

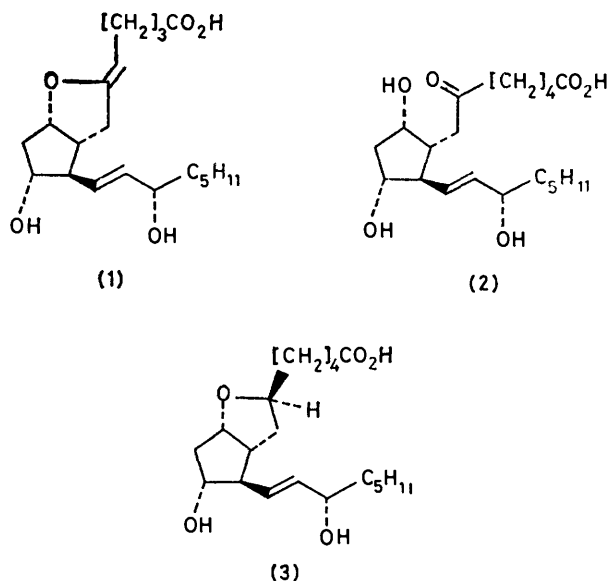
Synthesis of (\pm)-6 β -Prostaglandin I₁ and (\pm)-6 β -Decarboxyprostaglandin I₁

By Mark A. W. Finch and Stanley M. Roberts, Department of Chemistry, Salford University, Salford, Lancashire M5 4WT

Roger F. Newton,* Chemical Research Department, Glaxo Group Research Ltd., Ware, Hertfordshire SG12 0DJ

The known hydroxy-aldehyde (5) has been converted into 6 β -decarboxyprostaglandin I₁ (19) and 6 β -prostaglandin I₁ (3) by (i) reaction with an appropriate organometallic reagent, (ii) cyclisation *via* the intermediate formation of an iodonium ion, and (iii) hydrodeiodination and desilylation.

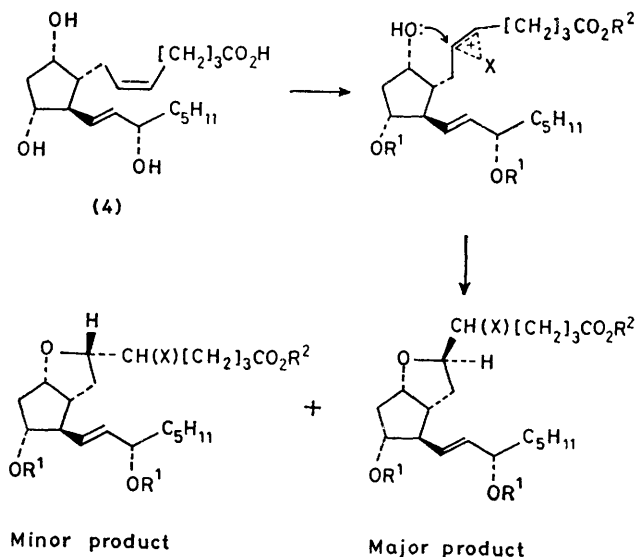
PROSTAGLANDIN I₂ (1) is a naturally occurring compound and a potent inhibitor of blood-platelet aggregation. The enol ether moiety renders the molecule unstable in aqueous solutions at pH < 7, hydrolysis giving the biologically inactive 6-oxoprostaglandin F_{1 α} (2). Stable analogues of prostaglandin I₂ have been sought as



potentially useful clinical drugs and in recent years 6 β -prostaglandin I₁ (3) has been shown to possess the desired stability to hydrolysis while retaining some of the desirable biological activity of the natural compound.¹

