

Synthesis of the key component for preparation of 6-keto-prostaglandins by a two-component coupling process: synthesis of 6-keto-prostaglandin E₁, ornoprostil and Δ²-trans-6-keto-prostaglandin E₁

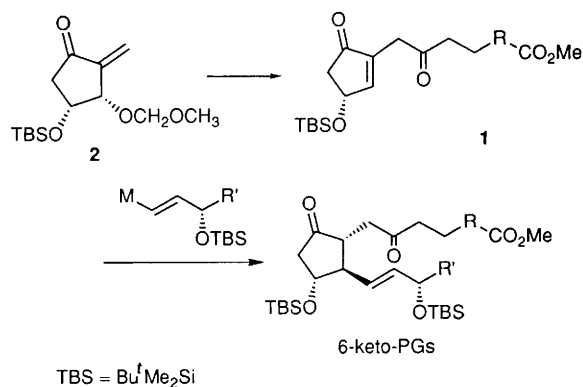
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Starting with commercially available (3*S*,4*R*)-3-(methoxymethoxy)-2-methylidene-4-siloxycyclopentanone **2**, useful 6-keto-prostaglandin intermediates **1** have been prepared in good yields by a sequence of reactions which includes treatment with NaBr in the presence of BF₃·OEt₂, Pd-catalysed coupling of the resulting 2-bromomethyl-4-siloxycyclopent-2-enone **3** with the alkenylborane **4** or **9** and conversion of the alkenyl moiety into an epoxy and then into a keto group. The synthesis of 6-keto-PGE₁, ornoprostil and Δ²-trans-6-keto-PGE₁ by using **1** is also described.

Naturally occurring 6-keto-prostaglandin E₁ (6-PGE₁) has attracted substantial interest, because it plays an important role in human physiology.¹ Artificial 6-keto-prostaglandins have also attracted much interest as being useful therapeutic agents,² and, since only chemical synthesis can supply sufficient quantities,³ much effort has been expended in this area.

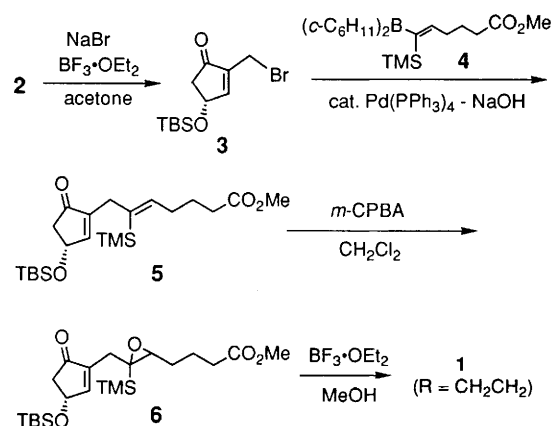
In connection with our interest in establishing a two-component coupling synthesis of PGs as an efficient and industrially viable process,⁴ we were interested in the development of a practical and general method for synthesis of 6-keto-PGs by this methodology. Herein reported is an efficient synthetic method for preparation of *endo*-enones **1** which have 6-keto α-side chains from readily available starting material **2**†,4a and synthesis of 6-keto-PGs by 1,4-addition of ω side-chain units to **1** (Scheme 1).



Scheme 1

Results and discussion

The synthetic procedure of **1** from **2** is summarized in Scheme 2. The reaction of **2** with NaBr in the presence of BF₃·OEt₂ provided 2-bromomethyl-4-siloxycyclopent-2-enone **3** in 89% yield. Coupling of **3** with the alkenylborane **4**, synthesized *in situ* by the hydroboration of the corresponding alkyne with



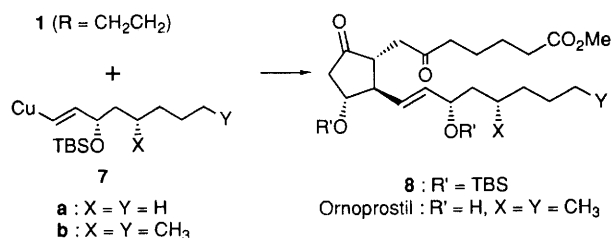
Scheme 2

BH(cyclo-C₆H₁₁)₂,⁵ in the presence of [Pd(PPh₃)₄] afforded **5** in 81% yield.⁶ The conversion of **5** into **1** (R = CH₂CH₂) was carried out in 73% overall yield by regiospecific epoxidation with *m*-chloroperbenzoic acid followed by treatment of the resulting crude compound **6** with BF₃·OEt₂.⁷

