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Synthetic Studies on Prostanoids. XX.[1] Synthesis of Stable (±)-Prostaglandin H_1 Analogs

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(±)-PGH_1 analogs (9,11-epoxymethano PGH_1, 11,9-epoxymethano PGH_1, 9,11-epoxycarbonyl PGH_1, and 11,9-epoxycarbonyl PGH_1) were synthesized from 9- or 11-substituted prostaglandin derivatives or their synthetic intermediates. These analogs showed interesting biological activities, different from those of PGH_2 analogs.

Keywords——synthesis; PGH_1 analogs; platelet aggregation; aorta contraction; prostaglandin

Since the isclation of prostaglandins (PG's) by the Karolinska Institute (Sweden) in 1960,[3a] these compounds have been the subject of intensive research in the fields of synthetic chemistry and biochemistry. In 1973, the successful isolation of the highly unstable compounds PGG_2 and PGH_2[3] by Samuelsson and Nugteren was a major setp forward, resulting in the discovery of the extremely unstable compounds thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) by Samuelsson and Vane, respectively. PGG_2 and PGH_2 are now known to be key intermediates in the biosynthesis of primary PG's, TXA_2 and PGI_2. Recent chemical research on PGG and PGH seems to have been mainly focussed on the synthesis of PGH_2[4a-c] and its stable analogs, which show strong activities in platelet aggregation,[5a-f] aorta contraction, and inhibition of the biosynthesis of TXA_2.[5g,h] According to a report by Willis[6] PGH_1 lacks pro-aggregatory activity and does not alter the ability of LASS (PGH_2) to produce platelet aggregation. Interestingly, it has been reported that PGH_1 is not converted to TXA_1 by human platelet microsomes.[7] These findings suggest that PGH_1 may play a considerably different role from PGH_2, and prompted us to synthesize the following stable PGH_1 analogs[8]: 9α,11α-epoxymethano-15α-hydroxy-prost-13*E*-enoic acid (I),[9] 11α,9α-epoxymethano-15α-

1) Part XIX: K. Inoue, S. Amemiya, Y. Tajima, and K. Sakai, *Chem. Lett.*, **1978**, 1121.
2) Location: *1-2-58 Hiromachi, Shinagawaku, Tokyo, 140, Japan.*
3) *a*) S. Bergström and J. Sjövall, *Acta. Chem. Scand.*, **14**, 1693, 1701 (1960); *b*) For example, see Advances in Prostaglandin and Thromboxane Research I and II edited by Samuelsson and Paoletti, Raven Press, 1976.
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6) A.L. Willis, F.M. Vane, D.C. Kuhn, C.G. Scott, and M. Petrin, *Prostaglandins* **8**, 453 (1974).
7) P. Needleman, M. Minkos, and A. Raz, *Science* **163**, July 9 (1976).
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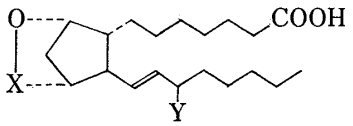
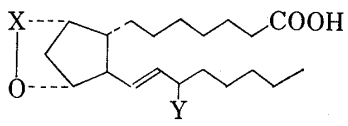
9) See the nomenclature used by Upjohn for PGH_2 analogs (ref. 5*c*).



I : X=CH_2 Y=⋯OH
III : X=CO Y=~OH



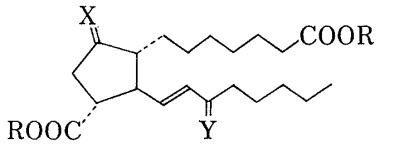
II : X=CH_2 Y=⋯OH
IVa : X=CO Y=⋯OH
IVb : X=CO Y=━OH

Chart 1

hydroxy-prost-13*E*-enoic acid (II), 9α,11α-epoxycarbonyl-15-hydroxy-prost-13*E*-enoic acid (III), and 11α,9α-epoxycarbonyl-15α-hydroxy-prost-13*E*-enoic acid (IVa).

