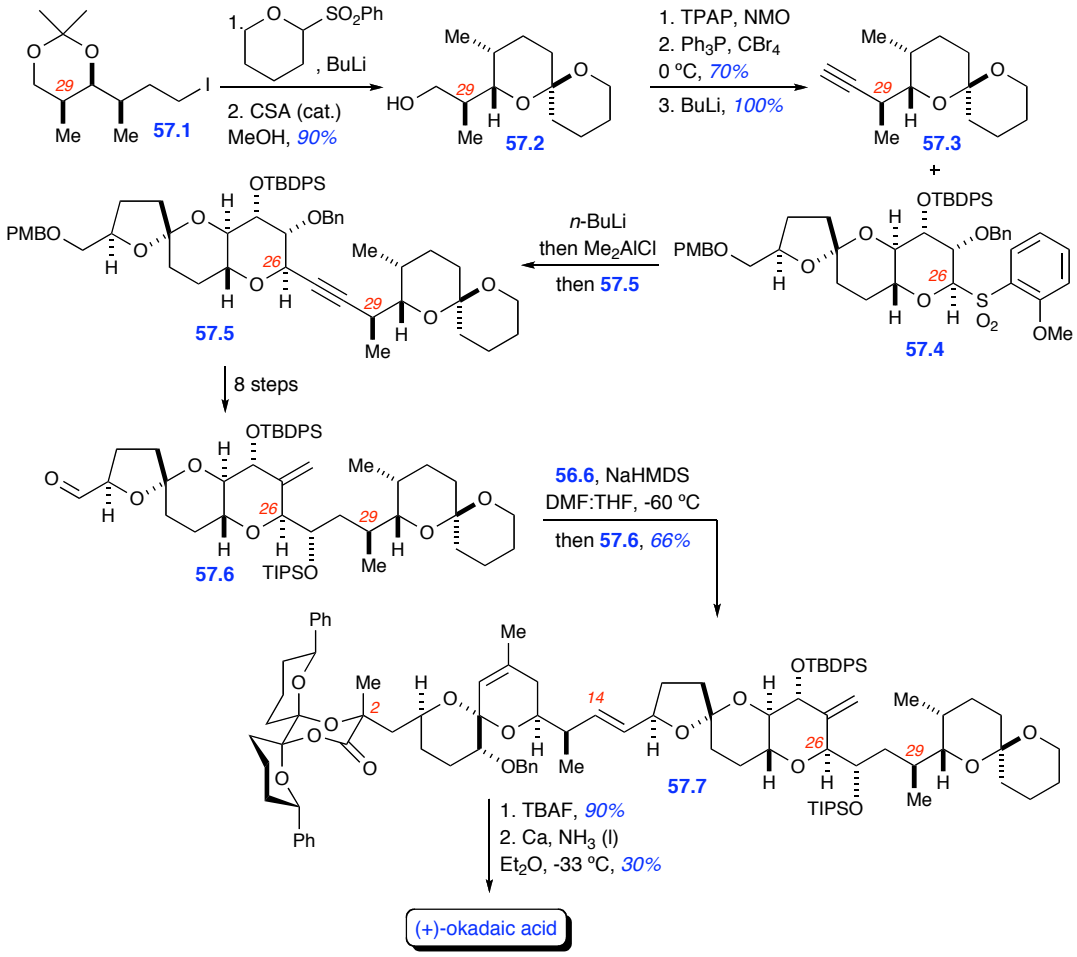
asymmetric synthesis of α-hydroxy acids. Glycolic acid was reacted with (*S*,*S*)-bis(dihydropyran) **56.1** (Scheme 56) in the presence of Ph_3P•HBr to generate dispiroketal **56.2** as a diastereomerically pure crystalline solid. The authors explain that the selectivity is governed by the strong equatorial preference of the phenyl groups in combination with the optimal anomeric effects at the newly formed spiro-centers. Sequential alkylation of dispiroketal **56.2** with methyl iodide and the allyl bromide yields **56.3**, which following by Sharpless dihydroxylation and Sharpless-Kolb epoxidation provides epoxide **56.4**. Further vinyl addition, hydroboration, and TPAP oxidation provided lactone **56.5** as the C1-C7 component. Further elaboration via an eight step procedure provides the C1-C14 fragment **56.6**.

Scheme 56



The generation of the C27-C28 fragment employed a Ley protocol for spiroketalization. Reaction of the anion from 2-(phenylsulfonyl)tetrahydropyran with iodide **57.1** (Scheme 57) followed by treatment with camphorsulfonic acid in methanol produced spiroketal **57.2** in 90% yield. In the reaction, alkylation of iodide **57.1** is followed by spontaneous antiperiplanar elimination of sufinic acid. Upon addition of camphorsulfonic acid, acid mediated isopropylidene deprotection and enol ether protonation instigate spirocyclization. Subsequent oxidation to the aldehyde followed by Corey-Fuchs elaboration to the alkyne **57.3** provides the necessary C27-C38 fragment. This was coupled to the C15-C26 central subunit **57.4** via deprotonation of alkyne **57.3** and transmetallation with dimethylaluminum chloride provides a Lewis acidic reagent that increases the sulfone reactivity by chelating with the *ortho*-methoxy group on the sulfone aryl ring, providing fused alkyne **57.5** in 70% yield. An additional eight steps provided aldehyde **57.6** for completion of the carbon skeleton. Coupling of aldehyde **57.6** with the anion of **56.6** provides the desired *E*-olefin **57.7** as the major product. Silyl deprotection followed by reductive removal of the benzyl group and diphenyldispiroketal provided okadaic acid. The Ley group synthesis proceeded in 60 steps, with 24 step longest linear sequence from (*S*,*S*)-bis(dihydropyran) **56.1** and in 0.7% overall yield from (*S*,*S*)-bis(dihydropyran) **56.1**.

Scheme 57



1.9 Fostriecin

Fostriecin (CI-920, Figure 12) is a biologically potent metabolite first isolated from *Streptomyces pulveraceus* in 1983 by workers at Warner Lambert-Parke Davis.[94] It displays in vitro activity against a broad range of cancerous cell lines including lung cancer, breast cancer, and ovarian cancer,[95] as well as in vivo antitumor activity. In addition, fostriecin has demonstrated activity against leukemia (L1210, IC_{50} 0.46 μM and P338).[96] Its mode of action appears to operate via an inhibitory pathway of the mitotic entry checkpoint. Evidence of this pathway is

shown in fostriecin's potent and selective inhibition of a number of protein phosphatases.[97,98] In 1997, Boger and coworkers determined the relative and absolute stereochemistry in fostriecin that confirmed previous assignments in a family of biologically active and structurally related natural products, including leustroducsin B, phospholine (phoslactomycin B), and phosphazomycin C.[99] It is the most selective PP2A inhibitor to date with an IC_{50} value of 1.5-3.0 nM.[2,100]

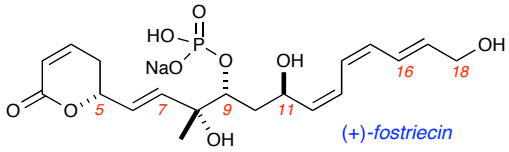
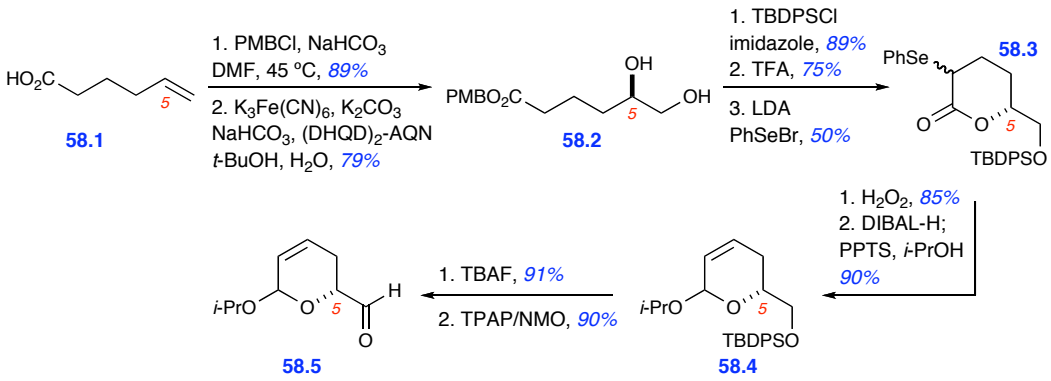


Figure 12

The Boger group published the first total synthesis of fostriecin in 2001.[101] The synthesis initiated with the generation of the lactone skeleton from 5-hexenoic acid (**58.1**, Scheme 58). Conversion to the ester followed by Sharpless asymmetric dihydroxylation provided the C5 stereocenter in 88-92% ee, which upon recrystallization provided the diol **58.2** in 98% ee. Selective protection of the primary alcohol followed by TFA-mediated lactonization and subsequent deprotonation in the presence of PhSeBr allowed for formation of α-phenylselenyl lactone **58.3**.[99] Lactone **58.3** was summarily oxidized to the corresponding selenoxide followed by in situ elimination to generate the internal olefin. Subsequent Dibal-H reduction and protection with isopropanol provided lactol **58.4**. Deprotection of the primary TBDPS ether allowed for oxidation to aldehyde **58.5**, the necessary partner for Wadsworth-Horner-Emmons coupling with the remaining C7-C18 backbone of the natural product.

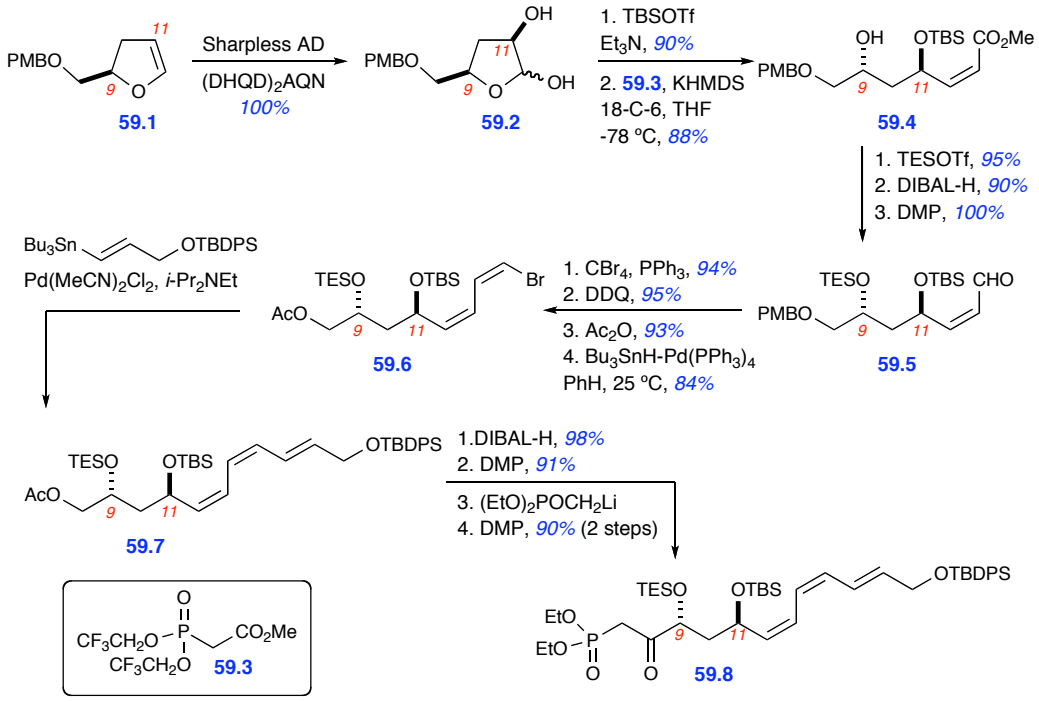
Scheme 58



Generation of the C7-C18 backbone realized installation of the C11 hydroxyl group via a Sharpless asymmetric dihydroxylation of dihydrofuran **59.1** to produce lactol **59.2** (Scheme 59). The newly formed C11 hydroxyl group was then TBS protected and the lactol condensed with the Still-Gennari phosphonate **59.3** to yield the *Z*-olefin bearing ester **59.4**. The authors note that attempts to utilize the Stork-Zhao protocol[102] to afford the *Z*-iodoalkene were not successful. The two-step reduction/oxidation protocol to generate the aldehyde **59.5** from ester **59.4** proceeded smoothly, at which point the authors attempted to form the *Z*,*Z*-iododiene only to witness modest stereoselectivity, an inability to separate the isomers, and interconversion of the isomers during purification. Instead, selective generation of the chromatographically stable *Z*,*Z*-bromodiene **59.6** was achieved via Corey-Fuchs homologation of aldehyde **59.5** followed by exchange of the PMB group for an acetyl group and subsequent selective reduction of the dibromide with Bu_3SnH-$Pd(PPh_3)_4$. Vinyl bromide **59.6** then underwent Stille coupling under rigorously investigated conditions to yield triene **59.7** in good yield with excellent preservation of the olefin geometries present. Deaceylation/oxidation of triene **59.7** allowed for addition of the

anion of diethyl methylphosphonate, where addition in toluene was found to be far superior than addition in THF. Oxidation of the resulting epimeric mixture provided ketophosphonate **59.8**.

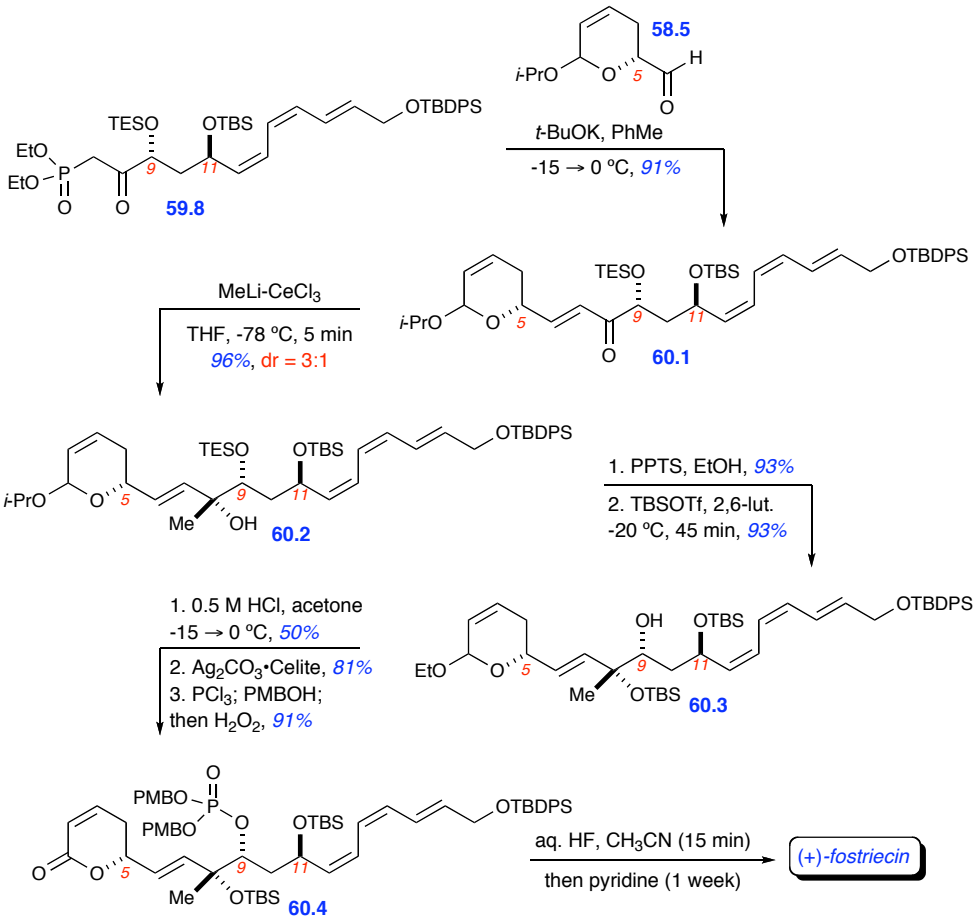
Scheme 59



Coupling the ketophosphate **59.8** with aldehyde **58.5** afforded α,β-unsaturated ketone **60.1** (Scheme 60). Installation of the methyl group via an organometallic addition proved to be difficult, with the authors discovering the best results required introduction of a toluene solution of ketone **60.1** to a MeLi/$CeCl_3$ slurry in THF at -78 ºC to provide tertiary alcohol **60.2** as a 3:1 mixture of diastereomers. The TES group was selectively deprotected (with concomitant exchange of the isopropoxy group of the lactol for ethoxy) under acidic conditions and the C8 alcohol selectively protected by addition of TBSOTf at -20 ºC, where at this elevated temperature (versus -78 ºC, which provided C9 protection) the C9-to-C8 *O*-silyl migration presumably occurs to

deliver the selectively protected alcohol **60.3**. Deprotection of the lactol followed by oxidation with Fetizon's reagent to provide the lactone allowed for phosphorylation to yield protected fostriecin **60.4**. Brief treatment with HF (15 min.) allowed for cleavage of the PMB esters followed by addition of pyridine to slowly deprotect the silyl ethers under buffered conditions, thereby affording the first total synthesis of the natural product (+)-fostriecin in 27 linear steps. The authors did not provide a yield for this final step in either the report or in the supplementary information.

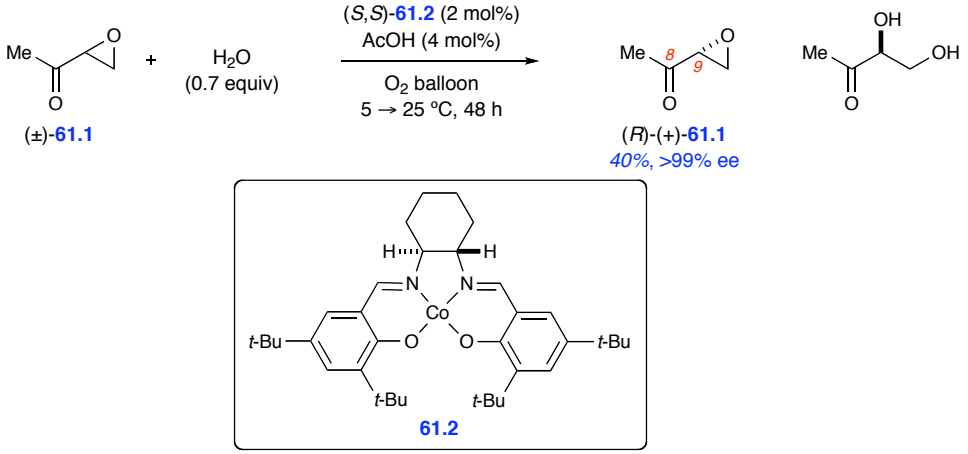
Scheme 60



The Jacobsen group provided the second total synthesis of the natural product later that year,[103] embarking upon the synthesis via synthons derived from their

hydrolytic kinetic resolution methodology[104] and their asymmetric hetero-Diels-Alder methodology.[105] Application of the former to the epoxide derived from methyl vinyl ketone (**61.1**, Scheme 61) proved to be challenging as under standard conditions the catalyst precipitated as the reduced complex with low substrate conversion. The solution to the problem involved running the reaction under O_2 atmosphere instead of N_2 to provide enantiopure epoxide (*R*)-**61.1** in 40% yield, thereby establishing the C9 stereocenter.

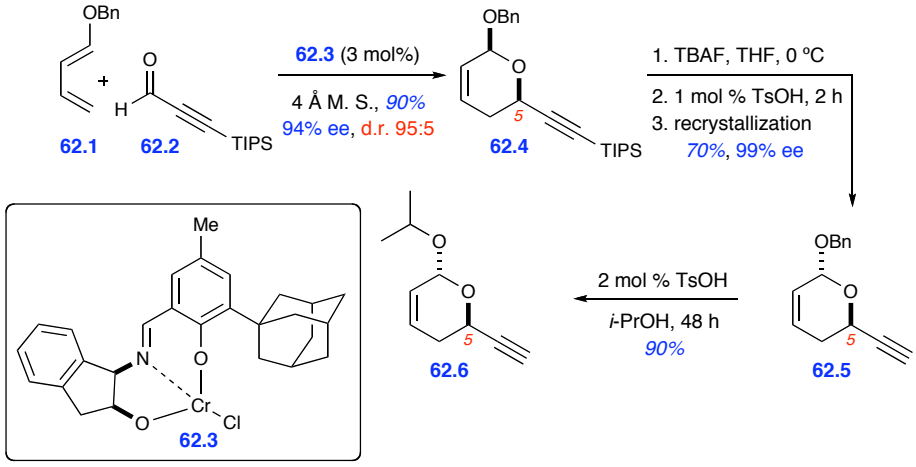
Scheme 61



Generation of the western lactone skeleton was approached through the aforementioned asymmetric hetero-Diels-Alder methodology. Formation of the desired lactol precursor[106] in the total synthesis proceeded with a formal hetero-Diels-Alder annulation of diene **62.1**[107] and aldehyde **62.2**[108] mediated by catalyst **62.3** (Scheme 62) to provide benzylated lactol **62.4** in high enantiomeric excess. Subsequent deprotection and epimerization of the anomer leads to terminal alkyne **62.5**, followed by conversion to the isopropyl acetal **62.6**.[109] This protocol efficiently

established the C5 stereogenic center as well as provides a synthon readily available for coupling with epoxyketone (*R*)-**61.1**.

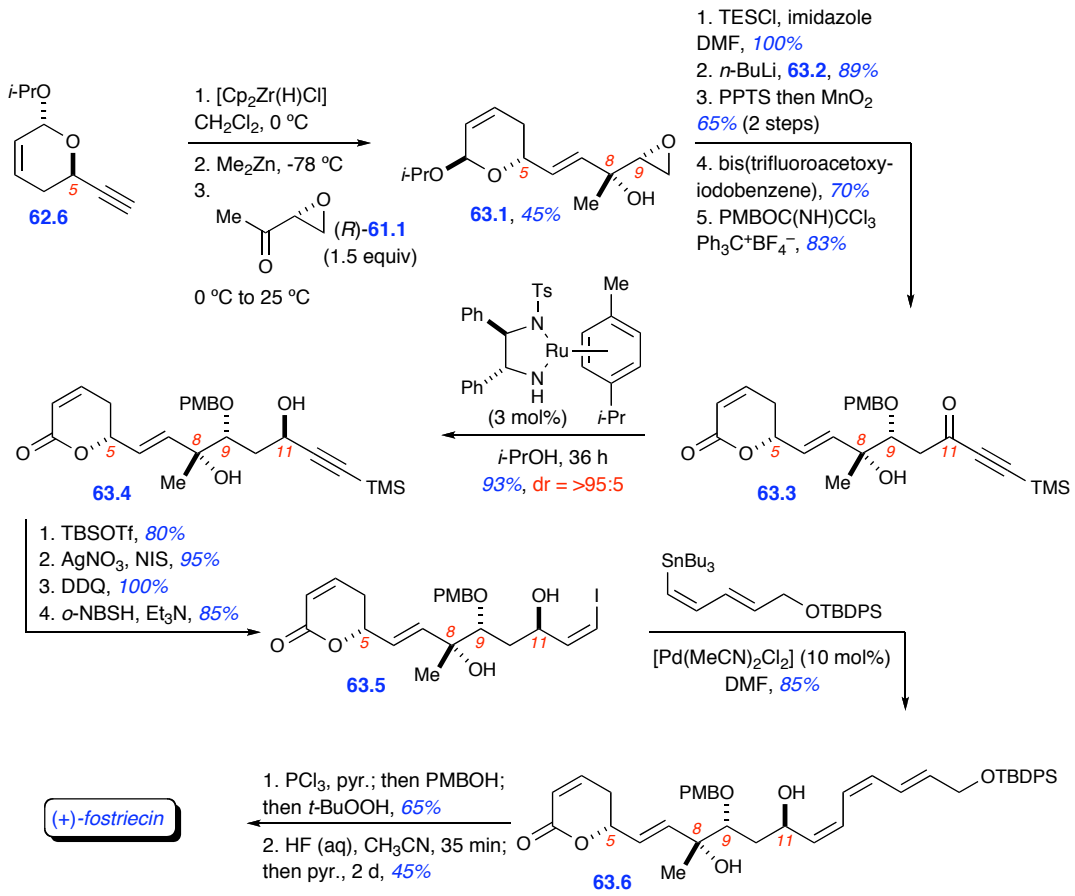
Scheme 62



The Jacobsen group desired to directly append the lactone skeleton while simultaneously establishing the C8 stereogenic center via a direct hydrometallation of the terminal alkyne with subsequent addition of this species into the epoxyketone **61.1**. This approach was predicated on Wipf's hydrozirconation[110]/zinc transmetallation protocol[111] for addition to aldehydes, where the Jacobsen group posited that the enhanced electrophilicity of the α-oxy ketone could exhibit enhanced reactivity in contrast to a typical ketone's unreactive nature. The Jacobsen group found that employing equimolar quantities of Schwartz's reagent, alkyne **62.6**, and Me_2Zn with 1.5 equivalents α-epoxyketone **61.1** at 25 ºC provided **63.1** in >30:1 diastereoselectivity and 45% yield (Scheme 63). TES protection of the C8 alcohol followed by dithiane addition, two-step lactol oxidation, cleavage of the dithiane and C9 PMB protection afforded ketone **63.2**. Ketone **63.2** was transformed stereoselectively into the desired C11 alcohol **63.4** by Noyori's transfer

hydrogenation methodology,[112] thereby establishing the final stereogenic center.

Scheme 63

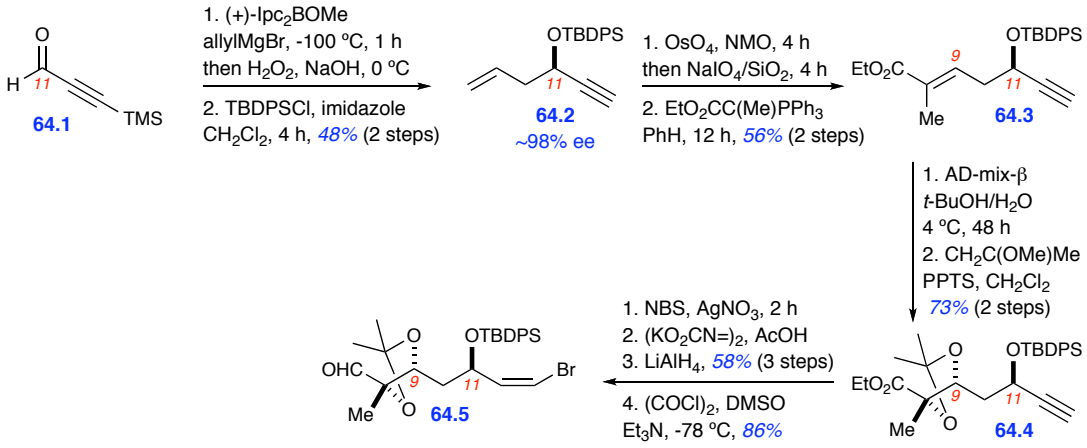


Four more steps, including diimide reduction to set the C12-C13 *Z*-olefin, provided vinyl iodide **63.5** which was transformed to the desired *Z*,*Z*,*E*-triene **63.6** via Stille coupling. Phosphate installation and global deprotection were performed in an analogous manner to the Boger group synthesis to provide (+)-fostriecin in 19 linear steps from commercially available material.

The Falck group's report detailing their total synthesis of the natural product appeared in 2002.[113] Enantioselective generation of the C11 hydroxyl group occurred with asymmetric allylation of propynal **64.1** followed by protection of the alcohol to

produce alkyne **64.2**. The terminal alkene was then oxidized to the aldehyde and subsequently homologated to (*E*)-α,β-unsaturated ester **64.3**, allowing for Sharpless asymmetric dihydroxylation to provide the C8 and C9 stereocenters as a 3:1 mixture with the undesired diastereomeric diol. Acetonide protection allowed for separation of the diastereomers to provide alkyne **64.4**. Bromination of the terminal alkyne followed by diimide reduction set the C12-C13 *Z*-olefin, which was subjected to a two-step reduction/oxidation protocol to afford aldehyde **64.5**.

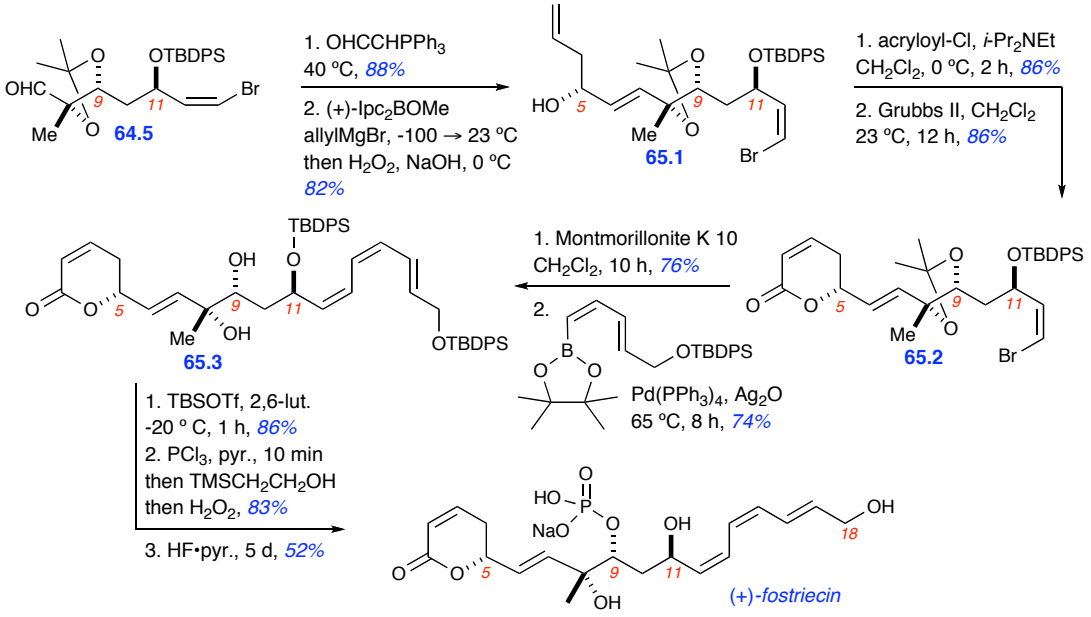
Scheme 64



Installation of the final stereogenic center occurred by homologation of aldehyde **64.5** to α,β-unsaturated aldehyde, followed by asymmetric allylation to stereoselectively afford the C5 alcohol **65.1** (Scheme 65). Acylation with acryloyl chloride provided the ring closing metathesis (RCM) primed ester, where ring closing metathesis with Grubbs II catalyst yielded the essential unsaturated lactone **65.2**. Acetonide deprotection provided the diol, which was summarily modified via Suzuki-Miyaura coupling to provide triene **65.3**. Protection of the C8 alcohol prevented formation of a cyclic phosphate upon phosphorylation, a problem encountered during

the authors' attempts at selective phosphorylation. Deprotection of the trimethylsilylethyl phosphate allowed for the authors to avoid acidic cleavage conditions, such that utilizing Olah's reagent for 5 days provided (+)-fostriecin and completion of the total synthesis in 20 linear steps from propargyl alcohol.

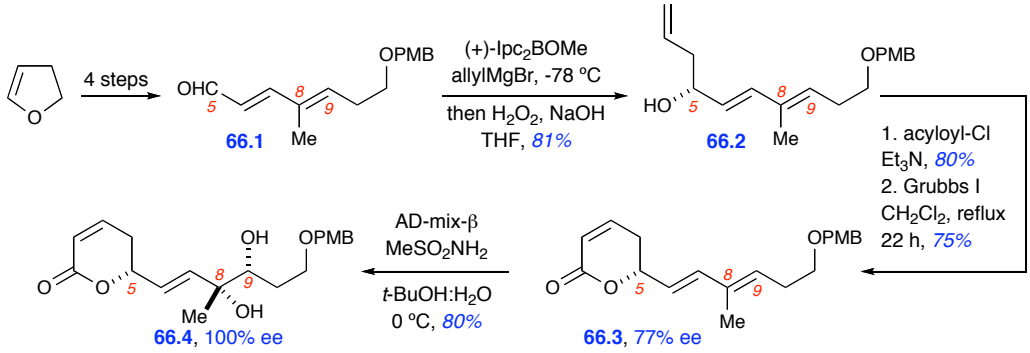
Scheme 65



November of that same year, the Hatakeyama group's synthesis of fostriecin was unveiled to the literary arena.[114] The first stereogenic center, the C5 center, was set via Brown asymmetric allylation of aldehyde **66.1** to afford alcohol **66.2** (Scheme 66), where the enantiopurity was not determined due to instability issues. Acryloylation allowed for selective RCM of the terminal alkenes to form lactone **66.3**, where the authors noted that no RCM product from participation of the conjugated diene was observed. Diene **66.3** was determined to be a 77% ee mixture by chiral HPLC, where the subsequent selective Sharpless asymmetric dihydroxylation of the less hindered olefin produced *enantiomerically pure* C8,C9

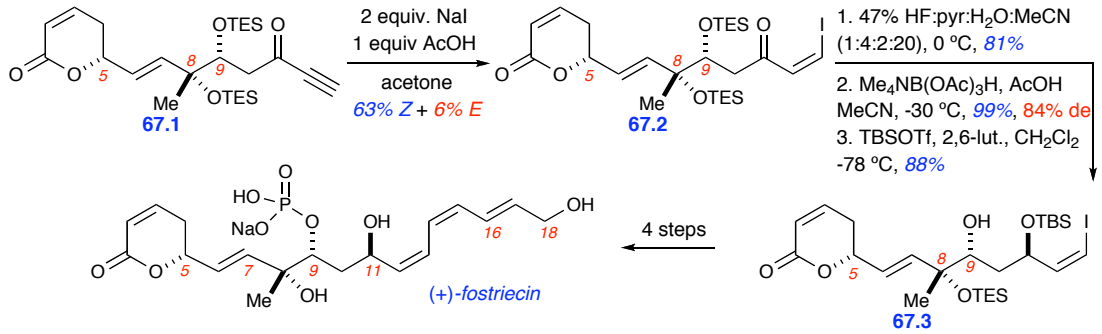
diol **66.4** as a single regio- and diastereomer in 80% yield. The authors note that the asymmetric dihydroxylation was accompanied by a kinetic resolution, thereby providing the desired enantiopure stereotriad.

Scheme 66



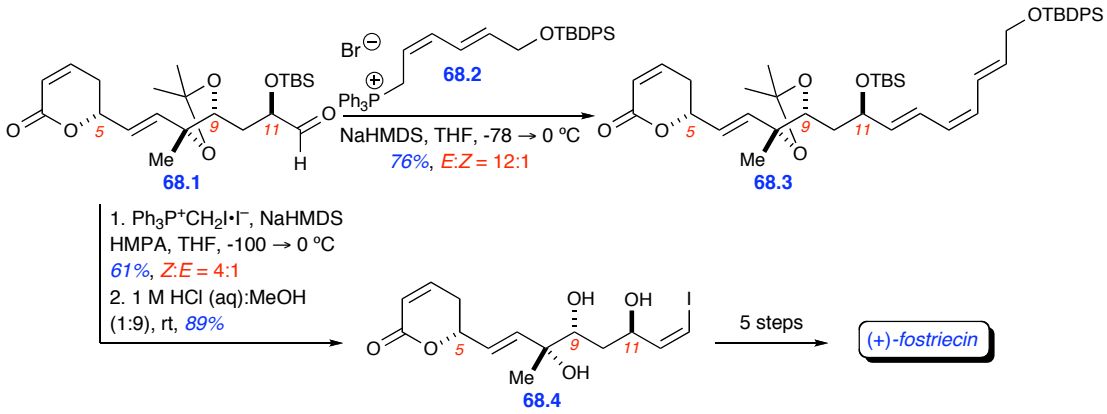
Five steps later, installation of the C12-C13 *Z*-olefin was attempted on ynone **67.1** utilizing Kishi's solventless conditions[115] only to afford the thermodynamically stable, and undesired, *E*-isomer. Experimentation by the authors found that running in acetone with 2 equivalents of NaI and 1 equivalent of AcOH at room temperature provided the desired *Z*-iodide **67.2** as the major product of a chromatographically separable 91:9 mixture in 63% yield (Scheme 67). Following selective TES deprotection of the C9 hydroxyl, generation of the C11 stereogenic center occurred via Evan's *anti*-selective reduction.[116] The desired diol was afforded in 84% de, which was selectively TBS protected at the C11 hydroxyl to afford the C9 exposed alcohol **67.3**. This was then transformed into the triene via Stille coupling, phosphorylated at C9 to yield the bis-allyl phosphate, phosphate deprotected with $Pd(PPh_3)_4$, and silyl deprotected to provide fostriecin. Overall, the total synthesis of fostriecin by Hatakeyama's group utilized 21 linear steps from dihydrofuran.

Scheme 67



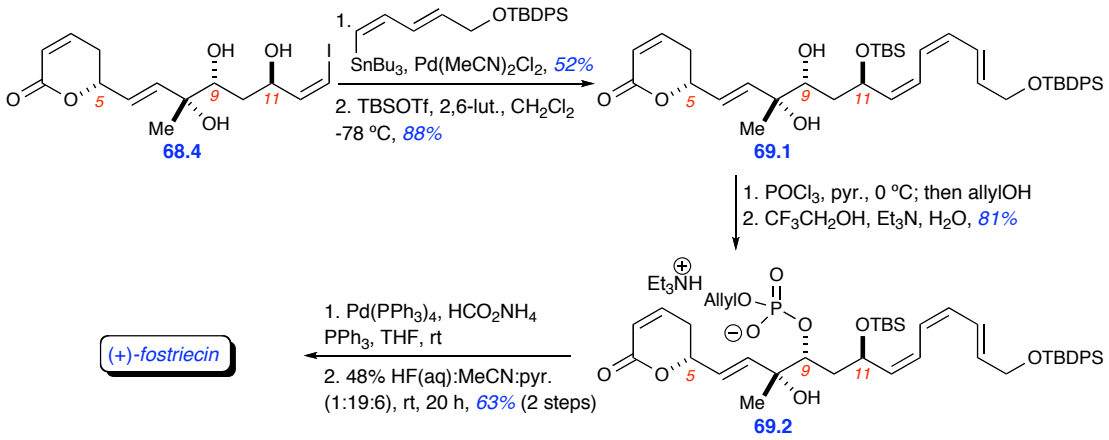
Imanishi's group reported their approach to the total synthesis in 2003, where they include an interesting attempt towards installing the triene via a Wittig reaction as well as utilizing a previously unutilized method to install the C9 phosphate.[117] With regard to the Wittig, the group decided to probe whether an ylide conjugated with a *Z*-olefin could form a *Z*-olefinic bond.[118] The group thus attempted condensation of their advanced aldehyde intermediate **68.1** with Wittig salt **68.2** under a variety of conditions, but all attempts provided the *E*-isomer product **68.3** (Scheme 68). The authors postulate that serious steric repulsion prevents the formation of the desired C12-C13 *Z*-olefin in this fashion. They therefore opted to generate the *Z*-iodide via the Stork-Zhao protocol[102] followed by acetonide deprotection to afford triol **68.4**. Five more steps provided fostriecin in 7% yield from triol **68.4**, and overall in 25 steps from commercially available materials.

Scheme 68



The Imanishi group attempted selective phosphorylation of the C9 alcohol (with a C11 protected alcohol) in the presence of the unprotected C8 tertiary alcohol only to yield diphosphate or a cyclic phosphate as explicitly found in similar investigations by the Falck group.[113] The Imanishi group, however, sought to utilize a selective cleavage of the cyclic phosphate to facilitate the synthetic endeavor. Thus, Stille coupling of **68.4** followed by selective TBS protection of the C11 hydroxyl provided diol **69.1**. Treatment of diol **69.1** with $POCl_3$ and allyl alcohol provided the cyclic triester, which was immediately hydrolyzed to provide monoanion **69.2** as the major product. Deprotection of the allyl phosphate followed by global silyl deprotection provided fostriecin, a six step sequence from triol **68.4** in 23% yield from triol **68.4**, illustrating the efficiency of the cyclic phosphate method.

Scheme 69



1.10 Conclusions

The previous highlights of phosphatase inhibitor total syntheses draws attention to a several aspects important to the context of synthetic efforts in phosphate tether methodology. In particular, the incorporation of suspected highly reactive functionalities can be realized, and in several cases enhances the overall efficiency and success of the total synthesis. Explicit examples of this are the calyculins (various transformations in the presence of the phosphate), Isobe group synthesis of tautomycin with the intact anhydride, and the Koert group synthesis of phoslactomycin A. The appeal of a robust methodology to generate stereogenic centers and/or facilitate synthetic elaborations is evident. Danishefsky and Boukouvalas's approach to dysidiolide generated stereochemical complexity in a concise fashion, condensing the requisite number of transformations. It is also noticeable, in regard to the Corey's synthesis of dysidiolide, that engaging functionally compact molecular entities in chemospecific, stereoelectronically governed transformations elegantly construct complexity in a rigorously defined

scenario. In this light, the previous review of synthetic accomplishments in formation of various natural product phosphatase inhibitors provides a lens with which to examine the doctoral work presented. This work embodies two underdeveloped areas of phosphate chemistry, namely their use as (i) *temporary tethers*[119] that are capable of (ii) *multivalent activation* (activating one, two or all three of the phosphate ester appendages), where the following dissertation provides additional empirical evidence that counters historical and traditional views associated with the utilization of phosphates in synthesis.

1.11 References:

(1) Pinna, L. A.; Cohen, P. T. W. Inhibitors of Protein Kinases and Protein Phosphatases. *Handbook of Experimental Pharmacology* **2005**, *167*, preface pp V-VI.

(2) Honkanen, R. E. "Serine/Threonine Protein Phosphatase Inhibitors with Antitumor Activity" in Inhibitors of Protein Kinases and Protein Phosphatases. *Handbook of Experimental Pharmacology* **2005**, *167*, 295-317.

(3) (a) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; Basabe, P.; Hernández, F. A.; Broughton, H. B.; Urones, J. G. Synthesis and Absolute Configuration of the Supposed Structure of Cladocoran A and B. *Synlett* **2002**, 105-109. (b) Miyaoka, H.; Yamanishi, M.; Kajiwara, Y.; Yamada, Y. Total Synthesis of Cladocorans A and B: A Structural Revision. *J. Org. Chem.* **2003**, *68*, 3476-3479 and pertinent references therein.

(4) (a) Loukaci, A.; Le Saout, I.; Samadi, M.; Leclerc, S.; Damiens, E.; Meijer, L.; Debitus, C.; Guyot, M. Coscinosulfate, a CDC25 Phosphatase Inhibitor from the Sponge *Coscinoderma Mathewsi*. *Bioorg. Med. Chem.* **2001**, *9*, 3049-3054. (b) Poigny, S.; Nouri, S.; Chiaroni, A.; Guyot, M.; Samadi, M. Total Synthesis and Determination of the Absolute Configuration of Coscinosulfate. A New Selective Inhibitor of Cdc25 Protein Phosphatase. *J. Org. Chem.* **2001**, *66*, 7263-7269 and pertinent references therein.

(5) Yu, L.; McGill, A.; Ramirez, J.; Wang, P. G.; Zhang, Z.-Y. Synthesis and Bioassy of a Protein Tyrosine Phosphatase Inhibitor, Dephostatin. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1003-1006 and pertinent references therein.

(6) Forsyth, C. J.; Wang, C. Synthesis and stereochemistry of the terminal spiroketal domain of the phosphatase inhibitor dinophysistoxin-2. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3043-3046 and pertinent references therein.

(7) (a) Fürstner, A.; Ruiz-Caro, J.; Prinz, H.; Waldmann, H. Structure Assignment, Total Synthesis, and Evaluation of the Phosphatase Modulating Activity of Glucolipsin A. *J. Org. Chem.* **2004**, *69*, 459-467. (b) Kang, E. J.; Lee, E. Total Synthesis of Oxacyclic Macrolide Natural Products. *Chem. Rev.* **2005**, *105*, 4348-4378 and pertinent references therein.

(8) Gong, J.-X.; Shen, X.; Yao, L.-G.; Jiang, H.; Krohn, K.; Guo, Y.-W. Total Synthesis of Gymnorrhizol, an Unprecedented 15-Membered Macrocyclic Polydisulfide from the Chinese Mangrove *Bruguiera gymnorrhiza*. *Org. Lett.* **2007**, *9*, 1715-1716 and pertinent references therein.

(9) (a) Toivola, D. M.; Eriksson, J. E.; Brautigan, D. L. Identification of protein phosphatase 2A as the primary target for microcystin-LR in rat liver homogenates. *FEBS Lett.* **1994**, *344*, 175-180. (b) Humphrey, J. M.; Aggen, J.

B.; Chamberlin, A. R. Total Synthesis of the Serine-Threonine Phosphatase Inhibitor Microcystin-LA. *J. Am. Chem. Soc.* **1996**, *118*, 11759-11770 and pertinent references therein.

(10) (a) Li, W.-R.; Lin, S. T.; Hsu, N.-M.; Chern, M.-S. Efficient Total Synthesis of Pulchellalactam, a CD45 Tyrosine Phosphatase Inhibitor. *J. Org. Chem.* **2002**, *67*, 4702-4706. (b) Bryans, J. S.; Chessum, N. E. A.; Huther, N.; Parsons, A. F.; Ghelfi, F. Metal-catalysed radical cyclisations leading to *N*-heterocycles: new approaches to gabapentin and pulchellalactam. *Tetrahedron* **2003**, *59*, 6221-6231. (c) Mangaleswaran, S.; Argade, N. P. A Facile Synthesis of CD45 Protein Tyrosine Phosphatase Inhibitor Marine Natural Product Pulchellalactam. *Synthesis* **2004**, 1560-1562. (d) Hermet, J.-P.; Caubert, V.; Langlois, N. Short Synthesis of Pulchellalactam. *Synth. Commun.* **2006**, *36*, 2253-2257. (e) Chavan, S. P.; Pathak, A. B.; Dhawane, A. N.; Kalkote, U. R. Total Synthesis of Pulchellalactam via an RCM Strategy. *Synth. Commun.* **2007**, *37*, 1503-1510. (f) Felluga, F.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Pattarozzi, M.; Roncaglia, F.; Valentin, E. A Novel Short Approach to (*Z*)-Pulchellalactam through Transition-Metal-Catalyzed Atom-Transfer Radical Cyclization of 1-Isopropylprop-2-enyl Dichloroacetate. *Synthesis* **2007**, 1882-1886 and pertinent references therein.

(11) (a) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. Total Synthesis of (+)-Thyrsiferol, (+)-Thyrsiferyl 23-Acetate, and (+)-Venustatriol. *J. Org. Chem.* **1990**, *55*, 5088-5107. (b) González, I. C.; Forsyth, C. J. Total Synthesis of Thyrsiferyl 23-Acetate, a Specific Inhibitor of Protein Phosphatase 2A and an Anti-Leukemic Inducer of Apoptosis. *J. Am. Chem. Soc.* **2000**, *122*, 9099-9108. (c) Nishiguchi, G. A.; Graham, J.; Bouraoui, A.; Jacobs, R. S.; Little, R. D. 7,11-*epi*-Thyrsiferol: Completion of Its Synthesis, Evaluation of Its Antimitotic Properties, and the Further Development of an SAR Model. *J. Org. Chem.* **2006**, *71*, 5936-5941 and pertinent references therein.

(12) (a) Fürstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. Total Synthesis and Reassignment of the Phosphatase-Inhibitory Activity of the Antitumor Agent TMC-69-6H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5361-5364. (b) Fürstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. Synthesis and evaluation of the antitumor agent TMC-69-6H and a focused library of analogs. *Tetrahedron* **2004**, *60*, 9543-9558 and pertinent references therein.

(13) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. Calyculin A, a Novel Antitumor Metabolite from the Marine Sponge *Discodermia calyx*. *J. Am. Chem. Soc.* **1986**, *108*, 2780-2781.

(14) (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. Isolation and Structure Elucidation of Calyculins B, C, and D, Novel Antitumor Metabolites, from the Marine Sponge *Discodermia calyx*. *J. Org. Chem.* **1988**,

53, 3930-3932. (b) Matsunaga, S.; Fujiki, H.; Sakata, D.; Fusetani, N. Calyculins E, F, G, and H, additional inhibitors of protein phosphatases 1 and 2a, from the marine sponge *Discodermia calyx*. *Tetrahedron* **1991**, *47*, 2999-3006.

(15) Evans, D. A.; Gage, J. R.; Leighton, J. L. Total Synthesis of (+)-Calyculin A. *J. Am. Chem. Soc.* **1992**, *114*, 9434-9453.

(16) For a detailed report on the Evan's group efforts towards calyculin A, see: (a) Evans, D. A.; Gage, J. R.; Leighton, J. L. Asymmetric Synthesis of Calyculin A. 1. The C1-C25 Spiroketal Fragment. *J. Org. Chem.* **1992**, *57*, 1958-1961. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. Asymmetric Synthesis of Calyculin A. 2. The C26-C37 γ-Amino Acid Fragments. *J. Org. Chem.* **1992**, *57*, 1961-1964. (c) Evans, D. A.; Gage, J. R.; Leighton, J. L. Asymmetric Synthesis of Calyculin A. 3. Assemblage of the Calyculin Skeleton and the Introduction of a New Phosphate Monoester Synthesis. *J. Org. Chem.* **1992**, *57*, 1964-1966.

(17) In late 1991 two studies established that the absolute stereochemistry of naturally occuring calyculin A was enantiomeric to (+)-calyculin A (the structure reported in 1986) see: (a) Matsunaga, S.; Fusetani, N. Absolute Stereochemistry of the Calyculins, Potent Inhibitors of Protein Phosphatases 1 and 2A. *Tetrahedron Lett.* **1991**, *32*, 5605-5606. (b) Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shioiri, T. Stereoselective Synthesis of 2,3-dihydroxy-4-dimethylamino-5-methoxypentanoic acid, a fragment of calyculins – determination of the absolute configuration of calyculins. *Tetrahedron Lett.* **1991**, *32*, 5983-5986.

(18) In 2001, a formal total synthesis was reported utilizing crotyldiisopinocampheylboranes to generate key northern and southern hemisphere advanced intermediates; see Anderson, O. P.; Barret, A. G. M.; Edmunds, J. J.; Hachiya, S.-I.; Hendrix, J. A.; Horita, K.; Malecha, J. W.; Parkinson, C. J.; VanSickle, A. Applications of crotyldiisopinocampheylboranes in synthesis: a formal total synthesis of (+)-calyculin A. *Can. J. Chem.* **2001**, *79*, 1562-1592.

(19) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. The Synthesis of Naturally Occuring (–)-Calyculin A. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 673-675.

(20) The authors note the improvement in synthesizing this fragment since a prior publication regarding the enantiomer, see: Vaccaro, H. A.; Levy, D. E.; Sawabe, A.; Jaetsch, T.; Masamune, S. Towards the Synthesis of Calyculin: A Synthetic Intermediate Corresponding to the C(26)-C(37) Fragment. *Tetrahedron Lett.* **1992**, *33*, 1937-1940.

(21) Smith, A. B., III; Friestad, G. K.; Duan, J. J.-W.; Barbosa, J.; Hull, K. G.;

Iwashima, M.; Qiu, Y.; Spoors, P. G.; Bertounesque, E.; Salvatore, B. A. Total Synthesis of (+)-Calyculin A and (–)-Calyculin B. *J. Org. Chem.* **1998**, *63*, 7596-7597.

(22) (a) Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. Total Synthesis of (+)-Calyculin A and (–)-Calyculin B: Asymmetric Synthesis of the C(9-25) Spiroketal Dipropionate Subunit. *J. Am. Chem. Soc.* **1999**, *121*, 10468-10477. (b) Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Duan, J. J.-W.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Salvatore, B. A. Total Synthesis of (+)-Calyculin A and (–)-Calyculin B: Cyanotetraene Construction, Asymmetric Synthesis of the C(26-37) Oxazole, Fragment Assembly, and Final Elaboration. *J. Am. Chem. Soc.* **1999**, *121*, 10478-10486.

(23) Ogawa, A. K.; Armstrong, R. W. Total Synthesis of Calyculin C. *J. Am. Chem. Soc.* **1998**, *120*, 12435-12442. See also: (a) Ogawa, A. K.; DeMattei, J. A.; Scarlato, G. R.; Tellew, J. E.; Chong, L. S.; Armstrong, R. W. Asymmetric Synthesis of Calyculin C. 2. Synthesis of the C26-C37 Fragment and Model Wittig Couplings. *J. Org. Chem.* **1996**, *61*, 6153-6161. (b) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. Asymmetric Synthesis of Calyculin C. 1. Synthesis of the C1-C25 Fragment. *J. Org. Chem.* **1996**, *61*, 6139-6152.

(24) Gunasekera, G. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. Dysidiolide: A Novel Protein Phosphatase Inhibitor from the Caribbean Sponge *Dysidea etheria* de Laubenfels. *J. Am. Chem. Soc.* **1996**, *118*, 8759-8760.

(25) Blanchard, J. L.; Epstein, D. M.; Boisclair, M. D.; Rudolph, J.; Pal, K. Dysidiolide and related γ-hydroxy butenolide compounds as inhibitors of the protein tyrosine phosphatase, cdc25. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2537-2538.

(26) Takahashi, M.; Dodo, K.; Sugimoto, Y.; Aoyagi, Y.; Yamada, Y.; Hashimoto, Y.; Shirai, R. Synthesis of the novel analogues of dysidiolide and their structure-activity relationship. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2571-2574.

(27) Corey, E. J.; Roberts, B. E. Total Synthesis of Dysidiolide. *J. Am. Chem. Soc.* **1997**, *119*, 12425-12431.

(28) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. A Concise Total Synthesis of Dysidiolide through Application of a Dioxolenium-Mediated Diels-Alder Reaction. *J. Am. Chem. Soc.* **1998**, *120*, 1615-1616.

(29) While the endgame of the Danishefsky group echoes that of the Corey group,

the Danishefsky publication was submitted before the Corey report was published; see 27 and 28.

(30) Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. Total Synthesis of (+)-Dysidiolide. *J. Org. Chem.* **1998**, *63*, 228-229.

(31) Boukouvalas, J.; Lachance, N. A Mild, Efficient and General Method for the Synthesis of Trialkylsilyl (*Z*)-4-Oxo-2-alkenoates and γ-Hydroxybutenolides. *Synlett* **1998**, 31-32.

(32) Takahashi, M.; Dodo, K.; Hashimoto, Y.; Shirai, R. Concise asymmetric synthesis of dysidiolide. *Tetrahedron Lett.* **2000**, *41*, 2111-2114.

(33) Demeke, D.; Forsyth, C. J. Novel Total Synthesis of the Anticancer Natural Product Dysidiolide. *Org. Lett.* **2000**, *2*, 3177-3179.

(34) A detailed account of the synthetic efforts invoved were disclosed in 2002: Demeke, D.; Forsyth, C. J. Total synthesis of (±)-dysidiolide. *Tetrahedron* **2002**, *58*, 6531-6544.

(35) Miyaoka, H.; Kajiwara, Y.; Hara, Y.; Yamada, Y. Total Synthesis of Natural Dysidiolide. *J. Org. Chem.* **2001**, *66*, 1429-1435.

(36) The Yamada group had previously reported the racemic total synthesis of dysidiolide utilizing the intramolecular Diels-Alder route; see: Miyaoka, H.; Kajiwara, Y.; Yamada, Y. Synthesis of marine sesterterpenoid dysidiolide. *Tetrahedron Lett.* **2000**, *41*, 911-914.

(37) Miyaoka, H.; Kajiwara, Y.; Hara, M.; Suma, A.; Yamada, Y. Synthesis of optically active 3-alkoxy-6-hydroxymethyl-6-methyl-2-cyclohexenone. *Tetrahedron: Asymmetry* **1999**, *10*, 3189-3196.

(38) Dilip de Silva, E.; Williams, D. E.; Andersen, R. J.; Klix, H.; Holmes, C. F. B.; Allen, T. M. Motuporin, A Potent Protein Phosphatase Inhibitor Isolated from the Papua New Guinea Sponge *Theonella swinhoel* Gray. *Tetrahedron Lett.* **1992**, *33*, 1561-1564.

(39) Maynes, J. T.; Luu, H. A.; Cherney, M. M.; Andersen, R. J.; Williams, D.; Homes, C. F. B.; James, M. N. G. Crystal Structures of Protein Phosphatase-1 Bound to Motuporin and Dihydromicrocystin-LA: Elucidation of the Mechanism of Enzyme Inhibition by Cyanobacterial Toxins. *J. Mol. Biol.* **2006**, *356*, 111-120.

(40) Valentekovich, R. J.; Schreiber, S. L. Enantiospecific Total Synthesis of the Protein Phosphatase Inhibitor Motuporin. *J. Am. Chem. Soc.* **1995**, *117*, 9069-9070.

(41) For other syntheses of protected Adda, refer to: (a) Namikoshi, M.; Rinehart, K. L.; Dahlem, A. M.; Beasley, V. R.; Carmichael, W. W. Total Synthesis of Adda, the unique C20 amino acid of cyanobacteial hepatotoxins. *Tetrahedron*

Lett. **1989**, *30*, 4349-4352. (b) Chakraborty, T. K.; Joshi, S. P. Total synthesis of *N*-phthaloyl adda methyl ester: All stereocenters originating from a single chiral epoxyalcohol. *Tetrahedron Lett.* **1990**, *31*, 2043-2046. (c) Beatty, M. F.; Jennings-White, C.; Avery, M. A. (2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda), the amino acid characteristic of microcystins and nodularin. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1637-1641 as well as references 43, 47, and 48.

(42) For other syntheses of β-alkyl aspartates, please regard: (a) Dener, J. M.; Zhang, L.-H.; Rapoport, H. An Effective Chirospecific Synthesis of (+)-Pilocarpine from L-Aspartic Acid. *J. Org. Chem.* **1993**, *58*, 1159-1166. (b) Hanessian, S.; Sumi, K.; Vanasse, B. The Stereocontrolled Synthesis of (2*S*,3*R*)-3-Alkyl-L-aspartic Acids Using a 2-Azetidinone Framework as a Chiral Template. *Synlett* **1992**, 33-34. (c) Seebach, D.; Wasmuth, D. Alkylation of Amino Acids without Loss of Optical Activity: α- and β-Alkylation of an Aspartic Acid Derivative. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 971. (d) Baldwin, J. E.; Moloney, M. G.; North, M. Non-proteinogenic amino acid synthesis. The β-anion derived from aspartic acid, and its application to α-amino acid synthesis. *Tetrahedron* **1989**, *45*, 6309-6318 as well as reference 43.

(43) Samy, R.; Kim, H. Y.; Brady, M.; Toogood, P. L. Total Synthesis of Motuporin and 5-[L-Ala]-Motuporin. *J. Org. Chem.* **1999**, *64*, 2711-2728.

(44) Marshall, J. A.; Garofalo, A. W. Oxidative Cleavage of Mono-, Di-, and Trisubstituted Olefins to Methyl Esters through Ozonolysis in Methanolic NaOH. *J. Org. Chem.* **1993**, *58*, 3675-3680.

(45) Batten, R. J.; Dixon, A. J.; Taylor, R. J. K. A New Method for Removing the t-Butyldimethylsilyl Protecting Group. *Synthesis* **1980**, 234-235.

(46) Shiori, T.; Ninomiya, K.; Yamada, S.-I. Diphenylphosphoryl Azide. A New Convenient Reagent for a Modified Curtius Reaction and for the Peptide Synthesis. *J. Am. Chem. Soc.* **1972**, *94*, 6203-6205.

(47) Hu, T.; Panek, J. S. Total Synthesis of (–)-Motuporin. *J. Org. Chem.* **1999**, *64*, 3000-3001.

(48) Hu, T.; Panek, J. S. Enantioselective Synthesis of the Protein Phosphatase Inhibitor (–)-Motuporin. *J. Am. Chem. Soc.* **2002**, *124*, 11368-11378.

(49) (a) Matteson, D. S.; Sadhu, K. M. Synthesis of 1-Amino-2-phenylethane-1-boronic Acid Derivatives. *Organometallics* **1984**, *3*, 614-618. (b) Matteson, D. S.; Beedle, E. C. A directed chiral synthesis of amino acids from boronic esters. *Tetrahedron Lett.* **1987**, *28*, 4499-4502. (c) Matteson, D. S.; Beedle, E. C. A Chiral Synthesis of (2*S*,3*S*)-phenylalanine-3-2*H* via boronic esters. *J. Labeled Compd. Radiopharm.* **1988**, *25*, 675-683. (d) Matteson, D. S.; Kandil,

A. A.; Soundararajan, R. Synthesis of Asymmetrically Deuterated Glycerol and Dibenzylglyceraldehyde via Boronic Esters. *J. Am. Chem. Soc.* **1990**, *112*, 3964-3969. (e) Matteson, D. S. Recent advances in asymmetric synthesis with boronic esters. *Pure Appl. Chem.* **1991**, *63*, 339-344.

(50) Bauer, S. M.; Armstrong, R. W. Total Synthesis of Motuporin (Nodularin-V). *J. Am. Chem. Soc.* **1999**, *121*, 6355-6366.

(51) Cheng. X.-C.; Kihara, T.; Kusakabe, H.; Magae, J.; Kobayashi, T.; Fang, R.-P.; Ni, Z.-F.; Shen, Y.-C.; Ko, K.; Yamaguchi, I.; Isono, K. A New Antibiotic, Tautomycin. *J. Antibiot.* **1987**, *40*, 907-909.

(52) Magae, J.; Watanabe, C.; Osada, H.; Cheng, X.-C.; Isono, K. Induction of Morphological Change of Human Myeloid Leukemia and Activation of Protein Kinase C by a Novel Antibiotic, Tautomycin. *J. Antibiot.* **1988**, *41*, 932-937.

(53) (a) Magae, J.; Osada, H.; Fujiki, H.; Saido, T. C.; Suzuki, K.; Nagai, K.; Yamasaki, M.; Isono, K. Morphological Changes of Human Myeloid Leukemia K562 Cells by a Protein Phosphatase Inhibitor, Tautomycin. *Proc. Jpn. Acad. Ser. B.* **1990**, *66*, 209-212. (b) MacKintosh, C.; Klumpp, S. Tautomycin from the bacterium *Streptomyces verticillatus*. Another potent and specific inhibitor of protein phosphatases 1 and 2A. *FEBS Lett.* **1990**, *277*, 137-140. (c) Takai, A.; Sasaki, K.; Nagai, H.; Mieskes, G.; Isobe, M.; Isono, K.; Yasumoto, T. Inhibition of specific binding of okadaic acid to protein phosphatase 2A by microcystin-LR, calyculin-A, and tautomycin: methods of analysis of interactions of tight-binding ligands with target protein. *Biochem. J.* **1995**, *306*, 657-665.

(54) (a) Takai, A.; Tsuboi, K.; Koyasu, M.; Isobe, M. Effects of modification of the hydrophobic C1-C16 segment of tautomycin on its affinity to type-1 and type-2 protein phosphatases. *Biochem. J.* **2000**, *350*, 81-88. (b) Oikawa, H. Synthesis of Specific Protein Phosphatase Inhibitors, Tautomycin and Tautomycetin toward Structure-Activity Relationship Study. *Curr. Med. Chem.* **2002**, *9*, 2033-2054.

(55) Oikawa, H.; Oikawa, M.; Ueno, T.; Ichihara, A. Total Synthesis of Tautomycin: Efficient aldol coupling of two large subunits. *Tetrahdedron Lett.* **1994**, *35*, 4809-4812.

(56) Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. Total Synthesis of Tautomycin. *J. Org. Chem.* **1995**, *60*, 5048-5068.

(57) Ichikawa, Y.; Tsuboi, K.; Jiang, Y.; Naganawa, A.; Isobe, M. Total synthesis of (+)-tautomycin. *Tetrahedron Lett.* **1995**, *36*, 7101-7104.

(58) Tsuboi, K.; Ichikawa, Y.; Jiang, Y.; Naganawa, A.; Isobe, M. Total Synthesis of (+)-Tautomycin. *Tetrahedron* **1997**, *53*, 5123-5142.

(59) Shimizu, S.; Nakamura, S.; Nakada, M.; Shibasaki, M. Total Synthesis of (+)-Tautomycin. *Tetrahedron* **1996**, *52*, 13363-13408.

(60) Nakamura, S.; Shibasaki, M. Synthetic studies on tautomycin. Stereoselective construction of the C1-C26 region. *Tetrahedron Lett.* **1994**, *35*, 4145-4148.

(61) Sheppeck, J. E., II; Liu, W.; Chamberlin, A. R. Total Synthesis of the Serine/Threonine-Specific Protein Phosphatase Inhibitor Tautomycin. *J. Org. Chem.* **1997**, *62*, 387-398.

(62) (a) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. The Total Synthesis of Ionophore Antibiotics. A Convergent Synthesis of Lasalocid A (X537A). *J. Am. Chem. Soc.* **1983**, *105*, 1988-2006. (b) Ireland, R. E.; Thaisrivongs, S.; Dussualt, P. H. An Approach to the Total Synthesis of Aplysiatoxin. *J. Am. Chem. Soc.* **1988**, *110*, 5768-5779.

(63) (a) Oertle, K.; Beyeler, H.; Dunthaler, R. O.; Lottenbach, W.; Riediker, M.; Steiner, E. A Facile Synthesis of Optically Pure (–)-(*S*)-Ipsenol Using a Chiral Titanium Complex. *Helv. Chim. Acta* **1990**, *73*, 353-358. (b) Dunthaler, R. O.; Herold, P.; Wyler-Helfer, S.; Riediker, M. Enantio- and Diastereoselective Aldol-Reaction of 2,6-Dimethylphenyl Propionate Using Titanium-Carbohydrate Complexes. *Helv. Chim. Acta* **1990**, *73*, 659-673.

(64) (a) Fushimi, S.; Nishikawa, S.; Shimazu, A.; Seto, H. Studies on New Phosphate Ester Antifungal Antibiotics Phoslactomycins. I. Taxonomy, Fermentation, Purification and Biological Activities. *J. Antibiot.* **1989**, *42*, 1019-1025. (b) Fushimi, S.; Furihata, K.; Seto, H. Studies on New Phosphate Ester Antifungal Antibiotics Phoslactomycins. II. Structure Elucidation of Phoslactomycins A to F. *J. Antibiot.* **1989**, *42*, 1026-1036. (c) Ozasa, T.; Suzuki, K., Sasamata, M.; Tanaka, K.; Kobori, M.; Kadota, S.; Nagai, K.; Saito, T.; Watanabe, S.; Iwanami, M. Novel Antitumor Antibiotic Phospholine. 1. Production, Isolation and Characterization. *J. Antibiot.* **1989**, *42*, 1331-1338. (d) Ozasa, T.; Tanaka, K.; Sasamata, M.; Kaniwa, H.; Shimizu, M.; Matsumoto, H.; Iwanami, M. Novel Antitumor Antibiotic Phospholine. 2. Structure Determination. *J. Antibiot.* **1989**, *42*, 1339-1343.

(65) (a) Usui, T.; Marriot, G.; Inagaki, M.; Swarup, G.; Osada, H. Protein Phosphatse 2A Inhibitors, Phoslactomycins. Effects on the Cytoskeleton in NIH/3T3 Cells. *J. Biochem.* **1999**, *125*, 960-965. (b) Lewy, D. S.; Gauss, C.-M.; Soenen, D. R.; Boger, D. L. Fostriecin: Chemistry and Biology. *Curr. Med. Chem.* **2002**, *9*, 2005-2032. (c) Buck, S. B.; Hardouin, C.; Ichikawa, S.; Soenen, D. R.; Gauss, C.-M.; Hwang, I.; Swingle, M. R.; Bonness, K. M.; Honkanen, R. E.; Boger, D. L. Fundamental Role of the Fostriecin Unsaturated Lactone and Implications for Selective Protein Phosphatase Inhibition. *J. Am. Chem. Soc.* **2003**, *125*, 15694-15695.

(66) Teruya, T.; Simizu, S.; Kanoh, N.; Osada, H. Phoslactomycin targets cysteine-269 of the protein phosphatase 2A catalytic subunit in cells. *FEBS Lett.* **2005**, *579*, 2463-2468.

(67) Palaniappan, N.; Kim, B. S.; Sekiyama, Y.; Osada, H.; Reynolds, K. A. Enhancement and Selective Production of Phoslactomycin B, a Protein Phosphatase IIa Inhibitor, through Identification and Engineering of the Corresponding Biosynthetic Gene Cluster. *J. Bio. Chem.* **2003**, *278*, 35552-35557.

(68) Alhamadsheh, M. M.; Palaniappan, N.; DasChouduri, S.; Reynolds, K. A. Modular Polyketide Synthases and *cis* Double Bond Formation: Establishment of Activated *cis*-3-Cyclohexylpropenoic Acid as the Diketide Intermediate in Phoslactomycin Biosynthesis. *J. Am. Chem. Soc.* **2007**, *129*, 1910-1911.

(69) Wang, Y.-G.; Takeyama, R.; Kobayashi, Y. Total Synthesis of Phoslactomycin B and Its Biosynthetic Deamino Precursor. *Angew. Chem. Int. Ed.* **2006**, *45*, 3320-3323.

(70) In 2007, the group published an improvement in the generation of the central core of the molecule: Nonaka, H.; Maeda, N.; Kobayashi, Y. Improved synthesis of the polyhydroxylated central part of phoslactomycin B. *Tetrahedron Lett.* **2007**, *48*, 5601-5604.

(71) Shibahara, S.; Fujino, M.; Tashiro, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. Asymmetric Total Synthesis of (+)-Phoslactomycin B. *Org. Lett.* **2008**, *10*, 2139-2142.

(72) König, C. M.; Gebhardt, B.; Schleth, C.; Dauber, M.; Koert, U. Total Synthesis of Phoslactomycin A. *Org. Lett.* **2009**, *11*, 2728-2731.

(73) Shimada, K.; Kapuragi, Y.; Fukuyama, T. Total Synthesis of Leustroducsin B. *J. Am. Chem. Soc.* **2003***, 125,* 4048-4049.

(74) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. Total Synthesis of Leustroducsin B. *J. Org. Chem.* **2008***, 73,* 5360-5370.

(75) (a) Hayashi, T. Rhodium-Catalyzed Asymmetric 1,4-Addition of Organoboronic Acids and Their Derivatives to Electron Deficient Olefins. *Synlett* **2001**, 879-887. (b) Hayashi, T.; Yamasaki, K. Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. *Chem. Rev.* **2003**, *103*, 2829-2844.

(76) Allred, G. D.; Liebeskind, L. S. Copper-Mediated Cross-Coupling of Organostannanes with Organic Iodides at or below Room Temperature. *J. Am. Chem. Soc.* **1996**, *118*, 2748-2749.

(77) Williams, D. E.; Roberge, M.; Van Soest, R.; Andersen, R. J. Spirastrellolide A, An Antimitotic Macrolide Isolated from the Caribbean Marine Sponge *Spirastrella coccinea*. *J. Am. Chem. Soc.* **2003**, *125*, 5296-5297.

(78) Williams, D. E.; Lapawa, M.; Feng, X. D.; Tarling, T.; Roberge, M.; Andersen, R. J. Spirastrellolide A: Revised Structure, Progress toward the Relative Configuration, and Inhibition of Protein Phosphatase 2A. *Org. Lett.* **2004**, *6*, 2607-2610.

(79) For a reviews detailing the stereochemical confirmation of spirastrellolide A via synthesis and synthetic efforts undertaken, please see: (a) Perkins, M. V. Total Synthesis of Enzyme Inhibitor Spirastrellolide A – Stereochemical Confirmation. *Angew. Chem. Int. Ed.* **2008**, *47*, 2921-2925. (b) Paterson, I.; Dalby, S. M. Synthesis and stereochemical detemination of the spirastrellolides. *Nat. Prod. Rep.* **2009**, *26*, 865-873.

(80) (a) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. Total Synthesis of Spirastrellolide A Methyl Ester – Part 1: Synthesis of an Advanced C17-C40 Bis-spiroacetal Subunit. *Angew. Chem. Int. Ed.* **2008**, *47*, 3016-3020. (b) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. Total Synthesis of Spirastrellolide A Methyl Ester – Part 2: Subunit Union and Completion of the Synthesis. *Angew. Chem. Int. Ed.* **2008**, *47*, 3021-3025.

(81) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Maltas, P.; Moessner, C. Synthesis of the DEF-*bis*-spiroacetal of spirastrellolide A exploiting a double asymmetric dihydroxylation/spiroacetalisation strategy. *Chem. Commun.* **2006**, 4186-4188.

(82) Hu. S.; Jayaraman, S.; Oehlschlager, A. C. Diastereo- and Enantioselective Synthesis of *syn*-α-Vinylchlorohydrins and *cis*-Vinylepoxides. *J. Org. Chem.* **1996**, *61*, 7513-7520.

(83) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Enger, D. V.; Clardy, J.; Gopichand, Y.; Schmitz, F. Okadaic Acid, a Cytotoxic Polyether from Two Marine Sponges of the Genus *Halichondria*. *J. Am. Chem. Soc.* **1981**, *103*, 2469-2471.

(84) (a) Muraka, Y.; Oshima, Y.; Yasumoto, T. Identification of Okadaic Acid As a Toxic Component of a Marine Dinoflagellate *Prorocentrum lima*. *Bull. Japan Soc. Sci. Fish.* **1982**, *48*, 69-72. (b) Murata, M.; Shimatani, M.; Sugitani, H.; Oshima, Y.; Yasumoto, T. Isolation and Structural Elucidation of the Causative Toxin of the Diarrhetic Shellfish Poisoning. *Bull. Japan Soc. Sci. Fish.* **1982**, *48*, 549-552.

(85) Bialojan, C.; Takai, A. Inhibitory effect of marine-sponge toxin, okadic acid, on protein phosphatases. Specificity and kinetics. *Biochem. J.* **1988**, *256*, 283-290.

(86) Boudreau, R. T. M.; Hoskin, D. W. The use of okadaic acid to elucidate the intracellular role(s) of protein phosphatase 2A: Lessons from the mast cell model system. *Int. Immunopharmacol.* **2005**, *5*, 1507-1518.

(87) Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. Efficient Synthesis of Okadaic Acid. 1. Convergent Assembly of the C15-C38 Domain. *J. Am. Chem. Soc.* **1998**, *120*, 2523-2533.

(88) Isobe, M.; Ichikawa, Y.; Goto, T. Synthetic Studies Toward Marine Toxic Polyethers [5] The Total Synthesis of Okadaic Acid. *Tetrahedron Lett.* **1986**, *27*, 963-966.

(89) For a full account, see the following four successive publications: (a) Ichikawa, Y.; Isobe, M.; Bai, D.-L.; Goto, T. Synthesis of a marine polyether toxin, okadaic acid [1] – Strategy and synthesis of segment A. *Tetrahedron* **1987**, *43*, 4737-4748. (b) Ichikawa, Y.; Isobe, M.; Goto, T. Synthesis of a marine polyether toxin, okadaic acid [2] – Synthesis of segment B. *Tetrahedron* **1987**, *43*, 4749-4758. (c) Ichikawa, Y.; Isobe, M.; Masaki, H.; Kawai, T.; Goto, T. Synthesis of a marine polyether toxin, okadaic acid [3] – Synthesis of segment C. *Tetrahedron* **1987**, *43*, 4759-4766. (d)Isobe, M.; Ichikawa, Y.; Bai, D.-L.; Masaki, H.; Goto, T. Synthesis of a marine polyether toxin, okadaic acid [4] – Total synthesis. *Tetrahedron* **1987**, *43*, 4767-4776.

(90) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Goto, T. Acyclic stereocontrol by heteroconjugate addition-4 *Anti*-diastereoselection by a β-chelation effect. *Tetrahedron* **1986**, *42*, 2862-2872.

(91) Forsyth, C. J.; Sabes, S. F.; Urbanek, R. A. An Efficient Total Synthesis of Okadaic Acid. *J. Am. Chem. Soc.* **1997**, *119*, 8381-8382.

(92) Sabes, S. F.; Urbanek, R. A.; Forsyth, C. J. Efficient Synthesis of Okadaic Acid. 2. Synthesis of the C1-C14 Domain and Completion of the Total Synthesis. *J. Am. Chem. Soc.* **1998**, *120*, 2534-2542.

(93) Ley, S. V.; Humphries, A. C.; Eick, H.; Downham, R.; Ross, A. R.; Boyce, R. J.; Pavey, J. B. J.; Pietruszka, J. Total synthesis of the protein phosphatase inhibitor okadaic acid. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3907-3911.

(94) (a) Tunac, J. B.; Graham, B. D.; Dobson, W. E. Novel antitumor agents CI-920, PD 113,270 and PD 113,271. I. Taxonomy, fermentation and biological properties. *J. Antibiot.* **1983**, *36*, 1595-1600. (b) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. Novel

antitumor agents CI-920, PD 113,270 and PD 113,271. II. Isolation and characterization. *J. Antibiot.* **1983**, *36*, 1601-1605. (c) Hokanson, G. C.; French, J. C. Novel antitumor agents CI-920, PD 113,270, and PD 113,271. 3. Structure determination. *J. Org. Chem*. **1985**, *50*, 462-466.

(95) (a) Jackson, R. C.; Fry, D. W.; Boritzki, T. J.; Roberts, B. J.; Hook, K. E.; Leopold, W. R. The biochemical pharmacology of CI-920, a structurally novel antibiotic with antileukemic activity. *Adv. Enzyme Regul.* **1985**, *23*, 193-215. (b) De Jong, R. S.; De Vires, E. G. E.; Mulder, N. H. Fostriecin: a review of the preclinical data. *Anti-Cancer Drugs* **1997**, *8*, 413-418.

(96) Scheithauer, W.; Von Hoff, D. D.; Clark, G. M.; Shillis, J. L.; Elslager, E. F. In vitro activity of the novel antitumor antibiotic fostriecin (CI-920) in a human tumor cloning assay. *Eur. J. of Cancer Clin. Oncol*. **1986**, *22*, 921-926.

(97) Walsh, A. H.; Cheng, A.; Honkanen, R. E. Fostriecin, an antitumor antibiotic with inhibitory activity against serine/threonine protein phosphatases types 1 (PP1) and 2A (PP2A), is highly selective for PP2A. *FEBS Lett.* **1997**, *416*, 230-234.

(98) Hastie, C. J.; Cohen, P. T. W. Purification of protein phosphatase 4 catalytic subunit: inhibition by the antitumor drug fostriecin and other tumor suppressors and promoters. *FEBS Lett.* **1998**, *431*, 357-361.

(99) Boger, D. L.; Hikota, M.; Lewis, B. M. Determination of the Relative and Absolute Stereochemistry of Fostriecin (CI-920). *J. Org. Chem.* **1997**, *62*, 1748-1753.

(100) Walsh, A. H.; Cheng, A.; Honkanen, R. E. Fostriecin, an antitumor antibiotic with inhibitory activity against serine/threonine protein phosphatases types 1 (PP1) and 2A (PP2A), is highly selective for PP2A. *FEBS Lett.* **1997**, *416*, 230-234.

(101) Boger, D. L.; Ichikawa, S.; Zhong, W. Total Synthesis of Fostriecin (CI-920). *J. Am. Chem. Soc.* **2001**, *123*, 4161-4167.

(102) Stork, G.; Zhao, K. A stereoselective synthesis of (*Z*)-1-iodo-1-alkenes. *Tetrahedron Lett.* **1989**, *30*, 2173-2174.

(103) Chavez, D. E.; Jacobsen, E. N. Total synthesis of fostriecin (CI-920). *Angew. Chem, Int. Ed.* **2001**, *40*, 3667-3670.

(104) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. Asymmetric Catalysis with Water: Efficient Kinetic Resolution of Terminal Epoxides by Means of Catalytic Hydrolysis. *Science* **1997**, *277*, 936-938. (b) Jacobsen, E. N. Asymmetric Catalysis of Epoxide Ring-Opening Reactions. *Acc. Chem. Res.* **2000**, *33*, 421-431.

(105) (a) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. Highly Enantio- and

Diastereoselective Hetero-Diels-Alder Reactions Catalyzed by New Chiral Tridentate Chromium(III) Catalysts. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398-2400. (b) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. Highly Enantioselective Inverse-Electron Demand Hetero-Diels-Alder Reactions of a,b-unsaturated Aldehydes *Angew. Chem. Int. Ed.* **2002**, *41*, 3059-3061. (c) Chavez, D. E.; Jacobsen, E. N.; Grabowski, E. J. J.; Kubryk, M. An efficient, highly diastereo- and enantioselective hetero-Diels-Alder catalyst. Preparation of (2*S*,6*R*)-6-(*tert*-butyldimethylsiloxymethyl)-2-methoxy-2,5-dihydropyran. *Organic Synthesis* **2005**, *82*, 34-42.

(106) While no experimentals are provided in the report, full details and experimentals are provided in the following reference: Chavez, D. E. The Total Synthesis of Fostriecin (CI-920). The Development and Applications of an Asymmetric Hetero-Diels-Alder Reaction. Ph. D. Thesis, Harvard University, Cambridge, MA, 2003.

(107) Burke, S. D.; Cobb, J. E.; Takeuchi, K. Total Synthesis of (+)-Phyllanthocin. Introduction of Intramolecular Hydroformylation for Complex Molecule Functionalization. *J. Org. Chem.* **1990**, *55*, 2138-2151.

(108) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. New Cobalt Catalyzed Cycloisomerization of ε-Acetylenic β-Keto Esters. Application to a Powerful Cyclization Reactions Cascade. *J. Org. Chem.* **1996**, *61*, 2699-2708.

(109) The isopropyl acetal was found to be the superior form of this protected lactol for the desired transformations. See references 103 and 106.

(110) For a review of hydrozirconation, see: Wipf, P.; Jahn, H. Synthetic applications of organochlorozirconocene complexes. *Tetrahedron* **1996**, *52*, 12853-12910.

(111) (a) Wipf, P.; Xu, W. Preparation of allylic alcohols by alkene transfer from zirconium to zinc. *Tetrahedron Lett.* **1994**, *35*, 5197-5200. (b) Wipf, P.; Ribe, S. Zirconocene-Zinc Transmetalation and in Situ Catalytic Asymmetric Addition to Aldehydes. *J. Org. Chem.* **1998**, *63*, 6454-6455.

(112) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. Asymmetric Transfer Hydrogenation of α,β-Acetylenic Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739.

(113) Reddy, Y. K.; Falck, J. R. Asymmetric Total Synthesis of (+)-Fostriecin. *Org. Lett.* **2002**, *4*, 969-971.

(114) Esumi, T.; Okamoto, N.; Hatakeyama, S. Versatile enantiocontrolled synthesis of (+)-fostriecin. *Chem. Commun.* **2002**, 3042-3043.

(115) Taniguchi, M.; Kobayashi, S.; Nakagawa, M.; Hino, T.; Kishi, T. β-Halovinyl ketones: Synthesis from acetylenic ketones. *Tetrahedron Lett.* **1986**, *27*, 4763-4766.

(116) Evans, D. A.; Chapman, T.; Carreira, E. M. Directed Reduction of β-Hydroxy Ketones Employing Tetramethylammonium Triacetoxyborohydride. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.

(117) Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. Total Synthesis of an Antitumor Antibiotic, Fostriecin (CI-920). *J. Am. Chem. Soc.* **2003**, *125*, 8238-8243.

(118) Wittig reactions of ylides conjugated with *E*-olefins to produce *Z*-olefinic bonds had been reported previously: (a) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. Leukotriene B. Total Synthesis and Assignment of Stereochemistry. *J. Am. Chem. Soc.* **1980**, *102*, 7984-7985. (b) Niwa, H.; Watanabe, M.; Inagaki, H.; Yamada, K. Didemnilactones A and B and neodidemnilactone three new fatty acid metabolites isolated from the tunicate *Didemnum moseleyi* (Herdman). *Tetrahedron* **1994**, *50*, 7385-7400.

(119) For examples of other P(III)/P(V)-based tethers, see: (a) Rubinstenn, G.; Esnault, J.; Mallet, J.-M.; Sinay, P. Radical-mediated synthesis of N-acetyl-D-galactosamine containing C-disaccharides via a temporary phosphoramidic connection. *Tetrahedron: Asymmetry* **1997**, *8*, 1327-1336. (b) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. A Temporary Phosphorus Tether/Ring-Closing Metathesis Strategy to Functionalized 1,4-Diamines. *Org. Lett.* **2001**, *3*, 3939-3942.

Chapter 2

Phosphate Tethers in Synthesis:
Divalent Activation and Highly Selective Cuprate Displacement Reactions

2.1 Introduction

We have reported the use of tripodal-phosphate tethers for coupling of both simple and complex allylic alcohols using ring-closing metathesis (RCM).[1] This method highlights the ability of a phosphate tether to bestow multivalent activation throughout phosphate ester appendages, thereby providing latent leaving group ability yet possessing orthogonal stability. This wetted our interest in developing a new strategy employing phosphate tethers, in which a phosphate ester serves a dual role as both a tether for coupling two allylic alcohols via ring-closing metathesis (RCM) and as a subsequent leaving group in selective *anti*-S_N2' displacement reactions with organocuprate nucleophiles.

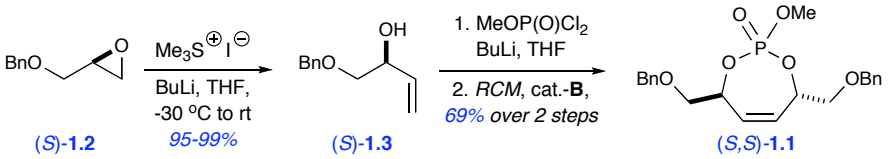
An underlying principle of this approach utilizes the well-documented superiority of phosphates as leaving groups in copper mediated *anti*-S_N2' displacement reactions, initially highlighted by Yamamoto and coworkers.[2] This feature, where the stereochemistry of an allylic phosphate is inverted in an *anti*-S_N2' displacement, has been successfully employed in previous strategies that exploit high stereospecificity for chirality transfer.[3] Further advances in this area have recently uncovered enantioselective *anti*-S_N2' displacements with chiral Schiff base cuprates as a viable means of desymmetrizing meso-1,3-*syn* allylic phosphates,[4] as well as reagent-controlled asymmetric allylic phosphate displacements catalyzed by copper.[5] The method we report herein initially focuses on the use of symmetry breaking cuprate additions to readily prepared *pseudo*-C_2-symmetric monocyclic phosphate

(*S*,*S*)-**1.1** (Scheme 1). To the best of our knowledge, this system is the first of its kind where a central phosphate tether imparts divalent activation to the unique doubly allylic phosphate subunit. In the discussion that follows, intriguing conformational effects led us to extend the study into unsymmetric phosphates, ultimately providing experimental insight into the Corey mechanism of cuprate displacements.

2.2 Reactivity of the pseudo-C_2-Symmetric Monocyclic Phosphate

Our study began with the generation of (*S,S*)-monocyclic phosphate **1.1**, which was readily achieved in three steps and in good overall yields (Scheme 1). Allylic alcohol (*S*)-**1.3** is readily generated on multi-gram scale using the Mioskowski-Christie protocol[6] with commercially available glycidol ether (*S*)-**1.2**. Upon condensation of the alkoxide of **1.3** with $(MeO)POCl_2$, the phosphate triester tether mediates coupling of two olefins via RCM in good yield using $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (Grubbs II; cat.-**B**);[7] use of catalyst $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (Grubbs I; cat.-**A**) gave poor yields of **1.1**. Optimized RCM conditions required elevated temperatures (90 °C in toluene) with continuous argon purging.[8]

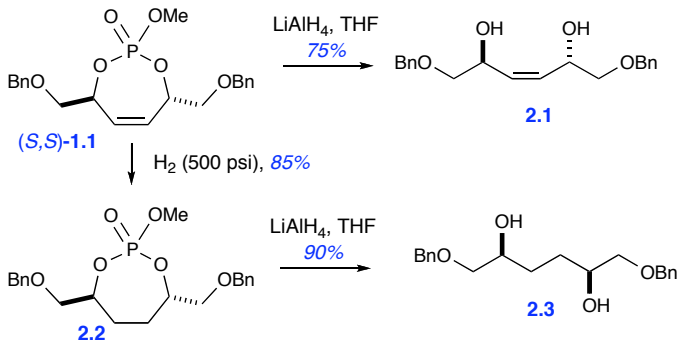
Scheme 1



We first examined a number of conditions as part of our initial probe into orthogonal reactivity patterns within cyclic phosphates containing multiple allylic phosphate positions. Attempts to cleave out the phosphate tether using the $LiAlH_4$

reduction protocol of Bartlett's[9] successfully generated the C_2-symmetric *Z*-configured-1,2,5,6-tetraol subunit **2.1** (Scheme 2). Alternatively, post-RCM hydrogenation of **1.1** via the Louie-Grubbs procedure[10] led cleanly to formation of saturated cyclic phosphate **2.2**. Wilkinson's catalyst was also found to be a suitable hydrogenation partner, but other typical hydrogenation catalysts (Pd/C) lead to complete decomposition of starting material. As anticipated, cleavage of saturated phosphate **2.2** afforded the tether-cleaved diol **2.3** in higher yield.

