Synthesis of Biologically Active Phosphorus Heterocycles

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Synthesis of Biologically Active Phosphorus Heterocycles

Giri Raj Gnawali

M.S. Chemistry, University of Missouri-St. Louis, 2019

A Dissertation Submitted to The Graduate School at the University of Missouri-St. Louis
in partial fulfillment of the requirements for the degree
Doctor of Philosophy with an emphasis in Organic Chemistry

December 2020

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Abstract

Synthesis of Biologically Active Phosphorus Heterocycles

Giri Raj Gnawali

Doctor of Philosophy

University of Missouri-St. Louis

Prof. Christopher D. Spilling, Advisor

This dissertation work is divided into two parts. The first part is focused in the development of methodology for the synthesis of phostones and phosphonosugars and advancement thereof. The second part is focused in the development of affinity probes based on analogs of natural products cyclophostin and the cyclipostins.

Phostone (3) and phosphonosugars are cyclic phosphonates. The anomeric carbon of sugar is replaced by a phosphorus atom. The synthesis of phostones has been achieved starting from the key intermediate, γ,δ-epoxy vinyl phosphonate (1). The palladium catalyzed ring opening of γ,δ-epoxy vinyl phosphonates by a nucleophile results in the formation of δ-hydroxy phosphonates (2), which on further reduction and cyclization yields phostones (3). Various primary alcohols have been used as the nucleophiles for the opening of γ,δ-epoxy vinyl phosphonate (1).
The synthesized phostones have been further functionalized and submitted to test their potency as LPS antagonists. Sugar-based methylene phosphonates have been prepared and tested as well.

Cyclophostin (4) and the cyclipostins (5) are bicyclic organophosphates. Previously published studies of analogs of cyclophostin (4) and the cyclipostins (5) have shown that they inhibit the growth of *Mycobacterium tuberculosis* either in infected macrophage or in a broth medium. This suggests that these analogs could represent a new class of multi-target inhibitors. To assist in the study of the mode of action and the target identification, two series of compounds were synthesized as the affinity probes. The synthesized compounds were submitted to collaborators to study their activity against *Mycobacterium tuberculosis*.

![Chemical Structures](image)

**R = Me; Cyclophostin (4)**
**R = Lipophilic chains; Cyclipostins (5)**

![Chemical Structures](image)

**X = O, CH₂**
**R = fluorescent or alkyne moiety**
Dedication

This Dissertation is Dedicated to my Family
Acknowledgement

First and foremost, I express my sincere gratitude to Prof. Christopher D. Spilling for his enduring support and guidance. He was there to encourage and push me to do the right thing at the right time. It is impossible to see this work accomplished without his mentorship.

I express my sincere thanks to committee members Prof. James S. Chickos, Prof. Alexei V. Demchenko and Prof. Michael R. Nichols for valuable suggestions and going through each and every lines of this manuscripts and providing the critical comments.

I am greatly thankful to Prof. Bruce C. Hamper for his support with HPLC work. He was always there for any help during the whole work. I am thankful to Mr. Joe Cramer for his help in Mass Spectrometry. I express my thanks to Prof. Rensheng Luo for his help in NMR Spectroscopy and Mass Spectrometry. I am also thankful to Prof. Nigam P. Rath for X-ray crystallographic study of my compound. I am whole-heartedly thankful to all the faculty members and staff at the Department of Chemistry and Biochemistry, the graduate school and the NSF for supporting the first half of this work.

I express my thanks to Kapur Dhami from Prof. Nichol’s lab, for conducting biochemical assays of some of the compounds included in this work.

I would like to thank my previous lab member Jeremy N. Ridenour for helping me in the lab even during the weekend. I also would like to thank previous lab member Christopher Tipton and my current lab mates Rishi Poudel and Saroj Kafle for creating a working culture and maintaining positive vibes.
I would not have been able to accomplish this work without the support and love of my family. I am highly grateful to my father Lekh Nath Gnawali, mother Jiwakala Gnawali, brother Krishna Gnawali and sisters Rama, Mira and Janaki for their love and support throughout this period. I highly appreciate my wife Sabita Gautam for her unconditional love, patience, encouragement and emotional support towards me, my family and our beautiful son Prasun.
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Chapter I

1 Introduction

1.1 Organophosphorus compounds

Phosphorus, first isolated in 1669 in its elemental form, is an essential element and is a key component of the major building blocks of life (Figure 1.1). Inherent properties like polarizability, low to medium electronegativity and low coordination number makes the phosphorus atom highly important in chemical and biological science.\(^1\) Organophosphorus compounds are a significant class of chemicals which play an important role in pharmacology and synthetic organic chemistry.\(^2\)

1.2 Phosphates and Phosphonates

Phosphate group is an essential component of the life process since both DNA and RNA are phosphodiesters.\(^3\) Phosphonates are characterized by the presence of phosphorus-carbon bond (P-C), which is more metabolically stable than the phosphorus-oxygen bond (P-O) present in phosphates. Phosphodiesters are more stable to hydrolysis than the

Figure 1.1 Structure of RNA fragment and ATP
corresponding carboxylate esters, because they are negatively charged at physiological pH (Figure 1.2). The phosphonate analogs of phosphate esters are formed by replacing P-O bond with P-C bond and are the mimics of the phosphate with promising physiological properties.

Figure 1.2 pKa values of the first and second deprotonation of methyl phosphate and methyl phosphonate

Phosphate and phosphonate compounds are found in nature. Known P-C bond bearing compounds found in nature includes aminophosphonates and phosphonolipids. The phosphonolipids are further classified as glycerophosphonolipids and sphingophosphonolipids which have been isolated from numerous organisms including humans, mammals, fish, insects, sea anemones, sponges, numerous species of fresh water, and marine mollusks, seeds of plants, protozoa and bacteria among others. The first naturally occurring phosphonate Cilatine was isolated in 1959 from ciliated protozoa in the rumen of sheep. Nearly 10% of dissolved and particulate phosphorus in the ocean consists of phosphonates. Phosphonates are mostly concentrated as dissolved organic phosphorus (DOP). The composition of the DOP pool is complex and largely unknown,
but phosphonates account for one-third of its high molecular weight fraction, and seems to be an important resource to aquatic lifes.¹ Other low molecular weight phosphonates which are metabolically related to Cilatine are Fosfomycin 1.7 and fosfonochlorin 1.8 (Figure 1.3), which are isolated from a fermentation broth and act as antibiotics and herbicides.⁴,¹

Figure 1.3 Representative structure of some naturally occurring phosphonates

1.3 Phosphorus Heterocycles

Among the various organophosphorus compounds, phosphorus containing heterocycles are of particular interest. Phosphorus heterocycles have application as flame retardants, asymmetric catalysts, agrochemicals, and pharmaceuticals.⁶ Phosphorus heterocycles possess unique biological activities as enzyme inhibitors and anticancer agents. Cyclophosphamide⁷ and certain oxaphosphinanes⁸ are found to have anticancer properties.⁹ The six-membered ring phostone cidovir¹⁰ is a prodrug of an antiviral nucleoside. Related compounds are active against liver diseases such as hepatitis B and C.¹¹ Among the phosphorus heterocycles, six-membered heterocycles are therapeutically important agents in the treatment of cancer and as haptens for the development of catalytic antibodies.¹² Recently, it has been observed that certain phosphorus-containing heterocycles bind to bovine serum albumin¹³, and this could be of great interest in
examining the pharmacological action of phosphorus containing heterocycles. A few examples of biologically important phosphorus containing heterocycles are listed below (Figure 1.4).\textsuperscript{8,14,10,15,16}

**Figure 1.4 Examples of biologically active phosphorus containing heterocycles**

1.4 **Cyclic Phosphonates and Phosphates**

Phosphorus heterocycles based on carbohydrates, where the oxygen atom is replaced by a phosphorus atom, are named as phospha sugars and have C-P-C bond. They are synthetic and have not been found in nature yet.\textsuperscript{4} Similarly, phosphorus heterocycles with C-P-O bonds that are pseudo-sugars and classified as phostones and phosphonosugars are also not observed in nature yet. These carbohydrate-based phosphorus heterocycles have gained interest in the arena of synthetic chemistry because of their interesting biological activity. In short, phostones and phosphonosugars can simply be defined as cyclic phosphonates.
A class of cyclic phosphate that are the natural products are cyclophostin and the cyclipostins.\textsuperscript{17} Cyclophostin 1.15, a bicyclic organophosphate isolated from a fermentation solution of \textit{Streptomyces lavendulae} (strain NK901093), was found to inhibit acetylcholinesterase in the nanomolar range. The cyclipostins 1.16 are structurally related phosphate ester, containing long chain lipophilic alcohols, were found to have good inhibitory activity against Hormone Sensitive Lipase (HSL), a therapeutic target for Diabetes II.\textsuperscript{18} Our laboratory has reported that the analogs of cylophostin and cyclipostin to possess inhibitory activity against various microbial lipases.\textsuperscript{19}

![Figure 1.5 Structure of cyclophostin and the cyclipostins]

Our laboratory synthesized and studied the chiral discrimination of the four stereoisomers of analogs of cyclophostin towards the lipolytic activity of three microbial lipases from \textit{Fusarium solani} cutinase, Rv0183, and LipY from \textit{Mycobacterium tuberculosis} (Table 1.1).
Table 1.1 Inhibition data of monocyclic enolphosphonate against various microbial lipases\textsuperscript{18,21}

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cutinase</th>
<th>Rv0183</th>
<th>LipY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% inhibition ($\chi I = 20$)</td>
<td>$\chi_{150}$</td>
<td>% inhibition ($\chi I = 20$)</td>
</tr>
<tr>
<td>MeO(\text{PO}^{\text{Me}})H(\text{C}<em>{10})(\text{H}</em>{21})(\text{PO}^{\text{Me}})H</td>
<td>57.5 ± 1.45</td>
<td>14.6</td>
<td>92.5 ± 1.33</td>
</tr>
<tr>
<td>1.17(α) racemic \textit{trans} isomers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO(\text{PO}^{\text{Me}})H(\text{C}<em>{10})(\text{H}</em>{21})(\text{PO}^{\text{Me}})H</td>
<td>97.3 ± 2.47</td>
<td>1.98</td>
<td>96.1 ± 0.870</td>
</tr>
<tr>
<td>1.18(β) racemic \textit{cis} isomers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO(\text{PO}^{\text{Me}})H(\text{C}<em>{10})(\text{H}</em>{21})(\text{PO}^{\text{Me}})H</td>
<td>22.5 ± 1.04</td>
<td>97.3</td>
<td>78.7 ± 3.09</td>
</tr>
<tr>
<td>1.19(α)-(S\text{c}, R\text{p})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO(\text{PO}^{\text{Me}})H(\text{C}<em>{10})(\text{H}</em>{21})(\text{PO}^{\text{Me}})H</td>
<td>93.2 ± 1.23</td>
<td>2.52</td>
<td>96.6 ± 1.45</td>
</tr>
<tr>
<td>1.20(β)-(S\text{c}, S\text{p})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO(\text{PO}^{\text{Me}})H(\text{C}<em>{10})(\text{H}</em>{21})(\text{PO}^{\text{Me}})H</td>
<td>86.5 ± 1.39</td>
<td>4.07</td>
<td>93.1 ± 1.63</td>
</tr>
<tr>
<td>1.21(α)-(R\text{c}, S\text{p})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO(\text{PO}^{\text{Me}})H(\text{C}<em>{10})(\text{H}</em>{21})(\text{PO}^{\text{Me}})H</td>
<td>91.8 ± 1.57</td>
<td>3.38</td>
<td>87.7 ± 2.50</td>
</tr>
<tr>
<td>1.22(β) (R\text{c}, R\text{p})</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A new class of cyclophostin and the cyclipostins (CyC) analogs have been found to inhibit the growth of *Mycobacterium tuberculosis* H37Rv (*M. tb*) grown either in a broth medium or inside macrophages with very low toxicity (comparable to most potent drugs used against tuberculosis) (Figure 1.6) towards host macrophages.\textsuperscript{19-20}

CyC17 1.31 was found to show the most potential extracellular antitubercular activity (MIC\(_{50} = 500\) nM) and was selected to identify the potential target through the activity-based protein profiling, and 23 serine or cysteine enzymes involved in *M. tb*. lipid metabolism and/or cell wall biosynthesis were identified as potential targets (Table 1.2).
### Table 1.2 Antibacterial activities of the most active CyC analogs

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Extracellular Growth</th>
<th>Intracellular Macrophage growth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;(μM)</td>
<td>MIC&lt;sub&gt;5&lt;/sub&gt;(μM)</td>
</tr>
<tr>
<td>Isoniazid (INH)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Ethionamide (ETO)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Rifampicin (RIF)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>0.01</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>1.26 CyC&lt;sub&gt;6(β)&lt;/sub&gt;</strong></td>
<td>No effect</td>
<td>12.6</td>
</tr>
<tr>
<td><strong>1.27 CyC&lt;sub&gt;7(α)&lt;/sub&gt;</strong></td>
<td>92.6</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>1.28 CyC&lt;sub&gt;7(β)&lt;/sub&gt;</strong></td>
<td>16.6</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>1.29 CyC&lt;sub&gt;8(α)&lt;/sub&gt;</strong></td>
<td>40.4</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>1.30 CyC&lt;sub&gt;8(β)&lt;/sub&gt;</strong></td>
<td>&gt;100</td>
<td>11.7</td>
</tr>
<tr>
<td><strong>1.31 CyC&lt;sub&gt;17&lt;/sub&gt;</strong></td>
<td>0.50</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>1.32 CyC&lt;sub&gt;18(α)&lt;/sub&gt;</strong></td>
<td>24.4</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>1.33 CyC&lt;sub&gt;18(β)&lt;/sub&gt;</strong></td>
<td>1.7</td>
<td>No effect</td>
</tr>
</tbody>
</table>

To further explore the study to find the best antitubercular agent, several new series of analogs of cyclophostin and cyclipostin have been synthesized with promising inhibitory activity. These analogs are not only active against *Mycobacterium tuberculosis* but also active against *Mycobacterium abscessus, Mycobacterium marinum, Mycobacterium bovis* BCG, and, two Gram negative bacteria. It is also reported that the analogs of cyclophostin and cyclipostin CyC<sub>7β</sub> (1.28), CyC<sub>8β</sub> (1.30), and CyC<sub>17</sub> (1.31) inhibits the
antigen 85C from *Mycobacterium tuberculosis* both in vitro and in vivo, validating Ag85 complex as a pharmacological target of CyC analogs.\(^{24}\)

### 1.5 Synthesis of Phosphorus Heterocycles

There are various methods reported in the literature for the synthesis of phosphorus heterocycles. Our main interests are in the synthesis of cyclic phosphonates and the cyclic phosphates. Most of the methods are based on: a) pyrophosphate, phosphoric acid, phosphonic acid; b) reactions of phosphite P(III) followed by the oxidation to P(V); c) nucleophilicity of the phosphoryl oxygen; and d) ring closing metathesis (Figure 1.7).\(^ {25}\)

![Figure 1.7 Methods of preparation of cyclic phosphates and phosphonates](attachment:image.png)

**Figure 1.7 Methods of preparation of cyclic phosphates and phosphonates**

### 1.6 Phostones and Phosphonosugars

There are several methods employed for the synthesis of phostone, several of which involve the addition of carbohydrate derived aldehydes to dialkyl or trialkyl phosphites. Wang and Whistler synthesized the first family of phosphorus containing cyclic analogs of
sugar, referred to phasasugars in 1968. These researchers described the preparation of α-D-xylopyranose phosphinic analogs. Gunther and coworker synthesized phostones by reacting diisopropylidene mannofuranose with dimethylphosphite using an Abramov, reaction followed by internal transesterification.26 Gallagher and Ranasinghe reported the stereoselective synthesis of 2-deoxy-3-phosphahexoses (Scheme 1.1) by the addition of a phosphinate to (R)-2,3-O-isopropylideneglyceraldehyde.27

![Scheme 1.1 Stereoselective synthesis of Phosphasugars](image)

Carbohydrates having a phosphorus atom in the anomeric position have been synthesized by Wroblewski in 1984.28 Six membered cyclic phosphate and phosphonate heterocycles29 (1.49) were synthesized by Jia Zhou and Rayuchen in 1998. Cis- and trans- 1.49 were obtained by a one-pot procedure using tris(diethylamino)phosphine (1.47) activated by iodine as the phosphorylating and ring-closing reagent (Scheme 1.2).29
Scheme 1.2 Synthesis of six-membered cyclic phosphate-phosphonates based on sulfur and selenium

Phosphonosugar derivatives of 5-membered heterocyclic 1-deoxy pentofuranose and pentofuranose sugars (1.54) were prepared by Yamashita et. al. starting from 2- and 3-phospholenes (Scheme 1.3).\textsuperscript{30}

Scheme 1.3 Synthesis of 1,4-dideoxy-4-[(5)-methoxyphosphinyl]-D-ribofuranose

Hanessian et. al. reported the synthesis of stereoisomeric monosaccharide δ-phostones in 1994.\textsuperscript{31} They utilized an Abramov reaction to prepare the isomeric monosaccharide phostones from appropriate pentose derivatives using HP(O)(OBn)\textsubscript{2} (1.56) in DBU (Scheme 1.4).
Cyclic analogs of D-glucopyranose and D-mannopyranose have been prepared by the acid-catalyzed addition of trimethyl phosphite to the carbonyl of a hydroxyl-protected open-chain D-arabinose derivative. The subsequent removal of a formate ester from the 4-hydroxyl group and base-catalyzed transesterification/cyclization resulted in the formation of D-glucopyranose and D-mannopyranose (Scheme 1.5).

Scheme 1.4 Synthesis of a carbohydrate-based phostone

Scheme 1.5 Synthesis cyclic phosphonate analogs of D-glucopyranose and D-mannopyranose
Harvey et al. reported the synthesis of cyclic phosphonate analogs of ribose and arabinose sugars applying a similar strategy as Darrow et al. using cyclic phosphonate analogs of pentose, namely xylo (1.74, 1.76) and lyxo analogs (1.75 α and β). The relative amounts of four isomers was estimated to be 10:5:2:3 for 1.74 – 1.76 through NMR spectra of crude products (Scheme 1.6).

![Scheme 1.6 Synthesis cyclic phosphonate analogs of ribose and arabinose](image)

Hanessian and Rogel in their continuous attempt to prepare glycomimetics, reported the synthesis of cyclic phosphonate analogs of L-fucose (1.77), N-acetyl-D-glucosamine (1.78), N-acetyl-D-mannosamine (1.79), and N-acetyl neuraminic acid (1.80) (Scheme 1.7) by using an acid catalyzed Abramov reaction with respective starting material followed by base catalyzed cyclization.
Scheme 1.7 Cyclic phosphonate analogs of L-fucose, N-acetyl-D-glucosamine, N-acetyl-D-mannosamine, and N-acetyl neuraminic acid

Hetherington and his group reported the synthesis of phosphorus heterocycles as a part of their study to prepare new transition state analogs for antibody catalysis, by applying a ring closing strategy of dienes (Scheme 1.8).³⁴

Scheme 1.8 Synthesis of phosphorus heterocycles by ring closing metathesis of diene

Bisseret et. al. synthesized arabino configured cyclic phosphonomethyl phosphinates³⁵ by the condensation of triethylesters of \( H \)-phosphinylphosphonate with an arabinal derived hydroxy aldehyde 1.88 (Scheme 1.9).³⁶
Cristau and coworkers reported the first synthesis of 2-phenyl-1,2-oxaphosphinanes 1.96 by the addition of phenylphosphinate to [2,3:5,6]-di-O-isopropylidene-β-D-mannofuranose 1.93 followed by base catalyzed transesterification and deprotection (Scheme 1.10).
Scheme 1.10 Synthesis of P-aryl-phosphinosugars

As part of their continuous effort in developing a transition metal catalyzed approach for the synthesis of phosphorus-containing compounds, Hanson et. al. reported the synthesis of phostone analogs of carbohydrates using ring closing metathesis (Scheme 1.11)\textsuperscript{38}

Scheme 1.11 Synthesis of phostones analogs using RCM
Cyclic allylic phosphonates 1.100 and 1.103 have been synthesized by RCM of mixed allylic phenyl esters of allylphosphonic acid 1.99 and 1.102 (Scheme 1.11). Compounds 1.100 and 1.102 were further functionalized to get polyhydroxylated phostone analogs. 38

Cristeau and coworkers synthesized novel phosphorus heterocycles containing a P–C–O or P–C–N motif in their cyclic framework. They reported the synthesis of 5,6-diphenyl-1,4,2-oxazaphosphinanes (1.106) through the formation of 1.105, which was found to be a mixture of four diastereomers as determined by 31P NMR. The cyclic compound 1.106 was obtained by the base promoted cyclization of 1.105. It was reported that the cyclization resulted in the formation of two diastereomers with 1.106a as the major product. The result of two diastereomers was rationalized due to the rapid epimerization at phosphorus, during base catalyzed cyclization (Scheme 1.12). 39

\[
\begin{array}{cccc}
(\pm)-1.104 & \overset{\text{HPO}_2O}{\text{Ph}} & \overset{\text{HPO}_2OMe}{\text{Ph}} & \overset{\text{THF, 20°C}}{1.105} \\
& & & \overset{0°C - 20°C, 18h}{1.106a, 1.106b}
\end{array}
\]

Scheme 1.12 Synthesis of 5,6-diphenyl-1,4,2-oxazaphosphinanes

The same group reported the synthesis of 2,3-dihydro-1,3-oxaphospholes (1.109) by reaction of α-chloroalkylphosphinic or phosphonic chlorides 1.107 with a malonic diester 1.108 in presence of two equivalents of base (Scheme 1.13). These cyclic compounds
1.106a and 1.109 were further subjected to various reactions either at phosphorus atom or at the enol ether position.\textsuperscript{39}

Zhang and coworkers reported the synthesis of acyloxy substituted six membered cyclic phosphonate using RCM (ring closing metathesis), followed by dihydroxylolation and acylation, in their attempt to synthesize analogs of (Lyso)phosphatidic Acid.\textsuperscript{16} The oleoyloxy-substituted cyclic phosphonate 1.117 was found to be a selective LPA\textsubscript{2} agonist that can distinguish between LPA\textsubscript{1} and LPA\textsubscript{2} (Scheme 1.14).\textsuperscript{16}

Scheme 1.14 Synthesis of cyclic phosphonate analogues of (Lyso)phosphatidic acid

Shengming et. al. reported the Pd (II) catalyzed coupling-cyclization of 1,2 alkenyl phosphonic acid monoesters with allylic halides to form 1-ethoxy 1,3-dihydro[2,1]benzoxaphosphole 1-oxide (Scheme 1.15).\textsuperscript{40}
Scheme 1.15 Pd (II)-catalyzed coupling–cyclization of 1,2-allenyl phosphonic acid monoethyl esters and with allyl bromide

Pierre et. al. in their effort to the synthesize phosphorus-containing heterocycles as potential fungicides, utilized the RCM (ring closing metathesis) for the synthesis of unsaturated phosphinates and phosphonates. The reactions proceeded by the synthesis of unsymmetrical allyl vinylphosphonates, unsymmetrical allyl allylphosphonates and the unsymmetrical allyl α-hydroxy allylphosphinates as the precursor for the RCM (Scheme 1.16). The cyclized compounds 1.124 is formed from 1.123 and 1.126 from 1.125 respectively.

Scheme 1.16 RCM of unsymmetrical and functional precursors
Pungente et. al. reported the synthesis of the cyclic phosphonate 1.131a and 1.131b (Scheme 1.16) starting from 1,3-butanediol. The stereochemistry of the two diastereomers was assigned on the basis of $^{31}\text{P}$ NMR signals, together with $^1\text{H}$ NMR nuclear Overhauser effects (NOE) difference experiments.\textsuperscript{42}

![Chemical diagrams](image)

**Scheme 1.17 Synthesis of 6-membered ring phosphonates**

Clarion et. al. reported the design and the synthesis of phostines with [1,2]oxaphosphinane core.\textsuperscript{8} Phostines are a new class of compound which are described as the C-glycoside mimetics. A total of twenty-six compounds were synthesized and tested for their antiproliferative activity against different cancer cell lines. The synthesis was carried out by the reaction of tris-(O-benzyl protected)-D-arabinofuranose 1.132 with various ethyl arylphosphinates 1.133 in the presence of catalytic amount of potassium t-butoxide (Scheme 1.18). The same group latter 2014 reported the design and synthesis of eighteen new phostines as the C- glycoside mimetics (D-glycero-D-talo- and D-glycero-D galacto pyranose analogs) (Scheme 1.19) and tested their anticancer properties, of which compound 1.143 was found to have high antitumor activity against glioblastoma.\textsuperscript{14,43} Latter in 2017 compound 1.134a.1 was found to targets MGAT5 and inhibits Glioblastoma-initiating cell invasiveness and proliferation.\textsuperscript{44}
Scheme 1.18 Synthetic route to hydroxy-oxaphosphinane

Scheme 1.19 Synthetic routes of the D-glycero-D-talo- or D-glycero-D-galactopyranose analogs

Crich and coworkers reported the stereoselective syntheses of P-chiral ammonium phosphonite-borane complexes in the *gluco-* and *manno-* series.\textsuperscript{45} Initial attempts for the synthesis of phostones followed the strategy developed by Drueckhammer\textsuperscript{15} and further modified to increase the diastereoselectivity using a chiral agent catalyst for asymmetric phosphonylation step.\textsuperscript{46-47} Furthermore, these ammonium phosphonite-borane complexes were coupled with alcohols to form β-gluco and α- and β-manno-configured phostones of primary alcohols, which were deprotected to get α- or β-(1→6)-linked glycomimetics. Later in 2013, the same group reported the improved synthesis of P-chiral *gluco-* and
manno-phosphonite-borane complexes by the addition of diethyl phosphonate borane to a glucal-derived aldehyde, followed by a cyclization, coupled with an ethyl/methyl exchange. This approach was further used in the formation of phostone dimers (Scheme 1.20)\textsuperscript{48}

Scheme 1.20 Synthesis of phostone dimers

Unnatural phosphonosugar analogs of deoxy-ribose and deoxy-xylose were synthesized in racemic form starting from 2,3 butane diol 1.149. The key steps involved a Michaelis–Arbuzov reaction, epoxidation, epoxide ring opening in aqueous acidic medium and final cyclization assisted by PTSA to give 5-membered ring (Scheme 1.21).\textsuperscript{49}

Scheme 1.21 Synthesis of the unnatural phosphasugar analogs
Medium fused ring phosphorus heterocycles were prepared starting from phenol derivatives by Gnaï et al. The synthetic method utilizes a Claisen rearrangement and ring closing metathesis. This method was found to be effective to get benzo-fused phosphorus heterocycles (Scheme 1.22).

\[
\begin{align*}
&\text{R}^4 \text{OH} \quad \text{Cl}^- \quad \text{EtO}_2\text{P} \quad \text{EtO}_2\text{P} \quad \text{Br} \quad \text{O}^\odot \text{P} \quad \text{EtO}^\odot \text{P} \quad \text{OEt} \\
&\text{Dry Et}_2\text{O}, \text{Et}_3\text{N} \quad 0^\circ \text{C}, 9\text{h} \quad \text{DCM, reflux} \\
&\text{1.156} \quad \text{1.157a} \quad \text{1.157b} \quad \text{1.157c} \quad \text{1.157d} \\
&\text{R}^4 = \text{R}^3 = \text{R}^4 = \text{H}, \text{ R}^2 \text{Br} \quad \text{R}^4 = \text{R}^3 = \text{R}^4 = \text{H}, \text{ R}^2 \text{Me} \quad \text{R}^4 = \text{R}^3 = \text{R}^4 = \text{H}, \text{ R}^2 \text{OME} \quad \text{R}^4 = \text{R}^3 = \text{R}^4 = \text{H}, \text{ R}^2 = \text{t-Bu}
\end{align*}
\]

**Scheme 1.22 Synthesis of benzo-fused phosphorus heterocycles**

Pungente and coworker reported the synthesis of 14-membered ring phosphonate using an intramolecular Mitsunobu reaction (Scheme 1.23).

\[
\begin{align*}
&\text{Ph}_3\text{P}, \text{DEAD} \quad \text{benzene, rt, 2h} \\
&\text{1.159} \quad \text{1.160a} \quad \text{1.160b}
\end{align*}
\]

**Scheme 1.23 Synthesis of phosphorus-containing macrocycles**

Suárez and his coworkers synthesized 2-methylene-1-phospha-pentofuranoses 1.162 and 1.163 from the vinylphosphonates 1.161 (Scheme 1.24).
These cyclic phosphonates were further used for the synthesis of β-aminophosphonates 1.164 and 1.167 by Michael addition of the amino acid Gly-OMe·HCl to 1.162 and 1.163. 1,4-Conjugate addition on the β-side of the molecule gave 1.167, while a mixture of isomers was obtained from 1.162. As a result of conjugate elimination of the vicinal benzyl ether, side products (1.166 and 1.168) were obtained in both the cases (Scheme 1.24).52

Pirat and coworkers reported the synthesis of α-halogenated oxaphosphinane in their attempt to investigate anticancer agents (Scheme 1.25).53
Recently, Suárez and co-workers successfully applied the anomeric ARF (anomeric alkoxy radical β-fragmentation) reaction for the synthesis of 1-phosphahexopyranose, 1-phosphahexofuranose, and 5-phosphapentopyranose sugars. Two approaches are described for the synthesis of phosphorus heterocycles. The first pathway (a) of the synthesis starts with a 2-deoxy-sugar and the phosphorus is introduced in the final steps by the Michaelis–Arbuzov reaction of the iodide generated by the ARF reaction. The phosphinates or phosphonates were obtained after hydrolysis, which undergoes cyclization to 2-oxo-1, 2-oxaphosphinanes. This pathway results in 1-phosphasugars maintaining the ring size and the stereochemistry of the original 2-deoxy-sugar (Scheme 1.27). The second pathway (b) proceeds in such a way that phosphorus is introduced at earlier point of the synthesis and before the ARF reaction. Further hydrolysis, ARF reaction and final cyclization by a tandem ARF-nucleophilic addition on the intermediate oxocarbenium ion occur. The ring expansion occurs in relation to the initial sugar and result in the formation of 4-deoxy-5-phosphapyranose sugar (Scheme 1.26). This pathway results in the formation of 5-phosphasugars (Scheme 1.28).
Scheme 1.26 An ARF approach for the Synthesis of phosphasugars

Scheme 1.27 Synthesis of 1-phosphasugars based on pathway (a) (Scheme 1.26)
The pathway (b) results in the formation of 5-phosphasugars, in which the phosphorus is introduce before the ARF reaction.

Scheme 1.28 Synthesis of 5-phosphasugars based on pathway (a) (Scheme 1.25)

1.7 Summary

Phosphorus heterocycles, either cyclic phosphonates or the phosphates, are an important class of compounds. The analogs of cyclophostin and cyclipostin are promising lipase inhibitors from *Mycobacterium* species. It is necessary to identify the target enzyme and mode of action of the various analogs of cyclophostin and cyclipostin in order to develop lead compounds. For this purpose, various labeled analogs of cyclophostin and cyclipostin will be synthesized in this work for chemical based proteomic analysis.

The other class of cyclic phosphonates i.e. phostones and phosphonosugars also show important biological activity and hence there are demands for new and more sophisticated methods for their synthesis. Based on the literature review of the synthesis of phostone and
phosphonosugars, it is observed that most of the methods rely on carbohydrate based starting material. In this dissertation, a novel de-novo method will be developed based on vinyl epoxy phosphonate chemistry. The synthesis and reaction of vinyl epoxy phosphonate will be briefly discussed in chapter II.
1.8 References


38. Stoianova, D. S.; Hanson, P. R., A ring-closing metathesis strategy to phosphonosugars. *Organic letters* **2001**, *3* (21), 3285-3288.


Chapter II

2 Synthesis of Phostones and Phosphonosugar Analogs

2.1 Introduction

Phostones are heterophosphacyclanes\textsuperscript{1} with a pentavalent phosphorus atom bearing P(O)-C bond, and phostones (phosphonosugars) are of interest as glycomimetics. The literature review in chapter I shows that there are various methods of synthesizing phostones and phosphonosugars. Carbohydrate-based phostones are synthesized by the addition of dialkyl or trialkyl phosphites to the carbohydrate derived aldehydes.\textsuperscript{2-11} More recently ring closing metathesis (RCM) was used as a synthetic method for the synthesis of phostones.\textsuperscript{12-13} In this chapter, a novel method for the synthesis of phostones will be described. The synthetic methodology developed utilizes the γ,δ-vinyl epoxy phosphonate (2.2) as the key intermediate. The concept of this methodology is based on the related observation on the chemistry of γ, δ-epoxy unsaturated carboxylate ester (2.1).\textsuperscript{14-17} The epoxide opening of γ,δ-vinyl epoxy phosphonate with various nucleophiles results in the formation of δ-hydroxy vinyl phosphonates. Further reduction and cyclization ultimately gives phostones. The cyclization to form the phostones displays high diastereoselectivity towards one of the two possible diastereomers. This type of diastereoselectivity has been observed previously.\textsuperscript{18}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure2.1.png}
\caption{γ,δ-vinyl epoxy phosphonate and γ,δ-epoxy unsaturated carboxylate ester}
\end{figure}
2.2 Retrosynthetic analysis of phostones

Based on the structure of the phostone (2.3) the following retrosynthetic analysis was envisioned (Figure 2.2). The retrosynthetic strategy reveals the P-O bond cleavage to give the δ-hydroxy phosphonate (2.4). It is found that the similar phosphonates undergo base catalyzed cyclization to give phostones. The alkene functionalization by the addition of $R^3$ and $R^4$, can be carried out in various ways. Among the various methods, hydrogenation was employed in the first attempt.

![Retrosynthetic analysis of for the synthesis of phostones](image)

The other possible functionalization includes asymmetric dihydroxylation, aminohydroxylation, α-hydroboration, and β-hydroboration. The resulting hydroxy phosphonates are, in turn, obtained by the regioselective and stereospecific ring openings of γ,δ-epoxy vinyl phosphonates (2.6).

A review of the literature provides the basis for the opening of the epoxy ring by a nucleophile in the presence of a palladium catalyst. Spilling and coworkers have investigated the chemistry of vinyl phosphonate under palladium catalyzed conditions, where α- and γ-phosphono allylic carbonates (2.7) and (2.8) reacts with methyl acetoacetate.
(2.9) to give the same product (2.14) through a Π-allyl intermediate (2.13) (Scheme 2.1).\cite{20,21,29-30,33-36}

![Chemical Reaction Diagram](image)

**Scheme 2.1 Palladium-catalyzed reactions of α- and γ-phosphono allylic carbonates**

2.3 Synthesis of vinyl epoxide

Vinyl epoxides are characterized by the presence of strained oxirane ring in proximity to a double bond. The combination of these two groups make vinyl epoxides unique in terms of utility and chemistry, and hence they are good building blocks for organic synthesis.\cite{32,37}

Based on a review of the literature, the different strategies adopted for the synthesis of vinyl epoxides is discussed in the following section.

2.3.1 From dienes

2.3.1.1 Epoxidation of more electron-deficient double bonds

A chemoselective method, where the nucleophilic monoepoxidation occurs with a peroxide, is known as Weitz-Zcheffer epoxidation.\cite{38} Chemoselective epoxidation of α,β,γ, δ-biunsaturated trichloro ketone (2.15) has been achieved by TBHP (2.17) in the presence of prolinol (2.16) as catalyst and proceeds via complex (2.18) (Scheme 2.2).\cite{39} A similar monoepoxidation has been achieved for the nitrile derivative (2.20) using TBHP and catalyst (2.16) (Scheme 2.2), albeit with reduced selectivity.\cite{40}
2.3.1.2 Epoxidation of a more electron rich carbon-carbon double bond

Electrophilic monoepoxidation can be carried out using mCPBA (2.23). The more electron rich alkene is oxidized regardless of steric hindrance (Scheme 2.3).[^41]

Scheme 2.3 Epoxidation of electron rich double bond

Asymmetric Shi epoxidations have been carried with both Z- and E- alkenes (2.25). Z-alkenes were found to undergo epoxidation more rapidly. The epoxidation of a Z-alkene is selective irrespective of a similar electronic environment (Scheme 2.4).[^42]
Scheme 2.4 Selective epoxidation of a Z-alkene in the presence of an E-alkene

Asymmetric Shi epoxidation using catalyst 2.26 has been applied in the total synthesis of (-) balanol\textsuperscript{16} and the members of the labdane family\textsuperscript{43}, where the more electron rich double bond is converted to an epoxide (Scheme 2.5).

