Total Synthesis of Prostaglandin-$F_{2\alpha}$ through Homoconjugate Addition of an Organocuprate Reagent to a Tricyclo[3.2.0.$0^{2,7}$]heptanone

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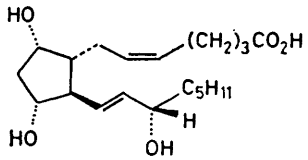
Prostaglandin-$F_{2\alpha}$ has been synthesised from cyclopentadiene in a highly stereoselective ten-step sequence of reactions. The key step involves the coupling of a protected 3-hydroxyoct-1-enyl unit to 3-dimethyl-t-butylsilyloxytricyclo[3.2.0.$0^{2,7}$]heptan-6-one through the use of a mixed organocuprate reagent.

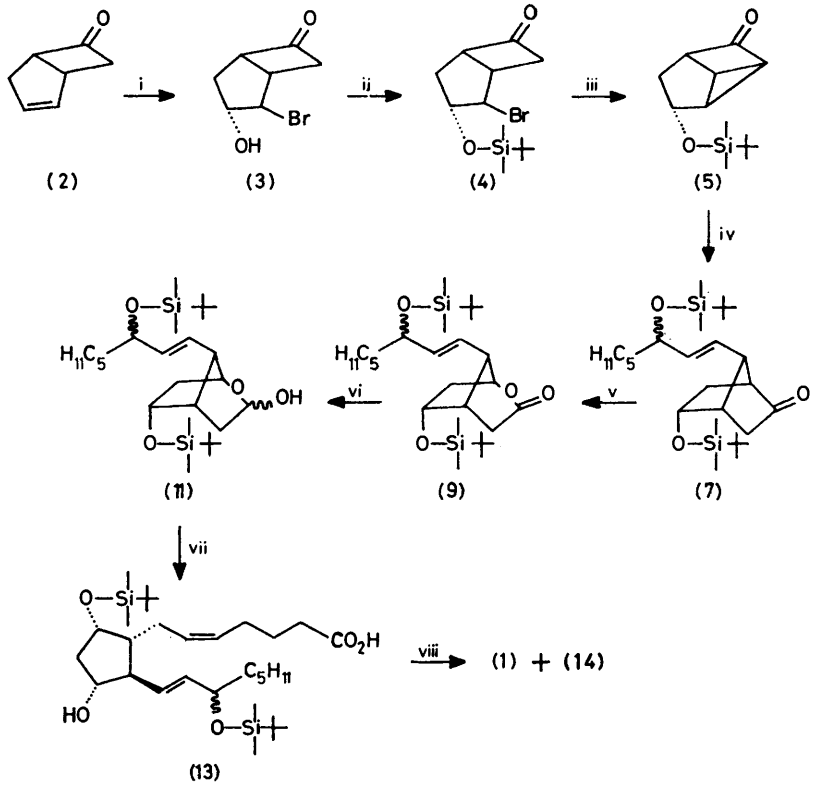
We report a simple, highly stereoselective synthesis of prostaglandin $F_{2\alpha}$(PG-$F_{2\alpha}$) (1) in eight steps from the



(1)

readily available bicyclo[3.2.0]heptenone (2).[1] A key step in the sequence allows the introduction of the eight carbon Ω-side chain of the prostaglandin through a homoconjugate addition reaction involving a mixed organocuprate reagent and a tricyclo[3.2.0.$0^{2,7}$]heptan-6-one. Using this strategy, the gain in efficiency on introducing the Ω-side chain as one unit is combined with the high degree of stereocontrol offered by the inflexible tricyclic molecule in reactions with nucleophiles.[2]

Reaction of bicyclo[3.2.0]hept-2-en-6-one (2) with *N*-bromoacetamide (NBA) in aqueous acetone gave 2-*exo*-bromo-3-*endo*-hydroxybicyclo[3.2.0]heptan-6-one (3) in 75% yield after one recrystallisation from light petroleum (Scheme).[3] The very high stereoselectivity of this reaction is crucial; it is noteworthy that the hydroxy group introduced onto the five-membered ring in this step is destined to become the 9-hydroxy group in PG-$F_{2\alpha}$. Protection of the bromohydrin (3) as the t-butyldimethylsilyl derivative (4) was accomplished in the usual manner.[4]

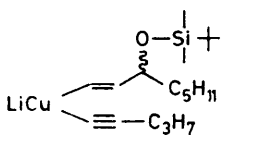


Scheme Reagents: i, NBA–H_2O–Me_2CO; ii, Me_2Bu^tSiCl; iii, $Bu^tO^-K^+$; iv, (6); v, $MeCO_3H$; vi, DIBAl–H; vii, (12); viii, H^+

[1] Preliminary communication, M. J. Dimsdale, R. F. Newton, D. K. Rainey, C. F. Webb, T. V. Lee, and S. M. Roberts, *J.C.S. Chem. Comm.*, 1977, 716; Dutch P.; application no. 7,613,429.
[2] T. V. Lee, S. M. Roberts, and R. F. Newton, following paper.
[3] Z. Grudzinski and S. M. Roberts, *J.C.S. Perkin I*, 1975, 1767.
[4] E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, 1972, **94**, 6190.