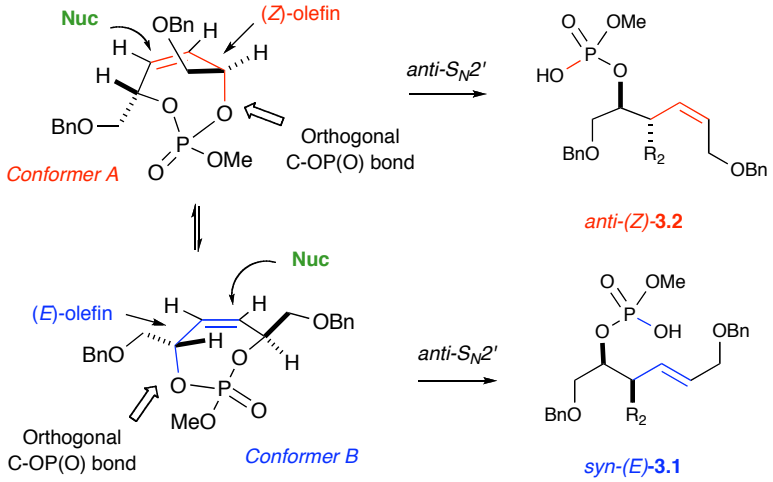
Scheme 2



We then shifted focus towards *anti*-S_N2'-allylic displacement studies using soft organocuprate nucleophiles. A prerequisite for this reaction requires the leaving group to be orthogonal to the π system, i.e. co-planar alignment of the σ^* and π^* orbitals. Monocyclic phosphate (*S*,*S*)-**1.1** possesses the ability to align the phosphate moiety in two requisite anti-periplanar relationships outlined in Scheme 3. In both conformers it was initially anticipated that energies related to the orthogonally-aligned phosphate leaving group would be roughly equal in energy, since both are secondary allylic phosphates. When considering only electronic factors, this would imply transition states of equal energy as described by the original Corey mechanism[2b] which invokes a bidentate coordination of incoming cuprate to both π^*

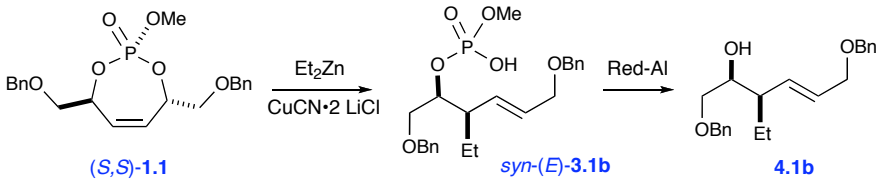
and σ^* orbitals, vide infra. Attack of cuprate nucleophiles on **1.1** can potentially occur through any of four diastereotopic olefinic orbitals. Symmetry, however, presents two (not four) stereodivergent pathways for *anti*-S_N2'-allylic displacement, ultimately leading to only two possible diastereomeric products.[11] Pathway A occurs through conformer A with addition *anti* to the vicinal CH_2OBn group generating *anti-(Z)* diastereomer **3.2**, while pathway B occurs via conformer B with addition *syn* to the vicinal CH_2OBn group leading to *syn-(E)* diastereomer **3.1**.

Scheme 3



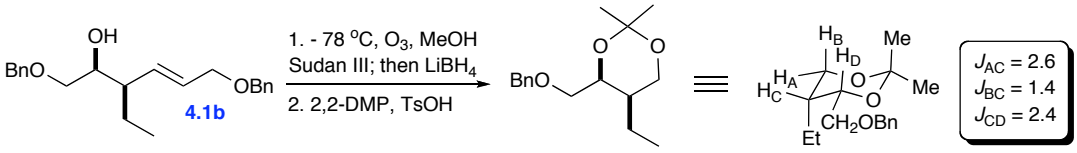
Pleasingly, *anti*-S_N2' displacement of allylic phosphate **1.1** using Et_2Zn/CuCN•2LiCl, and after acid workup, led to formation of phosphate acid **3.1b** as a single diastereomer (>20:1) as witnessed by ^{31}P NMR (Scheme 4). Subsequent

Scheme 4



treatment with Red-Al® led to good yields of homoallylic alcohol **4.1b**. Initial tentative assignment of the relative stereochemistry within phosphate acid **3.1b** was made based on the proposed model for cuprate addition and the observed olefinic coupling constant consistent with an (*E*)-configured olefin (J = 15.7 Hz). Unambiguous determination of relative stereochemical relationship at C(2,3) within **4.1b** was ultimately achieved using Karplus-analysis of vicinal protons contained within the six-membered ring derived from reductive ozonolysis/acetonide formation of **4.1** (Scheme 5).[12] Analysis of J_{AC}, J_{BC}, J_{CD} coupling constants provided small coupling values (1.4-2.6 Hz) consistent with the assigned structure. These values were identical to previously reported spectral data when R^1 = Me.[13]

Scheme 5



The remarkable selectivity for this transformation can be rationalized using Corey's proposed concerted, asynchronous mechanism[2b] for cuprate additions as highlighted in Figure 1. In this mechanism, Corey surmises that the reacting cuprate simultaneously coordinates both the π^* orbital of the olefin and σ^* orbital of the phosphate ester leaving group. The asynchronous nature of the transformation predicts a transition state in which substantial bond-lengthening occurs with respect to the σ^* bonding orbital. When applied to conformers A and B in (*S*,*S*)-**1.1**, it is anticipated the σ^* orbitals are roughly equal in energy, since both are secondary allylic phosphates. Therefore, the stereoselectivity displayed in the cuprate reaction

with **1.1** must ultimately be dictated by the lower steric requirements of conformer B to attain the requisite coplanar alignment of π^* and σ^* orbitals with the cuprate d-orbital; the greater allylic 1,3-strain ($A^{1,3}$ strain) within conformer A due to the CH_2OBn-sidechain disfavors cuprate addition via this conformer (Scheme 3).[14]

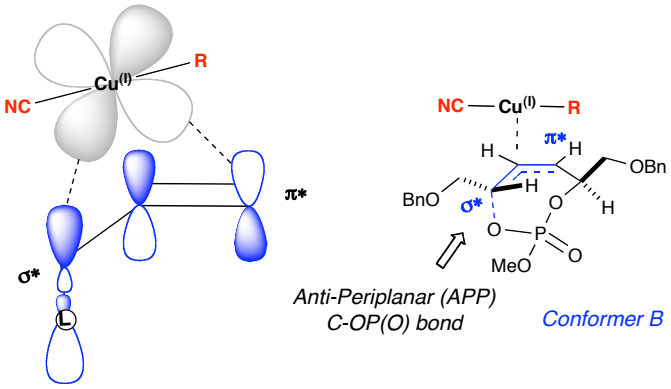
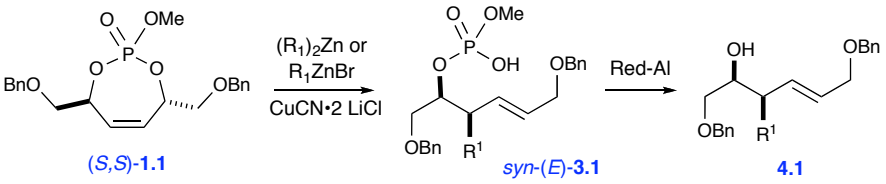


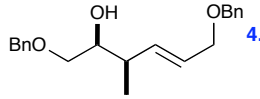
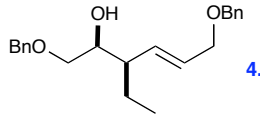
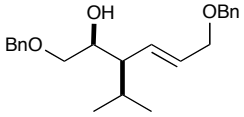
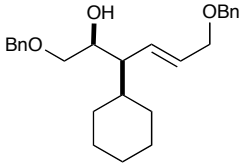
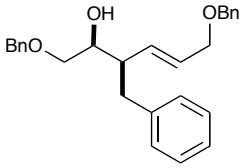
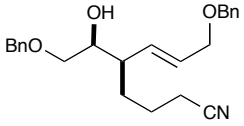
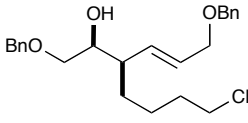
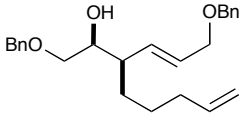
Figure 1: Corey Model for Rationalizing Stereoselectivity

Additional reactions of **1.1** with an array of zinc-based organocuprates gave similar high yields and selectivities when using 4-5 equivalents of dialkylzinc-derived organocuprates (entries 1-3, Table 1). Treatment of **1.1** with 8-9 equivalents of the mixed zinc-copper reagents using alkyl halide-derived, functionalized organozinc reagents (entries 4-8, Table 1) provided similar yields and diastereoselectivities. The specified excess reagents were used in all cases to ensure complete consumption of starting materials and overall provided cleaner post-workup mixtures.[15] Following acidic workup, the phosphate acids were directly subjected to Red-Al® to afford the corresponding homoallylic substrates **4.1a-4.1h** in good to excellent yields.

Table 1

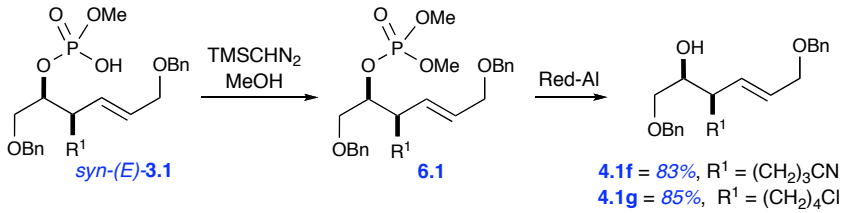


(*S,S*)-**1.1** *syn*-(*E*)-**3.1** **4.1**

entry	$(R^1)_2Zn$ or R^1ZnBr	phosphate acid - **3.1** %/dr	homoallylic alcohol - **4.1**	% yield
1	Me_2Zn (5 equiv)	*99*/>20:1 **3.1a**	 **4.1a**	*83*
2	Et_2Zn (5 equiv)	*99*/>20:1 **3.1b**	 **4.1b**	*90*
3	iPr_2Zn (5 equiv)	*99*/>20:1 **3.1c**	 **4.1c**	*95*
4	c-HexZnI (9 equiv)	*99*/>20:1 **3.1d**	 **4.1d**	*70*
5	BnZnBr (9 equiv)	*99*/>20:1 **3.1e**	 **4.1e**	*84*
6	$CN(CH_2)_3ZnBr$ (9 equiv)	*99*/>20:1 **3.1f**	 **4.1f**	*31*
7	$Cl(CH_2)_4ZnBr$ (9 equiv)	*99*/>20:1 **3.1g**	 **4.1g**	*71*
8	$CH_2=CH(CH_2)_3ZnBr$ (9 equiv)	*99*/>20:1 **3.1h**	 **4.1h**	*65*

While cleavage of the phosphate acid using Red-Al® afforded the majority of products **4.1** in good yields, lower yields were observed for reductions in which substrates **3.1** contained functionally-sensitive R^1 groups. To circumvent this problem, in situ methylation of the crude phosphate acid using $TMSCHN_2$ produced **6.1**, and upon Red-Al® reduction led to overall higher yields of **4.1** (Scheme 6).

Scheme 6

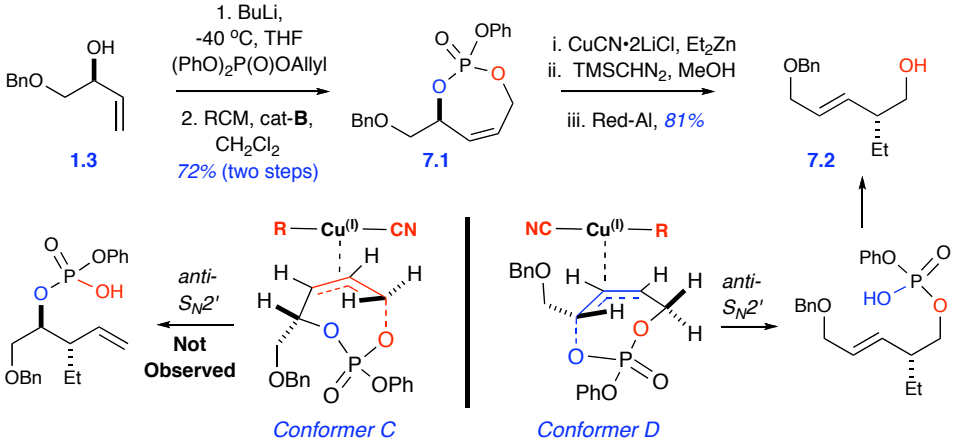


2.3 Cuprate Additions to Unsymmetric Monocyclic Phosphates

We next turned our attention to the construction of unsymmetric monocyclic phosphates containing similar steric environments with regards to the incoming cuprate, but disparate electronic energies at the σ^* orbitals of the leaving phosphate ester (i.e., primary versus secondary allylic phosphate ester leaving groups). In contrast to phosphate **1.1**, an energetic bias for the corresponding allylic phosphates was thus anticipated. Dioxaphosphacycle **7.1** was generated via the coupling of one equivalent of allylic alcohol **1.3** with allyldiphenyl phosphate, followed by RCM to afford **7.1** in good yields over two steps (Scheme 7). Treatment of **7.1** with 3.0 equivalents of diethyl zinc-derived organocuprates, and subsequent phosphate cleavage, led to formation of a single product **7.2** produced via cuprate displacement at the secondary allylic phosphate position. In contrast to (*S*,*S*)-**1.1**, no dominant

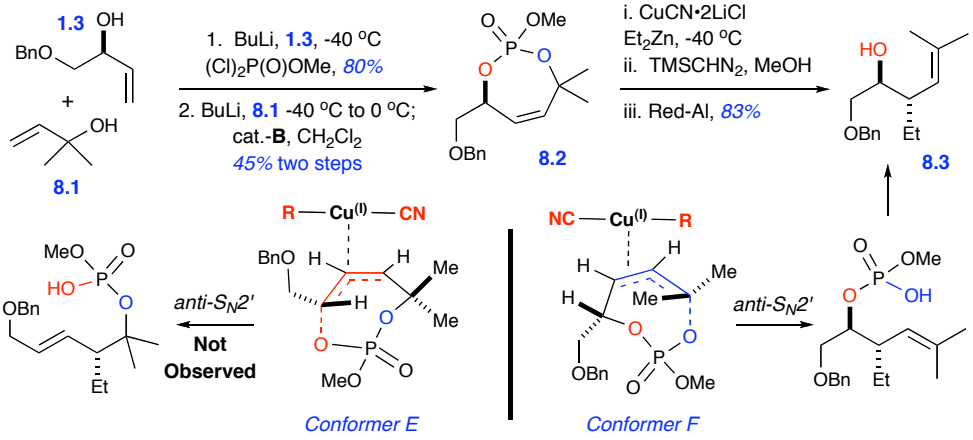
conformational preferences exist between the two described reactive conformations of **7.1**, indicating that regioselectivity is dictated by electronic effects, vide infra.

Scheme 7



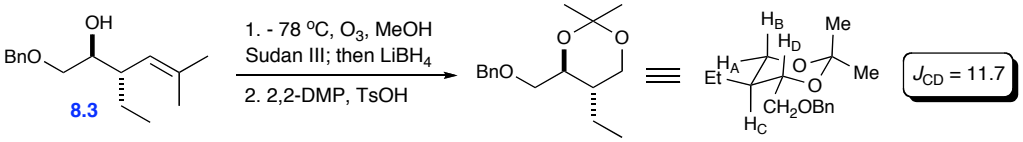
This intriguing result led us to explore yet a third paradigm, the unsymmetric cyclic phosphate **8.2**, containing both secondary and tertiary allylic phosphate positions (Scheme 8). Phosphate **8.2** was assembled via differential coupling of secondary allylic alcohol **1.3** and 2-methylbut-3-en-2-ol (**8.1**) with dichloromethyl phosphate. The resulting labile acyclic phosphate was immediately subjected to metathesis affording phosphate **8.2** in moderate yields over the two-step sequence.

Scheme 8



Treatment of **8.2** with 3.0 equivalents of diethyl zinc-derived organocuprate at -40 °C, and subsequent phosphate cleavage, led to formation of a single product **8.3**. Using the aforementioned Karplus analysis of the resulting acetonide of **8.3**, unambiguous assignment of *anti*-relationship was established (Scheme 9).

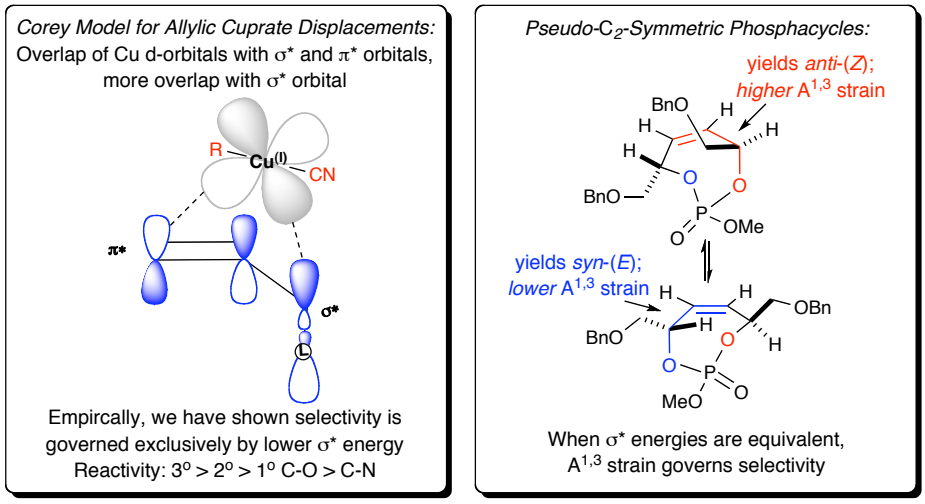
Scheme 9



The regioselectivity of cuprate displacement in **8.2** is most surprising in that the requisite conformer F leading to product **8.3** (Scheme 8) contains an unfavorable $A^{1,3}$ interaction generated by the gem-dimethyl moiety. However, the observed selectivity is consistent with the results obtained with **7.1** in which the cuprate displaces the more substituted phosphate leaving group. Since the Corey model for cuprate addition predicts significant bond breakage through σ^*, the lower energy σ^* (i.e. the most substituted carbon) in the asynchronous concerted transition state dictates the reaction pathway over substantial $A^{1,3}$ steric interactions.

In rationalizing and summarizing regio- and diastereoselective cuprate additions with symmetric (*S*,*S*)-**1.1** and unsymmetric phosphates **7.1** and **8.2**, both steric and stereoelectronic effects appear to play major roles. In the case of **7.1** and **8.2**, cuprate displacements proceeded via the more substituted σ^* positions, secondary and tertiary, respectively. When σ^* energies are equivalent as in (*S*,*S*)-**1.1**, allylic strain appears to govern the cuprate addition.

2.4 Summary



In conclusion, monocyclic phosphates undergo a highly selective *anti*-S_N2' allylic phosphate displacement. Subsequent cleavage affords an array of *syn-(E)*-homoallylic alcohols when *pseudo*-C_2-symmetric monocyclic phosphates are employed. In extending this method to unsymmetric phosphates, cuprate addition proceeded through the more substituted allylic phosphate position (lower σ^* energy) with the general reactivity pattern being 1° < 2° < 3°, allowing access to *anti*-configured homoallylic alcohols, in which the resulting stereochemistry is exclusively produced via chirality transfer from a remote stereogenic center. In probing these systems, the Corey mechanism for allylic organocuprate displacements was examined and further substantiated, although testing systems with additional dissymmetric substitution on the olefin is necessary to rule out nucleophilic avoidance of steric interactions as the operative model.

2.5 References:

(1) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. Multivalent Activation in Temporary Phosphate Tethers: A New Tether for Small Molecule Synthesis. *Org. Lett.* **2005***, 7*, 3375-3378.

(2) Initial report of the superiority of phosphate ester leaving groups in *anti*-S_N2' displacements: (a) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. Superiority of Phosphate Esters as Leaving Group for Organocopper Reactions. Highly S_N2'-, (*E*)-, and Antiselective Alkylation of Allylic Alcohol Derivatives. *Synlett.* **1991**, *4*, 251-253. Proposed mechanism for allylic phosphate displacement via organocuprates: (b) Corey, E. J.; Boaz, N. W. d-Orbital Stereoelectronic Control of the Stereochemistry of S_N2' Displacements by Organocuprate Reagents *Tetrahedron Lett.* **1984**, *25*, 3063-3066.

(3) For chirality transfer in *anti*-S_N2' allylic phosphate displacements see: (a) Belelie, J. L.; Chong, M. Stereoselective Reactions of Acyclic Allylic Phosphates with Organocopper Reagents. *J. Org. Chem.* **2001**, *66*, 5552-5555. (b) Calaza, M. I.; Hupe, E.; Knochel, P. Highly *anti*-Selective S_N2' Substitutions of Chiral Cyclic 2-Iodo-Allylic Alcohol Derivatives with Mixed Zinc-Copper Reagents *Org. Lett.* **2003**, *5*, 1059-1061 and references therein.

(4) (a) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. A Catalytic and Enantioselective Desymmetrization of *meso* Cyclic Allylic Bisdiethylphosphates with Organozinc Reagents *Angew Chem., Int. Ed. Engl.* **2003**, *42*, 234-236. (b) Piarulli U.; Claverie, C.; Daubos, Gennari, C.; Minnaard, A. J.; Feringa, B. L. Copper Phosphoramidite-Catalyzed Enantioselective Desymmetrization of *meso*-Cyclic Allylic Bisdiethyl Phosphates. *Org. Lett.* **2003**, *5*, 4493-4496.

(5) (a) Kacprznski, M. A.; Hoveyda, A. H. Cu-Catalyzed Asymmetric Allylic Alkylations of Aromatic and Aliphatic Phosphates with Alkylzinc Reagents. An Effective Method for Enantioselective Synthesis of Tertiary and Quaternary Carbons. *J. Am. Chem. Soc.* **2004** *126*, 10676-10681. (b) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex. *J. Am. Chem. Soc.* **2004**, *126*, 11130-11131.

(6) Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. Homologation of allylic alcohols. An approach to cyclic and acyclic polyoxygenated compounds. *Tetrahedron Lett.* **2000**, *41*, 1255-1259.

(7) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org.*

Lett. **1999**, *1*, 953-956.

(8) Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O. Optimization of Ring-Closing Metathesis: Inert Gas Sparging and Microwave Irradiation. *Adv. Synth. Catal.* **2005**, *347*, 1869-1874.

(9) Bartlett, P.A.; Jernstedt, K. K. A stereocontrolled synthesis of the methyl ester of (±)-nonactic acid. *Tetrahedron Lett.* **1980**, *21*, 1607-1610.

(10) Louie, J.; Bielawski, C. H.; Grubbs, R. H. Tandem Catalysis: The Sequential Mediation of Olefin Metathesis, Hydrogenation, and Hydrogen Transfer with Single-Component Ru Complexes. *J. Am. Chem. Soc.* **2001**, *123*, 11312-11313.

(11) Cuprate addition leads to loss of the prochiral phosphorus center, thereby providing only two potential products via four diastereomeric pathways. These pathways correspond to addition syn- or anti- to the P=O or OMe groups attached to the prochiral phosphorus atom. The other two possible diastereomers, *anti-(E)*-**7** and *syn-(Z)*-***8*** can not be accessed from *(S,S)*-***1*** via an *anti*-S_N2'-allylic displacement mechanism. Use of *meso*-**1** would be required to access these two diastereomers.

(12) See supporting information for acetonide characterization and analysis.

(13) Ghosh, A. K.; Kim, J.-H. Highly Diastereoselective *anti*-Aldol Reactions Utilizing the Titanium Enolate of *cis*-2-Arylsulfonamido-1-acenaphthenyl Propionate. *Org. Lett.* **2003**, *5*, 1063-1066.

(14) (a) Hoffmann, R. W. Allylic 1,3-strain as a controlling factor in stereoselective transformations. *Chem. Rev.* **1989**, *89*, 1841-1860. (b) $A^{1,3}$ strain in acyclic allylic phosphates, see: Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. Highly stereoselective *anti*-S_N2' substitutions of *Z*-allylic pentafluorobenzoates with polyfunctionalized zinc-copper reagents. *Org. Lett.* **2003**, *5*, 2111-2114.

(15) Acid quench and extraction provided clean ^1H and ^{31}P NMR spectra of crude phosphate acids without column chromatography.

Chapter 3

Phosphate Tethers in Synthesis:
Generation of the Central Core of Fostriecin Towards Library Development

3.1 Introduction

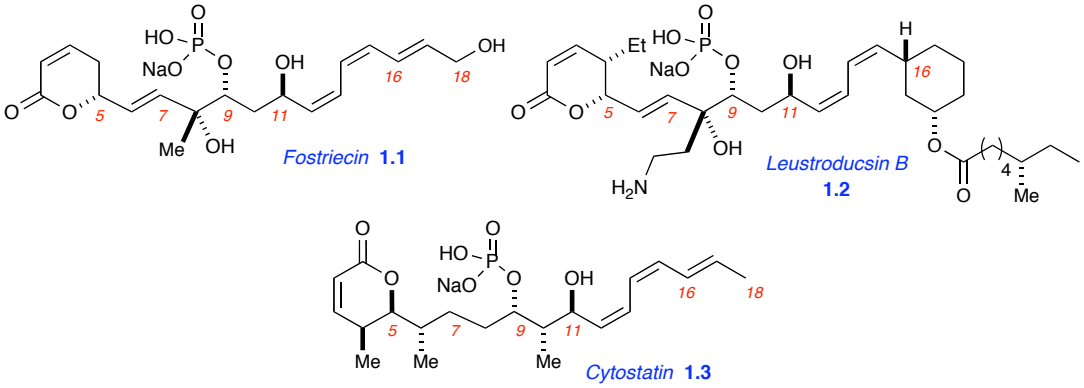
While the use of phosphates in chemical synthesis is limited, they are ubiquitous in nature and provide structural and chemical keystones in dynamic biological systems making them ideal targets for both pharmaceutical and agricultural applications.[1] The ability of phosphates to exist with defined tetrahedral geometry and stable anionic charge, present it as a well-suited pharmacophore. Consequently, organophosphates and their analogs have served as surrogates for carboxylic acids, amino acids, and anomeric carbons in carbohydrates, to name a few. Furthermore, direct application of the phosphate moiety towards kinase and phosphatase regulation is evident and realized in several naturally occurring inhibitors.

Investigation of phosphatase inhibitors as pharmacologically viable targets is relatively new compared to investigations on kinase inhibitors.[2] While initially phosphatases were regarded as enzymes that "clean-up" after more essential regulatory kinases, a large body of evidence dismisses this misconception in light of the pivotal role of phosphatases in the body.[3] In particular, protein phosphatase 2A (PP2A) regulates myriad cellular processes, including: metabolism, transcription, translation, cell cycle, signal transduction, differentiation, and oncogenic transformation.[4] Moreover, recent research has linked PP2A and other phosphatases with the mechanism associated with motor learning.[5] Given this wide range of regulation it is not surprising to find that particular naturally occurring phosphatase inhibitors are involved in certain diseases, such as hepatocarcinoma and HIV-1.[4] Yet, it has also been shown that other phosphatase inhibitors (particularly, selective

inhibitors of PP2A)[6] can be used to disrupt cancerous cells, thus paving the way towards development of this class of inhibitors as viable drug targets.[2]

The leustroducsins (**1.2**) are a class of phosphate-containing molecules that were isolated from the culture broth of *Streptomyces platensis* SANK 60191 belonging to the phoslactomycin group of antibiotics.[7] In particular, leustroducsin B has been shown to exhibit an array of biological activities. The *in vitro* induction of cytokine production through transcriptional and posttranscriptional activation of NF-kB[8] and significant *in vivo* thrombopoietic, anti-infective, and anti-metastatic activities of leustroducsin B appear to be due to specific inhibition of PP2A.[6,7]

Scheme 1



The most selective inhibitor of PP2A to date is the molecule fostriecin (**1.1**, aka CI-920, NSC 339638, and PD 110,161) with an IC_{50} value of 1.5-3.0 nM.[3,9] Boger and coworkers determined that the unsaturated αβ-unsaturated lactone, completely unprotected phosphate and C(11) hydroxyl moieties are essential for activity.[10] The terminal hydroxyl group on the triene tail was found to play no role in the activity of the molecule.

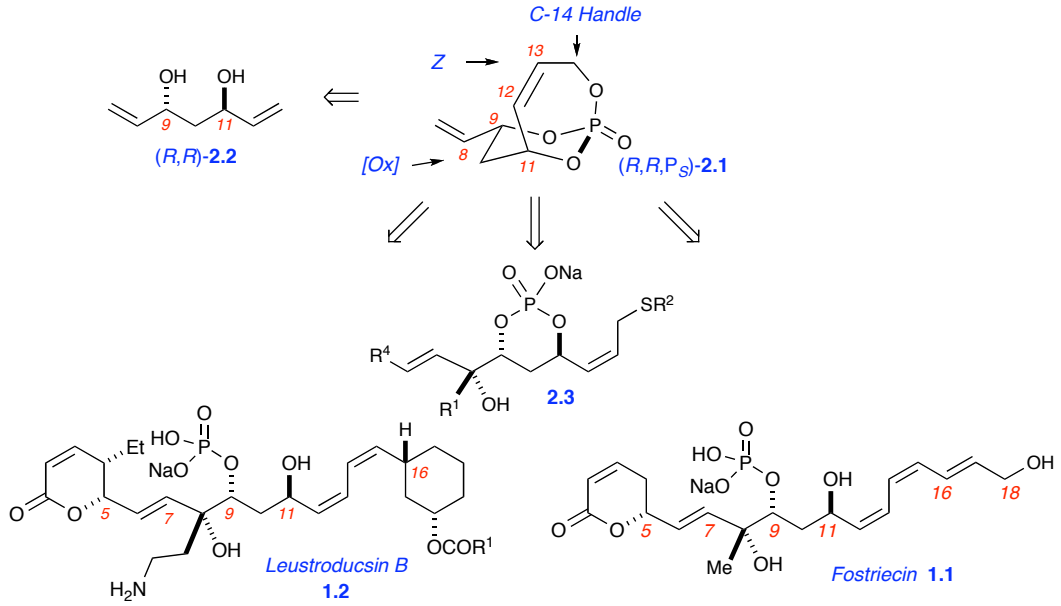
Cytostatin (**1.3**) is yet another phosphate-containing compound and a member of the fostriecin family. It has been shown to prevent metastasis, inhibit tumor cell growth, inhibit cell adhesion and cause apoptosis in certain cell lines due to its exquisitely selective inhibition of PP2A.[6] Analogous to fostriecin, it was found that the αβ-unsaturated lactone ring, completely unprotected phosphate and C(11) hydroxyl moieties are essential for activity in cytostatin, while the triene was merely beneficial for binding but did not drastically effect activity.[11] The activity granted by the unsaturated lactone ring in cytostatin (as well as fostriecin) is believed to come from a nucleophilic conjugate addition in the enzyme,[12] while the deprotected phosphate ensures a very tight, yet non-covalent, interaction. The triene, while proven to be non-essential, seems to help substrate binding and thereby enhance activity. Indeed, it was shown that the triene moiety could be replaced with a vinyl iodide to yield an analog nearly as potent (IC_{50} 39 nM at pH = 8.1) as cytostatin itself (IC_{50} 33 nM at pH = 8.1; IC_{50} 210 nM at pH = 7.5).[11]

While the essential features of leustroducsin B, fostriecin, and cytostatin are well evidenced, these structurally similar compounds differ in placement of groups and functionality on C(6), C(8) and C(10). In particular, while Boger surmised that the C(8) stereocenter of fostriecin might serve to mimic the PP2A substrate stereocenter, no systematic study of this center has been performed. However, in Kanai and Shibasaki's synthesis of fostriecin and 8-*epi*-fostriecin, they deduced the epimer was a more selective PP2A inhibitor.[13] The high specificity of cytostatin, which bears no C(8) stereocenter but a stereocenter at C(10), begs study of differing

substitution in these regions. The proposed methods towards leustroducsin B, fostriecin, and cytostatin allow for developing analogs with differing substitution in these areas, particularly at the C(8) position in fostriecin and leustroducsin B, and the C(10) position in cytostatin. The method also allows for substitution of the triene tail with groups of similar lipophilicity and geometric disposition. It has been postulated that the triene tail is the culprit for degradation in the storage of fostriecin and cytostatin.[3,11]

The architecture and SAR of the above molecules have prompted our investigation of fostriecin, leustroducsin B, and analogs thereof, starting with our bicyclic phosphate system (*R*,*R*,P$_S$)-**2.1** (Scheme 2). The key feature in these planned syntheses revolved around a pivotal terminus differentiation strategy of the C_2-symmetric *anti*-diol (*R*,*R*)-**2.2** using a phosphate tether and RCM to derive (*R*,*R*,P$_S$)-**2.1**. This desymmetrization step serves to assemble, in a single step, the requisite

Scheme 2

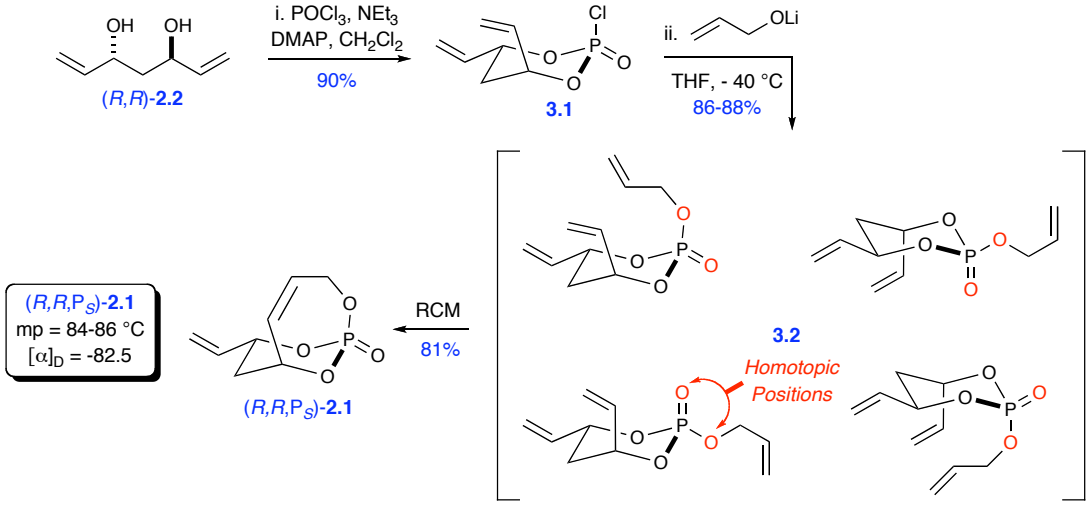


C(12)/C(13) Z-olefin, the C(7) terminal olefin armed for regioselective oxidation, and triol protection at the C(9), C(11), and C(14) carbinol centers. We deemed the potential fruits of such a synthetic investigation to be too enticing to overlook.

3.2 Selective Oxidation of the Exocyclic Olefin

Generation of the bicyclic phosphate required has been reported previously in our group.[14,15] Construction of *P*-chiral bicyclic[4.3.1]-phosphate triester (*R*,*R*,P$_S$)-**2.1** began with coupling of C_2-symmetric diene 1,3-diol (*R*,*R*)-**2.2**[16] with phosphoryl trichloride producing the pseudo-C_2-symmetric compound **3.1** possessing interchangeable, homotopic Cl and P=O groups. Concurrent addition of lithium allyloxide into phosphoryl monochloride **3.1** yields phosphate triester triene **3.2**. Ring-closing metathesis (RCM) using Grubbs second-generation catalyst[17] afforded desired phosphate (*R*,*R*,P$_S$)-**2.1** in good yield.

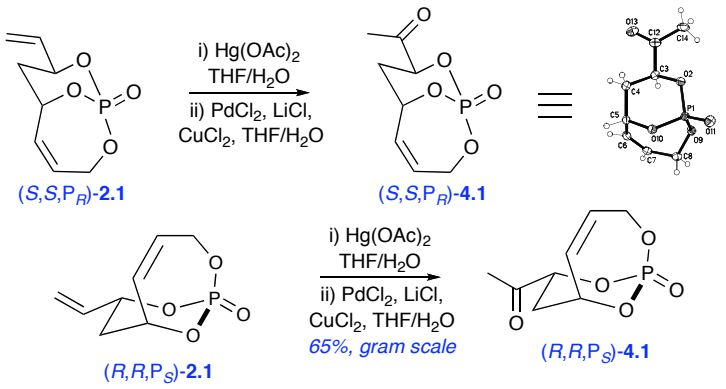
Scheme 3



Key to the formation of fostriecin and fostriecin-based libraries was the realization of an oxidation of the exocyclic olefin in bicyclic phosphate (*R*,*R*,P$_S$)-**2.1**.

Reactions under standard Wacker conditions,[18] however, for up to 12-16 hours resulted in complete recovery of starting material in 80-90% yield. This is turns out to be unsurprising, as protected allylic alcohols are known to be problematic,[19] if not completely unreactive, towards Wacker oxidation. Indeed, the electron withdrawing nature of the phosphate may prevent the necessary ligation of Pd^{II}. Upon rigorous investigation, it was found that employing modified-Wacker conditions[20,21,22] with bicyclic phosphate (S,S,P_R)-**2.1** provided initial yields of 40% of desired ketone (S,S,P_R)-**4.1**, whereby structural confirmation was achieved using X-ray crystallographic analysis. (Scheme 4). Optimization of this protocol utilizing (R,R,P_S)-**2.1** yields (R,R,P_S)-**4.1** in 65% yield on gram scale.

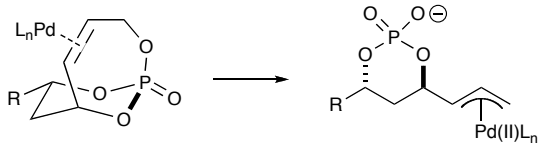
Scheme 4



The reaction was extremely time-dependent, where erring on either side of the optimal time[23] even slightly resulted in drastic losses in yield. It was also notable that while most transformations utilized warming of the mixture after $PdCl_2$ addition to achieve desirable yields, the oxidation of phosphate (R,R,P_S)-**2.1** was poor at temperatures above 40 ºC. A putative mechanism invoked[24] in this process involves oxymercuration of the substrate, followed by addition of cupric chloride and $PdCl_2$

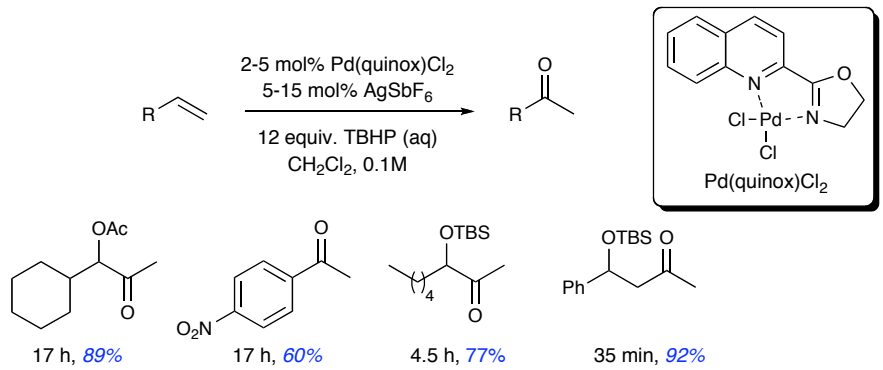
(traditional reagents utilized for the standard Wacker oxidation) whereby transmetallation allows for oxidation to the ketone. As the reaction is performed under strictly anaerobic conditions, cupric chloride is the terminal oxidant for the Pd^0 formed during oxidation of substrate. This same transient Pd^0 species is what we postulate to be the detrimental species in the formation of ketone (*R*,*R*,P_S)-**4.1** from (*R*,*R*,P_S)-**2.1** (Scheme 5); the intermediacy of Pd-allyl species formed from bicyclic phosphate (*R*,*R*,P_S)-**2.1** has been utilized in this lab in the generation of the northern hemisphere of the dolabelides.[25]

Scheme 5



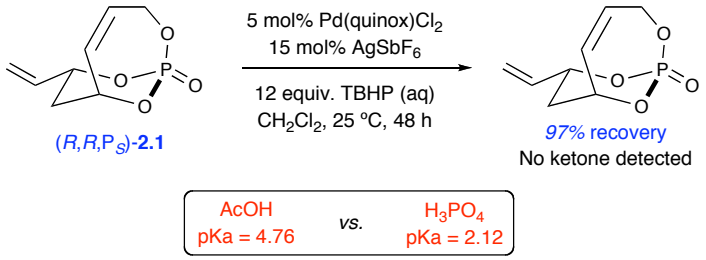
It was hypothesized that if a Pd^0 species could be avoided, several problems could be circumvented, namely: strict time dependence, large quantities of palladium, and starting material/product degradation. Investigation into several alternatives proved to be fruitless. Recently, however, hope for a catalytic process was resurrected by a Sigman group publication that described the conversion of protected allylic alcohols into acyloin products via a catalytic Pd complex[24] (Scheme 6). Not only did the catalyst avoid the use of mercuric salts altogether and involvement of a Pd^0 intermediate, the reaction proceeded with good yields on electron deficient protected allylic alcohols and with no loss of enantiomeric excess on chiral non-racemic substrates.

Scheme 6 *Sigman's Survey with Pd(quinox)Cl_2*



We enthusiastically employed the requisite conditions on our bicyclic phosphate (R,R,P_S)-**2.1** only to quantitatively recover starting material (Scheme 7). Attempts to attenuate the conditions to afford oxidized product, including heating the solution, yielded the same initial result. Comparison of the relative pKa's of acetic acid and phosphoric acid is illustrative, as the greater electron withdrawing nature of the phosphate appears to provide an inadequate alkene ligand for the Pd(quinox)Cl_2 complex upon which to engage.

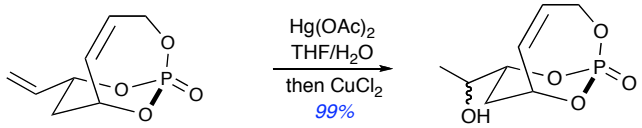
Scheme 7



While the use of mercury salts has not been circumvented as of yet, bypassing the use of large amounts of palladium was heralded by the observation that cupric chloride was demercurating the intermediate generated in the oxymercuration reaction. Initial attempts to perform the classical $NaBH_4$ demercuration led to

extensive degradation of the intermediate, thus leading to a reinterpretation of the mechanism of the modified Wacker oxidation. Rather than the transmetallation of mercury by palladium, simple addition of cupric chloride to the oxymercuration mixture could allow for rapid protonation, followed by slower Pd^{II} oxidation of the alcohol. The Pd^{II} oxidation of alcohols[26] utilizes similar conditions to the those utilized in the modified Wacker. This interpretation was bolstered by performing the experiment with the omission of $PdCl_2$, as depicted in Scheme 8, to provide a quantitative yield of the hydrated exocyclic olefin (**8.1**).

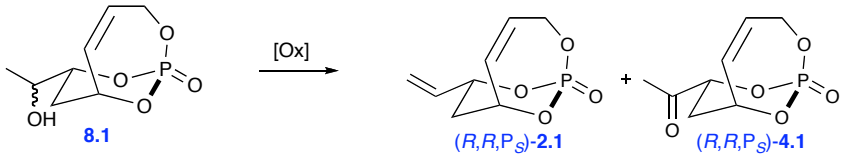
Scheme 8



(R,R,P_S)-**2.1** **8.1**

Noting this, the oxidation of alcohol **8.1** was screened using several different oxidation conditions detailed in Scheme 13. Initial attempts at using Swern oxidation conditions lead to exclusive dehydration to regenerate (R,R,P_S)-**2.1**. Dess-Martin periodinane with pyridine curiously also formed the dehydration adduct as the major product. Upon comparing pyridinium dichromate and pyridinium chlorochromate, the desired ketone was generated to a larger extent with PCC. These observations were the basis of the speculation that acidic media is more favorable so as to prevent elimination. Thusly, employing Jones reagent afforded the desired ketone (R,R,P_S)-**4.1** without an observable trace (by ^{1}H-NMR) of elimination product. It should also be noted that TPAP oxidation in acetonitrile also provided clean conversion to the ketone, albeit with longer reaction duration and with less facile purification.

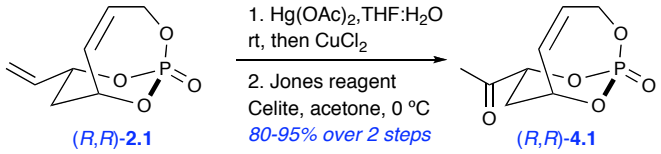
Scheme 9



$(COCl)_2$,DMSO, Et_3N	>95	<5
SO_3•pyr,DMSO, Et_3N	>95	<5
DMP, pyr	83	16
PDC	61	39
PCC	52	48
H_2CrO_4, acetone	<5	>95
TPAP, NMO	<5	>95

Currently, the most optimized conditions employ oxymercuration followed by addition of $CuCl_2$ to relinquish alcohol **8.1**, after which the solvent is removed and the crude alcohol is directly oxidized via Jones oxidation to provide (*R*,*R*,P$_S$)-**4.1** in gram scale affording yields of 80-95% (Scheme 10). Not only is the oxidation rapid, but purification involves simply passage of the crude mixture through a short silica plug to remove any associated metal ions. This protocol, while more robust than the palladium mediated route, also highlights the exquisite acid stability of the bicyclic

Scheme 10



phosphate system. As illustrated in Figure 1, lack of anti-periplanar (*app*) lone pairs in phosphate (*R*,*R*,P$_S$)-**2.1** imparts increased acid stability.[14,27] When oxygen lone pairs occupy *trans-app* to an adjacent polar bond (P-OR), they donate electron density from their lone pair orbital, n, to the antibonding P-O σ*, thus weakening the

P=O bond and increasing the basicity at O; conversely, lack of *app* lone pairs imparts orthogonal stability to hydrolysis with acid.[27]

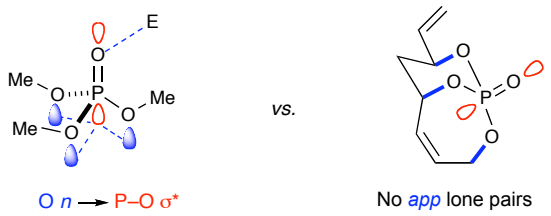
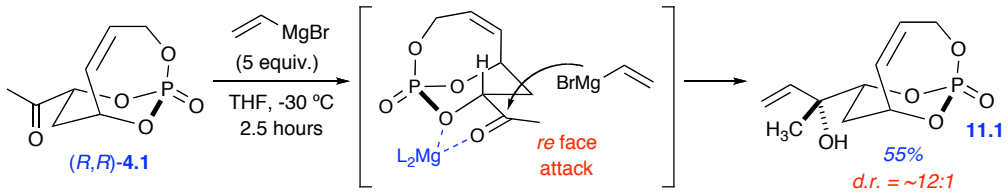


Figure 1: *Stereoelectronic effects within an acyclic phosphate vs. (S,S, P_R)-**2.1***

3.3 Probing a Diastereoselective Grignard Addition with the α-Ketophosphate

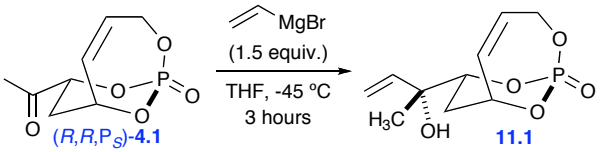
Realization of the exocyclic olefin oxidation of (*R*,*R*,P_S)-**2.1** allowed for investigation into a diastereoselective Grignard addition of vinyl magnesium bromide to yield tertiary alcohol **11.1** (Scheme 11). Previous models of analogous systems employing 1,2-stereoinduction under chelating conditions[28,29] provided strong precedent for such a selective addition. The vinyl group was chosen as both a handle for library development as well as possible employment in the total synthesis of fostriecin, where such a handle was anticipated to readily lend itself available to incorporation of diverse moieties via cross-metathesis. Initial attempts employing 5 equivalents of commercially available vinyl magnesium bromide at -30 ºC pleasingly provided the desired addition product **11.1**, where tentative assignment of the stereochemistry of alcohol **11.1** was made based upon the aforementioned precedent, in a ~12:1 ratio based on ^{31}P-NMR.

Scheme 11



Optimization of this key C8 stereocenter generation entailed investigating temperature, equivalents, and chelating additives to potentially enhance diastereoselectivity. The new, commercially obtained vinyl magnesium bromide appeared to perform best at -45 ºC in THF, as at lower temperatures the addition appeared to occur very sluggishly and at temperatures higher than -30 ºC attack at phosphorous appeared to compete. Illustrative to the screening of additives is the investigation of additional $MgBr_2 \bullet OEt_2$, detailed in Scheme 16. It was observed that increasing the equivalents of the chelation reagent appeared to decrease yields by forcing the already highly polar substrate out of solution, thus impeding addition.

Scheme 12

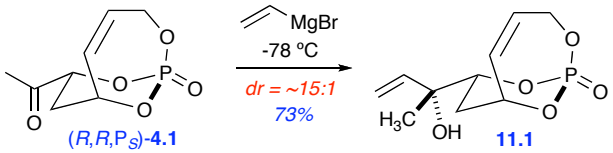


additive	yield
none	70%
1 eq $MgBr_2$	42%
3 eq $MgBr_2$	27%

Fortunately, based upon the difference in reactivity with certain substrates of commercial vinyl magnesium bromide versus freshly prepared vinyl magnesium bromide, we reinvestigated the addition utilizing freshly prepared vinyl magnesium bromide. A very different reactivity was observed; one of the first observations was that -45 ºC was too high of a temperature and that -78 ºC was optimal. This allowed

for diastereoselectivities of 15:1 (based on ^{31}P-NMR) and a greater recovery of unreacted starting material. While the yield was not significantly different, the presence of $MgBr_2 \bullet OEt_2$ did not prove to be detrimental unlike with commercial vinyl Grignard. Therefore, utilizing 3 equivalents of freshly prepared vinyl Grignard at -78 ºC for 7 hours provides 73% yield of tertiary alcohol **11.1** on gram scale (Scheme 13).

Scheme 13



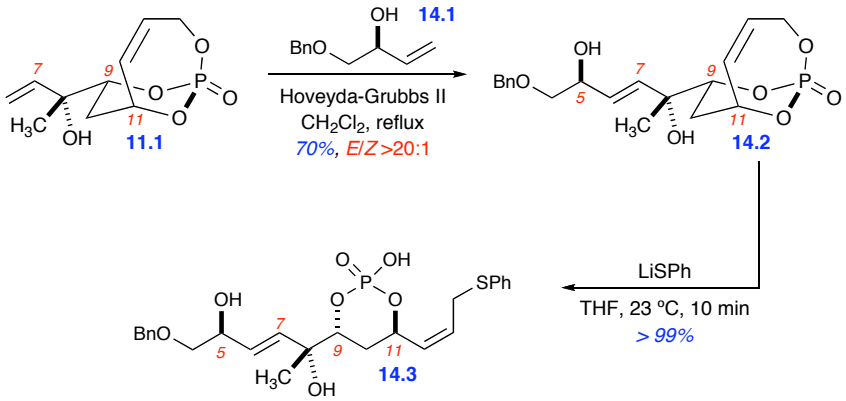
3.4 Generating the Fostriecin Core: Library Proof of Concept

The next task towards forming the fostriecin core was to engage the newly installed olefin of **11.1** in the aforementioned selective cross-metathesis. The reactive nature of the olefin generated, however, was in question, as previous explorations on the reactive nature of the exocyclic olefin in (*R*,*R*,P*S*)-**2.1** had concluded (*R*,*R*,P*S*)-**2.1** exhibited Type III olefin behavior.[15,30] While unprotected tertiary allylic alcohols are typified as exhibiting Type II reactivity, protected allylic alcohols are also classed as Type II olefins.[31] Given that the exocyclic olefin of (*R*,*R*,P*S*)-**2.1** is a protected allylic alcohol, it's Type III reactivity profile seems to deviate from a blanket assessment. The role the phosphate played in attenuating the reactivity of the unprotected tertiary alcohol of **11.1** was also at issue, an assessment that is elaborated upon in Chapter 4 (vide infra). At this stage of the investigation the olefin was believed to be Type III

given the electron withdrawing nature of the phosphate bearing carbinol in combination with the steric interactions presented by the bicyclic system.

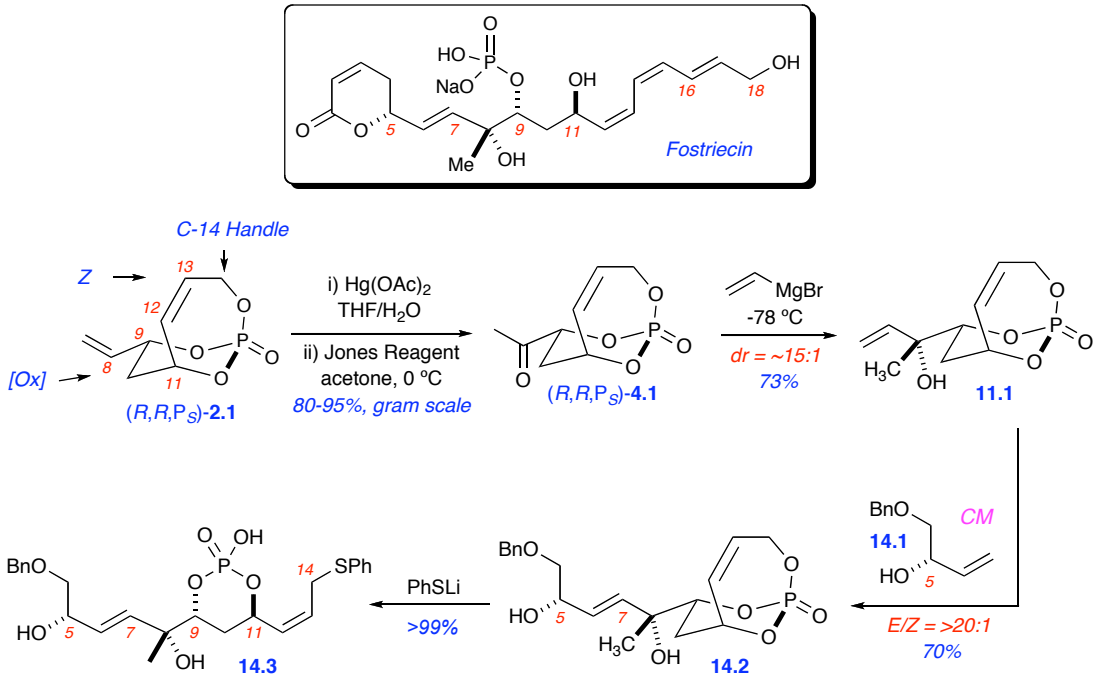
Nevertheless, employing 5 equivalents of glycidol-derived allylic alcohol **14.1** with phosphate **11.1** in the presence of 10 mol % Hoveyda-Grubbs II catalyst generates diol **14.2** with exquisite *E*/*Z* selectivity in 70% yield (Scheme 14).

Scheme 14



Subsequent attack of lithium thiophenol, as precedented by our earlier work,[14] exploits the orthogonal leaving group ability of the phosphate to reveal the requisite stereo-tetrad of fostriecin **14.3** in quantitative yield with a malleable C(14) handle. These results also solidify our proposed method in generation of a fostriecin-like library, and open the door for use in the synthesis of leustroducsin B.

3.5 Summary



An approach towards fostriecin and fostriecin-like libraries utilizing rapid functionalization of bicyclic phosphate (*R*,*R*,P*S*)-**2.1** was investigated. This compact, multifaceted core coupled with an array of selective reactive pathways begged the synthetic queries enacted. Key to unraveling and expanding upon this central core of the molecule was realization of an exocyclic olefin oxidation to generate (*R*,*R*,P*S*)-**4.1**. Diastereoselective Grignard addition yields **11.1**, where the source of Grignard used was found to play a non-trivial role. Selective cross-metathesis of the olefin of **11.1** with glycidol-derived allylic alcohol **14.1** generates diol **14.2** with exquisite *E*/*Z* selectivity in good yield. Subsequent attack of lithium thiophenol exploits the orthogonal leaving group ability of the phosphate to reveal the requisite stereo-tetrad of fostriecin **14.3** in quantitative yield. Not only does this sequence serve as a proof

of concept approach for the total synthesis of fostriecin, it also serves as an archetype for the generation of fostriecin-like and phoslactomycin-like libraries.

3.6 References:

(1) (a) Kafarski, P.; Lejczak, B. Aminophosphonic acids of potential medical importance. *Current Medicinal Chemistry: Anti-Cancer Agents* **2001**, *1*, 301-312. (b) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience, New York, 2000. (c) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids*; John Wiley & Sons, Inc.: New York, 2000. (d) Seto, H.; Kuzuyama, T. Bioactive natural products with carbon-phosphorus bonds and their biosynthesis. *Nat. Prod. Rep.* **1999**, *16*, 580-596. (e) Mader, M. M.; Bartlett, P. A. Binding Energy and Catalysis: The Implications for Transition State Analogs and Catalytic Antibodies. *Chem. Rev.* **1997**, *97*, 1281-1301. (f) Franz, J. E.; Mao, M. K.; Sikorski, J. A. *Glyphosate: A Unique Global Herbicide*; American Chemical Society: Washington, D. C., 1997. (g) Engel, R. *Handbook of Organo-phosphorus Chemistry*; Marcel Dekker, Inc.: New York, 1992. (h) Kafarski, P.; Lejczak, B. Biological activity of aminophosphonic acids. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193-215.

(2) Pinna, L. A.; Cohen, P. T. W. Inhibitors of Protein Kinases and Protein Phosphatases. *Handbook of Experimental Pharmacology* **2005**, *167*, preface pp V-VI.

(3) Honkanen, R. E. "Serine/Threonine Protein Phosphatase Inhibitors with Antitumor Activity" in Inhibitors of Protein Kinases and Protein Phosphatases. *Handbook of Experimental Pharmacology* **2005**, *167*, 295-317.

(4) Zolnierowicz, S. Type 2A Protein Phosphatase, the Complex Regulator of Numerous Signaling Pathways. *Biochem. Pharmacol.* **2000**, *60*, 1225-1235.

(5) Launey, T.; Endo, S.; Sakai, R.; Harano, J.; Ito, M. Protein phosphatase 2A inhibition induces cerebellar long-term depression and declustering of synaptic AMPA receptor. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 676-681.

(6) Kawada, M.; Kawatsu, M.; Masuda, T.; Ohba, S.; Amemiya, M.; Kohama, T.; Ishizuka, M.; Takeuchi, T. Specific inhibitors of protein phosphatase 2A inhibit tumor metastasis through augmentation of natural killer cells. *Int. Immunopharmacol.* **2003**, *3*, 179-188.

(7) Shimada, K.; Koishi, R.; Kohama, T. Leustroducsins, Low Molecular Weight Thrombopoietic Agents: Discovery, Biological Properties and Total Synthesis. *Annu. Rep. Sankyo Res. Lab.* **2004**, *56*, 11-28.

(8) (a) Koishi, R.; Serizawa, N.; Kohama, T. The effect of leustroducsin B on the production of cytokines by human mesenchymal cells. *J. Interferon Cytokine Res.* **1998**, *18*, 863-869. b) Koishi, R.; Yoshimura, C.; Kohama, T.; Serizawa, N. Leustroducsin B activates nuclear factor-κB via the acidic

sphingomyelinase pathway in human bone marrow-derived stromal cell line KM-102. *J. Interferon Cytokine Res.* **2002**, *22*, 343-350.

(9) Walsh, A. H.; Cheng, A.; Honkanen, R. E. Fostriecin, an antitumor antibiotic with inhibitory activity against serine/threonine protein phosphatases types 1 (PP1) and 2A (PP2A), is highly selective for PP2A. *FEBS Lett.* **1997**, *416*, 230-234.

(10) Buck, S. B.; Hardouin, C.; Ichikawa, S.; Soenen, D. R.; Gauss, C.-M.; Hwang, I.; Swingle, M. R.; Bonness, K. M.; Honkanen, R. E.; Boger, D. L. Fundamental Role of the Fostriecin Unsaturated Lactone and Implications for Selective Protein Phosphatase Inhibition. *J. Am. Chem. Soc.* **2003**, *125*, 15694-15695.

(11) Bialy, L.; Waldmann, H. Total Synthesis and Biological Evaluation of the Protein Phosphatase 2A Inhibitor Cytostatin and Analogues. *Chem. Eur. J.* **2004**, *10*, 2759-2780.

(12) Evidence of this interaction can be extrapolated from information on phoslactomycin A: Teruya, T.; Simizu, S.; Kanoh, N.; Osada, H. Phoslactomycin targets cysteine-269 of the protein phosphatase 2A catalytic subunit in cells. *FEBS Lett.* **2005**, *579*, 2463-2468.

(13) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. Catalyst-Controlled Asymmetric Synthesis of Fostriecin and 8-*epi*-Fostriecin. *J. Am. Chem. Soc.* **2005**, *127*, 17111-17117.

(14) Whitehead, A.; McReynolds, M.D.; Moore, J.D.; Hanson, P. R.; Multivalent Activation in Phosphate Tethers: A New Tether for Small Molecule Synthesis. *Org. Lett.* **2005**, *7,* 3375-3378.

(15) Waetzig, J. D.; Hanson, P. R. Temporary Phosphate Tethers: A Metathesis Strategy to Differentiated Polyol Subunits. *Org. Lett.* **2006**, *8*, 1673-1676.

(16) Following the protocol of Rychnovsky and co-workers, we have synthesized **2.2** on a 100-g scale starting from 2,4-pentanedione; see: Rychnovsky, S. D.; Griesgraber, G.; Powers, J. P. *Org. Synth.* **2000**, *77*, 1-11.

(17) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

(18) Tsuji, J. Addition Reactions with Formation of Carbon-Oxygen Bonds: (iv) The Wacker Oxidation and Related Reactions. In *Comprehensive Organic Synthesis, Vol. 7*, Trost, B. M.; Fleming, I.; Ley, S. V., Eds., Pergamon: New York, 1991, pp. 449-468.

(19) Muzart, J. Aldehydes from Pd-catalyzed oxidation of terminal olefins. *Tetrahedron* **2007**, *63*, 7505-7521.

(20) Rodeheaver, G. T.; Hunt, D. F. Conversion of Olefins into Ketones with Mercuric Acetate and Palladium Chloride. *J. Chem. Soc., Chem. Commun.* **1971**, 818-819.

(21) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. Total Synthesis of Sarcodictyins A and B. *J. Am. Chem. Soc.* **1998**, *120*, 8661–8673.

(22) Crimmins, M. T.; Brown, B. H.; Plake, H. R. An Intramolecular Diels-Alder Approach to the Eunicellins: Enantioselective Total Synthesis of Ophirin B and Astrogorgin. *J. Am. Chem. Soc.* **2006**, *128*, 1371-1378.

(23) The optimal time was typically 1 hour, however this varied with each reaction such that rigorous monitoring of the reaction (i.e. 5 minute intervals) after addition of $PdCl_2$ was necessary to afford the highest yields.

(24) Michel, B. W.; Camelio, A. M.; Cornell, C. N.; Sigman, M. S. A General and Efficient Catalyst System for a Wacker-Type Oxidation Using TBHP as the Terminal Oxidant: Application to Classically Challenging Substrates. *J. Am. Chem. Soc.* **2009**, *131*, 6076-6077.

(25) Waetzig, J. D.; Hanson, P. R. A Multifaceted Phosphate Tether: Application to the C1−C14 Subunit of Dolabelides A−D. *Org. Lett.* **2008**, *10*, 109-112.

(26) For recent reviews covering palladium mediated alcohol oxidations, see: (a) Muzart, J. Palladium-catalyzed oxidation of primary and secondary alcohols. *Tetrahedron* **2003**, *59*, 5789-5816. (b) Arends, I. W. C. E.; ten Brink, G.-J.; Sheldon, R. A. Palladium-Neocuprine catalyzed aerobic oxidation of alcohols in aqueous solvents. *J. Mol. Catal. A.: Chem.* **2006**, *251*, 246-254. (c) Schultz, M. J.; Sigman, M. S. Recent advances in homogeneous transition metal-catalyzed aerobic alcohol oxidations. *Tetrahedron* **2006**, *62*, 8227-8241.

(27) (a) Deslongchamps, P. Stereoelectronic Effects In Organic Chemistry; Pergamon Press: Oxford, **1983**. (b) Vande Griend, L. J.; Verkade, J. G.; Pennings, J. F. M.; Buck, H. M. Structure-Basicity Relations Among Phosphate and Phosphite Esters. CNDO/2 and Protonation Studies. *J. Am. Chem. Soc.,* **1977**, *99*, 2459-2463.

(28) (a) Overman, L. E.; Lin, N.-H. Enantioselective Total Synthesis of (+)-Pumiliotoxin A. *J. Org. Chem.* **1985**, *50*, 3669-3670. (b) Ramachandran, P. V.; Liu, H.; Reddy, M. V. R.; Brown, H. C. Synthesis of Homoallylic Chiral Tertiary Alcohols via Chelation-Controlled Diastereoselective Nucleophilic Addition on α-Alkoxyketones: Application for the Synthesis of the C_1-C_{11} Subunit of 8-*epi*-Fostriecin. *Org. Lett.* **2003**, *5*, 3755-3757.

(29) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B.T. Dinuclear Asymmetric Zn Aldol Additions: Formal Asymetric Synthesis of Fostriecin. *J. Am. Chem. Soc.* **2005**, *127*, 3666-3667.

(30) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

(31) The assignments of olefins, Type I, II and III, were based on reactivity patterns with Type I being the most active. Although, Type I olefins readily homo-dimerize, they are capable of undergoing CM via homo-dimer or monomer pathways. Type II olefins are characterized by slow homo-dimerization and once homo-dimerized the species is sluggish to further metathesis. Type III olefins, such as isobutylene, do not homo-dimerize but do participate in cross-metathesis with more reactive olefin partners. Type IV olefins are spectators to cross-metathesis, not participating in the reaction. See reference 30.

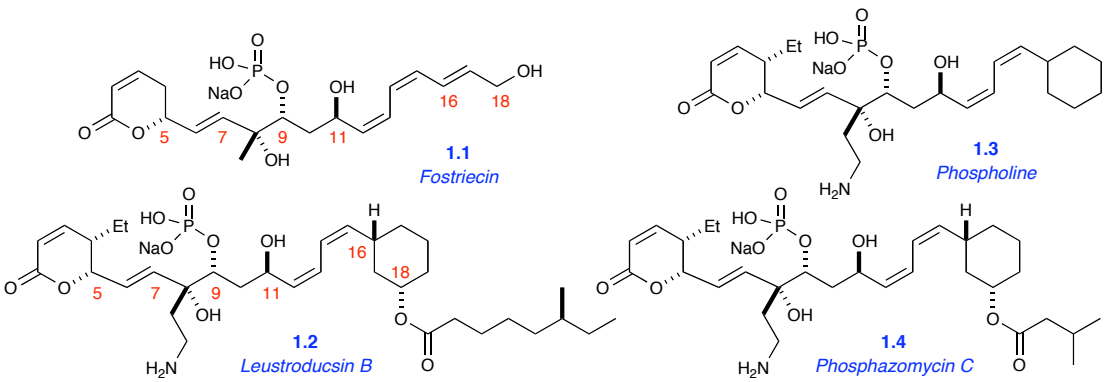
Chapter 4

Phosphate Tethers in Synthesis:
Routes Towards Fostriecin through Cross Metathesis Investigations

4.1 Introduction

Fostriecin (**1.1**, CI-920, Scheme 1) is a biologically potent metabolite first isolated from *Streptomyces pulveraceus* in 1983 by workers at Warner Lambert-Parke Davis.[1] It displays in vitro activity against a broad range of cancerous cell lines including lung cancer, breast cancer, and ovarian cancer,[2] as well as in vivo antitumor activity. In addition, fostriecin has demonstrated activity against leukemia (L1210, IC_{50} 0.46 μM and P338).[3] Its mode of action appears to operate via an inhibitory pathway of the mitotic entry checkpoint. Evidence of this pathway is shown in fostriecin's potent and selective inhibition of a number of protein phosphatases.[4,5] In 1997, Boger and coworkers determined the relative and absolute stereochemistry in fostriecin that confirmed previous assignments in a family of biologically active and structurally related natural products, including leustroducsin B (LSN-B, **1.2**), phospholine (**1.3**), and phosphazomycin C (**1.4**).[6]

Scheme 1 *Fostriecin and members of the phoslactomycin family*



Leustroducsin B (LSN-B) was originally purified as a colony-stimulating factor inducer from the broth of *Streptomyces platensis* by Sankyo in 1993 and has been shown to exhibit a variety of biological activities.[7] Shibata and coworkers

determined the absolute configuration of leustroducsin H (LSN-H) in 1995,[8] which allowed Matsuhashi in 2002 to confirm the absolute configuration of LSN-B via the chemical transformation of LSN-H.[9] In vivo, leustroducsin B has been found to increase host resistance against *Escherichia coli* in addition to inducing thrombocytosis in mice. In vitro activity has been shown to induce granulocyte-CSF and granulocyte-macrophage-CSF production by KM-102 cells. Recent studies have suggested that LSN-B induces cytokine production via NF-κB activation at the transcriptional and post-transcriptional levels.[10] In 2003, Fukuyama and coworkers reported the first total synthesis of leustroducsin B, achieving this pioneering synthesis in 46-linear steps.[10] More recently, Imanishi and coworkers achieved the total synthesis of leustroducsin B in 2008.[11]

Since the first total synthesis by Boger and coworkers in 2001,[12] several total syntheses[13] and synthetic studies[14] have been reported for fostriecin. In 2001 Jacobsen completed the total synthesis of fostriecin in 17 steps, highlighted by the use of a Cr-catalyzed hetero-Diels-Alder followed by a zirconium mediated addition to a chiral epoxy aldehyde to set three of the four stereocenters in >99% ee.[13a] Imanishi's 2002 synthesis utilized Horner-Wadsworth-Emmons chemistry and Stille coupling to complete the total synthesis in 24 linear steps.[13c,e] More recently in 2005, Trost completed dephospho-fostriecin in 14 linear steps employing a direct asymmetric Zn-catalyzed aldol reaction,[15] while Shibasaki's formal synthesis utilized four asymmetric catalysts to set the four stereogenic centers.[16,17]

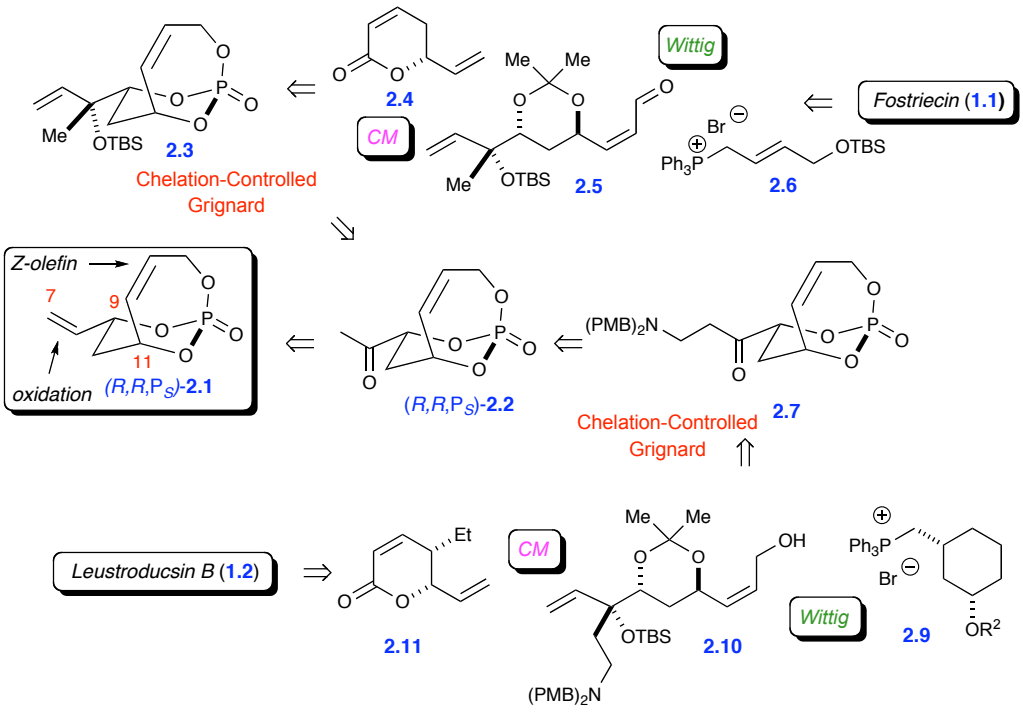
Key structural features in this class include a C(1)-C(5) α,β-unsaturated δ-lactone, a central anti-1,3-diol moiety at C(9)/C(11), a C(8) tertiary carbinol stereocenter, a C(9) phosphate, a *Z,Z,E*-triene subunit extending from C(12)-C(17) in fostriecin (**1.1**), and the corresponding *Z,Z*-diene subunit extending from C(12)-C(15) in LSN-B (**1.2**), **1.3**, and **1.4**. In addition, a C(8)-β-ethyl amine functionality and added complexity of a C(16)-1,3-disubstituted cyclohexyl system in LSN-B pose formidable synthetic challenges. We are proposing the utilization of versatile bicyclic phosphate (*R*,*R*,P_S)-**2.1** for the total syntheses of leustroducsin B (**1.2**), fostriecin (**1.1**) and potential analogs (Scheme 2).

4.2 Retrosynthetic Analysis of Fostriecin and Leustroducsin B

The key feature in these highly convergent syntheses revolves around a pivotal terminus differentiation strategy of the C_2-symmetric *anti*-diol (3*R*,5*R*)-hepta-1,6-diene-3,5-diol using a phosphate tether and RCM to derive (*R*,*R*,P_S)-**2.1**. This desymmetrization step serves to assemble in a single step the requisite C(12)/C(13) *Z*-olefin, the C(7) terminal olefin armed for regioselective oxidation, and triol protection at the C(9), C(11), and C(14) carbinol centers. Additional features include a late-stage installation of the α,β–unsaturated δ-lactone moiety and setting the C(6)/C(7) *E*-configured olefin utilizing a critical CM coupling between the central 1,3-*anti*-diol subunits in **2.5** and **2.10** (assessed as Type III CM partners)[18] and **2.4** and **2.11** (assessed as Type II CM partners). Wittig olefination of the aldehyde **2.5** with the ylide of **2.6**, or of **2.10** with the ylide of phosphonium salt **2.9**, would install the eastern side-chains, respectively. A key diastereoselective vinyl Grignard addition

into ketophosphates **2.2** and **2.7** using literature precedence will set the C(8) tertiary carbinol center and insert a "vinyl linchpin" residing in **2.3** or **2.10** for subsequent CM. This addition is preceded by C(8) sidechain installation relying on regioselective oxidation of (*R*,*R*,P$_S$)-**2.1** using a oxidation/enolization/CM sequence to derive ketone **2.7**. Overall, this highly convergent pathway (Plan A) encompasses an 16 linear-step sequence to fostriecin and 19 linear-step sequence to leustroducsin B, applicable to other members in this family and unnatural analogs.

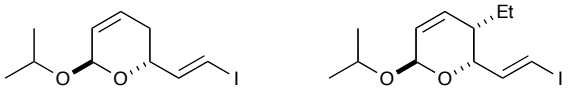
Scheme 2 *Retrosynthesis of fostriecin (***1.1***) and leustroducsin B (***1.2***) via CM*



Another possible route (Plan B) involved installation of the lactone at an earlier stage via a diastereoselective Grignard addition of isopropyl-protected lactols **3.1** and **3.2** (Scheme 3). The most notable change in the synthetic sequence would be generation of the lactone via the lactol in the latter part of the synthesis versus cross-metathesis installation of the intact lactone. Such a secondary route was envisioned

to circumvent promiscuous reactivity of the lactone if such a phenomena was witnessed. The drawback to such a route appeared to be twofold: 1) the operational manner of the oxidation, as deprotection to the lactol prior to oxidation or direct oxidation of the protected lactol could potentially suffer from functional/protecting group compatibility issues that the cross-metathesis route avoids, and 2) the linearity of a route utilizing a protected lactol Grignard. As such, the former synthetic route (Plan A) was to be investigated in depth while plausibility of the latter route (Plan B) queried concurrently.

Scheme 3



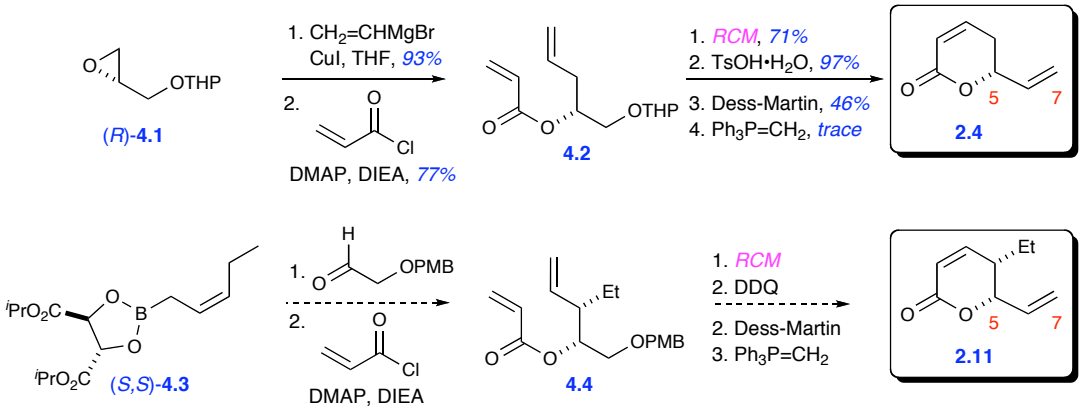
3.1 3.2

4.3 Generation of the Lactone Precursor and Organometallic Addition Studies

Generation of the western lactone portion of fostriecin was initially planned through use of the chiral, non-racemic glycidol ethers, with the lactone of leustroducsin B arriving from an analogous route (Scheme 4). Starting from (*R*)-THP-protected glycidol **4.1**, Grignard addition in the presence of CuI and acryloylation would derive diene **4.2**. Ring-closing metathesis, deprotection, Dess-Martin oxidation, and Wittig methylenation would afford lactone **2.4**. In a similar manner, asymmetric allylboration with (*S,S*)-tartrate-derived *Z*-crotylboronate[19] (*S,S*)-**4.3** would set the requisite C(4)/C(5) *syn* stereorelationship in lactone **2.11**. Coupling with acryloyl chloride presents diene **4.4** which could be followed by subsequent RCM as demonstrated by Cossy.[14a] Deprotection with DDQ, Dess-Martin oxidation,

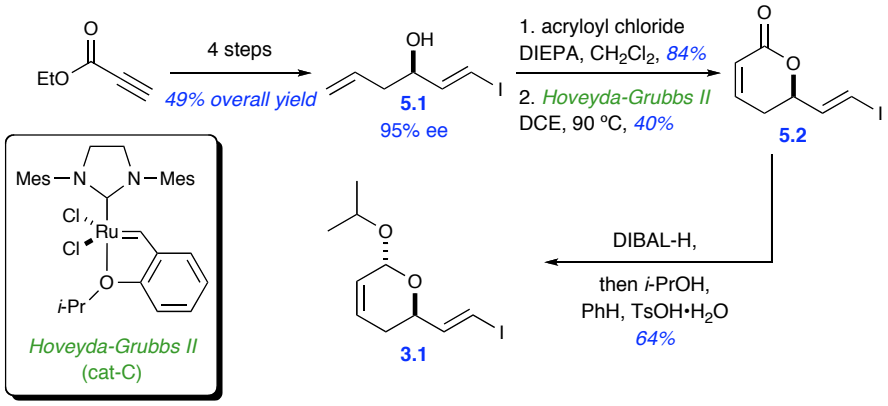
and Wittig olefination would then afford **2.11** in a concise 6-step sequence. In practice, the proposed route toward lactone **2.4** proceeded well prior to the oxidation/methylenation sequence, where the fugacious aldehyde formed via Dess-Martin oxidation provided a variety of products upon treatment with phosphonium ylide, with the desired olefin product only present in trace amounts.

Scheme 4



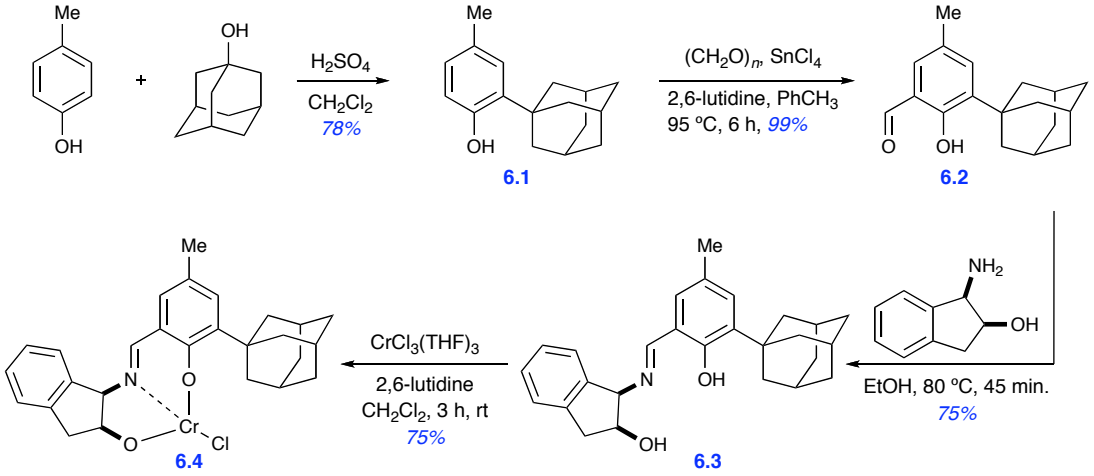
Initial attempts at generation of a protected lactol available for organometallic addition to the ketone were likewise problematic. Attempts to generate iodide **3.1** (Scheme 5) from Trost's (*R*,*E*)-1-iodohexa-1,5-dien-3-ol[15] (**5.1**) were set aside upon observation of reluctant ring-closing metathesis of the lactone in the presence of the vinyl iodide, where the solution turned black upon addition of Hoveyda-Grubbs II catalyst with apparent catalyst inactivation shortly thereafter. This inactivation and decomposition of starting material may be due to initial metathesis of the vinyl iodide providing a species capable of deactivating the metathesis catalyst.[20]

Scheme 5



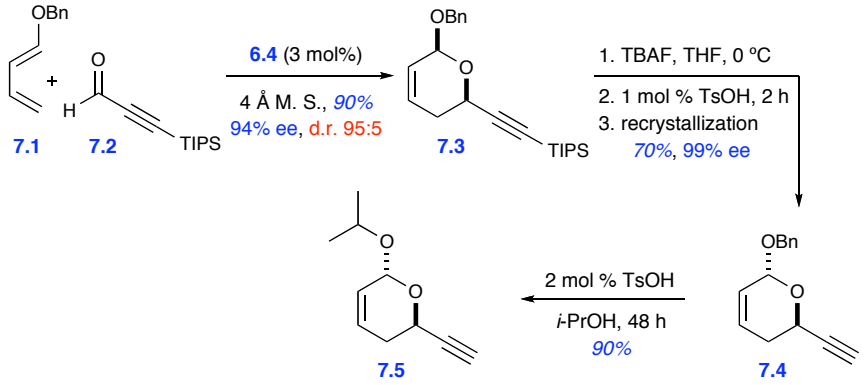
Reassessing the situation we saw an opportunity to capitalize on Jacobsen's hetero-Diels-Alder methodology[13,21] towards generating the desired cross metathesis and Grignard addition precursors for fostriecin.[22] Initiation of the synthetic sequence relied upon generation of the precatalyst, a process previously reported by the Jacobsen group.[21bc] Precatalyst preparation commenced through Friedel-Crafts adamantylation of *p*-cresol (Scheme 6). The 2-adamantyl-1-*p*-cresol (**6.1**) is then subjected to a net formylation via electrophilic addition of formaldehyde presumably with subsequent oxidation by excess formaldehyde through a Oppenauer-type oxidation.[23] The resulting aldehyde (**6.2**) is immediately condensed with (1*R*, 2*S*)-(+)-*cis*-1-amino-2-indanol to form ligand **6.3**. The active precatalyst **6.4** is formed by combination of ligand **6.3** with chromium(III) chloride:tris-THF complex.

Scheme 6



With the necessary precatalyst **6.4** in hand, formation of the desired lactol precursor[24] proceeded with a formal hetero-Diels-Alder annulation of diene **7.1**[25] and aldehyde **7.2**[26] (Scheme 7) to provide benzylated lactol **7.3** in high enantiomeric excess. Subsequent deprotection and epimerization of the anomer leads to terminal alkyne **7.4**, followed by conversion to the isopropyl acetal **7.5**.[27]

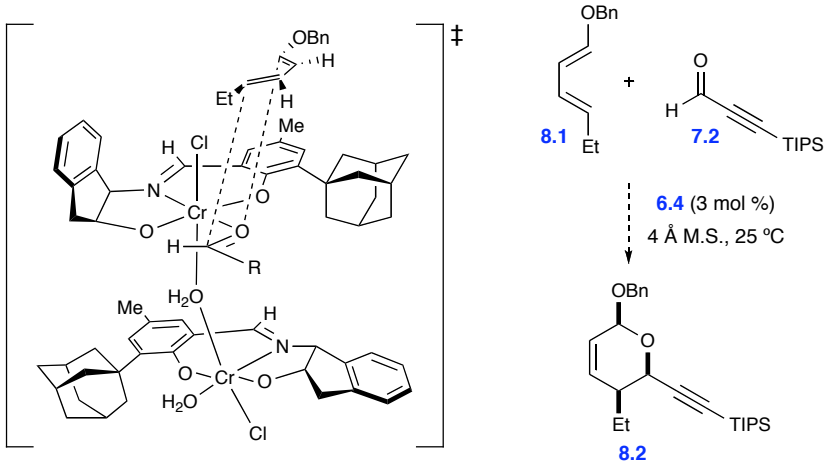
Scheme 7



Not only was **7.5** posited to be a versatile precursor for our studies towards the proposed synthesis of fostriecin, but application of the model for catalyst enantioselectivity with diene **8.1**[28] (Scheme 8) and aldehyde **7.2** foresaw application

towards leustroducsin B, hence discoveries made with lactol **7.5** were anticipated to be readily applicable towards leustroducsin B.

