Neighbouring Group Participation in the Cleavage of Steroidal α-Hydroxy-acetals[1]

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Both 6,6-ethylenedioxy-5-hydroxy-3β-methoxy-5α-cholestane **13** and its 5β-epimer **17** undergo cleavage of the acetal ring with skeletal rearrangement to give 5-(2-hydroxyethoxy)-3β-methoxy-4aα-methyl-4a-homo-7-nor-5β-cholestan-4aβ-ol **19** upon treatment with MeMgI in refluxing toluene; in a second rearrangement the 4a-homo-7-norsteroid **19** is smoothly converted into 3β-methoxy-5-methyl-5α-cholestan-6-one **25**.

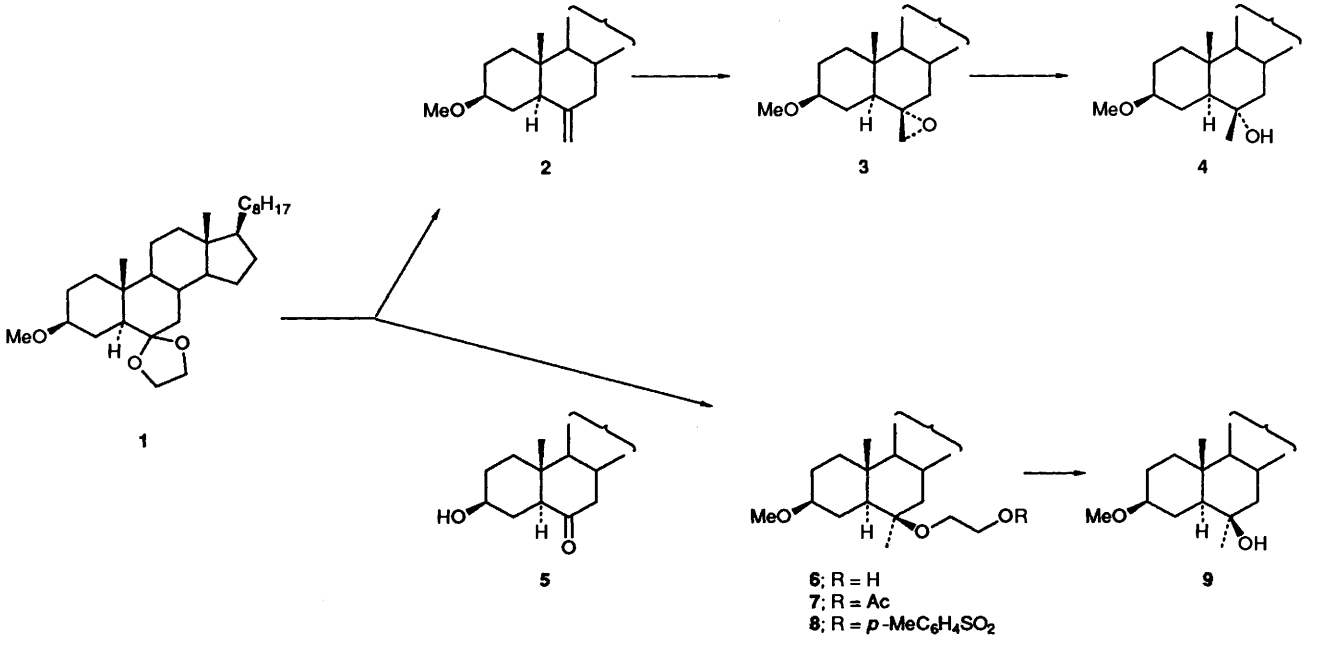
In general, when ethylene acetals derived from steroidal 3-, 17- and 20-ketones are treated with Grignard reagents under forcing conditions they undergo cleavage initiated by nucleophilic attack at C-1 of the acetal ring.[2] It is now shown that this is the case also with steroidal 6-acetals; thus, when compound **1**, obtained from 3β-hydroxy-5α-cholestan-6-one **5**[3] by successive acetalisation and methylation, is treated with MeMgI in refluxing toluene the acetal ring undergoes cleavage by nucleophilic attack of the Grignard reagent at C-6. The products obtained are the hydroxyethoxy compound **6** and the 6-methylene compound **2** arising from it by elimination of the elements of ethylene glycol. The structure of compound **6** followed from its NMR spectrum and that of its acetate **7**, and was confirmed by reduction of the derived toluene-*p*-sulphonate **8** with zinc and sodium iodide[4] to give the known alcohol **9**.[5] The epimeric carbinol **4** was obtained from the olefin **2** by successive epoxidation (with *m*-chloroperbenzoic acid) and reduction with lithium aluminium hydride.

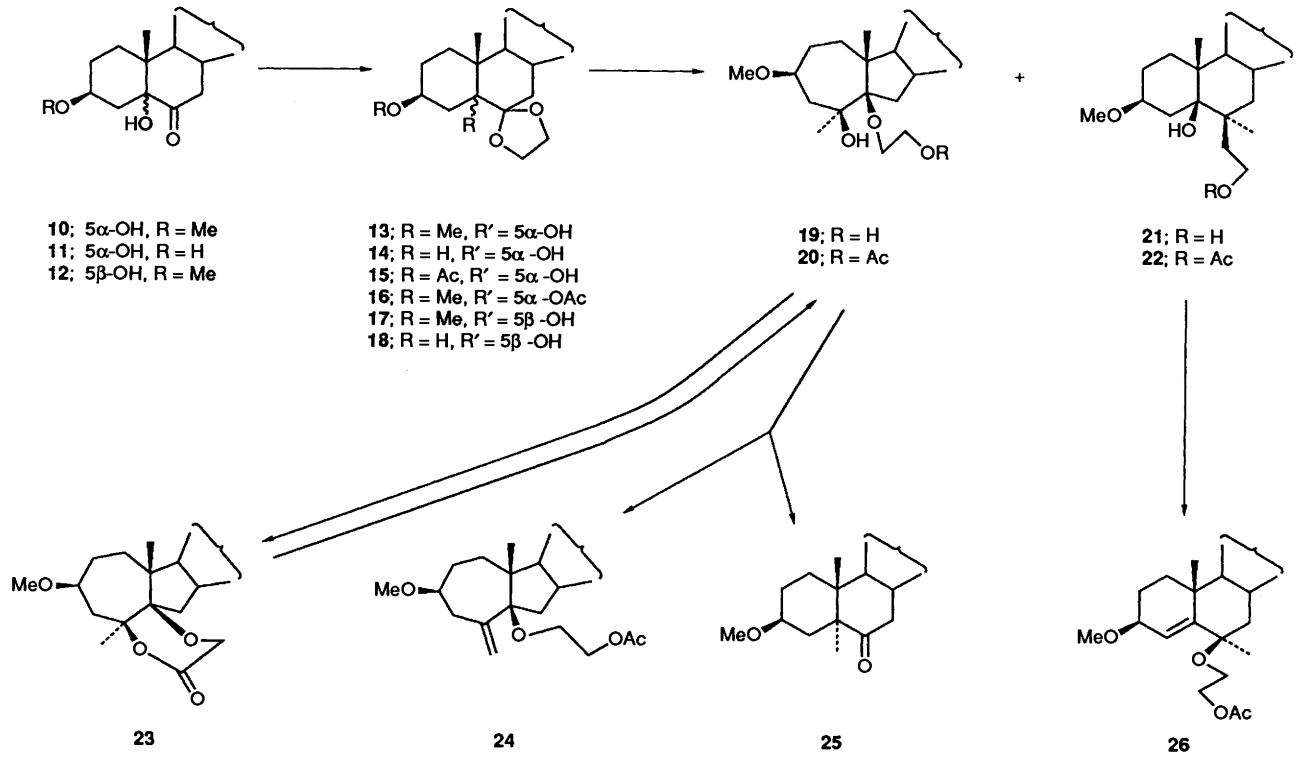
In the cleavage of steroidal epoxides the outcome of the reaction is profoundly affected by the intervention of a neighbouring acetoxy,[6] hydroxy[5,7] or methoxy group.[8] We now report that, when a neighbouring hydroxy group is present in a steroidal 6-acetal, cleavage of the dioxolane ring by the action of MeMgI is accompanied by rearrangement to produce a 4a-homo-7-norsteroid.[9]

6,6-Ethylenedioxy-5-hydroxy-3β-methoxy-5α-cholestane **13** was readily prepared by the action of ethanediol and toluene-*p*-sulphonic acid on 5-hydroxy-3β-methoxy-5α-cholestan-6-one **10**.[10] The same material was also obtained from 3β,5-dihydroxy-5α-cholestan-6-one **11**[11] by successive acetalisation with ethanediol and toluene-*p*-sulphonic acid (to give the acetal **14**, characterised as its acetate **15**) and methylation with silver oxide and methyl iodide. Upon treatment with potassium hydrogen sulphate and acetic anhydride compound **13** afforded the derived tertiary acetate **16**; its failure to form compound **29** by a Westphalen rearrangement[12] may be attributed to the presence of a strongly electron-withdrawing group at C-6 which inhibits the formation of carbocationic character at C-5.