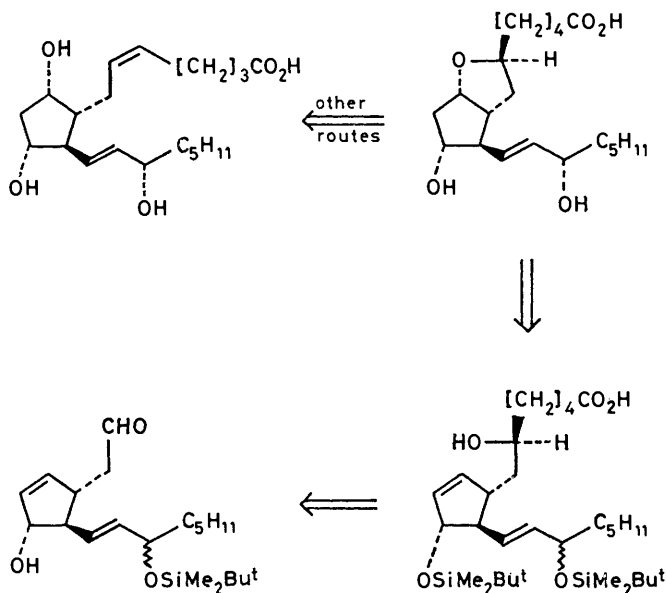
All but one of the reported syntheses of prostaglandin I₁ involve the modification of prostaglandin F_{2 α} (4) as described in Scheme 1.^{2,3} If necessary, the carboxylic acid group and the 11- and 15-hydroxy-groups are protected, before the 9-hydroxy-group is encouraged to attack C-6, by the formation of a halogenium ion or an organomercury ion from the *cis*-alkene unit. 6 β -Prostaglandin I₁ is available from the major product of this cyclisation process by straightforward transformations.

The other documented synthesis of prostaglandin I₁ involves the reduction of 6-oxoprostaglandin F_{1 α} using sodium cyanoborohydride in an acid medium.³ This method suffers from the inaccessibility of the starting ketone.

