CHAPTER II

EXPERIMENTAL

2.1 General and materials

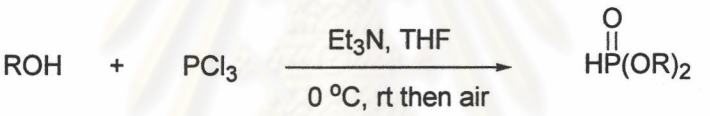
Dialkyl phosphite and benzaldehyde were distilled. Reactions requiring anhydrous conditions were conducted in oven-dried apparatus under nitrogen. Solvents were distilled from a suitable drying agent (given in parentheses); Tetrahydrofuran (sodium benzophenone ketyl), dichloromethane (calcium hydride), toluene (calcium hydride). Distilled commercial grade solvents were used for column chromatography. The following compounds were purchased from Fluka Co., Ltd.: anisaldehyde, 4-nitrobenzaldehyde, 4-tolualdehyde, cinnamaldehyde, 4-fluoro benzaldehyde, 2-fluorobenzaldehyde, 3-bromobenzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 4-iso-butylbenzaldehyde, 4-*tert*-butylbenzaldehyde, butyraldehyde, isobutyraldehyde, 1-heptaldehyde, isovaleraldehyde, pivalaldehyde, cyclohexanecarboxaldehyde, lithium aluminium hydride 1 M in THF ($LiAlH_4$), *N*,*N*-dicyclohexylcarbodiimide (DCC), 4,4-dimethylaminopyridine (DMAP), and (*R*)- or (*S*)-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid ((*R*)-MTPA or (*S*)-MTPA). Phosphorus trichloride, valeraldehyde, ethanol, and methanol were purchased from Merck Co., Ltd.. Titanium isoproproxide ($Ti(O^iPr)_4$) was purchased from Aldrich Co., Ltd.. All reagents were used as received.

Evaporation of solvents was carried out on an R-114 Büchi Rotavapor equipped with a B-480 Büchi water bath. The progress of the reactions was followed by thin layer chromatography (TLC) performed on Merck D.C. silica gel 60 F254, 0.2 mm pre-coated aluminium plates and visualized using UV light (254 nm), iodine, or potassium permanganate. The isolation of products was performed by flash column chromatography on 230-400 mesh silica gel or the 70-230 mesh for column chromatography. Melting points were recorded on an Electrothermal 9100.

Gas chromatographic (GC) experiments were performed by Miss Jirawit Yanchinda under the supervision of Dr. Aroonsiri Shitangkoon on Agilent gas chromatograph equipped with a flame ionization detector (FID) (model GC 6890) using a 0.25 mm × 0.25 μm 10% BSiMe in PS255 or 25.5% BSiMe in OV-1701 capillary column.

Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker ACF200 spectrometer operating at 200 MHz for ^{1}H and 50 MHz for ^{13}C, a Varian Mercury 400 spectrometer operating at 400 MHz for ^{1}H and 202.35 MHz for ^{31}P at the Department of Chemistry, Faculty of Science, Chulalongkorn University, and a Varian Gemini 2000 YH200 spectrometer operating at 200 MHz for ^{1}H at Chulabhorn Research Institute (CRI). Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or with the solvent as an internal reference for ^{1}H and ^{13}C NMR. A phosphoric acid (H_3PO_4) capillary in an appropriate solvent was used as an external reference (0.00) for ^{31}P spectra. Multiplicities are abbreviated as followed: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (J) are reported as a proton-proton (J_{HH}) and Proton-phosphorus (J_{HP}) and are reported in Hertz (Hz).

2.2 Synthesis of dialkyl phosphites.



A solution of an alcohol (0.45 mol) in dry THF (500 mL) was placed in a three-necked round bottom flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel which was charged with a solution of phosphorus trichloride (0.15 mol) in dry THF (50 mL) under a nitrogen atmosphere. The flask was cooled in an ice bath. With vigorous stirring, the phosphorus trichloride solution was added dropwise. After the addition, the mixture was allowed to warm up to room temperature and stirred for additional 2-3 h. Air was then bubbled through the mixture for 0.5 h. A triethylamine (0.33 mol) solution in THF (100 mL) was introduced to the reaction mixture at 0 °C, and then allowed to warm to room temperature for about 2 h with stirring. The suspension, containing a precipitate of triethylamine hydrochloride, was filtered with suction. The amine salt was washed with THF. The filtrate was concentrated and distilled under vacuum to afford a colorless liquid.

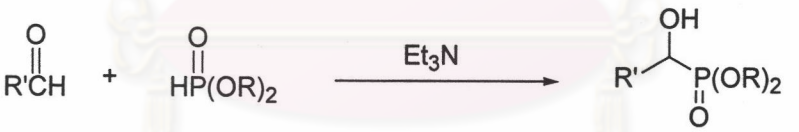
Dimethyl phosphite (49a) was prepared from a reaction of methyl alcohol (20 mL, 0.45 mol), phosphorus trichloride (13 mL, 0.15 mol) and triethylamine (46 mL, 0.33 mol) according to the procedure outlined above to give dimethyl phosphite (9 mL, 0.07 mol, 46%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (d, $^3J_{HH}$ = 11.7 Hz, 3H, OC*H*$_3$), 6.75 (d, $^1J_{HP}$ = 699.0 Hz, 1H, *H*P=O).

Diethyl phosphite (49b). A reaction of ethyl alcohol (29 mL, 0.45 mol), phosphorus trichloride (13 mL, 0.15 mol) and triethylamine (46 mL, 0.33 mol) gave diethyl phosphite (12 mL, 0.08 mol, 54%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (t, $^3J_{HH}$ = 7.6 Hz, 3H, OCH_2CH_3), 4.17 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2CH_3), 6.80 (d, $^1J_{HP}$ = 668.0 Hz, 1H, *H*P=O).

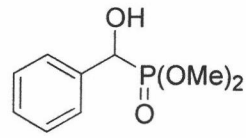
Diisopropyl phosphite (49c). A reaction of isopropyl alcohol (37.8 mL, 0.50 mol), phosphorus trichloride (13.0 mL, 0.15 mol) and triethylamine (46.0 mL, 0.33 mol) gave diisopropyl phosphite (15.0 mL, 0.09 mol, 61%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (bs, 12H, C*H*$_3$), 4.62 (bs, 2H, C*H*$(CH_3)_2$), 6.73 (d, $^1J_{HP}$ = 688.0 Hz, 1H, *H*P=O).

2.3 General procedure for the synthesis of racemic α-hydroxyphosphonates.

2.3.1 General procedure for the synthesis of racemic α-hydroxy phosphonates using triethylamine.

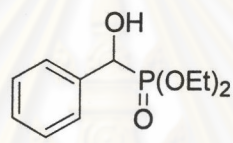


To a solution of an aldehyde (3.7 mmol) and dialkyl phosphite (3.7 mmol) was added triethylamine (0.37 mmol). The solution was heated to 75 °C until indicated consumption of the aldehyde (by TLC). The solution was diluted with EtOAc and washed twice with 1 M aq. HCl, once with water, dried, and evaporated under vacuum. The residue was chromatographed (SiO_2, EtOAc) or recrystallized (EtOAc, hexanes) to yield pure α-hydroxyphosphonate.



