Synthesis of Aromatic Modified Prostaglandins from PGA_2

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A general synthetic scheme, starting from PGA_2 (obtained from the marine coral *Plexaura homomalla*), of prostaglandins modified in the upper chain is detailed. Key aldehyde intermediates have been secured from 11-deoxy-$PGF_{2\alpha}$ and $PGF_{2\alpha}$ by an efficient regioselective hydroxylation procedure followed by cleavage of the 5,6-double bond. Wittig reaction with these aldehydes provided the novel prostaglandins (5)—(8), belonging to the E and F families, and containing an aromatic ring in the upper chain.

The broad range of biological properties associated with prostaglandin (PG) molecules has stimulated much interest among chemists and biologists.[1] Numerous novel, conceptually imaginative synthetic approaches have been developed [2] which have led to a broad variety of prostanoids, some exhibiting an unusual or interesting biological profile.[1,3] Nevertheless, the marine coral *Plexaura homomalla* remains an extremely convenient source of starting material for the preparation of a number of prostanoids,[4,5] in particular because 15(*S*)-PGA_2 (1a) provides the prostaglandin framework, with the 'natural' stereochemistry at all asymmetric centres, in the optically active form.[4,5]

In this paper we report the synthesis, from PGA_2 (1a), of novel prostanoids presenting an aromatic functionality in the upper chain in the 11-deoxy as well as the 11-oxygenated series.†

First, the PGA_2 molecule was adequately protected at positions 1 and 15. After investigating a number of protecting groups of the hydroxy function at C-15, the PGA_2 t-butyldimethylsilyl derivative (1c) [6] was finally chosen. Then, different reducing agents were investigated, and K-Selectride appeared to be appropriate for achieving the regioselective reduction of the Δ^{10}-double bond and the stereoselective reduction of the ketone at position 9 without cleavage of the ester. Thus, compound (1c) was treated with an excess of K-Selectride in tetrahydrofuran (THF) solution at low temperature [7] to afford the desired 9-hydroxyprostanoid (2a). The assignment of α-stereochemistry to the hydroxy group in compound (2a) was based on its physical properties, as well as on its chemical behaviour (see below).

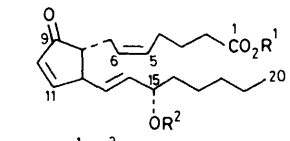
After a survey of several reagents, it was found that cleavage of the Δ^5-double bond in compound (2a) could be effected regioselectively in high yield by *cis*-hydroxylation followed by cleavage of the resulting α-glycol. Thus, the 11-deoxy-$PGF_{2\alpha}$ derivative (2a) was treated with a catalytic amount of osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide,[8] affording the 5,6-dihydroxy prostanoid (3a). Oxidative cleavage of the α-glycol functionality was achieved in *ca.* quantitative yield using sodium metaperiodate in aqueous dioxan solution,[9] thus providing the aldehyde (4a).

This aldehyde (4a) was submitted to a Wittig reaction by treatment with the anion of (*p*-methoxybenzyl)triphenylphosphonium in anhydrous dimethyl sulphoxide (DMSO),[10] thus affording, in 71% yield, a mixture of *cis*- (5a) and *trans*- (6a) styrene derivatives which could be separated by preparative layer chromatography (p.l.c.). The geometry of the double bond in these isomeric prostanoids was assigned on the basis of the coupling constants obtained by high-resolution n.m.r. spectroscopy, *i.e.* *J* 15.7 Hz for the more polar *trans*-isomer (6a) and *J* 11.7 Hz for the *cis*-isomer (5a).

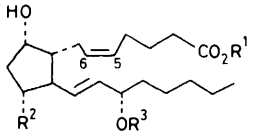
Cleavage of the silyl ether at position 15 in compound (6a) was achieved in 88% yield by treatment with tetrabutylammonium fluoride in THF solution,[11] conditions which do not affect the methoxy group. The novel prostanoid (6b), containing a methoxyphenyl grouping with the *trans*-styrene configuration, was thus obtained. Similarly, its *cis*-counterpart (5b) was prepared by hydrolysis of the 15-ether functionality of compound (5a) under identical conditions.

The 11-deoxy-$PGF_{2\alpha}$ derivatives (5a) and (6a) were converted by oxidation into their 9-keto analogues (7a) and (8a) respectively. Acid cleavage of the silyl ether grouping in the 9-keto prostanoids (7a) and (8a) afforded the corresponding 11-deoxy-PGE_2 analogues (7b) and (8b).

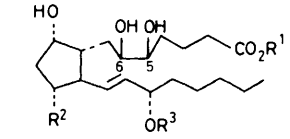
Having established the appropriate reaction conditions for the regioselective cleavage of the upper chain in the 11-deoxy-$PGF_{2\alpha}$ derivative (3a) and for the Wittig reaction on the key aldehyde intermediate (4a), this sequence was applied to the 11-hydroxylated series as follows. The appropriately protected PGA_2 derivative (1c) was treated with alkaline hydrogen peroxide [12] to give the epoxy ketone (9) in high



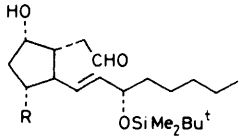
(1)a; $R^1 = R^2 = H$
b; $R^1 = Me$, $R^2 = H$
c; $R^1 = Me$, $R^2 = SiMe_2Bu^t$



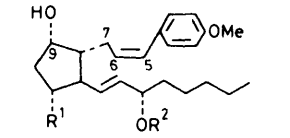
(2)a; $R^1 = Me$, $R^2 = H$, $R^3 = SiMe_2Bu^t$
b; $R^1 = Me$, $R^2 = OH$, $R^3 = SiMe_2Bu^t$
c; $R^1 = Me$ $R^2 = OH$, $R^3 = H$
d; $R^1 = R^3 = H$, $R^2 = OH$
e; $R^1 = H$, $R^2 = OH$, $R^3 = SiMe_2Bu^t$



