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Synthetic Studies on Prostanoids. III.[1] Stereochemistry of the Key Intermediate (IV) in the Total Synthesis of Prostaglandin $F_{1\alpha}$

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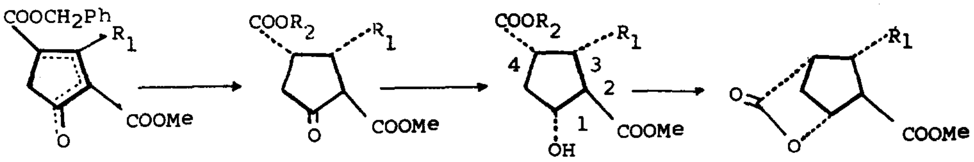
In a preceding paper we described the stereoselective total synthesis of $PGF_{1\alpha}$ via the key intermediate (IV). In this communication, we wish to report the configuration of hydroxyester (IV)[2], which was stereospecifically derived by Pd-C reduction (II), esterification with CH_2N_2 (III)[4] and $NaBH_4$ reduction from the starting material (I).



I

II R_2=H

IV R_2=Me

V

R_1=$-(CH_2)_6COOEt$

III R_2=Me

The Dieckmann condensation of the diester VI with dimethyl glyoxalate in the presence of NaOMe gave, in 60% yield, the enol ester VII. The ester VII was treated with ethanedithiol-BF_3 at room temperature to afford two isomeric mixtures, oily VIII A and crystalline VIII B, which could be separated by crystallization from MeOH. On treatment with Raney Ni in boiling EtOH, VIII A and VIII B yielded a corresponding ketoester IX A and IX B respectively. As well as the ir spectrum, the mass spectrum of both compounds also exhibited a similar pattern possessing a peak of highest mass number at m/e=312 (M^+). However the pattern of nmr spectrum are clearly distinctive. Two methyl ester of IX B were observed as an overlapping signals at 3.76 and five protons on five membered ring were observed as multiplet at 2.6—3.1.

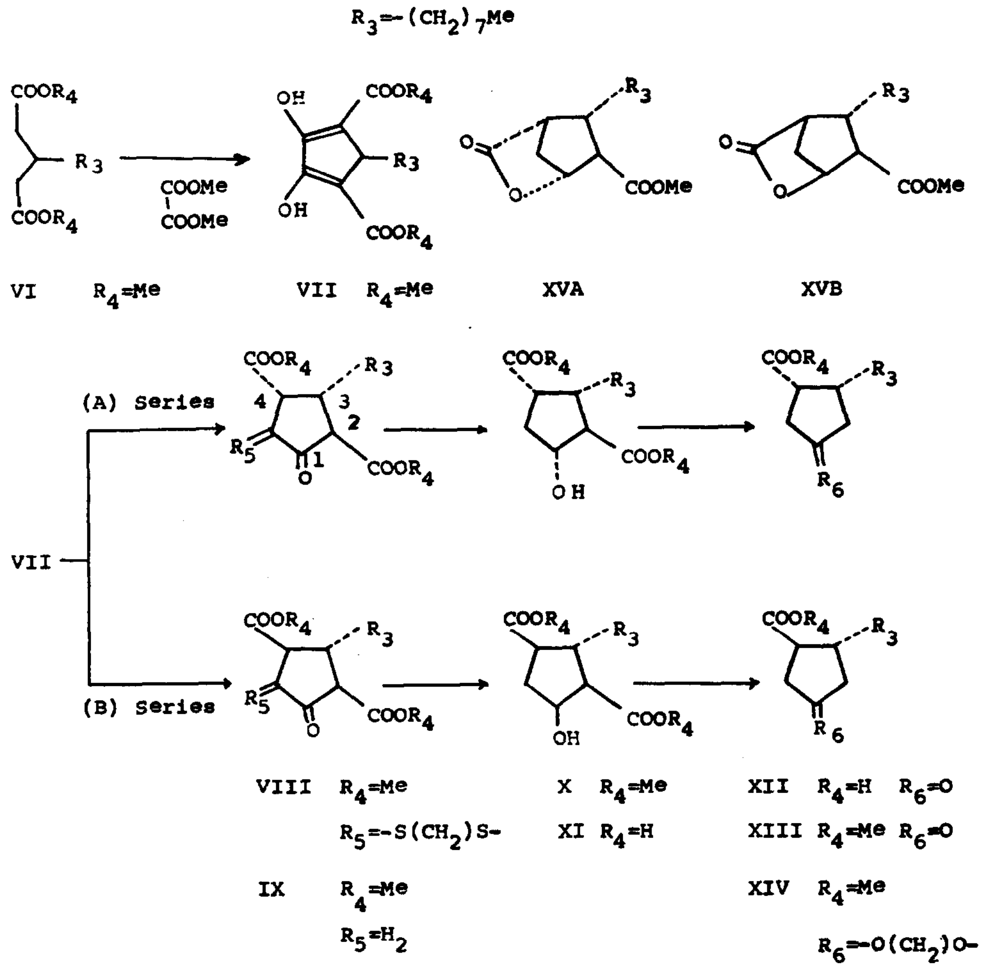
On the other hand, the nmr spectrum of IX A showed two distinguishable methyl ester signals at 3.75 and 3.69, and the five protons signals at 2.45—2.60 (2H, m), 2.65-3.08 (1H, m) and 3.15-3.45 (2H, m).

The relative configuration at H_2 and H_3 in IX A and IX B should be a more stable trans, because of an easily enolisable β-ketoester. As the ketotriester III revealed a remarkable similarity in nmr and ir spectrum to IX A, rather than to IX B, both III and IX A should be obviously the same configuration.

