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Total Synthesis of 15(RS)-5,6-Dehydro-8-*epi*-PGF$_{2\alpha}$ Methyl Ester by a Biomimetic Process.

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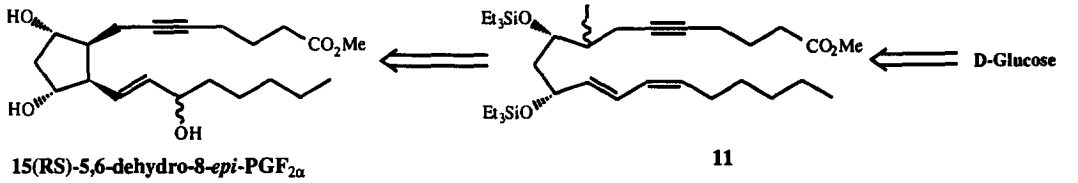
Abstract. The first total synthesis of 15(RS)-5,6-dehydro-8-*epi*-PGF$_{2\alpha}$ methyl ester **1** with high stereoselectivity and good yield, is described using D-glucose as starting material. This novel isoprostane is a potent precursor of labelled (deutered and/or tritiated) 8-*epi*-PGF$_{2\alpha}$, an useful tool for biological studies. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Since the discovery of isoprostaglandines by Roberts *et al*[1], there has been a growing interest in the total synthesis[2] of these optically active prostanoids[3].These natural products synthesized *in vivo* by a free radical-catalyzed mechanism[1], are indeed endowed with a powerful biological activity[3]. It has also been identified as a minor by-products in the enzymatic cyclooxygenases[4-5] peroxidation of arachidonic acid (AA). With reference to the kinetic stereocontrol of hex-5-enyl radical cyclization giving preferentially *cis*-substituted cyclopentane derivatives[6], we describe herein a biomimetic route to the total synthesis of isoprostane series, namely, 15(RS)-5,6-dehydro-8-*epi*-PGF$_{2\alpha}$ methyl ester **1** (Scheme 1). The key step is the cyclization reaction of iodo-precursor **11**, under radical conditions (Bu_3SnH, BEt_3) and a stream of dry argon, followed by injection of dry air and finally addition of Ph_3P as reducing agent. On the other hand, the total synthesis of this isoprostane-F_2 series has become an interesting target, specially for the development of the analytical methodology with the easy access to labelled isoPG compounds and the understanding of this new metabolic non-enzymatic pathway of AA cascade.



15(RS)-5,6-dehydro-8-*epi*-PGF$_{2\alpha}$

1

11

Scheme 1

The synthesis of 15(RS)-5,6-dehydro-8-*epi*-PGF$_{2\alpha}$ methyl ester **1** from the commercially available diacetone-D-glucose **2** as starting material, is shown in Scheme 2. The first steps leading to acetylenic methyl ester **4** was achieved according to the procedure published by Just *et al*, on oxidation products of AA[7]. Treatment of homopropargylic alcohol **4** with triflic anhydride in pyridine/dichloromethane[8] gave the corresponding triflate **5** in 85% yield.

