Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2105–2108

TETRAHEDRON LETTERS

Total synthesis of phytoprostane F_1 and its 16 epimer

Siham El Fangour, Alexandre Guy, Jean-Pierre Vidal, Jean-Claude Rossi and Thierry Durand*

UMR CNRS 5074, Université Montpellier I, Faculté de Pharmacie, 15. Av. Ch. Flahault, F-34093 Montpellier cedex 05, France

Received 10 January 2003; accepted 16 January 2003

Abstract—The first synthesis of the two enantiomers of phytoprostane F_1 methyl ester **1** and **2** is described using the *syn–anti–syn* alcoxy ester **3** as starting material.

Isoprostanes (IsoPs) are a complex family of compounds produced, in vivo, from peroxidation of polyunsaturated fatty acids (AA, DHA, EPA) via a free-radical-catalyzed mechanism.[1] Thus, quantification of these IsoPs in the biological fluids and tissues as markers of lipid peroxidation appears as an important insight in the exploration of the role of the oxidative stress in human pathology.[2] Higher plants generally do not synthesize the precursor arachidonate required for isoPs formation, but rather utilize α-linolenic acid for the formation of isoprostane F_2-like compounds which have been termed phytoprostanes F_1.[3] Jasmonates are established plant signal compounds that induce defense response.[4] Preliminary data indicates that phytoprostanes also induce phytoalexins in a variety of plant species suggesting a possible function of phytoprostanes as mediators of plant defense reactions in response to oxidative stress.[5] During the last two years, Zanoni et al. reported the first synthesis of phytoprostane A_1[6] and Spur et al. just published the synthesis of 15-E_2-isoP (PPE_2).[7]

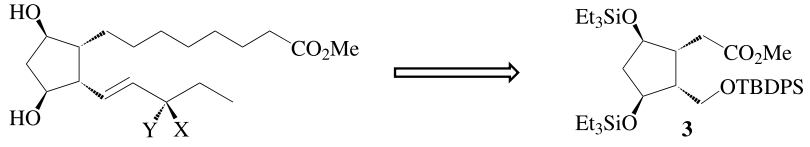
In connection with our program directed towards the synthesis of isoprostanes,[8] we now report the first synthesis of *ent*-phytoprostane F_1 type I (PPF_1) **1** and its 16-epimer **2** from the *syn–anti–syn* alcoxyester **3**[9] (Scheme 1).

The synthesis of PPF_1 type I **1** and its 16(*R*) epimer **2** from the commercially available diacetone-D-glucose as starting material, is shown in Schemes 3 and 4. The first nine steps leading to cyclopentane alcoxyester **3** were achieved in 27% overall yield by using iodo pathway, according to our procedure.[9]

Synthon **4** was selected and prepared using the following procedure outlined in Scheme 2.

The commercially available ε-caprolactone was transformed to the corresponding hydroxy methyl ester **5** using acidic conditions in 97% yield. Halogenation with PPh_3/I_2 in CH_2Cl_2 gave iodo ester **6** in good yield. Phosphorylation of the iodide derivative **6** in the presence of PPh_3 and 1% of K_2CO_3 in the reaction mixture afforded the phophonium salt **7** in 98% yield.

The alcoxyester **3** was converted into the aldehyde **8** by treatment with DIBAL-H in anhydrous toluene with 97% yield (Scheme 3). The introduction of the α-chain of the phytoprostane was achieved by using the

