Synthesis of a Fluorinated Analogue of Anticancer Active Ether Lipids

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The synthesis of racemic 2′-(trimethylammonium)ethyl-3-hexadecyloxy-2-fluoro-2-(methoxymethyl)-prop-1-yl-phosphate (**6**), a fluorinated analogue of an anticancer active ether lipid **5** was realized with 3% overall yield in a nine-step synthesis starting from 2-methylene-1,3-propanediol (**7**) using a bromofluorination as the key step. Both enantiomers of the precursor **8** of the ether lipid **6** were synthesized by lipase-catalyzed desymmetrization of the diacetate **17**, either by hydrolysis (83% ee) or by lipase-catalyzed acetylation of the diol **22** (82% ee). The antitumor activity of **6** has been found in an in vivo model of the methylcholanthrene-induced fibrosarcoma of mice.

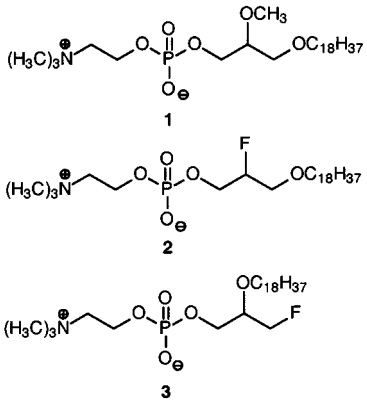
Introduction

There has been a steady growth of interest in the platelet activating factor (*R*)-1-*O*-hexadecyl-2-acetyl-*sn*-glycero-3-phosphocholine and in many synthetic ether lipids of related structure because of their cytostatic and cytotoxic activity.[1] Edelfosine (1-*O*-octadecyl-2-*O*-methyl-*rac*-glycero-3-phosphocholine) **1** is one of the most investigated of this class of compounds, since it exhibits in vitro and in vivo cytotoxic activity against numerous human and murine tumor cell strains.[2]

Among the many anticancer ether lipids thus far synthesized, few contain fluorine.[3] Brachwitz et al. have shown that the racemic monofluorinated regioisomers **2** and **3** exhibit cytotoxic activity against the Ehrlich-Ascites tumor, an activity similar to that of edelfosine **1**.[4] Exchange of the trimethylammonium group with an L-serine moiety increases the inhibition of proliferation of malignant cells of the aforementioned tumor.[5]

The variation of the substitution pattern around the stereogenic center of compound **1** led to 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. The enantiomers of **4** and **5** showed different activity.[2,6]

In connection with our ongoing research[7] on the synthesis of monofluorinated analogues of natural products and of biologically active compounds, we became interested in the synthesis of the ether lipid **6**, which bears a fluorine on its stereogenic center.[8]



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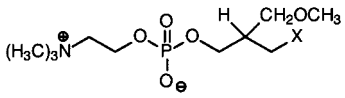
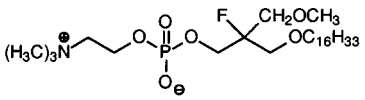


4 (X = $SC_{16}H_{33}$)

5 (X = $OC_{16}H_{33}$)



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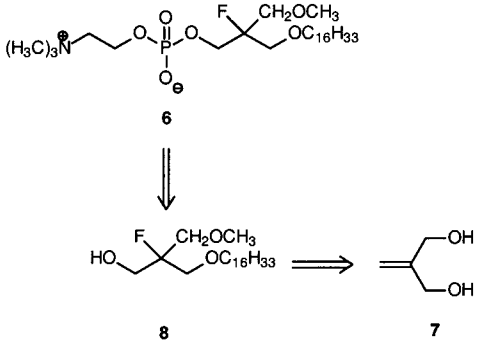
Results and Discussion

Retrosynthetic analysis of the title compound **6** leads to 2-methylenepropane-1,3-diol **7** via the fluorohydrin **8**.

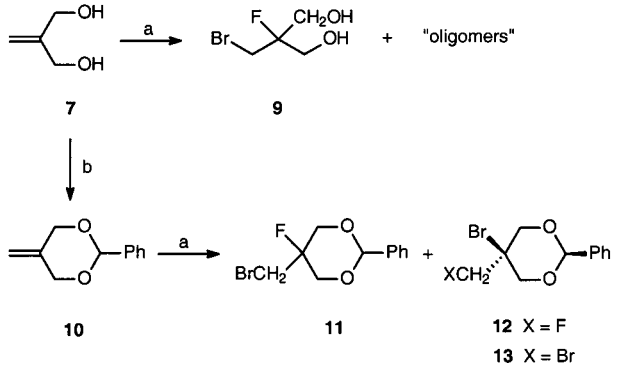


6 **8** **7**

However, the key step of the planned synthesis, the bromofluorination[9] of **7** with *N*-bromosuccinimide (NBS) and triethylamine tris(hydrogenfluoride) ($Et_3N{\cdot}3HF$), gave only 30% of the desired bromofluoride **9**. Also observed were nonfluorinated "oligomeric" products formed by nucleophilic attack of one of the OH groups of a second molecule of **7** at the cationic intermediate formed from **7** and NBS. Evidence for the regioisomer of **9** or for other fluorinated compounds was not found in the ^{19}F NMR spectrum of the crude reaction product. Bromofluorination of allyl alcohol[10] and of other allylic compounds[11] gave both regioisomers (Scheme 1).

To remove the competition of the OH functions and the fluoride donor for the intermediate cation, the free hydroxyl groups of **7** were protected with benzaldehyde. The bromofluorination of the thus-formed 1,3-dioxane **10**[26] gave both regioisomeric bromofluorides **11** and **12**, but the unwanted isomer **12** was the main product. We also obtained some amount of the dibromide **13**.[27] Dibromides, arising from Br_2 accumulation, are known to be formed under bromofluorination conditions, particularly when the double bond is unreactive and the fluorinating agent is relatively nucleophilic.[11h,12]

Scheme 1[a]



7 **9** **10** **11** **12** X = F **13** X = Br

[a] Reagents and conditions: (a) NBS/$Et_3N{\cdot}3HF$, CH_2Cl_2, 0 °C → r.t., (b) PhCHO, H^+.

