Synthesis of Phosphonomethyl Tetrahydrofurans and Phostones

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Synthesis of Phosphonomethyl Tetrahydrofurans and Phostones

Rishi R. Paudel

M.S., Organic 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 in Chemistry with an emphasis in Organic Chemistry

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ABSTRACT

This work has been divided into two major projects:

1) **Synthesis of phosphonomethyl tetrahydrofurans by using the Mori-Tamaru reaction:** The Mori-Tamaru reaction of phosphonate-substituted dienes is unexplored, and the directing effects of the phosphono-group are uncertain. The objectives of this research are to develop the homoallylation of phosphonodienes with different aldehydes, followed by their cyclization to phosphonomethyl tetrahydrofuran ring systems through an oxa-Michael reaction (Scheme 1).

![Scheme 1: Synthesis of phosphonomethyl tetrahydrofuran](image)

This method has also been applied for the synthesis of 3-hydroxy substituted phosphonomethyl tetrahydrofuran rings (9) which might lead to the synthesis of 2’deoxy C-nucleosides (Scheme 2).

![Scheme 2: Synthesis of 3-hydroxy phosphonomethyl tetrahydrofuran](image)
2) Synthesis of vinyl phosphonates and phostones: Synthetic approaches for phostones are still not fully explored. A recent study of some examples of biologically active phostone derivatives demonstrated that there is a need for additional versatile approaches to phostone synthesis. We have developed a new synthetic approach for phostones starting from readily available starting materials. Our approach to the synthesis of phostones involves the formation of vinyl phosphonates followed by reduction to saturated δ-hydroxy phosphonates, which on cyclization results in phostones (Scheme 3).

Scheme 3: Synthesis of phostones
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CHAPTER I  
SYNTHESIS OF HOMOALLYL ALCOHOLS FROM PHOSPHONODIENES  
USING THE MORI-TAMARU REACTION

1.1. INTRODUCTION
Carbon-carbon bond formation is one of the most useful and fundamental processes for the formation of essential molecules because the C-C bond is the ‘backbone’ of all organic molecules.⁴ Selective and efficient C-C bond formation is always challenging for the synthesis of complex organic molecules.⁵ A number of reliable methods have been established for carbon-carbon bond formation and their application in medicinal chemistry and natural product synthesis. Over the past three decades, a limited number of reactions have been used repeatedly for the synthesis of organic molecules, which narrows the availability of structurally new classes of chemical compounds.⁶ This shows the necessity of development of new and improvement of other less commonly studied reactions. Among the C-C bond forming reactions, metal-catalyzed reductive coupling of olefin-derived nucleophiles with carbonyl compounds has been studied for a very long time and represents an alternative to stoichiometric organometallic reagents in carbonyl addition.⁷ Conjugated dienes are important building blocks in organic chemistry, which can be selectively functionalized with nickel catalysts to generate allyl and homoallyl anions (Scheme 1.1).⁸

Scheme 1.1. Selective formation of allyl anion and homoallyl anion under nickel catalysis
Homoallylation (one additional methylene group compared to allylation) is less common than vinylation and allylation probably, due to limited availability of homoallyl metal species and the lower nucleophilicity of the metal-coordinated intermediate.\(^6\) Initially, Mori introduced the nickel catalyzed coupling of carbonyls with olefins\(^7\) and later Tamaru explored the mechanism of diene-carbonyl reductive coupling.\(^5\), 8-11 The nickel catalyzed homoallylation (reductive coupling) of carbonyls with various 1,3-dienes in the presence BEt\(_3\) or Et\(_2\)Zn was reported as a successful tool for the synthesis of bis-homoallylic alcohols with good yields and excellent levels of 1,3-anti-diastereoselectivity (Scheme 1.2). As Mori and Tamaru explored the nickel catalyzed reaction of olefins with carbonyl compounds, it has become known as the Mori-Tamaru reaction. This reaction has been carried out with a wide variety of dienes and carbonyl compounds.\(^7\)-11

![Scheme 1.2. General representation of Mori-Tamaru reaction](image)

The promoting agents used in the Mori-Tamaru reaction have a double role as 1) an activating agent for the aldehyde making it more electrophilic, and 2) a reducing agent for the reduction of nickel (II) to nickel (0). There are only a limited number of promoting agents used in the literature. Initially, Mori has used the mixture of Et\(_3\)SiH and PPh\(_3\) or DIBAL-H and PPh\(_3\) for intramolecular reductive coupling of diene with aldehyde\(^7\). Later, Tamaru had disclosed Lewis acids such as BEt\(_3\) or Et\(_2\)Zn as promoting agents.\(^5\)-6, 8-11

### 1.1.1. BEt\(_3\) promoted homoallylation

In general, the Mori-Tamaru reaction involves the homoallylation of aldehydes with 1,3-dienes in the presence of catalytic amounts of Ni(acac)\(_2\) and stoichiometric amounts of triethylborane to provide bis-homoallylic alcohols.\(^5\)-6 Different types of 1,3-dienes can be employed in the reaction (Scheme 1.3 & Scheme 1.4).
Kimura has explored the Mori-Tamaru reaction with various dienes. The regioselectivity and stereoselectivity of the product is dependent upon the nature of the diene. For regioselectivity, electron donating substituents at the C2 position direct the addition of the aldehyde to the C1 position resulting bis-homoallylic alcohols. Substituents at the C1 position are less effective than substituents at the C2 position, which direct the addition of the aldehyde to the distal C4 position as well. For stereoselectivity, C2 substituted dienes result in 1,3-anti stereoselectivity, whereas the stereoselectivity of C1-substituted dienes depend upon the geometry of the starting diene. Z-Dienes result exclusively in the 1,2-syn isomers, whereas E-dienes result in 1,2-anti isomers. 1,3-Butadienes with silyloxy or methoxy groups at the C1 or C2 position undergo homoallylic addition of aldehyde with high regio- and stereoselectivity. Kimura also performed a comparative study to show the relative reactivity of substituted dienes (Scheme 1.5). Various dienes were reacted with benzaldehyde in the presence of the Ni(acac)$_2$ catalyst and BEt$_3$ (Scheme 1.5). 2-Silyloxybutadiene (1.1h) is three times more reactive than isoprene (1.1b), but the 1-siloxy isomer (1.1k) is 100 times less reactive than isoprene. Similarly, methyl sorbate (1.1g) is five times less reactive than piperylene (1.1d). This study showed that the relative reactivity is not only dependent on the electronic density of the diene, but also on sterics. In general, the 2-siloxy group has been found to increase the
reactivity but the 1-siloxo group resulted in a decrease in the reactivity of the diene.

| Scheme 1.5. Relative reactivity of dienes toward homoallylation with PhCHO promoted by BEt$_3$.

Mechanistic studies of the reaction by *Kimura* demonstrated that there is a delocalization of electrons through a sequence. The dienes push electron density towards the aldehyde and pull electron density from the nickel (0) species. The pull of electron density from the nickel species becomes effective by the coordination of a Lewis acid to the aldehyde. Due to these two factors, both electron-rich and electron-deficient dienes undergo homoallylation. *Kimura* have used a wide variety of aldehydes in nickel catalyzed reductive coupling with isoprene promoted by BEt$_3$ (Scheme 1.6).

| Scheme 1.6. Aldehydes undergoing homoallylation with isoprene promoted by BEt$_3$. |
Isoprene has been reacted with 50% aqueous solution of glutaraldehyde regioselectively and stereoselectively in the presence of Ni(acac)$_2$ and BEt$_3$ to obtain the homoallylation product (1.5, Scheme 1.7).$^{10}$ The product is 1,3-anti with respect to the tetrahydropyrananyl oxygen and the methyl group. This reaction shows the compatibility of the Mori-Tamaru reaction in water.

\[
\text{1.1b} + \text{CHOCHO} \xrightarrow{\text{cat. Ni(acac)$_2$}} \text{1.5}
\]

Scheme 1.7. Homoallylation of glutaraldehyde with isoprene promoted by BEt$_3$.$^{10}$

Under identical conditions, the cyclic hemiacetal (1.6) was also successfully homoallylated with isoprene to give the corresponding linear alcohol (1.7) (Scheme 1.8).$^{10}$ The successful homoallylation of aqueous glutaraldehyde and a hemiacetal extended the scope of Mori-Tamaru reaction to carbohydrate related chemistry.$^{10}$

\[
\text{1.1b} + \text{HO-} \xrightarrow{\text{cat. Ni(acac)$_2$}} \text{1.7}
\]

Scheme 1.8. Homoallylation of cyclic hemiacetal with isoprene promoted by BEt$_3$.$^{10}$

1.1.1.1. A Mechanistic study of the Mori-Tamaru reaction to rationalize the stereoselectivity:

In the reaction mechanism, the ethylmetal compound (MEt$_n$) has a double role in activating the aldehyde as well as the reducing nickel (II) to nickel (0) species. The regioselectivity of the addition to the carbonyl carbon with an unsymmetrical diene favors the terminal position, which has higher electron density. The nickel (0) complex coordinates with the diene and aldehyde and the reaction proceeds through oxidative cyclization to give the intermediate π-allyl nickel complexes I and VII (Scheme 1.9).
Scheme 1.9. Plausible reaction mechanism leading to the 1,3-anti isomer 5 (Kimura, M.; Tamaru, Y., Nickel-catalyzed reductive coupling of dienes and
During this process, the electron density is not only pushed towards the aldehyde but is also pulled from the nickel (0) species. The former factor is important in electron-rich dienes, whereas the electron pulling factor plays the major role in the reactivity of electron-deficient dienes. Due to these contrary factors, the electronic character of dienes cannot solely determine the reactivity. The π-allyl nickel complex intermediate I is preferred over intermediate VII because the later one suffers from 1,3-diaxial repulsion between the alkyl group of the aldehyde and methyl of the isoprene. This nickel complex transfers an ethyl group from boron to nickel to form an allyl-ethyl nickel complex II in which the Ni-O bond changes from ionic bond character to a coordination bond.

The intermediate II undergoes β-H elimination through a β-agostic interaction accompanied by Ni-O bond cleavage. There are two pathways for the β-hydride elimination, but the route leading to the formation of the intermediate IV through the transition state III is more favored. The resulting complex IV undergoes reductive elimination to give the homoallylation product (anti-1.8). This mechanism helps to understand the rationale for the 1,3-anti-diastereoselectivity in the Mori-Tamaru reaction.

1.1.2. Et₂Zn promoted homoallylation
Et₂Zn has also been employed instead of BEt₃ for the reductive coupling of aldehydes with dienes.⁶ Et₂Zn is more reactive than BEt₃ resulting in a faster reaction. It can promote homoallylation with less reactive aldehydes and ketones which were unreactive with BEt₃.⁶,⁸ However, the homoallylation of ketones with Et₂Zn is less regioselective and stereoselective.⁸ For example, ketone (1.11, Scheme 1.10) with isoprene in the presence of Ni(acac)₂ and Et₂Zn resulted in the formation of alcohol 1.13 (11%) in addition to expected product 1.12 (59%). Similarly, cyclohexanone (1.14) resulted in the formation of alcohol 1.15 (61%) in
addition to compound 1.16 (11%, Scheme 1.10). Formation of these alcohols is due to the addition of carbonyl group to C1 as well as distal C4 position of isoprene. The Et₂Zn-promoted reaction also undergoes ethylation of the aldehyde as a side reaction, which decreases the amount of the homoallylation products. The unsaturated aldehydes may also suffer from Michael addition of Et₂Zn.

![Scheme 1.10](image1)

**Scheme 1.10.** Homoallylation of ketones with isoprene promoted by Et₂Zn.

The diene 1.1m is much less reactive than isoprene as it reacts only with aromatic aldehydes when using Et₃B-Ni catalysis and failed with less electrophilic unsaturated and aliphatic aldehydes. However, homoallylation (1.17) was successful with dihydrocinnamaldehyde (1.2c) promoted by Et₂Zn accompanied with the formation of ethylation product (1.18, Scheme 1.11).

![Scheme 1.11](image2)

**Scheme 1.11.** Homoallylation of electron rich diene with dihydro cinnamaldehyde promoted by Et₂Zn.

However, nickel catalyzed reductive coupling of 1,3-cyclohexadiene (1.19) with benzaldehyde promoted with Et₂Zn resulted in the allylated product (1.20, Scheme 1.12). The rationale for allylation is based on the relative stability of the cyclic σ-allylnickel complex from the s-cis diene, cyclohexadiene. The
homoallylation results from the geometrically more stable $\sigma$-allylnickel complex of the $s$-trans diene.$^5$

Scheme 1.12. Allylation of cyclohexadiene with benzaldehyde promoted by Et$_2$Zn.$^5$

Our group has studied the Mori-Tamaru reaction of 1,3-dienes with hemiacetals and epoxyaldehydes. Hemiacetals 1.21a and 1.21b undergo homoallylation with isoprene to give 1.22 and 1.23 in 1:6 and 1:3 diastereomeric ratio, respectively. Similarly, epoxyaldehyde 1.24 produced the homoallylation products 1.25a and 1.25b in 2.5:1 diastereomeric ratio under standard Mori-Tamaru conditions (Scheme 1.13).$^{12}$

Scheme 1.13. Homoallylation of hemiacetals and epoxyaldehyde with isoprene

Similarly, our group has also studied the Mori-Tamaru reactions of various chiral and achiral aldehydes with chiral dienes. The homoallylation of $R$-aldehyde (1.26) with chiral pentadienoate (1.27) resulted in the separable diastereomeric mixture of corresponding alcohols (1.28a and 128b) in 5:1 ratio (Scheme 1.14).$^{13}$
Scheme 1.14. Homoallylation of \( R \)-aldehyde with chiral pentadienoate

The homoallylation of \( S \)-aldehyde (1.26) with chiral pentadienoate (1.27) resulted in the products (1.30a and 1.30b) with a lower diastereomeric ratio 2:1 (Scheme 1.15).\(^\text{13}\)

Scheme 1.15. Homoallylation of \( S \)-aldehyde with chiral pentadienoate

Our group has also applied the Mori-Tamaru reaction to the synthesis of the C1-C9 fragment of amphidinolides C and F (1.36), where Mori-Tamaru reaction of an ester-functionalized diene has been used to avoid an expensive olefin metathesis step. Bis-homoallylic alcohol 1.34 can be synthesized with a Mori-Tamaru reaction from 1.35 (Scheme 1.16).\(^\text{13}\)

Scheme 1.16. Application of Mori-Tamaru reaction in Amphidinolide synthesis
1.2. RESULTS AND DISCUSSION

The Mori-Tamaru reaction of phosphonate substituted dienes (1.42a-c, Scheme 1.17) is unexplored and the directing effects of this phosphono-group are uncertain. The objectives of this chapter of the thesis are to develop and modify the homoallylation of phosphonodienes with different aldehydes. Based on previous reactions and the structural variety of dienes and aldehydes, it was postulated that the phosphonodiene should also react with aldehydes in a similar pattern to give the corresponding phosphono bis-homoallylic alcohol (vinyl phosphonate, 1.38). Herein, nickel catalyzed reductive coupling of phosphonodiene with aldehydes will be discussed.

Scheme 1.17. Retrosynthesis of phosphono bis-homoallylic alcohol

1.2.1. Synthesis of phosphonodienes

The dienes 1.41a-c were synthesized via the Horner-Wadsworth-Emmons (HWE) reaction between the tetraethyl methylene bis-phosphonate (1.40) and the corresponding aldehydes (1.39a-c, Scheme 1.18).

Scheme 1.18. HWE reaction for the synthesis of phosphonodienes

The aldehyde 1.39c was prepared from 1,1,3,3-tetraethoxyp propane by following a published procedure.14-15 Initially, The tetraethoxyp propane (1.37) was subjected to acid hydrolysis followed by conversion to the malondialdehyde
tetrabutylammonium salt (1.38),\textsuperscript{14} which was benzylated with BnBr in the presence of benzoquinone as a radical scavenger (Scheme 1.19).\textsuperscript{15}

\[
\begin{align*}
\text{EtO} & \quad \text{OEt} \\
\text{OEt} & \quad \text{EtO} \\
\text{1.37} & \quad \text{i) 1N HCl, H2O} \\
& \quad \text{ii) TBA-OH (in MeOH)} \\
& \quad \text{iii) glyme (recrystallization)} \\
\text{55%} & \quad \text{OHC} - \text{O} \\
& \quad \text{NBu4} \\
\text{1.38} & \quad \text{MS 3 Å, 24 h, 40 °C, 71%} \\
\text{BnBr (1.3 equiv), DMF} & \quad \text{Benzoquinone (0.02 equiv)} \\
\text{1.39c} & \quad \text{OHC} \quad \text{OBn}
\end{align*}
\]

Scheme 1.19. Synthesis of benzylated aldehyde (3-(benzyloxy)propenal (1.39c)

1.2.2. Mori-Tamru reaction of phosphonodiene

Reaction of the phosphonodiene 1.41a under standard Mori-Tamru conditions gave the corresponding vinyl phosphonate (1.42, Scheme 1.20). The isolated yields were lower than expected because the reaction was complicated by the formation of byproducts. Therefore, the reaction conditions needed to be optimized. The byproducts were isolated and identified as alkenes (1.43 & 1.44, Scheme 1.20). These alkenes were assumed to be formed by reduction of the diene with nickel hydrides formed by the decomposition of the catalyst.

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{1.41a} & \quad \text{Ni(acac)2 (10 mol%)} \\
& \quad \text{OCHO} \\
& \quad \text{BEt3 or AlEt3} \\
& \quad \text{THF} \\
\text{RCHO} & \quad \text{EtO} \quad \text{EtO} \\
\text{EtO} & \quad \text{1.42} \\
& \quad \text{OH} \\
& \quad \text{EtO} \quad \text{EtO} \\
\text{1.43} & \quad \text{EtO} \quad \text{1.44}
\end{align*}
\]

Scheme 1.20. Mori-Tamru reaction of phosphonodiene and aldehydes

More reactive alkyl metals were postulated to decrease the reaction time and increase the activation of aldehyde, which may reduce byproduct formation ultimately increasing the yields of the product. Different alkyl metal reagents such as AlEt3, Et2Zn, AlEt2Cl, and i-PrMgCl were examined among which AlEt3 turned out to be the most efficient. The use of AlEt3 instead of BEt3, resulted in a higher product yield (Table 1.1) with similar 1,3-anti diastereoselectivity. The ratio of products and byproducts were reduced from 3:1:2 (1.42:1.43:1.44) to 10-40:2:1 (1.42:1.43:1.44). The reaction time was also reduced from 36 h to 5 h. Unfortunately, 4-hydroxy benzaldehyde did not give the desired product 1.42g with AlEt3. The possible reason may be the side reaction of phenol with AlEt3 resulting in triphenoxy aluminium complex.
Table 1.1. Mori-Tamaru reaction of phosphonodiene 1.41a with aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (R)</th>
<th>Yield of 1.42 with BEt₃ (%)&lt;sup&gt;i&lt;/sup&gt;</th>
<th>Yield of 1.42 with AlEt₃ (%)&lt;sup&gt;ii&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>45</td>
<td>72</td>
</tr>
<tr>
<td>b</td>
<td>Ethyl</td>
<td>41</td>
<td>65</td>
</tr>
<tr>
<td>c</td>
<td>2-furyl</td>
<td>26</td>
<td>63</td>
</tr>
<tr>
<td>d</td>
<td>2-thiophenyl</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>e</td>
<td>2-naphthyl</td>
<td>47</td>
<td>61</td>
</tr>
<tr>
<td>f</td>
<td>4-fluorophenyl</td>
<td>36</td>
<td>60</td>
</tr>
<tr>
<td>g</td>
<td>4-hydroxyphenyl</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>h</td>
<td>1-butyl</td>
<td>-</td>
<td>21</td>
</tr>
</tbody>
</table>

Reaction conditions: i) BEt₃ (1M in THF) 2.6 equiv, Ni(acac)<sub>2</sub> 0.1 equiv, RCHO 2 equiv, THF, rt, 36 h; ii) AlEt₃ (1M in hexane) 3.5 equiv, Ni(acac)<sub>2</sub> 0.36 equiv, RCHO 3.5 equiv, THF, -50 °C to 0 °C, 5 h

The Mori-Tamaru reaction of N-methyl-indole-3-carboxaldehyde, N-methyl pyrrole carboxaldehyde, pyridine carboxaldehyde and unsaturated aldehydes (crotonaldehyde, ethyl-trans-4-oxo-2-butenooate) failed to form the desired product (Scheme 1.21 and Scheme 1.22).

Scheme 1.21. Mori-Tamaru reaction attempt with N-heterocyclic aldehydes failed
Scheme 1.22. Mori-Tamaru reaction attempts with unsaturated aldehydes failed

The reason behind these failures may be the reaction of Lewis acid with electron rich species rather than activating aldehyde.

Mori-Tamaru reactions of both the 4-methyl diene (1.41b) and the 4-O-benzyl substituted diene (1.41c) failed with AlEt₃ (Scheme 1.23). However, the 4-methyl substituted diene 1.41b reacted with BEt₃ and Ni(acac)₂ to give a small amount of impure bis-homoallylic alcohol, which was cyclized directly to tetrahydrofuran resulting in 16% overall yield (see Chapter II).

Scheme 1.23. Mori-Tamaru reaction attempts of 4-position substituted dienes

1.2.3. Synthesis of OTBS substituted phosphonodiene
The OTBS substituted phosphonodiene (1.41d) was prepared from the keto phosphonate (1.52). Initially, the keto vinyl phosphonate (1.52, Scheme 1.24) was synthesized by a cross metathesis reaction between diethyl vinyl phosphonate (1.50) and methyl vinyl ketone (1.51) using Hoveyda Grubbs catalysis. However, the reaction was incomplete and resulted in only partial (~20%) conversion to the product.
Scheme 1.24. Cross metathesis reaction for keto vinyl phosphonate 1.52

To avoid the expensive and incomplete olefin metathesis reaction, the keto vinyl phosphonate (1.52, Scheme 1.25) was synthesized by reaction of methyl vinyl ketone (1.51) and triethyl phosphite (1.53). The reaction involves the formation of pentacovalent oxaphospholene intermediate 1.54, which reacts with electrophilic bromine (Br$_2$) to give the $\alpha$-bromo-keto phosphonate 1.55. Pentacovalent oxaphospholene 1.54 is highly sensitive to hydrolysis; therefore, the reaction should be run under an argon purge in the presence of freshly activated molecular sieves. The $\alpha$-bromo-keto phosphonate 1.55 undergoes an elimination reaction with triethyl amine to give keto-vinyl phosphonate (1.52). Once the keto-vinyl phosphonate 1.52 has been synthesized, it was subjected to silylation with TBSOTf utilizing 2,6-luitidine as the base to obtain the OTBS substituted diene 1.41d (Scheme 1.25). All the reactions related to the OTBS substituted diene synthesis can be monitored with $^{31}$P {$^1$H} NMR. Using this method, preparation of the OTBS substituted diene was significantly improved compared to the previously known methods and could be run on a multigram scale.$^{16-17}$

Scheme 1.25. Synthesis of OTBS substituted diene
1.2.4. Mori-Tamaru reaction of OTBS substituted phosphonodiene

We were pleased to observe that Mori-Tamaru reaction of the OTBS substituted diene (1.41d, Scheme 1.26) with benzaldehyde using Ni(acac)$_2$ and AlEt$_3$ gave the expected product of bis-homoallylic alcohol (1.57) with 72% yields and excellent 1,3-anti diastereoselectivity (Scheme 1.26). This reaction was not successful when using standard Mori-Tamaru reaction conditions with BEt$_3$. This reaction has demonstrated potential application of the Mori-Tamaru reaction for the synthesis of oxygen containing building blocks.

\[
\text{EtO} \begin{array}{c} \P \O \\ \O \end{array} \begin{array}{c} \O \\ \O \end{array} \text{PhCHO, Ni(acac)$_2$, AlEt$_3$, THF} \\
\text{OTBS} \begin{array}{c} \O \\ \O \end{array} \text{EtO} \begin{array}{c} \P \O \\ \O \end{array} \text{Ph} \\
\text{OTBS} \begin{array}{c} \O \\ \O \end{array} \text{EtO} \begin{array}{c} \P \O \\ \O \end{array} \text{OH} \\
\pm 1.57
\]

Scheme 1.26. Mori-Tamaru reaction of a OTBS substituted diene with benzaldehyde

Similarly, the diene (1.41d) also reacted with piperonal (1.58, Scheme 1.27) diastereoselectively under modified Mori-Tamaru conditions to give the corresponding bis-homoallylic alcohol (1.59, Scheme 1.27).

\[
\text{EtO} \begin{array}{c} \P \O \\ \O \end{array} \begin{array}{c} \O \\ \O \end{array} \text{OTBS} \begin{array}{c} \O \\ \O \end{array} \text{OH} \\
\text{Ni(acac)$_2$, AlEt$_3$, THF} \\
\text{PhO} \begin{array}{c} \O \\ \O \end{array} \text{O} \\
\pm 1.59
\]

Scheme 1.27. Mori-Tamaru reaction of the OTBS substituted diene (1.41d) with piperonal (1.58)
1.3. SUMMARY

1) The Mori-Tamaru reaction of phosphonodienes has been reported for the first time and various aldehydes ranging from alkyl to aryl and heteroaryl substituted aldehydes were implemented for the nickel catalyzed reductive coupling with different phosphonodienes.

2) Standard Mori-Tamaru reaction conditions (i.e., with BEt₃) were partially successful for the 3-methyl substituted phosphonodiene, whereas they were not applicable for the 3-OTBS substituted phosphonodiene. This limitation has been overcome using AlEt₃ instead of BEt₃.

3) The Mori-Tamaru reaction of 4-substituted hydroxy benzylated diene was unsuccessful with both BEt₃ and AlEt₃.

4) During the synthesis of 3-OTBS substituted dienes, an improved synthetic approach has been developed which can be performed on a multigram scale.

