Stereocontrolled Synthesis of the Brassinolide Side-chain: Formal Synthesis of Brassinolide

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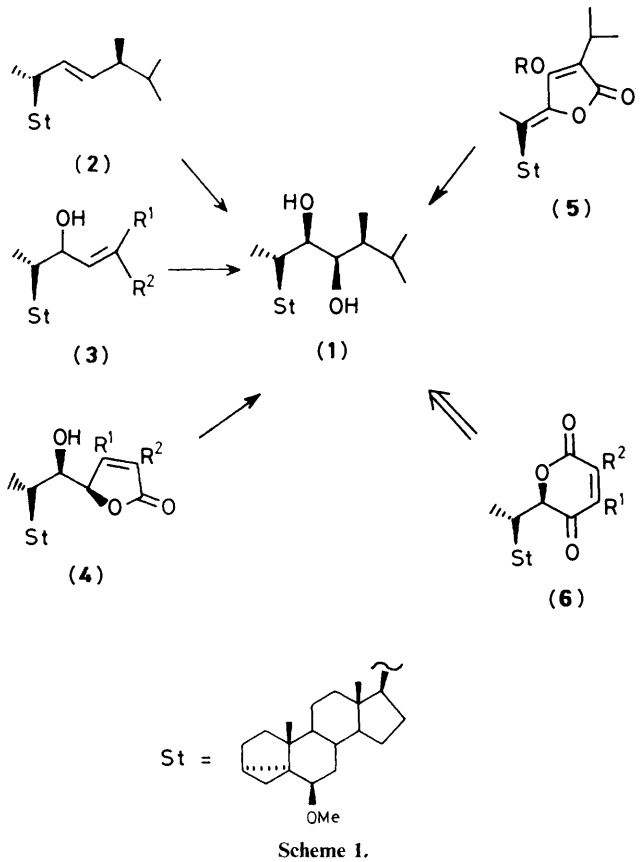
The stereoselective introduction of the brassinolide side-chain, having a (20*S*,22*R*,23*R*,24*S*)-22,23-diol functionality, was examined. The catalytic reduction of (20*S*,22*R*,24*Z*)-6β-methoxy-23-oxo-3α,5-cyclo-5α-stigmast-24(28)-eno-29,22-lactone (**11**), derived from the 20-carbaldehyde (**7**) and 3-isopropyl-2-lithiofuran in three steps, afforded (20*S*,22*R*,23*R*,24*S*)-22-hydroxy-6β-methoxy-3α,5-cyclo-5α-stigmastano-29,23-lactone (**14**), an important intermediate for the stereoselective synthesis of brassinolide.

The stereocontrolled introduction[1] of side-chains into steroids has been widely explored since physiologically active steroids, such as the ecdysones,[2] the brassinolides,[3] and the withanolides,[4] all possess side-chains of specific stereochemistry. As part of our continuing studies[5,6] on the synthesis of steroids using furan and butenolide as synthons, we have been investigating a stereoselective reduction on a side-chain to control the stereochemistry. Here we report a new method for the construction of the brassinolide side-chain bearing a (22*R*,23*R*)-diol functionality. Although there have been many attempts to control the stereochemistry at C-22 and C-23 (Scheme 1) by



