Total Synthesis of Prostaglandin A_2 involving the Reaction of a Hetero-cuprate Reagent with an Allyl Epoxide

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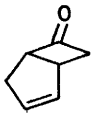
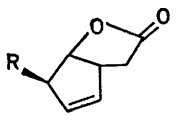
A new route to prostaglandin A_2 (18) involves as the key step the S_N' *anti* reaction of the allyl epoxide (12) and the cuprate reagent (9).

As part of our studies into the synthesis of prostaglandins, we wished to prepare prostaglandin A_2 [1] using starting materials that we have used previously for the formation of other classes of these naturally occurring compounds.[2] We now report the successful completion of this work.[3]

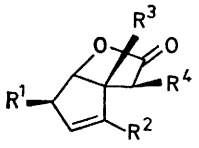
Bicyclo[3.2.0]hept-2-en-6-one (1) was converted into the lactone (2) using peracetic acid.[4] On irradiation of



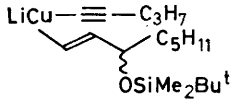
(1)



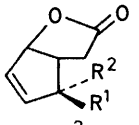
(2) R = H
(3) R = Br
(13) R = CH:CHCHC$_5$H$_{11}$ (OSiMe$_2$Bu^t)



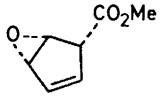
(5) $R^1 = R^3 = Br$; $R^2 = R^4 = H$
(6) $R^1 = R^4 = Br$; $R^2 = R^3 = H$
(7) $R^1 = R^2 = Br$; $R^3 = R^4 = H$
(8) $R^1 = R^2 = R^4 = H$; $R^3 = Br$



(9)



(4) $R^1 = Br$; $R^2 = H$
(10) $R^1 = H$; R^2 = CH:CHCHC$_5$H$_{11}$ (OSiMe$_2$Bu^t)
(11) R^1 = CH:CHCHC$_5$H$_{11}$ (OSiMe$_2$Bu^t); $R^2 = H$



(12)

Ph$_3$PCH(CH$_2$)$_3$CO$_2^-$

(15)

the lactone (2) in carbon tetrachloride containing *N*-bromosuccinimide (NBS) a mixture of the two bromolactones (3) and (4) (ratio 3 : 2) was formed. On large-scale runs trace amounts of the bromolactones (5)—(8) were isolated by chromatography and identified by spectroscopy. Only a small quantity of each of the bromolactones (3) and (4) could be obtained in a pure state by chromatography but fortuitously the major isomer (3) crystallized preferentially on cooling the mixture to −20 °C. After washing the crystals with cold carbon tetrachloride the required lactone (3) was obtained in 35% yield.

On removal of the major amount of the lactone (3) in this way, the residual oil, considerably enriched in the isomer (4), was dissolved in boiling toluene. N.m.r. spectroscopy indicated that the ratio of the bromolactones (3) : (4) in the hot solution altered from *ca.* 1 : 1 to *ca.* 4 : 1 during 24 h. On evaporating the toluene and cooling the residue, a further quantity of 2-oxa-8-bromobicyclo[3.3.0]oct-6-en-3-one (3) crystallized out. In this way, the readily available bicyclic lactone (2) was converted into the bromolactone (3) in 50% yield.

