Synthesis of Stable Prostacyclin Analogues from 2,3-Disubstituted Bicyclo[3.2.0]heptan-6-ones

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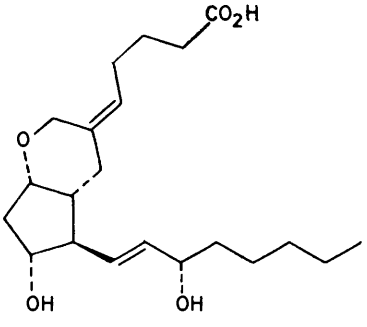
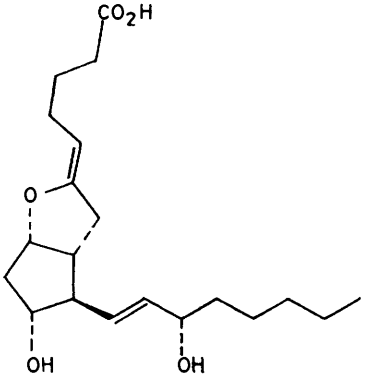
A short synthesis of 9-deoxy-6,9α-methanoepoxy-Δ^5-prostaglandin F_1 (14) from bicyclo[3.2.0]heptan-6-one (3) is described. The ketone (3) can be converted by known methods into the vinyl ether (8). In the presence of mercury(II) acetate at 100 °C, the 5-hydroxyalk-1-enyl methyl ether (8) undergoes a novel intramolecular vinyl transetherification reaction to give the Δ^2-dihydropyran (9). Hydroboration–oxidation of the dihydropyran (9) furnished selectively the tetrahydropyran-3-ol (10). Subsequent elaboration *via* oxidation, Wittig olefination, and deprotection afforded 9-deoxy-6,9α-methanoepoxy-Δ^5-prostaglandin F_1 (14). The protected bicyclo-[3.2.0]heptan-6-one (16) underwent a ring expansion with diazomethane, producing a 1 : 1 mixture of the two homologated ketones (17) and (18). Wittig olefination and deprotection of these ketones provided 15-*epi*-9-deoxy-6,9α-methano-Δ^5-prostaglandin F_1 (19) and its structural isomer (20). The two bicyclo[3.2.0]heptan-6-ones (3) and (4) also led directly to a series of 9-deoxy-6,9α-cycloprostaglandins F_1 *via* Wittig reactions.

A RECENT report [1] of the preparation of (5*Z*)-9-deoxy-6,9α-methanoepoxy-Δ^5-prostaglandin F_1 [2] (2), a stable analogue of prostacyclin (2),[3] has prompted us to disclose our own synthesis of this compound (1) and some related work. The potent biological activity of prostacyclin (2) indicates its potential therapeutic usefulness as an antithrombotic agent.[4] A major limitation, however, is the chemical instability of the enol ether group in (2) under physiological conditions, and this has resulted in a search for more stable analogues, having similar activity.[5] Here, we describe the versatility of the readily available bicyclo[3.2.0]heptan-6-ones [6] (3) and (4) as intermediates in the synthesis of such compounds. The synthesis of 9-deoxy-6,9α-methanoepoxy-Δ^5-prostaglandin F_1 (14) described here (Scheme 1) is notably shorter than the recently published preparation.[1]



(1)

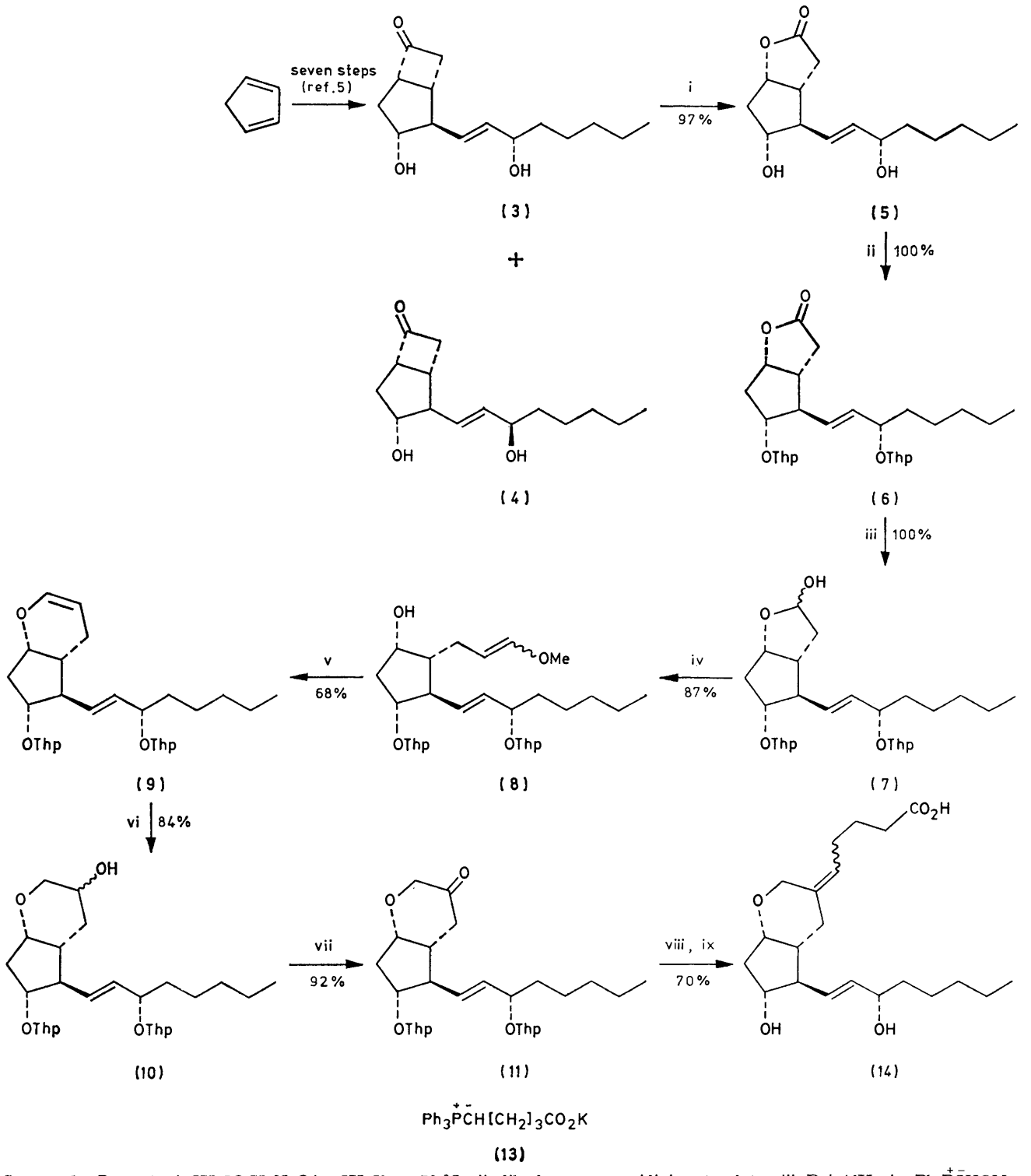


(2)

