Stereochemical Course of the Chemical and Catalytic Reduction of 11-Oxo-5α,14β-cholest-8-en-3β-ol. Synthesis of 8α,9α,14β-, 8α,9β,14β-, and 8β,9α,14β-Steroids[1]

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The lithium–ammonia overreduction of 11-oxo-5α,14β-cholest-8-en-3β-ol (1) was shown to give equal amounts of 5α,8α,9α,14β-cholestane-3β,11β-diol (2) and 5α,8β,9α,14β-cholestane-3β,11α-diol (3) by conversion of the diols to hydrocarbons of known stereochemistry. In contrast to 14α- and 14β-steroidal 11-ketosapogenins (which are stable to base), the 5α,8α,9α,14β-11-ones in the present study provided through base equilibration a route to the unknown 8α,9β,14β stereochemistry. The CD spectra of the 11-keto-5α,8α,9α,14β-, and -5α,8β,9α,14β-, and -5α,8α,9β,14β-steroids provide evidence for nonchair conformations in rings B and/or C of the steroid skeleton.

The identification and use of sterane stereochemistry have become important in organic geochemistry for such problems as source rock/oil correlations,[2] oil/oil correlations,[3] and in understanding the mechanism of the processes of formation of the hydrocarbons of the geosphere.[4] This interest in sterane stereochemistry has prompted the synthesis of various stereoisomers to evaluate methods of identification of steranes from geological sources.[5] The actual experimental details of the synthesis[5] of these stereoisomers have not yet been published. Because of the interest in stereoisomers of steranes[6] and a lack of published synthetic methods,[5] we present here a synthetic method for generating the hitherto unknown 8α,9α and 8α,9β B/C ring junctures as well as the "normal" 8β,9α stereochemistry in steroids with the 14β (C/D cis) stereochemistry.

Recently we had cause to prepare the Δ^8-11-ketone 1 in a study of the effect of the 17β-alkyl group on the relative stabilities of the C/D cis and trans ring junctures.[7] Additionally, this compound was to serve as an intermediate in the synthesis of certain deuterium labeled steroidal 8β,9α,14β-hydrocarbons needed for mass spectral studies. A key reaction in these labeling experiments was to be the lithium–ammonia reduction of **1**, which was expected to give the "natural" 8β,9α B/C ring juncture based on the results of previous studies with steroidal sapogenins.[8] The unexpected results of the lithium–ammonia reduction of the unsaturated ketosterol 1 prompted subsequent experimental work to establish the stereochemistry of the B/C ring juncture as depicted in Scheme I.

The lithium–ammonia complete reduction of 1 gave equal amounts of the two C-11 epimeric diols **2** and **3.** These two diols were separable on silica gel, and the less polar compound **3** was oxidized under Jones conditions to the 3,11-dione **4**, which was stable to base. Subsequent Wolff–Kishner reduction afforded 14β-cholestane (**5**), which was identical in all respects with authentic material prepared by a published route[9] or via the 12-ketone **17** (Scheme I). The stereochemistry at C-8 in compounds **3** and **4** is thus established to be 8β. The NMR spectrum of compound **3** displays a broad multiplet (3.9–3.4 ppm) for the hydrogens at carbons 3 and 11 as well as a downfield doublet triplet at 2.38 ppm. The high-field position of the 11-H,[10] the close distance (~1.8 Å) between the 11α-OH and the 1β-H,[11] and the very close agreement between the observed chemical shifts of the angular C-18 and C-19 methyl groups and the values calculated according to the tables of Zürcher[12] [1.00 ppm (18-CH_3), calcd 0.98 ppm; 0.92 ppm (19-CH_3), calcd 0.90 ppm] are consistent with the assigned structure and cannot be accommodated by the alternatives.

Similarly, the diol **2** was oxidized to the 3,11-diketone **6,** which was identical with material synthesized by catalytic hydrogenation of **1** to the 3β-hydroxy-11-ketone **7** followed by Jones oxidation to the dione **6.** This diketone **6,** when subjected to Wolff–Kishner conditions, afforded the known[5a,c,11] 5α,8α,14β-cholestane (**8**) as the major product with a minor amount of the hydrocarbon **11.** The stereochemistry at C-8 is thus established to be 8α in **2, 6,** and **7.**[11] There are four stereochemical possibilities for the configuration at C-9 and C-11 in compound **2,** but two of these, 9β,11β-H and 9α,11β-H, can be ruled out because the 11β-H NMR signal would be expected to have a narrow half-bandwidth due to three small vicinal couplings. The two remaining possibilities, 9β,11α-H and 9α,11α-H, cannot be distinguished on the basis of the half-bandwidth of the 11α-H since the signal should be broad in both stereoisomers. However, a differentiation can be made based on the NMR spectrum of the polydeuterated analogue **2a,** where the dihedral angle between 9β-H and 11α-H is approximately 180° and that of 9α-H and 11α-H is approximately 60°. In the former configuration a large vicinal coupling constant (8–14 Hz)[13] is anticipated, whereas in the latter a smaller coupling constant (1–5 Hz)[13] is expected. The observed slightly broadened doublet (J = 5 Hz) at 3.97 ppm in compound **2a** is consistent with the 9α,11α-H stereochemistry for compound **2** shown in Scheme I.[11] 5α,8α,14β-Cholestane-3β,11β-diol (**2**) was further characterized by the di-*p*-bromobenzoate **2b** as well as by the diacetate **2c** and the monoacetate **2d.**

The Jones oxidation of **2** and **3** to the diketones **4** and **6** presumably took place without epimerization at C-9. This method has been used previously for oxidation of alcohols to enolizable ketones without epimerization of a chiral center α to the ketone function.[14] Subsequent base-catalyzed equilibration of **6** gave an equilibrium mixture consisting of 73% **6** and 27% 9β epimer **9.**[15] Likewise, equilibration of the catalytic hydrogenation product **7** gave an equilibrium mixture consisting of 74% **7** and 26% 9β epimer **10.**[15] The diketones **6** and **9** as well as the monoketones **7** and **10** show large differences in their mass spectral fragmentation patterns from the "normal" (8β,9α) B/C ring juncture diketone **4** (14β configuration), which in turn is quite different from the "normal" (8β,9α,14α) diketone **19.** The latter dione was synthesized by Jones oxidation of 11-oxo-5α-cholestan-3α-ol (**18**).[16] Deuterium labeling studies which allowed the elucidation of the mechanism for the major fragmentations of these 11-ketones will be published elsewhere.[17]

