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Synthesis of 5,6-Difluoroarachidonic Acid, a Potential Inhibitor of 5-Lipoxygenase

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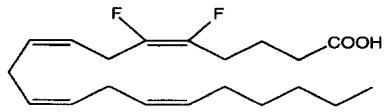
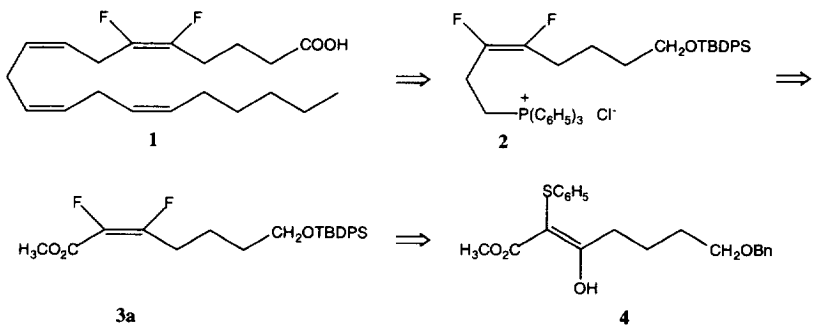
Abstract: The synthesis of 5,6-difluoroarachidonic acid **1** is described. The vicinal difluorinated double bond was prepared from the α-phenylthio-β-ketoester **4**. Copyright © 1996 Elsevier Science Ltd

Introduction of fluorine into biologically active compounds very often alters their pharmacological properties[1]. Fatty acids, which are involved in several metabolic pathways, were modified by fluorination of the double bonds involved in those pathways[2]. Such chemical modification had been already fruitful with arachidonic acid : 5- and 6-fluoroarachidonic acids were found to be potent inhibitors of 5-lipoxygenase[3]. Difluorination of the 5,6- double bond in arachidonic acid might lead to a more potent 5-lipoxygenase inhibitor. The synthesis of 5,6-difluoroarachidonic acid (**1**) is thus described hereafter.



1

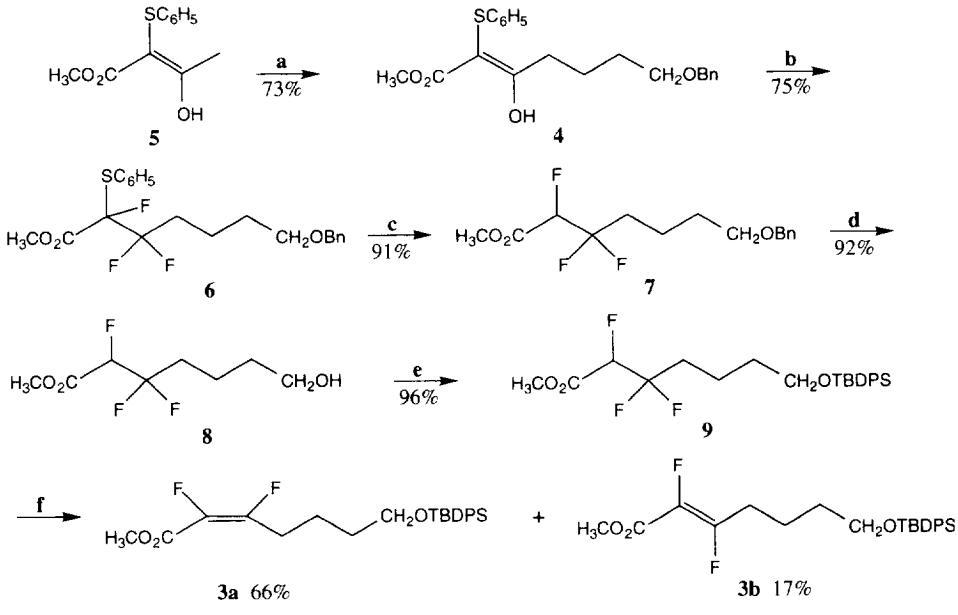
The retrosynthetic strategy is built around the preparation of *Z* tetrasubstituted vicinal difluorinated olefine and is shown in scheme 1. Wittig reaction between phosphonium **2,** containing a *Z* difluoroolefine, and (*Z,Z*)-3,6-dodecadienal[3] would generate double bond 8,9. Phosphonium **2** could be obtained from α,β-unsaturated difluoroester **3a** which derives from α-phenylthio-β-ketoester **4**.



