Studies of the synthesis of 5-hydroxy 6-keto steroids and related 6-keto steroids

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Syntheses of 5-hydroxy-5α- and 5β-cholestan-6-one (**11** and **13**) and their 3β-acetoxy (**10** and **21**) and 3β-benzyloxy derivatives (**12** and **19**) are described, as are syntheses of the 7α-deutero derivatives of **10** and **21**. Related investigations of the syntheses of the 5-methoxy and 5-methyl analogues of these compounds are also discussed. Treatment of **12** with potassium *tert*-butoxide has been shown to give 5-hydroxy-5β-cholest-3-en-6-one (**14**) and its Δ^2 isomer **15**. Reaction of 6-nitrocholesteryl acetate (**50**) with lithium dimethylcuprate gives 3α,5-cyclo-5α-cholestan-6-one (*E*)-oxime (**51**) as the major product.

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On décrit la synthèse des hydroxy-5 5α- et 5β-cholestanones-6 (**11** et **13**) et de leurs dérivés acétoxy-3β (**10** et **21**) et benzyloxy-3β (**12** et **19**) ainsi que celle des dérivés deutéro-7α des composés **10** et **21**. On discute aussi des études apparentées orientées vers la synthèse des analogues méthoxy-5 et méthyl-5 de ces composés. On a démontré que la réaction du composé **12** avec le *tert*-butylate de potassium conduit à l'hydroxy-5 5β-cholestène-3 one-6 (**14**) et à son isomère Δ^2 (**15**). Le produit principal de la réaction de l'acétate de nitro-6 cholestéryle (**50**) avec le diméthylcuprate de lithium est l'oxime-(*E*) de la cyclo-3α,5 5α-cholestanone (**51**).

[Traduit par la revue]

In the course of our work on the photochemistry of cyclic α-hydroxy ketones (1), we have had occasion to investigate the synthesis of a number of 5-hydroxy 6-keto steroids and their 7-deutero derivatives together with related 6-keto steroids with other C-5 substituents. Since these studies were extensive and gave results of intrinsic interest, we discuss them separately here and plan to give a detailed account of the photochemical results separately.

Synthesis of steroidal ketols

5α-Hydroxy 6-keto steroids **10–12** were synthesized by the general sequence shown in Scheme 1. Treatment of cholest-5-enes **1–3** with *m*-chloroperoxybenzoic acid gave in each case a mixture of α- and β-epoxides **4–6** that was not separated, since the mixtures gave solely the 5α,6β-diols **7–9** upon treatment with aqueous acid. *p*-Toluenesulfonic acid in aqueous dioxane proved particularly useful for this transformation. Preferential *trans* diaxial ring opening accounts for the observed stereoselectivity (2). Oxidation of the 5α,6β-diols to the 5α-ketols **10–12** was achieved with several reagents; pyridinium chlorochromate is favored as the most reliable and easiest to use. *N*-Bromosuccinimide, the work-horse reagent in these systems (3), gave in our hands variable results.

Spectral data for the compounds in Scheme 1 are in accord with expectation. In the ^{1}H nmr spectra of the ketols **10–12** a triplet (J = 13 Hz) at δ 2.7–2.8 is assigned to the 7α proton. Deshielding of protons situated in a 1,3-diaxial relationship to electronegative substituents such as hydroxyl has been documented (9).

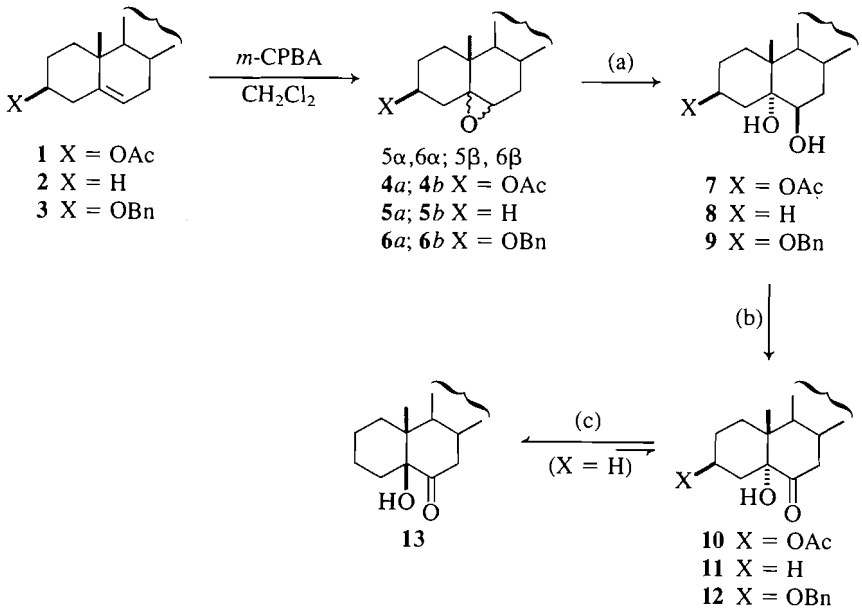
5α-Hydroxy 6-keto steroids have long been recognized to equilibrate under basic conditions with their 5β counterparts (10). Preponderance of the 5β epimer in these equilibria has been attributed to intramolecular hydrogen bonding between the hydroxyl and carbonyl groups in the 5β-ketols where it is geometrically favored. Epimerization of 5-hydroxy-5α-cholestan-6-one (**11**) with methanolic 10% potassium hydroxide (10) gave a ~9:1 mixture of the 5β-ketol **13** and **11**, which were separated chromatographically. The 5β-ketol **13** was also obtained from hydrogenation of the Δ^3-5β-ketol **14** (*vide infra*).

Treatment of the 3β-benzyloxy-5α-ketol **12** with methanolic potassium hydroxide as above did not effect epimerization; largely unconsumed starting material was recovered even after 56 h. Attempted epimerization of **12** with potassium *tert*-butoxide in *tert*-butyl alcohol resulted instead in a facile synthesis of 5-hydroxy-5β-cholest-3-en-6-one (**14**) (Scheme 2). In the ^{1}H nmr spectrum of **14** the hydroxyl proton signal appears as a sharp singlet at δ 4.20, indicative of intramolecular hydrogen bonding (11) and strongly suggesting the 5β configuration. This was confirmed by hydrogenation of **14** to the 5β-ketol **13**. The ^{1}H nmr spectrum of **14** displays two one-proton multiplets at δ 5.42 (width = 13 Hz) and 6.00 (width = 17 Hz), consistent with the Δ^3 position assigned to the olefinic bond. Based on observed correlations between the vicinal coupling constant in H—C—C—H systems and the allylic coupling constant in H—C=C—C—H systems with dihedral angles (12, 13), the multiplet at δ 6.00 is assigned to the C-3 vinyl proton and that at δ 5.42 to the C-4 vinyl proton.

Treatment of **12** with potassium *tert*-butoxide in *tert*-butyl alcohol also gave rise to a minor product, considered to be 5-hydroxy-5-cholest-2-en-6-one (**15**) (Scheme 2). The Δ^2- and Δ^3-5β-ketols **14** and **15** were separated by flash chromatography on a silver nitrate impregnated silica gel column. A sharp singlet at δ 4.05 in the ^{1}H nmr spectrum of **15** again signaled the 5β configuration. A narrow two-proton multiplet ($W_{1/2}$ = 4 Hz) at δ 5.67 arising from the vinyl protons (14) and a peak in its mass spectrum at m/z 346 (80) (M − C_4H_6), considered to originate from a retro Diels–Alder fragmentation, distinguished the Δ^2-5β-ketol **15** from the Δ^3-5β-ketol **14**.

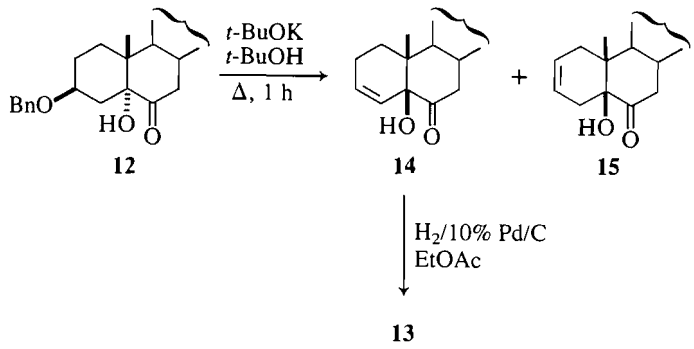
The Δ^3-ketol **14** is postulated to arise by elimination of benzyloxy anion from the enolate of the *A*-homo *B*-nor ketol **16** to give **17** (Scheme 3). Mazur and Nussim (10) have provided evidence to support their postulate that such an *A*-homo *B*-nor ketol is an intermediate in the epimerization of 5-hydroxy-5α-cholestan-6-one (**11**) to its 5β epimer **13**. The presence, under the basic reaction conditions, of a small amount of the Δ^2-ketol **18** in equilibrium with its Δ^3 isomer **17** accounts for the formation of the Δ^2-ketol **15**.

In continuing pursuit of the conversion of **12** to its 5β epimer we next investigated its reaction with Grignard reagents, which can induce rearrangements of α-hydroxy ketones, albeit with the complication of addition to the carbonyl group (15, 16). We found that the very sterically congested 2-mesitylmagnesium

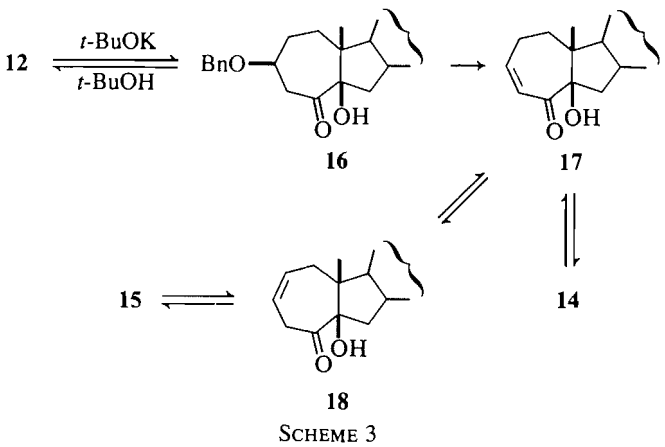


(a) **4**: 70% $HClO_4$/aq. acetone (4); **5**, **6**; *p*-TSA/aq. dioxane, 1.5 h
(b) **7**: PCC/Al_2O_3/CH_2Cl_2 (5) or Ag_2CO_3 on Celite/C_6H_6, 96 h (6);
8: NBS/aq. dioxane (7); **9** PCC/3 Å molecular sieves/Al_2O_3/CH_2Cl_2 (8)
(c) **11**: 10% of KOH/CH_3OH, Δ, 8 h (10)

SCHEME 1



SCHEME 2



SCHEME 3

bromide cleanly epimerized the 3β-benzyloxy-5α-ketol **12** to its 5β epimer **19**, the only other component of the reaction product being unconsumed **12** (~30%) (Scheme 4). Care in the preparation of the Grignard reagent was critical to the success of this reaction. We found that it was important that Grignard reagent formation be initiated as early as possible during addition of 2-bromomesitylene to magnesium. Failure to ensure this often resulted in a delayed, exothermic reaction between the magnesium and halide, which was detrimental to the capability of the reagent to effect epimerization. We thus found it advantageous to ensure smooth formation of the reagent by entrainment of the magnesium with 1,2-dibromoethane.

