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Synthesis of Fluorine-Containing Analogues of 1-Lysoglycerophospholipids via Horner–Wadsworth–Emmons Reaction

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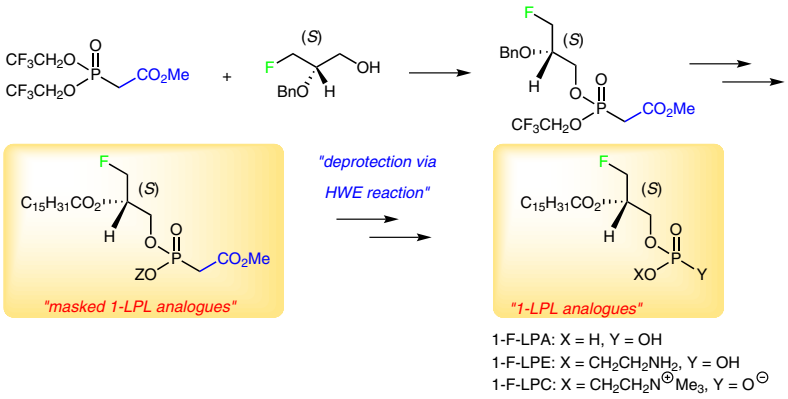

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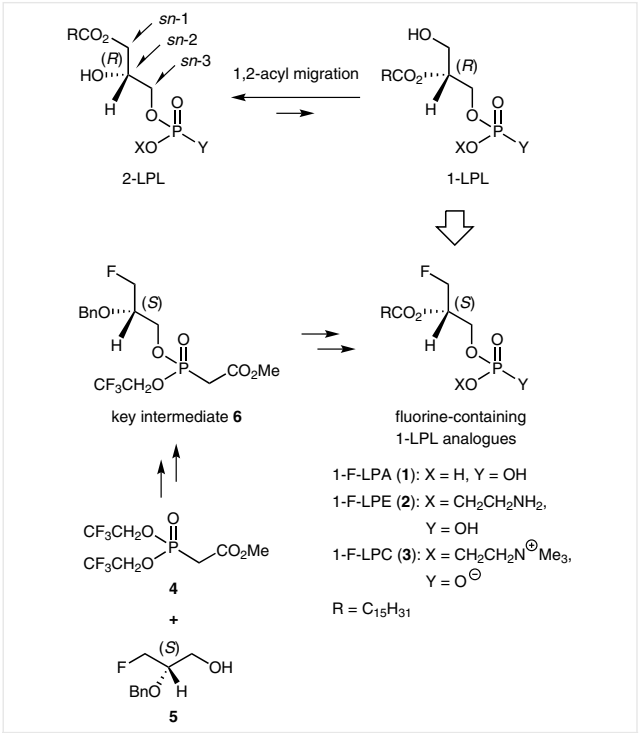
Abstract An efficient method of synthesizing fluorine-containing analogues of 1-lysoglycerophospholipids (1-LPLs) by introducing a palmitoyl moiety starting from bis(2,2,2-trifluoroethyl)phosphonoacetate (Still–Gennari reagent) is described. The method effectively employs Horner–Wadsworth–Emmons reagents as masked 1-LPL derivatives to prepare a series of analogues of 1-lysophosphatidic acid (1-LPA), 1-lysophosphatidylethanolamine (1-LPE), and 1-lysophosphatidylcholine (1-LPC).

Key words lysoglycerophospholipid, Horner–Wadsworth–Emmons reaction, fluorine, lysophosphatidic acid, lysophosphatidylethanolamine, lysophosphatidylcholine

Lysoglycerophospholipids (LPLs), in which only one acyl chain is attached to the glycerol moiety at the *sn*-2 position (1-LPL) or *sn*-1 position (2-LPL), are of considerable current interest as important signaling molecules in living biological systems.[1] Intramolecular acyl chain migration is known to give an equilibrium mixture of 1-LPL and 2-LPL under physiological conditions; the equilibrium generally favors 2-LPL, as shown in Scheme 1.[2] On the other hand, fluorine is the most electronegative element of the periodic table and can be considered a reasonable surrogate of a hydroxy group.[3] Thus, replacement of a hydroxy group of 1-LPL by a fluorine atom is an important strategy for blocking the acyl migration of 1-LPL to 2-LPL.[4] In this context, we have been intrigued with *sn*-2 palmitoyl 1-F-LPA (**1**), 1-F-LPE (**2**), and 1-F-LPC (**3**), which are fluorine-containing analogues of 1-lysophosphatidic acid (1-LPA), 1-lysophosphatidylethanolamine (1-LPE), and 1-lysophosphatidylcholine (1-LPC), respectively. However, the literature contains only one report on the synthesis of **1**, by Prestwich et al.,[4b] and there are no reports on the synthesis of **2** or **3**.

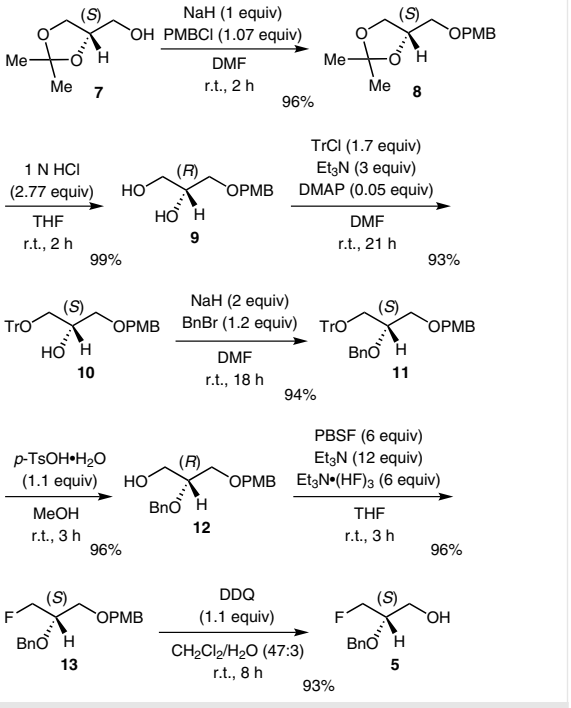


Scheme 1 Synthesis of fluorine-containing analogues **1–3** of 1-LPLs

Recently, we reported a novel approach to synthesize glycerophospholipids (PLs) based on the Horner–Wadsworth–Emmons (HWE) reaction of easily handled mixed phosphonoacetate, which serves as a masked precursor of PLs.[5] Herein we describe the facile synthesis of fluorine-containing analogues **1–3** using HWE reagent **6** as a key intermediate, which was derived from methyl bis(2,2,2-

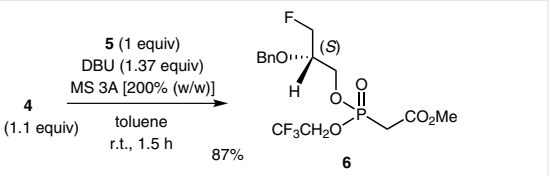
trifluoroethyl)phosphonoacetate (Still–Gennari reagent, **4**)[6,7] and fluorine-containing chiral alcohol **5** as shown in Scheme 1.

