Total Synthesis of Prostaglandin-$F_{2\alpha}$ involving Stereocontrolled and Photo-induced Reactions of Bicyclo[3.2.0]heptanones

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A short total synthesis of prostaglandin-$F_{2\alpha}$ from cyclopentadiene is described. Acetalisation of bicyclo[3.2.0]-hept-2-en-6-one (1) followed by formation of a single bromohydrin gave on treatment with base the epoxyacetal (4). Reaction of (4) with the appropriate organocuprate reagent introduced both the 12β side-chain and 11α-hydroxy-group of the embryonic prostaglandin. The fused cyclobutane ring is important as it controls both the stereoselectivity of epoxide formation and the regioselectivity of the subsequent ring-opening reaction. Furthermore, the unusual photochemical behaviour of cyclobutanones was exploited in this synthesis. Irradiation of the bicyclo[3.2.0]heptan-6-one (9) in aqueous solution and subsequent Wittig olefination afforded prostaglandin-$F_{2\alpha}$. Baeyer–Villiger oxidation of the same ketone (9) furnished the lactone (16), a known precursor of prostaglandin-E.

BICYCLO[3.2.0]HEPT-2-EN-6-ONE (1) is prepared from cyclopentadiene in two steps.[1] It is readily converted into the crystalline bromohydrin (2) [2] and we have shown that derivatives of this bromohydrin can be used to prepare prostaglandin-$F_{2\alpha}$,[3] -C_2,[4] and -E_2,[5] through initial formation of the corresponding tricyclo[3.2.0.$0^{2,7}$]-heptan-6-one. In this paper we describe an alternative strategy for the conversion of the bicycloheptenone (1) into prostaglandins (Scheme).[6]

RESULTS AND DISCUSSION

The bromohydrin (2) was converted into the acetal (3); base-induced dehydrobromination gave the epoxy-acetal (4) [82% from (2)]. Alternatively formation of the acetal (5) from the ketone (1) followed by treatment of (5) with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in aqueous acetone gave (3), which was dehydrobrominated *in situ* using potassium carbonate to give the acetal (4) [72% from (1)].

The cuprate reagent (6) reacted with the epoxide (4) at −78 to −30 °C to give, after chromatography, the required hydroxyacetal (7) (66%) and the isomer (8) (14%). The pronounced regioselectivity of this epoxy-ring-opening reaction is due to the presence of the adjacent cyclobutane ring.[2,7]

Hydrolysis of the acetal (7) using mineral acid gave a mixture of the diastereoisomers (9) and (10) (97%) from which the required isomer (9) could be separated only by repeated chromatography over silica. On the other hand the hydroxyacetals (11) and (12), obtained by desilylation of (7) using fluoride ion, were readily separated by chromatography and treatment of the more polar acetal (11) with acid gave the required ketone (9).

In addition we found a viable alternative to the organocuprate process: the epoxyacetal (4) reacted with the alane (13) in toluene at 80 °C to give the alkynol (14) (63%) and the isomer (15) (34%) after desilylation and chromatography. Reduction of (14) with lithium aluminium hydride gave the required acetal (11) (43%) and the epimer (12) (49%). In this manner the dihydroxyketone (9) was obtained from (4) in 26% yield.

Peracetic acid oxidation of the ketone (9), during 4 d at −78°C gave an almost quantitative yield of the lactone (16), contaminated with a trace amount of the isomeric species (17). Higher reaction temperatures led to the formation of unacceptable amounts of the unwanted isomer (17) (Table). Likewise, ketone (10) gave the

Baeyer–Villiger oxidation of ketones (9) and (10)

Starting material	Temp. (°C)	Time (h)	Ratio of products [a]
(9)	20	0.25 [b]	87 : 13 (16) : (17)
(10)	20	0.25 [b]	87 : 13 (18) : (19)
(10)	−20	4 [b]	91 : 9 (18) : (19)
(9)	−78	96 [b]	97 : 3 (16) : (17)
(10)	−78	24 [c]	96 : 4 (18) : (19)

[a] By g.l.c. [b] Conversion complete: quantitative yield of lactones. [c] Conversion incomplete: isolated yield of lactones was 91% after chromatography, based on ketone consumed.

lactones (18) and (19) on Baeyer–Villiger oxidation. Using peracetic acid, no evidence for concurrent epoxidation of the olefinic linkage was obtained even when the reaction was conducted at ambient temperature: more reactive peracids were less satisfactory in this respect.