Scheme 2.5 Shi epoxidation of more electron rich alkenes

The chemoselective epoxidation of cross conjugated sulfonyl dienes was reported using either mCPBA or alkaline H\textsubscript{2}O\textsubscript{2}. Epoxidation at the more electron rich double bond was brought about by mCPBA and epoxidation at the electron poor double bond was brought about by alkaline hydrogen peroxide (Scheme 2.6).\textsuperscript{44}
Jacobsen’s catalyst (2.36) was found effective in the asymmetric epoxidation of more electron rich double bonds of cyclic sulfonyl diene (Scheme 2.7). Six membered (2.35) and seven membered cyclic compound (2.38) were effectively oxidized with the use of catalyst (2.36), while the reaction was problematic with an acyclic unsaturated sulfone.\(^{45}\)

The same catalyst (2.36) was found to be highly effective in multigram scale.\(^ {46}\)

Silica-bound manganese (II) bis-phenanthroline complex (2.41) has been used by Terry and coworker for the oxidation of alkenes and dienes. The oxidation occurred in highly electron rich double bonds to give racemic products in quantitative yield (Scheme 2.8).\(^ {47}\)
Epoxidation of dienes by peracids and metal complexes can be directed by the functional groups present in the molecule.\textsuperscript{32} Allylic alcohol (2.44)\textsuperscript{48} was oxidized by mCPBA with high diastereoselective ratio of 20:1, and the allylic alcohol (2.46)\textsuperscript{49} was oxidized by Vo(acac)\textsubscript{2} (2.47)/TBHP, albeit with low diastereoselectivity (Scheme 2.9).

Zhang and coworkers reported the synthesis of diastereomeric vinyl epoxides (2.51) and (2.53) starting from enone (2.49).\textsuperscript{50} The diastereoselective reduction of the enone was carried out to form the β-alcohol by the attack from the less hindered side and the subsequent directed epoxidation resulted in the formation of epoxide (2.51). The

Scheme 2.8 Epoxidation of dienes by peracids in presence of silica-bound manganese (II) bis-phen complex

2.3.1.3 Directed monoepoxidation of dienes

Scheme 2.9 Directed epoxidation
nucleophilic epoxidation was carried out on the enone, and then the ketone was reduced to give epoxy alcohol (2.53) by the attack from the less hindered face (Scheme 2.10).\textsuperscript{50}

Scheme 2.10 Stereoselective epoxidation of an enone

Sharpless asymmetric epoxidation\textsuperscript{51} is also an example of directed epoxidation of allylic alcohols. Vinyl epoxide intermediates 2.57 and 2.59 were prepared by Sharpless asymmetric epoxidation during the synthesis of goniodomin A.\textsuperscript{52,53} Utilizing the same method, epoxide 2.62 was prepared by Takamura et. al. for the synthesis of gummiferol (Scheme 2.11).\textsuperscript{54}

Scheme 2.11 Sharpless epoxidation for the synthesis of allylic epoxide
2.3.1.4 Epoxide from enediol

Epoxides have been synthesized by selective activation of diols. Naturally occurring polyols can be used as starting material for the synthesis of vinyl epoxide.\textsuperscript{32} The development of desymmetrization strategies has allowed to use the substrate other than from the chiral pool. Kamimura and Nakano reported the synthesis of vinyl epoxide (2.65) from strained ring in the formal synthesis of Oseltamivir (Tamiflu) (2.66). Basic hydrolysis and transesterification of compound (2.63) resulted in the formation of endoepoxide (2.64) which on treatment with LDA and HMPA resulted the formation of vinyl epoxide (2.65) (Scheme 2.12).

![Scheme 2.12 Epoxide formation from enediol](image)

2.3.2 From epoxy aldehydes/ketone

Epoxy aldehydes or ketones can be transformed into vinyl epoxides through olefination reactions. Allylic alcohols are initially converted into epoxides, which are then converted to an aldehyde using different oxidizing methods like Swern oxidation, Parikh-Doering...
Oxidation, IBX oxidation, DMP oxidation, TPAP oxidation, or the TEMPO oxidation in which the epoxy ring remains intact.\textsuperscript{32}

2.3.2.1 Olefination by Wittig-type reaction

Wittig reaction and Horner-Wardsworth Emmons (HWE) olefination reactions have been applied in the synthesis of vinyl epoxides. Chandrasekhar and coworkers\textsuperscript{56}, Fukui and coworkers\textsuperscript{57} and Yokoyama and coworkers\textsuperscript{58} have all used this strategy successfully in the synthesis of vinyl epoxides (Scheme 2.13).

\begin{center}
\begin{tikzpicture}
\node[draw,shape=rectangle] (1) at (0,0) {1. IBX (2.68), EtOAc \hspace{1cm} 2. \text{Ph}_3\text{P}=\text{CHCOOEt (2.69)} \hspace{0.5cm} \text{DCM}};
\node[draw,shape=rectangle] (2) at (3,0) {2.70};
\node[draw,shape=rectangle] (3) at (0,-2) {1. \text{SO}_3\text{Py, Et}_3\text{N} \hspace{1cm} \text{DMSO, DCM} \hspace{1cm} \text{NaHMDS} \hspace{1cm} \text{Ph}_3\text{PCH}_3\text{Br (2.72)}};
\node[draw,shape=rectangle] (4) at (3,-2) {2.73};
\node[draw,shape=rectangle] (5) at (0,-4) {1. (\text{COCl})_2, \text{Et}_3\text{N} \hspace{1cm} \text{DCM, DMSO} \hspace{1cm} \text{NaH} \hspace{1cm} (\text{EtO})_2\text{P(O)}\text{CH}_2\text{COOEt (2.75)}};
\node[draw,shape=rectangle] (6) at (3,-4) {2.76};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.13 Synthesis of vinyl epoxide using HWE method}

2.3.2.2 Olefination by Aldol-type condensation

Jung and coworkers also used this strategy successfully in the synthesis of vinyl epoxide 2.79 or 2.83 (Scheme 2.14).\textsuperscript{59-60-62}
2.3.3 Synthesis of vinyl epoxides through an aldol condensation reaction

2.3.3.1 Corey-Chaykovski epoxidation

The Corey-Chaykovski epoxidation involves the reaction of a carbonyl group with a sulfanylde as the reactive intermediate. Piccini et al. developed the sulfonium salt (2.87) by the reaction of catalytic amount of tetrahydrothiophene (2.86) with alkyl iodide or methyl trifluoromethanesulfonate and further reacted with carbonyl compound to give epoxide. The same group reported the asymmetric synthesis of vinyl epoxide (R)-2.89 by the use of chiral sulfonium salt (2.90) in stoichiometric amount (Scheme 2.15).
2.3.3.2 Using diazomethane

Ferreira and coworkers reported the synthesis of vinyl epoxide by the reaction of enone with diazomethane. The product was reported along with the formation of a side product resulting from cyclopropanation (Scheme 2.16).\textsuperscript{66}

2.3.3.3 Darzen-type reaction

Vinyl epoxide are also synthesized by the reaction of enone/enals via a Darzen type of reaction.\textsuperscript{32} Krafts and co-workers prepared vinyl epoxide from $\alpha,\beta$- unsaturated aldehydes or ketones by one pot Darzen’s condensation of a $\alpha$-bromoester enolate.\textsuperscript{67} The selectivity for cis or trans was poor with $\alpha$-bromo esters while the trans- selectivity was increased with $t$-butyl ketone as the substrate (Scheme 2.17).
2.3.4 From aldehydes

2.3.4.1 Corey-Chaykovsky epoxidation

Vinyl epoxides can be prepared by the diastereoselective reaction of stabilized sulfur ylides with aldehydes.\textsuperscript{32} Metzner et al. reported the use of racemic sulfonium ylide for the epoxidation aldehydes from an allylic bromide derivative with good to excellent diastereoselectivity (dr: = 5-95%) in the presence of catalytic amount of thiolane (2.86).\textsuperscript{68}

The reaction proceeds by the \textit{in-situ} generation of a sulfur ylide. The same group used chiral thiolane (2.100) for the asymmetric synthesis of epoxide (2.102) and reported 64\% ee of the \textit{trans} epoxide (Scheme 2.18).
Scheme 2.18 Epoxidation of carbonyl derivatives by in-situ generated ylide

2.3.4.2 Synthesis via halohydrin intermediate

Kang and Britton reacted chiral aldehyde (2.102) with vinyl lithium reagents (2.103) to get halohydrin (2.104), which was then treated with base to get vinyl epoxide (2.105) (Scheme 2.19).^69

Scheme 2.19 Synthesis of vinyl epoxide via halohydrin formation

2.4 Reactions of Vinyl Epoxides

Vinyl epoxides, where the epoxy ring is flanked by a double bond are a peculiar class of substrate in organic synthesis. These vinyl epoxides combine the reactivity of an epoxy ring in combination with a double bond. Vinyl epoxides undergoes various reactions which are described in the literature, but here the discussion is limited only to the nucleophilic ring openings of the epoxide mainly focused on nitrogen and oxygen nucleophiles. The
common reactions are nucleophilic opening of the epoxy ring, eliminative ring opening reactions, rearrangements, radical reactions and cycloaddition reactions.\textsuperscript{32, 37}

2.4.1 Nucleophilic openings

Because of the strained oxirane ring, the nucleophilic ring openings of vinyl epoxides is the most common reaction. The nucleophilic attack is possible at all the four carbons (2.106), (Figure 2.3) and which are summarized below.\textsuperscript{32, 37}

a. Nucleophilic attack through path \textit{a}, S\textsubscript{N}2’ lead to 1,4-addition (conjugated addition) and usually occurs with soft nucleophiles.

b. Nucleophilic attack through path \textit{b}, proceeds through a S\textsubscript{N}2 process resulting in 1,2-addition product.

c. Nucleophilic attack/addition occurring through path \textit{c} proceeds through a S\textsubscript{N}2’ mechanism, but this type of addition is usually not observed.

d. Nucleophilic addition via pathway \textit{d} has been observed only for the substrate where R (2.106) is an electron withdrawing group that competes with the reactivity of the epoxide.
2.4.1.1 Nitrogen nucleophiles

Amines and azides are the common nitrogen nucleophiles. The epoxide ring opening may be palladium catalyzed to give 1,4-addition or 1,2- addition product or may be assisted by a Lewis acid. The opening of an unsubstituted epoxide by allyl amine has been achieved wherein the amine prefers to attack at the less hindered side. Evans and coworkers have further utilized this strategy in their synthesis of an aza sugar (Scheme 2.20).

In terminally substituted epoxides in the absence of any other electronic factors, the nucleophilic attack proceeds through an $S_N 2$ pathway to give bisallyl amine as major the product (Scheme 2.21).
Scheme 2.20 Opening of epoxide rings by amines

Scheme 2.21 Opening of epoxide rings assisted by MW or Lewis acid

The ring opening of vinyl epoxy alcohol ((±)-2.117) activated by LiClO₄ resulted in a mixture of regioisomer in moderate yield, while the regioselectivity was enhanced using titanium (IV) isopropoxide, as the activating agent. The chelation of titanium both with the oxygen results in amine addition at the allylic position (Scheme 2.22).
Scheme 2.22 Epoxide ring opening assisted by Ti(Oi-Pr)$_4$

Saotome et al. reported the reaction of α,β-unsaturated γ,δ-epoxy ester (2.121) with amines. The reaction with only amine resulted in the formation of two products (2.123) and (2.124) in the ratio of 68% to 22%. The reaction in presence of methanol as solvent changed the ratio of the product to 30% to 66%. The presence of methanol was found to accelerate the retro-Michael reaction. Ring opening was thermodynamically controlled and irreversible giving allyl amine, while the conjugate addition is kinetically controlled (Scheme 2.23).

Depending upon the electronic factors, Lewis acid promoted ring opening proceeds through an S$_{N}$$^{2}$ pathway. It was observed that, the presence of electron withdrawing groups at R$_2$ (2.126), the nucleophilic attack at the allylic position was prominent (Scheme 2.24).
Scheme 2.23 Reaction of a α,β-unsaturated γ,δ-epoxy ester with an amine

\[
\begin{align*}
\text{R}^1 & = \text{R}^2 = \text{nC}_3\text{H}_7 & 2.127:2.128 = 55:45 \\
\text{R}^1 & = \text{alkyl} & \text{R}^2 = \text{COOEt, CN or Ph} & 2.127:2.128 = 95:5 \\
\text{R}^1 & = \text{Ph} & \text{R}^2 = \text{COOEt} & 2.127:2.128 = 60:40
\end{align*}
\]

Scheme 2.24 Azidolysis of a vinyl epoxide

In the azidolysis of the D-glucal derived vinyl oxirane (2.129) by tetramethylguanidinium azide (TMGA, 2.130), 1,2- addition product was obtained with anti-selectivity. The reaction of (2.129) with TMSN\(_3\) (2.131) resulted in the formation of a mixture of products. The \textit{syn}-1,4-adduct (2.135) was also found to undergo [3,3]-sigmatropic rearrangement to form \textit{syn}-1,2-adduct (2.137) (Scheme 2.25).
In the Pd-catalyzed Tsuji-Trost reaction of vinyl epoxide 2.138, the nucleophilic attack occurs at the allylic position. The reaction proceeds through the formation of Π-allyl palladium (II) complex 2.141. This complex was isolated by column chromatography and characterized by $^1$H NMR (Scheme 2.26). 80

Scheme 2.26 Formation of a Π-allyl palladium (II) complex

Szabó and coworkers also showed the reaction of epoxide (2.142) under palladium catalyzed condition proceeds through the formation of Π-allyl palladium (II) complex. The substitution product is obtained by further reaction of the Π-allyl palladium (II) complex.
with the nucleophile, with reaction occurring from the less hindered side in the absence of any directing groups (Scheme 2.27).

Scheme 2.27 Palladium catalyzed reaction of vinyl epoxides

Backvall and coworkers in their synthesis of (+)-pseudoconhydrine (2.148) reported that the external nucleophile attacks at the least hindered side in the absence of directing effects. A similar result was reported in the amination of furanose derivative (2.150) by Gomez et. al. (Scheme 2.28).

Scheme 2.28 Pd-catalyzed amination of epoxides giving 1,4-addition products
The nucleophilic ring opening of bromo vinyl epoxide (2.153) was found to proceed through 1,2-addition even in the presence of a palladium catalyst. The palladium did however, catalyze a Suzuki coupling in the same pot. The presence of bromine deactivated the double bond and prevented the formation of a Π-allyl complex, thus uncatalyzed epoxy ring opening was possible (Scheme 2.29).

Scheme 2.29 Pd-catalyzed amination of an epoxide giving 1,2-addition product
Waegell et. al. reported that the azidolysis reaction also proceeded via a Π-allyl palladium complex to give 1,4 selectivity, which is different from the nucleophilic reactions in absence of Pd-catalyst (Scheme 2.30).

Scheme 2.30 Pd catalyzed azidolysis to give a 1,4 product
Apparent 1,2-addition in the palladium catalyzed addition of hydrazine was reported. The allylic epoxide (Z-2.158) underwent reaction to form the more stable Π-allylpalladium(II)
complex (2.161) from less stable complex (2.160) prior to the 1,4 addition of N-isopropylidene-N'-2-nitrobenzenesulfonylhydrazine (2.159 IPNBSH). An allylic diazene (2.162) was obtained by the decomposition of sulfonyl hydrazine, and the final reduction product was obtained by sigmatropic rearrangement and loss of N₂. The geometry of the double bond was reversed, while in the reaction of (E-2.158) (Scheme 2.31) the geometry of double bond was retained.

![Scheme 2.31 Opening of an epoxide ring through 1,2-addition](image)

Regioselective reaction was observed by Miyashita et. al. that occurred through an S_N2 mechanism in the case of palladium catalyzed reaction of α,β-unsaturated γ,δ-epoxy ester (2.165) with TMSN₃ (2.131) to give azide alcohol with double inversion of configuration. Both cis- and trans- epoxide were found to go the ring opening in similar fashion (Scheme 2.32).
Scheme 2.32 Palladium catalyzed epoxide opening to give 1,2 addition products

This reaction was utilized by Chandrasekhar in the synthesis of hyacinthacine A₁ (2.170) and Muthyala in the synthesis of (-) balanol (2.173) (Scheme 2.33).¹⁶

Scheme 2.33 Palladium catalyzed epoxide opening and its synthetic application

The intramolecular ring opening of epoxides by nitrogen nucleophiles have also been reported under several other conditions³² but is not discussed here.

2.4.1.2 Oxygen nucleophiles

Beside nitrogen nucleophiles, oxygen nucleophiles are one of the most widely studied nucleophiles. The cleavage of the epoxide ring is facilitated by water or other Lewis acids
or bases. Protonation of epoxides in acidic conditions promotes the alcoholysis of vinyl epoxides, usually with regio- and stereoselective 1,2 addition with inversion of configuration (Scheme 2.34).  

![Scheme 2.34 Opening of epoxide rings assisted by acid catalysts](image1)

Base mediated hydrolysis has also been reported by Lopez and coworkers which proceeds through an $S_N2$ pathway to give diols with inversion of configuration (Scheme 2.35).  

![Scheme 2.35 Base mediated opening of an epoxide](image2)

Crich and coworkers reported the regioselective ring opening of vinyl epoxide 2.182 with oxime 2.183 in their attempt to prepare of $\beta$-hydroxy $O$-alkyl hydroxylamine. The attack
of the nucleophile occur from the less hindered side via S_N2 reaction in the presence of base (Scheme 2.36).^{89}

\[ 
\begin{array}{cccc}
\text{2.182} & \text{N-OH} & \text{2.183} & \text{2.184} \\
\text{Ph} & \text{1.5 eq} & \text{KOH, DMF} & \\
\end{array}
\]

**Scheme 2.36 Epoxide opening from less hindered side**

Hsung and coworkers observed S_N1 type process in the opening of vinyl epoxide during the total synthesis of (±) Phomactin A.^{90} The compound (2.185) undergoes either an S_N1 type of reaction via the formation of cationic intermediate with the nucleophilic attack from the less hindered face or hydrolyzed with anchimeric assistance from the pyran oxygen (Scheme 2.37).^{90}

\[ 
\begin{array}{cccc}
\text{2.185} & \text{1.10 mol\% Mg(OTf)_2} & \text{EtoAc/MeCN/H_2O(1:1:1)} & \text{2.188} \\
\text{2. TESOTf, 2,6-Lutidine} & \\
\end{array}
\]

**Scheme 2.37 Ring opening of an epoxide ring in a strained system**
The use of Bronsted acids, Lewis acids or transition metal catalysts activate the nucleophilic additions of alcohols to vinyl epoxides. The reaction of (2.189) with (2.190) in the presence of Lewis acid resulted (2.191) in a 32% yield on using BF₃.OEt₂ and 67% yield with Cu(OTf)₂ (Scheme 2.38).⁹¹

![Scheme 2.38](image)

**Scheme 2.38 Lewis acid assisted opening of an epoxide**

Pineshi et. al. observed the metal free stereoselective ring opening of a cyclic vinyl epoxide using (ArO)₃B. Aryl borates acts as activating nucleophiles to give syn-1,2 addition products (Scheme 2.39).⁹²

![Scheme 2.39](image)

**Scheme 2.39 Regioselective opening of a cyclic vinyl epoxide**

Miyashita et. al. reported the epoxide ring opening by alcohol nucleophiles in the presence of Pd(0) catalyst and B(OPh)₃ or B₂O₃/Pinnacol to give syn-1,2- addition product with high diastereoselectivity resulting from double inversion (Scheme 2.40).¹⁴ The structure, electronic and steric demands of the vinyl epoxide could alter the typical regioselectivity to yield 1,4-addition products as the major products.
The Pd-catalyzed opening of an epoxide ring was applied in the synthesis of Fukuyama’s total synthesis of (±) morphine (2.203) (Scheme 2.41).\textsuperscript{93}

Trost et. al. has reported the Pd-Asymmetric Allylic Alkylation (PD-AAA) for the opening of an epoxide ring with an alcohol nucleophile.\textsuperscript{94} Furthermore, they were able to use enols
as the nucleophile in their total synthesis of (-) Terpestacin, where high enantioselectivity was observed (Scheme 2.42)\textsuperscript{95-96}

\begin{equation}
\text{Scheme 2.42 Palladium catalyzed asymmetric opening of epoxides}
\end{equation}

As mentioned earlier, vinyl epoxide undergoes 1,4-addition when favored by structure, electronic and or steric factors. Hanna et. al. reported Yb(OTf)\textsubscript{3}-catalyzed alcoholysis of some bicyclic vinyl epoxides under S\textsubscript{N}2' process. In all cases, a mixture of anti and syn diastereomers was obtained. Fused systems because of steric hindrance are supposed to give S\textsubscript{N}2' product more often (Scheme 2.43).\textsuperscript{97}

\begin{equation}
\text{Scheme 2.43 Opening of epoxides through S\textsubscript{N}2' addition}
\end{equation}
Vinyl epoxides derived from the carba-analogs of D-glucose (2.215) were found to undergo an $S_N2$ process in presence of an acid catalyst (Scheme 2.44).\textsuperscript{98}

![Scheme 2.44 Opening of epoxides through $S_N2'$ or $S_N2$ addition](image)

The reaction for the addition of alcohols to D-glucal derivative of $\beta$- and $\alpha$-vinyl oxirane proceeds to give syn 1,4 addition products. The difference in the regioselectivity between compound 2.215 and 2.218 and 2.221 is attributed to the presence of the pyran oxygen (Scheme 2.44).\textsuperscript{98}

Many examples of intramolecular oxygen nucleophiles leading to cyclization are presented in the literature. Nicolau et. al. investigated the stereo- and regioselective opening of hydroxy epoxides under acid catalysis resulting in the formation of tetrahydropyrans and tetrahydrofurans.\textsuperscript{99} Cyclization occurs either through exocyclic vinyl groups via 6-endo-tet
or 7-endo-tet giving the desired product, but these cyclization modes are disfavored by Baldwins ring closure rule. Endocyclization is more favored than the 5-exo-tet cyclization, because the reaction proceeds through an $S_N1$-like mechanism via an electrophilic allyl cation intermediate in the presence of pyridinium p-toluenesulfonate (PPTS) or camphorsulfonic acid (CSA) (Scheme 2.45).32

![Scheme 2.45 Opening of epoxides resulting to endocyclization](image-url)

The intramolecular 5-exo cyclization favored by Baldwin’s rules have been observed by Rao et. al. in the total synthesis of (+)-varitriol.100 In the synthesis of highly toxic polyether of marine origin, Nicolau applied the strategy of using an internal oxygen nucleophile resulting in cyclization (Scheme 2.46).101

![Scheme 2.46 Intramolecular cyclization via opening of a vinyl epoxide](image-url)

Intramolecular cyclization has also been induced by base via 6-exo cyclization.32 A stereospecific $S_N2$ cyclization was observed by Harvey et al. in the Pd-catalyzed reactions of $\alpha,\beta$-unsaturated $\gamma,\delta$-epoxy ester leading to the formation of C-furanosides.102 $\alpha$-
furanoside was obtained with \((E-2.230)\) and the \(\beta\)-furanoside was obtained with \((Z-2.230)\). The \(\beta\) product is possible because of the isomerization of the double bond prior to cyclization. The nucleophilic cyclization under basic condition was reported to go through an oxa-Michael reaction to generate epoxy C-pyranoside. The mixture of \(\alpha\)- and \(\beta\)- isomers were obtained with \((E-2.230)\) and \(\beta\)- product from \((Z-2.230)\) (Scheme 2.47).

Scheme 2.47 Intramolecular cyclization and Oxa Michael reaction under different conditions

### 2.4.1.3 Carbon nucleophile

The addition of carbon nucleophiles can be classified based on the mechanism involved.\(^3\)\(^2\) Friedel-Crafts-type of cyclization promoted by BF\(_3\).Et\(_2\)O to give 7-endo selective cyclization was observed as a result of intramolecular attack (Scheme 2.48).\(^1\)\(^0\)\(^3\)

Scheme 2.48 Intramolecular cyclization
Stereoselective reaction was reported by the use of a Lewis acid catalyst in which anisole (2.236) acted as the carbon nucleophile. A similar result was obtained with substituted epoxide (2.238) (Scheme 2.49).

Scheme 2.49 Lewis acid assisted epoxide opening

Aromatic heterocycles like indoles on an activated silica surface have also been used to open the epoxy ring of cyclic vinyl epoxides. Gruber et. al. reported the similar reaction with indole using a Ruthenium catalysis (Scheme 2.50).

Scheme 2.50 Indole as a carbon nucleophile in opening of epoxides
Alkenes and enol ethers undergo addition to activated epoxides through carbocation intermediates. This type of reaction can lead to a cascade reaction, a strategy which has been applied to the synthesis of polycyclic natural products.\textsuperscript{32}

\textbf{Scheme 2.51 Addition of an alkene to a vinyl epoxide leading to a cascade reaction}
Nicolaou and coworkers applied this type of cascade strategy to the synthesis of hirsutellone B.\textsuperscript{107} The cascade reaction was initiated by an electron-deficient vinyl epoxide finally leading to cyclization. The activation of vinyl epoxide was carried out using Et\textsubscript{2}AlCl. The final tricyclic product (2.252) was obtained by an \textit{in-situ} intramolecular Diels–Alder reaction (Scheme 2.51).\textsuperscript{107}

Reaction of vinyl epoxides with hard nucleophiles from organometallic reagents like alkyllithium reagents, Grignard reagents, alkylzincates, and alkylaluminates undergo \textit{S}\textsubscript{N}2 like addition, while soft nucleophiles like organocopper(I) favor \textit{S}\textsubscript{N}2' type of addition.\textsuperscript{32} The regioselective nucleophilic attack by carbon nucleophiles was described by Mahapatra, who reported that the nucleophilic attack depends upon chelating properties of the reagent. The high chelating property of lithium, alkyllithium resulted syn-1,4-adducts 2.216 and
2.218 through coordinated transition states (Scheme 2.52)\textsuperscript{78, 108-109} while Grignard reagents were generally unreactive toward these vinyl oxirane compounds, except for one case involving PhMgCl\textsuperscript{78, 108}.

![Scheme 2.52 Opening of epoxides by alkyl lithium reagents](image)

Organocopper reagents and cuprates undergo S\textsubscript{N}2’ type of addition to vinyl epoxide. The addition usually occurs to give anti addition giving an allylic alcohol (Scheme 2.53)\textsuperscript{110}.

![Scheme 2.53 Opening of an epoxide with an organocuprate](image)

The mechanistic details of various organocopper reagents is still not clear.\textsuperscript{32} According to recent studies, Π-allylcopper(III) (2.259) is generated via an anti-elimination due to more effective orbital overlap in preference to a syn elimination. The π-allylcopper(III) complex...
(2.259) equilibrates with the less stable \( \sigma \)-allylcopper(III) complex (2.263) assisted by a fourth ligand such as a solvent molecule. Depending on the ligands on copper, such as cyanide groups in the case of heterocuprates, another configurationally stable \([\sigma + \pi]\)-type of allylcopper(III) complex (2.267) (Figure 2.5) is the most stable intermediate. The reaction of the \( \pi \)-allylcopper(III) complex is kinetically favored, proceeding via an enyl \([\sigma + \pi]\)-like transition state (2.260) (Figure 2.4).\(^{32}\)

\[
\begin{align*}
\text{2.259} & \quad \text{2.260} & \quad \text{2.261} \\
\text{\( \pi \)-allylcopper(III)} & \quad \text{enyl \([\sigma + \pi]\)} & \quad \text{reductive elimination} \\
\text{2.262} & \quad \text{2.263} & \quad \text{2.264} \\
\text{\( \sigma \)-allylcopper(III)} & \quad \text{reductive elimination} & \quad \text{-L}
\end{align*}
\]

**Figure 2.4 Mechanism of reaction of organocuprates(I) with epoxides**

For unsymmetrically substituted (2.259) (R\(^1\) ≠ H), reductive elimination at the unsubstituted position is preferred, and it is even more favored when the allyl system has an electron-rich substituent.\(^{111}\)
The cuprate addition to epoxycyclohexene (2.273) gives a mixture 1,4 and 1,2 adducts with low regioselectivity, whereas the reaction with MeMgBr/CuCN resulted in a higher anti-1,4-selectivity. In a similar type of reaction, epoxide (2.215) gave higher selectivity with anti-1,4-adduct (Scheme 2.54). 

Scheme 2.54 Opening of cyclic epoxides to give 1,4-addition
Vinyl epoxide (2.278) undergoes conjugate addition to give 1,4-adduct in the absence of metal like magnesium or lithium through an SN2’ pathway. An SN2 product is obtained upon addition of LiBr or use of cuprate derived from Grignard’s reagent or LiCl. An SN2’ product is supposed to occur through (2.281) while, the SN2 product is obtained through (2.282) where the metal coordinates with cyanide group and ester oxygen (Scheme 2.55).  

Scheme 2.55 Opening of epoxides by dialkyl zinc reagents in presence of CuCN  

Vinyl epoxides react with various other nucleophiles like sulphur and halogens as well. The other type of reactions that are observed with vinyl epoxides includes rearrangements, radical, cycloaddition and formal cycloaddition. These other types of reactions are not covered here.
Vinyl epoxides are an important class of compounds. The strained oxirane ring along with the presence of double bond makes these compounds of very versatile use. Our approach of opening of the epoxide ring lies in the property of the double bond and the reactivity of the oxirane ring. The use of a palladium catalyst utilizes the property of the double bond to form a Π-allyl complex, so that the nucleophilic attack can occur at C2 and thus the oxygen of the oxirane acts as the leaving group. This chemistry is analogous to the chemistry of α- and γ- carbonates as discussed in a previous section. Based on this fact, our plan was to use a palladium catalyst that can undergo the formation of a Π-allyl complex, so that nucleophile attack is facilitated leading to the formation of δ-hydroxy phosphonates.

2.5 Results and discussion

2.5.1 Synthesis of γ,δ-epoxy vinyl phosphonates

γ,δ-epoxy vinyl phosphonates are the key intermediate in the synthesis of phostones. The synthesis of γ,δ-epoxy vinyl phosphonate started with allylic alcohol 2.283. The double bond was oxidized using either Sharpless Asymmetric Epoxidation conditions or peracids like mCPBA (2.23). The allylic alcohols 2.283(a-d) were selected in order to explore substituent and alkene geometric variation. Although the benzyl protected alcohol was selected, there is always a possibility of using various protecting group based on silicon (e.g.--OTBS) that would allow the opportunity to differentially deprotect the alcohol in the final product (phostone). When using benzyl (Bn-) protecting group, precaution needs to be taken during hydrogenation of the double bond in order to prevent the removal of the benzyl group. This can be done by poisoning the catalyst using small amount of pyridine.

The initial epoxidation was carried out using meta-chloroperoxybenzoic acid (2.23) as the oxidizing agent. This type of epoxidation using peroxo acids is also known as Prilezhaev’s
reaction, was first used by N. Prilezhaev in 1909.\textsuperscript{115} This reaction is stereospecific in which \textit{trans}-alkene gives \textit{trans}-epoxide and \textit{cis}-alkene gives \textit{cis}-epoxide. The epoxidation proceeds with \textit{syn} addition of the oxygen atom to the double bond in a concerted process which is assumed to have butterfly transition structure (Figure 2.6).\textsuperscript{115}

\[
\begin{align*}
\text{2.283} & \xrightarrow{\text{mCPBA, CH}_2\text{Cl}_2, 0^\circ\text{C, 3 - 5 h}} \text{2.285} \\
& \quad | \\
\text{2.284a} & + \text{- m-Chlorobenzoic acid} \\
\text{2.285(I)} & \text{2.284b} \\
& \quad | \\
\text{2.285(II)} & \text{- m-Chlorobenzoic acid}
\end{align*}
\]

**Figure 2.6 General mechanism of epoxidation by mCPBA**

\[
\begin{align*}
\text{R=CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \quad \text{89\%} \\
\text{R=CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \quad \text{78\%} \\
\text{R=-CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \quad \text{(Trans)} \quad \text{81\%} \\
\text{R=-CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \quad \text{(Cis)} \quad \text{91\%}
\end{align*}
\]

**Scheme 2.56 Synthesis of epoxy alcohol from allyl alcohol**

 Allylic alcohols (2.283c) and (2.283d) were synthesized using literature methods. For the synthesis of \textit{trans}-2-butene-1,4-diol, 2-butyne-1,4-diol (2.286) was monoprotected benzyl
bromide (2.288) under basic condition and then alkyne was stereoselectively reduced to the \textit{trans} alkene using RedAl (Scheme 2.57)\textsuperscript{116}

![Scheme 2.57 Synthesis of 4-benzyloxy \textit{trans}-2 butenol](image)

The starting material (2.283d) was obtained by mono-benzylation of commercially available \textit{cis}-2-butene-1,4-diol (2.287) in the presence of base (Scheme 2.58), utilizing a literature method.\textsuperscript{117}

![Scheme 2.58 Synthesis of 4-benzyloxy \textit{cis}-2-butenol](image)

Epoxy alcohols can be oxidized to epoxy aldehydes in various ways. Common methods of oxidation of primary alcohols include Swern oxidation, Parikh-Doering Oxidation, IBX oxidation, DMP oxidation, TPAP oxidation, or the TEMPO oxidation in which the epoxy ring remains intact.\textsuperscript{32}

In the present work, the oxidation was carried out using the Parikh-Doering Oxidation method\textsuperscript{118}, which utilizes a pyridine sulfur trioxide complex (2.290), DMSO (2.291) and a base like triethylamine (2.292) (Scheme 2.59). Dimethyl sulfoxide (2.291a) is activated by reaction with sulfur trioxide (2.299).
Figure 2.7 General mechanism of Parikh Doering Oxidation reaction

The active DMSO reacts with the alcohol to generate the alkoxy sulfonium ion (2.296). Deprotonation of methyl group occurs to generate sulfur ylide (2.297), which eliminates dimethyl sulfide to form an aldehyde or ketone (2.298) (Figure 2.7).

Scheme 2.59 Synthesis of epoxy aldehyde

The oxidation of epoxy alcohols was carried out following a literature method to obtain the epoxy aldehydes 2.300 (a-d)\textsuperscript{119-122} (Scheme 2.59). The reaction was smooth and no over oxidation leading to the formation of carboxylic acids was observed. Under the low temperature reaction condition, aldehydes for all the substrate were obtained in good yield. The epoxy aldehydes were further subjected to olefination reaction utilizing Horner-
Wadsworth-Emmons (HWE) reaction. The HWE reaction, which is an adaption of the Wittig-olefination reaction, utilizes a phosphonate anion. The resulting alkene product is formed with the trans geometry for the double bond.

Figure 2.8 The HWE reaction

The HWE reaction is versatile and applicable under different conditions. Various modifications have been reported, some allowing formation of the cis olefin. The mechanism for HWE reaction is outlined below (Figure 2.9). In the presence of metallic base like NaH the proton is removed from the methylene group and forms the phosphonate carbanion 2.306. The phosphonate carbanion may undergo isomerization to form 2.307 or 2.308. The phosphonate carbanion undergoes the reaction with an aldehyde either through anti addition or syn addition. The trans product is formed through the (2.312), trans-oxaphosphetane, which is in equilibrium with (2.311). The byproduct is the phosphate salt, which is water soluble. The cis product is formed through the (2.316), cis-oxaphosphetane. The general reaction leads to the formation of trans product.
The epoxy aldehydes 2.300(a-d) were subjected to the HWE reaction following a literature method. The aldehydes were treated with the carbanion generated from the reaction of tetraethyl methylenedisphosphonate (2.305) and sodium hydride. The reactions resulted in the formation of γ,δ-epoxy vinyl phosphonates 2.313 (a-d). All the reactions were carried out in ice bath, using 1.5 equivalent of (2.305) and 1.1 equivalent of sodium hydride as the base. The yields for the reactions were good to excellent. All the compounds are
novel and were fully characterized during this work. Prior synthesis and study of these compounds have not been documented except for (313a).123

\[ \text{R} \cdot \overset{\text{O}}{\text{O}} \cdot \overset{\text{O}}{\text{O}} \cdot \overset{\text{P}}{\text{O}} \cdot \overset{\text{O}}{\text{Et}} \cdot \overset{\text{Et}}{\text{Et}} \overset{\text{O}}{\text{O}} \cdot \overset{\text{O}}{\text{O}} \cdot \overset{\text{O}}{\text{O}} \cdot \overset{\text{P}}{\text{O}} \cdot \overset{\text{O}}{\text{Et}} \overset{\text{Et}}{\text{Et}} \]

\[ \text{NaH (1.1 eq), THF} \]

\[ 0^\circ\text{C}, 2 - 3\text{ h} \quad 77 - 90\% \]

\[ \text{R} \cdot \overset{\text{O}}{\text{O}} \cdot \overset{\text{O}}{\text{O}} \cdot \overset{\text{O}}{\text{O}} \cdot \overset{\text{O}}{\text{Et}} \cdot \overset{\text{Et}}{\text{Et}} \]

Scheme 2.60 Synthesis of γ,δ-epoxy vinyl phosphonate

2.5.2 Synthesis of γ,δ-epoxy vinyl phosphonates

γ,δ-epoxy vinyl phosphonates are the key intermediates for the synthesis of phostones and the opening of the epoxide ring is an important and challenging step. The success of the methodology relies in the successful opening of the epoxide ring. The palladium catalyzed opening of epoxides of analogous γ,δ-epoxy vinyl esters, has been reported and was discussed in the previous sections. The work presented here involves the application of oxygen nucleophiles from various alcohols. The general protocol for the palladium catalyzed opening of the epoxide ring is represented in Scheme 2.61. The opening of the epoxide ring is stereospecific and single diastereomer of a monoprotected diol is formed. The addition occurs via the formation of π-allyls (2.315), where the double inversion occurs to give syn- or anti- products (Scheme 2.61).
Scheme 2.61 Palladium catalyzed stereospecific ring opening of γ,δ-epoxy vinyl phosphonates

The initial attempt of the proposed opening of epoxide ring was carried out with substrate (2.313a), and benzyl alcohol (2.314) as the nucleophile (Scheme 2.62).