Previous work from our laboratories has shown that the ketone (3) can be oxidised regioselectively to the γ-lactone (5) † in almost quantitative yield by the action of buffered peracetic acid in dichloromethane at −78 °C for 4 days.[7] The hydroxy-groups in lactone (5) were then protected by formation of their tetrahydropyranyl ethers. The use of freshly distilled, dry dihydropyran, with pyridinium toluene-*p*-sulphonate [8] as acid catalyst, gave the protected lactone (6) in quantitative yield without recourse to chromatographic purification. Reduction of the lactone (6) with di-isobutylaluminium hydride at −78 °C afforded the lactol (7), also in quantitative yield. Treatment of the lactol (7) with 4 equiv. of the Wittig reagent derived from (methoxymethyl)triphenylphosphonium chloride and potassium t-butoxide in tetrahydrofuran furnished the acyclic vinyl ether (8) (87%) after chromatography. The transformation (5) ⟶ (8) using slightly different reaction conditions has been reported previously by the Upjohn group.[9]

The cyclisation of the 5-hydroxyalk-1-enyl methyl ether (8) to the Δ^2-dihydropyran (9) is the key step in Scheme 1. Retrosynthetic analysis and a literature survey [10,11] had suggested that Δ^2-dihydropyrans such as (9) are the most synthetically useful precursors of tetrahydropyran-3-ones such as (11). The vinyl transetherification reaction (Scheme 2) is well established,[12] but no literature precedent could be found for the intramolecular variant (8) ⟶ (9). Since β-substituted vinyl ethers do undergo the intermolecular reaction, albeit with some difficulty,[13] then the corresponding novel intramolecular reaction (to give a five- or six-membered ring), having a more favourable entropy factor, was considered possible. Preliminary studies with the vinyl

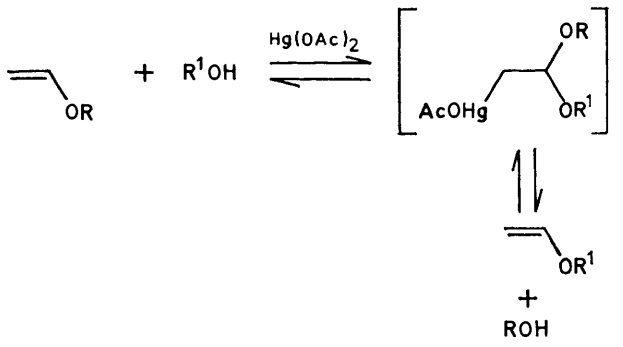
† The presence of 3% of an isomeric lactone, discussed in ref. 7, was ignored and for all practical purposes did not interfere after the chromatographic purification of the vinyl ether (8).



SCHEME 1 *Reagents:* i, CH_3CO_3H, NaOAc, CH_2Cl_2, −78 °C; ii, dihydropyran, pyridinium tosylate; iii, $Bu^i{}_2AlH$; iv, $Ph_3\overset{+}{P}\overset{-}{C}HOMe$; v, $Hg(OAc)_2$, 100 °C; vi, 9-borabicyclononane, then basic H_2O_2; vii, pyridinium chlorochromate, NaOAc; viii, compound (13); ix, 0.3M aq. HCl, acetone

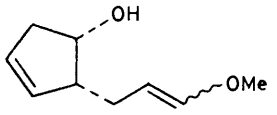
ether (12) [14] indicated that the intramolecular reaction catalysed by mercury(II) acetate was extremely slow in refluxing dichloromethane.

However, evaporation of the solution and pyrolysis of the residue until methanol was observed to condense in



SCHEME 2

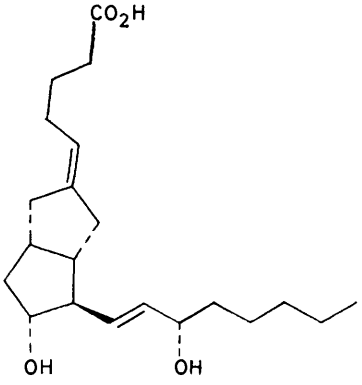
a cooler part of the apparatus promoted the desired reaction. Thus a homogeneous mixture of the vinyl ether (8) and 0.2 equiv. of freshly crystallised [15] mercury(II) acetate was heated at 100 °C and 20 mmHg for 2 h, in a bulb-to-bulb distillation apparatus, to give the Δ^2-dihydropyran (9) (68%) after chromatography. The absence of any significant by-products in this reaction (t.l.c. analysis) justifies the initial choice of tetrahydropyranylation for hydroxy-group protection, and reflects the relatively low Lewis-acidity of mercury(II) acetate (*cf.* acetal by-product formation in ref. 13).



(12)

Conversion of Δ^2-dihydropyrans into tetrahydropyran-3-ols *via* regiospecific hydroboration–oxidation of the olefinic bond using diborane [10] has ample precedent. Hydroboration of Δ^2-dihydropyran (9) with 9-borabicyclo[3.3.1]nonane,[16] followed by work-up with basic hydrogen peroxide, afforded the tetrahydropyran-3-ol (10) (84%) after chromatography. Oxidation of the alcohol (10) with buffered pyridinium chlorochromate under standard conditions [17] was slow, did not go to completion, and led to some loss of the tetrahydropyranyl group in the octenol side chain. Six equiv. each of the oxidising agent and sodium acetate, however, resulted in a clean conversion into the tetrahydropyran-3-one (11) (92%).

