Articles

Synthesis of a Novel 1α,5α-Cyclocholestane†,‡

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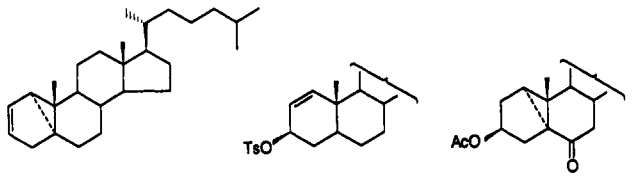
The synthesis of 4,4-dimethyl-1α,5α-cyclocholesta-3,7-dione (11), by lithium- or ytterbium-liquid ammonia reduction of the bis-α,β-unsaturated ketone, 4,4-dimethylcholesta-1,5-diene-3,7-dione (10), is described. The chemistry of the reductive cyclization is discussed. The ^{1}H NMR spectra of the corresponding dihydroxy derivatives of 11 reveal an unusually high-field signal due to H-9. X-ray diffraction analysis of the 7β-monool **13a** indicates that ring B of the steroid nucleus is in a boat conformation and that H-9 partially eclipses the C-1–C-10 bond of the cyclopropyl ring. An anisotropic ring current effect is postulated to account for the chemical shifts of H-9 in these cyclosteroids. The chemistry of these compounds is described.

Introduction

The 1α,5α-cyclosteroids are relatively rare. Laing and Sykes[1,2] in 1968 reported the synthesis of 1α,5-cyclo-5α-cholest-2-ene (1) directly from the in-situ formed *p*-toluenesulfonate (2) of 3β-hydroxy-5α-cholest-1-ene. These authors also reported[3] the synthesis of 3β-acetoxy-1α,5-cyclo-5α-cholestan-6-one (3) using a procedure which in our hands failed to yield any of this product.[4] The only



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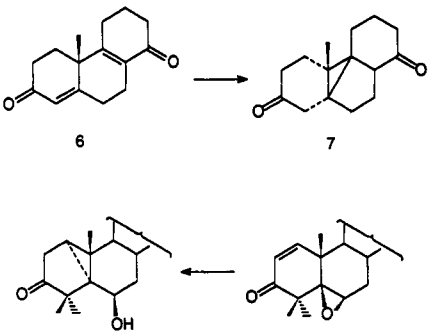
other published synthesis of a 1α,5α-cyclosteroid is that due to Christensen and Reusch[5] who synthesized 1-hydroxy-1,5α-cyclocholestan-7-one (4) via lithium–liquid ammonia reduction of cholest-5-ene-1,7-dione (5). Previous attempts by ourselves using other precursors to synthesize the corresponding 1α,5α-cyclosteroids have been unsuccessful.[4,6,7]

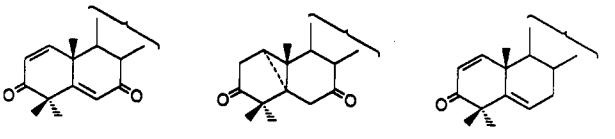
4 5

In 1989 Wenkert and Moeller[8] described an intramolecular reductive coupling in the bis-α,β-unsaturated ketone 6 to give 7 in 97% yield. Our attempts to form the 1α,5α-cyclosteroid 8 via an intramolecular reductive cyclization of 5β,6β-epoxy-4,4-dimethylcholest-1-en-3-one (9) were unsuccessful.[7] We were therefore interested in



6 7 8 9

determining whether the bis-α,β-unsaturated ketone 10 could undergo a similar intramolecular coupling of C-1 and C-5 to give the diketone 11. The chemistry of 10 and 11 and the unusual ^{1}H NMR spectra of the 1α,5α-cyclosteroids derived from 11 form the subject of this paper.



10 11 12

Results and Discussion

The dienedione 10 was prepared by photooxidation[9] of the dienone 12 in dioxane with *N*-bromosuccinimide. When 10 was reduced with lithium in liquid ammonia, a mixture of several products was obtained. The mixture could be simplified considerably by direct oxidation using pyri-

† This paper constitutes part 3 of approaches to the synthesis of 1α,5α-cyclosteroids. For part 2 see ref 7.

‡ Presented in part at the Ninth International Conference on Organic Synthesis, Montreal, Canada, June 28–July 2, 1992.

