Stereoselective synthesis of petrosterol and a formal synthesis of aragusterols

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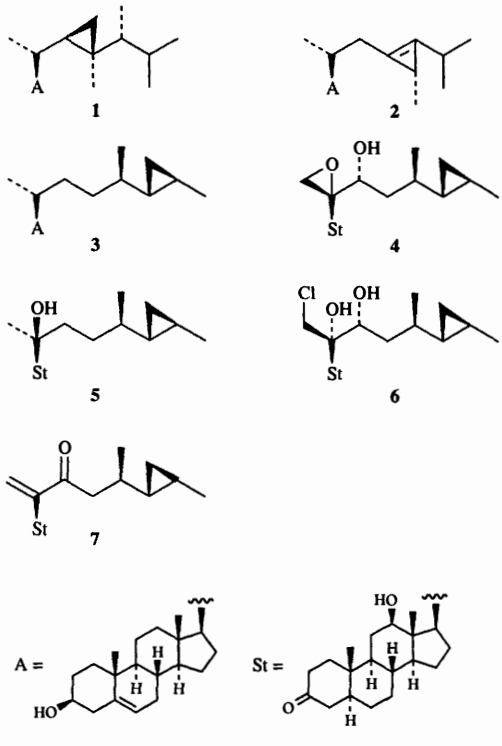
Stereoselective construction of a steroidal side chain containing a 26–27 cyclopropane ring, compound 22, has been achieved by an intramolecular cyclisation of the corresponding β-methylsulfonyloxy cyanide 16, derived from a chiral cyclopentane derivative. Compound 22 has been further utilised in the synthesis of the naturally occurring steroid petrosterol 3.

Sterols with cyclopropyl-containing side chains have attracted increasing attention as a result of their structural novelty and interesting biological activity. Such compounds are typified by gorgosterol **1** with a 22–23 cyclopropane ring,[1] calysterol **2** with a 23–28 cyclopropane ring[2] and petrosterol **3** with a 26–27 cyclopropane ring.[3]

Recently, potent antitumour marine steroids, the aragusterols A–D **4–7**, have been isolated from the Okinawan sponge of the genus *Xestospongia*. The structures of these have been shown to contain a 26–27 cyclopropane ring, the stereochemistry of which is the same as that of petrosterol.[4]

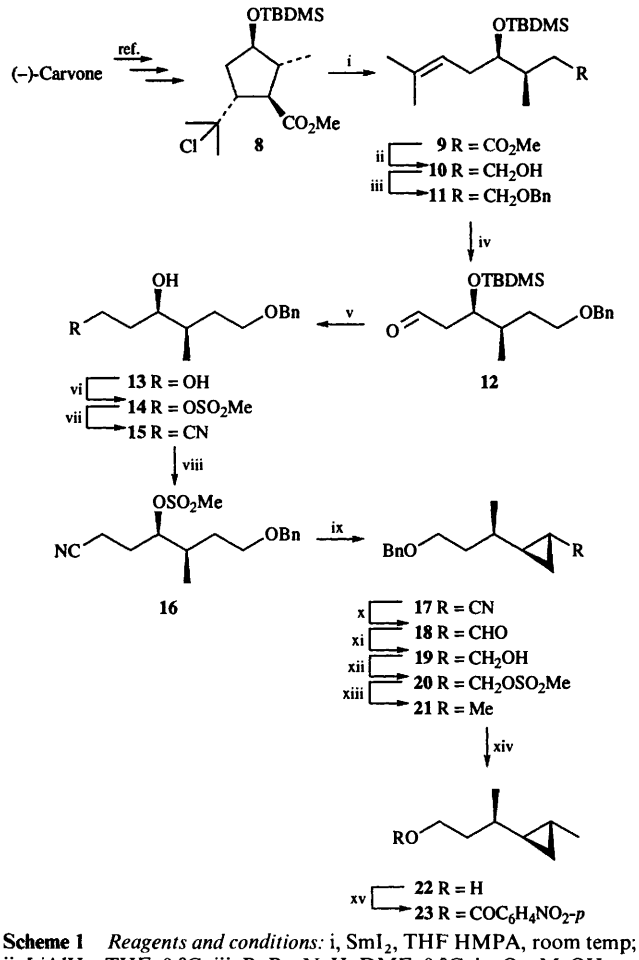
In connection with our studies of the synthesis of physiologically active steroids,[5] we have been interested in the stereoselective construction of a steroidal side chain containing a 26–27 cyclopropane ring in an optically active form. Here we report a novel synthetic pathway to such a ring system and its utilisation in the synthesis of petrosterol **3**, isolated from the marine sponge *Petrosia ficiformis*.[6]

