Total Synthesis of Prostaglandin-$F_2\alpha$, and the 9-*O*-Benzyl Derivatives of Prostaglandins-$F_2\alpha$, -$F_1\alpha$, -D_2, and -D_1

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As an extension of the method whereby prostaglandin-$F_2\alpha$ may be prepared by homoconjugate addition of an organocuprate reagent to the 3-*endo*-silyloxytricyclo[3.2.0.0.^{2,7}]heptan-6-one (3), 3-*endo*-benzyloxytricyclo-[3.2.0.0^{2,7}]heptan-6-one (4) has been used to give the prostaglandin intermediate (14), in which the three hydroxy-functions at C-9, C-11, and C-15 are fully differentiated. Unmasking of the C-9 hydroxy-group gives the 15-silylated PG-$F_2\alpha$ (15). The novel 9-*O*-benzyl derivatives of prostaglandin 5-$F_2\alpha$, -$F_1\alpha$, -D_2, and -D_1 were also prepared from (14) as possible antagonists of the natural compounds.

We have shown[1] that prostaglandin-$F_2\alpha$ may be prepared by homoconjugate addition of an organocuprate reagent to the 3-*endo*-silyloxytricyclo[3.2.0.0^{2,7}]heptan-6-one (3). In this paper, bicyclo[3.2.0]hept-2-en-6-one[2] (1) was converted into 3-*endo*-benzyloxy-2-*exo*-bromobicyclo[3.2.0]heptan-6-one[3] (2), which on treatment with potassium t-butoxide cyclised to give 3-*endo*-benzyloxytricyclo[3.2.0.0^{2,7}]heptan-6-one (4) [92% from (2)]. Reaction of the ketone (4) with the mixed organocuprate reagent[1] (5) proceeded smoothly at −60 °C in ether–dichloromethane to yield, after 2 h, the 5-*endo*-benzyloxybicyclo[2.2.1]heptan-2-one (6) (71%). Baeyer–Villiger oxidation of the bicyclo[2.2.1]heptan-2-one (6) using peracetic acid in dichloromethane afforded a mixture of the corresponding lactones (7) and (8) (ratio 7 : 3, respectively) in 74% yield after chromatography.

Although this mixture was inseparable by column chromatography the required isomer (7) may be obtained in a pure state by removal of the unwanted lactone using a selective hydrolysis procedure.[4] Thus when the crude mixture of lactones (7) and (8) was treated with aqueous acetic acid for 8 days at 20 °C the lactone (8) was completely hydrolysed to the corresponding hydroxy-acid (12), which was readily removed during work-up, whereas the lactone (7) was converted into the corresponding desilylated hydroxy-lactone (11) (99% pure by g.l.c.). In this way lactone (11) was obtained from the ketone (6) in 68% yield without recourse to chromatography. Selective base-catalysed hydrolysis may also be used to remove the unwanted lactone, and under these conditions concurrent loss of silyl protecting groups did not occur.[4] The crude mixture of lactones (7) and (8) was reduced with di-isobutylaluminium hydride and the products separated by chromatography. The major component was isolated in 50% yield and exists as a tautomeric mixture of the hydroxy-aldehyde (9a) and the lactol (9b). The ratio (9a) : (9b) was *ca.* 3 : 1 in $CDCl_3$ as determined by ^1H n.m.r. The minor product was also a mixture of tautomers (10a) and (10b), present in about equal amounts in $CDCl_3$.

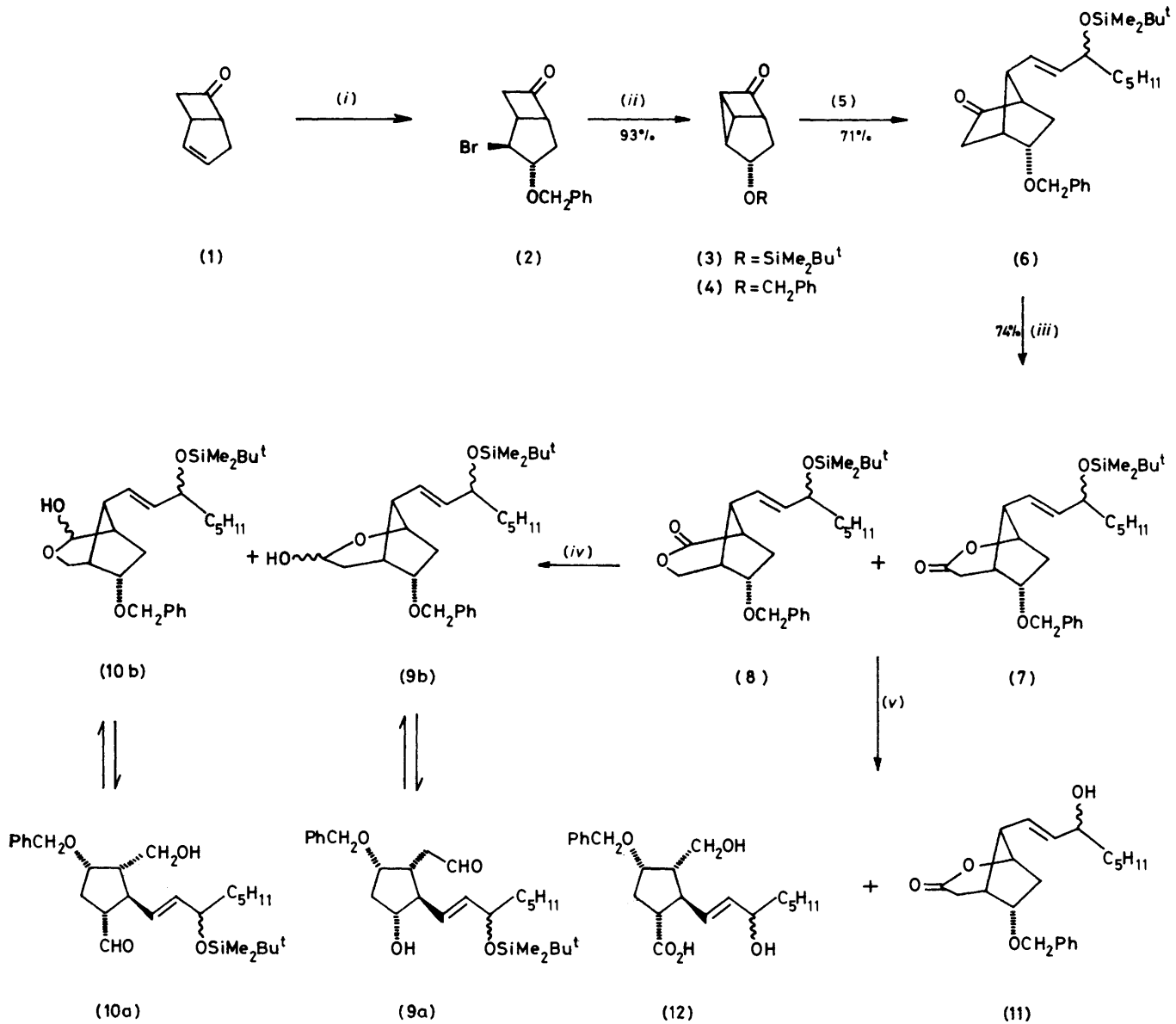
The hydroxy-aldehyde (9a) could also be obtained from the lactone (11) by re-silylation with t-butyldimethylsilyl chloride and subsequent reduction with di-isobutylaluminium hydride.