(1) Laing, S. B.; Sykes, P. J. *J. Chem. Soc. C* **1968**, 421–427.
(2) Laing, S. B.; Sykes, P. J. *J. Chem. Soc. C* **1968**, 653–656.
(3) Laing, S. B.; Sykes, P. J. *J. Chem. Soc. C* **1968**, 937–941.
(4) Georghiou, P. E.; Just, G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 70–73.
(5) Christensen, J. R.; Reusch, W. E. *J. Org. Chem.* **1983**, *48*, 3741–3744.
(6) Georghiou, P. E.; MacDiarmid, M. A. *Can. J. Chem.* **1980**, *58*, 1759–1762.
(7) Georghiou, P. E.; Ren, Y. *Can. J. Chem.*, in press.
(8) Wenkert, E.; Moeller, P. D. R. *Isr. J. Chem.* **1989**, 143–146.
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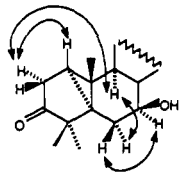


Figure 1. Selected NOE correlations for 13a.

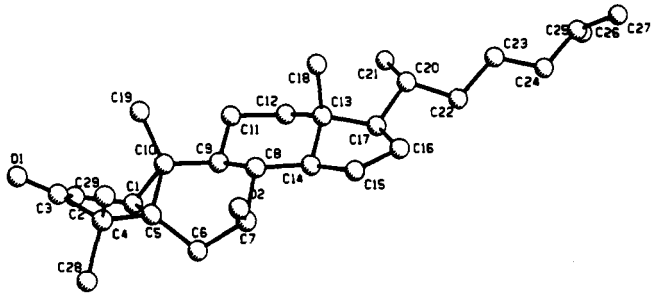


Figure 2. PLUTO drawing of the X-ray crystal structure of 13a.

dinium chlorochromate (PCC) to afford a single product in 72% yield. This product showed two carbonyl absorptions in its IR spectrum, at 1742 cm^{-1} and at 1713 cm^{-1}, which are indicative of a cyclopentanone and a cyclohexanone, respectively. These data and the mass spectrum are consistent with the 1α,5α-cyclosteroid structure 11. However, there was no cyclopropyl C–H infrared absorption discernible in the 3040 cm^{-1} region. Furthermore, the ^{1}H-NMR spectrum was ambiguous. An anticipated high-field signal corresponding to the cyclopropyl proton[10] on C-1 (H-1) was not evident.

Although 11 was crystalline, and a data set was collected by X-ray diffraction, there were insufficient data points to solve a structure since two crystallographically distinct steroid molecules were found to be present in the unit cell. Treatment of 11 with sodium borohydride selectively reduced the less hindered C-7 ketone to give the 7β-hydroxy compound **13a** as the major product and the 7α-epimer **13b** as the minor product. The IR spectrum of **13a** showed only a single carbonyl band at 1739 cm^{-1} and a sharp absorption at 3620 cm^{-1} corresponding to the hydroxyl group. The ^{1}H NMR spectrum revealed an unexpected doublet of triplets centered at δ = 0.52 and the C-18 methyl signal at δ = 0.71. Surprisingly, COSY indicated that the δ = 0.52 signal belonged to H-9 and confirmed that it was not due to the cyclopropyl H-1, as might have been expected. In fact, H-1 appeared as a doublet at δ = 0.93. The doublet of triplets due to H-9 is not as clearly evident in the ^{1}H NMR spectrum of **13b** because it is shifted downfield into the envelope region and could not be clearly discerned in the 300-MHz spectrum. HETCOR, APT, and NOED experiments (Figure 1) were consistent with these assignments. For example, irradiation of the signals due to H-2α at δ = 2.74, and also of the H-9 signals, enhanced the H-1 doublet. Correspondingly, irradiation of H-1 enhanced the H-2α and H-9 signals.

X-ray diffraction analysis on **13a** confirmed the 1α,5α-cyclosteroidal structure (Figure 2). Ring B is in a clearly defined boat conformation, which is also consistent with the NOED data.

(10) Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*; *4th ed.*; McGraw-Hill Book Company (UK) Ltd: Maidenhead, 1989.

