[Chem. Pharm. Bull. 31(12)4448—4455(1983)]

# Synthesis of *dl*-9(*O*)-Methano-$\Delta^6$-prostaglandin $I_1$

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(Received May 11, 1983)

Biologically interesting 9(*O*)-methano-$\Delta^6$-prostaglandin $I_1$ (9(*O*)-methano-$\Delta^6$-$PGI_1$), a chemically stable analog of prostacyclin ($PGI_2$), was efficiently synthesized from 1,3-cyclooctadiene with high stereo- and regiochemical control. In all three biological test systems examined, 9(*O*)-methano-$\Delta^6$- $PGI_1$ was found to be considerably less active than prostaglandin $E_1$ ($PGE_1$).

**Keywords**——prostacyclin; 9(*O*)-methanoprostacyclin; $\Delta^6$-prostaglandin $I_1$; prostaglandin $E_1$; 1,3-cyclooctadiene; mixed organocuprate; decarboxylative elimination; regiospecific hydrogenation; inhibition of platelet aggregation

Prostacyclin ($PGI_2$, **1**), a recently discovered metabolite of arachidonic acid, has been shown to be a potent inhibitor of human platelet aggregation and a relaxer of certain vascular tissues. These biological properties coupled with its short half-life have led to the synthesis of a large number of analogs in the search for stable and therapeutically useful mimics as possible new antithrombotic drugs.[4] Among them, it has been shown that 9(*O*)-methanoprostacyclin (**2**) is the most attractive analog. In fact, closely related compounds (**3** and **4**) are now being studied in Phase I clinical trials.[5] Based on these results together with the fact that chemically unstable $\Delta^6$-prostaglandin $I_1$ ($\Delta^6$-$PGI_1$) (**5**) is highly active in inhibiting platelet aggregation,[6]

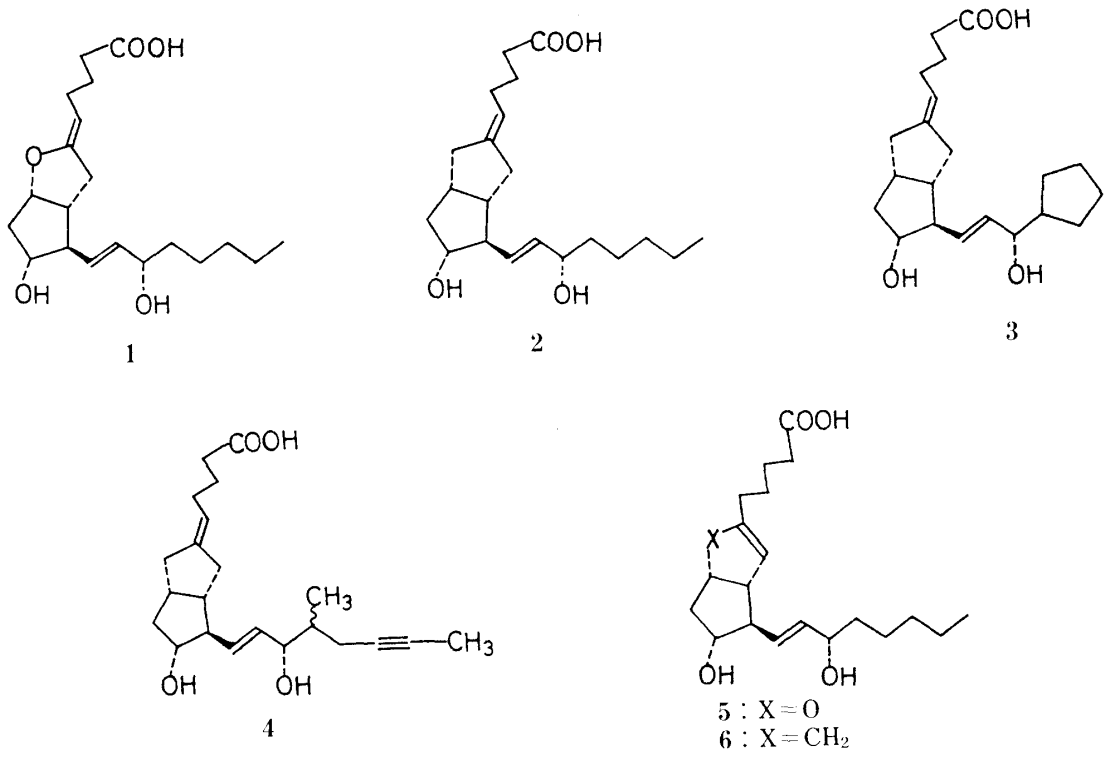



Fig. 1

we have undertaken the synthesis of 9(*O*)-methano-$\Delta^6$-$PGI_1$ (**6**) in order to evaluate its biological activities with the aim of developing useful drugs.[7] Herein we wish to present a detailed account of the synthesis of **6** including preliminary details of its biological activities.