Consequently, only one of the hydroxyl functions was protected with a long chain alkyl group using known procedures[6a,13] to form 2-(hexadecyloxymethyl)-2-propen-1-ol (**14**). This species, on bromofluorination with NBS/$Et_3N{\cdot}3HF$ at room temperature, gave the bromofluoride **15** in 60% yield. The more reactive system NBS/$Me_3N{\cdot}3HF$ at −10 °C gave the desired product **15** in 70% yield. In both cases, no evidence for other fluorinated compounds were detected by ^{19}F NMR spectroscopy of the crude products (Scheme 2).

Subsequent nucleophilic substitution of bromine with acetate using conditions which have been applied to similar substrates[14] gave a 43:10:47 mixture (GC) of the monoacetate **16a**, the diacetate **17a**, and the oxetane **18**. Under modified conditions (cf. Experimental Section), the amount of **18** was minimized to 23% in the best-case synthesis. The products were separated by column chromatography.

The diacetate **17a** was available more selectively by acetylation of **15** with acetic anhydride in pyridine to form **19**. Subsequent nucleophilic substitution of bromide with acetate gave **17a** in 67% overall yield.

The next step of the sequence required the *O*-methylation of **16a**, followed by the hydrolysis of the acetate function to **8**, the crucial precursor for the synthesis of the fluorinated ether lipid **6**. However, all attempts to etherify the base-labile **16a**, according to procedures[15] known for related compounds, failed. Therefore, the OH group of **16a** was protected as a phenylcarbamate, a functionality which is known to be relatively stable under basic conditions.[16] Subsequent saponification of the acetate group of the thus-formed carbamate **21**, yielding **22**, followed by methylation of the liberated OH group and the NH moiety of **22** gave the *N*-methylated methoxy compound **23**. The carbamate **23** was hydrolyzed by refluxing with KOH/MeOH to give the precursor **8** of the racemic title compound **6** in 69% yield. The overall yield was 8% based on **14** (Scheme 3).

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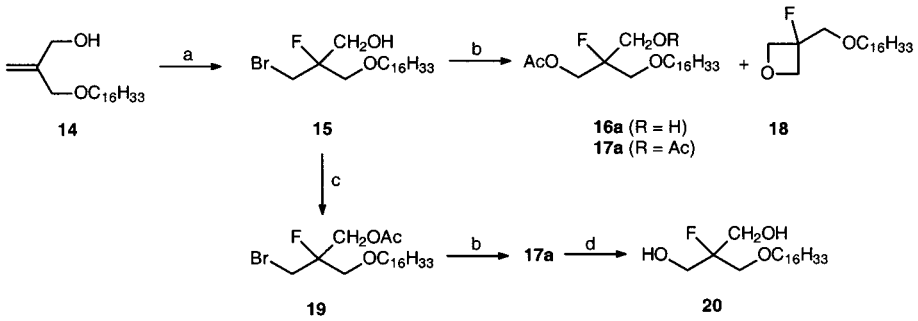
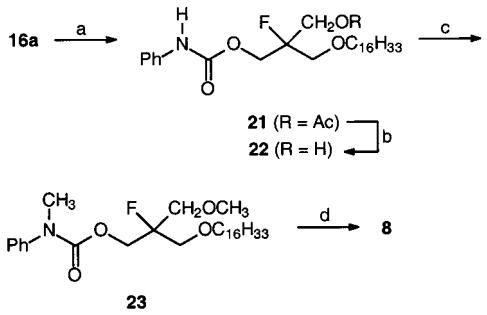
Scheme 2[a]



[a] Reagents and conditions: (a) NBS/$Alk_3N{\cdot}3HF$, CH_2Cl_2, 0 °C → rt, (b) KOAc, DMF, 24 h reflux, (c) Ac_2O, pyridine, r.t., (d) KOH, MeOH, r.t., 4 h.

Scheme 3[a]



[a] Reagents and conditions: (a) PhNCO, petroleum ether, 110 °C, 10 h, (b) KOH, MeOH, r.t., 2 h, (c) KOH, DMSO, MeI, r.t., 90 min, (d) KOH, MeOH, reflux, 14 h.

To synthesize the enantiomers of **8**, we tested several lipases for deracemization by acetylation in organic solvents. The best result obtained was a 23% ee for the unreacted **8** and 32% ee for the acetate thus formed.[17] We therefore decided to attempt the desymmetrization of **17a** by enzymatic hydrolysis. We also pursued the desymmetrization of the diol **20**, obtained from **17a** by saponification with methanolic KOH (80% yield, Scheme 3), by lipase-catalyzed acetylation.

In 1997 the Haufe group first succeeded in the catalytic deracemization of fluorinated acetates by using lipase from *Pseudomonas cepacia* (Amano PS).[18] These acetates bore a tertiary fluorine substituent at the stereogenic center along with a vicinal primary acetate function. Several deracemizations of β-fluorohydrins bearing a secondary hydroxyl function have been described.[19] There is little in the literature about lipase-catalyzed hydrolyses of substrates having an alkoxymethylene group attached to the stereogenic center.[7b,20] Fluorinated compounds of this type have, to our knowledge, never been investigated. We therefore first screened several lipases for their ability to desymmetrize **17a** or **20** (Table 1) (Scheme 4).

Porcine pancreatic lipase (PPL) and *Candida rugosa* lipase (CRL) gave unsatisfactory transformation of **17a** even after 75 days or 11 days, respectively. *Candida antarctica* lipase (CAL) did not significantly hydrolyze the diacetate **17a** when THF was present in the mixture. Without this cosolvent, a small amount of the monoacetate **16a** was detected in the product mixture. Mainly starting material **17a** and the diol **20** were found after 24 h of reaction time. The lipase from *Pseudomonas cepacia* (Amano PS) was shown to be the most effective enzyme of those investigated, giving a 30% isolated yield of the desired optically active product **16a** ($[\alpha]^{20}_D = -3.6$) after 6.5 h of reaction time. Additionally, 45% of the diol **20** and 20% of starting material **17a** were isolated by column chromatography (Table 1).

