Synthesis and Characterisation of Selectively Fluorinated Stearic Acids (Octadecanoic Acids) and Their Tristearins: The Effect of Introducing One and Two Fluorine Atoms Into a Hydrocarbon Chain

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The synthesis and physical properties of 2,2',2"- and 12,12',12"-trifluorotristearins **2** and **3** and 12,12,12',12',12",12"-hexafluorotristearin **4** are described. NMR, X-ray powder diffraction, melting point and differential scanning calorimetry analyses of these compounds are reported and comparisons are drawn with tristearin **1**. Analysis of Langmuir film isotherms of the stearic acids gave the average area occupied by each molecule in a condensed monolayer and was used as a method to probe disorder in the hydrocarbon chains. Of the compounds studied, **3** possesses the closest behaviour to tristearin. The incorporation of a CF_2 group into the lipid chain in **4** imparts unique physical properties to the tristearin and a novel thermodynamically stable polymorphic form (β") is observed. This is attributed to a conformational change in the hydrocarbon chain induced by the CF_2 groups. Langmuir film analysis of the selectively fluorinated stearic acids (octadecanoic acids) **7** and **8** reinforce this conclusion.

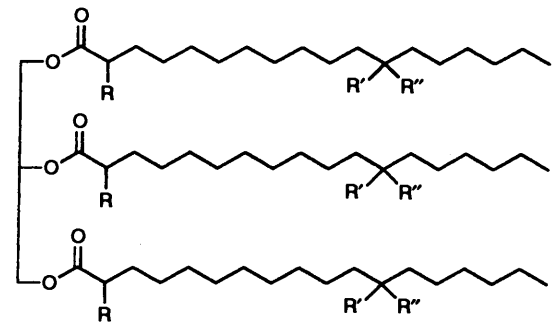
The selective replacement of hydrogen by fluorine is widely practised in bioorganic and medicinal chemistry.[1] It is generally perceived that fluorine exerts only a moderate steric influence relative to hydrogen in organic compounds,[2] but that the electronegativity of fluorine can have significant electronic influences. This has led, for example, to a central role for organofluorine compounds as mechanistically based inhibitors in enzymatic systems.[3] We have a general interest in probing the steric and stereoelectronic influence of fluorine in organic compounds[2a,4] and were attracted by the prospect of exploring the effect that one and two fluorine atoms will induce when placed in the middle of a hydrocarbon chain. The electronic influence of fluorine in such an environment should be minimised, and changes in the physical properties of such materials from their hydrocarbon counterparts would be expected to arise predominantly from induced steric, geometric and conformational changes. For this study we chose to assess the physical properties of selectively fluorinated stearic (octadecanoic) acids and tristearins. These and related lipids have been used as probes for investigations in biological systems using ^{19}F NMR as an analytical tool.[5] The fluorinated tristearins emerge as ideal candidates particularly as tristearins have complex polymorphic phases[6] which are susceptible to conformational changes and which can be monitored by a range of techniques, but particularly differential scanning calorimetry (DSC),[6] and X-ray powder diffraction.[6b] In this paper we outline the synthesis of three fluorinated stearic acids and their corresponding tristearins **2**–**4**. Langmuir films of the stearic acids **5**, **7** and **8**, and X-ray powder diffraction and differential scanning calorimetry (DSC) analyses of the tristearins **1**–**4** are reported. It is concluded that substitution of a single fluorine in the hydrocarbon chain induces only minor but perceptible perturbations and that substitution of a second geminal fluorine atom has a more dramatic influence on the conformation of the hydrocarbon chain and physical properties of the tristearin.

