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Synthesis of *dl*-9(*O*)-Methanoprostaglandin-I_1

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The synthesis of both 9(*O*)-methano-6α-prostaglandin-I_1 (9(*O*)-methano-6α-PGI_1) and 9(*O*)-methano-6β-prostaglandin-I_1 (9(*O*)-methano-6β-PGI_1) has been accomplished *via* the same synthetic intermediate obtainable from 1,3-cyclooctadiene. These analogs showed weak inhibitory activity in rabbit platelet aggregation induced by adenosine diphosphate. Furthermore, 9(*O*)-methano-6β-PGI_1 did not show any cytoprotective action on rabbit, stomach epithelial cells at the concentration of 10^{-6} M.

Keywords——antiulcer effect of prostaglandin-I_2; 6β-prostaglandin-I_1; conformational analysis of *cis*-bicyclo[3.3.0]octane derivative; deoxygenation of hydroxy group; inhibitory activity in platelet aggregation

In addition to antiaggregatory and vasodilating properties, prostacyclin (**1**) (PGI_2) inhibits gastric acid secretion and further prevents the lining of the stomach from becoming inflamed. Accordingly, attempts have been made to develop stable and therapeutically useful mimics with potent antiulcer effects. The chemically stable analogs **2**[3] and **3**[4] appear to be the most promising in this respect, since they retain potent antiulcer effects with weak antiaggregatory and vasodilating activities. During the course of our synthetic studies on carbon analogs of PGI_2 (**1**)[5] we became particularly interested in the stereocontrolled synthesis of either the carbon analog of 6α-prostaglandin-I_1 (**5**) (6α-PGI_1) or the carbon analog of 6β-prostaglandin-I_1 (**4**) (6β-PGI_1) in order to evaluate their antiulcer effects as well as their antiaggregatory and vasodilating properties. Herein we wish to report the synthesis of both **4** and **5** and the preliminary determination of their biological activities.

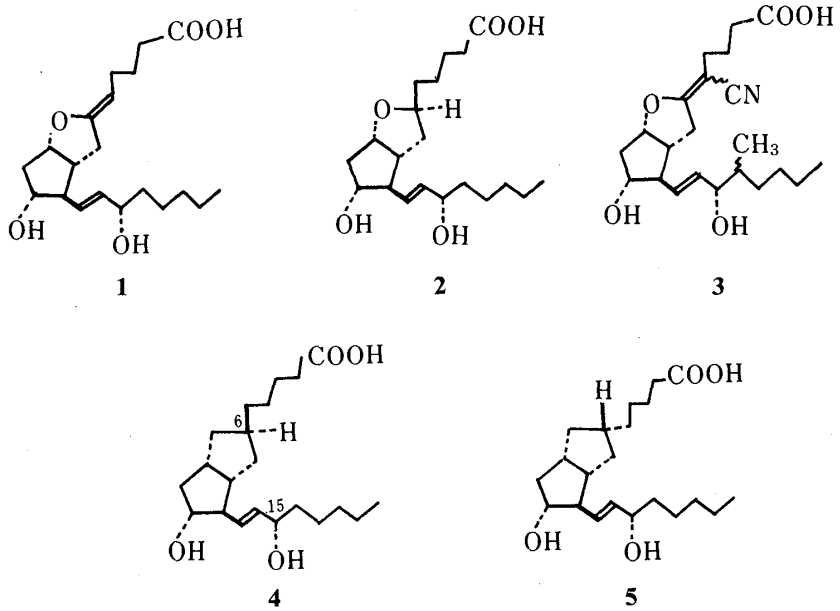
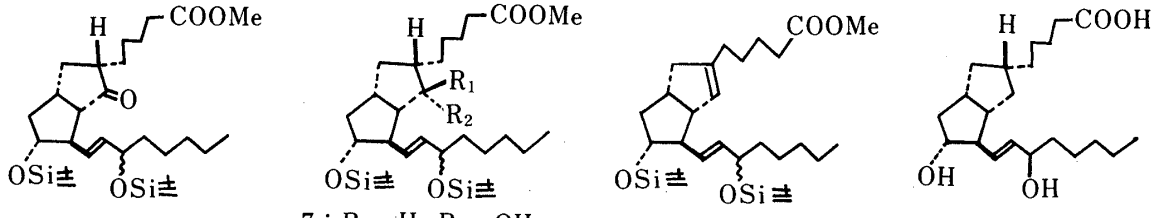


Fig. 1

For the synthesis of either **4** or **5**, the ketone (**6**), which is efficiently obtainable from 1,3-cyclooctadiene,[5] appeared to be a reasonable synthetic intermediate.

