Syntheses of some polyunsaturated trifluoromethyl ketones as potential phospholipase A_2 inhibitors

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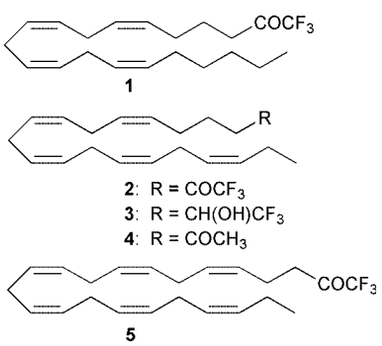
Starting from (all-*Z*)-icosa-5,8,11,14,17-pentaenoic acid [(all-*Z*)-eicosa-5,8,11,14,17-pentaenoic acid, EPA] and (all-*Z*)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA) several trifluoromethyl ketones, containing sulfur or oxygen atoms at the β-position, have been synthesized as potential inhibitors of cytosolic phospholipase A_2. As part of this work EPA and DHA have been oxidatively degraded to (all-*Z*)-pentadeca-3,6,9,12-tetraenal and (all-*Z*)-octadeca-3,6,9,12,15-pentaenal, respectively, in 75% overall yields.

Introduction

The enzyme cytosolic phospholipase A_2 ($cPLA_2$) catalyzes the release of arachidonic acid and other polyunsaturated fatty acids from the *sn*-2 position of glycerophospholipids. It seems that the release of arachidonic acid from glycerophospholipids is the rate limiting step in the biosynthesis of eicosanoids and consequently, the inhibition of $cPLA_2$ will strongly affect the formation of this group of compounds.[1] Eicosanoids like prostaglandins, leukotrienes, thromboxanes and prostacyclins are involved in many adverse biochemical reactions in humans, connected with pain, inflammation, allergy and blood platelet aggregation.[2]

Several structurally different compounds have been reported as inhibitors of $cPLA_2$. We were particularly interested in the trifluoroketone **1**, derived from arachidonic acid, which is a



potent inhibitor of human $cPLA_2$.[3,4] The carbonyl carbon of **1** is strongly electrophilic due to the adjacent trifluoromethyl group, forming the hydrate in the presence of water. The inhibitory effect is most likely due to a hemiketal, formed from interaction of the carbonyl group with the hydroxy group of a serine amino acid, present at the active site of $cPLA_2$.[5] Hence, the inhibitor **1** probably acts as a transition state analogue, in very much the same way as related ketones are believed to inhibit other esterases and proteases.[5] In a previously published study[6] we converted (all-*Z*)-icosa-5,8,11,14,17-pentaenoic acid (EPA) to the trifluoroacetyl derivative **2** in 70% overall yield, essentially by the same procedure as that used for the preparation of **1** from arachidonic acid. According to the ^{1}H NMR spectrum the reaction product consisted of compound **2**, isolated as a mixture containing mainly the ketone with only a minor part as the corresponding hydrate. The compound exhibited an *in vitro* inhibitory effect on $cPLA_2$ comparable to that of the analogue **1**, while the alcohol **3**[6] was quite inactive in the same test system, indicating that the trifluoroacetyl moiety is essential for the inhibitory activity of compound **2**. This result is in complete agreement with those previously observed for similar derivatives of compound **1**.[3,4] It seems reasonable to assert that the extent of hydrate formation would reflect the inhibitory power of such trifluoromethyl ketones towards $cPLA_2$. Hence, we aimed at the synthesis of related trifluoroketones containing a more electrophilic carbonyl carbon than that of compound **2**. The present paper describes research towards this goal.

Results and discussion

We first prepared the ketone **4** by reaction of EPA with methyllithium; as expected it was devoid of any inhibitory effect on $cPLA_2$. In order to obtain information about the influence of an extended lipophilic residue on the desired biological activity, the trifluoroacetyl derivative **5** was prepared from (all-Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA) by the same protocol as that used for the preparation of the analogue **2**; the acid chloride from DHA was treated with trifluoroacetic anhydride in the presence of pyridine to give compound **5** in 59% overall yield.[7] The compound exhibited only low inhibitory activity in the PLA_2 test system, indicating that a chain length of 23 atoms and the degree of unsaturation are not optimal structural features for an inhibitory effect on $cPLA_2$. According to the ^{19}F NMR spectra the hydrate component of both compounds **2** and **5** was only 1–2%, which contrasts the >90% reported by Street *et al.* for an aqueous micellar solution of compound **1**.[4] The discrepancy is not surprising since our measurement was made in chloroform and an equilibrium between the two forms had not been reached. As expected the ratios of hydrate to ketone for a particular compound showed poor reproducibility. The hydrate component of the product mixtures caused some problems during the chromatographic purification, which led inevitably to lower yields. Furthermore, the polyunsaturated compounds reported in the present paper were generally quite unstable, particularly towards oxygen. However, they can be stored unchanged for several months frozen in benzene at −20 °C.

Replacement of the methylene group β to the carbonyl group of the ketone **2** with either oxygen or sulfur atoms should stabilize the hydrate form by intramolecular hydrogen bonding and there is strong support for such an assumption in the literature.[8] The preparation of the sulfur analogue **6** could be achieved by either reaction of (all-*Z*)-1-bromoocta-3,6,9,12,15-pentaene[9]

