

Communications to the Editor

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A STEREOSELECTIVE TOTAL SYNTHESIS OF A STABLE PROSTACYCLIN ANALOG,
dl-9(0)-METHANO- $\Delta^{6(9\alpha)}$ -PROSTAGLANDIN I_1

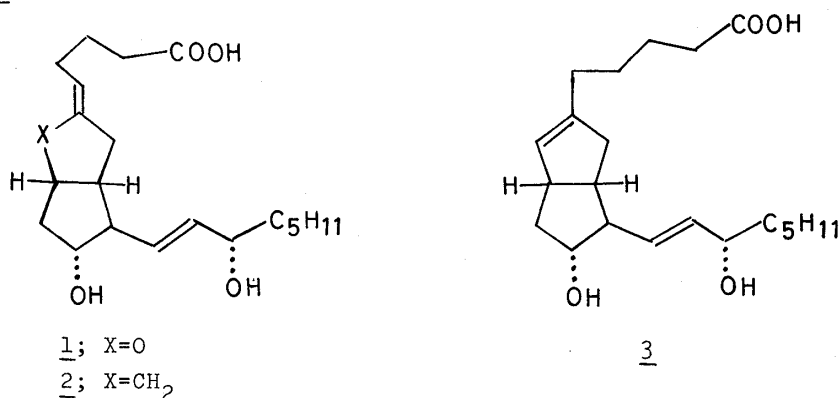
Kazuo Koyama and Koichi Kojima*

Chemical Research Laboratories, Sankyo Co., Ltd.,
1-2-58 Hiromachi Shinagawa-ku, Tokyo 140, Japan

9(0)-Methano- $\Delta^{6(9\alpha)}$ -PGI₁ (3), a stable analog of PGI₂, has been synthesized regio- and stereoselectively *via* cyclopropylketo-ester (14)

KEYWORDS—prostacyclin analog; methano-PGI₁; cyclopropane ring; stereoselective synthesis; bicyclo[3.3.0]octane

Currently, the stable prostacyclin (PGI₂, 1) analogs are attracting a great deal of attention because of their potential for use as therapeutic agents. One of the most promising compounds is 9(0)-methanoprostacyclin (2), whose synthesis has already been described by ourselves¹⁾ and others.²⁾ Recently the synthesis of 9(0)-methano- $\Delta^{6(9\alpha)}$ -PGI₁ (3), the double bond isomer of 9(0)-methanoprostacyclin (2), has been reported³⁾ and found to have more potent activity than 2 in inhibition of platelet aggregation. We herein describe a new stereoselective total synthesis of 3 *via* the olefinic intermediate (19).



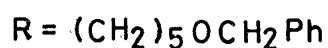
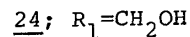
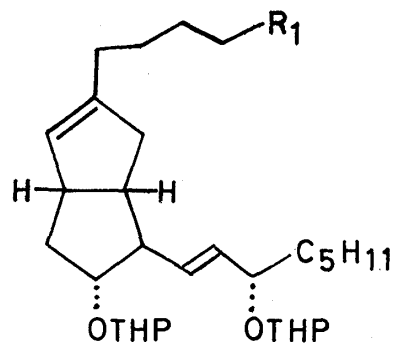
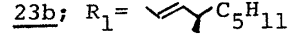
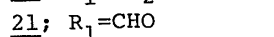
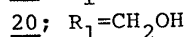
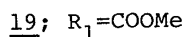
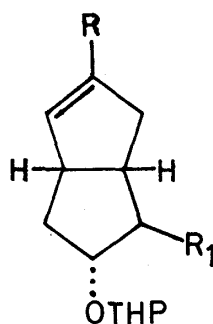
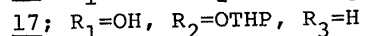
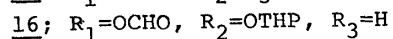
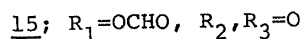
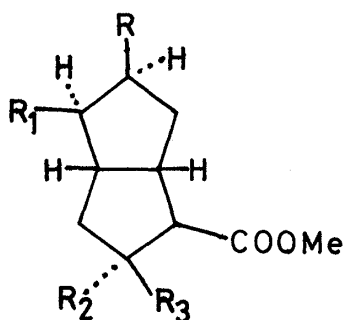
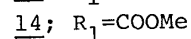
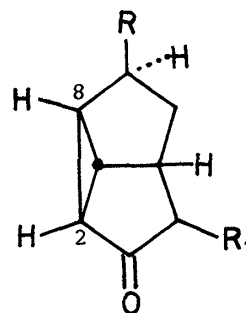
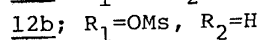
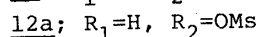
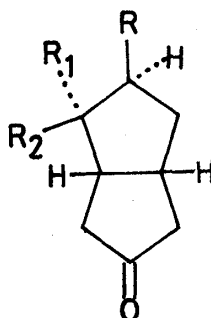
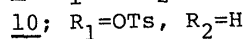
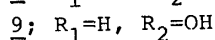
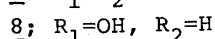
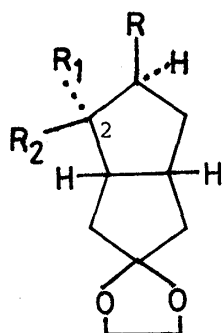
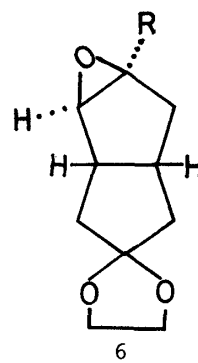
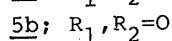
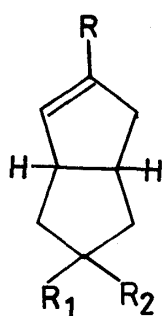
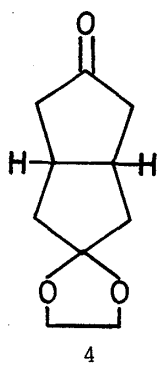
In order to synthesize the olefin (19) regio- and stereoselectively, we selected as a key intermediate, the cyclopropylketoester (14), which was synthesized as follows.