Scheme 2.62 Attempted opening of epoxide ring

The reaction was carried out in the presence of triphenyl borate (2.317) as co-catalyst and excess of benzyl alcohol as nucleophile. Pd$_2$(dba)$_3$ was used as the source of Pd(0) with dppe as the ligand and THF solvent. The expected monoprotected diol (2.316a) was not obtained, instead the elimination product (2.319a) was obtained (Scheme 2.62). The above reaction was also tested with Pd(PPh$_3$)$_4$ as the catalyst, but the outcome was unchanged. The assumption is that, when the attack of nucleophile is slow, the β-elimination is faster.
and the elimination product (2.319a) is obtained via (2.318a) (Scheme 2.63). The phenyl ring could help to the facile elimination of the proton. This result opens the possibility that switching phenyl substituent to alkyl group adjacent to Π-allyl may prevent the competing elimination reaction. Another possibility is to switch to another catalyst or attempting the epoxide ring opening under the assistance of Lewis acid catalysis like BF$_3$.OEt$_2$.

Scheme 2.63 Possible reaction mechanism for the formation of the elimination product

The reaction of other substrates 2.313(b-d) under the palladium-catalyzed reactions conditions with benzyl alcohol were studied. The reaction of these epoxy vinyl phosphonates resulted in the formation of addition products 2.316(b-d) in good yields. The reaction was stereospecific, in which trans-epoxide 2.316(b-c) gave monoprotected syn-diol and cis-epoxide (2.316d) gave anti-diol (Scheme 2.65).
To understand the importance of triphenyl borate, reaction of trans-epoxy vinyl phosphonate (2.313c) was carried out omitting triphenyl borate. The ketone (2.319c) was obtained as an elimination product (Scheme 2.65) and not the diol as expected. This suggest that the co-ordination of boron with the epoxide ring makes the carbon more electrophilic and susceptible to the attack by the nucleophile. Furthermore, the nucleophile could be transferred from the boronate in an intramolecular fashion.

Scheme 2.65 Palladium catalyzed stereospecific ring opening of trans-epoxy vinyl phosphonate 2.313c in the absence of co-catalyst
Based on the plan, vinyl phosphonates 2.316(b-d) were then subjected to hydrogenation using hydrogen over palladium on carbon poisoned with 5–50 mol % of pyridine. This reaction resulted in the formation of saturated phosphonates 2.320(b-d). The use of pyridine prevents debenzylation (Scheme 2.66). This reaction is critical in terms of the use of pyridine. It was always difficult to determine the amount of pyridine to be used. Large amounts of pyridine lead to the slow reaction and longer reaction time.

Scheme 2.66 Hydrogenation of vinyl phosphonate

The vinyl phosphonates can be functionalized as discussed in the earlier chapter. This section is only focused on the reduction of double bond and the cyclization to form the phostones. A successful reaction sequence would provide the proof of concept for the methodology, which could be further extended. With the saturated vinyl phosphonates in hand, the next step was to investigate the cyclization through intramolecular transesterification. Tordo et. al. has observed the cyclization of δ-hydroxy phosphonates using catalytic amount of sodium hydride in 1,2-dimethoxyethane at 60°C (Scheme 2.67). In the present work, cyclization was carried out by treating the saturated vinyl phosphonates with sodium hydride in THF at ice bath temperature. As anticipated,
phostones 2.323(b-d) were obtained as single diastereomer in good yields (Scheme 2.68). The stereochemistry at phosphorus atom was elucidated by X-ray crystallography of the phostone 2.323b. The high diastereoselectivity for the cyclization of substituted δ-hydroxy phosphonates have also been reported by Ruiz et. al.18

![Chemical Structure](image)

**Scheme 2.67 Cyclization of δ-hydroxy phosphonate under base catalyzed condition**

The cyclization of δ-hydroxy phosphonate in the presence of base proceeds through intramolecular transesterification. The nucleophilic attack of the alcohol to the phosphorus atom leads to the cyclized product (Scheme 2.68). There is the possibility for the oxygen atom to attack from either position, but a single diastereomer is obtained, and the attack of the nucleophile occurs only from one side, which is revealed by the X-ray crystallographic structure of 2.323b.
Scheme 2.68 Cyclization of phosphonates to phostones

The cyclization with good yield is evidence that the proposed methodology works. This opens the possibility to use other alcohols as the nucleophiles, which is discussed in the latter section of this chapter. Beside the alcohol nucleophile other nucleophiles can also be used for the ring opening of the epoxy vinyl phosphonates.

Scheme 2.69 Intramolecular transesterification for cyclization

2.5.3 X-ray crystallographic structure of 323b

The X-ray quality crystals for 2.323b were obtained by slow evaporation of a hexane solution. Initially the amorphous solid was dissolved in hot hexane. Single crystal studies were carried out at 299 K. X-ray analysis revealed that the crystal at 299K belongs to the
monoclinic system with space group P21/c. The crystal structures of phostone 2.323b at low temperature is presented below (Figure 2.10).

The X-ray crystallography reveals that, the alkyl chain at C4 and benzyloxy group at C3 are cis to each other, while the ethoxy group at phosphorus on the opposite side.

![Projection view of phostone 2.323b at 299K](image)

**Figure 2.10 Projection view of phostone 2.323b at 299K**

Table 1: Physical properties of X-ray crystal of phostone 2.323b

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Phostone 2.323b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>199(2) K</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 19.6012(17) Å</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------</td>
</tr>
<tr>
<td></td>
<td>b = 10.1533(10) Å</td>
</tr>
<tr>
<td></td>
<td>c = 9.6226(7) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>1914.7(3) Å³</td>
</tr>
<tr>
<td>Density</td>
<td>1.181 Mg/m³</td>
</tr>
<tr>
<td>Absorption Coefficient</td>
<td>0.160 m/m⁻¹</td>
</tr>
<tr>
<td>Crystal Size (mm³)</td>
<td>0.564 x 0.238 x 0.076 mm³</td>
</tr>
</tbody>
</table>

2.6 Reaction of benzyloxymethyl substituted trans-epoxy vinyl phosphonate 2.313c with other alcohol nucleophiles

To expand the scope of the methodology, the opening of the epoxy ring was carried out with different alcohols. For this, primary alcohols with different chain length e.g. methanol, 1-pentanol, 1-decanol, and 1-pentadecanol; cyclic alcohols e.g. cyclohexylmethanol, p-methoxybenzyl alcohol; and secondary alcohols e.g. isopropyl alcohol and cyclohexanol were used for the opening of the epoxide ring (Scheme 2.70). The reactions were carried out under similar conditions, and the results were very consistent for primary alcohols resulting in the syn-product. In the case of secondary alcohols like isopropyl alcohol and cyclohexanol, a mixture of products were obtained. It was also revealed that phenoxide ion in the triphenyl borate was a competent nucleophile and also formed an addition product.
With methanol as nucleophile, the yield was increased by using trimethyl borate as the co-catalyst.

Scheme 2.70 Palladium catalyzed stereospecific ring opening of γ,δ-epoxy vinyl phosphonates

As stated above, the reaction with primary alcohols underwent smoothly. However, the yield with pentadecanol was low. The low solubility of pentadecanol in THF solvent could be a factor contributing to the low yield. On the other hand, the reaction with isopropyl
alcohol resulted in the addition of phenol from the triphenyl borate. A mixture of products was obtained with cyclohexanol as revealed by $^{31}$P NMR.

Again, with all these results the further hydrogenation of vinyl phosphonates 2.325(a-f) were carried out in palladium catalyzed conditions in the presence of pyridine. The saturated phosphonates were obtained in quantitative yield for all the substrates (Scheme 2.71).

![Scheme 2.71 Hydrogenation of vinyl phosphonates](image)

The final cyclization of saturated phosphonates 2.327(a-f) was then carried out using sodium hydride in THF at ice bath temperature. As anticipated, phostones 2.328(a-f) were obtained as single diastereomers. The diastereomeric selectivity of this methodology is one of the beauties of this reaction.
Summary:
The synthesis of cyclic phosphonates i.e. the phostones has been accomplished. The key intermediate \(\gamma,\delta\)-epoxy vinyl phosphonates undergo stereospecific palladium-catalyzed addition of primary alcohols to give vinyl phosphonates. The cyclization of the saturated phosphonates yields phostones as single diastereoisomer. The present findings could be used to investigate the opening of the epoxy ring with other nucleophiles, and the \(\gamma,\delta\)-epoxy vinyl phosphonates could be of potential importance as the building blocks for the synthesis of various organophosphorus compounds.

As a proof of concept using \(\gamma,\delta\)-epoxy vinyl phosphonates as the essential building block, substrate (2.313b) was subjected to the ring opening using BF\(_3\).OEt\(_2\) and anisole as a source.
of carbon nucleophile.\textsuperscript{105} The reaction resulted in the opening of epoxide, but a mixture of products were obtained and no further investigation was carried. This initial finding suggests that \(\gamma,\delta\)-epoxy vinyl phosphonate are also important building block for the construction of C-C bond. Since this is not the scope of this dissertation no further investigations were carried out at this time. But this finding also increases the scope of the methodology developed.
2.8 General Experimental

General Experimental Procedures

All reactions were carried out in oven-dried glassware under an atmosphere of argon unless otherwise noted. $^1$H, $^{13}$C, and $^{31}$P NMR spectra were recorded in CDCl$_3$ at 300, 75, and 121 MHz, respectively. $^1$H NMR spectra are referenced to CDCl$_3$ (7.27 ppm), $^{13}$C NMR spectra are referenced to the center line of CDCl$_3$ (77.23 ppm), and $^{31}$P NMR spectra are referenced to external H$_3$PO$_4$. Coupling constants, J, are reported in hertz (Hz). High resolution mass spectral analyses were carried out on a JEOL MStation-JMS700 spectrometer. Analytical thin-layer chromatography (TLC) analyses were performed on silica gel plates 60PF$_{254}$. Visualization was accomplished with UV light or KMnO$_4$ solution.

![Structure](image)

4-(benzyloxy)but-2-yn-1-ol (2.289)$^{116}$

1,4-Butynediol (2.286) (20.31 g, 236 mmol) was dissolved in KOH (13.2 g, dissolved in 166 ml water) solution and sealed for 5 minutes at room temperature. To this solution was added benzyl bromide (10 g, 59 mmol) over 10 minutes. The resulting mixture was stirred for 48 hr at room temperature. To the reaction mixture, was added NH$_4$Cl and extracted 3X by CH$_2$Cl$_2$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO$_2$, 20 - 30% EtOAc in hexanes) to give colorless liquid 2.289 (8.70 g, 84%). The $^1$HNMR data were in correspondence to the literature value.$^{116}$
(E)-4-(benzyloxy)but-2-en-1-ol (2.283c).\textsuperscript{116}

To a suspension of Red-Al\textsuperscript{®} (8.86 g, 43.8 mmol) in dry THF (2ml/mmol), was added the solution of 2.289 (3.86g, 21.9 mmol) in THF(5ml/mmol) dropwise through the addition funnel over 1 hr. The reaction mixture was then stirred at room for 2 hrs. Completion of reaction was checked by TLC. After the completion, reaction mixture was quenched by the addition of saturated solution of potassium sodium tartarate (10 ml), followed by dilution with EtOAc. Then the mixture was filtered and washed with EtOAc and the solvent was removed by rotatory evaporator. Then pure 2.283c (2.72 g, 70\%) was obtained by column chromatography (SiO\textsubscript{2}, 30\% EtOAc in hexanes) to give colorless liquid. The \textsuperscript{1}HNMR data were in correspondence to the literature value.\textsuperscript{116} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.42 – 7.28 (m, 5H), 6.05 – 5.68 (m, 2H), 4.54 (s, 1H), 4.30 – 4.14 (m, 2H), 4.06 (d, $J_{HH} = 5.1$ Hz, 2H); 3.18 (br, 1H); \textsuperscript{13}C{\textsuperscript{1}H} NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 138.0, 132.6, 128.4, 127.8, 127.7, 127.1, 72.2, 70.1, 62.5.

(Z)-4-(benzyloxy)but-2-en-1-ol (2.283d).\textsuperscript{117}

To the solution of cis-2-butene-1,4-diol (2.287) (26.43 g, 300 mmol) in THF (150 ml) was added sodium hydride (4.2 g, 60\% dispersion in mineral oil) in ice bath under argon atmosphere. The reaction was stirred at rt for 30 min. Benzyl bromide (12 ml, 100 mmol) was then added dropwise at 0\°C, and then refluxed for 1 hr. After cooling to rt, saturated
NH₄Cl was added maintaining the temperature below 5°C. Water was added till the dissolution of any white solid. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was dried by MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂, 30% EtOAc in hexanes) to give pure 2.283d (13.31 g, 74%) as colorless liquid. The ¹H NMR data were in correspondence to the literature value.¹²⁵¹H NMR (300 MHz, CDCl₃) δ 7.40 – 7.29 (m, 5H), 5.90 – 5.68 (m, 2H), 4.54 (s, 2H), 4.19 (d, JHH = 5.9 Hz, 2H), 4.14 – 4.04 (m, 2H), 1.86 (br, 1H); ¹³C¹H NMR (75 MHz, CDCl₃) δ 137.8, 132.5, 128.4, 127.9, 127.8, 72.4, 65.6, 58.4.

**General procedure for the synthesis of epoxy alcohols (2.285a-d)**

To the ice bath cooled solution of mCPBA in dry CH₂Cl₂ (4 mL/mol) was added the solution of allyl alcohol dropwise through addition funnel over a period of one hour. The reaction mixture was stirred at ice bath temperature till completion (3-5 hr). The completion of reaction was checked by TLC. After completion, the reaction was diluted by adding CH₂Cl₂, resulting solution was washed with saturated NaHSO₃ and brine, and dried over Na₂SO₄. The solution was concentrated under reduced pressure and the pure epoxy alcohol was isolated by column chromatography (SiO₂, 20-30% EtOAc in Hexane).

![Image of 2.285a](image-url)

(3-phenyloxiran-2-yl)methanol (2.285a).¹²⁶

Cinnamyl alcohol (5.0 g, 37.26 mmol) was reacted as above to get 2.285a (4.9 g, 89%). The ¹H NMR data were in correspondence to the literature value.¹²⁶ ¹H NMR (300 MHz,
CDCl₃ δ 7.52 – 7.31 (m, 5H), 4.14 – 7.08 (m, 1H), 3.99 (d, J₉H = 2.1 Hz, 1H), 3.94 – 3.78 (m, 1H), 3.30 – 3.27 (m, 1H), 1.94 (br, 1H).

(3-pentyloxiran-2-yl)methanol (2.285b).¹²⁷

trans-2-Octen-1-ol (1.0 g, 7.80 mmol) was reacted as above to get 2.285b (0.88 g, 78%). The ¹H NMR data were in correspondence to the literature value.¹²⁷ ¹H NMR (300 MHz, CDCl₃) δ 3.98 – 3.93 (m, 1H), 3.83 – 3.55 (m, 1H), 3.19 – 2.87 (m, 2H), 2.08 (br, 1H), 1.66 – 1.56 (m, 2H), 1.55 – 1.43 (m, 2H), 1.37 – 1.34 (m, 2H), 0.93 (t, J₉H = 6.5 Hz, 3H).

(3-((benzyloxy)methyl)oxiran-2-yl)methanol (2.285c).¹²⁸

trans-4-Benzylcxyloxy-2-buten-1-ol (8.0 g, 45 mmol) was reacted as above to get 2.285c (7.04 g, 81%). The ¹H NMR data were in correspondence to the literature value.¹²⁸ ¹H NMR (300 MHz, CDCl₃) δ 7.50 – 7.35 (m, 5H), 4.64 (dd, J₉H = 27.2, 11.7 Hz, 2H), 3.89 – 3.65 (m, 4H), 3.39 – 3.23 (m, 2H).

(3-((benzyloxy)methyl)oxiran-2-yl)methanol (2.285d).

cis-4-Benzylcxyloxy-2-buten-1-ol (6.0 g, 33.6 mmol) was reacted as above to get 2.285d (5.9 g, 91%). The ¹H NMR data were in correspondence to the literature value.¹²⁸ ¹H NMR (300 MHz, CDCl₃) δ 7.52 – 7.31 (m, 5H), 4.14 – 7.08 (m, 1H), 3.99 (d, J₉H = 2.1 Hz, 1H), 3.94 – 3.78 (m, 1H), 3.30 – 3.27 (m, 1H), 1.94 (br, 1H).
MHz, CDCl$_3$) $\delta$ 7.43 – 7.29 (m, 5H), 4.59 (dd, $J_{HH} = 27.3$, 11.8 Hz, 2H), 3.80 – 3.61 (m, 4H), 3.38 – 3.21 (m, 2H), 1.60 (br, 1H).

**General procedure for the synthesis of epoxy aldehydes (2.300a-d)**

To the ice bath cooled solution of epoxy alcohol in dry CH$_2$Cl$_2$ (4 mL/mol) was added Et$_3$N (6 eq). Then a solution of pyridine sulfur trioxide (1.5 eq) in dry DMSO (1.5 ml/mmol) was added slowly via an addition funnel over a period of one hour. The reaction mixture was stirred at ice bath temperature for an additional three hours. The reaction was quenched by the addition of 10% aqueous citric acid and resulting aqueous solution was extracted three times using CH$_2$Cl$_2$. The combined organic layer was washed with saturated NaHCO$_3$ and brine and dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure and the pure epoxy aldehyde was isolated by column chromatography (SiO$_2$, 10-20% EtOAc in hexane). $^1$H NMR spectrum for each epoxide was consistent with the literature values.

![2.300a](image)

**3-phenyloxirane-2-carbaldehyde (2.300a)**

(3-phenyloxiran-2-yl)methanol (2.285a) (4.9 g, 32.65 mmol) was reacted as above to give (2.300a) (2.71 g, 56%). The $^1$HNMR data were in correspondence to the literature value.$^{119}$

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.21 (d, $J_{HH} = 6.1$ Hz, 1H), 7.47 – 7.36 (m, 3H), 7.32 – 7.28 (m, 2H), 4.18 (d, $J_{HH} = 1.8$ Hz, 1H), 3.46 (dd, $J_{HH} = 6.1$, 1.8 Hz, 1H).
3-pentyloxirane-2-carbaldehyde (2.300b).\textsuperscript{120}

(3-pentyloxiran-2-yl)methanol (2.285b) (3.80 g, 26.35 mmol) was reacted as above to give 2.300b (2.28 g, 61\%). The \textsuperscript{1}HNMR data were in correspondence to the literature value.\textsuperscript{120} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 9.06 (d, \(J_{HH} = 6.3\) Hz, 1H), 3.31 – 3.25 (m, 1H), 3.29 – 3.17 (m, 1H), 1.76 – 1.66 (m, 2H), 1.54 – 1.50 (m, 2H), 1.43 – 1.36 (m, 4H), 0.95 (t, \(J_{HH} = 6.7\) Hz, 3H).

3-((benzyloxy)methyl)oxirane-2-carbaldehyde (2.300c).\textsuperscript{122}

2.285c (7.0 g, 36.06 mmol) was reacted as above to get 2.300c (5.9 g, 86\%). The \textsuperscript{1}HNMR data were in correspondence to the literature value.\textsuperscript{122} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 9.06 (d, \(J_{HH} = 6.3\) Hz, 1H), 7.42 – 7.30 (m, 5H), 4.65 – 4.54 (m, 2H), 3.86 (dd, \(J_{HH} = 11.7, 2.7\) Hz, 1H), 3.59 (dd, \(J_{HH} = 11.7, 5.0\) Hz, 1H), 3.52 – 3.46 (m, 1H), 3.37 – 3.34 (m, 1H).

3-((benzyloxy)methyl)oxirane-2-carbaldehyde (2.300d).\textsuperscript{121}

2.285d (7.0 g, 36.06 mmol) was reacted as above to get 2.300d (5.9 g, 86\%). The \textsuperscript{1}HNMR data were in correspondence to the literature value.\textsuperscript{121}

General procedure for the synthesis of vinyl epoxy phosphonates (2.313a-d).
Sodium hydride (1.1 eq.) was suspended in dry THF (1 mL/mmol). The suspension was cooled in an ice bath and then tetraethyl methylenebis(phosphonate) (2.305) (1.5eq) was added slowly over 5 minutes. The resulting mixture was stirred for one hour, then the epoxy aldehyde (1 eq.) dissolved in dry THF (3mL/mmol) was added dropwise. The reaction mixture was stirred for two hours at ice bath temperature then the reaction was quenched with 10% aqueous NH₄Cl. After 10 minutes, the aqueous solution was extracted three times with EtOAc. The combined organic layer was washed with aqueous NaHCO₃ and brine, and then dried over anhydrous Na₂SO₄. The solution was concentrated under reduced pressure and pure epoxy vinyl phosphonate was isolated by column chromatography (SiO₂, 30-60% EtOAc in hexane).

![2.313a](image)

(-)-Diethyl (E)-2((2S,3S)-3-Phenyloxiran-2-yl)-vinylphosphonate (2.313a).¹²⁸

Epoxy cinnamaldehyde 2.300a (1.8 g, 12.5 mmol) was reacted as above to give 2.313a as a thick yellow oil (3.17 g, 90%). ᵃ¹H NMR (CDCl₃) δ 7.32–7.18 (m, 5H), 6.67 (ddd, ᵃJHP = 21.5, ᵃJHH = 17.1, 6.2 Hz, 1H), 6.08 (ddd, ᵃJHP = 18.6, ᵃJHH = 17.1, 0.6 Hz, 1H), 4.04 (m, 4H), 3.73 (d, ᵃJHH = 1.6 Hz, 1H), 3.39 (m, 1H), 1.27 (dt, ᵃJHH = 7.0, ᵃJHP = 1.5 Hz, 6H); ᵃ¹³C{¹H} NMR (CDCl₃) δ 147.5 (d, ᵃJCP = 6.1 Hz), 135.9, 128.6, 128.5, 125.4, 120.1 (d, ᵃJCP = 187.5 Hz), 61.9 (d, ᵃJCP = 5.2 Hz), 61.3, 61.0 (d, ᵃJCP = 1.5 Hz), 16.3 (d, ᵃJCP = 6.3 Hz); ᵃ³¹P{¹H} NMR (CDCl₃) δ 16.8; HRMS (FAB, MH⁺) calcd for C₁₄H₂₀O₄P 283.1099 found 283.1117.
Diethyl (E)-(2-(3-pentyloxiran-2-yl)vinyl)phosphonate (2.313b).

Epoxy octanal (2.300b) (2.29 g, 16 mmol) was reacted to give (2.313b) as a pale-yellow oil (3.39 g, 77%). IR (neat) 2928, 2858, 1631 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 6.54 (ddd, \(J_{HP} = 21.5, J_{HH} = 17.1, 6.4\) Hz, 1H), 5.9 (ddd, \(J_{HP} = 19.0, J_{HH} = 17.1, 0.7\) Hz, 1H), 4.08 (m, 4H), 3.19 (m, 1H), 2.85 (m 1H), 1.60 (m, 2H), 1.43 (m, 2H), 1.32 (m, 10H), 0.89 (t, \(J_{HH} = 7.1\) Hz, 3H); \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta\) 148.8 (d, \(J_{CP} = 6.0\) Hz), 119.2 (d, \(J_{CP} = 188.2\) Hz), 61.5 (d, \(J_{CP} = 21.7\) Hz), 56.8 (d, \(J_{CP} = 27.7\) Hz), 31.5 (d, \(J_{CP} = 25.5\) Hz), 25.3, 22.4, 16.2 (d, \(J_{CP} = 6.0\) Hz), 13.6; \(^{31}\)P\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta\) 16.9; HRMS (FAB, MH\(^+\)) calcd for C\(_{13}\)H\(_{26}\)O\(_4\)P 277.1568, found 277.1582.

\[ \text{EtO} \ begun{array}{c} \ stackrel{\text{P}}{= \text{O}} \ stackrel{\text{O}}{= \text{C}_{\text{H}}_{11}} \end{array} \]

\(2.313\text{b}\)

(±)-Diethyl (E)-2-(2S,3S)-3-(Benzyloxyethyl)oxiran-2-yl)-vinylphosphonate (2.313c).

\textit{trans}-Benzyloxy epoxy butanal 2.300c (2.40 g, 12.45 mmol) was reacted as above to give 2.313c as a yellow oil (3.27 g, 81%). IR (neat) 2981, 2862, 1632, 1240 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.33–7.11 (m, 5H), 6.44 (ddd, \(J_{HP} = 21.5, J_{HH} = 17.1, 6.5\) Hz, 1H), 5.95 (ddd, \(J_{HP} = 18.6, J_{HH} = 17.1, 0.6\) Hz, 1H), 4.48 (q, \(J_{HH} = 11.9\) Hz, 2H), 3.99 (m, 4H), 3.57 (m, 2H), 3.32 (m, 1H), 3.04 (m, 1H), 1.23 (m, 6H); \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta\) 147.8 (d, \(J_{CP} = 6.2\) Hz), 137.5, 128.4, 127.8, 127.7, 120.4 (d, \(J_{CP} = 188.2\) Hz), 73.4, 69.0, 61.9 (d, \(J_{CP} =
6.0 Hz), 59.5 (d, $J_{CP} = 1.5$ Hz), 54.3 (d, $J_{CP} = 29.2$ Hz), 16.4 (d, $J_{CP} = 6.7$ Hz); $^{31}$P{$^1$H} NMR (CDCl$_3$) $\delta$ 16.6; HRMS (FAB, MH$^+$) calcd for C$_{16}$H$_{24}$O$_5$P 327.1361, found 327.1376.

![2.313d](image)

(±)-Diethyl (E)-2-(2S,3R)-3-(Benzyloxymethyl)oxiran-2-yl)- vinylphosphonate (2.313d).

cis-Benzylxy epoxy butanal 2.300d (2.5 g, 13.01 mmol) was reacted as above to give (2.313d) as a pale-yellow oil (3.68 g, 87%). IR (neat) 2980, 2903, 1629, 1243 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.40–7.30 (m, 5H), 6.62 (ddd, $J_{HP} = 21.6$, $J_{HH} = 17.1$, 6.0 Hz, 1H), 6.05 (ddd, $J_{HP} = 18.7$, $J_{HH} = 17.1$, 1.0 Hz, 1H), 4.57 (q, $J_{HH} = 11.8$ Hz, 2H), 4.06 (m, 4H), 3.60 (m, 3H), 3.45 (m, 1H), 1.32 (m, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 145.1 (d, $J_{CP} = 6.6$ Hz), 137.6, 128.5, 128.0, 127.8, 122.3 (d, $J_{CP} = 188.6$ Hz), 73.4, 67.5, 62.0 (d, $J_{CP} = 5.5$ Hz), 57.5, 55.1 (d, $J_{CP} = 28.2$ Hz), 16.4 (d, $J_{CP} = 6.4$ Hz); $^{31}$P{$^1$H} NMR (CDCl$_3$) $\delta$ 16.3; HRMS (FAB, MH$^+$) calcd for C$_{16}$H$_{24}$O$_5$P 327.1361, found 327.1367.

**General Procedure for the Synthesis of Vinylphosphonates (2.316, 2.319 or 2.325).**

To a solution of triphenyl borate (1.5 eq) in dry THF (1 mL/mmol) was added respective alcohol (6 eq). The resulting solution was stirred for two hours. In a separate flask, Pd$_2$ dba$_3$ (0.04 eq) and dppe (0.1 equiv) were added to a solution of the epoxy vinyl phosphonates 2.313 (1 eq) in THF (3 mL/mmol). After one hour of stirring, the palladium solution was added to the alcohol solution and the resulting mixture was stirred for one hour at ice-bath temperature. The reaction mixture was then allowed to warm to room temperature and stirring was continued until the reaction was complete (as observed by $^{31}$P
NMR and TLC, 2–3 h). The reaction was quenched by the addition of 10% aqueous NH₄Cl and extracted with three times with EtOAc. The combined organic layer was washed with aqueous saturated NaHCO₃ and brine and then dried over anhydrous Na₂SO₄. The solution was concentrated under reduced pressure, and pure products (2.316, 2.319 or 2.325) were isolated by column chromatography (SiO₂, 60–80% EtOAc in hexanes).

Diethyl (E)-(4-Oxo-4-phenylbut-2-en-1-yl)phosphonate (2.319a).

Epoxy vinyl phosphonate 2.313a (0.1 g, 0.354 mmol) was reacted as above to give 2.319a (0.093 g, 93%). ¹H NMR (CDCl₃) δ 7.93–7.90 (m, 2H), 7.59–7.41 (m, 3H), 6.97 (s, 2H), 4.12 (m, 4H), 2.85 (dd, J_HP = 23.5, J_HH = 7.0 Hz, 2H), 1.32 (t, J_HH = 7.1 Hz, 6H); ¹³C{¹H} NMR (CDCl₃) δ 190.1 (d, J_CP = 2.9 Hz), 137.8 (d, J_CP = 11.4 Hz), 137.5, 133.2, 130.2 (d, J_CP = 13.3 Hz), 128.8 (s), 62.6 (d, J_CP = 6.7 Hz), 31.3 (d, J_CP = 138.1 Hz), 16.7 (d, J_CP = 6.0 Hz); ³¹P{¹H} NMR (CDCl₃) δ 24.5; HRMS (ESI, MH⁺) calcd for C₁₄H₂₀O₄P 283.1099, found 283.1093.

Diethyl (E)-(5-(Benzyloxy)-4-oxopent-2-en-1-yl)-phosphonate (2.319c).

This compound was formed from epoxy vinyl phosphonate 2.313c (0.1 g, 0.306 mmol) as the above reaction, but in the absence of B(OPh)₃ (0.041 mg, 41%). IR (neat) 2980, 2904, 1692, 1625, 1243 cm⁻¹; ¹H NMR (CDCl₃) δ 7.38–7.27 (m, 5H), 6.87 (m, 1H), 6.43 (m,
(±)-Diethyl (3S,4S,E)-3-(Benzyloxy)-4-hydroxynon-1-enylphosphonate (2.316b).

Epoxy vinyl phosphonate 2.313b (0.5 g, 1.81 mmol) was as above reacted to give 2.316b as a yellow oil (0.425 g, 61%). IR (neat) 3412, 2946, 2862, 1201 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.29–7.17 (m, 5H), 6.61 (ddd, Jₜ = 22.3, JₜH = 17.3, 5.7 Hz, 1H), 5.9 (ddd, Jₜ = 20.6, JₜH = 17.2, 1.0 Hz, 1H), 4.40 (q, JₜH = 11.4 Hz, 2H), 3.98 (m, 4H), 3.74 (m, 1H), 3.47 (t, JₜH = 5.6 Hz, 1H), 2.90 (br, 1H), 1.36 (m, 2H), 1.21 (m 12H), 0.77 (t, JₜH = 6.7 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 149.1 (d, JₜC = 5.0 Hz), 137.4, 128.4, 127.9, 127.8, 120.1 (d, JₜC = 186.6 Hz), 82.8 (d, JₜC = 21.1 Hz), 72.9, 71.6, 61.8 (d, JₜC = 5.6 Hz), 32.4, 31.7, 25.1, 22.5, 16.3 (d, JₜC = 6.3 Hz), 14.0; ³¹P{¹H} NMR (CDCl₃) δ 17.4 HRMS (FAB, MH⁺) calcd for C₂₀H₃₄O₅P 385.2143, found 385.2162.
(±)-Diethyl (3S,4S,E)-3,5-Bis(benzyloxy)-4-hydroxypent-1-enylphosphonate (2.316c).

Epoxy vinyl phosphonate 2.313c (0.5 g, 1.53 mmol) was reacted to give 2.316c as a yellow oil (0.459 g, 69%). IR (neat) 3412 (br), 2981, 1201 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.24–7.21 (m, 10H), 6.66 (ddd, $J_{HP} = 22.1$, $J_{HH} = 17.3$, 5.7 Hz, 1H), 5.94 (ddd, $J_{HP} = 20.4$, $J_{HH} 17.3$, 1.3 Hz, 1H), 4.45 (q, $J_{HH} = 11.4$ Hz, 2H), 4.44 (s, 2H), 4.10 (m, 1H), 3.9 (m, 4H), 3.75 (m, 1H), 3.46 (m, 2H), 2.49 (d $J_{HH} = 4.7$ Hz, 1H), 1.25 (t, $J_{HH} = 7.1$ Hz, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 148.7 (d, $J_{CP} = 5.1$ Hz), 137.8, 137.4, 128.5, 128.5, 128.0, 127.8, 119.9 (d, $J_{CP}$ = 187.0 Hz), 79.5 (d, $J_{CP} = 21.5$ Hz), 73.5, 72.2, 72.0, 61.9 (d, $J_{CP} = 5.5$ Hz), 16.4 (d, $J_{CP} = 6.2$ Hz); $^{31}$P{$^1$H} NMR (CDCl$_3$) $\delta$ 17.3; HRMS (FAB, MH$^+$) calcd for C$_{23}$H$_{32}$O$_6$P 435.1936, found 435.1938.

![2.316d](image)

(±)-Diethyl (3R,4S,E)-3,5-Bis(benzyloxy)-4-hydroxypent-1-enylphosphonate (2.316d).

Epoxy vinyl phosphonate 2.313d (0.5 g 1.53 mmol) was reacted as above to give 2.316d as a yellow oil (0.493 g, 74%). IR (neat) 3364 (br), 3028, 2980, 2864, 1630, 1225 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.38–7.29 (m, 10H), 6.79 (ddd, $J_{HP} = 22.1$, $J_{HH} = 17.2$, 5.6 Hz, 1H), 6.00 (ddd, $J_{HH} = 20.6$, $J_{HH} = 17.2$, 1.3 Hz, 1H), 4.52 (s, 2H), 4.52 (q, $J_{HH} = 11.5$ Hz, 2H), 4.08 (m, 5H), 3.89 (m, 1H), 3.59 (m, 2H), 2.43 (d, $J_{HH} = 5.3$ Hz, 1H), 1.33 (t, $J_{HH} = 7.1$ Hz, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 149.3, 137.9, 137.6, 128.6, 128.6, 128.0, 128.0, 127.9, 120.0 (d, $J_{CP} = 186.4$ Hz), 79.8 (d, $J_{CP} = 21.6$ Hz), 73.5, 72.3 (d, $J_{CP} = 1.2$ Hz), 70.5, 62.0 (d, $J_{CP}$
= 5.6 Hz, 16.5 (d, J_{CP} = 6.4 Hz); {^{31}P}^{1}H NMR (CDCl_{3}) \delta 17.5. HRMS (FAB, MH^+) calcd for C_{23}H_{32}O_{6}P 435.1936, found 435.1925.

(±)-Diethyl (3S,4S,E)-(5-(Benzyloxy)-4-hydroxy-3-methoxypent-1-enyl)phosphonate (2.325a).

Epoxy vinyl phosphonate 2.313c (0.5 g, 1.53 mmol) was reacted to give 2.325a as a yellow oil (0.364 g, 66%). IR (neat) 3363 (br), 2980, 2912, 1225 cm\(^{-1}\); \(^1\)H NMR; (CDCl\(_3\)) \delta 7.35–7.27 (m, 5H), 6.63 (ddd, J_{HP} = 22.3, J_{HH} = 17.3, 5.7 Hz, 1H), 5.94 (ddd, J_{HP} = 20.5, J_{HH} = 17.3, 1.3 Hz, 1H), 4.51 (q, J_{HH} = 12.1 Hz, 2H), 4.08 (m, 4H), 3.88 (m, 1H), 3.74 (m, 1H), 3.51 (m, 2H), 3.33 (s, 3H), 2.87 (s, br, 1H), 1.28 (t, J_{HH} = 7.1 Hz, 6H); \(^{13}\)C\(^{1}\)H\(^{1}\) NMR (CDCl\(_3\)) \delta 148.5 (d, J_{CP} = 5.2 Hz), 137.9, 128.6, 128.0, 120.1 (d, J_{CP} = 186.9 Hz), 82.1 (d, J_{CP} = 21.5 Hz), 73.7, 72.3, 70.3, 62.1 (d, J_{CP} = 4.8 Hz), 58.1, 16.5 (d, J_{CP} = 6.3 Hz); {^{31}P}^{1}H NMR (CDCl\(_3\)) \delta 17.4; HRMS (FAB, MNa\(^{+}\)) calcd for C\(_{17}\)H\(_{27}\)O\(_{6}\)PNa\(^{+}\) 381.1442, found 381.1436.

