Supporting Information

Synthesis of α-Fluorinated Phosphonates from α-Fluorovinylphosphonates: A New Route to Analogues of Lysophosphatidic Acid

Yong Xu, Lian Qian, and Glenn D. Prestwich

Department of Medicinal Chemistry

The University of Utah

419 Wakara Way, Suite 205

Salt Lake City, Utah 84108-1257

gprestwich@pharm.utah.edu

General Procedures

Reagent chemicals were obtained from Aldrich and Acros Chemical Corporation and were used without prior purification. Solvents used were of reagent grade and were distilled before use: THF was distilled from sodium wire, and CH_2Cl_2 was distilled from CaH_2. Reactions were performed under an inert atmosphere (N_2 or Ar), unless otherwise indicated. Chromatography refers to flash chromatography on silica gel. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz (^{1}H), 101 MHz (^{13}C), 162 MHz (^{31}P) and 376 MHz (^{19}F), at 25°C. Proton and carbon chemical shifts are given in ppm with relative to TMS as internal standard; external standards used were ^{31}P, 85% H_3PO_4 ($\delta = 0.00$) and ^{19}F, $CFCl_3$ ($\delta=0.00$). (*R*)-1,4-Dioxaspiro[4,5]decane-2-carbaldehyde was prepared from 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol according to Schick s method.[1]

Tetraethyl fluoromethylenebisphosphonate 2

NaH (0.641 g, 16.03 mmol, 60% in mineral oil) was placed in a flame-dried flask under Ar, washed with Et_2O, and then dry THF (90 mL) was added. The suspension was cooled (~0°C, ice bath), and compound **2** (4.40 g, 15.26 mmol) in THF (10 mL) was added. The solution was stirred (0°°C for 15 min, ambient temperature for 60 min, cooled to 0°C), and Selectfluor (6.76 g, 19.08 mmol) was added in one portion. After 15 min, dry DMF (35 mL) was added, the ice-bath was removed after 5 min, and stirring was continued at ambient temperature for 2 h. The reaction mixture was cooled to 0°C, and CH_2Cl_2 (40 mL) and saturated NH_4Cl/H_2O (40 mL) were slowly added. After 5 min, the organic layer was separated, and the aq. layer was extracted (CH_2Cl_2). The combined organic phase was washed (saturated $NaHCO_3/H_2O$, brine), dried ($MgSO_4$), evaporated, and chromatographed (EtOAc:CH_3OH = 100:3, R_f = 0.54) to give 2.40 g (7.84 mmol, 52% yield) of the ester **2**. ^{1}H NMR ($CDCl_3$): 4.93 (dt, *J* = 46.0, 13.6 Hz, 1H), 4.20 (m, 8H), 1.29 (t, *J* = 7.2 Hz, 12H). ^{19}F NMR ($CDCl_3$): -288.26 (td, *J* = 62.9, 45.9 Hz, 1F). ^{31}P°NMR ($CDCl_3$): 12.20 (d, *J* = 63.0 Hz).

(3*R*)-Diethyl 1-fluoro-3,4-*O*-cyclohexylidene-3,4-dihydroxybut-1-enylphosphonate 4

Treatment of **2** (0.184 mg, 0.601 mmol in 5 mL dry hexane) with *n*-BuLi (0.601 mL, 1.0 M solution in hexane) at -78°C under dry nitrogen gas was followed by addition of (*R*)-1,4-dioxaspiro[4,5]decane-2-carbaldehyde (0.143 g, 0.841 mmol). The mixture was stirred at -78°C and allowed to slowly warm to rt overnight. Filtration and evaporation under reduced temperature, followed by chromatography (EtOAc:hexane = 3:2) gave two isomers **4a** (R_f = 0.19, 0.178 g, 0.553 mmol, 92%) and **4b** (R_f = 0.25, 0.015 g, 0.047 mmol, 7%).

(*E*)-Isomer **4a**: ^{1}H NMR ($CDCl_3$): 5.99 (dt, *J* = 39.2, 7.6 Hz, 1H), 4.98 (m, 1H), 4.17-4.08 (m, 5H), 3.63 (dd, *J* = 7.6, 6.4 Hz, 1H), 1.56 (m, 10H), 1.32 (m, 6H). ^{13}C NMR ($CDCl_3$): 151.85 (dd, *J* = 278.0, 233.2 Hz), 124.36 (dd, *J* = 27.6, 3.0 Hz), 110.6 (s), 68.67 (dd, *J* = 12.3, 6.9 Hz), 68.45 (m), 63.29 (dd, *J* = 5.3, 3.0 Hz), 36.09 (s), 35.17 (s), 24.97 (s), 23.78 (s), 16.17 (d, *J* = 6.1 Hz). ^{19}F NMR ($CDCl_3$): -127.04 (dd, *J* = 99.0, 39.1 Hz, 1F). ^{31}P NMR ($CDCl_3$): 4.68 (d, *J* = 98.9 Hz). MS (CI) *m/z* 323 (M^++1, 69.89), 99 ($OC_6H_{11}^+$, 100.00). HRMS, M^+, Found: 322.1354. Calcd for $C_{14}H_{24}FO_5P$, 322.1345. $[\alpha]^{20}_D$ = +51.68 (c = 0.15, EtOH).

(*Z*)-Isomer **4b**: ^{1}H NMR ($CDCl_3$): 6.08 (ddd, *J* = 30.8, 26.8, 9.6 Hz, 1H), 5.41 (m, 1H), 4.16 (m, 5H), 3.62 (dd, *J* = 8.0, 6.0 Hz, 1H), 1.59 (m, 8H), 1.34 (m, 8H). ^{19}F NMR ($CDCl_3$): -118.34 (dd, *J* = 101.6, 26.3 Hz, 1F). ^{31}P NMR ($CDCl_3$): 3.74 (d, *J* = 101.0 Hz).

