Tetrahedron Letters No. 5, pp 433 - 436.

0040-4039/79/0129-0433$02.00/0

NEW SYNTHETIC ROUTES TO 9(O)-METHANOPROSTACYCLIN. A HIGHLY STABLE AND BIOLOGICALLY POTENT ANALOG OF PROSTACYCLIN

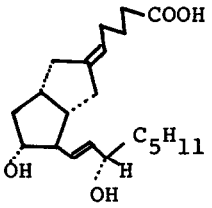
Masakatsu Shibasaki[a], Jun-ichi Ueda[b], and Shiro Ikegami[a*]

[a]Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan and [b]National Institute of Radiological Sciences, Anagawa, Chiba 280, Japan

As a part of our synthetic program of chemically stable prostacyclin analogs with similar biological activity,[1] practically useful total synthesis of 9(O)-methanoprostacyclin (I) was undertaken. In this communication, we wish to describe new and efficient synthetic routes to I from the simple starting materials, 1,3-cyclooctadiene and cis-bicyclo[3.3.0]octane-3,7-dione. The recent report[2] on the synthesis of I by Kojima and Sakai has prompted us to publish our different synthetic routes to I.

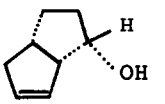
The endo-alcohol (III) derived from 1,3-cyclooctadiene via the epoxide (II)[3] was transformed stereospecifically into the endo-epoxide (IV)[4] by the Sharpless method (catalytic amount of vanadyl acetylacetonate and 1.2 equiv. t-butyl hydroperoxide[5] in benzene, 3 hr at reflux) in 70-75% yield. Then, the t-butyldimethylsilyl ether (V) was subjected to react with 2 equiv. 1,3-bis(methylthio)allyllithium[6] in THF at -25° for 1 hr [(VI) and the regio-isomer], followed by treatment with mercuric chloride (4 equiv.) and calcium carbonate (5.5 equiv.) in acetonitrile-water (4:1) at 50° for 2 hr to give a mixture of two unsaturated aldehydes. The more polar component (Rf 0.19, silica gel, ether-petr.ether 2:1), obtained in 44% yield, was proved to be the desired hydroxy aldehyde (VII), whereas the less polar component (Rf 0.39, 22% yield) could be assigned as the position-isomeric structure (VIII).[7] Treatment of the aldehyde (VII) with n-amyllithium in THF at -78° for 10 min led quantitatively to a mixture of epimeric secondary alcohols; the more polar alcohol (IXa)[8](Rf 0.04, silica gel, ether-petr.ether 2:1, 80% yield) and the less polar isomer (IXb) (Rf 0.08, 20% yield).

This novel stereoselective formation of the 15α isomer (PG numbering) might be attributed to the presence of a t-butyldimethylsilyloxy group located at the favorable position, since the coupling reaction of the aldehyde (VIII) with n-amyllithium under the same conditions is non-stereoselective. The more polar alcohol (IXa) was converted to the bis-THP ether (X), followed by treatment with tetra-n-butylammonium fluoride in THF at room temperature for 12 hr to afford the endo-alcohol (XI) in quantitative yield. In order to transpose the alcohol functionality from the 7 to the 6-position (PG numbering), the alcohol (XI) was reacted with methanesulfonyl chloride (2 equiv.) and triethylamine (2 equiv.) in methylene chloride at 0°

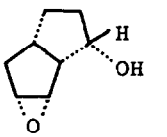


(I)

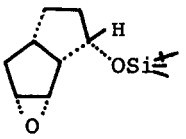
(II)



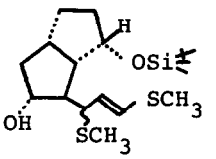
(III)



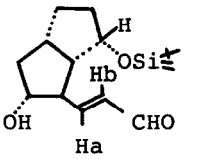
(IV)



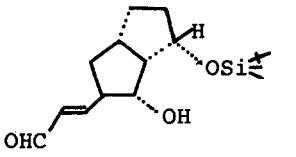
(V)



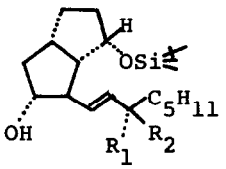
(VI)



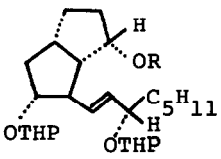
(VII)



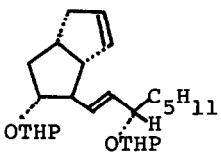
(VIII)



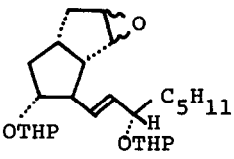
(IXa): R_1= OH, R_2= H
(IXb): R_1= H, R_2= OH