Figure 1 displays the CD spectra of the various 11-ketones from Scheme I. The octant projection **20** [(●) atoms in rear positive octant; (○) atoms in rear negative octant; (▲) atoms in front octant], which is applicable to compounds **4, 13, 18,** and **19,** would predict a positive Cotton effect in these com-

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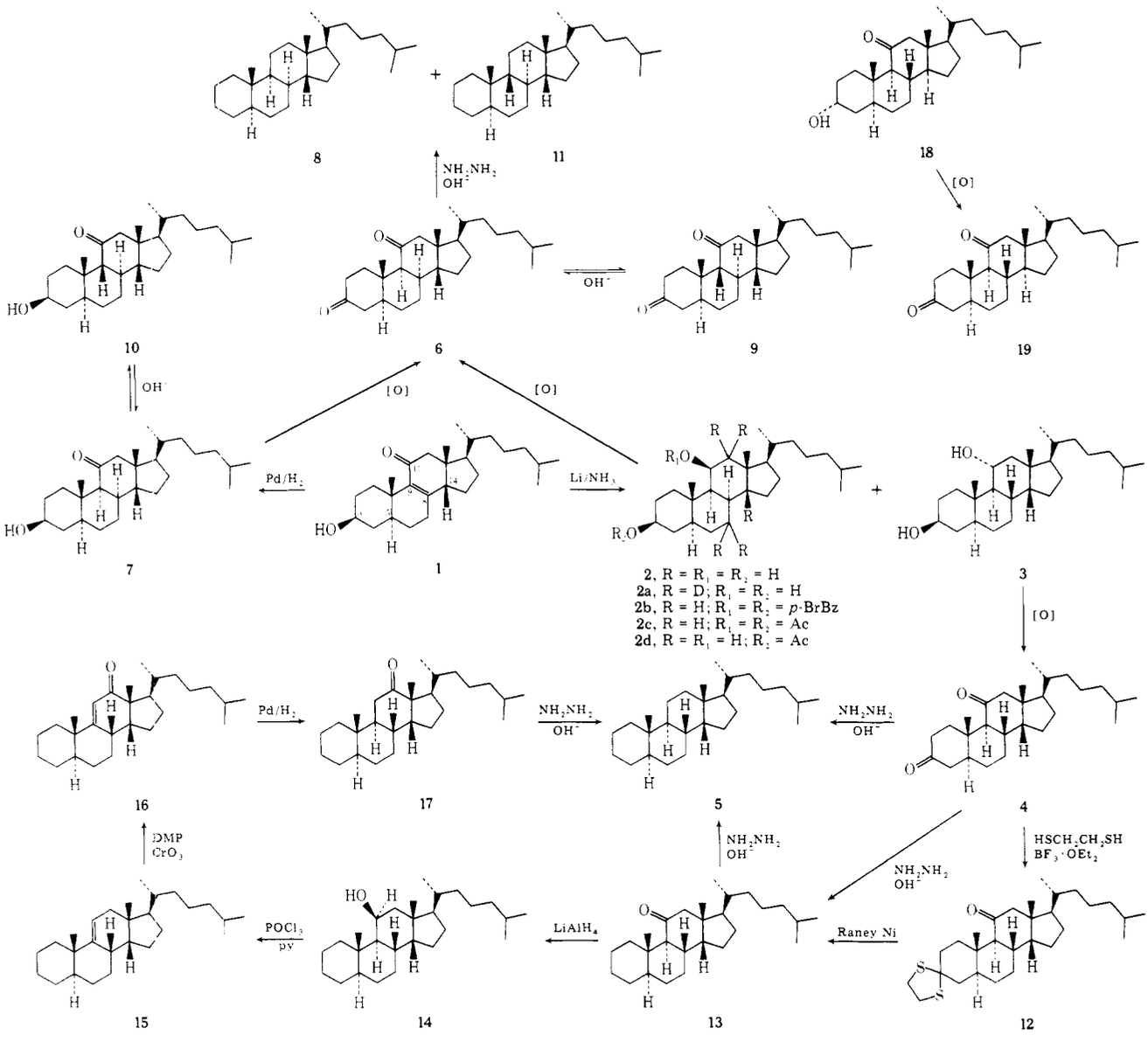
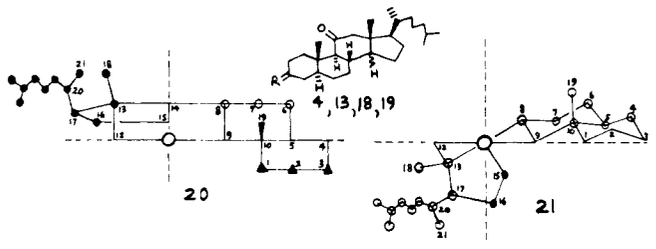
Scheme I

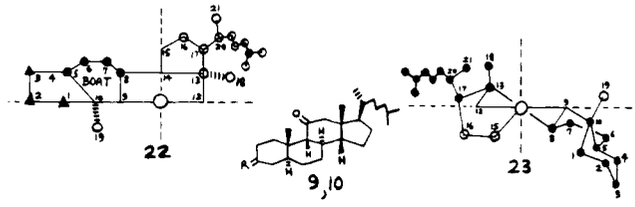


pounds. Compounds **18** and **19** in the 14α series show a mild positive Cotton effect in accord with the predictions of **20** and previous measurements[18,19] on 14α-11-ones. Compounds **4**

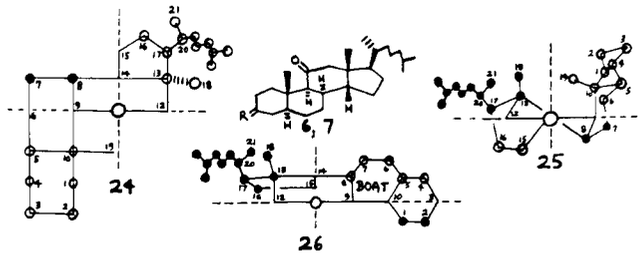


and **13** both show a negative Cotton effect, which is in accord with previous measurements on 14β-11-ketosteroids.[18] The opposite sign of the Cotton effect has been attributed to an "abnormal" conformation of ring C in these compounds.[19,20] The twist conformation **21** would rationalize the relatively large negative Cotton effect in compound **13** since nearly all of the atoms lie in negative octants.

The octant projection **22**, which is applicable to compounds **9** and **10**, would predict a negative Cotton effect, and the large positive effect observed could be accounted for by the alternate twist conformation **23** in which nearly all of the atoms lie in positive octants.