The hydroxy-aldehyde (9a) was treated with the ylide (13) (derived from 4-butoxycarbonyltriphenylphosphonium bromide)[5] to give the 9-*O*-benzyl-15-*O*-silyl-prostaglandin precursor (14) (88%) as a mixture of C-15 epimers. Sodium–liquid ammonia reduction of (14) gave a nearly quantitative recovery of the corresponding mixture of 15-silylated PG-$F_2\alpha$ and 15-*epi*-PG-$F_2\alpha$ (15).

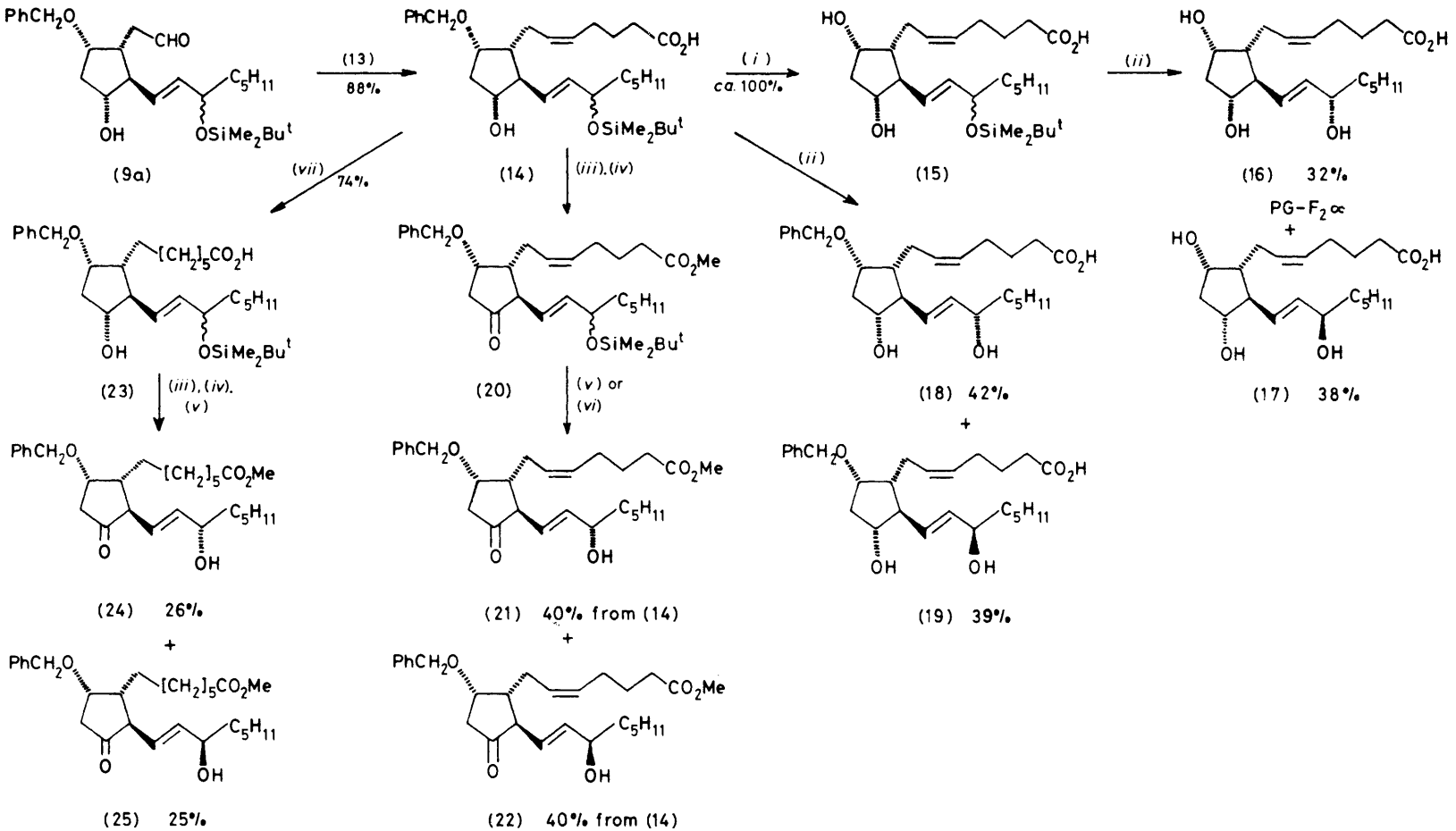
Treatment of this mixture (15) with tetra-n-butylammonium fluoride in THF[6] gave, after chromatographic separation, PG-$F_2\alpha$ (16) (32%) and 15-*epi*-PG-$F_2\alpha$ (17) (38%) which were identical (i.r., n.m.r., t.l.c.) with authentic samples. A similar deprotection of the intermediate (14) afforded 9-*O*-benzyl-PG-$F_2\alpha$ (18) (42%) and 15-*epi*-9-*O*-benzyl-PG-$F_2\alpha$ (19) (32%).

