Stereoselective Synthesis of the 5,5-Difluoro-(12*R*)- and -(12*S*)-Leukotrienes B_3

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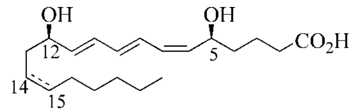
Keywords: Fluorine / Leukotrienes / Eicosanoids / Enantioselectivity / Stereoselective synthesis

The first synthesis of the 5,5-difluoro-(12*R*)- and -(12*S*)-leukotrienes B_3 is reported which uses a flexible and convergent strategy. The key steps involve a Sonogashira coupling between the bromodienone **4** and the propargylic difluoride **5**; this is followed by a CBS type reduction to establish the (12*R*) or (12*S*) stereocenters. A final semihydrogenation, under controlled conditions, affords the required E,E,Z trienic system.

Introduction

The fluorine atom has unique steric properties (it is only slightly larger than the hydrogen atom and is similar in size to an OH group) and has the highest electronegativity of all atoms. This is the basis for the strong modifications induced in the physical, chemical and biological properties of fluorinated molecules.[1] Such properties have already been extensively used in fluorobioorganic chemistry: the replacement of key C–H or C–OH bonds by C–F, as well as the exchange of CH_2, CH–OH or CO by CF_2 moieties has afforded important information on various enzymatic systems. Furthermore, such exchanges, as well as the introduction of CF_3 groups, can afford compounds which demonstrate a higher metabolic stability.[2] In the family of lipids these properties have also been used, and a number of fluorinated analogues of fatty acids and corresponding metabolites have been prepared.[3] The leukotrienes are important arachidonic metabolites with very potent biological properties. In particular, the leukotriene B_4 is strongly implicated as a mediator in inflammation and allergic diseases.[4] It has been demonstrated that the leukotriene B_3, lacking the terminal 14–15 double bond, has a very similar biological profile[5] (Figure 1).



LTB_4: double bond in position 14–15
LTB_3: single bond in position 14–15

Figure 1. Leukotrienes B_4 and B_3.

A few fluorinated analogues of LTB_4 have been prepared by total synthesis: they include the 13,13-diF-LTB_4 and the derivative having a CF_3 group in terminal position (i.e. 20-CF_3 LTB_4).[3] Several years ago we started a programme dealing with the development of new methodologies to introduce selectively one or two fluorine atoms in positions vicinal to π systems.[6] A particularly challenging case was the fluorination vicinal to polyunsaturated systems, and in this context the fluorinated LTB_3 analogues appeared as very attractive target molecules.[7] Therefore, our programme involved the preparation of the different monofluorinated analogues (with sequential exchanges of the two OH groups by F atoms) and the two difluorinated analogues (successive exchanges of each CH–OH by a CF_2 moiety). The purpose of this paper is to report the first step of this study through the selective preparation of the 5,5-diF-(12*R*)- and 5,5-diF-(12*S*)-LTB_3 analogues **1**. In line with previous studies, the synthesis of these fluorinated compounds confirms the potentialities of the approach through propargylic systems.[8]

Results and Discussion

Our strategy to prepare the 5,5-difluoro-(12*R*)-leukotriene B_3 (**1a**) and the (12*S*) enantiomer **1b** was mainly based on previous work demonstrating that the diethyl amino sulfur trifluoride (DAST) mediated mono- and gem-difluorination reactions are greatly facilitated in the case of propargylic systems.[8] Therefore, the retrosynthesis for our target molecules **1** is given in Scheme 1.

The double bond in position 6–7 should be obtained by a controlled hydrogenation of the dienynes **2**. The *R* (or the *S*) stereochemistry at carbon 12 should be introduced by an asymmetric reduction of **3**. This polyunsaturated system could be prepared by a Sonogashira type coupling between the bromodienone **4** and the difluoropropargylic derivative **5**. Finally, both components should be obtained in a few steps from known products: the *E*,*E*-bromodienal **6** and the propargylic ketone **7**.