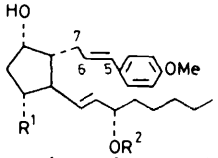
(3)a; $R^1 = Me$, $R^2 = H$, $R^3 = SiMe_2Bu^t$
b; $R^1 = Me$, $R^2 = OH$, $R^3 = SiMe_2Bu^t$
c; $R^1 = H$, $R^2 = OH$, $R^3 = SiMe_2Bu^t$
d; $R^1 = R^3 = H$, $R^2 = OH$



(4)a; R = H
b; R = OH

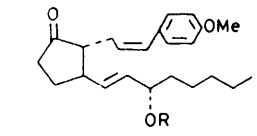


(5)a; $R^1 = H$, $R^2 = SiMe_2Bu^t$
b; $R^1 = R^2 = H$
c; $R^1 = OH$, $R^2 = SiMe_2Bu^t$
d; $R^1 = OH$, $R^2 = H$

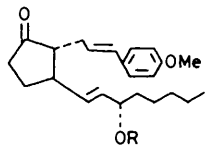


(6)a; $R^1 = H$, $R^2 = SiMe_2Bu^t$
b; $R^1 = R^2 = H$
c; $R^1 = OH$, $R^2 = SiMe_2Bu^t$
d; $R^1 = OH$, $R^2 = H$

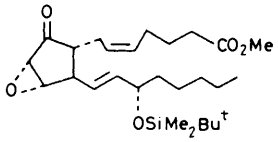
† Prostaglandin numbering is used throughout this paper.



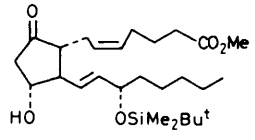
(7) a; R = $SiMe_2Bu^t$
b; R = H



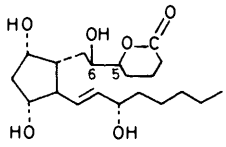
(8) a; R = $SiMe_2Bu^t$
b; R = H



(9)



(10)



(11)

yield. Cleavage of the epoxide (9) with aluminium amalgam [12] furnished the β-ketol (10) in *ca.* quantitative yield. Reduction of the 9-keto grouping in intermediate (10) with K-Selectride in THF solution at low temperature [7] provided, stereoselectively, the 9α-hydroxy derivative (2b) in 80% yield. In order to ascertain the α-stereochemistry at C-9 and C-11, the 15-(t-butyldimethylsilyl) ether group of the intermediate (2b) was cleaved by reaction with hydrofluoric acid in acetonitrile solution [11] to give (2c), followed by alkaline hydrolysis, thus affording, in *ca.* quantitative yield, $PGF_{2\alpha}$ (2d),[13] indistinguishable from an authentic sample by the usual criteria.

Reaction of the $PGF_{2\alpha}$ derivative (2b) with a catalytic amount of osmium tetraoxide in acetone–t-butyl alcohol solution in the presence of *N*-methylmorpholine *N*-oxide [8] yielded the corresponding 5,6-dihydroxy prostanoid (3b) regioselectively, in 65% yield. Hydrolysis of the ester group in compound (3b) with methanolic lithium hydroxide gave the tetrahydroxy acid (3c). Cleavage of the 15-(t-butyldimethylsilyl) ether function with hydrofluoric acid in acetonitrile solution [11] then provided the pentahydroxylated prostanoid (3d), highly soluble in water. This substance was accompanied by the corresponding δ-lactone (11) as a mixture of isomers at positions 5 and 6 since the hydroxylation of the Δ^5-double bond in compound (2b) is not a stereoselective process. Although the stereoisomers (3d) could be separated (see Experimental section) this was obviously not necessary for our present synthetic objective. The isomeric lactones (11) could also be separated by flash column chromatography (f.c.c.).[14]

Sodium periodate cleavage [9] of the α-glycol functionality in the tetraol (3b) afforded, in 70% yield, the aldehyde (4b) which exists in equilibrium with the hemiacetal form, as evidenced by its i.r. and n.m.r. properties (see Experimental section). Reaction of the aldehyde (4b) with the anion of (*p*-methoxybenzyl)-triphenylphosphonium in anhydrous DMSO gave a mixture of geometric isomers (5c) and (6c) in 74% yield. Separation of the pure *cis* and *trans* isomers was achieved by p.l.c. on silica gel plates. Cleavage of the t-butyldimethylsilyl ether grouping in the *cis*-isomer (5c) and its *trans*-counterpart (6c) was achieved by treatment with tetrabutylammonium fluoride,[11] thus providing the new $PGF_{2\alpha}$ analogues (5d) and (6d), respectively.† The geometry of the double bond was again based on the coupling constants associated with the Δ^5-vinylic protons in the isomers (5d) and (6d) (see above).

The synthesis of these new prostanoids benefitted greatly from various features. Firstly, the stereoselective reduction of the carbonyl group at C-9 in compounds (1c) and (10) which furnished the 9α-hydroxy derivatives (2a) and (2b), respectively, took place in high yield. Secondly, the regioselective and high-yielding hydroxylation procedure, affecting exclusively the Δ^5-*cis*-double bond, followed by a clean oxidative cleavage of the resulting α-glycol, conveniently gave the expected aldehydes (4). Thirdly, the t-butyldimethylsilyl ether proved to be an appropriate protecting group at O-15 while allowing chemical modifications in the upper side-chain and the prostanoid ring. Clearly, the easy access to aldehydes of type (4), described above, provides a new entry for the synthesis of novel prostanoids modified in the upper chain, as well as in the ring.[5]

† All new compounds are currently being submitted to biological evaluation. The results of this study will appear elsewhere.