An attempt to prepare the C-5-epimeric acetal **17** by treatment of the 5β-hydroxy ketone **12**[6] with ethanediol and toluene-*p*-sulphonic acid gave a product which, although appearing to be chromatographically homogeneous, was revealed by its NMR spectrum to be a 2:1 mixture of the 5β- and 5α-dioxolanes **17** and **13** respectively. The 5β-hydroxy acetal **17** was obtained in a pure state by methylation of the dihydroxy acetal **18**.[13]

When the 5α-hydroxy acetal **13** was treated with MeMgI in refluxing toluene cleavage of the dioxolane ring was accompanied by skeletal rearrangement to afford the 4a-homo-7-norsteroid **19** in a yield of 93%. The structure of the rearrangement product followed from its spectra and from its



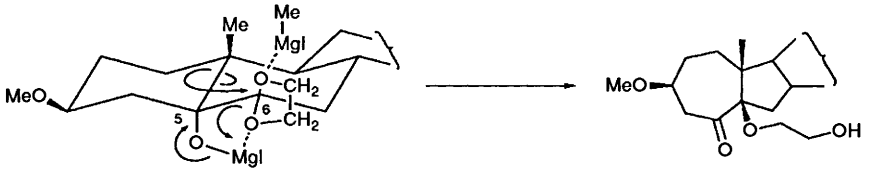


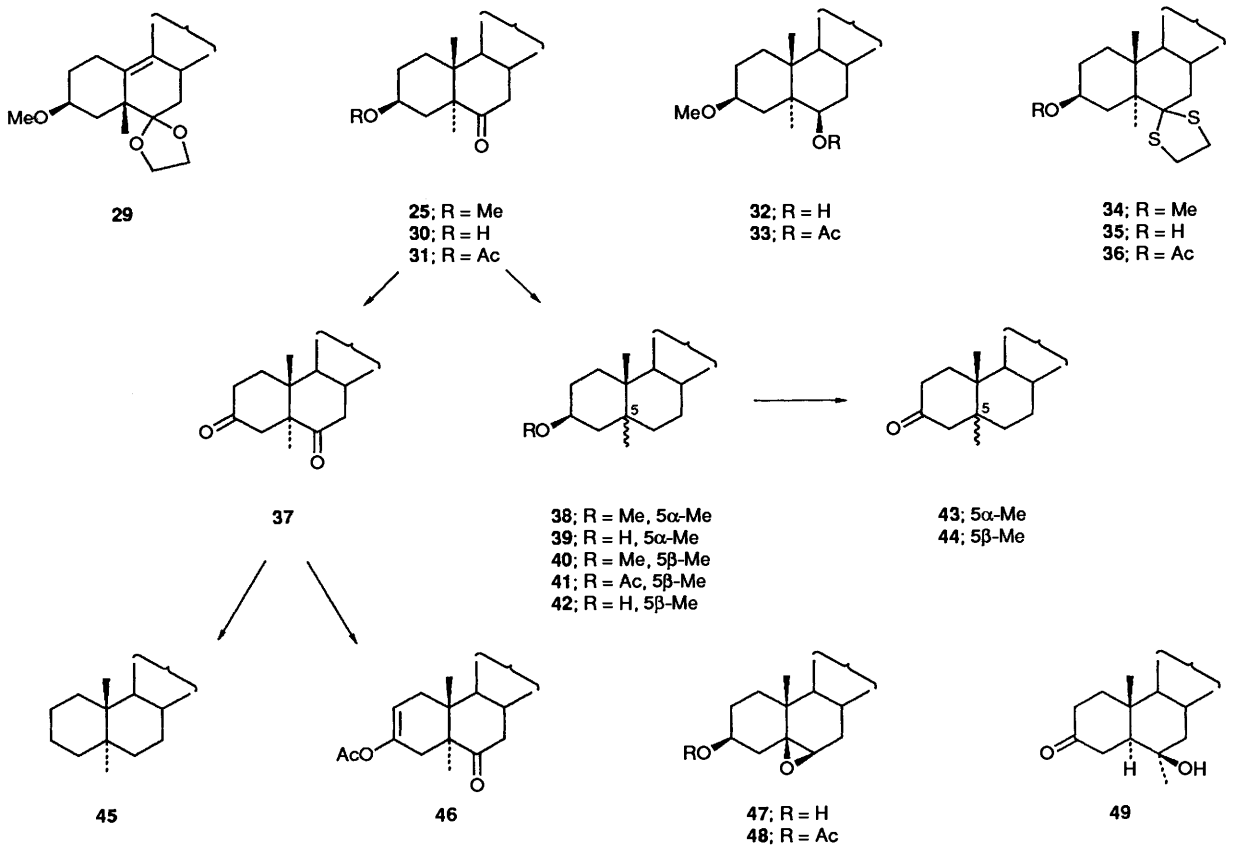
chemical behaviour. In accord with its assigned structure the hydroxyethoxy compound **19** was oxidised with chromyl chloride under very mild conditions to afford the lactone **23**; the absence of any further rearrangement during the oxidation was established by the observation that compound **23** gave back the alcohol **19** upon reduction with lithium aluminium hydride. Dehydration of the derived acetate **20** with thionyl chloride and pyridine at 0 °C gave the *exo*-methylene compound **24** in low yield, together with a ketone to which the rearranged structure **25** has been assigned, on the evidence outlined below. The same ketone was obtained in a yield of 91% by treatment of the diol **19** with methanesulphonyl chloride and collidine in *N*,*N*-dimethylformamide that had been saturated with sulfur dioxide.[14]

Formation of the 4a-homo-7-norsteroid **19** may occur by rearrangement of the Grignard-complexed acetal **27**, in which the C-10–C-5 and C-6α–O bonds have the antiperiplanar relationship appropriate for a 1,2-migration, followed by nucleophilic attack by the Grignard reagent on the resulting ketone **28**. In accord with this view the 5β-hydroxy acetal **17**, in which the 5β and 6α-oxygen functions are likely to be less strongly chelated in the Grignard complex, affords the diol **19** in a lower yield (63%), together with the unrearranged steroid **21** arising by direct nucleophilic attack at C-6. The rearrangements undergone by the hydroxy acetals **13** and **17** find an analogy in the behaviour of the ethylene acetal of 3β,17α-dihydroxypregn-5-en-20-one when subjected to similar conditions.[15] The structure assigned to the diol **21** was supported by the observation that its monoacetate **22** underwent dehydration with thionyl chloride and pyridine to afford the olefin **26** in which the methoxy group was shown by suitable NMR double irradiation to be in an allylic position.

The ketone **25** described above afforded the 6β-hydroxy compound **32**, characterised as the derived acetate **33**, by reduction with lithium aluminium hydride. Cleavage of the methoxy group in the ketone **25** with sodium iodide and trimethylsilyl chloride gave 3β-hydroxy-5-methyl-5α-cholestan-6-one **30**, from which the corresponding acetate **31** was obtained by the action of acetic anhydride and pyridine.

When the methoxy ketone **25** was treated with boron trifluoride–diethyl ether and ethanedithiol the derived thioacetal **34** was obtained; if prolonged reaction conditions were employed the methoxy group was cleaved and the product was the hydroxy thioacetal **35**, which afforded the acetate **36**. Attempts to convert compound **25** into a 6-deoxy derivative by desulfurisation of the thioacetals **34** and **35** were unsuccessful. However, Huang–Minlon reduction of the ketone **25** afforded 3β-methoxy-5-methyl-5α-cholestane **38** in good yield. The structures assigned to all the compounds in this series were confirmed by demethylation of the methyl ester **38** and oxidation of the resulting alcohol **39** to give 5-methyl-5α-cholestan-6-one **43**, shown to be identical with a sample obtained as previously described[16] from cholest-4-ene-3-one. The preparation of the 5β-epimer **40** of compound **38**, and the corresponding acetate **41** from cholest-4-en-3-one *via* 5-methyl-5β-cholestan-3-one **44** and 5-methyl-5β-cholestan-3β-ol **42** is described in the Experimental section.