Results and Discussion

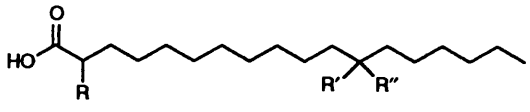
Our first synthetic target was 2,2',2"-trifluorotristearin **2**. 2-Fluorostearic acid **6**[7] was converted, *via* its acid chloride, to tristearin **2** after condensation with glycerol.[8] Tristearin **2** proved to have a lower melting point than tristearin (59 *c.f.* 72 °C). The proximity of the fluorine atoms to the glycerol unit maximise diastereoisomeric interactions and presumably also change the electronic profile of the molecule and therefore we reasoned that it would be more informative to move the fluorine atoms further along the chain. To this end we prepared 12,12',12"-trifluorotristearin **3**. Methyl (*R,S*) 12-hydroxystearate **9** was treated with diethylaminosulfur trifluoride (DAST)[9] to give a mixture of **10** and **11** (9:1). The minor eliminated component **11** was removed after ester hydrolysis, by recrystallisation of the resultant carboxylic acids to generate analytically pure 12-fluorostearic acid **7**. This was then converted to the corresponding tristearin **3**. 12,12',12"-Trifluorotristearin **3** had a similar melting point (73 °C) to tristearin **1** and, as expected, substitution by fluorine at the 12-position over the 2-position has a less pronounced effect on the properties of the material.

To extend the study and assess the effect of two fluorines in the hydrocarbon chain, 12,12,12',12',12",12"-hexafluorotristearin **4** was prepared. Thus oxidation of **9** with pyridinium chlorochromate[10] generated methyl 12-ketostearate **12** and then treatment of this ketone with sulfurtetrafluoride and hydrogen fluoride[11] afforded methyl 12,12-difluorostearate **13**, which was isolated in moderate yield after chromatography. Hydrolysis of this ester gave the carboxylic acid **8** which was then coupled with glycerol to generate the required tristearin **4**. This material has a significantly lower melting point than tristearin (57.7 *c.f.* 72 °C) and clearly the introduction of the second fluorine atom is of some consequence. The melting points of the stearic acids and the tristearins are collated in Table 1 for comparison.

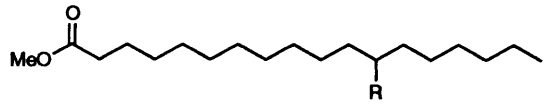
X-Ray Powder Diffraction Analysis and Differential Scanning Calorimetry (DSC) Studies of Tristearin and the Fluorinated Analogues.—Fig. 1 shows the X-ray powder diffraction patterns of the prepared fluorinated tristearins and compares them directly with tristearin. All of the samples were prepared in a similar manner by recrystallisation from light petroleum (boiling fraction 40–60 °C). The α, β and β' polymorphic forms



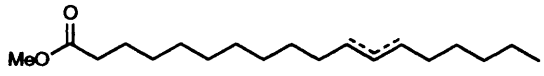
1 R = R′ = R″ = H
2 R = F, R′ = R″ = H
3 R = R′ = H, R″ = F
4 R = H, R′ = R″ = F



5 R = R′ = R″ = H
6 R = F, R′ = R″ = H
7 R = R′ = H, R″ = F
8 R = H, R′ = R″ = F



9 R = OH
10 R = F



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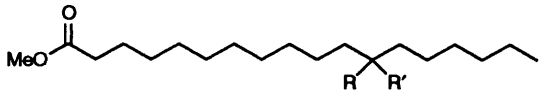
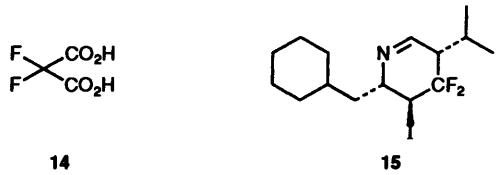


12 R, R′ = O
13 R = R′ = F



14 15

Table 1 Melting points of stearic acid, tristearin and their fluorinated analogues

	Stearic acid	Mp/°C	Tristearin	Mp/°C
Stearate	**5**	69	**1**	72
2-Fluorostearate	**6**	89	**2**	59
12-Fluorostearate	**7**	72.5	**3**	73
12,12-Difluorostearate	**8**	73.7	**4**	57.7

of tristearin are well defined and the data in Fig. 1, accumulated for tristearin, is entirely consistent with the more stable β-polymorph.[6,12] It is evident that 12,12′,12″-fluorotristearin **3** has a similar diffraction pattern to tristearin itself, indicating that the lipid chains are similarly orientated in the β-form in the solid state. Therefore a single fluorine substitution at a central