(3*R*)-Diethyl 1-fluoro-3,4-*O*-cyclohexylidene-3,4-dihydroxybut-1-phosphonate 5

A solution of **4** (0.128 g, 0.398 mmol) in absolute ethanol (8 mL) containing 10% Pd-C catalyst (10 mg) was stirred at ambient temperature under hydrogen (1 atm) until gas uptake ceased (18 h). Filtration and evaporation under reduced pressure gave compound **5** as a colorless liquid (0.126 g, 0.390 mmol, 98% yield). ^{1}H NMR ($CDCl_3$): 4.99-4.76 (m, 1H), 4.33-4.01 (m, 5H), 3.63-3.54 (m, 1H), 2.25-1.98 (m, 2H), 1.56 (m, 8H), 1.31 (m, 8H). ^{13}C NMR ($CDCl_3$): 109.70 (s), 109.66 (s), 86.14 (dd, *J* = 179.4, 171.8 Hz), 86.00 (dd, *J* = 179.4, 171.8 Hz), 71.92 (dd, *J* = 11.5, 3.0 Hz), 71.27 (dd, *J* = 11.5, 3.0 Hz), 68.94 (s), 68.33 (s), 63.09 (dd, *J* = 39.9, 6.9 Hz), 62.98 (dd, *J* = 33.7, 4.6 Hz), 36.70 (s), 36.1417 (s), 35.06 (s), 34.81 (s), 33.99 (d, *J* = 19.1 Hz), 16.40 (d, *J* = 6.1 Hz).

^{19}F NMR ($CDCl_3$): -207.52 (m), -212.53 (m). ^{31}P NMR ($CDCl_3$): 18.76 (d, *J* = 73.8 Hz), 18.47 (d, *J* = 73.8 Hz). MS (CI) *m/z* 325 (M^++1, 100.00). HRMS, M^+, Found: 324.1519. Calcd for $C_{14}H_{26}FO_5P$, 324.1502. $[\alpha]^{20}_D$ = -5.59 (c = 0.34, EtOH).

(3*R*)-Diethyl 1-fluoro-3,4-dihydroxybut-1-phosphonate 6

pTsOH (7 mg, 0.035 mmol, 0.10 eq.) was added to a solution of **5** (0.114 g, 0.352 mmol) in MeOH (5 mL), and the solution was stirred at rt for 24 h. After addition of solid $NaHCO_3$ to neutralize the reaction mixture, the solvent was removed under reduced pressure. Chromatography provided a TLC-homogeneous product (75 mg, 0.306 mmol, 87%). ^{1}H NMR ($CDCl_3$): 5.11-4.87 (m, 1H), 4.19-4.08 (m, 5H), 3.96 (br, 1H), 3.79 (br, 1H), 3.59 (m, 1H), 3.40 (m, 1H), 2.15-1.77 (m, 2H), 1.30 (t, *J* = 6.8 Hz, 8H). ^{19}F NMR ($CDCl_3$): -207.43 (m), -211.70 (m). ^{31}P NMR ($CDCl_3$): 19.89 (d, *J* = 74.0 Hz), 19.36 (d, *J* = 75.9 Hz). $[\alpha]^{20}_D$ = -13.42 (c = 0.73, EtOH).

Diethyl [1-fluoro-3 *(S)*-hydroxyl-4-(oleoyloxy)butyl] phosphonate 7a

To a solution of diol **6** (38 mg, 0.155 mmol) and oleic acid (42 mg, 47 L, 0.147 mmol) in dry CH_2Cl_2 (1 mL) at rt was added dropwise a solution of DCC (30 mg, 0.147 mmol) and DMAP (6 mg, 0.048 mmol) in dry CH_2Cl_2 (1 mL). The mixture was stirred at rt for 18 h and filtered, the solvent removed *in vacuo*, and the residue was purified by chromatography (*n*-hexane:EtOAc = 1:1, R_f = 0.28) to afford 35 mg of a waxy solid (0.070 mmol, 45%). ^{1}H NMR ($CDCl_3$): 5.29 (m, 2H), 5.10-4.89 (m, 1H), 4.22-3.98 (m, 7H), 3.48 (br, 1H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.18-2.03 (m, 2H), 1.93 (m, 4H), 1.58 (m, 2H), 1.33-1.22 (m, 28H), 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.84 (s), 173.81

(s), 129.92 (s), 129.64 (s), 86.49 (dd, *J* = 171.0, 172.6 Hz), 84.71 (dd, *J* = 171.1, 172.6 Hz), 68.06 (s), 67.48 (s), 66.01 (dd, *J* = 10.0, 3.8 Hz), 65.07 (dd, *J* = 13.1, 3.0 Hz), 63.55 (d, *J* = 6.9 Hz), 63.30 (d, *J* = 6.9 Hz), 63.06 (d, *J* = 6.9 Hz), 62.98 (d, *J* = 8.4 Hz), 34.36 (d, *J* = 19.9 Hz), 33.81 (d, *J* = 18.4 Hz), 31.82 (s), 29.67 (s), 29.61 (s), 29.43 (s), 29.23 (s), 29.09 (s), 27.13 (s), 27.08 (s), 24.86 (s), 22.59 (s), 16.35 (m), 14.02 (s). ^{19}F NMR ($CDCl_3$): -208.26 (1F, m), -211.75 (1F, m). ^{31}P NMR ($CDCl_3$): 19.36 (d, *J* = 73.8 Hz), 19.10 (d, *J* = 76.1 Hz). MS (CI) *m/z* 509.4 (M^++1, 29.75), 463.3 (M^+-OC_2H_5, 100.00). HRMS, M^++1, Found: 509.3400. Calcd for $C_{26}H_{51}FO_6P$, 509.3407. $[\alpha]^{20}_D$ = -2.61 (c = 2.38, MeOH).

Diethyl [1-fluoro-3 *(S)*-hydroxyl-4-(linoleoyloxy)butyl] phosphonate 7b

The method of **7a** was followed using lineolic acid to provide a 61% yield of **7b**. ^{1}H NMR ($CDCl_3$): 5.30 (m, 4H), 5.10-4.90 (m, 1H), 4.17-4.01 (m, 7H), 3.51 (br, 0.5H), 3.24 (br, 0.5H), 2.70 (m, 2H), 2.29 (t, *J* = 6.8 Hz, 3H), 2.15-1.98 (m, 6H), 1.57 (m, 2H), 1.29 (m, 20H), 0.83 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.77 (s), 130.10 (s), 129.91 (s), 127.95 (s), 127.80 (s), 85.95 (dd, *J* = 178.7, 171.1 Hz), 85.19 (dd, *J* = 179.5, 171.3 Hz), 68.02 (s), 67.45 (s), 65.99 (dd, *J* = 9.3, 3.9 Hz), 65.00 (dd, *J* = 9.8, 9.7 Hz), 63.40 (dd, *J* = 25.5, 6.8 Hz), 63.00 (dd, *J* = 6.8, 6.8 Hz), 34.14 (dd, *J* = 41.4, 19.2 Hz), 31.41 (s), 29.49 (s), 29.24 (s), 29.07 (s), 29.00 (s), 27.09 (s), 25.52 (s), 24.78 (s), 22.46 (s), 16.36 (d, *J* = 4.5 Hz), 13.96 (s). ^{19}F NMR ($CDCl_3$): -208.25 (m), -211.79 (m). ^{31}P NMR ($CDCl_3$): 19.37 (d, *J* = 73.8 Hz), 19.09 (d, *J* = 76.1 Hz). MS (CI) *m/z* 507 (M^++1, 100.00), 463.3 (M^+-OC_2H_5, 48.19). HRMS, M^+, Found: 506.3174. Calcd for $C_{26}H_{48}FO_6P$, 506.3173. $[\alpha]^{20}_D$ = -4.29 (c = 0.14, EtOH).