Very ready 1,3-dehydrobromination occurred on treating the protected bromohydrin (4) with potassium t-butoxide in ether at low temperature and the ring-closed product, 3-*endo*-dimethyl-t-butylsilyloxytricyclo-[3.2.0.$0^{2,7}$]heptan-6-one (5) was obtained as an oil in quantitative yield using a non-aqueous work-up procedure. The tricyclic ketone (5) was stable at room temperature for days in the absence of air and light and could be stored indefinitely at −20°.

Reaction of the ketone (5) with the mixed organocuprate (6) took place rapidly at −78 °C and gave after 2 h, the bis-(dimethyl-t-butylsilyloxy)bicycloheptanone (7) in 88% yield after chromatography over silica. Premature quenching of the cuprate reaction with cold ammonium chloride solution led to the formation of significant quantities of 7-chlorobicycloheptan-2-one (8). This chloroketone (8) could be separated chromatographically from the less polar prostaglandin precursor (7) and recycled, since treatment of (8) with t-butoxide regenerated the tricyclic ketone (5) in high yield.[5] Organocuprate reagents with the prostaglandin Ω-side chain as the mobile ligand have been used previously in conventional Michael additions to cyclopent-2-enones *en route* to prostaglandin-E:[6] the same reagents have been used also in a synthesis of prostaglandin-A_2 through an S_N2 displacement of an allylic acyloxy unit.[7]



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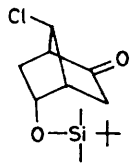

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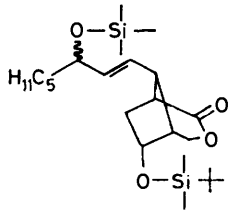

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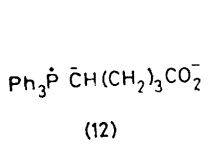
The ketone (7) was subjected to Baeyer–Villiger oxidation employing peracetic acid in buffered acetic acid at room temperature for three days. The required lactone (9) was obtained in 65% yield, after chromatography over silica to remove minor amounts of more polar compounds probably resulting from slow desilylation under the acidic reaction conditions. A trace amount of the isomeric lactone (10) was also obtained. Larger quantities of the latter lactone (10) were obtained on attempting to enhance the rate of the oxidation, for example by employing a stronger peracid.[8]

Reduction of the lactone (9) to the lactol (11) was performed using di-isobutylaluminium hydride (DIBAlH), and the lactol (11) was reacted with the ylide (12) (preformed from 4-carboxybutyltriphenylphosphonium bromide using n-butyl-lithium in tetrahydrofuran or sodium pentaoxide in benzene) in the prescribed manner[9] to give the 11,15-bis-silylated PG-$F_{2\alpha}$ (13). Desilylation of (13) using mineral acid afforded PG-$F_{2\alpha}$ (1) which was separated from an approximately equal amount of 15-*epi*-PG-$F_{2\alpha}$ (14) by chromatography.



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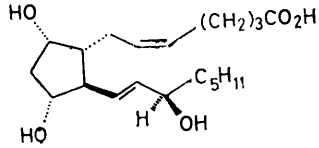

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We believe that this route is superior in brevity, simplicity of operation, and overall yield to the previously documented syntheses of PG-$F_{2\alpha}$. The full versatility of the scheme both in providing other prostaglandin systems[10] and in giving access to a range of novel prostanoids will be described in due course.

EXPERIMENTAL

N.m.r. spectra were recorded on Varian A60, Varian EM360, or Perkin-Elmer R32 spectrometers. I.r. spectra were obtained on a Perkin-Elmer 257 spectrophotometer. Silica gel MFC was used for column chromatography and silica gel G for thin layer chromatography. Anhydrous magnesium sulphate was used as a drying agent for solutions in organic solvents.