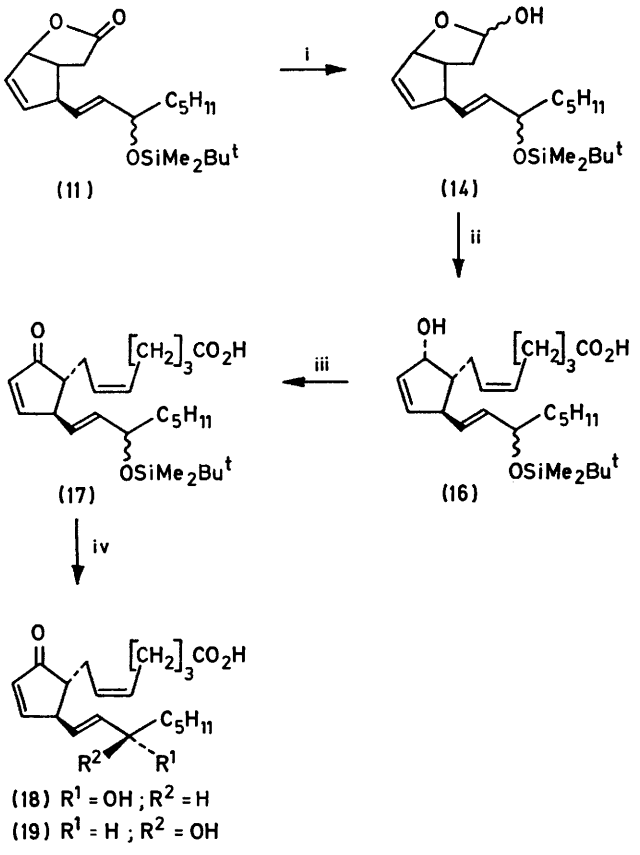
Separate experiments involving heating pure samples of the bromolactones (3) and (4) in toluene showed that the same ratio (*viz* 4 : 1) of the two isomers was formed indicating that a facile halogen shift was occurring and that the observed ratio of isomers was due to a thermodynamic control.

Reaction of the bromolactone (3) with the hetero-cuprate reagent (9) unexpectedly gave the lactone (10) as the only isolated product in low yield. From this and other results [5] we concluded that the desired S_N' reaction was taking place but that the alkenylation was occurring from the *endo*-face of the carbocyclic ring *anti* to the departing bromine atom.

Since it is the isomeric lactone (11) that is the required prostaglandin A_2 precursor, we reasoned that the cuprate reagent must be encouraged to deliver the octenyl side chain to C-6 from the β-face, requiring that the departing moiety must be displaced from the α-face. This was arranged by transforming the bromolactone (3) into the epoxyester (12) (83% yield) using potassium carbonate in ether–methanol. Unfortunately the isomeric bromolactone (4) did not afford the epoxide (12) under these conditions.

Treatment of the epoxide (12) with the heterocuprate reagent (9) for 6 h at −78 °C followed by chromatography over silica furnished the lactone (11) (43%) and the less-polar isomer (13) (14%).

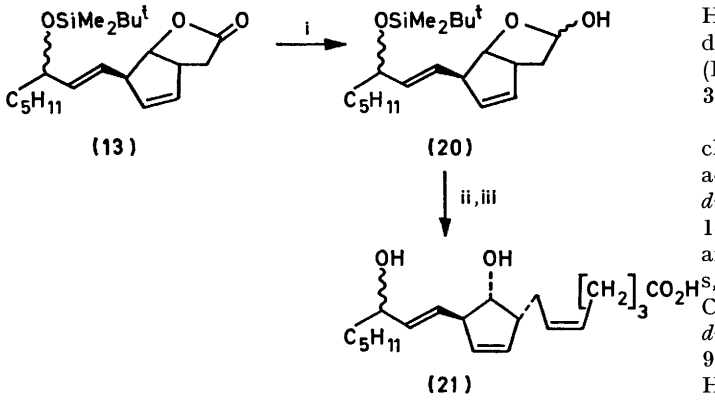
Conversion of the lactone (11) into prostaglandin A_2 was achieved by standard methodology (Scheme 1).[1]



SCHEME 1 *Reagents:* i, Bu^i_2AlH; ii, tetrahydrofuran, reagent (15); iii, CrO_3, pyridine; iv, tetrahydrofuran, $MeCO_2H$, H_2O

Partial reduction of (11) using di-isobutylaluminium hydride (Dibal) gave the lactol (14) (100%) which was treated with the ylide (15) to give the prostanoid (16) (70%). Collins oxidation of (16) gave the cyclopentenone (17) (70%) which on treatment with aqueous acetic acid followed by chromatography afforded (±)-prostaglandin A_2 (18) and (±)-15-epi-prostaglandin A_2 (19). The sample of (±) prostaglandin A_2 prepared in this manner was spectroscopically, chromatographically, and biologically identical to an authentic sample.