Our synthesis commenced with the synthesis of the known olefinic ester **9** which seems to have suitable functionalities for cyclopropane ring formation and also a secondary methyl group corresponding to the 29-position with the correct configuration (Scheme 1).[7] It was readily accessible *via* the cyclopentane derivative **8**, from (−)-carvone by a known procedure[7] involving samarium diiodide-promoted regioselective carbon–carbon bond fragmentation. Thus, regioselective fragmentation of **8** using samarium diiodide gave the olefinic ester **9** (89%), which on reduction with lithium aluminium hydride afforded the alcohol **10** (93%). Benzylation of **10** with benzyl bromide and sodium hydride gave the benzyl ether **11** which was subjected to ozonolysis to provide the aldehyde **12** (83% yield from **10**). Reduction of **12** with lithium aluminium hydride gave the diol **13** (87%), where desilylation also occurred simultaneously. One-carbon elongation of **13** was carried out in the usual manner by selective methanesulfonylation of the primary alcohol of **13** and subsequent substitution of the methanesulfonate **14** with sodium cyanide in dimethyl sulfoxide to give the cyanide **15** (86%). Cyclopropane ring formation was achieved on treatment of **16**, derived from **15** with methanesulfonyl chloride, with potassium *tert*-butoxide in tetrahydrofuran to afford the cyanide **17** (86%) as the sole product; no other isomers were isolated under these reaction conditions. The structural identity of compound **17** was further confirmed by its conversion into the known compound **22** as follows. The successive reduction of the cyanide **17** with diisobutylaluminium hydride and sodium borohydride afforded the alcohol **19** *via* the aldehyde **18**. After treatment of **19** with methanesulfonyl chloride, the resulting methanesulfonate **20** was converted into the desired compound **21** (78% yield from **17**). Debenzylation of **21** by a catalytic reduction over palladium–carbon gave the alcohol **22**, which was further converted into the *p*-nitrobenzoate **23**. The spectroscopic data of **23** including its specific optical rotation, $[\alpha]_D$ −21.1† (*c* 0.4, $CHCl_3$) {lit.,[4] $[\alpha]_D$ −20.3 (*c* 0.07, $CHCl_3$); lit.,[8] $[\alpha]_D$ −25.1 (*c* 0.39, $CHCl_3$)}, were identical with those reported.[4] Since the alcohol **22** was very recently prepared by an asymmetric cyclopropanation and also employed in the synthesis of aragusterols A–D by Yamada and co-workers,[8] this synthesis constitutes their formal synthesis.



We next focussed our attention on the utilisation of **22** in the synthesis of petrosterol (Scheme 2). The alcohol **22** was converted into the bromide **24**, whose addition to the 20-oxosteroid **25** using the corresponding lithium salt or Grignard reagent gave the desired product **26**, but in only poor yield however. After a number of attempts to induce this carbon–carbon bond formation, we found that samarium diiodide-promoted coupling[9] of **25** with **24** gave the best result. The

† All $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}.



Scheme 1 *Reagents and conditions:* i, SmI_2, THF HMPA, room temp; ii, $LiAlH_4$, THF, 0 °C; iii, BnBr, NaH, DMF, 0 °C; iv, O_3, MeOH, −78 °C then Ph_3P; v, $LiAlH_4$, THF, 0 °C; vi, MsCl, Et_3N, CH_2Cl_2, 0 °C; vii, NaCN, DMSO, 60 °C; viii, MsCl, Et_3N, CH_2Cl_2, 0 °C; ix, KOBu^t, THF, room temp.; x, DIBAL, THF, −78 °C to room temp.; xi, $NaBH_4$, THF, 0 °C to room temp.; xii, MsCl, Et_3N, CH_2Cl_2, 0 °C; xiii, $LiAlH_4$, THF, 0 °C; xiv, Pd–C, H_2, MeOH; xv, *p*-$NO_2C_6H_4COCl$ pyridine, CH_2Cl_2, room temp.

stereochemistry at the 20-position of **26** was assumed to be *S*, since a similar reaction of **25** with 1-bromo-4-methylpentane provided the known 20*S*-addition product, 20α-hydroxycholesterol **27**,[10] stereoselectively, as the sole product.

In order to complete the synthesis, compound **26** was treated with conc. hydrochloric acid in refluxing methanol[11] in order to dehydrate the alcohol which furnished the *endo*-**28** and *exo*-olefins **29** (98%; in a ratio of 15:1) as an inseparable mixture. Since attempted stereoselective reduction of the 20,22-double bond by hydroboration[12] gave none of the desired product, we then tried direct catalytic reduction. After protection of the double bond at the 5-position by formation of the cyclopropane ring in the usual manner,[13] the mixture of the olefins **30** and **31** was subjected to catalytic hydrogenation over palladium–carbon to give **32** (89%). Ring-opening of the 3,5-cyclopropane by acid treatment provided petrosterol **3** (55%), mp 155–157 °C (lit.,[14] 157–159 °C) and its 20-epimer **33** (36%). The spectroscopic data and specific optical rotation of the synthetic compound **3**, $[\alpha]_D$ −33.4 (*c* 0.3, $CHCl_3$) {lit.,[14] $[\alpha]_D$ −36.4 ($CHCl_3$)}, were consistent with its structure.[14]

In summary, we have described the stereoselective construction of a steroidal side chain with a 26–27 cyclopropane ring in an optically active form and its utilisation in the synthesis of petrosterol. The synthetic procedure developed in our work would be applicable to the synthesis of other naturally occurring steroids having a cyclopropane ring on their side chains.

Experimental

General methods

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded for solutions in $CHCl_3$ on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX 270 instrument (270 MHz), and chemical shifts are reported in ppm on the δ scale from internal Me_4Si; *J* values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter. All new compounds described in the Experimental section were homogeneous on TLC. Ether refers to diethyl ether, DMF to dimethylformamide and THF to tetrahydrofuran.

