Synthesis of Fluorolipids: 1-*O*-Alkyl-2,3-*O*-diacylglycerols as Targeted Insecticides

Glenn D. Prestwich,* Kathleen A. Plavcan, and Michael E. Melcer

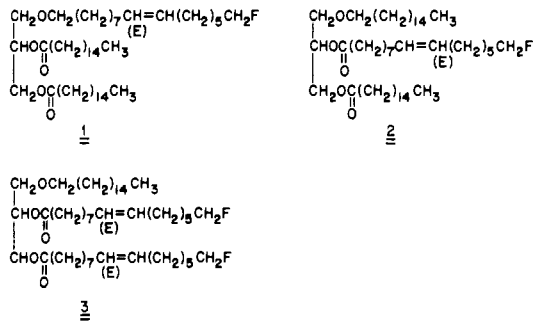
The syntheses of (*E*)- and (*Z*)-16-fluoro-9-hexadecenoic acid and of (*E*)-16-fluoro-9-hexadecen-1-ol are described; their incorporation into mixed 1-*O*-alkyl-2,3-*O*-diacyl-*rac*-glycerols **1**, **2**, and **3** with palmitic acid and hexadecan-1-ol is presented. Ether linkages are cleaved slowly in vivo and provide a slow-release mechanism for the highly toxic ω-fluoroalkoxyl group. ω-Fluoroacyl moieties are selectively introduced into *rac*-1 and *rac*-2 positions to enable biological testing for in vivo lipolytic lability. Modified etherification and esterification methods are introduced to improve yields and to avoid 2 → 3 acyl migrations.

Monofluoroacetic acid occurs as the toxic principle of over 36 plants in the genera *Dichapetalum*, *Acacia*, *Oxylobium*, and *Gastrolobium* (Peters, 1972). Fluoroacetate, one of the first poisons for which the biochemical mode of action was precisely described, substitutes for acetate in the tricarboxylic acid cycle. Peters (1957) found that a "lethal synthesis" occurred, resulting in the production of α-fluorocitrate, which inhibited aconitase and caused a lethal accumulation of citrate in specific tissues. More recently, Kun (1976) found that fluorocitrate in intact mitochondria irreversibly inhibits a membrane-associated process essential for the energy-dependent tricarboxylic acid (citric acid) translocation. In addition to the parent C_2 acid, C_{12}, C_{14}, C_{16}, and C_{18} ω-fluoro fatty acids have been isolated by saponification of the seed lipids of *Dichapetalum toxicarium* from Sierra Leone (Peters et al., 1960). The high toxicity of the even-carbon ω-fluoro fatty acids (Pattison et al., 1956b; Dear and Pattison, 1963) and ω-fluoro fatty alcohols (Pattison et al., 1956a), combined with the very low toxicity of the homologous odd-carbon compounds, provided convincing evidence for the hypothesized β-oxidation degradative sequence in fatty acid metabolism (Pattison, 1959; Goldman, 1969). Thus, the successive loss of two carbon units (as acetyl-CoA) in the energy-releasing catabolism of even-carbon ω-fluoro fatty acids would yield fluoroacetate, while odd-carbon ω-fluoro acids would yield the 100-fold less toxic β-fluoropropionate. We envisaged the use of the latent toxicity of ω-fluoro fatty acids to provide experimental probes into the nature of intermediates involved in acylglyceride metabolism and into the timing of lipid metabolism in economically important insect pests.

Despite the potential utility of fluoroacetate and its derivatives and higher homologues in pest control, the lack of selectivity for target species has prevented its widespread use (Hollingworth, 1976). Nonetheless, we felt that impregnation of milligram quantities of ω-fluoro acids and the derived glyceryl ethers and esters into bait blocks would enable the use of these compounds as targeted termite control agents (Beard, 1974; Esenther and Beal, 1974).

Glycerol esters derived from ω-fluoro fatty acids are less water soluble and may be more readily absorbed than the parent acids (Gilbert, 1967; Prestwich et al., 1981). Many insects transport glycerol derivatives as lipoprotein complexes of 1,2-*sn*-diacylglycerols (Gilbert and Chino, 1974; Downer and Matthews, 1976), and lipolysis occurs most slowly at the 2-position acyl moiety. Introduction of a toxic fluoroacyl group in this position may enable a substantial toxicity lag time needed for trophallactic exchange of food with other colony members. Glyceryl ethers (alkoxy lipids) derived from ω-fluoro alcohols were attractive synthetic targets based on the relatively slow cleavage of the ether linkage in vivo (Mangold, 1979).

Scheme I. 1-*O*-Alkyl-2,3-*O*-diacyl-*rac*-glycerides Required for Bioassay



In this paper we present the synthesis of positionally defined *O*-acyl- and *O*-alkyl-*rac*-glycerol derivatives (Scheme I). The bioassay of these compounds as termitocidal agents, including toxicity levels, poison exchange by trophallaxis, and toxicity lag times, will be summarized elsewhere (Prestwich et al., 1981). Compounds **1**, **2**, and **3** were prepared by modification of existing techniques of glyceride synthesis in order to provide high positional purity of the fluoroalkyl or fluoroacyl moieties. The 1-*O*-hexadecyl group was employed to decrease acyl migration both in vivo and during synthetic procedures. The choice of the (*E*)-16-fluoro-9-hexadecenoic acid as the *O*-fluoroacyl moiety reflects (1) the ready availability of the corresponding 16-hydroxy acid in one step (Singh et al., 1978) from commercially available aleuritic acid (*threo*-9,10,16-trihydroxyhexadecanoic acid), (2) the ability to monitor incorporation by ^1H NMR using the ratios of $-CH_2F$, vinylic, and allylic protons to $-CH_2O-$ and $-C(=O)CH_2-$ protons, and (3) increased delay time for β-oxidation of the unnatural (*E*) double bond.

