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(*E*) Enol ethers from the stereoselective reduction of α-alkoxy-β-ketophosphonates and Wittig type reaction

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When α-alkoxy-β-ketophosphonates, prepared by the Rh(II) mediated insertion reaction of α-diazo-β-ketophosphonates into the OH bond of primary alcohols, were reduced either by $NaBH_4$ in the presence of $CaCl_2$ or by DIBAL, they respectively gave the corresponding *anti* or *syn* stereomeric hydroxyphosphonates with pronounced to complete stereoselectivity. Submitted to the action of potassium *tert*-butoxyde, *syn* isomers led to the corresponding pure (*E*) enol ethers in moderate to good yields. Under the same conditions *anti* isomers led to a mixture of (*Z*) and (*E*) enol ethers in rather poor yields. The sequence was applied to the preparation of some allyl-vinyl ethers with a (*E*) configuration for the vinylic double bond.

α-alkoxy-β-ketophosphonates, reduction, insertion, rhodiocarbenoids, Wittig-Wadsworth-Emmons, enol ethers

1 Introduction

O-alkyl enol ethers are significant intermediates in organic synthesis, which are used in various cycloaddition reactions and Claisen rearrangement [1]. However, stereoselective methods for their preparation are relatively rare [2]. Several years ago, Kluge *et al.* [3] and Warren *et al.* [4] simultaneously reported the preparation of some alkyl enol ethers by performing a Wittig type reaction from α-alkoxy-β-hydroxy diethylphosphonates or diphenylphosphine oxides, respectively. The latter compounds resulted from the condensation of the appropriate anions on aldehydes or ketones and consisted of a mixture of stereoisomers leading to a mixture of (*Z*) and (*E*) enol ethers. However, it was shown by Warren et al. that when the Wittig-Horner reaction was carried out on pure *anti* or *syn* β-hydroxy-diphenylphosphine oxides, it respectively led to the corresponding pure (*E*) or (*Z*) enol ethers [5]. To our knowledge the same study has not been conducted on the Wadsworth-Emmons reaction with the *anti* and *syn* α-alkoxy-β-hydroxyphosphonates. As part of our continuing interest in the chemistry of α-diazo-β-ketophosphonates [6], we have explored the use of these compounds as starting materials for the stereoselective preparation of enol ethers and here we report our results.

The route that we envisaged for the synthesis of target compounds is depicted in Scheme 1. The insertion reaction of rhodio-carbenoids generated from α-diazo-β-ketophosphonates **2** into the OH bond of alcohols would afford the alkoxy-ketophosphonates **3**. The stereoselective reduction of compounds **3** would lead to either the hydroxy-phosphonates **4**-*anti* or their stereoisomers **4**-*syn*, which submitted to the action of a base would respectively give the (*Z*) or (*E*) enol ethers **5** [7].

2 Experimental

2.1 General experimental

Solvents were distilled and dried before use: diethyl ether

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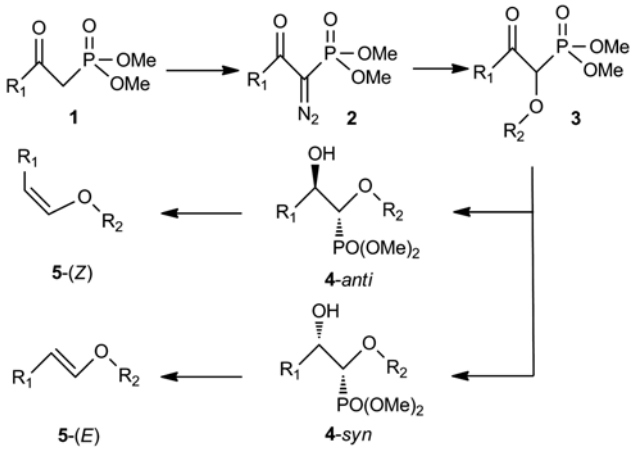


Scheme 1 Envisaged sequence for the stereoselective preparation of (*Z*) and (*E*) enol ethers from alkoxy-ketophosphonates **3** (**3** and **4** are racemic mixtures).

from potassium hydroxide, pentane from phosphorus pentoxide, tetrahydrofuran from sodium benzophenone ketyl, and pyridine from calcium hydride. Toluene was dried over sodium. Organic solutions were dried over anhydrous sodium sulfate. The reactions were performed under a constant flow of nitrogen. The reactions were monitored by TLC. on Silica Gel 60 F_{254} (Merck) and detection was carried out by charring with a 5% phosphomolybdic acid solution in ethanol containing 10 % of H_2SO_4. Silica gel (Kieselgel 60, 70–230 mesh ASTM, Merck) was employed for column chromatographies. Melting points were determined on a Kofler block apparatus. IR spectra were recorded on a Perkin-Elmer 1310 spectrometer and are expressed in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker AC200 (200/50.32 and 300 MHz) spectrometer. All NMR recordings were referenced to $CHCl_3$ resonances (7.26 and 77.0 ppm). Chemical shifts are given in ppm. Coupling constants are expressed in Hertz and splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; M, massif; p, pseudo. Multiplicity (^{13}C NMR) was determined by DEPT sequences. The HR mass spectra were recorded with a ThermoFinnigan spectrometer. Elemental analyses were performed by "Service Central de Microanalyses du CNRS" 69 Solaize (France).

2.2 Synthesis of α-diazo-β-ketophosphonates (2a) and (2b)

Dimethyl-(2-oxo-hexadecyl)phosphonate ***(1a)***

To a solution of trimethylphosphonate (40 mmol) in 15 mL of anhydrous THF cooled at −60 °C was added 14.6 mL of a 2.5 M solution of *n*-butyllithium in hexanes (36.5 mmol). The reaction mixture was allowed to warm to −30 °C and stirred at this temperature for 15 m before the addition of a solution of 4.7 g (18.3 mmol) methyl pentadecanoate in pentane (40 mL). At the end of the addition the reaction mixture was stirred for 2 h at room temperature and then hydrolyzed with saturated aqueous ammonium chloride solution (20 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried. After solvent evaporation in vacuo the residue was purified by chromatography (ethyl acetate/pentane: 10/3) to give first (R_f = 0.94) 1g of unreacted starting ester, and then (R_f = 0.44) **1a** (4.74 g, 74%). IR: 1710. ^1H NMR: δ 0.88 (t, J = 6.4 Hz, 3H), 1.25 (m, 22H), 1.58 (quint, J = 6.7 Hz, 2H), 2.6 (t, J = 7.3 Hz, 2H), 3.08 (d, $^2J_{H\text{-}P}$ = 22.7 Hz, 2H), 3.79 (d, $^3J_{H\text{-}P}$ = 11.2 Hz, 6H). ^{13}C NMR: δ 14.13, 22.72, 23.43, 28.97, 29.39, 29.41, 29.50, 29.64, 29.69, 29.71, 32.0, 41.25 (d, $^1J_{C\text{-}P}$ = 128.3 Hz), 44.3 (d, $^3J_{C\text{-}P}$ = 1.5 Hz), 53.0 (d, $^2J_{C\text{-}P}$ = 6.5 Hz), 202.01 (d, $^2J_{C\text{-}P}$ = 6.3 Hz). Anal. calcd for $C_{18}H_{37}O_4P_1$: C, 61.89; H, 10.60; found: C, 61.79; H, 10.68.

*Dimethyl-(1-diazo-2-oxo-hexadecyl) phosphonate (**2a**)*

To a dispersion of NaH (0.18 g, 4.54 mmol) (washed twice with 30 mL of dry pentane) in THF (30 mL) at 0 °C was added a solution of **1a** (1.32 g, 3.8 mmol). The reaction mixture was stirred for 10 min at room temperature, and then a solution of tosylazide (*Caution*: tosylazide is highly toxic and suspected of being explosive) [8] (0.97 g, 4.93 mmol) in THF (20 mL) was added and the stirring was pursued for 30 min. Brine (20 mL) was added and the solvent was evaporated in vacuo. The residue was extracted with EtOAc (2 × 50 mL) and the organic layer was washed with 10% NaOH aq (20 mL), water (20 mL) and dried. After solvent evaporation the crude diazo was chromatographed (diethylether/pentane; 3/1) to give 1.35 g (95%) of pure **2a**. IR: 2120, 1650. ^1H NMR: δ 0.88 (t, J = 6.8 Hz, 3H), 1.25 (m, 22H), 1.63 (m, 2H), 2.53 (t, J = 7.5 Hz, 2H), 3.84 (d, $^3J_{H\text{-}P}$ = 12 Hz, 6H). ^{13}C NMR: δ 13.85, 22.34, 23.90 (10C), 31.22, 39.45, 53.52 (2d, $^2J_{C\text{-}P}$ = 5.6 Hz), 62.85 (d, $^1J_{C\text{-}P}$ = 220.6 Hz), 192.75 (d, $^2J_{C\text{-}P}$ = 13.0 Hz). Anal. calcd for $C_{18}H_{35}N_2O_4P_1$: C, 57.56; H, 9.33. Found: C, 58.19; H, 9.82.

