Synthesis of a Fluorinated Ether Lipid Analogous to a Platelet Activating Factor

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Dedicated to Professor Dieter Hoppe on the occasion of his 60th birthday

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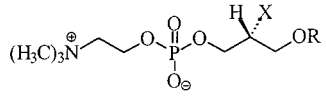
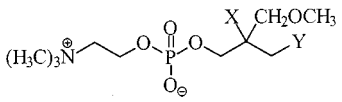
The synthesis of racemic 2-fluoro-3-hexadecyloxy-2-methylprop-1-yl 2′-(trimethylammonio)ethyl phosphate (**10**), a fluorinated analogue of the anticancer active and blood platelet activating ether lipids **8** and **9**, has been achieved in a six-step sequence from methallyl alcohol (**11**). Etherification of **11** with hexadecyl bromide gave allylic ether **12**, bromofluorination of which afforded the bromo-substituted fluoride **13**, which was subsequently transformed into the acetate **14**. Hydrolysis of **14** gave the key intermediate 2-fluoro-2-(hexadecyloxymethyl)propanol (**15**), which was attached to the phosphocholine residue in the final step. Enzyme-catalyzed deracemization of the fluorohydrin **15** by acetylation with several lipases gave optically active compounds **14** and **15**, with a maximum *ee* of 61% for **15** with *Candida antarctica* lipase catalysis after 74% conversion. An enantioselective synthesis of **10**, based on a planned eight-step synthesis starting from α-methylstyrene, failed. The anticancer activity of racemic **10** has been observed in an in vivo model of methylcholanthrene-induced mouse fibrosarcoma.

Introduction

Since the discovery of the physiological activity of compounds **1** as platelet activating factor (PAF) in the early 1970s[1] and their first isolation from basophilic leukocytes,[2] there has been growing interest in both natural and synthetic ether lipids.[3] In 1979 the structure of natural PAF was assigned as a mixture of two (*R*)-2-acetyl-1-*O*-alkyl-*sn*-glycero-3-phosphocholines **1** (Scheme 1), with $C_{16}H_{33}$ and $C_{18}H_{37}$ long-chain alkyl groups.[4]



1 (X = OAc, R = $C_{16}H_{33}$, $C_{18}H_{37}$)
2 (X = OH, R = $C_{16}H_{33}$, $C_{18}H_{37}$)
3 (X = OMe, R = $C_{18}H_{37}$)



4 (X = H, Y = $SC_{16}H_{33}$)
5 (X = H, Y = $OC_{16}H_{33}$)
6 (X = F, Y = $OC_{16}H_{33}$)

Scheme 1

Structural elucidation and several syntheses[5] of the naturally occurring enantiomers of **1** were followed by investigation of the chemistry and biochemistry of biologically active ether lipids. The cytotoxic effects of the PAF **1**, and in particular its lyso compounds **2**, stimulated systematic investigations into the cytotoxic properties of several synthetic analogues of PAF.[6] The metabolic instability of **1** and **2**[7] encouraged the development of more stable ether lipids. One of the most intensely investigated antitumoral ether lipids of this type is 2-*O*-methyl-1-*O*-octadecyl-*rac*-glycero-3-phosphocholine (edelfosine, **3**).[8] This compound exhibits strong cytotoxicity against numerous human and murine tumor cell strains both in vitro and in vivo. Clinical tests have been performed.[9] Variation of the substituent pattern around the stereogenic center of compounds **1** resulted in substances of high potency against different tumor cell strains. Tests of ilmofosine (**4**) and its oxygen analogue **5**, as well as the C_{18} homologues, were very promising.[9,10] A fluorinated analogue **6** also exhibited anticancer activity.[11]

The etiology of the cytotoxic activity of ether lipids is as yet largely unknown. The anticancer activity of these compounds is probably different from that of most other anticancer drugs, which interfere with DNA synthesis or function.[12] Because of the structural relationship of these ether lipids to PAF, the question arose of whether or not the PAF receptor is decisive for their cytotoxicity. The PAF activity of edelfosine (**3**) might be an indication of that cytotoxic origin.[13] This cytotoxicity against tumor cells is not influenced by PAF receptor antagonists;[14] the cyclic ether analogue SRI 62-834 (**7**) binds to the receptor independently of its cytotoxicity.[15] The ether lipids **8** and **9** exhibit pronounced cytotoxicity against a number of human tumor cell strains; this cytotoxicity is different for each enantiomer.[9,10] These ether lipids also influence the aggregation of blood platelets (Scheme 2).[9,16]

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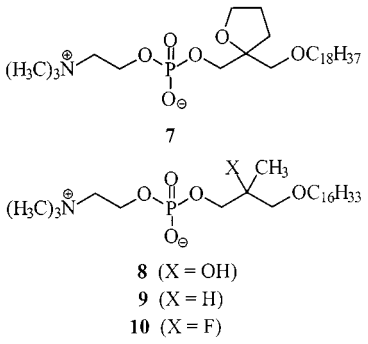