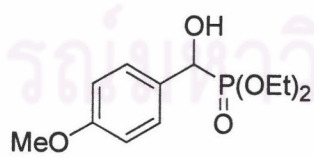
50a

Dimethyl 1-hydroxyphenylmethylphosphonate (50a) was prepared from benzaldehyde (0.39 g, 3.7 mmol) and dimethyl phosphite (0.41 g, 3.7 mmol). The reaction yielded 0.40 g of α-hydroxyphosphonate **50a** as a white solid (1.85 mmol, 50%): m.p. 86-87 °C (lit.[38] 86-87 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.60 (m, 3H, OCH_3), 4.99 (d, $^2J_{HP}$ = 11.2 Hz, 1H, $CHOH$), 7.24-7.42 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.7 (OCH_3), 53.9 (OCH_3), 70.6 (d, $^1J_{CP}$ = 126.7 Hz, $CHP(O)$), 127.0, 128.2, 128.4, 136.2.



50b

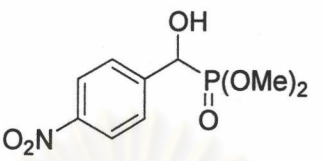
Diethyl 1-hydroxyphenylmethylphosphonate (50b) was prepared from benzaldehyde (0.39 g, 3.7 mmol) and diethyl phosphite (0.51 g, 3.7 mmol). The reaction yielded 0.71 g of α-hydroxyphosphonate **50b** as a white solid (2.89 mmol, 78%): m.p. 78-80 °C (lit.[38] 78-80°C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (t, $^3J_{HH}$ = 6.9 Hz, 3H, OCH_2CH_3), 3.97 (m, 2H, OCH_2CH_3), 4.95 (d, $^2J_{HP}$ = 11.2 Hz, 1H, $CHOH$), 7.23-7.42 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4 (OCH_2CH_3), 63.0 (OCH_2CH_3), 63.1 (OCH_2CH_3), 70.7 (d, $^1J_{CP}$ = 126.6 Hz, $CHP(O)$), 127.1, 128.2, 127.9, 136.6.



50c

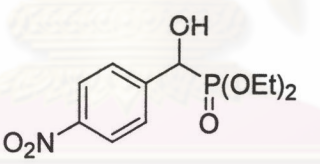
Diethyl 1-hydroxy-(4-methoxyphenyl)methylphosphonate (50c) was prepared from 4-anisaldehyde (0.50 g, 3.7 mmol) and diethyl phosphite (0.51 g, 3.7 mmol). The reaction yielded 0.07 g of α-hydroxyphosphonate **50c** as a white solid (0.26 mmol, 7%): m.p. 118-120 °C (lit.[38] 118-120 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (m, 6H, OCH_2CH_3), 1.76 (bs, 1H, OH), 3.78 (t, 3H, $C_6H_5OCH_3$), 4.03 (m, 4H,

OCH_2CH_3), 4.94 (d, $^2J_{HP}$ = 10.0 Hz, 1H, C*H*OH), 6.91 (d, $^3J_{HH}$ = 7.8 Hz, 2H, Ar), 7.41 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4 (OCH_2CH_3), 55.2 ($C_6H_5OCH_3$), 63.0 (OCH_2CH_3), 63.4 (OCH_2CH_3), 70.3 (d, $^1J_{CP}$ = 128.9 Hz, *C*HP(O)), 113.7, 128.4, 128.5. 157.5.



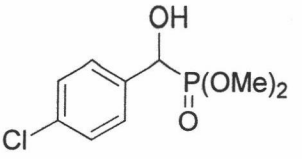
50d

Dimethyl 1-hydroxy-(4-nitrophenyl)methylphosphonate (50d) was prepared from 4-nitrobenzaldehyde (0.56 g, 3.7 mmol) and dimethyl phosphite (0.41 g, 3.7 mmol). The reaction yielded 0.37 g of α-hydroxyphosphonate **50d** as a pale yellow solid (1.41 mmol, 38%): m.p.118-120 °C (lit.[38] 119 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.74 (m, 3H, OCH_3), 5.19 (d, $^2J_{HP}$ = 12.4 Hz, 1H, C*H*OH), 7.66 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar), 8.20 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.7 (OCH_3), 54.5 (OCH_3), 69.9, (d, $^1J_{CP}$ = 158.2 Hz, *C*HP(O)), 123.4, 127.7, 144.0, 147.6.



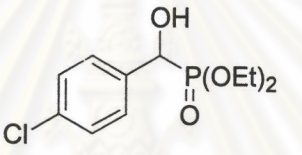
50e

Diethyl 1-hydroxy-(4-nitrophenyl)methylphosphonate (50e) was prepared from 4-nitrobenzaldehyde (0.56 g, 3.7 mmol) and diethyl phosphite (0.51 g, 3.7 mmol). The reaction yielded 0.31 g of α-hydroxyphosphonate **50e** as a pale yellow solid (1.07 mmol, 29%): m.p. 85-86 °C (lit.[38] 82-84 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (m, 3H, OCH_2CH_3), 4.07 (m, 2H, OCH_2CH_3), 5.14 (d, $^2J_{HP}$ = 12.0 Hz, 1H, C*H*OH), 7.66 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar), 8.18 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3 (OCH_2CH_3), 16.4 (OCH_2CH_3), 63.3 (OCH_2CH_3), 64.0 (OCH_2CH_3), 70.0 (d, $^1J_{CP}$ = 157.4 Hz, *C*HP(O)), 123.3, 127.7, 144.2, 147.4.



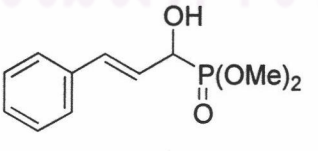
50f

Dimethyl 1-hydroxy-(4-chlorophenyl)methylphosphonate (50f) was prepared from 4-chlorobenzaldehyde (0.52 g, 3.7 mmol) and dimethyl phosphite (0.41 g, 3.7 mmol). The reaction yielded 0.18 g of α-hydroxyphosphonate **50f** as a white solid (0.74 mmol, 20%): m.p. 71-72 °C (lit.[38] 69 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.63 (m, 3H, OC*H*$_3$), 2.82 (bs, 1H, O*H*), 5.04 (d, $^2J_{HP}$ = 11.2 Hz, 1H, C*H*OH), 7.41 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.7 (O*C*H$_3$), 54.1 (O*C*H$_3$), 69.8 (d, $^1J_{CP}$ = 160.2 Hz, *C*HP(O)), 128.4, 128.5, 134.0, 135.2.



