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A Convenient Synthesis of (+)-9(*O*)-Methanoprostacyclin[1)]

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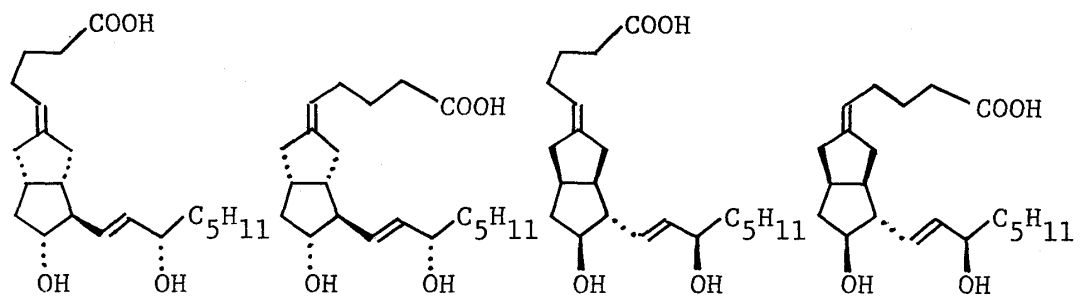
(+)-9(*O*)-Methanoprostacyclin (**1a**) and (−)-*ent*-9(*O*)-methanoprostacyclin (**1c**) were synthesized from the bicyclic esters, methyl (+)-(1*S*,2*R*,3*R*,5*R*)-3-hydroxy-7,7-ethylenedioxybicyclo-[3.3.0]octane-2-carboxylate (**2a**) and methyl (−)-(1*R*,2*S*,3*S*,5*S*)-3-hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylate (**2b**), respectively, which were obtained by optical resolution of the racemic acid (**3**), followed by esterification. The absolute configurations of **2a** and **2b** were determined by the chemical correlation method. (+)-9(*O*)-Methanoprostacyclin (**1a**) was found to be as active as prostaglandin E_1, and (−)-*ent*-9(*O*)-methanoprostacyclin (**1c**) was considerably less active than **1a**, in inhibiting platelet aggregation.

Keywords——prostacyclin; 9(*O*)-methanoprostacyclin; bicyclo[3.3.0]octane; carboxylation reaction; optical resolution; absolute configuration; *ent*-9(*O*)-methanoprostacyclin; platelet aggregation inhibitor

Prostacyclin (PGI_2), discovered by Vane *et al.* in 1976,[2)] is of interest owing to its potent platelet antiaggregating and vasodilating properties. However, it is extremely unstable due to the enol ether moiety of the molecule. Although the sodium salt[3)] of prostacyclin is more stable than the parent free acid, care is still necessary in handling it. Therefore many groups have prepared stable analogs[4)] in the hope of finding a more useful therapeutic agent. Among these analogs, 9(*O*)-methanoprostacyclin (carbacyclin) and its analogs[5)] appear to be the most promising candidate drugs for preventing thrombosis.

The synthesis of 9(*O*)-methanoprostacyclin was first reported by ourselves[6a)] and Nicolaou *et al.*[6b)] in 1978. Since then, several additional syntheses have been published.[6c,d)] Our original synthesis[6a)] of 9(*O*)-methanoprostacyclin was stereospecific but required many steps. We describe here a short synthesis of 9(*O*)-methanoprostacyclin in an optically active form.

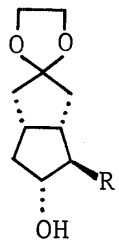


1a **1b** **1c** **1d**

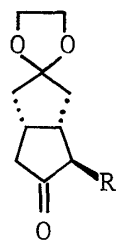
Chart 1

In order to synthesize the optically active (+)-9(*O*)-methanoprostacyclin (**1a**) we have used the optical resolution method of the racemic acid (**3**), which could be synthesized from the racemic ester (**2**)[6a] by alkaline hydrolysis. Nicolaou *et al.*[6b] and Shibasaki *et al.*[6c] described an efficient process for the synthesis of **2** or its ethyl ester analog from the monoacetal (**4**), which was synthesized from *cis*-bicyclo[3.3.0]octane-3,7-dione[7] in good yield. Although this method is useful for the synthesis of the ester (**2**), it is much better to introduce the carboxylic function, required for optical resolution, directly into **4**. Thus, treatment of **4** with carbon dioxide in the presence of sodium 2,6-di-*tert*-butyl-4-methylphenolate in dimethoxyethane (DME) yielded the unstable β-keto-acid (**5**) (mp 85—90 °C) in 73% yield. This compound was found to exist in the enol form in the crystalline state on the basis of its infrared (IR) spectrum. Because of the unstable nature of the β-keto-acid functionality, sodium borohydride reduction of **5** resulted in the formation of the by-product derived from the decarboxylation product of **5** along with the main product (**3**). In order to prevent the undesired decarboxylation reaction, the sodium salt of **5** in DME, formed *in situ* in the carboxylation reaction described above, was directly reduced with sodium borohydride in aqueous tertiary butanol to afford stereoselectively desired acid (**3**) in 75% yield.

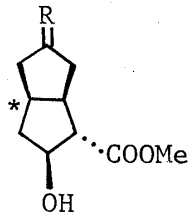
As described above the synthesis of **3** could easily be accomplished by a one-pot reaction from **4** in good yield. Next, optical resolution of **3** was investigated. After an intensive search for both resolving agents and recrystallization solvents we finally found that optical resolution of **3** could be easily accomplished by recrystallization of its salt with *d*(+)-α-methylbenzylamine or with *l*(−)-α-methylbenzylamine from chloroform. Recrystallization of a mixture of **3** and *l*(−)-α-methylbenzylamine (1 : 1) from chloroform yielded (+)-(1*S*,2*R*,3*R*,5*R*)-3-hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylic acid *l*(−)-α-methylbenzylamine salt (mp 159—160 °C, $[\alpha]_D^{23}$ +10.1 °), from which methyl (+)-(1*S*,2*R*,3*R*,5*R*)-3-hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylate (**2a**) ($[\alpha]_D^{23}$ +22.5 °) was generated by treatment with diazomethane. Similar treatment of **3** with *d*(+)-α-methylbenzylamine afforded methyl (−)-(1*R*,2*S*,3*S*,5*S*)-3-hydroxy-7,7-ethylenedioxybicy-



