Synthesis of Some 13-Oxaprostanoids

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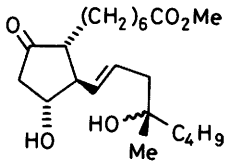
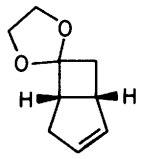
A new route to biologically interesting 13-oxaprostanoids is described. Reaction of an unhindered secondary hydroxy group with t-butyldiphenylsilyl chloride in the presence of an adjacent hindered hydroxy group allows rapid access to the key synthon (**7**), from which prostanoids of the F series [*e.g.* compound (**13**)] and I series [*e.g.* compound (**18**)] were prepared.

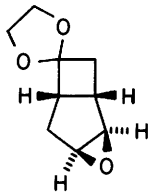
After twenty years of intensive research the first prostaglandins [*e.g.* misoprostol (**1**)][1] are now being introduced into the clinic with some success. The major problem has been the identification and exploitation of prostanoids with more selective biological activity than that displayed by the natural products.[2] Compounds with a heteroatom at the 13-position (prostaglandin numbering) have been shown to have interesting patterns of biological activity with the 13-aza-[3] and 13-oxa-systems[4] being of special note. Herein we report a new method of preparation of 13-oxaprostaglandins that involves, in a key step, the reaction of t-butyldiphenylsilyl chloride with an unencumbered secondary hydroxy group in the presence of an adjacent, hindered secondary hydroxy group.



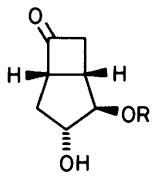
(**1**)



(**2**)



(**3**)

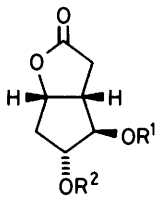


(**4**) R = H
(**5**) R = SiBu^{t}Ph$_2$

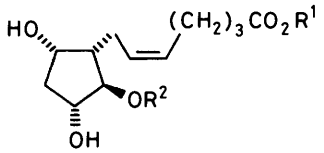
The known acetal (**2**)[5] gave the *exo*-epoxide (**3**) (95%) with high selectivity on reaction with *m*-chloroperbenzoic acid. Hydrolysis of the oxirane and concomitant removal of the dioxolane protecting group was accomplished using perchloric acid and afforded the crystalline diol (**4**) (87%) as a colourless solid. Reaction of this compound with t-butyldiphenylsilyl chloride in dimethylformamide containing imidazole at 0 °C for 18 h gave the silylether (**5**). Treatment of (**5**) with excess silylating reagent did not result in any further reaction. In contrast, t-butyldimethylsilyl chloride and methyldiphenylsilyl chloride reacted with the diol (**4**) to give the corresponding bis-silylethers; the use of equimolar quantities of each of these silylating reagents demonstrated that the two hydroxy groups reacted at similar rates. The exquisite selectivity of the t-butyldiphenylsilylating reagent[6] is underlined.

Baeyer–Villiger oxidation of the ketone (**5**) under mild conditions (peracetic acid, −20 °C) gave the 2-oxabicyclo-octan-3-one (**6**) in high yield (96%). More vigorous oxidation conditions (*e.g. m*-chloroperbenzoic acid) led to the formation of (**6**) together with an impurity, probably the corresponding 3-oxabicyclo-octan-2-one.[7]

Reaction of the 3-*endo*-hydroxylactone (**6**) with dihydropyran under acidic conditions followed by desilylation using fluoride ion gave the 6-*exo*-hydroxylactone (**7**). Etherification of the free hydroxy group in compound (**7**) was best effected using silver oxide and a reactive alkyl halide.[8] Thus methyl iodide reacted with the alcohol (**7**) under the prescribed conditions to give the methyl ether (**8**) while 1-iodoheptane was almost inert. Silver (I) catalysed coupling of 3-bromoprop-1-ene and the alcohol (**7**) was facile and the allyl ether (**9**) was isolated in good yield.

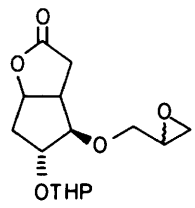


(**6**) R^1 = SiBu^{t}Ph$_2$, R^2 = H
(**7**) R^1 = H, R^2 = THP
(**8**) R^1 = CH$_3$, R^2 = THP
(**9**) R^1 = CH$_2$CH=CH$_2$, R^2 = THP
(**10**) R^1 = CH$_2$CH(OH)C$_5$H$_{11}$, R^2 = THP
(**11**) R^1 = CH$_2$CH(OH)C$_5$H$_{11}$, R^2 = H



