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Synthesis and Biological Activity of Fluorine-Modified Platelet Activating Factors¹⁾

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Fluorine-modified acetyl glyceryl ether phosphorylcholines (platelet activating factors; PAFs) were efficiently synthesized in an enantioselective manner by the coupling of a D-threitol derivative with fluorinated long-chain alkoxy methanesulfonates. The introduction of a trifluoromethyl group at the terminal of the alkyl ether chain decreased the hypotensive activity and platelet activation considerably. As the number of fluorine atoms in the alkyl ether chain was increased, both activities were gradually restored, but no selective agonist was obtained from among the fluorinated PAFs.

Keywords—platelet activating factor; fluorine-modified platelet activating factor; D-threitol derivative; alkylation

Since the characterization of platelet activating factors (PAFs) (**1a**, **1b**) by Hanahan *et al.*,²⁾ and Benveniste *et al.*,³⁾ in 1979, this new class of biologically active lipids has been the subject of a great deal of synthetic study in the field of medicinal chemistry. They act as powerful mediators in physiological or pathological processes such as anaphylaxis and inflammation.⁴⁾ We reported in a previous communication⁵⁾ an efficient methodology for the preparation of both enantiomers of C₁₆- and C₁₈-PAFs, starting from D- and/or L-tartaric acids as chiral synthons, and found that the unnatural PAFs possess far lower biological activities than the natural ones. Some analogues with modifications of the hydrophilic quaternary ammonium moiety were also synthesized and their biological activities were investigated. The modification of the cationic moiety of PAF caused a large diminution or enhancement of both biological activities (platelet activation and hypotension), in the same direction.

platelet activating factor

1a: $n = 16$

1b: $n = 18$

We were next interested in modification of the lipophilic alkyl moiety, especially the introduction of fluorine atoms into the chain. In general, introduction of fluorines into biologically active compounds is expected to change the properties of the parent hydrogen-substituted compounds in the direction of enhanced lipophilicity and metabolic stability

without appreciable change of steric bulkiness.^{6,7)}

Thus, to examine the substituent effect of fluorine on the biological activities of PAF, some analogues having fluorine atoms in the 1-*O*-alkyl chain were synthesized and their biological activities were investigated.

Chart 1

Synthesis of Fluorinated C₁₆–C₁₈ Alcohols (Chart 1)

The C₁₆–C₁₈ alcohols (**4c** and **8a–c**) were prepared as follows. The radical addition reaction of perfluoroalkyl iodide (**1a–c**) to the terminal olefinic compound (**2**) catalyzed by

Chart 2

$\text{Fe}_3(\text{CO})_{12}$ ⁸⁾ afforded the adducts (**3a—c**), which were in turn reduced with Zn dust in acetic acid followed by saponification to give the fluorinated alcohols (**4a—c**). The Grignard coupling reaction of ω -benzyloxyalkyl magnesium bromide (**6a, b**) with the bromides (**5a, b**) derived from **4a** and **4b** proceeded in the presence of a catalytic amount of Li_2CuCl_4 ⁹⁾ to give the benzyl ethers (**7a—c**), which were converted to the C_{16} – C_{18} alcohols (**8a—c**) by debenzylation ($\text{H}_2/\text{Pd-C}$).

Synthesis of 1-*O*-Fluoroalkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholines (Fluorine-Modified PAFs) (Chart 2)

The C_{16} – C_{18} alcohols were converted to the methanesulfonyl esters and coupled with 2-*O*-benzyl-3,4-*O*-isopropylidene-D-threitol, and then converted to 1-*O*-fluoroalkyl-2-*O*-benzyl-*sn*-glycerol following the methods described in the previous communication.⁵⁾

Then phosphorylcholine groups were introduced into the *sn*-3-position of the glycerols, and the benzyl groups were removed and acetylated to afford fluorine-modified PAFs.

Biological Activities of Fluorine-Modified PAFs (Table I)

The biological activities (platelet activation and hypotensive) of fluorine-modified PAFs were investigated. The results are summarized in Table I, showing the relative biological activities of the analogues. Their ability to induce irreversible platelet aggregation was determined by measuring aggregation and the release of ^{14}C -serotonin from rabbit platelets¹⁰⁾ and their hypotensive activities were examined by using male Wistar strain rats.¹¹⁾ The activities of the analogues are expressed relative to that of C_{16} -PAF (reciprocals of the concentrations required).

The results showed that no selective analogue with high hypotensive activity but with low platelet activation was present among the modified PAFs with fluorinated alkyl ether chains. However, it should be noted that the introduction of a trifluoromethyl group at the terminal of the alkyl ether chain (**17a**) decreased both activities considerably, and as the number of fluorine atoms in the alkyl ether chain was increased, both activities were gradually restored (**17b**, **17c**, **17d**). Although the results obtained here are difficult to explain in terms of lipophilicity and metabolic stability, the structure–activity relationships of PAF should be explored further, not only from the viewpoint of constitutional modification, but also by conformational analysis.¹²⁾

TABLE I. Biological Activities of Fluorine-Modified PAFs

	Relative activity	
	Platelet activation	Hypotension
C_{16} -PAF	1	1
17a	0.10	0.10
17b	0.33	0.33
17c	0.58	1
17d	0.63	0.30

Experimental

All the reactions were performed under an argon atmosphere unless otherwise specified, using a standard syringe technique for the transfer of materials. The solvents were generally redistilled before use. Tetrahydrofuran (THF) and ether were dried over sodium and distilled before use. Thin-layer chromatography (TLC) was performed on Merck 60 F_{254} (0.25 mm) sheets, and the spots were visualized with molybdophosphoric acids in sulfuric acid. Wakogel C-200 was employed for the column chromatography. Melting points were taken on a hot-stage microscope (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded using a Jasco IRA-1 spectrophotometer.

Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were recorded on a Varian EM 390L instrument and the chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. $^{19}\text{F-NMR}$ spectra were recorded on a Varian EM 360L spectrometer and the chemical shifts are reported in parts per million relative to benzotrifluoride as an internal standard. The optical rotations were measured with a JASCO DIP 140 polarimeter. The mass spectra (MS) were recorded with a JEOL JMS-DX 300 apparatus. Perfluoroalkyl iodides were purchased from PCR Inc., Gainesville, Florida.

11,11,11-Trifluoroundecan-1-ol (4a)—A 30 ml test-tube containing 9-decenyl acetate (6.0 g, 30.3 mmol), ethanol (3 ml), pyridine (0.9 ml) and $\text{Fe}_3(\text{CO})_{12}$ (150 mg) was placed in a stainless-steel autoclave, and trifluoromethyl iodide (7.42 ml, 89 mmol) was introduced. The autoclave was heated at 80°C for 2 h, then at 110°C for 16 h. The reaction mixture was diluted with ether, washed successively with 1 N HCl and brine, then dried over MgSO_4 . After removal of the solvent *in vacuo*, the residue was treated with Zn powder (6.53 g) in a mixture of acetic acid (60 ml) and ether (60 ml) at room temperature for 15 h. The precipitate was filtered off through Celite and washed with ether. The filtrate was washed with 1 N HCl, NaHCO_3 solution and brine, then dried over MgSO_4 . The solvent was removed *in vacuo* to leave crude 11,11,11-trifluoroundecanyl acetate (5.95 g), which was saponified by treatment with 4.3% methanolic KOH (50 ml) at room temperature for 2 h. The reaction mixture was evaporated to remove the solvent and the residue was diluted with water. This was extracted with ether, then the extract was dried over MgSO_4 and concentrated *in vacuo*. The residue was submitted to column chromatography (SiO_2 , 10% ethereal hexane as the eluent) to give 11,11,11-trifluoroundecan-1-ol (**4a**, 2.556 g, 37%) as a colorless oil. **4a**: $^1\text{H-NMR}$ (CDCl_3) δ : 3.63 (2H, t, $J=6$ Hz, $-\text{CH}_2\text{OH}$). $^{19}\text{F-NMR}$ (CDCl_3) δ : -3.67 (t, $J=9.4$ Hz). IR (neat): 3300, 2920, 2850, 1270, 1140 cm^{-1} . MS m/z : 208 ($\text{M}^+ - \text{H}_2\text{O}$), 180, 166, 152, 138, 97, 83, 69. High-resolution MS Calcd for $\text{C}_{11}\text{H}_{19}\text{F}_3$: 208.14438. Found: 208.14448.

1-Bromo-11,11,11-trifluoroundecane (5a)—A dimethylformamide (DMF) solution (10 ml) of **4a** (2.056 g, 8.7 mmol) was added to a suspension of triphenylphosphine dibromide [prepared from triphenylphosphine (3.10 g, 11.8 mmol) and bromine (1.746 g, 10.9 mmol)] in acetonitrile (10 ml) at 0°C . The reaction mixture was stirred for 12 h at room temperature, diluted with water and extracted with ether. The organic layer was washed with water, dried over MgSO_4 , and then chromatographed (SiO_2 , 10% ethereal hexane) to give the bromide (**5a**, 2.465 g, 94%) as a colorless oil. **5a**: $^1\text{H-NMR}$ (CDCl_3) δ : 3.10 (2H, t, $J=7$ Hz, $-\text{CH}_2\text{Br}$). MS m/z : 290 M^+ (^{81}Br), 288 M^+ (^{79}Br), 209, 135, 133. High-resolution MS Calcd for $\text{C}_{11}\text{H}_{20}\text{BrF}_3$: 289.0699. Found: 289.0692.

1-Benzyloxy-16,16,16-trifluorohexadecane (7a)—A 0.1 M THF solution of Li_2CuCl_4 (0.5 ml) was added to a solution of the Grignard reagent [prepared from 5-benzyloxypentyl bromide (780 mg) and Mg (100 mg)] in THF (10 ml), followed by the addition of the bromide **5a** (300 mg, 1.04 mmol). The reaction mixture was stirred for 8 h at room temperature. After the usual extractive work-up (ether for extraction), the extract was purified by column chromatography (SiO_2 , 0.5% AcOEt in hexane) to give the coupling product **7a** (350 mg, 88%) as a colorless oil. **7a**: $^1\text{H-NMR}$ (CDCl_3) δ : 3.50 (2H, m, $-\text{CH}_2\text{OBn}$), 4.53 (2H, s, $-\text{OCH}_2\text{Ph}$), 7.37 (5H, s, Ph). $^{19}\text{F-NMR}$ (CDCl_3) δ : -3.3 (t, $J=11.3$ Hz). MS m/z : 386 (M^+), 295, 276. High-resolution MS Calcd for $\text{C}_{23}\text{H}_{37}\text{F}_3\text{O}$: 386.2793. Found: 386.2781. IR (neat): 3030, 2935, 2860, 1100 cm^{-1} .