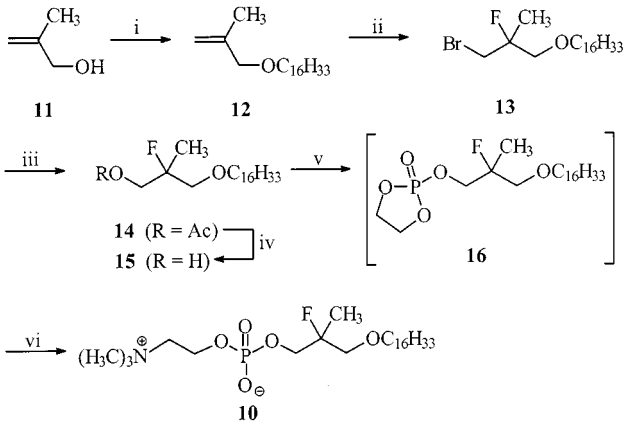
Scheme 2

Many molecules are known in which substitution of a fluorine for a hydrogen atom or a hydroxy function produces different chemical and physical properties, and biological activity in the fluoro analog distinctly different from that in the unmodified species. This change of activity is presumably due to modification of some electronic, steric, or general metabolic behavior.[17] The extreme electronegativity of fluorine effects changes of electron density in molecules and hence changes the acidities and reactivities of neighboring groups.[18] The high electron density of the fluorine substituent causes its low polarizability. However, this high electron density also gives rise to the ability of fluorine substituents to act as acceptors in intra- and intermolecular hydrogen bonds,[19] and these interactions can result in modified binding to a receptor.[20] The generally higher metabolic stability of fluorinated compounds may be responsible for inhibition of essential biochemical reactions.[17b,20] Presumably, because of the similarity in the sizes of hydrogen and fluorine substituents (van der Waals radii of H = 1.20 Å and of F = 1.47 Å),[21] fluorinated analogues of biologically active compounds often mimic the natural metabolism of the parent compounds.[22] In many cases partial fluorine substitution increases both the lipophilicity and the hydrophilicity of a particular molecule, which improves its resorption and its transport in the organism.[17b,23]

Among the known synthetic ether lipids with cytotoxic and PAF-antagonistic properties there are only a few monofluorinated compounds.[7,24] Brachwitz et al. have shown that the racemic 2-deoxy-2-fluoro-1-*O*-hexadecyl-*rac*-glycero-3-phosphocholine (**3**, X = F, R = $C_{16}H_{33}$) and edelfosine (**3**) have almost identical cytotoxic activities against Ehrlich−Ascites tumor. Compound **3** also has PAF-antagonistic properties.[25] In view of these facts we thought it desirable to synthesize a fluorinated analogue **10** of both the PAF active ether lipids **8** and **9**. We believed that the analogue **10** might exhibit some interesting physiological behavior.

Results and Discussion

Retrosynthetic analysis of racemic **10** suggested a linear synthesis starting from methallyl alcohol (**11**). *O*-Alkylation of **11** with hexadecyl bromide and potassium hydroxide in DMSO, in analogy with a procedure used by Bittman et al.,[10a] gave the ether **12** in 50% yield (Scheme 3). Subsequent bromofluorination of **12** with NBS/$Et_3N{\cdot}3HF$[26] (or even better with NBS/$Me_3N{\cdot}3HF$[27]) gave the Markovnikov-oriented bromo-substituted fluoride **13** with good regioselectivity and in 77% yield. Neither the regioisomer of **13** nor other fluorinated compounds were detected in the crude reaction product (^{19}F NMR).[28]



Scheme 3. Reagents and conditions: (i) KOH, DMSO, 1-bromohexadecane, room temp., 4 h; (ii) NBS, $Me_3N{\cdot}3HF$, CH_2Cl_2, −10 °C, 96 h; (iii) KOAc, DMF, reflux, 24 h; (iv) KOH, MeOH, room temp., 5 h; (v) Et_3N, 2-chloro-2-oxo-1,3,2-dioxaphospholane, THF, 0 °C 30 min, then room temp., 6 h, separation of $Et_3N{\cdot}HCl$; (vi) −78 °C, Me_3N, MeCN, then 60 °C, sealed tube, 68 h

The bromofluoride **13** was transformed into **14** in 73% yield without significant elimination of hydrogen bromide, by use of a previously developed recipe (KOAc, DMF, reflux[11]).[29] Fluorohydrin **15** was obtained in 77% yield by saponification of **14**.

In order to synthesize the enantiomers of **15**, we screened several lipases previously applied with related substrates[11,30] for deracemization by acetylation in organic solvents, using vinyl acetate as the acylating reagent (Scheme 4, Table 1). Porcine pancreas lipase (PPL) was the slowest enzyme, giving 48% conversion after 168 h reaction time. The observed enantiomeric excess was as low as 17% *ee* for the residual fluorohydrin **15** and 23% *ee* for the formed acetate **14**. The results with *Candida rugosa* lipase (CRL) or immobilized *Pseudomonas cepacia* lipase (PCL, Amano PS) were only slightly better. With *Candida antarctica* lipase, the fastest enzyme under the conditions used, a 61% *ee* for the fluorohydrin **15** and a 25% *ee* for the acetate **14** were obtained after 74% conversion. Thus, the enantioselectivities of all the tested lipases were quite low (Table 1).

For the final coupling of the racemic fluorohydrin **15** to the choline moiety, a procedure described by Guivisdalsky and Bittman[33] for a similar (but non-fluorinated) long-chain hydroxy ether was used. Compound **15** was treated with a threefold excess of 2-chloro-2-oxo-1,3-dioxa-2-phospholane and triethylamine in THF at room temperature. The crude cyclic phosphoric acid triester intermediate **16**

Table 1. Results of the lipase-catalyzed deracemization of the fluorohydrin **15** by acetylation with vinyl acetate in toluene

Entry	Enzyme [mg]	Time [h]	Conversion [%]	Product	Yield [%]	*ee*[a] [%]	*E*[b]
1	PPL[150]	168	48	**15**	33	17	1.7
				14	29	23	1.1
2	CRL[35]	15	48	**15**	45	28	2.4
				14	33	29	2.3
3	immobilized PCL[70]	4	50	**15**	47	27	2.2
				14	48	23	2.0
4	CAL[5]	1	74	**15**	22	61	2.6
				14	62	25	3.2

[a] Determined by ^{19}F NMR spectroscopy after esterification of the fluorohydrins **15** (after hydrolysis of **14** if necessary) by Mosher's method,[31] by integration of the signals at $\delta = -158.22$ and $\delta = -158.43$. – [b] The *E* value is a measure for the selectivity of an enzyme.[32]