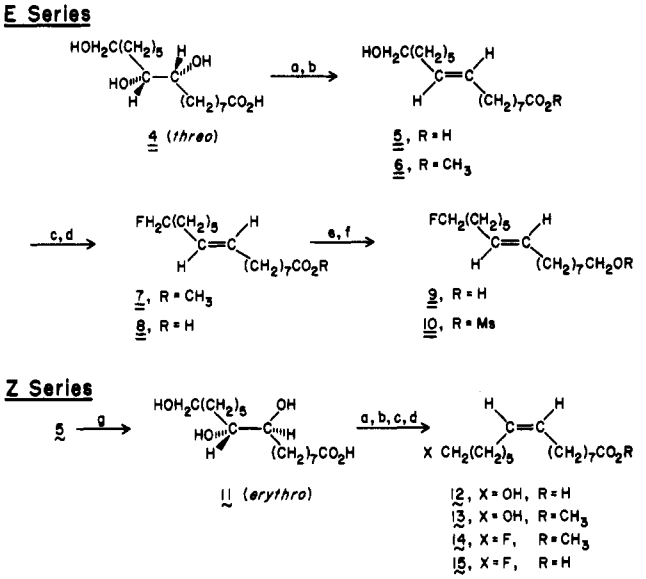
RESULTS

The fluoro acids and fluoro alcohols required as alkyldiacylglycerol side chains were prepared from aleuritic acid, the natural threo isomer of 9,10,16-trihydroxyhexadecanoic acid (**4**) as shown in Scheme II. Thus, heating aleuritic acid and ethyl orthoformate in the presence of benzoic acid, followed by pyrolysis of the resulting 2-ethoxy-1,3-dioxolan, afforded the (*E*)-9-hydroxy acid **5** in 88% yield after recrystallization from CCl_4 (Singh et al., 1979). On a large scale, the crude acid was converted to methyl ester **6** and fluorinated with *N*-2-chloro-1,1,2-trifluoroethyl-*N*,*N*-diethylamine (Cross and Hendley, 1975; Knox et al., 1964). Flash chromatography (Still et al., 1978) of the crude product afforded fluoro ester **7** which was hydrolyzed

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794.

0021-8561/81/1429-1018$01.25/0

Scheme II. Synthesis of 16-Fluoro-9-hexadecenoic Acids and (*E*)-16-Fluoro-9-hexadecenyl Alcohol[a]



[a] Reagents employed were as follows: (a) $HC(OC_2H_5)_3$, $C_6H_5CO_2H$, Δ; (b) CH_3OH, H^+, Δ; (c) $ClFCHCF_2N(C_2H_5)_2$, CH_2Cl_2; (d) 2 N KOH, CH_3OH, Δ; (e) $NaAlH_2(OCH_2CH_2OCH_3)_2$, C_6H_6-THF, Δ; (f) MsCl, Py; (g) H_2O_2, HCO_2H.

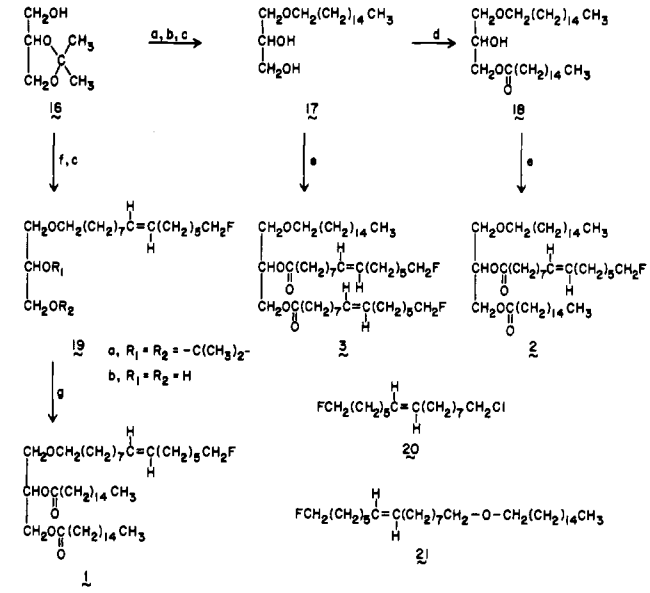
to give fluoro acid **8** in 31% overall yield from aleuritic acid (not optimized).

Trans hydroxylation of the (*E*)-9-hydroxy acid **5** to the erythro diastereomer **11** (82%), followed by a sequence analogous to that above, afforded the (*Z*)-9-fluoro acid **15** in 47% overall yield. Finally, hydride reduction of **8** afforded a fluoro alcohol **9** (84%) which was converted to the corresponding mesylate **10** for glyceryl ether preparation (Baumann, 1972; Baumann and Mangold, 1964). Preparation of **10** was accompanied by the production of a compound identified as the ω-fluorohexadecenyl chloride **20**, the production of which was associated with the use of prolonged reaction times and undistilled methanesulfonyl chloride (Shani, 1979).