For the highly stereo- and regiocontrolled synthesis of the target molecule (**6**), the ketone (**9**) was selected as the key synthetic intermediate. The facile synthesis of the ketone (**9**) was performed in 73% yield by the conjugate addition of the mixed organocuprate (**8**) to the enone (**7**) which was efficiently prepared starting with 1,3-cyclooctadiene.[8] The stereochemistry of **9**, which had been anticipated by considering that the conjugate addition of the mixed organocuprate (**8**) should occur from the convex face of the enone (**7**) owing to the steric environment of the bicyclo[3.3.0]octenone system, was unequivocally determined by the following fact. The bis-*tert*-butyldimethylsilyl derivative (**9**) was deprotected by treatment with a fluoride anion in tetrahydrofuran (THF) to afford the diol (**10**), which was identical with an authentic sample obtained with unambiguous stereochemistry (infrared (IR) spectrum, proton nuclear magnetic resonance ($^1$H-NMR), mass spectrum (MS), thin-layer chromatography (TLC)).[8c,9]

In order to introduce the double bond at C-6 (PG numbering) in a regiocontrolled manner, transformation of 9 to the target molecule (**6**), which involved decarboxylative elimination of salts of $\beta$-mesyloxy-acids as the key step, was first attempted. Toward this end, the ketone (**9**) was converted to the keto-ester (**11**) in 85% yield. The regiochemistry of this methoxycarbonylation was confirmed by the fact that the keto-ester (**11**) was successfully alkylated to afford **12** in excellent yield (*ca.* 80% yield), although the direct alkylation of **9** provided none of the desired products (**26** and **29**) under various reaction conditions. The ketone (**12**) was reduced with sodium borohydride to give a mixture of the diastereomeric alcohols (**13**) in *ca.* 90% yield, which was subsequently converted to the mesylate (**14**). The stereochemistry of the mesylate (**14**), a mixture of the stereoisomers, was not expected to be a serious problem, since it is already recognized that decarboxylative elimination of salts of $\beta$-halo-acids proceeds *via* a nonstereospecific mechanism involving the initial ionization of the $\beta$-carbon ($E_1$ elimination) in highly polar solvents.[10] The mesylate (**14**) was heated with sodium hydroxide in methanol–water (2 : 1) at 95 °C for 1 h. Under these conditions, it was probable that the ester moieties of **14** would be initially hydrolyzed, followed by decarboxylative elimination of the resulting sodium salt to afford the desired product (**15**). In fact, the compound (**15**) was obtained, though in low yield (<10%). Although many experiments were carried out, our attempts to improve the yield turned out to be unsuccessful. The compound (**15**) was then treated with $CH_3COOH$–$H_2O$–THF (3 : 1 : 1) to hydrolyze the silyl protective groups to give 9(*O*)-methanol-$\Delta^6$-$PGI_1$ as a mixture of the diastereoisomers at C-15 (PG numbering).

Although the analog (**6**) was successfully synthesized with unequivocal regiochemical control, the above-mentioned synthetic route did not provide a sufficient amount of **6** for studying its biological activity in detail. These results prompted us to develop another efficient synthesis of **6**.

In the second route, we selected the enone (**17**) as the synthetic intermediate, which was found to be obtained from **9** in 70% yield *via* Aldol condensation followed by dehydration. The enone (**17**) was subsequently converted to the alcohol (**18**), probably a mixture of the *exo*-alcohol and the *endo*-alcohol, by treatment with sodium borohydride in methanol at −25 °C. It was anticipated that the allylic carbanion intermediate (**21**) or the allylic radical intermediate (**22**) would produce **16** in a highly regiocontrolled manner owing to the difference of thermodynamic stability between **16** and **23**. In order to generate the active species (**21** or **22**) from either **19** or **24**, transformation of **18** into the bromide (**19**) was first attempted by treatment with carbon tetrabromide and triphenylphosphine in methylene chloride, resulting in the formation of a complex mixture. Next, preparation of the sulfoxide (**24**) from **17** *via* the