16,16,16-Trifluorohexadecan-1-ol (8a)—Hydrogenolysis of the benzyl ether **7a** (291 mg, 0.75 mmol) on 5% Pd-C in EtOH (5 ml) under a pressure of 3 atm at room temperature followed by recrystallization from *n*-hexane gave the alcohol **8a** (156 mg, 70%) as colorless crystals. **8a**: mp $56-56.5^\circ\text{C}$. $^1\text{H-NMR}$ (CDCl_3) δ : 1.17–1.85 (26H, m), 1.85 (1H, s, $-\text{OH}$), 1.80–2.40 (2H, m, CF_3CH_2-), 3.65 (2H, t, $J=5$ Hz, $-\text{CH}_2\text{O}-$). $^{19}\text{F-NMR}$ (CDCl_3) δ : -3.8 (t, $J=10.3$ Hz). IR (KBr): 3360, 2918, 2842, 1155 cm^{-1} . MS m/z : 278 ($\text{M}^+ - 18$), 250. High-resolution MS Calcd for $\text{C}_{16}\text{H}_{29}\text{F}_3$: 278.2219. Found: 278.2202.

11,11,12,12,13,13,13-Heptafluorotridecan-1-ol (4b)—A mixture of heptafluoro-1-iodopropane (6.694 g, 22.6 mmol), 9-decenyl acetate (3.775 g, 19 mmol) and $\text{Fe}_3(\text{CO})_{12}$ (100 mg) in a Pyrex glass sealed tube was heated at 80°C for 5.5 h. The reaction mixture was dissolved in a mixture of acetic acid (33 ml) and ether (33 ml), and treated with Zn powder (1.95 g) at room temperature for 1 h. Extractive work-up (ether for extraction) followed by chromatographic purification (SiO_2 , 20% ethereal pentane) gave crude heptafluorotridecanyl acetate (5.268 g, 76%), which was saponified by treatment with 5% methanolic KOH (35 ml) at room temperature for 2 h to give **4b** (4.569 g, 71% overall yield) as a colorless oil. **4b**: bp $135-142^\circ\text{C}/4\text{ mm}$ (Kugelröhr). $^1\text{H-NMR}$ (CDCl_3) δ : 3.69 (2H, t, $J=6$ Hz, $-\text{CH}_2\text{OH}$). $^{19}\text{F-NMR}$ (CDCl_3) δ : -18.1 (3F, t, $J=9.4$ Hz), -52.5 (2F, m), -65.1 (2F, m). IR (neat): 3300 cm^{-1} . MS m/z : 308 ($\text{M}^+ - 18$), 280.

1-Bromo-11,11,12,12,13,13,13-heptafluorotridecane (5b)—By the same method as used for the preparation of **5a**, **5b** was obtained in 85% yield. **5b**: Colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ : 3.43 (2H, t, $J=7$ Hz, $-\text{CH}_2\text{Br}$). $^{19}\text{F-NMR}$ (CDCl_3) δ : -17.3 (3F, t, $J=9.4$ Hz), -52.3 (2F, m), -65.0 (2F, m). IR (neat): 2920, 2850, 1225, 1170 cm^{-1} . MS m/z : 390 M^+ (^{81}Br), 388 M^+ (^{79}Br).

1-Benzyloxy-14,14,15,15,16,16,16-heptafluorohexadecane (7b)—In the same manner as described for the preparation of **7a**, the reaction of the Grignard reagent [prepared from 3-benzyloxypentyl bromide (3.054 g, 13.3 mmol) and Mg (470 mg, 20 mmol)] with **5b** (1.577 g, 4.1 mmol) in the presence of Li_2CuCl_4 (0.05 mmol) in THF at room temperature for 5 h gave the benzyl ether **7b** (742 mg, 40%) as a colorless oil. **7b**: $^1\text{H-NMR}$ (CDCl_3) δ : 3.50 (2H, t, $J=7$ Hz, $-\text{CH}_2\text{OBn}$), 4.53 (2H, s, $-\text{OCH}_2\text{Ph}$), 7.40 (5H, s, Ph). $^{19}\text{F-NMR}$ (CDCl_3) δ : -17.7 (3F, t, $J=9.4$ Hz),

–51.8 (2F, m), –64.5 (2F, m). MS m/z : 458 (M^+), 367, 348, 321, 91. High-resolution MS Calcd for $C_{23}H_{33}F_7O$: 458.2416. Found: 458.2390.