To enhance the yield of the monoacetate **16a**, we next examined the reverse process, that is, the lipase-catalyzed acetylation of the diol **20**. As mentioned above, the deracemization of β-fluorohydrins containing a primary hydroxyl function and a tertiary fluorine substituent has been previously realized.[18] Recently the Takeuchi group[21] and others[22] were able to desymmetrize 2-fluoro-1,3-propanediols.

The reaction of **20** with 2 equiv of vinyl acetate and CAL in toluene gave a 44% isolated yield of **16a** and a 12% yield of the diacetate **17a**. The starting material was also isolated (23% recovery). The monoacetate **16a** did not show any optical rotation. The esterification using vinyl chloroacetate and CAL gave partially the monoester **16b** (isolated in 32% yield), which was also optically inactive (Scheme 5).

The reaction of **20** with immobilized *Pseudomonas cepacia* lipase was very slow with 2 equiv of vinyl acetate in toluene. We therefore decided to use vinyl acetate as both substrate and solvent. This resulted, after a 3 h reaction time, in a product mixture consisting of 4% of starting material **20**, 73% of the monoacetate **16a**, and 23% of the diacetate **17a** (GC analysis). The optically active **16a** ($[\alpha]^{20}_D = +3.3$) was isolated in 71% yield (Table 2).

In conclusion, the enantiomers of the monoacetate **16a** were formed either by *Pseudomonas cepacia* lipase-catalyzed hydrolysis of the diacetate **17a** or by acetylation of the diol **20**.

It was very difficult to determine the enantiomeric excess of the isolated products. We examined the product **16a** by ^1H and ^{19}F NMR spectroscopy using different shift reagents such as $Eu(hfc)_3$ or $Eu(facam)_3$. No line separation was obtained even after the addition of 150 mol % of the shift reagent. With 20 mol % of $Pr(hfc)_3$, a high

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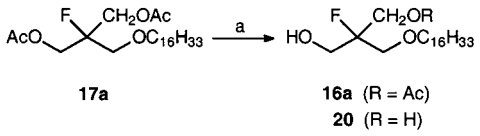
Table 1. Lipase-Catalyzed Hydrolyses of the Diacetate 17a

entry	**17a** [mg]	THF [ml]	enzyme [mg]	time	**17a** mg, [%][a](%)[b]	**16a** mg, [%][a](%)[b]	**20** mg [%][a](%)[b]
1	160	3	PPL (200)	75 d	120 [84] (78)	10 [13] (7)	2 [3] (<2)
2	100	2	CRL (5)	11 d	70 [87] (71)	7 [11] (8)	2 [2] (<2)
3	100	2	CAL (5)	48 h	90 [100] (91)	-	-
4	200	-	CAL (20)	24 h	95 [51] (48)	5 [5] (3)	61 [44] (38)
5	100	2	Amano PS (5)	6.5 h	20 [26] (18)	30 [29] (30)[c]	36 [45] (45)

[a] Part of the product mixture, GC. [b] Isolated yield. [c] $[\alpha]^{20}_D = -3.6$, $c = 1.1$ in chloroform (83% ee).[24]

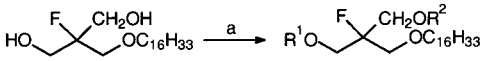
Scheme 4[a]



17a **16a** (R = Ac) **20** (R = H)

[a] Reagents and conditions: (a) Lipase, THF, 0.1 M phosphate buffer, pH 7.0, r.t.

Scheme 5[a]



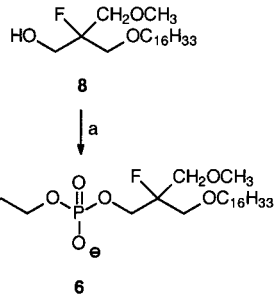
20 **16a** (R^1 = H, R^2 = Ac) **17a** (R^1 = R^2 = Ac) **16b** (R^1 = H, R^2 = $COCH_2Cl$) **17b** (R^1 = R^2 = $COCH_2Cl$)

[a] Reagents and conditions: (a) Lipase, toluene, vinyl acetate or vinyl chloroacetate, respectively.

field shift resulting in the partial separation of the methyl signals of the acetoxy function of **16a** was observed. With a higher concentration of the shift reagent, line broadening and overlap of the signals in the aliphatic part of the ^{1}H NMR spectrum were observed. No line separation was observed in the ^{19}F NMR spectra.

Another strategy for the NMR spectroscopic determination of the enantiomeric excess of chiral alcohols is the transformation of these alcohols into diastereomeric esters.[23] In this case ^{19}F NMR spectroscopy may be particularly useful because the shift differences of the relevant diastereomers are usually bigger than in the corresponding ^{1}H NMR spectra, and overlap of signals is rarely observed. We therefore used (1*S*)-(−)-camphanic acid chloride, (1*S*)-(−)-camphorsulfonic acid chloride, and (*S*)-(+)-chloropropanoic acid chloride as derivatizing reagents, but no signal separation was found in either the ^{1}H or the ^{19}F NMR spectra. After derivatization of **16a** with (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid), no line separation was observed in the product ^{19}F spectrum. When (*S*)-(+)-methoxymandelic acid was used as the derivatizing agent, a small shift-difference of 0.06 ppm was found in ^{1}H NMR of the methoxy groups of the product, but the signals could not be baseline resolved. Consequently, an exact integration of the signals was impossible using these methods. We succeeded in the determination of the enantiomeric excess of **16a** using the new derivatizing reagent α-cyano-α-fluoro(2-naphthyl)acetic acid (2-CFNA), which we recently described.[24] By using 2-CFNA, it was found that the product **16a**, obtained by hydrolysis of **17a** using lipase Amano PS (Table 1, entry 5), had an 83% ee (^{19}F NMR).

Scheme 6[a]



[a] Reagents and conditions: (a) (i) 2-chloro-2-oxo-1,3-dioxa-2-phospholane, Et_3N, THF, r.t., (ii) Me_3N, MeCN, 60 °C, sealed tube, 72 h.

