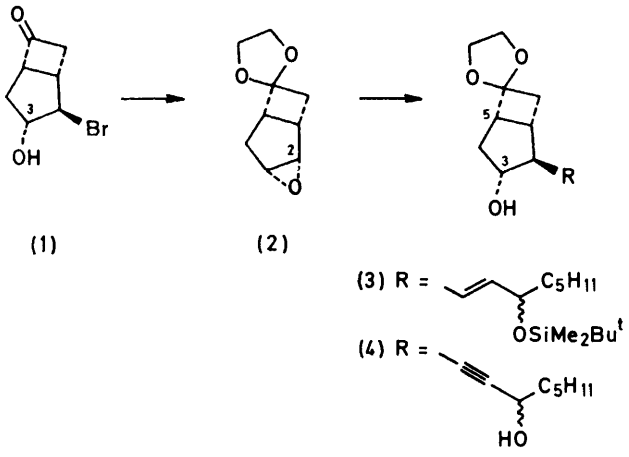
Total Synthesis of (±)-Prostaglandin E_2 Methyl Ester from *exo*-2-Bromo-*endo*-3-hydroxybicyclo[3.2.0]heptan-6-one using Dimethyl-t-butylsilyl Protected Intermediates

By **Colin Howard, Roger F. Newton,*** and **Derek P. Reynolds,** Chemical Research Department, Glaxo Group Research Ltd., Ware, Herts. SG12 0DJ
Stanley M. Roberts,* The Ramage Laboratories, Department of Chemistry and Applied Chemistry, Salford University, Salford, Lancs. M5 4WT

Peracetic acid oxidation at −78 °C of the dihydroxybicyclo[3.2.0]heptan-6-one (23) afforded the dihydroxylactone (24) which was protected as its bisdimethyl-t-butylsilyl ether (26) and reduced to the corresponding lactol (27). A Wittig reaction on (27), carried out in benzene with a short reaction time, gave mainly the required 11α-silyl ether (28) together with a trace of the 9α-silyl ether (29) which results from 1,5-migration of the silyl group. Oxidation of (28) followed by quantitative deprotection using aqueous HF in acetonitrile afforded (±)-PGE_2 methyl ester (20). This short stereo- and regio-selective total synthesis proceeds in an overall yield of 10% starting from cyclopentadiene.

We have recently developed two complementary strategies for converting the readily available bromo-ketone (1) into prostaglandin $F_2\alpha$.[1,2] Substitution of the bromine atom by an hydroxyoctenyl side-chain with retention of configuration is a key step, and this was accomplished using a double S_N2 process. In the more recently described approach [2] an alkoxide anion was generated from the hydroxy-group bonded to C-3 and intramolecular S_N2 displacement of bromide ion resulted in epoxide formation. Organometallic nucleophiles react selectively at C-2 of the protected epoxide (2) [3] to give prostaglandin intermediates such as (3) and (4) (Scheme 1). The free



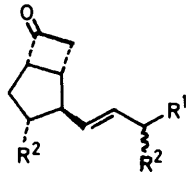
Scheme 1

hydroxy-group attached to C-3 is destined to become the C-11 hydroxy-substituent of the target prostaglandin. We envisaged that, after protection of this hydroxy-group, elaboration of the intermediate to give PGE_2 would be straightforward.

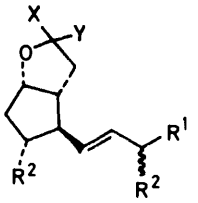
The most obvious choice for hydroxy-group protection was the tetrahydropyranyl (THP) group, as its use is well established in prostaglandin synthesis. However, when brought into contact with peroxy-reagents, the THP group can form sensitive organic peroxides which may cause serious explosions.[4] An alternative which would safely withstand the conditions of a Baeyer-Villiger oxidation was desired. The dimethyl-t-butylsilyl protecting group appeared ideal since it is claimed [5] to be removed readily by acidic hydrolysis under conditions similar to those used for removal of THP ethers. It has the additional advantage of not possessing a chiral centre. In practice we encountered problems which were not anticipated at the outset and which were directly attributable to our choice of the $SiMe_2Bu^t$ group for hydroxy-group protection.

Hydrolysis of the readily available acetal (3) [2] using mineral acid followed by direct silylation using dimethyl-t-butylsilyl chloride afforded the bis-(dimethyl-t-butylsilyloxy)bicycloheptanone (5) in 90% overall yield. Alternatively, reduction of the alkynol (4) [2] with lithium aluminium hydride, followed by a work-up procedure incorporating mineral acid, afforded a crude diol which after silylation gave the same bis-protected bicycloheptanone (5) [70% yield from (4)].