For the synthesis of **5**, (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol [(*S*)-solketal, **7**][8] was chosen as the starting material (Scheme 2). The *p*-methoxybenzylation of **7** with *p*-methoxybenzyl chloride (PMBCl) in the presence of sodium hydride in DMF provided **8** in 96% yield. Deprotection of the acetonide of **8** under acidic conditions afforded diol **9** in 99% yield. Selective protection of the primary hydroxy group of diol **9** with triphenylchloromethane (TrCl) in the presence of triethylamine and *N*,*N*-dimethylaminopyridine (DMAP) gave secondary alcohol **10** in 93% yield. Benzylation of **10** with benzyl bromide in the presence of sodium hydride in DMF resulted in the formation of **11** in 94% yield. Selective removal of the triphenylmethyl group of **11** was easily performed with *p*-toluenesulfonic acid in methanol to afford primary alcohol **12** in 96% yield. Deoxyfluorination of alcohol **12** by a combination of perfluoro-1-butanesulfonyl fluoride (PBSF), triethylamine, and triethylamine trihydrofluoride provided the corresponding fluoride **13** in 96% yield.[9] The desired chiral alcohol **5** was obtained in 93% yield by oxidative cleavage of the PMB ether of **13** using 1,2-dichloro-4,5-dicyanobenzoquinone (DDQ) as an oxidant in a dichloromethane/water mixed solvent system.[10]



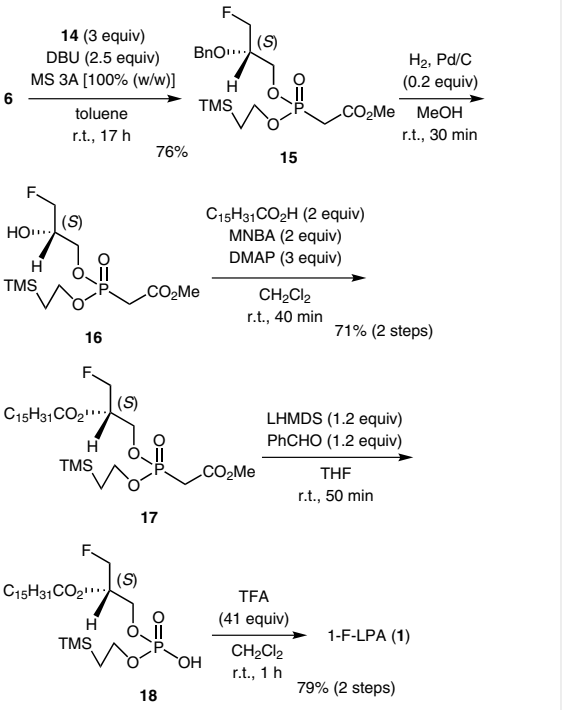
Scheme 2 Synthesis of chiral alcohol **5**

Nucleophilic substitution of the chiral alcohol **5** at the phosphorus center of Still–Gennari reagent (**4**) in the presence of 1.37 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and molecular sieves (type 3A) furnished the key intermediate **6** as an inseparable diastereomeric mixture (ca. 1:1) in 87% yield as shown in Scheme 3.[5,11]



Scheme 3 Synthesis of key intermediate **6**

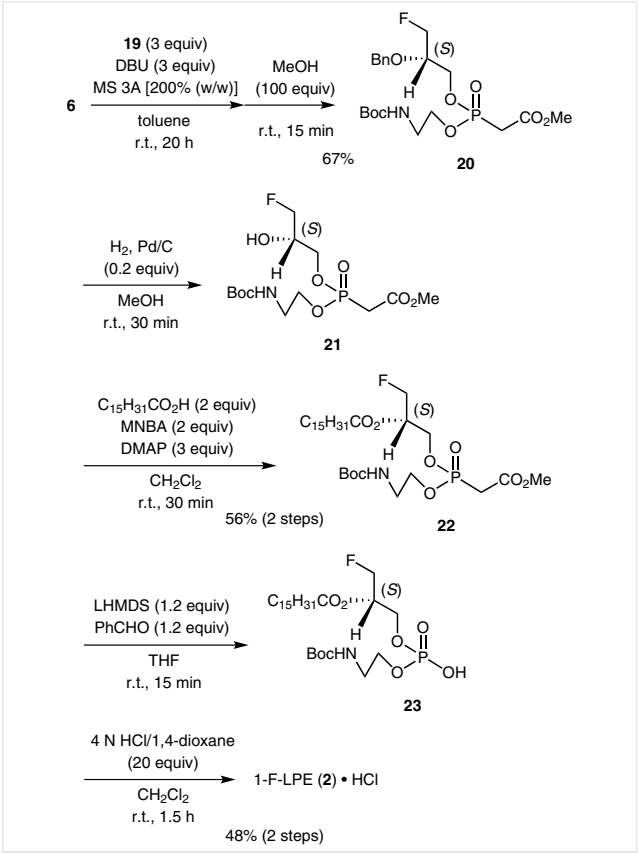
1-F-LPA (**1**), the fluorine-containing analogue of 1-lysophosphatidic acid (1-LPA), was prepared using an HWE reaction of mixed phosphonoacetate **17** with benzaldehyde as the key reaction as shown in Scheme 4. The nucleophilic substitution of 2-(trimethylsilyl)ethanol (**14**)[12] at the phosphorus center of the key intermediate **6** in the presence of excess amounts of **14** and DBU gave phosphonoacetate **15** in 76% yield. After removal of the benzyl group of **15** by hydrogenolysis using a palladium on carbon (Pd/C) catalyst, palmitic acid was incorporated into the resultant secondary alcohol **16** with 2-methyl-6-nitrobenzoic anhydride (MNBA)[13,14] and DMAP to afford **17** in 71% yield (two steps). The HWE reaction of **17** with benzaldehyde in the presence of lithium hexamethyldisilazide (LHMDS) provided the expected phosphodiester **18**, then deprotection of the 2-(trimethylsilyl)ethyl group of the resultant **18** furnished 1-



Scheme 4 Synthesis of 1-F-LPA (**1**)