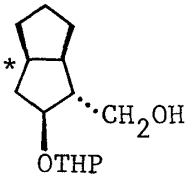
2 : R=COOMe
2a : (+)-(1*S*, 2*R*, 3*R*, 5*R*)-2
2b : (-)-(1*R*, 2*S*, 3*S*, 5*S*)-2
3 : R=COOH



4 : R=H
5 : R=COOH



6 : R=SCH$_2$CH$_2$S
7 : R=H,H



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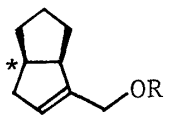
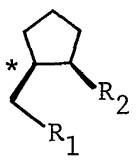
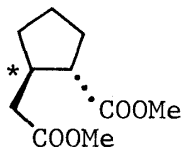


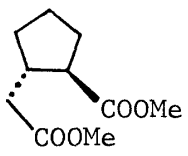
9 : R=H
10 : R=Bz



11 : R_1=COOH
R_2=$COCH_2OBz$
12 : R_1=R_2=COOMe



13b



13a

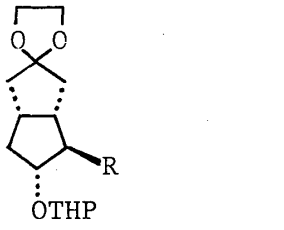
Chart 2

clo[3.3.0]octane-2-carboxylate (**2b**) ($[\alpha]_D^{23}$ −28.8°). The absolute configurations of **2a** and **2b** were determined by leading **2b** to methyl (+)-(1*R*,2*S*)-2-methoxycarbonylcyclopentane-acetate (**13b**) with known absolute stereochemistry[8] through the following sequence of reactions.

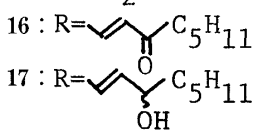
The thioacetalization of **2b** with ethylenedithiol and boron trifluoride etherate yielded the thioacetal (**6**) ($[\alpha]_D^{23}$ −25.1°). Desulfurization of **6** with Raney nickel in methanol gave the ester (**7**) ($[\alpha]_D^{23}$ −7.3°). In order to cleave the carbon (2)–carbon (3) bond in **7**, the olefinic linkage was introduced by means of the following reactions. The reaction of **7** with dihydropyran in the presence of picric acid, followed by lithium aluminum hydride reduction in ether, afforded the alcohol (**8**) ($[\alpha]_D^{23}$ +30.2°). Successive treatment of **8** with chromium trioxide pyridine complex (Collins reagent)[9] in methylene chloride, piperidine acetate in benzene, and then sodium borohydride in methanol yielded the olefin (**9**) ($[\alpha]_D^{23}$ −13.8°). The cleavage of the double bond in **9** was performed after protection of the hydroxy group as the benzoate by treatment of **9** with benzoyl chloride in pyridine. Thus, successive treatment of the benzoate (**10**) ($[\alpha]_D^{23}$ −15.6°) with a mixture of osmium tetraoxide and sodium metaperiodate, and then Jones reagent[10] in acetone afforded the keto-acid (**11**) ($[\alpha]_D^{23}$ −65.3°, mp 115—116 °C).

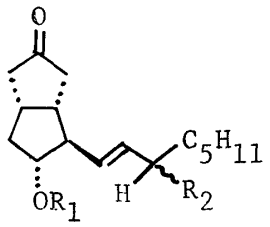
Sodium borohydride reduction of **11**, followed by *trans*-esterification with potassium carbonate in methanol yielded a glycolic compound, which was oxidized with sodium metaperiodate and then Jones reagent, affording, after esterification with diazomethane, the *cis*-diester (**12**) ($[\alpha]_D^{23}$ −45.7°).

The epimerization of the *cis*-diester (**12**) with sodium methoxide in methanol yielded the more stable *trans*-diester (**13b**) ($[\alpha]_D^{23}$ +44.8°) in good yield. This *trans*-diester (**13b**) was identical, in terms of thin layer chromatographic (TLC) behavior and IR, proton nuclear magnetic resonance (^{1}H-NMR) and mass spectra (MS), with methyl (−)-(1*S*,2*R*)-2-

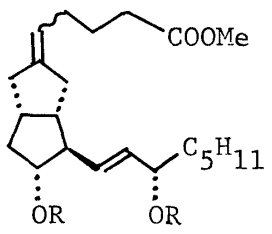


14 : R=COOMe
15 : R=CH_2OH

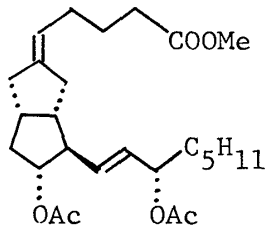




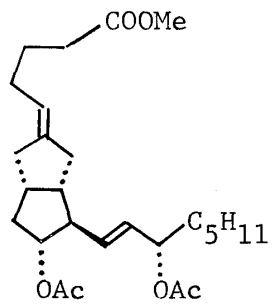
18 : R_1=H, R_2=···OH
19 : R_1=H, R_2=—OH
20 : R_1=THP, R_2=···OTHP



21 : R=THP
22 : R=H



23



24

Chart 3

methoxycarbonylcyclopentaneacetate (**13a**), whose absolute configuration has already been established by ourselves.[8] However the sign of the optical rotation was opposite: **13a**; $[\alpha]_D^{23}$ $-44.6°$ ($c=1$, $CHCl_3$), **13b**; $[\alpha]_D^{23}$ $+44.8°$ ($c=1$, $CHCl_3$).