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Jones' oxidation[17] of the ketol **30** afforded 5-methyl-5α-cholestane-3,6-dione **37**, which was characterised as the derived enol acetate **46**. The diketone **37** was converted into 5-methyl-5α-cholestane **45** by Huang–Minlon reduction. Structure **37** has previously been assigned[18] to a compound of quite different m.p. obtained by chromic acid oxidation of the product resulting from cleavage of 5,6β-epoxycholestan-3β-ol **49** with MeMgI. A reinvestigation of these reactions has shown that the compound obtained by the earlier workers was in fact 6β-hydroxy-6α-methyl-5α-cholestan-3-one **49**. The assignment[18] of structure **45** to the product obtained by Clemmensen reduction of that ketone is, therefore, also erroneous.

Experimental

M.p.s were measured on a Kofler hot-stage apparatus. IR spectra (Nujol mulls unless stated otherwise) were recorded on a Perkin-Elmer 1420, a Perkin-Elmer 157G, or a Pye Unicam SP 2000 spectrophotometer. NMR spectra were recorded on a Perkin-Elmer R32A, a Jeol FX90Q, or a Bruker AM400 instrument, with deuteriochloroform as solvent unless stated otherwise. Mass spectra were measured on an A.E.I. MS902 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polameter or on a Thorn NPL automatic polarimeter type 243 for solutions in chloroform and values are recorded in 10^{-1} deg cm^2 g^{-1}. Merck Kieselgel G (type 60) was used for column chromatography unless stated otherwise, and TLC was carried out using plates prepared from Merck Kieselgel GF_{254}. Light petroleum refers to the fraction of boiling range 60–80 °C. Ether refers to diethyl ether. Solutions in organic solvents were dried with anhydrous sodium sulfate or magnesium sulfate.

6,6-*Ethylenedioxy*-3β-*methoxy*-5α-*cholestane* **1**.—A mixture of 3β-hydroxy-5α-cholestan-6-one **5** (4.75 g), toluene-*p*-sulfonic acid (575 mg) and ethylene glycol (25 ml) in toluene (125 ml) was rapidly stirred and slowly distilled for 6 h with frequent additions of fresh toluene. After the mixture had cooled, the glycol layer was separated, diluted with aq. sodium hydrogen carbonate and extracted successively with toluene and ether. These extracts were combined with the original toluene solution and the whole then washed successively with aq. sodium hydrogen carbonate and saturated brine, dried, and evaporated under reduced pressure to yield 6,6-ethylenedioxy-3β-hydroxy-5α-cholestane as an oil (4.82 g, 92%) that slowly crystallised.

A solution of the crude dioxolane (1.65 g) in benzene (20 ml) was heated under reflux for 2 h with sodium hydride (795 mg). Freshly distilled methyl iodide (5 ml) was added and heating was continued for a further 45 min. Water was added to the cooled mixture which was then extracted with ether. The organic layer was separated, washed with water, dried, and evaporated under reduced pressure to give a clear oil (1.66 g) which crystallised with time. Recrystallisation from methanol–chloroform afforded the *title compound* **1** (1.04 g, 61%), m.p. 113–114 °C; $[\alpha]_D^{20}$ +18.4 (*c* 1.19) (Found: C, 78.05; H, 11.05%; M$^+$, 460.3916. $C_{30}H_{52}O_3$ requires C, 78.2; H, 11.4%; *M*, 460.3916); ν_{max}/cm^{-1} 1177, 1109 and 1042; δ_H 0.66 (3 H, s, 18-H_3), 0.87 (3 H, s, 19-H_3), 2.9–3.3 (1 H, m, 3α-H), 3.33 (3 H, s, OCH_3) and 3.85 (4 H, m, OCH_2CH_2O).

Reaction of 6,6-*Ethylenedioxy*-3β-*methoxy*-5α-*cholestane* **1** *with Methylmagnesium Iodide*.—A Grignard solution prepared from methyl iodide (2 ml) and magnesium (530 mg) in ether (10 ml) was added to a solution of the acetal **1** (1.03 g) in dry toluene (35 ml), and solvent was removed by distillation until the internal temperature reached 106 °C. More toluene (10 ml) was added and the mixture was heated under reflux in an atmosphere of nitrogen for 26 h. After the mixture had cooled, saturated aq. ammonium chloride was added, and the mixture was extracted with ether. The ether extract was washed successively with dilute hydrochloric acid and water, dried and then chromatographed (80 g column; chloroform as eluent).

From the earlier fractions 3β-*methoxy*-6-*methylene*-5α-*cholestane* **2** (272 mg, 30%) was obtained, m.p. 74–75 °C (ex methanol–chloroform); $[\alpha]_D^{20}$ +3.9 (*c* 1.03) (Found: C, 83.8; H, 12.0%; M^+, 414.3869. $C_{29}H_{50}O$ requires C, 84.0; H, 12.15%; *M*, 414.3861); ν_{max}/cm^{-1} 1648, 1106 and 887; δ_H 0.63 and 0.66 (each 3 H, ang. CH_3 groups), 2.9–3.3 (1 H, m, 3α-H), 3.35 (3 H, s, OCH_3) and 4.46 and 4.70 (each 1 H, s, $W_{\frac{1}{2}}$ 4.5, olefinic H atoms).

Further elution afforded 6β-(2-*hydroxyethoxy*)-3β-*methoxy*-6α-*methyl*-5α-*cholestane* **6** (698 mg, 67%) as a gum which could not be crystallised. Distillation (190 °C/0.01 Torr) gave an analytical sample, $[\alpha]_D^{20}$ +18.5 (*c* 2.01) [Found: C, 77.4; H, 12.0%; *m/z* 461.3998. $C_{31}H_{56}O_3$ requires C, 78.1; H, 11.85%; $C_{30}H_{53}O_3$ ($M - CH_3$) requires *m/z* 461.3994]; ν_{max}/cm^{-1} 3600–3200 and 1100; δ_H 0.67 (3 H, s, 18-H_3), 0.98 (3 H, s, 19-H_3), 1.11 (3 H, s, 6α-CH_3), 2.03 (1 H, s, exchangeable with D_2O, OH), 2.9–3.33 (1 H, m, 3α-H), 3.30 (2 H, m, OCH_2CH_2OH), 3.37 (3 H, s, OCH_3) and 3.63 (2 H, m, $W_{\frac{1}{2}}$ 14 Hz, OCH_2CH_2OH). The derived acetate **7** (147 mg, 86%) was obtained [by acetylation of the alcohol **6** (157 mg) with pyridine (2 ml) and acetic anhydride (1 ml) overnight at room temperature] as a gum which distilled at 185 °C (0.005 Torr); $[\alpha]_D$ +10.9 (*c* 1.3); *m/z* 503 ($M^+ - CH_3$); ν_{max}(film)/cm^{-1} 1747, 1248–1235 and 1107; δ_H 0.67 (3 H, s, 18-H_3), 0.94 (3 H, s, 19-H_3), 1.08 (3 H, s, 6α-CH_3), 2.01 (3 H, s, OAc), 2.85–3.3 (1 H, m, 3α-H), 3.33 (3 H, s, OCH_3), 3.41 (2 H, m, OCH_2CH_2OAc) and 4.10 [2 H, dd, *J* 4 and 5, OCH_2CH_2OAc; this signal collapsed to a br s, $W_{\frac{1}{2}}$ 6 Hz, upon irradiation at δ 3.36].

Cleavage of the Hydroxyethoxy Group of 6β-(2-*Hydroxyethoxy*)-3β-*methoxy*-6α-*methyl*-5α-*cholestane* **6**.—A solution of toluene-*p*-sulfonyl chloride (311 mg) and the hydroxyethoxy compound **6** (560 mg) in pyridine (3 ml) was kept overnight at −40 °C. After warming to room temperature, the mixture was treated with aq. lactic acid (3 drops, 85%) and then poured into dilute aq. lactic acid (200 ml, 2%) and extracted with ether. The extract was washed successively with water, dil. hydrochloric acid, water, aq. sodium hydrogen carbonate, water, and saturated brine and then dried and evaporated under reduced pressure. A solution of the residue in 1,2-dimethoxyethane (5 ml) was stirred and heated under reflux for 3 h in a nitrogen atmosphere with sodium iodide (615 mg) and zinc powder (628 mg). When cool, the mixture was filtered into aq. sodium thiosulfate (5%; 100 ml) and extracted with ether. The ether extract was washed successively with aq. sodium thiosulfate (1.5%), aq. sodium hydrogen carbonate and brine, and then dried and evaporated under reduced pressure. The residue was chromatographed [60 g column; chloroform–ethyl acetate (2:1) as eluent] to afford, from the early fractions, a pale yellow powder (270 mg) from which a compound, thought to be 6β-(2-iodoethoxy)-3β-methoxy-6α-methyl-5α-cholestane (195 mg, 28%) was obtained by extraction with ether.

