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Note

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*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00905 • Publication Date (Web): 29 May 2019



is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

# Synthesis of Phostones via the Palladium-Catalyzed Ring Opening of Epoxy vinyl phosphonates

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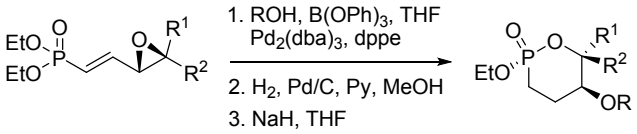
*Supporting Information*

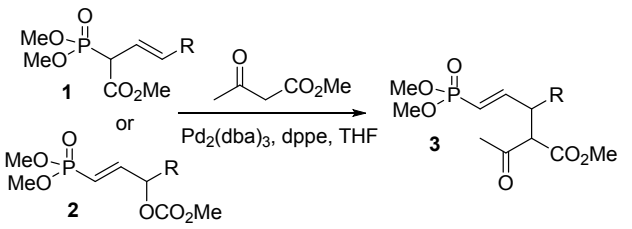



**ABSTRACT:** Reaction of epoxy aldehydes with tetraethyl methylenediphosphonate gave γ,δ-epoxy vinyl phosphonates. The palladium-catalyzed addition of primary alcohols gave the monoprotected diols as single diastereoisomers. The *trans* and *cis* epoxides lead to opposite (*syn* and *anti*) diastereoisomers of the addition products. The alkene of the vinyl phosphonates was subjected to hydrogenation and the resulting saturated phosphonates underwent base catalyzed cyclization to give phostones with very high diastereoselectivity in the formation of the new chiral center at phosphorus.

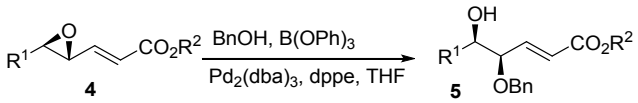
Phostones and phostines are 5- and 6-membered cyclic phosphonates and phosphinates, respectively, which contain a P-O bond within the heterocyclic ring. These hetraphosphacyclanes are more formally called oxaphospholanes and oxaphosphorinanes.[1] Of particular interest are the carbohydrate-based phostones (or phosphonosugars).[2-5] There are a growing number of examples of carbohydrate-based phostones and phostines that show interesting biological activity.[2,5b] Carbohydrate-based phostones are typically prepared by the addition of trialkyl phosphites or dialkyl phosphites to carbohydrate-derived aldehydes.[3,4] More recent methods for the synthesis of these phostones include the application of a ring closing metathesis strategy.[5] Although phostones were first synthesized more than four decades ago, there has recently been renewed interest in their synthesis utilizing alternative modern synthetic methods.[4,5]

Based on our experience with the chemistry of phosphono allylic carbonates (**1** and **2**)[6,7] and the known chemistry of γ,δ-epoxy unsaturated carboxylate esters **4**[8] (Scheme 1 and 2), we proposed an alternative approach to phostone synthesis employing γ,δ-epoxy vinyl phosphonate chemistry.

**Scheme 1. Palladium-catalyzed reactions of α and γ phosphono allylic carbonates**



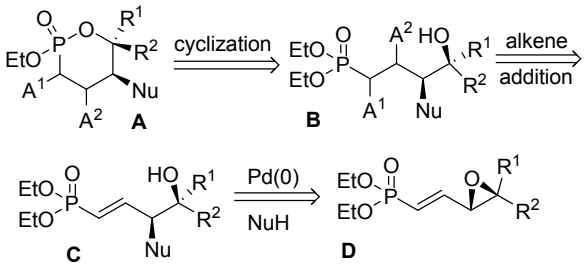

**Scheme 2. Palladium-catalyzed reactions of γ,δ-epoxy unsaturated esters**




In a retrosynthetic analysis (Scheme 3), opening the internal ring P-O bond of the phostones (**A**) reveals δ-hydroxy phosphonates (**B**). Similar phosphonates are known to undergo base catalyzed cyclization to give the phostones.[9] The substituents $A^1$ and $A^2$ can be installed by an alkene addition reaction on the vinyl phosphonate moiety (**C**).[10-13] For example, the alkene of the

vinyl phosphonates can be subjected to asymmetric dihydroxylation (AD),[10] selective α-hydroboration,[7h,11] β-hydroboration,[7a,12] or simple hydrogentation.[7b,7d,13] This leads to the critical reaction involving the regioselective and stereospecific ring opening of an γ,δ-epoxy vinyl phosphonates (**D**), which are in turn prepared in a straight forward manner from the large array of readily available non racemic epoxy aldehydes (and epoxy alcohols).[14,15]

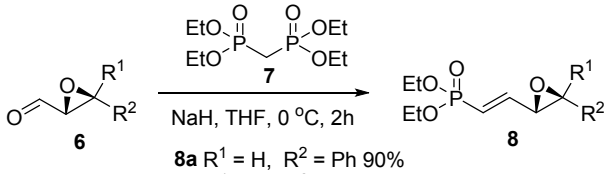
**Scheme 3. A retro synthetic analysis for the synthesis carbohydrate-based phostones**




By analogy with the reactions of γ,δ-epoxy unsaturated carboxylate esters,[8] the palladium-catalyzed addition of nucleophiles (e.g. benzyl alcohol) to γ,δ-epoxy vinyl phosphonates is expected to give the monoprotected diols as single diastereoisomers. The *trans* and *cis* epoxides lead to opposite (*syn* and *anti*) isomers of the addition products. Furthermore, we have demonstrated that both α and γ phosphono allylic carbonates (**1** and **2**) undergo palladium-catalyzed reactions with methyl acetoacetate leading to the same vinyl phosphonate product **3**, presumably via a common π-allylintermediate.[6] Interestingly, the vinyl phosphonate (γ carbonate) **2** converts to product about 6 times faster than the α-carbonate **1**. This precedent gave us high confidence that the proposed approach to phostones would be successful.

Reaction of epoxy aldehydes (**6**)[15] with tetraethyl methylenediphosphonate (**7**) gave γ,δ-epoxy vinyl phosphonates (**8**) in good yield (Scheme 4). The initial attempts to add benzyl alcohol to the epoxide **8a** using palladium catalysis resulted in formation of the unsaturated ketone **10a** (Scheme 5). It is believed that the ketone **10a** is formed from elimination (of proton and palladium) from the π-allyl intermediate **11**, which may occur faster than the competing reaction of the alcohol nucleophile. It is probable that the presence of the phenyl contributes to the facile proton loss due to conjugation with the resulting dienolate. Therefore switching from a phenyl substituent to alkyl group adjacent to the π-allyl may reduce the propensity for elimination.