50g

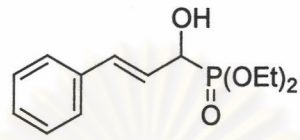
Diethyl 1-hydroxy-(4-chlorophenyl)methylphosphonate (50g) was prepared from 4-chlorobenzaldehyde (0.52 g, 3.7 mmol) and diethyl phosphite (0.51 g, 3.7 mmol). The reaction yielded 0.26 g of α-hydroxyphosphonate **50g** as a white solid (0.92 mmol, 25%): m.p. 72-73 °C (lit.[38] 70-72 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.31 (t, $^3J_{HH}$ = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 4.01-4.16 (m, 4H, OC*H*$_2$CH$_3$), 5.04 (d, $^2J_{HP}$ = 10.8 Hz, 1H, C*H*OH), 7.38 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.46 (d, $^3J_{HH}$ = 8.5 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4 (d, $^3J_{CP}$ = 4.1 Hz, OCH$_2$*C*H$_3$), 63.2 (d, $^2J_{CP}$ = 6.8 Hz, O*C*H$_2$CH$_3$), 63.4 (d, $^2J_{CP}$ = 6.1 Hz, O*C*H$_2$CH$_3$), 69.8 ($^1J_{CP}$ = 158.4 Hz, *C*HOH), 128.4, 128.5, 133.8, 135.3.



50h

Dimethyl 1-hydroxy-3-phenyl-2-propenylphosphonate (50h) was prepared from cinnamaldehyde (0.49 g, 3.7 mmol) and dimethyl phosphite (0.41 g, 3.7 mmol). The reaction yielded 0.15 g of α-hydroxyphosphonate **50h** as a white solid (0.63 mmol, 17%): m.p. 87-88 °C (lit.[38] 87-88 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.82 (m,

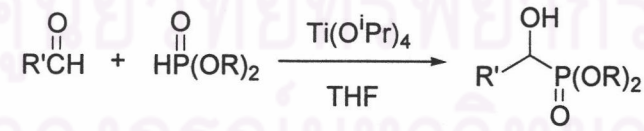
3H, OCH_3), 4.69 (dd, $^3J_{HH}$ = 6.3 Hz, $^2J_{HP}$ = 13.7 Hz, 1H, C*H*OH), 6.31 (dt, $^3J_{HH}$ = 6.0, 10.0 Hz, C*H*=CHPh), 6.77 (dd, $^3J_{HH}$ = 4.0, 16.0 Hz, CH=C*H*Ph), 7.31 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.7 (O*C*H_3), 54.0 (O*C*H_3), 69.2 (d, $^1J_{CP}$ = 128.4 Hz, *C*HP(O)), 126.6 (PhCH=*C*HCHP(O)), 127.9 (Ph*C*H=CHCHP(O)), 128.5, 132.5, 132.6, 136.2.



50i

Diethyl 1-hydroxy-3-phenyl-2-propenylphosphonate (50i) was prepared from cinnamaldehyde (0.49 g, 3.7 mmol) and diethyl phosphite (0.51 g, 3.7 mmol). The reaction yielded 0.09 g of α-hydroxyphosphonate **50i** as a white solid (0.33 mmol, 9%): m.p. 106 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 3H, OCH_2CH_3), 1.33 (t, $^3J_{HH}$ = 7.0 Hz, 3H, OCH_2CH_3), 4.18 (m, 2H, OCH_2CH_3), 4.66 (dd, $^3J_{HH}$ = 6.2 Hz, $^2J_{HP}$ = 12.8 Hz, 1H, C*H*OH), 6.32 (dt, $^3J_{HH}$ = 8.0, 12.0 Hz, 1H, C*H*=CHPh), 6.73 (dd, $^3J_{HH}$ = 4.0, 14.0 Hz, CH=C*H*Ph), 7.34 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0 (OCH_2CH_3), 16.5 (OCH_2CH_3), 63.3 (OCH_2CH_3), 63.5 (OCH_2CH_3), 69.4 (d, $^1J_{CP}$ = 128.3 Hz, *C*HP(O)), 118.1 (PhCH=*C*HCHP(O)), 123.6 (Ph*C*H=CHCHP(O)), 127.2, 128.5, 130.4, 132.4.

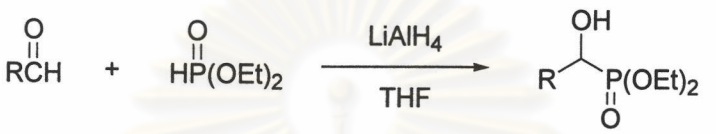
2.3.2 Synthesis of racemic α-hydroxyphosphonate using Ti(O^{i}Pr)$_4$



α-Hydroxyphosphonates was prepared following the method by Shibuya *et al.*.[50] Ti(O^{i}Pr)$_4$ (14.2 mg, 0.05 mmol) was added to a solution of diethyl phosphite (71 μL, 0.55 mmol) in freshly dried THF at 0 °C. The solution was stirred for 30 min and then benzaldehyde (25.4 μL, 0.25 mmol) was added. When the reaction was complete, as indicated by TLC (SiO_2, EtOAc:hexanes; 1:1) the mixture was concentrated under vacuum and then diluted with EtOAc and washed with H_2O. The layers were separated and the aqueous was re-extracted with EtOAc. The combined EtOAc extracts were washed with H_2O, dried (Na_2SO_4) and evaporated under vacuum

to give the crude α-hydroxyphosphonate. Purification by column chromatography (SiO_2, gradient from 50% EtOAc in hexanes to 100% EtOAc) gave diethyl 1-hydroxyphenylmethylphosphonate (59 mg, 0.24 mmol, 96% yield). The NMR data was identical with diethyl 1-hydroxyphenylmethylphosphonate (**50b**).

2.3.3 General procedure for the synthesis of racemic α-hydroxyphosphonate *via* lithium aluminium hydride catalyzed reaction.

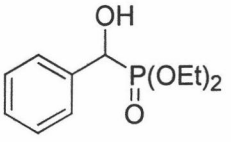


Method A

Diethyl phosphite (35.5 μL, 0.275 mmol) was added to a solution of lithium aluminium hydride (25 μL, 0.025 mmol) in dry THF at room temperature. The solution was stirred for 30 min, and then the aldehyde (0.25 mmol) was added. When the reaction was complete, as indicated by TLC, (SiO_2, 50% EtOAc in hexanes) the mixture was concentrated under vacuum and then diluted with EtOAc and washed with H_2O. The layers were separated and the aqueous layer was re-extracted with EtOAc. The combined EtOAc extracts were washed with H_2O, dried (Na_2SO_4) and evaporated under vacuum to give crude α-hydroxyphosphonate. Purification by column chromatography (SiO_2, gradient from 50% EtOAc in hexanes to 100% EtOAc) gave the desired α-hydroxyphosphonate.