The dihydroxylactone (16) was identical with material prepared by an independent route [5] and it has been converted into prostaglandin-E_2 in five steps.[8]

In an alternative pathway for the conversion of the ketone (9) into prostaglandins, advantage was taken of the peculiar behaviour of cyclobutanones on photo-excitation.[9] It is well documented that cyclobutanones rearrange to oxacarbenes on photolysis and that these carbenes can be trapped by alcohols to form cyclic acetals: [10] in one experiment an oxacarbene was treated with water to give a γ-lactol.[11]

Photolysis of the ketone (9) in aqueous acetonitrile over 4.5 h employing quartz-filtered light gave a mixture containing mainly the lactol (20) and the alkene (21). The latter product is formed by cyclo-elimination of keten. The crude product was not purified but was treated directly with the ylide (22) in tetrahydrofuran After chromatography were obtained (±)-prostaglandin-$F_{2\alpha}$ (23) (48%) and the alkene (21) (15%).

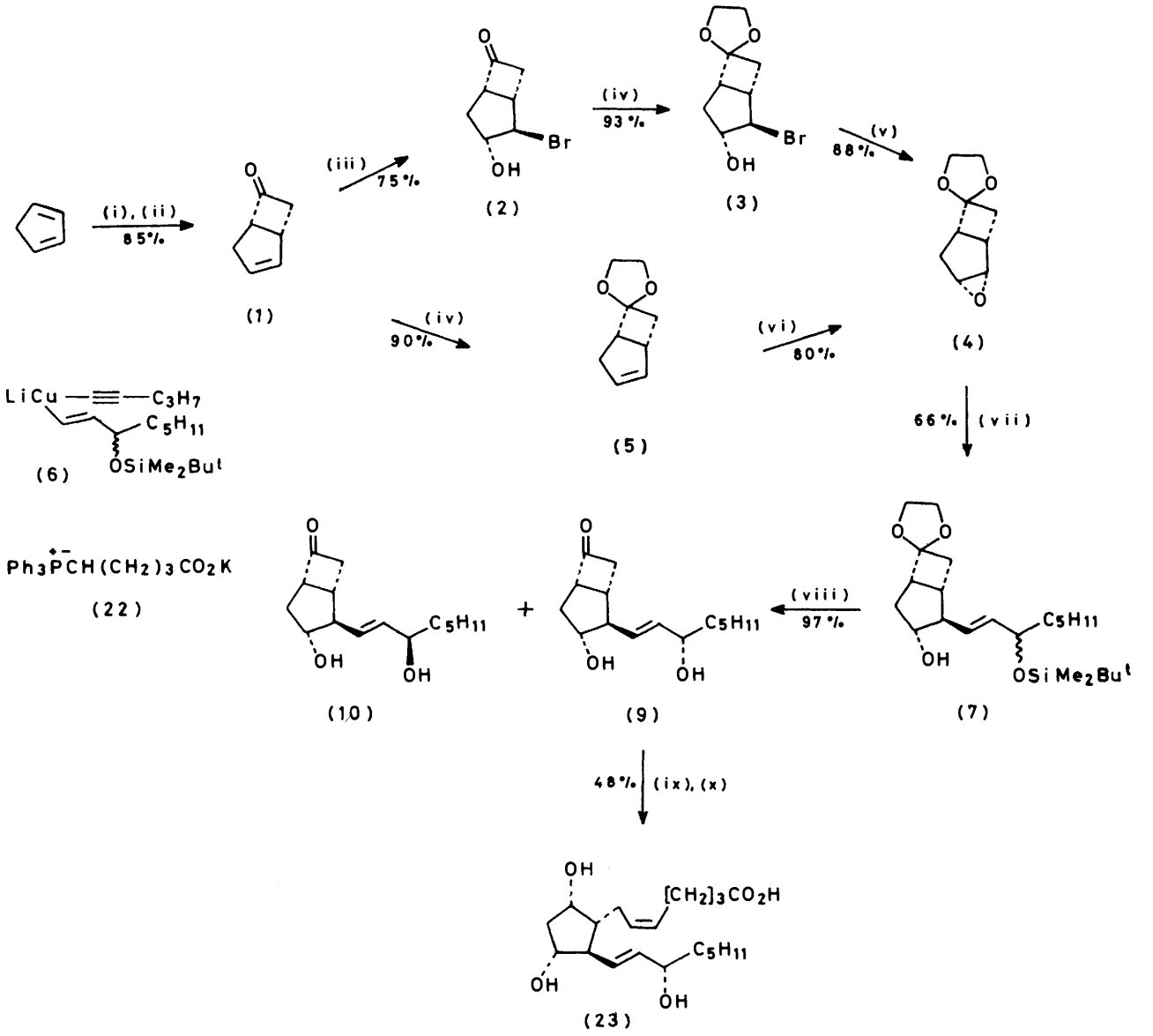
Thus in the Scheme we describe a highly attractive

