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Conversion of Methylenomycin A to Prostaglandin Analogues

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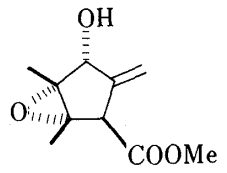
Methylenomycin A (**3a**) was converted to 10α,11β-dimethyl-prostaglandin E_2 (PGE_2) (**23**), -$PGF_{2\alpha}$ (**27**), -$PGF_{2\beta}$ (**28**) and -PGA_2 (**29**).

Keywords——cleavage of α,β-epoxyalcohol; Wittig reaction; prostaglandin; cyanation; epoxy ketone; methylenomycin A; absolute configuration; boron trifluoride

Methylenomycin A (**3a**)[1] is an antibiotic which was isolated from a strain of *Streptomyces vioraceoruber*, and seems to possess convenient functional groups for the synthesis of prostaglandin (PG) analogues. For example, the exo-methylene group conjugated to the cyclopentanone is suggestive of the introduction of the α-chain by 1,4-addition, and the α,β-epoxide and carboxyl function seem appropriate for the introduction of the α-hydroxy group at the C_{11} position (PG numbering) and the ω-chain, respectively.

In addition to these advantages, the absolute stereochemistry of methylenomycin A (**3a**)[2] was found to be favorable for the synthesis of PG analogues based on the fundamental structure of prostanoic acid. In a preliminary experiment (Chart 1), we succeeded in the conversion of the α,β-epoxyalcohol (**1**) to the β-ketol (**2**) by treatment with boron trifluoride (BF_3) etherate. As exemplified in Corey's PG synthesis,[3] one of the known methods for the introduction of the ketone function at the C_9 position is based on oxidation of the corresponding alcohol, and there is no precedent for the synthesis of PGE (β-ketol) by cleavage of the α,β-epoxy alcohol. Therefore, this conversion reaction represents a new approach to the synthesis of PGs and PG analogues. On the basis of this finding, we have investigated the conversion of methylenomycin A (**3a**) to PG analogues.



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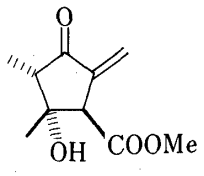

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Chart 1

In order to avoid the cycloaddition of CH_2N_2 to the α,β-unsaturated ketone, **3a** was esterified by treatment with CH_3I in the presence of $KHCO_3$ in dimethylformamide (DMF), and the ester was obtained in 90% yield. Previously, Stork *et al.*,[4] succeeded in the direct introduction of the α-chain by 1,4-addition to the exo-methylene cyclopentanone using lithium divinyl cuprate. However, as methylenomycin A methyl ester (**3b**) seemed to be insufficiently stable under these reaction conditions, we investigated the stepwise introduction

of the α-chain.

Reaction of **3b** with acetone cyanohydrin in the presence of Na_2CO_3 in CH_3CN at room temperature afforded the cyanomethyl ketone (**4**) in quantitative yield. Although **4** gave a single spot on thin-layer chromatography (TLC, AcOEt–hexane 2 : 1), reduction of **4** with $NaBH_4$ afforded a mixture of three isomeric alcohols in 84% yield. Therefore, it seems reasonable to assume that **4** consisted of a mixture of the $C_2\alpha$- and $C_2\beta$-cyanomethyl functions. The mixture of three isomeric alcohols was first separated by column chromatography into the less polar fraction (the *cis*, *cis* alcohol **6**) eluted with 7.0—20% AcOEt in benzene (v/v) and the polar fraction (a mixture of the *cis*, *trans* alcohol **5** and *trans*, *cis* alcohol **7**) eluted with 25—35% AcOEt in benzene (Chart 2).