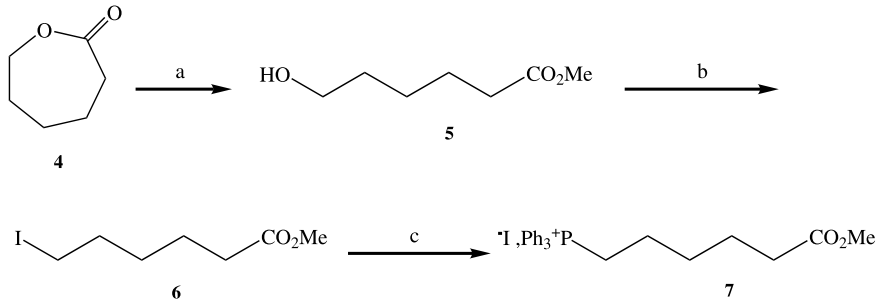


1 X=H, Y=OH
2 X=OH, Y=H

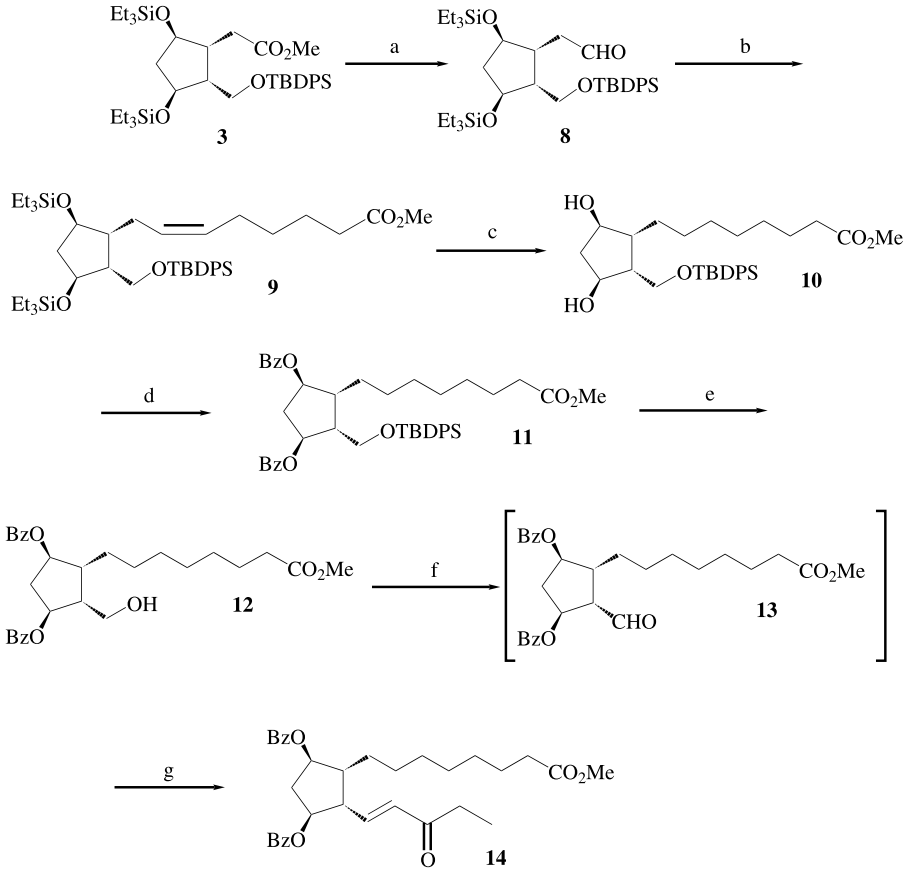
Scheme 1.

* Corresponding author. Tel.: +33-4-6754-8623; fax: +33-4-6754-8625; e-mail: thierry.durand@pharma.univ-montp1.fr

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00171-0



Scheme 2. *Reagents and conditions*: (a) MeOH, H_2SO_4, rt, 30 min, 97%; (b) I_2, PPh_3, imidazole, CH_2Cl_2, −10°C, 2 h, 61%; (c) PPh_3, CH_3CN, 1% K_2CO_3, 18 h, 98%.