synthesis of prostaglandin-$F_{2\alpha}$ which owes its brevity and efficiency to the high degree of stereocontrol available in reactions involving the bicyclo[3.2.0] system.

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.

Conversion of Bicyclo[3.2.0]*hept-2-en-6-one* (1) *into the Epoxyacetal* (4).—(i) *Three-step procedure.* 1,3-Dibromo-5,5-dimethylhydantoin (1.5 g) was added in portions to a stirred solution of the bicycloheptenone (1) (1.0 g) in acetone (20 ml) and water (5 ml). After 16 h at ambient temperature the solvent was evaporated under reduced pressure. The residue was treated with water (10 ml) and extracted with dichloromethane. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to leave a yellow oil. Short-column chromatography on silica gel, eluting with 20% ethyl acetate–light petroleum, gave (2-*exo*,3-*endo*)-2-bromo-3-hydroxybicyclo-[3.2.0]heptan-6-one (2) (1.41 g, 75%), m.p. 87—89 °C (identical with an authentic specimen [2]).



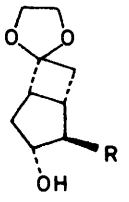
SCHEME (*i*) $Cl_2C{=}C{=}O$; (*ii*) Zn,AcOH; (*iii*) DBDMH,H_2O, Me_2CO; (*iv*) $HOCH_2CH_2OH,H^+$; (*v*) NaOMe,MeOH; (*vi*) DBDMH,H_2O,-Me_2CO (18 h) then add K_2CO_3; (*vii*) compound (6); (*viii*) 0.2N H_2SO_4; (*ix*) *hν*,H_2O,MeCN; (*x*) compound (22)

The bromohydrin (2) was converted into the acetal (3) (93% yield) and then dehydrobrominated using sodium hydroxide in methanol (88% yield) to give the epoxyacetal (4). The details have been described previously.[12]

(ii) *Two-step procedure.* Ethane-1,2-diol (100 g) and toluene-*p*-sulphonic acid (50 mg) were added to the bicycloheptanone (1) (32.4 g) in benzene (250 ml). The solution was heated under reflux and water removed using a Dean–Stark trap. After cooling, the reaction mixture was shaken

with saturated aqueous potassium carbonate (10 ml). The aqueous layer was separated and extracted with light petroleum. The organic fractions were combined, washed with water, and dried (Na_2SO_4). Evaporation of the solvent followed by bulb-to-bulb distillation (Buchi Kugelrohr) at 85 °C and 10 mmHg gave the acetal (5) (41.1 g, 90%).

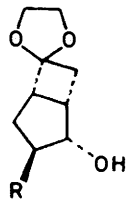
A solution of the acetal (5) (15.2 g) in acetone (100 ml) and water (100 ml) was cooled in ice and 1,3-dibromo-5,5-dimethylhydantoin (16.0 g) added in portions during 1 h.



(11) R = CH=CHCHC$_5$H$_{11}$ (OH, E)

(12) R = CH=CHCHC$_5$H$_{11}$ (OH, E)

(14) R = C≡CCH(OH)C$_5$H$_{11}$

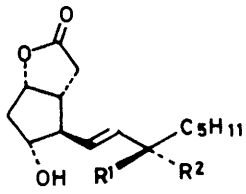


(8) R = CH=CHCH(OSiMe$_2$Bu^t)C$_5$H$_{11}$ (E)

(15) R = C≡CCH(OH)C$_5$H$_{11}$

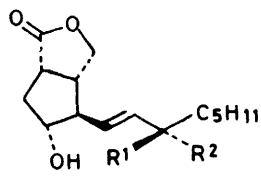
Me$_2$Al—C≡C—CH(OSiMe$_3$)C$_5$H$_{11}$

(13)