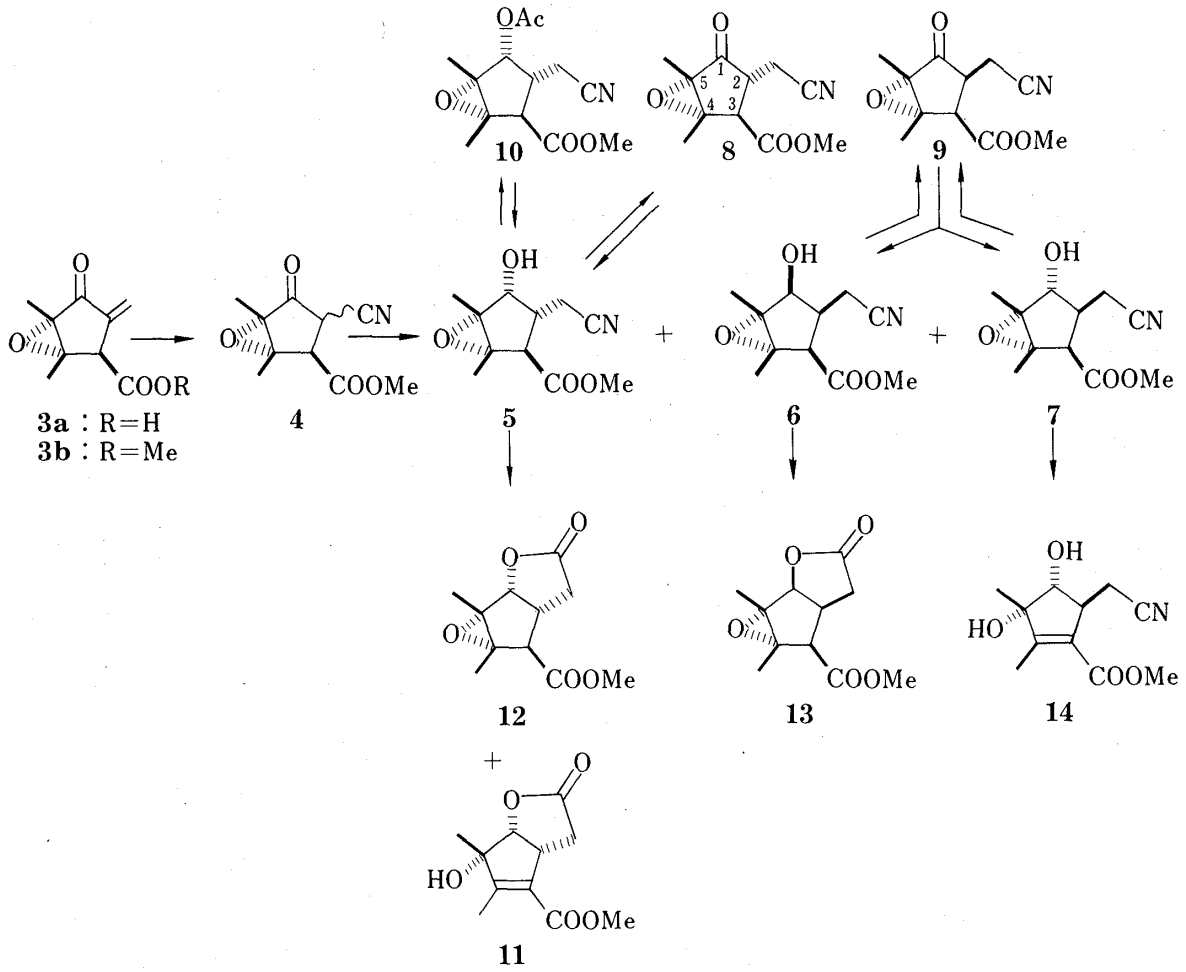

Chart 2

The polar fraction showed two adjacent spots (*Rf* 0.5 and 0.6) on TLC (AcOEt–hexane 1 : 2), and it was difficult to separate the components by column chromatography. However, recrystallization of the acetates was very effective for the separation. Acetylation of the polar fraction with Ac_2O/pyridine afforded a mixture of the acetates as colorless crystals, from which the pure acetate (**10**), mp 77 °C, was isolated by several recrystallizations from AcOEt–hexane. Hydrolysis of **10** with K_2CO_3 in MeOH yielded the desired *cis*, *trans* alcohol (**5**) having *Rf* 0.5. Attempts to isolate the acetate of the undesired *trans*, *cis* alcohol (**7**) having *Rf* 0.6 from the mother liquor were unsuccessful.

The *trans*, *cis* alcohol (**7**, *Rf* 0.6) was obtained as follows. Jones oxidation of the less polar fraction (**6**) yielded the cyanomethyl ketone (**9**), which was reduced with $NaBH_4$ to afford two

epimeric alcohols, the *trans, cis* alcohol (**7**) and the *cis, cis* alcohol (**6**). These alcohols could be separated by column chromatography on silica gel. The α-cyanomethyl ketone (**8**) was obtained by Jones oxidation of **5**. Reduction of **8** with $NaBH_4$ yielded **5** as a sole product, and no other isomeric alcohol was detected. This stereospecific reduction suggests that the α-site of the five-membered ring ketone in **8** is sterically hindered by the α-epoxide and the $C_2\alpha$–cyanomethyl function. The fact that reduction of **4** with $NaBH_4$ yielded three isomeric alcohols may be rationalized on the basis of the above results in the reduction of **8** and **9**.

In the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **8** and **9**, the C_3–hydrogen (*R*-configuration) signal in **8** was observed at δ 3.27 as a broad singlet. This indicates that the bond angle of C_2–H and C_3–H is approximately 90 °. Consideration of a cpk molecular model suggested that the configuration of the C_2–hydrogen should be β. Accordingly, the cyanomethyl group at the C_2 position should be assigned as *trans* relative to the $C_3\beta$–methyl ester. On the other hand, the signal of the C_3–hydrogen in **9** was observed at δ 3.67 as a doublet ($J=8$ Hz), suggesting $C_2\alpha$–hydrogen, and hence the C_2–cyanomethyl function is considered to be *cis* relative to the $C_3\beta$–methyl ester.

The configuration of the C_1–alcohol in **5** was established as follows. By treatment with K_2CO_3 in MeOH for 0.5 h, **5** was easily converted in 56% yield to the epoxy γ-lactone (**12**) and hydroxy γ-lactone (**11**). The easy formation of the γ-lactone suggests that the C_1–alcohol is *cis* relative to the $C_2\alpha$–cyanomethyl group. In a similar manner, **6** was also converted in 61% yield to the corresponding γ-lactone (**13**), suggesting that the C_1–alcohol in **6** is *cis* relative to the $C_2\beta$–cyanomethyl group, but the hydroxy lactone corresponding to **11** was not detected. Therefore, the cleavage of the α-epoxide in **12** seems to be induced by the repulsion between the α-epoxide and the γ-lactone located at the α-site. The *trans, cis* alcohol (**7**) underwent cleavage of the epoxide under similar reaction conditions, and the γ-lactone was not obtained. Hence, it is concluded that the configuration of the C_1–alcohol in **7** is α and *trans* relative to the $C_2\beta$–cyanomethyl group.

Thus, among the three epimeric alcohols, **5**, **6** and **7**, the *cis, trans* alcohol (**5**) was found to be preferable for the synthesis of PG analogues. The ketone (**9**), which was obtained by Jones oxidation of the undesired alcohols **6** and **7**, could be recycled through an easy epimerization to **4** with triethylamine.

Next, our attention was directed to a synthesis of 10α,11β-dimethyl-PGE_2 from **5**. In order to avoid any side reaction, the hydroxy group in **5** was protected with an α-ethoxyethyl function, which was easily removable under mild acidic conditions. The ester and the nitrile in the α-ethoxyethyl ether (**15**) were concurrently reduced with diisobutylaluminum hydride (DIBAL-H) to yield the aldehyde alcohol (**16**). Wittig reaction of **16** with (4-sodiocarboxybutylidene)triphenylphosphorane proceeded smoothly to afford, in 42% yield from **15**, the alcohol (**17**), which was esterified with CH_2N_2. The introduction of the ω-chain, as well as that of the α-chain, proceeded without any difficulties. By Collins oxidation, followed by treatment with 2-oxoheptylidene-tributylphosphorane, **17** was converted to the enone **19** in 40% yield (Chart 3). Treatment with $NaBH_4$ in MeOH, aq. AcOH in tetrahydrofuran (THF) and 5% NaOH in MeOH then provided the crystalline epoxide (**22**), mp 75 °C, in 64% yield from **19**. An inseparable mixture of the C_{15}-epimers of **22** was subjected to cleavage of the epoxide with BF_3-etherate. As in the preliminary experiment, treatment of **22** with BF_3-etherate at 3—5 °C afforded in 73% yield the desired β-ketol, which could be separated to the $C_{15}\alpha$–OH (**23**) and $C_{15}\beta$–OH (**24**) by careful column chromatography on silica gel. Thus, 10α,11β-dimethyl-PGE_2 (**23**) was synthesized by the new method *via* the cleavage of an α,β-epoxy alcohol.

