Synthesis and Biological Activity of Fluorine-Modified Platelet Activating Factors\textsuperscript{1)}

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Fluorine-modified acetyl glyceryl ether phosphorycholines (platelet activating factors; PAFs) were efficiently synthesized in an enantioselective manner by the coupling of a D-threitol derivative with fluoroalkylated long-chain alkyl esters. 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.,\textsuperscript{2)} and Benveniste et al.,\textsuperscript{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.\textsuperscript{4)} We reported in a previous communication\textsuperscript{5)} an efficient methodology for the preparation of both enantiomers of C\textsubscript{16}- and C\textsubscript{18}-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.

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.
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.

\[
\text{CF}_3(\text{CF}_2)_n\text{I} + \text{CH}_2=\text{CH}(\text{CH}_2)\text{Br} \xrightarrow{\text{Fe}(\text{CO})_3\text{H}} \text{CF}_3(\text{CF}_2)_n\text{CH}_2\text{CH}(\text{CH}_2)\text{Br} \xrightarrow{\text{EtOH}, \text{pyridine}} \text{CF}_3(\text{CF}_2)_n\text{CH}_2\text{CH}(\text{CH}_2)\text{Ac}
\]

\[ \begin{array}{lll} 
1 & 2 & 3 \ a, b, c \\
\text{a : } & n = 0 \\
\text{b : } & n = 2 \\
\text{c : } & n = 6 \\
\end{array} \]

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.

\[ \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{OH} \xrightarrow{\text{Ph}_3\text{P}, \text{Br}_2} \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{Br} \]

\[ \begin{array}{lll} 
4 \ a, b, c & 5 \ a, b \\
\text{a : } & n = 0 \\
\text{b : } & n = 2 \\
\end{array} \]

\[ \text{CF}_3(\text{CH}_2)\text{Br} \xrightarrow{\text{THF}} \text{CF}_3(\text{CH}_2)\text{Br} \]

\[ \begin{array}{lll} 
5 \ a & 6 \ a, \text{Li}_2\text{CuCl}_4 & 7 \ a, b, c, d \\
\text{a : } & n = 0 \\
\text{b : } & n = 2 \\
\end{array} \]

\[ \text{CF}_3(\text{CH}_2)\text{Br} \xrightarrow{\text{THF}} \text{CF}_3(\text{CH}_2)\text{Br} \]

\[ \begin{array}{lll} 
5 \ a & 6 \ a, \text{Li}_2\text{CuCl}_4 & 7 \ a, b, c, d \\
\text{a : } & n = 0 \\
\text{b : } & n = 2 \\
\end{array} \]

\[ \text{CF}_3(\text{CH}_2)\text{Br} \xrightarrow{\text{THF}} \text{CF}_3(\text{CH}_2)\text{Br} \]

\[ \begin{array}{lll} 
5 \ a & 6 \ a, \text{Li}_2\text{CuCl}_4 & 7 \ a, b, c, d \\
\text{a : } & n = 0 \\
\text{b : } & n = 2 \\
\end{array} \]

\[ \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{OH} \xrightarrow{\text{KH}, \text{PhH}} \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{OMs} \]

\[ \begin{array}{lll} 
8 \ a, b, c, d & 11 \ a, b, c, d \\
\text{a : } & n = 0 \\
\text{b : } & n = 2 \\
\end{array} \]

\[ \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{OH} \xrightarrow{2\text{NCl}-\text{THF}} \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{OH} \]

\[ \begin{array}{lll} 
12 \ a, b, c, d & 13 \ a, b, c, d \\
\text{a : } & n = 0 \\
\text{b : } & n = 2 \\
\end{array} \]

\[ \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{OH} \xrightarrow{\text{1. Cl}_2\text{PO}, \text{Br}, \text{Et}_3\text{N}} \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{OH} \]

\[ \begin{array}{lll} 
14 \ a, b, c, d & 15 \ a, b, c, d \\
\text{a : } & n = 0 \\
\text{b : } & n = 2 \\
\end{array} \]