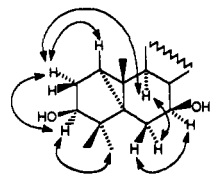
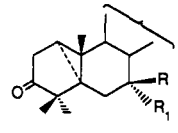


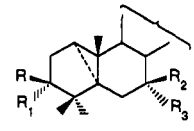
Figure 3. Selected NOE correlations for 14a.

Lithium aluminum hydride reduced the C-3 carbonyl of **13a** to produce diol **14a** and a small amount of the C-3 epimeric diol **14c**. The ^{1}H-NMR spectrum of **14a** also showed the doublet of triplets, although it was shifted upfield to δ = 0.37. COSY confirmed that this signal was due to H-9. The H-1 doublet was now at δ = 0.72. HETCOR, APT, and NOED spectra of **14a** were also consistent with these structural assignments. Thus, irradiation of the signals due to H-2α at δ = 2.48, and also the H-9 signals, enhanced the H-1 doublet. Correspondingly, irradiation of H-1 enhanced the H-9 signals (Figure 3).

When compound 11 itself was reduced with lithium aluminum hydride, a 2:1 mixture of **14a** and its C-7 α-epimer **14b** was obtained. The chemical shifts of H-9 in **14a** and **14c** are further upfield by approximately 0.15 and 0.21 ppm relative to those of H-9 in **13a**.



13a: R = OH; R_1 = H
13b: R = H; R_1 = OH



14a: R = R_2 = OH; R_1 = R_3 = H
14b: R = R_3 = OH; R_1 = R_2 = H
14c: R_1 = R_2 = OH; R = R_3 = H

The high-field ^{1}H-NMR signals for H-9 at δ = 0.52 in **13a** and at δ = 0.37 in **14a**, respectively, are unprecedented for such a methine proton in a steroid. Molecular models of **13a** indicate that the C-9–H-9 bond nearly eclipses the C-1–C-10 bond, slightly skewed toward the C-5–C-10 bond of the cyclopropyl ring. This is especially so when ring B is in the boat conformation that is observed in the crystal structure of **13a** and that is suggested by our NOED experiments. Since suitable crystals for the X-ray crystallographic analysis of the other 1α,5-cyclosteroids that were synthesized could not be obtained, we conducted molecular modeling calculations.[11] The calculated torsion angles in **11**, **13a**, **13b**, and **14a** indicate that the C-9–H-9 bond nearly eclipses the C-1–C-10 bond and is skewed toward the C-5–C-10 bond of the cyclopropyl ring in all cases, within a very narrow range. The H_9–C_9–C_{10}–C_1 and the corresponding $H_{6\alpha}$–C_6–C_5–C_1 torsion angles obtained directly from the crystal structure of **13a** are −12° and −7°, respectively, and those from the modeling calculations are −7.1° and −7.0°, respectively. The corresponding torsion angles are −6.9° and −5.9° for **11**, −7.8° and −6.4° for **13b**, and −5.9° and −5.0° for **14a**. It is possible that the unusual signals observed for H-9 are influenced by an anisotropic cyclopropyl ring current effect. If so, this effect is in turn obviously strongly influenced by the nature of the functional groups at C-3 and C-6.

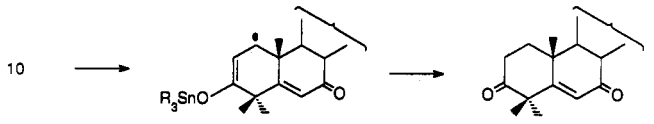
With samples of compounds **11**, **13a–b**, and **14a–c** isolated and characterized, the lithium–liquid ammonia

(11) *PC-Model. Molecular Modeling Software*, Sereena Software: Bloomington, IN.

reduction of **10** was reinvestigated, and the crude mixture obtained directly from the reduction was chromatographed. The products consisted of **11**, the epimeric monoalcohols **13a–b**, and the epimeric diols **14a–c**. The combined yield of these products amounts to an overall yield of 80–90% of 1α,5α-cyclosteroids. PCC oxidation of the mixture to **11** results in a decrease in yield. Reduction using ytterbium[12] in liquid ammonia, followed by PCC oxidation of the crude reduction mixture, gave the same overall yield of diketone **11** as was obtained with lithium–liquid ammonia.