Esterification of (14) with diazomethane and subsequent oxidation using pyridinium chlorochromate afforded the ketone (20) as a mixture of C-15 epimers. Deprotection using acetic acid–THF–water at 20 °C was slow and gave after 4 days a mixture of the required isomers (21) and (22) which were separated chromatographically. In this way 9-*O*-benzyl-PG-D_2 methyl ester (21) (29%) and 15-*epi*-9-*O*-benzyl-PG-D_2 methyl ester (22) (31%) were obtained. Subsequent investigation showed that aqueous HF in acetonitrile was a far superior reagent for the removal of the t-butyldimethylsilyl protecting group.[7] Using this reagent desilylation was accomplished in 35 min at 20 °C to give the epimers (21) and (22) in a combined yield of 80%.

Hydrogenation of the intermediate (14) over 5% Pd–C in absolute ethanol[8] at −23 °C selectively reduced the 5,6-double bond and furnished the corresponding 9-*O*-benzyl-15-*O*-silyl-PG-$F_1\alpha$ derivative (23) (73%) as a mixture of C-15 epimers. Esterification using diazomethane and subsequent oxidation with pyridinium chlorochromate afforded the corresponding ketone. The crude product was treated with acetic acid–THF–water to remove the t-butyldimethylsilyl protecting group, and



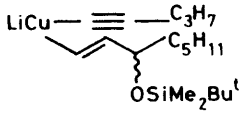
SCHEME 1 (*i*) NBA, $PhCH_2OH$; (*ii*) $KOBu^t$, THF; (*iii*) $MeCO_3H$, CH_2Cl_2; (*iv*) $Al(CH_2CHMe_2)_2H$; (*v*) $MeCO_2H$, H_2O



SCHEME 2 (*i*) Na, NH_3; (*ii*) Bu^n_4NF; (*iii*) CH_2N_2; (*iv*) C_5H_5N, CrO_3Cl; (*v*) $MeCO_2H$, THF, H_2O; (*vi*), HF, H_2O, (*vii*) 5%Pd–C, H_2

the C-15 epimers were separated by chromatography. This gave 9-*O*b-enzyl-PG-D_1 methyl ester (24) (26%) and 15-*epi*-9-*O*-benzyl-PG-D_1 methyl ester (25) (25%).

The benzyl protecting group offers several advantages over the t-butyldimethylsilyl protecting group which we used in our previous syntheses of PG-$F_{2\alpha}$.[9] Thus it may be introduced directly onto the bicyclo[3.2.0]hept-2-en-6-one starting material (1) to give the prostaglandin precursor (2). [The silylated analogue of (2) requires a two



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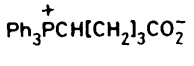

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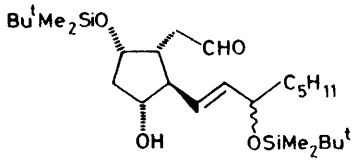

(26)

stage synthesis from (1).] Benzyl alcohol is also considerably cheaper than t-butyldimethylsilyl chloride. When using the 9,15-disilylated prostaglandin precursor (26) it is necessary to control very carefully the conditions of the Wittig reaction, otherwise scrambling of the t-butyldimethylsilyl group from the C-9 to the C-11 hydroxy-group occurs.[10] The corresponding benzyloxy-intermediate (9a) does not suffer from this disadvantage. The 3-*endo*-benzyloxy-2-*exo*-bromobicyclo[3.2.0]heptan-6-one (2) may be readily converted into the very flexible intermediate (14), wherein the three hydroxy-groups have been chemically differentiated. Finally the benzyl group is easily removed from (14) in excellent yield to furnish 15-t-butyldimethylsilyl-PG-$F_{2\alpha}$ (15), a potential precursor for PG-E_2[11] and PG-D_2.[12]

EXPERIMENTAL

Mass spectra were determined by electron impact (e.i.m.s.), or after chemical ionisation using ammonia or isobutane (c.i.m.s.). T.l.c. was carried out on Camlab 'Polygram' pre-coated silica gel plates and short-path column chromatography on Merck Kieselgel H or G. Light petroleum refers to the fraction of b.p. 60—80 °C and all solvents for chromatography were distilled before use.

3-endo-*Benzyloxytricyclo*[3.2.0.$0^{2,7}$]*heptan*-6-*one* (4).—A solution of 3-*endo*-benzyloxy-2-*exo*-bromobicyclo[3.2.0]heptan-6-one [3] (2) (4.81 g, 1.63×10^{-2} mol) was added dropwise to a solution of potassium t-butoxide (2.06 g, 1.84×10^{-2} mol) in dry THF (30 ml), with stirring, under dry nitrogen at −65 °C. After 1 h reaction was complete (t.l.c.) and the mixture was allowed to warm to −10 °C and diluted with dry ether (200 ml) containing Celite. After filtration under nitrogen and concentration under reduced pressure, the title compound (4) was obtained as colourless rosettes, m.p. 60—61 °C (3.22 g, 92%); $\nu_{max.}$ (mull in mineral oil) 1 725, 1 070, 740, and 690 cm^{-1}; τ ($CDCl_3$) 2.68 (5 H, s, aromatic H), 5.4 (1 H, d, J_{AB} 12 Hz, CH_AH_B–Ph), 5.55 (1 H, d, J_{AB} 12 Hz, CH_AH_B–Ph), 5.62 (1 H, m, H-3), 6.75—7.0 (2 H, m, H-5 and H-7), 7.2—7.4 (2 H, m, H-1 and H-2), 7.88 (1 H, ddd, *J* 15, 7, 4.5 Hz, H-4-*exo*), and 8.2 (1 H, br d, *J* 15 Hz, H-4-*endo*).