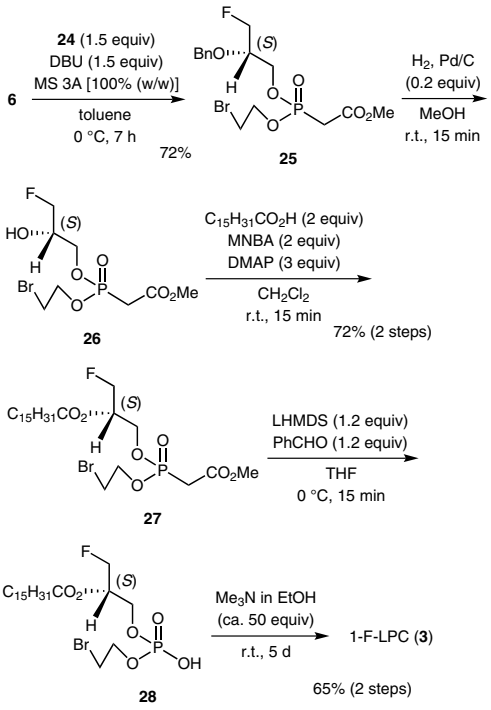
F-LPA (**1**) in 79% yield (two steps). In the synthetic strategy, HWE reagent **17** should be regarded as the masked precursor of *sn*-2 palmitoyl 1-F-LPA (**1**). Compounds **15**–**17** were all obtained as inseparable diastereomeric mixtures (ca. 1:1), similar to the key intermediate **6**.

Subsequently, we explored the preparation of 1-F-LPE (**2**) and 1-F-LPC (**3**) based on the synthetic route of 1-F-LPA (**1**) through **6** as the common key intermediate. The divergent synthesis of 1-F-LPE (**2**), fluorine-containing analogues of 1-lysophosphatidylethanolamine (1-LPE), is shown in Scheme 5. The substitution of *tert*-butyl (2-hydroxyethyl)carbamate (*N*-Boc-ethanolamine, **19**) instead of **14** at the phosphorus center of **6** afforded phosphonoacetate **20** in 67% yield. Hydrogenolysis of **20** using a Pd/C catalyst, followed by condensation of **21** with palmitic acid in the presence of MNBA and DMAP, gave **22** in 56% yield (two steps). The HWE reaction of **22** with benzaldehyde in the presence of LHMDS, followed by deprotection of the Boc group of the resultant phosphodiester **23** under acidic conditions using hydrogen chloride in 1,4-dioxane, afforded 1-F-LPE (**2**) as hydrochloride salt in 48% yield (two steps).



Scheme 5 Synthesis of 1-F-LPE (**2**)

Furthermore, Scheme 6 shows the synthesis of 1-F-LPC (**3**), a fluorine-containing analogue of 1-lysophosphatidylcholine (1-LPC). 2-Bromoethanol (**24**) was used in the reaction with the key intermediate **6** to afford the corresponding phosphonoacetate **25** in 72% yield in a manner similar to that described for the reaction of **6** with **14** and **19**. After hydrogenolysis of **25** using a Pd/C catalyst, condensation of the resultant **26** with palmitic acid using MNBA and DMAP provided **27** in 72% yield (two steps). The HWE reaction of **27** with benzaldehyde in the presence of LHMDS gave phosphodiester **28**, then amination of the resultant **28** in the presence of excess amounts of trimethylamine in ethanol furnished 1-F-LPC (**3**) in 65% yield (two steps).[15]



Scheme 6 Synthesis of 1-F-LPC (**3**)

In conclusion, we have described a novel and efficient method of synthesizing *sn*-2 palmitoyl 1-F-LPA (**1**), 1-F-LPE (**2**), and 1-F-LPC (**3**) as 1,2-acyl migration-blocked analogues of 1-LPLs. Considering the operational ease based on the use of HWE reagents as fluorine-containing masked analogues of 1-LPLs via the common key intermediate **6**, we believe this synthetic strategy will be valuable for the chemistry and biochemistry of phospholipids classified as glycerophospholipids (PLs) and sphingophospholipids (SPLs).

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-6200 IR Fourier transform spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker AV500 spectrometer. Chemical shifts are given in δ values (parts per million) using TMS as an internal standard. Mass spectra

(ESI) were recorded on a Waters LCT Premier spectrometer. Elemental combustion analyses were performed using a J-SCIENCE LAB JM10 analyzer. Optical rotations were recorded using a P-2200 JASCO digital polarimeter. All reactions were monitored by TLC employing 0.25 mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Silica Gel 60N (Kanto Chemical) or COSMOSIL 75 SL-II-PREP (Nacalai Tesque)]. Anhydrous THF, CH_2Cl_2, DMF, and toluene were used as purchased from Kanto Chemical. DBU and Et_3N were distilled prior to use. All other reagents were used as purchased.

(*S*)-4-{[(4-Methoxybenzyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolane (8)[16]

To a suspension of NaH (50–72% in mineral oil, 187 mg, 3.90–5.61 mmol) in anhyd DMF (10 mL) was added **7** (0.5 mL, 4.05 mmol), and the reaction mixture was stirred at 0 °C for 30 min under argon. After the addition of PMBCl (0.58 mL, 4.28 mmol), the mixture was allowed to warm to r.t. and then stirred for 2 h under argon. H_2O (10 mL) was added to the mixture, and then extracted with EtOAc–*n*-hexane (1:1) (3 × 50 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (4:1)] to afford **8** (986 mg, 96%) as a colorless oil; $[\alpha]_D^{24}$ +22.5 (*c* 1.01, $CHCl_3$).

IR (neat): 2986, 2935, 2865, 1613, 1514, 1457, 1371, 1249 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 2 H), 6.90–6.85 (m, 2 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.48 (d, *J* = 11.7 Hz, 1 H), 4.28 (quint, *J* = 6.2 Hz, 1 H), 4.04 (dd, *J* = 8.3, 6.4 Hz, 1 H), 3.80 (s, 3 H), 3.72 (dd, *J* = 8.3, 6.3 Hz, 1 H), 3.53 (dd, *J* = 9.8, 5.6 Hz, 1 H), 3.42 (dd, *J* = 9.8, 5.7 Hz, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 130.1, 129.3, 113.8, 109.4, 74.8, 73.2, 70.8, 67.0, 55.3, 26.8, 25.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}O_4Na$: 275.1259; found: 275.1238.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.35; H, 8.08.

(*R*)-3-[(4-Methoxybenzyl)oxy]propane-1,2-diol (9)[16,17]

A mixture of **8** (912 mg, 3.61 mmol), aq 1 M HCl (10 mL, 10 mmol), and THF (10 mL) was stirred at r.t. for 2 h. Then, sat. aq $NaHCO_3$ (10 mL) was added to the reaction mixture and extracted with EtOAc (3 × 70 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: $CHCl_3$–MeOH (15:1)] to afford **9** (760 mg, 99%) as a white solid; mp 37.5–39 °C (white powder, $CHCl_3$–*n*-hexane); $[\alpha]_D^{25}$ –2.2 (*c* 1.23, $CHCl_3$).

