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SELECTIVE INCORPORATION OF CF_2-GROUP INTO THE NATURAL COMPOUNDS MOLECULES. SYNTHESIS OF 14,14-DIFLUOROCORIOLIC ACID

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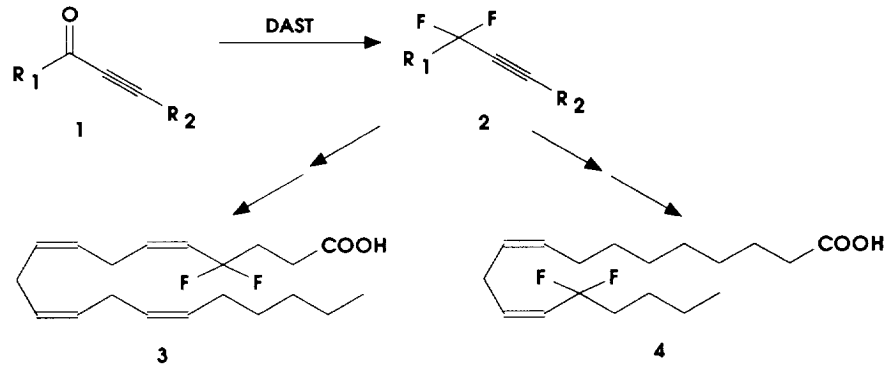
Abstract: The difluorides obtained in the reaction of DAST with appropriate ketones could serve as a suitable starting materials for the selective incorporation of CF_2-group into the molecules of the unsaturated chiral natural compounds. As an example, stereoselective synthesis of (*R*)-14,14-difluoro-13-hydroxy-9(*Z*),11(*E*)-octadecadienoic acid [(*R*)-14,14-difluorocoriolic acid] **6** is reported.

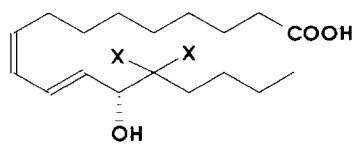
Introduction

In recent years the difluoromethylene group has attracted much attention, because the compounds containing such a moiety exhibit excellent biological activities [1]. This moiety has a steric profile similar to that of the methylene group, but has a very different polarity and drastically altered reactivity. In addition, it has been argued that the difluoromethylene functionality could be regarded as an isopolar and isosteric replacement for the oxygen [2] and that exchange of the oxygen at the biochemically labile position for the difluoromethylene unit may impart stability with retention of biological activities shown by the parent compounds [3,4]. However, general methods for the mild and selective introduction of a CF_2-group into the molecules are limited. The most widely used method for the introduction of this functionality has been Reformatsky reaction employing halogenodifluoro acetates and (bromodifluoromethyl)-acetylene derivatives. This method has been applied for the synthesis of gem-difluorinated analogs of natural products, such as deoxy sugar [5], β-lactams [6], and malic acid [7].

As a part of our synthetic work on difluoro analogs of biologically important fatty acids and their metabolites, we have developed another approach, based on the reaction of appropriate ketones **1** with DAST and subsequent functionalisation of the difluorides **2** thus obtained. Our first targets contained the CF_2-moiety in the α-position to the double bond, so we had to investigate the reaction of alkynyl ketones with DAST (we used morpholinosulfur trifluoride) [8]. We succeeded in obtaining in good yields the appropriate difluorides and in functionalising them into the 4,4-difluoroarachidonic (**3**) and 14,14-difluorolinoleic (**4**) acids [9,10].



The next step in the our investigations was to develop the method of selective incorporation of the CF_2-moiety into the α-position to a chiral hydroxyl group with the aim to synthesizing 14,14-difluorocoriolic acid (**6**). (9*Z*, 11*E*, 13*S*)-13-Hydroxyoctadeca-9,11-dienoic acid (coriolic acid, **5**) is an important and biologically active metaboilite of linoleic acid. It has been isolated from the resistant cultivar of rice plant [11] and has been shown to act as a self defense substance against rice blast disease. It is also present in sera of patients with Familial Mediterranean Fever [12] and possesses cation-specific ionophoric activity.