Several possible circumstances could account for the Michael addition of one metal–enolate carbanion to the other α,β-unsaturated ketone. For example, if the enolate carbanion is formed at C-1 the transannular cyclization by intramolecular Michael addition to the α,β-unsaturated ketone at C-5–C-7 can be envisioned as being favored by a 3-*exo-trig* and/or a 5-*exo-trig* ring closure.[13] When the dienedione **10** reacts with triphenyltin hydride (TPTH) or tri-*n*-butyltin hydride (TBTH) (see below), the C-1–C-2 double bond is preferentially reduced with no corresponding reduction of the C-5–C-6 double bond, suggesting that carbanion formation at C-1 would indeed be favored. If the carbanion is generated more rapidly at C-5, intramolecular Michael cyclization from this direction would involve a 3-*exo-trig* and/or a 5-*endo-trig* (disfavored) mode of cyclization.

TPTH and TBTH reduce α,β-unsaturated ketones[14,15] via tin enolate radicals. When a dilute solution of **10** in benzene was treated with TPTH (or TBTH) and azobisisobutyronitrile (AIBN), the only product obtained besides starting material was 4,4-dimethylcholest-5-ene-3,7-dione (**16**). This result suggests that the putative tin enolate **15**



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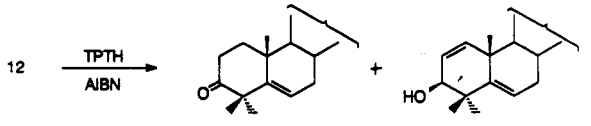
abstracts a hydrogen atom faster than intramolecular addition to the C-5–C-7 α,β-unsaturated ketone or that cyclization is reversible, favoring the uncyclized radical. Little[16] has shown that cyclization can occur after only a single electron has been transferred, followed by rapid reduction of the cyclized radical. When **12** was subjected to the same TPTH/AIBN reaction, **17** and **18** were obtained in 71% and 12% yields, respectively.



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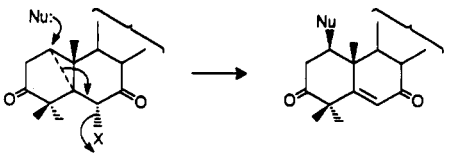
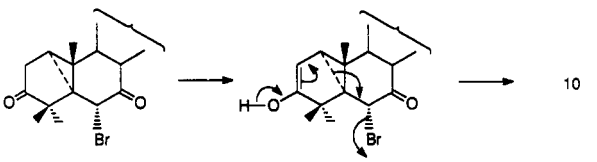
In 1α,5α-cyclosteroids the introduction of a functional group at C-6 would produce a system that could potentially undergo a cyclopropylcarbinyl rearrangement to afford a C-1-substituted steroid (Scheme I). Introduction of a bromine at C-6 was accomplished by photocatalyzed *N*-bromosuccinimide reaction of **11** to afford the 6α-bromide **19**. This product was not stable enough to be purified. When the crude reaction mixture was flash chromatographed, **19** was isolated in only 8% overall yield. The major product was **10** which could result from enolization of **19** and subsequent transannular elimination of hydrogen bromide as depicted in Scheme II.

Scheme I



Scheme II



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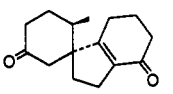
Wenkert and Moeller[8] noted that exposure of **7** to methanol in 25% sulfuric acid resulted in a rearrangement to afford a spirodiketone **20**. When we subjected cyclo-



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steroid **11** to the same conditions, no change could be observed, even after reflux for several hours. The stability of the 1α,5α-cyclosteroid to these acidic conditions was unexpected. We are currently evaluating the reactivity of this system to other reagents.

In summary, we have synthesized a novel 1α,5α-cyclosteroid by intramolecular reductive coupling. The 3-keto-7β-hydroxy and the 3α,7β- and 3β,7β-dihydroxy derivatives demonstrate an unusually high-field ^{1}H NMR signal for a methine proton on a steroid nucleus.

Experimental Section

Melting points are uncorrected. ^{1}H-NMR spectra were recorded at 300 MHz in $CDCl_3$. Microanalyses were conducted by Canadian Microanalytical Service Ltd., Delta, B.C.