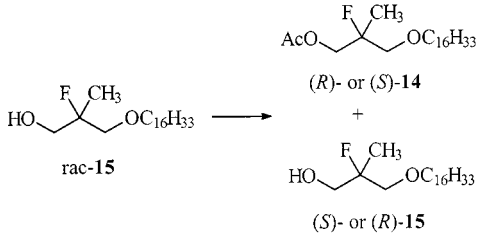
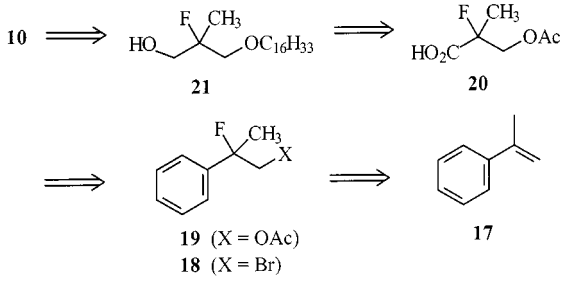


Table 1. Reagents and conditions: lipase, vinyl acetate, toluene, room temp. (cf. Table 1)

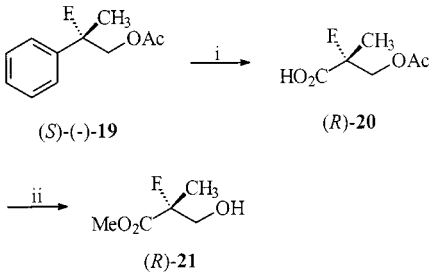
was used without isolation. After 68 h at 60 °C in a sealed tube with trimethylamine in acetonitrile, the resulting phosphocholine derivative **10** was isolated in 40% yield; 9% overall, based on methallyl alcohol (**11**) (Scheme 3).

Since deracemization of **15** had given the desired products with quite a low enantiomeric excess, an alternative sequence was designed. Retrosynthetic analysis of **10** suggested a highly functionalized, crucial C_4 moiety **21**, which should be available from α-methylstyrene (**17**) via **18**, **19**, and **20** (Scheme 5).



Scheme 5

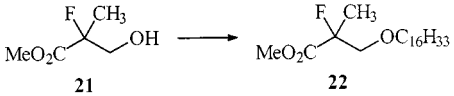
The synthesis of **19** from **17** by bromofluorination using the NBS/Me_3N·3HF combination[27] followed by removal of the bromo substituent in the produced 1-bromo-2-fluoro-2-phenylpropane (**18**) by acetate exchange with KOAc in DMF has already been described.[30b] Oxidation of the phenyl ring is a necessary next step. This type of oxidation of aromatic compounds was first achieved by Caputo and Fuchs, with ruthenium tetraoxide and sodium periodate in a two-phase system of tetrachloromethane and water.[34] This procedure was improved by Sharpless et al.[35] and was used by Murato and Kitazume for the oxidation of (1*R*)-1-acetoxy-2,2-difluoro-1-phenylethane to (2*R*)-2-acetoxy-3,3-difluoropropanoic acid in 35% yield.[36] We adapted the Sharpless conditions for the oxidation of **19** to **20**, which was obtained in a 67% yield in a preparative scale transformation by use of 6.6 mol % of $RuCl_3$·H_2O and 23 equiv. of $NaIO_4$ in a 2:2:3 mixture of water/tetrachloromethane/acetonitrile at room temperature (Scheme 6).[37]



Scheme 6. Reagents and conditions: (i) $NaIO_4$ (23 equiv.), $RuCl_3$ (6.6 mol %), $H_2O/CCl_4/CH_3CN$, 48 h, room temp.; (ii) DMP, MeOH

This procedure was applied to oxidize the optically active **19** in order to examine whether or not the oxidation proceeds without racemization. Oxidation of (*S*)-(+)-**19** (53% *ee*), obtained by a preparative-scale enzyme-catalyzed acetylation of the corresponding fluorohydrin according to the procedure described in ref.[30b], thus gave the optically active carboxylic acid **20**. The determination of the enantiomeric excess of (*R*)-**20** was difficult.[38] After several failures, the acetate (*R*)-**20** was finally transformed into the hydroxycarboxylic ester (*R*)-**21** in 74% yield by treatment with 2,2-dimethoxypropane (DMP) in methanol. The enantiomeric excess (50% *ee*) was determined by ^{19}F NMR spectroscopy after derivatization with Mosher's acid[31] and DCC/DMAP. The optically active building block **21** has previously been synthesized by several different procedures and was used in the various syntheses.[39]

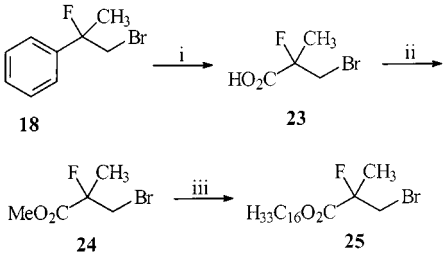
We tested the next step of the planned synthetic sequence to form **10** with racemic **21**. However, treatment of **21** with NaH and either hexadecyl bromide or hexadecyl mesylate[42] gave only 4% of the desired long-chain ether **22** (Scheme 7). The main reaction was most probably an intermolecular transesterification resulting in higher molecular weight material, which was not fully characterized. Most of the starting mesylate was recovered.



Scheme 7. Reagents and conditions: NaH, hexadecylmesylate, Et_2O, 6 h reflux

We therefore decided to modify the components of the Williamson ether synthesis. The bromo-substituted fluoride **18** was oxidized in 70% yield to the C_4 building block **23**, which was esterified with 2,2-dimethoxypropane in meth-

anol to give **24** in 50% yield (Scheme 8). Unfortunately, the conditions used by Bittman et al.[10a] for etherification of a similar, but non-fluorinated, compound did not work in our case. Treatment of **24** with copper hexadecanolate, formed in situ from hexadecanol, butyllithium, and copper(I) iodide, did not give the desired ether **22**. In addition to unchanged **24**, 14% of the transesterification product **25** was isolated as the only reaction product. Thus, the attempt to synthesize the optically active key intermediate **21** starting from α-methylstyrene **17** was not successful.



