Synthesis of 12,13-Didehydroprostaglandin J_2 Methyl Ester

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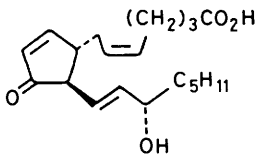
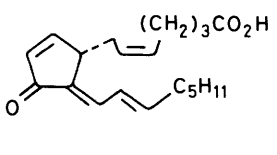
A new class of prostanoid has been synthesized. The carboxylic acid ester (**3**) is an analogue of prostaglandin J_2 and contains an allene moiety at C_{12}. The novel compound (**3**) is available from 7-chloronorbornadiene (**5**) in a route which has two key steps. The first is the reaction of (**5**) with an alkynyl Grignard reagent to give the dienyne (**7**). The second is the regioselective epoxidation of the dienyne (**7**), rearrangement of the epoxide (**8**) to give the aldehyde (**9**), followed by an oxa-Cope rearrangement; the derived enol (**10**) was hydrolysed to give the useful prostaglandin synthon (**14**) directly.

In view of the current interest in prostaglandin J_2 (PGJ_2) (**1**)[1] and related compounds [*e.g.* (**2**)][2] as anti-neoplastic agents against a variety of tumour types, we wish to report a short flexible route to the allene (**3**) (Scheme).



(1)



(2)

Commercially available 7-t-butoxynorbornadiene (**4**) was converted into 7-chloronorbornadiene (**5**) using HCl in ether.[3] Reaction of (**5**) with the Grignard reagent (**6**) gave the dienyne (**7**) in 73% yield.[4]

The critical step in this route to the new prostanoid is the selective oxidation of the alkyne (**7**). Reaction of (**7**) with buffered peracetic acid at 0 °C gave, *via* the *exo-anti*-epoxide (**8**), the required aldehyde (**9**) [which exists in equilibrium with the enol ether (**10**)][5] in admixture with small amounts of the *syn*(**11**) and the *anti-endo*-oxirane (**12**).

The equilibrating mixture of tautomers (**9**) $\rightleftharpoons$ (**10**) proved to be difficult to separate from the epoxides (**11**) and (**12**) using the usual chromatographic techniques. This problem was resolved by treating a methylene chloride solution of the crude reaction mixture obtained on peracetic acid oxidation of (**7**) with 2M-hydrochloric acid. The enol ether (**10**) was hydrolysed under these conditions,[6] while the epoxides did not react. Two new products were formed, the chlorohydrin (**13**) [presumably formed from the unstable *exo-anti* epoxide (**8**)] and the desired product (**14**). The polar hydroxy aldehyde (**14**) was readily separated from the minor products (**11**)—(**13**) and was isolated in a satisfactory 61% yield from the dienyne (**7**).

The stereochemistry of the minor products (**12**) and (**13**) was established by n.O.e. experiments. For the epoxide (**12**), irradiation of 8-H gave enhancement at 1-H, 2-H, 4-H, and 5-H). Irradiation of 2-H and 3-H in compound (**13**) gave enhancement of the signals due to 1-H, 4-H, 5-H, and 6-H. The structure of the epoxide (**11**) was elucidated by comparison of the n.m.r. spectrum with that obtained for the isomeric epoxide (**12**).

The hydroxy aldehyde (**14**) was converted into the carboxylic acid (**15**) under the prescribed conditions.[6] The corresponding ester (**16**) was obtained by treatment of (**15**) with diazomethane. The required allene (**3**) was prepared from (**16**) by oxidation under basic conditions (Collins reagent)[7] followed by removal of the silyl protecting group (HF in acetonitrile).[8]

