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PROSTAGLANDINS II - AN IMPROVED SYNTHESIS AND STRUCTURAL PROOF OF (±)-11-DEOXYPROSTAGLANDIN $F_{1\beta}$

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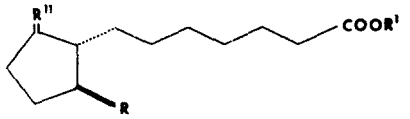
In an earlier communication [1] from our laboratory we reported the total synthesis of a physiologically active analogue (V) of prostaglandin. The asymmetric centres C-8, C-9 and C-12 were assumed to have configurations shown in the formula. In this communication, we report an improved synthesis and physicochemical evidences for the stereochemical assignments of (±)-11-deoxyprostaglandin $F_{1\beta}$. The acid chloride (I) [1] on treatment with heptyne in the presence of aluminum chloride yielded the chlorovinyl ketone II ($C_{21}H_{33}O_4Cl$; ν max.[3] 1735, 1685, 1590 cm^{-1}; λ max 248mμ (4.00) [2]; n.m.r. 0.86 δ 3H poorly resolved triplet, terminal methyl[4]; 3.54 δ 3H, methoxyl; 6.30 δ 1H, vinyl proton singlet). Treatment of ketone II with sodium hydroxide in methanol yielded the enol-ether III ($C_{22}H_{36}O_5$; ν max 1735, 1670, 1574 cm^{-1}; λ max 262mμ (4.21); n.m.r. 0.85 δ 3H terminal methyl, 3.53 δ and 3.62 δ 3H each, methoxyls, 5.35 δ 1H singlet, vinyl proton). The enol ether III was hydrolysed in the usual manner to the correspondin carboxylic acid (III, R'=H). The acid III (R'=H) was reduced with sodium borohydride in isopropanol and, after acidification, was worked up to give a mixture of products from which α,β-unsaturated ketone IV was isolated ($C_{20}H_{34}O_4$; eq. wt. 329; ν max 1726, 1670, 1620 cm^{-1}; λ max 228mμ (3.97); n.m.r. 0.85 δ 3H terminal methyl [4], 3.95 δ 1H, carbinolic, 6.0 δ and 6.6 δ 1H each vinyl protons. The ketone IV was then reduced with sodium borohydride and iso-



I R = COCl, R^1 = CH_3, R^{11} = =O

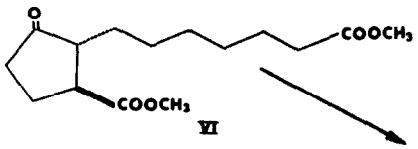
II R = -C(=O)-CH=C(Cl)-$(CH_2)_4$-CH_3, R^1 = CH_3, R^{11} = =O

III R = -C(=O)-CH=C(OCH_3)-$(CH_2)_4$-CH_3, R^1 = CH_3, R^{11} = =O

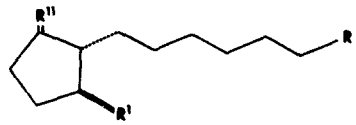
IV R = -CH=CH-C(=O)-$(CH_2)_4$-CH_3, R^1 = H, R^{11} = H, OH

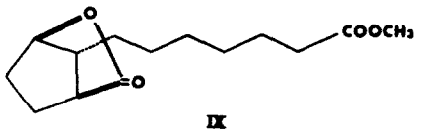
V R = -CH=CH-C(OH)-$(CH_2)_4$-CH_3, R^1 = H, R^{11} = H, OH

XIII R = -CH=CH-CHO, R^1 = CH_3, R^{11} = H, OH



VI





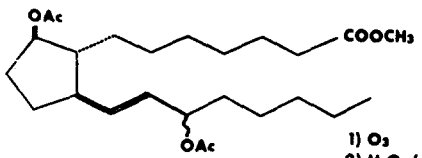
IX

VII R=R^1= $COOCH_3$, R^{11}= H, OH

VIII R=R^1= $COOCH_3$, R^{11} = OH, H

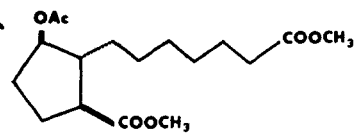
X R=R^1= CH_2OH, R^{11}= H, OH

XI R=R^1 = CH_2OH, R^{11}= OH, H



XII

1) O_3
2) H_2O_2/AcOH
3) CH_2N_2



propanol. The chromatography of the crude product gave (±)-11-deoxy-prostaglandin $F_{1\beta}$ identical in all respects with that described before [1]. The trans stereochemistry of the side chains in V was assigned based on the mode of synthesis of the intermediates [5]. The stereochemistry of the alcohol grouping in V was decided as follows: The cyclopentanone diester VI ($C_{15}H_{24}O_5$; ν max 1735 cm^{-1}; m/e 284,M; m/e 253, M-31;) obtained from corresponding diacid [1] was reduced with sodium borohydride in methanol, or with platinum oxide in acetic acid to yield a mixture of epimeric alcohols (85:15) [6]. The major component VII (R_f on T.L.C. 0.25) was separated by column chromatography. The minor isomer VIII (R_f on T.L.C. 0.33) was selectively obtained unchanged during the hemiphthalate formation of the mixture enriched in VIII. The pure alcohols VII and VIII [$C_{15}H_{26}O_5$; m/e 286, M; m/e 268, M-18; m/e 237, M-(18 + 31)] showed essentially identical infrared spectra (ν max 3600, 3400, 1725 cm^{-1}). The carbinolic proton signal (multiplet) in the n.m.r. spectra of VII and VIII were located at 3.91 δ and 4.25 δ and those of their acetates were shifted downfield to 4.85 δ and 5.27 δ respectively. The G.L.C. retention times for the free alcohols and their ethers are listed in Table I. The pure sample of free alcohol VII exhibited two peaks in its G.L.C. at 10.45 and 11.41 minutes. That the latter peak was an artifact, occurring on the column, was established by (a) its elimination in the G.L.C. of its ethers and (b) by variation of its intensity upon varying the temperature. The alcohol VII on pyrolytic elimination gave lactone IX ($C_{14}H_{22}O_4$; m/e 254, M; m/e 223, M-31; m/e 195, M-59; ν max 1775 [7], 1726 cm^{-1}; n.m.r. 3.58 δ 3H methoxy, 4.50 δ 1H carbinolic). The alcohol VIII was obtained unchanged under identical conditions. The structure of the lactone was confirmed by (a) its conversion back to alcohol VII on treatment with alcoholic sodium hydroxide, followed by esterification with diazomethane and (b) reduction of both,alcohol VII and