With compound **1** (R = CH₂CH₂) in hand, it was possible to synthesize 6-keto-PGs having a variety of ω side-chain units by 1,4-addition. Reported next is the synthesis of naturally occurring 6-keto-PGE₁ and ornoprostil which is currently marketed as an anti-ulcer agent (Scheme 3). Thus, the reaction of **1** (R = CH₂CH₂) with the alkenylcopper compound **7a** provided the bis-silyl ether of 6-keto-PGE₁ methyl ester **8a** in 74% yield. Similarly, ornoprostil was prepared by the reaction of **1** (R = CH₂CH₂) with the alkenylcopper compound **7b** (74%) and the following protodesilylation using HF-pyridine in acetonitrile (93%).

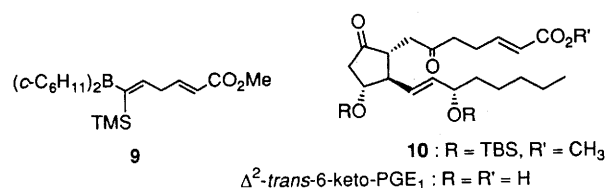
The present methodology also allows the synthesis of PGs having various 6-keto α side-chains other than natural ones by changing the alkenylboranes used for the coupling with **3** in Scheme 2. Although PGs having a *trans*-double bond at the 2 position (Δ²-*trans*-PGs) have attracted much pharmaceutical interest,⁸ Δ²-*trans*-6-keto-PGE₁ has not been developed. Thus, we were interested in synthesizing Δ²-*trans*-6-keto-PGE₁ by using the present methodology. The enone **1** [R = (*E*)-

† Commercially available from Nissan Chemical Industries, Ltd. (Japan).



Scheme 3

CH=CH] was prepared by using the alkenylborane **9**, generated *in situ* by the hydroboration of the corresponding alkyne with BH(cyclo-C₆H₁₁)₂, instead of **4** in the coupling step with **3** in Scheme 2 (48% overall yield from **3**). The reaction of **1** [R = (E)-CH=CH] with the organocopper compound **7a** afforded **10** in 71% yield which, in turn, was converted into Δ²-trans-6-keto-PGE₁ by successive treatment with HF-pyridine (95%) and porcine liver esterase (84%).



In summary, a highly efficient method for the synthesis of **1**, the key intermediate for the preparation of 6-keto-PGs, has been developed, which involves (i) the preparation of 2-bromomethyl-4-siloxycyclopent-2-enone **3** from commercially available **2**, (ii) the Suzuki–Miyaura coupling reaction of **3** with alkenylboranes and (iii) the conversion of the vinylsilane moiety of the coupling product into the keto group.

Experimental

IR spectra were determined using a JASCO A-100 spectrophotometer. ¹H and ¹³C NMR spectra were determined in CDCl₃ (SiMe₄ or residual CHCl₃ as internal reference) using a Varian Gemini-300 spectrometer operating at 300 MHz for ¹H NMR or at 75 MHz for ¹³C NMR. The *J* values are in Hz. [α]_D values were determined using a JASCO DIP-370 polarimeter. Mass spectra (FAB-HRMS) were measured with a JEOL JMX-102 spectrometer. Column chromatography was carried out with Wako Silica gel C-200 (100–200 mesh) and TLC was carried out with Merck Kieselgel 60 F₂₅₄.