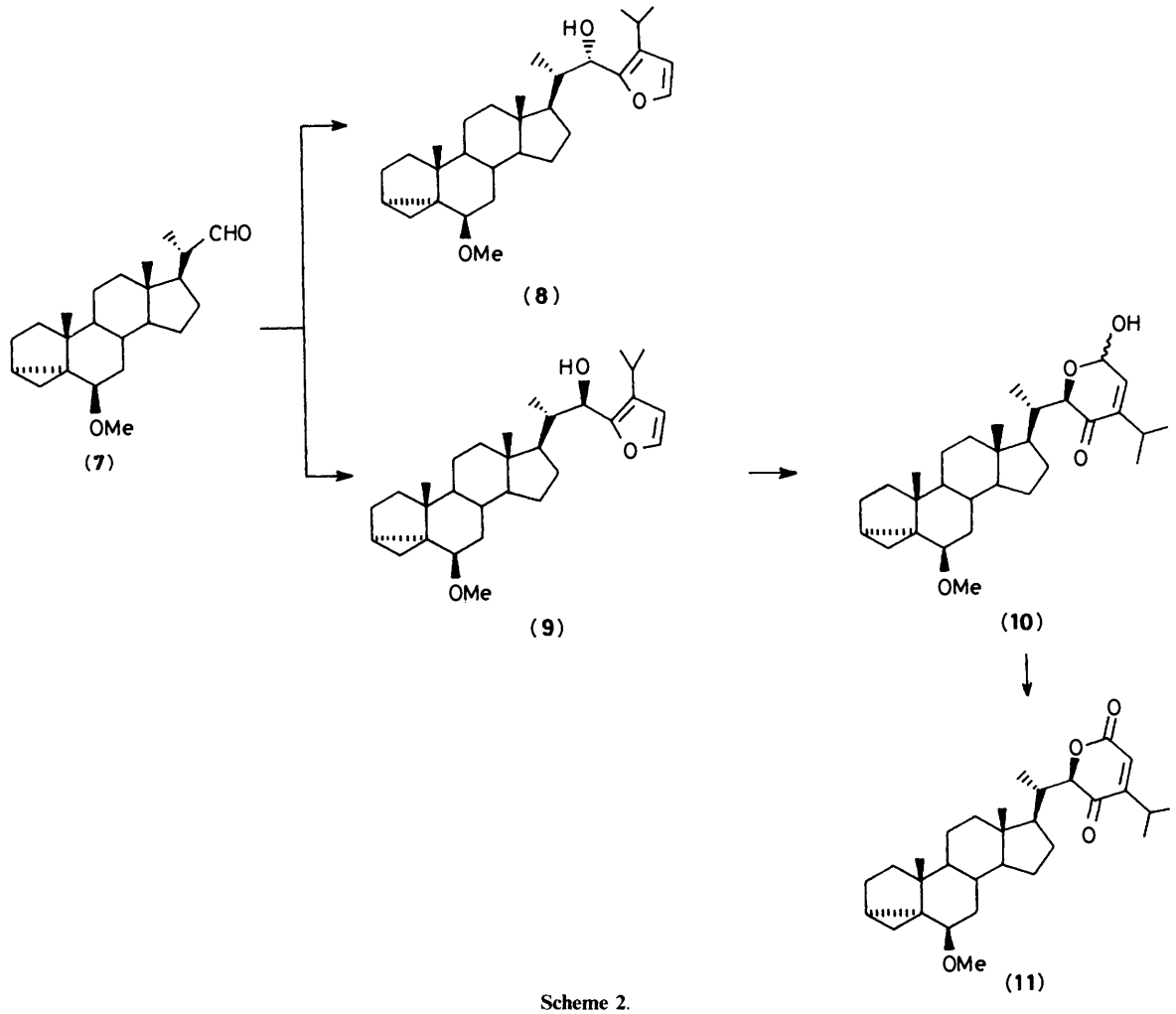
Scheme 1.

osmylation[7] of the 22-olefin (**2**), epoxidation[8] of the allyl alcohol (**3**), alkylation[9] of the butenolide (**4**), and hydrogenation[6] of the 5-ylidenetetronate (**5**), some of the products lack the required stereoselectivity. The key feature of our synthetic strategy is based on a stereoselective reduction of the unsaturated lactone (**6**) to incorporate the required stereochemistry at C-23 and C-24.