The fluorolipids were prepared by modification of usual literature procedures for *O*-acyl- and *O*-alkylglycerol synthesis (Mangold, 1979; Jensen and Pitas, 1976; Buchnea, 1978) (Scheme III). In particular, we found that addition of 10 mol % of 18-crown-6 to the etherification reactions both improved yields (from 80 to 87%) and decreased reaction times (from 18 to 1 h). Use of the 4-(dimethylamino)pyridine (DMAP)-catalyzed condensation of acids with hindered alcohols in the presence of dicyclohexylcarbodiimide (DCC) (Neises and Steglich, 1978) provided a convenient method for acylation of the 2 and 3 positions of 1-*O*-alkyl- or 1-*O*-alkyl-3-*O*-acylglycerols. This was a superior approach in three ways: (1) the preparation of the acid chloride was unnecessary, (2) a large excess of a precious reagent (e.g., **8**) was not required, and (3) the chance of 1,2 ⇄ 1,3 isomerization during acylation is minimized by the milder conditions.

2,3-*O*-Isopropylidene-*rac*-glycerol (**16**) was converted to its potassium alkoxide with K metal in dry benzene and then alkylated with the mesylate of 1-hexadecanol in the presence of 10 mol % of 18-crown-6. Hydrolysis in aqueous methanolic hydrogen chloride afforded 1-*O*-hexadecyl-*rac*-glycerol (**17**) in 87% yield (Baumann and Mangold, 1964). Acylation of **17** with 1 equiv of palmitoyl chloride gave 1-alkyl-3-acylglycerol **18**, which could then be converted with DCC/DMAP to fluorolipid **2** (25% after careful chromatography to remove traces of difluoroacyl

Scheme III. Synthesis of Fluorolipids[a]



[a] Reagents employed were as follows: (a) K, C_6H_6, Δ; (b) $CH_3(CH_2)_{14}CH_2OMs$, 18-crown-6, Δ; (c) H_3^+O, CH_3OH, Δ; (d) $CH_3(CH_2)_{14}C(=O)Cl$ (1 equiv), $CHCl_3$, Py; (e) fluoro acid **8**, DCC, DMAP, CH_2Cl; (f) fluoroalkyl mesylate **10**, 18-crown-6, Δ; (g) $CH_3(CH_2)_4CO_2H$, DCC, DMAP, CH_2Cl_2.

Table I. Toxicity and Delay Times for Ingestion of Fluorolipids by *R. flavipes*

compd[a]	lethal dose,[b] μg/termite	delay,[c] h
1 (1.0 mg)	0.24 ± 0.10	60
2 (1.0 mg)	0.34 ± 0.06	56
3 (1.0 mg)	0.21 ± 0.04	44
8 (0.2 mg)	0.23 ± 0.4	85
9 (0.02 mg)	0.023 ± 0.004	70
20 (1.0 mg)	0.13 ± 0.02	106
21 (1.0 mg)	1.35 ± 0.40	>192

[a] Structures are identified in Schemes I–III. [b] Six replicates per compound, each containing 20 termites and a filter pad impregnated with the fluorolipid and ~20 000 dpm of [16-^{14}C]palmitic acid. The "lethal dose" in this case refers to the quantity ingested as determined by liquid scintillation counting of $CHCl_3$–MeOH extracts of dead termites [see Prestwich et al. (1981) for details] after 1 week of feeding. [c] Time required for 50% mortality at the indicated dose.

material), possessing a single toxic fluoroacyl group in the lipolytically least accessible *rac*-2 position. Alternatively, **17** was acylated with 2.2 equiv of fluoro acid **8** by using the DCC/DMAP method to give fluorolipid **3** (59% chromatographed), containing a fluoroacyl moiety in the lipolytically labile *rac*-3 position as well as the less labile 2 position.

Reaction of the potassium alkoxide of **16** with fluoroalkyl mesylate **10** in the presence of 18-crown-6 gave the 2,3-*O*-acetonide of **19** which was chromatographed before further use to remove mesylation byproduct **20**. Hydrolysis as before, followed by acylation of **19** with 2.5 equiv of palmitic acid and DCC/DMAP, afforded the 1-*O*-fluoroalkyl-2,3-*O*-diacyl compound **1** in 20% overall yield after chromatography.

Work is in progress to optimize yields and to increase the variety of synthetic *O*-(fluoroalkyl)- and *O*-(fluoroacyl)glycerol derivatives available for biological testing. In parallel, we are investigating the biological activities of these synthetic compounds in manipulating termite lipid metabolism for the purpose of pest control. Preliminary

results from toxicity tests in subterranean termites are presented in Table I. Detailed information on the time course and dosage dependence of mortality is presented in the following paper (Prestwich et al., 1981).

EXPERIMENTAL SECTION

Solvents were distilled under nitrogen and dried as follows: tetrahydrofuran (THF) was dried over molecular sieves (4 Å) and distilled from benzophenone sodium ketyl; dichloromethane was washed with water, dried over $CaCl_2$, and distilled from P_2O_5; chloroform was washed with water, distilled, and stored in a brown bottle; benzene was dried by azeotropic distillation and stored over sieves; pyridine was distilled from BaO and stored over molecular sieves; thionyl chloride and mesyl chloride were freshly distilled before use. Hexanes, ethyl acetate, and anhydrous ether were Fisher HPLC grade and used without further purification.

