Tetracyclic Triterpenes. Part 15.[1] Ring Expansion of Steroidal Acyloins: 3-Acetyl-3-Hydroxy-14α-methyl-4-nor-5α- and -5β-cholest-8-ene

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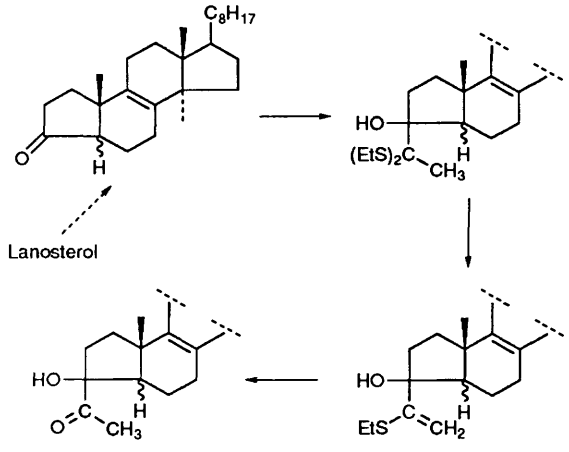
The base- and acid-catalysed ring A expansion of steroidal acyloins, 3-acetyl-3-hydroxy-14α-methyl-4-nor-5α- and -5β-cholest-8-ene, gave 3,14-dimethyl-4-oxo-5α- and -5β-cholestane derivatives. The regioselective migration of the secondary carbon atom C-3 is explained by the steric factors and conformational preference for the formation of the chair-like transition state.

In earlier papers[2,3] we reported a rearrangement aimed at the synthesis of 4β-demethyllanosterol. Thus, the acid-catalysed reaction of α-hydroxy dithioacetals, derivatives of 3-acetyl-3-hydroxy-14α-methyl-4-nor-5α- and -5β-cholest-8-ene, resulted in the exclusive migration of a secondary carbon atom to give 3,14-dimethyl-4-oxo steroids.[2] The required 4β-demethyl-5α-lanost-8-en-3β-ol was prepared by treatment of 3α-acetyl-3β-hydroxy-14α-methyl-4-nor-5α-cholest-8-ene *p*-tolylsulfonylhydrazone under Bamford–Stevens conditions.[3] In the course of these investigations on the transformation of lanosterol, the acyloins **1** and **2**, possessing a five-membered ring A and A/B *trans* or A/B *cis* ring junction, have been prepared[2] from 14α-methyl-4-norcholestan-3-one *via* α-hydroxy dithioacetal intermediates[4] (Scheme 1). In view of the possible ring expansion to

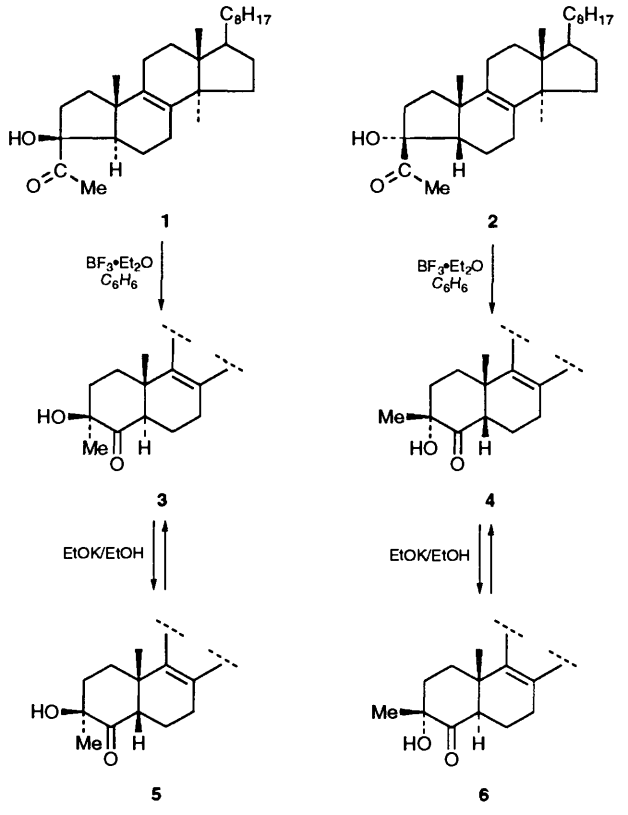


Scheme 1

4β-demethyllanosterol, these α-hydroxy ketones appeared to be interesting substrates for the investigation of acyloin rearrangement.