IR (KBr): 3330, 2934, 2870, 1612, 1514, 1250 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 2 H), 6.90–6.86 (m, 2 H), 4.47 (s, 2 H), 3.90–3.84 (m, 1 H), 3.80 (s, 3 H), 3.71–3.65 (m, 1 H), 3.63–3.57 (m, 1 H), 3.55–3.48 (m, 2 H), 2.85 (br s, 1 H), 2.41 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.4, 129.8, 129.5, 113.9, 73.3, 71.5, 70.7, 64.1, 55.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{16}O_4Na$: 235.0946; found: 235.0924.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.95; H, 7.61.

(*S*)-1-[(4-Methoxybenzyl)oxy]-3-(trityloxy)propan-2-ol (10)[17]

To a solution of **9** (1.34 g, 6.31 mmol) in anhyd DMF (10 mL) were added Et_3N (2.63 mL, 18.9 mmol), DMAP (38 mg, 0.311 mmol), and TrCl (3.06 g, 11.0 mmol) at r.t. under argon. The reaction mixture was stirred for 21 h. Then, H_2O (10 mL) was added to the mixture and extracted with EtOAc–*n*-hexane (1:1) (3 × 50 mL). The combined organic layers were washed with H_2O (30 mL), dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:1 to 4:1)] to afford **10** (2.67 g, 93%) as a yellow oil; $[\alpha]_D^{28}$ –0.6 (*c* 1.01, $CHCl_3$).

IR (neat): 3454, 3058, 3032, 2932, 2870, 1612, 1513, 1448, 1249 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.41 (m, 6 H), 7.30–7.20 (m, 11 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.46 (s, 2 H), 3.96 (sept, *J* = 5.6 Hz, 1 H), 3.80 (s, 3 H), 3.57 (dd, *J* = 9.7, 4.3 Hz, 1 H), 3.52 (dd, *J* = 9.6, 6.2 Hz, 1 H), 3.22 (dd, *J* = 9.4, 5.7 Hz, 1 H), 3.19 (dd, *J* = 9.4, 5.3 Hz, 1 H), 2.39 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 143.8, 130.0, 129.3, 128.6, 127.8, 127.0, 113.7, 86.6, 73.0, 71.2, 69.9, 64.5, 55.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{30}O_4Na$: 477.2042; found: 477.2047.

(*S*)-({2-(Benzyloxy)-3-[(4-methoxybenzyl)oxy]propoxy}methanetriyl)tribenzene (11)

To a solution of **10** (1.70 g, 3.74 mmol) and benzyl bromide (533 µL, 4.48 mmol) in anhyd DMF (8 mL) was added NaH (50–72% in mineral oil; washed with several portions of anhyd *n*-pentane, 179 mg, 7.46 mmol) at 0 °C under argon. The reaction mixture was stirred at r.t. for 18 h under argon. Then, H_2O (10 mL) was added to the mixture and extracted with EtOAc–*n*-hexane (1:1) (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 30 mL), dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (8:1 to 10:1)] to afford **11** (1.91 g, 94%) as a yellow oil; $[\alpha]_D^{23}$ –6.8 (*c* 0.88, $CHCl_3$).

IR (neat): 3060, 3031, 2931, 2868, 1612, 1513, 1449, 1248 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 6 H), 7.36–7.15 (m, 16 H), 6.85–6.81 (m, 2 H), 4.66 (d, *J* = 12.0 Hz, 1 H), 4.63 (d, *J* = 12.0 Hz, 1 H), 4.44 (d, *J* = 11.7 Hz, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 3.77 (s, 3 H), 3.79–3.72 (m, 1 H), 3.63 (dd, *J* = 10.2, 4.6 Hz, 1 H), 3.59 (dd, *J* = 10.2, 5.8 Hz, 1 H), 3.29–3.22 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 144.1, 138.7, 130.5, 129.1, 128.7, 128.3, 127.7, 127.4, 126.9, 113.7, 86.6, 77.7, 72.9, 72.2, 70.3, 63.6, 55.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{37}H_{36}O_4Na$: 567.2511; found: 567.2511.

(*R*)-2-(Benzyloxy)-3-[(4-methoxybenzyl)oxy]propan-1-ol (12)[18]

To a solution of **11** (100 mg, 0.184 mmol) in MeOH (1.8 mL) was added *p*-TsOH·H_2O (39 mg, 0.205 mmol) at r.t. The reaction mixture was stirred for 3 h. Then, aq 5 N NaOH (1 mL) was added to the mixture and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:1)] to afford **12** (53.2 mg, 96%) as a colorless oil; $[\alpha]_D^{23}$ +17.8 (*c* 0.98, $CHCl_3$).

IR (neat): 3440, 3031, 2868, 1612, 1514, 1455, 1248 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 7.26–7.22 (m, 2 H), 6.89–6.85 (m, 2 H), 4.69 (d, *J* = 11.8 Hz, 1 H), 4.60 (d, *J* = 11.8 Hz, 1 H), 4.47 (d, *J* = 11.6 Hz, 1 H), 4.46 (d, *J* = 11.6 Hz, 1 H), 3.80 (s, 3 H), 3.77–3.71 (m, 1 H), 3.70–3.63 (m, 2 H), 3.62–3.54 (m, 2 H), 2.16 (br t, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 138.2, 130.0, 129.3, 128.4, 127.8, 113.8, 78.0, 73.2, 72.1, 69.9, 62.9, 55.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{22}O_4Na$: 325.1416; found: 325.1416.

(*S*)-1-{[2-(Benzyloxy)-3-fluoropropoxy]methyl}-4-methoxybenzene (13)

To a solution of **12** (1.14 g, 3.77 mmol) in anhyd THF (10 mL) were added Et_3N (6.24 mL, 45.0 mmol), $Et_3N{\cdot}(HF)_3$ (3.66 mL, 22.5 mmol), and PBSF (3.96 mL, 22.5 mmol) at r.t. under argon. The reaction mixture was stirred for 3 h. Then, H_2O (10 mL) was added to the mixture and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (7:1)], then again by column chromatography [*n*-hexane–EtOAc (10:1)] to afford **13** (1.10 g, 96%) as a colorless oil; $[\alpha]_D^{24}$ +13.4 (*c* 1.02, $CHCl_3$).

