The Synthesis of the 9,11-Hydroxyethano-prostaglandin Endoperoxide H_2 Analogue

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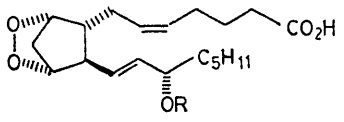
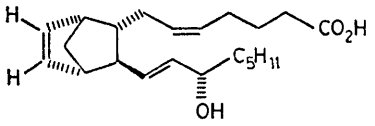
The 9,11-hydroxyethano-prostaglandin endoperoxide H_2 analogue (4a) and its methyl ester (4b) have been prepared in 4.3 and 10% yield respectively from the readily prepared 3-*exo*-methoxycarbonyl-6-*endo*-hydroxy-5-*exo*-iodonorborn-2-*endo*-ylacetic acid δ-lactone (5).

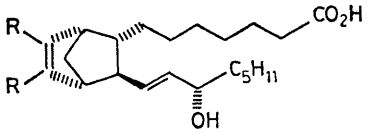
THE interesting and potent biological activity of the prostaglandin endoperoxides (1a) and (1b) [1,2] has prompted the synthesis of stable analogues of these compounds. To date a number of compounds including the norbornene derivatives (2),[3] (3a),[4] and (3b) [5] have been reported and found to be biologically active. We set out to synthesise the norbornane analogues (4a) and (4b), bearing an oxygen function at the C-9a position.



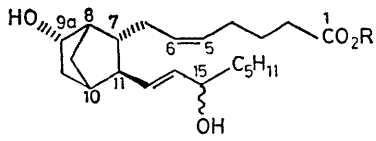
(1) a, R = OH
b, R = H



(2)



(3) a, R = H
b, R = Me



(4) a, R = H
b, R = Me

There is little scope for preparing such compounds directly from (2) and (3a) since it is unlikely that reaction at the norbornene double bond could be accomplished without also causing reaction at the allylic system in the side-chain. Secondly, reactions on the norbornene double bond usually take place to give *exo*-derivatives [6] whereas by analogy with the natural prostaglandins the introduction of an *endo*-hydroxy-group as in (4a) and (4b) is more desirable.

RESULTS AND DISCUSSION

Our recent studies [7] on glutaconic anhydride and its utility in the Diels–Alder reaction have enabled us to prepare the iodolactone (5), which is a key starting material for the present work. Deiodination using freshly prepared tri-n-butylstannane in tetrahydrofuran furnished the corresponding lactone ester (6) (95%).

Treatment of (6) with aqueous potassium hydroxide at room temperature resulted in complete hydrolysis of the ester function together with partial hydrolysis of the lactone group to afford a mixture of the required acid lactone (7) and the corresponding hydroxy-dicarboxylic acid. The latter would not re-lactonise on treatment with acid. However when the mixture of (7) and the hydroxy-dicarboxylic acid was stirred with an excess of acetic anhydride–pyridine (1 : 1) for 48 h at room temperature, the required acid lactone (7) was obtained in a yield of 82% from (6). This product (7) was reduced to the corresponding hydroxy-lactone (8) (76%) by treatment with an excess of borane in tetrahydrofuran for 1 h at 0 °C. Oxidation of the hydroxy-lactone (8) using pyridinium chlorochromate [8] afforded the required aldehyde (9) (72%). This was converted into the corresponding keto-lactone (10) (72%) by means of a Horner–Emmons reaction using sodium hydride and dimethyl (2-oxoheptyl)phosphonate.[9] The use of an excess of sodium hydride caused substantial polymer formation, and the yield of product was very sensitive to the presence of water. Zinc borohydride reduction of (10) furnished the allylic alcohols (11) (64%).