Subsequently, some unchanged starting material **6** (26 mg, 5%) was obtained, followed by some mixed fractions (161 mg) and finally, 3β-methoxy-6α-methyl-5α-cholestan-6β-ol **9** (106 mg, 21%) identified by direct comparison (TLC, m.p., mixed m.p., NMR) with an authentic specimen.[5]

3β-*Methoxy*-5α-*cholestane*-6-(S)-*spiro*-2′-*oxirane* **3**.—A solution of 3β-methoxy-6-methylene-5α-cholestane **2** (249 mg) was treated overnight at room temperature with 3-chloroperoxybenzoic acid (455 mg). The mixture was diluted with ether, washed successively with aq. sodium metabisulphite, aq. sodium hydrogen carbonate, and brine and then dried and chromatographed (20 g column; chloroform as eluent) to yield the *title compound* **3** (222 mg, 86%), m.p. 111–112 °C (ex methanol); $[\alpha]_D^{20}$ +25.6 (*c* 1.37) (Found: C, 80.5; H, 11.85%; M^+, 430.3818. $C_{29}H_{50}O_2$ requires C, 80.85; H, 11.7%; *M*, 430.3811); ν_{max}/cm^{-1} 1106 and 820; δ_H 0.65 (3 H, s, 18-H_3), 0.91 (3 H, s, 19-H_3), 2.51 and 2.71 (each 1 H, d, *J* 4.5, oxiranic protons), 2.9–3.3 (1 H, m, 3α-H) and 3.30 (3 H, s, OCH_3).

3β-*Methoxy*-6β-*methyl*-5α-*cholestan*-6α-*ol* **4**.—A solution of the epoxide **3** (191 mg) in ether (20 ml) was heated under reflux with lithium aluminium hydride (296 mg) for 2 h and then cooled and quenched by the addition of ethyl acetate and dil. hydrochloric acid. The organic layer was diluted with ether and then washed successively with dil. hydrochloric acid and water, dried, and evaporated under reduced pressure. Chromatography of the residue (20 g column; chloroform as eluent) afforded the *title compound* **4** (147 mg, 77%) as prisms, m.p. 99–101 °C (ex light petroleum); $[\alpha]_D^{18}$ +17.7 (*c* 1.53) (Found: C, 80.5; H, 12.05% M^+, 432.3972. $C_{29}H_{52}O_2$ requires C, 80.5; H, 12.1%; *M*, 432.3967); ν_{max} 3600–3200 and 1106–1095 cm^{-1}; δ_H 0.68 (3 H, 18-H_3), 0.85 (3 H, s, 19-H_3), 1.10 (3 H, s, 6β-CH_3), 1.71 (1 H, s, exchangeable with D_2O, OH), 2.95–3.35 (1 H, m, 3α-H) and 3.36 (3 H, s, OCH_3).

3β,5-*Dihydroxy*-6,6-*ethylenedioxy*-5α-*cholestane* **14**.—This compound was prepared from 3β,5-dihydroxy-5α-cholestan-6-one **11**[9] (3.29 g), ethylene glycol (25 ml), toluene-*p*-sulfonic acid (170 mg) and toluene (100 ml) as described above for the preparation of compound **1**. Chromatography of the crude product [300 g column, ethyl acetate–chloroform (7:3) as eluent] afforded the *title compound* **14** (2.72 g, 75%), which formed rectangular plates from methanol. The crystals did not melt sharply, but turned into a glass in the range 85–89 °C; $[\alpha]_D^{18}$ +7.0 (*c* 2.04) (Found: C, 75.25; H, 11.05%; M, 462.3716. $C_{29}H_{50}O_4$ requires C, 75.3; H, 10.9%; *M*, 462.3709); ν_{max}/cm^{-1} 3600–3200, 1095, 970 and 950; δ_H 0.67 (3 H, s, 18-H_3), 1.08 (3 H, s, 19-H_3), 1.96 (2 H, exchangeable with D_2O, OH) and 3.6–4.3 (5 H, m, 3α-H and OCH_2CH_2O).

Treatment of the dihydroxy acetal **14** (310 mg) with acetic anhydride (1.5 ml) and pyridine (4 ml) at room temperature for 15 h gave 3β-*acetoxy*-5-*hydroxy*-5α-*cholestane*-6-*spiro*-2′-(1′,3′-*dioxolane*) **15** (244 mg, 73%), m.p. 158–160 °C (ex. methanol); $[\alpha]_D^{17}$ −14.0 (*c* 1.7) (Found: C, 73.8; H, 10.55%; M^+, 504.3819. $C_{31}H_{52}O_5$ requires C, 73.75; H, 10.4%; *M*, 504.3815); ν_{max}/cm^{-1} 3455, 1728, 1248, 1162 and 1105; δ_H 0.67 (3 H, s, 18-H_3), 1.09 (3 H, s, 19-H_3), 1.99 (1 H, s, exchangeable with D_2O, OH), 2.02 (3 H, s, OAc), 3.6–4.15 (4 H, m, OCH_2CH_2O) and 4.98–5.43 (1 H, m, 3α-H).

6,6-*Ethylenedioxy*-5-*hydroxy*-3β-*methoxy*-5α-*cholestane* **13**.—(*a*) Treatment of a mixture of 5-hydroxy-3β-methoxy-5α-cholestan-6-one **10**[10] (1.7 g), toluene-*p*-sulphonic acid (51 mg), ethylene glycol (10 ml), and toluene (40 ml) as described above in the preparation of compound **1** afforded the *title compound* **13** (1.52 g, 82%), m.p. 114–116 °C (ex. methanol); $[\alpha]_D^{18}$ −0.67 (*c* 0.78) (Found: C, 75.9; H, 10.8. $C_{30}H_{52}O_4$ requires C, 75.6; H, 11.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3610, 1100 and 950; δ 0.67 (3 H, s, 18-H_3), 1.07 (3 H, s, 19-H_3), 1.83 (1 H, s, exchangeable with D_2O, OH), 3.37 (3 H, s, OCH_3), 3.4–3.8 (1 H, m, 3α-H) and 3.7–4.2 (4 H, m, OCH_2CH_2O).

When the acetal **13** (127 mg) was heated under reflux for 90 min with 2 mol dm^{-3} hydrochloric acid (10 ml) and THF (5 ml) it was hydrolysed back to the ketol **10** (105 mg, 91%).

(b) 3β,5-*Dihydroxy*-6,6-*ethylenedioxy*-5α-*cholestane* **14** (863 mg), methyl iodide (20 ml), silver oxide (2.19 g) and benzene (20 ml) were stirred and heated under reflux for 96 h. The cooled reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. Chromatography of the resulting residue [70 g column; chloroform–ethyl acetate (1:2) as eluent] gave the methoxy acetal **13** (247 mg, 28%), identical with the material described above. Later fractions afforded unchanged starting material **14** (510 mg, 59%).

5-*Acetoxy*-6,6-*ethylenedioxy*-3β-*methoxy*-5α-*cholestane* **16**.—

6,6-Ethylenedioxy-5-hydroxy-3β-methoxy-5α-cholestane **13** (244 mg), potassium hydrogen sulfate (289 mg) and acetic anhydride (2 ml) were heated together on a steam-bath for 15 min. Methanol (5 ml) was added, and the mixture was cooled, poured into water and extracted with ether. The ether extract was washed successively with aq. sodium hydrogen carbonate and water and then dried and chromatographed (25 g column; chloroform as eluent) to afford the *title compound* **16** (158 mg, 60%) as an oil which could not be crystallised (Found: C, 74.7; H, 10.65%; M^+, 518.3970. $C_{32}H_{54}O_5$ requires C, 74.1; H, 10.5%; *M*, 518.3971); ν_{max}/cm^{-1} 1748, 1225, 1105 and 1090; δ_H 0.66 (3 H, s, 18-H_3), 1.08 (3 H, s, 19-H_3), 2.01 (3 H, s, OAc), 3.2–3.6 (1 H, m, 3α-H), 3.33 (3 H, s, OCH_3) and 3.76–4.20 (4 H, m, OCH_2CH_2O).