5) The Mori-Tamaru reaction of 3-OTBS substituted diene can be useful for the synthesis of building blocks for biologically important organic molecules such as C-nucleosides.
1.4. GENERAL EXPERIMENTAL

All reactions were carried out in oven-dried glassware under an atmosphere of argon unless otherwise noted. THF was distilled from Na/benzophenone, toluene from CaH₂, MeOH from Mg/Mg(OMe)₂, and CH₂Cl₂ from CaH₂. ¹H, ¹³C{¹H}, and ³¹P{¹H} NMR spectra were recorded in CDCl₃ at 300, 75, and 121 MHz, respectively. ¹H NMR spectra are referenced to CDCl₃ (7.27 ppm), ¹³C{¹H} NMR spectra are referenced to the center line of CDCl₃ (77.23 ppm), and ³¹P{¹H} NMR spectra are referenced to external H₃PO₄. Coupling constants, J, are reported in hertz (Hz). Analytical thin-layer chromatography (TLC) analyses were performed on silica gel plates 60PF₂₅₄. Visualization was accomplished with UV light and KMnO₄ solution.

(E)-Diethyl-3-methylbuta-1,3-dienylphosphonate (1.41a)¹⁸

![Chemical structure](image)

To a stirred ice-cold suspension of NaH (60% in mineral oil, 1.28 g, 32.20 mmol, 1.2 equiv) in dry THF (30 mL), was slowly added tetraethyl methylene bisphosphonate (8 mL, 32.20 mmol, 1.2 equiv). The resulting mixture was stirred for 20 min at 0 °C and then methacrolein (1.39a) (1.87 g, 26.68 mmol, 1.0 equiv) in THF (5 mL) was slowly added. The resulting mixture was stirred for 2 h at 0 °C and then the reaction mixture was warmed up to room temperature and stirred for additional 1 h (monitored by TLC). The reaction was quenched by the addition of saturated aqueous NH₄Cl, followed by extraction with CH₂Cl₂. The organic layer was washed with saturated NaHCO₃, brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (SiO₂, EtOAc: hexanes, 40:60) to give the pure diene (1.41a)¹⁸ (4.80 g, 23.51 mmol, 88%) as a colorless liquid. ¹H and ¹³C{¹H} NMR spectra were consistent with published values.¹⁸
(1E, 3E)-Diethyl-penta-1,3-dienylphosphonate (1.41b)\textsuperscript{19}

\[
\begin{array}{c}
\text{EtO}_2\text{P} \\
\text{O} \\
\text{EtO} \\
\end{array}
\]

To a stirred ice-cold suspension of NaH (60% in mineral oil, 0.35 g, 8.56 mmol, 1.2 equiv) in dry THF (10 mL), was slowly added tetraethyl methylene bisphosphonate (2.12 mL, 8.56 mmol, 1.2 equiv). The resulting mixture was stirred for 20 min at 0 °C, then crotonaldehyde (1.39b) (0.5 g, 7.13 mmol, 1.0 equiv) in THF (5 mL) was slowly added. The resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was then warmed to room temperature and stirred for additional 1 h (monitored by TLC). The reaction was quenched by the addition of saturated aqueous NH\textsubscript{4}Cl, followed by extraction with CH\textsubscript{2}Cl\textsubscript{2}. The organic layer was washed with saturated NaHCO\textsubscript{3}, brine and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (SiO\textsubscript{2}, EtOAc: hexanes, 50:50) to give the pure diene (1.41b,\textsuperscript{19} 1.12 g, 5.49 mmol, 77%) as a pale-yellow liquid. \textsuperscript{1}H and \textsuperscript{13}C\{\textsuperscript{1}H\} NMR spectra were consistent with published values.\textsuperscript{19}

(E)-3-(Benzyloxy)propanal (1.39c)

\[
\begin{array}{c}
\text{OHC} \\
\text{OBn} \\
\end{array}
\]

A solution of 1,1,3,3-tetrahydroxypropane (2.2 g, 10 mmol, 1 equiv.) (1.37) in water (5 mL) and 1N HCl (2 mL) was stirred at 50 °C for 30 minutes and then at room temperature for another 30 minutes to obtain a homogeneous solution. 1M solution of tetrabutylammonium hydroxide in methanol (10 mL, 1 equiv.) was added slowly at 0 °C. After stirring for 30 minutes, the reaction mixture was evaporated in vacuo and the residue was dissolved in dimethoxy ethane and left for crystallization in the refrigerator overnight. The orange-colored needle-shaped malondialdehyde tetrabutylammonium salt (1.38) was formed after recrystallization (1.71g, 5.51 mmol, 55%). The MDA salt (1.38) (2.0 g, 6.38 mmol) was dissolved in DMF (30 mL) in the presence of Molecular sieves 3 Å (6.5 g) followed by benzoquinone (0.015 g, 0.13 mmol, 0.02 equiv.) addition. Then, benzyl bromide (1.42 g, 8.29 mmol, 1.3 equiv.) was added and stirred for
24 h at 40 °C. The product was filtered through silica pad with CH₂Cl₂ and concentrated in vacuo followed by purification with column chromatography (SiO₂, EtOAc: hexanes, 40:60) to obtain the product as a reddish brown liquid (0.732 g, 4.51 mmol, 71%).

(1E, 3E)-Diethyl-4-(benzyloxy)buta-1,3-dienylphosphonate (1.41c)

\[
\begin{array}{c}
\text{EtO} \quad \text{P} \quad \text{O} \\
\text{EtO} \quad \text{O} \quad \text{OBn}
\end{array}
\]

To a stirred ice-cold suspension of NaH (60% in mineral oil, 0.097 g, 2.44 mmol, 1.2 equiv) in dry THF (5 mL), was slowly added tetraethyl methylene bisphosphonate (0.7 mL, 2.44 mmol, 1.2 equiv). The resulting mixture was stirred for 20 min at 0 °C and then 3-(benzyloxy)propenal (0.33 g, 2.03 mmol, 1.0 equiv) in THF (2 mL) was slowly added and the solution was stirred for 2 h at 0 °C. The reaction mixture was warmed up to room temperature and stirred for additional 1 h (monitored by TLC). The reaction was quenched by the addition of saturated aqueous NH₄Cl, followed by extraction with CH₂Cl₂. The organic layer was washed with saturated NaHCO₃, brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (SiO₂, EtOAc: hexanes, 40:60) to give diene (1.41c) (0.39 g, 1.32 mmol, 65%) as a pale-yellow liquid. IR (neat) 2981, 2909, 2117, 1717, 1012 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.31 (m, 5H), 7.01 (ddd, J_HP = 21.1, J_HH = 16.6, 11.1 Hz, 1H), 6.91 (d, J_HH = 9 Hz, 1H), 5.77-5.69 (m, 1H), 5.43 (dd, J_HP = 19.3, J_HH = 16.7 Hz, 1H), 4.86 (s, 2H), 4.09–3.99 (m, 4H), 1.30 (t, J_HH = 7.1 Hz, 3H), 1.30 (t, J_HH = 7.1 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 156.9 (d, J_CP = 1.0 Hz), 147.2 (d, J_CP = 7.2 Hz), 135.8, 128.8, 128.6, 127.8, 110.5 (d, J_CP = 193 Hz), 106.9 (d, J_CP = 27.5 Hz), 72.7, 61.6 (d, J_CP = 5.3 Hz), 16.5 (d, J_CP = 6.6 Hz); ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 20.9; HRMS (FAB) m/z: [M+H]⁺ Calcd for C₁₅H₂₂O₄P 297.1255; Found 297.1252.
\textbf{(E)-Diethyl 3-oxobut-1-enylphosphonate (1.52)}^{16}

To an oven dried flask containing freshly activated 3 Å molecular sieves (7 g), was added methyl vinyl ketone (1.0 mL, 12.55 mmol, 1.0 equiv.) and triethyl phosphite (3.0 mL, 0.018 mmol, 1.1 equiv.) sequentially (a small of dry toluene can be used to aid in the stirring the reaction mixture). The reaction mixture was stirred for 15 h at room temperature (monitored by $^{31}$P{\textsuperscript{1}H} NMR). The reaction mixture was cooled to 0 °C and dry toluene (10 mL) was added via syringe, followed by Br$_2$ and stirring was continued for 2 h at 0 °C. The reaction mixture was filtered through a celite pad washing with CH$_2$Cl$_2$ and the organic solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO$_2$, EtOAc: hexanes, 40:60) to give the α-bromo-keto phosphonate 1.55 (1.85 g, 6.45 mmol, 51%) as a yellow oil which was used directly in the next step (Note: It is a quite stable compound and can be stored in a fridge). To a solution of α-bromo-keto phosphonate 1.55 (1.9 g, 6.62 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (25 mL) at 0 °C, was added Et$_3$N (1.85 mL, 13.2 mmol, 2.0 equiv) and the resulting solution stirred for 2.5 h (monitored by TLC). The reaction was quenched by addition of water (5 mL), extracted with CH$_2$Cl$_2$ (3x30 mL) and the combined extracts were dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography (SiO$_2$, EtOAc: hexanes, 70:30) to give the keto vinyl phosphonate (1.52)$^{16}$ (1.29 g, 6.25 mmol, 95%). $^1$H and $^{13}$C{\textsuperscript{1}H} NMR spectra were consistent with published values.$^{16}$

\textbf{Diethyl (1E, 3E)-3-(tert-butylidimethylsilyloxy)buta-1,3-dienyl phosphonate (1.41d)}

To a solution of keto vinyl-phosphonate (1.52) (1.0 g, 4.85 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (40 mL) at 0 °C, was added 2,6-luitidine (1.7 mL, 14.6 mmol, 3.0 equiv).
The reaction mixture was stirred for 30 min at 0 °C under argon atmosphere and then TBSOTf (3.4 mL, 14.6 mmol, 3.0 equiv) was added dropwise. The resulting solution was stirred 3 h at 0 °C (monitored by TLC). Additional 2,6-luitidine (0.56 mL, 4.85 mmol, 1.0 equiv) and TBSOTf (1.13 mL, 4.85 mmol, 1.0 equiv) was added and the solution was stirred for an additional 1 h at 0 °C. The reaction mixture was quenched by addition of water and then filtered through a silica pad washing with CH₂Cl₂. The solution was concentrated under reduced pressure and residue was purified by column chromatography (SiO₂, EtOAc: hexanes, 30:70) to give the silyl dienyl ether (1.41d) (1.49 g, 4.65 mmol, 96%) as a colorless liquid. ¹H and ¹³C{¹H} NMR spectra were consistent with published values.¹⁷

**General Procedure (A): Mori Tamaru Reaction of Diene 1.42a using BEt₃**

To a flask containing dienylphosphonate (1.41a) (0.1 g, 0.49 mmol, 1.0 equiv) and Ni(acac)₂ (0.013 g, 0.049 mmol, 0.1 equiv) was added freshly distilled THF (6 mL). The mixture was stirred for 10 min at room temperature and then the aldehyde (0.98 mmol, 2.0 equiv) followed by BEt₃ in THF (1.0M, 1.3 mL, 1.3 mmol, 2.6 equiv) were added. The reaction was stirred for 36 h at room temperature. The reaction was quenched by addition of 1N HCl (2 mL) with continuous stirring. After 5 min, the mixture was extracted with EtOAc (3x20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The products 1.42a-g, 1.43 and 1.44 were isolated by column chromatography (SiO₂, 80-100% EtOAc in hexanes).

**General Procedure (B): Mori Tamaru Reaction of Diene 1.42a using AlEt₃**

To a flask containing dienylphosphonate 1.41a (0.1 g, 0.49 mmol, 1.0 equiv) and Ni(acac)₂ (0.045 g, 0.18 mmol, 0.36 equiv) was added freshly distilled THF (6mL). The mixture was stirred for 10 min at room temperature and then the aldehyde (1.72 mmol, 3.5 equiv) was added. After an additional 10 min, the solution was cooled to -50 °C and AlEt₃ in hexanes (1.0 M, 1.72 mL, 1.72 mmol,
3.5 equiv) was added slowly. Stirring was continued for an additional 20 min at -50 °C, then the solution temperature was increased to 0 °C and the reaction mixture was stirred for 4 h (monitored by TLC). The reaction was quenched by addition of 1N HCl (2 mL) with continuous stirring. After 5 min, the mixture was extracted with EtOAc (3x20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The products 1.42a-h isolated by column chromatography (SiO₂, 80-100% EtOAc in hexanes).

(±) Diethyl (3S, 5S, E)-(5-hydroxy-3-methyl-5-phenyl)-pent-1-enyl phosphonate (1.42a)

Following the general procedure B, phosphonodiene 1.41a (0.1 g, 0.49 mmol, 1.0 equiv) was reacted to obtain 1.42a (0.109 g, 0.35 mmol, 72%) as a colorless viscous liquid after column chromatography (SiO₂, EtOAc: hexanes 90:10). IR (neat) 3356, 2977, 2121, 1624, 1222, 1018 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.22 (m, 5H), 6.71 (ddd, Jᵢ جهة = 22.3, Jᵢ جهة = 17.2, 7.3 Hz, 1H), 5.55 (ddd, Jᵢ جهة = 18.4, Jᵢ جهة = 17.2, 1.1 Hz, 1H), 4.69 (dd, Jᵢ جهة = 12 Hz, Jᵢ جهة = 6 Hz, 1H), 4.02 (m, 4H), 3.14 (s, 1H), 2.45 (m, 1H), 1.97-1.87 (m, 1H), 1.65-1.56 (m, 1H), 1.31 (t, Jᵢ جهة = 6.0 Hz, 6H), 1.10 (d, Jᵢ جهة = 6.5 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 158.9 (d, JᵢCₚ = 4.0 Hz), 144.9, 128.5, 127.5, 126.0, 114.7 (d, JᵢCₚ = 188 Hz), 71.8, 61.7 (d, JᵢCₚ = 5.5 Hz), 44.9, 35.0 (d, JᵢCₚ = 21.1 Hz), 18.8, 16.4 (d, JᵢCₚ = 6.6 Hz); ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 19.2; HRMS (FAB) m/z: [M+Na]+ Calcd for C₁₆H₂₅O₄PNa 335.1388, Found 335.1384.

(±) Diethyl (3S, 5R, E)-(5-hydroxy-3-methyl) hept-1-enyl phosphonate (1.42b)
Following the general procedure B, phosphonodiene 1.41a (0.1 g, 0.49 mmol, 1.0 equiv) was reacted to obtain 1.42b (0.084 g, 0.32 mmol, 65%) as a colorless liquid after column chromatography (SiO<sub>2</sub>, EtOAc: hexanes, 90:10). IR (neat) 3400, 2960, 2119, 1624, 1225, 1020 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.68 (ddd, J<sub>HP</sub> = 22.3, J<sub>HH</sub> = 17.2, 7.1 Hz, 1H), 5.53 (ddd, J<sub>HP</sub> = 20.9, J<sub>HH</sub> = 17.2, 1.3 Hz, 1H), 3.99-3.90 (m, 4H), 3.50-3.42 (m, 1H), 2.84 (s, 1H), 2.53-2.44 (m, 1H), 1.50-1.32 (m, 4H), 1.21 (t, J<sub>HH</sub> = 7.1 Hz, 6H), 0.99 (d, J<sub>HH</sub> = 6.7 Hz, 3H), 0.82 (t, J<sub>HH</sub> = 7.4 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ 159.6 (d, J<sub>CP</sub> = 3.7 Hz), 114.0 (d, J<sub>CP</sub> = 188 Hz), 70.2, 61.6 (d, J<sub>CP</sub> = 5.4 Hz), 42.7, 34.7 (d, J<sub>CP</sub> = 20.9 Hz), 30.7, 18.3, 16.3 (d, J<sub>CP</sub> = 6.4 Hz), 9.9; <sup>31</sup>P{<sup>1</sup>H} NMR (121 MHz, CDCl<sub>3</sub>) δ 19.5; HRMS (FAB) m/z: [M+H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>26</sub>O<sub>4</sub>P 265.1569, Found 265.1572.

(±) Diethyl (3S, 5S, E)-5-hydroxy-3-methyl-5-(fur-2-yl)-pent-1-enyl phosphonate (1.42c)

Following the general procedure B, phosphonodiene 1.41a (0.1 g, 0.49 mmol, 1.0 equiv) was reacted to obtain 1.42c (0.095 g, 0.31 mmol, 63%) as a colorless viscous liquid after column chromatography (SiO<sub>2</sub>, EtOAc: hexanes, 90:10). IR (neat) 3363, 2929, 1625, 1220, 1018 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.36-7.34 (m, 1H), 6.70 (ddd, J<sub>HP</sub> = 22.2, J<sub>HH</sub> = 17.2, 7.4 Hz, 1H), 6.31 (m, 1H), 5.58 (ddd, J<sub>HP</sub> = 20.5, J<sub>HH</sub> = 17.2, 1.1 Hz, 1H), 4.69 (t, J<sub>HP</sub>= 7.0 Hz, 1H), 4.04 (m, 4H), 2.46 (m, 2H), 2.03-1.91 (m, 1H), 1.85-1.75 (m, 1H), 1.30 (m, 6H), 1.08 (d, J<sub>HH</sub> = 6.7 Hz, 4H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ 158.2 (d, J<sub>CP</sub> = 4.1 Hz), 156.4, 142.1, 115.4 (d, J<sub>CP</sub> = 188 Hz), 110.2, 106.2, 65.4, 61.7 (d, J<sub>CP</sub> = 5.5 Hz), 41.2, 34.8 (d, J<sub>CP</sub> = 21.2 Hz), 18.1, 16.1 (d, J<sub>CP</sub> = 6.5 Hz); <sup>31</sup>P{<sup>1</sup>H} NMR (121 MHz, CDCl<sub>3</sub>) δ 19.0; HRMS (FAB) m/z: [M+Na]<sup>+</sup> Calcd for C<sub>14</sub>H<sub>23</sub>O<sub>5</sub>PNa 325.1179, Found 325.1175.
(±) Diethyl (3S, 5S, E)-(5-hydroxy-3-methyl-5-(thiophen-2-yl)-pent-1-enyl phosphonate (1.42d)

Following the general procedure B, phosphonodiene 1.41a (0.1 g, 0.49 mmol, 1.0 equiv) was reacted to obtain 1.42d (0.092 g, 0.29 mmol, 59%) as a colorless liquid after column chromatography (SiO₂, EtOAc: hexanes, 90:10). IR (neat) 3333, 2976, 2926, 1624, 2116, 1221, 1018 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.21 (m, 1H), 6.94-6.89 (m, 2H), 6.70 (ddd, Jₜp = 22.2, Jₜh = 17.2, 7.4 Hz, 1H), 5.57 (ddd, Jₜp = 20.6, Jₜh = 17.2, 1.1 Hz, 1H), 4.92 (dd, Jₜp = 8.0, Jₜh = 6.1 Hz, 1H), 4.08-3.97 (m, 4H), 3.13 (s, 1H), 2.52-2.43 (m, 1H), 2.05-1.96 (m, 1H), 1.78-1.69 (m, 1H), 1.32-1.27 (m, 6H), 1.08 (d, Jₜh = 6.7 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ: 158.4 (d, J_CP = 4.1 Hz), 148.9, 126.8, 124.7, 123.9, 115.3 (d, J_CP = 188 Hz), 67.8, 61.8 (d, J_CP = 5.6 Hz), 45.1, 35.1 (d, J_CP = 21.3 Hz), 18.9, 16.5 (d, J_CP = 5.7 Hz); ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 19.1; HRMS (FAB) m/z: [M+Na]⁺ Calcd for C₁₄H₂₃O₄PSNa 341.0952, Found 341.0946.

(±) Diethyl (3S, 5S, E)-(5-hydroxy-3-methyl-5-(naphtha-2-yl)-pent-1-enyl phosphonate (1.42e)

Following the general procedure B, phosphonodiene 1.41a (0.1 g, 0.49 mmol, 1.0 equiv) was reacted to obtain 1.42e (0.106 g, 0.29 mmol, 61%) as a colorless liquid after column chromatography (SiO₂, EtOAc: hexanes 90:10). IR (neat) 3357, 2976, 2926, 2089, 1624, 1221, 1018 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.84-7.74 (m, 4H), 7.50-7.43 (m, 3H), 6.76 (ddd, Jₜp = 22.2, Jₜh = 17.2, 7.4 Hz, 1H), 5.58 (ddd, Jₜp = 20.6, Jₜh = 17.2, 1.1 Hz, 1H), 4.86 (dd, Jₜp = 7.8, Jₜh = 6.0 Hz, 1H), 4.10-3.96 (m, 4H), 2.63 (s, 1H), 2.53-2.39 (m, 1H), 2.07-1.92 (m, 1H), 1.81-1.66 (m, 1H), 1.37-1.26 (m, 6H), 1.10 (d, Jₜh = 6.7 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ: 158.6 (d, J_CP = 3.9 Hz), 141.9, 133.3, 133.1, 128.5, 127.9,
127.7, 126.3, 126.0, 124.8, 124.0, 115.1 (d, \( J_{CP} = 186 \) Hz), 72.3, 61.7 (d, \( J_{CP} = 6.4 \) Hz); \(^{31}\)P{\(^1\)H} NMR (121 MHz, CDCl\(_3\)) \( \delta \) 19.2; HRMS (FAB) \( m/z \): [M+Na]\(^+\) Calcd for C\(_{20}\)H\(_{27}\)O\(_4\)PNa 385.1545, Found 385.1539.

(±) Diethyl (3S, 5S, E)-(5-hydroxy-3-methyl-5-(4-fluorophenyl)-pent-1-enyl phosphonate (1.42f)

Following the general procedure B, phosphonodiene 1.41a (0.1 g, 0.49 mmol, 1.0 equiv) was reacted to obtain 1.42f (0.097 g, 0.29 mmol, 60%) as a colorless liquid after column chromatography (SiO\(_2\), EtOAc: hexanes 90:10). IR (neat) 3378, 2978, 2906, 2056, 1601, 1506, 1221, 1019 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.25-7.20 (m, 2H), 7.00-6.91 (m, 2H), 6.64 (ddd, \( J_{HP} = 22.2 \) Hz, \( J_{HH} = 17.2, 17.2, 1.2 \) Hz, 1H), 5.49 (ddd, \( J_{HP} = 20.7 \) Hz, \( J_{HH} = 17.2, 1.2 \) Hz, 1H), 4.60 (dd, \( J_{HP} = 8.1 \) Hz, \( J_{HH} = 5.8 \) Hz, 1H), 4.06-3.90 (m, 4H), 3.00 (s, 1H), 2.36 (m, 1H), 1.87-1.78 (m, 1H), 1.56-1.47 (m, 1H), 1.23 (m, 6H), 1.01 (d, \( J_{HH} = 6.7 \) Hz, 3H); \(^{13}\)C{\(^1\)H} NMR (75 MHz, CDCl\(_3\)) \( \delta \) 162.2 (d, \( J_{CF} = 244 \) Hz), 158.6 (d, \( J_{CP} = 4.1 \) Hz), 140.5 (d, \( J_{CF} = 3.2 \) Hz), 127.6 (d, \( J_{CF} = 8.0 \) Hz), 115.3 (d, \( J_{CF} = 21 \) Hz), 115.0 (d, \( J_{CP} = 187 \) Hz), 71.4, 61.8 (d, \( J_{CP} = 7.2 \) Hz), 45.0, 35.1 (d, \( J_{CP} = 21.2 \) Hz), 18.9, 16.4 (d, \( J_{CP} = 6.2 \) Hz); \(^{31}\)P{\(^1\)H} NMR (121 MHz, CDCl\(_3\)) \( \delta \) 19.1; HRMS (FAB) \( m/z \): [M+Na]\(^+\) Calcd for C\(_{16}\)H\(_{24}\)FO\(_4\)PNa 353.1293, Found 353.1288.

(±) Diethyl (3S, 5S, E)-(5-hydroxy-3-methyl-5-(4-hydroxyphenyl)-pent-1-enyl phosphonate (1.42g)

Following the general procedure A, phosphonodiene 1.41a (2.0 g, 9.78 mmol, equiv) was reacted to obtain 1.42g (0.467 g, 1.43 mmol, 17%) as a colorless
liquid after column chromatography (SiO₂, EtOAc: hexanes, 90:10). IR (neat) 3244, 2087, 1612, 1204 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.15 (s, 1H), 7.03 (d, J₃H = 8.5 Hz, 2H), 6.75 (d, J₃H = 8.5 Hz, 2H), 6.63 (ddd, J₂H = 22.5, J₃H = 17.2, 7.4 Hz, 1H), 5.46 (ddd, J₂H = 21.3, J₃H = 17.2, 1.1 Hz, 1H), 4.42 (dd, J₂H = 12 Hz, J₃H = 6 Hz, 1H), 4.00 (m, 4H), 2.69 (s, 1H), 2.25 (m, 1H), 1.73 (m, 1H), 1.50 (m, 1H), 1.25 (t, J₃H = 6 Hz), 0.96 (d, J₃H = 6.7 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 159.4 (d, JCP = 4.2 Hz), 156.6, 135.2, 127.4, 115.7, 114.3 (d, JCP = 188 Hz), 71.9, 62.1 (d, JCP = 5.6 Hz), 44.4, 35.1 (d, JCP = 21.2 Hz), 19.0, 16.4 (d, JCP = 6.4 Hz); ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 19.6; HRMS (FAB) m/z: [M+Na]⁺ Calcd for C₁₆H₂₅O₅PNa 351.1336, Found 351.1331.

