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Total Synthesis of 12-*epi*-$PGF_{2\alpha}$

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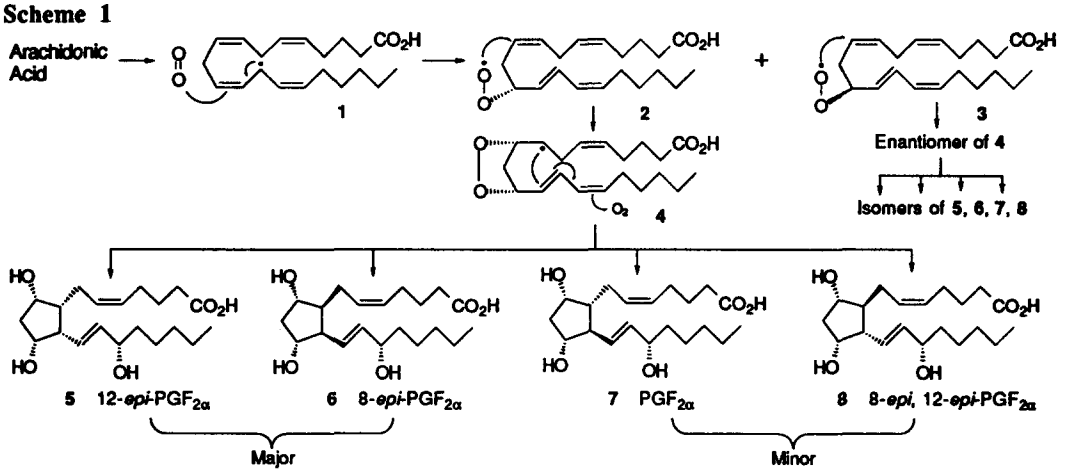
Abstract: A novel synthesis of 12-*epi*-$PGF_{2\alpha}$ **5** is described. The key synthon **11**, which has been used as a starting point for the synthesis, is produced by a radical cyclization process using thionocarbonate **9a**. The radical cyclization of **9a** to **11** has been studied in some detail.

A new class of prostaglandin-like compounds, called isoprostanes, was discovered recently *in vivo* in humans. These natural products are formed as a result of a new biochemical pathway of arachidonic acid (AA). They are generated non-enzymatically *in vivo* during free radical-initiated lipid peroxidation.[1] In addition, the isoprostanes differ from the more familiar prostanoids by the *cis*-stereochemistry at the five-membered ring junction. 8-*Epi*-$PGF_{2\alpha}$ **6**, the main isoprostane identified so far, is generated, at least in part, on membrane phospholipids[2] and released in free acid form, presumably by the action of phospholipases. 8-*Epi*-$PGF_{2\alpha}$ is a potent renal and pulmonary vasoconstrictor.[1b,3] Scheme 1 shows our proposal leading to the formation of 8-*epi*-$PGF_{2\alpha}$ **6** by a free-radical oxygenation. This analysis also anticipates the formation of 12-*epi*-$PGF_{2\alpha}$ **5**.[4] The oxygenation of AA is not unlike the enzymatic process. The cyclization of the intermediate radical **4**, however, is unlike the enzymatic process and is shown to yield a preponderance of the *cis* products, **5** and **6**. Cyclization of secondary radicals to form *gem*-disubstituted cyclopentane derivatives yields mostly *cis*-disubstituted products.[5] This is in contrast to the enzymatic process in which the cyclooxygenases-1 and -2 produce the prostaglandins, e.g. $PGF_{2\alpha}$ **7**, which have a *trans* relationship of the two side chains.

