

Total synthesis of 4(*RS*)-F_{4t}-isoprostane methyl ester

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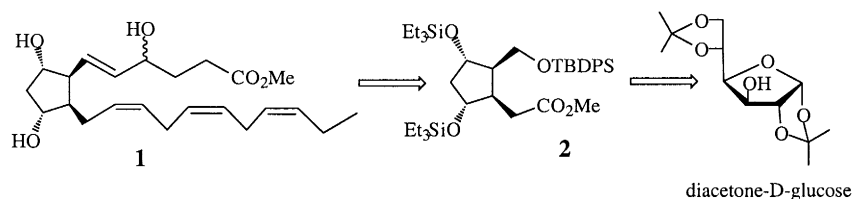
Abstract

The first total synthesis of 4(*RS*)-F_{4t}-isoprostane methyl ester **1** is described using diacetone-D-glucose as starting material. This new isoprostane (neuroprostane) would be very useful in neurological studies as a potent lipid peroxidation index to obtain an integrated assessment of oxidative stress in the human brain. © 2000 Elsevier Science Ltd. All rights reserved.

F₂-Isoprostanes are prostaglandin-like compounds derived by free radical-catalyzed peroxidation from arachidonic acid (AA)¹ and are endowed with a powerful biological activity.² During the last decade, there has been a growing interest in the total synthesis of these optically active prostanoids.³ Free radicals have been implicated in the pathogenesis of a wide variety of human disorders,⁴ specifically in Alzheimer's disease.⁵ The measurement of levels of endogenous unmetabolized F₂-isoprostanes has proven to be a valuable approach to assess oxidative stress in vivo.

Docosahexaenoic acid (DHA) is an essential requirement for the development of the brain and retina ranges from 20 to 60% of the total fatty acid content, and is present esterified to phospholipids.⁶ Peroxidation of DHA produces F₄-isoprostanes (neuroprostanes).⁷ Eight subfamilies of F₄-isoprostanes could be formed from DHA owing to free catalyzed attacks at positions C6, C9, C12, C15 and C18. These different families of isoprostanes should be unique biomarkers of peroxidation of fatty acids and would be very useful in neurological studies if they could be quantified in the human brain.

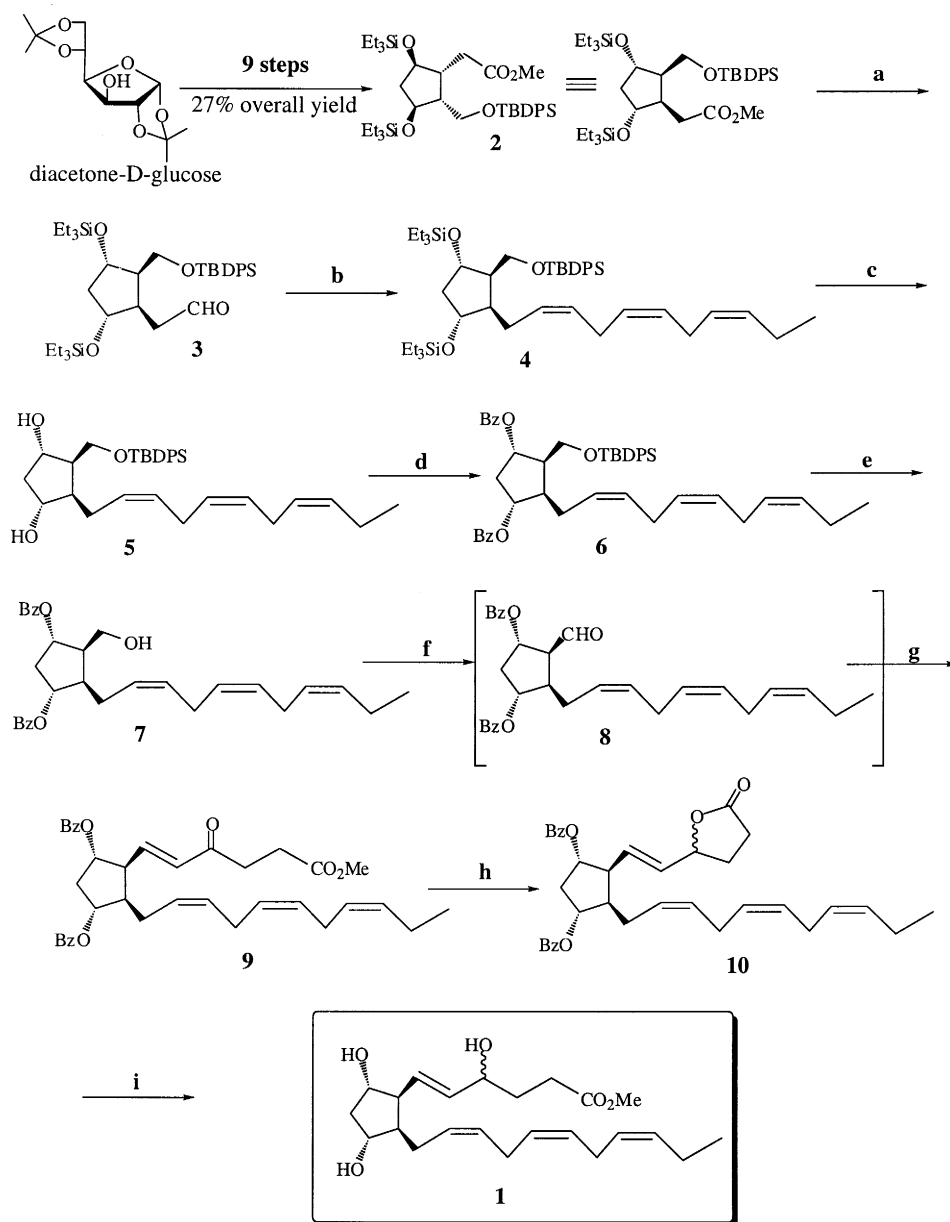
In connection with our program directed towards the synthesis of isoprostanes, we now report the first total synthesis of 4(*RS*)-F_{4t}-isoprostane methyl ester **1** from the alcoxyester **2**⁸ (Scheme 1).



