Pergamon

Tetrahedron Letters 39 (1998) 6181–6184

TETRAHEDRON LETTERS

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

Alexandre Guy, Thierry Durand*, Arlene Roland, Emmanuelle Cormenier and Jean-Claude Rossi.

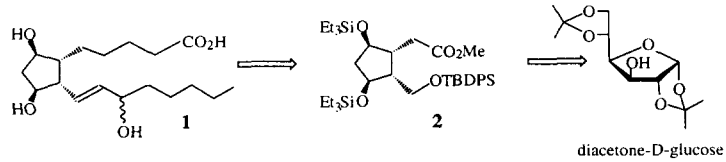
Laboratoire de Chimie Biomoléculaire et Interactions Biologiques associé au C.N.R.S., Université Montpellier I, Faculté de Pharmacie, 15 Av. Ch. Flahault, F-34060 Montpellier, France.

Received 18 May 1998; accepted 18 June 1998

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.

Since the discovery of isoprostaglandins by Roberts *et al*[1], there has been a growing interest in the total synthesis of these optically active prostanoids[2]. These new natural products synthesized *in vivo* by a free radical-catalyzed mechanism[1], are indeed endowed with a powerful biological activity[3]. They have also been identified as minor by-products in the enzymatic cyclooxygenases[4-5] peroxidation of arachidonic acid (AA). Free radicals have been implicated in the pathogenesis of a wide variety of human disorders[6]. 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 time[7].

Recently, Roberts and co-workers[7] 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).