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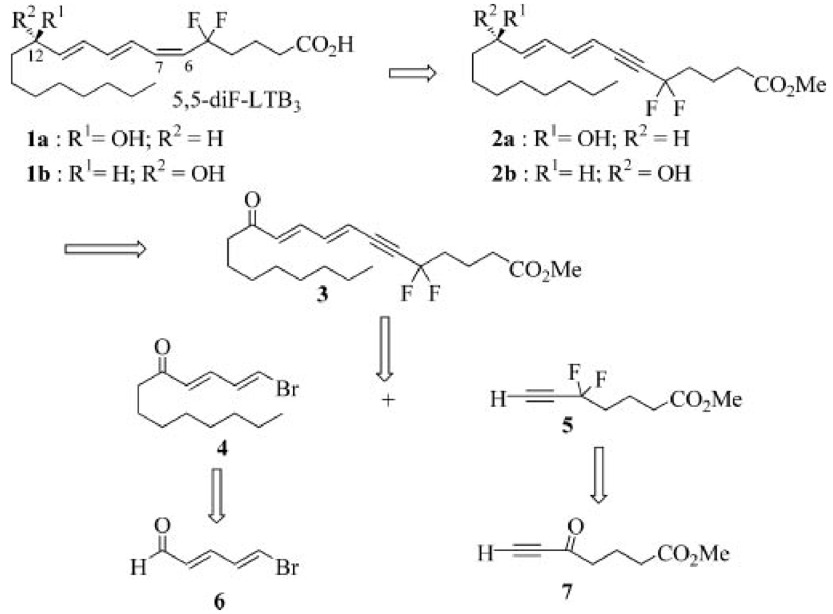
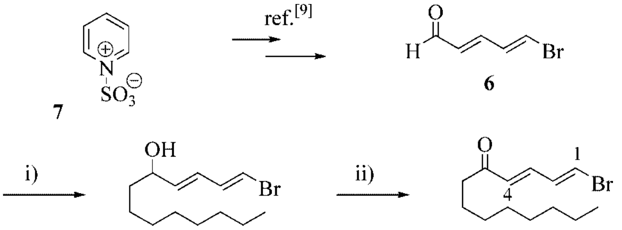
DOI: 10.1002/ejoc.200500200



Scheme 1. Retrosynthesis of the 5,5-difluoro leukotrienes B_3 **1**.

Several challenging problems have to be considered: i) the control in the semihydrogenation, especially with the fluorine atoms in the propargylic position; ii) the asymmetric reduction of a ketone conjugated to a polyunsaturated system, and iii) the palladium-catalysed coupling reactions with such fluorine-containing molecules.

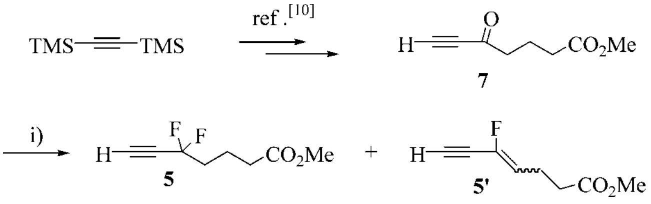
The synthesis of the first component, the bromodienone **4**, is indicated in Scheme 2.



Scheme 2. Synthesis of the bromodienone **4**. i) $C_8H_{17}MgBr$, ether, –40 °C to –10 °C, 94%; ii) PDC, 4 Å MS, CH_2Cl_2, 80%.

The *E*,*E* bromodienal **6** was prepared in two steps from the SO_3-Py complex, following the literature procedure.[9] It proved to be important to start the next steps from the crystalline pure *E*,*E* isomer **6**, since separation of pure isomers proved to be very challenging at a later stage of the synthesis. The addition of the Grignard reagent gave the expected alcohol **8** in excellent yield. The oxidation to give the dienone **4** was performed by pyridinium dichromate (PDC) in dichloromethane at room temperature in good yield. The oxidation of **8** using IBX (*o*-iodoxybenzoic acid) in DMSO also gave the dienone in 76% yield. The *E*,*E* stereochemistry of **4** was easily established from the NMR spectroscopic data: $J_{1,2}$ = 13.5 Hz; $J_{3,4}$ = 15.4 Hz.