Method B

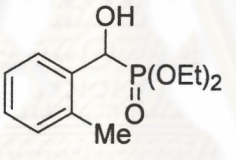
Diethyl phosphite (35.5 μL, 0.275 mmol) was added to a solution of lithium aluminium hydride (25 μL, 0.025 mmol) in dried THF at room temperature. The solution was stirred for 30 min, and then the aldehyde (0.25 mmol) was added. At the completion of the reaction, the mixture was concentrated under vacuum and then purified by column chromatography (SiO_2, gradient from 50% EtOAc in hexanes to 100% EtOAc) giving the desired α-hydroxyphosphonate.



50b

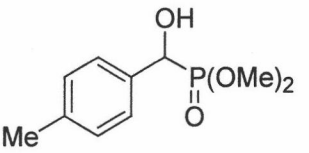
Diethyl 1-hydroxyphenylmethylphosphonate (50b) was prepared by method A from benzaldehyde (25.5 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 48.8 g of α-hydroxyphosphonate (**50b**) as a white solid (0.20 mmol, 80%): m.p. 77-79 °C (lit.[38] 78-80 °C). The NMR data was consistent with the literature.[38]

Diethyl 1-hydroxyphenylmethylphosphonate (50b) the compound was also prepared by method B from benzaldehyde (25.5 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 51.3 g of α-hydroxyphosphonate **50b** as a white solid (0.21 mmol, 84%): m.p. 76-81 °C (lit.[38] 78-80 °C); the NMR data was consistent with the literature.[38]



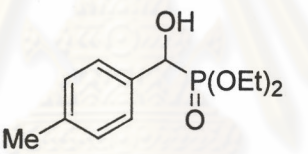
50j

Diethyl 1-hydroxy-(2-methylphenyl)methylphosphonate (50j) was prepared by method B from 4-tolualdehyde (29.6 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 40.2 mg of α-hydroxyphosphonate **50j** as a white solid (0.16 mmol, 62%): m.p.100-102 °C (lit.[20] 98-100 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, $^3J_{HH}$ = 7.1 Hz, 3H, OCH_2CH_3), 1.31 (t, $^3J_{HH}$ = 7.1 Hz, 3H, OCH_2CH_3), 2.41 (s, 3H, CH_3), 3.34 (bs, 1H, OH), 3.92-4.02 (m, 2H, OCH_2CH_3), 4.04-4.13 (m, 2H, OCH_2CH_3), 5.30 (d, $^2J_{HP}$ = 10.7 Hz, 1H, CHOH), 7.17-7.30 (m, 3H, Ar), 7.67 (d, $^3J_{HH}$ = 7.4 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 16.4 (OCH_2CH_3), 20.0 (2-$CH_3C_6H_5$), 63.0 (OCH_2CH_3), 63.4 (OCH_2CH_3), 67.1 (d, $^1J_{CP}$ = 160.2 Hz, CHOH), 126.1, 127.3, 127.9, 130.2, 135,5, 135.8.



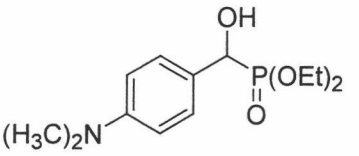
50k

Dimethyl 1-hydroxy-(4-methylphenyl)methylphosphonate (50k) was prepared by method B from 4-tolualdehyde (29.6 μL, 0.25 mmol) and dimethyl phosphite (25 μL, 0.27 mmol). The reaction yielded 28.4 mg of α-hydroxyphosphonate **50k** as a white solid (0.12 mmol, 49%): m.p. 97-98 °C (lit.[38] 90 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H, 4-C*H*$_3$C$_6$H$_4$), 3.70 (d, $^3J_{HH}$ = 10.4 Hz, 3H, OC*H*$_3$), 3.76 (d, $^3J_{HH}$ = 10.4 Hz, 3H, OC*H*$_3$), 5.05 (d, $^2J_{HP}$ = 10.4 Hz, 1H, C*H*OH), 7.23 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar), 7.41 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 21.2 (4-*C*H$_3$C$_6$H$_5$), 53.7 (d, $^2J_{CP}$ = 7.0 Hz, O*C*H$_3$), 54.0 (d, $^2J_{CP}$ = 7.0 Hz, O*C*H$_3$), 70.5 (d, $^1J_{CP}$ = 160.1 Hz, *C*HOH), 126.9, 127.0, 129.2, 133.3, 133.1, 138.1.



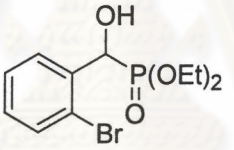
50l

Diethyl 1-hydroxy-(4-methylphenyl)methylphosphonate (50l) was prepared by method B from 4-tolualdehyde (29.6 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 40.2 mg of α-hydroxyphosphonate **50l** as a white solid (0.16 mmol, 62%): m.p.100-102 °C (lit.[20] 98-100 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 2.37 (s, 3H, 4-C*H*$_3$C$_6$H$_4$), 2.80 (bs, 1H, O*H*), 3.92-3.99 (m, 2H, OC*H*$_2$CH$_3$), 4.01-4.10 (m, 2H, OC*H*$_2$CH$_3$), 5.01 (d, $^2J_{HP}$ = 10.0 Hz, 1H, C*H*OH), 7.22 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ar), 7.40 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 16.4 (d, $^3J_{CP}$ = 5.1 Hz, OCH$_2$*C*H$_3$), 21.2 (4-*C*H$_3$C$_6$H$_4$), 63.2 (d, $^2J_{CP}$ = 6.9 Hz, O*C*H$_2$CH$_3$), 70.7 (d, $^1J_{CP}$ = 159.5 Hz, *C*HOH), 127.0, 127.1, 129.0, 133.5, 137.8, 137.9.



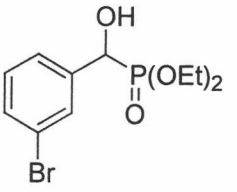
50m

Diethyl 1-hydroxy-(4-dimethylaminophenyl)methylphosphonate (50m) was prepared by method B from 4-dimethylaminobenzaldehyde (37.3 mg, 0.25mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 25.8 mg of α-hydroxyphosphonate **50m** as a pale yellow solid (0.09 mmol, 36%): m.p. 82-84 °C (lit.[20] 81-83 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 1.28 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 2.95 (s, 6H, $N(CH_3)_2$), 3.90-3.99 (m, 2H, OCH_2CH_3), 4.01-4.10 (m, 2H, OCH_2CH_3), 4.89 (d, $^2J_{HP}$ = 9.6 Hz, 1H, CHOH), 6.76 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ar), 7.35 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 16.5 (d, $^3J_{CP}$ = 5.8 Hz, OCH_2CH_3), 40.9 (4-$N(CH_3)_2C_6H_4$), 112.6, 112.7, 112.8, 112.9, 128.3, 128.4.