4,4-Dimethylcholesta-1,5-diene-3,7-dione (10). A suspension of $CaCO_3$ (505 mg, 5.05 mmol) in a solution of 4,4-dimethylcholesta-1,5-dien-3-one[17] (**12**) (1.07 g, 2.61 mmol) in dioxane (200 mL) containing water (20 mL) was irradiated at rt, and NBS (1.06 g, 5.97 mmol) was added in a single batch. After 1 h, the mixture was filtered into water and extracted with ether, and the combined ether layers were washed, dried, and evaporated as usual. Flash chromatography of the residue using hexane–ethyl acetate gave **10** (952 mg, 86%), mp 93–94 °C: IR (CCl_4) 1692 and 1672 cm^{-1}; ^{1}H NMR δ 0.75 (3 H, s, C-18), 0.86 (3 H, d, J = 6.6 Hz, C-26), 0.87 (3 H, d, J = 6.6 Hz, C-27), 0.93 (3 H, d, J = 6.5 Hz, C-21), 1.69 (1 H, dd, J = 3.7, 12.8 Hz), 1.75–1.81 (2 H, m), 1.84–1.95 (1 H, m), 2.11 (1 H, dt, J = 3.2, 13.0 Hz, C-12β), 2.20–2.32 (1 H, m), 2.41 (1 H, t, J = 11.0 Hz, C-8), 5.97 (1 H, s, C-6), 6.04 (1 H, d, J = 10.4 Hz, C-2), 6.93 (1 H, d, J = 10.4 Hz,

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(17) Barton, D. H.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2209–2213.

C-1); MS *m/e* (relative intensity): 424 (13, M^+), 409 (10), 381 (2), 275 (55), 247 (8), 216 (10), 149 (30), 43 (100); HRMS M^+ 424.3363, calcd for $C_{29}H_{44}O_2$ 424.3339. Anal. Calcd for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44. Found: C, 82.05; H, 10.34.

4,4-Dimethyl-1α,5α-cyclocholestane-3,7-dione (11). Freshly condensed NH_3 (15 mL, dried over sodium at −78 °C) was allowed to distill into a stirred suspension of lithium (40 mg, 5.6 mmol) in dry THF (2.5 mL) at −78 °C. The stirring was continued until the metal had dissolved. A solution of dienedione **10** (463 mg, 1.10 mmol) in anhydrous THF (5 mL) was added over 3 h using a syringe pump. The solution was stirred at −78 °C for a further 1 h. Ammonium acetate was added to discharge the blue color, and the NH_3 was allowed to evaporate. The residue was extracted with ether and water. The aqueous layer was extracted with ether, and the combined ether solutions were washed, dried over $MgSO_4$, and evaporated to dryness. The crude residue (457 mg) was suspended in dry CH_2Cl_2 (100 mL), and pyridinium chlorochromate (PCC) (550 mg, 2.19 mmol) was added in one portion to the stirred solution. After 2 h the mixture was transferred onto a short silica gel column which was eluted with ether. Evaporation of the solvent left a residue (368 mg). Flash chromatography of the residue using hexane–ethyl acetate gave diketone **11** (335 mg, 72%), mp 107.0–108.0 °C: IR (CCl_4) 1713 and 1742 cm^{-1}; ^1H NMR 0.72 (3 H, s, C-18), 0.86 (3 H, d, J = 6.6 Hz, C-26), 0.86 (3, H, d, J = 6.6 Hz, C-27), 0.87 (3 H, s, C-19), 0.92 (3 H, d, J = 6.6 Hz, C-21), 0.96 (3 H, s, C-4β), 1.07 (3 H, s, C-4α), 1.34 (1 H, d, J = 6.0 Hz, C-1α), 2.03 (1 H, t, J = 11.8 Hz, C-8), 2.28 (1 H, d, J = 19.0 Hz, 2β-H), 2.44 (1 H, d, J = 16.0 Hz, C-6α), 2.60 (1 H, d, J = 16.0 Hz, C-6β), 2.81 (1 H, dd, J = 6.1, 19.0 Hz, C-2α); MS *m/e* (relative intensity) 426 (100, M^+), 411 (12), 383 (8), 355 (12), 328 (14), 275 (40), 247 (17), 163 (32), 135 (78), 95 (76), 55 (100); HRMS M^+ 426.3461, calcd for $C_{29}H_{46}O_2$ 426.3495. Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.77; H, 10.73.

