Synthesis of the key component for preparation of 6-keto-prostaglandins by a two-component coupling process: synthesis of 6-keto-prostaglandin E_1, ornoprostil and Δ^2-*trans*-6-keto-prostaglandin E_1

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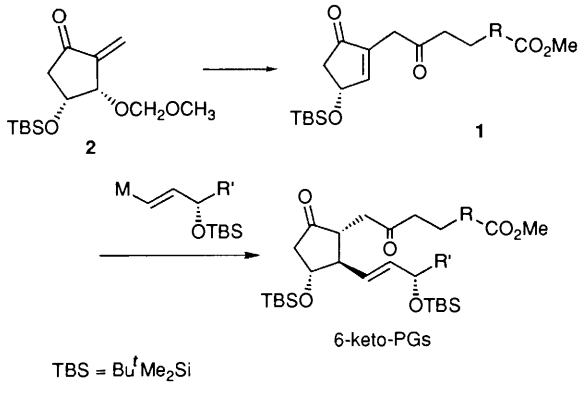
Starting with commercially available (3*S*,4*R*)-3-(methoxymethyloxy)-2-methylidene-4-siloxycyclopentanone 2, useful 6-keto-prostaglandin intermediates 1 have been prepared in good yields by a sequence of reactions which includes treatment with NaBr in the presence of BF_3·OEt_2, Pd-catalysed coupling 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-PGE_1, ornoprostil and Δ^2-*trans*-6-keto-PGE_1 by using 1 is also described.

Naturally occurring 6-keto-prostaglandin E_1 (6-PGE_1) 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.

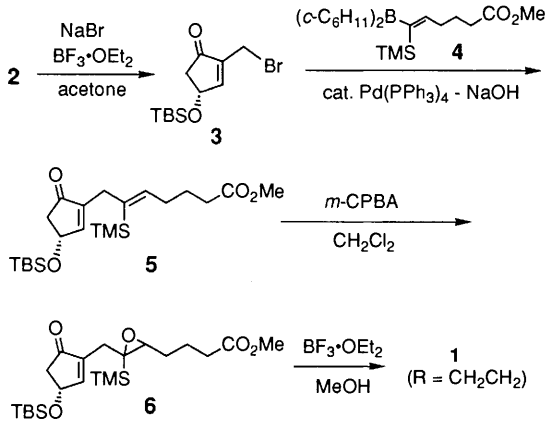
In connection with our interest in establishing a two-component coupling synthesis of PGs as an efficient and industrially viable process,[4] we were interested in the development of a practical and general method for synthesis of 6-keto-PGs by this methodology. Herein reported is an efficient synthetic 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 BF_3·OEt_2 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



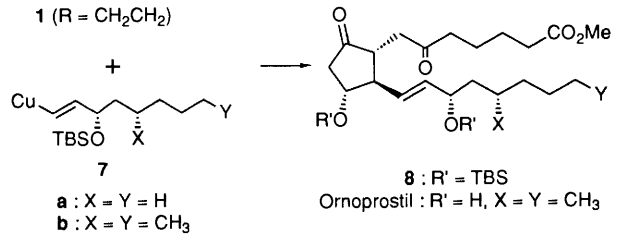
Scheme 2

$BH(cyclo\text{-}C_6H_{11})_2$,[5] in the presence of $[Pd(PPh_3)_4]$ afforded **5** in 81% yield.[6] The conversion of **5** into **1** (R = CH_2CH_2) was carried out in 73% overall yield by regiospecific epoxidation with *m*-chloroperbenzoic acid followed by treatment of the resulting crude compound **6** with BF_3·OEt_2.[7]

With compound **1** (R = CH_2CH_2) 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 occuring 6-keto-PGE_1 and ornoprostil which is currently marketed as an anti-ulcer agent (Scheme 3). Thus, the reaction of **1** (R = CH_2CH_2) with the alkenylcopper compound **7a** provided the bis-silyl ether of 6-keto-PGE_1 methyl ester **8a** in 74% yield. Similarly, ornoprostil was prepared by the reaction of **1** (R = CH_2CH_2) with the alkenylcopper compound **7b** (74%) and the following protodesilylation using HF–pyridine in acetonitrile (93%).