Infrared spectra (IR) were obtained on a Perkin-Elmer 727 instrument. ^{13}C NMR spectra were recorded by using a Varian CFT-20 and proton noise decoupling. ^1H NMR spectra were obtained on EM-360 and HFT-80 spectrometers. All NMR samples were prepared in $CDCl_3$ containing 0.2% Me_4Si; shifts are reported in ppm relative to $\delta(Me_4Si) = 0$. Only diagnostic values for IR absorption maxima and for NMR shifts and coupling constants are presented. Detailed proton noise decoupled ^{13}C NMR spectra for fluorolipids **1**, **2**, **3**, **9**, **15**, **17**, and **20** are listed in the supplementary material (see paragraph at end of paper regarding supplementary material).

Thin-layer chromatography was performed by using (A) Merck silica gel G (5 × 20 cm) and (B) MN Polygram Sil G/UV254 (4 × 8 cm) TLC plates. Lipids were compared by TLC on the Merck plate with 70:30:2 hexanes–ether–acetic acid and visualized by charring after spraying with 10% H_2SO_4 in ethanol. R_f values are reported for this system only. Other intermediates were examined by TLC on the Polygram plates using ethyl acetate–hexane mixtures and were visualized with an ethanolic vanillin–H_2SO_4 reagent. Column chromatography was performed on Florisil (100–200 mesh) by elution with ethyl acetate–hexane mixtures. Flash chromatography (Still et al., 1978) was performed under N_2 pressure on Merck silica gel G (400–230 mesh) by using ethyl acetate-hexane mixtures. Gas chromatography of the more volatile products was performed on a Perkin-Elmer Model 900 equipped with a glass column (2 m × 2 mm i.d.) packed with 3% OV-17 on 80/100 Gas-Chrom Q.

Samples for microanalysis were prepared by evaporative distillation at 0.2 mm using a Büchi Kugelrohrofen and were analyzed by Galbraith Laboratories. Low-resolution mass spectra were recorded by P. Chang on a Hewlett-Packard 5710A GC interfaced to an HP 5980A mass spectrometer with an HP5933A data system. High-resolution GC–MS were performed by Dr. C. Iden on an Atlas MS-9 interfaced with an HP7920 gas chromatograph.

All glycerol derivatives were stored in the dark at −20 °C to minimize degradation known to occur with unsaturated acylglycerols. Melting points are uncorrected.

(*E*)-16-Fluoro-9-hexadecenoic Acid (8). Commercial aleuritic acid **4** (Tridom-Fluka) could be converted to (*E*)-16-hydroxy-9-hexadecenoic acid (**5**), recrystallized from CCl_4, mp 64–66 °C (lit. mp 69–70 °C) (Singh et al., 1978). On a preparative scale, the crude acid was converted to the methyl ester prior to fluorination to enable purification by chromatography. Thus, the crude acid **5** resulting from reaction of 32.00 g of aleuritic acid was dissolved in 200 mL of methanol containing 2 drops of concentrated H_2SO_4 and refluxed overnight. The reaction was diluted with 2 volumes of water; the product was extracted with three 200-mL portions of ether and then washed with $NaHCO_3$ solution and dried over $MgSO_4$. Removal of solvents in vacuo afforded 29.69 g (99%) of methyl ester **6**.

The crude ester **6** was dissolved in 500 mL of CH_2Cl_2 and cooled to 0 °C under N_2. To this solution was added slowly 28.67 g of *N*-(2-chloro-1,1,2-trifluoroethyl)-*N*,*N*-diethylamine (Knox et al., 1964) and the reaction was stirred 3 h at 20 °C. Excess reagent and solvent were removed by distillation (60 °C/12 mmHg), and the crude mixture of **6** and fluoro ester **7** was purified by flash chromatography (10% ethyl acetate–hexane) in three lots to give 12.57 g of **7** (42%) which was homogeneous by GLC and TLC (B): IR (film) 1750 (C=O), 975 cm^{-1} (*trans*-HC=CH); NMR ($CDCl_3$) δ 5.37 (vinylic, br t, 3 Hz, 2 H), 4.36 ($-CH_2F$, dt, 48 Hz, 6 Hz, 2 H), 3.65 (OCH_3, s, 3 H), 2.23 ($-CH_2C(=O)$, t, 7 Hz, 2 H), 1.94 (allylic, m, 4 H); mass spectrum (70 eV) *m*/*z* (rel intensity) 287 (0.3, M + 1), 266 [13, M − 20 (HF)], 255 [21, M − 31 (OCH_3)], 96 (100), 74 (93).

The chromatographed ester was refluxed for 16 h in 50 mL of methanol and 50 mL of 2 N KOH. Acidification followed by ether extraction and the usual workup afforded 8.90 g of **8** (75%): mp 44.5–45.5 °C; IR ($CHCl_3$) 2900 (br, OH), 1705 (C=O), 975 cm^{-1} (*trans*-HC=CH); ^1H NMR ($CDCl_3$) δ 8.50 (CO_2H, br, s 1 H), 5.37 (vinylic, br t, 3 Hz, 2 H), 4.36 ($-CH_2F$, dt, 48 Hz, 6 Hz, 2 H), 2.23 ($-CH_2C(=O)$, t, 7 Hz, 2 H), 1.94 (allylic, m, 4 H); ^{13}C NMR ($CDCl_3$) 180.4 (CO_2H), 130.52, 130.56 (C=C), 84.2 ($-CH_2F$, d, $^1J_{CF}$ = 164 Hz), 34.2, 32.6, 30.9, 30.0, 29.6, 29.1 (2 C), 29.0, 28.8, 25.2, 24.9, 24.7. Anal. Calcd for $C_{16}H_{29}O_2F$: C, 70.55; H, 10.73; F, 6.97. Found: C, 70.78; H, 10.45; F, 6.84.