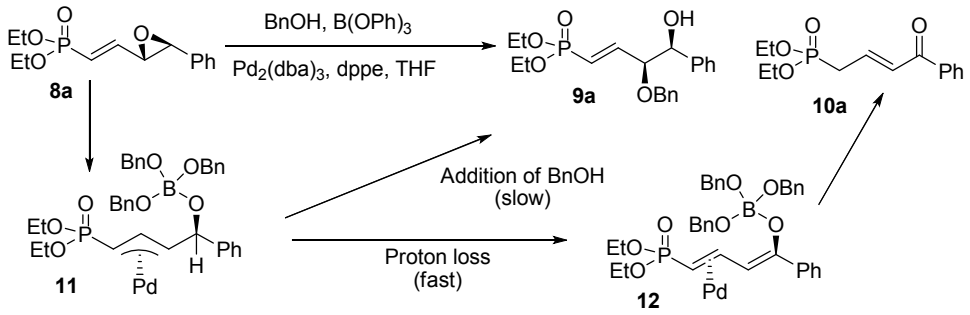
**Scheme 4. Preparation of γ,δ-epoxy vinyl phosphonates**




**8a** $R^1$ = H, $R^2$ = Ph 90%
**8b** $R^1$ = H, $R^2$ = $nC_5H_{11}$ 77%
**8c** $R^1$ = H, $R^2$ = $CH_2OBn$ (trans) 81%
**8d** $R^1$ = $CH_2OBn$, $R^2$ = H (cis) 87%

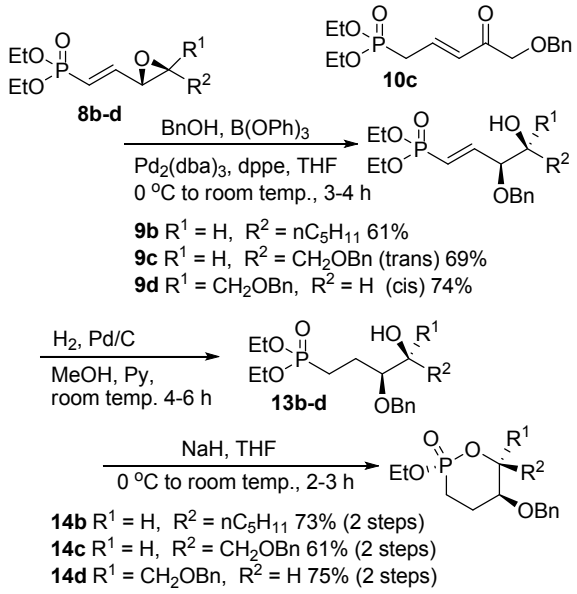
Consequently, three additional epoxy vinyl phosphonates **8b-d** were investigated (Scheme 6). We were pleased to find that palladium-catalyzed reaction of these epoxy vinyl phosphonate with benzyl alcohol gave the addition product **9b-d** in in good yields. As anticipated, the ring opening reactions are stereospecific with the *trans* epoxide **8c** giving mono protected *syn* diol **9c**, and the cis epoxide **8d** the *anti* diastereoisomer **9d**. In a single experiment with epoxide **8c**, omission of the $B(OPh)_3$ from the reaction mixture resulted in ketone **10c** formation.

**Scheme 5. A possible reaction mechanism to account for the competitive formation of the unsaturated ketone.**



Hydrogenation of the vinyl phosphonates **9** using hydrogen over palladium on carbon, poisoned with 5-50 mol% of pyridine (Scheme 6), gave the saturated phosphonate **13** without over reduction and loss of the benzyl protecting group. Treatment of the saturated phosphonates **13** with sodium hydride in THF resulted in cyclization and the formation of phostones **14** as single diastereoisomers. The stereochemistry at the phosphorus atom was elucidated via X-ray crystallography with phostone **14b** (details in supporting information). The highly diastereoselective nature of the cyclization was somewhat surprising. However, a review of the published literature indicated that other substituted δ-hydroxy phosphonates also undergo highly diastereoselective cyclizations.[16]

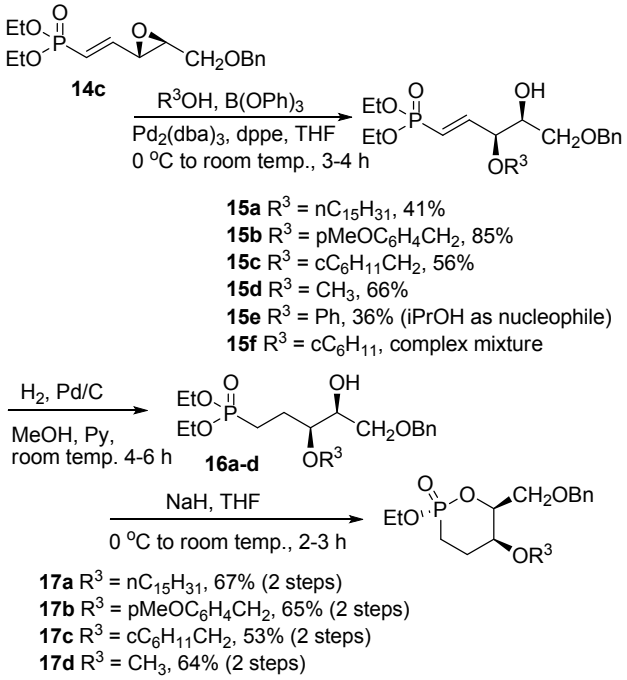
**Scheme 6. Palladium-catalyzed addition of benzyl alcohol to γ,δ-epoxy vinyl phosphonates**




To expand the scope of the method, the reaction of the benzyloxymethyl substituted *trans*-epoxy vinyl phosphonate **9c** with other alcohol nucleophiles was examined (Scheme 7). In general, primary alcohols reacted smoothly to give *syn* monoprotected diols **15a-d**. However, the yield with pentadecanol was low due to the lack of solubility of this alcohol in the reaction solvent (THF). Attempted reaction of secondary alcohols, such as *i*PrOH and cyclohexanol, lead to complex mixtures and often the phenol released from the $B(OPh)_3$ was a more competent nucleophile leading to the formation of **15e**. When using methanol as a nucleophile, $B(OMe)_3$ was used as the co-catalyst.

Again, hydrogenation of the vinyl phosphonates **15a-d** using hydrogen over palladium on carbon, poisoned with pyridine, gave the saturated phosphonates **16a-d**. Treatment of the saturated phosphonates **16a-d** with sodium hydride in THF resulted in cyclization and the formation of phostones **17a-d** as single diastereoisomers (Scheme 7).

**Scheme 7. Palladium-catalyzed addition of alcohols to a γ,δ-epoxy vinyl phosphonates**




In summary, we have demonstrated γ,δ-epoxy vinyl phosphonates undergo stereospecific palladium-catalyzed addition of primary alcohols to give vinyl phosphonates. Reduction and cyclization of the vinyl phosphonates yields phostones as single diastereoisomers. An investigation of stereoselective mono and dihydroxylation reactions of vinyl phosphonates is ongoing.

## Experimental Section

All reactions were carried out in oven dried glassware under an atmosphere of argon unless otherwise noted. THF was distilled from Na/benzophenone, MeOH from $Mg/Mg(OMe)_2$, $CH_2Cl_2$ from $CaH_2$, *t*-Butanol from Na/*t*-BuONa) and $CH_3CN$ was stored over activated 3Å

molecular sieves prior to use. $^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded in $CDCl_3$ at 300, 75 and 121 MHz, respectively. $^1$H NMR spectra are referenced to $CDCl_3$ (7.27 ppm), $^{13}$C NMR spectra are referenced to the center line of $CDCl_3$ (77.23 ppm) and $^{31}$P NMR spectra are referenced to external $H_3PO_4$. Coupling constants, *J*, are reported in Hz. Analytical thin-layer chromatography (TLC) analyses were performed on silica gel plates $60PF_{254}$. Visualization was accomplished with UV light, $KMnO_4$ solution or iodine.

**General procedure for the synthesis of epoxy aldehydes (6a-d).** To the ice bath cooled solution of epoxy alcohol in dry $CH_2Cl_2$ (4 mL/mmol) was added $Et_3N$. Then a solution of pyridine sulfur trioxide in dry DMSO (1.5 mL/mmol) was added slowly via an addition funnel over a period of one hour. The reaction mixture was stirred at ice bath temperature for an additional three hours. The reaction was quenched by the addition of 10% aqueous citric acid and resulting aqueous solution was extracted three times using $CH_2Cl_2$. The combined organic layer was washed with saturated $NaHCO_3$ and brine, and dried over $Na_2SO_4$. The solution was concentrated under reduced pressure and the pure epoxy aldehyde was isolated by column chromatography ($SiO_2$, 10-20% EtOAc in hexane). The $^1$H NMR spectrum for each epoxide was consistent with the literature values (see supporting information).