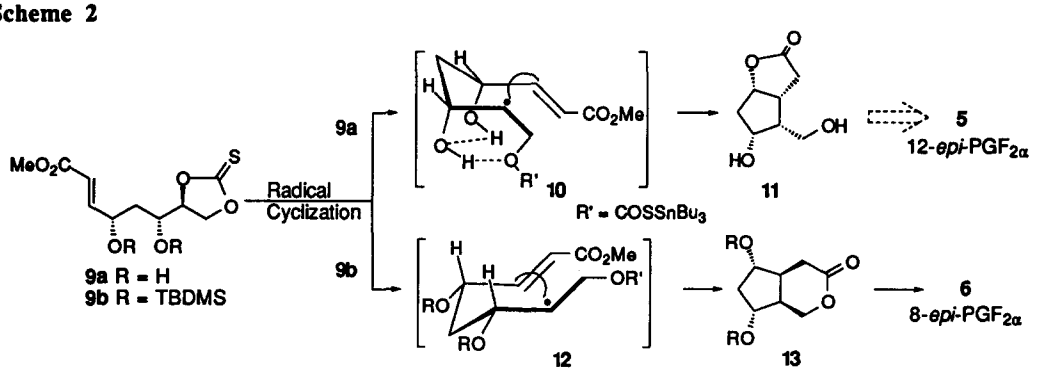
Scheme 1



Recently, we reported the first total synthesis of 8-*epi*-$PGF_{2\alpha}$ 6[6] as the first step of a program designed to synthesize and identify new isoprostanes *in vivo*, study their biological activity and, as importantly, study their mechanism of formation and their impact on cell membranes. The generation of polar molecules, such as 8-*epi*-$PGF_{2\alpha}$ or 12-*epi*-$PGF_{2\alpha}$, on cell membrane phospholipids in the midst of a hydrophobic environment might cause changes in membrane fluidity, creation of leaks and eventual cell death.

The present report describes the total synthesis of 12-*epi*-$PGF_{2\alpha}$. Larock and coworkers have reported recently the synthesis of 12-*epi*-$PGF_{2\alpha}$ *via* organopalladium intermediates.[7] Our approach is part of a general strategy we outlined previously.[6] Scheme 2 shows the essential part of this design in which we used a radical cyclization step at the ring-forming junction of the 5-membered ring. This strategy, which proved successful, was based on our intention to obtain, by controlling the cyclization step, a general methodology that would provide access not only to the *cis-anti-cis* stereochemistry of 8-*epi*-$PGF_{2\alpha}$ 6, but also to the all-*syn* configuration found in 12-*epi*-$PGF_{2\alpha}$ 5.