Synthesis of the Carbon Analog of 6α-PGI$_1$ (9(*O*)-Methano-6α-PGI$_1$ (5))

The ketone (**6**) was reduced with sodium borohydride, giving the *endo*-alcohol (**7**) and the *exo*-alcohol (**9**) in a ratio of *ca.* 3:1. On the other hand, reduction of **6** with L-Selectride proceeded stereoselectively to provide only the *endo*-alcohol (**7**).[5] The stereochemistry of both **7** and **9** was spectroscopically determined by using the mesylates (**8** and **10**). The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the mesylate (**8**) showed a one-proton broad singlet (δ 5.04, Ha), while the spectrum of **10** displayed a one-proton double doublet (δ 4.84, Hb, J=6, 9 Hz). Since the mesylates (**8** and **10**) should exist mainly in the W-shaped conformation,[6] the coupling constants observed in the ^{1}H-NMR spectra strongly supported the illustrated structures of both **8** and **10**. The alcohols (**7** and **9**) could be converted back to the parent ketone (**6**) without epimerization at C-6 (PG numbering) by treatment with pyridinium dichromate (PDC) in dimethylformamide (DMF).[7] In order to deoxygenate the secondary hydroxy group of **7**, conversion of **7** to the bromide (**11**) was first attempted, but resulted in the recovery of **7** under various reaction conditions. On the other hand, treatment of the *exo*-alcohol (**9**) with carbon tetrabromide and triphenylphosphine in methylene chloride cleanly afforded the elimination product (**15**) *via* the unstable bromide (**12**).[5] Reaction of either **7** or **9** with 1,1′-thiocarbonyldiimidazole also afforded none of the desired product, giving recovery of the starting alcohol. However, according to the Robins method,[8] the sterically less crowded **9** could be converted to the phenoxythiocarbonyl derivative (**13**) in 58% yield. In the case of the sterically more crowded **7**, the reaction did not take place at all. Reduction of the phenoxythiocarbonyl derivative (**13**) with tributyltin hydride provided the deoxygenated product (**14**) in 92% yield, and then treatment with tetrabutylammonium fluoride and potassium hydroxide afforded the carbon analog of 6α-PGI$_1$ (**5**) with its stereoisomer (**16**) at C-15 (PG numbering). Based on the thin layer chromatographic behavior, the more polar product was tentatively assigned as the 15α-isomer (**5**) (PG numbering).



7 : R_1=H, R_2=OH
8 : R_1=H_a, R_2=OMs
9 : R_1=OH, R_2=H
10 : R_1=OMs, R_2=H_b
11 : R_1=Br, R_2=H
12 : R_1=H, R_2=Br
13 : R_1=OCSOPh, R_2=H
14 : R_1=R_2=H

Fig. 2

Synthesis of the Carbon Analog of 6β-PGI$_1$ (9(*O*)-Methano-6β-PGI$_1$ (4))

In order to synthesize the carbon analog of 6β-PGI$_1$ (**4**), base-catalyzed isomerization of the ketone (**6**) to the thermodynamically more stable stereoisomer (**17**) was attempted. Treatment of **6** with sodium methoxide in methanol at room temperature afforded mainly the desired ketone (**17**) in a ratio of 5 (**17**) : 3 (**6**). Because the separation of the stereoisomers (**17**