The racemic fluoro alcohol **8** was transformed to the desired analogue **6** of the ether lipid **5** analogously to the method described by Guivisdalsky and Bittman.[25]

The fluorohydrin **8** was treated with a 3-fold excess of 2-chloro-2-oxo-1,3-dioxa-2-phospholane and triethylamine in THF at room temperature. The crude phosphoric acid triester intermediate was subsequently heated with trimethylamine in acetonitrile at 60 °C in a sealed tube for 72 h. The resulting phosphocholine derivative **6** was isolated in 35% yield. The overall yield of **6** was 3% based on **14** (Scheme 6).

The anticancer activity of **6** was tested in an in vivo model of the methylcholanthrene induced fibrosarcoma of mice. The activity of **6** was compared to that of cisplatin and ilmofosine. While a significant antitumor activity (IC_{50} 1.13 mg/mL, 48 h incubation time) of **6** was found, this activity was lower than that of cisplatin (IC_{50} 0.17 mg/mL) or ilmofosine (IC_{50} 0.23 mg/mL), all measured under the same experimental protocol.

Experimental Section

General. IR spectra, KBr pellets, $\tilde{\nu}$ [cm^{-1}]. ^{1}H NMR (300.1 MHz), ^{13}C NMR (75.5 MHz), and ^{19}F NMR (282.3 MHz) were recorded from ca. 20% solutions in $CDCl_3$ (if not stated otherwise). Chemical shifts are reported as δ values [ppm] relative to TMS (^{1}H), $CDCl_3$ (^{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 the DEPT operation. Mass spectra (electron impact ionization, 70 eV) were recorded by GC/MS coupling. The composition of crude reaction products and the conversion of substrates during enzymatic transformations was followed by GC using 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),

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Table 2. Lipase-Catalyzed Acetylation of the Diol 20

entry	**20** [mg]	toluene (mL)	enzyme (mg)	acylation reagent (mg)	time	product mixture	composition[a] [%]	yield [mg] (%)	$[\alpha]^{20}_D$
			CAL	vinyl		**20**	30	46 (23)	-
1	200	23	(40)	acetate	12 h	**16a**	54	100 (44)	0
				(51)		**17a**	16	30 (12)	-
			CAL	vinyl		**20**	40	50 (35)	-
2	140	16	(28)	chloroacetate	4 d	**16b**	47	56 (32)	0
				(49)		**17b**	13	20 (10)	-
			immobil.	vinyl		**20**	4	5 (2)	-
3	200	-	Amano	acetate[b]	3 h	**16a**	73	160 (71)	+3.3[c]
			PS (97)	(4 mL)		**17a**	23	45 (19)	-

[a] Part of the product mixture, GC. [b] Used as the solvent. [c] $c = 1.06$ in chloroform.

temperature program, 40 °C → 280 °C with a 10 °C/min heating rate, N_2 as the carrier gas. The ratio of compounds was 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). Optical rotations were measured at the Na_D line ($\lambda = 589$ nm). Enantiomeric excesses were measured as described in ref 24. Microanalyses were carried out by the "Mikroanalytisches Laboratorium, Organische Chemie", University of Münster using a CHNO analyzer.

Bromofluorination of 2-(Hexadecyloxymethyl)-2-propen-1-ol (14). A solution of **14** (770 mg, 2.46 mmol) prepared according to ref 13 and $Me_3N{\cdot}3HF$ (400 mg, 3.81 mmol) in dichloromethane (10 mL) was treated with NBS (481 mg, 2.70 mmol) in portions at −10 °C and stirred for 17 h. Subsequently the mixture was poured into ice−water (50 mL) and neutralized with 26% aq ammonia. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 0.1 N hydrochloric acid followed by 5% aq sodium bicarbonate solution and dried over magnesium sulfate. The solvent was evaporated, and the residue was purified by column chromatography (pentane/diethyl ether, 5:1) to obtain 3-bromo-2-fluoro-2-(hexadecyloxymethyl)-propan-1-ol (**15**) as white crystals. Yield: 708 mg (70%). Mp 39 °C (pentane/diethyl ether 5:1).^{1}H NMR: δ 0.88 (t, $^3J_{H,H} = 6.5$ Hz, 3 H), 1.21−1.39 (m, 26 H), 1.52−1.62 (m, 2 H), 2.00 (s, 1 H), 3.49 (t, $^3J_{H,H} = 6.4$ Hz, 2 H), 3.60−3.90 (m, 6 H);^{13}C NMR: δ 14.1 (q), 22.7 (t), 26.0 (t), 29.4 to 29.7, (11t), 31.1 (dt, $^2J_{C,F} = 28.0$ Hz), 31.9 (t), 64.0 (dt, $^2J_{C,F} = 25.4$ Hz), 70.7 (dt, $^2J_{C,F} = 28.0$ Hz), 72.3 (t), 95.1 (ds, $^1J_{C,F} = 175.5$ Hz); ^{19}F NMR: δ −169.0 (ttt, $^3J_{H,F} = 17.2$ Hz); Mass spectrum (after silylation), *m*/*z* (%): 482/484 (0.2), 467/469 (1), 403 (1), 384 (9), 383 (40), 243/245 (9), 159 (30), 143 (59), 133 (60), 103 (46), 99 (9), 98 (9), 85 (37), 83 (19), 73 (38), 76 (13), 71 (57), 69 (29). Anal. Calcd for $C_{20}H_{40}BrFO_2$ (411.44): C, 58.37; H, 9.80. Found C, 58.37; H, 9.87.

Nucleophilic Substitution of 3-Bromo-2-fluoro-2-(hexadecyloxmethyl)propan-1-ol (15) with Acetate. A mixture of **15** (580 mg, 1.14 mmol) and potassium acetate (894 mg, 9.12 mmol) in dry DMF (5 mL) was refluxed for 24 h. After cooling the reaction mixture to room temperature, a 1:1 mixture of cyclohexane/ethyl acetate (5 mL) was added, and the precipitated potassium bromide was filtered off. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was vacuum evaporated. Gas chromatographic analysis of the crude product showed a mixture of **15** (5%), **16a** (56%), **17a** (7%), and **18** (32%). This mixture was separated by column chromatography to give pure compounds **16a** and **18**. Unfortunately, **17a** was obtained in fractions either together with **16a** or **18**, but **17a** was shown to be identical with an authentic sample obtained in another way (see below). Refluxing **15** with 4 equiv of KOAc for 24 h gave **16a** (43%), **17a** (10%), and **18** (47%). Heating of **15** with 8 equiv of KOAc at 100 °C for 90 h gave a 27:50:23 mixture, respectively, of these compounds.