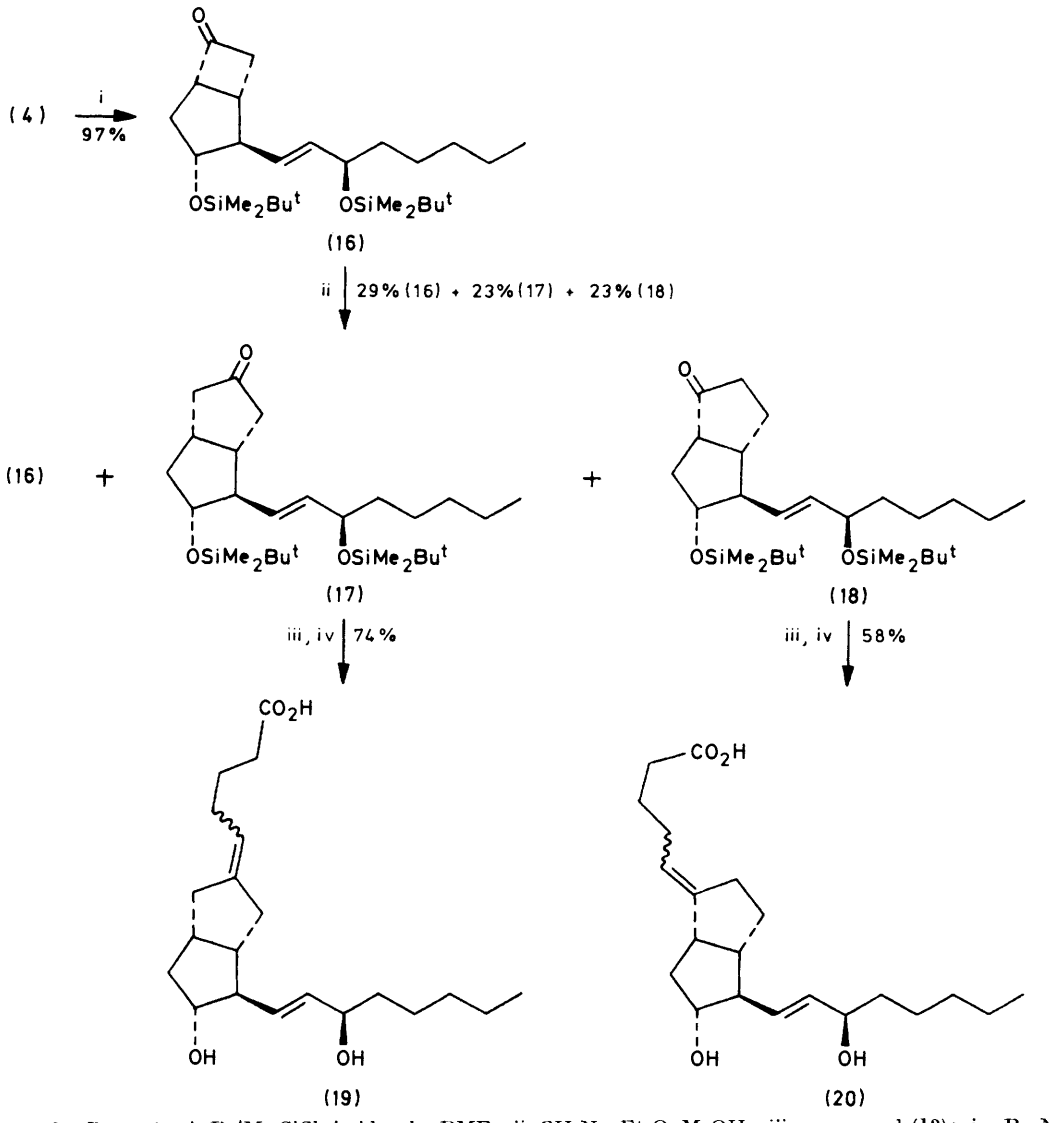
Wittig reaction of the ketone (11) with the requisite ylide (13), deprotection with mineral acid, and chromatography furnished the desired prostacyclin analogue (14) as a gum (70%, homogeneous by t.l.c.) which slowly solidified. Crystallisation gave (±)-9-deoxy-6,9α-methanoepoxy-Δ^5-prostaglandin F_1 (14) (44%) as a 9 : 1 mixture of isomers (h.p.l.c. analysis) at the newly formed olefinic bond. That this material was predominantly the biologically more interesting 5*Z*-isomer (1) was judged from its ^{13}C n.m.r. spectrum, which exhibited the mutual shielding effect of two *cis*-substituents on a double bond relative to the corresponding *trans*-configuration.[18] Assignments for the major isomer were C-7 (32.6) and C-6a (65.5), and for the minor isomer C-7 (29.6) and C-6a (67.7). The shielding effect of C-4 on C-6a (5*Z*-configuration) and on C-7 (5*E*) leads to the conclusion that the 5*Z*/5*E* ratio is 9 : 1. This was later confirmed by the work of Skuballa,[1] who succeeded in separating the two isomers and making configurational assignments by ^1H n.m.r. spectroscopy.



(15)

Prior to the above work we examined a potential synthesis of (5*Z*)-9-deoxy-6,9α-methano-Δ^5-prostaglandin F_1 (15) from the bicyclo[3.2.0]heptan-6-one epimer (3). Our initial studies were carried out using the bicyclo[3.2.0]heptan-6-one (4) having the unnatural C-3′ configuration and are summarised in Scheme 3. When Gandolfi [19] released the first details of a total synthesis of the carbon analogue (15) [20] of prostacyclin (2) we decided not to pursue its preparation further and have thus only synthesised 15-*epi*-9-deoxy-6,9α-methano-Δ^5-prostaglandin F_1 (19).

The less polar dihydroxy-ketone isomer (4) was initially protected (97% yield) by formation of its bis-t-butyldimethylsilyl ether (16), in order to eliminate hydroxy-group interactions with diazomethane, previously observed in the esterification of prostaglandin $F_{2\alpha}$.[21] The ring expansion of cyclobutanone (16) in methanol with ethereal diazomethane [22] was monitored by g.l.c. to optimise the formation of monohomologated ketones, which inevitably react further to form bishomologated products, *etc.* Multiple elution preparative t.l.c. led to the separation of two major products (23% yield each) with almost identical i.r. spectral bands near 1 730 cm^{-1} indicating the presence of a cyclopentanone group in each. Comparison of the two ^{13}C n.m.r. spectra (with offset decoupling) allows an unambiguous assignment of the pentalen-1-one structure (18) to the less polar isomer (R_F 0.35) and that of the pentalen-2-one (17) to the



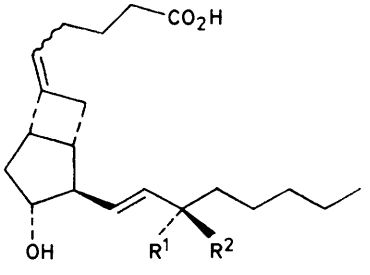
SCHEME 3 *Reagents:* i, Bu^tMe_2SiCl, imidazole, DMF; ii, CH_2N_2, Et_2O, MeOH; iii, compound (13); iv, Bu_4NF

isomer of R_F 0.27. The characteristic features of the pentalen-1-one (18) spectrum, not compatible with the alternative structure (17), are the resonances for C-6a (doublet at δ 48.6) and C-3 (triplet at δ 24.1). A single enantiomer of the racemic pentalen-2-one (17) was subsequently described by Morton and Brokaw.[23]

The Wittig reaction of the pentalen-2-one (17) with 4 equiv. of ylide (13), followed by desilylation with tetrabutylammonium fluoride, afforded (±)-15-*epi*-9-deoxy-6,9α-methano-Δ^5-prostaglandin F_1 (19) (74%) as an inseparable mixture (by t.l.c.) of Δ^5-isomers (ratio 71 : 29). Such Wittig conditions were used by us routinely, and hence we never encountered the problem [enolisation of the ketone (17) with 1 equiv. of ylide (13)] initially met by Morton and Brokaw.[23]

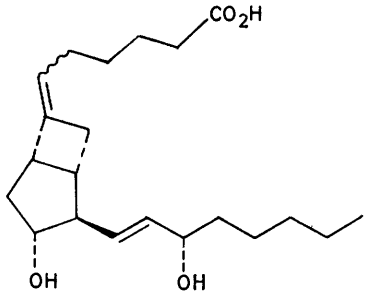
Similar Wittig reactions (and desilylation as above where necessary) with ketones (18), (3), and (4) furnished the (±)-cycloprostaglandins F_1 (20) (58%), (21) (73%), and (22) (48%), respectively. All products were inseparable mixtures of isomers at the newly formed olefinic bonds (see Experimental section for ratios).