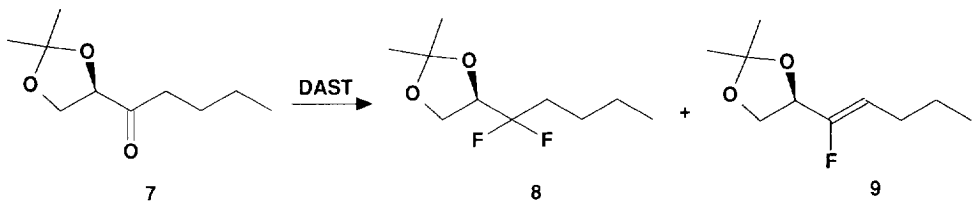


5 X = H

6 X = F

Results and Discussion

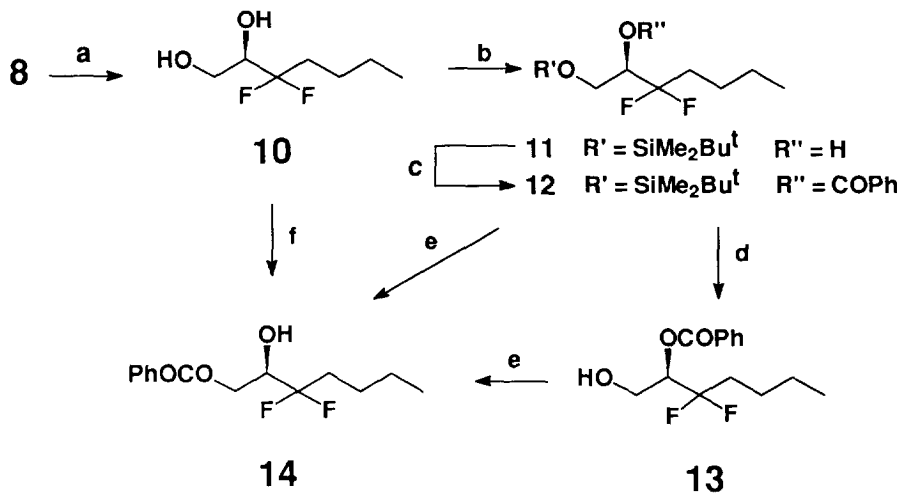
We have reported in our previous communication [13] about the successful synthesis of 14,14-difluoro-coriolic acid. Now we would like to describe some experimental observations and data. We have investigated the reaction of ketone (**7**) with DAST under different conditions. The choice of the solvent influenced



Scheme 1

dramatically the composition of the reaction mixture: in hexane, benzene and CH_2Cl_2 the ratio of **8** to **9** was about 72:28, in diglyme it was just about equal (52:48), and in N-methyl pyrrolidone we have observed an

excess of olefin (30:70). The highest isolated yields of the products **8** and **9** were found with CH_2Cl_2 (about 63% for the difluoride (**8**)). Dilution of the solution led to a delay in the reaction, but an increase in the yield of difluoride (**8**) (the ratio **8** to **9** was 76:24 was observed). Increase of the reaction mixture concentration led to the appearance of the *cis*-isomer of **9** (up to 15% from the yield of **9**). We have compared the reactivity of diethylsulfur trifluoride and morpholinosulfur trifluoride: the results were the same, but the rate of the former process was twice that of the latter.