On reduction with $NaBH_4$ in MeOH, IX A afforded the hydroxy ester X A as a sole product, which was subjected to hydrolysis with 5% KOH-MeOH to yield a corresponding diacid XI A[3]. On the Jones oxidation, followed by decarboxylation by thermal decomposition at 110-130° in the presence of Cu powder, the diacid XI A was, in good yield, converted into the ketoacid XII A. On treatment with CH_2N_2, XII A gave the ketoester XIII A which was not so stable as to survive under the isomerization conditions of MeOH-MeONa. The ketal XIVA was obtained in 80% yield by the reaction of XIII A with ethyleneglycol-BF_3 at 0° for 10 min. In a similar way an isomeric ester XIVB was also derived from IX B. Thus, either isomeric ester XIVA or XIVB was expected to be transformed into a more stable one under a base-catalyzed isomerization conditions. On treatment with 5% NaOMe-MeOH at room temperature for 10 hrs, XIVA was isomerized into the isomeric ketoester XIVB, which on treatment with acetone-HCl gave XIIIB.

On the bases of the above data, a favored configuration of the keto-diester IXA, accordingly the ketotriester III, will be trans (H_2-H_3), cis (H_3-H_4). It is therefore reasonable that trans (H_2-H_3) - trans (H_3-H_4) configuration will be assigned to a thermodynamically more stable IXB.

Each hydroxy ester (XA and XB) in refluxing benzene in the presence of p-toluene-sulphonic acid was converted into the γ -lactone XVA (ir: 1795) and XVB (ir: 1790), which are indicative of cis configuration at H_1 and



R_3=-$(CH_2)_7Me$

VI R_4=Me

VII R_4=Me

XVA

XVB

VIII R_4=Me
R_5=-S(CH_2)S-

IX R_4=Me
R_5=H_2

X R_4=Me

XI R_4=H

XII R_4=H R_6=O

XIII R_4=Me R_6=O

XIV R_4=Me
R_6=-O(CH_2)O-

H_4. These facts allow us to conclude that the hydroxy ester XA should be trans (H_1-H_2), trans (H_2-H_3), cis (H_3-H_4) configuration, which are just the same configuration as $PGF_{1\alpha}$, and an isomeric XB should be cis (H_1-H_2), trans (H_2-H_3), trans (H_3-H_4) configuration.

The hydroxy triester IV is unequivocally to be the same configuration (trans-trans-cis) as XA, because of a marked similarity of IV to XA in ir, nmr spectrum and chemical behavior yielding the γ-lactone V (ir: 1795) in the same way. This conclusion was also supported by the nmr spectrum using shift reagent.

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Reference and Footnotes

1) Part II: K. Kojima and K. Sakai, Tetrahedron Letters

2) Reduction of ketoester (III) with $NaBH_4$ gave the same product as that obtained by reduction of ketoacid (II), followed by treatment with CH_2N_2.

3) The integrity of configuration was confirmed by reconversion with CH_2N_2 into the original diester (XA).

4) Spectroscopic data of all compounds obtained. The nmr (δ) spectrum in $CDCl_3$ with tetramethylsilane as internal reference. The ir (cm^{-1}) spectrum in liquid for oily, nujol for crystalline compound.

III: Oil, ir: 1760, 1730, nmr: 3.77, 3.70 (3Hx2, s, COOMe), 3.18-3.41 (2H, m, H_2 and H_4), 2.60-2.95 (1H, m, H_3), 2.45-2.60 (2H, m, $2H_5$)

IV: oil, ir: 3500, 1740, 1720, nmr: 3.71 (3Hx2, s, COOMe)

V: oil, ir: 1795, 1740, nmr: 4.90 (1H, br. s, H_1)

VII: mp 68-71°, ir: 3350, 3330, 1675, 1620, 1585

VIII A: oil, ir: 1740, nmr: 3.72 (3H, s, COOMe), 3.81 (3H, s, COOMe)
B: mp 111° ir: 1740, 1729, nmr: 3.80 (3Hx2, s, COOMe)

IX A: mp 37.5°, ir: 1767, 1740, nmr: 3.75 (3H, s, COOMe), 3.69 (3H, s, COOMe), 3.15-3.45 (2H, m, H_2 and H_4), 2.65-3.08 (1H, m, H_3), 2.45-2.60 (2H, m, $2H_5$) B: oil, ir: 1765, 1745, nmr: 3.76 (3Hx2, s, COOMe), 2.60-3.1 (5H, m, H_2, H_3, H_4 and $2H_5$)

X A: oil, ir: 3450, 1730, 1715, nmr: 3.70 (3Hx2, s, COOMe) B: mp 39°, ir: 3450, 1732, 1710, nmr: 3.69 (3Hx2, s, COOMe)
The analysis of nmr spectra using shift reagent ($Eu(DPM)_3$) will be discussed in detail elsewhere.

XI A: mp 95-8°, ir: 3500, 3400, 1700 B: mp 109-111°, ir: 3540, 3460, 1705

XII A: mp, 58-9°, ir: 3030-3200, 1740, 1700 B: mp 48°, ir: 3030-3200 1740, 1720

XIII A: oil, ir: 1750, 1200, nmr: 3.68 (3H, s, COOMe) B: oil, ir: 1744, 1200, nmr: 3.73 (3H, s, COOMe)

XIV A: oil, ir: 1750, 1200, 1044 B: oil, ir: 1746, 1200, 1030

XV A: oil, ir: 1795, 1740, nmr: 4.90 (1H, br. s, H_1), 3.73 (3H, s, COOMe) B: mp 42°, ir: 1790, 1740, nmr: 5.06 (1H, br. s, H_1) 3.73 (3H, s, COOMe).