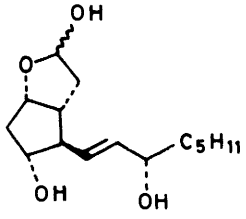
(16) R^1 = H, R^2 = OH

(18) R^1 = OH, R^2 = H

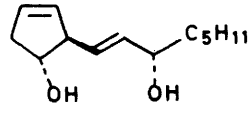


(17) R^1 = H, R^2 = OH

(19) R^1 = OH, R^2 = H



(20)



(21)

After 72 h potassium carbonate (40 g) was added and the mixture stirred for a further 24 h. The acetone was evaporated off and the aqueous suspension extracted with ether. The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was distilled (Kugelrohr) at 90 °C and 0.005 mmHg to furnish the epoxide (4) [13.5 g, 80% from (5)] as a clear oil. This was >99% pure by g.l.c. (3% OV 275, 140 °C) and was identical (t.l.c., g.l.c., n.m.r.) with authentic material [12] (Found: C, 64.1; H. 7.55. Calc. for $C_9H_{12}O_3$: C, 64.3; H, 7.2%).

Reaction of the Epoxyacetal (4) *with the Lithium Organocuprate* (6).—1.35M n-Butyl-lithium in hexane (96.5 ml, 0.13 mol) was added to a stirred solution of 3-(t-butyldimethylsilyloxy)-1-iodo-oct-1-ene [13] (48.2 g, 0.13 mol) in anhydrous diethyl ether at −78 °C under nitrogen. After 1 h a solution of pent-1-ynylcopper(I) (17.2 g, 0.13 mol) and hexamethylphosphorotriamide (45 ml, 0.26 mol) in ether was added. After stirring for a further 2 h at −78 °C, a solution of the epoxyacetal (4) (20.0 g, 0.12 mol) in ether (100 ml) was added dropwise over 1 h. The reaction was stirred for a further 3 h at −78 °C then stood in a freezer at −20 °C for 16 h. Saturated aqueous ammonium chloride was added and the mixture stirred at ambient temperature for 1 h. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with cold 2N hydrochloric acid (200 ml) and water (200 ml), dried ($MgSO_4$), and evaporated. The residue was purified by short-column chromatography on silica gel (1 700 g) with elution by dichloromethane, and two adducts were isolated. The major isomer (higher R_F) was (1α,5α)-2α-[(E)-3-(*t-butyldimethylsilyloxy*)*oct-1-enyl*]{*spirobicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-3β-*ol* (7), isolated as a colourless oil (32.2 g, 66%); τ ($CDCl_3$) 4.5—4.9 (2 H, m, CH=CH), 5.9—6.3 (6 H, complex, OCH_2CH_2O and 2 × CHO–), 6.9—7.9 (6 H, complex, H-1, H-2, H-5, H-7α, H-7β, and OH), 8.06 (2 H, m, H-4α and H-4β), 8.4—9.0 (8 H, complex, 2 × CH_2CH_2), 9.06 (12 H, singlet overlapped by multiplet, CMe_3 and CH_2CH_3), 10.03 and 10.05 (6 H, 2 × s,

$SiMe_2$) (Found: C, 66.9; H, 10.4 $C_{23}H_{42}SiO_4$ requires C, 67.2; H, 10.1%).

The minor isomer (lower R_F) was (1α,5α)-3α-[(E)-3-(*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]*spiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-2β-*ol* (8), isolated as a colourless oil (7.0 g, 14%); τ ($CDCl_3$) 4.2—4.7 (2 H, m, CH=CH), 5.90 [1 H, m, *CH*($OSiMe_2Bu^+$)CH=CH], 6.0—6.3 (5 H, complex, H-2α and OCH_2CH_2O), 7.1—7.8 (5 H, complex, H-1, H-3, H-5, H-7α, and H-7β), 8.07 (1 H, dd, *J* 13 and 6 Hz, H-4β), 8.22 (1 H, br s, OH), 8.3—8.9 (9 H, complex, H-4α and $CH_2CH_2CH_2$-CH_2), 9.09 (12 H, singlet overlapped by a multiplet, CMe_3 and CH_2CH_3), 9.98 (6 H, s, $SiMe_2$) [c.i.m.s. (NH_3 ionisation); Found: $(M + NH_4)^+$ 428.316 6. $C_{23}H_{42}SiO_4$ requires $(M + NH_4)$ 428.319 6].