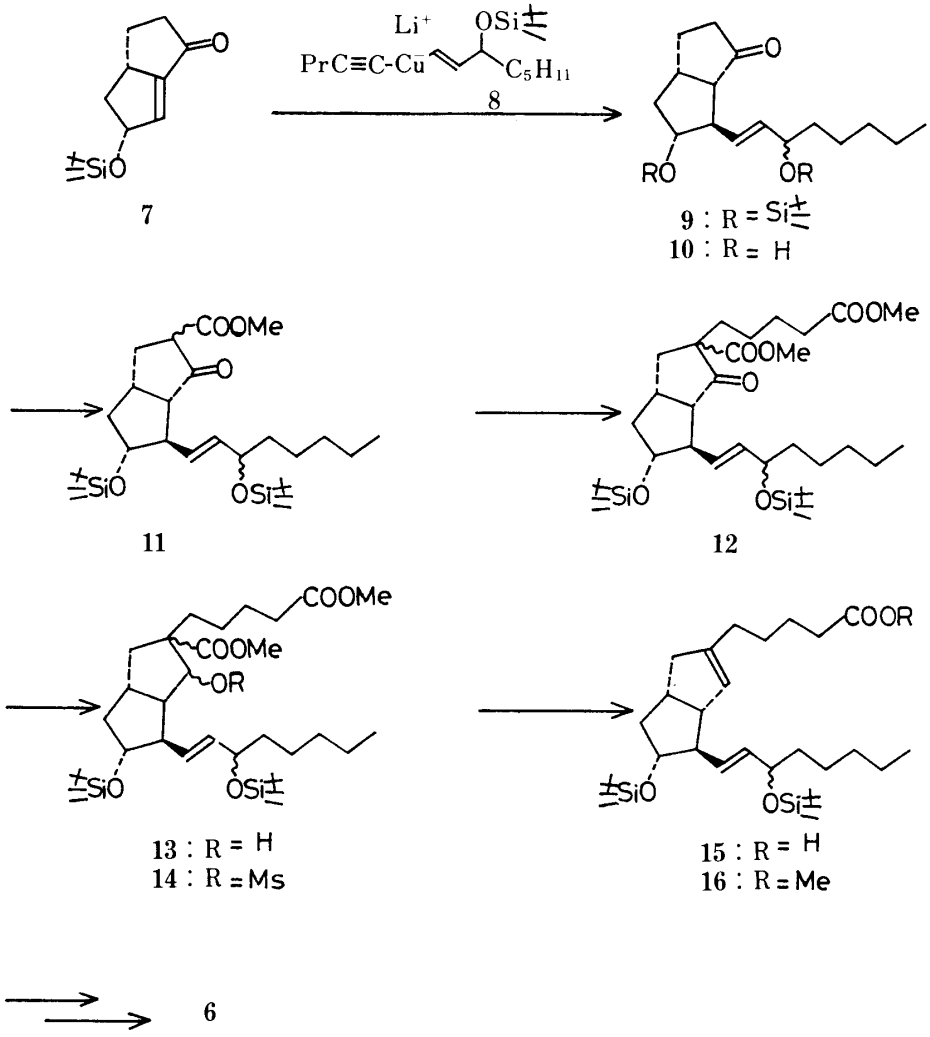
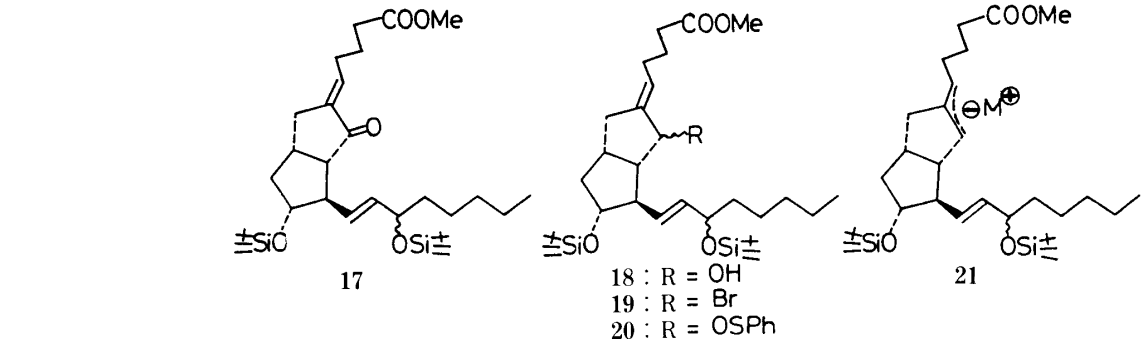



Fig. 2



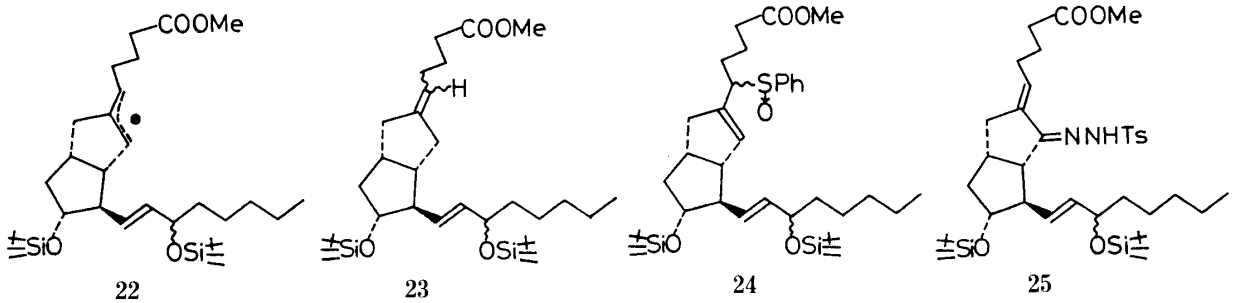




Fig. 3

sulfenate (**20**) was tested. However, in this case too, a complex mixture was formed. Thus, we turned our attention to direct preparation of **16** from **17**, which involved the reduction of the tosylhydrazone (**25**) with catecholborane.[11] Even under these conditions, none of the desired product was obtained.