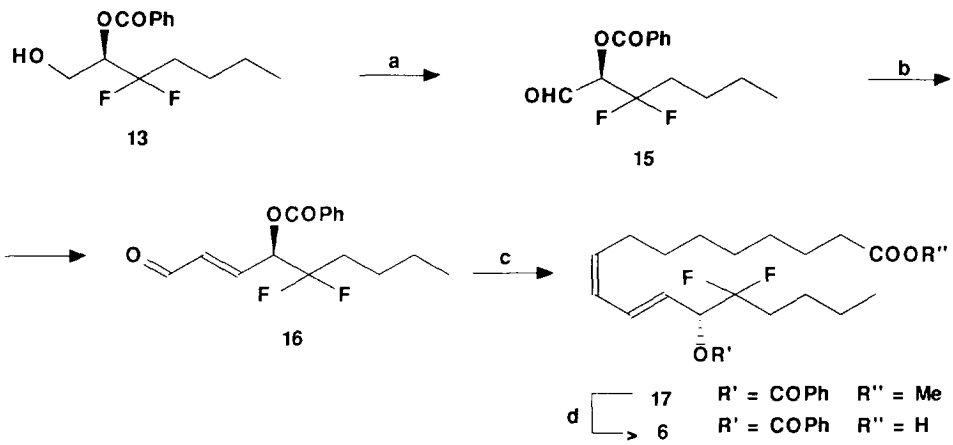


(a) 4N HCl - THF (1:4), 20°C, 12 h; (b) *tert*-$BuMe_2SiCl$, DMAP, CH_2Cl_2, 20°C, 16 h; (c) PhCOCl, Py, CH_2Cl_2, 20°C, 16 h; (d) dioxane-H_2O-HCl_{conc} (100:2:5), 20°C, 20 h; (e) *n*-Bu_4NF or silica gel; (f) PhCOCl, Py, CH_2Cl_2, 20°C, 16 h.

Scheme 2

Using standard procedures we synthesized the diprotected alcohol (**12**) in a good yield (see the experimental section). But when we tried to remove the *tert*-$BuMe_2Si$-group by *n*-Bu_4NF, the product of the rearrangement of alcohol (**13**) - the alcohol (**14**) was obtained. The deprotection of the compound (**12**) in acidic conditions was more successful, but after the purification on silica gel we isolated the mixture of isomers **13** and **14**. Actually, when we treated the compound (**13**) with silica gel, the rearrangement proceeded with almost quantitative yield over 2 days. Only the addition of 1% of the acetic acid into eluent permitted us in obtaining pure alcohol (**13**).

After the standard functionalisation reactions we have succeeded to obtain the diprotected acid (**17**), which on hydrolysis by K_2CO_3 led to the target acid (**6**). It is interesting to note, that the hydrolysis proceeded in two stages: during first hour we have observed (TLC) the deprotection of the benzoyl moiety, and while about 20 h were required for the deprotection of the methyl ester.



(a) $C_5H_5NH^+ClCrO_3^-$, 3A molecular sieves, CH_2Cl_2, 20°C, 2 h; (b) $Ph_3P{=}CHCHO$, C_6H_6, reflux, 1 h; (c) $Ph_3P{=}CH(CH_2)_7COOCH_3$ (**18**), -78°C to 0°C, 1 h; (d) K_2CO_3, MeOH-H_2O (4:1), 20°C, 20 h.

Scheme 3

The enantiomeric purity of the alcohols (**10**) and (**11**) was analyzed by ^1H NMR of the corresponding Mosher esters using the racemic compounds for comparison. The geometrical (>99%) and enantiomeric (98-99%) purity of (**17**) was estimated during experiments with shift reagents $Eu(fod)_3$ and $Eu(tfc)_3$ respectively.

In conclusion the described approach could be used for the synthesis of different types of fluorine-containing compounds with multiple bonds, hydroxyl and other functional moieties (for example, chiral β,β-difluoro-α-hydroxycarboxylic acids).

Experimental Section

General details. NMR spectra were recorded on either a Varian VXR-300 or Varian Gemini-200 spectrometer, with $CDCl_3$ as a solvent and tetramethylsilane (^1H) and $CFCl_3$ (^{19}F) as internal standards. Optical rotations were determined over a 20 sm path length using Palomat A polarimeter. Analytical thin-layer chromatography (TLC) was used to monitor reactions. Column chromatography was performed on silica gel 60 (40-63 μm), with using hexane-ether (v/v) as the eluent. All products have a > 95% purity based on ^1H and ^{19}F NMR data.

Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl, dichloromethylene, ethyl acetate, acetone and benzene were dried by the distillation over P_2O_5, hexane and dimethylformamide were distilled from CaH_2. All anhydrous solvents were stored over molecular sieves 3A and 4A.

(2*R*)-1,2-O-Isopropylidene-3-oxoheptan-1,2-diol (7). To the stirred solution of $(COCl)_2$ (2.41 ml, 28.05 mmol) in 60 ml CH_2Cl_2 at -60°C DMSO (3.98ml, 56.1 mmol) was added. The solution was stirred during 0.25 h and (2*R*)-1,2-O-isopropylidene-3-hydroxyheptan-1,2-diol (4.8 g, 25.5 mmol) in 25 ml of CH_2Cl_2 was added. The reaction mixture was stirred for 0.75 h and Et_3N (17.77 ml, 127.5 mmol) was added. The solution was allowed to warm to the room temperature and was treated by water (125 ml). The organic layer was separated and the aqueous layer was extracted with the CH_2Cl_2. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed (hexane-ether 20:1) to produce 4.3 g (90.6% yield) of keton (7) as a colorless oil. $[\alpha]_D^{20}$ + 59.2 (c 1.9, $CHCl_3$). ^{1}H-NMR, δ: 0.92 (t, 3H, J=7.2 Hz), 1.09-1.82 m (10H), 2.57-2.65 m (2H), 3.98 dd (1H, J=8.6 and 5.6 Hz), 4.21 dd (1H, J=8.6 and 7.8 Hz), 4.44 dd (1H, J=7.8 and 5.6 Hz). IR (CH_2Cl_2): 1710 (C=O). Anal. Calcd. for $C_{10}H_{18}O_3$: C 64.57; H 9.72. Found : C 64.49, H 9.74.

(2*R*)-1,2-O-Isopropylidene-3,3-difluoroheptan-1,2-diol (8). To the solution of keton (7) (1.6 g, 8.59 mmol) in 10 ml of CH_2Cl_2 DAST (2 ml, 16 mmol) was added at room temperature. After 96 h the reaction mixture was cooled and poured carefully to the stirring solution of $NaHCO_3$. The organic layer was separated, and the aqueous layer extracted with 5 ml of CH_2Cl_2. The combined organic portions were washed with brine and dried (Na_2SO_4). *m*-CPBA (88%, 0.843 g, 4.2 mmol) was added to the obtained solution with stirring. After stirring the reaction mixture for 8 h at rt, it was washed with aqueous solutions of Na_2SO_3 and $NaHCO_3$, dried (Na_2SO_4) and concentrated (on the cool bath) to give crude product. This material was purified by chromatography (pentane-ether 100:1 and 40:1) to afford 1.13 g (63%) of difluoride (**8**). $[\alpha]_D^{20}$ + 4.0 (s 1.2, $CHCl_3$). ^{19}F NMR, δ: -109.2 m (1F) and -114.9 m (1F). ^{1}H-NMR, δ: 0.93 (t, 3H, J=7.2 Hz), 1.32-1.47 m (10H), 1.82-1.99 m (2H), 4.06-4.26 dd (3H). Anal. Calcd. for $C_{10}H_{18}F_2O_2$: C 57.47; H 8.71. Found: C 58.08, H 8.64.