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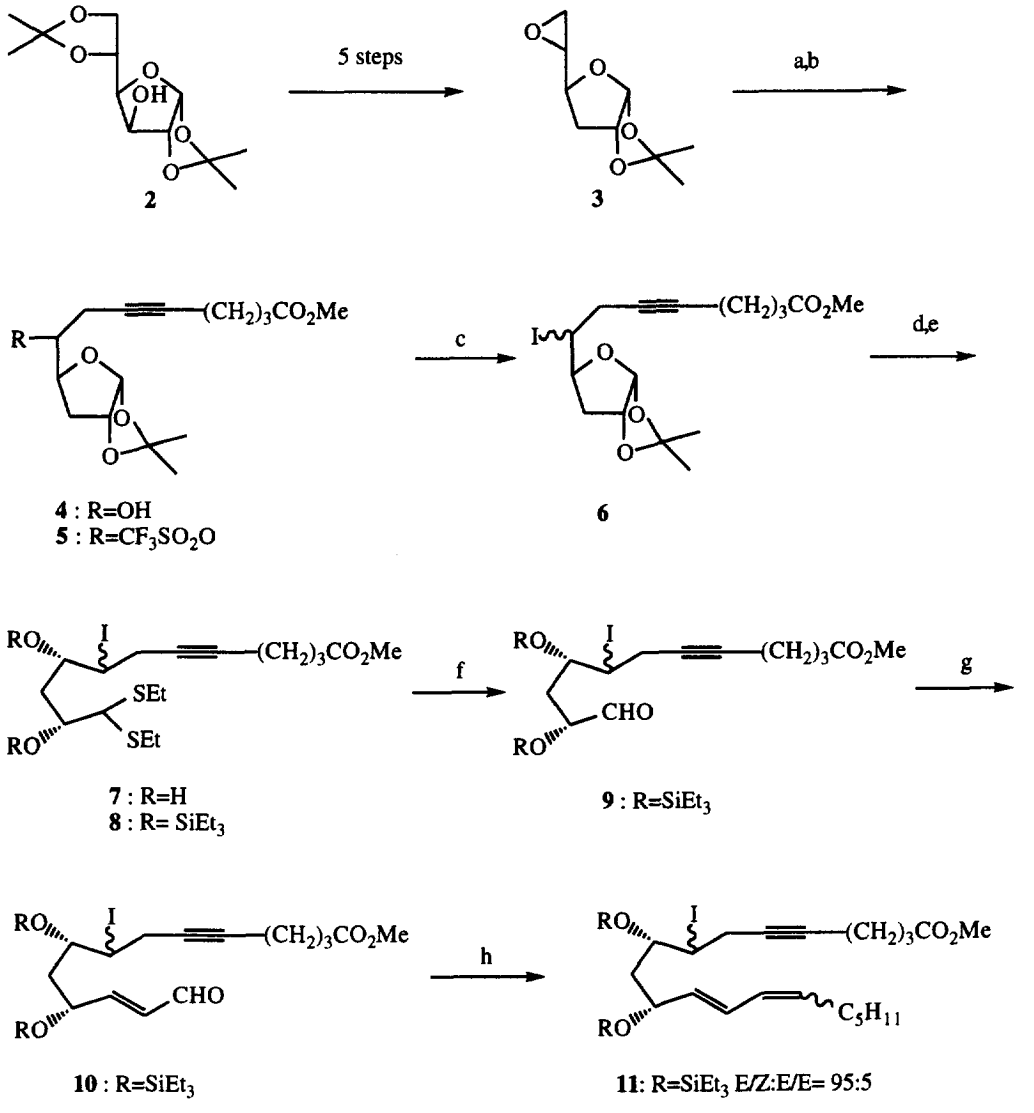
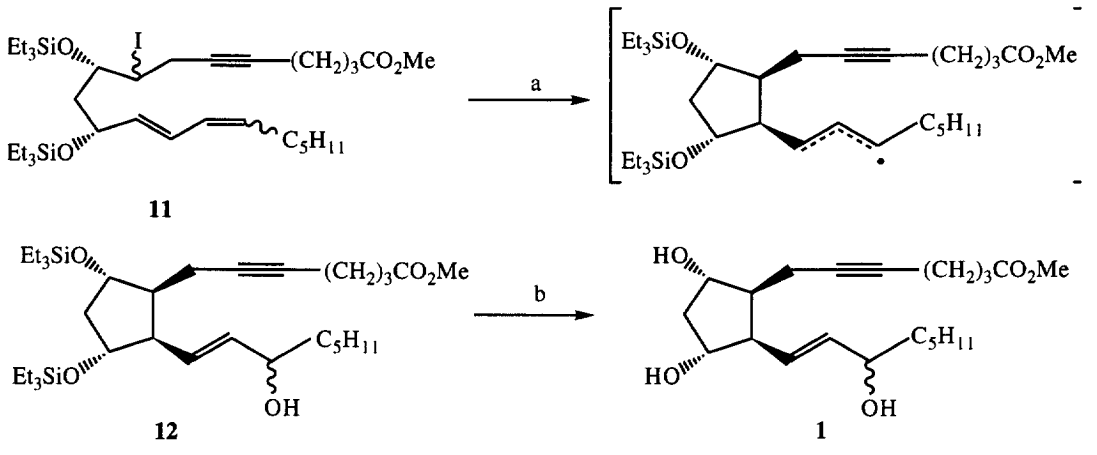
Iodo derivative **6**[8,9] was obtained using n-Bu_4NI in benzene in 75% yield. Treatment of compound **6** with $ZnCl_2$ in ethanethiol at -15°C afforded diol-thioacetal **7** in 85% yield, which was protected into disilyl ether **8** in the presence of triethylsilyl chloride in pyridine at room temperature in 89% yield. Removal of the thioacetal group under neutral conditions ($HgCl_2$/HgO) in acetone/water gave the unstable aldehyde **9** which was immediately used in the next step without further purification.