Experimental

M.p.s were determined with a Fisher-Johns apparatus and are not corrected. I.r. spectra were obtained with a Beckman infrared spectrometer model IR-10. U.v. spectra were taken with a Perkin-Elmer 576 ST spectrophotometer. Optical rotations were taken in chloroform solution (*c* 1.0), between 16 and 22 °C with a 1 dm tube at the sodium D-line, with a Carl Zeiss 42017 polarimeter. Unless otherwise stated, ^1H n.m.r. spectra were recorded with a Varian EM-360 60 MHz spectrometer and a Nicolet NT-300 WB instrument, at 300 MHz for 5—8% w/v solutions in deuteriochloroform containing tetramethylsilane as internal reference. Coupling constants are accurate to ± 1 Hz. Mass spectra were recorded with a Dupont instrument, model 21-490, ionizing energy 70 eV.

Column chromatography was carried out using silica gel (Kieselgel 60, Art 9385, 230—400 mesh, Merck Darmstadt). T.l.c. was carried out with Camlab ' Polygram ' pre-coated silica plates, and Merck 2-mm thickness preparative plates were used for p.l.c.

PGA_2 Methyl Ester (1b).—To a solution of PGA_2 (1a) (8.2 g) in absolute diethyl ether (30 ml) cooled to 0—5 °C was added an ethereal solution of diazomethane [prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (14 g)]. After the solution had been kept for 30 min at 0—5 °C the solvent was removed and the crude PGA_2 methyl ester (1b) was obtained as a pale brown oil. An analytical sample of PGA_2 methyl ester (1b) was obtained by column chromatography on silica gel with gradient elution using ethyl acetate–hexane; the product had $[\alpha]_D$ +137°; $\nu_{max.}$ (neat) 3 450, 1 730, 1 705, 1 580, and 960 cm^{-1}; $\lambda_{max.}$ 218 nm (ε 10 200); δ 3.68 (s, CO_2Me), 4.00 (m, 15-H_β), 5.28—5.42 (m, 5- and 6-H), 5.55—5.68 (m, 13- and 14-H), 6.15 (dd, *J* 2 Hz, 10-H), and 7.5 (dd, *J* 2 Hz, 11-H).

15α-O-t-Butyldimethylsilyl-PGA_2 Methyl Ester (1c).[6]—To a solution of crude PGA_2 methyl ester (1b) 00 g) in dry dimethylformamide (DMF) (30 ml) were added imidazole (4 g) and t-butyldimethylsilyl chloride (4.3 g). This solution was stirred at room temperature under nitrogen for 2 h. It was then treated with saturated aqueous sodium chloride and extracted with methylene dichloride several times. The combined extracts were washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a brown oil which was purified twice by column chromatography on silica gel (70—230 mesh) with gradient elution using ethyl acetate–hexane as eluant. Thus was obtained the 15-silyl derivative

(1c) as an oil [7.3 g, 64% overall yield from (1a)], $[\alpha]_D$ +124°; $\nu_{max.}$ (neat) 1 735, 1 710, 1 585, and 960 cm^{-1}; δ 0.87 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.68 (s, CO_2Me), 4.07 (m, 15-H_β), 5.4—5.57 (4 H, m, 5-, 6-, 13-, and 14-H), 6.17 (dd, *J* 2 Hz, 10-H), and 7.45 (dd, *J* 2 Hz, 11-H); *m/z* 405 ($M^+ - C_4H_9$) and 391 ($M^+ - C_5H_{11}$).

15α-O-(t-Butyldimethylsilyl)-11-deoxy-PGF$_{2\alpha}$ Methyl Ester (2a).—A solution of the ketone (1c) (1.2 g, 2.6 mmol) in dry THF (10 ml; distilled over $LiAlH_4$) was cooled to −60 °C under nitrogen. To this solution was added slowly 1M K-Selectride in THF (7.8 ml) and the mixture was stirred at between −45 and −55 °C for 3 h. The reaction was then quenched with water (2 ml). 3M Aqueous sodium hydroxide (2 ml) was then added, followed by 30% hydrogen peroxide (2 ml), and the mixture was stirred at −10 °C for 2 h and then treated with 1M sulphuric acid to pH 8. The solvent was removed and the residue was extracted with methylene dichloride several times. The combined extracts were washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulphate. An oily material was obtained which was purified by column chromatography (gradient elution with ethyl acetate–hexane as eluant). Three products were eluted: (i) 15α-*O*-(t-butyldimethylsilyl)-11-deoxy-PGE_2 methyl ester, (ii) a by-product (not characterized), and (iii) the pure alcohol (2a) (0.75 g, 62%), $[\alpha]_D$ +40°; $\nu_{max.}$ (neat) 3 500, 1 740, 1 250, 1 070, and 970 cm^{-1}; δ 0.84 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.52 (s, CO_2Me), 3.91—4.21 (m, 15-H_β), and 5.2—5.42 (4 H, m, 5-, 6-, 13-, and 14-H); *m/z* 466 (M^+), 409 ($M^+ - C_4H_9$), 395 ($M^+ - C_5H_{11}$), 391 ($M^+ - C_4H_9 - H_2O$), and 377 ($M^+ - C_5H_{11} - H_2O$).

15α-O-(t-Butyldimethylsilyl)-11-deoxy-5,6-dihydro-5,6-dihydroxy-PGF$_{2\alpha}$ Methyl Ester (3a).—To a mixture of *N*-methylmorpholine *N*-oxide·$2H_2O$ (166 mg; 1.4 mmol), water (2 ml), acetone (2 ml), and osmium tetraoxide (0.02 mol) in t-butyl alcohol (5 ml) was added a solution of the olefin (2a) (0.51 g, 1.09 mmol) in acetone (3 ml) at 0—5 °C. After 40 min sodium hydrogensulphite (disodium dithionite) (1 g) was added. The mixture was stirred at 0—5 °C for 1 h and was then filtered. The solid residue was washed several times with acetone. The combined filtrate and washings were evaporated under reduced pressure to afford an oil which was purified by f.c.c. (ethyl acetate–hexane as eluant) to give the glycol (3a) as a pale yellow oil (350 mg, 65%), $[\alpha]_D$ +27°; $\nu_{max.}$ (neat) 3 400, 1 730, 1 250, 1 070, and 960 cm^{-1}; δ 0.84 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.65 (s, CO_2Me), and 5.3—5.45 (2 H, m, 13- and 14-H); *m/z* 411 ($M^+ - CH_2CH_2CO_2Me$), 405 ($M^+ - C_4H_9 - 2H_2O$), and 393 ($M^+ - CH_2CH_2CO_2Me - H_2O$).