4,4-Dimethyl-7β- and -7α-hydroxy-1α,5α-cyclocholestan-3-ones (13a,b). A solution of **11** (105 mg, 0.246 mmol) in methanol (30 mL), $NaBH_4$ (85 mg, 2.2 mmol), and $CeCl_3{\cdot}7H_2O$ (111 mg, 0.298 mmol) was stirred at rt for 48 h. A small amount of water was added to quench the reaction. The resulting solution was extracted with ether, and the combined ether layers were washed, dried, and evaporated as usual. Flash chromatography using hexane–ethyl acetate yielded **13a** (81 mg, 77%), mp 207.5–208.5 °C, and **13b** (8 mg, 7%). Compound **13a** had the following properties: IR (CCl_4) 3620 and 1739 cm^{-1}; ^1H NMR δ 0.52 (1 H, dt, J = 5.0, 12.0 Hz, C-9), 0.71 (3 H, s, C-18), 0.82 (3 H, s, C-19), 0.86 (3 H, d, J = 6.6 Hz, C-26), 0.87 (3 H, d, J = 6.6 Hz, C-27), 0.91 (3 H, d, J = 6.4 Hz, C-21), 0.93 (1 H, d, J = 6.5 Hz, C-1), 1.08 (3 H, s, C-4α), 1.11 (3 H, s, C-4β), 1.20 (1 H, dt, J = 4.7, 11.0 Hz, C-8), 1.65 (1 H, dd, J = 5.2, 15.8 Hz, C-6α), 2.00 (1 H, dd, J = 3.2, 15.8 Hz, C-6β), 2.24 (1 H, d, J = 18.9 Hz, C-2β), 2.74 (1 H, dd, J = 6.2, 19.0 Hz, C-2α), 3.73 (1 H, br s, C-7); MS *m/e* (relative intensity) 428 (7, M^+), 410 (22), 395 (9), 325 (4), 297 (15), 187 (14), 152 (100), 95 (43), 43 (64); HRMS M^+ 428.3618, calcd for $C_{29}H_{48}O_2$ 428.3652. Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.14; H, 11.26. Compound **13b** had the following spectral properties: IR (CCl_4) 3629 and 1736 cm^{-1}; ^1H NMR δ 0.70 (3 H, s, C-18), 0.85 (3 H, s), 0.86 (3 H, d, J = 6.6 Hz, C-26), 0.86 (3 H, d, J = 6.6 Hz, C-27), 0.91 (3 H, d, J = 6.5 Hz, C-21), 1.03 (3 H, s), 1.04 (3 H, s), 2.27 (1 H, d, J = 19.1 Hz, C-2α), 2.72 (1 H, dd, J = 6.0, 19.1 Hz, C-2β), 3.96 (1 H, br s, C-7).

X-ray Data for 13a. Crystal data for **13a**: $C_{29}H_{48}O_2$, monoclinic, space group $P2_1$ (#4), a = 6.748 (2) Å, b = 10.872 (2) Å, c = 17.789 (2) Å, β = 97.10 (2)°, Z = 2, $D_{(calcd)}$ = 1.099 g cm^{-3}, crystal size = 0.40 × 0.20 × 0.12 mm. Intensity data were measured at 298 K on a Rigaku AFC6S diffractometer with graphite-monochromated CuKα radiation (λ = 1.541 78 Å) to $2\theta_{max}$ (deg) = 120.2°; 2064 unqiue reflections converged to a final R = 0.057, for 1054 reflections with $I_{net}/\sigma I_{net} \geq 2.5$; R_w = 0.045, G.o.F. = 1.68. Additional details of the structure solution are given in the supplementary material.