(±) Diethyl ((3S,4S,E)-5-(benzyloxy)-4-hydroxy-3-(pentyloxy)pent-1-en-1-yl)phosphonate (2.325b).
Epoxy vinyl phosphonate 2.313c (0.430 g, 1.318 mmol) was reacted to give 2.325b as a yellow oil (0.284 g, 52%). IR (neat) 3363 (br), 2980, 2912, 1225 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.42 – 7.23 (m, 5H), 6.67 (ddd, \(J_{HP} = 22.3, J_{HH} = 17.3, 5.4\) Hz, 1H), 6.10 – 5.79 (m, 1H), 4.67 – 4.41 (m, 2H), 4.21 – 3.92 (m, 5H), 3.76 (br, 1H), 3.61 – 3.45 (m, 3H), 3.37 – 3.33 (m, 1H), 2.62 (d, \(J_{HH} = 4.0\) Hz, 1H), 1.64 – 1.50 (m, 2H), 1.34 – 1.29 (m, 10H), 0.89 (t, \(J_{HH} = 5.8\) Hz, 3H); \(^{13}\)C\{\(^1\)H\} NMR (75 MHz, CDCl\(_3\)) \(\delta\) 149.20 (d, \(J_{CP} = 5.1\) Hz), 137.9, 128.5, 127.9, 119.5 (d, \(J_{CP} = 187.0\) Hz), 80.1 (d, \(J_{CP} = 21.3\) Hz), 73.6, 72.3, 70.6, 70.3, 61.9 (d, \(J_{CP} = 5.5\) Hz), 29.5, 28.3, 22.6, 16.5 (d, \(J_{CP} = 6.1\) Hz), 14.1; \(^{31}\)P\{\(^1\)H\} (121 MHz, CDCl\(_3\)) \(\delta\) 17.6; HRMS (FAB, M\(\text{Na}^+\)) calcd for C\(_{21}\)H\(_{35}\)O\(_6\)P\(\text{Na}^+\) 437.2068, found 437.2063.

\[\text{EtO} \quad \text{P} \quad \text{O} \quad \text{EtO} \quad \text{OH} \quad \text{OBn} \quad \text{OC}_{10}\text{H}_{21}\]

**2.325c**

(±) Diethyl ((3S,4S,E)-5-(benzyloxy)-3-(decyloxy)-4-hydroxypent-1-en-1-yl)phosphonate (2.325).

Epoxy vinyl phosphonate 2.313c (0.600 g, 1.839 mmol) was reacted to give 2.325c as a yellow oil (0.534 g, 60%). IR (neat) 3363 (br), 2980, 2912, 1225 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.38 – 7.28 (m, 5H), 6.79 – 6.54 (m, 1H), 5.95 (m, 1H), 4.60 – 4.49 (m, 2H), 4.0 – 4.49 (m, 5H), 3.78 – 3.65 (m, 1H), 3.61 – 3.45 (m, 3H), 3.36 – 3.29 (m, 1H), 2.58 (d, \(J_{HH} = 3.8\) Hz, 1H), 1.58 – 1.53 (m, 2H), 1.33 – 1.25 (m, 20H), 0.88 (t, \(J_{HH} = 6.2\) Hz, 3H); \(^{13}\)C\{\(^1\)H\} NMR (75 MHz, CDCl\(_3\)) \(\delta\) 149.3 (d, \(J_{CP} = 5.3\) Hz), 138.0, 128.6, 127.9, 119.5 (d, \(J_{CP} = 186.8\) Hz), 80.2 (d, \(J_{CP} = 21.4\) Hz), 73.6, 72.3, 70.7, 70.3, 61.9 (d, \(J_{CP} = 4.7\) Hz), 32.0,
29.9, 29.7, 29.6, 29.5, 26.2, 22.8, 16.5 (d, \( J_{CP} = 6.0 \) Hz), 14.3; \(^{31}\text{P}\{^1\text{H}\} \) NMR (121 MHz, CDCl\(_3\)) \( \delta \) 17.6; HRMS (FAB, MH\(^+\)) calcd for C\(_{26}\)H\(_{46}\)O\(_6\)P 485.3032, found 485.3027.

![2.325d](image)

(±)-Diethyl (3S,4S,E)-5-(Benzyloxy)-4-hydroxy-3-(pentadecyloxy)pent-1-enylphosphonate (2.325d).

Epoxy vinyl phosphonate 2.213c (0.5 g, 1.53 mmol) was reacted as above to give 2.325d as a yellow oil (0.346 g, 41%). IR (neat) 3431 (br), 2920, 2851, 1224 cm\(^{-1}\); \(^1\text{H}\) NMR (CDCl\(_3\)) \( \delta \) 7.39–7.30 (m, 5H), 6.67 (ddd, \( J_{HP} = 22.5, J_{HH} = 17.2, 5.4 \) Hz, 1H), 5.95 (ddd, \( J_{HH} = 20.7, J_{HH} = 17.3, 1.2 \) Hz, 1H), 4.56 (m, 2H), 4.06 (m, 5H), 3.75 (m, 1H), 3.54 (m, 3H), 3.33 (m, 1H), 2.60 (d, \( J_{HH} = 4.5 \) Hz, 1H), 1.56 (m, 2H), 1.30 (m, 30H), 0.88 (t, \( J_{HH} = 6.9 \) Hz, 3H); \(^{13}\text{C}\{^1\text{H}\} \) NMR (CDCl\(_3\)) \( \delta \) 149.3 (d, \( J_{CP} = 5.2 \) Hz), 1387.9, 128.6, 127.9, 119.5 (d, \( J_{CP} = 187.0 \) Hz), 80.1 (d, \( J_{CP} = 21.4 \) Hz), 73.7, 72.3, 70.7, 70.2, 62.0 (d, \( J_{CP} = 4.5 \) Hz), 32.0, 29.9, 29.8, 29.7, 29.7, 29.6, 29.5, 26.2, 22.8, 16.5 (d, \( J_{CP} = 6.1 \) Hz), 14.3; \(^{31}\text{P}\{^1\text{H}\} \) NMR (CDCl\(_3\)) \( \delta \) 17.6; HRMS (FAB, MH\(^+\)) calcd for C\(_{31}\)H\(_{56}\)O\(_6\)P 555.3814, found 555.3790.

![2.325e](image)

(±)-Diethyl (3S,4S,E)-5-(Benzyloxy)-4-hydroxy-3-(4-methoxybenzyloxy)pent-1-enylphosphonate (2.325e).
Epoxy vinyl phosphonate 2.313c (0.423 g, 1.30 mmol) was reacted as above to give 2.325e as a yellow oil (0.512 g, 85%). IR (neat) 3381 (br), 2980, 2904, 2864, 1610, 1241 cm⁻¹; ¹H NMR (CDCl₃) δ 7.39–7.29 (m, 5H), 7.25–7.20 (m, 2H), 6.90–6.85 (m, 2H), 6.73 (ddd, Jₜ婕 = 22.1, J_HH = 17.2, 5.7 Hz, 1H), 6.0 (ddd, J_HP = 20.5, J_HH = 17.3, 1.3 Hz, 1H), 4.51 (s, 2H), 4.45 (q, J_HH = 11.1 Hz, 2H), 4.08 (m, 5H), 3.79 (m, 4H), 3.52 (m, 2H), 1.32 (t, J_HH = 7.1 Hz, 6H); ¹³C{¹H} NMR (CDCl₃) δ 159.5, 148.9 (d, J_CP = 5.3 Hz), 137.9, 129.8, 129.5, 128.5, 127.92, 112.0 (d, J_CP = 186.9 Hz), 114.0, 79.1 (d, J_CP = 21.5 Hz), 73.6, 72.3, 71.8, 70.3, 62.0 (d, J_CP = 4.1 Hz), 55.4, 16.5 (d, J_CP = 6.2 Hz); ³¹P{¹H} NMR (CDCl₃) δ 17.4; HRMS (FAB, MH⁺) calcd for C₂₄H₃₄O₇P 465.2042, found 465.2052.

![Image of 2.325f](image-url)

(±)-Diethyl (3S,4S,E)-5-(Benzyloxy)-3-(cyclohexylmethoxy)-4-hydroxypent-1-enyl)phosphonate (2.325f).

Epoxy vinyl phosphonate 2.313c (0.5 g, 1.53 mmol) was reacted as above to give 2.325f as a yellow oil (0.376 g, 56%). IR (neat) 3356 (br), 2920, 2850, 1232 cm⁻¹; ¹H NMR (CDCl₃) δ 7.36–7.24 (m, 5H), 6.65 (ddd, J_HP = 22.2, J_HH = 17.1, 5.4 Hz, 1H), 5.92 (ddd, J_HP = 20.7, J_HH = 17.2, 1.3 Hz, 1H), 4.51 (m, 2H), 4.02 (m, 5H), 3.75 (m, 1H), 3.50 (m, 2H), 3.19 (m, 2H), 1.68 (m, 5H), 1.54 (m, 1H), 1.23 (m, 10H), 0.89 (m, 2H); ¹³C{¹H} NMR (CDCl₃) δ 149.3 (d, J_CP = 5.1 Hz), 137.9, 128.5, 127.9, 127.8, 119.3 (d, J_CP = 186.9 Hz), 80.1 (d, J_CP = 21.3 Hz), 76.2, 73.6, 72.2, 70.2, 70.0 (d, J_CP = 1.7 Hz), 38.2, 30.1, 30.0, 26.5, 25.8, 16.4 (d, J_CP = 5.7 Hz); ³¹P{¹H} NMR (CDCl₃) δ 17.7 HRMS (FAB, MH⁺) calcd for C₂₃H₃₈O₆P 441.2406, found 441.2387.
(±)-Diethyl (3S,4S,E)-(5-(Benzyloxy)-4-hydroxy-3-methoxypent-1-enyl)phosphonate (2.325g).

Epoxy vinyl phosphonate 2.313c (0.5 g, 1.53 mmol) was reacted to give 2.325g as a yellow oil (0.364 g, 66%). IR (neat) 3363 (br), 2980, 2912, 1225 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.35–7.27 (m, 5H), 6.63 (ddd, $J_{HP} = 22.3$, $J_{HH} = 17.3$, 5.7 Hz, 1H), 5.94 (ddd, $J_{HP} = 20.5$, $J_{HH} = 17.3$, 1.3 Hz, 1H), 4.51 (q, $J_{HH} = 12.1$ Hz, 2H), 4.08 (m, 4H), 3.88 (m, 1H), 3.74 (m, 1H), 3.51 (m, 2H), 3.33 (s, 3H), 2.87 (s, br, 1H), 1.28 (t, $J_{HH} = 7.1$ Hz, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 148.5 (d, $J_{CP} = 5.2$ Hz), 137.9, 128.6, 128.0, 120.1 (d, $J_{CP} = 186.9$ Hz), 82.1 (d, $J_{CP} = 21.5$ Hz), 73.7, 72.3, 70.3, 62.1 (d, $J_{CP} = 4.8$ Hz), 58.1, 16.5 (d, $J_{CP} = 6.3$ Hz); $^{31}$P{$^1$H} NMR (CDCl$_3$) $\delta$ 17.4; HRMS (FAB, MNa$^+$) calcd for C$_{17}$H$_{27}$O$_6$PNa$^+$ 381.1442, found 381.1436.

**General Procedure for Hydrogenation of the Vinyl Phosphonate.**

The vinyl phosphonate (2.316 or 2.325) was dissolved in MeOH (3 mL/mmol) containing pyridine (0.05–0.5 equiv.), and then moist 5% Pd/C (10% by weight of vinyl phosphonate) was added. The flask was flushed with argon, followed by H$_2$ (balloon pressure). H$_2$ pressure was maintained, while the reaction mixture was rapidly stirred. The reaction progress was followed by $^{31}$P NMR spectroscopy. After complete reduction (4–6 h), the reaction mixture was filtered through Celite, rinsed with MeOH, and evaporated under
reduced pressure to give the saturated phosphonate (2.320 or 2.327), typically in quantitative yields.

![Image of 2.320b]

(±)-Diethyl (3S,4S)-3-(Benzyloxy)-4-hydroxynonylphosphonate (2.320b).

Vinyl phosphonate 2.316b (0.339 g, 0.88 mmol) was reduced to give 2.320b in a quantitative yield. IR (neat) 3388 (br), 2928, 2858, 1223 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.36–7.26 (m, 5H), 4.56 (q, \(J_{HH} = 11.3\) Hz, 2H), 4.06 (m, 4H), 3.53 (m, 1H), 3.35 (m, 1H), 1.95 (m, 1H), 1.77 (m, 3H), 1.44 (m, 3H), 1.27 (m, 11H), 0.87 (t, \(J_{HH} = 6.9\) Hz, 3H); \(^13\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta\) 138.1, 128.5, 127.9, 127.8, 81.5 (d, \(J_{CP} = 15.6\) Hz), 72.4 (d, \(J_{CP} = 25.2\) Hz), 61.5 (d, \(J_{CP} = 6.4\) Hz), 33.1, 31.9, 25.5, 22.9 (d, \(J_{CP} = 4.5\) Hz), 22.6, 21.10 (d, \(J_{CP} = 141.3\) Hz), 16.4 (d, \(J_{CP} = 5.9\) Hz), 14.1; \(^31\)P\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta\) 32.4. HRMS (FAB, MH\(^+\)) calcd for C\(_{20}\)H\(_{36}\)O\(_5\)P 387.2300, found 387.2315.

![Image of 2.320c]

(±)-Diethyl (3S,4S)-3,5-Bis(benzyloxy)-4-hydroxypentylphosphonate (2.320c).

Vinyl phosphonate 2.316c (0.450 g, 1.17 mmol) was reduced to give 2.320c in a quantitative yield. IR (neat) 34373 (br), 2979, 2903, 1228 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35 (m, 10H), 4.57 (m, 4H), 4.08 (m, 4H), 3.86 (s, 1H), 3.59 (m, 3H), 2.89 (s, 1H), 1.89 (m, 4H), 1.32 (t, \(J_{HH} = 7.1\) Hz, 6H); \(^13\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta\) 138.0, 137.9,
128.4, 128.0, 127.8, 127.7, 78.6 (d, $J_{CP} = 16.3$ Hz), 73.4, 72.6, 71.2, 71.1, 61.5 (d, $J_{CP} = 6.4$ Hz), 23.3 (d, $J_{CP} = 4.5$ Hz), 21.5 (d, $J_{CP} = 142.0$ Hz), 16.5 (d, $J_{CP} = 6.0$ Hz); $^{31}$P{$^{1}$H} NMR (CDCl$_3$) $\delta$ 32.3; HRMS (FAB, MNa$^+$) calcd for C$_{23}$H$_{33}$O$_6$PNa$^+$ 459.1912, found 459.1906.

(±)-Diethyl (3R,4S)-(3,5-Bis(benzyloxy)-4-hydroxypentylphosphonate (2.320d).

Vinyl phosphonate 2.316d (0.1 g, 0.230 mmol) was reduced to give 2.320d in a quantitative yield. IR (neat) 3246 (br), 2980, 2905, 1201 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.36–7.29 (m, 10H), 4.53 (m, 4H), 4.10 (m, 4H), 3.84 (m, 1H), 3.59 (m, 3H), 2.58 (d, $J_{HH} = 4.6$ Hz, 1H), 1.85 (m, 4H), 1.31 (t, $J_{HH} = 7.1$ Hz, 6H); $^{13}$C{$^{1}$H} NMR (CDCl$_3$) $\delta$ 138.2, 138.0, 128.5, 128.5, 128.0, 127.9, 127.9, 78.6 (d, $J_{CP} = 15.7$ Hz), 73.5, 72.2, 71.2, 71.0, 61.7 (d, $J_{CP} = 6.4$ Hz), 22.6 (d, $J_{CP} = 4.4$ Hz), 20.6 (d, $J_{CP} = 142.0$ Hz), 16.6 (d, $J_{CP} = 6.0$ Hz); $^{31}$P{$^{1}$H} NMR (CDCl$_3$) $\delta$ 33.0; HRMS (FAB, MH$^+$) calcd for C$_{23}$H$_{34}$O$_6$P 437.2093, found 437.2075.

(±)-Diethyl ((3S,4S)-5-(Benzyloxy)-4-hydroxy-3-methoxypentyl)phosphonate (2.327a).

Vinyl phosphonate 2.325a (0.3 g, 0.837 mmol) was reduced to give 2.327a in a quantitative yield. IR (neat) 3385 (br), 2977, 2864, 1226 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.37–1.25
(m, 5H), 4.53 (s, 2H), 4.06 (m, 4H), 3.76 (m, 1H), 3.51 (m, 2H), 3.38 (s, 3H), 3.39 (m, 1H), 1.83 (m, 4H), 1.29 (t, $J_{HH} = 7.0$ Hz, 6H); $^{13}$C{¹H}NMR (CDCl₃) $\delta$ 138.0, 128.6, 127.9, 80.6 (d, $J_{CP} = 16.4$ Hz), 73.6, 76.1, 71.2, 61.7 (d, $J_{CP} = 6.5$ Hz), 58.6, 22.9 (d, $J_{CP} = 4.6$ Hz), 21.3 (d, $J_{CP} = 142.4$ Hz), 16.6 (d, $J_{CP} = 6.0$ Hz); $^{31}$P{¹H} NMR (CDCl₃) $\delta$ 32.3; HRMS (FAB, MNa⁺) calcd for C₁₇H₂₉O₅Na⁺ 383.1599, found 383.1595.

![2.327b](image)

(±)-Diethyl ((3S,4S)-5-(Benzyloxy)-4-hydroxy-3-(pentyloxy)pentyl)phosphonate (2.327b).

Vinyl phosphonate 2.325b (0.672 g, 1.62 mmol) was reduced to give 2.327b in a quantitative yield. IR (neat) 3380 (br), 2928, 2860, 1228 cm⁻¹; $^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.41–7.22 (m, 5H), 4.54 (s, 2H), 4.19–3.98 (m, 4H), 3.81–3.67 (m, 1H), 3.58–3.48 (m, 2H), 3.46–3.38 (m, 2H), 2.58 (br, 1H), 1.94–1.65 (m, 4H), 1.58–1.43 (m, 2H), 1.35–1.20 (m, 10H), 0.88 (t, $J_{HH} = 6.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 138.05, 128.57, 127.95, 127.92, 78.95 (d, $J_{CP} = 16.7$ Hz), 73.62, 71.45, 71.19, 61.68 (d, $J_{CP} = 6.4$ Hz), 29.94, 28.45, 23.52 (d, $J_{CP} = 4.5$ Hz), 22.65, 21.54 (d, $J_{CP} = 142.3$ Hz), 16.61 (d, $J_{CP} = 6.0$ Hz), 14.19; $^{31}$P NMR (121 MHz, CDCl₃) $\delta$ 32.4; HRMS (FAB, MH⁺) calcd for C₂₁H₃₈O₆P 417.2406, found 417.2401.
Vinyl phosphonate 2.325c (0.500 g, 1.03 mmol) was reduced to give 2.327c in a quantitative yield. IR (neat) 3370 (br), 2920, 2850, 1228 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35 – 7.30 (br, 5H), 4.61 – 4.45 (m, 2H), 4.14 – 4.05 (m, 5H), 3.80 – 3.75 (m, 1H), 3.60 – 3.49 (m, 3H), 3.46 – 3.42 (m, 1H), 1.97 – 1.71 (m, 4H), 1.35 – 1.28 (m, 22H), 0.90 (t, \(J_{HH} = 6.4\) Hz, 3H); \(^{13}\)C\(^{\text{\{1H\}}}\)NMR (75 MHz, CDCl\(_3\)) \(\delta\) 137.9, 128.4, 127.8, 127.7, 127.6, 78.8 (d, \(J_{CP} = 16.7\) Hz), 73.5, 71.3, 71.1 (d, \(J_{CP} = 1.9\) Hz), 61.6 (d, \(J_{CP} = 6.4\) Hz), 31.9, 30.1, 29.6, 29.6, 29.5, 29.3, 23.4 (d, \(J_{CP} = 4.6\) Hz), 22.7, 21.4 (d, \(J_{CP} = 142.3\) Hz), 16.5 (d, \(J_{CP} = 6.1\) Hz), 14.1; \(^{31}\)P\(^{\text{\{1H\}}}\)NMR (121 MHz, CDCl\(_3\)) \(\delta\) 32.4; HRMS (FAB, M\(\text{Na}^+\)) calcd for C\(_{26}\)H\(_{48}\)O\(_6\)P 487.3188, found 487.3183.

Vinyl phosphonate 2.325c (0.329 g, 0.593 mmol) was reduced to give 2.327d in a quantitative yield. IR (neat) 3370 (br), 2920, 2850, 1228 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.36–7.31 (m, 5H), 4.55 (s, 2H), 4.09 (m, 4H), 3.76 (s, 1H), 3.52 (m, 3H), 3.42 (m, 2H),
2.50 (s, br, 1H), 1.84 (m, 4H), 1.52 (m, 2H), 1.29 (m, 3OH), 0.88 (t, JHH = 6.9 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl$_3$) δ 138.0, 128.6, 127.9, 127.9, 78.9 (d, $J_{CP} = 16.7$ Hz), 73.6, 71.4, 71.2, 71.1, 61.7 (d, $J_{CP} = 6.4$ Hz), 32.1, 30.2, 29.8, 29.8, 29.6, 29.5, 26.3, 23.4 (d, $J_{CP} = 4.5$ Hz, 22.8, 21.5 (d, $J_{CP} = 142.3$ Hz), 16.6 (d, $J_{CP} = 6.0$ Hz), 14.3; $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl$_3$) δ 32.4; HRMS (FAB, MH$^+$) calcd for C$_{31}$H$_{58}$O$_6$P 557.3971, found 557.3991.

(±)-Diethyl (3S,4S)-5-(Benzyloxy)-4-hydroxy-3-(4-methoxybenzyloxy)pentylphosphonate (2.327e).

Vinyl phosphonate 2.325e (0.380 g, 1.17 mmol) was reduced to give 2.327e in a quantitative yield. IR (neat) 3346 (br), 2978, 2905, 1609, 1241 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.30–7.24 (m, 5H), 7.20–7.17 (m, 2H), 6.84–6.80 (m, 2H), 4.46 (m, 4H), 4.02 (m, 5H), 3.76 (m, 4H), 3.49 (m, 3H), 2.74 (s, 1H), 1.83 (m, 4H), 1.26 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl$_3$) δ 159.3, 137.9, 130.2, 129.7, 128.5, 128.4, 127.9, 127.8, 127.8, 113.8, 78.2 (d, $J_{CP} = 16.5$ Hz), 73.5, 72.3, 71.3, 71.1, 61.6, 61.5, 55.2, 23.3 (d, $J_{CP} = 4.6$ Hz), 21.5 (d, $J_{CP} = 142.0$ Hz), 16.5 (d, $J_{CP} = 6.0$ Hz); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl$_3$) δ 32.3; HRMS (FAB, M$^+$) calcd for C$_{24}$H$_{35}$O$_7$PNa$^+$ 489.2018, found 489.1999.
(±)-Diethyl (3S,4S)-5-(Benzyloxy)-3-(cyclohexylmethoxy)-4-hydroxypentylphosphonate (2.327f).

Vinyl phosphonate 2.325f (0.325 g, 0.737 mmol) was reduced to give 2.327f in a quantitative yield. IR (neat) 3378 (br), 2919, 2850, 1227 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.38–7.29 (m, 5H), 4.55 (s, 2H), 4.07 (m, 4H), 3.75 (m, 1H), 3.51 (m, 2H), 3.30 (m, 3H), 1.79 (m, 11H), 1.26 (m, 9H), 0.90 (m, 2H); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 137.8, 128.3, 127.7, 127.7, 78.7 (d, $J_{CP} = 16.5$ Hz), 73.3, 71.4, 71.1, 61.5 (d, $J_{CP} = 6.4$ Hz), 38.3, 30.0 (d, $J_{CP} = 2.1$ Hz), 26.4, 25.7, 23.2 (d, $J_{CP} = 4.5$ Hz), 22.2, 21.3 (d, $J_{CP} = 148.4$ Hz), 16.4 (d, $J_{CP} = 5.9$ Hz); $^{31}$P{$^1$H} NMR (CDCl$_3$) $\delta$ 33.0; HRMS (FAB, MNa$^+$) calcd for C$_{23}$H$_{39}$O$_6$PNa$^+$ 465.2381, found 465.2390.

**General Procedure for Cyclization.**

To a stirred suspension of sodium hydride (1.1 equiv.) in dry THF (2 mL/mm mol) was added a solution of saturated phosphonate (2.320 or 2.327) in THF dropwise at ice-bath temperature. The reaction mixture was allowed to warm to room temperature and stirring was continued until the reaction was complete (2–3 hr). The reaction was quenched by the addition of 10% NH$_4$Cl and then extracted with EtOAc (three times). The combined organic layer was washed with saturated NaHCO$_3$, brine, and dried over anhydrous Na$_2$SO$_4$. The solution was concentrated under reduced pressure, and the pure phostone (2.323 or 2.328) was isolated by column chromatography (SiO$_2$ 60–80% EtOAc in hexane).
(±)-(5S)-(Benzyloxy)-2-ethoxy-6-pentyl-1,2-oxaphosphinane 2-oxide (2.323b).

Phosphonate 2.320b (0.319 g, 0.83 mmol) was reacted as above to give phostone 2.323b (0.204 g, 73%), which was recrystallized from hexane: mp 82.6 °C. IR (neat) 2924, 2855, 1243 cm⁻¹; ¹H NMR (CDCl₃) δ 7.34–7.26 (m, 5H), 4.53 (q, J_HH = 12.0 Hz, 2H), 4.11 (m, 3H), 3.39 (m, 1H), 2.39 (m, 1H), 1.89 (m, 5H), 1.49 (m, 2H), 1.33 (t, J_HH = 7.0, 3H), 1.24 (m, 4H), 0.86 (t, J_HH = 6.7 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 137.9, 128.5, 127.9, 127.8, 83.2 (d, J_CP = 7.9 Hz), 72.0 (d, J_CP = 5.3 Hz), 70.8, 60.6 (d, J_CP = 6.5 Hz), 32.3 (d, J_CP = 7.4 Hz), 31.6, 25.1, 24.8 (d, J_CP = 7.8 Hz), 22.7, 17.4 (d, J_CP = 128.3 Hz), 16.6 (d, J_CP = 5.6 Hz), 14.2; ³¹P{¹H} NMR (CDCl₃) δ 23.3; HRMS (FAB, MNa⁺) calcd for C₁₈H₂₉O₄PNa⁺ 363.1701, found 363.1704.

(±)-(5S)-5-(Benzyloxy)-6-((benzyloxy)methyl)-2-ethoxy-1,2-oxaphosphinane 2-oxide (2.323c).

Phosphonate 2.320c (0.430 g, 0.985 mmol) was reacted as above to give phostone 2.323c as a pale-yellow product (0.243 g, 61%). IR (neat) 2976, 2924, 2866, 1242 cm⁻¹; ¹H NMR (CDCl₃) δ 7.36–7.26 (m, 10H), 4.50 (m, 4H), 4.37 (m, 1H), 4.13 (m, 2H), 3.79 (m 1H), 3.68 (m, 2H), 2.38 (m, 1H), 2.09 (m, 1H), 1.89 (m, 2H), 1.35 (t, J_HH = 7.0 Hz, 3H); ¹³C{¹H}
NMR (CDCl$_3$) $\delta$ 137.8, 137.7, 128.3, 127.7, 127.6, 127.5, 81.0 ($d, J_{CP} = 7.3$ Hz), 73.1, 70.3, 69.9 ($d, J_{CP} = 5.6$ Hz), 69.3 ($d, J_{CP} = 9.5$ Hz), 60.8 ($d, J_{CP} = 6.5$ Hz), 24.6 ($d, J_{CP} = 8.0$ Hz), 17.2 ($d, J_{CP} = 120.6$ Hz), 16.3 ($d, J_{CP} = 2.8$ Hz); $^{31}$P{$^1$H} NMR (CDCl$_3$) $\delta$ 23.2; HRMS (FAB, MH$^+$) calcd for C$_{21}$H$_{28}$O$_5$P 391.1674, found 391.1680.

(±)-(5R)-5-(Benzyloxy)-6-((benzyloxy)methyl)-2-ethoxy-1,2-oxaphosphinane 2-oxide (2.323d).

Phosphonate 2.320d (0.492 g, 1.13 mmol) was reacted as above to give phostone 2.323d as a yellow oil (0.333 g, 75%). IR (neat) 2925, 2866, 1240 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.27–7.14 (m, 10H), 4.48 (m, 4H), 4.10 (m, 3H), 3.66 (m, 3H), 2.25 (m, 1H), 1.82 (m, 3H), 1.26 (t, $J_{HH} = 7.1$ Hz, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 138.1, 137.6, 128.5, 128.3, 127.9, 127.8, 127.6, 127.64, 81.5 ($d, J_{CP} = 7.5$ Hz), 73.6, 72.7 ($d, J_{CP} = 5.0$ Hz), 72.1, 69.5 ($d, J_{CP} = 7.0$ Hz), 61.2 ($d, J_{CP} = 6.5$ Hz), 26.0 ($d, J_{CP} = 7.7$ Hz), 20.3 ($d, J_{CP} = 128.8$ Hz), 16.4 (d, $J_{CP} = 5.7$ Hz); $^{31}$P{$^1$H} NMR (CDCl$_3$) $\delta$ 23.6; HRMS (FAB, MNa$^+$) calcd for C$_{21}$H$_{27}$O$_5$PNa 413.1493, found 413.1515.

(±)-6-((Benzyloxy)methyl)-2-ethoxy-5-methoxy-1,2-oxaphosphinane 2-oxide (2.328a).

Phosphonate 2.327a (0.216 g, 0.603 mmol) was reacted as above to give phostone 2.328a
as a pale-yellow oil (0.121 g, 64%). IR (neat) 2927, 2867, 1244 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35–7.24 (m, 5H), 4.55 (q, \(J_{HH} = 11.8\) Hz, 2H), 4.31 (m, 1H), 4.10 (m, 2H), 3.69 (m, 2H), 3.41 (m, 1H), 3.20 (s, 3H), 2.39 (m, 1H), 1.96 (m, 1H), 1.76 (m, 2H), 1.31 (t, \(J_{HH} = 7.0\) Hz, 3H); \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta\) 138.0, 128.5, 127.7, 127.8, 81.0 (d, \(J_{CP} = 7.3\) Hz), 77.7, 77.2, 76.8, 73.6, 72.2 (d, \(J_{CP} = 5.6\) Hz), 69.4 (d, \(J_{CP} = 9.4\) Hz), 60.9 (d, \(J_{CP} = 6.5\) Hz), 56.8, 23.8 (d, \(J_{CP} = 8.0\) Hz), 17.1 (d, \(J_{CP} = 128.2\) Hz), 16.5 (d, \(J_{CP} = 5.7\) Hz); \(^{31}\)P\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta\) 23.1; HRMS (FAB, MNa\(^+\)) calcd for C\(_{15}\)H\(_{23}\)O\(_5\)PNa\(^+\) 337.1180, found 337.1182.

\(\pm\)-6-((benzyloxy)methyl)-2-ethoxy-5-(pentyloxy)-1,2-oxaphosphinane 2-oxide (2.328b).

Phosphonate 2.327b (0.300 g, 0.72 mmol) was reacted as above to give phostone 2.328b as a pale-yellow oil (0.132 g, 50%). IR (neat) 2927, 2867, 1244 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.57–7.09 (m, 5H), 4.63–4.49 (m, 2H), 4.37–4.30 (m, 1H), 4.19–4.06 (m, 2H), 3.86–3.77 (m, 1H), 3.70–3.59 (m, 1H), 3.57–3.48 (m, 2H), 3.33–3.17 (m, 1H), 2.47–2.28 (m, 1H), 2.13–1.96 (m, 1H), 1.87–1.68 (m, 2H), 1.57–1.48 (m, 2H), 1.40–1.23 (m, 7H), 0.89 (t, \(J_{HH} = 6.6\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 138.0, 128.5, 127.9, 127.9, 81.2 (d, \(J_{CP} = 7.1\) Hz), 73.8, 70.7 (d, \(J_{CP} = 5.6\) Hz), 69.5, 69.4 (d, \(J_{CP} = 7.2\) Hz, 69.4, 60.9 (d, \(J_{C} = 6.5\) Hz), 29.7, 28.5, 24.7 (d, \(J_{CP} = 8.0\) Hz), 22.6, 17.2 (d, \(J_{CP} = 129\) Hz), 16.5 (d, \(J_{C} = 5.8\) Hz), 14.2; \(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\) 23.4; HRMS (FAB, MH\(^+\)) calcd for C\(_{19}\)H\(_{32}\)O\(_5\)P 371.1987, found 371.1982.
(±)-6-((benzyloxy)methyl)-5-(decyloxy)-2-ethoxy-1,2-oxaphosphinane 2-oxide (2.328c).

Phosphonate 2.327c (0.418 g, 0.85 mmol) was reacted as above to give phostone 2.328c as a pale-yellow oil (0.229 g, 61%). IR (neat) 2927, 2867, 1244 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.43 – 7.26 (m, 5H), 4.55 (q, J_HH = 11.7 Hz, 2H), 4.33 (t, J_HH = 6.3 Hz, 1H), 4.22 – 4.04 (m, 2H), 3.87 – 3.60 (m, 2H), 3.58 – 3.45 (m, 2H), 3.28 – 3.21 (m, 1H), 2.49 – 2.23 (m, 1H), 2.15 – 1.94 (m, 1H), 1.85 – 1.70 (m, 2H), 1.59 – 1.48 (m, 2H), 1.36 – 1.26 (m, 17H), 0.88 (t, J_HH = 6.3 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 138.1, 128.6, 128.0, 127.9, 81.3 (d, J_CP = 7.1 Hz), 73.8, 70.7 (d, J_CP = 5.6 Hz), 69.5, 61.0 (d, J_CP = 6.4 Hz), 32.1, 30.0, 29.8, 29.6, 29.5, 26.4, 24.8 (d, J_CP = 7.9 Hz), 23.0, 17.4 (d, J_CP = 115.9 Hz), 16.5 (d, J_CP = 7.4 Hz), 16.5, 14.3; ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 23.3; HRMS (FAB, MNa⁺) calcd for C₁₂H₂₄O₅P 441.2769, found 441.2764.

(±)-(5S)-6-((Benzyloxy)methyl)-2-ethoxy-5-(pentadecyloxy)-1,2-oxaphosphinane 2-oxide (2.328d).

Phosphonate 2.327d (0.25 g, 0.45 mmol) was reacted as above to give phostone 2.328d as a pale-yellow oil (0.154 g, 67%). IR (neat) 2919, 2850, 1248 cm⁻¹; ¹H NMR (CDCl₃) δ
7.39–7.28 (m, 5H), 4.55 (q, J_HH = 11.7 Hz, 2H), 4.33 (m, 1H), 4.13 (m, 2H), 3.81 (m, 2H), 3.64 (m, 1H) 3.53 (m, 2H), 3.25 (m, 1H), 2.37 (m, 1H), 2.05 (m, 1H), 1.78 (m, 2H), 1.52 (m, 2H), 1.29 (m, 27H), 0.88 (t, J_HH = 6.9 Hz, 3H); $^{13}$C{^1}H NMR (CDCl$_3$) δ 138.0, 128.5, 127.9, 127.8, 81.2 (d, J_CP = 7.3 Hz), 77.6, 77.2, 76.8, 73.7, 70.7, 70.6, 69.4 (d, J_CP = 6.8 Hz), 60.9 (d, J_CP = 6.4 Hz), 32.0, 29.9, 29.8, 29.7, 29.6, 29.5, 26.4, 24.7 (d, J_CP = 7.9 Hz), 22.8, 17.2 (d, J_CP = 128.4 Hz), 16.4 (d, J_CP = 5.7 Hz), 14.2; $^{31}$P{^1}H NMR (CDCl$_3$) δ 23.4; HRMS (FAB, MH$^+$) calcd for C$_{29}$H$_{52}$O$_5$P 511.3552, found 511.3527.

(±)-6-((benzyloxy)methyl)-2-ethoxy-5-((4-methoxybenzyl)oxy)-1,2-oxaphosphinane 2-oxide (2.328e).

Phosphonate 2.327e (0.191 g, 0.40 mmol) was reacted as above to give phostone 2.328e as a pale-yellow oil (0.109 g, 65%). IR (neat) 2928, 2865, 1609, 1297 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.38–1.27 (m, 5H), 7.21 (d, J_HH = 8.5 Hz, 2H), 6.85 (d J_HH = 8.5 Hz, 2H), 4.50 (m, 5H), 4.13 (m, 2H), 3.79 (s, 3H), 3.75 (m 1H), 3.64 (m, 2H), 2.23 (m, 2H), 1.80 (m, 2H), 1.34 (t, J_HH = 7.0 Hz, 3H); $^{13}$C{^1}H NMR (CDCl$_3$) δ 159.3, 137.9, 129.8, 129.4, 128.48, 127.8, 127.8, 113.8, δ 81.2 (d, J_CP = 7.3 Hz), 73.6, 70.5, 69.5, 69.4 (d, J_CP = 2.1 Hz), 60.9 (d, J_CP = 6.5 Hz), 55.3, 17.3 (d, J_CP = 128.25 Hz), 16.5 (d, J_CP = 6.0 Hz); $^{31}$P{^1}H NMR (CDCl$_3$) δ 23.2; HRMS (FAB, MNa$^+$) calcd for C$_{22}$H$_{29}$O$_6$PNa$^+$ 443.1599, found 443.1577.
(±)-6-((Benzyloxy)methyl)-5-(cyclohexylmethoxy)-2-ethoxy-1,2-oxaphosphinane 2-oxide (2.328f).

