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Stereoselective synthesis of an isoprostane synthon via 8,12-free-radical cyclization

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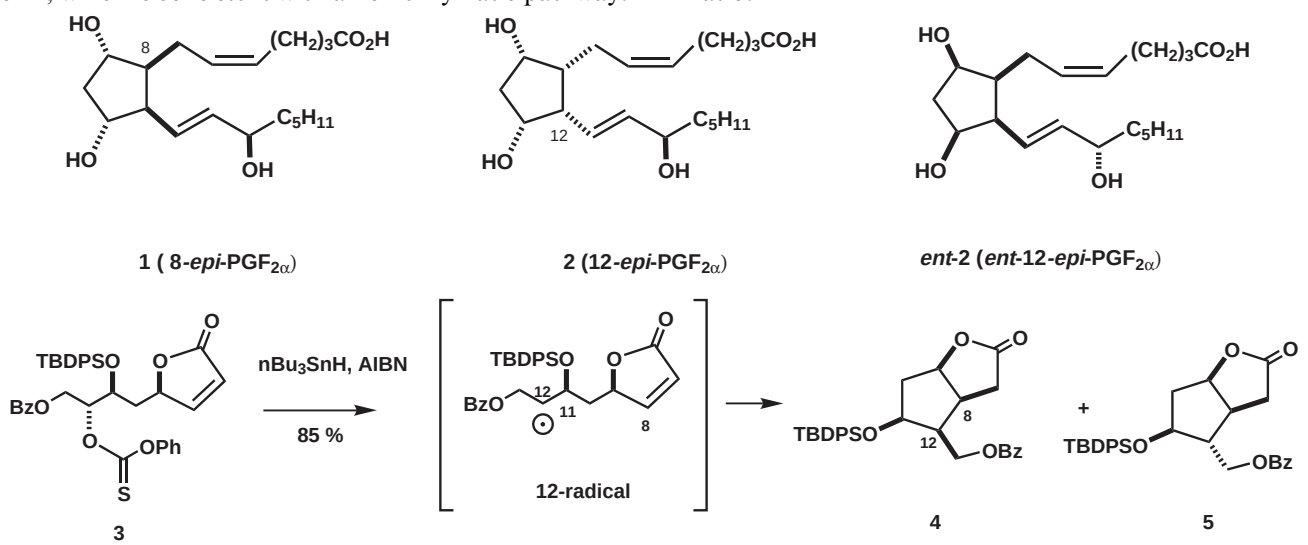
Abstract—Aiming at a stereocontrolled biomimetic synthesis of isoprostanes a fully stereocontrolled 8,12-free radical cyclization has been achieved via intermediate **10** by annulating an endocyclic radical to a butenolide acceptor double bond. In this way *ent*-12-*epi*-$PGF_{2\alpha}$ (*ent*-**2**) can be prepared.

Isoprostanes are the products of a non-enzymatic oxidation of arachidonic acid (AA) in the mammalian cell which, in contrast to the cyclooxygenase mediated process, results in the formation of prostanoids with a *cis*-arrangement of the 8- and 12-sidechain (Scheme 1).[1]

Characteristic examples are 8- and 12-*epi*-$PGF_{2\alpha}$ (**1** and **2**), of which **1** has been isolated and shown to be a potent renal and pulmonary vasoconstrictor.[2] **2**, however, has not been found in nature, so far, though it should also be formed via the above-mentioned free radical cascade. Isoprostanes are generated in racemic form, which is consistent with a non enzymatic pathway. However, for biological evaluation both enantiomers of the compounds would be desirable. As several syntheses of 'natural' 12-*epi*-$PGF_{2\alpha}$ (**2**) have been reported,[3] we decided to prepare the unnatural enantiomer (*ent*-**2**) via a stereocontrolled biomimetic free radical 8,12-cyclization. There is ample literature precedence for isoprostane syntheses via such a process, in particular from the Rockach group;[4] however, in all cases diastereomeric mixtures were obtained. Some time ago we studied the free radical annulation of a 12-radical to a butenolide acceptor. Thus, thiocarbonate **3** furnished the Corey-lactone derivatives **4** and **5** in a 2:1 ratio.[5]