(*E*)-16-Fluoro-9-hexadecen-1-ol (9). To a 100-mL flask equipped with an oil bath, a magnetic stirrer, a dropping funnel, and an N_2 inlet was added sodium bis(2-methoxyethoxy)aluminum hydride (3.82 mL of a 3.5 M solution) in 10 mL of THF. (*E*)-16-Fluorohexadec-9-enoic acid (**8**) (1.190 g, 4.36 mmol) was dissolved in 5 mL of THF and added dropwise. The mixture was refluxed for 2 h. HCl (1 N) was added in order to quench the reaction and the flask was placed in an ice bath to precipitate the salts. The mixture was transferred with ethyl ether–water to a 250-mL separatory funnel and extracted with water. The organic layer was washed several times with saturated NaCl solution followed by a water wash. The aqueous layers were reextracted with ether. The organic layers were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to give 949 mg (84%) of crude alcohol **9**. The product was purified by evaporative distillation to give 799 mg (71%) of **9** as a clear oil homogeneous by GLC and TLC (A, R_f 0.14) and which solidifies below 20 °C: IR (film) 3360 (br, OH), 975 cm^{-1} (*trans*-HC=CH); NMR ($CDCl_3$) δ 5.37 (vinylic, br t, 3 Hz, 2 H), 4.44 ($-CH_2F$, dt, 48 Hz, 6 Hz, 2 H), 3.61 ($-CH_2OH$, t, 6 Hz, 2 H), 1.97 (allylic, m, 4 H); mass spectrum (70 eV) *m*/*z* (rel intensity) 240 (0.6, M − 18), 82 (67), 81 (71), 67 (82), 55 (100), 41 (39). Anal. Calcd for $C_{16}H_{31}OF$: C, 74.37; H, 12.09; F, 7.35. Found: C, 74.53; H, 12.22; F, 7.09.

(*E*)-16-Fluoro-9-hexadecen-1-yl Methanesulfonate (10). In a 100-mL flask equipped with magnetic stirrer and N_2 inlet was placed (*E*)-16-fluorohexadec-9-en-1-ol (1.000 g, 3.86 mmol) and 20 mL of pyridine (dried over KOH). The solution was cooled to 0 °C and methanesulfonyl chloride (668 mg, 5.83 mmol) was added dropwise. The ice bath was removed and the reaction was allowed to proceed at room temperature for 5 h. It is important that the reaction does not proceed for a longer time, since a high R_f side product, (*E*)-1-chloro-16-fluoro-9-hexadecene

(**20**) forms slowly and irreversibly.

The following extractions were carried out in the cold room in order to minimize hydrolysis of the mesylate (Baumann and Mangold, 1964). The reaction mixture was transferred to a 250-mL separatory funnel by using an ethyl ether–O_2-free water mixture. The aqueous layer was removed and placed in an ice bath. The ether layer was washed with 50 mL of H_2O, 30 mL of 20% H_2SO_4, and 50 mL of H_2O, twice with 30 mL of 1% K_2CO_3 (until basic), and with 50 mL of H_2O. Saturated NaCl solution was used to clear any emulsions.

The basic and original water washes were extracted with ether, which was used in turn to extract the acidic washes. The organic layers were combined and dried ($MgSO_4$), and the solvents removed in vacuo to give 804 mg (62%) of mesylate **10** as a viscous oil which contained 20–30% of side product **20** as estimated by NMR: IR (film) 1375, 1185 (SO_2), 975 cm^{-1} (*trans*-HC=CH); NMR ($CDCl_3$) δ 5.36 (vinylic, br t, 3 Hz, 2 H), 4.44 (–CH_2F, dt, 48 Hz, 6 Hz, 2 H), 4.31 (–CH_2O–, t, 6 Hz, 2 H), 2.99 (–O_3SCH_3, s, 3 H), 1.95 (allylic, m, 4 H). The mesylate **10** was used without further purification, as we were unable to crystallize it from hexane as in the hexadecyl mesylate case.

The high R_f side product was isolated from one 20-h reaction mixture by chromatography over Florisil to give **20** as a clear oil, homogeneous by GLC and TLC (A, R_f 0.58): IR (film) 975 cm^{-1} (*trans*-HC=CH), carbonyl, hydroxyl, sulfonate absorptions absent; NMR ($CDCl_3$) δ 5.35 (vinylic, br t, 3 Hz, 2 H), 4.38 (–CH_2F, dt, 48 Hz, 6 Hz, 2 H), 3.50 (–CH_2O–, t, 7 Hz, 2 H), 1.95 (allylic, m, 4 H); mass spectrum *m/e* 278 (9.5) and 276 (30.4), M^+. Anal. Calcd for $C_{16}H_{31}FCl$: C, 70.22; H,, 11.06; F, 6.95. Found C, 70.34; H, 11.39; F, 6.31.