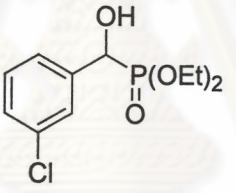
50n

Diethyl 1-hydroxy-(-2-bromophenyl)methylphosphonate (50n) was prepared by method B from 2-bromobenzaldehyde (28.9 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 61 mg of α-hydroxyphosphonate **50n** as a colorless oil (0.19 mmol, 76%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, $^3J_{HH}$ = 7.1 Hz, 3H, OCH_2CH_3), 1.36 (t, $^3J_{HH}$ = 7.1 Hz, 3H, OCH_2CH_3), 3.94-4.11 (m, 2H, OCH_2CH_3), 4.13-4.27 (m, 2H, OCH_2CH_3), 5.56 (d, $^2J_{HP}$ = 11.7 Hz, 1H, CHOH), 7.21 (t, $^3J_{HH}$ = 7.7 Hz, 1H, Ar), 7.40 (t, $^3J_{HH}$ = 7.5 Hz, 1H, Ar), 7.58 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar), 7.76 (d, $^3J_{HH}$ = 7.8 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4 (OCH_2CH_3), 63.5 (OCH_2CH_3), 69.6 (d, $^1J_{CP}$ = 160.4 Hz, CHOH), 123.3, 127.6, 129.5, 129.6, 132.6, 136.5.



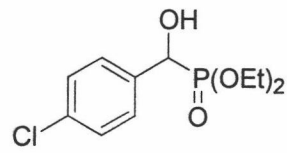
50o

Diethyl 1-hydroxy-(3-bromophenyl)methylphosphonate (50o) was prepared by method B from 3-bromobenzaldehyde (29 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 54.4 mg of α-hydroxyphosphonate **50o** as a colorless oil (0.17 mmol, 67%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27-1.33 (m, 6H, OCH_2CH_3), 1.71 (bs, 1H, OH), 4.07-4.13 (m, 4H, OCH_2CH_3), 5.03 (d, $^{2}J_{HP}$ = 11.2 Hz, 1H, C*H*OH), 7.24-7.69 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 16.4 (d, $^{3}J_{CP}$ = 5.2 Hz, OCH_2CH_3), 63.3 (d, $^{2}J_{CP}$ = 7.0 Hz, OCH_2CH_3), 63.8 (d, $^{2}J_{CP}$ = 6.5 Hz, OCH_2CH_3), 70.1 (d, $^{1}J_{CP}$ = 159.8 Hz, *C*HOH), 122.3, 125.7, 129.7, 130.1, 131.0, 139.2.



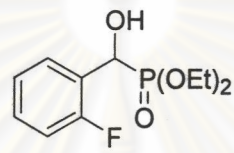
50p

Diethyl 1-hydroxy-(3-chlorophenyl)methylphosphonate (50p) was prepared by method B from 3-chlorobenzaldehyde (22.5 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 29 mg of α-hydroxyphosphonate **50p** as a white solid (0.10 mmol, 42%): m.p. 63-64 °C (lit.[20] 53-54 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, OCH_2CH_3), 1.32 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, OCH_2CH_3), 4.03-4.18 (m, 4H, OCH_2CH_3), 5.04 (d, $^{2}J_{HP}$ = 11.2 Hz, 1H, C*H*OH), 7.31-7.35 (m, 2H, ArH_2), 7.37-7.41 (m, 1H, Ar), 7.54 (s, 1H, Ar); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 16.4 (d, $^{3}J_{CP}$ = 5.6 Hz, OCH_2CH_3), 63.2 (d, $^{2}J_{CP}$ = 7.3 Hz, OCH_2CH_3), 63.7 (d, $^{2}J_{CP}$ = 7.1 Hz, OCH_2CH_3), 70.1 (d, $^{1}J_{CP}$ = 159.2 Hz, *C*HOH), 125.2, 127.1, 128.1, 129.4, 134.2, 138.8.



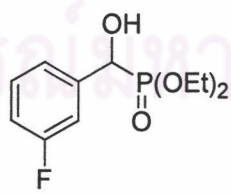
50g

Diethyl 1-hydroxy-(4-chlorophenyl)methylphosphonate (50g) was prepared by method B from 4-chlorobenzaldehyde (35.1 mg, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 40.5 mg of α-hydroxyphosphonate **50g** as a white solid (0.14 mmol, 58%): m.p. 73-74 °C (lit.[20] 70-72 °C); the NMR data was identical with those of diethyl 1-hydroxy-(4-chlorophenyl)methylphosphonate (**50g**).



50q

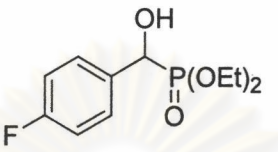
Diethyl 1-hydroxy-(2-fluorophenyl)methylphosphonate (50q) was prepared by method B from 2-fluorobenzaldehyde (20.4 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 46.2 mg of α-hydroxyphosphonate **50q** as a colorless oil (0.17 mmol, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 1.35 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 4.01-4.12 (m, 2H, OCH_2CH_3), 4.13-4.23 (m, 2H, OCH_2CH_3), 5.41 (d, $^{2}J_{HP}$ = 11.6 Hz, 1H, CHOH), 7.08 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, Ar), 7.23 (t, $^{3}J_{HH}$ = 7.4 Hz, 1H, Ar), 7.30-7.36 (m, 1H, Ar), 7.69 (t, $^{3}J_{HH}$ = 7.4 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (d, $^{3}J_{CP}$ = 5.6 Hz, OCH_2CH_3), 63.2 (d, $^{2}J_{CP}$ = 7.0 Hz, OCH_2CH_3), 63.7 (d, $^{2}J_{CP}$ = 7.1 Hz, OCH_2CH_3), 63.7 (d, $^{1}J_{CP}$ = 150 Hz, CHOH), 115.0, 124.4, 128.9, 129.3, 158.5, 160.3.



50r

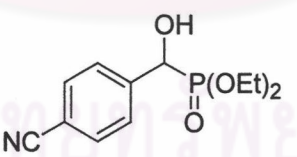
Diethyl 1-hydroxy-(3-fluorophenyl)methylphosphonate (50r) was prepared by method B from 3-fluorobenzaldehyde (20 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 43.4 mg of α-hydroxyphosphonate **50r** as a white solid (0.17 mmol, 66%): m.p.78-80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t,

$^3J_{HH}$ = 7.0 Hz, 3H, OCH_2CH_3), 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 3H, OCH_2CH_3), 1.67 (bs, 1H, OH), 4.04-4.16 (m, 4H, OCH_2CH_3), 5.06 (d, $^2J_{HP}$ = 10.9 Hz, 1H, CHOH), 7.04 (t, $^3J_{HH}$ = 7.8, 8.5 Hz, 1H, Ar), 7.26-7.39 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4 (d, $^3J_{CP}$ = 5.1 Hz, OCH_2CH_3), 63.5 (d, $^2J_{CP}$ = 6.4 Hz, OCH_2CH_3), 62.2 (d, $^1J_{CP}$ = 159.3 Hz, CHOH), 114.4, 122.7, 129.6, 139.4, 161.5, 163.7.