Baeyer-Villiger oxidation of the bicycloheptanone (5) was unexpectedly non-regiospecific. Treatment of (5) with peracetic acid in dichloromethane at −20 °C gave a quantitative yield of the isomeric lactones (6) and (7) in the ratio 85 : 15 (by g.l.c. and ^1H n.m.r. analysis). Because thin-layer chromatography failed to separate the isomers (6) and (7), the mixture was reduced directly with di-isobutyl aluminium hydride at −78 °C. The resultant mixture of lactols (8) and (9) was treated with the Wittig ylide (10; M = K) (4 equiv.) prepared from (4-carboxybutyl)triphenylphosphonium bromide and potassium t-butoxide in tetrahydrofuran. The reaction was quenched after 15 min and yielded, following treatment with diazomethane, a mixture of four isomeric methyl esters: after separation by chromatography over silica gel the combined yield was 81% based on the mixture of lactones (6) and (7). The two most-polar products were derived from the minor lactol component (9) and had ^1H n.m.r. spectra consistent with structures (11) and (12). That each contained a primary alcohol function was confirmed by oxidation with pyridinium chlorochromate to give aldehydic material. The

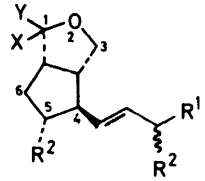


(5)



(6) X,Y = =O

(8) X = OH; Y = H



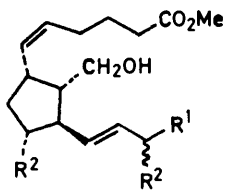
(7) X,Y = =O

(9) X = OH; Y = H

(10) $Ph_3P{=}CHCH_2CH_2CH_2CO_2^-\ M^+$

$R^1 = C_5H_{11}$, $R^2 = OSiMe_2Bu^t$

relative stereochemistry at C-2, C-3, and C-4 on the cyclopentane ring follows from the known stereochemistry of the lactone precursor (7). Epimerisation at C-1 presumably occurs during the Wittig reaction but it was not possible to determine which of the products had the stereochemistry (11) and which had the structure (12).



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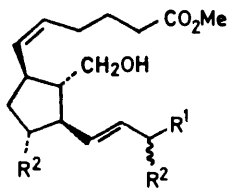

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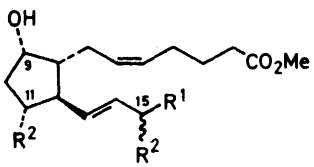

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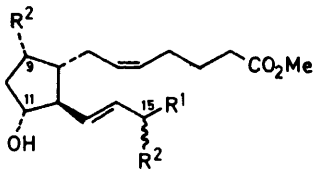

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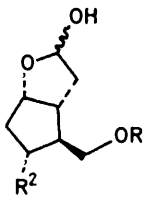
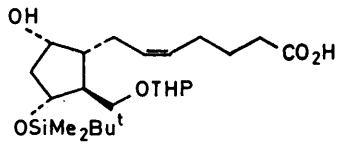


(15)

$R^1 = C_5H_{11}$, $R^2 = OSiMe_2Bu^t$

The other products from the Wittig reaction were the PGE_2 precursor (13) and the PGD_2 precursor (14) (combined yield 68%; ratio 87 : 13). Both derive from the major lactol component (8). Thus 1,5-migration of a dimethyl-t-butylsilyl group had occurred during the Wittig reaction to give the 9α-silyl ether (14). This was surprising in view of the report by Corey and Venkateswarlu [5] that the dimethyl-t-butylsilyl group in the lactol (15: R = CH_2Ph) remained in place during reaction with the ylide (10; M = Na). Recently, the reaction of the same Wittig reagent (10; M = Na) with the closely related lactol (15; R = THP) has been investigated and shown to yield an equilibrium mixture of the silyl ethers (16) and (17). A base-induced migration *via* a six-membered



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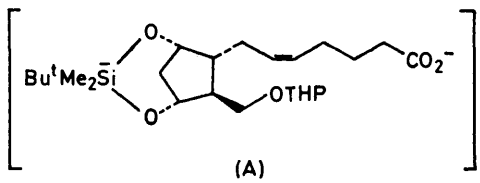
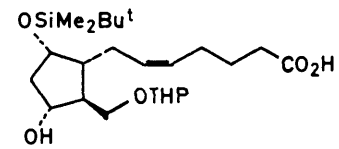


(A)



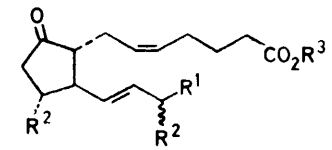
(17)

SCHEME 2

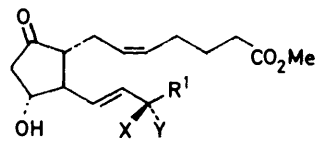
bicyclic transition state (A) involving pentacovalent silicon was postulated (Scheme 2).[6]

Oxidation of the 11,15-bis-silyl ether (13) by pyridinium chlorochromate gave the ketone (18) (92%). Ready conversion of this compound into PGE_2 methyl ester was anticipated because satisfactory deprotection of the tris-(dimethyl-t-butylsilyl) derivative (19) of PGE_2 using acetic acid–water–tetrahydrofuran (3 : 1 : 1) at 25 °C for 20 h had been reported.[5] However, it was found that this reagent required six days to effect the removal of both $SiMe_2Bu^t$ groups from the ketone (18). (±)-Prostaglandin E_2 methyl ester (20) and (±)-15-*epi*-prostaglandin E_2 methyl ester (21) were each isolated in only 20% yield after separation by chromatography over silica gel. Other unidentified products were detected and presumably arose from acid-catalysed decompositions of the sensitive β-ketols (20) and (21). Thus, although the bis-(dimethyl-t-butylsilyl)-protected bicycloheptanone (5) had been converted into PGE_2 methyl ester, the over-

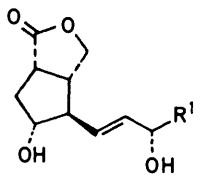
all yield was low for the following reasons. (i) Baeyer-Villiger oxidation of the bicycloheptanone (5) was not regiospecific, (ii) migration of the $SiMe_2Bu^t$ group occurred during the Wittig reaction, and (iii) deprotection of the β-silyloxy-ketone (18) was unsatisfactory.



