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SYNTHETIC STUDIES ON PROSTANOIDS V.
TOTAL SYNTHESIS OF PROSTAGLANDIN E_1 AND $F_{1\beta}$

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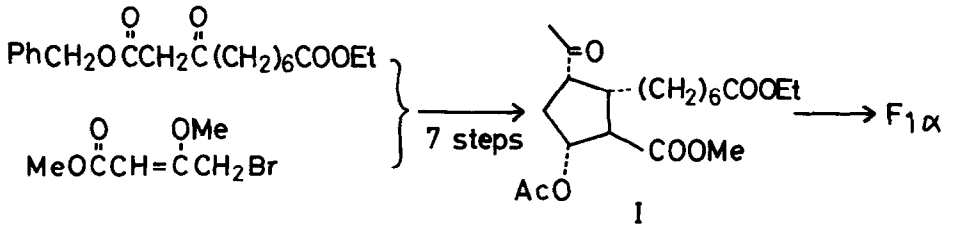
In a previous paper we have reported the stereospecific total synthesis of prostaglandin $F_{1\alpha}$[1], in which we have found that a trisubstituted cyclopentanol of the same configuration as Prostaglandin F was easily prepared with high stereospecificity[2]. In this report[3] we describe the total synthesis of prostaglandin E_1[4] and $F_{1\beta}$[5] using the important key intermediate I in our synthesis of $PGF_{1\alpha}$.

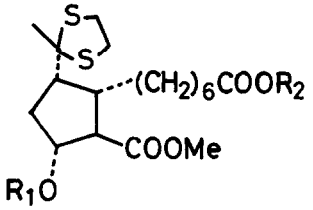


I

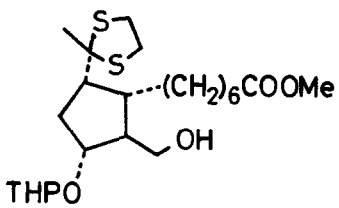
Treatment of the methylketone I, synthesized from benzyl 3-oxo-9-ethoxycarbonyl nonanoate and methyl γ-bromo-β-methoxycrotonate in 7 steps[1], with ethanedithiol and borontrifluoride - ether complex in dichloromethane at 0°C gave the ethylenethioketal II. ir*1; 1738 nmr ($CDCl_3$), 8.22 (3H, s, CH_3). Transesterification of II with potassium carbonate in anhydrous methanol yielded the alcohol III. ir; 3450, 1730 nmr ($CDCl_3$); 6.30 (3H, s, COOMe), 6.34 (3H, s, COOMe), which was treated with dihydropyrane in benzene in the presence of picric acid to give the pyranyl IV. ir; 1730, 1030. Selective

hydrolysis of the ester groups of IV with potassium carbonate in aqueous methanol produced the monoacid V. nmr; 6.30 (3H, s, COOMe). Potassium salt of V was reduced with lithium borohydride in tetrahydrofurane, followed by esterification of the carboxyl function with diazomethane, to yield the alcohol VI in 32% yield from I. ir; 3460, 1735 nmr; 6.41 (3H, s, COOMe). Treatment[6] of VI with mercuric oxide (red) and borontrifluoride-ether complex in aqueous tetrahydrofurane at 0°C gave the trans-trans-cis methyl ketone VII. nmr; 7.88 (3H, s, $COCH_3$). Isomerization of the acetyl function of VII using potassium carbonate in methanol produced the more stable all trans VIII. ir ; 3460, 1738 nmr; 7.86 (3H, s, $COCH_3$). Baeyer-Villiger oxidation of the methyl ketone VIII using excess m-chloroperbenzoic acid and sodium bicarbonate in methylene chloride afforded the acetate IX in 57.5% yield. nmr; 8.02 (3H, s, OAc). Oxidation of IX with chromic anhydride-pyridine complex[7] in anhydrous methylene chloride yielded the aldehyde X. ir; 2700, which was used in the next step without purification. Wittig reaction of X with tri-n-butyl phosphoranylidene-2-heptanone in ether yielded the enone XI. ir; 1738, 1695, 1675, 1630 nmr; 3.0 - 4.2 (2H, m, olefin), 9.10 (3H, t, CH_3). Sodium borohydride reduction of XI in absolute methanol at 0°C produced a mixture of the 15 epimers XII. The 15α and β mixture was then separated into the more polar 15α diol XIII and the less polar 15β diol XIV using silica gel column chromatography after removal of the tetrahydropyranyl group of XII with acetic acid: water: tetrahydrofurane (5:3:1), because they can be separated more easily at this stage. XIII: mp 40 - 42°C ir (melted film); 3400, 1700 XIV: oil ir; 3400, 1740. Hydrolysis of XIII using potassium hydroxide in aqueous methanol afforded crystalline prostaglandin $F_{1\beta}$ which was recrystallized from the mixed solvent of ethyl acetate and n-hexane. mp 115.5 - 6°C (Lit.[5] mp 116°C) ir (nujol); 3270, 1710, 968 nmr (CD_3COCD_3); 9.10 (3H, t, CH_3), 4.47 (2H, m, olefin) Mass Spectrum; M^+-H_2O=m/e=338.