Diethyl [1-fluoro-3 *(S)*-hydroxyl-4-(palmitoyloxy)butyl] phosphonate 7c

The method of **7a** was followed using palmitic acid to give **7c** in 51% yield. ^{1}H NMR ($CDCl_3$): 5.11-4.90 (m, 1H), 4.23-3.99 (m, 7H), 3.42 (br, 1H), 2.31 (t, *J* = 7.6 Hz, 2H), 2.19-1.90 (m, 2H), 1.68-1.55 (m, 2H), 1.33 (t, *J* = 6.8 Hz, 6H), 1.60 (m, 24H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.92 (s), 173.89 (s), 86.56 (dd, *J* = 171.0, 168.2 Hz), 84.78 (dd, *J* = 171.0, 168.2 Hz), 68.10 (s), 67.53 (s), 66.11 (dd, *J* = 9.3, 3.8 Hz), 65.21 (dd, *J* = 13.0, 3.1 Hz), 63.48 (dd, *J* = 24.6, 6.9 Hz), 63.05 (dd, *J* = 9.3, 6.8 Hz), 49.03 (s), 34.36 (d, *J* = 19.9 Hz), 31.87 (s), 29.63 (s), 29.60 (s), 29.41 (s), 29.22 (s), 29.09 (s), 25.59 (s), 24.86 (s), 22.63 (s), 16.41 (d, *J* = 5.3 Hz), 16.37 (d, *J* = 4.6 Hz), 14.06 (s). ^{19}F NMR ($CDCl_3$): -208.37 (1F, m), -211.62 (1F, m). ^{31}P NMR ($CDCl_3$): 19.34 (d, *J* = 73.8 Hz), 19.11 (d, *J* = 76.1 Hz). MS (CI) *m/z* 483.4 (M^++1, 55.29), 437.4 (M^+-OC_2H_5, 100.00). HRMS, M^++1, Found: 483.3244. Calcd for $C_{24}H_{49}FO_6P$, 483.3251. $[\alpha]^{20}_D$ = -2.20 (c = 1.00, MeOH).

[1-Fluoro-3 *(S)*-hydroxyl-4-(oleoyloxy)butyl] phosphonate 8a

A thoroughly dried aliquot of intermediate **7a** (64 mg, 0.126 mmol, 5 h at <˚0.1˚mm Hg) was dissolved in anhydrous methylene chloride (1 mL) at rt. Bromotrimethylsilane (193 mg, 1.260 mmol) was added with a dry syringe and the mixture was stirred for 4 h at rt, at which time TLC indicated that all of the starting material had been consumed. Solvents were removed under reduced pressure and the residue was dried *in vacuo*, dissolved in 95% methanol (1 mL) for 1 h, reconcentrated under reduced pressure and redried under vacuum, to give 55 mg of **8a** (0.121 mmol,

96% yield.). ^{1}H NMR (CD_3OD): 5.34 (m, 2H), 5.21-5.17 (m, 1H), 4.79 (m, 1H), 3,68 (dd, *J* = 11.60, 4.40 Hz, 1H), 3.57 (m, 1H), 2.35 (m, 4H), 2.01 (m, 4H), 1.63 (m, 2H), 1.33-1.22 (m, 20H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (CD_3OD): 174.33 (s), 174.17 (s), 130.84 (s), 130.74 (s), 88.16 (dd, *J* = 170.3, 168.7 Hz), 86.39 (dd, *J* = 170.3, 168.7 Hz), 71.30 (dd, *J* = 14.6, 2.3 Hz), 69.52 (dd, *J* = 14.6, 2.3 Hz), 35.12 (d, *J* = 19.3 Hz), 34.93 (d, *J* = 18.9 Hz), 33.04 (s), 30.84 (s), 30.77 (s), 30.61 (s), 30.44 (s), 30.35 (s), 30.26 (s), 30.16 (s), 30.13 (s), 28.14 (s), 28.13 (s), 23.72 (s), 14.55 (s). ^{19}F NMR (CD_3OD): -208.60 (1F, m), -210.99 (1F, m). ^{31}P NMR (CD_3OD): 16.21 (d, *J* = 72.7 Hz), 15.95 (d, *J* = 73.8 Hz). MS (CI) *m/z* 435.3 (M^+-OH, 60.85), 283.3 (M^+-C_4H_9-CFH_3PO_3, 100.00). HRMS, M^+-OH, Found: 435.2678. Calcd for $C_{22}H_{41}FO_5P$, 435.2676. $[\alpha]^{20}_D$ = -2.13 (c = 0.14, MeOH).

[1-Fluoro-3 *(S)*-hydroxyl-4-(linoleoyloxy)butyl] phosphonate 8b

The method of **8a** was employed to give **8b** in 93% yield. ^{1}H NMR (CD_3OD): 5.30 (m, 4H), 5.10-4.90 (m, 1H), 4.17-4.01 (m, 3H), 3.51 (br, 0.5H), 3.24 (br, 0.5H), 2.70 (m, 2H), 2.29 (t, *J* = 6.8 Hz, 3H), 2.15-1.98 (m, 6H), 1.57 (m, 2H), 1.29 (m, 14H), 0.83 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (CD_3OD): 174.33 (s), 174.17 (s), 130.84 (s), 130.74 (s), 88.16 (dd, *J* = 170.3, 168.7 Hz), 86.39 (dd, *J* = 170.3, 168.7 Hz), 71.30 (dd, *J* = 14.6, 2.3 Hz), 69.52 (dd, *J* = 14.6, 2.3 Hz), 35.12 (d, *J* = 19.3 Hz), 34.93 (d, *J* = 18.9 Hz), 33.04 (s), 30.84 (s), 30.77 (s), 30.61 (s), 30.44 (s), 30.35 (s), 30.26 (s), 30.16 (s), 30.13 (s), 28.14 (s), 28.13 (s), 23.72 (s), 14.55 (s). ^{19}F NMR (CD_3OD): -208.25 (m), -211.79 (m). ^{31}P NMR (CD_3OD): 19.37 (d, *J* = 73.8 Hz), 19.09 (d, *J* = 76.1 Hz). HRMS, M^+-OH, Found: 433.2502. Calcd for $C_{22}H_{39}FO_5P$, 433.2519. $[\alpha]^{20}_D$ = -2.78 (c = 0.22, MeOH).