(18) R^3= Me
(19) R^3= $OSiMe_2Bu^t$



(20) X = H; Y = OH
(21) X = OH; Y = H



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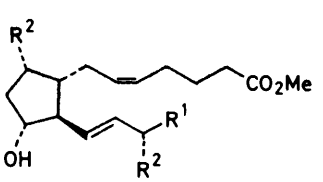


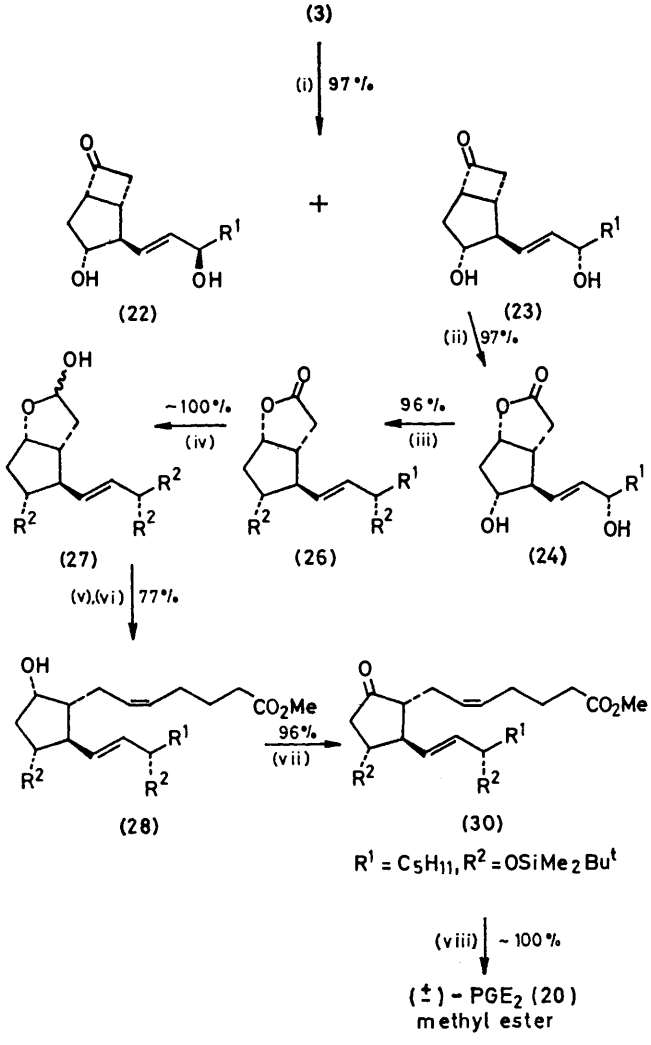
(29)

R^1 = C_5H_{11}, R^2= $OSiMe_2Bu^t$

Therefore, the sequence of reaction had to be revised and new techniques developed to overcome these disadvantages. Baeyer-Villiger oxidation of the ketone (23) with peracetic acid in dichloromethane at −20 °C gave a quantitative yield of isomeric lactones (24) and (25) in the ratio 91 : 9 (by g.l.c.). This showed that the bulky $SiMe_2Bu^t$ group had adversely affected the regioselectivity of the reaction. Furthermore, our original assumption that a bulky protecting group on the allylic hydroxy-group would be needed to prevent epoxidation of the double bond was obviously incorrect.

We have found that temperature has an important effect on the regioselectivity of the peracetic acid oxidation of the dihydroxy-ketone (23). Thus, at −78 °C a near quantitative yield of the dihydroxy-lactone (24) was obtained, contaminated with only a trace (3% by g.l.c.) of isomer (25). Silylation with dimethyl-t-butylsilyl chloride then afforded the bis-protected lactone (26) (96%) and this was reduced quantitatively by diisobutylaluminium hydride at −78 °C to give the lactol (27). Investigation of the Wittig reaction showed that silyl migration is slow in non-polar solvents and that short reaction times minimised silyl group migration. Reaction of the lactol (27) with the ylide (10; M = Na) in benzene at 75 °C for 10 min gave, after methylation with diazomethane, the 11α-silyl ether (28) (77%) and only a trace of the 9α-silyl ether (29) (4%).