In addition the lactone (13) was reduced with Dibal to gave the lactol (20) which after reaction with the ylide (15) and treatment with aqueous acid furnished the biologically inactive prostanoid (21) (Scheme 2) as an inseparable mixture of diastereoisomers.



SCHEME 2 *Reagents:* i, Bu^i_2AlH; ii, tetrahydrofuran, reagent (15); iii, tetrahydrofuran, $MeCO_2H$, H_2O

EXPERIMENTAL

N.m.r. spectra were obtained with a Varian EM-360 or Perkin-Elmer R-32 spectrometer ($CDCl_3$ as solvent). I.r. spectra were recorded with a Perkin-Elmer 257 spectrometer for neat films unless otherwise stated. Anhydrous magnesium sulphate was used as a drying agent for solutions in organic solvents. Precoated plates with silica gel GF supplied by Anachem were used for t.l.c.

2-Oxabicyclo[3.3.0]*oct-6-en-3-one* (2) [4].—To bicyclo[3.2.0]-hept-2-en-6-one (1) (5 g, 46.2 mmol) in glacial acetic acid (30 ml) at 0 °C was slowly added an ice-cold mixture of 30% hydrogen peroxide (20 ml) in glacial acetic acid (20 ml). The resulting pale yellow solution was left for 48 h at 0 °C and then diluted with chloroform (100 ml). The solution was washed with water (3 × 50 ml) and the water layers were back extracted with chloroform (2 × 25 ml). The combined organic layers were dried and evaporated to give a yellow oil (5.3 g). Vacuum distillation afforded the desired product (5.15 g) as a colourless oil (b.p. 70 °C at 6×10^{-2} mmHg; $\nu_{max.}$ 2 960 and 1 780 cm^{-1}; δ ($CDCl_3$), 5.85 (2 H, m, H-6 and H-7), 5.10 (1 H, m, H-1), 3.66 (1 H, m, H-5), 2.75 (3 H, m, 2 × H-4 and H-8-*exo*), and 2.35 (1 H, dd, *J* 3, 18 Hz, H-8-*endo*).

Allylic Bromination of 2-Oxabicyclo[3.3.0]*oct-6-en-3-one.*—To 2-oxabicyclo[3.3.0]oct-6-en-3-one (2) (5 g, 40.3 mmol) in dry carbon tetrachloride (50 ml) was added *N*-bromosuccinimide (7.5 g, 42.6 mmol). The mixture was irradiated at reflux temperature for 1 h. On cooling succinimide was removed by filtration. The filtrate was washed with 10% HCl (50 ml) which was back extracted with carbon tetrachloride (2 × 25 ml). The combined organic layers were dried and evaporated to afford a mixture of bromolactones (7.5 g).

Recrystallisation from carbon tetrachloride afforded 8-exo-*bromo-2-oxabicyclo*[3.3.0]*oct-6-en-3-one* (3) as a white crystalline solid (2.8 g, 35%, m.p. 92 °C). The oil obtained on evaporation of the mother liquor was refluxed in toluene (50 ml) for 24 h. Evaporation of the solvent and recrystallisation of the residue from carbon tetrachloride gave a further 1.45 g (18%) of the required bromolactone (3), $\nu_{max.}$ 2 960 and 1 780 cm^{-1}; δ ($CDCl_3$), 6.07 (1 H, m, H-6 or H-7), 5.84 (1 H, brd, *J* 5 Hz, H-7 or H-6), 5.14 (1 H, d, *J* 5 Hz, H-1), 4.96 (1 H, s, H-8), 3.72 (1 H, m, H-5), 2.85 (1 H, dd, *J* 9, 18 Hz, H-4 *exo*), 2.34 (1 H, dd, *J* 3, 18 Hz, H-4-*endo*) (Found: C, 41.0; H, 3.4. $C_7H_7BrO_2$ requires C, 41.4; H, 3.5%).