Of the prostacyclin analogues (14) and (19)—(22), only the cycloprostaglandin F_1 (21) showed activity as an



(21) R^1 = OH, R^2 = H
(22) R^1 = H, R^2 = OH

inhibitor of collagen-induced platelet aggregation. Interestingly, the homologated analogue (23), prepared as above but utilising the ylide (24), showed enhanced potency (EC_{50} 0.8 μg ml^{-1}).



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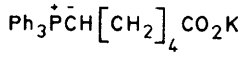

(24)

EXPERIMENTAL

^1H N.m.r. spectra were recorded at 90 MHz on a Varian EM 390 spectrometer. ^{13}C N.m.r. spectra were recorded on a JEOL FX-100 spectrometer; chemical shifts are reported downfield from tetramethylsilane. I.r. spectra were obtained on a Perkin-Elmer 357 (or 377) spectrophotometer. H.p.l.c. analyses were carried out using either a Du Pont 830 Liquid Chromatograph or a Perkin-Elmer Series 2 Pump. For analytical t.l.c. Camlab ' Polygram ' pre-coated silica gel plates were used, and for preparative t.l.c. Merck pre-coated silica gel plates of 2 mm thickness. Short-column chromatography was performed with Merck 7736 or Whatman SO TLC silica gel. Light petroleum refers to the fraction of b.p. 60—80 °C and all solvents for chromatography were distilled before use. Reactions were carried out at ambient temperature except where otherwise stated. Distillations were accomplished by using the Büchi Kugelröhr (bulb-to-bulb) system and the temperatures reported are oven temperatures at distillation.

(3aα,6aα)-5β-*Tetrahydropyran*-2-*yloxy*-4α-[(E)-(3S*)-3-*tetrahydropyran*-2-*yloxyoct*-1-*enyl*]*perhydrocyclopenta*[b]-*furan*-2-*one* (6).—A solution of the dihydroxy-lactone (5) (2.51 g, 9.36 mmol), dry dihydropyran (2.8 ml, 30 mmol), and pyridinium toluene-*p*-sulphonate (250 mg, 1 mmol) in dry dichloromethane (70 ml) was stirred for 18 h. Ether (180 ml) was added and the mixture washed with water (25 ml) and saturated aqueous sodium chloride (25 ml), dried ($MgSO_4$), and evaporated to give the protected lactone (6) (4.06 g, 99%) as a colourless oil homogeneous by t.l.c.; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 1 763 (C=O) and 973 cm^{-1} (*trans*-CH=CH); τ (CCl_4) 4.4—4.9 (2 H, m, CH=CH), 5.14 (1 H, m, H-6aα) 5.25—5.55 (2 H, m, 2 × O–CH–O), 5.9—6.8 (6 H, complex, H-5α, CH=CH–C*H*–O, and 2 × CH_2–O), 7.2—8.9 (26 H, complex), and 9.10 (3 H, br, t, CH_2CH_3).

(3aα,6aα)-5β-*Tetrahydropyran*-2-*yloxy*-4α-[(E)-(3S*)-3-*tetrahydropyran*-2-*yloxyoct*-1-*enyl*]*perhydrocyclopenta*[b]-*furan*-2-*ol* (7).—Di-isobutylaluminium hydride (10 ml of a 2.0M-solution in hexane; 20 mmol) was added dropwise to a stirred solution of the lactone (6) (4.02 g, 9.17 mmol) in dry toluene (120 ml) at −78 °C under nitrogen. After stirring for 1 h, a mixture of tetrahydrofuran (80 ml) and water (40 ml) was added and the resulting mixture stirred at ambient temperature for 2 h. The precipitate was filtered off and washed well with ether. The filtrate was diluted with water (100 ml) and the mixture equilibrated and separated. The aqueous layer was further extracted with ether (4 × 50 ml). The combined extracts were washed with saturated aqueous sodium chloride (1 × 50 ml), dried (Na_2SO_4), and evaporated to give the lactol (7) (4.04 g, 100%) as a colourless oil homogeneous by t.l.c.; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 580 and 3 370 (OH), and 975 cm^{-1} (*trans*-CH=CH); τ (CCl_4) 4.3—4.9 (3 H, complex, CH=CH and O–C*H*–OH), 5.2—5.7 (1 H, m, H-6aα), 5.37 (2 H, br, s, 2 × O–CH–O), 5.9—6.8 (6H, complex, H-5α, CH=CH–C*H*–O, and 2 × CH_2–O), 7.4—8.9 (27 H, complex), and 9.10 (3 H, br, t, CH_2CH_3).

2α-(3-*Methoxyprop*-2-*enyl*)-4α-*tetrahydropyran*-2-*yloxy*-3β-[(E)-(3R*)-3-*tetrahydropyran*-2-*yloxyoct*-1-*enyl*]*cyclopentan*-1α-*ol* (8).—Methoxymethyltriphenylphosphonium chloride (9.26 g, 27 mmol) was added in portions over 5 min to a stirred solution of potassium t-butoxide (3.03 g, 27 mmol) in dry tetrahydrofuran (70 ml) at 0 °C. After stirring for 30 min at 0 °C a solution of the lactol (7) (4.0 g, 9.1 mmol) in dry tetrahydrofuran (13 ml) was added dropwise. The red suspension was stirred for 30 min at ambient temperature and then the reaction was quenched by addition of aqueous sodium chloride (30 ml). After equilibration and separation of the layers, the aqueous layer was extracted with ether (3 × 30 ml). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by short-column chromatography on silica gel (550 g), eluting with ethyl acetate–light petroleum (3 : 7), to give a mixture of the *cis*- and *trans*-isomers (ratio 36 : 64 by n.m.r.) of the vinyl ether (8) (3.69 g, 87%) as a colourless oil; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 600 and 3 515 (OH), 1 658 (C=C–OMe), and 972 cm^{-1} (*trans*-CH=CH); τ (CCl_4) 3.75 and 4.15 (1 H, d, *J* 12 Hz for *trans*-isomer; d, *J* 6 Hz for *cis*-isomer, CH=C*H*–OMe), 4.3—4.9 (2 H, m, C*H*=C*H*–CH–O), 5.1—5.8 (1 H, m, C*H*=CH–OMe), 5.39 (2 H, br, s, two O–CH–O), 6.40 and 6.55 (3 H, two s, OCH_3), 5.8—6.8 (7 H, complex, H-1β, H-4β, CH=CHC*H*–O, and 2 × CH_2–O), 7.3—8.9 (27 H, complex), and 9.10 (3 H, br, t, CH_2CH_3); [Found (c.i. mass spec., NH_3): $(M + NH_4)^+$, 484.3625. Calc. for $C_{27}H_{46}O_6$: $(M + NH_4)$, 484.3638].