5-endo-*Benzyloxy*-7-anti-[(E)-3-(*t-butyldimethylsilyloxy-oct*-1-*enyl*]*bicyclo*[2.2.1]*heptan*-2-*one* (6).—n-Butyl-lithium in hexane (1.6 M; 55.4 ml, 8.86×10^{-2} mol) was added dropwise with stirring during 20 min to a solution of 1-iodo-3-(t-butyldimethylsilyloxy)oct-1-ene (29.69 g, 8.05×10^{-2} mol) in dry ether (150 ml) at −70 °C under dry nitrogen. After 30 min the metallation reaction was complete (t.l.c.).

Pent-1-ynylcopper (10.53 g, 8.05×10^{-2} mol) was dissolved in hexamethylphosphorus triamide (29.3 ml, 16.1×10^{-2} mol) and dry ether (50 ml) over 30 min, filtered through Celite under dry nitrogen, and added dropwise to the lithio-derivative at −70 °C during 20 min. After a further 1 h a solution of 3-*endo*-benzyloxytricyclo[3.2.0.$0^{2,7}$]heptan-6-one (4) (11.5 g, 5.35×10^{-2} mol) in dry dichloromethane (80 ml) was added dropwise with stirring over 20 min and the reaction mixture held at −60 °C for 2 h. Saturated ammonium chloride solution (250 ml) was then added and the mixture allowed to warm to room temperature (20 °C). The organic layer was separated and washed with ice-cold 2% sulphuric acid (2 × 250 ml) and 8% sodium hydrogencarbonate solution (2 × 250 ml), dried ($MgSO_4$), and evaporated to give the crude product as a colourless oil (37 g). Chromatography on Kieselgel (1.6 kg) eluting with light petroleum–ethyl acetate (9 : 1) afforded 5-endo-*benzyloxy*-7-anti-[(E)-3-*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]*bicyclo*[2.2.1]-*heptan*-2-*one* (6) as a colourless oil (17.45 g, 71%); $\nu_{max.}$ (film) 1 750, 1 250, 1 060, 968, 836, and 775 cm^{-1}; τ ($CDCl_3$) 2.68 (5 H, s, aromatic H), 4.2—4.7 (2 H, m, olefinic H), 5.52 (2 H, s, CH_2Ph), 5.6—6.0 (2 H, m, H-5 and H-3'), 7.0—8.9 (15 H, m; 7.95, 1 H, dd, *J* 18 and 4 Hz, H-3-*exo*), 9.0—9.2 (12 H, m, Bu^t and Me), and 9.91 and 9.95 (6 H, 2 × s, SiMe) (Found: C, 73.2; H, 9.6. $C_{28}H_{44}O_3Si$ requires C, 73.6; H, 9.7%).

6-endo-*Benzyloxy*-8-anti-[(E)-3-(*t-butyldimethylsilyloxy*)-*oct*-1-*enyl*]-2-*oxabicyclo*[3.2.1]*octan*-3-*ol* (9b).—7-*anti*-[(*E*)-3-t-Butyldimethylsilyloxy]oct-1-enyl]-5-*endo*-benzyloxy-bicyclo[2.2.1]heptan-2-one (6) (6 g, 1.32×10^{-2} mol) was stirred with 40% peracetic acid (27.6 ml) and sodium acetate (13.5 g, 1.65×10^{-2} mol) in dichloromethane (250 ml) at 20 °C for 16 h. The excess of peracid was destroyed by the addition of aqueous sodium thiosulphate solution until the mixture was neutral to starch–iodide paper. Water (250 ml) was added and the organic layer separated, washed with water (2 × 250 ml), sodium hydrogencarbonate solution (250 ml), dried, and evaporated to give the crude lactone mixture (7) + (8) (6.1 g, 98%). A small sample (2.2 g) was chromatographed on Kieselgel (220 g) eluting with light petroleum–ethyl acetate (4 : 1) to give the pure lactone mixture (7) + (8) (1.75 g, 74%); $\nu_{max.}$ (film) 1 743, 1 075, 1 250, 970, 835, and 775 cm^{-1}; τ ($CDCl_3$) 2.68 (5 H, s, aromatic H), 4.2—4.9 (2 H, m, olefinic H), 5.45 (1 H, m, H-1), 5.50 (2 H, s, CH_2Ph), 5.6—6.2 (2 H, m, H-6 and H-3'), 6.90 (1 H, dd, J_{vic} 3, J_{gem} 19.5 Hz, H-4-*endo*), 7.08 (1 H, br d, *J* 4.5 Hz, H-8), 7.2—7.8 (3 H, m, H-4-*exo*, H-7-*exo*, and H-5), 8.0 (1 H, br d, H-7-*endo*), 8.5—9.0 (8 H, m, $-[CH_2]_4$, 9.1 (12 H, m, Bu^t and Me), 9.97—10.02 (6 H, 2 × s, $SiMe_2$) (Found: C, 71.0; H, 9.5. $C_{28}H_{44}O_4Si$ requires C, 71.1; H, 9.4%); g.l.c. on a 3% OV-275 column at 250 °C indicated a

two-component mixture, 30% (8) with R_t 21 min and 70% (7) with R_t 24 min. The spectral data thus applies mainly to isomer (7). The presence of (8) is most obviously indicated by H-4-*endo* at *ca.* τ 5.25.