(*Z*)-16-Fluoro-9-hexadecenoic Acid (15). The (*E*)-9-hydroxy acid **5** was converted via performic acid oxidation to *erythro*-aleuritic acid 11 [82%; mp 120–123 °C (lit. mp. 125–126 °C)] and then bisdehydroxylation to the corresponding (*Z*)-9-hydroxy acid **12** (81%; oil) (Singh et al., 1978). The crude acid was esterified (81%), fluorinated and chromatographed (68%), and hydrolyzed (85%) as described above for the *E*-9 acid, giving the (*Z*)-9-fluoro acid **15** as a clear oil which solidified below 20 °C: IR 1978). 2900 (bd, OH), 1700 (C=O), 975 cm^{-1} absent; NMR ($CDCl_3$) δ 5.34 (vinylic, t, 4.6 Hz, 2 H), 4.43 (–CH_2F, dt, 48 Hz, 6 Hz, 2 H), 2.34 (–CH_2CO, t, 7 Hz, 2 H), 1.97 (allylic, m, 4 H). Anal. Calcd for $C_{16}H_{29}O_2F$: C, 70.55; H, 10.73; F, 6.97. Found: C, 70.68; H, 10.85; F, 5.64.

1-*O*-[(*E*)-16-Fluoro-9-hexadecen-1-yl]-2,3-*O*-isopropylidene-*rac*-glycerol (19a). Into a dry 250-mL flask with a reflux condenser, an N_2 inlet, a dropping funnel, and a magnetic stirrer was placed freshly cut potassium metal (48 mg, 1.23 mmol) and 50 mL of dry benzene. The mixture was refluxed for 2 h under N_2. Solketal (**16**; Aldrich; 2,3-*O*-isopropylidene-*rac*-glycerol) (163 mg, 1.23 mmol) was added dropwise and refluxing was continued for 4 h. Ten mole percent 18-crown-6 (29 μL of a 3.78 M solution in benzene) was added, followed by a solution of crude (*E*)-16-fluorohexadec-9-en-1-yl methanesulfonate **10** (365 mg, 1.08 mmol) dissolved in 20 mL of dry benzene (added dropwise). Reflux was continued for 15 h.

The flask was chilled and the contents were transferred to a separatory funnel by using O_2-free water and two portions of ethyl ether. The combined organic layers were washed with water and dried (K_2CO_3), and the solvent was removed in vacuo to give 526 mg of crude glyceryl ether **19**. Chromatography on Florisil with 5–10% ethyl acetate in hexane eluted 47 mg of fluorochloroalkene **20**, 191 mg of GLC, TLC (A, R_f 0.45) homogeneous **19**, and 44 mg of fluoro alcohol **9** (77% recovery of fluoroalkyl moiety). Physical constants for **19** are as follows: IR (film), 1380, 1375 (*gem*-dimethyl), 975 cm^{-1} (*trans*-CH=CH); NMR ($CDCl_3$) δ 5.35 (vinylic, br t, 3 Hz, 2 H), 4.38 (–CH_2F, dt, 48 Hz, 6 Hz, 2 H), 4.25 (glyceryl H-2, quintet, 6 Hz, 1 H), 3.97 (glyceryl H-3a, d, 7 Hz, 1 H), 3.70 (glyceryl H-3b, dd, 9 Hz, 7 Hz, 1 H), 3.45 (glyceryl H-1 and –OCH_2R, t overlaid on m, 4 H), 1.95 (allylic, m, 4 H), 1.44, 1.36 (*gem*-dimethyl, s, s, 6 H); mass spectrum (70 eV) *m/z* (rel intensity) 372 (0.4, M^+), 357 (10, M – 15), 101 [100, $(CH_3)_2C$–(–O^+=$CHCH_2O$–)]. Anal. Calcd for $C_{22}H_{41}O_3F$: C, 70.92; H, 11.09; F, 5.10. Found: C, 70.98; H, 11.03; F, 4.95.

1-*O*-[(*E*)-16-Fluoro-9-hexadecen-1-yl]-*rac*-glycerol (19b). A solution of **19a** (152 mg) in 50 mL of methanol containing 0.5 mL of concentrated HCl was refluxed 2 h. The contents of the flask were transferred to a 250-mL separatory funnel with O_2-free water and ethyl ether and extracted. The aqueous layer was reextracted with ether, and the combined organics were washed with H_2O, 1% K_2CO_3, and H_2O and dried ($MgSO_4$). Solvents were removed in vacuo to give 137 mg (99%) of **19b** as a clear oil, which was used without further purification. TLC (A, 30% hexane–70% ether–2% acetic acid, R_f 0.26) indicated complete hydrolysis. NMR ($CDCl_3$) confirmed the presence of the *O*-fluoroalkyl moiety and loss of the isopropylidene moiety: δ 5.35 (vinylic, br t, 3 Hz, 2 H), 4.38 (–CH_2F, dt, 48 Hz, 6 Hz, 2 H), 3.75–3.25 (m, –CHO–, –CH_2O–, m, 7 H), 1.95 (allylic, m, 4 H).

1-*O*-[(*E*)-16-Fluoro-9-hexadecen-1-yl]-2,3-*O*-dihexadecanoyl-*rac*-glycerol (1). Into a 50-mL flask equipped with an N_2 inlet were placed Sigma grade II (95%) hexadecanoic acid (231 mg, 0.90 mmol), crude 1-*O*-alkylglycerol **19b** (123 mg, 0.36 mmol), 4-(dimethylamino)pyridine (DMAP; 11 mg, 0.09 mmol, 0.25 equiv), and 20 mL of dry CH_2Cl_2. The flask was cooled to 0 °C and dicyclohexylcarbodiimide (DCC; 186 mg, 0.90 mmol) was added in one portion. The reaction was stirred at 20 °C overnight.