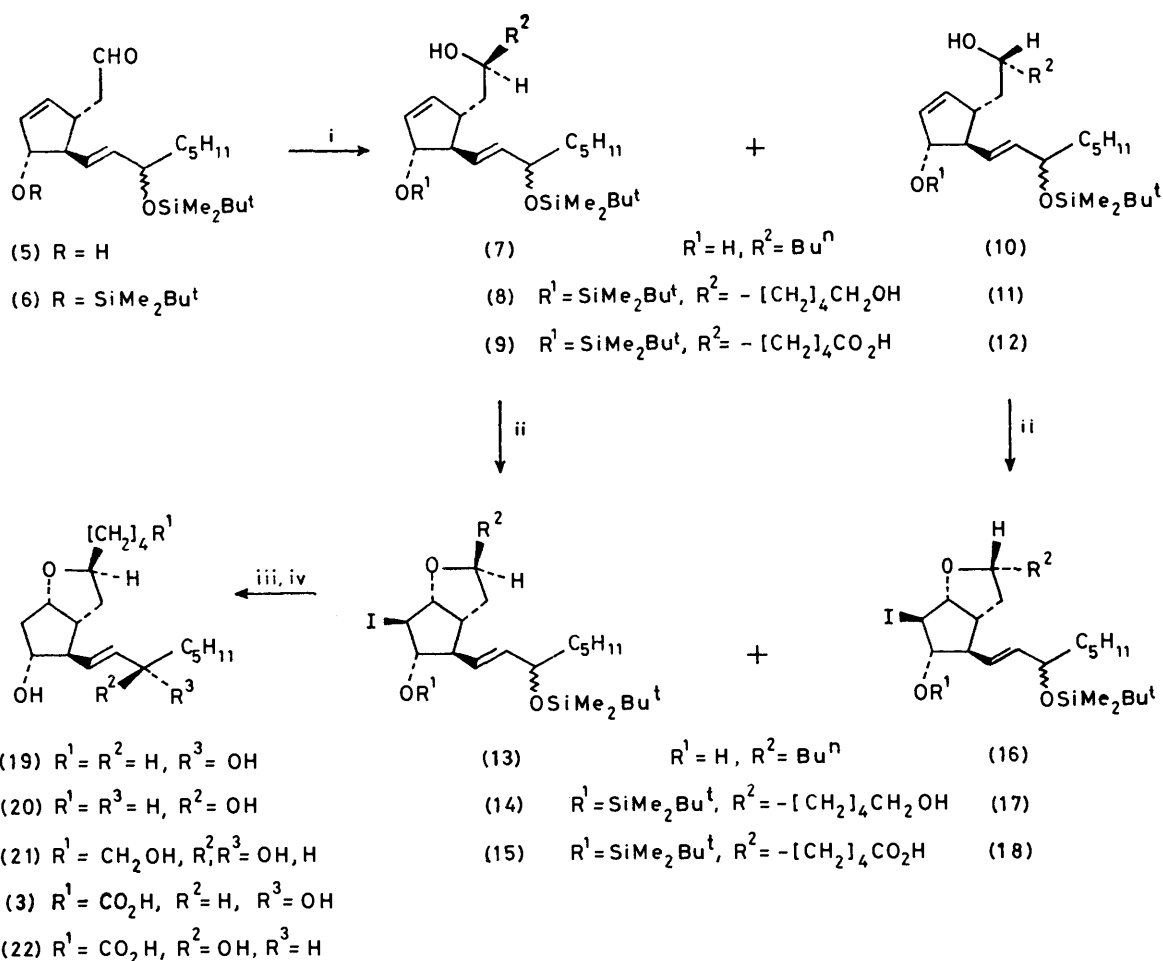


SCHEME 1

Our strategy to synthesise prostaglandin I₁ differed from the preceding examples in that the key cyclisation step was to involve a hydroxy-group on the carboxylic



SCHEME 2



SCHEME 3 Reagents: i, n-BuLi or (23) or (24); ii, KI₃, H₂O, NaHCO₃, ether; iii, n-Bu₃SnH, C₆H₆; iv, HF, H₂O, MeCN

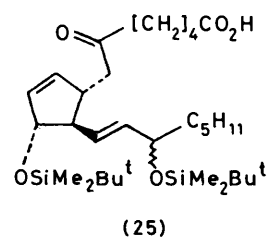
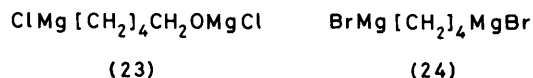
acid side-chain and an endocyclic alkene unit (Scheme 2). This retrosynthetic analysis led to the conclusion that the cyclopentenyl-acetaldehyde system (5) was a suitable synthon. We have already described the synthesis of the aldehyde (5) from bicyclo[3.2.0]hept-2-en-6-one⁴ and we now report that the compound (5) may be transformed readily into prostaglandin I₁ and analogues.⁵

RESULTS AND DISCUSSION

The aldehyde (5) was treated with n-butyl-lithium to give a pair of diastereoisomers (7) and (10) (ratio 1 : 1). These isomers were not separated. Treatment of the mixture with iodine and potassium iodide in a water-ether two-phase system gave the iodo-ether (13), a small amount of the isomeric ether (16), and recovered starting material that was rich in the diastereoisomer (10). The iodo-ether (13) was purified by chromatography and characterised by n.m.r. spectroscopy.^{3,6} Hydrodeiodination of (13) using tri-n-butyltin hydride and subsequent desilylation gave (±)-decarboxyprostaglandin I₁ (19) and (±)-15-*epi*-decarboxyprostaglandin I₁ (20) (Scheme 3).

Two routes to (±)-6β-prostaglandin I₁ (3) were investigated. In the first route, the silyloxyaldehyde (6)

was treated with the Grignard reagent (23)⁷ to give, after an aqueous work-up procedure, the diols (8) and (11) in almost quantitative yield. Treatment of these diastereoisomers with iodine and potassium iodide gave

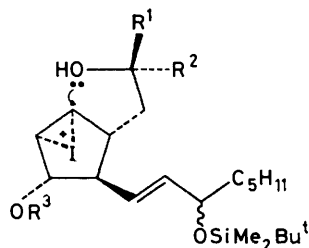


the iodo-ethers (14) and (17) in the ratio 5 : 1. Chromatography furnished a pure sample of the ether (14) (40%) (identified by n.m.r. spectroscopy) and allowed recovery of the starting material (40%) which was significantly enriched in the diol (11). The iodo-ether (14) was

hydrodeiodinated and desilylated to give the triol (21). The primary hydroxy-group of the latter compound was oxidised selectively, but in low yield, by oxygen in aqueous acetone containing reduced Adam's catalyst⁸ to give (\pm)-6 β -prostaglandin I₁ (3) (18%) and (\pm)-15-*epi*-6 β -prostaglandin I₁ (22) (18%). The 6 β -prostaglandin I₁, isolated in this manner, was identical (t.l.c. and n.m.r.) to an authentic sample and displayed the same profile of biological activity.