(4aα,7aα)-4,4a,5,6,7,7a-*Hexahydro*-6β-*tetrahydropyran*-2-*yloxy*-5α-[(E)-(3S*)-3-*tetrahydropyran*-2-*yloxyoct*-1-*enyl*]-*cyclopenta*[b]*pyran* (9).—A solution of the hydroxy-vinyl ether (8) (3.62 g, 7.75 mmol) and mercury(II) acetate (495 mg, freshly crystallised from ethanol, 1.55 mmol) in dry dichloromethane (10 ml) was evaporated to give a colourless, viscous oil, which was heated (in a Büchi Kugelröhr apparatus) at 100 °C and 20 mmHg for 2 h. The residue was treated with aqueous 0.5N-sodium carbonate (100 ml) and extracted with ether (3 × 70 ml). The combined extracts were dried (Na_2SO_4 and K_2CO_3) and evaporated to give an oil. Short-column chromatography on silica gel (350 g), eluting with triethylamine–ethyl acetate–light petroleum (1 : 40 : 160), gave the *cyclic vinyl ether* (9) (2.30 g, 68%) as a colourless oil; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 1 645 (C=C–O) and 972 cm^{-1} (*trans*-CH=CH); τ (CCl_4) 3.79 (1 H, br, d, *J* 6 Hz, O–C*H*=CH), 4.3—4.9 (2 H, m, C*H*=C*H*–CH–O), 5.3—5.65 (3 H, complex, O–CH=C*H* and 2 × O–CH–O), 5.8—6.5 (5 H, complex, H-6α, H-7aα, CH=CHC*H*–O, and one each of 2 × CH_2–O), 6.5—6.8 (2 H, m, one each of 2 × CH_2–O), 7.3—8.9 (26 H, complex), and 9.10 (3 H,

br, t, CH_2CH_3); [Found (c.i. mass spec., NH_3): $(M + NH_4)^+$, 452.3356. $C_{26}H_{42}O_5$ requires $(M + NH_4)$, 452.3376].

(4aα,7aα)-6β-*Tetrahydropyran-2-yloxy*-5α-[(E)-(3S*)-3-*tetrahydropyran-2-yloxyoct*-1-*enyl*]*perhydrocyclopenta*[b]*pyran*-3-*ol* (10).—9-Borabicyclo[3.3.1]nonane (62 ml of a 0.13M-solution in dry tetrahydrofuran, 8.3 mmol) was added dropwise to a stirred solution of the cyclic vinyl ether (9) (2.04 g, 4.69 mmol) in dry tetrahydrofuran (10 ml) under nitrogen. After 17 h, the mixture was poured into ethanol (60 ml) and treated with aqueous 5N-sodium hydroxide (9 ml) and 28% w/v aqueous hydrogen peroxide (18 ml). After the ensuing exothermic reaction had slowed down, the mixture was heated at 50 °C for 3 h, cooled, diluted with saturated aqueous sodium chloride (500 ml), and extracted with ether (3 × 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give a colourless oil. Short-column chromatography on silica gel (500 g), eluting with triethylamine–ethyl acetate–light petroleum (1 : 66 : 132), gave the *alcohol* (10) (1.79 g, 84%) as a colourless oil; $\nu_{max.}$ (0.1% solution in CCl_4) 3 635 (OH) and 972 cm^{-1} (*trans*-CH=CH); τ (CCl_4) 4.4—4.75 (2 H, m, CH=CH), 5.25—5.5 (2 H, m, 2 × O–CH–O), 5.9—6.5 (7 H, complex, H-3, H-5α, H-6aα, CH=CH–C*H*–O, and one each of 2 × CH_2–O and H-2), 6.5—6.8 (2 H, m, one each of 2 × CH_2–O), 7.11 (1 H, t, *J* 12 Hz, one of H-2), 7.3—9.0 (27 H, complex), and 9.10 (3 H, br, t, CH_2CH_3); [Found (c.i. mass spec., NH_3) $(M + NH_4)^+$, 470.3469. $C_{26}H_{44}O_6$ requires $(M + NH_4)$, 470.3481].

(4aα,7aα)-6β-*Tetrahydropyran-2-yloxy*-5α-[(E)-(3S*)-3-*tetrahydropyran-2-yloxyoct*-1-*enyl*]*perhydrocyclopenta*[b]-*pyran*-3-*one* (11).—A suspension of pyridinium chlorochromate (2.28 g, 10.6 mmol), sodium acetate (850 mg, 10.6 mmol), and the alcohol (10) (800 mg, 1.77 mmol) in dry dichloromethane (25 ml) was stirred for 2.5 h. Dichloromethane was removed by evaporation and the residue extracted many times with ether. The combined extracts were filtered through a pad of silica gel (Merck 7736), washing well with more ether. The filtrate was washed with saturated aqueous ammonium chloride (1 × 20 ml) and aqueous 8% sodium hydrogencarbonate (2 × 20 ml), dried ($MgSO_4$), and evaporated to give the ketone (11) (730 mg, 92%), homogeneous by t.l.c.; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 1 730 (C=O) and 972 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.3—4.75 (2 H, m, CH=CH), 5.2—5.45 (2 H, m, 2 × O–CH–O), 5.8—6.3 (5 H, complex, H-5α, H-6aα, CH=CH–C*H*–O, and one each of 2 × CH_2–O), 6.3—6.7 (2 H, m, one each of 2 × CH_2–O), 5.85 and 6.23 (2 H, 2 components of AB system, *J* 18 Hz, H-2), 7.2—7.7 (4 H, complex, including H-4 and H-5β), 7.7—8.9 (22 H, complex), and 9.10 (3 H, br, t, CH_2CH_3). A sample for analysis was obtained by preparative t.l.c. (silica gel, ether) (Found: C, 69.35; H, 9.6. Calc. for $C_{26}H_{42}O_6$: C, 69.3; H, 9.4%).