The key compound (**11**) was prepared as outlined in Scheme 2. Reaction of (20*S*)-carbaldehyde (**7**)[10] with 3-isopropyl-2-lithiofuran[11] in tetrahydrofuran at −78 °C gave the (22*S*)- and (22*R*)-furylmethanol (**8**) and (**9**) in 17.9 and 81.1% yields, respectively. The preferred stereochemistry at C-22 is predicted by the Felkin–Anh models for the transition state.[1a,12] Ring enlargement of compound (**9**) with *m*-chloroperbenzoic acid afforded the lactol (**10**), oxidation of which using pyridinium chlorochromate gave the desired lactone (**11**) in 87.2% yield from (**9**). In order to introduce the (22*R*,23*R*,24*S*)-22,23-diol functionality, the reduction of compound (**11**) was carried out under various conditions (Scheme 3). Catalytic hydrogenation of lactone (**11**) with platinum oxide in ethyl acetate gave the saturated lactone (**12**) in 34% yield, and an inseparable mixture of hydroxy lactones (**13**) and (**14**), the former of which was further isomerized with 0.5M sodium hydroxide to give the thermodynamically stable γ-lactone (**14**) as the sole product in 62% yield. Under medium pressure hydrogenation of (**11**) using various catalysts, such as platinum oxide, 10% palladium on carbon, and 5% rhodium on alumina, also gave a mixture of three products. The low reactivity of the enone of (**11**) toward hydrogenation would arise from steric hindrance of the bulky substitution at α and a′ positions. Sodium borohydride reduction of the ketone (**12**) in methanol and dichloromethane gave a mixture of compounds (**13**) and (**14**), which on isomerization gave (**14**) in 90.8% yield. Sodium borohydride reduction of compound (**11**) gave the allyl alcohol (**15**), in 91.6% yield, which was subjected to hydrogenation and subsequent isomerization to afford (**14**) and (**17**) in 72.5 and 24.9% yields, respectively (Scheme 3). The structures and stereochemistry of compound (**14**), a key intermediate for the synthesis of brassinolide,[8] and its stereoisomer (**17**) were determined by direct comparison with authentic samples[8] provided by Professor McMorris. Stereoselectivity in the reduction of compounds (**11**), (**12**), and (**15**) would be rationalized by assuming that reaction will occur from the less hindered side of the lactone ring as indicated in Figure 1. In the case of (**15**) (see C), interaction between the pseudo-axial hydroxy group and the catalyst, the so-called hydroxy group effect,[13] would diminish the stereoselectivity.

Experimental

M.p.s were measured with a Yanagimoto micro melting point apparatus and are uncorrected. I.r. spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H N.m.r. spectra were