(**12**) R^1 = H, R^2 = Me
(**13**) R^1 = Me, R^2 = CH$_2$CH(OH)C$_5$H$_{11}$

The methyl ether (**8**) was converted into the prostanoid (**12**) using a standard series of reactions.[9] The allyl ether (**9**) was oxidized using *m*-chloroperbenzoic acid to give the epoxide (**14**) as a 2:1 mixture of diastereoisomers. Reaction of these epoxides with lithium dibutylcuprate gave the alcohol (**10**) as a result of attack by the cuprate reagent on the epoxide unit at the less hindered position. The lactone (**10**) was converted into the protected prostanoids (**15**) and (**16**) in five conventional steps. [Removal of the tetrahydropyranyl group from compound (**10**)



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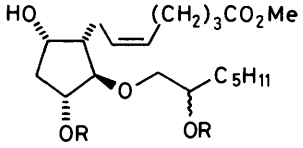
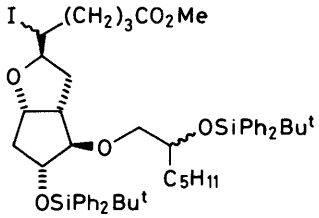


(15) R = Bu^tMe_2Si
(16) R = Bu^tPh_2Si



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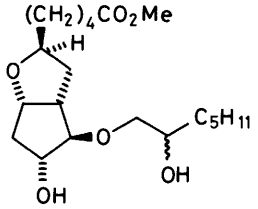

(18)

has to be performed under carefully controlled conditions due to the acid-lability of the diol (**11**)]. The bis-silyl ether (**15**) was converted into the prostaglandin analogue (**13**). Iodoetherification of the alkene (**16**) gave the iodo ethers (**17**) and subsequent hydrodeiodination (with tributyltin hydride) and deprotection (with fluoride) gave the compound (**18**), an analogue of prostaglandin I_1.[10]

Experimental

^1H N.m.r. spectra were measured for solutions in deuteriochloroform, with tetramethylsilane as the internal standard, on a Brüker AM250 spectrometer. Low resolution mass spectra were recorded on a VG micromass 16F and high resolution mass spectra were recorded on a VG 12-253 spectrometer. I.r. spectra were recorded on a Perkin-Elmer 357 grating infrared spectrometer. Starting materials and solvents were routinely purified by conventional techniques. $MgSO_4$ was used to dry extracts.

T.l.c. was performed on Merck 60F-254 (0.25 mm thickness Art. 5715) glass packed silica gel plates and medium pressure preparative flash column chromatography was carried out using silica gel 60H (Merck 9385). Compositions of solvent mixtures are quoted as ratios by volume.

2-exo-3-endo-*Dihydroxybicyclo*[3.2.0]*heptan*-6-*one* (**4**).—*m*-Chloroperbenzoic acid (70 g, 0.406 mol) in dry dichloromethane (1400 ml) was cooled to −20 °C under N_2. The alkene (**2**) (50 g, 0.294 mol) in dry dichloromethane (200 ml) was added slowly. The reaction mixture was warmed slowly to 0 °C and was stirred overnight. The mixture was washed with saturated aqueous sodium sulphite (2 × 100 ml), saturated aqueous sodium hydrogen carbonate (2 × 100 ml), and then saturated brine (100 ml). The aqueous extracts were back-extracted with dichloromethane (100 ml) and the combined organic phases were dried and evaporated to give a liquid which distilled at 78—79 °C at 0.1 mmHg as a colourless liquid. Purification by chromatography [diethyl ether–light petroleum (b.p. 40—60 °C) (1:1)] gave the epoxide (**3**) in 95% yield; δ($CDCl_3$) 3.9 (4 H, m, OCH_2CH_2O), 3.54 (1 H, td, *J* 4.5 and 1 Hz, 3-H) 3.44 (1 H, dd, *J* 2.3 and 1 Hz, 2-H) 3.2 (2 H, m, 7-*exo*-H and 7-*endo*-H) 2.38 (1 H, td, 5-H), and 2.1 (3 H, m, 4-*exo*-H, 4-*endo*-H, and 1-H). The epoxide (**3**) (12 g, 0.071 mol) was stirred in diethyl ether (200 ml) at 0 °C and 3M perchloric acid (48 ml) was added slowly over 30 min. The mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous sodium hydrogen carbonate was added to pH 8, the two layers were separated, and the aqueous layer was extracted continuously for 48 h using ethyl acetate (4 × 1l). The combined organic fractions were dried and the solvent was evaporated to give a viscous oil which was chromatographed [eluant, diethyl ether–methanol (95:5)] to afford the *diol* (8.8 g, 0.062 mol, 87%) which partially solidified when kept at 0 °C for 2 weeks and crystallized from ethyl acetate–chloroform to give a white solid, m.p. 70—72 °C; δ(CD_3OD) 4.3 (1 H, dd, 3-H), 4.2 (1 H, s, 2-H), 3.75 (1 H, m, 5-H), 3.2 (2 H, m, 7-*exo*-H and 7-*endo*-H), 2.8 (1 H, m, 1-H), and 2.2 (3 H, m, 4-*exo*-H, 4-*endo*-H, and OH); $\nu_{max.}$(neat) 3 400 and 1 770 cm^{-1} [Found: $(M + NH_4)^+$, 160.0978. $C_7H_{14}NO_3$ requires $M + NH_4$, 160.0973].