(R)-2-Bromomethyl-4-(tert-butyldimethylsiloxy)cyclopent-2-enone **3**

Sodium bromide (2.33 g, 22.69 mmol) and boron trifluoride-diethyl ether (1.54 cm³, 12.49 mmol) were added under an atmosphere of dry argon to a solution of **2** (3.25 g, 11.35 mmol) in acetone (57 cm³) at ambient temperature. After being stirred for 0.5 h, the mixture was poured into a stirred mixture of saturated aqueous NaHCO₃ (100 cm³) and ether (150 cm³). The organic layer was separated and the aqueous layer was extracted with hexane (50 cm³). The combined organic layers were washed with saturated aqueous Na₂S₂O₃ and saturated aqueous NaHCO₃ (50 cm³), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **3** (3.1 g, 89%) as a clear oil; [α]_D²⁵ + 28.4 (*c* 1.09 in CHCl₃); ν_{max}/cm⁻¹ 2930, 2852, 1710, 1460, 1342, 1250, 1082, 906, 830 and 775; δ_H 0.12 and 0.14 (each 3 H, 2 s), 0.90 (9 H, s), 2.36 (1 H, dd, *J* 18.0, 2.2), 2.83 (1 H, dd, *J* 18.0, 6.0), 4.02 (2 H, s), 4.91–4.97 (1 H, m) and 7.38–7.41 (1 H, m); δ_C –4.7 (2 C), 18.1, 21.0, 25.9 (3 C), 45.6, 68.6, 142.9, 160.5 and 202.8 (Found: C, 47.5; H, 7.0. C₁₂H₂₁BrO₂Si requires C, 47.2; H, 6.9%).

(R)-4-(tert-Butyldimethylsiloxy)-2-[(Z)-6-methoxycarbonyl-2-trimethylsilylhex-2-enyl]cyclopent-2-enone **5**

Under an atmosphere of dry argon, cyclohexene (0.2 cm³, 2.0 mmol) was added to a solution of borane–tetrahydrofuran (1 mol dm⁻³; 1.0 cm³, 1.0 mmol) in tetrahydrofuran at 0 °C. After being stirred for 1.5 h at 0 °C, the mixture was treated with a solution of methyl 6-trimethylsilylhex-5-ynoate (0.20 g, 1.0 mmol; prepared from 6-trimethylsilylhex-5-ynoic acid⁹ by treatment with a catalytic amount of concentrated H₂SO₄ and MeOH at room temperature for 10 h) in tetrahydrofuran (1.5 cm³). The resulting mixture was stirred for 1 h at ambient temperature to afford a solution of the alkenylborane reagent **4** (theoretically 0.345 mol dm⁻³). In a separate flask, [Pd(PPh₃)₄] (19 mg, 0.0164 mmol), a solution of the alkenylborane **4** prepared above and aqueous 3 mol dm⁻³ NaOH (0.22 cm³, 0.656 mmol) were added to a solution of compound **3** (100 mg, 0.327 mmol) in benzene (3.3 cm³) at ambient temperature. The resulting mixture was stirred at 65 °C for 1 h after which it was cooled to ambient temperature and extracted with ether (2 × 5 cm³). The combined extracts were washed with aqueous 1 mol dm⁻³ HCl (3 cm³) and saturated brine (5 cm³), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **5** (112 mg, 81%) as a clear oil; [α]_D²⁵ + 5.54 (*c* 1.03 in CHCl₃); ν_{max}/cm⁻¹ 2960, 2852, 1710, 1435, 1350, 1248, 1160, 1078, 835 and 775; δ_H 0.09 and 0.11 (each 3 H, 2 s), 0.08 (9 H, s), 0.89 (9 H, s), 1.65–1.77 (2 H, m), 2.15–2.25 (3 H, m), 2.33 (1 H, d, *J* 7.5), 2.74 (1 H, dd, *J* 18.3, 5.9), 2.80–2.95 (1 H, m), 3.67 (3 H, s), 4.82–4.88 (1 H, m), 5.93 (1 H, t, *J* 7.2) and 6.88–6.93 (1 H, m); δ_C –4.71 (2 C), 0.13 (3 C), 18.0, 25.1, 25.7 (3 C), 31.3, 32.8, 33.5, 45.7, 51.5, 68.7, 136.4, 144.6, 147.2, 157.8, 173.8 and 205.5 [Found: *m/z* (FAB-HRMS) M + K⁺, 463.2075. C₂₂H₄₀KO₄Si₂ requires *MK*⁺, 463.2102].

