Synthesis of 10α-Hydroxy-prostaglandins

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Summary Because of vicinal participation of the acetate in the iodo-lactone (**1**), acid-catalysed solvolysis with silver acetate of the iodine is stereospecific; selective hydrolysis of a tetrahydropyranyl ether function in the presence of an acetonide allows access to two distinct series of novel prostaglandins.

CONTINUING our effort aimed at the preparation of modified prostaglandins,[1] we report the total synthesis of novel prostaglandins with additional oxygen functionality in the five-membered ring.

Solvolysis of the iodo-lactone (**1**)[2] affords a mixture of hydroxyacetates (**2a**) and (**2b**), which is hydrolysed to the diol (**2c**), m.p. 101—102°; ν_{max} 3350 and 1775 cm^{-1},† in 89% overall yield. In the presence of toluene-*p*-sulphonic acid the acetonide (**3a**), m.p. 80—81°,‡ (86%) is obtained, thus establishing the α-configuration of the newly introduced hydroxy-group. Hydrogenolysis of the benzyl ether group with 10% Pd–C, in anhydrous acetone with a trace of $HClO_4$ affords the corresponding alcohol (**3b**), m.p. 142—143° (95%). Oxidation[3] gives the bicyclic aldehyde (90%), which is immediately treated with dimethyl 2-oxoheptylphosphonate, to provide the enone (**4**), λ_{max} 224 nm (ε 12,900), which is submitted to the sequence of reactions[1,2] in the Scheme.

Treatment of the 15α-ether (**5a**) with 65% aqueous AcOH for 6 h at room temperature cleaves both the 10,11α-acetonide group and the 15-ether linkage affording (±)-10α-hydroxy-$PGF_{2\alpha}$ (**6**). Conversely, Jones' oxidation of (**5a**) yields the ketone (**7a**), which with aqueous AcOH for 6 h provides (±)-10α-hydroxy-PGE_2 (**8**).

Selective hydrolysis of the 15-tetrahydropyranyl ether group of (**5a**) is achieved with aqueous AcOH at room temperature for 2 h, which gives the $PGF_{2\alpha}$ bicyclic analogue (**5b**). Similarly, mild acid hydrolysis of the tetrahydropyranyl ether group of (**7a**) gives (**7b**).

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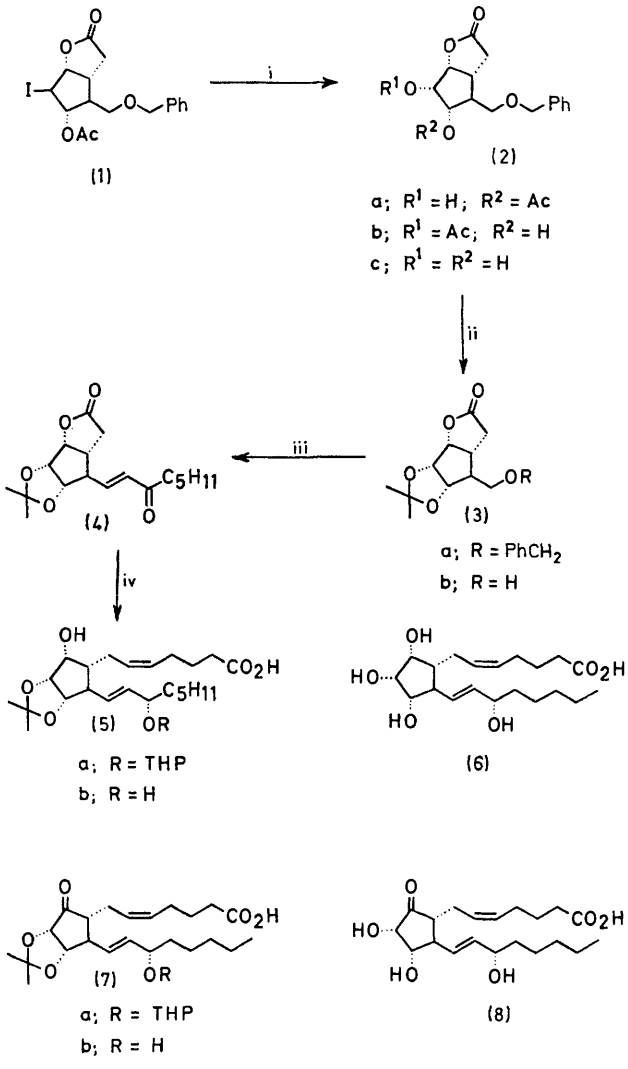

SCHEME

THP = tetrahydropyranyl
Reagents: i, AgOAc, AcOH–H_2O; ii, $Me_2C(OMe)_2$, Me_2CO; iii, a, CrO_3, pyridine–CH_2Cl_2, b, $C_5H_{11}C(O)\bar{C}HP(O)(OMe)_2$, iv, a, $Zn(BH_4)_2$, b, t.l.c., c, dihydropyran, TsOH, d, Bu^i_2AlH, e, $Ph_3\overset{+}{P}CH[CH_2]_3CO_2^-$.

† Satisfactory elemental analyses or mass spectra were obtained for all new compounds.

‡ N.m.r. and i.r. spectra consistent with their formulation.

[1] P. Crabbé, H. Carpio, and A. Guzmán, 'Proceedings on the Chemistry and Pharmacology of Prostaglandins,' Intra-Science Research Foundation, Santa Monica, California, in the press.
[2] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.
[3] J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 1968, 3363.