Keywords: isoprostanoids; free radical cyclization; biomimetic synthesis.
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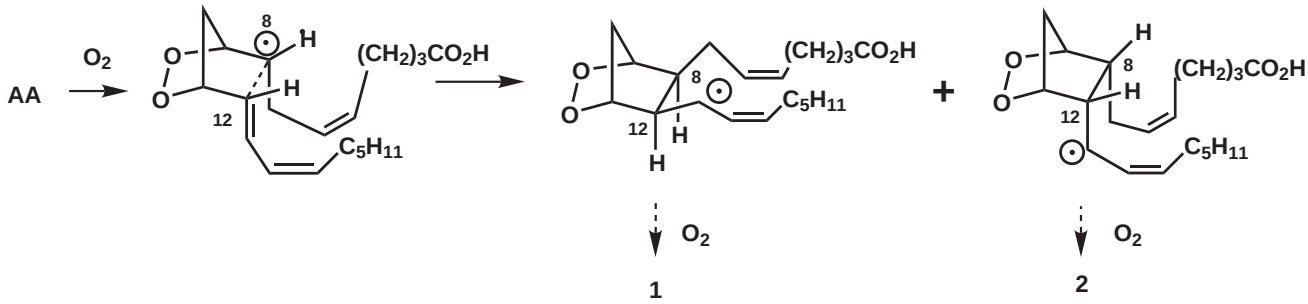
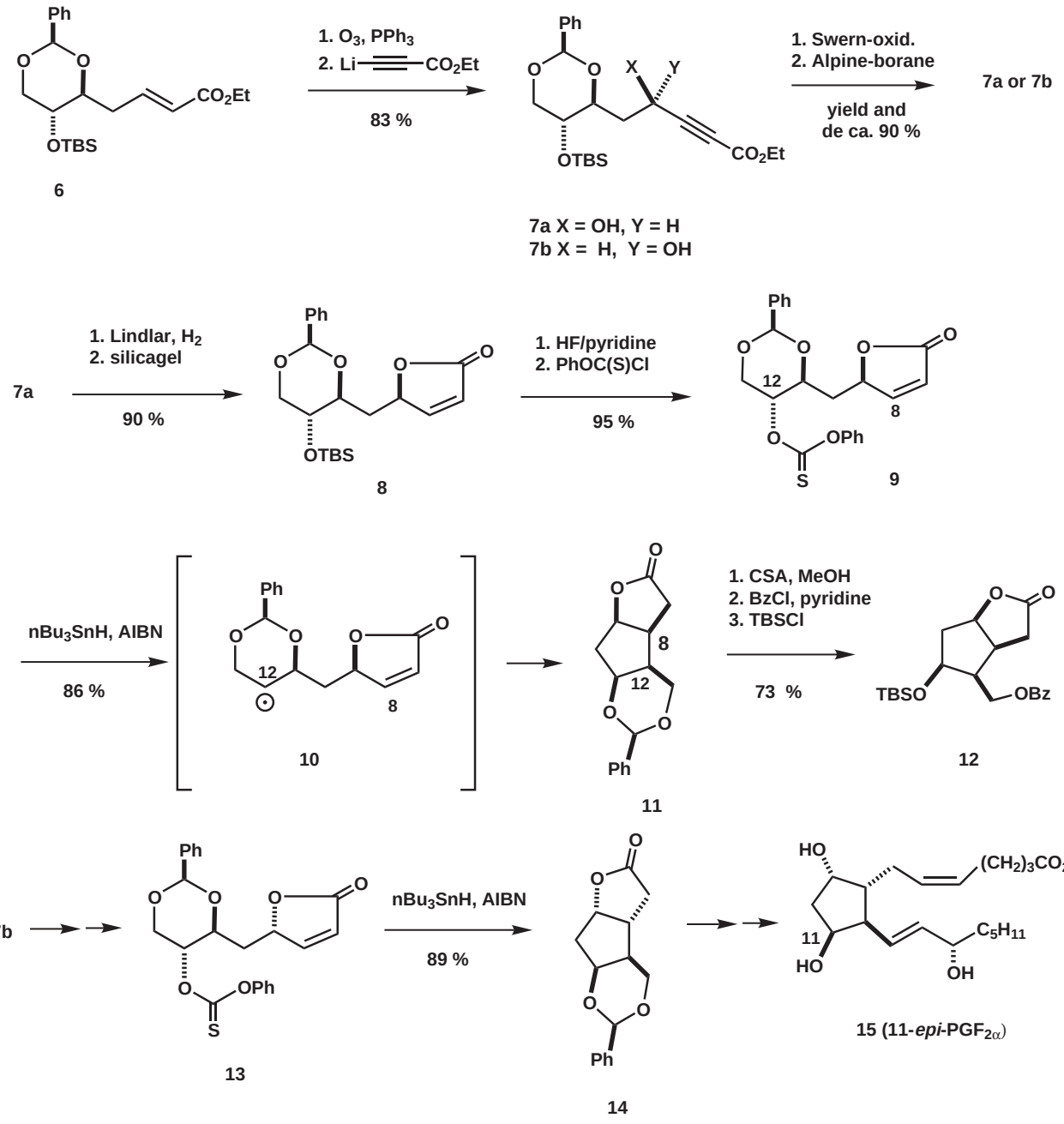