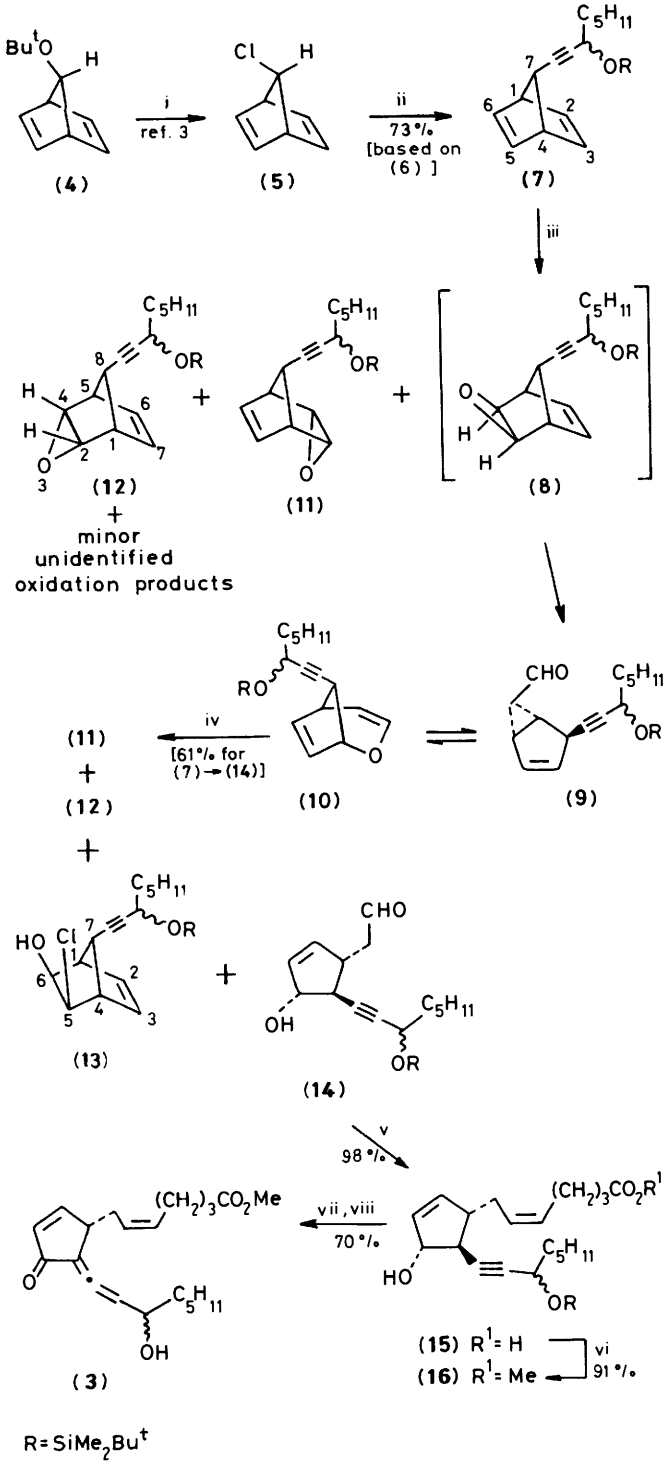
The allene (**3**) expands the range of cumulenes described in the prostaglandin literature. 4,5-Didehydroprostaglandin-E_2 and -$F_{2\alpha}$[9] and the 11-desoxyprostanoid (**17**)[10] have been described by other workers in the field.

In summary the prostanoid (**3**) has been prepared from 7-chloronorbornadiene in six steps and in an overall yield of 20%.

Experimental

M.p.s were determined using the capillary tube method. I.r. spectra were recorded on a Perkin-Elmer 257, 377 or a Unicam SP200 spectrometer for neat films unless otherwise stated. N.m.r. spectra were recorded on a Varian EM360 (60 MHz) or a Bruker WM250 or AM250 (250 MHz) spectrometer ($CDCl_3$ solvent). Electron impact (e.i.) mass spectra and accurate mass determinations were obtained on AEI-MS12 and MS902S spectrometers: chemical ionization (c.i.) mass spectra were obtained on a VG7070 mass spectrometer using ammonia as the carrier gas. Column chromatography was performed using Merck Kieselgel (60H) Art 7729 or 7736 unless stated otherwise; t.l.c. was accomplished using Polygram $SiLG/UV_{254}$ plates supplied by Camlab. Anhydrous magnesium sulphate was used as a drying agent for solutions in organic solvents. Light petroleum refers to the fraction boiling at 60—80 °C. Ether refers to diethyl ether.