Oxidative Cleavage of the Glycol (3a) *into the Aldehyde* (4a).—To a solution of sodium metaperiodate (0.33 g), in water (4 ml) and dioxan (12 ml) was added slowly during 15 min a solution of the glycol (3a) (0.64 g) in dioxan (2 ml). The mixture was then stirred at room temperature for 3 h. Further sodium metaperiodate (0.33 g) was added in two portions during 30 min. The reaction mixture was kept overnight and was then filtered and the residue was washed with diethyl ether. Removal of the solvent from the combined filtrate and washings under reduced pressure afforded an oil which was purified by f.c.c. with 20% ethyl acetate in hexane as eluant. The pure aldehyde (4a) was obtained as an oil (440 mg, 93%), $[\alpha]_D$ −10°; $\nu_{max.}$ (neat) 3 410, 2 700, 1 740, 1 250, 1 060, and 970 cm^{-1}; δ 0.84 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 5.3—5.5 (2 H, m, 13- and 14-H), and 9.7 (t, $w_{\frac{1}{2}}$ 4 Hz, CHO); *m/z* 350 ($M^+ - H_2O$), 311 ($M^+ - C_4H_9$), and 293 ($M^+ - C_4H_9 - H_2O$).

Alkylation of the Aldehyde (4a) *to give the Aromatic PG Derivatives* (5a) *and* (6a).—*Preparation of sodium methylsulphinylmethanide.* 50% Sodium hydride in oil (2 g) was washed three times with dried pentane (freshly distilled from CaH_2). Dried DMSO (20 ml; distilled over CaH_2) was then added and the mixture was stirred and heated at 65—70 °C for 1 h under nitrogen.

Alkylation reaction. To a suspension of (*p*-methoxybenzyl)-triphenylphosphonium (2 g) chloride in anhydrous DMSO (5 ml) was slowly added the above sodium methylsulphinylmethanide solution (2.3 ml) at 20 °C under nitrogen. A deep red coloured solution was obtained. The mixture was stirred for *ca.* 30 min whence a solution of the aldehyde (4a) (409 mg) in anhydrous DMSO (4 ml) was added. The mixture was then stirred for 27 h at room temperature, poured into ice–water, and extracted with ethyl acetate several times. The combined extracts were dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and an oily product was obtained; this was partially purified by f.c.c. Then the mixture of isomers (5a) and (6a) thus obtained was separated by p.l.c.; the more polar *trans*-isomer (6a) (206 mg) exhibited $[\alpha]_D$ +10°; $\nu_{max.}$ ($CHCl_3$) 3 400, 1 600, 1 570, 1 250, 1 070, and 960 cm^{-1}; δ(300 MHz) 0.859 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.767 (3 H, s, OMe), 4.04 (1 H, m, 7-H_β), 5.30—5.45 (2 H, m, 13- and 14-H), 6.08 (1 H, m, $J_{6,7}$ 7.86 and $J_{5,6}$ 15.75 Hz, 6-H), 6.36 (1 H, d, $J_{5,6}$ 15.75 Hz, 5-H), and 6.74 and 7.225 (total 4 H, m, ArH); *m/z* 472 (M^+), 415 ($M^+ - C_4H_9$), 401 ($M^+ - C_5H_{11}$), and 397 ($M^+ - C_4H_9 - H_2O$).

The less polar *cis*-isomer (5a) (170 mg) showed $[\alpha]_D$ +114°; $\nu_{max.}$ ($CHCl_3$) 3 450, 1 600, 1 240, and 960 cm^{-1}; δ(300 MHz) 0.878 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.798 (3 H, s, OMe), 4.02 (1 H, m, 9-H_β), 5.3—5.374 (2 H, m, 13- and 14-H), 5.618 (1 H, m, $J_{5,6}$ 11.7, $J_{7\alpha,6}$ 8.7, and $J_{7\beta,6}$ 6.0 Hz, 6-H), 6.406 (1 H, d, $J_{5,6}$ 11.7 Hz, 5-H), and 6.879—6.850 and 7.221 (total 4 H, m, ArH); *m/z* 472 (M^+), 454 ($M^+ - H_2O$), 415 ($M^+ - C_4H_9$), and 401 ($M^+ - C_5H_{11}$).

Hydrolysis of the 15-Ether Group of Compound (6a) *to give the 11-Deoxyprostaglandin Analogue* (6b).—To a solution of compound (6a) (56 mg) in anhydrous THF (1 ml) was added a 1M solution of tetrabutylammonium fluoride in THF (0.3 ml).[11] The mixture was stirred overnight at 48 °C. A further solution of tetrabutylammonium fluoride (0.1 ml) in dry THF (0.5 ml) was added and the mixture was stirred until no starting material could be detected by t.l.c. After extraction and isolation by the usual procedure, the product was purified by f.c.c. with 35% ethyl acetate in hexane as eluant. The pure novel prostanoid (6b) (38 mg, 88%) showed $[\alpha]_D$ +7°; $\nu_{max.}$ ($CHCl_3$) 3 400, 1 600, 1 570, 1 460, 1 240, 1 170, and 970 cm^{-1}; δ(300 MHz) 0.889 (3 H, s, 20-H_3), 3.794 (3 H, s, OMe), 4.05 (1 H, m, 9-H_β), 6.103 (1 H, m, $J_{6,7}$ 7.74 and $J_{5,6}$ 15.47 Hz, 6-H), 6.389 (1 H, d, $J_{5,6}$ 15.47 Hz, 5-H), and 6.813—6.841 and 7.239—7.268 (total 4 H, m, ArH); *m/z* 358 (M^+), 340 ($M^+ - H_2O$), and 322 ($M^+ - 2H_2O$).