a) 2 eq 5-hexynoic acid, 4 eq n-BuLi, HMPT, 0°C to 25°C, overnight, CH_2N_2. b) 2 eq $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 2hrs. c) 2 eq n-Bu_4NI, Benzene, 80°C, 1hr. d) 4 eq $ZnCl_2$, EtSH, -15°C, 1hr. e) 8 eq Et_3SiCl, pyridine, 20°C, 1day. f) HgO/$HgCl_2$, acetone/water, 20°C, 9hrs. g) 1.5 eq (formylmethylene triphenylphosphorane), DMF, 20°C, overnight. h) 2.1 eq hexyl triphenyl phosphonium bromide, 2 eq n-BuLi, THF, -78°C, 1hr.

Scheme 2

A first Wittig reaction in the presence of formylmethylene triphenylphosphorane (1.5 eq) in dry DMF afforded the α, β-unsaturated aldehyde **10** in 69% yield. The Wittig reaction with commercial hexyltriphenyl phosphonium bromide (2.1 eq) and butyllithium (2 eq) in dry THF at -78°C proceeded smoothly to give the mixture (E/Z, E/E) olefins **11**[10] in a ratio 95:5 in 90% yield.



a) 1.2 eq n-Bu_3SnH, 1 eq BEt_3, O_2, xylene, 20°C, 0.5 hr, 1.1 eq Ph_3P b) 1 eq n-Bu_4NF, THF, 20°C, 2hrs.

Scheme 3

Finally, the cyclization of **11** was achieved using Bu_3SnH (1.2 eq) and BEt_3 (1 eq) in dry xylene at room temperature, under a stream of dry argon, followed by injection of dry air and addition of Ph_3P to afford the protected isoprostane **12** in 55% yield as a mixture of 15-epimers as a major product of the reaction. The deprotection of the bis-silyl groups in **12** was carried out using tetrabutylammonium fluoride in dry THF at room temperature to give 15(RS)-5,6-dehydro-8-*epi*-$PGF_{2\alpha}$ methyl ester **1**[11] in 90% yield.

In conclusion, we have shown that the 5-*exo*-radical cyclization applied on a highly functionnalized precursor could be an efficient generator of β-hydroxy carbon free radicals. Our biomimetic pathway with molecular oxygen trapping under classical tin hydride conditions have allowed us the synthesis of 15(RS)-5,6-dehydro-8-*epi*-$PGF_{2\alpha}$ methyl ester **1** , which will be transformed after specific reduction of the triple bond into different labelled (deutered and/or tritiated) 8-*epi* -$PGF_{2\alpha}$. On the other hand, these results clearly demonstrate that the cyclization reaction can run on esterified arachidonate and provide the chemical evidence that the cyclization reaction catalyzed by free radicals can be realized, *in situ*, on the membranes as described by Roberts and coworkers [12].