2-exo-*Bromo*-3-endo-*t-butyldimethylsilyloxybicyclo*[3.2.0]-*heptan-6-one* (4).—Chloro-t-butyldimethylsilane (3 g, 21.1 mmol), imidazole (2.72 g, 40.5 mmol), and 2-*exo*-bromo-3-*endo*-hydroxybicyclo[3.2.0]heptan-6-one (3) (3.28 g, 16.6 mmol) were stirred in dry dimethyl formamide (15 ml) for 18 h. The solution was diluted with water (20 ml), washed with diethyl ether (2 × 20 ml), dried, and evaporated to afford a yellow oil which was distilled under reduced pressure. The *title compound* (4) was obtained as an oil (75%), b.p. 91 °C at 0.1 mmHg, which crystallised on standing, m.p. 50—54 °C, $\nu_{max.}$ 1 770, 1 250, and 1 080 cm^{-1} δ($CDCl_3$) 4.48br (1 H, d, *J* 3 Hz, H-3), 4.18 (1 H, s, H-2), 3.7 (1 H, m, H-1), 3.25 (2 H, m, H-7 *exo* and *endo*), 2.4 (2 H, m, H-4 *exo* and *endo*), 0.9 (9 H, s, Bu^t), and 0.1 (6 H, s, 2 × Me) (Found: C, 49.0; H, 7.25. $C_{13}H_{23}BrO_2Si$ requires C, 48.9; H, 7.3%).

3-endo-*Dimethyl-t-butylsilyloxytricyclo*[3.2.0.$0^{2,7}$]*heptan-6-one* (5).—The heptan-6-one (4) (28.7 g, 90 mmol) in dry tetrahydrofuran was added to a suspension of potassium t-butoxide (16.73 g, 149.4 mmol) in dry tetrahydrofuran (100 ml), under nitrogen at −78 °C with stirring. After 1 h decolourising charcoal was added to the solution which was

[5] For an analogous reaction see J. T. Lumb and G. H. Whitham, *Chem. Comm.*, 1966, 400.

[6] A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Amer. Chem. Soc.*, 1972, **94**, 7827; C. J. Sih, P. Price, R. Sood, R. Salomon, G. Peruzzotti, and M. Casey, *ibid.*, p. 6260; J. W. Patterson and J. H. Fried, *J. Org. Chem.*, 1972, **39**, 2506; K. Ogura, M. Yamashita, and G. Tsuchihashi, *Tetrahedron Letters*, 1976, 759 and references therein.

[7] E. J. Corey and J. Mann, *J. Amer. Chem. Soc.*, 1973, **95**, 6832.

[8] Z. Grudzinski, S. M. Roberts, C. Howard, and R. F. Newton, *J.C.S. Perkin I*, 1978, 1182.

[9] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.

[10] *E.g.* synthesis of prostaglandin-C_2 and -E_2, N. M. Crossland, S. M. Roberts, R. F. Newton, and C. F. Webb, *J.C.S. Chem. Comm.*, 1978, 660.

then filtered through a bed of Celite. Evaporation of solvent afforded the ketone (5) as an oil which became crystalline on standing (100%), $\nu_{max.}$ 1 780, 1 250, and 1 080 cm^{-1}, $\delta(CDCl_3)$ 4.65 (1 H, m, H-3), 3.05 (2 H, m, H-1 and -7), 2.65 (2 H, m, H-2 and -5), 2.3—1.35 (2 H, m, H-4 *exo* and *endo*), 0.9 (9 H, s, Bu^t), and 0.1 (6 H, s, 2 × Me) (Found: C, 65.5; H, 9.3. $C_{13}H_{22}O_2Si$ requires, C, 65.5; H, 9.3%).

7-anti-(3-*Dimethyl-t-butylsilyloxyoct*-1-*enyl*)-5-endo-*dimethyl-t-butylsilyloxybicyclo*[2.2.1]*heptan*-2-*one* (7).—n-Butyl-lithium (5.4 g, 84 mmol) was added to a stirred solution of 3-dimethyl-t-butylsilyloxyoct-1-enyl iodide (30.0 g, 84 mmol) in dry light petroleum (60 ml) under argon at −78 °C. After 30 min a freshly prepared solution of pent-1-ynylcopper (10.7 g, 84 mmol) in dry diethyl ether (50 ml) and hexamethylphosphorus triamide (27.5 g, 168 mmol) was slowly added and the mixture was stirred for a further 20 min at −78 °C. A solution of the heptan-6-one (5) (20 g, 84 mmol) in dry diethyl ether (50 ml) was added. The yellow-orange solution was kept at − 78 °C for 2 h, warmed to −40 °C, and poured into a saturated aqueous ammonium chloride solution (50 ml). The organic layer was washed with ice-cold 2% sulphuric acid (150 ml), filtered to remove the copper salts, and washed with sodium hydrogencarbonate solution (2 × 100 ml). Drying and evaporation gave a yellow oil which, after column chromatography using increasing proportions of ethyl acetate in light petroleum as eluant, afforded the *bicycloheptanone* (7) as an oil (88%), $\nu_{max.}$ 1 740 cm^{-1} (Found: C, 67.3; H, 10.7. $C_{27}H_{52}O_3Si_2$ requires C, 67.4; H, 10.9%).

