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Total synthesis of 4-F_{3t}-neuroprostane and its 4-epimer

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ABSTRACT

The first synthesis of 4-F_{3t}-Neuroprostane **1a** and its 4-epimer is described. This molecule presents an important contribution to the study of neuronal oxidative stress in DHA-ω3 depleted brain. The key step involves the introduction of two unsaturated side chains into the chiral polyfunctional cyclopentane **4** via *E* selective HWE reaction and *Z* selective Wittig olefination for α and ω chains, respectively.

Polyunsaturated fatty acids (PUFAs) play an important role in the defence of living organisms against the toxic effects of oxygen due to their ability to transform the diradical to degradable organic compounds. Neuroprostanes along with isoprostanes and phytoprostanes belong to a large family of prostaglandin-like compounds, which are formed in vivo from these PUFAs.[1] Neuroprostanes are created by the action of reactive oxygen species (ROS) on the membrane phospoholipids via non-enzymatic, free-radical peroxidation of docosahexaenoic acid (DHA; C22:6ω3).[2]

The formation of neuroprostanes increases dramatically under conditions of an oxidative stress, therefore their measurement could provide a unique marker of oxidative neuronal injury and could mean an important advance in our ability to explore the role of free radicals in the pathogenesis of human diseases.[3] Investigation of rats depleted in long-chain polyunsaturated ω3 fatty acid (ω3-depleted rats) showed a significant non-reciprocal increase in a concentration of docosapentaenoic acid (DPA; C22:5ω6) in neuronal tissues.[4] This experimental model represents an occidental human being with a deficit of ω3 PUFAs in nutrition.[5] Our interest to confirm the formation of such lipids prompted us to prepare these F_3-neuroprostanes by total chemical synthesis, which should broaden the knowledge concerning their role as mediators of oxidative stress.

Our project focuses on one potential metabolite of peroxidation of DPA—4-F_{3t}-neuroprostane **1a**—(Scheme 1), and it presents a first total synthesis of compound **1a** starting from the commercially available (*E*)-3-(furan-2-yl)acrylic acid **2** (Scheme 2).

The first 12 steps leading to the substrate **3** were completed in 9% overall yield via our previously reported procedure.[6]

Compound **4** was obtained in excellent yield and with well-defined diastereoselectivity using diimide, by reduction of the tetrasubstituted double bond **3** (Scheme 3). These controlled conditions afforded substrate **4** with the required *syn–anti–syn* orientation.[6]

Having the starting compound **4** in our hands we could switch to an introduction of α and ω chains. Firstly, the ester function was reduced by treatment of DIBAL-H. The adjunction of the ω chain of the neuroprostane was achieved by using (*Z*)-non-3-enyl triphenylphosphonium iodide **6**, which was prepared from commercially available *cis*-non-3-en-1-ol by iodination and subsequent addition of PPh_3.[7] The presence of K_2CO_3 was required to avoid epimerization of the double bond (Scheme 4). The Wittig reaction between aldehyde **5** and the ylide derived from the phosphonium salt **6** occurred smoothly in the presence of NaHMDS, and afforded the pure all *cis* dienic **7** in good 70% total yield after 2 steps (Scheme 4).

No traces of trans olefination could be detected by ^{13}C or ^{1}H NMR analysis. Subsequently, the α-chain of the neuroprostane was introduced by a Horner–Wadsworth–Emmons (HWE) reaction using β-ketophosphonate **9**, prepared in 2 steps (Scheme 4).[8] Acetal **7** was converted by acidic hydrolysis into aldehyde **8**, and the crude was directly applied in the next step. The olefination of aldehyde **8** underwent under same conditions as the previous Wittig