The second, novel route to prostaglandin I₁ commenced with reaction of the aldehyde (6) with the Grignard reagent (24).⁹ When consumption of the aldehyde (6) was judged complete by t.l.c., dried CO₂ gas was passed into the solution for a short time. The work-up procedure involved a sodium hydrogencarbonate wash to remove adipic acid formed from the unchanged reagent (24), and subsequent evaporation of the organic solvent gave only the hydroxy-acids (9) and (12). This mixture was treated with potassium tri-iodide to give mainly the iodo-ether (15) and the hydroxy-acid (12), and also a small amount of the ether (18). The starting material recovered from the cyclisation reaction was oxidised to the oxo-acid (25) (75%) using Collins' reagent.¹⁰ The oxo-acid (25) was reduced with sodium borohydride to give equal amounts of the hydroxy-acids (9) and (12) (100%). Cyclisation of (9) and (12) under the usual conditions gave a further quantity of the iodo-ether (15) (58%, based on recovered starting material). The iodo-ether (15) was desilylated and hydrodeiodinated to give (\pm)-6 β -prostaglandin I₁ (3) and (\pm)-15-*epi*-6 β -prostaglandin I₁ (22).

A key feature in the above synthetic work is the significantly faster rates of cyclisation of the unsaturated alcohols (7)–(9) compared with the corresponding isomers (10)–(12). The Figure illustrates why this effect



FIGURE

is observed. For the alcohols (7)–(9), the bulky substituent R¹ does not interact with the five-membered ring in the transition state for cyclisation, while for the isomers (10)–(12) a severe and unfavourable interaction between the bulky substituent R² and the cyclopentane ring must occur during the cyclisation process.

The total synthesis of prostaglandin I₂, using the same strategy, is in progress.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 297 spectrophotometer for neat films. ¹H N.m.r. spectra were recorded

on a Varian EM-360 or Perkin-Elmer R-32 spectrometer (CDCl₃ solvent). Mass spectra were determined after ionisation by electron impact at 70 eV (e.i.m.s.) or chemical ionisation using ammonia (c.i.m.s.). Camlab silica plates were used for t.l.c., Anachem Uniplates were used for thick layer chromatography, and Merck Kieselgel H was used for short column chromatography.¹¹ Light petroleum refers to the fraction of b.p. 60–80 °C and all solvents for chromatography were distilled before use. Anhydrous magnesium sulphate was used for drying solutions in organic solvents. N-Butyl-lithium was used as a 1.6M solution in hexane.

(\pm)-Decarboxyprostaglandin I₁ (19).—To a stirred solution of the aldehyde (5)⁴ (0.4 g), in dry diethyl ether under an atmosphere of nitrogen, was added n-butyl-lithium (2.2 equiv.). After 1 h, water (20 ml) and ether (40 ml) were added. The aqueous layer was separated and extracted with ether (40 ml). The combined organic extracts were washed with water (2 × 20 ml), dried, and evaporated *in vacuo*. The residue was chromatographed over silica using ethyl acetate in light petroleum as eluant to give the diols (7) and (10) (0.3 g); ν_{\max} 3350 cm⁻¹, δ 5.85 (2 H, m, 9-H and 10-H), 5.55 (2 H, m, 13-H and 14-H), 4.50 (1 H, m, 11-H), 4.0 (1 H, m, 15-H), 3.7 (1 H, m, 6-H), 2.5 (1 H, m, 8-H), 2.2 (1 H, m, 12-H), 1.8–1.1 (18 H, 8 × CH₂ and 2 × OH), 0.9 (15 H, m, 5 × Me), and 0.1 (6 H, s, SiMe₂); [Found (c.i.m.s.) ($M + NH_4$)⁺ 442.3722. C₂₅H₄₈O₃Si requires ($M + NH_4$) 442.3717].