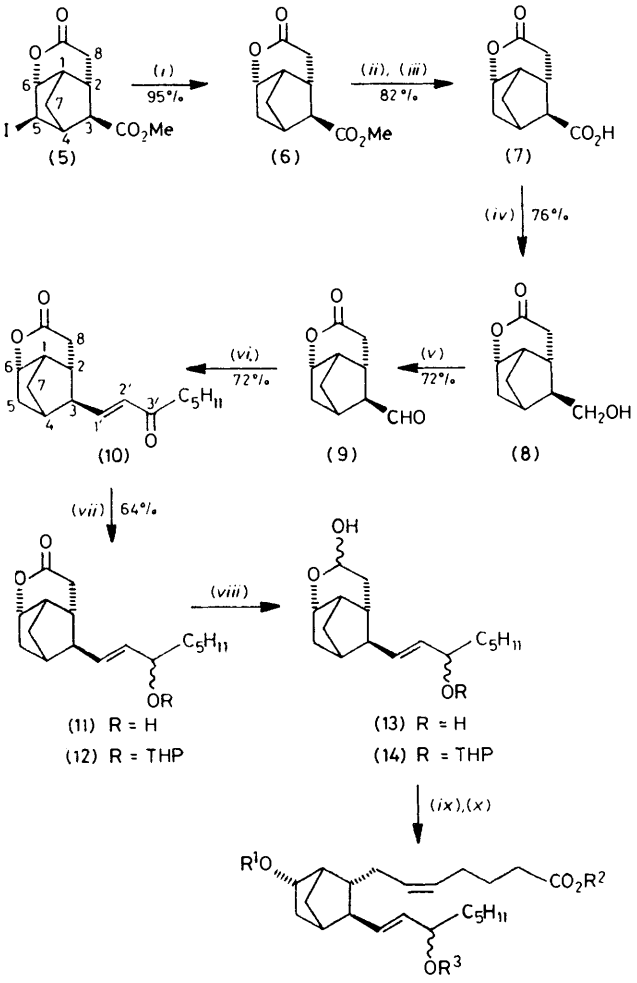
Reduction of the lactone moiety of (11) using di-isobutylaluminium hydride in toluene and reaction of the crude lactol (13) with the ylide derived from (4-butoxycarbonyl)triphenylphosphonium bromide gave the prostanoid (4a). Methylation using diazomethane then afforded the methyl ester (4b) in 51% overall yield from (11).

Alternatively, protection of the allylic alcohol (11) as the tetrahydropyranyl ether (12) (67%) and di-isobutylaluminium hydride reduction yielded the corresponding lactol (14). A Wittig reaction to elaborate the acid side-chain, followed by methylation with diazomethane and subsequent acetylation with acetic anhydride in pyridine, then yielded the corresponding prostanoid (4d) [32% from (12)]. This differentially protected intermediate is useful for the synthesis of further analogues of (4a), and was readily converted into the prostanoid (4e) by treatment with acetic acid.

Partial separation of the C-15 epimers of (4b) was

achieved by chromatography over silica gel. By analogy with other C-15 prostaglandin epimers, the most polar isomer was tentatively assigned the α-configuration.[10]

Interestingly, although (4a) was virtually inactive



SCHEME (*i*) Bu_3SnH, THF; (*ii*) KOH, H_2O; (*iii*) $(MeCO)_2O$, C_5H_5N; (*iv*) B_2H_6, THF; (*v*) pyridinium chlorochromate; (*vi*) $(MeO)_2P(O)CH_2COC_5H_{11}$; (*vii*) $ZnBH_4$; (*viii*) HAl(CHMe$_2$)$_2$; (*ix*) $Ph_3\overset{+}{P}\overset{-}{C}H[CH_2]_3CO_2^-$; (*x*) CH_2N_2

in the collagen-induced platelet aggregation test, it was some 55 times more potent than $PGF_{2\alpha}$ in causing contraction of isolated guinea pig lung.

EXPERIMENTAL

Light petroleum had b.p. 60—80 °C.