Phosphonate 2.327f (0.219 g, 0.494 mmol) was reacted as above to give phostone 2.328f as a pale-yellow oil (0.105 g, 53%): IR (neat) 2919, 2849, 1721, 1245 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.42–7.31 (m, 5H), 4.55 (q, \(J_{\text{HH}} = 11.7\) Hz, 2H), 4.37 (m, 1H), 4.17 (m, 2H), 3.85 (m, 1H), 3.68 (m, 1 H), 3.52 (d, \(J_{\text{HH}} = 1.5\) Hz, 1H), 3.22 (m, 2H), 2.42 (m, 1H), 2.07 (m, 1H), 1.86 (m, 7H), 1.55 (m 1H), 1.37 (t, \(J_{\text{HH}} = 7.0\) Hz, 3H), 1.22 (m, 3H), 0.96 (2H); \(^{13}\)C\(^{1}\)H NMR (CDCl\(_3\)) \(\delta\) 138.0, 128.6, 127.9, 81.3 (d, \(J_{\text{CP}} = 7.2\) Hz), 75.2, 73.8, 70.7 (d, \(J_{\text{CP}} = 5.6\) Hz), 69.5 (d, \(J_{\text{CP}} = 9.6\) Hz), 60.9 (d, \(J_{\text{CP}} = 6.5\) Hz), 38.3, 30.2 (d, \(J_{\text{CP}} = 1.2\) Hz), 26.7, 26.0, 24.5 (d, \(J_{\text{CP}} = 8.0\) Hz), 17.3 (d, \(J_{\text{CP}} = 128.5\) Hz), 16.6 (d, \(J_{\text{CP}} = 5.8\) Hz), 16.4; \(^{31}\)P\(^{1}\)H NMR (CDCl\(_3\)) \(\delta\) 23.5; HRMS (FAB, MNa\(^+\)) calcd for C\(_{21}\)H\(_{33}\)O\(_3\)PNa 419.1963, found 419.1974.
2.9 References


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Chapter III

3 Synthesis of phostones and carbohydrate methylene phosphonate as a Lipid A Antagonists

3.1 Introduction

Sepsis is a condition caused by body’s response to an infection that results in the whole-body inflammation. When the sepsis progresses to septic shock the result is typically death. Most often sepsis occurs in people who are hospitalized or recently hospitalized. Sepsis is associated with a high mortality rate. According to CDC, each year 1.7 million of American develops sepsis and 270,000 death are related to sepsis.\(^1\) The development of septicemia is often related to the release of bacterial endotoxin called as Lipopolysaccharide (LPS) into the blood stream.\(^2\-^3\)

3.2 Structure of LPS

LPS (Figure 3.1) is an essential component of Gram-negative bacteria and is structurally comprised of three distinct regions. LPS is similar in all Gram-negative bacteria consisting of core oligosaccharide, as serotype specific sugar chain and a Lipid A structure.\(^4\)

Lipid A consists of β (1,6) linked disaccharide core with phosphate esters at C1 and C4’ and usually six asymmetrically bound C12-C14 fatty acids. The pathogenicity is highly correlated with LPS. It is found that there are increased levels of LPS in patients with sepsis. In some cases, the increased LPS level have also been found in patients with Gram-positive bacterial and fungal infection too. Peptidoglycan and Lipoteichoic acid from
Gram-positive bacteria are also responsible for the inflammation in the patients, but they are less potent than LPS.\(^4\)

![Figure 3.1 Structure of E. Coli LPS](image)

**Figure 3.1 Structure of E. Coli LPS**

### 3.3 Signaling Pathways

As described above, sepsis is a systematic inflammation caused in response to bacterial antigens. Gluck and Opal have clearly described that, “Lipid A is responsible for the toxicity leading to inflammation, where the key molecules in this process are LPS-binding serum proteins i.e. LPS binding protein (LBP), CD11/CD18/CD14 complex and the Toll Like Receptor (TLR) on the monocyte and macrophages.”\(^4\) An important receptor that recognizes the LPS is TLR4 (Toll Like Receptor 4). The signaling pathway begins with the binding of LPS with LPS binding protein (LBP), which then interacts with the CD14. The recognition of this complex by TLR4 requires small myeloid differentiation protein-2 (MD-2).\(^5\) This activated LPS is now responsible for the propagation of LPS signal inside the cell, that develops signaling pathway inside the cells and leads to the production of pro-inflammatory molecules (cytokines, TNF\(\alpha\)).\(^3\)
3.4 Therapeutic Strategies

Various therapeutic strategies are applied for the treatment of sepsis. The major therapeutic strategies employed includes neutralizing LPS or blocking early LPS-induced signaling events; blocking the intracellular signals induced by endotoxin; inhibiting the release of cytokines and cellular mediators; and blocking the paracrine effects of inflammatory mediators produced by the infected cells.\textsuperscript{4,6} There is the lack of complete understanding of the pathogenicity of LPS, which limits the development of antimicrobial agents. The most potent therapeutic strategy could be the one which prevents the binding of LPS with LPS binding protein. This could prevent the generation of a signaling cascade, thus preventing the sepsis.\textsuperscript{6} The molecules that prevent the binding of LPS with LBP act as Lipid A antagonists. Various natural and synthetic analogs of Lipid A have been developed that act as antagonists and block LPS binding.\textsuperscript{7} Findings from these studies have provided a myriad of information about the structure activity relationship of Lipid A, but still remains a huge need for effective antagonists. It has been well documented that not only the disaccharide that closely resembles to Lipid A are antagonist, but monosaccharides with variations in the substituent are also active as antagonists (Figure 3.2).\textsuperscript{7}

3.5 Development of Lipid A mimetics

Closely examining the structure 3.3 – 3.7 it is evident that replacing glucosamine and acyl groups by more robust ether groups can also maintain the antagonistic activity. Lipid X (3.3) is a biosynthetic precursor of the lipid A but lacks both endotoxic and immunostimulatory properties.\textsuperscript{5} However, derivatives of Lipid X have shown to as antagonist of lipid A or LPS. On the other spectrum, Boons et. al. have reported that the
disaccharide 3.2 bearing a lactone moiety at reducing end also possess antagonistic activity.\textsuperscript{7-9}

![Chemical structures](image)

**Figure 3.2 Structure of Lipid X (3.3) and lipid A antagonists (3.2, 3.4 - 3.7)**

To modulate the structure of Lipid X (3.3) in order to explore lipid A antagonist, we proposed two concepts based on the phosphonates. The first method involves the replacement of the labile phosphate group with methylene phosphonate, and the acyl group with more robust ether group, while the second incorporates the phosphonate in the ring. Thus, in this dissertation, phostones (cyclic phosphonate) and phosphonosugar analogs will be developed and tested for their antagonistic property.

### 3.6 Results and Discussion

As mentioned in the above section, this works will be divided in two parts.
3.6.1 Methylene phosphonate analogs of the anomeric phosphate

The synthesis of different analogs based on the methylene phosphonates were earlier achieved by Spilling’s group (Scheme 3.1). The synthesized compounds were tested to identify the antagonistic property. The synthesis of Lipid X mimetics initially followed literatures procedures starting from penta-O-acylated glucose (3.8). Pentaacetyl glucose was converted to tetraacylated β-thioglucoside (3.9). The removal of the acyl esters was carried out to give (3.10) which was then selectively converted to benzylidene protected thioglycoside (3.11). The benzylidene protected thioglycoside was then subjected to O-alkylation using alkyl halide in the presence of a base. This resulted in the fully protected compound (3.12).

Scheme 3.1 Synthesis of methylene phosphonate analogs of glucose
The hydrolysis of the thiophenyl moiety was carried out to give hydroxyl group at anomeric position (3.13), which was then subjected to the Horner-Wadsworth-Emmons (HWE) reaction for the introduction of methylene phosphonate. This reaction resulted in the formation of four diastereomers containing glucose and mannose analogs, which were separated by preparative HPLC. The four diastereomers were identified to be α- and β-anomers of glucose and mannose analogs. Glucose analogs (3.14) were further subjected to either hydrogenolysis or selective cleavage of benzylidene ring to get methylene phosphonate analog of Lipid X.

As it was shown that a disaccharide lactone shows the antagonistic activity, we decided to prepare the lactone derivative of Lipid X. For this purpose, compound (3.13) was subjected to oxidation to get the lipid X D-gluconolactone derivative (3.17) (Scheme 3.2). Thus, the obtained glucono lactone could be also subjected to either hydrogenolysis or selective cleavage of the benzylidene ring.

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{O} & \quad \text{OH} \\
C_{14}H_{29} & \quad \text{O} & \quad \text{OC}_{14}H_{29}
\end{align*}
\]

\[
\begin{align*}
\text{NMO, DCM} & \quad \text{TPAP} & \quad 2-3 \text{ hr}, 85\% \\
\text{O} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
C_{14}H_{29} & \quad \text{O} & \quad \text{OC}_{14}H_{29}
\end{align*}
\]

\[
\begin{align*}
15\% \text{TFA} & \quad \text{DCM wet} & \quad \text{rt, 1hr}, 77\% \\
\text{HO} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 3.2 Anomeric oxidation and hydrogenolysis to get D-glucono-δ-lactone}
\end{align*}
\]

Based on Schemes 3.1 and 3.2 the following library of compounds were prepared and selected for the test of antagonistic properties.
The initial proposal was to test the biological activity of all the compound library synthesized to evaluate the anti-inflammatory potential against LPS-induced human acute monocytic leukemia (THP-1) cells. Completely protected compound Compounds 3.14α and 3.14β were insoluble in DMSO for the biological test, while the compounds 3.16α, and 3.16β were also not soluble enough to be tested. The initial test was performed with 3.15α and 3.18 preincubating THP-1 cells with the compounds prior to cell stimulation with of *E. coli* LPS. Modulation of TNFα production was analyzed *in vitro* and measured by ELISA. Spilling’s group investigated the antagonistic property of D-glucono-δ-lactone derivative 3.18, which showed antagonistic property by dose dependent manner. The production of TNFα was reduced by 41% at the lowest tested concentration of 1 μM, which was further reduced to 52% and 64% with increased concentration of 3 μM and 10 μM respectively. However, compound 3.15α did not demonstrate LPS antagonism. In this dissertation work, the problem related to the solubility was addressed for compounds 3.15α and 3.15β. We thought that the solubility issue could be resolved by the deprotection of the phosphonate that could result in the formation of phosphonic acid. For this purpose, compounds 3.15α and 3.15β were subjected to cleave the methyl protecting group at the phosphorus atom, to get phosphonic acid by treating with excess of TMSBr and then stirred.
with MeOH and few drops of water, which resulted in the precipitation of 3.19α and 3.19β (Scheme 3.4).9-10

Scheme 3.4 Cleavage of methyl group to obtain phosphonic acid

Compounds (3.19α, 3.19β) were then evaluated for anti-inflammatory potential against LPS-induced human acute monocytic leukemia (THP-1). These compounds were far more soluble in DMSO, but the data suggested possible aggregation. Both of these compounds displayed antagonistic property in the dose dependent manner. The biological test was performed in Prof. Nichols’s lab (Figure 3.3).

Figure 3.3 LPS antagonistic activity of 3.19β (blue) and 3.19α (red)
According to the data obtained, α-anomer is more promising than the β-anomer, but the same issue of solubility is the factor again. The issue related to solubility could be resolved by functionalizing selectively at C4 and C6, which is also the future direction.

3.6.2 Synthesis of phostone analogs as LPS antagonists

Phostones or the phosphonosugars are hydroxyl substituted cyclic phosphonates. Details about the biological importance and the synthetic methodology available in the literature was discussed in chapter I and chapter II. In a nutshell, the traditional synthetic method relies on the reaction of aldehydes derived from carbohydrates and dimethyl or trimethyl phosphite followed by the cyclization of the intermediate phosphonate. Other methods used include a ring closing metathesis strategy. These methods suffer from selectivity and limited structural variation. In order to solve this problem, we investigated a de novo method for the synthesis of phostones which employs the chemistry of γ,δ-epoxy vinyl phosphonate. This is discussed in depth in chapter II.

The primary goal was to apply the asymmetric synthetic pathway for the synthesis of phostones and further extend the scope of the compounds developed in chapter I to form the analogs with potential LPS antagonistic property. In order to proceed through the asymmetric synthesis, the following synthetic pathway was designed.

The synthesis begins with the asymmetric epoxidation of allylic alcohols (3.20), which can be obtained by Sharpless asymmetric epoxidation. The substitution R (3.20) can be varied according to the synthetic requirement. The following step is the oxidation of the epoxy alcohol (3.21) to the epoxy aldehyde (3.22), which can be achieved in the same manner as described in chapter I. Epoxy aldehyde (3.22) on reaction with either tetraethyl
(or tetramethyl) methylenebisphosphonate (3.23) under HWE conditions result in the formation of γ,δ-epoxy vinyl phosphonate (3.24).\textsuperscript{12-13}

\begin{equation}
\text{Scheme 3.5: General strategy for the synthesis of phosphonosugars}
\end{equation}

We have investigated the palladium catalyzed opening of epoxide ring in a stereospecific and regioselective manner using different alcohols as nucleophile. The trans- and cis-epoxide lead to the formation of syn and anti- monoprotected diol as a single diastereomer respectively.\textsuperscript{14-17} To further functionalize the double bond, the free alcohol needs to be protected, which can be done by the introduction of benzoate group. The double bond of the vinyl phosphonate can be subjected to Sharpless Asymmetric Dihydroxylation\textsuperscript{18-19}, using an asymmetric variant as needed in order to control the stereochemistry. Double alkylation\textsuperscript{20} followed by cyclization should yield the phosphonosugar (3.30).

The initial work started with trans-4-benzyloxy-2-butene (3.20a). The Sharpless asymmetric epoxidation was brought about by TBHP (4.0 eq), in the presence of titanium
isopropoxide (1.1 eq), and (-)-DET (1.1 eq) at -25 to -30°C. The reaction was carried out for 5 hrs. The ee of epoxy alcohol was determined by chiral AD-H column eluting with 5% IPA in Hexane and found to be 94%. The epoxy aldehyde (3.22a) was obtained by oxidation of the epoxy alcohol in the presence of the pyridine sulphur trioxide complex, DMSO and triethyl amine. The epoxy aldehyde was then further subjected to HWE reaction in order to get the γ, δ-epoxy vinyl phosphonate (3.24a). The reaction was smooth with 85% yield. The ee of compound (3.24a) was determined to be 94%. The critical step was the opening of the epoxide ring with the nucleophile under palladium catalysis. We have demonstrated the opening of the epoxy ring with various nucleophiles resulting in the formation of single diastereomer. We utilized the method developed and carried out the reaction with benzyl alcohol as the nucleophile in the presence of Pd$_2$dba$_3$ catalyst, dppe ligand and B(OPh)$_3$ as the cocatalyst. The reaction resulted in the δ-hydroxy vinyl phosphonate (3.25a) in good yield. Before functionalization of the alkene, the free hydroxyl group needs to be protected, in this case in the form of an ester. The benefit of this is that removal of ester under basic conditions can be brought about at the same time as the final cyclization. Depending upon the requirements, the free alcohol can be converted to silyl ether as well. For our initial work, the alcohol was treated with benzoyl chloride in presence of pyridine, to obtain (3.27a). The hydroxylation of alkene have not been investigated in our previous work, but it is evident from the literature that, asymmetric dihydroxylation is achievable.\textsuperscript{18-19}

With 3.27a in hand, the attempted dihydroxylation of the double bond was carried out with AD-mix-α and AD-mix-β separately. Unfortunately, no product was obtained and only starting material was recovered after stirring for 3 days (Scheme 3.7).
Scheme 3.6 Synthesis of 3.26a starting from allylic alcohol 3.19a

The dihydroxylation reaction was also carried out with δ-hydroxy vinyl phosphonate (3.25a), but no product was observed.

Scheme 3.7 Attempted dihydroxylation of vinyl phosphonate

This failure suggests that, there is the necessity of finding an alternative reaction in order to increase the functionality. There are other ways to functionalize the alkene of vinyl phosphonates. Asymmetric hydroboration or the addition of sulphur or selenium
nucleophile could also be possible. In a single attempt, reaction of 3.27a was carried out with bispinacolactoneborane (3.31), CuCl, (R,R)-Et-Duphos (3.32) as the ligand, and potassium tertiary butoxide as the base, but no product was observed. This reaction needs more investigation, as this type of reaction have been previously observed with highly functionalized vinyl phosphonates by Spilling and coworkers. Yun and coworkers have also recently reported the copper-catalyzed asymmetric β-borylation of selected vinyl phosphonates.21

![Scheme 3.8 Attempted asymmetric hydroboration](image)

If this reaction worked, then further oxidation and cyclization would yield phostones with an increased level of substitution. This should be a future direction for this project. Again, the substitution level can be increased by reaction of (3.25a) with benzaldehyde in the presence of base to yield acetal 3.34 (Scheme 3.9). This type of acetal protection have been observed in case of analogous unsaturated esters.19
With the above findings, we turned to the synthesis of phostone analogs prepared from the racemic epoxide in chapter II. The initial attempt was to carry out the Williamsons etherification reaction to obtain the long chain ether derivatives. For this purpose, compound 2.323c and 2.328d (Chapter II) were selected. These compounds were first subjected to hydrogenolysis and then treated with alkyl bromide under basic condition. Unfortunately, the product was not obtained. This could possibly be due to ring opening of phosphonate ester under basic condition leading to phosphonic acid (Scheme 3.10).

With this unsuccessful result, we considered other methods to insert the long chain at C6 position. To attain the long chain at C6, we started from the first step and reacted 1,4-butyne-diol (3.38) with 1-bromo tetradecane, which was then reduced to a trans alkene with Red Al. The epoxidation reaction was carried out followed by oxidation of primary
alcohol as previously reported. The resulting aldehyde (3.42) was then subjected to the HWE reaction, which resulted in the formation of \( \gamma,\delta \)-epoxy vinyl phosphonate (3.43) with a long C14 chain. Epoxide ring opening reaction using the method described above resulted in the formation of \( \delta \)-hydroxy phosphonate (3.44), which was then hydrogenated to obtain the saturated phosphonate. This phosphonate was then subjected cyclization to obtain the phostone (Scheme 3.11).

Scheme 3.11 Synthesis of phostone analog

With this accomplishment, we decided to look at synthesis of acylated analogs of phostone. For this purpose, phostones 2.323c and 2.328c prepared from chapter II were selected. This selection was based on the availability of an acylating partner. The
compounds \textbf{2.323c} and \textbf{2.328c} were initially hydrogenated to get free hydroxy group, which was then subjected to acylation to get product \textbf{3.48a} and \textbf{3.48b} \textbf{(Scheme 3.12)}.  

![Chemical reaction diagram]

\textbf{Scheme 3.12 Synthesis of acylated analog of phostone}

With these analogs of phostone, the next step was to obtain the free hydroxyl group at phosphorus atom. This was accomplished by reacting the phostone analogs \textbf{3.46}, \textbf{3.48a} and \textbf{3.48b} with TMSBr followed by the treatment with methanol and water \textbf{(Scheme 3.13)}. The purpose of this was to investigate the antagonistic property of these compounds against LPS. The evidence from this should provide guidance for future modification of the phostone to make them potential LPS antagonist.

![Chemical reaction diagram]

\textbf{Scheme 3.13 Cleavage of ethyl group to obtain phosphonic acid}

All these compounds were obtained in their solid form in decent yields. The selected compounds \textbf{3.49a}, and \textbf{3.49b} were submitted to evaluate their biological activity.
3.7 Summary

In summary, we described the methods for the preparation of lipid X analogs, with antagonistic property against LPS and acting to reduce the production of TNFα. This investigation provides the scientific community information about the structure activity relationship of lipid A antagonist and shows that small change in the structure also brings a considerable change in the activity of the molecule. Still the phosphonic acids prepared are not highly soluble in DMSO, but it is predicted that the solubility can be increased by introducing amino or phosphate or the phosphonate groups at either C4-OH or C6-OH position.

We also expanded the scope of the methodology developed for the synthesis of phostones and provided future directions. The functionalization of the alkene moiety needs further investigation. Still there are ways to increase the substitution level of the phostones, which are the future directions.

The newly synthesized phostones, upon testing, should provide more insight into their potential as LPA antagonist. It is also possible that the phostones can tested for their antimicrobial property too.
3.8 General Experimental

General Experimental Procedures

All the compounds from 3.8 to 3.16 were prepared by Chris Tipton in his work. In this dissertation, free phosphonic acid was prepared as a novel compound. Along with some of the compounds were resynthesized for characterization purpose.

Phenyl 4,6-O-benzylidene-2,3-di-O-tetradecyl-1-thio-β-D-glucopyranoside (3.12)

\[
\text{[α]}^{23.160}_{\text{D}} = -19.14^\circ (c = 1.0, \text{CHCl}_3); \text{IR}(\text{neat}) 3060, 2913, 2846, 1461, 1078 \text{ cm}^{-1}; \text{^1H NMR (600 MHz, CDCl}_3\delta 7.56 - 7.46 (m, 4H), 7.40 - 7.28 (m, 6H), 5.55 (s, 1H), 4.66 (d, } J_{\text{HH}} = 9.8 \text{ Hz, 1H), 4.36 (dd, } J_{\text{HH}} = 10.5, 5.0 \text{ Hz, 1H), 3.86 (dt, } J_{\text{HH}} = 9.2, 6.6 \text{ Hz, 1H), 3.81 - 3.75 (m, 3H), 3.70 (dt, } J_{\text{HH}} = 9.3, 6.8 \text{ Hz, 1H), 3.58 - 3.50 (m, 2H), 3.45 - 3.38 (m, 1H), 3.22 (dd, } J_{\text{HH}} = 9.6, 8.0 \text{ Hz, 1H), 1.64 - 1.55 (m, 4H), 1.41 - 1.23 (m, 44H), 0.89 (t, } J_{\text{HH}} = 7.0 \text{ Hz, 6H); } \text{^13C}\{\text{^1H}\} \text{ NMR (151 MHz, CDCl}_3\delta 137.5, 133.7, 132.2, 129.1, 129.1, 128.4, 127.8, 126.2, 101.2, 88.7, 83.5, 81.4, 81.0, 74.3, 73.8, 70.5, 68.9, 32.2, 30.6, 29.9, 29.9, 29.9, 29.8, 29.8, 29.6, 26.4, 22.9, 14.3; HRMS (ESI, MH\text{+}) \text{ calcd for C}_{47}\text{H}_{77}\text{O}_{5}\text{S 753.5491, found.753.5486.}
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4,6-O-benzylidene-2,3-di-O-tetradecyl-α/β-D-glucopyranose (3.13)
[α]^{22.72°}_{D} = -14.44° (c = 1.0, CHCl₃); IR(neat) 3413, 2912, 2846, 1465, 1088 cm⁻¹; \(^1^H\) NMR (300 MHz, CDCl₃) δ 7.54 – 7.46 (m, 2H), 7.40 – 7.36 (m, 3H), 5.54 (s, 1H), 5.30 (d, \(J_{HH} = 3.6\) Hz, 0.5H), 4.72 (d, \(J_{HH} = 7.6\) Hz, 0.5H), 4.38 – 4.23 (m, 1H), 4.05 (td, \(J_{HH} = 9.9, 4.9\) Hz, 1H), 3.91 – 3.79 (m, 2H), 3.78 – 3.64 (m, 4H), 3.59 – 3.48 (m, 1H), 3.48 – 3.34 (m, 1H), 3.14 (t, \(J_{HH} = 8.1\) Hz, 1H), 1.71 – 1.52 (m, 4H), 1.31 – 1.29 (m, 44H), 0.89 (t, \(J_{HH} = 6.4\) Hz, 6H); \(^1^C\{^1^H\} NMR (75 MHz, CDCl₃) δ 137.6, 137.5, 129.0, 128.3, 126.2, 126.1, 101.3, 101.2, 97.9, 92.2, 83.6, 81.8, 81.5, 81.4, 80.5, 78.4, 73.9, 73.7, 72.3, 69.2, 68.8, 66.4, 62.7, 32.1, 30.5, 30.3, 29.9, 29.8, 29.7, 29.6, 26.3, 26.2, 22.9, 14.3; HRMS (ESI, MH⁺) calcd for C₄₁H₇₃O₆ 661.5407, found 661.5402.

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\text{2,6-Anhydro-5,7-}O\text{-benzyldene-1-deoxy-1-dimethylphosphono-3,4-di-}O\text{-tetradecyl-D-glycero-D-gulo/ido-heptitol (3.14).}
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D-Glycero-D-ido: [α]^{22.39°}_{D} = -18.04° (c = 1.0, CHCl₃); IR(neat) 2913, 2846, 1463, 1235, 1023 cm⁻¹; \(^1^H\) NMR (300 MHz, CDCl₃) δ 7.50 – 7.47 (m, 2H), 7.39 – 7.32 (m, 3H), 5.59 (s, 1H), 4.24 (dd, \(J_{HH} = 10.3, 4.9\) Hz, 1H), 4.04 – 3.97 (m, 2H), 3.94 – 3.81 (m, 2H), 3.79 – 3.69 (m, 8H), 3.66 – 3.59 (m, 1H), 3.57 – 3.49 (m, 2H), 3.47 – 3.37 (m, 1H), 2.21 (ddd, \(J_{HP} = 18.4, J_{HP} = 6.5, 1.2\) Hz, 2H), 1.65 – 1.53 (m, 4H), 1.37 – 1.25 (m, 44H), 0.88 (t, \(J_{HH} = 6.7\) Hz, 6H); \(^1^C\{^1^H\} NMR (151 MHz, CDCl₃) δ 140.2, 131.3, 130.7, 128.6, 103.8, 83.6, 81.2, 80.5 (d, \(J_{CP} = 8.0\) Hz), 77.3, 76.9, 74.5, 74.2, 71.0, 55.3 (d, \(J_{CP} = 6.5\) Hz), 54.7 (d, \(J_{CP} = 6.5\) Hz), 34.5, 32.9, 32.7, 32.3, 32.3, 32.2, 32.1, 32.0, 29.9 (d, \(J_{CP} = 142.1\) Hz), 28.7
(d, J<sub>CP</sub> = 5.1 Hz), 25.3, 16.7; 31P{<sup>1</sup>H} NMR (121 MHz, CDCl<sub>3</sub>) δ 31.1; HRMS (ESI, MH<sup>+</sup>) calcd for C<sub>44</sub>H<sub>80</sub>O<sub>8</sub>P 767.5590, found 767.5657

**D-Glycero-D-gulo:** [α]<sup>22.28</sup> D -22.21° (c = 1.0, CHCl<sub>3</sub>); IR(neat) 2912, 2847, 1469, 1240, 1025 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.50 – 7.43 (m, 2H), 7.43 – 7.31 (m, 3H), 5.52 (s, 1H), 4.31 (dd, J<sub>HH</sub> = 10.3, 4.6 Hz, 1H), 3.95 – 3.82 (m, 2H), 3.78 – 3.62 (m, 9H), 3.58 – 3.42 (m, 4H), 3.12 – 2.95 (m, 1H), 2.43 – 2.31 (m, 1H), 2.04 – 1.83 (m, 1H), 1.59 – 1.53 (m, 4H), 1.26 – 1.24 (m, 44H), 0.88 (t, J<sub>HH</sub> = 6.7 Hz, 6H); 13C{<sup>1</sup>H} NMR (151 MHz, CDCl<sub>3</sub>) δ 140.0, 131.5, 130.8, 128.6, 109.9, 103.7, 85.7 (d, J<sub>CP</sub> = 2.8 Hz), 84.8 (d, J<sub>CP</sub> = 14.7 Hz), 84.6, 77.9 (d, J<sub>CP</sub> = 6.6 Hz), 76.4, 75.9, 73.1, 71.3, 55.1 (d, J<sub>CP</sub> = 6.3 Hz), 34.5, 33.06 (d, J<sub>CP</sub> = 6.0 Hz), 32.3, 32.3, 32.22 (d, J<sub>CP</sub> = 1.8 Hz), 32.0, 30.9 (d, J<sub>CP</sub> = 143.6 Hz), 28.83 (d, J<sub>CP</sub> = 2.2 Hz), 25.3, 16.7; 31P{<sup>1</sup>H} NMR (121 MHz, CDCl<sub>3</sub>) δ 31.1; HRMS (ESI, MH<sup>+</sup>) calcd for C<sub>43</sub>H<sub>80</sub>O<sub>8</sub>P 767.5590, found 767.5657

![Structural formula](image)

**3.15β**

2,6-Anhydro-1-deoxy-1-demethyl phosphono-3,4-di-O-tetradecyl-D-glycero-D-gulo-heptitol (3.15β).

Compound 3.14β (0.210 g, 0.274 mmol) was dissolved in 4 ml of 15% TFA in DCM (v/v) and stirred for 5 minutes, then 4 drops of water was added. The reaction was stirred at room temperature for 1 hr till completion as observed by TLC. The reaction was concentrated in vacuo and azeotroped with toluene and pure 3.15β (0.145 g, 78%) was obtained after prep HPLC separation. [α]<sup>22.28</sup> D -86.37° (c = 1.0, CHCl<sub>3</sub>); IR(neat) 3250 (br), 2914, 2847, 1462, 1221, 1026 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 3.89 – 3.68 (m, 11H), 3.60 – 3.42.
(m, 4H), 3.36 – 3.28 (m, 1H), 3.22 (t, J$_{HH}$ = 9.0 Hz, 1H), 2.95 (t, J$_{HH}$ = 9.2 Hz, 1H), 2.32 (ddd, J$_{HP}$ = 19.8, J$_{HH}$ = 15.4, 2.2 Hz, 1H), 2.04 – 1.85 (m, 2H), 1.63 – 1.46 (m, 4H), 1.34 – 1.18 (m, 44H), 0.87 (t, J$_{HH}$ = 7.0 Hz, 6H); $^{13}$C{$^1$H} NMR (151 MHz, CDCl$_3$) δ 88.9 (d, J$_{CP}$ = 2.9 Hz), 85.0 (d, J$_{CP}$ = 14.3 Hz), 82.2, 77.0 (d, J$_{CP}$ = 7.1 Hz), 76.3, 76.0, 73.5, 65.1, 55.2 (d, J$_{CP}$ = 6.4 Hz), 55.1 (d, J$_{CP}$ = 6.4 Hz), 53.3, 34.5, 33.1 (d, J$_{CP}$ = 13.8 Hz), 32.3, 32.3, 32.3, 32.3, 32.3, 32.2, 32.2, 32.0, , 30.6 (d, J$_{CP}$ = 143.5 Hz), 828.8 (d, J$_{CP}$ = 2.1 Hz), 25.3, 16.7; $^{31}$P{$^1$H} NMR (243 MHz, CDCl$_3$) δ 28.8; HRMS (ESI, MH$^+$) calcd for C$_{37}$H$_{76}$O$_8$P 679.5277, found 679.5272

![Chemical Structure](image)

$^{3.15\alpha}$

2,6-Anhydro-1-deoxy-1-demethylphosphono-3,4-di-O-tetradecyl-D-glycero-D-ido-heptitol (3.15$\alpha$).

Compound 3.14$\alpha$ (0.196 g, 0.255 mmol) was dissolved in 4 ml of 15% TFA in DCM (v/v) and stirred for 5 minutes, then 4 drops of water was added. The reaction was stirred at room temperature for 1 hr till completion as observed by TLC. The reaction was concentrated in vacuo and azeotroped with toluene and pure 3.15$\alpha$ (0.27 g, 75%) was obtained after prep HPLC. [α]$^{22,39\alpha}$D − 11.30° (c = 1.0, CHCl$_3$); IR(neat) 3500 – 3150(br), 2954, 2914, 2847, 1462, 1026 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 3.88 (dd, J$_{HH}$ = 11.6, 3.4 Hz, 1H), 3.85 – 3.79 (m, 2H), 3.78 – 3.69 (m, 10H), 3.49 – 3.40 (m, 2H), 3.36 (ddd, J$_{HH}$ = 9.6, 6.2, 3.6 Hz, 1H), 3.25 (dd, J$_{HH}$ = 9.4, 2.5 Hz, 1H), 2.52 (br, 1H), 2.25 (dd, J$_{HP}$ = 15.2, J$_{HH}$ = 6.9 Hz, 1H), 2.13 (dd, J$_{HP}$ = 15.2, J$_{HH}$ = 6.0 Hz, 1H), 1.67 – 1.51 (m, 4H), 1.39 – 1.21 (m, 44H), 0.88 (t, J$_{HH}$ = 7.0 Hz, 6H); $^{13}$C{$^1$H} NMR (151 MHz, CDCl$_3$) δ 84.8, 79.8, 75.4 (d, J$_{CP}$ =
8.5 Hz), 73.7 (d, $J_{CP} = 3.8$ Hz), 70.3, 67.5, 63.3, 52.8 (d, $J_{CP} = 6.5$ Hz), (52.5), 32.1, 30.5, 30.2, 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 27.6 (d, $J_{CP} = 142.2$ Hz), 26.3, 26.3, 22.9, 14.3; $^{31}$P{$_1$H} NMR (243 MHz, CDCl$_3$) $\delta$ 28.2; HRMS (ESI, MH$^+$) calcd for C$_{37}$H$_{76}$O$_8$P 679.5277, found 679.5272.

To the solution of 3.15a (0.040 g, 0.059 mmol) in dry DCM (1 ml), was added excess TMSBr (0.078 ml, 0.59 mmol) and stirred for 3 hr. The completion of the reaction was checked by $^{31}$P NMR. After the complete conversion of the starting material, solvent was dried under vacuo. Then MeOH (2 ml) was added followed by the addition of few drops of water. The reaction mixture was further stirred for 1 hr and the solvent was removed to get the precipitate of 3.19a (0.032 g, 83%). $[\alpha]^{22,390^\circ}$D = –52.22° (c = 1.0, CHCl$_3$); IR(neat) 3500 – 3200 (br), 2914, 2847, 1467, 1032 cm$^{-1}$, $^1$H NMR (300 MHz, MeOD) $\delta$ 3.88 (dd, $J_{HH} = 14.1, 5.2$ Hz, 1H), 3.79 (d, $J_{HH} = 2.5$ Hz, 1H), 3.74 – 3.64 (m, 1H), 3.66 – 3.51 (m, 1H), 3.25 (dt, $J_{HH} = 10.3, 5.3$ Hz, 1H), 2.15 (dt, $J_{HH} = 11.4, 5.2$ Hz, 1H), 1.70 – 1.54 (m, 1H), 1.36 (m, 7H), 0.90 (t, $J_{HH} = 6.7$ Hz, 1H). $^{13}$C{$_1$H} NMR (75 MHz, MeOD) $\delta$ 85.8, 82.6, 78.0 (d, $J_{CP} = 8.8$ Hz), 75.0 (d, $J_{CP} = 42.4$ Hz), 71.8, 68.3, 63.4, 33.3, 31.5, 31.0, 30.1, 30.9, 30.8 (d, $J_{CP} = 138.7$ Hz), 30.8, 30.7, 27.5 (d, $J_{CP} = 15.0$ Hz), 23.9, 14.6; $^{31}$P{$_1$H} NMR (121 MHz, MeOD) $\delta$ 26.4; HRMS (ESI, MNa$^+$) calcd for C$_{35}$H$_{77}$O$_8$PNa 673.4784, found 673.4777.
2,6-Anhydro-1-deoxy-1-phosphono-3,4-di-O-tetradecyl-D-glycero-D-gulo-heptitol (3.19β)

To the solution of 3.15β (0.039 g, 0.057 mmol) in dry DCM (1 ml), was added excess TMSBr (0.076 ml, 0.57 mmol) and stirred for 4 hr. The completion of the reaction was checked by $^{31}$P NMR. After the complete conversion of the starting material, solvent was dried under vacuo. Then MeOH (2 ml) was added followed by the addition of few drops of water. The reaction mixture was further stirred for 1 hr and the solvent was removed to get the precipitate of 3.19β (0.029 g, 78%); $[\alpha]^{22.22\circ}_D - 7.96\circ$ (c = 1.0, CHCl$_3$); IR(neat) 2953, 2913, 2846, 1470; $^1$H NMR (300 MHz, MeOD) $\delta$ 3.92 – 3.77 (m, 4H), 3.70 (dd, $J_{HH} = 15.8$, 7.0 Hz, 1H), 3.59 (s, 4H), 3.27 – 3.12 (m, 3H), 2.92 (t, $J_{HH} = 9.0$ Hz, 1H), 2.36 – 1.80 (m, 1H), 1.71 – 1.48 (m, 1H), 1.29 (s, 46H), 0.90 (t, $J_{HH} = 6.7$ Hz, 6H); $^{13}$C{$^1$H} NMR (75 MHz, MeOD) $\delta$ 88.2, 82.1, 76.3, 74.8, 74.5, 72.2, 62.9, 33.2, 31.7 (d, $J_{CP} = 3.3$ Hz), 31.0, 31.0, 30.9, 30.6, 27.5, 23.9, 14.6; $^{31}$P{$^1$H} NMR (121 MHz, MeOD) $\delta$ 26.4; HRMS (ESI, MNa$^+$) calcd for C$_{35}$H$_{71}$O$_8$PNa 673.4784, found 673.4751.