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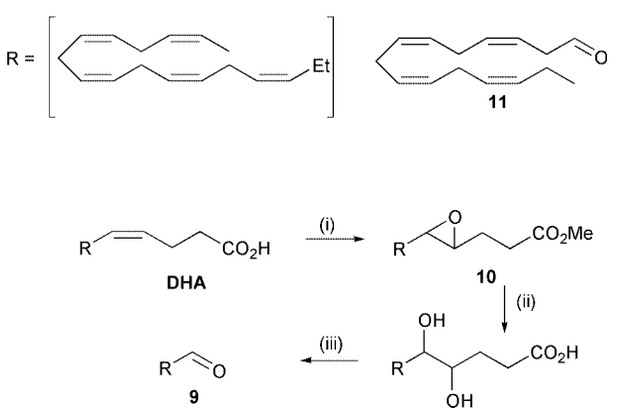
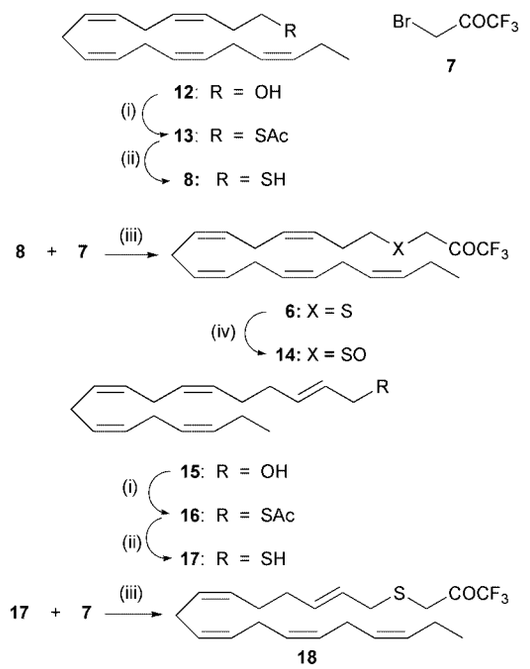
with 3-mercapto-1,1,1-trifluoropropan-2-one or reaction of 3-bromo-1,1,1-trifluoropropan-2-one (**7**) with the appropriate thiol **8**. The latter appeared to be the strategy of choice because the halide **7** is commercially available, and moreover, attempts to transform the halide to the corresponding thiol by displacement of bromide with thiourea were unsuccessful. Hence, a route to the thiol **8** was sought, and the C-18 aldehyde **9** seemed a convenient starting material. We had previously prepared this aldehyde in about 30% overall yield by selectively degrading (all-*Z*)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA) using the iodolactone protocol of Corey;[9] however, the yield was certainly not satisfactory. The reactions leading to the intermediate epoxide **10** proceeded almost quantitatively, but the subsequent oxidative cleavage of the epoxide with periodic acid suffered from byproduct formation as well as poor reproducibility. The problem was solved by first opening the epoxide ring to the diol, using formic acid in the presence of acetic anhydride, followed by oxidative cleavage with sodium periodate. This change of protocol resulted in a considerable improvement and the aldehyde **9** was obtained in a reproducible 75% overall yield from DHA; by the same procedure EPA was converted to the corresponding C-15 aldehyde **11** in a similar overall yield. Good yields of these aldehydes certainly render the degradation approach to derivatives of EPA and DHA more competitive with total synthesis. Furthermore, the transformations occurred without any detectable stereoisomerization of the double bonds (Scheme 1).



Scheme 1 *Reagents and conditions*: i, I_2, KI, $KHCO_3$, THF–H_2O; K_2CO_3, MeOH, rt; ii, HCO_2H, Ac_2O, rt; LiOH, MeOH–H_2O; iii, $NaIO_4$, MeOH–H_2O.

Reduction of the aldehyde **9** with sodium borohydride afforded the alcohol **12** (Scheme 2).[9] We were unable to convert the alcohol directly to the thiol using the Lawesson reagent.[10] However, the alcohol was transformed by a Mitsunobu type reaction to the thioester **13**, which was subsequently reduced with LAH to the desired thiol **8** in 73% overall yield. As expected, in the presence of sodium bicarbonate the thiol **8** displaced bromide from the bromoketone **7**, furnishing the trifluoroacetyl derivative **6** in 65% yield. A small amount of the disulfide corresponding to the thiol **8** was also isolated by chromatography. Compound **6** exhibited IR absorption bands at 1740 and 3430 cm^{-1} indicating the presence of both the ketone and its hydrate. According to signals at −76.3 and −85.9 ppm in the ^{19}F NMR spectrum, the keto and hydrate forms were present in a ratio of 1 : 3, respectively. The corresponding sulfoxide **14** was prepared from the sulfide by oxidation with *m*-chloroperbenzoic acid and was formed predominantly as the hydrate; no carbonyl absorption was observed in the IR spectrum, which indicated strong intramolecular hydrogen bonding of the hydrate hydroxy to the sulfoxide oxygen. According to the ^{19}F NMR spectrum the ratio between the two forms was 1 : 28 in favour of the hydrate.

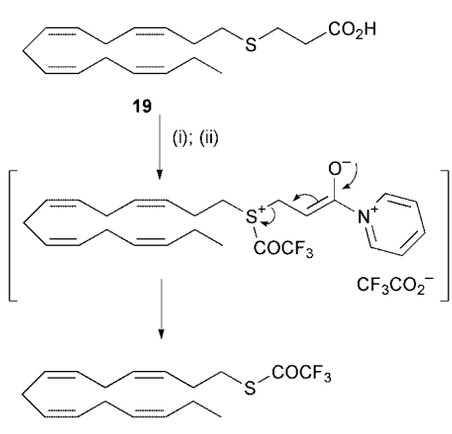
We have previously shown that the aldehyde **9** isomerizes quantitatively to the α,β-unsaturated aldehyde in the presence



Scheme 2 *Reagents and conditions*: i, DIAD, Ph_3P, HSAc, THF, 0 °C–rt; ii, LAH, Et_2O; iii, $NaHCO_3$, EtOH–H_2O, rt; iv, MCPBA, $CHCl_3$, −20 °C.

of DBU,[9] and subsequent reduction with sodium borohydride gave the alcohol **15**. The latter was transformed to the thiol **17** by the same method used for the preparation of the thiol **8**. Reaction of **17** with the bromoketone **7** gave the ketone **18** in 71% yield. In this case a 1 : 2 mixture of the ketone and hydrate was obtained as shown by the ^{19}F NMR spectrum (Scheme 2).

It was of interest to prepare a trifluoroacetyl derivative with a sulfur atom at the γ-position from the carbonyl group. The acid **19**[9] was available to us and seemed a convenient starting material. The reaction of the acid with oxalyl chloride proceeded normally, but further treatment with trifluoroacetic anhydride in pyridine furnished in 62% yield the trifluorothioacetic ester derivative **20** containing one carbon fewer than the starting material. Clearly a fragmentation had taken place and the formation of **20** is rationalized in Scheme 3. The crucial step

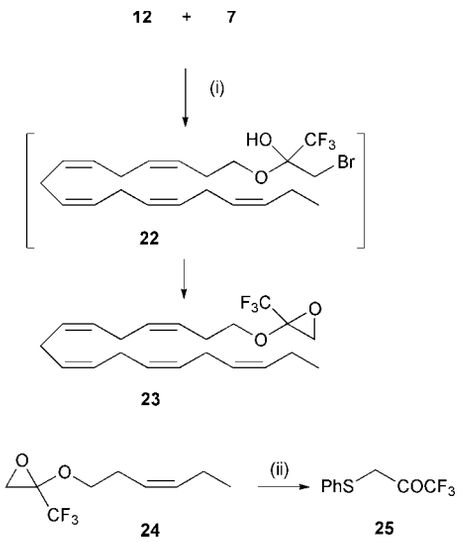


Scheme 3 *Reagents and conditions*: i, $(COCl)_2$, CH_2Cl_2, rt; ii, TFAA, pyridine, CH_2Cl_2, 0 °C–rt.

is a preferred reaction of the anhydride with the sulfur atom forming a sulfonium intermediate, which subsequently undergoes the depicted fragmentation.

