Synthesis of (±)-7-Oxaprostaglandin $F_{1\alpha}$

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THE prostaglandins, a recently discovered family of biologically highly active substances[1] have received considerable attention. Total syntheses of prostaglandin $F_{1\alpha}$,[2] dihydroprostaglandin E_1,[3] and related substances[4] have been reported. Difficulties in achieving stereoselectivity in these syntheses are readily apparent from these reports, and none of the final products obtained was crystalline. Studying the relationship between chemical structure and biological activity, we have synthesised substances related to the natural hormones, with special emphasis on the development of stereoselective methods. We now report a synthesis of (±)-7-oxaprostaglandin $F_{1\alpha}$ and related substances, in which all steps but the last, the introduction of the 15-hydroxyl group, are stereospecific.

all-cis-1,2-Epoxycyclopentane-3,5-diol (Ia)[5,6] on benzylation of its dianion (NaH) with benzyl chloride in dimethylformamide, afforded in 80% yield the dibenzyl ether (Ib), m.p. 62—63°; n.m.r.,†[7] τ 8·40 (2t, 4α-H, $J_{3,4\text{-}cis}$ 7·5, $J_{3,4\text{-}trans}$ 8·5, J_{gem} 12), 7·86 (2t, 4β-H), 6·50 (s, HC(O)CH), 6·15 (q, 3- and 5-CH), 5·40 (s, CH_2Ph). Failure to open the oxiran ring of (Ib) with alkali or magnesium acetylides even under rigorous conditions[8,9] necessitated exploration of an alternative approach,[10] which has resulted in an efficient procedure for converting epoxides stereospecifically into the *trans*-acetylenic alcohols by using a dialkylalkynylaluminium reagent.[11] The latter was generated *in situ* according to Binger:[12,13]

$$Et_3Al{\leftarrow}NEt_3 + HC{\equiv}CR \rightarrow Et_2Al(C{\equiv}CR)(NEt) + C_2H_6$$

and employed directly as a solution in toluene. The following procedure has given consistent yields of 65—70%: to a 20% toluene solution of triethylaluminium (9 ml. 17·2 mmoles)‡ at 20° under nitrogen was added triethylamine (0·36 ml. 2·5 mmoles) in 1·5 ml. toluene, and 1-octyne (2·54 ml. 17·2 mmoles) in 2·5 ml. of toluene. After 15 min. the temperature was raised slowly to 90° and held there until the evolution of ethane had subsided. The epoxide (Ib) (1 g., 3·37 mmoles) in 5·5 ml. of toluene was added to the cooled mixture containing (II) and the solution heated again to 90° for 4 hr. Careful acidification with dilute HCl at 0° and extraction with chloroform gave (III).§

The stereochemistry of the reaction was established to be *trans* as follows: 2-octynylcyclopentanol, b.p.$_5$ 112—114°, and 2-octynylcyclohexanol, b.p.$_3$ 89—91°, prepared as described above, were acetylated and oxidized with aqueous permanganate to *trans*-2-acetoxycyclopentanecarboxylic acid and *trans*-2-acetoxycyclohexanecarboxylic acid (m.p. 101·5—102·5°, lit.[14] 104·5—105·3°), respectively, which were hydrolyzed, without inversion,[15] to the corresponding *trans*-hydroxy acids, m.p.s. 65—67·5°, (lit.[15] 68·5—69°) and 107·5—108·5° (lit.[14] 111°).