(±) Diethyl (3S, 5R, E)-(5-hydroxy-3-methyl) non-1-enyl phosphonate (1.42h)

Following the general procedure B, phosphonodiene 1.41a (0.1 g, 0.49 mmol, 1.0 equiv) was reacted to obtain 1.42h (0.03 g, 0.11 mmol, 21%) as a colorless liquid after column chromatography (SiO₂, EtOAc: hexanes, 80:20). IR (neat) 3398, 2955, 2927, 2085, 1624, 1225, 1019, 957 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.75 (ddd, J₂H = 22.3, J₃H = 17.2, 7.1 Hz, 1H), 5.62 (ddd, J₂H = 18.2, J₃H = 17.2, 1.2 Hz, 1H), 4.09-4.01 (m, 4H), 3.67-3.61 (m, 1H), 2.59-2.52 (m, 1H), 1.60-1.40 (m, 4H), 1.34-1.29 (m, 10H), 1.07 (d, J₃H = 6.7 Hz, 3H), 0.90 (t, J₃H = 7.0 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 159.4 (d, JCP = 2.7 Hz), 114.7 (d, JCP = 186.8 Hz), 69.6, 61.8 (d, JCP = 5.5 Hz), 43.4 (d, JCP = 1.1 Hz), 37.9, 35.0 (d, JCP = 20.9 Hz), 27.9, 22.9, 18.7 (d, JCP = 1.2 Hz), 16.5 (d, JCP = 6.4 Hz), 14.3; ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 19.4; HRMS (FAB) m/z: [M+H]⁺ Calcd for C₁₄H₃₀O₄P 292.1803, Found 293.1876
(±) Diethyl (3S, 5S, E)-3-(tert-butyldimethylsiloxyl)-5-hydroxy-5-phenylpent-1-enylphosphonate (1.57)

\[
\text{EtO}_2\text{P} \quad \begin{array}{c}
\text{O} \\
\text{EtO} \\
\text{TBSO} \\
\text{OH}
\end{array} \quad \begin{array}{c}
\text{C} \\
\text{C}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

Following the general procedure B, TBS-protected phosphonodiene 1.41d (0.1 g, 0.31 mmol, 1 equiv) was reacted for 12 h to obtain 1.57 (0.096 g, 0.22 mmol, 72%) as a colorless liquid after column chromatography (SiO₂, EtOAc:hexanes, 70:30). IR (neat) 3360, 2927, 2086, 1230, 1021 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.28-7.20 (m, 5H), 6.80 (ddd, \(J_{HP} = 22.0\), \(J_{HH} = 17.0\), 3.8 Hz, 1H), 5.93 (ddd, \(J_{HP} = 20.4\), \(J_{HH} = 16.9\), 1.6 Hz, 1H), 4.82 (d, \(J_{HH} = 8.6\) Hz, 1H), 4.62 (s, 1H), 4.07-3.96 (m, 4H), 3.10 (s, 1H), 2.00-1.91 (m, 1H), 1.78-1.71 (m, 1H), 1.27 (t, \(J_{HH} = 7.0\) Hz, 6H), 0.91 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 154.0 (d, \(J_{CP} = 5.7\) Hz), 144.4, 128.5, 127.5, 125.6, 116.5 (d, \(J_{CP} = 188\) Hz), 71.1 (d, \(J_{CP} = 21.2\) Hz), 70.8, 61.8 (d, \(J_{CP} = 5.4\) Hz), 61.8 (d, \(J_{CP} = 5.4\) Hz), 45.1, 25.9, 18.2, 16.4 (d, \(J_{CP} = 6.4\) Hz), -4.60, -5.15; ³¹P{¹H} NMR(121 MHz, CDCl₃) δ 18.7; HRMS (FAB) m/z: [M+H]+ Calcd for C₂₁H₃₈O₅PSi 429.2226, Found 429.2218.

(±) Diethyl (3S, 5S, E)-3-(tert-butyldimethylsiloxyl)-5-hydroxy-5-(3,4-methylenedioxy)phenylpent-1-enylphosphonate (1.59)

\[
\text{EtO}_2\text{P} \quad \begin{array}{c}
\text{O} \\
\text{EtO} \\
\text{TBSO} \\
\text{OH}
\end{array} \quad \begin{array}{c}
\text{C} \\
\text{C}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\]

Following the general procedure B, TBS-protected phosphonodiene 1.41d (0.16 g, 0.50 mmol, 1 equiv) was reacted for 8 h to obtain 1.59 (0.173 g, 0.37 mmol, 73%) as a colorless liquid after column chromatography (SiO₂, EtOAc: hexanes, 80:20). IR (neat) 3356, 2927, 2091, 1484, 1233, 1020 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.28-7.20 (m, 5H), 6.89-6.74 (m, 4H), 6.01-5.89 (m, 3H), 4.75 (d, \(J_{HH} = 8.6\) Hz, 1H), 4.64 (s, 1H), 4.11-4.00 (m, 4H), 3.14 (s, 1H), 2.00-1.91 (m, 1H), 1.79-1.70 (m, 1H), 1.34-1.29 (m, 6H), 0.94 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H);
$^{13}$C\{$^1$H\} NMR (75 MHz, CDCl$_3$) $\delta$ 153.9 (d, $J_{CP} = 5.6$ Hz), 147.8, 146.9, 138.6, 118.9, 116.5 (d, $J_{CP} = 186.9$ Hz), 108.1, 106.3, 101.1, 71.0 (d, $J_{CP} = 21.2$ Hz), 70.6, 61.8 (d, $J_{CP} = 5.4$ Hz), 61.8 (d, $J_{CP} = 5.4$ Hz), 45.2, 25.8, 18.2, 16.4 (d, $J_{CP} = 6.4$ Hz), -4.60, -5.15; $^{31}$P\{$^1$H\} NMR (121 MHz, CDCl$_3$) $\delta$ 18.7; HRMS (FAB) $m$/z: [M+Na]$^+$ Calcd for C$_{22}$H$_{37}$O$_7$PSiNa 495.1943, Found 495.1938.
1.5. REFERENCES


CHAPTER II
OXA-MICHAEL CYCLIZATION OF BIS-HOMOALLYLIC ALCOHOLS

2.1. INTRODUCTION
The Michael addition is one of the most effective routes to C-C bond formation and involves the addition of a carbon nucleophile to a conjugated acceptor. Michael introduced the reaction of stabilized anions with α,β-unsaturated ester in 1887 (Scheme 2.1). The Michael addition has been extensively researched with a diverse set of carbanions and acceptor molecules. Acceptor molecules are mainly electron-deficient alkenes such as conjugated carbonyls or nitro compounds. The Michael addition is used for the synthesis of a wide variety of natural products and pharmaceuticals.

Scheme 2.1. Representation of Michael reaction

Even though the oxa-Michael reaction was reported prior to the carbon Michael addition by Loydl in 1878, the advancement of the oxa-Michael reaction gained less attention in the beginning. The reason may be due to the low nucleophilicity of alcohols, reversibility of the reaction, and the lack of stereoselectivity. Recently, a general protocol for oxa-Michael transformations was reported, and thus, the scope of the oxa-Michael reaction was increased considerably. The oxa-Michael reaction has a broad applicability in the synthesis of protected β-hydroxy ketones, esters and amides, β-amino alcohols, and oxygen heterocycles. These functional moieties are found in various natural products. Recently, different types of catalysis and asymmetric oxa-Michael reaction have been explored.
2.1.1. General reaction protocols

Problems such as the low reactivity of alcohols and the reversibility of the reaction should be addressed appropriately to explore the possible application of the oxa-Michael reaction. The feasibility of the oxa-Michael reaction is dependent on different factors such as the strength of the base, the nature of alcohol and its nucleophilicity. Primary alcohols undergo oxa-Michael reaction more easily than sterically hindered alcohols and higher ordered alcohols need a strong base. Similarly, intramolecular oxa-Michael reactions are more common than the intermolecular oxa-Michael reactions. The intramolecular reaction can overcome the lack of reactivity and reversibility because both the donor and acceptor molecules are anchored in close proximity. 

Path A: Base induced

Path B: Iminium catalysis

Scheme 2.2. Common oxa-Michael reaction pathways

During the past few decades, base catalysis was the most common method of activation in the oxa-Michael reaction. This involves the addition of an alkoxide ion to electron deficient double bond of α,β-unsaturated carbonyls leading to an enolate intermediate, which protonates to give β-alkoxy carbonyl compounds. This mechanism can also be applied in case of other α,β-unsaturated species, for example nitro-compounds, nitriles, and sulfonyls. (pathway A, Scheme 2.2). Recently, the reaction has also been catalyzed by Lewis acids or Brønsted acids, phosphine-based catalysts, organo-catalysts, and organometallic
catalysts\textsuperscript{13}, which activate the conjugate acceptor. Nowadays, organocatalytic oxa-Michael reactions have been explored significantly due to their potential synthetic applications. Various efficient synthetic protocols have been developed (pathway B, Scheme 2.2)\textsuperscript{8}. The intermediate obtained after alkoxide attack (2.6 and 2.11, Scheme 2.2), can also further react with other electrophiles in a domino reaction. Recently, the domino reaction has been broadened substantially and exploited for the synthesis of complex heterocyclic compounds.\textsuperscript{14}

2.1.2. Types of activation
2.1.2.1. Base catalyzed oxa-Michael reaction
The base catalyzed oxa-Michael reaction proceeds through the deprotonation of the alcohol to enhance its nucleophilicity. The alkoxide ion attacks the electron deficient conjugated double bond, followed by protonation to form a $\beta$-alkoxy carbonyl. Evans developed an intramolecular oxa-Michael reaction with the homoallylic alcohol (2.13) during the diastereoselective synthesis of syn-1,3-diols (Scheme 2.3). They used potassium tert-butoxide ($t$-BuOK) as a base to deprotonate the alcohol resulting in an alkoxide ion, which adds to benzaldehyde generating an acetal alkoxide intermediate. This alkoxide serves as a tethered oxygen nucleophile, which undergoes conjugate addition to an $\alpha,\beta$-unsaturated ester to give the benzylidene acetal (2.14, Scheme 2.3).\textsuperscript{15} This reaction demonstrates the broad applicability of the oxa-Michael reaction and has been used in several natural product syntheses.\textsuperscript{8}

\[
\begin{align*}
\text{R} & \quad = \text{Et, } \text{i-Pr, } \text{PhCH}_2\text{CH}_2 \\
\text{2.13} & \\
\text{R} & \quad = \text{Et, } \text{i-Pr, } \text{PhCH}_2\text{CH}_2 \\
\text{2.14} & \quad \text{PhCHO} \\
& \quad \text{Ph} \\
& \quad \text{71-79% yield, } >95:5 \text{ de} \\
\end{align*}
\]

Scheme 2.3. Diastereoselective synthesis of protected syn 1,3-diols

Verkade reported oxa-Michael additions of primary alcohols (2.16), which are more accessible for deprotonation, to various $\alpha,\beta$-unsaturated carbonyls (2.15)
catalyzed with non-ionic strong base proazaphosphatranes \([P(RNCH_2CH_2)_3N]\) (2.17) in isobutyronitrile to give the corresponding \(\beta\)-alkoxy carbonyls (2.18, Scheme 2.4).\(^4\) These metal free catalysts can be easily removed from the products and are useful for more diverse \(\alpha,\beta\)-unsaturated compounds.\(^4\)

Scheme 2.4. Proazaphosphatane-catalyzed oxa-Michael reaction

2.1.2.2. Acid catalyzed oxa-Michael reaction

The oxa-Michael reaction can be catalyzed by both Lewis acids as well as Brønsted acids. The Lewis acid catalysis of oxa-Michael reactions proceeds through the activation of a conjugate Michael acceptor, wherein the Lewis acid co-ordinates to the carbonyl oxygen to increase the electrophilicity of the double bond. Several Lewis acids have been used in oxa-Michael reactions.\(^16\) Tamariz reported the BF\(_3\)-OEt\(_2\) catalyzed oxa-Michael addition for the first time in 2006 (Scheme 2.5).\(^9\)

![Scheme 2.5. Lewis acid catalyzed Oxa-Michael reaction](image)

Similarly, Brønsted acid-catalyzed hetero-Michael reactions, with broader substrate scope were developed by Spencer in 2003 (Scheme 2.6).\(^10\) Strong acids, such as bis(trifluoromethanesulfon)imide, activate the conjugate acceptor (2.22) through the protonation of the carbonyl group. The activated acceptor undergoes hetero-Michael addition in the presence of weakly basic nucleophiles such as alcohols. However, more basic nucleophiles limit the efficiency of the reaction due to leveling effects. This reaction works well for various conjugate
acceptors with alkyl and benzyl alcohols but it is not useful for aryl alcohols due to a competing Friedel-Craft reaction (Scheme 2.6).\textsuperscript{10}

\[ \begin{array}{c}
\text{2.22} \\
\text{R}^1 \rightarrow \underset{\text{2.23}}{\text{R}^2} + \text{ROH} \quad \text{Tf}_2\text{NH (0.1 equiv)} \end{array} \rightarrow \begin{array}{c}
\text{2.24} \\
\text{R}^1 \rightarrow \underset{\text{2.25}}{\text{R}^2} \quad \text{R} = \text{alkyl, benzyl}. \end{array} \]

\textbf{Scheme 2.6.} Brønsted-acid catalyzed oxa-Michael reaction.

\subsection*{2.1.2.3. Phosphine catalyzed oxa-Michael reaction}

Phosphine-based catalysts have also been used in the oxa-Michael reaction as reported by Toste in 2003.\textsuperscript{11} The mechanism of activation is different from the base-catalyzed reactions. A mechanistic study showed that the phosphine undergoes conjugate addition to the Michael acceptor resulting in the phosphonium enolate \textit{2.28}. The enolate abstracts a proton from the alcohol to give an alkoxide ion; then the reaction proceeds as in base catalysis (Scheme 2.7).\textsuperscript{11}

\[ \begin{array}{c}
\text{2.25} \\
\text{R}^1 = \text{H, Me, Ph} \\
\text{EWG} = \text{COMe, CO}_2\text{Me, CN} \\
\end{array} \]

\[ \begin{array}{c}
\text{2.26} \\
\text{R} = \text{Me, i-Pr, Ph} \\
\text{59 - 85\% yield} \\
\end{array} \]

\textit{a)}

\[ \begin{array}{c}
\text{2.27} \\
\text{PMe}_3 \\
\text{2.28} \\
\text{2.29} \\
\text{2.30} \\
\text{2.26} \\
\text{R}^1 \rightarrow \underset{\text{2.25}}{\text{R}^2} + \text{ROH} \quad \text{PMe}_3 (5 \text{ mol} \%) \end{array} \]

\textbf{Scheme 2.7.} (a) Phosphine catalyzed oxa-Michael reaction (b) Proposed catalytic cycle
2.1.2.4. NHCs catalyzed oxa-Michael reaction

Scheidt introduced N-heterocyclic carbenes (NHCs) for the intermolecular oxa-Michael addition of primary and secondary alcohols to conjugate systems. These reactions can be carried out under mild conditions, and no competing substrate oligomerization was observed. (Scheme 2.8). This reaction involves the formation of NHC-alcohol complex I, which facilitates the 1,4-addition of alcohol to the conjugate acceptor 2.32, generating the enolate II. The enolate II is stabilized by the addition of Lithium counterion. The protonation of enolate results in β-alkoxy ketone 2.34 (Scheme 2.8).

![Scheme 2.8. (a) NHCs catalyzed oxa-Michael reaction (b) Proposed catalytic cycle](image)
2.1.2.5. Transition metal-catalyzed oxa-Michael reaction

Abu Omar reported palladium-catalyzed hydroalkoxylation and hydroaminations in 2001.\textsuperscript{13} With the help of kinetic studies of the reaction, they observed that the vinyl ketone is activated via $\eta^2$-coordination of the alkene to palladium (II) and alcohol selectively attacks beta carbon. The regioselectivity is supposed to be due to the activation of the carbonyl group by interaction with a positively charged palladium catalyst. This reaction has directed the further possibility of organometallic asymmetric hydroalkoxylation (Scheme 2.9).\textsuperscript{13}

\begin{center}
\begin{align*}
\text{ROH} + \text{2.36} &\xrightarrow{\text{Pd(CH}_3\text{CN)}_2\text{Cl}_2} \text{2.37} \\
\text{CHCl}_3, \text{rt} (4 \text{ mol} \%) &\quad \text{76-97\text{% yield}}
\end{align*}
\end{center}

Scheme 2.9 Palladium catalyzed hydroalkoxylation of MVK

Feng employed a chiral organometallic catalyst ($N, N'$-dioxide nickel (II) complex) for the enantioselective intramolecular oxa-Michael addition (Scheme 2.10). The reaction was used for the enantioselective synthesis of flavanone derivatives. They optimized the reaction conditions with nickel trifluoroacetylacetetonate as a metal salt and a proline derivative as a ligand. This reaction has excellent enantioselectivity.\textsuperscript{17}

\begin{center}
\begin{align*}
\text{2.38} &\xrightarrow{1. \text{Ni(Tfacac)}_2\text{2H}_2\text{O}(5 \text{ mol}\%)} \text{2.39} \\
\text{Ligand (5 mol\% PhOMe, 30 °C)} &\quad \text{upto 99\text{% yield}} \\
&\quad \text{upto 98\text{% ee}}
\end{align*}
\end{center}

Scheme 2.10. Enantioselective flavanone synthesis with an organometallic catalysis
2.1.2.6. Asymmetric oxa-Michael reaction with chiral auxiliaries

Various chiral auxiliaries have been used for the asymmetric oxa-Michael reaction. Some examples are proline-type catalysts\textsuperscript{18} and alkaloid-based bifunctional catalysts\textsuperscript{19-20}. Jørgensen used diarylprolinol ethers (2.42, Scheme 2.11) chiral catalysts for the enantioselective addition of benzaldehyde oxime (2.40) to various \(\alpha,\beta\)-unsaturated aldehydes (2.41). The oxa-Michael product 2.43 was directly reduced to the corresponding alcohol 2.44 due to the instability of aldehyde (Scheme 2.11).\textsuperscript{18} The reaction pathway has been proposed to involve an iminium ion formation (Scheme 2.2, pathway B).\textsuperscript{18}

![Scheme 2.11 Proline type organo-catalyzed oxa-Michael addition](image)

Similarly, thiourea-based catalysts have also been used for asymmetric oxa-Michael addition.\textsuperscript{20-21} Matsubara used cinchona-alkaloid-thiourea-based bifunctional organo-catalyst (2.46) for the asymmetric synthesis of tetrahydrofuran rings (2.47) using oxa-Michael addition via cycloetherification (Scheme 2.12).\textsuperscript{19}

![Scheme 2.12. Asymmetric oxa-Michael reaction mediated by bifunctional organo-catalyst](image)
2.1.3. Scope of the oxa-Michael reaction

In the above discussion of ways to activate the oxa-Michael addition, we observed that a wide variety of organic compounds could be synthesized. Based on the functionality of the products, the reaction has been classified into the following major classes of oxa-Michael products. Some of the examples of oxa-Michael products have already been discussed.

2.1.3.1. Synthesis of β-alkoxy aldehydes, ketones, esters, and imides

As described in the previous examples, synthesis of β-alkoxy aldehydes, ketones, and esters can be achieved through oxa-Michael addition of an alkoxide ion to the corresponding α,β-unsaturated carbonyls. Jacobson synthesized alkoxy imide derivatives (2.51) through oxa-Michael addition of oxime nucleophiles (2.49) to α,β-unsaturated imides (2.48) using the Lewis acid [(R, R)-(salen)Al]₂O (2.50) as catalyst (Scheme 2.13).²²

![Scheme 2.13. Synthesis of β-hydroxy imide by oxa-Michael addition](image)

2.1.3.2. Synthesis of β-alkoxy nitriles, nitro compounds

The oxa-Michael reaction can be used for the synthesis of β-alkoxy nitrile (Scheme 2.7a) and nitro compounds. Enders used N-formyl norephedrine (2.52) as an oxygen nucleophile for oxa-Michael addition to α,β-unsaturated nitro compounds (2.53) to obtain β-alkoxy nitro compound (2.54, Scheme 2.14).²³
2.1.3.3. Polymerization of vinyl sulfone and alcohols

Divinyl sulfone (DVS) (2.55) undergoes an oxa-Michael addition with alcohols in the presence of various nucleophilic bases. Slugovc reported the nucleophile mediated oxa-Michael addition reaction of divinyl sulfone and alcohols. The mechanism proposed for this reaction is similar to phosphine-based catalysis. This reaction turns into a polymerization reaction of divinyl sulfone with di- or multifunctional alcohols (2.56, Scheme 2.15). This reaction also shows an application of vinyl sulfone oxa-Michael reaction in polymer chemistry.

\[
\text{Scheme 2.15. Oxa-Michael addition polymerization of vinyl sulfone and alcohols}
\]

2.1.3.4. Synthesis of $\beta$-alkoxy phosphonate from vinyl phosphonate

The intermolecular oxa-Michael reaction of vinyl phosphonates is not well explored. This chapter of the thesis will be mainly focused on the intramolecular oxa-Michael addition of bis-homoallylic alcohol (vinyl phosphonate) and the corresponding Mitsunobu esters.
2.1.4. Application of oxa-Michael reaction

2.1.4.1. Application of oxa-Michael reaction in the synthesis of heterocycles and natural products

The intramolecular oxa-Michael reaction is useful for the synthesis of the oxygen-heterocycles, mainly tetrahydrofuran and tetrahydropyran rings.\(^5\)\(^8\) Several natural products contain oxygen-heterocycles as a skeletal moiety.\(^8\) Those oxygen-heterocycles can be synthesized by oxa-Michael reactions. Similarly, the oxa-Michael reaction has been used for the synthesis of various bioactive molecules as well as drug-like molecules. Some of the important natural products that are synthesized using oxa-Michael reaction are as flavanone (Scheme 2.16), diversenol, crotistatins, longianone (Scheme 2.17), and more.\(^8\)

![Scheme 2.16. Direct organocatalytic synthesis of flavanone](image)

![Scheme 2.17. Total synthesis of longianone](image)

2.1.4.2. Application of the oxa-Michael reactions in the synthesis of tetrahydrofuran and pyranose derivatives

Kobayashi cyclized a bis-homoallyl alcohol (2.64) to a tetrahydrofuran ring (2.65) with TBAF during the synthesis of Amphidinolide C. They determined the absolute stereochemistry of the groups by COSY and NOESY analysis (Scheme 2.18).\(^26\)
Similarly, Roush applied an oxa-Michael cyclization approach to bis-homoallylic alcohol (2.66). They have observed that the cyclization proceeds with kinetic control. They attempted isomerization of tetrahydrofuran diastereomer (2.68) but were unsuccessful. The rationale behind the diastereoselectivity is to avoid 1,3-allylic strain of methyl group (transition state B) as explained by Hoffman (Scheme 2.19).\textsuperscript{27-28}

\textbf{Scheme 2.19.} Mechanistic study of cyclization

Ghosh studied the stereochemistry of substituted tetrahydrofuran.\textsuperscript{29} The tetrahydrofuran derivatives was synthesized via an oxa-Michael cyclization of
alcohol (2.69, Scheme 2.20) using KHMDS as the base, followed by the opening of the tetrahydrofuran ring into an acyclic structure (2.71). Zn(OTf)$_2$ was employed as the catalyst to open the methyl-substituted tetrahydrofuran giving an anti-aldol acyclic substrate (2.71, Scheme 2.20).$^{29}$

Scheme 2.20. Stereochemistry study of tetrahydrofuran through ring opening

Our group also studied the oxa-Michael cyclization of bis-homoallylic alcohols (2.72) to obtain the substituted tetrahydrofuran (2.73a and 2.73b) during a formal synthesis of C1-C9-fragment of Amphidinolide C (Scheme 2.21).$^{30}$ Silyl group migration was observed during the cyclization from secondary 2.73a to primary position 2.73b (Scheme 2.21).

Scheme 2.21. Cyclization of bis-homoallylic alcohol

The oxa-Michael reaction of vinyl phosphonates is not well explored and there are only limited examples found in the literature. Allan applied the intramolecular oxa-Michael addition in order to synthesize multi-substrate bicyclic pyrimidine nucleoside inhibitors of human thymidine phosphorylase. The resulting bicyclic phosphonate ester (2.75) from the alcohol 2.74 was obtained in a 3:1 diastereomeric mixture (Scheme 2.22).$^{31}$
Scheme 2.22. Intramolecular oxa-Michael cyclization of vinyl phosphonate

Hultin employed oxa-Michael cyclization of vinyl phosphonate (2.76) to substituted pyranose derivative (2.77) in the presence of potassium carbonate (Scheme 2.23).\(^{32}\)

Scheme 2.23. Oxa-Michael cyclization of vinyl phosphonate to pyranose derivatives

O’Hagan utilized the Wadsworth-Emmons reaction for intramolecular oxa-Michael cyclization, to obtain the 4:1 ratio of \(\alpha/\beta\) isomers (2.80) (Scheme 2.24).\(^{33}\)

Scheme 2.24. In situ oxa-Michael addition following a Wadsworth-Emmons reaction
2.2. RESULTS AND DISCUSSION

The general objective of this chapter is to explore the intramolecular oxa-Michael addition of vinyl phosphonates to obtain tetrahydrofurans having various substituents. The bishomoallylic alcohols obtained after Mori-Tamaru reaction between phosphonodienes and aldehydes in Chapter 1 were subjected to oxa-Michael cyclization to form phosphono-substituted tetrahydrofurans. Various bases were examined for their ability to induce the cyclization of the vinyl phosphonates. The intramolecular oxa-Michael cyclization was achieved using NaOMe in MeOH to give the phosphonomethyl substituted tetrahydrofurans (2.82a-g, Scheme 2.25). The reaction proceeded with good yields (36-89%) and excellent diastereoselectivity (> 95% dr) (Table 2.1). Other bases such as DBU, TEA, DIPEA were unreactive and failed to induce cyclization. Whereas stronger bases such as t-BuOK, resulted in the formation of multiple products. NaH was successful for the cyclization of bis-homoallylic alcohol giving the similar yields as NaOMe.