The configuration of the C_{15}–alcohol was tentatively assigned according to a general rule in PG chemistry, *i.e.*, the $C_{15}\alpha$–OH configuration was assigned to the more polar fraction and the $C_{15}\beta$–OH configuration to the less polar fraction on TLC. The configuration of the $C_{10}\alpha$–

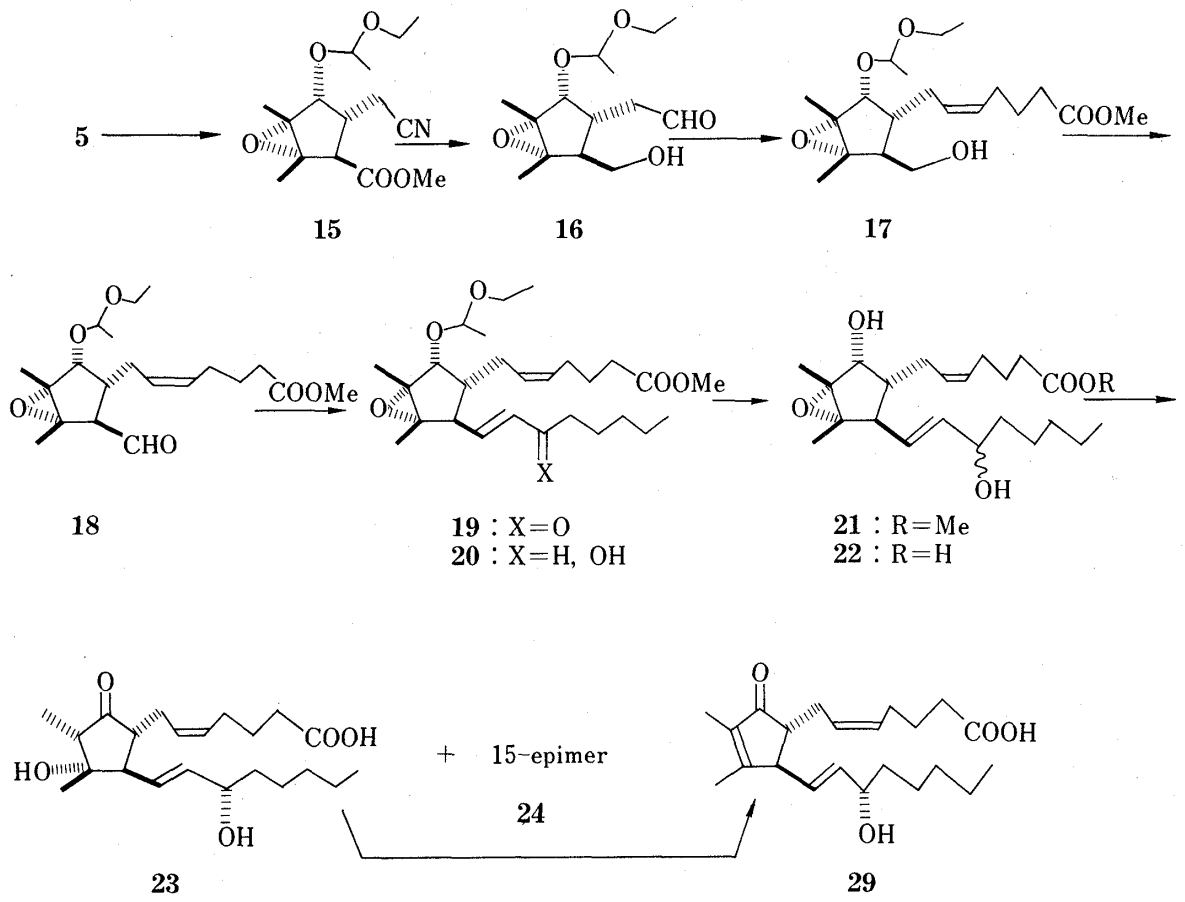

Chart 3

methyl group will be discussed in connection with the synthesis of 10α,11β-dimethyl-$PGF_{2\alpha}$.

10α,11β-Dimethyl-PGE_2 methyl ester (**25**) was reduced with a bulky reducing agent, potassium tri-*sec*-butylborohydride (K-selectride) in THF at 3—5 °C. Unexpectedly, the 9,11-diol was not obtained, but a stable, cyclic *sec*-butyl boronate ester (**26**) was isolated. The structure of **26** was deduced from the appearance of the methyl signal due to the secondary butyl group in the ^{1}H-NMR spectrum and a weak absorption in the alcohol region (3400—3500 cm^{-1}) in the infrared (IR) spectrum. A concurrent hydrolysis of the methyl ester and boronate ester in **26** with 5% NaOH afforded, in 70% yield from **25**, 10α,11β-dimethyl-$PGF_{2\alpha}$ (**27**), mp 106 °C, as colorless needles. Isolation of the cyclic boronate ester (**26**) supports the conclusion that the configuration of the C_9–alcohol is α, as in natural PGs. This stereospecific reduction by a bulky reducing agent seems to be caused by the steric hindrance arising from the C_{10}α–methyl and the α-chain located at the C_8α-position. In this reduction, the C_9β–alcohol (**28**) was not detected. Reduction of **25** with $NaBH_4$ in MeOH yielded two isomeric alcohols which were separated by preparative TLC into the more polar fraction and the less polar fraction. The less polar fraction afforded **27** on hydrolysis with 5% NaOH. Therefore, the isomeric alcohol (**28**) obtained by similar hydrolysis of the more polar fraction should be 10α,11β-dimethyl-$PGF_{2\beta}$. The ^{1}H-NMR spectra of **27** and **28** showed signals attributable to the C_9–carbinolic proton at δ 3.97 and 3.55, respectively. It is known that, in the ^{1}H-NMR spectrum[5] of a five-membered ring, when a ring hydroxy group is *cis* relative to a vicinal substituent, the carbinolic proton is observed at lower field than in the case of the *trans* configuration. As the C_9–hydrogen in **27** was observed at lower field (δ 3.97) than that (δ 3.55) in **28**, the C_{10}–methyl group in **27** should be assigned as *cis* relative to the C_9α–alcohol. Thus,

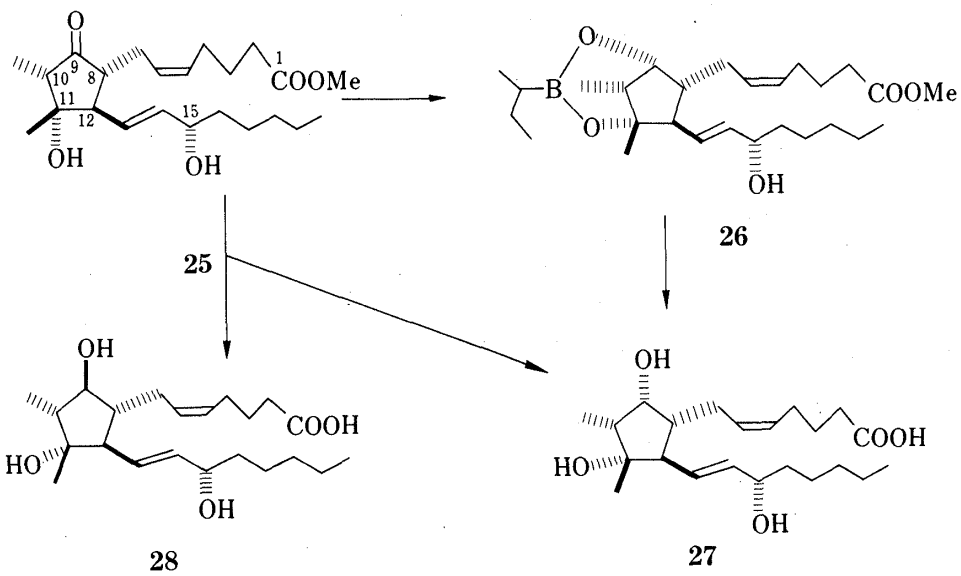

Chart 4

the configuration of the C_{10}–methyl group was determined to be α (Chart 4).