1 **2** **3a** **4**

Scheme 1

Treatment of methyl 2-phenylthioacetoacetate[4] **5** with one equivalent of sodium hydride followed by n-butyllithium (1 eq) at 0°C afforded, after alkylation by 3-benzyloxy-1-bromopropane, the β-ketoester **4** (73%). Thus, **4** was converted into *Z* difluoroolefine **3a** using a method described by us[5] after exchanging the benzyl ether with a t-butyldiphenylsilyl ether. A 8/2 mixture of *Z* and *E* olefines **3a, 3b**[10] was obtained and the two isomers were easily separated by silica gel chromatography (Scheme 2).

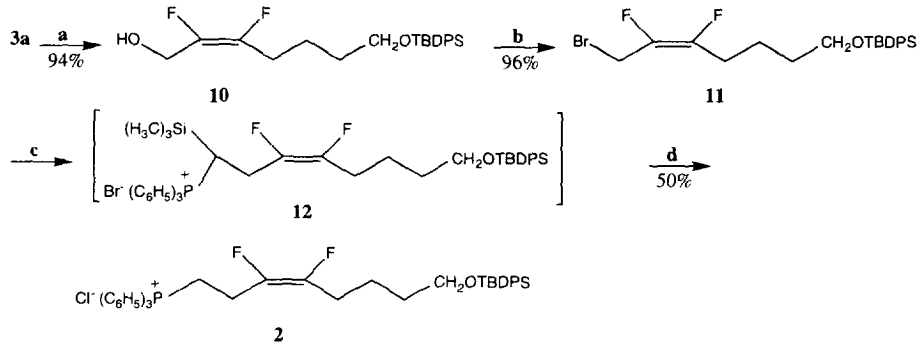


Bn = $C_6H_5CH_2$
TPDPS = t-$C_4H_9(C_6H_5)_2Si$

a) NaH (1eq), n-BuLi (1eq), THF, 0°C; then $BnO(CH_2)_3Br$, THF, 0°C to RT; b) MeDAST (1.25eq), CH_2Cl_2, 0°C then RT, 48h; c) $(n\text{-}Bu)_3SnH$ (1.6eq), AIBN (cat.), $C_6H_5CH_3$, reflux, overnight; d) Pearlman's catalyst, H_2 (1atm), $CH_3COOC_2H_5$, 6h; e) TBDPSCl (1.1eq), $(C_2H_5)_3N$, DMAP (cat.), CH_2Cl_2, RT, overnight; f) $[(CH_3)_3Si]_2N^-Na^+$ (1.02eq), THF, RT, 1h.

Scheme 2

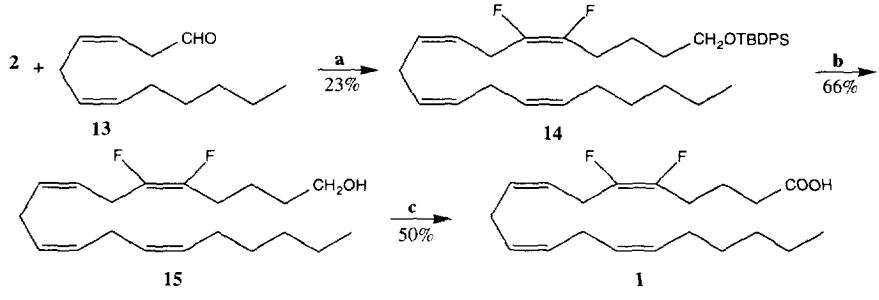
Reduction of ester **3a** afforded pure *Z* isomer of alcohol **10** which was converted into bromide **11** using 1-bromo-N,N-2-trimethyl-propenylamine[6]. **11** was homologated to phosphonium **12** by alkylation with trimethylsilyl methylenetriphenylphosphorane[7] which reacted exclusively on the allylic carbon of bromide **11**. Treatment of phosphonium **12** with Amberlyst A21® (HCl form), without isolation, cleaved the trimethylsilyl group to yield phosphonium **2** . The counter ion of the phosphonium salt was homogenized with Amberlyst A26® Cl^- form (Scheme 3).



a) DIBAL (1M hexane) (3eq), Diethyl ether, -78°C to RT, 1h; b) $(CH_3)_2C{=}CBr[N(CH_3)_2]$ (1.5eq), CH_2Cl_2, 0°C 15min; c) $(C_6H_5)_3P{=}CHSi(CH_3)_3$ (2eq), THF, 12h, RT; d) Amberlyst A21 HCl form, 1.5h; Amberlyst A26 Cl^-.

Scheme 3

Phosphonium **2** underwent Wittig reaction with (*Z,Z*) 3,6-dodecadienal[3] **13** in THF using n-butyllithium (1 eq) in presence of HMPTA (9 eq) to yield tetraene **14**[9]. Cleavage of the silyl ether followed by Jones oxidation[8], afforded 5,6-difluoroarachidonic acid **1**[10] (Scheme 4).



a) n-BuLi (1eq), THF, -78°C, 5min, then -18°C, 10min; HMPTA (9eq), -78°C; **13** (1.1eq), THF, -78°C, 30min, 0°C, 1h,then RT, 30min; b) n-$Bu_4N^+F^-$ (1.5eq), THF, 2h, RT; c) Jones reagent 2.76M, CH_3COCH_3, 0°C.