![Scheme 2.25 Oxa-Michael cyclization of vinyl phosphonate](image)

**Table 2.1. Oxa-Michael cyclization with various substituents**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituent (R)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>85</td>
</tr>
<tr>
<td>b</td>
<td>Ethyl</td>
<td>55</td>
</tr>
<tr>
<td>c</td>
<td>2-Furyl</td>
<td>62</td>
</tr>
<tr>
<td>d</td>
<td>2-Thiophenyl</td>
<td>89</td>
</tr>
<tr>
<td>e</td>
<td>2-Naphthyl</td>
<td>85</td>
</tr>
<tr>
<td>f</td>
<td>4-fluorophenyl</td>
<td>75</td>
</tr>
<tr>
<td>g</td>
<td>4-hydroxyphenyl</td>
<td>36</td>
</tr>
</tbody>
</table>
The compound \textbf{2.82g} was solid crystals however, the yield of cyclization for this species was lower compared to other ring substituents. As the reaction has resulted in multiple peaks in $^{31}\text{P}^{'\text{1}H}$ NMR spectrum, the possible reason may be the formation of sodium phenoxide as a side-products due to the acidic nature of phenoxide ion stabilized by the resonance.

The stereochemistry (2S, 3S, 5S) of the phosphonomethyl tetrahydrofuran ring was assigned based on the precedent established in the cyclization of similar unsaturated esters.\textsuperscript{26-27, 29} It was later confirmed by X-ray crystallographic analysis of compound \textbf{2.82g} (Figure 2.1).

\textbf{Figure 2.1. X-ray crystal structure of 2.82g}

The stereochemistry of the tetrahydrofuran obtained after cyclization of the bis-homoallylic alcohol was inconsistent with that of C-nucleosides. In order to correct the stereochemistry, the bis-homoallylic alcohol (\textbf{2.81a}) was subjected to Mitsunobu inversion. The bis-homoallylic alcohol (\textbf{2.81a}) was treated with triphenylphosphine, di-isopropyl azodicarboxylate, and \textit{p}-nitrobenzoic acid to obtain \textit{p}-nitrobenzoate (\textbf{2.83}, Scheme 2.26). The reaction proceeded under mild
conditions with 96% yield and clean inversion of stereochemistry. Stereochemistry has been assigned based on the general principle of Mitsunobu reaction. It was later confirmed by the fact that cyclization of the ester 2.83 lead different isomers of the tetrahydrofuran than that from the alcohol 2.81a.

![Scheme 2.26. Mitsunobu inversion of bis-homoallylic alcohol](image)

The Mitsunobu benzoate ester was cyclized with NaOMe in MeOH. Initially, the alcohol is formed in situ by ester hydrolysis, followed by the cyclization to the tetrahydrofuran ring as a diastereomeric mixture (4:1 ratio, Scheme 2.27).

![Scheme 2.27. Cyclization of Mitsunobu benzoate ester](image)

Cyclization of bis-homoallylic alcohol (2.81a) has also been achieved with NaH resulting with diastereoselectivity and similar yields (85%) to those observed with NaOMe. Not surprisingly, cyclization of benzoate ester (2.83) with NaH was unsuccessful because the hydride cannot take part in the ester hydrolysis. (Scheme 2.28).
Diene 1.39b with the terminal methyl group was subjected to the Mori-Tamaru reaction using BEt₃. Isolation of the vinyl phosphonate from the mixture of reaction products proved challenging. Therefore, the crude product was directly cyclized with NaOMe/MeOH to obtain the corresponding tetrahydrofuran (2.85, 16% two-step yield). The reaction of diene (1.39b) with AlEt₃ was not successful (Scheme 2.29).

Cyclization of the OTBS substituted bis-homoallylic alcohol (2.86) with NaOMe/MeOH resulted in a diastereomeric mixture of two OTBS substituted tetrahydrofurans (2.87a & 2.87b) along with TBS deprotected trans-hydroxy tetrahydrofuran (2.88a) (Scheme 2.30).
The deprotection of TBS group of the *trans* diastereomer 2.87a with TBAF resulted in alcohol 2.88a (Scheme 2.31), whereas the TBS deprotection of the *cis* diastereomer 2.87b resulted in the mixture of alcohol 2.88b and the bicyclic phosphostone 2.89 (Scheme 2.32). The formation of the bicyclic phosphostone was observed when the alcohol is in a *cis* relationship with the phosphonate. This cyclization therefore confirmed the assigned stereochemistry of the compounds.

Scheme 2.31. TBS-deprotection of *trans*-diastereomer with TBAF

```
EtO_P_O
EtO
TBSO
± 2.87a
```

```
EtO_P_O
EtO
TBAF, THF
3 h, 0 °C
90%
```

```
EtO_P_O
EtO
HO
± 2.88a
```

Scheme 2.32. TBS-deprotection of *cis*-diastereomer with TBAF

```
EtO_P_O
EtO
TBSO
± 2.87b
```

```
EtO_P_O
EtO
THF
3 h, 0 °C
```

```
EtO_P_O
EtO
HO
± 2.88b (41%)
```

```
EtO_P_O
EtO
TBSO
± 2.89 (36%)
```

Mitsunobu inversion of OTBS substituted bis-homoallylic alcohol (2.86) required some modifications to the reaction conditions. It was achieved by switching the phosphine reagent from triphenylphosphine to tributylphosphine. The reaction of OTBS substituted alcohol with tributyl phosphine, di-isopropyl azodicarboxylate, and *p*-nitrobenzoic acid resulted in the corresponding *p*-nitrobenzoate (2.90) with excellent yield and clean inversion of stereochemistry (Scheme 2.33).

Scheme 2.33 Mitsunobu inversion of OTBS substituted bis-homoallylic alcohol

```
EtO_P_O
EtO
TBSO
± 2.86
```

```
PbBu3, DIAD, PNBA, THF
-50 °C - 0 °C, 4 h,
96%
```

```
EtO_P_O
EtO
TBSO
± 2.90
```

```
EtO_P_O
EtO
Ph
OH
```

```
EtO_P_O
EtO
Ph
```

```
± 2.90
```
The cyclization of ester 2.90 with NaOMe/MeOH resulted in a diastereomeric mixture of tetrahydrofurans in a 1:1.5 ratio (2.91a & 2.91b respectively) (Scheme 2.34).

The deprotection of the TBS group from the trans-diastereomer (2.91a) with TBAF resulted in 3'-hydroxy phosphonomethyl tetrahydrofuran 2.92a (Scheme 2.35) whereas the TBS deprotection from cis-diastereomer (2.91b) resulted in the mixture of alcohol 2.92b and the diastereomeric mixture (1:1) of bicyclic phostones 2.93 (Scheme 2.36). Cyclization of the cis-diastereomer forming bicyclic phostone confirmed the assigned stereochemistry.

Similarly, piperonal derived bis-homoallylic alcohol (1.59) has also been cyclized to tetrahydrofuran with NaOMe/MeOH which resulted in a diastereomeric mixture
(1:3 ratio) of tetrahydrofuran (2.94) (Scheme 2.37). Isolation of the individual diastereomers was unsuccessful and as a result, the compounds were characterized as a diastereomeric mixture.

**Scheme 2.37.** Cyclization of bis-homoallylic alcohol derived from piperonal

The bis-homoallylic alcohol 1.59 was subjected to Mitsunobu inversion to obtain the benzoate ester 2.95. The Mitsunobu inversion resulted in a mixture of two diastereomers (2:1 ratio).

**Scheme 2.38.** Mitsunobu inversion of bis-homoallylic alcohol derived from piperonal

The formation of diastereomeric mixture may be due to the cation-stabilizing (electron donating) effect of the oxygens present in the side ring. Due to the formation of a stable cation, the reaction progressed with some of the S_N1 character. The S_N1 reaction competed with the Mitsunobu inversion reaction resulting in the formation of two diastereomers (Scheme 2.39 (b)).
Scheme 2.39. Mechanism of Mitsunobu reaction a) inversion b) retention
2.3. SUMMARY

1) In order to explore the intramolecular oxa-Michael addition of vinyl phosphonates, the bis-homoallylic alcohols obtained after a Mori-Tamaru reaction were cyclized with NaH/THF or NaOMe/MeOH to obtain phosphonomethyl tetrahydrofurans. Various substituents have been employed ranging from alkyl, aryl and heteroaryl groups. The cyclizations were achieved with >95% diastereoselectivity.

2) The stereochemistry of substituted tetrahydrofuran obtained after cyclization of bis-homoallylic alcohol, was different than that of the C-nucleosides. To correct the stereochemistry, a Mitsunobu inversion of the alcohol was carried out. The cyclization of benzoate ester with NaOMe in MeOH resulted in phosphonomethyl tetrahydrofuran in 4:1 diastereomeric ratio via the formation of the alcohol in situ.

3) In order to synthesize 3-hydroxy tetrahydrofurans, intramolecular oxa-Michael addition of bis-homoallylic alcohols, obtained after Mori-Tamaru reaction of OTBS substituted dienes, resulted in a mixture of diastereomers. Deprotection of TBS from cis diastereomers with TBAF has resulted a mixture of alcohols and bicyclic phostones whereas the trans diastereomers has resulted only 3-hydroxy phosphonomethyl tetrahydrofurans.

4) The stereochemistry of 3-hydroxy tetrahydrofurans has also been corrected using a Mitsunobu inversion of the corresponding bis-homoallylic alcohol. Subsequent cyclization of benzoate esters with NaOMe/MeOH resulted in a mixture of two diastereomers. The stereochemistry of the diastereomers have been assigned by deprotection of TBS group with TBAF in which the cis-diastereomer resulted bicyclic phostone along with hydroxy tetrahydrofuran while the trans-diastereomers resulted in only the hydroxy tetrahydrofuran.
2.4. GENERAL EXPERIMENTAL

All reactions were carried out in oven-dried glassware under an atmosphere of argon unless otherwise noted. THF was distilled from Na/benzophenone, toluene from CaH₂, MeOH from Mg/Mg(OMe)₂, and CH₂Cl₂ from CaH₂. ¹H, ¹³C{¹H}, and ³¹P{¹H} NMR spectra were recorded in CDCl₃ at 300, 75, and 121 MHz, respectively. ¹H NMR spectra are referenced to CDCl₃ (7.27 ppm), ¹³C{¹H} NMR spectra are referenced to the center line of CDCl₃ (77.23 ppm), and ³¹P{¹H} NMR spectra are referenced to external H₃PO₄. Coupling constants, J, are reported in hertz (Hz). Analytical thin-layer chromatography (TLC) analyses were performed on silica gel plates 60PF₂₅₄. Visualization was accomplished with UV light and KMnO₄ solution.

2.4.1. General procedure for the synthesis of phosphonomethyl tetrahydrofurans (2.82a-g)

To a solution of the bishomoallylic alcohol (2.81a-g) (1 equiv) in dry MeOH (5 mL/mmol) was added NaOMe (25 wt. % in MeOH, 2.5 equiv) and the resulting solution was stirred for 24 h at room temperature. The reaction was quenched by addition of 1N HCl and the solution was concentrated under reduced pressure. The residue was filtered through celite pad washing with EtOAc. The products (2.82a-g) were isolated by column chromatography (SiO₂, 80-100% EtOAc in hexanes).

(±) Diethyl ((2S, 3S, 5S)-3-methyl-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.82a)

Following the general procedure, bishomoallylic alcohol (2.81a) (0.3 g, 0.96 mmol, 1 equiv) was reacted with NaOMe (0.52 mL, 2.4 mmol, 2.5 equiv) in 5 mL MeOH to obtain (2.82a) (0.256 g, 0.82 mmol, 85%) as a colorless liquid after column chromatography (SiO₂, EtOAc:hexanes, 70:30). IR (neat) 2960, 2870,
2116, 1450, 1228, 1019, 956 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.36-7.26 (m, 5H), 5.09 (dd, \(J_{HP} = 9.5\) Hz, \(J_{HH} = 6.2\) Hz, 1H), 4.22-4.13 (m, 4H), 4.10-4.02 (m, 1H), 2.60-2.51 (m, 1H), 2.27-2.09 (m, 3H), 1.58 (m, 1H), 1.34 (m, 6H), 1.12 (d, \(J_{HP} = 6.5\) Hz, 3H); \(^{13}\)C\(^{\{1\}H}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 143.7, 128.3, 127.1, 125.3, 80.6 (d, \(J_{CP} = 5.0\) Hz), 79.8, 61.9 (d, \(J_{CP} = 6.2\) Hz), 61.4 (d, \(J_{CP} = 6.3\) Hz), 44.3, 41.8 (d, \(J_{CP} = 12.2\) Hz), 31.2 (d, \(J_{CP} = 139\) Hz), 16.5 (d, \(J_{CP} = 6.2\) Hz), 16.4 (d, \(J_{CP} = 6.3\) Hz), 16.3; \(^{31}\)P\(^{\{1\}H}\) NMR (121 MHz, CDCl\(_3\)) \(\delta\) 28.8; HRMS (FAB) \(m/z\): [M+H]\(^+\) Calcd for C\(_{16}\)H\(_{26}\)O\(_4\)P 313.1569, Found 313.1563.

(\(\pm\)) Diethyl ((2S, 3S, 5R)-5-ethyl-3-methyltetrahydrofuran-2-yl)methylphosphonate (2.82b)

Following the general procedure, bishomoallylic alcohol (2.81b) (0.1 g, 0.38 mmol) was reacted to obtain (2.82b) (0.055 g, 0.21 mmol, 55%) as a colorless liquid after column chromatography (SiO\(_2\), EtOAc:hexanes 70:30). IR(neat) 2958, 2929, 2872, 1250 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.22-4.09 (m, 4H), 3.98-3.92 (m, 1H), 3.83-3.78 (m, 1H), 2.12-2.06 (m, 1H), 2.00-1.77 (m, 4H), 1.56-1.49 (m, 1H), 1.43-1.36 (m, 1H), 1.36 (t, \(J_{HH} = 7.1\) Hz, 6H), 1.17-1.10 (m, 1H), 0.97 (d, \(J_{HH} = 6.5\) Hz, 3H), 0.82 (t, \(J_{HH} = 7.4\) Hz, 3H); \(^{13}\)C\(^{\{1\}H}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 79.5, 79.3 (d, \(J_{CP} = 5.0\) Hz), 61.3 (d, \(J_{CP} = 6.2\) Hz), 60.9 (d, \(J_{CP} = 6.3\) Hz), 41.1 (d, \(J_{CP} = 12.7\) Hz), 40.4, 30.3 (d, \(J_{CP} = 140\) Hz), 28.8, 16.4, 16.1 (d, \(J_{CP} = 6.2\) Hz), 16.0 (d, \(J_{CP} = 6.3\) Hz), 10.0; \(^{31}\)P\(^{\{1\}H}\) NMR (121 MHz, CDCl\(_3\)) \(\delta\) 29.1; HRMS (FAB) \(m/z\): [M+Na]\(^+\) Calcd for C\(_{12}\)H\(_{25}\)O\(_4\)PNa 287.1385, Found 287.1382.
\((\pm)\) Diethyl \((2S, 3S, 5S)-5\text{-}(furan-2-yl)-3\text{-}methyltetrahydrofuran-2-yl)methylphosphonate (2.82c)

Following the general procedure, bishomoallylic alcohol (2.81c) \((0.1 \text{ g}, 0.33 \text{ mmol})\) was reacted to obtain (2.82c) \((0.062 \text{ g}, 0.21 \text{ mmol}, 62\%)\) as a colorless liquid after column chromatography (SiO\(_2\), EtOAc:hexanes 70:30). IR (neat) 2973, 2872, 2126, 1228, 1019 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.36 (m, 1H), 6.31-6.24 (m, 2H), 5.05-5.00 (m, 1H), 4.13-4.06 (m, 4H), 3.96-3.89 (m, 1H), 2.45-2.36 (m, 1H), 2.20-2.02 (m, 3H), 1.92-1.81 (m, 1H), 1.32-1.26 (m, 6H), 1.13 (d, \(J_{\text{HH}} = 6.5 \text{ Hz}, 3\)H); \(^{13}\)C\({^{1}\text{H}}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 155.0, 142.3, 110.1, 106.8, 80.0 (d, \(J_{\text{CP}} = 4.5 \text{ Hz}\)), 72.7, 61.8 (d, \(J_{\text{CP}} = 6.3 \text{ Hz}\)), 61.6 (d, \(J_{\text{CP}} = 6.3 \text{ Hz}\)), 41.1 (d, \(J_{\text{CP}} = 10.9 \text{ Hz}\)), 39.2, 30.9 (d, \(J_{\text{CP}} = 140 \text{ Hz}\)), 16.4 (d, \(J_{\text{CP}} = 6.6 \text{ Hz}\)), 16.3; \(^{31}\)P\({^{1}\text{H}}\) NMR (121 MHz, CDCl\(_3\)) \(\delta\) 28.4; HRMS (FAB) \(m/z\): [M+H]\(^+\) Calcd for C\(_{14}\)H\(_{24}\)O\(_5\)P 303.1358, Found 303.1355.

\((\pm)\) Diethyl \((2S, 3S, 5S)-3\text{-}methyl-5\text{-}(thiophen-2-yl)tetrahydrofuran-2-yl)methylphosphonate (2.82d)

Following the general procedure, bishomoallylic alcohol (2.81d) \((0.059 \text{ g}, 0.19 \text{ mmol})\) was reacted to obtain (2.82d) \((0.056 \text{ g}, 0.18 \text{ mmol}, 89\%)\) as a colorless liquid after column chromatography (SiO\(_2\), EtOAc:hexanes, 70:30). IR (neat) 2961, 2870, 2129, 1231, 1024 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.23-7.21 (m, 1H), 6.96-6.93 (m, 2H), 5.30-5.25 (m, 1H), 4.22-4.07 (m, 4H), 4.02-3.97 (m, 1H), 2.60-2.51 (m, 1H), 2.23-1.98 (m, 3H), 1.79-1.68 (m, 1H), 1.34-1.28 (m, 6H), 1.12 (d, \(J_{\text{HH}} = 6.6 \text{ Hz}, 3\)H); \(^{13}\)C\({^{1}\text{H}}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 147.2, 126.7, 124.5, 123.7, 80.3 (d, \(J_{\text{CP}} = 4.8 \text{ Hz}\)), 76.0, 62.0 (d, \(J_{\text{CP}} = 6.7 \text{ Hz}\)), 61.6 (d, \(J_{\text{CP}} = 6.0 \text{ Hz}\)),

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44.0, 41.7 (d, \( J_{CP} = 11.6 \) Hz), 31.1 (d, \( J_{CP} = 140 \) Hz), 16.6 (d, \( J_{CP} = 6.1 \) Hz), 16.5 (d, \( J_{CP} = 6.1 \) Hz), 16.5; \(^{31}\)P\(\{^1\)H\}\) NMR (121 MHz, CDCl₃) \( \delta \) 28.5; HRMS (FAB) \( m/z \): [M+Na]⁺ Calcd for C₁₄H₂₃O₄PSNa 341.0952, Found 341.0959.

(±) Diethyl ((2S, 3S, 5S)-3-methyl-5-(naphthalen-2-yl)tetrahydrofuran-2-yl)methylphosphonate (2.82e)

Following the general procedure, bishomoallylic alcohol (2.81e) (0.24 g, 0.66 mmol) was reacted to obtain (2.82e) (0.205 g, 0.56 mmol, 85 %) as a colorless liquid after column chromatography (SiO₂, EtOAc:hexanes, 70:30). IR (neat) 2959, 2118, 1226, 1019 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.72 (d, \( J_{HH} = 7.6 \) Hz, 4H), 7.37-7.33 (m, 3H), 5.15-5.10 (m, 1H), 4.09-4.02 (m, 5H), 2.51-2.44 (m, 1H), 2.16-2.04 (m, 3H), 1.58-1.51 (m, 1H), 1.26-1.19 (m, 6H), 1.02 (d, \( J_{HH} = 6.5 \) Hz, 3H); \(^{13}\)C\(\{^1\)H\}\) NMR (75 MHz, CDCl₃) \( \delta \) 141.1, 133.3, 132.8, 128.2, 127.9, 127.7, 126.1, 125.6, 123.9, 123.7, 80.8 (d, \( J_{CP} = 5.1 \) Hz), 80.0, 63.0 (d, \( J_{CP} = 6.1 \) Hz), 61.5 (d, \( J_{CP} = 6.4 \) Hz), 44.3, 41.9 (d, \( J_{CP} = 12.3 \) Hz), 31.2 (d, \( J_{CP} = 140 \) Hz), 16.5 (d, \( J_{CP} = 6.3 \) Hz), 16.3; \(^{31}\)P\(\{^1\)H\}\) NMR (121 MHz, CDCl₃) \( \delta \) 28.9; HRMS (FAB) \( m/z \): [M+Na]⁺ Calcd for C₂₀H₂₇O₄PNa 385.1545, Found 385.1539.

(±) Diethyl ((2S, 3S, 5S)-5-(4-fluorophenyl)-3-methyltetrahydrofuran-2-yl)methylphosphonate (2.82f)

Following the general procedure, bishomoallylic alcohol (2.81f) (0.78 g, 0.24 mmol) was reacted to obtain (2.82f) (0.058 g, 0.18 mmol, 75 %) as a colorless liquid after column chromatography (SiO₂, EtOAc:hexanes, 70:30). IR (neat) 2959, 2871, 2125, 1507, 1219 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.36-7.31 (m,
2H), 7.07-7.01 (m, 2H), 5.07 (m, 1H), 4.23-4.13 (m, 4H), 4.09-4.00 (m, 1H), 2.57-2.26 (m, 1H), 2.27-2.09 (m, 3H) 1.55 (m, 1H), 1.37 (t, $J_{HH} = 7.1$ Hz, 3H), 1.33 (t, $J_{HH} = 7.1$ Hz, 3H), 1.13 (d, $J_{HH} = 6.6$ Hz, 3H); $^{13}$C{¹H} NMR (75 MHz, CDCl₃) δ 162.1 (d, $J_{CF} = 243$ Hz), 139.5 (d, $J_{CF} = 3.0$ Hz), 127.0 (d, $J_{CF} = 7.9$ Hz), 115.1 (d, $J_{CF} = 21.2$ Hz), 80.8 (d, $J_{CP} = 5$ Hz), 79.4, 62.0 (d, $J_{CP} = 6.0$ Hz), 61.6 (d, $J_{CP} = 6.0$ Hz), 44.6, 42.0 (d, $J_{CP} = 12.1$ Hz), 31.4 (d, $J_{CP} = 140$ Hz), 16.7 (d, $J_{CP} = 6.7$), 16.6 (d, $J_{CP} = 6.7$), 16.4; $^{31}$P{¹H} NMR (121 MHz, CDCl₃) δ 28.7; HRMS (FAB) m/z: [M+Na]$^+$ Calcd for C₁₆H₂₄O₅PNa 353.1293, Found 353.1291.

(±) Diethyl ((2S, 3S, 5S)-5-(4-hydroxyphenyl)-3-methyltetrahydrofuran-2-yl)methylphosphonate (2.82g)

Following the general procedure, bishomoallylic alcohol (2.81g) (0.467 g, 1.42 mmol) was reacted to obtain (2.82g) (0.167 g, 0.51 mmol, 36%) as a white crystalline solid after column chromatography (SiO₂, EtOAc:hexanes, 70:30). M.p. = 84.7 °C; IR (neat) 3138, 2954, 2859, 2088, 1613, 1514, 1200, 1014 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.26 (s, 1H), 7.13 (d, $J_{HH} = 8.4$ Hz, 2H), 6.87 (d, $J_{HH} = 8.5$ Hz, 2H), 4.98 (m, 1H), 4.19-4.11 (m, 4H), 4.09-3.99 (m, 1H), 2.47-2.39 (m, 1H), 2.24-1.96 (m, 3H), 1.58-1.47 (m, 1H), 1.33 (t, $J_{HH} = 7.0$ Hz, 3H), 1.26 (t, $J_{HH} = 7.0$ Hz, 3H), 1.07 (d, $J_{HH} = 6.5$ Hz, 3H); $^{13}$C{¹H} NMR (75 MHz, CDCl₃) δ 156.3, 134.4, 126.7, 115.3, 80.2 (d, $J_{CP} = 6.0$ Hz), 80.1, 62.5 (d, $J_{CP} = 6.2$ Hz), 61.6 (d, $J_{CP} = 6.6$ Hz), 44.4 (d, $J_{HH} = 1.4$ Hz), 42.3 (d, $J_{CP} = 14.9$ Hz), 31.2 (d, $J_{CP} = 142$ Hz), 16.4 (d, $J_{CP} = 6.2$ Hz), 15.9; $^{31}$P{¹H} NMR (121 MHz, CDCl₃) δ 29.6. HRMS (FAB) m/z: [M+Na]$^+$ Calcd for C₁₆H₂₅O₅PNa 351.1336, Found 351.1332.
(±) Diethyl ((2S, 4R, 5S)-4-methyl-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.85)

\[
\begin{align*}
\text{EtO}_2\text{P} & \quad \text{O} \quad \text{O} \quad \text{Ph} \\
\text{EtO} & \quad \text{EtO} \quad \text{O} \quad \text{O} \quad \text{Ph}
\end{align*}
\]

To a solution of (1E, 3E)-diethyl-penta-1,3-dienylphosphonate (1.39b) (0.2 g, 0.98 mmol, 1.0 equiv) and Ni(acac)\(_2\) (0.026 g, 0.098 mmol, 0.1 equiv) in freshly distilled THF (10 mL) at room temperature was added benzaldehyde (198 µL, 1.96 mmol, 2 equiv) followed by BEt\(_3\) in THF (1.0 M, 2.45 mL, 2.45 mmol, 2.5 equiv). The resulting mixture was stirred for 36 h at room temperature. The reaction was quenched with 1N HCl and the aqueous solution was extracted with EtOAc. The organic layer was washed with water, NaHCO\(_3\) and brine, dried with Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The residue was partially purified by column chromatography (SiO\(_2\), 80-100 % EtOAc in hexanes) to give the impure pale yellow liquid of bishomoallylic alcohol (0.074 g, 0.24 mmol, 25 %). 73% pure by \(^{31}\)P\{\(^1\)H\} NMR) product was used directly in the next step. The alcohol was dissolved in MeOH (1 mL) and NaOMe (25 wt. % in methanol, 100 µL, 0.36 mmol) was added and the resulting solution was stirred for 24 h at room temperature. The reaction was quenched by addition of 1N HCl. The reaction mixture was concentrated under reduced pressure and residue was filtered through celite with washing with EtOAc. The pure tetrahydrofuran (2.85) as a colorless liquid was isolated (0.048 g, 0.15 mmol, 16% for two-step) by column chromatography (SiO\(_2\), 70-100% EtOAc in hexanes). IR (neat) 2958, 2089, 1245, 1018 cm\(^{-1}\); 1H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.25 (m, 5 H), 4.61-4.52 (m, 1H), 4.41 (d, \(J_{HP} = 9.2\) Hz, 1H), 4.17-4.08 (m, 4H), 2.52-2.29 (m, 2H), 2.20-2.00 (m, 2H), 1.63-1.52 (m, 1H), 1.36-1.30 (m, 6H), 1.07 (d, \(J_{HH} = 6.5\) Hz, 3H); \(^{13}\)C\{\(^1\)H\} NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.1, 128.5, 127.7, 126.3, 87.61, 74.5, 61.9 (d, \(J_{CP} = 6.3\) Hz) 61.7 (d, \(J_{CP} = 6.4\) Hz), 44.4, 43.1 (d, \(J_{CP} = 5.2\) Hz), 33.4 (d, \(J_{CP} = 136\) Hz), 16.6 (d, \(J_{CP} = 5.9\) Hz), 15.9; \(^{31}\)P\{\(^1\)H\} NMR (121 MHz, CDCl\(_3\)) \(\delta\) 28.0; HRMS (FAB) \(m/z\): [M+H\(^+\)] Calcd for C\(_{16}\)H\(_{26}\)O\(_4\)P 313.1569, Found 313.1561.
(±) Diethyl ((2S, 3S, 5S)-3-(tert-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.76a), (±) Diethyl ((2R, 3S, 5S)-3-(tert-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.76b) and (±) Diethyl ((2S, 3S, 5S)-3-hydroxy-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.77a)

Following the general procedure for cyclization, TBS-protected alcohol (2.86) (0.210 g, 0.49 mmol, 1 equiv) was reacted with NaOMe (25 wt % in methanol, 281 µL, 1.3 mmol, 2.5 equiv) to obtain a separable mixture of diastereoisomers of 2.87a, 2.87b & 2.88a in 2:1:1 ratio (overall 75%) as a colorless liquid after column chromatography (SiO₂, 55% EtOAc in hexanes for 2.87a, 65 % EtOAc in hexanes for 2.87b, and 10% IPA in EtOAc for 2.88a).