2-exo-*t-Butyldiphenylsilyloxy*-3-endo-*hydroxybicyclo*[3.2.0]*heptan*-6-*one* (**5**).—To the ketodiol (**4**) (6.0 g) in dry dimethylformamide (200 ml) was added imidazole (3.0 g). The mixture was stirred at 0 °C for 5 min under N_2, whereupon t-butyldiphenylsilyl chloride (12.6 g) was added dropwise. The resultant mixture was stirred at 0 °C overnight and water (300 ml) was added. The mixture was extracted with ethyl acetate (4 × 150 ml), and the combined extracts were washed with saturated aqueous ammonium chloride (2 × 150 ml), water (80 ml), and brine (80 ml), dried, and evaporated. The crude product was chromatographed over silica [eluant, diethyl ether–light petroleum (b.p. 40—60 °C) (1:1)] to give the *monosilyl alcohol* (**5**) (9.0 g, 57%) as a white solid which was crystallized from diethyl ether–light petroleum (b.p. 40—60 °C), m.p. 109—110 °C; δ($CDCl_3$) 7.7 (4 H, m, ArH), 7.4 (6 H, m, ArH), 4.2 (2 H, br s, 2-H and 3-H), 3.7 (1 H, m, 5-H), 2.9 (2 H, m, 7-*endo*-H and 7-*exo*-H), 2.75 (1 H, m, 1-H), 2.32 (1 H, tdd, 4-*exo*-H), and 2.12 (1 H, d, 4-*endo*-H); $\nu_{max.}$($CDCl_3$) 3 400 br and 1 715 cm^{-1} [Found: $(M + NH_4)^+$, 398.2149 $C_{23}H_{32}NO_3Si$ requires $M + NH_4$, 398.2147].

Oxidation of 2-exo-*t-Butyldiphenylsilyloxy*-3-*endo-hydroxybicyclo*[3.2.0]*heptan*-6-*one* (**5**) *using Peracetic Acid*.—The alcohol (**5**) (110 mg) in 90% acetic acid (0.8 ml) was stirred with 30% hydrogen peroxide (0.08 ml) in 90% acetic acid (0.8 ml) at −20 °C for 48 h. The mixture was basified with saturated aqueous sodium hydrogen bicarbonate and extracted with ethyl acetate (3 × 20 ml). The extracts were washed with water (2 × 10 ml) and brine (10 ml), evaporated, and the crude product was chromatographed over silica [eluant, light petroleum (b.p. 40—60 °C)–diethyl ether] to afford the *lactone* (**6**) (82 mg, 72%) as an oil, in addition to some starting material (25 mg); δ($CDCl_3$) 7.7 (4 H, m, ArH), 7.4 (6 H, m, ArH), 5.14 (1 H, dm, *J* 6 Hz, 5-H), 4.19 (1 H, m, 3-H), 4.03 (1 H, d, 2-H), 2.78 (1 H, m, 1-H), 2.4 (2 H, ddm, 8-*exo*-H and 8-*endo*-H), 2.23 (1 H, dd, 4-*exo*-H), 2.1 (1 H, d, 4-*endo*-H), 1.49 (1 H, d, OH), and 1.1 (9 H, s, $C(Me_3)$; $\nu_{max.}$(neat) 3 400 and 1 765 cm^{-1} [Found $(M + NH_4)^+$ 414.2105. $C_{23}H_3NO_4Si$ requires $M + NH_4$, 414.2110].

6-exo-*Hydroxy*-7-endo-*tetrahydropyranyloxy*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (**7**).—The lactone (**6**) was allowed to react with dihydropyran under acid catalysis in a standard fashion to give the diprotected lactone (98%). This lactone (1.4 g) in dry tetrahydrofuran (30 ml) was stirred with 1M aqueous tetrabutylammonium fluoride (9 ml, 3 equiv.) at room temperature for 12 h. The solvent was evaporated, saturated aqueous sodium hydrogen carbonate (25 ml) was added to the residue, and the mixture was extracted with ethyl acetate (4 × 25 ml). The combined organic extracts were washed with brine (20 ml),

dried, and evaporated and the product was chromatographed over silica to afford the 6-exo-*alcohol* (**7**) (0.62 g, 89%) as a viscous oil; δ ($CDCl_3$) 5.1 and 4.9 (1 H, m, 1-H), 4.62 and 4.78 (1 H, 2 × m, OCHO), 4.4 and 4.2 (1 H, 2 × m, 7-H), 4.05 (1 H, m, 6-H), 3.9 (2 H, m, OCH_2), 3.58 (1 H, m, 5-H), 2.8 (2 H, m, 4-*exo*-H and 4-*endo*-H), 2.5—2.1 (3 H, m, 8-*exo*-H, 9-*endo*-H, and OH), and 1.5 (6 H, m, 3 × CH_2); $\nu_{max.}$(neat) 3 450 and 1 750 cm^{-1}.

