**Multivalent Activation in Temporary Phosphate Tethers:
A New Tether For Small Molecule Synthesis**

by
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Abstract

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The use of phosphate esters as temporary tethers, capable of multivalent activation is the broad focus of the dissertation research reported herein. Specifically, the utility of phosphate tethers has been demonstrated through the divalent activation of allylic C_2 -symmetric monocyclic phosphates. Within these systems, the temporary phosphate tether mediates a highly diastereoselective desymmetrization event via copper-mediated allylic alkylation. Studies were extended to include C_2 -unsymmetric monocyclic phosphates, in which steric and electronic effects were further probed. In general, the method provided access to both *syn*- and *anti*-1,2- homoallylic alcohols. We next explored multivalent activation via a temporary phosphate tether, in which all three phosphate ester appendages have been activated. This was achieved through the formation of a triply allylic bicyclic phosphate, containing unique steric and stereoelectronic properties, enabling our study of selective cleavage reactions mediated by a temporary phosphate tether. Several selective reactions were realized, taking advantage of the diverse reactivity profile possessed within the bicyclic phosphate. The application of these selective cleavage reactions towards the synthesis of non-phosphorus polyketide fragments was further shown. With the methodology in place, we turned our attention towards the synthesis of the C1-C15 fragment of the dolabelide family of macrolides. Two routes were realized, both taking advantage of the protecting group aspect, and latent leaving group ability of the temporary phosphate tether, supplying the C15-C30 fragment in 12-steps from the bicyclic phosphate. Lastly, the use of a ring-closing metathesis (RCM)/template based approach towards the production of *P*-chiral phosphono sugars was explored. The method took advantage of a diastereoselective displacement reaction at phosphorus with chiral secondary allylic alcohols, followed by RCM to afford an allylic phostone template. These templates could subsequently be stereoselectively

reacted with oxygen and nitrogen nucleophiles to afford an array of fully substituted phosphono sugars.

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CONTENTS	Page #
Title Page	i.
Acceptance Page	ii.
Abstract	iii.
Acknowledgments	v.
Table of Contents	vii.
Abbreviations	x.
Chapter 1: Introduction: Overview of Phosphate Leaving Groups in Synthesis	1
1.1. Introduction	2
1.2. Allylic Phosphates	3
1.2.1. Copper-Mediated Allylic Alkylation Reactions	4
1.2.1.1. Mechanism for Allylic Alkylation Reactions	5
1.2.1.2. Reagent and Substrate Scope	6
1.2.1.3. Asymmetric Copper-Catalyzed Alkylations	11
1.2.2. Pd(0)-catalyzed Allylic Alkylations	13
1.2.3. Miscellaneous Allylic Substitution	15
1.2.4. Allylic Carbonylation Reactions	17
1.2.5. Allylic Phosphate Anionic Equivalents	18
1.2.6. Propargylic and Allenylic Phosphate Reactions	20
1.3. Enol Phosphates	22
1.3.1. Suzuki-Miyaura Coupling	23
1.3.2. Kumada Coupling	24
1.3.3. Negishi Coupling	26
1.3.4. Stille Coupling	26
1.3.5. Carbonylation Reactions	29
1.3.6. Natural Product Synthesis	29
1.4. Aliphatic Phosphates	31
1.4.1. Reductive Cyclization Reactions	31
1.3.2. Cyclization Under Non-reducing Conditions	33
1.5. Anomeric Phosphates	34
1.6. Summary	37
1.7. References	38

CONTENTS (continued)	Page #
Chapter 2: Multivalent Activation in Temporary Phosphate Tethers	58
2.1. Introduction	59
2.1.1. Transition Metal-Catalyzed Routes to <i>P</i> -Heterocycles	59
2.1.2. Temporary Phosphate Tethers	60
2.2. Results and Discussion	62
2.2.1. Phosphate Tethers as Leaving Groups in Copper-Mediated Allylic Alkylation Reactions	62
2.2.2. Initial Studies of Monocyclic Phosphates	63
2.2.3. Anti-S _N 2'-Alkylation with C ₂ -Symmetric Monocyclic Phosphates	64
2.2.4. Anti-S _N 2'-Alkylation with C ₂ -Unsymmetric Monocyclic Phosphates	70
2.2.5. Multivalent Activation in Bicyclic Phosphates	73
2.3. Summary	82
2.2. References	84
Chapter 3: Phosphate Tether Approach to the C15-C30 Fragment of DolabelidesA	93
3.1. Introduction	94
3.1.1. Overview of the Dolabelide Family	94
3.1.2. Synthetic Studies Towards the C15-C30 Fragment	94
3.1.3. Retrosynthetic Analysis of Dolabelide	95
3.2. Results and Discussion	97
3.2.1. 1 st Generation Synthesis of the C15-C30 Fragment	97
3.2.2. 2 nd Generation Synthesis of the C15-C30 Fragment	105
3.2.3. Stereochemical Analysis of the C23 Carbinol Position	107
3.3. Summary	110
3.4. References	111
Chapter 4: <i>P</i>-Heterocyclic Building Blocks: Application to the Stereoselective Synthesis of <i>P</i>-Sugars	115
4.1. Introduction	116
4.2. Results and Discussion	118
4.3. Summary	128
4.4. References	129

CONTENTS (continued)	Page #
Chapter 5: Experimental Data	134
5.1. General Methods	135
5.2. Chapter 2 Data	136
5.3. Chapter 3 Data	190
5.4. Chapter 4 Data	225
 Appendix A: NMR Spectra	 255
 Appendix B: X-Ray Data	 331

Abbreviations

2,2-DMP	2,2-dimethoxypropane
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
aq	aqueous
Bn	benzyl
COSY	correlation spectroscopy
CM	Copper-Mediated
Cu	Copper
Cy	cyclohexyl
DCE	dichloroethane
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminum hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin Periodinane
dr	diastereomeric ratio
ee	enantiomeric excess
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
GC	gas chromatography
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography

HRMS	high resolution mass spectrometry
hr	hour
ⁱ Bu	isobutyl
IMes ₂	1,3-dimesityl-4,5-dihydroimidazol-2-ylidene
IR	infrared radiation
ⁱ Pr	isopropyl
KHMDS	potassium bis(trimethylsilyl)amide
LiAlH ₄	lithium aluminum hydride
LDA	lithium diisopropylamide
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
Mo	molybdenum
<i>N</i> -	nitrogen-
NaH	sodium hydride
<i>n</i> -BuLi	<i>n</i> -butyl lithium
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMM	<i>N</i> -methylmorpholine
NMR	nuclear magnetic resonance
[O]	oxidation
<i>P</i> -	phosphorus-
P(III)	phosphorus-(III)
P(V)	phosphorus-(V)
Pd	palladium
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl
<i>P</i> -sugar	phosphono sugar
<i>P</i> -tether	phosphorus tether
py	pyridine
RCM	ring-closing metathesis

Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
ROM	ring-opening metathesis
rt	room temperature
Ru	ruthenium
Sat'd	saturated
SM	starting material
TBP	trigonal bipyramidal
TBSOTf	tertbutyldimethylsilyl triflate
^t Bu	tertiary butyl
TCE	1,1,2,2-tetrachloroethane
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Ti	titanium
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TIPSCl	triisopropylsilyl chloride
Ts	<i>p</i> -toluenesulfonyl
Val	valine
Vitride	Sodium bis(2-methoxyethoxy)aluminum hydride
Zn	zinc
Zr	zirconium

Chapter 1

Introduction: Overview of Phosphate Leaving Groups in Synthesis

1.1. Introduction

Phosphate triesters and their derivatives are important synthetic and naturally occurring compounds due to their unique chemical properties. Among their several attributes, three of the more dominant ones include, (i) leaving group ability in both S_N2 and S_N2' displacement pathways (ii) hydrolytic stability of both mono- and dianions, and (iii) multivalent linking capabilities (tethers) in both DNA and RNA.¹ Despite their ubiquity and extensive use in nature, the use of phosphate esters as leaving groups for synthetic transformations did not surface until the late 1980's. This emergence was largely due to their stability, facile assembly, and ideal mono-anion pKa profiles, which has now placed them within the category of other widely employed leaving groups.

Classical application of phosphates in complex synthesis has focused primarily on nucleophilic displacement reactions of allylic phosphates and cross-coupling/reduction reactions with enol phosphates. In all cases, the leaving group ability of phosphate mono-anions is exploited in a phosphate triester, in which only a single-group is activated (monovalent activation), with the other two-phosphate ester groups being ancillary. This is a surprising observation when one considers the vast extent that phosphates are exploited in nature, *vide supra*. The focus of this dissertation will be on recent studies from our group employing multivalent activation via temporary phosphate tethers as applied to small-molecule synthesis. To preface this discussion, the opening chapter will provide a literature review of previous applications of monovalent activation in phosphate esters. The review will cover

seminal reports and prominent synthetic applications in the area of (i) allylic phosphate displacement reactions, (ii) enol phosphate coupling reactions, (iii) aliphatic and (iv) anomeric phosphate displacement reactions.

1.2. Allylic phosphates

The most widely utilized phosphate moiety for synthetic manipulation is the allylic phosphate. Allylic phosphates function as α/γ leaving group for allylic substitution with carbon and heteroatom nucleophiles, or as latent allylic anion equivalents. In addition to other allylic leaving groups (esters, carbonates, tosylates, halides) that have been successfully used in allylic substitution reactions, allylic phosphates have found wide application in metal-mediated transformations. The excellent leaving group capabilities of allylic phosphates make them indispensable functionalities in situations where less reactive allylic esters or carbonates fail to react. In contrast to more reactive allylic leaving groups (halides, tosylates, and triflates), allylic phosphates often offer greater stability, or can be used without extensive purification (i.e. chromatography, distillation).

Allylic phosphates (**1.3**) can be easily prepared from array of commercially available allylic alcohols, or chiral secondary allylic alcohols that can be purchased or readily accessed via a range of asymmetric methodology.² Phosphorylation conditions typically employ either neutral bases (Et_3N , pyridine, etc.) or anionic conditions (BuLi , LDA , NaH , etc.) in the presence of an allylic alcohol **1.1**, and commercially available chlorophosphate reagents **1.2** (Scheme 1.1). While the

stability of allylic phosphates varies between substrates, they can typically be purified via column chromatography.

Scheme 1.1

1.2.1 Copper-Mediated Allylic Alkylation Reactions

One of the most extensive uses of allylic phosphates has been as electrophiles for copper-mediated (CM) alkylation reactions. In lieu of earlier reports of phosphate leaving groups in CM allylic alkylation reactions,³ it was not until the early-to-mid 1990's that CM alkylation of allylic phosphates found regular employment in synthesis. In 1991, separate reports by Tanaka⁴ and Yamamoto⁵ touted the exceptional S_N2', γ-regioselective displacement of allylic phosphates within elaborate synthetic systems (1.4 and 1.6) using both mixed zinc-copper and magnesium-copper systems respectively (Scheme 1.2, eq. 1 and 2). Yamamoto and coworkers included studies of the *anti*-S_N2' nature of the allylic phosphate displacement reactions, comparing them to other allylic leaving groups (Scheme 1.2, eq. 2). The authors noted the "superiority" of phosphates leaving groups relative to their chloride and sulfonate counterparts in terms of regioselectivity, geometry of the formed olefin, and preferential *anti*-addition relative to the phosphate leaving group, which occurred with high levels of chirality transfer.⁶

Scheme 1.2

1.2.1. Mechanism for Copper-Mediated Alkylations.

Mechanistic and synthetic studies of both allylic esters and carbonates have shed light on the mechanism for CM-reactions with allylic esters and the origin of regio- and stereoselectivity for these transformations. A general mechanism was first put forth by Corey for the reaction of Cu(I) reagents with allylic esters in which he described the occupied d-orbitals of copper as having overlap with both the π^* and σ^* orbitals of the allylic ester (**1.8**, Figure 1.1).⁷ It was proposed that addition occurs via a nonsymmetric concerted pathway with extensive bond lengthening of the ester leaving group as a result of occupied d-orbital to σ^* interactions. Goering, Backvall and others have extended this discussion to include a Cu(III) intermediate in which addition of the copper reagent first occurs at the γ -position (**1.10a**).⁸ The η^1 -Cu(III) complex subsequently can undergo either reductive elimination to form the γ -coupled **1.1**, or can slip to the π -allyl intermediate **1.10b** which is in equilibrium with the η^1 -Cu(III) at the α -position (**1.10c**). Subsequently, **1.10c** can undergo reductive elimination to afford the α -coupled product **1.12**.

Figure 1.1. *Asynchronous Concerted and Step-wise Mechanisms*

1.2.2. Reagent and Substrate Scope for CM-Allylic Alkylation Reactions

The copper source in allylic phosphate alkylations has a strong impact on the α,γ -selectivity of nucleophilic addition.⁹ Typically, CuCN is employed for S_N2' displacement reactions, showing high preference for γ -coupling. CM displacement reactions commonly make use of organozinc or organomagnesium reagents. However, numerous organometallic species have proven effective transmetallating reagents for the formation of mixed-metal organocuprates capable of allylic phosphate displacements (Scheme 1.3). Although some the better examples in terms of yield and selectivity are given, in general these “alternative” organometallic sources react with preference for γ -coupling with CuCN, even with S_N2 activated primary cinnamic phosphates. Both triorgano-aluminum¹⁰ and indium reagents¹¹ were found to produce high levels of γ -alkylation with allylic phosphates (**1.13**), in the presence of catalytic amounts of varying copper sources (optimal conditions shown). While allylic phosphates were the preferred leaving groups for aluminum-derived cuprates, organoindium cuprates showed comparable results for both allylic phosphates and halides. Furthermore, regioselectivity for allylic phosphate

displacement with organocopper-indium reagents was dependent on the triorganoindium sources, with Ph₃In providing a 1:1 γ : α mixture with allylic phosphates. This result is in accordance with other reports of sp²-organocopper allylic alkylation reagents which provide decreased γ -selectivity,¹² presumably due to competing isomerization via a π -allyl complex to the terminal σ -complex at the α -position. In comparison, organotitanium reagents provided high levels of γ -coupled substrates in excellent yields.¹³ Furthermore, secondary allylic phosphates underwent smooth *anti*-S_N2' displacement in the presence of organotitanium-copper reagents. Allyl phosphates were found to be the preferred allylic electrophiles for coupling with *in situ* derived organozirconium **1.15**.¹⁴ Reactions were run with stoichiometric amounts of copper reagent, affording high levels of regioselectivity for γ -position with a broad range of allylic phosphate substrates, with α -coupling observed relative to the allylic zirconium **1.15**. The effectiveness of S_N2' CM allylic phosphate displacement reactions with a wide variety of organometallic reagents is further exemplified by the sharp contrast observed when either Ni or Fe catalysts are employed.⁹ Yamamoto and coworkers demonstrated that both Ni and Fe catalysts with Grignard reagents provides exclusive S_N2 displacement at the α -position to afford products (**1.18**) in both high yields, and high regioselectivity. Grignard displacements without metal additives also show preference for S_N2, α -selective displacements, but with decreased regioselectivity.¹⁵

Scheme 1.3

The overall utility of CM-allylic phosphate is exemplified in the versatility and complexity of both donating alkyl functionalities and the acceptor allylic phosphate moieties employed in these transformations. Complex allylic phosphates have been utilized in CM- $\text{S}_{\text{N}}2'$ displacement reactions for the synthesis of natural products and other bioactive molecules of interest.¹⁶ Mourino and coworkers eloquently demonstrated the versatility of the CM-allylic phosphate alkylations in which a single secondary allylic phosphate was converted into several vitamin-D₂ analogs (Scheme 1.4).¹⁷ The observed chirality transfer was excellent for the secondary allylic phosphates, providing analogs in good yields (not shown). The authors further demonstrated the stability and “protecting group” capability of a secondary allylic phosphate via the Horner-Wittig olefination reaction performed in the presence of allylic phosphate **1.19** (Scheme 1.4). Following olefination, $\text{S}_{\text{N}}2'$ γ -coupling with a methylmagnesium Grignard derived cuprate afforded the synthetic target 1 α ,25-dihydroxyvitamin D₂ **1.20** in good yield and with excellent diastereoselectivity.

Scheme 1.4

The diversity of alkylating reagents employed in CM-allylic phosphate alkylations has expanded the breadth of accessible substrates available from the allylic phosphate moiety. In several reports,¹⁸ Backvall and coworkers have studied the reactivity of primary and secondary allylic phosphates with organosilylcuprates derived via the *in situ* treatment of coppersilane reagents with acetylenes, styrenes, allenes, and 1,3-dienes (last example shown in Scheme 1.5). A representative example shows that when 1,3-diene **1.21** is treated with a coppersilane reagent, nucleophilic silylated allylcuprate intermediate **1.22** is formed, which is in equilibrium via a π -allyl complex with regioisomer **1.23**. When intermediate cuprate reagents **1.22** and **1.23** were reacted with highly reactive electrophiles such as H₂O or I₂, varying ratios of regioisomers were reported. With allylic phosphates, however, nearly complete regioselective formation of **1.25** and **1.27** was observed, via coupling of the σ -allyl cuprate **1.23** (>98 % rs). Interestingly, while phosphates **1.24** and **1.26** might both be expected to afford γ -coupled substrates, branched and linear respectively, they divergently provided linear products in which **1.24** is γ -coupled and **1.26** is α -coupled. The authors rationalize the observed regioselectivity via a Cu(III)

intermediate formed plausibly from reaction of cuprate **1.23** with either of phosphates **1.24** and **1.26** to form a σ -allyl complex at γ -position of the phosphate. The reaction with allylic phosphates however only proceeds via terminal coupling, and in the case of primary phosphate **1.26** must slip to the primary σ -complex, presumably via a π -allyl intermediate, prior to coupling.

Scheme 1.5

Knochel and coworkers demonstrated the scope of CM-allylic phosphate reactions with various mixed and functionalized organozinc reagents with chiral cyclic 2-iodo substituted allylic phosphates (Scheme 1.6).¹⁹ Polyfunctionalized organozincates, in the presence of CuCN , underwent coupling with 2-iodocyclohexenyl phosphate **1.28** in good yield, and with high levels of chirality transfer. Although in less sterically encumbered systems, pentafluorobenzoates were comparable leaving groups to phosphates in terms of chirality transfer and yield, more sterically demanding systems (**1.28**) proceeded in higher yields when phosphate-leaving groups were employed.^{19a}

Scheme 1.6

1.2.1.3. Asymmetric Copper-Catalyzed Allylic Alkylation Reactions

In addition to the numerous studies of chirality transfer within enantioenriched secondary allylic phosphates, researchers have endeavored to develop catalytic asymmetric CM-allylic phosphate alkylation reactions in which primary- or secondary *meso*-allylic phosphates afford chiral alkylation products starting from achiral allylic phosphates.

Hoveyda and coworkers have published a number of reports of allylic alkylation reactions employing CM-catalysis with phosphate leaving groups.²⁰ Highlights of this asymmetric method include general substrate compatibility with a variety of substituted allylic phosphates in which high levels of both $\text{S}_{\text{N}}2'$ addition and asymmetric induction are observed. An early report by Hoveyda probed the use of Schiff base ligands for asymmetric alkylation of α,β -unsaturated allylic phosphate esters, for the construction of α -substituted esters (Scheme 1.7).^{20c} Treatment of **1.30** with catalytic amounts of $\text{Cu}(\text{OTf})_2$ and ligand **1.31** and stoichiometric amounts of diorganozinc reagents afforded substrates **1.32** in good yields and with high enantiomeric excess (ee). The method was further highlighted via a brief synthesis of (-)-elenic acid **1.33**. Hoveyda and coworkers have additionally utilized tri-substituted aliphatic allylic phosphates to generate quaternary carbon centers^{20e} with both chiral

Schiff bases and N-heterocyclic carbenes ligands^{20f} with good-to-excellent levels of asymmetric induction. An interesting aspect of these asymmetric alkylation reactions is the apparent role of the phosphate moiety for obtaining high levels of ee.^{20a} Hoveyda found that when allylic bromides were incorporated, <2% ee was observed. Moreover, when an allylic thioester phosphate-leaving group was used, substrates were formed with both low conversion and in low ee.

Scheme 1.7

Piarulli, Gennari, and coworkers explored asymmetric CM-allylic alkylations for desymmetrization of *meso* cyclic di-allylic phosphates.²¹ As with Hoveyda's allylic alkylation reactions, $\text{Cu}(\text{OTf})_2$ was the preferred copper source for catalytic asymmetric desymmetrization in the presence of chiral Schiff-base ligands. In addition, phosphoramidite ligands **1.35** were found to be effective for asymmetric desymmetrization of six- and seven-membered bis-phosphates affording *anti*- $\text{S}_{\text{N}}2'$ products with excellent regioselectivity and in good to excellent ee's (Scheme 1.8). In the case of achiral bis-phosphate **1.34**, catalytic Cu(I)-phosphoramidite complex of **1.35** in the presence of diethyl zinc afforded **1.36** as a single diastereomer and in 86% ee.

Scheme 1.8

1.2.2. Pd(0)-Mediated Allylic Phosphate Substitution Reactions.

Metal-promoted allylic substitution reactions with Pd(0) catalysts, using either carbon enolate or heteroatom nucleophiles, have predominantly employed carbonate leaving groups, which more readily undergo oxidative addition with the Pd(0) catalyst than allylic phosphate and carboester derivatives.²² Despite this, several examples of allylic phosphate displacements with both carbon and heteroatom have been reported. In 1981, Tanigawa and coworkers demonstrated the first examples of Pd(0)-catalyzed allylic phosphate displacement reactions with both amines and malonates (Scheme 1.9).²³ In general, allylic displacement occurred in high yields and with good stereoselectivity for the formed olefin, regardless of the starting olefin geometry. The high reactivity of allylic phosphates towards Pd(0)-catalyzed substitution reactions, under mild reaction conditions, is evident in substrates **1.38** and **1.39**, in which phosphate displacement occurs with complete chemoselectivity over an allylic acetate.

Scheme 1.9

The same chemoselectivity was observed with both azide and chelated enolate amino acids nucleophiles in the presence of doubly allylic esters **1.40** (Scheme 1.10).²⁴ Catalytic Pd(0) in the presence of NaN_3 afforded the primary azide in a 4:1 ratio of linear to branched product, with complete *E*-olefin geometry. With a zinc-chelated amino ester, complete regio- and chemoselectivity was observed, with preservation of the *Z*-olefin geometry (**1.42**). Hydroxylamines have additionally been employed as nucleophiles for Pd(0)-catalyzed alkylations, and similarly exhibit complete chemoselectivity with di-allylic esters to afford **1.41**.²⁵ Additional nucleophiles for Pd(0)-catalyzed allylic phosphate alkylation reactions include α -isocyanoacetates,²⁶ α,α -disubstituted amino-acid esters,²⁷ pyrimidines,²⁸ ketone enolates,²⁹ Grignard reagents,³⁰ and unsymmetric β -keto esters.³¹

Scheme 1.10

In addition to achiral alkylation reactions, high levels of chirality transfer has been observed under Pd(0) catalysis with chiral secondary allylic phosphates. Allylic cyanohydrin **1.43**, which could be generated in enantioenriched form from the corresponding α,β -unsaturated aldehyde, underwent allylic substitution with both

amine and oxygen nucleophiles to afford **1.44** and **1.45** with excellent olefin geometry and chirality transfer (Scheme 1.11).³² Interestingly, the authors note that within the systems probed, allylic phosphates typically afforded higher selectivity in terms of γ -substitution and selectivity for the *E*-olefin geometry, when compared with similar carbonate derivatives, under both palladium and iridium catalysis.^{32a}

Scheme 1.11

1.2.3. Other Metal-Mediated Allylic Substitution Reactions.

In contrast to Pd(0) catalyzed allylic alkylation reactions which primarily have utilized carbonate or carboester leaving groups, allylic phosphates have found wider application with other metal-catalyzed systems employed in allylic substitution reactions. Complimentary to the favored linear substitution pattern of Pd(0)-catalyzed allylic substitution reactions, alternative metal catalysts that favor branch substituted products have been explored for allylic alkylation reactions with acyclic esters, specifically in the context of asymmetric synthesis. Prominent examples of allylic phosphate displacement reactions have been found with Ir,³³ W,³⁴ Fe,³⁵ Ti,³⁶ and Mo-³⁷ catalysts, in which in certain cases, phosphate esters have been the preferred allylic ester moiety.

In 2003, Takemoto and coworkers employed allylic phosphates for enantio- and diastereoselective allylic alkylation reactions with glycinic ester **1.47**, in the

presence of a Ir-phosphite catalyst system (Scheme 1.12).^{33d} Good yields and good to excellent ee's were observed with moderate to high levels of *syn:anti* diastereocontrol. The *syn/anti* diastereoselectivity was largely dependant on the choice of base. By switching the base from aqueous KOH to LHMDS, the predominant *anti*-isomer was obtained.

Scheme 1.12

Pfaltz and coworkers utilized the enriched reactivity of allylic phosphates as substrates for asymmetric tungsten-catalyzed allylic alkylation reactions (Scheme 1.13).³⁴ Allylic carbonates were found to be, in most situations, unreactive with the tungsten catalysts, requiring the use of allylic phosphates **1.46**. Use of 10-mol % of catalyst **1.50** produced high levels of branched, γ -substituted malonates in good yields and high ee.

Scheme 1.13

Sato and coworkers have explored a number of Ti-mediated intramolecular cyclization reactions with alkyne tethered allylic phosphates substrates (Scheme 1.14).³⁸ In the presence of a $\text{Ti}(\text{O}^i\text{Pr})_4$ and $^i\text{PrMgCl}$, substrate **1.51** undergoes cyclization to form the substituted cyclopentane **1.53** in good yield with excellent chirality transfer and *E*-olefin geometry (Scheme 1.14). It was found that the *E*-configured olefin geometry of **1.53** could be reversed by switching from an allylic phosphate leaving group to an allylic silyl ether. The authors rationalized the observed selectivity via transition state **1.52**, in which the preferred *anti*-coplanar alignment of the phosphate leaving group relative to the Ti(IV)-metallocycle intermediate imparts high levels of the observed *E*-selectivity.

Scheme 1.14

1.2.4. Allylic Phosphate Carbonylation Reactions.

A powerful subset of the allylic phosphate alkylation reaction is allylic carbonylation. While allylic halides are reactive towards carbonylation, allylic alcohol derived carboesters typically require harsher reactive conditions. The π -allyl complexes of allylic acetates that result from initial oxidative insertion with palladium are in equilibrium with starting material, and therefore compete with CO as a nucleophile. The low reactivity of CO nucleophiles therefore typically requires either harsh conditions, or more reactive electrophiles (less nucleophilic leaving

groups). As such, allylic phosphates have found broader utilization for carbonylation reactions employing Pd,³⁹ Rh,⁴⁰ and Ir⁴¹ complexes. In 1988, Murahashi and coworkers demonstrated that allylic phosphates undergo carbonylation under mild conditions to afford α -substituted β,γ -unsaturated esters of type **1.54** (lower left example, Scheme 1.15).⁴² Allylic acetates were found to react under similar conditions, but required catalytic amounts of NaBr as an additive.⁴³ Allyl phosphates have additionally been used in carbonylation reactions towards unsymmetrical ketones (**1.57**),⁴⁴ and β -lactams (**1.58**) under Pd(0)-catalysis.⁴⁵ By switching to a Rh-catalyst, amide derived substrates (**1.55**) could be formed selectively over competing amination products in good yields.⁴⁶

Scheme 1.15

1.2.5. Allylic Phosphate Anionic Equivalents.

In contrast to reactions that utilize allylic phosphate substrates as electrophiles for neutral and anionic nucleophiles, another class of metal-mediated reactions has explored the use of allylic phosphates as an allylic anion equivalent, for reaction with an electrophilic source. Examples of electrophilic trapping of an allylic phosphate

anion equivalent has been shown with $\text{Sm}(\text{I})_2$,⁴⁷ $\text{In}(0)$,⁴⁸ and $\text{Cr}(\text{Cl})_2$ ⁴⁹ metal-promoters.

One of the more synthetically useful applications of allylic phosphate derived anions, is that of the Hiyama-Nozaki type reaction, in which an allylic anion is reacted with a carbonyl functionality in the presence of a $\text{Cr}(\text{II})$ -source. Knochel and coworkers extensively probed the reaction with allylic phosphates,⁵⁰ in which various substituted phosphates were reacted with saturated and unsaturated aldehydes (**1.16**). The reactions proceeded with excellent γ -regioselectivity (nucleophilic addition at the more substituted position), and high levels of diastereoselectivity, rationalized via the six-membered transition state **1.60**. When β -substituted or γ -disubstituted olefins are employed, the stereoselective outcome of the reaction is dependant on the configuration of the starting material olefin due to unfavorable isomerization of intermediate **1.60**. Under the reaction conditions probed, allylic phosphates were found to be less reactive with ketones, requiring the more reactive allylic mesylate esters.

Scheme 1.16

Similarly, $\text{Sm}(\text{II})$ -reagents were shown to undergo anionic cross-coupling reactions with allylic phosphates (left-side, Scheme 1.17).^{47a} In comparison to $\text{Cr}(\text{II})$ -systems, $\text{Sm}(\text{II})$ readily promoted the allylic addition with a range of ketone moieties. While reactions were typically high yielding, low regioselectivity was often observed.

Sm(II) reagents have additionally been used to reduce allylic phosphates in the presence of a proton source.^{47b} The regioselectivity of protonolysis was dependant on the size of the proton source, with bulky ^tBuOH favoring the α -product **1.64** in a 4:1 ratio.

Scheme 1.17

1.2.6. Metal-Promoted Propargylic/Allenlyc Phosphate Reactions

With properties akin to allylic phosphates, propargylic and allenlyc phosphate esters have additionally been probed as leaving groups in metal-mediated displacement reactions, albeit to a lesser degree. Metals used within this class of reactions include Cu(I),⁵¹ Pd(0),⁵² Al(X),⁵³ and Ti(IV) reagents.⁵⁴

An interesting application was for the formation of carbapenam skeletons (**1.66**) via an intramolecular cyclization reaction of β -lactam **1.65** (Scheme 1.18).⁵² In the presence of Pd₂(dba)₂, propargylic phosphate **1.65** forms an intermediate η^3 -propargyl palladium complex, which can subsequently react with the β -lactam portion of **1.65**, subsequently forming a reactive η^3 -allyl palladium complex. Subsequent reaction with sodium acetate affords adduct **1.66** in good yield and diastereoselectivity. Within this sequence, the propargylic phosphate ester was found to be the favored leaving group compared with benzoate leaving groups, providing the desired adducts in slightly better yields.

Scheme 1.18

In contrast to electrophilic propargylic phosphate reactions shown above, Sato and coworkers have demonstrated a number of examples of nucleophilic propargylic phosphate substitution reactions with a variety of electrophiles.⁵⁴ The reaction proceeds via an *in situ* derived allenyltitanium complex **1.68**, formed from the treatment of propargylic phosphate **1.67** with $\text{Ti}(\text{O}^i\text{Pr})_4$ and $^i\text{PrMgCl}$ (Scheme 1.19). An intriguing application of this chemistry is reaction of **1.68** with an array of Michael acceptors, in which high levels of chirality transfer from phosphate **1.67** to the 1,4-adduct **1.69** was observed.^{54a} The reactions proceeded with high levels of chirality transfer and diastereoselectivity to produce products in good yields.

Scheme 1.19

One of the few examples¹⁴ of allenic phosphate transformation was demonstrated by Murahashi, Imada, and coworkers for the asymmetric amination of racemic allenic phosphates (Scheme 1.20).⁵⁵ A variety of substituted phosphates (**1.70**) underwent amination with moderate to excellent observed levels of enantioselectivity.

Scheme 1.20

1.3. Metal-Mediated Enol Phosphate Cross-Coupling Reactions

One of the more widely employed uses of phosphates in organic synthesis is that of metal-catalyzed cross-coupling reactions of keto- and ester-derived enol phosphate derivatives. Enol phosphates function as good electrophiles for a host of cross-coupling reactions employing nucleophilic reagents commonly used in Pd(0)-catalysis (organotin reagents, alkynes, boronic acids, etc.), in addition to less common organometallic coupling partners.⁵⁶ In contrast to the analogous enol triflates, which require expensive triflating reagents (N-phenyltrifluoromethane sulfonimide, $\text{PhN}(\text{Tf})_2$), enol phosphates can be produced from cheap, commercially available monochloride phosphates **1.2**. Furthermore, compared to the more reactive enol triflate, enol phosphates offer greater stability, and can often be purified by silicon chromatography. They are commonly prepared through the reaction of keto- or ester enolates and phosphoryling reagents **1.2** (Scheme 1.21). Additionally, enol phosphates can be formed via the Perkow reaction between an α -chloro ketone (**1.73**) and phosphite reagent.

Scheme 1.21

1.3.1. Suzuki-Miyaura Cross Coupling Reactions.

One of the more common coupling protocols for enol phosphates is metal catalyzed cross-couplings with arylboronic acids (Suzuki-Miyaura coupling). An initial example of enol phosphate couplings with aryl boronic acids was recently demonstrated by Yang and coworkers, who showed that in the presence of a Ni(0) catalyst, non electron poor enol phosphates readily underwent cross-coupling with aryl boronic acids in moderate to good yields.⁵⁷ When Pd(0) catalysts were used, little to no product was observed, owing to the lower reactivity of the keto-derived enol phosphates towards oxidative insertion. Coudert and coworkers reported the extension of Suzuki-type cross coupling reactions to include electron poor (activated) ketene aminal phosphates (Scheme 1.22, eq 1).⁵⁸ Employing Pd(PPh₃)₄, a variety of aryl and heteroaryl boronic acids were successfully coupled with enol phosphate **1.74** under mild reaction conditions, affording products in good to excellent yields. Occhiato and coworkers demonstrated that vinyl boronic acids also provided suitable cross-coupling partners for the Suzuki-Miyaura coupling (Scheme 1.22, eq 2).⁵⁹ Imide derived ketene aminal phosphate **1.76** readily underwent cross coupling with a variety of both vinylboronic acids and esters to afford to afford *E*-configured external olefins in good yield. Substrate **1.76** was additionally reported to undergo Stille and Sonagashira type couplings (not shown).

Scheme 1.22

Begtrup and coworkers extended vinyl phosphate Suzuki-Miyaura coupling to include Pd(0) catalyzed cross coupling of non-activated (non-electron poor) enol phosphates derived from 4-piperidone.⁶⁰ This was achieved employing microwave heating in the presence of Pd(OAc)_2 and Buchwald's 2-(di-*tert*-butylphosphino)-biphenyl ligand to afford a variety of aryl coupled products in moderate yields. The authors also reported one of the few examples of a Fe(acac)_3 catalyzed Grignard cross-coupling reaction with enol phosphates, generating aliphatic substituted **1.78a** in reasonable yield.

Scheme 1.23

1.3.2. Kumada Cross Coupling Reactions.

In addition to Suzuki-type couplings, both Grignard and cuprate reagents⁶¹ have been exploited as cross coupling partners with enol phosphates substrates. In 1981, Kumada and coworkers were the first to demonstrate cross-coupling reactions

between a Grignard reagent and enol phosphates (Kumada coupling).⁶² In the presence of both Pd(0) and Ni(0) catalysts, silylmethylmagnesium halides underwent cross coupling with cyclic, acyclic, conjugated, and non-conjugated enol phosphate substrates to afford both aliphatic (**1.79a**) and aromatic (**1.79b**) allylsilanes in moderate to excellent yields (Scheme 1.24). In the same year, Kumada and coworkers reported similar Nickel-catalyzed cross-couplings between aryl phosphates with both Grignard and organoaluminum reagents.⁶³ Claesson and coworkers extended Kumada couplings of enol phosphates to include Nickel-catalyzed cross-coupling reactions with vinyl Grignards to produce substituted diene moieties.⁶⁴ Backvall and coworkers similarly explored the formation of substituted dienes via cyclic and acyclic α,β -unsaturated ketone derived enol phosphate couplings with aliphatic and aromatic Grignard reagents.⁶⁵

Scheme 1.24

Miller further demonstrated both the efficiency and potential of Kumada couplings of enol phosphates via a one-pot phosphorylation and cross-coupling sequence (Scheme 1.25).⁶⁶ Enol phosphate **1.81**, *in situ* derived through pretreatment of **1.80** with one equivalent of mesityl Grignard, was subsequently reacted with both alkyl and aromatic Grignard reagents in the presence of $\text{Cl}_2\text{Pd(PPh}_3)_2$. The reaction

proceeded with a range of both ketone substrates and Grignard reagents to afford coupled products in good to excellent yields (**1.82a**).

Scheme 1.25

1.3.3. Negishi Cross Coupling Reactions.

While few examples exist, organozinc reagents have also been found to be viable cross-coupling partners with enol phosphate substrates. In addition to early reports for Negishi-type coupling reactions of ketene aminal phosphates,⁶⁷ Yang and coworkers demonstrated zincate compatibility with coumarin derived enol phosphate **1.83** (Scheme 1.26).⁶⁸ NiCl₂(dppe)₂ catalyzed Negishi coupling with a variety of aliphatic, aromatic, and functionalized organozinc halides afforded array of 4-substituted coumarin analogs in moderate to good yields under notably mild reaction conditions.