TABLE I

GAS LIQUID CHROMATOGRAMS [9a]

	Before Pyrolysis		After Pyrolysis	
Alcohol VII				
Free	10.45	11.41 [9c]	10.5	11.4 [9c]
TMSE [9b]	11.15		-	
DMVSE [9b]	14.1		14.2	11.5
Alcohol VIII				
Free	10.4		10.5	
TMSE [9b]	11.4		-	
DMVSE [9b]	14.2		14.4	
Lactone IX		11.45		

TABLE II

	Ring Carbinolic Proton in δ [8]
Trans-Trans Series	
VII	3.91
VII acetate	4.85
X	3.91
X triacetate	4.89
Cis-Trans Series	
VIII	4.25
VIII acetate	5.27
XI	4.24
XI triacetate	5.26
Intermediates	
IV	3.95
V	3.75- 4.18
V diacetate	4.9
XIII	4.02

lactone IX exhaustively with lithium aluminum hydride to the same triol X. A prerequisite for the formation of lactone IX is 1,3-cis stereochemistry of the hydroxyl and carbomethoxy groups in its progenitor VII. The relative stereochemistry of asymmetric centres in alcohols VII and VIII are thus established as shown. Alcohol VIII on reduction with lithium aluminum hydride gave a triol XI. The triols X and XI and their acetates exhibited the similar differences in the signals of the carbinolic proton (on cyclopentane ring) as those noted for alcohols VII and VIII above. The positions of the ring carbinolic proton signals are listed in Table II. The signals of the intermediates and that of compound V are in complete consonance with those of the compounds of trans-trans series. The stereochemistry of asymmetric centres in compounds IV, V and XIII[1] are therefore assigned as shown in the formula. Finally, the correctness of the above assignments was confirmed by the following experiments. Ozonolysis of the diacetoxy methyl ester XII, followed by decomposition of the ozonide with 30% hydrogen peroxide in acetic acid, at 50° over forty two hours, gave a crude mixture. Esterification of the acidic product with diazomethane followed by chromatography yielded an acetoxy diester identical in all respects with that obtained from alcohol VII. The above evidence assigns conclusively the stereochemistry at carbon atoms C-8, C-9 and C-12. In the ($\pm$)-11-deoxyprostaglandin $F_{1\beta}$ the mode of genesis of asymmetric centre at C-15 is beyond stereochemical control and a mixture of stereoisomers would be expected.

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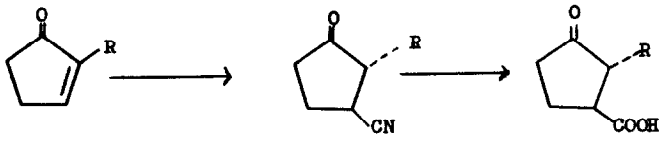
1. J.F. Bagli, T. Begri, R. Deghenghi, K. Wiesner, Tetrahedron Letters, 465, (1965).

2. A.E. Pohland, W.R. Benson, Chem. Rev., 66, 161(1966).

3. Infrared spectra and ultraviolet spectra were recorded in chloroform and 95% ethanol respectively. N.m.r. were recorded on 60 Mc Varian Spectrometer in $CDCl_3$. Mass spectra were recorded on Hitachi RMU-6D Spectrometer.

4. B. Samuelsson, J. Am. Chem. Soc., 85, 1878(1963).

5. Cis-2,3-dialkylcyclopentanone is transformed to the trans isomer quantitatively under alkaline conditions [D. Varech et al., Bull. Soc. Chim. 6, 1662(1965)]. Since nitrile (i) (See Ref. 1) was generated by a Michael-type addition in alkaline medium, ketonization of the intermediate enolate anion should give rise to thermodynamically more stable trans isomer. Subsequent alkaline hydrolysis yielded acid (ii). Elaboration of two side chains juxtaposition to each other should favour the retention of trans stereochemistry.



(i) (ii)

6. The composition of the products from catalytic reduction and hydride reduction were approximately the same.

7. D.S. Noyce, J.S. Fessenden., J. Org. Chem., 24, 715(1959).

8. Similar variations in the n.m.r. signals of ring carbinolic protons of cis-trans isomers of cyclopentanols in other rigid [P.G. Gassman et al., J. Am. Chem. Soc., 88, 2822(1964)] and non-rigid [A. Lapoivre et al., Bull. Soc. Belg., 73, 285(1964)] systems have also been observed.

9. (a) Column; SE 30 (15%), 9 ft. at 243°, R_t in minutes,
   (b) TMSE = trimethylsilyl ether, DMVSE = dimethylvinylsilyl ether
   (c) The intensity of 11.4 min. peak is markedly increased after pyrolysis.