Scheme 8. Reagents and conditions: (i) $NaIO_4$ (23 equiv.), $RuCl_3$ (6.6 mol%), $H_2O/CCl_4/CH_3CN$, 48 h, room temp.; (ii) DMP, MeOH; (iii) hexadecanol, *n*BuLi, THF, CuI (10 mol%), −78 °C, 6 h

The anticancer activity of racemic **10** was tested in an in vivo model of methylcholanthrene-induced mouse fibrosarcoma, comparing the activity of **10** to that of cisplatin and ilmofosine (**4**). While significant anticancer activity (IC_{50} = 1.82 mg/mL, 48 h incubation time) was found for **10**, this activity was lower than that of cisplatin (IC_{50} = 0.17 mg/mL) or ilmofosine (**4**) (IC_{50} = 0.23 mg/mL), all measured under identical experimental regimes.

Experimental Section

General Remarks: ^1H (300.1 MHz), ^{13}C (75.5 MHz), and ^{19}F NMR (282.3 MHz) were recorded in ca. 20% solutions in $CDCl_3$ (if not stated otherwise). Chemical shifts are reported as δ values [ppm] relative to TMS (^1H), $CDCl_3$ (^{13}C), or $CFCl_3$ (^{19}F), respectively, as internal standards. For ^{31}P NMR (121.5 MHz), 80% phosphoric acid was used as an external standard. The multiplicity of ^{13}C signals was determined by DEPT. Mass spectra (electron impact ionization, 70 eV) were recorded by GC/MS coupling. The compositions of crude reaction products and the conversions of substrates during enzymatic transformations were monitored by GC with quartz capillary columns: 25 m × 0.33 mm, 0.52 μm HP-1 (Hewlett−Packard) and 30 m × 0.32 mm, 0.25 μm SPB-1 (Supelco), temperature program, 40 °C → 280 °C with a 10 °C/min heating rate, N_2 as the carrier gas. Compound ratios were determined by integration of the peak areas. The products, including those of enzymatic transformations, were separated by column chromatography (silica gel, Merck 60, 70−230 mesh). Microanalyses were carried out by the "Mikroanalytisches Laboratorium, Organische Chemie", University of Münster, with a CHN-O analyzer.

3-Hexadecyloxy-2-methylpropene (12): In analogy with the procedure given in ref.[40], powdered KOH (4.3 g, 15.0 mmol) and methallyl alcohol (**11**, 4.3 g, 55.6 mmol) in DMSO (40 mL) were treated with 1-bromohexadecane (58.1 g, 0.2 mol) and stirred at room temperature for 3.5 h. The mixture was then poured into 500 mL of a saturated aqueous solution of NaCl and extracted with 3 × 200 mL of diethyl ether. The combined ethereal layers were washed with 2 × 200 mL of water and dried with magnesium sulfate. The solvent was removed and the residue chromatographed (silica gel; pentane/diethyl ether, 20:1) to give **12** as a colorless oil (10% 1-bromohexadecane impurity). Yield: 8.3 g (50%). The ^1H NMR spectroscopic data agree with those published.[16a] ^{13}C NMR: δ = 14.1 (q, 16′-C), 19.4 (q, 4-C), 22.7 (t, 15′-C), 26.3 (t, 3′-C), 29.4−29.8 (11 t, 4′-C to 14′-C), 31.9 (t, 2′-C), 70.3 (t, 1′-C), 74.8 (t, 3-C), 111.6 (t, 1-C), 142.6 (q, 2-C). GC/MS: *m/z* (%) = 296 (26) [$M^{+\cdot}$], 72 (100) [$C_4H_8O^{+\cdot}$].

1-Bromo-2-fluoro-3-hexadecyloxy-2-methylpropane (13): A solution of **12** (4.0 g, 13.5 mmol) and $Me_3N{\cdot}3HF$ (2.4 mL, 26.1 mmol) was treated in portions with NBS (2.5 g, 14.9 mmol) in CH_2Cl_2 (50 mL) and stirred at −10 °C for 96 h. The mixture was poured into 250 mL of ice/water and neutralized with 26% aqueous ammonia. The organic layer was separated and the aqueous layer was extracted with 3 × 50 mL of ethyl acetate. The combined organic layers were washed with 25 mL of 0.1 N HCl followed by 25 mL of aqueous $NaHCO_3$ solution and dried with magnesium sulfate. The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel; pentane/diethyl ether, 100:1) to give **13** as a colorless oil (10% impurity of 1-bromohexadecane). Yield: 4.1 g (77%). ^1H NMR: δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 16′-H), 1.21−1.38 (m, 26 H, 3′-H to 15′-H), 1.47 (d, $^3J_{H,F}$ = 21.5 Hz, 3 H, 4-H), 1.55−1.62 (m, 2 H, 2′-H), 3.43−3.65 (m, 6 H, 1′-H, 1-H, 3-H). ^{13}C NMR: δ = 14.1 (q, 16′-C), 21.3 (dq, $^2J_{C,F}$ = 22.9 Hz, 4-C), 22.7 (t, 15′-C), 26.0 (t, 3′-C), 29.3 to 29.7 (11t, 4′-C to 14′-C), 31.9 (t, 2′-C), 35.6 (dt, $^2J_{C,F}$ = 28.0 Hz, 1-C), 72.1 (t, 1′-C), 73.4 (dt, $^2J_{C,F}$ = 25.4 Hz, 3-C), 94.3 (ds, $^1J_{C,F}$ = 175.5 Hz, 2-C). ^{19}F NMR: δ = −152.6 (m). GC/MS: *m/z* (%) = 374/376 (0.7/0.7) [$M^{+\cdot}$ − HF], 315 (31) [$M^{+\cdot}$ − Br], 295 (1) [315 − HF], 255 (100) [$C_{16}H_{33}OCH_2^+$], 225 (31) [$C_{16}H_{33}^+$], 224 (24) [$C_{16}H_{32}^{+\cdot}$], 196 (6) [$C_{14}H_{28}^{+\cdot}$], 183 (6) [$C_{13}H_{27}^+$], 168 (8) [$C_{12}H_{24}^{+\cdot}$], 167 (4) [$C_{12}H_{23}^+$], 155 (16) [$C_{11}H_{23}^+$], 153 (11) [$C_{11}H_{21}^+$], 141 (19) [$C_{10}H_{21}^+$], 139 (12) [$C_{10}H_{19}^+$], 127 (19) [$C_9H_{19}^+$], 125 (19) [$C_9H_{17}^+$], 113 (16) [$C_8H_{17}^+$], 111 (30) [$C_8H_{15}^+$], 99 (41) [$C_7H_{15}^+$], 98 (10) [$C_7H_{14}^{+\cdot}$], 97 (57) [$C_7H_{13}^+$], 96 (10) [$C_7H_{12}^{+\cdot}$], 85 (44) [$C_6H_{13}^+$], 84 (38) [$C_6H_{12}^{+\cdot}$], 83 (68) [$C_6H_{11}^+$], 82 (24) [$C_6H_{10}^{+\cdot}$], 71 (93) [$C_5H_{11}^+$], 70 (26) [$C_5H_{10}^{+\cdot}$], 69 (71) [$C_5H_9^+$], 68 (20) [$C_5H_8^{+\cdot}$], 57 (95) [$C_4H_9^+$]. GC/MS (CI): *m/z* = 412/414 [M + NH_4^+].