Therefore the absolute configuration of the ester (**13b**) was assigned as (1*R*,2*S*). Moreover, the absolute configuration of the carbon marked by an asterisk (*) is retained during the transformations from **2b** to **13b** described above. From these data, the absolute configuration of the (−)-ester (**2b**) was assigned as (1*R*,2*S*,3*S*,5*S*), and hence the (+)-ester (**2a**) has (1*S*,2*R*, 3*R*, 5*R*)-stereochemistry. Thus, the absolute configuration of **2a** was found to be appropriate for the synthesis of (+)-9(*O*)-methanoprostacyclin (**1a**) having absolute configuration similar to that of natural prostacyclin. We then converted the (+)-ester (**2a**) to (+)-9(*O*)-methanoprostacyclin (**1a**) through the following reactions.

Tetrahydropyranylation of **2a** with dihydropyran and picric acid, followed by lithium aluminum hydride reduction gave the alcohol (**15**) ($[\alpha]_D^{23}$ $-22.8°$) in 85% yield. The oxidation[11] of **15** with sulfur trioxide pyridine complex and triethylamine in dimethyl sulfoxide yielded the aldehyde, which without purification, was treated with tributyl 2-oxoheptylidenephosphorane[12] in ether to afford the enone (**16**) ($[\alpha]_D^{23}$ $+16.1°$) in 79% yield. Sodium borohydride reduction of **16** yielded the hydroxy compound (**17**) ($[\alpha]_D^{23}$ $+3.1°$) as a 15*S*- and 15*R*-hydroxy mixture (prostaglandin numbering), which gave two very close spots on TLC over silica gel. The separation of the C-15 epimers in **17** was not easy on a preparative scale, but it was accomplished without difficulty after deprotection of both the hydroxy and oxo protecting groups. Thus, treatment of **17** with aqueous acetic acid, followed by purification by silica gel column chromatography, gave the 15*S*-alcohol (**18**) ($[\alpha]_D^{23}$ $-11.5°$, more polar) and the 15*R*-alcohol (**19**) ($[\alpha]_D^{23}$ $-31.0°$, less polar) in almost equal amounts.

The stereochemical assignments at C-15 in **18** and **19** were based on the assignment done previously by ourselves during the synthesis of (±)-9(*O*)-methanoprostacyclin:[6a] according to a general rule in prostaglandin chemistry the more polar and more biologically active epimer in the final prostaglandin stage can be assigned as the 15*S*-hydroxy compound, and the less polar and less biologically active epimer as the 15*R*-hydroxy compound. Thus the more polar epimer (**18**), which was converted to **1a**, was assigned as the 15*S*-compound and hence the less polar epimer (**19**) as the 15*R*-compound. Practical conversion of **18** to **1a** and **1b** was accomplished by means of the following reactions.

Tetrahydropyranylation of **18** with dihydropyran and *p*-toluenesulfonic acid afforded the tetrahydropyranyl compound (**20**) ($[\alpha]_D^{23}$ $-28.2°$). The Wittig reaction of **20** with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide and sodium methylsulfinylmethide in dimethyl sulfoxide, followed by esterification with diazomethane yielded an inseparable mixture of (5*E*,*Z*)-methyl ester (**21**) ($[\alpha]_D^{23}$ $+12.2°$). These C-5 isomers were smoothly separated by converting the tetrahydropyranyl protecting groups in **21** into the acetates: Treatment of **21** with aqueous acetic acid, followed by acetylation with acetic anhydride in pyridine afforded the (5*Z*)-diacetate (**23**) ($[\alpha]_D^{23}$ $-10.8°$, less polar) and (5*E*)-diacetate (**24**) ($[\alpha]_D^{23}$ $+13.0°$, more polar) after chromatographic purification on silica gel.

TABLE I. Biological Activity[a]

Prostaglandin E_1 (PGE_1)	1
1a	1.0
1b	0.085
1c	0.003

a) Relative potency based on inhibition of ADP-induced platelet aggregation in rabbit platelet-rich plasma ($PGE_1=1$).

Hydrolysis of **24** with potassium hydroxide in aqueous methanol yielded (+)-9(*O*)-methanoprostacyclin (**1a**) ($[\alpha]_D^{23}$ +74.0°, mp 60—61 °C) in 95% yield. Similar treatment of **23** afforded (+)-(5*Z*)-9(*O*)-methanoprostacyclin (**1b**) ($[\alpha]_D^{23}$ +71.2°, mp 104—106 °C). The stereochemistry at the C-5 position in **1a** and **1b** was tentatively assigned on the basis of relative potency of platelet antiaggregating activity. Thus, the more polar isomer (**1a**) having the more potent activity was assigned as the 5*E*-isomer and the less polar isomer (**1b**) as the 5*Z*-isomer. Recently, this assignment was supported by the ^{1}H-NMR analysis of **1a**.[13]

By using a sequence of reactions similar to that described for the synthesis of **1a**, the (−)-ester (**2b**) was led to (−)-*ent*-9(*O*)-methanoprostacyclin (**1c**) ($[\alpha]_D^{23}$ −68.5°, (c=1, $CHCl_3$), mp 59 °C) and (−)-*ent*-(5*Z*)-9(*O*)-methanoprostacyclin (**1d**) ($[\alpha]_D^{23}$ −65.4° (c=0.90, $CHCl_3$), mp 103—105 °C).

The biological activities of the products are summarized in Table I.[14]

Experimental

Melting points are uncorrected. IR spectra were determined on a Jasco IRA-2 spectrometer, ^{1}H-NMR spectra on a Varian T-60 spectrometer, and MS on a JEOL JMS-OLSG spectrometer. Optical rotation was measured with a Perking Elmer model 141 polarimeter. Removal of solvents *in vacuo* was accomplished with a rotating flash evaporator at 20—30 mmHg and usually at 35—50 °C. Plates for thin layer chromatography (TLC) were Silica gel 60 F_{254} (E. Merck AG) and spots were visualized by spraying a solution of 0.5% vanillin in 20% ethanol in sulfuric acid (v/v), followed by heating. Columns for ordinary chromatography were prepared with Kanto silica gel or alumina (GII-III) (E. Merck AG).