6,6-*Ethylenedioxy*-5-*hydroxy*-3β-*methoxy*-5β-*cholestane* **17**.—A solution of 3β,5-dihydroxy-5β-cholestane-6-spiro-2′-(1′,3′-dioxolane) **18**[13] (235 mg) in benzene (15 ml) was heated under reflux (N_2 atmosphere) with sodium hydride (184 mg) for 2 h. Methyl iodide (2 ml) was added and heating was continued for a further 45 min. After the mixture had cooled, saturated aq. ammonium chloride was added and the benzene layer was separated, and the aq. phase was extracted with ether. The organic solutions were combined, washed with brine, dried, and evaporated under reduced pressure. The residual oil was purified by chromatography [20 g column; chloroform–ethyl acetate (3:1) as eluent] to afford the *title compound* **17** (239 mg, 99%) as a gum that would not crystallise, $[\alpha]_D^{20}$ +27.0 (*c* 1.02) (Found: C, 75.5; H, 10.8%; M^+, 476.3861. $C_{30}H_{52}O_4$ requires C, 75.6; H, 11.0%; *M*, 476.3865); ν_{max}/cm^{-1} 3490, 1190 and 1085; δ_H 0.68 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), 3.32 (3 H, s, OCH_3), 3.62 (1 H, m, $W_{\frac{1}{2}}$ 7.5, 3α-H), 3.89 (1 H, $W_{\frac{1}{2}}$ 3 Hz, exchangeable with D_2O, OH) and 3.8–4.3 (4 H, m, OCH_2CH_2O).

Reaction of 6,6-*Ethylenedioxy*-5-*hydroxy*-3β-*methoxy*-5α-*cholestane* (**13**) *with Methylmagnesium Iodide*.—A solution of compound **13** (1.94 g) in toluene (50 ml) was treated with a Grignard solution prepared from methyl iodide (4.5 ml) and magnesium (1.46 g) in ether (20 ml) under the conditions already described above for the analogous reaction with the dioxolane **1**. After the usual work-up procedure, chromatography (100 g column, chloroform as eluent) afforded 5-(2-*hydroxyethoxy*)-3β-*methoxy*-4aα-*methyl*-4a-*homo*-7-*nor*-5β-*cholestan*-4aβ-*ol* **19** (1.86 g, 93%) as a colourless gum which crystallised as fine needles from dimethyl sulfoxide, m.p. 66–73 °C; $[\alpha]_D^{25}$ −2.3 (c 1.2) (Found: C, 75.25; H, 11.15%; M^+, 492.4167. $C_{31}H_{56}O_4$ requires C, 75.55; H, 11.45%; *M*, 492.4178); ν_{max}(chloroform)/cm^{-1} 3550–3150 and 1110–1000; δ_H 0.69 (3 H, s, 18-H_3), 0.94 (3 H, s, 19-H_3), 1.32 (3 H, s, 4aα-CH_3), 1.70 (1 H, s, exchangeable with D_2O, OH), 3.2–3.4 [2 H (1 exchangeable with D_2O), m, 3α-H and OH], 3.35 (3 H, s, OCH_3) and 3.6–3.9 (4 H, m, OCH_2CH_2O).

Treatment of the diol **19** (640 mg) with acetic anhydride (2 ml) and pyridine (10 ml) overnight at room temperature afforded the derived *monoacetate* **20** (636 mg, 91%) as a colourless oil, $[\alpha]_D^{20}$ −2.6 (*c* 0.6) (Found: C, 74.25; H, 11.05%; M^+, 534.4281. $C_{33}H_{58}O_5$ requires C, 74.1; H, 10.95%; *M*, 534.4284); ν_{max}(chloroform)/cm^{-1} 3530, 1738 and 1085; δ_H 0.69 (3 H, s, 18-H_3), 0.93 (3 H, s, 19-H_3), 1.31 (3 H, s, 4aα-CH_3), 2.08 (3 H, s, OAc), 2.96 (1 H, exchangeable with D_2O, OH), 3.05–3.50 (1 H, m, 3α-H), 3.36 (3 H, s, OCH_3), 3.78 (2 H, dd, *J* 4 and 9, collapsing to a singlet upon irradiation at δ 4.21, OCH_2CH_2OAc) and 4.21 (2 H, dd, *J* 4 and 9, collapsing to a singlet upon irradiation at δ 3.78, OCH_2CH_2OAc).

4aβ-*Hydroxy*-3β-*methoxy*-4aα-*methyl*-4a-*homo*-7-*nor*-5β-*cholestan*-5-*yloxyacetic Acid Lactone* **23**.—A solution of chromyl chloride (1.0 g) in carbon tetrachloride (2.5 ml) was added over 50 min to a solution of the diol **19** (513 mg) in dichloromethane (20 ml) and pyridine (1.5 ml) under a nitrogen atmosphere at −78 °C. The mixture was stirred and brought to room temp. over 2 h after which methanol (5 ml) was added. After 30 min, ether (75 ml) was added and the resulting suspension was stirred overnight. The organic layer was decanted and the residue was washed with ether. The combined organic solutions were washed successively with aq. potassium hydroxide, dil. hydrochloric acid and brine and then dried and evaporated under reduced pressure. Chromatography of the residue [50 g column; chloroform–light petroleum (1:1) as eluent] gave the *lactone* **23** (345 mg, 68%) as a colourless gum (Found: C, 76.3; H, 10.75%; M^+, 488.3863. $C_{31}H_{52}O_4$ requires C, 76.2; H, 10.7%; *M*, 488.3865; ν_{max}(chloroform)/cm^{-1} 1733, 1280, 1120 and 1085; δ_H 0.67 (3 H, s, 18-H_3), 0.95 (3 H, s, 19-H_3), 0.95 (3 H, s, 19-H_3), 1.50 (3 H, s, 4aα-CH_3), 2.98–3.5 (1 H, m, 3α-H), 3.34 (3 H, s, OCH_3) and 4.31 (2 H, s, $W_{\frac{1}{2}}$ 3, OCH_2CO_2).

Reduction of the lactone **23** (81 mg) with lithium aluminium hydride (195 mg) in refluxing ether (4 ml) gave back the diol **19** (50 mg, 62%).

3β-*Methoxy*-5-*methyl*-5α-*cholestan*-6-*one* **25**.—A mixture of collidine (1 ml), methanesulfonyl chloride (0.2 ml) and dimethylformamide, saturated with sulfur dioxide, was added to a solution of the diol **19** (183 mg) in dimethylformamide (5 ml). The reaction mixture was stirred for 5 min and then poured into dil. hydrochloric acid (75 ml) and extracted with ether. The extract was washed successively with dil. hydrochloric acid, aq. sodium hydrogen carbonate and water, and then dried and evaporated under reduced pressure. Chromatography (5 g column, 230–400 mesh Kieselgel; chloroform as eluent) gave 3β-*methoxy*-5-*methyl*-5α-*cholestan*-6-*one* **25** (144 mg, 91%), m.p. 96–97 °C (ex. methanol); $[\alpha]_D^{20}$ −61.7 (*c* 0.85) (Found: C, 80.8; H, 11.5%; M^+, 430.3806. $C_{29}H_{50}O_2$ requires C, 80.85; H, 11.7%; *M*, 430.3811); ν_{max}(chloroform)/cm^{-1} 1700; δ_H 0.65 (3 H, s, 18-H_3), 0.85 (3 H, s, 19-H_3), 1.22 (3 H, s, 5α-CH_3), 2.15 (1 H, dd, *J* 15 and 6, 7β-H), 2.38 (1 H, dd, *J* 15 and 12, 7α-H), 3.34 (3 H, s, OCH_3) and 3.38 (1 H, 8 lines, 3α-H).