The octant projection **24** clearly predicts a large negative Cotton effect, while compounds **6** and **7** both show moderately positive Cotton effects (Figure 1). The ring B "boat" conformation **26** or the ring C "twist" conformation **25** could account



for the observed Cotton effect. While the arguments used to assign stereochemistry in the diols **2** and **3** were based on all-chair conformations,[11] the above proposed deviations in ring

Table I. Relative Mass Spectral Intensities for Isomers of Cholestane

compd	mass spectra 70 eV 218/217	70 eV 151/149	15 eV 218/217	15 eV 151/149	^{1}m* (70 eV) 218/217	ref[a]
5	1.72	0.17	2.98	0.25	0.79	1
5	1.82	0.30				3
8	0.76	0.17	1.02	0.25	0.43	1
8	0.81	0.18				3
11	0.53	0.17	0.71	0.22	0.72	1
20	0.66	0.20	1.05	0.27	0.52	1
20	0.75	0.22				3
21	0.55	0.21				2
22	0.48	0.15				2
23	0.46	0.34				2
24	0.40	1.07				2
25	0.43	1.31				4
26	1.67	0.47				4
27	1.96	0.64				4
28	1.72	0.57				4
29	1.16	0.32				4
30	1.52	0.18				4
31	1.56	0.14				4
32	1.56	0.14				4

[a] 1 = present work, MS-9 (probe); 2 = Mulheirn and Ryback,[5a] AEI MS-30 (GC inlet); 3 = Mulheirn and Ryback,[5c] MS-9 (probe); 4 = Seifert and Moldowan,[6] GC/MS (40 eV), Nuclide 12-90-G, these authors have assigned stereochemistries based on mass spectra and GC retention times.

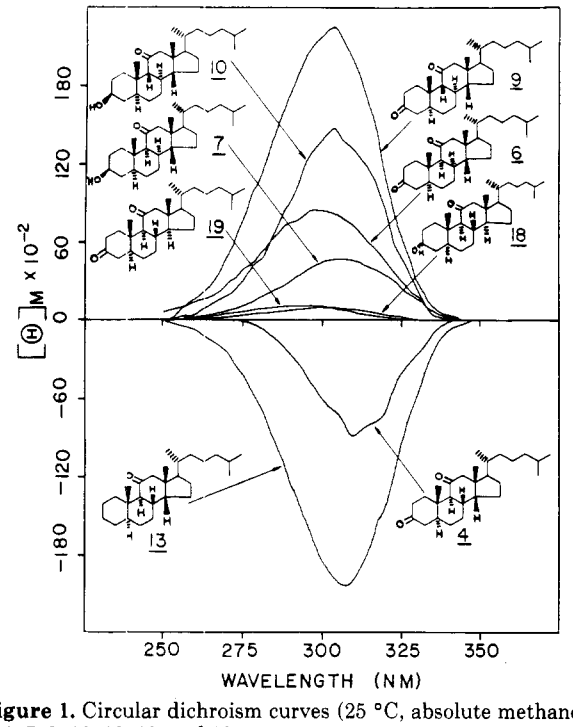
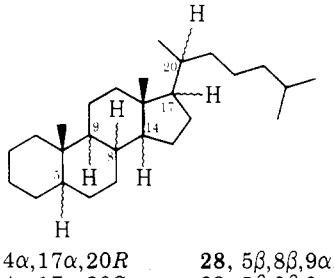


Figure 1. Circular dichroism curves (25 °C, absolute methanol) of **4, 6, 7, 9, 10, 13, 18,** and **19.**

C and/or B for compounds **4, 6, 7, 9, 10,** and **13** may be due to the change in hybridization (sp^3 to sp^2) at C-11. The energy difference, for example, between the chair and flexible forms in cyclohexanone is only about half as much as in cyclohexane.[21]

Wolff–Kishner reduction of an equilibrium mixture of the diones **6** and **9** furnished a mixture of two hydrocarbons, the known[5a,c] 5α,8α,14β-cholestane (**8**) and **11**, which could be separated by preparative GLC or reverse-phase high-pressure liquid chromatography. The assigned structure of this new hydrocarbon, 5α,8α,9β,14β-cholestane (**11**),[11] is supported by the synthetic method (Scheme I) and by the fact that its spectroscopic properties are different from the other 15 stereoisomers of cholestane which have been reported[5,6] (see Table I and supplementary material for Table II). The epimers with a *m/z* 218/217 ratio greater than 1 at 70 eV (Table I) all have the 8β,14β stereochemistry in common. The small value of this ratio for **11** suggests the 8α,14β stereochemistry. This 8α,14β stereochemistry then requires the 9β-H configuration since 9α-H would give compound **8**.[11] Further support for the stereochemical assignments in **11** can be obtained by an examination of Figure 2 (see supplementary material), which depicts the mass spectra for compounds **20, 5, 8,** and **11.** The *m/z* 149 ion (which represents C ring cleavage)[22] increases in importance in the 5α,14β series at 70 eV (**11**, Σ_{50} 6.4% > **8**, Σ_{50} 5.6% > **5**, Σ_{50} 3.2%). The differences are even more pronounced at lower (15 eV) ionizing energy (**11**, Σ_{50} 7.6% > **8**, Σ_{50} 5.5% > **5**, Σ_{50} 2.3%). This order of C ring cleavage is what would be predicted based on a conformational analysis[8] of the B/C ring epimers. In particular, the 5α,8α,9β,14β stereochemistry in **11** requires that ring B be in a "boat" conformation (while **8** and **5** can exist in all-chair conformations[11]), and cleavage through ring C (*m/z* 149) would reduce the inherent strain in the B/C ring juncture.



20, 5α,8β,9α,14α,17α,20*R*
21, 5α,8β,9α,14α,17α,20*S*
22, 5α,8β,9α,14α,17β,20*R*
23, 5α,8β,9α,14α,17β,20*S*
24, 5β,8β,9α,14α,17α,20*R*
25, 5β,8β,9α,14α,17α,20*S*
26, 5β,8β,9α,14β,17α,20*R*
27, 5β,8β,9α,14β,17α,20*S*
28, 5β,8β,9α,14β,17β,20*S*
29, 5β,8β,9α,14β,17β,20*R*
30, 5α,8β,9α,14β,17β,20*S*
31, 5α,8β,9α,14β,17β,20*R*
32, 5α,8β,9α,14β,17α,20*S*
5, 5α,8β,9α,14β,17α,20*R*
8, 5α,8α,9α,14β,17α,20*R*
11, 5α,8α,9β,14β,17α,20*R*

Experimental Section

General Information. Microanalyses were performed by E. H. Meier, Department of Chemistry, Stanford University. All melting

points are uncorrected and were taken with a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained for solutions in chloroform with a Perkin-Elmer 700 spectrometer. NMR spectra were recorded under the supervision of Dr. L. J. Durham on a Varian Associates T-60 or XL-100 spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal reference. Routine optical rotations were recorded with a Perkin-Elmer Model 141 spectropolarimeter for solutions in hexane or chloroform. Circular dichroism curves were determined for solutions in absolute methanol by Mrs. R. Records with a JASCO J-40 circular dichrometer. Low-resolution mass spectra were determined by Mr. R. G. Ross with an AEI MS9 spectrometer operating at 70 eV by the use of the direct inlet system. Exact masses were determined by Miss Annemarie Wegmann on a Varian-Mat 711 high-resolution mass spectrometer.

