



Total Synthesis of *ent*-15(RS)-2,3-dinor-5,6-dihydro-8-*epi*-PGF₂α

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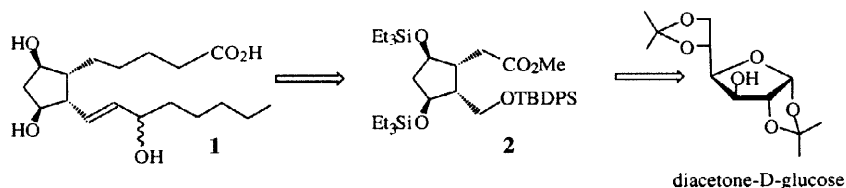
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Abstract. The first total synthesis of *ent*-15(RS)-2,3-dinor-5,6-dihydro-8-*epi*-PGF₂α **1** is described using diacetone-D-glucose as starting material. The major urinary metabolite of the isoprostane 8-*epi*-PGF₂α is 2,3-dinor-5,6-dihydro-8-*epi*-PGF₂α, which is a potent lipid peroxidation index to obtain an integrated assessment of oxidative stress in humans. © 1998 Elsevier Science Ltd. All rights reserved.

Since the discovery of isoprostaglandins by Roberts *et al*¹, there has been a growing interest in the total synthesis of these optically active prostanoids². These new natural products synthesized *in vivo* by a free radical-catalyzed mechanism¹, are indeed endowed with a powerful biological activity³. They have also been identified as minor by-products in the enzymatic cyclooxygenases⁴⁻⁵ peroxidation of arachidonic acid (AA). Free radicals have been implicated in the pathogenesis of a wide variety of human disorders⁶. Measurement of levels of endogenous unmetabolized F₂-isoprostanes has proven to be a valuable approach to assess oxidative stress *in vivo*. However, measurement of levels of urinary metabolites of F₂-isoprostanes in timed urine collections offers an advantage over measuring unmetabolized F₂-isoprostanes, e.g. in a plasma sample, in that it can provide an integrated index of isoprostane production over time⁷.

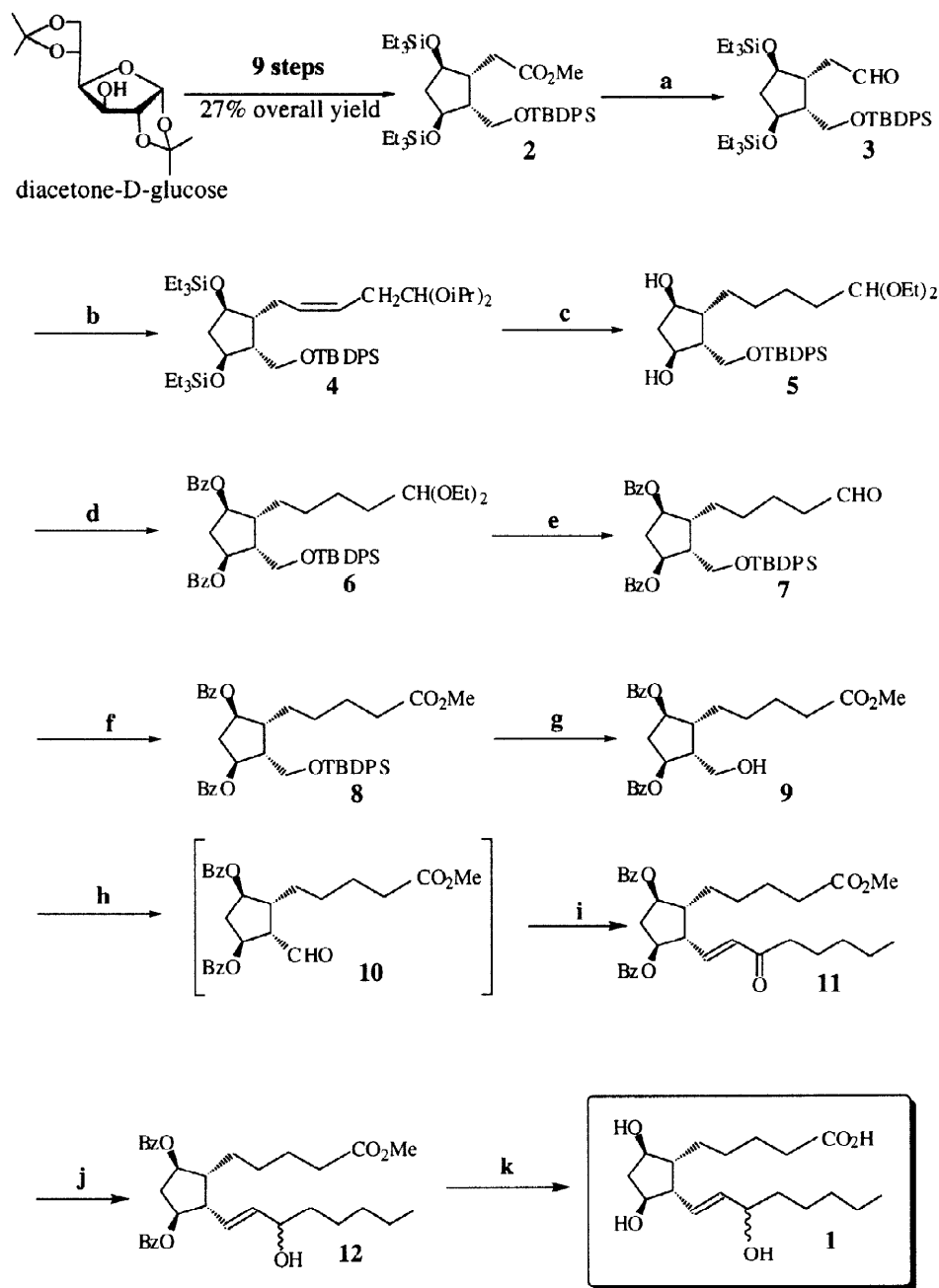
Recently, Roberts and co-workers⁷ published the identification of 2,3-dinor-5,6-dihydro-8-*epi*-PGF₂α as the major urinary metabolite of 8-*epi*-prostaglandin F₂α. In connection with our programme directed towards the synthesis of isoprostanes, we now report the total synthesis of *ent*-15(RS)-2,3-dinor-5,6-dihydro-8-*epi*-PGF₂α from the alcoxyester **2**⁸ (Scheme 1).