**(±) 3-phenyloxirane-2-carbaldehyde (6a)**[17]

**(±) 3-pentyloxirane-2-carbaldehyde (6b)**[15b]

**(±) 3-((benzyloxy)methyl)oxirane-2-carbaldehyde (6c)**[15d]

**(±) 3-((benzyloxy)methyl)oxirane-2-carbaldehyde (6d)**[15c]

**General procedure for the synthesis of vinyl epoxy phosphonates (8a-d).** Sodium hydride (1.5 eq) was suspended in dry THF (1 mL/mmol). The suspension was cooled in an ice bath and then tetraethyl methylenebis(phosphonate) (**7**) (1.5 eq) was added slowly over 5 minutes. The resulting mixture was stirred for one hour, then the epoxy aldehyde **6** (1 eq) dissolved in dry THF (3 mL/mmol) was added dropwise. The reaction mixture was stirred for two hours at ice bath temperature, then the reaction was quenched with 10% aqueous $NH_4Cl$. After 10 minutes, the aqueous solution was extracted three times with EtOAc. The combined organic layer was washed with aqueous $NaHCO_3$ and brine, and then dried over anhydrous $Na_2SO_4$. The solution was concentrated under reduced pressure and pure epoxy vinylphosphonate **8** was isolated by column chromatography ($SiO_2$, 30-60% EtOAc in hexane).

**(±) Diethyl (*E*)-2((2*S*3*S*)-3-phenyloxiran-2-yl)vinylphosphonate (8a).**[18] Epoxy cinnamaldehyde (**6a**) (1.8 g, 12.5 mmol) was reacted as above to give (**8a**) as thick yellow oil (3.17 g, 90%). $^1$H NMR ($CDCl_3$) δ 7.32-7.18 (m, 5H), 6.67 (ddd, $J_{HP}$ = 21.5, $J_{HH}$ = 17.1, 6.2 Hz, 1H), 6.08 (ddd, $J_{HP}$ = 18.6, $J_{HH}$ = 17.1, 0.6 Hz, 1H), 4.04 (m, 4H), 3.73 (d, $J_{HH}$ = 1.6 Hz, 1H), 3.39 (m, 1H), 1.27 (dt, $J_{HH}$ = 7.0, $J_{HP}$ = 1.5 Hz, 6H); $^{13}$C{$^1$H} NMR ($CDCl_3$) δ 147.5 (d, $J_{CP}$ = 6.1 Hz), 135.9, 128.6, 128.5, 125.4, 120.1 (d, $J_{CP}$ = 187.5 Hz), 61.9 (d, $J_{CP}$ = 5.2 Hz), 61.3, 61.0 (d, $J_{CP}$ = 1.5 Hz), 16.3 (d, $J_{CP}$ = 6.3 Hz); $^{31}$P{$^1$H} NMR ($CDCl_3$) δ 16.8; HRMS (FAB, MH+) calcd for $C_{14}H_{20}O_4P$: 283.1099, Found 283.1117.

**(±) Diethyl (*E*)-2-((2*S*,3*S*)-3-pentyloxiran-2-yl)vinylphosphonate (8b).** Epoxy octanal (**6b**) (2.29 g, 16 mmol) was reacted as above to give (**8b**) as a pale yellow oil (3.39 g, 77%). IR (neat) 2928, 2858, 1631 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 6.54 (ddd, $J_{HP}$ = 21.5, $J_{HH}$ = 17.1, 6.4 Hz, 1H), 5.9 (ddd, $J_{HP}$ = 19.0, $J_{HH}$ 17.1, 0.7 Hz, 1H), 4.08 (m, 4H), 3.19 (m, 1H), 2.85 (m 1H), 1.60 (m, 2H), 1.43 (m, 2H), 1.32 (m, 10H), 0.89 (t, $J_{HH}$ 7.1 Hz, 3H); $^{13}$C{$^1$H} NMR ($CDCl_3$) δ 148.8 (d, $J_{CP}$ = 6.0 Hz), 119.2 (d, $J_{CP}$ = 188.2 Hz), 61.5 (d, $J_{CP}$ = 21.7 Hz), 56.8 (d, $J_{CP}$ = 27.7 Hz), 31.5 (d, $J_{CP}$ = 25.5 Hz), 25.3, 22.4, 16.2 (d, $J_{CP}$ = 6.0 Hz), 13.6; $^{31}$P{$^1$H} NMR ($CDCl_3$) δ 16.9; HRMS (FAB, $MH^+$) calcd For $C_{13}H_{26}O_4P$: 277.1568, Found 277.1582.

**(±) Diethyl (*E*)-2-(2*S*,3*S*)-3-(benzyloxymethyl)oxiran-2-yl)vinylphosphonate (8c).** *trans*-Benzyloxy epoxy butanal (**6c**) (2.40 g, 12.45 mmol) was reacted as above to give (**8c**) as a yellow oil (3.27 g, 81 %). IR (neat) 2981, 2862, 1632, 1240 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.33-7.11 (m, 5H), 6.44 (ddd, $J_{HP}$ = 21.5, $J_{HH}$ 17.1, 6.5 Hz, 1H), 5.95 (ddd, $J_{HP}$ = 18.6, $J_{HH}$ 17.1, 0.6 Hz, 1H), 4.48 (q, $J_{HH}$ =11.9 Hz, 2H), 3.99 (m, 4H), 3.57 (m, 2H),

3.32 (m, 1H), 3.04 (m, 1H), 1.23 (m, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) δ 147.8 (d, $J_{CP}$ = 6.2 Hz), 137.5, 128.4, 127.8, 127.7, 120.4 (d, $J_{CP}$ = 188.2 Hz), 73.4, 69.0, 61.9 (d, $J_{CP}$ = 6.0 Hz), 59.5 (d, $J_{CP}$ = 1.5 Hz), 54.3 (d, $J_{CP}$ = 29.2 Hz), 16.4 (d, $J_{CP}$ = 6.7 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$) δ 16.6; HRMS (FAB, $MH^+$) calcd For $C_{16}H_{24}O_5P$: 327.1361, Found 327.1376.

**(±) Diethyl (*E*)-2-(2*S*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)vinylphosphonate (8d).** *cis*-Benzyloxy epoxy butanal (**6d**) (2.5 g, 13.01 mmol) was reacted as above to give (**8d**) as a pale yellow oil (3.68 g, 87%). IR (neat) 2980, 2903, 1629, 1243 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$) δ 7.40-7.30 (m, 5H), 6.62 (ddd, $J_{HP}$ = 21.6, $J_{HH}$ = 17.1, 6.0 Hz, 1H), 6.05 (ddd, $J_{HP}$ = 18.7, $J_{HH}$ = 17.1, 1.0 Hz, 1H), 4.57 (q, $J_{HH}$ = 11.8 Hz, 2H), 4.06 (m, 4H), 3.60 (m, 3H), 3.45 (m, 1H), 1.32 (m, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) δ 145.1 (d, $J_{CP}$ = 6.6 Hz), 137.6, 128.5, 128.0, 127.8, 122.3 (d, $J_{CP}$ = 188.6 Hz), 73.4, 67.5, 62.0 (d, $J_{CP}$ = 5.5 Hz), 57.5, 55.1 (d, $J_{CP}$ = 28.2 Hz), 16.4 (d, $J_{CP}$ = 6.4 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$) δ 16.3; HRMS (FAB, $MH^+$) calcd For $C_{16}H_{24}O_5P$, 327.1361, Found 327.1367.