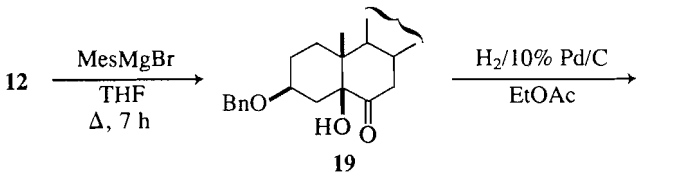
Hydrogenolysis of **19** gave 3β,5-dihydroxy-5β-cholestan-6-one (**20**), which on acetylation afforded 3β-acetoxy-5-hydroxy-5β-cholestan-6-one (**21**) in high yield. Interestingly, the mass spectra of the 3-acetoxy- and 3-deoxy-5β-ketols **21** and **13** each exhibit a base peak at m/z 318, which is an ion of low relative abundance in the spectra of the corresponding 5α epimers **10** and **11**. This fragment, assigned the composition $C_{22}H_{38}O$ on the basis of an accurate mass measurement, can be envisioned to arise as depicted in Scheme 5.[1] The reason for the divergent fragmentation behaviour observed for the 5α- and 5β-ketols is not apparent.

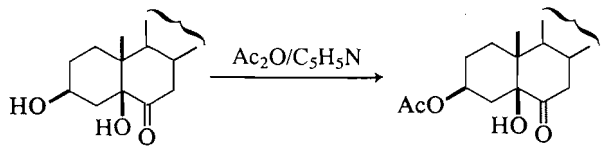
Synthesis of 7α-deutero steroidal ketols

The reaction sequence used for the synthesis of the 7α-deutero-3β-acetoxy 5α- and 5β-ketols **23** and **25** is shown in Scheme 6. Bromination of **10** with bromine in acetic acid and chloroform, according to the method of Rodewald *et al.* (18), gave the 7α-bromo-5α-ketol **22** in high yield. Application of this procedure to **21** proved equally successful, yielding solely the 7α-bromo-5β-ketol **24**. The stereochemistry at C-7 in **22** and **24** was witnessed by the narrow multiplets observed for the C*H*Br proton signals at δ 4.18 and 4.42, respectively, in their ^{1}H nmr spectra (19).

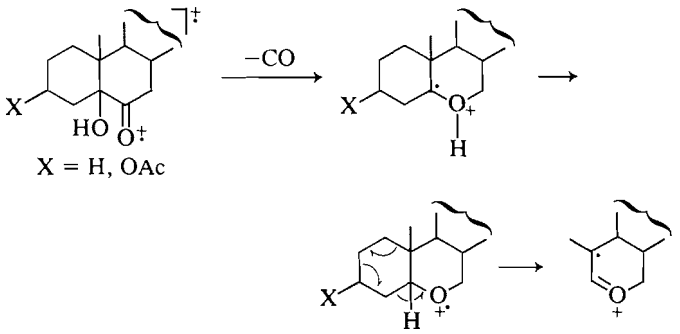
Reduction of **22** and **24** with zinc and *O*-deuteroacetic acid (19, 20) provided an excellent method for the stereoselective

[1]A similar fragmentation pattern has been suggested to account for the intense m/z 318 ions observed in the mass spectra of a number of 3-substituted 6-oxa-*B*-homo-5a-cholestan-7-ones (17).

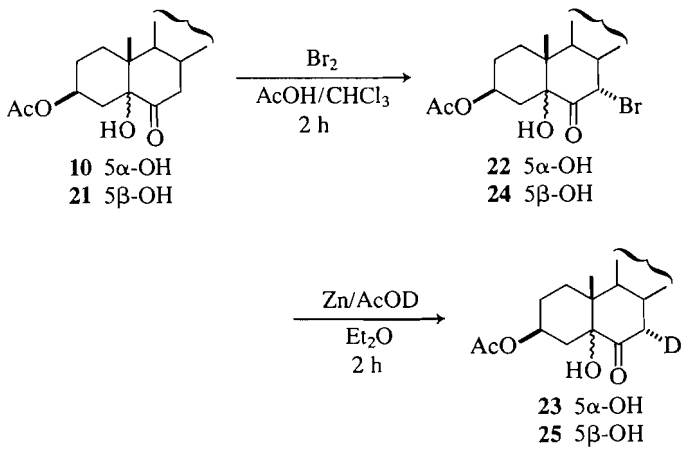




SCHEME 4



SCHEME 5



SCHEME 6

introduction of deuterium into the 7α site. The deuterated ketols **23** and **25** were thus obtained in high chemical yield as well as with good incorporation of deuterium label. The deuterium content, d_0, d_1, and d_2, was calculated from the mass spectra according to the method of Budzikiewicz, Djerassi, and Williams (21). The intensities of the molecular ions were relatively weak, and the low signal-to-noise ratios that resulted led to wide scatter in the values calculated for the deuterium content. Therefore, calculations of the deuterium content were based on the more abundant (M − AcOH) fragments. These calculations, which are considered to be valid since the loss of acetic acid from the molecular ions is not expected to involve the C-7 methylene group, gave d_0 15%, d_1 80%, and d_2 5% for **23**.

The deuterium content of **23** and **25** was also calculated from their ^{1}H nmr spectrum. In the spectrum of the undeuterated 3β-acetoxy-5α-ketol **10**, the axial 5-hydroxyl group deshields the 7α proton, whose signal appears at δ 2.76, downfield of the steroidal envelope. Upon deuteration, this signal almost completely disappeared; the weak intensity residual signal for **23** had an area that was 12% of that observed for the C*H*OAc proton at δ 5.03 and thus established that the deuterium content at the 7α site was 88%. Calculations based on the mass spectrum gave a d_1 value of 80% and a maximum deuterium content of 85%. Both of these values were lower than that obtained from the ^{1}H nmr analysis, showing that all of the deuterium label in **23** resided in the 7α site. In the light of the margins of error accompanying deuterium content calculations from the mass and ^{1}H nmr spectra (22 (also pp. 218–221), 23, 24), differences between the two of 5–10% were routinely observed and are considered acceptable.

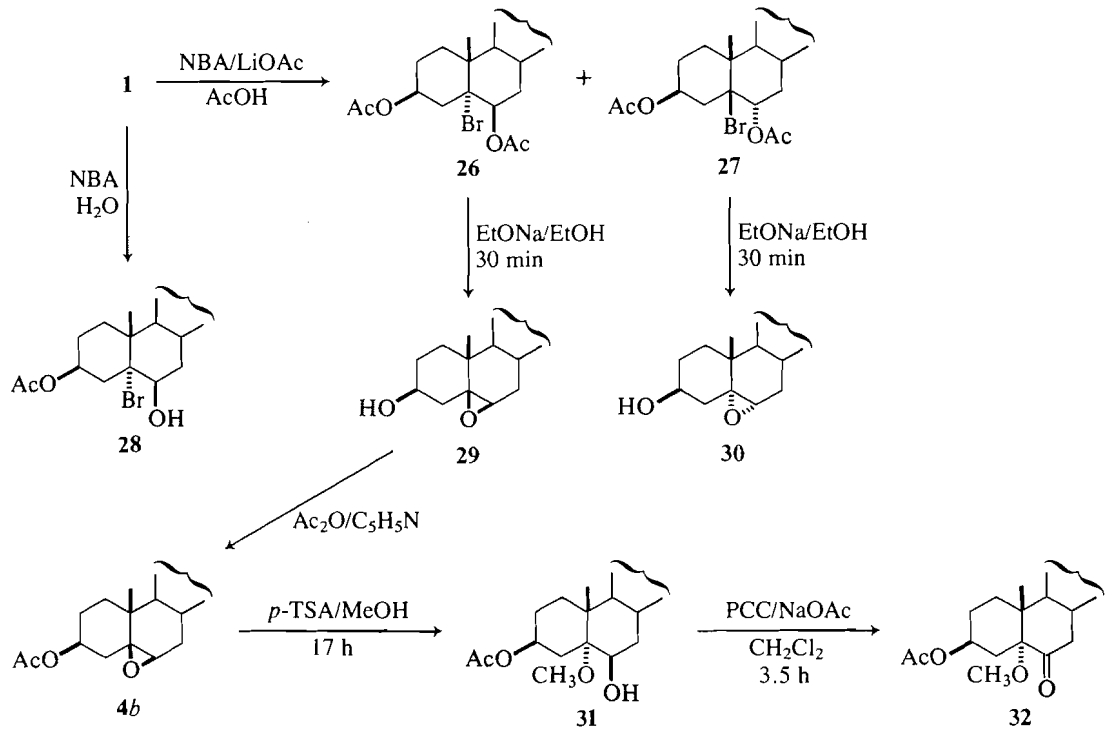
The situation for **25** is somewhat more complex. The ^{1}H nmr spectrum of the undeuterated ketol **21** exhibits a two-proton multiplet at δ 2.17–2.30 and a one-proton doublet of doublets at δ 2.42 (J = 14, 4 Hz). The latter signal is readily assignable to the 7β proton on the basis of the coupling constants. Upon deuteration, the signal at δ 2.42 collapsed to a doublet (J = 3 Hz) showing that the 14-Hz coupling is attributable to a geminal interaction, as expected. In addition, a doublet of doublets at δ 2.24 (J = 15, 4 Hz) was revealed, thereby demonstrating that the multiplet at δ 2.17–2.30 in the spectrum of **21** is composed of two doublets of doublets, one at δ 2.23 (J = 14, 12 Hz) and the other at δ 2.24 (J = 15, 4 Hz). The former is assigned on the basis of the 12-Hz coupling constant, indicative of an axial–axial interaction, to the 7α proton, while the latter is tentatively ascribed to either the 4α or the 4β proton. In the spectrum of **25** the areas of the δ 2.24 doublet of doublets and of the doublet at δ 2.42 assigned to the 7β proton were observed to be equal. This established that the 7β site was completely protonated and that all the deuterium label again was present in the 7α configuration. From the mass spectrum of **25**, the deuterium content was calculated to be 80–85%.

Studies of the synthesis of 5-methoxy 6-keto steroids

Despite the seeming simplicity of the approach, *O*-methylation of the 3β-acetoxy-5α- and 5β-ketols **10** and **21** under a variety of conditions did not provide a useful synthesis of the corresponding 5-methoxy 6-keto steroids. In the 5α series, a route from the 5β,6β-epoxide **4*b*** to the methoxy ketone **32** was therefore devised (Scheme 7). Since the 5α,6α-epoxide **4*a*** is known to afford the 5-hydroxy 6-methoxy regiochemistry upon acid-catalyzed addition of methanol (25), the mixture of α- and β-epoxides **4*a*** and **4*b*** described previously could not be used in the synthesis of **32**. The required stereoselective synthesis of the β-epoxide **4*b*** was achieved via the 5α-bromo-6β-acetate **26**. This was formed as the major product, together with its stereoisomer **27**, from the reaction of cholesteryl acetate (**1**) with *N*-bromoacetamide and lithium acetate in acetic acid (cf. ref. 26). The structural assignments for **26** and **27** were based on comparison of their ^{1}H nmr spectra with the spectrum of 5-bromo-5α-cholestane-3β,6β-diol 3-acetate **28**, prepared by bromination of cholesteryl acetate (**1**) in aqueous medium (27).