[1-Fluoro-3 *(S)*-hydroxyl-4-(palmitoyloxy)butyl] phosphonate 8c

The method of **8a** was employed to give **8c** in 91% yield. ^{1}H NMR (CD_3OD): 5.27-5.18 (m, 1H), 4.78 (m, 1H), 3.68 (dd, *J* = 10.80, 4.00 Hz, 1H), 3.57 (m, 1H), 2.40-2.25 (m, 4H), 1.64 (m, 2H), 1.33-1.22 (m, 24H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): 172.33 (s), 172.30 (s), 87.06 (dd, *J* = 170.3, 168.7 Hz), 85.29 (dd, *J* = 170.3, 168.7 Hz), 69.33 (dd, *J* = 14.2, 2.4 Hz), 67.56 (dd, *J* = 14.2, 2.4 Hz), 33.04 (d, *J* = 7.7 Hz), 31.92 (s), 31.06 (s), 28.77 (s), 28.75 (s), 28.71 (s), 28.58 (s), 28.47 (s), 28.39 (s), 28.15 (s), 24.05 (s), 23.97 (s), 23.92 (s), 21.72 (s), 12.48 (s). ^{19}F NMR ($CDCl_3$): -208.73 (1F, m), -211.07 (1F, m). ^{31}P NMR ($CDCl_3$): 16.21 (d, *J* = 72.7 Hz), 15.95 (d, *J* = 73.8 Hz). MS (CI) *m/z* 409.2 (M^++1-OH-CH_3, 2.29), 225.2 (M^+-$C_{14}H_{29}$-OH, 100.00). HRMS, M^+-OH-CH_3, Found: 408.2432. Calcd for $C_{20}H_{38}FO_5P$, 408.2441. $[\alpha]^{20}_D$ = -1.83 (c = 0.17, MeOH).

Diethyl [1-fluoro-3 *(S)*-hydroxyl-4-*(tert*-butyldimethylsilyl)-butyl] phosphonate 9

To a solution of phosphate **6** (0.386 g, 1.582 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl) (0.250 g, 1.661 mmol, 1.05 eq.) in anhydrous CH_2Cl_2 (8 mL) was added 4-dimethylaminopyridine (DMAP) (0.010 g, 0.080 mmol, 0.05 eq.) and triethylamine (0.168 g, 1.661 mmol, 1.05 eq.). The reaction mixture was stirred at rt for 16 h. The solution was diluted with CH_2Cl_2 (20 mL), and the solution was washed with saturated aq. NH_4Cl solution and brine. After drying with anhydrous Na_2SO_4, the organic layer was concentrated *in vacuo*. The residue was purified by chromatography (EtOAc:hexane = 1:1, R_f = 0.13) to afford **9** as a colorless liquid (0.413 g, 1.155 mmol,

73%). ^{1}H NMR ($CDCl_3$): 5.12-4.88 (m, 1H), 4.19 (m, 4H), 3.96-3.82 (m, 1H), 3.67-3.43 (m, 2H), 2.83 (d, *J* = 4.4 Hz, 0.5H), 2.60 (d, *J* = 5.2 Hz, 0.5H), 2.23-1.79 (m, 2H), 1.33 (t, *J* = 6.8 Hz, 6H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$): 86.43 (dd, *J* = 178.7, 171.0 Hz), 85.63 (dd, *J* = 178.7, 171.0 Hz), 68.47 (dd, *J* = 10.0, 3.8 Hz), 67.10 (dd, *J* = 13.0, 3.8 Hz), 66.96 (s), 66.39 (s), 63.26 (dd, *J* = 15.3, 6.8 Hz), 62.86 (dd, *J* = 9.3, 6.9 Hz), 33.81 (d, *J* = 18.4 Hz), 25.81 (s), 18.24 (s), 18.22 (s), 23.78 (s), 16.49 (d, *J* = 3.8 Hz), 16.38 (d, *J* = 3.8 Hz), -5.43 (s), -5.47 (s). ^{19}F NMR ($CDCl_3$): -207.18 (m), -211.77 (m). ^{31}P NMR ($CDCl_3$): 19.60 (d, *J* = 75.0 Hz), 19.24 (d, *J* = 77.1 Hz). MS (CI) *m/z* 359.0 (M^++1, 100.00). HRMS, M^++1, Found: 359.1819. Calcd for $C_{14}H_{33}FO_5PSi$, 359.1819. $[\alpha]^{20}_D$ = -20.91 (c = 0.88, EtOH).

Diethyl [1-fluoro-3 *(S)*-*O*-methyl-4-*(tert*-butyldimethylsilyl)-butyl] phosphonate 10

Method A: To a vigorously stirred mixture of **9** (0.046 g, 0.136 mmol) and aq. HBF_4 (42% aq. fluoroboric acid, 0.028 g, 20 μL) in CH_2Cl_2 (1 mL) was added $TMSCHN_2$ (2.0 M hexane solution, 136 μL) at 0°C. The stirring was continued at 0°C, and three further portions of $TMSCHN_2$ (68 μL × 3) were added dropwise at intervals of 20 min. The mixture was stirred at 0°C for additional 30 min, at rt for another 30 min, and 10% $NaHCO_3$ solution (0.1 mL) was added. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (EtOAc:hexane = 2:3, R_f = 0.31) to afford a colorless liquid (0.034 g, 0.091 mmol, 67%).