**General procedure for the synthesis of vinylphosphonates (9 or 15).** To a solution of triphenyl borate (1.5 eq) in dry THF (1 mL/mmol) was added benzyl alcohol (6 eq). The resulting solution was stirred for two hours. In a separate flask, $Pd_2dba_3$ (0.04 eq) and dppe (0.1 eq) were added to a solution of the epoxy vinyl phosphonates **8** (1 eq) in THF (3 mL/mmol). After one hour of stirring, the palladium solution was added to the alcohol solution and the resulting mixture was stirred for one hour at ice bath temperature. The reaction mixture was then allowed to warm to room temperature and stirring was continued until the reaction was complete (as observed by $^{31}P$ NMR and TLC, 2-3 h). The reaction was quenched by addition of 10% aqueous $NH_4Cl$ and extracted with three times with EtOAc. The combined organic layer was washed with aqueous saturated $NaHCO_3$ and brine, and then dried over anhydrous $Na_2SO_4$. The solution was concentrated under reduced pressure and pure products (**9**, **10** or **15**) were isolated by column chromatography ($SiO_2$, 60-80% EtOAc in hexanes).

**Diethyl (*E*)-(4-oxo-4-phenylbut-2-en-1-yl)phosphonate (10a).**[19] Epoxy vinylphosphonate (**8a**) (0.1 g, 0.354 mmol) was reacted as above to give (**10a**) (0.093 g, 93 %). $^{1}H$ NMR ($CDCl_3$) δ 7.93-7.90 (m, 2H), 7.59-7.41 (m, 3H), 6.97 (m, 2H), 4.12 (m, 4H), 2.85 (dd, $J_{HP}$ = 23.5, $J_{HH}$ = 7.0 Hz, 2H), 1.32 (t, $J_{HH}$ = 7.1 Hz, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) δ 190.1 (d, $J_{CP}$ = 2.9 Hz), 137.8 (d, $J_{CP}$ = 11.4 Hz), 137.5, 133.2, 130.2 (d, $J_{CP}$ = 13.3 Hz), 128.8 (s), 62.6 (d, $J_{CP}$ = 6.7 Hz), 31.3 (d, $J_{CP}$ = 138.1 Hz), 16.7 (d, $J_{CP}$ = 6.0 Hz).$^{31}P\{^{1}H\}$ NMR ($CDCl_3$) δ 24.5; HRMS (ESI, $MH^+$) calcd For $C_{14}H_{20}O_4P$: 283.1099, Found 283.1093

**Diethyl (*E*)-(5-(benzyloxy)-4-oxopent-2-en-1-yl)phosphonate (10c).** Formed from epoxy vinyl phosphonate (**8c**) (0.1 g, 0.306 mmol) as above reaction, but in the absence of $B(OPh)_3$ (0.041 mg, 41 %). IR (neat) 2980, 2904, 1692, 1625, 1243 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$) δ 7.38-7.27 (m, 5H), 6.87 ( m, 1H), 6.43 (m, 1H), 4.60 (s, 2H), 4.22 (s, 2H), 4.10 (m, 4H), 2.75 (ddd, $J_{HP}$ = 23.2, $J_{HH}$ = 7.8, 1.3 Hz, 2H), 1.30 (t, $J_{HH}$ = 7.1 Hz, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) δ 196.2, 137.2, 137.0 (d, $J_{CP}$ = 11.1 Hz), 130.0 (d, $J_{CP}$ = 13.4 Hz), 128.6, 128.1 (d, $J_{CP}$ = 5.6 Hz), 128.1, 74.2, 73.5, 62.5 (d, $J_{CP}$ = 6.6 Hz), 31.2 (d, $J_{CP}$ = 138.1 Hz), 16.5 (d, $J_{CP}$ = 5.9 Hz). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$) δ 24.1; HRMS (FAB, $MNa^+$) calcd For $C_{16}H_{23}O_5PNa$: 349.1180, Found 349.1182.

**(±) Diethyl (3*S*,4*S*,*E*)-3-(benzyloxy)-4-hydroxynon-1-enylphosphonate (9b).** Epoxy vinyl phosphonate (**8b**) (0.5 g, 1.81 mmol) was as above reacted to give (**9b**) as a yellow oil (0.425 g, 61%). IR (neat) 3412, 2946, 2862, 1201 $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 7.29-7.17 (m, 5H), 6.61 (ddd, $J_{HP}$ = 22.3, $J_{HH}$ = 17.3, 5.7 Hz, 1H), 5.9 (ddd, $J_{HP}$ = 20.6, $J_{HH}$ 17.2, 1.0 Hz, 1H), 4.40 (q, $J_{HH}$ = 11.4 Hz, 2H), 3.98 (m, 4H), 3.74 (m, 1H), 3.47 (t $J_{HH}$ = 5.6 Hz, 1H), 2.90 (br, 1H), 1.36 (m, 2H), 1.21 (m 12H), 0.77 (t, $J_{HH}$ = 6.7 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 149.1 (d, $J_{CP}$ = 5.0 Hz), 137.4, 128.4, 127.9, 127.8, 120.1 (d, $J_{CP}$ = 186.6 Hz), 82.8 (d, $J_{CP}$ = 21.1 Hz), 72.9, 71.6, 61.8 (d, $J_{CP}$ = 5.6 Hz), 32.4, 31.7, 25.1, 22.5, 16.3 (d, $J_{CP}$ = 6.3 Hz), 14.0; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$) δ 17.4 HRMS (FAB, $MH^+$) calcd For $C_{20}H_{34}O_5P$: 385.2143, Found 385.2162.

**(±) Diethyl (3*S*,4*S*,*E*)-3,5-bis(benzyloxy)-4-hydroxypent-1-enylphosphonate (9c).** Epoxy vinyl phosphonate (**8c**) (0.5 g, 1.53 mmol) was reacted to give (9c) as a yellow oil (0.459 g, 69%). IR (neat) 3412 (br), 2981, 1201 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.24-7.21 (m, 10H), 6.66 (ddd, $J_{HP}$ = 22.1, $J_{HH}$ = 17.3, 5.7 Hz, 1H), 5.94 (ddd, $J_{HP}$ = 20.4, $J_{HH}$ 17.3, 1.3 Hz, 1H), 4.45 (q, $J_{HH}$ = 11.4 Hz, 2H), 4.44 (s, 2H), 4.10 (m, 1H), 3.9(m, 4H), 3.75 (m, 1H), 3.46 (m, 2H), 2.49 (d $J_{HH}$ = 4.7 Hz, 1H), 1.25 (t, $J_{HH}$ = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 148.7 (d, $J_{CP}$ = 5.1 Hz), 137.8, 137.4, 128.5, 128.5, 128.0, 127.8, 119.9 (d, $J_{CP}$ = 187.0 Hz), 79.5 (d, $J_{CP}$ = 21.5 Hz), 73.5,72.2, 72.0, 61.9 (d, $J_{CP}$ = 5.5 Hz), 16.4 (d, $J_{CP}$ = 6.2 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 17.3; HRMS (FAB, $MH^+$) calcd For $C_{23}H_{32}O_6P$ 435.1936, Found 435.1938.