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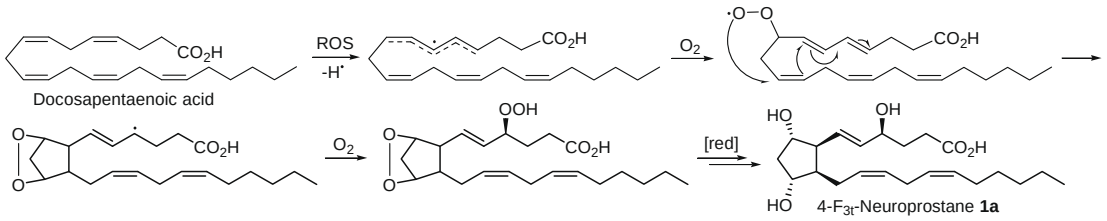
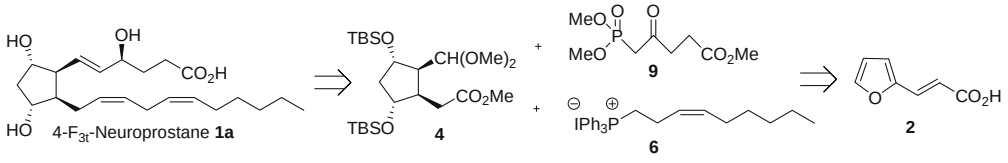
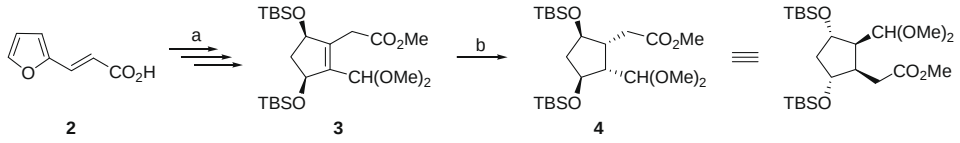


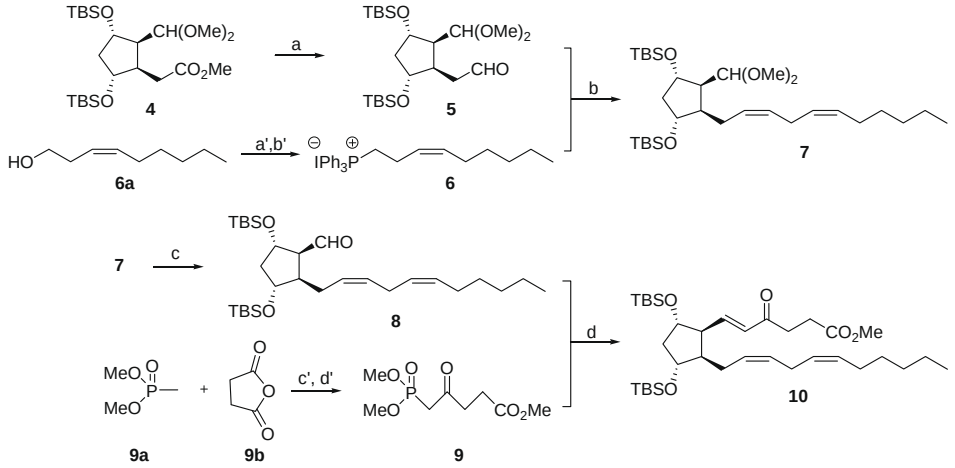
Scheme 1. Possible pathway of free-radical cyclization of DPA.



Scheme 2. Retrosynthesis of 4-F_{3t}-Neuroprostane **1a**.



Scheme 3. Reagents and conditions: (a) see Ref. 6; (b) dipotassium diazodicarboxylate salt, AcOH, MeOH, butanone, pyridine, reflux, 3 days, 72%.



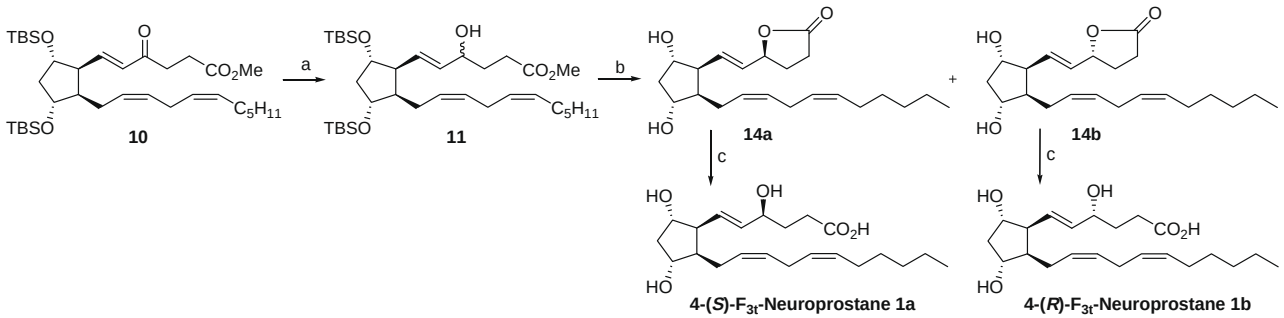
Scheme 4. Reagents and conditions: (a) DIBAL-H, toluene, −78 °C, 1 h; (b) NaHMDS, THF, −78 °C to rt, 2 h, 70% (2 steps); (c) I_2, PPh_3, Im, CH_2Cl_2, 0 °C, 2 h, 94%; (d) PPh_3, toluene, K_2CO_3, reflux, 24 h, 87%; (e) *p*-TsOH, acetone, reflux, 30 min; (f) NaHMDS, THF, −78 °C to rt, 4 h, 55% (2 steps); (g) *n*-BuLi, Et_2O, −78 °C; (h) MeOH, H_2SO_4, 2 h, 48%.

reaction affording the *trans* α,β-enone ester **10** in acceptable 55% overall yield after 2 steps (Scheme 4).[9] The prompt purification of the resulting ketone allowed to avoid elimination or epimerization.