(±) Diethyl ((2S, 3S, 5S)-3-(tert-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.87a)

(2.87a) colorless liquid (0.077 g, 0.18 mmol, 37%). IR (neat) 2927, 2896, 2090, 1248, 1020 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.16 (m, 5H), 5.03 (t,  J HH = 7.6 Hz, 1H), 4.23-4.14 (m, 2H), 4.12-4.01 (m, 4H), 2.59-2.49 (m, 1H), 2.13-1.80 (m, 3H), 1.27-1.21 (m, 6H), 0.78 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 143.7, 128.5, 127.3, 125.9, 80.4 (d, J CP = 4.9 Hz), 79.0, 77.2 (d, J CP = 12.6 Hz), 62.0 (d, J CP = 6.2 Hz), 61.8 (d, J CP = 6.3 Hz), 43.2, 30.0 (d, J CP = 139.7 Hz), 25.9, 18.1, 16.6 (d, J CP = 6.1 Hz), 16.5 (d, J CP = 6.2 Hz), -4.5, -4.6; ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 28.2; HRMS (FAB) m/z: [M+H]⁺ Calcd for C₂₁H₃₈O₅PSi 429.2226, Found 429.2217.
(±) Diethyl ((2R, 3S, 5S)-3-(tert-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.87b)

(2.87b) colorless liquid (0.038 g, 0.088 mmol, 18%) IR (neat) 2927, 2899, 2123, 1250, 1026 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.17 (m, 5H), 4.89 (dd, J₉HP = 8.3 Hz, J₉HH = 6.4 Hz, 1H), 4.35-4.32 (m, 1H), 4.23-4.17 (m, 1H), 4.15-4.05 (m, 4H), 2.61-2.52 (m, 1H), 2.26-2.23 (m, 1H), 2.21-2.17 (m, 1H), 1.86-1.79 (m, 1H), 1.30 (t, J₉HH = 7.1 Hz, 3H), 1.26 (t, J₉HH = 7.1 Hz, 3H), 0.81 (s, 9H) 0.03 (s, 3H), -0.07 (s, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 143.3, 128.3, 127.3, 126.4, 79.5, 78.5 (d, J₉CP = 2.7 Hz), 73.7 (d, J₉CP = 10.6 Hz), 62.1 (d, J₉CP = 6.1 Hz), 61.6 (d, J₉CP = 6.2 Hz), 44.5, 26.8 (d, J₉CP = 141.5 Hz), 25.9, 18.2, 16.7, 16.6 (d, J₉CP = 6.2 Hz), -4.4, -4.9; ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 30.3; HRMS (FAB) m/z: [M+H]⁺ Calcd for C₂₁H₃₆O₅PSi 429.2226, Found 429.2218.

(±) Diethyl ((2S, 3S, 5S)-3-hydroxy-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.88a)

(2.88a) colorless liquid (0.030 g, 0.095 mmol, 20%). Also obtained by deprotection of 2.87a with TBAF resulting in 90% yield. (see below).

Tetrahydrofuran 2.87a (0.045 g, 0.104 mmol, 1.0 equiv) was reacted with TBAF (1M in THF, 260 µL, 0.26 mmol, 2.5 equiv) in dry THF (6 mL) at 0 °C for 3 h. After the reaction was complete (monitored with TLC), the reaction was quenched by addition of water, extracted with EtOAc (4 x 25 mL) and organic layer was dried with Na₂SO₄ followed by concentration under reduced pressure. Purification by column chromatography (SiO₂, 10% IPA in EtOAc). gave 2.88a
(0.030 g, 0.095 mmol, 90%). IR (neat) 3390, 2960, 2121, 1255, 1009 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.27 (m, 5H), 5.07 (dd, Jₘₚ = 9.8 Hz, Jₘ₞ = 6.1 Hz, 1H), 4.87 (s, 1H), 4.34-4.26 (m, 1H), 4.20-4.13 (m, 5H), 2.78-2.70 (m, 1H), 2.51-2.39 (m, 1H), 2.19-1.96 (m, 2H), 1.39-1.34 (m, 6H); ¹³C(¹H) NMR (75 MHz, CDCl₃) δ 142.7, 128.7, 127.8, 126.0, 79.1 (d, Jₖₚ = 5.4 Hz), 78.7 (d, Jₖₚ = 0.7 Hz), 77.2 (d, Jₖₚ = 1.1 Hz), 62.5 (d, Jₖₚ = 6.6 Hz), 62.4 (d, Jₖₚ = 6.4 Hz) (high), 42.5, 31.5 (d, Jₖₚ = 134.6 Hz), 16.6 (d, Jₖₚ = 6.0 Hz), 16.5 (d, Jₖₚ = 6.0 Hz);
³¹P(¹H) NMR (121 MHz, CDCl₃) δ 29.7; HRMS (FAB) m/z: [M+H]⁺ Calcd for C₁₅H₂₃O₅P 315.1361, Found 315.1360.

(±) Diethyl ((2R,3S,5S)-3-hydroxy-5-phenyltetrahydrofuran-2-yl)methylphosphonate 2.88b and bicyclic phostone 2.89

![Diagram of 2.88b and 2.89](image)

Tetrahydrofuran 2.87b (0.027 g, 0.063 mmol, 1 equiv) was reacted with TBAF (1M in THF, 158 µL, 0.158 mmol, 2.5 equiv) in dry THF (1.5 mL) at 0 °C for 3 h. After the reaction was complete (monitored with TLC), the reaction was quenched by addition of water, extracted with EtOAc (4 x 25 mL) and organic layer was dried with Na₂SO₄ followed by concentration under reduced pressure. Separation by column chromatography (SiO₂, 100% EtOAc) gave 2.88b (0.0082 g, 0.026 mmol, 41%) and 2.89 (IPA: EtOAc, 10:90) (0.0061 g, 0.023 mmol, 36%).

(±)-Diethyl ((2R,3S,5S)-3-hydroxy-5-phenyltetrahydrofuran-2-yl)methylphosphonate 2.88b

![Diagram of 2.88b](image)
(2.88b) Colorless liquid; IR (neat) 3376, 2977, 2922, 1216, 1017 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\) \(\delta\) 7.44-7.27 (m, 5H), 4.77 (t, \(J_{HH} = 7.8\) Hz, 1H), 4.57 (s, 1H), 4.19-4.06 (m, 5H), 3.94 (s, 1H), 2.80-2.71 (m, 1H), 2.56-2.85 (m, 2H), 2.02-1.94 (m, 1H), 1.39-1.34 (m, 6H); \(^{13}\)C\({^1}\)H NMR (75 MHz, CDCl\(_3\) \(\delta\) 141.8, 128.6, 127.9, 126.7, 79.9, 78.5 (d, \(J_{CP} = 3.2\) Hz), 72.8 (d, \(J_{CP} = 1.7\) Hz), 62.6 (d, \(J_{CP} = 6.2\) Hz), 62.2 (d, \(J_{CP} = 6.7\) Hz), 43.3, 29.9, 26.5 (d, \(J_{CP} = 136.4\) Hz), 16.6 (d, \(J_{CP} = 6.2\) Hz), 16.5 (d, \(J_{CP} = 5.9\) Hz); \(^{31}\)P\({^1}\)H NMR (121 MHz, CDCl\(_3\) \(\delta\) 29.5; HRMS (FAB) \(m/z\): [M+H]\(^+\) Calcd for C\(_{15}\)H\(_{23}\)O\(_5\)P 315.1361, Found 315.1365.

**Bicyclic phostone 2.89**

(2.89) Colorless liquid; IR (neat) 2960, 2925, 2234, 1250, 1020 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\) \(\delta\) 7.45-7.32 (m, 5H), 5.05-5.02 (m, 1H), 4.86-4.80 (m, 1H), 4.70-4.57 (m, 1H), 4.26-4.22 (m, 2H), 2.84-2.79 (m, 1H), 2.44-2.18 (m, 3H), 1.40 (t, \(J_{HH} = 7.0\) Hz, 3H); \(^{13}\)C\({^1}\)H NMR (75 MHz, CDCl\(_3\) \(\delta\) 140.3, 128.7, 128.4, 126.6, 82.7 (d, \(J_{CP} = 10.3\) Hz), 81.2, 80.1 (d, \(J_{CP} = 3.2\) Hz), 63.1, 63.0, 42.8 (d, \(J_{CP} = 4.0\) Hz), 26.7 (d, \(J_{CP} = 119.7\) Hz), 16.7 (d, \(J_{CP} = 6.4\) Hz); \(^{31}\)P\({^1}\)H NMR (121 MHz, CDCl\(_3\) \(\delta\) 48.2; HRMS (FAB) \(m/z\): [M+H]\(^+\) Calcd for C\(_{13}\)H\(_{18}\)O\(_4\)P 269.0942, Found 269.0947.

(±) (1R, 3S, E)-5-(Diethoxyphosphoryl)-3-methyl-1-phenylpent-4-enyl 4-nitrobenzoate (2.83)

The bishomoallylic alcohol (2.81a) (0.2 g, 0.64 mmol, 1.0 equiv), p-nitrobenzoic acid (0.161 g, 0.96 mmol, 1.5 equiv) and triphenyl phosphine (0.252 g, 0.96
mmol, 1.5 equiv) were dissolved in a mixture of THF (12 mL) and toluene (3 mL). The solution was cooled to -50 °C and then di-isopropyl azodicarboxylate (190 µL, 0.96 mmol, 1.5 equiv) was added with stirring. After 15 min, the solution was warmed up to room temperature and stirred for an additional 24 h (monitored by TLC). The reaction was quenched by addition of EtOH (0.2 mL) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, EtOAc:hexanes, 40:60) and then reverse phase HPLC (Triphenyl phosphine oxide (TPPO) elutes with MeOH:water, 50:50 and the product elutes with MeOH:water,70:30) to give a pale yellow liquid of the pure benzoate ester (2.72, 0.283 g, 0.61 mmol, 96%). IR (neat) 2976, 2905, 2086, 1720, 1523, 1265 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.31–8.21 (m, 4H), 7.39–7.33 (m, 5H), 6.76 (ddd, J₇₅P= 22.0 Hz, J₅₇H = 17.2, 7.8 Hz 1H), 6.0 (m, 1H), 5.60 (m, 1H), 4.15-4.05 (m, 4H), 2.47-2.35 (m, 1H), 2.25-2.16 (m, 1H), 2.05-1.99 (m, 1H), 1.37-1.29 (m, 6H), 1.16 (d, J₅₇H = 6.7 Hz, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 163.9, 158.2 (d, JCP = 4.5 Hz), 150.8, 139.6, 135.7, 131.0, 129.0, 128.8, 126.6, 123.8, 115.9 (d, JCP = 186 Hz), 76.0, 62.5 (d, JCP = 5.2 Hz), 62.4 (d, JCP = 5.7 Hz), 42.3, 35.4 (d, JCP = 20.8 Hz), 19.6, 16.5 (d, JCP = 6.1 Hz), 16.4 (d, JCP = 6.2 Hz), 16.0; ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 18.6; HRMS (FAB) m/z: [M+H]+ Calcd for C₂₃H₂₉NO₇P 462.1682, Found 462.1688.

(±) Diethyl ((2S, 3S, 5R)-3-methyl-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.84a) and diethyl ((2R, 3S, 5R)-3-methyl-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.84b)

To a solution of the benzoate ester (2.83) (0.120 g, 0.26 mmol, 1.0 equiv) in dry MeOH was added sodium methoxide (25 wt. % in methanol, 140 µL, 0.65 mmol, 2.5 equiv) and the resulting solution was stirred for 24 h at room temperature. The reaction was quenched by addition of 1N HCl and the reaction mixture was
concentrated under reduced pressure. The residue was filtered through celite washing with EtOAc. Purification by column chromatography (SiO$_2$, 80-100% EtOAc in hexanes) gave a mixture of two diastereoisomers 2.84a and 2.84b in a 4:1 ratio, isolated (0.070 g, 0.224 mmol, 85%) as a colorless liquid. Data for mixture. IR (neat) 2960, 1448, 1248,1017 cm$^{-1}$; HRMS (FAB) m/z: [M+H]$^+$ Calcd for C$_{16}$H$_{26}$O$_4$P 313.1569, Found 313.1573.

(±) Diethyl ((2R,3S,5R)-3-methyl-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.84a) [Major (trans) diastereoisomer]

(±) Diethyl ((2S,3S,5R)-3-methyl-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.84b) [Minor (cis) diastereoisomer]
43.2, 37.1 (d, $J_{CP} = 9.0$ Hz), 28.1 (d, $J_{CP} = 140$ Hz), 16.7, 16.6, 14.1; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 29.3.

($\pm$) (1R, 3S, E)-3-(tert-Butyldimethylsilyloxy)-5-(diethoxyphosphoryl)-1-phenylpent-4-enyl 4-nitrobenzoate (2.90)

Diethyl (E)-3-(tert-butyldimethylsilyloxy)-5-hydroxy-5-phenyl-pent-1-enyl phosphonate (2.86) (0.058 g, 0.14 mmol, 1.0 equiv) and $p$-nitrobenzoic acid (0.047 g, 0.28 mmol, 2.0 equiv) were dissolved in a mixture of THF (4 mL) and toluene (1 mL) and the resulting solution was cooled to -50 °C. To the cooled solution was added PBu$_3$ (69 µL, 0.28 mmol, 2.0 equiv) and di-isopropyl azodicarboxylate (DIAD) (55 µL, 0.28 mmol, 2.0 equiv) sequentially. After 20 min., the solution was warmed to 0 °C and stirred for an additional 2 h (monitored with TLC). The solution was again cooled to -50 °C and 1 equivalent of each PNBA, PBu$_3$ and DIAD were added. After 10 min at -50 °C, the solution was warmed to 0 °C and stirred for an additional 1 h. The reaction was quenched by addition of EtOH (0.2 mL) and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, EtOAc:hexanes, 30:70) to give the benzoate ester (2.90, 0.075 g, 0.13 mmol, 96 %) as pale yellow solid. M.p. = 71.9 °C ; IR (neat) 2976, 1720, 1523, 1265 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.27-8.16 (m, 4H), 7.36-7.23 (m, 5H), 6.88-6.79 (m, 1H), 6.15-6.11 (m, 1H), 5.83 (ddd, $J_{HP}$= 20.4 Hz, $J_{HH}$ = 16.9, 1.7 Hz, 1H), 4.33 (s, 1H), 3.99-3.89 (m, 4H), 2.45-2.38 (m, 1H), 2.20-2.09 (m, 1H), 1.28-1.16 (m, 6H), 0.90 (s, 3H), 0.0 (s, 3H), -0.02 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 163.6, 153.8 (d, $J_{CP} = 5.7$ Hz), 150.6, 139.6, 135.5, 130.9, 128.9, 128.6, 126.6, 123.6, 116.2 (d, $J_{CP} = 188$ Hz), 74.0, 69.6 (d, $J_{CP} = 22.0$ Hz), 61.7 (d, $J_{CP} = 5.6$ Hz), 61.6 (d, $J_{CP} = 5.8$ Hz), 43.6, 25.8, 18.2, 16.4 (t, $J_{CP} = 6.3$ Hz), -4.4, -4.9; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 18.3; HRMS (FAB) m/z: [M+Na]$^+$ Calcd for C$_{28}$H$_{40}$NO$_8$PSiNa 600.2150, Found 600.2153.

Paudel, Rishi, 2020, UMSL
(±) Diethyl ((2S, 3S, 5R)-3-(tert-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.91a) and diethyl ((2R, 3S, 5R)-3-(tert-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.91b)

To a solution of the benzoate (2.90) (0.1 g, 0.17 mmol, 1 equiv) in dry MeOH (5 mL) was added sodium methoxide (25 wt % in methanol, 75 µL, 0.43 mmol, 2.5 equiv) and the resulting solution was stirred for 24 h at room temperature. The reaction was quenched by addition of 1N HCl (1 mL), the mixture was concentrated under reduced pressure, and residue was filtered through celite washing with EtOAc. The products (2.91a: 2.91b = 1:1.5) were isolated (overall 0.056 g, 0.131 mmol, 77%,) by column chromatography (30% EtOAc in hexanes for 2.91a and 50% EtOAc in hexanes for 2.91b).

(±) Diethyl ((2S, 3S, 5R)-3-(tert-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.91a)

Minor diastereoisomer 2.91a (0.023 g, 0.054 mmol, 32 %) as a colorless liquid. IR (neat) 2927, 2855, 2125, 1248, 1021 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.28-7.21 (m, 5H), 5.10 (dd, ⁶JHP = 9.7, ⁶JHH = 5.8 Hz, 1H), 4.29-4.27 (m, 1H), 4.17-4.12 (m, 1H), 4.10-4.04 (m, 4H), 2.13-1.83 (m, 4H), 1.28-1.23 (m, 6H), 0.86 (s, 9H) 0.06 (s, 3H), 0.05 (s, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 142.1, 128.3, 127.4, 125.9, 82.1, 80.2, 77.2 (d, ⁶JC₃ = 10.9 Hz), 61.9 (d, ⁶JC₃ = 6.3 Hz), 61.6 (d, ⁶JC₃ = 6.3 Hz), 43.5, 31.4 (d, ⁶JC₃ = 139 Hz), 25.8, 18.0, 16.5, 16.4, -4.6, -4.7; ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 27.5; HRMS (FAB) m/z: [M+H]⁺ Calcd for C₂₁H₃₈O₅PSi 429.2226, Found 429.2236.
(±) Diethyl ((2R, 3S, 5R)-3-(tert-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.91b)

![Chemical structure of 2.91b](image)

Major diastereoisomer 2.91b (0.033 g, 0.077 mmol, 45 %) as a colorless liquid. IR (neat) 2927, 2126, 1248, 1022 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.28-7.19 (m, 5H), 5.21-5.15 (dd, JₜP = 9.9, Jₜₜ = 6.2 Hz, 1H), 4.44-4.39 (m, 1H), 4.38-4.36 (m, 1H), 4.11-4.04 (m, 4H), 2.29-2.22 (m, 1H), 2.18-2.16 (m, 2H), 2.12-2.10 (m, 1H), 1.27 (t, Jₜₜ = 7.1 Hz, 3H), 1.25 (t, Jₜₜ = 7.1 Hz, 3H), 0.89 (s, 9H) 0.08 (s, 3H), 0.07 (s, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 143.3, 128.4, 127.2, 125.4, 79.0, 78.4, 74.3 (d, JₐP = 9.6 Hz), 61.9 (d, JₐP = 6.1 Hz), 61.5 (d, JₐP = 6.2 Hz), 45.0, 26.9 (d, JₐP = 141 Hz), 25.9, 18.1, 16.5 (d, JₐP = 6.1 Hz), 16.4 (d, JₐP = 6.1 Hz), -4.5, -4.9; ³¹P{¹H} NMR (121 MHz, CDCl₃) δ 30.1; HRMS (FAB) m/z: [M+H]⁺ Calcd for C₂₁H₃₈O₅PSi 429.2226, Found 429.2237.

(±) Diethyl ((2S, 3S, 5R)-3-hydroxy-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.92a)

![Chemical structure of 2.92a](image)

3-(tert-butyldimethylsilyloxy)-2-(diethylphosphonomethylene)-5-phenyltetrahydrofuran 2.91a (0.09 g, 0.210 mmol) was dissolved in dry THF (10 mL) and cooled to 0 °C then TBAF in 1M THF (0.53 mL, 0.53 mmol, 2.5 equiv) was added dropwise and the resulting solution was stirred for 4 h at 0 °C. After the reaction was complete (monitored with TLC), the reaction was quenched by addition of water, extracted with EtOAc (4 x 25 mL) and organic layer was dried with Na₂SO₄ followed by concentration under reduced pressure. The product 2.92a was isolated by column chromatography (SiO₂, 5% IPA in EtOAc) a colorless liquid (0.06 g, 0.191 mmol, 91%). IR (neat) 3352, 2979, 2120, 1214,
1016 cm\(^{-1}\); \(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.25-7.20 (m, 5H), 5.05-4.10 (m, 1H), 4.42 (s), 4.21-4.16 (m, 1H), 4.12-4.06 (m, 4H), 3.99-3.94 (m, 1H), 2.35-2.24 (m, 2H), 2.14-2.03 (m, 2H), 1.28 (t, \(J_{HH} = 7.0\) Hz); \(^{13}C\)\(^{1}H\) NMR (75 MHz, CDCl\(_3\)) \(\delta\): 142.0, 128.5, 127.7, 126.0, 81.1 (d, \(J_{CP} = 3.7\) Hz), 79.5, 76.4 (d, \(J_{CP} = 3.0\) Hz), 62.5 (d, \(J_{CP} = 6.6\) Hz), 62.3 (d, \(J_{CP} = 6.4\) Hz), 42.4, 31.0 (d, \(J_{CP} = 137\) Hz), 16.5 (d, \(J_{CP} = 6.1\) Hz), 16.4 (d, \(J_{CP} = 6.1\) Hz); \(^{31}P\)\(^{1}H\) NMR (121 MHz, CDCl\(_3\)) \(\delta\): 29.1; HRMS (FAB) \(m/z\): [M+H]\(^+\) Calcd for C\(_{15}\)H\(_{24}\)O\(_5\)P 315.1361, Found 315.1369.

(±) Diethyl ((2R, 3S, 5R)-3-hydroxy-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.92b) and Phostones (2.93a) and (2.93b)

3-(tert-butyldimethylsilyloxy)-2-(diethylphosphonomethylene)-5-phenyl-tetrahydrofuran 2.80b (0.2 g, 0.46 mmol) was dissolved in dry THF (10 mL) and cooled to 0 °C then TBAF in 1M THF (1.15 mL, 1.15 mmol, 2.5 equiv) was added dropwise and stirred for 4 h at 0 °C under argon purge. After reaction completion (monitored with TLC), the reaction was quenched by addition of water, extracted with EtOAc (4 x 25 mL) and organic layer was dried with Na\(_2\)SO\(_4\) followed by concentration under reduced pressure. Three different products (2.93a, 2.93b and 2.92b) were isolated with 100% EtOAc to 15% iso-propanol (IPA) in EtOAc. The order of elution is 2.93a (100% EtOAc), 2.92b (5%-10% IPA in EtOAc) and 2.93b (15% IPA in EtOAc).