7-[3′(*Dimethyl-t-butylsilyloxy*)*oct*-1′-*ynyl*]*bicyclo*-[2.2.1]*hepta*-2,5-*diene* (**7**).—To a stirred solution of magnesium turnings (1.65 g) in dry tetrahydrofuran (THF) (10 ml) was added redistilled bromoethane (6.8 g). After 1 h, 3-t-butyldimethylsilyloxyoct-1-yne (15.0 g) was added and the solution was heated to reflux for 1 h. On cooling, copper(I) chloride (400 mg) and, after 0.25 h, 7-chloronorbornadiene (**5**)[3] (10.3 g) were added. The reaction mixture was stirred for 0.25 h, heated to reflux for 1.5 h, cooled, and poured into water (500 ml) and ether (600 ml). The organic phase was separated and washed with water (2 × 400 ml). The combined aqueous layers were



Scheme. *Reagents:* i, HCl, ether; ii, $BrMgC{\equiv}CCH(OR)C_5H_{11}$ (**6**), CuCl, tetrahydrofuran, reflux; iii, $MeCO_3H$, $MeCO_2H$, $MeCO_2Na$, CH_2Cl_2, 0 °C; iv, HCl, CH_2Cl_2; v, $Ph_3\overset{+}{P}\overline{C}H(CH_2)_3CO_2^-$, tetrahydrofuran, $KOBu^t$; vi, CH_2N_2; vii, Collins' reagent; viii, HF, MeCN

extracted with ethyl acetate (8 × 300 ml). The combined organic extracts were washed with water (2 × 300 ml), dried, and evaporated to give an orange oil. Column chromatography using silica (Merck 9385) with hexane as eluant gave the *dienyne* (**7**) (15.0 g, 72.7%); $\nu_{max.}$ 2 225 cm^{-1}; δ 6.75 (2 H, t, *J* 2.0 Hz, 5-H and 6-H), 6.68 (2 H, t, *J* 2.0 Hz, 1-H and 2-H), 4.27 (1 H, td, *J* 6.5 and 1.5 Hz, 3'-H), 3.63 (2 H, sextet, *J* 2.0 Hz, 1-H and 4-H), 3.06 (1 H, dt, *J* 1.5 and 2.0 H_3, 7-H), 1.59 (2 H, m, 2 × 4'-H), 1.35 (6 H, 3 × CH_2), 0.90 (12 H, m, 4 × Me) and 0.10 (6 H, 2 × s, $Si(Me)_2$) (Found: C, 76.1; H, 10.6. $C_{21}H_{34}OSi$ requires C, 76.3; H, 10.4%).

[*5'-(3''-Dimethyl-t-butylsilyloxyoct-1''-ynyl)-4'-hydroxycyclopent-2'-enyl*]*ethanol* (**14**).—To a vigorously stirred solution of the dienyne (**7**) (4.5 g) and anhydrous sodium carbonate (2.45 g) in dry dichloromethane (25 ml) at 0 °C was added peracetic acid (40% w/w; 1.04 g). After continued stirring at 0 °C for 30 h the solution was filtered and the filter cake was washed with dichloromethane (50 ml). The organic material was washed with saturated aqueous sodium hydrogen sulphite (25 ml), 8% aqueous sodium hydrogen carbonate (25 ml), and water (25 ml), dried, and evaporated. The residual oil contained the aldehyde (**9**), the enol ether (**10**), and the epoxides (**11**) and (**12**) as shown by n.m.r. spectroscopy. Chromatography of an aliquot over silica (Merck 9385) using 2% ethyl acetate in light petroleum as eluant gave in the early fractions the bicyclic aldehyde (**9**) and the enol ether (**10**); $\nu_{max.}$ 2 730, 2 120, 1 720, and 1 595 cm^{-1}; δ (*inter alia*) 9.2 (d, *J* 1.1 Hz, CHO) (Found: C, 73.1; H, 10.0. $C_{21}H_{34}O_2Si$ requires C, 72.8; H, 9.9%).