(±)-9-*Deoxy*-6,9α-*methanoepoxy*-Δ^5-*prostaglandin* F_1 (14).—Dry tetrahydrofuran (50 ml) was added to a stirred mixture of potassium t-butoxide (1.35 g, 12 mmol) and (4-carboxybutyl)triphenylphosphonium bromide (2.66 g, 6 mmol) under nitrogen. The resulting red suspension was stirred for 30 min. A solution of the ketone (11) (681 mg, 1.51 mmol) in dry tetrahydrofuran (10 ml) was then added rapidly in a single portion with vigorous stirring and the resulting dark orange suspension was stirred for 2.5 h. Saturated aqueous ammonium chloride (200 ml) was added with stirring and the mixture extracted with ether (4 × 50 ml). The combined extracts were evaporated and the wet residue was dissolved in acetone (50 ml) and 0.3M-hydrochloric acid (10 ml). The yellow solution was left for 16 h. Acetone was removed by evaporation and the aqueous residue basified with aqueous 2N-sodium hydroxide. The resulting orange-brown solution was washed with ether (2 × 50 ml), acidified with 2N-hydrochloric acid, and extracted with ethyl acetate (4 × 50 ml). The combined extracts were washed with saturated aqueous sodium chloride (1 × 10 ml), dried ($MgSO_4$), and evaporated to give a viscous oil. Short-column chromatography on silica gel (50 g), eluting with acetic acid–ethyl acetate (2 : 100), gave the acid (14) (385 mg, 70%) as a viscous gum, homogeneous by t.l.c. Crystallisation from ether at −20 °C gave the acid (14) (243 mg) as a colourless solid, m.p. 79—80 °C; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 580 (OH), 1 735 (C=O, acid, monomer), 1 705 (C=O, acid, dimer), and 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.28 (3 H, vbr, s, OH), 4.3—4.65 (2 H, m, H-13 and H-14), 4.82 (*ca.* 1 H, br, t, *J* 7.5 Hz, H-5), 5.51 (*ca.* 1 H, d, *J* 13 Hz, one of H-6a of 5*Z*-isomer), 5.8—6.3 (3 H, complex, H-9, H-11, and H-15), 6.23 (*ca.* 1 H, d, *J* 13 Hz, one of H-6a of 5*Z*-isomer), 7.3—8.9 (20 H, complex), 9.10 (3 H, br, t, H-20); δ_C ($CDCl_3$) 5*Z*-isomer: 176.9 (s, C-1), 135.8 (d, C-14), 132.1 (s, C-6), 131.9 (d, C-13), 124.6 (d, C-5), 78.1 (d, C-9), 77.2 (d, C-11), 73.1 (d, C-15), 65.5 (t, C-6a), 53.3 (d, C-12), 44.8 (d, C-8), 40.7 (t, C-10), 36.9 (t, C-16), 33.2 (C-2), 32.6 (C-7), 31.7 (C-18), 26.3 (C-4), 25.2 (C-17), 24.6 (C-3), 22.6 (t, C-19), 14.0 (q, C-20); 5*E*-isomer (where distinguishable): 135.3 (d, C-14), 125.8 (d, C-5), 79.1 (d, C-9), 77.8 (d, C-11), 72.8 (d, C-15), 67.7 (C-6a), 52.7 (C-12), 41.1 (C-10), 29.6 (C-7), with an approximate 5*Z* : 5*E* isomer ratio of 9 : 1; h.p.l.c. analysis (20 cm × 5 mm 10μ silica gel, 91 : 9 : 0.5 hexane–ethanol–acetic acid) showed an isomer ratio of 90.5 : 9.5, with the more polar isomer predominating (Found: C, 68.85; H, 9.35. Calc. for $C_{21}H_{34}O_5$: C, 68.8; H, 9.35%).

A second crop of acid (14) (95 mg), m.p. 65—78 °C, was obtained with a corresponding isomer ratio of 71 : 29 (h.p.l.c. analysis).

(1α,5α)-3β-(*t-Butyldimethylsilyloxy*)-2α-[(E)-(3R*)-3-(*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]*bicyclo*[3.2.0]*heptan*-6-*one* (16).—A solution of the diol (4) (2.60 g, 10.3 mmol), t-butyldimethylsilyl chloride (4.40 g, 26.8 mmol), and imidazole (3.86 g, 56.8 mmol) in dry dimethylformamide (50 ml) was stirred for 16 h, poured into water (250 ml), and extracted with light petroleum (4 × 50 ml). The combined extracts were washed with water (2 × 40 ml), dried (Na_2SO_4), and evaporated, and the residue was distilled to give the *ketone* (16) (4.80 g, 97%) as an almost colourless oil, b.p. 150—160 °C at 0.05—0.1 mmHg; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 1 773 (C=O) and 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.35—4.85 (2 H, m, CH=CH), 5.90 (1 H, m, H-3α), 5.97 (1 H, m, CH=CHC*H*–O), 6.39 (1 H, m, H-5α), 6.75—6.9 (2 H, m, H-7), 7.1—7.45 (2 H, m, H-1α and H-2β), 7.75—8.3 (2 H, m, H-4), 84.—8.9 (8 H, m, $CH_2CH_2CH_2CH_3$), 9—9.25 (21 H, 2 × s, and br, t, 2 × CMe_3 and CH_2CH_3), and 9.93 (12 H, s, 2 × $SiMe_2$); δ_C ($CDCl_3$) 212.3 (s, C-6), 133.8 (d, C-2′), 130.0 (d, C-1′), 80.9 (d, C-3), 73.2 (d, C-3′), 63.1 (d, C-5), 55.9 (d, C-2), 52.5 (t, C-7), 38.9 (t, C-4), 38.2 (t, C-4′), 33.8 (d, C-1), 31.6 (t, C-6′), 25.8 and 25.5 (2 × q, 2 × C*Me*$_3$), 24.9 (t, C-5′), 22.6 (t, C-7′), 18.2 and 17.8 (2 × s, 2 × *C*Me$_3$), 13.9 (q, C-8′), and −4.2, −4.7, −5.0, and −5.0 (4 × q, 2 × $SiMe_2$) (Found: C, 67.75; H, 11.05. $C_{27}H_{52}O_3Si_2$ requires C, 67.45; H, 10.9%).

Ring expansion of (1α,5α)-3β-(*t-Butyldimethylsilyloxy*)-2α-[(E)-(3R*)-3-(*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]*bicyclo*-[3.2.0]*heptan*-6-*one* (16) *with Diazomethane*.—A solution of

the ketone (16) (481 mg, 1 mmol) in methanol (5 ml) was treated with portions of ethereal diazomethane at hourly intervals until monitoring by g.l.c. analysis (2% OV 17; 250 °C) showed that the peak area of the major product (retention time 14.5 min) was *ca.* 50% of the total peak area [ketone (16) *ca.* 40%, retention time 10 min; minor product *ca.* 10%, retention time 20 min; trace product 1—2%, retention time 27 min]. The total amount of diazomethane added was that derived from 1.5 g of *N*-methyl-*N*-nitroso-toluene-*p*-sulphonamide (' Diazald '). T.l.c. analysis (silica gel; acetone–dichloromethane, 1 : 100) showed the ketone (16) with R_F 0.47, two major products with R_F 0.35 and 0.27, and a minor product with R_F 0.21.