**bicyclic phostone diastereomer 2.93a**

(2.93a) (0.034 g, 0.127 mmol, 27%) as a colorless liquid. IR (neat) 2979, 2928, 2234, 1725, 1252, 1017 cm\(^{-1}\); \(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\); 7.27-7.19 (m, 5H),
5.27-5.21 (m, 1H), 5.02-4.85 (m, 2H), 4.18-4.08 (m, 2H), 2.63-2.57 (m, 1H), 2.22-2.16 (m, 2H), 1.99-1.89 (m, 1H), 1.29 (t, $J_{HP} = 7.1$ Hz, 3H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 140.4, 128.7, 128.2, 126.0, 82.5 (d, $J_{CP} = 8.0$ Hz), 80.0 (d, $J_{CP} = 4.9$ Hz), 79.9, 62.6 (d, $J_{CP} = 6.4$ Hz), 42.7 (d, $J_{CP} = 7.5$ Hz), 27.7 (d, $J_{CP} = 119$ Hz), 16.7 (d, $J_{CP} = 5.5$ Hz); $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 48.3; HRMS (FAB) m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{18}$O$_4$P 269.0942, Found 269.0945.

bicyclic phosphonate diastereomer 2.93b

![bicyclic phosphonate diastereomer 2.93b](image)

2.93b (0.033 g, 0.123 mmol, 26%) as a colorless liquid. IR (neat) 2979, 2925, 2237, 1720, 1254, 1017 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38-7.27 (m, 5H), 5.32-5.26 (m, 1H), 5.08-5.05 (m, 2H), 4.98-4.95 (m, 1H), 4.30-4.18 (m, 2H), 2.72-2.66 (m, 1H), 2.37-2.14 (m, 2H), 2.08-1.98 (m, 1H), 1.42-1.38 (m, 3H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 140.9, 128.7, 128.1, 125.7, 83.6 (d, $J_{CP} = 9.2$ Hz), 80.6, 80.6 (d, $J_{CP} = 3.0$ Hz), 63.1 (d, $J_{CP} = 6.2$ Hz), 42.9 (d, $J_{CP} = 5.0$ Hz), 28.0 (d, $J_{CP} = 118$ Hz), 16.6 (d, $J_{CP} = 5.5$ Hz); $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 48.9; HRMS (FAB) m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{18}$O$_4$P 269.0942, Found 269.0946.

(±) Diethyl ((2R, 3S, 5R)-3-hydroxy-5-phenyltetrahydrofuran-2-yl)methylphosphonate (2.92b)

![diethyl ((2R, 3S, 5R)-3-hydroxy-5-phenyltetrahydrofuran-2-yl)methylphosphonate](image)

2.92b (0.011 g, 0.035 mmol, 7%) as a colorless liquid. IR (neat) 3352, 2979, 2092, 1212, 1016 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.27-7.18 (m, 5H), 5.22-5.17 (m, 1H), 4.52-4.36 (m, 2H), 4.09-4.07 (m, 4H), 2.42-2.24 (m, 3H), 2.03-1.99 (m, 1H), 1.34-1.26 (m, 6H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 142.6, 128.7, 127.7, 125.9, 79.5, 78.9 (d, $J_{CP} = 4.4$ Hz), 73.4 (d, $J_{CP} = 1.6$ Hz), 62.7 (d, $J_{CP} = 6.0$ Hz).
62.2 (d, $J_{CP} = 6.7$ Hz), 44.0, 27.6 (d, $J_{CP} = 133$ Hz), 16.6 (d, $J_{CP} = 5.9$ Hz); $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 29.3; HRMS (FAB) m/z: [M+H]$^+$ Calcd for C$_{15}$H$_{23}$O$_5$P 315.1361, Found 315.1359.

(±) Diethyl ((2R or 2S, 3S, 5R)-3-(tert-butyldimethylsilyloxy)-5-(3,4-methylenedioxy)phenyl tetrahydrofuran-2-yl)methylphosphonate (2.94b)

Data for mixture: IR (neat) cm$^{-1}$ 2927, 2855, 1486, 1244, 1020; HRMS (FAB) m/z: [M+H]$^+$ Calcd for C$_{22}$H$_{38}$O$_7$PSi calcd. 473.2124, Found 473.2119.

Major Diastereomer (data extrapolated from spectra obtained on mixture of diastereoisomers): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.95-7.69 (m, 3H), 5.9 (s, 2H), 4.99 (t, $J_{HH} = 7.5$ Hz), 4.32-4.22 (m, 2H), 4.15-4.06 (m, 4H), 2.60-1.80 (m, 4H), 1.33-1.25 (m, 6H), 0.86 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 147.7, 146.7, 137.5, 119.2, 107.8, 107.1, 100.9, 80.4 (d, $J_{CP} = 4.5$ Hz), 78.8, 76.9 (d, $J_{CP} = 11.9$ Hz), 61.7 (d, $J_{CP} = 6.3$ Hz), 61.6 (d, $J_{CP} = 6.3$ Hz), 43.0, 29.8 (d, $J_{CP} = 139.5$ Hz), 25.7, 17.9, 16.5, 16.4, -4.6, -4.7; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 28.1

Minor Diastereomer (data extrapolated from spectra obtained on mixture of diastereoisomers): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.95-7.69 (m, 3H), 5.9 (s, 2H), 4.82 (t, $J_{HH} = 6.6$ Hz), 4.32-4.22 (m, 2H), 4.15-4.06 (m, 4H), 2.60-1.80 (m, 4H), 1.33-1.25 (m, 6H), 0.86 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$ 147.6, 146.7, 137.2, 119.6, 107.7, 106.7, 100.8, 79.3, 78.3 (d, $J_{CP} = 4.5$ Hz), 73.4 (d, $J_{CP} = 11.9$ Hz), 61.9 (d, $J_{CP} = 6.3$ Hz), 61.4 (d, $J_{CP} = 6.3$ Hz), 44.3, 26.5 (d, $J_{CP} = 141.6$ Hz), 25.8, 18.0, 16.5, 16.4, -4.5, -5.0; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) $\delta$ 30.1.
(±) (1R, 3S, E)-3-(tert-Butyldimethylsilyloxy)-5-(diethoxyphosphoryl)-1-(3,4-methylenedioxy)phenylpent-4-enyl 4-nitrobenzoate (2.95)

Following the general procedure of Mitsunobu reaction with PBu₃, a diastereomeric mixture of benzoate ester (2.95) was obtained (1:2 ratio). IR (neat) 2920, 2851, 1722, 1247, 1019 cm⁻¹; ^1H NMR (300 MHz, CDCl₃) δ 8.27-8.15 (m, 4H), 6.89-6.75 (m, 4H), 6.05-6.02 (m, 1H), 5.94 (s, 2H), 5.93-5.76(m, 1H)1.7 Hz, 1H), 4.33 (s, 1H), 4.03-3.88 (m, 4H), 2.4-2.34 (m, 1H), 2.17-2.0 (m, 1H), 1.27 (t, JCP = 6.2 Hz, 3H), 1.19 (t, JCP = 6.2 Hz, 3H), 0.90 (s, 9H), 0.01 (s, 3H), -0.00 (s, 3H); ^13C(^1H) NMR (75 MHz, CDCl₃) δ 163.6, 153.8, 150.5, 148.1, 147.8, 135.5, 133.3, 130.9, 123.6 120.9, 116.2 (d, JCP = 187.4 Hz), 108.4, 107.0, 101.3, 74.0, 69.6 (d, JCP = 22.2 Hz), 61.7 (d, JCP = 5.6 Hz), 61.6 (d, JCP = 5.8 Hz), 43.4, 25.8, 18.2, 16.3 (t, JCP = 6.3 Hz), -4.4, -4.9; ^31P(^1H) NMR (121 MHz, CDCl₃) δ 18.3; HRMS (FAB) m/z: [M+Na]^+ Calcd for C_{29}H_{40}NO_{10}PSiNa 622.2056, Found. 644.2063.

Crystal structure of 2.82g

Table 2.2. Crystal data and structure refinement for 2.82g (file cds15217) (CCDC 19839280)

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<td>C₁₆H₂₅O₅P</td>
</tr>
<tr>
<td>Formula weight</td>
<td>328.33</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁/c</td>
</tr>
</tbody>
</table>
Unit cell dimensions

\[ a = 12.5757(6) \text{ Å} \quad \alpha = 90^\circ. \]
\[ b = 15.1915(8) \text{ Å} \quad \beta = 111.809(3)^\circ. \]
\[ c = 9.4897(4) \text{ Å} \quad \gamma = 90^\circ. \]

Volume

1683.19(14) Å³

Z

4

Density (calculated)

1.296 Mg/m³

Absorption coefficient

0.183 mm⁻¹

F(000)

704

Crystal size

0.415 x 0.251 x 0.213 mm³

Theta range for data collection

1.744 to 30.605°.

Index ranges

-18 ≤ h ≤ 17, -21 ≤ k ≤ 15, -13 ≤ l ≤ 13

Reflections collected

19386

Independent reflections

5130 [R(int) = 0.034]

Completeness to theta = 25.242°

100.0 %

Absorption correction

Semi-empirical from equivalents

Max. and min. transmission

0.9420 and 0.8914

Refinement method

Full-matrix least-squares on F²

Data / restraints / parameters

5130 / 0 / 207

Goodness-of-fit on F²

1.033

Final R indices [I>2sigma(I)]

R1 = 0.0410, wR2 = 0.0893

R indices (all data)

R1 = 0.0613, wR2 = 0.1023

Largest diff. peak and hole

0.361 and -0.335 e.Å⁻³
Figure 2.2. Crystal structure of 2.82g
2.5. REFERENCES


CHAPTER III
SYNTHESIS OF VINYL PHOSPHONATES AND PHOSTONES

3.1. INTRODUCTION
Phosphorus-containing compounds are vital components for life and are found in hereditary processes and growth, development, and maintenance of all plants and animals.\(^1\) They are involved in different energy processes such as photosynthesis, nerve function, and metabolism.\(^1\) Phosphorus-containing organic compounds form one of the classes in organic chemistry called organophosphorus. Organophosphorus compounds containing \(\text{R-PO(OR)}_2\) groups (where \(\text{R} = \text{alkyl or aryl}\)) are called phosphonates (3.3, Figure 3.1). Phosphonate moieties are used as synthetic intermediates in organic synthesis, and in therapeutic drugs and industrial chemicals.\(^2\) Phosphonates are used as stable bioisosteres of phosphates (3.1) in medicinal chemistry and chemical biology.\(^3\) Several phosphonates are found in nature due to the chemical and thermal stability of the C-P bond compared to P-O bond. Phosphonates (3.5, Figure 3.2) can also mimic carboxyl groups (3.2) or the tetrahedral intermediates formed during enzyme catalyzed reactions.\(^4\)

\[
\text{3.1} \quad \text{3.2} \quad \text{3.3}
\]

\text{Figure 3.1. Alkyl phosphonate mimicry of phosphate esters or carboxylates}^{5-6} \text{Figure 3.2. Non-hydrolysable analogs of biological phosphates}^{4}

Several biologically active phosphonates (3.5, Figure 3.2) were reported as non-hydrolysable phosphate analogs.\(^4\) For example, fosfomycin (3.6, Figure 3.3) is a
broad-spectrum antibiotic that inhibits both gram-positive and gram-negative bacteria through cell wall biosynthesis.\(^7\) A natural amino acid glufosinate (phosphinothricin) (3.7) is a widely used herbicide.\(^8\) The rhizocitins (3.8) are phosphonate-containing oligopeptide antibiotics (antifungal) produced by gram-positive bacterium *Bacillus subtilis*.\(^9\)-\(^10\) The natural antibiotic fosmidomycin (3.9) and its derivative FR900098 (3.10) are also used as antimalarial clinical drugs.\(^11\)-\(^12\) Dehydrophos (3.11), isolated from *Streptomyces luridus*, has broad-spectrum antibiotic activity against both gram-positive and gram-negative bacteria.\(^4\)

![Chemical structures of fosomycin, phosphinothricin (glufosinate), rhizocitin A, fosmidomycin, FR90098, and dehydrophos](image)

**Figure 3.3.** Chemical structures of fosomycin, phosphinothricin (glufosinate), rhizocitin A, fosmidomycin, FR90098, and dehydrophos

Similarly, α-bromophosphonates (3.12, Figure 3.4) were found to inhibit G-protein coupled receptors (GPCRs) of LPA, which regulate cancer cell proliferation, invasion, and angiogenesis.\(^13\) Both *syn* and *anti* α-bromophosphonates (3.12) were found to be inhibitors of GPCRs. The diastereomeric mixture (1 : 1) of *syn* and *anti* α-bromophosphonates is termed Br-LPA (Figure 3.4).\(^13\)

![Chemical structure of Br-LPA](image)

**Figure 3.4.** Br-LPA as GPCRs inhibitor
Although the non-hydrolysable C-P bond of phosphonate moiety is resistant to enzymatic cleavage, phosphonates acting as phosphate bioisosteres have some drawbacks. The replacement of an oxygen atom with methylene group may reduce the solubility and the affinity to the phosphate-recognizing-protein-active site.\textsuperscript{13} The variation in pK\textsubscript{a} values of methyl phosphate (\ref{eq:methyl_phosphate}) and methyl phosphonate (\ref{eq:methyl_phosphonate}) are given below (Figure 3.5)\textsuperscript{3}:

\begin{align*}
\text{MeO-P-OH} & \xrightleftharpoons{pK_a = 1.5} \text{MeO-P-O}^- \\
\text{3.13} & \quad \text{Methyl Phosphate} \\
\text{MeO-P-O}^- & \xrightleftharpoons{pK_a = 2.4} \text{MeO-P-O}^- \\
\text{3.16} & \quad \text{Methyl Phosphonate} \\
\text{MeO-P-O}^- & \xrightleftharpoons{pK_a = 6.3} \text{MeO-P-O}^- \\
\text{3.14} & \\
\text{MeO-P-O}^- & \xrightleftharpoons{pK_a = 7.5} \text{MeO-P-O}^- \\
\text{3.17} & \\
\text{MeO-P-O}^- & \\
\text{3.18} & \\
\end{align*}

Figure 3.5. The pK\textsubscript{a} values for the deprotonations of methyl phosphate and phosphonate

The first pK\textsubscript{a} values show that both the compounds are ionizable at physiological pH. However, the second pK\textsubscript{a} values indicate the methyl phosphonate will be predominantly singly ionized at physiological pH in contrast to the di-anionic phosphate. Various structural modifications can be performed to address this issue in order to retain biological activity. For example, the introduction of more electronegative atoms in the methylene group can lower the pK\textsubscript{a} value.\textsuperscript{3} Among the various phosphonates, vinyl phosphonates are a crucial synthetic intermediate in organic chemistry. Synthesis and synthetic application of functionalized vinyl phosphonate have been demonstrated in the literature.\textsuperscript{14-19} Vinyl phosphonates are also used as a versatile synthetic reagents to prepare various biologically active molecules containing the phosphonate moiety.\textsuperscript{16} For example, Minami synthesized bicyclic compounds including Cadalane and Valerenic acid sesquiterpenoids through the intramolecular ene reaction of vinyl phosphonate intermediates.\textsuperscript{17}
Phosphorus-based sugars, which are used as glycomimetics, are the cyclic phosphonate analogs of carbohydrates bearing a phosphorus atom at the anomeric position.\textsuperscript{20} Based on the substituting nature of the phosphorus atom in the sugar, they are classified as phosphono-sugars (phostones) (3.19), phosphino-sugars (phostines) (3.20) and phospha-sugars (3.21, Figure 3.6).\textsuperscript{21}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.6.png}
\caption{Classification of phosphorus-based sugars}
\end{figure}

Phosphorus-based sugars are also called pseudo-sugars or phosphorus heterocycles.\textsuperscript{21} Various phosphorus-based sugars have been reported as anti-cancer agents.\textsuperscript{22-24} Some of the biologically active cyclic phosphonates (Figure 3.7) are given below;\textsuperscript{25-27}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.7.png}
\caption{Biologically active phosphorus-based sugars}
\end{figure}
The synthetic approaches for phosphorus-based sugars are still not fully explored as there are only limited methods available for the synthesis of phostones. A recent study of some examples of biologically active phostone derivatives demonstrated that there is a need for a detailed study of phostone synthesis. The most common methods for the synthesis of phostones are the Abramov reaction of sugar aldehydes, ring-closing metathesis (RCM), γ,δ-epoxy-vinyl phosphonate chemistry and anomeric alkoxy radical β-fragmentation (ARF) reaction.
3.2. RESULTS AND DISCUSSION
We have developed new synthetic approaches for the synthesis of phostones starting from easily available materials. Our approach involves the cyclization of δ-hydroxy phosphonates.

3.2.1. Synthesis of vinyl phosphonate from phosphono allylic carbonate
To synthesize vinyl phosphonate, we have employed the phosphono allylic carbonates (3.26, Scheme 3.1) one of the most commonly used starting materials in our lab for the preparation of various heterocyclic phosphonates.32-33 Former lab member Surendra Dawadi had started the work on phosphono allylic carbonate. There are some examples of transmetallation of electrophilic allyl palladium complexes to nucleophilic allyl indium species reported in the literature.34-35 We applied this umpolung concept to phosphono allylic carbonates.

Scheme 3.1. Synthesis of vinyl phosphonate by Indium mediated umpolung chemistry

The addition of benzaldehyde to phosphono allylic carbonate has been carried out in the presence of Pd(dppf)Cl₂ and indium iodide resulting in the formation of vinyl phosphonate (3.27). A possible mechanism (Scheme 3.2) based on literature35 is shown below:
Scheme 3.2. Possible mechanism of Indium mediated umpolung chemistry

Generally, the mono π-allylpalladium complexes such as 3.28 are electrophilic and undergo reaction with nucleophiles. However, herein, the electrophilic π-allyl palladium complexes can be converted into nucleophilic allyl indium species (3.29) through a transmetallation with indium (I) iodide (Scheme 3.2). The nucleophilic allyl indium species react with benzaldehyde to give a diastereomeric mixture of allylated products (homoallyl alcohol) (3.27). The indium (I) iodide used for transmetallation of the palladium complex is used in stoichiometric ratio to the reactants. It is an expensive reagent to use in stoichiometric amounts. Under an economic point of view, this reaction requires alternative methods for large scale vinyl phosphonates synthesis.

3.2.2. Synthesis of vinyl phosphonate from crotyl phosphonate
The second approach for the synthesis of vinyl phosphonate (3.27) starts with crotyl phosphonate (3.32). Crotyl phosphonate (3.32, Scheme 3.3) was synthesized by an Arbuzov reaction between trimethyl phosphite and crotyl bromide (3.31) in the presence of KI following the protocol published by Yamagishi et al.\textsuperscript{36} The complete purification of the crotyl phosphonate either by column chromatography or by distillation was unsuccessful due to the contamination of phosphate byproducts formed during the reaction. The purity of the crotyl phosphonate was found to be 73% pure contaminated with the
phosphates determined by $^{31}\text{P}[^{1}\text{H}]$ NMR. The crotyl phosphonate (3.32, Scheme 3.3) was subjected to the next step to synthesize vinyl phosphonate. Alternatively, the crotyl phosphonate (3.32) was synthesized from dimethyl phosphite and crotyl bromide (3.31) in the presence of n-butyl lithium, which resulted in pure crotyl phosphonate following the protocol published by Trenner et al.\textsuperscript{37} The product was purified by column chromatography, but in very low yield (11%).

![Scheme 3.3. Synthesis of vinyl phosphonate](image)

The crotyl phosphonate (3.32, Scheme 3.4) was deprotonated with n-butyl lithium, followed by the addition of benzaldehyde. The reaction of allylic anions has also been studied by Al-Badri in 1994.\textsuperscript{38} The addition reaction proceeded predominantly at the $\alpha$-position of the crotyl phosphonate to give a diastereomeric mixture of $\beta$-hydroxy phosphonates ($\alpha$-products) in 3:1 ratio (Scheme 3.4).

![Scheme 3.4. Addition of benzaldehyde to crotyl phosphonate in the $\alpha$-position](image)

The lithiated carbanion from 3.32 (Scheme 3.5), was converted to the boron derivative using Bu$_2$BOTf. The reaction with benzaldehyde resulted in a diastereomeric mixture (3:1) of vinyl phosphonates ($\gamma$-product) (3.27a and 3.27b, respectively). The mixture was successfully isolated by reverse phase column chromatography and characterized separately (3.27a and 3.27b). The boron plays a crucial role in switching the regio-chemistry from $\alpha$-attack to $\gamma$-attack.
Although, the structure of the intermediate (I) formed after boron coordination not confirmed yet, the reason for γ-attack might be the boron coordination with the lithiated phosphono carbanion.39

Scheme 3.5. Addition of benzaldehyde to crotyl phosphonate in the γ-position

The isomer with syn orientation of the hydroxyl group to methyl group (3.27a) is the major diastereomer. The stereochemistry of the diastereomers have been determined in the later stages of the reactions (i.e., cyclization). Based on NMR data, the major and minor products obtained (by both methods, either indium iodide or dibutyl boron triflate reactions) have resulted in a similar diastereomeric mixture.

The resulting vinyl phosphonate was subjected to controlled hydrogenation using hydrogen over Pd/C (5%) in the presence of pyridine to obtain the saturated phosphonates (3.36a and 3.36b). The diastereomeric ratio of the saturated phosphonates 3.36a and 3.36b was also 3:1 as in vinyl phosphonate.

Scheme 3.6. Hydrogenation of the vinyl phosphonates 3.27a and 3.27b
The diastereomeric mixture of saturated phosphonates (Scheme 3.6) was separated with preparative HPLC. The major diastereomer (3.36a) was cyclized with NaH /THF. The cyclized product was isolated as a mixture of two diastereomers in a 9:1 diastereomeric ratio (Scheme 3.7). The stereochemistry of the minor phostone diastereomer (3.37b) has been assigned using X-ray crystallography. This structure is helpful in assigning the stereochemistry of major diastereomeric phostone (3.37a), vinyl phosphonates (3.27a and 3.27b), and saturated phosphonates (3.36a and 3.36b). From this stereochemical assignment, it is concluded that the addition of aldehyde to crotlyl phosphonate mostly results in to the diastereomer with a *syn* relationship between the hydroxy group and the methyl group.

![Scheme 3.7. Cyclization of saturated phosphonate](image)

Our attempt to improve the stereoselectivity of the vinyl phosphonate synthesis has not been successful yet (Scheme 3.8). Following are some of the unsuccessful reactions for the diastereoselective synthesis of vinyl phosphonate:

![Scheme 3.8. Unsuccessful attempts for diastereoselective vinyl phosphonate synthesis](image)

All the reactions were monitored by $^{31}$P{$^{1}$H} NMR of the vinyl phosphonate, but all of these reagents were unable to produce the anticipated products. Based on
$^{31}$P$^1$H NMR spectra, TiCl$_4$ and Ti(O-i-Pr)$_4$ were also able to give a minor amount of gamma products as well as alpha products in addition to multiple unknown peaks. Bu$_3$SnCl has resulted in the isomerization of the crotyl phosphonate to vinyl phosphonate instead of stannane formation. The addition of TMSCl resulted in a mixture containing a minor amount of the silylated product along with unknown multiple peaks in the $^{31}$P$^1$H NMR and $^1$H NMR. All other reagents were failed to give the gamma products but resulted in a mixture of alpha products and multiple unknown peaks in $^{31}$P$^1$H NMR (Scheme 3.8).

Similarly, stereoselective addition of aldehyde to allylic carbonate (3.26) was also attempted with tin reagents for transmetallation with palladium but it was also not successful (Scheme 3.9).

\[
\text{MeO}^\text{P} \text{MeO}^\text{OCO}_2\text{Me} \quad \text{3.26} \quad \text{Pd(dppf)Cl}_2, \text{MR}_n, \text{PhCHO, THF} \rightarrow \text{MeO}^\text{P} \text{MeO}^\text{OH} \quad \text{3.27}
\]

Where, MR$_n$ = SnCl$_2$, [Sn(Bu)$_3$]$_2$

**Scheme 3.9.** Unsuccessful attempts for diastereoselective vinyl phosphonate synthesis

To extend the scope of the reaction, the functionalization of vinyl phosphonate was also attempted. Based on literature procedures, benzylidene protected diol can be deprotected to achieve the diol compounds (Scheme 3.10).

\[
\text{MeO}^\text{CO} \text{OH} \quad \text{3.38} \quad \text{PhCHO, t-BuOK, THF} \rightarrow \text{MeO}^\text{OCO} \text{Ph} \quad \text{OTBDPS} \quad \text{3.39} \quad \text{3.40}
\]

**Scheme 3.10.** Synthesis of a building block for total synthesis of Cochleamycin A

Functionalization of vinyl phosphonate with a hydroxyl group may lead to the synthesis of phostone with an additional hydroxyl group. We attempted to apply a similar principle to the phosphonic ester 3.27. Unfortunately, the reaction was unsuccessful, and no reaction was observed.
Scheme 3.11. Unsuccessful attempts of the synthesis of benzylidene protected 1,3-diol 3.41
3.3. SUMMARY:

1) The synthesis of vinyl phosphonates was carried out from readily available starting materials. However, the diastereomeric ratio of the vinyl phosphonate was 3:1. The vinyl phosphonate has been synthesized by two different methods:
   a) From phosphono crotyl carbonate: The allylation of phosphono crotyl carbonate with a palladium catalyst resulted in the formation of an electrophilic palladium (II) complex, which undergoes transmetallation with indium to give a nucleophilic allylindium species through an umpolung reaction. The nucleophilic allyl indium added to benzaldehyde to give δ-hydroxy vinyl phosphonate.
   b) From crotyl phosphonate: The carbanion obtained from deprotonation of crotyl phosphonate with n-BuLi was added to benzaldehyde. Reaction occurred at the α-position to give β-hydroxy phosphonates. The treatment of the resulting carbanion with boron (Bu₂B-OTf) followed by the addition of benzaldehyde afforded the γ-products (δ-hydroxy vinyl phosphonates).

2) Attempts to improve the diastereoselectivity of the vinyl phosphonate synthesis, several metal reagents were tested, among which Bu₂B-OTf performed better than other metal reagents used. The diastereomeric mixture of vinyl phosphonates (3 : 1) was separated by preparative HPLC and the diastereomers characterized separately. The stereochemistry of the vinyl phosphonate shows that the major product has the hydroxyl group cis to the methyl group.