The oil was dissolved in dichloromethane (35 ml) and hydrochloric acid (2M; 35 ml) was added. This two-phase solution was stirred for 68 h. Chloroform (45 ml) and water (40 ml) were added and the organic layer was separated and washed with water (2 × 25 ml). The aqueous phase was washed with chloroform (45 ml) and this organic phase was washed with water (25 ml). The combined organic material was dried, evaporated and the residue was chromatographed over silica (Merck 9385) using 5—25% ethyl acetate in light petroleum as eluant. The major product obtained was the *aldehyde* (**14**) (3.0 g, 61%); $\nu_{max.}$ (0.5% CHB_3 solution) 3 590, 2 725, 2 220, and 1 720 cm^{-1}; δ 9.84 (1 H, t, *J* 1.5 Hz, CHO), 5.84 (2 H, m, 2'-H and 3'-H), 4.85 (1 H, br d, *J* 6 Hz, 4'-H), 4.36 (1 H, td, *J* 6.0 and 2.0 Hz, 3''-H), 3.10 (1 H, m, 1'-H), 2.68 (2 H, m, CH_2CHO), 2.46 (1 H, ddd, *J* 7, 6, and 2 Hz, 5'-H), 2.10 (1 H, br s, OH), 1.70 (2 H, m, 2 × 4''-H), 1.30 (6 H, m, 3 × CH_2), 0.90 (12 H, m, 4 × Me), and 0.10 (6 H, 2 × s, $SiMe_2$) (Found: C, 69.25; H, 9.7. $C_{21}H_{36}O_3Si$ requires C, 69.2; H, 9.95%). From early fractions were obtained (in order of elution): the epoxide (**12**) (150 mg, 3%); $\nu_{max.}$ 2 120 cm^{-1}; δ 5.9 (2 H, m, 6-H and 7-H), 4.3 (1 H, m, 3'-H), 3.6 (2 H, m, 2-H and 4-H), 3.1 (1 H, m, 8-H), 3.0 (2 H, t, 1-H and 5-H), 1.6—1.3 (8 H, m, 4 × CH_2), 0.8 (12 H, m, 4 × Me), and 0.1 (6 H, 2 × s, $SiMe_2$) (Found: C, 72.4; H, 9.8. $C_{21}H_{34}O_2Si$ requires C, 72.8; H, 9.9%); the epoxide (**11**) (90 mg, 2%) had i.r. and n.m.r. spectra very similar to those described for compound (**12**), although the splitting of the epoxide signal was slightly different for the two isomers [(2.5 Hz for compound (**11**) and 4 Hz for compound (**12**)] and the chlorohydrin (**13**) (200 mg, 3.8%); $\nu_{max.}$ 3 450 and 2 120 cm^{-1}; δ 6.12 (2 H, m, 2-H and 3-H), 4.28 (1 H, dt, 3'-H), 4.03 (1 H, d, 5-H), 3.82 (1 H, br d, 6-H), 3.28 (1 H, br d, 7-H), 3.07 and 2.99 (2 H, 2 × br d, 1-H and 4-H), 2.5 (1 H, br s, OH), 1.7—1.2 (8 H, m, 4 × CH_2), 1.0—0.8 (12 H, m, 4 × Me), and 0.1 (6 H, 2 × s, $SiMe_2$) (Found: M^+, 325.1391. $C_{21}H_{35}ClO_2Si$ requires M − 57, 325.1394).