(2*R*)-3,3-Difluoroheptane-1,2-diol (10). The mixture of difluoride (**8**) (2.2 g, 10.56 mmol), 4N HCl (9 ml) and THF (40 ml) was stirred at rt for 12 h. The reaction was neutralized by aqueous solution of $NaHCO_3$ and extracted with ether. The combined organic portions were washed with brine, dried ($CaCl_2$) and concentrated. The residue was chromatographed (hexane-ether 1:1) to afford 1.38 g (77.5%) of diol (**10**). $[\alpha]_D^{20}$ +9.9 (c 1.3, $CHCl_3$). ^{19}F NMR, δ: -109.4 m (1F) and -112.1 m (1F). ^{1}H-NMR, δ: 0.93 (t, 3H, J=7.1 Hz), 1.27-1.57 m

(4H), 1.77-2.05 m (2H), 3.25 s (1H), 3.74-3.92 m (4H). Anal. Calcd. for $C_7H_{14}F_2O_2$: C 49.99; H 8.39. Found : C 49.78, H 8.17.

(2*R*)-1-Benzoyloxy-3,3-difluoro-2-hydroxyheptane (14). To the stirred solution of diol (**10**) (0.124 g, 0.74 mmol) in CH_2Cl_2 (1 ml) and pyridine (0.3 ml) benzoyl chloride (0.088 ml, 0.76 mmol) was added dropwise at 0°C. The reaction mixture was stirred at rt for 20 h and diluted by water. After the extraction by ether, combined organic portions were washed with aqueous solution of $NaHCO_3$, water, dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane-ether 20:1) to afford 0.134 g (81.7%) of benzoate (**14**). ^{19}F NMR, δ:-111.2 m (2F). ^1H-NMR, δ: 0.93 t (3H, J=7.2 Hz), 1.38 qt (2H, J=6.9 and 6.9 Hz), 1.53 tt (2H, J=6.9 and 6.9 Hz), 1.91-2.09 m (2H), 2.89 d (1H, J=6.0 Hz), 4.05-4.20 m (1H), 4.53 dd (1H, J=12.0 and 6.9 Hz), 4.61 dd (1H, J=12.0 and 3.3 Hz), 7.45 t (2H, J=8.0 Hz), 7.59 t (1H, J=8.0 Hz), 8.05 d (2H, J=8.0 Hz).

(2*R*)-1-*tert*-Butyldimethylsilyloxy-3,3-difluoro-2-hydroxyheptane (11). A mixture of diol (**10**) (0.43 g, 2.56 mmol), t-$BuMe_2SiCl$ (0.424 g, 2.82 mmol) and DMAP (0.688 g, 5.64 mmol) in CH_2Cl_2 (3 ml) was stirred for 16 h at rt. The reaction mixture was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane-ether 30:1) to afford 0.57 g (82.4%) of silyl ether (**11**). $[\alpha]_D^{20}$ +13.4 (c 1.3, $CHCl_3$). ^{19}F NMR, δ: -111.2 m (1F) and -112.1 m (1F). ^1H-NMR, δ: 0.1 s (6H), 0.91 s (9H), 0.93 t (3H, J=7.1 Hz), 1.32-1.54 m (4H), 1.80-2.04 m (2H), 2.8 d (1H, J=2.6 Hz), 3.74-3.86 m (3H). Anal. Calcd. for $C_{13}H_{28}F_2O_2Si$: C 55.28; H 9.99. Found : C 55.26, H 10.02.

(2*R*)-2-Benzoyloxy-1-*tert*-butyldimethylsilyloxy-3,3-difluoro-2-hydroxyheptane (12). To the stirred solution of silyl derivative (**11**) (0.85 g, 5.05 mmol) in CH_2Cl_2 (10 ml) and pyridine (4 ml) benzoyl chloride (0.7 ml, 6,03 mmol) was added dropwise at 0°C. The reaction mixture was stirred at rt for 20 h and diluted by water. After the extraction by ether, combined organic portions were washed with aqueous solution of $NaHCO_3$, water, dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane-ether 60:1) to afford 0.91 g (74.1%) of protected diol (**12**). $[\alpha]_D^{20}$ + 10.3 (c 1.7, $CHCl_3$). ^{19}F NMR, δ: -109.1 m (2F). ^1H-NMR, δ: 0.1 s (6H), 0.81 s (9H), 0.90 t (3H, J=7.2 Hz), 1.33 qt (2H, J=7.2 and 7.2 Hz), 1.52 m (2H), 1.94 m (2H), 3.91 dd (1H, J=11.1 and 7.2 Hz), 4.04 ddt (1H, J=11.1, 3.9 and 1.2 Hz), 5.46 m (1H), 7.46 t (2H, J=7.2 Hz), 7.59 t (1H, J=7.2 Hz), 8.08 d (2H, J=7.2 Hz). Anal. Calcd. for $C_{20}H_{32}F_2O_2Si$: C 62.14; H 8.35. Found : C 62.87, H 8.40.