3) The vinyl phosphonates were subjected to hydrogenation with H₂, and Pd/C in the presence of pyridine resulting in the formation of saturated phosphonates. The major diastereomer of the saturated phosphonate was been cyclized with NaH in THF to obtain a diastereomeric mixture of two phostones in 9:1 ratio. The stereochemistry has been assigned based on the X-ray crystallography of the minor diastereomer.
3.4. GENERAL EXPERIMENTAL

All reactions were carried out in oven-dried glassware under an atmosphere of argon unless otherwise noted. THF was distilled from Na/benzophenone, toluene from CaH₂, MeOH from Mg/Mg(OMe)₂, and CH₂Cl₂ from CaH₂. ¹H, ¹³C{¹H}, and ³¹P{¹H} NMR spectra were recorded in CDCl₃ at 300, 75, and 121 MHz, respectively. ¹H NMR spectra are referenced to CDCl₃ (7.27 ppm), ¹³C{¹H} NMR spectra are referenced to the center line of CDCl₃ (77.23 ppm), and ³¹P{¹H} NMR spectra are referenced to external H₃PO₄. Coupling constants, J, are reported in hertz (Hz). Analytical thin-layer chromatography (TLC) analyses were performed on silica gel plates 60PF₂₅₄. Visualization was accomplished with UV light and KMnO₄ solution.

3.4.1. General procedure for the synthesis of dimethyl crotyl phosphonate (3.32)

\[
\text{MeO} - \overset{\text{O}}{\text{P}} - \text{MeO}
\]

**Method 1:** (Yamagishi et al.)³⁶

Crotyl bromide (10 mL, 98 mmol, 1 equiv.) was dissolved in acetone: acetonitrile (55 mL + 45 mL) solvents followed by potassium iodide (16.3 g, 98 mmol, 1 equiv.) addition. After stirring 30 min at room temperature, trimethyl phosphite was added and stirred for another 2 h. The reaction temperature was raised to 55 °C and stirred overnight (monitored with TLC and ³¹P{¹H} NMR). The reaction mixture was decanted and filtered through celite with acetone, and purification has been carried out with column chromatography (70%, SiO₂, 20-40 % acetone in petroleum ether) to obtain the products in 73% spectroscopic purity with an impurity at 2 ppm in the ³¹P{¹H} NMR (tentatively assigned to a phosphate impurity) in ³¹P{¹H} NMR. Purification attempt by distillation was also unsuccessful. The 73% pure compound was used to optimize the next reaction because the effect of impurity was negligible.
Method 2: (Trenner et al.)

To a stirred solution of dimethyl phosphite in THF, n-BuLi was added dropwise and stirred for 5 min at -10 °C, crotyl bromide was added and stirred for 25 min at low temperature. The reaction was warmed to room temperature and quenched with saturated NH₄Cl and extracted with diethyl ether. The combined organic layers were washed with brine and dried with Na₂SO₄. Purification has been carried out with column chromatography (SiO₂, 70% EtOAc in hexanes).

3.4.2. General procedure for β-hydroxy phosphonate (α-products)

To a stirred solution of dimethyl crotyl phosphonate (0.2 g, 1.22 mmol, 1 equiv.) in dry THF (10 mL), n-BuLi (1.12 mL, 1.46 mmol, 1.2 equiv) (1.3 M solution in hexane) added dropwise at -78 °C. After 20 min, benzaldehyde was added slowly at -78 °C and stirred for 30 min. The reaction was quenched with saturated NH₄Cl (5 mL) and diluted with EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with NaHCO₃, water, brine, and dried over Na₂SO₄. The crude product showed the formation of diastereomeric mixture of α-products (3.34a + 3.34b, 0.144 g, 0.53 mmol, 43%) in 3:1 ratio isolated by column chromatography (SiO₂, 1.5% IPA/hexane).

(±) (3E)-2-Dimethylphosphonyl-1-hydroxy-1-phenyl-pent-3-ene (3.34a + 3.34b)

The major diastereomer was characterized after isolation with 5% IPA/hexane from the mixture but isolation of minor diastereomer was unsuccessful utilizing flash chromatography as well as reverse phase column chromatography. IR (neat) 3357, 2951, 1451, 1220, 1023 cm⁻¹; HRMS (FAB) m/z: [M+H]+ Calcd for C₁₃H₂₀O₄P, 271.1099, Found 271.1108.

![Chemical Structure](image-url)
Major diastereomer (isolated):

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.30 – 7.19 (m, 5H), 5.30 – 5.21 (m, 1H), 5.19-5.07 (m, 1H), 4.90-4.83 (m, 1H), 3.76 (d, $J_{HP} = 10.7$ Hz, 3H), 3.66 (d, $J_{HP} = 10.8$ Hz, 3H), 2.91-2.79 (m, 1H), 1.47 (m, 3H); $^{13}$C$^1$H NMR (CDCl$_3$) δ 141.6 (d, $J_{CP} = 14.2$ Hz), 131.7 (d, $J_{CP} = 13.1$ Hz), 128.1, 127.8, 126.9, 122.1 (d, $J_{CP} = 10.1$ Hz), 73.6 (d, $J_{CP} = 4.0$ Hz), 53.3, 53.0, 49.9 (d, $J_{CP} = 132.6$ Hz), 18.1 (d, $J_{CP} = 2.0$ Hz); $^{31}$P$^1$H NMR (CDCl$_3$) δ 30.9.

Minor diastereomer (data extrapolated from spectra obtained on mixture of diastereoisomers):

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.31 – 7.19 (m, 5H), 5.51 – 5.44 (m, 1H), 5.18-5.11 (m, 1H), 4.94-4.87 (m, 1H), 3.83 (d, $J_{HP} = 10.7$ Hz, 3H), 3.76 (d, $J_{HP} = 10.8$ Hz, 3H), 3.69-3.24 (m, 1H), 1.35 (m, 3H); $^{13}$C$^1$H NMR (CDCl$_3$) δ 141.4 (d, $J_{CP} = 16.1$ Hz), 129.1 (d, $J_{CP} = 12.5$ Hz), 128.1, 127.8, 126.9, 121.5 (d, $J_{CP} = 11.4$ Hz), 73.8, 53.4, 44.6 (d, $J_{CP} = 133.1$ Hz), 13.0 (d, $J_{CP} = 2.3$ Hz); $^{31}$P$^1$H NMR (CDCl$_3$) δ 31.1.

Following the general procedure for beta-hydroxy phosphonate (alpha product), diethyl crotyl phosphonate (3.33, 0.507 g, 2.64 mmol, 1 equiv) was reacted with $n$-BuLi (2.44 mL, 3.17 mmol, 1.2 equiv) and benzaldehyde (225 µL) in 20 mL dry THF to give a diastereomeric mixture of 3.35 in 3:1 ratio. The resulting product diethyl beta-hydroxy phosphonate (3.35, 0.411 g, 1.38 mmol, 52%) was isolated by a column chromatography (SiO$_2$, 40-50 % EtOAc in hexanes).

(±) (3E)-2-Diethylphosphonyl-1-hydroxy-1-phenyl-pent-3-ene (3.35a + 3.35b)
Diastereomer 1:
IR (neat) 3356, 2978, 1448, 1218, 1018 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.31 – 7.25 (m, 5H), 5.57 – 5.54 (m, 1H), 5.41-5.34 (m, 1H), 5.27-5.22 (m, 1H ), 4.19-4.03 (m, 4H), 3.79 (s, 1H), 2.85-2.75 (m, 1H ), 1.66-1.62 (m, 3H), 1.32 (t, \(J_{HH} = 7.1\) Hz, 3H), 1.27 (t, \(J_{HH} = 7.1\) Hz, 3H); \(^{13}\)C\({_\text{\{1\}H}\}) NMR (CDCl\(_3\)) \(\delta\) 141.6 (d, \(J_{CP} = 14.4\) Hz), 133.1 (d, \(J_{CP} = 13.6\) Hz), 128.1, 127.4, 126.4, 120.0 (d, \(J_{CP} = 7.7\) Hz), 72.2 (d, \(J_{CP} = 3.9\) Hz), 63.3 (d, \(J_{CP} = 6.8\) Hz), 62.1 (d, \(J_{CP} = 7.3\) Hz), 49.9 (d, \(J_{CP} = 133.7\) Hz), 72.2 (d, \(J_{CP} = 3.9\) Hz), 63.3 (d, \(J_{CP} = 6.8\) Hz), 62.1 (d, \(J_{CP} = 7.3\) Hz), 49.9 (d, \(J_{CP} = 133.7\) Hz), 18.4, 16.6 (d, \(J_{CP} = 5.4\) Hz), 16.5 (d, \(J_{CP} = 5.4\) Hz); \(^{31}\)P\(_{\text{\{1\}H}}\) NMR (CDCl\(_3\)) \(\delta\) 28.4; HRMS (FAB) \(m/z\): [M+Na]+ Calcd for C\(_{15}\)H\(_{23}\)O\(_4\)PNa, 321.1231, Found 321.1219.

Diastereomer 2:
IR (neat) 3348, 2979, 1451, 1217, 1018 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.29 – 7.22 (m, 5H), 5.30 – 5.16 (m, 2H), 4.92-4.85 (m, 1H), 4.71 (s, 1H), 4.19-4.03 (m, 4H), 2.85-2.87-2.78 (m, 1H), 1.52-1.49 (m, 3H), 1.34 (t, \(J_{HH} = 7.1\) Hz, 3H), 1.26 (t, \(J_{HH} = 7.1\) Hz, 3H); \(^{13}\)C\(_{\text{\{1\}H}}\) NMR (CDCl\(_3\)) \(\delta\) 141.7 (d, \(J_{CP} = 14.2\) Hz), 133.1 (d, \(J_{CP} = 12.8\) Hz), 128.2, 127.9, 127.1, 122.6 (d, \(J_{CP} = 10.0\) Hz), 73.9 (d, \(J_{CP} = 3.9\) Hz), 62.9 (d, \(J_{CP} = 6.7\) Hz), 62.6 (d, \(J_{CP} = 6.8\) Hz), 50.5 (d, \(J_{CP} = 132.2\) Hz), 18.4 (d, \(J_{CP} = 2.03\) Hz), 16.6 (d, \(J_{CP} = 5.8\) Hz), 16.5 (d, \(J_{CP} = 6.0\) Hz); \(^{31}\)P\(_{\text{\{1\}H}}\) NMR (CDCl\(_3\)) \(\delta\) 28.7; HRMS (FAB) \(m/z\): [M+Na]+ Calcd for C\(_{15}\)H\(_{23}\)O\(_4\)PNa, 321.1231, Found 321.1225.

3.4.3. General procedure for the synthesis of vinyl phosphonate (3.37)

**Method 1: Synthesis of vinyl phosphonate with Indium mediated umpolung chemistry**

A mixture of phosphono allylic carbonate (1.0 g, 4.2 mmol, 1 equiv.), Pd(dpdpf)Cl\(_2\) (0.150 g, 0.05 equiv.), InI (1.11 g, 4.6 mmol, 1.1 equiv.) and benzaldehyde (0.91 mL, 8.4 mmol, 2 equiv.) was dissolved in THF (15 mL) in a round bottom flask set up with a condenser under argon atmosphere. The reaction temperature was

Paudel, Rishi, 2020, UMSL 96
increased to 50 °C and stirred for 20 h. After reaction completion, the reaction mixture was diluted with CH₂Cl₂, followed by washing with Na₂HCO₃ and brine. The organic layer was extracted with CH₂Cl₂ was dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by column chromatography (SiO₂, 80-100% EtOAc/hexane) to afford the product (0.73 g, 2.71 mmol, 69% yield).

Method 2: Synthesis of vinyl phosphonate with Bu₂BOTf reaction
Crotyl phosphonate (2 g, 9.51 mmol, 1 equiv.) was dissolved in THF and cooled to -78 °C under argon atmosphere and n-BuLi (7.3 mL, 1 equiv.) (1.3 M solution in hexane) was added dropwise and stirred for 20 min. To the lithiated carbanion, dibutyl boron triflate solution (19.2 mL, 19.2 mmol, 2 equiv.) (1 M in CH₂Cl₂) added dropwise at -78 °C then stirred for 1 h. The reaction was quenched with NH₄Cl (20 mL) then diluted with CH₂Cl₂ for extraction. The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The diastereomeric mixture (3:1) of vinyl phosphonate (1.66 g, 6.14 mmol, 65% yield) was isolated with column chromatography (SiO₂, 80-100% EtOAc in hexane). The diastereomers have been isolated by reverse phase column chromatography.

(±) Dimethyl (3S, 4R, E)-4-hydroxy-3-methyl-4-phenyl-but-1-enyl)phosphonate (3.27a) (major diastereomer)

IR (neat) 3350, 2952, 2849, 1692, 1450,1226, 1021 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42 – 7.14 (m, 5H), 6.80 – 6.64 (m, 1H), 5.50-5.37 (m, 1H), 4.60 (d, JHH = 5.9 Hz, 1H), 3.53 (d, JHP =11.1 Hz, 3H), 3.48 (d, JHP =11.1 Hz, 3H), 2.71-2.65 (m, 1H), 1.06 (d, JHH = 6.7 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 156.7 (d, JCP = 4.7 Hz), 142.7, 128.2, 127.6, 126.6, 115.4 (d, JCP = 185.7 Hz), 76.6, 52.3, 52.2, 45.9 (d, JCP = 20.5 Hz), 14.3; ³¹P{¹H} NMR (CDCl₃) δ 21.7; HRMS (FAB) m/z: [M+H]^+ Calcd for C₁₃H₂₀O₄P 271.1099, Found 271.1098.
(±) Dimethyl (3S, 4S, E)-4-hydroxy-3-methyl-4-phenyl-but-1-enyl)phosphonate (3.27b) (minor diastereomer)

![Chemical structure of (±) Dimethyl (3S, 4S, E)-4-hydroxy-3-methyl-4-phenyl-but-1-enyl)phosphonate (3.27b) (minor diastereomer)]

IR (neat) 3357, 2953, 2090, 1692, 1450, 1225, 1019 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.36 – 7.30 (m, 5H), 6.97 – 6.81 (m, 1H), 5.70-5.57 (m, 1H), 4.52 (d, \(J_{HH} = 7.2\) Hz, 1H), 3.67 (d, \(J_{HP} =11.1\) Hz, 3H), 3.66 (d, \(J_{HP} =11.1\) Hz, 3H), 2.71-2.64 (m, 1H), 1.06 (d, \(J_{HH} = 6.8\) Hz, 3H); \(^{13}\)C\(\{^1\)H\}\) NMR (CDCl\(_3\)) \(\delta\) 156.7, 142.5, 128.4, 127.8, 126.6, 115.9 (d, \(J_{CP} = 185.9\) Hz), 77.5, 52.4, 52.3, 46.2 (d, \(J_{CP} = 20.8\) Hz), 15.9; \(^{31}\)P\(\{^1\)H\}\) NMR (CDCl\(_3\)) \(\delta\) 21.5; HRMS (FAB) \(m/z\): [M+H]\(^+\) Calcd for C\(_{13}\)H\(_{20}\)O\(_4\)P 271.1099, Found 271.1106.

3.4.4. General procedure for the hydrogenation of vinyl phosphonate

The vinyl phosphonate (0.5 g, 1.85 mmol, 1 equiv.) was dissolved in a dry MeOH and flushed with argon gas, and then Pd/C (5%) (0.1 g) (20% by weight of phosphonate) was added to it and stirred for 5 min followed by pyridine (250 µL, 3.1 mmol, 1.7 equiv) addition under argon atmosphere. Then, hydrogen gas was added with the help of a balloon. The reaction was completed within 2 h (monitored by \(^{31}\)P\(\{^1\)H\}\) NMR). The reaction mixture was filtered through the celite pad with EtOAc and concentrated in vacuo. The saturated phosphonate product (0.507 g, 1.82 mmol, 98%) was isolated by column chromatography as a mixture of two diastereomers in a 3:1 ratio (SiO\(_2\), 80-100% EtOAc/hexane). The diastereomeric mixture of product was further separated by reverse phase column chromatography with eluent 25-35% MeOH/H\(_2\)O.

(±) Dimethyl (3S, 4R)-4-hydroxy-3-methyl-4-phenyl butylphosphonate (3.36a) (major diastereomer)

![Chemical structure of (±) Dimethyl (3S, 4R)-4-hydroxy-3-methyl-4-phenyl butylphosphonate (3.36a) (major diastereomer)]
IR (neat) 3380, 2953, 2850, 2071, 1448,1212, 1023 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.31 – 7.18 (m, 5H), 4.54 (d, \(J_{HH} = 4.7\) Hz, 1H), 3.62 (d, \(J_{HP} = 10.8\) Hz, 3H), 3.62 (d, \(J_{HP} = 10.8\) Hz, 3H), 1.78 – 1.60 (m, 4H), 1.40 – 1.23 (m, 1H), 0.83 (d, \(J_{HH} = 6.6\) Hz, 3H); \(^{13}\)C\(^{\{1\}H}\) NMR (CDCl\(_3\)) \(\delta\) 143.6, 128.1, 127.1, 126.3, 76.5, 52.4 (d, \(J_{CP} = 6.6\) Hz), 52.4 (d, \(J_{CP} = 6.5\) Hz), 40.7 (d, \(J_{CP} = 15.6\) Hz), 25.5 (d, \(J_{CP} = 4.7\) Hz), 22.3 (d, \(J_{CP} = 139.6\) Hz), 13.9; \(^{31}\)P\(^{\{1\}H}\) NMR (CDCl\(_3\)) \(\delta\) 35.6; HRMS (FAB) \(m/z\): [M+H]\(^+\) Calcd for C\(_{13}\)H\(_{22}\)O\(_4\)P 273.1255, Found 273.1250.

(±) Dimethyl (3S, 4S)-4-hydroxy-3-methyl-4-phenyl butylphosphonate (3.36b) (minor diastereomer)

IR (neat) 3379, 2953, 2849, 2090, 1451,1215, 1024 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.27 (m, 5H), 4.37 (d, \(J_{HH} = 7.4\) Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 2.50 (s, 1H), 1.97 – 1.69 (m, 4H), 1.55 – 1.47 (m, 1H), 0.74 (d, \(J_{HH} = 6.7\) Hz, 3H); \(^{13}\)C\(^{\{1\}H}\) NMR (CDCl\(_3\)) \(\delta\) 143.5, 128.4, 127.7, 126.7, 78.7, 52.5, 52.4, 40.6 (d, \(J_{CP} = 16.02\) Hz), 25.1 (d, \(J_{CP} = 4.6\) Hz), 22.2 (d, \(J_{CP} = 139.7\) Hz), 15.7; \(^{31}\)P\(^{\{1\}H}\) NMR (CDCl\(_3\)) \(\delta\) 35.7; HRMS (FAB) \(m/z\): [M+H]\(^+\) Calcd for C\(_{13}\)H\(_{22}\)O\(_4\)P 273.1255, Found 273.1250.

3.4.5. General procedure for the cyclization of saturated phosphonate to phostones

NaH (60% in mineral oil, 0.069 g, 1.73 mmol, 1.2 equiv.) was dissolved in THF at 0 °C under argon atmosphere. A solution of the phosphonate (3.36a) (0.391 g, 1.43 mmol, 1 equiv.) in THF (15 mL) was added and stirred for 2 h at 0 °C. The reaction progress was monitored with TLC. The reaction mixture was quenched with saturated NH\(_4\)Cl, followed by dilution with EtOAc. The aqueous layer was washed with NaHCO\(_3\), water, and brine. The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. A mixture of two diastereomers (0.262
g, 1.09 mmol, 76%) obtained in 9:1 ratio after column chromatography (SiO$_2$, 80-100% EtOAc in hexane). The diastereomeric mixture of phostone was further separated with reverse phase column chromatography. The major diastereomer (3.37a) eluted with 25% MeOH/H$_2$O and minor diastereomer (3.37b) eluted with 35% MeOH/H$_2$O. The stereochemistry of the phostone (minor diastereomer) was assigned with the help of X-ray crystallography.

(±) 5S, 6R)-5-(methyl)-6-(phenyl)-2-methoxy-1,2-oxaphosphinane-2-oxide (major diastereomer) (3.37a)

![Chemical Structure](image)

IR (neat) 2936, 1906, 1449, 1296, 1030, 974 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.35−7.26 (m, 5H), 5.39 (s, 1H), 3.72 (d, $J_{HH} = 10.7$ Hz, 3H), 2.24-1.89 (m, 5H), 0.77 (d, $J_{HH} = 7.0$ Hz, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 139.1 (d, $J_{CP} = 8.0$ Hz), 128.2, 127.4, 125.0, 83.8 (d, $J_{CP} = 6.5$ Hz), 51.1 (d, $J_{CP} = 6.7$ Hz), 34.1 (d, $J_{CP} = 5.3$ Hz), 28.5 (d, $J_{CP} = 7.7$ Hz), 17.2 (d, $J_{CP} = 128.1$ Hz), 9.9; $^{31}$P{$^1$H} NMR (CDCl$_3$) $\delta$ 25.9; HRMS (FAB) m/z: [M+H]$^+$ Calcd for C$_{12}$H$_{18}$O$_3$P 241.0993, Found 241.0988.

(±) (5S, 6R)-5-(methyl)-6-(phenyl)-2-methoxy-1,2-oxaphosphinane-2-oxide (minor diastereomer) (3.37a)

![Chemical Structure](image)

IR (neat) 2950, 1905, 1450, 1286, 1040, 961 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.37−7.27 (m, 5H), 5.71 (s, 1H), 3.89 (d, $J_{HH} = 10.9$ Hz, 3H), 2.52-1.87 (m, 5H), 0.77 (d, $J_{HH} = 7.0$ Hz, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 139.4 (d, $J_{CP} = 8.0$ Hz), 128.4, 127.6, 125.2, 82.4 (d, $J_{CP} = 3.9$ Hz), 52.7 (d, $J_{CP} = 6.5$ Hz), 34.6 (d, $J_{CP} = 4.6$ Hz), 28.3 (d, $J_{CP} = 6.7$ Hz), 17.6 (d, $J_{CP} = 128.2$ Hz), 10.5; $^{31}$P{$^1$H} NMR (CDCl$_3$) $\delta$ 29.2; HRMS (FAB) m/z: [M+H]$^+$ Calcd for C$_{12}$H$_{18}$O$_3$P 241.0993, Found 241.0988.
Crystal Structure of minor diastereomeric phostone (3.37a):

(Preliminary data collected with the help of Prof. Alicia Beatty)

Figure 3.8. Crystal Structure of minor diastereomeric phostone
3.5. REFERENCES


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1, 2-oxaphosphacyclanes) using the anomic alkoxy radical \( \beta \)-fragmentation reaction as the key step. J. Org. Chem. \textbf{2020}, \textit{85} (7), 4861-4880.


CHAPTER IV
SYNTHESIS OF PHOSPHONATE C-NUCLEOSIDE ANALOGS

4.1. INTRODUCTION
Phosphono sugars are important compounds for the development of non-hydrolysable mimics of bioactive carbohydrate phosphates such as nucleosides. Various biologically active furanose derivatives have been prepared from sugar/nucleoside precursors.\textsuperscript{1,2} A phosphonate can mimic a biological phosphate. However, they are metabolically more stable than the corresponding phosphate. This is due to the additional stability of the C-P bond versus the O-P bond.\textsuperscript{2} Several nucleoside phosphonates have been synthesized as analogues of nucleoside phosphates. Vaghefi synthesized and investigated the biological activity of 5'-deoxynucleoside 5'-phosphonates, such as 9-[5'-deoxy-5'-(dihydroxyphosphinyl)-\textbeta-D-ribofuranosyl] cytosine (4.1, Figure 4.1) and 9-[5'-deoxy-5'-(dihydroxyphosphinyl)-\textbeta-D-ribofuranosyl] guanosine (4.2) and found that these compounds were phosphorylated by cellular enzymes. However, the extent of phosphorylation was found to be less compared to the natural (phosphate) substrates.\textsuperscript{3}

\begin{center}
\includegraphics[width=0.8\textwidth]{4.1-4.2.png}
\end{center}

**Figure 4.1.** Examples of 5'-deoxy nucleoside 5'-phosphonates

Wiemer synthesized 5'-hydroxy-5'-phosphonate\textsuperscript{1} and 5'-amino-5'-phosphonate\textsuperscript{4} derivatives of cytosine arabinoside (an anti-leukemia agent, Figure 4.2).
Similarly, Rosenberg synthesized a 2-deoxyribose series of nucleoside 5-C-phosphonates through base-catalyzed nucleophilic addition of phosphites to nucleoside 5'-aldehydes. However, the obtained nucleoside 5'-C-phosphonates were obtained as an epimeric mixture (Figure 4.3).³

The structure-activity relationship of nucleosides and their mechanism of action is an important area of the research.⁶ Most common nucleoside analogs have the ribose sugar linked to the nitrogen of the heterocyclic nucleobases (mostly purine and pyrimidine). Therefore, they are called N-nucleosides (4.11). If the sugar unit (ribofuranosyl or deoxy-ribofuranosyl) is linked to a heterocyclic base through a C-C bond, they are called C-nucleosides (4.12).⁷
Various C-nucleosides have been found to possess antiviral and antiproliferative activity.\(^8\) N-nucleosides are susceptible to loss of bioactivity through enzymatic and acid-catalyzed hydrolysis of the nucleosidic bond.\(^6\) Due to the change in the nature of the nucleosidic bond, C-nucleosides have different i) hydrolytic stability ii) hydrogen bonding ability, and iii) molecular recognition properties than those of N-nucleosides.\(^7,9\) C-nucleosides are useful in the study of RNA and DNA biology as well as in drug discovery.\(^9\) The C-nucleosides are an important class of compounds used in biological and medicinal chemistry.\(^10\) There are both natural as well as synthetic C-nucleosides reported in the literature. Some examples of natural C-nucleosides are Pseudouridine, Formycin A, Showdomycin, Pyrazomycin, Oxazinomycin, and Pseudouridimycin, etc.
The synthetic C-nucleosides include GS-5734 (remdesivir), GS-6620, tiazofurin, and benzamide riboside (BR), and more.

\[ \text{GS 5734 (Remdesivir)} \]

\[ \text{GS 6620 (HCV Polymerase inhibitor)} \]

\[ \text{Tiazofurin} \]

\[ \text{Benzamide riboside} \]

\[ \text{2'-deoxy benzamide riboside} \]

\[ \text{3,4-dihydroxyphenyl 2'-deoxy-C-nucleoside} \]

**Figure 4.6.** Some examples of synthetic C-nucleosides

There is a need for extensive research in C-nucleosides by modifying the chemical structures which could improve their efficacy, safety profile, and expand the activity spectrum. Some of the previous promising results show the possible applications of C-nucleosides. Some of the synthetic C-nucleoside analogs were found to retain the biological activity even with the replacement of the nitrogen heterocycle with functionalized benzene rings.