Finally, regio- and stereocontrolled conversion of **17** to the ketone (**26**) was attempted. The enone (**17**) was subjected to hydrogenation by treatment with 10% Pd on C in methanol at −25 °C under a hydrogen atmosphere, giving the desired ketone (**26**) in 93% yield with regio- and stereochemical control. The stereochemistry of **26**, which had been anticipated on the basis of the steric environment of the *cis*-bicyclo[3.3.0]octane skeleton, was confirmed by the following fact. Epimerization of **26** by treatment with 0.1 eq of sodium methoxide in methanol at room temperature for 15 h provided the thermodynamically more stable ketone (**29**) as a major product, the ratio being 5 (**29**) : 3 (**26**). The stereochemistry of **26** and **29** will be discussed in detail in the following paper.[12] Reduction of **26** with L-Selectride in THF at −78 °C furnished the *endo*-alcohol (**27**)[12] stereospecifically in 61% yield, and this was converted to the mesylate (**28**). The mesylate (**28**) was then heated at 80 °C in toluene containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the desired product (**16**) regiospecifically in 90% yield, suggesting that none of the regioisomer (**31**) was produced, probably due to its high strain energies. The compound (**16**) was subsequently converted to 9(*O*)-methano-$\Delta^6$-$PGI_1$ (**6**) and its stereoisomer (**30**) at C-15 (PG numbering) in 80% yield. In this way we have succeeded in the efficient synthesis of 9(*O*)-methano-$\Delta^6$-$PGI_1$ (**6**) and **30** with

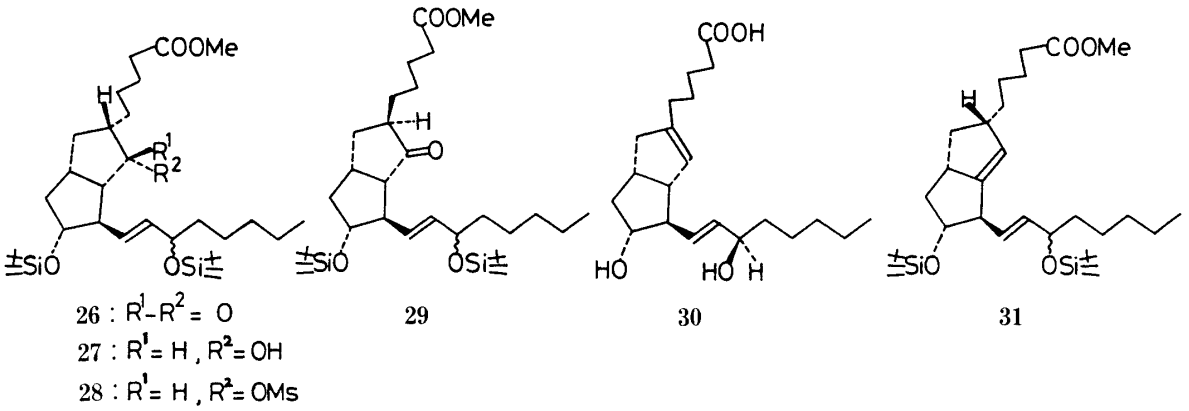



Fig. 4

TABLE I. Pharmacological Activities of **6** and **30**

| Compounds | Platelet | | Isolated ileum | | | Blood pressure | | |
|---|---|---|---|---|---|---|---|---|
| | $IC_{50}$[a] (μM) | P.R.[d] | Conc. (μM) | Contraction[b] (%) | P.R. | Dose (μg/kg *i.v.*) | Reduction[c] (%) | P.R. |
| $PGE_1$ | 0.04 | 1.0 | 0.015 | 28.4 | 1.0 | 3 | 26.6 | 1.0 |
| | | | 0.050 | 70.9 | | 10 | 53.5 | |
| **6** | 0.99 | 0.04 | 1.5 | 32.9 | 0.04 | 30 | 17.5 | 0.05 |
| | | | 5.0 | 61.0 | | 100 | 34.3 | |
| **30** | 9.60 | 0.004 | 5.0 | 7.4 | — | 100 | 0 | — |
| | | | 10.0 | 16.8 | | | | |

*a*) Concentration giving 50% inhibition of adenosine diphosphate-induced human platelet aggregation ($N=3$).
*b*) Relative values (%) with respect to the contraction induced by 0.1 μM acetylcholine in isolated guinea pigs ($N=2$).
*c*) Percent changes of blood pressure in anesthetized rats ($N=4$).
*d*) Potency ratio.

high stereo- and regiochemical control.

Pharmacological activities of **6** and **30** are summarized in Table I. In all three biological test systems examined, 9(*O*)-methano-$\Delta^6$-$PGI_1$ (**6**) was found to be considerably less active than prostaglandin $E_1$ ($PGE_1$).

## Experimental

Melting points are uncorrected. IR spectra were measured on a Hitachi 215 grating infrared spectrophotometer. $^1$H-NMR spectra were recorded with a Varian EM360A nuclear magnetic resonance (NMR) spectrometer or a Varian XL-100-12 NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained with a JEOL JMS-D300 mass spectrometer and high-resolution mass spectra with a JEOL JMS-01SG-2 mass spectrometer.

In general, reactions were carried out under an argon atmosphere unless otherwise mentioned.