Method B: To a stirred mixture of **9** (0.022 g, 0.061 mmol) and proton sponge (1,8-bis(dimethylamino)naphthalene) (0.016 g, 0.073 mmol) in CH_2Cl_2 (1 mL) was added Meerwein s trimethyloxonium tetrafluoroborate (0.009 g, 0.061 mmol) at rt. The

resulting solution was stirred at rt for 14 days before it was diluted with CH_2Cl_2 (2 mL) and quenched with water (0.1 mL). The solution was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (EtOAc:hexane = 2:3, R_f = 0.31) to afford a colorless liquid (0.010 g, 0.027 mmol, 43%). ^{1}H NMR ($CDCl_3$): 5.04-4.89 (m, 1H), 4.19 (m, 4H), 3.70-3.58 (m, 2H), 3.46 (m, 1H), 3.42 (s, 1.5H), 3.37 (s, 1.5H), 2.14-1.79 (m, 2H), 1.31 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$): 86.43 (dd, *J* = 178.7, 171.0 Hz), 85.63 (dd, *J* = 178.7, 171.0 Hz), 64.68 (s), 64.40 (s), 63.08 (m), 62.75 (m), 58.46 (s), 57.59 (s), 32.67 (d, *J* = 22.2 Hz), 31.77 (d, *J* = 19.2 Hz), 25.84 (s), 18.25 (s), 18.22 (s), 16.42 (d, *J* = 6.1 Hz), -5.46 (s). ^{19}F NMR ($CDCl_3$): -207.71 (m), -212.49 (m). ^{31}P NMR ($CDCl_3$): 19.76 (d, *J* = 76.1 Hz), 19.23 (d, *J* = 76.1Hz). MS˚(CI) *m/z* 373.19 (M^++1, 100.00). HRMS, M^++1, Found: 373.1974. Calcd for $C_{15}H_{34}FO_5PSi$, 373.1975. $[\alpha]^{20}_D$ = -13.96 (c = 0.48, EtOH).

Diethyl [1-fluoro-3 *(S)*-hydroxyl-4-*O*-methyl-butyl] phosphonate 11

To a stirred mixture of **6** (0.086 g, 0.352 mmol) and proton sponge (1,8-bis(dimethylamino)naphthalene) (0.091 g, 0.432 mmol) in CH_2Cl_2 (5 mL) was added Meerwein s trimethyloxonium tetrafluoroborate (0.053 g, 0.352 mmol) at rt . The resulting solution was stirred at rt for 4 d, then diluted with CH_2Cl_2 (5 mL) and quenched with water (0.1mL). After removal of solvents, EtOAc was added and the organic solution was washed with saturated NH_4Cl, dried with anhydrous $MgSO_4$, and concentrated. The residue was purified by chromatography (CH_2Cl_2:CH_3OH = 20:1, R_f = 0.25) to afford a colorless liquid (0.042 g, 0.163 mmol, 46%). ^{1}H NMR ($CDCl_3$): 5.10-4.89 (m, 1H), 4.13 (m, 4H), 4.10-3.90 (m, 1H), 3.41-3.40 (m, 3H),

3.33 (s, 3H), 2.15-2.01 (m, 2H), 1.30 (m, 6H). ^{19}F NMR ($CDCl_3$): -207.59 (m), -212.02 (m). ^{31}P NMR ($CDCl_3$): 19.76 (d, *J* = 76.1 Hz), 19.23 (d, *J* = 76.1Hz).

Diethyl [1-fluoro-3 *(S)*-(oleoyloxy)-4-*O*-methyl-butyl] phosphonate 12a

To a solution of alcohol **11** (0.036 g, 0.140 mmol) and oleic acid (0.043 g, 0.154 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of DCC (0.040 g, 0.196 mmol) and DMAP (0.010 g, 0.084 mmol) in dry CH_2Cl_2 (4 mL) at 0˚ßC. The solution was stirred for 16 h at rt, filtered, concentrated *in vacuo*, and the residue was chromatographed (*n*-hexane:EtOAc = 1:1, R_f = 0.34) to afford 0.061 g ester **12a** (0.117 mmol, 83%) as a waxy solid. ^{1}H NMR ($CDCl_3$): 5.31 (m, 2H), 5.21-5.16 (m, 1H), 4.93-4.77 (m, 1H), 4.19 (m, 4H), 3.49 (m, 1H), 3.43 (m, 1H), 3.32 (s, 3H), 2.32-2.13 (m, 4H), 1.98 (m, 4H), 1.59 (m, 2H), 1.34-1.23 (m, 26H), 0.84 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.20 (s), 173.07 (s), 129.95 (s), 129.69 (s), 84.85 (dd, *J* = 178.7, 171.0 Hz), 84.05 (dd, *J* = 178.7, 171.0 Hz), 73.46 (s), 73.03 (s), 69.35 (d, *J*˚= 14.6 Hz), 67.95 (d, *J* = 15.4 Hz), 63.32 (d, *J* = 6.8 Hz), 62.97 (d, *J* = 6.2 Hz), 59.16 (d, *J* = 4.6 Hz), 34.33 (s), 34.28 (s), 31.85 (s), 31.76 (s), 29.71 (s), 29.65 (s), 29.47 (s), 29.27 (s), 29.13 (s), 29.07 (s), 29.02 (s), 27.16 (s), 27.13 (s), 24.92 (s), 24.83 (s), 16.41 (m), 14.05 (s). ^{19}F NMR ($CDCl_3$): -208.71 (m), -211.47 (m). ^{31}P NMR ($CDCl_3$): 18.57 (d, *J* = 73.8 Hz), 18.21 (d, *J* = 76.1 Hz). MS (CI) *m/z* 523.4 (M^++1, 100.00). HRMS, M^++1, Found: 523.3586. Calcd for $C_{27}H_{53}FO_6P$, 523.3564.

Diethyl [1-fluoro-3 *(S)*-(palmitoyloxy)-4-*O*-methyl-butyl] phosphonate 12b

The method of **12a** was used with palmitic acid to give **12b** in 87% yield. ^{1}H NMR ($CDCl_3$): 5.21 (m, 1H), 4.99-4.65 (m, 1H), 4.15 (m, 4H), 3.54 (m, 1H), 3.42 (m, 1H), 3.28 (s, 3H), 2.31-2.09 (m, 4H), 1.57 (m, 2H), 1.31 (m, 4H), 1.17 (m, 26H), 0.84 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.14 (s), 173.05 (s), 84.81 (dd, *J* = 178.7, 171.0 Hz), 84.00 (dd, *J* = 178.7, 171.0 Hz), 73.41 (s), 72.98 (s), 69.31 (d, *J* = 14.6 Hz), 67.90 (d, *J* = 15.4 Hz), 63.27 (d, *J* = 6.8 Hz), 62.91 (d, *J* = 6.2 Hz), 59.11 (d, *J* = 4.6 Hz), 34.13 (s), 34.12 (s), 32.95 (s), 29.63 (s), 29.60 (s), 29.41 (s), 29.30 (s), 29.21 (s), 29.08 (s), 24.87 (s), 22.61 (s), 16.40 (d, *J* = 5.3 Hz), 14.06 (s). ^{19}F NMR ($CDCl_3$): -208.65 (m), -211.49 (m). ^{31}P NMR ($CDCl_3$): 18.51 (d, *J* = 73.7 Hz), 18.15 (d, *J* = 75.4 Hz). MS (CI) *m/z* 497.4 (M^++1, 100.00). HRMS, M^++1, Found: 497.3398. Calcd for $C_{25}H_{51}FO_6P$, 497.3407.