Scheme 8

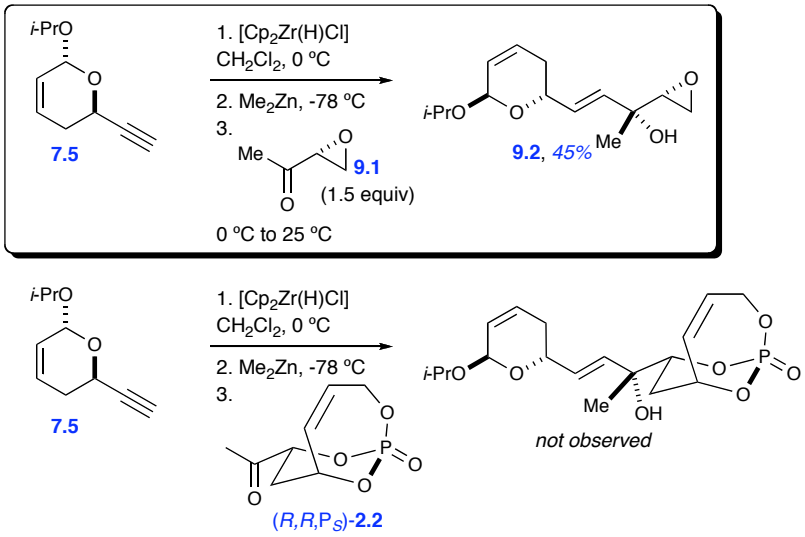


Investigations into organometallic addition thus started by attempting a similar direct hydrometallation of the terminal alkyne as performed by the Jacobsen group. This approach was predicated on Wipf's hydrozirconation[29]/zinc transmetallation protocol[30] for addition to aldehydes, where the Jacobsen group posited that the enhanced electrophilicity of the α-oxy ketone could exhibit enhanced reactivity in contrast to a typical ketone's unreactive nature. The Jacobsen group found that employing equimolar quantities of Schwartz's reagent, alkyne **7.5**, and Me_2Zn with 1.5 equivalents α-epoxyketone **9.1** at 25 ºC provided **9.2** in >30:1 diastereoselectivity and 45% yield (Scheme 9).[13a,24]

Prompted by the elegance of this direct approach and encouraged by the inertness of our monocyclic phosphates to dialkyl zinc species, we set forth to assess this method with regards to our exocyclic ketone **2.2**. We expected the α-phosphoryl oxygen of ketone **2.2** to exhibit a greater inductive withdrawing effect on the ketone,

if indeed such a rational was operative for this addition on our substrate. Attempts at applying this method to our bicyclic α-phosphoryl ketone **2.2** at a variety of temperatures and equivalents of hydrometallated alkyne **7.5** proved fruitless. At lower temperatures (< 0 ºC) no reaction was observed on the ketone, while temperatures above 0 ºC proceeded with attack of the organometallate on phosphorous without engaging the ketone.[31] While the phosphoryl oxygen may exhibit a greater inductive withdrawing effect on the ketone, the enhanced electrophilicity of the bicyclic phosphate (versus acyclic and our monocyclic systems) appears to outcompete any potential ketone addition.

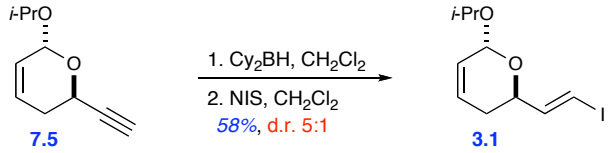
Scheme 9



Undaunted, the generation of a hydrometallated version of alkyne **7.5** was attempted via a stepwise approach. Initial trials utilized a hydroboration/iodination sequence to provide a species, iodide **3.1**, capable of lithium-halogen exchange in generating a more reactive hydrometallated variant as originally planned in retrosynthetic plan B (Scheme 10).[32] Hydroboration was attempted with

catecholborane, the Arase system employing catalytic dicyclohexylborane with catecholborane,[33] and with dicyclohexylborane[34] as the sole hydroboration reagent. It was found that the use of dicyclohexylborane exclusively provided the best yield following iodination, whereby subsequent iodination with either I_2 or *N*-iodosuccinimide (NIS) performed equally to form the requisite iodide **3.1**.

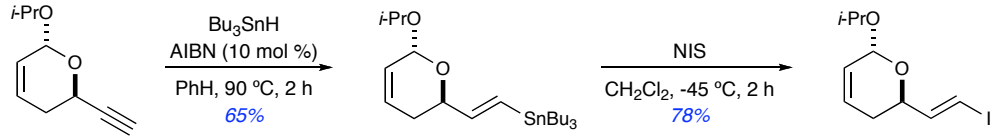
Scheme 10



7.5 3.1

Overall, the moderate selectivity of hydroboration on alkyne **7.5** and lackluster yield provided motivation for a different approach, where hydrostannylation could provide the necessary intermediate. Utilization of both radical[35] and Pd-mediated hydrostannylation[36] hydrostannylation protocols found that radical hydrostannylation provided the *E*-alkene **11.1** with the highest selectivity as a single observable geometric isomer (Scheme 11). Iodine/stannane exchange via NIS provided the desired *E*-iodide **3.1** in good yield with exquisite retention of geometric configuration.[37]

Scheme 11

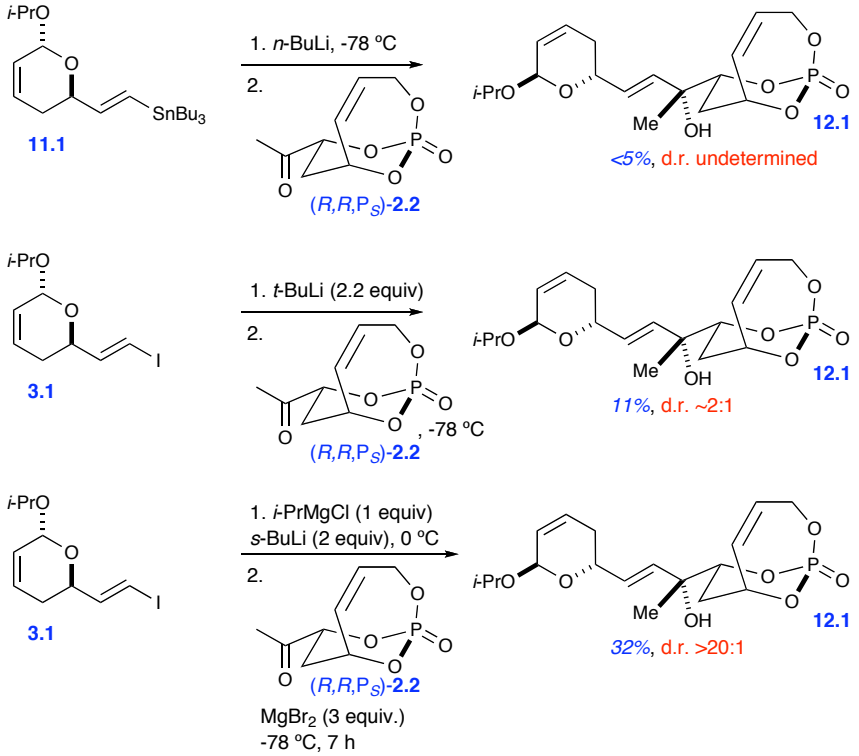


7.5 11.1 3.1

Both *E*-stannylalkene **11.1** and *E*-iodoalkene **3.1** were tested for their potential vinyl metal congeners to affect selective addition with ketone (*R*,*R*)-**2.2**. Direct lithiation of *E*-stannylalkene **11.1** by *n*-BuLi[38] provided poor metal exchange, an

uninspiring result especially when it was observed that the lithiated species derived reacted poorly (Scheme 12). In contrast, transmetallation of *E*-iodoalkene **3.1** proceeded smoothly when 2.2 equivalents of *t*-BuLi were employed.[39] The resulting vinyl lithium species, however, exhibited poor chemo- and diastereoselectivity. Utilizing a protocol developed by the Oshima group to generate a vinylmagnesium ate complex[40] for addition into ketones, *E*-iodoalkene **11.1** was transformed into magnesiate via addition of *E*-iodoalkene **11.1** to a mixture of 1 equivalent isopropylmagnesium chloride and 2 equivalents of *s*-BuLi in THF at 0 ºC. After exchange was assured, this solution was cooled to -78 ºC and subsequently cannulated into ketone (*R*,*R*,P_S)-**2.2** preincubated with freshly prepared $MgBr_2$.[41] While this produced the desired addition product **12.1** with excellent diastereoselectivity, significant problems associated with the solubility of ketone (*R*,*R*,P_S)-**2.2** with $MgBr_2$ and preferential addition of the magnesiate with the phosphate of **2.2** made this route unattractive. Indeed, the problems encountered utilizing commercial isopropylmagnesium chloride were almost identical to those observed when utilizing commercial vinylmagnesium bromide with ketone (*R*,*R*,P_S)-**2.2**, with the added detrimental phosphate addition attributed to the higher reactivity of the magnesiate versus Grignard.

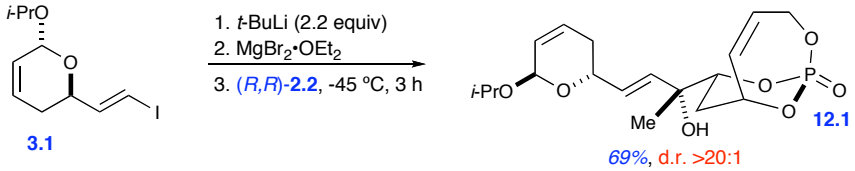
Scheme 12



Organometallic addition was achieved by conversion of *E*-iodoalkene **11.1** to the Grignard in a two-step process (Scheme 13). Lithium-halogen exchange with *t*-BuLi was followed by cannulation of the organolithium into $MgBr_2 \bullet OEt_2$ to form the corresponding Grignard. Subsequent cannulation into ketone **2.2** at -45 ºC provided addition adduct **12.1** as a single observable diastereomer in 69% yield. Bicyclic phosphate **12.1** presented a synthon with the correct stereotetrad and the carbocyclic skeleton of the lactone core in place. While this provided the necessary plausibility for retrosynthetic plan B, it was decided the coupling of the intact lactone core late stage as planned in retrosynthetic plan A was more convergent, easily amenable to modifications for advanced library development and leustroducsin B synthetic efforts, and would potentially avoid problems associated with lactone oxidation on an

advanced intermediate. It was this rational that initiated studies investigating the cross metathesis of the intact lactone core.

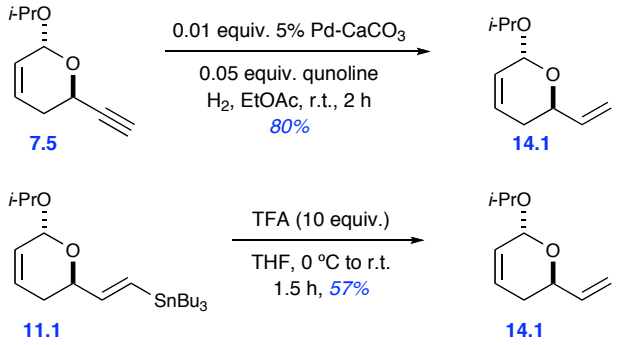
Scheme 13



4.4 Investigation of Lactone Installation Through Cross Metathesis

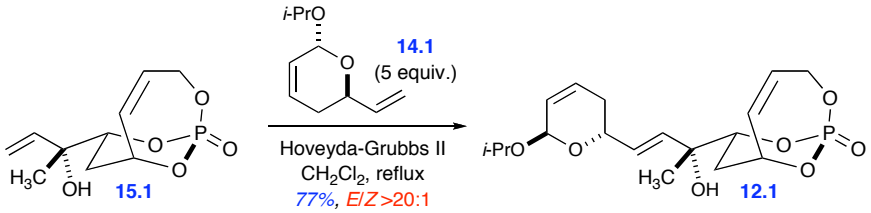
Formation of a lactone primed for cross metathesis (Plan A) began with conversion of the alkyne of **7.5** to an alkene. Preparation of the desired alkene was thought to be easily performed by a Lindlar hydrogenation of alkyne **7.5**, where Pd-$CaCO_3$ in the presence of freshly distilled quinoline in EtOAc under H_2 readily reduced the alkyne to alkene **14.1** in 80% yield on gram scale (Scheme 14). It is worth noting that allowing the reaction to proceed longer than 2 hours led to over hydrogenation of the exocyclic portion while the endocyclic olefin remained intact. At scales smaller than 1 gram poorer yields were obtained, with mixtures of over hydrogenated product, remaining starting material, and product necessitating tedious separation of the chromatographically similar compounds. In an attempt to access **14.1** on smaller scales and to avoid this dilemma, a separate protocol was developed where stannane **11.1** was protodemetallated with TFA at 0 ºC in THF to cleanly generate alkene **14.1**, however with modest yields. Nevertheless, the investigation proved fruitful toward the siphoning of material from retrosynthetic route B to route A, vide infra.

Scheme 14



Cross metathesis of the protected lactol **14.1** with tertiary alcohol **15.1** was performed to assess the viability of the coupling, where protected lactol **14.1** was added in five-fold excess to tertiary alcohol **15.1** with 10 mol % Hoveyda-Grubbs II catalyst (Scheme 15). Phosphate **12.1** was pleasingly provided in 77% yield with excellent selectivity for the *E*-isomer. Based on this unoptimized success, generation of the central segment of fostriecin was probed with concurrent investigations into the oxidation of alkene **14.1**.

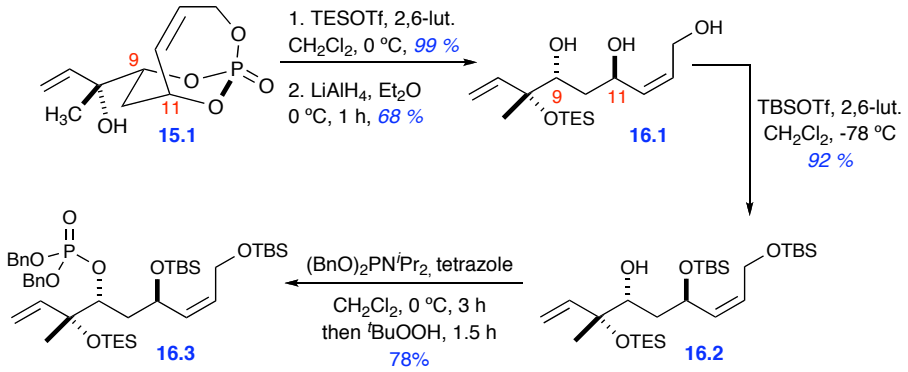
Scheme 15



Formation of the central segment of fostriecin proceeded from phosphate **15.1**, which itself arrives from selective manipulation of bicyclic phosphate (*R*,*R*,P*S*)-**2.1** as described in Chapter 3. The tertiary alcohol of phosphate **15.1** was protected as the TES ether generating **2.3** prior to phosphate tether removal[42] to provide monoprotected tetraol **16.1** (Scheme 16). Utilizing precedent set by Hatakeyama,[13d] the monoprotected tetraol **16.1** was selectively bis-protected at -78 ºC to afford

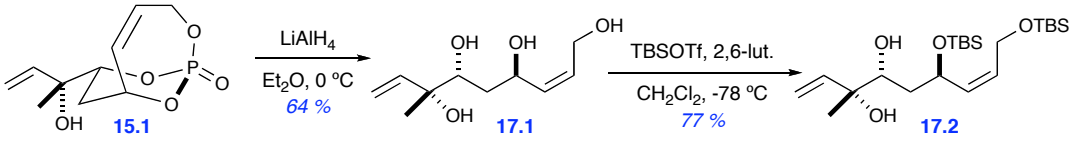
alcohol **16.2**, whereby the C9 alcohol was left untouched. From this differentiated synthon, phosphate **16.3** was generated by employing dibenzyl *N*,*N*-diisopropyl phosphoramidite and subsequent *tert*-butyl hydroperoxide oxidation. This sequence cleanly generated the core of fostriecin complete with phosphate and primed for cross metathesis.

Scheme 16



We concurrently generated the unprotected tertiary alcohol variant of alcohol **16.2** through an analogous route, where phosphate **15.1** was directly subjected to $LiAlH_4$-mediated phosphate tether cleavage to afford tetraol **17.1** (Scheme 17). Utilizing the same bis-protection protocol developed in the previous reaction series, selectively bis-protected tetraol **17.2** was produced to examine reactivity differences between **17.2**, alcohol **16.2**, and acyclic phosphate **16.3**.

Scheme 17



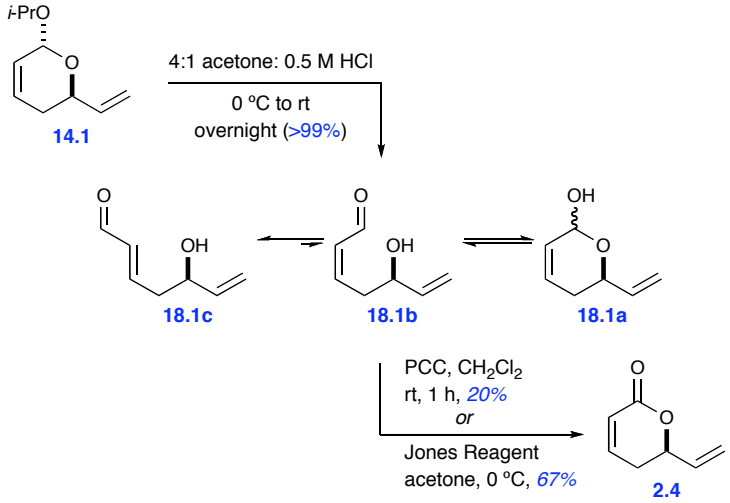
The investigation of the C9 DMB protected alcohol was also envisioned, as the DMB group could serve a role in late stage installation of the phosphate should

unforeseen modifications to the planned route prohibit early inclusion. Investigations were halted due to two observations: 1) attempts to protect the alcohol with the DMB group either yielded no reaction or extensive migration of the silyl groups under basic conditions, and 2) attempts to utilize the DMB and PMB groups in previous routes[13a,15] curiously converted the protecting group to another species without comment (adding steps) or removed it prior to triene formation. While the DMB group had been utilized by Yamada to avoid degradation of the α,β,γ,δ-unsaturated lactone upon deprotection in the synthesis of aplyronines A, B, and C,[43] the unwritten prose of previous synthetic efforts indicated that the deprotection conditions were detrimental to the triene of fostriecin.

Synthesis of the necessary cross metathesis partner involved exploring routes towards the oxidation of the protected lactol. Initially, it was believed deprotection of alkene **14.1** to lactol **18.1a** would allow for facile oxidation to lactone **2.4** (Scheme 18). Acidic deprotection of the isopropyl group provided deprotected **18.1a** and a mixture of acyclic *E* (**18.1c**) and *Z* (**18.1b**) isomers at the internal olefin.[44] It was posited that Lewis and/or Bronsted acids should help interconvert the olefin, with generation of the *Z*-isomer allowing conversion of the acyclic aldehyde **18.1b** to lactol **18.1a** whereby oxidation to desired lactone **2.4** would shift the overall equilibrium, ultimately allowing for reclamation of the *E*-isomer to generate desirable yields of lactone **2.4**. In practice, mildly Lewis acidic (Fétizon's reagent, MnO_2) and Bronsted acidic (PCC) oxidizing agents failed to appreciably convert the *E*-isomer

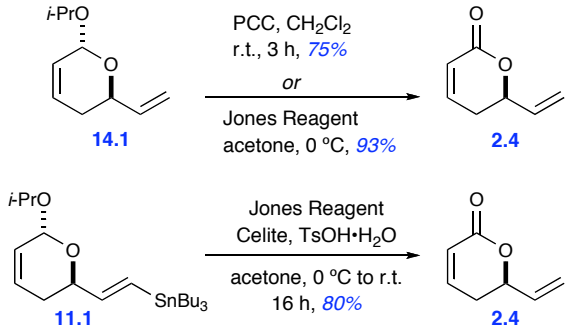
into lactone **2.4**. Employing Jones reagent, however, allowed for interconversion and afforded significantly better yields of lactone **2.4**.

Scheme 18



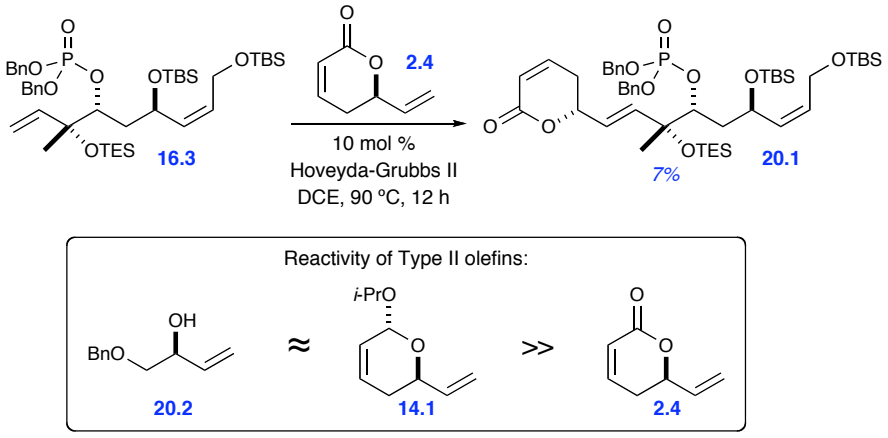
Avoiding the generation of lactol **18.1a** allowed for PCC to directly oxidize isopropyl protected lactol **14.1** (Scheme 19) in similarly good yields with some acyclic *E*-isomeric products present,[45] but direct oxidation of protected lactol **14.1** to lactone **2.4** by Jones reagent was clearly the desired route, affording product in 93% yield with very facile purification. In addition, it was found that vinyl stannane **11.1** could also be directly converted to lactone **2.4** through the Jones oxidation in 80% yield when additional *p*-toluenesulfonic acid was present, thereby presenting a route to lactone **2.4** from alkyne **7.5** on scales less than 1 gram (with respect to alkyne **7.5**).

Scheme 19



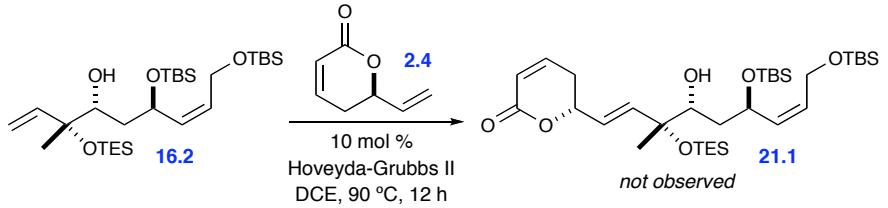
With lactone **2.4** in hand, attention turned to the desired direct cross metathesis with the central fostriecin core to append the western segment (Scheme 20). Cross metathesis of the assessed Type II lactone **2.4** with assigned Type III phosphate **16.3** utilizing 10 mol % Hoveyda-Grubbs II catalyst provided the desired coupling product **20.1** in good selectivity for the *E*-olefin isomer but in very dismal yield, a result that could not be improved despite changes in solvent, concentration and catalyst. While phosphate **16.3** was readily reclaimed, only scant traces of dimerized lactone were noticed. Given the conditions employed, if lactone **2.4** was a Type II olefin such as glycidol-derived allylic alcohol **20.2** or alkene **14.1**,[46] then large amounts of dimerized product should be observed.[47] Thusly, lactone **2.4** was concluded to be a sluggish Type II olefin as it ultimately did cross-metathesize and dimerize, albeit over long periods of time.

Scheme 20



It was suspected that the highly electron withdrawing nature of the α-phosphate of **16.3** may be reducing the reactivity of the olefin, providing our uninspiring yields. To test this, alcohol **16.2** was subjected to metathesis with lactone **2.4**, however at this stage no desired reaction product (**21.1**) was observed. Additionally, reclamation of alcohol **16.2** was poor as the substrate appeared to undergo olefin migration and elimination reactions to yield a convoluted variety of degradation products. It appeared the phosphate was not the problem, but rather was protecting the alcohol from participating in deleterious side reactions with the catalyst over the long reaction time.

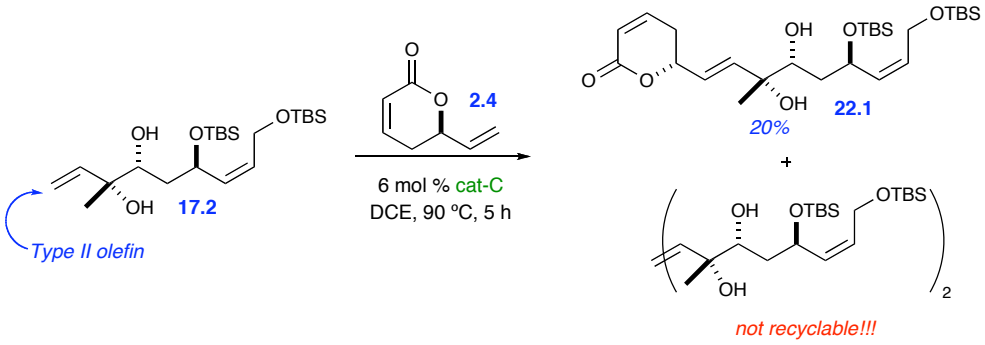
Scheme 21



Enhanced reactivity was surmised to occur by changing most proximal environment to the olefin by utilizing diol **17.2**. The unprotected tertiary allylic

alcohol **17.2** is a Type II olefin, and it was postulated reaction of **17.2** with excess lactone **2.4** should provide us with a better coupling of the western and central segments (Scheme 22). Empirically, however, it was found that only a slightly better coupling product **22.1** was observed, with the notable disadvantage that **22.1** co-elutes with lactone **2.4**. While dimerized **17.2** was initially thought to be recyclable, re-investigation of Grubbs seminal publication[18] on cross metathesis types found that tertiary allylic alcohols, while Type II, are unique in that the dimers are Type IV and therefore unavailable for recycling.

Scheme 22



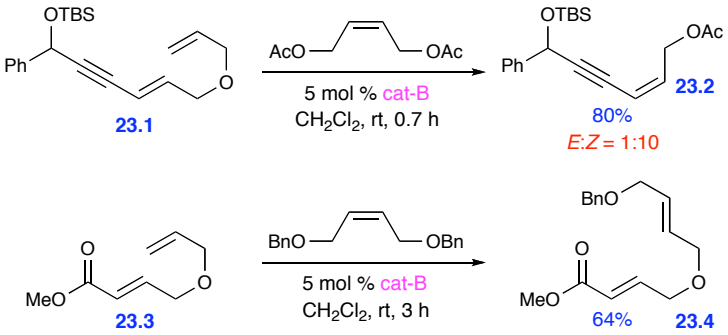
The newly acquired data previously outlined necessitated a reassessment of lactone **2.4** and the coupling method. At the outset of the investigations, we were apprehensive of the lactone, concerned with potentially promiscuous reactivity. On the contrary, the lactone was very stable to storage and appeared to show reluctant reactivity in cross metathesis, likely a result of the inductively withdrawing endocyclic α-oxygen of the lactone on the alkene. The reactivity starkly contrasted isopropyl protected lactol **14.2** in metathesis, a classical Type II olefin, such that the lactone was a near Type III olefin. Forming the necessary alkylidene seemed to be the issue; if initiation of metathesis on either the reluctant Type II lactone **2.4** or the

Type III terminal olefin in **16.3** (or potentially **16.2**) could be realized, an effective coupling could be affected.

4.5 Investigation of Lactone Installation via Relay Cross Metathesis

Relay metathesis appeared to be a plausible route towards resolving this predicament. While the majority of relay metathesis cases providing enhanced reactivity/product formation involve intramolecular cyclizations,[48] reports on relay cross metathesis are extremely sparse.[49] In Lee's investigation, conjugated enynes such as **23.1** efficiently underwent cross-metathesis with (*Z*)-but-2-ene-1,4-diyl diacetate (Scheme 23). Application of the same concept to afford a formal methacrylate cross-metathesis, though, found exclusive cross metathesis at the terminal olefin to produce **23.4** without catalyst delivery to form the enoate alkylidene. Performing the same reaction without external alkene allowed for the formation of methacrylate, thus indicating the cross-metathesis with (*Z*)-1,4-bis(benzyloxy)but-2-ene occurred at a significantly greater rate than the intramolecular metathesis event.

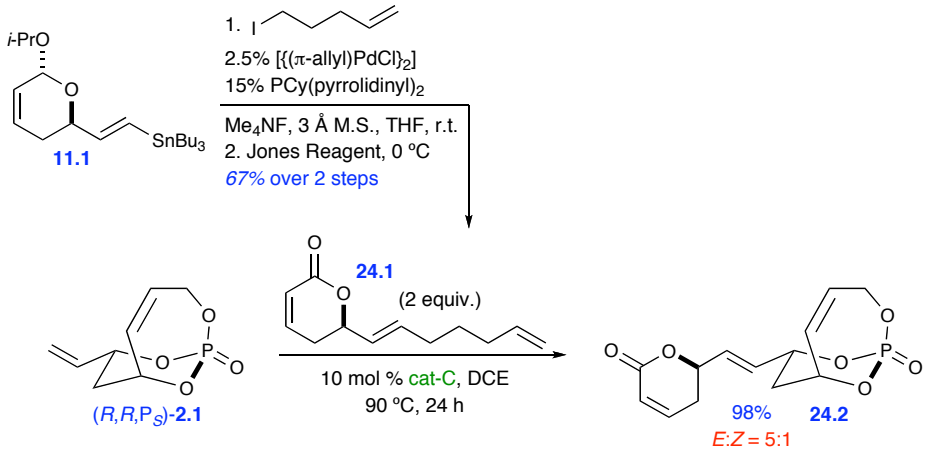
Scheme 23



The quandary of deciding upon either the modification of lactone **2.4** or phosphate **16.3** by a catalyst delivery vehicle was left to an empirical resolution.

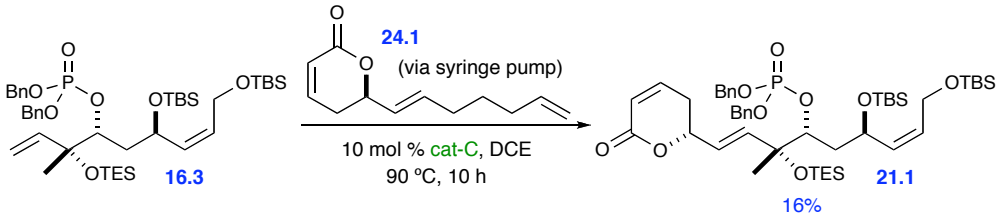
Lactone **2.4** was first to be tested, as we postulated that a Fu sp^2-sp^3 coupling[50] between vinyl stannane **11.1** and 5-iodopentene could readily modify the western segment towards formation of the desired relay lactone **24.1** (Scheme 24). Implementation of this protocol readily afforded lactone **24.1**, which was initially tested with phosphate (*R*,*R*,P_S)-**2.1** (a Type III olefin) to determine if our supposition had merit. The relay cross metathesis exceeded our expectations when the unoptimized reaction returned phosphate **24.2** quantitatively in a respectable ratio of geometric isomers, a pleasing contrast to attempting the reaction without the assistance of a catalyst delivery vehicle.

Scheme 24



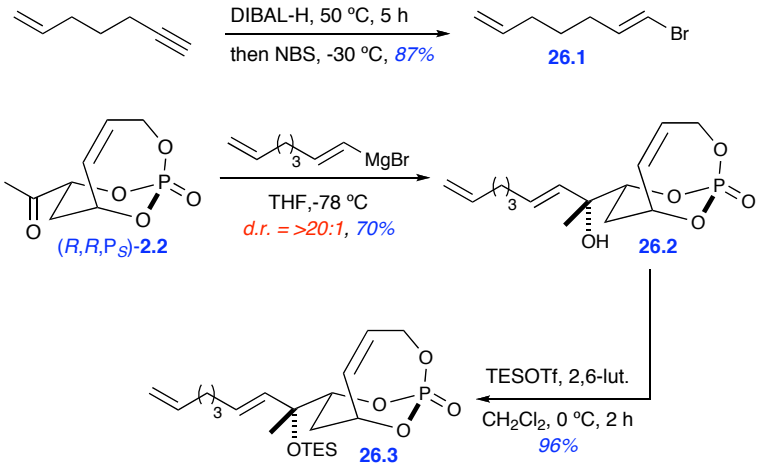
We then attempted the cross metathesis of our fostriecin core segment **16.3** with the relay-primed lactone **24.1**, were optimal conditions involved slow introduction of lactone **24.1** over the course of 6 hours (Scheme 25). While this method did provide an increased yield of product, the increase was disappointingly slight and certainly not useful for viable synthesis of fostriecin in light of previous syntheses of the said natural product.

Scheme 25



As the previous investigation indicated the sluggish reactivity of the exocyclic olefin in phosphate **16.3** may play a more significant role in the cross metathesis, construction of the relay analog proceeded with formation of (*E*)-1-bromo-1,6-heptadiene (**26.1**) from 1-hepten-6-yne by slightly modifying a Wolfe group procedure (Scheme 26).[51] Generation of the Grignard of **26.1** followed by addition into ketophosphate **2.2** provided relay analog **26.2**, which could be easily protected via TESOTf to provide phosphate **26.3**. Syringe pump addition of a solution of

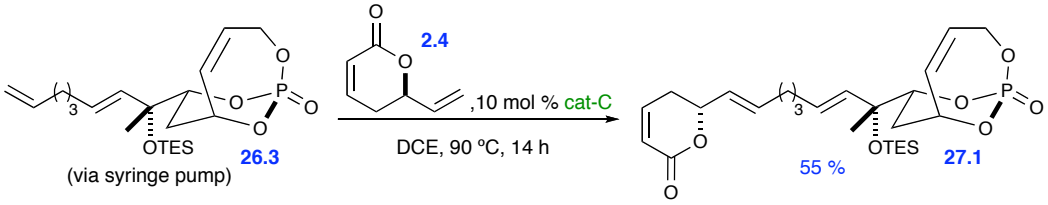
Scheme 26



phosphate **26.3** to refluxing lactone **2.4** in DCE provided none of the desired relay cross product (Scheme 27). Instead, cross metathesis proceeded at the terminal olefin of the relay linker to afford the extended chain variant (**27.1**). Modification of the

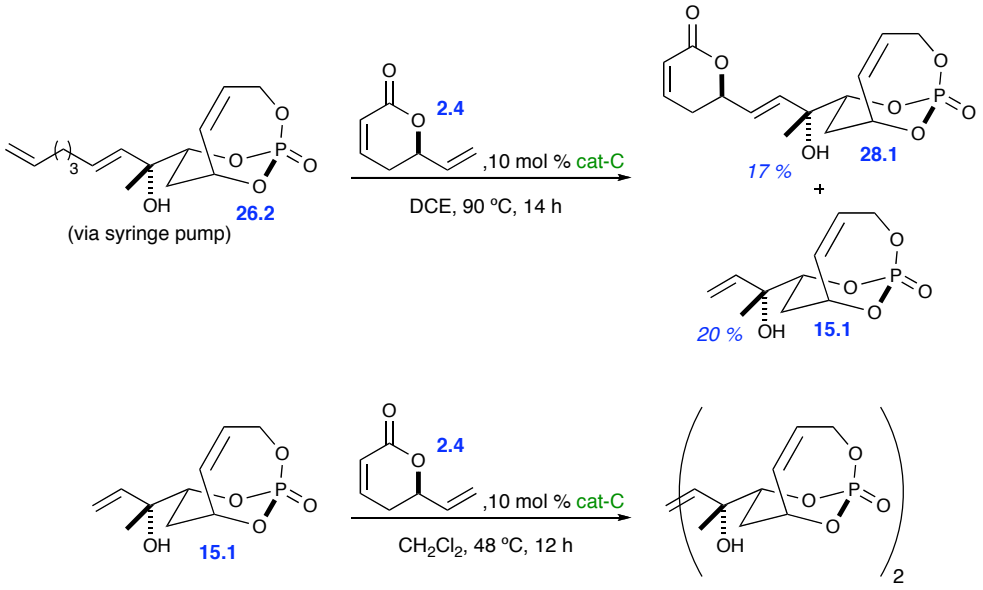
exocyclic olefin of phosphate **16.3** to the relay variant **26.3** appears to have produced a Type IV olefin, or at the very least a Type III olefin so inhibited towards metathesis that *intermolecular coupling outcompetes the intramolecular reaction* even under the dilute conditions applied.

Scheme 27



To circumvent this, the unprotected tertiary alcohol relay variant **26.2** was tested for coupling (Scheme 28). Unfortunately, the desired coupling product **28.1** was only obtained in 17% yield, with 20% recovery of phosphate **15.1** a testament to the sluggish reactivity of lactone **2.4** and with the remainder of material appearing to undergo isomerization/elimination reactions to generate a complex mixture of degradation products, indicating the unprotected tertiary alcohol alkylidene is problematic over long reaction periods when inadequate coupling partners are

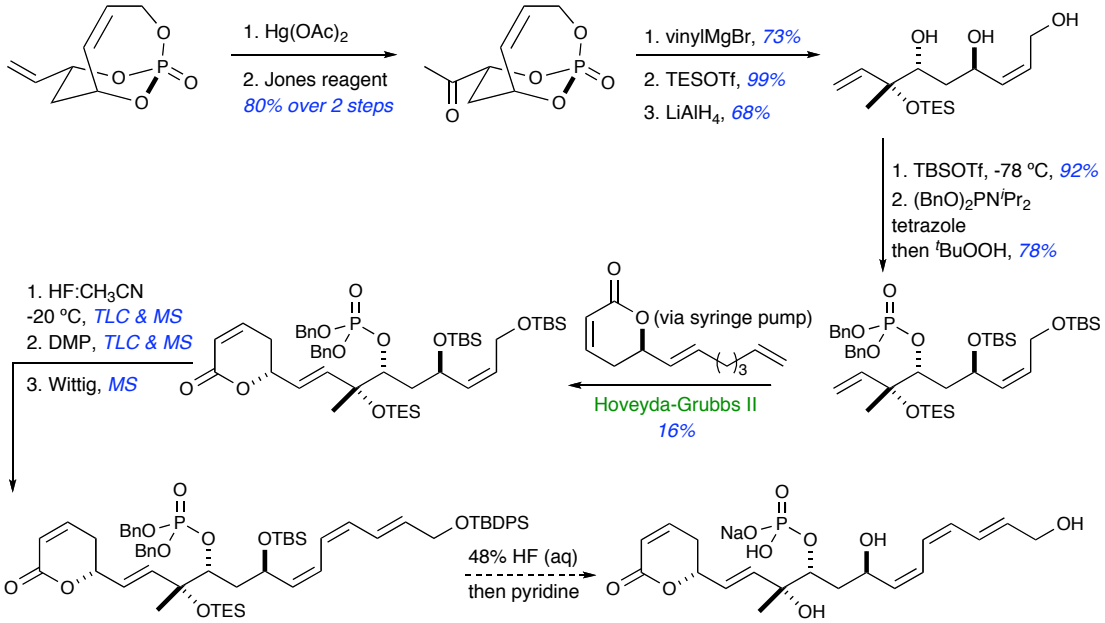
Scheme 28



present. Attempted coupling of phosphate **15.1** with lactone **2.4** provided dimerized bis-phosphate as the exclusive product, as irreversible self-coupling appeared to be the most facile reaction pathway.

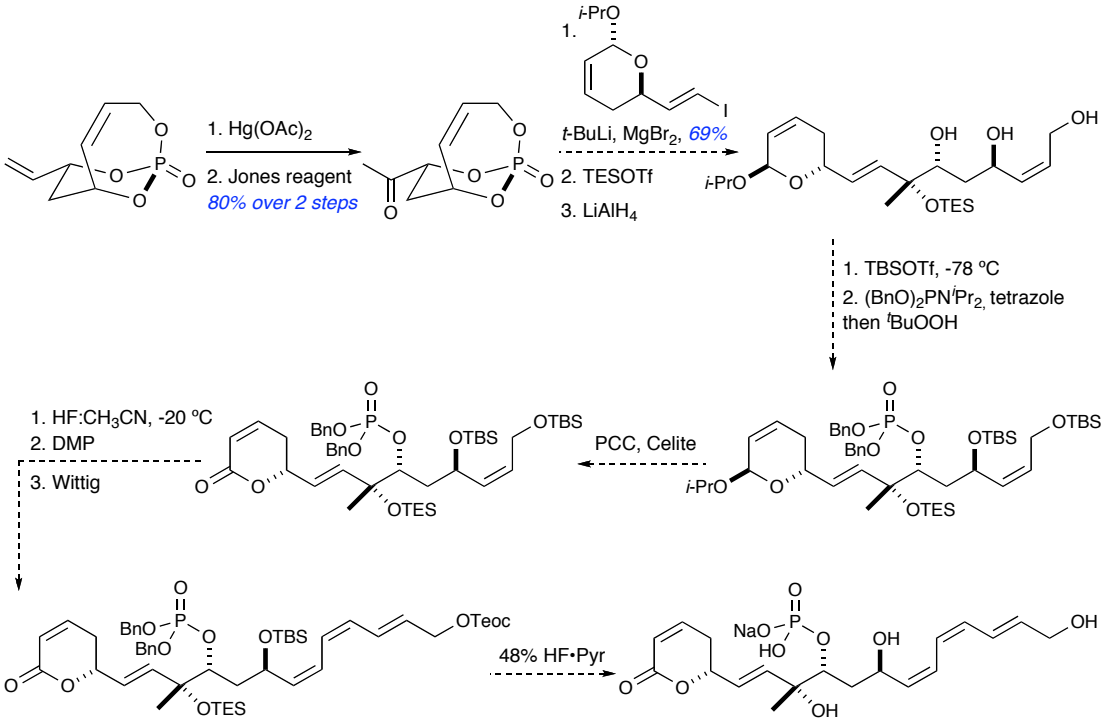
Given these results it appears cross metathesis, either utilizing a catalyst delivery vehicle (relay cross-metathesis) or direct coupling, is not a viable option for appending the intact lactone **2.4** in realizing a facile route from our compact functional synthon (*R*,*R*,P_S)-**2.1**. The cross metathesis investigations, however, were able to provide enough material to achieve the penultimate intermediate in the proposed synthesis (on microgram scale), and therefore allowed the establishment of a viable, efficient protocol towards achieving the total synthesis (Scheme 29).

Scheme 29



While cross-metathesis is a viable route toward library development, the research presented indicates that installation of the carbocyclic skeleton of the essential lactone of fostriecin in a high yielding, efficient manner may rely on implementing retrosynthetic plan B. The efficient and diastereoselective addition of isopropyl lactol **3.1** to ketone (*R*,*R*,P*S*)-**2.2** has been demonstrated, thus paving the way for implementation. In addition, upon perusal of the oxidation conditions utilized for lactone generation,[52] prohibitive protecting group incompatibilities are no longer expected to plague the synthetic route proposed (Scheme 30).

Scheme 30



4.6 Summary

Exploration of two synthetic approaches from (*R*,*R*,P$_S$)-**2.1** towards fostriecin were embarked upon simultaneously. Due to the anticipated elegant introduction of the western lactone of fostriecin, initial focus of our investigative energies centered upon realizing a cross metathesis of the lactone subunit with the central segment of fostriecin. Intensive studies found the deactivating nature of the carboxylate oxygen on the alkene of lactone **2.4** in conjunction with the lethargic protected tertiary allylic alcohol **16.3** provided unacceptable conversion upon metathesis, despite installation of catalyst delivery vehicles (lactone **24.1**). Attempts to utilize the unprotected variant **15.1** displayed preferential dimerization of allylic tertiary alcohol **15.1**, while the relay primed analog **26.2** was frustrated by competing elimination pathways. Analysis of Grignard addition of the lactone core **3.1** to ketone **2.2**, however,

propitiously heralds retrosynthetic plan B's viability. Future work in the total synthesis of fostriecin is expected to be enabled by application of this synthetic option, as well as guide the efforts in the total synthesis of leustroducsin B and other members of this class of molecules.

4.7 References:

(1) (a) Tunac, J. B.; Graham, B. D.; Dobson, W. E. Novel antitumor agents CI-920, PD 113,270 and PD 113,271. I. Taxonomy, fermentation and biological properties. *J. Antibiot*. **1983**, *36*, 1595-1600. (b) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. Novel antitumor agents CI-920, PD 113,270 and PD 113,271. II. Isolation and characterization. *J. Antibiot.* **1983**, *36*, 1601-1605. (c) Hokanson, G. C.; French, J. C. Novel antitumor agents CI-920, PD 113,270, and PD 113,271. 3. Structure determination. *J. Org. Chem*. **1985**, *50*, 462-466.

(2) (a) Jackson, R. C.; Fry, D. W.; Boritzki, T. J.; Roberts, B. J.; Hook, K. E.; Leopold, W. R. The biochemical pharmacology of CI-920, a structurally novel antibiotic with antileukemic activity. *Adv. Enzyme Regul.* **1985**, *23*, 193-215. (b) De Jong, R. S.; De Vires, E. G. E.; Mulder, N. H. Fostriecin: a review of the preclinical data. *Anti-Cancer Drugs* **1997**, *8*, 413-418.

(3) Scheithauer, W.; Von Hoff, D. D.; Clark, G. M.; Shillis, J. L.; Elslager, E. F. In vitro activity of the novel antitumor antibiotic fostriecin (CI-920) in a human tumor cloning assay. *Eur. J. of Cancer Clin. Oncol*. **1986**, *22*, 921-926.

(4) Walsh, A. H.; Cheng, A.; Honkanen, R. E. Fostriecin, an antitumor antibiotic with inhibitory activity against serine/threonine protein phosphatases types 1 (PP1) and 2A (PP2A), is highly selective for PP2A. *FEBS Lett.* **1997**, *416*, 230-234.

(5) Hastie, C. J.; Cohen, P. T. W. Purification of protein phosphatase 4 catalytic subunit: inhibition by the antitumor drug fostriecin and other tumor suppressors and promoters. *FEBS Lett.* **1998**, *431*, 357-361.

(6) Boger, D. L.; Hikota, M.; Lewis, B. M. Determination of the Relative and Absolute Stereochemistry of Fostriecin (CI-920). *J. Org. Chem.* **1997**, *62*, 1748-1753.

(7) Matsuhashi, H.; Shimada, K. Chemical Transformations of Leustroducsins: Synthesis of Leustroducsin B. *Tetrahedron* **2002**, *58*, 5619-5626.

(8) Shibata, T.; Kurihara, S.; Yoda, J.; Haruyana, H. Absolute configuration of leustroducsins. *Tetrahedron* **1995**, *51*, 11999-12012.

(9) Matsuhashi, H.; Shimada, K. Chemical Transformations of Leustroducsins: Synthesis of Leustroducsin B. *Tetrahedron* **2002**, *58*, 5619-5626.

(10) Shimada, K.; Kapuragi, Y.; Fukuyama, T. Total Synthesis of Leustroducsin B. *J. Am. Chem. Soc.* **2003***, 125,* 4048-4049.

(11) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. Total Synthesis of Leustroducsin B. *J. Org. Chem.* **2008***, 73,* 5360-5370.

(12) Boger, D. L.; Ichikawa, S.; Zhong, W. Total Synthesis of Fostriecin (CI-920). *J. Am. Chem. Soc.* **2001**, *123*, 4161-4167.

(13) (a) Chavez, D. E.; Jacobsen, E. N. Total synthesis of fostriecin (CI-920). *Angew. Chem, Int. Ed.* **2001**, *40*, 3667-3670. (b) Reddy, Y. K.; Falck, J. R. Asymmetric total synthesis of (+)-fostriecin. *Org. Lett.* **2002**, *4*, 969-971. (c) Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. Total synthesis of fostriecin (CI-920) via a convergent route. *Chem. Comm.* **2002**, 742-743. (d) Esumi, T.; Okamoto, N.; Hatakeyama, S. A versatile enantiocontrolled synthesis of fostriecin. *Chem. Comm.* **2002**, 3042-3043. (e) Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. Total Synthesis of an Antitumor Antibiotic, Fostriecin (CI-920). *J. Am. Chem. Soc.* **2003**, *125*, 8238-8243. (f) Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. Formal Catalytic Asymmetric Total Synthesis of Fostriecin. *Org. Lett.* **2003**, *5*, 733-736.

(14) (a) Cossy, J.; Pradaux, F.; BouzBouz, S. Synthesis of the C(1)-C(12) Fragment of Fostriecin. *Org. Lett.* **2001**, *3*, 2233-2235. (b) Kiyotsuka, Y.; Igarashi, J.; Kobayashi, Y. A Study Toward the Total Synthesis of Fostriecin. *Tetrahedron Lett.* **2002**, *43*, 2725-2729. (c) Wang, Y.-G.; Kobayashi, Y. Formal Total Synthesis of Fostriecin. *Org. Lett.* **2002**, *4*, 4615-4618. (d) Hayashi, Y.; Yamaguchi, H.; Toyoshima, M.; Okado, K.; Toyo, T.; Shoji, M. Formal Total Synthesis of Fostriecin via 1,4-Asymmetric Induction Using a Cobalt-Alkyne Complex. *Org. Lett.* **2008**, *10*, 1405-1408.

(15) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B.T. Dinuclear Asymmetric Zn Aldol Additions: Formal Asymetric Synthesis of Fostriecin. *J. Am. Chem. Soc.* **2005**, *127*, 3666-3667.

(16) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. Catalyst-Controlled Asymmetric Synthesis of Fostriecin and 8-*epi*-Fostriecin. *J. Am. Chem. Soc.* **2005**, *127*, 17111-17117.

(17) Shibasaki, M.; Kanai, M. Synthetic Strategies of Fostriecin. *Heterocycles* **2005**, *66*, 727-741.

(18) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

(19) (a) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. Asymmetric Synthesis Using Diisopropyl Tartrate Modified (*E*)- and (*Z*)-Crotylboronates: Preparation of the Chiral Crotylboronates and Reactions with Achiral Aldehydes. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348. (b) Roush, W. R.; Palkowitz, A. D.; Ando, K. Acyclic Diastereoselective Synthesis Using Tartrate Ester Modified Crotylboronates. Double Asymmetric Reactions with

α-Methyl Chiral Aldehydes and Synthesis of the C(19)-C(29) Segment of Rifamycin S. *J. Am. Chem. Soc.* **1990**, *112*, 6348-6359.

(20) Some time after this particular investigation conluded, the Johnson group published on the fate of phosphine bearing metathesis catalysts upon reaction with vinyl chlorides and vinyl bromides: Macnaughtan, M. L.; Johnson, M. J. A.; Kampf, J. W. Olefin Metathesis Reactions with Vinyl Halides: Formation, Observation, Interception, and Fate of the Ruthenium–Monohalomethylidene Moiety. *J. Am. Chem. Soc.* **2007**, *129*, 7708-7709.

(21) (a) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. Highly Enantio- and Diastereoselective Hetero-Diels-Alder Reactions Catalyzed by New Chiral Tridentate Chromium(III) Catalysts. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398-2400. (b) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. Highly Enantioselective Inverse-Electron Demand Hetero-Diels-Alder Reactions of a,b-unsaturated Aldehydes *Angew. Chem. Int. Ed.* **2002**, *41*, 3059-3061. (c) Chavez, D. E.; Jacobsen, E. N.; Grabowski, E. J. J.; Kubryk, M. An efficient, highly diastereo- and enantioselective hetero-Diels-Alder catalyst. Preparation of (2*S*,6*R*)-6-(*tert*-butyldimethylsiloxymethyl)-2-methoxy-2,5-dihydropyran. *Organic Synthesis* **2005**, *82*, 34-42.

(22) This methodology has facilitated several total syntheses including fostriecin: (a) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. Total Synthesis of FR901464. Convergent Assembly of Chiral Components Prepared by Asymmetric Catalysis. *J. Am. Chem. Soc.* **2000**, *122*, 10482-10483. (b) Bhattacharjee, A.; De Brabander, J. K. Synthesis of side chain truncated apicularen A. *Tetrahedron Lett*. **2000**, *41*, 8069-8073. (c) Liu, P.; Jacobsen, E. N. Total Synthesis of (+)-Ambruticin. *J. Am. Chem. Soc.* **2001**, *123*, 10772-10773. (d) Paterson, I.; Savi, C. D.; Tudge, M. Total Synthesis of the Microtubule-stabilizing Agent (–)-Laulimalide. *Org. Lett.* **2001**, *3*, 3149-3152. (e) Bonazzi, S.; Güttinger, S.; Zemp, I.; Kutay, U.; Glademann, K. Total Synthesis, Configuration, and Biological Evaluation of Anguinomycin C. *Angew. Chem. Int. Ed.* **2007**, *46*, 8707-8710.

(23) (a) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. Meerwein-Ponndorf-Verley Reductions and Oppenauer Oxidations: An Integrated Approach. *Synthesis* **1994**, 1007-1017. (b) Corma, A.; Domine, M. E.; Valencia, S. Water-resistant solid Lewis acid catalysts: Meerwein-Ponndorf-Verley and Oppenauer reactions catalyzed by tin-beta zeolite. *J. Catal.* **2003**, *215*, 294-304. (c) Boronat, M.; Corma, A.; Renz, M. Mechanism of the Meerwein-Ponndorf-Verley-Oppenauer (MPVO) Redox Equilibrium on Sn- and Zr-Beta Zeolite Catalysts. *J. Phys. Chem. B* **2006**, *110*, 21168-21174.

(24) Chavez, D. E. The Total Synthesis of Fostriecin (CI-920). The Development and Applications of an Asymmetric Hetero-Diels-Alder Reaction. Ph. D. Thesis, Harvard University, Cambridge, MA, 2003.

(25) Burke, S. D.; Cobb, J. E.; Takeuchi, K. Total Synthesis of (+)-Phyllanthocin. Introduction of Intramolecular Hydroformylation for Complex Molecule Functionalization. *J. Org. Chem.* **1990**, *55*, 2138-2151.

(26) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. New Cobalt Catalyzed Cycloisomerization of ε-Acetylenic β-Keto Esters. Application to a Powerful Cyclization Reactions Cascade. *J. Org. Chem.* **1996**, *61*, 2699-2708.

(27) The isopropyl acetal was found to be the superior form of this protected lactol for a variety of transformations enacted by several groups. See references 12, 13, and 22.

(28) Tivola, P. B.; Beccaria, L.; Deagostino, A.; Prandi, C.; Venturello, P. Preparation of Acetal- and Carbonyl-Substituted Allyl Chlorides from α,β-Unsaturated Acetals. *Synthesis* **2000**, 1615-1621.

(29) For a review of hydrozirconation, see: Wipf, P.; Jahn, H. Synthetic applications of organochlorozirconocene complexes. *Tetrahedron* **1996**, *52*, 12853-12910.

(30) (a) Wipf, P.; Xu, W. Preparation of allylic alcohols by alkene transfer from zirconium to zinc. *Tetrahedron Lett.* **1994**, *35*, 5197-5200. (b) Wipf, P.; Ribe, S. Zirconocene-Zinc Transmetalation and in Situ Catalytic Asymmetric Addition to Aldehydes. *J. Org. Chem.* **1998**, *63*, 6454-6455.

(31) Attack on phosphorous was deduced primarily upon examination of the ^{31}P NMR spectra of the crude reaction mixture in combination with the drastic increase of polarity (unlike successful additions of the skeleton, vide infra) and the ^{1}H NMR spectra.

(32) Hydrozirconation/iodination was also attempted, producing scant amounts (9% yield) of the desired iodide.

(33) (a) Arase, A.; Hoshi, M.; Mijin, A.; Nishi, K. Dialkylborane-Catalyzed Hydroboration of Alkynes with 1,3,2-Benzodioxaborole in Tetrahydrofuran. *Synth. Commun.* **1995**, *25*, 1957-1962. (b) Evans, D. A.; Starr, J. T. A Cycloaddition Cascade Approach to the Total Synthesis of (–)-FR182877. *J. Am. Chem. Soc.* **2003**, *125*, 13531-13540.

(34) Dicyclohexylborane was prepared according to the following method: Abiko, A.; Flamme, E. M.; Roush, W. R. Dicyclohexylboron trifluoromethanesulfonate. *Organic Syntheses* **2002**, *79*, 103-108.

(35) (a) Nicolaou, K. C.; Veale, C. A.; Webber, S. E.; Katerinopoulos, H. Stereocontrolled Total Synthesis of Lipoxins A. *J. Am. Chem. Soc.* **1985**, *107*, 7515-7518. (b) Nicolaou, K. C.; Webber, S. E. Stereocontrolled Total Synthesis of Lipoxins B. *Synthesis* **1986**, 453-461. (c) Onyango, E. O.;

Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. Total Synthesis of Neooxazolomycin. *Angew. Chem. Int. Ed.* **2007**, *46*, 6703-6705.

(36) (a) Zhang, H. X.; Guibé, F.; Balavoine, G. Palladium- and Molybdenum-Catalyzed Hydrostannation of Alkynes. A Novel Access to Regio- and Stereodefined Vinylstannanes. *J. Org. Chem.* **1990**, *55*, 1857-1867. (b) Hanessian, S.; Ma, J.; Wang, W. Total Synthesis of Bafilomycin A_1 on Iterative 1,2-Induction in Acyclic Precursors. *J. Am. Chem. Soc.* **2001**, *123*, 10200-10206. (c) Marshall, J. A.; Adams, N. D. Total Synthesis of Bafilomycin V_1: A Methanolysis Product of the Macrolide Bafilomycin C_2. *J. Org. Chem.* **2002**, *67*, 733-740. (d) Shao, J.; Panek, J. S. Total Synthesis of Cystothiazoles A and B. *Org. Lett.* **2004**, *6*, 3083-3085. (e) Skepper, C. K.; MacMillan, J. B.; Zhou, G.-X.; Masuno, M. N.; Molinski, T. F. Chlorocyclopropane Macrolides from the Marine Sponge *Phorbas* sp. Assignment of the Configurations of Phorbasides A and B by Quantitative CD. *J. Am. Chem. Soc.* **2007**, *129*, 4150-4151.

(37) Retention of configuration in this process is well precedented and spurred the investigation stated: (a) Va, P.; Roush, W. R. Total Synthesis of Amphidinolide E. *J. Am. Chem. Soc.* **2006**, *128*, 15960-15961. (b) Va, P.; Roush, W. R. Synthesis of 2-*epi*-Amphidinolide E: An Unexpected and Highly Selective C(2) Inversion during and Esterification Reaction. *Org. Lett.* **2007**, *9*, 307-310.

(38) de Vincente, J.; Huckins, J. R.; Rychnovsky, S. D. Synthesis of the C31-C67 Fragment of Amphidinol 3. *Angew. Chem. Int. Ed.* **2006**, *45*, 7258-7262.

(39) Please see the following article for the general procedure utilized: Hua, Z.; Carcache, D. A.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. The Synthesis and Preliminary Biological Evaluation of a Novel Steroid with Neurotrophic Activity: NGA0187. *J. Org. Chem.* **2005**, *70*, 9849-9856.

(40) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. Selective Halogen-Magnesium Exhange Reaction via Organomagnesium Ate Complex. *J. Org. Chem.* **2001**, *66*, 4333-4339.

(41) This protocol was developed by Trost's group to add a vinyl iodide segment to a similar ketone in the synthesis of dephospho-fostriecin; see reference 15.

(42) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R.; Multivalent Activation in Phosphate Tethers: A New Tether for Small Molecule Synthesis. *Org. Lett.* **2005**, *7,* 3375-3378.

(43) Kigoshi, H.; Suenaga, K.; Mutou, T.; Ishigaki, T.; Atsumi, T.; Ishiwata, H.; Sakakura, A.; Ogawa, T.; Ojika, M.; Yamada, K. Aplyronine A, a Potent Antitumor Substance of Marine Origin, Aplyronines B and C, and Artificial Analogues: Total Synthesis and Structure-Cytotoxicity Relationships. *J. Org.*

Chem. **1996**, *61*, 5326-5351.

(44) This olefin isomerization has been previously observed: Langille, N. F.; Panek, J. S. Total Synthesis of (–)-Callystatin A. *Org. Lett.* **2004**, *6*, 3203-3206.

(45) This direct oxidation by PCC of the α,β-unsaturated isopropyl acetal to the α,β-unsaturated lactone has been utilized previously, along with observation of some minor olefin isomerization: (a) Lautens, M.; Stammers, T. A. Oxabicyclo[3.2.1]oct-6-enes as Templates for the Stereoselective Synthesis of Polypropionates: Total Synthesis of Callystatin A and C19-*epi*-Callystatin A. *Synthesis* **2002**, 1993-2012. (b) Enders, D.; Steinbusch, D. An Efficient Asymmetric Synthesis of Tarchonanthuslactone. *Eur. J. Org. Chem.* **2003**, *22*, 4450-4454.

(46) Waetzig, J. D.; Hanson, P. R. A Multifaceted Phosphate Tether: Application to the C1−C14 Subunit of Dolabelides A−D. *Org. Lett.* **2008**, *10*, 109-112.

(47) Indeed, utilizing glycidol-derived allylic alcohol **20.2** under the conditions used for the reactions mentioned provided the dimer as the exclusive means of reclaiming and recycling unreacted **20.2**.

(48) For a recent mini-review, see: Wallace, D. J. Relay Ring-Closing Metathesis – A Strategy for Achieving Reactivity and Selectivity in Metathesis Chemistry. *Angew. Chem. Int. Ed.* **2005**, *44*, 1912-1915. For more up-to-date information, see: (a) Xie, Q.; Denton, R. W.; Parker, K. A. A Relay Ring-Closing Metathesis Synthesis of Dihydrooxasilines, Precursors of (*Z*)-Iodo Olefins. *Org. Lett.* **2008**, *10*, 5345-5348. (b) Marvin, C. C.; Voight, E. A.; Suh, J. M.; Paradise, C. L.; Burke, S. D. Synthesis of (+)-Didemniserinolipid B: Application of a 2-Allyl-4-fluorophenyl Auxiliary for Relay Ring-Closing Metathesis. *J. Org. Chem.* **2008**, *73*, 8452-8457 and pertinent references therein.

(49) Only two previous alkene-alkene relay cross-metathesis publications could be ascertained as of this writing: (a) Hansen, E. C.; Lee, D. Efficient and *Z*-Selective Cross-Metathesis of Conjugated Enynes. *Org. Lett.* **2004**, *6*, 2035-2038. (b) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. Asymmetric Total Synthesis of (+)-3-(*Z*)-Laureatin and (+)-3-(*Z*)-Isolaureatin by "Lone Pair–Lone Pair Interaction-Controlled" Isomerization. *J. Am. Chem. Soc.* **2007**, *129*, 2269-2274.

(50) (a) Menzel, K.; Fu, G. C. Room-Temperature Stille Cross-Couplings of Alkenyltin Reagents and Functionalized Alkyl Bromides that Possess β Hydrogens. *J. Am. Chem. Soc.* **2003**, *125*, 3718-3719. (b) Tang, H.; Menzel, K.; Fu, G. C. Ligands for Palladium-Catalyzed Cross-Couplings of Alkyl Halides: Use of an Alkyldiaminophosphane Expands the Scope of the Stille Reaction. *Angew. Chem. Int. Ed.* **2003**, *42*, 5079-5082.

(51) Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. Synthesis of *N*-Aryl-2-allyl Pyrrolidines via Palladium-catalyzed Carboamination of γ-(*N*-Arylamino)alkenes with Vinyl Bromides. *Adv. Synth. Catal.* **2005**, *347*, 1614-1620.

(52) The PCC oxidation of the isopropyl protected lactol proceeded in the presence of classically acid sensitive protecting groups such as TBS; note reference 45.

Chapter 5

Experimental Data:

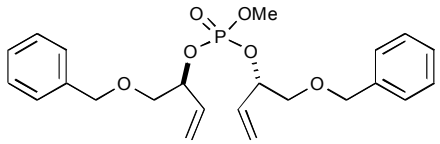
Chapters 2, 3 and 4

5.1 General Experimental Methods

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gastight syringes, cannulaes, and septa. Stirring was achieved with oven-dried magnetic stir bars. Et_2O, toluene, THF and CH_2Cl_2 were purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (Grubbs, R.H.; Rosen, R.K.; Timmers, F.J.; *Organometallics* **1996**, *15*, 1518-1520). Et_3N was purified by passage over basic alumina and stored over KOH. Butyl Lithium was purchased from Aldrich and titrated prior to use. Dialkyl zinc and alkyl zinc halide reagents were purchased from Aldrich and were used at the reported molarities. Grubb's second-generation olefin metathesis catalyst was acquired from Materia and used without further purification. Flash column chromatography was performed with Merck silica gel (EM-9385-9, 230-400 mesh). Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz, 100 MHz, and 162 MHz respectively or a Bruker Avance operating at 500 MHz and 125 MHz respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained on a VG Instrument ZAB double-focusing mass spectrometer.

5.2 Experimental Data: Chapter 2

_(S,S)_-acyclic diene phosphate triester



A solution of allylic alcohol **1.3** (2.05 g, 11.54 mmol) in THF (58 mL) was cooled to –30 ˚C. BuLi (2.47M, 11.02 mmol) was slowly added, followed by ten minutes of stirring. A solution of dichloromethyl phosphate (781 mg, 5.25 mmol) in THF (10.5 mL) was slowly cannulated into the reaction vessel containing the alkoxide. The reaction continued to stir at –30 ˚C for 30 minutes, the cold bath was removed and the solution was warmed to room temperature and stirred for an additional two hours. Upon completion (monitored by TLC), the reaction was quenched with 20 mL of NH_4Cl (sat'd aq). The separated aqueous layer was extracted with Et_2O (3x) and the combined organic layers washed with brine then dried ($MgSO_4$). Flash chromatography (2:1 hexanes/EtOAc) provided 1.96 g (87% yield) of the diene product as a faint yellow oil.

$[\alpha]_D$ = +0.54 (*c* = 0.37, CH_2Cl_2)

IR (neat) 2930, 1452, 1266, 1016, 734, 698 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4-7.3 (m, 10H), 5.91 (ddd, *J* = 17.2, 10.6, 6.4 Hz, 1H), 5.91 (ddd, *J* = 17.2, 10.6, 6.4 Hz, 1H), 5.45 (d, *J* = 17.2, 1H), 5.39 (d, *J* = 17.2, 1H), 5.30 (d, *J* = 10.5, 1H), 5.30 (d, *J* = 10.5, 1H), 4.98-5.09 (m, 2H), 4.59 (dd, *J* =

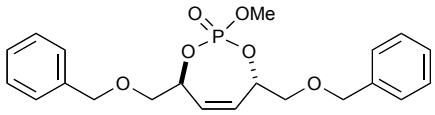
12.2, 5.1 Hz, 2H), 4.54 (dd, J = 12, 1.4 Hz, 2H), 3.72 (d, J = 11.4 Hz, 3H), 3.62 (dd, J = 10.6, 6.3 Hz, 2H), 3.57 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.11, 134.05, 134.02, 133.99, 128.56, 127.89, 118.84, 118.65, 78.13, 78.10, 78.09, 78.05, 73.44, 73.41, 72.47(d, J_{CP} = 0.8 Hz), 72.42 (d, J_{CP} = 1.5 Hz), 54.48, 54.44

^{31}P NMR (162 MHz, $CDCl_3$) δ 0.29

HRMS calculated for $C_{23}H_{29}O_6P$ $(M+H)^+$ 433.1780; found 433.1757 (FAB).

(*S,S)*-monocyclic phosphate: *(S,S)*-1.1



A flask containing the *(S,S)*-diene phosphate triester (1.45 g, 3.36 mmol) was charged with toluene (670 mL) that had been degassed for 20 minutes with argon. The solution was brought to reflux while continually sparging with argon, and $(ImesH_2)(PCy_3)(Cl_2)Ru{=}CHPh$ was added (200 mg, 0.235 mmol). The reaction was maintained at reflux under argon sparging for 30 minutes. Upon completion (monitored by TLC) the reaction was cooled to room temperature and concentrated under reduced pressure. Purification via flash chromatography (1:1 hexanes/EtOAc) supplied 927 mg (68% yield) of monocylic phosphate **1.1**.

$[\alpha]_D$ –52.6 (*c* = 1.6, CH_2Cl_2)

FTIR (neat) 3029, 1454, 1365, 1282, 1027 cm^{-1}

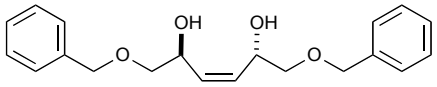
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.39 (m, 10H), 5.76 (ddd, *J* = 12.0, 1.8, 1.6 Hz, 1H), 5.72 (ddd, *J* = 12.0, 1.8, 1.6 Hz, 1H), 5.26-5.32 (m, 1H), 5.07-5.14 (m, 1H), 4.56-4.64 (m, 4H), 3.87 (d, J_{HP} = 11.1 Hz, 3H), 3.67 (dddd, *J* = 6.4, 5.5, 5.1, 0.9 Hz, 2H), 3.59 (dddd, *J* = 5.3, 5.1, 2.1, 0.5 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.56, 137.48, 129.49, 128.42, 128.09, 127.83, 127.81, 127.69, 127.63, 73.91, (d, J_{CP} = 7.0), 73.62 (d, J_{CP} = 4.5), 73.49, 73.33, 71.60 (d, J_{CP} = 11.9), 71.21 (J_{CP} = 12.1), 54.62 (d, J_{CP} = 5.1)

^{31}P NMR (162 MHz, $CDCl_3$) δ 3.61

HRMS calculated for $C_{21}H_{25}O_6P$ $(M+H)^+$ 405.1467; found 405.1437 (FAB).

(2*S*, 5*S*, 3*Z*)-1,6-bis(benzyloxy)hex-3-ene-2,5-diol: **2.1**



Phosphate **1.1** (30 mg, 0.074 mmol) was taken up in THF (0.20 mL) and cooled to 0 ˚C while stirring under argon. $LiAlH_4$ (0.010 mg, 0.24 mmol) was added slowly, and upon complete addition stirring continued for an additional 2 hours while warming to room temperature. The mixture was then cooled to 0 ˚C and slowly quenched with H_2O (0.1 mL) followed by 10% NaOH aq (0.2 mL). The layers were separated and the aqueous layer extracted with EtOAc (5x). The combined organic layers were concentrated under reduced pressure and dried (Na_2SO_4). Column chromatography (5:1 heptane:EtOAc) provided **4** (18.3 mg, 75%) as a clear oil.

$[\alpha]_D$ = + 21.7 (*c* = 1.7, CH_2Cl_2)

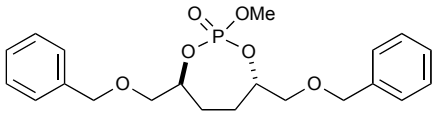
FTIR (neat) 3417, 3025, 2902, 1493, 1465, 1101, 1075, 737, 698 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.37 (m, 10H), 5.58-5.64 (m, 2H), 4.63-4.68 (m, 2H), 4.57 (s, 2H), 3.53 (dd, *J* = 9.4, 4.4 Hz 2H), 3.46 (dd, *J* = 9.5, 7.4 Hz, 1H), 2.65 (bs, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.62, 132.08, 128.47, 127.87, 127.84, 73.48, 73.42, 67.21.

HRMS calculated for $C_{20}H_{24}O_4$ $(M+Na)^+$ 351.1572; found 351.1582 (FAB).

(*S,S)*-hydrogenated monocyclic phosphate: 2.2



Post ring-closing metathesis (50 mg, 0.123 mmol) with $(ImesH_2)(PCy_3)(Cl_2)Ru{=}CHPh$ (33 mg, 0.040 mmol), the reaction was a concentrated under reduced pressure and the resulting brown oil was taken up in dry CH_2Cl_2 (10 mL). The reaction was cannulated to a hydrogen Parr bomb apparatus, followed by implementing three quick cycles of evacuation and hydrogen purging. The bomb was capped and charged with H_2 (300 psi) while heating at 80 ˚C. After stirring for two hours, the reaction mixture was concentrated under reduced pressure and immediately subjected to column chromatography (1:1 heptane:EtOAc) providing 45.4 mg of **2.2** (90 % yield) as a light brown oil (small ruthenium contamination estimated to be < 1%).

$[\alpha]_D$ = -2.15 (*c* = 0.33, CH_2Cl_2)

FTIR (neat) 2917, 1279, 1098, 1000, 737, 698 cm^{-1}

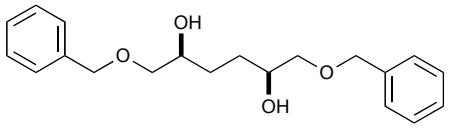
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.37 (m, 10H), 4.52-4.61 (m, 5H), 4.31-4.35 (m, 1H), 3.82 (d, J_{HP} = 11.1 Hz, 3H), 3.43-3.65 (m, 4H), 2.06 (dd, *J* = 11.9, 4.3 Hz, 1H), 1.98 (dd, *J* = 10.6, 3.8 Hz, 1H), 1.73-1.82 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.67 (d, J_{CP} = 2.6 Hz), 128.35, 127.72, 127.65, 127.55, 77.94 (d, J_{CP} = 6.4 Hz), 76.38 (d, J_{CP} = 3.7 Hz), 73.32 (d, J_{CP} = 10.6 Hz), 72.59 (d, J_{CP} = 11.1 Hz), 72.08 (d, J_{CP} = 11.1 Hz), 54.26 (d, J_{CP} = 4.9 Hz), 30.78, 30.51

^{31}P NMR (162 MHz, $CDCl_3$) δ 3.02

HRMS calculated for $C_{21}H_{27}O_6P$ $(M+H)^+$ 407.1624; found 407.1649 (FAB).

(2*S*, 5*S*)-1,6-bis(benzyloxy)hexane-2,5-diol: 2.3



Phosphate **2.2** (30 mg, 0.074 mmol) was dissolved in THF (1.2 mL) and cooled to 0 ˚C while stirring under argon. $LiAlH_4$ (0.0084 mg, 0.22 mmol) was added slowly, and upon complete addition stirring continued for an additional 2 hours while warming to room temperature. An additional amount of $LiAlH_4$ was added, and the solution stirred for an additional hour. The mixture was then cooled to 0 ˚C and slowly quenched with H_2O (0.1 mL) followed by 10% NaOH aq (0.2 mL), and then H_2O (0.1 mL). The layers were separated and the aqueous layer extracted with EtOAc (5x). The combined organic layers were concentrated under reduced pressure and dried (Na_2SO_4). Column chromatography (5:1 heptane:EtOAc) provided **6** (21.9 mg, 90%) as a clear oil.

$[\alpha]_D$ = +7.06 (*c* = 0.09, CH_2Cl_2)

FTIR (neat) 3436, 1096, 737, 698 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.37 (m, 10H), 4.55 (s, 2H), 3.82-3.88 (m, 2H), 3.49 (dd, *J* = 9.0, 3.5 Hz, 2H), 3.49 (dd, *J* = 9.0, 7.5 Hz, 2H), 2.25 (bs, 2H), 1.56-1.65 (m, 4H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.93, 128.46, 127.79, 127.75, 74.41, 73.34, 70.38, 29.53.

HRMS calculated for $C_{20}H_{24}O_4$ $(M+Na)^+$ 351.1572; found 351.1582 (FAB).

General Procedure A for Diakyl Zincate Derived Cuprates: To a solution of CuCN•2LiCl (1 mmol, 1M in THF) cooled to -30 ˚C was added dropwise the dialkyl zinc reagent as a solution in THF (1 mmol). After stirring 30-45 min (Me_2Zn required longer stirring times) at -25 ˚C to -30 ˚C, a solution of phosphate **1.1** (0.20 mmol) in THF (2 mL) was added. The reaction progress was monitored by TLC (products are baseline in EtOAc), and upon completion were quenched with 10% HCl aq. (1 mL) and stirred for 30 – 60 min. The aqueous layer was extracted was extracted with EtO_2 (4 x 1 mL) and the combined organic layers were subsequently washed with H_2O (1 x 1 mL) and filtered of the resulting white solids. The aqueous layer was removed and the organic layer was concentrated under reduced pressure. The crude acids were used without further purification.

General Procedure B for Alkyl Zinc halide Derived Cuprates: To a solution of CuCN•2LiCl (1 mmol, 1M in THF) cooled to -30 ˚C was added dropwise the alkyl zinc halide reagent as a solution in THF (1 mmol, 1.0M). After stirring for one hour at -25 ˚C to -30 ˚C, a solution of phosphate **1.1** (0.11 mmol) in THF (1.1 mL) was added. The reaction progress was monitored by TLC (products are baseline in EtOAc), and upon completion (~ 2 hours) were quenched with 10% HCl aq. (1 mL) and stirred for 30-60 min. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (4 x 1 mL) and the combined organic layers were subsequently washed with H_2O (1 x 1mL) and the resulting white solids were filtered off. The aqueous

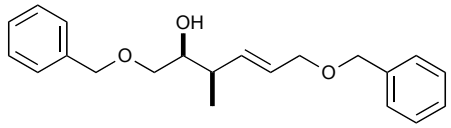
layer was removed and the organic layer was concentrated under reduced pressure. The crude acids were used without further purification.

General Procedure for Making Alkyl Zinc Iodides (Cy-Zn-I):

To a heterogeneous mixture of activated Zn dust (288 mg, 4.4 mmol) in THF (330 μL) under argon was added dibromoethane (15 μL, 0.176 mmol), which was heated to 65 ˚C for one minute and then cooled to room temperature. Trimethylsilyl chloride was then added (16 μL, 0.132 mmol) and the mixture was allowed to stir for 15 minutes, upon which time the appropriate alkyl iodide (4 mmol) in THF (1.6 mL) was added and the reaction heated to 40 ˚C with stirring. Upon completion (monitored by GC or Zn disappearance), the reagent was used immediately.

General Procedure for Red-Al® of Phosphate Acids: A stirring solution of the phosphate acid (0.124 mmol) in toluene (1.24 mL) was cooled to 0 ˚C and Red-Al (151 μL, 0.495 mmol) was added dropwise. The reaction was allowed to proceed for 30 minutes and monitored by TLC. If necessary, an additional 1 equivalent of Red-Al was added to ensure completion. Reaction was quenched with H_2O (1 mL) followed by slow addition of 10% HCl aq. (1 mL) at 0 ˚C. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (4 x) and the combined organic layers were subsequently washed with brine and dried ($MgSO_4$).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-methylhex-4-en-2-ol: 4.1a



Following procedure A (100 mg of **1.1**) and phosphate acid removal, column chromatography (heptane:EtOAc 4:1) afforded **4.1a** (67 mg, 83 %) as a clear oil over two steps.

$[\alpha]_D$ = +30.4 (*c* = 1.0, CH_2Cl_2)

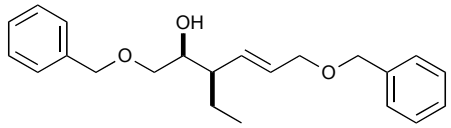
FTIR (neat) 3461, 2358, 1456, 1361, 1249, 1027 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 5.58-5.79 (m, 2H), 4.53 (d, *J* = 1.8 Hz, 2H), 4.48 (s, 2H), 3.96-3.97 (m, 2H), 3.64 (ddd, *J* = 7.2, 7.2, 3.0 Hz, 1H), 3.55 (dd, *J* = 9.5, 3.1, 1H), 3.39 (dd, *J* = 9.7, 7.7, 1H), 2.32-2.39 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.26, 137.90, 135.62, 128.44, 127.77, 127.71, 127.59, 127.05, 73.53, 73.34, 72.66, 71.98, 70.60, 39.80, 15.9.

HRMS calculated for $C_{21}H_{26}O_3$ $(M+Na)^+$ 349.1780; found 349.1817 (FAB).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-ethylhex-4-en-2-ol: 4.1b



Following procedure A (50 mg of **1.1**) and phosphate acid removal, column chromatography (heptane:EtOAc 4:1) afforded **4.1b** (38 mg, 90%) as a clear oil over two steps.

$[\alpha]_D$ = +4.87 (*c* = 0.58, CH_2Cl_2)

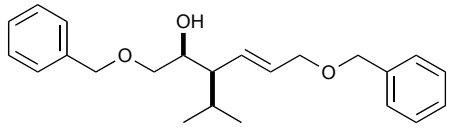
FTIR (neat) 3420, 2914, 1457, 1269, 1101, 1073, 737, 699 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 5.62 (dt, *J* = 15.4, 6 Hz, 1H), 5.44 (dd, *J* = 15.4, 9.3 Hz, 1H), 4.53 (d, *J* = 4.4 Hz, 2H), 4.49 (s, 2H), 3.99 (d, *J* = 5.9 Hz, 2H), 3.7-3.66 (m, 1H), 3.57 (d, *J* = 9.5 Hz, 1H), 3.38 (t, *J* = 9.3 Hz, 1H), 2.48 (s, 1H), 2.14-2.06 (m, 1H), 1.32-1.21 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.26, 137.89, 133.60, 129.01, 128.51, 128.41, 128.36, 127.75, 127.72, 127.69, 127.57, 126.94, 73.32, 72.94, 72.49, 71.77, 70.50, 47.92, 23.32, 11.56.

HRMS calculated for $C_{22}H_{28}O_3$ $(M+NH_4)^+$ 358.2382; found 358.2381 (FAB).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-isopropylhex-4-en-2-ol: 4.1c



Following procedure A (50 mg of **1.1**) and phosphate acid removal, column chromatography (heptane:EtOAc 5:1) afforded **4.1c** (44.5 mg, 89 %) as a clear oil over two steps.

$[\alpha]_D$ = +17.5, (*c* , 2.1 CH_2Cl_2)

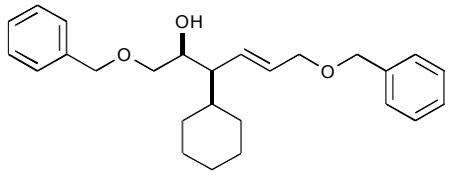
FTIR (neat) 3446, 2348, 1101 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 10H), 5.59 (ddd, *J* = 15.6, 6.0, 6.0 Hz, 1H), 5.43 (dd, *J* = 15.4, 10.0 Hz, 1H), 4.53 (dd, *J* = 23.0,11.7 Hz, 2H), 4.48 (dd, *J* = 12.2, 8.0 Hz, 2H) 3.92 (dd, *J* = 5.9, 1.0 Hz, 2H), 3.78-3.84 (m, 1H), 3.57 (dd, *J* = 9.5, 2.6 Hz, 1H), 3.33 (dd, *J* = 9.4, 7.6 Hz, 1H), 2.39 (bs, 1H), 2.13-2.21 (m, 1H), 2.07 (ddd, *J* = 9.6, 9.6, 3.1 Hz, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.28, 137.90, 130.41, 130.11, 128.42, 128.37, 127.75, 127.72, 127.70, 127.58, 73.49, 73.34, 71.70, 70.46, 70.04, 51.79, 26.66, 21.38, 16.82.

HRMS calculated for $C_{23}H_{30}O_3$ $(M+Na)^+$ 377.2093; found 377.2075 (FAB).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-cyclohexylhex-4-en-2-ol 4.1d:



Following procedure B (100 mg of **1.1**) and phosphate acid removal, column chromatography (heptane:EtOAc 5:1) afforded **4.1d** (68 mg, 70 %) as a clear oil.

$[\alpha]_D$ = +9.84 (*c* = 1.58, CH_2Cl_2)

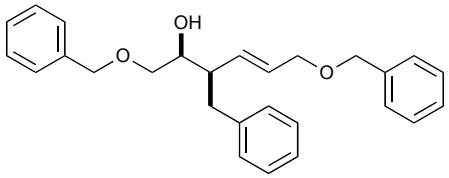
FTIR (neat) 3453, 3031, 2922, 2850, 1496, 1450, 1098, 737, 698 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 10H), 5.57 (dt, *J* = 15.4, 5.9 Hz, 1H), 5.44 (dd, *J* = 15.4, 10 Hz, 1H), 4.53 (dd, *J* = 11.8, 10.6 Hz, 2H), 4.49 (s, 2H), 3.98 (d, *J* = 5.9 Hz, 2H), 3.86 (td, *J* = 8.4, 2.5 Hz, 1H), 3.57 (dd, *J* = 9.5, 2.6 Hz, 1H), 3.32 (dd, *J* = 9.4, 7.8 Hz, 1H), 2.42 (d, *J* = 4 Hz, 1H), 2.07 (td, *J* = 9.6, 3.9 Hz, 1H), 1.80-1.70 (m, 4H), 1.65 (d, *J* = 12.7 Hz, 1H), 1.50 (d, *J* = 12.8 Hz, 1H), 1.33-1.20 (m, 2H), 1.14-1.06 (m, 2H), 0.94 (ddd, *J* = 13, 12.8, 3.1 Hz, 1H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.57, 138.19, 131.42, 130.15, 128.66, 128.62, 127.99, 127.95, 127.93, 127.83, 73.30, 73.58, 72.01, 70.73, 69.68, 52.07, 37.37, 32.16, 28.09, 26.90, 26.84, 26.75

HRMS calculated for $C_{26}H_{34}O_3$ $(M+Li)^+$ 401.2668; found 401.2678 (FAB).

(2*S*,3*R*,*E*)-3-benzyl-1,6-bis(benzyloxy)hex-4-en-2-ol: 4.1e



Following procedure B (100 mg **1.1**) and phosphate acid removal, column chromatography (heptane:EtOAc 4:1) afforded **4.1e** (81.0 mg, 82%) as a clear oil over two steps.

$[\alpha]_D$ = –6.2 (*c* 1.4, CH_2Cl_2)

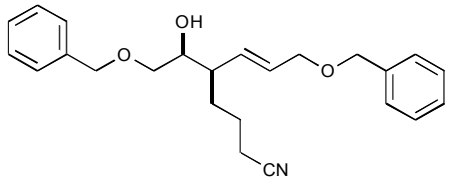
FTIR (neat) 3444, 1494, 1452, 1097 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.15 (m, 15H), 5.48 (dd, *J* = 15.7, 8.1 Hz, 1H), 5.43 (ddd, *J* = 15.7, 10.6, 5.3 Hz, 1H), 4.56 (dd, *J* = 11.9, 7.3 Hz 2H), 4.31 (dd, *J* = 12.0, 0.1 Hz, 2H), 3.91 (dd, *J* = 12.8, 4.1 Hz, 1H), 3.87 (dd, *J* = 12.3, 5.0 Hz, 1H), 3.78-3.73 (m, 1H), 3.65-3.57 (m, 1H), 3.50-3.43 (m, 1H), 3.12 (dd, *J* = 13.4, 4.0 Hz, 1H), 2.68 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.62-2.52 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.79, 138.31, 137.00, 132.81, 129.52, 129.38, 128.45, 128.31, 128.07, 127.82, 127.76, 127.67, 127.51, 125.85, 73.37, 72.68, 71.81, 71.37, 70.27, 47.82, 37.27.

HRMS calculated for $C_{37}H_{30}O_3$ $(M+Na)^+$ 425.2093; found 425.2083 (FAB).

(*R*,*E*)-8-(benzyloxy)-5-((*S*)-2-(benzyloxy)-1-hydroxyethyl)oct-6-enenitrile: 4.1f



Following procedure B (100 mg of **1.1**) and methylation/phosphate removal, column chromatography (heptane:EtOAc 4:1) afforded **4.1f** (78.0 mg, 83%) as a clear oil.

$[\alpha]_D$ = -12.0 (*c* = 1.5, CH_2Cl_2)

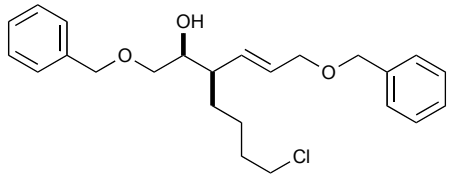
FTIR (neat) 3463, 3031, 2927, 2246, 742, 702 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 10H), 5.63 (ddd, *J* = 15.5, 5.7, 5.7 Hz, 1H), 5.43 (dd, *J* = 15.5, 9.5 Hz, 1H), 4.52 (dd, *J* = 11.8, 7.7 Hz, 2H), 4.48 (dd, *J* = 9.1, 0.1 Hz, 2H), 3.97 (d, *J* = 5.6 Hz, 2H), 3.62 (ddd, *J* = 7.4, 5.4, 2.3 Hz, 1H), 3.55 (dd, *J* = 9.5, 9.4 Hz, 1H), 3.36 (dd, *J* = 9.4, 7.6 Hz, 1H), 2.47 (bs, 1H), 2.32 (dddd, *J* = 14.3, 7.3, 7.0, 2.6 Hz 2H), 2.18 (ddd, *J* = 18.2, 10.1, 3.3 Hz, 1H), 1.96-1.86 (m, 1H), 1.78-1.67 (m, 1H), 1.55 (ddd, *J* = 6.9, 6.0, 4.8 Hz, 1H), 1.34-1.45 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.17, 137.78, 132.42, 129.90, 128.51, 128.46, 127.91, 127.80, 127.75, 127.72, 119.72, 73.44, 72.71, 72.49, 72.23, 70.30, 45.91, 29.76, 23.31, 17.27.

HRMS calculated for $C_{24}H_{29}NO_3$ $(M+NH_4)^+$ 397.2491; found 397.2483 (FAB).

(2*S*,3*R*)-1-(benzyloxy)-3-((*E*)-3-(benzyloxy)prop-1-enyl)-7-chloroheptan-2-ol: 4.1g



Following procedure B (100 mg of **1.1**) and methylation/phosphate removal, column chromatography (heptane:EtOAc 5:1) afforded **4.1g** (84.7 mg, 85 %) as a clear oil.

