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# TOTAL SYNTHESIS OF 9(0)-METHANOPROSTACYCLIN AND ITS ISOMERS[1)]

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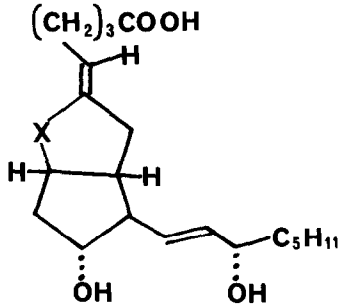
Prostacyclin($PGI_2$, I:X=O)[2)], a new member of prostaglandins, appears to have an important role in preventing thrombosis, stroke and heart attack. It is rapidly hydrolysed to the stable and less active 6-oxoprostaglandin $F_{1\alpha}$. This instability due to enol ether linkage seems to narrow the therapeutic perspective. Very recently 9(0)-thiaprostacyclin(I:X=S)[3)] has been synthesized with an expectation of increased stability. These synthesis prompted us to report the synthesis of another stable analogue of prostacyclin, namely 9(0)-methanoprostacyclin (I:X=$CH_2$), and its three isomers (XVII), (XVIII), and (XIX).




I(X=O,S,$CH_2$)

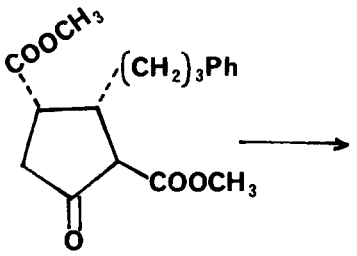
Prostacyclin (I:X=O)

9(0)-thiaprostacyclin (I:X=S)

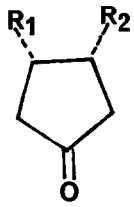
9(0)-methanoprostacyclin (I:X=$CH_2$)

Starting material, the trans-cis diester (II), was synthesized stereospecifically by the similar method described in our synthesis of 9-deoxy-9α-hydroxymethylprostaglandin $F_{2\alpha}$.[4)] Hydrolysis and decarboxylation of II with a mixture of hot dilute hydrochloric acid and acetic acid gave the cis monoacid (III) mp 76-8°C in good yield.

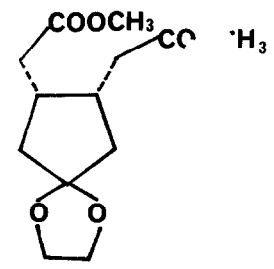
Carbon homologation of III by Arndt-Eistert method[5)] (i: oxalyl chloride, ii: diazomethane, iii: silver benzoate in methanol) yielded the ester (IV); ir: 1742. Introduction of an olefinic linkage in IV by the sequence (i: N-bromosuccinimide ii: sodium selenophenolate, iii: hydrogen peroxide) afforded the olefin (V); nmr: 6.12(1H, m), 6.55(1H, d). Cleavage of the olefinic



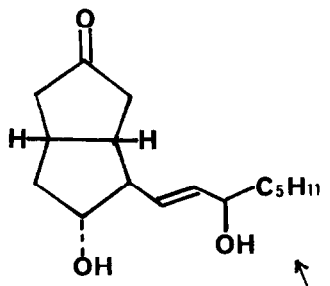
II



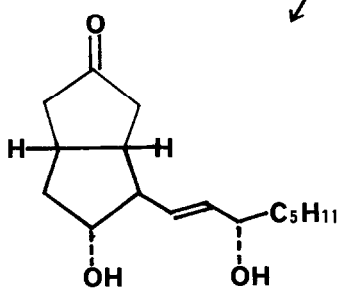
| | $R_1$ | $R_2$ |
|---|---|---|
| III | COOH | $(CH_2)_3Ph$ |
| IV | $CH_2COOMe$ | $(CH_2)_3Ph$ |
| V | $CH_2COOMe$ | $CH_2CHCHPh$ |
| VI | $CH_2COOMe$ | $CH_2COOMe$ |