7-(3′RS,5′SR-*Dihydroxy*-2′RS-*methoxycyclopent*-1SR-*yl*)-*hept*-5Z-*enoic Acid* (**12**).—The alcohol (**7**) (1.5 g) was stirred with silver (I) oxide (4.3 g) and methyl iodide (1.53 ml) in dry dimethylformamide under N_2 for 48 h. Water (30 ml) was added and the mixture was filtered through Keiselguhr to remove silver oxide and silver bromide. The Keiselguhr was washed with ethyl acetate (10 ml). The mixture was extracted with ethyl acetate (3 × 30 ml) and the combined extracts were washed with water (20 ml) and brine (20 ml) and dried. The solvent was evaporated and the crude product was chromatographed over silica [eluant, diethyl ether–methanol (96:4)] to afford the methyl ether (**8**) (1.47 g); δ ($CDCl_3$) 5.1 (1 H, m, 1-H), 4.78 (1 H, m, OCHO), 4.23 (1 H, m, 7-H), 3.8 (1 H, m, 6-H), 3.55 (2 H, m, OCH_2), 3.35 (3 H, s, OMe), 2.85 (2 H, m, 4-*exo*-H and 4-*endo*-H), 2.5 (1 H, m, 6-H), 2.2 (2 H, m, 8-*exo*-H and 8-*endo*-H), and 1.6 (6 H, m, 3 × CH_2); $\nu_{max.}$(neat) 1 760 cm^{-1}. The methyl ether (**8**) (170 mg) was stirred in dry toluene (3 ml) under N_2 at −78 °C. Di-isobutylaluminium hydride in toluene (1.2M, 0.72 ml) was added dropwise and the resulting mixture was stirred at that temperature for 3 h. Methanol (3 drops) was added followed by aqueous ammonium chloride (2 ml). The mixture was warmed to room temperature and the two layers were separated; the aqueous layer was further extracted with dichloromethane (3 × 5 ml). The combined organic extracts were washed with water (3 ml) and brine (3 ml), dried, and evaporated to afford the lactol which was dissolved in dry THF (5 ml). This solution was added at 0 °C to the Wittig reagent made from (4-carboxybutyl)triphenylphosphonium bromide (0.587 g) in dry THF (20 ml) using potassium t-butoxide (0.299 g). The resulting mixture was warmed slowly to room temperature and stirred for 1 h after which water (10 ml) was added followed by saturated aqueous ammonium chloride (10 ml). The mixture was extracted using ethyl acetate (3 × 20 ml) and the extracts were washed with water (10 ml) and brine (10 ml), dried, and evaporated. The crude product was chromatographed over silica using ethyl acetate to give the carboxylic acid (100 mg). This was dissolved in diethyl ether (20 ml) and treated with diazomethane. The ether was evaporated and the product was chromatographed over silica using diethyl ether to afford the corresponding methyl ester; δ($CDCl_3$) 5.48 (2 H, m × 2, 5-H and 6-H), 4.75 (1 H, m, OCHO), 4.2 (1 H, d × 2, 3′-H), 4.12 (1 H, t, 5′-H), 3.9 (1 H, m, 2′-H), 3.65 (3 H, s, MeCO), 3.55 (2 H, m, OCH_2), 3.3 and 3.4 (3 H, 2 × s, OMe), 2.35 (4 H, m, 4′-*exo*-H, 4′-*endo*-H, and 2 × 2-H), 2.1 (4 H, m, 2 × 4-H and 2 × 7-H), 1.7 (6 H, br m, 3 × CH_2), and 1.5 (4 H, m, 2 × 3-H and 2 × OH); $\nu_{max.}$($CDCl_3$) 3 520, 2 850, and 1 735 cm^{-1} [Found: $(M + NH_4)^+$ 374.2546. $C_{22}H_{34}O_3N_2$ requires $M + NH_4$, 374.2576]. This methyl ester (0.5 g) was stirred with dry methanol 50 ml), a catalytic quantity of pyridinium toluene-*p*-sulphonate (PPTS), and Amberlyst-15 ion-exchange resin at room temperature overnight. The mixture was filtered through Keiselguhr and the solvent was evaporated. The crude product was chromatographed over silica using diethyl ether to afford the diol-ester (310 mg); δ($CDCl_3$) 5.3 (2 H, q, 5-H and 6-H), 4.25 (1 H, t, 5′-H), 4.13 (1 H, m, 3′-H), 3.69 (3 H, s, CO_2Me), 3.49 (1 H, m, 1′-H), 3.43 (3 H, s, OMe), 2.8 (1 H, br s, OH), 2.38 (5 H, m, 2 × 2-H, 2 × 4′-H, and 4-H), 2.35 (3 H, m, 4-H and 2 × 7-H), 1.85 (1 H, m, 1′-H), and 1.7 (3 H, m, 2 × 3-H and OH).

