Tetrahedron Letters No. 2, pp 101 - 104, 1976. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 9-DEOXY-9α-HYDROXYMETHYL $PGF_{2\alpha}$

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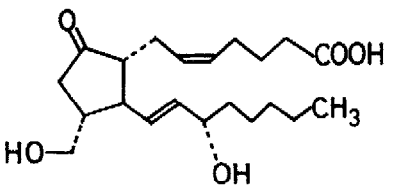
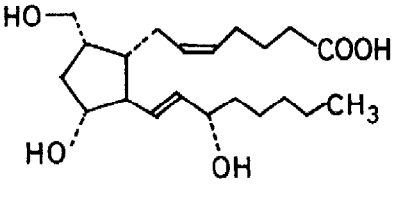
(Received in Japan 10 October 1975; received in UK for publication 24 November 1975)

In connection with 11-deoxy-11α-hydroxymethyl PGE_2 (I)[2,3], which showed a specific activity for uterus contraction, the synthesis of 9-deoxy-9α-hydroxymethyl $PGF_{2\alpha}$[3a] is of interest. Now, we wish to describe the total synthesis of 9-deoxy-9α-hydroxymethyl $PGF_{2\alpha}$ (XXIV)[1].



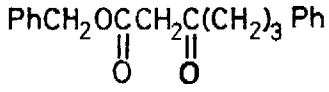
I



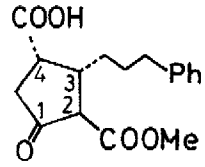
XXIV

By the application of the previous method[4] the 2,3-trans-3,4-cis keto acid III*[1] was stereospecifically synthesized from the keto ester II in 80% yield via 4 steps. III, ir 1725, 1755 nmr 3.70 (3H, s, COOMe).

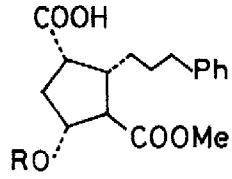
$NaBH_4$ reduction of the sodium salt of the acid III gave exclusively the trans, trans, cis acid IV which corresponds to PGF with regard to the configuration of the five membered ring. IV; 88% yield, m.p. 97~8°C, ir (nujol) 3420, nmr (CCl_4) 3.60 (3H, s, COOMe). Acetylation of the acid IV with Ac_2O/pyridine at room temperature gave the crystalline acetate V, accompanied by a small amount of the lactone VI. V; 92% yield, m.p. 71~3°C, ir (nujol) 1735, 1705, nmr 1.99 (3H, s, OAc) 5.30 (1H, m, ). VI; ir 1785, 1735, nmr 3.67 (3H, s, COOMe) 4.87 (1H, broad s, ). Direct conversion[5] of the carboxyl group to the corresponding alcohol was accomplished in the following way. Reaction of the acid V