The 5β-bromo-6α-acetate **27** can be conjectured to arise via attack of bromine on the β face of olefin **1** followed by attack of acetate ion at C-6 in the intermediate bromonium ion, thus avoiding an unfavorable 1,3-diaxial bromine–methyl interaction that would have resulted from addition in the opposite regiochemical sense.

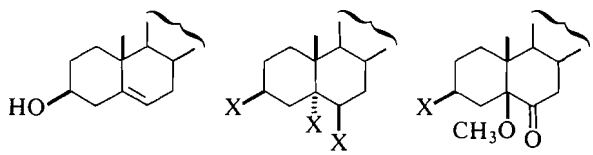
Treatment of the 5α-bromo 6β-acetoxy isomer **26** with ethanolic sodium ethoxide at room temperature gave the



SCHEME 7

3-hydroxy-5β,6β-epoxide **29**. Similar reaction with a mixture of **26** and **27** gave both **29** and the α-epoxide **30**, demonstrating the necessity for separation of **26** and **27** for a stereoselective synthesis of the β-epoxide. The structures of the α- and β-epoxides **30** and **29** were assigned on the basis of the higher field chemical shift of the C-19 methyl signal and the smaller coupling constant for the C-6 methine proton in the ^{1}H nmr spectrum of the β- relative to the α-epoxide (28). The α-epoxide appears to originate from the 5β-bromo 6α-acetate **27**, although the substituents are not aligned for an *anti*-periplanar displacement of bromide by the alkoxide formed from attack of ethoxide on the 6α-acetoxy group. However, participation of a boat form of ring B would permit an *anti*-periplanar transition state for displacement.

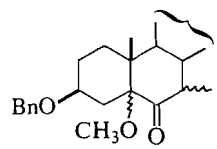
Epoxide **29** was also prepared by treatment of the triacetate **35** (29), obtained from cholesterol (**33**) via the triol **34** (30), with



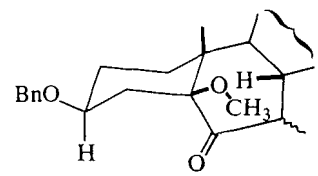
33 **34** X = OH, **35** X = OAc; **36** X = OBn, **37** X = OH

ethanolic sodium ethoxide. Acetylation of **29** gave the acetoxy β-epoxide **4*b***. Acid-catalyzed, regioselective opening of the epoxide ring of **4*b*** with methanol and oxidation of the resulting 5α-methoxy 6β-alcohol **31**, gave the desired 5α-methoxy ketone **32**.

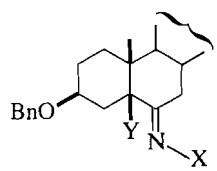
It was envisioned that synthesis of the 5β-methoxy ketone **37** could be accomplished by *O*-methylation of the 3β-benzyloxy-5β-ketol **19** to give the ether **36** followed by hydrogenolysis and acetylation. In the event, methylation of **19** gave a dimethylation product. The presence in its ^{1}H nmr spectrum of a doublet (J = 7 Hz) at δ 1.06 (CH_3CH) and a doublet of quartets (J = 7,



38 5α-OCH_3
39 5β-OCH_3



39*A*



40 X = Y = OH
41 X = OCH_3, Y = OH
42 X = Y = OCH_3

7 Hz) at δ 2.32 (CH_3CHCH) in addition to an *O*-methyl signal at δ 3.60 indicated that both *O*-alkylation and *C*-alkylation α to the carbonyl group had occurred. The 5α configuration as in **38** was initially suggested by the appearance of the C*H*OBn proton signal at δ 3.60 as a broad multiplet. However, other features of the ^{1}H nmr spectrum of the methylation product were not readily accommodated by the 5α-methoxy assignment **38**.[2]

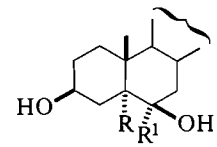
This circumstance and results from methylation of the C-5 hydroxyl group in systems in which the C-6 carbonyl group was protected (*vide infra*) led us to consider the possibility that the product from methylation of **19** had the 5β stereochemistry as in **39** and that the broad multiplet assigned to the C*H*OBn proton

[2]The possibility that methylation had occurred at C-4 via an *A*-homo *B*-nor intermediate was excluded by the observation that the C*H*OBn signal at δ 3.60 was unaffected by irradiation at δ 2.32, the chemical shift of the signal assigned to the C*H*CH_3 proton.

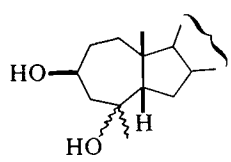
arose from an axial conformation of this proton resulting from the preference of either ring A or B in **39** to exist in a boat-like conformation. A conformation with ring A in a chair and ring B in a boat form as in **39***A* appears to be the most favorable conformation available to **39** consistent with an axial disposition of the C-3 methine proton. This conformation also reconciles the unusual chemical shifts observed in the ^{1}H nmr spectrum of the methylation product. In this conformer, the C-19 methyl group (δ 1.04) resides in a completely different environment from that in the 3β-benzyloxy-5β-ketol **19** (C-19 Me at δ 0.83), and a large difference in their chemical shifts is not unexpected. The unusually deshielded resonance at δ 2.67 for the C-8 methine proton is consistent with the propinquity of this proton to the methoxyl substituent (ref. 11, pp. 71, 72; ref. 31), as in **39***A*. Models demonstrate that the 4α proton is situated in the deshielding cone of the C-6 carbonyl group, and the unusually low field resonance for this proton at δ 2.60 provides further evidence for the existence of **39** in the ring B boat conformation and its assignment to the methylation product. The coupling of 7 Hz between the C-7 and C-8 methine protons did not permit an unambiguous assignment of the configuration at C-7 (ref. 9, p. 51; ref. 32).

We proceeded to protect the 6-keto group in **19** to inhibit *C*-methylation. The oxime **40** and oxime methyl ether **41** were prepared following standard procedures. In their ^{1}H nmr spectra they both exhibited broad doublets (J = 12 Hz) at δ 3.3, assigned to the 7β proton and indicative of the *E* geometry (33–36). Methylation of either **40** or **41** gave the 5β-methoxy 6-oxime methyl ether **42**. The ^{1}H nmr spectrum of **42** exhibited two three-proton singlets at δ 3.10 and 3.87. The former was assigned to the C-5 methoxyl protons and the latter to the oxime methyl ether protons, based on reported chemical shifts of oxime methyl ether signals (35). Since both **40** and **41** would be extremely unlikely to undergo epimerization under the mild methylation conditions employed, the 5-methoxy 6-oxime methyl ether **42** was assigned the 5β configuration. As in the case of the analogous 5β-methoxy ketone **39**, the ^{1}H nmr spectrum of **42** was consistent with the 5β stereochemistry with ring B existing in a boat conformation, resulting in an axial disposition of the C*H*OBn proton and a broad multiplet for its proton signal. The chemical shift of the C-19 methyl singlet of the oxime **42** at δ 1.03 reflects its similarity to that of **39**. Compound **42** was assigned the *E* configuration since oximes with an α quaternary center are known to prefer this geometry (37). The *E* geometry in **42**, unlike that in **40** and **41**, was not evident from its ^{1}H nmr spectrum: neither of the C-7 methylene protons was shifted downfield from the steroidal envelope. The deshielding for α protons *syn* to an oxime group has been attributed to the anisotropy of the lone pairs on oxygen (38), and has been observed to decrease as the dihedral angle between the relevant C—H bond and the C=N—OH plane increases (36). Since in the ring B boat conformer of **42** both of the C-7 methylene protons are out of the C=N—OMe plane, the fact that they do not give rise to signals usually associated with the *E* geometry of the oxime derivative is readily explicable.

Attempted hydrolysis of the oxime methyl ether group in **42** with aqueous perchloric acid and methyl pyruvate (39) gave, following chromatography, a major fraction comprising a ~70:30 mixture of two compounds containing a single methoxyl group. The ir and ^{1}H nmr spectra of this mixture indicated that the C-5 methoxyl group had been removed while the oxime methyl ether moiety had remained intact. With this result, the synthesis of the 5β-methoxy ketone **37** was not pursued further.



43 R = CH_3, R′ = H
44 R = H, R′ = CH_3



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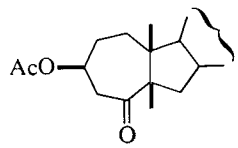

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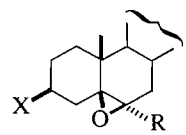
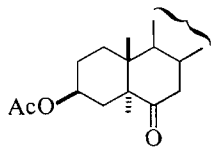


46 X = OAc, R = CH_3
49 X = $OCOCH_2COCH_3$, R = H



48

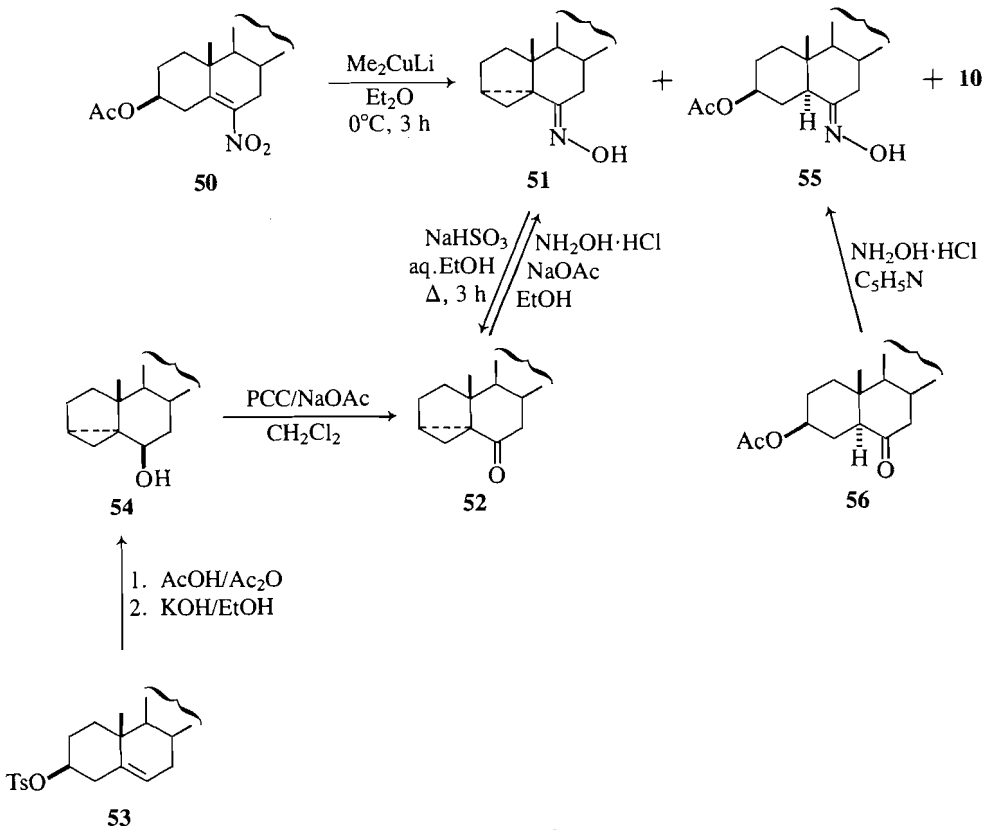
Approaches to the synthesis of 5-methyl 6-keto steroids