Scheme 1.26

1.3.4. Stille Cross Coupling Reactions.

One of the more investigated and widely employed form of enol phosphate coupling reactions is the Stille-type coupling of organotin reagents. In seminal work

by Nicolaou and coworkers,⁶⁹ they described the use of ketene acetal phosphates as stable counterparts to volatile ketene acetal triflates and illustrated the comparable reactivity profile of the enol phosphates to access complex ether structures (Scheme 1.27). Substrate **1.85** was shown to undergo Stille coupling with the complex organotin reagent **1.86** in the presence of a Pd(0) catalyst to afford the advanced cyclic ether **1.85b**. Additionally, substrate **1.85** could itself be coupled with hexamethyldistannane to afford the advanced vinyltin product **1.85a**. Nicolaou and coworkers further highlighted both the convenience and reactivity of ketene acetals phosphates for Stille coupling reactions towards the synthesis of the EFGH ring system as part of the total synthesis of brevetoxin A.⁷⁰

Scheme 1.27

Nicolaou and coworkers extended the methodology to include the first example of metal-catalyzed cross-coupling reactions with ketene aminal phosphates,⁶⁷ exploring their reactivity in the context of Stille (**1.86c**), Kumada (**1.86a**), Sonagashira (**1.86d**), and Negishi (**1.86d**) couplings (Scheme 1.28). Reaction conditions employed both Ni(0) and Pd(0) catalysts, which under mild reaction conditions afforded array of substituted cyclic enamines in good to excellent yields.

Scheme 1.28

Coudert and coworkers additionally explored the use of Stille couplings with ketene acetal phosphates and vinyl, aryl, and heteroaryl organotin reagents (Scheme 1.29).⁷¹ Benzoxazine substrates (**1.87a**) were generated in good to excellent in the presence of Pd(0) catalysis in refluxing THF. Ketene acetal phosphates could additionally be reduced in the presence of formic acid and Pd(0).

Scheme 1.29

Jiang and coworkers exploited the use of the Stille coupling reaction of ketene acetal phosphates in a one-pot tandem Stille/Diels-Alder sequence for the construction of substituted piperidines (Scheme 1.30).⁷² Following Stille coupling of **1.88** with tetravinyltin, the *in situ* derived diene **1.89** readily underwent Diels-Alder cycloaddition to afford several complex piperidine adducts in good yields from ketene aminal phosphates **1.88**.

Scheme 1.30

1.3.5. Pd(0)-Catalyzed Carbonylation Reactions.

Sazaki and coworkers demonstrated one of the few examples of Pd-catalyzed carbonylation reactions of enol phosphates in 2000 (Scheme 1.31).⁷³ Ketene acetal phosphates (**1.92**) were smoothly converted to the α,β -unsaturated esters in good yields and with general substrate compatibility in the presence of PdCl₂(dppf) as catalyst. In 2002, Sazaki and coworkers utilized the enol phosphate carbonylation sequence as a key transformation in the synthesis of the FGHIJKLM ring fragment of ciguatoxins.⁷⁴

Scheme 1.31

1.3.6. Enol Phosphate Cross-Couplings Reactions in Natural Product Synthesis.

The utility and substrate compatibility of enol phosphate cross-coupling reactions is evident in its extensive use in natural product synthesis.⁷⁰ One of the first applications of enol phosphate coupling in natural product synthesis was in 1988, when Danishefsky and coworkers employed a Kumada-type coupling for the construction of heptelidic acid (Scheme 1.32).⁷⁵ Treatment of the β -keto ester derived enol

phosphate **1.94** with $\text{TMSCH}_2\text{MgCl}$ in the presence of a $\text{Ni}(0)$ catalyst afforded allylsilane **1.95** in 86% yield.

Scheme 1.32

Sasaki and coworkers demonstrated a late-stage Suzuki cross coupling reaction between ketene acetal phosphate **1.96** and enol ether **1.97** (Scheme 1.33).⁷⁶ The impressive coupling proceeded in good yields to afford **1.98**, linking the HI and K ring fragments found in a number of polycyclic ether marine toxins including ciguatoxin (Scheme 1.33). Sasaki and coworkers later employed a similar Suzuki coupling transformation of a ketene acetal phosphate in the total synthesis of gambierol, in which the highly convergent coupling united two late-stage intermediates.⁷⁷

Scheme 1.33

In 2000, Coe highlighted the first use of an enol phosphate for the intramolecular Heck reaction (Scheme 1.34).⁷⁸ Mild heating of ketene aminal phosphate **1.99**, in the presence of catalytic $\text{Pd}(\text{OAc})_2$ afforded the tricyclic lactam **1.100** in good yield. The Heck cyclization represented the key transformation within

the brief 6-step synthesis of (±)-cytisine. The authors noted that ketene acetal phosphate **1.99** was formed quantitatively, and could be subsequently used without additional purification. While ketene acetal triflates similarly afforded Heck coupled product (52 % yield), triflate formation was typically low yielding.

Scheme 1.34

1.4. Aliphatic Phosphate Cyclization Reactions.

Allylic phosphate and enol phosphate functional groups have been widely employed in organic syntheses due to their high reactivity profiles. Under reported however is the use of less reactive aliphatic phosphates that can serve as $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ type leaving groups in nucleophilic substitution reactions. Recent efforts exploring the use of pendant aliphatic phosphates as leaving groups for intramolecular cyclization reactions with both carbon and heteroatom tethered nucleophiles for the formation of 5- to 6-membered ring systems have been reported. Aliphatic phosphates enjoy increased stability relative to their allylic- and enolic phosphate derivatives, and likewise can be readily formed under basic conditions with commercially available phosphorylating reagents, vide supra.

1.4.1. Reductive Cyclization Reactions.

In 1991, Grierson and coworkers demonstrated the ability of aliphatic phosphates to serve as leaving groups in medium-sized ring forming cyclization

reactions. They showed that aminonitriles, in the presence of potassium metal and [18]-crown-6, underwent reductive cyclization with a tethered phosphate-leaving group.⁷⁹ In 2003, Rychnovsky and coworkers explored reductive cyclizations of 2-cyanotetrahydropyrans containing a tethered phosphate electrophile (**1.101**, Scheme 1.35).⁸⁰ Similar to the work of Grierson, the reaction takes advantage of the fast reducing aminonitriles, which in the presence of lithium di-*t*-butylbiphenylide (LiDBB), forms a lithiate intermediate **1.102**.⁸¹ Subsequent cyclization with the adjacent aliphatic phosphate afforded the spiro-cyclized product **1.103** in excellent yield. Extending the phosphate tether by a carbon led to decreased product yields as a result of competing pathways between phosphate reduction and cyclization of the lithiate intermediate. Cyclization of lithium intermediates also proceeded with chloride leaving groups, but with modest decline in yield (84%). Rychnovsky has further expanded the method to include cyclizations with secondary phosphates⁸² and towards spiro-piperidine products (**1.103**).⁸³

Scheme 1.35

In addition to synthetic studies, the utility of aliphatic phosphate cyclization reactions has been reported in the context of natural product synthesis. Rychnovsky and coworkers, utilizing a previously described dialkoxy lithiate cyclization reaction,⁸⁴ reported a highly diastereoselective reductive cyclization reaction with a

pendant aliphatic phosphate for the construction of the core spiro-ketal of attenol A (Scheme 1.36). While chloride-leaving groups were compatible for the reductive cyclization, the ease of accessing the primary phosphate from the corresponding alcohol prompted the use of the more readily prepared phosphate. Cyclization in the presence of the cyano reductant LiDBB occurred in excellent yield to form the kinetically produced, nonanomeric unstabilized ketal **1.105** with nearly complete diastereoselectivity. Subsequent treatment of **1.105** with acid led to the formation of the requisite anomeric spiro-ketal for attenol A.

Scheme 1.36

1.4.2. Aliphatic Cyclization Under Non-Reducing Conditions.

Crich and coworkers have expanded the synthetic application of aliphatic phosphate cyclization reactions to include nucleophilic trapping of stabilized alkene radical cation/phosphate anion intermediates (Scheme 1.37).⁸⁵ The reaction is believed to occur through a dissociate mechanism where an ionic fragmentation of a β -phosphate alkyl radical (**1.106**) forms a radical cation/phosphate anion contact ion pair that can react intra- or intermolecularly with heteroatom nucleophiles.⁸⁶ In the case of **1.107**, tandem nucleophilic trapping and radical cyclization affords pyrrolizidine structures. Crich and coworkers have demonstrated an array of synthetic utility via reactions employing radical cation/phosphate anion intermediates

for the formation of oxygen and nitrogen heterocycles via both simple and tandem radical cyclization pathways.⁸⁵

Scheme 1.37

The role of the contact ion pair between the phosphate anion and the alkene radical cation has been surveyed for its effect on the stereochemical outcome of intramolecular cyclization reactions, in which the facial location of the planar ion pair derived from the initial phosphate stereochemistry provides enantio-⁸⁷ and diastereocontrol.⁸⁸ For example, high diastereoselectivities were observed with phosphate **1.110**, in which cyclization of intermediate **1.111** with an adjacent amine occurred with high levels of diastereoselectivity, affording *anti*-**1.112** in 18:1 ratio.⁸⁸ When the opposite phosphate epimer was employed, a 13:1 diastereomeric ratio was observed favoring the *syn*-pyrrolidine.

Scheme 1.38

1.5. Anomeric Phosphate Leaving Groups

The final class of phosphate leaving groups that will be reviewed is that of glycosyl phosphate donors in which a phosphate-leaving group is connected via the anomeric position. In light of several earlier examples, anomeric phosphates as

glycosylating reagents have only recently emerged in the literature. Despite their relative newness, glycosyl phosphates have quickly emerged as powerful coupling partners for oligosaccharide synthesis. In comparison with other commonly employed anomeric activating groups (trichloroacetimides and halides), glycosyl phosphates are in general stable, can be easily formed from readily available derivatives, and possess good coupling reactivity profiles.

One of the first reports of anomeric phosphate leaving groups in oligosaccharide synthesis was by Hashimoto and coworkers for the synthesis of 1,2-trans- β -linked glycosides with glycopyranosyl phosphates.⁸⁹ Boger and coworkers additionally explored glycosyl phosphate donors for the formation of the complex disaccharide **1.116** as part of the total synthesis of bleomycin A₂.⁹⁰ Glycosidation of diphenyl phosphate **1.114** with glycosyl acceptor **1.113** in the presence of TMSOTf was found to cleanly afford **1.115** after 15 minutes in 93 % yield, with complete retention of the α -linkage. **1.115** was subsequently converted to the corresponding β -glycosyl phosphate donor, which underwent further coupling with a β -hydroxy-L-histidine derivative to afford disaccharide **1.116** as a 13:1 mixture of α : β isomers in good yield.⁹¹

Scheme 1.39

A seminal paper by Seeberger and coworkers thoroughly examined numerous aspects of glycosyl phosphate chemistry including methods for producing anomeric phosphates, and reaction scope and selectivity for the generation of *O*-, *S*-, and *C*-glycosides.⁹² Subsequent reports have extensively explored the utility of TMSOTf promoted glycosylation reactions with anomeric phosphate leaving groups, in terms of reaction conditions (time and temperature), α,β -selectivity with both varying glycosyl acceptors and donors, substrate and functional group compatibility, solvent effects, etc., which will not be covered in this review.⁹³

One powerful extension of glycosyl phosphates chemistry is its use in automated oligosaccharide synthesis. Seeburger and coworkers have recently reported a number of examples demonstrating the use of anomeric phosphates for application in automated oligosaccharide preparation (Scheme 1.40).⁹⁴ One of their initial examples demonstrated an efficient assembly of branched dodecasaccharide **1.120** from glycoside **1.119** and phosphate disaccharide **1.118** taking advantage of selective cleavage of the 6-*O* levulinoyl ester-protecting group, iterative solid-phase

coupling, and RCM release.⁹⁵ Upon cleavage from the solid-phase resin, **1.120** was generated after 10 hours, in 89 % yield as judged by HPLC analysis.

Scheme 1.40

1.6. Summary.

The large array of synthetic transformations in which phosphate ester leaving groups have been employed is testament to their diverse reactivity profile and robust nature. Despite their qualities, the use of phosphates in synthesis has remained limited to monovalent activation via a single phosphate ester appendage. The following two chapters of this dissertation will cover our recent efforts in the area of multivalent activation in phosphate triesters, investigating: (i) selective cleavage reactions within di- and multivalent activated temporary phosphate tethers, and (ii) application of temporary phosphate tethers towards the C15-C30 fragment of dolabelide A-D.

1.7. References.

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Chapter 2

Multivalent Activation in Temporary Phosphate Tethers

2.1 Introduction

2.1.1. Transition Metal-Catalyzed Routes to *P*-Heterocycles

Over the last decade, a number of methods to generate unique *P*-heterocycles have emerged.¹ As part of this work, our group has explored several aspects of transition metal-catalyzed (TMC) phosphorus cyclization reactions, namely ring-closing metathesis (RCM)² and intramolecular cyclopropanation (ICP). In particular, we have worked in four areas, including; (i) desymmetrization of *pseudo*-C₂-symmetric phosphorus templates to generate constrained *P*-chiral, *P*-heterocycles **2.1** and **2.3** (Scheme 2.1), (ii) RCM of substrates bearing acid-labile temporary phosphoramidate and phosphonamidate tethers for the construction of functionalized 1,4-*anti* diamines (**2.5**), (iii) RCM on electron rich enol phosphates (**2.8**) and enol phosphonamidate,³ and (iv) an RCM assembled phosphonate-template approach to synthesize an array of functionalized phosphono sugars (see Chapter 4). Taken collectively, this body of work has provided the foundation for our initial investigations into a relatively unexplored area of synthetic phosphate chemistry, namely their use as temporary tethers that impart multivalent activation among two or more of its phosphate triester appendages. Multivalent activation is a term we have coined within the chemical arena to describe the concept of activating multiple positions via a single functionally reactive tether such as a phosphate. The following chapter (Chapter 2) focuses on our initial efforts in this area in which temporary phosphate tethers are used for the first time in small molecule synthesis. Moreover,

this background work sets the stage for application temporary phosphate tethers in natural product synthesis (see Chapter 3).

Scheme 2.1

2.1.2. Temporary Phosphate Tethers

The temporary tethering of two advanced intermediates is a powerful technique for enabling rapid assembly of complex molecules.⁴ Historically, silicon has been the most widely used tether,⁵ in which its orthogonal protecting group properties and coupling characteristics have served as the cornerstone of several synthetic strategies.^{6,7,8} In contrast, use of phosphorus-based tethers (*P*-tethers) has been limited to two examples,⁹ while use of phosphate tethers is completely absent from the literature. This is a surprising observation when one considers the potential of phosphorus tethers to mediate both di- and tripodal coupling and to serve as a leaving group providing multivalent activation for further transformations (**2.12** and

2.13, Figure 2.1). However, despite the vast research on organophosphorus compounds,¹⁰ the scope of phosphate triester use in synthesis has been relatively limited to date. Historically, their use in complex synthesis focused primarily on metal-mediated nucleophilic displacement reactions of allylic phosphates and cross-coupling/reduction reactions with enol phosphates, *vide supra*.¹¹ In both cases, the leaving group ability of phosphate mono-anions¹² is exploited in a phosphate triester, which possesses a mono-activated group (monovalent activation **2.11**) and two ancillary groups (R = ancillary group, Figure 2.1). The additional use of phosphate triesters in iodophosphonylation procedures¹³ and their obvious role in oligonucleotide synthesis¹⁴ further highlights both nucleophilic properties and facile coupling characteristics innate to phosphates.

Figure 2.1 Mono- Di- and Multivalent Activation via Phosphate Esters

As previously mentioned in the introductory chapter one, this reactivity profile is overshadowed by the vast extent to which nature uses the anionic counterparts, organophosphate mono- and dianions and tethering capabilities which play dominant roles in key biological processes.¹⁵ A seminal paper by Westheimer¹⁵ in 1987 sheds light on this matter. Westheimer surmises, "while nature capitalizes on the unique features of phosphate monoanions, chemists cannot afford to use

compounds as stable as the phosphate anion and with the poor leaving group capabilities of either phosphate anions or dianions". This viewpoint rapidly started to change with the emergence of the aforementioned body of work on allylic and enol phosphate displacement reactions. However, successes in these areas were limited in all cases to the activation of a single phosphate triester (monovalent activation) where the phosphate monoanion was extruded from the final product. The following chapter describes our initial efforts at using phosphate tethers to activate multiple carbinol and allylic carbinol centers in which the stability of the phosphate monoanions is exploited in selective cleavage processes.

2.2. Results and Discussions

2.2.1. *Phosphate Tethers as Leaving Groups in Copper-Mediated Allylic Alkylations*

Our initial studies into divalent activation began by exploring a monocyclic phosphate triester containing two activated, allylic phosphate esters and one ancillary ligand OR³. As such, the phosphate ester serves a dual role as both tether for coupling two allylic alcohols via ring-closing metathesis (RCM) and as a subsequent leaving group in γ -selective *anti*-S_N2' displacement reactions with cuprate 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 touted by Yamamoto and coworkers in 1991 (see Chapter One).¹⁶ This feature, in which 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.¹⁷ 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,¹⁸ as well as reagent-controlled asymmetric allylic phosphate displacements catalyzed by copper.¹⁹ The method we initially focused on utilizes symmetry breaking cuprate additions to readily prepared *pseudo*-C₂-symmetric monocyclic phosphate **2.16** (Scheme 2.2). 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 context of this work, intriguing conformational effects have led us to extend the study into unsymmetric phosphates, ultimately providing experimental insight into the Corey mechanism of cuprate displacements.

2.2.2. Initial Studies of Monocyclic Phosphates

Our study began with the generation of (*S,S*)-monocyclic phosphate **2.16**, which was achieved in three steps in good overall yields (Scheme 2.2). Allylic alcohol (*S*)-**2.15** is readily generated on multi-gram scale using the Christie protocol²⁰ with commercially available glycidol ether (*S*)-**2.14**.²¹ Upon condensation of the alkoxide of **2.15** with (MeO)POCl₂, the phosphate triester tether mediates coupling of two olefins via RCM in good yield using (IMesH₂)(PCy₃)(Cl)₂Ru=CHPh (cat.-**B**),²² use of catalyst (PCy₃)₂(Cl)₂Ru=CHPh (cat.-**A**) gave poor yields of **2.16**. Optimized RCM conditions required elevated temperatures (90 °C in toluene) with continuous argon purging.²³

Scheme 2.2

We initially probed several conditions as part of our overarching investigation of orthogonal reactivity patterns within cyclic phosphates containing multiple allylic phosphate positions (Scheme 2.3). Following metathesis, treatment of the doubly allylic **2.16** with LiAlH_4 afforded the C_2 -symmetric diol **2.17**.²⁴ Furthermore, following the Louie-Grubbs protocol,²⁵ post-metathesis treatment of the crude reaction mixture of **2.16** with 500 psi of H_2 in the presence of cat.-**B** afforded hydrogenated **2.18** in 85% yield. Cleavage of the saturated phosphate **2.18** generated aliphatic diol **2.19** in excellent yield.

Scheme 2.3

2.2.3. *Anti-S_N2'-Alkylation Reactions with C₂-Symmetric Monocyclic Phosphates*

We then shifted focus towards the *anti-S_N2'*-allylic displacement studies using soft organocuprate nucleophiles. A prerequisite for the 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 **2.16** possesses the ability to align the phosphate moiety in two requisite anti-periplanar relationships outlined in Scheme 2.4. In both conformers we initially anticipated that energies related to the orthogonally-aligned phosphate leaving group σ^* orbital 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 which invokes a bidentate coordination of incoming cuprate to both π^* and σ^* orbitals (vide infra). Attack of cuprate nucleophiles on **2.16** can potentially occur through any of four diastereotopic olefinic orbitals. Pseudo-symmetry, however, presents two (not four) stereodivergent pathways for *anti*-S_N2'-allylic displacement, ultimately leading to only two possible diastereomeric products.²⁶ Cuprate addition leads to loss of the prochiral phosphorus center, thereby providing only two potential products via four diastereomeric pathways. Specifically, these two 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*)-**2.20** and *syn*-(*Z*)-**2.21** can not be accessed from (*S,S*)-**2.16** via an *anti*-S_N2'-allylic displacement mechanism. Use of *meso*-**2.16** would be required to access these two diastereomers. Pathway A occurs through conformer **2.16a** with addition *anti* to the vicinal CH₂OBn group generating *anti*-(*Z*) diastereomer **2.20**, while pathway B occurs via conformer **2.16b** with addition *syn* to the vicinal CH₂OBn group leading to the *syn*-(*E*) diastereomer **2.21**.

Scheme 2.4

Pleasingly, $anti-S_N2'$ displacement of allylic phosphate **2.16** using $\text{Et}_2\text{Zn}/\text{CuCN}\cdot 2\text{LiCl}$, and after acid workup, led to formation of phosphate acid **2.22** as a single diastereomer (>20:1) as witnessed by ^{31}P NMR (Scheme 2.5). Subsequent treatment with Red-Al[®] led to good yields of homoallylic alcohol **2.23**. Initial tentative assignment of the relative stereochemistry within phosphate acid **2.22** 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).

Scheme 2.5

Unambiguous determination of relative stereochemical relationship at C(2,3) within **2.23** was ultimately achieved using Karplus analysis of vicinal protons contained within the six-membered ring derived from reductive ozonolysis/acetonide

protection of **2.24** affording **2.25** (Scheme 2.6). Analysis of J_{AC} , J_{BC} , J_{CD} coupling constants provided small coupling values (1.4-2.6 Hz), consistent with axial-equatorial evident in structure **2.25**. These values were identical to previously reported spectral data when $R^1 = \text{Me}$.²⁷

Scheme 2.6

The remarkable selectivity for this transformation can be rationalized using Corey's proposed concerted, asynchronous mechanism^{16b} for cuprate additions as highlighted in Figure 2.2. 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 **2.16a** and **2.16b**, 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 **2.16** must ultimately be dictated by the lower steric requirements of conformer **2.16b** 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 **2.16a** due to the CH_2OBn -sidechain disfavors cuprate addition via this conformer (Scheme 2.4).²⁸

Figure 2.2 Corey Model for Anti- S_N2' Allylic Ester Alkylation Reactions

Additional reactions of **2.16** 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 2.1). Treatment of **2.16** with 8-9 equivalents of the mixed zinc-copper reagents using alkyl halide-derived, functionalized organozinc reagents (entries 4-8, Table 2.1) 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.²⁹ Following acidic workup, the phosphate acids were directly subjected to Red-Al® to afford corresponding homoallylic substrates **2.27** in good to excellent yields.

Table 2.1 Cuprate Addition/Phosphate Acid Cleavage Sequence

entry	$(R^1)_2\text{Zn}$ or $R^1\text{ZnBr}$	phosphate acid - 2.26 %/dr	homoallylic alcohol - 2.27	% yield
1	Me_2Zn (5 equiv)	99/>20:1 2.26a	 2.27a	83
2	Et_2Zn (5 equiv)	99/>20:1 2.22	 2.27b	90
3	$i\text{Pr}_2\text{Zn}$ (5 equiv)	99/>20:1 2.26b	 2.27c	95
4	c-HexZnI (9 equiv)	99/>20:1 2.26c	 2.27d	70
5	BnZnBr (9 equiv)	99/>20:1 2.26d	 2.27e	84
6	$\text{CN}(\text{CH}_2)_3\text{ZnBr}$ (9 equiv)	99/>20:1 2.26e	 2.27f	31
7	$\text{Cl}(\text{CH}_2)_4\text{ZnBr}$ (9 equiv)	99/>20:1 2.26f	 2.27g	71
8	$\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{ZnBr}$ (9 equiv)	99/>20:1 2.26g	 2.27h	65

While cleavage of the phosphate acid using Red-Al[®] afforded the majority of products **2.27** in good yields, lower yields were observed for reductions in which substrates **2.26** contained functionally-sensitive R¹ groups. To circumvent this problem, in situ methylation of the crude phosphate acid using TMSCHN₂ produced **2.28** prior to Red-Al[®] reduction, and led to higher yields of **2.27** (Scheme 2.7).

Scheme 2.7

2.2.4. *Anti-S_N2'-Alkylation Reactions with C₂-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 (ie, primary versus secondary allylic phosphate ester leaving groups). In contrast to phosphate **2.16**, an energetic bias for the corresponding allylic phosphates was thus anticipated. Dioxaphosphacycle **2.29** was generated via the coupling of one equivalent of allylic alcohol **2.15** with allyldiphenyl phosphate, followed by RCM to afford **2.29** in good yields over two steps (Scheme 2.8). Treatment of **2.29** with 3.0 equivalents of diethyl zinc-derived organocuprates, and subsequent phosphate cleavage, led to formation of a single product **2.30** produced via cuprate displacement at the secondary allylic phosphate position. In contrast to **2.16**, no dominant

conformational preferences exist between the two described reactive conformations of **2.29**, indicating that regioselectivity is dictated by electronic effects, *vide infra*.

Scheme 2.8

This intriguing result led us to explore yet a third paradigm, the unsymmetric cyclic phosphate **2.32**, containing both secondary and tertiary allylic phosphate positions (Scheme 2.9). Phosphate **2.32** was assembled via differential coupling of secondary allylic alcohol **2.15** and 2-methylbut-3-en-2-ol with dichloromethyl phosphate. The resulting labile acyclic phosphate was immediately subjected to metathesis affording phosphate **2.32** in moderate yields over the two-step sequence. Treatment of **2.32** with 3.0 equivalents of diethyl zinc-derived organocuprate at -40 °C, and subsequent phosphate cleavage, led to formation of a single product **2.33**. Using the aforementioned Karplus analysis of the resulting acetone of **2.33**, unambiguous assignment of *anti*-relationship was established, *vide infra*.

The regioselectivity of cuprate displacement in **2.32** is most surprising in that the requisite conformer **2.32** leading to product **2.33** (Scheme 2.9) contains an

unfavorable $A^{1,3}$ interaction generated by the gem-dimethyl moiety. However, the observed selectivity is consistent with the results obtained with **2.29**, 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.

Scheme 2.9

Unambiguous determination of relative stereochemical relationship at C(2,3) within **2.33** was determined via Karplus-analysis within acetone **2.34** (Scheme 2.10). In comparison with 1,2-*syn* **2.25**, 1,2-*anti* **2.34** contains the larger J_{CD} coupling value of 11.7 Hz (compared with 2.4 Hz for **2.25**), consistent with equatorial-equatorial arrangement of H_D relative to H_C .

Scheme 2.10

In rationalizing and summarizing regio- and diastereoselective cuprate additions with symmetric **2.16** and unsymmetric phosphates **2.29** and **2.32**, both steric and stereoelectronic effects appear to play major roles. In the case of **2.29** and **2.32**, cuprate displacements proceeded via the more substituted σ^* positions, secondary and tertiary, respectively. When σ^* energies are equivalent as in **2.16**, allylic strain appears to govern the cuprate addition.

2.2.5. Multivalent Activation in Bicyclic Phosphates Bearing a Temporary Phosphate Tether

We next turned our attention at a more complex variation of this method whereby the phosphate tether mediates multipodal coupling and thereby provided multivalent activation. In this role the tether acts as a latent leaving group in a number of unprecedented selective cleavage reactions. In addition, stereoelectronic effects within the bicyclic framework lend orthogonal protecting group stability. Overall, this chapter highlights a fundamentally new role of phosphates in synthesis providing a facile approach to differentiated polyol building blocks for use in natural product synthesis.

We chose to utilize the tether desymmetrization method developed by Burke and coworkers³⁰ in order to construct the *P*-chiral bicyclo[4.3.1]phosphate **2.35** (Figure 2.3) containing ample steric and stereoelectronic differentiation for investigating chemo-, regio- and stereoselective transformations. Overall, **2.35** possesses electrophilic character at 7 of its 9 non-oxygen atoms allowing for nucleophilic attack at phosphorus or any of six carbinol and allylic phosphate carbons [C(3), C(6), and C(8)] and [C(4), C(5), and C(12)], respectively.

Figure 2.3 Assessment of bicyclic phosphate **2.35**

Our initial efforts in investigating trivalent activated systems have led us to optimize the synthesis of diene-1,3-diol **2.39** (Scheme 2.11), which serves as a key building block. Following the protocol of Rychnovsky and coworkers,³¹ we have synthesized dichloro-1,3-*anti*-diol **2.37** on 100-gram scale starting from 2,4-pentanedione (**2.36**). Isolation and reaction of diepoxide **2.38**, with trimethylsulfonium ylide led to good yields of diene (*S,S*)-**2.39**. In an optimized procedure,³² **2.37** is reacted with a 9-fold excess of sulfonium ylide, generating (*S,S*)-**2.39** directly (81-85%, 10 g scale), circumventing isolation of volatile epoxide **2.38**.

Scheme 2.11

Coupling of diol **2.39** with POCl₃ afforded the phosphoryl mono-chloride **2.40** in excellent yield. The surprising stability of monochloridate **2.40** was evident in its stability to silicon chromatography and mild acid conditions (aq. NH₄Cl workup).

While typically used immediately, **2.40** could be stored at 0 °C for short periods of time (~1 week) with little observable decomposition. Subsequent reaction with lithium allyloxide afforded the phosphate triester **2.41**. Triester **2.41** was also stable and could be easily isolated by silicon chromatography. Final ring-closing metathesis (RCM) using [(IMesH₂)(PCy₃)(Cl)₂Ru=CHPh; cat-**B**],³³ produced **2.35** (81%) as confirmed by X-ray crystallographic analysis. Use of Grubbs first generation catalyst (PCy₃)₂(Cl)₂Ru=CHPh (cat-**A**)³⁴ gave poorer yields.

Scheme 2.12

With **2.35** in hand, we initially examined hydrolytic protocols for tether removal. Although hydrolysis of phosphate esters, using both acid and base, has been extensively studied,³⁵ selective phosphate hydrolysis³⁶ is quite limited.³⁷ Exposure of **2.35** to a variety of acidic hydrolysis conditions [MeOH/HCl, 10% HCl (aq)/dioxane, and TMSCl], revealed a remarkable stability profile in **2.35**. This enhanced acid stability can be rationalized by the lack of lone pairs on the adjacent oxygen atoms anti-periplanar (*app*) to the P=O, and as evident in previously studied bicyclic phosphate systems. Studies have shown that when oxygen lone pairs occupy a *trans-app* position to an adjacent polar bond (P-OR), they donate electron density from their lone pair orbital, *n*, to the antibonding O-P σ*, thus weakening the P=O bond

and increasing the basicity at the phosphoryl oxygen. Conversely, lack of *app* lone pairs imparts orthogonal stability to hydrolysis with acid.³⁸

Alternatively, basic hydrolysis conditions are known to stop at the stage of the monoanion salt due to decreased electrophilicity at the P=O moiety.¹⁵ For example, the half-life of trimethyl phosphate (MeO)₃PO in a 1 M solution of NaOH in water at 35°C is 30 minutes; the corresponding half-life of the resulting hydrolyzed phosphate salt (MeO)₂PO₂Na is 11 years. Therefore, hydrolysis of **2.35** was thus anticipated to stop at one or more of the regioisomeric phosphate mono-acid salts **2.42-2.44** (Figure 2.4).

Figure 2.4 Potential basic hydrolysis products of **2.35**

Experimentally, treatment of **2.35** with LiOH (aq.) in dioxane led to quantitative and selective cleavage as evidenced by the appearance of a major singlet appearing at -0.06 ppm in the ^{31}P NMR spectrum ($rs = 44:1$). A ^{13}C NMR comparative analysis of both the product and **2.35** showed a diagnostic upfield shift of the resonance corresponding to the C(8) carbinol, indicating regioisomer **2.42** as the major cleavage product (Scheme 2.13). Further evidence for **2.42** is seen in the loss of C-P coupling at the C(8) carbinol position, as expected for cleavage of the C(8)O-P bond to form **2.42**. Studies focusing on mechanistic details of this selective hydrolysis event are underway. In contrast, treatment of **2.35** with PhSLi showed

complete selectivity ($rs = >99:1$) for phosphate displacement at C(3), leading to **2.45** containing the differentiated 1,3-*anti* diol subunit in quantitative yield (Scheme 2.14). This transformation is in agreement with precedent showing soft nucleophilic preference for attack at *C* vs. *P*.^{35a}

Scheme 2.13

We next examined reductive removal using conditions previously developed by Bartlett.³⁹ Reaction with LiAlH₄ (Et₂O at 0 °C, 15 min.) led to exhaustive removal of the phosphate tether to produce triol **2.46**, a building block for the central subunit in the potent phosphatase inhibitor fostriecin. This result is consistent with the addition of hard hydride anions at phosphorus and subsequent cleavage of all P-O

ester bonds. Phosphate **2.35** was completely stable to Super Hydride[®] (Et₃BHLi), LiBH₄ and BH₃•THF in THF at rt, demonstrating no product decomposition.

Scheme 2.14

Interest in revealing additional selective processes led us to examine regioselective and potentially diastereoselective S_N2' cuprate displacement reactions. Initial use of ethyl cuprate,⁴⁰ resulted in S_N2' attack at the more accessible external terminal olefin of **2.35** to yield phosphonic acid **2.47** in excellent yield (*rs* ~ 8:1). Subsequent reduction with Red-Al[®] removed the phosphonic acid tether to yield diol diene **2.48**.

With this latter example in hand, we next turned to investigating stereofacial bias and stereoelectronic effects in cuprate additions to phosphate triester **2.35** with the goal of producing 1,3,4-stereotriads **2.50** and **2.53** found in the southern hemisphere of dolabelides A-D.⁴¹ This stereotriad is also found in a number of other biologically active natural products including salicylihalamides A and B,⁴² bitungolides A-F,⁴³ rhizoxin and rhizoxin D,⁴⁴ and discodermolide.⁴⁵ Initially, we studied the reactivity of the partially hydrogenated analog **2.49** which was treated

with ethyl cuprate, followed by Red-Al[®] to provide diol **2.50** as the sole product (Scheme 2.15). This reaction occurs via a highly regio- and stereoselective *anti*-S_N2' attack⁴⁶ at the C(5) olefinic carbon (*rs* = >99:1, *ds* = >99:1), where proper orthogonal alignment of the C=C π* and C-OP(O) σ* orbitals in path A allows for *anti*-S_N2' attack to proceed exclusively at C(5) on the convex face of **2.49**.

Scheme 2.15

Having established the high selectivity for the cuprate addition into **2.35**, we turned our attention to generating more elaborate systems via preferential functionalization of the external olefin. Therefore, hydroboration of **2.35** with 9-BBN followed by mild oxidation of the borane with sodium perborate and subsequent TBDPS-protection afforded silyl protected primary alcohol **2.51** in moderate yield (Scheme 2.16). As anticipated, treatment with a Me₂Zn-derived cuprate produced the corresponding phosphate acid as a single product as witnessed by ³¹P NMR. Subsequent methylation to the phosphate ester afforded a 1:1 mixture of

diastereomers at phosphorus. Reductive cleavage of the phosphate ester with Red-Al afforded the fully deprotected triol **2.52** in excellent yields. Unexpected loss of the TBDPS protecting was observed in the course of the phosphate displacement.

Scheme 2.16

Additional oxidative functionalization of the external olefin was further examined for one-pot generation of methyl ketone **2.53** under Wacker conditions. Reaction under standard conditions for up to 12-16 hours resulted in complete recovery of starting material in 80-90% yield (Scheme 2.17). We turned our attention to modified-Wacker conditions⁴⁷ that were found effective for the oxidations of secondary allylic alcohols to the corresponding ketones. Treatment of bicyclic phosphate **(S,S)-2.35** with $\text{Hg}(\text{OAc})_2$, followed by heating in the presence of a stoichiometric amount of $\text{Pd}(\text{II})$ afforded cleanly, albeit in modest yields (40% unoptimized), the methyl ketone-bearing bicyclic phosphate **2.53**. The absolute configuration of the crystalline solid was determined using X-ray crystallographic analysis. Efforts to optimize this reaction are currently underway. Treatment of the methyl ketone **2.53** with vinyl magnesium bromide afforded a predominant diastereomer of tertiary carbinol **2.54** in ~50-55% yield. Crude ^1H NMR analysis indicated an ~12:1 mixture of diastereomers. While unambiguous assignment of **2.54**

remains, **2.54** represents promising preliminary efforts towards an advanced (*ent*)-synthon containing the central C7-C14 core of fostriecin bearing the requisite C8,C9, and C11 stereochemistry and C12-C13 *Z*-olefin. Ongoing efforts in our labs are focused on the application and optimization of these preliminary results towards total synthesis of fostriecin.

Scheme 2.17

Further potential of this method was showcased in the rapid assembly of tetrol **2.59**, which represents an advanced intermediate in the synthesis of feigrisolide B,⁴⁸ with direct application to tetranactin⁴⁹ (Scheme 2.18). In this example, the phosphate tether serves to mediate both the RCM desymmetrization event and to parlay the stereochemical complexity of diol **2.55** onto chloride **2.40**. Tandem RCM/exhaustive hydrogenation^{50,51} using the second generation Grubbs catalyst, afforded the saturated bicyclic phosphate **2.57**. Reduction of **2.57** with LiAlH_4 produced triol **2.59** in excellent yield (94%). Alternatively, selective hydrolysis using the aforementioned LiOH conditions generated **2.58** with quantitative conversion and complete

regioselectivity ($rs = >99:1$), further demonstrating the ability to generate complex differentiated polyol subunits.

Scheme 2.18

2.3. Summary

In conclusion, we have demonstrated the utility of functionally-active temporary phosphate tethers for the construction of polyol synthons. Furthermore, we have shown that both monocyclic and bicyclic phosphates constructed via temporary phosphate tethers undergo a number of selective displacement reactions. For example, monocyclic phosphates undergo a highly selective *anti*-S_N2' allylic phosphate displacement. Subsequent phosphate cleavage affords an array of *syn*-(*E*)-homoallylic alcohols when *pseudo*-C₂-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 $1^\circ < 2^\circ < 3^\circ$, allowing access to *anti*-configured homoallylic alcohols. In probing these systems, the Corey mechanism for allylic organocuprate displacements was examined and further substantiated.

Additionally, we have demonstrated the utility of multivalent activation via a phosphate tether where latent leaving group ability has been harnessed in selective cleavage reactions within the bicyclic framework of **2.35**. Taken collectively, these features uncover new dimensions in phosphate chemistry. Additional studies probing mechanistic features are still ongoing. Current application of this method in natural product synthesis is discussed in the following chapter.