[1-Fluoro-3 *(S)*-(oleoyloxy)-4-*O*-methyl-butyl] phosphonate 13a

Deprotection of the phosphonate diester **12a** was accomplished with TMSBr using the method for **8a** to give **13a** in 93% yield. ^{1}H NMR (CD_3OD): 5.34 (m, 2H), 5.26-5.22 (m, 1H), 4.91-4.4.40 (m, 1H), 3.57 (m, 1H), 3.47 (m, 1 H), 3.36 (s, 3H), 2.37-2.13 (m, 4H), 2.02 (m, 4H), 1.61 (m, 2H), 1.32-1.29 (m, 22H), 0.89 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (CD_3OD): 172.89 (s), 172.72 (s), 128.90 (s), 128.87 (s), 86.33 (dd, *J* = 178.7, 171.0 Hz), 85.52 (dd, *J* = 178.7, 171.0 Hz), 72.76 (s), 72.24 (s), 69.25 (s), 69.11 (s), 57.36 (s), 33.20 (s), 33.13 (s), 31.06 (s), 30.95 (s), 28.84 (s), 28.80 (s), 28.61 (s), 28.45 (s), 28.35 (s), 28.29 (s), 28.18 (s), 28.11 (s), 26.13 (s), 24.09 (s), 21.74 (s), 12.46 (s). ^{19}F NMR (CD_3OD): -208.66 (m), -211.40 (m). ^{31}P NMR (CD_3OD): 16.64 (s), 16.22 (s). MS (CI) *m/z* 449.2 (M^++1-H_2O, 100.00). HRMS, M^++1, Found: 449.2824. Calcd for $C_{23}H_{43}FO_5P$, 449.2832.

[1-Fluoro-3 *(S)*-(palmitoyloxy)-4-*O*-methyl-butyl] phosphonate 13b

Deprotection of the phosphonate diester **12b** was accomplished with TMSBr using the method for **8a** to give **13b** in 95% yield. ^{1}H NMR (CD_3OD): 5.22 (m, 1H), 4.98-4.66 (m, 1H), 3.61 (m, 1H), 3.48 (m, 1H), 3.37 (s, 3H), 2.34 (t, *J* = 6.0 Hz, 2H), 2.13-1.99 (m, 2H), 1.61 (m, 2H), 1.34 (m, 26H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (CD_3OD): 175.15 (s), 86.40 (dd, *J* = 178.7, 171.0 Hz), 85.59 (dd, *J* = 178.7, 171.0 Hz), 77.14 (s), 75.72 (s), 65.83 (s), 65.64 (s), 58.34 (s), 57.70 (s), 33.02 (d, *J* = 7.7 Hz), 31.90 (s), 31.03 (s), 28.76 (s), 28.78 (s), 28.73 (s), 28.56 (s), 28.45 (s), 28.36 (s), 28.14 (s), 24.02 (s), 23.96 (s), 23.90 (s), 21.70 (s), 12.47 (s). ^{19}F NMR (CD_3OD): -207.41 (m), -212.34 (m). ^{31}P NMR (CD_3OD): 17.34 (d, *J* = 73.7 Hz), 17.26 (d, *J* = 76.1 Hz). MS (CI) *m/z* 423.2 (M^+-OH, 79.26), 185.0 (M^+-$C_{15}H_{31}CO_2H$, 100.00). HRMS, M^++1, Found: 423.2671. Calcd for $C_{21}H_{41}FO_5P$, 423.2676.

Diethyl [1-fluoro-3 *(S)*-*O*-methyl-4-hydroxyl-butyl] phosphonate 14

A solution of **10** (0.024 g, 0.063 mmol) in THF (1 mL) was treated successively with acetic acid (15 μL, 0.254 mmol) and tetrabutylammoniumfluoride trihydrate (0.080˚g, 0.254 mmol) at rt. After stirring for 16 h, the reaction was complete (TLC control). Then the solvent was evaporated under reduced pressure and the crude product was purified by pass through a short column of silica gel (CH_2Cl_2:CH_3OH = 30:1, R_f = 0.13) to give 15 mg of **14** as a colorless liquid (0.059 mmol, 93%). ^{1}H NMR ($CDCl_3$): 5.02-4.79 (m, 1H), 4.18 (m, 4H), 3.83-3.67 (m, 1H), 3.59-3.46 (m, 2H), 3.42 (s, 1.5H), 3.38 (s, 1.5H), 2.21-1.98 (m, 3H), 1.35 (m, 6H). ^{13}C NMR ($CDCl_3$): 85.66 (dd, *J* = 184.8,

177.9 Hz), 63.32 (s), 63.15 (s), 62.92 (m), 57.90 (s), 57.14 (s), 32.29 (d, *J* = 19.9 Hz), 30.64 (d, *J* = 18.4 Hz), 16.43 (m). ^{19}F NMR ($CDCl_3$): -207.03 (m), -211.39 (m). ^{31}P˚NMR ($CDCl_3$): 19.40 (d, *J* = 75.0 Hz), 18.89 (d, *J* = 75.0 Hz).

Diethyl [1-fluoro-3 *(S)*-*O*-methyl-4-(oleoyloxy)-butyl] phosphonate 15a

Method A: To a vigorously stirred mixture of **7a** (0.030 g, 0.059 mmol) and aq.˚HBF_4 (0.012 g, 9 µL) in CH_2Cl_2 (1 mL) was added $TMSCHN_2$ (2.0 M hexane solution, 59 µL) at 0˚°C. The stirring was continued at 0˚°C, and three further portions of $TMSCHN_2$ (30 µL × 3) were added dropwise at intervals of 20 min. The mixture was stirred at 0˚℃ for further 30 min, at rt for another 30 min, and then 10% $NaHCO_3$ solution (0.1 mL) was added. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (EtOAc:hexane = 1:2, R_f = 0.11) to afford 26 mg of **15a** as a colorless liquid (0.051 mmol, 86%).