Direct methylation of 6-keto steroids has been reported to require vigorous reaction conditions, under which 5-methyl 6-keto steroids were obtained in poor yield (40). Addition of methylmagnesium iodide to the β-epoxide **29** has been claimed to give the 5α-methyl 6β-alcohol **43** (41), but Julia *et al.* (42) concluded that the product had structure **44**, and was formed via rearrangement of **29** (43). Our own investigation of the reaction has confirmed this conclusion (see Experimental) and also led to the isolation of a minor product to which we assign the structure **45**. It is considered to originate from initial isomerization of **29** to the *A*-homo *B*-nor 4a-ketone and subsequent Grignard addition. The 5β configuration was assigned based on analogy to the boron trifluoride catalyzed rearrangement of the 6α-methyl 5β,6β-epoxide **46**, which is reported to give the *A*-homo *B*-nor 5β-methyl 4a-ketone **47** together with the ketone **48** (44).

Lithium dialkylcuprate reagents also react with epoxides to give alkyl alcohols and have the advantage that they do not, in general, induce epoxide-to-ketone isomerizations; furthermore, reactions of cuprate reagents with epoxy esters have been observed to occur with chemoselective attack at the oxirane ring (45). However, reaction of the 3β-acetoxy β-epoxide **4***b* with lithium dimethylcuprate gave none of the desired 5-methyl 6-alcohol, but two other products—the 3-hydroxy β-epoxide **29** and its acetoacetic ester **49**. Bands at 5.73 and 5.81 μm in its ir spectrum and a broad two-proton singlet in its ^{1}H nmr spectrum at δ 3.42, which slowly disappeared upon treatment with deuterium oxide, indicated that the acetoacetic ester **49** exists largely as the keto ester tautomer, in accord with expectation (46). Abstraction of a proton α to the carbonyl moiety of the acetoxy group and acylation of the resulting enolate by another molecule of **46** accounts for the formation of both products.

In another approach to the synthesis of 5-methyl 6-keto steroids, we investigated the conjugate addition of lithium dimethylcuprate to 6-nitrocholesteryl acetate (**50**).[3] We hoped that this might provide a method for regioselective introduction of a methyl substituent at the C-5 site. Subsequent Nef reaction of the resulting 5-methyl 6-nitrocholestane would then afford a route to 5-methyl 6-keto steroids. Although reports of reactions between lithium dialkylcuprates and α,β-unsaturated nitro compounds are rare, conjugate addition has been observed in the reactions of 1-(4-chlorophenyl)-2-nitropropene with both lithium dimethyl- and diphenylcuprate (48). However, the reaction between **50**, prepared by nitration of cholesteryl acetate (**1**) (49), and lithium dimethylcuprate followed a different

[3]This study has been the subject of a preliminary communication (47).



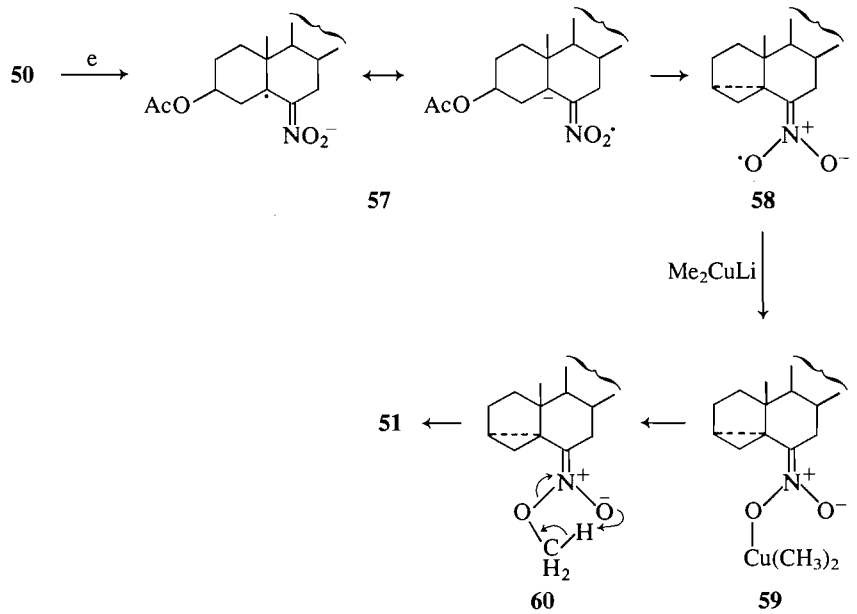
SCHEME 8

course, giving 3α,5-cyclo-5α-cholestan-6-one (*E*)-oxime (**51**) in 65% yield (Scheme 8). In the single frequency off-resonance decoupled ^{13}C nmr spectrum of **51**, a triplet at δ 8.0 and a singlet at δ 160.5 signaled cyclopropyl and oximino functions, respectively. The presence in its ^1H nmr spectrum of a broad doublet at δ 3.30 (J = 11 Hz) evidenced the *E* geometry about the C=N bond (33, 34, 36) and a high field multiplet at δ 0.49 is ascribed to the C-4 methylene protons of the cyclopropane ring. In the mass spectrum of **51**, a relatively abundant ion (40%) at m/z 383 is assigned to an ion formed by loss of an oxygen atom from the molecular ion. This type of fragmentation has been observed in the mass spectrum of cyclohexanone oxime (50). The structural assignment **51** was confirmed by treatment of the product with sodium bisulfite in aqueous ethanol to give the 3α,5α-cyclo ketone **52** (51).

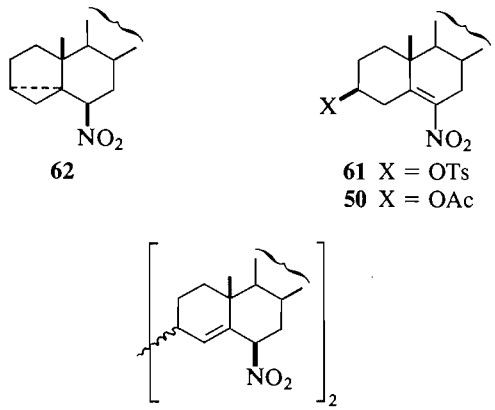
The structural assignment was further verified by an independent synthesis. 3α,5-Cyclo-5α-cholestan-6β-ol (**54**) formed by solvolysis of cholesteryl tosylate (**53**) (ref. 2*a*, pp. 236–248; ref. 52) was oxidized with pyridinium chlorochromate (PCC) in the presence of sodium acetate (2 equiv./mol PCC) to give the cyclopropyl ketone **52**. The amount of sodium acetate employed was critical to the success of this oxidation, since the product obtained following the recommended conditions (0.2 equiv. NaOAc/mol PCC) (53) contained olefinic and aldehydic side products presumed to arise from acid-initiated opening of the cyclopropyl ring. Oximination of ketone **52** gave the *E* oxime; the formation of the *E* geometrical isomer is considered to be due to the presence of the quaternary center at C-5 (37). A number of minor products were formed in the reaction between lithium dimethylcuprate and **50** (Scheme 8). We have identified 3β-acetoxy-5α-cholestan-6-one (*E*)-oxime (**55**), isolated in a mixture with the acetoxy 5α-ketol **10**, by direct comparison with a sample prepared by oximination of the parent ketone **56** (54).

A possible mechanism for the formation of oxime **51** from the reaction of lithium dimethylcuprate with **50** is detailed in Scheme 9. Introduction of an electron into the α,β-unsaturated nitro system would lead to a radical anion **57**. House and Umen (55) have reported that unsaturated systems with reduction potentials less negative than −2.4 V (in *N*,*N*-dimethylformamide) will accept an electron from lithium dimethylcuprate, and Sato *et al.* (56) have reported that the reduction potential of the nitro olefin **50** lies in the range −1.35 to −1.37 V (in *N*,*N*-dimethylformamide). Intramolecular nucleophilic displacement of the acetoxy group in **57** would generate the cyclopropane ring with the 3α,5α geometry.[4] The ability of anions at C-5 to displace good leaving groups in the β orientation at C-3 leading to 3α,5α-cyclo steroids is well documented (54), although this may be the first example in which an acetoxy group has been so displaced. Sato *et al.* (56) have observed that while electrolysis of the tosylate **61** gave a 43% yield of the cyclo nitro compound **62**, no evidence of any 3,5-cyclo products derived from internal displacement of the acetoxy group could be detected from similar electrolysis of the analogous acetate **50**, which gave the bimolecular product **63**. In the case of the cuprate reaction of **50**, displacement of the acetoxy group may be facilitated by complexation with lithium or copper species. To account for further reduction of **58** to oxime **51** (Scheme 9), complex **59** is postulated to form and undergo methyl insertion (55) to give the nitronate ester **60**.

[4]While a two-electron transfer mechanism cannot be excluded, related studies lead us to favor internal displacement from a radical anion formed by a one-electron process (56, 57).



SCHEME 9



This postulate is not without precedent, for in the reduction of nitroalkanes to oximes by carbon monoxide and copper salts Knifton (58) has suggested that carbon monoxide insertion into a copper–oxygen bond occurs in a related copper-bound nitronate anion. Decomposition of the nitronate ester **60** to afford the oxime **51**, as depicted, is well documented (58, 59). The stereochemical consequences for the oxime generated by the mechanism outlined in Scheme 9 are undefined; however, equilibration of the *Z* to the *E* isomer during work-up would account for isolation of only the latter from the reaction mixture. Oxime **51** was recovered unchanged following resubjection to lithium dimethylcuprate treatment.

Experimental[5]

Melting points were recorded on a Fisher–Johns melting point apparatus and are uncorrected. The ir spectra were recorded in chloroform and the ^{1}H nmr spectra at 60 MHz in deuterochloroform unless otherwise specified. For symmetrical multiplets in the latter the width at half-height ($W_{1/2}$) is recorded while for unsymmetrical multiplets the total width is given. Low resolution mass spectra were recorded with a Bell and Howell CEC 21-490 mass spectrometer. For the deuterium content calculations, 10–20 scans of the region of the spectrum containing the isotopic cluster associated with the molecular ion or, where appropriate, of the (M − CH_3CO_2H) fragment were obtained at a high signal-to-noise ratio and averaged. Accurate mass measurements were made with an AEI MS-3074 spectrometer with a DS-50 data system.