The diols (7) and (10) (0.6 g) were dissolved in ether (50 ml) and vigorously stirred with an aqueous solution of sodium hydrogencarbonate (8%, 50 ml) containing iodine (0.4 g) and potassium iodide (0.8 g). After 24 h a saturated, aqueous solution of sodium sulphite (50 ml) and ether (50 ml) were added. The aqueous layer was separated and washed with ether (50 ml). The combined organic extracts were washed with water (2 × 30 ml), dried, and evaporated. The residue was chromatographed over silica using ethyl acetate in light petroleum as eluant to give the unchanged diols (7) and (10) (0.1 g) and the iodo-ether (13) (0.4 g); ν_{\max} 3450 cm⁻¹; δ 5.7 (2 H, m, 13-H and 14-H), 4.7 (1 H, m, 9-H), 4.2–3.7 (4 H, m, 6-H, 10-H, 11-H, and 15-H), 2.8–1.1 (19 H, m, 8 × CH₂, 8-H, 12-H, and OH), 0.9 (15 H, m, 5 × Me), and 0.1 (6 H, s, SiMe₂) [Found (c.i.m.s.) ($M + NH_4$)⁺ 568.2673. C₂₅H₄₇IO₃Si requires ($M + NH_4$) 568.2683].

The iodo-ether (13) (0.2 g) was dissolved in benzene (5 ml) and ethanol (2 ml) containing tri-n-butyltin hydride (0.12 g) and one crystal of azoisobutyronitrile. After heating to reflux for 1 h the solvents were evaporated. The residue was taken up in ether (25 ml) and shaken with a saturated, aqueous solution of potassium fluoride (20 ml). After filtration, the organic layer was separated, washed with water (20 ml), dried, and evaporated. The residue was chromatographed over silica using ethyl acetate in light petroleum as eluant to give an oil (0.13 g), homogeneous by t.l.c. A solution of 40% aqueous hydrofluoric acid in acetonitrile (10%, 5 ml) was added to the oil (25 mg). After 30 min, water (15 ml) and chloroform (20 ml) were added. The aqueous layer was separated and washed with chloroform (20 ml). The combined chloroform extracts were washed with water (2 × 20 ml), dried, and evaporated to give an oil (17 mg) which was separated into two components by chromatography using ethyl acetate in light petroleum as eluant. The less polar compound was (\pm)-15-*epi*-decarboxyprostaglandin I₁ (20) [Found (e.i.m.s.) M^+ 310.2492. C₁₉H₃₄O₃ requires M 310.2507] and the more

polar compound was (\pm)-*decarboxyprostaglandin I₁* (19); ν_{\max} 3 400 cm^{-1} , δ 5.5 (2 H, m, 13-H and 14-H), 4.4 (1 H, m, 9-H), 4.2—3.5 (3 H, m, 6-H, 11-H, and 15-H), 2.5—1.1 (22 H, m, 9 \times CH₂, 2 \times OH, 8-H, and 12-H), and 0.8 (6 H, m, 2 \times Me) [Found (e.i.m.s. on the bistrimethylsilyl derivative) M^+ 455.3410. C₂₅H₅₁O₅Si₂ requires M 455.3376].