and **6**) was found to be extremely difficult, we sought a convenient method for the separation of the desired stereoisomer. Thus, exposure of **6** to the epimerization conditions followed by addition of a large excess of sodium borohydride at $-78\,^{\circ}C$ afforded the single alcohol (**18**) in 45% yield together with recovery of the starting ketone (**6**) (46%). The lower reactivity of the ketone (**6**) in reduction with sodium borohydride might be ascribed to the conformation of **6**. The ketone (**6**) should exist mainly in the W-shaped conformation,[6] shielding the carbonyl group from attack by sodium borohydride at $-78\,^{\circ}C$. On the other hand, the isomeric ketone (**17**) should exist mainly in the S-shaped conformation, allowing easy reduction with sodium borohydride even at low temperature. The stereochemistry of the alcohol (**18**) was again determined by using the mesylate (**19**). The ^{1}H-NMR spectrum of **19** displayed a one-proton triplet (δ 4.60, Ha, $J=8$ Hz), which could be reasonably explained by considering the preferred S-shaped conformation of **19**.[9] The *endo*-alcohol (**18**) was successfully converted to the phenoxythiocarbonyl derivative (**20**), followed by reduction with tributyltin hydride to afford the deoxygenated product (**21**) in 65% yield. Transformation of **21** into the carbon analog of 6β-PGI$_1$ (**4**) and its stereoisomer at C-15 (**22**) (PG numbering) was accomplished in the same way as described in the synthesis of **5** and **16**. In this case too, the more polar stereoisomer was tentatively assigned as the 15α-isomer (**4**) (PG numbering) on the basis of the potency of biological activities.

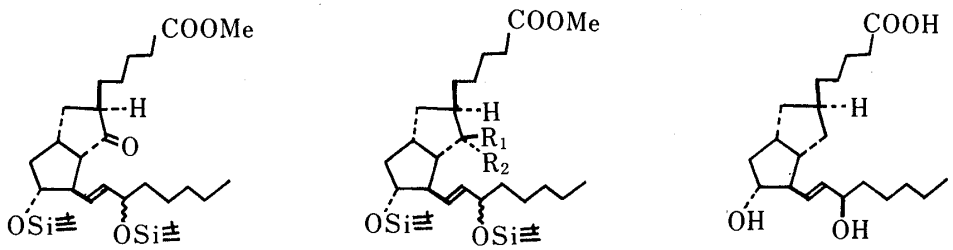


Fig. 3

TABLE I. Inhibitory Activity of PGI$_1$ Analogs in Platelet Aggregation (Rabbit, *in Vitro*)

Compounds	IC $\underline{50}^{a)}$ (μg)
PGE$_1$	1.6×10^{-3}
9(*O*)-Methano-6β-PGI$_1$ (**4**)	1.3×10^{-1}
22	3.0
9(*O*)-Methano-6α-PGI$_1$ (**5**)	2.0
16	1.2

a) Concentration giving 50% inhibition of ADP-induced platelet aggregation.

As was expected, all the analogs synthesized above showed weak inhibitory activity in platelet aggregation induced by adenosine diphosphate (ADP). The results are summarized in Table I. Furthermore, 9(*O*)-methano-6β-PGI$_1$ (**4**) did not show any cytoprotective action in rabbit stomach epithelial cells[10] at the concentration of 10^{-6} M.[11]

Experimental

Infrared (IR) spectra were measured on a Hitachi 215 grating infrared spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian EM360A NMR spectrometer or a Varian XL-100-12 NMR spectrometer in $CDCl_3$

solution with tetramethylsilane as an internal standard. Low-resolution mass spectra (LR-MS) were obtained with a JEOL JMS-D300 mass spectrometer and high-resolution mass spectra (HR-MS) with a JEOL JMS-01SG-2 mass spectrometer.