Acid Hydrolysis of the cis*-Isomer* (5a) *to give the 11-Deoxy-PGF$_{2\alpha}$ Analogue* (5b).—Compound (5a) (50 mg) was desilylated with tetrabutylammonium fluoride under the conditions [11] used for the *trans*-isomer. Work-up then gave the prostanoid (5b) (32 mg, 82%) which showed $[\alpha]_D$ +165°; $\nu_{max.}$ ($CHCl_3$) 3 400, 1 600, 1 570, 1 500, 1 460, 1 240, 1 170, and 960 cm^{-1}; δ(300 MHz) 0.88 (3 H, s, 20-H_3), 3.802 (3 H, s, OMe), 4.062 (1 H, m, 7-H_β), 5.622 (1 H, m, $J_{5,6}$ 11.5, $J_{7\alpha,6}$ 8.53, and $J_{7\beta,6}$ 6.0 Hz, 6-H), 6.416 (d, 5 vinylic H, *J* 11.5 Hz), and 6.884—6.856 and 7.223 (total 4 H, m, 4-H); *m/z* 358 (M^+), 340 ($M^+ - H_2O$), and 322 ($M^+ - 2H_2O$).

Oxidation of the Alcohol (6a) *to the* 5-trans-11-*Deoxy*-PGE_2 *Analogue* (8a).—Pyridinium chlorochromate [15] (140 mg) and sodium acetate (10.7 mg) were suspended in anhydrous methylene dichloride (1 ml). A solution of compound (6a) (140 mg) in methylene dichloride (2 ml) was added to the magnetically stirred solution. After the mixture had been stirred for 4 h, additional pyridinium chlorochromate (72 mg) and sodium acetate (11 mg) were added. The reaction was complete after 1.5 h (t.l.c.) and diethyl ether (10 ml) was added and the solution was stirred for 15 min. The suspension was decanted and the insoluble residue was washed with diethyl ether several times. The combined ethereal solutions were passed through Florisil and then evaporated to dryness under reduced pressure. The crude oil was first separated by f.c.c. on silica gel with 3% ethyl acetate in hexane as eluant and then further purified by p.l.c. The oily prostanoid (8a) was obtained (61 mg, 44%) and showed $[\alpha]_D$ −25°; $\nu_{max.}$ ($CHCl_3$) 1 740, 1 610, 1 580, 1 250, and 970 cm^{-1}; δ(300 MHz) 0.893 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.794 (3 H, s, OMe), 5.508—5.529 (2 H, m, 13- and 14-H), 5.965 (1 H, m, 6-H, *J* 7.8 Hz), 6.311 (1 H, d, *J* 15.9 Hz, 5-H), and 6.808—6.837 and 7.225—7.255 (4 H, m, ArH); *m/z* 470 (M^+), 455 ($M^+ - CH_3$), 427 ($M^+ - CH_3CO$), 413 ($M^+ - C_4H_9$), 399 ($M^+ - C_5H_{11}$).

Oxidation of the Alcohol (5a) *to give the* 11-*Deoxy*-PGE_2 *Analogue* (7a).—Chromium trioxide (176 mg) was added to a magnetically stirred solution of anhydrous pyridine (0.3 ml) in anhydrous methylene dichloride (5 ml) at room temperature.[16] After 15 min a deep burgundy solution was obtained. A solution of compound (5a) (120 mg) in methylene dichloride (a few ml), was then added to the above solution. A black deposit appeared in the bottom of the flask. After being stirred for 20 min at room temperature the solution was decanted and the residue was washed with diethyl ether several times. The combined organic solutions were dried and evaporated under vacuum. The resulting oil was initially purified by f.c.c. with 3% ethyl acetate in hexane as eluant and was then purified further by p.l.c. The oily compound (7a) (79 mg, 66%) had $[\alpha]_D$ −10°; $\nu_{max.}$ ($CHCl_3$) 1 740, 1 610, 1 580, 1 460, 1 250, and 970 cm^{-1}; δ 0.86 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.78 (3 H, s, OMe), 5.27—5.42 (2 H, m, 13- and 14-H), 5.6 (1 H, m, 6-H), 6.35 (1 H, d, *J* 12 Hz, 5-H), and 6.72—6.90 and 7.10—7.25 (4 H, m, ArH); *m/z* 470 (M^+), 455 ($M^+ - CH_3$), 427 ($M^+ - CH_3CO$), 413 ($M^+ - C_4H_9$), and 399 ($M^+ - C_5H_{11}$).

Acid Hydrolysis of the Ether (8a) *to give the Prostanoid* (8b).—n-Butylammonium fluoride (0.4 ml) was added to a solution of compound (8a) (61 mg) in dry THF (1.5 ml) and the mixture was stirred at 48 °C for 5 h. The solution was then evaporated under reduced pressure and the crude product was purified by f.c.c. with 3% ethyl acetate in hexane as eluant to give the prostanoid (8b) (21 mg, 45%) as an oil, $[\alpha]_D$ −9°; $\nu_{max.}$ ($CHCl_3$) 3 460, 1 735, 1 610, 1 580, 1 510, 1 460, 1 250, 1 180, and 970 cm^{-1}; δ 0.88 (3 H, s, 20-H_3), 3.76 (3 H, s, OMe), 5.50—5.65 (2 H, m, 13- and 14-H), 5.95 (1 H, m, 6-H), 6.35 (1 H, m, *J* 15.9 Hz, 5-H), and 6.69—6.85 and 7.15—7.25 (4 H, m, ArH); *m/z* 356 (M^+), 255 ($M^+ - CHOHC_5H_{11}$).