Hydrolysis of the Lactone Mixture (7) + (8).—A sample of the lactone mixture (7) + (8) (0.44 g, 9.3×10^{-4} mol) (69.7 : 30.3) was kept with glacial acetic acid (60 ml), water (20 ml), and sodium acetate (1 g) for 8 days. The solvents were removed under reduced pressure and the residue treated with water (80 ml) and extracted with ether (3×20 ml). The extract was washed with dilute sodium hydrogencarbonate solution (60 ml; 2N), dried, and evaporated. Chromatography on Kieselgel (25 g) eluting with ethyl acetate afforded the pure *hydroxy-lactone* (11) (0.23 g, 69%); $\nu_{max.}$ (film), 3 450, 1 740, 1 178, 1 105, 970, 735, and 695 cm^{-1}; τ ($CDCl_3$) 2.65 (5 H, s, aromatic H), 4.2—4.8 (2 H, m, olefinic H), 5.48 (1 H, m, H-1), 5.52 (2 H, s, CH_2Ph), 5.6—6.1 (2 H, m, H-6, H-3), 6.9 (1 H, dd, J_{gem} 19.5, J_{vic} 3 Hz, H-4-*endo*), 7.06 (1 H, br d, H-8), 7.2—8.2 (5 H, m, OH, H-4-*exo*, H-7-*endo*, H-7-*exo*, H-5), 8.3—9.0 (8 H, m, $[CH_2]_4$), and 9.15 (3 H, m, Me); g.l.c. as the trimethylsilyl ether on a 3% OV-275 column at 250 °C showed 1% with R_t 17.2 min [the unwanted isomer of (11)] and 99% with R_t 19.7 min [Found (c.i.m.s., NH_3): $(M + NH_4)^+$, 376.248 6. $C_{22}H_{30}O_4$ requires $(M + NH_4)^+$, 376.248 6].

Reduction of the Lactone Mixture (7) + (8).—The crude lactone mixture (7) + (8) (70 : 30) (2 g, 4.23×10^{-3} mol) was dissolved in dry dichloromethane (20 ml) under nitrogen. Di-isobutylaluminium hydride (Dibal) (2.2M; 3.74 ml) was added dropwise with stirring. The reaction mixture was held at −70 °C for 30 min, after which time water (10 ml) was added and the reaction mixture allowed to warm to 20 °C. Dilute sulphuric acid (2N, 5 ml) was added and the mixture poured into water (250 ml) and extracted with ether (2×100 ml). The combined organic extracts were washed with dilute sulphuric acid (2N, 150 ml) and water (250 ml), dried, and evaporated to give the crude lactol mixture (9) + (10) (1.6 g). Chromatography on Kieselgel (250 g) eluting with light petroleum–ethyl acetate (4 : 1) gave 6-endo-*benzyloxy*-8-anti-[(E)-3-*t-butyldimethylsilyloxy*]-*oct*-1-*enyl*]-2-*oxabicyclo*[3.2.1]*octan*-3-*ol* (9) (1 g, 50%) (R_F 0.45), $\nu_{max.}$ ($CHBr_3$) 3 580, 1 720 (CHO of aldehyde tautomer), 1 220, 1 250, 1 070, 970, 835, and 775 cm^{-1}; τ ($CDCl_3$) 0.2 (<1 H, s, CHO of aldehyde tautomer), 2.66 (5 H, m, aromatic H), 4.2—4.8 (>2 H, m, olefinic H and H-3 of lactol tautomer), 5.45 (1 H, d, J_{AB} 12 Hz, CH_AH_B–Ph), 5.72 (1 H, d, J_{AB} 12 Hz, CH_AH_B–Ph), 5.8—6.3 (3 H, m, H-1, H-6, and H-3′), 6.8—8.3 (7 H, m, H-4, H-5, H_2-7, H-8, and CHO*H*), 8.4—8.9 (8 H, m, $[CH_2]4$), 9.1 (12 H, m, Bu^t and Me), and 9.95 and 9.98 (6 H, 2 × s, $SiMe_2$).

Also obtained was the more-polar *isomer* (10) (0.45 g, 23%) (R_F 0.36); $\nu_{max.}$ ($CHBr_3$) 3 580, 1 720, 1 250, 1 070, 970, 835, and 775 cm^{-1}; τ ($CDCl_3$) 0.36 (<1 H, s, CHO of aldehyde tautomer), 2.7 (5 H, m, aromatic H), 4.3—4.7 (2 H, m, olefinic H), 4.92 (<1 H, br s, H-2 of lactol tautomer), 5.3—6.5 (6 H, m, CH_2Ph, OCH_2, H-6, and H-3′), 6.7—8.3 (6 H, m, H-1, H-5, H_2-7, H-8, and C*H*OH), 8.3—9.0 (8 H, m, $[CH_2]_4$), 9.12 (12 H, m, Bu^t and Me), and 9.99 (6 H, 2 × s, $SiMe_2$).

(5Z,13E)-(±)-9α-*Benzyloxy*-15-(*t-butyldimethylsilyloxy*)-11α-*hydroxyprosta*-5,13-*dienoic Acid* (14).—4-Butoxycarbonyltriphenylphosphonium bromide (3.75 g, 8.4×10^{-3} mol) was suspended in dry THF (75 ml) and potassium t-butoxide (1.9 g, 16.9×10^{-3} mol) was added in portions with stirring to give a bright red suspension. After stirring for 15 min, the lactol (9) (1 g, 2.1×10^{-3} mol) in dry THF (20 ml) was added dropwise and stirring continued for a further 30 min.