II

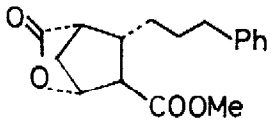


III

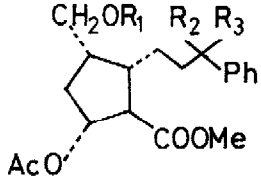


IV R = H

V R = Ac



VI



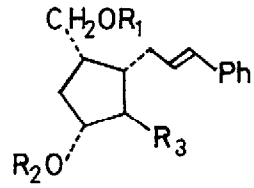
VII R_1= R_2= R_3= H

VIII R_1= Ac, R_2= R_3= H

IX R_1= Ac, R_2= Br, R_3= H

X R_1= Ac, R_2= R_3= O

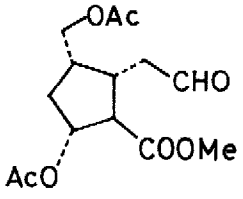
XI R_1= Ac, R_2= H, R_3= OH



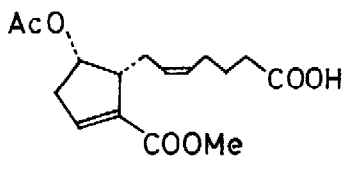
XIIa R_1= R_2= Ac, R_3= COOMe

XIIb R_1= R_2= Ac, R_3= COOH

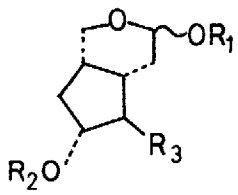
XV R_1= R_2= H, R_3= COOMe



XIII



XIV

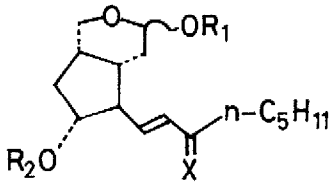


XVI R_1= R_2= H, R_3= COOMe

XVII R_1= Me, R_2= H, R_3= COOMe

XVIII R_1= Me, R_2= THP, R_3= COOMe

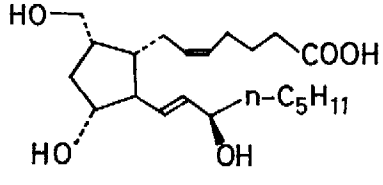
XIX R_1= Me, R_2= THP, R_3= CH_2OH



XX R_1= Me, R_2= THP, X = O

XXI R_1= Me, R_2= THP, X = 

XXII R_1= R_2= H, X = 



XXIII

with chloroethylcarbonate in the presence of triethylamine in THF at 0°C, followed by reduction of the resulting anhydride with $NaBH_4$ in aqueous THF, afforded the hydroxymethyl derivative VII. VII, 78% yield, ir 3500, 1735, nmr 1.98 (3H, s, OAc) 3.63 (3H, s, COOMe) 5.23 (1H, m, ).

In order to introduce the carboxyl side chain by the Wittig[6] reaction, the benzyl group was cleaved as follows. Bromination of the diacetate VIII obtained by the usual acetylation of VII by NBS in CCl_4 afforded in 85% yield the bromide IX[7] which on oxidation with CrO_3 in aqueous AcOH was converted into the ketone X. X; 90% yield, ir 1740, 1690, nmr 2.01 (6H, s, OAcx2) 3.63 3H, s, COOMe) 4.12 (2H, m, CH_2OAc) 5.26 (1H, m, ). Reduction of X with $NaBH_4$, followed by treatment of resulting alcohol XI with p-TsOH in boiling benzene, provided the olefins XIIa and XIIb in almost equal amount. The acid XIIb was converted into the ester XIIa by treatment with CH_2N_2. XI, 75% yield, ir 3450, 1735, nmr 4.56 (1H, t, τ=7, ) 3.60 (3H, s, COOMe). XIIa, 82% yield, ir 1735, nmr 6.38 (2H, m, ) 5.15 (1H, m, ) 4.05 (2H, m, CH_2OAc) 3.48 (3H, s, COOMe) 1.91 (3H, s, OAc) 1.89 (3H, s, OAc)

As, in a preliminary experiments, Wittig reaction of $Ph_3P^{\oplus}-CH^{\ominus}-(CH_2)_3COONa$ with the aldehyde XIII obtained by Lemieux-Johnson oxidation[8] ($NaIO_4$-OsO_4) of the olefin XIIa afforded the elimination product XIV as a main product, the alkyl side chain was first introduced prior to the carboxyl side chain.

The diol XV obtained by the hydrolysis (aqueous MeOH-K_2CO_3) of the diacetate XIIa was submitted to the oxidation ($NaIO_4$-OsO_4)[8] in aqueous dioxane at room temperature. The resulting aldehyde was obtained in 65% yield as the cyclic lactol XVI. XVI; ir 3400, 1730, nmr 3.63 (3H, s, COOMe) 4.94 (1H, broad ).

Treatment of the lactol XVI with anhydrous MeOH-BF_3 ether complex at 0°C for 2 hrs. gave in 82% yield the methylether XVII, consisting of the mixture of the epimeric methylethers. XVII, ir 3400, 1728, nmr 3.34, 3.30 (3H, OMe) 3.66 (3H, s, COOMe). Treatment of the methylether XVII with dihydropyrane in the presence of picric acid followed by reduction with $LiAlH_4$ provided the alcohol XIX. XIX; 55% yield, ir 3470, nmr 3.22 (3H, s, OMe).

Alkyl side chain was introduced into XIX by the established method[9]

(i. Collins oxidation ii. Wittig reaction). Thus, the enone XX was obtained in 72% yield. XX; ir 1690, 1670, 1625, nmr 6.20 (2H, m, olefin).

Reduction of the enone XX with $NaBH_4$ in MeOH gave the epimeric alcohols XXI. XXI; 89% yield, ir 3450, 1025, nmr 5.35 (2H, m, olefin). Removal of the protecting group of XXI was accomplished by treatment with 0.1N-HCl in CH_3CN at room temperature for 3 hrs. The lactol XXII was submitted to the subsequent Wittig reaction without purification. Thus, 9-deoxy-9α-hydroxymethyl $PGF_{2\alpha}$ XXIV and its 15-epimer XXIII were in 65% yield obtained as a mixture, which was separated by column chromatography. XXIV, m.p. 51~4°C, ir (nujol) 3350, 1703, 968, nmr 0.89 (3H, t, CH_3) 3.63 (2H, d, CH_2OH) 5.45 (4H, m, olefin). The corresponding methylester m.p. 54~6°C, ir (nujol) 3340, 1741, nmr 3.63 (3H, s, COOMe).

References and Footnotes

*1) ir (cm^{-1}) spectra were taken in neat liquid and nmr (δ) spectrum in $CDCl_3$ solutions containing tetramethylsilane as internal standard unless otherwise stated. All compounds obtained were supported by nmr, ir and mass spectra

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