The synthesis of the β-oxaketone **21** proved to be more complicated. The Williamson reaction of the alcohol **12** with the bromoketone **7** failed under a variety of conditions. At first this was surprising since kinetic data show that α-haloketones are

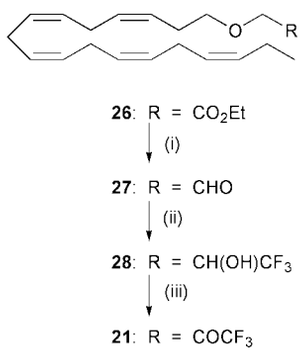
quite reactive in nucleophilic substitution reactions.[11] We assume that the alkoxide from **12** reacted preferentially with the bromoacetone derivative at the carbonyl carbon forming the oxyanion of the corresponding hemiacetal **22**. Under our conditions the anion apparently failed to react further to the epoxide **23**, since quenching with water resulted only in recovery of the alcohol **12**. However, reacting the alcohol with the bromoketone **7** in dichloromethane as solvent and in the presence of silver oxide gave the epoxide **23** (Scheme 4),



Scheme 4 *Reagents and conditions*: i, Ag_2O, CH_2Cl_2, rt; ii, NaH, PhSH, Et_2O, rt.

although in only 41% yield; obviously the silver oxide promoted the 1,3-elimination by assisting the bromide as leaving group. In order to study the reactivity of this type of epoxide with oxy and thioanions we prepared as a model substance the oxirane derivative **24** from hex-3-en-1-ol and the bromoacetone **7** by the silver-assisted displacement reaction. The epoxide **24** proved to be quite unreactive towards alkoxides, but with thiophenoxide the trifluoroketone **25** was obtained in 67% yield; the same compound was the only product from the reaction of **7** with thiophenoxide.[12] Bégué and co-workers have reported the successful ring opening of similar epoxy ethers with thiols[13] and amines,[14] but it is interesting to note that sodium azide required very special conditions for reaction to take place.[15] However, reactions of the epoxy ethers with alkoxides have so far produced complex mixtures.[16] Apparently alkoxides are not sufficiently nucleophilic for reaction to occur under our conditions, and therefore we abandoned this approach towards the preparation of compound **21**.

Several attempts to prepare the target compound using different fluorinating reagents[17] on a variety of substrates were futile. As a last resort we turned to the oxaester **26**, which we had prepared previously.[9] The direct conversion of this ester to **21** using (trifluoromethyl)trimethylsilane[18] was unsuccessful, and the corresponding acid chloride failed to react with trifluoroacetic anhydride in pyridine as well. The latter reaction most probably proceeds through an intermediate alkoxyketene, the formation of which is apparently not favoured in the present case. On the other hand, when the ester **26** was first reduced with DIBAL-H to the aldehyde **27**, the reaction of the latter with (trifluoromethyl)trimethylsilane proceeded to the alcohol **28** in 75% yield (Scheme 5).[18] Subsequent oxidation with periodinane, the Dess–Martin reagent, afforded the desired trifluoroketone **21** in good yield; the absence of carbonyl absorption and the presence of a strong broad band due to the OH stretching vibration at 3448 cm^{-1} in the IR spectrum showed that the compound was formed essentially as the hydrate. The NMR spectra confirm this assignment and the ^{19}F NMR spectrum indicates a 30 : 1 ratio of hydrate to ketone.



Scheme 5 *Reagents and conditions*: i, DIBAL-H, hexane, −78 °C; ii, TMS-CF_3, TBAF, THF, 0 °C; iii, Dess–Martin oxidation reagent, rt.

In conclusion, the trifluoroketones **6**, **14**, **18** and **21** have been prepared as potential inhibitors of $cPLA_2$; preliminary biological testing indicates that compounds **14** and **18** in particular are potent inhibitors of the enzyme.[19] The test results will be reported elsewhere in due course.

Experimental

The NMR spectra were recorded in $CDCl_3$ with a Bruker Avance DPX 200 instrument, a Bruker Avance DPX 300 instrument or with a Bruker Avance DRX 500 instrument. $CDCl_3$ was used as solvent, and $CFCl_3$ was used as reference for the ^{19}F NMR spectra. *J* values are given in Hz. The IR spectra were obtained with a Perkin-Elmer 1310 infrared spectrophotometer or a Nicolet Magna-IR 550 spectrometer. Mass spectra were recorded at 70 eV with a Fisons VG Pro spectrometer. All reactions were performed under nitrogen or argon atmospheres.

(all-*Z*)-Henicosa-6,9,12,15,18-pentaen-2-one 4

Methyllithium (1.2 ml, 1.9 mmol) was added to a stirred solution of (all-*Z*)-icosa-5,8,11,14,17-pentaenoic acid (EPA, 250 mg, 0.83 mmol) in 100 ml of dry ether kept at −78 °C. The solution was stirred for 1 h at this temperature and then slowly warmed to room temperature. After additional stirring for 2 h, the mixture was poured into ice and extracted with hexane. The extract was washed with brine and water and dried ($MgSO_4$). Evaporation of solvents under reduced pressure and purification by flash chromatography on silica gel (7 : 3 hexane–EtOAc) gave *ketone* **4** (120 mg, 48%) as an oil. ν_{max} (film)/cm^{-1} 3010, 2960, 1715; δ_H(200 MHz) 0.93 (3 H, t, *J* 7.5, CH_3), 1.6 (2 H, m, H-4), 1.9–2.1 (4 H, m, H-5, H-20), 2.08 (3 H, s, H-1), 2.39 (2 H, t, *J* 7.4, H-3), 2.7–2.9 (8 H, m, 4 × CH_2), 5.2–5.5 (10 H, m, 10 × CH=); δ_C(50 MHz) 14.17 (CH_3), 20.46, 23.45, 25.44, 26.40 (4 × CH_2), 25.53 (3 × CH_2), 29.80 (C-1), 42.87 (C-3), 126.91, 127.76, 127.98, 128.01, 128.12, 128.14, 128.45, 128.61, 129.09, 131.91 (10 × CH=), 208.67 (C-2); *m*/*z* (EI) 300 (M^+, 9%), 271, 79 (100) (HRMS: found: M^+ 300.2456. $C_{21}H_{32}O$ requires 300.2453).