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Chapter 3

Phosphate Tether Approach to the C15-C30 Fragment of Dolabelides A-D

3.1. Introduction

3.1.1. Overview of the Dolabelide Family

Dolabelide A and B (**3.1a** and **3.1b**)¹ are 22-membered macrolides collected from sea hares *Dolabella auricularia* and subsequently characterized. Upon further investigation of these extracts, researchers uncovered two additional 24-membered macrolide analogs of dolabelide A and B, and termed them dolabelide C and D.² Dolabelides A-D are a family of molecules that show cytotoxicity against human cervical cancer HeLa-S₃ cells with IC₅₀ values being 6.3, 1.3, 1.9, 1.5 $\mu\text{g/ml}$, respectively. The biological activity as well as the stereochemical complexity of this family presents a formidable synthetic challenge. However, biological data pertaining to the origin of cytotoxicity is void in the literature, thus their mechanism of action remains unknown.

Figure 3.1. Dolabelides A-D

3.1.2. Synthetic Studies Towards the C15-C30 Fragment

Five synthetic studies³ have recently been reported for this class, including one total synthesis by Leighton and coworkers in 2006.⁴ Of these synthetic studies, two reports toward the C15-C30 fragment have been reported, with Leighton having published the only complete C15-C30 fragment, bearing the requisite stereochemistry

(Scheme 3.1). Leighton's synthesis began with homo propargylic alcohol **3.2** that was used to generate the chiral silane **3.3** as a 4:1 mixture of diastereomers, employing an asymmetric silane alcoholysis methodology developed in their laboratories.⁵ Subsequent application of their tandem silylformylation-crotylsilylation method,⁶ followed by Brook rearrangement of the intermediate C25 vinyl silane, generated the C24-C25 trisubstituted olefin. This sequence afforded the requisite C23 carbinol and C22 methyl centers of **3.4** in a 4:1 diastereomeric ratio. Wacker oxidation at C21, followed by an asymmetric aldol, and Evan's *anti*-reduction afforded the C21 and C19 carbinol centers in good diastereoselectivity en route to **3.5**. The overall sequence produced the C15-C30 fragment in a 10-step sequence from known **3.2**.⁵

Scheme 3.1

3.1.3. Retrosynthetic Analysis of Dolabelide.

The dolabelide family differs only in ring-size and non-uniform acetylation pattern among the eight-stereogenic carbinol centers. The polyketide macrocycles dolabelide A/B and C/D are comprised of 22-membered and 24-membered lactones at C21 and C23 respectively, with all four possessing C14-C15 and C24-C25 trisubstituted olefins and a combined 11 stereocenters. From a convergence standpoint, the family of dolabelides can logically be disconnected into “northern” C1-C14 and “southern” C15-C30 fragments **3.7** and **3.9** (Scheme 3.2). Herein we

discuss our efforts towards the C15-C30 fragment of the dolabelides, in which we employ methodology centered on multivalent temporary phosphate tethers developed in our laboratories.⁷

Similar to Leighton's strategy to dolabelide D,⁴ our end-game approach utilizes a RCM macrocyclization sequence with an advanced intermediate to deliver the C(14)/C(15) trisubstituted olefin subunit within **3.6**. Macrocyclization is preceded by acid coupling between the C(1) carboxylic acid and the C(21) carbinol center contained within the advanced northern and southern intermediates **3.7** and **3.9** respectively. Convergent assembly of C15-C30 fragment via the C23-C24 bond is delivered from vinylate coupling of metallated **3.10** with aldehyde **3.11**. Analogously, both the 1,3-*anti* diol moiety contained within **3.7** (C7 and C9) and **3.9** (C19 and C21) subunits are derived from phosphate triester building blocks (*R,R*)-**3.8** and (*S,S*)-**3.8**, respectively. The phosphate triester building blocks in turn are

Scheme 3.2

constructed from readily produced enantiomeric, C_2 -symmetric *anti*-diols, (*R,R*)- **3.12** and (*S,S*)- **3.12**, respectively, as outlined in chapter 2.

3.2. Results and Discussion

3.2.1. 1st Generation Synthesis of the C15-C30 Fragment

Our synthesis begins with previously reported bicyclic phosphate (*S,S*)-**3.8** (Scheme 3.3).⁷ Mild NaBO_3 oxidation conditions were employed following hydroboration with 9-BBN, using a protocol that Burke and coworkers have recently shown to be compatible with multiple acetate protecting groups.⁸ As **3.8** was prone to hydrolysis under basic aqueous reaction conditions, reaction optimization was highly dependent on the amount of oxidant, equivalents of H_2O , and reaction times and has subsequently been optimized from our initial report.⁹ Therefore, PMB ether formation via the *p*-methoxybenzyl trichloroacetimidate of BnOH produced **3.13** in good yields over the two-step sequence. Employing copper-mediated selective phosphate cleavage protocol described in Chapter 2, cuprate displacement of **3.13** ($\text{CuCN}\cdot 2\text{LiCl}$, ZnMe_2 , THF, $-30\text{ }^\circ\text{C}$ to rt) exclusively afforded the $\text{S}_{\text{N}}2'$ displaced phosphate acid, which upon methylation (TMSCHN_2 and MeOH) afforded a cyclic phosphate ester as a 1:1 mixture of diastereomers at phosphorus in excellent overall yield (87%). Reductive cleavage of the monocyclic phosphate ester with LiAlH_4 in diethyl ether (Et_2O) quantitatively (96%) provided diol **3.14** as a single diastereomer. Ketal formation (1:1 DCM:2,2-dimethoxy propane, PPTS) followed by ozonolysis (O_3 , pyridine, Me_2S , $-78\text{ }^\circ\text{C}$ to rt) yielded aldehyde **3.16**.

Scheme 3.3

Concomitant with the production of aldehyde **3.16**, construction of the requisite C24-C30 vinyl iodide subunit was investigated (Scheme 3.4). Formation of **3.19** was achieved in two steps from known **3.17**,⁵ which is produced via commercially available *R*-(-)-epichlorohydrin, most notably employing Yamaguchi protocol for oxirane alkynylation (Scheme 3.4).¹⁰ Subsequent zirconocene-promoted carboalumination employing Wipf's water accelerated protocol¹¹ and iodine quench provided trisubstituted vinyl iodide **3.18** in 61% yield. Methylmethoxy (MOM) protection (MOMCl, *i*Pr₂NEt, DCE, 50 °C) ultimately afforded **3.19** in >95% conversion.

Scheme 3.4

With aldehyde **3.16** and vinyl iodide **3.19** in hand, methods for the construction of both C23-C24 C-C bond and C23 stereochemistry were investigated

(Scheme 3.5). Reaction of **3.16** with the lithium-halogen exchange metallate of **3.19** (^tBuLi, -78 °C to rt) provided Felkin selectivity at -78 °C, favoring the 1,3-*anti* product **3.21** in 2:1 diastereomeric ratio (d.r.) in 78% yield. Generation of the vinyl Grignard of **3.19** (^tBuLi, -78 °C, MgBr₂•Et₂O) increased the Felkin selectivity of the undesired 1,3-*anti* product **3.21** to a 4:1 d.r. in comparable yield. Selectivity for the undesired C23 carbinol was optimal employing Oshima protocol¹² for vinyl magnesiate formation in the presence of MgBr₂•Et₂O, in which selectivity as high as 8:1 was observed in favor of 1,3-*anti*-**3.21**. These results are in accordance with literature precedence that larger counterions effect the Felkin selectivity,¹³ and furthermore, that the 1,3-chelate is not the dictating factor for β-alkoxy substituents with Grignard reagents.¹⁴ Alternatively, however, Still and coworkers reported the use of Gilman-cuprates for high levels of stereo-induction with α-chiral-1,3-β-keto aldehydes favoring the *anti*-Felkin (1,2-*anti* relationship) with selectivity ostensibly dictated via the 1,3-β-alkoxy chelate.¹⁵ However, when **3.19** derived vinyl cuprate (^tBuLi, CuI•PBU₃) was reacted with **3.16**, an approximate 1:1 mixture of diastereomers was observed in 40% yield. This result was in accordance with Still's report that α,β-*anti*-stereocenters created a mismatch pair, leading to erosion in selectivity. These unfortunate results led us to examine reagent-controlled vinylate addition to form the 1,3-*syn anti*-Felkin product **3.20**. Attempts to employ asymmetric induction with a zinc vinylate-lithium alkoxy *N*-methylephedrine complex,¹⁶ recently described by Marshall for reagent controlled vinylate additions

with α -chiral aldehydes, provided a 1.5:1 ratio of diastereomers favoring the undesired product.

Scheme 3.5

With less than successful attempts to obtain the desired 1,3-*syn*-**3.20** under a variety of vinyl metallate conditions, we turned our attention to hydride reductions. Following Dess-Martin oxidation which smoothly provided the α,β -unsaturated ketone **3.22** in 95% yield, attempts to produce the minor isomer in good diastereoselectivity were once again unsuccessful (Scheme 3.6). The best result was obtained with LiAlH_4 (Et_2O , $-78\text{ }^{\circ}\text{C}$), providing **3.20** in a 1.5:1 ratio. DIBAL-H (toluene, $-78\text{ }^{\circ}\text{C}$) reduction on the other hand afforded undesired 1,3-*anti*-**3.21** in a 10:1 ratio with **3.20**. In the synthesis of rhizoxin, Boger and coworkers reported excellent levels of diastereoselectivity for 1,3-*syn* reduction with similar substrates containing a methyl flanked 1,3-hydroxy- α,β -unsaturated ketone protected as the

MOM ether.¹⁷ Given this, and the high preference for the formation of 1,3-*anti* **3.21** under the probed conditions, we decided to investigate hydride reductions under an alternative C19/C21 protection scheme.

Scheme 3.6

In contrast to the acetonide protecting group of **3.22**, we chose to investigate orthogonal protection at the C19/C21 positions, which would additionally be amenable to our end game strategy of dolabelide (Scheme 3.7). Employing less reactive conditions for silylation of secondary alcohols (TIPSCl, imidazole, rt), we were able to obtain the C19 monosilyl ether **3.23** in 86% yield, as a single regioisomer.¹⁸ Unreacted starting material could be recovered and resubmitted to conditions, producing >90% yield of **3.23** after one recycling. MOM-protection, followed by ozonolysis once again afforded aldehyde **3.24** in good yield.

Scheme 3.7

Treatment of **3.24** with vinyl-lithiate-derived **3.19** under the previously described conditions provided **3.25** as a 1:1 ratio of diastereomers in 80% yield (Scheme 3.8). Unfortunately, following oxidation (98% yield), various reduction protocols once again proved unselective for the desired isomer 1,3-*syn* **3.26**. Interestingly, a marked decrease in selectivity with DIBAL-H was observed (5:1, 1,3-*anti* **3.27**: 1,3-*syn* **3.26**) for **3.25** compared with the ketal protected **3.22**. Attempts to provide 1,3-induction via chelation-controlled reduction employing both Luche conditions and $\text{Zn}(\text{BH}_4)_2$, afforded reduced products as 1:1 mixture of diastereomers in low yields.¹⁹ This result is in accordance with previous reports by Evans, in which $\text{Zn}(\text{BH}_4)_2$ reductions with

Scheme 3.8

Conditions	% Yield	d.r.	
		1,3- <i>syn</i> 3.26	1,3- <i>anti</i> 3.27
DIBAL-H, -78 °C	75 %	1:5	
NaBH_4 , MeOH 0 °C	78 %	1:1	
$\text{Zn}(\text{BH}_4)_2$	58 %	1:1	
LiAlH_4 , Lil	90 %	4.3:1	

protected β -alkoxy ketones occur with a dramatic drop in 1,3-*syn* selectivity relative to β -hydroxy ketone derivatives.²⁰ Alternatively, Suzuki showed that acetonide-protected β -alkoxy ketones underwent 1,3-*syn* selective, chelation-controlled reductions with high diastereoselectivity employing LiAlH_4 reductant in the presence of LiI .²¹ Pleasingly, employing Suzuki's conditions we observed a swing in selectivity to afford the 1,3-*syn* **3.26** as 4.3:1 mixture of diastereomers in 90% yield.

Feeling that the new protection scheme more accurately represented those employed by Marshall, we reinvestigated the ephedrine-based asymmetric vinylzincate addition (Scheme 3.9). Pleasingly, we found that aldehyde **3.24** reacted with **3.19** under these conditions to obtain the 1,3-*syn* isomer **3.26** in a 11:1 ratio of diastereomers in 67% yield. Successful formation of **3.26** provided the advanced intermediate bearing the requisite stereochemistry of the southern fragment in a 9-step sequence from **3.8**.

Scheme 3.9

With **3.26** in place, only the installation of the C14-C16 terminal olefin was needed to complete the C15-C30 fragment of dolabelide. The final steps required an allylic extension from a C17 leaving group to install the three-carbon segment of the C1-C15 frame and requisite allyl moiety. DDQ removal of the PMB ether within **3.26** proceeded in good yield to afford the primary hydroxy product **3.29** (Scheme

3.10). Selective tosylation of the primary hydroxy group with 1 equiv of TsCl in 1:1 pyridine to MeOH provided the monotosylated product **3.31** as an essential single regioisomer in 50% yield along with > 45% recovered starting material. Treatment of the C23 free hydroxy **3.31** with allyl Grignard in the presence of stoichiometric CuI led to the formation of allylated product **3.33** and eight-membered C23 to C17 cyclization in ~ 50% yield as a 2:1 mixture of linear to cyclized product. To remedy this, the C23 carbinol was protected as the MOM ether generating **3.28** in 87% yield. Interestingly, attempts to protect the C23 position with TIPSOTf and 2,6-lutidine afforded only elimination products. With **3.28** in hand, PMB ether removal smoothly produced **3.30** in 85% yield. Sulfonylation with an excess of TsCl once again proceeded in modest yields to afford **3.32** in ~50%. Allyl-Grignard derived cuprate addition sluggishly afforded **3.34** as a mixture with starting material, which could be recovered in 80% yield. Additionally, **3.30** could be readily converted to the primary iodide in good yield (86%), but was less reactive under our allylation conditions. The sequence, while not fully optimized, represents a 12-step synthesis to **3.34** from **3.8**, bearing the requisite stereochemistry and framework for the C15-C30 fragment of dolabelide.

Scheme 3.10

3.2.2. 2nd Generation Synthesis of the C15-C30 Fragment.

The convenience of iodination and the sluggish reactivity of the tosylation-allyl Grignard sequence led us to investigate an alternative cross-metathesis route for the installation of the complete western C14-C18 fragment via cross-metathesis (CM) with PMB-ether **3.35**, which could be converted directly to the terminal olefin via E2 elimination of a primary leaving group (Scheme 3.11). Previously work from our laboratories has shown that both Type-I and Type-II olefins undergo clean, high yielding cross-metatheses with **3.8** in the presence of Hoveyda-Grubbs catalyst.²² As anticipated, **3.8** underwent CM in the presence of 6 mol% Hoveyda-Grubbs 2nd generation olefin metathesis catalyst in DCE to afford *E*-configured (>20:1) product in 82% yield. Selective reduction of the external olefin was achieved with *o*-nitrobenzenesulfonylhydrazide,²³ in which *in situ* generated hydrazine provided monohydrogenated **3.36** as an essential single regioisomer (>20:1) in 75% yield, under mild reaction conditions (Et_3N , DCM, rt). Unreacted starting material had an identical R_f with the product, however, the crude reaction mixture could be

resubmitted to hydrogenation conditions cleanly afford the product after one recycling in 80-85% yield along with ~ 4-8% of the undesired over-hydrogenated product, which was easily separated by silica chromatography. Under harsher conditions for hydrazine formation (tosyl hydrazine, NaOAc, H₂O, 90 °C), **3.36** readily decomposed. Regio- and diastereoselective methyl cuprate addition under the previously described conditions, and subsequent phosphate cleavage, readily afforded diol **3.37** in good yields. Following the two-step TIPS-MOM protection procedure, and ozonolysis, produced aldehyde **3.39** in excellent yields over the three-step sequence.

Scheme 3.11

From aldehyde **3.39**, 1,2-vinylmetallate addition with standard lithiation protocol afforded **3.40** as an easily separable 1:1 mixture of C23 epimers in 70% yield (Scheme 3.12). The requisite 1,3-*syn* isomer of **3.40** was subsequently MOM protected and the PMB-ether removed to afford primary hydroxide **3.41** in good yield over the two-step sequence. Subsequent iodination of the C14 hydroxy group occurred in 83% yield, followed by E2 elimination of a primary iodide in the

presence of t BuOK, generating **3.34** in 92% yield. Similar to our first-generation approach to **3.34**, the alternative sequence affords the target C15-C30 fragment **3.34** in 12 steps starting from **3.8**. Given the success, and convenience of the alternative elimination approach to the C15 olefin, we are currently investigating reagent controlled asymmetric zincate addition with **3.39** for selective formation of 1,3-*syn* **3.40**.

Scheme 3.12

3.2.3. Stereochemical Analysis of the C23 Carbinol Position.

The stereochemical assignment for the C23 carbinol center was based on vicinal ¹H coupling constant analysis of 1,3-*syn* and 1,3-*anti* isomers **3.20** and **3.21** respectively, with the structurally similar C15-C30 fragment reported by Leighton and coworkers (**3.42**, Figure 3.2). Key markers include the C22 methyl substituent, C23 proton, and C24 vinylic proton. Proton-proton interactions and coupling patterns were confirmed by 2D-COSY analysis. Good correlation was found between *syn*-**3.20** and Leighton's **3.42**, with both C22-Me and C24-H chemical shifts being in

close agreement. Most notable, however, are the identical shifts (4.26 to 4.27 ppm) and coupling constants (8.7 to 8.6 Hz) for the C23-H of **3.20** and **3.42**.

Figure 3.2 C23 stereochemical assignment.

These coupling constants are in accord with the analysis of Waldmann, Boger, and others, who have proposed both rigid twisted-boat (not shown) and chair confirmation H-bonding models (**3.43a**) for the analysis of the C10-C11 relative stereochemistry in cytostatin (Figure 3.3).²⁴ **3.43a** shows that the largely *anti*-periplanar relationship between H₁₀ and H₁₁ results in larger coupling constants of 8-10 Hz. Analogously, fragment **3.20** similarly could be imagined as existing in a chair conformation (**3.43b**) favoring the all-equatorial arrangement of C21 alkyl, C22 Me, and C23 vinyl groups. The preferred conformation of the C23-vinyl group would further explain the identical coupling constants observed between the H23-H22 and H23-H24 protons of **3.20**.

Figure 3.3 *H-Bonding Chair Model*

While the coupling constant for the 1,2-*syn* relation between the C22-H and C23-H could not be extrapolated from **3.21**, TIPS protection (84%) cleanly afforded an autonomous C23-H signal for ^1H analysis. The silylated C23 carbinol position with 1,3-*anti* **3.44** has an 8.6 Hz coupling with the adjacent vinylic proton, and an anticipated smaller coupling of 2.2 Hz with the *syn*-C22 proton. This correlates well with Leighton and coworkers reported TBS protected 1,3-*syn* **3.45**, in which the C22-H had the same chemical shift as the C22-H of **3.21** (4.81 ppm), but with a larger 5.0 Hz coupling constant with the adjacent C22 proton.

Scheme 3.13

Finally, removal of the ketal, followed by acetonide formation provided a mixture of starting material and regioisomeric acetonide **3.46** (Scheme 3.14). In accordance with Rychnovsky-Evans acetonide analysis,²⁵ ^{13}C analysis of the 1,3-*anti*

isomer **3.46** showed acetonide peaks at 25.44 ppm and 24.10 ppm, indicative of the newly formed 1,3-*anti* acetonide. The difference in chemical shifts of 25.44 ppm and 24.10 ppm ($\Delta = 1.34$ ppm) for **3.21** compared with that of 24.67 ppm and 24.54 ppm ($\Delta = 0.33$ ppm) for **3.46** is consistent with previous reports for larger methyl acetonide shifts with 1,3-*anti* acetonides of polyketide fragments, in which a methyl group is contained within the acetonide ring.

Scheme 3.14

3.3. Summary.

In conclusion, we have successfully completed the second synthesis of the C15-C30 fragment of dolabelides A-D containing the requisite stereochemistry and carbon framework. Our method made use of temporary phosphate tether methodology developed in our laboratories in which both a selective terminal oxidation and CM-selective hydrogenation sequence followed by a highly selective cuprate addition made use of the protecting- and leaving group nature of phosphate esters. Ongoing efforts towards the completed synthesis of dolabelide C are currently in progress.

3.4. References.

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Chapter 4

P-Heterocyclic Building Blocks: Application to the Stereoselective Synthesis of *P*-Sugars

4.1. Introduction

Carbohydrates offer excellent opportunities to exploit stereochemical diversity, since subtle changes in conformation, stereochemistry, and substituents at various positions are all known to elicit biological responses.¹ Recent interest in the development of new carbohydrate-based mimetics has focused on the development of scaffolds that can serve as effective biological probes and/or potential therapeutic agents.¹ A number of innovative synthetic approaches toward this goal have been undertaken,² including the development of new phosphorus-based sugars (*P*-sugars).³ The emergence of *P*-sugars has resulted largely from previous successes with organophosphorus compounds⁴ in both drug⁵ and agricultural⁶ discovery programs. Most notably, recent successes with anomERICALLY-modified *P*-sugars^{3f,3h} including ECE and Glycosidase inhibitors **4.1** and **4.2** respectively, have validated their utility and warranted the continued screening of new derivatives (Figure 4.1).³

Figure 4.1. Biologically active *P*-glycomimetics

Overall, a multitude of *P*-sugar analogs have been constructed starting from naturally occurring sugars.³ These routes have mainly employed the Abramov reaction between preformed or commercially available sugar aldehydes and di- or tri-alkyl phosphites, followed by intramolecular transesterification of the resulting

hydroxyphosphonates.^{7,4b} As part of our program aimed at the development of synthetic routes to new *P*-heterocycles with biological and synthetic utility,⁸ we herein report our continued efforts⁹ for the synthesis of novel *P*-sugars.

Our approach hinges on routes emphasizing stereochemical diversity,¹⁰ and focuses on the production of a key allylphostone building block **4.7**, using ring-closing metathesis (RCM).⁹ Prior to metathesis, diastereoselective addition of allylic alcohol **4.4** with **4.5** affords the *P*-chiral allylic phosphonate **4.6**. Allylic alcohols **4.4** can be readily derived from commercially available enantioenriched epoxides (**4.3**).

Scheme 4.1

Selective oxidation of allylphosphone **4.7** via epoxidation or dihydroxylation followed by elimination generates versatile epimeric vinylphostones **4.10** and **4.11** respectively (Scheme 4.2). These vinylphostone substrates serve as diverse building blocks for the stereo-controlled synthesis of C(3)-C(5) *O*- and *N*-substituted *P*-sugars (**4.12-4.14**, Scheme 4.2). Several attractive features of scaffold **4.7** are worth mentioning: (i) P(2) and C(6) stereogenic centers (phostone numbering) for directing stereoselective transformations upon the olefin moiety subunit of **4.7**; (ii) an activated C(3) methylene group that promotes base-mediated olefin transposition to generate vinyl phosphonates **4.8** and **4.9** possessing P(2) and C(5) stereocenters for

further stereoselective reactions; and (iii) a P(2)-stereogenic center containing an exchangeable phenyl phosphonate ester which allows for attenuation of the "stereochemical environment" at phosphorus. Overall, the method reported herein allows for the generation of an array of stereochemically rich phosphono sugars.

Scheme 4.2

4.2. Results and Discussion

Our strategy begins with a stereoselective alkoxide addition of the readily available allylic alcohols **4.15** to allyl diphenyl phosphonate (**4.5**) to derive dienes **4.16a-b** ($R^1 = \text{CH}_3$ **4.16a**, CH_2OBn **4.16b**, CH_2OTr **4.16c**) (Scheme 2). This diastereoselective process, first introduced by Moriarty,¹¹ effectively differentiates the two enantiotopic phenyl esters of **4.5** ($ds = 3.5\text{-}8\text{:}1$, selectivities determined by ^{31}P -NMR). This procedure has been shown to be successful with the commercially available racemic 3-butene-2-ol (**4.15a**) to yield products possessing a 1,3-*trans*-relationship between the PhO- and Me-groups,⁹ or the more elaborate allylic alcohols

4.16b and **4.16c**, vide infra. Subsequent RCM of the acyclic precursors **4.16** using the 1st generation Grubbs metathesis catalyst (cat-I),¹² provides allyl phostones **4.17** in excellent yields.

Scheme 4.3

Elaboration of allylphostone **4.17a**, via the aforementioned stereo-divergent oxidation pathways, is outlined in Scheme 4.3. As previously reported,⁹ both C(5) epimers are available from **4.17a** by employing either OsO₄ or trifluoromethyl dioxirane. Dihydroxylation of substrate **4.17a** provided diol **4.18** in high stereoselectivity (*ds* = 15:1) in a process that adheres to the Donohoe/Kishi model,¹³ whereby dihydroxylation occurs *anti* to the C(5) hydroxyl group.⁹ Subsequent eliminative opening of the corresponding carbonate or mesylate of the C(4)/C(5) diol subunit in **4.18** afforded vinyl phostones **4.19a** (R¹ = H) and **4.19b** (R¹ = Ms). Alternatively, epoxidation of **4.17a** led to the C(5) epimer **4.20** in modest selectivity (*ds* = 4:1), but in excellent isolated yields. As previously reported, we believe the latter is governed by electrostatic repulsion of the P-OR ester and the incoming dipolar dioxirane reagent.¹⁴ Opening of epoxide **4.20** with (nucleophilic) Li-alkoxide

(LiOMe or LiOBn) bases cleanly afforded the desired vinylphostone **4.21**, and also promoted phenoxy displacement with retention of configuration at phosphorus in addition to the eliminative opening. The relative stereochemistry of compounds **4.20** and **4.21b** ($R^2=Me$) was determined by X-ray crystallographic analysis.⁹ It is noteworthy that attempts to open the epoxide with non-nucleophilic bases such as KHMDS or LDA resulted in decomposition.

Scheme 4.4

Functionalization of vinyl phostone intermediate **4.19a** is highlighted in Scheme 4.5. Directed dihydroxylation using the Donohoe protocol¹⁵ with stoichiometric amounts of OsO_4 /TMEDA provided the C(3)-C(5) all *syn*-triol **4.22** with excellent selectivity ($ds = 13:1$). Hydrolysis of the osmate ester was accomplished with citric acid, which has been previously shown to facilitate catalytic osmium-promoted dihydroxylation reactions due to its ability to readily hydrolyze

osmate esters.¹⁶ The excellent selectivity of this directed-dihydroxylation reaction is in agreement with the results of Donahoe, showing that substrates possessing equatorial hydroxy-groups are very selective under hydrogen-bonding conditions.¹⁷

Dihydroxylation of **4.19a** under catalytic OsO₄ conditions was previously shown by X-ray crystallographic analysis of the product, to occur *anti* to the C(5) allylic hydroxy group to afford triol **4.23** in modest selectivity (*ds* = 5:1).⁹ We were able to improve this selectivity by protecting the hydroxy-group as a benzyl ether using *in situ* formed benzyl triflate to derive **4.24**. Subsequent dihydroxylation generated triol **4.25** in excellent yield (92%) and selectivity (15:1).¹⁸

Scheme 4.5

We assumed that the dihydroxylation of **4.24** occurred *anti* to the C(5) benzyloxy group to derive **4.25**, in an analogous manner to the dihydroxylation of **4.17a** affording **4.23**.¹⁹ This assumption was confirmed by three-bond coupling analysis of coupling constants (*J*_{HP}) between the C(4) proton and P(1) atoms in the

fully dihydroxylated compounds **4.25** and **4.22** as shown in Figure 4.2. A significantly higher coupling constant (35 Hz) is observed for **4.22** when the H-C-C-P dihedral angle is 180 degrees. Alternatively, an H-C-C-P dihedral angle of < 90 degrees in **4.25** affords a much smaller coupling constant (5.8 Hz). This coupling constant data was substantiated by a 5.8 Hz coupling in the previously reported X-ray supported structure **4.23**.¹⁹

Figure 4.2 Dihedral coupling constant analysis for compounds **4.22** and **4.25**.

Alternatively, introduction of nitrogen at the C(4) position could also be achieved from vinylphosphonate **4.19a** via treatment with Cl_3CCN to form the corresponding trichloroacetimidate, which underwent facile 1,4-conjugate addition to afford **4.26** in excellent yield. Attempts at the aminohydroxylation of **4.19a** have thus far been unsuccessful.

Introduction of nitrogen nucleophiles at the C(5) position was achieved from the mesylated vinylphosphonate **4.19b**. Thus, treatment with sodium azide afforded the C(5)-inverted azide product **4.27**. Subsequent dihydroxylation proceeded with

complete selectivity to afford **4.28** as a single diastereomer (Scheme 4). The relative stereochemistry of this compound was confirmed by X-ray crystallographic analysis.

Scheme 4.6

Having established this method with a racemic allylic alcohol, we turned to the use of non-racemic allyl alcohols, which we conveniently derived from commercially inexpensive enantioenriched (97-99 % ee) benzyl- and trityl-protected glycidyl ethers.^{20,21} Transformation of these readily available epoxides into their corresponding allyl alcohols **4.15b** and **4.15c** was achieved in a single step via addition of trimethylsulfonium ylide (Scheme 4.7).^{22,23} Diastereoselective addition of the benzyl protected (2*S*)-1,2-butenediol **4.15b** proceeded in good yield and selectivity (*ds* = 6:1) to produce phosphonate **4.16b** as a mixture of P(2)-epimers. RCM of **4.16b** provided the non-racemic allyl phostone intermediate **4.17b**.

Scheme 4.7

Dihydroxylation of substrate **4.17b** provided diol **4.29** as a single diastereomer using 1% OsO₄, *m*-CPBA and NMM (N-methyl morpholine) as shown in Scheme 4.8. It was noteworthy that reactions with 4% OsO₄, *m*-CPBA/NMM or OsO₄/NMO gave a dramatic decrease in selectivity (*ds* = 2-5:1). Subsequent carbonate formation using the aforementioned triphosgene conditions, and elimination led to vinylphosphonate (-)-**4.30** in good yield.

Scheme 4.8

Installation of nitrogen nucleophiles at the C(5) position within the framework of non-racemic benzyl-protected alcohol **4.29** was achieved using similar sequences as previously described for **4.19b** (Scheme 5.9). Formation of the mesylated diol intermediate followed by elimination provided vinyl phosphonate **4.31**. Addition of a single equivalent of azide produced the intermediate azide in excellent yield. Interestingly, displacement of the C(5) mesylate in compound **4.31** using a slight excess of sodium azide was complicated by the formation of an inseparable side product (5-10 mol%). This side product most likely arose from conjugative addition of a second azide into the vinylphosphonate. Dihydroxylation of the azide containing vinyl phosphonate produced azido *P*-sugar (+)-**4.32** as a single diastereoisomer in moderate yield.

Scheme 4.9

Alternatively, installation of nitrogen at the C(4) position can be accomplished from **4.30**, by facile formation of the trichloroacetimidate and subsequent Michael addition in the presence of DBU to yield the bicyclic trichlorooxazoline **4.33** (Scheme 4.10). Hydrolysis of **4.33** yielded the trichloroacetamide of the C(4)/C(5) amino alcohol **4.34**. Dihydroxylation of **4.30** gave triol **4.35** with excellent selectivity (*ds* = 15:1), but only moderate yield (53%).

Scheme 4.10

Problems associated with the base lability of phenoxy phosphonate esters led us to develop an alternate route employing BnO-substituted phosphonate esters. Thus, the mixed phosphonate ester **4.36** could be produced by displacement of the PhO-group in the acyclic mixed phosphonate with BnOLi in DME (Scheme 4.12).

This reaction occurs with inversion of the configuration at phosphorus²⁴ to afford **4.36**. Product **4.36** was contaminated with ~4% of the vinylphosphonate arising from double bond isomerization. Reactions run in THF gave extensive isomerization of the double bond (40%). Subsequent RCM afforded the phostone **4.37** possessing a *cis*-relationship between the C(6) trityloxymethyl group and the P(2)-benzyl phosphonate ester. Dihydroxylation of **4.37** with OsO₄/NMO in the presence of citric acid yielded diol **4.38** with excellent selectivity (*ds* = 10-14:1) and in good isolated yields. Based on the aforementioned selectivity seen in the dihydroxylation of the C(6)-Me-substituted allylphostone **4.17a**, we tentatively assigned the major product **4.38** occurring via dihydroxylation *anti* to the C(6)-trityloxymethyl group. This assignment was supported via exhaustive deprotection of compounds **4.29** and **4.38** that gave rise to a common free acid, thus confirming that diols **4.29** and **4.38** differ only in their substitution at phosphorus. Conversion of the diol **4.38** into the corresponding carbonate and treatment with KHMDS gave the vinyl phosphonate **4.39** (Scheme 4.12). Dihydroxylation of this compound under standard conditions (cat. OsO₄, NMO, citric acid) proceeded with very low selectivity (*ds* = 2:1), presumably due to the *anti*-relationship between of the P(2)-benzyloxy phosphonate ester and the equatorial C(5)-OH which provide opposing factors. Alternatively, directed-dihydroxylation using the Donohoe conditions¹⁵ provided the C(3)/C(4)/C(5) all *syn*-triol as a single diastereoisomer (*ds* > 20:1). Attempts to hydrolyze the osmate ester using literature conditions (HCl in MeOH)⁸ gave only decomposition of the product. Treatment with citric acid¹⁶ gave clean hydrolysis of the osmate without

cleaving the Tr-group. This product was filtered through silica gel²⁵ and treated with catalytic amount of TsOH to give the fully deprotected tetraol **4.40**.

Scheme 4.12

In our previous work outlined in Scheme 3, we used epoxidation to derive **4.20** as an alternative route of functionalizing the RCM product **4.17a**, and ultimately to derive diastereomer **4.21a**. Unlike the dihydroxylation of **4.17a** (Scheme 4.4), the major product of the epoxidation resulted from attack *syn* to the C(6)-methyl group. Unfortunately, all epoxidations of the non-racemic phosphonates **4.17b** and **4.37** were low yielding and not very selective. Attempts to access a vinyl phosphonate with a *syn* stereochemical relationship between the C(5) and C(6) substituents using Mitsunobu inversion of the C(5) hydroxy group in **4.39** gave only starting material. Alternatively, the desired intermediate was accessed by conversion of diol **4.38** into mesylate **4.41** and carrying out S_N2-substitution with an alkoxide-containing nucleophile. The best results were seen using KOBz in the presence of 18-Crown-6 in DMF. Use of other reagents (Bu₄NOAc, NaOAc, KO₂,

CH₃CH₂CO₂Cs/CH₃CH₂CO₂H) led to cleavage of the Bn-group on the P-atom and formation of a substantial amount of the free acid. Treatment of the phenoxy substituted *P*-sugar **4.31** (Scheme 4.9) with KOBz, 18-crown-6 in DMF gave almost exclusively the free acid. Dihydroxylation of **4.42** gave the diol **4.43** in good yields and selectivity, but attempts to deprotect this compound were unsuccessful. Deprotection of the benzoate in **4.42** using Mg(OMe)₂, followed by dihydroxylation, and cleavage of the Tr-group gave the desired tetraol **4.45** as a single diastereoisomer.

Scheme 4.13

Summary 4.3

In conclusion, a facile strategy has been developed that allows for the diastereoselective generation of a number of novel *P*-sugar analogs. Additional stereoselective routes to nonracemic phosphono sugars are currently being pursued as well as the generation of libraries of pertinent analogs. Further synthetic studies, the production of chemical libraries, and biological screening of these *P*-sugars are underway and will be reported in due course.

4.4. References

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Chapter 5

Experimental Data: Chapters 2-4

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, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. Et₂O, toluene, THF and CH₂Cl₂ were purified by passage through the Solv-Tek purification system employing activated Al₂O₃ (Grubbs, R.H.; Rosen, R.K.; Timmers, F.J.; *Organometallics* **1996**, *15*, 1518-1520). Et₃N was purified by passage over basic alumina and stored over KOH. Alkyl lithium reagents were 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, and Hoveyda-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 60F₂₅₄ plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ¹H, ¹³C and ³¹P 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, in CDCl₃ unless otherwise noted. 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

(1*S*)-methyl bis[1-[(phenylmethoxy)methyl]-2-propen-1-yl] ester phosphoric acid

A solution of (*S*)-1-(benzyloxy)but-3-en-2-ol (2.05 g, 11.54 mmol) in THF (58 mL) was cooled to $-30\text{ }^{\circ}\text{C}$. $n\text{-BuLi}$ (2.47M, 11.02 mmol) was slowly added, followed by ten min 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 $-30\text{ }^{\circ}\text{C}$ for 30 min, the cold bath was removed and the solution was warmed to room temperature and stirred for an additional two hours. Upon completion the reaction was quenched with 20 mL of NH_4Cl saturated aq. The separated aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine and then dried (MgSO_4). Flash chromatography (2:1 Hex/ EtOAc) provided 1.96 g (87% yield) of the diene product as a faint yellow oil.

$[\alpha]_{\text{D}}^{20} = +0.54$ ($c = 0.37$, CH_2Cl_2).

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

^1H NMR (500 MHz, CDCl_3) δ 7.4-7.3 (m, 10H), 5.91 (ddd, $J = 17.2, 10.6, 6.4\text{ Hz}$, 1H), 5.91 (ddd, $J = 17.2, 10.6, 6.4\text{ Hz}$, 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, $J = 12.2, 5.1\text{ Hz}$, 2H), 4.54 (dd, $J = 12.0, 1.4\text{ Hz}$, 2H), 3.72 (d, $J = 11.4\text{ Hz}$, 3H), 3.62 (dd, $J = 10.6, 6.3\text{ Hz}$, 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, $J_{\text{CP}} = 0.8$ Hz), 72.42 (d, $J_{\text{CP}} = 1.5$ Hz), 54.48, 54.44; **^{31}P NMR** (162 MHz, CDCl_3) δ 0.29.