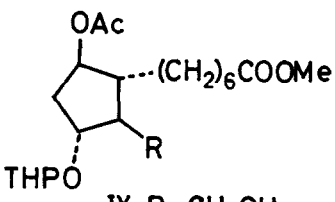
Prostaglandin E_1 was obtained as follows. Treatment of the diol XIII with dihydropyrane in benzene in the presence of picric acid gave the bis-tetrahydropyranyl derivative XV, followed by treatment with potassium hydroxide



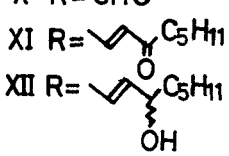
II R_1=Ac R_2=Et
III R_1=H R_2=Me
IV R_1=THP R_2=Me
V R_1=THP R_2=H



VI

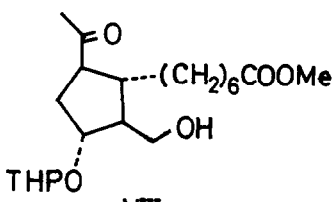


IX R=CH_2OH
X R=CHO

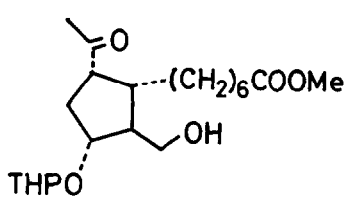


XI R=

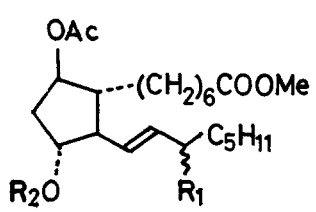
XII R=



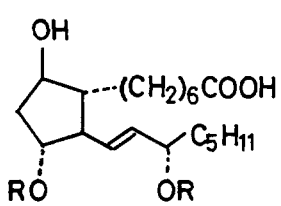
VIII



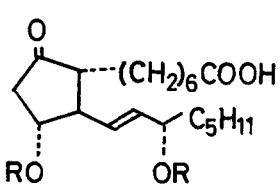
VII



XIII R_1=α-OH R_2=H
XIV R_1=β-OH R_2=H
XV R_1=α-OTHP R_2=THP



$PGF_{1\beta}$ R=H
XVI R=THP



XVII R=THP
PGE_1 R=H

in aqueous methanol, produced the carboxylic acid XVI. ir; 3400, 1715, 1020. The hydroxy group of XVI was then oxidized with Jones reagent in acetone at -13°C to yield the bistetrahydropyranyl derivative XVII of prostaglandin E_1. ir; 1740, 1710. Removal of the tetrahydropyranyl group of XVII with acetic acid:water:tetrahydrofurane (4:4:1) at 35°C yielded crystalline prostaglandin E_1, mp 111 - 112.5°C (Lit.[4] mp 112 - 3°C), which was recrystallized from ethyl acetate-n-hexane and identical with natural prostaglandin E_1 in T.L.C. behavior and spectroscopic properties.

Acknowledgement: The authors thank Director Dr. K. Arima, Assistant Director Dr. K. Kishida and former Assistant Director Dr. K. Tanabe of this laboratory for their valuable help and advice.

References and Footnotes

*1 ir (cm^{-1}) spectrum was taken in neats liquids and nmr (τ) spectrum was taken in CCl_4 solution containing tetramethylsilane as internal standard unless otherwise stated.

1) K. Kojima, K. Sakai, Tetrahedron Lett., 3333, 3337 (1972) For part IV, See Tetrahedron Lett., 4375 (1972).

2) A generality of this method will be published elsewhere.

3) This work was presented at the annual meeting of pharmaceutical society of Japan, April 1974, Abs. Papers II, p-153.

4) D. Taub, R.D. Hoffsommer, C.H. Kuo, H.L. Slates, Z.S. Zelawsky and N.L. Wendler, Tetrahedron 29 1447 (1973) and references cited therein.

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6) E. Vedejs and P.L. Fuchs, J. Org. Chem., 36 366 (1971).

7) J.C. Collins, W.W. Hess, and F.J. Franck, Tetrahedron Lett., 3363 (1968).