The residue obtained on evaporation of the solvent was chromatographed over silica using light petroleum in ethyl acetate as eluant to give (in order of elution), 5,8-exo-*dibromo-2-oxabicyclo*[3.3.0]*oct-6-en-3-one* (5) (1%), m.p. 141—144 °C $\nu_{max.}$ (Nujol) 1 780 cm^{-1}; δ 6.1 (2 H, m, H-6 and H-7), 5.5 (1 H, s, H-1), 4.9 (1 H, m, H-8), and 3.2 (2 H, s, 2 × H-4) (Found: C, 29.7; H, 2.2. $C_7H_6Br_2O_2$ requires C, 29.8; H, 2.15%) the *bromolactone* (3) (10%), 4-exo,8-exo-*dibromo-2-oxabicyclo*[3.3.0]*oct-6-en-2-one* (6) (1%), m.p. 90—92 °C, $\nu_{max.}$ (Nujol) 1 785 cm^{-1}; δ 6.20br (1 H, d, *J* 6 Hz, H-6 or H-7), 6.01br (1 H, d, *J* 6 Hz H-7 or H-6), 5.13 (1 H, d, *J* 4.5 Hz H-1), 4.97 (1 H, d, *J* 1 Hz, H-8), 4.77 (1 H, d, *J* 8 Hz, H-4), and 4.06 (1 H, ddm, *J* 8, 4.5 Hz, H-5) (Found: M^+

200.9605. $C_7H_6Br_2O_2$ requires M − Br 200.9602); 6,8-exo-*dibromo*-2-*oxabicyclo*[3.3.0]*oct*-6-*en*-2-*one* (7) (0.5%), m.p. 85—86 °C; $\nu_{max.}$ (Nujol) 1 790 cm^{-1}; δ (CCl_4) 6.04br (1 H, s, H-7), 5.08 (1 H, d, J 6 Hz, H-1), 4.76 (1 H, d, J 1.5 Hz, H-8), 3.67 (1 H, m, H-5), and 2.56 (2 H, m, 2 × H-4) (Found: M^+ 279.8735. $C_7H_6Br_2O_2$ requires M 279.8736); 6-exo-*bromo*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (4) (7%), b.p. 110 °C at 1 mmHg; $\nu_{max.}$ 1 770 cm^{-1}; δ (CCl_4) 6.23 (1 H, dd, J 6, 2 Hz, H-7 or H-8), 6.03 (1 H, dd, J 6, 1.5 Hz, H-8 or H-7), 5.66 (1 H, dt, J 7, 1 Hz, H-1), 4.87br (1 H, s, H-6), 3.47 (1 H, dt, J 10, 7 Hz, H-5), 2.85 (1 H, dd, J 18, 10 Hz, H-4-*exo*), and 2.25 (1 H, dd, J 18, 7 Hz, H-4-*endo*) (Found: M^+ 123.0446. $C_7H_7BrO_2$ requires M − Br 123.0446), and 5-*bromo*-2-*oxabicyclo*[3.3.0]*oct*-6-*en*-3-*one* (8) (1%), b.p. 100 °C at 3 × 10^{-2} mmHg; $\nu_{max.}$ 1 785 cm^{-1}; δ (CCl_4) 5.87 (2 H, m, H-6 and H-7), 5.18 (1 H, dm, J 4 Hz, H-1), 3.20 (2 H, m, 2 × H-4), 2.83 (1 H, d, J 4 Hz, H-8), and 2.70 (1 H, s, H-8) (Found: M^+ 123.0446. $C_7H_7BrO_2$ requires M − Br 123.0446.).

Methyl 4,5-*Epoxycyclopent*-2-*enylacetate* (12).—To 8-*exo*-bromo-2-oxabicyclo[3.3.0]oct-6-en-3-one (3) (5 g, 24.7 mmol) in dry methanol (50 ml) and dry diethyl ether (200 ml) was added potassium carbonate (7.5 g, 54.3 mmol). The mixture was refluxed for 48 h and then dry diethyl ether (50 ml) was added. After filtration and evaporation of the mixture to small volume (*ca.* 50 ml), chloroform (100 ml) was added to it. The solution was washed with water (2 × 75 ml) and the aqueous layer was back extracted with chloroform (2 × 50 ml). The combined organic layers were dried and evaporated to yield the crude product as a green oil (4.4 g) which was distilled to give the *epoxide* (12) as a colourless oil (3.15 g, 83%), b.p. 75 °C at 2 × 10^{-1} mmHg; $\nu_{max.}$ 1 730 cm^{-1}; δ ($CDCl_3$), 6.2 (1 H, dd, J 1, 4 Hz, H-2 or H-1), 5.88 (1 H, m, H-1 or H-2), 3.95 (2 H, m, H-3 and H-4), 3.78 (3 H, s, CH_3), 3.27 (1 H, m, H-5), and 2.56 (2 H, dd, J 2, 8 Hz, 2 × H-6) (Found: M^+ 154.062 7. $C_8H_{10}O_3$ requires M 154.063 0).