While D-homoannulations of 17-hydroxy-20-ketopregnane derivatives, to which the adrenal cortical hormones belong, have been extensively studied in order to evaluate steric, electronic and conformational effects governing the reaction,[5–9] interconversions within the group of five- and six-membered ring A steroidal acyloins have not been reported.

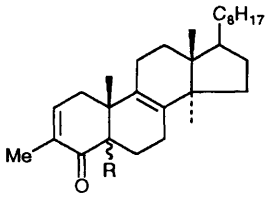
Lewis acid (BF_3·Et_2O)-catalysed rearrangement of the α-ketol **1**, a highly strained compound of *trans*-hydrindane type,[10] carried out in benzene gave a six-membered acyloin **3**,[2] as a kinetic product, in 98% yield. The same regioselectivity was achieved in the rearrangement of the *cis*-hydrindane α-ketol **2** which gave, under similar conditions, the acyloin **4**[2] in 86% yield. Base-catalysed (KOH–EtOH) reaction of the ketal **1** was a slow reaction and gave a mixture of six-membered acyloins: **4** (24%), **5** (31%) and **6** (21%). When compound **1** was treated with lithium methoxide in methanol a fast reaction occurred



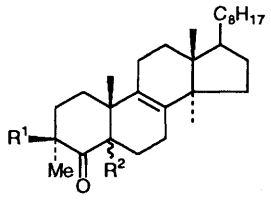
and only compound **3** was isolated in 80% yield. The attempted reaction of **1** with potassium *tert*-butoxide gave a complicated mixture of rearranged and, most probably, oxidized[11] products. These were not further investigated. In contrast to the 5α-isomer **1**, the 5β-ketol **2** was found to be resistant to basic conditions (KOH–EtOH or MeOLi–MeOH). Since neither acid- nor base-catalysed reaction of A-nor-5α- and -5β-ketols gave the desired 3-oxo regioisomer, the equilibration reactions of six-membered 3-hydroxy-4-oxo-5α- and -5β-derivatives were investigated. Thus, the reaction of **3** with potassium ethoxide in ethanol gave a mixture from which the ketol **5** and the substrate **3** were isolated in 58 and 30% yield. The reaction of **3** with potassium *tert*-butoxide in *tert*-butyl alcohol afforded compounds **3**, **4** and **5**, which were isolated in 25, 3 and 39% yield. When the ketol **4** was equilibrated under basic conditions (EtOK in refluxing EtOH) it gave a mixture of **4** and **6** in the ratio 76:20.

The structures of the six-membered ketols **3** and **4** followed from the mechanistic considerations concerning acid-catalysed ketol rearrangements in steroids[4,8] amd were further corroborated by their ^{1}H NMR spectra.[2] The stereochemistry of C-3 and C-5 in **6** followed from the position of a signal at δ 3.11 assigned to the 5α-proton. The remarkable deshielding of this proton was

caused by the 3α-hydroxy group in a 1,3-diaxial orientation and the carbonyl group at C-4. The splitting pattern of this signal (dd, J_1 10 Hz, J_2 5 Hz) was consistent with the 5α-configuration and the 5α-sofa conformation of ring **B**, as was the position of the proton[12] (δ 0.91) and carbon[13] (δ 18.3) signals of the 19-methyl group. The absorption at 3590 cm^{-1} in the IR spectrum ascribed to the free hydroxy group[8] was also in agreement with the proposed stereochemistry of **6**. Moreover, the sterochemistry of all synthesized six-membered ketols was confirmed by chemical transformations. Thus, dehydrations of the ketols **3**–**6** gave the respective 2-en-4-ones, while the reaction rates were strongly dependent on the orientation of the eliminated hydroxy group. The reaction of **5** and **6** with thionyl chloride in pyridine carried out at room temp. for 10 min gave a high yield of the enones **7** and **8**, respectively. On the other hand, the ketols **3** and **4**, possessing an equatorial hydroxy group, gave elimination products **7** and **8** after prolonged reaction (40 and 10 h, respectively) under the same conditions. The structures of the enones **7** and **8** were in full agreement with their spectral data (Experimental section). Acetylation of the ketols **3** and **5** gave the respective α-acetoxy ketones **9** and **10**. The reductive removal of the hydroxy group from **3** could not be achieved with the aid of conventional reagents (Zn/AcOH, HI/AcOH).[14] Also, deacetoxylation of **9** (Zn/AcOH, $CrCl_2/Me_2CO$ or HI/AcOH) failed. However, the α-acetoxy ketone **10**, when treated with tributyltin hydride and with azoisobutyronitrile gave the α-methyl ketone **11** (87%). The retention of the C-3 and C-5 configuration in **11** was evidenced by a small Cotton effect[15] (Δε = −0.05 at 292 nm) found in its CD spectrum.