In a previous paper, we reported the stereocontrolled synthesis of 11α-[10a] and 9α-[10b] substituted prostaglandin derivatives. These derivatives and their synthetic intermediate are considered to be potential precursors for the synthesis of I, II, III and IVa.

The keto diester **1**, which obtained by Jones oxidation of (±)-11-deoxy-11α-hydroxymethyl PGE_1,[10b] followed by treatment with diazomethane, afforded the diol **2** in good yield by reduction with K-selectride in tetrahydrofuran for 10 min at 8°. This reduction stereospecifically afforded the 9α-hydroxyl group, although the 15-hydroxyl group was obtained as a chromatographically inseparable mixture of the α- and β-configurations, which appeared as two very close spots on thin-layer chromatography (TLC). The selective oxidation of the 15-hydroxyl group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing dioxane for 1.5 hr yielded the enone **3** as the sole product in 60% yield. In the proton magnetic resonance (PMR) spectrum of **3**, the chemical shift of the 9β-hydrogen was observed at 4.23 ppm. Based on Bagli's report,[11] this value supports the view that the 9-hydroxyl group is in the *cis* configuration relative to the α-chain. The α-configuration of the 9-hydroxyl group was also chemically determined by the following lactonization.



1 : X=O Y=O R=Me
2 : X=  Y=~OH R=Me
3 : X=  Y=O R=Me
4 : X=  Y=O R=H

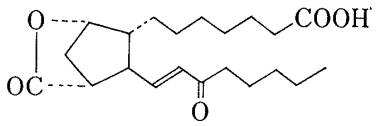


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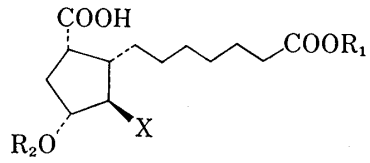
Chart 2

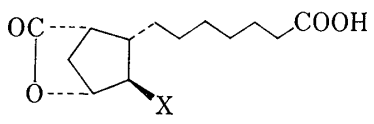
Lactonization of the diacid **4** obtained by the usual hydrolysis of **3** was accomplished in 65% yield by refluxing in a benzene-dioxane mixture containing a trace of *p*-toluenesulfonic acid. The structure of the lactone **5** is supported by the characteristic signal of the five-membered lactone at 1780 cm^{-1} in its infrared (IR) spectrum. Reduction of **5** with $NaBH_4$ in methanol at −20° afforded 9α,11α-epoxycarbonyl-15-hydroxy-prost-13*E*-enoic acid (III) as a mixture of 15-epimers. Attempts to separate the 15-epimers were unsuccessful. For comparison of the biological activities, the synthesis of 11α,9α-epoxycarbonyl-15α-hydroxy-prost-13*E*-enoic acid (IVa), in which the orientation of the lactone moiety is reversed, was also carried out.

10) *a*) K. Kojima and K. Sakai, *Tetrahedron Lett.*, **1972**; 3333; *b*) K. Sakai, J. Ide, and O. Oda, *ibid.*, **1975**, 3021.
11) J.F. Bagli and T. Bogli, *Tetrahedron Lett.*, **1967**, 5; *ibid.*, **1969**, 1639.

2α-(6-Ethoxycarbonylhexyl)-3β-methoxycarbonyl-4α-hydroxycyclopentane-1α-carboxylic acid (**6**), which was the key intermediate in the synthesis of $PGF_{1\alpha}$,[10a] possesses a suitable configuration for the synthesis of IVa. The selective reduction of the 12-methoxycarbonyl group[12] to the corresponding primary alcohol was effected by the following sequence.

