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A PROSTAGLANDIN SYNTHESIS

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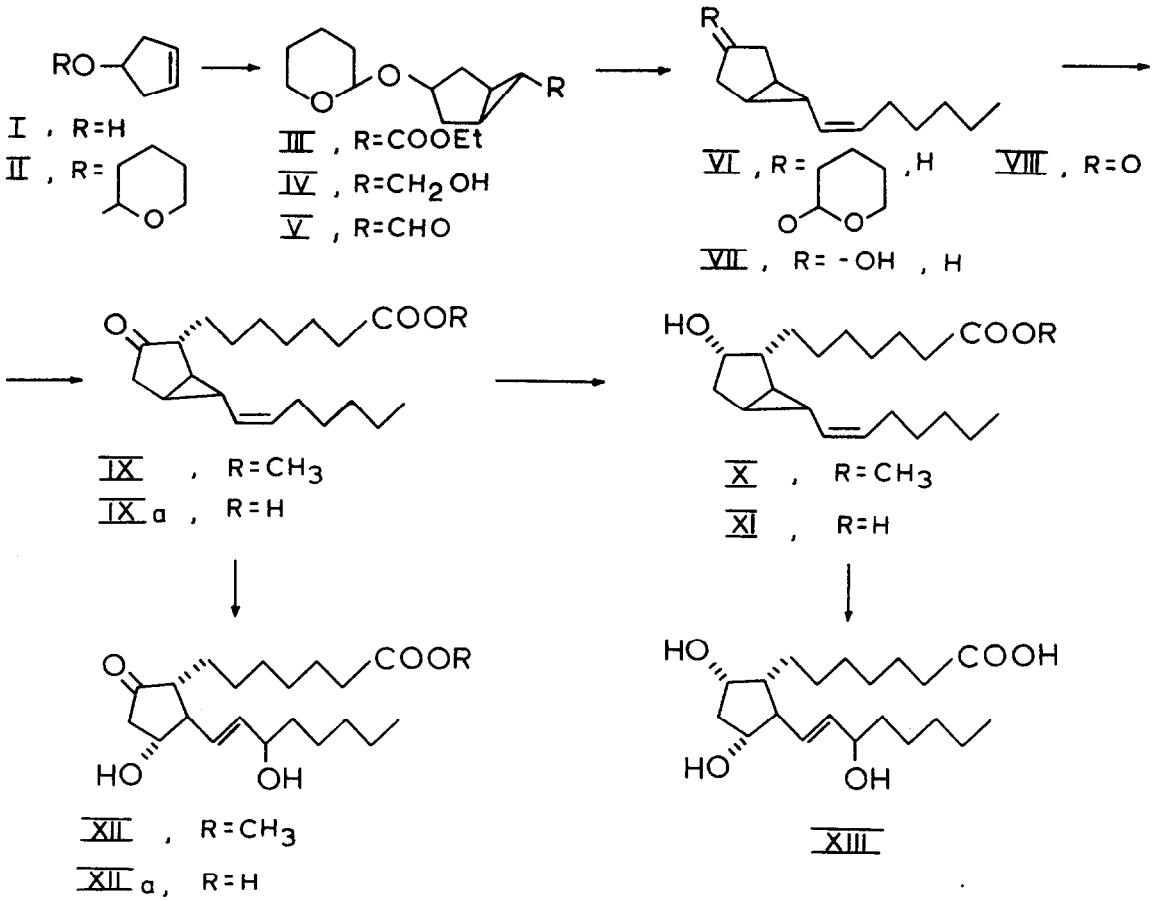
We wish to report a simple total synthesis of d,l-prostaglandin $F_{1\alpha}$[1]. In the course of the work, prostaglandin E_1 and its methyl ester were also obtained, but have as yet not been completely purified.

Treatment of cyclopentenol I[2] with dihydropyran and a few drops of phosphorus oxychloride[3] at 5° for 3 hours gave the tetrahydropyranyl ether II[4a], b.p. 120°/1mm, in quantitative yield. Reaction of II with ethyl diazoacetate in the presence of copper powder at 60-100°[5] gave III[4] as a mixture of syn-anti and exo-endo isomers.

Wiberg and Ashe[6] have shown that addition of ethyl diazoacetate to cyclopentene gave a similar bicyclic adduct in which the exo to endo ratio was 4:1. Treatment of III (exo-endo 4:1) with methanolic sodium methoxide for 4 hours under reflux gave III (pure exo, syn-anti mixture)[4a] b.p. 130-133°/1.1mm. Reduction of III (exo) with ethereal lithium aluminum hydride gave alcohol IV[4a] as a mixture of syn and anti isomers, which were separable by t.l.c. or g.l.c. The mixture of alcohols IV, b.p. 130-135°/0.05 mm, was oxidized with dilute (1:1) Jones reagent[7] at -15°. Aldehyde V was obtained in 80% yield as an oil[4a], which was characterized as its 2,4-dinitrophenyl hydrazone, m.p. 202°.