Reaction of the Epoxyacetal (4) *with the Alane* (13).—1.6M n-Butyl-lithium in hexane (31.25 ml, 50 mmol) was added over 10 min to a stirred solution of 3-(trimethylsilyloxy)oct-1-yne [14] (9.9 g, 50 mmol) in toluene (30 ml) at 0 °C under nitrogen. After 15 min a 25% solution of dimethylchloroalane in hexane (14.8 ml, 40 mmol) was added (over 10 min) followed, after stirring for a further 1 h, by (1α,5α)-2α,3α-epoxyspiro{bicyclo[3.2.0]heptane-6,2′-[1,3]dioxolan} (4) (3.36 g, 20 mmol) in toluene (10 ml). The mixture was heated to 80 °C with stirring for 8 h, then cooled to 0 °C and the reaction was quenched by addition of saturated aqueous sodium sulphate (100 ml). The mixture was clarified by filtration and the layers separated. The aqueous layer was extracted with ether and the combined organic layers washed with water, dried ($MgSO_4$), and evaporated to give an oil (15.15 g). This was dissolved in methanol (135 ml) and a solution of potassium carbonate (7.5 g) in water (30 ml) added. After 3 h at 20 °C the methanol was removed by evaporation and the residue extracted with ether. The dried ($MgSO_4$) extracts were evaporated to give an oil (9.5 g). Short-column chromatography on silica gel, eluting with 3% ethanol–chloroform, gave (in order of elution): (*a*) oct-1-yn-3-ol (2.8 g, 22 mmol), identical (i.r. and t.l.c.) with authentic material; (*b*) (1α,5α)-2α-(3-*hydroxyoct*-1-*ynyl*)*spiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1.3]*dioxolan*}-3β-*ol* (14) (3.7 g, 63%) as a colourless oil; τ ($CDCl_3$) 5.5—5.85 (2 H, complex, 2 × CHO–), 6.1 (4 H, s, OCH_2-CH_2O), 6.25 (1 H, d, ring OH), 6.90 (1 H, m, H-5α), 7.18 (1 H, br s, H-2β), 7.3—8.2 (5 H, complex, H-1, H-4α, H-4β, H-7α, H-7β), 7.8 (1 H, br s, side-chain OH), 8.3—8.9 (8 H, complex, $CH_2CH_2CH_2CH_2$), 9.10 (3 H, m, CH_2CH_3) (Found: C, 69.2; H, 8.85. $C_{17}H_{26}O_4$ requires C, 69.4; H, 8.85%).

(1α,5α)-3α-(3-*Hydroxyoct*-1-*ynyl*)*spiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-2β-ol (15) (1.85 g, 34%) as a colourless oil τ ($CDCl_3$) 5.70 (1 H, m, CHO– in side-chain), 5.97 (1 H, dd, *J* 6 and 9 Hz, H-2α), 6.1—6.3 (4 H, m, OCH_2CH_2O), 9.10 (3 H, m, CH_2CH_3), and 6.8—9.0 (16 H, complex) (Found: C, 69.3; H, 8.85. $C_{17}H_{26}O_4$ requires C, 69.4; H, 8.95%).

(1α,5α)-2α-[(E)-3-*Hydroxyoct*-1-*enyl*]*spiro*{*bicyclo*[3.2.0]-*heptane*-6,2′-[1,3]*dioxolan*}-3β-*ols* (11) *and* (12).—(a) *Reduction of the alkynol* (14) *with lithium aluminium hydride.* 2-(3-Hydroxyoct-1-ynyl)spiro{bicyclo[3.2.0]heptane-6,2′-[1,3]dioxolan}-3-ol (14) (1.76 g, 6 mmol) in anhydrous tetrahydrofuran (20 ml) was added dropwise to a stirred solution of lithium aluminium hydride (1.14 g, 30 mmol) in tetrahydrofuran (40 ml) under nitrogen. After heating under reflux the mixture was cooled to 0 °C and quenched by addition of 2N sodium hydroxide. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated to give an oil (1.87 g). T.l.c. (ethyl acetate) showed this to be a pure mixture of the epimeric alcohols (16) (R_F 0.47) and (17) (R_F 0.57), which were separated by short-column chromatography on silica gel (100 g). Elution with ethyl acetate–light petroleum (2 : 1) gave (1α,5α)-2α-[(E)-(3R*)-3-*hydroxyoct*-1-*enyl*]*spiro*-{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-3β-*ol* (12) (768 mg, 43%), m.p. 49—50 °C; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 590 (free OH) and 3 470 cm^{-1} (intramolecularly hydrogen-bonded OH); τ ($CDCl_3$) 4.2—4.8 (2 H, m, CH=CH), 5.6—6.4 (6 H, complex, OCH_2CH_2O and 2 × CHO–), 6.7—7.8 (7 H, complex), 8.0 (2 H, m, H-4α, H-4β), 8.2—8.9 (8 H, complex, $CH_2CH_2CH_2CH_2$), and 9.1 (3 H, br t, CH_2CH_3) (Found: C, 68.8; H, 9.8. $C_{17}H_{28}O_4$ requires C, 68.9; H, 9.5%).