Treatment of **23** with 5% Na_2CO_3 in MeOH at room temperature for 1 h afforded 10,11-dimethyl-PGA_2 (**29**) as a colorless oil in 60% yield. Although PGA_2, obtained by the dehydration of PGE_2 under basic conditions, is unstable and easily converted to PGB_2, 10,11-dimethyl-PGA_2 is stable, as expected, and 10,11-dimethyl-PGB_2 was not detected under the reaction conditions employed.

The biological activities of 10,11-dimethyl-PGs will be reported in a separate paper.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were taken on a Jasco IRA-2 spectrometer, ^{1}H-NMR spectra on a Varian T-60, and mass spectra on a JEOL 01SG. For column chromatography, Kanto Chemical silica gel (60—100 mesh) was used. Thin layer chromatography was carried out on Silica gel 60 F_{254} plates (Merck). Optical rotations were measured with a Perkin-Elmer model 141 polarimeter. Water saturated with NaCl was used as washing water, and anhydrous sodium sulfate was used as a drying agent.

(3*R*,4*R*,5*S*)-4,5-Dimethyl-4-hydroxy-3-methoxycarbonyl-2-methylene-1-cyclopentanone (2)——BF_3-etherate (0.5 ml) was added dropwise to a stirred solution of 1 (3.02 g) in CH_2Cl_2 (60 ml) at room temperature. The reaction mixture was stirred for 0.5 h, diluted with ice water (50 ml), and extracted with ether (50 ml × 3). The combined extract was washed with H_2O (100 ml × 2) and dried. Removal of the solvent afforded an oily residue which was subjected to column chromatography on silica gel (30 g). The fraction eluted with 10—20% AcOEt in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo* to afford **2** (2.68 g, 89%) as a colorless oil. IR (neat): 3510, 1740, 1650, 1200, 1180, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d, J=7 Hz, C_5–Me), 1.43 (3H, s, C_4–Me), 2.12 (1H, s, C_3–H), 2.80 (1H, q, J=7 Hz, C_5–H), 5.57 (1H, s, olefinic H), 6.30 (1H, s, olefinic H). *Anal.* Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.62; H, 7.19.

Methylenomycin A Methyl Ester (3b)——$KHCO_3$ (24.40 g) and MeI (68 ml) were added to a stirred solution of methylenomycin A (**3a**) (40.31 g) in DMF (800 ml) under ice water cooling. The mixture was stirred for 4 h at room temperature, then poured into H_2O (1.2 l) satd. with NaCl and extracted with AcOEt (500 ml × 3). The combined extract was washed with H_2O (300 ml × 2) and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (200 g). The fraction eluted with 5—30% AcOEt in hexane (v/v) was collected, and removal of the solvent *in vacuo* afforded **3** (38.90 g, 90%) as a colorless oil. IR (neat): 1740, 1645, 1320, 1165 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s, Me), 1.55 (3H, s, Me), 3.70 (3H, s, COOMe), 3.85 (1H, s, C_3–H), 5.60 (1H, d, J=2 Hz, olefinic H), 6.24 (1H, d, J=2 Hz, olefinic H). *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.11; H, 6.03.

(2ξ,3*R*,4*S*,5*S*)-2-Cyanomethyl-4,5-epoxy-3-methoxycarbonyl-4,5-dimethyl-1-cyclopentanone (4)——Acetone

cyanohydrin (17.84 g) and 10% Na_2CO_3 (10 ml) were added to a stirred solution of **3** (38.81 g) in CH_3CN (800 ml) under ice water cooling. The reaction mixture was stirred for 7 h at room temperature, then poured into ice water (1.50 l) and extracted with AcOEt (1 l×2). The combined extract was washed with H_2O (400 ml×2) and dried. Removal of the solvent *in vacuo* afforded an oily residue which was subjected to column chromatography on silica gel (200 g). The fraction eluted with 5—20% AcOEt in hexane (v/v) was collected, and removal of the solvent afforded **4** (41.00 g, quantitative) as a colorless oil. IR (neat): 2250, 1750, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, s, Me), 1.52 (3H, s, Me), 3.80 (3H, s, COOMe). *Anal.* Calcd for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.22; H, 5.83; N, 6.41.

(1*R*,2*R*,3*R*,4*S*,5*R*)-2-Cyanomethyl-4,5-epoxy-3-methoxycarbonyl-4,5-dimethyl-1-cyclopentanol (5), Its Acetate (10) and (1*S*,2*S*,3*R*,4*S*,5*R*)-2-Cyanomethyl-4,5-epoxy-3-methoxycarbonyl-4,5-dimethyl-1-cyclopentanol (6)——$NaBH_4$ (7.2 g) was added portionwise to a stirred solution of **4** (41.03 g) in MeOH (800 ml) at less than 10 °C. The reaction mixture was stirred for 0.5 h at the same temperature, poured into ice water (3 l), made acidic with 5% HCl, and extracted with AcOEt (1 l×3). The combined extract was washed with H_2O (1 l×2) and dried. Removal of the solvent *in vacuo* afforded an oily residue which was subjected to column chromatography on silica gel (500 g). The less polar fraction, eluted with 7—20% AcOEt in benzene (v/v), afforded **6** (18.61 g, 44%) as a colorless oil, and the polar fraction, eluted with 25—35% AcOEt in benzene (v/v), afforded a mixture (16.22 g, 40%) of **5** (*Rf* 0.5, AcOEt–hexane 1:2) and **7** (*Rf* 0.6, the same solvent system) as a colorless oil. The less polar fraction **6**: $[\alpha]_D^{25}$ +107.3° (c=1.76, $CHCl_3$). IR (neat): 3450, 2250, 1735, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36, (3H, s, Me), 1.48 (3H, s, Me), 3.27 (1H, d, J=7 Hz, C_3–H), 3.81 (3H, s, COOMe), 4.05 (1H, d, J=6 Hz, C_1–H). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.73; H, 6.80; N, 6.33.