Oxidation of (28) with pyridinium chlorochromate yielded the ketone (30) (96%). Since hydrolysis of this PGE_2 precursor (30) was unsatisfactory using the literature procedure we required a reagent which would cause rapid desilylation without decomposing the resultant sensitive β-ketol system. We therefore examined the use of HF which is a mild acid (pK_a in water at 25 °C = 3.45) [7] but possesses a better nucleophilicity for silicon than H_2O. Treatment of the ketone (30) with acetonitrile containing 15% (v/v) of a 40% (w/w) solution of HF in water at 20 °C for 1 h afforded analytically pure (±)-PGE_2 methyl ester (20) in quantitative yield. By-product formation was negligible during the course of the desilylation but if the mixture was allowed to stand at room temperature for several hours before work-up then impurities were detectable in addition to PGE_2 methyl



SCHEME 3 Reagents: (i) 0.2N-H_2SO_4; (ii) CH_3CO_3H, CH_2Cl_2, −78 °C; (iii) $Bu^t_2Me_2SiCl$; (iv) Bu^i_2AlH; (v) $Ph_3P{=}CHCH_2CH_2CO_2^-Na^+$, benzene; (vi) CH_2N_2; (vii) pyridinium chlorochromate; (viii) HF, CH_3CN

ester. It is noteworthy that additional water in the reaction medium slowed the rate of desilylation. Also, if methanol or tetrahydrofuran were used in place of acetonitrile as solvent the reaction was slower and less clean. Elevated temperatures were also detrimental and promoted acid-catalysed decompositions of the product.

In summary, by careful design of the reaction conditions the problems associated with the use of the dimethyl-t-butylsilyl protecting group in this prostaglandin synthesis have been overcome. The sequence outlined in Scheme 3 illustrates a short stereo- and regio-selective total synthesis of (±)-PGE_2 methyl ester in 10% overall yield from cyclopentadiene.

EXPERIMENTAL

Mass spectra were determined after chemical ionisation using ammonia (c.i.m.s.). T.l.c. was carried out with Camlab ' Polygram ' pre-coated silica-gel plates. Short-column chromatography used 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.

endo-3-(*Dimethyl-t-butylsilyloxy*)-anti-2-[3-(*dimethyl-t-butylsilyloxy*)*oct*-1-*enyl*]*bicyclo*[3.2.0]*heptan*-6-*one* (5).—(i) *From the acetal* (3). (*E*)-(1α,2α,3β,5α)-2-[3-(dimethyl-t-butylsilyloxy)oct-1-enyl]spiro{bicyclo[3.2.0]heptane-6,2′-[1,3]dioxolan}-3-ol (3)[3] (1.02 g, 2.5 mmol) in acetonitrile (15 ml), water (5.3 ml) and 2N-sulphuric acid (4.2 ml) was stirred at ambient temperature for 16 h. 8% Aqueous sodium hydrogencarbonate was added and the mixture extracted with ethyl acetate. The dried ($MgSO_4$) extracts were evaporated and the residual oil treated with dimethyl-t-butylsilyl chloride (1.13 g, 7.5 mmol) and imidazole (1.02 g, 15 mmol) in dimethylformamide (7.5 ml) for 24 h at ambient temperature. The mixture was diluted with water and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts followed by short-column chromatography on silica gel with 2.5% ethyl acetate–light petroleum as eluant gave endo-3-(*dimethyl-t-butylsilyloxy*)-anti-2-[3-(*dimethyl-t-butylsilyloxy*)*oct*-1-*enyl*]*bicyclo*[3.2.0]*heptan*-6-*one* (5) as a colourless oil (1.08 g, 90%) (Found: C, 67.3; H, 11.2%. $C_{27}H_{52}O_3Si_2$ requires C, 67.4; H, 10.9%); $\nu_{max.}$ ($CHBr_3$) 1 770 (C=O) and 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.4—4.9 (2 H, m, olefinic), 5.8—6.2 (2 H, m, 2 × CH–OSi), 6.40 (1 H, dt, H-5), 6.7—7.5 (4 H, m, H-1, H-2, H-7), 7.8—8.3 (2 H, m, H-4), 8.4—9.0 (8 H, m), 9.10 and 9.15 (21 H, 2 × s and m, 2 × CMe_3 and CH_2*Me*), and 9.95 (12 H, s, 2 × $SiMe_2$).

(ii) *From the alkynol* (4). (1α,2α,3β,5α)-2-(3-Hydroxyoct-1-ynyl)spiro{bicyclo[3.2.0]heptane-6,2′-[1,3]dioxolan}-3-ol (4) (882 mg, 3 mmol) was heated under reflux with lithium aluminium hydride (570 mg, 15 mmol) in tetrahydrofuran (30 ml) under nitrogen. The cooled mixture was quenched by sequential addition of water (0.5 ml), 5N-sodium hydroxide (0.5 ml), and then water (1.5 ml). The granular precipitate was filtered off and washed well with tetrahydrofuran. The filtrate (50 ml) was diluted with water (6 ml) and 2N-sulphuric acid (4 ml) was added. After 20 h the solution was basified with 2N-sodium carbonate (20 ml) and extracted with ethyl acetate. The dried ($MgSO_4$) extracts were evaporated to give an oil (600 mg) which was treated with dimethylformamide (10 ml), imidazole (1.0 g, 7.5 mmol), and dimethyl-t-butylsilyl chloride (1.1 g, 7.2 mmol). After 24 h, water (20 ml) was added and the mixture extracted with ether. The dried ($MgSO_4$) extracts were evaporated and the residue purified by short-column chromatography to give the ketone (5) as a colourless oil (1.004 g, 70%) identical (i.r., n.m.r. and t.l.c.) with the material described above.