3-Acetoxy-2-fluoro-2-(hexadecyloxymethyl)propan-1-ol (16a). Yield: 220 mg (43%). Mp 32 °C (pentane/diethyl ether 1:1). All spectroscopic data agree with those given for the optically active compound in ref 24.

2-Fluoro-2-(hexadecyloxymethyl)oxetane (18). Yield: 90 mg (21%). Mp 34 °C (pentane/diethyl ether 5:1). ^{1}H NMR: δ 0.88 (t, $^3J_{H,H} = 6.5$ Hz, 3 H), 1.22−1.38 (m, 26 H), 1.54−1.63 (m, 2 H), 3.52 (t, $^3J_{H,H} = 6.6$ Hz, 2 H), 3.76 (d, $^3J_{H,F} = 21.0$ Hz, 2 H), 4.60 (ABX, $^2J_{H,H} = 8.1$ Hz, $^3J_{H,F} = 18.1$ Hz, 2H), 4.77 (ABX, $^2J_{H,H} = 8.1$ Hz, $^3J_{H,F} = 19.3$ Hz); ^{13}C NMR: δ 14.1 (q), 22.7 (t), 26.0 (t), 29.3 to 29.8 (11t), 31.9 (t), 71.3 (dt, $^2J_{C,F} = 25.4$ Hz), 72.3 (t), 78.6 (dt, $^2J_{C,F} = 25.4$ Hz), 93.7 (ds, $^1J_{C,F} = 208.5$ Hz); ^{19}F NMR: δ −155.9 (ttt, $^3J_{H,F} = 19.1$ Hz); Mass spectrum, *m*/*z* (%): 331 (0.02), 299 (1), 279 (4), 253 (6), 239 (3), 224 (16), 196 (12), 161 (17), 153 (7), 139 (14), 125 (28), 119 (41), 111 (57), 107 (94), 99 (28), 98 (24), 97 (20), 96 (38), 89 (13), 85 (75), 84 (50), 83 (100), 82 (81), 71 (100), 70 (78), 69 (100), 68 (92). Anal. Calcd for $C_{20}H_{39}FO_2$ (330.52): C, 72.68; H, 11.89. Found C, 72.88; H, 12.07.

Acetylation of 3-Bromo-2-fluoro-2-(hexadecyloxymethyl)propan-1-ol (15). A solution of **15** (400 mg, 0.97 mmol), acetic anhydride (102 mg, 1 mmol), and pyridine (79 mg, 1 mmol) was stirred for 15 h at room temperature. Ice−water (5 mL) was added, and the mixture was extracted with dichloromethane. The combined organic layer was washed with 10% aq HCl, followed by water, and dried over magnesium sulfate. After evaporation of the solvent, the crude product was purified by column chromatography (pentane/diethyl ether 10:1), to give 1-acetoxy-3-bromo-2-fluoro-2-(hexadecyloxymethyl)-propane (**19**) as a white solid. Yield: 417 mg (95%). Mp 39 °C (pentane/diethyl ether, 10:1). ^{1}H NMR: δ 0.88 (t, $^3J_{H,H} = 6.7$ Hz, 3 H), 1.22−1.38 (m, 26 H), 1.51−1.60 (m, 2 H), 2.11 (s, 3 H), 3.48 (t, $^3J_{H,H} = 6.4$ Hz, 2 H), 3.50−3.74 (m, 4 H), 4.35 (d, $^3J_{H,F} = 19.6$ Hz, 2 H); ^{13}C NMR: δ 14.1 (q), 20.7 (q), 22.7 (t), 26.0 (t), 29.4 to 29.7 (11t), 31.1 (dt, $^2J_{C,F} = 28.0$ Hz), 31.9 (t), 64.1 (dt, $^2J_{C,F} = 22.9$ Hz), 70.0 (dt, $^2J_{C,F} = 25.4$ Hz), 72.3 (t), 93.9 (ds, $^1J_{C,F} = 180.6$ Hz), 170.1 (s); ^{19}F NMR: δ −166.8 (ttt, $^3J_{H,F} = 17.2$ Hz); Mass spectrum, *m*/*z* (%): 452/454 (0.04), 409/411 (1), 373 (7), 353 (28), 289 (4), 255 (17), 229/231 (7), 225 (6), 209/211 (7), 181/183 (5), 129 (64), 113 (21), 111 (10), 99 (12), 97 (20), 85 (41), 83 (25), 71 (62), 70 (23), 69 (32). Anal. Calcd for $C_{22}H_{42}BrFO_3$ (453.47): C, 58.27; H, 9.34. Found C, 58.27; H, 9.34.

1,3-Diacetoxy-2-fluoro-2-(hexadexyloxymethyl)propane (17a). A mixture of **19** (340 mg, 0.75 mmol) and potassium acetate (170 mg, 3 mmol) in dimethyl formamide (5 mL) was refluxed for 24 h. After cooling this reaction mixture to room temperature, a cyclohexane/ethyl acetate mixture (1:1, 5 mL) was added, and the precipitate thus formed was filtered off. The organic layer was washed with water and dried over magnesium sulfate. After the solvent was removed, the crude product was purified by column chromatography (pentane/diethyl ether, 3:1) to give pure **17a** as a white solid. Yield: 427 mg (70%). Mp 38 °C (pentane/diethyl ether 5:1); ^{1}H NMR: δ 0.88 (t, $^3J_{H,H} = 6.7$ Hz), 1.20−1.34 (m, 26 H), 1.50−1.60 (m, 2 H), 2.10 (s, 6 H), 3.46 (t, $^3J_{H,H} = 6.4$ Hz, 2 H), 3.62 (d, $^3J_{H,F} = 16.6$ Hz, 2 H), 4.23−4.38 (m, 4 H); ^{13}C NMR: δ 14.1 (q), 20.6 (2q), 22.6 (t), 26.0 (t), 29.3 to 29.6 (11t), 31.9 (t), 63.1 (2dt, $^2J_{C,F} = 25.4$ Hz), 69.5 (dt, $^2J_{C,F} = 28.0$ Hz), 72.3 (t), 94.1 (ds, $^1J_{C,F} = 180.6$ Hz), 170.2 (2s); ^{19}F NMR: δ −174.1 (m); Mass spectrum, *m*/*z* (%): 432 (1), 373 (1), 352 (8), 310 (31), 292 (8), 281 (4), 269 (2), 209 (14), 191 (16), 149 (46), 129 (6), 118 (47), 87 (12), 86 (14), 85 (18), 83 (14), 81 (12), 71 (14), 69 (16). Anal.