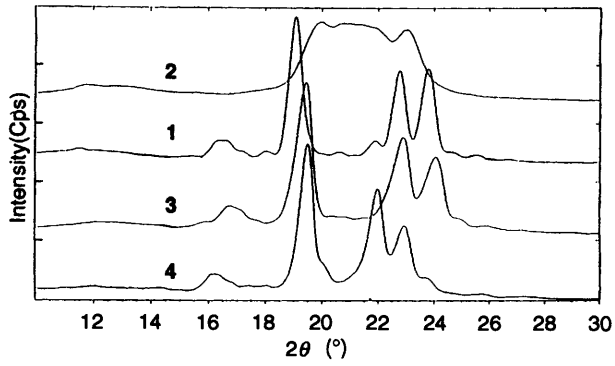


Fig. 1 X-Ray powder diffraction patterns of tristearin **1** and the fluorinated tristearins **2–4**

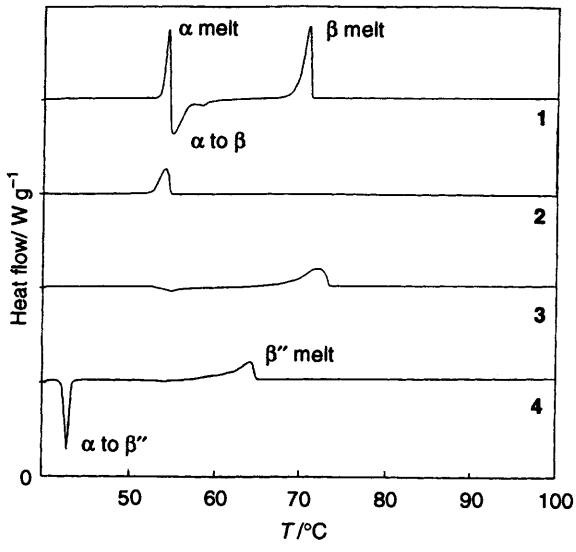


Fig. 2 Differential scanning calorimetry (DSC) thermogrammes of tristearin **1** and the fluorinated tristearin analogues **2–4**

position of the lipid chain has not significantly altered the solid state properties of the material. On the other hand for 12,12,12′,12′,12″,12″-hexafluorotristearin **4** there has been a shift in the d-spacing from 24° (2θ) to 22° (2θ) in the X-ray powder diffraction pattern. It is noteworthy that the melting point of **4** is significantly lower than tristearin (see Table 1) and the combined data clearly suggest a difference in molecular packing in this system. It should be noted that under the conditions used to prepare this sample the thermodynamically most stable polymorph of **4** will be generated, and clearly the presence of the CF_2 groups in the chain is dictating some conformational reorganisation in this lowest energy state (termed β″). 2-Fluorotristearin **2** is highly disordered in the solid state and the X-ray data is uninformative. For all of the samples **1–4** melting and cooling resulted in a single wide angle reflection [21.5° (2θ), data not shown] consistent with their conversion to the α-form, which is classic behaviour for tristearin and other triglycerides.[8,12]

Fig. 2 illustrates DSC thermogrammes of tristearin **1** and the fluorinated tristearins **2–4**. Prior to analysis the samples were heated to 100 °C and then cooled (5 °C min^{-1}) to solid such that they all had an identical thermal history. This treatment should ensure that the samples crystallise in their α-forms. The samples were then reheated at 1.3 °C min^{-1} and the data accumulated. Tristearin exhibits classic behaviour. The α-form melts (endotherm) at 55 °C followed closely by an α to β phase transition (exotherm) and then finally the β-form melts (endotherm) at 72 °C. It is clear that for the three fluorinated samples, 12,12′,12″-trifluorotristearin **3** most closely resembles

Table 2 Surface area per molecule extrapolated to zero surface pressure ($\Pi = 0$) for long chain molecules studied