Method B: To a solution of alcohol **14** (0.016 g, 0.063 mmol) and oleic acid (0.020 g, 0.069 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of DCC (0.016 g, 0.076 mmol) and DMAP (0.005 g, 0.038 mmol) in dry CH_2Cl_2 (1 mL) at 0ßC. The solution was stirred for 16 h at rt, filtered, concentrated *in vacuo*, and the residue was purified on silica gel (*n*-hexane:EtOAc = 2:1, R_f = 0.11) to afford 30 mg of ester **15a** (0.057 mmol, 91%) as a waxy solid. ^{1}H NMR ($CDCl_3$): 5.31 (m, 4H), 5.03-4.84 (m, 1H), 4.26-4.13 (m, 4H), 4.11-4.00 (m, 1.5H), 3.81 (m, 0.5H), 3.42 (s, 1.5H), 3.38 (s, 1.5H), 2.32 (t, *J* = 6.0 Hz, 2H), 2.21-2.04 (m, 2H), 2.01 (m, 4H), 1.61 (m, 2H), 1.56-1.24 (m, 26H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.60 (s), 129.98 (s), 129.70 (s), 86.43 (dd, *J* = 178.7, 171.0 Hz), 85.63 (dd, *J* = 178.7, 171.0 Hz), 75.47 (d, *J* = 8.4 Hz),

74.90 (d, *J* = 12.6 Hz), 64.56 (d, *J* = 3.6 Hz), 64.45 (d, *J* = 5.4 Hz), 63.26 (dd, *J* = 10.0, 5.6 Hz), 62.88 (t, *J* = 6.9 Hz), 58.21 (s), 57.50 (s), 34.15 (s), 33.81 (d, *J* = 18.4 Hz), 31.88˚(s), 29.74 (s), 29.67 (s), 29.49 (s), 29.29 (s), 29.15 (s), 29.08 (s), 27.19 (s), 27.14 (s), 24.88 (s), 22.66 (s), 16.43 (m), 14.08 (s). ^{19}F NMR ($CDCl_3$): -207.30 (m), -212.72 (m). ^{31}P NMR ($CDCl_3$): 19.25 (d, *J* = 76.1 Hz), 18.71 (d, *J* = 75.0 Hz). MS (CI) *m/z* 523.3 (M^++1, 100.00). HRMS, M^++1, Found: 523.3568. Calcd for $C_{27}H_{53}FO_6P$, 523.3564. $[\alpha]^{20}_D$ = -3.08 (c = 0.26, EtOH).

Diethyl [1-fluoro-3 *(S)*-*O*-methyl-4-(linolenoyloxy)-butyl] phosphonate 15b

Method B above was employed with **14** and palmitic acid to give **15b** in 82% yield. ^{1}H NMR ($CDCl_3$): 5.32 (m, 6H), 5.02-4.82 (m, 1H), 4.25-4.13 (m, 4H), 4.08 (dd, *J*˚= 12.0, 4.4 Hz, 1H), 4.01 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.65-3.55 (m, 1H), 3.41 (s, 1.5H), 3.37 (s, 1.5H), 2.76 (t, *J* = 8.0 Hz, 4H), 2.29 (t, *J* = 8.0 Hz, 2H), 2.19-1.92 (m, 6H), 1.58 (m, 2H), 1.34-1.21 (m, 14H), 0.93 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.50 (s), 131.88 (s), 130.18 (s), 128.22 (s), 128.18 (s), 127.67 (s), 127.05 (s), 85.47 (dd, *J* = 179.4, 171.8 Hz), 85.25 (dd, *J* = 179.4, 171.8 Hz), 75.41 (d, *J* = 12.3 Hz), 73.92 (d, *J* = 11.5 Hz), 64.56 (s), 64.46 (s), 63.23 (dd, *J* = 10.0, 6.9 Hz), 62.84 (t, *J* = 6.9 Hz), 58.16 (s), 57.45 (s), 34.09 (s), 34.15 (s), 32.94 (d, *J* = 21.1 Hz), 31.67 (d, *J* = 21.1 Hz), 29.51 (s), 29.10 (s), 29.02 (s), 27.13 (s), 25.55 (s), 25.46 (s), 24.83 (s), 20.48 (s), 16.40 (m), 14.20 (s). ^{19}F NMR ($CDCl_3$): -207.38 (m), -212.72 (m). ^{31}P NMR ($CDCl_3$): 19.25 (d, *J* = 75.0 Hz), 18.70 (d, *J* = 75.0 Hz). MS (CI) *m/z* 519.4 (M^++1, 84.26), 225.2 (M^+-$C_{17}H_{29}CO_2H$-CH_3, 100.00). HRMS, M^++1, Found: 519.3254. Calcd for $C_{27}H_{49}FO_6P$, 519.3251.

Diethyl [1-fluoro-3 *(S)*-*O*-methyl-4-(palmitoyloxy)-butyl] phosphonate 15c

Phosphonate **15c** was prepared using either of the methods above starting from the appropriate intermediate. **Method A**: 88% yield. **Method B**: 83% yield. ^{1}H NMR ($CDCl_3$): 5.04-4.76 (m, 1H), 4.26-4.14 (m, 4H), 4.11-4.00 (m, 1.5H), 3.81 (m, 0.5H), 3.42 (s, 1.5H), 3.38 (s, 1.5H), 2.30 (t, *J* = 8.0 Hz, 2H), 2.20-2.01 (m, 2H), 1.60 (m, 2H), 1.34 (t, *J* = 8.0 Hz, 6H), 1.31 (m, 26H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.61 (s), 86.43 (dd, *J* = 178.7, 171.0 Hz), 85.63 (dd, *J* = 178.7, 171.0 Hz), 75.47 (d, *J* = 9.3 Hz), 74.90 (d, *J* = 16.1 Hz), 64.59 (s), 64.50 (s), 63.32 (dd, *J* = 10.0, 6.8 Hz), 62.88 (t, *J* = 6.9 Hz), 58.20 (s), 57.50 (s), 34.17 (s), 34.15 (s), 32.97 (d, *J* = 21.5 Hz), 31.90 (s), 29.66 (s), 29.62 (s), 29.44 (s), 29.33 (s), 29.24 (s), 29.11 (s), 24.89 (s), 22.64 (s), 16.43 (d, *J* = 5.3 Hz), 14.09 (s). ^{19}F NMR ($CDCl_3$): -207.39 (m), -212.73 (m). ^{31}P NMR ($CDCl_3$): 19.26 (d, *J* = 75.0 Hz), 18.71 (d, *J* = 75.0 Hz). MS (CI) *m/z* 497.4 (M^++1, 100.00). HRMS, M^++1, Found: 497.3402. Calcd for $C_{25}H_{51}FO_6P$, 497.3407. $[\alpha]^{20}_{D}$ = -3.33 (c = 0.36, EtOH).