$[\alpha]_D$ = +5.8 (*c* = 0.625, CH_2Cl_2)

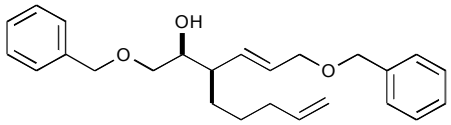
FTIR (neat) 3442, 3031, 2921, 2856, 1494, 1452, 1361, 1099, 736, 698 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.11 (m, 10H), 5.67-5.59 (m, 1H), 5.46 (dd, *J* = 15.5, 9.4 Hz, 1H), 4.54 (dd, *J* = 17.4, 11.9 Hz, 2H), 4.49 (app s, 2H), 3.99 (dd, *J* = 5.9, 1.1 Hz, 2H), 3.66 (ddd, *J* = 7.8, 7.8, 2.9 Hz, 1H), 3.57 (dd, *J* = 9.5, 2.9 Hz, 1H), 3.57-3.52 (m, 2H), 3.39 (dd, *J* = 9.5, 7.5 Hz, 1H), 2.22-1.88 (m, 3H), 1.84-1.69 (m, 3H), 1.48-1.24 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.27, 137.86, 133.35, 129.24, 128.45, 128.38, 127.73, 127.70, 127.61, 73.38, 72.71, 72.85, 72.62, 71.90, 70.34, 46.24, 45.00, 35.59, 29.70, 24.43.

HRMS calculated for $C_{24}H_{31}ClO_3$ $(M+NH_4)^+$ 420.2305; found 420.2310 (FAB).

(2*S*,3*R*,*E*)-1-(benzyloxy)-3-(3-(benzyloxy)prop-1-enyl)oct-7-en-2-ol: 4.1h



Following procedure B and phosphate acid removal, column chromatography (heptane:EtOAc 4:1) afforded **4.1h** (61 mg, 65%) as a clear oil.

$[\alpha]_D$ = +3.53 (*c* = 0.17, CH_2Cl_2)

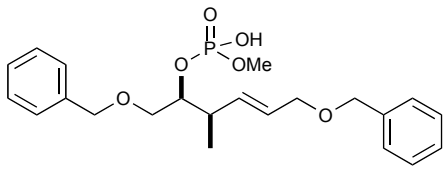
FTIR (neat) 3422, 1274, 750, 699 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 10H), 5.80 (ddt, *J* = 17, 10.2, 6.6 Hz, 1H), 5.62 (dt, *J* = 15.5, 6 Hz, 1H), 5.46 (dd, *J* = 15.5, 9.4 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.4 Hz, 1H), 4.94 (dd, *J* = 10.2, 1 Hz, 1H), 4.54 (dd, 18.3, 11.7, 2H), 4.49 (s, 2H), 3.99 (d, *J* = 6 Hz, 2H), 3.66 (td, *J* = 7.7, 3 Hz, 1H), 3.57 (dd, *J* = 9.5, 3 Hz, 1H), 3.38 (dd, J_{HH} = 9.3, 7.7 Hz, 1H), 2.40 (d, *J* = 4.2 Hz, 1H), 2.19 (ddd, *J* = 9.4, 7.9, 3.6 Hz, 1H), 2.09-2.00 (m, 2H), 1.77-1.73 (m, 1H), 1.49-1.45 (m, 1H), 1.31-1.27 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.07, 138.53, 138.15, 133.98, 129.20, 128.67, 128.61, 128.01, 127.95, 127.94, 127.82, 114.65, 73.59, 73.10, 72.94, 72.06, 70.72, 46.50, 34.03, 30.19, 26.73

HRMS calculated for $C_{25}H_{32}O_3$ $(M+NH_4)^+$ 398.2695; found 398.2696 (FAB).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-methylhex-4-en-2-yl methyl hydrogen phosphate: 3.1a



Using procedure A (50 mg of **1.1**) afforded **3.1a** (51.5 mg, 99%) as a clear viscous oil (compound was processed without further purification).

$[\alpha]_D$ = +15.6 (*c* = 4.5, CH_2Cl_2)

FTIR (neat) 2331, 1496, 1454, 1232 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (bs, 1H), 7.37-7.26 (m, 10H), 5.71-5.62 (m, 2H), 4.58-4.49 (m, 2H), 4.48 (s, 2H), 4.36-4.32 (m, 1H), 3.96 (s, 2H), 3.71-3.53 (m, 5H), 2.73-2.61 (m, 1H), 1.11 (d, *J* = 6.7 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.67, 138.30, 134.72, 128.81, 128.80, 128.25, 128.22, 128.11, 128.05, 81.45, 73.71, 72.44, 71.02, 70.45, 54.61, 38.80, 15.87

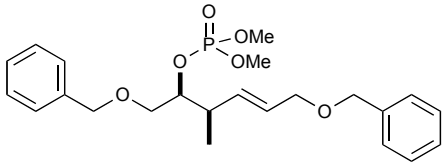
^{31}P NMR (162 MHz, $CDCl_3$) δ 2.67

HRMS calculated for $C_{22}H_{29}O_6P$ $(M+Na)^+$ 443.1599; found 443.1600 (FAB).

General Methylation procedure:

To a stirring solution of phosphate acid (0.295 mmol) in MeOH (0.6 mL) was slowly added (trimethylsilyl)diazomethane (2.0M, 1.48 mmol). Upon addition, the reaction was allowed to run for 20 minutes at room temperature with stirring to ensure completion (monitored by TLC), then quenched by dropwise addition of acetic acid until effervescence ceases. The reaction was concentrated under reduced pressure and pushed through a small plug of silica (4:1 hexanes/EtOAc) to supply the desired methyl phosphate ester.

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-methylhex-4-en-2-yl dimethyl phosphate: 6.1a



Using procedure A, methylation followed by column chromatography (EtOAc:heptane 2:1) afforded **6.1a** (50 mg, 95%) as a clear oil over two steps.

$[\alpha]_D$ = -27.0 (*c* = 2.0, CH_2Cl_2)

FTIR (neat) 3062, 2952, 1454, 1363, 1278, 1041 cm^{-1}

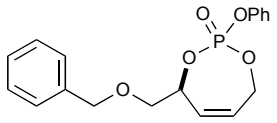
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 10H), 5.69-5.62 (m, 2H), 4.58-4.40 (m, 5H), 3.97-3.94 (m, 2H), 3.73 (d, J_{HP} = 11.2, 2H), 3.69 (d, J_{HP} = 11.2, 2H), 3.64-3.56 (m, 2H), 2.73-2.64 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.19, 137.79, 134.00, 128.34, 128.31, 127.89, 127.71, 127.69, 127.65, 127.57, 80.95 (d, J_{CP} = 6.3), 73.16, 71.99, 70.55, 70.07 (d, J_{CP} = 1.3), 54.28 (d, J_{CP} = 6.3), 54.23 (d, J_{CP} = 6.3), 38.44 (d, J_{CP} = 5.0), 15.43

^{31}P NMR (162 MHz, $CDCl_3$) δ 2.06

HRMS calculated for $C_{23}H_{32}O_6P$ $(M+H)^+$ 435.1937; found 435.1967 (FAB).

(*S*)-configured unsymmetrical monocyclic phosphate: 7.1



A flask containing allylic alcohol **1.3** (0.680 g, 3.83 mmol) was diluted up in THF (0.2 M, 20 mL) and cooled to -40 ˚C, followed by dropwise addition of BuLi (1.53, 2.5M). After 10 minutes of stirring, allyldiphenyl phosphate (1.45 g, 5 mmol) in THF (1M, 5 mL) was cannulated to the flask containing the alkoxide. The solution was stirred for eight hours while slowly warming to room temperature. The reaction was quenched with sat'd aq. NH_4Cl^- and the layers were separated and the aqueous layer extracted with Et_2O (2x). The combined organic layers were concentrated under reduced pressure and dried (Na_2SO_4). Column chromatography (1:1 Hex:EtOAc) afforded the acyclic phosphate ester (1.03 g, 71%) as an oil. To a flask containing the phosphate precursor was added degassed CH_2Cl_2 (0.05 M, 22.6 mL) and was subsequently fitted with a reflux condenser and needle, through which a slow steady stream of Ar flowed. Grubbs catalyst $(IMesH_2)(PCy_3)(Cl_2)Ru{=}CHPh$ (0.034 mg, 0.04 mmol) was added and the reaction lowered into an oil bath warmed to 50 ˚C. The reaction was monitored by TLC and after 1.0-1.5 hrs was deemed complete. Following cooling to room temperature, the reaction was concentrated and purified via column chromatograpy (2:1 hexanes:EtOAc), to yield cyclic phosphate **7.1** as a 1:1 mixture of diastereomers at phosphorus (0.301 g, 76%).

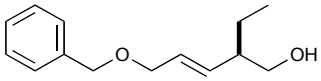
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.17 (m, 10H), 5.89-5.74 (m, 2H), 5.41-5.23 (m, 1H), 5.14-4.89 (m, 1H), 4.71-4.51 (m, 3H), 3.79-3.62 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.38 (d, J_{CP} = 16.1), 150.22 (d, J_{CP} = 16.1), 137.44, 129.68 (d, J_{CP} = 4.0), 128.61, 128.38, 128.23, 127.78, 127.67 (d, J_{CP} = 7.0), 127.42, 127.08, 125.22, (d, J_{CP} = 6.0), 120.11 (d, J_{CP} = 5.0), 119.87 (d, J_{CP} = 4.0), 74.35 (d, J_{CP} = 7.0), 74.01 (d, J_{CP} = 4.0), 73.47, 73.28, 71.58 (d, J_{CP} = 9.1), 71.15 (d, J_{CP} = 11.1), 64.87 (d, J_{CP} = 7.0), 64.80 (d, J_{CP} = 8.0)

^{31}P NMR (162 MHz, $CDCl_3$) δ -3.61 and -2.87

HRMS calculated for $C_{18}H_{19}O_5P$ $(M+Na)^+$ 369.0868; found 369.0872 (FAB).

(*R*,*E*)-5-(benzyloxy)-2-ethylpent-3-en-1-ol: 7.2



Following procedure A (90 mg of **7.1**) and methylation/phosphate removal, column chromatography (heptane:EtOAc 3:1) afforded **7.2** (42.1 mg, 81%) as a clear oil.

$[\alpha]_D$ = + 6.2 (*c* = 1.6, CH_2Cl_2)

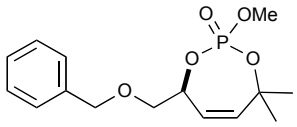
FTIR (neat) 3389, 2958, 1454, 1307, 1089, 1049 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.19 (m, 5H), 5.63 (dt, *J* = 15.4, 6.0 Hz, 1H), 5.43 (dd, *J* = 15.5, 8.7 Hz, 1H), 4.45 (s, 2H), 3.49 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.36 (dd, *J* = 10.6, 8.0 Hz, 1H) 2.12-2.03 (m, 1H), 1.71 (bs, 1H), 1.45-1.34 (m, 1H), 1.26-1.15 (m, 1H), 0.83 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.24, 135.15, 129.18, 128.43, 127.68, 127.58, 72.11, 70.67, 65.60, 47.26, 23.78, 11.67

HRMS calculated for $C_{14}H_{20}O_2$ $(M+Na)^+$ 243.1361; found 243.1361 (FAB).

(*S*)-configured unsymmetrical monocyclic phosphate: 8.2



A flask containing allylic alcohol **1.3** (0.239 g, 1.34 mmol) was diluted up in THF (0.2 M, 6.7 mL) and cooled to –30 ˚C, followed by dropwise addition of BuLi (0.537 mL, 2.5M). After 10 minutes of stirring, dichloromethyl phosphate (0.147, 1.47 mmol) was added to the flask containing the alkoxide. The solution was stirred for one hour while slowly warming to room temperature. The reaction was quenched with sat'd aq. NH_4Cl^- and the layers were separated and the aqueous layer extracted with Et_2O (2x). The combined organic layers were concentrated under reduced pressure and dried (Na_2SO_4). Column chromatography (4:1 Hex:EtOAc) afforded the monochloride phosphate ester (0.311 g, 80%) as an oil. The chloride was immediately used. A flask containing alcohol **8.1** (0.074 mg, 0.861 mmol) was charged with THF (0.2 M, 4.31 mL) and cooled to -30 ˚C, followed by dropwise addition of BuLi (0.346 mL, 2.4 M). After 10 minutes of stirring, a solution of the previously generated monochloride phosphate ester (0.200 g, 0.688 mmol) in THF (0.7 M, 1 mL) was cannulated to the flask containing the alkoxide. The solution was stirred for 1.5 hrs while slowly warming to room temperature. The reaction was quenched with sat'd aq. $NH_4^+Cl^-$ and the layers were separated and the aqueous layer extracted with Et_2O (2x). The combined organic layers were concentrated under reduced pressure and dried (Na_2SO_4). *Due to the instability of the acyclic phosphate, the reaction mixture was carried on without chromatography*. To a flask containing

the crude phosphate ester (assumed to be 0.688 mmol) was added degassed toluene (0.02 M, 34 mL) and was subsequently fitted with a reflux condenser, and needle through which a slow steady stream of Ar flowed. Grubbs catalyst $(ImesH_2)(PCy_3)(Cl_2)Ru{=}CHPh$ (0.029 mg, 0.034 mmol) was added and the reaction lowered into an oil bath warmed to 90 ºC. The reaction was monitored by TLC and after 1.0 hr was deemed complete. Following cooling to room temperature, the reaction was concentrated and purified via column chromatograpy (2:1 hexanes:EtOAc), to yield cyclic phosphate **8.2** as a 1:1 mixture of diastereomers at phosphorus (0.100 g, 47 %). One diastereomer could be purified, and was used for characterization.

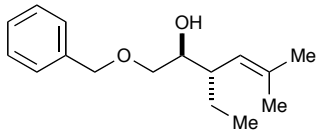
FTIR (neat) 3029, 2966, 1101, 737, 698 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 5.63 (dd, J = 12.1 Hz, J_{HP} = 2.3 Hz, 1H), 5.53 (dd, J = 12.1 Hz, J_{HP} = 3.1 Hz, 1H), 4.61 (dd, J = 12, 4.1 Hz, 2H), 3.81 (d, J_{HP} = 11.2 Hz, 3H), 3.67 (dd, J = 10.2, 6.9 Hz, 1H), 3.57 (ddd, J = 10.2, 5.2, 1.9 Hz, 1H), 1.75 (s, 3H), 1.48 (d, J_{HP} = 2.5 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.90, 137.66, 128.46, 127.68, 124.16, 82.10 (d, J_{CP} = 5.0 Hz), 73.55, 72.79 (d, J_{CP} = 6.3 Hz), 71.86 (d, J_{CP} = 10.1 Hz), 54.13 (d, J_{CP} = 5.0 Hz), 30.53 (d, J_{CP} = 11.3 Hz), 29.32

^{31}P NMR (162 MHz, $CDCl_3$) δ 0.07 and -0.90.

(*2S,3S*)-1-(benzyloxy)-3-ethyl-5-methylhex-4-en-2-ol: 8.3



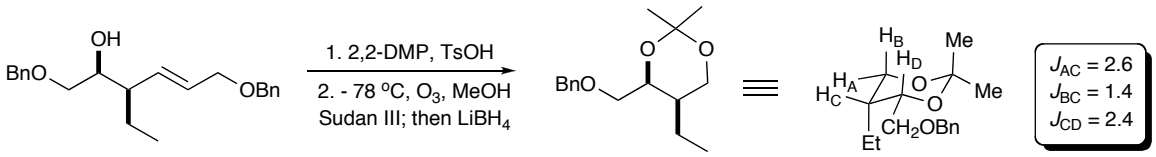
Following procedure A (90 mg of **8.2**) and methylation/phosphate removal, column chromatography (heptane:EtOAc 3:1) afforded **8.3** (58.0 mg, 81%) as a clear oil.

$[\alpha]_D$ = +13.1, (*c* = 1.5, CH_2Cl_2)

FTIR (neat) 3431, 3029, 2966, 1101 cm^{-1}

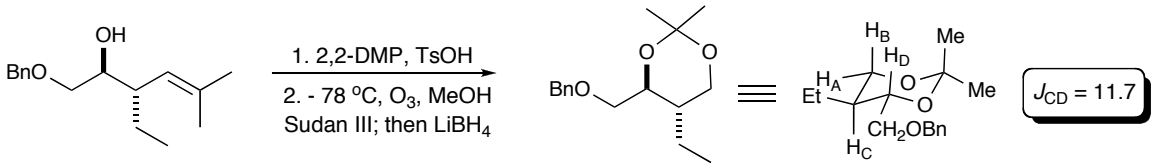
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.22 (m, 5H), 5.02 (d, *J* = 8.9 Hz, 1H), 4.50 (s, 2H), 3.81-3.74 (m, 1H), 3.54 (dd, *J* = 9.6, 3.1 Hz, 1H), 3.45 (dd, *J* = 9.6, 7.8, 1H), 2.37-2.28 (m, 1H), 2.24 (bs, 1H), 1.78 (s, 3H), 1.65, (s, 3H), 1.61-1.51 (m, 1H), 1.34-1.24 (m, 1H), 0.86, (t, *J* = 7.3, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.15, 134.65, 129.61, 128.44, 127.76, 124.40, 115.34, 73.40, 73.21, 73.02, 42.61, 26.05, 24.70, 18.45.



4-(benzyloxymethyl)-5-ethyl-2,2-dimethyl-1,3-dioxane:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.26 (ddd, *J* = 6.2, 6.2, 2.4 Hz, 1H), 3.97 (ddd, *J* = 11.9, 2.6, 1.11 Hz, 1H), 3.82 (dd, *J* = 11.9, 1.4 Hz, 1H), 3.49 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.43 (dd, *J* = 9.7, 5.9 Hz, 1H), 1.77-1.65 (m, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 1.35-1.27 (m, 2H), 0.92 (t, *J* = 7.2 Hz).

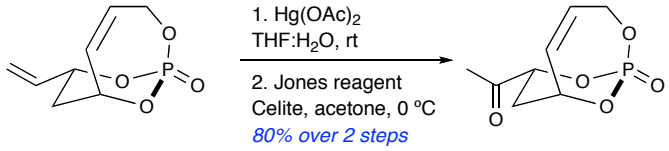


(*4S,5S*)-4-(benzyloxymethyl)-5-ethyl-2,2-dimethyl-1,3-dioxane:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (m, 5H), 4.63 (d, *J* = 12.3 Hz, 1H), 4.52 (d, *J* = 12.3 Hz, 1H), 3.87 (dd, *J* = 11.7, 5.4 Hz, 1H), 3.74 (ddd, *J* = 10.3, 5.0, 2.8 Hz, 1H),85 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.42, 128.33, 127.73, 127.56, 98.19, 73.58, 73.38, 71.50, 63.65, 37.02, 29.38, 21.08, 19.38, 10.05. HRMS calculated for $C_{16}H_{24}O_3$ $(M+Na)^+$ 287.1623; found 287.1628 (FAB).

5.3 Experimental Data: Chapter 3

1-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)ethanone: 4.1



To a 250 mL round bottom flask under Ar (g) equipped with large stir bar was added 8.91 g (27.95 mmol, 2 equiv.) mercuric acetate followed by 35 mL degassed deionized H_2O. To this stirring mixture was cannulated a solution of 2.82 g (13.98 mmol) phosphate **2.1**[1,2] in 105 mL of degassed THF. The mixture was stirred vigorously until completion (24-48 h, monitored by TLC, 100% EtOAc). A mixture of 2.35 g (27.95 mmol, 2 equiv.) solid $NaHCO_3$ and 2.86 g (16.77 mmol, 1.2 equiv.) $CuCl_2$•$2H_2O$ was then added and the ensuing mixture allowed to stir for 15 minutes. 100 mL EtOAc was then added, mixed, and the layers separated. The small aqueous layer was extracted 3 more times with 100 mL EtOAc to ensure recovery of the very polar product, followed by combination of the organic extracts which were washed with brine and dried with Na_2SO_4. Filtration into a 250 mL round bottom flask followed by solvent removal in vacuo provided 3.09 g of alcohol **8.1**, which was used immediately in the next reaction.

The 250 mL round bottom flask is equipped a stir bar and 140 mL of acetone is added to generate a 0.1 M solution followed by 21 g of Celite® (1.5 g/mmol). The stirring solution is cooled to 0 ºC, at which time 6.28 mL of Jones reagent (16.77 mmol, 1.2 equiv.) is added dropwise. The reaction is allowed to proceed with stirring

at 0 ºC until completion (TLC 20% acetone in ethyl acetate; ~ 2 h). Upon indication of reaction completion, 0.5 mL isopropyl alcohol is added to consume any leftover Jones reagent, followed by filtration. The filtrate is then concentrated to 40 mL, followed by addition of 100 mL ethyl acetate and careful addition of 10 mL $NaHCO_3$ (aq). The solution is mixed and the layers separated, followed by 3 x 100 mL extractions of the aqueous layer. The combined organic layers are washed with brine, dried with Na_2SO_4, filtered and silica added. The solvent is then removed and the product laden silica added to a very short silica gel column. Eluting the column with 100% ethyl acetate (1 column volume) removes any less polar constituents, followed by elution with 20% acetone in ethyl acetate to elute product. Solvent removal provides 3.05 g (80% yield) of phosphate **4.1**.

$[\alpha]_D$: -21 (*c* = 0.63, acetone, 25.6 ºC)

FTIR: (neat) 2970, 2924, 2893, 2850, 1724, 1292, 1259, 1091, 1058, 991, 946, 921, 885, 770 cm^{-1}

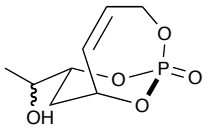
^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.11 (dddd, *J* = 11.9, 6.5, 3.0, 2.2 Hz, 1H), 5.65 (ddd, *J* = 11.9, 4.0, 2.7 Hz, 1H), 5.31 (dddd, *J* = 24.6, 3.9, 2.1, 1.9 Hz, 1H), 5.05 (dddd, *J* = 14.8, 11.2, 5.0, 2.7 Hz, 1H), 4.97 (dt, *J* = 12.1, 2.3 Hz, 1H), 4.43 (ddd, *J* = 28.3, 14.8, 6.7 Hz, 1H), 2.37 (s, 3H), 2.26 (ddddd, *J* = 14.8, 6.5, 5.2, 3.8, 2.5 Hz, 1H), 2.15 (dddd, *J* = 14.8, 2.6, 2.5, 1.5 Hz, 1H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 205.8 (d, J_{CP} = 12.0 Hz), 129.3, 128.7, 79.6 (d, J_{CP} = 7.2 Hz), 77.4 (d, J_{CP} = 7.1 Hz), 63.5 (d, J_{CP} = 6.4 Hz), 31.3 (d, J_{CP} = 6.0 Hz), 26.2

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -3.64

HRMS Exact Mass: calculate for $C_8H_{11}NaO_5P$ $(M+Na)^+$ 241.0242; found 241.0235 (ESI)

1-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)ethanol: 8.1



To a 10 mL round bottom flask under Ar (g) equipped with stir bar was added 312 mg (0.98 mmol, 2 equiv.) mercuric acetate followed by 1.25 mL degassed deionized H_2O. To this stirring mixture was cannulated a solution of 100 mg (0.49 mmol) phosphate **2.1** in 3.75 mL of degassed THF. The mixture was stirred vigorously until completion (24-48 h, monitored by TLC, 100% EtOAc). A mixture of 82 mg (0.98 mmol, 2 equiv.) solid $NaHCO_3$ and 100 mg (0.59 mmol, 1.2 equiv.) $CuCl_2 \bullet 2H_2O$ was then added and the ensuing mixture allowed to stir for 15 minutes. 20 mL EtOAc was then added, mixed, and the layers separated. The small aqueous layer was extracted 3 more times with 20 mL EtOAc to ensure recovery of the very polar product, followed by combination of the organic extracts which were washed with brine and dried with Na_2SO_4 and filtered. Silica was added followed by solvent removal, whereupon the impregnated silica was placed on a silica gel column and the product eluted with 20% acetone in EtOAc, which after solvent removal provided 107 mg (99% yield) of alcohol **8.1**.

FTIR: (neat) 3387, 2928, 1280, 1105, 1068, 1036, 978, 931, 769 cm^{-1}

^{1}H NMR (500 MHz, acetone-d_6) δ ppm 6.09 (dddd, J = 11.9, 5.2, 4.3, 2.2 Hz, 1H), 5.76 (ddd, J = 11.9, 3.8, 2.6 Hz, 1H), 5.33 (app d, J = 24.7 Hz, 1H), 4.89 (dddd, J =

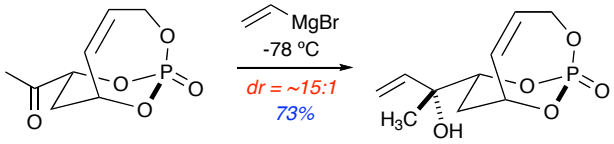
14.1, 6.2, 5.6, 2.7 Hz, 1H), 4.69 (d, J = 5.5 Hz, 1H), 4.45-4.31 (m, 2H), 4.16 (dddd, J = 6.3, 5.9, 5.9, 5.8 Hz, 1H), 2.24-2.12 (m, 3H), 2.09 (br s, 2H)

^{13}C NMR (126 MHz, acetone-d_6) δ ppm 131.2, 128.3, 82.0 (d, J_{CP} = 6.9 Hz), 78.6 (d, J_{CP} = 6.7 Hz), 72.5 (d, J_{CP} = 10.4 Hz), 63.6 (d, J_{CP} = 6.3 Hz), 34.9, 31.6 (J_{CP} = 5.9 Hz)

^{31}P NMR (162 MHz, acetone-d_6) δ ppm -4.20 (t, J_{PH} = 25.0 Hz)

HRMS Exact Mass: calculate for $C_{10}H_{16}HgO_7P$ $(M+HgOAc)^+$ 481.0340;
found 481.0364 (ESI)

(*R*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)but-3-en-2-ol: 11.1



A 25 mL flask containing 280 mg (1.28 mmol) of ketone **4.1** was placed under argon atmosphere and 13 mL of THF were added to generate a 0.1 M solution. The solution was then cooled to -78 ºC and freshly prepared vinyl magnesium bromide (3.86 mL, 1.0M in THF, 3 equiv.) was added slowly along the side of the flask. The reaction mixture was maintained in a cooling bath at -78 ºC for 7 h, after which time 13 mL of saturated aqueous NH_4Cl was added, the flask removed from the cooling bath, and the mixture allowed to reach room temperature. The reaction mixture was extracted with 3 x 30 mL EtOAc and the organic layers collected. The organic layers were then washed with 20 mL brine, dried with Na_2SO_4, filtered, SiO_2 added and the solvent removed *in vacuo*. The substrate impregnated SiO_2 was then placed on a short column, eluted with 2 column volumes of ethyl acetate, and then eluted with 10% acetone in EtOAc. Solvent removal afforded 230 mg (73% yield) of the desired tertiary alcohol **11.1**.

$[\alpha]_D$: -68.6 (*c* = 3.45, acetone, 27 ºC)

FTIR: (neat) 3406, 2981, 2935, 1263, 1224, 1161, 1072, 1031, 983, 921, 883, 771 cm^{-1}

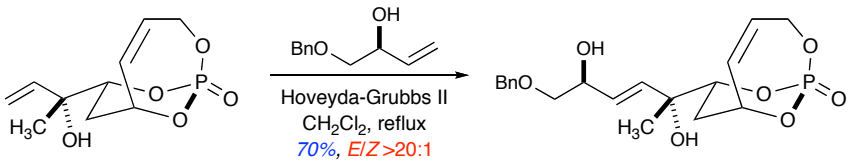
^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.03 (dddd, *J* = 6.9, 6.6, 3.7, 1.4 Hz, 1H), 5.80 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.58 (ddd, *J* = 11.85, 3.9, 2.7 Hz, 1H), 5.39 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.23 (dddd, *J* = 25.0, 2.2, 2.0, 1.0 Hz, 1H), 5.21 (dd, *J* = 10.9, 1.2 Hz, 1H), 5.00 (dddd, 14.7, 5.6, 5.6, 2.7 Hz, 1H), 4.39 (ddddd, 14.9, 10.3, 6.9, 1.8, 0.8 Hz, 2H), 2.37 (ddd, *J* = 14.9, 12.2, 6.4 Hz, 1H), 2.24 (br s, 1H), 1.75 (ddd, 14.8, 3.6, 2 Hz, 1H), 1.38 (s, 3H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 139.3, 130.1, 128.1, 115.7, 81.6 (d, J_{CP} = 7.2 Hz), 77.4 (d, J_{CP} = 6.9 Hz), 74.1 (d, J_{CP} = 9.1 Hz), 63.3 (d, J_{CP} = 6.4 Hz), 29.3 (d, J_{CP} = 5.5 Hz), 24.6

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -2.88 (t, J_{PH} = 25.0 Hz)

HRMS Exact Mass: calculate for $C_{10}H_{15}NaO_5P$ $(M+Na)^+$ 269.0555; found 269.0532 (ESI)

(2*S*,5*R*,*E*)-1-(benzyloxy)-5-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)hex-3-ene-2,5-diol: 14.2



A solution of 11 mg (0.0446 mmol) of phosphate **11.1** and 40 mg (0.223 mmol, 5 equiv.) of allylic alcohol **14.1** in 1 mL of degassed CH_2Cl_2 is prepared, thus generating a 0.05M solution with respect to phosphate **11.1**. The solution is added to a small, flame dried pressure tube containing a stir bar and 3 mg (0.0045 mmol, 0.1 equiv.) Hoveyda-Grubbs II catalyst, which is immediately flushed with argon, capped, and placed in a 48 ºC silicon oil bath. The reaction is allowed to stir for 12 hours at 48 ºC and then removed from heat to cool to room temperature. Addition of a slight amount of SiO_2 followed by solvent removal provides the impregnated SiO_2, which is placed on a column and eluted with 10% acetone in ethyl acetate to provide 12 mg (70% yield) of the desired cross-metathesis product as a single observable isomer.

$[\alpha]_D$: -60 (*c* = 0.10, acetone, 23.8 ºC)

FTIR: (neat) 3340, 2978, 2860, 1286, 1072, 1035, 987, 923, 742 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 7.34 (m, 5H), 5.99 (dddd, *J* = 11.9, 5.3, 4.5, 2.2 Hz, 1H), 5.85 (dd, *J* = 15.6, 5.1 Hz, 1H), 5.71 (dd, *J* = 15.6, 1.2 Hz, 1H), 5.45 (ddd, *J* = 11.9, 3.9, 2.5 Hz, 1H), 5.14 (ddd, *J* = 21.0, 2.1, 1.7 Hz, 1H), 4.99 (dddd, *J* = 11.9, 8.4, 5.6, 2.7 Hz, 1H), 4.56 (s, 2H), 4.39 (br s, 1H), 4.36 (ddd, *J* = 27.5, 12.1, 7.9, 2.0

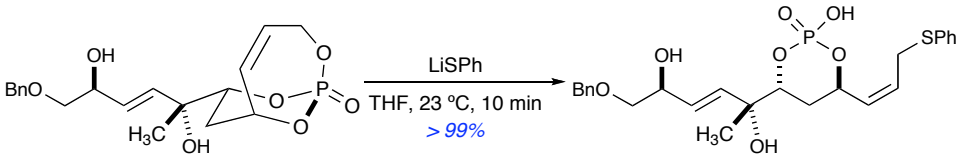
Hz, 2H), 3.58 (dd, J = 9.6, 3.4 Hz, 1H), 3.38 (dd, J = 9.5, 7.6 Hz, 1H), 2.50 (d, J = 3.3 Hz, 1H), 2.31 (ddd, J = 14.9, 12.2, 6.4 Hz, 1H), 2.21 (s, 1H), 1.69 (ddd, J = 14.9, 3.3, 2.2 Hz, 1H), 1.37 (s, 3H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 137.9, 132.5, 130.2, 129.5, 128.7, 128.2, 128.1, 128.0, 81.5 (d, J_{CP} = 7.3 Hz), 77.4 (d, J_{CP} = 6.8 Hz), 74.2, 73.8 (d, J_{CP} = 9.1 Hz), 73.7, 70.7, 63.4 (d, J_{CP} = 6.4 Hz), 29.3 (d, J_{CP} = 5.5 Hz), 25.2

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -2.88 (t, J_{PH} = 21.1 Hz)

HRMS Exact Mass: calculate for $C_{19}H_{25}NaO_7P$ $(M+Na)^+$ 419.1236; found 419.1229 (ESI)

Monocyclic Phosphate Acid 14.3



To a dry 5 mL round bottom flask under argon containing a stir bar and 5 mg (0.0126 mmol) of phosphate **14.2** was added 130 μL of THF to generate a 0.1M solution. 13 μL (0.013 mmol, 1 equiv.) of a 1.0M solution of LiSPh in THF was added dropwise, noting TLC (20% acetone in EtOAc solvent system) to determine the endpoint of the reaction via disappearance of starting material. An appropriately titrated reaction as described lends to a facile workup: addition of 10 μL of 1.25M HCl-methanol followed by solvent removal produces 6.4 mg (>99% yield) of phosphate acid **14.3**.

[α]$_D$: -13 (*c* = 0.10, MeOH, 24.4 ºC)

FTIR: (neat) 3628, 3340, 2978, 2860, 1286, 1072, 1035, 987, 923, 742, 681 cm^{-1}

^{1}H NMR (500 MHz, MeOH-d_4) δ ppm 7.30 (m, 10H), 5.78 (app s, 1H), 5.77 (app s, 1H), 5.75 (t, *J* = 9.4 Hz, 1H), 5.56 (dd, *J* = 18.4, 7.8 Hz, 1H), 4.53 (dd, *J* = 9.9, 3.0 Hz, 2H), 4.27 (dd, *J* = 10.9, 4.3 Hz, 1H), 4.12 (d, *J* = 5.9 Hz, 1H), 3.65 (dd, *J* = 13.8, 8.2 Hz, 1H), 3.56 (dd, *J* = 13.8, 7.4 Hz, 1H), 3.42 (ddd, *J* = 9.0, 4.5, 2.9 Hz, 2H), 1.99 (ddd, *J* = 12.7, 8.9, 4.9 Hz, 1H), 1.59 (ddd, *J* = 11.9, 10.2, 3.2 Hz, 1H), 1.31 (s, 3H), 1.29 (dd, *J* = 16.6, 10.4 Hz, 1H)

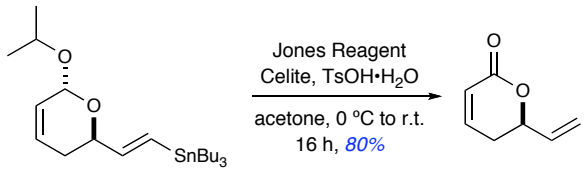
^{13}C NMR (126 MHz, MeOH-d_4) δ ppm 139.8, 137.4, 136.2, 131.3, 130.6, 130.2, 130.0, 129.5, 129.0, 128.8, 128.7, 127.6, 80.1, 75.6, 74.4, 72.1, 69.2, 40.3, 32.9, 32.1, 25.1

^{31}P NMR (162 MHz, MeOH-d_4) δ ppm -2.53

HRMS Exact Mass: calculate for $C_{25}H_{30}O_7PS$ $(M-H)^-$ 505.1455; found 505.1446 (ESI)

5.4 Experimental Data: Chapter 4

(*R*)-6-vinyl-5,6-dihydro-2*H*-pyran-2-one: 2.4



To a 50 mL round bottom flask equipped with comparably large stir bar is added 800 mg of stannane **11.1** (1.74 mmol), 2.62g Celite (1.5g/mmol) and 17.5 mL of acetone (0.1M with respect to **11.1**). The stirring mixture was brought to 0 ºC and 1.44 mL of Jones reagent (2.67M, 3.84 mmol, 2.2 equiv.) added dropwise, followed by addition of 1.99g of TsOH•H_2O (10.4 mmol, 6 equiv.). After 1 hour the reaction was allowed to stir at room temperature for 15 hours before the reaction was filtered and the solid washed with 10 mL of acetone. The filtrate was concentrated, 30 mL of EtOAc and 10 mL of brine added, and the mixture agitated. Separation of the organic layer followed by extraction of the aqueous layer with 3x 10ml portions of EtOAc preceeded combination of all organic layers, to which SiO_2 was added and the slurry concentrated to dryness. The impregnated SiO_2 was placed on a SiO_2 column, flushed with 1:1 petroleum ether: diethyl ether to remove more nonpolar components, followed by elution with 100% diethyl ether to elute 173 mg (80% yield) of desired lactone **2.4**.

$[\alpha]_D$: +93 (*c* = 0.55, CH_2Cl_2, 26.3 ºC)

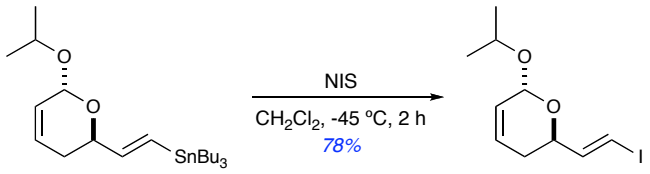
FTIR: (neat) 2957, 2924, 2854, 1722, 1420, 1385, 1246, 1034, 987, 935, 816, 669 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.88 (ddd, *J* = 9.8, 5.4, 3.1 Hz, 1H), 6.06 (ddd, *J* = 9.8, 2.3, 1.3 Hz, 1H), 5.95 (ddd, *J* = 16.5, 10.6, 5.7 Hz, 1H), 5.41 (dd, *J* = 16.5, 0.9 Hz, 1H), 5.30 (dd, *J* = 10.6, 0.8 Hz, 1H), 4.93 (ddd, *J* = 10.3, 5.4, 5.3 Hz, 1H), 2.47 (ttd, *J* = 18.5, 5.1, 1.3 Hz, 1H), 2.45 (dddt, *J* = 18.5, 12.8, 10.0, 2.55 Hz, 1H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 164.0, 144.6, 135.0, 121.9, 118.1, 78.0, 29.6

HRMS Exact Mass: calculate for $C_7H_8O_2Na$ $(M+Na)^+$ 147.0422; found 147.0419 (ESI)

(2*R*,6*R*)-2-((*E*)-2-iodovinyl)-6-isopropoxy-3,6-dihydro-2*H*-pyran: 3.1



To a flame dried 100 mL round botton flask under argon containing a stir bar is placed 1.99 g stannane **11.1** (4.34 mmol) and 62 mL of CH_2Cl_2 to generate a 0.07M solution. The mixture is placed in a cold bath and lowered to -45 ºC, at which time 1.17 g *N*-iodosuccinimide (5.21 mmol, 1.2 equiv.) is added to the stirring solution in the dark. The reaction is allowed to proceed in the dark until complete by TLC (30:1 hexane: diethyl ether; about 2 hours), at which time 50 mL 10% NaS_2O_3 (aq) is added and the mixture allowed to achieve room temperature while continuing to protect the vessel from light. The organic layer is separated and the aqueous layer extracted with 3x 15 mL diethyl ether. The combined organic layers are dried with $MgSO_4$, filtered, and the solvent removed. The crude mixture is then purified by flash column chromatography, initially using 100% petroleum ether to remove any stannane, followed by elution with 30:1 petroleum ether: diethyl ether to provide 995 mg (78% yield) of the vinyl iodide.

$[\alpha]_D$: +36 (*c* = 4.46, CH_2Cl_2, 26.0 ºC)

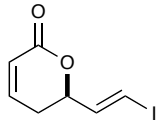
FTIR: (neat) 3043, 2968, 2924, 2895, 1464, 1380, 1315, 1180, 1124, 1099, 1059, 1026, 1002, 947, 783, 717 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 5.95 (ddt, *J* = 10.2, 5.7, 1.4 Hz, 1H), 5.70 (dtd, *J* = 10.2, 2.9, 1.3 Hz, 1H), 5.12 (d, *J* = 0.9Hz, 1H), 4.68 (ddd, *J* = 11.3, 2.9, 2.3 Hz, 1H), 4.05 (hept., *J* = 6.2 Hz, 1H), 2.45 (d, *J* = 4.5 Hz, 1H), 2.41 (dddt, *J* = 17.8, 7.7, 2.8, 1.8 Hz, 1H), 2.21 (dddd, *J* = 17.8, 5.7, 3.7, 1.3 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 1H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 127.8, 126.1, 93.1, 83.0, 72.9, 70.1, 57.1, 31.4, 24.0, 22.2

HRMS Exact Mass: calculate for $C_{10}H_{15}INaO_2$ $(M+Na)^+$ 317.0014; found 317.0015 (ESI)

(*R*,*E*)-6-(2-iodovinyl)-5,6-dihydro-2*H*-pyran-2-one: 5.2



To a 10 mL flame dried flask was added 200 mg (0.85 mmol) of alcohol **5.1**,[3] 253 µL (1.45 mmol, 1.7 equiv.) *i*-Pr_2NEt, and 4.3 mL of CH_2Cl_2 (0.2 M w/r **5.1**). The solution was cooled to 0 ºC with stirring, at which time 83 µL (1.03 mmol, 1.2 equiv.) acryloyl chloride was added dropwise. The reaction was allowed to stir at 0 ºC until completion, typically about 1.5 h. Upon completion, sat. NH_4Cl (aq) was added and the mixture extracted with 3 x 10 mL diethyl ether. The combined organic layers were washed with brine, dried with $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the crude material filtered through a silica plug with 20:1 hexanes: diethyl ether. Solvent removal provided 199 mg of the ester (0.71 mmol, 84 % yield), which was used immediately to prevent potential polymerization.

The ester was placed in a 100 mL flame dried flask equipped with reflux condenser under Ar atmosphere followed by 71 mL dry, degassed dichloroethane to generate a 0.01 M solution. The condenser was fitted with a vent and a long needle through which Ar was slowly introduced into the stirring mixture. The solution was heated to 90 ºC before 89 mg (0.14 mmol) Hoveyda-Grubbs II catalyst was introduced. Stirring was continued at 90 ºC until completion of the reaction by TLC (20:1 hexane: diethyl ether). Upon completion, the reaction was cooled and the solvent removed under reduced pressure. The crude material was purified by

chromatography (2:1 hexane: diethyl ether) to produce 71 mg (40% yield) of lactone **5.2** as a faint yellow oil.

$[\alpha]_D$: +68 (*c* = 0.40, CH_2Cl_2, 23.6 ºC)

FTIR: (neat) 2957, 2930, 2857, 1722, 1420, 1386, 1246, 1035cm^{-1}

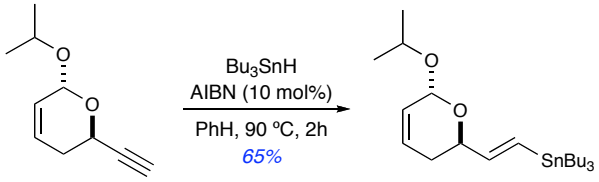
^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.87 (ddd, *J* = 9.8, 5.4, 3.1 Hz, 1H), 6.51 (br s, 2H), 6.06 (ddd, *J* = 9.8, 2.4, 1.3 Hz, 1H), 4.89 (dt, *J* = 10.3, 4.3 Hz, 1H), 2.53-2.40 (m, 2H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 163.2, 144.2, 141.9, 121.9, 81.4, 78.8, 29.1

HRMS Exact Mass: calculate for $C_7H_7INaO_2$ $(M+Na)^+$ 272.9388;

found 272.9402 (ESI)

tributyl((*E*)-2-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)vinyl)stannane: 11.1



To a flame dried 100 mL round bottom flask equipped with stir bar, water-jacketed reflux condenser and under argon was placed 3.76g (22.6 mmol) of alkyne **7.5**,[4] 12.2 mL of Bu_3SnH (45.2 mmol, 2 equiv.) and 23 mL of benzene (1M with respect to alkyne **7.5**). To this stirring mixture was added 370 mg (2.26 mmol, 10 mol %) of AIBN, brought to 90 ºC, and allowed to proceed at this temperature for 2 hours. After this duration of time, the reaction was allowed to cool to room temperature, the solvent removed, and the mixture placed on a pretreated SiO_2 column (pretreatment involves mixing 1mL Et_3N per 100g SiO_2), flushed with 100% hexanes to remove excess Bu_3SnH. After removal of excess Bu_3SnH, the product is eluted with a 1% Et_3N/ 1:1 hexane:CH_2Cl_2 system to afford 6.74g (65% yield) of the stannane.

$[\alpha]_D$: +25.9 (*c* = 2.90, CH_2Cl_2, 26.0 ºC)

FTIR: (neat) 3043, 2956, 2921, 2871, 2854, 1464, 1420, 1400, 1377, 1315, 1180, 1126, 974, 959, 946, 864, 717, 690, 665, 594, 501 cm^{-1}

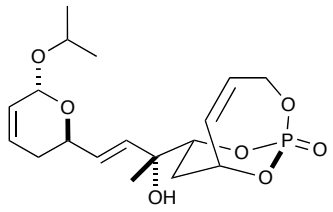
^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.22 (dd, *J* = 19.2, 1.3 Hz, 1H), 6.04 (dd, *J* = 19.2, 5.1 Hz, 1H), 6.01 (m, 1H), 5.72 (dddd, *J* = 10.1, 4.4, 2.8, 1.6 Hz, 1H), 5.13 (dd,

J = 1.5, 1.1 Hz, 1H), 4.40 (ddd, *J* = 9.4, 5.4, 4.3 Hz, 1H), 4.02 (hept., *J* = 6.2 Hz, 1H), 2.08 (ddd, *J* = 10.4, 2.5, 1.4 Hz, 1H), 2.07 (ddd, *J* = 5.1, 4.7, 1.4 Hz, 1H), 1.49 (dddd, *J* = 8.1, 7.4, 1.9, 1.7 Hz, 6H), 1.30 (dddd, *J* = 7.4, 7.3, 4.1, 3.3 Hz, 6H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.89 (q, *J* = 8.2 Hz, 9H), 0.88 (t, *J* = 7.3 Hz, 6H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 148.0, 129.3, 128.9, 126.3, 93.6, 69.9, 69.2, 30.6, 29.3, 24.0, 22.4, 13.9, 9.6

HRMS Exact Mass: calculate for $C_{22}H_{42}O_2NaSn$ $(M+Na)^+$ 481.2104; 481.2084 found (ESI)

(*R*,*E*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)-4-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)but-3-en-2-ol: 12.1



To a 5 mL flame dried round bottom flask flushed with Ar (g) and equipped with stir bar was added 40 mg (0.138 mmol, 3 equiv.) of iodide **3.1** and 0.34 mL of Et_2O (0.4 M with respect to **3.1**). This solution was cooled to -78 ºC with stirring, at which time 178 µL of *t*-BuLi (1.7 M in pentanes, 0.303 mmol, 2.2 equiv. with respect to **3.1**) was added and the reaction warmed to 0 ºC to stir for 30 minutes. The mixture was then cannulated into a -78 ºC solution of 36 mg $MgBr_2$•OEt_2 (0.138 mmol, 3 equiv.) in 0.46 mL of THF (0.3 M with respect to $MgBr_2$•OEt_2), warmed to 0 ºC and allowed to stir for 30 minutes. This solution was then *slowly* cannulated along the internal side of the reaction flask into a -45 ºC solution of 10 mg ketone **2.2** (0.046 mmol) in 0.16 mL of THF (0.3 M with respect to **2.2**). The reaction was allowed to stir at -45 ºC for 3 hours, at which time the reaction was quenched at -45 ºC by addition of 2 mL sat. NH_4Cl (aq) and allowed to warm to room temperature. The mixture was then added to 10 mL EtOAc in a separatory funnel and the layers separated, followed by extraction of the aqueous layer with 3 x 10 mL portions of EtOAc. The organic layers were then combined, washed with brine, dried (Na_2SO_4), filtered, and SiO_2 added. The solvent was then removed and the SiO_2-bound substrate added to a silica gel column, which was subjected to 2 CVs of 3:1

hexane:EtOAc followed by elution of the product with 100% EtOAc. Removal of the solvent provided 12 mg (69% yield) of phosphate **12.1** as a single observable diastereomer. [Note: Running the ketone addition reaction at -78 ºC rather than -45 ºC requires ~7 h reaction time.]

$[\alpha]_D$: –26 (*c* = 0.10, CH_2Cl_2, 24.9 ºC)

FTIR: (neat) 3381, 2970, 2924, 1292, 1180, 1126, 1072, 1031, 997, 924 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 5.99-5.92 (m, 3H), 5.86 (dd, *J* = 15.7, 5.1 Hz, 1H), 5.67 (ddd, *J* = 10.1, 4.9, 2.0 Hz, 1H), 5.61 (d, *J* = 15.8 Hz, 1H), 5.51 (tdd, *J* = 11.9, 3.9, 2.7 Hz, 1H), 5.16 (app d, 24.0 Hz, 1H), 5.04 (d, *J* = 2.3 Hz, 1H), 4.94 (dddd, *J* = 14.8, 5.6, 5.5, 2.9 Hz, 1H), 4.40 (ddd, *J* = 12.4, 5.7, 1.2 Hz, 1H), 4.32 (ddddd, *J* = 14.8, 12.3, 6.7, 2.0, 1.8 Hz, 2H), 3.90 (sept., *J* = 6.2 Hz, 1H), 2.30 (ddd, *J*= 13.0, 8.5, 5.8 Hz, 1H), 2.10 (d, 12.0 Hz, 1H), 1.98 (tt, *J* = 4.0, 2.1 Hz, 1H), 1.68 (dddd, *J* = 12.8, 11.6, 2.1, 1.8 Hz, 1H), 1.33 (s, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H)

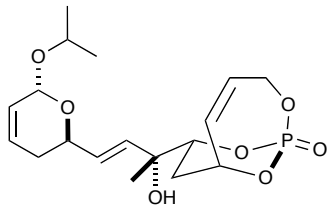
^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 139.3, 131.3, 130.1, 128.5, 128.1, 126.4, 93.8, 81.6 (d, J_{CP} = 7.2 Hz), 77.3 (d, J_{CP} = 2.9 Hz), 73.7 (d, J_{CP} = 9.1 Hz), 70.3, 65.9, 63.4 (d, J_{CP} = 6.3 Hz), 30.8, 29.4 (d, J_{CP} = 5.5 Hz), 25.1, 24.0, 22.5

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -2.89 (t, J_{PH} = 23.8 Hz)

HRMS Exact Mass: calculate for $C_{18}H_{27}NaO_7P$ $(M+Na)^+$ 409.1392;

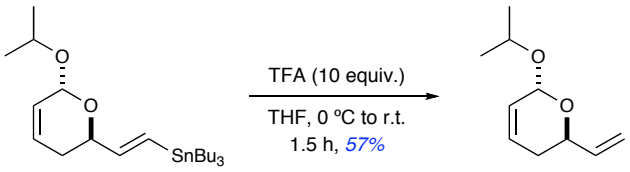
found 409.1393 (ESI)

(*R*,*E*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)-4-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)but-3-en-2-ol: 12.1



To a small dried Pyrex pressure tube under argon was placed 27 mg (0.16 mmol, 5 equiv.) of alkene **14.1** , 2.0 mg Hoveyda-Grubbs II catalyst (0.003 mmol, 10 mol %) and a stir bar. To this was added 7.8 mg (0.03 mmol) of phosphate **15.1** in 0.6 mL of degassed CH_2Cl_2 (0.05M with respect to phosphate **15.1**) and the solution immediately placed in a 46 ºC oil bath with stirring. After 12 h, the tube was removed from heat to cool, SiO_2 added and the solvent removed. Placement of the substrate impregnated silica on a column allowed for elution with 100% EtOAc to provide 9.4 mg (77% yield) of phosphate **12.1** as a single observable isomer.

(2*R*,6*R*)-6-isopropoxy-2-vinyl-3,6-dihydro-2*H*-pyran: 14.1



To a dried 50 mL round bottom flask under argon equipped with stir bar is placed 700 mg stannane **11.1** (1.53 mmol) followed by 15 mL THF to generate a 0.1M solution. This solution is lowered in temperature to 0 ºC via cold bath, after which time 3.06 mL of a 5.0M TFA solution in THF (15.28 mmol, 10 equiv.) is added dropwise. The reaction is allowed to proceed at 0 ºC for 1.5 h with stirring, after which time the reaction is quenced by slow addition of sat. aq. $NaCO_3$ (15 mL) and 15 mL diethyl ether added. The layers are separated, the aqueous layers extracted with Et_2O (3 x 5 mL), and the combined organic layers washed with brine. The organic layers were then dried with $MgSO_4$, filtered, solvent carefully removed via reduced pressure over a 0 ºC bath, and the product purified via column chromatography (50:1 petroleum ether: diethyl ether) to provide 146 mg (57% yield) of alkene **14.1**.

$[\alpha]_D$: +59 (*c* = 0.37, CH_2Cl_2, 24.8 ºC)

FTIR: (neat) 3080, 3045, 2970, 2924, 2894, 1647, 1458, 1423, 1398, 1381, 1182, 1126, 1101, 1034, 1009, 993, 962, 943, 924, 860, 719, 783 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.01 (m, 1H), 5.91 (ddd, *J* = 17.3, 10.6, 5.6 Hz, 1H), 5.73 (dtd, *J* = 10.0, 2.8, 1.5 Hz, 1H), 5.30 (dt, *J* = 17.3, 1.6 Hz, 1H), 5.16 (dt, *J* =

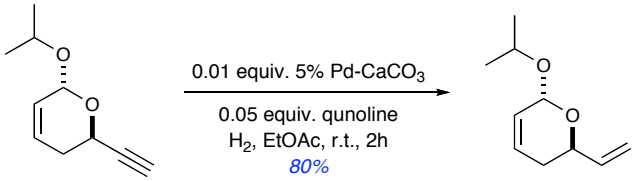
10.6, 1.6 Hz, 1H), 5.12 (ddd, *J* = 5.7, 1.5, 1.2 Hz, 1H), 4.43 (dddd, *J* = 10.0, 4.8, 4.6, 0.6 Hz, 1H), 4.01 (dq, *J* = 6.3, 6.2 Hz, 1H), 2.08 (dddd, *J* = 10.8, 4.2, 2.5, 0.9 Hz, 1H), 2.03 (dddd, *J* = 17.7, 5.6, 4.2, 1.4 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.18 (d, 6.2 Hz, 3H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 138.5, 128.6, 126.4, 115.6, 93.4, 69.9, 67.0, 30.5, 24.0, 22.3

HRMS Exact Mass: calculate for $C_{10}H_{16}NaO_2$ $(M+Na)^+$ 191.1048;

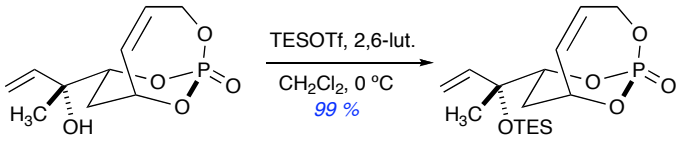
found 191.1052 (ESI)

(2*R*,6*R*)-6-isopropoxy-2-vinyl-3,6-dihydro-2*H*-pyran: 14.1



A 100 mL round bottom flask equipped with stir bar is charged with 1.10 g (6.53 mmol) of alkyne **7.5**, 42 mg (0.327 mmol, 0.05 equiv.) freshly distilled quinoline, and 65 mL degassed EtOAc (0.1M with respect to **7.5**) and is placed under a H_2 atmosphere via balloon. To this stirring mixture is added 139 mg 5% Pd-$CaCO_3$ (0.065 mmol Pd, 0.01 equiv.). The reaction was allowed to proceed for 2 h (monitored by GC) at which time the mixture was filtered through Celite and the solvent removed *gently*. The crude product was passed through a short SiO_2 plug, eluting with 20:1 petroleum ether: diethyl ether to provide 877 mg (80% yield) of the desired alkene **14.1**.

(1*S*,6*R*,8*R*)-8-((*R*)-2-(triethylsilyloxy)but-3-en-2-yl)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene



A flame dried 25 mL round bottom flask was charged with 320 mg phosphate **15.1** (1.3 mmol) and 13 mL of CH_2Cl_2 to generate a 0.1M solution, followed by 197 μL of 2,6-lutidine (1.69 mmol, 1.3 equiv.). The solution was then cooled to 0 ºC and 323 μL of TESOTf (1.43 mmol, 1.1 equiv.) was added dropwise to the solution with stirring. The solution was allowed to stir at 0 ºC until completion (about 1 hour). The reaction was quenched with 13 mL of saturated aqueous NH_4Cl, separated, and the aqueous layer re-extracted 3 more times. The combined organic layers were then washed with brine, dried with $MgSO_4$, and filtered. Addition of SiO_2 preceded removal of solvent, following which the impregnated SiO_2 was loaded onto a short column and the desired product eluted with 1:2 hexane: ethyl acetate to provide 468 mg (99% yield) of the silyl protected phosphate.

$[\alpha]_D$: -36.4 (*c* = 1.05, CH_2Cl_2, 26.5 ºC)

FTIR: (neat) 2955, 2914, 2876, 1294, 1263, 1236, 1220, 1134, 1074, 1061, 1042, 993, 978, 781, 737, 727, 694, 611, 433 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.00 (dddd, *J* = 11.9, 6.7, 3.6, 2.4 Hz, 1H), 5.80 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.56 (ddd, 11.9, 3.9, 2.6 Hz, 1H), 5.30 (dd, *J* = 17.3, 1.1 Hz, 1H), 5.21 (dddd, *J* = 25.0, 2.5, 1.9, 1.7 Hz, 1H), 5.17 (dd, *J* = 10.7, 1.1 Hz,

1H), 4.99 (dddd, J = 14.7, 5.6, 5.5, 2.7 Hz, 1H), 4.34 (ddd, J = 27.7, 14.2, 6.8 Hz, 1H), 4.24 (ddd, J = 11.9, 1.8, 1.7 Hz, 1H), 2.31 (ddd, J = 14.7, 11.9, 6.4 Hz, 1H), 1.79 (ddd, J = 13.1, 2.4, 1.8 Hz, 1H), 1.40 (s, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.61 (qd, J = 7.2, 1.6 Hz, 6H)

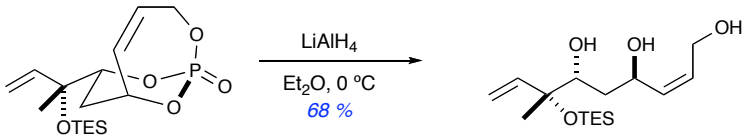
^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 142.0, 130.3, 128.0, 115.7, 81.5 (d, J_{CP} = 7.6 Hz), 77.4 (d, J_{CP} = 6.6 Hz), 76.4 (d, J_{CP} = 10.0 Hz), 63.2 (d, J_{CP} = 6.4 Hz), 29.0 (d, J_{CP} = 5.4 Hz), 22.7, 7.3, 6.9

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -2.86 (t, J_{PH} = 27.0 Hz)

HRMS Exact Mass: calculate for $C_{16}H_{29}NaO_5PSi$ $(M+Na)^+$ 383.1420;

found 383.1423 (ESI)

(4*R*,6*R*,7*R*,*Z*)-7-methyl-7-(triethylsilyloxy)nona-2,8-diene-1,4,6-triol: 16.1



A 0.06M solution of phosphate (250 mg, 0.70 mmol) in diethyl ether (12 mL) is prepared under argon atmosphere and subsequently cooled to 0 ºC with stirring. To this is slowly added $LiAlH_4$ (79 mg, 2.09 mmol, 3 equiv.) and to reaction allowed to continue stirring at 0 ºC. The reaction is monitored by TLC (1:2 hexane: ethyl acetate) until substrate appears to be consumed and allowed to continue for 15 more minutes at 0 ºC (total reaction time typically about 1 hour). The reaction is quenched by slow, dropwise addition of 79 mg of H_2O, followed by slow, dropwise addtion of 79 mg of 15 % NaOH (aq), and finishing with an addition of 237 mg of H_2O. At this point, the mixture is allowed to reach room temperature until all salts appear to have become a white color. SiO_2 is then added and the solvent removed, at which point the silica complexed product is placed on a short silica gel plug and eluted with a 1:4 hexane: ethyl acetate mixture, producing 150 mg (68% yield) of mono-protected tetraol **16.1**.

$[\alpha]_D$: +17.4 (*c* = 2.20, CH_2Cl_2, 27.6 ºC)

FTIR: (neat) 3342, 2955, 2912, 2877, 1458, 1413, 1238, 1099, 1049, 1010, 977, 921, 873, 740, 727 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 5.93 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.69 (dddd, *J* = 6.3, 5.0, 1.2, 1.1 Hz, 1H), 5.57 (ddt, *J* = 11.2, 7.8, 1.3 Hz, 1H), 5.31 (dd, *J* = 17.4,

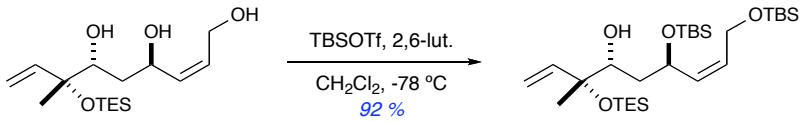
1.4 Hz, 1H), 5.13 (dd, *J* = 10.9, 1.4 Hz, 1H), 4.67 (dd, *J* = 8.4, 8.3 Hz, 1H), 4.28 (ddd, *J* = 7.0, 6.7, 6.1 Hz, 1H), 4.18 (ddd, *J* = 8.6, 7.1, 5.9 Hz, 1H), 3.82 (dd, *J* = 7.1, 3.9 Hz, 1H), 3.77 (br s, 1H),1.80 (ddd, *J* = 14.8, 6.7, 3.8 Hz, 1H), 1.58 (br s, 2H), 1.54 (ddd, *J* = 14.8, 7.0, 2.7 Hz, 1H), 1.27 (s, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.69 (q, *J* = 8.0 Hz, 6H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 142.0, 135.7, 130.0, 113.5, 76.2, 75.7, 65.3, 59.0, 40.6, 25.0, 7.2, 5.4

HRMS Exact Mass: calculate for $C_{16}H_{32}NaO_4Si$ $(M+Na)^+$ 339.1968;

found 339.1970 (ESI)

(5*R*,6*R*,8*R*,*Z*)-8-(*tert*-butyldimethylsilyloxy)-3,3-diethyl-5,13,13,14,14-pentamethyl-5-vinyl-4,12-dioxa-3,13-disilapentadec-9-en-6-ol: 16.2



A 0.1M solution of triol **16.1** (44 mg, 0.138 mmol) in CH_2Cl_2 (1.4 mL) is generated in a flame dried 5mL flask under Ar atmosphere, followed by addition of 2,6-lutidine (72 μL, 0.620 mmol, 4.5 equiv.). The solution is then submerged in a dry ice-acetone bath to bring the temperature to -78 ºC, at which time a slow addition of TBSOTf (70 μL, 0.303 mmol, 2.2 equiv.) is affected. The reaction is monitored by TLC to ensure the selective bis-protected product is produced, where the mono-protected species is visualized in a 2:1 hexane: diethyl ether system (R_f = 0.15) to note disappearance while the bis-protected species is visible through a 20:1 hexane: diethyl ether system (R_f = 0.21). After disappearance of the mono-protected species by TLC, the reaction is allowed to continue for 15 minutes more (total reaction time is about 45 minutes). Saturated aqueous NH_4Cl is then added and the reaction allowed to achieve room temperature, whereby the layers are then separated and the aqueous layer extracted with 3x 5mL portions of diethyl ether, the combined organic layers washed with brine, and then dried with $MgSO_4$. Filtration followed by solvent removal allows for purification via flash column chromatography utilizing a 20:1 hexane: diethyl ether solvent system to afford 69 mg (92% yield) of the desired product **16.2**.

$[\alpha]_D$: +4.4 (*c* = 3.34, CH_2Cl_2, 25.7 ºC)

FTIR: (neat) 3464, 3016, 2954, 2929, 2879, 2858, 1471, 1462, 1411, 1362, 1254, 1080, 1005, 923, 835, 775, 741, 727 cm^{-1}

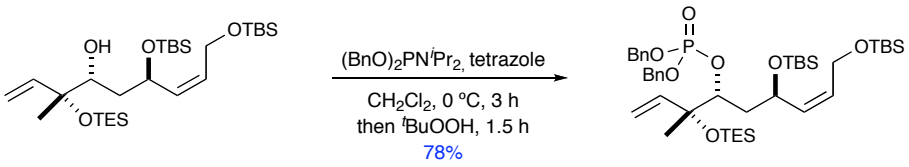
^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 5.93 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.48 (ddd, *J* = 10.8, 5.1, 5.0 Hz, 1H), 5.37 (ddd, *J* = 11.2, 6.2, 1.6 Hz, 1H), 5.28 (dd, *J* = 17.4, 1.6 Hz, 1H), 5.10 (dd, *J* = 10.8, 1.6 Hz, 1H), 4.48 (ddd, *J* = 9.4, 3.8, 3.6 Hz, 1H), 4.29 (ddd, *J* = 13.1, 7.0, 1.6 Hz, 1H), 4.13 (ddd, *J* = 13.1, 5.3, 1.7 Hz, 1H), 3.68 (dd, *J* = 5.8, 3.8 Hz, 1H), 2.59 (s, 1H), 1.90 (ddd, *J* = 14.5, 9.7, 3.8 Hz, 1H), 1.31 (dddd, *J* = 9.8, 5.8, 4.9, 3.9 Hz, 1H), 1.21 (s, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.66 (qd, *J* = 8.0,1.9 Hz, 6H), 0.07 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 142.3, 134.0, 129.7, 113.3, 75.9, 75.5, 66.8, 59.6, 43.0, 26.1, 24.0, 18.5, 18.3, 7.3, 5.7, -3.1, -4.3

HRMS Exact Mass: calculate for $C_{28}H_{60}NaO_4Si_3$ $(M+Na)^+$ 567.3697;

found 567.3688 (ESI)

dibenzyl (5*R*,6*R*,8*R*,*Z*)-8-(*tert*-butyldimethylsilyloxy)-3,3-diethyl-5,13,13,14,14-pentamethyl-5-vinyl-4,12-dioxa-3,13-disilapentadec-9-en-6-yl phosphate: 16.3



A flame dried 5 mL round bottom flask equipped with stir bar is charged with 63 mg of tris-protected tetraol **16.2** (0.116 mmol), 49 mg of 1*H*-tetrazole (0.699 mmol, 6 equiv.), and 1.2 mL of CH_2Cl_2 (0.1M with respect to **16.2**). The stirring mixture is cooled to 0 ºC at which time 127 μL of dibenzyl *N*,*N*-diisopropyl phosphoramidite (0.349 mmol, 3 equiv.) was added and allowed to continue stirring at 0 ºC. After completion as indicated by TLC using 20:1 hexane: diethyl ether (phosphite $R_f = 0.8$ vs. alcohol $R_f = 0.21$), the cloudy reaction mixture was allowed to stir for 30 minutes more (total time 3 h) before 70 μL of a 5.0M *t*-BuOOH in decane solution (0.349 mmol, 3 equiv.) was added at 0 ºC generating a clear solution and the reaction allowed to stir at 0 ºC for 1.5 h. The reaction was quenched by addition of 1 mL of 10% $Na_2S_2O_3$ (aq.) and allowed to stir for 30 min., at which time it was diluted with 5 mL of $NaHCO_3$, extracted with 3x 10 ml portions of CH_2Cl_2, dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography proceeded by elution with 5:1 hexane: diethyl ether to remove more non-polar impurities, followed by elution with 2:1 hexane: diethyl ether to provide 73 mg (78% yield) of phosphate **16.3**.

$[\alpha]_D$: +11.8 (*c* = 0.88, CH_2Cl_2, 25.6 ºC)

FTIR: (neat) 2954, 2930, 2881, 2856, 1458, 1411, 1379, 1362, 1254, 1080, 1001, 835, 775, 735, 696, 598 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 7.32 (m, 10H), 6.09 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.45 (ddd, *J* = 11.8, 6.6, 5.2 Hz, 1H), 5.35 (dddd, *J* = 11.2, 9.1, 4.1, 1.6 Hz, 1H), 5.30 (dd, *J* = 17.6, 0.6 Hz, 1H), 5.26 (dd, *J* = 11.0, 0.5 Hz, 1H), 4.99 (d, *J* = 2.6 Hz, 2H), 4.97 (d, *J* = 2.7 Hz, 2H), 4.46 (td, *J* = 9.7, 1.7 Hz, 1H), 4.30 (ddd, *J* = 13.2, 6.9, 1.6 Hz, 1H), 4.13 (ddd, *J* = 13.2, 5.1, 1.7 Hz, 1H), 3.89 (dd, *J* = 8.3, 1.3 Hz, 1H), 1.72 (ddd, *J* = 11.8, 10.4, 1.4 Hz, 1H), 1.46 (ddd, *J* = 16.5, 3.5, 3.4 Hz, 1H), 1.22 (s, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.89 (s, 9H), 0.86 (s, 9H), 0.65 (q, *J* = 8.0 Hz, 6H), 0.06 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 138.5, 136.5, 136.4, 134.0, 129.8, 128.62, 128.6, 128.4, 128.37, 128.0, 117.2, 87.6 (d, J_{CP} = 7.9 Hz), 75.2 (d, J_{CP} = 10.8 Hz), 69.0 (d, J_{CP} = 5.4 Hz), 68.8 (d, J_{CP} = 5.3 Hz), 66.0, 59.6, 42.8, 30.5, 26.1 (d, J_{CP} = 6.4 Hz), 19.9, 18.5, 18.3, 7.3, 5.8, -2.8, -4.2, -5.0

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -4.02 (t, J_{PH} = 8.0 Hz)

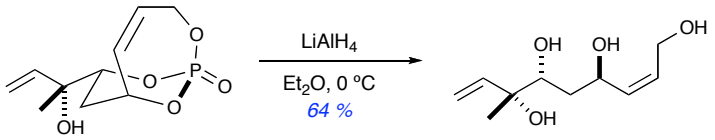
HRMS Exact Mass: calculate for $C_{42}H_{73}NaO_7PSi_3$ $(M+Na)^+$ 827.4299;

found 827.4328 (ESI)

Note: On larger scales, the minor diastereomer generated during the generation of tertiary alcohol **15.1** is separable and can be faintly observed and isolated at this point in the 5:1 hexane: diethyl ether elution (R_f = 0.25 in 5:1 hexane: diethyl ether). It is easily distinguishable by ^{13}C NMR from the major isomer: (126 MHz, $CHCl_3$-*d*) δ

ppm 143.2, 136.22, 136.16, 134.3, 129.6, 128.7, 128.64, 128.58, 128.4, 127.9, 125.7, 114.9, 82.5 (d, J_{CP} = 15.4 Hz), 77.2 (d, J_{CP} = 6.1 Hz), 69.26 (d, J_{CP} = 6.0 Hz), 69.22 (d, J_{CP} = 9.1 Hz), 65.6, 59.6, 40.2, 30.5, 26.1, 22.5, 18.4, 18.2, 7.3, 6.8, -3.6, -4.5, -4.9

(4*R*,6*R*,7*R*,*Z*)-7-methylnona-2,8-diene-1,4,6,7-tetraol: 17.1



A 0.06M solution of phosphate **15.1** (38 mg, 0.154 mmol) in THF (2.6 mL) is prepared under argon atmosphere and subsequently cooled to 0 ºC with stirring. To this is slowly added $LiAlH_4$ (18 mg, 0.463 mmol, 3 equiv.) and the reaction allowed to continue stirring at 0 ºC. The reaction is monitored by TLC (1:1 EtOAc: acetone) until substrate appears to be consumed and allowed to continue for 15 more minutes at 0 ºC (total reaction time typically about 1 h). The reaction is quenched by slow, dropwise addition of 18 mg of H_2O, followed by slow, dropwise addtion of 18 mg of 15 % NaOH (aq), and finishing with an addition of 54 mg of H_2O. At this point, the mixture is allowed to reach room temperature until all salts appear to have become a white color. SiO_2 is then added and the solvent removed, at which point the silica complexed product is placed on a short silica gel plug and eluted with a 1:1 EtOAc: acetone mixture, producing 20.2 mg (64% yield) of tetraol **17.1**.

$[\alpha]_D$: +46 (*c* = 0.05, acetone, 24.6 ºC)

FTIR: (neat) 3339, 2951, 2910, 2877, 1458, 1410, 1238, 1099 cm^{-1}

^{1}H NMR (500 MHz, acetone-d_6) δ ppm 5.96 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.50 (m, 2H), 5.28 (dd, *J* = 17.4, 2.0 Hz, 1H), 5.02 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.68 (dddd, *J* = 6.6, 4.6, 2.6, 2.3 Hz, 1H), 4.19 (ddd, *J* = 12.4, 5.4, 1.7 Hz, 1H), 4.10 (ddd, *J* = 12.6, 4.2, 3.8 Hz, 1H), 3.91 (d, *J* = 4.8 Hz, 1H), 3.73 (d, *J* = 5.5 Hz, 1H), 3.71 (s, 1H), 3.69

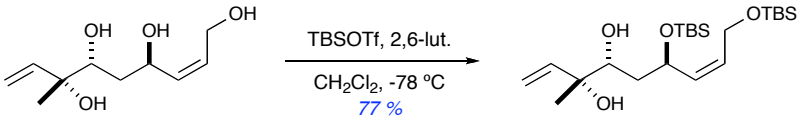
(dd, J = 5.7, 1.9 Hz, 1H), 3.54 (s, 1H), 1.67 (ddd, J = 15.0, 9.3, 1.9 Hz, 1H), 1.44 (ddd, J = 15.0, 7.8, 2.6 Hz, 1H), 1.22 (s, 3H)

^{13}C NMR (126 MHz, acetone-d_6) δ ppm 144.2, 135.9, 130.4, 112.7, 75.6, 74.6, 65.5, 58.7, 40.3, 24.7

HRMS Exact Mass: calculate for $C_{10}H_{18}NaO_4$ $(M+Na)^+$ 225.1103;

found 225.1105 (ESI)

(3*R*,4*R*,6*R*,*Z*)-6,9-bis(*tert*-butyldimethylsilyloxy)-3-methylnona-1,7-diene-3,4-diol: 17.2



A 0.1M solution of tetraol **17.1** (19 mg, 0.093 mmol) in CH_2Cl_2 (1 mL) is generated in a flame dried 5 mL flask under Ar atmosphere, followed by addition of 2,6-lutidine (49 μL, 0.421 mmol, 4.5 equiv.). The solution is then submerged in a dry ice-acetone bath to bring the temperature to -78 ºC, at which time a slow addition of TBSOTf (47 μL, 0.206 mmol, 2.2 equiv.) is affected. The reaction is monitored by TLC to ensure the selective bis-protected product is produced (4:1 hexane: diethyl ether, $R_f = 0.21$), although no mono-protected species was observed during the course of the reaction with this substrate After disappearance of the starting material is observed by TLC (1:1 EtOAc: acetone), the reaction is allowed to continue for 15 minutes more (total reaction time is about 45 minutes). 1 mL of sat. aq. NH_4Cl is then added and the reaction allowed to achieve room temperature. The layers are then separated and the aqueous layer extracted with 3x 5mL portions of diethyl ether, the combined organic layers washed with brine, and then dried with $MgSO_4$. Filtration followed by solvent removal allows for purification via flash column chromatography utilizing a 4:1 hexane: diethyl ether solvent system to afford 31 mg (77% yield) of the desired product.

$[\alpha]_D$: +17 (*c* = 0.25, CH_2Cl_2, 25.3 ºC)

FTIR: (neat) 3459, 3010, 2954, 2929, 2879, 2858, 1079, 1009, 923 cm^{-1}

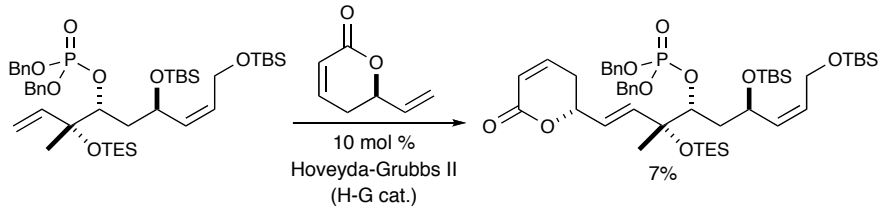
^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 5.82 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.59 (ddt, *J* = 11.4, 8.5, 1.5 Hz, 1H), 5.51 (ddd, *J* = 11.6, 6.2, 0.8 Hz, 1H), 5.29 (dd, *J* = 17.4, 1.6 Hz, 1H), 5.12 (dd, *J* = 10.9, 1.6 Hz, 1H), 4.83 (dt, *J* = 8.1, 4.4 Hz, 1H), 4.21 (ddd, *J* = 11.2, 6.5, 1.3 Hz, 1H), 4.13 (ddd, *J* = 13.4, 5.2, 1.7 Hz, 1H), 3.78 (ddt, *J* = 12.1, 8.4, 2.9 Hz, 1H), 3.77 (br s, 1H), 2.49 (br s, 1H), 1.64 (dd, *J* = 4.3, 4.2 Hz, 2H), 1.27 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.061 (s, 3H), 0.059 (s, 3H), 0.05 (s, 3H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 141.1, 133.7, 129.1, 114.0, 75.2, 74.6, 68.3, 59.6, 38.7, 26.1, 26.0, 24.9, 18.5, 18.2, -4.3, -4.98, -5.04, -5.06

HRMS Exact Mass: calculate for $C_{22}H_{46}NaO_4Si_2$ $(M+Na)^+$ 453.2832;

found 453.2811 (ESI)

dibenzyl (5*R*,6*R*,8*R*,*Z*)-8-(*tert*-butyldimethylsilyloxy)-3,3-diethyl-5,13,13,14,14-pentamethyl-5-((*E*)-2-((*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)vinyl)-4,12-dioxa-3,13-disilapentadec-9-en-6-yl phosphate: 20.1



To a small dried Pyrex pressure tube under argon was placed 10 mg (0.012 mmol) of phosphate **16.3** , 0.6 mg Hoveyda-Grubbs II catalyst (0.001 mmol, 10 mol %) and a stir bar. To this was added 8 mg (0.06 mmol) of lactone **2.4** in 0.12 mL of degassed dichloroethane (0.1 M with respect to phosphate **16.3**) and the solution immediately placed in a 90 ºC oil bath with stirring. After 12 hours, the tube was removed from heat to cool, SiO_2 added and the solvent removed. Placement of the substrate impregnated silica on a column allowed for elution with 2:1 hexane: diethyl ether to provide 0.8 mg (7% yield) of phosphate **20.1**.

$[\alpha]_D$: +9.6 (*c* = 0.01, CH_2Cl_2, 24.8 ºC)

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 7.44-7.20 (m, 5H), 6.93-6.87 (m, 5H), 6.90 (app dd, *J* = 5.6, 1.3 Hz, 1H), 6.07 (ddt, *J* = 16.0, 9.8, 1.9 Hz, 1H), 6.06 (ddd, *J* = 9.9, 2.5,1.4 Hz, 1H), 5.96 (ddd, *J* = 16.5, 10.6, 5.7 Hz, 1H), 5.61 (ddd, J =10.2, 6.9, 1.6 Hz, 1H), 5.30 (dt, *J* = 10.6, 1.2 Hz, 1H), 5.10 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 4.94 (m, [PhC$\underline{H}_2$O-]$_2$ + C_5-$\underline{H}$, 5H), 4.87 (dd, *J* = 7.3, 7.4 Hz, 1H), 4.56 (ddd, *J* = 6.1, 6.0, 5.9 Hz, 1H), 4.21 (dt, *J* = 4.1, 1.4 Hz, 1H), 2.55 (ddd, *J* = 6.1, 4.2, 1.8 Hz, 1H), 2.49-2.41

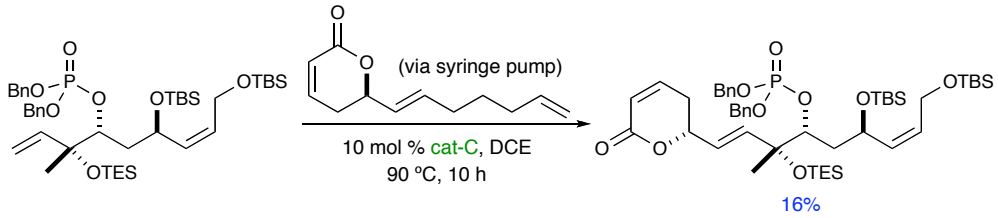
(m, 2H), 1.75 (ddd, J = 6.6, 1.6, 0.6 Hz, 1H), 1.43 (s, 3H), 0.91 (s, 18H), 0.89 (t, J = 8.0 Hz, 9H), 0.65 (q, J = 8.0 Hz, 6H), 0.07 (s, 6H), 0.04 (s, 3H), 0.036 (s, 3H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 164.1, 145.0, 144.7, 135.0, 133.7, 129.5, 129.2, 127.5, 126.0, 125.9, 125.7, 121.88, 121.85, 120.8, 79.2, 78.1, 77.7, 74.2 (d, J_{CP} = 6.9 Hz), 71.0, 66.1, 62.8, 42.9, 30.2, 29.9, 29.6, 26.1, 22.40, 22.36, 15.5, 14.3, 7.4, 5.9, -4.2, -5.1

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -4.13 (t, J_{PH} = 8.1 Hz)

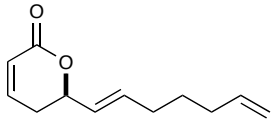
HRMS Exact Mass: calculate for $C_{47}H_{77}NaO_9PSi_3$ $(M+Na)^+$ 923.4511;

found 923.4528 (ESI)



To a small dried Pyrex pressure tube bearing a cap with Teflon septa and under argon was placed 6.3 mg (0.008 mmol) phosphate **16.3**, 0.5 mg Hoveyda-Grubbs II catalyst (0.0008 mmol, 10 mol %), 0.25 mL degassed dichloroethane and a stir bar. The solution is placed in a 90 ºC silicon oil bath and allowed to stir for 10 minutes. Another solution containing 3.0 mg of lactone **24.1** (0.016 mmol) in 500 μL of degassed dichloroethane is placed in a syringe and the needle of the syringe placed through the septa of the Pyrex tube. The syringe is then injected via syringe pump at a rate of 100 μL per hour and the reaction allowed to proceed overnight. The pressure tube is then removed from heat, SiO_2 added, and the solvent removed. The product bearing silica gel is then placed on a column for purification utilizing 2:1 hexane: diethyl ether to provide 1.1 mg (16% yield) of phosphate **20.1**.

(*R*,*E*)-6-(hepta-1,6-dienyl)-5,6-dihydro-2*H*-pyran-2-one: 24.1



In a glove box under Ar (g), 107 mg (0.03 mmol, 0.15 equiv.) of PCy(pyrrolidinyl)$_2$[5] and 39 mg (0.41 mmol, 1.9 equiv.) Me_4NF are added to a 5 mL round bottom flask containing 2 mg (0.005 mmol, 0.025 equiv.) of [(π-allyl)PdCl]$_2$ in 1.1 mL THF. This mixture is allowed to stir for 5 minutes at 25 ºC. 1.28 g (2.81 mmol) of stannane **11.1**, 1.40 g of freshly dried 3Å molecular sieves (500 mg/mmol **11.1**), and 660 mg of 5-iodo-1-pentene (3.37 mmol, 1.2 equiv.) was then added in that particular order. The vessel was capped with a Teflon lined cap and removed from the glove box. The mixture then stirred vigorously at 25 ºC for 24 h in the absence of light. After 24 h had passed, 1 mL 10% KF (aq) was added and the mixture allowed to stir for 30 minutes. The layers were separated and the aqueous layer extracted 3 more times with 5 mL diethyl ether. The combined organic layers were then washed with brine, dried with $MgSO_4$, filtered and solvent removed in vacuo. The residue was then placed on a silica gel column, eluted with 80:1 petroleum ether: diethyl ether to remove more non-polar species followed by elution with 30:1 petroleum ether: diethyl ether to elute the impure coupling product. The semi-pure product was used in the subsequent reaction.

To a 50 mL round bottom flask equipped with comparably large stir bar is added the semi-pure coupling product, 4.2 g Celite (1.5g/mmol) and 28 mL of acetone (0.1M with respect to **11.1**). The stirring mixture was brought to 0 ºC and

2.32 mL of Jones reagent (2.67M, 6.18 mmol, 2.2 equiv.) added dropwise. The reaction is allowed to proceed with stirring at 0 ºC until completion (TLC 2:1 hexane: diethyl ether; ~ 2 h). Upon indication of reaction completion, 0.5 mL isopropyl alcohol is added to consume any leftover Jones reagent, followed by filtration, addition of silica, and solvent removal. Placing the product saturated silica on a silica column allowed for elution of the desired product with 2:1 petroleum ether: diethyl ether, where solvent removal provided 361 mg (67% yield) of lactone **24.1** as a light colorless oil.

$[\alpha]_D$: +65 (*c* = 0.15, CH_2Cl_2, 25.7 ºC)

FTIR: (neat) 2909, 2872, 1722, 1420, 1385, 1294, 1237 cm^{-1}

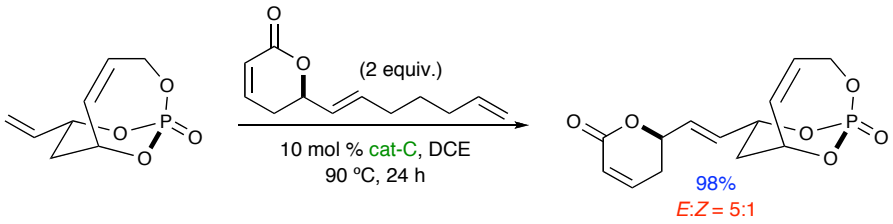
^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.89 (ddd, *J* = 9.8, 5.7, 2.7 Hz, 1H), 6.05 (ddd, *J* = 9.8, 2.5, 1.1 Hz, 1H), 5.78 (ddddd, *J* = 17.0, 10.3, 6.7, 6.7, 2.4 Hz, 1H), 5.66 (ddd, *J* = 14.6, 9.7, 4.1 Hz, 1H), 5.58 (dddd, *J* = 14.4, 8.3, 1.3, 1.2 Hz, 1H), 5.22 (dddd, *J* = 10.9, 8.4, 4.5, 0.8 Hz, 1H), 5.01 (ddd, *J* = 17.2, 3.5, 1.6 Hz, 1H), 4.98 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 2.42 (dddd, *J* = 18.5, 8.5, 2.7, 2.6 Hz, 1H), 2.34 (dddd, J = 18.4, 5.6, 4.5, 1.1 Hz, 1H) 2.18-2.04 (m, 4H), 1.50 (dddddd, *J* = 13.7, 13.4, 6.4, 6.3, 6.3, 6.1 Hz, 2H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 164.4, 145.0, 138.4, 135.4, 126.9, 121.8, 115.2, 74.0, 33.3, 30.0, 28.6, 27.3

HRMS Exact Mass: calculate for $C_{12}H_{17}O_2$ $(M+H)^+$ 193.1229;

found 192.1231 (ESI)

(*R*)-6-((*E*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)vinyl)-5,6-dihydro-2*H*-pyran-2-one: 24.2



To a small dried Pyrex pressure tube under argon was placed 2.0 mg (0.010 mmol) phosphate **2.1**, 0.6 mg Hoveyda-Grubbs II catalyst (0.001 mmol, 10 mol %) and a stir bar. To this was added a solution of 4.0 mg of lactone **24.1** (0.020 mmol, 2 equiv.) in 1 mL of degassed dichloroethane (0.01M with respect to phosphate **2.1**), the tube flushed one more time and capped, and the solution placed in a 90 ºC oil bath with stirring for 24 h. After the allotted time had passed, the tube was removed from heat to cool, SiO_2 added and the solvent removed. Placement of the substrate impregnated silica on a column allowed for elution with 5:1 EtOAc: acetone to provide 3.0 mg (99% yield) of phosphate **24.2** in a 5:1 ratio of trans:cis isomers.