(\pm)-6 β -*Prostaglandin I₁*.—(a) The aldehyde (5) was converted into the bis-silylated derivative (6) (72%) in the usual manner.¹² To a suspension of magnesium turnings (0.6 g) in dry tetrahydrofuran (THF) (20 ml) was added 1,4-dibromobutane (2.3 g) and one crystal of iodine. The reaction mixture was stirred for 30 min after reaction commenced then diluted with THF (25 ml) and cooled to 5 °C. To this solution was added the aldehyde (6) (1.5 g) in dry THF (15 ml) with stirring. After 30 min dried carbon dioxide gas was passed through the solution for 1 h. Hydrochloric acid (2M; 100 ml) and ether (100 ml) were added. The aqueous layer was separated and washed with ether (100 ml). The combined organic extracts were washed with water (100 ml) and a saturated aqueous solution of sodium hydrogencarbonate (100 ml). The combined, aqueous washes were extracted with ether (2 \times 30 ml). The combined organic fractions were dried and evaporated to give the acids (9) and (12) (0.92 g); ν_{\max} 3 400 and 1 710 cm^{-1} , δ 6.4 (2 H, m, 2 \times OH) 5.9—5.3 (4 H, m, 9-H, 10-H, 13-H, and 14-H), 4.3 (1 H, m, 11-H), 4.0 (1 H, m, 15-H), 3.6 (1 H, m, 6-H), 2.2 (2 H, m, 8-H and 12-H), 1.7—1.0 (18 H, m, 9 \times CH₂), 1.4 (21 H, m, 7 \times Me), and 0.1 (12 H, s, 2 \times SiMe₂). The acids (9) and (12) (0.8 g) were treated with iodine (0.5 g) and potassium iodide (0.9 g) as described above. Work-up gave an oil which was chromatographed over silica using ethyl acetate in light petroleum as eluant to give the starting material (0.4 g) and the *iodo-ether* (15) (0.28 g); ν_{\max} 3 400 and 1 710 cm^{-1} , δ 9.8 br (1 H, s, CO₂H), 5.6 (2 H, m, 13-H and 14-H), 4.7 (1 H, q, m, 9-H), 4.2—3.5 (4 H, m, 6-H, 10-H, 11-H, and 15-H), 2.6—1.1 (20 H, m, 9 \times CH₂, 8-H and 12-H), 0.9 (21 H, m, 7 \times Me), and 0.1 (12 H, s, 2 \times SiMe₂) [Found (e.i.m.s.) ($M - C_4H_9$)⁺ 651.2335. C₃₂H₆₁O₅Si₂ requires ($M - C_4H_9$) 651.2399]. The starting material (0.4 g) in dry dichloromethane (10 ml) was stirred with Collins' reagent¹⁰ (1.06 g) in dichloromethane (40 ml) for 30 min. The solvent was evaporated and ether (50 ml) was added. After filtration through Hyflo, the organic material was washed with hydrochloric acid (2M; 25 ml) and water (25 ml) and dried. Evaporation of the solvent gave an oil which was chromatographed over silica using ethyl acetate in chloroform to give the oxo-acid (25) (0.3 g), ν_{\max} 1 715 cm^{-1} , as an oil. This oil was stirred in ethanol containing sodium borohydride (0.2 g) for 2 h. The solvent was evaporated and the residue was dissolved in ether. The organic phase was washed with hydrochloric acid (2M; 20 ml) and water (20 ml), dried, and evaporated to give the acids (9) and (12) (0.3 g). Treatment of these acids with iodine and potassium iodide in the prescribed manner gave the *iodo-ether* (15) (0.1 g).

The *iodo-ether* (15) (0.28 g) was treated with a solution of 40% aqueous hydrofluoric acid in acetonitrile (20%, 10 ml), as described above. Work-up gave a colourless oil (0.17 g). This oil was treated with tri-*n*-butyltin hydride in the manner described above to give an oil (0.1 g) containing two components by t.l.c. Chromatography over silica using ethyl acetate in light petroleum as eluant gave, in the first fractions, (\pm) 15-*epi*-6 β -*prostaglandin I₁* (22) [Found (c.i.m.s.) ($M + NH_4$)⁺ 372.2727. C₂₀H₃₄O₅ requires ($M +$

NH₄) 372.2750]. Later fractions gave (\pm) 6 β -*prostaglandin I₁* (3); ν_{\max} 3 400 and 1 710 cm^{-1} , δ 5.5 (2-H, m, 13-H and 14-H), 5.05 (3 H, m, 3 \times OH), 4.45 (1 H, m, 9-H), 3.9 (3 H, m, 6-H, 11-H, and 15-H), 2.5—1.0 (22 H, m, 10 \times CH₂, 8-H, and 12-H), and 0.9 (3 H, m, Me) [Found (c.i.m.s.) ($M + NH_4$)⁺ 372.2795. C₂₀H₃₄O₅ requires ($M + NH_4$) 372.2750]. This material was identical (t.l.c., i.r., and n.m.r. spectroscopy) to an authentic sample prepared by the method of Johnson.³