50s

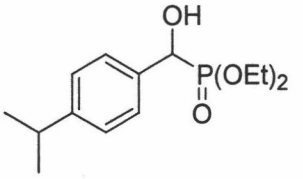
Diethyl 1-hydroxy-(4-fluorophenyl)methylphosphonate (50s) was prepared by method B from 4-fluorobenzaldehyde (17.6 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 39 mg of α-hydroxyphosphonate **50s** as a white solid (0.15 mmol, 59%): m.p. 58-59 °C (lit.[20] 57-59 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, $^3J_{HH}$ = 7.0 Hz, 3H, OCH_2CH_3), 1.31 (t, $^3J_{HH}$ = 7.0 Hz, 3H, OCH_2CH_3), 3.40-4.15 (m, 4H, OCH_2CH_3), 5.04 (d, $^2J_{HP}$ = 10.1 Hz, 1H, CHOH), 7.09 (t, $^3J_{HH}$ = 8.6 Hz, 2H, Ar), 7.50 (t, $^3J_{HH}$ = 6.2 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 16.42 (d, $^3J_{CP}$ = 4.5 Hz, OCH_2CH_3), 63.1 (d, $^2J_{CP}$ = 6.7 Hz, OCH_2CH_3), 63.5 (d, $^2J_{CP}$ = 5.9 Hz, OCH_2CH_3), 70.1 (d, $^1J_{CP}$ = 160.6 Hz, CHOH), 115.1, 115.3, 128.8, 132.4, 161.3, 163.8.



50t

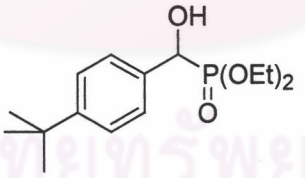
Diethyl 1-hydroxy-(4-cyanophenyl)methylphosphonate (50t) was prepared by method B from 4-cyanobenzaldehyde (33 mg, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 51.6 mg of α-hydroxyphosphonate **50t** as a pale yellow solid (0.19 mmol, 77%): m.p. 84-85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 4.06-4.16 (m, 4H, OCH_2CH_3), 5.13 (d, $^2J_{HP}$ = 12.0 Hz, 1H, CHOH), 7.63 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.65 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 16.4 (d, $^1J_{CP}$ = 4.9 Hz, OCH_2CH_3), 63.2 (d, $^2J_{CP}$ = 7.7 Hz, OCH_2CH_3), 63.9 (d, $^2J_{CP}$ = 7.1 Hz,

OCH_2CH_3), 70.1 (d, $^1J_{CP}$ = 159.2 Hz, *C*HOH), 111.5, 111.5, 118.8, 127.6, 131.9, 142.5.



50u

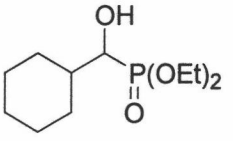
Diethyl 1-hydroxy-(4-isopropylphenyl)methylphosphonate (50u) was prepared by method B from 4-isopropylbenzaldehyde (38 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 56.7 mg of α-hydroxyphosphonate **50u** as a colorless oil (0.20 mmol, 79%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 1.27 (d, $^3J_{HH}$ = 6.8 Hz, 6H, $CH(CH_3)_2$), 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 1.73 (bs, 1H, O*H*), 2.91-2.97 (m, 1H, $CH(CH_3)_2$)3.97-4.03 (m, 2H, OCH_2CH_3), 4.06-4.14 (m, 2H, OCH_2CH_3), 5.02 (d, $^2J_{HP}$ = 10.5 Hz, C*H*OH), 7.26 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar), 7.43 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 16.4 ($^3J_{CP}$ = 5.9 Hz, OCH_2CH_3), 24.0 ($CH(CH)_3$), 33.8 ($CH(CH)_3$), 63.0 (d, $^2J_{CP}$ = 7.2 Hz, OCH_2CH_3), 63.3 (d, $^2J_{CP}$ = 7.0 Hz, OCH_2CH_3), 84.2 (d, $^1J_{CP}$ = 159.9 Hz, *C*HOH), 126.3, 126.6, 127.1, 127.2, 134.0, 148.8.



50v

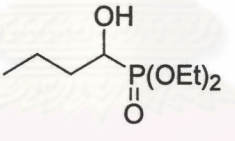
Diethyl 1-hydroxy-(4-*tert*-butylphenyl)methylphosphonate (50v) was prepared by method B from 4-*tert*-butylbenzaldehyde (42 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 62.5 mg of α-hydroxyphosphonate **50v** as a colorless oil (0.21 mmol, 83%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 1.28 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 1.33 (bs, 9H, CH_3), 3.96-4.09 (m, 4H, OCH_2CH_3), 5.00 (d, $^2J_{HP}$ = 10.8 Hz, 1H, C*H*OH), 7.37-7.44 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4 ($^3J_{CP}$ = 6.0 Hz, OCH_2CH_3), 31.4 (CH_3), 34.6 ($C(CH_3)_3$), 63.1 (d, $^2J_{CP}$ = 7.2 Hz, OCH_2CH_3),

63.3 (d, $^{2}J_{CP}$ = 6.9 Hz, O*C*H_2CH$_3$), 70.6 (d, $^{1}J_{CP}$ = 159.0 Hz, *C*HOH), 125.2, 126.9, 133.5, 151.0.



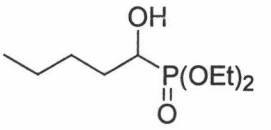
50w

Diethyl 1-hydroxycyclohexylphosphonate (50w) was prepared by method B from cyclohexanecarboxaldehyde (30 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 34.4 mg of α-hydroxyphosphonate **50w** as a colorless oil (0.14 mmol, 55%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16-1.34 (m, 4H, C*H*$_2$), 2.03 (d, $^{3}J_{HP}$ = 11.9 Hz, 2H, C*H*$_2$CH), 1.38 (t, $^{2}J_{HP}$ = 6.3 Hz, 6H, OCH$_2$C*H*$_3$), 1.79 (bs, 4H, C*H*$_2$), 2.27 (bs, 2H, O*H*, C*H*CH), 3.68-3.75 (m, 1H, C*H*OH), 4.16-4.27 (m, 4H, OC*H*$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5 (d, $^{3}J_{CP}$ = 5.5 Hz, OCH$_2$*C*H$_3$), 26.0 (*C*H$_2$), 26.2 (*C*H$_2$), 27.8 (*C*H$_2$), 29.0 (*C*H$_2$), 29.8 (CH$_2$), 39.7 (*C*HCH$_2$), 62.5 (d, $^{2}J_{CP}$ = 6.2 Hz, OCH$_2$CH$_3$), 72.4 (d, $^{1}J_{CP}$ = 156.3 Hz, C*H*OH).