14,14,15,15,16,16,16-Heptafluorohexadecan-1-ol (8b)—Hydrogenolysis of the benzyl ether **7b** (433 mg, 0.95 mmol) on 5% Pd–C in EtOH (2 ml) and acetic acid (0.5 ml) under atmospheric pressure, followed by recrystallization from *n*-hexane gave **8b** (281 mg, 80%). **8b**: mp 49.5–51 °C. 1H -NMR ($CDCl_3$) δ : 1.20–1.85 (23H, m), 1.92–2.30 (2H, m, $C_3F_7CH_2$ –), 3.67 (2H, t, $J=7$ Hz, $-CH_2OH$). ^{19}F -NMR ($CDCl_3$) δ : –17.8 (3F, t, $J=9.4$ Hz), –51.8 (2F, m), –64.5 (2F, m). MS m/z : 350 ($M^+ - 18$), 322, 294, 280. Anal. Calcd for $C_{16}H_{27}F_7O$: C, 52.17; H, 7.39; F, 36.10. Found: C, 52.23; H, 7.16; F, 36.15.

1-Benzyloxy-16,16,17,17,18,18,18-heptafluorooctadecane (7c)—85% yield. 1H -NMR ($CDCl_3$) δ : 3.50 (2H, t, $J=6$ Hz, $-CH_2OBn$), 4.53 (2H, s, $-OCH_2Ph$), 7.43 (5H, s, Ph). ^{19}F -NMR ($CDCl_3$) δ : –17.9 (3F, t, $J=9.4$ Hz), –52.3 (2F, m), –65.0 (2F, m). MS m/z : 486 (M^+), 395, 376, 91.

16,16,17,17,18,18,18-Heptafluorooctadecan-1-ol (8c)—87% yield; mp 55–57 °C (*n*-hexane). 1H -NMR ($CDCl_3$) δ : 1.20–1.85 (27H, m), 1.92–2.30 (2H, m, $C_3F_7CH_2$ –), 3.67 (2H, t, $J=7$ Hz, $-CH_2OH$). ^{19}F -NMR ($CDCl_3$) δ : –17.6 (3F, t, $J=9.4$ Hz), –52.3 (2F, m), –65.0 (2F, m). MS m/z : 378 ($M^+ - 18$), 350, 322. Anal. Calcd for $C_{18}H_{31}F_7O$: C, 54.54; H, 7.88; F, 33.55. Found: C, 54.33; H, 7.90; F, 33.72.

Pentadecafluoroheptadecan-1-ol (4c)—A mixture of perfluoroheptyl iodide (7.18 g, 14.5 mmol), 9-decenyln acetate (2.41 g, 12 mmol) and $Fe_3(CO)_{12}$ (50 mg) was heated at 60 °C for 1 h, and then at 80 °C for 1 h. The reaction mixture was dissolved in a mixture of acetic acid (30 ml) and ether (30 ml), and treated with Zn powder at room temperature for 3 h to give the crude acetate (4.82 g), which was saponified with 2.5% methanolic KOH (35 ml) at room temperature for 5 h. After extractive work-up (ether for extraction) and evaporation of the solvent, the residue was purified by sublimation (57–59 °C/3 mmHg) to give **4c** (2.751 g, 43% overall yield). **4c**: mp 61–63 °C. 1H -NMR ($CDCl_3$) δ : 1.23–1.90 (16H, m), 1.42 (1H, s, $-OH$), 1.92–2.50 (2H, m, $C_7F_{15}CH_2$ –), 3.68 (2H, t, $J=6$ Hz, $-CH_2OH$). ^{19}F -NMR ($CDCl_3$) δ : –17.3 (3F, t, $J=9.4$ Hz), –50.2 (2F, m), –58.0 (8F, m), –62.0 (2F, m). Anal. Calcd for $C_{17}H_{21}F_{15}O$: C, 38.80; H, 4.02; F, 54.14. Found: C, 38.76; H, 4.00; F, 53.93.

Methanesulfonylated Fluoroalcohols (11a–d)—The alcohols **8a**, **8b**, **8c** and **4c** (0.5 mmol) were each dissolved in dry pyridine (5 ml) and methanesulfonyl chloride (MsCl) (63 mg, 0.55 mmol) was added at 0 °C. Each mixture was stirred at room temperature for 1 h. The reaction mixture was poured into ice-water, and extracted with ether. The ethereal solution was washed with dil. HCl and brine, then dried on $MgSO_4$, and concentrated to afford **11a**, **11b**, **11c** or **11d**, respectively as white crystals.

11a: ($m=15$, $n=0$) yield (Y.) 83%, mp 45–46 °C. 1H -NMR ($CDCl_3$) δ : 1.2–1.48 (m, 24H), 1.90–2.24 (m, 2H), 1.84–2.36 (m, 2H), 3.00 (s, 3H), 4.20 (t, $J=7$ Hz, 2H). IR (KBr): 3070, 2950, 2880, 1480, 1355, 1192, 1140 cm^{-1} . MS m/z : 374 (M^+).

11b: ($m=13$, $n=2$) Y. 87%, mp 39–42 °C. 1H -NMR ($CDCl_3$) δ : 1.10–1.90 (m, 22H), 1.90–2.24 (m, 2H), 2.98 (s, 3H), 4.20 (t, $J=7$ Hz, 2H). IR (KBr): 2940, 2860, 1473, 1356, 1172, 1126, 1115, 1050 cm^{-1} . MS m/z : 446 (M^+).