The progress of all reactions and column chromatographies was monitored by thin-layer chromatography on silica gel (HF-254) microplates. The spots were detected by spraying with a 2% solution of cerium(IV) sulfate in 2 N sulfuric acid, followed by heating. Preparative thin-layer chromatoplates had a thickness of 0.75 mm of silica gel (HF-254), and the bands were detected either visually or by viewing under ultraviolet light. Gas–liquid phase chromatography (GLC) was performed on a Hewlett-Packard Model 402 high efficiency instrument using 6-ft glass columns packed with 1% OV-25 on Gas-Chrom Q (100–120 mesh) using helium as the carrier gas. Preparative LC was performed using a Haskel Model 28303 pump, a 0–5000 psi Ashrof gauge, and a Waters Associates dual cell refractometer. The separations were carried out on a Whatman Partisil M9 10/50 ODS-2 column (50 cm × 8 mm i.d., mobile phase was absolute methanol).

Lithium–Ammonia Reduction of 11-Oxo-5α,14β-cholest-8-en-3β-ol (1). A solution of 330 mg of **1** in 7 mL of dry ether was added dropwise to 110 mg of lithium in 200 mL of undistilled liquid ammonia. After complete addition, the mixture was stirred for an additional 2 h, excess lithium was destroyed with methanol, and after the mixture was stirred for an additional 30 min, 190 mg of lithium was added. The mixture was then stirred for an additional 75 min, excess lithium was destroyed with solid ammonium chloride, and the ammonia was allowed to evaporate. The crude product (330 mg) obtained by dilution with water and ether extraction was chromatographed on 25 g of TLC mesh silica gel and eluted with 100% ether. The first material (20 mg) to elute from the column was a mixture of two compounds (~55:45) by GLC analysis which could not be separated on silica gel. The IR spectrum showed no carbonyl stretch, and GC/MS (oven temperature 276 °C) of the mixture showed the same fragment ions (*m/z* 384, 369, 351, 271, 253, 230, 215 (BP), 197) for both compounds. However, in the short retention time peak the principal fragment ions were more intense. The mixture was unaffected by prolonged heating under reflux in a basic solution. Oxidation of this material under Jones conditions afforded a clear glass which was homogeneous by TLC (UV-active spot) and showed a single peak by GLC. The mass spectrum of this oxidation product (M^+, *m/z* 398) is consistent with **5α,14β-cholest-8-ene-3,11-dione.** The original mixture probably consists of the two allylic alcohols at C-11, **5α,14β-cholest-8-ene-3β,11β-diol** and **5α,14β-cholest-8-ene-3β,11α-diol.**

The second compound to elute from the column, **5α,14β-cholestane-3β,11α-diol (3),** provided 161.2 mg of a white powder: mp 63–66 °C; NMR δ 3.9–3.4 (m, 2 H, 11β-H, 3α-H), 2.38 (dt, 1 H, 1β-H, J = 13, 3.5, 3.5 Hz), 1.00 (s, 3 H, 18-CH_3; calcd 0.98), 0.92 (s, 3 H, 19-CH_3; calcd 0.90); GLC (265 °C) relative retention time (rrt) 0.82 (rrt of **2,** 1); mass spectrum, *m/z* (rel. intensity) 386 (77), 371 (35), 353 (8), 302 (32), 273 (19), 255 (14), 220 (46), 206 (64), 193 (100).

The third compound to elute from the column, **5α,8α,14β-cholestane-3β,11β-diol (2),** provided 148.3 mg of white crystalline materials: mp 100–103 °C; $[\alpha]^{19}_D$ + 32° (*c* 0.42); NMR δ 3.96 (11α-H, $W_{1/2} \approx 22$ Hz), 3.60 (3α-H, $W_{1/2} \approx 20$ Hz), 0.95 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3); mass spectrum, *m/z* (rel. intensity) 386 (72), 371 (57), 353 (17), 302 (6), 273 (62), 255 (14), 220 (32), 206 (57), 193 (100).

5α,8α,14β-Cholestane-3β,11β-diol-7,7,12,12,14-d_5 (2a). 11-Oxo-5α-cholest-8-en-3β-ol benzoate[7] (50.4 mg, 0.1 mmol) was heated under reflux in an atmosphere of nitrogen for 16 h in 10 mL of methanol-*O*-*d* to which had been added 69 mg of sodium metal. The solvent was then distilled, fresh methanol-*O*-*d* was added, and heating under reflux was continued for a further 26 h followed by concentration under reduced pressure, dilution with anhydrous ether, washing (D_2O), drying ($MgSO_4$) and evaporation to give a light yellow glassy solid. Crystallization from MeOD/D_2O afforded **11-oxo-5α,14β-cholest-8-en-3β-ol-7,7,12,12,14-d_5** (3% d_2, 8% d_4, 86% d_5, 3% d_6, 37.0 mg, 91%) as a white powder which exhibited physical and spectroscopic properties identical with those of authentic unlabeled material.[7] The NMR spectrum, however, showed no signals for the 12α and 12β hydrogens which were both resolved doublets at 2.14 and 2.48 ppm, respectively, in the unlabeled compound. The lithium–ammonia reduction of this labeled compound as described previously provided, after purification, **2a** which had physical and spectroscopic properties consistent with unlabeled **2:** NMR δ 3.97 (br d, 1 H, 11α-H, J = 5 Hz), 3.60 (3α-H, $W_{1/2} \approx 22$ Hz), 0.95 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3); mass spectrum, *m/z* (rel. intensity) 391 (36), 376 (30), 358 (7), 307 (4), 306 (4), 278 (38), 260 (7), 223 (21), 208 (26), 194 (100).

5α,8α,14β-Cholestane-3β,11β-diol Di-*p*-bromobenzoate (2b). The diol **2** was allowed to sit at room temperature for 46 h in a mixture of *p*-bromobenzoyl chloride and pyridine followed by conventional workup to give material which was purified by column chromatography and crystallization from acetone/methanol to afford fine needles: mp 146–148 °C; NMR δ 5.42 (11α-H, $W_{1/2} \approx 22$ Hz), 4.88 (3α-H, $W_{1/2} \approx 24$ Hz), 1.06 (s, 3 H, 18-CH_3 or 19-CH_3), 1.01 (s, 3 H, 19-CH_3 or 18-CH_3), 0.85 (d, 6 H, 26,27-CH_3).