$[\alpha]_D$: -12 (*c* = 0.10, CH_2Cl_2, 24.5 ºC)

FTIR: (neat) 2918, 2849, 1717, 1383, 1296, 1250, 1117, 1067, 1036, 966, 924, 820, 775 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.90 (ddd, *J* = 9.8, 5.7, 2.8 Hz, 1H), 6.09 (ddd, *J* = 6.7, 3.1, 2.1 Hz, 1H), 6.07 (ddd, *J* = 9.8, 2.4, 1.0 Hz, 1H), 6.03 (ddd, *J* = 15.5, 4.7, 1.5 Hz, 1H), 5.92 (dddd, *J* = 15.5, 4.4, 2.9, 1.5 Hz, 1H), 5.63 (ddd, *J* = 11.9, 3.9, 2.6 Hz, 1H), 5.23 (dddd, *J* = 23.7, 3.1, 2.2, 2.0 Hz, 1H), 5.11 (dddd, *J* = 12.0, 3.4, 2.0, 1.6

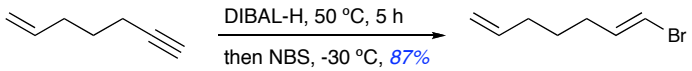
Hz, 1H), 5.03 (dddd, J = 14.7, 8.3, 5.6, 2.7 Hz, 1H), 4.99 (dtd, J = 9.5, 4.3, 1.3 Hz, 1H), 4.40 (ddd, J = 27.9, 14.8, 6.7 Hz, 1H), 2.51 (dddd, J = 18.4, 5.7, 4.3, 1.1 Hz, 1H), 2.41 (ddt, J = 21.1, 10.9, 2.7 Hz, 1H), 2.22 (ddd, J = 14.7, 12.1, 6.2 Hz, 1H), 1.83 (ddd, J = 14.7, 3.5, 2.3 Hz, 1H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 163.8, 144.8, 129.6, 129.3 (d, J_{CP} = 10.1 Hz), 129.1, 128.5, 121.8, 77.3 (d, J_{CP} = 32.0 Hz), 76.2, 74.9 (d, J_{CP} = 6.2 Hz), 63.3 (d, J_{CP} = 6.3), 35.3 (d, J_{CP} = 5.7 Hz), 29.7

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -3.76 (t, J_{PH} = 23.6 Hz)

HRMS Exact Mass: calculate for $C_{13}H_{15}NaO_6P$ $(M+Na)^+$ 321.0504; found 321.0508 (ESI)

(*E*)-1-bromohepta-1,6-diene: 26.1



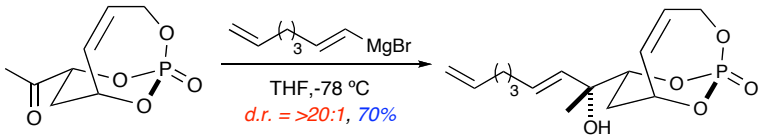
A flame dried 250 mL round bottom flask was purged with Ar, followed by addition of a stir bar and 4.7 g (50 mmol) of 1-hepten-6-yne. 55 mL of diisobutylaluminum hydride in hexanes (1.0 M, 55 mmol) was slowly added and the mixture allowed to stir at room temperature for 30 minutes, followed by warming to 50 ºC and stirring for 5 h. The mixture was then cooled to room temperature, 30 mL of diethyl ether added, and then cooled to -30 ºC with stirring. NBS was then added and the mixture stirred at -30 ºC for 15 min and then at room temperature for 15 h in the absence of light. The mixture was then poured into 100 mL 6 M HCl (aq) in crushed ice. The resulting solution was then extracted with petroleum ether (3 x 200 mL), the organic layers washed with 1 M NaOH (aq), then washed with 10% NaS_2O_3 (aq) and dried with Na_2SO_4, filtered, and solvent removed very gently at 22 ºC at 165 torr.[6] The crude material was then passed through a silica plug utilizing 40:1 petroleum ether: diethyl ether and the solvent carefully removed as indicated before to provide 7.65 g (87% yield) of (*E*)-1-bromohepta-1,6-diene **26.1**.

FTIR: (neat) 2975, 2856, 1639, 1620, 1439, 1280, 1230, 991, 935, 912, 706 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.17 (dt, *J* = 13.5, 7.32 Hz, 1H), 6.02 (dt, *J* = 13.5, 1.4 Hz, 1H), 5.78 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.01 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 4.97 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 2.06 (ddddd, *J* = 14.7, 7.2, 2.5, 1.5, 1.3 Hz, 4H), 1.50 (dt, *J* = 7.6, 7.4 Hz, 2H)

^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 138.3, 138.1, 115.2, 104.6, 33.1, 32.5, 27.9

(*R*,*E*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)nona-3,8-dien-2-ol: 26.2



A 10 mL flask containing 30 mg (0.14 mmol) of ketone **2.2** was placed under Ar atmosphere and 1.4 mL of THF were added to generate a 0.1 M solution. The solution was then cooled to -78 ºC and freshly prepared Grignard of **26.1** (420 μL, 1.0M in THF, 3 equiv.) was added slowly along the side of the flask. The reaction mixture was maintained in a cooling bath at -78 ºC for 7 h, after which time 2 mL of sat. aq. NH_4Cl was added, the flask removed from the cooling bath, and the mixture allowed to reach room temperature. The reaction mixture was extracted with 3 x 10 mL EtOAc and the organic layers collected. The organic layers were then washed with 20 mL brine, dried with Na_2SO_4, filtered, SiO_2 added and the solvent removed *in vacuo*. The substrate impregnated SiO_2 was then placed on a short column, eluted with 2 column volumes of 1:1 hexane: EtOAc, and then eluted with 10% acetone in EtOAc. Solvent removal afforded 31 mg (70% yield) of the desired tertiary alcohol **26.2**.

$[\alpha]_D$: -59 (*c* = 0.94, CH_2Cl_2, 25.0 ºC)

FTIR: (neat) 3393, 2976, 2926, 2854, 1290, 1072, 1036, 986, 923, 885, 838, 771, 711, 678, 650 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.03 (dddd, *J* = 11.3, 2.7, 2.4, 1.4 Hz, 1H), 5.80 (ddd, *J* = 17.3, 10.3, 3.1 Hz, 1H), 5.78 (dt, *J* = 15.5, 6.8 Hz, 1H), 5.58 (ddd, 11.9, 3.9, 2.6 Hz, 1H), 5.40 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.23 (dddd, *J* = 24.9, 4.2, 2.3, 1.6 Hz, 1H), 5.00 (ddd, *J* = 14.9, 5.7, 2.5 Hz, 1H), 4.99 (dd, *J* = 17.3, 1.7 Hz, 1H), 4.95 (ddd, 10.2, 2.0, 1.0 Hz), 4.38 (ddd, *J* = 14.8, 8.1, 4.6 Hz, 1H), 4.34 (dt, *J* = 12.3, 1.8 Hz, 1H), 2.35 (ddd, *J* = 14.7, 12.0, 6.2 Hz, 1H), 2.05 (tt, *J* = 7.9, 4.1 Hz, 4H), 1.74 (ddd, *J* = 14.8, 3.5, 2.1 Hz, 1H), 1.47 (dt, *J* = 15.0, 7.5 Hz, 2H), 1.42 (s, 1H), 1.36 (s, 3H)

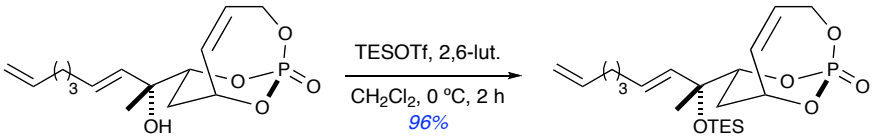
^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 138.7, 131.6, 131.3, 130.2, 128.1, 115.0, 82.1 (d, J_{CP} = 7.4 Hz), 77.4 (d, J_{CP} = 6.5 Hz), 73.7 (d, J_{CP} = 9.1 Hz), 63.3 (d, J_{CP} = 6.3 Hz), 33.4, 31.9, 29.4 (d, J_{CP} = 5.4 Hz), 28.5, 25.0

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm –2.76 (t, J_{PH} = 24.8 Hz)

HRMS Exact Mass: calculate for $C_{15}H_{23}NaO_5P$ $(M+Na)^+$ 337.1181;

found 337.1160 (ESI)

(1*S*,6*R*,8*R*)-8-((*R*,*E*)-2-(triethylsilyloxy)nona-3,8-dien-2-yl)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene: 26.3



A flame dried mL round bottom flask was charged with 16 mg phosphate **26.2** (0.051 mmol) and 0.5 mL of CH_2Cl_2 to generate a 0.1M solution, followed by 8 μL of 2,6-lutidine (0.066 mmol, 1.3 equiv.). The solution was then cooled to 0 ºC and 13 μL of TESOTf (0.056 mmol, 1.1 equiv.) was added dropwise to the solution with stirring. The solution was allowed to stir at 0 ºC until completion (about 1 h until complete by TLC, then allowed to proceed another 1 h). The reaction was quenched with 1 mL of sat. aq. NH_4Cl, separated, and the aqueous layer re-extracted 3 more times with 2 mL portions of diethyl ether. The combined organic layers were then washed with brine, dried with $MgSO_4$, and filtered. Addition of SiO_2 preceded removal of solvent, following which the impregnated SiO_2 was loaded onto a short column and the desired product eluted with 1:2 hexane: diethyl ether to provide 21 mg (96% yield) of silyl protected phosphate **26.3**.

$[\alpha]_D$: -34 (*c* = 0.10, CH_2Cl_2, 25.2 ºC)

FTIR: (neat) 2953, 2916, 2879, 1293, 1264, 1237, 1220, 1134, 1074, 1061, 1042, 994, 978 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 6.00 (dddd, *J* = 11.8, 3.0, 2.3, 1.3 Hz, 1H), 5.79 (dddd, *J* = 17.0, 10.2, 6.9, 6.7 Hz, 1H), 5.67 (dt, *J* = 15.5, 6.9 Hz, 1H), 5.56 (ddd,

11.8, 3.9, 2.6 Hz, 1H), 5.38 (dd, J = 16.7, 1.2 Hz, 1H), 5.21 (app dd, J = 24.4, 1.7 Hz, 1H), 5.00 (dd, J = 17.2, 1.8 Hz, 1H), 4.96 (ddd, J = 10.3, 1.2, 0.8 Hz, 1H), 4.34 (ddd, J = 21.5, 14.7, 6.8 Hz, 1H), 4.20 (dt, J = 10.3, 1.6 Hz, 1H), 2.29 (ddd, J = 14.8, 11.9, 6.3 Hz, 1H), 2.04 (q, J = 7.2 Hz, 4H), 1.81 (app d, J = 14.5 Hz, 1H), 1.47 (dd, J = 7.9, 0.9 Hz, 1H), 1.37 (s, 3H), 1.25 (br s, 2H), 0.93 (t, J = 7.9 Hz, 9H), 0.59 (qd, J = 7.9, 1.3 Hz, 6H)

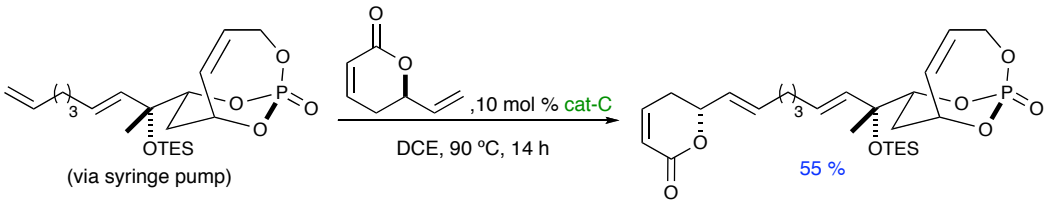
^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 138.8, 134.1, 131.5, 130.3, 127.9, 114.9, 81.9 (d, J_{CP} = 7.4 Hz), 77.8 (d, J_{CP} = 6.5 Hz), 75.8 (d, J_{CP} = 10.2 Hz), 63.2 (d, J_{CP} = 6.4 Hz), 33.4, 31.9, 29.9, 29.1 (d, J_{CP} = 5.3), 28.5, 22.8, 7.3, 6.8

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -2.81 (t, J_{PH} = 24.4 Hz)

HRMS Exact Mass: calculate for $C_{21}H_{37}NaO_5PSi$ $(M+Na)^+$ 451.2046;

found 451.2026 (ESI)

(*R*)-6-((*R*,1*E*,6*E*)-8-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)-8-(triethylsilyloxy)nona-1,6-dienyl)-5,6-dihydro-2*H*-pyran-2-one: 27.1



To a dry pressure tube equipped with stir bar was added 0.75 mg (0.001 mmol, 10 mol %) Hoveyda-Grubbs II catalyst, 3 mg (0.023 mmol, 2 equiv.) lactone **2.4**, and 0.8 mL dry, degassed dichloroethane. The reaction vessel was purged with Ar and fitted with a cap bearing a Teflon septa to which a ballon of Ar was affixed through a 21 gauge needle, followed by immersion of the vessel in an oil bath at 90 ºC. A 0.03 M solution of phosphate **26.3** (5 mg, 0.012 mmol, 0.8 mL) was added by syringe pump at a rate of 0.1 mL/h, hence leading to complete addition of substrate in 8 h. The reaction was allowed to proceed for 6 more hours before removing the vessel from the oil bath and allowing to cool to room temperature. SiO_2 was then added to the mixture and the solvent removed, followed by placement of the substrate impregnated silica on a column. Elution with 1:2 hexane: EtOAc provided 4.4 mg of a ~3:1 ratio of both product **27.1** and lactone dimer as an inseperable mixture discernable by spectroscopy.

FTIR: (neat) 2914, 2876, 1722, 1420, 1385, 1294, 1263, 1236, 1220, 1134, 1074, 1061, 1042, 993 cm^{-1}

^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm (discernable peaks) 5.82 (dddd, *J* = 15.7, 9.0, 6.5, 5.6 Hz, 1H), 5.65 (dtd, *J* = 15.6 , 6.7, 2.0 Hz, 1H), 5.58 (ddd, *J* = 16.5, 8.7, 3.6 Hz, 1H), 5.38 (d, *J* = 15.6 Hz, 1H), 5.22 (app d, *J* = 23.4 Hz, 1H), 4.88 (dd, *J* = 14.4, 7.0 Hz, 1H), 4.35 (dddd, *J* = 11.6, 8.0, 6.9, 6.6 Hz, 1H), 4.21 (dd, *J* = 14.2, 2.0 Hz, 1H), 2.27 (ddd, J = 14.9, 12.1, 6.8 Hz, 1H), 2.06 (ddd, J =7.5, 7.1, 6.9 Hz, 4H), 1.36 (s, 3H), 1.21 (dd, *J* = 7.1, 7.0 Hz, 2H), 0.93 (td, *J* = 7.8, 1.6 Hz, 9H), 0.58 (qd, *J* = 7.4, 2.4 Hz, 6H)

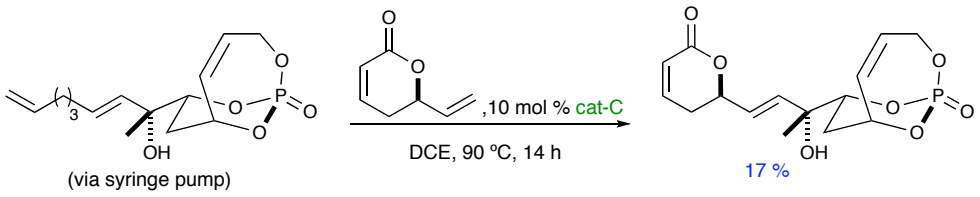
^{13}C NMR (126 MHz, $CHCl_3$-*d*) δ ppm 164.4, 145.1, 135.2, 134.3, 131.2, 130.3, 127.9, 127.4, 121.7, 81.8, 78.4, 75.7, 72.4, 63.2, 31.8, 31.7, 30.0, 29.2, 28.3, 22.6, 7.3, 6.8

^{31}P NMR (162 MHz, $CHCl_3$-*d*) δ ppm -3.11 (t, J_{PH} = 23.1 Hz)

HRMS Exact Mass: calculate for $C_{26}H_{41}NaO_7PSi$ $(M+Na)^+$ 547.2251;

found 547.2257 (ESI)

(*R*)-6-((*R*,*E*)-3-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)-3-hydroxybut-1-enyl)-5,6-dihydro-2*H*-pyran-2-one: 28.1



A small Pyrex pressure tube under Ar atmosphere bearing a cap with Teflon septa and stirring bar is charged with 1.5 mg Hoveyda-Grubbs catalyst (0.002 mmol, 10 mol %), 3 mg of lactone **2.4** (0.0232 mmol, 1 equiv.) and 1.0 mL degassed dichloroethane (0.02M with respect to **2.4**). The solution is placed in a 90 ºC silicon oil bath and allowed to stir for 10 minutes. Another solution containing 7.3 mg of phosphate **26.2** (0.0232 mmol) and 6 mg lactone **2.4** (0.0464 mmol, 2 equiv.) in 600 μL of degassed dichloroethane is placed in a syringe and the needle of the syringe placed through the septa of the Pyrex tube. The syringe is then injected via syringe pump at a rate of 100 μL per hour and the reaction allowed to proceed overnight. The pressure tube is then removed from heat, SiO_2 added, and the solvent removed. The product bearing silica gel is then placed on a column for purification utilizing 100% EtOAc to remove the more nonpolar components followed by elution with 50% acetone in EtOAc to provide 1.3 mg (17% yield) of lactone appended phosphate **28.1**.

$[\alpha]_D$: -16.9 (*c* = 0.07, acetone, 24.1 ºC)

FTIR: (neat) 3401, 2919, 2851, 1717, 1383, 1295, 1251, 1117, 1067, 1036, 966, 924, 820 cm^{-1}

^{1}H NMR (500 MHz, acetone-d_6) δ ppm 7.01 (ddd, J = 9.7, 5.7, 2.8 Hz, 1H), 6.08 (ttd, J = 8.9, 2.2, 1.3 Hz, 1H), 6.01 (dd, J = 15.6, 5.9 Hz, 1H), 5.95 (ddd, J = 9.7, 2.5, 1.2 Hz, 1H), 5.94 (d, J = 15.6 Hz, 1H), 5.73 (ddd, J = 11.9, 3.8, 2.6 Hz, 1H), 5.29 (app d, J = 24.3 Hz, 1H), 5.00 (dddd, J = 5.5, 5.4, 5.2, 4.8 Hz, 1H), 4.87 (dddd, J = 14.8, 8.4, 5.7, 2.7 Hz, 1H), 4.38 (m, 2H), 2.57 (dddd, J = 18.5, 4.4, 1.3, 1.0 Hz, 1H), 2.43 (ddt, J = 18.5, 10.8, 2.6 Hz, 1H), 2.28 (ddddd, J = 16.5, 12.1, 7.7, 6.4, 2.7 Hz, 2H), 1.34 (s, 3H), 1.30 (br s, 1H)

^{13}C NMR (126 MHz, acetone-d_6) δ ppm 164.0, 146.4, 137.1, 131.3, 128.4, 128.3, 121.8, 82.0 (d, J_{CP} = 7.4 Hz), 78.3 (d, J_{CP} = 7.0 Hz), 78.1, 73.7 (d, J_{CP} = 9.1 Hz), 63.6 (d, J_{CP} = 6.5 Hz), 30.5 (d, J_{CP} = 3.7 Hz), 29.5, 24.4

^{31}P NMR (162 MHz, acetone-d_6) δ ppm –3.01 (t, J_{PH} = 24.4 Hz)

HRMS Exact Mass: calculate for $C_{15}H_{19}NaO_7P$ $(M+Na)^+$ 365.0766;

found 365.0756 (ESI)

5.5 Experimental Data: References

(1) Whitehead, A.; McReynolds, M.D.; Moore, J.D.; Hanson, P. R.; Multivalent Activation in Phosphate Tethers: A New Tether for Small Molecule Synthesis. *Org. Lett.* **2005**, *7,* 3375-3378.

(2) Waetzig, J. D.; Hanson, P. R. Temporary Phosphate Tethers: A Metathesis Strategy to Differentiated Polyol Subunits. *Org. Lett.* **2006**, *8*, 1673-1676.

(3) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B.T. Dinuclear Asymmetric Zn Aldol Additions: Formal Asymetric Synthesis of Fostriecin. *J. Am. Chem. Soc.* **2005**, *127*, 3666-3667.

(4) Chavez, D. E. The Total Synthesis of Fostriecin (CI-920). The Development and Applications of an Asymmetric Hetero-Diels-Alder Reaction. Ph. D. Thesis, Harvard University, Cambridge, MA, 2003.

(5) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. P–N bond formation as a route to highly electron rich phosphine ligands. *Chem. Commun.* **2000**, 2065-2066.

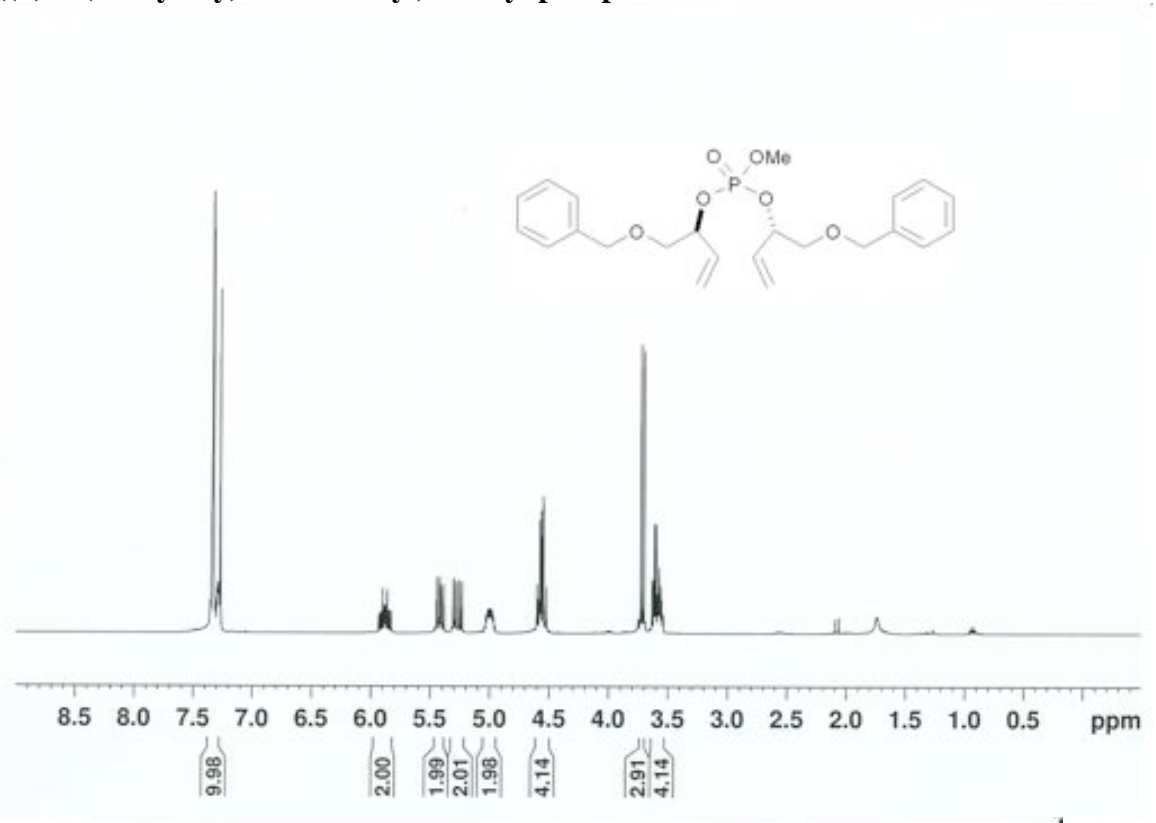
(6) Slightly modified from: Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. Synthesis of *N*-Aryl-2-allyl Pyrrolidines via Palladium-catalyzed Carboamination of γ-(*N*-Arylamino)alkenes with Vinyl Bromides. *Adv. Synth. Catal.* **2005**, *347*, 1614-1620.

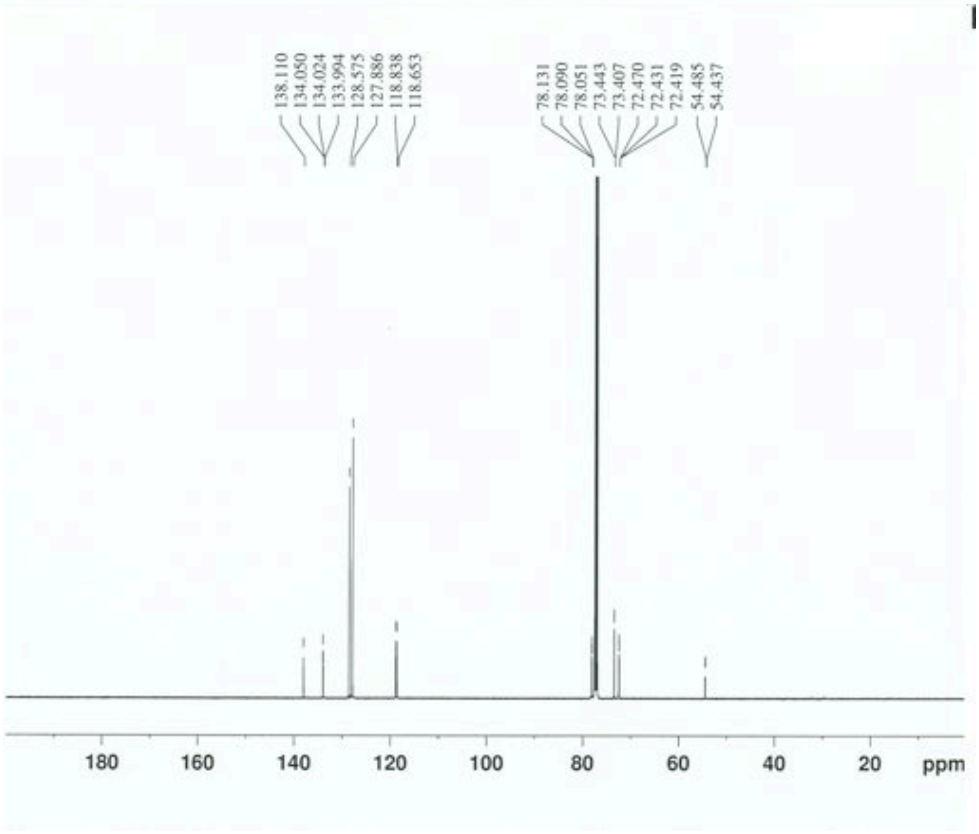
Appendix A

NMR Spectra and X-Ray Data

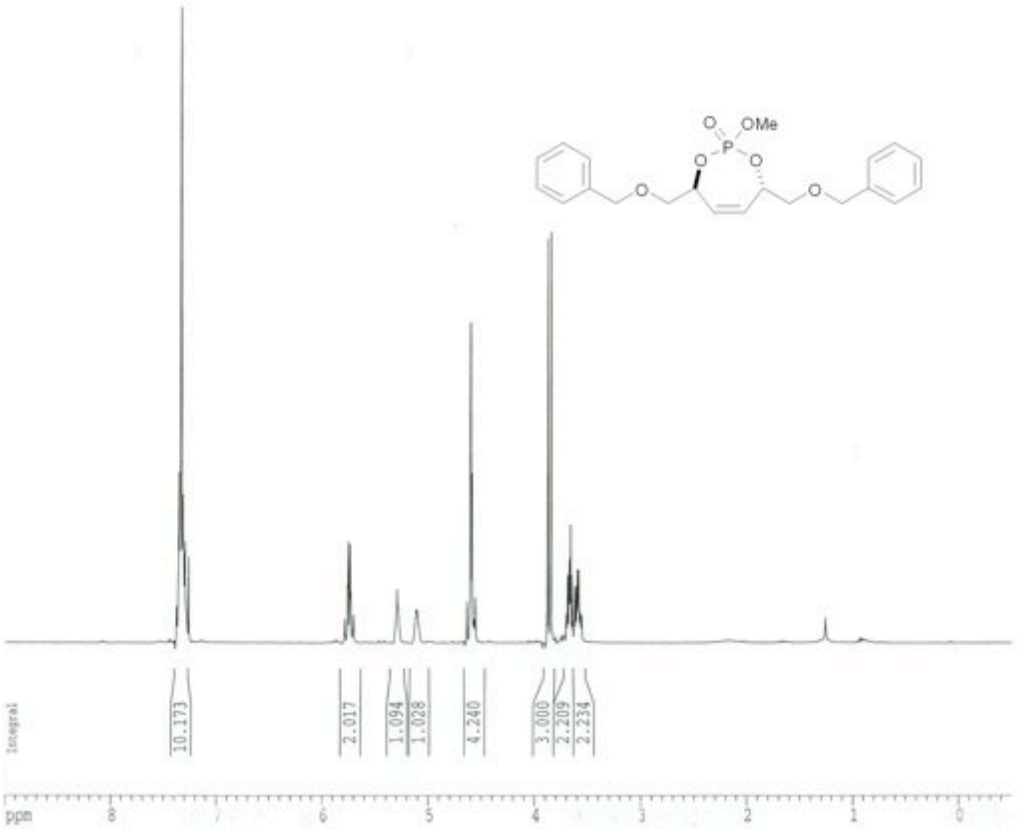
A.1: Chapter 2 Spectra

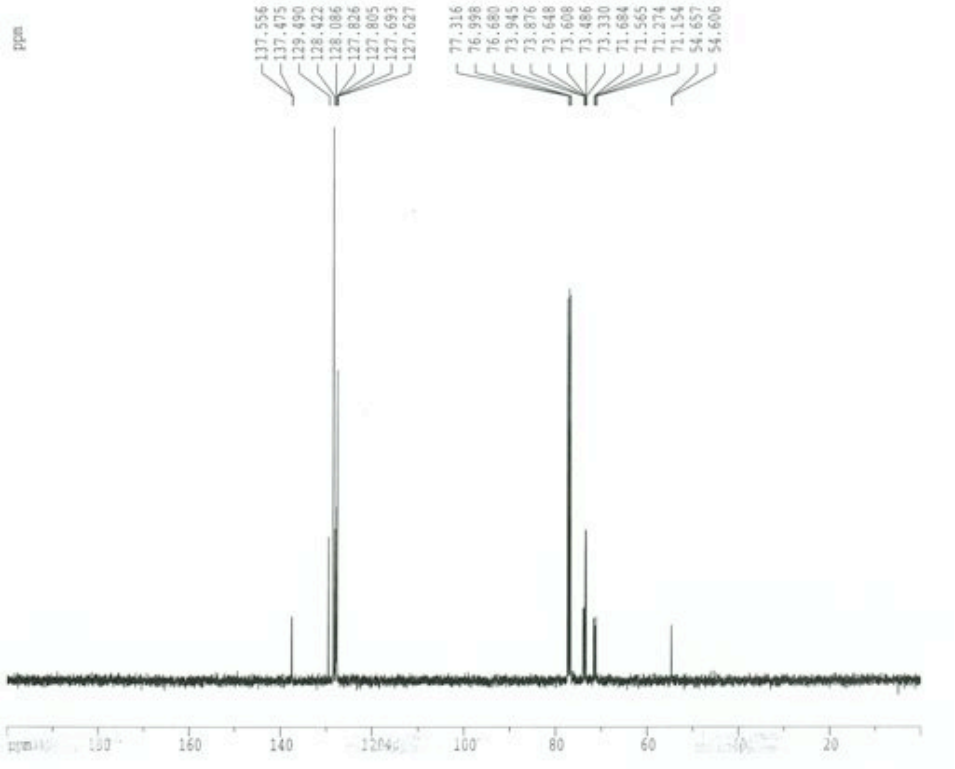
Bis((*S*)-1-(benzyloxy)but-3-en-2-yl) methyl phosphate

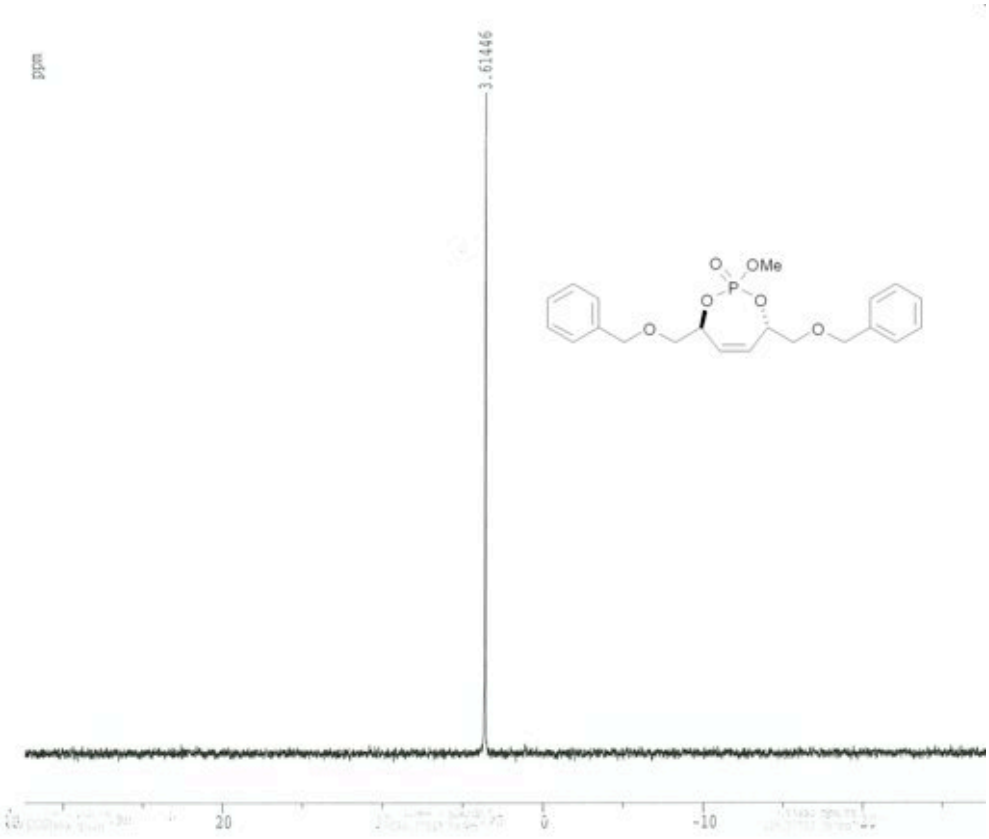




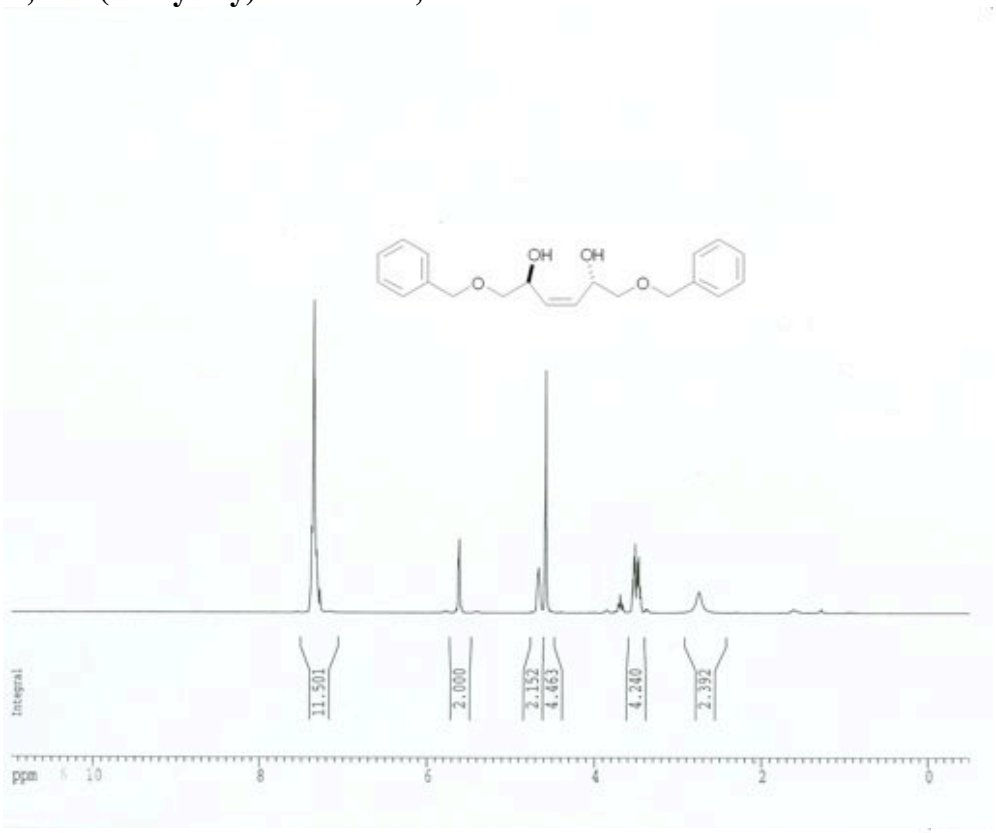
(*S*,*S*)-Monocyclic phosphate: (*S*,*S*)-1.1

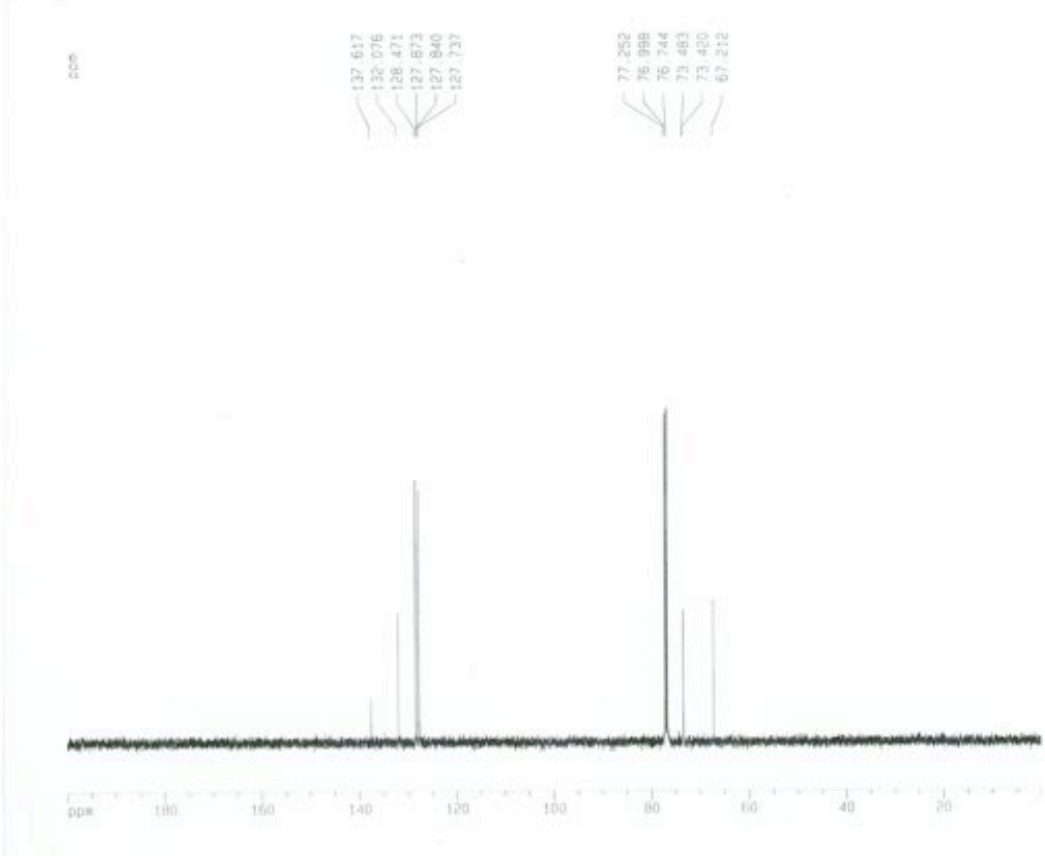




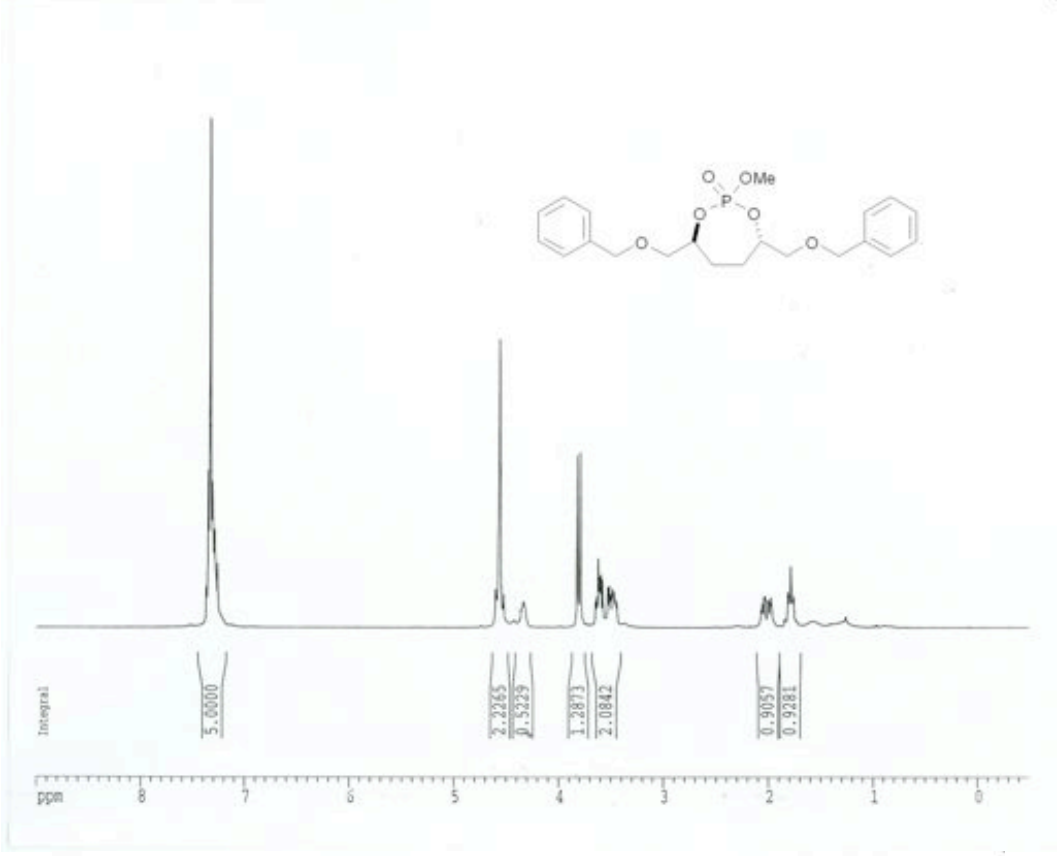

ppm
3.61446
OMe
O
P
O
O
O
O
20
0
-10

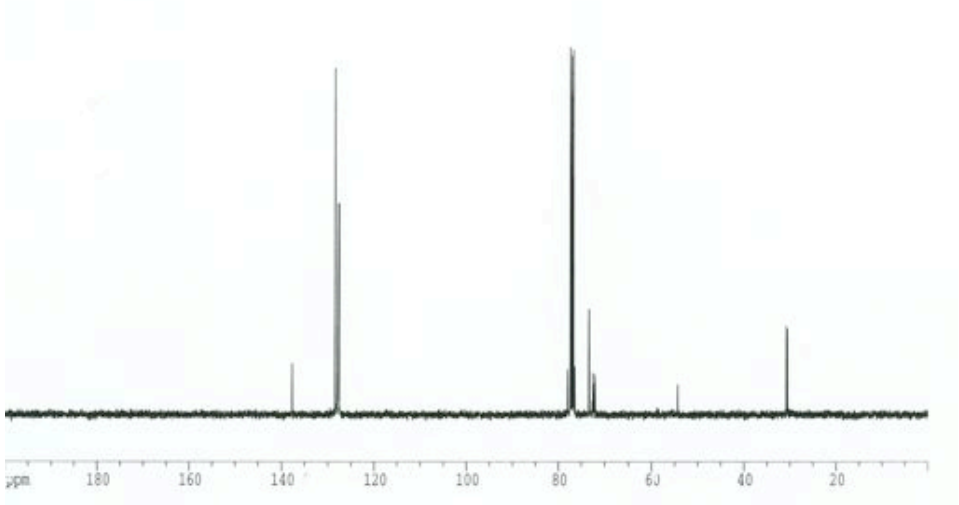
(2*S*,5*S*,*Z*)-1,6-bis(benzyloxy)hex-3-ene-2,5-diol: 2.1

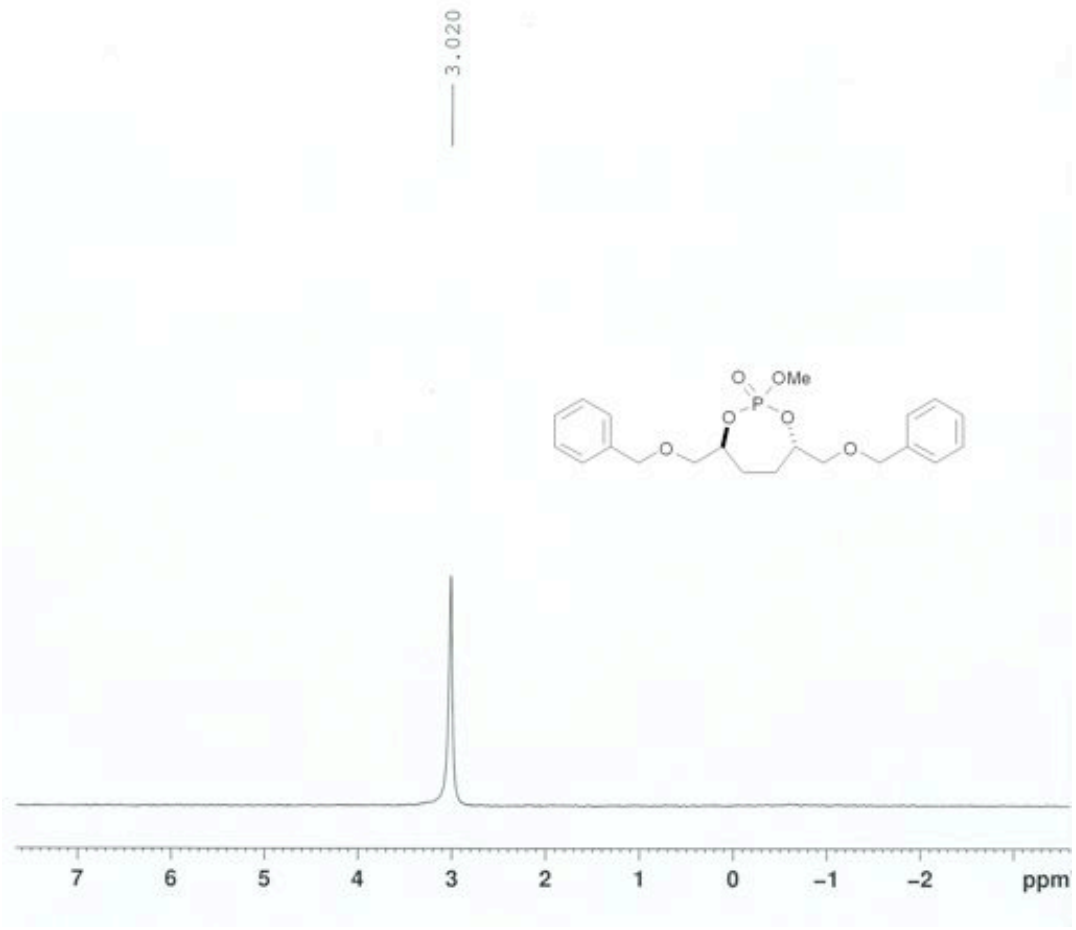




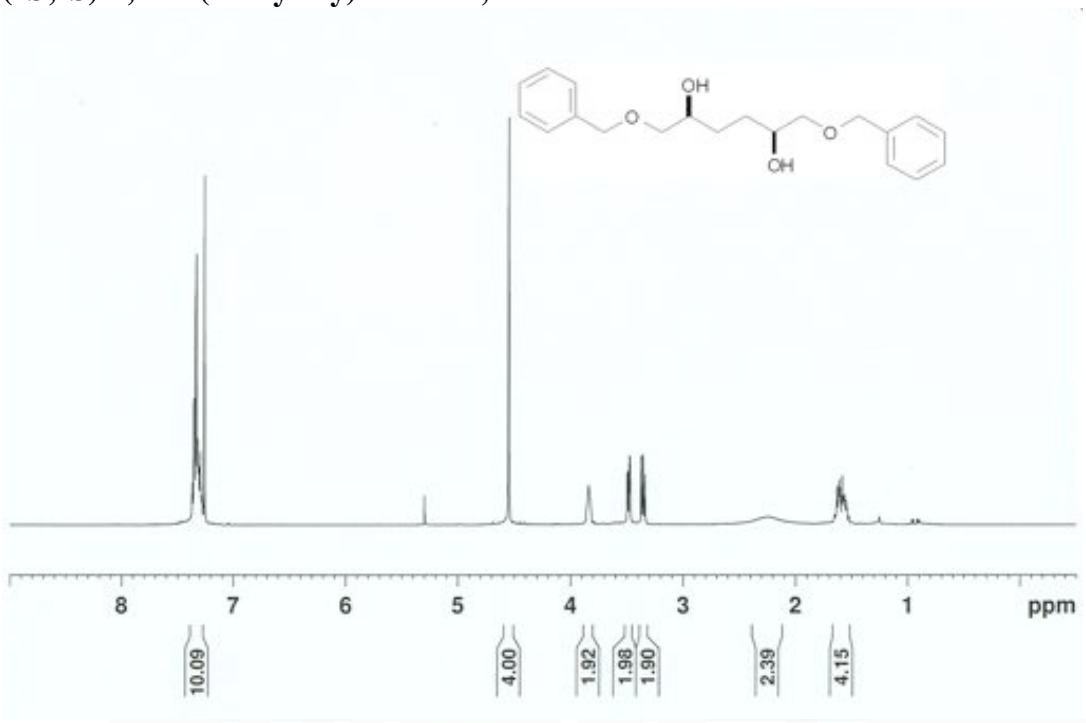
(*S*,*S*)-Hydrogenated monocyclic phosphate: 2.2

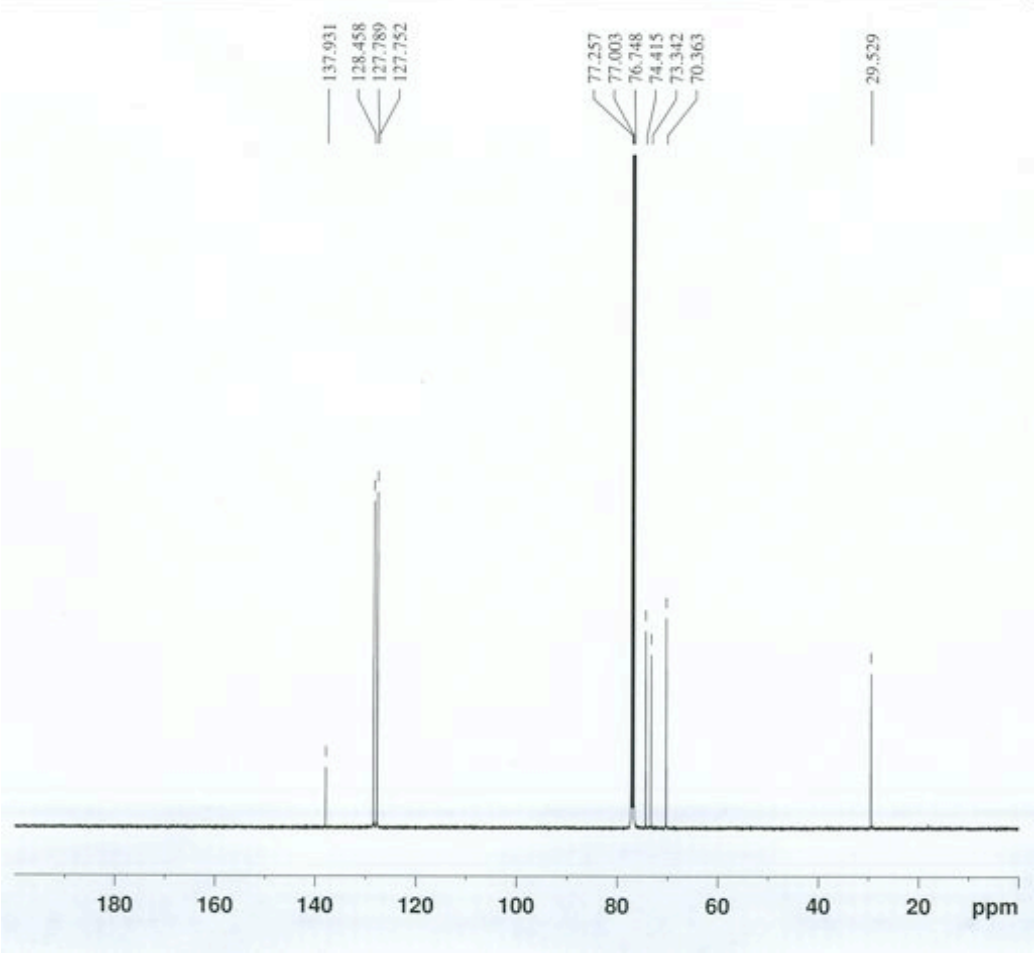




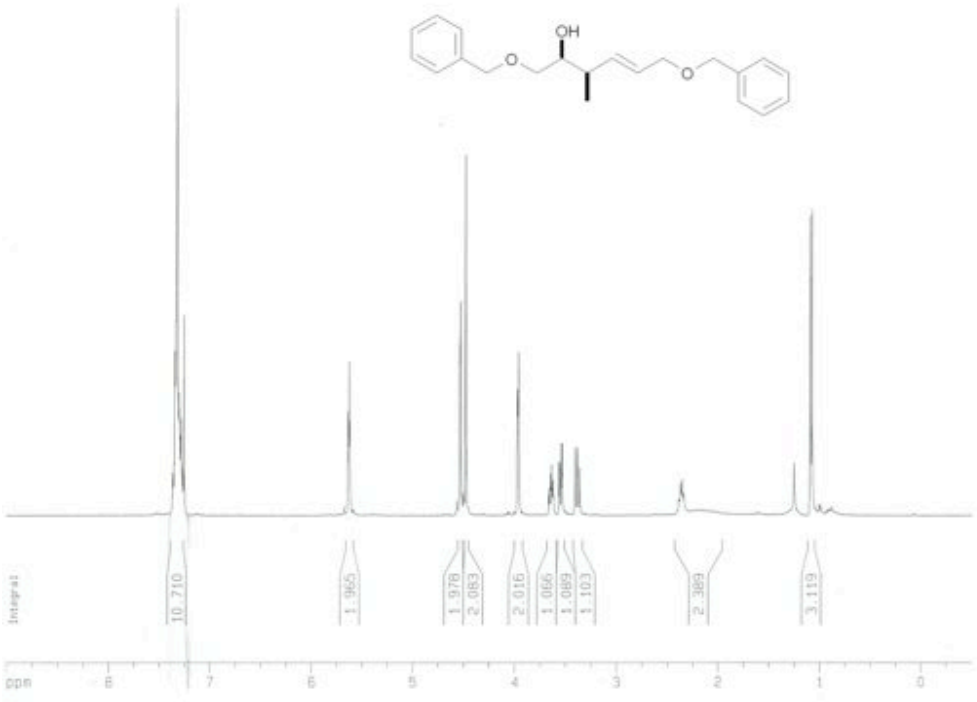

3.020
OMe
7
6
5
4
3
2
1
0
−1
−2
ppm

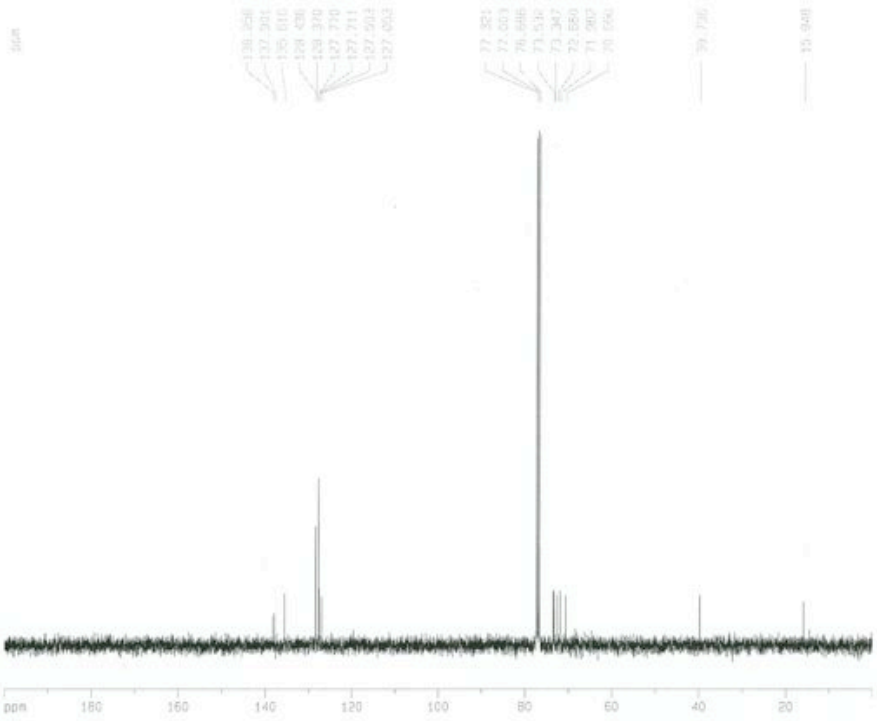
(2*S*,5*S*)-1,6-bis(benzyloxy)hexane-2,5-diol: 2.3



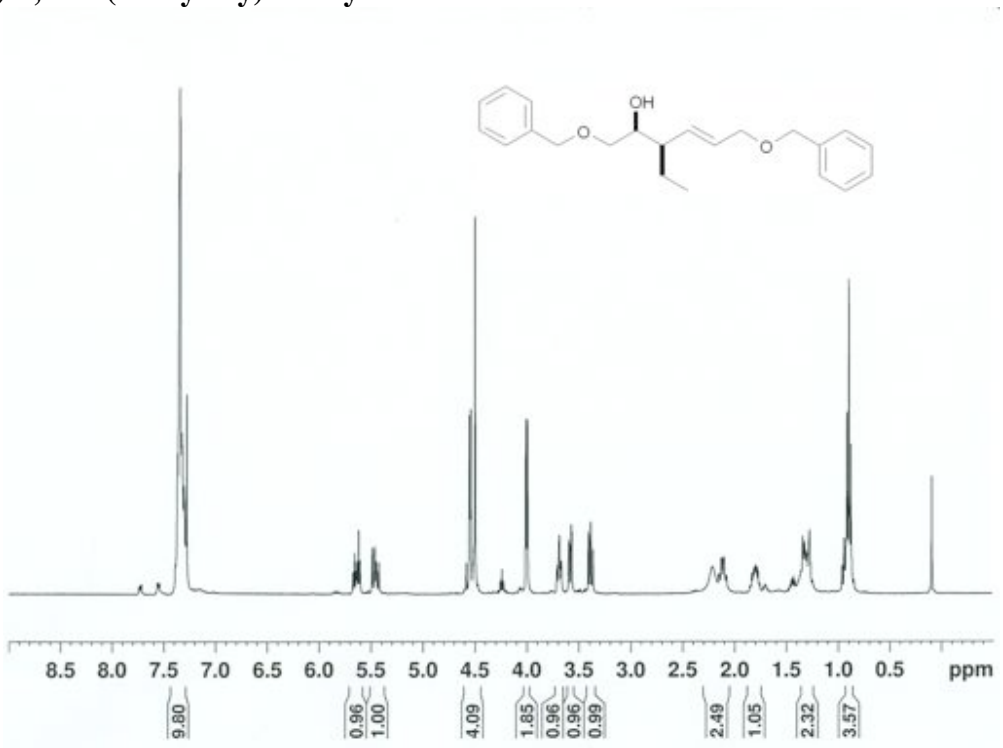


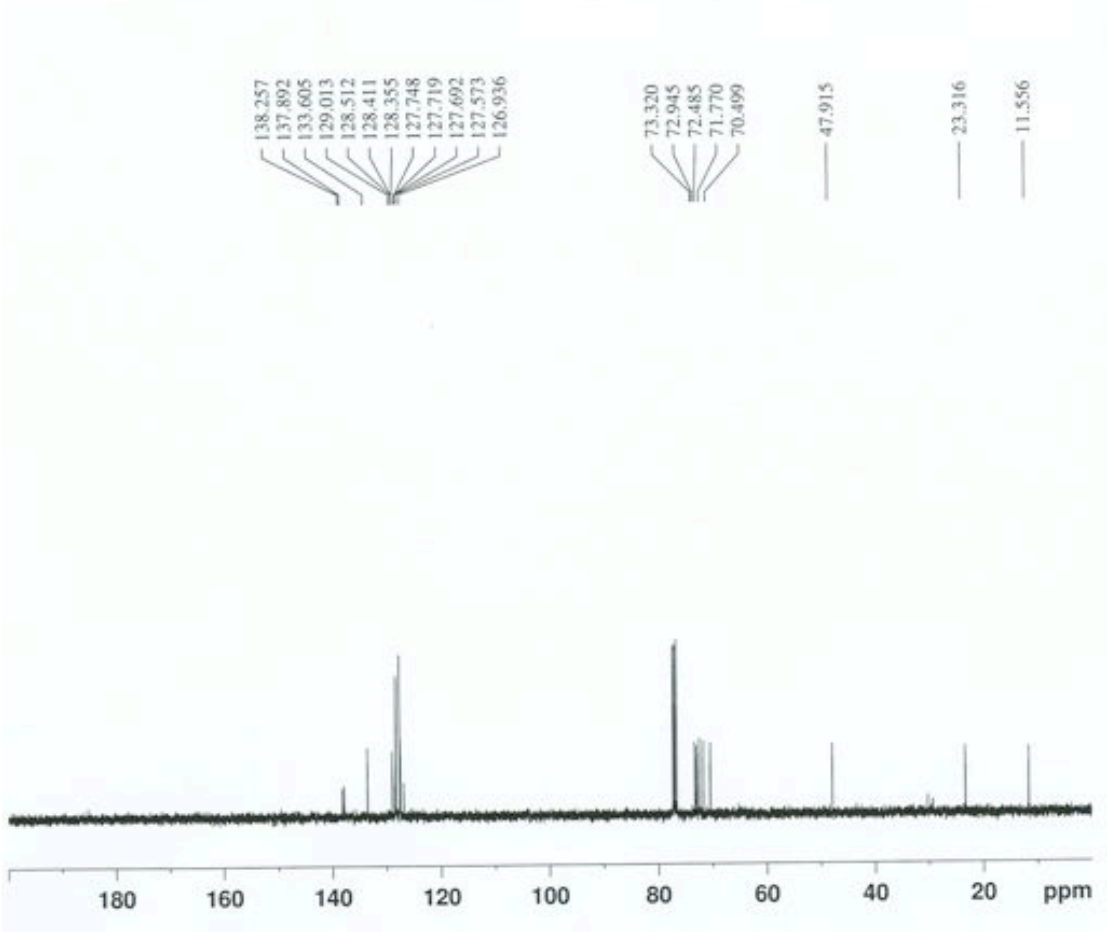
(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-methylhex-4-en-2-ol: 4.1a



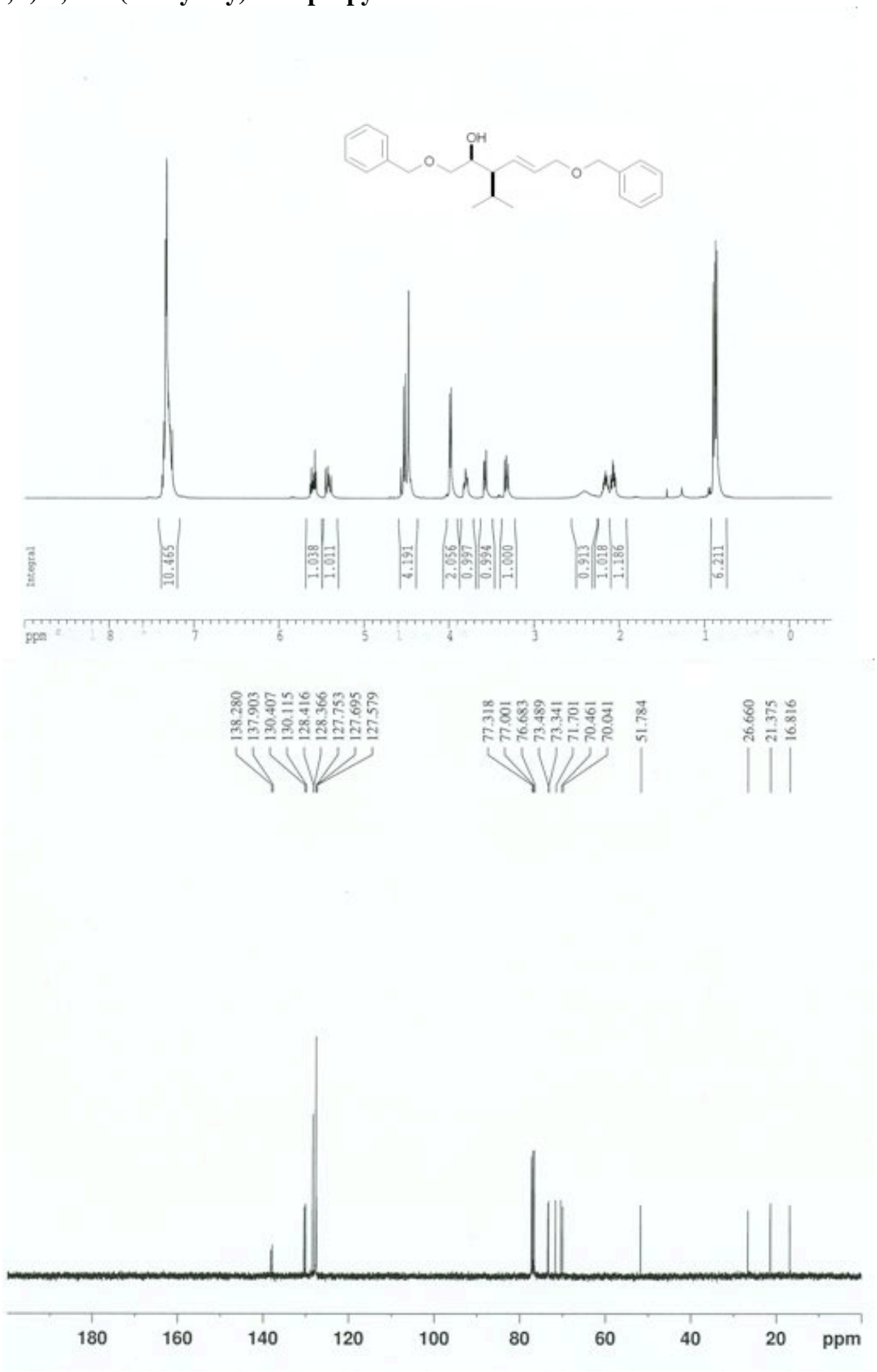


(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-ethylhex-4-en-2-ol: 4.1b

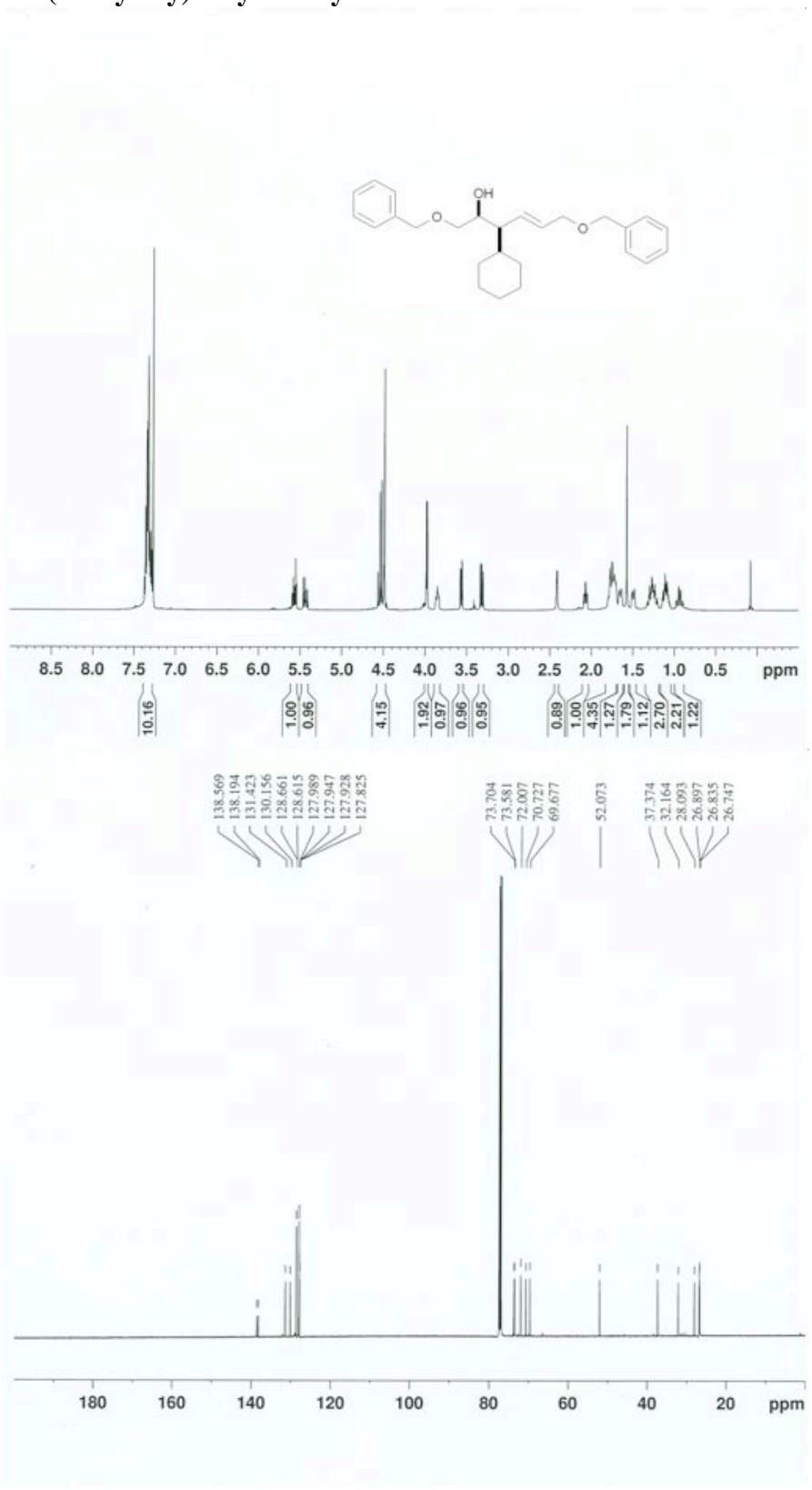




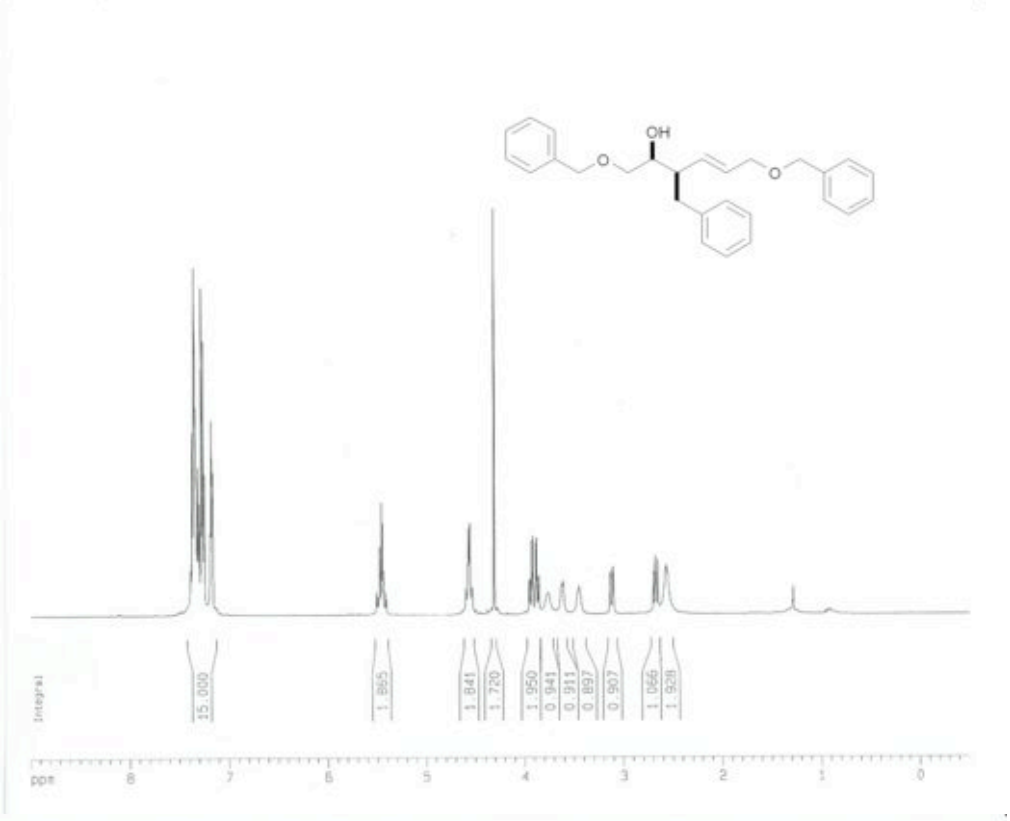
(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-isopropylhex-4-en-2-ol: 4.1c

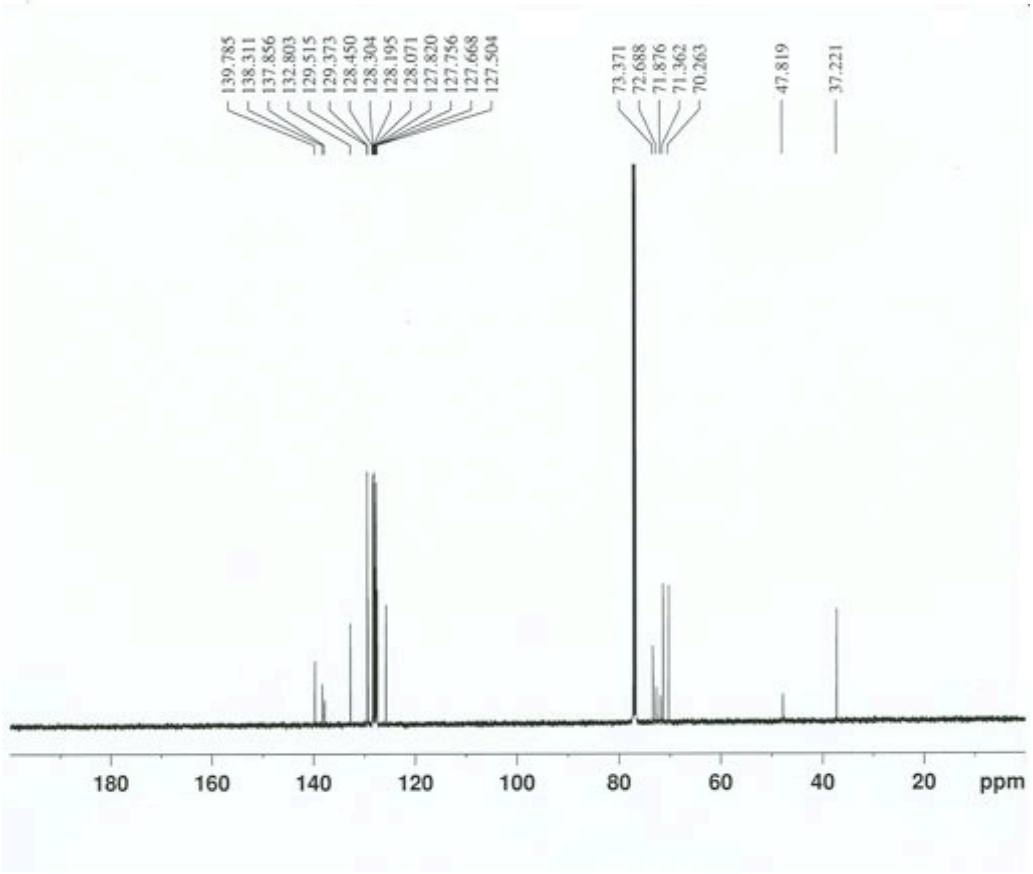


(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-cyclohexylhex-4-en-2-ol: 4.1d

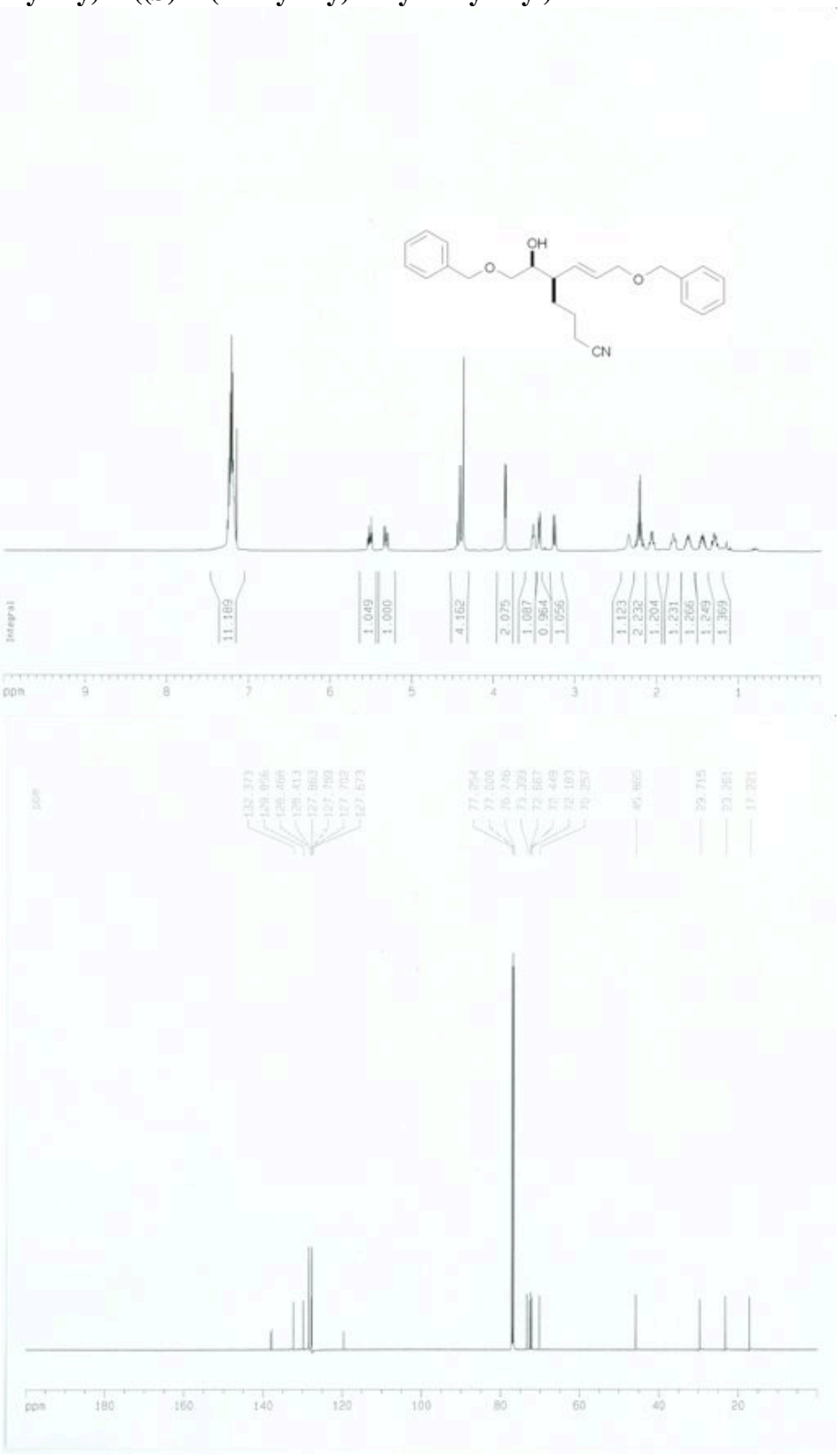


(2*S*,3*R*,*E*)-3-benzyl-1,6-bis(benzyloxy)hex-4-en-2-ol: 4.1e

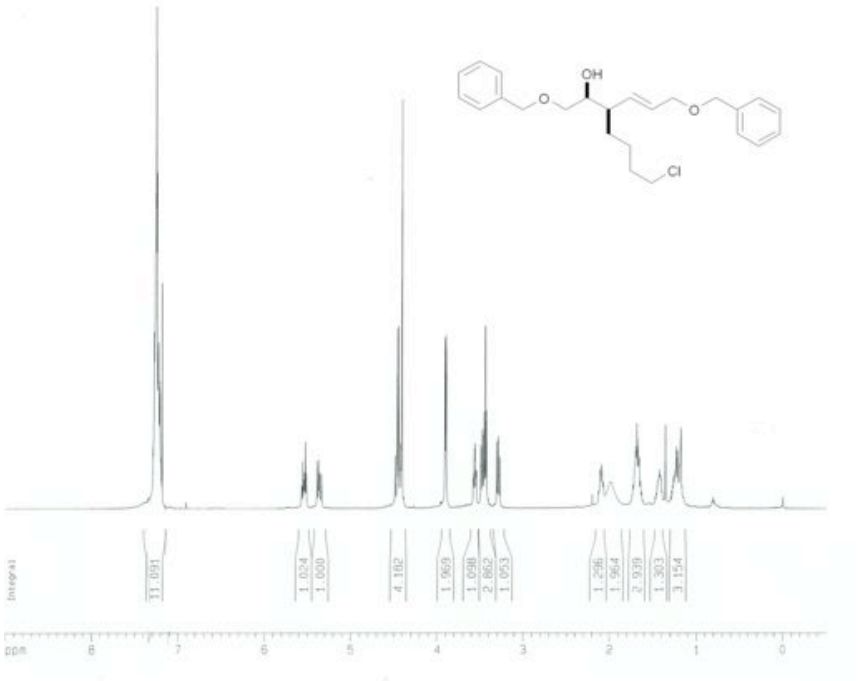


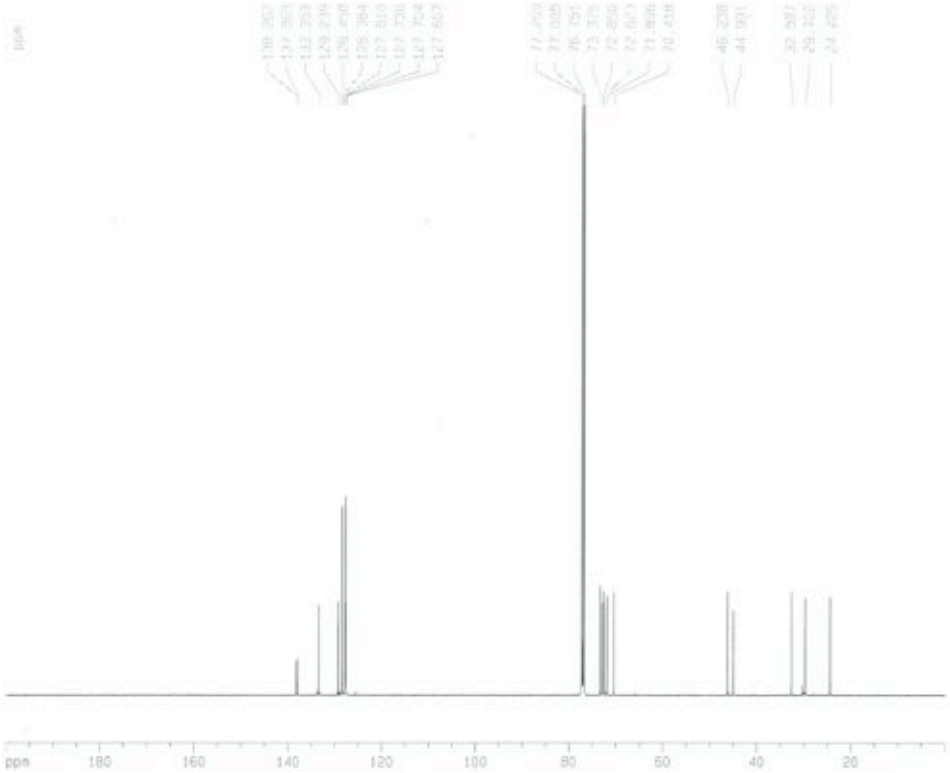


(*R*,*E*)-8-(benzyloxy)-5-((*S*)-2-(benzyloxy)-1-hydroxyethyl)oct-6-enenitrile: 4.1f

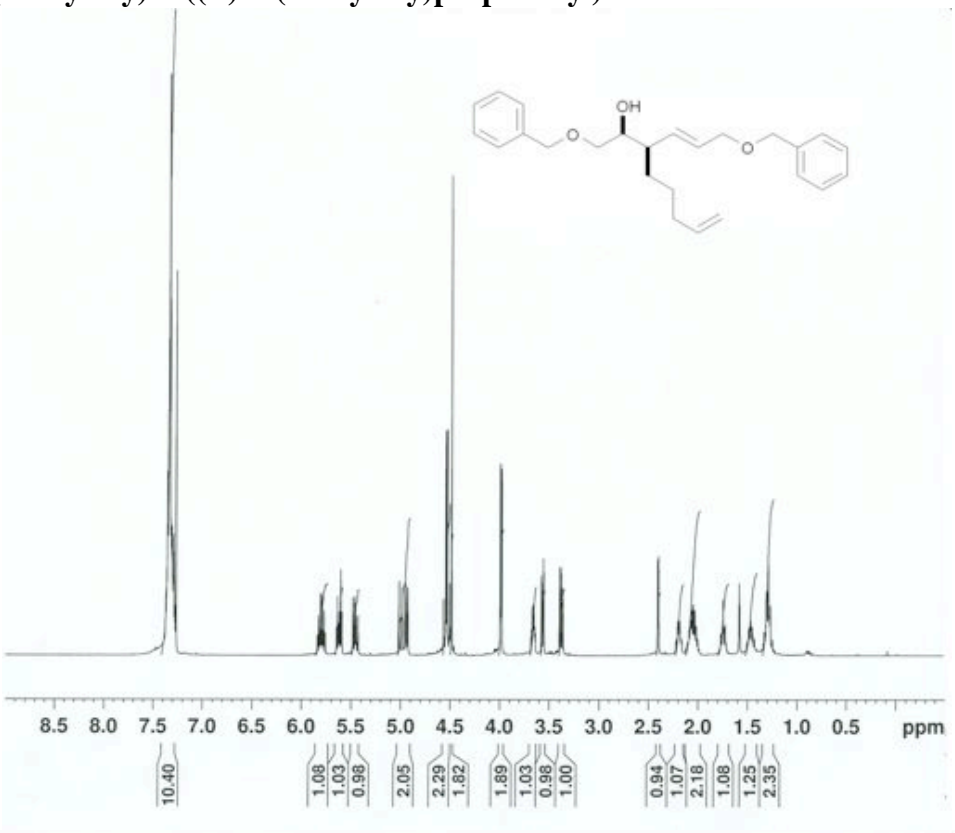


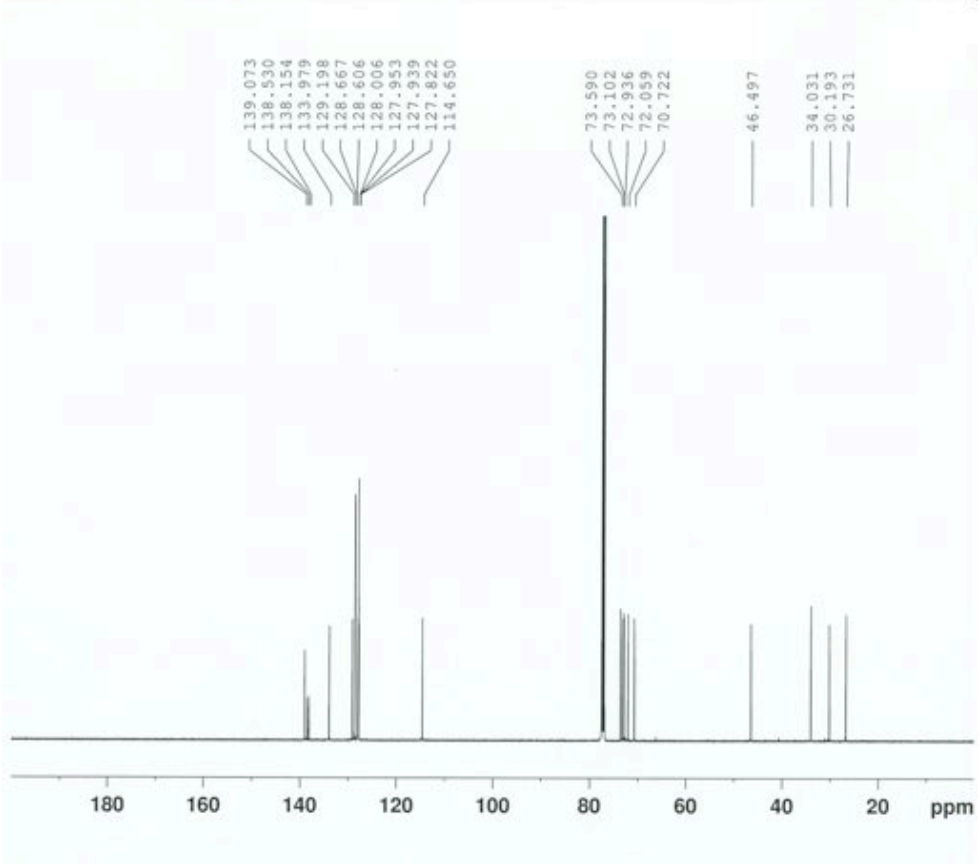
(2*S*,3*R*)-1-(benzyloxy)-3-((*E*)-3-(benzyloxy)prop-1-enyl)-7-chloroheptan-2-ol: 4.1g