Scheme 1

The synthesis of *ent*-15(RS)-2,3-dinor-5,6-dihydro-8-*epi*-PGF₂α **1** from the commercially available diacetone-D-glucose as starting material, is shown in Scheme 2. The first 9 steps leading to cyclopentane alcoxyester **2** were achieved in 27% overall yield by using iodo pathway, according to our procedure⁸. The alcoxyester **2** was converted into the aldehyde **3** by treatment with DIBAL-H in anhydrous toluene (Scheme 2) with 93% yield.

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a) 1.1 eq DIBAL-H (1M in toluene), toluene, -80°C , 30 min, 93%. b) 4 eq (3,3-diisopropoxypropyl)triphenylphosphonium bromide, 3.8 eq NaHMDS, THF, -80°C then 20°C , 2 hrs, 83%. c) H_2 on Pd/C, EtOH, 4 hrs, 95%. d) 4 eq BzCl, pyridine, 20°C , 1 hr, 91%. e) catalytic FeCl_3 , acetone, reflux, 3 hrs, 87%. f) 4 eq *m*-CPBA, THF, 20°C , overnight, followed by CH_2N_2 , 89%. g) HCl 3% in MeOH, 20°C , overnight, 83%. h) $(\text{COCl})_2/\text{DMSO}/\text{Et}_3\text{N}$, CH_2Cl_2 , -60°C , 1 hr. i) 1.2 eq diethyl oxoheptylphosphonate, 1.1 eq NaH, THF, 20°C , 30 min, 89%. j) 1.1 eq L-selectride, THF, -78°C , 20 min, 100%. k) 1N NaOH, THF-MeOH, 40°C , 3 hrs, 83%.

Scheme 2

The introduction of the α chain of the isoprostane was achieved by using a three-carbon homologating agent, the (3,3-diisopropoxypropyl)triphenyl phosphonium bromide⁹. The aldehyde **3** (0.05 M) reacted with the ylide derived from this phosphonium salt and NaHMDS as a base, in anhydrous THF at -80°C , to afford the pure *cis*- β,γ ethylenic diisopropyl acetal **4** in 83% yield. No trace of *trans* compound could be detected by ^{13}C and ^1H NMR analysis. All the relative configurations were achieved by homonuclear ^1H nOe experiments.