6-exo-(3′-*t*-*Butyldimethylsilyloxyoct*-1′-*enyl*)-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (11).—To a stirred solution of 1-iodo-3-t-butyldimethylsilyloxyoct-1-ene (31.6 g, 86 mmol) in dry ether (150 ml) at −78 °C and under an atmosphere of nitrogen was slowly added n-butyl-lithium (5.5 g, 86 mmol) as a 1.85M-solution in hexane. Hexamethylphosphorus triamide (28 g, 171 mmol) was added to a solution of copper pentyne (11.2 g, 86 mmol) in dry diethyl ether (150 ml) under an atmosphere of nitrogen. The resulting green solution was stirred for 30 min after which time it was filtered through Celite and added to the alkenyl-lithium solution at −78 °C. After 30 min a solution of the epoxide (12) (12 g, 78 mmol) in dry diethyl ether (150 ml) was added to the mixture which was then stirred for 3 h. A solution of saturated ammonium chloride (250 ml) was then added to it and the ether layer was separated; the aqueous layer was extracted with diethyl ether (2 × 100 ml). The combined ether layers were washed with 2M hydrochloric acid (250 ml), saturated sodium hydrogen carbonate (250 ml), and water (250 ml) and then dried and evaporated to give the crude product as an orange oil (49.5 g) which was purified by medium-pressure chromatography over silica using 5% EtOAc–petroleum (b.p. 60—80 °C) as eluant. This gave 6-exo-(3′-t-*butyl dimethylsilyloxyoct*-1′-*enyl*)-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (11) (12.2 g, 43%); $\nu_{max.}$ 1 780 and 1 260 cm^{-1}; δ 5.98 (2 H, s, H-7 and H-8), 5.51 (3 H, m, H-1′, H-2′, and H-1), 4.08 (1 H, m, H-3′), 3.28 (1 H, m, H-6), 2.95—2.1 (3 H, m, H-5 and 2 × H-4), 1.35 (8 H, m, 4 × CH_2), 0.9 [12 H, s, CH_3 and $C(CH_3)_3$], 0.1 [6 H, s, $Si(CH_3)_2$], M^+ 364, and 8-exo-(3′-t-*butyldimethylsilyloxyoct*-1′-*enyl*)-2-*oxabicyclo*[3.3.0]*oct*-6-*en*-3-*one* (13) (4.1 g, 14.5%); $\nu_{max.}$ 1 780 and 1 260 cm^{-1}; δ 5.8—5.3 (4 H, m, H-6, H-7, H-1′ and H-2′), 4.7 (1 H, m, H-1), 4.0 (1 H, m, H-3′), 3.5 (1 H, m, H-8), 2.9—2.3 (3 H, m, 2 × H-4 and H-5), 1.35 (8 H, m, 4 × CH_2), 0.9 [12 H, s, CH_3 and $C(CH_3)_3$], and 0.1 [6 H, s, $Si(CH_3)_2$]; M^+ 364.

6-endo-(3′-*t*-*Butyldimethylsilyloxyoct*-1′-*enyl*)-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (10).—Reaction of the bromolactone (3) with cuprate reagent as described above gave the title compound (12%) as a colourless oil after chromatography, $\nu_{max.}$ 1 780 cm^{-1}; δ (CCl_4) 5.91 (2 H, m, H-7 and H-8), 5.35 (3 H, m, H-1, H-1′ and H-2′), 4.0 (1 H, m, H-3′), 3.45 (1 H, m, H-5), 3.10 (1 H, t, J 7 Hz, H-6), 2.23 (2 H, m, 2 × H-4), 1.3 (8 H, m, 4 × CH_2), 0.9 (12 H, s, 4 × CH_3), and 0.0 [6 H, s, $Si(CH_3)_2$].