Calcd for $C_{24}H_{45}FO_5$ (432.61): C, 66.63; H, 10.48. Found C, 66.89; H, 10.49.

Saponification of 1,3-Diacetoxy-2-fluoro-2-(hexadecyloxymethyl)propane (17a). A solution of **17a** (280 mg, 0.65 mmol) and potassium hydroxide (232 mg, 4 mmol) in methanol (5 mL) was stirred at room temperature for 4 h. The mixture was poured into water (10 mL) and extracted with diethyl ether. The combined ethereal extract was washed with water, dried over magnesium sulfate, and filtered through silica gel (3 cm). After evaporation of the solvent, the diol **20** was obtained as a white solid. Yield: 173 mg (80%); ^{1}H NMR: δ 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26 (m, 26 H), 1.50−1.60 (m, 2 H), 2.26 (s, 2 H), 3.48 (t, $^3J_{H,H}$ = 6.6 Hz), 3.60 (d, $^3J_{H,F}$ = 16.9 Hz), 3.76 (dd, $^2J_{H,H}$ = 4.5 Hz, $^3J_{H,F}$ = 17.9 Hz, 4 H). ^{13}C NMR δ 14.1 (q), 22.7 (t), 26.0 (t), 29.4 to 29.7 (11t), 31.9 (t), 63.4 (2dt, $^2J_{C,F}$ = 25.4 Hz), 70.9 (dt, $^2J_{C,F}$ = 28.0 Hz), 72.4 (t), 96.5 (ds, $^1J_{C,F}$ = 172.9 Hz); ^{19}F NMR: δ −177.4 (tq, $^3J_{H,F}$ = 17.2 Hz); Mass spectrum, *m*/*z* (%): 348 (0.6), 328 (8), 297 (28), 255 (3), 253 (4), 241 (6), 225 (6), 224 (5), 196 (4), 167 (4), 155 (4), 125 (67), 111 (18), 97 (33), 85 (41), 83 (35), 71 (60), 70 (28), 69 (42). Anal. Calcd for $C_{20}H_{41}FO_3$ (348.54): C, 68.92; H, 11.86. Found C, 69.20; H, 12.16.

1-Acetoxy-2-fluoro-2-(hexadecyloxymethyl)-3-(phenylcarbamoyl)propane (21). A solution of **16a** (140 mg, 0.36 mmol) in dry petroleum ether (110 °C, 2 mL) was treated (syringe) with phenyl isocyanate (54 mg, 0.45 mmol) and refluxed for 10 h. At 0 °C the white solid **21** precipitated. This solid was purified by column chromatography (pentane/diethyl ether, 3:1). Yield: 150 mg (82%). Mp 64 °C (pentane/diethyl ether, 3:1); IR: $\tilde{\nu}$ 3344 (br), 2913 and 2848 (s), 1739 (s), 1707 (s), 1604 (m), 1541 (s), 1472 and 1446 (m), 1318 (m), 1242 (s), 1128 (m), 1088 (m), 1073 (m), 1051 (m), 688 (m); ^{1}H NMR: δ 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.22−1.38 (m, 26 H), 1.50−1.60 (m, 2 H), 2.09 (s, 3 H), 3.46 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H), 3.62 (d, $^3J_{H,F}$ = 16.0 Hz, 2 H), 4.26−4.45 (m, 4 H), 6.77 (s, 1 H), 7.05−7.09 (m, 1 H), 7.25−7.39 (m, 4 H); ^{13}C NMR: δ 14.1 (q), 20.6 (q), 22.6 (t), 26.0 (t), 29.3 to 29.6 (11t), 31.9 (t), 63.1 (t, $^2J_{C,F}$ = 25.4 Hz), 63.8 (t, $^2J_{C,F}$ = 25.4 Hz), 69.6 (t, $^2J_{C,F}$ = 25.4 Hz), 72.3 (t), 94.3 (ds, $^1J_{C,F}$ = 183.1 Hz), 118.8 (d), 123.7 (d), 129.1 (d), 137.5 (s), 152.6 (s), 170.2 (s); ^{19}F NMR: δ −174.0 (m); Mass spectrum (direct inlet), *m*/*z* (%): 510 (4), 509 (13), 225 (2), 169 (2), 167 (9), 155 (5), 153 (3), 149 (16), 129 (10), 127 (4), 125 (10), 120 (11), 119 (100), 99 (15), 98 (7), 97 (20), 96 (8), 93 (6), 91 (19), 85 (22), 83 (25), 82 (9), 73 (13), 71 (36), 70 (20), 69 (31), 68 (7). Anal. Calcd for $C_{29}H_{48}FNO_5$ (509.70): C, 68.34; H, 9.49; N, 2.75. Found C, 68.27; H, 9.54; N, 2.96.