Scheme 3. *Reagents and conditions*: (a) 1.1 equiv. DIBAL-H (1 M in toluene), toluene, −80°C, 30 min, 97%; (b) 2.25 equiv. methoxycarbonylpentyltriphenylphosphonium iodide, 2.2 equiv. $KN(SiMe_3)_2$, THF, −80 to 20°C, 2 h, 70%; (c) H_2, Pd/C 10%, EtOH, 4 h, 98%; (d) 3 equiv. BzCl, pyridine, 20°C, 1 h, 77%; (e) HCl 3% in MeOH, 20°C, overnight, 80%; (f) periodinane, CH_2Cl_2, rt, 2 h; (g) 3.3 equiv. dimethyl 2-oxobutylphosphonate, 3 equiv. $NaN(SiMe_3)_2$, THF, 20°C, 30 min, 60%.

methoxycarbonylpentyltriphenyl phosphonium iodide **7**. The aldehyde **8** reacted with the ylide derived from this phosphonium salt and potassium hexamethyldisilyl amide as a base, in anhydrous THF at −80°C, to afford the pure (*Z*) enic ether **9** in 70% yield. No trace of *trans* compound could be detected by ^{13}C and ^{1}H NMR analysis.

The *cis* double bond of **9** was reduced with H_2 on 10% Pd/C to give diol methyl ester **10** in 98% yield, Interestingly, during this hydrogenation we could avoid the deprotection of the triethylsilyl ethers. The protection of the hydroxy functions of **10** with benzoyl chloride in dry pyridine gave the colorless diester **11** in 77% yield.

The *tert*-butyldiphenylsilyl ether **11** was converted into the alcohol **12** with a solution of 3% hydrogen chloride[10] 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 (80%) than TBAF in THF. Dess–Martin oxidation[11] of **12** in CH_2Cl_2 gave the unstable aldehyde **13** which was immediately used in the next step without purification. The condensation of **13** with dimethyl 2-oxobutylphosphonate,[12] in the presence of sodium

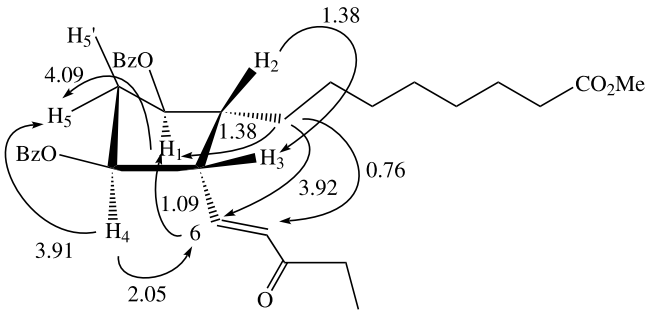


Figure 1. Observed NOEs resulting from irradiation of main protons are indicated with solid.

hexamethyldisilyl amide, in anhydrous THF at room temperature, afforded the *trans*-α,β enone ester **14** in 60% overall yield from the alcohol **12** (Scheme 3). We confirmed the relative configurations of the chiral centers by homonuclear ^{1}H steady-state-difference NOE spectroscopy (DNOES) experiments, as shown in Figure 1.

The diastereoselective reduction of the C-16 keto group in **14** with the chiral reducing agent[13] (*S*)-BINAL-H proceeded smoothly and gave the desired pure 16(*S*) derivative **15** in 85% yield. Similarly, reduction of **14** using the (*R*)-BINAL-H gave the 16(*R*) epimer **16** in 87% yield (Scheme 4).

Finally, deprotection of the benzoyl groups in **15** and **16**, with 1N NaOH at room temperature, followed by excess of CH_2N_2, afforded the desired *ent*-PPF_1 type I **2**[14] and its 16 epimer **1**[15] in 91 and 93% yields, respectively.