1-Acetoxy-2-fluoro-3-hexadecyloxy-2-methylpropane (14): A mixture of **13** (3.2 g, 8.4 mmol) and potassium acetate (1.9 g, 33.5 mmol) in dry DMF (50 mL) was refluxed for 24 h. After the mixture had cooled to room temperature, a 1:1 mixture of cyclohexane and ethyl acetate (50 mL) was added, and the precipitate was filtered off. The organic layer was washed with 20 mL of water and dried with magnesium sulfate. The solvent was vacuum-evaporated and the residue was purified by column chromatography (silica gel; pentane/diethyl ether, 20:1) to give pure **14** as a colorless oil, which became a waxy solid in the refrigerator at 4 °C. Yield: 2.3 g (73%). ^1H NMR: δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 16′-H), 1.23−1.36 (m, 26 H, 3′-H to 15′-H), 1.37 (d, $^3J_{H,F}$ = 21.7 Hz, 3 H, 4-H), 1.51−1.58 (m, 2 H, 2′-H), 2.09 (s, 3 H, 6-H), 3.47 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, 1′H,), 3.46 and 3.53 (2 dd, $^3J_{Ha,F}$ = 15.3 Hz, $^3J_{Hb,F}$ = 16.5 Hz, $^2J_{Ha,Hb}$ = 10.3 Hz, 2 H, 3-H), 4.17 and 4.23 (2 dd, $^3J_{Hc,F}$ = 19.3 Hz, $^3J_{Hd,F}$ = 19.8 Hz, $^2J_{Hc,Hd'}$ = 11.9 Hz, 2 H, 1-H). ^{13}C NMR: δ = 14.1 (q, 16′-C), 19.4 (dq, $^2J_{C,F}$ = 22.9 Hz, 4-C), 20.7 (q, 6-C), 22.6 (t, 15′-C), 26.0 (t, 3′-C), 29.3 to 29.7 (11t, 4′-C to 14′-C), 31.9 (t, 2′-C), 66.2 (dt, $^2J_{C,F}$ = 25.4 Hz, 1-C), 72.1 (t, 1′-C), 73.0 (dt, $^2J_{C,F}$ = 28.0 Hz, 3-C), 94.4 (ds, $^1J_{C,F}$ = 172.9 Hz, 2-C), 170.4 (s, 5-C). ^{19}F NMR: δ = −160.0 (m). GC/MS: *m/z* (%) =

374 (1) [$M^{+\cdot}$], 354 (18) [$M^{+\cdot}$ − HF], 311 (5) [354 − CH_3CO], 294 (30) [354 − CH_3COOH], 255 (20) [$C_{16}H_{33}OCH_2^+$], 225 (15) [$C_{16}H_{33}^+$], 196 (2) [$C_{14}H_{28}^{+\cdot}$], 183 (4) [$C_{13}H_{27}^+$], 169 (8) [$C_{12}H_{25}^+$], 167 (3) [$C_{12}H_{23}^+$], 155 (7) [$C_{11}H_{23}^+$], 153 (3) [$C_{11}H_{21}^+$], 151 (27) [$M^{+\cdot}$ − $C_{16}H_{31}$], 141 (9) [$C_{10}H_{21}^+$], 139 (5) [$C_{10}H_{19}^+$], 133 (18) [151 − H_2O], 131 (28) [$M^{+\cdot}$ − $C_{16}H_{33}$ − H_2O], 127 (10) [$C_9H_{19}^+$], 125 (6) [$C_9H_{17}^+$], 113 (16) [$C_8H_{17}^+$], 111 (13) [$C_8H_{15}^+$], 99 (18) [$C_7H_{15}^+$], 98 (6) [$C_7H_{14}^{+\cdot}$], 97 (31) [$C_7H_{13}^+$], 96 (9) [$C_7H_{12}^{+\cdot}$], 85 (47) [$C_6H_{13}^+$], 84 (8) [$C_6H_{12}^{+\cdot}$], 83 (33) [$C_6H_{11}^+$], 82 (13) [$C_6H_{10}^{+\cdot}$], 71 (100) [$C_5H_{11}^+$], 70 (38) [$C_5H_{10}^{+\cdot}$], 69 (37) [$C_5H_9^+$], 68 (9) [$C_5H_8^{+\cdot}$], 57 (88) [$C_4H_9^+$]. $C_{22}H_{43}FO_3$ (374.6): calcd. C 70.54, H 11.57; found C 70.36, H 11.48.