6-exo-(3′-*t*-*Butyldimethylsilyloxyoct*-1′-*enyl*)-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*ol* (14).—To 6-*exo*-(3′-t-butyldimethylsilyloxyoct-1′-enyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one (11) (0.3 g, 0.84 mmol) in dry petroleum (b.p. 60—80 °C) (18 ml) was slowly added dropwise, a 20% solution of di-isobutylaluminium hydride in hexane (10.47 g, 3.3 mmol) at −78 °C and under an atmosphere of nitrogen. After the mixture had been stirred for 20 min water (15 ml) and ice cold 2N-H_2SO_4 (30 ml) were added to it; it was then extracted with diethyl ether (50 ml). The ether layer was washed with 2N-H_2SO_4 (2 × 20 ml) and water (3 × 30 ml), dried, and evaporated to yield 6-exo-(3′-*t*-*butyldimethylsilyloxyoct*-1′-*enyl*)-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*ol* (14) as a pale green oil (0.3 g, 100%) requiring no further purification; $\nu_{max.}$ 3 400 cm^{-1}; δ 5.9—5.3 (4 H, m, H-7, H-8, H-1′ and H-2′), 5.25 (1 H, m, H-1), 4.05 (1 H, m, H-3′), 3.4 (2 H, m, H-3 and OH), 3.1 (1 H, m, H-5), 2.9—2.1 (3 H, m, H-6, 2 × H-4), 1.7—1.0 (8 H, m, 4 × CH_2), 0.9 [12 H, s, CH_3 and $SiC(CH_3)_3$], and 0.1 [6 H, s, $Si(CH_3)_2$].

11-*Deoxa*-10,11-*dehydro*-15-*t*-*butyldimethylsilyloxyprostaglandin* $F_{2\alpha}$ (16).—Potassium-t-butoxide (10.74 g, 6.6 mmol) was slowly added with stirring to a solution in dry THF (12 ml) of 4-carboxybutyltriphenylphosphonium bromide (1.42 g, 3.30 mmol) under an atmosphere of nitrogen at room temperature; the deep red solution was then stirred for 15 min. To this was slowly added 6-*exo*-(3′-t-butyldimethylsilyloxyoct-1′-enyl)-2-oxabicyclo[3.3.0]oct-7-en-3-ol (14) (0.3 g, 0.82 mmol) in dry tetrahydrofuran (8 ml). The solution turned chocolate brown and was then stirred for 3 h; water (50 ml) and 2N-H_2SO_4 (30 ml) were then added. Extraction with diethyl ether (50 ml) gave an organic fraction which was washed with 2N-H_2SO_4 (2 × 25 ml) and water (3 × 25 ml) and dried. Evaporation yielded the crude product (0.63 g) which was chromatographed over silica using 50% EtOAc in light petroleum (b.p. 60—80 °C) to give 11-*deoxa*-10,11-*dehydro*-15-*t*-*butyldimethylsilyloxyprostaglandin* $F_{2\alpha}$ (16) (0.25 g, 69%) as a yellow oil; $\nu_{max.}$ 3 350 and 1 710 cm^{-1}; δ 6.45br (2 H, s, OH and CO_2H), 5.95 (2 H, m, H-10 and H-11), 5.50 (4 H, m, H-5, H-6, H-13 and H-14), 4.75 (1 H, m, H-9), 4.15 (1 H, m, H-15), 3.05 (1 H, m, H-12), 2.60—1.10 (17 H, m, 2 × H-2, 2 × H-3, 2 × H-4, 2 × H-7, H-8 and 4 × CH_2), 0.9 [12 H, s, CH_3 and $SiC(CH_3)_3$], and 0.1 [6 H, s, $Si(CH_3)_2$].