Partial hydrolysis of the primary ester with 1.5% KOH in aqueous methanol afforded the monoester **7** in 45% yield. Its potassium salt was subjected to $LiBH_4$ reduction in refluxing isopropyl alcohol. The crude diol **8** was not purified by chromatography, because of its low solubility in organic solvents. Therefore, **8** was subjected to direct lactonization by refluxing in a benzene-dioxane mixture in the presence of *p*-toluenesulfonic acid. Thus, the bicyclic-lactone **9** was obtained in 25% yield from **7**. Collins oxidation of **9** followed by the usual Wittig reaction (see experimental section) afforded the enone acid **10**. $NaBH_4$ reduction of **10** in methanol at −20° gave a mixture of 15-epimeric alcohols which could be separated by preparative TLC into the more polar fraction IVa and the less polar fraction IVb. The stereochemistry of the 15-hydroxyl group in IVa and IVb was tentatively assigned as α- and β-configuration, respectively, on the basis of their mobilities on TLC.[13]





6: R_1=Et, R_2=H, X=COOMe
7: R_1=R_2=H, X=COOMe

8: R_1=R_2=H, X=CH_2OH

9: X=CH_2OH
10: X=

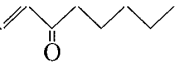
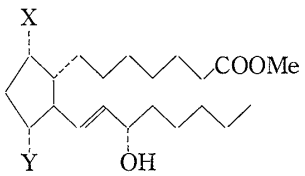


Chart 3



11: X=OH, Y=CH_2OH
12: X=OH, Y=CH_2OTs
13: X=CH_2OH, Y=OH
14: X=CH_2OTs, Y=OH

Chart 4

The biologically interesting activities (see below) of the 11,9- and 9,11-epoxycarbonyl compounds in platelet aggregation in addition to aorta contraction led us to synthesize the 9,11- and 11,9-epoxymethano compounds (I and II). Reduction of (±)-11-deoxy-11α-hydroxymethyl PGE_1 methyl ester with K-selectride in tetrahydrofuran at room temperature gave crystalline 11-deoxy-11α-hydroxymethyl $PGF_{1\alpha}$ methyl ester (**11**), mp 65.5°. The epoxymethano linkage was synthesized by a method similar to that of Bundy,[5c] which he applied to the synthesis of PGH_2 analogs.

Selective tosylation of the 11α-hydroxymethyl group with tosyl chloride (1 eq) in pyridine at 0° for 20 hr gave the monotosylate **12** in 43% yield, mp 57°. The formation of the ether linkage and the hydrolysis of the ester function of **12** were effected by treatment with 5% KOH in aqueous methanol. Thus, 9α,11α-epoxymethano-15α-hydroxy-prost-13*E*-enoic acid (I) was obtained as an oily compound in 84% yield. 11α,9α-Epoxymethano-15α-hydroxy-prost-13*E*-enoic acid (II), mp 79.5°, was similarly synthesized from (±)-9-deoxy-9α-hydroxymethyl $PGF_{1\alpha}$ methylester (**13**).[14]

12) According to the numbering for prostaglandin.
13) N.H. Anderson, *J. Lipids Research*, **10**, 316 (1969).
14) The synthesis of **13** will be reported elsewhere.

Biological Activities

Like PGH_2 analogs, 11,9-epoxymethano PGH_1 (II) and 11,9-epoxycarbonyl PGH_1 (IVa) showed strong platelet aggregating activity and were found to be 6.3 times[15] and 4.0 times as active as PGH_2 in rabbit platelet aggregation, respectively. These analogs seem to be rather different from PGH_1, which lacks aggregation activity. On the other hand, it is noteworthy that, unlike PGH_2 analogs, 9,11-epoxycarbonyl PGH_1 (III) and 9,11-epoxymethano PGH_1 (I) showed inhibitory activity against arachidonic acid-induced platelet aggregation. 11,9-Epoxymethano PGH_1 (II), 9,11-epoxymethano PGH_1 (I), and 11,9-epoxycarbonyl PGH_1 (IVa) were 6.2, 0.93 and 5.58 times as active as PGH_2 in rabbit aorta contraction, respectively. Surprisingly, in the same test 9,11-epoxycarbonyl PGH_1 (III) was 31 times as active as PGH_2. Therefore, III appears to possess the strongest known activity among endoperoxide analogs. Details will be reported elsewhere.