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

Methyl (1*S, 2*R**, 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 (9)**——Sodium borohydride (7.6 mg, 0.2 mM) was added to a stirred solution of the ketone (**6**) (122.0 mg, 0.2 mM) in methanol (4 ml) at 0 °C. After being stirred for 1 h at the same temperature, 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 (Et_2O–petr. ether, 1 : 10) to give the *endo*-alcohol (**7**) as a nearly colorless oil (85.8 mg, 70%) and the *exo*-alcohol (**9**) as a pale yellow oil (33.1 mg, 27%). The spectral data for **7** were identical with those of an authentic sample.[5] The spectral data for **9** were as follows. IR ν_{max}^{film} cm^{-1}: 3550, 3450, 1740, 1460, 1250, 835, 775. ^{1}H-NMR ($CDCl_3$) δ: 0.03 [12H, s, 2 × $Si(C\underline{H}_3)_2$], 0.08, 0.09 [21H, two s, 2 × $C(C\underline{H}_3)_3$ and $C\underline{H}_3$], 1.00—2.80 (23H, m), 2.32 (3H, t, J=7 Hz, $C\underline{H}_2COOMe$), 3.65 (3H, s, $COOC\underline{H}_3$), 3.77 (1H, d, J=10 Hz, O$\underline{H}$), 3.81—4.10 (3H, m, 3 × C$\underline{H}$–O), 5.42 (2H, m, olefinic protons). LR-MS *m/e*: 610 (M^+), 592 ($M^+ - H_2O$), 553 (M^+ – *tert*-Bu), 535 (M^+ – *tert*-Bu–H_2O), 478, 461, 421, 329. HR-MS *m/e*: 553.3736 (Calcd for $C_{30}H_{57}O_5Si_2$, 553.3744 M – *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-methylsulfonyloxybicyclo[3.3.0]octane-3-pentanoate (8)**——The mesylate (**8**) (a colorless oil) was prepared from the alcohol (**7**) in quantitative yield by treatment with methanesulfonyl chloride in pyridine at room temperature. The ^{1}H-NMR spectrum of **8** was as follows. ^{1}H-NMR ($CDCl_3$) δ: 0.03 [12H, s, 2 × $Si(C\underline{H}_3)_2$], 0.88 [21H, s, 2 × $C(C\underline{H}_3)_3$ and $C\underline{H}_3$], 1.10—2.70 (22H, m), 2.32 (2H, t, J=7 Hz, $C\underline{H}_2COOMe$), 2.99 (3H, s, $SO_2C\underline{H}_3$), 3.66 (3H, s, $COOC\underline{H}_3$), 3.79—4.09 (2H, m, 2 × C$\underline{H}$–O), 5.04 (1H, br s, C$\underline{H}$–OSO_2CH_3), 5.56 (2H, m, olefinic protons).

Methyl (1*S, 2*R**, 3*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-methylsulfonyloxybicyclo[3.3.0]octane-3-pentanoate (10)**——The mesylate (**10**) (a colorless oil) was prepared in the same way as described in the synthesis of **8**. The ^{1}H-NMR spectrum of **10** was as follows. ^{1}H-NMR ($CDCl_3$) δ: 0.03 [12H, s, 2 × $Si(C\underline{H}_3)_2$], 0.88 [21H, s, 2 × $C(C\underline{H}_3)_3$ and $C\underline{H}_3$], 1.10—2.90 (22H, m), 2.32 (2H, t, J= 7 Hz, $C\underline{H}_2COOMe$), 2.98 (3H, s, $SO_2C\underline{H}_3$), 3.66 (3H, s, $COOC\underline{H}_3$), 4.02 (2H, m, 2 × C$\underline{H}$–O), 4.83 (1H, dd, J=6, 9 Hz, $C\underline{H}SO_2CH_3$), 5.43 (2H, m, olefinic protons).

Oxidation of the *endo*-Alcohol (7) to the Ketone (6)——A solution of the alcohol (**7**) (24.8 mg, 0.0406 mM) and PDC (22.9 mg, 0.0609 mM) in DMF (0.3 ml) was stirred at room temperature for 12 h. The reaction mixture was poured into 3 ml of water, then extracted with ether. The combined ether extracts were washed with brine, then dried ($MgSO_4$). Removal of the solvent and purification of the residue by silica gel column chromatography (Et_2O–petr. ether, 1 : 10) afforded the ketone (**6**) (19.8 mg, 80% yield), whose spectral data and thin-layer chromatographic (TLC) behavior were identical with those of the parent ketone (**6**).