((2R,3R)-3-((benzyloxy)methyl)oxiran-2-yl)methanol (3.21a)$^{22-23}$

Initially DCM containing 4A° MS (2.2 g) was cooled to -25°C, and (-)DET (2.02 ml, 11.78 mmol) was added followed by the addition of Ti(i-OPr)$_4$ (2.9 ml, 9.817 mmol). This
mixture was stirred for 15 minutes and 4-benzylxy-2-buten-1-ol (7.0 g, 39.27 mmol) was added. After stirring for 30 minutes, TBHP (11.21 ml, 62.83 mmol) (5.6 M in decane) was added slowly. After stirring for 48 hours, the reaction mixture was brought to room temperature and was added the solution of FeSO₄ (0.15 g/mmol of alcohol) and citric acid (0.049 g/mmol of alcohol) in water (0.5 ml/mmol of alcohol) and stirred for 15 minutes. Then the layers were separated, while the aqueous layer was extracted with DCM. The combined organic layer was washed with brine and dried by Na₂SO₄. Then the solvent was removed under reduced pressure. Pure 3.21a (4.92 g, 65%) with 94% ee was obtained after column chromatography (SiO2, 30% EtOAc in Hexane). The ee was determined by chiral HPLC using chiral AD-H column, eluted by 5% Isopropyl alcohol in Hexane. [α]°D + 13.86° (c = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.41 – 7.28 (m, 5H), 4.66 – 4.53 (m, 1H), 3.96 (ddd, JHH = 12.8, 5.3, 2.4 Hz, 1H), 3.79 (dd, JHH = 11.5, 3.0 Hz, 1H), 3.69 (dd, JHH = 7.8, 4.2 Hz, 1H), 3.54 (dd, J = 11.5, 5.5 Hz, 1H), 3.26 (dt, JHH = 5.3, 2.6 Hz, 1H), 3.15 – 3.08 (m, 1H), 1.71 (t, J = 6.4 Hz, 1H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 137.7, 128.5, 127.9, 127.9, 73.4, 69.7, 61.3, 56.0, 54.4.

(2S,3R)-3-((benzyloxy)methyl)oxirane-2-carbaldehyde (3.22a). To the ice bath cooled solution of epoxy alcohol 3.21a (4.91 g, 25.29 mmol), in dry CH₂Cl₂ (4 mL/mol) was added Et₃N (19.71 mmol, 151.74 mmol). Then a solution of pyridine sulfur trioxide (8.85 g, 55.63 mmol) in dry DMSO (1.5 ml/mmol) was added slowly via an addition funnel over a period of one hour. The reaction mixture was stirred at ice bath
temperature for an additional three hours. The reaction was quenched by the addition of 10% aqueous citric acid and resulting aqueous solution was extracted three times using CH$_2$Cl$_2$. The combined organic layer was washed with saturated NaHCO$_3$ and brine and dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure and the pure epoxy aldehyde 3.22a (3.19 g, 66%) was isolated by column chromatography (SiO$_2$, 10-20% EtOAc in hexane). $^1$H NMR (300 MHz, CDCl$_3$) δ 9.06 (d, $J_{HH} = 6.3$ Hz, 1H), 7.42 – 7.30 (m, 5H), 4.60 (d, $J_{HH} = 2.1$ Hz, 2H), 3.87 (dd, $J_{HH} = 11.7$, 2.6 Hz, 1H), 3.59 (dd, $J_{HH} = 11.7$, 5.0 Hz, 1H), 3.49 (ddd, $J_{HH} = 4.9$, 2.6, 2.1 Hz, 1H), 3.36 (dd, $J_{HH} = 6.3$, 2.0 Hz, 1H).

![diethyl ((E)-2-((2R,3R)-3-((benzyloxy)methyl)oxiran-2-yl)vinyl)phosphonate (3.24a).](image)

Sodium hydride (0.586 g, 24.44 mmol) was suspended in dry THF (1 mL/mmol). The suspension was cooled in an ice bath and then tetraethyl methylenebisphosphonate (6.0 ml, 24.44 mmol) was added slowly over 5 minutes. The resulting mixture was stirred for one hour, then the epoxy aldehyde 3.22a (3.19 g, 16.29 mmol) dissolved in dry THF (3mL/mmol) was added dropwise. The reaction mixture was stirred for two hours at ice bath temperature then the reaction was quenched with 10% aqueous NH$_4$Cl. After 10 minutes, the aqueous solution was extracted three times with EtOAc. The combined organic layer was washed with aqueous NaHCO$_3$ and brine, and then dried over anhydrous Na$_2$SO$_4$. The solution was concentrated under reduced pressure and pure epoxy vinyl phosphonate 3.24a (4.39 g, 83%) was isolated by column chromatography (SiO$_2$, 60-80%
EtOAc in hexane); $\left[\alpha\right]^{22,50}_D + 6.42^\circ (c = 1.0, \text{CHCl}_3)$; IR (neat) 2980, 2904, 1692, 1625, 1243 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.39 – 7.27 (m, 5H), 6.54 (ddd, $J_{HP} = 21.5, J_{HH} = 17.1, 6.5$ Hz, 1H), 6.10 – 5.98 (m, 1H), 4.57 (s, 2 H), 4.13 – 4.03 (m, 4H), 3.79 – 3.52 (m, 2H), 3.43 (d, $J_{HH} = 6.4$ Hz, 1H), 3.14 – 3.12 (m, 1H), 1.33 (t, $J_{HH} = 7.0$ Hz, 6 H); $^{13}$C$\left[^1\text{H}\right]$ NMR (75 MHz, CDCl$_3$) δ 147.9 (d, $J_{CP} = 6.3$ Hz), 137.5, 128.4, 127.8, 127.7, 120.4 (d, $J_{CP} = 189.1$ Hz), 73.4, 69.0, 61.9 (d, $J_{CP} = 5.5$ Hz), 59.5, 54.3 (d, $J_{CP} = 28.7$ Hz), 16.3 (d, $J_{CP} = 6.4$ Hz); $^{31}$P$\left[^1\text{H}\right]$ NMR (121 MHz, CDCl$_3$) δ 16.6; HRMS (FAB, MH$^+$) calcd for C$_{16}$H$_{24}$O$_5$P 327.1361, found 327.1356.

![diethyl ((3R,4R,E)-3,5-bis(benzyloxy)-4-hydroxypent-1-en-1-yl)phosphonate (3.25a).](image)

diethyl ((3R,4R,E)-3,5-bis(benzyloxy)-4-hydroxypent-1-en-1-yl)phosphonate (3.25a).

To a solution of triphenyl borate (2.0 g, 6.9 mmol) in dry THF (1 mL/mmol) was added benzyl alcohol (3 ml, 27.60 mmol). The resulting solution was stirred for two hours. In a separate flask, Pd$_2$dba$_3$ (0.169 g, 0.184 mmol) and dppe (0.183 g, 0.46 mmol) were added to a solution of the epoxy vinyl phosphonates 3.24a (1.5 g, 4.60 mmol) in THF (3 mL/mmol). After one hour of stirring, the palladium solution was added to the alcohol solution and the resulting mixture was stirred for one hour at ice-bath temperature. The reaction mixture was then allowed to warm to room temperature and stirring was continued 4 hr until the reaction was complete (as observed by $^{31}$P NMR and TLC). The reaction was quenched by the addition of 10% aqueous NH$_4$Cl and extracted with three times with EtOAc. The combined organic layer was washed with aqueous saturated NaHCO$_3$ and brine and then dried over anhydrous Na$_2$SO$_4$. The solution was concentrated under reduced
pressure, and pure products 3.25a (1.51 g, 76%) was isolated by column chromatography (SiO₂, 60 – 80% EtOAc in hexane). [α]²²ο⁰C D – 8.87° (c = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.36 – 7.29 (m, 10H), 6.74 (ddd, Jₜp = 22.5, JₜH = 17.2, 5.5 Hz, 1H), 6.02 – 5.95 (m, 1H), 4.68 – 4.37 (m, 4H), 4.21 – 4.00 (m, 5H), 3.82 (br, 1H), 3.54 (ddd, JₜH = 25.8, 9.8, 5.1 Hz, 2H), 2.59 (br, 1H), 1.32 (t, JₜH = 7.0 Hz, 6H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 147.9 (d, J₅p = 6.2 Hz), 137.6, 128.5, 127.9, 127.8, 120.5 (d, J₅p = 189.1 Hz), 73.4, 69.0, 62.0 (d, J₅p = 5.5 Hz), 59.5, 54.4 (d, J₅p = 28.7 Hz), 16.4 (d, J₅p = 6.4 Hz); ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 17.3; HRMS (ESI, MH⁺) calcd for C₂₃H₃₂O₆P 435.1936 found 435.1931.

(2R,3R,E)-1,3-bis(benzyloxy)-5-(diethoxyphosphoryl)pent-4-en-2-yl benzoate (3.27a)

To the stirring solution of 3.25a (0.500 g, 1.15 mmol), pyridine (0.278 ml, 3.45 mmol) and DMAP (0.014 g, 0.115 mmol) in dry CH₂Cl₂ (2.5 ml) in ice bath condition was added benzoyl chloride (0.200 ml, 1.72 mmol) dropwise via syringe. After the complete addition, the reaction mixture was stirred at room temperature for 4 hr till completion. The completion of reaction was checked by TLC. The reaction mixture was washed by 10% NH₄Cl, saturated NaHCO₃, and brine, and extracted with CH₂Cl₂. Pure 3.27a (0.545 g, 88%) was obtained by column chromatography (SiO₂, 50% EtOAc in Hexane) of the crude product. [α]²²ο⁰C D – 9.38° (c = 1.0, CHCl₃); IR (neat) 2980, 2866, 1716, 1249 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.07 – 7.99 (m, 2H), 7.62 – 7.55 (m, 1H), 7.49 – 7.42 (m, 2H), 7.33 – 7.28 (m, 10H), 6.77 (ddd, Jₜp = 22.1, JₜH = 17.2, 4.8 Hz, 1H), 6.09 (ddd, Jₜp = 20.4,
$J_{HH} = 17.2, 1.5 \text{ Hz, 1H}$), 5.43 (dd, $J_{HH} = 10.5, 4.9 \text{ Hz, 1H}$), 4.69 – 4.46 (m, 4H), 4.46 – 4.40 (m, 1H), 4.06 – 3.87 (m, 4H), 3.74 (dd, $J_{HH} = 16.2, 10.4, 5.2 \text{ Hz, 2H}$), 1.24 (dt, $J_{HP} = 8.6, J_{HH} = 7.2 \text{ Hz, 6H}$); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 165.9, 147.9 (d, $J_{CP} = 5.7 \text{ Hz}$), 120.1 (d, $J_{CP} = 186.5 \text{ Hz}$), 73.4, 72.2, 68.1, 61.9 (d, $J_{CP} = 5.5 \text{ Hz}$), 16.4 (d, $J_{CP} = 2.6 \text{ Hz}$), 16.3 (d, $J_{CP} = 2.7 \text{ Hz}$); $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 17.3; HRMS (ESI, MH$^+$) calcd for C$_{30}$H$_{36}$O$_7$P 539.2198, found 539.1293.

(5S,6S)-2-ethoxy-5-hydroxy-6-(hydroxymethyl)-1,2-oxaphosphinane 2-oxide (3.36c).

Phostone 2.323c (0.415 g, 1.06 mmol) was dissolved in MeOH (5 mL/mmol) and then moist 10% Pd/C (0.10 g/mmol by weight of phostone) was added. The flask was flushed with argon, followed by H$_2$ (balloon pressure). H$_2$ pressure was maintained, while the reaction mixture was rapidly stirred. The reaction progress was followed by TLC. After complete reduction in 5 hr, the reaction mixture was filtered through Celite, rinsed with CH$_2$Cl$_2$, and evaporated under reduced pressure to give 3.36c (0.218 g, 98%). IR (neat) 3344 (br), 2930, 1219, 1025 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.17 – 4.11 (m, 3H), 4.04 (br, 1H), 4.01 – 3.91 (m, 2H), 3.39 (br, 1H), 3.21 (br, 1H), 2.36 – 2.19 (m, 2H), 2.04 – 1.70 (m, 2H), 1.36 (t, $J_{HH} = 7.0 \text{ Hz, 3H}$); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 82.1 (d, $J_{CP} = 7.3 \text{ Hz}$), 65.3 (d, $J_{CP} = 6.0 \text{ Hz}$), 63.6 (d, $J_{CP} = 8.0 \text{ Hz}$), 61.3 (d, $J_{CP} = 6.7 \text{ Hz}$), 28.8 (d, $J_{CP} = 7.9 \text{ Hz}$), 16.6 (d, $J_{CP} = 128.25 \text{ Hz}$), 16.5 (d, $J_{CP} = 5.9 \text{ Hz}$); $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 26.5; HRMS (ESI, MH$^+$) calcd for C$_7$H$_{16}$O$_5$P 211.0735, found 211.0730.
(5S,6S)-2-ethoxy-6-(hydroxymethyl)-5-(pentadecyloxy)-1,2-oxaphosphinane 2-oxide (3.36d).

Phostone 3.328d (0.128 g, 0.250 mmol) was dissolved in MeOH (5 mL/mmol) and then moist 10% Pd/C (0.10 g/mmol by weight of phostone) was added. The flask was flushed with argon, followed by H₂ (balloon pressure). H₂ pressure was maintained, while the reaction mixture was rapidly stirred. The reaction progress was followed by TLC. After complete reduction in 3 h, the reaction mixture was filtered through Celite, rinsed with CH₂Cl₂, and evaporated under reduced pressure to give 3.36d (0.101 g, 96%); IR (neat) 3331 (br), 2910, 2845, 1215, 963 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.25 – 4.19 (m, 1H), 4.18 – 4.07 (m, 2H), 3.99 – 3.93 (m, 1H), 3.71 – 3.67 (m, 1H), 3.55 – 3.47 (m, 2H), 3.25 (dd, Jₜₚ = 15.2, Jₚₜ = 6.5 Hz, 1H), 2.71 (br, 1H), 2.51 – 2.26 (m, 1H), 2.11 – 1.94 (m, 1H), 1.87 – 1.71 (m, 2H), 1.55 – 1.49 (m, 2H), 1.40 – 1.16 (m, 27H), 0.87 (t, Jₜₚ = 6.5 Hz, 3H); ¹³C⁻¹H NMR (75 MHz, CDCl₃) δ 83.3 (d, Jₚₜ = 7.5 Hz), 71.7 (d, Jₜₚ = 5.7 Hz), 69.3, 63.1 (d, Jₜₚ = 8.2 Hz), 61.0, 32.0, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 26.3, 26.3, 24.7 (d, Jₜₚ = 8.0 Hz), 22.8, 17.1 (d, Jₚₜ = 129.0 Hz), 16.5 (d, Jₜₚ = 5.8 Hz), 16.3, 14.2; ³¹P⁻¹H NMR (121 MHz, CDCl₃) δ 23.6; HRMS (ESI, MH⁺) calcd for C₂₂H₄₀O₅P 421.3082 found 421.3077.
4-(tetradecyloxy)but-2-yn-1-ol (3.39). To the solution of cis-2-butene-1,4-diol (9.3 g, 108.2 mmol) in DMF (150 ml) was added sodium hydride (2.59 g, 108.2 mmol) in ice bath under argon atmosphere. The reaction was stirred at rt for 1 hr. Then 1-bromotetradecane (11 ml, 36 mmol) was added dropwise at 0ºC. The reaction was left stirring for 16 hours at rt. The reaction was quenched with water and extracted with EtOAc, and solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO₂, 10-20% EtOAc in hexanes) to give pure 3.39 (7.2 g, 71%) as white solid with m.pt of 46.1ºC. IR (neat) 3304, 2953, 2913, 2845, 1094 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.32 (s, 2H), 4.17 (s, 2H), 3.49 (t, J_HH = 6.7 Hz, 2H), 1.75 (br, 1H), 1.63 – 1.54 (m, 2H), 1.30 – 1.26 (m, 22H), 0.88 (t, J_HH = 6.6 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 84.4, 82.3, 70.7, 58.5, 51.4, 32.1, 29.9, 29.8, 29.8, 29.7, 29.7, 29.6, 26.3, 22.9, 14.3; HRMS (ESI, MH⁺) calcd for C₁₈H₃₅O₂ 283.2632, found 283.2632.

(E)-4-(tetradecyloxy)but-2-en-1-ol (3.40)

To a suspension of Red-Al® (21 ml, 37.55 mmol) in dry THF (2 ml/mmol), was added the solution of 3.39 (5.3 g, 18.77 mmol) in THF (5 ml/mmol) dropwise through the addition funnel over 1 hr. The reaction mixture was then stirred in ice bath for 5 hrs. Completion of reaction was checked by TLC. After the completion, reaction mixture was quenched by the addition of saturated solution of potassium sodium tartarate (20 ml), followed by dilution with EtOAc. Then the mixture was filtered and washed with EtOAc and the solvent was
removed by rotatory evaporator. Then pure 3.40 (4.5 g, 84%) was obtained by column chromatography (SiO₂, 10 - 20% EtOAc in hexanes) to give white solid with m.pt. of 39-40°C. IR (neat) 3365, 2941, 2915, 2459, 975 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.96 – 5.75 (m, 2H), 4.17 (d, J_HH = 3.8 Hz, 2H), 3.97 (d, J_HH = 5.0 Hz, 2H), 3.43 (t, J_HH = 6.7 Hz, 2H), 1.83 (br, 1H), 1.64 – 1.56 (m, 2H), 1.26 (s, 22H), 0.88 (t, J_HH = 6.6 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 132.0, 128.2, 70.8, 63.2, 32.0, 29.9, 29.8, 29.7, 29.6, 29.5, 26.3, 22.8, 14.3; HRMS (ESI, MH⁺) calcd for C₁₈H₃₇O₂ 285.2793, found 285.2788.

3.41

((2S,3S)-3-((tetradecyloxy)methyl)oxiran-2-yl)methanol (3.41)

To the ice bath cooled solution of 3.40 (4.2 g, 15.01 mmol) in dry DCM (1.5 ml/mmol) was added mCPBA (4 g, 22.52 mmol) in dry CH₂Cl₂ (4 mL/mol) through addition funnel over a period of one hour. The reaction mixture was stirred at ice bath temperature till completion (5 hr). The completion of reaction was checked by TLC. After completion, the reaction was diluted by adding CH₂Cl₂, resulting solution was washed with saturated NaHSO₃ and brine, and dried over Na₂SO₄. The solution was concentrated under reduced pressure and the pure epoxy alcohol 3.41 (3.48 g, 77%) was isolated by column chromatography (SiO₂, 30% EtOAc in hexane), with m.pt. of 67-68°C. IR (neat) 3260, 2952, 2916, 2845, 1120 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.97 (dd, J_HH = 12.7, 1.8 Hz, 1H), 3.81 – 3.61 (m, 2H), 3.53 – 3.42 (m, 3H), 3.23 – 3.20 (m, 1H), 3.11 – 3.10 (m, 1H), 1.84 – 1.47 (m, 5H), 1.26 (br, 20H), 0.88 (t, J_HH = 6.5 Hz, 3H); ¹³C{¹H} NMR (75 MHz,
CDCl$_3$) $\delta$ 72.0, 70.4, 61.3, 55.8, 54.5, 32.1, 29.9, 29.8, 29.7, 29.6, 26.2, 22.9, 14.3; HRMS (ESI, MH$^+$) calcd for C$_{18}$H$_{37}$O$_3$ 301.2742, found 301.2737.

(2R,3S)-3-((tetradecyloxy)methyl)oxirane-2-carbaldehyde (3.42).

To the ice bath cooled solution of epoxy alcohol 3.41 (3.33 g, 11.0 mmol) in dry CH$_2$Cl$_2$ (1 mL/mol) was added Et$_3$N (9.5 ml, 66 mmol). Then a solution of pyridine sulfur trioxide (3.8 g, 24.2 mmol) in dry DMSO (1.5 ml/mmol) was added slowly via an addition funnel over a period of one hour maintaining ice bath temperature. The reaction mixture was stirred at room temperature for additional 4 hours. The reaction was quenched by the addition of 10% aqueous citric acid and resulting aqueous solution was extracted three times using CH$_2$Cl$_2$. The combined organic layer was washed with saturated NaHCO$_3$ and brine and dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure and the pure epoxy aldehyde 3.42 (2.32 g, 71%) was isolated by column chromatography (SiO$_2$, 10-20% EtOAc in hexane, with m.pt. of 42-43$^\circ$C. IR (neat) 2952, 2915, 2869, 2846, 1733, 1120, 1243 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.08 (d, $J_{HH} = 6.3$ Hz, 1H), 3.83 (dd, $J_{HH} = 11.7$, 2.3 Hz, 1H), 3.60 – 3.43 (m, 4H), 3.35 (dd, $J_{HH} = 6.2$, 1.4 Hz, 1H), 1.65 – 1.53 (m, 2H), 1.27 (s, 22H), 0.89 (t, $J_{HH} = 6.5$ Hz, 3H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 198.0, 72.2, 69.2, 56.4, 55.4, 32.1, 29.9, 29.8, 29.6, 29.5, 26.2, 22.9, 14.3; HRMS (ESI, MH$^+$) calcd for C$_{18}$H$_{35}$O$_3$ 299.2586, found 299.2581.
diethyl ((E)-2-((2S,3S)-3-((tetradecyloxy)methyl)oxiran-2-yl)vinyl)phosphonate (3.43).

Sodium hydride (0.241 g, 10.05 mmol) was suspended in dry THF (1 mL/mmole). The suspension was cooled in an ice bath and then tetraethyl methylenebisphosphonate (2.5 ml, 10.05 mmol) was added slowly over 5 minutes. The resulting mixture was stirred for one hour, then the epoxy aldehyde (3.42) (2.0 g, 6.70 mmol) dissolved in dry THF (3mL/mmol) was added dropwise. The reaction mixture was stirred for 4 hr at temperature then the reaction was quenched with 10% aqueous NH₄Cl. After 10 minutes, the aqueous solution was extracted three times with EtOAc. The combined organic layer was washed with aqueous NaHCO₃ and brine, and then dried over anhydrous Na₂SO₄. The solution was concentrated under reduced pressure and pure epoxy vinyl phosphonate 3.43 (2.30 g, 70%) was isolated as liquid by column chromatography (SiO₂, 40-50% EtOAc in hexane). IR (neat) 2916, 2847, 1733, 1118, 1022 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.64 – 6.45 (m, 1H), 6.64 – 6.12 – 5.99 (m, 1H), 4.23 – 3.98 (m, 4H), 3.72 (dd, J_HH = 11.7, 2.8 Hz, 1H), 3.57 – 3.35 (m, 4H), 3.15 – 3.05 (m, 1H), 1.65 – 1.50 (m, 2H), 1.39 – 1.16 (m, 28H), 0.88 (t, J_HH = 6.5 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 148.1 (d, J_CP = 6.3 Hz), 120.52(d, J_CP = 189.3 Hz), 72.0, 69.8, 62.1 (d, J_CP = 5.3 Hz), 59.7 (d, J_CP = 1.4 Hz), 54.5 (d, J_CP = 28.7 Hz), 32.0, 29.9, 29.7, 29.7, 29.7, 29.6, 29.5, 26.2, 22.8, 16.5 (d, J_CCP = 6.4 Hz), 14.2; ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 16.7, HRMS (ESI, MH⁺) calcd for C₂₃H₄₆O₅P 433.3082, found 433.3077.
diethyl ((3S,4S,E)-4-hydroxy-3,5-bis(tetradecyloxy)pent-1-en-1-yl)phosphonate (3.44).

To a solution of triphenyl borate (0.4 g, 1.30 mmol) in dry THF (1 mL/mmol) was added tetradecanol (0.991 g, 4.62 mmol). The resulting solution was stirred for two hours. In a separate flask, Pd$_2$dba$_3$ (0.074 g, 0.0805 mmol) and dppe (0.064 g, 0.161 mmol) were added to a solution of the epoxy vinyl phosphonates 3.43 (0.5 g, 1.15 mmol) in THF (3 mL/mmol). After one hour of stirring, the palladium solution was added to the alcohol solution and the resulting mixture was stirred at room temperature for 2 hr. (completion observed by $^{31}$P NMR and TLC). The reaction was quenched by the addition of 10% aqueous NH$_4$Cl and extracted with three times with EtOAc. The combined organic layer was washed with aqueous saturated NaHCO$_3$ and brine and then dried over anhydrous Na$_2$SO$_4$. The solution was concentrated under reduced pressure, and pure products 3.44 (0.440 g, 58%) were isolated by column chromatography (SiO$_2$, 60% EtOAc in hexanes).

IR (neat) 3400 (br), 2919, 2850, 1228, 1022 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.68 (ddd, $J_{HP} = 22.4$, $J_{HH} = 17.2$, 5.4 Hz, 1H), 6.03 – 5.90 (m, 1H), 4.13 – 4.04 (m, 4H), 3.98 (t, $J_{HH} = 5.6$ Hz, 1H), 3.73 – 3.68 (m, 1H), 3.58 – 3.29 (m, 6H), 2.20 (br, 1H), 1.55 (br, 4H), 1.38 – 1.08 (m, 50H), 0.87 (t, $J_{HH} = 6.4$ Hz, 6H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 149.2 (d, $J_{CP} = 5.0$ Hz), 148.6, 119.4 (d, $J_{CP} = 187.1$ Hz), 80.2 (d, $J_{CP} = 21.2$ Hz), 72.3, 71.8, 70.7, 61.9 (d, $J_{CP} = 4.6$ Hz), 32.0, 32.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 26.2,
diethyl ((3S,4S)-4-hydroxy-3,5-bis(tetradecyloxy)pentyl)phosphonate (3.45).

The vinyl phosphonate 3.44 (0.63 g, 0.974 mmol) was dissolved in MeOH (3 mL/mmol) and then moist 5% Pd/C (10% by weight of vinyl phosphonate) was added. The flask was flushed with argon, followed by H₂ (balloon pressure). H₂ pressure was maintained, while the reaction mixture was rapidly stirred. The reaction progress was followed by ³¹P NMR spectroscopy. After complete reduction 3 h, the reaction mixture was filtered through Celite, rinsed with CH₂Cl₂, and evaporated under reduced pressure to give the saturated phosphonate 3.45 (0.63 g, 99%). IR (neat) 3377, 2919, 2850, 1463, 1238, 1024 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.18 – 4.01 (m, 4H), 3.80 – 3.64 (m, 1H), 3.62 – 3.31 (m, 7H), 2.00 – 1.73 (m, 5H), 1.56 (b, 4H), 1.40 – 1.15 (m, 50H), 0.88 (t, Jₜₜ = 6.4 Hz, 6H); ¹³C {¹H} NMR (75 MHz, CDCl₃) δ 78.8, 71.8, 71.7, 71.4, 71.2, 61.7 (d, JCP = 6.4 Hz), 32.1, 30.3, 29.8, 29.86, 29.8, 29.7, 29.5, 26.(d, JCP = 3.5 Hz), 23.5 (d, JCP = 4.0 Hz), 22.9, 21.6(d, JCP = 142.3 Hz), 16.6 (d, JCP = 6.0 Hz), 14.3, ³¹P {¹H} NMR (121 MHz, CDCl₃) δ 32.5; HRMS (ESI, MH⁺) calcd for C₃₇H₇₈O₆P 649.5536, found 649.5531.
(5S,6S)-2-ethoxy-5-(tetradecyloxy)-6-((tetradecyloxy)methyl)-1,2-oxaphosphinane 2-oxide (3.46).

To a stirred suspension of sodium hydride (0.018 g, 0.733 mmol) in dry THF (2 mL/mmol) was added a solution of saturated phosphonate 3.45 (0.476 g, 0.733 mmol) in THF dropwise at ice-bath temperature. The reaction mixture was allowed to stir in ice bath till for 2 hr till completion. The reaction was quenched by the addition of 10% NH$_4$Cl and then extracted with EtOAc (three times). The combined organic layer was washed with saturated NaHCO$_3$, brine, and dried over anhydrous Na$_2$SO$_4$. The solution was concentrated under reduced pressure, and the pure phostone 3.46 (0.309 g, 70%) was isolated by column chromatography (SiO$_2$ 40-50% EtOAc in hexanes) as white solid with m.p.t. of 43.5-44.5°C. IR (neat) 2911, 2847, 1468, 1234, 1023 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.28 (t, $J_{HH} = 6.6$ Hz, 1H), 4.21 – 4.06 (m, 2H), 3.72 (t, $J_{HH} = 8.5$ Hz, 1H), 3.61 – 3.37 (m, 5H), 3.31 – 3.24 (m, 1H), 2.46 – 2.29 (m, 1H), 2.15 – 1.93 (m, 1H), 1.86 – 1.70 (m, 2H), 1.63 – 1.50 (m, 4H), 1.40 – 1.15 (m, 47H), 0.88 (t, $J_{HH} = 6.5$ Hz, 6H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 81.2 (d, $J_{CP} = 7.2$ Hz), 71.9, 70.6 (d, $J_{CP} = 5.6$ Hz), 69.6 (d, $J_{CP} = 9.5$ Hz), 69.5, 60.8 (d, $J_{CP} = 6.5$ Hz), 32.1, 30.0, 29.8, 29.8, 29.8, 29.6 (d, $J_{CP} = 1.3$ Hz), 29.5, 26.3 (d, $J_{CP} = 9.1$ Hz), 24.7 (d, $J_{CP} = 7.9$ Hz), 22.8, 17.3 (d, $J_{CP} = 128.25$ Hz), 16.5 (d, $J_{CP} = 5.7$ Hz), 14.2; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 23.5; HRMS (ESI, MH$^+$) calcd for C$_{35}$H$_{72}$O$_5$P 603.5117, found 603.5112.

(5S,6S)-5-(decyloxy)-2-ethoxy-6-(hydroxymethyl)-1,2-oxaphosphinane 2-oxide (3.47).
Phostone **2.328c** (0.229 g, 0.520 mmol) was dissolved in MeOH (5 mL/mmol) and then moist 10% Pd/C (0.10 g/mmol by weight of phostone) was added. The flask was flushed with argon, followed by H₂ (balloon pressure). H₂ pressure was maintained, while the reaction mixture was rapidly stirred. The reaction progress was followed by TLC. After complete reduction in 3 h, the reaction mixture was filtered through Celite, rinsed with CH₂Cl₂, and evaporated under reduced pressure to give **3.47** (0.180 g, 98%) as a white solid with m.pt. of 69-70°C. IR (neat) 3331, 2911, 2847, 1216 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.27 – 4.19 (m, 3H), 4.08 – 3.97 (m, 1H), 3.74 – 3.67 (m, 1H), 3.57 – 3.47 (m, 2H), 3.29 – 3.22 (m, 1H), 2.50 – 2.31 (m, 1H), 2.13 – 1.72 (m, 5H), 1.58 – 1.50 (m, 2H), 1.38 – 1.26 (m, 16H), 0.88 (t, _J_HH_ = 6.4 Hz, 3 H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 83.3 (d, _J_CP_ = 7.7 Hz), 72.0 (d, _J_CP_ = 5.7 Hz), 69.5, 63.5, 61.2, 32.1, 30.1, 29.8, 29.7, 29.6, 26.5, 24.9 (d, _J_CP_ = 8.0 Hz), 23.0, 17.3 (d, _J_CP_ = 129 Hz), 16.7 (d, _J_CP_ = 6.0 Hz), 14.4; ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 23.7; HRMS (ESI, MH⁺) calcd for C₁₇H₃₆O₅P 351.2300, found 351.2114.

![3.48a](image)

**3.48a**

(2-ethoxy-2-oxido-5-(undecanoyloxy)-1,2-oxaphosphinan-6-yl)methyl undecanoate (3.48a).

The solution of undecanoic acid (0.094 g, 0.23 mmol) in dry DCM (3 ml) was added EDC (0.095 g, 0.576 mmol) and DMAP (0.064 g, 0.523 mmol) and stirred at room temperature for 10 min. To this mixture, was added the solution of **3.36c** (0.050 g, 0.23 mmol) in DCM
(5 ml). The whole reaction mixture was left stirring at room temperature for 18 hrs. the completion of reaction was checked by TLC. The reaction mixture was then diluted with DCM, washed by water and the solvent was dried with Na$_2$SO$_4$. The mixture was concentrated under reduced pressure and purified by column chromatography (SiO$_2$, 50% EtOAc in Hexane) to get pure 3.48a (0.083 g, 66%) in its solid form with m.pt. 52-53°C. IR (neat) 2952, 2913, 2847, 1727, 1239 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.03 (br 1H), 4.53 – 4.48 (m, 1H), 4.23 – 4.08 (m, 4H), 2.39 – 2.25 (m, 4H), 2.11 – 1.77 (m, 4H), 1.66 – 1.59 (m, 4H), 1.40 – 1.17 (m, 31H), 0.86 (t, $J_{HH} = 6.6$ Hz, 6H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) δ 173.4, 173.0, 78.4 (d, $J_{CP} = 7.2$ Hz), 65.2 (d, $J_{CP} = 6.0$ Hz), 62.8 (d, $J_{CP} = 9.0$ Hz), 61.6 (d, $J_{CP} = 6.6$ Hz), 34.4, 34.2, 32.1, 29.7, 29.75, 29.6, 29.5, 29.4, 29.4, 29.3, 26.5 (d, $J_{CP} = 8.4$ Hz), 25.2, 25.0, 22.9, 17.6 (d, $J_{CP} = 130.4$ Hz), 16.6 (d, $J_{CP} = 5.4$ Hz), 14.3; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) δ 22.3, HRMS (ESI, MH$^+$) calcd for C$_{29}$H$_{56}$O$_7$P 547.3763, found 547.3758

![3.48b](image-url)

(5-(deoxyloxy)-2-ethoxy-2-oxido-1,2-oxaphosphinan-6-yl)methyl undecanoate (3.48b).

The solution of undecanoic acid (0.032 g, 0.171 mmol) in dry DCM (3 ml) was added EDC (0.033 g, 0.171 mmol) and DMAP (0.021 g, 0.171 mmol) and stirred at room temperature for 10 min. To this mixture, was added the solution of 3.47 (0.050 g, 0.142 mmol) in DCM (5 ml). The whole reaction mixture was left stirring at room temperature for 5 hrs. the completion of reaction was checked by TLC. The reaction mixture was then diluted with
DCM, washed by water and the solvent was dried with Na$_2$SO$_4$. The mixture was concentrated under reduced pressure and purified by column chromatography (SiO2, 50% EtOAc in Hexane) to get pure 3.48b (0.060 g, 84%) as a sticky liquid. IR (neat) 2920, 2851, 1737, 1249, 1027 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.37 – 4.27 (m, 3H), 4.14 (dq, $J_HP$ = 14.3, $J_{HH}$ = 7.1 Hz, 2H), 3.53 (dt, $J_{HH}$ = 8.8, 6.4 Hz, 1H), 3.43 (br 1H), 3.25 (dt, $J_{HH}$ = 8.8, 6.4 Hz, 1H), 2.54 – 2.26 (m, 3H), 2.12 – 1.96 (m, 1H), 1.89 – 1.69 (m, 2H), 1.63 – 1.50 (m, 4H), 1.40 – 1.18 (m, 31H), 0.87 (t, $J_{HH}$ = 6.6 Hz, 6H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 173.7, 80.1 (d, $J_{CP}$ = 7.1 Hz), 71.2 (d, $J_{CP}$ = 5.8 Hz), 69.5, 64.0 (d, $J_{CP}$ = 9.2 Hz), 61.0 (d, $J_{CP}$ = 6.5 Hz), 34.3, 32.0, 29.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 26.4, 25.1, 24.6 (d, $J_{CP}$ = 8.1 Hz), 22.9, 17.2 (d, $J_{CP}$ = 129.0 Hz), 16.6 (d, $J_{CP}$ = 5.4 Hz), 14.3; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 23.1; HRMS (ESI, MH$^+$) calcd for C$_{28}$H$_{56}$O$_6$P 519.3814, found 519.3809.

![3.49](image.png)

2-hydroxy-5-(tetradecyloxy)-6-((tetradecyloxy)methyl)-1,2-oxaphosphinane 2-oxide (3.49).

To the solution of 3.46 (0.050 g, 0.082 mmol) dry DCM (2 ml), was added excess TMSBr (0.108 ml, 0.82 mmol) and stirred for 4 hr. The completion of the reaction was checked by TLC. After the complete conversion of the starting material, solvent was dried and MeOH (5 ml) was added followed by the addition of few drops of water. The reaction mixture was further stirred for 1 hr and the solvent was removed to get the precipitate of 3.49 (0.042 g, 89%) with the m.pt. of 70-71°C. IR (neat) 2952, 2913, 2869, 2846, 1465, 1118, 1021 cm$^{-1}$;
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 10.31 (br, 1H), 4.46 (br, 1H), 3.73 – 3.68 (m, 1H), 3.63 – 3.37 (m, 5H), 3.32 – 3.24 (m, 1H), 2.45 – 2.28 (m, 1H), 2.04 – 1.73 (m, 3H), 1.54 (br 4H), 1.26 (s, 44H), 0.88 (t, \(J_{HH} = 6.6\) Hz, 6H); \(^{13}\)C\(^{1}\)H\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 80.7, 71.8, 70.7 (d, \(J_{CP} = 1.3\) Hz), 69.6, 69.1, 32.1, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 26.4, 26.3, 24.4, 22.8, 17.6 (d, \(J_{CP} = 105.1\) Hz), 14.3; \(^{31}\)P\(^{1}\)H\) NMR (121 MHz, CDCl\(_3\)) \(\delta\) 27.6; HRMS (ESI, MH\(^+\)) calcd for C\(_{33}\)H\(_{68}\)O\(_5\)P 575.4804, found 575.4799.