**(±) Diethyl (3R,4*S*,*E*)-3,5-bis(benzyloxy)-4-hydroxypent-1-enylphosphonate (9d).** Epoxy vinyl phosphonate (**8d**) (0.5 g 1.53 mmol) was reacted as above to give (**9d**) as a yellow oil (0.493 g, 74%). IR (neat) 3364 (br), 3028, 2980, 2864, 1630, 1225 $cm^{-1}$ $^1H$ NMR ($CDCl_3$) δ 7.38-7.29 (m, 10H), 6.79 (ddd, $J_{HP}$ = 22.1, $J_{HH}$ = 17.2, 5.6 Hz, 1H), 6.00 (ddd, $J_{HP}$ = 20.6, $J_{HH}$ = 17.2, 1.3 Hz, 1H), 4.52 ( s, 2H), 4.52 (q, $J_{HH}$ = 11.5 Hz, 2H), 4.08 (m, 5H), 3.89 (m, 1H), 3.59 (m, 2H), 2.43 (d, $J_{HH}$ = 5.3 Hz, 1H), 1.33 (t, $J_{HH}$ = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 149.3, 137.9, 137.6, 128.6, 128.6, 128.0, 128.0, 127.9, 120.0 (d, $J_{CP}$ = 186.4 Hz), 79.8 (d, $J_{CP}$ = 21.6 Hz), 73.5, 72.3 (d, $J_{CP}$ = 1.2 Hz), 70.5, 62.0 (d, $J_{CP}$ = 5.6 Hz, 16.5 (d, $J_{CP}$ = 6.4 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 17.5. HRMS (FAB, $MH^+$) calcd For $C_{23}H_{32}O_6P$: 435.1936, Found 435.1925.

**(±) Diethyl (3*S*,4*S*,*E*)-5-(benzyloxy)-4-hydroxy-3-(pentadecyloxy)pent-1-enylphosphonate (15a).** Epoxy vinyl phosphonate (**8c**) (0.5 g, 1.53 mmol) was reacted as above to give (**15a**) as a yellow oil (0.346 g, 41%). IR (neat) 3431 (br), 2920, 2851, 1224 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.39-7.30 (m, 5H), 6.67 (ddd, $J_{HP}$ = 22.5, $J_{HH}$ = 17.2, 5.4 Hz, 1H), 5.95 (ddd, $J_{HP}$ = 20.7, $J_{HH}$ = 17.3, 1.2 Hz, 1H), 4.56 (m, 2H), 4.06 (m, 5H), 3.75 (m, 1H), 3.54 (m, 3H), 3.33 (m, 1H), 2.60 (d, $J_{HH}$ = 4.5 Hz, 1H), 1.56 (m, 2H), 1.30 (m, 30H), 0.88 (t, $J_{HH}$ = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 149.3 (d, $J_{CP}$ = 5.2 Hz), 1387.9, 128.6, 127.9, 119.5 (d, $J_{CP}$ = 187.0 Hz), 80.1 (d, $J_{CP}$ = 21.4 Hz), 73.7, 72.3, 70.7, 70.2, 62.0 (d, $J_{CP}$ = 4.5 Hz), 32.0, 29.9, 29.8, 29.7, 29.7, 29.6, 29.5, 26.2, 22.8, 16.5 (d, $J_{CP}$ = 6.1 Hz), 14.3; $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 17.6; HRMS (FAB, $MH^+$) calcd For $C_{31}H_{56}O_6P$: 555.3814, Found 555.3790.

**(±) Diethyl (3*S*,4*S*,*E*)-5-(benzyloxy)-4-hydroxy-3-(4-methoxybenzyloxy)pent-1-enyl)phosphonate (15b).** Epoxy vinyl phosphonate (**8c**) (0.423 g, 1.30 mmol) was reacted as above to give (**15b**) as a yellow oil (0.512 g, 85%). IR (neat) 3381 (br), 2980, 2904, 2864, 1610, 1241 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.39-7.29 (m, 5H), 7.25-7.20 (m, 2H), 6.90-6.85 (m, 2H), 6.73 (ddd, $J_{HP}$ = 22.1, $J_{HH}$ = 17.2, 5.7 Hz, 1H), 6.0 (ddd, $J_{HP}$ = 20.5, $J_{HH}$ = 17.3, 1.3 Hz, 1H), 4.51 ( s, 2H), 4.45 (q, $J_{HH}$ = 11.1 Hz, 2H), 4.08 (m, 5H), 3.79 (m, 4H), 3.52 (m, 2H), 1.32 (t, $J_{HH}$ = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 159.5, 148.9 (d, $J_{CP}$ = 5.3 Hz), 137.9, 129.8, 129.5, 128.5, 127.92 112.0 (d, $J_{CP}$ = 186.9 Hz), 114.0, 79.1 (d, $J_{CP}$ = 21.5 Hz).73.6, 72.3, 71.8, 70.3, 62.0 (d, $J_{CP}$ = 4.1 Hz), 55.4, 16.5 (d, $J_{CP}$ = 6.2 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 17.4. HRMS (FAB, $MH^+$) calcd For $C_{24}H_{34}O_7P$: 465.2042, Found 465.2052.

**(±) Diethyl (3*S*,4*S*,*E*)-5-(benzyloxy)-3-(cyclohexylmethoxy)-4-hydroxypent-1-enyl)phosphonate (15c).** Epoxy vinyl phosphonate (**8c**) (0.5 g, 1.53 mmol) was reacted as above to give (**15c**) as a yellow oil (0.376 g, 56%). IR (neat) 3356 (br), 2920, 2850, 1232 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.36-7.24 (m, 5H), 6.65 (ddd, $J_{HP}$ = 22.2, $J_{HH}$ = 17.1, 5.4 Hz, 1H), 5.92 (ddd, $J_{HP}$ = 20.7, $J_{HH}$ = 17.2, 1.3 Hz, 1H), 4.51 (m, 2H), 4.02 (m, 5H), 3.75 (m, 1H), 3.50 (m, 2H), 3.19 (m, 2H), 1.68 (m, 5H), 1.54 (m, 1H), 1.23 (m, 10H), 0.89 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 149.3 (d, $J_{C-P}$ = 5.1 Hz), 137.9, 128.5, 127.9, 127.8, 119.3 (d, $J_{CP}$ = 186.9 Hz), 80.1 (d, $J_{CP}$ = 21.3 Hz), 76.2, 73.6, 72.2, 70.2, 30.0 (d, $J_{CP}$ = 1.7 Hz), 38.2, 30.1, 30.0, 26.5, 25.8, 16.4 (d, $J_{CP}$ = 5.7 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 17.7 HRMS (FAB, $MH^+$) calcd For $C_{23}H_{38}O_6P$: 441.2406, Found 441.2387.

**(±) Diethyl (3*S*,4*S*,*E*)-(5-(benzyloxy)-4-hydroxy-3-methoxypent-1-enyl)phosphonate (15d).** Epoxy vinyl phosphonate (**8c**) (0.5 g, 1.53 mmol) was reacted to give (**15d**) as a yellow oil (0.364 g, 66%). IR (neat) 3363 (br), 2980, 2912,

1225 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.35-7.27 (m, 5H), 6.63 (ddd, $J_{HP}$ = 22.3, $J_{HH}$ = 17.3, 5.7 Hz, 1H), 5.94 (ddd, $J_{HP}$ = 20.5, $J_{HH}$ = 17.3, 1.3 Hz, 1H), 4.51 (q, $J_{HH}$ = 12.1 Hz, 2H), 4.08 (m, 4H), 3.88 (m, 1H), 3.74 (m, 1H), 3.51 (m, 2H), 3.33 (s, 3H), 2.87 (s, br, 1H), 1.28 (t, $J_{HH}$ = 7.1 Hz, 6H); $^{13}$C{$^1$H} NMR ($CDCl_3$) δ 148.5 (d, $J_{CP}$ = 5.2 Hz), 137.9, 128.6, 128.0, 120.1 (d, $J_{CP}$ = 186.9 Hz), 82.1 (d, $J_{CP}$ = 21.5 Hz), 73.7, 72.3, 70.3, 62.1 (d, $J_{CP}$ = 4.8 Hz), 58.1, 16.5 (d, $J_{CP}$ = 6.3 Hz); $^{31}$P{$^1$H} NMR ($CDCl_3$) δ 17.4; HRMS (FAB, $MNa^+$) calcd For $C_{17}H_{27}O_6PNa^+$: 381.1442, Found 381.1436.