(R)-4-(tert-Butyldimethylsiloxy)-2-(6-methoxycarbonylhexan-2-on-1-yl)cyclopent-2-enone **1** (R = CH₂CH₂)

m-Chloroperoxybenzoic acid [70% (0.463 g); net: 0.324 g, 1.88 mmol] was added to a solution of **5** (613 mg, 1.44 mmol) in dichloromethane (14 cm³) and the mixture was stirred at ambient temperature for 1 h. After this the mixture was treated with saturated aqueous NaHCO₃ (10 cm³) and diluted with diethyl ether (10 cm³). The organic layer was separated, dried (MgSO₄) and concentrated under reduced pressure to give crude compound **6**, which was used in the next reaction without purification.

Boron trifluoride–diethyl ether (2–3 drops, *ca.* 100 mm³) was added to a solution of the crude compound **6** in MeOH (14 cm³) at 0 °C. After being stirred for 0.5 h the mixture was treated with saturated aqueous NaHCO₃ (10 cm³) and diluted with ether (10 cm³). The organic layer was separated, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **1** (R = CH₂CH₂) (388 mg, 73% from **5**) as a clear oil; [α]_D²⁵ –3.90 (*c* 0.93 in CHCl₃); ν_{max}/cm⁻¹ 2940, 2850, 1710, 1630, 1455, 1430, 1400, 1340, 1240, 1190, 1160, 1079, 960, 906, 828 and 768; δ_H 0.11 and 0.12 (each 3 H, 2 s), 0.90 (9 H, s), 1.55–1.70 (4 H, m), 2.27 (1 H, dd, *J* 18.3, 2.1), 2.26–2.36 (2 H, m), 2.48–2.55 (2 H, m), 2.76 (1 H, dd, *J* 18.3, 5.9), 3.22 (1 H, d, *J* 17.3), 3.39 (1 H, d, *J* 17.3), 3.65 (3 H, s), 4.94–4.99 (1 H, m) and 7.30–7.32 (1 H, m); δ_C –4.7 (2 C), 18.1, 23.0, 24.3, 25.8 (3 C), 33.7, 37.7, 42.6, 44.7, 51.5, 69.2, 139.4, 160.3, 173.7, 205.2 and 205.6; FAB-HRMS [Found (FAB-HRMS): M + K⁺, 407.1677. C₁₉H₃₂KO₅Si requires *MK*⁺, 407.1656].

Methyl (E)-6-trimethylsilylhex-2-en-5-ynoate

A solution of trimethylsilyl ethynylmagnesium bromide in tetrahydrofuran [93.5 mmol, prepared from trimethylsilylacetylene (13.2 cm³, 93.5 mmol) by treatment with ethylmagnesium bromide (2.06 mol dm⁻³ in tetrahydrofuran; 45.4 cm³, 95.3 mmol) in tetrahydrofuran (187 cm³) at 0 °C for 1 h] was

added dropwise under an atmosphere of argon to a mixture of CuBr (1.22 g, 8.50 mmol) and methyl (*E*)-4-bromobut-2-enoate (10.0 cm³, 85.0 mmol) in tetrahydrofuran (50 cm³) at -10°C . The resulting mixture was stirred at 0°C for 1 h and then at room temperature for 1 h. After addition of saturated aqueous NH₄Cl (150 cm³) and ether (200 cm³) to the mixture, the organic layer was separated and the aqueous layer was extracted with ether (100 cm³). The combined organic layers were dried (MgSO₄), concentrated under reduced pressure and passed through a short silica gel column to give the title ester (13.7 g, 82%) as a light brown oil which was sufficiently pure as obtained for the following reaction; $\nu_{\text{max}}/\text{cm}^{-1}$ 2970, 2180, 1728, 1660, 1440, 1420, 1340, 1278, 1269, 1175, 1070, 1050, 1020, 990, 938, 850, 760 and 700; δ_{H} 0.16 (9 H, s), 3.15 (2 H, dd, *J* 2.0, 5.2), 3.73 (3 H, s), 6.12 (1 H, dt, *J* 2.0, 15.4), 6.89 (1 H, dt, *J* 5.2, 15.4); δ_{C} -0.07 (3 C), 22.9, 51.5, 88.6, 100.8, 122.6, 142.3 and 166.6.