(2*R*)-2-Benzoyloxy-1-hydroxy-3,3-difluoroheptane (13). To the solution of dioxan-HCl_{conc}-H_2O (20 ml, ratio 100:5:2) protected diol (**12**) was added and the mixture was stirred for 20 h at rt. Then the reaction mixture was extracted with the ether, combined organic portions were washed with water, dried (Na_2SO_4) and

concentrated. The residue was chromatographed (hexane-ether-acetic acid 100:10:1, then 10:10:0.2) to afford 0.23 g (90.9%) of silyl ether (**13**). $[\alpha]_D^{20}$ - 2.3 (c 2.0, $CHCl_3$). ^{19}F NMR, δ: -108.4 m (2F). ^1H-NMR, δ: 0.90 t (3H, J=7.2 Hz), 1.35 qt (2H, J=7.4 and 7.4 Hz), 1.52 tt (2H, J=7.4 and 7.4 Hz), 1.85-2.02 m (2H), 2.9 s (1H), 3.96 dd (1H, J=12.6 and 6.8 Hz), 4.1 dd (1H, J=12.6 and 3.6 Hz), 5.39 m (1H), 7.49 t (2H, J=8.0 Hz), 7.62 t (1H, J=8.0 Hz), 8.12 d (2H, J=8.0 Hz). Anal. Calcd. for $C_{14}H_{18}F_2O_3$: C 61.75; H 6.66. Found : C 62.03, H 6.72.

(2*R*)-Benzoyloxy-3,3-difluoroheptanal (15). The suspension of PCC (0.43 g, 1.99 mmol), molecular sieves 3A (powder, 0.5 g) in CH_2Cl_2 (3 ml) was stirred for 5 min. under argon. Then the alcohol (**13**) (0.272 g, 1 mmol) was added and the reaction mixture was stirred for 1 h at rt. Then the ether (6 ml) was added and the mixture was stirred for several minutes. After the decantation the residue was washed with ether and combined organic portion was passed through the thin pad of silica gel and washed several times by the mixture of hexane-ether (2:1). After the concentration crude aldehyde (**15**) (0.242 g, 89.6%) was obtained and used without additional purification. ^{19}F NMR, δ: -103.9 m (2F). ^1H-NMR, δ: 0.92 t (3H, J=7.0 Hz), 1.28-1.63 m (4H), 1.90-2.18 m (2H), 5.56 dd (1H, J=12.9 and 11.8 Hz), 7.4-7.7 m (3H), 8.11 m (2H), 9.75 t (1H, J=1.5 Hz).

(4*R*)-4-Benzoyloxy-5,5-difluoro-2*E*-nonenal (16). The solution of aldehyde (**15**) (0.89 g, 3.3 mmol) and formylmethylene triphenylphosphorane (1.12 g, 3.7 mmol) in benzene (10 ml) was refluxed for 1 h. The reaction mixture was passed through the thin pad of silica gel, washed several times by the mixture of hexane-ether 3:1 and concentrated. The residue was chromatographed (hexane-ether, 20:1) to give enal (**16**) (0.694 g, 71% yield). $[\alpha]_D^{20}$ + 134.3 (c 1.7, $CHCl_3$). ^{19}F NMR, δ: -106.4 ddt (1F, J=255, 18 and 7.5 Hz) and -108.2 ddt (1F, J=255, 17.5 and 15.5 Hz). ^1H-NMR, δ: 0.91 t (J=7.4 Hz, 3H), 1.26 - 1.63 m (4H), 1.90 - 2.18 m (2H), 5.99 m (1H), 6.39 ddd (J=15.5, 7.5 and 1.8 Hz, 1H), 6.91 dd (J=15.5 and 4.8 Hz, 1H), 7.4 - 7.7 m (3H), 8.10 m (2H), 9.64 d (J=7.7 Hz, 1H). Anal. Calcd. for $C_{16}H_{18}F_2O_3$: C 64.85; H 6.12. Found: C 64.77, H 6.07.