Anal. Calcd for $C_{41}H_{54}O_4Br_2$: C, 63.90; H, 7.06; Br, 20.74. Found: C, 63.74; H, 6.95; Br, 20.52.

5α,8α,14β-Cholestane-3β,11β-diol Diacetate (2c). The diol **2** (33.3 mg) was added to a mixture of 0.75 mL of pyridine and 0.75 mL of acetic anhydride; after 10 min at 0 °C, the mixture was warmed to room temperature (10 min) followed by conventional workup to give a clear syrup. This material was purified by preparative TLC (60% ether/hexane) to give 2.3 mg of the diacetate **2c** as a clear glass which was homogeneous by GLC and TLC (R_f 0.7, 55% ether/hexane): NMR δ 5.16 (dt, 1 H, 11α-H, J = 11, 5.5, 5.5 Hz), 4.68 (3α-H, $W_{1/2} \approx 24$ Hz), 2.01 (3 H, OAc), 1.99 (3 H, OAc), 0.97 (s, 3 H, 18-CH_3 or 19-CH_3), 0.93 (s, 3 H, 19-CH_3 or 18-CH_3), 0.86 (d, 6 H, 26,27-CH_3).

The chromatography also provided 5.5 mg of **5α,8α,14β-cholestane-3β,11β-diol 3β-acetate (2d)** as a clear glass which was homogeneous by GLC and TLC (R_f 0.4, 55% ether/hexane): NMR δ 4.64 (3α-H, $W_{1/2} \approx 24$ Hz), 3.90 (11α-H, $W_{1/2} \approx 22$ Hz), 2.01 (s, 3 H, OAc), 0.95 (s, 3 H, 18-CH_3 or 19-CH_3), 0.89 (s, 3 H, 19-CH_3 or 18-CH_3), 0.86 (d, 6 H, 26,27-CH_3).

In addition, the chromatography provided 5.8 mg of an unidentified material which was probably **5α,8α,14β-cholestane-3β,11β-diol 11β-acetate** (R_f 0.2, 55% ether/hexane) as well as 11.5 mg of the starting diol **2** (R_f 0.1, 55% ether hexane).

5α,14β-Cholestane-3,11-dione (4), Jones reagent (1.0 mL) was added dropwise to an ice-cooled solution of 161 mg of **3** in 30 mL of acetone. After 2 min at 0 °C, the solution was allowed to warm to room temperature and then was diluted with water. The usual workup gave 160 mg of white crystalline compound, mp 99–102 °C. Recrystallization from aqueous methanol afforded flat plates: mp 106–107 °C; NMR δ 1.08 (s, 3 H, 19-CH_3; calcd 1.21), 1.03 (s, 3 H, 18-CH_3; calcd 0.95), 0.91 (d, 3 H, 21-CH_3), 0.86 (d, 6 H, 26,27-CH_3); CD $[\theta]_{309}$ −8607; GLC (265 °C) rrt 0.74 (rrt of **6,** 1); mass spectrum, *m/z* (rel. intensity) 400.3355 (M^+, 70; calcd for $C_{27}H_{44}O_2$, 400.3341), 385 (12), 382 (16), 342 (5), 289 (100), 263 (9), 246 (32), 229 (8), 219 (10), 193 (76).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.64; H, 10.91.

5α,14β-Cholestane (5). The dione **4** (147 mg, 0.37 mmol) was dissolved in 10 mL of diethylene glycol and 3 mL of *n*-butyl alcohol to which was added 1.3 mL of 97% anhydrous hydrazine, and the mixture was heated under reflux for 1 h. Upon cooling the mixture to about 100 °C, 810 mg of KOH dissolved in 1 mL of water was added and heating was continued without a reflux condenser until the temperature reached 205 °C. After being heated under reflux between 200 and 215 °C for an additional 210 min, the reaction mixture was cooled and poured into water. The aqueous phase was extracted five times with ether, and the ether extracts were washed with water, dried ($MgSO_4$), and evaporated to give a clear oil. Purification by thin-layer chromatography on silica gel [benzene/hexane (1:1)] afforded 100 mg of a clear liquid (lit.[5a] liquid): $[\alpha]^{20}_D$ +91° (*c* 0.11); NMR ($CDCl_3$) δ 0.98 (s, 3 H, 18-CH_3; calcd 0.94; lit.[5a] 0.981), 0.87 (d, 6 H, 26,27-CH_3; lit.[5a] 0.865), 0.83 (d, 3 H, 21-CH_3; lit.[5a] 0.835), 0.75 (s, 3 H, 19-CH_3; calcd 0.75; lit.[5a] 0.753); NMR (benzene-d_6) δ 1.07 (s, 3 H, 18-CH_3; lit.[5a] 1.07), 0.95 (d, 3 H, 21-CH_3; lit.[5a] 0.948), 0.92 (d, 6 H, 26,27-CH_3; lit.[5a] 0.92), 0.77 (s, 3 H, 19-CH_3; lit.[5a] 0.771); GLC (209 °C) rrt 0.84 (rrt of 14α-cholestane, 1); mass spectrum, *m/z* (rel. intensity) 372.3758 (M^+, 36; calcd for $C_{27}H_{48}$, 372.3756), 357 (20), 262 (5), 259 (11), 232 (7), 219 (42), 218 (100), 217 (58), 203 (17), 175 (10), 163 (16), 151 (6), 149 (36).

Alternatively, **5** could also be synthesized by the addition of boron trifluoride etherate (0.2 mL) to a solution of the dione **4** (160 mg, 0.4 mmol) in 1.5 mL of ethanedithiol. After being stirred at room temperature for 7 min, the mixture was diluted with methanol and the solid material was collected by filtration. Recrystallization from hexane/methanol furnished the thioketal **12** as long fine needles (167.4

mg): mp 142–142.5 °C; IR 5.86 μm.