Ac_2O (2.5 ml) was added to a stirred solution of the polar fraction (2.32 g) in pyridine (5 ml) under ice water cooling. After being stirred for 2 h at room temperature, the reaction mixture was poured into ice water (50 ml) and extracted with AcOEt (50 ml×3). The combined extract was washed with H_2O (50 ml×2), 5%HCl (20 ml×2) and H_2O again (50 ml×2), then dried. Removal of the solvent *in vacuo* afforded a crystalline residue which was recrystallized from AcOEt–hexane to provide **10** (1.43 g, 52%) as colorless needles, mp 75—77 °C. $[\alpha]_D^{25}$ +92.0° (c=1.39, $CHCl_3$). IR (Nujol): 2220, 1730, 1223 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (6H, s, Me×2), 2.17 (3H, s, OCOMe), 3.07 (1H, s, C_3–H), 3.78 (3H, s, COOMe), 5.57 (1H, d, J=7 Hz, C_1–H). *Anal.* Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.33; H, 6.32; N, 5.36.

K_2CO_3 (100 mg) was added to a stirred solution of **10** (580 mg) in MeOH (50 ml) under ice water cooling. The mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with H_2O (200 ml) satd. with NaCl and extracted with AcOEt (100 ml×3). The combined extract was washed with H_2O (100 ml×2), satd. with $(NH_4)_2SO_4$ and dried. The solvent was evaporated off *in vacuo*, to leave an oily residue (503 mg), which was subjected to column chromatography on silica gel (20 g). The fraction eluted with 5—30% AcOEt in benzene (v/v) was collected, and removal of the solvent *in vacuo* afforded **5** (317 mg, 64%) as a colorless oil. $[\alpha]_D^{25}$ +65.1° (c=2.08, $CHCl_3$). IR (neat): 3460, 2240, 1730, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s, Me), 1.42 (3H, s, Me), 3.08 (1H, s, C_3–H), 3.76 (3H, s, COOMe). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.41; H, 6.59; N, 6.10.

(2*S*,3*R*,4*S*,5*S*)-2-Cyanomethyl-4,5-epoxy-3-methoxycarbonyl-4,5-dimethyl-1-cyclopentanone (9)——Jones reagent (39 ml) was added dropwise to a stirred solution of **6** (23.74 g) in acetone (400 ml) at 5—10 °C. After 1 h, isopropanol (5 ml) was added to decompose excess reagent. The reaction mixture was poured into ice water (1 l), and extracted with ether (300 ml×3). The combined extract was washed with H_2O (200 ml×2) and dried. The solvent was evaporated off *in vacuo* to afford an oily residue (23.21 g), which was subjected to column chromatography on silica gel (200 g). The fraction eluted with 3—7% AcOEt–hexane (v/v) was evaporated to dryness *in vacuo* to afford **9** (14.24 g, 60%) as a colorless oil. $[\alpha]_D^{25}$ +133.5° (c=2.01, $CHCl_3$). IR (neat): 2240, 1750, 1730, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, s, Me), 1.50 (3H, s, Me), 3.67 (1H, d, J=8 Hz, C_3–H), 3.80 (3H, s, COOMe). *Anal.* Calcd for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.03; H, 5.79; N, 6.22.

(1*R*,2*S*,3*R*,4*S*,5*R*)-2-Cyanomethyl-4,5-epoxy-3-methoxycarbonyl-4,5-dimethyl-1-cyclopentanol (7) and 6——$NaBH_4$ (650 mg) was added portionwise to a stirred solution of **9** (3.83 g) in MeOH (120 ml), at less than 10 °C. After 0.5 h, the reaction mixture was poured into ice water (300 ml), and extracted with AcOEt (200 ml×3). The combined extract was washed with H_2O (200 ml×2) and dried. The solvent was evaporated off *in vacuo* to yield an oily residue (3.81 g), which was subjected to column chromatography on silica gel (50 g). The fraction eluted with 10—30% AcOEt in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo* to afford **6** (3.12 g, 81%) as a colorless oil. The fraction eluted with 30—50% AcOEt in hexane (v/v) afforded **7** (430 mg, 11%, *Rf* 0.6 in AcOEt–hexane 1:1) as colorless needles, mp 78—79 °C. **7**: $[\alpha]_D^{25}$ +161.0° (c=1.92, $CHCl_3$). IR (Nujol): 3400, 2240, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, s, Me), 1.43 (3H, s, Me), 3.80 (3H, s, COOMe), 4.00 (1H, d, J=8 Hz, C_1–H). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.79; H, 6.59; N, 6.18.

(2*R*,3*R*,4*S*,5*S*)-2-Cyanomethyl-4,5-epoxy-3-methoxycarbonyl-4,5-dimethyl-1-cyclopentanone (8)——In a manner similar to that described for **9**, oxidation of **5** (317 mg) yielded **8** (228 mg, 72%) as a colorless oil. $[\alpha]_D^{25}$ +25.4° (c=1.85, $CHCl_3$). IR (neat): 2240, 1750, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, s, Me), 1.50 (3H, s, Me), 3.27 (1H, s, C_3–H), 3.80 (3H, s, COOMe). *Anal.* Calcd for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.39; H,

5.70; N, 6.22.

5 from 8——In a manner similar to that described for **6** and **7**, reduction of **8** afforded **5** as a single product.

(1*R*,5*R*,8*S*)-8-Hydroxy-6-methoxycarbonyl-7,8-dimethyl-2-oxabicyclo[3.3.0]oct-6-ene-3-one (11) and (1*R*,5*R*,6*R*,7*S*,8*R*)-7,8-Epoxy-6-methoxycarbonyl-7,8-dimethyl-2-oxabicyclo[3.3.0]octan-3-one (12)——K_2CO_3 (184 mg) was added to a stirred solution of **5** (295 mg) in MeOH (15 ml). The mixture was stirred for 0.5 h at room temperature, then diluted with H_2O (100 ml) satd. with NaCl, and the whole was extracted with AcOEt (50 ml × 3). The combined extract was washed with H_2O and dried. The solvent was evaporated off *in vacuo*. The crystalline residue (270 mg) was recrystallized from hexane to afford **11** (96 mg, 32%) as colorless needles, mp 147—148 °C. The oily residue obtained from the mother liquor was subjected to column chromatography on silica gel (3 g). The fraction eluted with 30—40% AcOEt in hexane (v/v) was collected, and removal of the solvent *in vacuo* afforded **12** (71 mg, 24%) as a colorless oil. **11**: mp, 147—148 °C. IR (Nujol): 3500, 1787, 1773, 1700, 1690, 1646 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s, Me), 2.12 (3H, s, vinyl Me), 2.80 (2H, m, $COCH_2$), 3.65 (1H, m, C_5–H), 3.80 (3H, s, COOMe), 4.65 (1H, d, J=6 Hz, C_1–H). *Anal.* Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.53; H, 6.11. **12**: IR (neat): 1780, 1730, 1165, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, s, Me), 1.46 (3H, s, Me), 3.73 (3H, s, COOMe), 5.05 (1H, d, J=8 Hz, C_1–H). *Anal.* Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.63; H, 6.14.