		Area per molecule/nm^2
Stearic acid	**5**	0.21 ± 0.01
12-Fluorostearic acid	**7**	0.23 ± 0.01
12,12-Difluorostearic acid	**8**	0.255 ± 0.005; and 0.108 ± 0.005

tristearin in its melting behaviour. 2,2′,2″-Trifluorotristearin **2** appears only to have a melting point with no obvious polymorphic phase behaviour. 12,12,12′,12′,12″,12″-Hexafluorotristearin **4** on the other hand has a unique thermogramme with a very clear exotherm at 44 °C corresponding to a well defined phase transition. From the X-ray powder diffraction data we concluded that **4** adopts a novel thermodynamically stable form (termed β″). The DSC thermogramme is consistent with this analysis where the exotherm at 44 °C corresponds to the α to β″ phase transition. Therefore these two complementary techniques reinforce each other and force a similar conclusion.

Langmuir Films of Fluorinated Stearic Acids.—In order to investigate the effect of fluorine substitution at C-12 of stearic acid, and to probe the conformational mobility of the hydrocarbon chain induced by the CF_2 group, Langmuir films of the fluorinated stearic acids **7** and **8** were studied. The equipment and experimental procedures for measuring surface pressure *versus* area isotherms have been described previously.[13] The materials were dissolved in dichloromethane to a concentration of approximately 1 g l^{-1} and applied to the subphase surface using a microsyringe. The isotherms were recorded on a purified water subphase adjusted to pH 4.8 ± 1 with HCl, 20 ± 2 °C, compression rate (3.0 ± 0.2) × 10^{-3} nm^2 molecules^{-1} s^{-1}. Following compression, the floating monolayers were expanded and then recompressed to check for reproducibility.

Both stearic acid **5** and the 12-fluorostearic acid **7** showed condensed pressure *versus* area curves. The areas per molecule, measured by extrapolating the steeply rising portion of the isotherm to zero pressure, are compared in Table 2. It is evident that the incorporation of the fluorine atom has resulted in a small increase in the area occupied by each molecule. The isotherm for 12,12-difluorostearic acid **8** is somewhat unusual and is shown in Fig. 3. On the first compression a surface pressure *versus* area curve similar to 12-fluorostearic acid **7** was measured, but with an increased area per molecule (0.255 ± 0.005 nm^2). On recompression, a plateau region was observed. Further compressions resulted in a similar isotherm to that measured initially; however, the area per molecule was now considerably smaller (0.108 ± 0.005 nm^2). The constant pressure plateau region in the isotherm in Fig. 1 is reminiscent of the expanded to condensed phase change noted in many long-chain fatty acid materials.[14] However in our case the final stabilised area per molecule is much less than that expected from a monolayer film. Our current rationale is that the monolayer is unstable due to a combination of adverse steric effects and conformational defects in the hydrocarbon chains containing the CF_2 groups, and on the second compression undergoes a transition to a thermodynamically more stable bilayer. The disorder induced by the CF_2 groups may allow some interdigitation of the alkyl chains, accounting for the area per molecule being slightly less than one half that of the monolayer. It is interesting to contrast the effect of the CF_2 group with that of a methyl side group near the middle of the hydrocarbon chain.[15] In the latter case, expanded isotherms are generally measured with the molecular area of the lowest

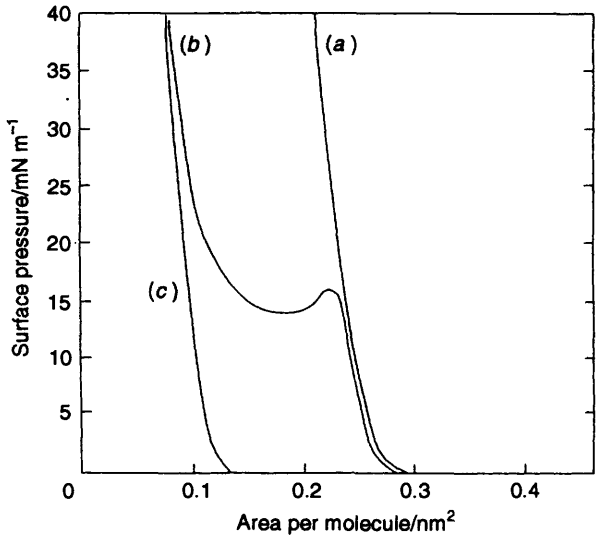


Fig. 3 Langmuir isotherms for 12,12-difluorostearic acid **8** showing condensed pressure *versus* area curves for three successive compressions: (*a*) first; (*b*) second; (*c*) third compression