7 R = α-H
8 R = β-H

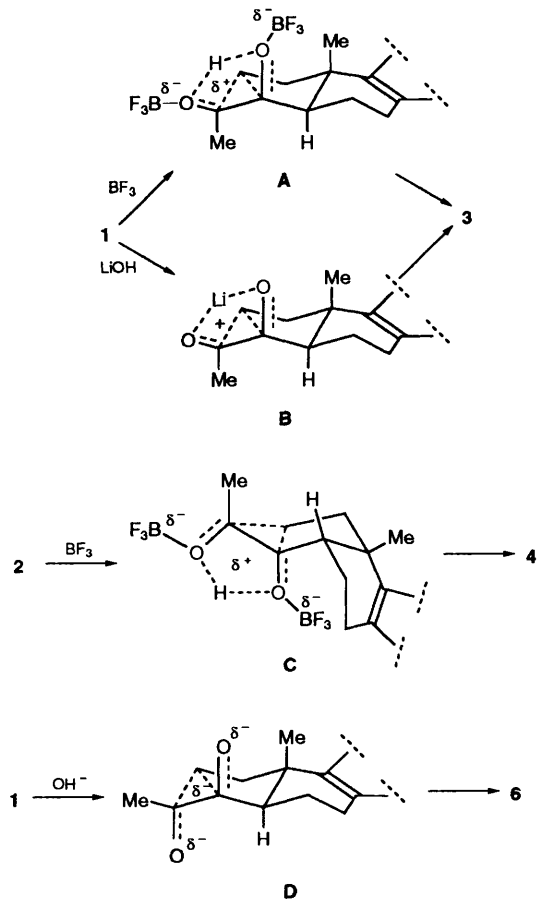


9 R^1 = AcO, R^2 = α-H
10 R^1 = AcO, R^2 = β-H
11 R^1 = H, R^2 = β-H

Discussion

D-Homoannulations of 17-hydroxypregnan-20-ones have been studied extensively.[5,6,8,9] Mechanistic aspects of these reactions have been discussed in terms of steric interactions, quaternary *vs.* secondary distinction between C-13 and C-16 migrations, solvent and substituent effects as well as of the incipient conformation of ring D in the transition state leading to the products. Base-catalysed acyloin rearrangements of either 17α-hydroxypregnan-20-ones or 17β-hydroxy-17α-pregnan-20-ones[5c,9] gave 17a-hydroxy-17a-methyl-D-homoandrostan-17-one derivatives by specific migration of the C(13)–C(17) bond. This indicated the electronic preference for migration of the quaternary carbon C-13 over the secondary one C-16, even despite the boat conformation of the transition state involved in these D-homoannulations.

In the present studies, the BF_3·Et_2O-catalysed rearrangement of **1** gives **3**, the product of C(2)–C(3) bond migration proceeding through a chair-like transition state **A**[8] stabilized by an intramolecular hydrogen bond between the OH group and the carbonyl oxygen of the acetyl group. This hydrogen bonding is preserved in the product. In a similar fashion (chair-like transition state **C**, hydrogen bonding) the 5β-ketol **2** rearranges to the ketone **4** with the equatorial 3α-hydroxy group. In the reaction of **1** catalysed by lithium methoxide, the ketol **3** is formed *via* a transition state **B** with a lithium cation coordinating two oxygen atoms in the s-*cis* conformation. Base-catalysed rearrangement of the ketol **1** proceeds through a chair-like transition state **D** in which the 3-hydroxy and the carbonyl oxygen of the acetyl group are in an *anti* conformation. This results in C(2)–C(3) bond migration to give the ketol **6** followed by a base-catalysed isomerization. The unreactivity of the 5β-ketol **2** under basic conditions most probably may be explained by (i) the greater stability of the five-membered ring ketol in the *cis*-hydrindane arrangement; (ii) the steric hindrance preventing the abstraction of proton from the 3α-hydroxy group. This is required in the initial step of the rearrangement.