Later fractions off the column afforded (1α,5α)-2α-[(E)-(3S*)-(3-*hydroxyoct*-1-*enyl*]*spiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-3β-*ol* (11) (874 mg, 49%) as a viscous oil; $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 590 (free OH) and 3 470 br (intramolecularly hydrogen-bonded OH) cm^{-1}; τ ($CDCl_3$) 4.2—4.8 (2 H, m, CH=CH), 5.6—6.4 (6 H, complex, OCH_2-CH_2O and 2 × CHO–), 6.7—7.8 (7 H, complex), 8.0 (2 H, m, H-4α and H-4β), 8.2—8.9 (8 H, complex, $CH_2CH_2CH_2$-CH_2), and 9.1 (3 H, br t, CH_2CH_3) (Found: C, 68.9; H, 9.8. $C_{17}H_{28}O_4$ requires C, 68.9; H, 9.5%).

(b) *By desilylation of the acetal* (7) *using fluoride ion.* A solution of (7) (27.0 g, 65 mmol) and tetra-n-butylammonium fluoride (70.0 g, 270 mmol) in anhydrous tetrahydrofuran was set aside at ambient temperature for 3 d. The solvent was evaporated under reduced pressure, water added, and the mixture extracted with ethyl acetate. The dried ($MgSO_4$) extracts were evaporated and the residue purified by short column chromatography on silica gel (1 500 g) eluting with ethyl acetate–light petroleum (2 : 1). (1α, 5α)-2α-[(E)-(3R*)-3-*Hydroxyoct*-1-*enyl*]*spiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-3β-*ol* (12) was obtained as an oil (8.45 g, 44%) which solidified on standing, m.p. 49—50 °C, and was identical (i.r., n.m.r., t.l.c.) with the material described above.

(1α,5α)-2α-[(E)-(3S*)-3-*Hydroxyoct*-1-*enyl*]*spiro*{*bicyclo*-[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-3β-*ol* (11) was also isolated as a viscous oil (6.7 g, 35%), identical with material obtained by the previous method.

(1α,5α)-3β-*Hydroxy*-2α-[(E)-3-*hydroxyoct*-1-*enyl*]*bicyclo*-[3.2.0]*heptan*-6-*ones* (9) *and* (10).—(i) *Acid hydrolysis of the acetal* (7). A solution of the acetal (7) (1.02 g) 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 residue was purified by short-column chromatography on silica gel (20 g), eluting with ethyl acetate, to give a colourless oil (609 mg, 97%). T.l.c. showed this to be a pure mixture of the bicycloheptanone (9) (R_F 0.62) and its isomer (10) (R_F 0.65); $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 600 (free OH), 1 770 (C=O), and 975 cm^{-1} (*trans*-CH=CH) (Found: C, 71.0; H, 9.5. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.5%).