The thioketal **12** (167.4 mg, 0.351 mmol), which was dissolved in 95% ethanol (100 mL), was stirred at room temperature with fresh W-7 Raney nickel (prepared from 25 g of alloy) for 2 h followed by heating under reflux for 1 h. The catalyst was removed by filtration and washed well with ethanol. To the ethanol solution was added 100 mL of benzene, and the solvents were evaporated to give the desired ketone **5α,14β-cholestan-11-one (13;** 132.5 mg, 98%) as a clear glass which was homogeneous by TLC and GLC: NMR δ 2.30 (d, 1 H, J = 13 Hz), 2.13 (d, 1 H, J = 13 Hz), 1.00 (s, 3 H, 19-CH_3; calcd 0.97), 0.90 (s, 3 H, 18-CH_3; calcd 0.91); CD $[\theta]_{308}$ −20 265; mass spectrum, m/z (rel. intensity) 386.3541 (M^+, 100; calcd for $C_{27}H_{46}O$, 386.3549), 371 (15), 289 (76), 276 (32), 261 (11), 232 (26), 219 (12), 218 (9), 217 (8), 206 (8), 193 (38), 177 (8), 149 (19), 135 (19), 122 (36), 109 (37), 95 (43), 81 (54). The ketone **13** could also be synthesized from the dione **4** by the Wolff–Kishner procedure described above using 85% hydrazine hydrate and heating under reflux between 200 and 215 °C for 150 min.

To the 11-ketone **13** (132.5 mg) in 50 mL of ether was added excess lithium aluminum hydride, and the mixture was heated under reflux for 2 h followed by the dropwise addition of saturated Na_2SO_4 until all solid material was white and at the bottom of the flask. Filtration, washing of the solid material, and evaporation of the combined ether solution furnished 130.8 mg of a clear glass. The crude product was chromatographed on 9 g of TLC mesh silica gel with 2% ether/hexane to give **5α,14β-cholestan-11β-ol (14,** 110.5 mg) as a clear glass which was homogeneous by TLC and GLC: NMR δ 4.22 (11α-H, $W_{1/2} \approx 8$ Hz), 1.22 (s, 3 H, 18-CH_3; calcd 1.18), 1.00 (s, 3 H, 19-CH_3; calcd 1.01), 0.86 (d, 6 H, 26,27-CH_3), 0.84 (d, 3 H, 21-CH_3); mass spectrum, m/z (rel. intensity) 388 (M^+, 23), 370 (76), 355 (48), 286 (9), 257 (34), 230 (24), 217 (93), 216 (100), 215 (33), 201 (27), 193 (14), 192 (18), 161 (27), 149 (34), 147 (28), 135 (37), 121 (50), 109 (79), 95 (71), 81 (86).

A solution of the sterol **14** (19.0 mg) in pyridine (2 mL) at 0 °C was slowly treated with phosphoryl chloride (15 drops) and kept at 0 °C for 105 min. The mixture was then poured onto ice and extracted with ether, and the ether extracts were washed, dried, and evaporated to give the olefin **5α,14β-cholest-9(11)-ene (15;** 17.5 mg, 97%) as a clear oil which was homogeneous by TLC and GLC: NMR δ 5.14–5.28 (m, 1 H, 11-H), 2.38 (1 H, $W_{1/2} \approx 20$ Hz), 0.92 (s, 3 H, 19-CH_3; calcd 0.892), 0.89 (s, 3 H, 18-CH_3; calcd 0.875); mass spectrum, m/z (rel. intensity) 370.3582 (M^+, 43; calcd for $C_{27}H_{46}$, 370.3599), 355 (72), 286 (99), 271 (14), 257 (57), 220 (12), 217 (13), 216 (16), 215 (17), 206 (21), 193 (26), 176 (38), 161 (39), 149 (27), 147 (40), 135 (26), 121 (33), 109 (43), 107 (46), 105 (45), 95 (60), 81 (100).

Chromium trioxide (72.4 mg, 0.724 mmol) was suspended in dry (distilled from P_2O_5) methylene chloride (10 mL) at −23 °C and 3,5-dimethylpyrazole (69.6 mg, 0.724 mmol) was added in one portion. After the mixture was stirred at −23 °C for 15 min, the steroid **15** (13.4 mg, 0.0362 mmol) dissolved in 2 mL of CH_2Cl_2 was added and the mixture was allowed to stir at −23 °C for 4 h. The mixture was then diluted with ether and passed through a column of Florisil (60–100 mesh) followed by evaporation of the ether to give an oil. Preparative TLC (8% ether/hexane) and isolation of only UV-active bands gave 1.3 mg of a clear glass (R_f 0.60, 10% ether/hexane) which is probably **14β-cholest-8-en-11-one:** NMR δ 2.48 (d, 1 H, J = 13 Hz), 2.12 (d, 1 H, J = 13 Hz), 1.12 (s, 3 H, 19-CH_3), 1.00 (s, 3 H, 18-CH_3), 0.88 (d, 3 H, 21-CH_3) 0.86 (d, 6 H, 26,27-CH_3); mass spectrum, m/z (rel. intensity) 384 (M^+, 100), 369 (37), 356 (13), 355 (15), 271 (4), 243 (5), 232 (16), 219 (7), 218 (5), 217 (6), 193 (6), 190 (6), 177 (12), 161 (10). The NMR and mass spectra of this compound are consistent with those reported for compound **1** when the lack of oxygen at C-3 is taken into account.

The chromatography also provided 7 mg of a clear glass (R_f 0.45, 10% ether/hexane) which was slightly contaminated by a lower R_f material (R_f 0.42, 10% ether/hexane). Purification of this material by reverse-phase LC (100% methanol, 560 psi) gave the desired unsaturated ketone **5α,14β-cholest-9(11)-en-12-one (16;** 6.2 mg, 45%) as a clear glass which was homogeneous by TLC, GLC, and LC (retention time (rt) = 45 min; rt of unidentified impurity (0.4 mg) = 30 min): NMR δ 5.75 (d, 11-H, J = 2.5 Hz), 2.74 (1 H, $W_{1/2} \approx 20$ Hz), 1.06 (s, 3 H, 18-CH_3 or 19-CH_3), 1.05 (s, 3 H, 19-CH_3 or 18-CH_3), 0.94 (d, 3 H, 21-CH_3), 0.87 (d, 6 H, 26,27-CH_3). The mass spectrum showed m/z 384 as the molecular ion. In addition, the mass spectrum showed *no* m/z 218 (which is characteristic of cholest-8(14)-en-7-one),[23a] *no* m/z 216 (which is characteristic of cholest-8-en-7-one),[23a] and also *no* peaks characteristic of cholest-8(14)-en-15-one.[23b] The principal fragment ions of **16** are m/z 369 (M − CH_3), 271 (M − side chain), and 121.