(1*S,2*R**,3*R**,5*R**)-3-Hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylic Acid (3)**——i) Method a: A mixture of methyl (1*S**,2*R**,3*R**,5*R**)-3-hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylate (**2**: 421 mg)[6a] and 5% KOH in 30% H_2O in MeOH (v/v) (5 ml) was stirred at 5 °C for 18 h. The reaction mixture was concentrated to a small volume, acidified to pH 5 with conc. hydrochloric acid, saturated with $(NH_4)_2SO_4$, and then extracted with EtOAc. The extracts were washed with a small volume of sat. $(NH_4)_2SO_4$ solution and dried (Na_2SO_4). Removal of the solvent gave a crystalline residue, which was recrystallized from EtOAc–hexane mixture to give 219 mg of **3**. mp 125—127 °C. IR (Nujol): 1708, 3320 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (4H, s, CH_2CH_2), 4.21 (1H, m, >CHOH), 6.34 (2H, br, COOH, OH). *Anal.* Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.73; H, 7.03.

ii) Method b: 2,6-Di-*tert*-butyl-4-methylphenol (1.82 g) was added to a suspension of 55% NaH in oil (377 mg) in DME (20 ml) and the mixture was heated at 50 °C for 20 min, then cooled to room temperature and treated with CO_2 gas for 30 min under stirring. The ketone (**4**) (0.50 g) in DME (3 ml) was added to the reaction mixture and the whole was stirred at 16—17 °C for 3.5 h. The excess CO_2 gas was replaced by N_2 gas, then $NaBH_4$ (200 mg) in a mixture of *tert*-BuOH (10 ml) and water (3.5 ml) was added to the reaction mixture at 3—11 °C. The whole was stirred for 10 min and partitioned after the addition of brine. The organic phase was washed with brine (twice). The aqueous phase was acidified with 7% hydrochloric acid saturated with $(NH_4)_2SO_4$ and extracted with EtOAc. The extracts were washed with sat. $(NH_4)_2SO_4$ solution and dried over Na_2SO_4. Evaporation of the solvent gave a crystalline residue, which was recrystallized from EtOAc–hexane mixture to give 468 mg of **3**, mp 125—127 °C.

(1*S,2*R**,5*R**)-3-Oxo-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylic Acid (5)**——A solution of 2,6-di-*tert*-butyl-4-methylphenol (11.2 g) in tetrahydrofuran (THF) (150 ml) was cooled at 0 °C, and 55% NaH in oil (2.16 g) was added. The reaction mixture was stirred at room temperature for 30 min and then CO_2 gas was introduced for 30 min under stirring. The ketone (**4**: 1.82 g) in a small amount of THF was added to the reaction mixture and the whole was stirred at room temperature for 2 h. The reaction mixture was partitioned with water and the aqueous phase was acidified with dil. hydrochloric acid (pH 5), and extracted with EtOAc. The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was recrystallized from EtOAc–hexane mixture to give 1.60 g of **5**, mp 85—90 °C. IR (Nujol): 3200, 2650, 1660, 1585, 1230 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.89 (4H, s, OCH_2CH_2O). *Anal.* Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.38; H, 6.24.

The Optical Resolution of 3——1) Method a with *l*(−)-α-Methylbenzylamine: *l*(−)-α-Methylbenzylamine (22.8 g) was added to a suspension of **3** (39.0 g) in $CHCl_3$ (615 ml); a clear solution was formed upon warming. This mixture was allowed to stand at 5 °C overnight, and the precipitated crystalline solid was collected by filtration. This crystalline material was twice recrystallized from $CHCl_3$ (650 ml and 900 ml), affording 27.0 g of (+)-(1*S*,2*R*,3*R*,5*R*)-3-hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylic acid *l*(−)-α-methylbenzylamine salt, mp 159—161 °C. IR (Nujol): 3438 cm^{-1}. ^{1}H-NMR (MeOH-d_4) δ: 1.60 (3H, d, J=6 Hz, Me), 3.28 (1H, m, >CHMe), 3.87 (4H, m, CH_2CH_2), 7.40 (5H, s, arom-H). *Anal.* Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79. Found: C, 65.27; H, 7.73. $[\alpha]_D^{23}$ +10.1° (c=1, MeOH).

2) Method b with *d*(+)-α-Methylbenzylamine: Treatment of **3** (5.70 g) and *d*(+)-α-methylbenzylamine (3.35 g)

by method a described above afforded 2.621 g of (−)-(1*R*,2*S*,3*S*,5*S*)-3-hydroxy-7,7-ethylenedioxybicyclo-[3.3.0]octane-2-carboxylic acid *d*(+)-α-methylbenzylamine salt, mp 159—161 °C. IR (Nujol): 3438 cm^{-1}. ^{1}H-NMR MeOH-d_4) δ: 1.60 (3H, d, J=6 Hz, Me), 3.28 (1H, m, >CHMe), 3.87 (4H, m, CH_2CH_2), 7.40 (5H, s, arom-H). *Anal.* Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79. Found: C, 65.28; H, 7.76. $[\alpha]_D^{23}$ −9.6° (c=1, MeOH).

Methyl (+)-(1*S*,2*R*,3*R*,5*R*)-3-Hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylate (2a)——A suspension of (+)-(1*S*,2*R*,3*R*,5*R*)-3-hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylic acid *l*(−)-α-methylbenzylamine salt (21.59 g) in ether (100 ml) was treated with excess CH_2N_2 in ether until the evolution of N_2 ceased. The solvent was removed, and the residue was chromatographed over silica gel (50 g). Elution with 30—40% EtOAc in hexane (v/v) afforded 12.4 g of **2a** as an oil. IR (neat): 3450, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.75 (3H, s, Me), 3.98 (4H, s, CH_2CH_2), 4.33 (1H, m, >CHOH). MS *m/e*: 242 (M^+), 224. $[\alpha]_D^{23}$ +22.5° (c=1, MeOH).

Methyl (−)-(1*R*,2*S*,3*S*,5*S*)-3-Hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylate (2b)——Treatment of (−)-(1*R*,2*S*,3*S*,5*S*)-3-hydroxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylic acid *d*(+)-α-methylbenzylamine salt (3.75 g) by a method similar to that described for the preparation of **2a** yielded 2.50 g of **2b** as an oil. IR (neat): 3450, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.75 (3H, s, Me), 3.98 (4H, s, CH_2CH_2), 4.33 (1H, m, >CHOH). MS *m/e*: 242 (M^+), 224. $[\alpha]_D^{23}$ −28.8° (c=1, $CHCl_3$).