\[ \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{OH} \xrightarrow{\text{Ac}_2\text{O}, \text{pyridine}} \text{CF}_3(\text{CF}_2)_n(\text{CH}_2)\text{OH} \]

\[ \begin{array}{lll} 
16 \ a, b, c, d & 17 \ a, b, c, d \\
\text{a : } & m = 15, \ n = 0 \\
\text{b : } & m = 13, \ n = 2 \\
\text{c : } & m = 15, \ n = 2 \\
\text{d : } & m = 10, \ n = 6 \\
\end{array} \]
Fe₃(CO)₁₂ affording 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 Li₂CuCl₄ to give the benzyl ethers (7a–c), which were converted to the C₁₆–C₁₈ alcohols (8a–c) by debenzylation (H₂/Pd–C).

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

The C₁₆–C₁₈ 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. 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 ¹⁴C-serotonin from rabbit platelets and their hypotensive activities were examined by using male Wistar strain rats. The activities of the analogues are expressed relative to that of C₁₆-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 fluoride 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.

<table>
<thead>
<tr>
<th></th>
<th>Relative activity</th>
<th>Hypotension</th>
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<tbody>
<tr>
<td>C₁₆-PAF</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>17a</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>17b</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td>17c</td>
<td>0.58</td>
<td>1</td>
</tr>
<tr>
<td>17d</td>
<td>0.63</td>
<td>0.30</td>
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</tbody>
</table>

**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 F₂₅₄ (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.
11,11,11-Trifluoroundecan-1-ol (4a)—A 30 ml test-tube containing 9-deceny acetate (6.0 g, 30.3 mmol), ethanol (3 ml), pyridine (0.9 ml) and Fe$_3$(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-trifluoroundecanyle 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 residual 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: 1H-NMR (CDCl$_3$) $\delta$: 3.63 (2H, t, J= 7 Hz, -CH$_2$OBn), 4.53 (2H, s, -OCH$_2$Ph), 7.40 (5H, s, Ph). 19F-NMR (CDCl$_3$) $\delta$: - 17.3 (3F, t, J= 9.4 Hz), - 52.5 (2F, m), - 65.1 (2F, m). IR (neat): 3030, 2918, 2842, 1155 cm$^{-1}$. MS m/z: 278 (M$^+$ - 18), 250.

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: 1H-NMR (CDCl$_3$) $\delta$: 3.10 (2H, t, J= 7 Hz, -CH$_2$Br). MS m/z: 290 M$^+$ (81Br), 288 M$^+$ (79Br), 209, 135, 133. High-resolution MS Calcd for C$_{13}$H$_{25}$BrF$_3$: 289.0699. Found: 289.0692.

1-Benzyloxy-16,16,16-trifluoroheptadecane (7a)—A 0.1 M THF solution of Li$_2$CuCl$_4$ (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: 1H-NMR (CDCl$_3$) $\delta$: 1.17-1.85 (26H, m), 3.43 (2H, t, J= 7 Hz, -CH$_2$Br). 19F-NMR (CDCl$_3$) $\delta$: - 3.5 (t, J= 9.4 Hz), - 52.3 (2F, m), - 65.0 (2F, m). IR (neat): 3030, 2918, 2842, 1100 cm$^{-1}$. MS m/z: 386 (M$^+$ - 18), 295, 276. High-resolution MS Calcd for C$_{18}$H$_{29}$BrF$_3$: 386.2793. Found: 386.2781.  

16,16,16-Trifluoroheptadecan-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 °C. 1H-NMR (CDCl$_3$) $\delta$: 1.17-1.85 (26H, m), 3.65 (2H, t, J= 7 Hz, -CH$_2$OH). 19F-NMR (CDCl$_3$) $\delta$: - 17.3 (3F, t, J= 9.4 Hz), - 52.5 (2F, m), - 65.1 (2F, m). IR (neat): 3360, 2918, 2842, 1155 cm$^{-1}$. MS m/z: 278 M$^+$ (79Br), 250. High-resolution MS Calcd for C$_{16}$H$_{29}$F$_7$: 278.2293. Found: 278.2229.