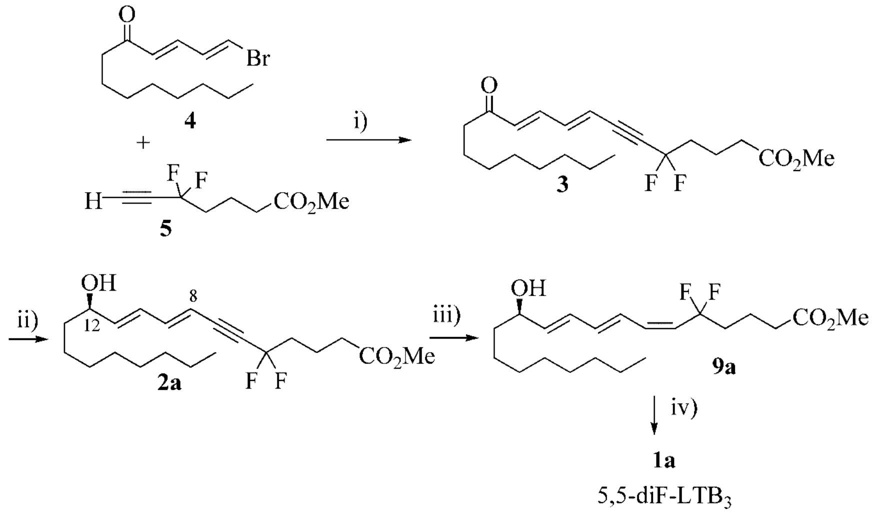
The preparation of the second component, the gemdifluoro propargylic derivative **5**, is shown in Scheme 3.



Scheme 3. Synthesis of the gemdifluoro propargylic component **5**. i) DAST, 50 °C, 2.5 h, 52%.

The propargylic ketone **7** was prepared in two steps in 42% yield from bistrimethylsilylacetylene, following the literature procedure: a Friedel–Crafts type reaction with methyl 4-(chloroformyl) butyrate, followed by the Borax-mediated cleavage of the C–Si bond.[10] The geminal difluorination reaction was conveniently performed using neat DAST at 50 °C. Alternatively, the Deoxo-fluor™ reagent with a trace of EtOH can also be used for this reaction.[11] Under these conditions the desired compound **5** was obtained, together with small amounts of the enynes **5′** (as a mixture of stereoisomers). The gemdifluoro derivative **5** was isolated in 52% yield after chromatography on SiO_2.

The completion of the synthesis to give **1** is indicated in Scheme 4. The Sonogashira coupling between **4** and **5** was best performed under Linstrumelle's reaction conditions.[12] Furthermore, the use of triethylamine as a base was very important for this coupling: in the case of piperidine, the yield was lower (51%), due to the competitive formation of the product resulting from nucleophilic substitution of the bromine atom. Under these optimised reaction conditions, the desired compound **3** was isolated in 84% yield and no homocoupling product from **5** was observed. It is interesting to note that, under the same reaction conditions, the



Scheme 4. Completion of the synthesis of the 5,5-difluoro leukotriene B_3 (**1a**). i) $Pd(PPh_3)_4$, CuI, Et_3N, toluene, room temperature, 3 h, 84%; ii) CBS/BMS, THF, –40 °C, 15 min, 89%; iii) H_2, Lindlar, pentane, room temperature, 82%; iv) LiOH, H_2O, THF, MeOH, room temperature, 30 h, 63%.

alcohol (+/–)-**8** reacted with **5** to give only a low yield (36%) of the dienyne (+/–)-**2**, together with a large amount of the homocoupling product. Therefore, the carbonyl group plays an important role in favouring the heterocoupling between **4** and **5**. The next step was the asymmetric reduction of the ketone, and we have found that the best conditions were those developed recently by Danishefsky.[13] After careful optimisation of the reaction conditions, and using the (*S*)-CBS reagent, we obtained the desired alcohol **2a** in 89% yield. The spectral and analytical data are in full agreement with the indicated structure: the *E*,*E* stereochemistry of the dienic moiety is maintained, as indicated by the ^1H NMR spectroscopic data ($J_{8,9}$ = 15.7 Hz; $J_{10,11}$ = 15.2 Hz). The analysis by NMR spectroscopy in the presence of $Eu(hfc)_3$ indicates a high enantioselectivity (>80% *ee*) for this compound. This was confirmed by the chiral HPLC analysis affording an 87% *ee* for (+)-**2a**. The *R* stereochemistry was attributed following the literature data on the asymmetric reduction of enones by the CBS reagents.[14] It is important to notice that this reduction appears highly sensitive to the concentration. The best result (87% *ee*) was obtained at a 0.2 M concentration, while more dilute solutions afforded lower *ee* values: for instance at 0.08 M the alcohol **2a** was obtained in only 68% *ee*.