Scheme 1.

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The synthesis of 4(*RS*)-F_{4t}-isoprostane methyl ester **1** from the commercially available diacetone-D-glucose as starting material, is shown in Scheme 2. The first nine steps leading to cyclopentane alcoxyester **2** were achieved in 27% overall yield by using the *iodo* pathway, according to our procedure.⁸



Scheme 2. (a) 1.1 equiv. DIBAL-H (1 M in toluene), toluene, -80°C , 30 min, 93%; (b) 4 equiv. [(*Z,Z*)-3,6-nonandiene-1-yl] triphenylphosphonium iodide, 3.8 equiv. $\text{NaN}(\text{SiMe}_3)_2$, THF, -80°C to 20°C , 2 h, 68%; (c) NH_4F , THF–MeOH, 4 h, 92%; (d) 4 equiv. BzCl , pyridine, 20°C , 1 h, 86%; (e) HCl 3% in MeOH, 20°C , overnight, 73%; (f) periodinane, CH_2Cl_2 , rt, 2 h; (g) 1.2 equiv. diethyl[4-(methoxycarbonyl)-oxobutyl]phosphonate, 1.1 equiv. $\text{NaN}(\text{SiMe}_3)_2$, THF, 20°C , 30 min, 64%; (h) 1.1 equiv. L-Selectride®, THF, -78°C , 20 min, 65%; (i) 1N NaOH, THF–MeOH, rt, 1 h, then CH_2N_2 63%

The alcoxyester **2** was converted into the aldehyde **3** by treatment with DIBAL-H in anhydrous toluene (Scheme 2) with 93% yield.

The introduction of the ω chain of the neuroprostane was achieved by using a nine-carbon homologating agent, [(*Z,Z*)-3,6-nonandiene-1-yl]triphenylphosphonium iodide.⁹ The aldehyde **3** reacted with the

ylide derived from this phosphonium salt and sodium hexamethyldisilyl amide as a base, in anhydrous THF at -80°C , to afford the pure *all*-(*Z*) trienic ether **4** in 68% yield.¹⁰ No trace of the *trans* compound could be detected by ^{13}C and ^1H NMR analysis. All the relative configurations were checked by homonuclear ^1H NOE experiments.

