Synthesis of 11-Deoxy-10α-hydroxyprostaglandins

By PIERRE CRABBÉ,*† ALICIA CERVANTES, and M. CARMEN MEANA
(*Research Laboratories, Syntex, S.A., Apartado Postal* 10-820, *Mexico* 10, *D.F., Mexico*)

Summary The β-elimination of the 11-acetoxy-grouping of the aldehyde (**2**) by ready anion formation at C-12 gives the conjugated aldehyde (**3**); catalytic hydrogenation of (**3**), followed by alkylation under equilibrating conditions, allows access to novel prostaglandins, which are isomeric with $PGF_{2\alpha}$ and PGE_2.

FOR some time we have been interested in the chemical synthesis of modified prostaglandins.[1] In particular, the preparation of several 11-deoxyprostaglandins,[2] and 10-hydroxyprostaglandins[3] has been described. We now report the total synthesis of two new 11-deoxy-10-hydroxy-prostaglandins.

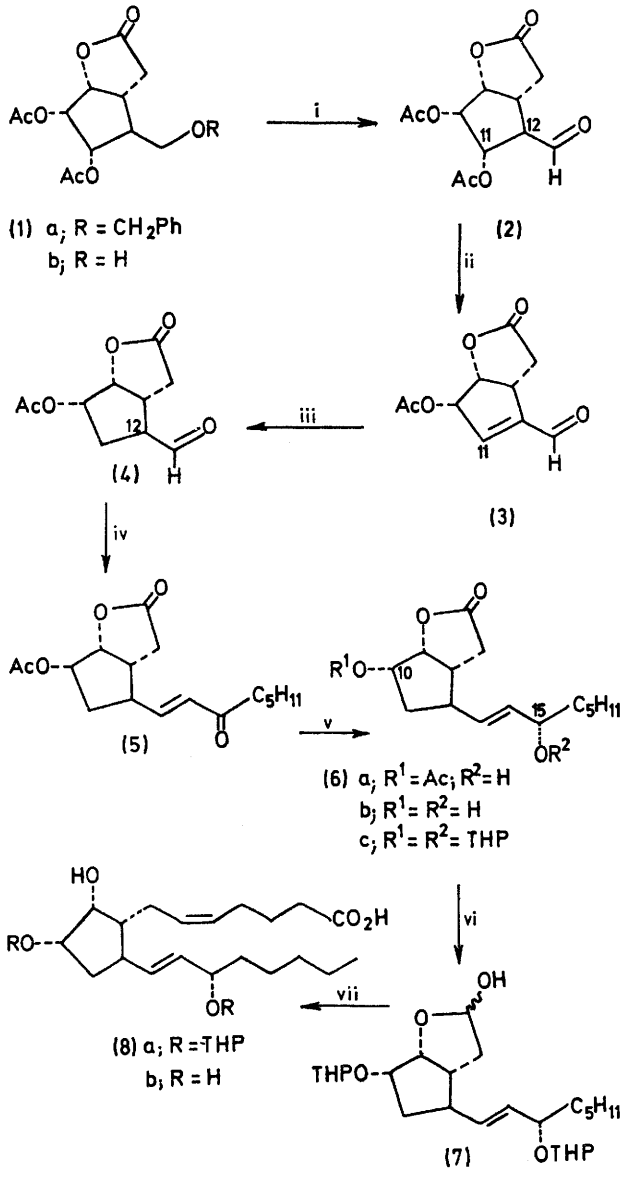
This synthesis makes use of the ready elimination of acetate at C-11 by base treatment of the acetoxy-aldehyde (**2**), which provided the conjugated aldehyde (**3**). The alcohol (**1b**), m.p. 95—97°, ν_{max} 3400, 1770, 1740 cm^{-1},‡ readily prepared from (**1a**),[1,3] is oxidised with Collins' reagent[4] to afford the diacetoxy-aldehyde (**2**), which when treated with pyridine for several minutes, provides the conjugated aldehyde (**3**), m.p. 113°, λ_{max} 227 nm (ε 4040), in 50% overall yield from (**1b**).