Methyl (1*S, 2*R**, 3*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-phenoxythiocarbonyloxybicyclo[3.3.0]octane-3-pentanoate (13)**——4-Dimethylaminopyridine (61 mg, 0.50 mM) and phenyl chlorothionocarbonate (56 mg, 0.33 mM) was successively added to a stirred solution of the alcohol (**9**) (20.0 mg, 0.033 mM) in acetonitrile (4 ml) at room temperature, and the resulting yellow suspension was stirred under the same conditions for 4 d. After dilution of the suspension with ether, the organic layer was washed with brine, then dried ($MgSO_4$). Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (Et_2O–petr. ether, 1 : 10) to afford the desired product (**13**) as a pale yellow oil [11.1 mg, 58% yield based on the recovery of the starting alcohol (**9**)]. IR ν_{max}^{film} cm^{-1}: 1740, 1590, 1490, 1460, 1360, 1280, 1250, 1190, 830, 770. ^{1}H-NMR ($CDCl_3$) δ: 0.02 [12H, s, 2 × $Si(C\underline{H}_3)_2$, 0.90 [21H, s, 2 × $C(C\underline{H}_3)_3$ and $C\underline{H}_3$], 1.10—3.00 (22H, m), 2.32 (2H, t, J=7 Hz, $C\underline{H}_2COOMe$), 3.68 (3H, s, $COOC\underline{H}_3$), 4.01 (2H, m, 2 × C$\underline{H}$–O), 5.42 (2H, m, olefinic protons), 5.69 (1H, br dd, J=6, 8 Hz, C$\underline{H}$OCSOPh), 7.00—7.60 (5H, m, aromatic protons). LR-MS *m/e*: 746 (M^+), 689 (M^+ – *tert*-Bu), 673. HR-MS *m/e*: 689.3758 (Calcd for $C_{37}H_{61}O_6Si_2S$, 689.3727 M – *tert*-Bu). The starting alcohol (**9**) (4.4 mg) was also recovered from the crude reaction mixture.

Methyl (1*S, 3*S**, 5*S**, 7*R**, 8*R**)-7-*tert*-butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)bicyclo[3.3.0]octane-3-pentanoate (14)**——A solution of the phenoxythiocarbonyl derivative (**13**) (25.5 mg, 0.034 mM) in toluene (15 ml) containing *n*-Bu_3SnH (0.34 mM) and a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) was stirred at 75—80 °C for 1 h. After removal of the solvent *in vacuo*, the residue was purified by silica gel column chromatography to give **16** as a nearly colorless oil (18.7 mg, 92% yield). IR ν_{max}^{film} cm^{-1}: 1740, 1460, 1430, 1355, 1250, 1190, 1160, 1110, 830, 770. ^{1}H-NMR ($CDCl_3$) δ: 0.03 [12H, s, 2 × $Si(C\underline{H}_3)_2$], 0.88 [21H, s, 2 × $C(C\underline{H}_3)_3$ and $C\underline{H}_3$], 1.10—2.50 (24H, m), 2.31 (2H, t, J=7 Hz, $C\underline{H}_2COOMe$), 3.60 (3H, s, $COOC\underline{H}_3$), 3.70—4.20 (2H, m, 2 × C$\underline{H}$–O), 5.45 (2H, m, olefinic protons). LR-MS *m/e*: 595 (M^+ + 1), 594 (M^+), 593, 592, 579 ($M^+ - CH_3$), 537 (M^+ – *tert*-Bu). HR-MS *m/e*: 537.3792 (Calcd for $C_{30}H_{57}O_4Si_2$, 537.3795 M – *tert*-Bu).