The results presented lead to the conclusion that ring enlargements of the steroidal five-membered ring A ketols **1** and **2** are controlled by a combination of two main factors acting simultaneously: (1) steric interactions in the transition state, that is repulsion between substituents in position 4 and hydrogens at C-6 and C-19 (in the reaction of **1**) or at C-7 (in the reaction of **2**), therefore opposing C(3)–C(5) bond migration; (2) conformational preference for formation of the strain-free, chair-like transition state leading to regioselective C(2)–C(3) bond migration with the formation of 4-oxo steroids having a 5α or 5β configuration. Electronic factors, that is charge stabilization in the transition state which might result in distinction between tertiary and secondary carbon migration (C-2 *vs.* C-5), are not operative in the reactions under study.

Experimental

For the general experimental conditions see ref. 3.

Rearrangement of the Ketol **1**.—(a) *With* BF_3·Et_2O. BF_3·Et_2O (0.10 cm^3) was added at room temperature to a stirred solution of the ketol **1** (120 mg, 0.28 mmol) in benzene

(30 cm^3). After 1 min pyridine (1 cm^3) was added to the mixture which was then washed with brine and water (3 × 10 cm^3), dried ($MgSO_4$), filtered and evaporated to give chromatographically pure crude product (117 mg, 98%). This was crystallized from methanol to afford 3β-hydroxy-3α,14α-dimethyl-5α-cholest-8-en-4-one **3** (110 mg, 92%), m.p. 106–108 °C. ^1H NMR and IR spectra of this sample were identical with those of an authentic sample.[2]

(b) *With* MeOLi. A solution of **1** (22 mg, 0.051 mmol) in anhydrous methanol (5 cm^3) was added to a solution of MeOLi prepared by addition of lithium (100 mg) to anhydrous methanol (10 cm^3) and the reaction mixture was refluxed for 30 min. Work-up gave crude product (21 mg), which crystallized from MeOH to give **3** as needles (17.5 mg, 80%), m.p. 106–108 °C, identical with the sample prepared in (a).

Reaction of the Ketol **2** *with* BF_3·Et_2O.—BF_3·Et_2O (0.05 cm^3) was added to a stirred solution of the ketol **2** (85 mg, 0.199 mmol) in benzene (15 cm^3), at room temperature. After 2 min pyridine (0.5 cm^3) was added to the mixture. Work-up then gave chromatographically pure crude product as an oil, which crystallized from methanol to give 3α-hydroxy-3β,14α-dimethyl-5β-cholest-8-en-4-one **4** (73 mg, 86%), m.p. 101–102 °C. Its IR and ^1H NMR spectra were identical with those of an authentic sample.[2]

Equilibration of the Ketol **3** *under Basic Conditions.*—(a) *With* EtOK *in ethanol.* A solution of **3** (120 mg, 0.280 mmol) in absolute EtOH (10 cm^3) was added to a solution of potassium ethoxide [prepared by addition of potassium metal (300 mg, 7.67 mmol) to absolute ethanol (30 cm^3) at −78 °C] and the reaction mixture was refluxed under argon for 18 h. Benzene (40 cm^3) was added to the mixture which was then washed with brine and water, dried with anh. K_2CO_3 and evaporated to give crude product as an oil. This was chromatographed on silica gel (7 g) with methylene dichloride as eluent. The following compounds were obtained: the substrate **3** (36 mg, 30%); 3β-hydroxy-3α,14α-dimethyl-5β-cholest-8-en-4-one **5** (69 mg, 58%), m.p. 127–129 °C (from methanol); ν_{max}/cm^{-1} 3490, 1695 and 1145; CD Δε (λ/nm) +0.73 (312); δ(500 MHz) 3.212 (1 H, br s, OH), 2.509 (1 H, dd, *J* 4.8 and 3.3, 5β-H), 1.322 (3 H, s, 3α-CH_3), 1.054 (3 H, s, 19-CH_3), 0.896 (3 H, d, *J* 6.4, 21-CH_3), 0.870 (3 H, d, *J* 6.6, 26-CH_3), 0.865 (3 H, d, *J* 6.6, 27-CH_3), 0.858 (3 H, s, 14α-CH_3) and 0.728 (3 H, s, 18-CH_3); *m*/*z* 428 (M^+), 413, 410, 395, 259, 247, 95, 55 and 43 (Found: C, 81.1; H, 11.3. $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.29%).

(b) *With* Bu^{t}OK *in* Bu^{t}OH. Solid Bu^{t}OK (200 mg) was added to a solution of **3** (106 mg, 0.248 mmol) in *tert*-butyl alcohol (10 cm^3) and the reaction mixture was refluxed under argon for 1.5 h. After work-up and separation as above the following compounds were obtained: the ketol **4** (3.5 mg, 3.3%), m.p. 101–102 °C (^1H NMR spectrum identical with that of an authentic sample); the ketol **3** (26 mg, 25%) and the ketol **5** (41 mg, 39%), m.p. 126–128 °C (^1H NMR spectrum identical with that of an authentic sample).