3-exo-*Methoxycarbonyl*-6-endo-*hydroxynorborn*-2-endo-*ylacetic Acid* δ-*Lactone* (6).—Tri-n-butylstannane (3.06 g, 10.5 mmol), prepared by the method of Kuivila,[11] in tetrahydrofuran (10 ml) at 25 °C under nitrogen was treated with a solution of 3-*exo*-methoxycarbonyl-6-*endo*-hydroxy-5-*exo*-iodonorborn-2-*endo*-ylacetic acid δ-lactone (5) (3.22 g, 9.6 mmol) in tetrahydrofuran (10 ml). The solution was stirred and irradiated with a Philips 300-W u.v. lamp for 20 min and then the solvent removed by evaporation. The resultant residue was purified by chromatography on a silica column (75 g) using ethyl acetate–light petroleum as eluant, followed by recrystallisation from the same solvent, to afford the *ester* δ-*lactone* (6) (1.95 g, 1.9 mmol, 95%) as a white crystalline solid, m.p. 53.5—56 °C (Found: C, 62.8; H, 6.9. $C_{11}H_{14}O_4$ requires C, 62.84; H, 6.71%); t.l.c. R_F 0.35 [silica gel; ethyl acetate–light petroleum (40 : 60)]; $\nu_{max.}$ (cm^{-1}, CCl_4) 1 735 (C=O), 1 165 (C–O); δ(90 MHz, $CDCl_3$) 1.37 (m, H-7-*anti*), 1.55 (m, H-5-*endo*), 1.77 (m, H-7-*syn*), 2.18 (m, H-2-*exo* and H-5-*exo*), 2.55 (m, H-1, H-3-*endo*, H-4), 2.71 (br s, CH_2COO), 3.70 (s, CO_2-Me), and 4.95 (m, H-6-*exo*); *m/e* 210 ($M^{+\cdot}$), 182 ($M^{+\cdot} - C_2H_4$), 179 ($M^{+\cdot}$ — OMe), and 150 ($M^{+\cdot} - HCO_2Me$).

3-exo-*Carboxy*-6-endo-*hydroxynorborn*-2-endo-*ylacetic Acid* δ-*Lactone* (7).—The ester δ-lactone (6) (2.15 g, 10.25 mmol) was added to a solution of potassium hydroxide (1.15 g, 20.5 mmol) in water (60 ml) and the mixture stirred for 1 h. The resulting solution was washed with ethyl acetate (2 × 20 ml), acidified to pH 2 with concentrated hydrochloric acid, and then extracted with ethyl acetate (5 × 25 ml). The combined extracts from the acidified solution were dried ($MgSO_4$), filtered, and the solvent evaporated. The resulting semi-solid residue was treated with a mixture of acetic anhydride (10 ml) and pyridine (10 ml) and stirred under nitrogen for 48 h. The acetic anhydride and pyridine were removed by azeotropic distillation with toluene to leave an oily liquid, which was dissolved in an excess of saturated aqueous sodium hydrogencarbonate solution. This solution was washed with ethyl acetate (2 × 20 ml), acidified to pH 2, and extracted with ethyl acetate (5 × 25 ml). The combined extracts from the acidified solution were dried over magnesium sulphate, filtered, and concentrated by evaporation to afford a white solid residue. Recrystallisation of the residue from ethyl acetate–light petroleum afforded the *carboxylic acid* δ-*lactone* (7) (1.64 g, 8.4 mmol, 82%) as white crystals, m.p. 151.5—153.5 °C (Found: C, 60.95; H, 5.95. $C_{10}H_{12}O_4$ requires C, 61.21; H, 6.17%); $\nu_{max.}$ (cm^{-1}, $CHCl_3$) 3 500—2 500 (OH) and 1 725 br (C=O); δ(90 MHz, [$^2H_6$]DMSO) 1.24 (m, H-7-*anti*), 1.51 (m, H-5-*endo* and H-7-*syn*), 1.9—2.3 (m, H-2-*exo* and H-5-*exo*), 3.01 (m, H-1, H-3-*endo*, and H-4), 2.62 (d, *J* 4 Hz, H-8), 4.84 (m, H-6-*exo*), and 12.25 (m, CO_2H); *m/e* 196 ($M^{+\cdot}$), 178 ($M^{+\cdot} - H_2O$), 168 ($M^{+\cdot}$ — CO), and 150 ($M^{+\cdot} - HCO_2H$).

6-endo-*Hydroxy*-3-exo-(*hydroxymethyl*)*norborn*-2-endo-*ylacetic Acid* δ-*Lactone* (8).—The carboxylic acid δ-lactone (7) (235 mg, 1.2 mmol) was dissolved in tetrahydrofuran (5 ml) under nitrogen and the solution cooled to 0 °C; a solution of borane in tetrahydrofuran (3.0 ml, *ca.* 0.4M), prepared by the method of Brown and Sharp,[12] was added *via* a syringe. After stirring the reaction mixture for 1 h a saturated aqueous solution of ammonium chloride (2 ml) was added, the solution diluted with chloroform (50 ml), washed with saturated aqueous sodium hydrogencarbonate (2 × 15 ml), and dried ($MgSO_4$). The solution was filtered and the solvent evaporated to afford a residue which was purified by column chromatography [silica, 20 g; methanol–chloroform (10 : 90)] to afford the *hydroxy* δ-*lactone* (8) (166 mg, 0.91 mmol, 76%) as a white semi-solid (Found; C, 63.55; H, 7.65. $C_{10}H_{14}O_3 \cdot 0.5H_2O$ requires C, 62.81:

H, 7.91%); t.l.c., R_F 0.35 [silica gel; methanol–chloroform (10 : 90)]; $\nu_{max.}$ (cm^{-1}, $CHCl_3$) 3 400 (OH) and 1 725 (C=O); δ(60 MHz, $CDCl_3$) 1.40 (m, H-7-*anti*), 1.46 (m, H-5-*endo* and H-2-*exo*), 1.65 (m, H-7-*syn*), 1.9—2.3 (m, H-3-*endo*, H-4, and H-5-*exo*), 2.36 (m, H-1), 2.64 (d, *J* 4 Hz, H-8), 3.51 (octet, CH_2OH), 4.94 (octet, H-6-*exo*), and 5.31 (s, 2 × OH); *m/e* 182 ($M^{+\cdot}$), 164 ($M^{+\cdot} - H_2O$), and 138 ($M^{+\cdot} - CO_2$).

3-exo-*Formyl*-6-endo-*hydroxynorborn*-2-endo-*ylacetic Acid* δ-*Lactone* (9).—A solution of the hydroxy-δ-lactone (8) (307 mg, 1.68 mmol) in methylene chloride (7.5 ml) was added to a stirred suspension of pyridinium chlorochromate [8] (542 mg, 2.52 mmol) in methylene chloride (7.5 ml) under nitrogen at room temperature. After stirring for 2 h the solution was poured on to a silica column (20 g) and eluted with methylene chloride. The solvent was evaporated from the eluant to afford the *aldehyde* δ-*lactone* (9) (218 mg, 1.21 mmol, 72%) as a colourless oil; t.l.c. R_F 0.45 [silica gel, ethyl acetate–light petroleum (80 : 20)]; $\nu_{max.}$ (cm^{-1}, $CHCl_3$) 1 725 br (C=O); δ(60 MHz, $CDCl_3$) 1.2—1.7 (m, H-5-*endo* and H-7), 2.0—3.0 (m, H-1, -2, -3, -4, -5-*exo*), 4.90 (m, H-6-*exo*), and 9.71 (s, CHO); *m/e* 180 ($M^{+\cdot}$), 152 ($M^{+\cdot} - CO$), and 136 ($M^{+\cdot} - CO_2$).

6-endo-*Hydroxy*-3-exo-(trans-3′-*oxo-oct*-1′-*enyl*)*norborn*-2-endo-*ylacetic Acid* δ-*Lactone* (10).—Sodium hydride (120 mg, 2.5 mmol as a 50% dispersion in oil) was placed in a flask purged with nitrogen, washed with dry hexane (3 ml), suspended in dimethoxyethane (30 ml), and treated with dimethyl (2-oxoheptyl)phosphonate (666 mg, 3.0 mmol). After the mixture had been stirred for 1 h at room temperature, the aldehyde δ-lactone (9) (218 mg, 1.21 mmol) was added and stirring continued for a further 3 h. Acetic acid (5 drops) was added to the reaction mixture, and the solvent evaporated to leave an oily residue which was purified by column chromatography [silica, 20 g; ethyl acetate–light petroleum (40 : 60)] to afford the *unsaturated keto*-δ-*lactone* (10) (239 mg, 0.87 mmol, 72%) as a viscous oil (Found: C, 73.5; H, 8.7. $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75%); t.l.c. R_F 0.75 [silica gel, ethyl acetate–light petroleum (60 : 40)]; $\nu_{max.}$ (cm^{-1}, CCl_4) 1 740 (lactone C=O), 1 695, 1 675 (ketone C=O), and 1 625 (C=C); δ(60 MHz, $CDCl_3$) 0.9 (t, Me), 1.1—1.8 (m, H-5-*endo*, H-7, H-5′, -6′, -7′), 1.9—2.6 (m, H-1, H-2-*exo*, H-3-*endo*, H-4, H-4′, H-5-*exo*), 2.67 (d, H-8), 4.96 (m, H-6-*exo*) 6.09 (d, H-2′), and 6.75 (dd, H-1′); *J* (Hz) 16 (1′, 2′) and 7.5 (1′, 3-*endo*); *m/e* 276 ($M^{+\cdot}$), 261 ($M^{+\cdot}$ — Me), 247 ($M^{+\cdot}$ — Et), 233 ($M^{+\cdot} - C_3H_7$), 220 base ($M^{+\cdot} - C_4H_8$), 217 ($M^{+\cdot} - MeCO_2$), and 205 ($M^{+\cdot} - C_5H_{11}$).