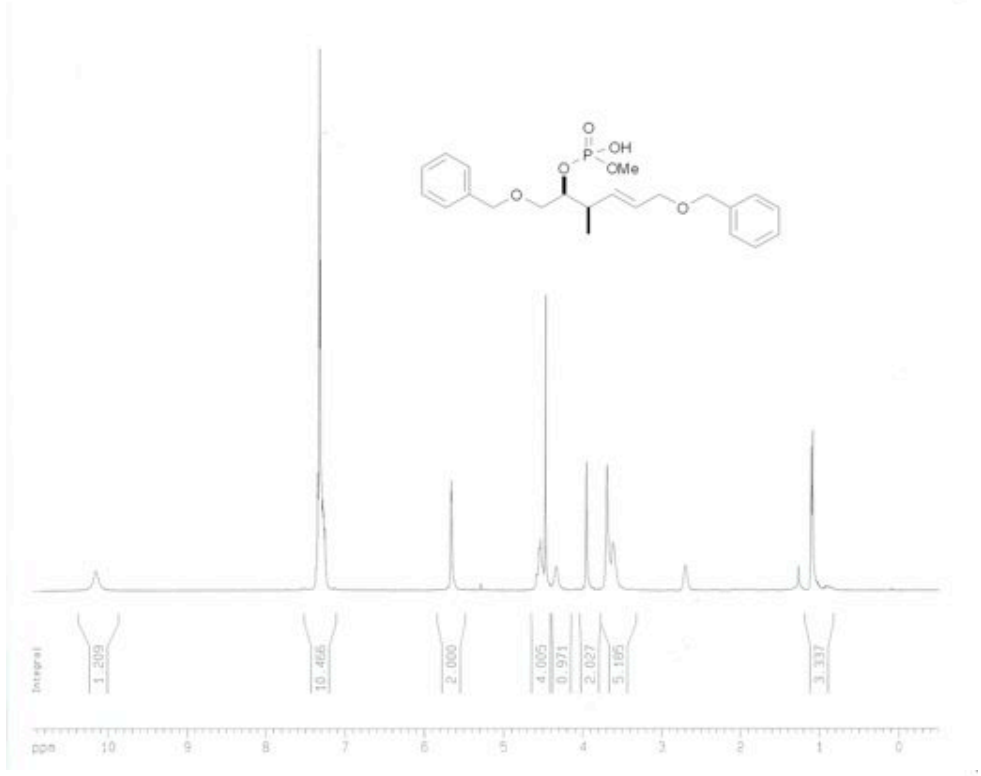


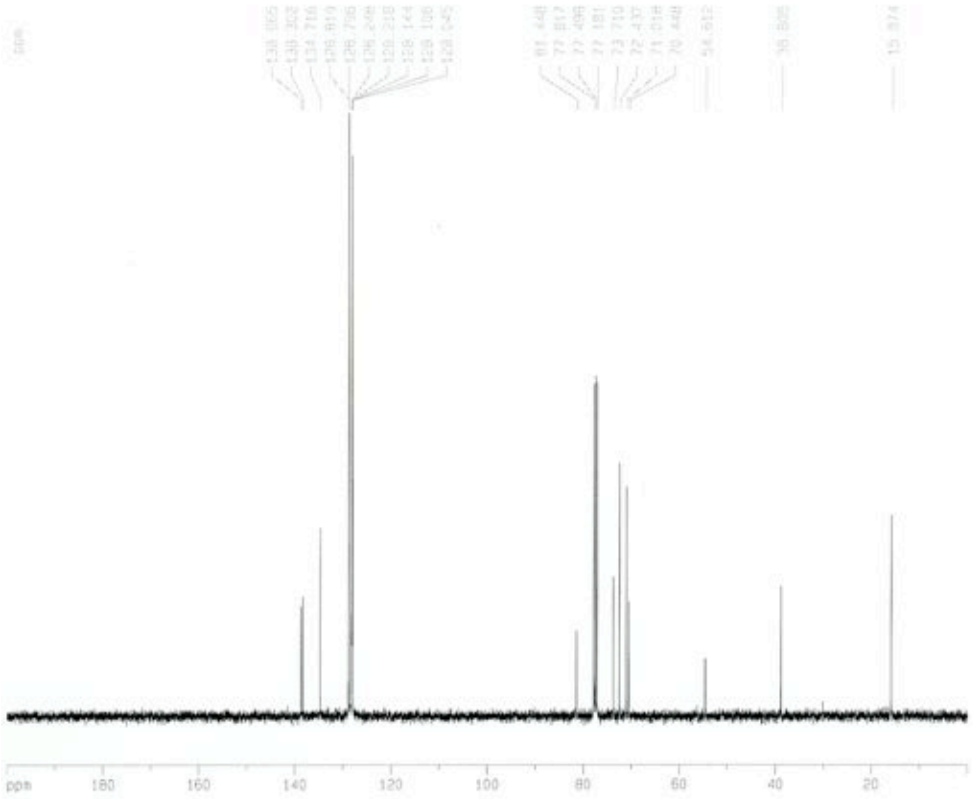
(2*S*,3*R*)-1-(benzyloxy)-3-((*E*)-3-(benzyloxy)prop-1-enyl)oct-7-en-2-ol: 4.1h

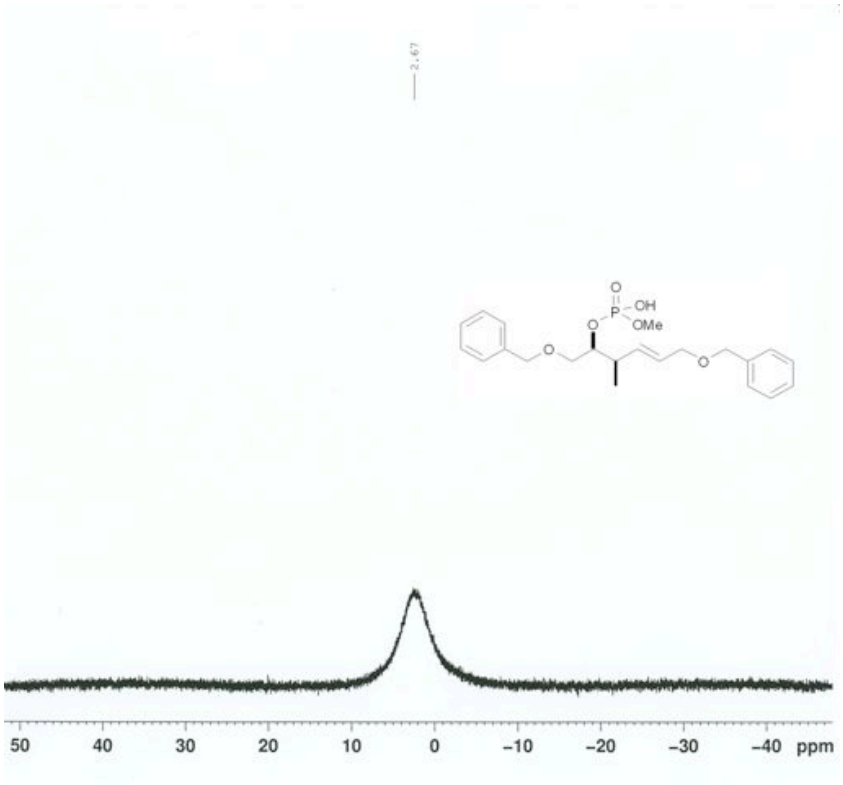




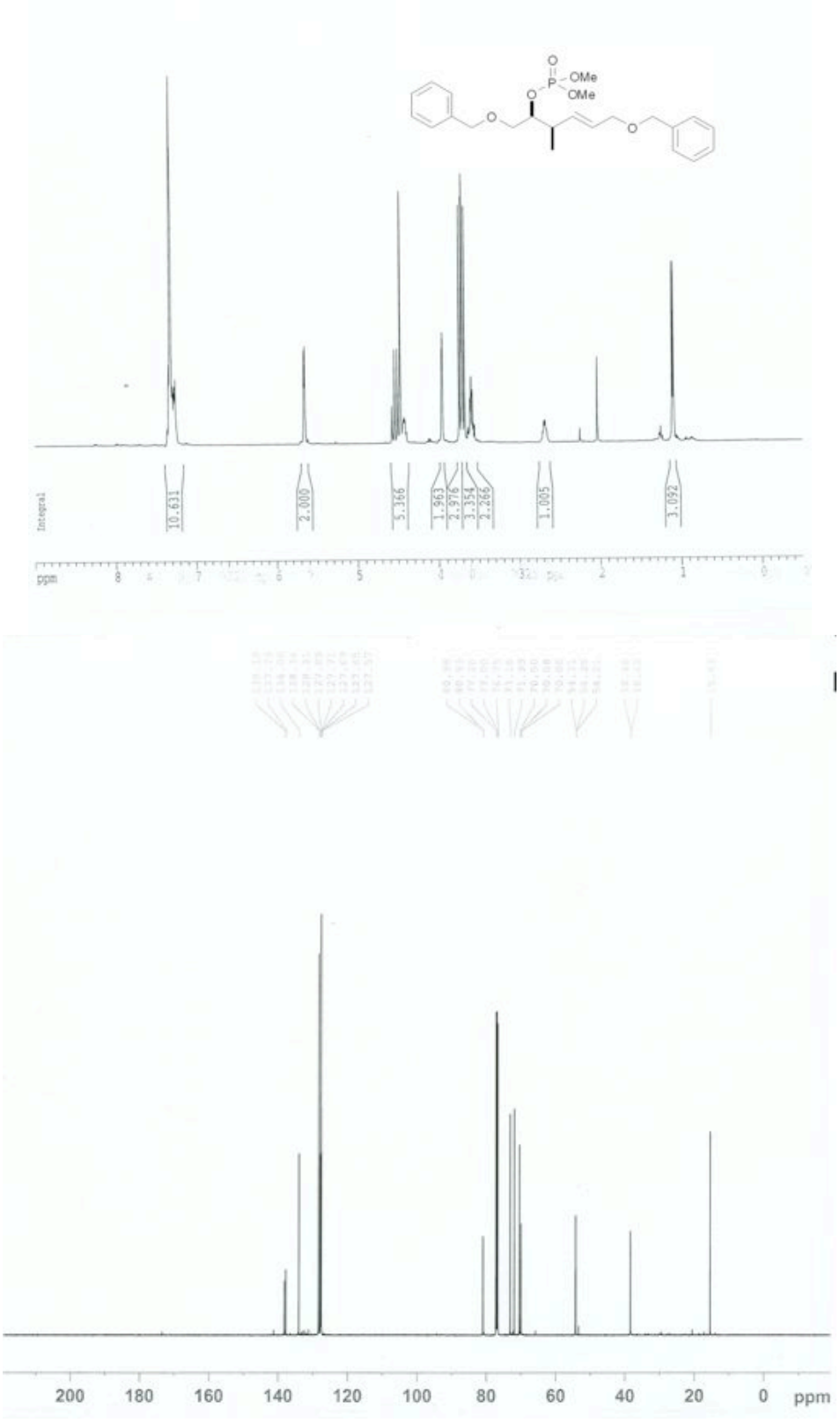
(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-methylhex-4-en-2-yl methyl hydrogen phosphate: 3.1a

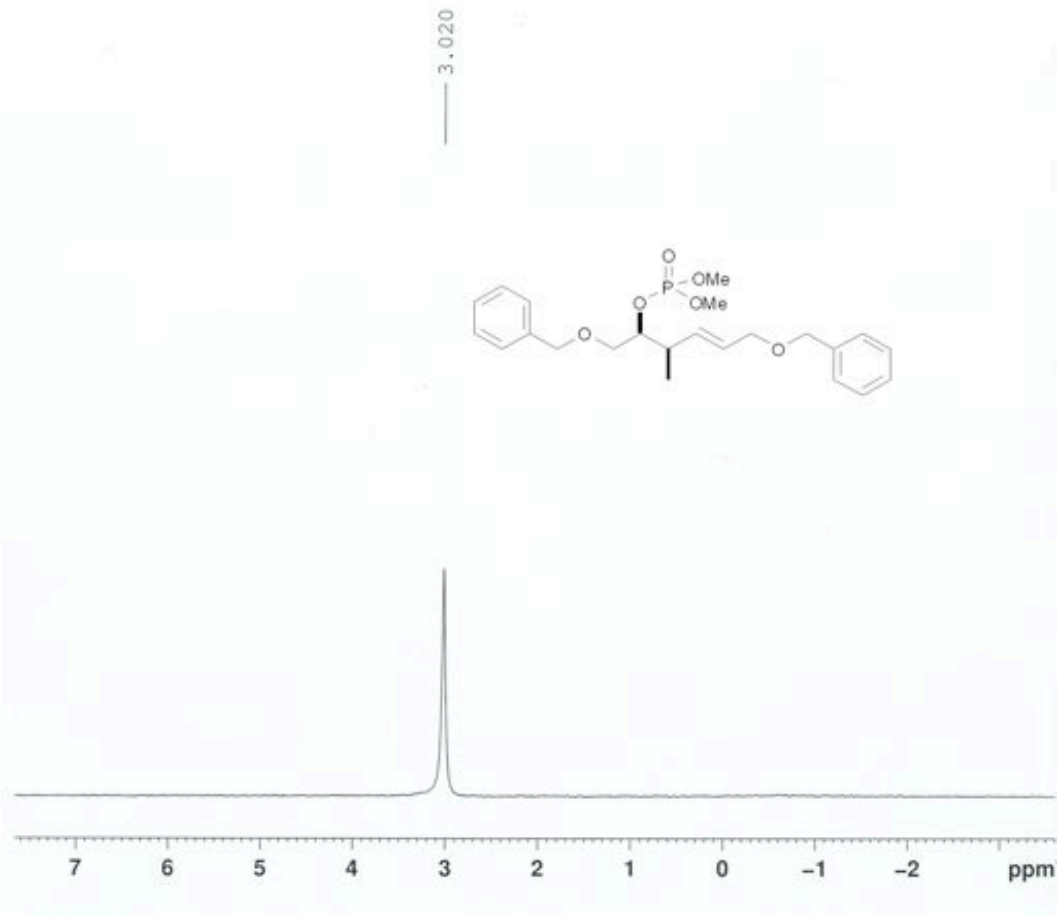




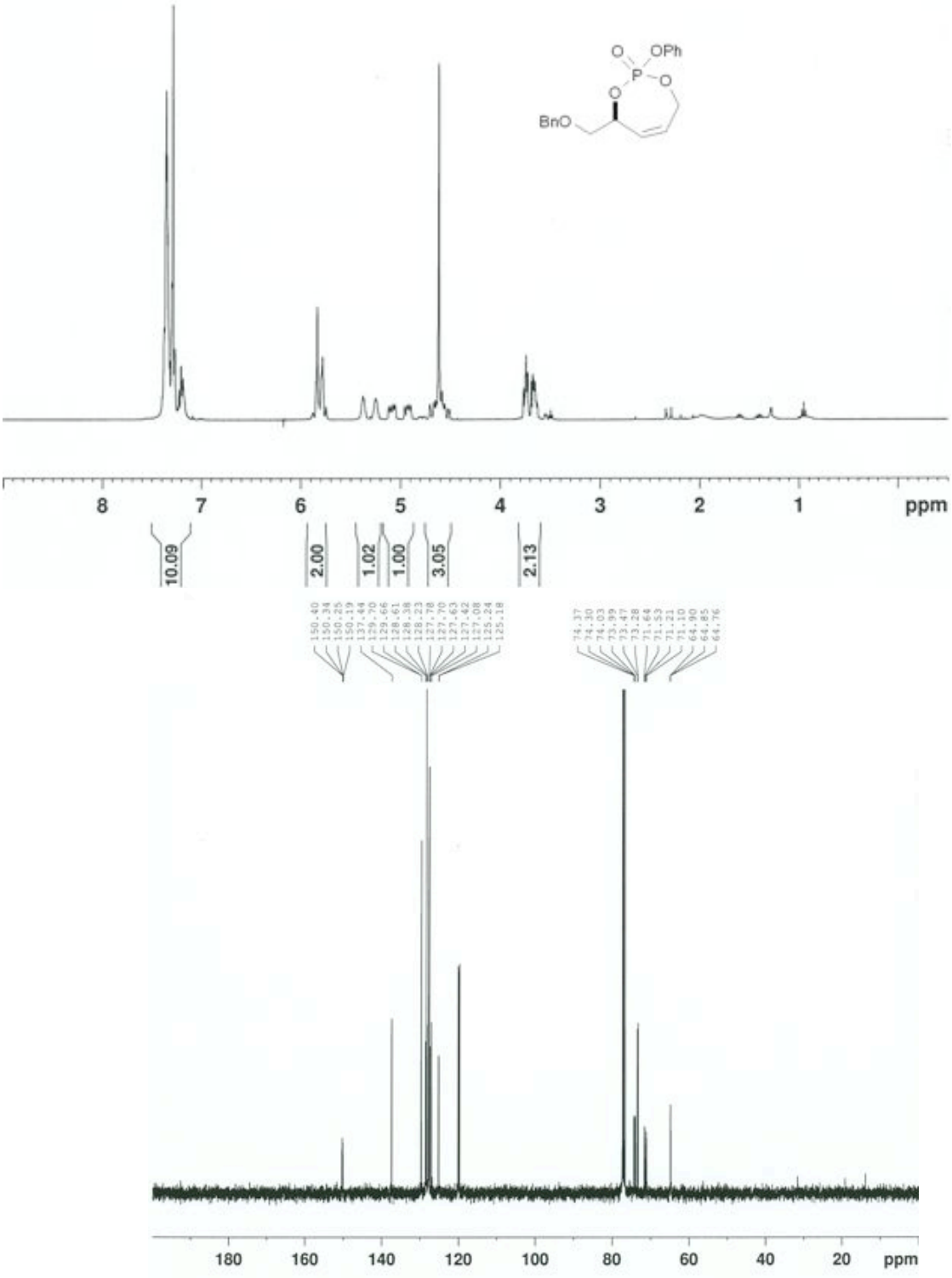

2.67
O
P
OH
OMe
O
O
O
50
40
30
20
10
0
−10
−20
−30
−40
ppm

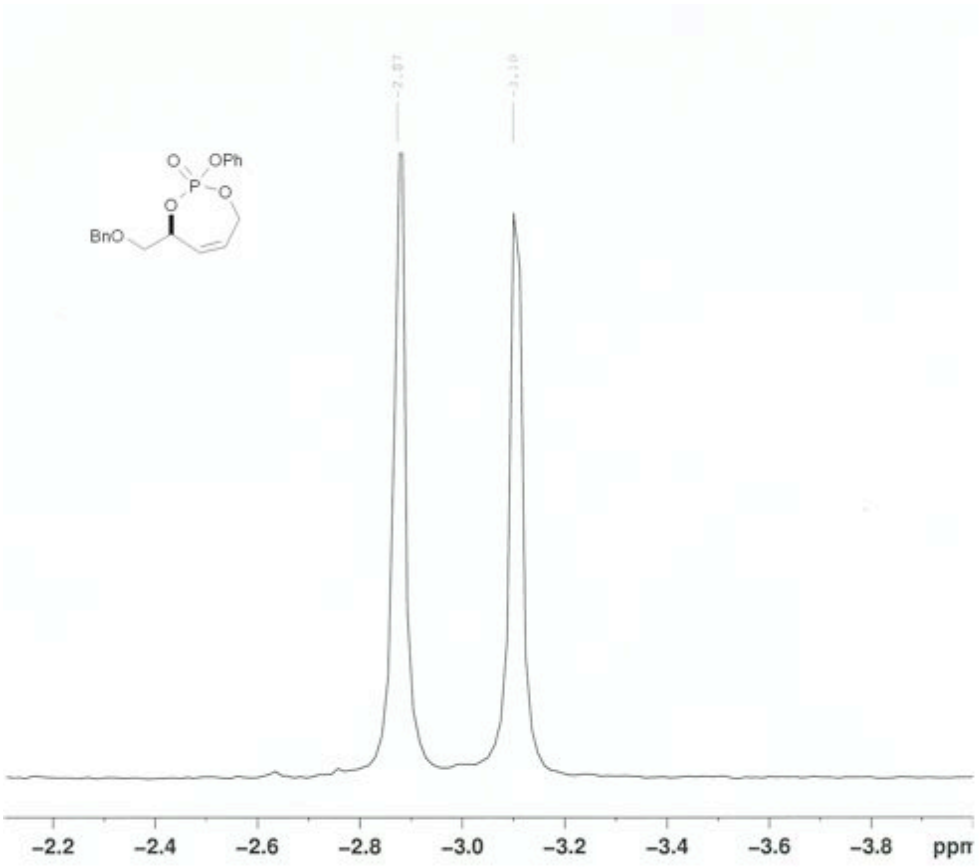
(2S,3R,E)-1,6-bis(benzyloxy)-3-methylhex-4-en-2-yl dimethyl phosphate: 6.1a



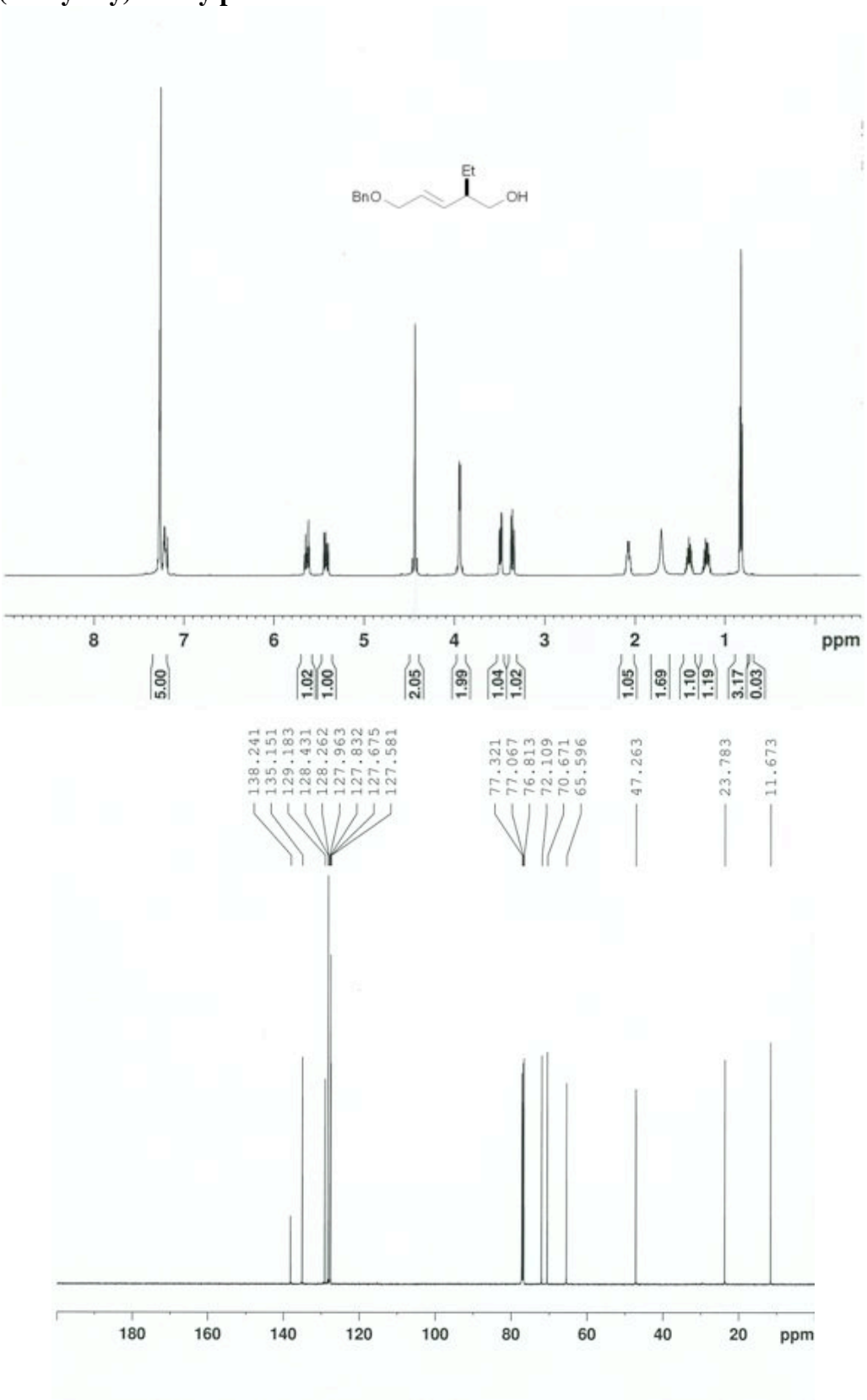

3.020
OMe
OMe
7
6
5
4
3
2
1
0
−1
−2
ppm

Unsymmetric Monophosphate: 7.1

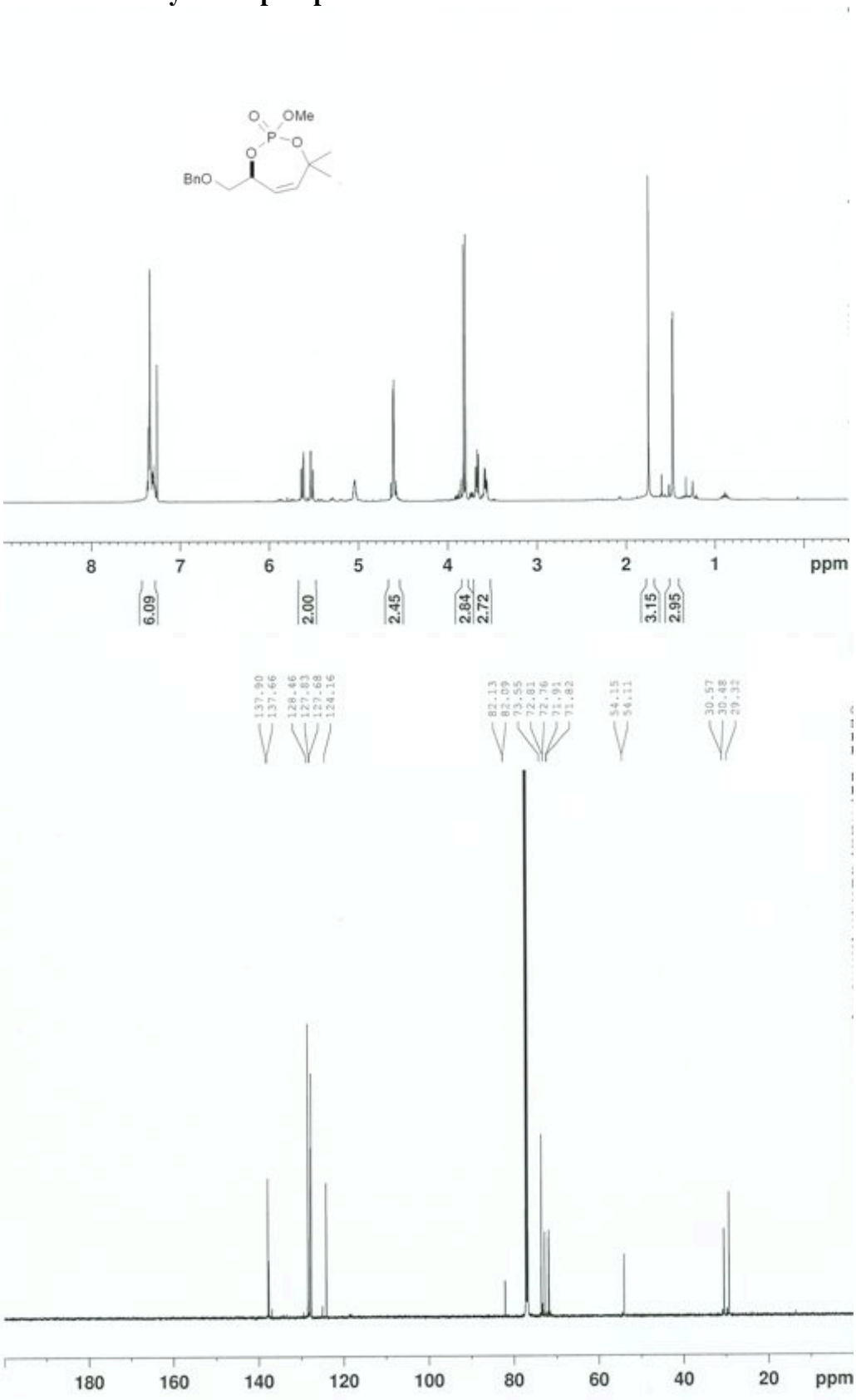


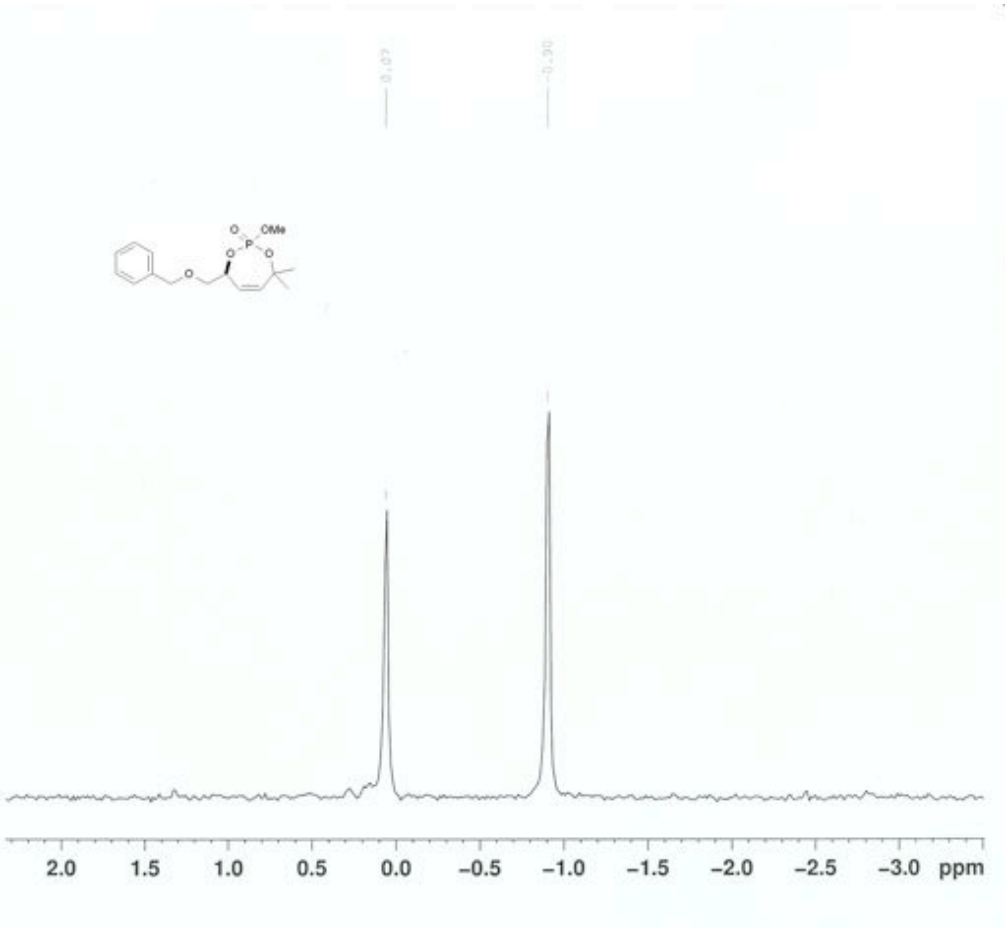

OPh
P
O
BnO
-2.87
-3.10
−2.2
−2.4
−2.6
−2.8
−3.0
−3.2
−3.4
−3.6
−3.8
ppm

(*R*,*E*)-5-(benzyloxy)-2-ethylpent-3-en-1-ol: 7.2

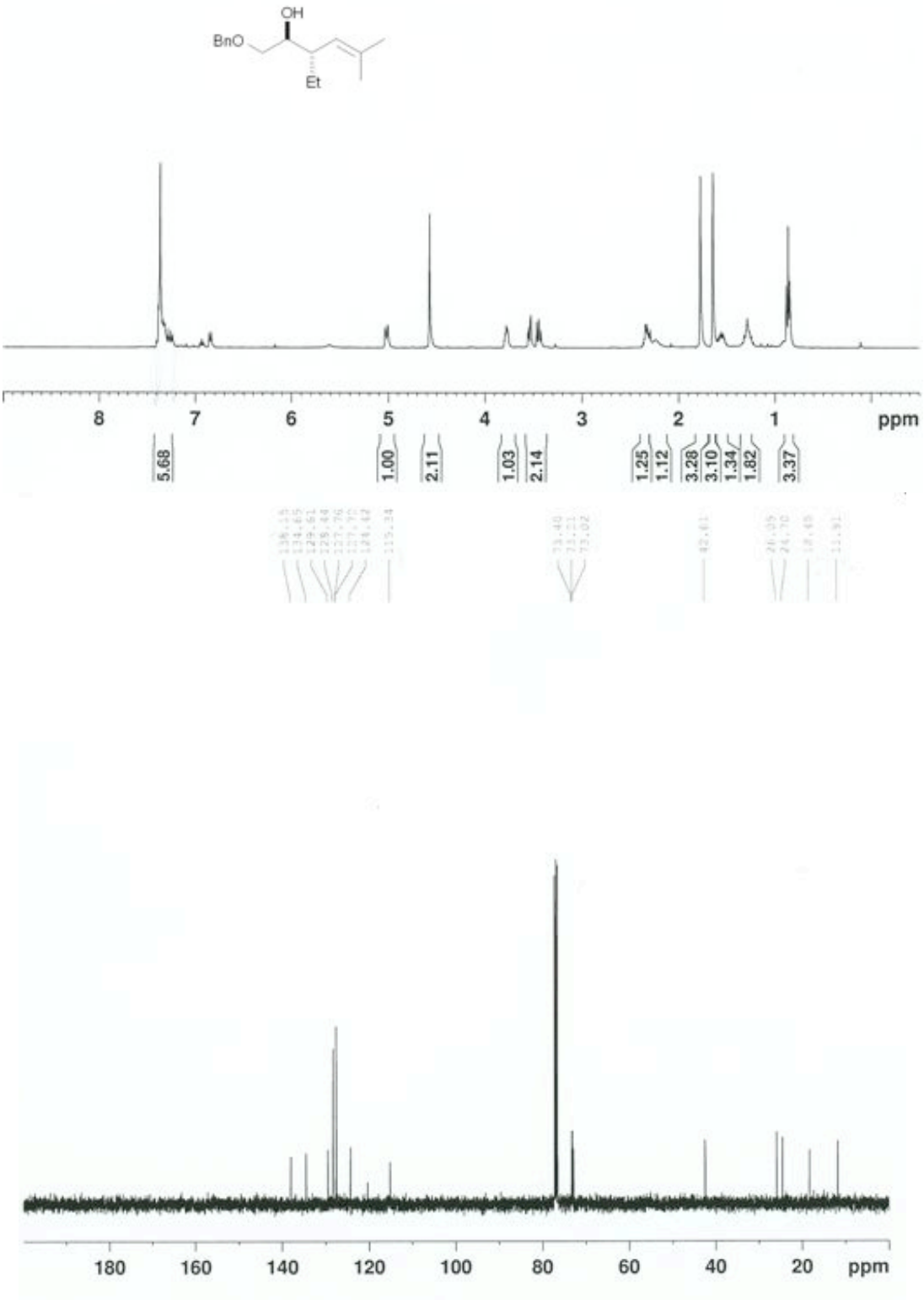


Unsymmetrical dimethyl monophosphate: 8.2

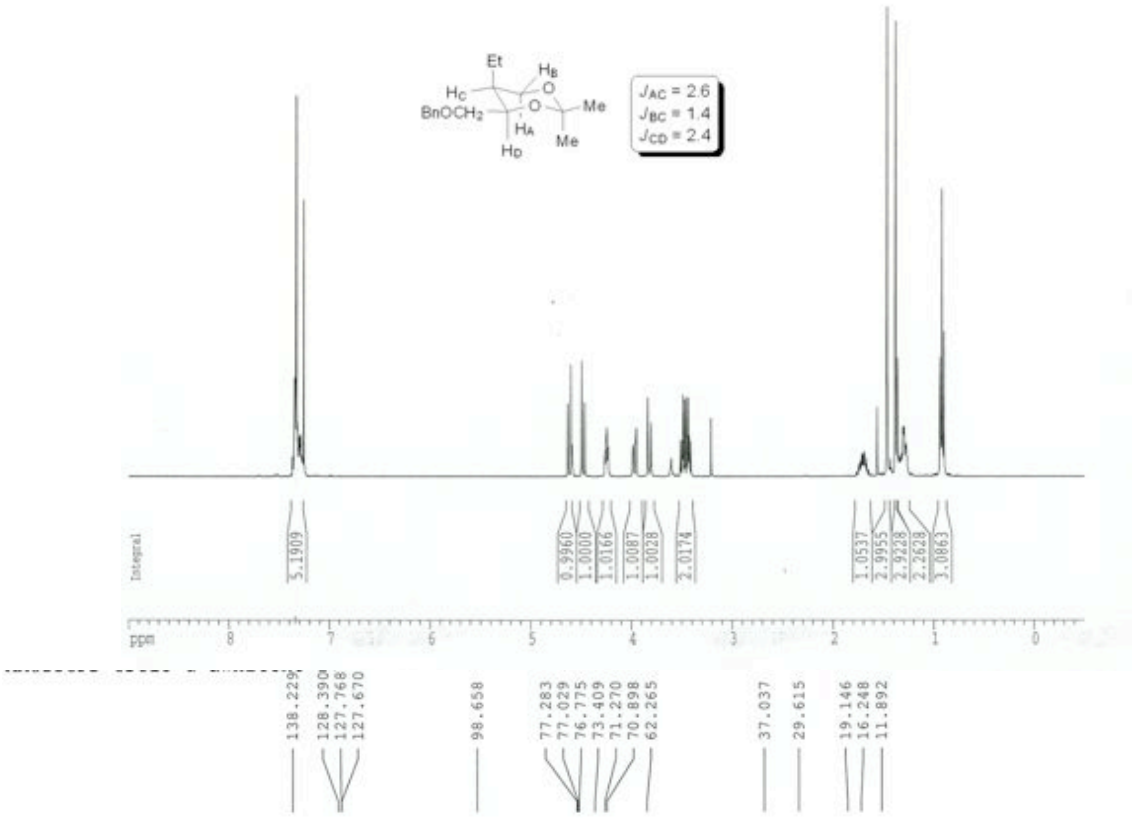


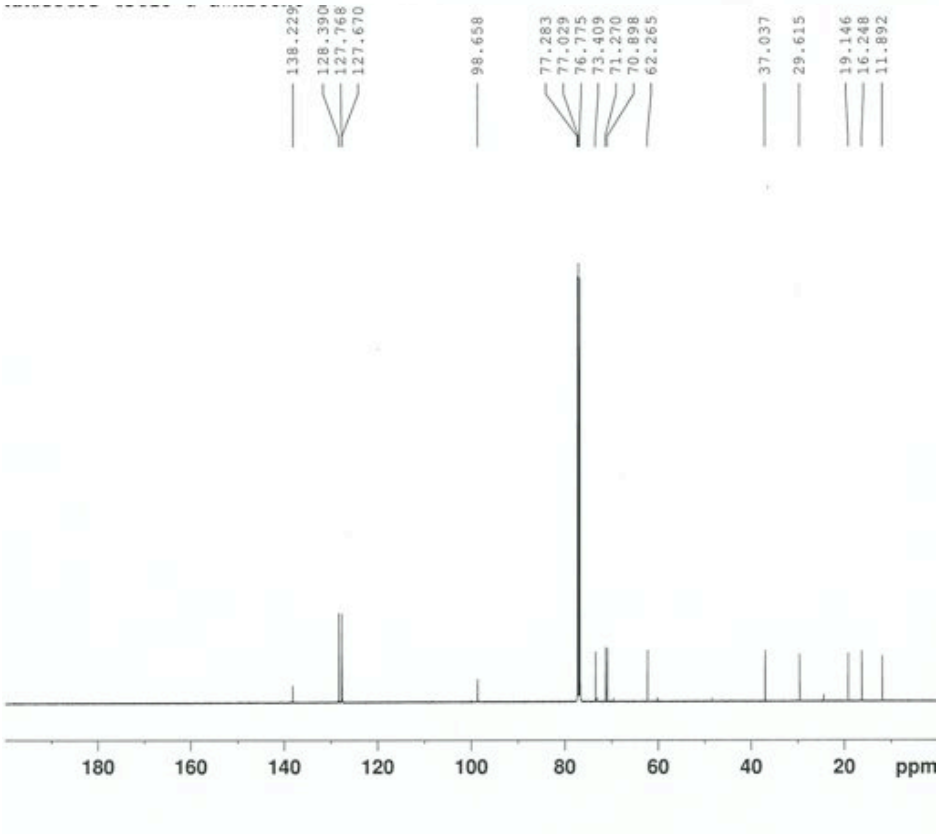

OMe
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
−3.0
ppm

***(2S,3S)*-1-(benzyloxy)-3-ethyl-5-methylhex-4-en-2-ol: 8.3**

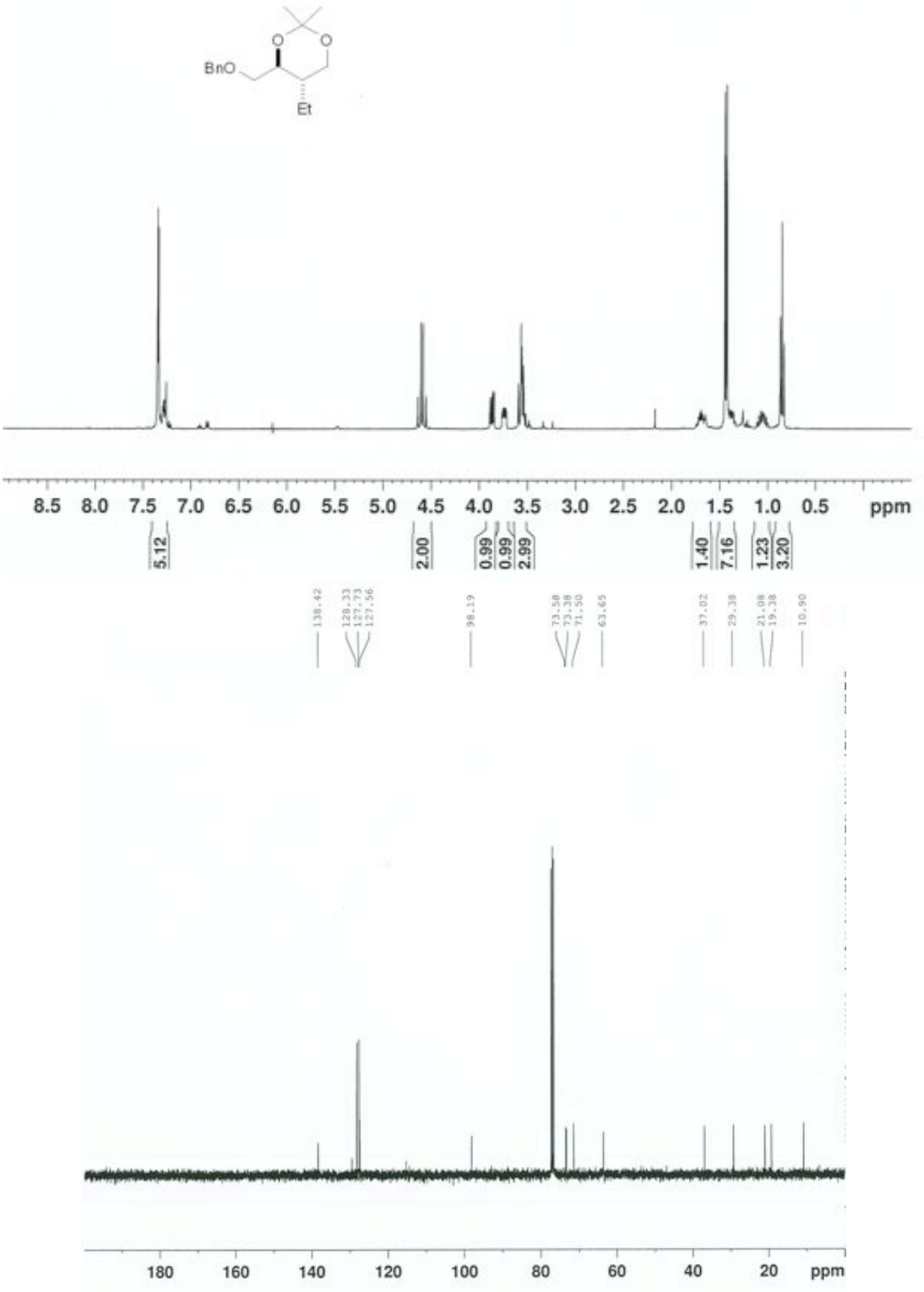


4-(benzyloxymethyl)-5-ethyl-2,2-dimethyl-1,3-dioxane



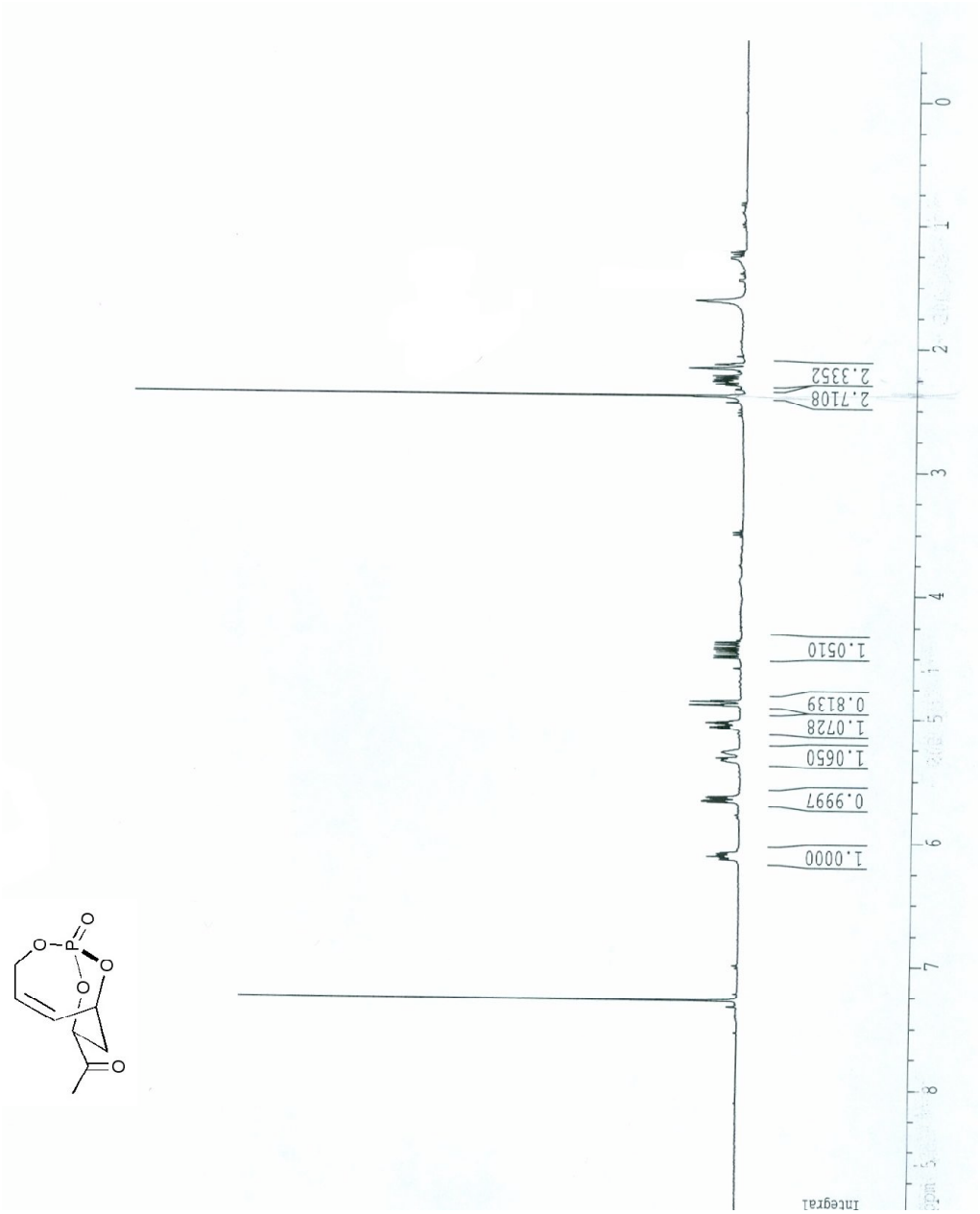


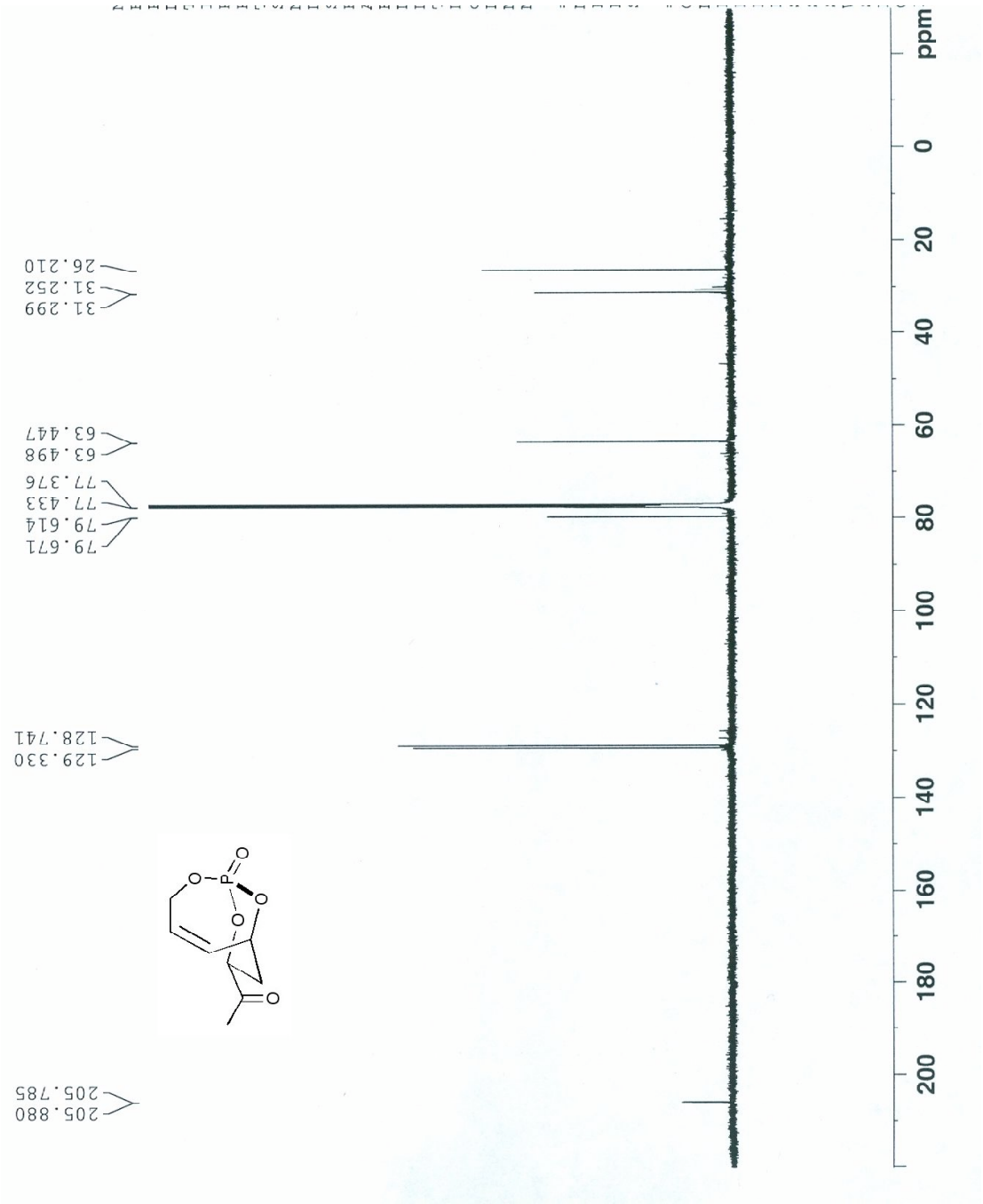
(*4S*,*5S*)-4-(benzyloxymethyl)-5-ethyl-2,2-dimethyl-1,3-dioxane

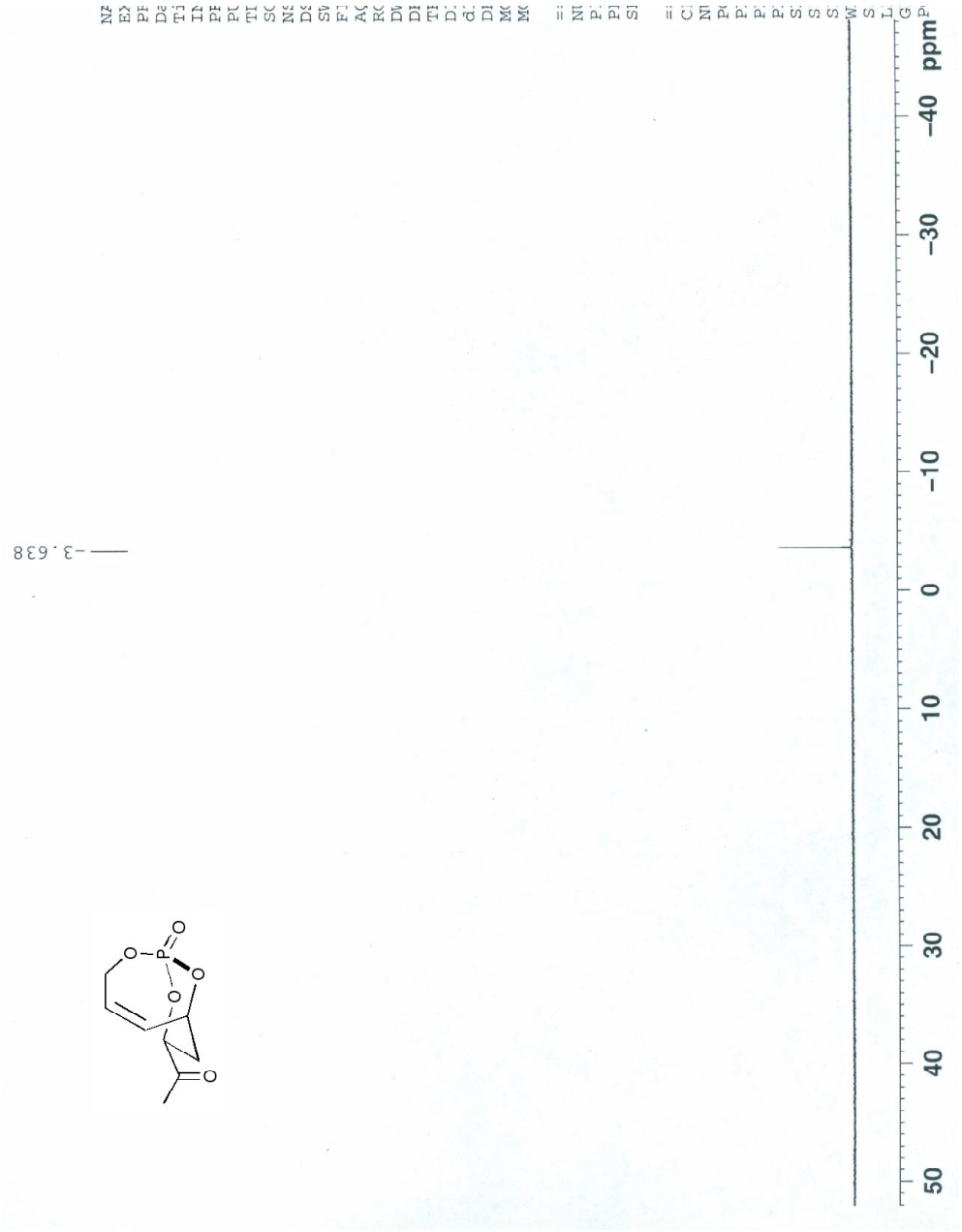


A.2 : Chapter 3 Spectra

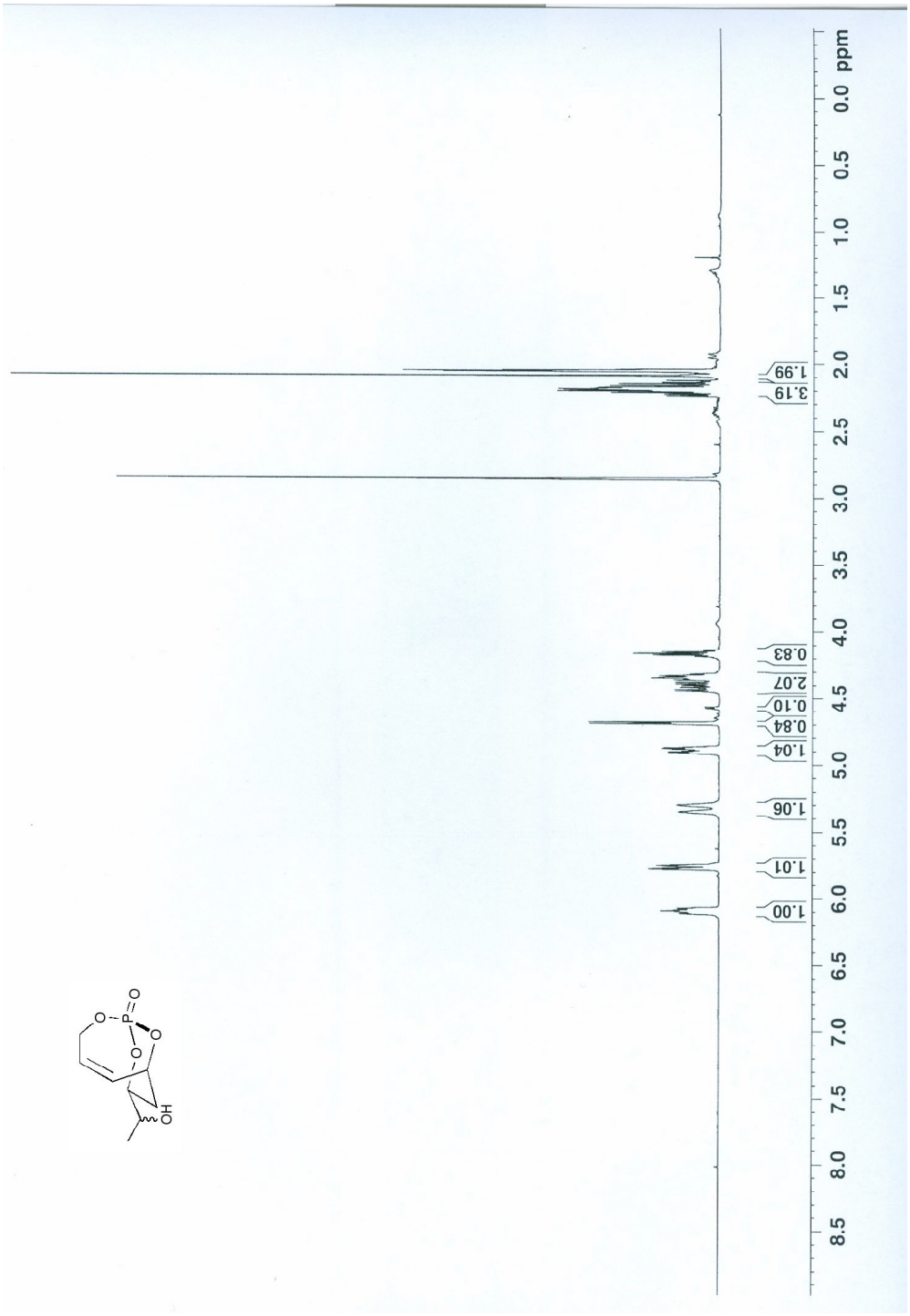
1-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)ethanone: 4.1



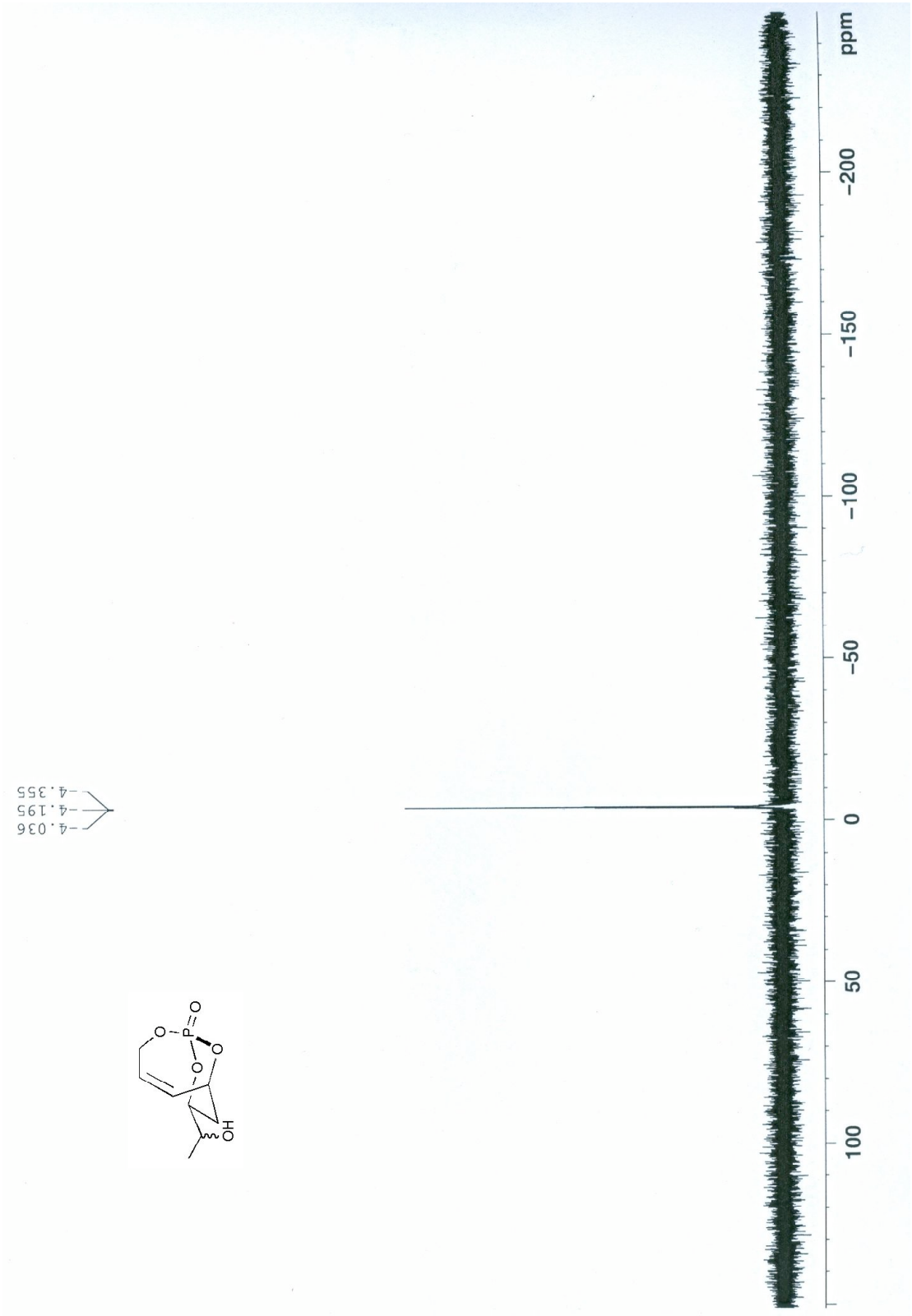

205.880
205.785
128.741
129.330
79.671
79.614
77.433
77.376
63.498
63.447
31.299
31.252
26.210
ppm
0
20
40
60
80
100
120
140
160
180
200


-3.638
50
40
30
20
10
0
-10
-20
-30
-40
ppm

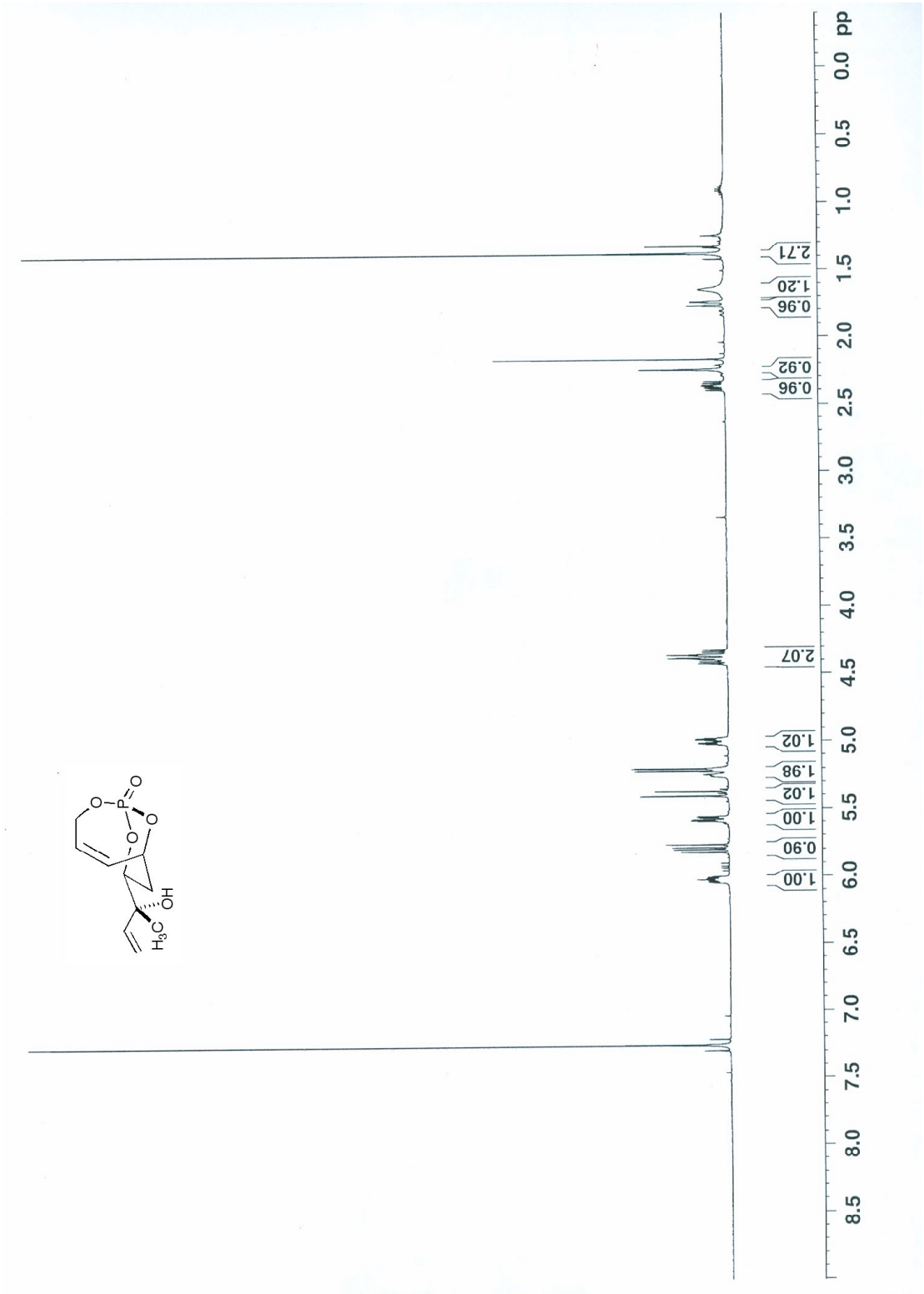
1-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)ethanol: 8.1

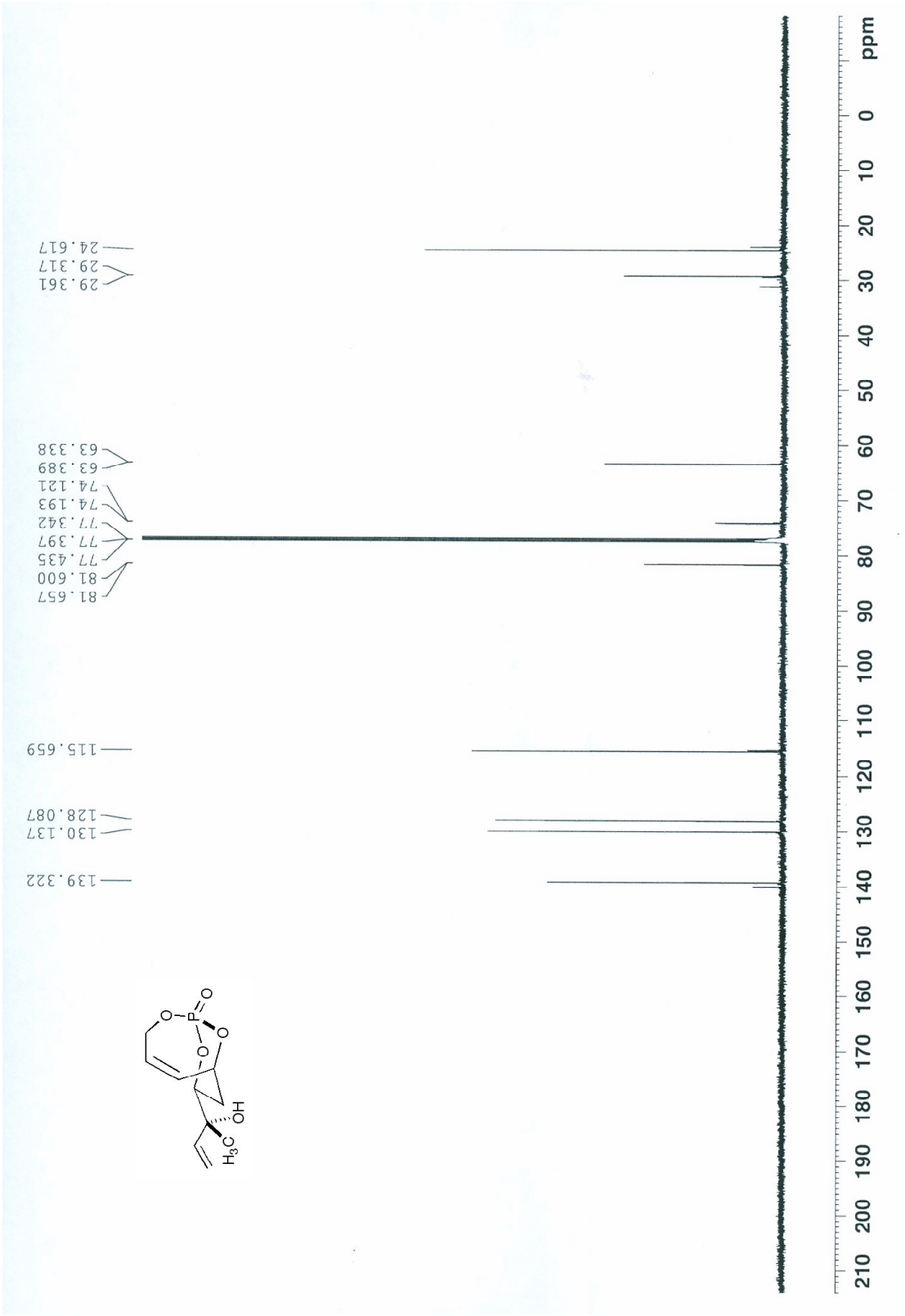


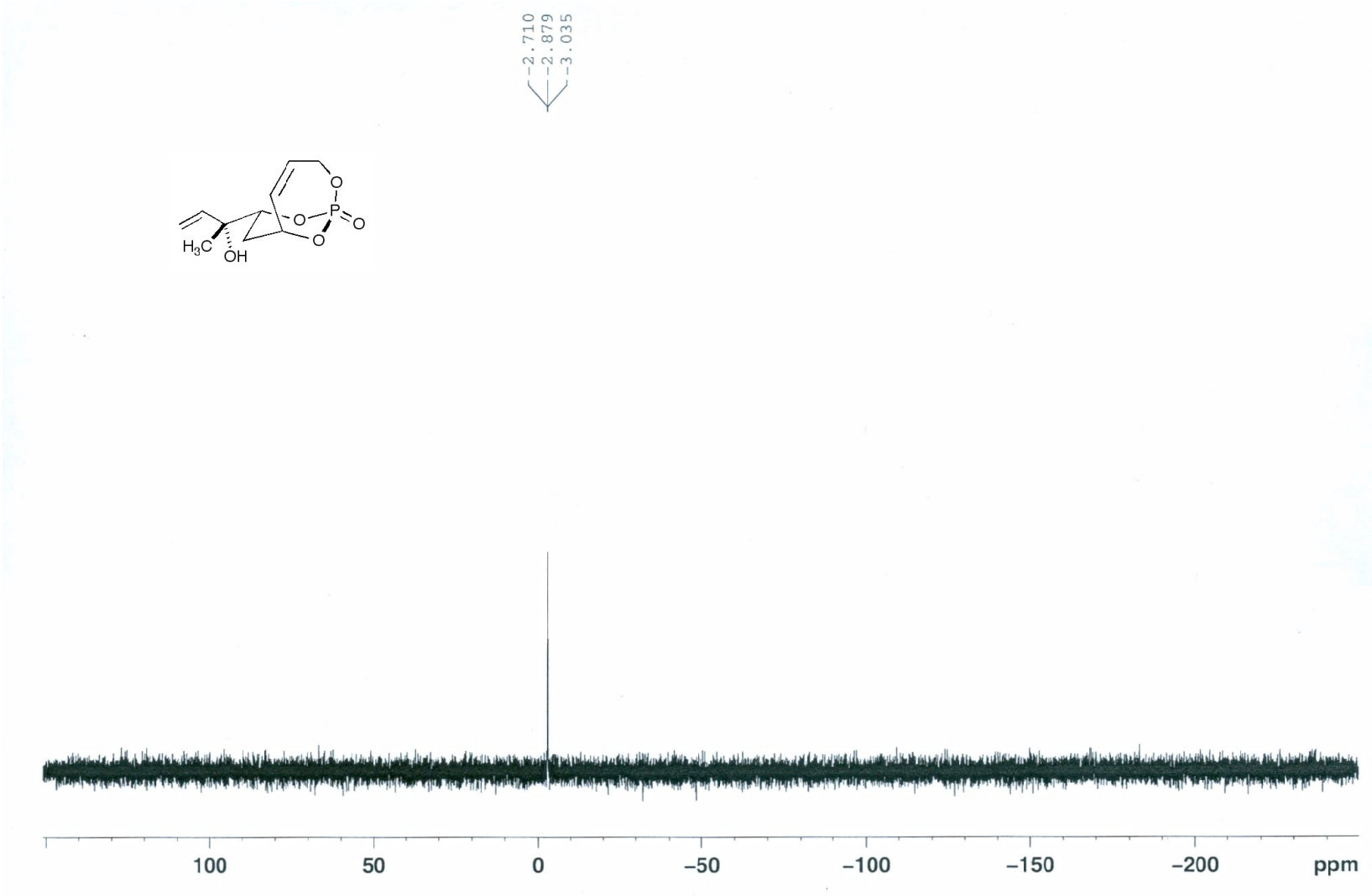
34.877
31.657
31.610
63.601
63.651
72.439
72.521
78.591
78.644
82.006
82.060
131.206
128.331
ppm


-4.036
-4.195
-4.355
ppm
100
50
0
-50
-100
-150
-200

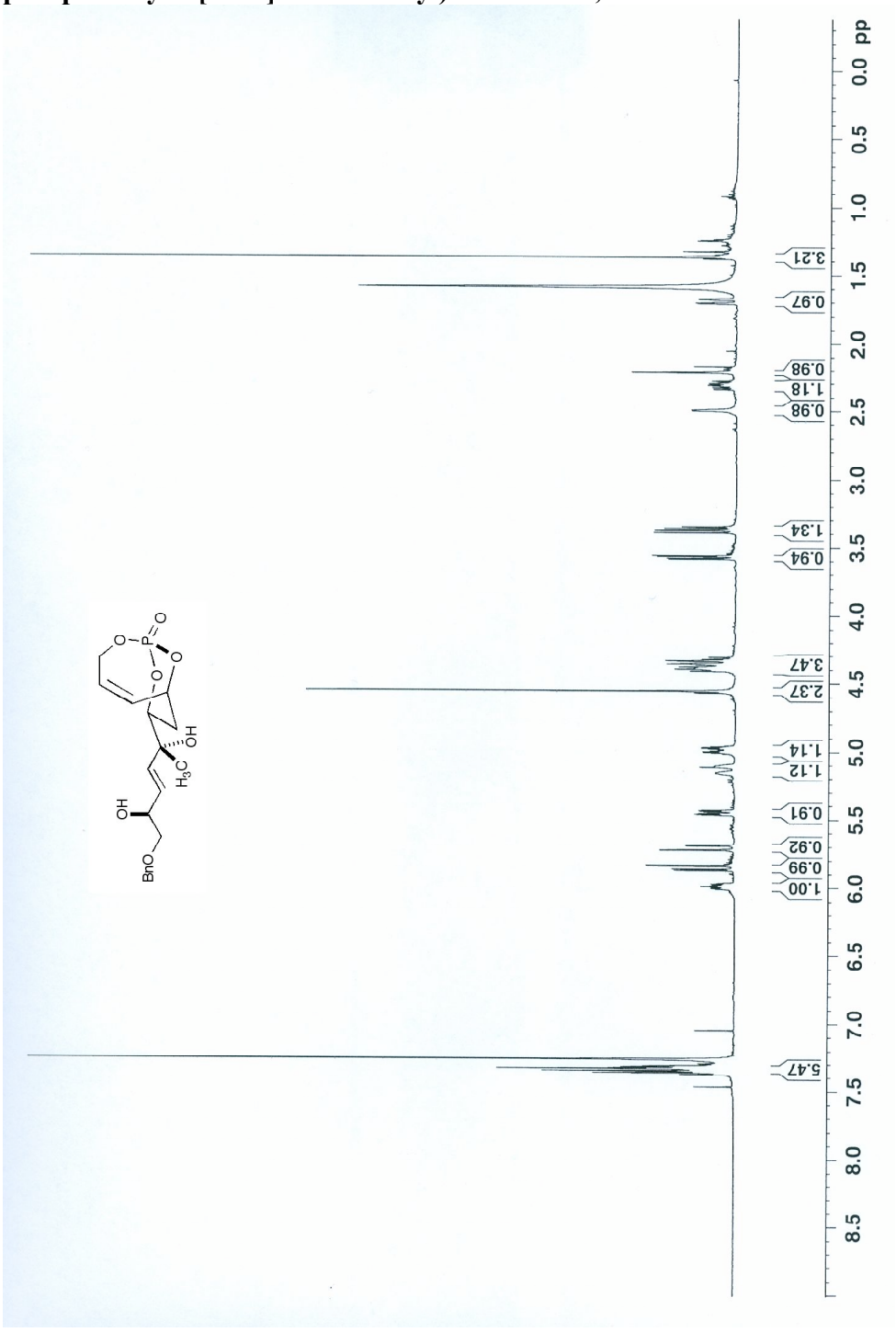
(*R*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)but-3-en-2-ol: 11.1



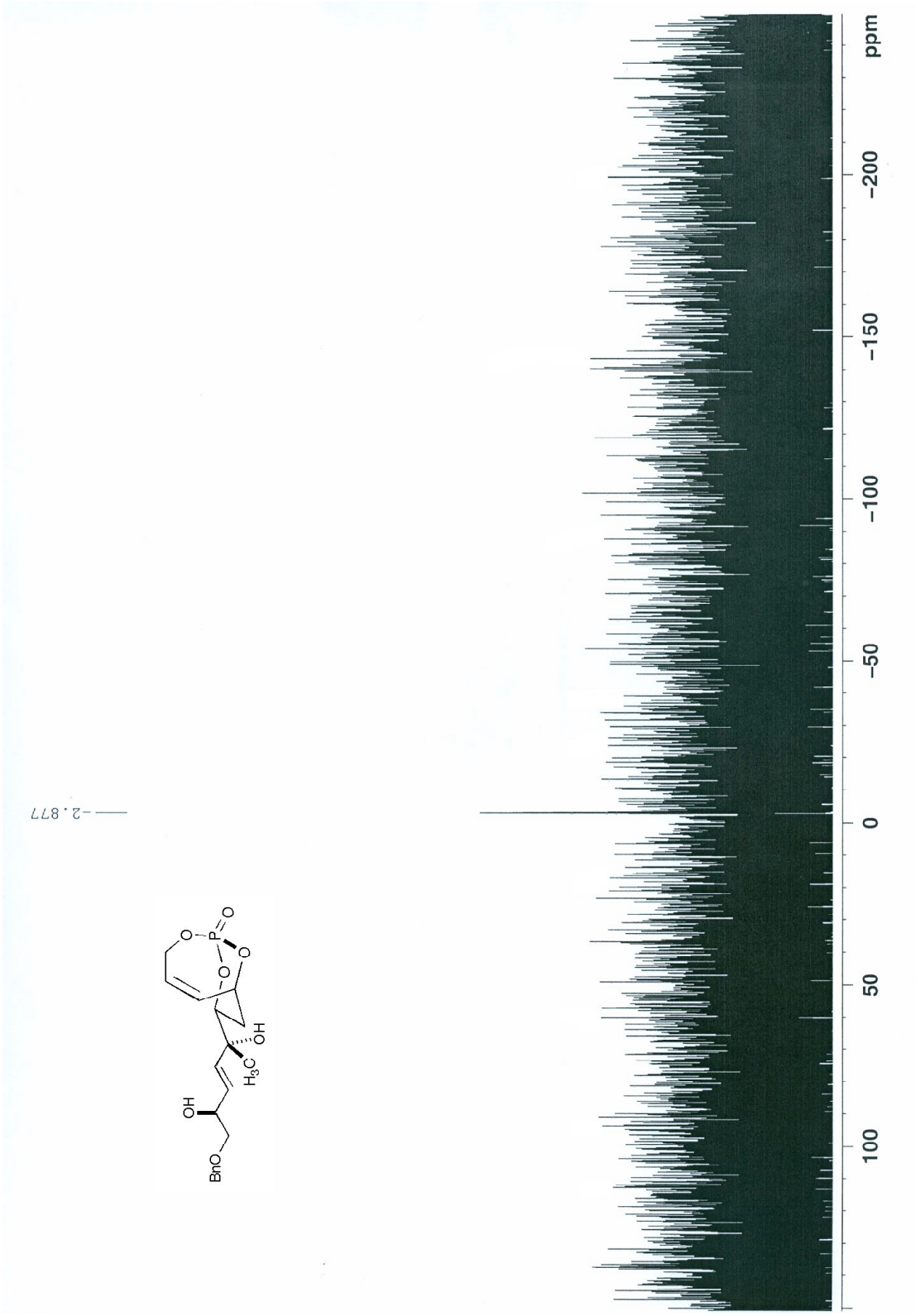

24.617
29.317
29.361
63.338
63.389
74.121
74.193
77.342
77.397
77.435
81.600
81.657
115.659
128.087
130.137
139.322
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


-2.710
-2.879
-3.035
O
O
P
O
O
H3C
OH
100
50
0
−50
−100
−150
−200
ppm

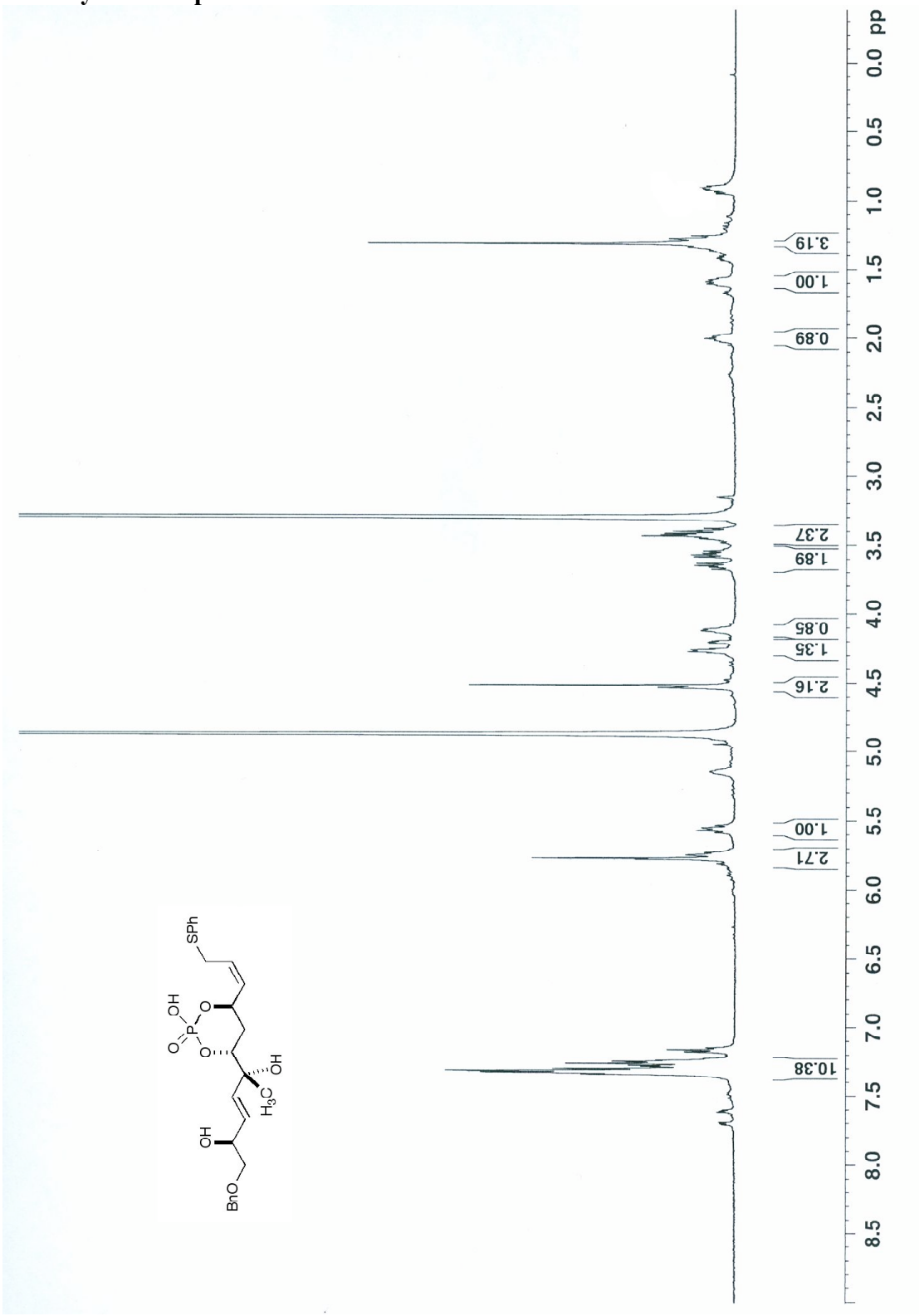
(2*S*,5*R*,*E*)-1-(benzyloxy)-5-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)hex-3-ene-2,5-diol: 14.2