**General procedure for hydrogenation of the vinyl phosphonate.** The vinyl phosphonate (**9** or **15**) was dissolved in MeOH (3 mL/mmol) containing pyridine (0.05-0.5 eq.) and then moist 5% Pd/C (10% by weight of vinyl phosphonate) was added. The flask was flushed with argon, followed by $H_2$ (balloon pressure). $H_2$ pressure was maintained while the reaction mixture was rapidly stirred. The reaction progress was followed by $^{31}$P NMR spectroscopy. After complete reduction (4-6h), the reaction mixture was filtered through Celite®, rinsed with MeOH, and evaporated under reduced pressure to give the saturated phosphonate (**13** or **16**), typically in quantitative yields.

**(±) Diethyl (3*S*,4*S*)-3-(benzyloxy)-4-hydroxynonylphosphonate (13b).** Vinyl phosphonate (**9b**) (0.339 g, 0.88 mmol) was reduced to give (**13b**) in quantitative yield. IR (neat) 3388 (br), 2928, 2858, 1223 cm$^{-1}$ $^1$H NMR ($CDCl_3$) δ 7.36-7.26 (m, 5H), 4.56 (q, $J_{HH}$ = 11.3 Hz, 2H), 4.06 (m, 4H), 3.53 (m, 1H), 3.35 (m, 1H), 1.95 (m, 1H), 1.77 (m, 3H), 1.44 (m, 3H), 1.27 (m, 11H), 0.87 (t, $J_{HH}$ = 6.9 Hz, 3H); $^{13}$C{$^1$H} NMR ($CDCl_3$) δ 138.1, 128.5, 127. 9, 127.8, δ 81.5 (d, $J_{CP}$ = 15.6 Hz), 72.4 (d, $J_{CP}$ = 25.2 Hz), 61.5 (d, $J_{CP}$ = 6.4 Hz), 33.1, 31.9, 25.5, 22.9 (d, $J_{CP}$ = 4.5 Hz), 22.6, 21.10 (d, $J_{CP}$ = 141.3 Hz), 16.4 (d, $J_{CP}$ = 5.9 Hz), 14.1; $^{31}$P{$^1$H} NMR ($CDCl_3$) δ 32.4. HRMS (FAB, $MH^+$) calcd For $C_{20}H_{36}O_5P$: 387.2300, Found 387.2315

**(±) Diethyl (3*S*,4*S*)-3,5-bis(benzyloxy)-4-hydroxypentylphosphonate (13c).** Vinyl phosphonate (**9c**) (0.450 g, 1.17 mmol) was reduced to give (**13c**) in quantitative yield. IR (neat) 34373 (br), 2979, 2903, 1228 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 10H), 4.57 (m, 4H), 4.08 (m, 4H), 3.86 (s, 1H), 3.59 (m, 3H), 2.89 (s, 1H), 1.89 (m, 4H), 1.32 (t, $J_{HH}$ = 7.1 Hz, 6H); $^{13}$C{$^1$H} NMR ($CDCl_3$) δ 138.0, 137.9, 128.4, 128.0, 127.8, 127.7, 78.6 (d, $J_{CP}$ = 16.3 Hz), 73.4, 72.6, 71.2, 71.1, 61.5 (d, $J_{CP}$ = 6.4 Hz), 23.3 (d, $J_{CP}$ = 4.5 Hz), 21.5 (d, $J_{CP}$ = 142.0 Hz), 16.5 (d, $J_{CP}$ = 6.0 Hz); $^{31}$P{$^1$H} NMR ($CDCl_3$) δ 32.3; HRMS (FAB, $MNa^+$) calcd For $C_{23}H_{33}O_6PNa^+$: 459.1912, Found 459.1906.

**(±) Diethyl (3*R*,4*S*)-(3,5-bis(benzyloxy)-4-hydroxypentylphosphonate (13d).** Vinyl phosphonate (**9d**) (0.1 g 0.230 mmol) was reduced to give (**13d**) in quantitative yield. IR (neat) 3246 (br), 2980, 2905, 1201 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.36-7.29 (m, 10H), 4.53 (m, 4H), 4.10 (m, 4H), 3.84 (m, 1H), 3.59 (m, 3H), 2.58 (d, $J_{HH}$ = 4.6 Hz, 1H), 1.85 (m, 4H), 1.31 (t, $J_{HH}$ = 7.1 Hz, 6H); $^{13}$C{$^1$H} NMR ($CDCl_3$) δ 138.2, 138.0, 128.5, 128.5, 128.0, 127.9, 127.9, 78.6 (d, $J_{CP}$ = 15.7 Hz), 73.5, 72.2, 71.2, 71.0, 61.7 (d, $J_{CP}$ = 6.4 Hz), 22.6 (d, $J_{CP}$ = 4.4 Hz), 20.6 (d, $J_{CP}$ = 142.0 Hz), 16.6 (d, $J_{CP}$ = 6.0 Hz); $^{31}$P{$^1$H} NMR ($CDCl_3$) δ 33.0; HRMS (FAB, $MH^+$) calcd For $C_{23}H_{34}O_6P$: 437.2093, Found 437.2075.

**(±) Diethyl (3*S*,4*S*)-5-(benzyloxy)-4-hydroxy-3-(pentadecyloxy)pentylphosphonate (16a).** Vinyl phosphonate (**15a**) (0.329 g, 0.593 mmol) was reduced to give (**16a**) in quantitative yield. IR (neat) 3370 (br), 2920, 2850, 1228 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.36-7.31 (m, 5H), 4.55 (s, 2H), 4.09 (m, 4H), 3.76 (s, 1H), 3.52 (m, 3H), 3.42 (m, 2H), 2.50 (s, br, 1H), 1.84 (m, 4H), 1.52 (m, 2H), 1.29 (m, 30H), 0.88 (t, $J_{HH}$ = 6.9 Hz, 3H); $^{13}$C{$^1$H} NMR ($CDCl_3$) δ 138.0, 128.6, 127.9, 127.9, 78.9 (d, $J_{CP}$ = 16.7 Hz), 73.6, 71.4, 71.2, 71.1, 61.7 (d, $J_{CP}$ = 6.4 Hz), 32.1, 30.2, 29.8, 29.8, 29.6, 29.5, 26.3, 23.4 (d, $J_{CP}$ = 4.5 Hz , 22.8, 21.5 (d, $J_{CP}$ = 142.3 Hz), 16.6 (d, $J_{C-}$ = 6.0 Hz), 14.3; $^{31}$P{$^1$H} NMR ($CDCl_3$) δ 32.4; HRMS (FAB, $MH^+$) calcd For $C_{31}H_{58}O_6P$: 557.3971, Found 557.3991.