Equilibration of the Ketol **4** *with* EtOK.—A solution of **4** (74 mg, 0.173 mmol) in absolute EtOH (5 cm^3) was added to a solution of EtOK [prepared from potassium metal (150 mg) and absolute EtOH (15 cm^3)] and the reaction mixture was refluxed under argon for 144 h. Work-up and chromatography on silica gel (4 g) with benzene as eluent gave the substrate **4** (56 mg, 76%) and 3α-hydroxy-3β,14α-dimethyl-5α-cholest-8-en-4-one **6** (14.5 mg, 20%), m.p. 150–152 °C (needles from MeOH–H_2O); ν_{max}/cm^{-1} 3590, 3420, 1712 and 1135; CD Δε (λ/nm) −1.17 (308); δ 3.11 (1 H, dd, *J* 10 and 4.9, 5α-H), 1.76 (1 H, br s, OH), 1.29 (3 H, s, 3β-CH_3), 0.91 (3 H, s, 19-CH_3) and 0.69 (3 H, s, 18-CH_3); *m*/*z* 428 (M^+) and 413 (Found: C, 81.2; H, 11.25. $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.29%).

Reaction of the Ketol **1** *with Potassium Hydroxide in Ethanol.*—Compound **1** (120 mg, 0.28 mmol) was added to a solution of potassium hydroxide (1.5 g) in ethanol (15 cm^3, 96%) and the solution was refluxed under argon for 26 h. Work-up gave a crude product which was chromatographed on silica gel (8 g) with benzene–methylene dichloride 2:1 as eluent. The following compounds were obtained: the ketal **5** (37 mg, 31%), m.p. 125–127 °C, the ketol **4** (29 mg, 24%), m.p. 100–102 °C and the ketol **6** (25 mg, 21%), m.p. 149–151 °C. The identity of these samples was proved by ^1H NMR and mass spectroscopy.

Dehydration of the Ketols **3**, **4**, **5** *and* **6**.—*General procedure.* Thionyl chloride was added to a ketol dissolved in anhydrous pyridine and the reaction mixture was left in the dark at room temp. until the substrate disappeared (TLC test). The reaction mixture was diluted with water and extracted twice with benzene–ether (1:1). The extract was washed with aq. HCl (5%), aq. $NaHCO_3$ (5%) and water (×2), dried (Na_2SO_4), filtered and evaporated to dryness. The product was purified by passage through a short column of silica gel and crystallization.

(a) The ketol **3** (20 mg, 0.048 mmol) [pyridine (2.0 cm^3), thionyl chloride (0.10 cm^3); reaction time 40 h] gave 3,14α-dimethyl-5α-cholesta-2,8-dien-4-one **7** (14 mg, 73%), m.p. 126–127 °C (plates from MeCN); ν_{max}/cm^{-1} 1668 and 1620; λ_{max}/nm 7300 (ε/dm^3 mol^{-1} cm^{-1} 235); CD Δε (λ/nm) −0.88 (330), +11.81 (233); δ 6.55 (1 H, m, $w_{\frac{1}{2}}$ 12, 2-H), 1.78 (3 H, d, *J* 1, 3-CH_3), 0.93 (3 H, s, 19-CH_3), 0.71 (3 H, s, 18-CH_3), 0.90 and 0.83; *m*/*z* 410 (M^+), 395 (Found: M^+, 410.354 10. $C_{29}H_{46}O$ requires *M*, 410.354 87).

(b) The ketol **4** (45 mg, 0.105 mmol) [pyridine (5 cm^3), thionyl chloride (0.20 cm^3); reaction time 12 h] gave 3,14α-dimethyl-5β-cholesta-2,8-dien-4-one **8** (38 mg, 88%), m.p. 94–95 °C (needles from MeCN); ν_{max}/cm^{-1} 1660 and 1615; λ_{max}/nm 7600 (ε/dm^3 mol^{-1} cm^{-1} 232); CD Δε (λ/nm) +0.06 (325), +1.39 (271) and +9.33 (229); δ 6.54 (1 H, m, $w_{\frac{1}{2}}$ 11, 2-H), 1.74 (3 H, d, *J* 1, 3-CH_3), 1.12 (3 H, s, 19-CH_3), 0.77 (3 H, s, 32-CH_3), 0.73 (3 H, s, 18-CH_3), 0.90 and 0.83; *m*/*z* 410 (M^+), 395, 241, 105 and 95 (Found: M^+, 410.354 63. $C_{29}H_{46}O$ requires *M*, 410.354 87.