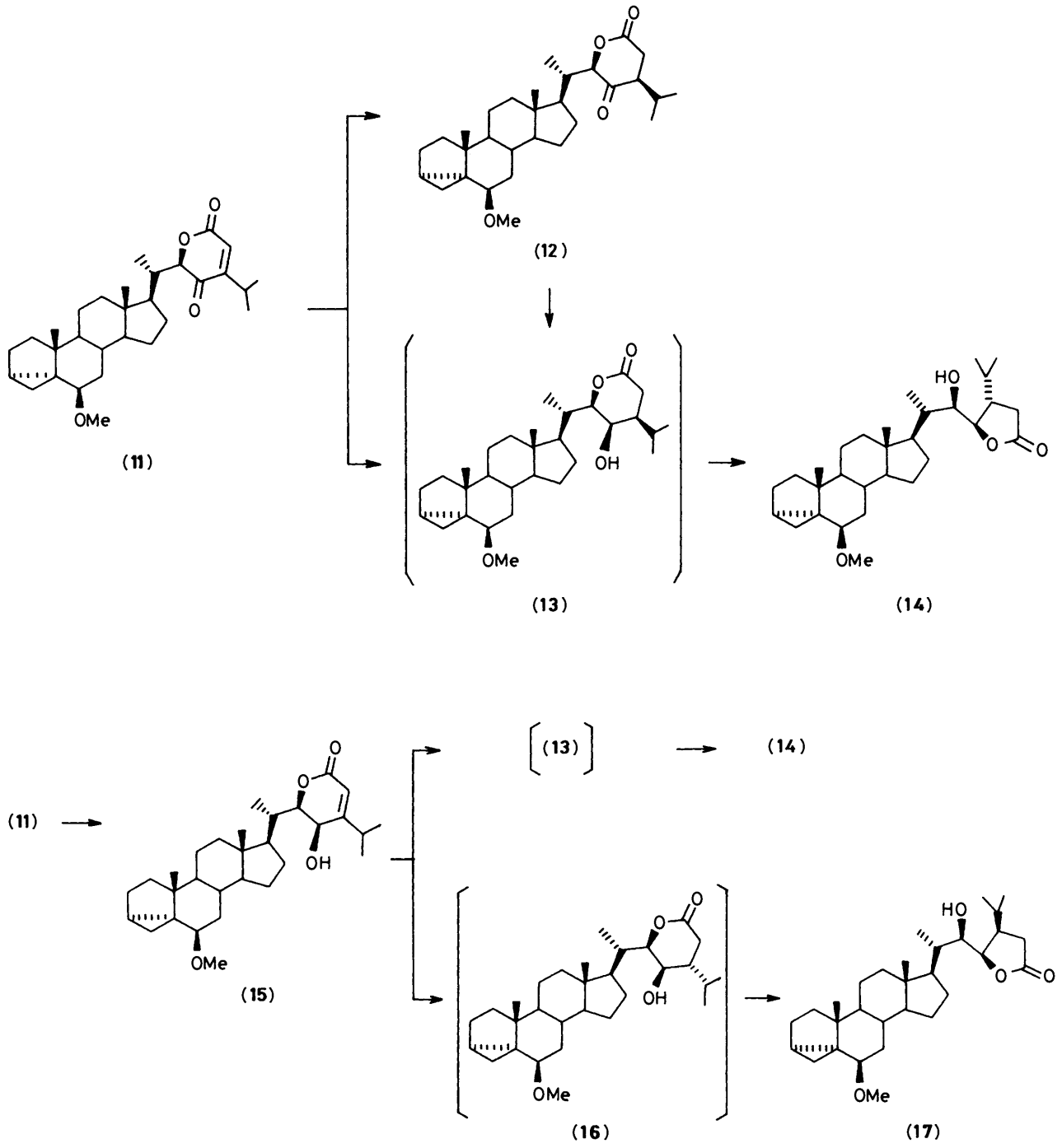


Scheme 2.

obtained for solutions in $CDCl_3$ on JEOL PMS-60 (60 MHz) and JEOL JNM GX-400 (400 MHz) spectrometers, and chemical shifts are expressed in p.p.m. downfield from internal tetramethylsilane. Mass spectra were measured with a JEOL JMS D-300 spectrometer.

Reaction of the Aldehyde (**7**) *with* 3-*Isopropyl*-2-*lithiofuran*.—A solution of (20*S*)-6β-methoxy-3α,5-cyclo-5α-pregnane-20-carbaldehyde[10] (1.19 g, 3.48 mmol) in anhydrous tetrahydrofuran (THF) (3 ml) was added to a stirred solution of 3-isopropyl-2-lithiofuran [prepared from 2-bromo-3-isopropylfuran[11] (1.31 g, 6.9 mmol) in anhydrous THF (4 ml) and butyllithium (1.57M; 4.44 ml)] at −78 °C under nitrogen and the reaction mixture was stirred for 1.5 h at room temperature. After being quenched with aqueous ammonium chloride solution, the product was extracted with ethyl acetate and the organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave a crude product which was purified by column chromatography on silica gel (hexane and ethyl acetate). The first fraction gave (20S,22R,23E,28Z)-23,29-*epoxy*-22-*hydroxy*-6β-*methoxy*-3α,5-*cyclo*-5α-*stigmasta*-23,28-*diene* (**9**) (1.268 g, 81.1%), as a yellow oil; $\nu_{max.}$ 3 360 cm^{-1}; δ(60 MHz) 0.73 (3 H, s, 18-H_3), 0.97 (3 H, s, 21-H_3), 1.03 (3 H, s, 19-H_3), 1.15 (6 H, d, *J* 6 Hz, 26-H_3 and 27-H_3), 3.29 (3 H, s, OMe), 4.83 (1 H, br s, $W_{1/2}$ 10 Hz, 22-H), 6.21 (1 H, d, *J* 2 Hz, 28-H), and 7.19 (1 H, d, *J* 2 Hz, 29-H); *m*/*z* (Found: M^+, 454.3418. $C_{30}H_{46}O_3$ requires *M*, 454.3447). The second fraction gave (20S,22S,23E,28Z)-23,29-*epoxy*-22-*hydroxy*-6β-*methoxy*-3α,5-*cyclo*-5α-*stigmasta*-23,28-*diene* (**8**) (280 mg, 17.9%) as a colourless oil; $\nu_{max.}$ 3 410 cm^{-1}; δ(60 MHz) 0.77 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.12 (3 H, s, 21-H_3), 1.15 (6 H, d, *J* 6 Hz, 26-H_3 and 27-H_3), 3.28 (3 H, s, OMe), 4.71 (1 H, d, *J* 7 Hz, 22-H), 6.23 (1 H, d, *J* 2 Hz, 28-H), and 7.24 (1 H, d, *J* 2 Hz, 29-H); *m*/*z* (Found: M^+, 454.3449. $C_{30}H_{46}O_3$ requires *M*, 454.3447).