Acid Hydrolysis of the Ether (7a) *to the Prostaglandin Derivative* (7b).—A solution of compound (7a) (76 mg) in a mixture of acetic acid (0.6 ml), THF (0.4 ml), and water (0.4 ml) was stirred at room temperature for 12 h,[17] then at 48 C for 24 h. After the addition of benzene the aqueous solvent was removed under reduced pressure. The crude product was purified by p.l.c. with 30% ethyl acetate in hexane as developer. The novel prostanoid (7b) was obtained as an oil (43 mg, 75%), $[\alpha]_D$ −17°; $\nu_{max.}$ ($CHCl_3$) 3 450, 1 740, 1 610, 1 580, 1 510, 1 460, 1 250, 1 180, and 970 cm^{-1}; δ(300 MHz) 0.887 (3 H, s, 20-H_3), 3.804 (3 H, s, OMe), 5.3—5.374 (2 H, m, 13- and 14-H), 5.531 (1 H, m, 6-H), 6.406 (1 H, d, *J* 11.52 H_3, 5-H), and 6.843—6.872 and 7.18—7.209 (4 H, m, ArH); *m/z* 356 (M^+), 338 ($M^+ - H_2O$), and 267 ($M^+ - C_5H_{11} - H_2O$).

Epoxidation of the PGA_2 *Ester* (1c) *to give the PG Derivative* (9).—A solution of compound (1c) (3.76 g) in methanol (58 ml) was cooled to −30 °C and treated with 30% hydrogen peroxide (5.6 ml) and then slowly with 3M aqueous lithium hydroxide (1.4 ml). The mixture was stirred at between −25 and −30 °C for 5 h. Then saturated aqueous ammonium chloride (14 ml) was added at −40 °C and the methanol was removed under reduced pressure. The aqueous residue was extracted with ethyl acetate and the combined extracts were washed with saturated aqueous sodium chloride, dried, and evaporated to leave the oily epoxide (9) (4.25 g, 95%) which was used directly for the next reaction. Compound (9) had $[\alpha]_D$ +16°; $\nu_{max.}$ ($CHCl_3$) 1 735, 1 240, 1 060, and 960 cm^{-1}; δ 0.86 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.44 (1 H, m, 11-H), 3.65 (3 H, s, CO_2Me), 3.72 (1 H, m, 10-H), 5.3—5.6 (4 H, m, 5-, 6-, 13-, and 14-H); *m/z* 478 (M^+), 447 ($M^+ - 31$), 421 ($M^+ - C_4H_9$), and 407 ($M^+ - C_5H_{11}$).

15α-O-(*t-Butyldimethylsilyl*)-PGE_2 *Methyl Ester* (10).—To a well stirred solution of compound (9) (4.25 g) in a mixture of THF (100 ml) and methanol (12 ml) was added saturated aqueous sodium hydrogen carbonate. This was cooled in a water-bath (5—10 °C) and aluminium amalgam [prepared from granular aluminium metal, 20 mesh (22 g)],[4] was added. After being stirred for 2 h at 10 °C the mixture was then stirred at room temperature for an additional 4 h. The suspension was filtered under reduced pressure through a sintered glass funnel and the residue was quickly washed with methylene dichloride several times. After removal of the solvent under reduced pressure, a crude oil (3 g) was obtained which was purified by column chromatography on silica gel (gradient elution with ethyl acetate in hexane). The pure PGE_2 ester (10) was isolated as an oil [2.24 g, 57% overall yield from (1c)], $[\alpha]_D$ −54°; $\nu_{max.}$ (neat) 3 460, 1 730, 1 250, 1 150, 1 070, and 960 cm^{-1}; δ 0.9 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.67 (3 H, s, CO_2Me), 5.2—5.4 (2 H, m, 5- and 6-H), and 5.48—5.68 (2 H, m, 13- and 14-H); *m/z* 423 ($M^+ - C_4H_9$) and 405 ($M^+ - C_4H_9 - H_2O$).

15α-O-(*t-Butyldimethylsilyl*)-$PGF_{2\alpha}$ *Methyl Ester* (2b).—To a solution of K-Selectride (4.6 ml) in dry THF (5 ml) cooled to −50 °C was added a solution of compound (10) (1.85 g) in anhydrous THF (11 ml) under nitrogen. The mixture was stirred at between −45 and −50 °C for 5 h. The reaction was then quenched with water (2 ml) at −40 °C. Then 3M aqueous sodium hydroxide (2 ml) was added, followed by 30% hydrogen peroxide (2 ml). [If 6M aqueous sodium hydroxide was used with 30% H_2O_2 and the solution stirred at room temperature, in addition to the compound (2b) the acid (2e) was also isolated.] The mixture was stirred at between −10 and +10 °C for 2 h and was then treated with 1M sulphuric acid until the pH of the solution was *ca.* 8. The solution was evaporated to dryness under reduced pressure. Purification of the crude product by column chromatography on silica gel (gradient elution with ethyl acetate in hexane) gave the oily product (2b) (1.48 g, 80%), $[\alpha]_D$ −15°; $\nu_{max.}$ ($CHCl_3$) 3 450, 1 735, 1 250, 1 080, and 960 cm^{-1}; δ 0.87 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.67 (3 H, s, CO_2Me), and 5.4—5.55 (4 H, m, 4-, 5-, 13-, and 14-H); *m/z* 425 ($M^+ - C_4H_9$), 407 ($M^+ - C_4H_9 - H_2O$), and 389 ($M^+ - C_4H_9 - 2\ H_2O$).

The free acid (2e) had $\nu_{max.}$ ($CHCl_3$) 3 600—2 300, 1 700, 1 250, 1 080, and 960 cm^{-1}; δ 0.87 (12 H, s, $SiMe_2Bu^t$ and

20-H_3), 5.2—5.6 (4 H, m, 5-, 6-, 13-, and 14-H), and 8.85 (1 H, s, CO_2H).