*Dimethyl-(1-diazo-2-oxo-propyl)phosphonate (**2b**)*

To a solution of commercially available dimethyl-(2-oxo-propyl)phosphonate **1b** (8.37 mmol) in acetonitrile (5 mL) was added first tosylazide (2.14 g, 10.9 mmol) and then potassium carbonate (1.62 g, 11.7 mmol). The reaction mixture was stirred at room temperature for 2 h and then a saturated aqueous ammonium chloride solution (15 mL) was added. After extraction (EtOAc, 2 × 30 mL), the combined organic layers were dried and the solvent was evaporated in vacuo. The crude product was chromatographed (EtOAc) to afford 1.56 g (97%) of **2c** as a yellow oil. IR: 1650, 2120. ^1H NMR: δ 2.27 (s, 3H), 3.82 (d, $^3J_{H\text{-}P}$ = 12 Hz, 6H). ^{13}C NMR: δ 27.15 (d, $^4J_{C\text{-}P}$ = 1.0 Hz), 53.64 (d, $^2J_{C\text{-}P}$ = 5.5 Hz), 63.49 (d, $^1J_{C\text{-}P}$ = 220.2 Hz), 189.8 (d, $^2J_{C\text{-}P}$ = 13.0 Hz).

2.3 Preparation of α-alkoxy-β-ketophosphonates (3a–k) and allylic esters (6f–h)

To a solution of alcohol (5.34 mmol) in dry toluene (20 mL) was added a catalytic amount of $Rh_2(OAc)_4$ (0.1 mol%) at

80 °C and then, over 10 min, a solution of diazo **2a** or **2b** (2.67 mmol) in 10 mL of toluene. The reaction mixture was maintained at 80 °C for an additional hour. The solvent was evaporated in vacuo and the crude product was chromatographed.

*Dimethyl-1-(benzyloxy)-2-oxo-hexadecylphosphonate (**3a**)*

Chromatography (Et_2O/pentane; 2/1). Yield: 77% as green oil. IR (CCl_4): 1715. ^{1}H NMR: δ 0.88 (t, J = 6.7 Hz, 3H), 1.25 (m, 22H), 1.67 (m, 2H), 2.62 (d x sext, J = 17.8 Hz, J = 7.3 Hz, 2H), 3.80 (d, $^2J_{H\text{-}P}$ = 10.9 Hz, 6H), 4.35 (d, $^1J_{H\text{-}P}$ = 19.6 Hz, 1H), 4.78 (d, $^3J_{H\text{-}P}$ = 11.9 Hz, 2H), 7.35 (s, 5H arom). ^{13}C NMR: δ 14.14, 22.71, 39.86, 53.94 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 54.06 (d, $^2J_{C\text{-}P}$ = 6.7 Hz), 74.3 (d, $^2J_{C\text{-}P}$ = 10.0 Hz), 81.41 (d, $^1J_{C\text{-}P}$ = 150.3 Hz), 128.42, 128.47, 128.64, 136.19, 205.8.

*Dimethyl-1-(diisopropylideneglycerol)-2-oxo-hexadecylphospho-nate (**3b**)*

IR (CCl_4): 1715. ^{1}H NMR: δ 0.86 (t, J = 3.0 Hz, 3H), 1.23 (m, 30H), 2.7 (t, J = 7.0 Hz, 2H), 3.83 (d, ^3J = 11.0 Hz, 6H), 3.50–4.40 (m, 7H), 4.50 (d, $J_{H\text{-}P}$ = 20.0 Hz, 1H). ^{13}C NMR: δ 14.15, 22.73, 25.33, 25.71, 26.77, 29.56, 31.97, 33.09, 53.70 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 54.38 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 66.35, 70.81 (d, $^2J_{C\text{-}P}$ = 5.2 Hz), 70.91 (d, $^2J_{C\text{-}P}$ = 5.3 Hz), 73.49 (d, $J_{C\text{-}P}$ = 2.63 Hz), 74.55, 74.97 (d, $J_{C\text{-}P}$ = 2.32 Hz), 78.28 (d, $^1J_{C\text{-}P}$ = 159.8 Hz), 83.54 (d, $^1J_{C\text{-}P}$ = 150.2 Hz), 109.66. Anal. calcd for $C_{24}H_{45}O_7P_1$: C 60.12, H 9.81, P 6.68, O 23.38; found: C 60.53, H 9.88.

*Dimethyl-1-(benzyloxy)-2-oxo-propylphosphonate (**3c**)*

IR (CCl_4): 1715. ^{1}H NMR: δ 2.29 (s, 3H), 3.81 (d, $^3J_{H\text{-}P}$ = 11.0 Hz, 3H), 3.80 (d, J = 11.0 Hz, 3H), 4.33 (d, J = 20.0 Hz, 1H), 4.64 and 4.74 (AB, J = 12.0 Hz, 2H), 7.35 (s, 5H arom.). ^{13}C NMR: δ 27.47, 54.00 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 54.04 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 74.35 (d, $^2J_{C\text{-}P}$ = 10.0 Hz), 81.73 (d, $^1J_{C\text{-}P}$ = 150.0 Hz), 128.37, 128.48, 128.64, 136.1, 203.75. Anal. calcd for $C_{12}H_{17}O_5P_1$: C, 52.75; H, 6.23; found: C, 52.40; H, 6.12.

*Dimethyl-1-(trans-hex-2-enyloxy)-2-oxo-propylphosphonate (**3d**)*

Chromatography (EtOAc). Yield: 81% as green oil. IR (CCl_4): 1720. ^{1}H NMR: δ 0.82 (t, J = 7.4 Hz, 3H), 1.32 (m, 2H), 1.95 (m, 2H), 2.24 (s, 3H), 3.76 (2d, $^3J_{H\text{-}P}$ = 10.8 Hz, 6H), 4.02 (m, J = 6.6 Hz, 2H), 4.26 (d, $^1J_{H\text{-}P}$ = 20.2 Hz, 1H), 5.55 (m, J_{trans} = 15.3 Hz, J_{cis} = 6.5 Hz, 2H). ^{13}C NMR: δ 13.54. 21.96, 27.39, 34.21, 53.95 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 53.90 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 73.28, 81.27 (d, $^1J_{C\text{-}P}$ = 151.0 Hz), 124.53, 137.57, 204.17. HRMS (FAB) [M^+] calcd for $C_{11}H_{21}O_5P_1$: 264.1126; found: 264.1127.

*Dimethyl-1-(cis-hex-2-enyloxy)-2-oxo-propylphosphonate (**3e**)*

Chromatography (EtOAc). Yield: 83% as green oil. IR (CCl_4): 1720. ^{1}H NMR: δ 0.83 (t, J = 7.4 Hz, 3H), 1.33 (m, 2H), 2.26 (s, 3H), 1.96 (m, 2H), 3.78 (2d, $^3J_{H\text{-}P}$ = 10.8 Hz, 6H), 4.16 (m, J = 6.4 Hz, 2H), 4.25 (d, $^1J_{H\text{-}P}$ = 19.9 Hz, 1H), 5.56 (m, J_{cis} = 11.0 Hz, 2H). ^{13}C NMR: δ 13.62, 22.55, 29.49, 27.36, 53.96 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 54.02 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 67.82, 81.72 (d, $^1J_{C\text{-}P}$ = 151.0 Hz), 124.11, 136.16, 204.17. HRMS (FAB) [M^+] calcd for $C_{11}H_{21}O_5P_1$: 264.1126; found: 264.1124.