(20S,22R,24Z)-22,29-*Epoxy*-29-*hydroxy*-6β-*methoxy*-3α,5-*cyclo*-5α-*stigmast*-24(28)-*en*-23-*one* (**10**).—A solution of *m*-chloroperbenzoic acid (250 mg, 1.45 mmol) in $CHCl_3$ (5 ml) was added dropwise to a suspension of compound (**9**) (400 mg, 0.88 mmol) and sodium acetate (73 mg, 0.88 mmol) in $CHCl_3$ (5 ml) at 0 °C and the reaction mixture was stirred for 2 h at the same temperature. The product was extracted with diethyl ether and the organic layer was washed with aqueous sodium thiosulphate, saturated aqueous sodium hydrogen carbonate, and brine, and dried (Na_2SO_4). Evaporation of the solvent gave the crude product which was purified by column chromatography on silica gel with hexane and ethyl acetate to afford the *lactol* (**10**) [406 mg, 98%]; $\nu_{max.}$ 3 580, 3 360, and 1 680 cm^{-1}; δ(60 MHz) 0.76 (3 H, s, 18-H_3), 0.83 (3 H, s, 21-H_3), 1.03 (3 H, s, 19-H_3), 1.10 and 1.15 (each 3 H, each d, *J* 3 Hz, 26-H_3 and 27-H_3), 3.29 (3 H, s, OMe), 4.53 (1 H, d, *J* 2 Hz, 22-H), 5.71 (1 H, m, 29-H), and 6.62 (1 H, d, *J* 4 Hz, 28-H), *m*/*z* (Found: M^+, 470.3388. $C_{30}H_{46}O_4$ requires *M*, 470.3380).



Scheme 3.

(20S,22R,24Z)-6β-*Methoxy*-23-*oxo*-3α,5-*cyclo*-5α-*stigmast*-24(28)-*eno*-29,22-*lactone* (**11**).—A solution of the lactol (**10**) (406 mg, 0.86 mmol) in dry dichloromethane (5 ml) at room temperature was added rapidly to a stirred suspension of pyridinium chlorochromate (370 mg, 1.72 mmol) and sodium acetate (142 mg, 1.72 mmol) in dry dichloromethane (5 ml). The reaction mixture was stirred for 2 h and then diluted with anhydrous ether (30 ml). The insoluble precipitate was removed by decantation using anhydrous ether. The organic layer was washed with brine, dried (Na_2SO_4), and the solvent evaporated to afford a residue which was purified by column chromatography on silica gel with dichloromethane to give the *lactone* (**11**) (360 mg, 89.1%) as colourless needles, m.p. 131—133 °C (from acetone–methanol); $\nu_{max.}$ 1 720 and 1 695 cm^{-1}; δ(400 MHz) 0.77 (3 H, s, 18-H_3), 0.86 (3 H, d, *J* 7 Hz, 21-H_3), 1.02 (3 H, s, 19-H_3), 1.12 and 1.14 (each 3 H, each d, *J* 4 Hz, 26-H_3 and 27-H_3), 3.33 (3 H, s, OMe), 4.90 (1 H, d, *J* 2 Hz, 22-H), and 6.64 (1 H, d, *J* 1 Hz, 28-H); *m/z* (M^+, 468.3234) (Found: C, 76.6; H, 9.6. $C_{30}H_{44}O_4$ requires C, 76.9; H, 9.45%).