Evaporation left an oil which was purified by short-column chromatography on silica gel (100 g). Elution with dichloromethane gave unchanged ketone (16) (141 mg, 29%) as an oil, identical (t.l.c., i.r.) with an authentic sample. Further elution with acetone–dichloromethane (1 : 99) gave the products with R_F 0.35, 0.27, and 0.21 as a mixture (334 mg). Purification of this mixture by preparative t.l.c. [silica gel, three elutions with acetone–dichloromethane (1 : 200)] gave the three separated components: R_F 0.35 (124 mg), R_F 0.27 (129 mg), and R_F 0.21 (61 mg). Distillation of the component R_F 0.35 gave (3aα,6aα)-5β-(*t-butyldimethylsilyloxy*)-4α-[(E)-(3S*)-3-(*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]*perhydropentalen*-1-*one* (18) (116 mg, 23%) as a colourless oil, b.p. 170 °C at 0.05 mmHg; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 1 728 (C=O) and 968 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.35—4.8 (2 H, m, CH=CH), 5.96 (1 H, m, H-5α), 6.17 (1 H, q, *J* 6 Hz, CH=CHC*H*–O), 7.3—8.9 (17 H, complex), 9—9.25 (21 H, 2 × s and br, t, 2 × CMe_3 and CH_2CH_3), and 9.98 (12 H, s, 2 × $SiMe_2$); δ_C ($CDCl_3$) 222.1 (s, C-1), 135.3 (d, C-2′), 129.9 (d, C-1′), 78.7 (d, C-5), 73.5 (d, C-3′), 56.6 (d, C-4), 48.6 (d, C-6a), 43.7 (d. C-3a), 38.3 (t, C-4′), 37.6 (t, C-6), 35.9 (t, C-2), 31.8 (t, C-6′), 25.8 and 25.7 (2 × q, 2 × C*Me*$_3$), 24.8 (t, C-5′), 24.1 (t, C-3), 22.6 (t, C-7′), 18.2 and 18.0 (2 × s, 2 × *C*Me$_3$), 14.1 (q, C-8′), and −4.1, −4.6, −4.6, and −4.8 (4 × q, 2 × $SiMe_2$) (Found: C, 68.15; H, 11.15. $C_{28}H_{54}O_3Si_2$ requires C, 67.95; H, 11.0%).

Distillation of the component R_F 0.27 gave (3aα,6aα)-5β-(t-butyldimethylsilyloxy)-4α-[(*E*)-(3*S**)-3-(t-butyldimethylsilyloxy)oct-1-enyl]perhydropentalen-2-one (17) (117 mg, 23%) as a colourless oil, b.p. 170 °C at 0.05 mmHg; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 1 730 (C=O, and 968 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.35—4.8 (2 H, m, CH=CH), 5.85—6.1 (1 H, m, H-5α), 6.09 (1 H, q, *J* 7 Hz, CH=CHC*H*–O), 7.15—8.3 (8 H, complex), 8.3—8.9 (9 H, complex), 9—9.25 (21 H, 2 × s and br, t, 2 × CMe_3 and CH_2CH_3), and 9.97 (12 H, s, 2 × $SiMe_2$); δ_C ($CDCl_3$) 219.7 (s, C-2), 135.3 (d, C-2′), 129.8 (d, C-1′), 78.9 (d, C-5), 73.4 (d, C-3′), 57.5 (d, C-4), 45.8 (t, C-3), 43.1 (t, C-1), 42.7 (d, C-3a), 42.3 (t, C-6), 38.3 (t, C-4′), 35.5 (d, C-6a), 31.8 (t, C-6′), 25.8 and 25.8 (2 × q, 2 × C*Me*$_3$), 24.8 (t, C-5′), 22.6 (t, C-7′), 18.2 and 18.0 (2 × s, 2 × *C*Me$_3$), 14.1 (q, C-8′), and −4.1, −4.1, −4.6 and −4.6 (4 × q, 2 × $SiMe_2$) (Found: C, 67.9; H, 10.9. Calc. for $C_{28}H_{54}O_3Si_2$: C, 67.95; H, 11.0%).

(±)-15-epi-9-*Deoxy*-6,9α-*methano*-Δ^5-*prostaglandin* F_1 (19).—Dry tetrahydrofuran (50 ml) was added to a stirred mixture of potassium t-butoxide (1.22 g, 10.9 mmol) and (4-carboxybutyl)triphenylphosphonium bromide (2.42 g, 5.45 mmol) under nitrogen. The resulting red suspension was stirred for 30 min. A solution of the more polar homologated ketone (17) (674 mg, 1.36 mmol) in dry tetrahydrofuran (10 ml) was then added rapidly in a single portion with vigorous stirring and the resulting dark orange suspension stirred for 1 h. Saturated aqueous ammonium chloride (40 ml) was added, followed by 2N-hydrochloric acid (5 ml), with stirring, and the mixture was extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give a viscous oil. Short-column chromatography on silica gel (100 g), eluting with ethyl acetate–light petroleum (1 : 4), gave the Wittig product (670 mg) as a gum; $\nu_{max.}$ (film) 1 708 cm^{-1} (C=O); homogeneous by t.l.c. (R_F 0.12 with silica gel; ethyl acetate–light petroleum, 1 : 9). A solution of this gum and tetra-n-butylammonium fluoride (2.6 g, 10 mmol) in dry tetrahydrofuran (15 ml) was left at 40—45 °C for 24 h, poured into water (300 ml), and extracted with ethyl acetate (4 × 50 ml). The combined extracts were washed with saturated aqueous sodium chloride (1 × 20 ml), dried (Na_2SO_4), and evaporated to give an oil. Short-column chromatography on silica gel (50 g), eluting with acetic acid–ethyl acetate–light petroleum (1 : 100 : 100) followed by acetic acid–ethyl acetate (1 : 200), gave the acid (19) (352 mg, 74%) as a colourless gum; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 590 (OH), 3 490 (OH, acid, monomer), 1 735 (C=O, acid, monomer), 1 705 (C=O, acid, dimer), and 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.2—5.1 (5 H, m, 3 × OH, H-13 and H-14), 4.80 (1 H, br, t, *J* 7 Hz, H-5) 5.94 (1 H, m, H-11), 6.30 (1 H, m, H-15), 7.3—8.9 (23 H, complex), and 9.10 (3 H, br, t, H-20) (Found: C, 71.55; H, 10.05. Calc. for $C_{21}H_{34}O_4$: C, 71.95; H, 9.8%). H.p.l.c. analysis (20 cm × 4.6 mm Partisil 10, 24 : 1 ethyl acetate–acetic acid) showed the isomer ratio at the newly formed olefinic bond to be 71 : 29, with the more polar isomer predominating.