*Dimethyl-1-(1-methylprop-2-enyloxy)-2-oxo-propylphosphonate (**3f**)*

Chromatography (EtOAc). Yield: 21% as a green oil (mixture of diastereoisomers 55/45). IR (CCl_4): 1720. Major isomer (55%) ^{1}H NMR: δ 1.34 (d, J = 6.3 Hz, 3H), 2.31 (s, 3H), 3.83 (2d, $^2J_{H\text{-}P}$ = 10.8 Hz, 6H), 4.12 (m, J = 8.0 Hz, 1H), 4.41 (d, $^1J_{H\text{-}P}$ = 21.9 Hz, 1H), 5.00–5.40 (m, 2H), 5.79–6.00 (m, 1H). ^{13}C NMR: 21.36, 27.45, 54.15 (d, $^2J_{C\text{-}P}$ = 6.4 Hz), 79.06, 80.02 (d, $^1J_{C\text{-}P}$ = 151.7 Hz), 118.85, 137.81, 204.59. Minor isomer (45%) ^{1}H NMR: δ 1.42 (d, J = 6.4 Hz, 3H), 2.26 (s, 3H), 3.75 (q, J = 8.0 Hz, 1H), 3.83 (2d, $^2J_{H\text{-}P}$ = 10.8 Hz, 6H), 4.27 (d, $^1J_{H\text{-}P}$ = 19.3 Hz, 1H), 5.00–5.40 (m, 2H), 5.5–5.78 (m, 1H). ^{13}C NMR: δ 21.36; 27.45, 53.87 (d, $^2J_{C\text{-}P}$ = 6.4 Hz), 79.29, 81.32 (d, $^1J_{C\text{-}P}$ = 97.9 Hz), 118.71, 138.38, 204.43. HRMS (FAB) [(M+H)$^+$] calcd for $C_9H_{17}O_5P_1$: 237.0892; found: 237.0894.

*2-Dimethylphosphonate-1-methylprop-2-enyl propanoate (**6f**)*

Yield: 17% as green oil. IR (CCl_4): 1735. ^{1}H NMR: δ 1.34 (d, J = 6.5 Hz, 3H), 1.46 (dd, $^2J_{H\text{-}P}$ = 18.4 Hz, J = 6.6 Hz, 3H), 3.1 (qd, $^1J_{H\text{-}P}$ = 23.4 Hz, J = 7.3 Hz, 1H), 3.78 (m, 1H), 3.78 (2d, $^3J_{H\text{-}P}$ = 10.8 Hz, 6H), 5.14–5.43 (m, 2H), 5.76–5.94 (m, 1H). HRMS (FAB) [(M+H)$^+$] calcd for $C_9H_{17}O_5P_1$: 237.0892; found: 237.0894.

*Dimethyl-1-(1-ethylprop-2-enyloxy)-2-oxo-propylphosphonate (**3g**)*

Chromatography (EtOAc). Yield: 19% as green oil (mixture of diastereoisomers 55/45). IR (CCl_4): 1720. Major isomer (55%). ^{1}H NMR: δ 0.91 (t, J = 7.4 Hz, 3H), 1.65 (m, 2H), 2.29 (s, 3H), 3.77 (m, 1H), 3.79 (d, $^3J_{H\text{-}P}$ = 10.8 Hz, 6H), 4.44 (d, $^1J_{H\text{-}P}$ = 21.9 Hz, 1H), 5.04–5.34 (m, 2H), 5.75–5.80 (m, 1H). ^{13}C NMR: δ 9.63, 27.55, 28.25, 54.15 (d, $^2J_{C\text{-}P}$ = 7.0 Hz), 78.31, 82.53 (d, $^1J_{C\text{-}P}$ = 153.8 Hz), 120.22, 136.49, 204.53 (d, ^2J = 5.7 Hz). Minor isomer ^{1}H NMR: δ 0.91 (t, J = 7.4 Hz, 3H), 1.65 (m, 2H), 2.29 (s, 3H), 3.77 (m, 1H), 3.79 (d, $^3J_{H\text{-}P}$ = 10.8 Hz, 6H), 4.44 (d, $^1J_{H\text{-}P}$ = 21.9 Hz, 1H), 5.04–5.34 (m, 2H), 5.75–5.80 (m, 1H). ^{13}C NMR: 9.53, 27.71, 27.96, 53.71 (d, $^2J_{C\text{-}P}$ = 7.0 Hz), 77.36, 82.53 (d, $^1J_{C\text{-}P}$ = 96.2 Hz), 119.97, 137.12, 204.49 (d, $^2J_{C\text{-}P}$ = 4.9 Hz). HRMS (FAB) [(M+H)$^+$] calcd for $C_{10}H_{19}O_5P$: 251.1048; found: 251.1047.

*2-Dimethylphosphonate-1-ethylprop-2-enyl propanoate (**6g**)*

Yield: 18% as green oil. IR (CCl_4): 1735. ^{1}H NMR: δ 1.34

(t, J = 7.3 Hz, 3H), 1.45 (dd, $^3J_{H\text{-}P}$ = 18.3, J = 7.3 Hz, 3H), 1.76 (q, J = 7.2 Hz, 2H), 3.07 (qd, $^1J_{H\text{-}P}$ = 23.4 Hz, J = 7.3 Hz, 1H), 3.78 (2d, $^2J_{H\text{-}P}$ = 10.8 Hz, 6H), 3.86 (m, 1H), 5.15–5.47 (m, 2H), 5.68–5.85 (m, 1H). ^{13}C NMR (mixture of diastereoisomers 55/45). Major isomer: δ 9.25, 11.63 (d, J = 1.9 Hz), 27.15, 39.07 (d, $^1J_{H\text{-}P}$ = 33.9 Hz), 53.23, 77.40, 117.23, 135.81, 168.85. Minor isomer: δ 9.31, 11.69 (d, J = 1.9 Hz), 27.15, 39.02 (d, J = 33.9 Hz), 53.35, 77.31, 117.18, 135.68, 168.95. HRMS (FAB) [(M+H)$^+$] calcd for $C_{10}H_{19}O_5P$: 251.1048; found: 251.1049.

Dimethyl-1-(2,2-methylprop-2-enyloxy)-2-oxo-propylphosphonate (***3h***)

Chromatography (EtOAc). Yield: 6% as green oil. ^{1}H NMR: δ 1.27 (s, 3H), 1.35 (s, 3H), 2.31 (s, 3H), 3.83 (2d, $^3J_{H\text{-}P}$ = 10.8 Hz, 6H), 4.32 (d, $^1J_{H\text{-}P}$ = 22.3 Hz, 1H), 5.19 (m, 2H), 5.80 (dd, $^3J_{trans}$ = 17.6 Hz, J_{cis} = 10.3 Hz, 1H). HRMS (FAB) [(M +H)$^+$] calcd for $C_{10}H_{19}O_5P_1$ 251.1048; found: 251.1041.

2-Dimethylphosphonate-2,2-dimethylprop-2-enyl propanoate (***6h***)

Yield: 27% as green oil. IR (CCl_4): 1735. ^{1}H NMR: δ 1.46 (dd, $^2J_{H\text{-}P}$ = 18.1 Hz, J = 7.3 Hz, 3H), 1.63 (s, 6H), 3.1 (qd, $^1J_{H\text{-}P}$ = 22.5 Hz, J = 7.3 Hz, 1H), 3.78 (2d, $^3J_{H\text{-}P}$ = 10.9 Hz, 6H), 5.07–5.26 (m, 2H), 6.07 (dd, J_{trans} = 17.4 Hz, J_{cis} = 10.1 Hz, 1H). ^{13}C NMR: δ 11.55, 26.26, 26.31, 39.60 (d, $^1J_{C\text{-}P}$ = 133.0 Hz), 53.23 (d, J = 6.4 Hz), 82.17, 113.11, 141.98, 168.22. HRMS (FAB) [(M+H)$^+$] calcd for $C_{10}H_{19}O_5P_1$: 251.1048; found: 251.10413.