The diol ester (200 mg) was stirred with methanol (3 ml) and 1M aqueous sodium hydroxide (7.5 ml) at room temperature overnight. The mixture was acidified with HCl and extracted with ethyl acetate (3 × 30 ml). The extract was dried and evaporated and the crude product was chromatographed over silica using ethyl acetate and 0.1% acetic acid as eluant to afford the *acid* (**12**) (170 mg) as a foam; δ($CDCl_3$) 6.00 (3 H, br s, 3 × OH), 5.4 (2 H, m, 5-H and 6-H), 4.15 (2 H, m, 3′-H and 5′-H), 3.45 (1 H, d, *J* 6.7 Hz, 2′-H), 3.37 (3 H, s, OMe), 2.3 (4 H, m, 2 × 2-H, 4′-*exo*-H and 4′-*endo*-H), 2.10 (3 H, m, 2 × 4-H and 7-H), and 1.7 (3 H, m, 7-H, and 2 × 3-H) $\nu_{max.}$($CDCl_3$) 3 400—2 910 and 1 710 cm^{-1} [Found $(M + NH_4)^+$ 276.18105. $C_{13}H_{22}O_5$ requires $M + NH_4$, 276.18105].

Methyl 9SR,11RS,15R,S-*Trihydroxy*-13-*oxa*-13,14-*dihydro*-*prost*-5Z-*enoate* (**13**).—6-*exo*-Hydroxy-7-*endo*-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (**7**) (1.5 g) was stirred with dry dimethylformamide (30 ml), silver(I) oxide (4.25 g) and allyl bromide (24.8 mmol) at room temperature for 36 h. Water (40 ml) was added and then the mixture was filtered through Keiselguhr and washed with ethyl acetate (20 ml). The filtrate was extracted with ethyl acetate (4 × 30 ml) and the combined organic extracts were washed with water (20 ml) and brine (20 ml), dried, and evaporated. The product was chromatographed over silica using diethyl ether as eluant to afford the allyl ether (**9**) (1.66 g, 89%) as a colourless liquid; δ($CDCl_3$) 5.89 (1 H, m, C=CH), 5.2 (3 H, m, C=CH_2 and 1-H), 4.7 (1 H, m, OCHO), 4.3 and 4.2 (1 H, m × 2, 7-H), 4.00 (2 H, m, allyl OCH_2), 3.8 (2 H, d × 2, THP OCH_2), 3.5 (1 H, m, 6-H), 2.9 (2 H, m, 4-*exo*-H and 4-*endo*-H), 2.5 (1 H, m, 5-H), 2.3 (2 H, m, 8-*exo*-H and 8-*endo*-H), and 1.4—1.9 (6 H, m, 3 × CH_2); $\nu_{max.}$(neat) 1 775 cm^{-1}.

The allyl ether (**9**) (1 g) was stirred with *m*-chloroperbenzoic acid (1.8 g) and sodium hydrogen carbonate (1 g) in dichloromethane (30 ml) at 0 °C. The mixture was warmed slowly and stirred for 16 h, after which it was washed with saturated aqueous sodium sulphite (2 × 10 ml), saturated aqueous sodium hydrogen carbonate (2 × 10 ml), water (10 ml), and brine (10 ml) and then evaporated. The product was chromatographed over silica [eluant, diethyl ether–MeOH (95:5)] to afford the epoxide (**14**) (1.03 g, 100%); δ($CDCl_3$) 5.2 (1 H, m, 1-H), 4.75 and 4.6 (1 H, m, OCHO), 4.3 and 4.2 (1 H, t × 2, 7-H), 3.8 (3 H, m, allyl OCH_2 and 6-H), 3.4 (2 H, m, THP OCH_2), 3.03 (1 H, m, 5-H), 2.9 (1 H, m, epoxide CHO), 2.7 (2 H, m, 4-*exo*-H and 4-*endo*-H) 2.5 (2 H, m, epoxide CH_2O), 2.3 (2 H, m, 7-*endo*-H and 7-*exo*-H), and 1.4—1.7 (6 H, m, 3 × CH_2); $\nu_{max.}$(neat) 1 775 cm^{-1}.