(all-*Z*)-1,1,1-Trifluorotricosa-5,8,11,14,17,20-hexaen-2-one 5

To a solution of (all-*Z*)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA; 2.5 g, 7.6 mmol) in dry CH_2Cl_2 (150 ml) was added oxalyl chloride (756 μl, 8.8 mmol). The reaction mixture was stirred at 20 °C for 3 h. Solvent and excess oxalyl chloride were removed by distillation under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (150 ml), cooled to 0 °C, and TFAA (5.8 ml, 41.1 mmol) and pyridine (4.2 ml, 52.0 mmol) were added. The cooling bath was removed, and after 1.5 h at room temperature the reaction mixture was poured into water. The layers were separated and the aqueous phase extracted with CH_2Cl_2. The extract was washed with water and dried ($MgSO_4$). Evaporation of solvents under reduced pressure followed by

flash chromatography on silica gel (95 : 5 hexane–EtOAc) gave the *ketone* **5** (1.7 g, 59%) as an oil; 1–2% of the product consisted of the *hydrate*. ν_{max} (film)/cm^{-1} 3511, 3014, 2966, 1765, 1653, 1206, 1145; δ_H(200 MHz) 0.95 (3 H, t, *J* 7.5, CH_3), 2.05 (2 H, m, H-22), 2.44 (2 H, m, H-4), 2.7–2.9 (12 H, m, 6 × CH_2), 5.2–5.5 (12 H, m, 12 × CH=); δ_C(75 MHz) 14.18 (CH_3), 25.60 (3 × CH_2), 20.25, 20.51, 25.49, 25.54, 36.29 (5 × CH_2), 115.49 (q, J_{CF} 290, CF_3), 128.27 (2 × CH=), 126.47, 126.98, 127.65, 127.82, 127.94, 127.99, 128.47, 128.54, 130.27, 131.98 (10 × CH=), 190.79 (q, J_{CCF} 35, *C*(O)CF_3); δ_F(188 MHz) −79.8 (*ketone*), −86.9 (*hydrate*); *m/z* (EI) 380 (M^+, 1%), 311, 244, 204, 79 (100) (HRMS: found: M^+ 380.2348. $C_{23}H_{31}OF_3$ requires 380.2327).

(all-*Z*)-Octadeca-3,6,9,12,15-pentaenal 9

A solution of methyl (all-*Z*)-4,5-epoxydocosa-7,10,13,16,19-pentaenoate (**10**)[9] (2.0 g, 5.6 mmol) in formic acid (60 ml) and acetic anhydride (6 ml) was stirred at room temperature overnight. Evaporation of the volatile components under reduced pressure gave a residue, which was dissolved in methanol (40 ml) and cooled to 0 °C. A solution of LiOH (1.2 g, 28 mmol) in water (40 ml) was added. The slurry was stirred at room temperature overnight, neutralised (5% HCl) and extracted with ether. The extract was washed with water and the ether evaporated under reduced pressure. The residue was dissolved in methanol (50 ml), cooled to 0 °C and a solution of sodium periodate (1.8 g, 8.4 mmol) in water (15 ml) was added. The mixture was stirred for 1.5 h, diluted with water and the product extracted with hexane. The extract was washed successively with saturated $NaHCO_3$, brine and water and was then dried ($MgSO_4$). Evaporation of solvents under reduced pressure gave the *aldehyde* **9** (1.24 g, 86%) as an oil. The spectral data were in agreement with those of the literature.[9]

(all-*Z*)-Pentadeca-3,6,9,12-tetraenal 11

A solution of methyl (all-*Z*)-5,6-epoxyicosa-8,11,14,17-tetraenoate[9] (2.0 g, 6.0 mmol) in formic acid (60 ml) and acetic anhydride (6 ml) was stirred at room temperature overnight. Volatile compounds were evaporated under reduced pressure and the residue was dissolved in methanol (60 ml), and K_2CO_3 (1.2 g, 8.6 mmol) was added. After stirring for 3 h at ambient temperature water was added and the product extracted with ether. The extract was washed with water and the ether evaporated. The residue was dissolved in methanol (50 ml), cooled to 0 °C and a solution of sodium periodate (2 g, 9.0 mmol) in water (15 ml) was added. The mixture was stirred for 1.5 h, diluted with water and the product extracted with hexane. The extract was washed with water, dried ($MgSO_4$) and the solvents evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (1 : 1 hexane–EtOAc) to give the *aldehyde* **11** (1.16 g, 88%) as an oil. The spectral data were in agreement with those of the literature.[9]

(all-*Z*)-3-Thiahenicosa-6,9,12,15,18-pentaen-2-one 13

Diisopropyl azodicarboxylate (DIAD) (3.0 ml, 15.5 mmol) was added to a stirred solution of triphenylphosphine (4.0 g, 15.2 mmol) in THF (40 ml) at 0 °C, and the mixture was stirred at this temperature for 30 min. A solution of (all-*Z*)-octadeca-3,6,9,12,15-pentaen-1-ol (**12**)[9] (2.0 g, 7.7 mmol) and thioacetic acid (1.1 ml, 15.4 mmol) in THF (20 ml) then was added dropwise over 10 min. The mixture was stirred for 1 h at 0 °C and for an additional hour at ambient temperature. The mixture was concentrated and purified by flash chromatography on silica gel (hexane to 95 : 5 hexane–EtOAc) to give the *thioacetic ester* **13** (2.0 g, 82%) as an oil. ν_{max} (film)/cm^{-1} 3012, 2964, 1693, 1133; δ_H(200 MHz) 0.94 (3 H, t, *J* 7.5, CH_3), 2.04 (2 H, m, H-20), 2.2–2.4 (2 H, m, H-5), 2.28 (3 H, s, H-1), 2.6–2.9 (10 H, m, 4 × CH_2, H-4), 5.2–5.5 (10 H, m, 10 × CH=); δ_C(50 MHz) 14.15 (CH_3), 25.51 (2 × CH_2), 20.44, 25.42, 25.59, 27.19, 28.86 (5 × CH_2), 30.48 (CO*C*H_3), 126.90, 127.15, 127.73, 127.80, 127.91, 128.13, 128.17, 128.41, 129.91, 131.85 (10 × CH=), 195.51 (C-2); *m/z* (EI) 318 (M^+, 0.5%), 275, 43 (100) (HRMS: found: M^+ 318.2028. $C_{20}H_{30}SO$ requires 318.2017).