9(*O*)-Methano-6α-PGI$_1$ (5) and Its Stereoisomer (16)——A solution of **14** (15.5 mg, 0.026 mM) and tetrabutylammonium fluoride (34 mg, 0.13 mM) in tetrahydrofuran (THF) (2 ml) was stirred at room temperature for 18 h. The reaction was quenched by the addition of saturated NH_4Cl aq., followed by extraction with ether. The combined organic 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 (7.4 mg). A solution of the desilylated product (7.4 mg) in methanol (1 ml) and 10% NaOH aq. (0.2 ml) was stirred at room temperature for 5 h. The reaction mixture was acidified by the addition of pH 4.0 buffer solution (NH_4Cl), followed by extraction with ether. The combined ether extracts were washed with brine, then dried ($MgSO_4$). Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (Et_2O–petr ether, 1 : 10) to give the carbon analog of 6α-PGI_1 (**5**) and its stereoisomer (**16**) at C-15 (PG numbering) as a nearly colorless viscous oil (4.1 mg, 45% yield). The oil thus obtained was further purified by silica gel preparative TLC (AcOEt). The less polar product, which was tentatively assigned as the 15β-isomer (**16**), was isolated as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3400, 1705, 1460, 1410, 1380, 1080, 970, 910. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=6 Hz, C$\underline{H}_3$), 1.10—2.80 (24H, m), 2.34 (2H, t, J=7 Hz, C$\underline{H}_2$COOH), 3.82 (1H, m, C$\underline{H}$–O), 4.08 (1H, m, C$\underline{H}$–O), 4.66 (3H, m, 2×O$\underline{H}$ and COO$\underline{H}$), 5.60 (2H, m, olefinic protons). The MS of the corresponding methyl ester was as follows. LR-MS *m/e*: 366 (M^+), 348 (M^+-H_2O), 330 (M^+-2H_2O). HR-MS *m/e*: 348.2653 (Calcd for $C_{22}H_{36}O_3$, 348.2664 M−H_2O). 9(*O*)-Methano-6α-PGI_1 (**5**) was obtained as the more polar product (a colorless viscous oil). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3400, 1705, 1460, 1410, 1380, 1080, 970. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=6 Hz, C$\underline{H}_3$), 1.10—2.70 (24H, m), 2.36 (2H, t, J=7 Hz, C$\underline{H}_2$COOH), 3.50—4.30 (5H, m, 2×C$\underline{H}$–O, COO$\underline{H}$ and 2×O$\underline{H}$), 5.60 (2H, m, olefinic protons). The MS of the corresponding methyl ester was as follows. LR-MS *m/e*: 366 (M^+), 348 (M^+-H_2O), 330 (M^+-2H_2O). HR-MS *m/e*: 348.2656 (Calcd for $C_{22}H_{36}O_3$, 348.2664 M−H_2O).

Methyl (1*S, 2*S**, 3*R**, 5*S**, 7*R**, 8*R**)-7-*tert*-butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-hydroxybicyclo[3.3.0]octane-3-pentanoate (18)**——A solution of sodium methoxide (0.033 mM) in MeOH (0.1 ml) was added to a stirred solution of the ketone (**6**) (202.1 mg, 0.33 mM) in methanol (8 ml) at room temperature, and the resulting mixture was stirred under the same conditions for 15 h. The solution was then chilled to −78 °C, followed by the addition of sodium borohydride (31 mg, 0.83 mM). Stirring was continued at the same temperature for 24 h, and the reaction was quenched 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 purified by silica gel column chromatography (Et_2O–petr. ether, 1 : 10) to give the *endo*-alcohol (**18**) as a nearly colorless oil [90.2 mg, 82% yield based on the recovery of the ketone (**6**) (92.8 mg, 46% recovery)]. IR ν_{max}^{film} cm^{-1}: 3550, 3450, 1740, 1460, 1360, 1250, 835, 775. ^{1}H-NMR ($CDCl_3$) δ: 0.06 [12H, m, 2×Si(C$\underline{H}_3$)$_2$], 0.89 [21H, s, 2×C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.10—2.80 (23H, m), 2.32 (2H, t, J=7 Hz, C$\underline{H}_2$COOMe), 3.67 (3H, s, COOC$\underline{H}_3$), 3.60—3.90 (2H, m, 2×C$\underline{H}$–O), 4.10 (1H, m, C$\underline{H}$–O), 5.52 (2H, m, olefinic protons). LR-MS *m/e*: 610 (M^+), 592 (M^+-H_2O), 553 (M^+−*tert*-Bu), 535, 478, 461, 421, 329. HR-MS *m/e*: 553.3742 (Calcd for $C_{30}H_{57}O_5Si_2$, 553.3744 M−*tert*-Bu). The spectral data for recovered **6** were identical with those of the starting ketone (**6**).

Methyl (1*S, 2*S**, 3*R**, 5*S**, 7*R**, 8*R**)-7-*tert*-butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-methylsulfonyloxybicyclo[3.3.0]octane-3-pentanoate (19)**——The mesylate (**19**) was prepared in the same way as described in the synthesis of **8**. The ^{1}H-NMR spectrum of **19** was as follows. ^{1}H-NMR ($CDCl_3$) δ: 0.03 [12H, s, 2×Si(C$\underline{H}_3$)$_2$], 0.89 [21H, s, 2×C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 2.32 (2H, t, J=7 Hz, C$\underline{H}_2$COOMe), 1.10—2.70 (22H, m), 2.96 (3H, s, $SO_2C\underline{H}_3$), 3.66 (3H, s, COOC$\underline{H}_3$), 4.10 (1H, m, 2×C$\underline{H}$–O), 4.60 (1H, t, J=8 Hz, C$\underline{H}$–OSO_2CH_3), 5.56 (2H, m olefinic protons).