(3*R*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-3,7-dimethyloct-6-en-1-ol 10

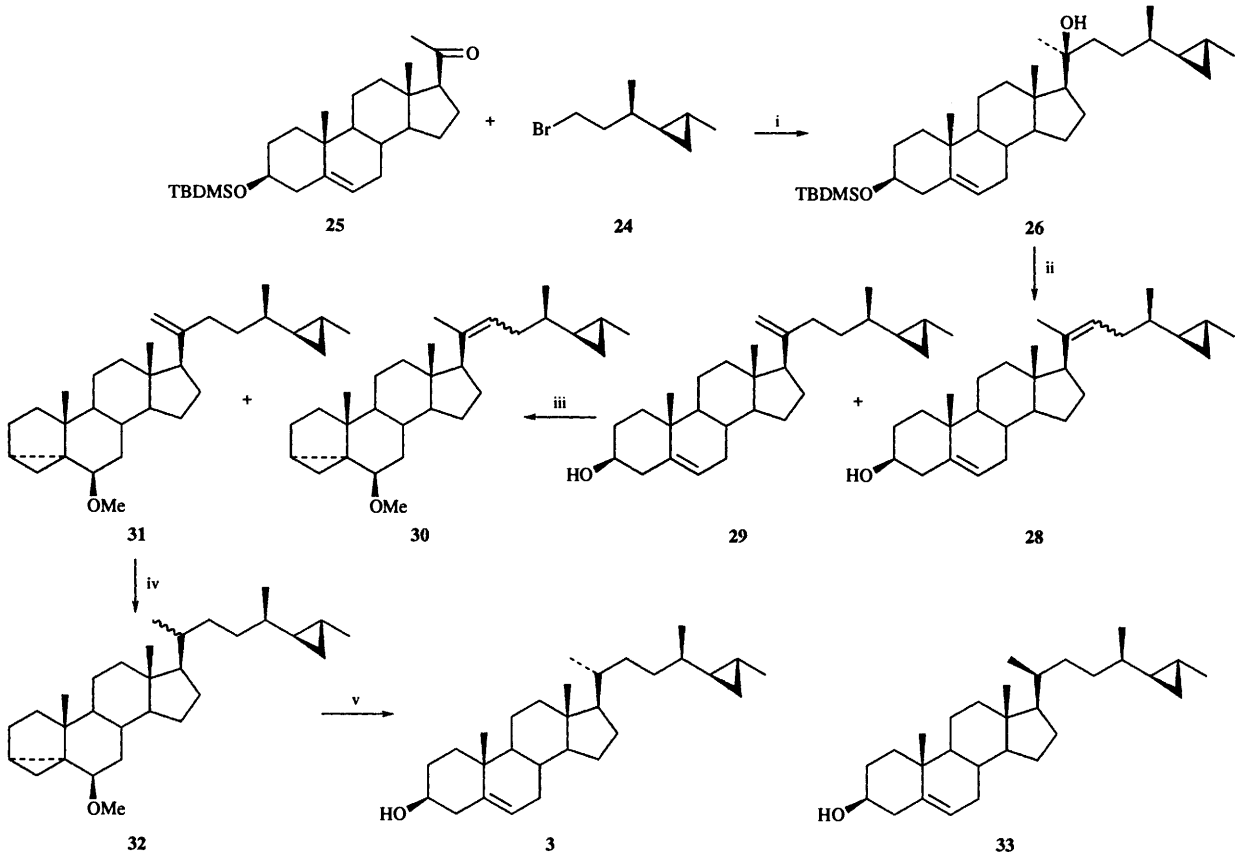
To a stirred suspension of lithium aluminium hydride (0.12 g, 1 mmol) in THF (60 cm^3) was added a solution of the ester **9** (1.3 g, 4.3 mmol) in THF (10 cm^3) over a period of 30 min at 0 °C under argon and the mixture was stirred for 30 min. The reaction was quenched by addition of 10% aq. NaOH to the mixture after which the insoluble materials formed were removed by filtration of the mixture through a Celite pad. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (2:1, v/v) afforded the alcohol **10** (1.14 g, 93%) as a colourless oil; $[\alpha]_D$ +8.4 (*c* 1.1, $CHCl_3$) (Found: C, 67.00; H, 11.75. $C_{16}H_{34}O_2Si$ requires C, 67.05; H, 11.95); ν_{max}($CHCl_3$)/cm^{-1} 3400 and 2860; δ_H 0.04 (6 H, s, 2 × Me), 0.89 (12 H, br s, Bu^t and 3-Me), 1.34–1.51 (1 H, m, 3-H), 1.62 and 1.69 (each 3 H, each s, 2 × 7-Me), 1.71–1.82 (2 H, m, 2-H_2), 2.02–2.29 (2 H, m, 5-H_2), 2.57 (1 H, br s, OH), 3.53–3.82 (3 H, m, 4-H and 1-H_2) and 5.03–5.15 (1 H, m, 6-H).

(3*R*,4*R*)-1-Benzyloxy-3-(*tert*-butyldimethylsiloxy)-3,7-dimethyloct-6-ene 11

To a stirred solution of the alcohol **10** (14 g, 49 mmol) in DMF (200 cm^3) in the presence of sodium hydride (4.9 g, 0.12 mol) was added benzyl bromide (12.8 cm^3, 0.11 mol) at 0 °C, and the resulting mixture was stirred for a further 2 h at ambient temperature. The mixture was then treated with saturated aqueous ammonium chloride and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to afford a residue. This was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (99:1, v/v) afforded the benzyl ether **11** (18.4 g, 100%) as a colourless oil; $[\alpha]_D$ +4.8 (*c* 0.7, $CHCl_3$) (Found: C, 73.00; H, 10.70. $C_{23}H_{40}O_2Si$ requires C, 73.35; H, 10.70); ν_{max}($CHCl_3$)/cm^{-1} 2850; δ_H 0.02 (6 H, s, 2 × Me), 0.86–0.89 (12 H, m, Bu^t and 3-Me), 1.39–1.51 (1 H, m, 3-H), 1.60 and 1.69 (each 3 H, each s, 2 × 7-Me), 1.71–1.82 (2 H, m, 2-H_2), 2.12 (2 H, dd, *J* 6.5 and 7.5, 5-H_2), 3.44–3.59 (3 H, m, 4-H and 1-H_2), 4.49 (2 H, s, OCH_2Ph), 5.03–5.14 (1 H, m, 6-H) and 7.27–7.38 (5 H, m, ArH).