(all-*Z*)-Octadeca-3,6,9,12,15-pentaene-1-thiol 8

A solution of the thioester **13** (1.8 g, 5.7 mmol) in dry ether (20 ml) was added dropwise to a suspension of LAH (228 mg, 6.0 mmol) in dry ether (10 ml). The mixture was stirred for 2 h at ambient temperature. Excess LAH was destroyed by careful addition of 1 M HCl. The organic layer was separated and dried ($MgSO_4$). Evaporation of the ether under reduced pressure followed by flash chromatography on silica gel (98 : 2 hexane–EtOAc) gave the *thiol* **8** (1.4 g, 89%) as an oil. ν_{max} (film)/cm^{-1} 3012, 2963, 1433; δ_H(200 MHz) 0.95 (3 H, t, *J* 7.5, CH_3), 1.41 (1 H, t, *J* 7.5, SH), 2.05 (2 H, m, 17-H), 2.3–2.5 (2 H, m, CH_2), 2.5–2.7 (2 H, m, CH_2), 2.7–2.9 (8 H, m, 4 × CH_2), 5.2–5.5 (10 H, m, 10 × CH=); δ_C(50 MHz) 14.22 (CH_3), 25.59 (2 × CH_2), 20.51, 24.43, 25.50, 25.77, 31.55 (5 × CH_2), 126.95, 127.26, 127.79, 127.90, 127.97, 128.25, 128.27, 128.52, 130.12, 131.96 (10 × CH=); *m/z* (EI) 276 (M^+, 17%), 79 (100) (HRMS: found: M^+ 276.1924. $C_{18}H_{28}S$ requires 276.1912).

(all-*Z*)-1,1,1-Trifluoro-4-thiadocosa-7,10,13,16,19-pentaen-2-one 6

A mixture of the thiol **8** (650 mg, 2.4 mmol) and $NaHCO_3$ (420 mg, 5 mmol) in ethanol (15 ml) and water (10 ml) was stirred for 10 min at ambient temperature before addition of the bromoketone **7** (311 µl, 3.0 mmol). After stirring overnight the mixture was extracted with ether. The extract was washed with brine and water, and dried ($MgSO_4$). Evaporation of solvents under reduced pressure followed by flash chromatography on silica (9 : 1 hexane–EtOAc) gave compound **6** (600 mg, 65%) as an oil consisting of a 1 : 3 mixture of *ketone* and *hydrate*, as determined by ^{19}F NMR. ν_{max} (film)/cm^{-1} 3430, 3005, 2960, 1740, 1185; δ_H(300 MHz) *ketone*: 0.96 (3 H, t, *J* 7.5, CH_3), 2.06 (2 H, m, H-21), 2.37 (2 H, m, H-6), 2.55 (2 H, t, *J* 7.3, H-5), 2.7–2.9 (8 H, m, 4 × CH_2), 3.49 (2 H, s, H-3), 5.2–5.6 (10 H, m, 10 × CH=); *hydrate*: 0.96 (3 H, t, *J* 7.5, CH_3), 2.06 (2 H, m, H-21), 2.37 (2 H, m, H-6), 2.75 (2 H, t, *J* 7.4, H-5), 2.7–2.9 (8 H, m, 4 × CH_2), 2.90 (2 H, s, H-3), 4.00 (2 H, s, OH), 5.2–5.6 (10 H, m, 10 × CH=); δ_C(75 MHz) mixture of *ketone* and *hydrate*: 14.19 (CH_3), 20.50, 25.49, 25.58, 25.60, 25.67, 25.69, 26.52, 27.13, 31.68, 33.30, 34.73, 36.42, 92.40 (q, J_{CCF} 32, *C*(OH)$_2$-CF_3), 126.84, 126.97, 127.10, 127.70, 127.79, 127.95, 128.31, 128.40, 128.42, 128.56, 130.09, 130.18, 132.00, 185.02 (q, J_{CCF} 35, *C*(O)CF_3); δ_F(188 MHz) −76.3 (*ketone*), −85.9 (*hydrate*); *m/z* (EI) 386 (M^+, 1%), 317, 275, 79 (100) (HRMS: found: M^+ 386.1883. $C_{21}H_{29}OF_3S$ requires 386.1891).

A small amount of *bis[(all-Z)-octadeca-3,6,9,12,15-pentaenyl] disulfide* was also isolated. ν_{max} (film)/cm^{-1} 3012, 2963, 1441; δ_H(200 MHz) 0.96 (3 H, t, *J* 7.5, CH_3), 1.9–2.1 (2 H, m, CH_2), 2.3–2.6 (2 H, m, CH_2), 2.70 (2 H, t, *J* 7.5, SCH_2), 2.6–2.9 (8 H, m, 4 × CH_2), 5.2–5.6 (10 H, m, 10 × CH=); δ_C(50 MHz) 14.22 (CH_3), 25.57 (2 × CH_2), 20.50, 25.48, 25.71, 27.00 (4 × CH_2), 38.41 (SCH_2), 128.22 (2 × CH=), 126.94, 127.29, 127.77, 127.87, 127.95, 128.49, 129.68, 131.92 (8 × CH=); *m/z* (EI) 550 (M^+, 1%), 275, 79 (100) (HRMS: found: M^+ 550.3685. $C_{36}H_{54}S_2$ requires 550.3667).