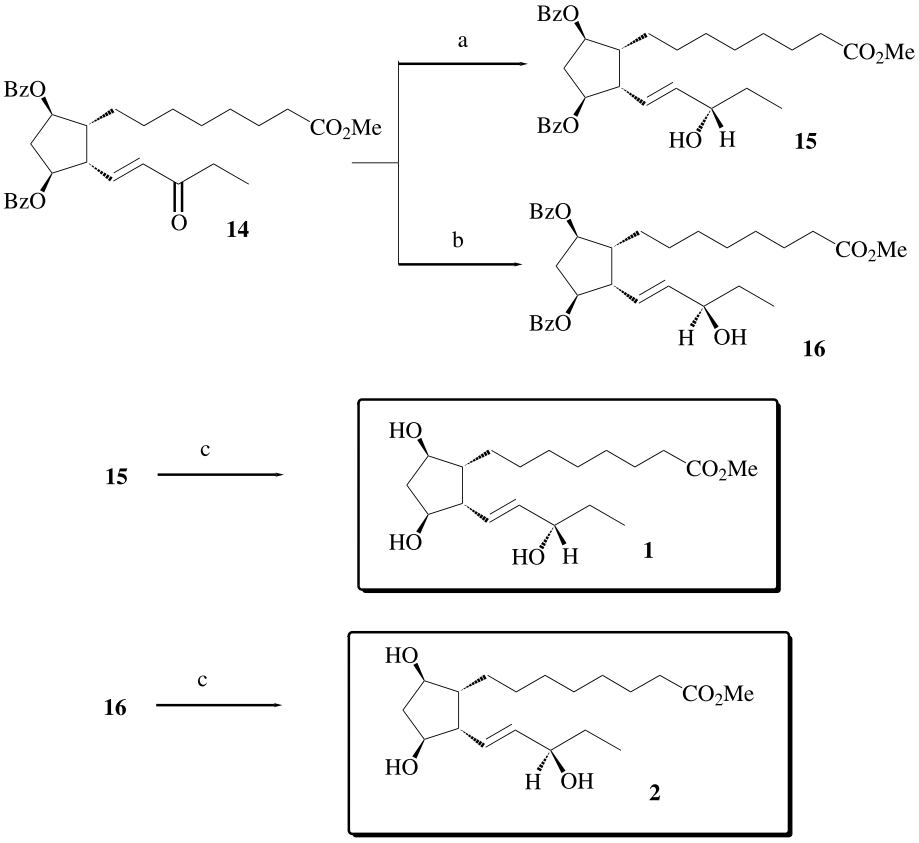
In conclusion, we have developed a practical synthesis of phytoprostane F_1 type I **2** and its 16 epimer **1** from our intermediate, the *syn–anti–syn* alcoxyester **3** in nine steps. The extension of this strategy towards type II PPF_1 and other phytoprostanes will be reported in due course.

Acknowledgements

We wish to thank the Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche for financial support for one of us (S.E.).

References

1. Morrow, J. D.; Hill, K. E.; Burk, R. F.; Nammour, T. M.; Badr, K. F.; Roberts, L. J., II. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 9383–9387.
2. Cracowski, J. L.; Durand, T.; Bessard, G. *Trends Pharmacol. Sci.* **2002**, *23*, 360–366.



Scheme 4. *Reagents and conditions*: (a) (*S*)-BINAL-H, −100°C, 2 h, 85%; (b) (*R*)-BINAL-H, −100°C, 2 h, 87%; (c) 1N NaOH, THF–MeOH, rt, 1 h, then CH_2N_2, 93%.