**(1*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-Butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)bicyclo[3.3.0]octan-2-one (9)**——*tert*-Butyllithium (1.10 ml, 2.37 mM, 2.15 M solution in pentane) was added to (*E*)-3-*tert*-butyldimethylsilyloxy-1-iodo-1-octene (479 mg, 1.30 mM) in ether (4.5 ml) at −78 °C, and the solution was stirred under the same conditions for 3 h. The resulting alkenyllithium solution was injected with a syringe into a yellow solution of *n*-propylethynylcopper[13] (180 mg, 1.38 mM) in hexamethylphosphoramide (HMP) (0.5 ml) and ether (0.8 ml) at room temperature, and the mixture was stirred at the same temperature for 10 min and again cooled to −78 °C. (5*S**, 7*R**)-7-*tert*-Butyldimethylsilyloxybicyclo[3.3.0]oct-8-en-2-one[8] (247 mg, 0.98 mM) in ether (1.5 ml) was then added to this mixed organocuprate solution. The mixture was stirred for 1 h under the same conditions, then the reaction was quenched by the addition of saturated $NH_4Cl$ aq., followed by extraction with ether. The combined ether extracts were successively washed with 2% $H_2SO_4$ aq., saturated $NaHCO_3$ and brine, then dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification of the residue by silica gel column chromatography afforded the ketone (**9**) as a nearly colorless oil (352 mg, 73% yield). IR $\nu_{max}^{film}$ cm$^{-1}$: 1720, 1460, 1360, 1255. $^1$H-NMR ($CDCl_3$) $\delta$: 0.00 [12H, s, 2×Si(C$\underline{H}_3$)$_2$], 0.84, 0.87 [21H, two s, 2×C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.13—2.57 (15H, m), 2.84 (2H, m), 3.96 (2H, m, 2×C$\underline{H}$–O), 5.46 (2H, m, olefinic protons). MS *m/e*: 494 ($M^+$), 479 ($M^+ - CH_3$), 437 ($M^+$-*tert*-Bu), 423. *m/e* 437.2907 (Calcd for $C_{24}H_{45}O_3Si_2$, 437.2907, P−*tert*-Bu). The ketone (**9**) (49 mg, 0.1 mM) was treated with AcOH–$H_2O$–THF (3 : 1 : 1) (1 ml) at 45 °C for 6 h. After removal of the volatile solvents *in vacuo*, the residual oil was dissolved in ethyl acetate. The organic layer was successively washed with saturated $NaHCO_3$ aq. and brine, then dried ($MgSO_4$). Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography to give the diol (**10**) as a nearly colorless oil (25 mg, 95% yield). IR $\nu_{max}^{film}$ cm$^{-1}$: 3400, 1720, 1460, 1400. $^1$H-NMR ($CDCl_3$) $\delta$: 0.89 (3H, t, $J$=6 Hz, C$\underline{H}_3$), 1.06—3.04 (19H, m), 4.02 (2H, m), 5.64 (2H, m). MS *m/e*: 248 ($M^+ - H_2O$), 204, 192, 177, 149. *m/e* 248.1770 (Calcd for $C_{16}H_{24}O_2$, 248.1776, P–$H_2O$). The diol thus obtained was identical with an authentic sample.[8c,9]

**Methyl (1*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-Butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-oxobicyclo[3.3.0]octane-3-carboxylate (11)**——The ketone (**9**) (150 mg, 0.30 mM) in dimethyl carbonate (0.4 ml) was added to a stirred suspension of sodium hydride (29 mg, 1.21 mM) in dimethyl carbonate (0.5 ml) at room temperature. After the subsequent addition of ethanol (3 $\mu$l), the suspension was stirred for 5 h under the same conditions. The reaction was quenched by the addition of saturated $NH_4Cl$ aq., followed by extraction with ether. The combined ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by silica gel column chromatography to give the $\beta$-keto ester (**11**) as a pale yellow oil (130 mg, 78%). IR $\nu_{max}^{film}$ cm$^{-1}$: 1755, 1735, 1730, 1660, 1620, 1460, 1440, 1360, 1250, 1195, 1005, 965, 840. $^1$H-NMR ($CDCl_3$) $\delta$: 0.03 [12H, s, 2×Si(C$\underline{H}_3$)$_2$], 0.86, 0.90 [21H, two s, 2×C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.00—3.50 (16H, m), 3.70 (3H, s, COOC$\underline{H}_3$), 3.97 (2H, m, 2×C$\underline{H}$–O), 5.43 (2H, m, olefinic protons). MS *m/e*: 536 ($M^+ - CH_3 - 1$), 494 ($M^+$ − *tert*-Bu − 1), 462 ($M^+$ − *tert*-Bu − $OCH_3$ − 2). *m/e*: 494.2872 (Calcd for $C_{26}H_{46}O_5Si_2$, 494.2884, P−*tert*-Bu–H).