Dimethyl-1-(prop-2-enyloxy)-2-oxo-hexadecylphosphonate (***3i***)

Chromatography (Et_2O). Yield: 62% as green oil. IR (CCl_4): 1715. ^{1}H NMR: δ 0.88 (t, 3H), 1.25 (s, 22H), 1.58 (m, 2H), 2.64 (m, 2H), 2.64 (m, 2H), 3.80 (qt, J = 22.0 Hz, J = 12.0 Hz, 2H), 3.83 (2d, $^3J_{H\text{-}P}$ = 10.8 Hz, 6H), 4.35 (d, J = 19.8 Hz, 1H), 5.31 (m, 2H), 5.91 (ddt, J_{trans} = 17.7 Hz, J_{cis} = 10.2 Hz, J = 5.8 Hz, 2H). ^{13}C NMR: δ 4.09, 22.09, 22.67, 23.127, 29.40, 31.91, 39.77, 53.91 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 53.98 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 73.46, 81.54 (d, $^1J_{C\text{-}P}$ = 150.7 Hz), 119.34, 132.98, 205.96. HRMS (FAB) [(M+H)$^+$] calcd for $C_{21}H_{41}O_5P_1$: 405.2769; found: 405.2769.

Dimethyl-1-(hex-2-enyloxy)-2-oxo-hexadecylphosphonate (***3j***)

Chromatography (Et_2O). Yield: 71% as a green oil. IR (CCl_4): 1720. ^{1}H NMR: δ 0.86 (m, 6H), 1.41 (m, 26H), 2.01 (m, 2H), 2.64 (m, 2H), 3.80 (2d, $^3J_{H\text{-}P}$ = 10.8 Hz, 6H), 4.32 (d, $^1J_{H\text{-}P}$ = 20.0 Hz, 1H), 4.65 (m, 2H), 5.62 (ddt, J_{trans} = 15.5 Hz, J_{cis} = 10.3 Hz, J = 6.5 Hz, 2H), ^{13}C NMR: δ 13.66, 14.13, 22.09, 22.71, 23.127, 29.4, 34.34, 39.85, 53.87 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 54.01 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 73.33, 80.94 (d, $^1J_{C\text{-}P}$ = 150.8 Hz), 124.69, 137.58, 206.34. HRMS (FAB) [(M+H)$^+$] calcd for $C_{24}H_{47}O_5P_1$: 447.3239; found, 447.3239.

2.4 Reduction of 3a-c by $NaBH_4/CaCl_2$

To a solution of ***3*a–c** (0.22 mmol) in dry MeOH (5 mL) at −10 °C was added $CaCl_2$ (0.22 mmol). The reaction mixture was stirred for 10 min and $NaBH_4$ (0.24 mmol) was added. The stirring continued for an extra 1.5 h at −10 °C. Then the reaction mixture was allowed to warm at 0 °C and acetic acid was added dropwise (pH 4) and the stirring was continued for an additional 15 min. Then $NaHCO_3$ 10% aq was added (pH 7). After partial evaporation, the solvent was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried and concentrated in vacuo.

Dimethyl-1-(benzyloxy)-2-hydroxy-hexadecaylphosphonate (***4a***)

Yield: 86%. (mixture of diastereoisomers. *anti*/*syn* : 90/10). Major isomer (**4a**-*anti*) ^{1}H NMR: δ 0.88 (t, J = 6.4 Hz, 3H), 1.25 (m, 24H), 1.35–1.7 (m, 3H), 2.67 (s, 1H, OH), 3.68 (q, J = 3.5 Hz, 1H), 3.81 (d, $^3J_{H\text{-}P}$ = 10.6 Hz, 3H), 3.85 (d, $^3J_{H\text{-}P}$ = 10.6 Hz, 3H), 4.60 and 4.88 (AB, J = 11.3 Hz, 2H), 7.32 (s, 5H arom.). ^{13}C NMR: δ 13.93, 22.51, 25.56, 29.18–29.51, 31.75, 33.29 (d, J = 9.0 Hz), 52.78 (d, J = 7.0 Hz), 52.91 (d, J = 7.0 Hz), 70.47 (d, J = 2.7 Hz), 74.40 (d, J = 2.3 Hz), 76.87 (d, $^1J_{C\text{-}P}$ = 160.0 Hz), 128.06, 128.29, 128.42, 136.76. Minor isomer (**4a**-*syn*) ^{1}H NMR: δ 0.88 (t, J = 6.4 Hz, 3H), 1.25 (m, 24H), 1.41 (m, 2H), 1.72 (m, 1H), 3.09 (s, 1H, OH), 3.63 (dd, $J_{H\text{-}P}$ = 6.9 Hz, J = 5.0 Hz, 1H), 3.79 (d, $^3J_{H\text{-}P}$ = 12.5 Hz, 3H), 3.84 (d, J = 12.3 Hz, 3H), 4.59 and 4.80 (AB, J = 11.3 Hz, 2H), 7.30 (s, 5H arom.). ^{13}C NMR: δ 13.95, 22.52, 25.22, 29.19–29.52, 31.76, 32.59 (d, J = 8.0 Hz), 52.93 (d, $^2J_{C\text{-}P}$ = 7.0 Hz), 53.07 (d, $^2J_{C\text{-}P}$ = 7.0 Hz), 70.82 (d, J = 2.7 Hz), 74.40 (d, J = 3.3 Hz), 78.22 (d, $^1J_{C\text{-}P}$ = 157.0 Hz), 128.0, 128.19, 128.31, 136.85. Anal. calc for $C_{25}H_{45}O_5P$: C, 65.64; H, 9.85; found: C, 65.41; H, 9.54. (mixture of 4a-*syn* and 4a-*anti*).

Dimethyl-1-(diisopropylideneglycerol)-2-hydroxy-hexadecylphosphonate (***4b***)

Yield: 78%. (mixture of diastereoisomers. *anti*/*syn*: 95/5). Major isomer (**4b**-*anti*) mp 59 °C. IR (CCl_4): 3410. ^{1}H NMR: δ 0.88 (t, J = 6.4 Hz, 3H), 1.25 (s, 24H), 1.35 (s, 3H), 1.43 (s, 3H), 1.58 (m, 2H), 3.05 (m, OH), 3.58 (m, 2H), 3.79 (d, $^3J_{H\text{-}P}$ = 10.6 Hz, 3H), 3.82 (d, $^3J_{H\text{-}P}$ = 10.6 Hz, 3H), 3.74–3.89 (m, H+2H), 4.06 (q, $J_{H\text{-}P}$ = 8.4 Hz, 1H), 4.30 (dt, J = 4.1 Hz, J = 5.7 Hz, 1H). ^{13}C NMR: δ 14.15, 22.73, 25.33, 25.71, 26.77, 29.56, 31.97, 33.09, 53.30 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 53.98 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 66.35, 70.81 (d, $^2J_{C\text{-}P}$ = 5.2 Hz), 70.91 (d, $^2J_{C\text{-}P}$ = 5.3 Hz), 73.49 (d, $J_{C\text{-}P}$ = 2.63 Hz), 74.55, 74.97 (d, $J_{C\text{-}P}$ = 2.32 Hz), 78.28 (d, $^1J_{C\text{-}P}$ = 159.8 Hz), 81.45 (d, $^1J_{C\text{-}P}$ = 159.9 Hz), 109.66. Minor isomer (**4b**-*syn*). IR (CCl_4): 3440. ^{1}H NMR: δ 0.88 (t, J = 6.4 Hz, 3H), 1.25 (s, 24H), 1.35 (s, 3H), 1.43 (s, 3H), 1.50 (m, 2H), 3.18 (m, OH), 3.58 (m, 2H), 3.79 (d, $^3J_{H\text{-}P}$ = 10.6 Hz, 3H), 3.82 (d, $^3J_{H\text{-}P}$ = 10.6 Hz, 3H), 3.74–3.89 (m, 9H), 4.06 (q, $J_{H\text{-}P}$ = 8.4 Hz, 1H),

4.30 (dt, J = 4.1 Hz, J = 5.7 Hz, 1H). ^{13}C NMR: δ 14.13, 22.71, 25.30, 25.58, 26.75, 29.51, 31.96, 33.01, 53.33 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 53.57 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 66.49, 70.93 (d, $^{2}J_{C\text{-}P}$ = 4.1 Hz), 70.91 (d, $^{2}J_{C\text{-}P}$ = 3.4 Hz), 73.49 (d, $J_{C\text{-}P}$ = 3.4 Hz), 74.57, 74.48 (d, $J_{C\text{-}P}$ = 3.3 Hz), 79.00 (d, $^{1}J_{C\text{-}P}$ = 158.9 Hz), 82.14 (d, $^{1}J_{C\text{-}P}$ = 158.2 Hz), 109.57. Anal. calcd for $C_{24}H_{47}O_7P_1$: C 59.87, H 10.19; found: C, 59.76; H 10.09.