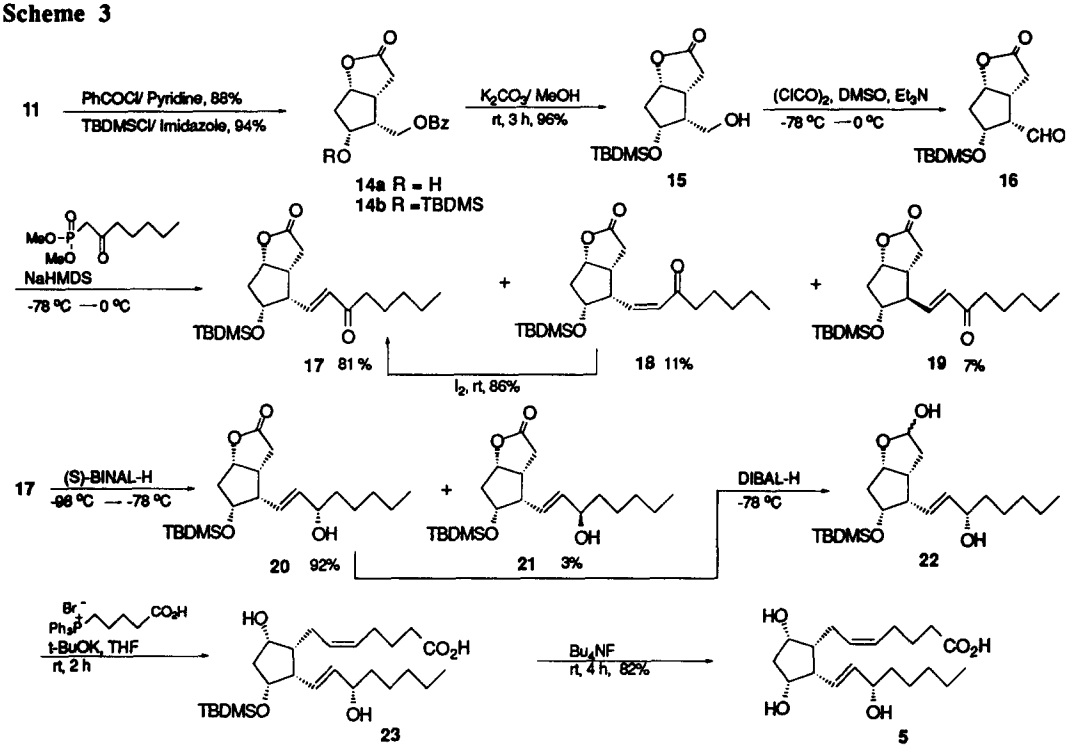
Scheme 2



The total synthesis of 12-*epi*-$PGF_{2\alpha}$ 5 (Scheme 3) starts with the all-*syn* lactone **11**,[6] obtained by the tributyltinhydride (TBTH)-mediated radical cyclization of thionocarbonate **9a** (see Scheme 4). The selective protection of primary alcohol in **11** was carried out by treatment of benzoyl chloride in pyridine at room temperature to give **14a** in 88% yield. The secondary hydroxyl group in **14a** was protected as silyloxy using tert-butyldimethylsilyl chloride and imidazole in DMF to give **14b** in 94% yield. The benzoyl protecting group was hydrolyzed with potassium carbonate to afford **15** in 96% yield. The Swern oxidation of **15** using oxalyl chloride, DMSO and triethylamine yielded aldehyde **16**. Because of its fragility, crude aldehyde **16** was used as such, and was reacted with the ylide generated from commercial dimethyl (2-oxoheptyl) phosphonate and sodium bis(trimethylsilyl)amide at -78 °C in THF. Flash column chromatography afforded **17** in 81% yield. In addition to **17**, we also isolated two more products and characterized them as **18** and **19**,[8] respectively. Extensive ^1H, ^{13}C, DEPT, ^1H-^1H COSY, and NOE NMR studies confirmed the stereochemical assignments for the three products. The minor (11%) Z-isomer **18** was easily converted to **17** by treatment with a catalytic amount of iodine in methylene chloride at room temperature overnight. Thus, the overall isolated yield of **17** from **15** was 91%. The enantioselective reduction of the C_{15} keto group in **17** with chiral reducing agent (*S*)-BINAL-H proceeded well and afforded, after flash column chromatography, the desired pure 15(*S*) derivative **20** in 92% yield. The epimeric 15(*R*) isomer **21** was also isolated in 3% yield. The reduction of lactone **20** with DIBAL-H in methylene chloride at -78 °C, followed by aqueous acidic work-up, afforded the two

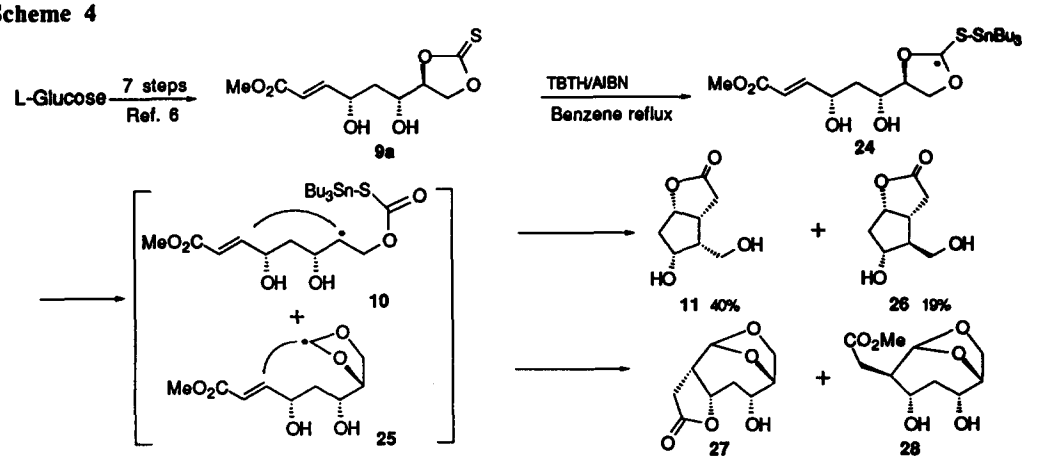
epimeric lactols **22** in quantitative yield, which were used as such in the next step.[9] The Wittig reaction to introduce the upper side chain, using commercially available (4-carboxybutyl)triphenylphosphonium bromide (3 equivalents) and potassium tert-butoxide (5.99 equivalents) at room temperature, proceeded smoothly to give **23**. Purification of **23**, however, proved difficult because of comigration with the phosphonium reagent. Finally, the crude **23** was treated with tetrabutylammonium fluoride in THF to give the desired 12-*epi*-$PGF_{2\alpha}$ **5**[10] in 82% yield from **22**.

Scheme 3



We have studied in more detail the TBTH-mediated radical cyclization of **9a** to **11** (Scheme 4). In addition to the desired all *syn* lactone **11**, 19% of lactone **26** with the *trans* side chains was obtained. The structure of **26** was assigned based on NMR studies and was found identical to commercial Corey lactone. Two other minor by-products, **27** and **28**, were also isolated. The structural assignment is based on NMR and high resolution mass spectrometry. The presence of the 5-membered lactone in the case of **27** is indicative of *cis*-stereochemistry, and the presence of hydroxyl and carbomethoxy groups in **28** of *trans* stereochemistry. The formation of radicals such as **24** has been proposed initially by Barton *et al.* as a first step in TBTH-mediated reduction of thioxanthates.[11] The formation of **27** and **28** provide, to our knowledge, the first documented evidence of the trapping of such radicals. The formation of **27** and **28** is interesting as it gives us some information about the energetics of the various radical species. Once the first radical species **24** is produced, the transformation to the desired radical **10** appears to require an activation energy in order to cause the cleavage of the C-O bond. Some support for such an analysis can be found in the TBTH reduction of 5-membered ring thionocarbonates to methylenedioxy derivatives at a lower temperature.[12]