![Structure of 3.49a](image)

\((5S,6S)-2\)-hydroxy-2-oxido-5-(undecanoyloxy)-1,2-oxaphosphinan-6-yl)methyl undecanoate (3.49a).

To the solution of 3.48a (0.050 g, 0.091 mmol) dry DCM (2 ml), was added excess TMSBr (0.120 ml, 0.91 mmol) and stirred for 4 hr. The completion of the reaction was checked by TLC. After the complete conversion of the starting material, solvent was dried and MeOH (5 ml) was added followed by the addition of few drops of water. The reaction mixture was further stirred for 1 hr and the solvent was removed to get the precipitate of 3.49a (0.037 g, 78%) with the m.pt. of 50-51\(^\circ\)C. IR (neat) 2916, 2849, 1726,1076 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.02 (br, 1H), 4.64 (br, 1H), 4.24 – 4.00 (m, 2H), 2.39 – 2.33 (m, 5H), 2.14 – 1.83 (m, 3H), 1.57 – 1.83 (br, 4H), 1.22 (br, 28H), 0.84 (t, \(J_{HH} = 6.4\) Hz, 6H); \(^{13}\)C\(^{1}\)H\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 173.3, 172.9, 78.0, 77.3, 65.3, 34.21 (d, \(J_{CP} = 18.7\) Hz), 32.0, 29.7, 29.7, 29.6, 29.4, 29.4, 29.2, 25.0 (d, \(J_{CP} = 14.0\) Hz), 22.8, 14.2; \(^{31}\)P\(^{1}\)H\) NMR (121 MHz, CDCl\(_3\)) \(\delta\) 25.7; HRMS (ESI, MH\(^+\)) calcd for C\(_{27}\)H\(_{52}\)O\(_7\)P 519.3450, found 519.3445.
(5-(decyloxy)-2-hydroxy-2-oxido-1,2-oxaphosphinan-6-yl)methyl undecanoate (3.49b).

To the solution of 3.48b (0.050 g, 0.099 mmol) dry DCM (2 ml), was added excess TMSBr (0.130 ml, 0.96 mmol) and stirred for 4 hr. The completion of the reaction was checked by TLC. After the complete conversion of the starting material, solvent was dried and MeOH (5 ml) was added followed by the addition of few drops of water. The reaction mixture was further stirred for 1 hr and the solvent was removed to get viscous 3.49b (0.036 g, 74%).

IR (neat) 2914, 2846, 1737, 1060 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.52 (br, 1H), 4.35 – 4.23 (m, 2H), 3.60 – 3.39 (m, 2H), 3.28 – 3.21 (m, 1H), 2.52 – 2.20 (m, 3H), 1.96 – 1.82 (br 3H), 1.61 – 1.52 (m, 4H), 1.26 (s, 28H), 0.88 (t, \(J_{HH} = 6.4\) Hz, 6H); \(^{13}\)C\(^{1}\)H NMR (75 MHz, CDCl\(_3\)) \(\delta\) 173.6, 79.7, 71.3, 69.5, 63.4, 34.2, 32.0, 29.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 26.3, 25.02, 24.2 (d, \(J_{CP} = 6.0\) Hz), 22.8, 17.2 (d, \(J_{CP} = 126.0\) Hz), 14.26; \(^{31}\)P\(^{1}\)H NMR (121 MHz, CDCl\(_3\)) \(\delta\) 25.6; HRMS (ESI, MH\(^+\)) calcd for C\(_{26}\)H\(_{52}\)O\(_6\)P 491.3501, found 491.3496.
3.9 References


Chapter IV

4 Synthesis of Affinity Probes for the Chemical Based Proteomic Analysis of Mycobacterium Tuberculosis

4.1 Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*M.tb*), which is a huge global health challenge. TB is one of the leading causes of death worldwide. According to WHO, around 10 million people were infected by TB in 2018 and an estimated death of 2.1 million people was recorded in the same year. The most TB cases as reported by WHO in 2018 were South-East Asia, Africa, and the Western Pacific with smaller percentages in the Eastern Mediterranean, the Americas, and Europe. The drug-resistant TB is a global challenge. As of the report from 2018, 3.4% of new TB cases and 18% of previously treated cases had multi drug resistant TB or rifampicin-resistant TB (MDR/RR-TB).\(^1\) The emergence of new drug resistant strains demands the development of novel therapeutic methods.

With the development of bacterial resistance, efforts are under way to develop novel therapeutics.\(^2\) The physiological relation of *M. tb.* with human immune system is one of the hurdle in the development of novel therapeutics.\(^3\) Granuloma are developed as a result of the response of human immune system to the bacteria. The Granuloma also provide shelter for the bacteria and can evade antibiotics, which then latter develop as latent TB. On the other hand, the complex structural feature of *M.tb.* is also the major problem in the development of novel therapeutics.\(^4\)-\(^9\) Most of the current first line drugs and new drugs under clinical trial inhibit cell wall biosynthetic enzymes.\(^10\) All these facts necessitates the
development of novel therapeutics that are multi target against *M.tb.* under different physiological conditions. One of the challenges in the design of novel therapeutics is identifying suitable physiologically relevant targets within the disease-causing organism. Our lab have reported the synthesis and biological activity of several mono and bicyclic phosphonate and phosphate analogs based on the natural products cyclophostin and cyclipostin. These analogs are found to inhibit the microbial growth both on extracellular growth as well as in infected macrophages with moderate to good IC\textsubscript{50} values (Figure 4.1).\textsuperscript{7-8, 10, 16-17}

\[ \text{Figure 4.1 Structure of cyclophostin, cyclipostins and analogs} \]

The analog \textbf{1.31} has an the IC\textsubscript{50} value in nanomolar range and is the most promising lipase inhibitor. The most important fact is that, these analogs are not toxic towards the host cells.\textsuperscript{17} Preliminary experiments have demonstrated that these compounds are multi target inhibitors against several serine and cysteine based enzymes. Furthermore, enzyme
digestion and mass spectroscopy have shown that these enol phosphonates and phosphates covalently modify the active serine site (or cysteine).\textsuperscript{10-11, 15-20}

The introduction of a visible moiety into the compound while maintaining activity would help in the identification of the target enzyme by creating an affinity probe. Nonspecific phosphorus fluoride based fluorescent probes are well known and extremely useful.\textsuperscript{21} When fluorescent inhibitors are used, the tagged enzyme becomes “visible” and can be detected and quantified on the basis of the fluorescent signal.\textsuperscript{22} Fluorescently labeled phosphonates have proven useful as probes for sensitive and rapid detection of active proteins by one- or two-dimensional gel electrophoresis either in pure form or in a complex proteome sample. Hence, we planned to use an activity based protein profiling (ABPP) approach for target identification. The ABPP probe consists of a reactive site, a linker, and a reporter tag (Figure 4.2).\textsuperscript{23} The reporter tag facilitates the target characterization and may be a fluorophore, biotin, and a latent analytical handle. The latent analytical handle may be alkyne or azide, which can further be modified by click chemistry\textsuperscript{24} to visualize the enzyme.\textsuperscript{23} For the purpose of target identification, we planned to introduce the fluorescent tag in our first approach, while the second approach constitutes the presence of an alkyne moiety in the analogs of cyclophostin and cyclipostin.

![Figure 4.2](image)

**Figure 4.2** Representative structure of an ABPP probe containing a reactive group, a linker and a reporter tag
The nitrobenzo-2-oxa-1,3-diazole (NBD) and dansyl fluorophores are both suitable labels widely used for fluorescently labeling lipase inhibitors and tolerance by microorganisms. Based on the preliminary results, we rationalized that fluorescent tag could be placed at the end of the lipophilic chain, either at the phosphate ester or at the C5 substituent. This dissertation describes an alternative synthetic approach to achieve the labelled tag at C5 (Scheme 4.1) with dansyl group as labeled tag.

![Diagram of synthetic target containing fluorescent tag](image)

**Figure 4.3 Synthetic target containing fluorescent tag**

### 4.2 Introduction of the fluorescent tag at C5 and at phosphorus atom

The initial work was done in our laboratory in which the fluorescent tag was introduced at the late stage of synthesis. The late-stage installation strategy was compatible with the dansyl group, though with low isolated yield of the final product. This dissertation describes an alternative synthetic plan to attach the labelled tag at C5 (Scheme 4.1) with dansyl group as labeled tag.

#### 4.2.1 Retrosynthetic plan

The cyclized product 4.1 results from the cyclization of dimethyl phosphonate 4.4, which in turn could be obtained by hydrogenation of vinyl phosphonate 4.5. The vinyl phosphonate 4.5 could be obtained by the palladium catalyzed reaction of olefin 4.6 with...
methyl acetoacetate. Olefin 4.6 could be obtained via the olefin metathesis reaction of the olefin 4.7 and phosphono allylic carbonate 4.9 (Scheme 4.1).

![Scheme 4.1 Retrosynthetic analysis for the installation of the labelled tag at C5](image)

4.2.2 Results and discussions

According to the envisioned strategy, the early synthesis of undecanamine 4.8 was necessary. The synthesis was carried out by the reaction of commercially available Undecylenic acid (4.10) with thionyl chloride followed by treating with aqueous ammonium hydroxide to get an amide 4.11. The reduction of amide was carried out by treating amide with lithium aluminum hydride in THF at reflux (Scheme 4.2).

![Scheme 4.2 Synthesis of undecanamine](image)
The reaction of dansyl chloride (4.12) with undecenamine (4.8) gave the dansyl sulfonamide labeled alkene 4.7. The cross-metathesis reaction of labelled alkene 4.7 with phosphono allylic carbonate (4.9) give carbonate (4.6). Further reaction of carbonate with methyl acetoacetate via a palladium \(\pi\)-allyl intermediate gave the addition product 4.5 in good yield. Hydrogenation followed by the final cyclization results in the formation of diastereomeric product 4.1α and 4.1β (Scheme 4.3), which were separated by column chromatography using a long column and slow elution with a 61% yield.

Scheme 4.3 Synthesis of labelled analog of cyclophostin

Following our success installing a fluorescent label at C5, we moved towards the installation of a fluorescent tag at the phosphorus atom. For this purpose, it was necessary to synthesize the monocyclic enol phosphate and phosphonate, which on transesterification
would give the desired product. The synthesis of monocyclic phosphonate and monocyclic enol phosphate was carried out following the experimental procedure established in our laboratory and transesterified with bromides prepared using three different approaches. 

(Scheme 4.4) \(^7,12\)

![Scheme 4.4 Installation of labelled probe at phosphorus atom through a transesterification reaction](image)

The alkyl bromide with a terminal fluorescent tag was synthesized using two different approaches. The first strategy was to synthesize labelled bromide with 15 carbons, through olefin metathesis, and further carry out the transesterification (Scheme 4.6) \(^7,12\). The cross-metathesis reaction of labelled alkene 4.7 with bromoalkene resulted product 4.17, which was then subjected to transesterification with 4.13. The hydrogenation of the resulting product 4.19 gave the labeled analog 4.2a.

![Scheme 4.5 Attempted synthesis of labeled analog using cross metathesis reaction](image)
HRMS data (Figure 4.4) for the product 4.2a revealed the presence mixture of compounds with varying chain length (M-CH₂, M and M+CH₂), which was later confirmed by LCMS.

Figure 4.4 LCMS report for product 4.2a

The variation in the chain length could be the result of the metathesis reaction. Hanson et al. had observed similar variation of ring size from the ring closing metathesis reaction in the total synthesis of Dolabelide C. The probable reasoning could be the isomerization of the alkene during the cross metathesis (Scheme 4.6). We found that switching from Grubbs
II catalyst to Hoveyda Grubbs catalyst could overcome the isomerization leading to the clean formation of the targeted product.

Scheme 4.6 Possible pathway for the formation of mixtures of product

It is hypothesized that the mixture of products could be the result of cross metathesis after isomerization of the alkene. The compound 4.20 may undergo isomerization to give 4.21. When these compounds undergo the cross-metathesis reaction they would give either 4.23 which is the desired product or 4.24 which is a result of loss of a methylene group. Another pathway that could occur is homodimerization of 4.20 giving 4.25. This product also could undergo isomerization and may undergo further cross-metathesis reaction with another alkene 4.22 to give 4.26 with addition of extra CH₂ group or 4.24 with the loss of CH₂ group.
With this result, we moved to the synthesis of the labelled product, in which transesterification was carried out with bromo hexene followed by cross metathesis reaction with labeled alkene and final hydrogenation (Scheme 4.7). The transesterification of 4.13 with bromo hexene went smoothly with 74% yield, while the yield for the cross metathesis reaction was low. The low yield is because of homodimerization. Though the final product was shown to be pure through MS analysis, the HPLC chromatogram was never found to be single peak even after multiple chromatographic separation, which forced us to abandon this strategy also.

![Scheme 4.7 Alternative synthesis of 4.3a](image)

We then turned to the other strategy to synthesize the long chain with labeled analog starting from readily available starting material 11-bromo-1-undecanol (4.28). Compound 4.28 was refluxed with potassium phthalimide and white crystal of 4.29 were obtained after purification in 95% yield. Compound 4.29 was then reacted with hydrazine hydrate to get compound 4.30 after work up, which was then directly refluxed in HBr to get 4.31 in 42% yield. Compound 4.31 was then reacted with dansyl chloride to get the labeled bromoalkane 4.32 in 41% yield. Finally, transesterification with monocyclic enol phosphonate
and phosphate was carried out in the presence of TBAI under refluxing toluene to get 4.2b or 4.3 (Scheme 4.9). The final compounds were fully characterized by NMR and MS showing the formation of pure product.

Scheme 4.8 Synthesis of labeled analogs of monocyclic enol phosphate and phosphonate

4.3 Synthesis of analogs of monocyclic phosphonate and phosphate containing alkyne moiety

The second approach for the introduction of ABPP is the introduction of an alkyne moiety to the monocyclic enolphosphonate and enolphosphate. The alkyne analogs would be first incubated with the cells and then reacted with the labeled azide via click reaction. It is believed that the alkyne containing inhibitors resembles more closely with the known inhibitor, without modifying the physicochemical properties and potency of the resulting compounds. Such strategy have been used in M. bovis BCG or M. tb H37Rv.
For this approach, we envisioned the following analogs as the target compounds. This again provides two different strategy for the introduction of alkyne moiety either at C5 or at the phosphorus atom. As usual the alkyne moiety could be introduced to the phosphorus atom by transesterification of the monocyclic phosphonate or the phosphate methyl esters. However, the introduction of a terminal alkyne at C5 would be more challenging, as our established synthetic methodology is not friendly to the presence of an alkyne moiety.

![Chemical structures](image.png)

**Figure 4.5 Synthetic target for click chemistry**

### 4.3.1 Retrosynthetic analysis

Our synthetic plan for the introduction of alkyne moiety at C5 was thought to utilize a modified version of the established methodology. The retrosynthetic analysis is shown in Scheme 4.9.

![Scheme 4.9](image.png)

**Scheme 4.9 Retrosynthetic analysis for the synthesis of alkyne installed analog at C5**
According to the retrosynthetic plan, the monocyclic phosphonate analog with alkyne moiety 4.33 could be obtained by homologation of aldehyde 4.36 obtained from 4.37. Aldehyde undergoes conversion to alkyne through homologation reaction following Ohira Bestmann reaction.\(^4\) Compound 4.37 could be obtained by the cyclization of phosphonate 4.38. Compound 4.38 could be obtained by the hydrogenation of 4.39, which in turn could be obtained from the palladium catalyzed reaction of 4.40 with methyl acetoacetate. Carbonate 4.40 could be obtained by the cross-metathesis reaction of olefin 4.41 with phosphonic allylic carbonate (4.9).

### 4.3.2 Results and discussions

The synthetic attempt was carried out by the cross-metathesis reaction of 10-undecen-1-ol (4.41) with phosphono allylic carbonate. Our initial plan was to convert 4.40 to aldehyde 4.42 and subject it to the Ohira-Bestmann reaction to obtain the alkyne 4.43 at the terminal position (Scheme 4.10). Unfortunately, the conversion was not successful. This failure changed our thoughts, and we decided to introduce the alkyne only at the late stage of the synthesis. Thus, the above-mentioned retrosynthetic plan was envisioned.

**Scheme 4.10 Attempted synthesis of terminal alkyne**
Product 4.40 was reacted with methyl acetoacetate in the presence of a palladium catalyst. Similar reactions have been carried out smoothly with large variety of substrates. This reaction was unsuccessful resulting in the formation of elimination product 4.45, which was identified by $^{31}$PNMR analysis of the crude mixture. With this failure, we then masked the free alcohol of alkene 4.41 with a benzyl and TBS group and carried out the cross-metathesis reaction followed by the reaction with methyl acetoacetate in presence of the palladium catalyst. The desired product was not obtained with the alcohol protected substrate as well. Only the elimination products 4.45a and 4.45b were obtained, which were identified by $^{31}$P NMR analysis of the crude mixture. Only the elimination product 4.45a was fully characterized. (Scheme 4.11).

Scheme 4.11 Attempted Pd-catalyzed addition of nucleophile

Again, with this failure, we halted our plan to obtain alkyne moiety at C5 position and moved forward to the introduction of alkyne moiety at phosphorus atom. For this purpose, we started using the commercially available starting material to shorten the synthesis.
Commercially available 10-undecyn-1-ol (4.46) was transformed to bromoalkyne (4.47).\textsuperscript{41} Finally, transesterification reaction of monocyclic phosphate and phosphonate was carried out in the presence of TBAI under reflux in toluene or 1,4-dioxane to give the desired products 4.34 and 4.35 respectively in modest yield (Scheme 4.12). The monocyclic phosphate analog with C11 alkyl chain was also synthesized. This could provide the data that can be compared with the activity of 4.35a.

![Reaction Scheme](image)

Scheme 4.12 Transesterification of monocyclic enol phosphate and phosphonate to get alkyne substituted synthetic target

As it is evident that the monocyclic phosphate analog with C16 alkyl chain at phosphorus atom is the most promising, the alkyne moiety with the same number of carbons should be more effective in our plan for target identification. Though the inhibitors with any number of carbons should be useful as proof of concept, we planned to introduce the terminal
alkyne with C16 carbon chain. For this, the following synthetic plan can be executed as a future work (Scheme 4.13).

![Scheme 4.13 Introduction of C16 alkyne chain](image)

Commercially available compound 4.48 could be converted to get terminal alkyne 4.49 via alkyne zipper reaction and then transformed to bromo alkyne 4.50 by treating with PPh₃ and CBr₄. Bromo alkyne 4.50 can now be subjected to transesterification reaction with monocyclic enol phosphate 4.14 to get C16 alkyne substituted product 4.51.

### 4.4 Summary

In summary, we described the synthesis of ABPP probes of monocyclic enol phosphonate and enol phosphate. The introduction of fluorescent tag at C5 of monocyclic enol phosphate underwent smoothly. While the introduction of alkyne moiety at C5 was not achieved. The introduction of the alkyne chain seems to be challenging and need further investigation.

The introduction of affinity probes at phosphorus atom of monocyclic enol phosphonate and enol phosphate were achieved through transesterification reaction, though the yield for all these reactions was low.
We have not yet tested the activity of these compounds, but eventually they will be tested against *M. tb*. The result obtained after the testing should provide more insight and the direction for the lead identification along with the understanding of the mode of action and the target enzyme identification.
4.5 General Experimental

General Experimental Procedures

All reactions were carried out in oven dried glassware under an atmosphere of argon unless otherwise noted. THF was distilled from sodium and benzophenone, CH$_2$Cl$_2$ and CH$_3$CN were distilled from CaH$_2$, and MeOH. All chemicals and reagents were purchased from commercial suppliers and used directly unless otherwise noted. $^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded at 300, 75 and 121 MHz, respectively. $^1$H NMR spectra are referenced to CDCl$_3$ (7.27 ppm), $^{13}$C NMR spectra are referenced to CDCl$_3$ (77.23 ppm), and $^{31}$P NMR spectra are referenced to external H$_3$PO$_4$.

Undec-10-en-1-amine (4.8).

Undecylenic acid (20.25 g, 109.9 mmol) was dissolved in thionyl chloride (136 mL). The solution was heated at reflux for 1 h, and then concentrated by distillation of the remaining thionyl chloride. The resulting oil was dissolved in CH$_2$Cl$_2$ and added dropwise to concentrated aqueous NH$_4$OH at 0 °C. The mixture was diluted with water and CH$_2$Cl$_2$ until two clear layers formed. The organic phase was washed with 1N HCl and brine was added to aid the separation. The organic phase was dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo giving the amide (19.91 g, 99%) as a pale pink solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.82 (ddt, $J_{HH} = 17.1$, 10.2, 6.8 Hz, 1H), 5.38 (br s, 2H), 4.98 (m, 2H), 2.23 (t, $J_{HH} = 7.5$ Hz, 2H), 2.04 (q, $J_{HH} = 6.9$ Hz, 2H), 1.64 (p, $J_{HH} = 7.5$ Hz, 2H), 1.31 (m, 12H).
LiAlH₄ (2.3 g, 60.6 mmol) was slowly added to the flask containing THF (50 mL). The suspension was heated at reflux for 30 min. The mixture was cooled to room temperature and a solution of the amide (5.0 g, 27.3 mmol) in THF (100 mL) was added dropwise. The mixture was again heated at reflux for 24 h. EtOAc (20 mL) was added dropwise and then the mixture was cooled to 0°C in an ice water bath. Saturated aqueous Na₂SO₄ (40 mL) was added slowly and the resulting white suspension was filtered, rinsing 5 times with EtOAc (20 mL each). The organic phase was separated, dried, and concentrated in vacuo. The resulting oil was distilled (kugelrohr oven) to give amine 4.8 (3.12 g, 68%) as a green oil. ¹H NMR (300 MHz, CDCl₃) δ 5.82 (ddt, J_HH = 17.0, 10.1, 6.7 Hz, 1H), 4.97 (m, 2H), 2.68 (t, J_HH = 6.9 Hz, 2H), 2.05 (q, J_HH = 7.0 Hz, 2H), 1.29 (m, 14H).

5-(dimethylamino)-N-(undec-10-en-1-yl)naphthalene-1-sulfonamide (4.7).

To the solution of 4.8 (2.0 g, 11.82 mmol) in 2 mL dry DCM was added DIPEA (4.3 mL, 24.882 mmol) followed by the addition of Dansyl chloride (3.49 g, 13 mmol) dissolved in 5 mL DCM slowly, over five minutes. The reaction mixture was stirred for 72 hours at room temperature. Then 137 mL of brine was added followed by addition of 500 mL of EtOAc and washed several times with water to bring to neutral pH. Finally washed with brine and the organic phase was evaporated in vacuo. The crude mixture was purified by column chromatography (SiO₂, 5-15 % EtOAc in Hexane) to get green viscous liquid 4.7 (3.845 g, 81%). IR (neat) 3291, 3071, 2921, 2850 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ
8.55 (d, $J_{HH} = 8.5$ Hz, 1H), 8.30 (d, $J_{HH} = 8.7$ Hz, 1H), 8.26 (dd, $J_{HH} = 7.3$, 1.2 Hz, 1H), 7.57 (m, 2H), 7.21 (s, 1H), 5.80 (ddt, $J_{HH} = 16.9$, 10.2, 6.7 Hz, 1H), 5.06 – 4.80 (m, 2H), 4.64 (t, $J_{HH} = 6.0$ Hz, 1H), 2.95 – 2.84 (m, 8H), 2.06 – 1.90 (m, 2H), 1.35 – 1.09 (m, 14H);

$^{13}$C{\textsuperscript{1}H} NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 152.2, 139.4, 139.0, 134.9, 130.6, 130.0, 129.9, 129.8, 128.6, 123.4, 118.9, 115.3, 114.3, 45.6, 43.5, 33.9, 29.7, 29.5, 29.2, 29.1, 29.0, 26.6; HRMS (FAB, NBA, MNa\textsuperscript{+}) calcd for C\textsubscript{23}H\textsubscript{34}N\textsubscript{2}O\textsubscript{2}SNa\textsuperscript{+}: 425.2238, found 425.2238.

(±)-(E)-1-(dimethoxyphosphoryl)-12-((5-(dimethylamino)naphthalene)-1-sulfonamido)dodec-2-en-1-yl methyl carbonate (4.6).

To the solution of 4.7 (2.58 g, 6.409 mmol) in dry DCM, phosphono allylic carbonate (2.88 g, 12.818 mmol). Then Grubbs 2\textsuperscript{nd} generation catalyst (326 mg, 0.385 mmol) and CuI (98 mg, 0.512 mmol) were added. The mixture was heated at reflux for 5 hours. The completion of reaction was checked by TLC and $^{31}$P NMR. The reaction mixture was cooled and concentrated \textit{in vacuo} and then purified by Column Chromatography (SiO\textsubscript{2}, 70% EtOAc in Hexane) to give viscous green product 4.6 (3.45 g, 90%). IR (neat) 3175, 2924, 2851, 1750 cm\textsuperscript{-1}; $^{1}$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 8.51 (d, $J = 8.5$ Hz, 1H), 8.31 (d, $J_{HH} = 8.7$ Hz, 1H), 8.23 (dd, $J_{HH} = 7.3$, 1.1 Hz, 1H), 7.60 – 7.44 (m, 2H), 7.16 (d, $J_{HH} = 7.5$ Hz, 1H), 5.93 (m, 1H), 5.61 – 5.35 (m, 2H), 5.02 (t, $J_{HH} = 6.0$ Hz, 1H), 3.85 – 3.74 (m, 9H), 2.86 (m, 8H), 2.05 (m, 2H), 1.40 – 1.26 (m, 4H), 1.25 – 0.99 (m, 10H). $^{13}$C{\textsuperscript{1}H} (75 MHz, CDCl\textsubscript{3}) $\delta$ 154.8 (d, $J_{CP} = 9.8$ Hz), 152.0, 139.1 (d, $J_{CP} = 12.5$ Hz), 135.0, 130.4, 129.9, 129.7, 129.6,
128.37 (s), 123.3, 120.2 (d, \( J_{CP} = 3.8 \) Hz), 118.9, 115.2, 73.1 (d, \( J_{CP} = 171.1 \) Hz), 55.4, 53.9 (d, \( J_{CP} = 7.1 \) Hz), 53.8 (d, \( J_{CP} = 6.5 \) Hz), 45.5, 43.4, 32.4, 29.6, 29.3, 29.2, 29.0, 28.9, 26.4.

\( ^{31}P\{^1H\} \) NMR (121 MHz, CDCl\(_3\)) \( \delta \) 19.9; HRMS (FAB, NBA, MNa\(^+\)) calcd for C\(_{28}\)H\(_{43}\)N\(_2\)O\(_8\)PSNa\(^+\): 621.2375, found 621.2367.

(±)Methyl\((E)\)-2-acetyl-3-(2-(dimethoxyphosphoryl)vinyl)12-((5-(dimethylamino)naphthalene)-1-sulfonamido)dodecanoate (4.5).

To an oven dried RB flask, Pd\(_2\)(dba)\(_3\) (111.0 mg, 0.121 mmol) and dppe (121.0 mg, 0.303 mmol) were added. To this flask 2 mL of dry THF was added and the mixture was stirred for 10 minutes at room temperature under Argon atmosphere. Then methyl acetoacetate (3 equivalent, 9.11 mmol, 1mL) was added and left stirring for about 5 minutes. To this mixture the solution of 4.6 (1.82 g, 3.4 mmol) in THF (5 mL/mmol) was added through canula and rinsed with additional 0.5 mL THF, and the reaction mixture was heated at reflux for 4 hours till completion, which was checked by TLC and \( ^{31}P \) NMR. The reaction mixture was extracted with EtOAc and washed with brine and dried over Na\(_2\)SO\(_4\). Solvents were removed under reduced pressure and the pure product was isolated by column chromatography (SiO\(_2\), 20-40% Acetone in Hexane) to get viscous green product 4.5 (1.645 g, 85%). IR (neat) 3161, 2924, 2851, 1738, 1713 cm\(^{-1}\); \(^1H\) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.49 (d, \( J_{HH} = 8.5 \) Hz, 1H), 8.30 (d, \( J_{HH} = 8.7 \) Hz, 1H), 8.20 (dd, \( J_{HH} = 7.3, 1.2 \) Hz, 1H), 7.49 (dt, \( J_{HH} = 8.6, 7.6 \) Hz, 2H), 7.14 (d, \( J_{HH} = 7.4 \) Hz, 1H), 6.51 (m, 1H), 5.74 – 5.54 (m,
1H), 5.27 (t, $J_{HH} = 5.7$ Hz, 1H), 3.72 – 3.61 (m, 9H), 3.52 (m, 1H), 3.00 – 2.77 (m, 9H), 2.17 (m, 3H), 1.46 – 1.24 (m, 4H), 1.05 (m, 12H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 201.4 (d, $J_{CP} = 2.5$ Hz), 168.4 (d, $J_{CP} = 12.2$ Hz), 153.4 (d, $J_{CP} = 4.5$ Hz), 151.9, 135.0, 130.2, 129.9, 129.7, 129.5, 128.2, 123.2, 118.9, 118.6 (d, $J_{CP} = 184.5$ Hz), 115.1, 63.6 (d, $J_{CP} = 8.5$ Hz), 52.7, 52.4 (d, $J_{CP} = 3.75$ Hz) 45.4, 44.0 (43.7) (d, $J_{CP} = 3.9$ Hz), 43.3, 31.6, 31.5 (d, $J_{CP} = 10.8$ Hz), 31.5, 30.2, 29.9, 29.5, 29.1, 29.0, 28.8, 26.8 (d, $J_{CP} = 10.4$ Hz), 26.4; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 19.9, 20.0; HRMS (FAB, NBA, MNa$^+$) calcd for C$_{31}$H$_{47}$N$_2$O$_8$PSNa$: 661.2684$, found 661.2682.

(±)-Methyl2-acetyl-3-(2-(dimethoxyphosphoryl)ethyl)-12-((5-(dimethylamino)naphthalene)-1-sulfonamido)dodecanoate (4.4).

To a solution of 4.5 (1.139 g, 1.78 mmol) in Methanol (3 mL/mmol) were added 10% palladium on charcoal (0.05g/mmol). The solution was first flushed with Argon followed by H$_2$ (balloon pressure). H$_2$ pressure was maintained, while the reaction mixture was vigorously stirred. The completion of reaction was observed by $^{31}$P NMR analysis. After complete reduction (4 h), the reaction mixture was filtered through Celite and washed with CH$_2$Cl$_2$, solvent removed under reduced pressure to get mixture of saturated phosphonate 4.4 in quantitative yield. IR ( neat): 3159, 3144, 2924, 2850, 1734, 1709 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.45 (d, $J_{HH} = 8.5$ Hz, 1H), 8.25 (d, $J_{HH} = 8.7$ Hz, 1H), 8.16 (dd, $J_{HH} = 7.3$, 1.2 Hz, 1H), 7.54 – 7.37 (m, 2H), 7.10 (d, $J_{HH} = 7.5$ Hz, 1H), 5.19 (t, $J_{HH} = 6.0$ Hz,
1H), 3.70 – 3.59 (m, 9H), 3.39 (m, 1H), 2.87 – 2.74 (m, 8H), 2.20 (m 4H), 1.71 – 1.48 (m, 4H), 1.34 – 0.95 (m, 16H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) δ 202.8 (d, $J_{CP} = 3.0$ Hz), 169.5 (d, $J_{CP} = 2.9$ Hz), 151.9, 135.0, 130.2, 129.9, 129.7, 129.4, 128.2, 123.2, 118.9, 115.1, 62.8 (d, $J_{CP} = 6.7$ Hz), 52.4 (d, $J_{CP} = 6.6$ Hz), 52.3, 45.4, 43.2, 37.9, 37.7, 30.3 (d, $J_{CP} = 8.9$ Hz), 29.7 (29.13), 27.6 (d, $J_{CP} = 188.0$ Hz) 26.1 (d, $J_{CP} = 3.4$ Hz), 23.4 (d, $J_{CP} = 4.7$ Hz), 23.2 (d, $J_{CP} = 4.6$ Hz), 23.4 (23.23), 22.4 (d, $J_{CP} = 4.5$ Hz), 20.5 (d, $J_{CP} = 4.5$ Hz); $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) δ 34.4, 34.2; HRMS (FAB, NBA, MNa$^+$) calcd for C$_{31}$H$_{49}$N$_2$O$_8$PSNa$^+$: 663.2844, found 663.2842.

$^{4.1}$α/$^{4.1}$β

(±)-Methyl 5-(9-((5-(dimethylamino)naphthalene)-1-sulfonamido)nonyl)-2-methoxy-7-methyl-3,4,5-trihydro-1,2-oxaphosphepine-6-carboxylate 2-oxide (4.1).

To a solution of 4.4 (3.1 g, 4.9 mmol) in CH$_3$CN (2.4 mL/mmol) in an oven dried RB flask, NaI (0.809 g, 5.402 mmol) was added. This solution was refluxed at 80°C for 24 hours. The completion of reaction was observed through $^{31}$P NMR. The resulting sodium salt was dried under reduced pressure. The solid sodium salt of phosphonate was dissolved in 20 ml of DMF (4ml/mmol) with 1.5 mL of diisopropyl ethyl amine (0.3 mL/mol). Then HBTU (2.80 g, 7.36 mmol) was added. After three hours the red solution was then partitioned between saturated NH$_4$Cl and CH$_2$Cl$_2$. The organic layer was then washed with NaHCO$_3$ and brine and concentrated in vacuo. The crude product was chromatographed (SiO$_2$, 20-30% Acetone in Hexane) to get viscous, sticky green liquid of diastereomer 4.1 (1.819 g,
2.98 mmol, 61%), further separated to give 4.1α and 4.1β.  

**α**: IR (neat) 3175, 2923, 2851, 1711 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.59 (d, \(J_{HH} = 8.5\) Hz, 1H), 8.34 (d, \(J_{HH} = 8.7\) Hz, 1H), 8.29 (dd, \(J_{HH} = 7.3, 1.2\) Hz, 1H), 7.65 – 7.53 (m, 2H), 7.23 (d, \(J_{HH} = 7.4\) Hz, 1H), 4.75 (t, \(J_{HH} = 6.1\) Hz, 1H), 3.86 (d, \(J_{HP} = 11.2\) Hz, 3H), 3.78 (s, 3H), 3.02 – 2.88 (m, 9H), 2.27 (m, 3H), 2.13 – 1.75 (m, 4H), 1.51 (m, 4H), 1.28 – 1.12 (m, 12H); \(^{13}\)C\{\(^1\)H\} NMR (75 MHz, CDCl\(_3\)) \(\delta\) 168.9 (d, \(J_{CP} = 1.7\) Hz), 155.6 (d, \(J_{CP} = 7.3\) Hz), 151.9, 135.0, 130.2, 129.8, 129.6, 129.4, 128.2, 123.2, 123.0 (d, \(J_{CP} = 5.3\) Hz), 118.9, 115.1, 52.0 (d, \(J_{CP} = 7.1\) Hz), 51.9, 45.4, 43.2, 37.1, 30.6, 29.5, 29.2, 28.9, 27.6, 26.3, 24.9 (d, \(J_{CP} = 6.9\) Hz), 21.8 (d, \(J_{CP} = 134.21\) Hz), 21.2 (d, \(J_{CP} = 1.4\) Hz); \(^3\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\) 26.2; HRMS (FAB, NBA, MNa\(^+\)) calcd for C\(_{30}\)H\(_{45}\)N\(_2\)O\(_7\)PSNa\(^+\) 631.2582, found 631.2581.