*Dimethyl-1-(benzyloxy)-2-hydroxy-propylphosphonate (**4c**)*

Yield: 97% (*anti*/*syn* : 65/35). Major isomer (**4c**-*anti*) IR: 3400. ^{1}H NMR: δ 1.25 (dd, J = 6.4 Hz, J = 0.3 Hz, 3H), 3.02 (s, 1H; OH), 3.60 (dd, J = 6.1 Hz, J = 4.7 Hz, 1H), 3.78 (d, J = 7.8 Hz, 3H), 3.83 (d, J = 7.8 Hz, 3H), 4.07 (m, 1H), 4.60 (ABX, J = 11.3 Hz, J = 1.3 Hz, 1H), 4.88 (AB, 1H), 7.36 (m, 5H arom). ^{13}C NMR: δ 19.40 (d, J = 7.6 Hz), 53.01 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz), 53.15 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz), 66.80 (d, J = 4.5 Hz), 74.84 (d, J = 2.5 Hz), 78.76 (d, $^{1}J_{C\text{-}P}$ = 160.0 Hz), 128.27, 128.50, 128.52, 136.95. Anal. calcd for $C_{12}H_{19}O_5P_1$: C, 52.36; H, 6.91; found: C, 52.37; H, 6.99. Minor isomer (4c-*syn*): IR (CCl_4): 3400. ^{1}H NMR: δ 1.30 (d, J = 6.4 Hz, 3H), 3.49 (s, 1H; OH), 3.63 (dd, J = 6.4 Hz, J = 5.8 Hz, 1H), 3.77 (d, J = 11.0 Hz, 3H), 3.82 (d, J = 11.0 Hz, 3H), 4.10 (m, 1H), 4.62 (ABX, J = 11.3 Hz, J = 1.1 Hz, 1H), 4.81 (AB, 1H), 7.34 (m, 5H arom.).^{13}C NMR: 19.31 (d, J = 8.8 Hz), 52.80 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz), 53.60 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz), 67.30 (d, J = 4.5 Hz), 74.71 (d, J = 2.5 Hz), 74.18 (d, $^{1}J_{C\text{-}P}$ = 157.0 Hz), 128.19, 128.34, 128.49, 137.04. Anal. calcd for $C_{12}H_{19}O_5P_1$: C, 52.36; H, 6.91; found: C, 52.56; H, 7.03.

2.5 Reduction of 3a-e and 3i–j by DiBAL

To a solution of ethers **3a–e** and **3i–j** (1 mmol) in anhydrous THF (35 mL) at −78 °C was added a solution of DiBAL 1.6M in toluene (2 mL, 3.2 mmol). 3 h later, the reaction mixture was allowed to warm to −30 °C and was acidified to pH 3 with HCl 3 N (2 mL). The stirring was continued for 45 min at 0 °C before $NaHCO_3$ 10% was added (pH 7). The aqueous layer was extracted with diethyl ether (3 × 30 mL), and the organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The crude product was then purified by chromatography on silica gel (Et_2O 100%) to afford β-hydroxyphosphonates **4a–e** and **4i–j**.

*Dimethyl-1-(benzyloxy)-2-hydroxy-hexadecaylphosphonate (**4a**-syn)*

Yield: 88%. ^{1}H NMR: δ 0.88 (t, J = 6.4 Hz, 3H), 1.25 (m, 24H), 1.41 (m, 2H), 1.72 (m, 1H), 3.09 (s, 1H, OH), 3.63 (dd, $J_{H\text{-}P}$ = 6.9 Hz, J = 5.0 Hz, 1H), 3.79 (d, J = 12.5 Hz, 3H), 3.84 (d, J = 12.3 Hz, 3H), 4.59 and 4.80 (AB, J = 11.3 Hz, 2H), 7.30 (s, 5H arom). ^{13}C NMR: δ 13.95, 22.52, 25.22, 29.19–29.52, 31.76, 32.59 (d, J = 8 Hz), 52.93 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz), 53.07 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz), 70.82 (d, J = 2.73 Hz), 74.40 (d, J = 3.3 Hz), 78.22 (d, $^{1}J_{C\text{-}P}$ = 157.0 Hz), 128.0, 128.19, 128.31, 136.85.

*Dimethyl-1-(diisopropylideneglycerol)-2-hydroxy-hexadecylphosphonate (**4b**-syn)*

Yield: 65%. IR: 910, 1370, 3440. ^{1}H NMR: δ 0.88 (t, J = 6.4 Hz, 3H), 1.25 (s, 24H), 1.35 (s, 3H), 1.43 (s, 3H), 1.50 (m, 2H), 3.18 (m, OH), 3.58 (m, 2H), 3.79 (d, $^{3}J_{H\text{-}P}$ = 10.6 Hz, 3H), 3.82 (d, $^{3}J_{H\text{-}P}$ = 10.6 Hz, 3H), 3.74-3.89 (m, 9H), 4.06 (q, $J_{H\text{-}P}$ = 8.4 Hz, 1H), 4.30 (dt, J = 4.1 Hz, J = 5.7 Hz, 1H). ^{13}C NMR: δ 14.13, 22.71, 25.30, 25.58, 26.75, 29.51, 31.96, 33.01, 53.33 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 53.57 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 66.49, 70.93 (d, $^{2}J_{C\text{-}P}$ = 4.1 Hz), 70.91 (d, $^{2}J_{C\text{-}P}$ = 3.4 Hz), 73.49 (d, $J_{C\text{-}P}$ = 3.4 Hz), 74.57, 74.48 (d, $J_{C\text{-}P}$ = 3.3 Hz), 79.00 (d, $^{1}J_{C\text{-}P}$ = 158.9 Hz), 82.14 (d, $^{1}J_{C\text{-}P}$ = 158.2 Hz), 109.57. Anal. calcd for $C_{24}H_{47}O_7P_1$: C 59.87, H 10.19; found: C, 59.76; H 10.09.

*Dimethyl-1-(benzyloxy)-2-hydroxy-propylphosphonate (**4c**-syn)*

Yield: 50%. IR (CCl_4): 3400. ^{1}H NMR: δ 1.30 (d, J = 6.4 Hz, 3H), 3.49 (s, 1H; OH), 3.63 (dd, J = 6.4 Hz, J = 5.8 Hz, 1H), 3.77 (d, J = 11.0 Hz, 3H), 3.82 (d, J = 11.0 Hz, 3H), 4.10 (m, 1H), 4.62 (ABX, J = 11.3 Hz, J = 1.1 Hz, 1H), 4.81 (AB, 1H), 7.34 (m, 5H arom).^{13}C NMR: δ 19.31 (d, J = 8.8 Hz), 52.80 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz), 53.60 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz), 67.30 (d, J = 4.5 Hz), 74.71 (d, J = 2.5 Hz), 74.18 (d, $^{1}J_{C\text{-}P}$ = 157.0 Hz), 128.19, 128.34, 128.49, 137.04. Anal. calcd for $C_{12}H_{19}O_5P_1$: C, 52.36; H, 6.91; found: C, 52.56; H, 7.03.

*Dimethyl-1-(trans-hex-2-enyloxy)-2-hydroxy-propylphosphonate (**4d**-syn)*

Yield: 87%. IR (CCl_4): 3380. ^{1}H NMR: δ 0.89 (t, ^{3}J = 7.3 Hz, 3H), 1.28 (m, 3H), 1.44 (m, 2H), 2.03 (m, 2H), 3.81 (2d, $^{3}J_{H\text{-}P}$ = 10.4 Hz, 6H), 4.12 (m, 2H), 4.14 (d, $^{1}J_{H\text{-}P}$ = 20.2 Hz, 1H), 5.55 (m, 2H). ^{13}C NMR: δ 13.66, 19.35, 34.32, 53.95, (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 53.90 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 67.28, 78.32 (d, $^{1}J_{C\text{-}P}$ = 157.4 Hz), 125.48, 136.41. HRMS (FAB) [(M+H)$^{+}$]: calcd for $C_{11}H_{23}O_5P_1$: 267.1361; found: 267.1359.