6-endo-*Hydroxy*-3-exo-(trans-3′-*hydroxyoct*-1′-*enyl*)-*norborn*-2-endo-*ylacetic Acid* δ-*Lactone* (11).—A freshly prepared solution of zinc borohydride [13] in dimethoxyethane (10 ml, 0.5M) was added to a stirred solution of the unsaturated keto-δ-lactone (10) (200 mg, 0.725 mmol) in dimethoxyethane (14 ml) at room temperature under a nitrogen atmosphere. After 1 h unreacted zinc borohydride was destroyed by the addition of a saturated aqueous solution of ammonium chloride (1.0 ml). The reaction mixture was diluted with methylene chloride (50 ml), dried over magnesium sulphate, filtered, and the solvent removed by evaporation to give a residue which was purified by column chromatography [silica 20 g, ethyl acetate–light petroleum (50 : 50)] to afford the *allylic alcohol* δ-*lactone* (11) (129 mg, 0.464 mmol, 64%) as a viscous oil; t.l.c. R_F 0.3 and 0.35 for the two epimeric allylic alcohols [ethyl acetate–light petroleum (50 : 50)]; $\nu_{max.}$ (cm^{-1}, CCl_4) 3 600 (OH) and 1 735 (C=O); δ(60 MHz, CCl_4) 0.9 (t, Me), 1.1—1.5 (m, H-5-*endo*, H-7, H-5′, -6′, -7′), 1.5—2.5 (H-1, H-2-*exo*, H-3-*endo*, H-4, H-5-*exo*, H-4′, OH), 2.52 (d, H-8), 3.92 (m, H-3′), 4.79 (m, H-6-*exo*), and 5.46 (m, H-1′, -2′); *m/e* 278 ($M^{+\cdot}$).

6-endo-*Hydroxy*-3-exo-(trans-3′-*hydroxyoct*-1′-*enyl*)-*norborn*-2-endo-*ylacetic Acid* δ-*Lactone Tetrahydropyranyl Ether* (12).—A small crystal of *p*-toluenesulphonic acid (*ca.* 1 mg) was added to a solution of dihydropyran (126 mg, 1.5 mmol) and the allylic alcohol δ-lactone (11) (67.4 mg, 0.24 mmol) in dry methylene chloride (1.5 ml). The mixture was shaken for 35 min, pyridine (1 drop) added, and the solvent evaporated. The residue was purified by preparative plate chromatography [silica gel; ethyl acetate–light petroleum (60 : 40)] to afford the *tetrahydropyranyl ether* δ-*lactone* (12) (59 mg, 0.336 mmol, 67%) as a viscous oil; $\nu_{max.}$ (cm^{-1}, CCl_4) 1 740 (C=O); δ(90 MHz, $CDCl_3$) 0.88 (t, Me), 1.1—2.3 (m, H-2-*exo*, -5, -7, -4′, -5′, -6′, -7′, and protons in tetrahydropyran ring not adjacent to oxygen), 2.42 (m, H-1, H-4), 2.63 (d, H-8), 3.5—4.0 (m, protons adjacent to oxygen in tetrahydropyran ring), 4.65 (m, H-3′), 4.85 (m, H-6-*exo*), 5.20 (dd, H-2′), and 5.61 (dd, H-1′); *J* (Hz) 15.4 (1′, 2′) and 7.5 (1′, 3-*endo* = 2′, 3′); *m/e* 362 ($M^{+\cdot}$), 344 ($M^{+\cdot} - H_2O$), 291 ($M^{+\cdot} - C_5H_{11}$), 278 ($M^{+\cdot}$ — dihydropyran), and 261 base ($M^{+\cdot}$ — O — tetrahydropyran).