Methyl (−)-(1*R*,2*S*,3*S*,5*S*)-3-Hydroxy-7,7-ethylenedithiobicyclo[3.3.0]octane-2-carboxylate (6)——A mixture of **2b** (350 mg) in $CHCl_3$ (10 ml) and ethanedithiol (1 ml) was treated, under ice-cooling, with BF_3 etherate (3 drops). After 30 min, the reaction mixture was quenched with ice-water mixture and extracted with EtOAc. The extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave a gummy residue, which was chromatographed over silica gel (5 g). Elution with 10—20% EtOAc in hexane (v/v) afforded 398 mg of **6**, which gave a pure sample of mp 59—60 °C by recrystallization from EtOAc–hexane mixture. IR (melted film): 3450, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.22 (4H, s, CH_2CH_2), 3.61 (3H, s, Me), 4.22 (1H, m, >CHOH). *Anal.* Calcd for $C_{12}H_{18}O_3S_2$: C, 52.55; H, 6.62. Found: C, 52.49; H, 6.64. $[\alpha]_D^{23}$ −25.1° (c=1, MeOH).

Methyl (−)-(1*R*,2*S*,3*S*,5*R*)-3-Hydroxybicyclo[3.3.0]octane-2-carboxylate (7)——A mixture of **6** (1.854 g) in MeOH (70 ml) and Raney nickel (Kawaken Fine Chemical Co., 45 ml as a suspension in water) was stirred at room temperature for 3 h. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was chromatographed over silica gel (20 g). Elution with 7—10% EtOAc in hexane (v/v) afforded 1.004 g of **7** as an oil. IR (neat): 1740, 3430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (3H, s, Me), 4.08 (1H, m, >CHOH). MS *m/e*: 184 (M^+), 182, 166, 164, 156, 153. $[\alpha]_D^{23}$ −7.3° (c=1, MeOH).

(+)-(1*R*,2*R*,3*S*,5*R*)-3-(Tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane-2-methanol (8)——A mixture of **7** (70 mg) in benzene (2 ml) and dihydropyran (1 ml) was treated with a catalytic amount of picric acid, and stirred at room temperature for 1.5 h. The reaction mixture was diluted with hexane, washed with dil. $NaHCO_3$ solution, and brine, and then dried over Na_2SO_4. Evaporation of the solvent gave a crude tetrahydropyranyl ether compound as an oil, which was directly reduced with $LiAlH_4$ (100 mg) in Et_2O (10 ml) at room temperature for 20 min. The reaction mixture was quenched with 4% NaOH solution (0.4 ml) and stirred for 3 h. The white precipitate was filtered off and the filtrate was evaporated to dryness. The oil obtained was chromatographed over silica gel (3 g). Elution with 5—10% EtOAc in hexane (v/v) afforded 89 mg of **8** as an oil. IR (neat): 3450, 1032, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.4—4.7 (1H, br, OCHO). MS *m/e*: 241, 240 (M^+), 239, 223, 222, 139, 138. $[\alpha]_D^{23}$ +30.2° (c=1, MeOH).

(−)-(1*R*,5*R*)-2-Bicyclo[3.3.0]octene-2-methanol (9)——The alcohol **8** (1.20 g) in CH_2Cl_2 (20 ml) was added to the Collins reagent [prepared from CrO_3 (4.5 g) and pyridine (6.3 ml) in CH_2Cl_2 (150 ml)] at room temperature. After 30 min the reaction mixture was diluted with ether, washed with water, and dried over Na_2SO_4. Evaporation of the solvent gave a residue (one spot on TLC; aldehyde), which was treated with piperidine acetate (1.6 g) in benzene (20 ml) at 50 °C for 20 min. The reaction mixture was cooled, diluted with Et_2O, and washed with brine, dil. hydrochloric acid and then brine, and dried (Na_2SO_4). Removal of the solvent afforded an oil (UV-positive on TLC, Silica gel F_{254}). A solution of this oil in MeOH (20 ml) was treated with $NaBH_4$ (500 mg) under ice cooling. After being stirred for 15 min the reaction mixture was quenched with AcOH, diluted with brine, and extracted with EtOAc. The extracts were washed with brine and dried with Na_2SO_4. Evaporation of the solvent afforded a residue, which was purified by column chromatography over silica gel (20 g). Elution with 7—10% EtOAc in hexane (v/v) yielded 125 mg of **9** as an oil. IR (neat): 3330, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.05 (2H, br s, $-CH_2OH$), 5.36 (1H, br s, =CH–). MS *m/e*: 138 (M^+), 123, 120, 109, 107. $[\alpha]_D^{23}$ −13.8° (c=1, MeOH).

(−)-(1*R*,5*R*)-2-Benzoyloxymethylbicyclo[3.3.0]oct-2-ene (10)——Benzoyl chloride (0.5 ml) was added to the solution of **9** (120 mg) in pyridine (2 ml) under ice cooling, and the reaction mixture was left to stand at 5 °C overnight, then quenched with water and extracted with EtOAc. The extracts were successively washed with brine, dil. hydrochloric acid, dil. $NaHCO_3$ solution and brine and then dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was chromatographed over neutral alumina (GII, 10 g). Elution with 1% EtOAc in hexane (v/v) afforded 163 mg of **10** as an oil. IR (neat): 1725, 1602, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.78 (2H, br s, $-CH_2OH$), 5.54 (1H, br s, =CH–), 7.1—8.0 (5H, m, arom-H). MS *m/e*: 242 (M^+), 149, 120, 105, 92, 91. $[\alpha]_D^{23}$ −15.6° (c=1, MeOH).