*Dimethyl-1-(cis-hex-2-enyloxy)-2-hydroxy-propylphosphonate (**4e**-syn)*

Yield: 66%. IR (CCl_4): 3380. ^{1}H NMR: δ 0.83 (t, J = 7.3 Hz, 3H), 1.31 (m, 5H), 2.03 (m, 2H), 3.28 (s, 1H), 3.80 (2d, $^{3}J_{H\text{-}P}$ = 10.8 Hz, 7H), 4.13 (d, $^{1}J_{H\text{-}P}$ = 22.2 Hz, 1H), 4.14 (m, 2H), 5.56 (m, 2H). ^{13}C NMR: δ 13.66, 19.35, 21.04, 25.03, 53.96 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 53.28 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 68.16, 68.19, 78.91 (d, $^{1}J_{C\text{-}P}$ = 157.2 Hz), 124.07, 134.91. HRMS (FAB) [(M+H)$^{+}$] calcd for $C_{11}H_{23}O_5P_1$: 267.1361; found: 267.1361.

*Dimethyl-1-(prop-2-enyloxy)-2-hydroxy-hexadecylphosphonate (**4i**)*

Yield: 70%. IR : 3400. ^{1}H NMR: δ 0.87 (t, 3H), 1.25 (s, 22H), 1.50 (m, 2H), 1.73 (m, 2H), 3.12 (m, OH), 3.56 (q, J = 5.6 Hz, J = 6.8 Hz, 1H), 3.83 (2d, $^{3}J_{H\text{-}P}$ = 10.6 Hz, 6H), 4.08 (m, 1H), 4.25 (q large, 1H), 5.26 (m, 2H), 5.90 (ddt, J =

17.1 Hz, J = 10.3 Hz, J = 5.8 Hz, 2H). ^{13}C NMR: δ 14.08, 22.66, 25.53, 29.34, 29.61, 29.67, 31.91, 33.05, 53.91 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 53.98 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 70.91, 73.61, 78.43 (d, $^{1}J_{C\text{-}P}$ = 157.7 Hz), 118.24, 133.82. HRMS (FAB) [(M+H)$^{+}$] calcd for $C_{21}H_{43}O_5P_1$: 407.2927; found: 407.2926.

*Dimethyl-1-(hex-2-enyloxy)-2-hydroxy-hexadecylphosphonate (**4j**)*

Yield: 80%. IR (CCl_4): 3400. ^{1}H NMR: δ 0.86 (m, 6H), 1.41 (m, 26H), 2.01 (q, J = 6.9 Hz), 3.26 (s, 1H), 3.78 (2d, $^{3}J_{H\text{-}P}$ = 10.4 Hz, 7H), 4.15 (d, $^{1}J_{H\text{-}P}$ = 20.0 Hz, 1H), 4.07 (m, 2H), 5.59 (qt, J = 15.3 Hz, J = 6.5 Hz, 2H). ^{13}C NMR: δ 13.67, 14.12, 22.13, 22.69, 29.64, 29.71, 31.94, 34.34, 53.08 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz), 53.22 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz), 70.44, 73.36, 77.59 (d, $^{1}J_{C\text{-}P}$ = 157.0 Hz), 125.47, 136.39. HRMS (FAB) [(M+H)$^{+}$] calcd for $C_{24}H_{49}O_5P_1$: 449.3396; found: 449.3396.

2.6 Preparation of 5a-e and 5i-k

To a solution of **4a–e**-*syn* and **4i–k**-*syn* (0.5 mmol) in dry THF at 0 °C was added a solution of *t*-BuOK 1 M in THF (1 mL, 1 mmol). After 40 min at 0 °C, the solvent was evaporated in vacuo. The crude product was then purified by chromatography on silica gel (Pentane) to afford **5a–e** and **5i–k**.

*Hexadec-1-enyloxymethyl-benzene (**5a**-E)*

Yield: 70%. ^{1}H NMR: δ 0.88 (t, J = 6.4 Hz, 3H), 1.25 (m, 24H), 1.91 (q, J = 6.7 Hz, 2H), 4.70 (s, 2H), 4.88 (dt, J = 12.6 Hz, J = 7.3 Hz, 1H), 6.31 (d, 1H), 7.35 (m, 5H). Anal. calcd for $C_{23}H_{38}O$: C, 83.37; H, 11.59; found: C, 83.14; H, 11.34.

*Hexadec-1-enyloxymethyl-benzene (**5a**-Z)*

Yield: 40%. ^{1}H NMR: δ 0.88 (t, J = 6.4 Hz, 3H), 1.25 (m, 24H), 2.09 (m, 1H), 4.37 (q, J = 7.0 Hz, 1H), 4.78 (s, 2H), 6.0 (dt, J = 6.3 Hz, J = 1.4 Hz, 1H), 7.31 (m, 5H). Anal. calcd for $C_{23}H_{38}O$: C, 83.37; H, 11.59; found: C, 83.06; H, 11.28.

*4-Hexadec-1-enyloxymethyl-2,2-dimethyl-[1,3]dioxolane (**5b**-E)*

Yield: 82%. IR (CCl_4): 1655. ^{1}H NMR: δ 0.86 (t, J = 7.2 Hz, 3H), 1.27 (m, 24H), 1.37 (s, 3H), 1.43 (s, 3H), 1.89 (q, J = 6.5 Hz, 2H), 3.63 (AB, J = 5.6 Hz, 1H), 3.71 (AB, J = 5.6 Hz, 1H), 3.77 (q, J = 6.2 Hz, 1H), 4.08 (q, J = 6.4 Hz, 1H), 4.33 (dt, J = 5.9 Hz, 1H), 4.28 (dt, J = 14.7 Hz, J = 7.4 Hz, 1H), 6.25 (d, J = 12.6 Hz, 1H). ^{13}C NMR: δ 14.14, 22.73, 23.94, 25.39, 25.38, 26.71, 29.32, 29.40, 29.56, 29.70, 29.74, 30.67, 66.74, 72.27, 74.12, 109.52, 15.82. Anal. calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94; found: C, 74.40; H, 11.82.

*4-Hexadec-1-enyloxymethyl-2,2-dimethyl-[1,3]dioxolane (**5b**-Z)*

Yield: 36%. ^{1}H NMR: δ 0.86 (t, J = 7.2 Hz, 3H), 1.27 (m, 24H), 1.37 (s, 3H), 1.42 (s, 3H), 2.05 (q, J = 6.6 Hz, 2H), 3.71 (q, J = 5.9 Hz, J = 10.7 Hz, 1H), 3.81 (q, J = 4.8 Hz, J = 10.9 Hz, 1H), 3.83 (dd, J = 6.1 Hz, J = 8.5 Hz, 1H), 4.07 (dd, J = 6.3 Hz, J = 8.4 Hz, 1H), 4.27 (m, 1H), 4.36 (dt, J = 6.3 Hz, J = 7.3 Hz, 1H), 5.94 (d, J = 6.3 Hz, 1H). ^{13}C NMR: δ 14.14, 22.73, 23.94, 25.39, 25.48, 26.70, 29.32, 29.40, 29.60, 29.70, 31.96, 66.62, 69.65, 74.48, 107.89, 144.80. Anal. calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94; found: C, 74.36; H, 11.76.

*Propenyloxymethyl-benzene (**5c**-E)*

Yield: 45%. ^{1}H NMR: δ 1.55 (dd, J = 6.6 Hz, J = 1.4 Hz, 3H), 4.89 (dq, J = 13.0 Hz, J = 6.5 Hz, 1H), 4.70 (s, 2H), 6.3 (dd, J = 12.5 Hz, J = 1.4 Hz, 1H), 7.34 (m, 5H arom.). Anal. calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16; found: C, 79.90; H, 7.98.

*Propenyloxymethyl-benzene (**5c**-Z)*

Yield: 24%. ^{1}H NMR: δ 1.62 (dd, J = 6.8 Hz, J = 1.7 Hz, 3H), 4.44 (m, 1H), 4.78 (s, 2H), 6.0 (dd, J = 6.2 Hz, J = 1.7 Hz, 1H), 7.33 (m, 5H arom.). HRMS (FAB) [(M+H)$^{+}$] calcd for $C_{10}H_{12}O$: 148.0888; found: 148.0889.