(*R*)-4-(*tert*-Butyldimethylsiloxy)-2-[(2*Z*,5*E*)-6-methoxycarbonyl-2-trimethylsilylhex-2,5-dienyl]cyclopent-2-enone

According to the same procedure described above for preparation of compound **5**, the title compound (1.01 g, 81%) was synthesized from **3** (0.900 g, 2.94 mmol) and methyl (*E*)-6-trimethylsilylhex-2-en-5-ynoate (785 mg, 4.0 mmol) using BH₃·THF (1.0 mol dm⁻³ in THF; 4.0 cm³, 4.0 mmol), cyclohexene (0.81 cm³, 8.0 mmol), THF (5.5 cm³), [Pd(PPh)₄] (102 mg, 0.088 mmol, 3 mol %), 3 mol dm⁻³ NaOH (2.7 cm³, 8.1 mmol) and benzene (33 cm³) as a clear oil; $[\alpha]_{\text{D}}^{22} + 2.14$ (*c* 0.58 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$ 2930, 2870, 1718, 1660, 1620, 1470, 1440, 1410, 1350, 1330, 1260, 1200, 1170, 1080, 1010, 901, 840, 780 and 760; δ_{H} 0.09 and 0.10 (15 H, *ca.* 1:2, 2 s), 0.88 (9 H, s), 2.28 (1 H, dd, *J* 18.3, 2.0), 2.75 (1 H, dd, *J* 18.3, 5.9), 2.88–3.01 (2 H, m), 3.03–3.11 (2 H, m), 3.72 (3 H, s), 4.81–4.92 (1 H, m), 5.83 (1 H, dt, *J* 15.7, 1.7), 5.94 (1 H, t, *J* 7.5), 6.89–6.94 (1 H, m) and 6.96 (1 H, dt, *J* 15.7, 6.2); δ_{C} -4.7 (2 C), 0.09 (3 C), 18.0, 25.7 (3 C), 32.7, 34.5, 45.6, 51.4, 68.7, 121.5, 139.1, 139.4, 146.6, 146.9, 158.0, 166.8 and 205.4.

(*R*)-4-(*tert*-Butyldimethylsiloxy)-2-[(*E*)-6-methoxycarbonyl-2-oxohex-5-enyl]cyclopent-2-enone **1 [R = (*E*)-CH=CH-]**

By a procedure similar to that described for the preparation of **1** (R = CH₂CH₂) from **5**, compound **1** [R = (*E*)-CH=CH] (519 mg, 59%) was synthesized from (*R*)-4-(*tert*-butyldimethylsiloxy)-2-[(2*Z*,5*E*)-6-methoxycarbonyl-2-trimethylsilylhex-2,5-dien-1-yl]cyclopent-2-enone (1.01 g, 2.389 mmol) as a clear oil; $[\alpha]_{\text{D}}^{21} + 3.89$ (*c* 0.72 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$ 2930, 2860, 1710, 1660, 1420, 1350, 1280, 1250, 1200, 1170, 1080, 970, 905, 820 and 780; δ_{H} 0.11 and 0.12 (each 3 H, 2 s), 0.89 (9 H, s), 2.27 (1 H, dd, *J* 18.3, 2.1), 2.42–2.54 (1 H, m), 2.62–2.70 (2 H, m), 2.76 (1 H, dd, *J* 18.3, 5.9), 3.23 (1 H, d, *J* 17.2), 3.41 (1 H, d, *J* 17.2), 3.71 (3 H, s), 4.93–5.04 (1 H, m), 5.82 (1 H, dt, *J* 15.7, 1.6), 6.90 (1 H, dt, *J* 15.7, 6.8) and 7.28–7.39 (1 H, m); δ_{C} -4.7 (2 C), 18.1, 25.8 (3 C), 25.9, 37.8, 40.9, 44.7, 51.4, 69.2, 121.8, 139.2, 147.1, 160.5, 166.8, 204.2 and 205.1 [Found (FAB-HRMS): M + K⁺, 405.1509. C₁₉H₃₀KO₅Si requires MK⁺, 405.1500].