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a JASCO IRA-2 spectrometer, PMR spectra on a Varian T-60, and mass spectra on a JEOL OISCT. The following abbreviations are used: s, singlet; d, doublet; q, quartet; m, multiplet; b, broad. 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).

Methyl 11α-Methoxycarbonyl-9,15-dioxo-prost-13*E*-enoate (1)——Jones reagent (7 ml) was added dropwise with stirring to a solution of 11-deoxy-11α-hydroxymethyl PGE_1 methyl ester (1.92 g) in acetone (60 ml) under ice-water cooling. The mixture was stirred for 5 min at 5° then for 10 min at 10°. The reaction mixture was poured into ice-water, extracted with AcOEt (20 ml×3), dried (Na_2SO_4), and evaporated to dryness *in vacuo* to afford an oily residue (2.08 g), which was treated with an ether solution of diazomethane under ice-water cooling by the usual method. The oily ester (2.1 g) was subjected to column chromatography on silica gel (20 g). The fraction eluted with 2—5% AcOEt in benzene (v/v%) was collected, and the solvent was evaporated off *in vacuo* to afford **1** (1.78 g) as an oil. IR ν_{max}^{liq} cm^{-1}: 1740 (CO), 1700 (ester), 1670 (CO), 1630 (CH=CH). PMR ($CDCl_3$) δ: 3.64 (3H, s, COOMe), 3.70 (3H, s, COOMe), 6.15 (1H, d, 14-H), 6.72 (1H, q, 13-H). *Anal.* Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.53; H, 8.75.

Methyl 9α-15-Dihydroxy-11α-methoxycarbonyl-prost-13*E*-enoate (2)——K-selectride (0.5 M tetrahydrofuran solution 25.8 ml) was added dropwise with stirring to a solution of **1** (2.28 g) in tetrahydrofuran (50 ml) under an Ar atmosphere at 8° over a period of 10 min. The reaction mixture was diluted with ice-water (150 ml) containing 2% HCl (10 ml), and extracted with AcOEt (50 ml×3). The extract was washed with H_2O, dried (Na_2SO_4), and concentrated *in vacuo* to afford an oily residue (3.79 g), which was purified by column chromatography on silica gel (30 g). The fraction eluted with 20—50% AcOEt in benzene (v/v%) was evaporated to dryness *in vacuo* to afford **2** (2.3 g) as an oil. IR ν_{max}^{liq} cm^{-1}: 3500 (OH), 1740 (ester), 1310, 1210, 1170. PMR ($CDCl_3$) δ: 3.63 (6H, m, COOMe×2), 4.10 (1H, m, 15-H), 4.52 (1H, m, 9β-H), 5.47 (2H, m, 13- and 14-H). *Anal.* Calcd for $C_{23}H_{40}O_6$: C, 66.96; H, 9.77. Found: C, 66.79; H, 9.82.

Methyl 9α-Hydroxy-11α-methoxycarbonyl-15-oxo-prost-13*E*-enoate (3)——A mixture of **2** (1.5 g) in dioxane (30 ml) and DDQ (1.5 g) was refluxed for 1.5 hr. After cooling, the reaction mixture was diluted with hexane–AcOEt (200 ml, 1: 1 ratio). The resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford an oily residue (2.90 g), which was subjected to column chromatography on silica gel (30 g). The fraction eluted with 15—30% AcOEt in benzene (v/v%) was evaporated to dryness *in vacuo* to afford **3** (844 mg) as an oil. IR ν_{max}^{liq} cm^{-1}: 3520 (OH), 1730 (ester), 1670 (CO), 1630 (CH=CH), 1200, 1170. PMR ($CDCl_3$) δ: 3.70 (6H, s, COOMe×2), 4.23 (1H, m, 9β-H), 6.12 (1H, d, 14-H), 6.75 (1H, q, 13-H). *Anal.* Calcd for $C_{23}H_{38}O_6$: C, 67.29; H, 9.33. Found: C, 67.41; H, 9.39.