Following reduction of the ketone under Luche conditions[10] involving $NaBH_4$ in the presence of $CeCl_3$ afforded a diastereoisomeric mixture of alcohols **11** in high yield (Scheme 5). A separation of both diastereoisomers was the final crucial issue of this synthesis. First approach was based on the coupling of (*R*) or (*S*)-*O*-acetyl mandelic acid with free alcohols **11**.[11] Unfortunately, the hydroxyl group in 4-position close to carboxyl function is hindered and unreactive, and this reaction occurred with poor results.

Afterwards, the stereospecific reduction using Noyori's (*S*)-BINAL-H[12] was tried but this strategy failed as well because in our case, it was carried out only selectively not specifically. Besides, this procedure enabled to confirm the absolute stereochemistry at C4. The technique usually used for such types of compound is reverse phase HPLC, but this method was not suitable in our case because of total decomposition of the substrate under acidic conditions. Fortunately, after the deprotection of both TBS groups in the presence of tetrabutylammonium fluoride (TBAF), the two lactones **14a** and **14b** were obtained in high yield.[13] We were pleased to uncover the separability of the diastereoisomers using an appropriate size of chromatographic column, although always with approximately 30% of mixed fractions. Subsequently, the opening of lactone occurred smoothly using LiOH, in THF and final product 4(*S*)-F_{3t}-neuroprostane **1a** and its 4-epimer **1b** were obtained in quantitative yield (Scheme 5).[14]

In conclusion, the first total synthesis of both optically pure diastereoisomers of the 4(*S*)-F_{3t}-neuroprostane **1a** and 4(*R*)-F_{3t}-neuro-



Scheme 5. Reagents and conditions: (a) $CeCl_3$, $NaBH_4$, MeOH, 0 °C, 5 min, 87%; (b) TBAF in THF, 4 h, rt, 91%; (c) LiOH, THF, 4 h, quantitative yield.

prostane **1b** was accomplished in 20 steps and 22% overall yield after eight steps starting from cyclopentene **3**. Our strategy which enables us to introduce the ω and α chains into the cyclopentane ring **4** is based on the Wittig and HWE reactions. Further studies regarding the biological activity of 4-F_{3t}-neuroprostane **1a** and its 4-epimer **1b** in order to profoundly understand their role in ω3-depleted organism are in progress and will be reported in due time.