3-[(all-*Z*)-Octadeca-3,6,9,12,15-pentaenylsulfinyl]-1,1,1-trifluoropropan-2-one 14

To a solution of the sulfide **6** (60 mg, 0.16 mmol) in $CHCl_3$ (2 ml) kept at −20 °C was added a solution of MCPBA (55 mg, 0.16 mmol) in $CHCl_3$ (2 ml). After stirring for 2 h at this temperature, the mixture was filtered and immediately added to a

saturated, aqueous solution of $NaHCO_3$. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and purification of the residue by flash chromatography on silica gel (7:3 hexane–EtOAc) afforded the *sulfoxide* **14** (50 mg, 75%) as a waxy liquid consisting of a 1:28 mixture of *ketone* and *hydrate*, as determined by ^{19}F NMR. *Hydrate*: ν_{max} (ATR)/cm^{-1} 3334, 3117, 3013, 2964, 1264, 1175; δ_H(500 MHz) 0.94 (3 H, t, *J* 7.5, CH_3), 2.04 (2 H, m, H-21), 2.56 (2 H, m, H-6), 2.7–2.9 (9 H, m, H-5, 4 × CH_2), 3.0–3.2 (3 H, m, H-3, H-5′), 5.25–5.45 (9 H, m, 9 × CH=), 5.46–5.55 (1 H, m, CH=), 5.90 (1 H, br s, OH), 6.44 (1 H, br s, OH); δ_C(126 MHz) 14.23 (CH_3), 20.32 (C-6), 20.52 (C-21), 25.49, 25.58, 25.60, 25.61 (4 × CH_2), 50.18 (C-3), 52.71 (C-5), 94.09 (q, J_{CCF} 34, $C(OH)_2CF_3$), 121.62 (q, J_{CF} 285, CF_3), 125.09, 126.96, 127.25, 127.77, 127.82, 128.41, 128.59, 128.80, 131.55, 132.04 (10 × CH=); δ_F(188 MHz) −79.5 (*ketone*), −87.5 (*hydrate*); *m*/*z* (EI) 402 (M^+, 1%), 385, 299, 79 (100) (HRMS: found: M^+ 402.1837. $C_{21}H_{29}O_2F_3S$ requires 402.1840).

(5*E*,9*Z*,12*Z*,15*Z*,18*Z*)-3-Thiahenicosa-5,9,12,15,18-pentaen-2-one 16

Reaction of (2*E*,6*Z*,9*Z*,12*Z*,15*Z*)-octadeca-2,6,9,12,15-pentaen-1-ol (**15**)[9] with DIAD, triphenylphosphine and thioacetic acid as described for the preparation of **13** gave the *thioacetic ester* **16** (84%) as an oil. ν_{max} (film)/cm^{-1} 3012, 2964, 1694, 1133; δ_H(200 MHz) 0.95 (3 H, t, *J* 7.5, CH_3), 2.0–2.2 (6 H, m, H-7, H-8 and H-20), 2.29 (3 H, s, H-1), 2.7–2.9 (6 H, m, 3 × CH_2), 3.46 (2 H, d, *J* 6.9, H-4), 5.2–5.9 (10 H, m, 10 × CH=); δ_C(50 MHz) 14.22 (CH_3), 20.51, 25.49, 25.58, 25.62, 26.78, 31.34, 32.14 (7 × CH_2), 30.42 (C(O)*C*H_3), 124.92, 126.98, 127.86, 128.05, 128.20, 128.26, 128.47, 129.10, 131.96, 133.79 (10 × CH=), 195.31 (CO); *m*/*z* (EI) 318 (M^+, 0.5%), 275, 43 (100) (HRMS: found: M^+ −43, 275.1830. $C_{18}H_{27}S$ requires 275.1833).

(2*E*,6*Z*,9*Z*,12*Z*,15*Z*)-Octadeca-2,6,9,12,15-pentaene-1-thiol 17

Reduction of the thioester **16** with LAH as described for **8** gave the *thiol* **17** (79%) as an oil. ν_{max} (film)/cm^{-1} 3012, 2963, 1433; δ_H(200 MHz) 0.95 (3 H, t, *J* 7.5, CH_3), 1.38 (1 H, t, *J* 7.5, SH), 1.9–2.2 (6 H, m, H-4, H-5 and H-17), 2.7–2.9 (6 H, m, 3 × CH_2), 3.0–3.2 (2 H, m, H-1), 5.2–5.5 (8 H, m, 4 × *Z*-CH=CH), 5.5–5.6 (2 H, m, *E*-CH=CH); δ_C(50 MHz) 14.23 (CH_3), 20.52, 25.50, 25.59, 25.65, 26.77, 26.88, 31.98 (7 × CH_2), 126.98, 127.86, 128.07, 128.19, 128.26, 128.48, 129.15, 129.51, 131.26, 131.97 (10 × CH=); *m*/*z* (EI) 276 (M^+, 0.6%), 243, 79 (100) (HRMS: found: M^+ 276.1908. $C_{18}H_{28}S$ requires 276.1912).

(6*E*,10*Z*,13*Z*,16*Z*,19*Z*)-1,1,1-Trifluoro-4-thiadocosa-6,10,13,16,19-pentaen-2-one 18

Reaction of **17** with bromide **7** as described for **6** gave the *ketone* **18** (71%) as a waxy solid, consisting of a 1:2 mixture of ketone and hydrate as determined by ^{19}F NMR. ν_{max} (film)/cm^{-1} 3430, 2990, 2950, 1740, 1180; δ_H(200 MHz) *ketone*: 0.96 (3 H, t, *J* 7.5, CH_3), 1.9–2.2 (6 H, m, H-8, H-9, H-21), 2.7–2.9 (6 H, m, 3 × CH_2), 3.07 (2 H, d, *J* 7.1, H-5), 3.43 (2 H, s, H-3), 5.2–5.8 (10 H, m, 10 × CH=), *hydrate*: 0.96 (3 H, t, *J* 7.5, CH_3), 1.9–2.2 (6 H, m, H-8, H-9, H-21), 2.7–2.9 (8 H, m, 3 × CH_2, H-3), 3.24 (2 H, d, *J* 7.0, H-5), 3.82 (2 H, s, OH), 5.2–5.8 (10 H, m, 10 × CH=); δ_C(50 MHz) mixture of *ketone* and *hydrate*: 14.16 (CH_3), 20.47, 25.45, 25.53, 25.59, 26.78, 26.83, 32.10, 32.17, 32.69, 33.44, 34.39, 34.84, 92.55 (q, J_{CCF} 32, $C(OH)_2CF_3$), 124.02, 124.73, 126.84, 127.78, 127.82, 128.04, 128.10, 128.37, 128.46, 128.96, 128.99, 131.95, 135.16, 135.58, 185.31 (q, J_{CCF} 35, $C(O)CF_3$); δ_F(188 MHz) −76.7 (ketone), −86.0 (hydrate); *m*/*z* (EI) 386 (M^+, 2%), 275, 79 (100) (HRMS: found: M^+ 386.1913. $C_{21}H_{29}OF_3S$ requires 386.1891).

