Design of Prostaglandin Synthesis

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Summary A 13-stage stereoselective synthesis of prostaglandin $F_{2\alpha}$ is described utilizing bicyclo[3,3,0]octane intermediates.

ORGANIC synthesis for commercial ends necessarily suffers constraints additional to those of academic work. With these in mind we sought to design a versatile synthesis of the prostaglandins. In designing the route we have taken note of recent theories[1] and chose to adopt the methods of Corey[2] for elaborating the side chains and double bonds of $PGF_{2\alpha}$ (I). This left us to generate the structural equivalent of the dialdehyde (II). In the previous work[2] the aldehyde groups of the equivalent (II) appeared at different oxidation levels requiring extra synthetic oxidative and reductive operations; we chose to generate the two aldehyde groups as such by disconnection of a single olefin. Furthermore we chose to control the *cis*-disposition of the two hydroxyl oxygen atoms of equivalent (II) by replacing them by carbon atoms and connecting them as a bridge on the five-membered ring.[3] *endo*-Dicyclopentadiene (III) contains all the necessary features except that the intended C-12 atom has a configuration opposite to that of $PGF_{2\alpha}$(I). An epimerization was envisaged involving an appropriate carbonylic intermediate.

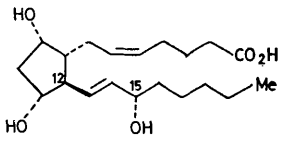
endo-Dicyclopentadiene (III) was converted ($KMnO_4$– aq. EtOH, 0°) into the *cis*-diol (IV; R = H)† (28%), m.p. 57—58°, the structure of which was established in particular by the n.m.r. spectrum of the diacetate (IV; R = Ac),† m.p. 65—66°. Sodium periodate cleavage of the diol (IV; R = H) yielded the dialdehyde (V; R = CHO)† (100%), m.p. 45·5—46°, which was oxidised (8N-chromic–sulphuric acid[4]) to the diacid (V; R = CO_2H)† (69%), m.p. 201—205°. Alternatively the diacid (V; R = CO_2H) was available (18%†) by direct ozonisation of *endo*-dicyclopentadiene (III). An excess of methyl-lithium converted the diacid (V; R = CO_2H) into the dimethyl ketone (V; R = Ac)† (48%), m.p. 121·5—122·5, which was also prepared by a Grignard reaction of the dialdehyde (V; R =

† Acceptable analytical and spectroscopic data were obtained.

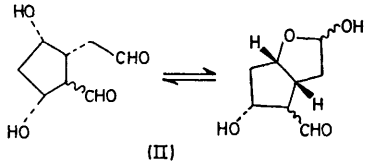
Yields are quoted after recrystallisation.

CHO) and subsequent oxidation[4] of the secondary alcohols.

The diketone (V; R = Ac) was converted ($KClO_3$ in aq. dioxan, 80° with a catalytic amount of OsO_4) into the diol (VI; R^1 = Ac, R^2 = OH),‡ m.p. 178—184° which on acetylation gave the diacetate (VI; R^1 = Ac, R^2 = OAc)† (59% over two steps), m.p. 123—125°. Treatment with *m*-chloroperbenzoic acid[5] in refluxing CH_2Cl_2 for 13 days then gave the tetra-acetate (VI; R^1 = R^2 = OAc)† (53%), m.p. 130—131°, which was hydrolysed to the oily tetrol (VI; R^1 = R^2 = OH)† (100%).



(I)



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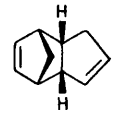

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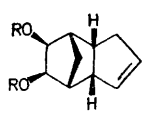

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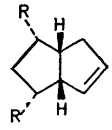

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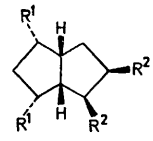
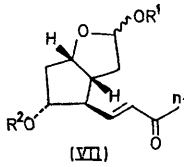


(VI)



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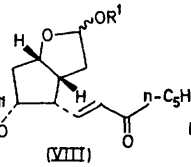
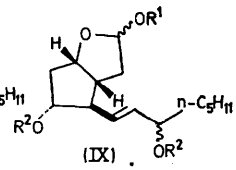


(VIII)



(IX)

When the tetrol (VI; R^1 = R^2 = OH) was cleaved with sodium periodate in aq. t-butyl alcohol containing K_2CO_3 it gave the unstable aldehyde (II) which was immediately treated with the required phosphonate anion[2] in dimethoxyethane. Two isomeric enones (VII; R^1 = R^2 = H)‡ (33% over three steps) and (VIII; R^1 = R^2 = H)‡ (12%) were obtained and separated by the first chromatography of the synthesis. The structures and stereochemistry of these enones were established in particular by n.m.r. spectroscopy§ and by subsequent conversion into prostaglandins. In the preparation of these enones there was no evidence of Wittig reaction at the alternative aldehyde function masked as the hemi-acetal.

The enone (VII; R^1 = R^2 = H) was protected as the rapidly formed trichloroethyl derivative (VII; R^1 = CCl_3CH_2, R^2 = H)‡ (100%) and reduced with $NaBH_4$ to the epimeric 15-alcohols (IX; R^1 = CCl_3CH_2, R^2 = H).‡ Without separation these were acetylated and the trichloroethyl group removed with Zn–aq. HOAc to give the hemi-acetals (IX; R^1 = H, R^2 = Ac)‡ (38% over four steps) purified by a second chromatography.

The hemi-acetals (IX; R^1 = H, R^2 = Ac) were subjected to the final Wittig process[2] followed by complete removal of acetoxyl groups with methanolic KOH. $PGF_{2\alpha}$ (I) and 15-epi $PGF_{2\alpha}$ were separated from the acidic products by modifications of literature methods.[6] The synthetic racemic $PGF_{2\alpha}$ (I) (15%) proved to be indistinguishable from natural $PGF_{2\alpha}$¶ on several sensitive t.l.c. systems and by i.r. and mass spectrometry. The identity of the synthetic $PGF_{2\alpha}$ was further established by bioassays.

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‡ Satisfactory t.l.c. and spectroscopic data were obtained.

§ The n.m.r. spectra were determined by Dr. I. A. Selby and will form the subject of a separate communication.

¶ From Cambrian Chemicals Ltd., Croydon.

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[2] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.

[3] For recent similar approaches see J. Katsube, H. Shimomura, and M. Matsui, *Agric. and Biol. Chem.* (*Japan*), 1971, **35**, 1828, and G. Jones, R. A. Raphael, and S. Wright, *J.C.S. Chem. Comm.*, 1972, 609.

[4] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.

[5] In preliminary experiments we have shown that this expensive reagent may be replaced by the reusable peroxymaleic acid, E. G. E. Hawkins, *J. Chem. Soc.* (*C*), 1969, 2691, and thank Dr. H. P. Crocker for suggesting this modification.

[6] N. H. Andersen, *J. Lipid Res.*, 1969, **10**, 316.