HRMS calculated for $\text{C}_{23}\text{H}_{29}\text{O}_6\text{P}$ ($\text{M}+\text{H}$) $^{+}$ 433.1780; found 433.1757 (FAB).

3,4-dideoxy-1,6-bis-O-(phenylmethyl)-cyclic 2,5-(methyl phosphate)-D-threo-Hex-3-enitol (2.16)

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 min with argon. The solution was brought to reflux while continually sparging with argon, and (ImesH₂)(PCy₃)(Cl₂)Ru=CHPh was added (200 mg, 0.235 mmol). The reaction was maintained at reflux under argon sparging for 30 min. Upon completion (monitored by TLC) the reaction was cooled to room temperature and concentrated under reduced pressure. Purification via flash chromatography (1:1 Hex/EtOAc) supplied 927 mg (68% yield) of monocyclic phosphate **2.16**.

$[\alpha]_D^{20} = -52.6$ ($c = 1.6$, CH₂Cl₂).

FTIR (neat) 3029, 1454, 1365, 1282, 1027 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (100 MHz, CDCl₃) 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, $J_{CP} = 5.1$).

³¹P NMR (162 MHz, CDCl₃) δ 3.61.

HRMS calculated for $\text{C}_{21}\text{H}_{25}\text{O}_6\text{P}$ $(\text{M}+\text{H})^+$ 405.1467; found 405.1437 (FAB).

(2*S*, 5*S*, 3*Z*)-1,6-bis(benzyloxy)hex-3-ene-2,5-diol (2.17)

Phosphate **2.16** (30 mg, 0.074 mmol) was taken up in THF (0.20 mL) and cooled to 0 °C while stirring under argon. LiAlH₄ (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 H₂O (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 (Na₂SO₄). Column chromatography (5:1 Heptane:EtOAc) provided **2.17** (18.3 mg, 75%) as a clear oil.

$$[\alpha]_D^{20} = [\alpha]_D + 21.7 \ (c = 1.7, \text{CH}_2\text{Cl}_2).$$

FTIR (neat) 3417, 3025, 2902, 1493, 1465, 1101, 1075, 737, 698 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (100 MHz, CDCl₃) δ 137.62, 132.08, 128.47, 127.87, 127.84, 73.48, 73.42, 67.21.

HRMS calculated for C₂₀H₂₄O₄ (M+Na)⁺ 351.1572; found 351.1582 (FAB).

3,4-dideoxy-1,6-bis-O-(phenylmethyl)-cyclic-2,5-(methyl phosphate)-D-threo-Hexitol
(2.18)

Post ring-closing metathesis product **2.16** (50 mg, 0.123 mmol) with (ImesH₂)(PCy₃)(Cl₂)Ru=CHPh (33 mg, 0.040 mmol), the reaction was concentrated and the resulting brown oil was taken up in dry CH₂Cl₂ (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 H₂ (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 EtOAc:Heptane) providing 45.4 mg of **2.18** (90 % yield) as a light brown oil (small ruthenium contamination estimated to be < 1%).

$[\alpha]_D^{20} = -2.15$ ($c = 0.33$, CH₂Cl₂); IR (neat) 2917, 1279, 1098, 1000, 737, 698 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (100 MHz, CDCl₃) 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.

³¹P NMR (162 MHz, CDCl₃) δ 3.02.

HRMS calculated for $\text{C}_{21}\text{H}_{27}\text{O}_6\text{P}$ ($\text{M}+\text{H}$)⁺ 407.1624; found 407.1649 (FAB).

(2*S*, 5*S*)-1,6-bis(benzyloxy)hexane-2,5-diol (2.19)

Phosphate **2.18** (30 mg, 0.074 mmol) was dissolved in THF (1.2 mL) and cooled to 0 °C while stirring under argon. LiAlH₄ (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 LiAlH₄ was added, and the solution stirred for an additional hour. The mixture was then cooled to 0 °C and slowly quenched with H₂O (0.1 mL) followed by 10% NaOH aq (0.2 mL), and then H₂O (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 (Na₂SO₄). Column chromatography (5:1 Heptane:EtOAc) provided **2.19** (21.9 mg, 90%) as a clear oil.

$[\alpha]_D^{20} = +7.06$ ($c = 0.09$, CH₂Cl₂); IR (neat) 3436, 1096, 737, 698 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) 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).

¹³C NMR (125 MHz, CDCl₃) δ 137.93, 128.46, 127.79, 127.75, 74.41, 73.34, 70.38, 29.53.

HRMS calculated for C₂₀H₂₄O₄ (M+Na)⁺ 351.1572; found 351.1582 (FAB).

General Procedure A for R₂Zn 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 (Me₂Zn required longer stirring times) at -25 °C to -30 °C, a solution of phosphate **2.16** (0.20 mmol) in THF (2 mL) was added. The reaction progress was monitored by TLC (products are baseline in EtOAc), and upon completion where quenched with 10% aq. HCl (1 mL) and stirred for 30 – 60 min. The aqueous layer was extracted was extracted with Et₂O (4x 1 mL) and the combined organic layers were subsequently washed with H₂O (1x 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 **2.16** (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 CH₂Cl₂ (4x 1 mL) and the combined organic layers were subsequently washed with H₂O (1x 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 μ L) under argon was added dibromoethane (15 μ L, 0.176 mmol), which was heated to 65 °C for one minute and then cooled to room temperature. Trimethylsilyl chloride was then added (16 μ L, 0.132 mmol) and the mixture was allowed to stir for 15 min, 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 μ L, 0.495 mmol) was added dropwise. The reaction was allowed to proceed for 30 min and monitored by TLC. If necessary, an additional 1 equivalent of Red-Al was added to ensure completion. Reaction was quenched with H₂O (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 CH₂Cl₂ (4 x) and the combined organic layers were subsequently washed with brine and dried (MgSO₄).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-methylhex-4-en-2-ol (2.27a)

Following procedure A (100 mg of **2.16**) and phosphate acid removal, column chromatography (Heptane:EtOAc 4:1) afforded **2.27a** (67 mg, 83 %) as a clear oil over two steps.

$[\alpha]_D^{20} = +30.4$ ($c = 1.0$, CH_2Cl_2)

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

^1H 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 $\text{C}_{21}\text{H}_{26}\text{O}_3$ ($\text{M}+\text{Na}$) $^+$ 349.1780; found 349.1817 (FAB).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-ethylhex-4-en-2-ol (2.23)

Following procedure A (50 mg of **2.16**) and phosphate acid removal, column chromatography (Heptane:EtOAc 4:1) afforded **2.23** (38 mg, 90%) as a clear oil over two steps.

$[\alpha]_D^{20} = +4.87$ ($c = 0.58$, CH_2Cl_2)

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

^1H 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 $\text{C}_{22}\text{H}_{28}\text{O}_3$ ($\text{M}+\text{NH}_4$) $^+$ 358.2382; found 358.2381 (FAB).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-isopropylhex-4-en-2-ol (2.27b)

Following procedure A (50 mg of **2.16**) and phosphate acid removal, column chromatography (Heptane:EtOAc 5:1) afforded **2.27b** (44.5 mg, 89 %) as a clear oil over two steps.

$[\alpha]_D^{20} = +17.5$, (c , 2.1 CH₂Cl₂)

FTIR (neat) 3446, 2348, 1101 cm⁻¹

¹H NMR (400 MHz, CDCl₃) 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)

¹³C NMR (100 MHz, CDCl₃) 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 C₂₃H₃₀O₃ (M+Na)⁺ 377.2093; found 377.2075 (FAB).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-cyclohexylhex-4-en-2-ol (2.27c)

Following procedure B (100 mg of **2.16**) and phosphate acid removal, column chromatography (Heptane:EtOAc 5:1) afforded **2.27c** (68 mg, 70 %) as a clear oil.

$[\alpha]_D^{20} = +9.84$ ($c = 1.58$, CH_2Cl_2)

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

^1H 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 $\text{C}_{26}\text{H}_{34}\text{O}_3$ ($\text{M}+\text{Li}^+$) 401.2668; found 401.2678 (FAB).

(2*S*,3*R*,*E*)-3-benzyl-1,6-bis(benzyloxy)hex-4-en-2-ol (2.27d)

Following procedure B (100 mg **2.16**) and phosphate acid removal, column chromatography (Heptane:EtOAc 4:1) afforded **2.27d** (81.0 mg, 82%) as a clear oil over two steps.

$[\alpha]_D^{20} = -6.2$ (*c* 1.4, CH₂Cl₂)

IR (neat) 3444, 1494, 1452, 1097 cm⁻¹

¹H NMR (400 MHz, CDCl₃) 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)

¹³C NMR (100 MHz, CDCl₃) 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 C₃₇H₃₀O₃ (M+Na)⁺ 425.2093; found 425.2083 (FAB).

(*R,E*)-8-(benzyloxy)-5-((*S*)-2-(benzyloxy)-1-hydroxyethyl)oct-6-enenitrile (2.27e**)**

Following procedure B (100 mg of **2.16**) and methylation/phosphate removal, column chromatography (Heptane:EtOAc 4:1) afforded **2.27e** (78.0 mg, 83%) as a clear oil.

$[\alpha]_D^{20} = -12.0$ ($c = 1.5$, CH_2Cl_2)

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

^1H 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 $\text{C}_{24}\text{H}_{29}\text{NO}_3$ ($\text{M}+\text{NH}_4$) $^+$ 397.2491; found 397.2483 (FAB).

(2*S*,3*R*)-1-(benzyloxy)-3-((*E*)-3-(benzyloxy)prop-1-enyl)-7-chloroheptan-2-ol (2.27f)

Following procedure B (100mg of **2.16**) and methylation/phosphate removal, column chromatography (Heptane:EtOAc 5:1) afforded **2.27f** (84.7 mg, 85 %) as a clear oil.

$[\alpha]_D^{20} = +5.8$ ($c = 0.625$, CH_2Cl_2).

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

^1H 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, 70.3420, 46.24, 45.00, 35.59, 29.70, 24.43.

HRMS calculated for $\text{C}_{24}\text{H}_{31}\text{ClO}_3$ ($\text{M}+\text{NH}_4$) $^+$ 420.2305; found 420.2310 (FAB).

(2*S*,3*R*,*E*)-1-(benzyloxy)-3-(3-(benzyloxy)prop-1-enyl)oct-7-en-2-ol (2.27g)

Following procedure B (100 mg, **2.16**) and phosphate acid removal, column chromatography (Heptane:EtOAc 4:1) afforded **2.27g** (61 mg, 65%) as a clear oil

$[\alpha]_D^{20} = +3.53$ ($c = 0.17$, CH₂Cl₂)

FTIR (neat) 3422, 1274, 750, 699 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) 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).

¹³C NMR (125 MHz, CDCl₃) 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 C₂₅H₃₂O₃ (M+NH₄)⁺ 398.2695; found 398.2696 (FAB).

(2*S*,3*R*,*E*)-1,6-bis(benzyloxy)-3-methylhex-4-en-2-yl methyl hydrogen phosphate
(2.26, R¹ = Me)

Using procedure A (50 mg of **2.16**) afforded **2.26** (Me) (51.5 mg, 99%) as a clear viscous oil (compound was characterized without further purification).

$[\alpha]_D^{20} = +15.6$ ($c = 4.5$, CH₂Cl₂).

FTIR (neat) 2331, 1496, 1454, 1232 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) 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)

¹³C NMR (100 MHz, CDCl₃) 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.

³¹P NMR (162 MHz, CDCl₃) δ 2.67.

HRMS calculated for C₂₂H₂₉O₆P (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 min 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 Hex/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 (2.28, R¹ = Me)

Using procedure A (50 mg, **2.1**), subsequent methylation followed by column chromatography (EtOAc:Heptane 2:1) afforded **2.28**(Me) (50 mg, 95%) as a clear oil over two steps.

$[\alpha]_D^{20} = -27.0$ ($c = 2.0$, CH₂Cl₂).

FTIR (neat) 3062, 2952, 1454, 1363, 1278, 1041 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (125 MHz, CDCl₃) 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.

³¹P NMR (162 MHz, CDCl₃) δ 2.06.

HRMS calculated for C₂₃H₃₂O₆P (M+H)⁺ 435.1937; found 435.1967 (FAB).

(4S)-1,3,2-Dioxaphosphepin, 4,7-dihydro-2-phenoxy-4-[(phenylmethoxy)methyl]-2-oxide (2.29)

A flask containing allylic alcohol **2.15** (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 *n*BuLi (1.53, 2.5M). After 10 min 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 saturated aq. NH₄Cl and the layers were separated and the aqueous layer extracted with Et₂O (2 x). The combined organic layers were concentrated under reduced pressure and dried (Na₂SO₄). 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 CH₂Cl₂ (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 (ImesH₂)(PCy₃)(Cl₂)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 chromatography (2:1 Hex:EtOAc), to yield cyclic phosphate **2.29** as a 1:1 mixture of diastereomers at phosphorus (0.301 g, 76%).

¹H NMR (400 MHz, CDCl₃) 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, $J_{\text{CP}} = 16.1$), 150.22 (d, $J_{\text{CP}} = 16.1$), 137.44, 129.68 (d, $J_{\text{CP}} = 4.0$), 128.61, 128.38, 128.23, 127.78, 127.67 (d, $J_{\text{CP}} = 7.0$), 127.42, 127.08, 125.22, (d, $J_{\text{CP}} = 6.0$), 120.11 (d, $J_{\text{CP}} = 5.0$), 119.87 (d, $J_{\text{CP}} = 4.0$), 74.35 (d, $J_{\text{CP}} = 7.0$), 74.01 (d, $J_{\text{CP}} = 4.0$), 73.47, 73.28, 71.58 (d, $J_{\text{CP}} = 9.1$), 71.15 (d, $J_{\text{CP}} = 11.1$), 64.87 (d, $J_{\text{CP}} = 7.0$), 64.80 (d, $J_{\text{CP}} = 8.0$).

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

HRMS calculated for $\text{C}_{18}\text{H}_{19}\text{O}_5\text{P}$ ($\text{M}+\text{Na}$) $^{+}$ 369.0868; found 369.0872 (FAB).

(*R,E*)-5-(benzyloxy)-2-ethylpent-3-en-1-ol (2.30)

Following procedure A (90 mg of **2.29**) and methylation/phosphate removal, column chromatography (Heptane:EtOAc 3:1) afforded **2.30** (42.1 mg, 81%) as a clear oil.

$[\alpha]_D^{20} = +6.2$ ($c = 1.6$, CH_2Cl_2).

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

^1H 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 $\text{C}_{14}\text{H}_{20}\text{O}_2$ ($\text{M}+\text{Na}$) $^+$ 243.1361; found 243.1361 (FAB).

**(7S)-1,3,2-Dioxaphosphepin,4,7-dihydro-2-methoxy-4,4-dimethyl-7-
[(phenylmethoxy)methyl]-2-oxide (2.32)**

A flask containing allylic alcohol **2.15** (0.239 g, 1.34 mmol) was diluted up in THF (0.2 M, 6.7 mL) and cooled to $-30\text{ }^{\circ}\text{C}$, followed by dropwise addition of $n\text{BuLi}$ (0.537 mL, 2.5M). After 10 min 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 saturated 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 **2.31** (0.074 mg, 0.861 mmol) was charged with THF (0.2 M, 4.31 mL) and cooled to $-30\text{ }^{\circ}\text{C}$, followed by dropwise addition of $n\text{BuLi}$ (0.346 mL, 2.4 M). After 10 min 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 saturated 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). *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 (ImesH₂)(PCy₃)(Cl₂)Ru=CHPh (0.029 mg, 0.034 mmol) was added and the reaction lowered into an oil bath warmed to 90 °C. 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 chromatography (2:1 Hex:EtOAc), to yield cyclic phosphate **2.32** 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.

¹H NMR (500 MHz, CDCl₃) 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).

¹³C NMR (125 MHz, CDCl₃) 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.

³¹P NMR (162 MHz, CDCl₃) δ 0.07 and -0.90.

(2*S*,3*S*)-1-(benzyloxy)-3-ethyl-5-methylhex-4-en-2-ol (2.33)

Following procedure A (90 mg of **2.32**) and methylation/phosphate removal, column chromatography (Heptane:EtOAc 3:1) afforded **2.33** (58.0 mg, 81%) as a clear oil.

$[\alpha]_D^{20} = +13.1$, ($c = 1.5$, CH_2Cl_2).

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

^1H 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

¹H NMR (400 MHz, CDCl₃) 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).

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

¹H NMR (400 MHz, CDCl₃) 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), 3.58 (t, $J = 7.6$ Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) 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.

(3*S*,5*S*)-hepta-1,6-diene-3,5-diol (2.39)

A flask containing $\text{Me}_3\text{S}^+\text{I}^-$ (59.0 g, 289.0 mmol) in THF (289.0 mL) was lowered to -40°C . Butyl lithium (2.44M, 107 mL) was slowly added via an addition funnel over 35 min. Upon addition, the reaction mixture was stirred for an additional 10 min, followed by slow cannulation of a THF solution (29 mL) containing (2*S*,4*S*)-1,5-dichloro-penta-2,4-diol **2.37** (5.0 g, 28.9 mmol). The mixture was stirred for 30 min and allowed to *slowly* warm to rt in the dry ice bath (white precipitate formed, fast warming results in lower yields). After an additional two hrs of stirring, 400 mL of NH_4Cl (saturated aq.) was added slowly and the layers separated. The aqueous layer was extracted with EtOAc (3x), the combined organic layers were washed with NaHCO_3 (saturated aq.), brine, and dried (Na_2SO_4). Flash chromatography (2:1 Hex/EtOAc) provided (3*S*,5*S*)-hepta-1,6-diene-3,5-diol **2.39** as a clear oil in 82% yield (3.02 g).

$[\alpha]_{\text{D}}^{20} = -29.9$ (c 0.33, CH_2Cl_2); IR (neat) 3353, 1421, 1117, 1056 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 5.90 (dddd, $J = 17.2, 8.7, 5.4, 3.2$ Hz, 2H), 5.27 (ddd, $J = 17.2, 1.5, 1.5$ Hz, 2H), 5.12 (dd, $J = \text{ddd}, J = 10.5, 1.6, 1.6$ Hz, 2H), 2.75-3.09 (bs, 2H), 1.75 (ddd, $J = 6.01, 6.01, 3.58$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 140.4, 114.5, 70.3, 41.9.

HRMS calculated for $\text{C}_7\text{H}_{13}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 129.0916; found 129.0943 (FAB).

(4*S*,6*S*)-3,2-Dioxaphosphorinane, 2-chloro-4,6-diethenyl-2-oxide (2.40)

A flask was charged with diol **2.39** (1.0 g, 7.80 mmol), NEt₃ (1.740 g, 17.2 mmol), and DMAP (0.190g, 1.56 mmol) in DCM (39 mL). The solution was cooled to 0 °C, and freshly distilled POCl₃ was added dropwise. After 25 min stirring in the ice bath, 20 mL of ether was added, and the salts filtered off. The concentrated reaction mixture was purified by flash chromatography (1:1 Hexane/EtOAc) to supply 1.4 g (90% yield) of the (3*S*,5*S*)-phosphate monochloride **2.40** as a clear oil.

[α]_D²⁰ = +81.0 (*c* 1.14, CH₂Cl₂).

FTIR (neat) 1429, 1413, 1302, 1108, 1024, 987, 970 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 6.13 (¹H NMR δ 6.13 (ddd, *J* = 16.7, 10.7, 5.9 Hz, 1H), 5.88 (dddd, *J* = 15.8, 12.7, 5.9 Hz, *J*_{HP} = 2.1 Hz, 1H), 5.50 (dd, *J* = 17.1, 0.9 Hz, 1H), 5.43 (dd, *J* = 7.26, 1.2 Hz, 1H), 5.35-5.39 (m, 2H), 5.11-5.26 (m, 2H), 2.25-2.29 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 133.7 (d, *J*_{CP} = 9.0 Hz), 133.4 (d, *J*_{CP} = 2.0 Hz), 119.4, 118.5, 81.1 (d, *J*_{CP} = 8.6 Hz), 77.9 (d, *J*_{CP} = 7.1 Hz), 34.2 (d, *J*_{CP} = 9.1 Hz).

³¹P NMR (162 MHz, CDCl₃) δ -3.76.

HRMS Exact mass: calculated for C₇H₁₄NO₃ (M+NH₃) 226.0399; found 226.0400 (FAB).

(4S,6S)-1,3,2-Dioxaphosphorinane,-4,6-diethenyl-2-(2-propenyloxy)-2-oxide (2.41)

A solution of allyl alcohol (0.468 g, 8.06 mmol) in THF (40.3 mL) was cooled to -30 °C. ⁿBuLi (2.47 M, 7.72 mmol) was slowly added, followed by five min of stirring. A solution of phosphate monochloride **2.40** (1.40 g, 6.71 mmol) in THF (13.4 mL) was slowly cannulated into the reaction vessel containing the alkoxide. The reaction was stirred at -30 °C for two hrs and was quenched with 40 mL of NH₄Cl saturated aq. The separated aqueous layer was extracted EtOAc (3x), and the combined organic layers were washed with NaHCO₃ (saturated aq.), brine, and dried (Na₂SO₄). Flash chromatography (2:1 Hex/EtOAc) provided **2.41** (1.40 g, 91% yield) of the triene product as a clear oil.

$$[\alpha]_D^{20} = +59.2 \text{ (} c=1.3, \text{CH}_2\text{Cl}_2 \text{)}$$

FTIR (neat) 2360, 1281, 1016 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 6.03 (dd, $J_{\text{HH}} = 16.7, 10.6, 5.63$ Hz, 1H), 5.86-5.98 (m, 2H), 5.45 (d, $J_{\text{HH}} = 17.1$ Hz, 1H), 5.38 (d, $J_{\text{HH}} = 17.6$ Hz, 1H), 5.36 (dd, $J_{\text{HH}} = 17.1, 1.4$ Hz, 1H), 5.31 (d, $J_{\text{HH}} = 10.6$ Hz, 1H), 5.29 (d, $J_{\text{HH}} = 10.6$ Hz), 5.25 (dd, $J_{\text{HH}} = 10.4, 0.9$ Hz, 2H), 4.97-5.09 (m, 2H), 4.57-4.61 (m, 2H), 2.14-2.21 (m, 1H), 2.02-2.08 (m, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 135.4, 135.3, 133.0, 132.9, 118.7, 118.0, 78.3 (d, $J_{\text{CP}} = 6.9$ Hz), 76.7 (d, $J_{\text{CP}} = 6.1$ Hz), 68.6 (d, $J_{\text{CP}} = 5.3$ Hz), 35.6 (d, $J_{\text{CP}} = 7.7$ Hz).

³¹P NMR (162 MHz, CDCl₃) δ -6.51.

HRMS Exact Mass: calculated for C₁₀H₁₆O₄P (M+H)⁺ 231.0786; found 231.0792 (FAB)

(1*S*,6*S*,8*S*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-8-ethenyl-1-oxide (2.35)

A flask containing triene phosphate **2.41** (0.325 g, 1.4 mmol) was charged with CH₂Cl₂ (280 mL) that had been degassed 10 min with argon. (ImesH₂)(PCy₃)(Cl)₂Ru=CHPh, was added (35 mg, 0.042 mmol) and the reaction mixture was refluxed for 30-45 min. Upon completion (monitored by TLC) the reaction was cooled to rt and concentrated under reduced pressure. Purification via flash chromatography (2:1 Hex/EtOAc) supplied 226 mg (80% yield) of the bicyclic phosphate as a solid.

$[\alpha]_D^{20} = -78.3$ ($c = 3.4$, CH₂Cl₂)

FTIR (neat) 2359, 2341, 1290, 1087 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 6.01 (ddd, $J_{HH} = 9.53, 6.72, 3.28$, Hz, 1H), 5.81 (dddd, $J_{HH} = 16.2, 10.5, 5.3$ Hz, $J = 1.7, 0.9$ Hz, 1H), 5.59 (ddd, $J_{HH} = 11.8, 3.3, 3.0$ Hz, 1H), 5.38 (dd, $J_{HH} = 17.2, 0.7$ Hz, 1H), 5.21 (dd, $J_{HH} = 10.6, 0.6$ Hz, 1H), 5.12-5.14 (m, 1H) 4.91-5.00 (m, 2H), 4.33 (ddd, $J = 21.5, 14.7$ Hz, $J_{HH} = 6.71$ Hz, 1H), 2.17 (ddd, $J_{HH} = 14.6$ Hz, $J = 12.1, 6.2$ Hz, 1H), 1.78 (d, $J_{HH} = 14.7$ Hz, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 134.6 (d, $J_{CP} = 10.6$ Hz), 129.5, 127.8, 117.3, 77.0 (d, $J_{CP} = 6.5$ Hz), 76.2 (d, $J_{CP} = 6.1$ Hz), 62.9 (d, $J_{CP} = 6.3$ Hz), 34.7 (d, $J_{CP} = 5.7$ Hz).

³¹P NMR (162 MHz, CDCl₃) δ -2.68.

HRMS Exact Mass: calculated for C₈H₁₃O₄P (M+H)⁺ 203.0473; found 203.0500 (FAB).

2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-8-ethyl-1-oxide (2.49)

Wilkinson's catalyst (0.069 g, 0.0757mmol) was added to an oven-dried flask under the inert conditions of a glove box. Bicyclic phosphate **2.35** was cannulated over to the catalyst as a solution in toluene (0.631 mL, slight heating was necessary to dissolve phosphate). Upon addition of the phosphate solution, the reaction flask was evacuated (2 sec), and H₂ was bubbled through the solution under the pressure of a balloon. This was repeated two more times and the reaction was stirred for 45 min. Upon complete consumption of the starting material (GC analysis), the reaction was filtered through a cotton/sand plug and concentrated. The reaction mixture which contained the desired product and the fully hydrogenated system was purified via flash chromatography (1:1 CH₂Cl₂:EtOAc) to provide 62 mg (40% yield) of the desired product as a clear oil.

$[\alpha]_D^{20} = +78.3$ ($c=1.36$, CH₂Cl₂).

FTIR (neat) 1463, 1260, 1068 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 5.99-6.03 (m, 1H), 5.58 (ddd, $J_{HH} = 11.8, 3.7, 2.8$ Hz, 1H), 5.14-5.20 (m, 1H), 4.94-5.00 (m, 1H), 4.45-4.51 (m, 1H), 4.34 (ddd, $J = 27.7, 14.7, 6.7$ Hz, 1H), 2.15 (ddd, $J = 14.6, 11.9, 6.3$ Hz, 1H), 1.69-1.78 (m, 2H), 1.59-1.66 (m, 1H), 0.98 (t, $J_{HH} = 7.4$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 129.89, 127.79, 77.9 (d, $J_{CP} = 6.8$ Hz), 77.2 (d, $J_{CP} = 6.7$ Hz), 62.9 (d, $J_{CP} = 6.4$ Hz), 34.4 (d, $J_{CP} = 5.9$ Hz), 28.7 (d, $J_{CP} = 10.1$ Hz), 8.99.

^{31}P NMR (162 MHz, CDCl_3) δ -2.06.

HRMS Exact Mass: calculated for $\text{C}_8\text{H}_{17}\text{NO}_4\text{P}$ ($\text{M}+\text{NH}_4$) $^+$ 222.0895; found 222.0874 (FAB).

(α S,4S)-1,3,2-Dioxaphosphepin-4-ethanol- α -ethenyl-4,7-dihydro-2-hydroxy-2-oxide monolithium salt (2.42)

Phosphate **2.35** (0.074g, 0.366 mmol) was taken up in dioxane (7.32 mL) followed by the addition of a 0.06 M aqueous LiOH solution (7.32 mL). The reaction was run at rt with progress monitored by TLC. Upon completion (2-2.5 hrs), H₂O and dioxane were removed to near complete dryness. One gram of silica gel was added and the dry pack mixture was added to the top of a small plug of silica. The column was flushed with 4:1 EtOAc/MeOH. Upon concentration, the product was dried overnight in a vacuum oven (45 °C, 30 mm Hg), to provide 75 mg of the bicyclic phosphate as a white hygroscopic solid (97% yield, 44:1 selectivity via ³¹P NMR of crude reaction mixture).

¹H NMR (400 MHz, CD₃OD) δ 5.89 (ddd, *J*_{HH} = 16.8, 10.7, 3.5 Hz, 1H), 5.65-5.75 (m, 2H), 5.30 (d, *J*_{HH} = 17.1 Hz, 1H), 5.16 (d, *J*_{HH} = 10.6 Hz, 1H), 4.84-4.92 (m, 2H), 4.57 (ddd, *J* = 20.3, 13.6, 5.6 Hz, 1H), 4.29-4.36 (m, 1H), 1.80-1.96 (m, 2H).

¹³C NMR (100 MHz, CD₃OD) δ 140.5, 139.8, 124.4, 114.6, 76.6 (d, *J*_{CP} = 4.8 Hz), 69.0, 62.8 (d, *J*_{CP} = 5.0 Hz), 44.4.

³¹P NMR (162 MHz, CD₃OD) δ -0.06.

HRMS MS *m/z* (M⁺)(rel. intensity) 227(7), 154(100), 136(65), 107(17).

(4S,6S)-1,3,2-Dioxaphosphorinane-4-ethenyl-2-hydroxy-6-[(1Z)-3-(phenylthio)-1-propenyl]-2-oxide lithium salt (2.45)

Phosphate **2.35** (0.023 g, 0.114 mmol) was taken up in THF (1.14 mL), followed by the slow addition of LiSPh (1.0M, 0.284 mL) at rt. After stirring for five min the reaction was concentrated and ran through a short plug of silica (5:1 EtOAc/MeOH) to remove excess thiophenol. A light brown semi-solid was recovered (35.2 mg, 98% yield, one peak by ^{31}P NMR analysis of crude reaction mixture).

$[\alpha]_D^{20} = +99.1 (c=3.16, \text{CH}_2\text{Cl}_2)$.

FTIR (neat) 1637, 1220, 1099, 1062 cm^{-1} .

^1H NMR = (400 MHz, CD_3CN) δ 7.15-7.38 (m, 5H), 6.02 (ddd, $J_{\text{HH}} = 16.5, 10.5, 5.6$ Hz, 1H), 5.92-5.97 (m, 1H), 5.56-5.63 (m, 1H), 5.29 (d, $J_{\text{HH}} = 17.2$ Hz, 1H), 5.17-5.20 (m, 1H), 5.14 (d, $J_{\text{HH}} = 17.2$ Hz, 1H), 4.84-4.87 (m, 1H), 3.74 (dd, $J_{\text{HH}} = 13.7$ Hz, $J_{\text{HP}} = 8.8$ Hz, 1H), 3.53 (dd, $J_{\text{HH}} = 13.8$ Hz, $J_{\text{HP}} = 3.5$ Hz, 1H), 1.73-1.76 (m, 1H).

^{13}C NMR = (100 MHz, CD_3CN) δ 139.1 d, $J_{\text{CP}} = 6.1$ Hz), 137.2, 133.5 (d, $J_{\text{CP}} = 6.1$ Hz), 131.2, 130.4, 128.4, 127.8, 116.7, 75.7 (d, $J_{\text{CP}} = 4.9$ Hz), 71.8 (d, $J_{\text{CP}} = 5.4$ Hz), 37.6 (d, $J_{\text{CP}} = 5.2$ Hz), 32.0.

^{31}P NMR (162 MHz, CD_3CN) δ -3.63.

(4S)-1,3,2-Dioxaphosphepin-4-(2E)-2-hexenyl-4,7-dihydro-2-hydroxy-2-oxide (2.47)

A flame-dried flask containing CuCN (0.191 g, 2.14 mmol) and LiCl (0.185 g, 4.28 mmol) was evacuated and flushed with argon (3x). THF was added (2.14 mL) and the solution was lowered to -30°C and stirred for five min. ZnEt_2 (1.0 M solution in THF, 2.25 mL) was added dropwise to the mixture and stirred for 30 min (brown solution took on a light green tint). A solution of phosphate **2.35** (0.216 g, 1.07 mmol) in THF (10.7 mL) was slowly cannulated into the cuprate while maintaining the temperature at -30°C . The reaction was stirred for one hour and quenched with 15 mL of 10% HCl (the reaction was stirred until all copper solid dissolves). The layers were separated, and the aqueous layer was extracted CH_2Cl_2 (4x). The combined organic layers were washed with H_2O (1x) and concentrated to provide 148 mg (84% yield, 7.7:1 selectivity by ^{31}P analysis of the crude reaction mixture. Flash chromatography (9:1 EtOAc/MeOH) provided acid **2.47** as a near single product for analysis (44:1 by ^{31}P NMR).

$[\alpha]_{\text{D}} +14.5$ ($c = 1.2$, CH_2Cl_2); IR (neat) 1454, 1226, 1026 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 9.50-9.53 (m, 1H), 5.62-5.69 (m, 2H), 5.56 (dt, $J_{\text{HH}} = 15.3$, 6.6 Hz, 1H), 5.40 (dt, $J_{\text{HH}} = 15.4$, 6.5 Hz, 1H), 5.01-5.02 (m, 1H), 4.86 (ddd, $J = 16.7$, 8.1, 2.9 Hz, 1H), 4.42 (ddd, $J = 25.4$, 15.3, 2.0 Hz, 1H), 2.41 (ddd, $J = 13.0$, 7.3, 6.2 Hz, 1H), 2.39 (ddd, $J = 14.2$, 7.1, 7.0 Hz, 1H), 1.99 (dt, $J_{\text{HH}} = 7.1$, 6.4 Hz, 2H), 1.40 (q, $J_{\text{HH}} = 14.6$, 7.4 Hz, 2H), 0.91 (t, $J_{\text{HH}} = 6.8$, 6.8, Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 135.0, 130.5, 126.6, 123.7, 74.4 (d, $J_{\text{CP}} = 5.6$ Hz), 64.3 (d, $J_{\text{CP}} = 5.6$ Hz), 39.0 (d, $J_{\text{CP}} = 10.1$ Hz), 34.6, 29.7, 22.4, 13.6.

^{31}P NMR (162 MHz, CDCl_3) δ 5.12.

(*S*,2*Z*,6*E*)-deca-2,6-diene-1,4-diol (2.48)

Phosphate acid **2.47** (0.035 mg, 0.151 mmol) was taken up in toluene (2.0 mL) and cooled to 0 °C. Red-Al (0.229 mL, 0.754 mmol of 65% solution in toluene) was slowly added and the reaction brought to rt. After an hour, an additional 3 eq. (0.138 mL, 0.140 mmol) of Red-Al was added, followed by 2 hrs of stirring. The reaction was quenched with 2.5 mL of NH₄Cl (saturated aq.), followed by the addition of 10% HCl (0.5 mL). The layers were separated and the aqueous layer extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na₂SO₄), and concentrated under reduced pressure. Flash chromatography (1:1.5 EtOAc/CH₂Cl₂) provided 21 mg (84% yield) of the title compound. $[\alpha]_D^{20} = +23.1$ ($c = 0.585$, CH₂Cl₂)

FTIR (neat) 3334, 1022 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 5.70-5.76 (m, 1H), 5.51-5.59 (m, 2H), 5.32-5.39 (m, 1H), 4.77 (dd, $J = 14.1, 7.2$ Hz, 1H), 4.27 (ddd, $J = 13.1, 7.3, 1.1$ Hz, 1H), 4.10 (ddd, $J = 13.1, 5.1, 1.1$ Hz, 1H), 2.34-2.47 (m, 2H), 2.24 (dd, $J = 6.9, 6.9$ Hz, 2H), 1.99 (q, $J = 14.2, 7.1, 7.1$ Hz, 2H), 1.37 (dt, $J = 14.8, 7.4, 7.4$ Hz, 2H), 0.88 (t, $J = 7.3, 7.3$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 135.1, 134.3, 130.5, 124.9, 67.2, 58.6, 40.8, 34.70, 22.5, 13.6.

HRMS Exact Mass: calculated for C₁₀H₂₂NO₃ (M+NH₄)⁺ 188.1651; found 188.1643 (FAB).

(4*S*,6*S*,*Z*)-octa-2,7-diene-1,4,6-triol (2.46)

Bicyclic phosphate **2.35** (0.500, 2.47 mmol) was dissolved in THF (30 mL) and cooled in an ice bath with stirring for a period of five min. LiAlH_4 (0.189 g, 4.95 mmol) was added in three increments over a 10-minute period. The reaction was stirred for an additional hour followed by a nonaqueous quench (0.51 mL H_2O slow addition, 0.51 mL 15% NaOH slow addition, and 1.53 mL H_2O). The salts were filtered and washed with ether (5x) to provide 238 mg (62% yield) of the triol as a clear oil.

$[\alpha]_D^{20} = -5.0$ ($c = 0.26$, CH_2Cl_2); IR (neat) 3334, 1022 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 5.94 (dddd, $J = 17.0, 10.5, 5.5, 1.0$ Hz, 1H), 5.62-5.75 (m, 2H), 5.32 (dd, $J = 17.2, 1.3$ Hz, 1H), 5.17 (dd, 10.5, 1.2 Hz, 1H), 4.78 (ddd, $J = 7.5, 3.1, 3.1$ Hz, 1H), 4.42-4.50 (m, 1H), 4.28 (dd, $J = 13.1, 6.8$ Hz, 1H), 4.22 (dd, $J = 13.2, 5.8$ Hz, 1H), 2.81 (bs, 3H), 1.86 (dddd, $J = 12.2, 8.6, 3.4, 1.0$ Hz, 1H), 1.68 (dddd, $J = 12.5, 7.8, 3.2, 1.0$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 140.3, 134.8, 129.9, 114.8, 70.4, 65.6, 58.6, 42.5 Hz.