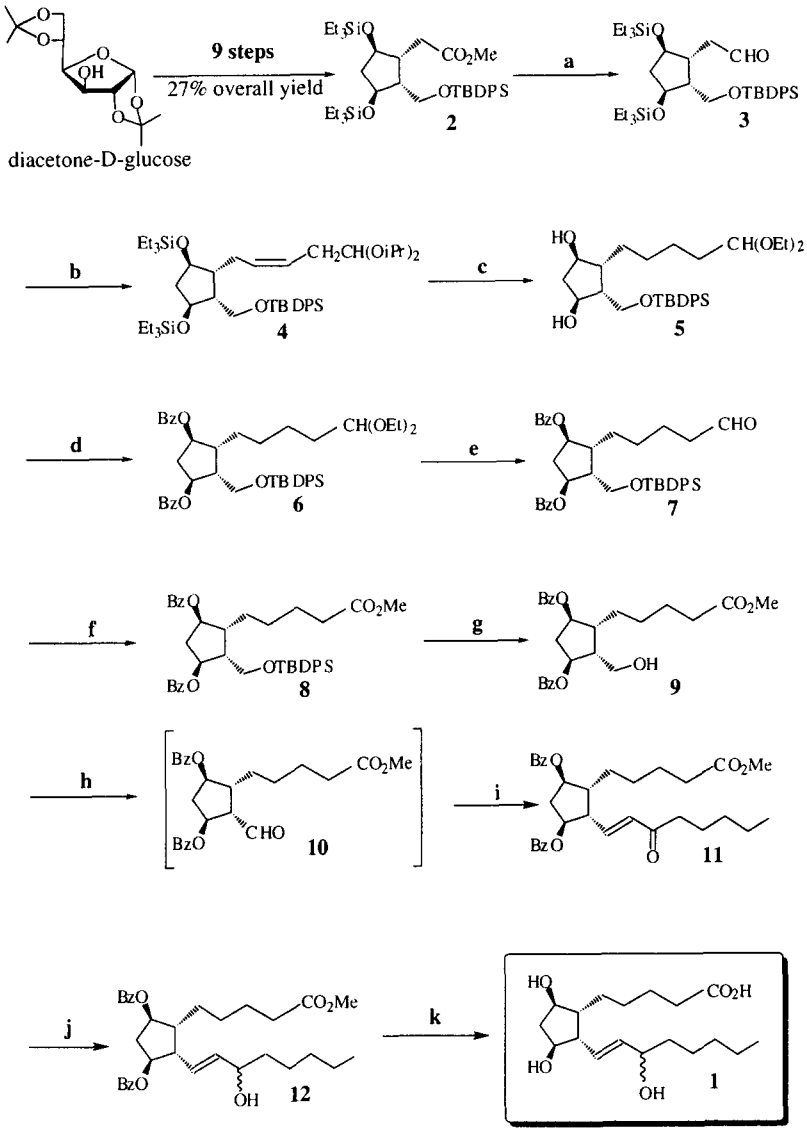


Scheme 1

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 procedure[8]. The alcoxyester **2** was converted into the aldehyde **3** by treatment with DIBAL-H in anhydrous toluene (Scheme 2) with 93% yield.

* Fax : 33-4-67-54-86-25 E-mail : Thierry.Durand@pharma.univ-montp1.fr

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01290-8



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) $(COCl)_2$/DMSO/Et_3N, 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 acheived by using a three-carbon homolating agent, the (3,3-diisopropoxypropyl)triphenyl phosphonium bromide[9]. 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 ^{1}H NMR analysis. All the relative configurations were acheived by homonuclear ^{1}H nOe experiments.

The *cis*-double bond of **4** was reduced with H_2 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 $FeCl_3$ 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/Et_3N in CH_2Cl_2 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-Selectride[10] 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*-PGF2α **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*-PGF2α, the major urinary metabolite of 8-*epi*-PGF2α 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.

Acknowledgments

We wish to thank Dr. Jacques Viala for helpfull discussion and Prof Erik Anggärd from the William Harvey Research Institute for financial support of this research and one of us (A.G.).

References and Notes

1. Morrow, J.D.; Hill, K.E.; Burk, R.F.; Nammour, T.M.; Badr, K.F.; Roberts II, L.J. *Proc. Natl. Acad. Sci. USA.* **1990**, *87*, 9383-9387.
2. Corey, E.J.; Shih, C.; Shih, N-Y.; Shimoji, K. *Tetrahedron Lett.* **1984**, *25*, 5013-5016. Corey, E.J.; Shimoji, K.; Shih, C. *J. Am. Chem. Soc.* **1984**, *106*, 6425-6427. Larock, R.C.; Lee, N.H. *J. Am. Chem. Soc.* **1991**, *113*, 7815-7816. Rondot, B.; Durand, T.; Girard, J.P.; Rossi, J.C.; Schio, L.; Khanapure, S.P.; Rokach, J. *Tetrahedron Lett.* **1993**, *34*, 8245-8248. Vionnet, J.P.; Renaud, P. *Helv. Chim. Acta.* **1994**, *77*, 781-790 and references herein. Mulzer, J.; Kermanchahi, A.K.; Buschmann, J.; Luger, P. *Liebigs. Ann. Chem.* **1994**, 531-539. Rondot, B; Durand, T; Vidal, J.P.; Girard, J.P.; Rossi, J.C. *J. Chem. Soc. Perkin Trans. 2* **1995**, 1589-1594. Roland, A.; Durand, T.; Rondot, B.; Vidal, J.P.; Rossi, J.C. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1149-1154. Guy, A.; Durand, T.; Vidal, J.P.; Rossi, J.C. *Tetrahedron Lett.* **1997**, *38*, 1543-1546. Taber, D.F.; Herr, R.J.; Gleave, D.M. *J. Org. Chem.* **1997**, *62*, 194-198. Rokach, J.; Khanapure, S.P.; Hwang, S.W.; Adiyaman, M.; Schio, L.; FitzGerald, G.A. *Synthesis*, **1998**, 569-580.
3. Takahashi, K.; Nammour, T.M.; Fukunaga, M.; Ebert, J.; Morrow, J.D.; Roberts, II L.J.; Hoover, R.L.; Badr, K.F. *J. Clin. Invest.* **1992**, *90*, 136-141. Kang, K.H.; Morrow, J.D.; Roberts II, L.J.; Newman, J.H.; Banerjee, M.J. *J. Appl. Physiol.* **1993**, *74*, 460-465. Fukunaga, M.; Makita, N.; Roberts, II L.J.; Morrow, J.D.; Takahashi, K.; Badr, K.F. *Am. J. Physiol.* **1993**, *264*, C1619-C1624. Fukunaga, M.; Takahashi, K.; Badr, K.F. *Biochem. Biophys. Res. Commun.* **1993**, *195*, 507-515. Morrow, J.D.; Minton, T.A.; Mukundan, C.R.; Cambell, M.D.; Zackert, W.E.; Daniel, V.C.; Badr, K.F.; Blair, I.A.; Roberts, II L.J. *J. Biol. Chem.* **1994**, *269*, 4317-4326. Morrow, J.D.; Roberts, II L.J. *Biochem. Pharmacol.* **1996**, *51*, 1-9 and references therein.