A. Reduction of 13a. To a solution of 4,4-dimethyl-7β-hydroxy-1α,5α-cyclocholestan-3-one (**13a**) (51 mg, 0.12 mmol) in dry ether (10 mL) was injected a solution of $LiAlH_4$ (30 mg, 0.79 mmol) in dry ether (20 mL) over 30 min. The mixture was stirred at room temperature for 4 h before a small amount of water was added to quench the reaction. The solution was extracted with ethyl acetate, and the combined organic layers were washed, dried and evaporated as usual. Chromatography of the residue and elution with 10% ethyl acetate in hexane yielded 4,4-dimethyl-1α,5α-cyclocholestane-3β,7β-diol (**14a**) (39 mg, 76%) and 4,4-dimethyl-1α,5α-cyclocholestane-3α,7β-diol (**14c**) (5 mg, 10%). Compound **14a**, mp 212 °C, had the following spectral properties: IR (CCl_4) 3640 cm^{-1}; NMR δ 0.37 (1 H, dt, J = 4.7, 12.1 Hz, C-9), 0.71 (3 H, s, 18-Me), 0.72 (1 H, d, J = 5.0 Hz, C-1), 0.86 (3 H, d, J = 6.6 Hz, C-26), 0.86 (3 H, d, J = 6.6 Hz, C-27), 0.91 (3 H, d, J = 6.6 Hz, C-21), 1.04 (3 H, s, C-4β), 1.10 (3 H, s, C-4α), 1.18 (1 H, dt, J = 3.5, 10.8 Hz, C-8), 1.30 (3 H, s, C-19), 1.51 (1 H, dd, J = 3.8, 14.9 Hz, C-6α), 1.60 (1 H, dd, J = 2.1, 14.2 Hz, C-2β), 1.98 (1 H, dd, J = 3.1, 14.9 Hz, C-6β), 2.48 (1 H, ddd, J = 6.6, 9.7, 15.0 Hz, C-2α), 3.63 (1 H, br s, C-7), 4.07 (1 H, dd, J = 2.4, 9.7 Hz, C-3). Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.61; H, 11.67. The minor product **14c** had the following spectral properties: IR (CCl_4) 3621 cm^{-1}; NMR δ 0.31 (1 H, dt, J = 4.7, 12.1 Hz, C-9), 0.70 (3 H, s, C-18), 0.86 (3 H, d, J = 6.6 Hz, C-26), 0.86 (3 H, d, J = 6.6 Hz, C-27), 0.90 (3 H, d, J = 6.5 Hz, C-21), 0.98 (3 H, s, Me), 1.05 (3 H, s, Me), 1.06 (3 H, s, Me), 3.69 (1 H, br s, 7-H), 3.90 (1 H, t, J = 8.4 Hz, 3-H).

B. Reduction of 11. A solution of $LiAlH_4$ (30 mg, 0.79 mmol) in dry ether (20 mL) was added over 30 min to a solution of **11** (50 mg, 0.12 mmol) in dry ether (10 mL). After the addition was completed, the mixture was refluxed for 6 h before a small amount of water was added to quench the reaction. The solution was extracted with ethyl acetate, and the combined organic layers were washed, dried, and evaporated as usual. TLC showed a single spot, but ^1H NMR showed it to be a 2:1 mixture of 4,4-dimethyl-1α,5α-cyclocholestane-3β,7β-diol (**14a**) and its epimer 4,4-dimethyl-1α,5α-cyclocholestane-3β,7α-diol (**14b**) which could not be separated by column chromatography.

4,4-Dimethylcholest-5-ene-3,7-dione (16). To a solution of **10** (121 mg, 0.285 mmol) refluxing in dry benzene (50 mL) under argon was added a solution of tri-*n*-butyltin hydride (TBTH) (0.15 ml, 0.56 mmol) and a trace amount of AIBN in dry benzene (30 mL) dropwise over 5 h. The mixture was refluxed for 24 h, and then the reaction was quenched by the addition of a small amount of water. The residue obtained after evaporating the solvent was chromatographed by flash chromatography. Elution first with benzene eluted the TBTH derivatives; on the same column, elution with 5% ethyl acetate–hexane gave **16** (46 mg, 38%) and unreacted **10** (64 mg, 53%). For compound **16**, mp 164–165 °C (lit.[18] mp 163–165 °C): IR (CCl_4) 1716 and 1676 cm^{-1}; NMR δ 0.70 (3 H, s, C-18), 0.86 (3 H, d, J = 6.6 Hz, C-26), 0.87 (3 H, d, J = 6.6 Hz, C-27), 0.93 (3 H, d, J = 6.6 Hz, 21-Me), 1.07 (3 H, s, Me), 1.31 (3 H, s, Me), 1.32 (3 H, s, Me), 1.48–1.57 (2 H, mm), 1.60–1.66 (2 H, mm), 1.79–1.93 (2 H, mm), 2.04–2.18 (2 H, mm), 2.30 (1 H, t, J = 11.04 Hz, 8-H), 2.38–2.41 (1 H, m), 2.61 (1 H, dd, J = 6.6, 11.5 Hz, 2-H), 2.63 (1 H, d, J = 10.6 Hz, 2-H), 5.90 (1 H, s, 6-H).