2-Fluoro-3-hexadecyloxy-2-methylpropan-1-ol (15): A solution of **14** (2.0 g, 5.3 mmol) and KOH (1.68 g, 30.0 mmol) in methanol (10 mL) was stirred at room temperature for 3 h. The mixture was poured into 25 mL of water and extracted with 3 × 10 mL of diethyl ether. The combined ethereal extracts were washed with 10 mL of water, dried with magnesium sulfate, and filtered through silica gel (5 cm). After evaporation of the solvent, the fluorohydrin **15** was obtained as a white solid. Yield: 1.37 g (77%). M.p. 41 °C (diethyl ether). ^{1}H NMR: δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 16′-H), 1.23−1.35 (m, 26 H, 3′-H to 15′-H), 1.34 (d, $^3J_{H,F}$ = 22.2 Hz, 3 H, 4-H), 1.52−1.62 (m, 2 H, 2′-H), 2.02 (s, 1 H, 1-OH), 3.42−3.64 (m, 4 H, 1′-H, 3-H), 3.67 (dd, $^3J_{Ha,F}$ = 16.7 Hz, $^2J_{Ha,Hb}$ = 12.2 Hz, 1 H, 1-H_a), 3.73 (dd, $^3J_{Hb,F}$ = 19.8 Hz, $^2J_{Ha,Hb}$ = 12.2 Hz, 1 H, 1-H_b). ^{13}C NMR: δ = 14.1 (q, 16′-C), 19.5 (dq, $^2J_{C,F}$ = 22.9 Hz, 4-C), 22.7 (t, 15′-C), 26.0 (t, 3′-C), 29.3 to 29.7 (11t, 4′-C to 14′-C), 31.9 (t, 2′-C), 66.6 (dt, $^2J_{C,F}$ = 25.4 Hz, 1-C), 72.2 (t, 1′-C), 73.8 (dt, $^2J_{C,F}$ = 28.0 Hz, 3-C), 95.9 (ds, $^1J_{C,F}$ = 170.4 Hz, 2-C). ^{19}F NMR: δ = −163.1 (m). GC/MS: *m*/*z* (%) = 332 (0.8) [$M^{+\cdot}$], 312 (25) [$M^{+\cdot}$ − HF], 255 (6) [$C_{16}H_{33}OCH_2^+$], 253 (7) [$C_{16}H_{31}OCH_2^+$], 225 (17) [$C_{16}H_{33}^+$], 224 (5) [$C_{16}H_{32}^{+\cdot}$], 196 (5) [$C_{14}H_{28}^{+\cdot}$], 183 (3) [$C_{13}H_{27}^+$], 169 (4) [$C_{12}H_{25}^+$], 167 (1) [$C_{12}H_{23}^+$], 155 (5) [$C_{11}H_{23}^+$], 153 (4) [$C_{11}H_{21}^+$], 141 (6) [$C_{10}H_{21}^+$], 139 (5) [$C_{10}H_{19}^+$], 127 (8) [$C_9H_{19}^+$], 125 (11) [$C_9H_{17}^+$], 113 (11) [$C_8H_{17}^+$], 111 (19) [$C_8H_{15}^+$], 99 (18) [$C_7H_{15}^+$], 98 (6) [$C_7H_{14}^{+\cdot}$], 97 (31) [$C_7H_{13}^+$], 96 (10) [$C_7H_{12}^{+\cdot}$], 89 (17) [$M^{+\cdot}$ − $C_{16}H_{33}$ − H_2O], 88 (18), 85 (49) [$C_6H_{13}^+$], 84 (9) [$C_6H_{12}^{+\cdot}$], 83 (38) [$C_6H_{11}^+$], 82 (17) [$C_6H_{10}^{+\cdot}$], 72 (40) [$M^{+\cdot}$ − $C_{16}H_{33}OH$ − H_2O], 71 (76) [$C_5H_{11}^+$], 70 (28) [$C_5H_{10}^{+\cdot}$], 69 (38) [$C_5H_9^+$], 68 (11) [$C_5H_8^{+\cdot}$], 57 (100) [$C_4H_9^+$]. $C_{20}H_{41}FO_2$ (332.6): calcd. C 72.24, H 12.43; found C 72.29, H 12.45.

2-Fluoro-3-hexadecyloxy-2-methylprop-1-yl 2′-(Trimethylammonio)-ethyl Phosphate (10): In analogy with the procedure given in ref.[41], a mixture of the fluorohydrin **15** (183 mg, 0.55 mmol) and triethylamine (250 μL, 1.73 mmol) in dry THF (20 mL) was prepared in an argon-flushed, dried Schlenk vessel. A solution of 2-chloro-2-oxo-1,3,2-dioxaphospholane (160 μL, 1.70 mmol) in dry THF (8 mL) was added to this flask at 0 °C, and the resulting mixture was stirred at this temperature for 30 min. The mixture was then allowed to warm to room temperature and stirred for an additional 6 h. The precipitated triethylammonium chloride was filtered through silica gel under argon (1 cm, THF as eluent), and the solvent was evaporated in vacuo. The residue was dissolved in 20 mL of dry acetonitrile under argon, placed in a pressure vessel, and cooled to −78 °C. Trimethylamine (2.5 mL) was condensed into the vessel, which was sealed and heated at 60 °C for 68 h. The resulting liquid was separated and maintained at −20 °C for 4 h. The precipitated white solid was filtered off and purified by column chromatography (silica gel; chloroform/methanol/water, 65:25:4) to obtain, in addition to starting material, the ether lipid **10** as a white, waxy solid. Yield: 110 mg (40%). ^{1}H NMR: δ = 0.89 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H, 16′-H), 1.24−1.37 (m, 26 H, 3′-H to 15′-H), 1.38 (d, $^3J_{H,F}$ = 21.9 Hz, 3 H, 4-H), 1.53−1.62 (m, 2 H, 2′-H), 3.24 (s, 9 H, 7-H to 9-H), 3.47−3.58 (m, 4 H, 1′-H, 3-H), 3.65−3.68 (m, 2 H, 6-H), 3.88−4.08 (m, 2 H, 1-H), 4.26−4.35 (m, 2 H, 5-H). ^{13}C NMR: δ = 13.2 (q, 16′-C), 18.1 (dq, $^2J_{C,F}$ = 23.6 Hz, 4-C), 22.0 (t, 15′-C), 25.4 (t, 3′-C), 28.7 to 29.1 (11t, 4′-C to 14′-C), 31.3 (t, 2′-C), 53.4 (3tq, $^1J_{C,N}$ = 3.5 Hz, 7-C to 9-C), 58.7 (dt, $^2J_{C,P}$ = 4.2 Hz, 5-C), 65.8 (mt, 6-C), 67.7 (ddt, $^2J_{C,F}$ = 25.0 Hz, $^2J_{C,P}$ = 5.0 Hz, 1-C), 71.6 (t, 1′-C), 72.3 (dt, $^2J_{C,F}$ = 26.4 Hz, 3-C), 94.9 (dds, $^1J_{C,F}$ = 172.7 Hz, $^3J_{C,P}$ = 7.5 Hz, 2-C). ^{19}F NMR ($CDCl_3$): δ = −159.7 (ttq, $^3J_{H,F}$ = 19.1 Hz, $^3J_{H,F}$ = 21.0 Hz). ^{31}P NMR ($CDCl_3$/CD_3OD, 1:1): δ = 5.59 (m). MS (Maldi-TOF): *m*/*z* = 498±0.05% [M^+ + H].