4. Pratico, D.; Lawson, J.A.; FitzGerald, G.A. *J. Biol. Chem.* **1995**, *270*, 9800-9808.
5. Patrignani, P.; Panara, M.R.; Cipollone, F.; Greco, A.; Ciabattoni, G.; Patrono, G. *J. Invest. Med.* **1995**, *43*, Supp.2, 335A. Pratico, D.; FitzGerald, G.A. *J. Biol. Chem.* **1996**, *271*, 8919-8924.
6. Halliwell, B.; Gutteridge, J.M.C. *Methods Enzymol.* **1990**, *186*, 1-85. Southorn, P.A.; Powis, G. *Mayo. Clin. Proc.* **1988**, *63*, 390-408. Ames, B.N. *Science* **1983**, *221*, 1256-1264. Harman, D. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 7124-7128.
7. Roberts II, L.J.; Moore, K.P.; Zackert, W.E.; Oates, J.A.; Morrow, J.D. *J. Biol. Chem.* **1996**, *271*, 20617-20620.
8. Rondot, B.; Durand, T.; Vidal, J.P.; Girard, J.P.; Rossi, J.C. *J. Chem. Soc. Perkin Trans 2*, **1995**, 1589-1594. Rondot, B.; Durand, T.; Rollin, P.; Rossi, J.C. *Carbohydr. Res.* **1994**, *261*, 149-156. The synthesis of alcoxyester **2** and others isomers from diacetone-D-glucose using iodo pathway will be described in our forthcoming paper.
9. Viala, J.; Santelli, M. *Synthesis* **1988**, 395-397.
10. Corey, E.J.; Becker, K.B.; Varma, R.K. *J. Am. Chem. Soc.* **1972**, *94*, 8616-8618. Fortuno, J.M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194-2200.
11. Compound **6** : ^{1}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, $OSiC(CH_3)_3$). ^{13}C-NMR (90 MHz, $CDCl_3$) δ : 166.3 (*CO*Ph), 166.1(*CO*Ph), 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 ($OSiC(CH_3)_3$), 25 (C-3), 19.1 ($OSiC(CH_3)_3$), 15.3 (OCH_2CH_3). IR (NaCl) υ : 1710. Anal. calc. for $C_{45}H_{56}O_7Si$ (737.02) : C 73.34, H 7.66; found C 73.45, H 7.59.
12. Compound **9** : ^{1}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}C-NMR (90 MHz, $CDCl_3$) δ : 174 (C-1), 166.8 (*CO*Ph), 166.2 (*CO*Ph), 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) υ : 3520, 1720, 1710. Anal. calc. for $C_{26}H_{30}O_7$ (545.52) : C 68.71, H 7.35; found C 68.79, H 7.29.
13. Compound **11** : ^{1}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}C-NMR (90 MHz, $CDCl_3$) δ : 199.8 (C-13), 173.8 (C-1), : 166.1 (*CO*Ph), 166 (*CO*Ph), 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) υ : 1720, 1710, 1670. Anal. calc. for $C_{33}H_{40}O_7$ (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}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), 0.85-8.89 (m, 3H, H-18). ^{13}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) υ : 3520.