11c: ($m=15$, $n=2$) Y. 100%, mp 49–51 °C. 1H -NMR ($CDCl_3$) δ : 1.08–1.27 (m, 24H), 1.27–1.87 (m, 2H), 1.87–2.20 (m, 2H), 2.97 (s, 3H), 4.20 (t, $J=7$ Hz, 2H). IR (KBr): 2940, 2860, 1473, 1356, 1172, 1126, 1115, 1050 cm^{-1} . MS m/z : 474 (M^+).

11d: ($m=10$, $n=6$) Y. 87%, mp 59.5–62.5 °C. 1H -NMR ($CDCl_3$) δ : 1.13–1.44 (m, 14H), 1.44–1.88 (m, 2H), 1.89–2.25 (m, 2H), 2.97 (s, 3H), 4.20 (t, $J=7$ Hz, 2H). IR (KBr): 2940, 2860, 1472, 1357, 1170, 1126, 1116, 1052, 1006 cm^{-1} . MS m/z : 604 (M^+).

1-O-Fluoroalkyl-2-O-benzyl-3,4-O-isopropylidene-D-threitol (12a–d)—A 22% potassium hydride oil dispersion (0.27 ml, 1.5 mmol) was slowly added to a solution of 2-O-benzyl-3,4-O-isopropylidene-D-threitol⁵¹ (175 mg, 0.7 mmol) in benzene (10 ml) at room temperature. The reaction mixture was stirred for an additional 30 min, and then **11** (0.46 mmol) in benzene (10 ml) was added. The reaction mixture was stirred for 10 h at room temperature, cooled to 0 °C, diluted with hexane (10 ml), and quenched by successive addition of EtOH (1 ml) and water (5 ml). The organic layer was separated, and the aqueous layer was washed with AcOEt. The combined organic layer was dried on $MgSO_4$, concentrated and purified by silica gel column chromatography (benzene) to afford **12** as a colorless oil.

12a: ($m=15$, $n=0$) Y. 66%. 1H -NMR ($CDCl_3$) δ : 1.17–1.34 (m, 24H), 1.39 (s, 3H), 1.43 (s, 3H), 1.57–1.87 (m, 2H), 1.87–2.31 (m, 2H), 3.41 (t, $J=7$ Hz, 2H), 3.51–4.40 (m, 6H), 4.78 (s, 2H), 7.27–7.47 (m, 5H). IR (neat): 3450, 2920, 2860, 1455, 1370, 1220, 1160 cm^{-1} . MS m/z : 530 ($M^+ - 15$).

12b: ($m=13$, $n=2$) Y. 75%. 1H -NMR ($CDCl_3$) δ : 1.16–1.72 (m, 22H), 1.36 (s, 3H), 1.42 (s, 3H), 1.90–2.40 (m, 2H), 3.38 (t, $J=12$ Hz, 2H), 3.47–4.40 (m, 6H), 4.71 (s, 2H), 7.16–7.48 (m, 5H). IR (neat): 3450, 2920, 2860, 1445, 1370, 1150 cm^{-1} . MS m/z : 602 (M^+), 587 ($M^+ - 15$).

12c: ($m=15$, $n=2$) Y. 89%. 1H -NMR ($CDCl_3$) δ : 1.16–1.72 (m, 26H), 1.36 (s, 3H), 1.40 (s, 3H), 1.89–2.28 (m, 2H), 3.41 (t, $J=7$ Hz, 2H), 3.51–4.40 (m, 6H), 4.72 (s, 2H), 7.28 (m, 5H). IR (neat): 3450, 2920, 2860, 1455, 1370, 1160 cm^{-1} . MS m/z : 630 (M^+), 615 ($M^+ - 15$).

12d: ($m=10$, $n=6$) Y. 66%. 1H -NMR ($CDCl_3$) δ : 1.16–1.48 (m, 14H), 1.34 (s, 3H), 1.43 (s, 3H), 1.49–1.88 (m, 2H), 1.89–2.25 (m, 2H), 3.40 (t, $J=7$ Hz, 2H), 3.44–4.10 (m, 5H), 4.10–4.30 (m, 1H), 4.75 (s, 2H), 7.22–7.48 (s, 5H). IR (neat): 3450, 2920, 2840, 1455, 1370, 1160 cm^{-1} . MS m/z : 760 (M^+), 745 ($M^+ - 15$).

1-O-Fluoroalkyl-2-O-benzyl-D-threitol (13a–d)—The *O*-alkylated derivative **12** (0.4 mmol) was stirred in

THF (15 ml) and 2N HCl (5 ml) at room temperature for 2 h, then the solution was concentrated to a small volume (ca. 5 ml) under reduced pressure. After water (10 ml) had been added, the mixture was extracted with ethyl acetate (20 ml $\times$ 3). Evaporation of the solvent gave a residue, which was chromatographed on silica gel to give **13** as white crystals.

13a: Y. 73%, mp 36–38 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.17–1.48 (m, 24H), 1.48–1.76 (m, 2H), 1.87–2.31 (m, 4H), 3.41 (t, J = 7 Hz, 2H), 3.60–3.88 (m, 6H), 4.38 (d, J = 12 Hz, 1H), 4.78 (d, J = 12 Hz, 1H), 7.27–7.37 (m, 5H). IR (KBr): 3300, 2920, 2860, 1460, 1210, 1150 cm^{-1} .