IR (neat): 2865, 1613, 1514, 1455, 1249 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 7.25–7.21 (m, 2 H), 6.89–6.85 (m, 2 H), 4.68 (d, *J* = 12.0 Hz, 1 H), 4.67 (d, *J* = 12.0 Hz, 1 H), 4.55 (ddd, $^2J_{H,F}$ = 47.3 Hz, $^2J_{H,H}$ = 9.8 Hz, $^3J_{H,H}$ = 3.7 Hz, 1 H), 4.47–4.45 (m, 2 H), 4.51 (ddd, $^2J_{H,F}$ = 47.5 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 5.5 Hz, 1 H), 3.80 (s, 3 H), 3.86–3.78 (m, 1 H), 3.60–3.53 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 138.2, 130.0, 129.3, 128.4, 127.8, 127.7, 113.8, 83.5 (d, $^1J_{C,F}$ = 170.8 Hz), 76.6 (d, $^2J_{C,F}$ = 19.0 Hz), 73.2, 72.4, 68.4 (d, $^3J_{C,F}$ = 8.0 Hz), 55.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{21}FO_3Na$: 327.1372; found: 327.1374.

(*S*)-2-(Benzyloxy)-3-fluoropropan-1-ol (5)[19]

To a solution of **13** (1.40 g, 4.60 mmol) in CH_2Cl_2 (47 mL)/H_2O (3 mL) was added DDQ (1.15 g, 5.07 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 8 h. Then, sat. aq Na_2CO_3 (10 mL) was added to the mixture and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:1)] to afford **5** (791 mg, 93%) as a colorless oil; $[\alpha]_D^{24}$ +14.8 (*c* 1.01, $CHCl_3$).

IR (neat): 3416, 2953, 2885, 1455, 1348, 1209, 1119, 1060 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 4.72 (d, *J* = 11.7 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.53 (ddd, $^2J_{H,F}$ = 47.2 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 4.4 Hz, 1 H), 4.51 (ddd, $^2J_{H,F}$ = 47.3 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 5.2 Hz, 1 H), 3.78–3.70 (m, 2 H), 3.67–3.60 (m, 1 H), 2.12 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9, 128.6, 128.0, 127.9, 82.8 (d, $^1J_{C,F}$ = 170.8 Hz), 77.9 (d, $^2J_{C,F}$ = 19.1 Hz), 72.5, 61.4 (d, $^3J_{C,F}$ = 7.4 Hz).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{13}FO_2Na$: 207.0797; found: 207.0784.

Methyl 2-{[(*S*)-2-(Benzyloxy)-3-fluoropropoxy](2,2,2-trifluoroethoxy)phosphoryl}acetate (6)

A solution of alcohol **5** (607 mg, 3.30 mmol) in anhyd toluene (120 mL) was added to a solution of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**4**; 773 µL, 3.62 mmol), DBU (673 µL, 4.51 mmol), and molecular sieves 3A (1.28 g) in anhyd toluene (44 mL) at r.t. under argon. After stirring the reaction mixture at r.t. for 1.5 h, aq 1 M HCl (10 mL) was added and then extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:2)] to afford **6** (diastereomeric mixture, 1.16 g, 87%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H), 4.70 (dd, *J* = 11.6, 1.5 Hz, 1 H), 4.67 (dd, *J* = 11.6, 2.3 Hz, 1 H), 4.53 (ddd, $^2J_{H,F}$ = 46.9 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 4.9 Hz, 1 H), 4.51 (ddd, $^2J_{H,F}$ = 46.9 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 5.2 Hz, 1 H), 4.43–4.31 (m, 3 H), 4.25–4.15 (m, 1 H), 3.89–3.81 (m, 1 H), 3.74/3.73 (2 s, 3 H), 3.08 (br dd, 0.94 H for one diastereomer), 3.06 (d, $^2J_{H,P}$ = 21.4 Hz, 1.06 H for one diastereomer).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.5 (d, $^2J_{C,P}$ = 5.4 Hz), 137.4, 137.3, 128.6, 128.13, 128.10, 128.00, 127.96, 122.7 (qd, $^1J_{C,F}$ = 277.6 Hz, $^3J_{C,P}$ = 8.3 Hz), 81.6 (d, $^1J_{C,F}$ = 172.3 Hz), 75.66, 75.65, 75.62, 75.6, 75.5, 75.49, 75.46, 75.44, 72.44, 72.43, 64.65, 64.59, 64.53, 64.47, 62.7 (qd, $^2J_{C,F}$ = 37.8 Hz, $^2J_{C,P}$ = 5.3 Hz), 52.82, 52.8, 33.9 (d, $^1J_{C,P}$ = 141.8 Hz for one diastereomer), 33.8 (d, $^1J_{C,P}$ = 141.5 Hz for one diastereomer).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}F_4O_6PNa$: 425.0753; found: 425.0747.

Methyl 2-{[(*S*)-2-(Benzyloxy)-3-fluoropropoxy][(2-trimethylsilyl)ethoxy]phosphoryl}acetate (15)

DBU (283 µL, 1.90 mmol) was added to a solution of **6** (300 mg, 0.746 mmol), 2-(trimethylsilyl)ethanol (**14**; 319 µL, 2.24 mmol), and molecular sieves 3A (300 mg) in anhyd toluene (10 mL) at r.t. under argon. After stirring the reaction mixture at r.t. for 17 h, aq 1 M HCl (10 mL) was added and then extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:2)] to afford **15** (diastereomeric mixture, 240 mg, 76%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 4.72 (d, *J* = 11.8 Hz, 1 H), 4.68 (d, *J* = 11.8 Hz, 1 H), 4.56 (ddd, $^2J_{H,F}$ = 47.0 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 4.6 Hz, 1 H), 4.53 (ddd, $^2J_{H,F}$ = 47.0 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 5.3 Hz, 1 H), 4.36–4.29 (m, 1 H), 4.26–4.13 (m, 3 H), 3.90–3.81 (m, 1 H), 3.723/3.715 (2 s, 3 H), 3.05–2.93 (m, 2 H), 1.12–1.06 (m, 2 H), 0.03/0.02 (2 s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1 (d, $^2J_{C,P}$ = 4.7 Hz), 137.62, 137.59, 128.5, 127.96, 127.95, 127.9, 127.8, 82.0 (d, $^1J_{C,F}$ = 171.7 Hz), 76.0, 75.9, 75.81, 75.76, 72.34, 72.32, 65.62, 65.56, 65.5, 65.4, 64.13, 64.08, 64.03, 63.97, 63.91, 63.85, 52.58, 52.55, 34.2 (d, $^1J_{C,P}$ = 136.1 Hz for one diastereomer), 34.1 (d, $^1J_{C,P}$ = 135.3 Hz for one diastereomer), 19.80, 19.76, –1.52, –1.53.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{30}FO_6PSiNa$: 443.1431; found: 443.1431.