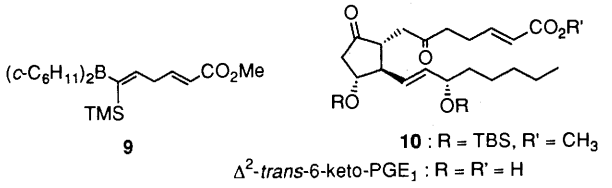
The present methodology also allows the synthesis of PGs having various 6-keto α side-chains other than natural ones by changing the alkenylboranes used for the coupling with **3** in Scheme 2. Although PGs having a *trans*-double bond at the 2 position (Δ^2-*trans*-PGs) have attracted much pharmaceutical interest,[8] Δ^2-*trans*-6-keto-PGE_1 has not been developed. Thus, we were interested in synthesizing Δ^2-*trans*-6-keto-PGE_1 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-C_6H_{11})$_2$, 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 Δ^2-*trans*-6-keto-PGE_1 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. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ ($SiMe_4$ or residual $CHCl_3$ as internal reference) using a Varian Gemini-300 spectrometer operating at 300 MHz for ^{1}H NMR or at 75 MHz for ^{13}C NMR. The *J* values are in Hz. $[\alpha]_D$ 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 F_{254}.

(*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 cm^3, 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 cm^3) at ambient temperature. After being stirred for 0.5 h, the mixture was poured into a stirred mixture of saturated aqueous $NaHCO_3$ (100 cm^3) and ether (150 cm^3). The organic layer was separated and the aqueous layer was extracted with hexane (50 cm^3). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (50 cm^3), dried ($MgSO_4$) 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; $[\alpha]_D^{25}$ +28.4 (*c* 1.09 in $CHCl_3$); 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. $C_{12}H_{21}BrO_2Si$ 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 cm^3, 2.0 mmol) was added to a solution of borane–tetrahydrofuran (1 mol dm^{-3}; 1.0 cm^3, 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 acid[9] by treatment with a catalytic amount of concentrated H_2SO_4 and MeOH at room temperature for 10 h) in tetrahydrofuran (1.5 cm^3). 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, [$Pd(PPh_3)_4$] (19 mg, 0.0164 mmol), a solution of the alkenylborane **4** prepared above and aqueous 3 mol dm^{-3} NaOH (0.22 cm^3, 0.656 mmol) were added to a solution of compound **3** (100 mg, 0.327 mmol) in benzene (3.3 cm^3) 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 cm^3). The combined extracts were washed with aqueous 1 mol dm^{-3} HCl (3 cm^3) and saturated brine (5 cm^3), dried ($MgSO_4$) 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; $[\alpha]_D^{25}$ +5.54 (*c* 1.03 in $CHCl_3$); 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. $C_{22}H_{40}KO_4Si_2$ requires *M*K$^+$, 463.2102].

(*R*)-4-(*tert*-Butyldimethylsiloxy)-2-(6-methoxycarbonylhexan-2-on-1-yl)cyclopent-2-enone 1 (R = CH_2CH_2)

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 cm^3) and the mixture was stirred at ambient temperature for 1 h. After this the mixture was treated with saturated aqueous $NaHCO_3$ (10 cm^3) and diluted with diethyl ether (10 cm^3). The organic layer was separated, dried ($MgSO_4$) 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 mm^3) was added to a solution of the crude compound **6** in MeOH (14 cm^3) at 0 °C. After being stirred for 0.5 h the mixture was treated with saturated aqueous $NaHCO_3$ (10 cm^3) and diluted with ether (10 cm^3). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **1** (R = CH_2CH_2) (388 mg, 73% from **5**) as a clear oil; $[\alpha]_D^{25}$ −3.90 (*c* 0.93 in $CHCl_3$); 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. $C_{19}H_{32}KO_5Si$ requires *M*K$^+$, 407.1656].