HRMS Exact Mass: calculated for $\text{C}_8\text{H}_{15}\text{O}_3(\text{M}+\text{H})^+$ 159.1021; found 159.1025 (FAB).

(3*R*,5*S*,6*R*)-6-ethyloct-7-ene-3,5-diol (2.50)

A thoroughly dried flask was charged with a solution of CuCN·2LiCl in THF (1.1 mL, 1.0 M solution) and lowered to $-30\text{ }^{\circ}\text{C}$. Et₂Zn in THF (1.1 mL, 1.0 M solution) was slowly added. Upon addition, the mixture was stirred for 30 min at $-30\text{ }^{\circ}\text{C}$ (mossy green color). A solution of phosphate **12** (0.05 g, 0.245 mmol) in THF (2.45 mL) was cannulated slowly into the cuprate solution (at $-30\text{ }^{\circ}\text{C}$). The reaction was stirred for 3 hrs and quenched with 10% HCl (15 mL, the reaction was stirred until copper solids dissolved). The two layers were separated, and the aqueous layer was washed with CH₂Cl₂ (4x). The combined organic layers were washed with H₂O (1x) and concentrated under reduced pressure to provide 46 mg of the crude phosphonic acid (one product peak by ³¹P analysis) as an oil. The acid was taken up in toluene (2.0 mL) and cooled to $0\text{ }^{\circ}\text{C}$. Red-Al (0.600 mL of 65% solution in toluene) was slowly added over a 10-minute period. Upon addition of Red-Al, the flask was warmed to rt and stirred for 3 hrs. The reaction was quenched with 3 mL of NH₄Cl (saturated, aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na₂SO₄), and concentrated under reduced pressure. Flash chromatography (1:1 EtOAc.CH₂Cl₂) provided the title compound (69% combined yield from phosphate **12**).

$[\alpha]_{\text{D}}^{20} = -22.3$ ($c = 0.31$, CH₂Cl₂).

FTIR (neat) 3380, 1072 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 5.01 (ddd, *J* = 17.4, 9.3, 9.3 Hz, 1H), 5.24 (d, *J* = 10.2 Hz, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 3.76-3.87 (m, 2H), 2.07-2.24 (bs, 2H), 1.47-1.56 (m, 3H), 1.23-1.27 (m, 1H), 0.95 (t, *J* = 7.4, 7.4 Hz, 3H), 0.88 (t, *J* = 7.4, 7.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 139.2, 119.1, 71.1, 71.0, 53.0, 39.7, 30.6, 23.8, 12.3, 10.6.

(4*S*,6*S*)-1,3,2-Dioxaphosphorinane-4,6-diethenyl-2-[[*(1S)*-1-[1-methyl-2-(phenylmethoxy)ethyl]-2-propenyl]oxy]-2-oxide

Benzyl protected secondary allyl alcohol **2.55** (0.295g, 1.44 mmol) in THF (8 mL) was cooled to $-10\text{ }^{\circ}\text{C}$ and stirred for 10 min, upon which time $n\text{BuLi}$ (2.5 M, 0.605 mL) was slowly added. The reaction was stirred for five min, followed immediately by the cannulation of phosphate monochloride **2.40** (0.390 g, 1.87 mmol) in THF (4 mL). The reaction was warmed to rt and stirred for an additional 2 hrs. The mixture was quenched with 10 mL NH_4Cl (saturated aq.). The separated aqueous layer was washed with EtOAc (3x), and the combined organic layers were washed once with NaHCO_3 , brine, and dried (Na_2SO_4), followed by concentration under reduced pressure. Flash chromatography (1:1 Hex/EtOAc) provided 0.465 g (86% yield) of the triene phosphate as a clear oil.

$[\alpha]_D^{20} = +29.5$ ($c = 0.74$, CH_2Cl_2); IR (neat) 1454, 1363, 1283, 1004 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.26-7.34 (m, 5H), 5.82-6.02 (m, 3H), 5.44 (d, $J_{\text{HH}} = 17.1$ Hz), 5.37-5.468 (m, 5H), 5.06-4.95 (m, 2H), 4.53 (dd, $J_{\text{HH}} = 11.8$, 2.0 Hz, 1H), 4.43 (dd, $J_{\text{HH}} = 11.8$, 2.0 Hz, 1H), 3.47 (ddd, $J_{\text{HH}} = 9.0$, 7.0, 2.0 Hz, 1H), 2.01-2.16 (m, 3H), 0.97 (dd, $J_{\text{HH}} = 6.9$, 2.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 138.4, 135.3 (d, $J_{\text{CP}} = 4.0$), 135.3, 135.1 (d, $J_{\text{CP}} = 6.7$), 135.1, 128.3, 127.7, 127.5, 117.7, 117.6, 117.4, 81.0 (d, $J_{\text{CP}} = 6.4$ Hz), 77.2 (d, $J_{\text{CP}} =$

6.4 Hz), 76.1 (d, $J_{\text{CP}} = 6.1$ Hz), 73.2, 71.7, 38.7 (d, $J_{\text{CP}} = 6.4$ Hz), 35.2 (d, $J_{\text{CP}} = 7.3$ Hz), 11.61.

^{31}P NMR (162 MHz, CDCl_3) δ 2.70.

HRMS Exact Mass: calculated for $\text{C}_{20}\text{H}_{28}\text{O}_5\text{P}$ ($\text{M}+\text{H}$) $^+$ 379.1674; found 379.1647 (FAB)

(1*S*,3*S*,6*S*,8*S*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-8-ethenyl-3-[(1*S*)-1-methyl-2-(phenylmethoxy)ethyl]-1-oxide (2.56)

Toluene (15 mL) was degassed with argon for 10 min and added to a flask containing the triene metathesis precursor (48 mg, 0.1322 mmol). (ImesH₂)(PCy₃)(Cl)₂Ru=CHPh was added (0.003 g, 0.004 mmol) and the reaction was refluxed for two hrs. Upon completion (TLC analysis), concentration of the reaction mixture followed by flash chromatography (2:1 Hex/EtOAc then EtOAc) afforded 37 mg (80% yield) of bicyclic **2.56** as an oil.

¹H NMR +56.2 (*c* = 0.35, CH₂Cl₂).

FTIR (neat) 1299, 1265, 1091, 1068, 736 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.25-7.36 (m, 5H), 5.81-5.91 (m, 2H), 5.6 (ddd, *J* = 11.8, 1.9, 1.9 Hz, 1H), 5.39-5.43 (m, 2H), 5.25 (d, *J*_{HH} = 10.7 Hz, 1H), 5.13-5.20 (m, 1H), 4.96 (dd, *J*_{HP} = 11.7 Hz, *J*_{HH} = 4.3 Hz, 1H), 4.60 (d, *J*_{HH} = 11.7 Hz, 1H), 4.46 (d, *J*_{HH} = 11.7 Hz, 1H), 2.19 (ddd, *J*_{HH} = 14.4 Hz, 12.2, *J*_{HP} = 6.2 Hz, 1H), 2.00-2.16 (m, 1H), 1.77 (d, *J*_{HH} = 14.6 Hz, 1H), 0.98 (d, *J*_{HH} = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 138.2, 134.8 (d, *J*_{CP} = 6.4 Hz), 131.9, 129.4, 128.3, 127.8, 127.5, 117.1, 76.8 (d, *J*_{CP} = 6.5 Hz), 76.1 (d, *J*_{CP} = 6.2 Hz), 73.9 (d, *J*_{CP} = 6.3 Hz), 73.4, 71.4, 39.0 (d, *J*_{CP} = 9.7 Hz), 34.9 (d, *J*_{CP} = 6.0 Hz), 10.2.

³¹P NMR (162 MHz, CDCl₃) δ -3.58.

HRMS Exact Mass: calculated for $\text{C}_{18}\text{H}_{24}\text{O}_5\text{P}$ ($\text{M}+\text{H}$)⁺ 351.1361; found 351.1345 (FAB).

(1*S*,3*S*,6*S*,8*R*)2,9,10-trioxa-1-phosphabicyclo[4.3.1]decane-8-ethyl-3-[(1*S*)-1-methyl-2-(phenylmethoxy)ethyl]-1-oxide (2.57)

Toluene (100 mL) was degassed with argon for 10 min and added to a flask containing the acyclic triene (0.391 g, 1.03 mmol). $(\text{ImesH}_2)(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHPh}$ was added (0.026 g, 0.031 mmol) and the reaction was refluxed for two hrs. Upon completion (TLC analysis), the reaction was concentrated and transferred with 20 mL of dry CH_2Cl_2 to a H_2 Parr bomb apparatus. The solution was purged with H_2 and the bomb sealed. The mixture was heated at 70 °C and 500 psi H_2 for 7 hrs. Concentration under reduced pressure and purification of the mixture via flash chromatography (2:1 Hex/EtOAc then EtOAc) supplied 288 mg of the hydrogenated bicyclic phosphate **2.57** (79% yield) as a clear oil.

$[\alpha]_{\text{D}}^{20} = +25.7$ ($c = 0.28$, CH_2Cl_2).

FTIR (neat) 1365, 1294, 1101, 1027 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 6.98-7.10 (m, 5H), 4.47-4.52 (m, 1H), 4.35-4.39 (m, 1H), 4.33 (d, $J_{\text{HH}} = 11.9$ Hz, 1H), 4.19 (d, $J_{\text{HH}} = 11.7$ Hz, 1H), 4.17-4.21 (m, 1H), 3.23 (dd, $J_{\text{HH}} = 9.1, 7.8$ Hz, 1H), 3.13 (dd, $J_{\text{HH}} = 9.2, 5.5$ Hz, 1H), 1.33-2.00 (m, 8H), 0.73 (t, $J_{\text{HH}} = 7.4$ Hz, 3H), 0.70 (d, $J_{\text{HH}} = 6.9$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 138.8, 128.8, 128.3, 128.0, 79.8 (d, $J_{\text{CP}} = 6.6$ Hz), 79.2 (d, $J_{\text{CP}} = 6.4$ Hz), 76.5 (d, $J_{\text{CP}} = 6.1$ Hz), 73.9, 72.6, 40.1 (d, $J_{\text{CP}} = 10.2$ Hz), 38.9 (d, $J_{\text{CP}} = 8.0$ Hz), 32.9, 30.1, 30.0 (d, $J_{\text{CP}} = 8.4$ Hz), 11.0, 9.80.

^{31}P NMR (162 MHz, CDCl_3) δ -3.89.

(3*R*,5*R*,8*S*,9*S*)-10-(benzyloxy)-9-methyldecane-3,5,8-triol (2.59)

Phosphate **2.57** (0.250 g, 0.712 mmol) was taken up in THF (7.1 mL) and lowered to 0 °C. LiAlH₄ (0.076 mg, 2.00 mmol) was added in 25 mg increments over a five-minute period. Upon complete addition of LiAlH₄, the reaction was warmed to rt and stirred for one hour. The reaction was quenched under non-aqueous conditions (0.076 mL H₂O slowly, 0.076 mL 15% NaOH slowly, and 0.229 mL H₂O). Salts were filtered and washed (5x with ether) to supply 0.210 mg of triol **2.59** (96% yield) as an oil.

$[\alpha]_D^{20} = -8.8$ ($c = 0.48$, CH₂Cl₂); IR (neat) 3382, 1452, 1090, 1072 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.25-7.35 (m, 5H), 4.49 (s, 2H), 3.93-4.00 (m, 1H), 3.77-3.85 (m, 2H), 3.52 (d, $J = 5.5$ Hz, 2H), 3.30-3.57 (bs, 3H), 1.83-1.92 (m, 1H), 1.41-1.69 (m, 8H), 0.95 (d, $J = 7.1$ Hz, 3H), 0.91 (t, $J = 7.4$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 137.9, 128.4, 127.7, 127.6, 74.5, 74.1, 73.3, 70.5, 68.6, 41.9, 38.2, 34.3, 30.1, 29.9, 11.0, 10.1.

HRMS Exact Mass: calculated for C₁₈H₃₁O₄ (M+H)⁺ 311.2222; found 311.2203 (FAB).

**(α S,4S,7S)-1,3,2-Dioxaphosphepin-4-ethanol- α -ethenyl-4,7-dihydro-2-hydroxy-7-
[(1S)-1-methyl-2-(phenylmethoxy)ethyl]-2-oxide monolithium salt (2.58)**

Phosphate **2.56** (0.029g, 0.082 mmol) was taken up in dioxane (1.6 mL) and subjected to a 0.06 M aqueous LiOH solution (1.6 mL). The reaction was run at rt with progress monitored by TLC. Upon completion (2.5-3 hrs), H₂O and dioxane were removed to near complete dryness. The product was dried overnight in a vacuum oven (45 °C, -30 mm Hg) and analyzed without further purification.

¹H NMR (400 MHz, CD₃OD) δ 7.18-7.40 (m, 5H), 5.80-5.87 (m, 1H), 5.37-5.46 (m, 2H), 5.29 (d, J_{HH} = 17.1 Hz, 1H), 5.39-5.43 (m, 2H), 5.29 (d, J_{HH} = 17.1 Hz, 1H), 4.97-5.05 (m, 4H), 4.78-5.89 (m, 2H) 4.53 (d, J_{HH} = 11.9 Hz, 1H), 4.46 (d, J_{HH} = 11.9 Hz, 1H), 1.93-2.00 (m, 1H), 1.70-1.84 (m, 2H), 1.10 (d, J_{HH} = 6.4 Hz, 3H).

¹³C NMR (100 MHz, CD₃OD) δ 140.5, 140.0, 137.4, 129.4, 128.9, 128.7, 127.6, 114.5, 77.4 (d, J_{CP} = 2.9 Hz), 76.1 (d, J_{CP} = 2.9 Hz), 74.3, 74.0, 69.8, 44.6, 40.7 (d, J_{CP} = 6.7 Hz), 13.2.

³¹P NMR (162 MHz, CD₃OD) δ -0.18.

(1*S*,6*S*,8*R*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-8-[2-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-1-oxide (2.51)

Phosphate **2.35** (0.135 g, 0.667 mmol) was taken up in THF (1 mL), followed by the slow addition of a 0.5M solution 9-BBN in THF (6.67 mL, 3.34 mmol). The solution stirred at rt for three hrs (monitored by TLC). H₂O was added (2 mL) followed by the addition of sodium perborate (1.54 g, 10.0 mmol). Following 12 hrs of stirring at rt, CH₂Cl₂ (2 mL) was added and the organic layer removed. The aqueous layer was extracted with CH₂Cl₂ (**4x**). The combined organic layers were extracted with brine and dried (Na₂SO₄). Concentration under reduced pressure, followed by flash chromatography (EtOAc) provided 64 mg (44% yield) of the primary alcohol. The alcohol (60 mg, 0.27 mmol) was taken up in CH₂Cl₂ (0.27 mL), followed by the addition of 2,6-lutidine (0.064 mL, 0.548 mmol) and *t*-BuPh₂SiCl at rt. The reaction was complete after stirring four hrs at rt. The reaction mixture was concentrated under reduced pressure and directly chromatographed (6:1 Hex/EtOAc) to provide 0.118 mg (94% yield) of **2.51** as an oil.

$[\alpha]_D^{20} = +27.7$ ($c = 2.8$, CH₂Cl₂).

FTIR (neat) 3014, 2956, 1724, 1303, 1087, 976 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 7.63-7.66 (m, 4H), 7.36-7.46 (m, 6H), 6.02-6.07 (m, 1H), 5.60 (ddd, $J = 11.9, 3.5, 3.5$ Hz, 1H), 5.16-5.24 (m, 1H), 4.96-5.06 (m, 2H), 4.37 (ddd, $J = 27.9, 14.8, 6.7$ Hz, 1H), 3.86 (ddd, $J = 10.0, 9.3, 4.2$ Hz, 1H), 3.73 (ddd, $J = 10.2, 5.0,$

5.0 Hz, 1H), 2.22 (ddd, $J = 14.3, 12.2, 6.2$ Hz, 1H), 1.94 (ddd, $J = 18.0, 8.6, 4.4$ Hz, 1H), 1.82 (ddd, $J = 18.6, 9.2, 4.7$ Hz, 1H), 1.75-1.78 (m, 1H), 1.04 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 135.6, 135.5, 133.6, 133.2, 129.9, 129.8, 127.9, 127.8, 127.5, 77.4 (d, $J_{\text{CP}} = 6.4$ Hz), 73.7 (d, $J_{\text{CP}} = 6.7$ Hz), 63.0 (d, $J_{\text{CP}} = 6.3$ Hz), 58.9, 38.3 (d, $J_{\text{CP}} = 9.4$ Hz), 35.0 (d, $J_{\text{CP}} = 6.0$ Hz), 26.8, 19.2.

(3*R*,5*S*,6*R*)-6-methyloct-7-ene-1,3,5-triol (2.52)

CuCN (0.031 mg, 0.346 mmol) and LiCl (0.029 mg, 0.698 mmol) were added to an oven-dried flask under the inert conditions of a glove box. THF was added (0.35 mL) followed by five min of stirring at rt. The reaction vessel was cooled to $-30\text{ }^{\circ}\text{C}$ followed by slow addition of a 2.0M solution of Me_2Zn in THF (0.175 mL, 0.349 mmol). The reaction was stirred for 35-40 min at $-30\text{ }^{\circ}\text{C}$ at which point a solution of **2.51** in THF (0.87 mL) was cannulated into the flask with the cuprate. The reaction vessel was removed from the bath and allowed to warm to rt. Upon completion (3.5 hrs), NH_4Cl (2 mL, saturated aq.) was added and the reaction stirred for an additional hour. After an hour (aqueous layer should be dark blue), the reaction is acidified to a pH of 1 with 10% aq. HCl. The aqueous layer was extracted with CH_2Cl_2 (4x) and the combined organic layers washed with H_2O (1x). The reaction was concentrated under reduced pressure to afford as a clear oil the silyl-protected phosphate acid intermediate that was carried on without further purification. To a flask containing the acid was added MeOH (1.0 mL). The flask was cooled to $0\text{ }^{\circ}\text{C}$ followed by the addition of a 2.0 M solution of TMSCHN_2 in THF (1.0 mL). After thirty min the reaction was slowly quenched with NH_4Cl (3 mL, saturated, aq.), and the aqueous layer is extracted CH_2Cl_2 (3x) and dried (Na_2SO_4). Concentration under reduced pressure followed by silicon chromatography (2:1 Hex/EtOAc) afforded 41.3 mg (95% yield). The phosphate (0.42 mg, 0.086 mmol) was taken up in toluene (1 mL). The reaction flask was cooled to $0\text{ }^{\circ}\text{C}$, followed by the addition of a 65% solution of Red-Al in toluene (0.104 mL, 0.344 mmol). The reaction was brought to rt and stirred

for three hrs. The reaction was quenched with NH_4Cl (1 mL, saturated aq.) and extracted with CH_2Cl_2 (6x). The organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Silicon chromatography (EtOAc) afforded 13.5 mg (88% over 3 steps) of **2.52** as an oil.

^1H NMR (400 MHz, CDCl_3) δ 5.68-5.75 (m, 1H), 5.14 (d, $J = 16.2$, 1H), 5.12 (d, $J = 9.1$, 1H) 4.17-4.26 (m, 1H), 3.80-3.91 (m, 2H), 3.70-3.75 (m, 1H), 2.75 (bs, 3H), 1.76-1.85 (m, 1H), 1.58-1.72 (m, 3H), 1.03 (d, $J = 6.8$, 3H).

^{13}C NMR (100MHz, CDCl_3) δ 140.3, 116.8, 71.8, 69.4, 61.2, 44.4, 39.6, 38.3, 16.1.

5.3. Experimental Data: Chapter 3

(1*S*,6*S*,8*R*)-2,9,10-Trioxa-1-phoshabicyclo[4.3.1]dec-4-ene-8-[2-[[*(*1,1-dimethylethyl)4-methoxybenzyloxy]ethyl]-1-oxide (3.13)

To a solution of NaH (38 mg, 0.955 mmol) in Et₂O (5 mL) was slowly cannulated a solution of PMBOH (5.28 g, 38.2 mmol) in Et₂O (19 mL) at rt. After stirring for 40 min. the solution was cooled to 0 °C and Cl₃CCN (5.52 g, 38.2 mmol) was slowly added via dropwise addition. After 5-10 min., the solution was removed from the bath and stirred for an additional hour. The reaction was quenched with 10 mL of NaHCO₃ saturated aq, and the layers separated. The aqueous layer was further extracted with Et₂O (3x), the combined organic layers were dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). The crude mixture was then cannulated with CH₂Cl₂ (96 mL) to a flask containing the phosphate (2.1 g, 9.55 mmol), followed by the addition of PPTS (239 mg, 0.96 mmol). After stirring for 16 h the reaction was quenched with 50 mL of NH₄Cl saturated aq., and the layers separated. The aq. layer was extracted with DCM (3x), and the combined organic layers washed with brine (1x), dried (anhydrous Na₂SO₄), and concentrated (rotary evaporator). Flash chromatography (EtOAc) provided 2.89 g (89% yield) of **3.13** as a viscous, light yellow oil.

$[\alpha]_D^{20} = +63.8.3$ ($c = 3.1$, CH₂Cl₂).

FTIR (neat) 2934, 1730, 1612, 1514, 1299, 1091 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 7.23, (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.98-6.05 (m, 1H), 5.56 (ddd, 11.9, 3.8, 2.6 Hz, 1H), 5.16 (d, *J* = 24.4 Hz, 1H), 4.95-5.04 (m, 1H), 4.76-4.84 (m, 1H), 4.42 (s, 2H), 4.30-4.46 (m, 1H), 3.82 (s, 3H), 3.52-3.65 (m, 2H), 2.13-2.24 (m, 1H), 1.83-2.00 (m, 2H), 1.74 (d, *J* = 14.4 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 159.13, 130.11, 129.75, 129.17, 127.71, 113.70, 77.20 (d, *J*_{CP} = 6.5 Hz), 74.04 (d, *J*_{CP} = 6.7 Hz), 72.72, 64.66, 62.91, 55.17, 35.84 (d, *J*_{CP} = 9.5 Hz), 34.80 (d, *J*_{CP} = 6.0 Hz).

³¹P NMR (162 MHz, CDCl₃) δ -2.29.

HRMS calculated for C₁₆H₂₁O₆P (M+Na)⁺ 369.0973; found 369.0984 (FAB).

(3*S*,5*S*,6*R*)-3,5-dioxaphosphorinane-methoxy-1-(4-methoxybenzyloxy)-6-methyloct-7-ene -oxide

Within a drybox, CuCN (3.28 g, 36.6 mmol, dried overnight in a vacuum oven at 60 °C/0.3 mmHg and stored in a drybox), and LiCl (3.10 g, 73.3 mmol, dried overnight in a vacuum oven at 60 °C/0.3 mmHg and stored in a drybox) were added to a round bottom flask and sealed with a septa. The flask was removed from the drybox and placed under a balloon of argon. THF (37 mL) was added and the mixture was stirred for 20 min at rt, then cooled to -30 °C. A solution of Me₂Zn (33.3 mL, 1.2 M in toluene) was then added fast drop wise and the solution stirred for 30 min at -30 °C (solution turns deep green). After 30 min, the phosphite (2.5 g, 7.33 mmol) in THF (7.3 mL) was cannulated fast dropwise (0.5 mL rinse), and the solution immediately removed from the bath and stirred at rt for 2 h. Upon completion (monitored by TLC, baseline spot in EtOAc), the reaction was cooled to 0 °C and slowly quenched with 10% HCl (4 mL) followed by water (20 mL), and stirred at rt for 10 min (pepper colored salts form). The solution was filtered through a pad of celite and rinsed thoroughly with EtOAc. To the resulting bilayer solution was added 10% HCl (5 mL), and the layers separated. The aq layer was extracted with EtOAc (2x), and the combined organic layers were concentrated via a rotary evaporator. The resulting oil was taken up in MeOH (~20 mL), followed by the dropwise addition of TMSCHN₂ (2 M in Et₂O, ~10 mL), resulting in a deep yellow solution. Excess TMSCHN₂ was quenched via slow dropwise addition of glacial acetic

acid (3-4 drops), and the solution dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). Flash chromatography (2:1 EtOAc) provided 2.37 g (87% yield) of the title compound as a clear oil, and as a ~1:1 mixture of diastereomers at phosphorus.

¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J*_{HH} = 8.6 Hz, 2H), 6.87 (d, *J*_{HH} = 8.6 Hz, 2H), 5.80 (dddd, *J* = 17.4, 10.4, 7.6, 1.7, 1H), 5.06-5.13 (m, 2H), 4.67-4.80 (m, 1H), 4.30-4.48 (m, 3H), 3.81 (s, 3H), 3.77 (d, 7.24 (d, *J*_{HP} = 5.4 Hz, 1.5H), 3.74 (d, *J*_{HP} = 5.4 Hz, 1.5H), 3.54-3.68 (m, 2H), 2.37-2.55 (m, 1H), 2.06-2.22 (m, 2H), 1.67-1.98 (m, 2H), 1.09 (d, *J*_{HH} = 6.9 Hz, 1.5H), 1.05 (d, *J*_{HH} = 6.9 Hz, 1.5H).

¹³C NMR (100 MHz, CDCl₃) δ 159.11, 138.18, 137.66, 130.03, 129.94, 129.17, 116.57, 116.25, 113.65, 79.81 (d, *J*_{CP} = 6.4 Hz), 78.78 (d, *J*_P = 7.0 Hz), 76.27 (d, *J*_{CP} = 7.2 Hz), 74.30 (d, *J*_{CP} = 6.2 Hz), 72.73, 65.61, 65.17, 55.10, 54.20 (d, *J*_{CP} = 6.1 Hz), 53.65 (d, *J*_{CP} = 5.7 Hz), 42.33 (d, *J*_{CP} = 7.9 Hz), 41.62 (d, *J*_{CP} = 5.2 Hz), 35.42 (d, *J*_{CP} = 6.1 Hz), 34.12, 32.81 (d, *J*_{CP} = 7.2 Hz), 32.01 (d, *J*_{CP} = 7.9 Hz), 15.71, 15.34.

³¹P NMR (162 MHz, CDCl₃) δ -4.17, -4.50.

(3*R*,5*S*,6*R*)-1-(4-methoxybenzyloxy)-6-methyloct-7-ene-3,5-diol (3.14)

The 1:1 diastereomeric phosphate mixture (2.27 g, 6.19 mmol) was taken up in Et₂O (103 mL) and cooled to 0 °C. LiAlH₄ (0.464 g, 12.2 mmol) was slowly added in ~ 0.1 g increments. Upon complete addition, the reaction was stirred at 0 °C for 2.5 h, and quenched via slow sequential addition of H₂O (464 μl), 10% NaOH (464 μl), and H₂O (1.4 mL), and removal from the bath. After stirring for 30 min, 15 mL of 10% HCl was added and the layers separated. The aq layer was extracted with Et₂O (3x), and the combined organic layers rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). The resulting clear oil was pushed through a short plug of silica (1:1 EtOAc:Hex) to afford 1.76 g of **3.14** (96% yield) as a clear oil.

$[\alpha]_D^{20} = -6.8$ ($c = 6.4$, CH₂Cl₂).

FTIR (neat) 3407, 2916, 1612, 1514, 1247, 1091, 1035 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 7.23 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.71-5.80 (m, 1H), 5.08 (s, 1H), 5.04 (d, $J = 2.2$, 1H), 4.43 (s, 2H), 4.06-4.13 (m, 1H), 3.72 (s, 3H), 3.71-3.77 (m, 1H), 3.55-3.68 (m, 2H), 3.53 (bs, 2H), 2.15-2.24 (m, 1H), 1.64-1.73 (m, 1H), 1.51-1.59 (m, 2H), 0.99 (d, $J = 6.9$, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 159.09, 140.42, 129.85, 129.16, 72.73, 71.35, 68.48, 68.38, 55.06, 44.04, 39.86, 36.28, 15.80.

(4*S*,6*R*)-4-((*R*)-but-3-en-2-yl)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane (3.15)

The diol (0.079 g, 0.269 mmol) was dissolved in DCM (1 mL) followed by the addition of 2,2-DMP (1 mL), and PPTS (3.3 mg, 0.013 mmol). Upon completion (~15 min, monitored by TLC) the reaction was quenched with NaHCO₃ (saturated aq., 20 μ L), and anhydrous Na₂SO₄ was added, filtered through a short plug of silica (EtOAc), and concentrated (rotary evaporator), to provide acetone **3.15** (0.088 g, 98%) that was used without further purification.

$[\alpha]_D^{20} = -17.3$ ($c = 2.8$, CH₂Cl₂).

FTIR (neat) 2983, 1612, 1514, 1379, 1247 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 8.6$ Hz, 2H), 5.85 (ddd, $J = 17.6, 10.6, 7.2$ Hz, 1H), 5.06 (d, $J = 6.7$ Hz, 1H), 5.02 (d, $J = 0.8$ Hz, 1H), 3.67 (ddd, $J = 12.6, 6.3, 3.2$ Hz, 1H), 3.50-3.58 (m, 2H), 2.21-2.29 (m, 1H), 1.79 (d, $J = 4.3$ Hz, 1H), 1.76 (d, $J = 6.4$ Hz, 1H), 1.71 (ddd, $J = 15.5, 9.6, 6.0$ Hz, 1H), 1.43-1.55 (m, 2H), 1.35 (s, 6H), 1.01 (d, $J = 6.8$ Hz, 3H), 3.80 (s, 3H), 3.56 (bs, 1H), 3.41-3.56 (m, 2H), 2.13-2.22 (m, 1H), 1.91-2.08 (m, 2H), 1.70 (ddd, $J = 14.8, 10.6, 4.3$ Hz, 1H), 1.53 (ddd, $J = 14.6, 4.0, 1.8$ Hz, 1H), 1.04-1.09 (m, 21H), 1.00 (d, $J = 6.9$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 159.10, 140.76, 130.54, 129.32, 114.36, 113.72, 100.30, 72.74, 69.92, 66.34, 63.34, 63.86, 55.25, 41.99, 36.02, 35.94, 24.63, 24.31, 15.20.

HRMS calculated for C₂₀H₃₀O₄ (M+Na)⁺ 357.2042; found 357.2046 (FAB).

(*R,E*)-1-iodo-2-methylhept-1-en-4-ol (3.18)

Cp_2ZrHCl (3.93 g, 13.40 mmol) was taken up in DCM (223 mL) followed by the addition of Me_3Al (2.0 M solution in toluene, 41.5 mL, 83.02 mmol) at rt under argon. The solution was cooled to 0 °C, and H_2O (0.482 mL, 26.78 mmol) was added over 10 min. After an additional 20 min. of stirring, the alkyne (3.0 g, 26.78 mmol) was cannulated in DCM (14 mL) and the reaction warmed to rt and stirred for 12 hr. The reaction was cooled to -30 °C, and quenched via cannulation of I_2 (13.6 g, 53.56 mmol) in THF (100 mL). The reaction was warmed to rt and stirred for an additional 20 min., followed by the slow addition of saturated K_2CO_3 (2 mL) and 30 min. of stirring (white salts form). Anhydrous Na_2SO_4 is added and the reaction filtered through a pad of Celite, and concentrated (rotary evaporator). Flash chromatography (4:1 Hex:EtOAc) afforded **3.18** (4.2 g, 61 %) as a light yellow oil.

$[\alpha]_{\text{D}}^{20} = -13.6$ (c 2.7, CH_2Cl_2).

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

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

^{13}C NMR (100 MHz, CDCl_3) δ 145.14, 77.20, 68.68, 47.67, 39.12, 24.09, 18.81, 14.03.

(*R,E*)-1-iodo-4-(methoxymethoxy)-2-methylhept-1-ene (3.19)

The alcohol (1.56 g, 6.2 mmol) was dissolved in DCE (31 mL) followed by the addition of *i*Pr₂NEt (8.0 g, 61.9 mmol) and MOMCl (2.49 g, 31.0 mmol) at rt under argon. The flask was fitted with a reflux condenser under argon, and the reaction was heated to 50 °C for 3-4 hr. Upon completion (monitored by TLC), the reaction was cooled to rt and Et₂O (20 mL) was added followed by slow addition of 10% HCl (10 mL). The layers are separated, and the aq. layer extracted with Et₂O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (4:1 Hex:EtOAc) to **3.19** (1.76 g, 95%) as a clear oil.

$[\alpha]_D^{20} = +1.2$ (*c* 12.8, CH₂Cl₂).

FTIR (neat) 3058, 2956, 2931, 1377, 1274, 1149 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 5.97 (s, 1H), 4.63 (d, *J* = 7.1 Hz, 1H), 4.59 (d, *J* = 7.1 Hz, 1H), 3.65-3.72 (m, 1H), 3.33 (s, 3H), 2.43 (dd, *J* = 13.8, 7.3 Hz, 1H), 2.32 (dd, *J* = 13.7, 5.3 Hz, 1H), 1.85 (s, 3H), 1.26-1.49 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 144.91, 95.26, 77.07, 74.68, 55.57, 44.79, 36.66, 24.42, 18.45, 14.11.

(2*R*,3*R*,7*R*,*E*)-2-((4*S*,6*R*)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-7-(methoxymethoxy)-5-methyldec-4-en-3-ol (*syn*-3.20** and *anti*-**3.21**)**

Procedure for vinyl lithiate addition: To a solution of the vinyl iodide (0.036 mg, 0.119 mmol) in Et₂O (0.265 mL) at - 78 °C was ^tBuLi (1.7 M in pentane, 0.140 mL, 0.231 mmol), and the reaction was immediately warmed to 0 °C for 25 min. The reaction was recooled to - 78 °C, and the aldehyde (0.020 g, 0.059 mmol) was slowly added via syringe in Et₂O (0.180 mL, 20 μ L rinse). After 1 hr, the reaction was quenched at - 78 °C with NH₄Cl (saturated, aq), warmed to rt, and the layers separated. The aq. layer was extracted with Et₂O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na₂SO₄), and concentrated (rotary evaporator). Flash chromatography (3:1 Hex:EtOAc) afforded a 2:1 mixture of **3.21:3.20** (ratio determined by ¹H NMR analysis of crude reaction mixture, 21 mg, combine yield of diastereomers 68%).

Procedure for vinyl Grignard addition: To a solution of the vinyl iodide (0.080 mg, 0.269 mmol) in Et₂O (0.331 mL) at - 78 °C was added ^tBuLi (1.65 M in pentane, 0.154 mL, 0.253 mmol), and the reaction (pale yellow color) stirred for 15 min. A MgBr₂·Et₂O solution (0.3 M in THF, 0.993 mL, 0.298 mmol) was added and the reaction was warmed to 0 °C and stirred for 15 min (white precipitates form). After 15 min, the aldehyde (0.050 mg, 0.149 mmol) is cannulated in Et₂O (0.82 mL, 0.100 mL rinse) and the

reaction stirred at temperature for 3 hr. The reaction was quenched with 4 mL of NH_4Cl saturated aq., and the layers separated. The aq. layer was extracted with Et_2O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (3:1 Hex:EtOAc) afforded a 4:1 mixture of **3.21:3.20** (ratio determined by ^1H NMR analysis of crude reaction mixture, 54 mg, combine yield of diastereomers 73%).

Procedure for vinyl magnesiate addition: To a solution of $^i\text{PrMgCl}$ (2.0 M in THF, 0.316 mL, 0.600 mmol) at 0 °C was added $^s\text{BuLi}$ (1.4 M in cyclohexane, 0.920 mL, 1.20 mmol) and the reaction (light yellow color) stirred for 10 min. The vinyl iodide (0.178 mg, 0.600 mmol) in THF (1.0 mL) was cannulated slowly, and the reaction stirred for 30 min at which point it was cooled - 78 °C. The aldehyde (0.100 g, 0.300 mmol), which was stirred for 20 min with $\text{MgBr}_2\cdot\text{Et}_2\text{O}$ solution (0.3 M in THF, 2 mL, 0.60 mmol, light heating was used to insure the mixture remained homogenous), was then cannulated to the vinyl magnesiate and stirred for 2 hr at - 78 °C. The reaction was quenched with 5 mL of NH_4Cl saturated aq., and the layers separated. The aq. layer was extracted with Et_2O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na_2SO_4), and concentrated (rotary evaporator). Flash chromatography (3:1 Hex:EtOAc) afforded a 8:1 mixture of **3.21:anti-3.20** (ratio determined by ^1H NMR analysis of crude reaction mixture, 103 mg, combine yield of diastereomers 68%).

Procedure for asymmetric vinyl zincate addition: The vinyl iodide (0.111 g, 0.373 mmol) was dissolved in Et_2O (0.933 mL) and cooled to -78 °C followed by the fast dropwise addition of $^i\text{BuLi}$ (1.65 M in pentane, 0.442 mL, 0.730 mmol). The solution was stirred for 40 min. at -78 °C, followed by the addition of ZnBr_2 (0.89 M in Et_2O ,

0.452 mL, 0.402 mmol) and transfer to a 0 °C bath. After 40 min., a solution of (1*R*,2*S*)-LiNME [(*R,S*)-NME (0.067 g, 0.373 mmol) in 1.89 mL toluene at 0 °C was added ⁿBuLi (2.5 M in hexane, 0.146 mL, 0.365 mmol) and stirred for 20 min.] was slowly cannulated to the flask containing the zincate and stirred for 1 hr. at 0 °C. After 1 hr., the aldehyde (0.05 g, 0.149 mmol) was cannulated as a solution in toluene (0.300 mL, 0.050 mL rinse) and the solution stirred for 1.5 hr at 0 °C. The reaction was quenched with 4 mL of NH₄Cl saturated aq., and the layers separated. The aq. layer was extracted with Et₂O (3x), and the combined organic layers washed with brine (1x), dried (anhydrous Na₂SO₄), and concentrated (rotary evaporator). Flash chromatography (3:1 Hex:EtOAc) afforded a 1.5:1 mixture of **3.21:3.20** (ratio determined by ¹H NMR analysis of crude reaction mixture, 103 mg, combine yield of diastereomers 68%). Compound characterization for 1,3-*anti* **3.21**.