(2*S*)-1-Fluoro-3-({(2-methoxy-2-oxoethyl)[2-(trimethylsilyl)ethoxy]phosphoryl}oxy)propan-2-yl Palmitate (17)

A mixture of **15** (43 mg, 0.102 mmol) and 10% Pd/C (21 mg, 0.0197 mmol) in MeOH (1 mL) was stirred at r.t. for 30 min under H_2 atmosphere. The reaction mixture was filtered and concentrated in vacuo to afford **16**. A solution of **16** in anhyd CH_2Cl_2 (3 mL) was added to a solution of palmitic acid (52 mg, 0.203 mmol), 2-methyl-6-nitrobenzoic anhydride (70 mg, 0.203 mmol), and DMAP (37 mg, 0.303 mmol) in anhyd CH_2Cl_2 (10 mL) at r.t. under argon. The mixture was stirred for 40 min. Aq 1 M HCl (2 mL) was added to the mixture and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:2)] to afford **17** (diastereomeric mixture, 41 mg, 71%, two steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.26–5.16 (m, 1 H), 4.64–4.60 (m, 1 H), 4.55–4.51 (m, 1 H), 4.38–4.16 (m, 4 H), 3.74 (s, 3 H), 3.00 (d, $^2J_{H,P}$ = 21.6 Hz, 1 H for one diastereomer), 2.98 (d, $^2J_{H,P}$ = 21.5 Hz, 1 H for one

diastereomer), 2.37 (br td, 2 H), 1.67–1.59 (m, 2 H), 1.34–1.22 (m, 24 H), 1.11 (t, *J* = 8.6 Hz, 2 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.047/0.045 (2 s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.83, 172.82, 165.9 (d, $^2J_{C,P}$ = 6.2 Hz), 80.8 (d, $^1J_{C,F}$ = 172.8 Hz for one diastereomer), 80.7 (d, $^1J_{C,F}$ = 173.4 Hz for one diastereomer), 70.3, 70.23, 70.18, 70.13, 70.07, 70.0, 65.7, 65.6, 63.33, 63.28, 63.22, 63.17, 52.6, 34.14, 34.11 (d, $^1J_{C,P}$ = 136.1 Hz for one diastereomer), 34.07 (d, $^1J_{C,P}$ = 135.4 Hz for one diastereomer), 31.9, 29.7, 29.69, 29.66, 29.6, 29.5, 29.4, 29.3, 29.1, 24.8, 22.7, 19.83, 19.82, 19.79, 19.77, 14.1, –1.51.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{54}FO_7PSiNa$: 591.3258; found: 591.3248.

(*S*)-1-Fluoro-3-(phosphonooxy)propan-2-yl Palmitate [1-F-LPA (1)][4b]

To a solution of **17** (70 mg, 0.123 mmol) in anhyd THF (1.26 mL) was added LHMDS (1.1 mol/L in *n*-hexane, 137 µL, 0.151 mmol) and the solution was stirred at 0 °C for 5 min under argon. After the addition of benzaldehyde (15 µL, 0.147 mmol), the reaction mixture was allowed to warm to r.t. and then stirred for 50 min under argon. Aq 1 M HCl (2 mL) was added to the mixture and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The crude **18** was dissolved in anhyd CH_2Cl_2 (1.25 mL), and TFA (385 µL, 5.03 mmol) was added. After stirring at r.t. for 1 h, the mixture was concentrated in vacuo. The residue was purified by column chromatography [COSMOSIL 75 SL-II-PREP: $CHCl_3$–MeOH (100:1 to 6:1)] to afford 1-F-LPA (**1**) (39.9 mg, 79%, two steps) as a white solid; mp 80–93 °C; $[\alpha]_D^{27}$ +4.8 (*c* 0.79, $CHCl_3$).

IR (KBr): 2918, 2849, 1729, 1468, 1179 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.23 (br d, 1 H), 4.93 (br s, 2 H), 4.58 (br d, 2 H), 4.23–4.10 (m, 2 H), 2.44–2.31 (m, 2 H), 1.68–1.55 (m, 2 H), 1.40–1.10 (m, 24 H), 0.88 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 80.8 (d, $^1J_{C,F}$ = 173.5 Hz), 70.6 (d, $^2J_{C,F}$ = 17.3 Hz), 64.0, 34.2, 31.9, 29.74, 29.72, 29.69, 29.68, 29.5, 29.4, 29.3, 29.1, 24.8, 22.7, 14.1.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{19}H_{37}FO_6P$: 411.2312; found: 411.2310.

Methyl 2-([(*S*)-2-(Benzyloxy)-3-fluoropropoxy]{2-[(*tert*-butoxycarbonyl)amino]ethoxy}phosphoryl)acetate (20)

To a solution of **6** (53.4 mg, 0.133 mmol), *tert*-butyl (2-hydroxyethyl)carbamate (**19**; 64.2 mg, 0.398 mmol), and molecular sieves 3A (107 mg) in anhyd toluene (2 mL) was added DBU (59.4 µL, 0.398 mmol) at r.t. under argon. After stirring at r.t. for 20 h, MeOH (537 µL, 13.3 mmol) was added and the reaction mixture was stirred at r.t. for another 15 min. The mixture was filtered, and a 1/15 M phosphate buffer (pH 7.4, 10 mL) was added to the filtrate, and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (1:2 to 1:3)] to afford **20** (diastereomeric mixture, 41.3 mg, 67%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H), 5.15 (br s, 1 H), 4.70 (dd, *J* = 11.7, 2.9 Hz, 1 H), 4.68 (d, *J* = 11.7 Hz, 1 H), 4.61–4.54 (m, 1 H), 4.51–4.45 (m, 1 H), 4.38–4.28 (m, 1 H), 4.23–4.05 (m, 3 H), 3.89–3.81 (m, 1 H), 3.74/3.73 (2 s, 3 H), 3.43–3.28 (m, 2 H), 3.08–2.96 (m, 2 H), 1.44 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1 (d, $^2J_{C,P}$ = 3.6 Hz for one diastereomer), 166.0 (d, $^2J_{C,P}$ = 2.9 Hz for one diastereomer), 155.8, 137.42, 137.41, 128.5, 128.07, 128.05, 127.95, 127.94, 81.7 (d, $^1J_{C,F}$ = 171.7 Hz), 79.6, 75.81, 75.76, 75.75, 75.70, 75.65, 75.60, 75.59, 75.54, 72.4, 72.3, 66.21, 66.17, 64.5, 64.4, 64.38, 64.35, 64.30, 64.2, 52.74, 52.71, 41.0, 33.9 (d, $^1J_{C,P}$ = 137.3 Hz for one diastereomer), 33.8 (d, $^1J_{C,P}$ = 137.1 Hz for one diastereomer), 28.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{31}FNO_8PNa$: 486.1669; found: 486.1647.