11,11,12,13,13,13-Heptafluorotridecane-1-ol (4b)—A mixture of heptafluoro-1-iodopropane (6.694 g, 22.6 mmol), 9-deceny acetate (3.757 g, 19 mmol) and Fe$_3$(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, diluted with water and extracted with ether. The organic layer was washed with water, dried over MgSO$_4$, and then chromatographed (SiO$_2$, 0.5% AcOEt in hexane) to give the coupling product 4b (4.569 g, 76%), which was saponified by treatment with 4.3% methanolic KOH (35 ml) at room temperature for 2 h to give 4b (4.651 g, 85% overall yield) as a colorless oil. 4b; by 135-142 °C/4 mm (Kugelrihr). 1H-NMR (CDCl$_3$) $\delta$: 3.69 (2H, t, J= 7 Hz, -CH$_2$OH). 19F-NMR (CDCl$_3$) $\delta$: - 18.11 (3F, t, J= 9.4 Hz), - 52.5 (2F, m), - 65.1 (2F, m). IR (neat): 3300 cm$^{-1}$. MS m/z: 308 M$^+$ (81Br), 280.

1-Bromo-11,11,12,13,13,13-heptafluorotridecane (5b)—By the same method as used for the preparation of 5a, 5b was obtained in 85% yield. 5b: Colorless oil. 1H-NMR (CDCl$_3$) $\delta$: 3.43 (2H, t, J= 7 Hz, -CH$_2$Br). 19F-NMR (CDCl$_3$) $\delta$: - 17.3 (3F, t, J= 9.4 Hz), - 52.3 (2F, m), - 65.0 (2F, m). IR (neat): 2920, 2850, 1270, 1140 cm$^{-1}$. MS m/z: 390 M$^+$ (81Br), 388 M$^+$ (79Br).

1-Benzoxy-14,14,15,16,16-heptafluoroheptadecane (7b)—In the same manner as described for the preparation of 7a, the reaction of the Grignard reagent [prepared from 3-benzyloxypropyl 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$_2$CuCl$_4$ (0.05 mmol) in THF at room temperature for 5 h gave the benzyl ether 7b (742 mg, 40%) as a colorless oil. 7b: 1H-NMR (CDCl$_3$) $\delta$: 3.50 (2H, t, J= 7 Hz, -CH$_2$OBn), 4.53 (2H, s, -OCH$_2$Ph), 7.40 (5H, s, Ph). 19F-NMR (CDCl$_3$) $\delta$: - 17.7 (3F, t, J= 9.4 Hz), - 52.3 (2F, m), - 65.1 (2F, m). IR (neat): 3300 cm$^{-1}$. MS m/z: 390 M$^+$ (81Br), 388 M$^+$ (79Br).
C17H21F15O: C, 38.80; H, 4.02; F, 54.14. Found: C, 38.76; H, 4.00; F, 53.93.

C18H31F7O: C, 54.54; H, 7.88; F, 33.55. Found: C, 54.33; H, 7.90; F, 33.72.

5H). IR (neat): 3450, 2920, 2840, 1455, 1370, 1160 cm⁻¹. MS m/z: 760 (M⁺), 745 (M⁺ 15).

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: 458 (M⁺), 454 (M⁺ 15).

Pentadecafluorohexadecan-1-ol (8c)—87% yield. 1H-NMR (CDCl₃): δ: 1.20-1.85 (27H, m), 1.90-2.24 (m, 2H), 2.97 (s, 3H). IR (KBr): 2940, 2860, 1455, 1356, 1192, 1140 cm⁻¹. MS m/z: 446 (M⁺).

11c: (m = 15, n = 2) Y. 100%, mp 49-51 °C. 1H-NMR (CDCl₃): 6: 1.08-1.27 (m, 24H), 1.27-1.87 (m, 2H), 1.90-2.24 (m, 2H), 2.97 (s, 3H). IR (KBr): 2940, 2860, 1473, 1356, 1172, 1126, 1115, 1052, 1006 cm⁻¹. MS m/z: 458 (M⁺), 454 (M⁺ 15).