13b: Y. 77%, mp 32–34 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.15–1.85 (m, 22H), 1.92–2.20 (m, 2H), 2.85 (brs, 2H), 3.42 (t, J = 7 Hz, 2H), 3.55–3.90 (m, 6H), 4.53 (d, J = 12 Hz, 1H), 4.73 (d, J = 12 Hz, 1H), 7.17–7.52 (m, 5H). IR (KBr): 3350, 2940, 2880, 1240, 1210, 1160 cm^{-1} .

13c: Y. 76%, mp 41–44 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.15–1.72 (m, 26H), 1.91–2.20 (m, 4H), 3.42 (t, J = 7 Hz, 2H), 3.53–3.87 (m, 6H), 4.55 (d, J = 12 Hz, 1H), 4.75 (d, J = 12 Hz, 1H), 7.29 (s, 5H). IR (KBr): 3450, 2920, 2840, 1470, 1355, 1210, 1150 cm^{-1} . CI-MS m/z : 591 ($\text{M}^+ + 1$).

13d: Y. 88%, mp 51–54 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.16–1.48 (m, 14H), 1.49–1.88 (m, 2H), 1.89–2.25 (m, 2H), 2.79 (brs, 2H), 3.44 (t, J = 7 Hz, 2H), 3.55–3.88 (m, 6H), 4.56 (d, J = 12 Hz, 1H), 4.76 (d, J = 12 Hz, 1H), 7.32 (s, 5H). IR (KBr): 3350, 2940, 2880, 1240, 1210, 1150 cm^{-1} .

1-O-Fluoroalkyl-2-O-benzyl-*sn*-glycerols (14a–d)—Under vigorous stirring **13** (0.3 mmol) in benzene (10 ml) was added to a solution of $\text{Pb}(\text{OAc})_4$ (200 mg, 0.45 mmol) in benzene (20 ml) over a 2 h period at room temperature. After being stirred for an additional hour, the reaction mixture was cooled to 0 °C and saturated aqueous sodium bicarbonate was added. The resulting insoluble material was filtered through a celite layer and washed with benzene. The organic layer was separated, dried over Na_2SO_4 , and concentrated to afford the corresponding crude aldehyde in quantitative yield as a colorless oil. This was used without further purification for the next step. NaBH_4 (113 mg, 3 mmol) was slowly added to a solution of the crude aldehyde (0.3 mmol) in methanol (10 ml) at room temperature. The reaction mixture was allowed to stand at room temperature overnight, cooled to 0 °C, acidified with dil. hydrochloric acid, and concentrated to dryness under reduced pressure. The product was extracted with ethyl acetate (20 ml $\times$ 3), and the organic layer was dried over Na_2SO_4 . After the removal of the solvent, the residue was chromatographed on silica gel to afford **14** as a colorless oil (**14a, b, d**) or white crystals (**14c**).

14a: Y. 81%, oil. $^1\text{H-NMR}$ (CDCl_3) δ : 1.17–1.48 (m, 24H), 1.49–1.76 (m, 2H), 1.87–2.31 (m, 3H), 3.41 (t, J = 7 Hz, 2H), 3.44–3.80 (m, 5H), 4.62 (d, J = 12 Hz, 1H), 4.64 (d, J = 12 Hz, 1H), 7.28 (s, 5H). IR (neat): 3400, 2910, 2840, 1460, 1450, 1230, 1135 cm^{-1} . $[\alpha]_D^{20}$ = 5.98° (c = 0.57, CHCl_3). MS m/z : 460 (M^+).

14b: Y. 72%, oil. $^1\text{H-NMR}$ (CDCl_3) δ : 1.15–1.85 (m, 22H), 1.86–2.37 (m, 3H), 3.43 (t, J = 7 Hz, 2H), 3.53–3.97 (m, 5H), 4.67 (s, 2H), 7.21–7.51 (m, 5H). IR (neat): 3400, 2920, 2840, 1460, 1450, 1230, 1140 cm^{-1} . $[\alpha]_D^{20}$ = 12.4° (c = 0.54, CHCl_3). MS m/z : 532 (M^+).

14c: Y. 72%, white crystals, mp 36–38 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.16–1.72 (m, 26H), 1.91–2.20 (m, 2H), 3.41 (t, J = 7 Hz, 2H), 3.51–3.95 (m, 5H), 4.64 (s, 2H), 7.21–7.47 (m, 5H). IR (KBr): 3450, 2920, 2840, 1470, 1355, 1205, 1140 cm^{-1} . $[\alpha]_D^{20}$ = 9.28° (c = 1.12, CHCl_3). MS m/z : 560 (M^+).

14d: Y. 73%, oil. $^1\text{H-NMR}$ (CDCl_3) δ : 1.16–1.48 (m, 14H), 1.49–1.88 (m, 2H), 1.89–2.25 (m, 2H), 3.40 (t, J = 7 Hz, 2H), 3.44–3.80 (m, 5H), 4.62 (d, J = 12 Hz, 1H), 4.64 (d, J = 12 Hz, 1H), 7.28 (s, 5H). IR (neat): 3350, 2920, 2840, 1465, 1452, 1320, 1240, 1210, 1140 cm^{-1} . $[\alpha]_D^{20}$ = 6.20° (c = 1.37, CHCl_3). MS m/z : 704 (M^+).