(3*R*,4*R*)-6-Benzyloxy-3-(*tert*-butyldimethylsiloxy)-4-methylhexanal 12

A stirred solution of the olefin **11** (13 g, 0.03 mol) in methanol (650 cm^3) was saturated with ozone at −78 °C. The solution was stirred for 10 min after which the ozone was removed by exchange with argon, and the mixture treated with triphenylphosphine (13.6 g, 0.05 mol) and then warmed to room temperature. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (10:1, v/v) afforded the aldehyde **12** (10.0 g, 83%) as a colourless oil; $[\alpha]_D$ +19.8 (*c* 1.1, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2850 and 1720; δ_H 0.03 (6 H, s, 2 × Me), 0.86 (9 H, s, Bu^t), 0.87 (3 H, d, *J* 6.0, 4-Me), 1.27–1.43 (1 H, m, 4-H),



Scheme 2 *Reagents and conditions:* i, SmI_2, THF–HMPA, room temp.; ii, conc. HCl, MeOH, reflux; iii, TsCl, pyridine, room temp. then MeOH–pyridine, 75 °C; iv, Pd–C, H_2, EtOAc, room temp.; v, TsOH, dioxane–water, 80 °C

1.70–1.98 (2 H, m, 5-H_2), 2.44 (1 H, ddd, *J* 2.0, 5.0 and 16.0, 2-H), 2.55 (1 H, ddd, *J* 2.0, 7.5 and 16.0, 2-H), 3.44–3.58 (2 H, m, 6-H_2), 4.10–4.18 (1 H, m, 3-H), 4.49 (2 H, s, OCH_2Ph), 7.27–7.28 (5 H, m, ArH) and 9.79 (1 H, apparent t, *J* 2.0, CHO) [Found: *m/z* 350.2276. Calc. for $C_{20}H_{34}O_3Si$ (M^+): *m/z* 350.2276].

(3*R*,4*R*)-6-Benzyloxy-4-methylhexane-1,3-diol 13

To a stirred suspension of lithium aluminium hydride (1.5 g, 0.04 mol) in THF (150 cm^3) was added a solution of the aldehyde **12** (9 g, 0.03 mol) in THF (50 cm^3) over a period of 30 min at 0 °C under argon and the mixture was stirred for a further 30 min. The reaction was quenched by addition of 10% aq. NaOH to the mixture after which the insoluble materials formed were removed by filtration of the mixture through a Celite pad. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (2:1, v/v) afforded the diol **13** (4.78 g, 87%) as a colourless oil; $[\alpha]_D$ +9.6 (*c* 0.7, $CHCl_3$) (Found: C, 70.35; H, 9.40. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.30); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 2860; δ_H 0.91 (3 H, d, *J* 6.5, 4-Me), 1.49–1.86 (5 H, m, 2-H_2, 4-H and 5-H_2), 2.70–2.90 (1 H, br s, OH), 3.26–3.38 (1 H, br s, OH), 3.44–3.68 (2 H, m, 6-H_2), 3.74–3.90 (3 H, m, 1-H_2 and 3-H), 4.49 and 4.54 (each 1 H, each d, *J* 12.0, OCH_2Ph) and 7.28–7.40 (5 H, m, ArH) [Found: *m/z* 220.1468. Calc. for $C_{14}H_{20}O_2$ (M^+ − 18): *m/z* 220.1463].

(3*R*,4*R*)-6-Benzyloxy-1-methylsulfonyloxy-4-methylhexan-3-ol 14

To a stirred solution of the diol **13** (0.8 g, 3.4 mmol) in dichloromethane (24 cm^3) in the presence of triethylamine (1.0 cm^3, 7.4 mmol) was added methanesulfonyl chloride (0.29 cm^3, 3.7 mmol) at 0 °C and the resulting mixture was stirred at the same temperature for 2 h. After treatment with saturated aq. ammonium chloride, the mixture was extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue. This was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (1:2, v/v) afforded the sulfonate **14** (1.05 g, 99%) as a colourless oil; $[\alpha]_D$ +26.7 (*c* 1.8, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 2870, 1350 and 1160; δ_H 0.90 (3 H, d, *J* 6.5, 4-Me), 1.52–1.90 (5 H, m, 2-H_2, 4-H and 5-H_2), 2.96 (3 H, s, SO_2Me), 2.97–3.05 (1 H, br s, OH), 3.45–3.67 (2 H, m, 6-H_2), 3.68–3.80 (1 H, m, 3-H), 4.30–4.44 (2 H, m, 1-H_2), 4.18 and 4.56 (each 1 H, each d, *J* 13.0, OCH_2Ph) and 7.28–7.40 (5 H, m, ArH) [Found: *m/z* 316.1344. Calc. for $C_{15}H_{24}O_5S$ (M^+): *m/z* 316.1344].