(−)-(1*R*,2*R*)-2-(1-Oxo-2-benzoyloxyethyl)cyclopentaneacetic Acid (11)——A mixture of **10** (160 mg) in Et_2O (15 ml) and osmiun tetroxide (185 mg) was allowed to stand at room temperature overnight. Removal of the solvent

afforded a brown residue (osmate), which was dissolved in a mixture of pyridine (3 ml) and water (3 ml) and treated with $NaHSO_3$ (3.5 g) at room temperature for 2.5 h under stirring. The reaction mixture was diluted with brine and extracted with EtOAc. The extracts were washed with brine, dil. hydrochloric acid, brine, dil. $NaHCO_3$ solution and brine, and then dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by column chromatography over silica gel (3 g). Elution with 30—50% EtOAc in hexane (v/v) afforded crystalline diols (almost one spot on TLC). A mixture of the diols (180 mg) in 80% aqueous THF (10 ml) and $NaIO_4$ (540 mg) was stirred at room temperature for 1 h. The reaction mixture was diluted with Et_2O, the precipitate was filtered off, and the filtrate was concentrated to give the crude aldehyde. This aldehyde in acetone (20 ml) was treated with the Jones reagent at room temperature until the brown color persisted. The reaction mixture was treated with iso-PrOH, diluted with brine and extracted with EtOAc. The extracts were dried with Na_2SO_4 and evaporated to yield a residue, which was chromatographed over silica gel (3 g). Elution with a gradient of 20% EtOAc in hexane (v/v) to EtOAc gave 168 mmHg of **11**, mp 115—116 °C, recrystallized from EtOAc–hexane mixture. IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.85 (2H, s, CH_2OBz), 7.2—8.1 (5H, m, arom-H). *Anal.* Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.05; H, 6.21. $[\alpha]_D^{23}$ −65.3° (c=1, $CHCl_3$).

Methyl (−)-(1*R*,2*R*)-2-Methoxycarbonylcyclopentaneacetate (12)——Water (3 ml), sat. $NaHCO_3$ solution (0.5 ml) and then $NaBH_4$ (300 mg) were added to a solution of **11** (160 mg) in EtOH (10 ml) at room temperature. The reaction mixture was stirred for 20 min, then quenched with AcOH to neutrality. KOH (1.5 g) and water (10 ml) were added to this reaction mixture. After 2 h at room temperature, the EtOH was evaporated off and the water phase obtained was diluted with THF (10 ml). This solution was treated with $NaIO_4$ (1 g) at room temperature. After 75 min of stirring, the reaction mixture was diluted with Et_2O, and dried with Na_2SO_4. Evaporation of the solvent afforded a residue (crude aldehyde). The acetone solution (20 ml) of this aldehyde was treated with the Jones reagent (1 ml) at room temperature for 20 min. The reaction mixture was quenched with iso-PrOH, and excess Et_2O was added, affording a blue precipitate. After removal of the precipitate by filtration, the filtrate was evaporated to dryness, yielding an oil, which was esterified with CH_2N_2 in Et_2O. Evaporation of the Et_2O gave a residue, which was chromatographed on silica gel (5 g). Elution with benzene to 1% EtOAc in benzene (v/v) afforded 78 mg of **12**. IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.54 (3H, s, Me), 3.55 (3H, s, Me). MS *m/e*: 200 (M^+), 169, 168, 141, 140, 127. $[\alpha]_D^{23}$ −45.7° (c=1, MeOH).

Methyl (+)-(1*R*,2*S*)-2-Methoxycarbonylcyclopentaneacetate (13b)——A mixture of 70 mg of **12** in MeOH (20 ml) and 3.62% NaOMe in MeOH (5 ml) was allowed to stand at room temperature for 1 h and then heated at reflux for 15 min. After cooling, the reaction mixture was quenched with AcOH and concentrated to small volume. The residue obtained was partitioned with brine and EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. The evaporation of the solvent gave a residue, which was chromatographed over silica gel (4 g). Elution with a gradient of 80% benzene in hexane (v/v) to benzene afforded 41 mg of **13b**. IR (neat): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (3H, s, Me), 3.59 (3H, s, Me). MS *m/e*: 200 (M^+), 169, 168, 141, 140. $[\alpha]_D^{23}$ +44.8° (c=1, $CHCl_3$).

Methyl (+)-(1*S*,2*R*,3*R*,5*R*)-3-(Tetrahydropyran-2-yl)oxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-carboxylate (14)——Dihydropyran (30 ml) and then a catalytic amount of picric acid were added to a solution of **2a** (12.4 g) in benzene (50 ml). The reaction mixture was allowed to stand at room temperature for 135 min, then treated with dil. $NaHCO_3$ solution and extracted with EtOAc. The extracts were washed with brine and dried with Na_2SO_4. Evaporation of the solvent gave a residue, which was chromatographed over alumina (GIII, 120 g). Elution with a gradient of hexane to 40% EtOAc in hexane (v/v) afforded 16.7 g of **14**. IR (neat): 1738, 1025, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s, Me), 3.90 (4H, s, OCH_2CH_2O), 4.62 (1H, br, OCHO). MS *m/e*: 326 (M^+), 298, 295, 241, 224. $[\alpha]_D^{23}$ +9.0° (c=1, MeOH).

(−)-(1*S*,2*S*,3*R*,5*R*)-3-(Tetrahydropyran-2-yl)oxy-7,7-ethylenedioxybicyclo[3.3.0]octane-2-methanol (15)——$LiAlH_4$ (4 g) was added to the ester (**14**; 19.1 g) in Et_2O (500 ml) at room temperature. The reaction mixture was stirred at room temperature for 70 min and quenched with 4% NaOH solution (16 ml). The precipitate was filtered off and the filtrate was evaporated to dryness to afford an oily residue, which was purified by column chromatography over silica gel (170 g). Elution with a gradient of 50% EtOAc in hexane (v/v) to EtOAc yielded 14.8 g of **15** as an oil. IR (neat): 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.82 (4H, s, OCH_2CH_2O), 4.55 (1H, br, OCHO). MS *m/e*: 299 (M^++1), 215, 213, 198, 197, 179. $[\alpha]_D^{23}$ −22.8° (c=1, MeOH).