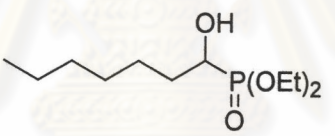
50x

Diethyl 1-hydroxybutylphosphonate (50x) was prepared by method B from butyraldehyde (22.4 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 6.8 mg of α-hydroxyphosphonate **50x** as colorless oil (0.03 mmol, 12%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H, C*H*$_3$), 1.38 (t, $^{3}J_{HH}$ = 7.0 Hz, 6H, OCH$_2$C*H*$_3$), 1.44-1.51 (m, 2H, CH(OH)CH$_2$C*H*$_2$CH$_3$), 1.66-1.77 (m, 2H, CH(OH)C*H*$_2$CH$_2$CH$_3$), 2.31 (bs, 1H, OH), 3.89-3.92 (m, 1H, C*H*OH), 4.17-4.24 (m, 4H, OC*H*$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (*C*H$_3$), 16.6 (OCH$_2$*C*H$_3$), 18.7 (CH(OH)CH$_2$*C*H$_2$CH$_3$), 18.9 (CH(OH)*C*H$_2$CH$_2$CH$_3$), 33.3 (*C*HOH), 62.7 (O*C*H$_2$CH$_3$), 62.8 (O*C*H$_2$CH$_3$).



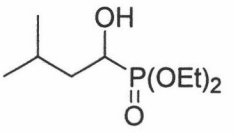
50y

Diethyl 1-hydroxypentylphosphonate (50y) was prepared by method B from valeraldehyde (26.6 μL, 0.25 mmol) and diethyl phosphite 35.5 μL (0.27 mmol). The reaction yielded 30 mg of α-hydroxyphosphonate **50y** as a colorless oil (0.13 mmol, 53%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, $CH(OH)(CH_2)_3CH_3$), 1.37 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 1.36 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3), 1.30-1.46 (m, 2H, $CH(OH)(CH_2)_2CH_2CH_3$), 1.56-1.68 (m, 2H, $CH(OH)CH_2CH_2CH_2CH_3$), 1.70-1.81 (m, 2H, $CH(OH)CH_2(CH_2)_2CH_3$), 3.88 (dt, $^{2}J_{HP}$ = 10.0 Hz, $^{3}J_{HH}$ = 4.0 Hz, 1H, CHOH), 4.15-4.21 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (CH_3), 16.5 (d, $^{3}J_{CP}$ = 5.2 Hz, OCH_2CH_3), 22.4 ($CH(OH)(CH_2)_2CH_2CH_3$), 27.9 ($CH(OH)CH_2CH_2CH_2CH_3$), 31.0 ($CH(OH)CH_2(CH_2)_2CH_3$), 62.6 (d, $^{2}J_{CP}$ = 6.9 Hz, OCH_2CH_3), 67.8 (d, $^{1}J_{CP}$ = 160.2 Hz, CHOH).



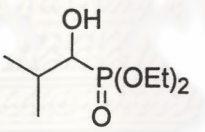
50z

Diethyl 1-hydroxyheptylphosphonate (50z) was prepared by method B from 1-heptaldehyde (34.9 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 2 mg of α-hydroxyphosphonate **50z** as a colorless oil (0.008 mmol, 3%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, $^{3}J_{HH}$ = 6.4 Hz, 3H, $CH(OH)(CH_2)_5CH_3$), 1.32-1.44 (m, 14H, CH_2, OCH_2CH_3), 1.59-1.81 (m, 10H, $CH(OH)(CH_2)_5CH_3$), 2.77 (bs, 1H, OH), 3.88 (dt, $^{3}J_{HH}$ = 4.1 Hz, $^{2}J_{HP}$ = 9.9 Hz, 1H, CHOH), 4.16-4.24 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 ($CH(OH)(CH_2)_5CH_3$), 16.6 ($^{3}J_{CP}$ = 5.4 Hz, OCH_2CH_3), 22.6 ($CH(OH)(CH_2)_4CH_2CH_3$), 25.70 ($CH(OH)(CH_2)_3CH_2CH_2CH_3$), 29.0 ($CH(OH)(CH_2)_2CH_2(CH_2)_2CH_3$), 31.3 ($CH(OH)CH_2CH_2(CH_2)_3CH_3$), 31.7 ($CH(OH)CH_2(CH_2)_4CH_3$), 62.6 (d, $^{2}J_{CP}$ = 7.8 Hz, OCH_2CH_3), 62.6 (d, $^{2}J_{CP}$ = 7.6 Hz, OCH_2CH_3), 67.9 (d, $^{1}J_{CP}$ = 159.9 Hz, CHOH).



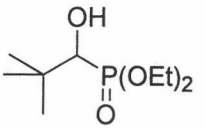
50aa

Diethyl 1-hydroxy-3-methylbutylphosphonate (50aa) was prepared by method B from isovaleraldehyde (27.0 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 46.5 mg of α-hydroxyphosphonate **50aa** as a colorless oil (0.21 mmol, 83%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, $^{3}J_{HH}$ = 6.8 Hz, 3H, $CH(OH)CH_2CH(CH_3)_2$), 0.98 (d, $^{3}J_{HH}$ = 6.8 Hz, 3H, $CH(OH)CH_2CH(CH_3)_2$), 1.35 (t, $^{3}J_{HH}$ = 7.6 Hz, 6H, OCH_2CH_3), 1.42-1.51 (m, 1H, $CH(OH)CH_2CH(CH_3)_2$), 1.68-1.78 (m, 2H, $CH(OH)CH_2CH(CH_3)_2$), 3.83 (bs, 1H, O*H*), 3.97 (dt, $^{2}J_{HP}$ = 11.6 Hz, $^{3}J_{HH}$ = 4.0 Hz, 1H, C*H*OH), 4.14-4.20 (m, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5 ($^{3}J_{CP}$ = 5.2 Hz, OCH_2CH_3), 21.1 ($CH(OH)CH_2CH(CH_3)_2$), 23.5 ($CH(OH)CH_2CH(CH_3)_2$), 24.1 ($CH(OH)CH_2CH(CH_3)_2$), 39.9 ($CH(OH)CH_2CH(CH_3)_2$), 62.6 (d, $^{2}J_{CP}$ = 7.2 Hz, OCH_2CH_3), 66.4 (d, $^{1}J_{CP}$ = 160.8 Hz, *C*HOH).



50bb

Diethyl 1-hydroxy-2-methylpropylphosphonate(50bb) was prepared by method B from isobutyraldehyde (22.8 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 22.6 mg of α-hydroxyphosphonate **50bb** as a colorless oil (0.11 mmol, 43%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, $CH(OH)CH(CH_3)_2$), 1.34 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, OCH_2CH_3), 2.04-2.17 (m, 1H, $CH(OH)CH(CH_3)_2$), 3.64 (t, $^{2}J_{HP}$ = 5.9 Hz, C*H*OH), 4.14-4.21 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5 (OCH_2CH_3), 17.7 ($CH(OH)CH(CH_3)_2$), 19.9 ($CH(OH)CH(CH_3)_2$), 30.1 ($CH(OH)CH(CH_3)_2$), 62.4 (OCH_2CH_3), 73.1 (d, $^{1}J_{CP}$ = 155.7 Hz, *C*HOH).