(1*S*,5*S*,6*R*,7*S*,8*R*)-7,8-Epoxy-6-methoxycarbonyl-7,8-dimethyl-2-oxabicyclo[3.3.0]octan-3-one (13)——In a manner similar to that described for **11** and **12**, **6** (180 mg) afforded **13** (110 mg, 61%) as a colorless oil. IR (neat): 1780, 1720, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s, Me), 1.45 (3H, s, Me), 3.80 (3H, s, COOMe). *Anal.* Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: H, 58.21; H, 6.11.

(1*R*,2*S*,5*S*)-2-Cyanomethyl-1,5-dihydroxy-3-methoxycarbonyl-4,5-dimethyl-cyclopent-3-ene (14)——In a manner similar to that described for **11** and **12**, **7** (170 mg) afforded **14** (37 mg, 22%) as a colorless oil, but most of **7** was recovered unchanged (117 mg, 68%). IR (neat): 3450, 2250, 1725, 1710, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s, Me), 2.10 (3H, s, vinyl Me), 3.80 (3H, s, COOMe). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found; C, 58.72; H, 6.66; N, 6.31.

(1*R*,2*R*,3*R*,4*S*,5*R*)-2-Cyanomethyl-4,5-epoxy-3-methoxycarbonyl-4,5-dimethyl-cyclopentan-1-yl α-Ethoxyethyl Ether (15)——*p*-Toluenesulfonic acid (50 mg) was added to a stirred solution of **5** (1.03 g) in ethyl vinyl ether (10 ml) at room temperature, and the mixture was stirred for 0.5 h, then poured into 5% $NaHCO_3$ (50 ml). The whole was extracted with AcOEt (50 ml × 2). The combined extract was washed with H_2O (50 ml × 2) and dried. Removal of the solvent *in vacuo* yielded an oily residue (**15**) (1.29 g, 94%), which was reduced with DIBAL-H without purification. IR (neat); 2240, 1740, 1170, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.75 (3H, s, COOMe), 4.80 (1H, m, O–CH–O).

(1*R*,2*R*,3*S*,4*S*,5*R*)-4,5-Epoxy-2-formylmethyl-3-hydroxymethyl-4,5-dimethyl-cyclopentan-1-yl α-Ethoxyethyl Ether (16)——DIBAL-H (120 ml; content 25 g in 100 ml of hexane) was added dropwise to a stirred solution of **15** (19.71 g) in toluene (300 ml) over 0.5 h at 10—15 °C. After completion of the reaction, aq. THF (600 ml, THF–H_2O 3 : 1) was added dropwise under ice water cooling. The reaction mixture was stirred for 2 h, then extracted with AcOEt (200 ml × 3). The combined extract was washed with H_2O (200 ml × 2) satd. with $(NH_4)_2SO_4$, and dried. The solvent was evaporated off *in vacuo* to afford an oily residue (18 g), which was subjected to column chromatography on silica gel (100 g). The fraction eluted with 25—40% AcOEt in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo*, yielding **16** (11.14 g, 62%) as a colorless oil. IR (neat): 3470, 1725, 1250, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.80 (2H, m, $-CH_2O-$), 9.95 (1H, t, J=5 Hz, CHO).

(1*R*,2*R*,3*S*,4*S*,5*R*)-4,5-Epoxy-2-[(*Z*)-6-methoxycarbonyl-2-hexenyl]-4,5-dimethyl-3-hydroxymethylcyclopentan-1-yl α-Ethoxyethyl Ether (17)——(4-Sodiocarboxybutylidene)triphenylphosphorane was prepared by the reaction of (4-carboxybutyl)triphenylphosphonium bromide (54 g) with sodium methylsulfinylmethide, which was prepared from dimethylsulfoxide (DMSO, 450 ml) and NaH (50% content, 10.7 g) in the usual manner. To the above Wittig reagent, a solution of **16** (11.01 g) in DMSO (50 ml) was added dropwise with stirring at room temperature under an Ar atmosphere. The reaction mixture was stirred for 2 h, then poured into ice water (1.5 l) containing 7% HCl (150 ml) and extracted with ether (1.5 l × 4). The combined extract was washed with H_2O (500 ml × 3) and dried. Removal of the solvent *in vacuo* afforded an oily residue (18.11 g) which was esterified with CH_2N_2 in the usual manner and then subjected to column chromatography on silica gel (180 g). The fraction eluted with 60—80% AcOEt in hexane (v/v) was evaporated to dryness *in vacuo* to afford **17** (10.25 g, 68%) as a colorless oil. IR (neat): 3520, 1740, 1380, 1100, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (2H, d, J=6 Hz, $-CH_2O-$), 3.67 (3H, s, COOMe), 4.80 (1H, m, O–CH–O), 5.40 (2H, m, olefinic H). *Anal.* Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.99; H, 9.19.

(1*R*,2*R*,3*R*,4*S*,5*R*)-4,5-Epoxy-2-[(*Z*)-6-methoxycarbonyl-2-hexenyl]-4,5-dimethyl-3-formylcyclopentan-1-yl α-Ethoxyethyl Ether (18)——A solution of **17** (4.53 g) in CH_2Cl_2 (30 ml) was added dropwise to Collins reagent [prepared from pyridine (15.42 g) and CrO_3 (9.77 g)] in CH_2Cl_2 (260 ml) with stirring at 3—5 °C. The mixture was stirred for 0.5 h, then ether (500 ml) was added, and the resulting precipitate was filtered off. The filtrate was washed with H_2O (200 ml × 2) and dried. The solvent was removed *in vacuo* to afford an oily residue (6.11 g), which was subjected to column chromatography on silica gel (60 g). The fraction eluted with 10—30% AcOEt in benzene (v/v) was collected and the solvent was removed *in vacuo* to yield the unstable aldehyde **18** (2.82 g, 62%) as a colorless oil. IR (neat): 2740, 1740, 1380, 1192, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (3H, s, COOMe), 5.40 (2H, m, olefinic H),

9.80 (1H, d, $J=5$ Hz, CHO).

(1*R*,2*R*,3*S*,4*S*,5*R*)-4,5-Epoxy-2-[(*Z*)-6-methoxycarbonyl-2-hexenyl]-4,5-dimethyl-3-[(*E*)-3-oxo-1-octenyl]cyclopentan-1-yl α-Ethoxyethyl Ether (19)——2-Oxoheptylidene-tributylphosphorane (6.17 g) in benzene (20 ml) was added dropwise to a stirred solution of **18** (6.57 g) in benzene (60 ml) at room temperature. After being stirred for 2 h, the reaction mixture was washed with H_2O (50 ml × 2) and dried. Removal of the solvent *in vacuo* afforded an oily residue (13.10 g), which was subjected to column chromatography on silica gel (130 g). The fraction eluted with 10—25% AcOEt in benzene (v/v) was collected, and evaporated to dryness *in vacuo* to afford **19** (5.43 g, 66%) as a colorless oil. IR (neat): 1740, 1700, 1675, 1630, 1380, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.10 (1H, d, $J=16$ Hz, C_{14}–H), 6.63 (1H, dd, $J=16$ Hz, $J=7$ Hz, C_{13}–H). *Anal.* Calcd for $C_{27}H_{44}O_6$: C, 69.79; H, 9.55. Found: C, 69.83; H, 9.62.