Dehydration of 5-(2-*Acetoxyethoxy*)-3β-*methoxy*-4aα-*methyl*-4a-*homo*-7-*nor*-5β-*cholestan*-4aβ-*ol* **20**.—A solution of the acetate **20** (645 mg) in pyridine (9 ml) was treated with thionyl chloride (1 ml) at 0 °C for 40 min. The reaction mixture was poured into water and extracted with ether. The extract was washed successively with dil. hydrochloric acid and water, dried, and evaporated under reduced pressure. The residue was chromatographed [60 g column; chloroform–light petroleum (1:1) as eluent] to give, from the early fractions, 5-(2-*acetoxyethoxy*)-3β-*methoxy*-4a-*methylene*-4a-*homo*-7-*nor*-5β-*cholestane* **24** (45 mg, 7%), as a non-crystallisable gum (Found: M^+, 516.4163. $C_{33}H_{56}O_4$ requires *M*, 516.4178); ν_{max}(chloroform)/cm^{-1} 1734, 1089 and 910; δ_H 0.69 (3 H, s, 18-H_3), 0.97 (3 H, s, 19-H_3), 2.06 (3 H, s, OAc), 2.9–3.6 (3 H, m, 3α-H and OCH_2CH_2OAc, simplifed to m, $W_{\frac{1}{2}}$ 5 Hz at δ 3.25 upon irradiation at δ 4.14), 3.39 (3 H, s, OCH_3), 4.14 (2 H, t, *J* 5, OCH_2CH_2OAc, collapsing to s, $W_{\frac{1}{2}}$ 2, upon irradiation at δ 3.26) and 5.02 and 5.06 (2 H, m, 4a-CH_2).

The middle fraction gave a mixture (160 mg) that was estimated (NMR) to consist of the methylene compound **24** and the ketone **25** in a ratio of 1:4.

Further elution gave the ketone **25** (165 mg) identical with material obtained as described in the preceding experiment.

Reaction of 6,6-*Ethylenedioxy*-5-*hydroxy*-3β-*methoxy*-5β-*cholestane* **17** *with Methylmagnesium iodide*.—A solution of 6,6-ethylenedioxy-5-hydroxy-3β-methoxy-5β-cholestane **17** (1.81 g) in toluene (50 ml) was treated with Grignard solution

prepared from methyl iodide (5 ml) and magnesium (1.53 g) in ether (25 ml) under the conditions already described for the analogous reactions of the dioxolanes **1** and **13**. After work-up, chromatography [150 g column; chloroform–ethyl acetate (93:7) as eluent] gave, from the early fractions, 6β-(2-*hydroxyethoxy*)-3β-*methoxy*-6α-*methyl*-5β-*cholestan*-5-*ol* **21** (679 mg, 36%) as an oil which was distilled at 0.005 Torr (bath temperature, 206 °C), $[\alpha]_D^{18}$ +32.0 (*c* 1.1) (Found: C, 75.25; H, 11.3%; M^+, 492.4172. $C_{31}H_{56}O_4$ requires C, 75.55; H, 11.45%; *M*, 492.4178); ν_{max}(film)/cm^{-1} 3440, 1114, 1080 and 1050; δ_H 0.68 (3 H, s, 18-H_3), 1.10 (3 H, s, 19-H_3), 1.14 (3 H, s, 6α-CH_3), 2.98 (1 H, exchangeable with D_2O, OH), 3.32 (3 H, s, OCH_3), 3.45–3.77 (5 H, m, 3α-H and OCH_2CH_2O) and 4.06 (1 H, exchangeable with D_2O, OH). Treatment of the diol **21** (360 mg) with acetic anhydride (2 ml) and pyridine (3 ml) at room temperature overnight gave the derived *acetate* **22** (300 mg, 77%) as an oil which was distilled at 0.003 Torr (bath temperature 195 °C); $[\alpha]_D^{20}$ +11 (*c* 0.06) (Found: C, 74.55; H, 10.95%; M^+, 534.4279. $C_{33}H_{58}O_5$ requires C, 74.10; H, 10.9; *M*, 534.4284); ν_{max}(film)/cm^{-1} 3490, 1743, 1245, 1115 and 1085; δ_H 0.69 (3 H, s, 18-H_3), 1.08 (3 H, s, 19-H_3), 1.13 (3 H, s, 6α-CH_3), 2.04 (3 H, s, OAc), 3.31 (3 H, s, OCH_3), 3.5–3.76 (3 H, m, 3α-H and OCH_2CH_2OAc), 3.75 (1 H, exchangeable with D_2O, OH) and 4.18 (2 H, t, *J* 5, collapsing to a singlet upon irradiation at δ 3.63, OCH_2CH_2OAc).

Later fractions afforded the rearranged diol **19** (1.17 g, 63%), identical (IR, NMR, TLC) to the material obtained by Grignard cleavage of the acetal **13**.

6β-(2-*Acetoxyethoxy*)-3β-*methoxy*-6α-*methylcholest*-4-*ene* **26**.—Thionyl chloride (0.5 ml) was added to a solution of the hydroxy acetate **22** (124 mg) in pyridine (3 ml) and the mixture was kept at 0 °C for 1 h; it was then poured into crushed ice and conc. hydrochloric acid and extracted with ether. The extract was washed with water, dried, and evaporated under reduced pressure at room temperature to afford the *title compound* **26** (108 mg, 91%) as an oil (Found: M^+, 516.4188. $C_{33}H_{56}O_4$ requires *M*, 516.4178); ν_{max}(film)/cm^{-1} 2820, 1745, 1100 and 796; δ_H 0.70 (3 H, s, 18-H_3), 1.16 (3 H, s, 19-H_3), 1.23 (3 H, s, 6α-CH_3), 2.02 (3 H, s, OAc), 3.28–3.48 (2 H, m, OCH_2CH_2OAc), 3.39 (3 H, s, OCH_3), 3.68–3.92 (1 H, br t, *J* 8, 3α-H), 4.12 (2 H, t, *J* 5.5, collapsing to a br s, $W_{\frac{1}{2}}$ 5.5 upon irradiation at δ 3.34) and 5.63 (1 H, m, $W_{\frac{1}{2}}$ 5.5), collapsing to a sharp s upon irradiation at δ 3.82, 4-H).

3β-*Methoxy*-5-*methyl*-5α-*cholestan*-6β-*ol* **32**.—A solution of 3β-methoxy-5-methyl-5α-cholestan-6-one **25** (120 mg) in ether (10 ml) was heated under reflux with lithium aluminium hydride (275 mg) for 5 h. After cooling, the mixture was stirred with dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, dried and evaporated under reduced pressure to afford the *title compound* **32** (103 mg, 86%) which crystallised from methanol as needles, m.p. 151–152 °C; $[\alpha]_D^{20}$ −16.3 (*c* 0.94) (Found: C, 80.4; H, 12.35%; M^+, 432.3963. $C_{29}H_{52}O_2$ requires C, 80.5; H, 12.1%; *M*, 432.3967); ν_{max}/cm^{-1} 1085 and 1055; δ_H 0.70 (3 H, s, 18-H_3), 0.92 (3 H, s, 5α-CH_3), 1.22 (3 H, s, 19-H_3), 1.64 (1 H, exchangeable with D_2O, OH), 3.37 (3 H, s, OCH_3), 3.3–3.8 (1 H, m, 3α-H) and 3.50 (1 H, m, $W_{\frac{1}{2}}$ 7, 6α-H).

Treatment of the alcohol **32** (145 mg) with acetic anhydride (2 ml) and pyridine (5 ml) on a steam-bath for 2 h afforded, after work-up and chromatography [15 g column; chloroform–light petroleum (1:1) as eluent], the derived *acetate* **33** (120 mg, 76%), which crystallised from methanol as plates, m.p. 81–83 °C; $[\alpha]_D^{20}$ −41.4 (*c* 1.45) (Found: C, 78.7; H, 11.3%; M^+, 474.4056. $C_{31}H_{54}O_3$ requires C, 78.45; H, 11.45%; *M*, 474.4073); ν_{max}/cm^{-1} 1739, 1245 and 1100; δ_H 0.69 (3 H, s, 18-H_3), 1.04 (3 H, s, 5α-CH_3), 1.19 (3 H, s, 19-H_3), 2.07 (3 H, s, OAc), 3.33 (3 H, s, OCH_3), 3.30–3.77 (1 H, m, 3α-H) and 4.71 (1 H, m, $W_{\frac{1}{2}}$ 5, 6α-H).

3β-*Hydroxy*-5-*methyl*-5α-*cholestan*-6-*one* **30**.—A mixture of 3β-methoxy-5-methyl-5α-cholestan-6-one **25** (226 mg), sodium iodide (236 mg), trimethylsilyl chloride (0.2 ml) and acetonitrile (9 ml) was heated under reflux for 2.5 h and then poured into water and extracted with ether. The extract was washed successively with aq. sodium thiosulphate and water, dried and evaporated under reduced pressure. Chromatography of the residue (10 g column, 230–400 mesh Kieselgel; chloroform as eluent) gave the *title compound* **30** (136 mg, 62%) which crystallised from ethanol–methanol as prisms, m.p. 157–158 °C; $[\alpha]_D^{22}$ −55.5 (*c* 0.49) (Found: C, 80.7; H, 11.9%; M^+, 416.3658. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%; *M*, 416.3654); ν_{max}(carbon tetrachloride)/cm^{-1} 1710 and 3620; δ_H 0.65 (3 H, s, 18-H_3), 0.85 (3 H, s, 19-H_3), 1.21 (3 H, s, 5α-CH_3), 2.15 (1 H, dd, *J* 15 and 6, 7β-H), 2.38 (1 H, dd, *J* 15 and 12, 7α-H) and 3.87 (1 H, septet, J_{aa} 11, J_{ae} 5.5, 3α-H).