Copper(I) iodide (1.14 g) was stirred in dry diethyl ether (8.4 ml) at −30 °C under N_2. Butyl-lithium (1.57M; 7.74 ml) was added dropwise and stirred for 15 min, after which the mixture was cooled to −78 °C. The epoxide (**14**) (300 mg) was dissolved in dry diethyl ether (3 ml) and added dropwise. The resulted mixture was stirred for 6 h, after which ammonium chloride (10 ml) was added and the mixture warmed to room temperature and stirred for a minimum of 15 min. The two layers were separated and the aqueous layer was further extracted with diethyl ether (3 × 10 ml). The combined organic fractions were washed with saturated brine, dried, and evaporated. The product was stirred with dry methanol (10 ml), a catalytic quantity of PPTS, and Amberlyst-15 ion-exchange resin at room temperature overnight after which it was evaporated. The crude product was chromatographed over silica to afford the diol (**11**) (110 mg); δ($CDCl_3$) 5.3 (1 H, t, 1-H), 4.22 (1 H, s, 7-H), 3.62 (2 H, s, 2 × 1′-H), 3.44 (1 H, m, 2′-H), 3.4 (1 H, br s, OH), 3.3 (1 H, m, 6-H), 2.8 (3 H, m, 4-*exo*-H, 4-*endo*-H, and OH), 2.52 (1 H, d, 4-H), 2.1 (2 H, m, 8-*exo*-H and 8-*endo*-H), 1.3 (8 H, m, 4 × CH_2), and 0.9 (3 H, t, Me); $\nu_{max.}$(neat) 3 700, 3 400, and 1 765 cm^{-1}.

The dihydroxy lactone (**11**) (130 mg) was stirred with t-butyldimethylsilylchloride (360 mg) and imidazole (162 mg) in

dry dimethylformamide (10 ml) at room temperature for 24 h. Water (20 ml) was added and the mixture was extracted with ethyl acetate (3 × 30 ml). The extracts were washed with water (20 ml) and brine (20 ml), dried, and evaporated. The product was chromatographed over silica [eluant, diethyl ether–light petroleum (b.p. 40—60 °C) (7:3)] to afford the bis-silylated compound (**15**) (220 mg); δ($CDCl_3$) 5.08 (1 H, m, 1-H), 4.2 (1 H, m, 7-H), 3.7 (1 H, m, 2′-H), 3.6 (1 H, s, 6-H), 3.3 (2 H, d, 2 × 1′-H), 2.9 (1 H, m, 4-*endo*-H), 2.72 (1 H, m, 4-*exo*-H), 2.5 (1 H, m, 5-H), 2.05 (2 H, m, 8-*exo*-H and 8-*endo*-H), 1.3 (8 H, m, 2 × 3′-H, 2 × 4′-H, 2 × 5′-H, and 2 × 6′-H), 0.9 (21 H, m, 2 × CMe_3 and 3 × 7′-H), and 0.08 (12 H, 2 × s, 2 × $SiMe_2$).

The bis-silylated (**15**) compound (100 mg, 0.2 mol) was stirred in dry dichloromethane (3 ml) at −78 °C under N_2. Di-isobutylaluminium hydride in toluene (1.2M; 0.5 ml) was added dropwise and the mixture was stirred at that temperature for 4 h. Saturated aqueous ammonium chloride (5 ml) was then added followed by water (2 ml) and methanol (1 ml). The mixture was warmed to room temperature, the two layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 ml). The combined organic solvents were evaporated, diethyl ether (40 ml) was added to the residue, and the solution was washed with water (2 × 8 ml) and brine (2 × 10 ml), dried and evaporated to afford the lactol (85 mg). The lactol was dissolved in dry tetrahydrofuran (10 ml) and added to a stirred mixture of 4-(carboxybutyl)triphenylphosphonium bromide (441 mg) and potassium t-butoxide (224 mg) in dry tetrahydrofuran (15 ml). The resultant mixture was stirred at room temperature for 1.5 h, after which water (30 ml) was added followed by saturated aqueous ammonium chloride (40 ml). The mixture was extracted with ethyl acetate (3 × 50 ml), and the extracts were washed with brine (30 ml), dried, and evaporated and the crude product was chromatographed over silica (eluant, diethyl ether containing 0.5% acetic acid) to afford the acidic material.

This material was dissolved in diethyl ether and treated with diazomethane. The ether was evaporated and the product was chromatographed over silica [eluant, diethyl ether–light petroleum (b.p. 40—60 °C) (15:85)] to afford the required methylated material (90%). This material (35 mg) was stirred with dry tetrahydrofuran (5 ml), tetrabutylammonium fluoride (0.6 ml), and triethylamine at room temperature overnight. The solvent was evaporated and the crude product was chromatographed over silica (eluant, methanol–diethyl ether, 5:95) to afford the *methyl ester* (**13**) (12 mg, 80%) as a foam; δ($CDCl_3$) 5.4 (2 H, m, 5-H and 6-H), 4.2 (1 H, m, 9-H), 4.13 (1 H, d, 11-H), 3.75 (1 H, m, 12-H), 3.7 (3 H, s, OMe), 3.65 (2 H, m, 2 × 14-H), 3.4 (1 H, m, 15-H), 3.2—2.6 (3 H, br s, 3 × OH), 2.35 (4 H, q, 2 × 2-H and 2 × 10-H), 2.1 (3 H, m, 2 × 7-H and 8-H), 1.72 (4 H, m, 2 × 3-H and 2 × 4-H), 1.4 (8 H, m, 2 × 16-H, 2 × 17-H, 2 × 18-H, and 2 × 19-H), and 0.89 (3 H, t, Me) [Found $(M + 1)^+$ 373.2592. $C_{20}H_{36}O_6$ requires $(M + 1)$, 373.2594].