15-*t*-*Butyldimethylsilyloxyprostaglandin* A_2 (17).—To a solution of chromium trioxide–dipyridine complex (0.85 g, 3.3 mmol) in dry dichloromethane (10 ml), was added a solution of the prostanoid (16) (0.25 g, 0.55 mmol) in dichloromethane (5 ml), at 5 °C with stirring. After the mixture had been stirred for 30 min ice-cold 2N-HCl (50 ml) was added to it; the solution was then extracted with dichloromethane

(2 × 40 ml). The combined organic layers were washed with water (3 × 30 ml) and dried. Evaporation yielded the crude product as a brown oil (0.45 g) which was purified over silica using 50% EtOAc–light petroleum (b.p. 60—80 °C) as the eluant. Ethyl acetate extraction yielded *15-t-butyldimethylsilyloxyprostaglandin* A_2 (17) as a yellow oil (0.17 g, 70%); $\nu_{max.}$ 1 710 and 1 590 cm^{-1}; δ ($CDCl_3$), 7.45 (1 H, dm, *J* 6 Hz, H-11), 6.15 (1 H, dm, *J* 6 Hz, H-10), 5.45 (4 H, m, H-5, H-6, H-13, and H-14), 4.05 (1 H, m, H-15), 3.20 (1 H, m, H-12), 2.60—1.10 (17 H, m, H-8, and 8 × CH_2), 0.90 [12 H, s, CH_3 and $C(CH_3)_3$] and 0.1 [6 H, s, $Si(CH_3)_2$].

Prostaglandin-A$_2$ (18).—15-t-Butyldimethylsilyloxyprostaglandin A_2 (17) (0.2 g, 0.45 mmol) was dissolved in a mixture of acetic acid, tetrahydrofuran and water (2 ml 1 : 1) and allowed to stand for 18 h. Evaporation, addition of chloroform, and further evaporation gave the crude product. Chromatography over silica using 50% ethyl acetate in light petroleum (b.p. 60—80 °C) as eluant yielded *prostaglandin* A_2 (18), $\nu_{max.}$ 3 400, 1 710, and 1 590 cm^{-1}; δ ($CDCl_3$) 7.45 (1 H, dm, *J* 6 Hz, H-11), 6.15 (1 H, dm, *J* 6 Hz, H-10), 5.7—5.3 (4 H, m, H-5, H-6, H-13 and H-14), 4.75 (2 H, m, OH and CO_2H), 4.15 (1 H, m, H-15), 3.20 (1 H, m, H-12), 2.60—0.80 (20 H, H-8, 2 × H-2, 2 × H-3, 2 × H-4, 2 × H-7, and C_5H_{11}) (Found: M^+ 334.214 2. $C_{20}H_{30}O_4$ requires M^+ 334.214 2); and *15-epi-prostaglandin* A_2 (19) $\nu_{max.}$ 3 400, 1 710, and 1 590 cm^{-1}; δ 7.5 (1 H, dm, *J* 6 Hz, H-11), 6.20 (1 H, dm, *J* 6 Hz, H-10), 5.7—5.35 (4 H, m, H-5, H-6, H-13, and H-14), 4.6—4.0 (3 H, m, –OH, CO_2H and H-15), 3.20 (1 H, m, H-12), and 2.60—0.8 (20 H, m, 2 × H-2, 2 × H-3, 2 × H-4, 2 × H-7, H-8 and C_5H_{11}).