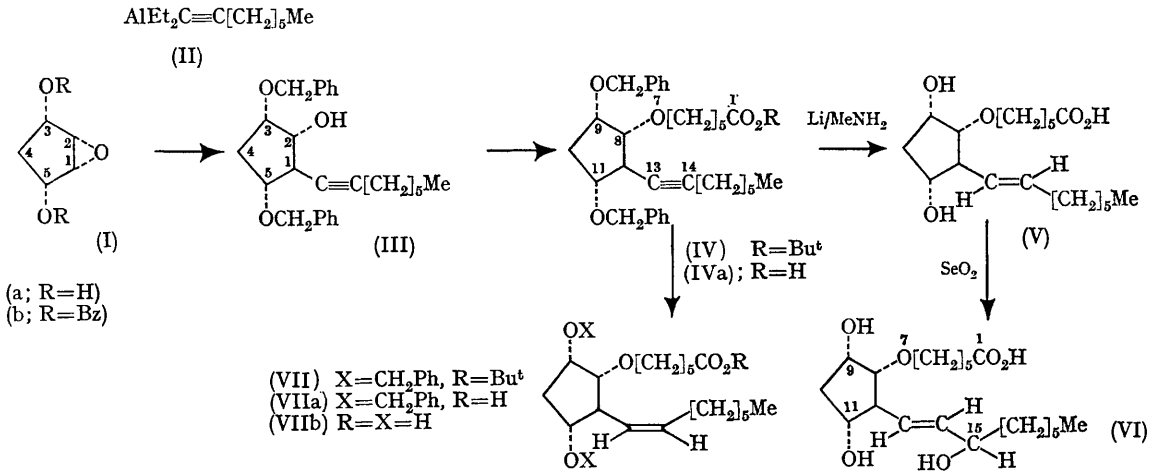
Compound (III) had λ_{max} 2·90, 9·73, 13·6 and 14·35μ; n.m.r., τ 9·11 (t, J 5, Me), 8·65 (b.p. [$(CH_2)_4$], 7·63—8·08 (m, ring CH_2 and $CH_2C{\equiv}C$), 6·87—7·42 (m, OH and $CHC{\equiv}C$), 5·88—6·33 (m, 3-CHOR), 5·33, 5·43, 5·40, 5·50 (q, J_{gem} 11·5, 2 CH_2Ph), 2·70 (s, Ph); *m/e* 406·24790 (M^+), 321 ($M-C_6H_{13}$), 315 ($M-C_7H_7$), 298 ($M-C_7H_8O$), 207 ($M-C_7H_8O-C_7H_7$), 107, 91 (base peak); 3,5-dinitrobenzoate, m.p. 20—22°; τ 4·64 (t, J 5, CHOCO); *m/e*, 600·25073 (M^+). Alkylation of (III) with t-butyl 6-iodohexanoate (3·5 mole equiv.) and dimsyl sodium (2 equiv.) in dimethyl sulphoxide gave the ester (IV) in 65% yield, λ_{max} 5·78, 8·70, 9·72, 13·60, and 14·35μ; n.m.r., τ 9·11 (Me), 8·57 (s, Bu^t), 8·33—8·83 (CH_2), 7·63—8·12 (ring CH_2, CH_2CO, $CH_2C{\equiv}C$), τ 6·99 (t, J 6·5 $CHC{\equiv}C$), 6·43 (t, J 5·5, CH_2O), 5·92—6·33 (m, 9-CHO), 5·37 (s, CH_2Ph), 5·32, 5·44 (q, J_{gem} 12, CH_2Ph), 2·70 (s, Ph). Removal of the t-butyl group was accomplished with trifluoroacetic acid in hexane at 0° or with formic acid at room temperature[16] to form the acetylenic acid (IVa) in 85% yield, λ_{max} 5·82, 6·25, 9·73, 13·60, and 14·34μ; n.m.r., as (IV) except τ 7·68 (t, J 6, CH_2CO_2H), 1·98 (s, CO_2H). Reduction of (IVa) with Li in methylamine afforded in 50% yield the dihydroxyacid (V), m.p. 63—67°; λ $(KBr)_{max}$ 2·9—3·0, 5·85,

† N.m.r. spectra were in $CDCl_3$ on a Varian A-60 instrument.

‡ In larger scale experiments the molar ratio of alane reagent to epoxide was reduced from 5 to 3.

§ This and subsequent compounds were purified by thick layer chromatography on silica gel and/or alumina. All yield figures refer to materials purified in this manner.

6·45 and 10·35μ; n.m.r., τ 9·11 (Me), 8·17—8·92 (m, CH_2), 7·72—8·17 (m, 10-CH_2, 15-CH_2), 7·68 (t, J 6·5, CH_2CO_2H), 7·35 (t J 6, C*H*CH=C), 6·62 (q, J 4, 8-CH), 6·46 (t, J 6, OCH_2), 6·23 (q, J 4, 11-CH) 5·83 (q, J 4, 9-CH), 4·61 (s, OH, CO_2H), 4·50 (m, HC=CH). Oxidation of (V) with SeO_2 in dioxan gave 7-oxaprostaglandin $F_{1\alpha}$ and its 15-epimer (VI) as a product more polar than (V) on t.l.c., λ $(KBr)_{max}$ 3·00, 5·85 and 10·35μ; its n.m.r. spectrum differing from that of (V) in that it possesses a second CHO signal centred at τ 5·83 (15-CH), lacks the 15-CH_2 signal at 7·72—8·17, and has a multiplet centred at 4·37 for the vinyl protons.



Catalytic reduction of (IV) over Pd—$BaSO_4$ and quinoline in methanol gave the *cis*-ester (VII), λ_{max} 5·80, 6·25, 8·70, 9·72, 13·60 and 14·35μ, which was converted into the acid (VIIa) (combined yield 63%), and the latter debenzylated with Li in ethylamine to afford in 60% yield the *cis*-acid (VIIb), oil, λ_{max} 2·94, 5·84μ; n.m.r., τ 7·65 (t, J 6·5, CH_2CO_2H), 7·01 (m, CHC=C), 6·62 (q, J 4, 8-CH), 6·48 (t, J 7, OCH_2), 6·20 (q, J 5, 11-CH), 5·81 (q, J 3·5, 9-CH), 4·96 (s, OH, COOH), vinyl protons as in (VII).

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