Baeyer-Villiger Oxidation of the Bicyclo[3.2.0]*heptan*-6-*one* (5).—A cooled solution of the ketone (5) (240 mg, 0.5 mmol) in dichloromethane (0.5 ml) was added to a solution of commercial peracetic acid (6.6M) (0.9 ml, 6.0 mmol) and anhydrous sodium acetate (492 mg, 6.0 mmol) in dichloromethane (3.0 ml) at −20 °C. After 24 h at this temperature (freezer) the mixture was quenched by addition of aqueous sodium sulphite and extracted with dichloromethane. The organic extracts were washed with aqueous sodium carbonate, dried ($MgSO_4$), and evaporated to give a viscous oil (250 mg, 100%), homogeneous by t.l.c., which was a mixture of the isomeric lactones (6) and (7) (ratio 85 : 15 as determined by g.l.c. on OV 210 at 210 °C). Microanalysis was performed directly on the unpurified reaction product (Found: C, 67.05; H, 9.3. Calc. for $C_{15}H_{24}O_4$: C, 67.2, H, 9.0%). The major component (6) was identical (g.l.c., t.l.c., and n.m.r.) with authentic material prepared by an independent route.[8] Signals due to the minor component, 5β-(dimethyl-t-butylsilyloxy)-4α-{[(*E*),(3*S*)]-3-(dimethyl-t-butylsilyloxy)oct-1-enyl}-*cis*-(3a*αH*,6a*αH*)-hexahydro-1*H*-cyclopenta[*c*]furan-1-one (7), were discernible in the ^1H n.m.r. spectrum ($CDCl_3$) of the mixture at τ 5.55 (AB part of ABX multiplet, H-3α and H-3β) and 7.05 (td, H-6aα).

The Preparation of the Lactols (8) *and* (9), *and their subsequent Wittig Olefination.*—Di-isobutylaluminium hydride (1.35 ml of a 2.2M-solution in hexane, 3.0 mmol) was added dropwise to a solution of the lactones (6) and (7) (745 mg of an 85 : 15 mixture, 1.5 mmol) in dichloromethane (10 ml) at −78 °C under nitrogen. After it had been stirred for 1.5 h, water (10 ml) and 2N-sulphuric acid were added to the mixture which was then allowed to warm to room temperature; the layers were then separated, and the aqueous layer further extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) extracts gave the mixture of lactols (8) and (9) as an oil (745 mg, 100%). A portion (700 mg, 1.4 mmol) was dissolved in dry tetrahydrofuran (20 ml) and added to a stirred mixture of potassium t-butoxide (1.34 g, 12 mmol) and (4-carboxybutyl)triphenylphosphonium bromide (2.65 g, 66 mmol) in tetrahydrofuran (50 ml) at 20 °C under nitrogen. After 15 min, the reaction was quenched by sequential addition of aqueous ammonium chloride and 2N-hydrochloric acid (6 ml) and the layers were then separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed (H_2O), dried ($MgSO_4$), and evaporated. The residue was treated with ethereal diazomethane and then subjected to chromatography on silica gel (100 g) with 10% ethyl acetate–light petroleum as eluant. Four products were obtained: (i) *Methyl* (5*Z*,13*E*)9α,15-*bis*(*dimethyl-t-butylsilyloxy*)-11α-*hydroxyprosta*-5,13-*dienoate* (14) (R_F 0.35) (76 mg, 9%) as a colourless oil which was identical (t.l.c., ^1H n.m.r., i.r., and c.i.m.s.) with authentic material prepared by an alternative route;[9] (ii) *methyl* (5*Z*,13*E*)-11α,15-*bis*(*dimethyl-t-butylsilyloxy*)-9α-*hydroxyprosta*-5,13-*dienoate* (13) (R_F 0.25) (493 mg, 59%) as a colourless oil; $\nu_{max.}$ ($CHBr_3$) 3 500 (OH) 1 730 (C=O), and 968 cm^{-1} (*trans* CH=CH); τ($CDCl_3$) 4.3—4.9 (4 H, m, olefinic protons), 5.8—6.1 (3 H, m, H-9, H-11, and H-15) 6.36 (3 H, s, OMe), 7.5—9.0 (21 H, complex), 9.12 (21 H, br s, 2 × CMe_3 and CH_2*Me*), 9.96 (12 H, 2 × $OSiMe_2$) {Found: (c.i.m.s., NH_3) [*M* + NH_4]$^+$ 614.4625; [*M* + H]$^+$, 597.4380. $C_{33}H_{64}O_5Si_2$ requires *M* + NH_4, 614.4635; *M* + H, 597.4371} (Found: C, 65.9; H, 10.5. $C_{33}H_{64}O_5Si_2$ requires C, 66.3; H, 10.7%); (iii) *Methyl* 6-[4-(*dimethyl-t-butylsilyloxy*)-3-[3-(*dimethyl-t-butylsilyloxy*)*oct*-1-*enyl*]-2-*hydroxymethylcyclopentyl*]*hex*-5-*enoate* [isomer A, stereochemistry as in either (11) or (12)] (R_F 0.2) as a