(ii) *Acid hydrolysis of the acetal* (11). A solution of the acetal (11) (5.5 g) in acetonitrile (65 ml), water (25 ml), and 2N sulphuric acid (10 ml) was allowed to stand at ambient temperature for 7 h. The reaction was worked up in the manner described above, and the product purified by column chromatography to give (1α,5α)-3β-*hydroxy*-2α-

[(E)-(3*S**)-3-*hydroxyoct*-1-*enyl*]*bicyclo*[3.2.0]*heptan*-6-*one* (9) as a colourless oil (4.3 g, 92%); $\nu_{max.}$ (0.5% solution in $CHBr_3$), 3 600 (free OH), 1 770 (C=O), and 975 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.3—4.7 (2 H, m, CH=CH), 5.8—6.1 (2 H, m, 2 × *CH*OH), 6.40 (1 H, m, H-5), 6.7—7.0 (2 H, m, H-7α, H-7β), 7.1—7.5 (2 H, m, H-1, H-2), 7.57 (2 H, br, 2 × OH), 7.8—8.1 (2 H, m, H-4α, H-4β), 8.3—8.9 (8 H, complex, $[CH_2]_4$), and 9.12 (3 H, br t, CH_2CH_3) (Found: C, 71.3; H, 9.7. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%).

(iii) *Acid hydrolysis of the acetal* (12). A solution of the acetal (12) (11.8 g) in acetonitrile (135 ml), water (47 ml) and 2N sulphuric acid (20 ml) was allowed to stand at ambient temperature for 5 h. Isolation and purification as described above afforded (1α,5α)-3β-*hydroxy*-2α-[(E)-(3R*)-3-*hydroxyoct*-1-*enyl*]*bicyclo*[3.2.0]*heptan*-6-*one* (10) as a colourless oil (10.0 g, 99%); $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 585 (free OH), 1 770 (C=O), and 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.3—4.7 (2 H, m, olefinic), 5.8—6.1 (2 H, m, 2 × CH–O), 6.40 (1 H, m, H-5), 6.7—7.0 (2 H, m, H-7α, H-7β), 7.1—7.6 (4 H, complex, H-1, H-2, 2 × OH), 7.8—8.0 (2 H, m, H-4α, H-4β), 8.3—8.9 (8 H, complex, CH_2CH_2-CH_2CH_2), and 9.12 (3 H, br t, CH_2CH_3) (Found: C, 71.3; H, 9.8. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%).

Baeyer–Villiger Oxidation of the Ketones (9) *and* (10).—Baeyer–Villiger oxidations of the ketones (9) and (10) were performed in dichloromethane using an excess of commercial 40% peracetic acid buffered with anhydrous sodium acetate. Isomer ratios were determined by g.l.c. of the bis-trimethylsilyl ether derivatives (3% OV 275, 220 °C). The results at various temperatures are summarised in the Table and the best conditions for synthesis of lactones (16) and (18) are outlined below.

(i) (3aα,6aα)-5β-*Hydroxy*-4α-[(E)-(3S*)-3-*hydroxyoct*-1-*enyl*]*perhydrocyclopenta*[b]*furan*-2-*one* (16). A mixture of the ketone (9) (540 mg) and anhydrous sodium acetate (1.5 g) in dichloromethane (20 ml) was cooled to −78 °C. 40% Peracetic acid in acetic acid (4.8 ml) was added dropwise. The reaction vessel was then sealed and immersed in a Dewar flask packed with solid carbon dioxide. By topping up as necessary with solid CO_2, the reaction was maintained at −78 °C for 4 d. The cold mixture was poured into a solution of sodium hydrogencarbonate and sodium sulphate in water, and the layers separated. Extraction with dichloromethane and evaporation of the dried ($MgSO_4$) solution afforded the *lactone* (16) as a viscous oil (578 mg, 100%), homogeneous by t.l.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%). This material was identical (i.r., n.m.r., t.l.c., g.l.c.) with an authentic sample of lactone (16),[5] but contained a trace (3% by g.l.c.) of the isomer (17). Signals due to (3aα,6aα)-5β-hydroxy-4α-[(*E*)-(3S*)-3-hydroxyoct-1-enyl]-perhydrocyclopenta[*c*]furan-1-one (17) were just discernable in the n.m.r. spectrum ($CDCl_3$) at τ 5.57 (dd, *J* 9 and 7.5 Hz, H-3α), 5.78 (dd, *J* 9 and 2 Hz, H-3β), 7.00 (td, *J* 10, 10 and 4.5 Hz, H-6aα).