Scheme 4

The biological activity of 5,6-difluoroarachidonic acid will be published in due course.

References and Notes

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9. Wittig reaction, under the same conditions, of phosphonium **2** with a saturated aldehyde, *ie* hexanal, gave the expected diene with a 90% yield.

10. All new compounds gave analitycal and spectroscopic data in agreement with the assigned structure : **3a** (*Z* isomer) ^{19}F NMR δ (338 MHz, $CDCl_3$, C_6F_6) 7.5 (1F, q, J_{FF} = 3 Hz, F_2), 54.8 (1F, td, J_{HF} = 26 Hz, J_{FF} = 3 Hz, F_3); ^1H NMR δ (360 MHz, $CDCl_3$, TMS) 1.1 (9H, s, t-Bu), 1.4 (3H, J_{HH} = 7 Hz, O-C-CH_3), 1.6-1.7 (2H, m, H_6), 1.7-1.8 (2H, m, H_5), 2.8 (2H, dt, J_{HF} = 26 Hz, J_{HH} = 7 Hz, J_{HF} = 3 Hz, H_4), 3.7 (2H, t, J_{HH} = 7 Hz, H_7), 4.3 (2H, q, J_{HH} = 7Hz, O-CH_2), 7.3-7.5 (6H, m, Hs arom), 7.6-7.7 (4H, m, Hs arom); MNH_4^+ = 404; IR νC=O = 1732 cm^{-1}. **3b** (*E* isomer) ^{19}F NMR δ (188 MHz, $CDCl_3$, C_6F_6) -5 (1F, dt, J_{FF} = 129 Hz, J_{HF} =7 Hz, F_2), 37.1 (1F, dt, J_{FF} = 129 Hz, J_{HF} = 23 Hz, F_3). **15** ^{19}F NMR δ (188 MHz, $CDCl_3$, C_6F_6) 21.9 (1F, tdt, J_{HF} = 23Hz, J_{FF} = 9 Hz, J_{HF} = 2 Hz, F_5), 23.2 (1F, tdt, J_{HF} = 23 Hz, J_{FF} = 9 Hz, J_{HF} = 2 Hz, F_6); ^1H NMR δ (200 MHz, $CDCl_3$, TMS) 0.9 (3H, t, J_{HH} = 7 Hz, H_{20}), 1.2-1.5 (6H, m, $H_{17, 18, 19}$), 1.5-1.7 (4H, m, $H_{2, 3}$), 1.9-2.2 (2H, m, H_{16}), 2.2 (2H, J_{HF} = 23 Hz, J_{HH} = 6 Hz, J_{HF} = 2 Hz, H_4), 2.7-2.9 (4H, m, $H_{10, 13}$), 3.0 (2H, dd, J_{HF} = 23 Hz, J_{HH} = 7 Hz, H_7), 3.7 (2H, t, J_{HH} = 6 Hz, H_1) 5.3-5.6 (6H, m, $H_{8, 9, 11, 12, 14, 15}$); MH^+ = 327. **1** ^{19}F NMR δ (188 MHz, $CDCl_3$, C_6F_6) 21.6 (1F, td, J_{HF} = 23 Hz, J_{FF} = 9 Hz, F_5), 24.5 (1F, td, J_{HF} = 23 Hz, J_{FF} = 9 Hz, F_6); ^1H NMR δ (200 MHz, $CDCl_3$, TMS) 0.9 (3H, t, J_{HH} = 7 Hz, H_{20}) 1.2-1.5 (6H, m, $H_{17, 18, 19}$), 1.9 (2H, p, J_{HH} = 7 Hz, H_3), 2.04 (2H, q, J_{HH} = 7 Hz, H_{16}), 2.2 (2H, ddt, J_{HF} = 23 Hz, J_{HF} = 2 Hz, J_{HH} = 6 Hz, H_4), 2.4 (2H, t, J_{HH} = 7 Hz, H_2), 2.8 (2H, t, J_{HH} = 7Hz, H_{13}), 2.84 (2H, t , J_{HH} = 7Hz, H_{10}) 3.0 (2H, dd, J_{HF} = 23 Hz, J_{HH} = 7 Hz, H_7), 5.2-5.6 (6 H, m, Hs vinylic); MNH_4^+ = 358; IR νC=O = 1711cm^{-1}.

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