The $\Delta^{9(11)}$-12-one **16** (1.6 mg) in 25 mL of ethyl acetate and 10 mg of 10% palladium on carbon was stirred under hydrogen gas at room temperature for 19 h followed by conventional workup to give a clear glass which was purified by reverse-phase LC (100% methanol, 700 psi) to give **5α,14β-cholestan-12-one (17)** as a clear glass (LC rt = 41 min). The stereochemistry of **17** was confirmed by Wolff–Kishner reduction of this ketone to give **5α,14β-cholestane (5,** 0.6 mg) as the exclusive hydrocarbon product whose GLC retention time, mass spectrum, and NMR were identical with those of authentic **5.** The catalytic hydrogenation of **16** is apparently controlled by the angular methyl groups on the β face of the skeleton (as in the 14α series)[24] even though models indicate that the 14β configuration causes shielding of the α face by ring D.

5α,8α,14β-Cholestane-3,11-dione (6). Jones oxidation of **2** as previously described gave a quantitative yield of a clear glass which was crystallized from aqueous methanol to give a white crystalline compound: mp 80–83 °C; NMR δ 1.14 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3), 0.86 (d, 6 H, 26,27-CH_3); CD $[\theta]_{300}$ +8405; mass spectrum, m/z (rel. intensity) 400.3338 (M^+, 100; calcd for $C_{27}H_{44}O_2$, 400.3341), 385 (8), 382 (5), 342 (21), 289 (53), 263 (39), 246 (30), 229 (45), 219 (35), 193 (90).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.98; H, 10.88.

5α,8α,14β-Cholestane (8) and 5α,8α,9β,14β-Cholestane (11). The dione **6** was subjected to Wolff–Kishner reduction as described for 5α,14β-cholestane (**5**) to give an oil which was a mixture (88:12) of two compounds. Preparative GLC afforded the predominant component **5α,8α,14β-cholestane (8)** as a clear liquid (lit.[5a] liquid): $[\alpha]^{20}_D$ + 84° (c 0.038); NMR ($CDCl_3$) δ 0.90 (d, 3 H, 21-CH_3; lit.[5a] 0.90), 0.89 (s, 3 H, 18-CH_3 or 19-CH_3; lit.[5a] 0.888), 0.86 (d, 6 H, 26,27-CH_3; lit.[5a] 0.861), 0.85 (s, 3 H, 19-CH_3 or 18-CH_3; lit.[5a] 0.848); NMR (benzene-d_6) δ 1.02 (d, 3 H, 21-CH_3; lit.[5a] 1.014), 0.92 (s, 3 H, 18-CH_3 or 19-CH_3; lit.[5a] 0.908), 0.92 (d, 6 H, 26.27-CH_3; lit.[5a] 0.917), 0.89 (s, 3 H, 19-CH_3 or 18-CH_3; lit.[5a] 0.885); GLC (209 °C) rrt 1.00 (rrt of 14α-cholestane, 1.00); mass spectrum, m/z (rel. intensity) 372.3759 (M^+, 37; calcd for $C_{27}H_{48}$, 372.3756), 357 (32), 262 (10), 259 (4), 232 (18), 219 (18), 218 (76), 217 (100), 203 (23), 175 (11), 163 (9), 151 (12), 149 (67).

The second compound, **5α,8α,9β,14β-cholestane (11),** which probably resulted from epimerization at C-9 prior to reduction, was isolated by preparative GLC and represented 12% of the mixture: clear liquid; NMR ($CDCl_3$) δ 0.92 (d, 3 H, 21-CH_3), 0.876 (s, 3 H, 18-CH_3 or 19-CH_3), 0.87 (d, 6 H, 26,27-CH_3), 0.80 (s, 3 H, 19-CH_3 or 18-CH_3); NMR (benzene-d_6) δ 1.05 (d, 3 H, 21-CH_3), 0.91 (d, 6 H, 26,27-CH_3), 0.91 (s, 3 H, 18-CH_3 or 19-CH_3), 0.89 (s, 3 H, 19-CH_3 or 18-CH_3); GLC (209 °C) rrt 0.71 (rrt of 14α-cholestane, 1); mass spectrum, m/z (rel. intensity) 372 (M^+, 53), 357 (38), 262 (11), 259 (13), 232 (20), 219 (15), 218 (53), 217 (99), 203 (21), 175 (14), 163 (15), 151 (17), 149 (100).

The dione **6** could also be equilibrated in base followed by Wolff–Kishner reduction to afford 5α,8α,14β-cholestane (**8**) and 5α,8α,9β,14β-cholestane (**11**).

5α,8α,9β,14β-Cholestane-3,11-dione (9). The dione **6** was heated under reflux in 10% sodium methoxide for 122 h followed by a conventional workup to give a clear glass which was a mixture consisting of 73% of the 8α,9α-dione **6** and 27% of the 9β-epimer **9.** This material was purified by preparative TLC (40% ether/hexane) to give the original dione **6** with identical physical and spectroscopic properties with those of the starting dione **6** as well as a new dione **9** as a clear glass: NMR δ 1.28 (s, 3 H, CH_3), 0.87 (d, 6 H, 26.27-CH_3), 0.79 (s, 3 H, CH_3); CD $[\theta]_{303}$ +22 133; GLC (260 °C) rrt 0.71 (rrt of **6,** 1); mass spectrum, m/z 400 (M^+).

This dione **9** could be equilibrated in 10% sodium methoxide to give an equilibrium mixture consisting of 70% **6** and 30% **9** after 53 h.

11-Oxo-5α,8α,14β-cholestan-3β-ol (7). 11-Oxo-5α,14β-cholest-8-en-3β-ol (**1,** 100 mg) was hydrogenated over 10% palladium on carbon in ethanol at room temperature and 1 atm pressure for 48 h to give, after preparative TLC (70% ether/hexane), 76 mg of white crystalline material: mp 103–104.5 °C; $[\alpha]^{19}_D$ + 74° (c 0.25); NMR δ 3.56 (3α-H, $W_{1/2} \approx 22$ Hz), 2.59 (d, J = 13.5 Hz), 2.37 (d, J = 13.5 Hz), 0.97 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 0.86 (d, 6 H, 26,27-CH_3); CD $[\theta]_{307}$ +4882; mass spectrum, m/z (rel. intensity) 402.3495 (M^+, 56; calcd for $C_{27}H_{46}O_2$, 402.3498), 384 (12), 369 (10), 366 (13), 351 (8), 344 (13), 324 (8), 289 (100), 276 (26), 263 (48), 261 (17), 253 (34), 248 (44), 247 (13), 233 (14), 232 (10), 229 (14), 219 (56), 213 (10), 206 (17), 193 (70), 147 (24), 135 (29), 122 (46), 121 (41), 108 (100), 95 (57), 81 (72).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.69; H, 11.74.