The next step was the controlled hydrogenation of **2a** to **9a**. Such a reduction is always challenging in the case of polyunsaturated systems and even more when fluorine atom(s) are present in the propargylic position.[15] This reduction could be performed using Lindlar catalyst in pentane at room temperature. However, it is important to remark that a careful monitoring of the reaction had to be done in order to avoid the appearance of over reduction products.[16] The most convenient way was monitoring by ^{19}F NMR spectroscopy, performed directly on the reaction mixture: the signal of **2a** appeared at –81.3 ppm, while the peak corresponding to **9a** was at –90.2 ppm. Under these conditions, the triene was obtained in 82% yield. The *Z*,*E*,*E* geometry of the triene **9a** was established by ^1H NMR spectroscopy: $J_{6,7}$ = 11.7 Hz; $J_{8,9}$ = 12.9 Hz; $J_{10,11}$ = 14.1 Hz. A final saponification, under classical reaction conditions with LiOH, afforded the target molecule **1a**. The same series of reactions was performed using the (*R*)-CBS reagent to afford the (12*S*) enantiomer **1b** in 80% *ee*.

Conclusion

In conclusion, we have developed a versatile strategy to the 5,5-difluoro leukotrienes B_3 in four steps from the key intermediates **4** and **5**. This approach, via Pd-catalysed C–C bond formation, appears highly complementary to our previous strategy of using functionalised fluorinated intermediates and leading, for instance, to the HODE analogues.[17] Extension of these studies to the preparation of the other LTB_3-fluorinated analogues is under active study in our group and will be reported in due course.

Experimental Section

(1*E*,3*E*)-1-Bromotrideca-1,3-dien-5-ol (8): To a suspension of magnesium (0.47 g, 19.3 mmol, 1.8 equiv.) in diethyl ether (30 mL) at gentle reflux was added, under N_2 and dropwise, 1-bromo octane (3.36 mL, 12.3 mmol, 1.2 equiv.). At the end of the addition, the solution of the Grignard reagent was cooled to –40 °C. A solution of bromopentadienal **6**[9] (1.70 g, 10.6 mmol, 1 equiv.) in anhydrous THF (30 ml) was then added dropwise whilst stirring. The reaction mixture was stirred for 1 h between –40 °C to –10 °C. After addition of a saturated NH_4Cl solution, the reaction mixture was extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 using a 2:1 mixture (v/v) of petroleum ether/ether as eluent. The alcohol **8** was isolated as a colourless oil in 94% yield (2.73 g). R_f = 0.57 (petroleum ether/ether, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.71 (dd, *J* = 13.5, *J* = 10.7 Hz, 1 H, 2-*H*), 6.31 (d, *J* = 13.5 Hz, 1 H, 1-*H*), 6.15 (ddd, *J* = 15.2, *J* = 10.4, *J* = 0.5 Hz, 1 H, 3-*H*), 5.74 (dd, *J* = 15.2, *J* = 6.7 Hz, 1 H, 4-*H*), 4.13 (qd, *J* = 6.4, *J* = 1.0 Hz, 1 H, 5-*H*), 1.58 (broad s, 1 H, O*H*), 1.58–1.47 (m, 2 H, 6-*H*), 1.40–1.20 (m, 12 H, 7-, 8-, 9-, 10-, 11-, 12-*H*), 0.88 (t, J = 6.9 Hz, 3 H, 13-*H*) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.82 (*C*-1), 137.22 (*C*-4), 127.75 (*C*-3), 109.25 (*C*-2), 72.66 (*C*-5), 37 55 (*C*-6), 32.25 (*C*-11), 29.91 (2 *C*), 29.64 (1 *C*), 23.05 (*C*-7), 20.4(*C*-12), 14.51 (*C*-13) ppm. HRMS: $C_{13}H_{23}BrO^{79}$: calcd. 274.0932, found 274.0944 (4 ppm); $C_{13}H_{23}O$ $[M - Br]^+$: calcd. 195.1748, found 195.1735 (δ = 6 ppm).