$[\alpha]_D^{20} = -4.0$, (*c*, 0.3 CH₂Cl₂).

FTIR (neat) 3448, 2954, 1610, 1512, 1247, 1097 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.5, 2H), 5.34 (*J* = 8.9, 2H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.43-4.46 (m, 1H), 4.41 (s, 2H), 3.98-4.03 (m, 1H), 3.84-3.89 (m, 1H), 3.82 (s, 3H), 3.69-3.75 (m, 1H), 3.48-3.57 (m, 2H), 3.38 (s, 3H), 2.32 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.17 (dd, *J* = 13.7, 6.1 Hz, 1H), 1.81-1.86 (m, 1H), 1.74-1.81 (m, 1H), 1.72 (s, 3H), 1.56-1.71 (m, 2H), 1.43-1.51 (m, 3H), 1.41 (s, 3H), 1.35-1.41 (m, 1H), 1.34 (s, 3H), 0.93-0.96 (m, 3H), 0.83 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 159.20, 135.07, 130.54, 129.32, 127.88, 113.80, 100.70, 95.4, 75.53, 72.82, 70.91, 70.05, 66.18, 63.78, 55.51, 55.31, 45.27, 44.07, 37.64, 36.76, 35.76, 24.67, 24.55, 18.66, 17.18, 14.17, 11.84.

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

(3.23)

The diol (1.76 g, 5.98 mmol) was dissolved in DCM (40 mL) followed by the addition of imidazole (2.44 g, 35.88 mmol), and DMAP (73 mg, 0.598 mmol). TIPSCl (3.80 mL, 17.94 mmol) was then added dropwise over several min. The reaction was stirred at rt overnight. The reaction was diluted with Et₂O (100 mL) followed by 10% HCl (30 mL), and the layers separated. The aq layer was extracted with Et₂O (1x), and the combined organic layers rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). Flash chromatography (9:1 Hex:Et₂O to remove excess silane, then 5:1 Hex:EtOAc) yielded monosilylated **3.23** (2.31g, 86%) as a clear oil.

¹H NMR (500 MHz, CDCl₃) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.73-5.84 (m, 1H), 5.04 (s, 1H), 5.01 (d, *J* = 2.3 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.27-4.32 (m, 1H), 3.79-3.85 (m, 1H), 3.80 (s, 3H), 3.56 (bs, 1H), 3.41-3.56 (m, 2H), 2.13-2.22 (m, 1H), 1.91-2.08 (m, 2H), 1.70 (ddd, *J* = 14.8, 10.6, 4.3 Hz, 1H), 1.53 (ddd, *J* = 14.6, 4.0, 1.8 Hz, 1H), 1.04-1.09 (m, 21H), 1.00 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 159.13, 140.63, 136.32, 129.18, 114.84, 113.67, 72.57, 71.45, 69.85, 66.29, 55.17, 44.06, 37.66, 35.80, 18.06, 18.03, 15.33, 12.36.

HRMS calculated for C₂₆H₄₆O₄Si (M+Na)⁺ 473.3063; found 473.3029 (FAB).

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

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

$[\alpha]_{\text{D}}^{20} = +3.0$ ($c = 3.74$, CH_2Cl_2).

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

^1H NMR (500 MHz, CDCl_3) δ 7.26 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 5.74-5.84 (m, 1H), 5.06 (dd, $J = 2.0, 1.1$ Hz, 1H), 5.03 (dd, $J = 1.7, 1.3$ Hz, 1H), 4.69 (d, $J = 6.9$ Hz, 1H), 4.65 (d, $J = 6.9$, 1H), 4.44 (d, $J = 11.6$ Hz, 1H), 4.40 (d, $J = 11.6$, 1H), 4.05-4.11 (m, 1H), 3.80 (s, 3H), 3.65-3.69 (m, 1H), 3.53-3.57 (m, 2H), 3.37 (s, 3H), 2.46-2.56 (m, 1H), 1.81-1.89 (m, 2H), 1.64 (ddd, $J = 14.1, 6.9, 4.4$ Hz, 1H), 1.56 (ddd, $J = 14.6, 7.0, 5.0$ Hz, 1H), 1.04-1.07 (m, 24H).

^{13}C NMR (125 MHz, CDCl_3) δ 159.02, 140.06, 130.65, 129.11, 114.91, 113.61, 96.51, 79.46, 72.59, 67.98, 66.44, 55.61, 55.15, 41.23, 39.07, 37.73, 18.20, 14.35, 12.79.

HRMS calculated for $\text{C}_{28}\text{H}_{50}\text{O}_5\text{Si}$ ($\text{M}+\text{Na}$) $^{+}$ 517.3325; found 517.3300 (FAB).

(2S,3S,5R)-7-(4-methoxybenzyloxy)-3-(methoxymethoxy)-2-methyl-5-(triisopropylsilyloxy)heptanal (3.24)

The olefin (0.450 g, 0.910 mmol) was taken up in DCM:MeOH 1:1 (15 mL) followed by the addition of pyridine (0.720 g, 9.10 mmol) and SUDAN III (indicator, ~1 mg) at rt under argon. The solution was cooled to -78 °C, and a stream of O₃ was lightly bubbled through the solution until a light yellow color persisted. The stream of O₃ was removed and the reaction was stirred until the SM was consumed (monitored by TLC). The flask was flushed with Ar, and Me₂S (3.3 mL) was slowly added. The reaction was slowly warmed to over to rt over the a 4 hr period. After stirring for 1 hr. at rt, Et₂O (40 mL) was added and extracted with saturated CuSO₄ (2x 10 mL), and brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). Flash chromatography (7:2:1 Hex:Et₂O:EtOAc) afforded **3.24** (0.339 g, 75 %) as an off-white oil.

¹H NMR (500 MHz, CDCl₃) δ 9.71 (d, *J* = 1.3 Hz), 7.23 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.63 (d, *J* = 7.0 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 11.6, 1H), 4.09-4.15 (m, 2H), 3.79 (s, 3H), 3.49 (t, *J* = 6.6 Hz, 2H), 3.34 (s, 3H), 2.72-2.79 (m, 1H), 1.85-1.94 (m, 1H), 1.76-1.84 (m, 2H), 1.47 (ddd, *J* = 14.1, 7.7, 3.5 Hz, 1H), 1.11 (d, *J* = 7.0, 3H), 1.03-1.07 (m, 21H).

¹³C NMR (125 MHz, CDCl₃) δ 203.27, 159.03, 130.45, 129.09, 113.61, 96.76, 76.28, 72.60, 67.79, 66.21, 55.71, 55.12, 40.27, 37.86, 18.14, 12.82, 9.23.

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

The alcohol (0.050 g, 0.074 mmol) was taken up in DCM (2.5 mL) followed by the addition of pyridine (0.046 g, 0.590 mmol) and Dess-Martin periodinane (0.063 g, 0.149 mmol) at rt under argon. Upon completion (monitored by TLC), Et₂O (15 mL) was added, and the solution extracted with NaHCO₃ (saturated aq., 2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (1:1 Hex:EtOAc) to give the title compound (0.049 g, 98%) as a clear oil.

$[\alpha]_D^{20} = +24.1$ (*c* 2.1, CH₂Cl₂).

FTIR (neat) 1680, 1612, 1512, 1099, 1037 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.19 (s, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.66 (d, *J* = 7.0, 1H), 4.63 (s, 2H), 4.39 (d, *J* = 1.8 Hz, 2H), 4.02-4.13 (m, 2H), 3.80 (s, 3H), 3.72-3.79 (m, 1H), 3.46-3.53 (m, 2H), 3.35 (s, 6H), 2.98 (dq, *J* = 6.9, 1.7 Hz, 1H), 2.39 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.23 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.14 (s, 3H), 1.76-1.94 (m, 2H), 1.59-1.68 (m, 1H), 1.31-1.49 (m, 4H), 0.97-1.10 (m, 24H), 0.92 (t, *J* = 6.9, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 201.62, 159.04, 156.01, 130.66, 129.15, 125.28, 113.67, 96.96, 95.41, 75.35, 72.62, 67.80, 66.51, 55.80, 55.54, 55.24, 51.79, 46.85, 39.16, 38.11, 36.75, 19.91, 18.48, 18.23, 14.06, 12.88, 10.43.

HRMS calculated for $\text{C}_{37}\text{H}_{66}\text{O}_8$ ($\text{M}+\text{Na}$) $^+$ 689.4425; found 689.4425 (FAB).

Reduction with DIBAL-H: To a solution of the ketone (0.050 g, 0.0746 mmol) in toluene (0.746 mL) was slowly added DIBAL-H (1.0M in toluene, 0.149 mL) at $-78\text{ }^\circ\text{C}$. After two hours of stirring at $-78\text{ }^\circ\text{C}$, the reaction was quenched with NH_4Cl (saturated, aq.), and the reaction warmed to rt while stirring. The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (2:1 Hex:EtOAc) to afford the title compound as a 5:1 mixture (determined by ^1H NMR of crude reaction) of **3.27:3.26** (0.040 g, 80%) as a clear oil.

Reduction with $\text{LiAlH}_4/\text{LiI}$: To a solution of the ketone (0.030 g, 0.045 mmol) in Et_2O (0.563 mL) was added LiI (0.06 g, 0.45 mmol) at $0\text{ }^\circ\text{C}$ (solution turns reddish-brown color). Once the LiI is completely dissolved ($< 5\text{ min}$), the reaction was cooled to $-78\text{ }^\circ\text{C}$ and a solution of LiAlH_4 (1.0 M in Et_2O , 0.450 mL) was slowly added. After twenty min, the reaction was quenched with sodium-potassium tartrate (saturated, aq.), and the reaction warmed to rt while stirring. The layers were separated, and the aq. layer extracted with Et_2O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na_2SO_4), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (2:1 Hex:EtOAc) to afford the title compound

as a 4.3:1 mixture (determined by ^1H NMR of crude reaction) of **3.26:3.27** (0.028 g, 90%) as a clear oil.

(5*R*,9*R*,10*R*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(2-(4-methoxybenzyloxy)ethyl)-11-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-9-ol (1,3-*syn*-3.26 and 1,3-*anti*-3.27)

Procedure for vinyl lithiate addition: To a solution of vinyl iodide (0.522 mg, 1.75 mmol) in Et₂O (5.2 mL) at - 78 °C was added ^tBuLi (1.7 M in pentane, 2.06 mL, 3.5 mmol), and the reaction was immediately warmed to 0 °C for 25 min. The reaction was recooled to - 78 °C, and the aldehyde (0.350 g, 0.700 mmol) was slowly cannulated in Et₂O (1 mL, 0.10 mL rinse). After 1 hr, the reaction was quenched at - 78 °C with NH₄Cl (saturated, aq.), warmed to rt, and the layers separated. The aq. layer was extracted with Et₂O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na₂SO₄), and concentrated (rotary evaporator). Flash chromatography (2:1 Hex:EtOAc) afforded a 1:1 mixture of *syn*-3.26:*anti*-3.27 (ratio determined by ¹H NMR analysis of crude reaction mixture, 375 mg, combine yield of diastereomers 80 %).

Procedure for asymmetric zincate addition: The vinyl iodide (0.691 g, 2.32 mmol) was dissolved in Et₂O (3.8 mL) and cooled to -78 °C followed by the fast dropwise addition of ^tBuLi (1.7 M in pentane, 2.67 mL, 4.54 mmol). The solution was stirred for 40 min. at -78 °C, followed by the addition of ZnBr₂ (0.87 M in Et₂O, 2.87 mL, 2.50 mmol) and transfer to a 0 °C bath. After 40 min., a solution of (1*R*,2*S*)-LiNME [prepared from (*R,S*)-NME (0.416 g, 2.32 mmol) in 11.6 mL toluene at 0 °C was added ⁿBuLi

(2.5 M in hexane, 0.928 mL, 2.32 mmol) and stirred for 20 min.] was slowly cannulated to the flask containing the zincate and stirred for 1 hr. at 0 °C. After one hr., the aldehyde (0.460 g, 0.926 mmol) was cannulated as a solution in toluene (2.81 mL) and stirred for 1.5 hr at 0 °C. The reaction was quenched with 20 mL of NH₄Cl saturated aq., and the layers separated. The aq. layer was extracted with Et₂O (3x), and the combined organic layers washed with brine (1x), dried (anhydrous Na₂SO₄), and concentrated (rotary evaporator). Flash chromatography (2:1 Hex:EtOAc) afforded **3.26** as the major diastereomer (11:1 dr, 368 mg, 65 %) as a clear oil.

$[\alpha]_D^{20} = +1.1$, (*c*, 5.6 CH₂Cl₂).

FTIR (neat) 3469, 3103, 2939, 1612, 1514, 1463, 1097, 1040 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6, 2H), 5.24 (*J* = 8.6, 2H), 4.42 (s, 2H), 4.10-4.17 (m, 2H), 4.03-4.07 (m, 1H), 3.81 (s, 3H), 3.67-3.74 (m, 1H), 3.54 (t, *J* = 6.4, 2H), 3.37 (s, 3H), 3.36 (s, 3H), 2.31 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.15 (dd, *J* = 13.3, 7.3 Hz, 1H), 1.84-1.98 (m, 3H), 1.69 (s, 3H), 1.64-1.73 (m, 2H), 1.31-1.51 (m, 4H), 1.01-1.18 (m, 21H), 0.87-0.94 (m, 3H), 0.79 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 159.07, 135.76, 130.68, 130.03, 129.17, 113.69, 96.59, 95.42, 75.44, 72.63, 70.23, 68.59, 66.66, 55.74, 55.47, 55.23, 45.20, 43.11, 38.68, 38.09, 36.59, 18.41, 18.26, 17.06, 14.15, 12.94, 10.90.

HRMS calculated for C₃₇H₆₈O₈ (M+Na)⁺ 691.4581; found 691.4598 (FAB).

(3*R*,5*S*,6*R*,7*R*,11*R*,*E*)-5,11-bis(methoxymethoxy)-6,9-dimethyl-3-(triisopropylsilyloxy)tetradec-8-ene-1,7-diol (3.29)

The PMB ether (0.018 g, 0.026 mmol) was taken up in DCM (520 μ L) followed by the addition of pH buffer solution (0.027 mL) and DDQ (0.009 g, 0.024 mmol) at rt. Upon completion (~1 hr, monitored by TLC), Et₂O (2 mL) was added followed by NaHCO₃ (saturated aq, 1 mL). The layers were separated, and the aq. layer extracted with Et₂O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). Flash chromatography (1:1 Hex:EtOAc) afforded **3.29** (10.3 mg, 72%) as a clear oil

$[\alpha]_D^{20} = +5.3$ (*c* 2.0, CH₂Cl₂).

FTIR (neat) 3447, 2941, 1464, 1382, 1151, 1097, 1039 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 5.33 (d, *J* = 8.9 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.67 (s, 2H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.20-4.25 (m, 1H), 4.11 (dd, *J* = 9.3, 9.2 Hz, 1H), 3.98-4.02 (m, 1H), 3.89 (ddd, *J* = 11.2, 7.8, 4.5 Hz, 1H), 3.75-3.80 (m, 1H), 3.67-3.72 (m, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.30 (dd, *J* = 13.5, 6.2, 1H), 2.15 (dd, *J* = 13.5, 6.9), 1.91-2.00 (m, 2H), 1.76-1.87 (m, 3H), 1.76-1.87 (m, 3H), 1.78 (d, *J* = 1.1, 3H), 1.33-1.47 (m, 4H), 1.08-1.10 (m, 21H), 0.89-0.92 (m, 3H), 0.78 (d, *J* = 6.9, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 136.35, 129.91, 96.30, 95.45, 77.53, 70.84, 70.11, 59.69, 55.91, 55.48, 45.16, 42.70, 38.69, 37.06, 36.62, 18.41, 18.18, 16.98, 14.14, 12.66, 10.55.

(3*R*,5*S*,6*S*,7*R*,11*R*,*E*)-5,7,11-tris(methoxymethoxy)-6,9-dimethyl-3-(triisopropylsilyloxy)tetradec-8-en-1-ol (3.30)

The secondary alcohol (0.05 g, 0.074 mmol) was dissolved in DCE (300 μ L) followed by the addition of i Pr₂NEt (0.096 g, 0.740 mmol) and MOMCl (0.030 g, 0.372 mmol) at rt under argon. The flask was fitted with a reflux condenser under argon, and the reaction was heated to 50 $^{\circ}$ C for 3-4 hr. Upon completion (monitored by TLC), the reaction was cooled to rt and Et₂O (2 mL) was added followed by slow addition of 10% HCl (1 mL). The layers were separated, and the aq. layer extracted with Et₂O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (1:1 Hex:EtOAc) to the MOM-protected ether (0.044 g, 82%) as a clear oil. The MOM-protected PMB ether (0.05 g, 0.070 mmol) was taken up in DCM (1.4 mL) followed by the addition of pH buffer solution (0.07 mL) and DDQ (0.032 g, 0.139 mmol) at rt. Upon completion (~1 hr, monitored by TLC), Et₂O (2 mL) was added followed by NaHCO₃ (saturated aq, 1 mL). The layers were separated, and the aq. layer extracted with Et₂O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). Flash chromatography (2:1 Hex:EtOAc) afforded **3.30** (0.038 g, 92%) as a clear oil.

$[\alpha]_D^{20} = -26.0$ (c 0.77, CH₂Cl₂).

FTIR (neat) 3507, 2941, 2359, 2341, 1097, 1037 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 5.02 (d, *J* = 9.4, 1H), 4.61-4.68 (m, 6H), 4.38 (d, *J* = 6.5 Hz, 1H), 4.21-4.24 (m, 1H), 4.13 (dd, *J* = 9.2, 9.1, 1H), 4.00-4.03 (m, 1H), 3.85-3.90 (m, 1H), 3.75-3.81 (m, 1H), 3.68-3.73 (m, 1H), 3.39-3.51 (m, 9H), 2.52 (bs, 1H), 2.34 (dd, *J* = 13.3, 5.8 Hz, 1H), 2.17 (dd, *J* = 13.3, 5.4 Hz, 1H), 2.05-2.11 (m, 1H), 1.92-1.98 (m, 1H), 1.84-1.90 (m, 1H), 1.75-1.79 (m, 2H), 1.70 (d, *J* = 1.5 Hz, 3H), 1.42-1.48 (m, 3H), 1.33-1.37 (m, 1H), 1.07-1.10 (m, 21H), 0.90 (t, *J* = 6.9, 3H), 0.83 (d, *J* = 8.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 138.06, 126.86, 96.66, 95.42, 93.18, 77.13, 75.47, 73.19, 69.97, 59.60, 55.96, 55.72, 55.52, 45.11, 41.43, 39.11, 36.67, 36.53, 18.43, 18.20, 17.08, 14.13, 12.70, 10.52.

HRMS calculated for C₃₁H₆₄O₈Si (M+Na)⁺ 615.4268; found 615.4222 (FAB).

(5*R*,9*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-9,11-bis(methoxymethoxy)-7,10,16-trimethyl-13-(pent-4-enyl)-5-propyl-2,4,14-trioxa-15-silaheptadec-7-ene (3.34)

The primary alcohol (0.045 g, 0.076 mmol) was taken up in DCM (0.365 mL) and pyridine (0.365 mL), and TsCl was added (0.029 g, 0.152 mmol). The reaction was stirred until starting material was no longer being consumed (monitored by TLC). The reaction was quenched (aq NH₄Cl), the layers separated, and the aq. layer extracted with Et₂O (2x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). The mixture was pushed through a short plug of silica (3:1 Hex:EtOAc) to afford the tosylate (0.030 g, 53 %) as a clear oil, which was immediately used. The tosylate (0.030 g, 0.025 mmol) was taken up in THF (0.500 mL) and CuBr (0.013 g, 0.06 mmol) was added. The solution was cooled to – 50 °C and allylMgBr (1.0 M in Et₂O, 0.240 mL) was added. The reaction was warmed to rt and stirred for 3 hrs, at which time it was quenched with NH₄Cl (saturated, aq), layers separated, and the aqueous layer extracted with Et₂O (2 x). The combined organic layers were rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). Flash chromatography (2:1 Hex:EtOAc) afforded **3.34** (0.024 g, 80%, ~1:1 ratio with SM) as a clear oil (see pg 208 for ¹H and ¹³C data).

4-[(1*R*,6*R*,8*R*)-3,3-dimethyl-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl]-(3*E*)-pentane-1-4-methoxybenzyloxy (3.36)

The bicyclic phosphate (1.36 g, 6.67 mmol) was taken up in DCE (degassed 10 min. with Ar, 133.4 mL) followed by the addition of the PMB-ether protected terminal olefin (1.92 g, 10.0 mmol), and Hoveyda-Grubbs 2nd generation catalyst (0.208, 0.333 mmol) under argon at rt. The flask was fitted with a reflux condenser under argon, and lowered into a preheated 90 °C bath for 2 hr. Upon completion (monitored by ³¹P NMR analysis of aliquots of the reaction), the reaction was concentrated (rotary evaporator). Flash chromatography (1:2 Hex:EtOAc) afforded the cross-metathesis product (2.01 g, 82%, >20:1 *E*:*Z*) as a light brown oil. The cross-metathesized phosphate intermediate (1.5 g, 4.10 mmol) was taken up in DCM (82 mL) followed by the addition of Et₃N (18 mL, ~2 mL per gram of NBS-H), and NBS-H (8.90 g, 41.0 mmol). After the reaction was stirred for 12 hr, EtOAc (150 mL) was added, and the reaction extracted with NaHCO₃ (saturated aq, 2x). The aq layer was reextracted with EtOAc (1x). The combined organic layers were dried (anhydrous Na₂SO₄) and concentrated. Flash chromatography (1:2 Hex:EtOAc) afforded **3.36** (1.13 g, 75%) as a clear oil and 300 mg of starting material.

$[\alpha]_D^{20} = +50.3$ ($c = 5.4$, CH₂Cl₂).

FTIR (neat) 2936, 1612, 1512, 1300, 1247, cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 7.28, (d, *J* = 8.6, 2H), 6.98 (d, *J* = 8.7, 2H), 6.03 (dddd, *J* = 11.9, 6.7, 3.0, 2.1 Hz, 1H), 5.59 (ddd, 11.8, 3.8, 2.5 Hz, 1H), 5.18 (d, *J* = 24.3 Hz, 1H), 4.98-5.05 (m, 1H), 4.55-4.61 (m, 1H), 4.45 (s, 2H), 4.37 (ddd, *J* = 27.6, 14.7, 6.7 Hz, 1H), 3.82 (s, 3H), 3.45 (t, *J* = 6.5 Hz, 2H), 2.18 (ddd, *J* = 14.6, 11.9, 6.3 Hz, 1H), 1.68-1.81 (m, 2H), 1.35-1.80 (m, 7H).

¹³C NMR (125 MHz, CDCl₃) δ 158.89, 130.47, 129.74, 129.02, 127.56, 113.53, 7.13 (d, *J*_{CP} = 6.6 Hz), 76.55 (d, *J*_{CP} = 6.7 Hz), 72.30, 69.63, 62.70 (d, *J*_{CP} = 6.4 Hz), 55.07, 35.37 (d, *J*_{CP} = 9.4 Hz), 34.59 (d, *J*_{CP} = 5.9 Hz), 29.32, 25.62, 24.17.

³¹P NMR (162 MHz, CDCl₃) δ -2.96.

HRMS calculated for C₁₉H₂₇O₆P (M+Na)⁺ 405.1443; found 405.1427 (FAB).

(5*S*,7*R*)-5-((*R*)-but-3-en-2-yl)-9,9-diisopropyl-7-(5-(4-methoxybenzyloxy)pentyl)-10-methyl-2,4,8-trioxa-9-silaundecane (3.38)

Following cuprate addition protocol, CuCN (2.11 g, 23.56 mmol) and LiCl (2.0 g, 47.12 mmol) were stirred in THF (24 mL) for 20 min at rt, then cooled to -30 °C. A solution of Me₂Zn (1.2 M in toluene, 19.6 mL, 23.6 mmol) was added (stirred for 30 min), followed by phosphate addition (2.08 g, 5.62 mmol) in THF (6 mL, 0.4 mL rinse), and the solution immediately removed from the bath and stirred at rt for 2 h. Reaction workup, methylation, and flash chromatography (1:1 Hex:EtOAc) provided the monocyclic phosphate (2.05 g, 91 % yield) as a clear oil, and as a ~1:1 mixture of diastereomers at phosphorus. Following phosphate cleavage protocol, to the 1:1 diastereomeric phosphates (2.05 g, 5.13 mmol) in Et₂O (86 mL) was added LiAlH₄ (0.486 g, 12.8 mmol) at 0 °C. Reaction workup and flash chromatography (1:1 Hex:EtOAc) provided the diol (1.59 g, 92% yield) as a clear oil. Following monosilylation protocol, the diol (1.39 g, 4.13 mmol) in DCM (28 mL) was added imidazole (1.69 g, 24.8 mmol) and DMAP (50 mg, 0.413 mmol), followed by TIPSCl (2.39 g, 12.4 mmol). Reaction workup and flash chromatography (9:1 Hex:Et₂O, then 5:1 Hex:EtOAc) provided monosilylated product (1.36 g, 80%) as a clear oil. Following MOM protection protocol, to the secondary alcohol (0.830g, 1.68 mmol) in DCE (4.2 mL) and Et₂^{*i*}PrN (2.17 g, 16.8 mmol) was added MOMCl (0.678 g, 8.42 mmol). After heating at 50 °C for 3-4 hr, reaction workup

and flash chromatography (2:1 Hex:EtOAc) provided **3.38** (0.860 mg, 95%) as a clear oil.

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

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

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

^{13}C NMR (125 MHz, CDCl_3) δ 159.05, 140.18, 130.72, 129.12, 114.79, 113.67, 96.65, 79.65, 72.47, 70.09, 70.07, 55.58, 55.14, 41.41, 38.53, 37.89, 29.74, 26.54, 24.47, 18.23, 18.22, 14.26, 12.85.

HRMS calculated for $\text{C}_{31}\text{H}_{56}\text{O}_5\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 559.3795; found 559.3749 (FAB).

(5*R*,9*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-13-(5-(4-methoxybenzyloxy)pentyl)-9-(methoxymethoxy)-7,10,16-trimethyl-5-propyl-2,4,14-trioxa-15-silaheptadec-7-en-11-ol (3.40)

To a solution of vinyl iodide (0.140 mg, 0.469 mmol) in Et₂O (1.42 mL) at - 78 °C was added ^tBuLi (1.7 M in pentane, 0.529 mL, 0.901 mmol), and the reaction was immediately warmed to 0 °C for 25 min. The reaction was recooled to - 78 °C, and the aldehyde (0.101 g, 0.188 mmol) was slowly added via syringe in Et₂O (0.312 mL, 30 μL rinse). After 1 hr, the reaction was quenched at - 78 °C with NH₄Cl (saturated, aq), warmed to rt, and the layers separated. The aq. layer was extracted with Et₂O (2x), and the combined organic layers washed with brine (1x), dried (anhydrous Na₂SO₄), and concentrated (rotary evaporator). Flash chromatography (3:1 Hex:EtOAc) afforded a 1:1 mixture of **3.40** (ratio determined by ¹H NMR analysis of crude reaction mixture, 94 mg, combine yield of diastereomers 70 %). Separation of diastereomers was achieved using a Horizon Biotage flash chromatography system (Biotage Si 12M column, 5-10 % EtOAc gradient in Hex). Compound data for 1,3-*syn* **3.40**.

¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6, 2H), 5.28 (*J* = 8.7, 2H), 4.63-4.73 (m, 4H), 4.43 (s, 2H), 4.18 (dd, *J* = 9.2, 9.0 Hz, 1H), 4.05-4.10 (m, 1H), 3.98-4.03 (m, 1H), 3.85 (s, 3H), 3.70-3.75 (m, 1H), 3.45 (t, *J* = 6.5, 2H), 3.35-3.43 (m, 6H), 2.34 (dd, *J* = 13.2, 5.8 Hz, 1H), 2.19 (dd, *J* = 13.3, 7.4 Hz, 1H), 1.73 (s, 3H), 1.31-1.69 (m, 14 H), 1.04-1.12 (m, 21 H), 0.89-0.98 (m, 3H), 0.80 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 159.08, 135.79, 130.72, 129.91, 129.22, 113.73, 96.74, 95.39, 77.77, 75.40, 72.53, 70.63, 70.34, 70.14, 55.73, 55.49, 45.19, 43.14, 38.34, 38.25, 36.55, 29.80, 26.60, 24.85, 18.38, 17.09, 14.14, 13.01, 12.94, 10.94.

HRMS calculated for $\text{C}_{40}\text{H}_{74}\text{O}_8\text{Si}$ ($\text{M}+\text{Na}$) $^{+}$ 733.5051; found 733.5031 (FAB).

(5*R*,9*R*,10*S*,11*S*,13*R*,*E*)-15,15-diisopropyl-9,11-bis(methoxymethoxy)-7,10,16-trimethyl-13-(pent-4-enyl)-5-propyl-2,4,14-trioxa-15-silaheptadec-7-ene (3.34)

Following the same procedure for MOM protection, the alcohol (0.032 g, 0.045 mmol) was dissolved in DCE (0.225 mL) followed by the addition of $i\text{Pr}_2\text{NEt}$ (0.061 g, 0.468 mmol) and MOMCl (0.019 g, 0.234 mmol) at rt under argon. Reaction workup and flash chromatography (4:1 Hex:EtOAc) afforded the MOM-protected ether (0.031 g, 95%). Following the same procedure of PMB removal, tri-MOM protected PMB ether (0.031 g, 0.041 mmol) was taken up in DCM (0.820 mL) followed by the addition of pH 7 phosphate buffer solution (0.043 mL) and DDQ (0.019 g, 0.082 mmol) at rt. Reaction workup and flash chromatography (2:1 Hex:EtOAc) afforded the primary alcohol (0.024 g, 92%) as a clear oil. The primary alcohol was taken up in DCM (0.139 mL), followed by the addition of imidazole (0.003 mg, 0.0417 mmol), Ph_3P (0.011 mg, 0.042 mmol). The reaction was cooled to 0 °C and I_2 (0.007 mg, 0.0278 mmol) was added. Upon completion (reaction monitored by TLC, ~30 min.), the reaction was concentrated and subjected to flash chromatography (3:1 Hex:EtOAc) to afford the primary iodide (8.8 mg, 84 %). The iodide was subsequently taken up in THF (0.140 mL) and a solution of $t\text{BuOK}$ (1.0 M in THF, 0.018 mL) at rt. Upon completion (reaction monitored by TLC, ~30 min.), the reaction was concentrated and subjected to flash chromatography (3:1 Hex:EtOAc) to afford **3.34** (0.007 mg, 94%).

¹H NMR (400 MHz, CDCl₃) δ 5.76-5.8 (m, 1H), 4.98-5.04 (m, 2H), 4.93-4.97 (m, 1H), 4.73 (d, *J* = 6.7 Hz, 1H), 4.64-4.69 (m, 3H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.38 (d, *J* = 6.7 Hz, 1H), 4.15-4.19 (m, 1H), 4.12 (dd, *J* = 9.4, 9.3 Hz, 1H), 4.02-4.07 (m, 1H), 3.68-3.73 (m, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 2.35 (dd, *J* = 13.4, 5.6 Hz, 1H), 2.17 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.12-2.17 (m, 1H), 2.03-2.08 (m, 1H), 1.71 (d, *J* = 0.90 Hz, 3H), 1.42-1.65 (m, 14H), 1.04-1.09 (m, 21H), 0.88-1.92 (m, 3H), 0.82 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 138.88, 138.21, 127.20, 114.54, 97.76, 95.41, 92.78, 77.27, 75.48, 72.80, 69.58, 56.03, 55.86, 55.58, 45.13, 41.72, 38.29, 36.51, 36.09, 34.16, 24.22, 18.46, 18.39, 18.33, 17.21, 14.20, 13.00, 10.40.

(5*R*,9*R*,*E*)-9-((*S*)-1-((4*S*,6*R*)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-7,11,11,12,12-pentamethyl-5-propyl-2,4,10-trioxa-11-silatridec-7-ene (3.44)

The secondary alcohol (.064 g, 0.127 mmol) was dissolved in DCM (0.640 mL) followed by the addition of 2,6-lutidine (0.021 g, 0.165 mmol) under argon. The solution was cooled to 0 °C and after 5 min of stirring, TIPSOTf (0.051 g, 0.165 mmol) was slowly added. Upon completion (~30 min, monitored by TLC) the reaction was quenched with NaHCO₃ (saturated aq., 2 mL), and the layers separated. The aq. layer was extracted with DCM (2x), and the combined organic layers were rinsed with brine (1x), dried (anhydrous Na₂SO₄), filtered, and concentrated (rotary evaporator). Flash chromatography (7:1 Hex:EtOAc) provided **3.44** (0.071 g, 84%) as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.3, 2H), 5.37 (*J* = 8.5, 2H), 4.83 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.43 (s, 2H), 3.88-3.96 (m, 1H), 3.81-3.85 (m, 1H), 3.80 (s, 3H), 3.65-3.71 (m, 1H), 3.48-3.56 (m, 2H), 3.37 (s, 3H), 2.25 (dd, *J* = 13.7, 6.0 Hz, 1H), 2.08 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.71-1.79 (m, 2H), 1.64 (s, 3H), 1.41-1.61 (m, 7H), 1.34 (s, 3H), 1.30 (s, 3H), 1.26-1.35 (m, 1H), 0.97-1.09 (m, 21H), 0.87-0.9 (m, 3H), 0.83 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 159.13, 131.62, 131.29, 130.66, 129.28, 113.75, 100.07, 95.48, 75.52, 72.72, 68.80, 66.98, 66.47, 63.77, 55.4, 55.2, 46.64, 45.26, 37.01, 36.65, 36.01, 25.16, 24.97, 18.73, 18.26, 18.24, 16.66, 14.12, 12.89, 8.39.

5.4. Experimental Data: Chapter 4

(2*S*_p*,3*S**,4*R**,5*R**,6*R**) -6-Methyl-2-phenoxy-1,2-oxaphosphorinane-3,4,5-triol-2-oxide [(±)-**4.22**].

To a solution of **4.19a** (20 mg, 0.083 mmol) in CH₂Cl₂ (1.5 mL) were added OsO₄ (28 mg, 0.11 mmol) and TMEDA (13 mg, 0.11 mmol) at -60 °C. The reaction mixture was stirred for 2 hrs at -60 °C and warmed up to rt. Removal of the solvent under reduced pressure under reduced pressure afforded the crude osmate as a mixture of diastereoisomers (12.5:1 by ³¹P-NMR analysis). The product was dissolved in 1.5 mL MeOH and treated with citric acid overnight. Removal of the solvent under reduced pressure and flash chromatography (EtOAc/4% MeOH) afforded 16 mg (70%) of **4.22** as an oil.

¹H NMR δ 7.29-7.09 (m, 5H), 4.63-4.55 (m, 1H), 4.26 (dd, *J* = 35.2, 3.9, 2.5 Hz, 1H), 4.05 (dd, *J* = 7.6, 4.0 Hz, 1H), 3.38 (dd, *J* = 9.4, 2.2 Hz, 1H), 1.38 (dd, *J* = 6.3, 1.9 Hz, 3H).

¹³C NMR δ 150.0 (d, *J*_{CP} = 10.0 Hz), 129.5 (d, *J*_{CP} = 125.0 Hz), 120.3 (d, *J*_{CP} = 4.3 Hz), 74.4 (d, *J*_{CP} = 6.2 Hz), 72.5, 72.3, 66.3 (d, *J*_{CP} = 146.9 Hz), 18.4 (d, *J*_{CP} = 8.3 Hz); ³¹P NMR δ 16.4.

(2*S,5*S**,6*R**)-5,6-Dihydro-6-methyl-2-phenoxy-2*H*-1,2-oxaphosphorinane-5-methanesulfonate-2-oxide [(±)-4.19b].**

To a solution of the diol **4.18** (20 mg, 0.077 mmol) in CH₂Cl₂ (2.0 mL) was added a catalytic amount of DMAP (1.9 mg, 0.015 mmol), MsCl (0.02 mL, 0.26 mmol), and Et₃N (0.04 mL, 0.29 mmol) at 0 °C. The reaction mixture was warmed to rt over 1 h and stirred overnight. Brine was added, and extracted with EtOAc (3x) and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (7:3 EtOAc/Hex) afforded 19 mg (78%) of **4.19b**.

FTIR (neat) 3028, 2936, 1591, 1490, 1455, 1361, 1270, 1177, 1070, 1023, 931 cm⁻¹.

¹H NMR δ 7.38-7.18 (m, 5H), 6.82 (ddd, *J* = 46.8, 12.9, 2.0 Hz, 1H), 6.26 (ddd, *J* = 17.4, 12.9, 2.0 Hz, 1H), 5.17-5.13 (m, 1H), 4.75-4.70 (m, 1H), 3.12 (s, 3H), 1.57 (dd, *J* = 6.3, 2.0 Hz, 3H).

¹³C NMR δ 149.6, 146.1, 129.9, 125.4, 120.3, 119.7 (d, *J*_{CP} = 169.7 Hz), 76.3 (d, *J*_{CP} = 8.1 Hz), 75.1 (d, *J*_{CP} = 10.8 Hz), 38.8, 18.9 (d, *J*_{CP} = 6.9 Hz).

³¹P NMR δ 5.5.

HRMS Exact mass: calculated for C₁₂H₁₆O₆PS (*M*+1) 319.0405; found 319.0405 (FAB).