50cc

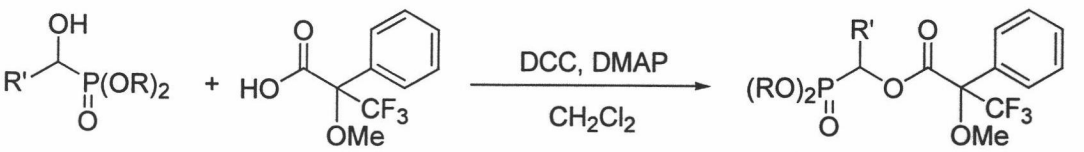
Diethyl 1-hydroxy-2,2-dimethylpropylphosphonate (50cc) was prepared by method B from pivaladehyde (27.5 μL, 0.25 mmol) and diethyl phosphite (35.5 μL, 0.27 mmol). The reaction yielded 27.5 mg of α-hydroxyphosphonate **50cc** as a colorless oil (0.12 mmol, 48%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 9H, CH(OH)C(CH_3)$_3$), 1.35 (t, $^3J_{HH}$ = 7.1 Hz, 6H, OCH$_2$CH_3), 3.07 (bs, 1H, O*H*), 3.60 (d, $^2J_{HP}$ = 7.5 Hz, C*H*OH), 4.15-4.23 (m, 4H, OCH_2CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5 (d, $^3J_{CP}$ = 5.9 Hz, OCH$_2$*C*H$_3$), 26.6 (d, $^3J_{CP}$ = 6.2 Hz, CH(OH)C(*C*H$_3$)$_3$), 34.6 (d, $^2J_{CP}$ = 2.9 Hz, CH(OH)*C*(CH$_3$)$_3$), 62.3 (d, $^2J_{CP}$ = 7.3 Hz, O*C*H$_2$CH$_3$), 62.5 (d, $^2J_{CP}$ = 7.1 Hz, O*C*H$_2$CH$_3$), 75.5 (*C*H(OH)C(CH$_3$)$_3$).

2.4 General method for optical purity determination of α-hydroxyphosphonates.

2.4.1 Analysis of α-hydroxyphosphonates using a chiral GC column.

An α-hydroxyphosphonate was dissolved in CH_2Cl_2. An aliquot of the solution was injected into a 10% BSiMe in a PS255 capillary column (0.25 mm × 0.25 μm) or 25.5% BSiMe in an OV-1701 capillary column (0.25 mm × 0.25 μm). Analyses were performed isothermally in the temperature range of 120-250 °C and in temperature program. α-Hydroxyphosphonates must be purified by flash column chromatography before analysed by chiral gas chromatographic analysis. Integrals of peak area were calculated to determine the enantiomeric excess of the mixture.

2.4.2 General procedure for preparation of MTPA ester of α-hydroxyphosphonates.



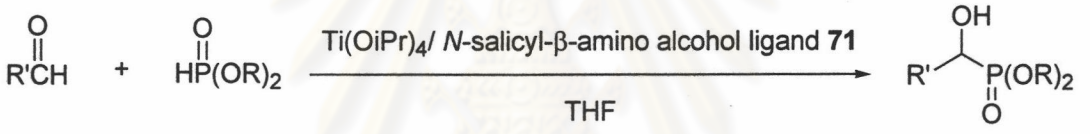
(*R*)- or (*S*)-MTPA

To a stirred solution of (2*R*)- or (2*S*)-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid ((*R*)- or (*S*)-MTPA) (2 equiv), *N*,*N*-dicyclohexylcarbodiimide

(DCC) (2 equiv) and 4,4-dimethylaminopyridine (DMAP) (0.2 equiv) in CH_2Cl_2 was added a solution of α-hydroxyphosphonate (1 equiv) in CH_2Cl_2 at 0 °C. The mixture was stirred at this temperature for 30 min and then kept at room temperature until the starting material was completely consumed as evidenced by TLC. The reaction was quenched by an addition of dilute hydrochloric acid to the mixture at 0 °C after which was extracted with $CHCl_3$. The extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was passed through silica gel. The filtrate was evaporated to leave MTPA ester of α-hydroxyphosphonate that was analyzed by ^1H NMR without purification.

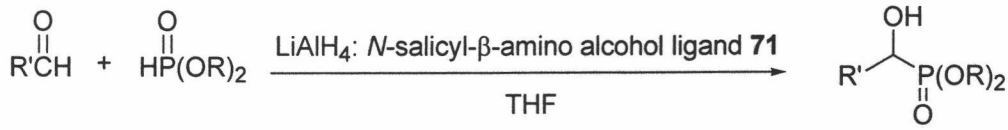
2.5 General procedure for asymmetric synthesis of α-hydroxyphosphonates

2.5.1 Representative procedure for Pudovik reactions with $Ti(O^iPr)_4$: *N*-salicyl-β-aminoalcohol complex.



To a stirred solution of *N*-salicyl-β-aminoalcohol ligand **71** (0.05 mmol) in dry THF (1 mL) was added $Ti(O^iPr)_4$ (12.2 mg, 0.05 mmol) at room temperature. The mixture was then treated with a solution of diethyl phosphite (42.6 μL, 0.33 mmol) in THF (1 mL) for 30 min. A solution of aldehyde (0.15 mmol) in THF (1 mL) was added to the reaction mixture after which was stirred at room temperature until the reaction was complete, as indicated by TLC (SiO_2, 50% EtOAc in hexanes). The mixture was then treated with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give a residue. Purification by flash chromatography (SiO_2, gradient from 50% EtOAc in hexanes to 100% EtOAc) gave α-hydroxyphosphonate.

2.5.2 Representative procedure for Pudovik reactions with $LiAlH_4$: *N*-salicyl-β-aminoalcohol complex.



To a stirred solution of *N*-salicyl-β-aminoalcohol ligand **71** (0.025 mmol) in dry THF was added $LiAlH_4$ (25 μL, 0.025 mmol) at room temperature. After being stirred for 1 h, the diethyl phosphite (71 μL, 0.250 mmol) was added and stirred for 30 min. An aldehyde (0.275 mmol) was then the added to the mixture after which was stirred at the same temperature until the reaction was completed, as indicated by TLC (SiO_2, 50% EtOAc in hexanes). The reaction was quenched with H_2O and extracted with EtOAc. The combined extracts were concentrated to give a residue. Purification by flash chromatography (SiO_2, gradient from 50% EtOAc in hexanes to 100% EtOAc) gave α-hydroxyphosphonates.