Lipase-Catalyzed Acetylation of 2-Fluoro-3-hexadecyloxy-2-methylpropan-1-ol (15): The enzyme (occasionally immobilized, cf. Table 1) was added to a solution of the fluorohydrin **15** (134 mg, 0.4 mmol) and vinyl acetate (35 mg, 0.4 mmol) in toluene (3 mL). The mixture was stirred at room temperature and the progress of the acetylation was monitored by gas chromatography after workup of 100-μL aliquots of the reaction mixture. After the length of time given in Table 1, the reaction was stopped by filtration of the mixture through a short column of silica gel (toluene as the eluent). The solvent was evaporated, and the residue was separated by column chromatography (silica gel; pentane/diethyl ether, 10:1). The enantiomeric excesses of the fluorohydrin **15** and of the acetate **14**, after hydrolysis according to the procedure given above, were determined by ^{19}F NMR spectroscopy (Table 1) after esterification with (*R*)-(+)-Mosher's acid[31] (cf. below).

3-Acetoxy-2-fluoro-2-methylpropanoic Acid (20): A suspension of $NaIO_4$ (60.02 g, 280.6 mmol) and $RuCl_3 \cdot H_2O$ (374 mg, 6.6 mol %) in a mixture of water (96 mL), CCl_4 (96 mL), and CH_3CN (192 mL) was stirred at room temperature for 1 h. The fluoro acetate **19** (2.39 g, 12.2 mmol), prepared in 69% overall yield from α-methylstyrene (**17**) according to ref.[30b], was then added and the mixture was stirred at room temperature for 72 h. The solid was filtered off and washed with 2 × 25 mL of $CHCl_3$. The aqueous layer was separated and extracted with 3 × 25 mL of $CHCl_3$. The combined organic layers were dried with magnesium sulfate and the solvent was removed in vacuo to give a hygroscopic, white solid. Yield: 1.21 g (61%). ^{1}H NMR: δ = 1.57 (d, $^3J_{H,F}$ = 21.0 Hz, 3 H, 4-H) 2.04 (s, 3 H, 6-H) 4.24−4.35 (m, 2 H, 3-H), 9.55 (br, 1 H, OH). ^{13}C NMR: δ = 20.3 (dq, $^2J_{C,F}$ = 25.4 Hz, 4-C), 20.5 (q, 6-C), 66.6 (dt, $^2J_{C,F}$ = 22.9 Hz, 3-C), 92.7 (ds,$^1J_{C,F}$ = 188.2 Hz, 2-C), 170.5 (s, 5-C), 174.2 (ds, $^2J_{C,F}$ = 28.0 Hz, 1-C). ^{19}F NMR: δ = −162.4 (tq, $^3J_{H,F}$ = 21.0 Hz). GC/MS of the $Si(CH_3)_3$ ester: *m*/*z* (%) = 221 (8) [M^+ − CH_3], 179 (98) [221 − C_2H_2O], 164 (16), 161 (11) [221 − $C_2H_4O_2$], 133 (34) [161 − CO], 117 (72) [$CO_2Si(CH_3)_3^+$], 85 (42), 77 (41), 75 (54) [$C_2H_7OSi^+$], 73 (97) [$Si(CH_3)_3^+$], 43 (100) [$C_2H_3O^+$]. GC/MS [CI, of the $Si(CH_3)_3$ ester]: *m*/*z* (%) = 254 [M + NH_4^+]. (*S*)-(−)-1-Acetoxy-2-fluoro-2-phenylpropane, (*S*)-(−)-**19** (53% *ee*), was also oxidized to (*R*)-**20** (50% *ee*) by this procedure. The enantiomeric excess of (*R*)-**20** was determined by ^{19}F NMR after transformation into (*R*)-**21** and esterification with (*R*)-(+)-Mosher's acid.[31]

Methyl 2-Fluoro-3-hydroxy-2-methylpropanoate (21): A solution of **20** (1.0 g, 6.1 mmol) in dry methanol (21 mL) was treated with 2,2-dimethoxypropane (200 μL) and one drop of conc. HCl. The solution was stirred at room temperature for 32 h, methanol was removed in vacuo, and the residue was dissolved in $CHCl_3$ (10 mL). The solution was washed with 5 mL of 5% aqueous $NaHCO_3$ solution and dried with magnesium sulfate, and the solvent was removed in vacuo to yield **20** as a yellowish oil. Yield: 610 mg (74%).