(1*E*,3*E*)-1-Bromotrideca-1,3-dien-5-one (4): To a suspension of pyridinium dichromate (1.67 g, 4.36 mmol, 1.5 equiv.) and 4 Å molecular sieves (1.67 g) in CH_2Cl_2 (120 mL) was added, at room temperature, a solution of alcohol **8** (0.800 g, 2.91 mmol, 1 equiv.) in CH_2Cl_2 (10 ml). The reaction mixture was stirred for 1 h under N_2. After addition of diethyl ether (50 mL), the reaction mixture was filtered through Celite. The resulting solution was evaporated under reduced pressure, and the residue was purified by chromatography on SiO_2 using as eluent a 5:1 mixture of petroleum ether and ether. The ketone **4** was isolated as white crystals in 80% yield (0.645 g). M.p. 46 °C –48 °C. R_f = 0.78 (petroleum ether/ether, 2:1). ^{1}H NMR (C_6D_6, 400 MHz): δ = 6.69 (dd, J = 15.4, J = 11.3 Hz, 1 H, 3-*H*), 6.34 (dd, J = 13.4 Hz, J = 11.3 Hz, 1 H, 2-*H*), 5.96 (d, J = 13.5 Hz, 1 H, 1-*H*), 5.71 (d, J = 15.4 Hz, 1 H, 4-*H*), 2.14 (t, J = 7.3 Hz, 2 H, 6-*H*), 1.59 (br quint., J = 7.3 Hz, 2 H, 7-*H*), 1.28–1.17 (m, 10 H, 8-, 9-, 10-, 11-, 12-*H*), 0.91 (t, J = 6.7 Hz, 3 H, 13-*H*) ppm. ^{13}C NMR (C_6D_6, 100 MHz): δ = 198.75 (*C*-5), 138.14 (*C*-3), 136.43 (*C*-2), 130.42 (*C*-4), 118.00 (*C*-1), 41.82 (*C*-6), 32.61 (*C*-11), 30.23, 30.00, 29.97 (*C*-8, *C*-9, *C*-10), 24.70 (*C*-7), 23.44 (*C*-12), 14.73 (*C*-13) ppm. $C_{13}H_{23}BrO$ (273.22): calcd. C 57.15, H 7.75; found C 57.52, H 7.80.

Methyl-5,5-difluorohept-6-ynoate (5): DAST (0.5 mL, 0.657 g, 3.90 mmol, 2 equiv.) was added to neat methyl-5-oxo-6-heptynoate[10] (0.30 g, 1.94 mmol, 1 equiv.) at room temperature under N_2. The temperature of the reaction mixture was raised slowly to 50 °C and stirred for 2.5 h. CH_2Cl_2 (25 mL) was added, and the reaction mixture was quenched, at room temperature, with a saturated Na_2CO_3 solution. The organic phase was washed with water (2×20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Due to the volatility of **5**, the bath temperature should be kept at or below 20 °C. The residue was purified by chromatography (pentane/ether, 9:1). The difluoro compound **5** was obtained as a light yellow oil (0.178 g, 52% yield). R_f = 0.47 (petroleum ether/ether, 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.71 (s, 3 H, 8-*H*), 2.80 (t, $J_{H,F}$ = 5.0 Hz, 1 H, 7-*H*), 2.42 (t, J = 7.5 Hz, 2 H, 2-*H*), 2.70–2.06 (m, 2 H, 4-*H*), 1.95–1.90 (m, 2 H, 3-*H*) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.16 (*C*-1), 113.92 (t, $J_{C,F}$ = 233.2 Hz, C-5), 76.26 (t, $J_{C,F}$ = 40.9 Hz, *C*-6), 75.52 (t, $J_{C,F}$ = 6.2 Hz, *C*-7), 51.71 (*C*-8), 38.20 (t, $J_{C,F}$ = 26.0 Hz, *C*-4), 32.90 (*C*-2), 18.20 (t, $J_{C,F}$ = 4.0 Hz, *C*-3) ppm. ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ –84.61 (td, J = 14.5 Hz, J = 4.8 Hz) ppm. HRMS: $C_7H_7F_2O$: calcd. 145.0465, found 145.0468 (δ = 2 ppm).