(all-*Z*)-1,1,1-Trifluoro-3-thiaoctadeca-6,9,12,15-tetraen-2-one 20

Reaction of (all-*Z*)-4-thianonadeca-7,10,13,16-tetraenoic acid (**19**)[9] with oxalyl chloride, TFAA and pyridine as described for the preparation of **5** gave the *thioester* **20** (62%) as an oil. ν_{max} (film)/cm^{-1} 3015, 2966, 1708, 1284, 1206, 1166; δ_H(200 MHz) 0.96 (3 H, t, *J* 7.5, CH_3), 2.06 (2 H, m, H-17), 2.43 (2 H, m, H-5), 2.7–2.9 (6 H, m, 3 × CH_2), 3.07 (2 H, t, *J* 7.3, H-4), 5.2–5.5 (8 H, m, 8 × CH=); δ_C(50 MHz) 14.17 (CH_3), 20.51, 25.49, 25.57, 25.63, 26.34, 29.09 (6 × CH_2), 115.54 (q, J_{CF} 289, CF_3), 128.62 (2 × CH=), 125.85, 126.90, 127.37, 127.63, 131.26, 131.99 (6 × CH=), 184.74 (q, J_{CCF} 40, $C(O)CF_3$); δ_F(188 MHz) −75.4 (ketone); *m*/*z* (EI) 332 (M^+, 2%), 276, 79 (100) (HRMS: found: M^+ 332.1429. $C_{17}H_{23}OF_3S$ requires 332.1422).

(all-*Z*)-3-Oxa-2-trifluoromethyl-1,2-epoxyhenicosa-6,9,12,15,18-pentaene 23

A mixture of the bromoketone **7** (140 μl, 1.3 mmol), the alcohol **12** (250 mg, 1.0 mmol) and Ag_2O (334 mg, 1.4 mmol) in dry CH_2Cl_2 was stirred at room temperature for 15 h. The product was isolated by filtration of the reaction mixture through a plug of silica. Evaporation of solvents under reduced pressure gave the *epoxide* **23** (150 mg, 41%) as an oil. ν_{max} (film)/cm^{-1} 3014, 2965, 1329, 1195; δ_H(200 MHz) 0.96 (3 H, t, *J* 7.5, CH_3), 2.06 (2 H, m, H-20), 2.37 (2 H, m, H-5), 2.7–2.9 (8 H, m, 4 × CH_2), 3.07 (1 H, d, *J* 3.7, H-1), 3.1–3.2 (1 H, m, H′-1), 3.5–3.8 (2 H, m, H-4), 5.2–5.5 (10 H, m, 10 × CH=); δ_C(50 MHz) 14.18 (CH_3), 20.50 (C-20), 25.57 (2 × CH_2), 25.48, 25.65 (2 × CH_2), 27.59 (C-5), 48.88 (q, J_{CCCF} 2, C-1), 65.96 (C-4), 79.92 (q, J_{CCF} 40, C-2), 121.26 (q, J_{CF} 278, CF_3), 127.80 (2 × CH=), 124.58, 126.95, 127.95, 128.26, 128.31, 128.53, 130.69, 131.97 (8 × CH=); δ_F(188 MHz) −78.3 (br s); *m*/*z* (EI) 370 (M^+, 0.5%), 79 (100) (HRMS: found: M^+ 370.2109. $C_{21}H_{29}O_2F_3$ requires 370.2120).

(*Z*)-3-Oxa-2-trifluoromethyl-1,2-epoxynon-6-ene 24

The reaction of (*Z*)-hex-3-en-1-ol with the bromoketone **7** as described for **23** gave the *epoxide* **24** (44%) as an oil. ν_{max} (film)/cm^{-1} 3017, 2967, 1328, 1195; δ_H(200 MHz) 0.95 (3 H, t, *J* 7.5, CH_3), 2.03 (2 H, m, H-8), 2.37 (2 H, m, H-5), 3.06 (1 H, d, *J* 3.7, H-1), 3.1–3.2 (1 H, m, H′-1), 3.5–3.8 (2 H, m, H-4), 5.2–5.5 (2 H, m, 2 × CH=); δ_C(50 MHz) 14.09 (CH_3), 20.58 (CH_2), 27.48 (CH_2), 48.87 (q, J_{CCCF} 2, C-1), 66.18 (C-4), 79.98 (q, J_{CCF} 40, C-2), 121.30 (q, J_{CF} 278, CF_3), 123.35, 134.62 (2 × CH=); δ_F(188 MHz) −78.8 (br s); *m*/*z* (EI) 210 (M^+, 4%), 181, 55 (100) (HRMS: found: M^+ 210.0856. $C_9H_{13}O_2F_3$ requires 210.0868).

1,1,1-Trifluoro-3-phenylthiopropan-2-one 25

Sodium hydride (40 mg, 60% dispersion in mineral oil, 1.0 mmol) was washed twice with dry hexane, suspended in dry ether and cooled in ice before benzenethiol (102 μl, 1.0 mmol) was added. The mixture was stirred for 30 min at room temperature before addition of the epoxide **23** (200 mg, 0.95 mmol). After 1 h at room temperature the mixture was quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with ether. The extract was washed with brine and dried ($MgSO_4$). Evaporation of ether under reduced pressure followed by flash chromatography on silica gel (6:4 hexane–EtOAc) gave compound **25** (140 mg, 67%) as an oil consisting of a 5:3 ratio of *ketone* and *hydrate,* as determined by ^{19}F NMR. ν_{max} (film)/cm^{-1} 3451, 3062, 2979, 1749, 1440, 1180; δ_H(200 MHz) *ketone*: 3.84 (2 H, s, CH_2), 7.1–7.4 (5 H, m, ArH), *hydrate*: 3.34 (2 H, s, CH_2), 3.96 (2 H, s, OH), 7.1–7.4 (5 H, m, ArH); δ_C(50 MHz) 39.10 (*C*C(O)CF_3), 39.91 (*C*C-$(OH)_2CF_3$), 92.47 (q, J_{CCF} 32, $C(OH)_2CF_3$), 127.42, 128.35, 129.21, 129.33, 130.29, 131.87 (ArC), 185.06 (q, J_{CCF} 35, *C*OCF_3); δ_F(188 MHz) −76.6 (*ketone*), −85.6 (*hydrate*); *m*/*z*

(EI) 220 (M^+, 67%), 123 (100) (HRMS: found: M^+ 220.0170. $C_9H_7OF_3S$ requires 220.0170).