[1-Fluoro-3 *(S)*-*O*-methyl-4-(oleoyloxy)-butyl] phosphonate 16a

Deprotection of the phosphonate diester **15a** was accomplished with TMSBr using the method for **8a** to give **16a** in 95% yield. ^{1}H NMR (CD_3OD): 5.33 (m, 2H), 4.92-4.77 (m, 1H), 4.34-4.02 (m, 2H), 3.72-3.61 (m, 1H), 3.44 (m, 1.5H), 3.39 (s, 1.5H), 2.34 (m, 2H), 2.16-2.09 (m, 2H), 2.03 (m, 4H), 1.61 (m, 2H), 1.32-1.29 (m, 22H), 0.89 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (CD_3OD): 175.18 (s), 130.89 (s), 130.80 (s), 86.43 (dd, *J* = 178.7, 171.0 Hz), 85.63 (dd, *J* = 178.7, 171.0 Hz), 77.17 (d, *J* = 12.3 Hz), 75.78 (d, *J* =

12.6 Hz), 65.88 (s), 65.73 (s), 58.38 (s), 57.75 (s), 34.96 (s), 34.95 (s), 34.08 (d, *J* = 19.9 Hz), 33.06 (s), 32.82 (d, *J* = 20.0 Hz), 30.84 (s), 30.79 (s), 30.61 (s), 30.45 (s), 30.35 (s), 30.27 (s), 30.17 (s), 28.13 (s), 26.03 (s), 23.74 (s), 14.45 (s). ^{19}F NMR (CD_3OD): -207.35 (m), -212.19 (m). ^{31}P NMR (CD_3OD): 17.41 (d, *J* = 75.0 Hz), 16.87 (d, *J* = 75.0 Hz). MS (CI) *m/z* 449.2 (M^++1-H_2O, 100.00), 185.0 (M^+-$C_{17}H_{33}CO_2H$, 72.11). HRMS, M^++1, Found: 449.2823. Calcd for $C_{23}H_{43}FO_5P$, 449.2832. $[\alpha]^{20}_D$ = -0.94 (c = 0.32, MeOH).

[1-Fluoro-3 *(S)*-*O*-methyl-4-(linolenoyloxy)-butyl] phosphonate 16b

Deprotection of the phosphonate diester **15b** was accomplished with TMSBr using the method for **8a** to give **16b** in 95%yield. ^{1}H NMR (CD_3OD): 5.40-5.26 (m, 6H), 4.94-4.76 (m, 1H), 4.27 (dd, *J* = 36.0, 8.0 Hz, 1H), 4.08 (dd, *J* = 32.0, 12.0 Hz, 1H), 3.65 (m, 1H), 3.44 (s, 1.5H), 3.39 (s, 1.5H), 2.80 (m, 4H), 2.13-1.99 (m, 2H), 2.14-1.99 (m, 6H), 1.61 (t, *J* = 8.0 Hz, 3H), 1.33 (m, 8H), 0.97 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (CD_3OD): 173.10 (s), 130.73 (s), 129.07 (s), 127.21 (s), 127.19 (s), 126.85 (s), 126.23 (s), 86.43 (dd, *J* = 178.7, 171.0 Hz), 85.63 (dd, *J* = 178.7, 171.0 Hz), 75.14 (d, *J* = 12.2 Hz), 73.73 (d, *J* = 14.6 Hz), 63.87 (s), 63.72 (s), 56.39 (s), 55.75 (s), 32.95 (s), 32.93 (s), 32.06 (d, *J* = 18.4 Hz), 30.80 (d, *J* = 19.9 Hz), 28.67 (s), 28.25 (s), 28.18 (s), 28.14 (s), 26.15 (s), 24.52 (s), 24.41 (s), 24.01 (s), 19.49 (s), 12.67 (s). ^{19}F NMR (CD_3OD): -207.34 (m), -212.21 (m). ^{31}P NMR (CD_3OD): 17.39 (d, *J* = 72.9 Hz), 17.03 (d, *J* = 73.8 Hz). MS (CI) *m/z* 445.2 (M^+-OH, 62.43), 185.0 (M^+-$C_{17}H_{29}CO_2H$, 100.00). HRMS, M^++1, Found: 445.2507. Calcd for $C_{23}H_{39}FO_5P$, 445.2519.

[1-Fluoro-3 *(S)*-*O*-methyl-4-(palmitoyloxy)-butyl] phosphonate 16c

Deprotection of the phosphonate diester **15c** was accomplished with TMSBr using the method for **8a** to give **16c** in 97% yield. ^{1}H NMR (CD_3OD): 4.95-4.78 (m, 1H), 4.34-4.30 (m, 1H), 4.24-4.14 (m, 1H), 3.72-3.61 (m, 1H), 3.44 (s, 1.5H), 3.39 (s, 1.5H), 2.34 (t, *J* = 6.0 Hz, 2H), 2.13-1.99 (m, 2H), 1.60 (m, 2H), 1.33 (m, 26H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (CD_3OD): 175.20 (s), 86.43 (dd, *J* = 178.7, 171.0 Hz), 85.63 (dd, *J* = 178.7, 171.0 Hz), 77.17 (d, *J* = 8.5 Hz), 75.76 (d, *J* = 16.1 Hz), 65.85 (s), 65.69 (s), 58.37 (s), 57.74 (s), 34.98 (s), 34.56 (s), 34.08 (d, *J* = 22.12 Hz), 33.08 (s), 32.82 (d, *J* = 18.40 Hz), 30.78 (s), 30.77 (s), 30.71 (s), 30.60 (s), 30.48 (s), 30.40 (s), 30.18 (s), 26.04 (s), 23.74 (s), 12.48 (s). ^{19}F NMR (CD_3OD): -207.42 (m), -212.27 (m). ^{31}P NMR (CD_3OD): 17.36 (d, *J* = 73.8 Hz), 17.01 (d, *J* = 75.0 Hz). MS (CI) *m/z* 423.2 (M^+-OH, 85.63), 185.0 (M^+-$C_{15}H_{31}CO_2H$, 100.00). HRMS, M^++1, Found: 423.2673. Calcd for $C_{21}H_{41}FO_5P$, 423.2676. $[\alpha]^{20}_D$ = -2.27 (c = 0.22, MeOH).

(1) Schrotter, E.; Luong, T. T.; Schick, H. *J. Prakt. Chemie.* **1990**, *332*, 191-197.