Methyl (8*E*,10*E*)-5,5-Difluoro-12-oxoeicosa-8,10-dien-6-ynoate (3): To a solution of bromodienone **4** (0.171 g, 0.62 mmol, 1.1 equiv.) and gemdifluoro compound **5** (0.100 g, 0.57 mmol, 1 equiv.) in anhydrous toluene (3 mL) were added, under N_2 at room temperature, freshly distilled triethylamine (0.16 mL, 1.14 mmol, 2 equiv.) and $Pd(PPh_3)_4$ (0.033 g, 0.03 mmol, 0.05 equiv.). After 15 min stirring, CuI (0.011 g, 0.06 mmol, 0.1 equiv.) was added. The reaction mixture was stirred for 3 h at room temperature and then quenched with a saturated NH_4Cl solution. The reaction mixture was extracted with diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 using as eluent an 8:2 mixture of pentane and ether. The dienyne **3** was obtained as white crystals in 84% yield (0.175 g). R_f = 0.30 (petroleum ether/ether, 4:1). M.p. 36 °C–38 °C.^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.12 (dd, J = 15.3 Hz, J = 11.3 Hz, 1 H, 10-*H*), 6.80 (ddd, J = 15.3 Hz, J = 11.1 Hz, J = 0.5 Hz, 1 H, 9-*H*), 6.29 (d, J = 15.4 Hz, 1 H, 11-*H*), 6.01 (dt, J = 15.6 Hz, $J_{H,F}$ = 4.0 Hz, 1 H, 8-*H*), 3.69 (s, 3 H, 21-*H*), 2.60 (t, J = 7.3 Hz, 2 H, 13-*H*), 2.45 (t, J = 7.6 Hz, 2 H, 2-*H*), 2.20–2.08 (m, 2 H, 4-*H*), 1.95–1.88 (m, 2 H, 14-*H*), 1.65–1.58 (m, 2 H, 3-*H*), 1.34–1.20 (m, 10 H, 15-, 16-, 17-, 18-, 19-*H*), 0.88 (t, J = 6.4 Hz, 3 H, 20-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 200.29 (*C*-12), 173.11 (*C*-1), 142.75 (t, $J_{C,F}$ = 3.4 Hz, *C*-9), 139.18 (*C*-10), 132.66 (*C*-11), 116.45 (t, $J_{C,F}$ = 3.4 Hz, *C*-8), 114.69 (t, $J_{C,F}$ = 233.1 Hz, *C*-5), 86.52 (t, $J_{C,F}$ = 40.7 Hz, *C*-6), 85.05 (t, $J_{C,F}$ = 7.0 Hz, *C*-7), 51.71 (*C*-21), 41.27 (*C*-13), 38.36 (t, $J_{C,F}$ = 26.5 Hz, *C*-4), 32.89 (*C*-2), 31.78, 29.34, 29.23, 29.14 (*C*-15, *C*-16, *C*-17, *C*-18), 24.15 (*C*-14), 22.61 (*C*-19), 18.35 (t, $J_{C,F}$ = 3.7 Hz, *C*-3), 14.06 (*C*-20) ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ –82.71 (td, J = 14.8 Hz, J = 4.1 Hz) ppm. HRMS: $C_{12}H_{30}F_2O_3$: calcd. 368.2163, found 368.2175. $C_{21}H_{30}F_2O_3$ (368.47): calcd. C 68.45, H 8.21; found C 68.72, H 8.50.

Methyl (8*E*,10*E*)-5,5-Difluoro-12-hydroxy-eicosa-8,10-dien-6-ynoate (2a): The (*S*)-Me-CBS reagent (0.813 mL, 0.8 mmol, 2 equiv., 1.0 M in toluene solution) was transferred into a freshly flame-dried flask, and toluene was completely removed in vacuo for 1 d. After dilution with THF (2 mL), the resulting solution was transferred at room temperature to a flask containing the ketone **3** (0.150 g, 0.4 mmol). The reaction mixture was cooled to –40 °C, and $BH_3{\cdot}Me_2S$ (BMS), (0.222 mL, 0.44 mmol, 1.1 equiv., 2.0 M in THF) was added slowly over 10 min. At the end of the addition of BMS, TLC analyses indicated the completion of the reaction. Methanol (0.5 mL) was added dropwise, and the temperature of the reaction mixture was allowed to rise slowly to room temperature. The mixture was then diluted with diethyl ether and washed with a saturated $NaHCO_3$ solution until the aqueous and the organic phases were clear. The organic phase was washed with brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by chromatography on SiO_2 using as eluent a 4:1 mixture of pentane and ether. The alcohol **2a** was obtained as a colourless oil in 89% yield (0.135 g). R_f = 0.43 (petroleum ether/ether, 1:1). $[\alpha]_D^{24}$: –16.7 (c = 0.24, $CHCl_3$). HPLC analysis (Chiracel OD-H column, 25cm×0.46cm ID; eluent: heptane/2-propanol 98:2; flow rate: 1 mL/min; retention times: **2a**: 16.4 min, **2b**: 17.8 min): *ee* = 87%. ^{1}H NMR (C_6D_6, 300 MHz): δ = 6.50 (dd, J = 15.6 Hz, J = 10.7 Hz, 1 H, 9-*H*), 5.95 (ddt, J = 15.2, J = 10.8 Hz, J = 0.6 Hz, 1 H, 10-*H*), 5.50 (ddd, J = 15.2 Hz, J = 5.8 Hz, J = 0.5 Hz, 1 H, 11-*H*), 5.30 (dt, J = 15.7 Hz, $J_{H,F}$ = 4.0 Hz, 1 H, 8-*H*), 3.74 (br q, 1 H, 12-*H*), 3.29 (s, 3 H, 21-*H*), 2.01–1.84 (m, 6 H, 2-, 3-, 4-*H*), 1.39–1.18 (m, 15 H, O*H*, 13-, 14-, 15-, 16-, 17-, 18-, 19-*H*), 0.94 (t, J = 6.4 Hz, 3 H, 20-*H*) ppm. ^{13}C NMR (C_6D_6, 75 MHz): δ = 172.43 (*C*-1), 145.13 (t, $J_{C,F}$ = 3.5 Hz, *C*-9), 142.42 (*C*-11), 127.70 (*C*-10), 115.41 (t, $J_{C,F}$ = 232.1 Hz, *C*-5), 107.42 (t, $J_{C,F}$ = 3.5 Hz, *C*-8), 86.58 (t, $J_{C,F}$ = 7.0 Hz, *C*-7), 83.83 (t, $J_{C,F}$ = 40.3 Hz, *C*-6), 71.51 (*C*-12), 50.87 (*C*-21), 38.60 (t, $J_{C,F}$ = 26.9 Hz, *C*-4), 37.28 (*C*-13), 32.57 (*C*-2), 32.02 (1 C), 29.75 (2 C), 29.47 (1 C), 25.46 (1 C), 22.83 (*C*-19), 18.55 (t, J = 3.8 Hz, *C*-3), 14.09 (*C*-20) ppm. ^{19}F NMR (C_6D_6, 282.4 MHz): δ –81.28 (td, J = 14.2 Hz, J = 4.0 Hz) ppm. HRMS: $C_{21}H_{32}F_2O_3$: calcd. 370.2319, found 370.2319 (δ = 0 ppm).