2-Fluoro-2-(hexadecyloxymethyl)-3-(phenylcarbamoyl)-propan-1-ol (22). A solution of **21** (110 mg, 0.22 mmol) and potassium hydroxide (73 mg, 1.3 mmol) in methanol (5 mL) was stirred at room temperature for 2 h. The mixture was poured into water (10 mL) and extracted with diethyl ether. The combined ethereal extract was washed with water, dried over magnesium sulfate, and filtered through silica gel (3 cm). After evaporation of the solvent the fluorohydrin **22** was obtained as a white solid. Yield: 85 mg (72%). Mp 71 °C (pentane/diethyl ether 1:1); IR: $\tilde{\nu}$ 3420 (br), 3344 (br), 2917 and 2849 (s), 1695 (s), 1600 (m), 1555 (s), 1472 and 1451 (m), 1322 (m), 1255 (m), 1123 (m), 1086 (m), 1073 (m), 1064 (s), 758 (m); ^{1}H NMR: δ 0.88 (t, $^3J_{H,H}$ = 6.7 Hz), 1.25−1.37 (m, 26 H), 1.52−1.62 (m, 2 H, OCH$_2$C*H*$_2$), 2.30 (br s, 1 H, OH), 3.49 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, OC*H*$_2$CH$_2$), 3.61−3.85 (m, 4 H), 4.41 (ABX, $^2J_{H,H}$ = 12.4 Hz, $^3J_{H,F}$ = 18.1 Hz, 1 H), 4.48 (ABX, $^2J_{H,H}$ = 12.4 Hz, $^3J_{H,F}$ = 21.7 Hz, 1 H), 6.71 (s, 1 H), 7.05−7.11 (m, 1 H), 7.27−7.39 (m, 4 H); ^{13}C NMR: δ 14.1 (q), 22.7 (t), 26.0 (t), 29.3 to 29.6 (11t), 31.9 (t), 62.2 (t, $^2J_{C,F}$ = 28.0 Hz), 63.8 (t, $^2J_{C,F}$ = 25.4 Hz), 70.4 (t, $^2J_{C,F}$ = 25.4 Hz), 72.4 (t), 95.8 (ds, $^1J_{C,F}$ = 178.0 Hz), 119.0 (d), 123.9 (d), 129.1 (d), 137.4 (s), 153.4 (s); ^{19}F NMR: δ −175.5 (m); Mass spectrum *m*/*z* (%): 468 (2), 467 (6), 224 (2), 196 (2), 167 (2), 155 (6), 154 (3), 153 (3), 149 (3), 141 (2), 140 (2), 139 (5), 137 (5), 127 (2), 126 (4), 125 (16), 124 (3), 120 (14), 119 (100), 96 (9), 93 (22), 91 (45), 87 (21), 86 (14), 85 (23), 84 (13), 83 (37), 82 (16), 71 (37), 70 (27), 69 (41), 68 (18). Anal. Calcd for $C_{27}H_{46}FNO_4$ (467.70): C, 69.34; H, 9.91; N, 3.00. Found C, 69.44; H, 9.88; N, 3.13.

2-Fluoro-2-(hexadecyloxymethyl)-1-methoxy-3-(phenyl-*N*-methylcarbamoyl)propane (23). A suspension of powdered potassium hydroxide (35 mg, 0.64 mmol) and dimethyl sulfoxide (5 mL) was stirred for 10 min at room temperature. At this temperature **22** (40 mg, 0.09 mmol) and methyl iodide (45 mg, 0.32 mmol) were added, and the resulting mixture was stirred for 90 min. At the end of this time, the mixture was poured into a brine solution (10 mL), and this mixture was extracted with diethyl ether. The combined extract was washed with water and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography (pentane/diethyl ether, 3:1) to obtain **23** as colorless viscous oil. Yield: 30 mg (67%). IR $\tilde{\nu}$ 2923 and 2852 (s), 1716 (s), 1598 (w), 1498 and 1456 (m), 1351 (m), 1276 (w), 1160 (m), 1114 (m), 770 (w), 658 (m); ^{1}H NMR: δ 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.21−1.35 (m, 26 H), 1.46−1.53 (m, 2 H), 3.31 (s, 6 H), 3.35−3.48 (m, 6 H), 4.31 (d, $^3J_{H,F}$ = 19.8 Hz, 2 H), 7.19−7.38 (m, 5 H); ^{13}C NMR: δ 14.1 (q), 22.6 (t), 26.0 (t), 29.3 to 29.6 (11t), 31.9 (t), 37.7 (q), 59.6 (q), 64.8 (t, $^2J_{C,F}$ = 25.4 Hz), 69.6 (t, $^2J_{C,F}$ = 25.4 Hz), 71.7 (t, $^2J_{C,F}$ = 22.9 Hz), 72.1 (t), 95.8 (ds, $^1J_{C,F}$ = 180.6 Hz), 125.9 (d), 126.3 (d), 128.8 (d), 143.1 (s), 154.0 (s); ^{19}F NMR: d −173.5 (ttt, $^3J_{H,F}$ = 19.1 Hz); Mass spectrum (direct inlet), *m*/*z* (%): 496 (22), 495 (66), 271 (12), 254 (9), 235 (6), 225 (1), 224 (2), 167 (1), 155 (3), 151 (11), 149 (7), 141 (3), 140 (1), 139 (2), 135 (10), 134 (100), 121 (14), 120 (14), 107 (21), 106 (38), 101 (96), 99 (14), 97 (15), 94 (11), 85 (63), 84 (21), 83 (24), 77 (18), 71 (76), 69 (37). Anal. Calcd for $C_{29}H_{50}FNO_4$ (495.70): C, 70.27; H, 10.17; N, 2.83. Found C, 70.27; H, 10.27; N, 3.00.

2-Fluoro-2-(hexadecyloxymethyl)-3-methoxypropan-1-ol (8). A solution of **23** (20 mg, 0.04 mmol) and potassium hydroxide (14 mg, 0.24 mmol) in methanol (2 mL) was refluxed for 14 h. After cooling, the solution was poured into water (10 mL) and extracted with diethyl ether. The combined extract was washed with water and dried over magnesium sulfate. The solvent was evaporated to give **8** as a viscous oil which was 90% pure (GC). Yield: 10 mg (69%). ^{1}H NMR: δ 0.88 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H), 1.20−1.38 (m, 26 H), 1.52−1.61 (m), 2.30 (br s, 1 H), 3.40 (s, 3 H), 3.48 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H), 3.62 and 3.65 (2 d, $^3J_{H,F}$ = 19.3 Hz, $^3J_{H,F}$ = 18.4 Hz, 4 H), 3.80 (d, $^3J_{H,F}$ = 16.9 Hz, 2 H); ^{13}C NMR: δ 14.1 (q), 22.7 (t), 26.0 (t), 29.3 to 29.7 (11t), 31.9 (t), 59.7 (q), 63.6 (dt, $^2J_{C,F}$ = 25.4 Hz), 70.6 (dt, $^2J_{C,F}$ = 25.4 Hz), 72.3 (t), 72.6 (dt, $^2J_{C,F}$ = 25.4 Hz), 96.5 (ds, $^1J_{C,F}$ = 175.5 Hz); ^{19}F NMR: δ −174.7 (ttt, $^3J_{H,F}$ = 19.1 Hz); Mass spectrum, *m*/*z* (%): 362 (0.2), 342 (4), 311 (44), 297 (14), 267 (3), 253 (2), 241 (3), 225 (2), 169 (1), 155 (3), 139 (49), 121 (17), 111 (10), 101 (14), 100 (21), 97 (21), 90 (17), 89 (25), 88 (18), 87 (63), 85 (41), 84 (21), 83 (31), 71 (86), 70 (25), 69 (60). Anal. Calcd for $C_{21}H_{43}FO_3$ (362.56): C, 69.57; H, 11.95. Found C, 69.56; H, 11.82.