The precipitated urea was filtered and the CH_2Cl_2 removed. The residue was redissolved in methylene chloride and the remaining urea filtered. The reaction mixture was transferred to a separatory funnel and washed twice with 20-mL portions of 1 N HCl and with two 20-mL 1 N NaOH washes to remove the excess fatty acid. The product was dried ($MgSO_4$) and the solvent removed in vacuo to give 259 mg of crude fluoroalkyl lipid **1**. Chromatography over Florisil with 5% ethyl acetate–hexanes afforded 163 mg (55%) of the TLC-homogeneous (A, R_f 0.45) fluorolipid **1** as a greasy solid: mp 37–38 °C; IR (film) 1735 (C=O), 975 cm^{-1} (*trans*-HC=CH); NMR ($CDCl_3$) δ 5.38 (vinylic, br t, 3 Hz, 2 H), 5.15 (glyceryl H-2, m, 1 H), 4.38 (–CH_2F, dt, 48 Hz, 6 Hz, 2 H); 4.15 (glyceryl H-3, m, 2 H); 3.52 (glyceryl H-1, d, 5 Hz, 2 H); 3.42 (–OCH_2R, t, 6 Hz, 2 H); 2.33 (–CH_2C(=O), t, 7 Hz, 4 H), 1.95 (allylic, m, 4 H), 0.90 (–CH_3, br t, 6 Hz, 6 H). Anal. Calcd for $C_{51}H_{97}O_5F$: C, 75.69; H, 12.08; F, 2.35. Found: C, 75.56; H, 12.26; F, 2.36.

1-*O*-Hexadecyl-3-*O*-hexadecanoyl-*rac*-glycerol (18). 1-*O*-Hexadecylglycerol (17) prepared by a modification of a published procedure (Baumann and Mangold, 1964) in which 10 mol % 18-crown-6 was added to the potassium alkoxide of isopropylideneglycerol prior to addition of the recrystallized hexadecyl mesylate (mp 51.5–53 °C). Conversion to the 1-*O*-hexadecanoyl-2,3-*O*-isopropylidene-*rac*-glycerol was complete in 1 h at reflux (TLC, A) instead of 18 h at reflux. Workup and hydrolysis gave **17** in 87% yield, mp 61–63 °C (lit. mp 65.5 °C), after recrystallization from hexanes.

To a 250-mL flask with a dropping funnel and an N_2 inlet was added 1.000 g (3.15 mmol) of 1-*O*-hexadecyl-

glycerol (17) in ~50 mL of ethanol-free, dry, distilled $CHCl_3$ containing 0.6 mL (5 mmol) of dry pyridine. Hexadecanoyl chloride (1.296 g, 4.71 mmol) was dissolved in $CHCl_3$ and added dropwise (Jensen and Pitas, 1976). The flask was shaken, cooled in an ice bath, and allowed to stir for 24 h at room temperature. Workup in the usual fashion afforded 704 mg (40%) of 18 as a greasy solid which was used without further purification.

1-*O*-Hexadecyl-2-*O*-[(*E*)-16-fluoro-9-hexadecenoyl]-3-*O*-hexadecanoyl-*rac*-glycerol (2) was prepared by the reaction of 200 mg (0.36 mmol) of crude 18 with 149 mg (0.54 mol) of fluoro acid 8, 111 mg (0.54 mmol) of DCC, and 7 mg (0.05 mmol) of DMAP as described above for 1. Chromatography of the crude product on Florisil with 5% ethyl acetate in hexanes afforded 76 mg (25%) of the mixed alkyldiacylglycerol (TLC, A, R_f 0.56) free from any traces of bis(fluoroacyl) compound 3 (R_f 0.52) prepared as described below. Lipid 2 has mp 38.5–40.5 °C; IR (film) 1737 (C=O), 975 cm^{-1} (*trans*-HC=CH); NMR ($CDCl_3$) δ 5.38 (vinylic, br t, 3 Hz, 2 H), 5.15 (glyceryl H-2, m, 1 H), 4.38 ($-CH_2F$, dt, 48 Hz, 6 Hz, 2 H), 4.20 (glyceryl H-3, m, 2 H), 3.52 (glyceryl H-1, d, 5 Hz, 2 H), 3.43 (RCH_2O-, t, 6 Hz, 2 H), 2.32 ($-CH_2CO-$, t, 7 Hz, 4 H), 1.95 (allylic, m, 4 H), 0.90 ($-CH_3$, br t, 6 Hz, 6 H). Anal. Calcd for $C_{51}H_{97}O_5F$: C, 75.69; H, 12.08; F, 2.35. Found: C, 75.53; H, 12.08; F, 2.60.

1-*O*-Hexadecanoyl-2,3-*O*-bis[(*E*)-16-fluoro-9-hexadecenoyl]-*rac*-glycerol (3) was prepared by the reaction of 200 mg (0.63 mmol) of recrystallized 1-*O*-hexadecyl-*rac*-glycerol (17) with 428 mg (1.57 mmol) of fluoro acid 8, 324 mg (1.57 mmol) of DCC, and 19 mg (0.16 mmol) of DMAP as described above for 1. Chromatography on Florisil with 5% ethyl acetate in hexanes afforded 309 mg (59%) of the alkylbis(fluoroacyl) lipid 3 (TLC, A, R_f 0.52) as a greasy solid melting at ~25 °C: IR (film) 1740 (C=O), 975 cm^{-1} (*trans*-HC=CH); NMR ($CDCl_3$) δ 5.38 (vinylic, br t, 3 Hz, 4 H), 5.20 (glyceryl H-2, m, 1 H), 4.38 ($-CH_2F$, dt, 48 Hz, 6 Hz, 4 H), 4.20 (glyceryl H-3, m, 2 H), 3.51 (glyceryl H-1, d, 5 Hz, 2 H), 3.42 (RCH_2O-, t, 6 Hz, 2 H), 2.34 ($-CH_2CO-$, t, 7 Hz, 4 H), 1.95 (allylic, m, 8 H), 0.90 ($-CH_3$, br t, 6 Hz, 3 H). Anal. Calcd for $C_{51}H_{94}O_5F_2$: C, 74.22; H, 11.48; F, 4.60. Found: C, 74.20; H, 11.67; F, 4.42.