(2*S*_p*,5*S,6*R**)-5,6-Dihydro-6-methyl-2-phenoxy-2*H*-1,2-oxaphosphorinane-5-phenylmethoxy-2-oxide [(±)-4.24].**

To a solution of the alcohol **4.19a** (10 mg, 0.042 mmol) in CH₂Cl₂ (0.6 mL) were added 2,6-di-*t*-butyl-4-methyl pyridine (55 mg, 0.26 mmol), AgOTf (54 mg, 0.21 mmol) and BnBr (0.03 mL, 0.25 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 3 hrs, diluted with CH₂Cl₂ and the filtrate was washed with brine. Removal of the solvent under reduced pressure and flash chromatography (4:1 Hex/EtOAc) afforded 10 mg (72%) of **4.24** as an oil.

FTIR (neat) 3061, 3031, 2982, 2934, 2871, 1723, 1593, 1490, 1454, 1364, 1270, 1202, 1095, 1067, 982, 928 cm⁻¹.

¹H NMR δ 7.41-7.31 (m, 7H), 7.21-7.15 (m, 3H), 6.83 (ddd, *J* = 48.2, 12.9, 1.6 Hz, 1H), 6.10 (ddd, *J* = 18.8, 12.9, 2.1 Hz, 1H), 4.72-4.57 (m, 3H), 4.03-3.99 (m, 1H), 1.49 (dd, *J* = 6.2, 2.0 Hz, 3H).

¹³C NMR δ 149.6, 136.6, 129.8, 128.7, 128.5, 125.1, 120.5 (d, *J*_{CP} = 4.6 Hz), 116.8 (d, *J*_{CP} = 170.8 Hz), 77.9 (d, *J*_{CP} = 8.2 Hz), 76.5 (d, *J*_{CP} = 10.1 Hz), 72.8, 19.1 (d, *J*_{CP} = 7.5 Hz).

³¹P NMR δ 7.7.

HRMS Exact mass: calculated for C₁₈H₂₀O₄P (M+1) 331.1099; found 331.1098 (FAB).

(2*S*_p*,3*R**,4*S**,5*S**,6*R**) -6-Methyl-2-phenoxy-1,2-oxaphosphorinane-3,4-diol-5-phenylmethoxy-2-oxide [(±)-**4.25**].

To a solution of **4.24** (15 mg, 0.045 mmol) in acetone (0.9 mL) and *t*-BuOH (0.3 mL) were added citric acid (19 mg, 0.10 mmol), NMO·H₂O (12 mg, 0.09 mmol) and OsO₄ (2 drops of a 4% solution in water). The reaction mixture was stirred for 24 hrs, followed by the addition of Na₂SO₃. Water was added and extracted with EtOAc (3x) and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (EtOAc/1% MeOH) afforded 15 mg (92%) of **4.25** as an oil.

¹H NMR δ 7.36-7.16 (m, 10H), 5.45 (br. s, 1H), 4.94 (d, *J* = 10.7 Hz, 1H), 4.65 (t, *J* = 10.8 Hz, 1H), 4.38 (q, *J* = 3.8 Hz, 1H), 4.22-4.11 (m, 2H), 3.62 (t, *J* = 9.2, 1H), 3.24 (d, *J* = 8.6, 1.6 Hz, 1H), 1.47 (dd, *J* = 6.2, 1.3 Hz, 3H).

¹³C NMR δ 149.6, 137.6, 130.0, 128.5, 128.2, 128.1, 125.4, 119.7 (d, *J*_{CP} = 4.7 Hz), 80.0, 75.7, 75.5 (d, *J*_{CP} = 5.8 Hz), 73.5 (d, *J*_{CP} = 6.2 Hz), 65.6 (d, *J*_{CP} = 144.3 Hz), 19.2 (d, *J*_{CP} = 9.0 Hz).

³¹P NMR δ 16.2.

(3a*R,5*S**,7*R**,7a*S**)-5H-[1,2]Oxaphosphorino[4,5-d]oxazole-3a,4,7,7a-tetrahydro-7-methyl-5-phenoxy-2-(trichloromethyl)-5-oxide [(±)-4.26]**

(2*S,5*R**,6*R**)-5,6-Dihydro-6-methyl-2-phenoxy-2*H*-1,2-oxaphosphorinane-5-azido-2-oxide [(±)-4.27].**

To a solution of mesylate **4.19b** (13 mg, 0.041 mmol) in DMF (0.5 mL) were added NaN₃ (13 mg, 0.20 mmol) and 15-crown-5 (9 mg, 0.041 mmol). The reaction mixture was stirred overnight at rt and the solvent was removed under reduced pressure. Flash chromatography of the residue (1:1 Hex/EtOAc) afforded 10 mg (92%) of **4.27**.

FTIR (neat) 3049, 2993, 2938, 2109, 1612, 1596, 1490, 1455, 1358, 1269, 1162, 1028, 968, 921 cm⁻¹.

¹H NMR δ 7.36-7.17 (m, 5H), 6.85 (ddd, *J* = 46.6, 12.5, 5.5 Hz, 1H), 6.44 (dd, *J* = 17.3, 12.5 Hz, 1H), 4.92-4.89 (m, 1H), 3.56-3.55 (m, 1H), 1.54 (dd, *J* = 6.4, 2.0 Hz, 3H).

¹³C NMR δ 149.8, 142.4, 129.9, 125.2, 121.7 (d, *J*_{CP} = 169.5 Hz), 120.2 (d, *J*_{CP} = 4.6 Hz), 76.8 (d, *J*_{CP} = 7.5 Hz), 57.1 (d, *J*_{CP} = 10.1 Hz), 18.5 (d, *J*_{CP} = 7.8 Hz).

³¹P NMR δ 5.8.

HRMS Exact mass: calculated for C₁₁H₁₃N₃O₃P (*M*+1) 266.0695; found 266.0692 (FAB).

(2*S**,3*S**,4*R**,5*R**,6*R**) -6-Methyl-2-phenoxy-1,2-oxaphosphorinane-3,4-diol-5-azido-2-oxide [(±)-**4.28**].

To a solution of **4.27** (5 mg, 0.019 mmol) in acetone (0.6 mL) and *t*-BuOH (0.2 mL) were added citric acid (4 mg, 0.021 mmol), NMOH₂O (3 mg, 0.022 mmol) and OsO₄ (1 drop 4% solution in water). The reaction mixture was stirred for 24 h, water was added and extracted with EtOAc (3x). Removal of the solvent under reduced pressure and flash chromatography (4:1 EtOAc/Hex) afforded 5 mg (88%) of **4.28**.

FTIR (neat) 3350, 2923, 2110, 1590, 1491, 1255, 1199, 1026, 987 cm⁻¹.

¹H NMR δ 7.33-7.16 (m, 5H), 5.84 (br. s, 1H), 5.10-5.04 (m, 1H), 4.40 (dt, *J* = 35.2, 4.2 Hz, 1H), 4.25 (t, *J* = 4.5 Hz, 1H), 3.42 (br. s, 1H), 3.73 (d, *J* = 4.2 Hz, 1H), 1.47 (dd, *J* = 6.6, 1.6 Hz, 3H).

¹³C NMR δ 150.2 (d, *J*_{CP} = 9.8 Hz), 129.7, 125.1, 120.4 (d, *J*_{CP} = 4.3 Hz), 73.4 (d, *J*_{CP} = 7.1 Hz), 71.8 (d, *J*_{CP} = 2.9 Hz), 65.2 (d, *J*_{CP} = 2.6 Hz), 63.7 (d, *J*_{CP} = 145.7 Hz), 18.0 (d, *J*_{CP} = 9.0 Hz).

³¹P NMR δ 15.9.

HRMS Exact mass: calculated for C₁₁H₁₅N₃O₅P (M+1) 300.0749; found 300.0754 (FAB).

(1*S*,*S*_p)-2-Propenyl-1-phenylmethoxymethyl-2-propenyl phenyl ester phosphonic acid [(+)-4.16b].

To a solution of the 2-benzyl-(2*R*)-1,2-butanediol **4.15b** (69 mg, 0.388 mmol) in dry THF (2 mL) was added BuLi (0.27 mL 1.4 M in Hex, 0.38 mmol) at $-40\text{ }^{\circ}\text{C}$, the solution was warmed to rt over 2 hrs and stirred at rt for 4 additional hrs. This solution was added to the diphenyl allylphosphonate (127 mg, 0.42 mmol) in THF (0.6 mL) and HMPA (0.1 mL) at $-78\text{ }^{\circ}\text{C}$ over 30 min. The reaction mixture was stirred overnight at $-78\text{ }^{\circ}\text{C}$, quenched with NH_4Cl (saturated aq.), extracted with EtOAc (3x) and dried (Na_2SO_4). Removal of the solvent under reduced pressure and flash chromatography (4:1 Hex/EtOAc) afforded 75 mg (54%) of **4.16b** as a mixture of diastereoisomers (6:1 by ^{31}P analysis).

$[\alpha]_D^{20} = +5.3$ (c 0.3, CH_2Cl_2); IR (neat) 3065, 3029, 2982, 2861, 1639, 1593, 1490, 1454, 1364, 1265, 1208, 1091, 1013, 926 cm^{-1} .

$^1\text{H NMR}$ (only signals for major isomer) δ 7.36-7.11 (m, 10H), 5.92-5.14 (m, 2H), 5.46-5.14 (m, 5H), 4.64-4.53 (m, 2H), 3.62-3.53 (m, 2H), 2.85-2.75 (m, 2H).

$^{13}\text{C NMR}$ (only signals for major isomer) δ 150.3 (d, $J_{\text{CP}} = 8.9\text{ Hz}$), 137.5, 129.4, 128.3, 127.7, 127.6, 124.7, 124.63, 120.59, 120.2 (d, $J_{\text{CP}} = 15.1\text{ Hz}$), 118.3, 76.5 (d, $J_{\text{CP}} = 6.6\text{ Hz}$), 73.0, 72.3 (d, $J_{\text{CP}} = 4.8\text{ Hz}$), 32.1 (d, $J_{\text{CP}} = 140.7\text{ Hz}$).

$^{31}\text{P NMR}$ δ 25.6.

HRMS Exact mass: calculated for $\text{C}_{20}\text{H}_{24}\text{O}_4\text{P}$ ($\text{M}+1$) 359.1412; found 359.1406 (FAB).

(2*S*_P,6*S*)-2-Phenoxy-6-[(phenylmethoxymethyl)-2*H*-1,2-oxaphosphorin-3,6-dihydro-2-oxide [(-)-4.17b].

To a solution of **4.16b** (75 mg, 0.23 mmol, 9:1 mixture) in dry CH₂Cl₂ (20 mL) was added (PCy₃)₂Cl₂Ru=CHPh (6 mg, 3 mol%) and the mixture was refluxed overnight. An additional amount of catalyst (3 mg, 0.0036 mmol) was added and reflux was continued for 14 hrs. The mixture was diluted with CH₂Cl₂, flushed with air, 3 drops DMSO were added, and the solution was stirred overnight at rt. Removal of the solvent under reduced pressure and flash chromatography (1:1 Hex/EtOAc) afforded 60 mg (83%) of **4.17b** as an oil.

[α]_D²⁰ = -42.1 (*c* 1.2, CH₂Cl₂).

FTIR (neat) 3062, 3033, 2905, 2866, 1592, 1491, 1454, 1297, 1254, 1207, 1083, 1026, 927 cm⁻¹.

¹H NMR δ 7.36-7.13 (m, 10H), 5.88-5.77 (m, 2H), 5.14-5.13 (m, 1H), 4.58 (s, 2H), 3.73-3.62 (m, 2H), 2.68-2.48 (m, 2H).

¹³C NMR δ 149.9 (d, *J*_{CP} = 7.8 Hz), 137.4, 129.7, 128.2, 127.6, 127.5, 126.2 (d, *J*_{CP} = 16.0 Hz), 124.8, 121.2 (d, *J*_{CP} = 9.8 Hz), 129.9 (d, *J*_{CP} = 4.5 Hz), 79.7 (d, *J*_{CP} = 8.5 Hz), 63.4, 71.6 (d, *J*_{CP} = 7.4 Hz), 21.4 (d, *J*_{CP} = 132.4 Hz).

³¹P NMR δ 17.5.

HRMS Exact mass: calculated for C₁₈H₂₀O₄P (M+1) 331.1099; found 331.1110 (FAB).

(2*S*,4*R*,5*S*,6*S*)-2-Phenoxy-6-[(phenylmethoxy)methyl]-1,2-oxaphosphorinane-4,5-diol-2-oxide [(+)-4.29].

To a solution of **4.17b** (12 mg, 0.036 mmol in 1.2 mL acetone and *t*-BuOH (0.4 mL) were added citric acid (10 mg, 0.052 mmol), *m*-CPBA (26 mg 70-75%), NMM (11 mg, 0.11 mmol) and OsO₄ (1 drop of a 1% solution in water). After stirring for 24 hrs one more drop of OsO₄ was added and the stirring continued for 24 hrs. The reaction mixture was diluted with CHCl₃, solid Na₂SO₃ and water was added, stirred for 30 min and extracted with CHCl₃. Removal of the solvent under reduced pressure and flash chromatography (EtOAc/1% MeOH) afforded 11 mg (84%) of **4.29** as a white solid;

mp = 145-148.

[α]_D²⁰ = +51.1 (*c* 0.980, CH₂Cl₂).

FTIR (neat) 3341, 3062, 2969, 1591, 1490, 1454, 1251, 1197, 933 cm⁻¹.

¹H NMR δ 7.32-7.11 (m, 10H), 4.71-4.68 (m, 1H), 4.55-4.48 (m, 2H), 4.12 (dd, *J* = 35.8, 1.8 Hz, 1H), 3.85 (br. s, 1H), 3.75-3.71 (m, 4H), 2.32 (ddd, *J* = 19.4, 15.8, 3.6 Hz, 1H), 2.04-1.94 (m, 1H).

¹³C NMR δ 149.6 (d, *J*_{CP} = 8.4 Hz), 137.6, 129.9, 129.6, 128.3, 127.7, 127.5, 125.1, 120.6 (d, *J*_{CP} = 4.3 Hz), 76.4 (d, *J*_{CP} = 6.7 Hz), 73.4, 69.9 (d, *J*_{CP} = 7.8 Hz), 68.0 (d, *J*_{CP} = 6.5 Hz), 67.1 (d, *J*_{CP} = 9.1 Hz), 27.2 (d, *J*_{CP} = 125.9 Hz).

³¹P NMR δ 20.2.

HRMS Exact mass: calculated for C₁₈H₂₂O₆P (*M*+1) 365.1154; found 365.1160 (FAB).

(2*S*_P,4*R*,5*S*,6*S*)-2-Phenoxy-6-[(phenylmethoxy)methyl]-1,2-oxaphosphorinane-4,5-carbonate-2-oxide.

To a solution of **4.29** (450 mg, 1.24 mmol) in CH₂Cl₂ (20 mL) were added triphosgene (770 mg, 2.59 mmol) and Et₃N (0.80 mL, 5.75 mmol) at -40 °C and the solution was warmed to 10 °C over 3 hrs. The reaction mixture was diluted with CH₂Cl₂, quenched with NH₄Cl (saturated aq.), extracted with CH₂Cl₂ (3x) and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (7:3 EtOAc/Hex) afforded 460 mg (95%) of the carbonate.

¹H NMR δ 7.42-7.18 (m, 10H), 5.25 (ddd, *J* = 25.0, 7.8, 6.2, 4.1 Hz, 1H), 4.94 (dd, *J* = 8.1, 4.5 Hz, 1H), 4.86-4.85 (m, 1H), 4.65 (d, *J* = 11.1 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 3.94 (dd, *J* = 11.1, 2.0 Hz, 1H), 3.80 (dt, *J* = 11.1, 3.0 Hz, 1H), 2.70 (ddd, *J* = 18.7, 16.3, 6.2 Hz, 1H), 2.48 (ddd, *J* = 17.6, 16.3, 4.0 Hz, 1H).

¹³C NMR δ 152.6, 149.3 (d, *J*_{CP} = 8.6 Hz), 136.4, 129.6, 128.4, 128.0, 127.7, 125.2, 120.1 (d, *J*_{CP} = 4.7 Hz), 77.9 (d, *J*_{CP} = 7.7 Hz), 73.6, 73.0 (d, *J*_{CP} = 6.1 Hz), 72.7 (d, *J*_{CP} = 11.9 Hz), 69.6 (d, *J*_{CP} = 3.8 Hz), 24.3 (d, *J*_{CP} = 128.2 Hz).

³¹P NMR δ 15.2.

(2*S*_p,5*S*,6*R*)-5,6-Dihydro-2-phenoxy-6-[(phenylmethoxy)methyl]-2H-1,2-oxaphosphorinane-5-ol-2-oxide [(-)-4.30].

To a solution of the carbonate (430 mg, 1.10 mmol) in THF (20 mL) was added KHMDS (2.5 mL, 0.5 M in toluene, 1.25 mmol) at $-50\text{ }^{\circ}\text{C}$ and the solution was warmed to $0\text{ }^{\circ}\text{C}$ over 2.5 hrs. The reaction mixture was quenched with NH_4Cl (saturated aq.), extracted with EtOAc (3x) and dried (Na_2SO_4). Removal of the solvent under reduced pressure and flash chromatography (9:1 EtOAc/Hex) afforded 280 mg (74%) of **4.30**.

$[\alpha]_{\text{D}}^{20} = -4.6$ (*c* 0.5, CH_2Cl_2).

FTIR (neat) 3341, 3062, 2869, 1591, 1490, 1454, 1356, 1251, 1198, 1077, 1007, 985, 932 cm^{-1} .

^1H NMR δ 7.34-7.12 (m, 10H), 6.68 (ddd, $J = 49.4, 12.9, 1.3\text{ Hz}$, 1H), 5.93-5.85 (m, 1H), 4.70-4.49 (m, 4H), 4.36 (d, $J = 1.5\text{ Hz}$, 1H), 3.83-3.71 (m, 1H).

^{13}C NMR δ 154.0, 149.5 (d, $J_{\text{CP}} = 8.5\text{ Hz}$), 137.5, 129.1, 128.3, 127.7, 127.5, 125.3, 120.5 (d, $J_{\text{CP}} = 4.2\text{ Hz}$), 114.4 (d, $J_{\text{CP}} = 171.7\text{ Hz}$), 81.4, 73.4, 69.7 (d, $J_{\text{CP}} = 7.5\text{ Hz}$), 64.3.

^{31}P NMR δ 8.0.

HRMS Exact mass: calculated for $\text{C}_{18}\text{H}_{20}\text{O}_5\text{P}$ ($\text{M}+1$) 347.1048; found 347.1055 (FAB).

(2*S*_P,5*S*,6*R*)-5,6-Dihydro-2-phenylmethoxy-2*H*-1,2-oxaphosphorinane-5-methanesulfonate-6-[(triphenyl-methoxy)methyl]-2-oxide [(+)-4.31].

To a solution of the diol (100 mg, 0.27 mmol) in CH₂Cl₂ (8 mL) were added a catalytic amount of DMAP (6.6 mg, 0.054 mmol) and MsCl (0.07mL, 0.90 mmol) at 0 °C, followed by Et₃N (0.15mL, 1.08 mmol). The reaction mixture was warmed to rt over 1 h and stirred overnight at rt. Et₃N (0.10 mL, 0.72 mmol) was added and the stirring was continued for 6 hrs. After addition of brine the mixture was extracted with EtOAc (3x) and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (1:1 Hex/EtOAc) afforded 95 mg (83%) of **4.31**.

[α]_D²⁰ = +30.7 (*c* 0.91, CH₂Cl₂).

FTIR (neat) 3060, 3044, 3023, 2931, 2896, 2865, 1590, 1491, 1454, 1348, 1268, 1204, 1171, 1101, 1018, 985, 939 cm⁻¹.

¹H NMR δ 7.37-7.16 (m, 10H), 6.87 (ddd, *J* = 47.2, 12.9, 1.9 Hz, 1H), 6.24 (ddd, *J* = 17.9, 12.9, 2.0 Hz, 1H), 5.53-5.49 (m, 1H), 4.76-4.71 (m, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 3.88-3.80 (m, 2H), 3.00 (s, 3H).

¹³C NMR δ 149.5 (d, *J*_{CP} = 8.2 Hz), 146.6, 137.0, 129.9, 128.4, 127.9, 127.8, 125.4, 120.4 (d, *J*_{CP} = 4.4 Hz), 119.3 (d, *J*_{CP} = 170.5 Hz), 78.7 (d, *J*_{CP} = 8.0 Hz), 73.8, 70.7 (d, *J*_{CP} = 10.7 Hz), 68.0 (d, *J*_{CP} = 7.1 Hz), 38.1.

³¹P NMR δ 6.1.

HRMS Exact mass: calculated for C₁₉H₂₂O₇PS (M+1) 425.0824; found 425.0809 (FAB).

**(2*S*_P,5*R*,6*R*)-5,6-Dihydro-2-phenoxy-2*H*-1,2-oxaphosphorinane-5-azido-6-
[(phenylmethoxy)methyl]-2-oxide**

Mesylated alcohol **4.31** (63 mg, 0.148 mmol) was taken up in DMF (0.3 mL) at rt, followed by the subsequent addition of 15-crown-5 ether (33 mg, 0.148 mmol), and sodium azide (9 mg, 0.140 mmol). Upon completion (2.5-3 hrs), removal of solvent under reduced pressure followed by flash chromatography (1:1 EtOAc/Hex) afforded 45 mg (82%) of the title compound.

$[\alpha]_D^{20} = -316.3$ (c 0.4, CH₂Cl₂).

FTIR (neat) 3062, 2106, 1590, 1488, 1271, 1198 cm⁻¹.

¹H NMR δ 7.12-7.39 (m, 10H), 6.85 (ddd, $J_{HP} = 46.4$, $J = 12.5$, 5.6 Hz, 1H), 6.44 (dd, $J = 17.4$, $J = 12.9$ Hz, 1H), 4.93 (ddd, $J = 11.4$, 6.9, 3.3 Hz, 1H), 4.59 (s, 2H), 3.89 (m, 1H), 3.84 (d, $J = 6.39$ Hz, 2H).

¹³C NMR δ 149.5 ($J_{CP} = 8.3$ Hz), 142.2, 137.3, 129.8 ($J_{CP} = 11.0$ Hz), 128.6 ($J_{CP} = 10.1$ Hz), 128.1 ($J_{CP} = 5.7$ Hz), 127.8, 125.4, 121.8 ($J_{CP} = 171.2$ Hz), 120.4 ($J_{CP} = 4.5$ Hz), 78.3 ($J_{CP} = 7.1$ Hz), 73.9, 69.1 ($J_{CP} = 9.3$ Hz), 54.2 ($J_{CP} = 11.1$ Hz).

³¹P NMR δ 5.72.

HRMS Exact mass: calculated for C₁₈H₁₉N₃O₄P (M+1) 372.1113; found 372.2313 (FAB).

(2*S*_P,3*S*,4*R*,5*R*,6*R*)-2-Phenoxy-6-[(phenylmethoxy)methyl]-1,2-oxaphosphorinane-3,4-diol-5-azido-2-oxide [(+)-4.32].

To a solution of vinyl phosphonate (12 mg, 0.032 mmol) in acetone (0.9 mL) and *t*-BuOH (0.3 mL) were added citric acid (6 mg, 0.031 mmol), NMO·H₂O (5 mg, 0.037 mmol) and OsO₄ (1 drop of a 4% solution in water). After stirring for 24 hrs at rt one more drop OsO₄ was added and the stirring was continued for 8 hrs. Water was added to the reaction mixture and extracted with EtOAc (3x). Removal of the solvent under reduced pressure and flash chromatography (3:2 EtOAc/Hex) afforded **4.32** (7 mg, 54%) as an oil.

[α]_D²⁰ = +41.1 (*c* 0.0072, CH₂Cl₂).

FTIR (neat) 3343, 3065, 2922, 2113, 1590, 1491, 1454, 1256, 1201, 1024, 981, 938 cm⁻¹.

¹H NMR δ 7.38-7.11 (m, 10H), 5.07-5.05 (m, 1H), 4.56 (s, 2H), 4.50-4.39 (m, 2H), 4.06 (d, *J* = 3.7 Hz, 1H), 3.78-3.70 (m, 2H).

¹³C NMR δ 150.0 (d, *J*_{CP} = 10.3 Hz), 137.2, 129.7, 128.5, 127.9, 125.2, 120.4 (d, *J*_{CP} = 4.2 Hz), 74.8 (d, *J*_{CP} = 6.8 Hz), 73.6, 71.7 (d, *J*_{CP} = 3.2 Hz), 68.1 (d, *J*_{CP} = 11.0 Hz), 64.3 (d, *J*_{CP} = 146.7 Hz), 61.6.

³¹P NMR δ 16.2.

HRMS Exact mass: calculated for C₁₈H₂₁N₃O₆P (*M*+1) 406.1168; found 406.1159 (FAB).

(2*S*_p,3*R*,4*S*,5*S*,6*R*)-2-Phenoxy-6-[(phenylmethoxy)methyl]-1,2-oxaphosphorinane-3,4,5-triol-5-2-oxide [(+)-4.35].

To a solution of **4.30** (65 mg, 0.187 mmol) in acetone (5.2 mL) and *t*-butanol (2.1 mL) was added citric acid (72 mg, 0.374 mmol), NMM (100 μ l, 0.560 mmol), and a 1% solution of OsO₄ in water (24 μ L). A solution of *m*-CPBA (137 mg, 0.560 mmol) in acetone (1 mL) was added over 30 min. After 24 hrs of stirring, additional amounts of OsO₄ (0.024 mL) and *m*-CPBA (70 mg) were added, and the reaction was stirred for an additional 24 hours. The reaction was quenched with Na₂SO₃ (saturated aq.), extracted with CH₂Cl₂ (3x), and the combined organic layers were dried (Na₂SO₄). ³¹P analysis of the crude reaction mixture showed a diastereomeric ratio of 15:1. Subsequent flash chromatography (9:1 EtOAc/MeOH) afforded 38 mg (53%) of **4.35** as the major isomer.

[α]_D²⁰ = +21.6 (*c* 0.94, CH₂Cl₂).

FTIR (CHCl₃) 3352, 2922, 1590, 1491, 1267, 1196, 736, 690 cm⁻¹.

¹H NMR δ 7.31-7.13 (m, 10H), 4.52-4.49 (m, 2H), 4.47-4.43 (m, 1H), 4.21-4.18 (m, 1H), 4.03 (dd, *J*_{HP} = 9.53, 9.53 Hz, 1H), 3.96 (dd, *J*_{HP} = 11.3, 1.81 Hz, 1H), 3.86-3.84 (m, 1H), 3.76 (dd, *J*_{HP} = 10.9, 5.81 Hz).

¹³C NMR δ 149.5 (d, *J*_{CP} = 9.6 Hz), 137.8, 130.0, 128.4, 127.6, 127.6, 125.5, 120.0 (d, *J*_{CP} = 4.4 Hz), 78.7 (d, *J*_{CP} = 3.6 Hz), 73.4, 73.3 (d, *J*_{CP} = 7.2 Hz), 69.8 (d, *J*_{CP} = 12.6 Hz), 66.8, 65.7 (d, *J*_{CP} = 145.9 Hz).

^{31}P NMR δ 17.1

HRMS Exact mass: calculated for $\text{C}_{18}\text{H}_{22}\text{O}_7\text{P}$ (M+1) 381.1025; found 381.1103 (FAB).

(3a*R*,5*S*,7*R*,7a*S*5*H*-[1,2]Oxaphosphorino[4,5-*d*]oxazole, 3a,4,7,7a-tetrahydro-5-phenoxy-7-[(phenylmethoxy)methyl]-2-(trichloromethyl)-5-oxide [(-)-4.33]

To a solution of **4.30** (32 mg, 0.092 mmol) in CH₂Cl₂ (2 mL) were added Cl₃CCN (0.01mL) and a catalytic amount of DBU at -50 °C. The solution was allowed to warm to -20 °C over 5 hrs. The reaction mixture was quenched with NH₄Cl (saturated aq.), extracted with CH₂Cl₂ (3x) and dried (Na₂SO₄). Removal of solvent under reduced pressure and flash chromatography (1:1 Hex/EtOAc) afforded 36 mg (80%) of **4.33**.

$[\alpha]_D^{20} = -1.88$ (*c* 2.6, CH₂Cl₂).

FTIR (neat) 3063, 3030, 2927, 2868, 1716, 1664, 1591, 1491 1454, 1271, 1203, 985, 930 cm⁻¹.

¹H NMR δ 7.38-7.15 (m, 10H), 5.12-5.08 (m, 1H), 4.99-4.89 (m, 1H), 4.70-4.57 (m, 3 H), 3.92 (d, *J* = 11.2 Hz, 1H), 3.82 (dd, *J* = 11.1, 4.6 Hz, 1H), 2.75 (dd, *J* = 18.2, 15.9, 7.0 Hz, 1H), 2.32 (dd, *J* = 17.0, 7.5 Hz, 1H).

¹³C NMR δ 162.3, 149.5 (d, *J*_{CP} = 8.5 Hz), 137.1, 129.8, 128.5, 128.0, 127.8, 120.7 (d, *J*_{CP} = 4.3 Hz), 85.8, 79.2 (d, *J*_{CP} = 7.6 Hz), 77.4, 73.8, 69.8 (d, *J*_{CP} = 5.9 Hz), 63.1 (d, *J*_{CP} = 3.7 Hz), 24.9 (d, *J*_{CP} = 126.3 Hz).

³¹P NMR δ 19.5.

HRMS Exact mass: calculated for C₂₀H₂₀Cl₃NO₅P (*M*+1) 490.0145; found 490.0145 (FAB).

2,2,2-trichloro-N-[(2*S*,4*R*,5*S*,6*R*)-5-hydroxy-2-oxido-2-phenoxy-6-[(phenylmethoxy)methyl]-1,2-oxaphosphorinan-4-yl]- [(+)-4.34].

Compound **4.33** (15 mg, 0.031 mmol) was dissolved in acetone (0.6 mL), followed by the addition of H₂O (0.1 mL). PPTS (2 mg, 0.0093 mmols) was added and the reaction was stirred at room temperature overnight. Concentration under reduced pressure and flash chromatography (3:2 EtOAc/Hex), provided 12 mg (76% yield) of the **4.34** as an oil.

$[\alpha]_D^{20} = +36.0$ (*c* 1.6, CH₂Cl₂).

¹H NMR δ 7.70 (d, *J* = 7.5 Hz, 1H), 7.37-7.19 (m, 10H), 4.17 (dddd, *J* = 33.6, 8.0, 8.0, 4.0 Hz, 1H), 4.62 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.48 (ddd, *J* = 8.8, 8.8, 4.4 Hz, 1H), 4.17 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.85 (m, 2H), 2.61 (dd, *J* = 15.9, 15.9, 4.6 Hz, 1H), 2.41 (ddd, *J* = 19.1, 15.9, 4.6 Hz, 1H).

¹³C NMR δ 163.2, 149.4 (d, *J*_{CP} = 9.3 Hz), 137.2, 130.2, 128.6, 128.1, 127.8, 125.8, 120.0 (d, *J*_{CP} = 4.6 Hz), 95.2, 73.9, 72.2, 70.0 (d, *J*_{CP} = 8.0 Hz), 68.5 (d, *J*_{CP} = 6.1 Hz), 49.4 (d, *J*_{CP} = 7.8 Hz), 25.3 (d, *J*_{CP} = 126.3 Hz).

³¹P NMR δ 18.7.

(1*S*,2*S*)-2-Propenyl-1-triphenylmethoxymethyl-2-propenyl phenylmethoxymethyl ester phosphonic acid [(-)-4.36].

To a solution of benzyl alcohol (0.51 mL, 4.93 mmol) in dry DME (25 mL) was added ⁿBuLi (3.2 mL 1.3 M in Hex) at -30 °C and the solution was warmed to rt over 1 h and stirred for an additional 4hrs. This solution was added to the mixed phosphonate (1.320 g, 2.59 mmol) in DME (15 mL) at -50 °C over 1 h. The resulting mixture was transferred back to the alkoxide flask at -50 °C and allowed to warm up to rt overnight. This mixture was stirred for 8 hrs at rt, quenched with NH₄Cl (saturated aq.), extracted with EtOAc (3x) and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (7:3 Hex/EtOAc) afforded 1.20 g (88%) of **4.36** as an oil.

$[\alpha]_D^{20} = -4.6$ (c 0.16, CH₂Cl₂).

FTIR (neat) 3059, 3032, 2931, 1638, 1490, 1448, 1257, 1215, 1078, 990 cm⁻¹;

¹H NMR δ 7.49-7.19 (m, 20H), 5.94-5.78 (m, 2H), 5.43-5.01 (m, 7H), 3.30-3.21 (m, 2H), 2.68 (dd, *J* = 21.1, 7.3 Hz, 2H).

¹³C NMR δ 143.6, 136.3 (d, *J*_{CP} = 6.9 Hz), 134.2 (d, *J*_{CP} = 3.1 Hz), 128.6, 128.3, 128.0, 127.7, 127.6, 127.3 (d, *J*_{CP} = 11.5 Hz), 127.0, 120.0 (d, *J*_{CP} = 14.8 Hz), 118.4, 86.7, 76.7 (d, *J*_{CP} = 15.6 Hz), 66.9 (d, *J*_{CP} = 6.4 Hz), 66.3 (d, *J*_{CP} = 5.2 Hz), 32.6 (d, *J*_{CP} = 139.6 Hz).

³¹P NMR δ 28.3.

HRMS Exact mass: calculated for C₃₃H₃₄O₄P (M+1) 525.2116; found 525.2195 (FAB).

(2*S*_P,6*S*)-2-Phenylmethoxy-6-[(triphenylmethoxy)methyl]-2*H*-1,2-oxaphosphorin-3,6-dihydro-2-oxide, [(-)-4.37].

To a solution of the **4.36** (70 mg, 0.13 mmol) in dry CH₂Cl₂ (13 mL) was added catalyst **A** (3 mg, 3 mol%) and the mixture was refluxed for 6 hrs, diluted with CH₂Cl₂, flushed with air and stirred overnight at rt. Removal of the solvent under reduced pressure and flash chromatography (7:3 EtOAc/Hex) afforded 63 mg (98%) of **4.37** as white solid.

mp 153-155 °C.

[α]_D²⁰ = −38.4 (*c* 0.56, CH₂Cl₂).

FTIR (neat) 3058, 3032, 2929, 1490, 1448, 1279, 1248, 1077, 1001, 899 cm^{−1}.

¹H NMR δ 7.45-7.21 (m, 20H), 5.82-5.72 (m, 2H), 5.19-5.14 (m, 2H), 4.19 (dd, *J* = 11.9, 8.3 Hz, 1H), 3.37 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.26 (dd, *J* = 9.6, 5.3 Hz, 1H), 2.50-2.04 (m, 2H).

¹³C NMR δ 143.5, 136.0 (d, *J*_{CP} = 6.3 Hz), 128.6, 128.5, 128.3, 127.8, 127.8, 127.1, 126.7 (d, *J*_{CP} = 16.9 Hz), 121.0 (d, *J*_{CP} = 9.5 Hz), 86.7, 78.8 (d, *J*_{CP} = 7.4 Hz), 67.1 (d, *J*_{CP} = 6.0 Hz), 65.6 (d, *J*_{CP} = 5.0 Hz), 22.3 (d, *J*_{CP} = 132.3 Hz).

³¹P NMR δ 21.4.

HRMS Exact mass: calculated for C₃₁H₃₀O₄P (*M*+1) 497.1882; found 497.1883 (FAB).

(2*S*_p,4*R*,5*S*,6*S*)-2-Phenylmethoxy-6-[(triphenylmethoxy)methyl]-1,2-oxaphosphorinane-4,5-diol-2-oxide [(+)-4.38].

To a solution of **4.37** (61 mg, 0.12 mmol) in acetone (2 mL) and *t*-BuOH (0.8 mL) were added citric acid (30 mg, 0.16 mmol), NMO (18 mg, 0.13 mmol) and OsO₄ (1 drop 4% solution in water). The reaction mixture was stirred for 48 hrs, solid Na₂SO₃ and 3% aq. NaHSO₄ were added, stirred for 30 min and extracted with EtOAc (3x). Removal of the solvent under reduced pressure and flash chromatography (EtOAc/4% MeOH) afforded 51 mg (81%) of **4.38** as an oil.

[α]_D²⁰ = +26.0 (*c* 0.19, CH₂Cl₂).

FTIR (neat) 3363, 3059, 3033, 2934, 1490, 1449, 1226, 1079, 1022, 983 cm⁻¹.

¹H NMR δ 7.44-7.19 (m, 20H), 5.13-5.01 (m, 2H), 4.70-4.64 (m, 1H), 4.26 (br. d, *J* = 31.6 Hz, 1H), 3.89 (d, *J* = 7.8 Hz, 1H), 3.39 (d, *J* = 2.8 Hz, 2H), 2.31 (ddd, *J* = 15.6, 15.2, 5.7 Hz, 1H), 1.98 (ddd, *J* = 18.1, 14.9, 3.4 Hz, 1H).

¹³C NMR δ 143.6, 135.6 (d, *J*_{CP} = 5.8 Hz), 128.6, 128.5, 127.9, 128.8, 127.1, 86.7, 76.5 (dd, *J*_{CP} = 4.9 Hz), 68.8 (d, *J*_{CP} = 5.4 Hz), 67.6 (d, *J*_{CP} = 6.4 Hz), 67.3 (d, *J*_{CP} = 7.1 Hz), 63.2 (d, *J*_{CP} = 6.4 Hz), 28.6 (d, *J*_{CP} = 124.6 Hz).

³¹P NMR δ 26.6.

(2*S*_P,4*R*,5*S*,6*S*)-2-Phenylmethoxy-6-[(triphenylmethoxy)methyl]-1,2-oxaphosphorinane-4,5-carbonate-2-oxide.