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 ether solution was washed with dil. HCl and brine, then dried on MgSO₄, and concentrated to afford 11a, 11b, 11c or 11d, respectively as white crystals.

11a: (m = 15, n = 0) yield (Y.) 83%, mp 45-50 °C. 1H-NMR (CDCl₃): δ: 1.0-1.84 (m, 2H), 3.67 (2H, t, J=7 Hz, -CH2OH). 19F-NMR (CDCl₃): -18.3 (3F, t, J=9.4 Hz), -64.5 (2F, m). MS m/z: 350 (M⁺), 322, 294, 280. Anal. Calcd for C₁₆H₂₇F₇O: C, 51.79; H, 7.39; F, 35.32. Found: C, 51.73; H, 7.35; F, 35.30.

11b: (m = 13, n = 2) Y. 87%, mp 39-42 °C. 1H-NMR (CDCl₃): δ: 1.10-1.90 (m, 22H), 1.90-2.24 (m, 2H), 2.98 (s, 3H). IR (KBr): 2940, 2860, 1473, 1356, 1172, 1126, 1115, 1052 cm⁻¹. MS m/z: 446 (M⁺).

11c: (m = 15, n = 2) Y. 100%, mp 49-51 °C. 1H-NMR (CDCl₃): δ: 1.08-1.27 (m, 24H), 1.27-1.87 (m, 2H), 1.87-2.20 (m, 2H), 2.97 (s, 3H). 19F-NMR (CDCl₃): δ: -18.3 (3F, t, J=9.4 Hz), -64.5 (2F, m). MS m/z: 458 (M⁺), 454 (M⁺ 15).

11d: (m = 10, n = 6) Y. 87%, mp 59-62.5 °C. 1H-NMR (CDCl₃): δ: 1.13-1.44 (m, 14H), 1.44-1.88 (m, 2H), 1.89-2.25 (m, 2H), 2.97 (s, 3H). IR (KBr): 2940, 2860, 1473, 1356, 1172, 1126, 1115, 1050 cm⁻¹. MS m/z: 604 (M⁺).

1-O-Fluoroalkyl-2-O-benzyl-3,4-O-isopropylidene-D-threitols (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-threitol (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 MgSO₄, concentrated and purified by silica gel chromatography (benzene) to afford 12 as a colorless oil.

12a: (m = 15, n = 0) Y. 66%. 1H-NMR (CDCl₃): 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). 1H-NMR (KBr): 2940, 2860, 1455, 1370, 1220, 1160 cm⁻¹. MS m/z: 530 (M⁺−15).

12b: (m = 13, n = 2) Y. 75%. 1H-NMR (CDCl₃): δ: 1.16-1.72 (m, 26H), 1.36 (s, 3H), 1.42 (s, 3H), 1.90-2.40 (m, 2H), 3.38 (t, J=7 Hz, 2H), 3.47-4.40 (m, 6H), 4.71 (s, 2H), 7.16-7.48 (m, 5H). 1H-NMR (KBr): 2940, 2860, 1445, 1370, 1150 cm⁻¹. MS m/z: 602 (M⁺), 587 (M⁺−15).

12c: (m = 15, n = 2) Y. 89%. 1H-NMR (CDCl₃): δ: 1.16-1.72 (m, 26H), 1.36 (s, 3H), 1.42 (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 (s, 5H). 1H-NMR (KBr): 2940, 2860, 1455, 1370, 1160 cm⁻¹. MS m/z: 630 (M⁺), 615 (M⁺−15).

12d: (m = 10, n = 6) Y. 66%. 1H-NMR (CDCl₃): 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). 1H-NMR (KBr): 2940, 2860, 1455, 1370, 1160 cm⁻¹. MS m/z: 760 (M⁺), 745 (M⁺−15).

