Synthesis of 9-Deoxa-9,10-dehydroprostaglandin-D_2 through Reaction of 2-Oxatricyclo[3.3.0.$0^{4,6}$]oct-7-en-3-one with a Cuprate Reagent

By S. MUBARIK ALI, MARK A. W. FINCH, and STANLEY M. ROBERTS*
(The Ramage Laboratories, Department of Chemistry and Applied Chemistry, Salford University, Salford, Lancs. M5 4WT)

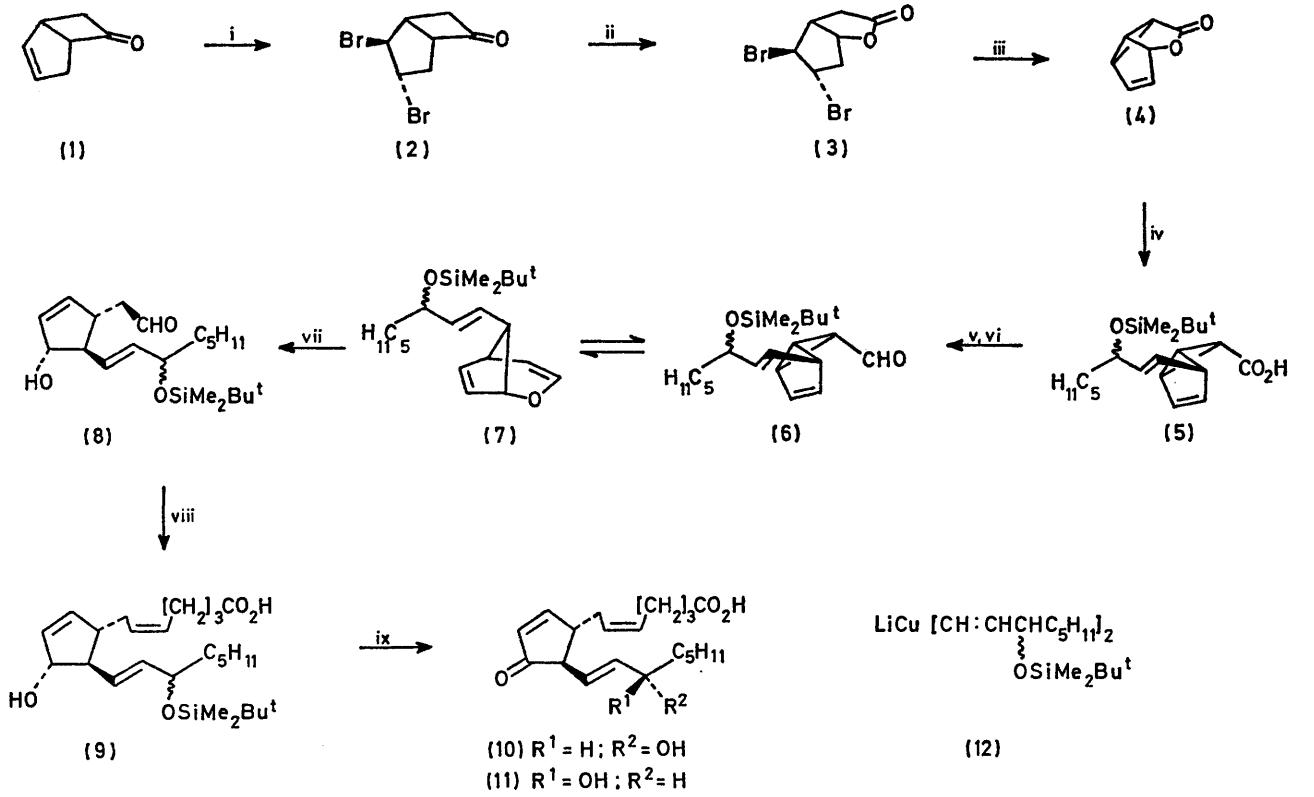
and ROGER F. NEWTON*
[Chemical Research Department, Glaxo-Allenburys Research (Ware) Ltd., Ware, Herts. SG12 0DJ]

Summary The prostanoid (**10**) has been prepared by reaction of the tricyclic lactone (**4**) with the cuprate reagent (**12**) to give the acid (**5**) and subsequent Cope rearrangement of the related aldehyde (**6**).

9-DEOXA-9,10-DEHYDROPROSTAGLANDIN-D_2 (**10**) and analogues are extremely active biologically as evidenced by the volume of the patent literature related to this system. Herein we report a new synthetic route to such compounds involving nine steps from the ketone (**1**).

Bromination of bicyclo[3.2.0]hept-2-en-6-one (**1**)[1] gave the dibromoketone (**2**),[2] from which the lactone (**3**) was formed by Baeyer–Villiger oxidation using *m*-chloroperoxybenzoic acid. 1,5-Diazabicyclo[5.4.0]undec-5-ene (DBU) dehydrobrominated the lactone (**3**) to furnish the tricyclic lactone (**4**)[3] in 77% overall yield from the ketone (**1**). The homocuprate reagent (**12**) reacted with the lactone (**4**) to give the cyclopropyl carboxylic acid (**5**)[4] (65%) from which the aldehyde (**6**) ⇌ enol ether (**7**) system was available by a two step procedure (59%). The enol ether (**7**) was hydrolysed to the hydroxyaldehyde (**8**)[5] (92%) using a two-phase system of chloroform and 4 N hydrochloric acid.

Wittig reaction of the aldehyde (**8**) and the appropriate phosphorane gave the cyclopentenol (**9**) (75%) which was subjected to a Collins oxidation (53%) and deprotected



Reagents: i, Br_2, $NaHCO_3$, ether. ii, *m*-$ClC_6H_4CO_3H$. iii, DBU. iv, Reagent (**12**), ether, −78 °C. v, $LiAlH_4$. vi, Collins oxidation. vii, HCl, H_2O, $CHCl_3$. viii, $Ph_3PCH[CH_2]_3CO_2^-$. ix, HF, H_2O, MeCN.

(95%) to give 9-deoxa-9,10-dehydroprostaglandin-D_2 (**10**)[6] and an equal quantity of the 15-epimer (**11**).

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[1] P. A. Grieco, *J. Org. Chem.*, 1972, **37**, 2363.
[2] Z. Grudzinski and S. M. Roberts, *J.C.S. Perkin I*, 1975, 1767.
[3] S. M. Ali, C. B. Chapleo, S. M. Roberts, and R. F. Newton, *Tetrahedron Letters*, 1979, 71.
[4] *cf.* E. J. Corey and J. Mann, *J. Amer. Chem. Soc.*, 1973, **95**, 6832.
[5] For other routes to this prostanoid system see E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, 1973, **95**, 6831; C. Gandolfi and G. Doria, *Farm. Ed. Sci.*, 1974, **29**, 405.
[6] Identical with an authentic sample prepared by Dr. R. J. Cave from prostaglandin $F_{2\alpha}$ as prescribed in U.S.P. 3,954,844 (1975) and 4,016,184 (1975).