Treatment of the hydroxy ketone **30** (19 mg) with acetic anhydride (1 ml) and pyridine (1 ml) overnight at room temperature gave the derived *acetate* **31** (18 mg, 85%), which crystallised from ethanol–methanol as prisms, m.p. 177–178 °C; $[\alpha]_D^{22}$ −58 (*c* 0.39) (Found: C, 78.45; H, 11.05%; M^+, 458.3763. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0%; *M*, 458.3760); ν_{max}(carbon tetrachloride)/cm^{-1} 1735 and 1710; δ_H 0.65 (3 H, s, 18-H_3), 0.87 (3 H, s, 19-H_3), 1.28 (3 H, s, 5α-CH_3), 2.01 (3 H, s, OAc), 2.15 (1 H, dd, *J* 15 and 6, 7β-H), 2.38 (1 H, dd, *J* 15 and 12, 7α-H) and 4.97 (1 H, septet, J_{aa} 11, J_{ae} 5.5, 3α-H). Structure **31** has previously been assigned to a minor product, m.p. 171–172 °C; $[\alpha]_D$ −26, obtained by the action of boron trifluoride–diethyl ether on 5,6β-epoxy-5β-cholestan-3β-yl acetate **48**.[19]

6,6-*Ethylenedithio*-3β-*methoxy*-5-*methyl*-5α-*cholestane* **34**.—A solution of 3β-methoxy-5-methyl-5α-cholestan-6-one **25** (112 mg) in acetic acid (3 ml) was treated for 1 h at room temperature with boron trifluoride–diethyl ether (1.5 ml) and ethanedithiol (1.5 ml). The reaction mixture was diluted with water (20 ml) and extracted with ether. The extract was washed successively with aq. sodium hydroxide and water, dried and evaporated under reduced pressure. Chromatography of the residue [20 g column, 230–400 mesh Kieselgel; light petroleum–chloroform (3:1) as eluent] gave, from the early fractions, the *title compound* **34** (62 mg, 47%), which crystallised from ethanol as plates, m.p. 132–133 °C; [α] −6.0 (*c* 0.24) (Found: C, 73.45; H, 10.7; S, 12.35%; M^+, 506.3625. $C_{31}H_{54}OS_2$ requires C, 73.45; H, 10.7; S, 12.65%; *M*, 506.3616); ν_{max}(carbon tetrachloride)/cm^{-1} 1100; δ_H 0.70 (3 H, s, 18-H_3), 1.25 and 1.30 (each 3 H, s, 19-H_3 and 5α-CH_3), 3.0–3.7 (5 H, m, SCH_2CH_2S and 3α-H) and 3.4 (3 H, s, 3β-OCH_3).

Later fractions afforded unchanged starting material **25** (42 mg, 38%).

6,6-*Ethylenedithio*-3β-*hydroxy*-5-*methyl*-5α-*cholestane* **35**.—A solution of 3β-methoxy-5-methyl-5α-cholestan-6-one **25** (198 mg) in ethanedithiol (17 ml) was treated with boron trifluoride–diethyl ether (10 ml) at room temperature for 5 days. After work-up as described in the preceding experiment, chromatography (20 g column; chloroform as eluent) gave the *title compound* **35** (82 mg, 36%) as a non-crystallisable oil (Found: M^+, 492.3460. $C_{30}H_{52}OS_2$ requires *M*, 492.3460); ν_{max}(chloroform)/cm^{-1} 3550–3300; δ_H 0.68 (3 H, s, 18-H_3), 1.23 and 1.29 (each 3 H, s, 19-H_3 and 5α-CH_3), 2.9–3.4 (4 H, m, SCH_2CH_2S) and 3.7–4.15 (1 H, m, 3α-H).

The alcohol **35** (73 mg), when treated at room temperature with acetic anhydride (1.5 ml) and pyridine (3 ml) gave the corresponding *acetate* **36** (72 mg, 91%) which crystallised as needles from methanol, m.p. 146–149 °C; $[\alpha]_D^{22}$ −10.0 (*c* 0.7)

(Found: C, 71.65; H, 9.85; S, 12.0%; M^+, 543.3557. $C_{32}H_{54}O_2S_2$ requires C, 71.85; H, 10.2; S, 12.0% *M*, 534.3565); ν_{max}(chloroform)/cm^{-1} 1739; δ_H 0.68 (3 H, s, 18-H_3), 1.25 and 1.34 (each 3 H, s, 19-H_3 and 5α-CH_3), 2.02 (3 H, s, OAc), 2.9–3.4 (4 H, m, SCH_2CH_2S) and 4.85–5.25 (1 H, m, 3α-H).

3β-*Methoxy*-5-*methyl*-5α-*cholestane* **38**.—3β-Methoxy-5-methyl-5α-cholestan-6-one **25** (106 mg), hydrazine hydrate (4 ml), potassium hydroxide (900 mg) and digol (25 ml) were heated under reflux for 1 h. The solvents were then distilled until the internal temperature reached 206 °C, when heating under reflux was continued for a further 5 h. The cooled solution was acidified with dilute hydrochloric acid and extracted with ether. The extract was washed successively with dil. hydrochloric acid and water, dried, and evaporated under reduced pressure to leave a residue which was chromatographed [10 g column, 230–400 mesh Kieselgel; chloroform–light petroleum (1:1) as eluent] to give the *title compound* **38** (87 mg, 84%) which crystallised from ethanol as needles, m.p. 80–81 °C; $[\alpha]_D^{23}$ +4.5 (*c* 1.38) (Found: C, 83.85; H, 12.6%; M^+, 416.4024. $C_{29}H_{52}O$ requires C, 83.6; H, 12.6%; *M*, 416.4018); δ_H 0.67 (3 H, s, 18-H_3), 0.98 (6 H, s, 19-H_3 and 5α-CH_3), 3.31 (3 H, s, OCH_3) and 3.3–3.7 (1 H, m, 3α-H).

5-*Methyl*-5α-*cholestan*-3β-*ol* **39**.—A solution of 3β-methoxy-5-methyl-5α-cholestane **38** (113 mg) in acetonitrile (10 ml) was heated with sodium iodide (236 mg) and trimethylsilyl chloride (0.2 ml) under reflux for 2.5 h after which it was poured into water and extracted with ether. The extract was washed successively with aq. sodium thiosulphate and water, dried, evaporated under reduced pressure, and the residue chromatographed (10 g column, 230–400 mesh Kieselgel; chloroform as eluent) to give the *title compound* **39** (73 mg, 67%), which crystallised from ethanol as needles, m.p. 156–157 °C; $[\alpha]_D^{21}$ +10.0 (*c* 0.71) (Found: C, 83.3; H, 12.65%; M^+, 402.3852. $C_{28}H_{50}O$ requires C, 83.5; H, 12.5%; *M*, 402.3861); ν_{max}(carbon tetrachloride)/cm^{-1} 3620 and 1035; δ_H 0.65 (3 H, s, 18-H_3), 0.98 and 0.99 (each 3 H, s, 19-H_3 and 5α-CH_3) and 3.99 (1 H, septet, *J* 6, 3α-H).