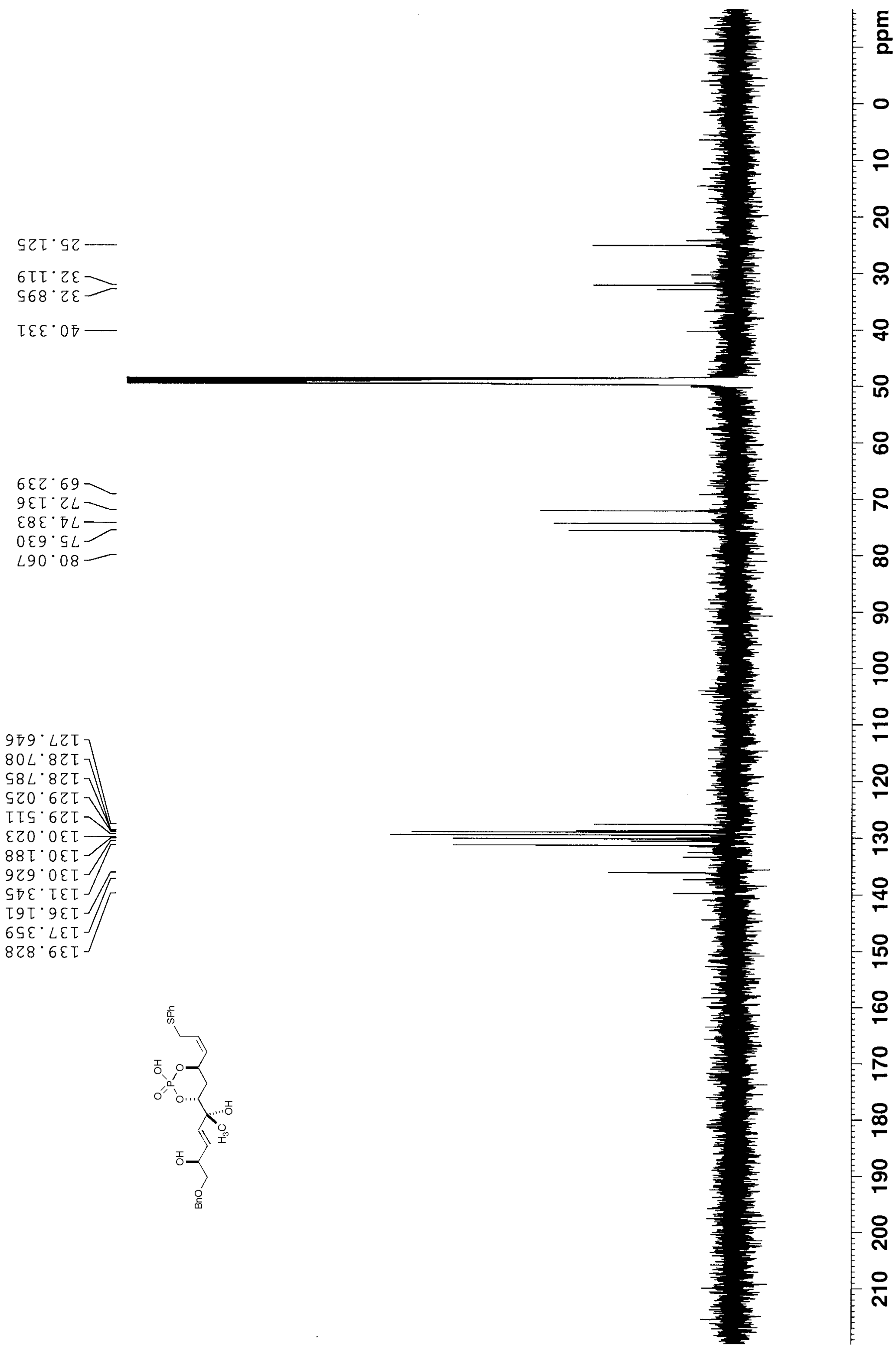


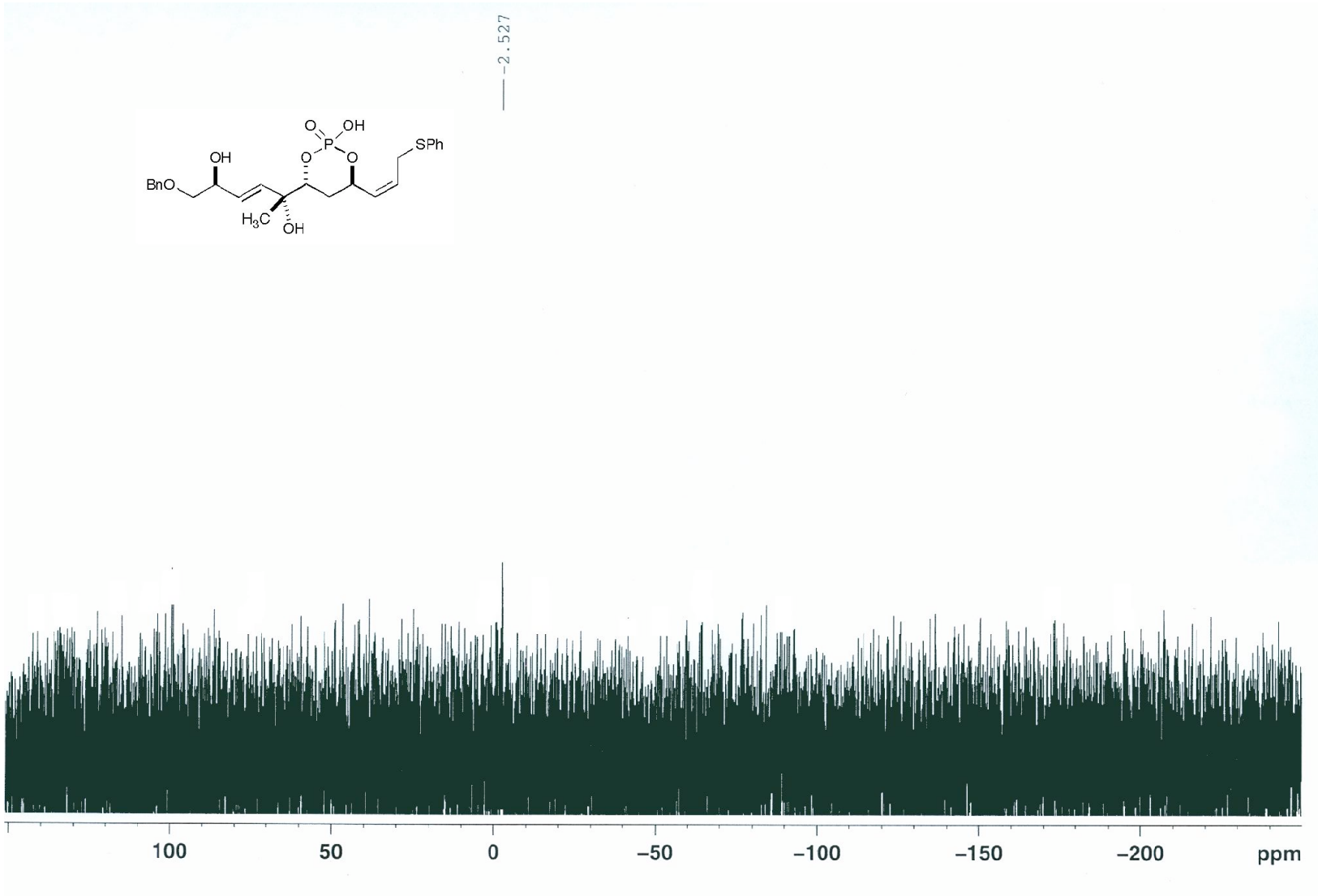
137.911
132.489
130.202
129.521
128.740
128.188
128.141
128.072
127.938
81.521
81.463
77.433
77.397
77.344
74.181
73.836
73.763
73.678
70.737
63.380
63.330
29.302
29.259
25.243
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
BnO
OH
OH
H3C


-2.877
ppm
100
50
0
-50
-100
-150
-200
OH
BnO
OH
H3C
O
O
O
O
P
O

Monocyclic Phosphate Acid 14.3

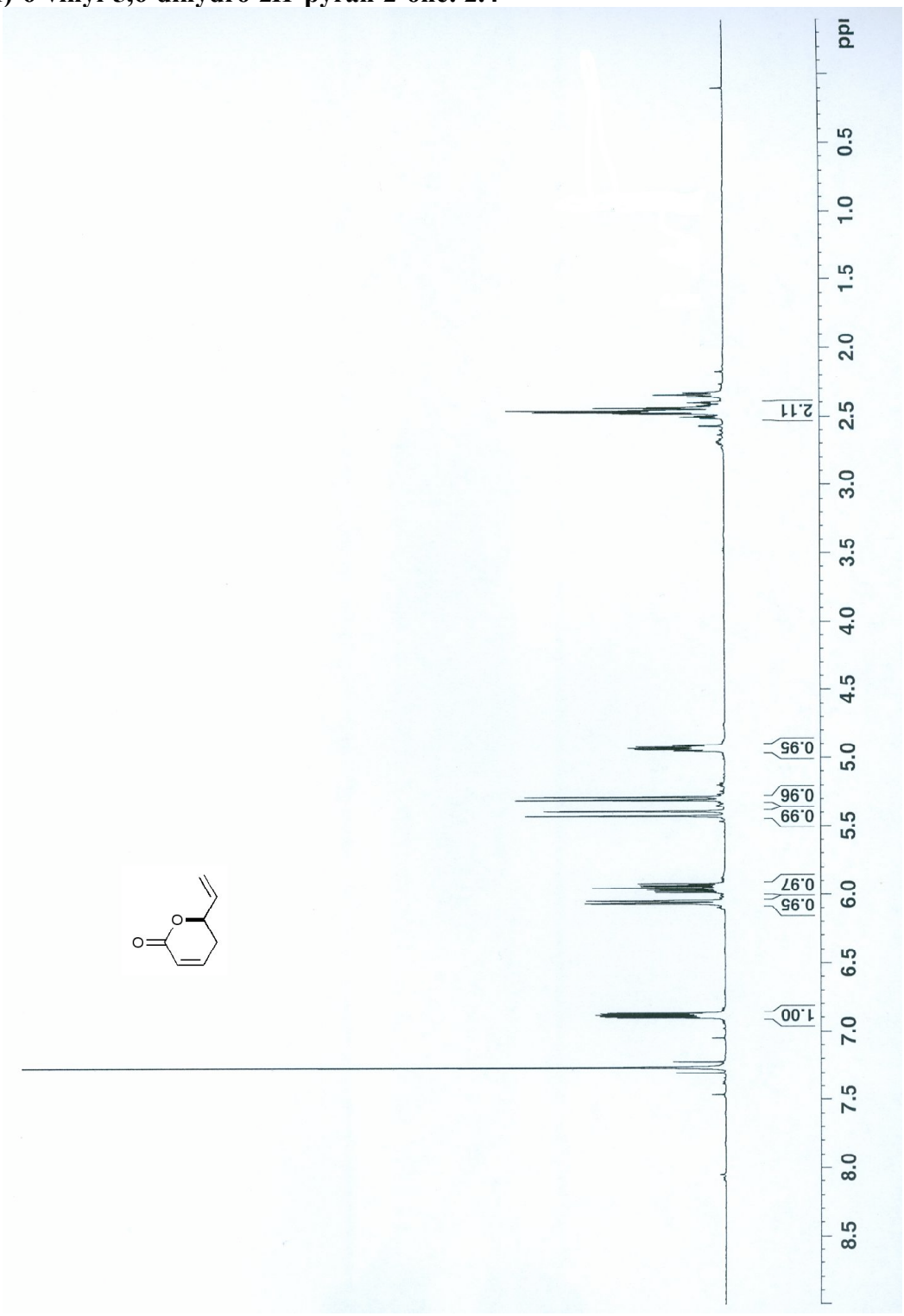


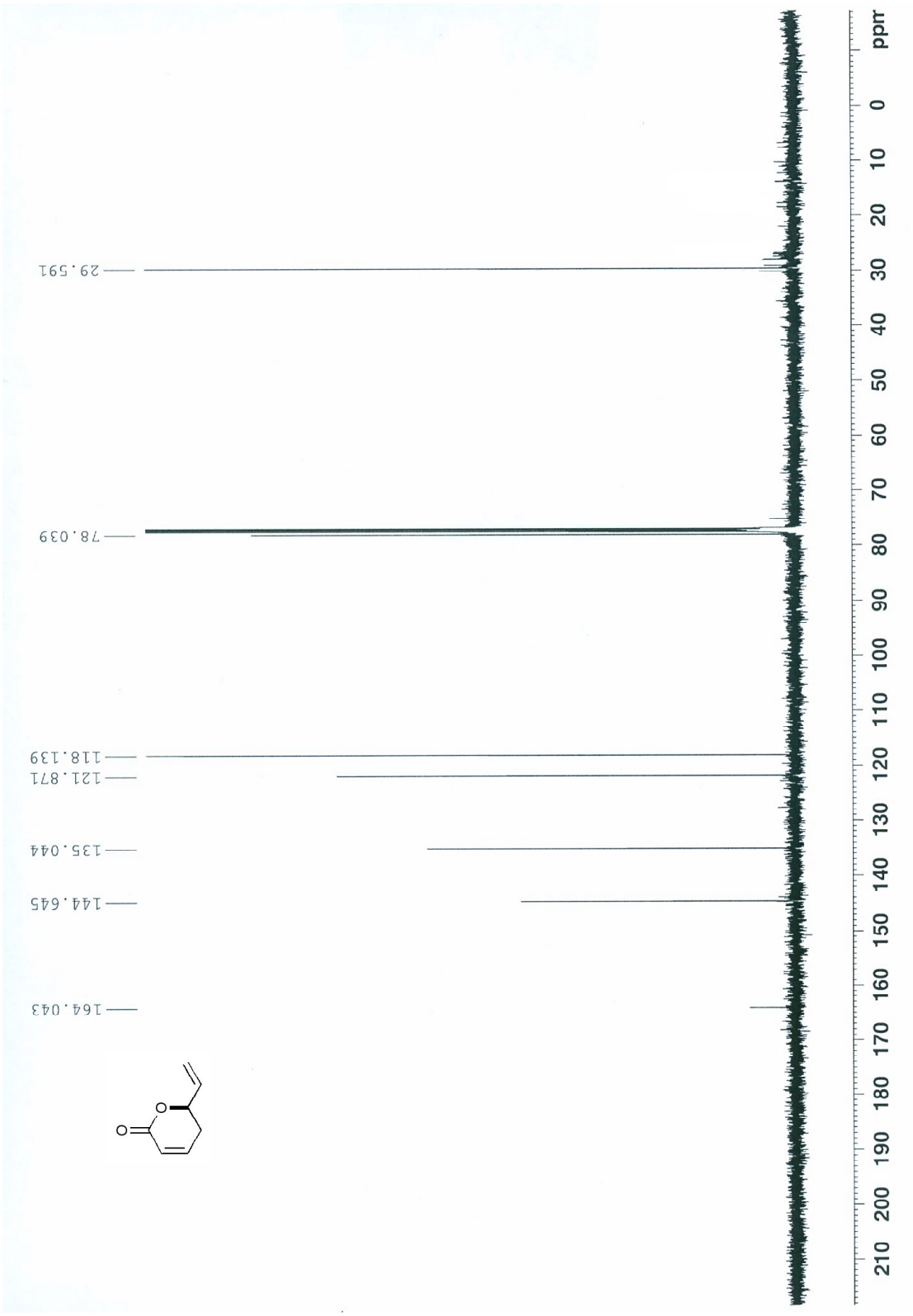

25.125
32.119
32.895
40.331
69.239
72.136
74.383
75.630
80.067
127.646
128.708
128.785
129.025
129.511
130.023
130.188
130.626
131.345
136.161
137.359
139.828
BnO
OH
H3C
OH
O
P
OH
SPh
ppm


-2.527
OH
O
P
OH
O
O
SPh
OH
BnO
H3C
OH
100
50
0
−50
−100
−150
−200
ppm

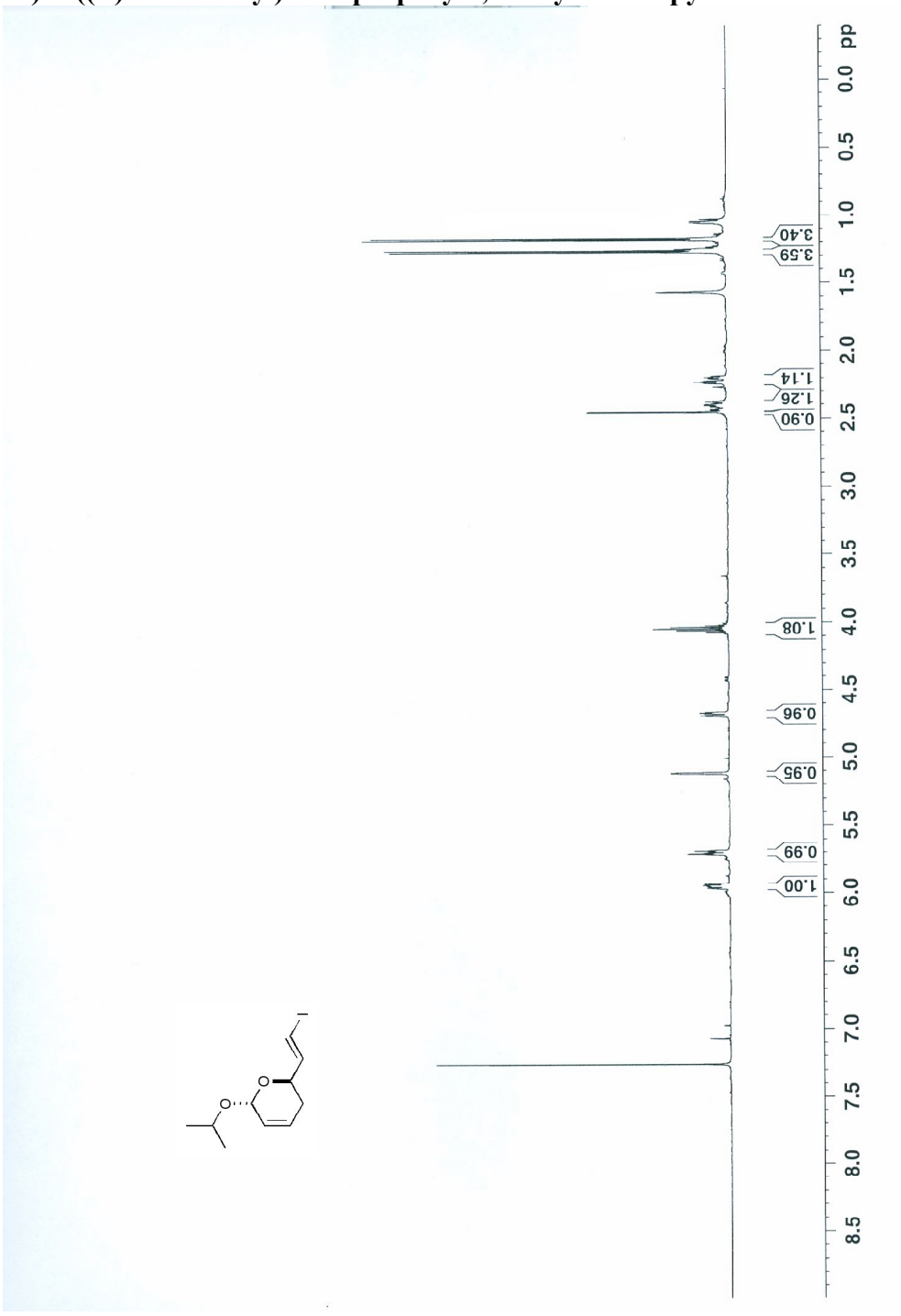
A.3: Chapter 4 Spectra

(*R*)-6-vinyl-5,6-dihydro-2*H*-pyran-2-one: 2.4



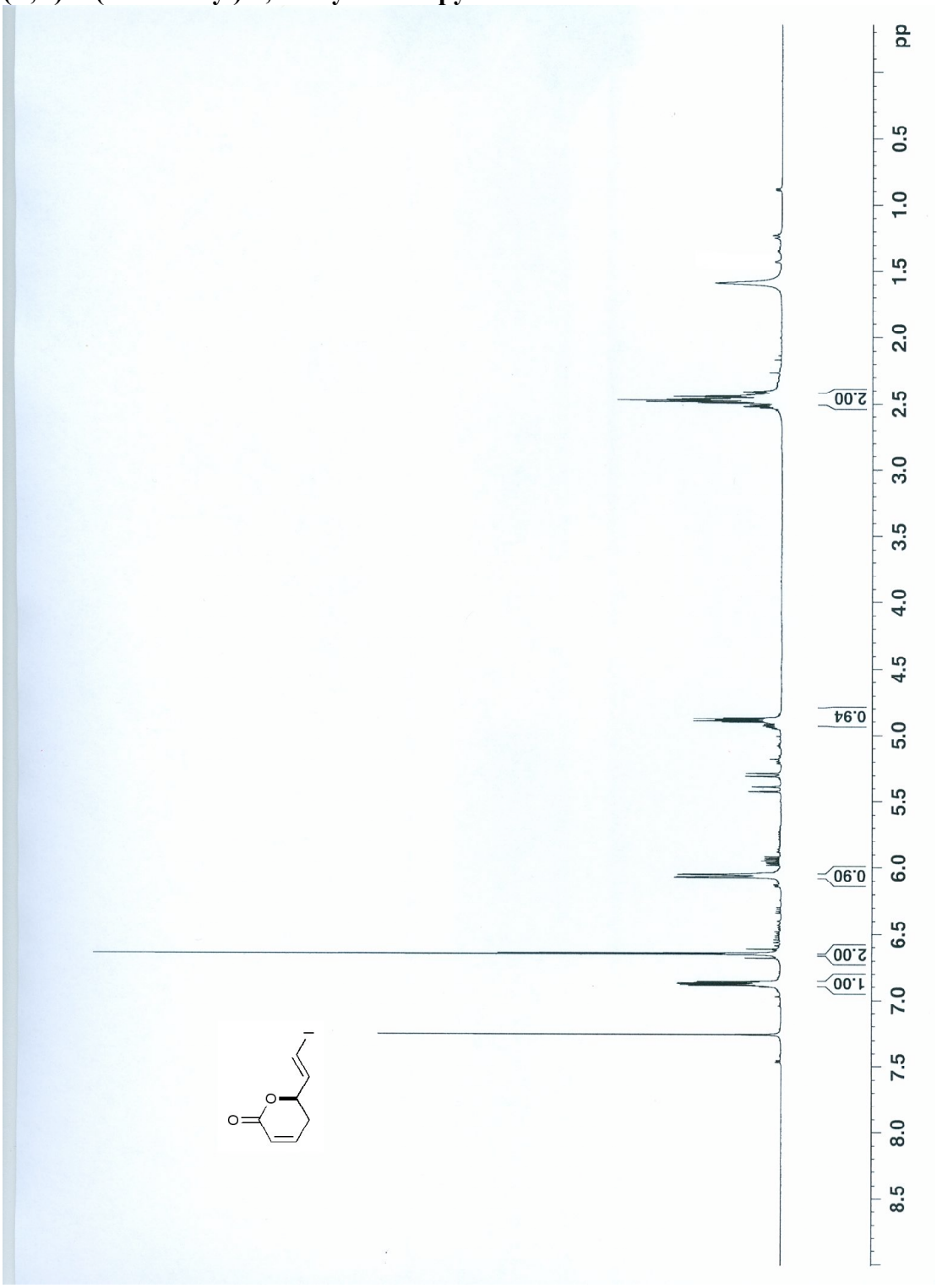

29.591
78.039
118.139
121.871
135.044
144.645
164.043
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

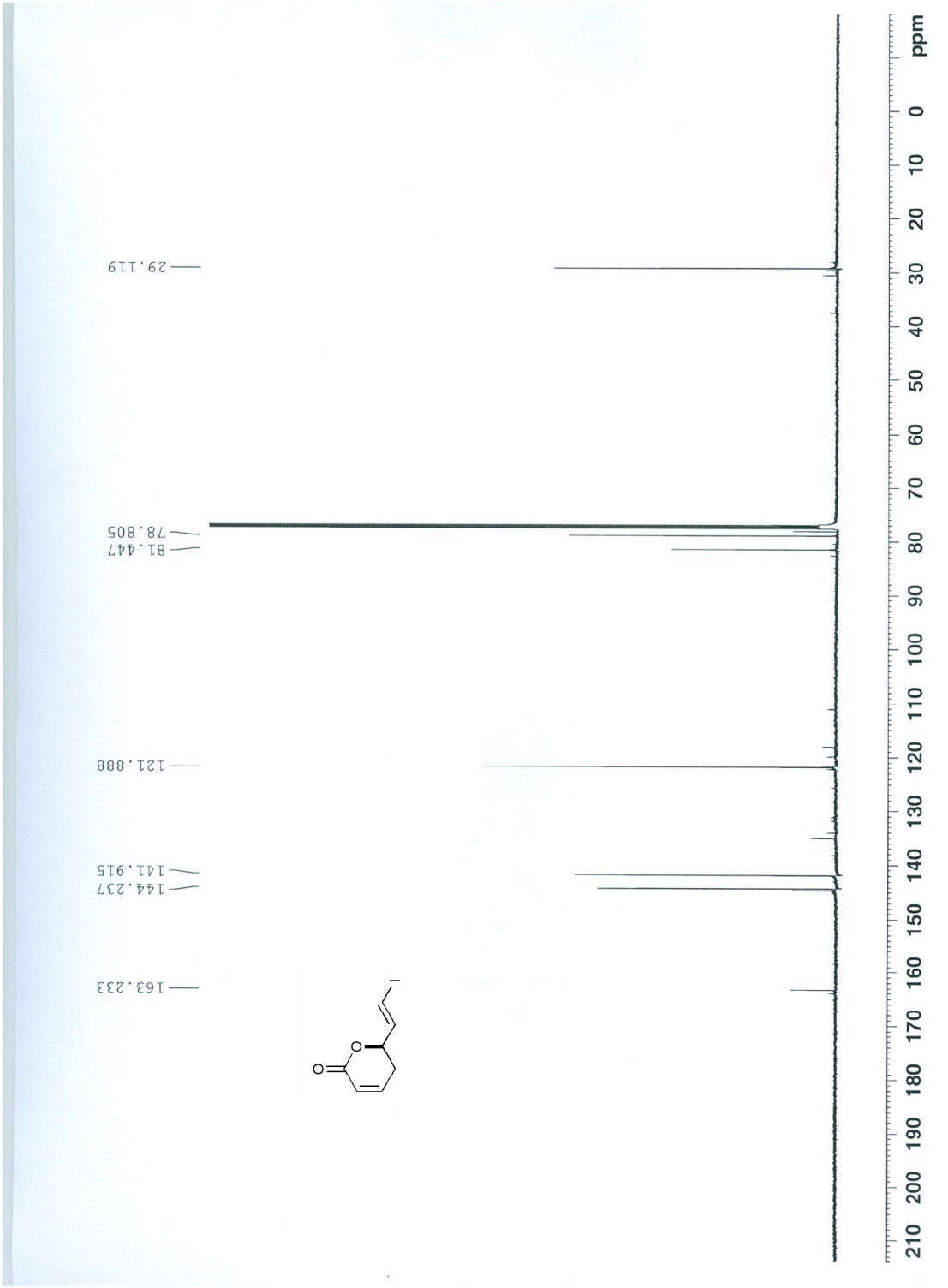
(2*R*,6*R*)-2-((*E*)-2-iodovinyl)-6-isopropoxy-3,6-dihydro-2*H*-pyran: 3.1



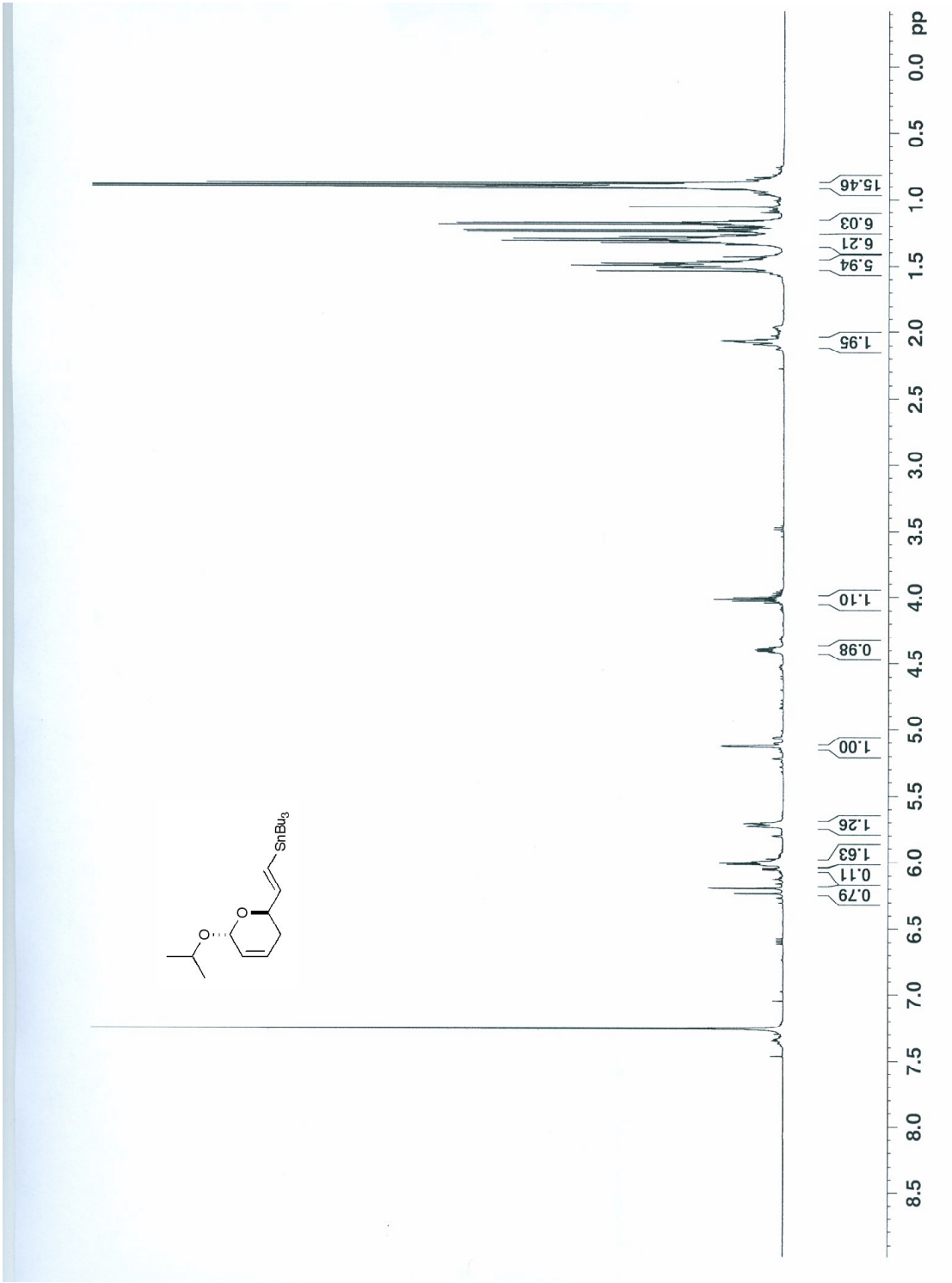
127.796
126.142
93.129
82.974
72.877
70.145
57.148
31.449
24.013
22.150
ppm

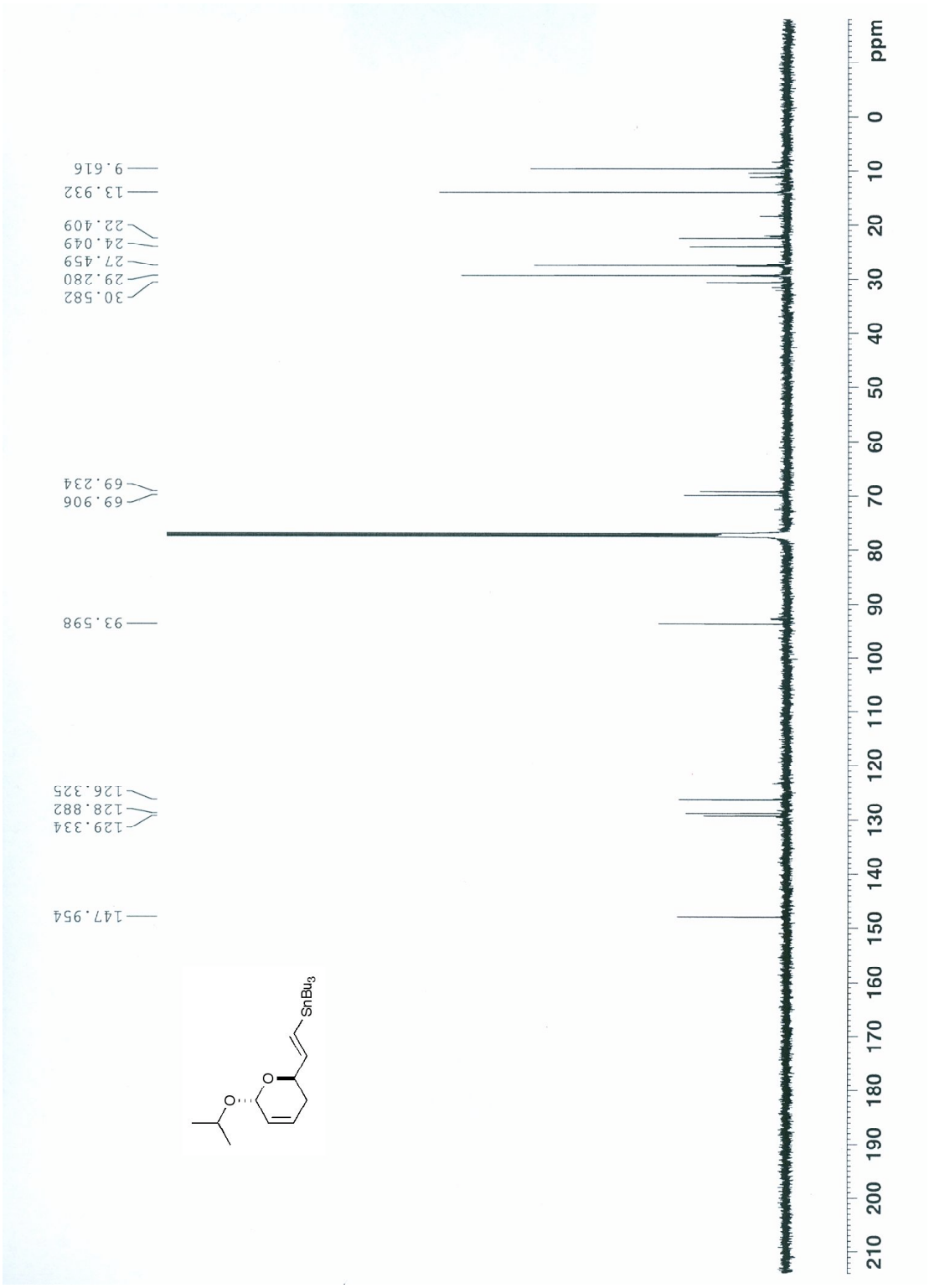
(*R*,*E*)-6-(2-iodovinyl)-5,6-dihydro-2*H*-pyran-2-one: 5.2



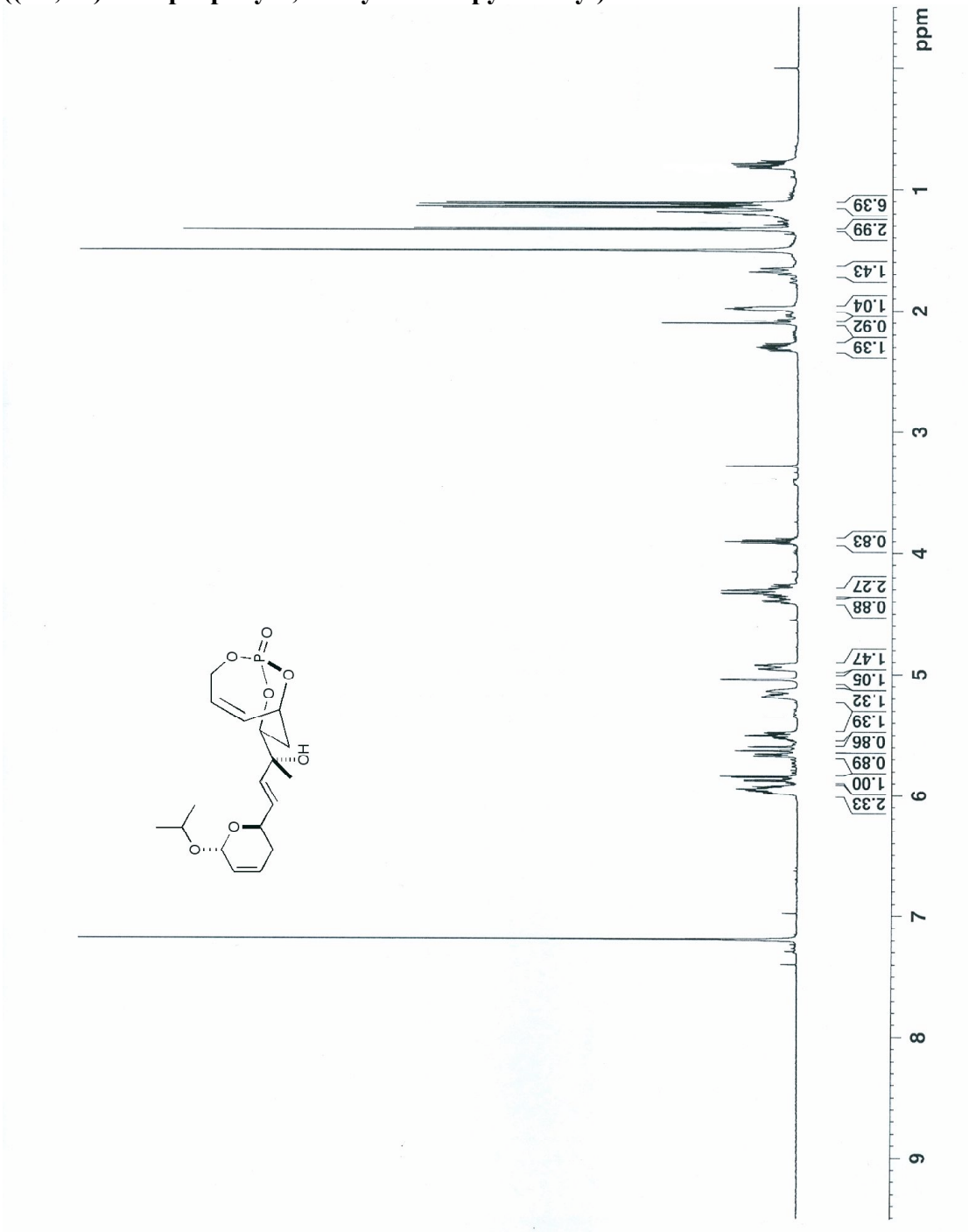

163.233
144.237
141.915
121.888
81.447
78.805
29.119
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

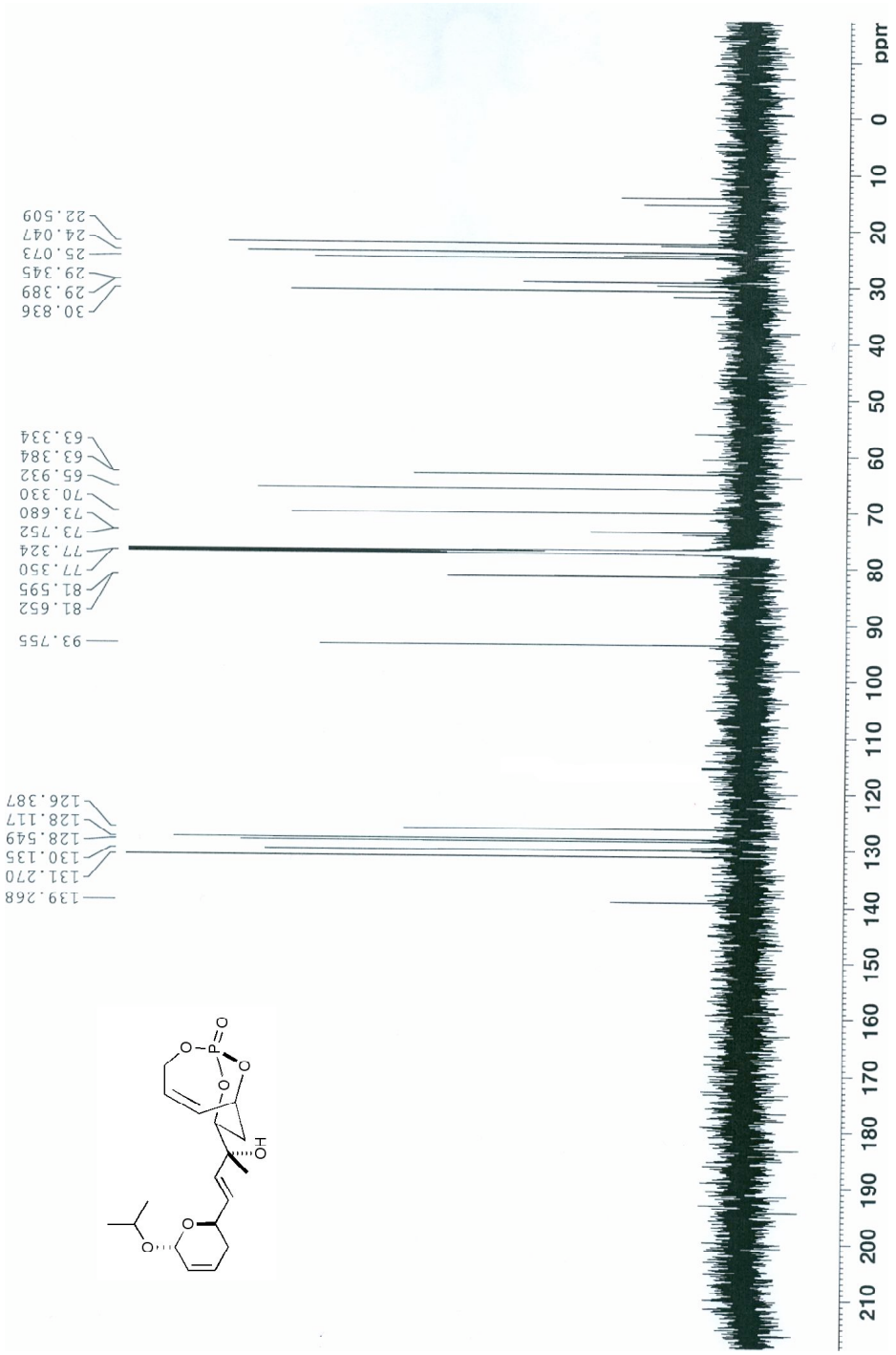
tributyl((*E*)-2-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)vinyl)stannane: 11.1

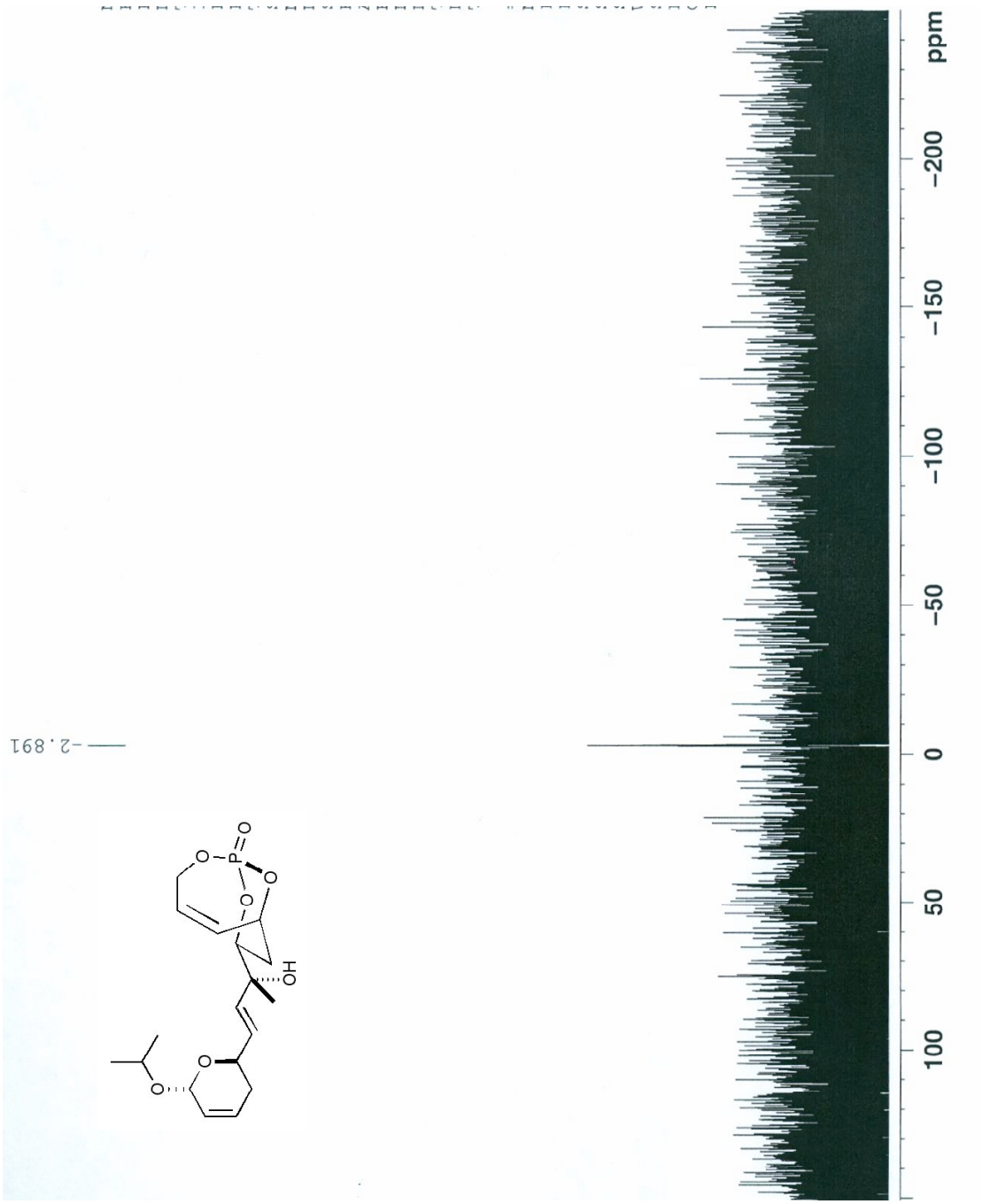



147.954
129.334
128.882
126.325
93.598
69.906
69.234
30.582
29.280
27.459
24.049
22.409
13.932
9.616
SnBu3
O
O
O
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

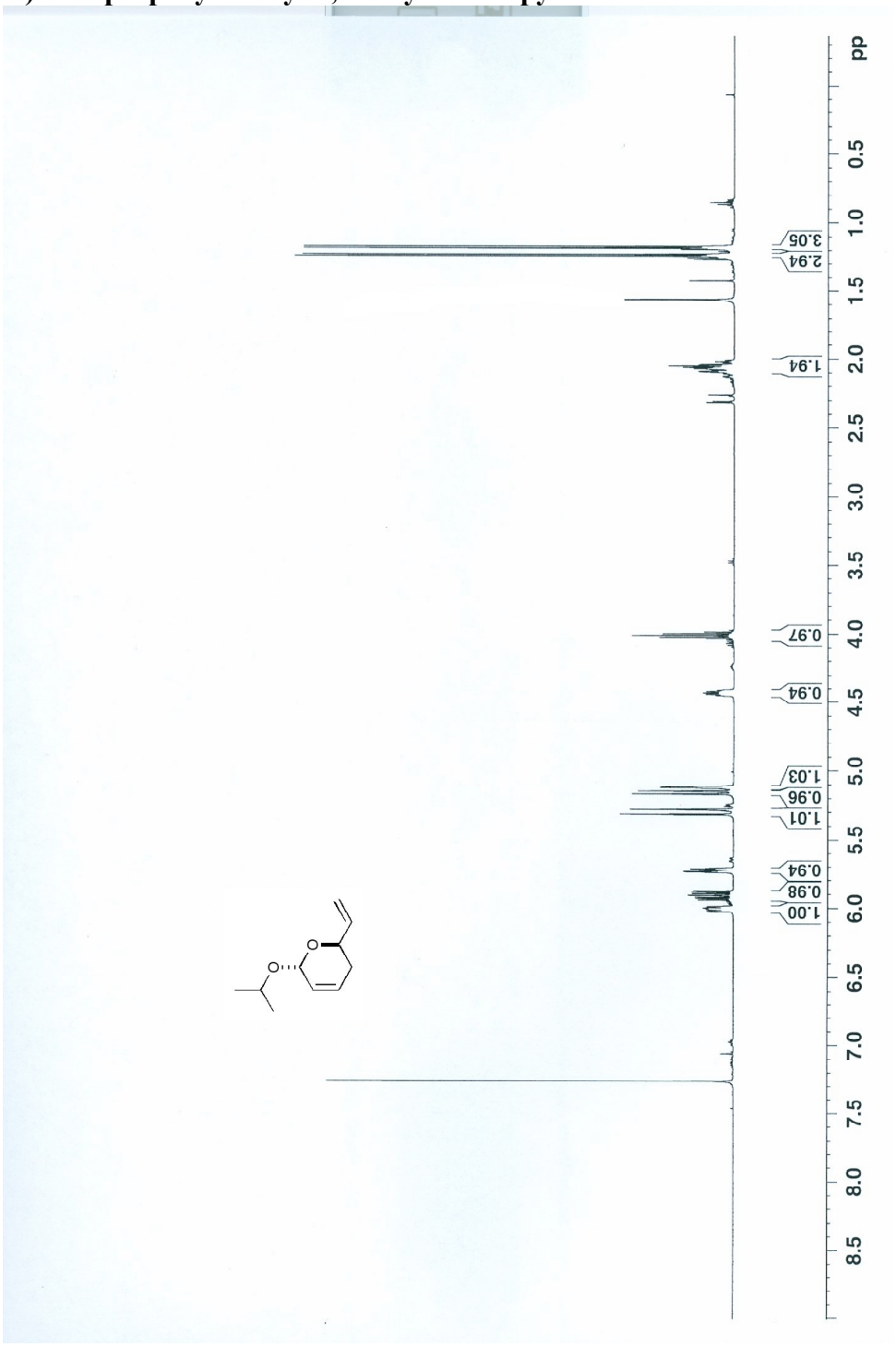
(*R*,*E*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)-4-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)but-3-en-2-ol: 12.1




139.268
131.270
130.135
128.549
128.117
126.387
93.755
81.652
81.595
77.350
77.324
73.752
73.680
70.330
65.932
63.384
63.334
30.836
29.389
29.345
25.073
24.047
22.509
ppm

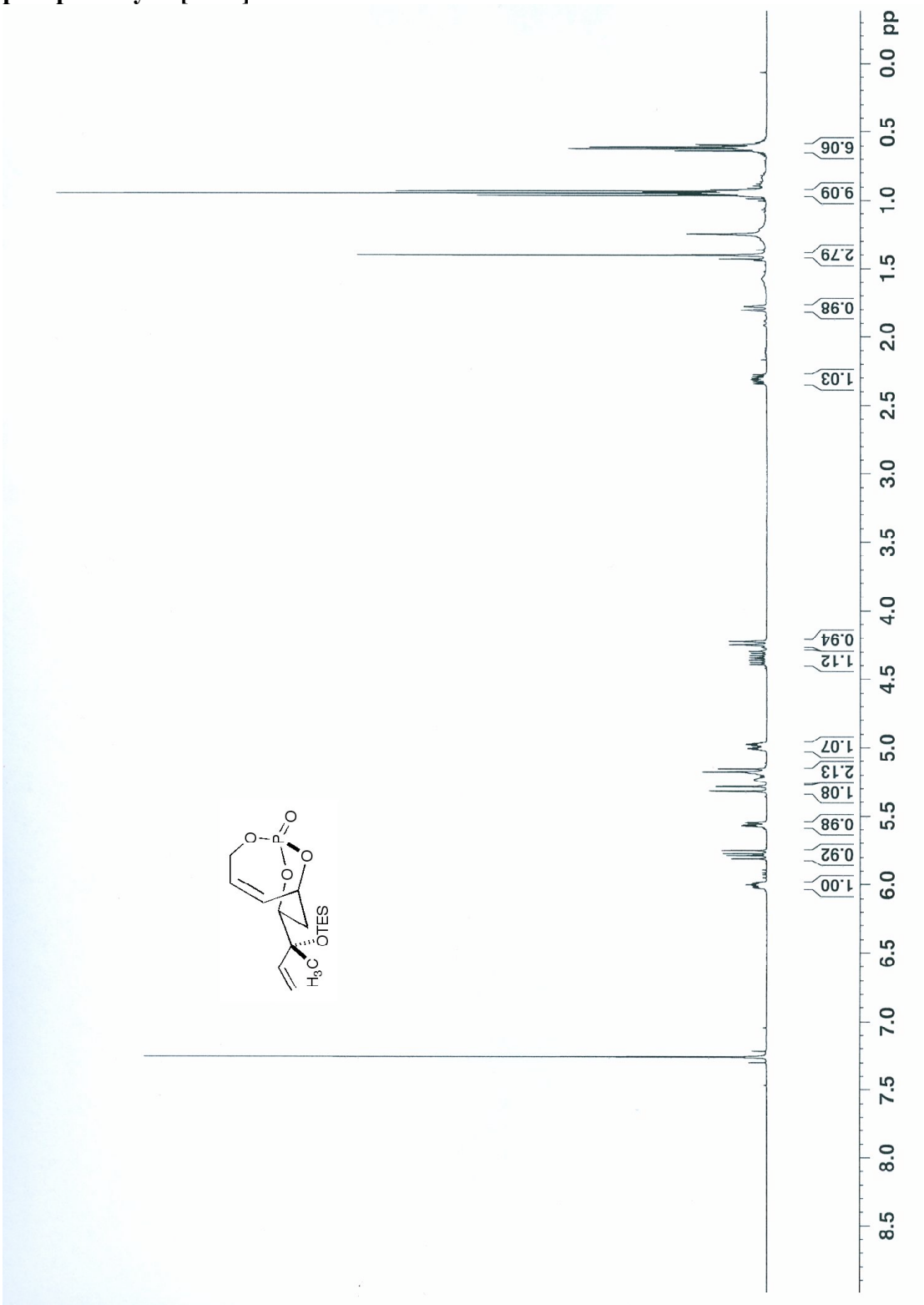

-2.891
ppm
100
50
0
-50
-100
-150
-200
OH

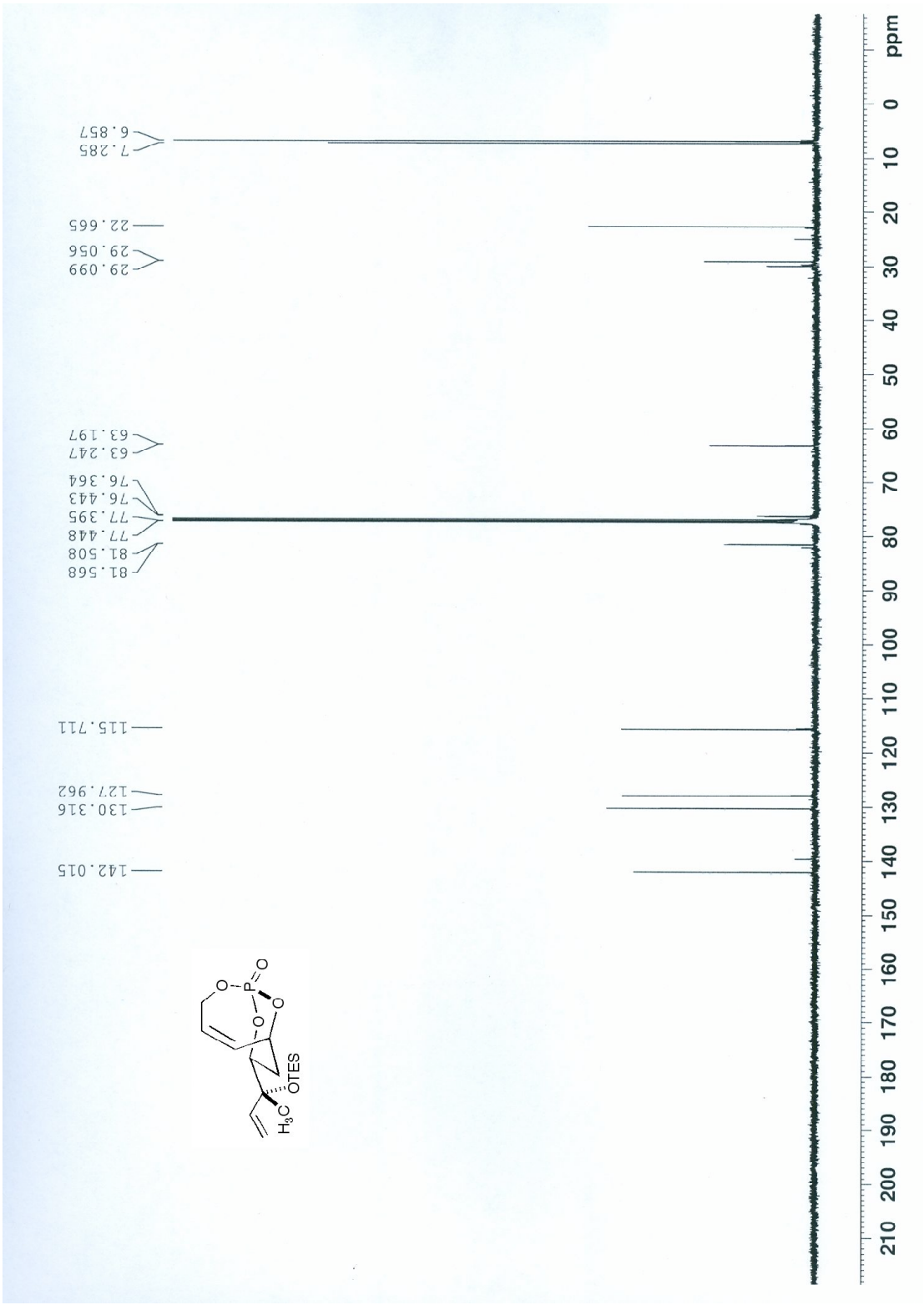
(2*R*,6*R*)-6-isopropoxy-2-vinyl-3,6-dihydro-2*H*-pyran: 14.1



138.472
128.643
126.354
115.614
93.394
69.867
67.001
30.511
24.034
22.325
ppm

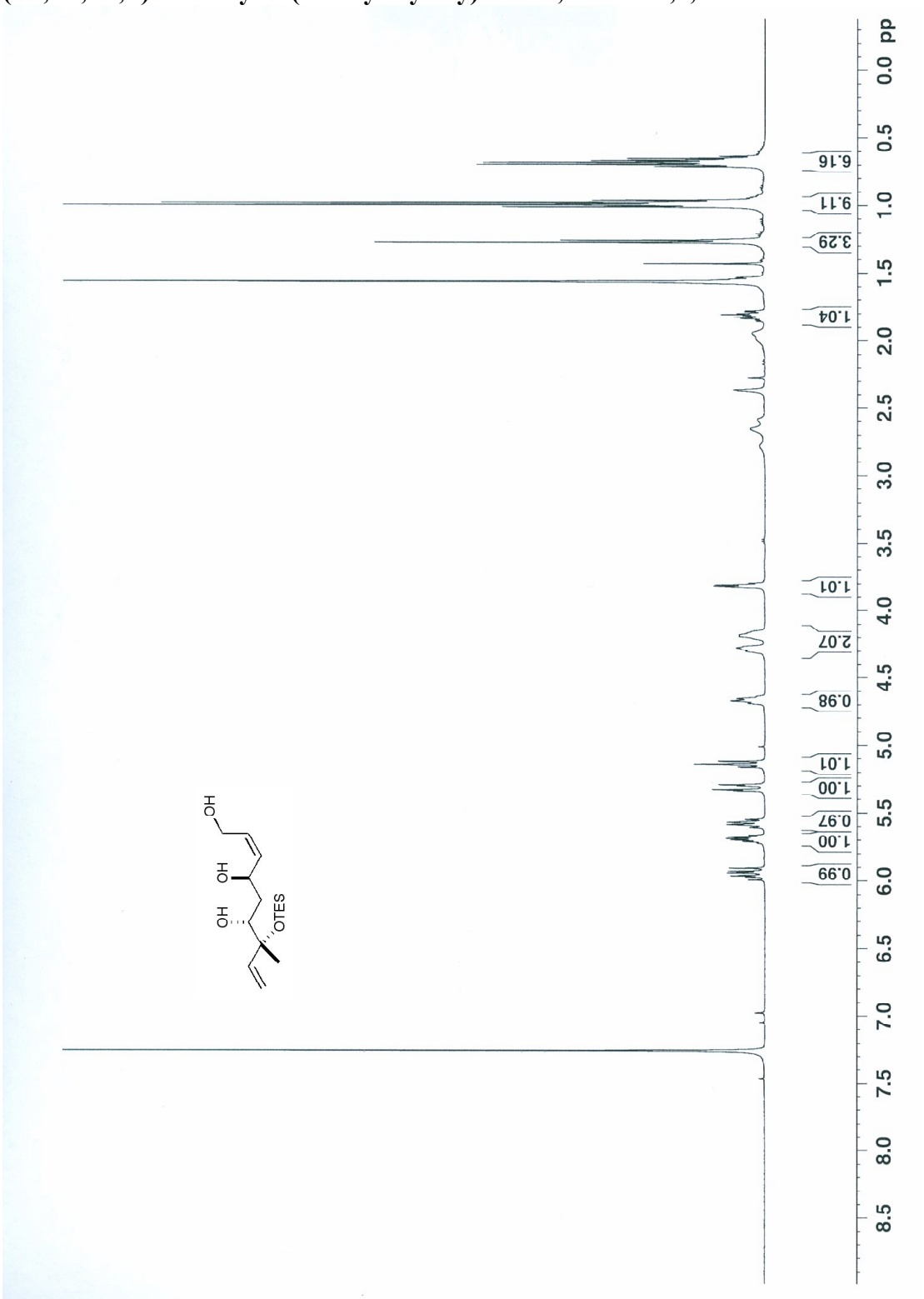
(1*S*,6*R*,8*R*)-8-((*R*)-2-(triethylsilyloxy)but-3-en-2-yl)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene

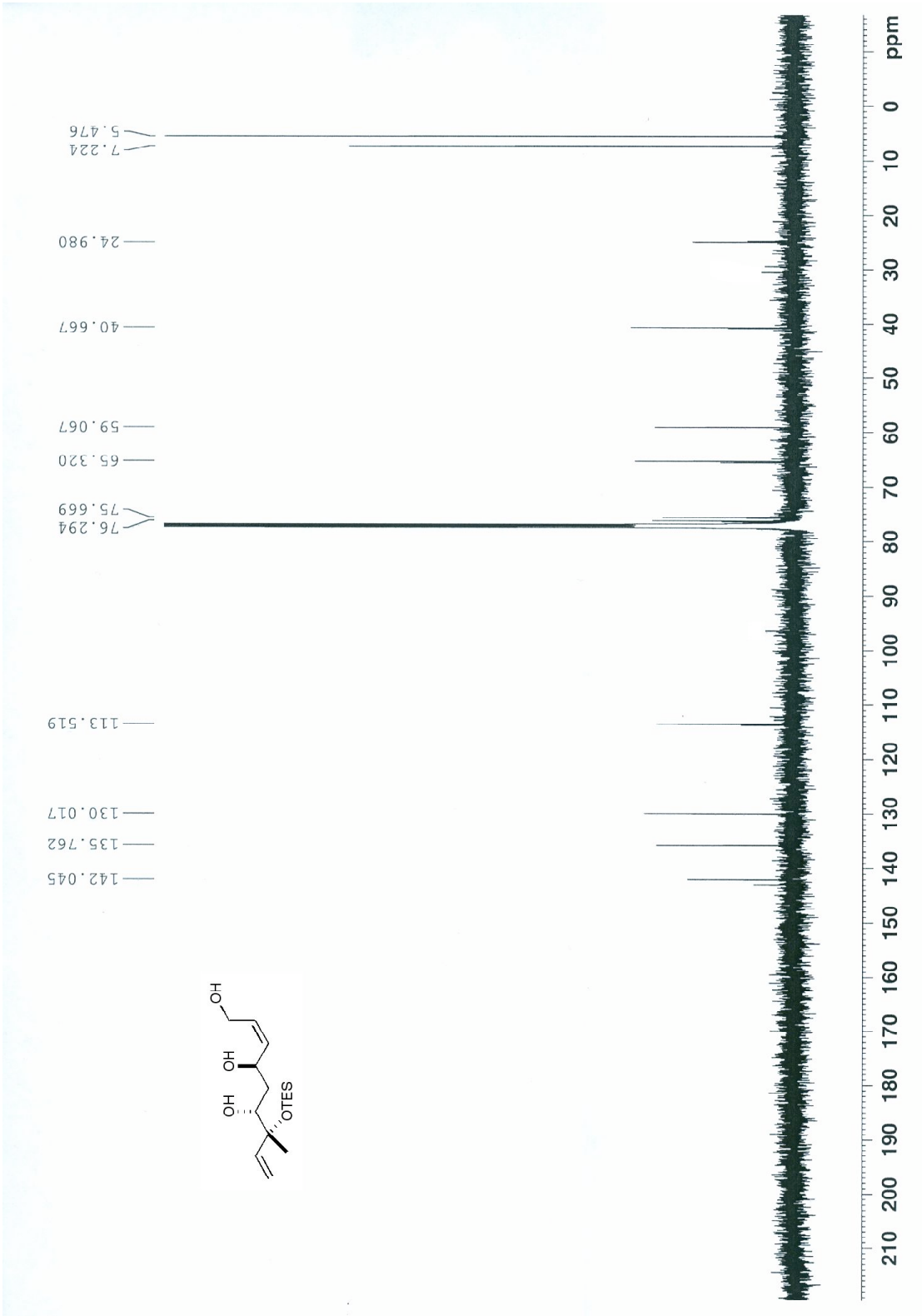



6.857
7.285
22.665
29.056
29.099
63.197
63.247
76.364
76.443
77.395
77.448
81.508
81.568
115.711
127.962
130.316
142.015
OTES
H_3C
O
P
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

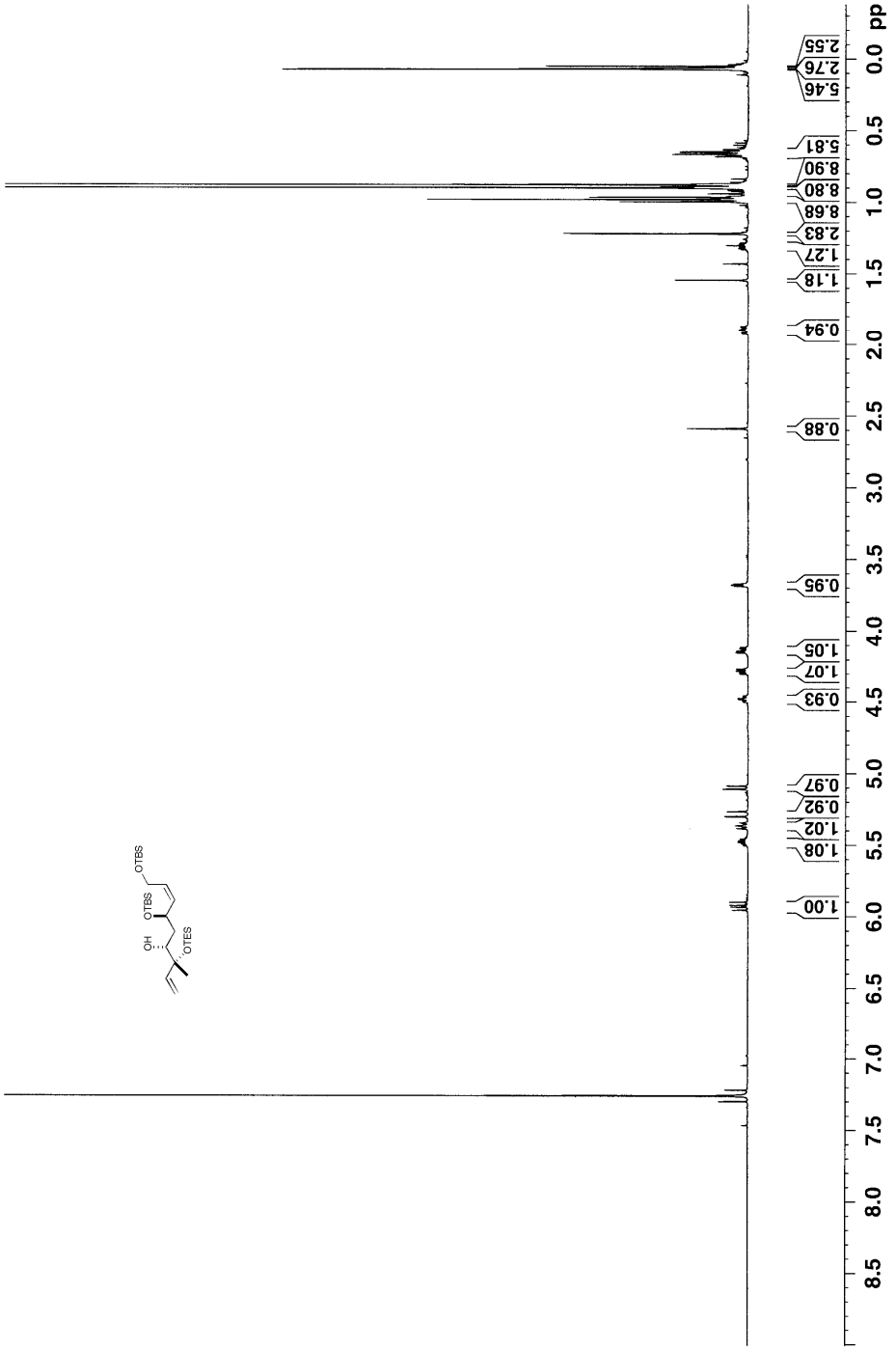
-2.702
-2.862
-3.022
100
50
0
-50
-100
-150
-200
ppm
OTES

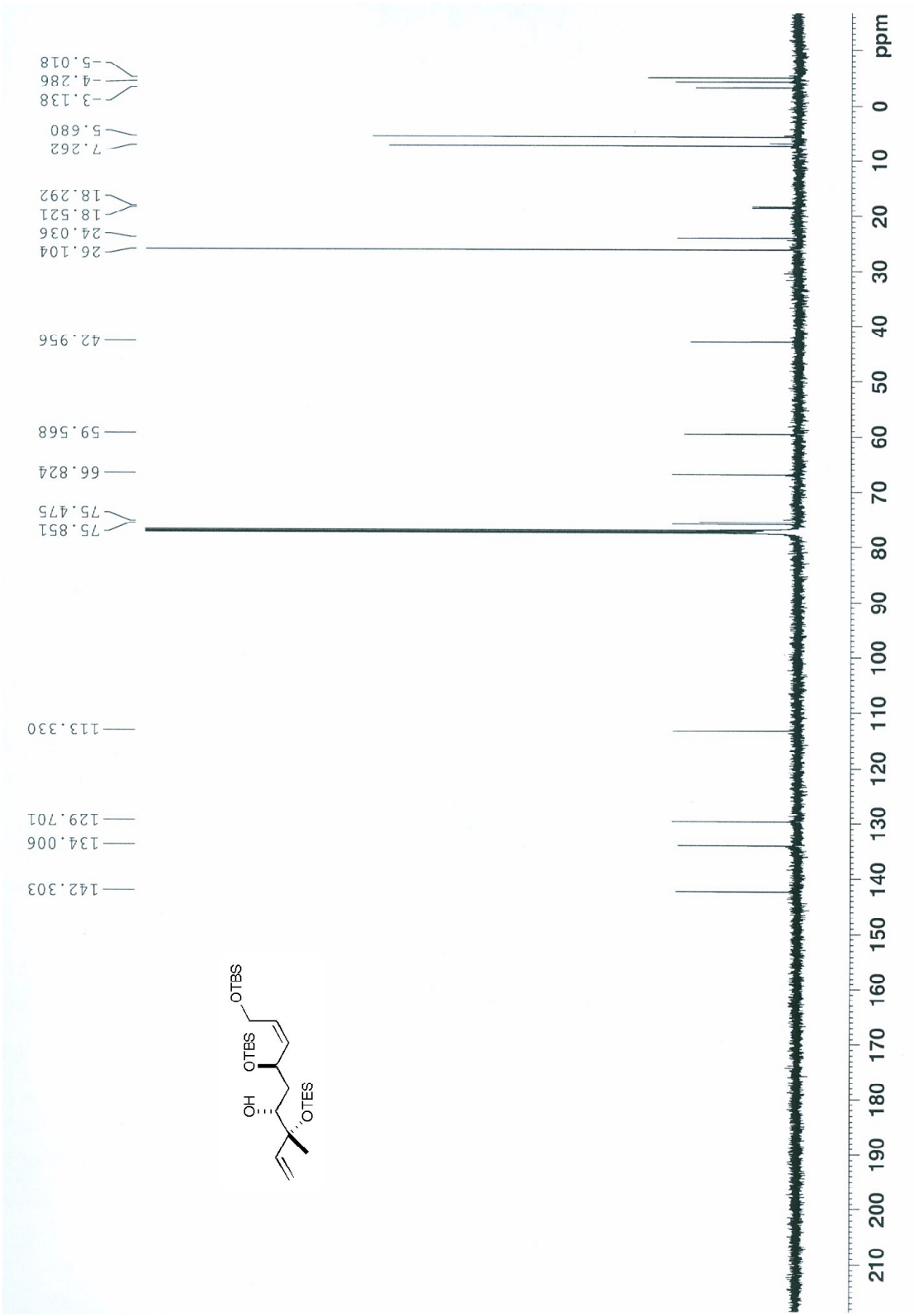
(4*R*,6*R*,7*R*,*Z*)-7-methyl-7-(triethylsilyloxy)nona-2,8-diene-1,4,6-triol: 16.1



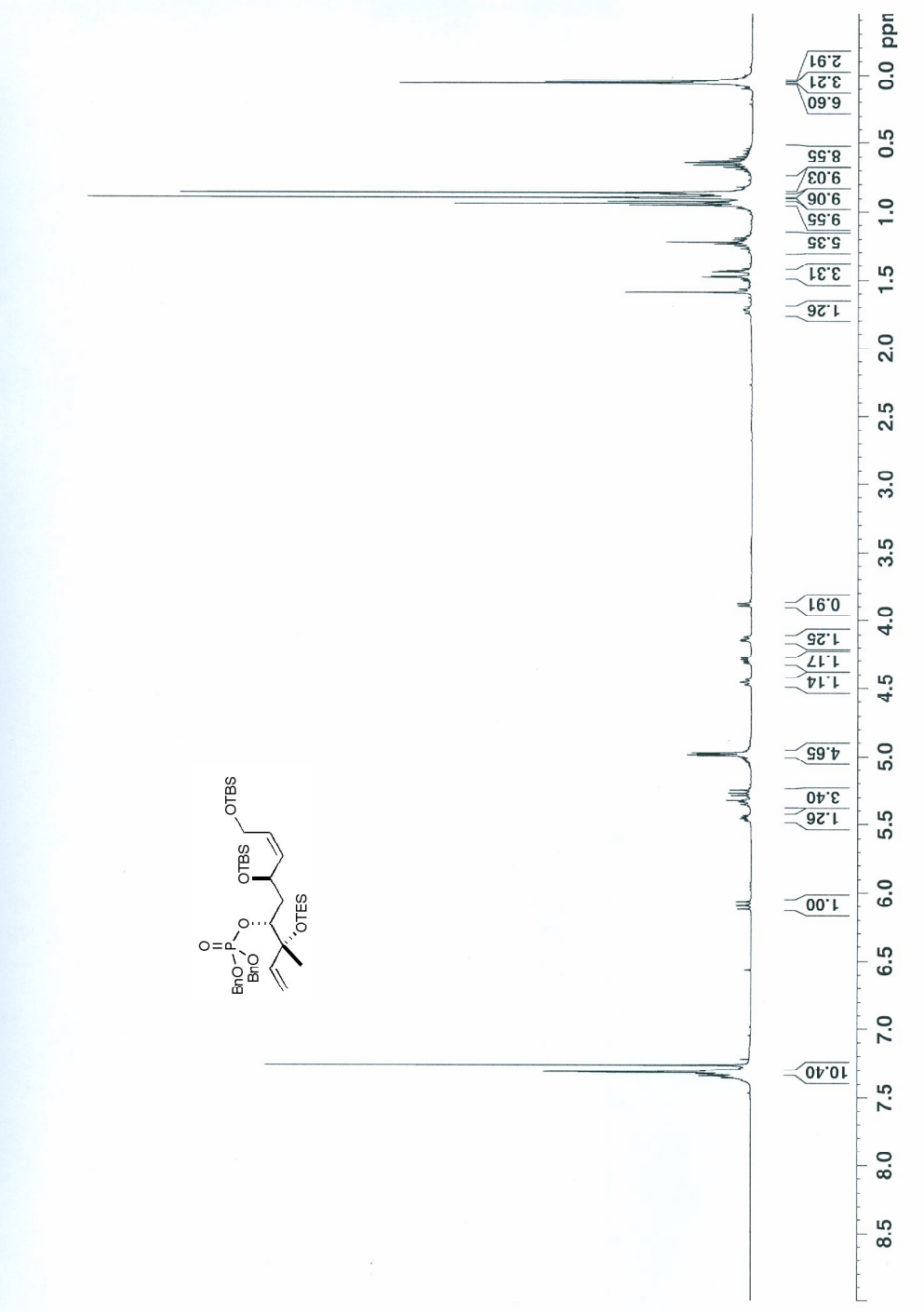

5.476
7.224
24.980
40.667
59.067
65.320
75.669
76.294
113.519
130.017
135.762
142.045
OH
OH
OH
OTES
ppm

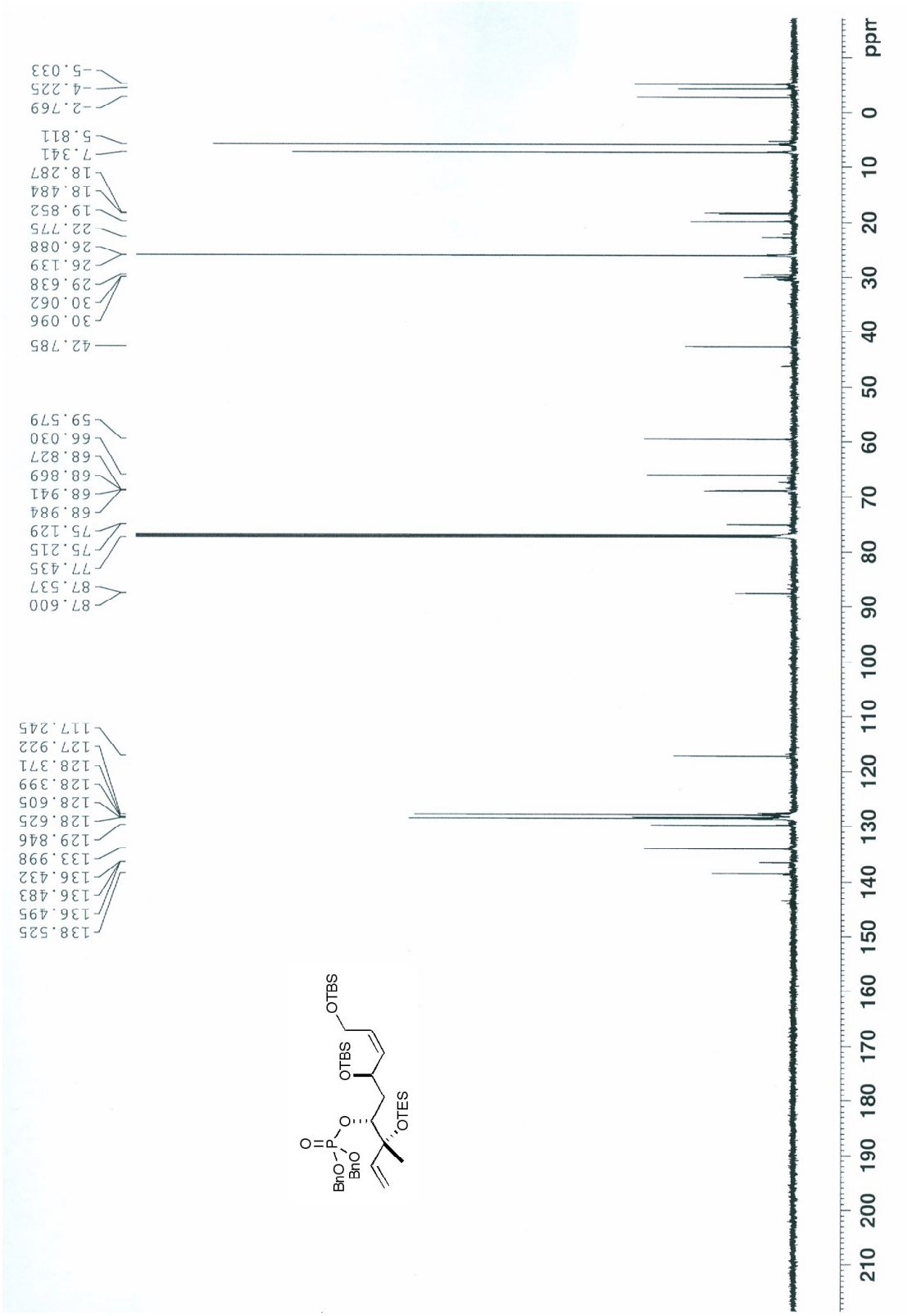
(5*R*,6*R*,8*R*,*Z*)-8-(*tert*-butyldimethylsilyloxy)-3,3-diethyl-5,13,13,14,14-pentamethyl-5-vinyl-4,12-dioxa-3,13-disilapentadec-9-en-6-ol: 16.2

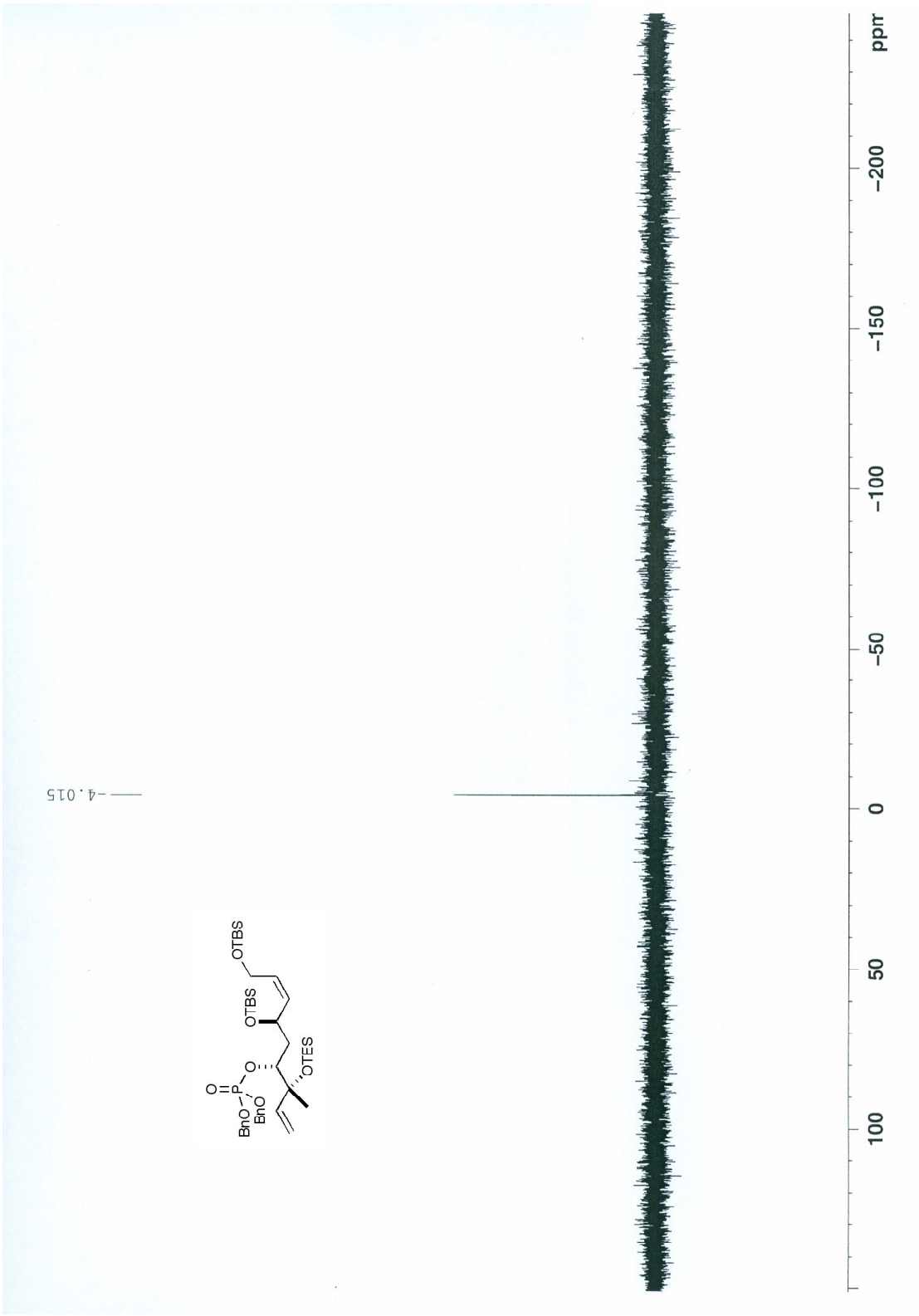



-5.018
-4.286
-3.138
5.680
7.262
18.292
18.521
24.036
26.104
42.956
59.568
66.824
75.475
75.851
113.330
129.701
134.006
142.303
OTBS
OTES
OH
OTES
ppm

