A Short Synthesis of Prostaglandins from 5-Chloro-5-cyano-7-*syn*-formylbicyclo[2,2,1]hept-2-ene

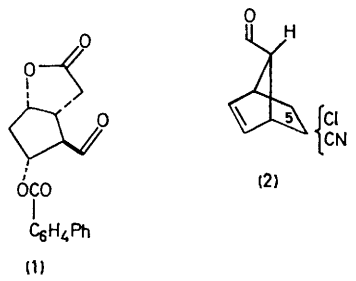
By EDWARD D. BROWN* and TIMOTHY J. LILLEY
(*ICI Ltd., Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire*, SK10 4TG)

Summary A direct route from 5-chloro-5-cyano-7-*syn*-formyl-bicyclo-[2,2,1]hept-2-ene† to the primary prostaglandins is described.

THE aldehyde (**1**) is a key intermediate in the synthesis of prostaglandins and their analogues and a number of synthetic routes to (**1**) and closely related compounds have appeared.[1] We have recently shown that the bicyclo-[2,2,1]heptene aldehydes (**2**)‡ can be converted into the aldehyde (**1**) in high yield.[2] However, the conversion of the bicyclo-heptene aldehydes (**2**) into for example prostaglandin $F_{2\alpha}$ (**9**) *via* the aldehyde (**1**) required a number of protection and deprotection reactions. We now report that the bicycloheptene aldehydes (**2**) can be converted directly and efficiently into prostaglandin $F_{2\alpha}$ (**9**) in a seven-stage synthesis. This route avoids the use of protecting groups and is one of the shortest syntheses of the primary prostaglandins described.

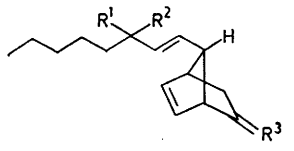
Reaction of the aldehydes (**2**) with the lithio derivative of dimethyl 2-oxoheptylphosphonate gave the *trans*-enones (**3**) which were reduced with aluminium iso-propoxide in refluxing toluene[3] to a 1:1 mixture of the allylic alcohols (**4**). Hydrolysis of the chloro-cyano group in the alcohols (**4**) with potassium hydroxide in dimethyl sulphoxide gave the ketones (**5**)§ [56% overall yield from the aldehydes (**2**)]. The ketones (**5**) are represented in the alternative form (**5a**) to demonstrate more clearly their relationship to prostaglandin $F_{2\alpha}$ (**9**). Baeyer-Villiger reaction of the ketones (**5**) using alkaline hydrogen peroxide¶ and iodolactonisation *in situ* of the resulting hydroxy-acid salt using potassium iodide and iodine gave the iodo-diols (**6**), which were deiodinated using tri-n-butyltin hydride to give the diols (**7**) [79% overall yield from the ketones (**5**)] identical in all respects to a sample prepared by known methods.[1a]

Reduction of the diols (**7**) with di-iso-butylaluminium hydride gave the hemiacetals (**8**) which on reaction with the sodium salt of (4-carboxybutyl)-triphenylphosphorane gave prostaglandin $F_{2\alpha}$ (**9**) together with its C-15 epimer. Chromatographic separation of this mixture gave racemic prostaglandin $F_{2\alpha}$ (**9**). The diol (**7**) may also be converted into prostaglandins of the E, A and B series using standard methods.[4]

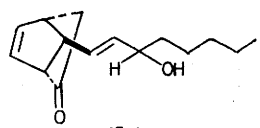


(1)

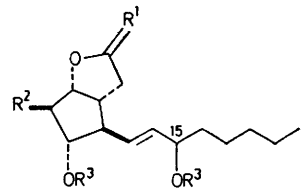
(2)



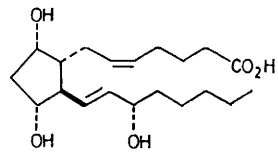
(3) $R^1, R^2 = O$; R^3 = Cl,CN.
(4) R^1, R^2 = H, OH; R^3 = Cl,CN.
(5) R^1, R^2 = H,OH; R^3 = O



(5a)



(6) $R^1 = O$; R^2 = I; R^3 = H.
(7) $R^1 = O$; R^2, R^3 = H.
(8) R^1 = H,OH; R^2, R^3 = H



(9)

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†*Syn* is used here to indicate that the formyl group is on the same side of the C-1 bridge as the double bond.

‡ Readily available as a mixture of epimers at C-5 in three stages from 6-acetoxyfulvene.

§ The method of conversion of the allylic alcohols (**4**) into the diol (**7**) is derived from that given in ref. 2.

¶ Peracid cannot be used to effect this reaction since epoxidation of the side chain olefinic linkage occurs.

[1] (a) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, 1971, **93**, 1491; (b) R. B. Woodward, J. Gosteli, I. Ernest, R. J. Friary, G. Nestler, H. Raman, R. Sitrin, Ch. Suter, and J. K. Whitesell, *ibid.*, 1973, **95**, 6853; (c) R. Peel and J. K. Sutherland, *J.C.S. Chem. Comm.*, 1974, 151.
[2] E. D. Brown, R. Clarkson, T. J. Leeney, and G. E. Robinson, *J.C.S. Chem. Comm.*, 1974, 642.
[3] J. Bowler, K. B. Mallion, and R. A. Raphael, *Synth. Comm.*, 1974, **4**, 211.
[4] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.