To a solution of **4.38** (23 mg, 0.043 mmol) and triphosgene (27 mg, 0.09 mmol) in CH₂Cl₂ (1.0 mL) was added Et₃N (0.03 mL, 0.22 mmol) at -40 °C and the solution was warmed to rt over 5 hrs. The reaction mixture was diluted with CH₂Cl₂, quenched with NH₄Cl (saturated aq.), extracted with CH₂Cl₂ and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (3:2 EtOAc/Hex) afforded 20 mg (84%) of the carbonate as a white solid.

mp 162-164 °C.

[α]_D²⁰ = +43.0 (*c* 3.6, CH₂Cl₂).

FTIR (neat) 3032, 2929, 1817, 1599, 1491, 1448, 1354, 1272, 1069, 1034, 965 cm⁻¹.

¹H NMR δ 7.46-7.26 (m, 20H), 5.25-5.19 (m, 2H), 5.07 (t, *J* = 8.7 Hz, 1H), 5.00-4.91 (m, 1H), 4.47-4.44 (m, 1H), 3.63 (dd, *J* = 11.0, 2.3 Hz, 1H), 3.36 (dt, *J* = 11.0, 3.0 Hz, 1H), 2.62-2.52 (m, 1H), 2.32 (ddd, *J* = 18.3, 15.8, 9.5 Hz, 1H).

¹³C NMR δ 152.5, 143.0, 135.2 (d, *J*_{CP} = 5.6 Hz), 128.9, 128.8, 128.4, 128.0, 127.9, 127.2, 86.9, 75.0 (d, *J*_{CP} = 5.7 Hz), 71.7, 71.1 (d, *J*_{CP} = 6.5 Hz), 68.3 (d, *J*_{CP} = 6.1 Hz), 61.9 (d, *J*_{CP} = 7.6 Hz), 24.7 (d, *J*_{CP} = 121.7 Hz).

³¹P NMR δ 21.6.

HRMS Exact mass: calculated for C₃₂H₃₀O₈P (*M*+1) 557.1729; found 557.1705 (FAB).

(2*S*_P,5*S*,6*R*)-5,6-Dihydro-2-phenylmethoxy-6-[(triphenylmethoxy)methyl]2H-1,2-oxaphosphorinane-5-ol-2-oxide [(+)-4.39].

To a solution of the carbonate (150 mg, 0.27 mmol) in THF (10.0 mL) was added KHMDS (0.71 mL 0.5 M in toluene, 0.35 mmol) at -40 °C and the solution was warmed to 0 °C over 3 hrs. The reaction mixture was quenched with NH₄Cl (saturated aq.), extracted with EtOAc (3x) and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (4:1 EtOAc/Hex) afforded 110 mg (80%) of **4.39**.

$[\alpha]_D^{20} = +82.9$ (*c* 1.64, CH₂Cl₂).

FTIR (neat) 3325, 3058, 3032, 2930, 1597, 1490, 1448, 1362, 1228, 1193, 1079, 1019, 982 cm⁻¹.

¹H NMR δ 7.40-7.17 (m, 20H), 6.69 (ddd, *J* = 47.7, 12.9, 1.5 Hz, 1H), 5.72 (ddd, *J* = 18.8, 12.9, 2.2 Hz, 1H), 5.08-4.97 (m, 2H), 4.55-4.51 (m, 2H), 3.70 (br. s, 1H), 3.44 (d, *J* = 1.8 Hz, 2H).

¹³C NMR δ 153.1, 143.4, 135.6, 128.5, 127.9, 127.8, 127.1, 115.7 (d, *J*_{CP} = 166.2 Hz), 86.8, 79.5 (d, *J*_{CP} = 5.6 Hz), 68.5 (d, *J*_{CP} = 5.7 Hz), 65.6 (d, *J*_{CP} = 10.0 Hz), 63.1 (d, *J*_{CP} = 7.7 Hz).

³¹P NMR δ 12.7.

HRMS Exact mass: calculated for C₃₁H₃₀O₅P (*M*+1) 513.1831; found 513.1812 (FAB).

(2*S*_P,3*S*,4*R*,5*S*,6*R*)-2-Phenylmethoxy-6-[hydroxymethyl]-1,2-oxaphosphorinane-3,4,5-triol-2-oxide (4.40).

To a solution of OsO₄ (43 mg, 0.017 mmol) in CH₂Cl₂ (0.6 mL) was added TMEDA (22 mg, 0.19 mmol) followed by the starting alcohol (68 mg, 0.13 mmol) in CH₂Cl₂ (1.0 mL) and at -78 °C. The reaction mixture was stirred for 3 hrs at -78 °C, warmed up to rt and stirred for 15 min. Removal of the solvent under reduced pressure afforded the crude osmate ester, which was dissolved in 1.0 mL MeOH and treated with citric acid (40 mg, 0.21 mmol) for 24 hrs. The solvent was removed, the residue was dissolved in a small amount of MeOH and filtered through silica gel with EtOAc/10%MeOH. The crude product was dissolved in 1.0 mL MeOH and treated with catalytic amount of TsOH·H₂O for 8 hrs. Removal of the solvent under reduced pressure and flash chromatography (EtOAc/10% MeOH) afforded 28 mg (71%) of **4.40**.

¹H NMR δ 7.44-7.31 (m, 5H), 5.21-5.11 (m, 2H), 4.55-4.50 (m, 1H), 4.24 (dt, *J* = 33.7, 2.7 Hz, 1H), 4.01 (dd, *J* = 9.8, 3.4 Hz, 1H), 3.90 (ddd, *J* = 12.5, 4.4, 2.9 Hz, 1H), 3.75 (dd, *J* = 9.8, 2.1 Hz, 1H).

¹³C NMR δ 137.7 (d, *J*_{CP} = 6.4 Hz), 129.7, 129.6, 129.2, 78.4 (d, *J*_{CP} = 4.4 Hz), 75.5 (d), 71.4, 69.6 (dt, *J*_{CP} = 6.4 Hz), 69.0 (d), 67.7 (d, *J*_{CP} = 144.5 Hz), 62.8 (dt, *J*_{CP} = 8.0 Hz).

³¹P NMR δ 24.5.

HRMS Exact mass: calculated for C₃₈H₃₆O₈P (M+1) 651.2148; found 651.2131 (FAB).

(2*S*_P,5*S*,6*R*)-5,6-Dihydro-2-phenylmethoxy-2H-1,2-oxaphosphorinane-5-methanesulfonate-6-[(triphenylmethoxy)-methyl]-2-oxide [(+)-4.41].

To a solution of diol 36 (180 mg, 0.339 mmol) in CH₂Cl₂ (10 mL) were added a catalytic amount of DMAP (8.3 mg, 0.068 mmol), MsCl (0.087 mL, 1.13 mmol) at 0 °C followed by Et₃N (0.191 mL, 1.36 mmol). The reaction mixture was warmed to rt over 1 h and stirred overnight at rt. Et₃N (0.034 mL, 0.339 mmol) was added and the stirring was continued for 6 hrs. After addition of brine the mixture was extracted with EtOAc (3x) and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (1:1 Hex/EtOAc) afforded 120 mg (60%) of **4.41**.

$[\alpha]_D^{20} = +105.2$ (*c* 1.9, CH₂Cl₂).

FTIR (neat) 3032, 2933, 1490, 1449, 1364, 1259, 1180, 985, 961, 853 cm⁻¹.

¹H NMR δ 7.44-7.24 (m, 20H), 6.81 (ddd, *J* = 45.9, 12.9, 2.1 Hz, 1H), 6.03 (ddd, *J* = 17.2, 12.9, 2.1 Hz, 1H), 5.64-5.60 (m, 1H), 5.20-5.18 (m, 2H), 4.75-4.71 (m, 1H), 3.70 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.30 (dt, *J* = 11.0, 3.0 Hz, 1H), 2.65 (s, 3H).

¹³C NMR δ 145.9, 142.8, 135.4 (d, *J*_{CP} = 5.9 Hz), 128.7, 128.69, 128.6, 128.0, 127.9, 127.4, 119.9 (d, *J*_{CP} = 165.8 Hz), 87.1, 76.9 (d, *J*_{CP} = 6.1 Hz), 70.9 (d, *J*_{CP} = 10.6 Hz), 68.7 (d, *J*_{CP} = 6.2 Hz), 61.4 (dt, *J*_{CP} = 6.3 Hz), 38.1.

³¹P NMR δ 10.9.

HRMS Exact mass: calculated for C₃₂H₃₂O₇PS (M+1) 591.1606; found 591.1591 (FAB).

(2S,5R,6R)-5,6-Dihydro-2-phenylmethoxy-2H-1,2-oxaphosphorinane-5-ol-benzoate-6-[(triphenylmethoxy)methyl]-2-oxide, [(-)-4.42].

To a solution of **4.41** (24 mg, 0.044 mmol) in DMF (0.5 mL) was added KOBz (10 mg, 0.062 mmol) and 18-Crown-6 (27 mg, 10 mmol). The resulting reaction mixture was stirred overnight at rt, quenched with NH₄Cl (saturated aq.), extracted with EtOAc and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (7:3 Hex/EtOAc) afforded 20 mg (74%) of **4.42**.

$[\alpha]_D^{20} = -100.0$ (*c* 0.51, CH₂Cl₂).

¹H NMR δ 7.82 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.61 (t, *J* = 1.2 Hz, 1H), 7.52-7.12 (m, 22H), 7.03 (ddd, *J* = 45.5, 12.5, 5.7 Hz, 1H), 6.12 (dd, *J* = 17.2, 12.5 Hz, 1H), 5.72-5.69 (m, 1H), 5.15-4.97 (m, 3H), 3.56 (dd, *J* = 8.7, 5.5 Hz, 1H), 3.40 (t, *J* = 8.8 Hz, 1H).

¹³C NMR δ 165.0, 143.0, 142.8, 135.5 (d, *J*_{CP} = 6.2 Hz), 133.4, 129.8, 129.0, 128.53, 128.48, 128.45, 128.3, 127.8, 127.6, 127.1, 122.5 (d, *J*_{CP} = 164.1 Hz), 87.0, 75.9 (d, *J*_{CP} = 5.1 Hz), 68.7 (dt, *J*_{CP} = 6.1 Hz), 63.9 (d, *J*_{CP} = 10.9 Hz), 61.0 (dt, *J*_{CP} = 10.5 Hz).

³¹P NMR δ 10.3.

HRMS Exact mass: calculated for C₃₈H₃₄O₆P (M+1) 617.2093; found 617.2082 (FAB).

(2*S*_P,5*R*,6*R*)-5,6-Dihydro-2-phenylmethoxy-2*H*-1,2-oxaphosphorinane-5-ol-6

[(triphenylmethoxy)methyl]-2-oxide [(+)-4.44].

To a solution of **4.42** (40 mg, 0.065 mmol) in MeOH (1.0 mL) was added Mg(OMe)₂ (0.06 mL 7-8% solution in MeOH) the mixture was stirred overnight at rt, quenched with NH₄Cl (saturated aq.). MeOH was removed, the residue extracted with EtOAc (3x) and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash chromatography (7:3 EtOAc/Hex) afforded 25 mg (75%) of **4.44**.

$[\alpha]_D^{20} = +1.27$ (c 0.63, CH₂Cl₂).

¹H NMR δ 7.45-7.24 (m, 20H), 6.82 (ddd, *J* = 45.9, 12.5, 5.5 Hz, 1H), 5.09 (dd, *J* = 17.7, 12.5 Hz, 1H), 5.16-5.02 (m, 2H), 4.79-4.75 (m, 1H), 4.28 (br.s, 1H), 3.56-3.45 (m, 2H).

¹³C NMR δ 146.1, 143.1, 135.8 (d, *J*_{CP} = 6.0 Hz), 128.5, 128.4, 128.1, 127.9, 127.3, 119.9 (d, *J*_{CP} = 165.5 Hz), 87.3, 76.9 (d, *J*_{CP} = 4.9 Hz), 68.7 (dt, *J*_{CP} = 6.1 Hz), 63.4 (d, *J*_{CP} = 10.4 Hz), 62.7 (dt, *J*_{CP} = 9.6 Hz).

³¹P NMR δ 12.1.

(2*S*,3*S*,4*R*,5*R*,6*R*)-2-Phenylmethoxy-6-[(triphenylmethoxy)methyl]-1,2-oxaphosphorinane-3,4-diol-5-ol-benzoate-2-oxide) [(-)-4.43**].**

To a solution of **4.42** (33 mg, 0.054 mmol) in acetone (1.5 mL) and *t*-BuOH (0.5 mL) were added citric acid (13 mg, 0.068 mmol), NMO·H₂O (9 mg, 0.067 mmol) and OsO₄ (1 drop 4% solution in water). After stirring for 24 hrs at rt one more drop of OsO₄ was added and the stirring was continued for 24 hrs. Water was added to the reaction mixture and extracted with EtOAc (3x). Removal of the solvent under reduced pressure and flash chromatography (EtOAc/1% MeOH) afforded 28 mg (80%) of **4.43** as an oil.

$[\alpha]_D^{20} = -36.4$ (*c* 1.3, CH₂Cl₂).

FTIR (neat) 3325, 3061, 3033, 2926, 1728, 1600, 1491, 1449, 1264, 1093, 999, 967 cm⁻¹.

¹H NMR δ 7.81-7.80 (m, 2H), 7.60-7.56 (m, 1H), 7.40-7.29 (m, 13H), 7.16-7.08 (m, 9H), 5.74 (d, *J* = 4.5 Hz, 1H), 5.38 (dd, *J* = 6.5, 6.5 Hz, 1H), 5.20-5.17 (m, 2H), 4.68 (ddd, *J* = 33.5, 3.8, 3.8 Hz, 1H), 4.19 (dd, *J* = 10.7, 2.7 Hz, 1H), 3.46 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.22 (dd, *J* = 8.6, 8.6 Hz, 1H).

¹³C NMR δ 164.5, 143.1, 135.5 (d, *J*_{CP} = 6.0 Hz), 133.4, 129.8, 129.0, 128.6, 128.5, 128.4, 128.0, 127.8, 127.0, 86.9, 74.6 (d, *J*_{CP} = 4.7 Hz), 71.5, 71.4, 68.9 (dt, *J*_{CP} = 6.1 Hz), 66.6 (d, *J*_{CP} = 140.9 Hz), 60.7 (dt, *J*_{CP} = 11.6 Hz).

³¹P NMR δ 24.3.

HRMS Exact mass: calculated for C₃₈H₃₆O₈P (*M*+1) 651.2148; found 651.2131 (FAB).

(2*S*_P,3*S*,4*R*,5*R*,6*R*)-2-Phenylmethoxy-6-[hydroxymethyl]-1,2-oxaphosphorinane-3,4-diol-5-ol-2-oxide (4.45).

To a solution of **4.44** (24 mg, 0.047 mmol) in acetone (0.9 mL) and *t*-BuOH (0.3 mL) were added citric acid (10 mg, 0.052 mmol), NMO·H₂O (7 mg, 0.052 mmol) and OsO₄ (1 drop 4% solution in water). The reaction was stirred for 24 hours. Upon completion water was added to the reaction mixture and extracted with EtOAc (3x). The crude mixture was taken up in MeOH (1 mL), followed by the addition of catalytic TsOH, and stirred for an additional 24 hours. Removal of the solvent under reduced pressure and flash chromatography (EtOAc/1% MeOH) afforded 10 mg (70%) of **4.45** as an oil.

FTIR (neat) 3350, 3025, 2970, 1211, 1045 cm⁻¹.

¹H NMR δ 7.31-7.44 (m, 5H), 5.10-5.49 (m, 2H), 4.77 (dt, *J* = 5.9, 2.4 Hz, 1H), 4.29 (dd, *J* = 9.7, 3.7 Hz, 1H), 4.22 (ddd, *J* = 33.4, 4.0, 4.0 Hz, 1H), 3.96 (d, *J* = 4.4 Hz, 1H), 3.76-3.84 (m, 2H).

¹³C NMR δ 136.7, 128.6, 128.4, 127.9, 77.6 (d, *J*_{CP} = 5.4 Hz), 70.5 (d, *J*_{CP} = 2.3 Hz), 68.5 (d, *J*_{CP} = 6.6 Hz), 64.5 (d, *J*_{CP} = 144.9 Hz), 61.5 (d, *J*_{CP} = 10.1 Hz).

³¹P NMR δ 20.8.

Appendix A

NMR Spectra-Chapters 2 and 3

2.16 (^1H , ^{13}C , and ^{31}P)

2.17 (^1H and ^{13}C)

2.18 (^1H , ^{13}C , and ^{31}P)

2.19 (^1H and ^{13}C)

2.27a (^1H and ^{13}C)

2.23 (^1H and ^{13}C)

2.27b (^1H and ^{13}C)

2.27c (^1H and ^{13}C)

2.27d (^1H and ^{13}C)

2.27e (^1H and ^{13}C)

2.27f (^1H and ^{13}C)

2.27g (^1H and ^{13}C)

2.26 R¹ = Me (¹H, ¹³C, and ³¹P)

2.28 R¹ = Me (¹H, ¹³C, and ³¹P)

2.29 (^1H , ^{13}C , and ^{31}P)

2.30 (^1H and ^{13}C)

2.32 (^1H , ^{13}C , and ^{31}P)

2.33 (^1H and ^{13}C)

2.25 (^1H and ^{13}C)

2.34 (^1H and ^{13}C)

2.39 (^1H and ^{13}C)

2.40 (^1H , ^{13}C , and ^{31}P)

2.41 (^1H , ^{13}C , and ^{31}P)

2.35 (^1H , ^{13}C , and ^{31}P)

2.49 (^1H , ^{13}C , and ^{31}P)

2.42 (^1H , ^{13}C , and ^{31}P)

2.45 (^1H , ^{13}C , and ^{31}P)

2.47 (^1H , ^{13}C , and ^{31}P)

2.48 (^1H and ^{13}C)

2.46 (^1H and ^{13}C)

2.50 (^1H and ^{13}C)

$(^1\text{H}, ^{13}\text{C}, \text{ and } ^{31}\text{P})$

2.56 (^1H , ^{13}C , and ^{31}P)

2.57 (^1H , ^{13}C , and ^{31}P)

2.59 (^1H and ^{13}C)

2.58 (^1H , ^{13}C , and ^{31}P)

3.13 (^1H , ^{13}C , and ^{31}P)

(^1H , ^{13}C , and ^{31}P)

3.14 (^1H and ^{13}C)

3.23 (^1H and ^{13}C)

(^1H and ^{13}C)

3.24 (^1H and ^{13}C)

3.18 (^1H and ^{13}C)

3.19 (^1H and ^{13}C)

3.26 (^1H and ^{13}C)

3.29 (^1H and ^{13}C)

3.30 (^1H and ^{13}C)

3.15 (^1H and ^{13}C)

3.21 (^1H and ^{13}C)

3.44 (^1H and ^{13}C)

3.22 (^1H and ^{13}C)

3.36 (^1H , ^{13}C , and ^{31}P)

3.37 (^1H and ^{13}C)

3.40 (^1H and ^{13}C)

3.34 (^1H and ^{13}C)

Appendix B

X-Ray Data

Contents for 2.35

Comments	333
Experimental	333
Figure B.1. Ellipsoid drawing of molecule	334
Figure B.2. Packing drawing	335
Table B.1. Crystal Data	336
Table B.2. Atom Coordinates	337
Table B.3. Bond Lengths and Angles	337
Table B.4. Anisotropic Displacement Parameters	338
Table B.5. Hydrogen Atom Parameters	339
Table B.6. Torsion Angles	340

Contents for 2.53

Figure B.3. Ellipsoid drawing of molecule	341
Figure B.4. Packing drawing	342
Table B.7. Crystal Data	343
Table B.8. Atom Coordinates	344
Table B.9. Bond Lengths and Angles	345
Table B.10. Anisotropic Displacement Parameters	346
Table B.11. Hydrogen Atom Parameters	347
Table B.12. Torsion Angles	348
References	349

Comment

The displacement ellipsoids were drawn at the 50% probability level.

Experimental

A colorless needle-shaped crystal of dimensions 0.38 x 0.14 x 0.11 mm was selected for structural analysis. Intensity data for this compound were collected using a Bruker APEX ccd area detector(1) mounted on a Bruker D8 goniometer using with graphite-monochromated Mo K α radiation ($\lambda = 0.71073$ Å). The sample was cooled to 100(2) K. The intensity data were measured as a series of ω oscillation frames each of 0.25 ° for 20 sec / frame. The detector was positioned 5.054 cm from the sample. Coverage of unique data was 99.9 % complete to 25.99 degrees in θ . Cell parameters were determined from a non-linear least squares fit of 5462 peaks in the range $2.43 < \theta < 26.00^\circ$. The first 50 frames were repeated at the end of data collection and yielded a total of 143 peaks showing a variation of 0.16 % during the data collection. A total of 5619 data were measured in the range $2.44 < \theta < 25.99^\circ$. The data were corrected for absorption by the semi-empirical method (2) giving minimum and maximum transmission factors of 0.8999 and 0.9695. The data were merged to form a set of 1772 independent data with $R(\text{int}) = 0.0207$.

The orthorhombic space group $P2_12_12_1$ 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 times the displacement parameters of the bonded atoms. A total of 118 parameters were refined against 1772 data to give $wR(F^2) = 0.1012$ and $S = 1.053$ for weights of $w = 1/[\sigma^2(F^2) + (0.0900 P)^2]$, where $P = [F_o^2 + 2F_c^2] / 3$. The final $R(F)$ was 0.0292 for the 1740 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 0.376 and -0.253 e/Å³, respectively. The absolute structure was determined by refinement of the Flack parameter(4).

Figure B.1. Ellipsoid drawing of **2.35**

Figure B.2. Packing drawing of **2.35**

Table B.1. Crystal data and structure refinement for **2.35**.

Empirical formula	C ₈ H ₁₁ O ₄ P
Formula weight	202.14
Crystal system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
Unit cell dimensions	<i>a</i> = 6.8895(14) Å α = 90° <i>b</i> = 7.8323(16) Å β = 90° <i>c</i> = 16.708(4) Å γ = 90°
Volume	901.6(3) Å ³
Z, Z'	4, 1
Density (calculated)	1.489 Mg/m ³
Wavelength	0.71073 Å
Temperature	100(2) K
<i>F</i> (000)	424
Absorption coefficient	0.283 mm ⁻¹
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9695 and 0.8999
Theta range for data collection	2.44 to 25.99°
Reflections collected	5619
Independent reflections	1772 [R(int) = 0.0207]
Data / restraints / parameters	1772 / 0 / 118
<i>wR</i> (<i>F</i> ² all data)	<i>wR</i> 2 = 0.1012
<i>R</i> (<i>F</i> obsd data)	<i>R</i> 1 = 0.0292
Goodness-of-fit on <i>F</i> ²	1.053
Observed data [I > 2σ(I)]	1740
Absolute structure parameter	-0.01(9)
Largest and mean shift / s.u.	0.001 and 0.000
Largest diff. peak and hole	0.376 and -0.253 e/Å ³

$$wR2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2] \}^{1/2}$$

$$R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$$

Table B.2. Atomic coordinates and equivalent isotropic displacement parameters for **2.35**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
P(1)	0.03594(5)	0.24501(5)	0.14889(2)	0.01464(17)
O(1)	0.22357(16)	0.12911(13)	0.15093(7)	0.0167(3)
C(2)	0.4145(2)	0.2133(2)	0.15600(10)	0.0168(3)
C(3)	0.4589(2)	0.2707(2)	0.23984(11)	0.0192(4)
C(4)	0.3401(2)	0.2866(2)	0.30147(9)	0.0185(4)
C(5)	0.1227(2)	0.2617(2)	0.30220(8)	0.0170(3)
O(6)	0.03127(16)	0.33842(14)	0.23248(7)	0.0165(3)
O(7)	0.07753(15)	0.39586(15)	0.08907(7)	0.0162(3)
C(8)	0.2657(2)	0.4865(2)	0.09724(9)	0.0162(3)
C(9)	0.4285(2)	0.3545(2)	0.09293(10)	0.0171(4)
C(10)	0.2753(2)	0.6112(2)	0.02991(10)	0.0185(3)
C(11)	0.2786(2)	0.7783(2)	0.04040(10)	0.0218(4)
O(12)	-0.13813(17)	0.14835(15)	0.12781(7)	0.0218(3)

Table B.3. Torsion angles [°] for **2.35**.

O(12)-P(1)-O(1)-C(2)	168.51(10)	O(1)-P(1)-O(6)-C(5)	-26.44(12)
O(7)-P(1)-O(1)-C(2)	44.25(12)	O(12)-P(1)-O(7)-C(8)	-171.08(10)
O(6)-P(1)-O(1)-C(2)	-64.50(11)	O(6)-P(1)-O(7)-C(8)	63.58(11)
P(1)-O(1)-C(2)-C(3)	78.72(15)	O(1)-P(1)-O(7)-C(8)	-47.06(11)
P(1)-O(1)-C(2)-C(9)	-49.33(15)	P(1)-O(7)-C(8)-C(10)	175.21(10)
O(1)-C(2)-C(3)-C(4)	-15.1(2)	P(1)-O(7)-C(8)-C(9)	54.59(14)
C(9)-C(2)-C(3)-C(4)	110.46(19)	O(7)-C(8)-C(9)-C(2)	-57.48(16)
C(2)-C(3)-C(4)-C(5)	-4.4(3)	C(10)-C(8)-C(9)-C(2)	-174.53(13)
C(3)-C(4)-C(5)-O(6)	-42.7(3)	O(1)-C(2)-C(9)-C(8)	55.23(17)
C(4)-C(5)-O(6)-P(1)	78.80(16)	C(3)-C(2)-C(9)-C(8)	-71.28(16)
O(12)-P(1)-O(6)-C(5)	98.31(12)	O(7)-C(8)-C(10)-C(11)	115.58(17)
O(7)-P(1)-O(6)-C(5)	-138.50(11)	C(9)-C(8)-C(10)-C(11)	-126.27(17)

Table B.4. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **2.35**.

P(1)-O(12)	1.4612(12)	O(1)-C(2)-H(2A)	106.8
P(1)-O(7)	1.5739(12)	C(3)-C(2)-H(2A)	106.8
P(1)-O(6)	1.5771(11)	C(9)-C(2)-H(2A)	106.8
P(1)-O(1)	1.5799(11)	C(4)-C(3)-C(2)	128.96(14)
O(1)-C(2)	1.4742(17)	C(4)-C(3)-H(3A)	115.5
C(2)-C(3)	1.502(2)	C(2)-C(3)-H(3A)	115.5
C(2)-C(9)	1.530(2)	C(3)-C(4)-C(5)	127.47(15)
C(2)-H(2A)	1.0000	C(3)-C(4)-H(4A)	116.3
C(3)-C(4)	1.321(2)	C(5)-C(4)-H(4A)	116.3
C(3)-H(3A)	0.9500	O(6)-C(5)-C(4)	111.68(13)
C(4)-C(5)	1.511(2)	O(6)-C(5)-H(5A)	109.3
C(4)-H(4A)	0.9500	C(4)-C(5)-H(5A)	109.3
C(5)-O(6)	1.4542(19)	O(6)-C(5)-H(5B)	109.3
C(5)-H(5A)	0.9900	C(4)-C(5)-H(5B)	109.3
C(5)-H(5B)	0.9900	H(5A)-C(5)-H(5B)	107.9
O(7)-C(8)	1.4839(17)	C(5)-O(6)-P(1)	120.58(10)
C(8)-C(10)	1.491(2)	C(8)-O(7)-P(1)	117.36(10)
C(8)-C(9)	1.527(2)	O(7)-C(8)-C(10)	106.42(12)
C(8)-H(8A)	1.0000	O(7)-C(8)-C(9)	108.26(12)
C(9)-H(9A)	0.9900	C(10)-C(8)-C(9)	112.04(12)
C(9)-H(9B)	0.9900	O(7)-C(8)-H(8A)	110.0
C(10)-C(11)	1.321(2)	C(10)-C(8)-H(8A)	110.0
C(10)-H(10A)	0.9500	C(9)-C(8)-H(8A)	110.0
C(11)-H(11A)	0.9500	C(8)-C(9)-C(2)	114.23(12)
C(11)-H(11B)	0.9500	C(8)-C(9)-H(9A)	108.7
O(12)-P(1)-O(7)	112.66(7)	C(2)-C(9)-H(9A)	108.7
O(12)-P(1)-O(6)	115.91(6)	C(8)-C(9)-H(9B)	108.7
O(7)-P(1)-O(6)	102.58(6)	C(2)-C(9)-H(9B)	108.7
O(12)-P(1)-O(1)	112.27(6)	H(9A)-C(9)-H(9B)	107.6
O(7)-P(1)-O(1)	107.22(6)	C(11)-C(10)-C(8)	123.36(16)
O(6)-P(1)-O(1)	105.31(6)	C(11)-C(10)-H(10A)	118.3
C(2)-O(1)-P(1)	118.31(9)	C(8)-C(10)-H(10A)	118.3
O(1)-C(2)-C(3)	111.65(12)	C(10)-C(11)-H(11A)	120.0
O(1)-C(2)-C(9)	109.86(12)	C(10)-C(11)-H(11B)	120.0
C(3)-C(2)-C(9)	114.42(14)	H(11A)-C(11)-H(11B)	120.0

Table B.5. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.35**. The anisotropic displacement factor exponent takes the form: $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
P(1)	14(1)	14(1)	16(1)	-3(1)	0(1)	0(1)
O(1)	16(1)	12(1)	22(1)	-2(1)	2(1)	1(1)
C(2)	10(1)	17(1)	23(1)	2(1)	2(1)	0(1)
C(3)	17(1)	16(1)	25(1)	5(1)	-4(1)	-2(1)
C(4)	19(1)	17(1)	19(1)	3(1)	-5(1)	-2(1)
C(5)	20(1)	16(1)	15(1)	2(1)	1(1)	-2(1)
O(6)	17(1)	16(1)	17(1)	-3(1)	-1(1)	3(1)
O(7)	16(1)	16(1)	17(1)	0(1)	-1(1)	-1(1)
C(8)	14(1)	16(1)	18(1)	-2(1)	-1(1)	-2(1)
C(9)	14(1)	18(1)	19(1)	1(1)	2(1)	3(1)
C(10)	17(1)	22(1)	17(1)	1(1)	0(1)	1(1)
C(11)	18(1)	21(1)	26(1)	7(1)	-1(1)	0(1)
O(12)	19(1)	21(1)	25(1)	-2(1)	-1(1)	-4(1)

	x	y	z	U(eq)
H(2A)	0.5139	0.1255	0.1417	0.020
H(3A)	0.5906	0.2995	0.2499	0.023
H(4A)	0.3981	0.3173	0.3510	0.022
H(5A)	0.0932	0.1380	0.3033	0.020
H(5B)	0.0681	0.3135	0.3513	0.020
H(8A)	0.2708	0.5481	0.1496	0.019
H(9A)	0.5544	0.4138	0.0993	0.021
H(9B)	0.4271	0.3013	0.0392	0.021
H(10A)	0.2792	0.5683	-0.0232	0.022
H(11A)	0.2748	0.8246	0.0929	0.026
H(11B)	0.2848	0.8523	-0.0046	0.026

Table B.6. Torsion angles [$^{\circ}$] for **2.35**.

O(12)-P(1)-O(1)-C(2)	168.51(10)
O(7)-P(1)-O(1)-C(2)	44.25(12)
O(6)-P(1)-O(1)-C(2)	-64.50(11)
P(1)-O(1)-C(2)-C(3)	78.72(15)
P(1)-O(1)-C(2)-C(9)	-49.33(15)
O(1)-C(2)-C(3)-C(4)	-15.1(2)
C(9)-C(2)-C(3)-C(4)	110.46(19)
C(2)-C(3)-C(4)-C(5)	-4.4(3)
C(3)-C(4)-C(5)-O(6)	-42.7(3)
C(4)-C(5)-O(6)-P(1)	78.80(16)
O(12)-P(1)-O(6)-C(5)	98.31(12)
O(7)-P(1)-O(6)-C(5)	-138.50(11)
O(1)-P(1)-O(6)-C(5)	-26.44(12)
O(12)-P(1)-O(7)-C(8)	-171.08(10)
O(6)-P(1)-O(7)-C(8)	63.58(11)
O(1)-P(1)-O(7)-C(8)	-47.06(11)
P(1)-O(7)-C(8)-C(10)	175.21(10)
P(1)-O(7)-C(8)-C(9)	54.59(14)
O(7)-C(8)-C(9)-C(2)	-57.48(16)
C(10)-C(8)-C(9)-C(2)	-174.53(13)
O(1)-C(2)-C(9)-C(8)	55.23(17)
C(3)-C(2)-C(9)-C(8)	-71.28(16)
O(7)-C(8)-C(10)-C(11)	115.58(17)
C(9)-C(8)-C(10)-C(11)	-126.27(17)

Figure B.3. Ellipsoid drawing of **2.53**

Figure B.4. Packing drawing of **2.53**

Table B.7. Crystal data and structure refinement for **2.53**.

Empirical formula	C ₈ H ₁₁ O ₅ P	
Formula weight	218.14	
Crystal system	Tetragonal	
Space group	<i>P</i> 4 ₃ 2 ₁ 2	
Unit cell dimensions	<i>a</i> = 6.3256(4) Å	α = 90°
	<i>b</i> = 6.3256(4) Å	β = 90°
	<i>c</i> = 46.035(6) Å	γ = 90°
Volume	1842.0(3) Å ³	
<i>Z</i> , <i>Z'</i>	8, 1	
Density (calculated)	1.573 Mg/m ³	
Wavelength	0.71073 Å	
Temperature	100(2) K	
<i>F</i> (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 [<i>R</i> (int) = 0.0283]	
Data / restraints / parameters	1764 / 0 / 127	
<i>wR</i> (<i>F</i> ² all data)	<i>wR</i> 2 = 0.0999	
<i>R</i> (<i>F</i> obsd data)	<i>R</i> 1 = 0.0360	
Goodness-of-fit on <i>F</i> ²	1.014	
Observed data [<i>I</i> > 2σ(<i>I</i>)]	1762	
Absolute structure parameter	0.10(14)	
Largest and mean shift / s.u.	0.001 and 0.000	
Largest diff. peak and hole	0.514 and -0.211 e/Å ³	

$$wR2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2] \}^{1/2}$$

$$R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$$

Table B.8. Atomic coordinates and equivalent isotropic displacement parameters for **2.53**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
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 B.9. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **2.53**.

P(1)-O(11)	1.4561(17)	C(5)-H(5)	1.0000
P(1)-O(10)	1.5697(16)	C(6)-C(7)	1.322(3)
P(1)-O(9)	1.5753(17)	C(6)-H(6)	0.9500
P(1)-O(2)	1.5800(15)	C(7)-C(8)	1.501(3)
O(2)-C(3)	1.459(3)	C(7)-H(7)	0.9500
C(3)-C(4)	1.517(3)	C(8)-O(9)	1.457(3)
C(3)-C(12)	1.522(3)	C(8)-H(8A)	0.9900
C(3)-H(3)	1.0000	C(8)-H(8B)	0.9900
C(4)-C(5)	1.526(3)	C(12)-O(13)	1.215(3)
C(4)-H(4A)	0.9900	C(12)-C(14)	1.495(3)
C(4)-H(4B)	0.9900	C(14)-H(14A)	0.9800
C(5)-O(10)	1.473(3)	C(14)-H(14B)	0.9800
C(5)-C(6)	1.499(3)	C(14)-H(14C)	0.9800
O(11)-P(1)-O(10)	112.93(9)	C(4)-C(5)-H(5)	107.1
O(11)-P(1)-O(9)	115.56(10)	C(7)-C(6)-C(5)	129.1(2)
O(10)-P(1)-O(9)	105.43(9)	C(7)-C(6)-H(6)	115.5
O(11)-P(1)-O(2)	112.08(9)	C(5)-C(6)-H(6)	115.5
O(10)-P(1)-O(2)	107.05(8)	C(6)-C(7)-C(8)	127.3(2)
O(9)-P(1)-O(2)	102.93(8)	C(6)-C(7)-H(7)	116.4
C(3)-O(2)-P(1)	116.73(13)	C(8)-C(7)-H(7)	116.4
O(2)-C(3)-C(4)	110.01(17)	O(9)-C(8)-C(7)	112.72(17)
O(2)-C(3)-C(12)	108.39(17)	O(9)-C(8)-H(8A)	109.0
C(4)-C(3)-C(12)	112.99(18)	C(7)-C(8)-H(8A)	109.0
O(2)-C(3)-H(3)	108.4	O(9)-C(8)-H(8B)	109.0
C(4)-C(3)-H(3)	108.4	C(7)-C(8)-H(8B)	109.0
C(12)-C(3)-H(3)	108.4	H(8A)-C(8)-H(8B)	107.8
C(3)-C(4)-C(5)	111.75(18)	C(8)-O(9)-P(1)	120.94(13)
C(3)-C(4)-H(4A)	109.3	C(5)-O(10)-P(1)	119.48(13)
C(5)-C(4)-H(4A)	109.3	O(13)-C(12)-C(14)	122.8(2)
C(3)-C(4)-H(4B)	109.3	O(13)-C(12)-C(3)	119.0(2)
C(5)-C(4)-H(4B)	109.3	C(14)-C(12)-C(3)	118.1(2)
H(4A)-C(4)-H(4B)	107.9	C(12)-C(14)-H(14A)	109.5
O(10)-C(5)-C(6)	111.91(18)	C(12)-C(14)-H(14B)	109.5
O(10)-C(5)-C(4)	109.04(16)	H(14A)-C(14)-H(14B)	109.5
C(6)-C(5)-C(4)	114.15(18)	C(12)-C(14)-H(14C)	109.5
O(10)-C(5)-H(5)	107.1	H(14A)-C(14)-H(14C)	109.5
C(6)-C(5)-H(5)	107.1	H(14B)-C(14)-H(14C)	109.5

Table B.10. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.53**. The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

	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 B.11. Hydrogen coordinates and isotropic displacement parameters for **2.53**.

	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 B.12. Torsion angles [$^{\circ}$] for **2.35**.

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)

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