Methyl (6*Z*,8*E*,10*E*)-5,5-Difluoro-12-hydroxyeicosa-6,8,10-trienoate (9a): To a solution of the gemdifluoro compound **2a** (0.04 g, 0.1 mmol, 1 equiv.) in pentane (1 ml) were added, at room temperature, pyridine (0.873 ml, 0.1 mmol, 1 equiv.) and Lindlar catalyst (0.008 g, 20% wt. equiv.). The suspension was stirred for 10 min under hydrogen. After addition of ether, the suspension was filtered through Celite, and the solution was evaporated under reduced pressure. The residue was dissolved again in pentane (1 ml), and the process (addition of pyridine and Lindlar catalyst) was repeated. The suspension was stirred at room temperature under H_2, and the progress of the hydrogenation was monitored by ^{19}F NMR spectroscopy on the crude reaction mixture. After 2 h, the reaction was complete, and the suspension was filtered through a short pad of SiO_2. The solvent was evaporated under vacuum, and the product was purified by chromatography on SiO_2 using as eluent a 1:1 mixture of petroleum ether and ether. The triene **9a** was obtained as a colourless oil in 82% yield (33 mg). R_f = 0.43 (petroleum ether/ether, 1:1). $[a]_{\mathrm{D}}^{24}$: –3.6 (c = 0.17, $CHCl_3$).^{1}H NMR (C_6D_6, 300 MHz): δ = 6.88 (t, J = 12.9 Hz, 1 H, 8-*H*), 6.20–6.10 (m, 2 H, 9-, 10-*H*), 6.02 (tt, J = 11.7 Hz, $J_{H,F}$ = 1.8 Hz, 1 H, 7-*H*), 5.66 (dd, J = 14.1 Hz, J = 6.9 Hz, 1 H, 11-*H*), 5.25 (dt, J = 11.7 Hz, $J_{H,F}$ = 14.7 Hz, 1 H, 6-*H*), 3.95 (q, J = 5.7 Hz, 1 H, 12-*H*), 3.32 (s, 3 H, 21-*H*), 2.00 (t, J = 7.0 Hz, 2 H, 2-*H*), 1.90–1.75 (m, 2 H, 4-*H*), 1.74–1.61 (m, 2 H, 3-*H*), 1.60–1.20 (m, 14 H, 13-, 14-, 15-, 16-, 17-, 18-, 19-*H*), 0.94 (t, J = 6.8 Hz, 3 H, 20-*H*) ppm. ^{13}C NMR (C_6D_6, 75 MHz): δ = 173.05 (*C*-1), 140.83 (*C*-11), 138.50 (t, $J_{C,F}$ = 2.0, *C*-9), 135.04 (t, $J_{C,F}$ = 5.8 Hz, *C*-7), 129.90 (*C*-10), 127.87 (t, $J_{C,F}$ = 2.0, *C*-8), 124.27 (t, $J_{C,F}$ = 26.9 Hz, *C*-6), 123.40 (t, $J_{C,F}$ = 239.8 Hz, *C*-5), 72.60 (*C*-12), 51.42 (*C*-21), 38.45 (t, $J_{C,F}$ = 27.0 Hz, *C*-4), 38.05 (*C*-13), 33.50 (*C*-2), 32.65 (1 C), 30.56 (1 C), 30.41 (1 C), 30.10 (1 C), 26.16 (1 C), 23.45 (*C*-19), 18.63 (t, $J_{C,F}$ = 4.3 Hz, *C*-3), 14.72 (*C*-20) ppm. ^{19}F NMR (C_6D_6, 282.4 MHz): δ –90.21 (q, J = 15.1 Hz) ppm. HRMS: $C_{21}H_{34}F_2O_3$: calcd. 372.2476, found 372.2468 (δ = 2 ppm).