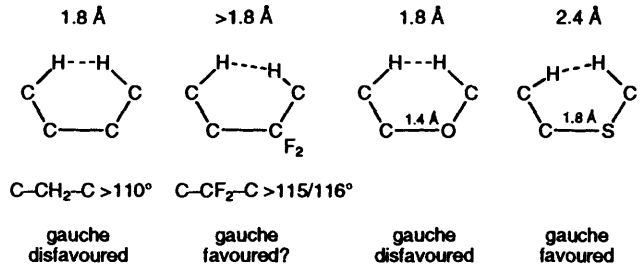


Fig. 4 Schematic representation of 1,4-hydrogen interactions in gauche conformations and the preference for gauche over anti zig-zag as the preferred conformation (see text)

measurable pressure being 0.44–0.48 nm^2. The disorder in the CF_2 systems is therefore considerably less.

Discussion

The above data for tristearins clearly indicate that replacement of hydrogen by a single fluorine at the 12-positions has a small effect on the physical properties of the tristearin whereas the introduction of a second geminal fluorine atom is more dramatic. Such a phenomenon has been noted previously with selectively fluorinated dipalmitoylphosphatidylchloline.[5c] The origin of this phenomenon appears to be conformational and may lie in the difference between the C–CH_2–C and C–CF_2–C bond angles. The size of the C–CF_2–C angle in a lipid chain is not known definitively, however theoretical *ab initio* analyses predict[16] that the C–CF_2–C angle is significantly wider, and the F–C–F bond narrower, than tetrahedral. A screen of the Cambridge Crystallographic Data Base revealed only seven structures[17] which possess a C–CF_2–C motif. The compounds are structurally diverse and the C–CF_2–C angles vary considerably ranging from 111°, for difluoromalonic acid **14**,[17d] to 119.9° in **15**. Conversely, the FCF angles in these structures range from 104.2, in **15**, to 107° in fluoromalonic acid **14**. Clearly the hybridisation (sp^3 or sp^2) of the carbon atoms adjacent to the CF_2 group, and the degree of strain in the system, influences the extent to which the C–CF_2–C bond widens. However from an assessment of the structures[17] it can be deduced that the C–CF_2–C angle in the chain will be at least 115–116 °C and possibly wider.

The widening of the C–CF_2–C angle should accommodate increased gauche conformations on the hydrocarbon chain.

Hydrocarbon chains predominantly adopt an *anti* zig-zag conformation as the gauche conformations introduce steric interactions between the 1,4-hydrogens in the chain. Similarly when an ether oxygen is introduced into a hydrocarbon chain the gauche conformation, shown in Fig. 4, is disfavoured as the 1,4-hydrogens come too close (1.8 Å) together.[18] This is also evident from X-ray structure data of crown ethers and has been widely discussed in this arena.[19,20a] On the other hand when a sulfur atom is introduced into a chain, the chain will adopt a gauche conformation[20] as the increased C–S bond length of 1.8 Å, over that for C–C (1.5 Å) or C–O (1.4 Å), increases the 1,4-hydrogen distance to 2.4 Å, similar to the sum of the van der Waals radii of the hydrogen atoms. Such an argument can be extended to CF_2 substitution in a hydrocarbon chain. The widening of the C–CF_2–C angle (115–116°) over the C–CH_2–C angle (110°) will result in an increase in the distance between the 1,4-hydrogen atoms and lower the energy of attainment of the gauche conformation as illustrated in Fig. 4. Clearly if a significant population of the chains adopt such a conformation in the crystalline β″ phase of tristearin **4**, then this would account for the distinct X-ray powder diffraction pattern and DSC thermogramme of **4**. Similarly for the Langmuir film study, the largest area per molecule for 12,12-difluorostearic acid, and the instability of the monolayer, is consistent with a population of non-linear chains.