Scheme 4



The synthesis of 12-*epi*-$PGF_{2\alpha}$ described here is an important step forward in our ongoing program of synthesis and biological evaluation of isoprostanes, and the assessment of their role in oxygen stress-related tissue damage *in vivo*.

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4. Non-enzymatic free radical oxygenation of arachidonic acid can also lead to initial radical formation at the C_7- or C_{10}-positions in addition to the one shown in Scheme 1. These radicals can lead to different types of isoprostanes (ref No. 6)
5. a) Porter, N. A.; Funk, M. O. *J. Org. Chem.* **1975**, *40*, 3614. b) O'Connor, D. E.; Mihelich, E. D.; Coleman, M. C. *J. Am. Chem. Soc.* **1984**, *106*, 3577. c) Corey, E. J.; Shih, C.; Shih, N-Y.; Shimoji, K. *Tetrahedron Lett.* **1984**, *25*, 5013. d) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759. e) Curran, D. P.; Chang, C-T. *J. Org. Chem.* **1989**, *54*, 3140. f) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. g) Beckwith, A. L. J.; Cliff, M. D.; Schiesser, C. H. *Tetrahedron* **1992**, *48*, 4641. h) Ziegler, F. E.; Zheng, Z-I. *Tetrahedron Lett.* **1987**, *28*, 5973. i) Mulzer, J.; Kermanchahi, A. K.; Buschmann, J.; Luger, P. *Liebigs Ann. Chem.* **1994**, 531.
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8. Such epimerization is not uncommon in prostaglandin synthesis and can occur during the oxidation step or the Wittig reaction. (^{1}H NMR of **16**, peak due to CHO at δ 9.89 and a minor peak at δ 9.73). a) Brewster, D.; Myers, M.; Ormerod, J.; Otter, P.; Smith, A. C. B.; Spinner, M. E.; Turner, S. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2796. b) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265. c) Chen, L-Y.; Ghosez, L. *Tetrahedron: Asymmetry* **1991**, *2*, 1181.
9. The lactols **22** are unstable, exposure to silica gel or even storage at -20 °C overnight resulted in extensive decomposition.
10. Spectral data for **5**: ^{1}H NMR ($CDCl_3$) δ 5.77 (dd, *J* = 15.3 and 10.6 Hz, 1 H, C_{13}-H), 5.46 (dd, *J* = 15.3 and 6.3 Hz, 1 H, C_{14}-H), 5.37-5.26 (m, 2 H, C_5-H and C_6-H), 5.0-4.2 (br s, 3 H, O*H*), 4.14 (m, 2 H, C_9-H and C_{11}-H), 4.07 (q, *J* = 6.7 Hz,1 H, C_{15}-H), 2.68 (m, 1 H, C_{12}-H), 2.28 (t, *J* = 6.6 Hz, 2 H, C_2-H_2), 2.24 (m, 1 H, C_7-H), 2.14-1.95 (m, 4 H, C_7-H, C_{10}-H and C_4-H_2), 1.95-1.76(m, 2 H, C_8-H and C_{10}-H), 1.63 (m, 2H, C_3-H_2), 1.47 (m, 2 H, C_{16}-H_2), 1.22 (m, 6 H, C_{17}-H_2, C_{18}-H_2 and C_{19}-H_2), 0.81 (t, *J* = 6.8 Hz, 3 H, C_{20}-H_3). ^{13}C NMR δ 177.90 (C_1), 137.30 (C_{14}), 130.07 (C_{13}), 129.51 (C_5), 129.04 (C_6), 75.54 (C_{15}), 73.71 (C_{11}), 73.00 (C_9), 50.25 (C_{12}), 47.37 (C_8), 42.80(C_2), 37.11, 33.22, 32.00 and 26.66 (C_4, C_7, C_{16} and C_{10}), 25.44, 24.72, 24.45 and 22.85 (C_3, C_{17}, C_{18} and C_{19}), 14.25 (C_{20}); Electrospray MS *m/z* 353.1 $(M - H)^+$.
11. a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574. b) Barton, D. H. R.; Crich, D.; Lobberding, A.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2329.
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