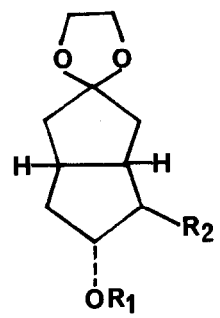
VII



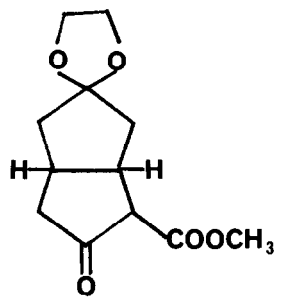
XIII +



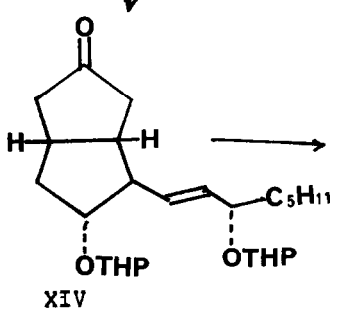
XII



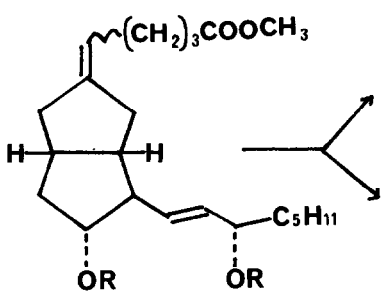
| | $R_1$ | $R_2$ |
|---|---|---|
| IX | H | COOMe |
| X | THP | COOMe |
| XI | THP | $CH_2OH$ |



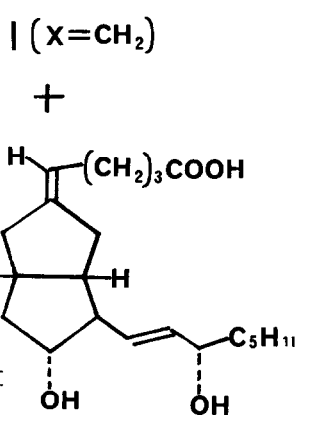
VIII



XIV



XV R=THP
XVI R=H



XVII

linkage in V with osmium tetraoxide and sodium metaperiodate, followed by oxidation with Jones reagent (chromic anhydride) yielded the carboxylic acid, which was esterified with diazomethane to give the diester (VI); nmr: 3.78(6H, s). Acetalization of VI with ethylene glycol and p-toluenesulphonic acid monohydrate in benzene under azeotropic removal of water yielded the acetal (VII); ir: 1740.

Dieckmann condensation of VII with sodium methoxide in dimethyl sulfoxide gave the cis bicyclic ketone (VIII); nmr: 3.78(3H, s), 3.90(4H, s). Sodium borohydride reduction of VIII afforded the desired trans alcohol (IX); ir: 1730, 3450 as a main product. Treatment of VIII with dihydropyran and picric acid yielded the ester (X), which was reduced with lithium aluminum hydride in ether to afford the alcohol (XI); ir: 3450.

Introduction of allyl alcoholic side chain in XI by the known method[4] (i: chromic anhydride pyridine complex in methylene chloride, ii: tri-n-butyl 2-oxoheptylidenphosphorane in ether, iii: sodium borohydride in methanol, iv: aqueous acetic acid) yielded the diol (XII) and (XIII) in almost equal amount after purification by column chromatography with silica gel: XII: ir: 1733, 3380 nmr: 0.89(3H, t), 5.50(2H, m), XIII: ir: 1732, 3380 nmr: 0.89(3H, t), 5.61(2H, m).

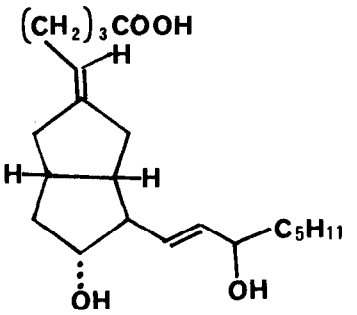
After tetrahydropyranylation of the two hydroxy groups in XII with dihydropyran and picric acid in benzene, the carboxylic side chain was introduced by the Wittig condensation.