*1-Propenyloxy-trans-hex-2-ene (**5d**-E)*

Yield: 30%. IR (CCl_4): 1670. ^{1}H NMR: δ 0.91 (t, J = 7.4 Hz, 3H), 1.41 (m, 2H), 1.56 (dd, J = 6.7 Hz, J = 1.6 Hz, 3H), 2.06 (dt, J = 5.7 Hz, J = 6.5 Hz, 2H), 4.12 (d, J = 5.9 Hz, 2H), 4.81 (qd, J_{trans} = 12.5 Hz, J = 6.7 Hz, 1H), 5.65 (m, 2H), 6.22 (qd, J = 12.5 Hz, J = 1.5 Hz, 1H). ^{13}C NMR: δ 12.64, 13.71, 24.82, 34.41, 70.14, 77.26, 99.09, 125.39, 135.27. HRMS (FAB) [(M+H)$^{+}$] calcd for $C_9H_{16}O$: 141.1279; found: 141.1279.

*1-Propenyloxy-cis-hex-2-ene (**5e**-E)*

Yield: 40%. IR (CCl_4): 1655. ^{1}H NMR: δ 0.92 (t, J = 7.3 Hz, 3H), 1.41 (m, 2H), 1.56 (dd, J = 6.7 Hz, J = 1.6 Hz, 3H), 2.06 (dt, J = 5.7 Hz, J = 6.5 Hz, 2H), 4.23 (d, J = 5.1 Hz, 2H), 4.81 (qd, J_{trans} = 12.6 Hz, J = 6.7 Hz, 1H), 5.65 (m, 2H), 6.23 (qd, J_{trans} = 12.6 Hz, J = 1.4 Hz, 1H). ^{13}C NMR: δ 12.64, 13.74, 22.65, 29.74, 64.96, 98.94, 125.26, 133.85, 146.21. HRMS (FAB) [(M+H)$^{+}$]: calcd for $C_9H_{16}O$: 141.1279; found: 141.1283.

*1-Propenyloxy-hexadec-1-ene (**5i**-E)*

Yield: 69%. IR (CCl_4): 1670. ^{1}H NMR: δ 0.89 (t, J = 7.2 Hz, 3H), 1.27 (m, 24H), 1.89 (m, 2H), 4.19 (dt, J = 12.5 Hz, J = 7.4 Hz, 1H), 4.82 (dd, J = 5.4 Hz, J = 1.5 Hz, 2H), 5.22 (ABX, J_{cis} = 10.4 Hz, J = 2.4 Hz, 1H), 5.31 (ABX, J_{trans} = 17.3 Hz, J = 2.4 Hz, ^{4}J = 1.5 Hz, 1H), 5.95 (ddt, J_{trans} = 17.2 Hz, J_{cis} = 10.6 Hz, J = 5.4 Hz, 1H), 6.23 (d, J_{trans} = 12.5 Hz, 1H). ^{13}C NMR: δ 14.15, 22.74, 29.07, 29.42, 29.55, 29.75, 30.72, 31.98, 70.05, 105.14, 117.27, 133.78, 145.56. HRMS (FAB) [(M+H)$^{+}$] calcd for $C_{19}H_{36}O_1$: 281.2844; found: 281.2845.

*1-trans-Hex-2-enyloxy-hexadec-1-ene (**5j**-E)*

Yield : 68%. IR (CCl_4): 1670. ^{1}H NMR: δ 0.91 (m, 6H),

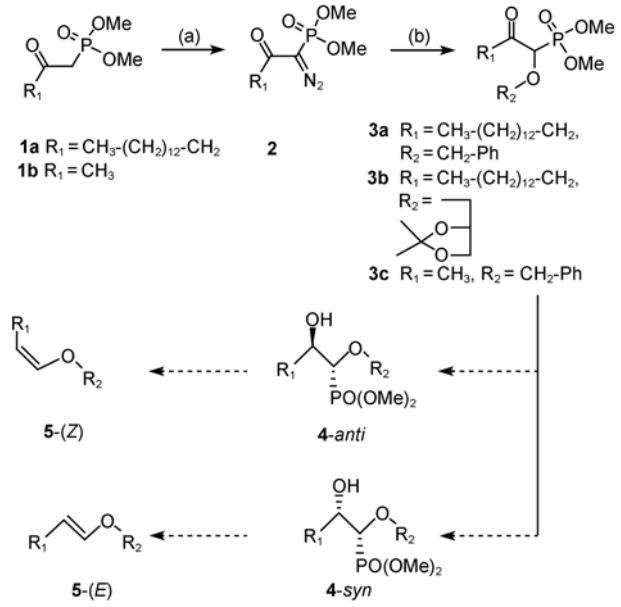
1.41 (m, 26H), 1.92 (m, 2H), 2.04 (dt, J = 7.3 Hz, J = 6.7 Hz, 2H), 4.12 (d, J = 5.9 Hz, 2H), 4.81 (dt, J = 12.5 Hz, J = 7.3 Hz, 1H), 5.58 (m, 1H), 5.75 (dtt, J_{trans} = 15.4 Hz, ^3J = 6.4 Hz, J = 5.9 Hz, 1H), 6.22 (d, J_{trans} = 12.5 Hz, 1H). ^{13}C NMR: δ 13.68, 14.15, 22.21, 22.74, 27.81, 29.08, 29.43, 29.57, 29.73, 29.76, 30.77, 31.99, 34.42, 70.02, 104.85, 125.43, 135.10, 145.61. HRMS (FAB) [(M+H)$^+$] calcd for $C_{22}H_{42}O_1$: 323.3314; found: 323.3313.

3 Results and discussion

3.1 Enol ethers from α-alkoxy-β-ketophosphonates

As we intended, in particular, to apply the sequence depicted in Scheme 1 for the preparation of (*Z*) 1-*O*-alkenyl-2-acyl-*syn*-glycerophosphocholines [9] the first experiments were conducted on diazo ketophosphonate **2a** bearing a fatty alkyl chain. This compound was obtained under reported conditions [6a] from ketophosphonate **1a** prepared by reaction of the lithio-derivative of trimethylphosphonate on methyl pentadecanoate. In order to test the feasibility of the stereoselective reduction, we prepared the model compound **3a** by the rhodium assisted decomposition of **2a** in the presence of benzyl alcohol (2 equiv) in refluxing toluene (Scheme 2) [10].

The reduction of **3a** into either *syn* or *anti* alcohol **4a** was carried out following the experimental conditions reported previously for similar stereoselective reduction of β-ketophosphine oxides or β-keto phosphonamidates [11]. Treatment of **3a** with $NaBH_4$ in the presence of $CeCl_3$ [11a] gave **4a** in 83% yield as a mixture of two isomers in the ratio

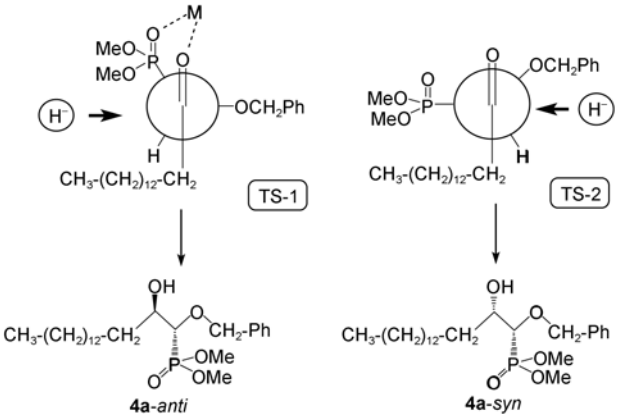


Scheme 2 Synthesis of alkoxyphosphonates **3a–c**. (a) K_2CO_3 (1.1 equiv), TsN_3 (1.1 equiv), CH_3CN (K_2CO_3 was replaced by NaH which was used for the synthesis of **2b**). (b) $Rh_2(OAc)_4$ (0.5 mol%), R_2-OH, $PhCH_3$.Δ.

82/18 (this ratio was determined from the ^{1}H NMR spectrum of the mixture). The *anti* stereochemistry was assigned to the major isomer assuming that the *O*-alkyl group does not interfere with the usual chelation and that the hydride had been delivered from the less hindered face of the intermediate chelate (Scheme 3, TS-1) (this assignment was further confirmed on the basis of the configuration of the enol-ethers double bonds). Slightly higher yield and stereoselectivity (86%, *anti*/*syn* = 90/10, Table 1) were observed when we used $CaCl_2$ as the chelating agent [12].

Reduction of **3a** with toluene solution of DiBAL [11c] at −60 °C led to the sole *syn* isomer in 88% yield. The observed *syn* stereoselectivity in this case could be explained in assuming that in the absence of a chelating agent, the reduction takes place through the Felkin-Anh transition state structure in which the largest and electron-withdrawing phosphonate group occupies a position perpendicular toward the carbonyl group (Scheme 3, TS-2) [13].