In summary this study has established that the introduction of a CF_2 group into the central region of a long hydrocarbon chain will induce conformational changes which can alter the physical properties of a material from its hydrocarbon counterpart. In this respect CF_2 is less than an ideal CH_2 mimic for biochemical applications.

Experimental

IR spectra were recorded on Perkin-Elmer F.T. 1720X or 1600 spectrometers. Low resolution mass spectra were recorded on a VG Analytical 7070E Organic mass spectrometer. Chemical ionisation utilised NH_3 as the carrier gas. Solution state NMR spectra were recorded on Varian VXR 400(S) (^1H at 399.952 MHz, ^{13}C at 100.577 MHz and ^{19}F at 376.289 MHz) and Bruker AMX-500 (^1H at 500.13 MHz and ^{13}C at 125.77 MHz) spectrometers. Chemical shifts are quoted relative to TMS ($\delta = 0$) for ^1H and ^{13}C in $CDCl_3$. Petrol refers to light petroleum boiling fraction 40–60 °C. DSC measurements were performed on a Perkin-Elmer DSC 7 differential scanning calorimeter. The heating and cooling scans were recorded at a heating rate of 1.3 °C min^{-1} and isothermal crystallisation processes were studied by recording the heat flow as a function of time. M.p.s were measured on a Gallenkamp melting apparatus and are not corrected. All solvents were dried over $MgSO_4$. Powder X-Ray diffraction measurements were performed using a Siemens D 5000 diffractometer equipped with K71OH earthed anode (X-ray tube FK60–04 × 12), run at 40 mA/40 kV, and a scintillation counter. Monochromatic Cu-Kα (1.54 Å) radiation was obtained by a Ni-Kβ filter. Samples (2 mm thick) were placed onto a sample holder. The measurements were recorded between zero to 30 ° (2θ) with a counting time of 12 s each 0.02° (2θ).

12-*Fluorostearic* (12-*Fluorooctadecanoic*) *Acid* **7**.—A solution of (*R*,*S*)-methyl 12-hydroxystearate (12-fluorooctadecanoate) **9** (11.6 g, 37 mmol) in dichloromethane (30 cm^3) was added slowly to a solution of diethylaminosulfur trifluoride (4 g, 24.6 mmol) in dichloromethane (50 cm^3) at −78 °C over 10 min. The reaction mixture was left to warm to ambient temperature and was quenched by the addition of water (30 cm^3). The organic layer was separated from the aqueous, washed with 5% $NaHCO_3$ solution and the solvent dried and removed. The residue was purified over silica gel eluting with hexane–diethyl ether (95:5) to give a mixture (8.2 g) containing methyl 12-fluorostearate (12-fluorooctadecanoate) **10** and **11** (10%). These were separated after hydrolysis of the mixture with 5% potassium hydroxide in methanol (25 cm^3), and then acidification. Crystallization from methanol furnished 12-fluorostearic acid **7** (6.6 g, 90%) as a white amorphous solid. Mp 72.5 °C (lit.,[21] 76 °C); δ_H 0.88 (3 H, t, *J* 14, CH_3), 1.2–1.7 (22 H, m, methylenes), 2.3 (2 H, t, *J* 14, CH_2CO_2) and 4.45 (1 H, dm, *J* 47, CHF); δ_C 14.07, 22.58, 24.65, 25.07, 25.09, 25.11, 25.14, 29.03, 29.18, 29.20, 29.37, 29.46, 29.48, 31.74, 33.95, 34.5 (d, *J* 21.7), 94.6 (d, *J* 166) and 179.69; δ_F 192.34 (m); *m*/*z* CI 320.44 (+17) (13%), 300.45 (72%), 283.39 (55%) (Found: C, 71.6; H, 11.61%. $C_{18}H_{35}O_2$ requires C, 71.4; H, 11.5%).