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9. *Selected physicochemical data for compound* **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (dd, *J* = 9.9, 15.6 Hz, 1H), 6.16 (d, *J* = 15.6 Hz, 1H), 5.43–5.24 (m, 4H), 3.99 (m, 1H), 3.86 (m, 1H), 3.66 (s, 3H), 2.86–2.77 (m, 3H), 2.74–2.66 (m, 2H), 2.61 (t, *J* = 6.8 Hz, 2H), 2.36 (dt, *J* = 6.9, 13.8 Hz, 1H), 2.22–2.10 (m, 1H), 2.10–1.88 (m, 4H), 1.57 (dt, *J* = 13.7 Hz, 4.8 Hz, 1H), 1.42–1.20 (m, 6H), 0.93–0.70 (m, 24H), 0.02 (s, 6H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 197.3, 173.2, 146.0, 130.9, 130.5, 129.2, 127.9, 127.3, 75.5, 75.3, 52.8, 51.7, 50.7, 44.3, 35.1, 31.4, 29.2, 27.8, 27.2, 26.4, 25.7 (2C), 22.5, 17.9, 13.9, −4.5, −4.7, −4.8 (2C).
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13. *Hydrolysis of lactone* **1a** *and selected physicochemical data for compound* **14a**: To a solution of lactone **14a** (0.07 mmol, 1.0 eq) in 1 mL of THF was added a 1 M solution of aqueous LiOH (207 mL, 0.21 mmol, 3 eq) at room temperature under N_2 atmosphere. After stirring for 4 h, the mixture was acidified with 0.1 M solution of $NaHSO_4$ (1 mL) and 10 mL of EtOAc were added. The layers were separated and the aqueous one extracted with 3 × 5 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and the solvents evaporated. The triol-acid **1a** was obtained as an yellow oil (25 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.64–5.61 (m, 2H), 5.42–5.24 (m, 4H), 4.93–4.86 (m, 1H), 4.05–3.95 (m, 2H), 2.87–2.77 (m, 1H), 2.75–2.68 (m, 2H), 2.54–2.48 (m, 2H), 2.45–2.40 (m, 2H), 2.23–2.12 (m, 1H), 2.05–1.89 (m, 7H), 1.65 (dt, *J* = 3.9, 14.5 Hz, 1H), 1.35–1.19 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 176.7, 132.2, 130.7, 130.2, 129.8, 127.8, 127.2, 80.2, 76.3 (2C), 53.4, 50.8, 42.4, 31.4, 29.2, 28.7, 28.4, 27.2, 26.9, 25.7, 22.5, 14.0; $[\alpha]_D^{20}$ +44.4 (*c* 5.0, $CDCl_3$); HR-MS (ES+) calcd for $C_{22}H_{35}O_4$ [M+H] 363.2535, found 363.2542.
Selected physicochemical data for compound **14b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.63–5.61 (m, 2H), 5.42–5.25 (m, 4H), 4.91–4.88 (m, 1H), 4.10–4.02 (m, 1H), 4.00–3.95 (m, 1H), 2.87–2.79 (m, 1H), 2.75–2.71 (m, 2H), 2.56–2.49 (m, 2H), 2.46–2.34 (m, 2H), 2.25–2.12 (m, 1H), 2.05–1.93 (m, 5H), 1.95–1.76 (br s, 2H), 1.66 (dt, *J* = 3.9; 14.5 Hz, 1H), 1.36–1.24 (m, 6H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 176.7, 132.4, 130.6, 130.1, 129.7, 127.9, 127.2, 80.3, 76.3, 76.1, 53.4, 50.7, 42.4, 31.4, 29.2, 28.7, 28.5, 27.2, 26.9, 25.7, 22.5, 14.0; $[\alpha]_D^{20}$ −5.0 (*c* 5.0, $CDCl_3$); HR-MS (ES+) calcd for $C_{22}H_{35}O_4$ [M+H] 363.2535, found 363.2529.
14. *Selected physicochemical data for compound* **1a**: ^{1}H NMR (300 MHz, CD_3OD): δ 5.56–5.51 (m, 2H), 5.46–5.27 (m, 4H), 4.08–4.01 (m, 1H), 3.98–3.92 (m, 1H), 3.88–3.82 (m, 1H), 2.79–2.74 (m, 2H), 2.72–2.63 (m, 1H), 2.45 (dt, *J* = 7.2, 14.2 Hz, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.14–1.97 (m, 5H), 1.77 (q, *J* = 6.8 Hz, 2H), 1.52 (dt, *J* = 5.1, 14.2 Hz, 1H), 1.41–1.22 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 180.7, 134.7, 129.6, 129.0, 128.4, 128.1, 127.5, 74.8, 74.7, 71.1, 52.1, 49.9, 42.1, 32.2, 31.2, 30.2, 29.0, 26.7, 25.9, 25.3, 22.1, 12.9; $[\alpha]_D^{20}$ −0.8 (*c* 2.5, MeOH); HR-MS (ES+) calcd for $C_{22}H_{37}O_5$ [M+H] 381.2641, found 381.2646.
Selected physicochemical data for compound **1b**: ^{1}H NMR (300 MHz, CD_3OD): δ 5.61–5.52 (m, 2H), 5.44–5.28 (m, 4H), 4.10–4.06 (m, 1H), 4.01–3.96 (m, 1H), 3.91–3.86 (m, 1H), 2.84–2.77 (m, 2H), 2.72–2.66 (m, 1H), 2.53–2.43 (m, 1H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.16–1.99 (m, 5H), 1.80 (q, *J* = 6.8 Hz, 2H), 1.54 (dt, *J* = 14.1 Hz, 5.1 Hz, 1H), 1.40–1.22 (m, 6H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 180.7, 135.2, 129.6, 128.6, 128.4, 128.1, 127.5, 74.9, 74.8, 72.0, 52.3, 49.9, 42.0, 33.5 (2C), 31.2, 29.0, 26.7, 26.0, 25.3, 22.1, 12.9; $[\alpha]_D^{20}$ −10.2 (*c* 5.0, MeOH); HR-MS (ES+) calcd for $C_{22}H_{37}O_5$ [M+H] 381.2641, found 381.2649.