(2*S*)-1-[({2-[(*tert*-Butoxycarbonyl)amino]ethoxy}(2-methoxy-2-oxoethyl)phosphoryl)oxy]-3-fluoropropan-2-yl Palmitate (22)

A mixture of **20** (54.3 mg, 0.117 mmol) and 10% Pd/C (24.9 mg, 0.0234 mmol) in MeOH (1 mL) was stirred at r.t. for 30 min under H_2 atmosphere. The reaction mixture was filtered and concentrated in vacuo to afford **21**, which was used in the next reaction without further purification. To a solution of palmitic acid (60 mg, 0.234 mmol), 2-methyl-6-nitrobenzoic anhydride (80.6 mg, 0.234 mmol), and DMAP (42.9 mg, 0.351 mmol) in anhyd CH_2Cl_2 (3 mL) was added a solution of **21** in anhyd CH_2Cl_2 (2 mL) at r.t. under argon. The mixture was stirred for 30 min. A 1/15 M phosphate buffer (pH 7.4, 3 mL) was added to the mixture, and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (1:1)] to afford **22** (diastereomeric mixture, 40.2 mg, 56%, two steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.26–5.14 (m, 2 H), 4.65–4.59 (m, 1 H), 4.55–4.49 (m, 1 H), 4.38–4.10 (m, 4 H), 3.76 (s, 3 H), 3.48–3.35 (m, 2 H), 3.04 (d, $^2J_{H,P}$ = 21.6 Hz, 0.97 H for one diastereomer), 3.02 (br dd, 1.03 H for one diastereomer), 2.37 (t, *J* = 7.6 Hz, 2 H), 1.67–1.60 (m, 2 H), 1.45 (s, 9 H), 1.34–1.23 (m, 24 H), 0.88 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.89, 172.88, 165.9 (d, $^2J_{C,P}$ = 5.8 Hz), 155.8, 80.7 (d, $^1J_{C,F}$ = 173.3 Hz for one diastereomer), 80.6 (d, $^1J_{C,F}$ = 173.4 Hz for one diastereomer), 79.6, 70.16, 70.11, 70.06, 70.00, 69.95, 69.90, 66.41, 66.36, 63.6, 63.53, 63.48, 63.43, 63.38, 52.8, 41.04, 41.01, 34.1, 33.8 (d, $^1J_{C,P}$ = 137.3 Hz for one diastereomer), 33.7 (d, $^1J_{C,P}$ = 137.1 Hz for one diastereomer), 31.9, 29.71, 29.69, 29.66, 29.62, 29.5, 29.4, 29.3, 29.1, 28.4, 24.8, 22.7, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{55}FNO_9PNa$: 634.3496; found: 634.3470.

(2*S*)-1-{[(2-Aminoethoxy)(hydroxy)phosphoryl]oxy}-3-fluoropropan-2-yl Palmitate Hydrochloride [1-F-LPE (2)·HCl]

To a solution of **22** (69.2 mg, 0.113 mmol) in anhyd THF (1 mL) was added LHMDS (1.02 mol/L in *n*-hexane, 133 µL, 0.136 mmol) and the solution was stirred at 0 °C for 5 min under argon. After adding benzaldehyde (13.9 µL, 0.136 mmol), the reaction mixture was allowed to warm to r.t. and stirred for 15 min under argon. A 1/15 M phosphate buffer (pH 7.4, 3 mL) was added to the mixture, and then concentrated in vacuo. The residue was purified by column chromatography [COSMOSIL 75 SL-II-PREP: $CHCl_3$–MeOH (100:1 to 2:1)] to afford **23**, which was used in the next reaction without further purification. A mixture of **23** and 4 M HCl in 1,4-dioxane (0.57 mL, 2.26 mmol) in CH_2Cl_2 (1 mL) was stirred at r.t. for 1.5 h and concentrated in vacuo. The residue was purified by column chromatography [Silica Gel 60N: $CHCl_3$–MeOH (2:1)] to afford 1-F-LPE (**2**)·HCl (26.6 mg, 48%, two steps) as a white solid; mp 188–191 °C; $[\alpha]_D^{27}$ +9.7 [*c* 0.55, $CHCl_3$–MeOH (2:1)].

IR (KBr): 2920, 2851, 1741, 1467, 1252, 1225, 1082 cm^{-1}.

^{1}H NMR [500 MHz, $CDCl_3$–CD_3OD (2:1)]: δ = 5.23–5.13 (m, 1 H), 4.61 (dd, $^2J_{H,F}$ = 47.1 Hz, $^3J_{H,H}$ = 4.1 Hz, 2 H), 4.07–3.99 (m, 4 H), 3.13–3.09 (m, 2 H), 2.39–2.34 (m, 2 H), 1.67–1.58 (m, 2 H), 1.36–1.22 (m, 24 H), 0.89 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR [125 MHz, $CDCl_3$–CD_3OD (2:1)]: δ = 173.9, 81.5 (d, $^1J_{C,F}$ = 171.8 Hz), 71.3 (dd, $^2J_{C,F}$ = 19.4 Hz, $^3J_{C,P}$ = 8.4 Hz), 62.8 (dd, $^3J_{C,F}$ = 7.4 Hz, $^2J_{C,P}$ = 5.2 Hz), 61.8 (d, $^2J_{C,P}$ = 5.2 Hz), 40.8 (d, $^3J_{C,P}$ = 5.4 Hz), 34.4, 32.2, 29.92, 29.89, 29.8, 29.7, 29.6, 29.5, 29.3, 25.1, 22.9, 14.2.

HRMS (ESI): *m*/*z* [M – H – HCl]$^-$ calcd for $C_{21}H_{42}FNO_6P$: 454.2734; found: 454.2732.

Anal. Calcd for $C_{21}H_{44}ClFNO_6P$: C, 51.26; H, 9.01; N, 2.85. Found: C, 51.23; H, 8.85; N, 2.98.