colourless oil (61 mg, 7%); $\nu_{max.}$ ($CHBr_3$) 3 590, 3 500 (OH), and 1 730 cm^{-1} (C=O); τ($CDCl_3$) 4.4—4.8 (4 M, m, olefinic), 5.8—6.1 (2 H, m, 2 × CH–O), 6.3 (3 H, s, CO_2Me), 6.4 (2 H, d, $CHCH_2OH$), 7.5—9.0 (20 H, complex), 9.09 (21 H, m, CH_2CH_3 and 2 × CMe_3), and 9.93 (12 H, s, 2 × $SiMe_2$) {Found: (c.i.m.s., NH_3): $[M + NH_4]^+$, 614.4671; $[M + H]^+$, 597.4387. $C_{33}H_{64}O_5Si_2$ requires $M + NH_4$, 614.4635; $M + H$, 597.4371}; (iv) *methyl* 6-{4-(*dimethyl-t-butylsilyloxy*)-3-[3-(*dimethyl-t-butylsilyloxy*)*oct*-1-*enyl*]-2-*hydroxymethylcyclopentyl*}*hex*-5-*enoate* [isomer B, stereochemistry as in either structure (11) or (12)] (R_F 0.15) as a colourless oil (53 mg 6%); $\nu_{max.}$ ($CHBr_3$) 3 590, 3 500br (OH), and 1 730 cm^{-1} (C=O); τ($CDCl_3$) 4.4—4.8 (4 H, m, olefinic, 5.8—6.2 (2 H, m, 2 × CH–O), 6.3 (3 H, s, CO_2Me), 6.4 (2 H, d, CH–CH_2OH), 7.3 (1 H, m, $CHCH$=CH), 7.5—9.0 (19 H, complex), 9.09 (21 H, m, 2 × CMe_3 and CH_2Me), and 9.93 (12 H, s, 2 × $SiMe_2$) {Found: (c.i.m.s., NH_3): $[M + NH_4]^+$, 614.4653; $[M + H]^+$, 597.4446. $C_{33}H_{64}O_5Si_2$ requires $M + NH_4$, 614.4635; $M + H$, 597.4371}.

Methyl (5*Z*,13*E*)-11α,15-*Bis*(*dimethyl-t-butylsilyloxy*)-9-*oxoprosta*-5,13-*dienoate*.—(5*Z*,9α,11α,13*E*)-11,15-Bis(dimethyl-t-butylsilyloxy)-9-hydroxyprosta-5,13-dienoic acid methyl ester (13) (316 mg, 0.53 mmol) pyridinium chlorochromate (430 mg) and sodium acetate (120 mg) in dichloromethane (7 ml) were stirred at ambient temperature for 3 h. Ether was added and the mixture filtered through a pad of silica gel. Evaporation afforded an oil (340 mg) which after short-column chromatography on silica gel (20 g) with 5% ethyl acetate–light petroleum as eluant afforded pure *methyl* (5*Z*,13*E*)-11α,15-*bis*(*dimethyl-t-butylsilyloxy*)-9-*oxoprosta*-5,13-*dienoate* (18) as a colourless oil (290 mg, 92%); $\nu_{max.}$ ($CHBr_3$) 1 730 (C=O) and 965 cm^{-1} (*trans*-CH=CH); τ($CDCl_3$) 4.4—4.7 (4 H, m, olefinic), 5.8—6.2 (2 H, m, H-9 and H-15), 6.33 (3 H, s, CO_2Me), 7.1—8.9 (20 H, complex), 8.9—9.3 (21 H, s + m, 2 × CMe_3 and CH_2Me), and 9.95 (12 H, s, 2 × $SiMe_2$) (Found: C, 66.2; H, 10.5. $C_{33}H_{62}O_5Si_2$ requires C, 66.6; H, 10.5%).

Acetic Acid-catalysed Deprotection of the Disilyl Ether (18).—The disilyl ether (18) (180 mg, 0.3 mmol) was stirred with acetic acid (1.8 ml), tetrahydrofuran (0.6 ml) and water (0.6 ml) for 6 days at ambient temperature. The mixture was neutralised by addition of sodium hydrogencarbonate and extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give an oil. Column chromatography was performed on silica gel with ethyl acetate as eluant and collection of 20-ml fractions. Evaporation of fractions 43—46 afforded (±)-15-*epi*-prostaglandin E_2 methyl ester (21) as an oil (20 mg, 20%); $\nu_{max.}$ ($CHBr_3$) 3 590 (free OH), 3 480 (H-bonded OH), 1 730 (C=O), and 970 cm^{-1} (*trans*-CH=CH); τ($CDCl_3$) 4.0—4.8 (4 H, complex, olefinic), 5.7—6.0 (2 H, m, H-11 and H-15), 6.30 (3 H, s, CO_2Me), 7.0—8.0 (12 H, complex), 8.25 (2 H, m, C-3-methylene), 8.3—8.8 (8 H, complex), and 9.10 (3 H, t, CH_2Me) {Found (c.i.m.s. NH_3): $[M + NH_4]^+$, 384.2812; $[M + NH_4 - H_2O]$, 366.2634. Calc. for $C_{21}H_{34}O_5$: $M + NH_4$, 384.2750; $M + NH_4 - H_2O$, 366.2645}. Evaporation of fractions 48—62 afforded (±)-prostaglandin E_2 methyl ester as an oil (20 mg, 20%) which was identical (t.l.c., mass spec., and bioassay) with authentic material.