Methyl (13*R*)-13-benzoyloxy-14,14-difluoro-9*Z*,11*E*-octadecadienoate (17). In a flame-dried round-bottom flask equipped with a magnetic stirrer and under argon THF (50 ml) and phosphonium salt (**18**) (1.66 g, 3.1 mmol) was added. After stirring for 20 min at rt, 1 M solution (2.5 ml, 2.5 mmol) of $LiN(TMS)_2$ in THF was added drop wise over a period of 2 min with cooling (0°C) and the stirring was continued for additional 20 min. The orange colored reaction mixture was cooled to -78°C and the solution of enal (**16**) (0.69 g, 2.2 mmol) in THF (5 ml) was added during 1 min. After 30 min the reaction (complete by TLC) was quenched with aqueous NH_4Cl and extracted with ether. The combined organic portion was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane-ether 40:1) to afford 0.52 g (53.6%)

of diprotected acid (**17**). $[\alpha]_D^{20}$ + 68.7 (c 1.6, $CHCl_3$). ^{19}F NMR, δ: -109.3 m (2F). ^1H NMR, δ: 0.91 t (J=7.0 Hz, 3H), 1.22 - 1.63 m (15H), 1.81 - 2.03 m (2H), 2.14 m (2H), 2.3 t (2H, J=7.5 Hz), 3.66 s (3H), 5.56 dt (1H, J=11.2 and 7.6 Hz), 5.75 m (2H), 6.04 t (1H, J=11.2), 6.76 dd (1H, J=14.9 and 11.2 Hz) 7.46 t (2H, J=7.9 Hz), 7.61 t (1H, J=7.9 Hz), 8.08 d (2H, J=7.9 Hz). Anal. Calcd. for $C_{26}H_{36}F_2O_4$: C 69.31; H 8.19. Found: C 69.83, H 8.27.

(13*R*)-13-Hydroxy-14,14-difluoro-9*Z*,11*E*-octadecadienoic acid (6). The suspension of diprotected acid (**17**) (71 mg, 0.15 mmol), MeOH (9 ml), H_2O (2.1 ml) and K_2CO_3 (142 mg, 1 mmol) was stirred for 20 h at rt. Then it was quenched with buffer (pH 7.0) and extracted with ether. The combined organic portions were washed with water, brine, dried (Na_2SO_4), concentrated. The residue was chromatographed (hexane-ether 1:1) to afford 39 mg (75%) of acid (**6**). $[\alpha]_D^{20}$ + 0.13 (c 0.3, $CHCl_3$). ^{19}F NMR, δ: -110.3 dm (J=247 Hz, 1F), -112.3 dm (J=247 Hz, 1F); ^1H NMR, δ: 0.92 t (J=6.9 Hz, 3H), 1.25 - 1.65 m (15H), 1.85 - 2.02 m (2H), 2.18 m (2H), 2.35 t (2H, J=7.5 Hz), 4.33 m (1H), 5.52 dt (1H, J=11.0 and 7.4 Hz), 5.69 dd (1H, J=15.1 and 6.3 Hz), 6.02 t (1H, 11.0 Hz), 6.70 dd (1H, J=15.1 and 11.0 Hz). Anal. Calcd. for $C_{18}H_{30}F_2O_3$: C 65.04; H 9.10. Found: C 65.77, H 8.85.

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