**(±) Diethyl (3*S*,4*S*)-5-(benzyloxy)-4-hydroxy-3-(4-methoxybenzyloxy)pentylphosphonate (16b).** Vinyl phosphonate (**15b**) (0.380 g 1.17 mmol) was reduced to give (**16b**) in quantitative yield. IR (neat) 3346 (br), 2978, 2905, 1609, 1241 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.30-7.24 (m, 5H), 7.20-7.17 (m, 2H), 6.84-6.80 (m, 2H), 4.46 (m, 4H), 4.02 (m, 5H), 3.76 (m, 4H), 3.49 (m,

3H), 2.74 (s, 1H), 1.83 (m, 4H), 1.26 (m, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 159.3, 137.9, 130.2, 129.7, 128.5, 128.4, 127.9, 127.8, 127.8, 113.8, 78.2 (d, $J_{CP}$ = 16.5 Hz), 73.5, 72.3, 71.3, 71.1, 61.6, 61.5, 55.2, 23.3 (d, $J_{CP}$ = 4.6 Hz), 21.5 (d, $J_{CP}$ = 142.0 Hz), 16.5 (d, $J_{CP}$ = 6.0 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 32.3; HRMS (FAB, $MNa^+$) calcd For $C_{24}H_{35}O_7PNa^+$: 489.2018 Found 489.1999.

**(±) Diethyl (3*S*,4*S*)-5-(benzyloxy)-3-(cyclohexylmethoxy)-4-hydroxypentylphosphonate (16c).** Vinyl phosphonate (**15c**) (0.325 g 0.737 mmol) was reduced to give (**16c**) in quantitative yield. IR (neat) 3378 (br), 2919, 2850, 1227 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.38-7.29 (m, 5H), 4.55 (s, 2H), 4.07 (m, 4H), 3.75 (m, 1H), 3.51 (m, 2H), 3.30 (m, 3H), 1.79 (m, 11H), 1.26 (m, 9H), 0.90 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 137.8, 128.3, 127.7, 127.7, 78.7 (d, $J_{CP}$ = 16.5 Hz), 73.3, 71.4, 71.1, 61.5 (d, $J_{CP}$ = 6.4 Hz), 38.3, 30.0 (d, $J_{CP}$ = 2.1 Hz), 26.4, 25.7, 23.2 (d, $J_{CP}$ = 4.5 Hz), 22.2, 21.3 (d, $J_{CP}$ = 148.4 Hz), 16.4 (d, $J_{CP}$ = 5.9 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 33.0; HRMS (FAB, $MNa^+$) calcd For $C_{23}H_{39}O_6PNa^+$: 465.2381, Found 465.2390.

**(±) Diethyl (3*S*,4*S*)-5-(benzyloxy)-4-hydroxy-3-methoxypentylphosphonate (16d).** Vinyl phosphonate (**15d**) (0.3 g 0.837 mmol) was reduced to give (**16d**) in quantitative yield. IR (neat) 3385 (br), 2977, 2864, 1226 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.37-1.25 (m, 5H), 4.53 (s, 2H), 4.06 (m, 4H), 3.76 (m, 1H), 3.51 (m, 2H), 3.38 (s, 3H), 3.39 (m, 1H), 1.83 (m, 4H), 1.29 (t, $J_{HH}$ = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 138.0, 128.6, 127.9, 80.6 (d, $J_{CP}$ = 16.4 Hz), 73.6, 71.3, 71.2, 61.7 (d, $J_{CP}$ = 6.5 Hz), 58.6, 22.9 (d, $J_{CP}$ = 4.6 Hz), 21.3 (d, $J_{CP}$ = 142.4 Hz), 16.6 (d, $J_{CP}$ = 6.0 Hz); δ $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 32.3; HRMS (FAB, $MNa^+$) calcd For $C_{17}H_{29}O_6PNa^+$: 383.1599, Found 383.1595.

**General procedure for cyclization.** To a stirred suspension of sodium hydride (1.1 eq) in dry THF (2 mL/mmol), was added a solution of saturated phosphonate (**13** or **16**) in THF dropwise at ice bath temperature. The reaction mixture was allowed to warm to room temperature and stirring was continued until the reaction was complete (2-3 h). The reaction was quenched by the addition of 10% $NH_4Cl$ and then extracted with EtOAc (three times). The combine organic layer was washed with saturated $NaHCO_3$, brine and dried over anhydrous $Na_2SO_4$. The solution was concentrated under reduced pressure and the pure phostone (**14** or **17**) was isolated by column chromatography ($SiO_2$ 60-80% EtOAc in hexanes).

**(±) (5*S*)-(benzyloxy)-2-ethoxy-6-pentyl-1,2-oxaphosphinane 2-oxide (14b).** Phosphonate (**13b**) (0.319 g, 0.83 mmol) was reacted as above to give phostone (**14b**) (0.204 g, 73%) which was recrystallized from hexane. m.p. 82.6 °C; IR (neat) 2924, 2855, 1243 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.34-7.26 (m, 5H), 4.53 (q, $J_{HH}$ = 12.0 Hz, 2H), 4.11 (m, 3H), 3.39 (m, 1H), 2.39 (m, 1H), 1.89 (m, 5H), 1.49 (m, 2H), 1.33 (t, $J_{HH}$ = 7.0, 3H), 1.24 ( m, 4H), 0.86 (t, $J_{HH}$ = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 137.9, 128.5, 127.9, 127.8, δ 83.2 (d, $J_{CP}$ = 7.9 Hz), 72.0 (d, $J_{CP}$ = 5.3 Hz), 70.8, 60.6 (d, $J_{CP}$ = 6.5 Hz), 32.3 (d, $J_{CP}$ = 7.4 Hz), 31.6, 25.1, 24.8 (d, $J_{CP}$ = 7.8 Hz), 22.7, 17.4 ( d, $J_{CP}$ = 128.3 Hz), 16.6 (d, $J_{CP}$ = 5.6 Hz), 14.2; $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 23.3; HRMS (FAB, $MNa^+$) calcd For $C_{18}H_{29}O_4PNa^+$: 363.1701, Found 363.1704.

**(±) (5S)-5-(benzyloxy)-6-((benzyloxy)methyl)-2-ethoxy-1,2-oxaphosphinane 2-oxide (14c).** Phosphonate (**13c**) (0.430 g, 0.985 mmol) was reacted as above to give phostone (**14c**) as pale-yellow product (0.243 g, 61%). IR (neat) 2976, 2924, 2866, 1242 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.36-7.26 (m, 10H), 4.50 (m, 4H), 4.37 (m, 1H), 4.13 (m, 2H), 3.79 (m 1H), 3.68 (m, 2H), 2.38 (m, 1H), 2.09 (m, 1H),1.89 (m, 2H), 1.35 (t, $J_{HH}$ = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 137.8, 137.7, 128.3, 127.7, 127.6, 127.5, 81.0 (d, $J_{CP}$ = 7.3 Hz), 73.1, 70.3, 69.9 (d, $J_{CP}$ = 5.6 Hz), 69.3 (d, $J_{CP}$ = 9.5 Hz), 60.8 (d, $J_{CP}$ = 6.5 Hz), 24.6 (d, $J_{CP}$ = 8.0 Hz), 17.2 (d, $J_{CP}$ = 120.6 Hz), 16.3 (d, $J_{CP}$ = 2.8 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 23.2; HRMS (FAB, $MH^+$) calcd For $C_{21}H_{28}O_5P$: 391.1674, Found 391.1680

**(±) (5R)-5-(benzyloxy)-6-((benzyloxy)methyl)-2-ethoxy-1,2-oxaphosphinane 2-oxide (14d).** Phosphonate (**13d**) (0.492 g, 1.13 mmol) was reacted as above to give phostone (**14d**) as yellow oil (0.333 g, 75%). IR (neat) 2925, 2866, 1240 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.27-7.14 (m, 10H), 4.48 (m, 4H),

4.10 (m, 3H), 3.66 (m, 3H), 2.25 (m, 1H), 1.82 (m, 3H), 1.26 (t, $J_{HH}$ = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 138.1, 137.6, 128.5 , 128.3, 127.9, 127.8, 127.6, 127.64, 81.5 (d, $J_{CP}$ = 7.5 Hz), 73.6, 72.7 (d, $J_{CP}$ = 5.0 Hz), 72.1, 69.5 (d, $J_{CP}$ = 7.0 Hz), 61.2 (d, $J_{CP}$ = 6.5 Hz), 26.0 (d, $J_{CP}$ = 7.7 Hz), 20.3 ( d, $J_{CP}$ = 128.8 Hz), 16.4 ( d, $J_{CP}$ = 5.7 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 23.6; HRMS (FAB, $MNa^+$) calcd For $C_{21}H_{27}O_5PNa$: 413.1493, Found 413.1515.