The *cis*-double bond of **4** was reduced with H₂ on Pd/C 10% in dry EtOH to give the diol diethyl acetal **5** in 95% yield. Interestingly, during this hydrogenation we could not avoid respectively the deprotection of the triethyl silyl ethers and the *trans* acetalisation with the solvent. The protection of the hydroxy functions of **5** with benzoyl chloride in dry pyridine gave the colourless diesters **6**¹¹ in 91% yield. Hydrolysis of the diethyl acetal **6** with aqueous FeCl₃ in acetone, at reflux afforded the aldehyde **7** in 87% yield. Oxidation of **7** with *m*-CPBA in dry THF, and further reaction with diazomethane, gave the methyl ester **8** in 89% yield. The *tert*-butyldiphenylsilyl ether **8** was converted into the alcohol **9**¹² with a HCl 3% methanolic solution, method which proved to be much milder and gave a higher yield (83%) than TBAF in THF. Swern oxidation of **9** with (ClCO)₂/DMSO/Et₃N in CH₂Cl₂ gave the unstable aldehyde **10** which was immediately used in the next step without purification to avoid any epimerization of the aldehyde. The condensation of **10** with diethyl oxoheptylphosphonate, in the presence of sodium hydride, in anhydrous THF at room temperature, afforded the *trans*- α,β enone **11**¹³ in 89% overall yield from the alcohol **9**. Reduction of the keto function of **11** with L-Selectride¹⁰ afforded quantitatively the epimeric allylic alcohols **12** as a 2:3 mixture, which could not be separated by flash chromatography.

Finally, the cleavage of the esters of **12** with 1N NaOH at 40°C yielded **1**¹⁴ in 83% yield.

In conclusion, we describe herein the first stereoselective synthesis of *ent*-15(RS)-2,3-dinor-5,6-dihydro-8-*epi*-PGF2 α **1** in 11 steps from the alcoxyester **2** (32% overall yield). This route allows the enantiospecific synthesis of 2,3-dinor-5,6-dihydro-8-*epi*-PGF2 α , the major urinary metabolite of 8-*epi*-PGF2 α which provides the basis for the development of methods of assay for its quantification as a means to obtain an integrated assessment of oxidative stress status in human. Such studies are currently being investigated.