Hexadecyl (*E*)-16-Fluorohexadec-9-en-1-yl Ether (21). To a solution potassium alkoxide of fluoro alcohol 9 (200 mg, 0.78 mmol) in refluxing benzene containing 10 mol % 18-crown-6 was added a solution of 285 mg (1 mmol) of recrystallized hexadecyl methanesulfonate in benzene. The mixture was refluxed overnight and worked up as usual to give a yellow oil. Chromatography over Florisil with 2% ethyl acetate–hexane gave 304 mg (87%) of a pale yellow waxy solid (mp 37–38 °C) which was a single spot by TLC (R_f 0.65): ^1H NMR δ 5.38 (vinylic, br t, 3 Hz, 2 H) 4.38 ($-CH_2F$, dt, 48 Hz, 6 Hz, 2 H), 3.38 ($-CH_2O-$, t, 6 Hz, 4 H), 1.94 (allylic, m, 4 H), 0.90 ($-CH_3$, br t, 6 Hz, 3 H).

Supplementary Material Available: Proton noise decoupled ^{13}C NMR spectra for the fluorolipids (1, 2, 3, 9, 15, 17, and 20) giving peak number, intensity, shift in hertz, and shift in parts per million (8 pages). Ordering information is given on any current masthead page.

LITERATURE CITED

Baumann, W. J. "Ether Lipids"; Snyder, F., Ed.; Academic Press: New York; 1972; pp 51–77.

Baumann, W. J.; Mangold, H. K. *J. Org. Chem.* **1964**, *29*, 3055–3059.

Beard, R. L. *Bull.—Conn. Agric. Exp. Stn., New Haven* **1974**, *No. 748*.

Buchnea, D. "Handbook of Lipid Research"; Kuksis, A., Ed.; Plenum Press: New York, 1978; Vol. 1, pp 233–287.

Cross, B. E.; Hendley, P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2523–2525.

Dear, R. E. A.; Pattison, F. L. M. *J. Am. Chem. Soc.* **1963**, *85*, 622–626.

Downer, R. G. H.; Matthews, J. R. *Am. Zool.* **1976**, *16*, 733–745.

Esenther, G. R.; Beal, R. H. *J. Econ. Entomol.* **1974**, *67*, 85–88.

Gilbert, L. I. *Adv. Insect Physiol.* **1967**, *4*, 69–211.

Gilbert, L. I.; Chino, H. *J. Lipid Res.*, **1974**, *15*, 439–456.

Goldman, P. *Science (Washintgon, D.C.)* **1969**, *164*, 1123–1129.

Hollingworth, R. M. "Insecticide Biochemistry and Physiology"; Wilkinson, C. F., Ed.; Plenum Press: New York, 1976; pp 431–506.

Jensen, R. G.; Pitas, R. E. *Adv. Lipid Res.* **1976**, *14*, 213–247.

Knox, L. H.; Velarde, E.; Berger, S.; Cuadriello, D.; Cross, A. D. *J. Org. Chem.* **1964**, *29*, 2187–2195.

Kun, E. "Biochemistry Involving Carbon-Fluorine Bonds"; Filler, R., Ed.; Americal Chemical Society: Washington, DC, 1976; pp 1–22.

Mangold, H. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 493–503.

Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524.

Pattison, F. L. M. "Toxic Aliphatic Fluorine Compounds"; Elsevier: Amsterdam and London, 1959.

Pattison, F. L. M.; Howell, W. C.; McNarmara, A. J.; Schneider, J. C.; Walker, J. F. *J. Org. Chem.* **1956a**, *21*, 739–747.

Pattison, F. L. M.; Hunt, S. B. D.; Stothers, J. B. *J. Org. Chem.* **1956b**, *21*, 883–886.

Peters, R. A. *Adv. Enzymol. Relat. Subj. Biochem.* **1957**, *18*, 113–159.

Peters, R. A. *Carbon-Fluorine Compd: Chem., Biochem. Biol. Act., CiBA Found. Symp., 1971* **1972**, 1–27.

Peters, R. A.; Hall, R. J.; Ward, P. F. V.; Sheppard, N. *Biochem. J.* **1960**, *77*, 17–23.

Prestwich, G. D.; Melcer, M.; Plavcan, K. *J. Agric. Food Chem.* **1981**, following paper in this issue.

Shani, A. *J. Chem. Ecol.* **1979**, *5*, 557–564.

Singh, A. N.; Mhaskar, V. V.; Dev, S. *Tetrahedron* **1978**, *34*, 595–598.

Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2924.

Received for review April 7, 1980. Revised manuscript received May 4, 1981. Accepted May 18, 1981. This work was supported in part by the University Awards Committee/Joint Awards Council of the State University of New York and the National Science Foundation (SPI-7827198 and DAR-7910321).