11-Oxo-5α,8α,9β,14β-cholestan-3β-ol (10). 11-Oxo-5α,8α,14β-cholestan-3β-ol (**7**) was heated under reflux in 10% sodium methoxide for 67 h followed by conventional workup to give a clear glass which was a mixture consisting of 74% of the 8α,9α-ketone **7** and

26% of the 9β-epimer **10**. This material was purified by preparative TLC (70% ether/hexane) to give the original ketone **7** with identical physical and spectroscopic properties with those of the starting ketone **7**. In addition, chromatography furnished a new ketone **10** as a white semicrystalline material: NMR δ 3.60 (3α-H, $W_{1/2} \approx 24$ Hz), 2.44 (d, J = 13.5 Hz), 2.30 (d, J = 13.5 Hz), 1.14 (s, 3 H, CH_3), 0.86 (d, 6 H, 26,27-CH_3) 0.77 (s, 3 H, CH_3); CD $[\theta]_{307}$ +14 740; GLC (262 °C) rrt 0.77 (rrt of **7**, 1); mass spectrum, m/z (rel. intensity) 402 (M^+, 75), 384 (11), 369 (8), 366 (9), 351 (6), 344 (15), 324 (4), 289 (94), 276 (22), 263 (50), 261 (12), 253 (28), 248 (12), 247 (10), 233 (10), 232 (11), 229 (6), 219 (55), 213 (10), 206 (18), 193 (83), 147 (24), 135 (24), 122 (31), 121 (35), 108 (100), 95 (60), 81 (80).

5α-Cholestane-3,11-dione (19). A crude sample of **11-oxo-5α-cholestan-3α-ol (18)**[16] was purified by preparative TLC (65% ether/hexane) to give material which was crystallized from aqueous methanol to give white plates: mp 137.5–138 °C; NMR δ 4.04 (3β-H, $W_{1/2} \approx 8$ Hz), 2.53 (d, 1 H, 12β-H, J = 13 Hz), 2.22 (br d due to W coupling with 18-CH_3, 1 H, 12α-H, J = 13 Hz), 1.00 (s, 3 H, 19-CH_3; calcd 0.992), 0.62 (s, 3 H, 18-CH_3; calcd 0.617); CD $[\theta]_{300}$ +950; mass spectrum, m/z (rel. intensity) 402 (M^+, 100), 387 (9), 384 (13), 369 (8), 289 (22), 276 (17), 263 (11), 261 (11), 253 (6), 248 (9), 247 (7), 229 (12), 193 (34), 147 (34), 124 (33), 107 (40), 95 (40), 81 (43).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.57; H, 11.51.

This 3α-ol **18** was oxidized under Jones conditions to material which was crystallized from aqueous methanol to give the dione **19** as white plates: mp 135.5–137 °C; NMR δ 1.21 (s, 3 H, 19-CH_3; calcd 1.234), 0.65 (s, 3 H, 18-CH_3; calcd 0.651); CD $[\theta]_{290}$ +1080; mass spectrum, m/z (rel. intensity) 400.3333 (M^+, 100; calcd for $C_{27}H_{44}O_2$, 400.3341), 385 (12), 382 (7), 372 (7), 289 (10), 288 (7), 287 (4), 276 (10), 263 (6), 259 (14), 245 (19), 191 (12), 163 (10), 149 (10), 137 (16), 135 (13), 124 (36), 95 (25), 81 (28).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.84; H, 11.19.

Registry No.—**1**, 62279-64-5; **2**, 69454-64-4; **2a**, 69454-65-5; **2b**, 69454-66-6; **2c**, 69454-67-7; **2d**, 69454-68-8; **3**, 69483-49-4; **4**, 69454-69-9; **5**, 40071-70-3; **6**, 69483-50-7; **7**, 69454-70-2; **8**, 55123-81-4; **9**, 69483-51-8; **10**, 69483-52-9; **11**, 69483-40-5; **12**, 69454-71-3; **13**, 69483-53-0; **14**, 69454-72-4; **15**, 69454-73-5; **16**, 69454-74-6; **17**, 69483-54-1; **18**, 69483-55-2; **19**, 69483-56-3; **20**, 481-21-0; **21**, 41083-75-4; **22**, 55123-82-5; **23**, 55176-78-8; **24**, 481-20-9; **25**, 69483-41-6; **26**, 69483-42-7; **27**, 69483-43-8; **28**, 69483-44-9; **29**, 69483-45-0; **30**, 69483-46-1; **31**, 69483-47-2; **32**, 69483-48-3; 5α,14β-cholest-8-ene-3,11-dione, 69454-75-7; 5α,14β-cholest-8-ene-3β,11β-diol, 69454-76-8; 5α,14β-cholest-8-ene-3β,11α-diol, 69454-77-9; 11-oxo-5α,14β-cholest-8-en-3β-ol-*7,7,12,12,14-d*$_5$, 69454-78-0; 5α,8α,14β-cholestane-3β,11β-diol β-acetate, 69454-79-1; 5α,14β-cholest-8-en-11-one, 69454-80-4.

Supplementary Material Available: Properties of cholestane isomers (Table II) and mass spectra of **5**, **8**, **11**, and **20** (Figure 2) (2 pages). Ordering information is given on any current masthead page.

References and Notes

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(11) In the diols **2** and **3** the 5α,8β,9β,14β and 5α,8β,9α,14β as well as the 5α,8α,9α,14β stereochemistries can exist in an all-chair conformation (this is in contrast to the 14α series where only the 8β,9α epimer can exist in an all-chair conformation). The conformational analysis is therefore more complex in the 14β series,[8b] and the stereochemical arguments in our paper are made with the assumption that compounds **2** and **3** exist in an all-chair conformation. In compound **2** the 5α,8α,9β,14β stereochemistry requires that ring B be in a "boat" conformation while rings A and C can be in "chair" conformations (this is in contrast to the 14α series where the 8α,9β stereochemistry requires that rings B and C be in "boat" conformations). If major deviations occur in any of the six-membered rings from the ideal "chair" conformation, incorrect stereochemistries may then be assigned to C-9 and C-11 in Scheme I. These deviations would not, however, alter the assignments of the 8β configuration in compound **3** and the 8α configuration in compound **2** which are crucial to establishing the stereochemistry of the lithium–ammonia reduction at the β-carbon atom. In addition, it should be mentioned that the 8α assignment in **2** is based on the identity of the spectroscopic properties of its transformation product **8** with those previously reported[5a,c] for this compound. The British authors,[5a,c] however, have never published the synthesis of this compound nor the method of arriving at the stereochemical assignment. It is therefore clear that the stereochemistry at C-9 in compounds **8** and **11** has not been rigorously established.
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