5-*Methyl*-5α-*cholestan*-3-*one* **43**.—Jones' reagent[17] (0.1 ml) was added to a solution of 5-methyl-5α-cholestan-3β-ol **39** (70 mg) in acetone (10 ml) at 0 °C. The solution was allowed to warm to room temperature over 10 min after which it was poured into water and extracted with ether. The extract was washed successively with aq. sodium hydrogen carbonate and water, dried, and evaporated under reduced pressure to give the title compound (66 mg, 97%), which crystallised from ethanol as plates, m.p. 163–164 °C; $[\alpha]_D^{20}$ +48 (*c* 0.75); ν_{max}(carbon tetrachloride)/cm^{-1} 1710; δ_H 0.67 (3 H, s, 18-H_3), 0.93 (3 H, s, 5α-CH_3), 1.15 (3 H, s, 19-H_3), 1.86 (1 H, dd, *J* 1.7 and 15, 4α-H), 2.47 (1 H, dd, *J* 1.1 and 15, 4β-H) and 2.33–2.40 (2 H, m, 2α- and 2β-H). The identity of this material was confirmed by direct comparison with an authentic sample prepared as described by Nagata *et al.*[16]

5-*Methyl*-5β-*cholestan*-3-*one* **44**.—Copper(I) iodide (976 mg) and ether (40 ml) were stirred under nitrogen and cooled in an ice-bath. Methyllithium (10 mmol dm^{-3}) was added, initially producing a deep-yellow precipitate which dissolved as the remainder of the methyllithium was added. A solution of cholest-4-en-3-one (1.47 g) in ether (50 ml) was added over 10 min, the ice-bath was removed, and the mixture was stirred for 2 h. The resulting suspension was poured onto crushed ice and dil. hydrochloric acid and extracted with ether. The ether extract was washed successively with aq. sodium hydrogen carbonate and water, dried, evaporated under reduced pressure, and chromatographed (100 g column; chloroform as eluent) to give the *title compound* **44** (731 mg, 48%), m.p. 87–89 °C (ex. acetone–methanol); $[\alpha]_D^{25}$ +27 (*c* 3.3) (lit.,[20] m.p. 88–89 °C; $[\alpha]_D$ + 35); δ_H 0.66 (3 H, s, 18-H_3), 0.85 and 0.89 (each 3 H, s, 19-H_3 and 5β-CH_3) and 3.03 (1 H, d, *J* 14.5, 4β-H). Unchanged cholest-4-en-3-one (180 mg, 12%) was also obtained.

5-*Methyl*-5β-*cholestan*-3β-*ol* **42**.—A solution of 5-methyl-5β-cholestan-3-one **44** (460 mg) in ethanol (15 ml) was stirred overnight with W-5 Raney nickel[21] in an atmosphere of hydrogen. The reaction mixture was filtered through Celite and evaporated under reduced pressure. Chromatography of the residue [50 g column; chloroform–light petroleum (1:1) as eluent] gave the title compound **42** (402 mg, 87%) which crystallised as needles from acetonitrile, m.p. 129–130 °C (lit.,[22] 132–134 °C), $[\alpha]_D^{20}$ +26.3 (*c* 1.67); ν_{max}/cm^{-1} 3500–3200 and 1025; δ_H 0.65 (3 H, s, 18-H_3), 0.84 (3 H, s, 19-H_3), 1.09 (3 H, s, 5β-CH_3), 1.42 (1 H, exchangeable with D_2O, OH) and 4.17 (1 H, m, $W_{\frac{1}{2}}$ 8.5, 3α-H).

Acetylation of the alcohol **42** (139 mg) with acetic anhydride (0.5 ml) and pyridine (2 ml) at room temperature overnight, gave, after work-up, followed by chromatography [15 g column; chloroform–light petroleum (1:2) as eluent] the derived *acetate* **41** (95 mg, 62%), which crystallised from methanol–ether as needles, m.p. 70–71 °C; $[\alpha]_D^{20}$ +23.2 (*c* 0.88) (Found: C, 80.85; H, 11.55%; M^+, 444.3961. $C_{30}H_{52}O_2$ requires C, 81.0; H, 11.8%; *M*, 444.3967); ν_{max}(film)/cm^{-1} 1741, 1245 and 1025; δ 0.65 (3 H, s, 18-H_3), 0.85 (3 H, s, 19-H_3), 1.00 (3 H, s, 5β-CH_2), 2.03 (3 H, s, OAc) and 5.11 (1 H, m, $W_{\frac{1}{2}}$ 7, 3α-H).

3β-*Methoxy*-5-*methyl*-5β-*cholestane* **40**.—5-Methyl-5β-cholestan-3β-ol **42** (207 mg), silver(I) oxide (687 mg) and methyl iodide (10 ml) were stirred and heated under reflux in benzene (6 ml) for 46 h. More silver oxide (500 mg) and methyl iodide (4 ml) were added and the mixture was refluxed for a further 46 h. It was then filtered through Celite, evaporated under reduced pressure, and the residue was chromatographed [15 g column; chloroform–light petroleum (1:3) as eluent] to give the *title compound* **40** (120 mg, 56%) which crystallised from methanol–chloroform as plates, m.p. 75–77 °C; $[\alpha]_D^{20}$ +26.9 (*c* 1.07) (Found: C, 83.6; H, 12.85%; M^+, 416.4008. $C_{29}H_{52}O$ requires C, 83.6; H, 12.6%; *M*, 416.4018; ν_{max}(film)/cm^{-1} 2830, 1110 and 1095; δ_H 0.65 (3 H, s, 18-H_3), 0.81 (3 H, s, 19-H_3), 1.01 (3 H, s, 5β-CH_3), 3.28 (3 H, s, OCH_3) and 3.49 (1 H, m, $W_{\frac{1}{2}}$ 8.5, 3α-H).

Elution with chloroform gave 5-methyl-5β-cholestan-3-one **44** (34 mg, 17%), followed by unchanged starting material **42** (36 mg, 17%).

5-*Methyl*-5α-*cholestane*-3,6-*dione* **37**.—A solution of 3β-hydroxy-5-methyl-5β-cholestan-6-one **30** (44 mg) in acetone (10 ml) was treated with Jones' reagent[17] (0.15 ml) at 0 °C for 10 min and then poured into water and extracted with ether. The extract was washed with water, dried, and evaporated under reduced pressure to afford the *title compound* **37** (38 mg, 83%), which crystallised from ethanol as prisms, m.p. 145–148 °C; $[\alpha]_D^{24}$ −16 (*c* 0.39) (Found: C, 81.15; H, 11.25%; M^+, 414.3507. $C_{28}H_{46}O_2$ requires C, 81.1; H, 11.2%; *M*, 414.3498); ν_{max}(carbon tetrachloride)/cm^{-1} 1715; δ_H 0.69 (3 H, s, 18-H_3), 1.14 and 1.15 (each 3 H, s, 19-H_3 and 5α-CH_3), 2.75 (1 H, dd, *J* 16 and 1, 4α-H).

3-*Acetoxy*-5-*methyl*-5α-*cholest*-2-*en*-6-*one* **46**.—A solution of 5-methyl-5α-cholestane-3,6-dione (12 mg) in benzene (10 ml) was heated under reflux for 1.75 h with isopropenyl acetate (5 ml) and dilute sulphuric acid (2 drops) and then diluted with benzene (20 ml) and washed successively with aq. sodium hydrogen carbonate and water. The solution was dried, and evaporated under reduced pressure to leave a residue,

chromatography of which (7 g column, 230–400 mesh Kieselgel; chloroform as eluent) gave the *title compound* **46**, m.p. 140–142 °C (ex. ethanol); $[\alpha]_D^{22}$ −3 (*c* 0.31) (Found: C, 78.75; H, 10.55%; M^+, 456.3613. $C_{30}H_{48}O_3$ requires C, 78.9; H, 10.6%; *M*, 456.3603); ν_{max}(carbon tetrachloride)/cm^{-1} 1760 and 1710; δ_H 0.66 (3 H, s, 18-H_3), 0.80 (3 H, s, 19-H_3), 1.20 (3 H, s, 5α-CH_3), 2.14 (3 H, s, OAc) and 5.32 (1 H, br, $W_{\frac{1}{2}}$ 8, 2-H).

5-Methyl-5α-cholestane **45**.—5-Methyl-5α-cholestane-3,6-dione **37** (30 mg), hydrazine hydrate (4 ml), potassium hydroxide (0.5 g) and digol (25 ml) were heated under reflux for 1 h. The solvent was distilled until the internal temperature reached 201 °C when the solution was heated under reflux for 5 h; it was then acidified with dil. hydrochloric acid and extracted with ether. The extract was washed successively with dil. hydrochloric acid, dil. sodium hydroxide, and water, and then dried and evaporated under reduced pressure. Chromatography [5 g column, 230–400 mesh Kieselgel:light petroleum–chloroform (3:1) as eluent] gave the *title compound* **45** (8 mg, 29%), which crystallised from ethanol–acetone as prisms, m.p. 70–71 °C; $[\alpha]_D^{21}$ +18 (*c* 0.17) (Found: C, 86.9; H, 12.95%; M^+, 386.3921. $C_{28}H_{50}$ requires C, 86.95; H, 13.0%; *M*, 386.3912); δ_H 0.67 (3 H, s, 18-H_3) and 0.99 and 1.03 (each 3 H, s, 19-H_3 and 5α-CH_3).

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