Reaction of the monoacetal (4) with Grignard reagent (PhCH₂O(CH₂)₅MgBr), prepared from 5-benzyloxy-1-bromopentane and Mg in ether, followed by treatment with p-TsOH in benzene in the presence of ethylene glycol under azeotropic distillation afforded the *endo*-olefin (5a) (¹H-NMR (CDCl₃) δ: 5.15 (1H, brs)) regioselectively⁴⁾ in 65% yield from 4. Epoxidation of 5a with *m*-chloroperbenzoic acid in CHCl₃ yielded the β-epoxide (6) in 69% yield. Treatment of 6 with

BF_3 etherate in toluene at -15°C gave a single product (7)⁵⁾ in 63% yield. Reduction of the ketone (7) with NaBH_4 yielded the α -alcohol (8) as the main product together with the β -alcohol (9) ($\alpha\text{-OH}:\beta\text{-OH}=4:1$).⁶⁾ The cyclopropane ring required for the regioselective introduction of the ω -side chain and $\Delta^{6(9\alpha)}$ -double bond (PG numbering), was then introduced after inversion of the α -hydroxy group in 8 into the β -hydroxy group by the following reactions. Treatment of 8 with TsCl and a catalytic amount of 4-dimethylaminopyridine in pyridine at room temperature for 20 hours afforded quantitatively the crystalline tosylate (10), mp $70\text{--}72^\circ\text{C}$. The tosylate (10) was then treated with 4 equivalent of KO_2 in the presence of 18-crown-6 (4 eq) in DMSO at room temperature under N_2 atmosphere to give the β -alcohol (9) in 65% yield. The hydroxy-acetal (9) was converted to the hydroxy-ketone (11) with 10% HCl in acetone at room temperature, which was then treated with $\text{MsCl-Et}_3\text{N}$ in CH_2Cl_2 to afford the mesylate (12a). The cyclopropanation reaction is now performed by DBU treatment (55°C , 20min) of 12a giving the compound (13) in 81% yield. Finally, treatment of 13 with dimethyl carbonate and NaH in 1,4-dioxane at 90°C for 3 hours yielded the desired β -ketoester (14) in 90% yield.

The 11α -hydroxy group and the $\Delta^{6(9\alpha)}$ -double bond (PG numbering) were then introduced regio- and stereoselectively as follows. The cleavage of the cyclopropane ring in 14 with formic acid in the presence of conc. sulfuric acid at room temperature afforded the β -formate (15) having the bicyclo[3.3.0]octane skeleton ($\text{C}_2\text{-C}_8$ bond cleavage)⁷⁾ in 58% yield with 36% recovery of the starting material (14). Stereoselective reduction¹⁾ of 15 with NaBH_4 in EtOH followed by protection of the hydroxy group as THP ether (dihydropyran and $p\text{-TsOH}$) afforded 16 in 79% yield. The methanolysis of the formate (16) with K_2CO_3 in MeOH gave the β -alcohol (17) in 97% yield. Treatment of 17 with $\text{MsCl-Et}_3\text{N}$ in CH_2Cl_2 gave the mesylate (18), which provided the desired olefin (19)⁸⁾ on treatment with PhSeNa ⁹⁾ in EtOH at 80°C in 77% yield from 17.