Organic solutions were concentrated on a rotary evaporator under water aspirator pressure. Column chromatography was carried out on silica gel (Grace Davison, grade 923, 100–200 mesh), neutral alumina (Merck, activity 1, 70–230 mesh, 90 Å mean pore diameter), or Florisil (Aldrich, 100–200 mesh). Flash chromatography was performed on 40–60 μm silica gel (Merck, grade 60, 230–400 mesh, 60 Å mean pore diameter) under air, nitrogen, or argon pressure so that the drop in solvent height was 5 cm/min.

Several compounds described here have been obtained previously. Full experimental details for their preparation in the present work are given only when a new method or a significant variation of an earlier method has been used.

*5,6α-Epoxy-5α- and 5,6β-epoxy-5β-cholestan-3β-yl acetate (**4**a and **4**b)*

Oxidation of cholesteryl acetate (**1**) (60) with *m*-chloroperoxybenzoic acid in dichloromethane gave a mixture of **4***a* and **4***b* (99%) as a white solid. Crystallization from aqueous 90% acetone gave a 50:50 mixture of **4***a* and **4***b* as white crystals, mp 103–109°C; ir λ_{max}: 5.78 μm; ^{1}H nmr δ: 0.62 (s, C-18 Me α-epoxide), 0.65 (s, C-18 Me β-epoxide), 1.03 (s, C-19 Me β-epoxide), 1.10 (s, C-19 Me β-epoxide), 2.03 (s), 2.83 (d, J = 4 Hz, α-epoxide) and 3.07 (d, J = 3 Hz, β-epoxide) (1H), 4.83 (br m, $W_{1/2}$ = 24 Hz, 1H); ms m/z: 444 (6), 384 (100).

*5,6α-Cholestane-3β,5,6β-triol 3-acetate (**7**)*

Perchloric acid (70%; 0.35 mL) was added dropwise to a solution of a 50:50 mixture of **4***a* and **4***b* (1.14 g, 2.57 mmol) in acetone (50 mL) and water (3 mL), and after the solution was stirred at room temperature for 5 h, water was added to precipitate the product. The collected product was washed with water and crystallized from aqueous 90% acetone to give **7** (1.02 g, 86%) as white crystals, mp 206.5–208.5°C (lit. (61) mp 207–208°C); ir λ_{max}: 3.02 (sh, w), 3.14 (br, w), 5.79 μm; ^{1}H nmr δ: 0.68 (s, C-18 Me), 1.20 (s, C-19 Me), 1.93 (br s, OH, absent after treatment with deuterium oxide), 2.03 (s), 3.53 (nar m, $W_{1/2}$ = 8 Hz, 1H), 5.13 (br m, $W_{1/2}$ = 20 Hz, 1H); ms m/z: 462 (20), 384 (100).

[5]For additional details of experimental procedures, see ref. 1*b*.

*3β-Acetoxy-5-hydroxy-5α-cholestan-6-one (**10**)*

*(i) Oxidation of **7** with pyridinium chlorochromate*

A solution of **7** (0.984 g, 2.13 mmol) in dichloromethane (55 mL) was added all at once to a stirred suspension of pyridinium chlorochromate (Aldrich; 1.15 g, 5.33 mmol) and neutral, activity I, 70–230 mesh alumina (Merck; 4.45 g) in dichloromethane (30 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h, and ether (25 mL) was added to the resulting brown suspension. The mixture was filtered through a Florisil column (2 × 12 cm) and the column was eluted with ether (100 mL). The combined organic solutions were concentrated to give **10** (0.86 g, 88%) as a white solid. Crystallization from methanol gave **10** as white needles, mp 231.5–233.5°C. Flash chromatography of the product on silica gel (2 × 14 cm) with chloroform – ethyl acetate (9:1 v/v) as eluent gave **10** (0.78 g, 79%), which crystallized from methanol as white needles, mp 235.5–238°C (lit. (30) mp 232–233°C); ir λ_{max}: 2.81 (sh, w), 2.95 (br, w), 5.83 μm; ^{1}H nmr (400 MHz) δ: 0.64 (s, C-18 Me), 0.81 (s, C-19 Me), 0.86 (d, J = 6 Hz, C-26,27 Me), 0.91 (d, J = 7 Hz, C-21 Me), 2.01 (s), 2.10 (dd, J = 13, 4 Hz), 2.76 (dd, J = 13, 13 Hz, 1H), 3.11 (br s, OH, 1H), 5.03 (br m, $W_{1/2}$ = 24 Hz, 1H); ms m/z: 460 (20), 400 (100).

*(ii) Oxidation of **7** with silver carbonate on Celite*

Silver carbonate precipitated on Celite was prepared following the method of Balogh, Fetizon, and Golfier (6). The Ag_2CO_3/Celite reagent was assumed to contain approximately 1 mmol of silver carbonate for every 0.57 g of reagent (6). A stirred suspension of **7** (216 mg, 0.47 mmol) and Ag_2CO_3/Celite (2.85 g, ~5 mmol) in anhydrous benzene (25 mL) under a nitrogen atmosphere was heated under reflux for 96 h with azeotropic removal of water by means of a Dean–Stark apparatus. The resultant dark green reaction mixture was filtered and concentrated to give a brownish colored solid. This was dissolved in chloroform, and the solution was filtered through Celite. The filtrate was concentrated to give **10** (210 mg, 98%) as a white solid, which on crystallization from methanol gave **10** as white needles, mp 233–235°C.

*5,6α-Epoxy-5α- and 5,6β-epoxy-5β-cholestane (**5**a and **5**b)*

Oxidation of 5-cholestene (**2**) (62) with *m*-chloroperoxybenzoic acid in dichloromethane gave a ~70:30 mixture of **5***a* and **5***b* (2.95 g) in quantitative yield as a pale yellow solid; ir λ_{max}: 3.47 μm; ^{1}H nmr δ: 0.60 (s, C-18 Me α-epoxide), 0.63 (s, C-18 Me β-epoxide), 1.00 (s, C-19 Me β-epoxide), 1.05 (s, C-19 Me α-epoxide), 2.83 (d, J = 4 Hz, α-epoxide) and 2.97 (d, J = 3 Hz, β-epoxide) (1H); ms m/z: 386 (90), 55 (100).

*5α-Cholestane-5,6β-diol (**8**)*

A solution of a 70:30 mixture of **5***a* and **5***b* (2.38 g, 6.17 mmol) and *p*-toluenesulfonic acid monohydrate (65 mg, 0.34 mmol) in dioxane–water (9:1 v/v; 43 mL) was stirred and heated under reflux for 1.5 h. The solution was allowed to cool to room temperature and poured into aqueous 10% Na_2CO_3 (20 mL). The dioxane was removed under water aspirator pressure on a rotary evaporator equipped with a cold trap condenser. The residue was extracted with ether (4 × 25 mL), and the combined ethereal extracts were washed with water (4 × 25 mL), dried (Na_2SO_4), and concentrated to give **8** (2.17 g, 87%) as a yellow oil that partially crystallized on standing; ir λ_{max}: 2.75 (sh, w), 2.88 (br, w) μm; ^{1}H nmr δ: 0.70 (s, C-18 Me), 1.17 (s, C-19 Me), 1.50 (m, OH, absent after treatment with D_2O), 3.48 (nar m, $W_{1/2}$ = 6 Hz, 1H); ms m/z: 404 (10), 386 (100).

*5-Hydroxy-5α-cholestan-6-one (**11**)*

Oxidation of **8** in dioxane–water with purified (63) *N*-bromosuccinimide gave **11** as a white solid (61%), which exhibited a ^{1}H nmr spectrum in accord with expectation. However, thin-layer chromatography indicated the presence of a very small amount of impurity, and a solution of the compound became darker yellow in color during attempted crystallization from methanol. The methanolic solution was concentrated, and flash chromatography of the yellow solid on silica gel (2 × 15 cm) with hexanes – ethyl acetate (9:1 v/v) gave **11** (284 mg, 44%). Crystallization from methanol gave **11** as fine white needles, mp 150–153°C (lit. (7) mp 152–153°C); ir λ_{max}: 2.75 (sh, w), 2.96 (br, w), 5.82 μm; ^{1}H nmr δ: 0.65 (s, C-18 Me), 0.78 (s, C-19 Me), 1.77 (br s, OH), 2.77 (dd, J = 12 Hz, 12 Hz); ms m/z: 402 (100).

*Cholesteryl benzyl ether (**3**)*

Benzylation of cholesterol (**33**) (64) in anhydrous benzene and anhydrous dimethyl sulfoxide with NaH (50% dispersion in oil) followed by purified benzyl bromide (65) gave a yellow solid, which on crystallization from acetone gave **3** (76%) as white needles, mp 115–116°C. The melt solidified on cooling, and the solid remelted at 119–121.5°C (lit. (66) mp 118.5°C). Compound **3**: ir λ_{max}: 6.19 (vw) μm; ^{1}H nmr δ: 0.70 (s, C-18 Me), 1.03 (s, C-19 Me), 3.25 (br m, $W_{1/2}$ = 20 Hz, 1H), 4.57 (s, 2H), 5.33 (nar m, $W_{1/2}$ = 8 Hz, 1H), 7.33 (s, 5H); ms m/z: 476 (2), 370 (100), 91 (98).

*5,6α-Epoxy-5α- and 5,6β-epoxy-5β-cholestan-3β-yl benzyl ether (**6**a and **6**b)*

Oxidation of **3** with *m*-chloroperoxybenzoic acid in dichloromethane gave an 80:20 mixture of **6***a* and **6***b* (94%) as a white solid, mp 102–113°C; ir λ_{max}: 3.55 μm; ^{1}H nmr δ: 0.60 (s, C-18 Me), 1.00 (s, C-19 β-epoxide), 1.07 (s, C-19 Me α-epoxide), 2.87 (d, J = 4 Hz, α-epoxide) and 3.00 (d, J = 3 Hz, β-epoxide) (1H), 3.60 (br m, $W_{1/2}$ = 24 Hz, 1H), 4.50 (s, 2H), 7.30 (s, 5H); ms m/z: 492 (5), 91 (100).

*5α-Cholestane-3β,5,6β-triol 3-benzyl ether (**9**)*

A suspension of an 80:20 mixture of **6***a* and **6***b* (79.7 g, 0.162 mol) and *p*-toluenesulfonic acid monohydrate (1.65 g, 0.009 mol) in dioxane (1 L) and water (100 mL) was stirred and heated under reflux under an argon atmosphere for 1.5 h. The resulting solution was allowed to cool to room temperature and was added to aqueous 10% Na_2CO_3 (500 mL). The dioxane was removed under water aspirator pressure on a rotary evaporator equipped with a cold trap condenser. The residue was dissolved by adding ether (550 mL), dichloromethane (200 mL), and water (150 mL), and the aqueous layer was extracted with ether (2 × 100 mL) and ether–dichloromethane (70:30 v/v; 1 × 100 mL). The combined organic phases were washed with water (300 mL, 5 × 50 mL), dried ($MgSO_4$), and concentrated to give **9** (77 g, 93%) as a white solid. Crystallization from hexanes–acetone (75:25 v/v; 650 mL) gave white needles, mp 185–187°C; (lit. (67) mp 185–186°C); ir λ_{max}: 2.88 (sh, w), 3.01 (br, w) μm; ^{1}H nmr δ: 0.67 (s, C-18 Me), 1.18 (s, C-19 Me), 1.57 (m, OH, absent after treatment with D_2O), 3.43 (nar m, $W_{1/2}$ = 5 Hz, 1H), 3.78 (br m, $W_{1/2}$ = 20 Hz, 1H), 4.53 (s, 2H), 7.30 (s, 5H); ms m/z: 510 (0), 91 (100).