### 4.1.1. Application of C-nucleosides in medicinal chemistry

Various C-nucleosides have been evaluated for their antiviral and antitumor activity. The first natural C-nucleoside is pseudouridine (Ψ), discovered by Cohn in the 1950s. Pseudouridine, present in all structural RNAs, is an isomer of uridine which stabilizes the RNA duplex. It is formed from uridine in a reaction catalyzed by pseudouridine synthases. Formycin A is a natural antibiotic isolated from *Nocardia interforma* which inhibits the growth of Yoshida rat sarcoma cells, *Mycobacterium* 607, and *Xanthomonas oryzae*. Showdomycin is an antibiotic first isolated from *Streptomyces showdoensis*. It was found to inhibit the growth
of gram-positive and gram-negative bacteria, particularly active against *Streptococcus haemolyticus* and *Streptococcus pyogenes*. Antitumor activity of Showdomycin was demonstrated against Ehrlich ascites cells and Hela cells.\textsuperscript{15} Pyrazomycin (Pyrazofurin) was first isolated from *Streptomyces candidus*.\textsuperscript{16} Originally, it showed potential antiviral, antitumor, and antibacterial activity. However, the activity failed in in-vivo tests.\textsuperscript{7} Oxazinomycin (Minimycin) is structurally similar to pseudouridine was discovered in 1971.\textsuperscript{17} It showed antitumor and antibacterial activity. It inhibits the growth of gram-positive and gram-negative bacteria.\textsuperscript{18}

Similarly, Tiazofurin acts as an inhibitor of the enzyme inosine-5'-monophosphate dehydrogenase (IMPDH).\textsuperscript{7} This compound also inhibits the growth of tumors such as Lewis lung carcinoma.\textsuperscript{7} Pseudouridimycin (PUM) is a recently discovered pseudouridine-containing C-nucleosidic antibiotic that inhibits bacterial RNA polymerase (RNAP). Donadio and Ebright discovered (in 2017) this peptidyl-nucleoside antibiotic by screening microbial fermentation extracts for RNAP inhibitors. Benzamide riboside (BR) is a C-glycosidic analog of nicotinamide riboside which has shown cytotoxicity against a variety of tumor cell lines.\textsuperscript{19} Krohn synthesized benzamide riboside as aromatic furanoside C-glycosides in 2002. Benzamide riboside was synthesized in an 8-step reaction sequence.\textsuperscript{20} 2-Deoxy benzamide riboside was synthesized as a benzamide RNA analog. Migaud provided a new methodology for C-nucleosides by synthesizing 2-deoxy benzamide riboside in 11 steps. The compound was also tested for activity against various cancerous cell lines. However, the inhibition of the cell line was not significant.\textsuperscript{8} GS-6620 is an example of C-nucleoside which was developed by Gilead Sciences to treat Hepatis C virus but there were some problems with the drug due to metabolic and pharmacokinetic issues.\textsuperscript{21} However, this compound may be a potential treatment for other viral diseases such as Ebola virus, yellow fever virus, Dengue virus, etc.\textsuperscript{7, 22} GS-5734 (Remdesivir) is another example of a potential C-nucleoside for the treatment of various RNA
viruses, including severe acute respiratory syndrome–CoV and the Middle East respiratory syndrome (MERS–CoV).\textsuperscript{23}

\subsection*{4.1.2. Synthetic methods available for C-nucleosides}
Several synthetic approaches for C-nucleosides have been reported in the literature, but many of them lack efficiency, broad applicability, and stereoselectivity.\textsuperscript{6} Synthesis of C-nucleosides mainly involve two methods i) linear construction of hetero(aryl) substituents on a C1’- functionalized ribosyl group (Scheme 4.1) ii) coupling of ribosyl moiety with functionalized hetero(aryl) compounds (Scheme 4.3).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {4.25};
\node (b) at (2,0) {4.26};
\node (c) at (4,0) {4.27};
\end{tikzpicture}
\end{center}

\textit{Scheme 4.1.} Sequential synthesis of C-nucleosides by the linear construction of hetero(aryl) substituents on C1’-functionalized ribosyl group

Seitz synthesized 2’-deoxyribofuranose-C-nucleosides (4.32) starting from the epoxidation of the furanose glycal (4.28) with dimethyldioxirane (DMDO) to form epoxy anhydrofuranose (4.29). The oxirane ring of anhydrofuranose was selectively opened with triaryllalanes to give arabinofuranose (4.30). The arabinofuranose (4.30) was deoxygenated at 2’-position by reaction with thiocarbonyldiimidazole (TCDI) followed by the treatment with tris(trimethylsilyl)silane and AIBN (azobisisobutyronitrile). The deprotection of the 2’-deoxynucleoside (4.31) with TBAF resulted in 2’-deoxyribofuranose-C-nucleoside (4.32) (Scheme 4.2).\textsuperscript{6, 24}
Scheme 4.2. Synthesis of β-Aryl-C-nucleosides from 1,2-Anhydrofuranose

The modular approach for the synthesis of C-nucleosides by a coupling reaction of the ribosyl moiety with hetero(aryl) compounds involves three specific modules: the carbohydrate part, the aromatic moiety, and the additional functional group (Scheme 4.3).6

\[
\text{Scheme 4.3. Modular synthesis by coupling of ribosyl and hetero(aryl) compounds}
\]

Various types of ribosyl analogues can be used in the synthesis of C-nucleosides by the coupling reaction with heteroaryl compounds (Scheme 4.4). The nucleophilic addition of heteroaryl substituents to D-ribonolactone is the most widely used approach for the synthesis of C-nucleosides. This approach allows the modification of the functionality at C1'-position of the ribosyl moiety.9
Scheme 4.4. Structure of ribosyl analogues that enable coupling reactions

The coupling reaction between the ribosyl group and hetero(aryl) substituents results in a mixture of stereoisomers (α and β) at the C1’-position. However, the biologically active naturally occurring nucleosides are β-anomers. 100% β-stereospecificity in C-C bond formation is difficult to attain with currently available methods.6,9

Kim synthesized 4-aza-7,9-dideazaadenine C-nucleosides (4.44, Scheme 4.5) starting tribenzyl lactone (4.41) and bromo pyrrolotriazine (4.42) in the presence of n-BuLi. The reaction was facilitated by temporary N-silyl protection with trimethylsilyl chloride. The cyanation of C-nucleoside (4.43) and tribenzyl deprotection results in an isomeric mixture (approx. β/α; 9:1 ratio) of 1-cyano modified adenine C-nucleoside (4.44) in approximately a 9:1 ratio. Scheme 4.5).25 This is one of the most applicable methods currently used in biologically active C-nucleosides. This approach has been used for the synthesis of previously mentioned antiviral C-nucleosides GS-5734 and GS-6620 developed by Gilead Sciences.26

Scheme 4.5. Modular synthesis of 4-aza-7,9-dideazaadenine C-nucleosides
4.2. RESULTS AND DISCUSSION

Since both, the phosphonate and C-nucleoside are important components in medicinal chemistry and chemical biology, there is a need for a new synthetic approach that could combine both the phosphonate and C-nucleoside in a single entity. Currently available methods for C-nucleoside have drawbacks with respect to efficiency, and stereoselectivity, and require multi-step reactions. Therefore, it is very important to develop a short and efficient method for the synthesis of C-nucleoside compounds and their derivatives. As discussed in Chapter I and Chapter II, we have developed a new approach for the synthesis of phosphonomethyl tetrahydrofuran. This approach can be used for the synthesis of phosphonomethyl C-nucleoside analogs. We have proposed the synthesis of the phosphonomethyl derivatives of the synthetic C-nucleosides 4.23 and 4.24.

As described in chapter II (Schemes 2.37, 2.38, and 2.39), piperonal derived bishomoallylic alcohol was formed as a mixture of two diastereomers when accessed through the Mitsunobu reaction. The reason for the formation of diastereomeric mixture is competitive S\textsubscript{N}1 reaction due to formation of carbocation stabilized by electron donating oxygen subring.

Isolation of the tetrahydrofuran ring obtained after direct cyclization of bishomoallylic alcohol has resulted in a mixture of diastereomers which could not be separated and were characterized as a mixture (Scheme 2.37).

![Scheme 2.37. Cyclization of bis-homoallylic alcohol derived from piperonal](image)

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Scheme 2.38. Mitsunobu inversion of bis-homoallylic alcohol derived from piperonal

4.2.1. Synthesis of 5-formyl salicylic acid derived tetrahydrofuran

We have applied the previously developed method to synthesize phosphonomethyl derivatives of 2'-deoxy benzamide riboside (4.23). The retrosynthetic approach for the compound 4.23 (Scheme 4.6) is shown below:

Scheme 4.6. Retrosynthetic approach for 2'-deoxy benzamide riboside analogs

The OTBS protected diene (1.41d) was reacted with acetonide protected 5-formyl salicylic acid (4.46). The 5-formyl salicylic acid has been protected by reaction with acetone, trifluoracetic acid (TFA), and trifluoroacetic anhydride (TFA) following a published procedure to give aldehyde 4.46 (Scheme 4.7).27
This aldehyde was subjected to Mori-Tamaru reaction with OTBS-substituted diene (1.41d) to obtain bishomoallylic alcohol (4.47, Scheme 4.8). The alcohol obtained was subjected to Mitsunobu inversion, with PPh₃, DIAD and PNBA in THF: toluene (4:1), which resulted in the inversion of stereochemistry (4.48, Scheme 4.09).

Attempted hydrolysis and cyclization of the ester (4.48) with NaOMe/MeOH resulted in a mixture of two diastereomers in addition to two unknown compounds (probably vinyl phosphonates) as observed in $^{31}$P{¹H} NMR and ¹H NMR. Isolation of the individual compounds was unsuccessful. In order to
introduce a new functional group, the ester (4.48) was also attempted to cyclize with ethylamine. A $^{31}$P{\(^1\)H} NMR spectrum of the mixture of products showed that cyclization happened but complete characterization of the product was not possible due to the difficulties in the separation of the mixture.

4.2.2. Synthesis of $\alpha$-bromo phosphonomethyl tetrahydrofuran
The bishomoallylic alcohol obtained after Mori-Tamaru reaction can be further functionalized with bromocyclization. Bromonium ion induced cyclization leads to the formation of a new stereocenter and a C-Br bond, which can be further transformed into other functional groups. Therefore, bromocyclization is synthetically useful to make new building blocks in organic synthesis.\(^{28}\) Rosenberg mentioned that the conversion of 5'-hydroxyphosphonate into 5'-halo phosphonates was unsuccessful (Scheme 4.10). This shows that we need a new method to introduce a halogen atom in nucleoside 5'-C-phosphonate.\(^5\)

Scheme 4.10. Reactions on the 5'-hydroxyphosphonate moieties\(^5\)

To address this issue in the case of phosphonomethyl tetrahydrofuran, we have reacted the bishomoallylic alcohol (2.81a, Scheme 4.11) with bromine in THF which successfully resulted in the formation of $\alpha$-bromo phosphonomethyl tetrahydrofuran (4.51) in a diastereomeric ratio of a 84:16 (Scheme 4.12).

Scheme 4.11. Bromocyclization of bishomoallylic alcohol
4.2.3 Oxidation of the bishomallylic alcohol to the ketone 4.53

We have also converted the bishomoallylic alcohol (4.52) to the corresponding ketone (4.53, Scheme 4.12) to extend the scope of the compounds available. The alcohol was subjected to Swern-oxidation. The ketone functionality may be useful for developing a new series of compounds. For example, nucleophilic addition to the ketone may lead to the formation of di-substituted products.

Scheme 4.12. Oxidation of the bishomoallylic alcohol to the ketone
4.3. SUMMARY

1) The previously modified Mori-Tamaru reaction was applied to synthesize phosphono derivatives of C-nucleosides.

2) A diastereomeric mixture of piperonal derived phosphonomethyl tetrahydrofuran as an analogue of a C-nucleoside was synthesized. However, the Mitsunobu reaction resulted in a mixture of ester diastereomers due to a competing S_N1 reaction.

3) The synthesis of bishomoallylic alcohol derived from protected 5-formyl salicylic acid through the Mori-Tamru reaction has resulted in good yields and excellent diastereoselectivity. The stereochemistry of the alcohol has also been successfully inverted with Mitsunobu reaction.

4) Cyclization of the 5-formyl salicylic acid derived Mitsunobu ester has also been observed through the $^{31}$P{$^1$H} NMR and $^1$H NMR analysis. However, complete characterization of the cyclized compounds has not been performed due to complications associated with isolation.

5) Functionalization of the phosphonomethyl tetrahydrofuran has also been studied with a different approach utilizing an oxa-Michael cyclization. For example, through bromocyclization a bromine substituent was introduced on the methylene carbon of the phosphonomethyl tetrahydrofuran.

6) Bishomoallylic alcohol was oxidized to the ketone utilizing Swern oxidation, which may lead to the synthesis of di-substitution at the C-5 carbon by nucleophilic addition.
4.4. GENERAL EXPERIMENTAL

All reactions were carried out in oven-dried glassware under an atmosphere of argon unless otherwise noted. THF was distilled from Na/benzophenone, toluene from CaH₂, MeOH from Mg/Mg(OMe)₂, and CH₂Cl₂ from CaH₂. ¹H, ¹³C{¹H}, and ³¹P{¹H} NMR spectra were recorded in CDCl₃ at 300, 75, and 121 MHz, respectively. ¹H NMR spectra are referenced to CDCl₃ (7.27 ppm), ¹³C{¹H} NMR spectra are referenced to the center line of CDCl₃ (77.23 ppm), and ³¹P{¹H} NMR spectra are referenced to external H₃PO₄. Coupling constants, J, are reported in hertz (Hz). Analytical thin-layer chromatography (TLC) analyses were performed on silica gel plates 60PF₂₅₄. Visualization was accomplished with UV light and KMnO₄ solution.

General procedure for the Mori-Tamaru reaction of OTBS-substituted diene (1.41d) and protected 5-formy-salicylic acid (4.46).

(±)Diethyl(E)-3-(tert-butyldimethylsilyloxy)-5-hydroxy-5-(2,2-Dimethyl-4-oxo-4H-benzo[d] [1,3]dioxine-7-enyl)-pent-1-enyl phosphonate (4.46)

To a flask containing dienylphosphonate (1.41d) (1.05 g, 3.28 mmol, 1.0 equiv), Ni(acac)₂ (0.303 g, 1.18 mmol, 0.36 equiv), and 2,2-Dimethyl-4-oxo-4H-benzo[d][1,3]dioxine-7-carboxaldehyde (2.02 g, 9.84 mmol, 3.0 equiv) was added freshly distilled THF (50 mL). The mixture was stirred for 10 min at room temperature. The solution was cooled to -50 °C and AlEt₃ in hexanes (1.0 M, 11.5 mL, 11.5 mmol, 3.5 equiv) was added slowly. After 3-5 min stirring at -50 °C, the solution temperature was increased to 0 °C and the reaction mixture was stirred for 4 h (monitored by TLC). The reaction was quenched by the addition of 1N HCl (20 mL) with continuous stirring. After 5 min, the mixture was extracted with EtOAc (3x20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The colorless viscous sticky product (1.16 g, 2.20 mmol, 67%) was
isolated by column chromatography (SiO$_2$, 80-100% EtOAc in hexane). IR (neat) 3350, 2958, 2929, 1738, 1017 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.88 (s, 1H), 7.52 (m, 1H), 6.90 (d, $J$$_{HH} = 8.5$ Hz, 1H), 6.80 (ddd, $J$$_{HP} = 21.6$ Hz, $J$$_{HH} = 17.0$, 3.7 Hz, 1H), 5.95 (m, 1H), 4.82 (d, $J$$_{HH} = 9.9$ Hz, 1H), 4.67 (s, 1H), 4.09-3.98 (m, 4H), 2.00-1.72 (m, 2H), 1.68 (s, 6H), 1.29 (t, $J$$_{HH} = 7.0$ Hz, 1H), 0.93 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) δ 161.3, 155.3, 153.9 (d, $J$$_{CP} = 5.3$ Hz), 139.4, 134.2, 126.7, 117.4, 116.6 (d, $J$$_{CP} = 186.9$ Hz), 113.3, 106.5, 70.9 (d, $J$$_{CP} = 21.3$ Hz), 69.8, 61.9 (d, $J$$_{CP} = 5.5$ Hz), 61.8 (d, $J$$_{CP} = 5.4$ Hz), 44.9, 25.9, 25.8, 18.3, 16.4 (d, $J$$_{CP} = 6.3$ Hz), -4.6, -5.1; $^{31}$P{$^1$H} NMR (121 MHz, CDCl$_3$) δ 18.5; HRMS (FAB) $m/z$: [M+H]$^+$ Calcd for C$_{25}$H$_{42}$O$_8$PSi 529.2386, Found 529.2381.

**General procedure for the Mitsunobu reaction of the bishomoallylic alcohol (4.47)**

(±) (1$R$, 3$S$, E)-3-(tert-Butyldimethylsilyloxy)-5-(diethoxyphosphoryl)-1-(2,2-Dimethyl-4-oxo-4H-benzo[d] [1,3]dioxin-7-enyl)-pent-4-enyl-4-nitrobenzoate (4.47)

(±)-Diethyl(E)-3-(tert-butyldimethylsilyloxy)-5-hydroxy-5-(2,2-Dimethyl-4-oxo-4H-benzo[d] [1,3]dioxin-7-enyl)-pent-1-enyl phosphonate (4.46, 0.4 g, 0.76 mmol, 1.0 equiv), p-nitrobenzoic acid (0.255 g, 1.52 mmol, 2 equiv), and PPh$_3$ (0.4 g, 1.52 mmol, 2.0 equiv) were dissolved in THF (40 mL) and toluene (15 mL), and the resulting solution was cooled to -50 °C. To the cold solution, di-isopropyl azodicarboxylate (DIAD) (300 µL, 1.52 mmol, 2.0 equiv) was added. After 10
min., the solution was warmed to room temperature and stirred for 24 h. The reaction was quenched by addition of EtOH (0.2 mL) and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, EtOAc: hexane, 30:70) to give the benzoate ester (0.386 g, 0.57 mmol, 75 %) as a colorless sticky liquid. IR (neat) 2952, 2855, 1734, 1619, 1526, 1257, 1021 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.21 (d, $J_{HH} = 8.7$ Hz, 2H), 8.12 (d, $J_{HH} = 8.7$ Hz, 2H), 7.94 (d, $J_{HH} = 1.3$ Hz, 1H), 7.54 (dd, $J_{HP} = 8.5$ Hz, $J_{HH} = 1.6$ Hz, 1H), 6.90 (d, $J_{HH} = 8.5$ Hz, 1H), 6.80 (ddd, $J_{HP} = 21.6$ Hz, $J_{HH} = 17.0$ Hz, 4.2 Hz, 1H), 6.08-6.03 (m, 1H), 5.85-5.74 (m, 1H), 4.32 (s, 1H), 4.00-3.84 (m, 4H), 2.46-2. (m, 1H), 6.15-6.11 (m, 1H), 5.83 (ddd, $J_{HP}= 20.4$ Hz, $J_{HH} = 16.9$, 1.7 Hz, 1H), 4.32 (s, 1H), 3.99-3.89 (m, 4H), 2.46-2.36 (m, 1H), 2.14-2.06 (m, 1H), 1.66 (s, 3H), 1.64 (s, 3H), 1.22 (t, $J_{HH} = 7.1$ Hz, 3H), 1.22 (t, $J_{HH} = 7.1$ Hz, 3H), -0.05 (s, 6H); $^{13}$C($^1$H) NMR (75 MHz, CDCl$_3$) $\delta$ 163.6, 160.8, 156.1, 150.7, 135.5, 135.2, 134.4, 131.0, 127.8, 123.7, 117.8, 116.6 (d, $J_{CP} = 187.7$ Hz), 113.7, 106.8, 73.0, 69.6 (d, $J_{CP} = 22.2$ Hz), 61.8 (d, $J_{CP} = 5.5$ Hz), 61.7 (d, $J_{CP} = 5.9$ Hz), 43.2, 26.0, 25.9, 18.2, 16.4 (d, $J_{CP} = 6.3$ Hz), -4.4, -4.9; $^{31}$P($^1$H) NMR (121 MHz, CDCl$_3$) $\delta$ 18.1; HRMS (FAB) $m/z$: [M+H]$^+$ Calcd for C$_{32}$H$_{45}$NO$_{11}$PSi 678.2499, Found 678.2494.

(±) Diethyl((3S)-3-methyl-5-phenyl-tetrahydofuran-2-yl)bromomethylphosphonate (4.51)

Bishomoallyl alcohol (2.81a) (0.1 g, 0.32 mmol, 1 equiv) was dissolved in dry THF (5 mL) under argon atmosphere and cooled to -78 °C. Bromine (50 µL, 0.96 mmol, 3 equiv) was added slowly and stirred for 4 h. After reaction completion, quenched with sodium thiosulfate solution, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, and then dried over sodium sulfate. The solvent was removed under vacuo and the product (4.51) was isolated (0.081 g, 0.21 mmol, 65%) with column chromatography (SiO$_2$, 20-30% EtOAc in hexane) in a diastereomeric rat 84:16.
The characterization data for major diastereomer was extrapolated from the spectra on a mixture of diastereomers. $^{31}$P{\textsuperscript{1}H} NMR (121 MHz, CDCl\textsubscript{3}) $\delta$ major diastereomer (17.2 ppm) and minor diastereomer (19.9 ppm); HRMS (FAB) $m/z$: [M+Na]$^+$ Calcd for C\textsubscript{16}H\textsubscript{24}BrO\textsubscript{4}PNa 413.0493, Found 413.0508, HRMS (FAB) $m/z$: [M+2+Na$^+$], Found 415.0488.

Major diastereomer: IR (neat) cm\textsuperscript{-1} 2974, 2870, 1466, 1366, 1252, 1015; $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.27-7.17 (m, 5H), 5.11-5.06 (m, 1H), 4.22-4.08 (m, 6H), 2.71-2.61 (m, 1H), 2.52-2.44 (m, 1H), 1.62-1.51 (m, 1H), 1.30-1.24 (m, 6H), 1.15 (d, $J_{\text{HH}}$ = 6.5 Hz, 3H); $^{13}$C{\textsuperscript{1}H} NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 142.2, 127.5, 125.7, 85.0 (d, $J_{\text{CP}}$ = 3.5 Hz), 81.4, 64.0 (d, $J_{\text{CP}}$ = 7.0 Hz), 63.3 (d, $J_{\text{CP}}$ = 6.8 Hz), 45.8 (d, $J_{\text{CP}}$ = 149.1 Hz), 45.1, 38.2 (d, $J_{\text{CP}}$ = 2.2 Hz), 18.6, 16.5 (d, $J_{\text{CP}}$ = 5.8 Hz), 16.4 (d, $J_{\text{CP}}$ = 6.1 Hz).

(±) Diethyl (3S, E)-(3-methyl-5-oxo-5-phenyl)-pent-1-enyl phosphonate (4.53)

\[
\text{EtO} \quad \text{P}^\beta \\
\text{EtO} \quad \text{O} \\
\text{EtO} \quad \text{O}
\]

The standard reaction protocol of Swern oxidation has been followed to oxidize bishomoallylic alcohol to the corresponding ketone.\textsuperscript{29} The oxalyl chloride (34 µL, 0.38 mmol, 1.2 equiv) dissolved in CH\textsubscript{2}Cl\textsubscript{2} was cooled to -78 °C and DMSO (68 µL, 0.96 mmol, 3 equiv) was added. After 2 min, the alcohol (0.050 g, 0.16 mmol, 1 equiv) was added to the reaction mixture followed by stirring 20 min. Then, triethyl amine was added to the reaction and the reaction mixture was slowly brought to room temperature. The reaction was washed with water and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under vacuo and the product was isolated (0.075 g, 0.24 mmol, 76%) with column chromatography (SiO\textsubscript{2}, 80-100% EtOAc in hexane). IR (neat) cm\textsuperscript{-1} 2977, 2930, 1681, 1239, 1018; $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.94 ((d, $J_{\text{HH}}$ = 7.4Hz, 2H), 7.59-7.46 (m, 3H), 6.89-6.73 (m, 1H), 5.75-5.63(m, 1H), 4.12-3.99 (m, 4H), 3.13-2.96 (m, 3H), 1.35-.128 (m, 6H), 1.16 (d, $J_{\text{HH}}$ = 6.4 Hz); $^{13}$C{\textsuperscript{1}H}}
NMR (75 MHz, CDCl$_3$) $\delta$ 198.1, 157.1, 136.9, 133.3, 128.7, 128.1, 115.7 (d, $J_{CP} = 186.5$ Hz), 61.7 (d, $J_{CP} = 5.4$ Hz), 44.0, 33.7 (d, $J_{CP} = 21.4$ Hz), 18.9, 16.4 (d, $J_{CP} = 7.0$ Hz); $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CDCl$_3$) $\delta$ 18.9; HRMS (FAB) $m/z$: [M+H]$^+$ Calcd for C$_{16}$H$_{24}$NO$_4$P; 311.1412, Found 311.1407.
4.5. REFERENCES