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

A solution of trimethylsilylethynylmagnesium bromide in tetrahydrofuran [93.5 mmol, prepared from trimethylsilylacetylene (13.2 cm^3, 93.5 mmol) by treatment with ethylmagnesium bromide (2.06 mol dm^{-3} in tetrahydrofuran; 45.4 cm^3, 95.3 mmol) in tetrahydrofuran (187 cm^3) 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 cm^3, 85.0 mmol) in tetrahydrofuran (50 cm^3) 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 NH_4Cl (150 cm^3) and ether (200 cm^3) to the mixture, the organic layer was separated and the aqueous layer was extracted with ether (100 cm^3). The combined organic layers were dried ($MgSO_4$), 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; ν_{max}/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 BH_3·THF (1.0 mol dm^{-3} in THF; 4.0 cm^3, 4.0 mmol), cyclohexene (0.81 cm^3, 8.0 mmol), THF (5.5 cm^3), $[Pd(PPh)_4]$ (102 mg, 0.088 mmol, 3 mol%), 3 mol dm^{-3} NaOH (2.7 cm^3, 8.1 mmol) and benzene (33 cm^3) as a clear oil; $[\alpha]_D^{22}$ +2.14 (*c* 0.58 in $CHCl_3$); ν_{max}/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 = CH_2CH_2) 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; $[\alpha]_D^{21}$ +3.89 (*c* 0.72 in $CHCl_3$); ν_{max}/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. $C_{19}H_{30}KO_5Si$ requires *M*K^+, 405.1500].

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

Bu^{t}Li (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*)-(*tert*-butyldimethylsiloxy)-1-iodo-5-methylnon-1-ene,†,[4] (1.5 mmol, > 99% ee[4]) in ether (10 cm^3) 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 cm^3; 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 cm^3) 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 cm^3) and sat. aq. NH_4Cl (30 cm^3). The organic layer was separated and the aqueous layer was extracted with hexane (20 cm^3). The combined organic layers were washed with brine (20 cm^3), dried ($MgSO_4$), 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 E_1 methyl ester 8a

Reaction of compound **1** (R = CH_2CH_2), (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^{t}Li (0.652 mmol) gave **8a** (98 mg, 74%);‡ $[\alpha]_D^{21}$ −38.6 (*c* 0.46 in MeOH), lit.,[3b] $[\alpha]_D^{22}$ −39.3 (*c* 1.04 in MeOH).

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

Reaction of compound **1** (R = CH_2CH_2) (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^{t}Li (0.642 mmol) gave **8b** (101 mg, 74%) as a clear oil; $[\alpha]_D^{21}$ −37.5 (*c* 1.164 in $CHCl_3$); ν_{max}/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 cm^3) and pyridine (0.18 cm^3) in MeCN (3.0 cm^3) at room temperature for 4 h gave ornoprostil (34.8 mg, 93%);‡ $[\alpha]_D^{26}$ −41.6 (*c* 0.52 in MeOH), lit.,[3c] $[\alpha]_D^{25}$ −44.9 (*c* 0.44 in MeOH).

Bis-*tert*-butyldimethylsilyl ether of Δ²-*trans*-6-keto-prostaglandin E_1 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; $[\alpha]_D^{21}$ −43.4 (*c* 0.67 in $CHCl_3$); ν_{max}/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.

Δ²-*trans*-6-Keto-prostaglandin E_1 methyl ester

Treatment of compound **10** (31.8 mg, 0.0524 mmol) with HF·pyridine (0.1 cm^3) and pyridine (0.11 cm^3) in MeCN (1.9 cm^3) at room temperature for 4 h gave Δ²-*trans*-6-keto-prostaglandin E_1 methyl ester (18.9 mg, 95%) as a sticky oil; $[\alpha]_D^{22}$ −55.1 (*c* 0.41 in $CHCl_3$); ν_{max}/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, 3*b* and 3*c*).

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 E_1

Treatment of Δ^2-*trans*-6-keto-prostaglandin E_1 methyl ester (18.9 mg, 0.0498 mmol) with porcine liver esterase (50 mm^3, *ca.* 120 units/ethyl butyrate, Sigma) in acetone (0.97 cm^3) and phosphate buffer (2.32 cm^3; pH 8) at room temperature for 6 h gave Δ^2-*trans*-6-keto-prostaglandin E_1 (15.3 mg, 84%) as a sticky oil; $[\alpha]_D^{22}$ −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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