Methyl 12-*Ketostearate* (12-*Oxooctadecanoate*) **12**.—Pyridinium chlorochromate (14.6 g, 63 mmol) was added to a solution of methyl 12-hydroxystearate **9** (13.5 g, 42 mmol) in dichloromethane (200 cm^3) and the reaction allowed to stir at 20 °C for 4 h. The dark reaction solution was filtered directly over neutral alumina and the alumina column washed with two additional volumes (100 cm^3) of dichloromethane. Removal of the solvent gave the title compound after recrystallisation from petrol, **12** (11.8 g, 88%) as an amorphous white solid. Mp 44.6 °C (lit.,[22] 44.5 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 3096, 2098, 1736 (COO), 1704 (CO), 1430 and 1215; δ_H 0.89 (3 H, t, *J* 14, CH_3), 1.2–1.4 (22 H, methylenes), 2.2–2.4 (6 H, t, *J* 14, CH_2CO) and 3.6 (3 H, s, OCH_3).

12,12-*Difluorostearic* (12,12-*Difluorooctadecanoic*) *Acid* **8**.—Tetrafluorothiane (9 g, 83 mmol) and liquid hydrogen fluoride (0.8 g, 40 mmol) were added by vacuum transfer to a solution of methyl 12-ketostearate **12** (9 g, 28 mmol) in dichloromethane (30 cm^3) at −78 °C in a steel bomb, and the vessel was heated at 110 °C for 24 h. After venting the gases through an aqueous solution of potassium hydroxide the vessel was opened, the organic layer was washed successively with 5% $NaHCO_3$ solution (20 cm^3) and water (20 cm^3) and dried. After solvent removal the dark residue was purified over silica gel, eluting with hexane–diethyl ether (95:5) to afford methyl 12,12-difluorostearate (12,12-difluorooctadecanoate) **13** (4 g, 11.9 mmol) as a low melting solid. The ester was hydrolysed by heating in a solution of potassium hydroxide in methanol (5%, 20 cm^3) for 4 h and the reaction acidified with dil. HCl. The acid was extracted into chloroform, dried and the solvent removed. Recrystallisation from warm petrol gave the title acid **8** (3.8 g, 42%) as a white amorphous solid. Mp 73.7 °C; δ_H 0.88 (3 H, t, *J* 14, Me), 1.2–1.9 (22 H, 2 m, methylenes) and 2.3 (2 H, t, *J* 14, CH_2CO_2H); δ_C 14.02, 22.25, 22.30, 22.33, 22.49, 24.63, 29.02, 29.07, 29.19, 29.34, 29.38, 31.58, 34.06, 36.01, 36.03, 36.28 (d, *J* 25.2), 125.45 (t, *J* 240) and 180.33; *m*/*z* CI 338 (+17) (97.54%), 320, 319, 299, 298 and 223 (Found: $M^+ + NH_4$, 338.2831. $C_{18}H_{38}NF_2O_2$ requires 338.2871).

Preparation of the Fluorostearoyl (*Fluorooctadecanoyl*) *Chlorides*.—2-Fluorostearoyl (2-fluorooctadecanoyl) chloride was obtained from 2-fluorostearic (2-fluorooctadecanoic) acid **6**[7] after treatment with thionyl chloride (2.5 equiv.) at 80 °C for 6 h. The excess of thionyl chloride was removed under reduced pressure and the acid chloride recovered as a colourless liquid by distillation (140 °C, 2 mmHg). 12-Fluoro- and 12,12-difluorostearoyl (-octadecanoyl) chlorides were prepared by stirring the corresponding acids with oxalyl chloride (4 equiv.) at room temperature for 24 h, followed by heating under reflux for 4 h. The excess oxalyl chloride was removed under reduced pressure. The residue was resuspended in hexane (10 volumes) and the solution washed with cold water (3 × 20 cm^3) and then dried. Removal of the solvent gave the crude acid chlorides (90% yield)

as colourless low melting solids. These materials were used directly for the synthesis of their corresponding tristearins following the general method described below.

Preparation of the Tristearins **2–4**. *General Method.*—A solution of the appropriate acid chloride (3 g, 9.4 mmol) in chloroform (50 cm^3) was added to a mixture of glycerol (0.29 g, 3.1 mmol), triethylamine (8 g, 9.4 mmol) and dimethylaminopyridine (DMAP) (90 mg, 0.7 mmol) in chloroform (40 cm^3) at 20 °C. The reaction was heated under reflux for 24 h and then the solution diluted with 20 volumes of 1:1 mixture of petrol–diethyl ether and washed twice with water (20 cm^3), dil. HCl (20 cm^3) and then water (20 cm^3). The organic extract was then dried and the solvent removed. Crystallisation from warm petrol gave the appropriate tristearins (> 80%) as white amorphous solids.