Saturated ammonium chloride solution (50 ml) was added followed by dilute hydrochloric acid (2N, 20 ml) and the organic layer separated. The aqueous layer was extracted with ether (3×60 ml) and the combined organic layers were washed with water, dried, and evaporated to give a pale yellow oil (3.6 g). The crude product was taken into chloroform and chromatographed on Kieselgel (50 g) eluting with 20% ethyl acetate–light petroleum to give (5Z,13E)-(±)-9α-*benzyloxy*-15-(*t-butyldimethylsilyloxy*)-11α-*hydroxyprosta*-5,13-*dienoic acid* (14) (1.03 g; 88%) (R_F 0.35, 40% ethyl acetate–light petroleum); $\nu_{max.}$ ($CHBr_3$) 3 580, 3 490, 1 740, 1 704, 1 250, 1 055, 970, 835, and 775 cm^{-1}; τ ($CDCl_3$) 2.62 (5 H, s, aromatic H), 4.3—4.9 (4 H, m, olefinic H), 5.4 (1 H, d, J 12 Hz, CH_AH_B–Ph), 5.65 (1 H, d, J 12 Hz, CH_AH_B–Ph), 5.8—6.4 (3 H, m, H-9, H-11, and H-15), 7.4—8.9 (22 H, m), 9.1 (12 H, m, Bu^t and Me), and 9.92 and 9.94 (6 H, 2 × s, $SiMe_2$) (Found: C, 70.4; H, 10.0. $C_{33}H_{54}O_5Si$ requires C, 70.9; H, 9.7%); g.l.c. of the trimethylsilyl ether methyl ester derivative on 3% OV-275 at 230 °C showed one component with R_t 25 min.

(5Z,13E)-(±)-15-(*t-Butyldimethylsilyloxy*)-9α,11α-*dihydroxyprosta*-5,13-*dienoic Acid* (15).—The benzyloxy-acid (14) (0.34 g, 6.08×10^{-4} mol) dissolved in dry ether (5 ml) was added dropwise to liquid ammonia, freshly distilled from sodium, at −70 °C with stirring. Freshly cut sodium metal (0.284 g, 12.3×10^{-3} g atom) was then added in portions to give a deep blue solution. After 45 min solid ammonium chloride was added in portions until the blue colouration faded and the liquid ammonia was allowed to evaporate overnight. The reaction mixture was poured into saturated ammonium chloride solution (150 ml) acidified with dilute hydrochloric acid solution (2N, 50 ml) and extracted with ethyl acetate (3×30 ml). The combined organic extracts were dried and evaporated to give a mixture of 15-t-butyldimethylsilyl-PG-$F_{2\alpha}$ and 15-*epi*-PG-$F_{2\alpha}$ (15) (0.284 g, 100%) (R_F 0.43, 80% ethyl acetate–19% light petroleum–1% acetic acid); $\nu_{max.}$ (film), 3 600—2 300 (broad), 1 710, 1 250, 970, 832, and 775 cm^{-1}; τ ($CDCl_3$) 4.3—4.8 (4 H, m, olefinic H), 4.5—5.8 (3 H, br s, 3 × OH), 5.8—6.1 (3 H, m, H-9, H-11, and H-15), 7.5—9.0 (20 H, m), 9.12 (12 H, m, Bu^t and Me), and 9.95 and 9.97 (6 H, 2 × s, $SiMe_2$), [Found (c.i.m.s., isobutane): $(M + H - H_2O)^+$, 451.327 4. $C_{26}H_{48}O_5Si$ requires $(M + H - H_2O)^+$, 451.324 3].

(±)-*Prostaglandin*-$F_{2\alpha}$ (16).—Tetra-n-butylammonium fluoride (3 g, 11.5×10^{-3} mol) freshly azeotroped with benzene was dissolved in dry THF (20 ml) and added to the mixture of 15-*O*-silyl-PG-$F_{2\alpha}$ epimers (15) (0.232 g, 4.95×10^{-4}) in dry THF (20 ml) and the mixture set aside for 16 h. After this time the THF was removed under reduced pressure and the residue partitioned between ether and water (100 ml). The ether layer was further washed with water, dried, and evaporated to give a colourless oil (0.19 g) which was chromatographed on Kieselgel (25 g) eluting with 80% ethyl acetate–19% light petroleum–1% acetic acid to give 15-epi-*prostaglandin*-$F_{2\alpha}$ (17) (0.067 g, 38%) (R_F 0.21); $\nu_{max.}$ (film) 3 650—2 300, 1 712, and 970 cm^{-1}; τ ($CDCl_3$) 4.3—4.8 (4 H, m, olefinic H), 5.05 (4 H, br s, 4 × OH), 5.6—6.5 (3 H, m, H-9, H-11, and H-15), 7.3—8.1 (8 H, m, H-2, H-4, H-7, H-8, and H-12), 8.1—8.9 (12 H, m, remainder), and 9.12 (3 H, br t, Me) [Found (c.i.m.s., NH_3): $(M + NH_4)^+$, 372.276 0; and $(M + NH_4 - H_2O)^+$, 354.263 6. $C_{20}H_{34}O_5$

requires $(M + NH_4)^+$, 372.275 0; and $(M + NH_4 - H_2O)^+$, 354.264 5] and *prostaglandin*-$F_2\alpha$ (16) (0.056 g; 32%) (R_F 0.11) which was identical (t.l.c., i.r., n.m.r., c.i.m.s.) with an authentic sample.