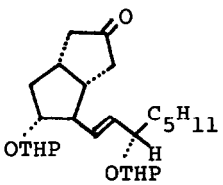
(X): R=Si
(XI): R=H
(XII): R=Ms



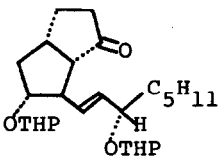
(XIII)



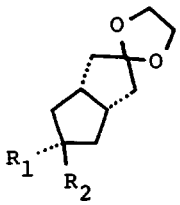
(XIV)



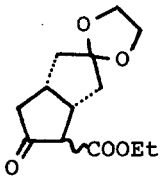
(XV)



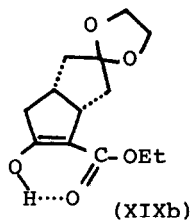
(XVI)



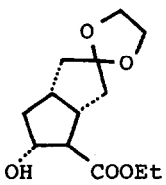
(XVII): R_1-R_2=OCH_2CH_2O
(XVIII): R_1-R_2= O



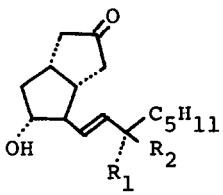
(XIXa)



(XIXb)



(XX)



(XXIa): R_1=OH, R_2=H
(XXIb): R_1=H, R_2=OH

for 0.5 hr to give the mesylate (XII), which underwent elimination to the diene (XIII) in 40-50% yield[9] when treated with 10 equiv. potassium hydroxide in ethanol at reflux for 5 hr.

Treatment of the diene (XIII) with 1.1 equiv. m-chloroperbenzoic acid in methylene chloride at 0° for 3 hr resulted in the epoxide (XIV) regiospecifically, which was reduced with lithium aluminum hydride in THF at reflux for 10 min to afford a mixture of several alcohols. Subsequent oxidation using Collins reagent (8 equiv.) in methylene chloride at room temperature for 12 hr yielded the desired ketone (XV) in 20% yield [Rf 0.31 (silica gel, ether-petr.ether 2:1), IR(ν , film): 1744cm^{-1}(ketone), 980cm^{-1}(trans disubstituted olefin), PMR($CDCl_3$,δ): 5.73-5.28 (olefinic protons, 2H)] and the isomeric ketone (XVI) in 40% yield (Rf 0.44).[10] The isomeric ketone (XVI) could be recycled to the endo-alcohol (XI) by stereospecific reduction with sodium borohydride in methanol at -25°.

Although the key intermediate (XV) to I was successfully synthesized with unambiguous stereochemistry, this route is still unsatisfactory from the practical point of view because of the low overall yield. Therefore, a more practical synthesis of I was further developed.

Acetalization of commercially available cis-bicyclo[3.3.0]octane-3,7-dione with ethylene glycol and p-toluenesulfonic acid in benzene under azeotropic removal of water gave the diketal (XVII) in quantitative yield. The selective hydrolysis was successfully achieved by treatment of XVII with 0.3 equiv. p-toluenesulfonic acid in acetone-water (3:1, 10 ml/g) at 30° for 2.5 hr to afford the ketone (XVIII) in 60-70% yield.[11]

Introduction of the ethoxycarbonyl group to XVIII was carried out by the standard method; reaction with 2 equiv. diethyl carbonate and 2.8 equiv. sodium hydride in benzene at reflux for 0.5 hr yielded the ester (XIX), whose PMR spectrum shows that XIX is in equilibrium with the keto-form (XIXa) and the enol-form (XIXb) (ratio ca. 1:1 in $CDCl_3$), in 60% yield. The most crucial reduction of XIX was run by treatment of XIX with sodium borohydride in methanol at -25° to give the alcohol (XX) [Rf 0.36 (silica gel, ether), IR(ν,film): 3450cm^{-1}(OH), 1730cm^{-1} (ester)] in 60% yield. The stereochemistry of XX was determined by the fact that XX was seccessfully converted to the diol (XXI).

The alcohol (XX) was transformed into XXI by the known method; i) DHP/H^+, ii) $LiAlH_4$-ether, iii) Collins oxidation, iv) $(CH_3O)_2P(O)CH_2COC_5H_{11}$, NaH, DME, v) $NaBH_4$-MeOH, vi) AcOH-H_2O-THF 3:1:1, 45°, 4 hr, overall yield 40-50%. A diastereomeric mixture of the allylic alcohol (XXIa) and (XXIb) was easily separated by preparative thin layer chromatography on silica gel using ethyl acetate as eluent to afford the 15α isomer (XXIa)[8] [Rf 0.19 (silica gel, ethyl acetate), mass(m/e),CI(NH_3): 284 (M^++ NH_4), IR(ν,film): 1730cm^{-1}(ketone), PMR($CDCl_3$,δ): 5.73-5.30 (2H, olefinic protons)] and the 15β isomer (XXIb)[Rf 0.24, mass(m/e),CI(NH_3): 288 (M^++ NH_4), IR(ν,film): 1730cm^{-1}(ketone), PMR($CDCl_3$,δ): 5.77-5.43 (2H, olefinic protons)] in a ratio of ca. 6:5. The ketone (XXIa) synthesized here was found to be spectroscopically and chromatographically identical with XXIa derived from XV prepared in the aforementioned former synthesis.[12]