**β** IR (neat) 3163, 2921, 2849, 1712, cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.51 (d, \(J_{HH} = 8.4\) Hz, 1H), 8.30 (d, \(J_{HH} = 8.6\) Hz, 1H), 8.22 (d, \(J_{HH} = 7.2\) Hz, 1H), 7.60 – 7.42 (m, 2H), 7.16 (d, \(J_{HH} = 7.5\) Hz, 1H), 5.05 (t, \(J_{HH} = 6.0\) Hz, 1H), 3.81 (d, \(J_{HP} = 2.4\) Hz, 3H), 3.73 (s, 3H), 2.87 (s, 8H), 2.26 – 2.11 (m, 4H), 1.98 (m, 4H), 1.53 (m, 2H), 1.33 (m, 2H), 1.28 – 1.04 (m, 12H); \(^{13}\)C\{\(^1\)H\} NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.5, 156.2 (d, \(J_{CP} = 7.3\) Hz), 135.4, 130.9, 130.4, 130.2, 129.8, 123.8, 123.6 (d, \(J = 5.2\) Hz), 119.34, 115.7, 52.6 (d, \(J = 7.1\) Hz), 52.5, 46.0, 43.9, 37.7, 31.2, 30.0 (d, \(J_{CP} = 3.2\) Hz), 29.8, 29.5, 28.1, 26.9, 25.4 (d, \(J_{CP} = 6.8\) Hz), 23.4 (d, \(J_{CP} = 134.25\) Hz), 21.8 (d, \(J_{CP} = 1.5\) Hz); \(^3\)P\{\(^1\)H\} NMR (121 MHz, CDCl\(_3\)) \(\delta\) 23.5; HRMS (FAB, NBA, MNa\(^+\)) calcd for C\(_{30}\)H\(_{45}\)N\(_2\)O\(_7\)PSNa: 631.2582, found 631.2593.

\[\text{N-(15-bromopentadecyl)-6-(dimethylamino)naphthalene-2-sulfonamide (4.18).}\]
To the solution of 4.7 (0.300 g, 0.745 mmol) in dry DCM (2ml), 5-bromo-Hex-1-ene (6 equivalent, 0.729 g, 4.48 mmol) was added in the RB flask under Argon pressure. Then Grubbs 2nd generation catalyst (0.038 g, 0.0447 mmol) was added, followed by the addition of CuI (0.011 g, 0.0596 mmol). The flask was then placed in the preheated Sand bath and refluxed for 6 hours. Completion of reaction was checked by TLC. The reaction mixture was dried and then purified by Column Chromatography (SiO$_2$, 5-10% EtOAc in Hexane) to get green viscous liquid 4.18 (0.295 g, 74%. IR(neat) 3297, 22920, 2849, 2784, 1308 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.56 (d, J$_{HH}$ = 8.5 Hz, 1H), 8.28 (dd, J$_{HH}$ = 14.4, 7.9 Hz, 2H), 7.56 (dt, J$_{HH}$ = 10.3, 8.0 Hz, 2H), 7.20 (d, J$_{HH}$ = 7.5 Hz, 1H), 5.50 – 5.23 (m, 2H), 4.65 (t, J$_{HH}$ = 6.0 Hz, 1H), 3.41 (m, 2H), 2.93 – 2.82 (m, 8H), 2.14 – 1.74 (m, 6H), 1.49 (m, 2H), 1.41 – 1.03 (m, 14H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) δ 153.4, 134.7, 131.3, 130.5, 129.9, 129.8, 129.7, 129.4, 128.5, 123.3, 118.7, 115.2, 45.5, 43.4, 34.0, 32.6, 32.3, 31.7, 29.6, 29.4, 29.7, 28.7, 26.5; HRMS (ESI, M$^+$) calcd for C$_{27}$H$_{42}$BrN$_2$O$_2$S: 537.2150, found 537.2145.

Methyl (E)-2-((15-((5-(dimethylamino)naphthalene)-1-sulfonamido)pentadec-5-en-1-yl)oxy)-7-methyl-3,4,5-trihydro-1,2-oxaphosphepine-6-carboxylate 2-oxide (4.19).

To the solution of 4.13 (0.081 g, 0.267 mmol) in dry DCM (2ml), labelled alkene 4.18 (0.324 g, 0.803 mmol) was added in the RB flask under Argon pressure. Then Hovyeda Grubbs catalyst (0.009 g, 0.00405 mmol) was added. The flask was then placed in the preheated Sand bath and refluxed for 6 hours. The completion of reaction was checked by
TLC and $^{31}$P NMR. The reaction mixture was dried and then purified by Column Chromatography (SiO$_2$, 30-50% EtOAc in Hexane) to get green viscous liquid 4.19 (0.089 g, 49.24%). IR(neat): 3172, 2921, 2850, 2785, 1713, 1643 cm$^{-1}$H; NMR (300 MHz, CDCl$_3$) $\delta$ 8.48 (d, $J_{HH} =$ 8.5 Hz, 1H), 8.27 (d, $J_{HH} =$ 8.6 Hz, 1H), 8.23 – 8.15 (m, 1H), 7.55 – 7.41 (m, 2H), 7.13 (d, $J_{HH} =$ 7.5 Hz, 1H), 5.43 – 5.22 (m, 2H), 4.97 (t, $J_{HH} =$ 6.0 Hz, 1H), 4.10 (m, 2H), 3.70 (s, 3H), 2.88 – 2.76 (m, 8H), 2.55 (m, 2H), 2.28 (s, 3H), 2.01 (m, 8H), 1.67 (m, 2H), 1.46 – 1.00 (m, 16H); $^{13}$C{$^{1}$H} NMR (75 MHz, CDCl$_3$) $\delta$ 168.2 (d, $J_{CP} =$ 1.8 Hz), 159.3 (d, $J_{CP} =$ 7.8 Hz), 152.0, 134.9, 131.3, 130.4, 129.9, 129.7, 129.6, 128.4, 123.3, 119.1 (d, $J_{CP} =$ 4.6 Hz), 118.9, 115.2, 66.0 (d, $J_{CP} =$ 7.0 Hz), 52.0 (s), 45.5, 43.4, 32.6, 32.0, 29.9 (d, $J_{CP} =$ 6.2 Hz), 29.6, 29.5, 29.4, 29.4, 29.1, 29.0, 26.6 (d, $J_{CP} =$ 133.5 Hz), 26.5, 26.3 (d, $J_{CP} =$ 2.7 Hz), 25.5, 21.2 (d, $J_{CP} =$ 7.5 Hz), 21.0 (d, $J_{CP} =$ 1.7 Hz); $^{31}$P{$^{1}$H} NMR (121 MHz, CDCl$_3$) $\delta$ 23.3. HRMS (FAB, NBA, MH$^+$) calcd for C$_{35}$H$_{54}$N$_2$O$_7$PS: 677.3389, found 677.3400.

![4.2a](image)

**Methyl 2-((15-((5-(dimethylamino)naphthalene)-1-sulfonamido)pentadecyl)oxy)-7-methyl-3,4,5-trihydro-1,2-oxaphosphepine-6-carboxylate 2-oxide (4.2a).**

To a solution of 4.19 (0.089 g, 0.131mmol) in Methanol (2 mL/mmol) were added 10% palladium on charcoal (0.05g/mmol, 0.007 g). The solution was first flushed with Argon and with hydrogen gas filled in the balloon. The reaction was stirred for 3 hours till completion. After the completion of reaction, the reaction mixture was filtered through Celite and washed with CH$_2$Cl$_2$. Solvents were removed in vacuo to get saturated
phosphonate 4.2a in quantitative yield. IR (neat): 3281, 3172, 2920, 2850, 2784, 1713, 1643 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.53 (d, \(J_{\text{HH}} = 8.5\) Hz, 1H), 8.29 (d, \(J_{\text{HH}} = 8.6\) Hz, 1H), 8.24 (d, \(J_{\text{HH}} = 7.2\) Hz, 1H), 7.53 (m, 2H), 7.17 (d, \(J_{\text{HH}} = 7.5\) Hz, 1H), 4.86 (t, \(J_{\text{HH}} = 5.7\) Hz, 1H), 4.23 – 4.04 (m, 2H), 3.74 (s, 3H), 2.93 – 2.82 (m, 8H), 2.58 (m, 2H), 2.32 (s, 3H), 2.20 – 2.01 (m, 2H), 1.95 (m, 2H), 1.67 (m, 2H), 1.38 – 1.03 (m, 24H); \(^{13}\)C\{\(^1\)H\} NMR (75 MHz, CDCl\(_3\)) \(\delta\) 168.3, 159.4 (d, \(J_{\text{CP}} = 7.8\) Hz), 152.1, 134.9, 130.5, 130.0, 129.8, 128.5, 123.4, 119.2 (d, \(J_{\text{CP}} = 4.6\) Hz), 118.9, 115.3, 66.3 (d, \(J_{\text{CP}} = 7.1\) Hz), 52.1, 45.6, 43.5, 30.6 (d, \(J_{\text{CP}} = 6.1\) Hz), 29.7, 29.7, 29.6, 29.5, 29.2, 29.1, 26.76 (d, \(J_{\text{CP}} = 132.75\) Hz), 26.5, 26.40 (d, \(J_{\text{CP}} = 2.6\) Hz), 25.62 (s), 21.28 (d, \(J_{\text{CP}} = 7.5\) Hz), 21.15 (d, \(J_{\text{CP}} = 1.6\) Hz); \(^{31}\)P\{\(^1\)H\} NMR (121 MHz, CDCl\(_3\)) \(\delta\) 23.2. HRMS (FAB, NBA, MNa\(^+\)) calcd for C\(_{35}\)H\(_{55}\)N\(_2\)O\(_7\)PSNa\(^+\): 701.3365, found 701.3344.

![4.27](image)

**Methyl-2-(hex-5-en-1-yloxy)-7-methyl-3,4,5-trihydro-1,2-oxaphosphepine-6-carboxylate 2-oxide (4.27).**

To the solution of 4.13 (0.468 g, 1.99 mmol) in 2 ml of Toluene (distilled over CaH\(_2\) and placed in 4 Å MS for 1 hour) was added TBAI (0.074 g, 0.199 mmol) followed by the addition of 6-bromo-hexene (3.24 g, 19.9 mmol) through syringe. The reaction mixture was refluxed till completion, which was monitored by TLC and \(^{31}\)PNMR. The reaction mixture was dried over reduced pressure and purified by column chromatography (SiO\(_2\) 30-50% EtOAc in Hexane) to get 4.27 (0.450 g, 75 %). IR (neat) 3073, 2931, 2862, 1711, 1639 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.74 (ddt, \(J_{\text{HP}} = 16.9\), \(J_{\text{HH}} = 10.2\), 6.7 Hz, 1H), 8.29 (d, \(J_{\text{HH}} = 8.6\) Hz, 1H);
5.08 – 4.82 (m, 2H), 4.25 – 4.01 (m, 2H), 3.70 (s, 3H), 2.69 – 2.37 (m, 2H), 2.28 (s, 3H), 2.13 – 1.95 (m, 4H), 1.94 – 1.79 (m, 2H), 1.67 (m, 2H), 1.50 – 1.38 (m, 2H); $^{13}$C{H} NMR (75 MHz, CDCl$_3$) $\delta$ 168.2 (d, $J_{CP}$ = 1.8 Hz), 159.4 (d, $J_{CP}$ = 7.8 Hz), 138.4, 119.3 (d, $J_{CP}$ = 4.6 Hz), 115.2, 66.0 (d, $J_{CP}$ = 7.0 Hz), 52.1, 33.3, 29.9 (d, $J_{CP}$ = 6.2 Hz), 26.8 (d, $J_{CP}$ = 133.5 Hz), 26.4 (d, $J_{CP}$ = 2.7 Hz), 24.9, 21.3 (d, $J_{CP}$ = 7.5 Hz), 21.2 (d, $J_{CP}$ = 1.7 Hz); $^{31}$P{H} NMR (121 MHz, CDCl$_3$) $\delta$ 23.2; HRMS (FAB, NBA, MNa$^+$) calcd for C$_{14}$H$_{23}$O$_5$PNa: 325.1180, found 325.1186.

\[\text{Br-}\overbrace{\text{H}}^{\text{NH}_2}\]

4.31

11-bromoundecan-1-amine (4.31). 33

4.31 was prepared following the literature method. The spectral data were in accordance to the cited literature.\textsuperscript{29,33,42-44}$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.03 (br, 2H), 3.42 (t, $J_{HH}$ = 6.9 Hz, 2H), 3.04 (dd, $J_{HH}$ = 13.6, 7.3 Hz, 2H), 1.90 – 1.76 (m, 4H), 1.45 – 1.29 (m, 14H); $^{13}$C{H} (75 MHz, CDCl$_3$) $\delta$ 40.30, 34.25, 33.02, 29.57, 29.52, 29.15, 28.95, 28.36, 27.80, 26.71; HRMS (FAB, NBA, MH$^+$) calcd for C$_{11}$H$_{25}$BrN: 250.1170, found 250.1168 (252.1150).

\[\text{Br-}\overbrace{\text{H}}^{\text{SO}}\]

4.32

N-(11-bromoundecyl)-5-(dimethylamino)naphthalene-1-sulfonamide (4.32).
To a solution of 11-bromoundecan-1-amine 4.31 (0.200 g, 0.802 mmol) in dry DCM (3 ml), Dansyl chloride was added (0.238 g, 0.883 mmol) slowly followed by the addition of DIPEA (0.294 mL, 1.686 mmol) and stirred for 6 hours at room temperature. To the reaction mixture brine was added followed by the addition of EtOAc and washed with water several times. Finally washed with brine and dried over MgSO₄. The solvents were removed under reduced pressure. The crude mixture was purified by column chromatography (SiO₂; 10-20% EtOAc in Hexane) to give viscous green liquid 4.32 (0.216 g, 55%). IR (neat) 3293, 3078, 2921, 2849, 1610, 1572 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.53 (d, JHH = 8.5 Hz, 1H), 8.33 (d, JHH = 8.6 Hz, 1H), 8.25 (d, JHH = 7.2 Hz, 1H), 7.61 – 7.44 (m, 2H), 7.17 (d, JHH = 7.6 Hz, 1H), 5.01 (t, JHH = 6.0 Hz, 1H), 3.39 (t, JHH = 6.8 Hz, 2H), 2.97 – 2.80 (m, 8H), 1.79 (m, 2H), 1.35 (m, 4H), 1.30 – 1.00 (m, 12H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 152.0, 134.9, 130.4, 129.9, 129.7, 129.7, 128.5, 123.3, 118.9, 115.2, 45.5, 43.4, 34.3, 32.9, 29.5, 29.4, 29.3, 29.0, 28.8, 28.2, 26.4; HRMS (FAB, NBA, MNa⁺) calcd for C₂₃H₃₅BrN₂O₂SNa⁺: 505.1482, found 505.1509.

![4.2b](image)

**Methyl 2-((9-((5-(dimethylamino)naphthalene)-1-sulfonamido)nonyl)oxy)-7-methyl-3,4,5-trihydro-1,2-oxaphosphepine-6-carboxylate 2-oxide (4.2b).**

To a solution of monocyclic phosphonate ester 3.13 (0.100 g, 0.4272 mmol) in dry toluene 1 ml (distilled) was added solution of solution 4.32 (226 mg, 0.4699 mmol) in dry toluene 1 ml followed by the addition of TBAI (0.021 g, 0.043 mmol) and heated in reflux for 7 hours till the completion of reaction as observed by TLC and ³¹P NMR. Solvents were
removed, and the crude mixture was purified through column chromatography (SiO₂, 50 % EtOAc in Hexane) to give viscous green liquid 4.2c (0.114 mg, 43%). IR (neat) 3283, 3165, 2923, 2851, 1712, 1643 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.51 (d, J_HH = 8.5 Hz, 1H), 8.29 (d, J_HH = 8.7 Hz, 1H), 8.22 (dd, J_HH = 7.3, 1.2 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.17 (d, J_HH = 7.1 Hz, 1H), 4.91 (t, J_HH = 6.1 Hz, 1H), 4.16 – 4.00 (m, 2H), 3.73 (s, 3H), 2.90 – 2.79 (m, 8H), 2.70 – 2.43 (m, 2H), 2.31 (s, 3H), 2.17 – 1.81 (m, 4H), 1.65 (m, 2H), 1.38 – 1.05 (m, 16H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 168.2, 159.3 (d, J_CP = 7.8 Hz), 152.0, 134.9, 130.4, 129.9, 129.76, 129.7, 128.4, 123.34, 119.2 (d, J_CP = 4.6 Hz), 118.9, 115.2, 66.2 (d, J_CP = 7.1 Hz), 52.0, 45.5, 43.4, 30.5 (d, J = 6.2 Hz), 29.6, 29.5, 29.4, 29.1, 29.0, 26.7 (d, J_CP = 132.75 Hz), 26.5, 26.3 (d, J_CP = 2.7 Hz), 25.52, 21.2 (d, J_CP = 7.4 Hz), 21.0 (d, J_CP = 1.7 Hz); ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 23.2. HRMS (FAB, NBA, MNa⁺) calcd for C₃₁H₄₇N₂O₇PSNa⁺ 645.2739 found 645.2751.

Methyl 2-(((11-((5-(dimethylamino)naphthalene)-1-sulfonamido)undecyloxy)-4-methyl-6,7-dihydro-1,3,2-dioxaphosphepine-5-carboxylate 2-oxide (4.3).

To a solution of monocyclic phosphate ester 4.14 (0.099 g, 0.4176 mmol) in dry dioxane (1 ml) was added 4.32 (0.222 g, 0.456 mmol) dissolved in dioxane through canula followed by the addition of TBAI (0.016 g, 0.042 mmol), and refluxed for 7 hours till the completion of reaction . The reaction mixture was evaporated to remove the solvents and the crude mixture was purified through column chromatography (SiO₂, 30-50 % EtOAc in Hexane) to give viscous green liquid 4.3 (0.114 g, 44%). IR(neat) 3276, 3208, 2922, 2851, 1715,
1645 cm⁻¹; ‑H NMR (300 MHz, CDCl₃) δ 8.52 (d, J_HH = 8.5 Hz, 1H), 8.29 (d, J_HH = 8.6 Hz, 1H), 8.23 (dd, J_HH = 7.2, 0.7 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.17 (d, J_HH = 7.5 Hz, 1H), 4.84 (t, J_HH = 6.0 Hz, 1H), 4.36 (m, 1H), 4.21–4.09 (m, 3H), 3.75 (s, 3H), 3.05–2.77 (m, 10H), 2.34 (s, 3H), 1.75 – 1.62 (m, 2H), 1.33 (m, 4H), 1.28 – 1.05 (m, 12H); ‑C{¹H} NMR (75 MHz, CDCl₃) δ 167.3, 161.1 (d, J_CP = 9.6 Hz), 152.2, 135.0, 130.5, 130.0, 129.8, 129.8, 128.5, 123.4, 118.9, 115.5 (d, J_CP = 3.8 Hz), 115.3, 69.2 (d, J_CP = 6.1 Hz), 68.4 (d, J_CP = 6.8 Hz), 52.3, 45.6, 43.5, 30.4 (d, J_CP = 6.6 Hz), 29.7, 29.5, 29.4, 29.1 (d, J_CP = 5.1 Hz), 28.3, 26.5, 25.4, 20.5 (d, J_CP = 3.9 Hz); ‑P{¹H} NMR (121 MHz, CDCl₃) δ -10.8; HRMS (ESI, MNa⁺) calcd for C₃₀H₄₅N₂O₅PSNa⁺ 647.2531, found 647.2509.

(E)-1-(dimethoxyphosphoryl)-12-hydroxydodec-2-en-1-yl methyl carbonate (4.40).

To the solution of phosphono allylic carbonate 4.9 (2.64 g, 11.80 mmol) in dry DCM was added 10-undecen-1-ol 4.41 (1.00 g, 5.97 mmol). Then Grubbs 2nd generation catalyst (0.249 g, 0.293 mmol) and CuI (0.078 g, 0.410 mmol) were added. The mixture was heated at reflux for 5 hours. The completion of reaction was checked by TLC and ‑P NMR. The reaction mixture was cooled and concentrated in vacuo and then purified by Column Chromatography (SiO₂, 50 - 70 % EtOAc in Hexane) to give viscous green product 4.40 (1.85 g, 86%). IR(neat) 3441, 2923, 2852, 1750, 1439, 1247 cm⁻¹; ‑H NMR (300 MHz, CDCl₃) δ 6.01 – 5.90 (m, 1H), 5.99 – 5.40 (m, 2H), 3.83 – 3.78 (m, 9H), 3.63 (t, J_HH = 6.6 Hz, 2H), 2.12 – 2.04 (m, 2H), 1.60 – 1.47 (m, 3H), 1.43 – 1.22 (m, 12H); ‑C{¹H} NMR
(75 MHz, CDCl$_3$) $\delta$ 154.77 (d, $J_{CP} = 9.9$ Hz), 139.18 (d, $J_{CP} = 12.7$ Hz), 120.1 (d, $J_{CP} = 3.6$ Hz), 73.0 (d, $J_{CP} = 171.3$ Hz), 62.7, 55.4, 53.9 (d, $J_{CP} = 7.1$ Hz), (53.84, 53.75) 32.7, 32.4, 29.5, 29.4, 29.3, 29.0, 28.5, 28.5, 25.8; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 19.9; HRMS (ESI, MH$^+$) calcd for C$_{16}$H$_{32}$O$_7$P 367.1885, found 367.1880.

(4.42)

(E)-1-(dimethoxyphosphoryl)-12-oxidodec-2-en-1-yl methyl carbonate (4.42).

PDC (0.353 g, 1.637 mmol) was charged to an oven dried RB flask to which DCM (2.5 ml/mmol) was added and stirred for 5 minutes. To this stirred solution carbonate 4.40 (0.500 g, 1.364 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. After completion, the mixture was diluted by the addition of diethyl ether and filtered through Celite pad and washed with DCM. The solvents was removed under reduced pressure. Pure 4.42 (0.266 g, 54%) was obtained by purification of the crude material (SiO$_2$, 50% EtOAc in Hexane). IR(neat) 2925, 2853, 1751, 1722, 1250 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.77 (s, 1H), 6.03 – 5.89 (m, 1H), 5.61 – 5.39 (m, 2H), 3.83 – 3.79 (m, 9H), 2.43 (t, $J_{HH} = 7.3$ Hz, 2H), 2.13 – 2.05 (m, br 2H), 1.62 – 1.55 (m, br 2H), 1.40 – 1.28 (m, 10H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 203.2, 154.8 (d, $J_{CP} = 9.8$ Hz), 139.2 (d, $J_{CP} = 12.5$ Hz), 120.2 (d, $J_{CP} = 3.8$ Hz), 73.1 (d, $J_{CP} = 171.4$ Hz), 55.5, 54.0 (d, $J_{CP} = 7.1$ Hz) (53.9, 53.8), 44.0, 32.4, 29.3, 29.2, 29.2, 29.1, 28.6 (d, $J_{CP} = 2.3$ Hz), 22.1; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 19.9; HRMS (ESI, MH$^+$) calcd for C$_{16}$H$_{30}$O$_7$P 365.1729 found 365.1724.
((undec-10-en-1-yloxy)methyl)benzene (4.41a). THF was added to sodium hydride (60% in mineral oil) (2.2 g, 55.0 mmol) followed by the addition of TBAI (0.53 g, 1.45 mmol). The suspension was placed in ice bath condition and alcohol 4.41 (4.9 g, 29 mmol) was added slowly via syringe and stirred at room temperature for 30 minutes. To this mixture, was added benzyl bromide (8.1 g, 47.5 mmol) and the mixture was stirred for 4 hr at room temperature. After the completion, the reaction was quenched by careful addition of water followed by washing with water. The organic layer was dried with MgSO$_4$ and concentrated under reduced pressure. Pure 4.41a (6.61 g, 88%) was obtained after chromatographic separation (SiO$_2$, 2 – 5% EtOAc in Hexane. IR(neat) 2924, 2852, 1459, 1429 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.55 – 7.29 (m, 5H), 5.83 (ddt, $J_{HH} = 16.9, 10.1, 6.6$ Hz, 1H), 5.12 – 4.82 (m, 2H), 4.52 (s, 2H), 3.48 (t, $J_{HH} = 6.6$ Hz, 2H), 2.05 – 2.01 (m, 2H), 1.66 – 1.58 (m, 2H), 1.36 – 1.29 (m, 12H); HRMS (ESI, MH$^+$) calcd for C$_{18}$H$_{29}$O 261.2218, found 261.2213.

tert-butyl(dimethyl(undec-10-en-1-yloxy)silane (4.41b). To the ice cooled flask containing 4.41 (8.50 g, 49.91 mmol) in DCM (3ml/mmol) was added TBSCl (11.30 g, 157.12 mmol) and imidazole (5.1 g 75 mmol). Then the reaction
mixture was stirred at room temperature for 2 hr till completion. Then 30 ml water was added and the reaction was extracted with DCM. The organic layer was dried by Na$_2$SO$_4$ and the solvents removed under reduced pressure. Pure 4.41b (13.54 g, 95%) was obtained after purification by column chromatography (SiO$_2$, 5 – 10% EtOAc in Hexane). IR(neat) 2924, 2853, 146 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.82 (ddt, $J_{HH}$ = 16.9, 10.1, 6.7 Hz, 1H), 4.97 (dd, $J_{HH}$ = 18.4, 13.7 Hz, 2H), 3.60 (t, $J_{HH}$ = 6.6 Hz, 2H), 2.04 (q, $J_{HH}$ = 6.8 Hz, 2H), 1.53 – 1.46 (m, 2H), 1.42 – 1.23 (m, 12H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C($^1$H) NMR (75 MHz, CDCl$_3$) δ 139.4, 114.3, 63.5, 34.0, 33.1, 29.8, 29.7, 29.7, 29.4, 29.2, 26.2, 26.0, 18.6, -5.0; HRMS (ESI, MH$^+$) calcd for C$_{17}$H$_{37}$OSi 285.2613, found 285.2608.

(E)-12-(benzyloxy)-1-(dimethoxyphosphoryl)dodec-2-en-1-yl methyl carbonate (4.40b).

To the solution of phosphono allylic carbonate 4.9 (1.5 g, 6.69 mmol) in dry DCM was added 4.41a (5.22 g, 20.07 mmol). Then Grubbs 2nd generation catalyst (0.284 g, 0.334 mmol) and CuI (0.089 g, 0.468 mmol) were added. The mixture was heated at reflux for 6 hours. The completion of reaction was checked by TLC and $^{31}$P NMR. The reaction mixture was cooled and concentrated in vacuo and then purified by Column Chromatography (SiO$_2$, 50% EtOAc in Hexane) to give viscous green product 4.40b (2.68 g, 88%). IR(neat) 2924, 2851, 1750, 1439, 1249 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.35 – 7.29 (m, 5H), 6.01 – 5.91 (m, 1H), 5.59 – 5.41 (m, 2H), 4.51 (s, 2H), 3.83 – 3.79 (m, 9H), 3.46 (t, $J_{HH}$ = 6.6 Hz, 2H), 2.12 – 2.05 (m, br, 2H), 1.66 – 1.56 (p, 2H), 1.36 – 1.26 (br,
12H); $^{13}$C{\textsuperscript{1}H} (75 MHz, CDCl$_3$) δ 154.7 (d, $J_{CP} = 9.8$ Hz), 139.0 (d, $J_{CP} = 12.0$ Hz), 138.6, 128.3, 127.5, 127.4, 120.1 (d, $J_{CP} = 3.7$ Hz), 74.1, 72.8, 71.8, 70.4, 55.3 , 53.8, 53.7, 53.6, 32.3, 29.7, 29.4, 29.4, 29.3, 29.0, 28.5 (d, $J_{CP} = 2.1$ Hz), 26.1; $^{31}$P{\textsuperscript{1}H} NMR (121 MHz, CDCl$_3$) δ 19.9; HRMS (ESI, MH$^+$) calcd for C$_{23}$H$_{38}$O$_7$P 457.2355, found 457.2350.

(E)-12-((tert-butyldimethylsilyl)oxy)-1-(dimethoxyphosphoryl)dodec-2-en-1-yl methyl carbonate (4.40c).

To the solution of phosphono allylic carbonate 4.19 (0.500 g, 2.23 mmol) in dry DCM (6 ml) was added 4.41b (1.26 g, 4.46 mmol). Then Grubbs 2$^{nd}$ generation catalyst (0.095 g, 0.111 mmol) and CuI (0.030 g, 0.156 mmol) were added. The mixture was heated at reflux for 4 hours. The completion of reaction was checked by TLC and $^{31}$P NMR. The reaction mixture was cooled and concentrated in vacuo and then purified by Column Chromatography (SiO$_2$, EtOAc in Hexane) to give viscous green product 4.40c (0.711 g, 66%). IR(neat) 2925, 2852, 1752, 1439, 1248 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 6.04 – 5.90 (m, 1H), 5.63 – 5.39 (m, 2H), 3.81 (d, $J_{HP} = 7.7$ Hz, 9H), 3.60 (t, $J_{HH} = 6.6$ Hz, 2H), 2.14 – 2.04 (m, 2H), 1.55 – 1.45 (m, 2H), 1.42 – 1.21 (m, 12H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}$C{\textsuperscript{1}H} NMR (75 MHz, CDCl$_3$) δ 154.8 (d, $J_{CP} = 9.8$ Hz), 139.1 (d, $J_{CP} = 12.4$ Hz), 120.1 (d, $J_{CP} = 3.8$ Hz), 73.1 (d, $J_{CP} = 171.1$ Hz), 63.3 , 55.3, 53.8(d, $J_{CP} = 2.1$ Hz), 53.8, 32.9, 32.4, 29.6, 29.4, 29.4, 29.1, 28.6 (d, $J_{CP} = 2.1$ Hz), 26.0, 25.8, 18.4, -5.2; $^{31}$P{\textsuperscript{1}H} NMR (121 MHz, CDCl$_3$) δ 19.9; HRMS (ESI, MH$^+$) calcd for C$_{23}$H$_{46}$O$_7$PSi 481.2750, found 481.2745.
dimethyl ((2E,4E)-12-(benzyloxy)dodeca-2,4-dien-1-yl)phosphonate (4.45a).

To an oven dried RB flask, Pd\(_2\)(dba)\(_3\) (0.029 g, 0.031 mmol) and dppe (0.020 g, 0.062 mmol) were added. To this flask 2 mL of dry THF was added and the mixture was stirred for 10 minutes at room temperature under Argon atmosphere. Then methyl acetoacetate (0.724 g, 6.24 mmol) was added and left stirring for about 5 minutes. To this mixture the solution of 4.40a (0.500 g, 1.04 mmol) in THF (5 mL/mmol) was added through canula and rinsed with additional 0.5 mL THF. The progress of reaction was monitored by TLC and \(^{31}\)P NMR. The reaction was left stirring for 5 hours till the starting material was consumed. The reaction mixture was extracted with EtOAc and washed with brine and dried over Na\(_2\)SO\(_4\). Solvents were removed under reduced pressure and the pure product was isolated by column chromatography (SiO\(_2\), 20-40% Acetone in Hexane) to get viscous green product (0.220 g, 56%). IR(neat) 2925, 2850, 1451, 1237 cm\(^{-1}\); \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.36 – 7.29 (m, 5H), 7.24 – 7.01 (m, 1H), 6.19 – 6.03 (m, 2H), 5.59 – 5.47 (m, 1H), 4.51 (s, 1H), 3.87 – 3.76 (m, 2H), 3.72 (d, \(J_{HP} = 11.1\) Hz, 6H), 3.47 (t, \(J_{HH} = 6.6\) Hz, 2H), 2.15 (q, 2H), 1.61 – 1.56 (m, 2H), 1.45 – 1.29 (m, 8H); \(^{13}\)C\(^{\{1\}}\)H\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 150.5 (d, \(J_{CP} = 6.3\) Hz), 144.8, 138.8, 129.4 (d, \(J_{CP} = 26.9\) Hz), 112.7 (d, \(J_{CP} = 192.4\) Hz), 73.0, 70.6, 52.5 (d, \(J_{CP} = 5.5\) Hz), 32.9, 29.9, 29.5, 29.2, 28.7, 26.3. \(^{31}\)P\(^{\{1\}}\)H\) NMR (121 MHz, CDCl\(_3\)) \(\delta\) 22.9; HRMS (ESI, MH\(^{+}\)) calcd for C\(_{21}\)H\(_{34}\)O\(_4\)P 381.2194, found 381.2189.
11-bromoundec-1-yne (4.47).\(^{47}\)

The solution of 10-undecyne-1-ol (2.5 g, 14.85 mmol) in DCM was cooled in ice bath condition, to which CBr\(_4\) (7.38 g, 22.27 mmol) was added followed by the addition of PPh\(_3\) (5.96 g, 22.27 mmol). The mixture was further stirred for 15 minutes and brought to room temperature. The reaction was poured to the mixture of petroleum ether (PE) and EtOAC (95:5), and the precipitate was filtered to get the filtrate. The filtrate was filtered, and the solvents was removed. Pure 4.47 (2.86 g, 83\%) was obtained after column chromatography SiO\(_2\) (1-2\% EtOAc in PE). The \(^1\)H NMR was in accordance to the literature value. IR (neat) 3301, 2924, 2852, 2114 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.41 (t, \(J_{HH} = 6.9\) Hz, 2H), 2.19 (td, \(J_{HH} = 7.0, 2.6\) Hz, 2H), 1.95 (t, \(J_{HH} = 2.6\) Hz, 1H), 1.91 – 1.81 (m, 2H), 1.58 – 1.30 (m, 12H).

Methyl 7-methyl-2-(undec-10-yn-1-yloxy)-3,4,5-trihydro-1,2-oxaphosphepine-6-carboxylate 2-oxide (4.34).

To a solution of monocyclic phosphonate ester 3.13 (0.085 g, 0.363 mmol) in dry toluene 1 ml (distilled) was added solution of solution 4.47 (0.185 g, 0.798 mmol) in dry toluene 1 ml followed by the addition of TBAI (0.013 g, 0.036 mmol) and heated in reflux for 4 hours till the completion of reaction as observed by TLC and \(^{31}\)P NMR. Solvents were
removed, and the crude mixture was purified through column chromatography (SiO$_2$, 50 % EtOAc in Hexane) to give viscous green liquid 4.34 (0.059 g, 44%). IR(neat) 2926, 2854, 1713, 1643 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.19 – 4.05 (m, 2H), 3.73 (s, 3H), 2.68 – 2.42 (m, 2H), 2.31 (s, 3H), 2.18 – 2.08 (m, 3H), 2.06 – 2.00 (m, 1H), 1.96 – 1.85 (m, 3H), 1.74 – 1.60 (m, 2H), 1.58 – 1.42 (m, 2H), 1.34 – 1.28 (br, 10H); $^{13}$C\{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 168.2, 159.4 (d, $J_{CP} = 7.8$ Hz), 119.2 (d, $J_{CP} = 4.6$ Hz), 84.8, 68.3, 66.2 (d, $J_{CP} = 7.1$ Hz), 52.0, 30.5 (d, $J_{CP} = 6.1$ Hz), 29.5, 29.2, 29.1, 28.8, 28.6, 27.7, 26.4 (d, $J_{CP} = 2.5$ Hz), 25.9, 25.6, 21. (d, $J_{CP} = 7.5$ Hz), 21.1 (d, $J_{CP} = 1.6$ Hz), 18.5; $^{31}$P\{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 23.2; HRMS (ESI, MH$^+$) calcd for C$_{19}$H$_{31}$O$_5$P 370.1909 found

Methyl 4-methyl-2-(undec-10-yn-1-yloxy)-6,7-dihydro-1,3,2-dioxaphosphepine-5-carboxylate 2-oxide (4.35).

To a solution of monocyclic phosphate ester 3.14 (0.100 g, 0.421 mmol) in 1 ml 1,4-dioxane was added the solution of 4.47 (215 mg, 0.928 mmol) in 1 ml of 1,4-dioxane followed by the addition of TBAI (0.016 g, 0.042 mmol) and heated in reflux for 7 hours till the completion of reaction as observed by TLC and $^{31}$P NMR. Solvents were removed, and the crude mixture was purified through column chromatography (SiO$_2$, 50 % EtOAc in Hexane) to give viscous green liquid of 4.35 (0.067 mg, 43%). IR(neat) 2925, 2853, 1716, 1644, 1284 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.44 – 4.30 (m, 1H), 4.26 – 4.09 (m, 3H), 3.78 (s, 3H), 3.10 – 2.76 (m, 2H), 2.37 (s, 3H), 2.19 (td, $J_{HH} = 7.0$, 2.6 Hz, 2H), 1.95 (t, $J_{HH} = 2.6$ Hz, 1H), 1.76 – 1.66 (m, 2H), 1.55 – 1.47 (m, 2H), 1.43 – 1.22 (m, 10H);
Methyl 4-methyl-2-(undecyloxy)-6,7-dihydro-1,3,2-dioxaphosphepine-5-carboxylate 2-oxide (4.35a).

To a solution of monocyclic phosphate ester 3.14 (0.100 g, 0.421 mmol) in 1 ml 1,4-dioxane was added bromoalkene (0.366 ml, 1.63 mmol) followed by the addition of TBAI (0.020 g, 0.054 mmol) and heated in reflux for 4 hours till the completion of reaction as observed by TLC and $^{31}$P NMR. Solvents were removed, and the crude mixture was purified through column chromatography (SiO$_2$, 30 % EtOAc in Hexane) to give viscous liquid of 4.35a (0.059 mg, 38%). IR(neat) 2921, 2851, 1717, 1644, 1287 cm$^{-1}$, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.43 – 4.28 (m, 1H), 4.23 – 4.08 (m, 3H), 3.75 (s, 3H), 3.06 – 2.76 (m, 2H), 2.34 (s, 3H), 1.76 – 1.64 (m, 2H), 1.40 – 1.17 (m, 16H), 0.86 (t, $J_{HH} = 6.4$ Hz, 3H); $^{13}$C$\{^1$H$\}$ NMR (75 MHz, CDCl$_3$) $\delta$ 167.2 (d, $J_{CP} = 1.9$ Hz), 161.1 (d, $J_{CP} = 9.6$ Hz), 115.4 (d, $J_{CP} = 3.8$ Hz), 69.2 (d, $J_{CP} = 6.0$ Hz), 68.2 (d, $J_{CP} = 6.6$ Hz), 52.2, 31.9, 30.3 (d, $J_{CP} = 6.6$ Hz), 29.6, 29.6, 29.5, 29.4, 29.1, 28.2, 25.4, 22.7, 20.40 (d, $J_{CP} = 3.8$ Hz), 14.2; $^{31}$P$\{^1$H$\}$ NMR (121 MHz, CDCl$_3$) $\delta$ -10.8; HRMS (ESI, MH$^+$) calcd for C$_{18}$H$_{30}$O$_6$P 373.1780, found 373.1775.
4.6 References


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