11α-Carboxy-9α-hydroxy-15-oxo-prost-13*E*-enoic Acid (4)——A solution of **3** (850 mg) in tetrahydrofuran (30 ml) was treated with 5% NaOH (6.0 ml), and the solution was stirred for 4 hr at room temperature. The reaction mixture was diluted with ice-water (100 ml) containing 7% HCl (10 ml), extracted with AcOEt (30 ml×5), and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the oily residue (970 mg) was subjected to column chromatography on silica gel (10 g). The fraction eluted with 40—50% AcOEt in benzene (v/v%) was collected, and the solvent was evaporated off *in vacuo*, yielding **4** (609 mg) as an oil. IR ν_{max}^{liq} cm^{-1}: 3450 (OH), 1730 (COOH), 1710 (CO), 1630 (CH=CH). PMR ($CDCl_3$) δ: 4.28 (1H, m, 9β-H), 6.45 (2H, m, 13- and 14-H), 7.65 (3H, b, COOH×2, OH). *Anal.* Calcd for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96.

15) These values were estimated by direct comparison with the activities of (±)-11,9-epoxymethano PGH_2, the optically active form of which (ref. 5*a*) was found to be 6.2 times as active as PGH_2 for rat aorta contraction and 3.7 times as active as PGH_2 in platelet aggregation.

Found: C, 66.10; H, 9.08.

9α,11α-Epoxycarbonyl-15-oxo-prost-13*E*-enoic Acid (5)——Compound **4** (580 mg) was dissolved in a mixture of benzene (50 ml) and dioxane (20 ml). The mixture was refluxed in the presence of *p*-TsOH (200 mg) for 4 hr, and newly formed H_2O was removed under azeotropic conditions. The reaction mixture was diluted with H_2O satd. with NaCl (100 ml), extracted with AcOEt (30 ml×4) and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the oily residue (570 mg) was subjected to column chromatography on silica gel (7 g). The fraction eluted with 15—25% AcOEt in benzene (v/v%) was evaporated to dryness *in vacuo* to afford **5** (385 mg) as an oil. IR ν_{max}^{liq} cm^{-1}: 1780 (lactone), 1730, 1700 (CO), 1630, 1620. PMR ($CDCl_3$) δ: 2.83 (1H, m, 11-H), 4.83 (1H, m, 9β-H), 6.20 (1H, d, 14-H), 6.80 (1H, q, 13-H). *Anal.* Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.09; H, 8.73.

9α-11α-Epoxycarbonyl-15-hydroxy-prost-13*E*-enoic Acid (III)——$NaBH_4$ (150 mg) was added portionwise to a stirred solution of **5** (370 mg) in MeOH (10 ml) at −20°. After 20 min, the reaction mixture was diluted with ice-water (30 ml) containing 5% HCl (5 ml), extracted with AcOEt (30 ml×3), and dried (Na_2SO_4). Removal of the solvent *in vacuo* yielded an oily residue (404 mg), which was subjected to column chromatography on silica gel (6 g). The fraction eluted with 30—60% AcOEt in benzene (v/v%) was evaporated to dryness *in vacuo* to afford I (350 mg) as an oil. Attempts to separate the 15-epimers were unsuccessful. IR ν_{max}^{liq} cm^{-1}: 3450 (OH), 1785 (lactone), 1760, 1730, 1710, 1165, 970. PMR ($CDCl_3$) δ: 2.70 (1H, m, 11β-H), 4.12 (1H, m, 15-H), 4.75 (1H, m, 9β-H), 5.63 (2H, m, 13- and 14-H), 6.25 (2H, b, COOH, OH). MS *m/e*: 348 ($M^+-18(H_2O)$). *Anal.* Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.99; H, 9.41.