Deprotection of the triethylsilyl groups with ammonium fluoride in a mixture of MeOH:THF (2:1) at 60°C gave the diol **5** in 92% yield. The protection of the hydroxy functions of **5** with benzoyl chloride in dry pyridine gave the colorless diesters **6** in 86% yield. The *tert*-butyldiphenylsilyl ether **6** was converted into the alcohol **7** with a solution of 3% hydrogen chloride¹¹ in methanol:diethyl ether (1:1, v/v), prepared freshly from acetyl chloride and methanol, a method which proved to be much milder and to give a higher yield (73%) than TBAF in THF. Dess–Martin oxidation¹² of **7** with periodinane in CH_2Cl_2 gave the unstable aldehyde **8** which was immediately used in the next step without purification. It is important to note that this Dess–Martin oxidation gave a higher yield avoiding any epimerization than our first attempts using Swern conditions. The condensation of **8** with diethyl [4-(methoxycarbonyl)-2-oxobutyl]phosphonate,¹³ in the presence of sodium hexamethyldisilyl amide, in anhydrous THF at room temperature, afforded the *trans*- α,β enone ester **9** in 64% overall yield from the alcohol **7**. Reduction of the keto function of **9** with L-Selectride[®]¹⁴ furnished the mixture of epimeric lactones **10** in 65% yield, which could not be separated by flash chromatography.

Finally, cleavage of the lactone and esters of **10** with 1N NaOH at room temperature, followed by excess of CH_2N_2 , afforded **1**¹⁵ in 63% yield.

In conclusion, we describe herein the first stereoselective synthesis of 4(*RS*)- F_{4t} -neuroprostane methyl ester **1** in nine steps from the alcoxyester **2**. This neuroprostane should be very useful in neurological studies as a potent lipid peroxidation index to obtain an integrated assessment of oxidative stress in the human brain.

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10. Compound **4**: ^1H NMR (200 MHz, CDCl_3) δ : 7.61–7.73 (m, 5H), 7.36–7.46 (m, 5H), 5.19–5.45 (m, 6H), 4.06–4.14 (m, 1H), 3.94 (q, 1H, $J=7.2$ Hz), 3.6 (d, 2H, $J=4.8$ Hz), 2.61–2.84 (m, 4H), 1.98–2.43 (m, 7H), 1.47–1.59 (td, 1H, $J=4$ and 14 Hz), 1.06 (s, 9H), 0.83–0.99 (m, 21H), 0.40–0.63 (m, 12H). ^{13}C NMR (50 MHz, CDCl_3) δ : 135.6, 133.4, 131.9, 129.6, 129.1, 128.3, 128.1, 128, 127.6, 127.1, 76.3, 73.2, 62.6, 50.6, 48.2, 45.1, 26.8, 25.7, 25.5, 25.4, 19.1, 14.2, 6.8, 6.7, 4.9, 4.7.
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15. Compound **1**: UV (ethanol) λ_{max} : 205 nm. ^1H NMR (360 MHz, CDCl_3) δ : 5.62–5.54 (m, 1H, H-5), 5.54–5.48 (m, 1H, H-6), 5.47–5.23 (m, 6H, H-13, H-14, H-16, H-17, H-19, H-20), 4.19–4.10 (m, 1H, H-4), 4.07–3.96 (m, 1H, H-8), 4.01–3.93 (m, 1H, H-10), 3.66 (s, 3H, OMe), 2.81–2.75 (m, 5H, H-7, H-15, H-18), 2.45–2.37 (m, 3H, H-9, H-2), 2.22–2.13 (m, 1H, H-11), 2.08–1.99 (m, 4H, H-12, H-21), 1.91 (dd, 1H, $J=5$ Hz, $J=1$ Hz, OH-8), 1.88–1.80 (m, 2H, H-3), 1.73 (dd, 1H, $J=5$ Hz, $J=3$ Hz, OH-10), 1.64 (td, 1H, $J_{9,9'}=15$ Hz, $J_{9',8}=J_{9',10}=4.5$ Hz, H-9'), 0.96 (t, 3H, $J_{22,21}=7.5$ Hz, H-22). ^{13}C NMR (90 MHz, CDCl_3) δ : 172.2 (C-1), 135.2 (C-5), 132.1 (C-20), 129.3 (C-6, C-16), 128.7 (C-17), 128.4 (C-14), 127.6 (C-13), 126.9 (C-19), 76.4 (C-8, C-10), 71.5 (C-4), 53.6 (C-7), 51.7 (OMe), 50.8 (C-11), 42.4 (C-9), 32.0 (C-3), 30.0 (C-2), 27.1 (C-12), 25.7 (C-15, C-18), 20.5 (C-21), 14.2 (C-22). IR (NaCl) ν : 3520, 1720.