*3β-Benzyloxy-5-hydroxy-5α-cholestan-6-one (**12**)*

*(i) Oxidation of **9** with pyridinium chlorochromate in the presence of molecular sieves and alumina*

A solution of **9** (20.0 g, 39.2 mmol) in anhydrous dichloromethane (100 mL) was added over a period of 5 min to a mechanically stirred mixture of pyridinium chlorochromate (Aldrich; 16.1 g, 74.6 mmol), 3 Å molecular sieves (BDH; 60 g), activated by crushing the $\frac{1}{8}$-in. pellets with a mortar and pestle and heating over a flame under a flow of argon for 2 h, and neutral, activity I, 70–230 mesh alumina (Merck; 57 g) in anhydrous dichloromethane (35 mL) under an argon atmosphere. Initially, the brown reaction mixture became warm, causing the dichloromethane to boil gently. After the mixture was stirred for 1 h, ether (100 mL) was added, and the mixture was filtered through a Florisil column (54 g, 4 × 10 cm). The column was eluted with ether (800 mL), and the combined organic solutions were concentrated to give a brown solid. A solution of the solid in ether (600 mL) was filtered through an alumina column (65 g, 4 × 8 cm), and the column was eluted with ether (800 mL). The combined ethereal solutions were concentrated to give **12** (13.9 g, 70%) as a white solid, mp 180.5–184°C. Crystallization from cyclohexane gave **12** as white needles, mp 189.5–190°C (lit. (68) mp 186–188°C); ir λ_{max}: 2.84 (sh, w), 3.00 (br, w), 5.82 μm; ^{1}H nmr δ: 0.65 (s, C-18 Me), 0.83 (s, C-19 Me), 2.13 (br s, OH, absent after treatment with D_2O), 2.70 (dd, J = 12, 12 Hz, 1H), 3.72 (br m, $W_{1/2}$ = 20 Hz, 1H), 4.53 (s, 2H), 7.32 (s, 5H); ms m/z: 508 (14), 91 (100).

*(ii) Oxidation of **9** with pyridinium chlorochromate in the presence of alumina*

A solution of **9** (6.10 g, 12.0 mmol) in anhydrous dichloromethane (310 mL) was added to a stirred suspension of pyridinium chlorochromate (Aldrich; 6.50 g, 30.2 mmol) and neutral, activity I, 70–230 mesh alumina (Merck; 25 g) in anhydrous dichloromethane (170 mL) under an argon atmosphere. The mixture was stirred at room temperature for 1.5 h, and ether (140 mL) was added to the resulting brown mixture. The mixture was filtered through a Florisil column (57 g, 4 × 14 cm), and the column was eluted with ether (300 mL); the organic solutions were concentrated to give a yellow solid. A solution of the solid in ether (200 mL) was passed through an alumina column (30 g, 2 × 12 cm), and the column was eluted with ether (50 mL). The combined ethereal solutions were concentrated to give **12** (5.76 g, 95%). Crystallization from cyclohexane gave **12** (5.05 g, 83%) as white needles, mp 179–181.5°C.

*Treatment of **12** with potassium* tert*-butoxide. Formation of 5-hydroxy-5β-cholest-3-en-6-one (**14**) and 5-hydroxy-5β-cholest-2-en-6-one (**15**)*

Compound **12** (3.01 g, 5.93 mmol) was added to a solution of potassium *tert*-butoxide (Aldrich; 13.9 g, 124 mmol) in anhydrous *tert*-butyl alcohol (75 mL), and the suspension was heated to give a red solution. The solution was boiled under reflux for 1 h, allowed to cool to room temperature, and poured into water (50 mL). The *tert*-butyl alcohol was removed under water aspirator pressure on a rotary evaporator equipped with a cold trap condenser, and the residue was extracted with ether (3 × 50 mL, 1 × 25 mL). The combined ethereal extracts were washed with saturated aqueous NaCl and water, dried ($MgSO_4$), and concentrated. Medium pressure liquid chromatography of the residual orange oil (2.73 g), in three portions, on a size B (3 × 25 cm) silica gel column (Merck) with hexanes – ethyl acetate (95:5 v/v) gave the Δ^3-ketol **14** as a white solid (1.55 g, 65%). The ^{13}C nmr spectrum suggested that the product contained a small amount of the Δ^2-ketol **15**. The mixture (1.30 g) of the two olefinic isomers was separated in 350-mg portions by flash chromatography with hexanes – ethyl acetate (95:5 v/v) on a column (2.5 × 14 cm) of silica gel containing 7% (w/w) $AgNO_3$. This was prepared by shaking 40–60 μm silica gel (Merck; 60 g) with a solution of $AgNO_3$ (4.3 g) in water (20 mL) and drying the adsorbent in an oven at 140°C overnight. Compound **15** (61 mg, 3%) was eluted first as a white solid that was crystallized from methanol to give white needles, mp 125–126.5°C (lit. (14, 69)[6] mp 122–124.5°C); ir λ_{max}: 2.96 (br, w), 5.85, 5.99 (w) μm; ^1H nmr δ: 0.67 (s, C-18 Me), 0.76 (s, C-19 Me), 4.05 (s, OH, 1H), 5.67 (nar m, $W_{1/2}$ = 4 Hz, 2H); ms *m/z*: 400 (38), 55 (100). *Accurate Mass* calcd. for $C_{27}H_{44}O_2$: 400.3341; found: 400.3349.

Further elution gave **14** (1.2 g, 58%) as a white solid. Crystallization from methanol gave **14** as white needles, mp 92–93.5°C; the melt was cooled, and the solid was remelted, mp 95–96.5°C. Compound **14**: ir λ_{max}: 2.95 (sh, w), 5.86 μm; ir λ_{max}(KBr): 2.89 (sh, m), 5.86, 6.05 (v w), 14.59 (w) μm; uv λ_{max} (ε) (ethanol): 283 (83); ^1H nmr (200 MHz) δ: 0.65 (s, C-18 Me), 0.77 (s, C-19 Me), 0.86 (d, *J* = 6 Hz, C-26,27 Me), 0.91 (d, *J* = 7 Hz, C-21 Me), 4.20 (s, OH, absent after treatment with D_2O, 1H), 5.42 (dt, *J* = 10, 2 Hz, 1H), 6.00 (dt, *J* = 10, 3.5 Hz, 1H); ms *m/z*: 400 (21), 55 (100). *Accurate Mass* calcd. for $C_{27}H_{44}O_2$: 400.3341; found: 400.3351. *Anal.* calcd. for $C_{27}H_{44}O_2$: C 80.86, H 11.02; found: C 80.94, H 11.07.

*5-Hydroxy-5β-cholestan-6-one (**13**)*

*(i) Hydrogenation of **14***

A solution of **14** (86 mg, 0.22 mmol) in ethyl acetate (3 mL) was stirred with 10% palladium on carbon (11 mg) in a Morton flask under an atmosphere of hydrogen for 48 h. The reaction mixture was filtered through anhydrous $MgSO_4$, and the solution was concentrated to give **13** (80 mg, 93%) as a white solid. Crystallization from methanol gave white needles, mp 104–105°C (lit. (69) mp 103–104°C); ir λ_{max}: 2.84 (w), 5.86 μm; ^1H nmr δ: 0.65 (s, C-18 Me), 0.70 (s, C-19 Me), 3.83 (s, OH, absent after treatment with D_2O, 1H); ms *m/z*: 402 (22), 318 (100).

*(ii) Epimerization of **11***

A solution of **11** (108 mg, 0.27 mmol) in methanolic 10% KOH (3 mL) was heated under reflux for 8 h. The solution was allowed to cool, and the methanol was removed. The residue was added to water (10 mL), and the mixture was extracted with ether (30 mL, 2 × 10 mL). The combined ethereal extracts were washed with saturated aqueous NaCl (4 × 10 mL), dried (Na_2SO_4), and concentrated. The resulting yellow oil (110 mg) was flash chromatographed on silica gel with hexanes – ethyl acetate (95:5 v/v) as eluent to afford **13** (83 mg, 77%) as a white solid that was crystallized from methanol as white needles, mp 103–104.5°C. Further elution gave **11** (9 mg, 8%) as a white solid.

*Epimerization of **12**. Formation of 3β-benzyloxy-5-hydroxy-5β-cholestan-6-one (**19**)*

1,2-Dibromoethane (0.17 mL, 1.97 mmol) was added dropwise to a stirred mixture of magnesium turnings (1.67 g, 68.9 mmol) in anhydrous tetrahydrofuran (11 mL) under an argon atmosphere. The reaction mixture warmed to approximately 40°C, and the edges of the magnesium turnings became tinged with black. After 10 min the mixture had cooled to room temperature, and a solution of a mixture of 2-bromomesitylene (5.92 mL, 38.7 mmol) and 1,2-dibromoethane (3.17 mL, 36.8 mmol) in anhydrous tetrahydrofuran (44 mL) was added dropwise over a period of 6 h. With this slow addition the temperature of the reaction mixture did not increase during the addition. After the addition, the mixture was stirred for an additional 30 min to ensure complete consumption of the magnesium. The resulting grey solution, containing a white precipitate, was devoid of any yellow color.[7] It was treated dropwise over a period of 30 min with a solution of **12** (5.00 g, 9.84 mmol) in anhydrous tetrahydrofuran (65 mL). The resulting grey solution, which contained less white precipitate than before the addition of **12**, was heated under reflux for 7 h. A gold-colored solution containing a very small amount of white precipitate resulted. This was poured into cold (0°C) water (40 mL), and the tetrahydrofuran was removed. Benzene (100 mL) and 2 *M* aqueous HCl (25 mL) were added to the residue and the mixture was filtered through Celite. The Celite was washed with benzene (2 × 25 mL), and the washings were combined with the filtrate. The benzene layer was separated and washed with saturated aqueous $NaHCO_3$ (25 mL) and water (3 × 15 mL), dried, and concentrated. The ^1H nmr spectrum of the residue suggested that it contained mesitylene or 2-bromomesitylene, and it was pumped under high vacuum (0.25 Torr; 1 Torr = 133.3 Pa) in a water bath at 80°C to give an oil. Preparative high performance liquid chromatography of the oil was performed on a PrePak-500 silica gel column (Waters Associates; 5.7 × 30 cm) with chloroform–hexanes – ethyl acetate (65:34:1 v/v/v) as eluent. Compound **19** was eluted first as a white solid (3.50 g, 70%). Crystallization from aqueous methanol gave white crystals, mp 113–114°C; the melt solidified on cooling, and the solid remelted at 124–125°C; ir λ_{max}: 2.98 (m), 5.83, 8.57 (m) μm; ir λ_{max} (KBr): 2.87 (sh, m), 5.84, 6.68 (w), 8.56 (sh, m), 13.68 (br, m), 14.40 (m) μm; ^1H nmr δ: 0.67 (s, C-18 Me), 0.83 (s, C-19 Me), 3.83 (nar m, $W_{1/2}$ = 8 Hz, 1H), 4.35 (s, OH, 1H), 4.53 (s, 2H), 7.28 (s, 5H); ms *m/z*: 508 (1), 402 (100). *Anal.* calcd. for $C_{34}H_{52}O_3$: C 80.26, H 10.30; found: C 80.29, H 10.37.