(b) To a stirred solution of *n*-butylmagnesium chloride (0.37 g) in dry THF (10 ml) at -20 °C under an atmosphere of nitrogen was added chloropentanol (0.45 g). After 20 min, magnesium turnings (0.15 g) were added and the reaction mixture was heated to reflux for 1 h. Dibromoethane (12 mg) was added and heating under reflux was continued for 1 h. A second batch of dibromoethane (12 mg) was added. After 2 h at reflux, the solution was cooled to 0 °C and diluted with dry THF (20 ml). A solution of the aldehyde (6) (0.6 g) in dry THF (5 ml) was added, with stirring. After 30 min, a saturated, aqueous solution of ammonium chloride (50 ml) was added. This mixture was extracted with ether (2 \times 75 ml). The combined ether layers were washed with water (2 \times 50 ml), dried, and evaporated. The residue was chromatographed over silica using ethyl acetate in light petroleum as eluant to give the *diols* (8) and (11) (0.7 g); ν_{\max} 3 350 cm^{-1} , δ 5.65 (4 H, m, 9-H, 10-H, 13-H, and 14-H), 4.5 (1 H, m, 11-H), 4.0 (1 H, m, 15-H), 3.65 (3 H, m, 6-H and 2 \times 1-H), 2.5—1.0 (22 H, m, 9 \times CH₂, 2 \times OH, 8-H, and 12-H), 0.9 (21 H, m, 7 \times Me), and 0.1 (12 H, s, 2 \times SiMe₂) [Found (e.i.m.s.) M^+ 568.4323. C₃₂H₆₄O₄Si₂ requires M 568.4343]. The *diols* (8) and (11) (0.45 g) were treated with iodine and potassium iodide as described above. Work-up and chromatography gave the starting material (0.2 g) and the *iodo-ether* (14); ν_{\max} 3 380 cm^{-1} , δ 5.45 (2 H, m, 13-H, and 14-H), 4.7 (1 H, m, 9-H), 3.95 (6 H, m, 2 \times 1-H, 6-H, 10-H, 11-H, and 15-H), 2.6—1.1 (21 H, m, 9 \times CH₂, 8-H, 12-H, and OH), 0.9 (21 H, m, 7 \times Me), and 0.1 (12 H, s, 2 \times SiMe₂) [Found (e.i.m.s.) ($M - C_4H_9$)⁺ 637.2573. C₃₂H₆₃O₄Si₂ requires ($M - C_4H_9$) 637.2604]. The *iodo-ether* (14) (0.22 g) was hydrodeiodinated using tri-*n*-butyltin hydride as described above to give an oil (0.17 g) which, upon treatment with hydrofluoric acid under the usual conditions, gave the *triol* (21) (80%); ν_{\max} 3 380 cm^{-1} [Found (e.i.m.s.) ($M - O$)⁺ 324.2650. C₂₀H₃₆O₄ requires ($M - O$) 324.2663]. Adam's catalyst (8) (150 mg) in water (10 ml) was hydrogenated at atmospheric pressure for 30 min. To this suspension was added sodium hydrogencarbonate (150 mg) and a solution of the *triol* (21) in acetone and water (ratio 3 : 1, 12 ml). The reaction mixture was heated under reflux for 5 h while air was bubbled through continuously. Hydrochloric acid (2M; 30 ml) and ether (50 ml) were added. The aqueous layer was separated and extracted with ether (50 ml). The combined organic fractions were filtered through Hyflo, washed with water (2 \times 30 ml), and dried. Evaporation gave a residue which was chromatographed over silica to give 6 β -*prostaglandin I₁* and 15 *epi*-6 β -*prostaglandin I₁* identical (t.l.c., i.r., n.m.r., and mass spectroscopy) to the samples of these materials obtained above.

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REFERENCES

- ¹ R. A. Johnson and E. G. Nidy in 'Chemistry, Biochemistry and Pharmacological Activity of Prostanoids, eds. S. M. Roberts and F. Scheinmann, Pergamon Press, Oxford, 1979, p. 274.
- ² E. J. Corey, H. L. Pearce, I. Szekely, and M. Ishiguro, *Tetrahedron Lett.*, 1978, 1023 and references therein.
- ³ R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, W. P. Schneider, and U. Axen, *J. Am. Chem. Soc.*, 1978, **100**, 7690.
- ⁴ S. M. Ali, M. A. W. Finch, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 679; *ibid.*, 1980, 74.
- ⁵ Preliminary communication, M. A. W. Finch, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1980, 589.
- ⁶ I. Tomoskozi, G. Galambos, G. Kovacs, and L. Radics, *Tetrahedron Lett.*, 1978, 581.
- ⁷ G. Cahiez, A. Alexahis, and J. F. Normant, *Tetrahedron Lett.*, 1978, 3013.
- ⁸ J. Fried and J. C. Sih, *Tetrahedron Lett.*, 1973, 3899.
- ⁹ P. Canonne, G. Foscolos, and G. Lemay, *J. Chem. Soc., Chem. Commun.*, 1979, 691.
- ¹⁰ J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 1968, 3363.
- ¹¹ B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1967, 1868.
- ¹² E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.