The compound (19) was then converted into 9(0)-methano- $\Delta^{6(9\alpha)}$ -PGI₁ (3) by the following sequence of reactions. After reduction of 19 with LiAlH_4 in THF, the obtained alcohol (20) was oxidized to the aldehyde (21) with excess SO_3 -pyridine complex and Et_3N in DMSO. The Wittig reaction of 21 with 2-oxoheptylidenetriethylphosphorane gave the ketone (22) in 83% yield from 19. Reduction of 22 with NaBH_4 in the presence of CeCl_3 in MeOH gave the more polar α -alcohol (23a) and the less polar β -alcohol (23b), ($15\alpha\text{-OH}:15\beta\text{-OH}=3:2$)¹⁰⁾ in 91% yield. The major isomer (23a) was treated with dihydropyran and $p\text{-TsOH}$ in CH_2Cl_2 followed by treatment with excess Na in liquid ammonia at -78°C yielding the alcohol (24) in 73% yield. Oxidation of 24 with $\text{CrO}_3\text{-H}_2\text{SO}_4$ in acetone at -25°C afforded the carboxylic acid (25) in 72% yield. Removal of the protecting groups of 25 with camphorsulfonic acid in aqueous acetone at 40°C for 3 hours gave the crystalline *dl*-9(0)-methano- $\Delta^{6(9\alpha)}$ -PGI₁ (3), mp $76\text{--}78^\circ\text{C}$, in 80% yield.



REFERENCES AND NOTES

- 1) K. Kojima and K. Sakai, *Tetrahedron Lett.*, **1978**, 3743.
- 2) S.M. Roberts and F. Scheinmann, ed., "New Synthetic Routes to Prostaglandin and Thromboxane," Academic Press, London, 1982.
- 3) Y. Ogawa and M. Shibasaki, *Tetrahedron Lett.*, **25**, 1067 (1984); M. Sodeoka and M. Shibasaki, *Chem. Lett.*, **1984**, 579, and references cited therein.
- 4) *exo*-Olefin isomer was not detected by $^1\text{H-NMR}$.
- 5) Assignment of β -orientation of the side chain is based on mechanistic consideration. See H.B. Henbest and T.I. Wringley, *J. Chem. Soc.*, **1957**, 4596.
- 6) The configuration of the hydroxy group was assigned from $^1\text{H-NMR}$ signals of $\text{C}_2\text{-H}$, (8, δ : 3.87 (t, $J=6.5\text{Hz}$); 9, 3.90 (d, $J=3\text{Hz}$)). Molecular model analysis suggested that the compound having the larger coupling constant is the α -alcohol (8). Moreover treatment of 12b, derived from 8 (i) 10% HCl in acetone ii) $\text{MsCl-Et}_3\text{N}$ in CH_2Cl_2), with DBU at 80°C resulted in recovery of 12b. This also supports the α -configuration of the hydroxy group in 8.
- 7) The bicyclo[3.3.0]octane skeleton of 15 was confirmed by the following reactions; Demethoxycarbonylation of 15 with NaI and AcOH in diglyme at 120°C , followed by methanolysis with K_2CO_3 in MeOH gave 11.
- 8) The $\Delta^{6(9\alpha)}$ -double bond was confirmed by the following reactions; Treatment of 19 with aq. AcOH at 50°C , followed by oxidation ($\text{CrO}_3\text{-H}_2\text{SO}_4$ in acetone) and demethoxycarbonylation (NaI and AcOH in diglyme) gave 5b, whose structure was confirmed by an alternative synthesis of 5b by treatment of 5a with 10% HCl in acetone.
- 9) Weak bases, such as AcOK or PhSNa, also convert 18 to 19, in much lower yields.
- 10) Configurational assignment at the C-15 position (PG numbering) was based on relative TLC mobilities (silica gel) in wide assortment of PG C-15 isomeric pairs. This was also supported by the relative TLC mobility and relative biological activity of 3 and its 15β -isomer in the final 9(O)-methano- $\Delta^{6(9\alpha)}$ -PGI₁ stage.
- 11) No isomer was detected by $^{13}\text{C-NMR}$ and HPLC analysis. 3: Anal. Calcd for $\text{C}_{21}\text{H}_{34}\text{O}_4$: C, 71.96; H, 9.78. Found: C, 71.88; H, 9.73. IR (CHCl_3) cm^{-1} : 3360, 1710, 1085, 970. $^1\text{H-NMR}$ (CDCl_3) δ : 3.00 (1H,m), 3.73 (1H,m), 4.10 (1H,m), 5.30 (1H,brs), 5.55 (2H,m).

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