Triphenyltin Hydride Reduction of 12. To a solution of **12** (110 mg, 0.268 mmol) refluxing in dry benzene (50 mL) under argon was added a solution of triphenyltin hydride (TPTH) (513 mg, 1.46 mmol) and a trace amount of AIBN in dry benzene (30 mL) dropwise over 5 h. The reaction was refluxed for 20 h before it was quenched by the addition of a small amount of water. The residue after evaporating the solvent was chromatographed directly. Elution first with pure benzene removed the TPTH derivatives; on the same column, chromatography using a hexane–ethyl acetate gradient system yielded 4,4-dimethylcholest-5-en-3-one (**17**) (79 mg, 71%) and 4,4-dimethylcholesta-1,5-dien-3β-ol (**18**) (13 mg, 12%). Compound **17** had mp 174–175 °C (lit.[19] mp 176–177 °C). Compound **18**, mp 190–191 °C (methanol), was identical with a sample prepared by $NaBH_4$ reduction of **12**. Its spectral properties were as follows: IR (CCl_4) 3650 cm^{-1}; NMR δ 0.69 (3 H, s, C-18), 0.86 (6 H, d, J = 6.5 Hz, C-26, C-27), 0.91 (3 H, d, J = 6.5 Hz, C-21), 1.04 (3 H, s, Me), 1.14 (3 H, s, Me), 1.14 (3 H, s, Me), 3.83 (1 H, d, J = 6.5 Hz, C-3), 5.43 (1 H, d, J = 10.3 Hz, C-1), 5.49 (1 H, t, J = 3.2 Hz, C-6), 5.73 (1 H, dd, J

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= 2.3, 10.3 Hz, C-2). Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.59; H, 11.74.

Bromination of 11. A solution of 11 (30 mg, 0.07 mmol) in dry CCl_4 (5 mL) was irradiated under visible light at room temperature while NBS (15 mg, 0.08 mmol) in dry carbon tetrachloride (10 mL) was added by syringe over 30 min, followed by a trace amount of AIBN. The mixture was stirred under irradiation for 24 h before the reaction was quenched by evaporation of the solvent. Column chromatography of the residue yielded 19 (3 mg, 8%) and 10 (22 mg, 74%). Compound 19 had the following spectral properties: IR (CCl_4) 1713 and 1746 cm^{-1}; NMR δ 0.72 (3 H, s, C-18), 0.86 (3 H, s, Me), 0.86 (3 H, d, J = 6.5 Hz, C-26), 0.87 (3 H, d, J = 6.5 Hz, C-27), 0.92 (3 H, d, J = 6.5 Hz, C-21), 0.97 (3 H, s, Me), 1.19 (3 H, s, Me), 1.81 (1 H, d, J = 6.3 Hz, C-1), 2.36 (1 H, d, J = 18.9 Hz, C-2β), 2.92 (1 H, dd, J = 6.3, 18.9 Hz, C-2α), 4.59 (1 H, s, C-6β).

Acidic Treatment of 11. To a solution of 11 (38 mg, 0.089 mmol) in methanol (3 mL) at 70 °C was added H_2SO_4 (3 M, 5 mL) dropwise over 30 min. The mixture was stirred at rt for 24 h with no change evidenced by TLC. The mixture was then refluxed for a further 5 h with still no change evident. After workup 11 was recovered unchanged.

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Supplementary Material Available: Crystal data (bond angles, bond lengths, positional and thermal parameters, measured and calculated torsion angles, etc., as well as a descriptive summary and literature references for the diffraction analysis) of 13a (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.