Methyl 2-{[(*S*)-2-(Benzyloxy)-3-fluoropropoxy](2-bromoethoxy)phosphoryl}acetate (25)

To a solution of **6** (50 mg, 0.124 mmol), 2-bromoethanol (**24**; 13 μL, 0.186 mmol), and molecular sieves 3A (50 mg) in anhyd toluene (0.8 mL) was added DBU (28 μL, 0.186 mmol) at 0 °C under argon. After stirring at 0 °C for 7 h, a 1/15 M phosphate buffer (pH 7.4, 3 mL) was added to the reaction mixture. The mixture was filtered, and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (2:3) to afford **25** (diastereomeric mixture, 38.4 mg, 72%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 5 H), 4.71 (dd, *J* = 11.7, 1.2 Hz, 1 H), 4.68 (dd, *J* = 11.7, 2.8 Hz, 1 H), 4.62–4.55 (m, 1 H), 4.53–4.45 (m, 1 H), 4.41–4.30 (m, 3 H), 4.25–4.17 (m, 1 H), 3.91–3.81 (m, 1 H), 3.74/3.73 (2 s, 3 H), 3.50/3.48 (2 t, *J* = 6.2, 6.1 Hz, 2 H), 3.06/3.04/3.03 (dd, $^2J_{H,P}$ = 21.9 Hz, $^2J_{H,H}$ = 14.8 Hz, dd, $^2J_{H,P}$ = 21.5 Hz, $^2J_{H,H}$ = 14.8 Hz, d, $^2J_{H,P}$ = 21.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8 (d, $^2J_{C,P}$ = 5.9 Hz), 137.5, 128.5, 128.0, 127.94, 127.91, 81.8 (d, $^1J_{C,F}$ = 172.1 Hz), 75.8, 75.7, 75.63, 75.59, 72.4, 72.3, 65.9, 65.8, 65.79, 65.74, 64.47, 64.42, 64.37, 64.34, 64.29, 64.23, 52.72, 52.70, 34.0 (d, $^1J_{C,P}$ = 138.9 Hz for one diastereomer), 33.9 (d, $^1J_{C,P}$ = 138.0 Hz for one diastereomer), 29.9, 29.83, 29.79, 29.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{21}BrFO_6PNa$: 449.0141; found: 449.0145.

(2*S*)-1-{[(2-Bromoethoxy)(2-methoxy-2-oxoethyl)phosphoryl]oxy}-3-fluoropropan-2-yl Palmitate (27)

A mixture of **25** (61.2 mg, 0.143 mmol) and 10% Pd/C (30 mg, 0.0282 mmol) in MeOH (1 mL) was stirred at r.t. for 15 min under H_2 atmosphere. The reaction mixture was filtered and concentrated in vacuo to afford **26**, which was used in the next reaction without further purification. To a solution of palmitic acid (73 mg, 0.286 mmol), 2-methyl-6-nitrobenzoic anhydride (99 mg, 0.286 mmol), and DMAP (52 mg, 0.426 mmol) in anhyd CH_2Cl_2 (6 mL) was added a solution of **26** in anhyd CH_2Cl_2 (4 mL) at r.t. under argon. The mixture was stirred for 15 min. A 1/15 M phosphate buffer (pH 7.4, 3 mL) was added to the mixture, and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (1:1)] twice to afford **27** (diastereomeric mixture, 59.6 mg, 72%, two steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.27–5.17 (m, 1 H), 4.64–4.61 (m, 1 H), 4.55–4.51 (m, 1 H), 4.45–4.24 (m, 4 H), 3.76 (s, 3 H), 3.55/3.54 (2 t, *J* = 6.2, 6.1 Hz, 2 H), 3.06 (d, $^2J_{H,P}$ = 21.5 Hz, 1 H for one diastereomer), 3.05 (d, $^2J_{H,P}$ = 21.5 Hz, 1 H for one diastereomer), 2.37 (t, *J* = 7.6 Hz, 2 H), 1.68–1.59 (m, 2 H), 1.35–1.20 (m, 24 H), 0.88 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 165.7 (d, $^2J_{C,P}$ = 5.4 Hz), 80.7 (d, $^1J_{C,F}$ = 173.3 Hz for one diastereomer), 80.6 (d, $^1J_{C,F}$ = 172.9 Hz for one diastereomer), 70.12, 70.08, 70.06, 70.02, 69.95, 69.91, 69.86, 66.0, 65.97, 65.95, 65.92, 63.7, 63.63, 63.58, 63.53, 63.5, 63.4, 52.8, 34.14, 34.12, 33.94 (d, $^1J_{C,P}$ = 138.7 Hz for one diastereomer), 33.89 (d, $^1J_{C,P}$ = 138.2 Hz for one diastereomer), 31.9, 29.7, 29.69, 29.66, 29.65, 29.62, 29.5, 29.4, 29.3, 29.1, 24.8, 22.7, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{45}BrFO_7PNa$: 597.1968; found: 597.1911.

(*S*)-3-Fluoro-2-(palmitoyloxy)propyl [2-(Trimethylammonio)ethyl] Phosphate [1-F-LPC (3)]

To a solution of **27** (68.6 mg, 0.119 mmol) in anhyd THF (1 mL) were added LHMDS (1.02 mol/L in *n*-hexane, 140 μL, 0.143 mmol) and benzaldehyde (14.6 μL, 0.143 mmol) at 0 °C under argon. The reaction mixture was stirred for 15 min under argon. A 1/15 M phosphate buffer (pH 7.4, 3 mL) was added to the mixture, and then concentrated in vacuo. The residue was purified by column chromatography [COSMOSIL 75 SL-II-PREP: $CHCl_3$–MeOH (100:1 to 3:1)] to afford **28**, which was used in the next reaction without further purification. A mixture of **28** and Me_3N (ca. 3 mol/L in EtOH, 2 mL, ca. 6 mmol) was stirred at r.t. for 5 d and then concentrated in vacuo. The residue was purified by column chromatography [Silica Gel 60N: $CHCl_3$–MeOH (3:1) to $CHCl_3$–MeOH–H_2O (5:5:1)] to afford 1-F-LPC (**3**) (38.7 mg, 65%, two steps) as a white solid; mp 65–67 °C; $[\alpha]_D^{27}$ +9.8 (*c* 1.09, $CHCl_3$).

IR (KBr): 2918, 2850, 1737, 1468, 1247, 1093 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.15 (br d, 1 H), 4.69–4.52 (m, 2 H), 4.35–4.26 (m, 2 H), 3.98–3.91 (m, 2 H), 3.82–3.76 (m, 2 H), 3.36 (s, 9 H), 2.35–2.28 (m, 2 H), 1.64–1.54 (m, 2 H), 1.34–1.20 (m, 24 H), 0.88 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 82.0 (d, $^1J_{C,F}$ = 171.8 Hz), 71.2 (dd, $^2J_{C,F}$ = 19.6 Hz, $^3J_{C,P}$ = 9.1 Hz), 66.2, 62.4, 59.6, 54.6, 34.3, 32.0, 29.78, 29.77, 29.71, 29.66, 29.5, 29.4, 29.2, 25.0, 22.7, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{49}FNO_6PNa$: 520.3179; found: 520.3178.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588826.

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