Further elution gave **12** (1.5 g, 30%) as a white solid.

*Hydrogenolysis of **19**. Formation of 3β,5-dihydroxy-5β-cholestan-6-one (**20**)*

A solution of **19** (1.54 g, 3.03 mmol) in ethyl acetate (65 mL) was stirred with 10% palladium on carbon (160 mg) under hydrogen at atmospheric pressure for 5 h. The reaction mixture was filtered through anhydrous $MgSO_4$, and the filtrate was concentrated to give **20** (1.27 g) in quantitative yield as a colorless oil; ^1H nmr δ: 0.67 (s, C-18 Me),

[6]Compound **15** was originally structure **14** (69).

[7]Grignard solutions that developed a yellow color did not effect epimerization.

0.77 (s, C-19 Me), 4.03 (m), 4.43 (br s, OH). It was not purified further, but was acetylated directly.

3β-Acetoxy-5-hydroxy-5β-cholestan-6-one (21)

A solution containing **20** (1.21 g, 2.90 mmol), anhydrous pyridine (6.8 mL, 84 mmol), and freshly distilled acetic anhydride (5.6 mL, 59 mmol) was allowed to stand under an argon atmosphere for 68 h. The resulting orange solution was added to ice-water (50 mL), and the yellow solid that precipitated was filtered, washed with water (25 mL), and dissolved in ether (125 mL). The ethereal solution was washed with 2 *M* aqueous HCl (2 × 5 mL), saturated aqueous $NaHCO_3$ (25 mL), and water (3 × 10 mL), dried (Na_2SO_4), and concentrated. The yellow solid obtained (1.22 g) was flash chromatographed on silica gel (2.5 × 17 cm) with chloroform as eluent to give **21** (1.18 g, 89%) as a white solid. Crystallization from methanol gave white needles, mp 143.5–145°C (lit. (70) mp 142.5–144.5°C); ir λ_{max}: 2.95 (br, w), 5.78, 5.84, 7.26 (m), 8.58 (m) μm; ir λ_{max} (KBr): 2.90 (sh, m), 5.80, 5.89, 8.74 (w), 8.98 (m) μm; ^{1}H nmr (200 MHz) δ: 0.66 (s, C-18 Me), 0.76 (s, C-19 Me), 0.87 (d, J = 6 Hz, C-26,27 Me), 0.92 (d, J = 6 Hz, C-21 Me), 2.07 (s), 2.17–2.30 (m, 2H), 2.42 (dd, J = 14, 4 Hz, 1H), 3.92 (s, OH, 1H), 5.07 (nar m, $W_{1/2}$ = 8 Hz, 1H); ms m/z: 460 (2), 318 (100). *Accurate Mass* calcd. for $C_{22}H_{38}O$ (M − $C_7H_{10}O_3$): 318.2923; found: 318.2921.

3β-Acetoxy-7α-bromo-5-hydroxy-5α-cholestan-6-one (22)

Compound **22** was prepared from **10** by the method (procedure d) of Rodewald *et al.* (18). The crude product was flash chromatographed on silica gel with chloroform – ethyl acetate (97:3 v/v) as eluent to give **22** in 84% yield as a colorless oil that solidified on standing. Crystallization from methanol gave **22** as a white powder, mp 172.5–174.5°C (lit. (18) mp 170–172°C); ir λ_{max}: 2.78 (sh, w), 2.98 (br, w), 5.79, 5.83 μm; ir λ_{max} (CCl_4): 2.72 (sh, w), 2.98 (br, w), 5.74, 5.82 μm; ^{1}H nmr δ: 0.68 (s, C-18 Me), 0.83 (s, C-19 Me), 2.02 (s), 3.08 (s, OH, 1H), 4.18 (nar m, $W_{1/2}$ = 5 Hz, 1H), 5.12 (br m, $W_{1/2}$ = 20 Hz, 1H); ms m/z: 400 (42), 43 (100).

3β-Acetoxy-7α-deutero-5-hydroxy-5α-cholestan-6-one (23)

In a separatory funnel, a solution of **22** (110 mg, 0.20 mmol) in ether (10 mL) was treated with D_2O (99.8%, Aldrich; 4 × 1 mL), and the organic phase was added via cannula to zinc dust (307 mg, 4.69 mmol) in a D_2O-pretreated flask under argon. The mixture was stirred, and (*O*-D) acetic acid (98%, Aldrich; 550 μL, 9.45 mmol) was added dropwise over a period of 1 min. The suspension was stirred at room temperature for 2 h, and solid Na_2CO_3 (~8 g) was added. The mixture was filtered, and the zinc and Na_2CO_3 solids were washed with ether (7 × 10 mL). The combined filtrate and washings were washed with a solution of 5% $NaHCO_3$ in D_2O (1 mL) and saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated to give **23** (76 mg, 81%) as a white solid. Crystallization from methanol gave white needles, mp 231–233°C; ir λ_{max}: 3.08 (br, w), 5.83 μm; ^{1}H nmr (200 MHz) δ: 0.64 (s, C-18 Me), 0.81 (s, C-19 Me), 0.86 (d, J = 7 Hz, C-26,27 Me), 0.91 (d, J = 7 Hz, C-21 Me), 2.00 (s), 2.76 (dd, J = 12, 12 Hz, 0.12H), 3.20 (br s, OH, 1H), 5.03 (br m, $W_{1/2}$ = 19 Hz, 1H); ms m/z: d_0 15%, d_1 80%, d_2 5% (based on M − AcOH); d_0 15%, d_1 82%, d_2 3% (based on M).

3β-Acetoxy-7α-bromo-5-hydroxy-5β-cholestan-6-one (24)

A solution of **21** (215 mg, 0.47 mmol) in chloroform (3.3 mL) was treated with 1.42 mL of a solution of bromine (0.40 mL) and acetic acid (1.0 mL) in chloroform (20 mL). The red solution was allowed to stand at room temperature for 2 h, and the resulting yellow solution was poured into aqueous 10% Na_2SO_3 (5 mL). The mixture was extracted with benzene (25 mL, 2 × 10 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL) and water (3 × 5 mL), dried (Na_2SO_4), and concentrated to give **24** as a pale yellow solid (256 mg) in quantitative yield. Flash chromatography on silica gel (2.5 × 17 cm) with dichloromethane–ether (98:2 v/v) gave **24** (230 mg, 91%) as a white solid. Crystallization from methanol gave white needles, mp 139–139.5°C (lit. (71) mp 137–138°C); ir λ_{max} (KBr): 2.89 (m), 5.76, 5.85 μm; ^{1}H nmr δ: 0.70 (s, C-18 Me), 0.80 (s, C-19 Me), 2.07 (s), 3.07 (dd, J = 16, 4 Hz, 1H), 3.65 (s, OH, 1H), 4.42 (nar m, $W_{1/2}$ = 5 Hz, 1H), 5.07 (nar m, $W_{1/2}$ = 8 Hz, 1H); ms m/z: 400 (30), 318 (100).

3β-Acetoxy-7α-deutero-5-hydroxy-5β-cholestan-6-one (25)

A solution of **24** (120 mg, 0.22 mmol) in ether (11 mL) was reduced with zinc dust (333 mg, 5.09 mmol) and (*O*-D) acetic acid (600 μL, 10.2 mmol) at room temperature for 2.5 h following the procedure for **23** (*vide supra*). The reaction mixture was neutralized with solid Na_2CO_3 (12 g), and work-up as for **23** gave **25** (79 mg, 77%) as a white solid. Crystallization from methanol gave transparent square plates, mp 143.5–144.5°C; ir λ_{max} (KBr): 2.90 (sh, w), 5.81, 5.88, 8.91 (w) μm; ^{1}H nmr (200 MHz) δ: 0.66 (s, C-18 Me), 0.76 (s, C-19 Me), 0.87 (d, J = 7 Hz, C-26,27 Me), 0.92 (d, J = 6 Hz, C-21 Me), 2.07 (s), 2.24 (dd, J = 15, 4 Hz, 1H), 2.40 (d, J = 3 Hz, 1H), 3.92 (s, OH, 1H), 5.07 (nar m, $W_{1/2}$ = 8 Hz, 1H); ms m/z: 461 (2), 319 (100); d_0 16%, d_1 78%, d_2 6% (based on M − AcOH).

Bromination of cholesteryl acetate (1) in acetic acid. Formation of 5-bromo-5α-cholestane-3β,6β-diol diacetate (26) and 5-bromo-5β-cholestane-3β,6α-diol diacetate (27)

Cholesteryl acetate (**1**) was treated with *N*-bromoacetamide in a solution of lithium acetate in acetic acid to give **26** accompanied by ~10–20% of **27**. The crude product was crystallized from methanol to give **26** (34%) as white needles, mp 91.5–93°C (lit. (72) mp 89–91°C). A second crop of crystals, found to be a mixture of **26** and **27**, was recrystallized from methanol to give a further amount of **26** (total 39%). The crystallized **26** was chromatographed on silica gel with cyclohexane–ether (9:1 v/v) as eluent; recrystallization from methanol raised the melting point to 95.5–96°C. Compound **26**: ir λ_{max}: 5.76 μm; ^{1}H nmr δ: 0.70 (s, C-18 Me), 1.30 (s, C-19 Me), 2.03 (s), 2.10 (s), 5.35 (nar m) and 5.47 (br m) (2H); ms m/z: 384 (82), 368 (95), 43 (100).

A portion of the mother liquor from the first crystallization was applied to a silica gel preparative thin-layer chromatography plate, and the plate was eluted twice with hexanes – ethyl acetate (4:1 v/v). The upper band (R_f 0.65) gave **27**; ir λ_{max}: 5.77 μm; ^{1}H nmr (100 MHz) δ: 0.70 (s, C-18 Me), 0.85 (d, J = 6 Hz, C-26,27 Me), 0.94 (d, J = 6 Hz, C-21 Me), 1.37 (s, C-19 Me), 2.00 (s), 2.06 (s), 2.86 (br dd, J = 14, 5 Hz, 1H), 4.66 (br m, $W_{1/2}$ = 20 Hz, 1H), 5.24 (nar m, $W_{1/2}$ = 8 Hz, 1H); ms m/z: 384 (80), 368 (80), 43 (100). The lower band (R_f 0.57) gave **26**.