(all-*Z*)-3-Oxahenicosa-6,9,12,15,18-pentaenal 27

DIBAL-H (1.6 ml, 1.6 mmol) was added to a solution of ethyl (all-*Z*)-3-oxahenicosa-6,9,12,15,18-pentaenoate (**26**)[9] (500 mg, 1.4 mmol) in dry hexane (10 ml) at −78 °C. The solution was stirred for 1.5 h at this temperature before quenching with 1 M HCl (3 ml). When the reaction mixture had reached ambient temperature, the organic layer was separated, and the aqueous phase extracted with ether. The extract was washed with brine and dried ($MgSO_4$). Evaporation of solvents followed by flash chromatography on silica gel (8:2 hexane–EtOAc) gave the *aldehyde* **27** (390 mg, 90%) as an oil. ν_{max} (film)/cm^{-1} 3455, 3013, 2964, 1738, 1126; δ_H(200 MHz) 0.95 (3 H, t, *J* 7.5, CH_3), 2.05 (2 H, m, H-20), 2.39 (2 H, m, H-5), 2.7–2.9 (8 H, m, 4 × CH_2), 3.53 (2 H, t, *J* 6.8, H-4), 4.04 (2 H, s, H-2), 5.2–5.5 (10 H, m, 10 × CH=), 9.70 (1 H, s, C(O)H); δ_C(50 MHz) 14.22 (CH_3), 25.58 (2 × CH_2), 20.51, 25.49, 25.69, 27.76, 71.47, 76.27 (6 × CH_2), 128.25 (2 × CH=), 125.36, 126.95, 127.80, 127.90, 127.97, 128.53, 130.24, 131.98 (8 × CH=), 200.84 (C(O)H); *m*/*z* (EI) 302 (M^+, 0.6%), 79 (100) (HRMS: found: M^+ 302.2240. $C_{20}H_{30}O_2$ requires 302.2246).

(all-*Z*)-1,1,1-Trifluoro-4-oxadocosa-7,10,13,16,19-pentaen-2-ol 28

To a solution of the aldehyde **27** (300 mg, 0.99 mmol) and TMS-CF_3 (176 µl, 1.19 mmol) in THF (12 ml) cooled to 0 °C, TBAF (100 µl, 0.1 mmol) was added. After 1 h at room temperature, HCl (5%, 2 ml) was added and the reaction mixture was stirred for another 10 min. The mixture was poured into water and extracted with ether. The extract was washed with brine and dried ($MgSO_4$). Evaporation of the ether under reduced pressure followed by flash chromatography on silica gel (8:2 hexane–EtOAc) gave the *alcohol* **28** (280 mg, 75%) as an oil. ν_{max} (film)/cm^{-1} 3423, 3014, 2962, 1274, 1176, 1146; δ_H(300 MHz) 0.95 (3 H, t, *J* 7.5, CH_3), 2.06 (2 H, m, H-21), 2.38 (2 H, m, 6-H), 2.7–2.9 (8 H, m, 4 × CH_2), 3.28 (1 H, d, *J* 6.3, OH), 3.52 (2 H, dt, *J* 6.8, *J* 1.4, H-5), 3.56–3.69 (2 H, m, H-3), 4.11 (1 H, m, H-2), 5.2–5.5 (10 H, m, 10 × CH=); δ_C(75 MHz) 14.18 (CH_3), 25.59 (2 × CH_2), 20.51, 25.50, 25.66, 27.62 (4 × CH_2), 68.91 (q, J_{CCCF} 2, C-3), 69.32 (q, J_{CCF} 31, *C*(OH)CF_3), 71.32 (C-5), 125.77, 127.38, 128.21, 128.28, 128.36, 128.67, 128.71, 128.94, 130.72, 132.38 (10 × CH=); δ_F(188 MHz) −78.3 (d, *J* 7.0); *m*/*z* (EI) 372 (M^+, 2%), 276, 236, 79 (100) (HRMS: found: M^+ 372.2221. $C_{21}H_{31}O_2F_3$ requires 372.2276).

(all-*Z*)-1,1,1-Trifluoro-4-oxadocosa-7,10,13,16,19-pentaen-2-one 21

The alcohol **28** (85 mg, 0.23 mmol) was added to a stirred solution of periodinane (Dess–Martin reagent; 344 mg, 0.81 mmol) in CH_2Cl_2 at room temperature. The mixture was stirred for 1 h, diluted with ether, and poured into a saturated aqueous $NaHCO_3$ solution (20 ml) containing $Na_2S_2O_3$ (893 mg, 3.6 mmol). After stirring for 15 min the organic phase was separated and the aqueous phase was extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine and then dried ($MgSO_4$). Evaporation of the ether followed by flash chromatography on silica gel (7:3 hexane–EtOAc) gave compound **21** (55 mg, 65%) as an oil consisting of a 1:30 mixture of *ketone* and *hydrate* as determined by ^{19}F NMR. ν_{max} (film)/cm^{-1} 3448, 3014, 2965, 1185, 1120; δ_H(200 MHz) *ketone*: 0.95 (3 H, t, *J* 7.5, CH_3), 2.06 (2 H, m, 21-H), 2.39 (2 H, m, 6-H), 2.7–2.9 (8 H, m, 4 × CH_2), 3.55 (2 H, t, *J* 6.8, 5-H), 4.50 (2 H, s, 3-H), 5.2–5.5 (10 H, m, 10 × CH=), *hydrate*: 0.95 (3 H, t, *J* 7.5, CH_3), 2.06 (2 H, m, H-21), 2.39 (2 H, m, H-6), 2.7–2.9 (8 H, m, 4 × CH_2), 3.62 (2 H, d, *J* 0.4, H-3), 3.64 (2 H, t, *J* 6.7, H-5), 4.00 (2 H, br s, OH), 5.2–5.5 (10 H, m, 10 × CH=); δ_C(50 MHz) *hydrate*: 14.20 (CH_3), 25.59 (2 × CH_2), 20.50, 25.48, 25.66, 27.66 (4 × CH_2), 69.82 (C-3), 71.97 (C-5), 92.37 (q, J_{CCF} 32, *C*(OH)$_2$$CF_3$), 127.79 (2 × CH=), 125.28, 126.96, 127.94, 128.30, 128.40, 128.57, 130.65, 132.02 (8 × CH=); δ_F(188 MHz) −78.4 (*ketone*), −85.8 (*hydrate*); *m*/*z* (EI) 370 (M^+, 3%), 274, 234, 79 (100) (HRMS: found: M^+ 370.2111. $C_{21}H_{29}O_2F_3$ requires 370.2120).

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