Methyl 13-*Oxa*-13,14-*dihydro*-6β-*prostaglandin-I*$_1$ (**18**).—The diol (**11**) (2.2 g) was stirred with dry dimethylformamide (30 ml), t-butyl diphenylsilylchloride (9.98 ml), and imidazole (2.612 g) at room temperature under nitrogen for 3 days. Water (30 ml) was added and the mixture was extracted with ethyl acetate (3 × 40 ml). The extracts were washed with water (20 ml) and brine (20 ml), dried, and evaporated and the crude product was chromatographed over silica [eluant, ethyl acetate–light petroleum (b.p. 40—60 °C) (1 : 9)] to give the disilyl compound (1.70 g); δ($CDCl_3$) 7.7 (8 H, m, ArH), 7.4 (12 H, m, ArH), 4.9 (1 H, m, 1-H), 4.08 (1 H, d, 7-H) 3.7 (1 H, m, 2′-H), 3.3 (1 H, d, 6-H), 2.9 (2 H, m, 2 × 1′-H), 2.6 (3 H, m, 2 × 4-H and 5-H) 2.1 (1 H, m, 8-*exo*-H), 1.7 (1 H, m, 8-*endo*-H), 1.25 (8 H, m, 2 × 3′-H, 2 × 4′-H, 2 × 5′-H, and 2 × 6′-H), 1.00 (18 H, 2 × s, 2 × CMe_3), and 0.88 (3 H, t, Me).

The disilyl compound (350 mg, 0.468 mol) was stirred in dry dichloromethane (5 ml). Di-isobutylaluminium hydride in toluene (1.2M; 1.26 ml) was added dropwise and the resultant mixture was stirred for 3 h. Methanol (2 ml) was added followed by saturated aqueous ammonium chloride (15 ml). The mixture was warmed to room temperature. Dichloromethane (10 ml) was then added and the two layers were separated. The aqueous layer was extracted with dichloromethane (2 × 15 ml) and the combined organic extracts were washed with water (2 × 10 ml) and brine (2 × 10 ml), dried, and evaporated to afford the corresponding lactol (290 mg, 83%). The lactol (380 mg) was dissolved in dry tetrahydrofuran (15 ml) and added to a refluxing mixture of 4-[carboxybutyl]triphenylphosphonium bromide (692 mg) and potassium t-butoxide (360 mg) in dry tetrahydrofuran (20 ml). The mixture was refluxed for 30 min, after which water (30 ml) was added followed by saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate (3 × 30 ml) and the combined organic extracts were washed with brine (20 ml), dried, and evaporated. The crude acid was chromatographed over silica (eluant, diethyl ether with 0.1% acetic acid) to afford the acid (390 mg). The acid was dissolved in dry diethyl ether (10 ml) and treated with diazomethane. The solvent was evaporated and the crude ester was chromatographed over silica (eluant, dichloromethane) to afford the ester (**16**) (346 mg, 87%); δ($CDCl_3$) 7.7 (8 H, m, ArH), 7.4 (12 H, m, ArH), 5.4 (2 H, m, 5-H and 6-H), 4.1 (1 H, m, 11-H), 3.8 (1 H, m, 9-H), 3.7 (3 H, s, OMe), 3.45 (4 H, m, 12-H, 2 × 14-H, and 15-H), 2.8 (2 H, m, 2 × 6-H), 1.6—2.5 (10 H, m, 2 × 2-H, 2 × 3-H, 2 × 4-H, 2 × 7-H, 8-H, and OH), 1.15 (26 H, m, 2 × 16-H, 2 × 17-H, 2 × 18-H, 2 × 19-H, and 2 × CMe_3), and 0.85 (3 H, Me). The methyl ester (**16**) (340 mg) was stirred with 8% aqueous sodium hydrogen carbonate (9 ml) in dichloromethane (15 ml) at 0 °C. Iodine (114 mg) dissolved in dichloromethane was added dropwise over 2 h and the resultant mixture was warmed slowly to room temperature and stirred for 25 h. The brown colour was discharged by addition of aqueous sodium thiosulphate. The two layers were separated and the organic layer was extracted with dichloromethane (3 × 20 ml). The combined organic fractions were dried and evaporated, and the product was chromatographed over silica (eluant, dichloromethane) to give the iodoethers (**17**); δ($CDCl_3$) 7.65 (8 H, m, ArH), 7.35 (12 H, m, ArH), 4.55 (1 H, m, 6-H), 4.0 (3 H, m, 5-H, 9-H, and 11-H), 3.65 (4 H, br s, OMe and 12-H), 3.3 (1 H, m × 2, 15-H), 3.00 (2 H, m, 2 × 14-H), 2.45 (3 H, m, 2 × 2-H and 8-H), 2.0—1.6 (8 H, m, 2 × 3-H, 2 × 4-H, 2 × 7-H, and 2 × 10-H), 1.4—1.1 (8 H, m, 2 × 16-H, 2 × 17-H, 2 × 18-H, and 2 × 19-H), 1.0 (18 H, 2 × s, 2 × CMe_3), and 0.8 (3 H, s, Me).