Baeyer–Villiger Oxidation of 3β-*Hydroxy*-2α-[(E)-3-*hydroxyoct*-1-*enyl*]-1αH,5αH-*bicyclo*[3.2.0]*heptan*-6-*one* (23).—(i) *At* −20 °C. The bicyclo[3.2.0]heptanone (23) [2] (270 mg) and anhydrous sodium acetate (0.75 g) in dichloromethane (10 ml) was cooled to −20 °C. A solution of commercial 40% peracetic acid in acetic acid (1.4 ml) was added dropwise. The mixture was kept in the freezer (−20 °C) for 16 h and then quenched by addition to an aqueous mixture of sodium hydrogencarbonate and sodium sulphite. Extraction with dichloromethane and evaporation of the dried ($MgSO_4$) solution afforded a mixture of the lactones (24) and (25) as a viscous oil (280 mg, 100%), homogenous by t.l.c. Microanalysis was performed directly on the unpurified reaction product (Found: C, 66.9; H, 9.1. Calc. for $C_{15}H_{24}O_4$: C, 67.2; H, 9.0%). The major component was identical (t.l.c., g.l.c., and n.m.r.) with authentic lactone (24) prepared by an independent route,[8] and the isomer ratio (24) : (25) in the product was 91 : 9 as determined by g.l.c. (3% OV 275, 220 °C) of the bis-trimethylsilyl ether derivatives. Diagnostic signals due to 5β-hydroxy-4α-[(*E*),(3*S*)-3-hydroxyoct-1-enyl]-*cis*-(3aα*H*,6aα*H*)-hexahydro-1*H*-cyclopenta[*c*]furan-1-one (25), were discernible in the ^1H n.m.r. spectrum ($CDCl_3$) of the mixture at τ 5.57(dd, *J* 9 and 7.5 Hz, H-3α), 5.78 (dd, *J* 9 and 2 Hz, H-3β), and 7.00 (td, *J* 10, 10, and 4.5 Hz, H-6aα).

(ii) *At* −78 °C. A pre-cooled mixture of the bicyclo[3.2.0]heptanone (23) [2] (540 mg) and sodium acetate (1.5 g) in dichloromethane (20 ml) at −78 °C, was treated with 40% peracetic acid in acetic acid (4.8 ml). The reaction flask was immersed in solid carbon dioxide in a Dewar flask and maintained at −78 °C for 4 days. The reaction was quenched and worked up in the manner described above to give the *product* (24) as a viscous oil (578 mg, 100%). This was identical (i.r., n.m.r., t.l.c., and g.l.c.) with authentic material [8] and contained only a trace (3% by g.l.c.) of the isomer (25). Microanalysis was performed directly on unpurified product (Found: C, 67.05; H, 9.3. Calc. for $C_{15}H_{24}O_4$: C, 67.2; H, 9.0%).

5β-(*Dimethyl-t-butylsilyloxy*)-4α-{[(E),(3*s*)]-3-(*dimethyl-t-butylsilyloxy*)*oct*-1-*enyl*}-*cis*-(3aαH,6aαH)-*perhydrocyclopenta*[b]*furan*-2-*one* (26).—A solution of the dihydroxylactone (24) (739 mg), dimethyl-t-butylsilyl chloride (2.0 g), and imidazole (2.0 g) in dimethylformamide (15 ml) was set aside at ambient temperature for 24 h, after which water was added to it. The mixture was extracted with ether and the organic extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to give an oil. Chromatography on silica gel and elution with 15% ethyl acetate–light petroleum gave 5β-(*dimethyl-t-butylsilyloxy*)-4α-[3-(*dimethyl-t-butylsilyloxy*)*oct*-1-*enyl*]*perhydrocyclopenta*[b]-*furan*-2-*one* (26) as a colourless oil (1.31 g, 96%) which solidified with time, m.p. 58—60 °C; $\nu_{max.}$ ($CHBr_3$) 1 760 (C=O) and 970 cm^{-1} (*trans*-CH=CH); τ($CDCl_3$) 4.3—4.8 (2 H, m, CH=CH), 5.10 (1 H, m, H-6a), 5.8—6.2 (2 H, m, H-5 and CH=CH*CH*–O), 7.2—8.4 (6 H, m, H-3α, H-3β, H-3a, H-4, H-6α, and H-6β); 8.4—8.9 (8 H, m, $CH_2CH_2CH_2$), 9.12 (21 H, s and m, 2 × CMe_3 and CH_2Me), and 9.9—10.0 (12 H, several s, 2 × $OSiMe_2$) (Found: C, 65.1; H, 10.5. $C_{27}H_{52}O_4Si_2$ requires C, 65.2; H, 10.65%).

5β-(*Dimethyl-t-butylsilyloxy*)-4α-{[(E),(3S)]-3-(5-*dimethyl-t-butylsilyloxy*)*oct*-1-*enyl*}-cis-(3aαH,6aαH)-*perhydrocyclopenta*[b]*furan*-2-*ol* (27).—Di-isobutylaluminium hydride (5.0 ml of a 1.0M-solution in hexane, 5 mmol) was added dropwise to a solution of the lactone (26) (994 mg, 2 mmol) in dichloromethane (15 ml) at −78 °C under nitrogen. After 1.5 h, water (10 ml) was added and the mixture allowed to warm to room temperature. 2N-Sulphuric acid (5 ml) was added and the layers separated. The aqueous layer was further extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) extracts gave 5-(*dimethyl-t-butylsilyloxy*)-4α-{[(E),(3S)]-3-(*dimethyl-t-butylsilyloxy*)*oct*-1-