(±)-15-epi-9-*Deoxy*-1a-*homo*-Δ^4-5,9α-*cycloprostaglandin* F_1 (20).—The less polar homologated ketone (18) (674 mg, 1.36 mmol) and (4-carboxybutyl)triphenylphosphonium bromide (2.42 g, 5.45 mmol) were used in a Wittig reaction in the manner already described for the isomer (17). Short-column chromatography on silica gel (100 g), eluting with ethyl acetate–light petroleum (1 : 9) followed by ethyl acetate–light petroleum (1 : 4), gave the Wittig product (530 mg) as a gum; $\nu_{max.}$ (film) 1 708 cm^{-1} (C=O); homogeneous by t.l.c. (R_F 0.07, silica gel; ethyl acetate–light petroleum, 1 : 9). This gum was desilylated with tetra-n-butylammonium fluoride (2.50 g, 9.6 mmol) in the manner already described. The resulting viscous oil was purified by short-column chromatography on silica gel (50 g). Elution with acetic acid–ethyl acetate–light petroleum (1 : 100 : 100) followed by acetic acid–ethyl acetate (1 : 200), gave the *acid* (20) (274 mg, 58%) as a colourless gum which slowly crystallised; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 585 (OH), 3 485 (OH, acid, monomer), 1 735sh (C=O, acid, monomer), 1 705 (C=O, acid, dimer), and 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.3—4.5 (2 H, m, H-13 and H-14), 4.5—5.1 (3 H, m, 3 × OH), 4.88 (1 H, br, t, *J* 7 Hz, H-4), 5.92 (1 H, m, H-11), 6.22 (1 H, m, H-15), 7.24 (1 H, m, H-9), 7.4—8.9 (22 H, complex), and 9.10 (3 H, br, t, H-20); [Found: (c.i. mass spec., NH_3): $(M + NH_4)^+$, 368.2798. $C_{21}H_{34}O_4$ requires $(M + NH_4)$, 368.2801]. H.p.l.c. analysis (20 cm × 4.6 mm Partisil 10; 24 : 1 ethyl acetate–acetic acid) showed the isomer ratio at the newly formed olefinic bond to be 86 : 14, with the less polar isomer predominating.

(±)-9-*Deoxy*-Δ^5-6,9α-*cycloprostaglandin* F_1 (21).—(4-Carboxybutyl)triphenylphosphonium bromide (1.77 g, 4 mmol) was added to a stirred solution of potassium t-butoxide (900 mg, 8 mmol) in dry tetrahydrofuran (40 ml) under nitrogen. After 10 min, a solution of the more polar di-

hydroxy-ketone (3) (252 mg, 1 mmol) in dry tetrahydrofuran (5 ml) was added rapidly in a single portion to the orange-red suspension. The resulting orange suspension was stirred for 1.5 h, poured into aqueous 2N-sodium hydrogensulphate (5 ml) and saturated aqueous sodium chloride (50 ml), and extracted with ethyl acetate (4 × 50 ml). The combined extracts were washed with saturated aqueous sodium chloride (1 × 30 ml), dried ($MgSO_4$), and evaporated to give a gum. The experiment was then repeated on three times the scale.

The two crude products were combined, dissolved in chloroform (250 ml), and extracted with aqueous 8% sodium hydrogencarbonate (1 × 100 ml, 2 × 50 ml). The combined aqueous extracts were washed with chloroform (2 × 20 ml), acidified with aqueous 2N-sodium hydrogensulphate, and extracted with ethyl acetate (4 × 50 ml). The combined organic extracts were washed with saturated aqueous sodium chloride (1 × 30 ml), dried (Na_2SO_4), and evaporated to give a gum. Short-column chromatography on silica gel (220 g) with acetic acid–ethyl acetate (1 : 50) as eluant gave the *acid* (21) (988 mg, 73%) as a gum; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 585 (OH), 3 490 (OH, acid, monomer), 1 735 (C=O, acid, monomer), 1 705 (C=O, acid, dimer), and 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.16 (3 H, br, s, 3 × OH), 4.4—4.7 (2 H, m, H-13 and H-14), 4.7—5.1 (1 H, m, H-5), 5.8—6.3 (2 H, m, H-11 and H-15), 6.80 (1 H, m, H-9), 7—8.9 (20 H, complex), and 9.10 (3 H, br, t, H-20) [Found (c.i. mass spec., NH_3): $(M + NH_4)^+$, 354.2658. $C_{20}H_{32}O_4$ requires $(M + NH_4)$, 354.2644]. H.p.l.c. analysis (20 cm × 4.6 mm Partisil 10; 24 : 1 ethyl acetate–acetic acid) showed the isomer ratio at the newly formed olefinic bond to be 62 : 38, with the less polar isomer predominating.

(±)-15-epi-9-*Deoxy*-Δ⁵-6,9α-*cycloprostaglandin* F_1 (22). —The less polar dihydroxy-ketone (4) (1.008 g, 4 mmol), (4-carboxybutyl)triphenylphosphonium bromide (7.08 g, 16 mmol), and potassium t-butoxide (3.60 g, 32 mmol) were used in a Wittig reaction in the manner described for its isomer (3) (single reaction only). Short-column chromatography on silica gel (220 g), eluting with acetic acid–ethyl acetate (1 : 100), gave the *acid* (22) (640 mg, 48%) as a gum; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 590 (OH), 3 490 (OH, acid, monomer), 1 740 (C=O, acid, monomer), 1 705 (C=O, acid, dimer), and 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.25—4.75 (2 H, m, H-13 and H-14), 4.68 (3 H, br, s, 3 × OH), 4.65—5.1 (1 H, m, H-5), 5.8–6.2 (2 H, m, H-11 and H-15), 6.75 (1 H, m, H-9), 6.9—8.9 (20 H, complex), and 9.10 (3 H, br, t, H-20), with a $Eu(fod)_3$ experiment indicating a *ca.* 3 : 2 isomer ratio at the newly formed olefinic bond [Found (c.i. mass spec., NH_3): $(M + NH_4)^+$, 354.2661. $C_{20}H_{32}O_4$ requires $(M + NH_4)$, 354.2644].

(±)-9-*Deoxy*-1a-*homo*-Δ⁵-6,9α-*cycloprostaglandin* F_1 (23). —(5-Carboxypentyl)triphenylphosphonium bromide (3.0 g, 7.1 mmol) was added to a stirred solution of potassium t-butoxide (1.56 g, 14 mmol) in dry tetrahydrofuran (40 ml) under nitrogen. After 30 min, a solution of the more polar dihydroxy-ketone (3) (300 mg, 1.19 mmol) in dry tetrahydrofuran (15 ml) was added dropwise to the orange-red suspension. The resulting mixture was stirred for 45 min, poured into water (30 ml), and washed with ether (1 × 30 ml) and ethyl acetate (2 × 30 ml). The aqueous layer was separated, acidified with 2N-hydrochloric acid (10 ml), and extracted with ethyl acetate (4 × 40 ml). The combined extracts were washed with saturated aqueous sodium chloride (50 ml), dried ($MgSO_4$), and evaporated to give an orange oil (2.1 g). Short-column chromatography on silica gel (150 g), eluting with acetic acid–light petroleum–ethyl acetate (1 : 20 : 180), gave the *acid* (23) (175 mg, 42%) as a pale straw coloured gum; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 590 (OH), 3 500 (OH, acid, monomer), 1 745 (C=O, acid, monomer), 1 705 (C=O, acid, dimer), and 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.15 (3 H, br, s, 3 × OH), 4.3—4.75 (2 H, m, H-13 and H-14), 4.65—5.1 (1 H, m, H-5), 5.85—6.25 (2 H, m, H-11 and H-15), 6.76 (1 H, m, H-9), 7—8.9 (22 H, complex), and 9.10 (3 H, br, t, H-20) (Found: C, 72.0; H, 10.15. $C_{21}H_{34}O_4$ requires C, 71.95; H, 9.8%).

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