2α-(6-Carboxyhexyl)-3β-methoxycarbonyl-4α-hydroxy-cyclopentane-1α-carboxylic Acid (7)——To a stirred solution of **6** (23 g) in MeOH (30 ml), 1.5% KOH (50 ml) in 20% H_2O–MeOH (v/v%) was added dropwise under ice-water cooling (3—5°). The mixture was stirred for 30 min at the same temperature then for 4 hr at room temperature. The reaction mixture was made acidic with 5% HCl satd. with NaCl (30 ml), extracted with AcOEt (50 ml×6) and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the oily residue (21.2 g) was subjected to column chromatography on silica gel (130 g). The fraction eluted with 50—80% AcOEt in benzene (v/v%) was concentrated to dryness *in vacuo* to afford **7** (10.3 g) as an oil. IR ν_{max}^{liq} cm^{-1}: 3150—3450 (OH), 1710—1740 (COOH, ester), 1210. PMR ($CDCl_3$) δ: 3.74 (3H, s, COOMe), 4.40 (1H, b, 11-H). *Anal.* Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 57.18; H, 7.86.

2α-(6-Carboxyhexyl)-3β-hydroxymethyl-4α-hydroxy-cyclopentane-1α-carboxylic Acid (8) and *endo*-2-(6-Carboxyhexyl)-*exo*-3-hydroxymethyl-5-oxa-6-oxo-bicyclo[2.2.1]heptane (9)——$KHCO_3$ (0.7 g) was added portionwise to a stirred solution of **7** (1.0 g) in 20% H_2O–MeOH (12 ml) at room temperature. After stirring for 30 min at 40—50°, the solvent was removed *in vacuo* to afford the potassium salt, which was dissolved in iso-PrOH (50 ml) containing $LiBH_4$ (500 mg). The mixture was heated under reflux for 2.5 hr. After cooling, the reaction mixture was poured into ice-water (100 ml) satd. with $(NH_4)_2SO_4$, acidified with 5% HCl (5 ml), extracted with AcOEt (50 ml×7), and dried (Na_2SO_4). The solvent was evaporated off *in vacuo* to afford an oily residue **8** (930 mg) which was subjected to lactonization without purification by chromatography. A mixture of **8** (930 mg), dioxane (10 ml) and benzene (60 ml) was heated under reflux in the presence of *p*-TsOH (100 mg). Newly formed H_2O was removed under azeotropic conditions. After 4.5 hr, the reaction mixture was cooled. The organic layer was washed with H_2O (30 ml) satd. with $(NH_4)_2SO_4$ and dried (Na_2SO_4). The solvent was removed *in vacuo* to afford an oily residue (970 mg) which was subjected to column chromatography on silica gel (6 g). The fraction eluted by changing the polarity from 70% AcOEt in benzene to 5% MeOH in AcOEt (v/v%) was collected. The solvent was evaporated off *in vacuo*. Compound **9** (250 mg) was obtained as an oily residue. IR ν_{max}^{liq} cm^{-1}: 3450 (OH), 1770 (lactone), 1730, 1195. PMR ($CDCl_3$) δ: 2.84 (1H, m, 1-H), 3.65 (2H, b, 3-CH_2), 4.85 (1H, m, 4-H). *Anal.* Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.31; H, 8.11.