Catalytic hydrogenation of the double bond at C-11 with 5% Pd–C in dimethoxyethane solution yields quantitatively the saturated aldehyde (**4**). Alkylation of (**4**) with the sodium salt of dimethyl 2-oxoheptylphosphonate gives the expected enone (**5**), λ_{max} 224 nm (ε 12,600), in 68% yield. Zinc borohydride reduction of the carbonyl function at C-15 provides a mixture of 15(*R*)- and 15(*S*)-isomeric alcohols separated by preparative t.l.c. The desired 15(*S*)-alcohol (**6a**) is treated with methanolic K_2CO_3 at room temperature, thus affording the corresponding 10,15-diol (**6b**) in 95% yield. Treatment of (**6b**) with dihydropyran in the presence of a catalytic amount of acid gives almost quantitatively the 10,15-bis-ether (**6c**).

The concluding steps of the synthesis are shown in the Scheme. Reaction of the lactone group with di-isobutylaluminium hydride provides the lactol (**7**) (95%). This is then treated with 5-triphenylphosphoniopentanoic acid, to give the novel prostanoic acid as its bistetrahydropyranyl ether derivative (**8a**).

Hydrolysis of the 10α,15α-bis-ether (**8a**) with aqueous AcOH at room temperature, affords (±)-11-deoxy-10α-hydroxy-$PGF_{2\alpha}$ (**8b**). Jones' oxidation[5] of (**8a**) provides the expected ketone (**9a**), which by exposure to aqueous AcOH affords (±)-11-deoxy-10α-hydroxy-PGE_2 (**9b**).

A novel feature of this synthesis is the formation of the conjugated aldehyde which could be hydrogenated quantitatively to the saturated aldehyde (**4**). Although the configuration of the aldehyde group in (**4**) is probably 12α, equilibration occurs during the alkylation step, which



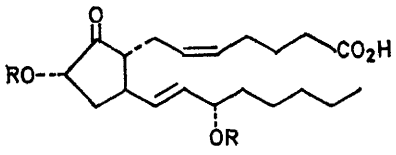
SCHEME

THP = tetrahydropyranyl

Reagents: i, CrO_3; ii, pyridine; iii, H_2, 5% Pd–C, DME; iv, $C_5H_{11}C(O)\bar{C}HP(O)(OMe)_2$, Na^+, DME; v, a, $Zn(BH_4)_2$, b, t.l.c, c, dihydropyran, TsOH; vi, Bu^i_2AlH–C_7H_8, −70°; vii, $Ph_3\overset{+}{P}CH[CH_2]_3\overset{-}{C}O_2^-$, $2Na^+$, Me_2SO.

† *Present address:* Laboratoire de Chimie Organique, C.E.R.M.O., Université Scientifique et Medicale, Boite Postale 53, 38·041, Grenoble, Cedex, France.

‡ Satisfactory elemental analyses or mass spectra were obtained for all new compounds. N.m.r. and i.r. spectra consistent with their formation.



(9) a; R = THP
b; R = H

provides the thermodynamically stable enone (**5**) with the desired β-configuration at C-12, as shown by its n.m.r. properties. This permitted the preparation of two novel prostaglandins in which the newly introduced hydroxy-group at C-10α is in an isomeric position with respect to the natural 11-hydroxylated prostanoic acid derivatives.

We thank Dr A. Guzmán for fruitful discussions.

(*Received*, 12*th December* 1972; *Com.* 2072.)

[1] P. Crabbé, *Archiv. Invest. Médica* (*Mexico*), 1972, **3**, suppl. 1, 151; P. Crabbé, H. Carpio, and A. Guzmán, 'Proceedings on the Chemistry and Pharmacology of Prostaglandins,' Intra-Science Research Foundation, Santa Monica, California, 1972, **6**, 55.
[2] P. Crabbé, and A. Guzmán, *Tetrahedron Letters*, 1972, 115; P. Crabbé, A. Cervantes, and A. Guzmán, *Tetrahedron Letters*, 1972, 1123.
[3] P. Crabbé, A. Guzmán, and E. Velarde, *J.C.S. Chem. Comm.*, 1972, 1126.
[4] J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 1968, 3363.
[5] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1945, 39.