(5Z,15S*)-(±)-9α-*Benzyloxy*-11α,15-*dihydroxyprosta*-5,13-*dienoic Acid* (18).—The benzyloxysilyloxy-acid (14) (0.717 g, 1.25×10^{-3} mol) was treated with tetra-n-butylammonium fluoride (3 g, 11.5×10^{-3} mol) in dry THF (50 ml) and set aside for 16 h. The reaction mixture was poured into water (100 ml) and extracted with ether (3×80 ml). The combined extracts were washed with water (200 ml) and brine (200 ml), dried, and evaporated to give the crude product (0.6 g). Chromatography on Kieselgel (50 g) eluting with 1% acetic acid–80% ethyl acetate–19% light petroleum afforded two isomers: the less-polar 15-epi-9-O-*benzyl-PG*-$F_2\alpha$ (19) (R_F 0.49, 2% acetic acid–ethyl acetate) (0.215 mg, 39%); $\nu_{max.}$ (film) 3 600—2 300, 1 710, 970, 735, and 700 cm^{-1}; τ ($CDCl_3$) 2.65 (5 H, s, aromatic H), 4.2—4.7 (4 H, m, olefinic H), 4.8 (3 H, br s, $3 \times$ OH), 5.4 (1 H, d, J_{AB} 12 Hz, CH_AH_BPh), 5.65 (1 H, d, J_{AB} 12 Hz, CH_AH_B–Ph), 5.8—6.2 (3 H, m, H-9, H-11, and H-15), 7.5—8.1 (8 H, m, H_2-2, H_2-4, H_2-7, H-8, and H-12), 8.2—8.9 (12 H, m), and 9.1 (3 H, br t, Me) (Found: C, 72.5; H, 9.4. $C_{27}H_{40}O_5$ requires C, 72.9; H, 9.1%); and the more polar 9-O-*benzyl-PG*-$F_2\alpha$ (18) (R_F 0.35, 2% acetic acid–ethyl acetate) (231 mg; 42%); $\nu_{max.}$ (film) 3 600—2 200, 1 730, 1 710, 970, 740, and 695 cm^{-1}; τ ($CDCl_3$) 2.63 (5 H, s, aromatic H), 4.2—4.7 (4 H, m, olefinic H), 4.8 (3 H, br s, $3 \times$ OH), 5.4 (1 H, d, J_{AB} 15 Hz, CH_AH_B–Ph), 5.65 (1 H, d, J_{AB} 12 Hz, CH_AH_B–Ph), 5.8—6.2 (3 H, m, H-9, H-11, and H-15), 7.5—8.1 (8 H, m, H_2-2, H_2-4, H_2-7, H-8, and H-12), 8.2—8.9 (12 H, m), and 9.10 (3 H, br t, Me) (Found: C, 72.7; H, 9.3. $C_{27}H_{40}O_5$ requires C, 72.9; H, 9.1%).

Methyl (5Z,13E,15S*)-(±)-9α-*Benzyloxy*-15-*hydroxy*-11-*oxoprosta*-5,13-*dienoate* (21).—(*a*) The 9-*O*-benzyl-15-*O*-silyl-PG-$F_2\alpha$ (14) (1.17 g, 2.1×10^{-3} mol) was converted into the methyl ester by treatment with ethereal diazomethane. The crude reaction product was dissolved in dry dichloromethane (20 ml) and added dropwise to a suspension of pyridinium chlorochromate (1.08 g, 5×10^{-3} mol), and anhydrous sodium acetate (0.08 g, 1×10^{-3} mol) in dichloromethane (20 ml) at 20 °C with stirring for 2 h. After this time t.l.c. indicated that the reaction had gone to completion and the reaction mixture was diluted with ether (200 ml) and filtered through a short column of Florisil to remove chromium residues. After removal of solvent, the crude reaction product (20) was treated with glacial acetic acid–THF–water (3 : 2 : 1) (24 ml) for 4 days at 20 °C. The acetic acid was neutralised with aqueous sodium hydrogencarbonate solution and the aqueous layer was thoroughly extracted with ether. The combined ether extracts were dried and evaporated and the residue (1.1 g) chromatographed on Kieselgel (200 g) eluting with 40% ethyl acetate–light petroleum. Fractions 47—60 (R_F 0.21) contained the title *compound* (21) (0.28 g, 29%); $\nu_{max.}$ (film) 3 450, 1 740, 970, 735, and 700 cm^{-1}; τ ($CDCl_3$) 2.69 (5 H, s, aromatic H), 4.2—4.8 (4 H, m, olefinic H), 5.45 (1 H, d, J_{AB} 12 Hz, CH_AH_BPh), 5.65 (1 H, d, J_{AB} 12 Hz, CH_AH_B–Ph), 5.8—6.1 (2 H, m, H-9 and H-15), 6.37 (3 H, s, OMe), 7.14 (1 H, m, H-12), 7.3—8.2 (10 h, m, H_2-2, H_2-4, H_2-7, H-8, H_2-10, and OH), 8.2—9.0 (10 H, m), and 9.12 (3 H, br t, Me) [Found (e.i.m.s.): $M^+ - H_2O$, 438.275 1 and $M^+ - C_5H_{11}$, 385.201 5. $C_{28}H_{40}O_5$ requires $M^+ - H_2O$, 438.277 0 and $M^+ - C_5H_{11}$, 385.201 5]; and fractions 35—45 (R_F 0.24) contained the 15-epi-*isomer* (22) (0.3 g, 31%); $\nu_{max.}$ (film) 3 450, 1 740, 970, 735, and 700 cm^{-1}; τ ($CDCl_3$) 2.69 (5 H, s, aromatic H), 4.2—4.8 (4 H, m, olefinic H), 5.45 (1 H, d, J_{AB} 12 Hz, CH_AH_B–Ph), 5.65 (1 H, d, J_{AB} 12 Hz, CH_AH_B–Ph), 5.8—6.1 (2 H, m, H-9 and H-15), 6.37 (3 H, s, OMe), 7.14 (1 H, m, H-12), 7.3—8.1 (10 H, m, H_2-2, H_2-4, H_2-7, H-8, H_2-10, and OH), 8.2—9.0 (10 H, m), and 9.12 (3 H, br t, Me) [Found (e.i.m.s.): $M^+ - H_2O$, 438.276 1 and $M^+ - C_5H_{11}$, 385.200 2. $C_{28}H_{40}O_5$ requires $M^+ - H_2O$, 438.277 0, and $M^+ - C_5H_{11}$, 385.201 5].

(*b*) As above except that the 15-silyloxyketone (20) (0.9 g) was deprotected by treatment with acetonitrile (30 ml) containing 40% (w/w) aqueous hydrofluoric acid (4 ml). The solution was stood at 20 °C in a polythene container until t.l.c. showed the reaction was complete (35 min). Ethyl acetate (150 ml) was added, and the organic solution washed with 8% aqueous sodium hydrogencarbonate, dried, and evaporated. The epimers (21) and (22) were obtained in a combined yield of 80% after separation by chromatography on Kieselgel.