(1*R*,2*R*,3*S*,4*S*,5*R*)-4,5-Epoxy-2-[(*Z*)-6-methoxycarbonyl-2-hexenyl]-4,5-dimethyl-3-[(*E*)-3-hydroxy-1-octenyl]cyclopentan-1-yl α-Ethoxyethyl Ether (20)——$NaBH_4$ (1.14 g) was added portionwise to a stirred solution of **19** (5.43 g) in MeOH (150 ml) at 0—5 °C, and the reaction mixture was stirred for 1 h, then diluted with H_2O (200 ml) satd. with NaCl and extracted with AcOEt (150 ml × 3). The combined extract was washed with H_2O (300 ml × 2) and dried. Removal of the solvent *in vacuo* afforded an oily residue (5.88 g), which was chromatographed on silica gel (60 g). The fraction eluted with 10—30% AcOEt in benzene (v/v) was evaporated to dryness *in vacuo* to yield **20** (5.24 g, 96%) as a colorless oil. IR (neat): 3480, 1740, 1200, 1130, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.78 (3H, s, COOMe), 5.30—5.62 (4H, m, olefinic H). *Anal.* calcd for $C_{27}H_{46}O_6$: C, 69.49; H, 9.94. Found: C, 69.71; H, 9.88.

(5*Z*,13*E*)-10α,11α-Epoxy-9α,15-dihydroxy-10β,11β-dimethyl-prost-5,13-dienoic Acid Methyl Ester (21)——The alcohol (**20**) (5.22 g) was dissolved in a mixed solvent (60 ml) of THF–H_2O–AcOH (1 : 2 : 3) and stirred for 1.5 h at room temperature. The reaction mixture was dilured with H_2O (200 ml) satd. with NaCl, and extracted with AcOEt (100 ml × 3). The combined extract was washed with H_2O (200 ml × 2) and dried. The solvent was evaporated off *in vacuo* to afford an oily residue (4.95 g), which was purified by column chromatography on silica gel (50 g). The fraction eluted with 20—50% AcOEt in benzene (v/v) was collected, and removal of the solvent *in vacuo* afforded **21** (3.28 g, 74%) as a colorless oil. IR (neat): 3460, 1740, 1200, 1060, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s, Me), 1.50 (3H, s, Me), 3.77 (3H, s, COOMe), 5.20—5.80 (4H, m, olefinic H). *Anal.* Calcd for $C_{23}H_{38}O_5$: C, 70.01; H, 9.71. Found: C, 70.22; H, 9.63.

(5*Z*,13*E*)-10α,11α-Epoxy-9α,15-dihydroxy-10β,11β-dimethyl-prost-5,13-dienoic Acid (22)——A stirred solution of **21** (3.19 g) in MeOH (60 ml) was treated with 5% NaOH (30 ml) at room temperature. The reaction mixture was stirred for 2 h, poured into ice water (200 ml), made acidic with 7% HCl, and extracted with AcOEt (200 ml × 3). The combined extract was washed with H_2O (200 ml × 2) and dried. Removal of the solvent *in vacuo* afforded an oily residue (3.46 g), which was purified by column chromatography on silica gel (40 g). The fraction eluted with 40—80% AcOEt in benzene yielded **22** (2.95 g, 95%) as colorless needles, mp 75 °C, recrystallized from AcOEt–hexane. IR (Nujol): 3420, 3340, 1710, 1233, 1195, 1070, 965 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, s, Me), 1.42 (3H, s, Me), 4.13 (1H, m,), 4.26 (1H, br), 5.50 (4H, m, olefinic H). *Anal.* Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.58; H, 9.39.

10α,11β-Dimethyl-PGE$_2$ (23) and Its 15-Epimer (24)——BF_3-etherate (0.5 ml) in ether (5 ml) was added dropwise to a stirred solution of **22** (2.082 g) in anhydrous ether (100 ml) at 3—5 °C. The reaction mixture was stirred for 0.5 h and diluted with ice water (300 ml) to separate an organic layer and an aqueous layer. The aqueous layer was extracted with ether (200 ml × 2). The combined organic layer was washed with H_2O (200 ml × 2) and dried. The solvent was evaporated off *in vacuo* to afford an oily residue (2.26 g), which was subjected to careful column chromatography on silica gel (50 g). The fraction eluted with 30—35% AcOEt in hexane (v/v) was collected, and removal of the solvent *in vacuo* afforded **24** (701 mg, 33%) as a colorless oil. The fraction eluted with 35—40% AcOEt in hexane (v/v) yielded **23** (830 mg, 40%) as a colorless oil. **23**: $[\alpha]_D^{25}$ +35.9° ($c=0.90$, THF). IR (neat): 3450, 1730, 1710, 1240, 1145, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, $J=7$ Hz, C_{10}–Me), 1.26 (3H, s, C_{11}–Me), 5.45 (2H, m, olefinic H), 5.66 (2H, m, olefinic H). MS *m/e*: 380 (M^+), 362, 344. *Anal.* Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.71; H, 9.52. **24**: $[\alpha]_D^{25}$ +29.2° ($c=0.93$, THF). IR (neat): 3450, 1730, 1710, 1250, 1145, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, $J=7$ Hz, C_{10}–Me), 1.27 (3H, s, C_{11}–Me), 5.50 (2H, m, olefinic H), 5.67 (2H, m, olefinic H). MS *m/e*: 380 (M^+), 362, 344. *Anal.* Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.50; H, 9.63.

10α,11β-Dimethyl-PGE$_2$ Methyl Ester (25)——10α,11β-Dimethyl-PGE$_2$ (**23**) (311 mg) was esterified with CH_2N_2 in ether in the usual manner to afford **25** (290 mg, 90%) as a colorless oil. $[\alpha]_D^{26}$ +31.5° ($c=0.81$, THF). IR (neat): 3470, 1740, 1247, 1223, 1170, 1150, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, $J=7$ Hz, C_{10}–Me), 1.29 (3H, s, C_{11}–Me), 3.70 (3H, s, COOMe), 4.12 (1H, m, C_{15}–H), 5.40 (2H, m, olefinic H), 5.63 (2H, m, olefinic H). MS *m/e*: 394 (M^+), 376, 358. *Anal.* Calcd for $C_{23}H_{38}O_5$: C, 70.01; H, 9.71. Found: C, 69.89; H, 9.68.