(6*Z*,8*E*,10*E*)-5,5-Difluoro-12-hydroxyeicosa-6,8,-6,8,10-trienoic Acid (1a): To a solution of the trienoate **9a** (0.05 g, 0.13 mmol) in THF/MeOH/H_2O (8:2:1 v/v, 2.5 ml) was added lithium hydroxide monohydrate (0.013 g, 0.3 mmol, 2.3 equiv.), and the reaction mixture was stirred for 30 h at room temperature. After addition of a saturated solution of NH_4Cl, the reaction mixture was extracted with diethyl ether (3×4 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by a short flash chromatography using as eluent a 2:3 mixture of ether and pentane. The acid **1a** was obtained as a colourless oil in 63% yield (0.03 g). R_f = 0.26 (pentane/ether, 6:4). $[a]_{\mathrm{D}}^{24}$: –9.5 (c = 0.21, $CHCl_3$).^{1}H NMR (C_6D_6, 500 MHz): δ = 6.90 (t, J = 12.6 Hz, 1 H, 8-*H*), 6.20–6.10 (m, 2 H, 9-, 10-*H*), 6.02 (t, J = 11.7 Hz, 1 H, 7-*H*), 5.67 (dd, J = 14.3 Hz, J = 6.4 Hz, 1 H, 11-*H*), 5.60–5.40 (br s, O*H*), 5.24 (dt, J = 11.7, $J_{H,F}$ = 14.5 Hz, 1 H, 6-*H*), 3.95 (q, J = 5.7 Hz, 1 H, 12-*H*), 2.00 (t, J = 6.9 Hz, 2 H, 2-*H*), 1.90–1.60 (m, 4 H, 3-, 4-*H*), 1.60–1.20 (m, 14 H, 13-, 14-, 15-, 16-, 17-, 18-, 19-*H*), 0.94 (t, J = 6.8 Hz, 3 H, 20-*H*) ppm. ^{13}C NMR (C_6D_6, 75 MHz): δ = 178.89 (*C*-1), 140.54 (*C*-11), 138.44 (t, $J_{C,F}$ = 2.0, *C*-9), 135.04 (t, $J_{C,F}$ = 5.8 Hz, *C*-7), 129.99 (*C*-10), 127.95 (t, $J_{C,F}$ = 2.0, *C*-8), 124.30 (t, $J_{C,F}$ = 26.9 Hz, *C*-6), 123.17 (t, $J_{C,F}$ = 239.8 Hz, *C*-5), 72.70 (*C*-12), 38.28 (t, $J_{C,F}$ = 27.0 Hz, *C*-4), 37.98 (*C*-13), 33.50 (*C*-2), 32.64 (1 C), 30.39 (1 C), 30.36 (1 C), 30.09 (1 C), 26.14 (1 C), 23.45 (*C*-19), 18.33 (t, $J_{C,F}$ = 4.3 Hz, *C*-3), 14.72 (*C*-20) ppm. ^{19}F NMR (C_6D_6, 282.4 MHz): δ –90.35 (q, J = 14.6 Hz) ppm. HRMS: $C_{20}H_{31}FO_3$ $[M - HF]^{+\cdot}$: calcd. 338.2257, found 338.2238 (δ = 5 ppm).

Acknowledgments

We thank Mr. E. Kerouredan and Dr. M. Prakesch for preliminary experiments towards this type of molecules. We thank Dr M. Capet and Mrs S. LeMoing (Bioprojet, Rennes) for the chiral HPLC analyses. Fruitful discussions with Dr A. S. K. Murthy are gratefully acknowledged.

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Received: March 17, 2005