(c) The ketol **5** (5.0 mg, 0.012 mmol) [pyridine (1.0 cm^3), thionyl chloride (0.025 cm^3); reaction time 10 min] gave **8** (4.0 mg, 83%), m.p. 94–95 °C; the identity of the compound was proved by TLC, ^1H NMR and mass spectroscopy.

(d) The ketol **6** (5.0 mg, 0.012 mmol) [pyridine (1.0 cm^3), thionyl chloride (0.025 cm^3); reaction time 10 min] gave **7** (3.5 mg, 72%), m.p. 126–127 °C; the identity of the compound was proved by TLC, ^1H NMR and UV spectroscopy.

3β-*Acetoxy*-3α,14α-*dimethyl*-5α-*cholest*-8-*en*-4-*one* **9**.—A solution of the ketol **3** (44 mg, 0.103 mmol) in acetic anhydride (10 cm^3) was kept at 80 °C for 2 h. The reaction mixture was cooled, diluted with brine (50 cm^3) and extracted with benzene (×2). The extract was washed with water (×3), dried ($MgSO_4$) and evaporated to give **9** (45 mg, 93%), m.p. 206–208 °C (needles from Et_2O–MeOH); ν_{max}/cm^{-1} 1735, 1716 and 1255; CD Δε (λ/nm) −2.79 (290); δ 2.09 (3 H, s, CH_3CO_2), 1.56 (3 H, s, 3α-CH_3), 1.10 (3 H, s, 19-CH_3), 0.69 (3 H, s, 18-CH_3), 0.90 and 0.83; *m*/*z* 470 (M^+), 455, 410 and 395 (Found: C, 78.9; H, 10.8. $C_{31}H_{50}O_3$ requires C, 79.10; H, 10.71%).

3β-*Acetoxy*-3α,14α-*dimethyl*-5β-*cholest*-8-*en*-4-*one* **10**.—A solution of the ketol **5** (15 mg, 0.035 mmol) in acetic anhydride (3 cm^3) containing 4-(*N*,*N*-dimethylamino)pyridine (10 mg) was kept at 80 °C for 1 h. Work-up as above and chromatography on silica gel (1 g) gave **10** (15 mg, 91%), m.p. 126–127 °C (from MeOH); ν_{max}/cm^{-1} 1730 and 1258; CD Δε (λ/nm) −0.20 (305); δ 2.44 (1 H, dd, *J* 4 and 3.5, 5β-H), 2.06 (3 H, s, CH_3CO_2), 1.37 (3 H, s, 3α-CH_3), 1.19 (3 H, s, 19-CH_3), 0.81 (3 H, s, 32-CH_3), 0.69 (3 H, s, 18-CH_3), 0.90 and 0.83; *m*/*z* 470 (M^+),

410, 395 and 173 (Found: C, 79.1; H, 10.9. $C_{31}H_{50}O_3$ requires C, 79.10; H, 10.71%).

3α,14α-*Dimethyl*-5β-*cholest*-8-*en*-4-*one* **11**.—Azoisobutyronitrile (25 mg) and a solution of tributyltin hydride (200 mg) in *m*-xylene (3 cm^3) were added to a solution of compound **10** (105 mg, 0.223 mmol) in sodium-dried *m*-xylene (20 cm^3) and the reaction mixture was refluxed under argon for 25 min. The mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel (10 g) with benzene–hexane (3:1) as eluent to give **11** (80 mg, 87%), m.p. 115–117 °C (from methanol); ν_{max}/cm^{-1} 1695; CD $\Delta\varepsilon$ (λ/nm) −0.05 (292); δ 2.12 (1 H, m, $w_{\frac{1}{2}}$ 14), 1.19 (3 H, s, 19-CH_3), 0.98 (3 H, d, *J* 6.4, 3α-CH_3), 0.77 (3 H, s, 32-CH_3), 0.70 (3 H, s, 18-CH_3) 0.90 and 0.83; *m*/*z* 412 (M^+), 397, 231 and 95 (Found: C, 84.2; H, 11.4. $C_{29}H_{48}O$ requires C, 84.40; H, 11.72%).

Acknowledgements

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