(3*R*,4*R*)-6-Benzyloxy-3-hydroxy-4-methylheptanenitrile 15

A stirred solution of the methanesulfonate **14** (0.94 g, 2.97 mmol) and sodium cyanide (0.44 g, 8.9 mmol) in dimethyl sulfoxide (9 cm^3) was heated at 60 °C for 6 h. After being cooled to room temperature, the mixture was treated with water (20 cm^3) and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (2:1, v/v) afforded the cyanide **15** (0.63 g, 86%) as a colourless oil; $[\alpha]_D$ +27.9 (*c* 1.4, $CHCl_3$) (Found: C, 72.80; H, 8.45; N, 5.65. $C_{15}H_{21}NO_2$ requires C, 72.85; H, 8.55; N, 5.65); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 2850 and 2250; δ_H 0.88 (3 H, d, *J* 6.5, 4-Me), 1.49–1.84 (5 H, m, 2-H_2, 4-H and 5-H_2), 2.44 (1 H, ddd, *J* 5.5, 6.5 and 10.0, 1-H), 2.49 (1 H, ddd, *J* 6.0, 6.5 and 10.0, 1-H), 3.03–3.23 (1 H, br s, OH), 3.43–3.67 (3 H, m, 3-H and 6-H_2), 4.51 (2 H, apparent s, OCH_2Ph) and 7.28–7.40 (5 H, m, ArH).

(3*R*,4*R*)-6-Benzyloxy-3-methylsulfonyloxy-4-methylheptanenitrile 16

To a stirred solution of the alcohol **15** (0.55 g, 2.23 mmol) and triethylamine (1.2 cm^3) in dichloromethane (17 cm^3) was added methanesulfonyl chloride (0.3 cm^3, 4.5 mmol) at 0 °C and the resulting mixture was stirred at the same temperature for a further 1 h. After treatment with saturated aq. ammonium

chloride, the mixture was extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (2:1, v/v) afforded the sulfonate **16** (0.71 g, 99%) as a colourless oil; $[\alpha]_D$ +15.1 (*c* 1.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2860, 2250, 1320 and 1160; δ_H 0.97 (3 H, d, *J* 6.5, 4-Me), 1.40–1.52 (1 H, m, 4-H), 1.78–2.19 (4 H, m, 2-H_2 and 5-H_2), 2.37–2.62 (2 H, m, 1-H_2), 3.03 (3 H, s, SO_2Me), 3.46–3.65 (2 H, m, 6-H_2), 4.45 and 4.53 (each 1 H, each d, *J* 12.0, OCH_2Ph), 4.71 (1 H, dt, *J* 5.0 and 8.5, 3-H) and 7.28–7.40 (5 H, m, ArH) [Found: *m/z* 325.1353. Calc. for $C_{16}H_{23}NO_4S$ (M^+): *m/z* 325.1348].

(1*R*,2*R*)-2-[(1*R*)-3-Benzyloxy-1-methylpropyl]cyclopropane-1-carbonitrile 17

To a stirred solution of potassium *tert*-butoxide (1.35 g, 12 mmol) in THF (20 cm^3) was added a solution of the cyanide **16** (1.3 g, 4 mmol) in THF (6 cm^3) at ambient temperature under argon and the resulting mixture was stirred at the same temperature for a further 2 h. After treatment with saturated aq. ammonium chloride, the mixture was extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (10:1, v/v) afforded the cyclopropane **17** (0.79 g, 86%) as a colourless oil; $[\alpha]_D$ −108.6 (*c* 1.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2890 and 2250; δ_H 0.70–0.83 (1 H, m, 3-H), 0.96 (3 H, d, *J* 5.0, 1′-Me), 0.96–1.29 (4 H, m, 1-H, 2-H, 3-H and 1′-H), 1.58–1.80 (2 H, m, 2′-H_2), 3.46–3.67 (2 H, m, 3′-H_2), 4.49 (2 H, s, OCH_2Ph) and 7.26–7.40 (5 H, m, ArH) [Found: *m/z* 229.1467. Calc. for $C_{15}H_{19}NO$ (M^+): *m/z* 229.1467].

(1*R*,2*R*)-2-[(1*R*)-3-Benzyloxy-1-methylpropyl]cyclopropane-1-carbaldehyde 18

To a stirred solution of the cyanide **17** (0.11 g, 0.48 mmol) in THF (6 cm^3) was added dropwise a 0.98 M hexane solution of diisobutylaluminium hydride (1.5 cm^3, 1.44 mmol) at −78 °C and the resulting mixture was stirred for a further 2 h. After treatment of the mixture with saturated aq. ammonium chloride, the resulting precipitate was removed by filtration of the mixture through a Celite pad. The filtrate was diluted with ethyl acetate, washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (2:1, v/v) afforded the aldehyde **18** (0.11 g, 94%) as a colourless oil; $[\alpha]_D$ −45.1 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2850 and 1690; δ_H 0.86–0.96 (1 H, m, 3-H), 1.00 (3 H, d, *J* 6.5, 1′-Me), 1.10–1.37 (3 H, m, 2-H, 3-H and 1-H), 1.53–1.80 (3 H, m, 1′-H and 2′-H_2), 3.50 (1 H, ddd, *J* 6.0, 6.5 and 12.0, 3′-H), 3.54 (1 H, ddd, *J* 6.0, 7.0 and 12.0, 3′-H), 4.46 and 4.51 (each 1 H, each d, *J* 11.5, OCH_2Ph), 7.26–7.39 (5 H, m, ArH) and 8.98 (1 H, d, *J* 5.5, CHO) [Found: *m/z* 232.1459. Calc. for $C_{15}H_{20}O_2$ (M^+): *m/z* 232.1462].