Hydrogenation of Lactone (**11**) *with* PtO_2.—A suspension of the lactone (**11**) (100 mg, 0.21 mmol) and platinum oxide (20 mg)

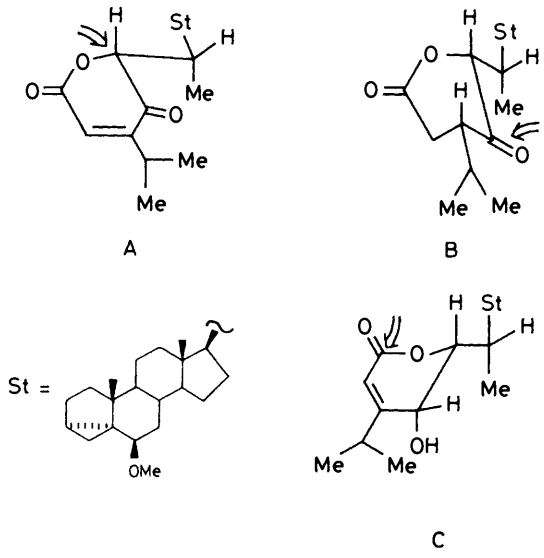


Figure 1.

in ethyl acetate (5 ml) was stirred under a hydrogen atmosphere for 1 h. The catalyst was filtered off and the solvent was evaporated to give the crude product which contained unstable (20S,22R,23R,24S)-23-*hydroxy*-6β-*methoxy*-3α,5-*cyclo*-5α-*stigmastano*-29,22-*lactone* (**13**); $\nu_{max.}$ 1 720 cm^{-1}. The crude product was treated with 0.5M NaOH solution (0.05 ml) in THF (5 ml) for 2 h at 0 °C, and was then extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4), and the solvent evaporated to give a residue. This was subjected to chromatography on silica gel (benzene–ethyl acetate) to give the first fraction, (20S,22R,24S)-6β-*methoxy*-23-*oxo*-3α,5-*cyclo*-5α-*stigmastano*-29,22-*lactone* (**12**) (34 mg, 34%) as a colourless oil; $\nu_{max.}$ 1 750 and 1 730 cm^{-1}; δ(400 MHz), 0.77 (3 H, s, 18-H_3), 0.89 (3 H, d, *J* 7 Hz, 21-H_3), 0.97 and 0.99 (each 3 H, each d, *J* 4 Hz, 26-H_3 and 27-H_3), 1.03 (3 H, s, 19-H_3), 3.32 (3 H, s, OMe), and 4.66 (1 H, d, *J* 2 Hz, 22-H); *m/z* (Found: M^+, 470.3034. $C_{30}H_{46}O_4$ requires *M*, 470.3026). The second fraction gave (-20S,22R,23R,24S)-22-*hydroxy*-6β-*methoxy*-3α,5-*cyclo*-5α-*stigmastano*-29,23-*lactone* (**14**) (62 mg, 62%) as a colourless oil; $\nu_{max.}$ 3 510 and 1 775 cm^{-1}; δ(400 MHz) 0.44 (1 H, dd, *J* 5.0 and 8.1 Hz, 4-H), 0.65 (1 H, t, *J* 5.0 Hz, 4-H), 0.74 (3 H, s, 18-H_3), 0.94 (3 H, each 3 H, d, *J* 2 Hz, 21-H_3), 0.93 and 0.96 (each 3 H, each d, *J* 12 Hz, 26-H_3 and 27-H_3), 1.02 (3 H, s, 19-H_3), 2.78 (1 H, t, *J* 2.8 Hz, 6-H), 3.33 (3 H, s, OMe),3.59 (1 H, d, *J* 5.1 Hz, 22-H), and 4.24 (1 H, t, *J* 5 Hz, 23-H); *m/z* (Found: M^+, 472.3560. $C_{30}H_{48}O_4$ requires *M*, 472.3553). These spectroscopic data were identical with those of an authentic sample.