(+)-(1*S*,2*R*,3*R*,5*R*)-2-(3-Oxooct-1(*E*)-enyl)-3-(tetrahydropyran-2-yl)oxy-7,7-ethylenedioxybicyclo[3.3.0]octane (16)——A solution of pyridine–SO_3 complex (12 g) in DMSO (80 ml) was added to a mixture of the alcohol **15** (2.88 g) in dimethyl sulfoxide (DMSO) (115 ml) and Et_3N (43 ml) under vigorous stirring at room temperaure. After being stirred for 30 min, the reaction mixture was poured into ice-water mixture and extracted with EtOAc. The extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude aldehyde. A solution of the aldehyde in ether (15 ml) was treated with tributyl 2-oxo-heptylidenephosphorane (3.2 g). After being stirred for 2 h at room temperature the reaction mixture was evaporated to dryness. The residue was purified by column chromatography over neutral alumina (GII, 120 g). Elution with 2% EtOAc in hexane (v/v) afforded 2.92 g of **16** as an oil. IR (neat): 1685, 1670, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (4H, s, OCH_2CH_2O), 4.65 (1H, br, OCHO). MS *m/e*: 308 (M^+ − 84), 291, 290, 264. $[\alpha]_D^{23}$ +16.1° (c=1, MeOH).

(+)-(1*S*,2*R*,3*R*,5*R*)-2-(3-Hydroxyoct-1(*E*)-enyl)-3-(tetrahydropyran-2-yl)oxy-7,7-ethylenedioxybicyclo-

[3.3.0]octane (17)——$NaBH_4$ (500 mg) was added to the enone (**16**; 2.70 g) in MeOH (40 ml) under ice-water cooling. After 1.5 h of stirring, the excess reagent was decomposed by adding acetic acid, and the reaction mixture was diluted with brine and extracted with EtOAc. The extracts were washed with brine and dried with Na_2SO_4. Evaporation of the solvent gave a residue, which was chromatographed over silica gel (30 g). Elution with 10% EtOAc in hexane (v/v) afforded 2.64 g of oily **17**. IR (neat): 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, Me), 3.90 (4H, s, OCH_2CH_2O), 4.67 (1H, br, OCHO), 5.58 (2H, m, CH=CH). MS *m/e*: 292 ($M^+ - 102$), 274, 190. $[\alpha]_D^{23}$ +3.1° (*c*=1, MeOH).

(−)-(1*S*,2*R*,3*R*,5*R*)-2-(3(*S*)-Hydroxyoct-1(*E*)-enyl)-7-oxobicyclo[3.3.0]octan-3-ol (18) and (−)-(1*S*,2*R*,3*R*,5*R*)-(3(*R*)-Hydroxyoct-1(*E*)-enyl)-7-oxobicyclo[3.3.0]octan-3-ol (19)——Water (6 ml) and then conc. hydrochloric acid (1 ml) were added to a solution of **17** (2.64 g) in acetone (20 ml) under ice cooling. The reaction mixture was stirred at 3 °C for 195 min, and then neutralized with sat. $NaHCO_3$ solution. Evaporation of the acetone afforded an aqueous residue, which was saturated with potassium sodium tartrate and extracted with EtOAc. The extracts were washed with sat. potassium sodium tartrate solution and dried with Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography over silica gel. Elution with 50—60% EtOAc in hexane (v/v) afforded 527 mg of **19** and then elution with 60—80% EtOAc in hexane (v/v) gave 789 mg of **18** as an oil. **18**: IR (nest): 3380, 1733 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, Me), 5.50 (2H, m, CH=CH). MS *m/e*: 248 ($M^+ - 18$), 230, 204, 178. $[\alpha]_D^{23}$ −11.5° (*c*=1, MeOH). **19**: IR (neat): 3380, 1732 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, Me), 5.61 (2H, m, CH=CH). MS *m/e*: 248 ($M^+ - 18$), 230, 204, 178. $[\alpha]_D^{23}$ −31.0° (*c*=1, MeOH).

(−)-(1*S*,2*R*,3*R*,5*R*)-2-[3(*S*)-Tetrahydropyran-2-yl)oxyoct-1(*E*)-enyl]-3-(tetrahydropyran-2-yl)oxybicyclo-[3.3.0]octan-7-one (20)——A catalytic amount of *p*-TsOH was added to a mixture of **18** (115 mg) in CH_2Cl_2 (5 ml) and dihydropyran (0.2 ml) under ice cooling. After 45 min, the reaction mixture was neutralized with sat. $NaHCO_3$ solution, diluted with brine, and extracted with Et_2O. The extracts were washed with brine and dried with Na_2SO_4. Evaporation of the solvent afforded a gummy residue, which was purified by column chromatography over neutral alumina (GII, 20 g). Elution with 20—30% Et_2O in hexane (v/v) gave 184 mg of **20** as an oil. IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, Me), 4.76 (2H, br, OCHO), 5.50 (2H, m, CH=CH). MS *m/e*: 332 ($M^+ - 102$), 279, 248, 222, 220. $[\alpha]_D^{23}$ −28.2° (*c*=1, $CHCl_3$).

(5*E*,*Z*)-9(*O*)-Methanoprostacyclin Methyl Ester 11,15-Bis(tetrahydropyran-2-yl) Ether (21)——A solution of sodium methylsulfinylmethide (prepared from 357 mg of 55% NaH in oil and 60 ml of DMSO) was treated with 2.01 g of (4-carboxybutyl)triphenylphosphonium bromide at 15—20 °C. After 30 min of stirring, the resulting red-colored solution was treated with 180 mg of **20** in DMSO (10 ml). The reaction mixture was stirred at room temperature overnight, diluted with water, acidified with AcOH, and extracted with Et_2O. The extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was esterified with diazomethane in Et_2O to afford a gummy residue. This residue was chromatographed over silica gel (20 g). Elution with 2—3% Et_2O in hexane (v/v) gave 97 mg of an oily product (**21**). IR (neat): 1742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, Me), 3.66 (3H, s, Me), 4.70 (2H, br, OCHO), 5.40 (2H, m, CH=CH). MS *m/e*: 430 ($M^+ - 102$), 386, 346, 328, 302. $[\alpha]_D^{23}$ +12.2° (*c*=1, $CHCl_3$).