(1*R*,2*R*)-2-[(1*R*)-3-Benzyloxy-1-methylpropyl]cyclopropane-1-methanol 19

To a stirred solution of the aldehyde **18** (0.08 g, 0.36 mmol) in THF (1 cm^3) was added sodium borohydride (0.02 g, 0.52 mmol) at 0 °C and the mixture was stirred at room temperature for 12 h. After treatment with saturated aq. ammonium chloride, the mixture was extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (2:1, v/v) afforded the alcohol **19** (0.08 g, 96%) as a colourless oil; $[\alpha]_D$ −17.0 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3430 and 2890; δ_H 0.22–0.38 (2 H, m, 3-H_2), 0.38–0.51 (1 H, m, 2-H), 0.81–1.05 (5 H, m, 1-H, 1′-H and 1′-Me), 1.69 (2 H, dt, *J* 6.0 and 6.5, 2′-H_2), 1.82–2.00 (1 H, br s, OH), 3.25 (1 H, dd, *J* 11.0 and 7.5, 1-C*H*HOH), 3.49 (1 H, dd, *J* 11.0 and 7.5, 1-C*H*HOH), 3.53–3.64 (2 H, m, 3′-H_2), 4.50 (2 H, s, OCH_2Ph) and 7.26–7.36 (5 H, m, ArH) [Found: *m/z* 234.1603. Calc. for $C_{15}H_{22}O_2$ (M^+): *m/z* 234.1618].

(1*R*,2*R*)-2-[(1*R*)-3-Benzyloxy-1-methylpropyl]-1-methylcyclopropane 21

To a stirred solution of the alcohol **19** (1.0 g, 4.3 mmol) and triethylamine (3.6 cm^3, 0.02 mol) in dichloromethane (16 cm^3) was added dropwise methanesulfonyl chloride (1.0 cm^3, 0.01 mol) at 0 °C and the mixture was stirred for a further 30 min. After treatment with saturated aq. ammonium chloride, the mixture was extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue. This, without further purification, was dissolved in THF (6 cm^3) and the solution added dropwise to a stirred suspension of lithium aluminium hydride (0.8 g, 0.02 mol) in THF (10 cm^3) at 0 °C. After being stirred for 30 min at the same temperature, this mixture was treated with 10% aq. NaOH and the insoluble materials formed were removed by filtration of the mixture through a Celite pad. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (50:1, v/v) afforded the benzyl ether **21** (0.8 g, 86%) as a colourless oil; $[\alpha]_D$ −30.3 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2850; δ_H 0.03–0.21 (3 H, m, 1-H and 3-H_2), 0.38–0.55 (1 H, m, 2-H), 0.78–1.00 (1 H, m, 1′-H), 0.93 (3 H, d, *J* 6.5, 1-Me), 0.97 (3 H, d, *J* 6.0, 1′-Me), 1.57–1.78 (2 H, m, 2′-H_2), 3.56 (2 H, t, *J* 6.0, 3′-H_2), 4.50 (2 H, s, OCH_2Ph) and 7.22–7.39 (5 H, m, ArH) [Found: *m/z* 218.1669. Calc. for $C_{15}H_{22}O$ (M^+): *m/z* 218.1669].

(1*R*,2*R*)-2-[(1*R*)-3-Hydroxy-1-methylpropyl]-1-methylcyclopropane 22

The benzyl ether **21** (76 mg, 0.35 mmol) in methanol (1 cm^3) in the presence of a catalytic amount of 10% palladium–carbon was hydrogenated under an atmospheric pressure of hydrogen for 12 h. The insoluble material was removed by filtration of the mixture through a Celite pad and the filtrate concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane–ethyl acetate (1:1, v/v) afforded the alcohol **22** (40 mg, 89%) as a colourless oil; $[\alpha]_D$ −48.7 (*c* 0.5, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 and 2890; δ_H 0.09–0.25 (3 H, m, 1-H and 3-H_2), 0.42–0.57 (1 H, m, 2-H), 0.76–0.92 (1 H, m, 1′-H), 0.95 (3 H, d, *J* 6.0, 1-Me), 1.01 (3 H, d, *J* 6.0, 1′-Me), 1.05–1.76 (2 H, m, 2′-H_2) and 3.73 (2 H, t, *J* 6.5, 3′-H_2) [Found: *m/z* 110.1104. Calc. for C_8H_{15} (M^+ − 18): *m/z* 110.1096].

***p*-Nitrobenzoate 23**

A solution of the alcohol **22** (20 mg, 0.16 mmol), *p*-nitrobenzoyl chloride (40 mg, 0.2 mmol) and pyridine (0.02 cm^3) in dichloromethane (1 cm^3) was stirred for 12 h under argon. The mixture was diluted with dichloromethane and washed successively with saturated aq. $KHSO_4$, saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (20:1, v/v) afforded the benzoate **23** (42 mg, 97%) as a colourless oil; $[\alpha]_D$ −21.8 (*c* 0.4, $CHCl_3$); δ_H 0.12–0.32 (3 H, m, 1-H and 3-H_2), 0.42–0.58 (1 H, m, 2-H), 0.83–0.98 (1 H, m, 1′-H), 1.02 (3 H, d, *J* 6.0, 1-Me), 1.04 (3 H, d, *J* 6.0, 1′-Me), 1.82 and 1.88 (each 1 H, each dt, *J* 6.5 and 7.5, 2′-H_2), 4.48 (2 H, t, *J* 6.5, 3′-H_2), 8.19 (2 H, d, *J* 8.5, ArH) and 8.29 (2 H, d, *J* 8.5, ArH). These data were identical with those reported.[4]