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11. Compound **6** : $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ : 8.01-8.07 (m, 4H, Ar), 7.67-7.71 (m, 4H, Ar), 7.54-7.59 (m, 2H, Ar), 7.36-7.47 (m, 10H, Ar), 5.41-5.45 (dt, 1H, $J=7$, 2 Hz, H-9), 5.32-5.35 (m, 1H, H-7), 4.42-4.46 (t, 1H, $J=6$ Hz, H-1), 3.84-3.88 (dd, 1H, $J=11$, 5 Hz, H-11), 3.68-3.72 (dd, 1H, $J=11$, 5 Hz, H-11'), 3.57-3.64 (qd, 4H, $J=7$, 2 Hz, OCH_2CH_3), 2.90-2.98 (td, 1H, $J=16$, 7 Hz, H-8), 2.53-2.63 (m, 2H, H-6, H-10), 1.89-1.95 (td, 1H, $J=15$, 3 Hz, H-8'), 1.52-1.59 (m, 2H, H-2), 1.38-1.50 (m, 4H, H-4, H-5), 1.27-1.36 (m, 2H, H-3), 1.16-1.21 (m, 6H, OCH_2CH_3), 1.1 (s, 9H, $\text{OSi}(\text{CH}_3)_3$). $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ : 166.3 (COPh), 166.1 (COPh), 135.7 (Ar), 133.1 (Ar), 132.8 (Ar), 129.7 (Ar), 129.6 (Ar), 128.3 (Ar), 127.7 (Ar), 102.9 (C-1), 79.5 (C-7), 77.9 (C-9), 61.8 (C-11), 60.9 (OCH_2CH_3), 48.8 (C-10), 45.5 (C-6), 38.8 (C-8), 33.5 (C-2), 28.2 (C-5), 27.8 (C-4), 26.9 ($\text{OSi}(\text{CH}_3)_3$), 25 (C-3), 19.1 ($\text{OSi}(\text{CH}_3)_3$), 15.3 (OCH_2CH_3). IR (NaCl) ν : 1710. Anal. calc. for $\text{C}_{45}\text{H}_{56}\text{O}_7\text{Si}$ (737.02) : C 73.34, H 7.66; found C 73.45, H 7.59.
12. Compound **9** : $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ : 8.03-8.08 (t, 4H, $J=9$ Hz, Ar), 7.56-7.60 (t, 2H, $J=7$ Hz, Ar), 7.41-7.47 (q, 4H, $J=7$ Hz, Ar), 5.38-5.42 (td, 1H, $J=7$, 3 Hz, H-9), 5.23-5.27 (m, 1H, H-7), 3.86-3.91 (dd, 1H, $J=11$, 5 Hz, H-11), 3.71-3.76 (dd, 1H, $J=11$, 7 Hz, H-11'), 3.66 (s, 3H, OCH_3), 2.86-2.95 (td, 1H, $J=15$, 7 Hz, H-8), 2.53-2.67 (m, 2H, H-6, H-10), 2.31-2.35 (t, 2H, $J=7$ Hz, H-2), 2.02-2.08 (dt, 1H, $J=15$, 3 Hz, H-8'), 1.65-1.72 (q, 2H, $J=7$ Hz, H-3), 1.39-1.59 (m, 4H, H-5, H-4). $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ : 174 (C-1), 166.8 (COPh), 166.2 (COPh), 137.9 (Ar), 137.3 (Ar), 129.6 (Ar), 128.4 (Ar), 78.9 (C-7), 77.2 (C-9), 60.7 (C-11), 51.5 (OCH_3), 49.3 (C-10), 45.7 (C-6), 38 (C-8), 33.9 (C-2), 27.7 (C-4), 27.3 (C-5), 25 (C-3). IR (NaCl) ν : 3520, 1720, 1710. Anal. calc. for $\text{C}_{26}\text{H}_{30}\text{O}_7$ (545.52) : C 68.71, H 7.35; found C 68.79, H 7.29.
13. Compound **11** : $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ : 8.01-8.04 (m, 4H, Ar), 7.53-7.56 (m, 2H, Ar), 7.24-7.45 (m, 4H, Ar), 6.67-6.74 (dd, 1H, $J=16$, 9 Hz, H-11), 6.25-6.3 (dd, 1H, $J=16$, 1 Hz, H-12), 5.29-5.32 (m, 1H, H-9), 5.22-5.26 (m, 1H, H-7), 3.62 (s, 3H, OCH_3), 3.23-3.29 (m, 1H, H-10), 2.91-2.99 (dt, 1H, $J=16$, 7 Hz, H-8), 2.57-2.56 (m, 1H, H-6), 2.51-2.55 (t, 2H, $J=7$ Hz, H-14), 2.25-2.29 (t, 2H, $J=7$ Hz, H-2), 1.98-2.04 (dt, 1H, $J=16$, 3 Hz, H-8'), 1.55-1.63 (m, 4H, H-3, H-15), 1.37-1.43 (m, 4H, H-4, H-5), 1.26-1.31 (m, 4H, H-16, H-17), 0.86-0.89 (t, 3H, $J=8$ Hz, H-18). $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ : 199.8 (C-13), 173.8 (C-1), : 166.1 (COPh), 166 (COPh), 137.9 (Ar), 141.5 (C-11), 132.4 (C-12), 129.6 (Ar), 128.4 (Ar), 78.4 (C-7), 77.5 (C-9), 51.5 (OCH_3), 50.2 (C-10), 47.7 (C-6), 41 (C-14), 38 (C-8), 33.8 (C-2), 31.4 (C-17), 28.3 (C-4), 27.5 (C-5), 24.9 (C-3), 23.8 (C-15), 22.5 (C-16), 13.9 (C-18). IR (NaCl) ν : 1720, 1710, 1670. Anal. calc. for $\text{C}_{33}\text{H}_{40}\text{O}_7$ (548.67) : C 72.24, H 7.35; found C 72.31, H 7.40.
14. Compound **1** : UV (ethanol) λ_{max} : 201 nm. $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ : 5.52-5.60 (m, 1H, H-12), 5.34-5.40 (m, 1H, H-11), 4.08-4.14 (m, 1H, H-13), 4.01-4.04 (m, 1H, H-9), 3.96-3.99 (m, 1H, H-7), 2.72-2.77 (m, 1H, H-10), 2.33-2.46 (m, 3H, H-8, H-2), 2.11-2.16 (m, 1H, H-6), 1.60-1.70 (m, 1H, H-8'), 1.34-1.39 (m, 2H, H-3), 1.25-1.32 (m, 8H, H-4, H-5, H-14, H-15), 1.23-1.24 (m, 4H, H-16, H-17), 0.85-0.89 (m, 3H, H-18). $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ : 171.8 (C-1), 135.9 (C-12), 128.9 (C-11), 76.4 (C-7), 75.6 (C-9), 73 (C-13), 53.6 (C-10), 49.9 (C-6), 42.4 (C-8), 37.1 (C-14), 31.7 (C-2), 31.6 (C-17), 27.4 (C-5), 25.7 (C-15), 25.1 (C-4), 24.6 (C-3), 22.6 (C-16), 14 (C-18). IR (NaCl) ν : 3520.