Wittig[8] reaction of V with hexyltriphenyl phosphonium bromide prepared from hexyl bromide and triphenylphosphine, gave crude olefin VI. G.l.p.c. showed the presence of four isomers. Column chromatography (alumina II-III) and elution with hexane-benzene (3:1) gave VI[4a] in 60-80%


RO
I , R=H
II , R=
III , R=COOEt
IV , R=CH2OH
V , R=CHO
R
VI , R= , H
VII , R= -OH , H
VIII , R=O
O
COOR
IX , R=CH3
IX a , R=H
HO
X , R=CH3
XI , R=H
XII , R=CH3
XII a , R=H
COOH
XIII

yield. The four isomers are due to geometric isomerism around the double-bond, and syn-anti isomerism of the cyclopropane ring and the tetrahydro-pyranyl function.

Hydrolysis of VI in refluxing methanol containing 0.5% oxalic acid for one hour gave alcohol VII as a mixture of four isomers, which were separated by t.l.c. and characterized by their i.r. spectra. The mixture of alcohols was oxidized with dilute (1:1) Jones reagent[7] at -5°. The resulting ketone VIII[4] consisted of two isomers, which were separated by t.l.c. The i.r. spectra of the cis and trans isomers were similar, the trans isomer having a strong absorption at 957 cm^{-1}[9].

The alkylation of VIII to IX presented major difficulties, and numerous reaction conditions were used before a reasonably satisfactory yield could be achieved. In part, the difficulty was due to the instability of IX, and the fact that VIII and IX had similar chromatographic mobilities. An effective separation could therefore be done only on the reduced product X. The best alkylation procedure was found to be the following: a solution of ketone VIII in dimethoxyethane was heated under reflux with four equivalents of potassium t-butoxide and six equivalents of methyl 7-iodoheptanoate. The reaction was followed by t.l.c. and interrupted, when decomposition of IX was noticeable (appr. 36 hours). The crude product was then dissolved in aqueous dimethylformamide and reduced with sodium borohydride[10]. Column chromatography (alumina, act. II-III) and elution with benzene-ether mixture gave X, slightly contaminated with VII (t.l.c.). Hydrolysis of ester X with aqueous methanolic sodium hydroxide gave acid XI. Reoxidation of XI with Jones reagent gave acid IXa[4b]. An alternate route for the alkylation consisted in transforming VIII to its morpholino or pyrrolidinoenamine, which was then treated with methyl 7-iodoheptanoate in DMSO at 60-65° for 4 hours. A 10-20% yield of IX was obtained in this manner.

Crude acid XI was dissolved in ice-cold formic acid (97-100%, 1% solution), buffered with two equivalents of sodium carbonate, and treated

with one equivalent of 30% hydrogen peroxide for thirty minutes at room temperature. The solvent was evaporated in vacuo, and the residue shaken for 1.5 hours with 10% aqueous sodium carbonate. Acidification to pH 2 in the cold and ether extraction gave a mixture which was separated by t.l.c. (AII-system[11]). Spots corresponding to starting material, prostaglandin $F_{1\alpha}$, (XIII) traces of prostaglandin $F_{1\beta}$, and three other products were detected. The spot corresponding to $PGF_{1\alpha}$ (XIII) was eluted. The yield of amorphous d,l-$PGF_{1\alpha}$ for the oxidative solvolysis was approximately 30%. The mass spectrum of XIII was identical, except for the intensities of some peaks below m/e 100, with that of natural $PGF_{1\alpha}$[12]. Preliminary biological testing on isolated smooth muscle preparations (guinea pig ileum, rabbit jejunum, rat stomach fundus) indicated biological activities 40-90% of natural crystalline prostaglandin $F_{1\alpha}$[13,14].

When IX or IXa were treated in formic acid - hydrogen peroxide (5 equivalents of base) as described above, t.l.c. indicated the formation of PGE_1 (XIIa) and its methyl ester (XII).

Preliminary biological investigation on impure XII showed it to possess 10-25% of the activity of natural material[14]. Treatment of XII with dilute aqueous sodium hydroxide gave material, λ_{max} 278 mμ[1].

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13. These tests were performed by Dr. J.R. Weeks, Pharmacology Unit, The Upjohn Co., Kalamazoo, Mich.

14. This test was performed by Dr. L. Wolfe, Montreal Neurological Institute, Montreal.