Scheme 1.



Scheme 2.

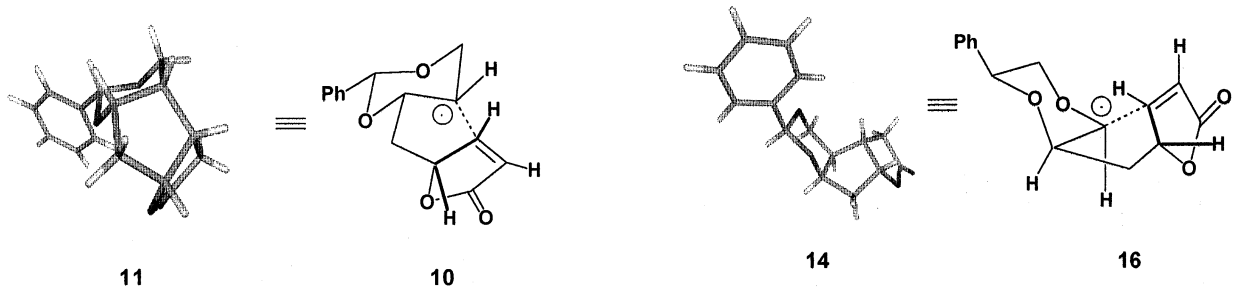


Figure 1. Transition states for the radical annulations as derived from the crystal structures of the cyclization products **11** and **14**.

The annulation to the butenolide exclusively generates the *cis*-fused system, however, the 12-radical, as in all the cases reported so far,[4] lacks facial selectivity, due to rapid rotation around the 11,12-axis. To inhibit such a rotation the incorporation of the 11,12-bond into a cyclic template appeared appropriate, following an earlier precedence by RajanBabu.[6] Thus, in our synthesis of *ent*-**2** the known benzylidene acetal (**6**)[7] was transformed into an epimeric mixture of the acetylides **7a**/**b**. To rectify the configuration of the C-4-carbinol the mixture was oxidized to the ketone and then reduced with Alpine-borane[8] to give either **7a** or **7b** with high diastereocontrol (Scheme 2). Pure alcohol **7a** was hydrogenated and cyclized to the butenolide **8**, which was converted into thiocarbonate **9** and then into free radical **10**.[9] Twofold *cis*-annulation occurred to give the *ent*-12-*epi*-Corey lactone derivative **11**[10,11] as a single stereoisomer in high yield. By routine functional group manipulation **11** was transformed into **12**, i.e. the enantiomer of Rockach's intermediate in his synthesis of **2**.[3b] Analogously thiocarbonate **13**, obtained from **7b**, was converted into **14**,[10,11] again as a single stereoisomer (Scheme 2), which may serve as an intermediate in a synthesis of 11-*epi*-$PGF_{2\alpha}$ (**15**).

The transition states of the respective free radical cyclizations may be rationalized in terms of the crystal structures of **11** and **14**, respectively (Fig. 1). This figure clearly indicates the stereochemical course of the addition of an endocyclic cyclohexyl type radical to the butenolide acceptor double bond. Both the *cis*-annulation to the six-membered acetal and the *cis*-annulation to the butenolide guarantee the stereochemical outcome of the cyclization. In conclusion we have described a fully stereocontrolled 8,12-free radical cyclization in the isoprostane series and demonstrated its utility for the synthesis of *ent*-**2**.