2,2′,2″-*Trifluorotristearin* (*Propane*-1,2,3-*triyl Tris*(2-*fluorooctadecanoate*) **2**. Mp 59 °C. $\nu_{max}(CHCl_3)/cm^{-1}$ 3019, 2926, 2854, 1765, 1466, 1215, 1092, 760 and 699; δ_H 0.88 (9 H, t, *J* 14, CH_3), 1.2–1.7 (90 H, m, methylenes), 4.1–4.3 (4 H, m, CH_2O), 4.4–4.6 (3 H, m, CHF) and 5.3 (1 H, m, CHO); δ_F −192 m; δ_C 14.1, 22.7, 24.4, 29.1–29.7 (multiplet, CH_2s), 31.9, 32.3, 32.4, 62.5, 69.6, 88.7 (d, *J* 180), 169.34 (d, *J* 24) and 169.47 (d, *J* 25); *m*/*z* CI 963 (+18) (14.4%), 643, 487, 385 and 359 (Found: C, 72.3; H, 11.4. $C_{57}H_{107}F_3O_6$ requires C, 72.34; H, 11.3%).

12,12′,12″-*Trifluorotristearin* (*Propane*-1,2,3-*triyl Tris*(12-*fluorooctadecanoate*) **3**. Mp 73 °C. $\nu_{max}(CHCl_3)/cm^{-1}$ 3018, 2929, 1736, 1466, 1215, 1092, 758 and 668.9; δ_H 0.88 (9 H, t, CH_3), 1.2–1.7 (90 H, methylenes), 2.3 (6 H, t, *J* 14, CH_2CO), 4.1–4.6 (7 H, m, CH_2O and CHF) and 5.3 (1 H, m, CHO); δ_C 14.1, 14.16, 22.6, 22.7, 24.8, 24.9, 25.1, 25.15, 25.2, 29.0–29.7 (multiplet, CH_2s), 31.7, 31.9, 34.0, 34.2, 35.1 (d, *J* 20.9), 62.1, 68.8, 94.6 (d, *J* 167), 172.8 and 173.3; δ_F −180 (m); *m*/*z* 962 (+17) (11%), 945 (6), 603, 339, 265 and 95 (Found: C, 72.24; H, 11.7. $C_{57}H_{107}F_3O_6$ requires C, 72.34; H, 11.3%).

12,12,12′,12′,12″,12″-*Hexafluorotristearin* (*Propane*-1,2,3-*triyl Tris*(12,12-*difluorooctadecanoate*) **4**. Mp 57.7 °C. $\nu_{max}(CHCl_3)/cm^{-1}$ 3018, 2929, 1736, 1466, 1215, 1092, 758 and 668.9; δ_H 0.88 (9 H, t, *J* 14, Me), 1.2–1.9 (84 H, methylenes), 2.3 (6 H, t, *J* 14, CH_2CO), 4.1–4.3 (4 H, m, CH_2O) and 5.3 (1 H, m, CHO); δ_C 14.01, 22.3, 22.32 (t, *J* 3.4), 24.8, 24.9, 29.0–29.7 (multiplet, CH_2s), 31.6, 33.9, 34.2, 36.3 (t, *J* 25.2), 62.1, 68.8, 125.41 (t, *J* 240), 172.8 and 173.2; *m*/*z* CI 1016 (+17) (100%), 679, 639, 565, 418, 377, 338, 263 and 171; δ_F −97.6 (m) (Found: C, 68.22; H, 10.5. $C_{57}H_{104}F_6O_6$ requires C, 68.4; H, 10.4%).

Note.—The monofluorinated compounds were all prepared in racemic form. **CAUTION** compounds **2**, **3**, **6**, **7** and **10** are highly toxic as they are metabolised to fluoroacetyl-CoA.

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