**Methyl (1*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-Butyldimethylsilyloxy-3-methoxycarbonyl-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-oxobicyclo[3.3.0]octane-3-pentanoate (12)**——A solution of potassium *tert*-butoxide (20 mg, 0.18 mM) in dimethyl sulfoxide (DMSO) (0.4 ml) was added to a stirred mixture of the $\beta$-keto ester (87 mg, 0.16 mM) and methyl 5-iodopentanoate (46 mg, 0.19 mM)[14] in DMSO (1 ml) at 55 °C, and the resulting solution was stirred under the same conditions for 6 h. The reaction was quenched by the addition of saturated $NH_4Cl$ aq., followed by extraction with ether. The ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by silica gel column chromatography to afford **12** as a mixture of the diastereoisomers (pale yellow oil, 77 mg, 74% yield). IR $\nu_{max}^{film}$ cm$^{-1}$: 1735, 1255, 1110, 835, 775, 735. $^1$H-NMR ($CDCl_3$) $\delta$: 0.00 [12H, s, 2×Si(C$\underline{H}_3$)$_2$], 0.86 [21H, s, 2×C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.00—3.07 (23H, m), 3.63 (3H, s, COOC$\underline{H}_3$), 3.77 (3H, s, COOC$\underline{H}_3$), 4.06 (2H, m, 2×C$\underline{H}$–O), 5.45 (2H, m, olefinic protons). MS *m/e*: 651 ($M^+ - CH_3$), 609 ($M^+$ − *tert*-Bu). *m/e* 609.3632 (Calcd for $C_{32}H_{57}O_7Si_2$, 609.3642, P−*tert*-Bu).

**Methyl (1*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-Butyldimethylsilyloxy-3-methoxycarbonyl-8-(3-*tert*-butyldimethylsilyloxy-*E*-**

**octenyl)-2-hydroxybicyclo[3.3.0]octane-3-pentanoate (13)**——A mixture of sodium borohydride (21 mg, 0.56 mM) and the ketone (**12**) (184 mg, 0.28 mM) in methanol (1 ml) was stirred at −25 °C for 0.5 h. The reaction was quenched by the addition of 10% HCl aq., and then quickly neutralized by the addition of saturated $NaHCO_3$ aq. Concentration of the solution *in vacuo* afforded a residue, to which water was added. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, then dried ($MgSO_4$). Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography to afford **13** as a mixture of the stereoisomers (nearly colorless oil, 166 mg, 90% yield). IR $\nu_{max}^{film}$ cm$^{-1}$: 3400, 1730, 1460, 1250, 835, 775. $^1$H-NMR ($CDCl_3$) $\delta$: 0.00 [12H, s, 2 × Si(C$\underline{H}_3$)$_2$], 0.90 [2H, s, 2 × C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.00—3.00 (24H, m), 3.67 (6H, s, 2 × COOC$\underline{H}_3$), 4.00 (3H, m, 3 × C$\underline{H}$–O), 5.43 (2H, m, olefinic protons). MS *m/e*: 611 (M$^+$ − *tert*-Bu), 593 (M$^+$ − *tert*-Bu − $H_2O$), 461, 327, 281, 250. *m/e* 611.3791 (Calcd for $C_{32}H_{59}O_7Si_2$, 611.3799, P − *tert*-Bu).

**Methyl (1*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-Butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)bicyclo-[3.3.0]oct-2-ene-3-pentanoate (16)**——Methanesulfonyl chloride (193 mg, 1.68 mM) was added to a stirred solution of the alcohol (**13**) (56 mg, 0.084 mM) and triethylamine (170 mg, 1.68 mM) in methylene chloride (1.5 ml) at 0 °C, and the mixture was stirred under the same conditions for 10 min, followed by dilution with ether. The organic layer was successively washed with saturated $NaHCO_3$ aq. and brine, and dried over $MgSO_4$. Removal of the solvent afforded the crude mesylate as a pale yellow oil, which was directly used for the next reaction without purification. Sodium hydroxide (161 mg, 4.0 mM) was added to a stirred solution of the crude mesylate in methanol–water (2 : 1) (9.9 ml) at room temperature, and the resulting mixture was heated at 95 °C for 1 h. Concentration of the solution *in vacuo* afforded a residue, to which water was added. The aqueous layer was carefully acidified with 10% HCl aq. to pH 4, followed by extraction with ether. The ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography to afford the carboxylic acid (**15**) as a pale yellow oil (5 mg, 9% yield). In order to determine the structure of **15** more securely, one part of **15** thus obtained was treated with ethereal diazomethane to give the methyl ester (**16**) in quantitative yield. IR $\nu_{max}^{film}$ cm$^{-1}$: 1740, 1460, 1250. $^1$H-NMR ($CDCl_3$) $\delta$: 0.02 [12H, s, 2 × Si(C$\underline{H}_3$)$_2$], 0.86, 0.89 [21H, two s, 2 × C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.04—2.84 (23H, m), 3.64 (1H, m, C$\underline{H}$–O), 3.68 (3H, s, COOMe), 4.07 (1H, m, C$\underline{H}$–O), 5.30 (1H, br s, one olefinic proton), 5.46 (2H, m, two olefinic protons). MS *m/e*: 592 (M$^+$), 535 (M$^+$ − *tert*-Bu). *m/e* 592.4323 (Calcd for $C_{34}H_{64}O_2Si_2$, 592.4343, P).