General procedure for the synthesis of 6-keto-PGs from the enone **1**

Bu^tLi (1.7 mol dm⁻³ in pentane; 3.0 mmol) was added under an atmosphere of dry argon to a solution of (*S,E*)-3-(*tert*-butyldimethylsiloxy)-1-iodooct-1-ene,^{†4} or (3*S*,5*S,E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-5-methylnon-1-ene,^{†4} (1.5 mmol, >99% ee⁴) in ether (10 cm³) at -78°C . After the mixture had been stirred for 30 min at this temperature, 2-thienyl(cyano)-copper lithium (0.25 mol dm⁻³ in THF, 7.2 cm³; 1.8 mmol) was added to it at -78°C . Stirring was continued at this temperature for 30 min after which a solution of **1** (1.0 mmol) in ether (5 cm³) was added dropwise to the mixture. After this had been stirred at -78°C for 1 h, the mixture was poured

into a stirred mixture of hexane (30 cm³) and sat. aq. NH₄Cl (30 cm³). The organic layer was separated and the aqueous layer was extracted with hexane (20 cm³). The combined organic layers were washed with brine (20 cm³), dried (MgSO₄), concentrated under reduced pressure and purified by column chromatography on silica gel to afford the bis-silyl ether of 6-keto-PG methyl ester.

Desilylation (HF-pyridine, pyridine, MeCN)³ and hydrolysis of the methyl ester moiety (PLE, phosphate buffer, acetone)¹⁰ of bis-silyl ether of PG methyl ester were carried out according to the customary literature procedures for the synthesis of PGEs.

Bis-*tert*-butyldimethylsiloxy ether of 6-keto-prostaglandin E₁ methyl ester **8a**

Reaction of compound **1** (R = CH₂CH₂), (80.0 mg, 0.217 mmol) with **7a** [0.326 mmol, prepared *in situ* as described in the general procedure from (*S,E*)-3-(*tert*-butyldimethylsiloxy)-1-iodooct-1-ene (120.1 mg, 0.326 mmol) and Bu^tLi (0.652 mmol) gave **8a** (98 mg, 74%); $[\alpha]_{\text{D}}^{21} - 38.6$ (*c* 0.46 in MeOH), lit.,^{3b} $[\alpha]_{\text{D}}^{22} - 39.3$ (*c* 1.04 in MeOH).

Bis-*tert*-butyldimethylsiloxy ether of ornoprostil **8b**

Reaction of compound **1** (R = CH₂CH₂) (79.0 mg, 0.214 mmol) with **7b** [0.321 mmol, prepared *in situ* as described in the general procedure from (3*S*,5*S,E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-5-methylnon-1-ene (127.2 mg, 0.321 mmol) and Bu^tLi (0.642 mmol) gave **8b** (101 mg, 74%) as a clear oil; $[\alpha]_{\text{D}}^{21} - 37.5$ (*c* 1.164 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$ 2930, 2850, 1736, 1718, 1460, 1430, 1360, 1240, 1155, 1093, 1050, 1000, 965, 937, 870, 830 and 770; δ_{H} 0.01 and 0.04 (each 6 H, s), 0.78–0.92 (6 H, m), 0.86 and 0.87 (each 9 H, s), 0.98–1.70 (13 H, m), 2.10–2.70 (10 H, m), 3.65 (3 H, s), 4.02–4.20 (2 H, m), 5.43–5.56 (2 H, m); δ_{C} -4.72 , -4.68 , -4.57 , -4.14 , 14.1, 18.0, 18.2, 20.0, 23.1, 24.4, 25.6, 25.8 (3 C), 25.9 (3 C), 29.1, 29.2, 33.8, 36.8, 39.9, 42.4, 46.2, 46.8, 49.6, 51.5, 52.8, 71.1, 73.4, 128.4, 136.8, 173.7, 207.5 and 214.2.

Ornoprostil

Treatment of compound **8b** (58.2 mg, 0.091 mmol) with HF-pyridine (0.154 cm³) and pyridine (0.18 cm³) in MeCN (3.0 cm³) at room temperature for 4 h gave ornoprostil (34.8 mg, 93%); $[\alpha]_{\text{D}}^{26} - 41.6$ (*c* 0.52 in MeOH), lit.,^{3c} $[\alpha]_{\text{D}}^{25} - 44.9$ (*c* 0.44 in MeOH).