(1*R*,2*R*)-2-[(1*R*)-3-Bromo-1-methylpropyl]-1-methylcyclopropane 24

A solution of the alcohol **23** (0.2 g, 1.6 mmol), triphenylphosphine (0.6 g, 2.3 mmol) and *N*-bromosuccinimide (0.4 g, 2.3

mmol) in dichloromethane (3 cm^3) was stirred at ambient temperature for 30 min after which it was washed with brine, dried (Na_2SO_4) and evaporated to give a residue. This was purified by distillation to afford the bromide **24** (0.22 mg, 74%) as a colourless oil; bp 75 °C/30 mmHg; $[\alpha]_D$ −45.8 (*c* 0.9, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2950; δ_H 0.07–0.24 (3 H, m, 1-H and 3-H_2), 0.48–0.66 (1 H, m, 2-H), 0.83–1.10 (1 H, m, 1′-H), 0.94 (3 H, d, *J* 6.0, 1-Me), 1.01 (3 H, d, *J* 6.0, 1′-Me), 1.79–2.03 (2 H, m, 2′-H_2) and 3.51 (2 H, t, *J* 6.5, 3′-H_2) [Found: *m/z* 190.0357. Calc. for $C_8H_{15}Br$ (M^+): *m/z* 190.0357].

(24*R*,25*R*,26*R*)-24,26-Dimethyl-3β-(*tert*-butyldimethylsiloxy)-25,27-cyclocholest-5-en-20α-ol 26

To a stirred suspension of samarium metal (0.6 g, 4.2 mmol) and 4 Å molecular sieves (0.5 g) in dry THF (9.5 cm^3) was added dropwise a solution of diiodoethane (1.1 g, 3.9 mmol) in THF (9.5 cm^3) at ambient temperature and the resulting solution was further stirred for 30 min. HMPA (2.4 cm^3) was added to the solution and stirring continued for 15 min. After this, a solution of the 20-oxo steroid **25** (0.45 g, 1.0 mmol) in THF (6 cm^3) and a solution of the bromide **24** (0.2 g, 1.0 mmol) in THF (2 cm^3) were added to the mixture which was then stirred for 10 min before being treated with saturated aq. $NaHCO_3$. Celite (*ca.* 20 g) and an excess of ether were added to the mixture which was then filtered through a Celite pad to remove the insoluble material. The filtrate was treated with water and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (6:1, v/v) afforded the coupling product **26** (0.51 g, 90%) as a colourless powder; mp 126–128 °C; $[\alpha]_D$ −41.8 (*c* 1.1, $CHCl_3$) (Found: C, 77.05; H, 11.55. $C_{35}H_{62}O_2Si$ requires C, 77.35; H, 11.50); $\nu_{max}(CHCl_3)/cm^{-1}$ 3100 and 2870; δ_H 0.06 (6 H, s, 2 × Me), 0.09–0.22 (2 H, m, 27-H_2), 0.36–0.72 (2 H, m, 25-H and 26-H), 0.83–0.94 (16 H, m, Bu^t, 24-Me, 18-Me and 24-H), 0.96–1.06 (6 H, m, 19-Me and 29-Me), 1.28 (3 H, s, 21-Me), 3.40–3.56 (1 H, m, 3-H) and 5.32 (1 H, apparent d, *J* 5.5, 6-H) [Found: *m/z* 524.4407. Calc. for $C_{35}H_{60}OSi$ (M^+ − 18): *m/z* 524.4412].

20α-Hydroxycholesterol 27

The coupling reaction of the 20-oxo steroid **25** (0.5 g, 1.2 mmol) with 1-bromo-4-methylpentane (0.2 g, 1.2 mmol) in the presence of samarium diiodide was carried out by a procedure similar to that used for the preparation of **26** to provide the 20α-hydroxy steroid (0.5 g), which was dissolved into THF (5 cm^3). To this solution was added a 1 M solution of tetrabutylammonium fluoride in THF (3.7 cm^3, 3.7 mmol) at ambient temperature and the resulting mixture was further stirred for 12 h. After this, the mixture was treated with water and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (3:1, v/v) afforded 20α-hydroxycholesterol **27** (0.38 g, 100%) as a colourless powder; mp 131–133 °C; δ_H 0.86 (3 H, s, 18-Me), 0.88 (6 H, d, *J* 6.0, 26- and 27-Me), 1.01 (3 H, s, 19-Me), 1.27 (3 H, s, 21-Me), 3.43–3.61 (1 H, m, 3-H) and 5.35 (1 H, apparent d, *J* 5.5, 6-H) [Found: *m/z* 402.3498. Calc. for $C_{27}H_{46}O_2$ (M^+): *m/z* 402.3497]. These data were identical with those reported.[10]

(24*R*,25*R*,26*R*)-24,26-Dimethyl-25,27-cyclocholesta-5,20(22)-dien-3β-ol 28 and (24*R*,25*R*,26*R*)-24,26-dimethyl-25,27-cyclocholesta-5,20(21)-dien-3β-ol 29

A solution of the 20-hydroxy steroid **26** (0.2 g, 0.37 mmol) and concentrated hydrochloric acid (0.15 cm^3) in methanol (25 cm^3) was heated at reflux for 30 min. After being cooled to room temperature, this solution was diluted with an excess of ether, washed with saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (6:1, v/v) afforded the olefins **28** and **29** (15:1) (0.15 g, 98%) as a colourless and amorphous solid; $\nu_{max}(CHCl_3)/cm^{-1}$ 3340 and 2950; δ_H 0.56 (2.8 H, s, 18-Me), 0.59 (0.2 H, s, 18-Me), 1.01 (3 H, s, 19-Me), 4.76 (0.06 H, m, 21-H), 4.87 (0.06 H, m, 21-H), 5.20–5.30 (0.94 H, m, 22-H) and 5.30–5.45 (1 H, m, 6-H) [Found: *m/z* 410.3549. Calc. for $C_{29}H_{46}O$ (M^+): 410.3549].