11α,9α-Epoxycarbonyl-15-oxo-prost-13*E*-enoic Acid (10)——Compound **9** (590 mg) in CH_2Cl_2 (15 ml) was added dropwise to stirred Collins reagent (prepared from CrO_3 (1.75 g), pyridine (2.42 g), and CH_2Cl_2 (50 ml)) under ice-water cooling. After 15 min, ether (100 ml) was added, and the resulting precipitate was filtered off. The filtrate was washed with H_2O satd. with NaCl (30 ml×2), and dried (Na_2SO_4). The solvent was removed *in vacuo* to afford an oily aldehyde (450 mg) which was extremely unstable. To a stirred solution of the aldehyde (450 mg) in benzene (20 ml), 2-oxo-heptylidene-tributylphosphorane (2.36 g) in $CHCl_3$ (10 ml) was added dropwise at room temperature. The mixture was stirred for 3 hr at room temperature. The reaction mixture was washed with 5% HCl satd. with NaCl (20 ml), and dried (Na_2SO_4). The solvent was evaporated off *in vacuo*. The oily residue (3.57 g) was subjected to column chromatography on silica gel (35 g). The fraction eluted with 30—49% AcOEt in benzene was collected, and the solvent was removed *in vacuo*, yielding **10** (510 mg) as an oil. IR ν_{max}^{liq} cm^{-1}: 1795 (lactone), 1743, 1715, 1680, 1635. PMR ($CDCl_3$) δ: 2.91 (1H, m, 9-H), 4.65 (1H, m, 11-H), 6.17 (1H, d, 14-H), 6.68 (1H, q, 13-H). *Anal.* Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.42; H, 8.99.

11α,9α-Epoxycarbonyl-15α-hydroxy-prost-13*E*-enoic Acid (IVa) and 11α,9α-Epoxycarbonyl-15β-hydroxy-prost-13*E*-enoic Acid (IVb)——$NaBH_4$ (400 mg) was added portionwise to a stirred solution of **10** (510 mg) in MeOH (20 ml) at −50°. After stirring for 10 min, the reaction mixture was diluted with ice-water (50 ml) containing 5% HCl (1 ml), extracted with AcOEt (30 ml×3), and dried (Na_2SO_4). The solvent was removed *in vacuo*. The semi-crystalline residue was recrystallized from hexane to afford crystalline IVb (211 mg),

mp 71—76°. The oily residue obtained from the mother liquor was subjected to column chromatography on silica gel (3 g). The more polar fraction eluted with 10—30% AcOEt in benzene (v/v%) was collected. The solvent was evaporated off *in vacuo* to afford IVa (160 mg) as an oil. IVa (more polar fraction) IR ν_{max}^{liq} cm^{-1}: 3400 (OH), 1780 (lactone). PMR ($CDCl_3$) δ: 4.61 (1H, m, 11β-H), 5.63 (2H, m, 13- and 14-H). MS *m/e*: 348 ($M^+-18(H_2O)$). *Anal.* Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 69.01; H, 9.39. IVb (less polar fraction): mp 71—76°. IR ν_{max}^{Nujol} cm^{-1}: 3500 (OH), 1750 (lactone), 1708. PMR ($CDCl_3$) δ: 4.61 (1H, m, 11β-H), 5.63 (2H, m, 13- and 14-H). MS *m/e*: 348 ($M^+-18(H_2O)$). *Anal.* Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.95; H, 9.40.

11-Deoxy-11α-hydroxymethyl PGF$_{1\alpha}$ Methyl Ester (11)——A stirred solution of 11-deoxy-11α-hydroxymethyl PGE_1 methyl ester (514 mg) was treated dropwise with K-selectride (0.5 M tetrahydrofuran solution 7 ml) with ice-water cooling under an Ar atmosphere. The mixture was stirred for 40 min, then decomposed by adding ice-water (50 ml) satd. with NaCl, acidified with 5% HCl (5 ml), extracted with AcOEt (30 ml×4), and dried (Na_2SO_4). The solvent was removed *in vacuo*. The oily residue (470 mg) was chromatographed on silica gel (5 g) and the fraction eluted with 50—70% AcOEt in benzene (v/v%) was collected. Removal of the solvent afforded **11** (340 mg), which was recrystallized from AcOEt–hexane, mp 64.5—65.5°. IR ν_{max}^{KBr} cm^{-1}: 3270 (OH), 1720 (ester). PMR ($CDCl_3$) δ: 3.72 (3H, s, COOMe), 5.45—5.55 (2H, m, 13- and 14-H). *Anal.* Calcd for $C_{22}H_{40}O_5$: C, 68.71; H, 10.49. Found: C, 68.82; H, 10.55.