**(±) (5S)-6-((benzyloxy)methyl)-2-ethoxy-5-(pentadecyloxy)-1,2-oxaphosphinane 2-oxide (17a).** Phosphonate (**16a**) (0.25 g, 0.45mmol) was reacted as above to give phostone (**17a**) as pale-yellow oil (0.154 g, 67%). IR (neat) 2919, 2850, 1248 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.39-7.28 (m, 5H), 4.55 (q, $J_{HH}$ = 11.7 Hz, 2H), 4.33 (m, 1H), 4.13 (m, 2H), 3.81 (m, 2H), 3.64 (m, 1H) 3.53 (m, 2H), 3.25 (m, 1H), 2.37 (m, 1H), 2.05 (m, 1H), 1.78 (m, 2H), 1.52 (m, 2H), 1.29 (m, 27H), 0.88 (t, $J_{HH}$ = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 138.0, 128.5, 127.9, 127.8, 81.2 (d, $J_{CP}$ = 7.3 Hz), 77.6, 77.2, 76.8, 73.7, 70.7, 70.6, 69.4 (d, $J_{CP}$ = 6.8 Hz), 60.9 (d, $J_{CP}$ = 6.4 Hz), 32.0, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 26.4, 24.7 (d, $J_{CP}$ = 7.9 Hz), 22.8, ), 17.2 (d, $J_{CP}$ = 128.4 Hz), 16.4 (d, $J_{CP}$ = 5.7 Hz), 14.2; $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 23.4; HRMS (FAB, $MH^+$) calcd For $C_{29}H_{52}O_5P$: 511.3552, Found 511.3527.

**(±) (5S)-5-(benzyloxy)-6-((benzyloxy)methyl)-2-ethoxy-1,2-oxaphosphinane 2-oxide (17b).** Phosphonate (**16b**) (0.191 g, 0.40 mmol) was reacted as above to give phostone (**17b**) as pale-yellow oil (0.109 g, 65%). IR (neat) 2928, 2865, 1609, 1297 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.38-1.27 (m, 5H), 7.21 (d, $J_{HH}$ = 8.5 Hz, 2H), 6.85 (d $J_{HH}$ = 8.5 Hz, 2H), 4.50 (m, 5H), 4.13 (m, 2H), 3.79 (s, 3H), 3.75 (m 1H), 3.64 (m, 2H), 2.23 (m, 2H), 1.80 (m, 2H), 1.34 (t, $J_{HH}$ = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 159.3, 137.9, 129.8, 129.4, 128.48, 127.8, 127.8, 113.8, δ 81.2 (d, $J_{CP}$ = 7.3 Hz), 73.6, 70.5, 69.5, 69.4 (d, $J_{CP}$ = 2.1 Hz), 60.9 (d, $J_{CP}$ = 6.5 Hz), 55.3, 17.3 (d, $J_{CP}$ = 128.25 Hz), 16.5 (d, $J_{CP}$ = 6.0 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 23.2; HRMS (FAB, $MNa^+$) calcd For $C_{22}H_{29}O_6PNa^+$: 443.1599, Found 443.1577.

**(±) 6-((benzyloxy)methyl)-5-(cyclohexylmethoxy)-2-ethoxy-1,2-oxaphosphinane 2-oxide (17c).** Phosphonate (**16c**) (0.219 g, 0.494 mmol) was reacted as above to give phostone (**17c**) as pale-yellow oil (0.105 g, 53%). IR (neat) 2919, 2849, 1721, 1245 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.42-7.31 (m, 5H), 4.55 (q, $J_{HH}$ = 11.7 Hz, 2H), 4.37 (m, 1H), 4.17 (m, 2H), 3.85 (m, 1H), 3.68 (m, 1 H), 3.52 (d, $J_{HH}$ = 1.5 Hz, 1H), 3.22 (m, 2H), 2.42 (m, 1H), 2.07 (m, 1H), 1.86 (m, 7H), 1.55 (m 1H), 1.37 (t, $J_{HH}$ = 7.0 Hz, 3H), 1.22 (m, 3H), 0.96 ( 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 138.0, 128.6, 127.9, 81.3 (d, $J_{CP}$ = 7.2 Hz), 75.2, 73.8, 70.7 (d, $J_{CP}$ = 5.6 Hz), 69.5 (d, $J_{CP}$ = 9.6 Hz), 60.9 (d, $J_{CP}$ = 6.5 Hz), 38.3, 30.2 (d, $J_{CP}$ = 1.2 Hz), 26.7, 26.0, 24.5 (d, $J_{CP}$ = 8.0 Hz), 17.3 (d, $J_{CP}$ = 128.5 Hz), 16.6 (d, $J_{CP}$ = 5.8 Hz), 16.4; $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 23.5; HRMS (FAB, $MNa^+$) calcd For $C_{21}H_{33}O_5PNa$: 419.1963 Found 419.1974

**(±) 6-((benzyloxy)methyl)-2-ethoxy-5-methoxy-1,2-oxaphosphinane 2-oxide (17d).** Phosphonate (**16d**) (0.216 g, 0.603 mmol) was reacted as above to give phostone (**17d**) as pale-yellow oil (0.121 g, 64%). IR (neat) 2927, 2867, 1244 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 4.55 (q, $J_{HH}$ = 11.8 Hz, 2H), 4.31 (m, 1H), 4.10 (m, 2H), 3.69 (m, 2H), 3.41 (m, 1H), 3.20 (s, 3H), 2.39 (m, 1H), 1.96 (m, 1H), 1.76 (m, 2H), 1.31 (t, $J_{HH}$ = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 138.0, 128.5, 127.7, 127.8, 81.0 (d, $J_{CP}$ = 7.3 Hz), 77.7, 77.2, 76.8, 73.6, 72.2 (d, $J_{CP}$ = 5.6 Hz), 69.4 (d, $J_{CP}$ = 9.4 Hz), 60.9 (d, $J_{CP}$ = 6.5 Hz), 56.8, 23.8 (d, $J_{CP}$ = 8.0 Hz), 17.1 (d, $J_{CP}$ = 128.2 Hz), 16.5 (d, $J_{CP}$ = 5.7 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 23.1; HRMS (FAB, $MNa^+$) calcd For $C_{15}H_{23}O_5PNa^+$: 337.1180 Found 337.1182.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

$^1H$, $^{13}C$ and $^{31}P$ NMR spectra for all compounds, X-ray crystallographic data (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENT

The project described was supported by a grant from the National Science Foundation (CHE-1465196). We are also grateful to the National Science Foundation for grants to purchase the NMR spectrometers (CHE-9974801 and 0959360), the x-ray diffractometer (CHE-0420497) and the mass spectrometer (CHE-9708640) used in this project. We thank Mahesh Paudel, Mercy Kiiru and Andrew Kamadulski for some preliminary studies.

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