Bis-*tert*-butyldimethylsilyl ether of Δ^2 -*trans*-6-keto-prostaglandin E₁ methyl ester **10**

Reaction of compound **1** [R = (*E*)-CH=CH] (27 mg, 0.0737 mmol) with **7a** (0.111 mmol) gave **10** (31.8 mg, 71%) as a clear oil; $[\alpha]_{\text{D}}^{21} - 43.4$ (*c* 0.67 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$ 2930, 2860, 1720, 1660, 1485, 1440, 1410, 1370, 1260, 1160, 1100, 1010, 970, 870, 840 and 780; δ_{H} 0.03 and 0.04 (each 6 H, s), 0.86–0.88 (21 H, m), 1.15–1.50 (8 H, m), 2.25–2.75 (10 H, m), 3.71 (3 H, s), 4.03–4.14 (2 H, m), 5.47 (1 H, dd, *J* 15.4, 6.6), 5.55 (1 H, dd, *J* 15.4, 4.4), 5.81 (1 H, d, *J* 15.7) and 6.91 (1 H, dt, *J* 15.7, 6.5); δ_{C} -4.75 , -4.70 , -4.60 , -4.30 , 14.0, 18.0, 18.2, 22.6, 25.0, 25.7 (4 C), 25.9 (3 C), 31.8, 38.4, 39.8, 40.8, 46.6, 49.9, 51.4, 53.1, 72.5, 73.2, 121.7, 128.1, 137.1, 147.2, 166.7, 206.0 and 214.0.

Δ^2 -*trans*-6-Keto-prostaglandin E₁ methyl ester

Treatment of compound **10** (31.8 mg, 0.0524 mmol) with HF-pyridine (0.1 cm³) and pyridine (0.11 cm³) in MeCN (1.9 cm³) at room temperature for 4 h gave Δ^2 -*trans*-6-keto-prostaglandin E₁ methyl ester (18.9 mg, 95%) as a sticky oil; $[\alpha]_{\text{D}}^{22} - 55.1$ (*c* 0.41 in CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$ 3375, 2920, 2860, 1710, 1660, 1440, 1410, 1320, 1280, 1200, 1160, 1070, 1040, 970, 850 and 750; δ_{H} 0.80–0.95 (3 H, m), 1.15–1.60 (8 H, m), 2.30–

[†] The spectroscopic data for **8a** and ornoprostil were in good agreement with the literature ones (see refs. 2, 3b and 3c).

2.83 (10 H, m), 3.71 (3 H, s), 4.01–4.16 (2 H, m), 5.51 (1 H, dd, J 15.2, 7.8), 5.61 (1 H, dd, J 15.2, 6.6), 5.81 (1 H, d, J 15.7) and 6.90 (1 H, dt, J 15.7, 6.6); δ_{C} 14.0, 22.6, 25.1, 25.9, 31.6, 37.2, 39.8, 40.9, 45.1, 50.4, 51.5, 54.2, 72.0, 72.6, 121.7, 130.4, 137.5, 147.2, 166.8, 206.4 and 213.0.

Δ^2 -trans-6-Keto-prostaglandin E₁

Treatment of Δ^2 -trans-6-keto-prostaglandin E₁ methyl ester (18.9 mg, 0.0498 mmol) with porcine liver esterase (50 mm³, ca. 120 units/ethyl butyrate, Sigma) in acetone (0.97 cm³) and phosphate buffer (2.32 cm³; pH 8) at room temperature for 6 h gave Δ^2 -trans-6-keto-prostaglandin E₁ (15.3 mg, 84%) as a sticky oil; $[\alpha]_{\text{D}}^{22}$ –48.1 (c 0.20 in MeOH); ν_{max} /cm^{–1} 3350, 2910, 2849, 1700, 1650, 1400, 1370, 1280, 1240, 1210, 1160, 1070, 960, 850 and 750; δ_{H} 0.80–1.00 (3 H, m), 1.05–1.65 (8 H, m), 2.31–2.72 (9 H, m), 2.78 (1 H, dd, J 18.4, 7.4), 4.01–4.17 (2 H, m), 5.45–5.65 (2 H, m), 5.80 (1 H, d, J 15.7) and 6.95 (1 H, dt, J 15.7, 6.3); δ_{C} 14.0, 22.6, 25.2, 26.0, 31.6, 37.0, 40.0, 40.6, 45.2, 50.4, 53.9, 72.1, 72.7, 121.6, 130.4, 137.5, 149.0, 170.0, 206.5 and 213.2.

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Paper 5/05342K

Received 9th August 1995

Accepted 25th September 1995