2′-(Trimethylammonium)ethyl 2-fluoro-2-(hexadecyloxymethyl)-3-methoxyprop-1-ylphosphate (6). Analogously to ref 25, a mixture of the fluorohydrin **8** (10 mg, 27 μmol) and triethylamine (12 μL, 80 μmol) in dry THF (1 mL) was prepared in an argon-flushed, dried Schlenk vessel. A solution of 2-chloro-2-oxo-1,3,2-dioxaphospholane (8 μL, 85 μmol) in dry THF (0.5 mL) was added to this flask at 0 °C, and the resulting mixture was stirred at this temperature for 30 min. At the end of this time, the mixture was allowed to warm to room temperature and stirred there 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 a vacuum. The residue was dissolved under argon in dry acetonitrile (1 mL), placed in a pressure vessel, and cooled to −78 °C. Trimethylamine (about 0.2 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. A yellowish waxy material precipitated. This was purified by column chromatography (chloroform/methanol/water, 65:25:4) to obtain, besides starting material (3.5 mg, 35%), the desired ether lipid **6** as a yellowish solid (5 mg, 35% yield). ^{1}H NMR ($CDCl_3$/CD_3OD, 1:1): δ 0.89 (t, $^3J_{H,H}$ = 6.6 Hz, 3 H), 1.25−1.34 (m, 26 H), 1.52−1.61 (m, 2 H), 3.24 (s, 9 H), 3.39 (s, 3 H), 3.48 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H), 3.61−3.68 (m, 6 H), 4.02−4.10 (m, 2 H) 4.23−4.31

(m, 2 H); ^{19}F NMR ($CDCl_3/CD_3OD$, 1:1): δ −173.7 (ttt, $^3J_{H,F}$ = 19.1 Hz). ^{31}P NMR ($CDCl_3/CD_3OD$, 1:1): δ 5.3 (m); Mass spectrum, Maldi-TOF, *m*/*z*: 529 ± 0.05% [M^+ + 2H].

Lipase-Catalyzed Deracemizations

(a) Lipase-Catalyzed Hydrolyses of (±)-1,3-Diacetoxy-2-fluoro-2-(hexadecyloxymethyl)propane (17a). The diacetate **17a**, dissolved in THF, was added to a phosphate buffer (10 mL, 0.1 M, pH = 7.0) containing the corresponding lipase and stirred at room temperature for the time given in Table 1. The reaction was stopped by addition of a small amount of NaCl, Celite 577 (2 g) and ethyl acetate (10 mL). The enzyme and Celite were removed by filtration. The filtrate was extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was passed through a short column (3 cm silica gel, ethyl acetate as eluent) and analyzed by GC in order to determine the product ratio. After evaporation of the solvent, the residue was separated by column chromatography (pentane/diethyl ether, 1:1). The exact parameters of the experiments and the results are given in Table 1.

(b) Lipase-Catalyzed Acetylation and Chloroacetylation of 2-Fluoro-2-(hexadecyloxyethyl)propane-1,3-diol (20). The diol **20** and the acyl donor were dissolved in toluene, and the enzyme (occasionally immobilized) was added. The mixture was stirred at room temperature for the length of time given in Table 2. The reaction was stopped by filtration of the mixture through a short column of silica gel (toluene as eluent). The mixture was analyzed by GC, the solvent was evaporated, and the residue was separated by column chromatography (pentane/diethyl ether, 1:1). The exact parameters of the experiments and the results are given in Table 2.

3-Chloroacetoxy-2-fluoro-2-(hexadecyloxymethyl)propan-1-ol (16b). Mp 53 °C (pentane/diethyl ether 3:1). ^{1}H NMR: δ 0.88 (t, $^3J_{H,H}$ = 6.5 Hz, 3 H), 1.22−1.38 (m, 26 H), 1.51−1.60 (m, 2 H), 2.01 (br s, 1 H), 3.48 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H), 3.59−3.71 (m, 2 H), 3.73−3.88 (m, 2 H), 4.10 (s, 2 H), 4.36−4.54 (m, 2 H); ^{13}C NMR: δ 14.1 (q), 22.6 (t), 26.0 (t), 29.3 to 29.7 (11t), 31.9 (t), 40.5 (t), 62.7 (dt, $^2J_{C,F}$ = 25.4 Hz), 64.7 (dt, $^2J_{C,F}$ = 25.4 Hz), 69.9 (dt, $^2J_{C,F}$ = 28.0 Hz), 72.4 (t), 95.1 (ds, $^1J_{C,F}$ = 178.0 Hz), 166.9 (s); ^{19}F NMR: δ −175.9 (m); Mass spectrum, *m*/*z* (%): 424/426 (0.5) [$M^{+\bullet}$], 310 (5), 255 (4), 225 (3), 223 (3), 201 (11), 183 (13), 167 (6), 155 (9), 149 (4), 141 (5), 125 (8), 111 (14), 99 (13), 97 (28), 87 (23), 86 (24), 85 (39), 83 (33), 71 (60), 70 (25), 69 (43). Anal. Calcd for $C_{22}H_{42}ClFO_4$ (425.02): C, 62.17; H, 9.96. Found C, 62.42; H, 10.04.

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Supporting Information Available: Syntheses, analytical and spectroscopic data of compounds **9**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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