References

1. Morrow, J. D.; Minton, T. A.; Mukundan, C. R.; Campell, M. D.; Zackert, W. E.; Daniel, V. C.; Badr, K. F.; Blair, I. A.; Roberts, II, L. J. *J. Biol. Chem.* **1994**, *269*, 4317 and earlier work.
2. (a) Morrow, J. D.; Hill, K. E.; Burk, R. F.; Mammour, T. M.; Badr, K. F.; Roberts, II, L. J. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 9383; (b) Takahashi, K.; Mammour, 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.
3. (a) Lai, S.; Lee, D.; U, J. S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 7213; (b) Hwang, S. W.; Adiyaman, M.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 779; (c) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815; (d) Brown, E. D. Ger. Offen. DE 2, 360, 893, 12 June 1973; *Chem. Abstr.* **1974**, *81*, 120096e; (e) Brewster, D.; Meyers, M.; Ormerod, J.; Otter, P.; Smith, A. C. B.; Spinner, M. E.; Turner, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2796.
4. (a) Hwang, S. W.; Adiyaman, M.; Khanapure, S.; Schio, L.; Rockach, J. *J. Am. Chem. Soc.* **1994**, *116*, 10829; (b) Rockach, J.; Khanapure, S. P.; Hwang, S.-W.; Adiyaman, M.; Schio, L.; FitzGerald, G. A. *Synthesis* **1998**, 569; (c) Rockach, J.; Khanapure, S. P.; Hwang, S.-W.; Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A. *Prostaglandins* **1997**, *54*, 823; (d) For an earlier example, see: Corey, E. J.; Shih, Ch.; Shih, N. Y.; Shimoji, K. *Tetrahedron Lett.* **1984**, *25*, 5012; (e) Corey, E. J.; Shih, C.; Shimoji, K. *J. Am. Chem. Soc.* **1984**, *106*, 6425.
5. Mulzer, J.; Kermanchahi, A. K.; Buschmann, J.; Luger, P. *Liebigs Ann. Chem.* **1994**, 531.
6. RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522.
7. Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517.
8. Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525.
9. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
10. **11**: mp 154°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 5.33 (s, 1H), 5.11 (t, $J=6.9$ Hz, 1H), 4.36–4.33 (m, 1H), 4.26–4.23 (m, 2H), 3.46 (dd, $J=18$ Hz, $J=3.3$ Hz, 1 H), 3.21–3.08 (m, 1H), 2.64 (dd, $J=18.5$ Hz, $J=11.9$ Hz, 1H), 2.38 (d, $J=15.8$. Hz, 1H), 1.98–1.87 (m, 2H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 177.30, 137.48, 128.99, 128.26, 126.25, 101.25, 85.37, 80.02, 65.92, 39.75, 39.73, 39.69, 31.29 ppm. MS (ESI): m/z 261.1 (M^+). $[\alpha]_D^{20}=-98.7$ (c 2.42, $CHCl_3$). Anal. calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 68.95; H, 6.31. **14**: mp 149°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.38 (s, 1H), 5.04 (m, 1H), 4.40–4.37 (m, 1H), 4.19–4.13 (m, 1H), 4.03 (d, $J=12$ Hz, 1H), 3.33–3.23 (m, 1H), 2.75 (dd, $J=18$ Hz, $J=9$ Hz, 1H), 2.80–2.28 (m, 2H), 2.12–2.02 (m, 1H), 1.67–1.61 (m, 1H): ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 176.31, 137.90, 128.90, 128.17, 125.76, 100.50, 85.17, 79.72, 65.44, 44.28, 40.37, 38.78, 33.60 ppm. MS (ESI) m/z 261.1 (M^+). $[\alpha]_D^{20}=-88.6$ (c 2.11, $CHCl_3$). Anal.

calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 68.99; H, 6.35.

11. Crystallographic data (excluding structure factors) for the structures of **11** and **14** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 157310 and 157311. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [(fax: +44(0)-1233-336033 or e-mail: deposit@ccdc.cam.ac.uk].