The Wittig reaction was first conducted on **4a**-*syn* separated from the **4a**-*anti* and **4a**-*syn* mixture by acetylation of alcohol **4a** and column chromatography (we were able to obtain pure **4a**-*anti* and **4a**-*syn* by acetylation (AcCl, Pyr) of alcohols **4a**, separation of the corresponding stereoisomeric acetates by column chromatography followed by methanolysis (MeONa cat, MeOH) of the ester function). A limited



Scheme 3 Proposed transition states for the stereoselective reduction of alkoxyketophosphonates **3** by either $NaBH_4/CaCl_2$ (TS-1) or DIBAL (TS-2). Compounds **3** and **4** are racemic mixtures.

Table 1 Enol ethers **5** from alkoxyketophosphonates **3a–c**

3	**3→4** $NaBH_4/CaCl_2$ Yield (%) (*syn*/*anti*)	**3→4** DIBAL Yield (%) (*syn*/*anti*)	**4→5** Yield (%) (*E*/Z)
3a	86%	88%	**4a**-*syn*→70% (100/0)
	(10/90)	(100/0)	**4a**-*anti*→40% (5/95)
3b	78%	65%	**4b**-*syn*→82% (100/0)
	(5/95)	(100/0)	**4b**-*anti*→36% (12/88)
3c	97%	50%	**4c**-*syn*→45% (100/0)
	(35/65)	(100/0)	**4c**-*anti*→24% (5/95)

investigation of optimum reaction conditions was carried out by varying both the nature of the base (NaH, *t*-BuOK, LDA) and/or the solvent (pentane, THF, DMF). The best results were observed when a THF solution of **4a**-*syn* was submitted to the action of a THF solution of *t*-BuOK. Under these conditions, after stirring at 0 °C for 30 min, pure enol ether **5a**-*E* was obtained in 70% yield after column chromatography (The presence of the *Z* isomer could not be detected, neither by TLC nor in the ^{1}H NMR spectrum of the crude product).

By contrast, when **4a**-*anti* was submitted to the same experimental conditions it gave **5a** in only 40% yield as a mixture of stereoisomers in the ratio *Z*/*E* = 95/5. Attempts to increase this yield either by raising the temperature or by changing the nature of the solvents or of the base were unsuccessful.

Similar results were obtained from ketophosphonate **3b** bearing a protected glyceridic moiety (Table 1). The pure **4b**-*syn*, obtained as described above for **4a**, and the mixture of **4b**-*anti*/**4b**-*syn*: 95/5 were involved in the Wittig reaction. Submitted to the action of a base, they gave pure **5b**-*E* in 82% yield and a mixture of **5b**-*Z* and **5b**-*E* (*E*/*Z* = 12/88) in 36% yield. In the above experiments, the lower yields observed when the Wadsworth-Emmons reaction was performed from **4a** (or **4b**) *anti*, compared to **4a** (or **4b**) *syn*, might be due to the steric repulsion of the fatty acid chain and the alkoxy groups in the transition state issued from the former compounds. However, when we performed the same experiments from the less hindered **4c** bearing a methyl group instead of the long alkyl chain, surprisingly both the (*Z*) and (*E*) corresponding enol ethers were obtained in lower yields (Table 1).

From these results it appears that only (*E*) enol ethers can be obtained stereoselectively in reasonable yields by conducting a Wadsworth-Emmons reaction on pure *syn* α-alkoxy-β-ketoalcohols. The same reaction, applied to *anti*- isomers, gave a mixture of stereoisomeric enol ethers in only moderate to poor yields. Thus in this case, the base catalyzed isomerization of the hydroxy phosphonates **4**-*anti* into **4**-*syn* *via* a retro-aldol type process precedes the Wadsworth-Emmons reaction [14].

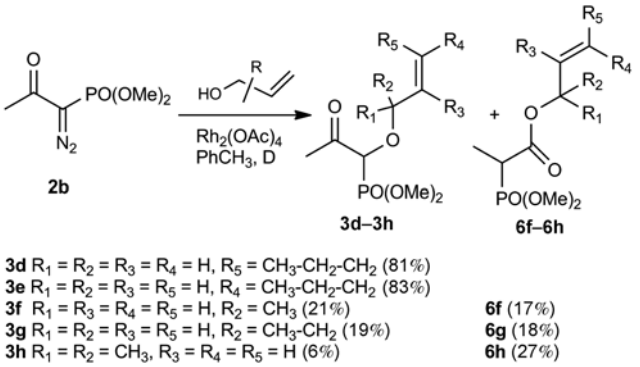
3.2 (*E*) Allyl-vinyl ethers from α-allyloxy β-ketophosphonates

Over the years the Claisen rearrangement has emerged as a powerful synthetic tool for the stereoselective creation of a carbon-carbon bond [15]. In this sigmatropic transposition, the enol is the key step to control the stereochemistry of the new chiral centers. We therefore decided to examine to what extend the sequence of Scheme 1 would allow the stereoselective preparation of allyl vinyl ethers with a (*E*) configuration for the vinylic double bond.

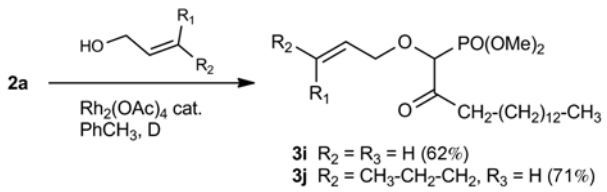
The preliminary study of the insertion reaction of diazo ketophosphonates into the hydroxyl bond of different allylic alcohols was carried out on **2c** easily prepared in large amounts from commercially available dimethyl acetylmethylphosphonate **1c**. The results are summarized in Scheme 4. With primary alcohols the reaction gave the expected allyl-ethers **3d** and **3e** in good yields (in the case of reactions performed with allylic alcohol, besides compounds **3**, we isolated a small amount of com-pounds resulting from insertion of diazo compounds into some residual water). We did not observe the competitive addition reaction of the intermediate rhodium-carbenoid species on the carbon-carbon double bond, as reported for diazo-keto-esters [16]. With secondary alcohols, the reaction gave a mixture of the insertion reaction products **3f** and **3g** and of allylic esters **6f** and **6g** resulting from a competitive Wolff rearrangement [17]. Finally, with the tertiary alcohol, a mixture mainly consisting of the ester **6h** besides a small amount of insertion product **3h** was obtained in a low yield.

In view of these preliminary results, further insertion reactions with diazo **2a** ($R_1 = CH_3(CH_2)_{12}CH_2$) were conducted exclusively with primary allylic alcohols and gave the expected insertion reaction products **3i** and **3j** in indicated yields (Scheme 5).

As shown in Table 2, the reduction of ketophosphonates



Scheme 4 Insertion reactions of α-diazo-β-ketophosphonate **2b** into the hydroxyl bond of primary, secondary and tertiary allylic alcohols.



Scheme 5 Insertion reactions of α-diazo-β-ketophosphonates (**2a**) into the hydroxyl bond of primary allylic alcohols.

Table 2 Allyl-vinyl ethers from α-allyloxy-β-hydroxyphosphonates **3**

3	**4**-*syn* Yield	**5**-*E* Yield
3d	87%	30%
3e	66%	40%
3i	70%	69%
3j	80%	68%

3d–e and **3i–j** with DIBAL gave the corresponding hydroxy-phosphonates **4** in good yields and complete *syn* stereoselectivity. When submitted to the action of a commercially available THF solution of *t*-BuOK, these compounds led to the corresponding pure enol ethers (*E)* **5** in moderate to good yields.

4 Conclusions

Though Wittig type olefination reaction is among the most effective methods for the formation of carbon-carbon double bonds with either (*Z*) or (*E*) stereochemistry, the stereoselective preparation of *O*-alkyl enol ethers using this methodology is limited. This seems to be partially due to difficulties encountered in obtaining the Wittig precursors. In the present work, we have shown that the three-step sequence: insertion reaction of a diazo ketophosphonate into the hydroxylic bond of a primary alcohol, DIBAL reduction of the alkoxyketophosphonate thus obtained and Wadsworth-Emmons elimination reaction, led to the corresponding (*E*) enol ethers in moderate to good yields. In certain cases this approach could be a valuable complement of existing methods.

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