1-O-Fluoroalkyl-2-O-benzyl-*sn*-glycero-3-phosphocholines (15a–d)—A mixture of **15** (0.19 mmol), 2-bromoethyl phosphoryl dichloride (69 mg, 0.29 mmol) and triethylamine (39 mg, 0.38 mmol) in dry ether (10 ml) was stirred under reflux for 12 h. Then water (0.2 ml) and triethylamine (0.1 ml) were added, and the reaction mixture was heated under reflux for 1 h. After cooling, 1N HCl (5 ml) was added and the mixture was extracted with chloroform (20 ml $\times$ 3). The organic layer was dried on MgSO_4 and concentrated to afford crude 2-bromoethyl 2-O-benzyl-L-1-O-fluoroalkyl-glyceryl hydrogen phosphate. The product was used without further purification in the next step. The phosphate was heated with trimethylamine (1 ml) and methanol (2 ml) to 55 °C in a sealed tube for 12 h. After removal of the solvent, AgOAc (80 mg, 0.48 mmol) in 90% aqueous methanol (20 ml) was added, and the reaction mixture was stirred for 2 h. The resulting precipitate was removed by filtration, and the filtrate was concentrated to give crude **15**. The product was purified by silica gel column chromatography to afford **15** as a white powder.

15a: Y. 52%, mp ca. 190 °C. $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.17–1.48 (m, 24H), 1.49–1.76 (m, 2H), 1.87–2.31 (m, 2H), 3.09 (s, 9H), 3.28–3.64 (m, 9H), 3.88–4.10 (m, 2H), 4.69 (s, 2H), 7.18–7.40 (m, 5H). IR (KBr): 3390, 3070, 3040, 2930, 2860, 1660, 1460, 1320, 1220, 1150 cm^{-1} . $[\alpha]_D^{20}$ = 1.20° (c = 0.40, $\text{CHCl}_3\text{-MeOH}$, 1:1).

15b: Y. 86%, mp 135–142 °C. $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.10–1.85 (m, 22H), 1.90–2.33 (m, 2H), 3.26 (s, 9H), 3.41 (t, J = 7 Hz, 2H), 3.30–3.70 (m, 4H), 3.70–4.37 (m, 5H), 4.70 (s, 2H), 7.18–7.50 (m, 5H). IR (KBr): 3420, 2940, 2850, 1465, 1230, 1085 cm^{-1} . $[\alpha]_D^{20}$ = 3.81° (c = 0.42, $\text{CHCl}_3\text{-MeOH}$, 1:1).

15c: Y. 68%, mp 229–233 °C (dec.). $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.10–1.73 (m, 26H), 1.91–2.33 (m, 2H), 3.11 (s, 9H), 3.41 (t, J = 7 Hz, 2H), 3.30–3.70 (m, 4H), 3.70–4.37 (m, 5H), 4.70 (s, 2H), 7.18–7.50 (m, 5H). IR (KBr): 3420, 2940, 2850, 1465, 1230, 1085 cm^{-1} . $[\alpha]_D^{20}$ = 2.61° (c = 0.94, $\text{CHCl}_3\text{-MeOH}$, 1:1).

15d: Y. 60%, mp 223–226 °C. $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.16–1.83 (m, 16H), 1.90–2.37 (m, 2H), 3.09 (s, 9H), 3.28–3.64 (m, 9H), 3.88–4.10 (m, 2H), 4.69 (s, 2H), 7.23 (s, 5H). IR (KBr): 3400, 2940, 2860, 1460,

1230, 1085 cm^{-1} . $[\alpha]_{\text{D}}^{20} + 2.11^\circ$ ($c = 1.11$, $\text{CHCl}_3\text{-MeOH}$, 1:1).

1-O-Fluoroalkyl-*sn*-glycero-3-phosphocholines (16a–d)—A mixture of **15** (0.13 mmol) and palladium black (10 mg) in ethanol was vigorously stirred under a hydrogen atmosphere (1 atm) for 6 h at 50 $^\circ\text{C}$. The catalyst was filtered off, and the filtrate was concentrated. The residual powder was purified on silica gel column chromatography to afford **16** as a white powder.

16a: Y. 100%, mp 230 $^\circ\text{C}$ (dec.). $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.17–1.48 (m, 24H), 1.49–1.76 (m, 2H), 1.87–2.31 (m, 2H), 3.21 (s, 9H), 3.30–3.76 (m, 9H), 3.88–4.10 (m, 2H). IR (KBr): 3420, 2940, 2850, 1465, 1210, 1150 cm^{-1} . $[\alpha]_{\text{D}}^{20} - 2.40^\circ$ ($c = 0.35$, $\text{CHCl}_3\text{-MeOH}$, 1:1).

16b: Y. 85%, mp 196 $^\circ\text{C}$ (dec.). $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.10–1.85 (m, 22H), 1.90–2.35 (m, 2H), 3.26 (s, 9H), 3.38–3.76 (m, 7H), 3.77–4.09 (m, 2H), 4.10–4.46 (m, 2H). IR (KBr): 3400, 2940, 2860, 1472, 1360, 1220, 1145 cm^{-1} . $[\alpha]_{\text{D}}^{20} - 2.00^\circ$ ($c = 1.17$, $\text{CHCl}_3\text{-MeOH}$, 1:1).

