Communications to the Editor

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

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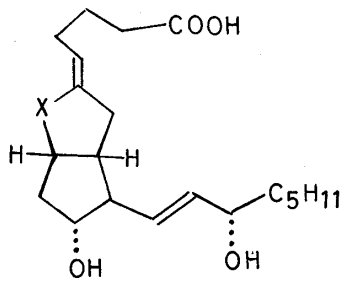
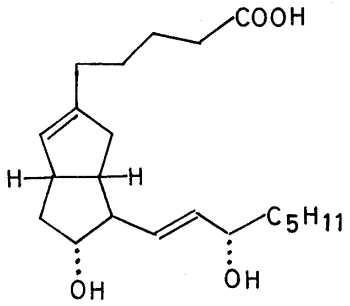
9(O)-Methano-$\Delta^{6(9\alpha)}$-PGI_1 (3), a stable analog of PGI_2, has been synthesized regio- and stereoselectively *via* cyclopropylketo-ester (14)

KEYWORDS——prostacyclin analog; methano-PGI_1; cyclopropane ring; stereoselective synthesis; bicyclo[3.3.0]octane

Currently, the stable prostacyclin (PGI_2, 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(O)-methanoprostacyclin (2), whose synthesis has already been described by ourselves[1] and others.[2] Recently the synthesis of 9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1 (3), the double bond isomer of 9(O)-methanoprostacyclin (2), has been reported[3] 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).



1; X=O
2; X=CH_2



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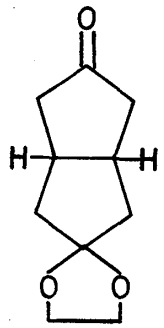
In order to synthesize the olefin (19) regio- and stereoselectively, we selected as a key intermediate, the cyclopropylketoester (14), which was synthesized as follows.

Reaction of the monoacetal (4) with Grignard reagent ($PhCH_2O(CH_2)_5MgBr$), 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) (^{1}H-NMR ($CDCl_3$) δ: 5.15 (1H, brs)) regioselectively[4] in 65% yield from 4. Epoxidation of 5a with m-chloroperbenzoic acid in $CHCl_3$ 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) (α-OH:β-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 70-72°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 MsCl-Et_3N 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 (C_2-C_8 bond cleavage)[7] in 58% yield with 36% recovery of the starting material (14). Stereoselective reduction[1] of 15 with $NaBH_4$ in EtOH followed by protection of the hydroxy group as THP ether (dihydropyran and p-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 MsCl-Et_3N 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(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1 (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-oxoheptylidenetributyl-phosphorane 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), (15α-OH:15β-OH=3:2)[10] in 91% yield. The major isomer (23a) was treated with dihydropyran and p-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 CrO_3-H_2SO_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(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1 (3), mp 76-78°C, in 80% yield.



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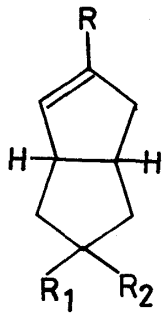
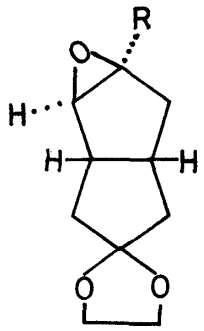


5a; $R_1,R_2=OCH_2CH_2O$
5b; $R_1,R_2=O$



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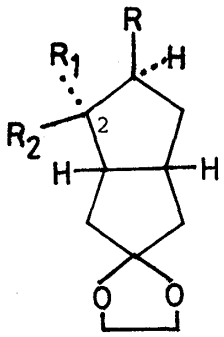
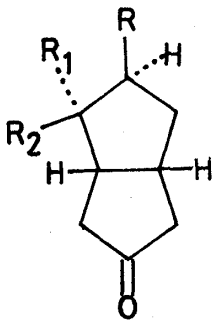
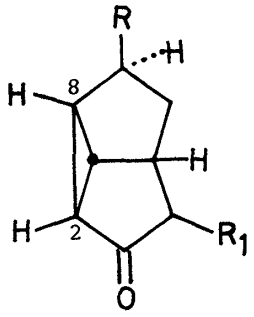


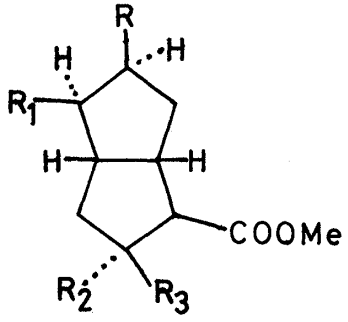
7; $R_1,R_2=O$
8; $R_1=OH$, $R_2=H$
9; $R_1=H$, $R_2=OH$
10; $R_1=OTs$, $R_2=H$



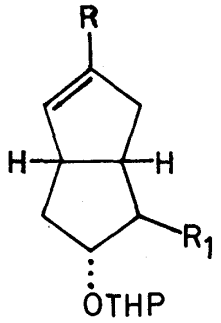
11; $R_1=H$, $R_2=OH$
12a; $R_1=H$, $R_2=OMs$
12b; $R_1=OMs$, $R_2=H$

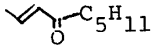
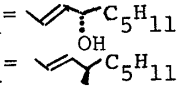
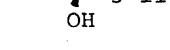


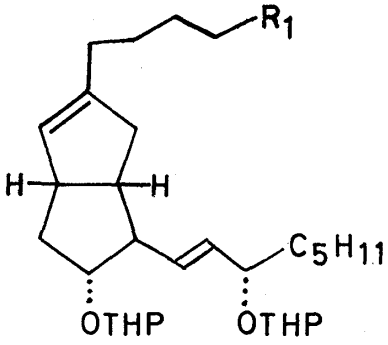
13; $R_1=H$
14; $R_1=COOMe$



15; $R_1=OCHO$, $R_2,R_3=O$
16; $R_1=OCHO$, $R_2=OTHP$, $R_3=H$
17; $R_1=OH$, $R_2=OTHP$, $R_3=H$
18; $R_1=OMs$, $R_2=OTHP$, $R_3=H$



19; $R_1=COOMe$
20; $R_1=CH_2OH$
21; $R_1=CHO$
22; $R_1=$ 
23a; $R_1=$ 
23b; $R_1=$ 



24; $R_1=CH_2OH$
25; $R_1=COOH$

$R = (CH_2)_5OCH_2Ph$

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}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}H-NMR signals of C_2-H, (8, δ: 3.87 (t, J=6.5Hz); 9, 3.90 (d, J=3Hz)). 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) MsCl-Et_3N 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 (CrO_3-H_2SO_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-$\Delta^{6(9\alpha)}$-PGI_1 stage.
11) No isomer was detected by ^{13}C-NMR and HPLC analysis. 3: *Anal.* Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.88; H, 9.73. IR ($CHCl_3$) cm^{-1}: 3360, 1710, 1085, 970. ^{1}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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