Formation of a Cyclic Boronate Ester (26) from 25——K-selectride (5 ml) was added dropwise to a stirred solution of **25** (240 mg) in THF (15 ml) under an Ar atmosphere, with ice water cooling. The reaction mixture was stirred for 0.5 h, diluted with ice water (50 ml), made acidic with 7% HCl and extracted with AcOEt (50 ml × 3). The combined extract was washed with H_2O (100 ml × 2) and dried. The solvent was evaporated off *in vacuo* to yield an oily residue (450 mg), which was chromatographed on silical gel (5 g). The fraction eluted with 4—10% AcOEt in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo* to afford **26** (270 mg, 96%) as a colorless oil.

IR (neat): 3450, 1715, 1240, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90—1.10 (15H, br, Me×5), 3.75 (3H, s, COOMe), 5.40—5.55 (4H, m, olefinic H).

10α,11β-Dimethyl-PGF$_{2\alpha}$ (27)——A stirred solution of **26** (115 mg) in MeOH (5 ml) was treated with 5% NaOH (3 ml) at room temperature. The reaction mixture was stirred for 1 h, then diluted with H_2O (50 ml), made acidic with 7% HCl and extracted with AcOEt (50 ml×3). The combined extract was washed with H_2O (50 ml×3), and dried. After addition of trimethylene glycol (0.5 ml) to prevent the easy reformation of a boronate ester, the organic layer was again washed with H_2O (20 ml×2) and dried. Removal of the solvent *in vacuo* afforded an oily residue (106 mg), which was purified by column chromatography on silica gel (2 g). The fraction eluted with 30—50% AcOEt in benzene (v/v) was collected, and the solvent was evaporated off *in vacuo* to yield **27** (82 mg, 84%) as colorless needles, mp 106 °C, recrystallized from AcOEt–hexane. $[\alpha]_D^{25}$ −3.73° (c=0.58, THF). IR (Nujol): 3430, 1710, 1232, 975 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, d, J=6 Hz, C_{10}–Me), 1.02 (3H, s, C_{11}–Me), 3.97 (1H, t, J=7 Hz, C_9–H), 4.10 (1H, m, C_{15}–H), 4.84 (4H, br, OH×3, COOH), 5.50 (4H, m, olefinic H). MS m/e: 382 (M^+), 364, 346, 328. *Anal.* Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 69.31; H, 10.08.

Reduction of 25 with $NaBH_4$——$NaBH_4$ (50 mg) was added portionwise to a stirred solution of **25** (250 mg) in MeOH (10 ml) under ice water cooling. The reacion mixture was stirred for 1 h, then diluted with H_2O (100 ml) containing 7% HCl (5 ml) and extracted with AcOEt (100 ml×3). The combined extract was washed with H_2O (100 ml×2) and dried. Removal of the solvent *in vacuo* afforded an oily residue (250 mg), which was separated into two fractions (Rf 0.3 and 0.4 in AcOEt–hexane 3:1) by preparative TLC. The fraction having Rf 0.4 afforded **27** methyl ester (23 mg, 9%) as colorless needles, mp 60 °C, recrystallized from AcOEt–hexane, and the fraction having Rf 0.3 afforded **28** methyl ester (206 mg, 82%) as a colorless oil. **27** methyl ester: $[\alpha]_D^{25}$ −4.20° (c=0.50, THF). IR (Nujol): 3330, 1740, 1160, 1025, 970, 905 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, d, J=6 Hz, C_{10}–Me), 1.02 (3H, s, C_{11}–Me), 3.68 (3H, s, COOMe), 3.97 (1H, t, J=7 Hz, C_9–H), 4.10 (1H, m, C_{15}–H), 5.46 (4H, m, olefinic H). *Anal.* Calcd for $C_{23}H_{40}O_5$: C, 69.66; H, 10.17. Found: C, 69.83; H, 10.29. **28** methyl ester: $[\alpha]_D^{25}$ +7.09° (c=0.86, THF). IR (neat): 3400, 1725, 1240, 1220, 1150, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, d, J=6 Hz, C_{10}–Me), 1.07 (3H, s, C_{11}–Me), 3.55 (1H, t, J=6 Hz, C_9–H), 3.67 (3H, s, COOMe), 4.07 (1H, m, C_{15}–H), 5.48 (4H, m, olefinic H). *Anal.* Calcd for $C_{23}H_{40}O_5$: C, 69.66; H, 10.17. Found: C, 69.79; H, 10.11.

10α,11β-Dimethyl-PGF$_{2\beta}$ (28)——A stirred solution of **28** methyl ester (183 mg) in MeOH (6 ml) was treated with 5% NaOH (2 ml) at room temperature. The mixture was stirred for 1.5 h, diluted with H_2O (50 ml), made acidic with 7% HCl and extracted with AcOEt (50 ml×3). The combined extract was washed with H_2O (100 ml×2) and dried. Removal of the solvent *in vacuo* gave a crystalline residue (180 mg). Recrystallization from AcOEt–hexane afforded **28** (150 mg, 85%) as colorless needles, mp 90 °C. $[\alpha]_D^{25}$ +6.8° (c=0.50, THF). IR (Nujol): 3440, 1708, 1290, 1250, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, J=6 Hz, C_{10}–Me); 1.08 (3H, s, C_{11}–Me), 3.55 (1H, t, J=7 Hz, C_9–H), 4.07 (1H, m, C_{15}–H), 5.53 (4H, m, olefinic H). MS m/e: 382 (M^+), 364, 346, 303. *Anal.* Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 69.20 H, 10.11.

27 From 27 Methyl Ester——In a manner similar to that described for **28**, hydrolysis of **27** methyl ester (17 mg) afforded **27** (14 mg, 85%).

10,11-Dimethyl-PGA$_2$ (29)——A mixture of **25** (145 mg), MeOH (10 ml) and 5% NaOH (2 ml) was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O (50 ml), made acidic with 7% HCl and extracted with AcOEt (50 ml×3). The combined extract was washed with H_2O (50 ml×2) and dried. The solvent was evaporated off *in vacuo* to afford an oily residue (95 mg), which was chromatographed on silica gel (2 g). The fraction eluted with 30—40% AcOEt in benzene (v/v) was collected. Removal of the solvent afforded **29** (87 mg, 65%) as a colorless oil. $[\alpha]_D^{25}$ +124° (c=0.59, THF). IR (neat): 3400, 1700, 1645, 1235, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (3H, s, vinyl Me), 2.00 (3H, s, vinyl Me), 4.17 (1H, m, C_{15}–H), 5.20—5.70 (4H, m, olefinic H). MS m/e: 362 (M^+), 344, 274. *Anal.* Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.01; H, 9.55.

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