3. Imbusch, R.; Mueller, M. J. *Plant Physiol.* **2000**, *124*, 1293–12303.
4. Stintzi, A.; Weber, H.; Reymond, P.; Browse, J.; Farmer, E. E. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 12837–12842.
5. Imbusch, R.; Mueller, M. J. *Free Rad. Biol. Med.* **2000**, *28*, 720–726.
6. Zanoni, G.; Porta, A.; Vidari, G. *J. Org. Chem.* **2002**, *67*, 4346–4351.
7. Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2002**, *43*, 9249–9253.
8. (a) Durand, T.; Guy, A.; Henry, O.; Vidal, J. P.; Rossi, J. C. *Eur. J. Org. Chem.* **2001**, *4*, 809–819 and references cited therein; (b) Durand, T.; Guy, A.; Vidal, J. P.; Rossi, J. C. *J. Org. Chem.* **2002**, *67*, 3615–3624 and references cited therein.
9. Roland, A.; Durand, T.; Egron, D.; Vidal, J. P.; Rossi, J. C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 245–251 and references cited therein.
10. Nashed, E. M.; Glaudemans, C. P. J. *J. Org. Chem.* **1987**, *52*, 5255–5260.
11. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156; (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
12. Coppola, G. M. *Synthesis* **1988**, 81–84.
13. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709–6716.
14. Compound **2**: UV (ethanol) λ_{max}: 203 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 5.54 (dd, $J_{15,16}=7.1$ Hz, $J_{15,14}=15.2$ Hz, 1H, H-15), 5.40 (dd, $J_{14,13}=9.7$ Hz, $J_{14,15}=15.2$ Hz, 1H, H-14), 4.02–3.93 (m, 1H, H-16), 4.03–3.95 (m, 1H, H-12), 3.97–3.90 (m, 1H, H-10), 3.66 (s, 3H, OCH_3), 2.77–2.71 (m, 1H, H-13), 2.42 (dt, $J_{11,10}=J_{11,12}=6.8$ Hz, $J_{11,11'}=14.5$ Hz, 1H, H-11), 2.29 (t, $J_{2,3}=7.5$ Hz, 2H, H-2), 2.11–2.01 (m, 1H, H-9), 1.68–1.58 (m, 1H, H-11′), 1.66–1.55 (m, 2H, H-3), 1.65–1.45 (m, 2H, H-17), 1.33–1.25 (m, 2H, H-4), 1.33–1.19 (m, 8H, H-5, H-6, H-7 and H-8), 0.90 (t, $J_{18,19}=7.5$ Hz, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 174.3 (C-1), 135.5 (C-15), 128.8 (C-14), 76.6 (C-10), 76.4 (C-12), 74.4 (C-16), 53.6 (C-13), 51.4 (OCH_3), 50.4 (C-9), 42.5 (C-11), 34.0 (C-2), 30.1 (C-17), 29.5 (C-8), 29.0 (C-4, C-5 and C-7), 28.0 (C-6), 24.8 (C-3), 9.6 (C-18); IR (NaCl) v: 3520, 1720 cm^{-1}; $[\alpha]_D^{20}=-30$ (c 1×10^{-2}, MeOH).
15. Compound **1**: UV (ethanol) λ_{max}: 203 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 5.57 (dd, $J_{15,16}=6.2$ Hz, $J_{15,14}=15.4$ Hz, 1H, H-15), 5.43 (dd, $J_{14,13}=5.4$ Hz, $J_{14,15}=15.4$ Hz, 1H, H-14), 4.05–3.96 (m, 1H, H-16), 4.04–3.99 (m, 1H, H-12), 3.98–3.93 (m, 1H, H-10), 3.66 (s, 3H, OCH_3), 2.79–2.73 (m, 1H, H-13), 2.41 (dt, $J_{11,10}=J_{11,12}=6.8$ Hz, $J_{11,11'}=14.5$ Hz, 1H, H-11), 2.29 (t, $J_{2,3}=7.7$ Hz, 2H, H-2), 2.12–2.04 (m, 1H, H-9), 1.68–1.59 (m, 1H, H-11′), 1.66–1.55 (m, 2H, H-3), 1.60–1.48 (m, 2H, H-17), 1.33–1.25 (m, 2H, H-4), 1.33–1.18 (m, 8H, H-5, H-6, H-7 and H-8), 0.90 (t, $J_{18,19}=7.3$ Hz, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 174.3 (C-1), 135.3 (C-15), 128.7 (C-14), 76.8 (C-10), 76.5 (C-12), 73.8 (C-16), 53.4 (C-13), 51.4 (OCH_3), 50.3 (C-9), 42.5 (C-11), 34.0 (C-2), 30.1 (C-17), 29.4 (C-8), 29.0 (C-4, C-5 and C-7), 28.0 (C-6), 24.8 (C-3), 9.6 (C-18); IR (NaCl) v: 3520, 1720 cm^{-1}; $[\alpha]_D^{20}=-13$ (c 1×10^{-2}, MeOH).