The alcohol (XXIa) could be readily converted to the corresponding tetrahydropyranyl ether (XV). The ketone (XV) was subjected to the standard Wittig reaction ($Ph_3P=CH(CH_2)_3COONa$, DMSO), followed by the detetrahydropyranylation, to 9(O)-methanoprostacyclin (I) and its 6Z-isomer (I') in a ratio of 7:2 (70% yield, Rf 0.14 (I), 0.17 (I'), silica gel, ether, three developments).

Surprisingly, biological activity of I was found to inhibit platelet aggregation induced by ADP or collagen in rabbit plasma on the same order as active as prostacyclin, whereas the Z-isomer (I') was one-hundredth as active.[13,14]

Acknowledgment. We thank Japan Electronic Optics Laboratory for taking mass spectra.

References and Notes

1) M.Shibasaki and S.Ikegami, Tetrahedron Letters, 4037 (1977); Idem, ibid., 559 (1978); D.Horii, T.Kanayama, M.Mori, M.Shibasaki, and S.Ikegami, European J. Pharmacol., 51, 313 (1978); K.C.Nicolaou, W.E.Barnette, G.P.Gasic, and R.L.Magolda, J. Am. Chem. Soc., 99, 7736 (1977); K.C.Nicolaou, W.E.Barnette, and R.L.Magolda, ibid., 100, 2567 (1978); K.C.Nicolaou, R.L.Magolda, and W.E. Barnette, Chem. Commun., 375 (1978); G.L.Bundy and J.M.Baldwin, Tetrahedron Letters, 1371 (1978).

2) K.Kojima and K.Sakai, Tetrahedron Letters, 3743 (1978). We are grateful to Dr. Sakai for allowing us to read their manuscript prior to publication.

3) J.K.Crandall and L.-H.Chang, J. Org. Chem., 32, 532 (1967).

4) The exo-epoxide (IV') was stereoselectively prepared by treatment of III with m-chloroperbenzoic acid in t-butyl alcohol at room temperature in a ratio of 1:9 for IV/IV'; observed Rf values on silica gel with CH_2Cl_2-ether 9:1 as solvent, 0.07 for IV' and 0.12 for IV. The stereochemistry of IV and IV' was determined on mechanistic ground for the epoxidation.

5) t-Butyl hydroperoxide (70%) was used.

6) E.J.Corey, B.W.Erickson, and R.Noyori, J. Am. Chem. Soc., 93, 1724 (1971).

7) The structures of these aldehydes (VII and VIII) were determined using the triols (XXII and XXIII) derived from VII and VIII. The triol (XXIII) yielded the acetonide (XXIV) by treatment of XXIII with acetone in the presence of a catalytic amount of p-toluenesulfonic acid, while the triol (XXII) remained unchanged under the same condition.

8) The first-eluted isomer was assigned the structure of the 15β-isomer and the second eluted one as the natural (15α) on the basis of the known chromatographic behavior of the natural PGs, N.H.Andersen, J. Lipid Res., 40, 316 (1969).

9) A small amount of the isomer (XIII') was also obtained.

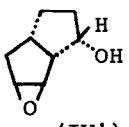
10) This ketone (XVI) was identified with the authentic material prepared directly from XI by Collins oxidation.

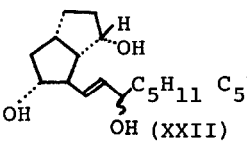
11) cis-Bicyclo[3.3.0]octane-3,7-dione and the starting ketal (XVII) were recovered in 30-40% yield.

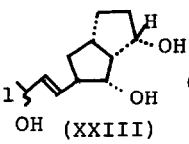
12) The diol (XXIb) was also identified with the authentic material synthesized from IXb.

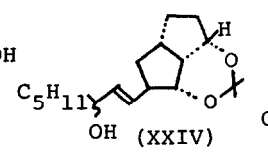
13) The stereochemistry of I and I' is based on these biological data: see Prostaglandin, 14,220 (1977); E.J.Corey, I.Szekely, and C.S.Shiner, Tetrahedron Letters, 3529 (1977).

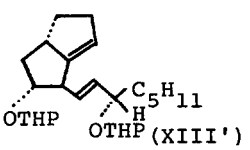
14) Test of biological activity was carried out by Dr. M.Mori and co-workers, Mitsubishi Pharmaceutical Co., Ltd., Japan.


(IV')


(XXII)


(XXIII)


(XXIV)


(XIII')

(Received in Japan 11 November 1978)