9,10,13,14-*Tetrahydro*-15-*dimethyl*-t-*butylsilyl*-9-*deoxa*-*prostaglandin* $F_{2\alpha}$ *Methyl Ester* (**16**).—To a stirred solution of carboxybutyltriphenylphosphonium bromide (1.28 g) in dry THF (1 ml) under argon at room temp. was added potassium t-butoxide (0.65 g). After 0.5 h the aldehyde (**14**) (300 mg) in dry THF (10 ml) was added and the solution stirred for 0.5 h). Saturated aqueous ammonium chloride (20 ml) was added and the mixture was poured into ethyl acetate (50 ml). The organic layer was separated and washed with hydrochloric acid (2M; 20 ml) and brine (20 ml). The combined aqueous layers were extracted with ethyl acetate (3 × 50 ml), and the combined organic extracts dried and evaporated. The residue was chromatographed over silica using 5—30% ethyl acetate in light petroleum as eluant to give the *acid* (**15**) (360 mg), $\nu_{max.}$ 3 500—3 050, 2 150, and 1 720 cm^{-1}; δ 5.77 (1 H, dm, *J* 6 Hz, 9-H), 5.71 (1 H, dm, *J* 6 Hz, 10-H), 5.42 (2 H, m, 5-H and 6-H), 4.75 (1 H, d, *J* 6 Hz, 11-H), 4.32 (1 H, td, *J* 6 and 1 Hz, 15-H), 2.68 (1 H. m, 12-H), 2.40—2.00 (7 H, m, 2 × 2-H), 2 × 4-H, 2 × 7-H, and 8-H), 1.80—1.20 (10 H, m, 5 × CH_2), 0.90 (12 H, m, 4 × Me), and 0.1 (6 H, s, $SiMe_2$) [Found: M^+, 448.7290. $C_{26}H_{44}O_4Si$ requires *M*, 448.7290]. The acid (**15**) (240 mg) in dry ether (4 ml) was added to an ethereal solution of diazomethane until a permanent yellow colour was obtained. Evaporation of the solvents and chromatography of the residue over silica using 7% ethyl acetate in light petroleum as eluant gave the *ester* (**16**) (225 mg); $\nu_{max.}$ 3 500, 2 225, and 1 730 cm^{-1}; δ 5.78 (2 H, s, 9-H and 10-H), 5.45 (2 H, m, 5-H and 6-H), 4.80 (1 H, m, 11-H), 4.38 (1 H, m, 15-H), 3.68 (3 H, s, CO_2Me), 2.90—1.10 (18 H, m, 8-H, 12-H, and 8 × CH_2), 0.90 (12 H, m, 4 × Me), and 0.1 (6 H, s, $SiMe_2$) (Found: C, 69.8; H, 10.3. $C_{27}H_{46}O_4Si$ requires C, 70.1; H, 10.0%).

12,13-*Didehydroprostaglandin* J_2 *Methyl Ester* (**3**).—To a stirred solution of Collins reagent (690 mg) in dichloromethane (25 ml) at 0 °C was added the ester (**16**) (205 mg) in dichloromethane (10 ml). After 0.25 h a further portion of Collins reagent (220 mg) was added. After 0.25 h the organic layer was decanted and the residual solid was triturated with dichloromethane (3 × 50 ml). The combined organic extracts were washed with ice-cold hydrochloric acid (2M; 50 ml) and water (70 mg). The organic phase was dried and evaporated. The residue was chromatographed over silica using 10% ethyl acetate in light petroleum as eluant to give 15-dimethyl-t-butylsilyl-12,13-didehydroprostaglandin J_2 methyl ester (170 mg). To this allene (160 mg) in dry acetonitrile (10 ml) was added aqueous hydrogen fluoride (40%; 0.8 ml). After 0.5 h, chloroform (50 ml) was added and the mixture was washed with water (3 × 30 ml). The combined aqueous layers were washed with the dichloromethane (40 ml) and the organic layer was back-extracted with water (30 ml). The combined organic fractions were dried and evaporated and the resultant oil was chromatographed over silica using 30% ethyl acetate in light petroleum as eluant to give the *prostanoid* (**3**) (100 mg) as a colourless oil, $\nu_{max.}$ 3 400, 1 960, 1 730, and 1 690 cm^{-1}; δ 7.37 (1 H, dt, *J* 6 and 1.5 Hz, 9-H), 6.19 (1 H, dt, *J* 6 and 1.5 Hz, 10-H), 5.80 (1 H, m, 14-H), 5.38 (2 H, m, 5-H and 6-H), 4.20 (1 H, m, 15-H), 3.58 (3 H, s, CO_2Me), 3.50 (1 H, m, 8-H), 2.74 (1 H, br s, OH), 2.40—1.07 (16 H, m, 8 × CH_2), and 0.82 (3 H, t, Me) [Found: M^+, 347.2203. $C_{21}H_{30}O_4$ requires (M + H), 347.2224].

Acknowledgements

We thank the S.E.R.C. and Glaxo Group Research for C.A.S.E. studentships (to A. D. B. and T. J.), and Dr. D. Middlemiss (Chemistry Division, C.G.R., Ware) for helpful advice.

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Received 14*th January* 1985; *Paper* 5/067