11-Deoxy-11α-*p*-toluenesulfonyloxymethyl PGF$_{1\alpha}$ Methyl Ester (12)——*p*-TsCl (175 mg) was added portionwise to a stirred solution of **11** (297 mg) in pyridine (2 ml) under ice-water cooling. The mixture was stirred for 20 hr at 5—7°, diluted with ice-water (5 ml), and extracted with AcOEt (10 ml×3). The combined organic layer was successively washed with H_2O (30 ml), 5% HCl (30 ml), and H_2O (30 ml), and dried (Na_2SO_4). The solvent was removed *in vacuo*. The oily residue (326 mg) was subjected to column chromatography on silica gel (4 g). The fraction eluted with 5—30% AcOEt in benzene (v/v%) afforded **12** (177 mg) as crystals, mp 55—57°. IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 1720, 1600 (aromatic). PMR ($CDCl_3$) δ: 3.65 (3H, s, COOMe), 5.30—5.37 (2H, m, 13- and 14-H). *Anal.* Calcd for $C_{29}H_{46}O_7S$: C, 64.65; H, 8.60. Found: C, 64.72; H, 8.43.

9α,11α-Epoxymethano-15α-hydroxy-prost-13*E*-enoic Acid (I)——Compound **12** (163 mg) was dissolved in 10 ml of 5% KOH in 30% H_2O–MeOH (v/v%), and stirred for 4 hr. The reaction mixture was made acidic with 5% HCl (6 ml), and extracted with AcOEt (30 ml×3). The combined organic layer was washed with H_2O satd. with NaCl (20 ml×2) and dried (Na_2SO_4). The solvent was evaporated off *in vacuo*. The oily residue (120 mg) was subjected to column chromatography on silica gel (1 g) and the fraction eluted with 10—15% AcOEt was collcted. The solvent was evaporated off *in vacuo* to afford I (96 mg) as an oil. IR ν_{max}^{liq} cm^{-1}: 3400 (OH), 1710 (COOH). PMR ($CDCl_3$) δ: 3.63 (2H, m, 11-CH_2), 4.10 (1H, m, 15-H), 4.20 (1H, s, 9-H), 5.5—5.6 (2H, m, 13- and 14-H). MS *m/e*: 334 ($M^+-18(H_2O)$). *Anal.* Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.80; H, 10.21.

9-Deoxy-9α-*p*-toluenesulfonyloxymethyl PGF$_{1\alpha}$ Methyl Ester (14)——In a manner similar to that described for **11**, tosylation of **13** (468 mg)[14] afforded **14** (169 mg) as an oil in 26% yield. IR ν_{max}^{liq} cm^{-1}: 3400 (OH), 1740 (ester), 1600. PMR ($CDCl_3$) δ: 3.73 (3H, s, COOMe), 5.43 (2H, b, 13- and 14-H). *Anal.* Calcd for $C_{29}H_{46}O_7S$: C, 64.65; H, 8.60. Found: C, 64.81; H, 8.35.

11α,9α-Epoxymethano-15α-hydroxy-prost-13*E*-enoic Acid (II)——In a manner similar to that described for I, II (43 mg) was obtained from **14** (168 mg). mp 78—79.5°. IR ν_{max}^{EtOH} cm^{-1}: 3300 (OH), 1710 (COOH). PMR ($CDCl_3$) δ: 3.66 (2H, m, 9-CH_2), 4.3 (1H, s, 11-H), 5.36—5.46 (2H, m, 13- and 14-H). MS *m/e*: 334 ($M^+-18(H_2O)$). *Anal.* Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.61; H, 10.24.