8-anti-(3-*Dimethyl-t-butylsilyloxyoct*-1-*enyl*)-6-endo-*dimethyl-t-butylsilyloxy*-2-*oxabicyclo*[3.2.1]*octan*-3-*one* (9).—30% Hydrogen peroxide (70 ml) and sodium acetate (10 g) were added to a stirred solution of the heptan-2-one (7) (11 g, 22.9 mmol) in glacial acetic acid (500 ml). The solution was stirred for 67 h at room temperature. Water (200 ml), sodium sulphite (40 g), and dichloromethane (2 × 200 ml), were added. After 1 h the organic layer was separated and neutralised with saturated potassium carbonate solution and washed with water (100 ml). Drying and evaporation gave an oil, which was purified by column chromatography with gradient elution of ethyl acetate in light petroleum, to give the *lactone* (9) (65%), $\nu_{max.}$ 1 740 and 1 250 cm^{-1} (Found C, 65.65; H, 10.6. $C_{22}H_{52}O_4Si_2$ requires C, 65.3; H, 10.8%).

8-anti-(3-*Dimethyl-t-butylsilyloxyoct*-1-*enyl*)-6-endo-*dimethyl-t-butylsilyloxy*-2-*oxabicyclo*[3.2.1]*octan*-3-*ol* (11).—A 20% solution of di-isobutylaluminium hydride in hexane (0.71 g, 5.0 mmol) was added to a light petroleum solution (20 ml) of the octan-3-one (9) (1 g, 2.5 mmol) under nitrogen at −70 °C. After 2 h the solution was diluted with water (10 ml) and washed with 2N-sulphuric acid (10 ml). The aqueous phase was separated and washed with light petroleum (2 × 30 ml). The combined organic layers were washed with 2N-sulphuric acid (2 × 20 ml), water (2 × 20 ml), and brine (20 ml) and dried. Evaporation afforded the *lactol* (11) as an oil (100%), $\nu_{max.}$ 3 300 and 1 720 cm^{-1} (Found: C, 64.7; H, 10.8. $C_{27}H_{54}O_4Si_2$ requires C, 65.0; H, 10.9%).

9α,15α-*Bisdimethyl-t-butylsilyloxy*-11α-*hydroxy*-5-cis,13-trans-*prostadienoic Acid* (13).—n-Butyl-lithium (0.4 g, 6.25 mmol) and 4-carboxybutyltriphenylphosphonium bromide (1.42 g, 3.2 mmol) in dry tetrahydrofuran were stirred under nitrogen for 15 min. A solution of the octan-3-ol (11) (0.8 g, 1.6 mmol) in dry tetrahydrofuran was then added to the deep red solution. After 18 h water (20 ml) was added followed by 2N-sulphuric acid (20 ml) and diethyl ether (50 ml). The organic layer was washed with sulphuric acid, water, and brine and then dried. Evaporation afforded a brown oil which, after t.l.c. with three elutions in 20% ethyl acetate–light petroleum, gave the acid (13) (40%), $\nu_{max.}$ 3 300, 1 710, and 1 250 cm^{-1}. The acid was converted to the *methyl ester* using diazomethane (Found: C, 65.9; H, 11.0. $C_{33}H_{64}O_5Si_2$ requires C, 66.3; H, 10.7%).

9α,11α,15α-*Trihydroxy*-5-cis,13-trans-*prostadienoic Acid* (1).—The acid (13) (87 mg, 0.15 mmol) was stirred in tetrahydrofuran (4 ml) containing 2N-hydrochloric acid (1 ml) for 5 days at ambient temperature. The solution was extracted with diethyl ether (20 ml) and the organic phase was washed with water (2 × 5 ml). Drying and evaporation afforded a yellow oil which, upon t.l.c. over silica using three elutions of 2% acetic acid–ethyl acetate, gave PG-$F_{2\alpha}$ (1) (45%) and 15-*epi*-PF-$F_{2\alpha}$ (14), both of which were identical (mass spectra, t.l.c.) with authentic samples.

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