16c: Y. 78%, mp 226–234 $^\circ\text{C}$ (dec.). $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.10–1.73 (m, 26H), 1.91–2.33 (m, 2H), 3.25 (s, 9H), 3.33–3.76 (m, 7H), 3.77–3.93 (m, 2H), 3.94–4.40 (m, 2H). IR (KBr): 3400, 2940, 2860, 1472, 1360, 1220, 1140 cm^{-1} . $[\alpha]_{\text{D}}^{20} - 3.61^\circ$ ($c = 0.64$, $\text{CHCl}_3\text{-MeOH}$, 1:1).

16d: Y. 90%, mp 222–224 $^\circ\text{C}$ (dec.). $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.16–1.83 (m, 16H), 1.90–2.37 (m, 2H), 3.21 (s, 9H), 3.30–3.94 (m, 2H). IR (KBr): 3420, 2940, 2850, 1465, 1210, 1140 cm^{-1} . $[\alpha]_{\text{D}}^{20} - 2.55^\circ$ ($c = 0.55$, $\text{CHCl}_3\text{-MeOH}$, 1:1).

1-O-Fluoroalkyl-2-O-acetyl-*sn*-glycero-3-phosphocholines (17a–d)—A solution of **16** (0.1 mmol) in acetic anhydride was mixed with pyridine, and the reaction mixture was heated to 70 $^\circ\text{C}$ for 2 h, then cooled to 50 $^\circ\text{C}$. Pyridine and acetic anhydride were removed under reduced pressure, and the resulting residue was chromatographed on silica gel to afford **17** as a white powder.

17a: Y. 55%, mp 272–276 $^\circ\text{C}$. $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.17–1.48 (m, 24H), 1.49–1.76 (m, 2H), 1.87–2.31 (m, 2H), 2.12 (s, 3H), 3.21 (s, 9H), 3.45 (t, $J = 7$ Hz, 2H), 3.59 (d, $J = 5$ Hz, 2H), 3.64 (m, 2H), 4.00 (m, 2H), 5.13 (quintet, $J = 5$ Hz, 1H). IR (KBr): 3420, 2920, 2850, 1732, 1627, 1465, 1374, 1235, 1140 cm^{-1} . $[\alpha]_{\text{D}}^{20} - 0.46^\circ$ ($c = 0.11$, $\text{CHCl}_3\text{-MeOH}$, 1:1). FAB-MS (glycerine) 578 ($M^+ + 1$).

17b: Y. 38%, mp 272–276 $^\circ\text{C}$ (dec.). $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.12–1.54 (m, 22H), 1.55–1.78 (m, 2H), 2.20 (s, 3H), 3.34 (s, 9H), 3.52–4.00 (m, 8H), 4.20–4.40 (m, 2H), 5.10–5.28 (m, 1H). IR (CHCl_3): 2930, 2850, 1735, 1220, 1080 cm^{-1} . $[\alpha]_{\text{D}}^{20} - 4.86^\circ$ ($c = 0.10$, $\text{CHCl}_3\text{-CD}_3\text{OD}$, 1:1). FAB-MS (glycerine) 650 ($M^+ + 1$).

17c: Y. 75%, mp 208–212 $^\circ\text{C}$ (dec.). $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.10–1.73 (m, 26H), 1.91–2.35 (m, 2H), 2.07 (s, 3H), 3.18 (s, 9H), 3.28–3.70 (m, 9H), 3.88–4.10 (m, 2H), 4.10–4.40 (m, 2H), 5.10–5.25 (m, 1H). $^{19}\text{F-NMR}$ (CDCl_3): -17.9 (t, $J = 9.5$ Hz, 3F), -52.6 (m, 2F), -65.1 (m, 2F). IR (KBr): 3350, 2940, 2860, 1735, 1465, 1230, 1150 cm^{-1} . $[\alpha]_{\text{D}}^{20} - 1.59^\circ$ ($c = 0.63$, $\text{CHCl}_3\text{-MeOH}$, 1:1). FAB-MS (glycerine) 678 ($M^+ + 1$).

17d: Y. 57%, mp 196–199 $^\circ\text{C}$ (dec.). $^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 3:1) δ : 1.16–1.83 (m, 16H), 1.90–2.37 (m, 2H), 2.90 (s, 3H), 3.20 (s, 9H), 3.45 (t, $J = 7$ Hz, 2H), 3.53–3.70 (m, 2H), 3.84–4.06 (m, 2H), 4.06–4.40 (m, 2H), 5.12 (quintet, $J = 5$ Hz, 1H). $^{19}\text{F-NMR}$ (CDCl_3): -18.0 (t, $J = 9.7$ Hz, 3F), -51.2 (m, 2F), -57.7 — -60.0 (m, 8F), -63.0 (m, 2F). IR (KBr): 3340, 2940, 2860, 1735, 1465, 1230, 1150 cm^{-1} . $[\alpha]_{\text{D}}^{20} - 4.75^\circ$ ($c = 0.33$, $\text{CHCl}_3\text{-MeOH}$, 1:1). FAB-MS (glycerine) 808 ($M^+ + 1$).

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References and Notes

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