The iodoethers (**17**) (180 mg, 0.185 mol) were stirred with dry toluene (3 ml), tributyltin hydride (55 μl), and one crystal of AIBN at 80 °C for 2 h under N_2. The solvent was evaporated and diethyl ether (15 ml) was added. The mixture was shaken with potassium fluoride and the two layers were separated. The ether layer was washed with water (5 ml) and brine (5 ml) dried, and evaporated. The product was chromatographed [eluant, diethyl ether–light petroleum (b.p. 40—60 °C), 1:4], to afford the de-iodinated ester (145 mg, 95%); δ($CDCl_3$) 7.7 (8 H, m, ArH), 7.4 (12 H, m, ArH), 4.4 (1 H, m, 6-H), 4.1 (1 H, m, 9-H), 4.0 (1 H, m, 11-H), 3.75 (1 H, m, 12-H), 3.7 (3 H, s, OMe), 3.4 (1 H, m, 15-H), 3.2 (2 H, m, 2 × 14-H), 2.3 (4 H, m, 2 × 10-H and 2 × 16-H), 2.0—1.0 (36 H, m), and 0.85 (3 H, s, Me).

The disilyl compound (140 mg) was stirred with dry THF (2 ml) and tetrabutylammonium fluoride (1.1M; 1.5 ml) under N_2 for 36 h. The THF was evaporated and the crude product was chromatographed over silica (eluant, ethyl acetate) to afford the *diol* (**18**) (41 mg, 69%) as an oil; δ($CDCl_3$) 4.45 (1 H, m, 6-H), 4.0 (2 H, m, 9-H and 11-H), 3.75 (1 H, m, 12-H), 3.65 (3 H, s, OMe), 3.4 (3 H, m, 2 × 14-H and 15-H), 2.8 (3 H, m, 8-H and 2 × OH),

2.5 (2 H, m, 2 × 7-H), 2.25 (4 H, m, 2 × 10-H and 2 × 2-H), 1.95 (2 H, m, 2 × 5-H), 1.7 (6 H, m, 2 × 3-H, 2 × 4-H, and 2 × 16-H), 1.2—1.5 (6 H, m, 2 × 17-H, 2 × 18-H, and 2 × 19-H), and 0.9 (3 H, t, Me) [Found $(M + H)^+$ 373.2608. $C_{20}H_{36}O_6$ requires $(M + 1)$, 373.2608].

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References

1 P. W. Collins, E. Z. Dajani, R. Pappo, A. F. Gasiecki, R. G. Bianchi, and E. M. Woods, *J. Med. Chem.*, 1983, **26**, 786.
2 P. W. Collins, *J. Med. Chem.*, 1986, **29**, 437.
3 E. W. Collington, H. Finch, P. Hallett, P. Hunt, T. Parkhouse, D. P. Reynolds, L. M. Smith, and C. J. Wallis, 'Proceedings of the Second SCI-RSC Medicinal Chemistry Symposium,' ed. J. C. Emmett, R.S.C. Special Publication, Dorchester, 1984, p. 299.
4 J.-C. Barrière, A. Chiaroni, J. Cléophax, S. D. Géro, C. Riche, and M. Vuilhorgne, *Helv. Chim. Acta*, 1981, **64**, 1140; J.-C. Barrière, J. Cléophax, S. D. Géro, and M. Vuilhorgne, *ibid.*, 1983, **66**, 1392; S. Géro, J. Cléophax, J.-C. Barrière, and A. Cier, B.P. 2 082 176 1981.
5 R. J. Cave, C. C. Howard, G. Klinkert, R. F. Newton, D. P. Reynolds, A. J. Wadsworth, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2954.
6 W. W. Wood and A. Rashid, *Tetrahedron Lett.*, 1987, **28**, 1933.
7 Z. Grudzinski, S. M. Roberts, C. Howard, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1182.
8 A. C. Ferguson and A. H. Haines, *J. Chem. Soc. C*, 1969, 372.
9 R. J. Cave, R. F. Newton, D. P. Reynolds, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1981, 646.
10 *cf.* L. Novák, J. Aszódi, and C. Szántay, *Tetrahedron Lett.*, 1982, **23**, 2135.

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