Hydrolysis of the Silyl Ether (2b) *to* $PGF_{2\alpha}$ (2d).—To a solution of compound (2b) (49 mg) in acetonitrile (2 ml) was added a solution of hydrofluoric acid in acetonitrile [40% HF (0.008 ml) in CH_3CN (0.2 ml)] dropwise at between −20 and −25 °C. The reaction mixture was stirred at −5 °C for 1 h and was then quenched by the addition of saturated aqueous sodium chloride. The mixture was extracted with methylene dichloride several times and the combined extracts were washed with saturated aqueous sodium chloride twice and dried over anhydrous sodium sulphate. The crude material was hydrolysed with base, followed by chromatography over silica gel. Pure $PGF_{2\alpha}$ (2d) (26 mg) was obtained and was shown to be identical with an authentic sample by all the usual criteria. The acid had $[\alpha]_D$ +23°; $\nu_{max.}$ ($CHCl_3$) 3 500, 1 710, 1 400, 1 250, 1 100, and 960 cm^{-1}; δ 0.82 (3 H, m, 20-H_3) and 5.25—5.52 (4 H, m, 5-, 6-, 13-, and 14-H); *m/z* 336 ($M^+ - H_2O$), 265 ($M^+ - C_5H_{11} - H_2O$), and 247 ($M^+ - C_5H_{11} - 2\ H_2O$).

15α-O-(*t-Butyldimethylsilyl*)-5,6-*dihydro*-5,6-*dihydroxy*-$PGF_{2\alpha}$ *Methyl Ester* (3b).—To a mixture of *N*-methylmorpholine *N*-oxide·2H_2O (298 mg), water (3 ml), acetone (3 ml), and osmium tetraoxide (0.02 mol) in t-butyl alcohol (10 ml) was added a solution of the $PGF_{2\alpha}$ derivative (2b) (1.026 g) in acetone (4 ml) at 5 °C. After the mixture had been stirred for 40 min sodium hydrogensulphite (2 g) was added. The suspension was stirred again at 5 °C for 1 h and was then filtered. After the usual work-up as described for compound (3a), column chromatography with ethyl acetate as eluant afforded compound (3b) (0.71 g, 65%) as an oil, $\nu_{max.}$ ($CHCl_3$) 3 400, 1 740, 1 250, 1 070, and 970 cm^{-1}; δ 0.87 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.65 (3 H, s, CO_2Me), and 5.3—5.5 (2 H, m, 13- and 14-H); *m/z* 439 ($M^+ - C_4H_9 - H_2O$) and 413 ($M^+ - [CH_2]_3CO_2Me$).

15α-O-(*t-Butyldimethylsilyl*)-5,6-*dihydro*-5,6-*dihydroxy*-$PGF_{2\alpha}$ (3c).—To a solution of compound (3b) (296 mg) in methanol (2 ml) was added 3M lithium hydroxide (0.3 ml). The mixture was stirred at room temperature for 2 h and was then acidified with 4% hydrochloric acid until the pH of the solution was *ca.* 7—8. The solvent was removed under reduced pressure to afford the acid (3c) as a syrupy oil, $\nu_{max.}$ ($CHCl_3$) 3 600—2 400, 1 730, 1 260, 1 080, and 970 cm^{-1}; δ 0.87 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 5.3—5.6 (2 H, m, 13- and 14-H). This material was used without further purification for the desilylation reaction.

5,6-*Dihydro*-5,6-*dihydroxy*-$PGF_{2\alpha}$ (3d).—To the above solution of the syrupy oil (3c) in acetonitrile (3 ml) was added a solution of hydrofluoric acid in acetonitrile [40% hydrofluoric acid (0.06 ml) in CH_3CN (1.5 ml)] at 0—5 °C. The mixture was stirred for 1.5 h and was then directly passed through a column of silica gel (18 g) and separated by f.c.c. with ethyl acetate–methanol (9 : 1) as eluant. The pure pentaol (3d) (46 mg) (highly soluble in water), existing as a mixture of isomers at C-5 and C-6, was obtained and had $[\alpha]_D$ +16°; $\nu_{max.}$ ($CHCl_3$) 3 400, 1 725, 1 250, 1 100, and 965 cm^{-1}; δ 0.89 (3 H, s, 20-H_3 and 5.4—5.6 (2 H, m, 13- and 14-H); *m/z* 352 ($M^+ - 2\ H_2O$), 334, 316, and 263.

Further f.c.c. of this isomeric mixture (3d) afforded separation into the pure isomers with ethyl acetate–methanol (9 : 1) as eluant.

Chromatographic separation of the crude product obtained after acidic hydrolysis of the 15-silyl ether (3c) also afforded a mixture of isomeric lactones (11) (90 mg), $[\alpha]_D$ +2°; $\nu_{max.}$ ($CHCl_3$) 3 450, 1 730, 1 240, 1 100, and 970 cm^{-1}; δ 0.89 (3 H, s, 20-H_3) and 5.5—5.75 (2 H, m, 13- and 14-H); *m/z* 352 ($M^+ - H_2O$), 334 ($M^+ - 2\ H_2O$), 316 ($M^+ - 3\ H_2O$), and 263 ($M^+ - C_5H_{11} - 2\ H_2O$). This stereoisomeric mixture at C-5 and C-6 could be separated by careful p.l.c.

Oxidative Cleavage of the α*-Glycol* (3b) *to the Aldehyde* (4b).—To a solution of sodium metaperiodate (0.58 g) in water (5 ml) and dioxan (4 ml) was added slowly (30 min) a solution of compound (3b) (0.73 g) in dioxan (6 ml). The mixture was stirred at room temperature and a large amount of white precipitate was produced. After 8.5 h the mixture was filtered and the residue was washed with diethyl ether. Removal of the solvents under reduced pressure afforded an oil which was purified by column chromatography with ethyl acetate–hexane as eluant. The aldehyde (4b) was thus obtained (380 mg, 70%) and had $[\alpha]_D$ −14°; $\nu_{max.}$ ($CHCl_3$) 3 400, 2 700, 1 720, 1 250, 1 070, and 970 cm^{-1}; δ 0.87 (12 H, s, $SiMe_2Bu^t$ and 20-H_3) and 5.36—5.5 (2 H, m, 13- and 14-H); *m/z* 327 ($M^+ - C_4H_9$), 313 ($M^+ - C_5H_{11}$), 309 ($M^+ - C_4H_9 - H_2O$), and 295 ($M^+ - C_5H_{11} - H_2O$).