(ii) (3aα,6aα)-5β-*Hydroxy*-4α-[(E)-(3R*)-3-*hydroxyoct*-1-*enyl*]*perhydrocyclopenta*[b]*furan*-2-*one* (18). The ketone (9) (504 mg) and anhydrous sodium acetate (1.5 g) in dichloromethane (20 ml) at −78 °C were treated with 40% peracetic acid in acetic acid (4.8 ml). The mixture was kept at this temperature for 24 h then the reaction was quenched by addition of an aqueous mixture of sodium carbonate and sodium sulphite. This was extracted with dichloromethane, and the combined extracts dried ($MgSO_4$) and evaporated. Short-column chromatography on silica gel (50 g) (eluting with 30% light petroleum–ethyl acetate) afforded the starting ketone (9) (135 mg, 27%) together with the lactone (18) (357 mg, 67%). This was a colourless oil, identical (t.l.c., g.l.c., i.r., n.m.r.) with an authentic sample [5] (Found: C, 66.9; H, 9.1. Calc. for $C_{15}H_{24}O_4$: C, 67.1; H, 9.0%). G.l.c. showed the presence of a trace (4%) of the isomer (19).

Preparation of Prostaglandin-F$_{2\alpha}$.—A degassed solution of the ketone (9) (378 mg, 1.5 mmol) in acetonitrile (17 ml) and water (68 ml) was irradiated (Hanovia medium-pressure mercury arc) through quartz for 4.5 h under nitrogen, and the solution was extracted with ethyl acetate (5 × 100 ml). Evaporation of the dried ($MgSO_4$) extracts gave an oil containing the lactol (20) [5] and the cyclopentene (21) (by t.l.c. comparison with authentic samples).

The oil was dissolved in anhydrous tetrahydrofuran (10 ml) and added to a stirred mixture of carboxybutylphosphonium bromide (2.65 g, 6 mmol) and potassium t-butoxide (1.35 g, 12 mmol) in dry tetrahydrofuran (50 ml). After 1 h the reaction was quenched by addition of saturated ammonium chloride and 2N hydrochloric acid (6 ml). The layers were separated and the aqueous layer further extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), evaporated, and the residue purified by short-column chromatography on silica gel (150 g), eluting with acetic acid–ethyl acetate–light petroleum (5 : 60 : 35). The later fractions off the column contained prostaglandin-$F_{2\alpha}$ which was dissolved in aqueous sodium carbonate, washed with ether, re-acidified with aqueous sodium hydrogensulphate, and extracted into chloroform. Evaporation of the dried ($MgSO_4$) extracts gave (±)-*prostaglandin* $F_{2\alpha}$ (23) (255 mg, 48%). This was spectroscopically (i.r., n.m.r., c.i.m.s.) and chromatographically (t.l.c.) identical with authentic material. G.l.c. analysis, after methylation and conversion into the tris(trimethylsilyl) ether derivative, showed only a single component. The Kovats Retention Index of this derivative on 3% OV 225 at 230 °C was 2 856. This compared with an index of 2 860 determined for authentic material.

Earlier fractions of the chromatography column contained the cyclopentene (21) contaminated with triphenylphosphine oxide. This was rechromatographed on a short column of silica gel, with elution by 40% ethyl acetate–light petroleum, to give 2β-[(E)-3-*hydroxyoct*-1-*enyl*]*cyclopent*-3-*en*-1α-*ol* (21) (48 mg, 15%) as an oil which solidified on standing; $\nu_{max.}$ (0.5% solution in CHBr), 3 590 (free OH), 970 cm^{-1} (*trans*-CH=CH); τ ($CDCl_3$) 4.25 (1 H, dq, *J* 6 and 2 Hz, one of cyclopentene CH=CH), 4.3—4.5 (3 H, m, olefinic protons), 5.85 (1 H, dt, *J* 6 and 4 Hz, H-1β), 5.97 [1 H, m, CH=CH-*CH*(OH)], 6.80 (1 H, m, H-2α), 7.28 (1 H, ddq, *J* 16, 6, and 2 Hz, H-5β), 7.75 (1 H, ddq, *J* 16, 4 and 2 Hz, H-5α), 7.9 (2 H, br s, 2 × OH), 8.3—8.9 (8 H, complex, $CH_2CH_2CH_2$-CH_2), and 9.10 (3 H, br t, CH_2CH_3); [c.i.m.s. (NH_3 ionisation) Found: $(M + NH_4)^+$, 228.193 0; $(M + NH_4 - H_2O)^+$, 210.183 8; $(M + H - H_2O)^+$, 193.158 6. $C_{13}H_{22}O_2$ requires $(M + NH_4)$, 228.196 3; $(M + NH_4 - H_2O)$, 210.185 7; $(M + H - H_2O)$, 193.159 3].

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