Methyl (1*S, 2*S**, 3*R**, 5*S**, 7*R**, 8*R**)-7-*tert*-butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)-2-phenoxythiocarbonyloxylbicyclo[3.3.0]octane-3-pentanoate (20)**——4-Dimethylaminopyridine (270 mg, 2.2 mM) and phenyl chlorothionocarbonate (254 mg, 1.47 mM) were successively added to a stirred solution of the alcohol (**18**) (90.0 mg, 0.147 mM) in acetonitrile (4 ml) at room temperature, and the resulting yellow suspension was stirred under the same conditions for 4 d. After dilution of the suspension with ether, the organic layer was washed with brine, then dried ($MgSO_4$). Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (Et_2O–petr. ether, 1 : 10) to afford the phenoxythiocarbonyl derivative (**20**) as a pale yellow oil [54.5 mg, 70% yield based on the recovery of the alcohol (**18**) (26.4 mg, 29% recovery)]. IR ν_{max}^{film} cm^{-1}: 1740, 1590, 1495, 1460, 1360. ^{1}H-NMR ($CDCl_3$) δ: 0.03 [12H, s, 2×Si(C$\underline{H}_3$)$_2$], 0.89 [21H, s, 2×C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.10—2.84 (22H, m), 2.32 (2H, t, J=7 Hz, C$\underline{H}_2$COOMe), 3.66 (3H, s, COOC$\underline{H}_3$), 3.50—3.70 (1H, m, C$\underline{H}$–O), 4.00—4.20 (1H, m, C$\underline{H}$–O), 5.31 (1H, dd, J=8 Hz, C$\underline{H}$–OCSOPh), 5.58 (2H, m, olefinic protons), 7.00—7.50 (5H, m, aromatic protons). LR-MS *m/e*: 746 (M^+), 731 (M^+-CH_3), 689 (M^+−*tert*-Bu). HR-MS *m/e*: 689.3707 (Calcd for $C_{37}H_{61}O_6Si_2S$, 689.3727 M−*tert*-Bu). The spectral data for recovered **18** were identical with those of the starting *endo*-alcohol (**18**).

Methyl (1*S, 3*R**, 5*S**, 7*R**, 8*R**)-7-*tert*-butyldimethylsilyloxy-8-(3-*tert*-butyldimethylsilyloxy-*E*-1-octenyl)bicyclo[3.3.0]octane-3-pentanoate (21)**——A solution of **20** (54.5 mg, 0.073 mM) and tributyltin hydride (212 mg, 0.73 mM) in toluene (10 ml) containing a catalytic amount of AIBN was stirred at 75—80 °C for 1 h. After removal of the dried solvent *in vacuo*, the residual oil was purified by silica gel column chromatography (Et_2O–petr. ether, 1 : 10) to give **21** as a nearly colorless oil (28.2 mg, 65%). IR ν_{max}^{film} cm^{-1}: 1740, 1460, 1360, 1250, 1120, 1005, 965, 935. ^{1}H-NMR ($CDCl_3$) δ: 0.03 [12H, s, 2×Si(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 0.90 [21H, s, 2×C(C$\underline{H}_3$)$_3$ and C$\underline{H}_3$], 1.10—2.50 (24H, m), 2.32 (2H, t, J=7 Hz, C$\underline{H}_2$COOMe), 3.66 (3H, s, COOC$\underline{H}_3$), 3.40—3.80 (1H, m, C$\underline{H}$–O), 3.90—4.20 (1H, m, C$\underline{H}$–O), 5.42 (2H, m, olefinic protons). LR-MS *m/e*: 595 (M^++1), 594 (M^+), 579 (M^+-CH_3), 563 (M^+-OCH_3), 537 (M^+−*tert*-Bu). HR-MS *m/e*: 537.3806 (Calcd for $C_{30}H_{57}O_4Si_2$, 537.3795 M−*tert*-Bu).