enyl}-cis-(3aαH,6aαH)-*perhydrocyclopenta*[b]*furan*-2-*ol* (27) as a colourless oil (1.002 g, 100%); $\nu_{max.}$ ($CHBr_3$) 3 580 (free OH), 3 340 (H-bonded OH), and 970 cm^{-1} (*trans*-CH=CH); τ($CDCl_3$) 4.4—4.8 [3 H, complex, CH=CH and O*CH*(OH)], 5.3—6.5 (3 H, complex, 3 × CH–O), 7.2—9.0 (15 H, complex), 9.15, 9.17 (18 H, s, and s, 2 × CMe_3), 9.15 (3 H, m, CH_2*Me*), 9.9—10.0 (12 H, several s, 2 × $SiMe_2$) (Found: C, 65.0; H, 11.2. $C_{27}H_{54}O_4Si_2$ requires C, 65.0; H, 10.9%).

Wittig Olefination of the Lactol (27).—Sodium 1,1-dimethylpropoxide in benzene (0.75 M; 10.6 ml, 8 mmol) was added to a stirred suspension of (4-carboxybutyl)triphenylphosphonium bromide (1.77 g, 4 mmol) and dimethyl sulphoxide (0.15 ml) in benzene (10 ml) at 75 °C. After 10 min at this temperature a solution of the lactol (27) (260 mg, 0.52 mmol) in benzene (2 ml) was added. After a further 10 min, the reaction was quenched by addition of aqueous ammonium chloride (30 ml) and the layers separated. The aqueous layer was further extracted with ether, and the combined organic layers dried ($MgSO_4$), and evaporated. After methylation with ethereal diazomethane the mixture was separated by short column chromatography on silica gel (100 g) with 5% ethyl acetate–light petroleum as eluant and collection of 15-ml fractions.

Evaporation of fractions 40—50 afforded *methyl* (5Z,15S)-9α,15-*bis*(*dimethyl-t-butylsilyloxy*)-11α-*hydroxyprosta*-5,13-*dienoate* (29) (12 mg, 4%) as a colourless oil {Found: (c.i.m.s., NM_4): $[M + NH_4]^+$, 614.4703; $[M + H]^+$, 597.4401. $C_{33}H_{64}O_5Si_2$ requires $M + NH_4$, 614.4636; $M + H$, 597.4370}. This material was spectroscopically (i.r. and ^1H n.m.r.) and chromatographically (t.l.c.) indistinguishable from the isomeric mixture (14) described above.

Evaporation of fractions 60—110 afforded *methyl* (5Z-15S)-11α,15-*bis*(*dimethyl-t-butylsilyloxy*)-9α-*hydroxyprosta*-5,13-*dienoate* (28) as a colourless oil (240 mg, 77%) {Found: (c.i.m.s., NH_3): $[M + H]^+$, 597.4341. $C_{33}H_{64}O_5Si_2$ requires $M + H$, 597 4371}. This material was spectroscopically (i.r. and n.m.r.) and chromatographically indistinguishable from the isomeric mixture (13) described above.

Methyl (5Z,13E,15S)-11α,15-*bis*(*dimethyl-t-butylsilyloxy*)-9-*oxoprosta*-5,13-*dienoate* (30).—The alcohol (29) (225 mg) in dichloromethane (3 ml) was added to a mixture of pyridinium chlorochromate (600 mg) and sodium acetate (250 mg) in dichloromethane (5 ml). After being stirred for 3 h at ambient temperature the mixture was applied to a column of silica gel (20 g). The product was eluted with dichloromethane followed by chloroform to give *methyl* (5Z,13E,15S)-11α,15-*bis*(*dimethyl-t-butylsilyloxy*)-9-*oxoprostadienoate* (198 mg, 96%) as a colourless oil {Found: (c.i.m.s., NH_4): $[M + NH_4]^+$, 612.4534. $C_{33}H_{62}Si_2O_5$ requires $M + NH_4$, 612.4479}. This material was indistinguishable by i.r., n.m.r., and t.l.c. from the isomeric mixture (18) described above.

(±)-*Prostaglandin* E_2 *Methyl Ester*.—Aqueous 40% hydrofluoric acid (1.5 ml) was added to a solution of the bis-silyl ether (30) in acetonitrile (8.5 ml) contained in a Polythene bottle. After 1 h at 20 °C the solution was diluted with dichloromethane and washed with aqueous 8% sodium hydrogencarbonate and then water. The organic solution was dried ($MgSO_4$) and evaporation gave (±)-*prostaglandin* E_2 *methyl ester* (20) (107 mg, 100%) as a colourless oil. This was homogeneous by t.l.c. and further purification was unnecessary. Spectroscopic and microanalytical data were obtained directly on this material; τ($CDCl_3$) 4.2—4.9 (4 H, m, olefinic), 5.8—6.1 (2 H, m, H-11 and H-15), 6.30 (3 H, s, CO_2Me_3), 6.4—8.9 (22 H, complex), and 9.10 (3 H, m, CH_2*Me*) (Found: C, 68.9; H, 9.4. Calc. for $C_{21}H_{34}O_5$: C, 68.8; H, 9.35%). The synthetic material was identical (t.l.c., mass. spec., and bioassay) with authentic material prepared by methylation (CH_2N_2) of commercially available PGE_2.

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