1-O-Fluoroalkyl-2-O-benzyl-D-threitols (13a–d)—The O-alkylated derivative 12 (0.4 mmol) was stirred in...
THF (15 ml) and 2 N 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 x 3) and the organic layer was dried over Na2SO4. After the removal of the solvent, the residue was chromatographed on silica gel to give 16 as white crystals.

13a: Y. 73%, mp 36–38 °C. 1H-NMR (CDCl3) 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): 3390, 3070, 2930, 2860, 1660, 1460, 1320, 1220, 1150 cm⁻¹. [α]20D = -6.2° (c = 0.54, CHCl3). MS m/z: 560 (M+).

13b: Y. 77%, mp 32–34 °C. 1H-NMR (CDCl3) 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, 1150 cm⁻¹.

13c: Y. 76%, mp 41–44 °C. 1H-NMR (CDCl3) 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 (M+ + 1).

13d: Y. 88%, mp 51–54 °C. 1H-NMR (CDCl3) 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, 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 Pb(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 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 x 3), and the organic layer was dried over Na2SO4. 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. 72%, oil. 1H-NMR (CDCl3) δ: 1.17–1.48 (m, 24H), 1.49–1.76 (m, 2H), 1.87–2.31 (m, 4H), 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. [α]20D = -5.98 (c = 0.57, CHCl3). MS m/z: 460 (M+).

14b: Y. 72%, oil. 1H-NMR (CDCl3) δ: 1.16–1.85 (m, 22H), 1.86–2.37 (m, 3H), 3.43 (t, J = 7 Hz, 2H), 3.53–3.97 (m, 4H), 4.67 (s, 2H), 7.21–7.51 (m, 5H). IR (neat): 3400, 2920, 2840, 1460, 1450, 1210, 1140 cm⁻¹. [α]20D = 12.4° (c = 0.54, CHCl3). MS m/z: 532 (M+).

14c: Y. 72%, white crystals. mp 36–38 °C. 1H-NMR (CDCl3) δ: 1.17–1.48 (m, 24H), 1.49–1.76 (m, 2H), 1.87–2.31 (m, 4H), 3.41 (t, J = 7 Hz, 2H), 3.51–3.95 (m, 5H), 4.64 (s, 2H), 7.21–7.47 (m, 5H). IR (neat): 3400, 2910, 2840, 1460, 1450, 1230, 1135 cm⁻¹. [α]20D = -9.8° (c = 1.21, CHCl3). MS m/z: 544 (M+).

14d: Y. 73%, oil. 1H-NMR (CDCl3) 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, 4H), 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, 1120, 1140 cm⁻¹. [α]20D = -6.2° (c = 1.37, CHCl3). MS m/z: 704 (M+).
16a: Y. 100%, mp 230 °C (dec.). 1H-NMR (CDCl3-CD3OD, 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, 2840, 1465, 1210, 1150 cm⁻¹. [α]D²⁰ -2.00 ° (c = 0.35, CHCl3-MeOH, 1:1).

16b: Y. 85%, mp 196 °C (dec.). 1H-NMR (CDCl3-CD3OD, 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). IR (KBr): 3400, 2940, 2860, 1472, 1360, 1220, 1145 cm⁻¹. [α]D²⁰ -2.40 ° (c = 1.11, CHCl3-MeOH, 1:1).

16c: Y. 78%, mp 226-234 °C (dec.). 1H-NMR (CDCl3-CD3OD, 3:1) δ: 1.10-1.73 (m, 26H), 1.91-2.33 (m, 2H), 3.25 (s, 9H), 3.30-3.76 (m, 7H), 3.77-3.93 (m, 2H), 3.94-4.40 (m, 2H). IR (KBr): 3400, 2940, 2860, 1472, 1360, 1220, 1145 cm⁻¹. [α]D²⁰ -2.55 ° (c = 0.55, CHCl3-MeOH, 1:1).

16d: Y. 90%, mp 222-224 °C (dec.). 1H-NMR (CDCl3-CD3OD, 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. [α]D²⁰ -2.55 ° (c = 0.55, CHCl3-MeOH, 1:1).

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References and Notes