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9. Compound **6 : ^{1}H-NMR** (360 MHz, $CDCl_3$) δ : 5.82-5.83 (d, J=3.6 Hz, 1H, H-1), 4.72-4.74 (t, J=4.2 Hz, 1H, H-2), 4.10-4.15 (td, J=3.6, J=7.2 Hz, 1H, H-5), 3.90-3.95 (m, 1H, H-4), 3.65 (s, 3H, OCH_3), 2.83-2.90 (m, 2H, H-6), 2.41-2.45 (t, J=7.4 Hz, 2H, H-11), 2.16-2.23 (m, 3H, H-3, H-9), 1.71-1.83 (m, 3H, H-3', H-10), 1.49 (s, 3H, $(\underline{CH_3})_2C$), 1.30 (s, 3H, $(\underline{CH_3})_2C$). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ : 173.6 (C-12), 111.6 $(CH_3)_2\underline{C}$), 105.6 (C-1), 81.8 (C-8), 80.5 (C-2), 79.2 (C-4), 78.8 (C-7), 51.5 (OCH_3), 38.8 (C-3), 34.8 (C-5), 32.9 (C-11), 28.3 (C-6), 26.9, 26.4 $(\underline{CH_3})_2C$), 23.9 (C-10), 18.2 (C-9).
10. Compound **11 : ^{1}H-NMR** (360 MHz, $CDCl_3$) δ : 6.38-6.44 (dd, J=11.1, J=15.2 Hz, 1H, H-13), 5.91-5.96 (t, J=10.9 Hz, 1H, H-14), 5.53-5.59 (dd, J=6.9, J=15.2 Hz, 1H, H-12), 5.39-5.46 (td, J=7.7, J=10.7 Hz, 1H, H-15), 4.18-4.23 (m, 2H, H-8, H-11), 3.65 (s, 3H, OCH_3), 3.40-3.44 (m, 1H, H-9), 2.70-2.90 (m, 2H, H-7), 2.41-2.45 (t, J=7.5 Hz, 2H, H-2), 2.13-2.18 (m, 4H, H-4, H-16) 1.63-1.98 (m, 4H, H-3, H-10), 1.32-1.39 (m, 2H, H-17), 1.23-1.28 (m, 4H, H-18, H-19), 0.90-0.97 (m, 18H, $OSiCH_2\underline{CH_3}$), 0.85-0.87 (t, J=6.9 Hz, 3H, H-20), 0.53-0.63 (m, 12H, $OSi\underline{CH_2}CH_3$).
    ^{13}C-NMR (90 MHz, $CDCl_3$) δ : 173.6 (C-1), 135.3 (C-12), 132.8 (C-15), 127.7 (C-14), 125.8 (C-13), 81.1 (C-5), 79.5 (C-6), 70.5 (C-11), 70.4 (C-9), 51.5 (OCH_3), 45.0 (C-10), 40.5 (C-8), 32.8 (C-2), 31.4, 22.5 (C-18, C-19), 29.3 (C-17), 27.7 (C-16), 27.2 (C-7), 23.9 (C-3), 18.2 (C-4), 14.0 (C-20), 6.8, 6.9 ($OSiCH_2\underline{CH_3}$), 5.0, 5.3 ($OSi\underline{CH_2}CH_3$).
11. Compound **1 : UV** (ethanol) λ_{max} : 202 nm. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ : 5.55-5.62 (dd, 1H, J=5.8, J=15.3 Hz, H-14), 5.37-5.46 (m, 1H, H-13), 4.09-4.14 (m, 1H, H-9), 4.02-4.07 (m, 2H, H-11, H-15), 3.66 (s, 3H, OCH_3), 2.76-2.77 (m, 1H, H-12), 2.39-2.43 (m, 3H, H-10, H-2), 2.25-2.34 (m, 1H, H-8), 2.18-2.20 (t, 2H, J=6.6 Hz, H-4), 2.00-2.09 (m, 2H, H-7), 1.76-1.80 (t, 2H, J=7.0 Hz H-3), 1.05-1.69 (m, 3H, H-10', H-16), 1.26-1.28 (m, 6H, H-17, H-18, H-19), 0.85-8.89 (m, 3H, H-20). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ : 174.2 (C-1), 136.7 (C-14), 127.7 (C-13), 80.2 (C-5, C-6), 76.2 (C-9), 76.1 (C-11), 74.5 (C-15), 53.6 (C-12), 51.6 (OCH_3), 49.7 (C-8), 42.3 (C-10), 37.3 (C-16) 32.9 (C-2), 31.7 (C-18), 25.1 (C-17), 24.1 (C-3), 22.5 (C-19), 19.1 (C-7), 18.1 (C-4), 13.9 (C-20).
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