Treatment of the ditetrahydropyranyl ether (XIV) with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid and sodio methylsulfinylcarbanide in dimethyl sulfoxide, followed by esterification with diazomethane yielded the methyl ester (XV); nmr: 3.66(3H, s) as a mixture of the regioisomers at the 5-position. Detetrahydropyranylation of XV with aqueous acetic acid afforded the diol (XVI); ir: 1735, 3350. Hydrolysis of XVI with potassium hydroxide in aqueous methanol at room temperature, followed by purification with preparative layer chromatography on silica gel (2 mm) yielded 9(O)-methanoprostacyclin (I:X=$CH_2$) as a main product and 6,9α-methylene-11α,15α-dihydroxyprost-5(Z),13(E)-dienoic acid (XVII)[6]; I(X=$CH_2$): mp 68-9°C, ir: 1710, nmr: 0.89(3H, t), 5.28(1H, m), 5.55(2H, m), XVII: mp 89-91°C, ir: 1710, nmr: 0.97 (3H, t), 5.25(1H, m), 5.53(2H, m).

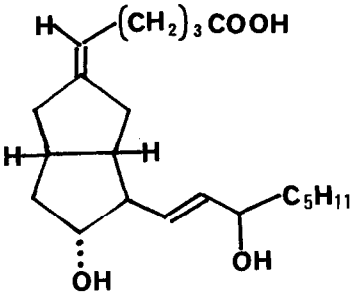
6,9α-Methylene-11α,15β-dihydroxyprost-5(E),13(E)-dienoic acid (XVIII) and its 5-Z isomer (XIX) were also synthesized from the diol (XIII) by the similar sequence of the reactions as described above[6]; XVIII: ir: 1710, nmr: 0.89(3H, t), 5.30(1H, m), 5.65(2H, m), XIX: ir: 1710, nmr: 0.89(3H, t), 5.30(1H, m), 5.65(2H, m).

All these stable prostacyclin analogues inhibit platelet aggregation by adenosine

diphosphate.[7]



XVIII



XIX

Acknowledgement: The authors are grateful to Dr. K. Arima, Director, and Dr. K. Murayama, Vice-director of these Laboratories, and Dr. Y. Kishida, Director of Chemical Research of these Laboratories for their valuable help and advice.

References and Notes

Infrared spectra($cm^{-1}$) were taken as neat liquid or melted film, and nuclear magnetic resonance spectra ($\delta$, ppm) were measured in deuteriochloroform solution containing tetramethyl silane as internal standard.

1) Synthetic studies on prostanoids XVII Part XVI N. Nakamura, K. Sakai Tetrahedron Letters 1549 (1978).

2) G.J. Dusting, S. Moncada, and J.R. Vane Prostaglandins 13 3 (1977) and references cited therein. Prostacyclin has been synthesized: K.C. Nicolaou and W.E. Barnette, G.P.Gasic, R.L. Magolda and W.J. Sipio, Chem. Comm. 630 (1977); R.A. Johnson, F.H. Lincoln, J.L. Thompson, E.G. Nidy, S.A. Mizak, and U. Axen, J. Am. Chem. Soc. 99 4182 (1977); E.J. Corey, G.E. Keck, and I. Szekely, J. Am. Chem. Soc. 99 2006 (1977); I. Tomoskozi, G. Galambos, V. Simonidesz and G. Kovacs, Tetrahedron Letters 2627 (1977); N. Whittaker, Tetrahedron Letters 2805 (1977).

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4) K. Kojima and K. Sakai, Tetrahedron Letters 101 (1976).

5) L.F. Fieser and M. Fieser, Reagents for Organic Synthesis Vol. I, p 1004.

6) Configurational Assignments of 15-position in the compounds I($X=CH_2$), XVII, XVIII, and XIX were based on relative thin layer chromatographic mobilities (silica gel) in a wide assortment of prostaglandin C-15 isomeric pairs. Geometrical assignments of 5-position in the compounds I($X=CH_2$), XVII, XVIII, and XIX were based on biological activities. Prostaglandins 14 220 (1977).

7) Details of biological studies will be published later.

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