9,11-*Dideoxy*-9,11-*ethano*-9a-endo-*acetoxyprostaglandin* $F_{2\alpha}$ *Methyl Ester* (4e).—The tetrahydropyranyl ether δ-lactone (12) (178 mg, 0.493 mmol) was dissolved in toluene (20 ml) under nitrogen. The solution was cooled to −72 °C and treated with a solution of di-isobutylaluminium hydride in toluene (0.6 ml, 25% w/v, *ca.* 0.9 mmol). The reaction mixture was stirred for 1 h and then poured into a saturated aqueous solution of ammonium chloride (100 ml). The aqueous solution was extracted with diethyl ether (4 × 100 ml), the combined extracts dried ($MgSO_4$), filtered, and evaporated to give the corresponding δ-lactol (14) characterised by $\nu_{max.}$ (cm^{-1}, liquid film) 3 400 (OH), with complete absence of (C=O) at 1 735. The δ-lactol (14) without purification was immediately dissolved in tetrahydrofuran (10 ml) and added to a solution of the ylide [derived from potassium t-butoxide (663 mg, 5.9 mmol) and (4-butoxycarbonyl)triphenylphosphonium bromide (1.309 g, 2.96 mmol) in tetrahydrofuran (30 ml)] and the mixture stirred at room temperature under nitrogen for 30 min. A saturated aqueous solution of ammonium chloride (100 ml) was added to the reaction mixture and the resultant aqueous solution neutralised by the addition of acetic acid (0.5 ml). The mixture was extracted with diethyl ether (5 × 50 ml), the combined extracts dried ($MgSO_4$) and filtered, and the solvent evaporated to afford a residue consisting of the crude carboxylic acid (4c). This product (4c) was methylated with diazomethane and acetylated by stirring overnight with a mixture of acetic anhydride (6 ml) and pyridine (6 ml). Removal of solvent and reagents gave the crude ester (4d), which was dissolved in acetic acid (12 ml, 70%) and stirred at room temperature for 24 h. The acetic acid was removed by azeotropic distillation with toluene to give a residue, which was purified by preparative plate chromatography [silica gel; ethyl acetate–light petroleum (30 : 70)] to afford the *esterified prostaglandin analogue* (4e) (67 mg, 0.16 mmol, 32.5%) as a viscous oil; t.l.c. R_F 0.35 and 0.4 for the two C-15 epimers [silica gel; ethyl acetate–light petroleum (30 : 70)]; $\nu_{max.}$ (cm^{-1}, CCl_4) 3 500 (OH) and 1 735 (C=O); δ(90 MHz, $CDCl_3$) 0.89 (t, Me), 1.1—1.9 (m, H-3,

-7, -8, -10, 11a-*endo*, -16—19), 2.02 (s, MeCO), 2.1—2.4 (m, H-2, -4, -11a-*exo*, -11, -12-*endo*), 2.49 (m, H-9), 3.66 (s, MeO), 4.04 (m, C*H*OH), 5.10 (m, H-9a-*exo*), and 5.45 (m, H-5, -6, -13, -14); *m/e* 420 ($M^{+\cdot}$), 402 ($M^{+\cdot} - H_2O$), 360 ($M^{+\cdot} - MeCO_2H$), 349 ($M^{+\cdot} - C_5H_{11}$), and 342 ($M^{+\cdot} - MeCO_2H - H_2O$).

9,11-*Dideoxy*-9,11-*ethano*-9a-endo-*hydroxyprostaglandin* $F_{2\alpha}$ (4a).—The esterified prostaglandin analogue (4e) (65 mg, 0.16 mmol) was dissolved in methanol (6 ml), and the solution cooled to 0 °C and treated with a solution of potassium hydroxide (100 mg, 1.8 mmol) in a mixture of water (3 ml) and methanol (3 ml). The stirred solution was allowed to warm to room temperature during 1 h, and stirring was continued overnight. The solution was diluted with water (30 ml), neutralised with sodium dihydrogenphosphate (0.5 g), and extracted with diethyl ether (4 × 20 ml). The combined ethereal extracts were dried ($MgSO_4$), filtered, and the solvent evaporated to afford the *prostaglandin analogue* (4a) (57 mg, 0.16 mmol, 100%) as an opaque semi-solid material; $\nu_{max.}$ (cm^{-1}, CCl_4) 2 500—3 600 (OH) and 1 710 (C=O); δ(90 MHz, $CDCl_3$) 0.88 (t, Me), 1.1—1.8 (m, H-3, -8-*exo*, -10, -11a-*endo*, -16—19), 1.9—2.5 (m, H-2, -4, -7, -9, -11, -11a-*exo*, -12-*endo*), 4.04 (m, H-15), 4.41 (m, H-9a-*exo*), 4.89 (m, 3 × OH), and 5.46 (m, H-5, -6, -13, -14); *m/e* 364 ($M^{+\cdot}$), 346 ($M^{+\cdot} - H_2O$), 328 ($M^{+\cdot} - 2H_2O$), 302 ($M^{+\cdot} - CO_2H - OH$), and 261 [$M^{+\cdot} - C_5H_{11}CH(OH)$].