Several experiments led to the isolation of the corresponding ethylene acetal as evidenced by the absence of a carbonyl group in the i.r. spectrum and the appearance of an acetal H in the n.m.r. spectrum (δ 4.36—4.74, br, symmetric signal).

Alkylation of the Aldehyde (4b) *to the Aromatic PG Derivatives* (5c) *and* (6c).—Sodium methylsulphinylmethanide was prepared as described above for the synthesis of compounds (5a) and (6a).

To a suspension of (*p*-methoxybenzyl)triphenylphosphonium chloride (1.7 g) in anhydrous DMSO (5 ml) was added a solution of sodium methylsulphinylmethanide (freshly prepared) in DMSO (2 ml) dropwise at 20 °C under nitrogen. A deep red coloured solution developed. After the solution had been stirred for 30 min a solution of the aldehyde (4b) (380 mg) in anhydrous DMSO (4 ml) was added. The mixture was stirred at room temperature under nitrogen for 36 h, then poured into ice–water, extracted with ethyl acetate, and dried over sodium sulphate. The solvent was removed under reduced pressure and a product was obtained which was purified by column chromatography on silica gel, with ethyl acetate–hexane as eluant, to give a pale yellow oil (360 mg, 74%); this oily mixture was separated into the *cis*-isomer (5c) and *trans*-isomer (6c) by p.l.c. with methylene dichloride–methanol (49 : 1) as developer.

The *cis*-isomer (5c) showed $[\alpha]_D$ +75°; $\nu_{max.}$ ($CHCl_3$) 3 400, 1 610, 1 580, 1 510, 1 465, 1 250, 1 180, 1 080, and 970 cm^{-1}; δ 0.88 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.8 (3 H, s, OMe), 5.4—5.6 (2 H, m, 13- and 14-H), 6.42 (1 H, d, $J_{5,6}$ 11.8 Hz, 5-H), and 6.86—6.89 and 7.22—7.26 (total 4 H, m, ArH); *m/z* 488 (M^+), 470 ($M^+ - H_2O$), 452 ($M^+ - 2\ H_2O$), 431 ($M^+ - C_4H_9$), 413 ($M^+ - C_4H_9 - H_2O$), and 399 ($M^+ - C_5H_{11} - H_2O$).

The *trans*-isomer (6c) showed $[\alpha]_D$ −5°; $\nu_{max.}$ ($CHCl_3$) 3 400, 1 610, 1 510, 1 465, 1 250, 1 180, 1 080, and 970 cm^{-1}; δ 0.89 (12 H, s, $SiMe_2Bu^t$ and 20-H_3), 3.8 (3 H, s, OMe), 5.4—5.6 (2 H, m, 13- and 14-H), 6.12—6.37 (1 H, m, 6-H), 6.4 (1 H, d, $J_{5,6}$ 15.7 Hz, 5-H), and 6.8 and 7.2 (total 4 H, m, ArH); *m/z* 488 (M^+), 470 ($M^+ - H_2O$), 431 ($M^+ - C_4H_9$), 413 ($M^+ - C_4H_9 - H_2O$), and 399 ($M^+ - C_5H_{11} - H_2O$).

Hydrolysis of the 15*-Ether Group in Compound* (5c) *and Formation of the* $PGF_{2\alpha}$ *Analogue* (5d).—To a solution of compound (5c) (29 mg) in dry THF (0.5 ml) was added a 1M solution of tetrabutylammonium fluoride in THF (0.5 ml).[11] The mixture was stirred at 48 °C for 14 h. After removal

of the solvent under reduced pressure the product was purified by f.c.c. (ethyl acetate as eluant), then by p.l.c. (ethyl acetate as developer). The crystalline prostaglandin analogue (5d) was obtained (13 mg, 57%), m.p. 43—45 °C $[\alpha]_D$ +143°: $\nu_{max.}$ ($CHCl_3$) 3 350, 1 610, 1 580, 1 510, 1 450, 1 250, 1 180, and 965 cm^{-1}; δ 0.87 (3 H, t, 20-H_3), 3.8 (3 H, s, OMe), 4.02 (1 H, m, 9-H_β), 5.4—5.6 (3 H, m, 6-, 13-, and 14-H), 6.4 (1 H, d, $J_{5,6}$ 11.5 Hz, 5-H), and 6.88 and 7.22 (total 4 H, m, ArH); *m/z* 374 (M^+), 356 ($M^+ - H_2O$), and 338 ($M^+ - 2\ H_2O$).

Hydrolysis of the 15-*Ether Derivative* (6c) *and Obtention of the Prostanoid* (6d).—To a solution of compound (6c) (29 mg) in dry THF (0.5 ml) was added a 1M solution of tetrabutylammonium fluoride in THF (0.5 ml).[11] The reaction mixture was stirred at 48 °C overnight. By the usual work-up as described above, followed by purification, compound (6d) was obtained as an oily product (17 mg, 76%), $[\alpha]_D$ −6°; $\nu_{max.}$ ($CHCl_3$) 3 350, 1 610, 1 580, 1 510, 1 450, 1 250, 1 180, and 965 cm^{-1}; δ(300 MHz) 0.88 (3 H, t, 20-H_3), 3.79 (3 H, s, OMe), 5.4—5.6 (2 H, m, 13- and 14-H), 6.06—6.13 (1 H, m, $J_{6,7}$ 7.4 Hz, 6-H), 6.4 (1 H, d, $J_{5,6}$ 15.91 Hz, 5-H), and 6.84 and 7.24 (total 4 H, *m*, ArH); *m/z* 374 (M^+), 356 ($M^+ - H_2O$), and 338 ($M^+ - 2\ H_2O$).

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