**9(*O*)-Methano-$\Delta^6$-PGI$_1$(6) and Its Stereoisomer (30) (the First Route)**——A solution of the carboxylic acid (**15**) (5 mg, 0.009 mM) in AcOH–$H_2O$–THF (3 : 1 : 1) (0.1 ml) was heated at 45 °C with stirring for 6 h. After removal of the volatile solvents *in vacuo*, the residual oil was purified by silica gel preparative thin-layer chromatography (TLC) (AcOEt). The less polar product, which was tentatively assigned as the 15$\beta$-isomer (**30**), was obtained as a colorless solid (1 mg). mp 48—50 °C. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3400, 1705, 1460. $^1$H-NMR ($CDCl_3$) $\delta$: 0.90 (3H, t, $J$=6 Hz, C$\underline{H}_3$), 1.10—3.00 (23H, m), 3.78 (1H, m, C$\underline{H}$–O), 4.10 (1H, m, C$\underline{H}$–O), 4.94 (3H, m, 2 × O$\underline{H}$ and COO$\underline{H}$), 5.36 (1H, br s, one olefinic proton), 5.64 (2H, m, two olefinic protons). MS *m/e*: 332 (M$^+$ − $H_2O$), 314 (M$^+$ − 2$H_2O$), 288 (M$^+$ − 2$H_2O$ − $CO_2$). *m/e* 332.2341 (Calcd for $C_{21}H_{32}O_3$, 332.2351, P − $H_2O$). The more polar product, which was tentatively assigned as the 15$\alpha$-isomer (**6**), was obtained as a colorless solid (1 mg). mp 36—39 °C. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3400, 1705, 1460. $^1$H-NMR ($CDCl_3$) $\delta$: 0.90 (3H, t, $J$=6 Hz, C$\underline{H}_3$), 1.10—3.00 (23H, m), 3.78 (1H, m, C$\underline{H}$–O), 4.10 (1H, m, C$\underline{H}$–O), 5.04 (3H, m, 2 × O$\underline{H}$ and COO$\underline{H}$), 5.35 (1H, br s, one olefinic proton), 5.60 (2H, m, two olefinic protons). MS *m/e*: 332 (M$^+$ − $H_2O$), 314 (M$^+$ − 2$H_2O$), 288 (M$^+$ − $H_2O$ − $CO_2$). *m/e* 332.2341 (Calcd for $C_{21}H_{32}O_3$, 332.2351, P–$H_2O$).

**Methyl (1*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-Butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-oxobicyclo[3.3.0]octane-*E*-$\Delta^{3,\delta}$-pentanoate (17)**——A solution of the ketone (**9**) (377 mg, 0.76 mM) in THF (1.5 ml) was gradually added to lithum diisopropylamide (LDA) (1.06 mM) in THF (4 ml) at −78 °C, and the mixture was stirred under the same conditions for 0.5 h. Then a solution of methyl 5-oxopentanoate (139 mg, 1.06 mM)[15] in THF (1.5 ml) was injected with a syringe at −78 °C, and the whole mixture was stirred at the same temperature for 10 min. The reaction was quenched by the addition of saturated $NH_4Cl$ aq., and extracted with ether. The ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which without purification was dissolved in benzene (3 ml). Triethylamine (152 mg, 1.5 mM) and methanesulfonyl chloride (229 mg, 2.0 mM) was successively added to this solution, and the resulting mixture was stirred at room temperature for 0.5 h. DBU (304 mg, 2.0 mM) was finally added to this mesylate solution. After being stirred at room temperature for 0.5 h, the reaction mixture was diluted with ether. The organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography to afford **17** as a nearly colorless oil (325 mg, 70% yield), which contained the *E*-isomer and the *Z*-isomer in a ratio of *ca.* 7 : 1. IR $\nu_{max}^{film}$ cm$^{-1}$: 1740, 1720, 1645, 1460, 1360, 1255. $^1$H-NMR ($CDCl_3$) $\delta$: 0.04 [12H, m, 2 × Si(C$\underline{H}_3$)$_2$], 0.81, 0.86 [21H, two s, 2 × C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.10—3.10 (19H, m), 2.36 (2H, t, $J$=7 Hz, C$\underline{H}_2$COOMe), 3.68 (3H, s, COOC$\underline{H}_3$), 4.02 (2H, m, 2 × C$\underline{H}$–O), 5.50 (2H, m, two olefinic protons), 5.88 (br t, $J$=7 Hz, proton of the *Z*-isomer), 6.46 (br t, $J$=7 Hz, proton of the *E*-isomer). MS *m/e*: 606 (M$^+$), 591 (M$^+$ − $CH_3$), 549 (M$^+$ − *tert*-Bu), 417, 403. *m/e* 549.3447 (Calcd for $C_{30}H_{53}O_5Si_2$, 549.3431, P − *tert*-Bu).

**Methyl (1*S**, 3*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-Butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-oxobicyclo[3.3.0]octane-3-pentanoate (26)**——A suspension of the enone (**17**) (289 mg, 0.48 mM) and 10% Pd on C

(60 mg) in methanol (10 ml) was stirred at −30 °C under a hydrogen atmosphere for 7 h. Filtration of the catalyst, followed by removal of the solvent *in vacuo*, afforded an oily residue, which was purified by silica gel column chromatography to afford the stereochemically pure ketone (**26**) as a nearly colorless oil (269 mg, 93% yield). IR $\nu_{max}^{film}$ cm$^{-1}$: 1740, 1460, 1360, 1255, 1080, 835, 775. $^1$H-NMR ($CDCl_3$) $\delta$: 0.01 [12H, s, 2×Si(C$\underline{H}_3$)$_2$], 0.86, 0.88 [21H, two s, 2×C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.12—3.00 (22H, m), 2.34 (2H, t, $J$=7 Hz, C$\underline{H}_2$COOMe), 3.68 (3H, s, COOC$\underline{H}_3$), 4.00 (2H, m, 2×C$\underline{H}$–O), 5.46 (2H, m, olefinic protons). MS *m/e*: 608 ($M^+$) 593 ($M^+-CH_3$), 577 ($M^+-OCH_3$), 551 ($M^+$ − *tert*-Bu), 453. *m/e* 551.3599 (Calcd for $C_{30}H_{55}O_5Si_2$, 551.3589, P − *tert*-Bu).