(24*R*,25*R*,26*R*)-24,26-Dimethyl-6β-methoxy-3α,5; 25,27-dicyclo-5α-cholest-20(22)-ene 30 and (24*R*,25*R*,26*R*)-24,26-dimethyl-6β-methoxy-3α,5;25,27-dicyclo-5α-cholest-20(21)-ene 31

A solution of the above mixture of compounds **28** and **29** (0.05 g, 0.12 mmol) and toluene-*p*-sulfonyl chloride (0.05 g, 0.24 mmol) in pyridine (0.4 cm^3) was stirred for 12 h at room temperature. The mixture was taken up in chloroform and the solution washed successively with saturated aq. $KHSO_4$, saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to give a residue. This, without further purification, was dissolved in methanol (0.7 cm^3) and pyridine (0.03 cm^3) and the resulting solution heated at 70 °C for 1 h. After being cooled to room temperature, the mixture was diluted with ethyl acetate and washed successively with saturated aq. $KHSO_4$, saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (10:1, v/v) afforded an inseparable mixture of the methoxy compounds **30** and **31** (45 mg, 87%) as a colourless and amorphous solid; $\nu_{max}(CHCl_3)/cm^{-1}$ 2950; δ_H 0.60 (2.8 H, s, 18-Me), 0.62 (0.2 H, s, 18-Me), 1.03 (3 H, s, 19-Me), 2.67–2.82 (1 H, m, 6-H), 3.33 (3 H, s, OMe), 4.76 (0.06 H, m, 21-H), 4.87 (0.06 H, m, 21-H) and 5.15–5.45 (0.94 H, m, 22-H) [Found: *m/z* 424.3706. Calc. for $C_{30}H_{48}O$ (M^+): *m/z* 424.3705].

(20*R*/*S*,24*R*,25*R*,26*R*)-24,26-Dimethyl-6β-methoxy-3α,5;25,27-dicyclo-5α-cholestane 32

The olefins **30** and **31** (45 mg, 0.11 mmol) in ethyl acetate (1 cm^3) in the presence of a catalytic amount of 10% palladium–carbon were hydrogenated under an atmospheric pressure of hydrogen for 12 h. The insoluble material was removed by filtration of the mixture through a Celite pad and the filtrate concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane–ethyl acetate (20:1, v/v) afforded compound **32** (40 mg, 89%) as a colourless and amorphous solid; $\nu_{max}(CHCl_3)/cm^{-1}$ 2950; δ_H 0.72 (3 H, s, 18-Me), 0.83 (1.2 H, d, *J* 6.0, 21-Me), 0.89 (1.8 H, d, *J* 6.5, 26-Me), 0.90 (1.2 H, d, *J* 6.5, 26-Me), 0.94 (1.8 H, d, *J* 6.0, 21-Me), 1.01 (3 H, d, *J* 6.5, 29-Me), 1.02 (3 H, s, 19-Me), 2.72–2.80 (1 H, m, 6-H) and 3.32 (3 H, s, OMe) [Found: *m/z* 426.3860. Calc. for $C_{30}H_{50}O$ (M^+): *m/z* 426.3860].

Petrosterol 3 and its 20-epimer 33

A solution of the methoxy derivative **32** (0.12 g, 0.28 mmol) and a catalytic amount of toluene-*p*-sulfonic acid in dioxane–water (2:1; 2 cm^3) was heated at 80 °C for 1 h and then evaporated. The residue was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (4:1, v/v) afforded petrosterol **3** (64 mg, 55%) as a colourless solid; mp 157–159 °C (MeOH); $[\alpha]_D$ −33.4 (*c* 0.3, $CHCl_3$); δ_H 0.02–0.20 (2 H, m, 27-H_2), 0.35–0.50 (1 H, m, 26-H), 0.54–0.65 (2 H, m, 24-H and 25-H), 0.68 (3 H, s, 18-Me), 0.89 (3 H, d, *J* 6.5, 28-Me), 0.92 (3 H, d, *J* 6.5, 21-Me), 1.01 (3 H, d, *J* 6.0, 29-Me), 1.01 (3 H, s, 19-Me), 3.44–3.61 (1 H, m, 3-H) and 5.31–5.38 (1 H, m, 6-H) [Found: *m/z* 412.3706. Calc. for $C_{29}H_{48}O$ (M^+): *m/z* 412.3705]. These data were identical with those reported.[14] Further elution with the same solvent system gave the 20-epimer **33** (42 mg, 36%); δ_H 0.02–0.20 (2 H, m, 27-H_2), 0.35–0.50 (1 H, m, 26-H), 0.54–0.65 (2 H, m, 24-H and 25-H), 0.68 (3 H, s, 18-Me), 0.83 (3 H, d, *J* 6.0, 21-Me), 0.90 (3 H, d, *J* 6.5, 28-Me), 1.01 (3 H, d, *J* 6.0, 29-

Me), 1.01 (3 H, s, 19-Me), 3.44–3.61 (1 H, m, 3-H) and 5.31–5.38 (1 H, m, 6-H) [Found: m/z 412.3702. Calc. for $C_{29}H_{48}O$ (M^+): m/z 412.3705]. This compound was contaminated with a trace of petrosterol and further purification could not, unfortunately, be achieved.

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