(+)-(5*E*,*Z*)-9(*O*)-Methanoprostacyclin Methyl Ester (22)——A mixture of **21** (1.940 g) in AcOH (14 ml) and water (14 ml) was stirred at 30—40 °C for 24 h. The reaction mixture was quenched with brine, made basic with $NaHCO_3$, and extracted with EtOAc. The extracts were washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (40 g). Elution with 70% EtOAc in hexane (v/v) gave 514 mg of **22** as an oil. IR (neat): 3350, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.75 (3H, s, Me), 5.22 (1H, br t, –CH=), 5.45 (2H, m, CH=CH). MS *m/e*: 346 ($M^+ - 18$), 328, 315, 314, 302. $[\alpha]_D^{23}$ +60.0° (*c*=1, $CHCl_3$).

(−)-(5*E*)-9(*O*)-Methanoprostacyclin Methyl Ester 11,15-Diacetate (24) and (+)-(5*Z*)-9(*O*)-Methanoprostacyclin Methyl Ester 11,15-Diacetate (23)——A solution of **22** (380 mg) in pyridine (3 ml) and Ac_2O (1.5 ml) was allowed to stand at 3 °C overnight. The excess reagent was decomposed by addition of water, and extracted with EtOAc. The extracts were washed with brine and dried with Na_2SO_4. Removal of the solvent gave a residue, which was chromatographed over silica gel (50 g). Elution with 7—9% EtOAc in hexane (v/v) gave 20 mg of **23** (oil), elution with 10—11% EtOAc in hexane (v/v) gave a mixture of **23** and **24** (225 mg), and then elution with 12—14% EtOAc in hexane yielded 188 mg of **24** as an oil. **23**: IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, Me), 1.95 (3H, s, Me), 1.98 (3H, s, Me), 3.60 (3H, s, Me), 4.65 (1H, m, =CH–), 5.0—5.6 (4H, m, CH=CH, >CHOAc×2). MS *m/e*: 388 ($M^+ - 60$), 346, 328, 297, 271. $[\alpha]_D^{23}$ −10.8° (*c*=1, $CHCl_3$). **24**: IR (neat): 1740 cm^{-1}. ^{1}H-NMR δ: 0.86 (3H, t, Me), 1.96 (3H, s, Me), 2.06 (3H, s, Me), 3.61 (3H, s, Me), 4.62 (1H, m, =CH–), 5.0—5.6 (4H, m, CH=CH, >CHOAc×2). MS *m/e*: 388 ($M^+ - 60$), 346, 328, 297, 271. $[\alpha]_D^{23}$ +13.0° (*c*=1, $CHCl_3$).

(+)-9(*O*)-Methanoprostacyclin (1a)——A mixture of **24** (290 mg) and 5% KOH in 30% H_2O–MeOH (10 ml) was stirred at room temperature for 2 h. The reaction mixture was diluted with brine, acidified with AcOH and extracted with EtOAc. The extracts were dried with Na_2SO_4. Evaporation of the solvent afforded a residue, which was purified by chromatography over acid-washed silica gel (3 g). Elution with 50% EtOAc in benzene (v/v) gave 216 mg of **1a**. Recrystallization from EtOAc–hexane mixture afforded a pure sample, mp 60—61 °C. IR ($CHCl_3$): 3350, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, Me), 3.70 (1H, br, >CHOH), 4.05 (1H, br, >CHOH), 5.28 (1H, m, =CH–), 5.55

(2H, m, CH=CH). MS *m/e*: 332 ($M^+ - 18$). *Anal.* Calcd for $C_{21}H_{34}O_4$: C, 71.76; H, 9.78. Found: C, 71.88; H, 9.64. $[\alpha]_D^{23}$ +74.0 ($c=1$, $CHCl_3$). Lit.:[6d] mp 62.4—63.3 °C, $[\alpha]_D$ +90° ($c=0.810$, MeOH).

(+)-(5*Z*)-9(*O*)-Methanoprostacyclin (1b)——A mixture of **23** (50 mg) and 5% KOH in 30% H_2O–MeOH (v/v, 3 ml) was stirred at room temperature for 2 h. Treatment as described for the synthesis of **1a** gave a crystalline residue (43 mg), which was recrystallized from EtOAc–hexane mixture to yield 35 mg of **1b**, mp 104—106 °C. IR ($CHCl_3$): 3350, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, Me), 3.70 (1H, br, >CHOH), 4.05 (1H, br, >CHOH), 5.25 (1H, m, =CH–), 5.53 (2H, m, CH=CH). MS *m/e*: 332 ($M^+ - 18$). *Anal.* Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.78; H, 9.65. $[\alpha]_D^{23}$ +71.2° ($c=1$, $CHCl_3$). Lit.:[6d] mp 107.5—108.8 °C, $[\alpha]_D$ +39° ($c=0.866$, MeOH).

(−)-*ent*-9(*O*)-Methanoprostacyclin (1c)——IR ($CHCl_3$): 3350, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, Me), 3.70 (1H, br, >CHOH), 4.05 (1H, br, >CHOH), 5.28 (1H, m, =CH–), 5.55 (2H, m, CH=CH). *Anal.* Calcd for $C_{21}H_{30}O_4$: C, 71.76; H, 9.78. Found: C, 71.83; H, 9.70. $[\alpha]_D^{23}$ −68.5° ($c=1$, $CHCl_3$). mp 59 °C.

(−)-(5*Z*)-*ent*-9(*O*)-Methanoprostacyclin (1d)——IR ($CHCl_3$): 3350, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, Me), 3.70 (1H, br, CHOH), 4.05 (1H, br, >CHOH), 5.25 (1H, m, =CH–), 5.53 (2H, m, CH=CH). *Anal.* Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.88; H, 9.69. mp 103—105 °C. $[\alpha]_D^{23} = -65.4°$ ($c=0.90$, $CHCl_3$).

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References and Notes

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