9,11-*Dideoxy*-9,11-*ethano*-9a-endo-*hydroxyprostaglandin* $F_{2\alpha}$ *Methyl Ester* (4b).—The allylic alcohol δ-lactone (11) (114 mg, 0.41 mmol) was dissolved in toluene (10 ml) under nitrogen and the solution cooled to −72 °C and treated with a solution of di-isobutylaluminium hydride (0.8 ml, 25% w/w, 1.2 mmol). The mixture was stirred for 1 h and then poured into a saturated aqueous solution of ammonium chloride (50 ml). The aqueous solution was extracted with diethyl ether (3 × 50 ml), and the extracts combined, dried ($MgSO_4$), and the solvent evaporated. The resultant δ-lactol (13) was not purified but immediately dissolved in tetrahydrofuran (10 ml) and the solution added to the ylide [formed from potassium t-butoxide (538 mg, 4.8 mmol) and (4-butoxycarbonyl)triphenylphosphonium bromide (1.064 g, 2.4 mmol) in tetrahydrofuran (20 ml)]. The reaction mixture was stirred at room temperature under nitrogen for 40 min and then diluted with a saturated aqueous solution of ammonium chloride (50 ml). The aqueous solution was neutralised with acetic acid (0.5 ml), extracted with diethyl ether (4 × 30 ml), the combined extracts dried ($MgSO_4$), filtered, and the solvent evaporated to give the crude prostaglandin analogue (4a). The crude (4a) was methylated with diazomethane and purified by column chromatography [silica 30 g; ethyl acetate–light petroleum as eluant (20 : 80)] to afford the *prostaglandin analogue methyl ester* (4b) (70 mg, 0.21 mmol, 51%) as a viscous oil; $\nu_{max.}$ (cm^{-1}, CCl_4) 3 500 (OH) and 1 735 (C=O); δ(90 MHz, $CDCl_3$) 0.88 (t, Me), 1.9—2.6 (m, H-2, -3, -4, -7, -8, -9, -10, -11, -11a, -12, -16, -17, -18, -19), 3.66 (s, OMe) 4.02 (m, C*H*OH), 4.35 (m, H-9a-*exo*), and 5.45 (m, H-5, -6, -13, -14); *m/e* 378 ($M^{+\cdot}$), 361 ($M^{+\cdot} - OH$), 343 ($M^{+\cdot} - OH - H_2O$), 318 ($M^{+\cdot} - HCO_3Me$).

The product (4b) (130 mg) was separated into its C-15 epimers by column chromatography (silica 70 g; ethyl acetate–light petroleum (20 : 80)] into the following three fractions: (*a*) the C-15 β-*epimer* of (4b) (56.4 mg); t.l.c. R_F 0.55 [silica gel; ethyl acetate–light petroleum (20 : 80)] *m/e* 378 ($M^{+\cdot}$): (*b*) a mixture of the C-15 α- and β-epimers of (4b) (16.3 mg); R_F 0.55 and 0.50 [silica gel; ethyl acetate–light petroleum (20 : 80)] (Found: C, 72.8; H, 10.2%; *M*, 378.277 2. $C_{23}H_{38}O_4$ requires C, 72.98; H, 10.12%; *M*, 378.277 0): and (*c*) the C-15 α-*epimer* of (4b) (35.4 mg); t.l.c. R_F 0.50 (a trace of β-epimer, R_F 0.55 contaminating) [silica gel; ethyl acetate–light petroleum (20 : 80)]; *m/e* 378 ($M^{+\cdot}$).

S. P. B. thanks the S.R.C. and Glaxo Group Research Ltd. (Ware) for a CASE research studentship.

[0/359 *Received*, 5*th March*, 1980]

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