Reduction of Compound (**12**) *with Sodium Borohydride*.—Sodium borohydride (3 mg, 0.07 mmol) was added to a solution of compound (**12**) (34 mg, 0.07 mmol) in methanol (1 ml) and dichloromethane (1 ml) at 0 °C, and the mixture was stirred for 3 h at room temperature. After being quenched with aqueous ammonium chloride, the product was extracted with ethyl acetate and the organic layer was washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the crude product was dissolved in THF (2 ml), 0.5M NaOH (0.05 ml) was added, and the mixture was stirred for 2 h at 0 °C. The reaction mixture was worked up as described above. The residue was subjected to chromatography on silica gel (benzene–ethyl acetate) to give the product (**14**) (31 mg, 90.8%).

(20S,22R,23R,24Z)-23-*Hydroxy*-6β-*methoxy*-3α,5-*cyclo*-5α-*stigmast*-24(28)-*eno*-29,22-*lactone* (**15**).—Sodium borohydride (10 mg, 0.26 mmol) was added to a stirred solution of compound (**11**) (100 mg, 0.21 mmol) in methanol (3 ml) and dichloromethane (3 ml) at 0 °C. Stirring was continued for 3 h at room temperature and the reaction mixture was worked up as described above. The residue was purified by column chromatography on silica gel (benzene-ethyl acetate) to afford the product (**15**) (92 mg, 91.6%); $\nu_{max.}$ 3 490 and 1 740 cm^{-1}; δ(400 MHz) 0.78 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.16 and 1.19 (each 3 H, each d, *J* 7 Hz, 26-H_3 and 27-H_3), 1.27 (3 H, d, *J* 7 Hz, 21-H_3), 3.33 (3 H, s, OMe), 4.03 (1 H, d, *J* 2.2 Hz, 23-H), 4.19 (1 H, br s, 22-H), and 5.81 (1 H, d, *J* 1 Hz, 28-H); *m/z* (Found: M^+, 470.3397. $C_{30}H_{46}O_4$ requires *M*, 470.3396).

Hydrogenation of Compound (**15**) *with* PtO_2.—A suspension of compound (**15**) (92 mg, 0.20 mmol) and platinum oxide (20 mg) in ethyl acetate (5 ml) was stirred under a hydrogen atmosphere for 3 h at room temperature. The catalyst was filtered off, the solvent was evaporated, and the crude product purified by column chromatography on silica gel (benzene–ethyl acetate) to afford compound (**14**) (67 mg, 72.5%) and (20S,22R,23R,24R)-22-*hydroxy*-6β-*methoxy*-3α,5-*cyclo*-5α-*stigmastano*-29,23-*lactone* (**17**) (23 mg, 24.9%) as colourless needles, m.p.199—201 °C (from benzene–hexane); $\nu_{max.}$ 3 500 and 1 770 cm^{-1}; δ(400 MHz), 0.44 (1 H, dd, *J* 5.0 and 7.9 Hz, 4-H), 0.66 (1 H, t, *J* 5.0 Hz, 4-H), 0.74 (3 H, s, 18-H_3), 0.94 (3 H, d, *J* 7 Hz, 26-H_3 or 27-H_3), 0.96 (3 H, d, *J* 6 Hz, 26-H_3 or 27-H_3), 1.02 (3 H, s, 19-H_3), 1.05 (3 H, d, *J* 7 Hz, 21-H_3), 2.78 (1 H, t, *J* 2.7 Hz, 6-H), 3.33 (3 H, s, OMe), 3.99 (1 H, br s, $W_{1/2}$ 17 Hz, 22-H), and 4.44 (1 H, dd, *J* 2 and 7.2 Hz, 23-H); *m/z* (Found: M^+, 472.3558. $C_{30}H_{48}O_4$ requires *M*, 472.3552). The spectroscopic data were identical with those of an authentic sample.

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