**Methyl (1*S**, 2*S*, 3*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-Butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-hydroxybicyclo[3.3.0]octane-3-pentanoate (27)**——L-Selectride (0.62 mM, 0.62 ml, 1 M solution in THF ) was added to a stirred solution of the ketone (**26**) (252 mg, 0.41 mM) in THF (5 ml) at −78 °C. After being stirred for 1 h at the same temperature, the reaction mixture was diluted with ether, followed by addition of 10% sodium hydroxide aq. (2 ml) then 30% hydrogen peroxide aq. (1.5 ml). The mixture was stirred for 6 h at 0 °C, and then carefully acidified with 10% HCl aq. to pH 4. The organic layer was separated from the aqueous layer, which was further extracted with ether. The combined organic extracts were successively washed with saturated $Na_2S_2O_3$ aq. and brine, then dried ($MgSO_4$). Removal of the solvent afforded an oily residue, which was then treated with ethereal diazomethane. The crude yellow oil was purified by silica gel column chromatography to afford the stereochemically pure alcohol (**27**) as a nearly colorless oil (61% yield). From the crude yellow oil, a mixture (80 mg) of the isomeric ketone (**29**) and the starting ketone (**26**) was also obtained. IR $\nu_{max}^{film}$ cm$^{-1}$: 3450, 1740, 1460, 1250. $^1$H-NMR ($CDCl_3$) $\delta$: 0.02 [6H, s, Si(C$\underline{H}_3$)$_2$], 0.08 [6H, s, Si(C$\underline{H}_3$)$_2$], 0.90 [21H, two s, 2×C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.00—3.00 (23H, m), 2.32 (2H, t, $J$=7 Hz, C$\underline{H}_2$COOMe), 3.65 (3H, s, COOC$\underline{H}_3$), 4.00 (3H, m, 3×C$\underline{H}$–O), 5.42 (2H, m, olefinic protons). MS *m/e*: 610 ($M^+$), 592 ($M^+-H_2O$), 553 ($M^+$ − *tert*-Bu), 535, 520, 478, 463, 422. *m/e* 610.4484 (Calcd for $C_{34}H_{64}O_5Si_2$, 610.4448, P).

**Methyl (1*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-Butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)bicyclo-[3.3.0]oct-2-ene-3-pentanoate (16)**——Methanesulfonyl chloride (132 mg, 1.15 mM) was added to a stirred solution of the alcohol (**27**) (234 mg, 0.38 mM) in pyridine (0.47 ml) at room temperature, and the mixture was stirred under the same conditions for 2 h. After dilution with ether, the organic layer was washed with saturated $CuSO_4$ aq. and brine, then dried ($MgSO_4$). Removal of the solvent afforded an oily residue, which was roughly purified by silica gel column chromatography to give the nearly pure mesylate (**28**) in quantitative yield. The mesylate thus obtained was dissolved in toluene (2.5 ml) containing DBU (0.3 ml), and the mixture was heated at 80 °C for 2 h. After dilution with ether, the organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography to give **15** as a nearly colorless oil (204 mg, 90% yield), whose spectra were superimposable on those of an authentic sample synthesized by the first route.

**9(*O*)-Methanol-$\Delta^6$-PGI$_1$ (6) and Its Stereoisomer (30) (the Second Route)**——A mixture of **15** (204 mg, 0.35 mM) and tetra-*n*-butylammonium fluoride (271 mg, 1.04 mM) in THF (2 ml) was stirred at room temperature for 8 h, followed by the addition of saturated $NH_4Cl$ aq. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, then dried ($MgSO_4$). Removal of the solvent afforded an oily residue, which was roughly purified by silica gel column chromatography to afford the desilylated product as a pale yellow oil (122 mg). A mixture of the desilylated product and 1 ml of 10% NaOH aq. in methanol (2 ml) was stirred at room temperature for 0.5 h, followed by removal of the methanol *in vacuo*. The residual aqueous layer was diluted with brine, and acidified with 10% HCl aq., then extracted with ethyl acetate. The combined organic extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography to give the isomeric acids (**6** and **30**) as a nearly colorless viscous oil (80% yield). From this viscous oil, the less polar **30** and the more polar **6** were separated by preparative silica gel TLC (ethyl acetate). The spectral data for **6** and **30** were identical with those of corresponding authentic samples.

**Acknowledgement** We are grateful to Dr. S. Mizogami and his coworkers, Research Laboratory, Mitsubishi Yuka Pharmaceutical Co., Ltd., for the tests of biological activity. We also thank Mrs. K. Uchida for the measurements of mass spectra. Financial support of this research by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, is gratefully acknowledged.

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