9(*O*)-Methano-6β-PGI$_1$ (4) and Its Stereoisomer (22)——A solution of **21** (28.2 mg, 0.047 mM) and tetrabutylammonium fluoride (62.0 mg, 0.237 mM) in THF (2 ml) was stirred at room temperature for 18 h. The reaction was quenched by the addition of saturated NH_4Cl aq., followed by extraction with ether. The combined organic extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was roughly purified by silica gel column chromatography (Et_2O–petr. ether, 1 : 10) to afford the desilylated product as a pale yellow oil (13.4 mg). A solution of the desilylated product (13.4 mg) in methanol (1 ml) and 10% KOH aq. (0.2 ml) was stirred at room temperature for 5 h. The reaction mixture was acidified by the addition of pH 4.0 buffer solution followed by extraction with ether. The combined 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 (Et_2O–petr. ether, 1 : 10) to give a mixture of 9(*O*)-methano-6β-PGI$_1$ (**4**) and its stereoisomer (**22**) at C-15 (PG numbering) as a nearly colorless viscous oil (8.3 mg, 49% yield). The oil thus obtained was further purified by silica gel preparative TLC (AcOEt). The less polar product, which was tentatively assigned as the 15β-isomer (**22**), was isolated as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3400, 1705, 1460, 1410, 1380, 970. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 6 Hz, C$\underline{H}_3$), 1.10—2.60 (26H, m), 2.90—3.90 (4H, m, CH–O, 2 × O$\underline{H}$ and COO$\underline{H}$), 4.10 (1H, m, C$\underline{H}$–O), 5.60 (2H, m, olefinic protons). The mass spectrum of the corresponding methyl ester was as follows. LR-MS *m/e*: 366 (M^+), 348 ($M^+ - H_2O$), 330 ($M^+ - 2H_2O$). HR-MS *m/e*: 348.2662 (Calcd for $C_{22}H_{36}O_3$, 348.2664 $M - H_2O$). 9(*O*)-Methano-6β-PGI$_1$ (**4**) was obtained as the more polar product (a colorless viscous oil). IR ν_{max}^{film} cm^{-1}: 3600, 3400, 1705, 1460, 1410, 1380, 1090. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 6 Hz, C$\underline{H}_3$), 1.10—2.80 (29H, m), 3.50—3.80 (1H, m, C$\underline{H}$–O), 4.00—4.30 (1H, m, C$\underline{H}$–O), 5.60 (2H, m, olefinic protons). The MS of the corresponding methyl ester was as follows. LR-MS *m/e*: 366 (M^+), 348 ($M^+ - H_2O$), 330 ($M^+ - 2H_2O$). HR-MS *m/e*: 348.2653 (Calcd for $C_{22}H_{36}O_3$, 348.2664 $M - H_2O$).

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References and Notes

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3) G. L. Kauffman, Jr., B. J. R. Whittle, D. Aures, J. R. Vane, and M. I. Grossman, *Gastroenterology*, **77**, 1301 (1979).
4) W. Skuballa, B. Radüchel, and H. Vorbrüggen, Abstracts of Papers, the 5th International PG Conference, Florence, 1982, p. 515.
5) K. Iseki, T. Mase, T. Okazaki, M. Shibasaki, and S. Ikegami, *Chem. Pharm. Bull.*, **31**, 4448 (1983).
6) I. Tabushi, K. Fujita, and R. Oda, *J. Org. Chem.*, **35**, 2383 (1970).
7) E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, **1979**, 399.
8) M. J. Robins and J. S. Wilson, *J. Am. Chem. Soc.*, **103**, 932 (1981).
9) B. Fuchs, "Topics in Stereochemistry," Vol. 10, ed. by E. L. Eliel and N. L. Allinger, John Wiley & Sons, New York, 1978, pp. 1—99.
10) For the biological test system, see K. Matsuoka, Y. Mitsui, and S. Murota, *J. Pharm. Dyn.*, **5**, 911 (1982).
11) At the concentration of 10^{-6} M, 9(*O*)-methano-$\Delta^{6(9\alpha)}$-PGI$_1$ showed marked cytoprotective action on rabbit stomach epithelial cells; see M. Shibasaki, Y. Torisawa, and S. Ikegami, *Tetrahedron Lett.*, **24**, 3493 (1983).