(13E)-(±)-9α-*Benzyloxy*-15-(*t-butyldimethylsilyloxy*)-11α-*hydroxyprosta*-13-*enoic Acid* (23).—The dienoic acid (14) (0.54 g, 0.97×10^{-3} mol) was hydrogenated over 5% Pd–C at −23 °C in absolute ethanol for 8 h. After filtration and removal of solvent, the crude product (23) was obtained as an oil (0.4 g, 74%); $\nu_{max.}$ ($CHBr_3$) 3 580, 3 500, 1 735, 1 704, 1 250, 1 070, 835, and 775 cm^{-1}; τ ($CDCl_3$) 2.70 (5 H, s, aromatic H), 4.3—5.3 (4 H, m, 2 H exchange with D_2O, olefinic H and $2 \times$ OH), 5.4 (1 H, d, J 12 Hz, CH_AH_B–Ph), 5.65 (1 H, d, J 12 Hz, CH_AH_BPh), 5.8—6.3 (3 H, m, H-9, H-11, and H-15), 7.5—8.2 (6 H, m, H_2-2, H-8, H_2-10, and H-12), 8.2—9.0 (18 H, m, H_2-3—H_2-7 and H_2-16—H_2-19), 9.17 (12 H, m, Bu^t and Me), and 9.98 and 10.0 (6 H, $2 \times$ s, $SiMe_2$).

Methyl (13E,15S*)-(±)-9α-*Benzyloxy*-15-*hydroxy*-11-*oxoprosta*-13-*enoate* (24).—The 9-*O*-benzyl-15-*O*-silyl-PG-$F_1\alpha$ (23) (0.4 g, 0.71×10^{-3} mol) was esterified in the usual way with diazomethane and the crude product was dissolved in dry dichloromethane (10 ml) and added dropwise to a suspension of pyridinium chlorochromate (0.54 g, 2.5×10^{-3} mol), and anhydrous sodium acetate (6.04 g, 0.5×10^{-3} mol) in dichloromethane (10 ml) at 20 °C with stirring for 2 h. Dilution of the reaction mixture with ether (100 ml) and filtration through Florisil furnished an oil upon removal of solvent. This product was then treated with glacial acetic acid–THF–water (3 : 2 : 1) (6 ml) for 2 days at 20 °C. After removal of solvents under reduced pressure the crude product was chromatographed on Kieselgel (60 g) eluting with 40% ethyl acetate–light petroleum. This afforded the *title compound* (24) (R_F 0.15) (0.084 g, 26%); $\nu_{max.}$ (film) 3 440, 1 740, 733, and 696 cm^{-1}; τ ($CDCl_3$) 2.65 (5 H, s, aromatic H), 4.2—4.8 (2 H, m, olefinic H), 5.35 (1 H, d, J_{AB} 12 Hz, CH_ACH_BPh), 5.65 (1 H, d, J_{AB} 12 Hz, CH_AH_B-Ph), 5.8—6.1 (2 H, m, H-9 and H-15), 6.34 (3 H, s, OMe), 7.0—8.9 (25 H, m), and 9.12 (3 H, br t, Me) [Found (c.i.m.s. NH_3): $(M + NH_4)^+$, 476.336 0 and $(M + NH_4 - H_2O)^+$, 458.329 9. $C_{28}H_{42}O_5$ requires $(M + NH_4)$, 476.337 6 and $(M + NH_4 - H_2O)$, 458.327 1]: and the 15-epi-*isomer* (25) (R_F 0.2) (0.082 g, 25%); $\nu_{max.}$ (film) 3 460, 1 740, 733, and 698 cm^{-1}; τ ($CDCl_3$) 2.65 (5 H, s, aromatic H), 4.2—4.8 (2 H, m, olefinic H), 5.45 (1 H, d, J_{AB} 12 Hz, CH_ACH_BPh), 5.65 (1 H, d, J_{AB} 12 Hz, CH_ACH_BPh), 5.8—6.0 (2 H, m, H-9 and H-15), 6.32 (3 H, s, OMe), 7.1—9.0 (25 H, m, remainder), and 9.10 (3 H, br t, Me) [Found (c.i.m.s. NH_3): $(M + NH_4)^+$, 476.333 1 and $(M + NH_4 - H_2O)^+$,

458.324 8. $C_{28}H_{42}O_5$ requires (M + NH_4), 476.337 6 and (M + NH_4 − H_2O), 548.327 1].

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REFERENCES

[1] T. V. Lee, S. M. Roberts, M. J. Dimsdale, R. F. Newton, D. K. Rainey, and C. F. Webb, *J.C.S. Perkin I*, 1978, 1172.
[2] P. A. Grieco, *J. Org. Chem.*, 1972, **37**, 2363.
[3] T. V. Lee, S. M. Roberts, and R. F. Newton, *J.C.S. Perkin I*, 1978, 1179.
[4] R. F. Newton, D. P. Reynolds, and S. M. Roberts, *J.C.S. Chem. Comm.*, 1979, 1150.
[5] *Cf*, E. J. Corey, N. M. Weinschenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.
[6] E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, 1972, **94**, 6190.
[7] R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly and S. M. Roberts, *Tetrahedron Letters*, 1979, 3981.
[8] E. J. Corey and R. K. Varma, *J. Amer. Chem. Soc.*, 1971, **93**, 7319.
[9] C. C. Howard, R. F. Newton, D. P. Reynolds, A. H. Wadsworth, D. R. Kelly, and S. M. Roberts, *J.C.S. Perkin I*, 1980, 852.
[10] R. F. Newton, D. P. Reynolds, and S. M. Roberts, unpublished observations
[11] M. Hayashi and T. Tanouchi, *J. Org. Chem.*, 1973, **38**, 2115.
[12] T. W. Hart, D. A. Metcalfe, and F. Scheinmann, *J.C.S. Chem. Comm.*, 1979, 156.