^{1}H NMR: δ = 1.53 (d, $^3J_{H,F}$ = 21.5 Hz, 3 H, 4-H) 2.08 (br. s, 1 H, OH) 3.75−3.96 (2dd, $^2J_{Ha,Hb}$ = 12.4 Hz, $^3J_{Hb,F}$ = 16.0 Hz, $^3J_{Ha,F}$ = 25.3 Hz, 2 H, 3-H), 3.83 (s, 3 H, 5-H). ^{13}C NMR: δ = 19.7 (dq, $^2J_{C,F}$ = 22.9 Hz, 4-C), 52.8 (q, 5-C), 66.8 (dt, $^2J_{C,F}$ = 22.9 Hz, 3-C), 95.5 (ds,$^1J_{C,F}$ = 185.60 Hz, 2-C), 171.1 (ds, $^2J_{C,F}$ = 25.4 Hz, 1-C). ^{19}F NMR: δ = −165.0 (m). GC/MS: *m/z* (%) = 136 (0.2) [$M^{+\cdot}$], 135 (0.1) [$M^{+\cdot}$ − 1], 116 (4) [$M^{+\cdot}$ − HF], 106 (100) [$M^{+\cdot}$ − CH_2O], 105 (5) [135 − CH_2O], 77 (36) [$M^{+\cdot}$ − $C_2H_3O_2$], 74 (57) [$C_3H_6O_2^+$], 59 (23) [$C_3H_4F^+$; $C_2H_3O_2^+$]. GC/MS (CI): *m/z* = 154 [M + NH_4^+]. $C_5H_9FO_3$ (136.1): calcd. C 44.12, H 6.66; found C 43.82, H 6.87. By the same procedure, (*R*)-**20** (40 mg, 0.24 mmol) was transformed into (*R*)-**21**. Yield: 20 mg (61%). The enantiomeric excess of this compound was determined by Mosher's method:[31] DCC (23 mg, 110 μmol) and DMAP (a few crystals) were added to a solution of (*R*)-**21** (5 mg, 37 μmol) and (*R*)-(+)-Mosher's acid (26 mg, 110 μmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at room temperature for 14 h, and the solid material was filtered off and washed with 1 mL of CH_2Cl_2. The organic layers were combined and the solvent was removed. The proton-decoupled ^{19}F NMR spectrum of the crude residue (reduced measuring range δ = −150 to −180) showed two baseline-separated signals for the CF groups at δ = −162.1 and δ = −162.2. The integration showed a ratio of 75:25, hence 50% *ee* [the small difference in the *ee* values of (*S*)-**19** and (*R*)-**21** is probably due to the different methods, GC or ^{19}F NMR, respectively, used for the determination]. The signals of the CF_3 groups at δ = −72.44 and δ = −72.49 were not baseline-separated and could not be used for the determination of the *ee*.

3-Bromo-2-fluoro-2-methylpropanoic Acid (23): According to the procedure given above for the synthesis of **20**, the bromo-substituted fluoride **18** (2.60 g, 12 mmol) was oxidized (reaction time 6 d) to **23**, and isolated as a hygroscopic white solid. Yield: 1.56 g (70%). ^{1}H NMR: δ = 1.75 (d, $^3J_{H,F}$ = 20.5 Hz, 3 H, 4-H) 3.62 (dd, $^3J_{Hb,F}$ = 14.5 Hz, $^2J_{Ha,Hb}$ = 11.5 Hz, 1 H, 3-H_b), 3.76 (dd, $^3J_{Ha,F}$ = 23.8 Hz, $^2J_{Ha,Hb}$ = 11.5 Hz, 1 H, 3-H_a), 7.74 (br, 1 H, OH). ^{13}C NMR (360 MHz): δ = 22.5 (dq, $^2J_{C,F}$ = 25.0 Hz, 4-C), 34.6 (dt, $^2J_{C,F}$ = 25.0 Hz, 3-C), 92.8 (ds, $^1J_{C,F}$ = 191.4 Hz, 2-C), 173.6 (ds, $^2J_{C,F}$ = 26.4 Hz, 1-C). ^{19}F NMR: δ = −155.6 (m). GC/MS [of the $Si(CH_3)_3$ ester]: *m/z* (%) = 212/214 (2/2) [$M^{+\cdot}$ − CO_2], 136/138 (4/4), 116/118 (1/1) [136/138 − HF], 93/95 (3/3) [CH_2Br^+], 85 (5), 77 (78), 73 (100) [$Si(CH_3)_3^+$], 59 (15) [$C_3H_4F^+$]. GC/MS [CI, of the $Si(CH_3)_3$ ester]: *m/z* = 274/276 [M + NH_4^+].

Methyl 3-Bromo-2-fluoro-2-methylpropanoate (24): A solution of **23** (1.52 g, 8.2 mmol) in dry methanol (30 mL) was treated with 2,2-dimethoxypropane (300 μL) and one drop of conc. HCl and stirred at room temperature for 32 h. After workup by the procedure given above for compound **21**, the ester **24** was isolated as a yellow oil. Yield: 850 mg (48%). The ^{1}H NMR spectroscopic data of this compound agree with those published.[41] ^{13}C NMR: δ = 22.4 (dq, $^2J_{C,F}$ = 22.9 Hz, 4-C), 35.1 (dt, $^2J_{C,F}$ = 22.9 Hz, 3-C), 52.9 (q, 5-C), 93.0 (ds, $^1J_{C,F}$ = 190.7 Hz, 2-C), 169.7 (ds, $^2J_{C,F}$ = 22.9 Hz, 1-C). ^{19}F NMR: δ = −155.4 (m). GC/MS: *m/z* (%) = 198/200 (6/6) [$M^{+\cdot}$], 178/180 (19/19) [$M^{+\cdot}$ − HF], 139/141 (11/11) [$M^{+\cdot}$ − $C_2H_3O_2$], 119 (11) [$M^{+\cdot}$ − Br], 99 (21) [178/180 − Br], 77 (38), 71 (11), 60 (22), 59 (100) [$C_3H_4F^+$; $C_2H_3O_2^+$].

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