8-exo-(*3′-t-Butyldimethylsilyloxyoct-1′-enyl*)-2-*oxabicyclo*-[3.3.0]*oct-6-en-3-ol* (20).—To 8-*exo*-(3′-t-butyldimethylsilyloxyoct-1′-enyl)-2-oxabicyclo[3.3.0]oct-6-en-2-one (13) (0.4 g, 1.1 mmol) in dry, light petroleum (b.p. 60—80 °C) (24 ml) was slowly added, dropwise, a 20% solution of diisobutylaluminium hydride in hexane (0.63 g, 4.4 mmol) at −78 °C under an atmosphere of nitrogen. After the mixture had been stirred for 20 min water (20 ml) and H_2SO_4 (30 ml) were added to it. Extraction with diethyl ether (50 ml) gave an organic fraction which was washed with 2N-H_2SO_4 (2 × 10 ml) and water (3 × 25 ml) and dried. Evaporation yielded 8-exo-(*3′-t-butyldimethylsilyloxyoct-1′-enyl*)-2-*oxabicyclo*[3.3.0]*oct-6-en-3-ol* (20) as a pale green oil (0.4 g, 100%) requiring no further purification, $\nu_{max.}$ 3 400 cm^{-1}; δ 5.8—5.3 (4 H, m, H-6, H-7, H-1′ and H-2′), 4.6 (1 H, m, H-1), 4.05 (1 H, m, H-3′), 3.4 (2 H, m, H-3 and OH), 2.4—1.7 (4 H, m, 2 × H-4, H-8 and H-5), 1.35 (8 H, m, C_4H_8), 0.9 [12 H, s, CH_3 and $SiC(CH_3)_3$], and 0.1 [6 H, s, $Si(CH_3)_2$].

7-[*4′-exo-(3″-Hydroxyoct-1″-enyl)-5′-hydrocyclopent-2′-enyl*]*hept-5-enioc Acid* (21).—To a solution of 4-carboxybutyltriphenylphosphonium bromide (1.89 g, 4.4 mmol) in dry THF (15 ml) was slowly added n-butyl-lithium (0.56 g, 8.8 mmol) with stirring at room temperature under an atmosphere of nitrogen. The resulting cherry-red solution was stirred for 10 min and 8-*exo*-(3′-t-butyldimethylsilyloxyoct-1′-enyl)-2-oxabicyclo[3.3.0]oct-6-en-3-ol (20) (0.4 g, 1.1 mmol) in dry tetrahydrofuran (5 ml) was added slowly to it. After the solution had been stirred for 2 h water (50 ml) and 2N-H_2SO_4 were added to it and the solution was extracted with chloroform (50 ml). The organic layer was washed with 2N-H_2SO_4 (2 × 25 ml) and water (3 × 30 ml), dried, and evaporated to give the crude product which was purified by chromatography over silica using 40% EtOAc in light petroleum (b.p. 60—80 °C) as eluant to give 7-[*4′exo-(3″-t-butyldimethylsilyloxyoct-1″-enyl)-5′-hydroxycyclopent-2′-enyl*]*hept-5-enoic acid* as a yellow oil (0.32 g 71%); $\nu_{max.}$ 3 400 and 1 710 cm^{-1}; δ 6.0—5.4 (8 H, m, OH, CO_2H, H-5, H-6, H-1″, H-2″, H-2′, and H-3′), 4.1 (2 H, m, H-5′ and H-3″), 3.2 (1 H, m, H-4′), 2.6—1.6 (9 H, m, 2 × H-2, 2 × H-3, 2 × H-4, 2 × H-7, and H-1′), 1.35 (8 H, m, 4 × CH_2), 0.9 [12 H, s, CH_3 and $SiC(CH_3)_3$], and 0.1 [6 H, s, $Si(CH_3)_2$]. This acid was dissolved in a mixture of acetic acid, tetrahydrofuran, and water (2 ml) (3 : 1 : 1) for 18 h. Evaporation of the solvents, dilution with chloroform, and further evaporation gave the crude product which was purified by chromatography over silica using ethyl acetate in light petroleum (b.p. 60—80 °C) (2 : 3) to give 7-endo-[4′-exo-(3″-*hydroxyoct-1″-enyl*]-5′-*hydroxycyclopent-2′-enyl*)*hept-5-enoic acid* (21) as a yellow oil (0.11 g, 67%), $\nu_{max.}$ 3 400 and 1 700 cm^{-1}; δ 5.7 (6 H, m, H-5, H-6, H-2′, H-3′, H-1″, and H-2″), 5.1 (3 H, s, 2 × OH and CO_2H), 4.1 (2 H, m, H-5′ and H-3″), 3.2 (1 H, m, H-4′), and 2.6—0.90 (20 H, m, 2 × H-2, 2 × H-3, 2 × H-4, 2 × H-7, H-1′, and C_5H_{11}).

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