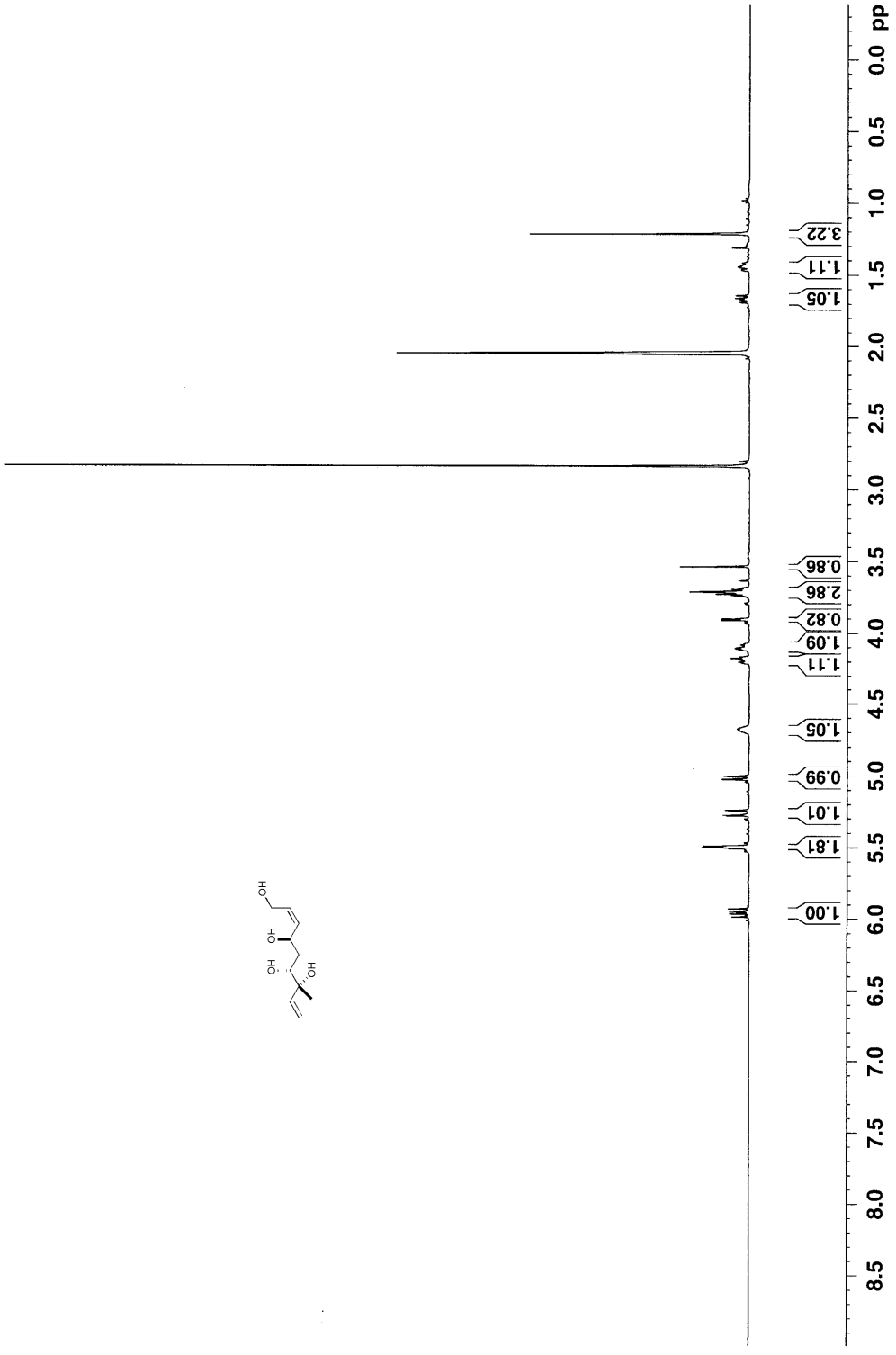
dibenzyl (5*R*,6*R*,8*R*,*Z*)-8-(*tert*-butyldimethylsilyloxy)-3,3-diethyl-5,13,13,14,14-pentamethyl-5-vinyl-4,12-dioxa-3,13-disilapentadec-9-en-6-yl phosphate: 16.3

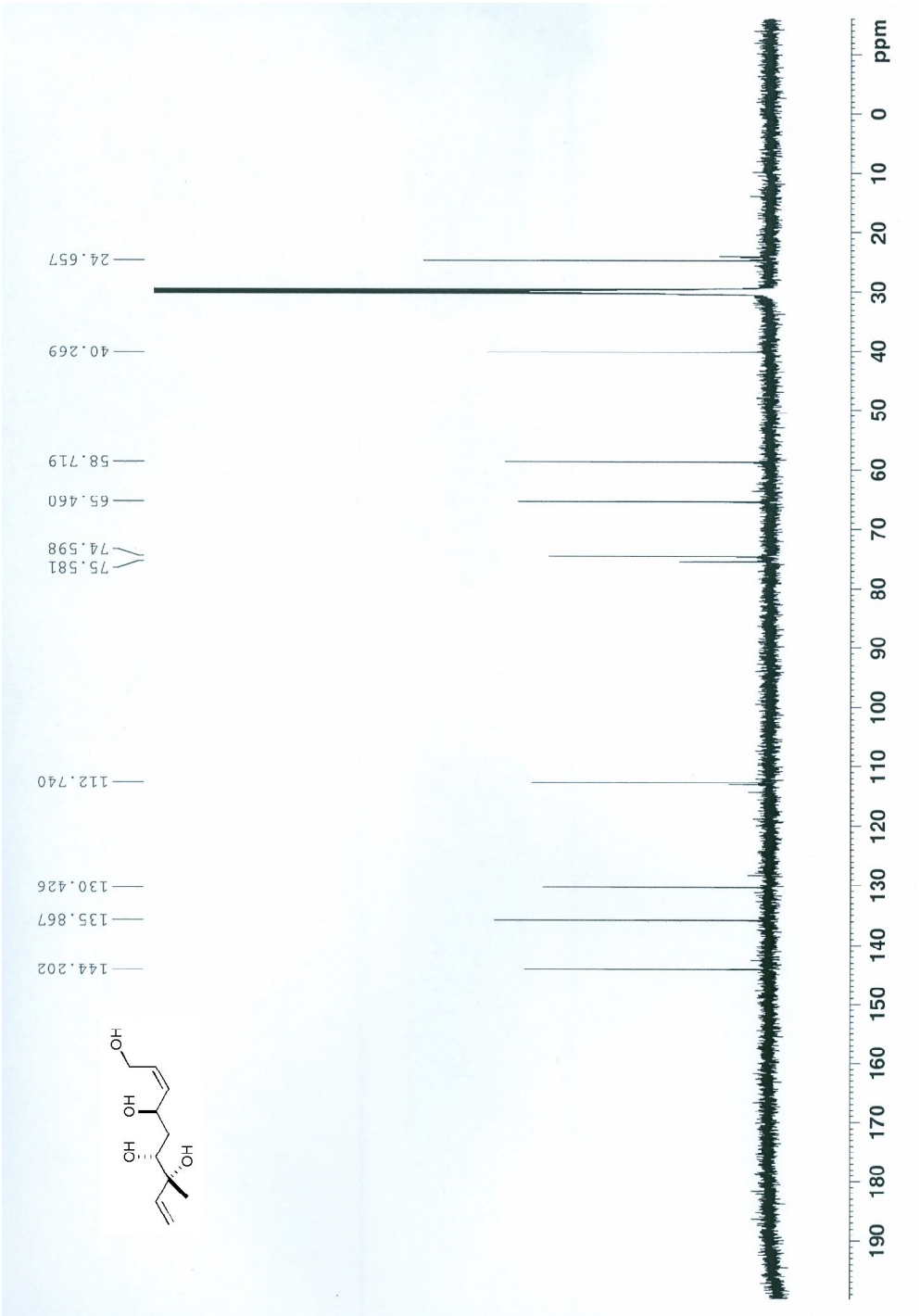



-5.033
-4.225
-2.769
5.811
7.341
18.287
18.484
19.852
22.775
26.088
26.139
29.638
30.062
30.096
42.785
59.579
66.030
68.827
68.869
68.941
68.984
75.129
75.215
77.435
87.537
87.600
117.245
127.922
128.371
128.399
128.605
128.625
129.846
133.998
136.432
136.483
136.495
138.525
OTBS
OTBS
OTES
BnO
BnO
O
P
O
O
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

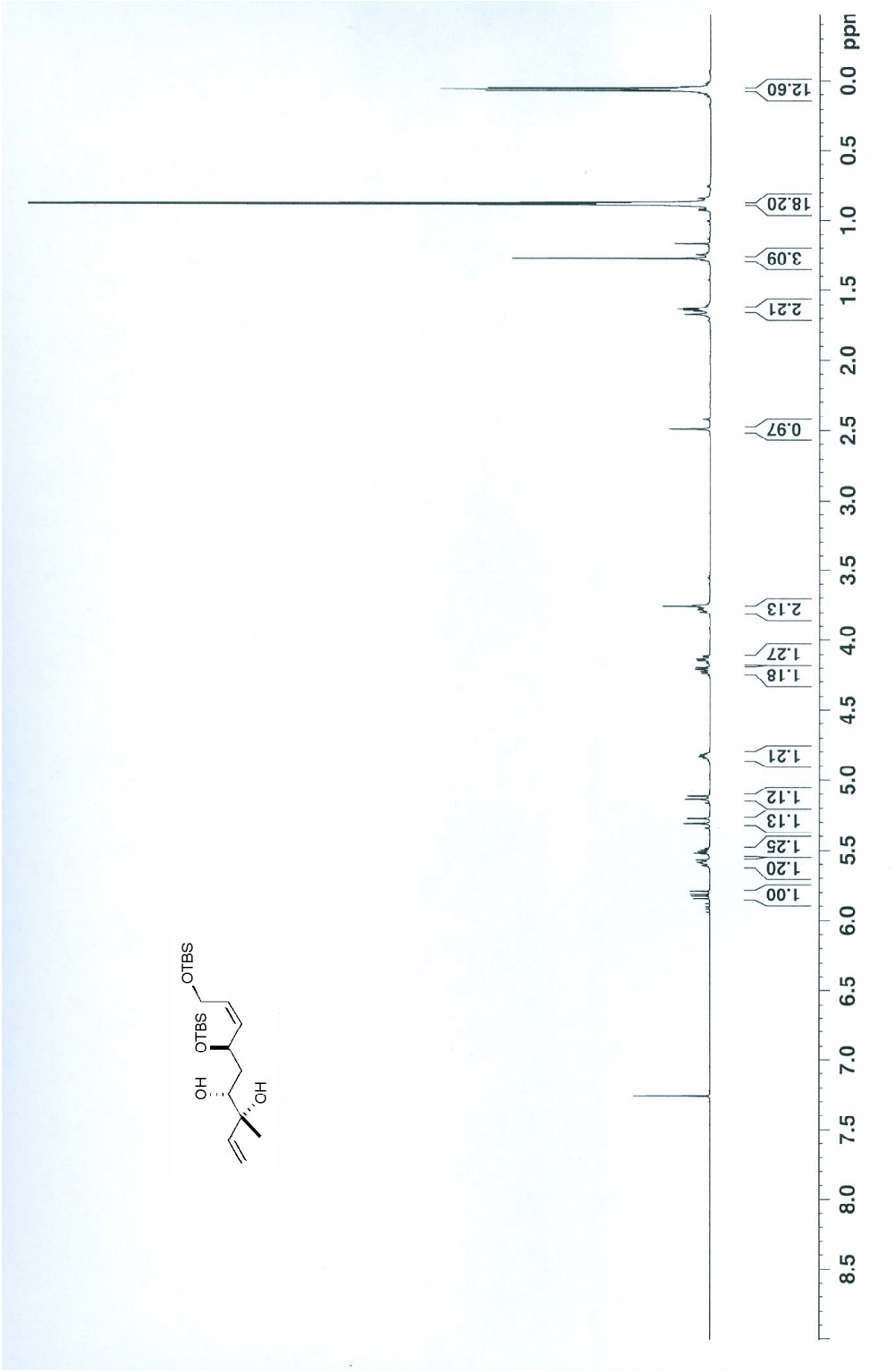

-4.015
OTBS
OTBS
OTES
BnO
BnO
O
P
O
100
50
0
-50
-100
-150
-200
ppm

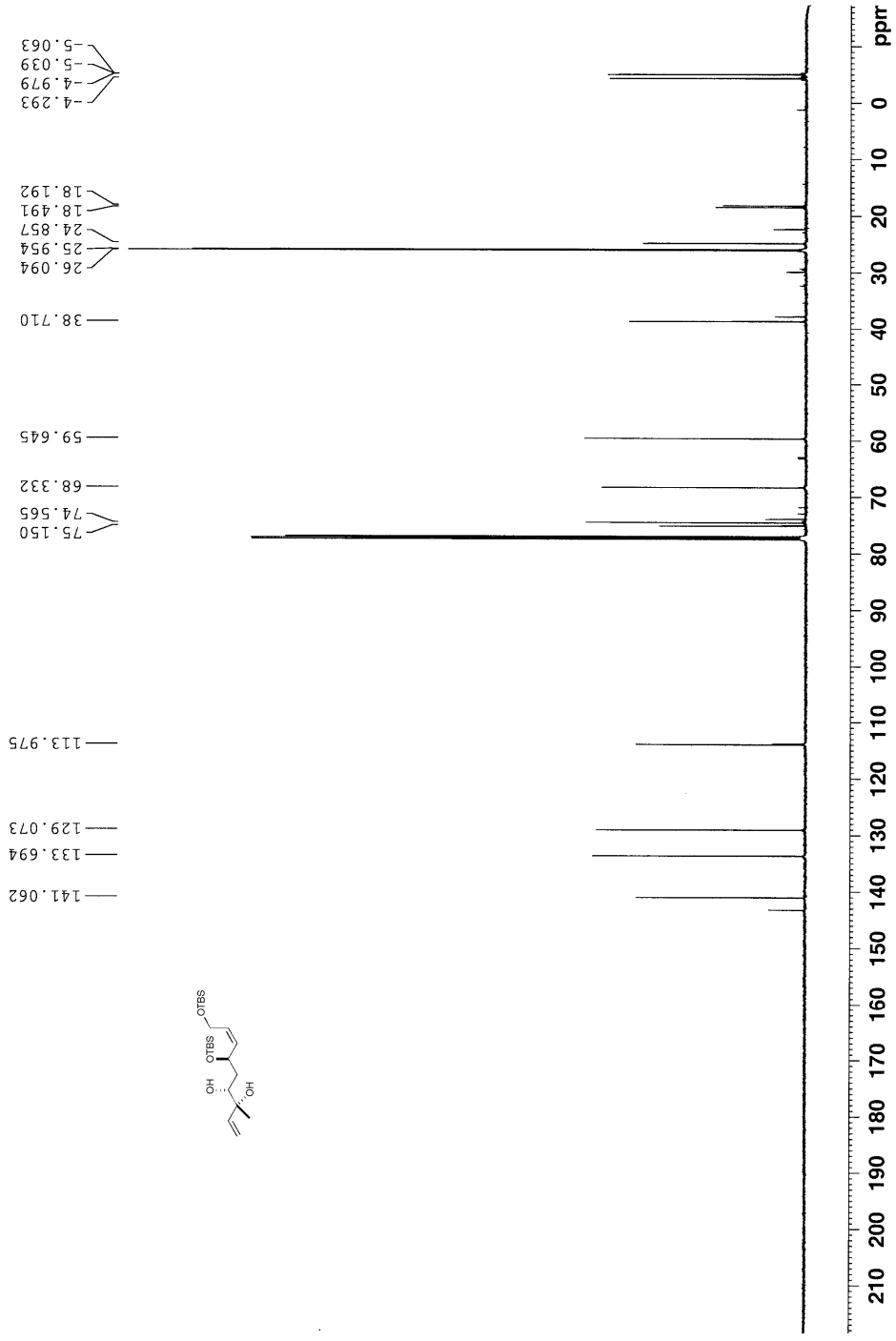
(4*R*,6*R*,7*R*,*Z*)-7-methylnona-2,8-diene-1,4,6,7-tetraol: 17.1



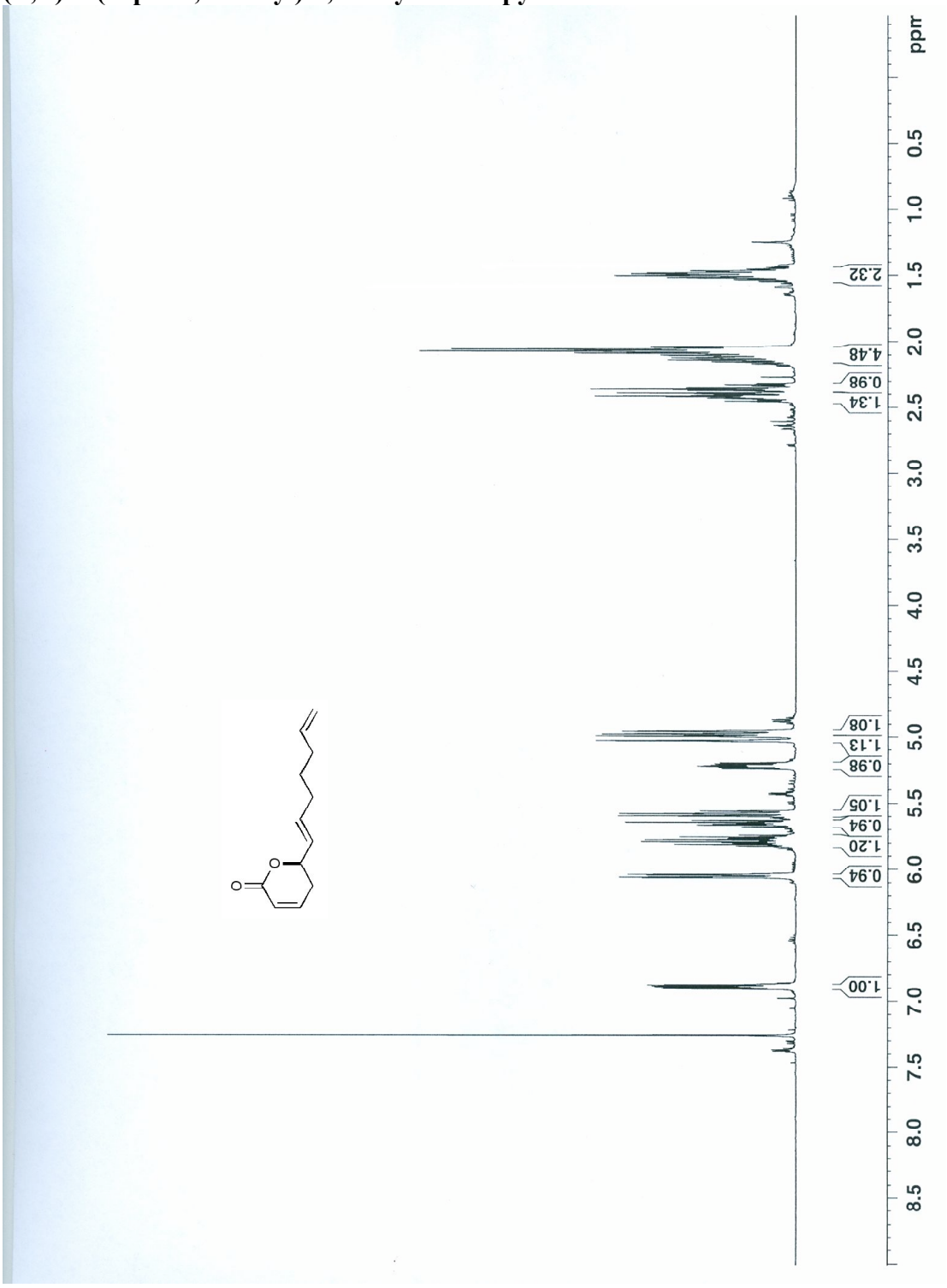

144.202
135.867
130.426
112.740
75.581
74.598
65.460
58.719
40.269
24.657
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
HO
OH
OH
HO

(3*R*,4*R*,6*R*,*Z*)-6,9-bis(*tert*-butyldimethylsilyloxy)-3-methylnona-1,7-diene-3,4-diol: 17.2



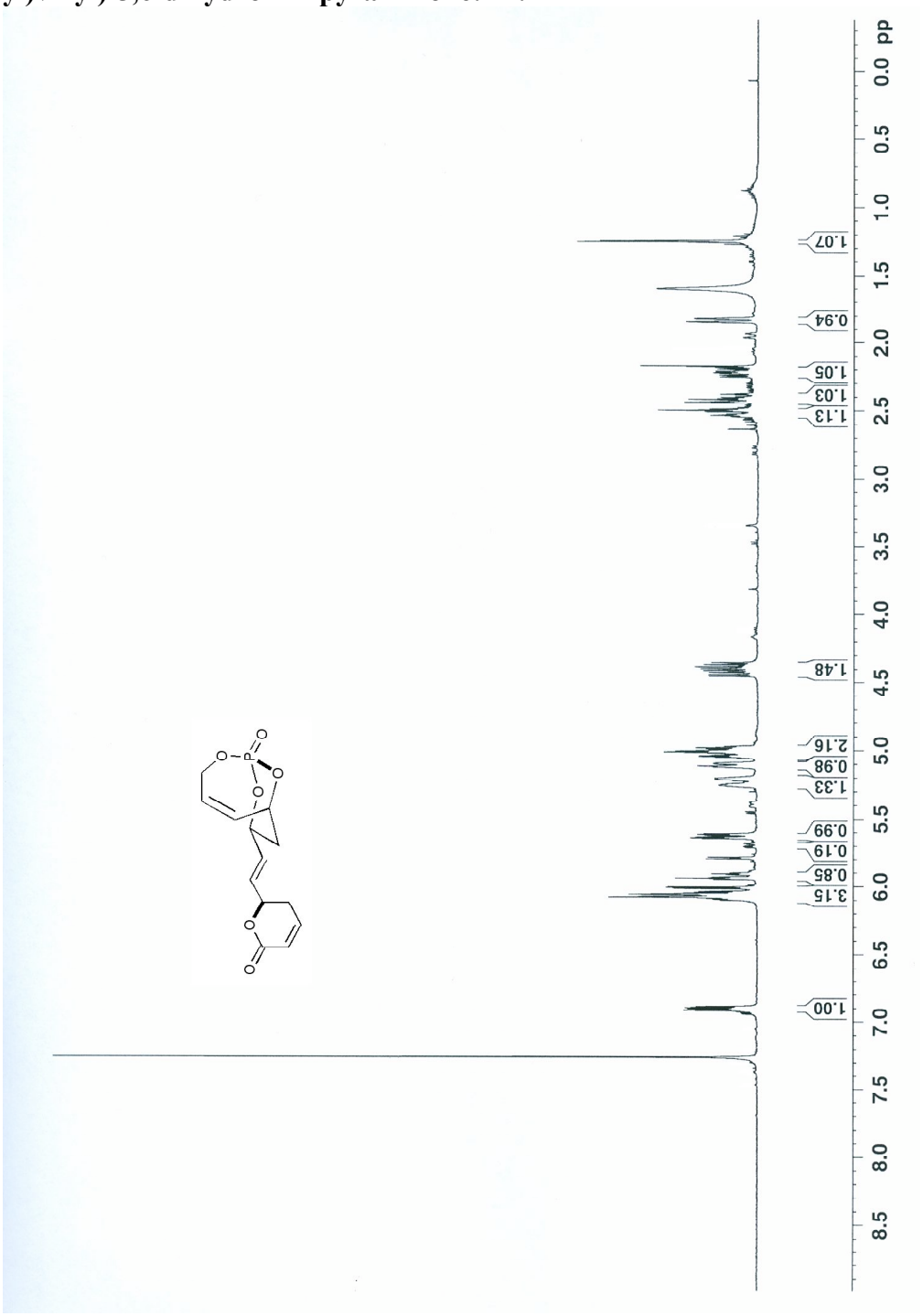

OTBS
OTBS
OH
OH
141.062
133.694
129.073
113.975
75.150
74.565
68.332
59.645
38.710
26.094
25.954
24.857
18.491
18.192
-4.293
-4.979
-5.039
-5.063
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

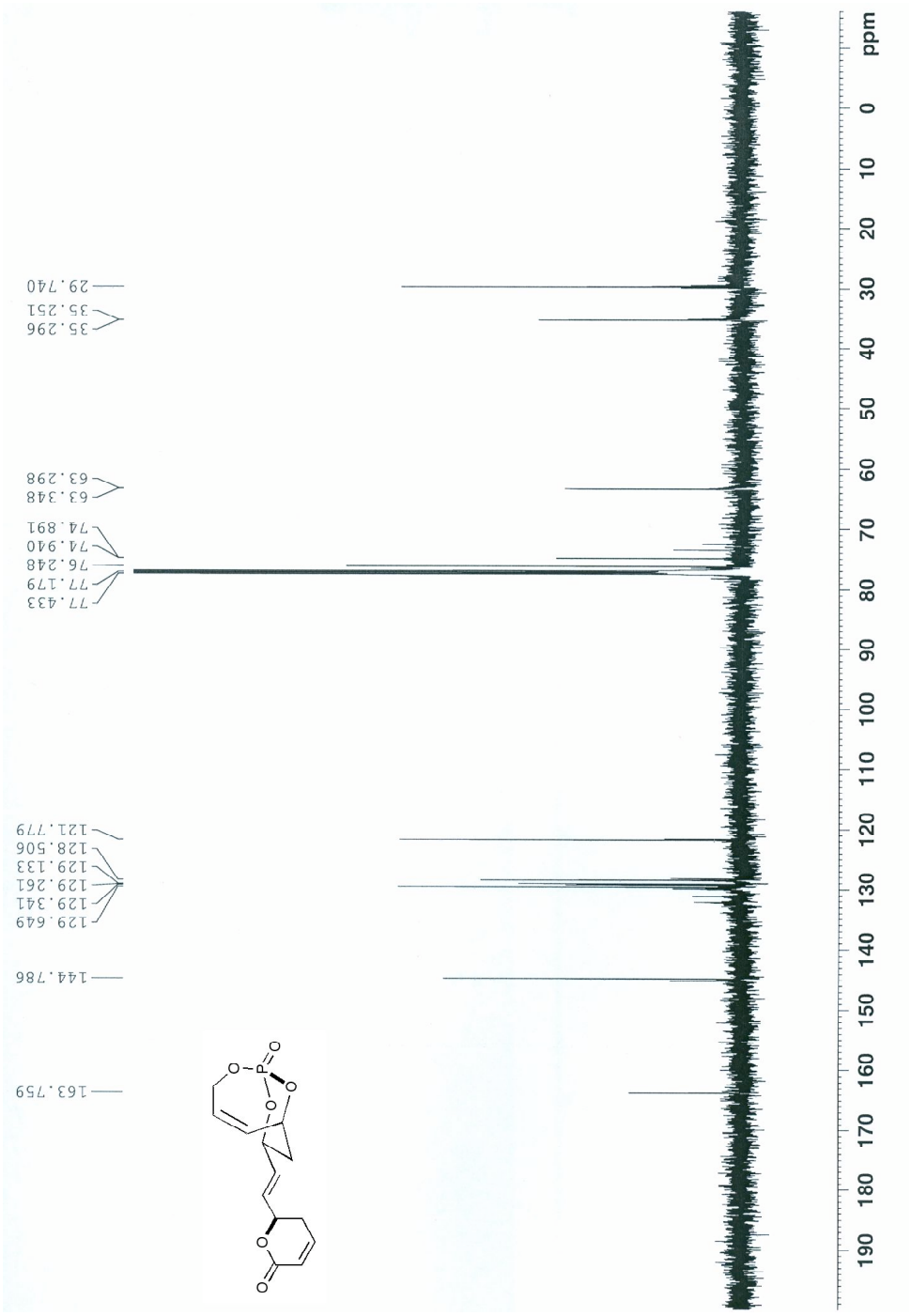
(*R*,*E*)-6-(hepta-1,6-dienyl)-5,6-dihydro-2*H*-pyran-2-one: 24.1



164.439
145.066
138.439
135.413
126.918
121.787
115.217
74.048
33.325
30.067
28.643
27.323
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

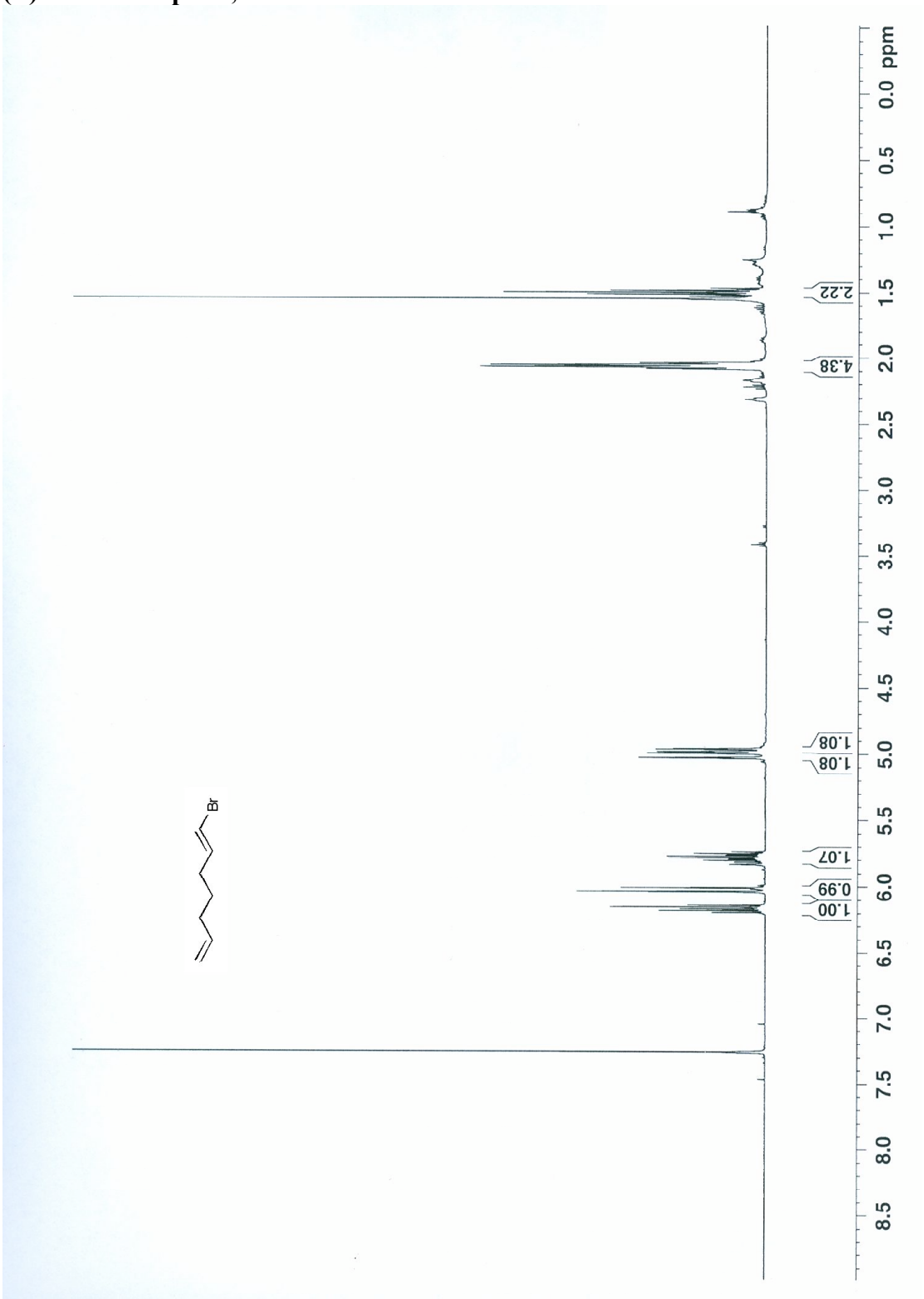
(*R*)-6-((*E*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)vinyl)-5,6-dihydro-2*H*-pyran-2-one: 24.2

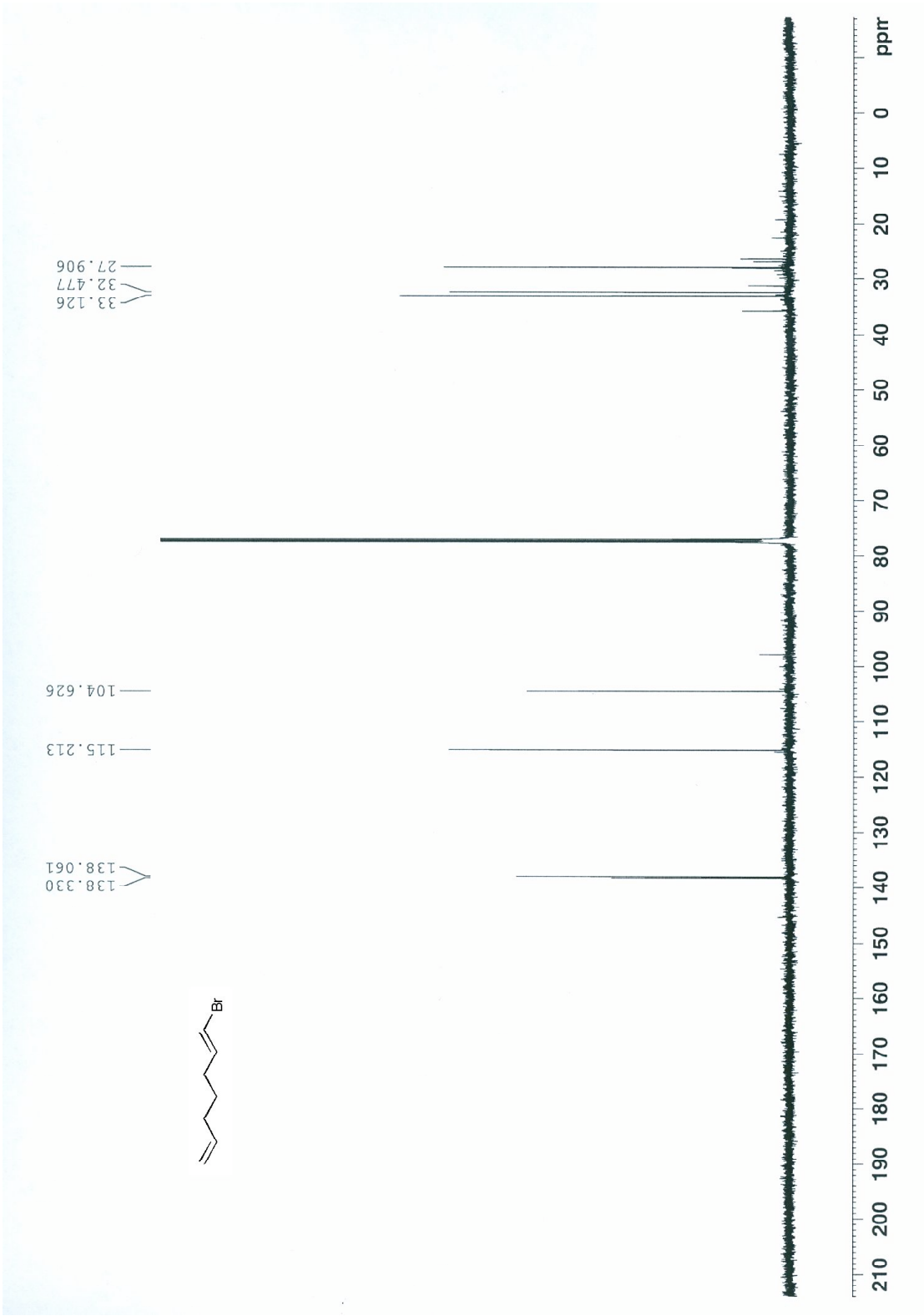



29.740
35.251
35.296
63.298
63.348
74.891
74.940
76.248
77.179
77.433
121.779
128.506
129.133
129.261
129.341
129.649
144.786
163.759
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

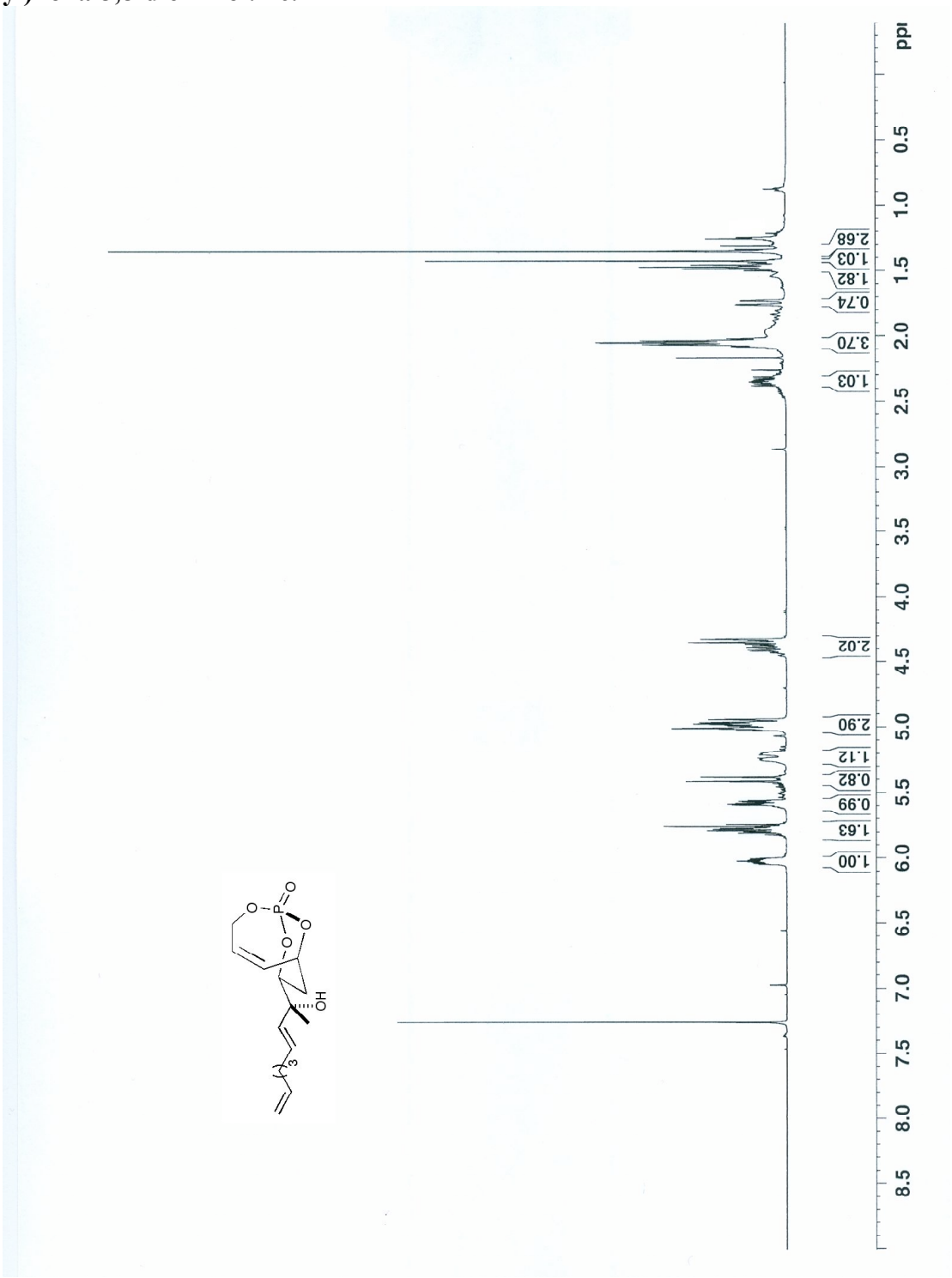
-3.617
-3.763
-3.953
100
50
0
-50
-100
-150
-200
ppm

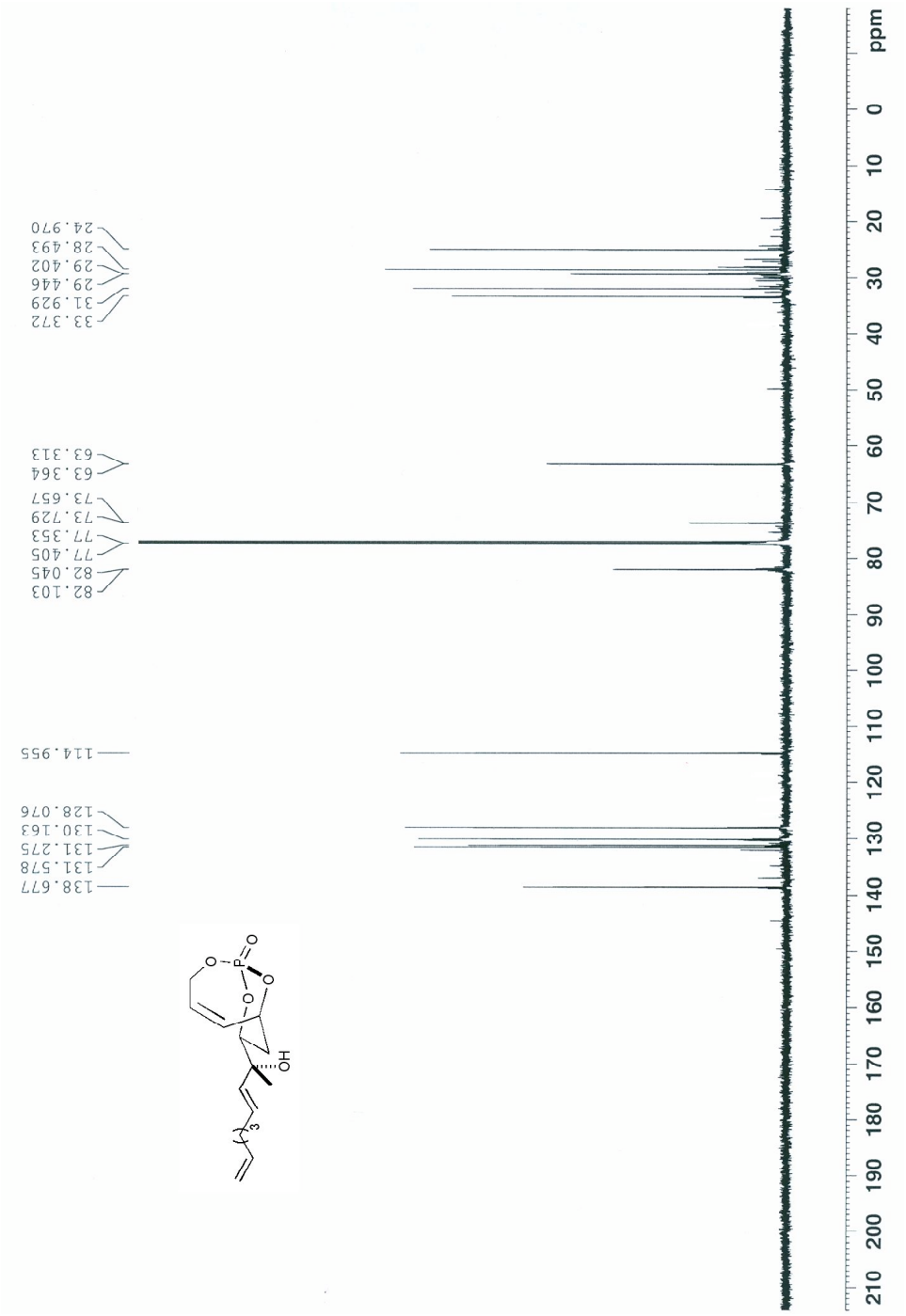
(*E*)-1-bromohepta-1,6-diene: 26.1




138.330
138.061
115.213
104.626
33.126
32.477
27.906
Br
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

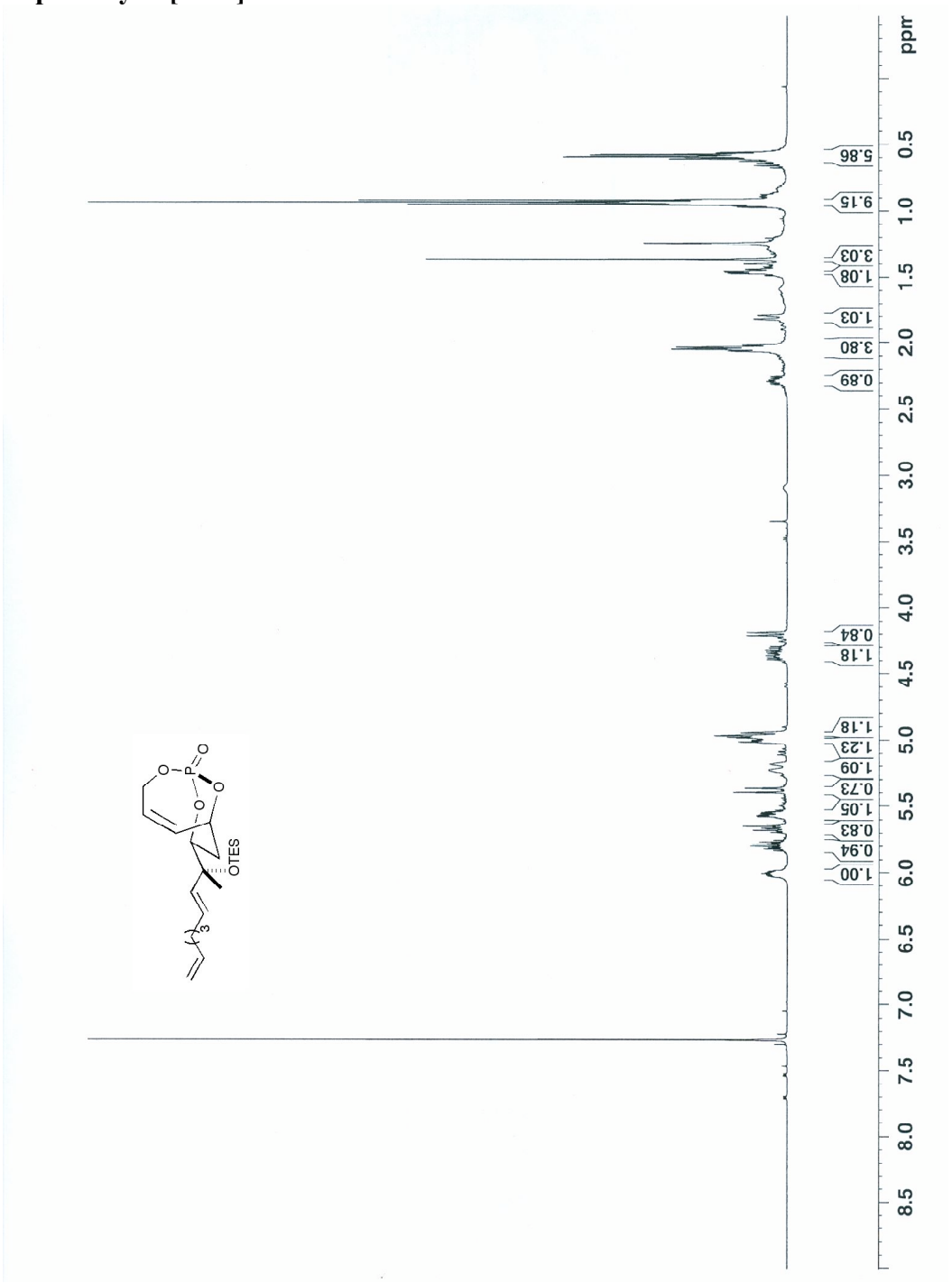
(*R*,*E*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)nona-3,8-dien-2-ol: 26.2




ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
24.970
28.493
29.402
29.446
31.929
33.372
63.313
63.364
73.657
73.729
77.353
77.405
82.045
82.103
114.955
128.076
130.163
131.275
131.578
138.677
OH

-2.758
100
50
0
-50
-100
-150
-200
ppm

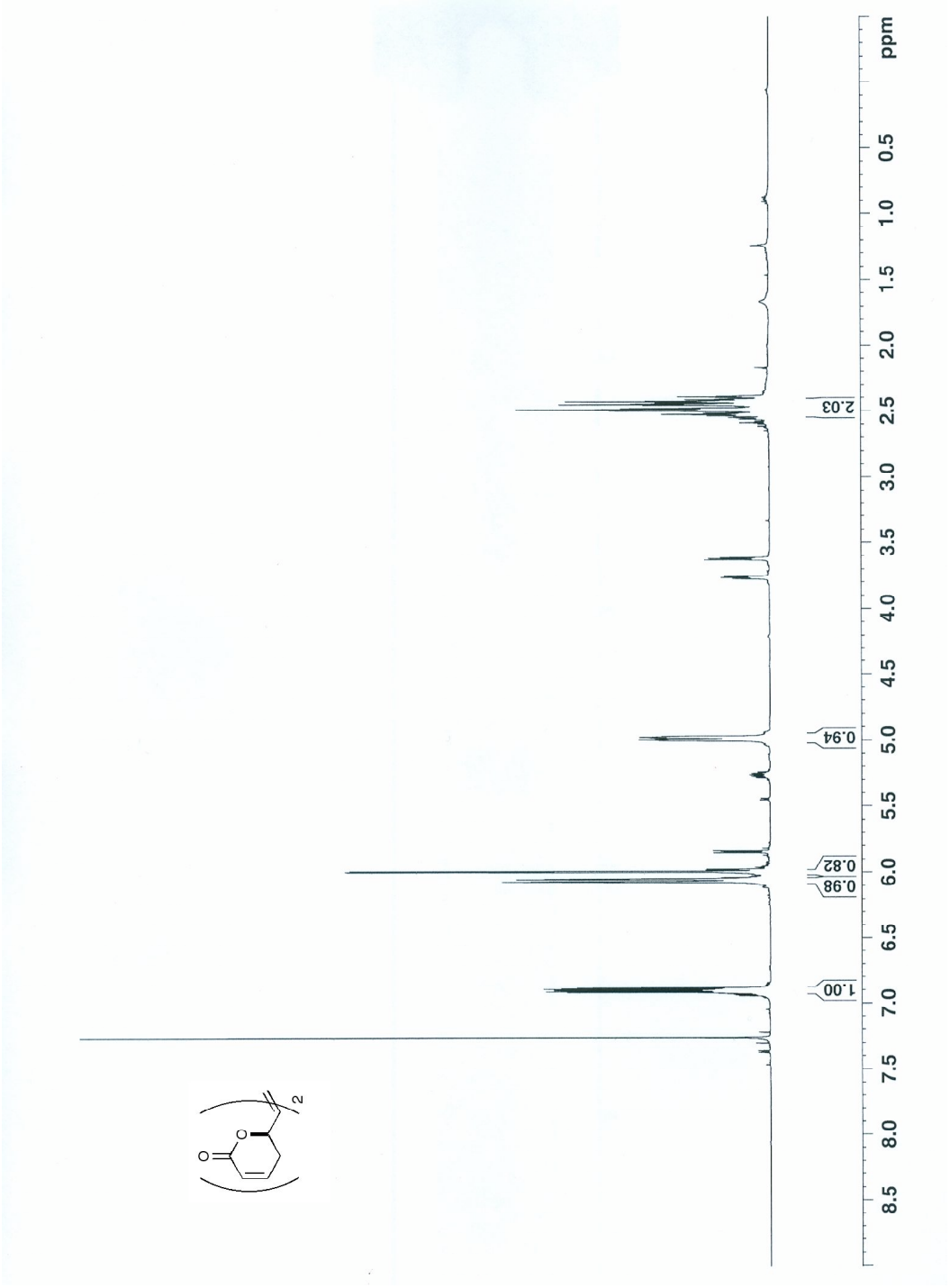
(1*S*,6*R*,8*R*)-8-((*R*,*E*)-2-(triethylsilyloxy)nona-3,8-dien-2-yl)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene: 26.3



138.765
134.076
131.537
130.340
127.930
114.918
81.917
81.858
77.810
77.758
75.829
75.748
63.228
63.178
33.444
31.908
29.923
29.169
29.127
28.517
22.846
7.306
6.842
OTES
ppm

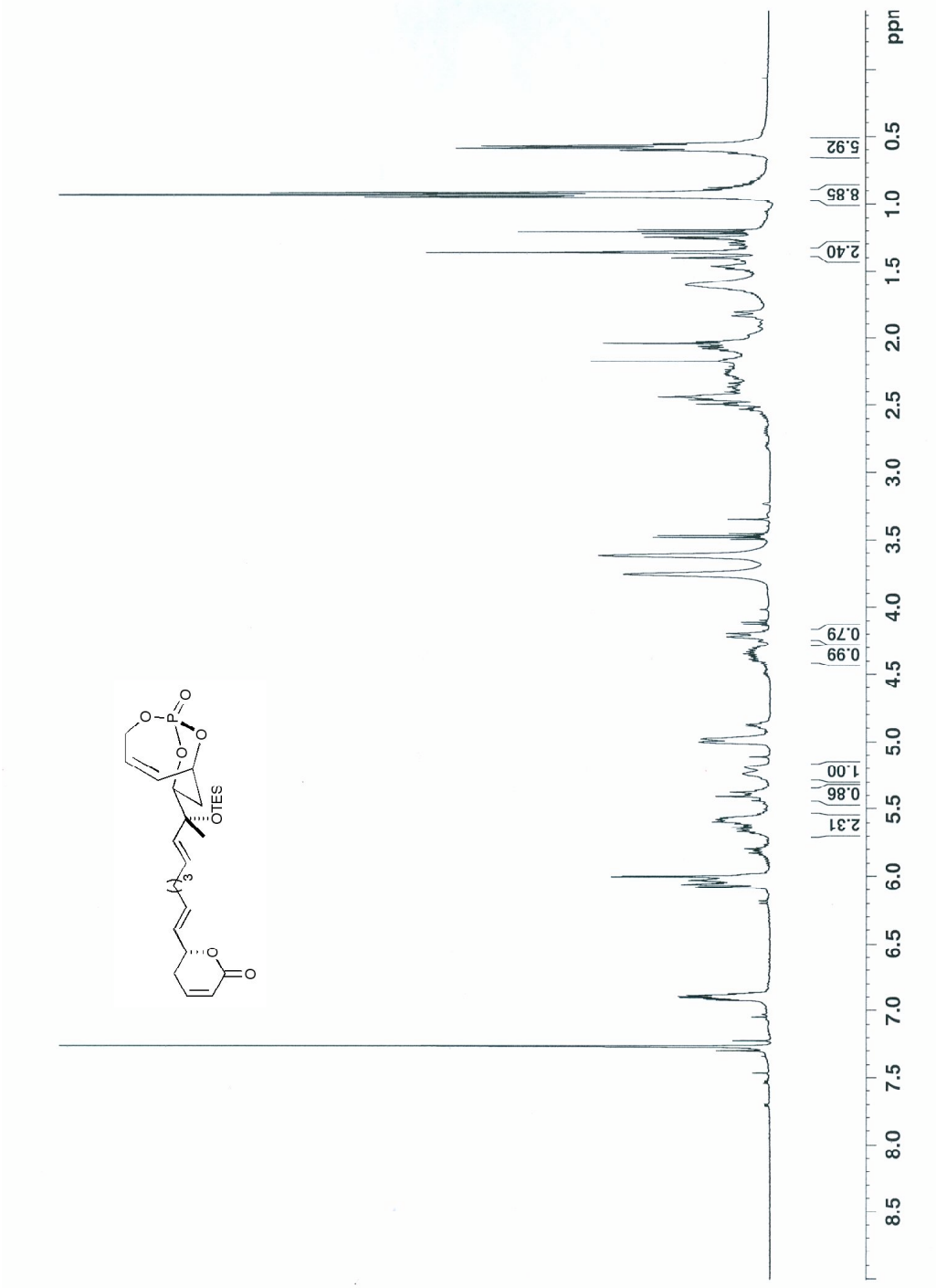
-2.627
-2.805
-2.980
OTES
100
50
0
-50
-100
-150
-200
ppm

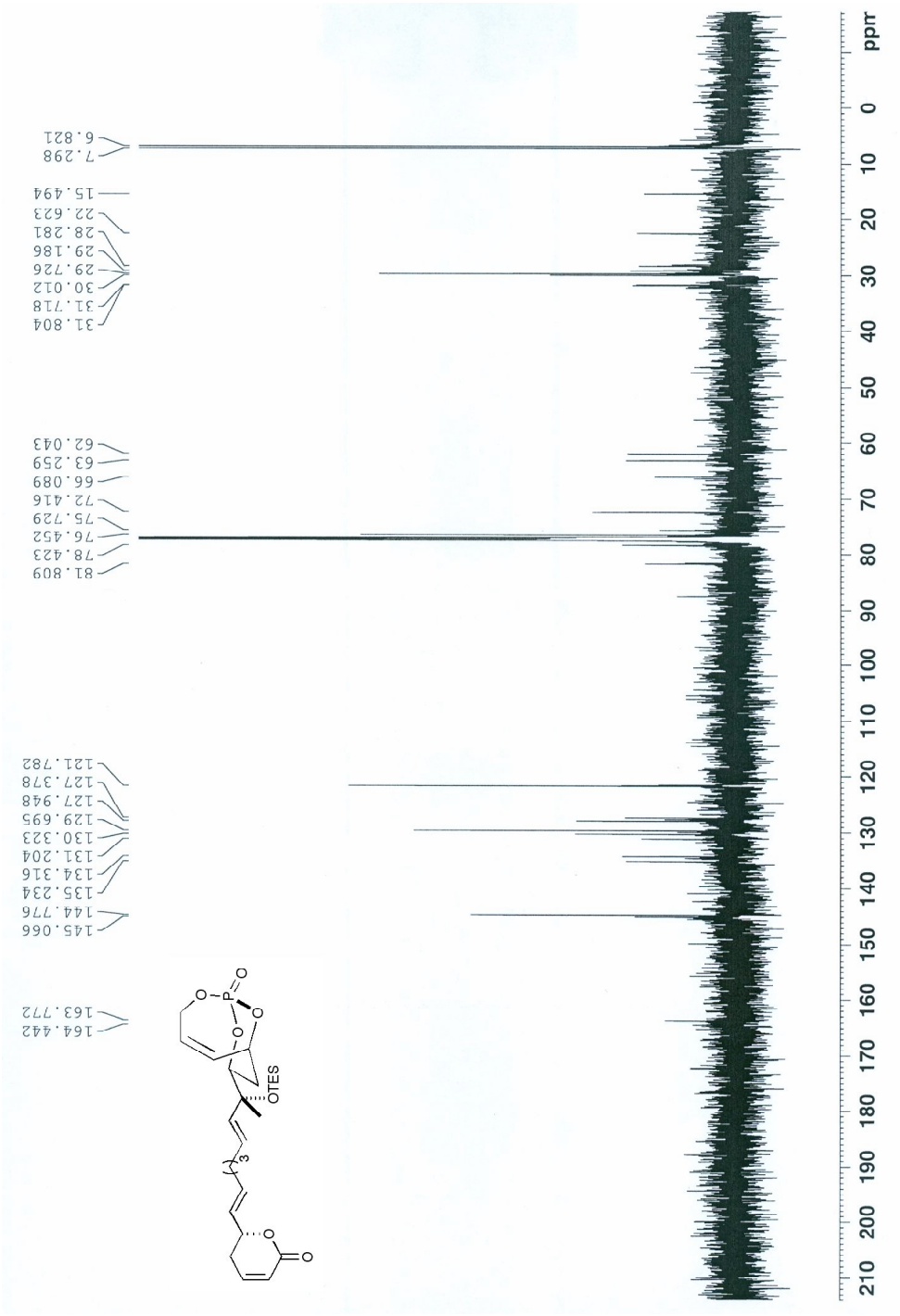
(6*R*,6'*R*)-6,6'-(ethene-1,2-diyl)bis(5,6-dihydro-2*H*-pyran-2-one): Dimer of 2.4



163.760
144.794
129.695
121.731
76.452
29.692
ppm

(*R*)-6-((*R*,1*E*,6*E*)-8-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)-8-(triethylsilyloxy)nona-1,6-dienyl)-5,6-dihydro-2*H*-pyran-2-one: 27.1

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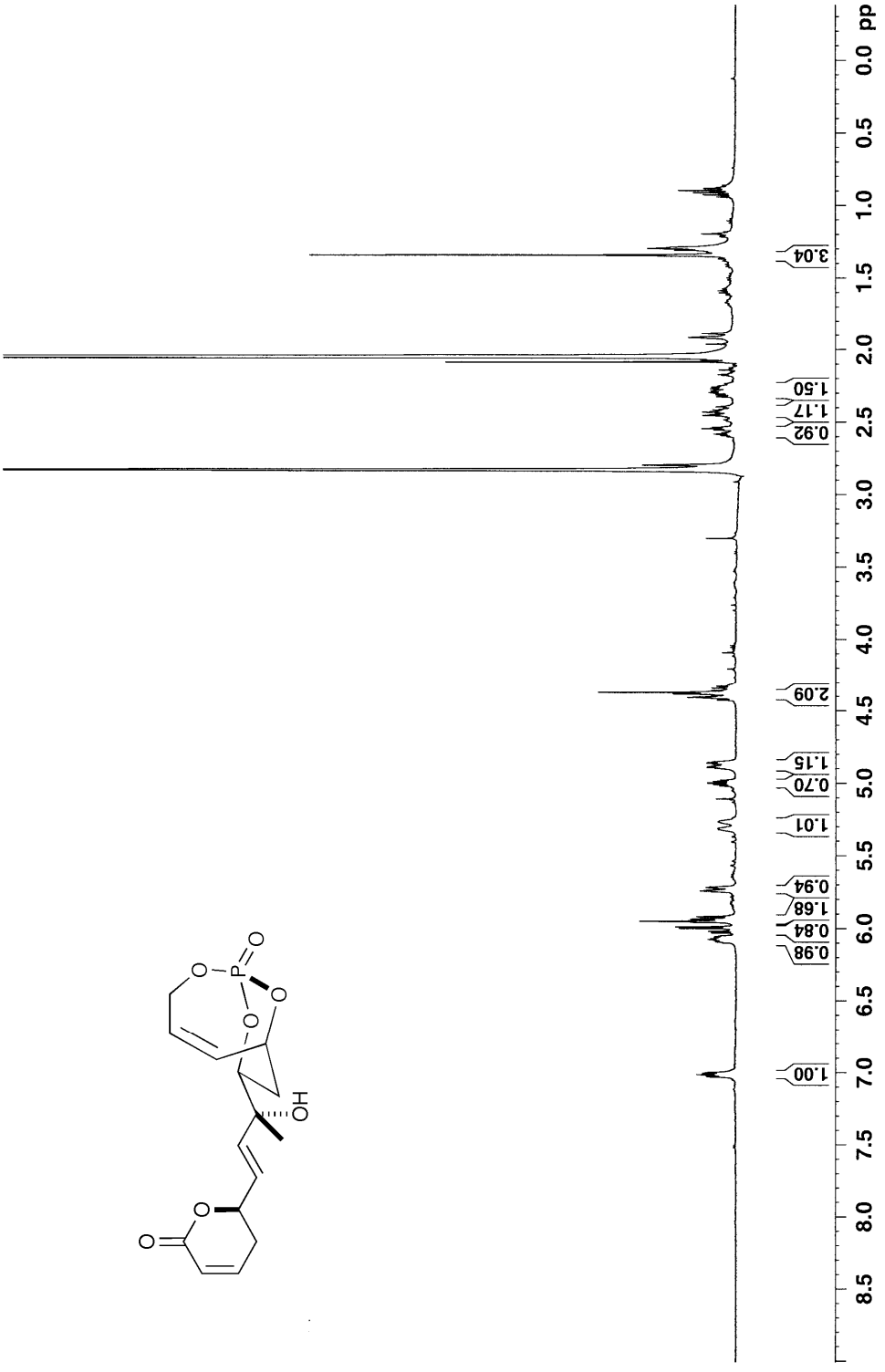
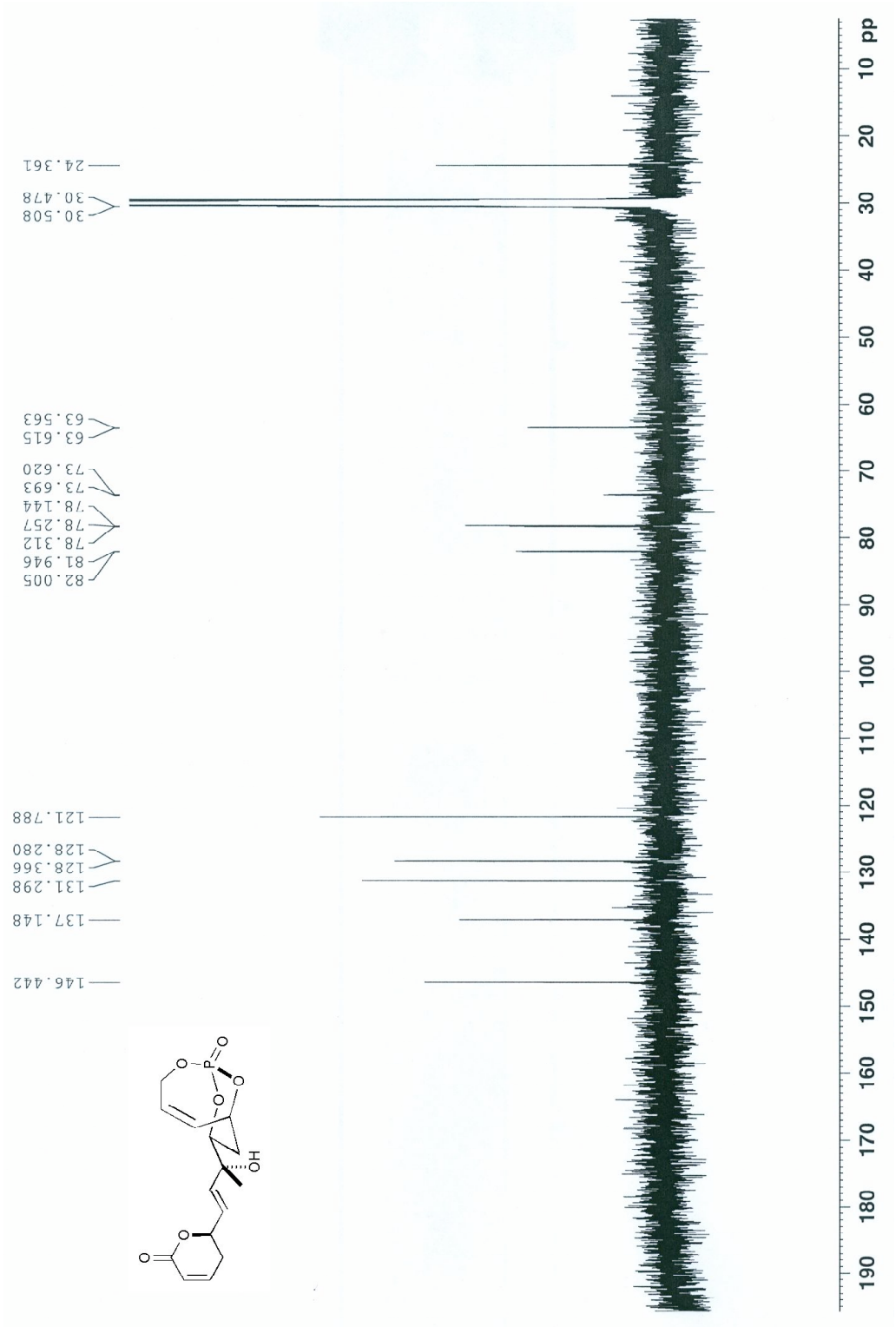
66.089
72.416
75.729
76.452
78.423
81.809
121.782
127.378
127.948
129.695
130.323
131.204
134.316
135.234
144.776
145.066
163.772
164.442
OTES
O
P
3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

-3.111
OTES
100
50
0
−50
−100
−150
−200
ppm

(*R*)-6-((*R*,*E*)-3-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)-3-hydroxybut-1-enyl)-5,6-dihydro-2*H*-pyran-2-one: 28.1

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30.478
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63.563
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73.693
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82.005
121.788
128.280
128.366
131.298
137.148
146.442
OH
O
P
O
O
O
O
O
10 pp
20
30
40
50
60
70
80
90
100
110
120
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140
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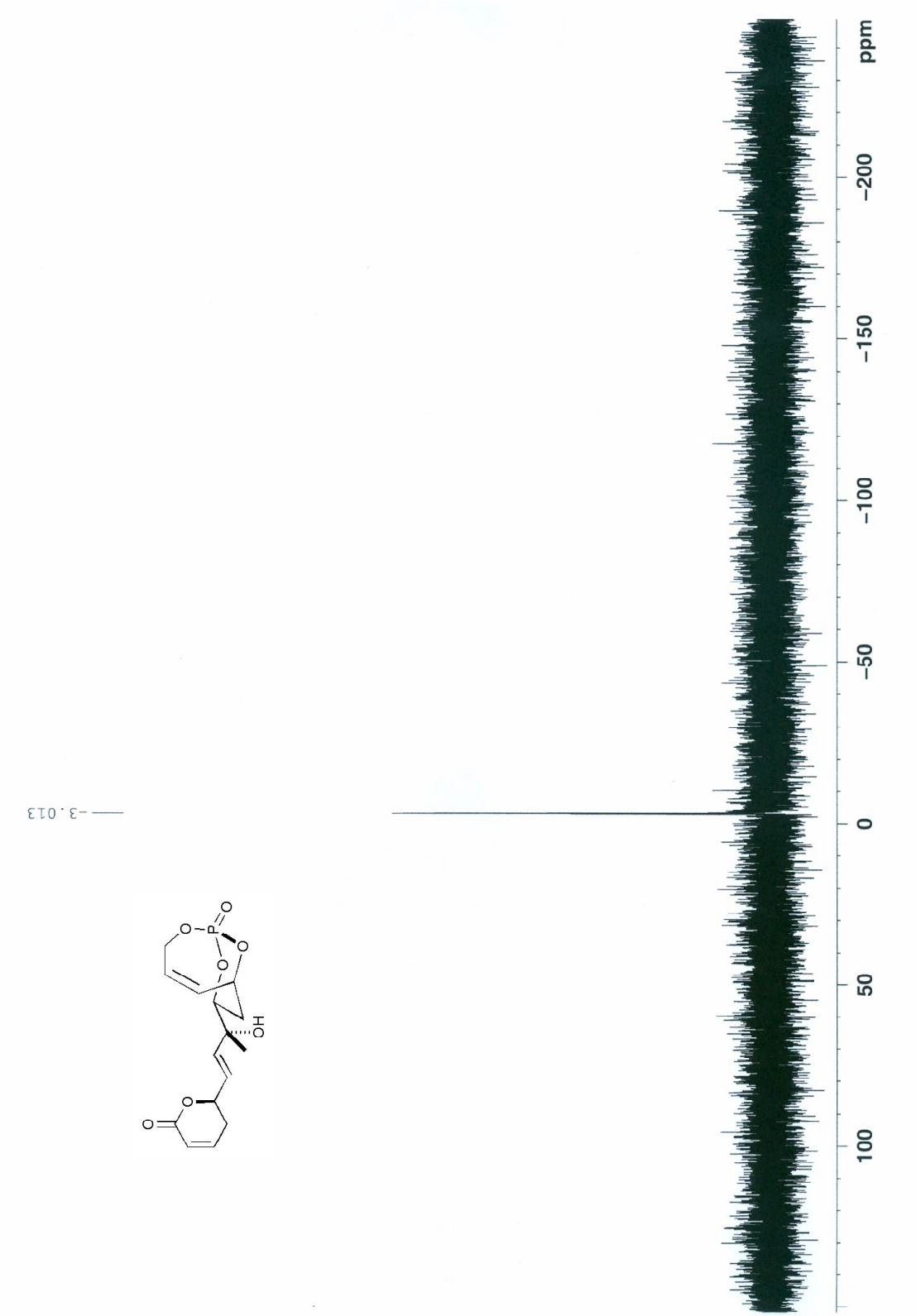
170
180
190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ppm
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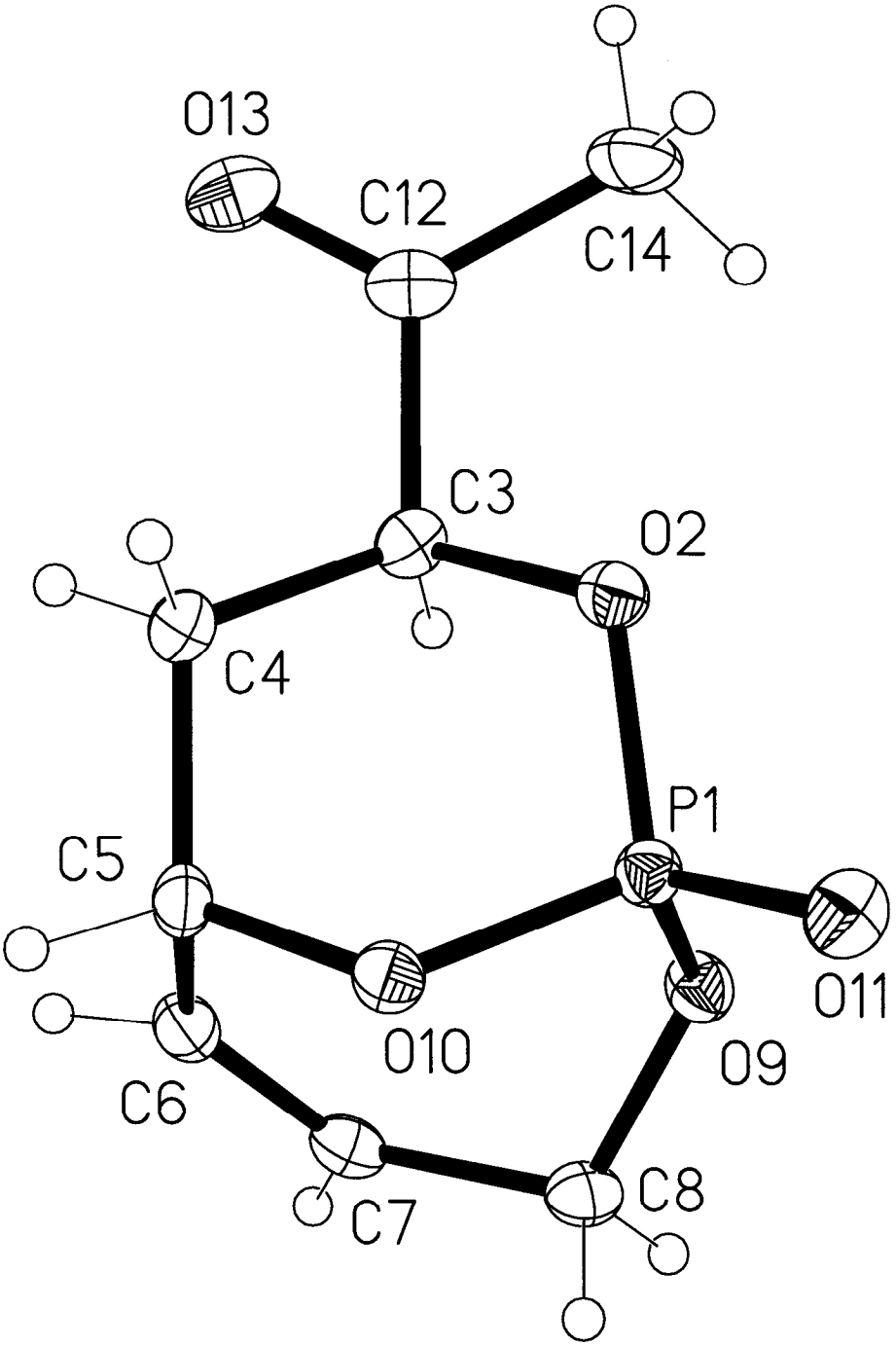
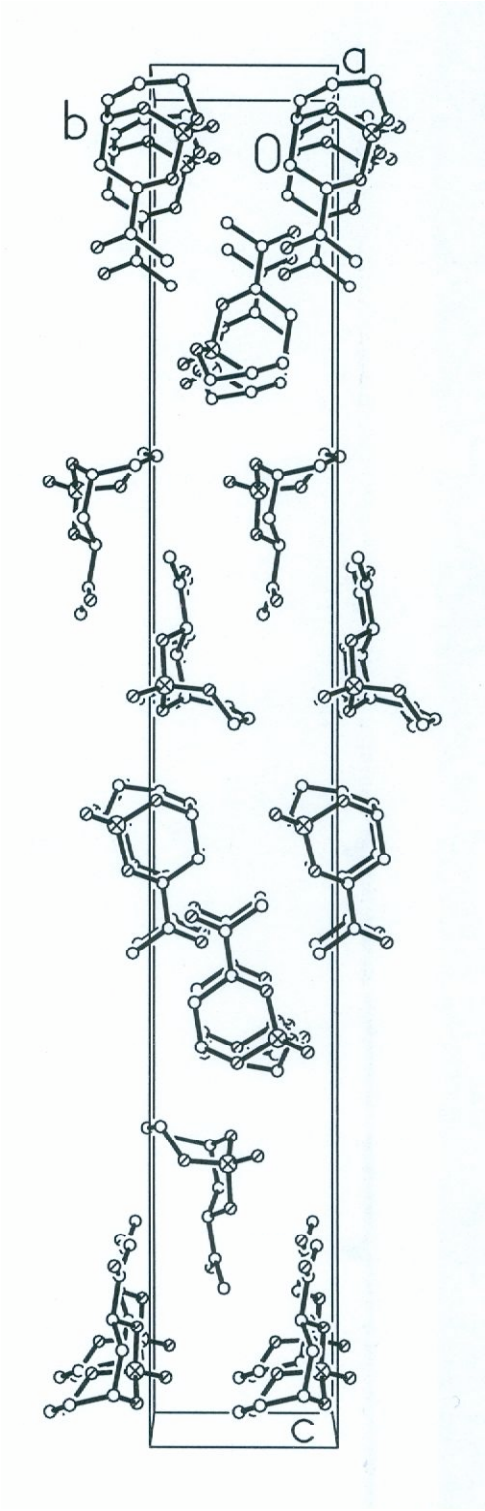
50
0
-50
-100
-150
-200
HO
O
O
O
O
O
O
O

A.4: X-ray Data for (S,S,P_R)-4.1




a
b
0
c

Comment

The displacement ellipsoids were drawn at the 50% probability level.

Experimental

A colorless plate-shaped crystal of dimensions 0.42 x 0.26 x 0.05 mm was selected for structural analysis. Intensity data for this compound were collected using a Bruker APEX ccd area detector (1) using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The sample was cooled to 100(2) K. The intensity data were measured as a series of ω oscillation frames each of 0.3 ° for 20 sec / frame. Coverage of unique data was 98.7 % complete to 26.00 degrees in θ. Cell parameters were determined from a non-linear least squares fit of 8023 peaks in the range $3.25 < \theta < 26.00°$. A total of 12193 data were measured in the range $3.25 < \theta < 26.00°$. The data were corrected for absorption by the semi-empirical method (2) giving minimum and maximum transmission factors of 0.884 and 0.986. The data were merged to form a set of 1764 independent data with R(int) = 0.0283.

The tetragonal space group $P4_32_12$ was determined by systematic absences and statistical tests and verified by subsequent refinement. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 (3). Hydrogen atom positions were initially determined by geometry and refined by a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom displacement parameters were set to 1.2 (1.5 for methyl) times the displacement parameters of the bonded atoms. A total of 127 parameters were refined against 1764 data to give $wR(F^2) = 0.0999$ and S = 1.014 for weights of $w = 1/[\sigma^2 (F^2) + (0.0700\ P)^2 + 1.3000\ P]$, where $P = [F_o^2 + 2F_c^2] / 3$. The final R(F) was 0.0360 for the 1762 observed, [$F > 4\sigma(F)$], data. The largest shift/s.u. was 0.001 in the final refinement cycle. The final difference map had maxima and minima of 0.514 and -0.211 e/Å^3, respectively. The absolute structure was determined by refinement of the Flack parameter(4).

Acknowledgment

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References

(1) (a) Data Collection: SMART Software Reference Manual (1998). Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA. (b) Data Reduction: SAINT Software Reference Manual (1998). Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

(2) G. M. Sheldrick (2002). SADABS. Program for Empirical Absorption Correction of Area Detector Data. University of Göttingen, Germany.

(3) (a) G. M. Sheldrick (2000). SHELXTL Version 6.10 Reference Manual. Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA. (b) *International Tables for Crystallography, Vol C,* Tables 6.1.1.4, 4.2.6.8, and 4.2.4.2, Kluwer: Boston (1995).

(4) H. D. Flack (1983). *Acta Cryst. A39*, 876-881.

Table 1. Crystal data and structure refinement for 05102.

Empirical formula	$C_8 H_{11} O_5 P$	
Formula weight	218.14	
Crystal system	Tetragonal	
Space group	$P4_32_12$	
Unit cell dimensions	a = 6.3256(4) Å	α= 90°
	b = 6.3256(4) Å	β= 90°
	c = 46.035(6) Å	γ= 90°
Volume	1842.0(3) $Å^3$	
Z, Z'	8, 1	
Density (calculated)	1.573 Mg/m^3	
Wavelength	0.71073 Å	
Temperature	100(2) K	
F(000)	912	
Absorption coefficient	0.292 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.986 and 0.884	
Theta range for data collection	3.25 to 26.00°	
Reflections collected	12193	
Independent reflections	1764 [R(int) = 0.0283]	
Data / restraints / parameters	1764 / 0 / 127	
$wR(F^2$ all data)	$wR2$ = 0.0999	
R(F obsd data)	$R1$ = 0.0360	
Goodness-of-fit on F^2	1.014	
Observed data [I > 2σ(I)]	1762	
Absolute structure parameter	0.10(14)	
Largest and mean shift / s.u.	0.001and 0.000	
Largest diff. peak and hole	0.514 and -0.211 e/$Å^3$	

$wR2 = \{ \Sigma [w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2] \}^{1/2}$

$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters for 05102. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
P(1)	0.41655(9)	0.32242(9)	0.699432(11)	0.01397(18)
O(2)	0.4293(2)	0.3823(2)	0.66616(3)	0.0167(4)
C(3)	0.3051(3)	0.5642(3)	0.65674(4)	0.0165(5)
C(4)	0.3620(3)	0.7566(4)	0.67479(5)	0.0173(5)
C(5)	0.3157(4)	0.7218(3)	0.70697(4)	0.0157(5)
C(6)	0.0850(4)	0.7083(4)	0.71416(5)	0.0181(5)
C(7)	-0.0262(4)	0.5432(4)	0.72292(5)	0.0182(5)
C(8)	0.0514(3)	0.3210(4)	0.72716(5)	0.0180(5)
O(9)	0.1808(2)	0.2467(2)	0.70304(3)	0.0170(3)
O(10)	0.4325(2)	0.5342(2)	0.71706(3)	0.0159(4)
O(11)	0.5774(3)	0.1690(3)	0.70765(3)	0.0203(4)
C(12)	0.3421(3)	0.5969(4)	0.62437(5)	0.0192(5)
O(13)	0.3219(3)	0.7730(3)	0.61422(3)	0.0253(4)
C(14)	0.3920(4)	0.4074(4)	0.60620(5)	0.0253(5)

Table 3. Bond lengths [Å] and angles [°] for 05102.

P(1)-O(11)	1.4561(17)
P(1)-O(10)	1.5697(16)
P(1)-O(9)	1.5753(17)
P(1)-O(2)	1.5800(15)
O(2)-C(3)	1.459(3)
C(3)-C(4)	1.517(3)
C(3)-C(12)	1.522(3)
C(3)-H(3)	1.0000
C(4)-C(5)	1.526(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-O(10)	1.473(3)
C(5)-C(6)	1.499(3)
C(5)-H(5)	1.0000
C(6)-C(7)	1.322(3)
C(6)-H(6)	0.9500
C(7)-C(8)	1.501(3)
C(7)-H(7)	0.9500
C(8)-O(9)	1.457(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(12)-O(13)	1.215(3)
C(12)-C(14)	1.495(3)
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800

O(11)-P(1)-O(10)	112.93(9)
O(11)-P(1)-O(9)	115.56(10)
O(10)-P(1)-O(9)	105.43(9)
O(11)-P(1)-O(2)	112.08(9)
O(10)-P(1)-O(2)	107.05(8)
O(9)-P(1)-O(2)	102.93(8)
C(3)-O(2)-P(1)	116.73(13)
O(2)-C(3)-C(4)	110.01(17)
O(2)-C(3)-C(12)	108.39(17)
C(4)-C(3)-C(12)	112.99(18)
O(2)-C(3)-H(3)	108.4
C(4)-C(3)-H(3)	108.4
C(12)-C(3)-H(3)	108.4
C(3)-C(4)-C(5)	111.75(18)

C(3)-C(4)-H(4A)	109.3
C(5)-C(4)-H(4A)	109.3
C(3)-C(4)-H(4B)	109.3
C(5)-C(4)-H(4B)	109.3
H(4A)-C(4)-H(4B)	107.9
O(10)-C(5)-C(6)	111.91(18)
O(10)-C(5)-C(4)	109.04(16)
C(6)-C(5)-C(4)	114.15(18)
O(10)-C(5)-H(5)	107.1
C(6)-C(5)-H(5)	107.1
C(4)-C(5)-H(5)	107.1
C(7)-C(6)-C(5)	129.1(2)
C(7)-C(6)-H(6)	115.5
C(5)-C(6)-H(6)	115.5
C(6)-C(7)-C(8)	127.3(2)
C(6)-C(7)-H(7)	116.4
C(8)-C(7)-H(7)	116.4
O(9)-C(8)-C(7)	112.72(17)
O(9)-C(8)-H(8A)	109.0
C(7)-C(8)-H(8A)	109.0
O(9)-C(8)-H(8B)	109.0
C(7)-C(8)-H(8B)	109.0
H(8A)-C(8)-H(8B)	107.8
C(8)-O(9)-P(1)	120.94(13)
C(5)-O(10)-P(1)	119.48(13)
O(13)-C(12)-C(14)	122.8(2)
O(13)-C(12)-C(3)	119.0(2)
C(14)-C(12)-C(3)	118.1(2)
C(12)-C(14)-H(14A)	109.5
C(12)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(12)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05102. The anisotropic displacement factor exponent takes the form:
$-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
P(1)	14(1)	14(1)	14(1)	0(1)	0(1)	-1(1)
O(2)	18(1)	18(1)	14(1)	0(1)	1(1)	1(1)
C(3)	14(1)	18(1)	18(1)	2(1)	-1(1)	1(1)
C(4)	18(1)	15(1)	19(1)	1(1)	1(1)	-2(1)
C(5)	18(1)	12(1)	17(1)	-1(1)	-1(1)	-1(1)
C(6)	21(1)	17(1)	16(1)	-2(1)	-1(1)	3(1)
C(7)	16(1)	23(1)	15(1)	-2(1)	2(1)	2(1)
C(8)	14(1)	22(1)	17(1)	1(1)	4(1)	0(1)
O(9)	16(1)	17(1)	18(1)	-2(1)	1(1)	-2(1)
O(10)	17(1)	16(1)	14(1)	-1(1)	-2(1)	-1(1)
O(11)	18(1)	20(1)	23(1)	2(1)	0(1)	0(1)
C(12)	11(1)	29(1)	18(1)	1(1)	-2(1)	-2(1)
O(13)	26(1)	30(1)	20(1)	7(1)	-1(1)	-1(1)
C(14)	31(1)	32(1)	13(1)	-2(1)	2(1)	-5(1)

Table 5. Hydrogen coordinates and isotropic displacement parameters for 05102.

	x	y	z	U(eq)
H(3)	0.1521	0.5316	0.6598	0.020
H(4A)	0.2802	0.8799	0.6678	0.021
H(4B)	0.5141	0.7886	0.6723	0.021
H(5)	0.3739	0.8463	0.7177	0.019
H(6)	0.0078	0.8363	0.7121	0.022
H(7)	-0.1713	0.5679	0.7270	0.022
H(8A)	0.1354	0.3141	0.7453	0.022
H(8B)	-0.0717	0.2258	0.7294	0.022
H(14A)	0.3651	0.4399	0.5857	0.038
H(14B)	0.3026	0.2887	0.6122	0.038
H(14C)	0.5411	0.3694	0.6087	0.038

Table 6. Torsion angles [°] for 05102.

O(11)-P(1)-O(2)-C(3)	-168.14(14)
O(10)-P(1)-O(2)-C(3)	-43.79(16)
O(9)-P(1)-O(2)-C(3)	67.06(15)
P(1)-O(2)-C(3)-C(4)	55.1(2)
P(1)-O(2)-C(3)-C(12)	179.08(14)
O(2)-C(3)-C(4)-C(5)	-60.8(2)
C(12)-C(3)-C(4)-C(5)	177.93(18)
C(3)-C(4)-C(5)-O(10)	57.2(2)
C(3)-C(4)-C(5)-C(6)	-68.8(2)
O(10)-C(5)-C(6)-C(7)	-13.4(3)
C(4)-C(5)-C(6)-C(7)	111.0(3)
C(5)-C(6)-C(7)-C(8)	-1.9(4)
C(6)-C(7)-C(8)-O(9)	-46.0(3)
C(7)-C(8)-O(9)-P(1)	76.3(2)
O(11)-P(1)-O(9)-C(8)	104.04(17)
O(10)-P(1)-O(9)-C(8)	-21.42(17)
O(2)-P(1)-O(9)-C(8)	-133.47(16)
C(6)-C(5)-O(10)-P(1)	77.1(2)
C(4)-C(5)-O(10)-P(1)	-50.2(2)
O(11)-P(1)-O(10)-C(5)	165.92(14)
O(9)-P(1)-O(10)-C(5)	-67.01(16)
O(2)-P(1)-O(10)-C(5)	42.10(16)
O(2)-C(3)-C(12)-O(13)	-153.2(2)
C(4)-C(3)-C(12)-O(13)	-31.0(3)
O(2)-C(3)-C(12)-C(14)	29.6(3)
C(4)-C(3)-C(12)-C(14)	151.8(2)