Bromination of 1 in aqueous medium. Formation of 28

Cholesteryl acetate (**1**) in acetone, ether, and water was treated with *N*-bromoacetamide to give a yellow solid, shown by ^{1}H nmr spectroscopy to contain at least two major products. Crystallization from hexanes gave **28** (15%) as a white powder, mp 167–170°C (lit. (73) mp 168–170°C); ir λ_{max}: 2.76 (sh, w), 2.90 (br, w), 5.78 μm; ^{1}H nmr δ: 0.67 (s, C-18 Me), 1.30 (s, C-19 Me), 1.77 (m, OH, absent after treatment with D_2O), 2.02 (s), 4.18 (nar m, $W_{1/2}$ = 7 Hz, 1H), 5.47 (br m, $W_{1/2}$ = 20 Hz, 1H); ms m/z: 384 (100).

5α-Cholestane-3β,5,6β-triol (34)

Compound **34** was prepared from cholesterol (**33**) according to the method of Fieser and Rajagopalan (30). Crystallization from methanol gave **34** in 79% yield as white needles, mp 229–232°C (lit. (30) mp 237–239°C); ir λ_{max}: 2.94 (sh, w), 3.07 (br, w) μm; ^{1}H nmr (dimethyl sulfoxide-d_6) δ: 0.63 (s, C-18 Me), 1.03 (s, C-19 Me), 3.50–4.40 (m), 3.57 (s, OH, absent after treatment with D_2O, 1H), 4.12 (d, J = 5 Hz, OH, absent after treatment with D_2O, 1H), 4.32 (d, J = 4 Hz, OH, absent after treatment with D_2O, 1H); ms m/z: 420 (2), 384 (100).

5α-Cholestane-3β,5,6β-triol triacetate (35)

Compound **35** was prepared in 98% yield by acetylation of **34** with acetic anhydride and *p*-toluenesulfonic acid monohydrate in acetic acid (28). Crystallization from methanol gave **35** (78%) as white needles, mp 149.5–151.5°C (lit. (28) mp 151.2–151.8°C); ir λ_{max}: 5.76 μm; ^{1}H nmr δ: 0.70 (s, C-18 Me), 1.20 (s, C-19 Me), 1.97 (s, one Ac), 2.07 (s, two Ac), 2.83 (br dd, J = 13, 5 Hz, 1H), 4.73 (br m, $W_{1/2}$ = 18 Hz, 1H), 5.83 (nar m, $W_{1/2}$ = 6 Hz, 1H); ^{1}H nmr (benzene) δ:

0.65 (s, C-18 Me), 1.17 (s, C-19 Me), 1.62 (s), 1.68 (s), 1.73 (s), 3.17 (dd, J = 14, 5 Hz), 5.08 (br m), 6.28 (nar m); ms m/z: 384 (100).

*5,6β-Epoxy-5β-cholestan-3β-ol (**29**)*

*(i) From **26** and ethanolic sodium ethoxide*

To a solution of sodium ethoxide in ethanol, prepared by the addition of sodium (5.90 g, 0.256 mol) to absolute ethanol (300 mL), **26** (7.50 g, 0.013 mol) was added, and the colorless solution was stirred at room temperature under nitrogen for 0.5 h. Water (30 mL) was added to the resulting pale yellow solution and the ethanol was removed on the rotary evaporator under water aspirator pressure. The residue was extracted with ether, and the combined organic extracts were washed with water, dried ($MgSO_4$), and concentrated to give **29** (6.33 g) as a white solid in quantitative yield. Two crystallizations from methanol gave **29** (4.1 g, 77%) as white needles, mp 139–140°C (lit. (28) mp 130–133.5°C (from acetone–methanol); ir λ_{max}: 2.72 (sh, w), 2.85 (br, w) μm; ^{1}H nmr δ: 0.65 (s, C-18 Me), 1.00 (s, C-19 Me), 1.83 (br s, OH, absent after treatment with D_2O), 3.03 (d, J = 3 Hz, 1H), 3.63 (br m, $W_{1/2}$ = 18 Hz, 1H).

*(ii) From **35** and ethanolic sodium ethoxide*

Treatment of **35** with sodium ethoxide in refluxing ethanol following the method of Rowland and Nace (29) gave **29** in 84% yield.

*5,6β-Epoxy-5β-cholestan-3β-yl acetate (**4**b) from **29***

Compound **29** was acetylated with acetic anhydride and pyridine (28) to give **4***b* in 70% yield; ir λ_{max}: 5.78 μm; ^{1}H nmr δ: 0.65 (s, C-18 Me), 1.02 (s, C-19 Me), 2.02 (s), 3.05 (d, J = 3 Hz, 1H), 4.73 (br m, $W_{1/2}$ = 22 Hz, 1H).

*5-Methoxy-5α-cholestane-3β,6β-diol 3-acetate (**31**)*

A solution of **4***b* (1.00 g, 2.25 mmol) and *p*-toluenesulfonic acid monohydrate (36 mg, 0.19 mmol) in methanol (250 mL) was allowed to stand at room temperature for 17 h. The solution was poured into saturated aqueous $NaHCO_3$ (100 mL) and the methanol was removed. The residue was extracted with ether (100 mL, 2 × 25 mL), and the combined organic extracts were washed with water (3 × 10 mL), dried (Na_2SO_4), and concentrated to give **31** (1.01 g, 94%) as a white solid. Crystallization from methanol gave white needles, mp 161–162°C (lit. (74) mp 152.5–154°C); ir λ_{max}: 2.83 (sh, w), 2.94 (br, w), 5.79 μm; ^{1}H nmr δ: 0.68 (s, C-18 Me), 1.18 (s, C-19 Me), 1.45 (m, OH, absent after treatment with D_2O), 2.02 (s), 3.18 (s, 3H), 3.85 (nar m, $W_{1/2}$ = 8 Hz, 1H), 4.85 (br m, $W_{1/2}$ = 20 Hz, 1H); ms m/z: 476 (3), 366 (100).

*3β-Acetoxy-5-methoxy-5α-cholestan-6-one (**32**)*

A solution of **31** (678 mg, 1.42 mmol) in dichloromethane (5 mL) was added to a stirred suspension of pyridinium chlorochromate (Aldrich; 503 mg, 2.34 mmol) and anhydrous sodium acetate (29 mg, 0.36 mmol) in dichloromethane (5 mL) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 3.5 h. Ether (5 mL) was added, and the brown mixture was applied to a Florisil column (18 g, 2 × 10 cm). The column was eluted with ether (40 mL), and the combined eluents were concentrated to give **32** (678 mg) as a white solid in quantitative yield. Crystallization from methanol gave white needles, mp 152–153°C (lit. (74) mp 149–150°C); ir λ_{max}: 5.78, 5.82 μm; ^{1}H nmr δ: 0.63 (s, C-18 Me), 0.80 (s, C-19 Me), 2.00 (s), 3.13 (s, 3H), 4.80 (br m, $W_{1/2}$ = 20 Hz, 1H); ms m/z: 474 (42), 414 (100). *Accurate Mass* calcd. for $C_{30}H_{50}O_4$: 474.3709; found: 474.3723.

*3β-Benzyloxy-5-methoxy-7α-methyl-5β-cholestan-6-one (**39**)*

Sodium hydride (80% dispersion in oil; 42.0 mg, 1.40 mmol) was added in three portions over a period of 30 min to a stirred solution of **19** (32.8 mg, 0.064 mmol) and iodomethane (1.0 mL, 16 mmol) in anhydrous tetrahydrofuran (5 mL) under argon. The reaction mixture was stirred at room temperature for a further 3.5 h and added cautiously to water (5 mL). The mixture was extracted with ether, and the combined ethereal extracts were washed with aqueous 10% Na_2SO_3 and water, dried (Na_2SO_4), and concentrated to give a colorless oil (42 mg). Flash chromatography of the oil on silica gel (1.5 × 12 cm) with chloroform–hexanes (4:1 v/v) as eluent gave **39** (25 mg, 73%) as a white solid. Crystallization from methanol gave white crystals shaped like fir trees, mp 107.5–109°C; ir λ_{max}: 5.85 μm; ^{1}H nmr (200 MHz) δ: 0.71 (s, C-18 Me), 0.87 (d, J = 7 Hz, C-26,27 Me), 0.91 (d, J = 7 Hz, C-21 Me), 1.04 (s, C-19 Me), 1.06 (d, J = 7 Hz), 2.32 (dq, J = 7, 7 Hz, 1H), 2.60 (dd, J = 12, 5 Hz, 1H), 2.67 (br m, $W_{1/2}$ = 20 Hz, 1H), 3.16 (s, 3H), 3.60 (br m, $W_{1/2}$ = 20 Hz, 1H), 4.58 (s, 2H), 7.33–7.36 (m, 5H); ms m/z: 536 (6), 91 (100). *Anal.* calcd. for $C_{36}H_{56}O_3$: C 80.55, H 10.52; found: C 80.38, H 10.51.

3β-Benzyloxy-5-hydroxy-5β-cholestan-6-one (E)*-oxime (**40**)*

Compound **19** was treated with hydroxylamine hydrochloride in 95% ethanol and pyridine to give **40** as a colorless oil (61 mg, 88%). Crystallization from methanol–hexanes gave **40** as colorless needles, mp 157.5–159°C; ir λ_{max}: 2.78 (sh, w), 2.88 (br, w), 6.12 (v w) μm; ^{1}H nmr δ: 0.67 (s, C-18 Me), 0.93 (s, C-19 Me), 3.37 (br d, J = 12 Hz, 1H), 3.80 (nar m, $W_{1/2}$ = 8 Hz, 1H), 4.50 (m, OH, absent after treatment with D_2O, 1H), 4.52 (s, 2H), 7.30 (s, 5H); ms m/z: 523 (1), 91 (100).

3β-Benzyloxy-5-hydroxy-5β-cholestan-6-one (E)*-oxime methyl ether (**41**)*

Compound **19** was treated with methoxylamine hydrochloride in anhydrous pyridine to give a pale yellow oil, which was flash chromatographed on silica gel (2 × 19 cm) with dichloromethane–ether (99:1 v/v) as eluent to give **41** (478 mg, 85%) as a colorless oil that resisted crystallization; ir λ_{max}: 2.99 (sh, m), 6.24 (w), 8.58 (m) μm; ^{1}H nmr δ: 0.67 (s, C-18 Me), 0.90 (s, C-19 Me), 3.27 (d, J = 12 Hz, 1H), 3.83 (nar m) and 3.93 (s) (4H), 4.43 (s, OH, 1H), 4.53 (s, 2H), 7.33 (s, 5H); ms m/z: 537 (<1), 91 (100). *Anal.* calcd. for $C_{35}H_{55}O_3N$: C 78.16, H 10.31, N 2.60; found: C 77.72, H 10.11, N 2.61.

3β-Benzyloxy-5-methoxy-5β-cholestan-6-one (E)*-oxime methyl ether (**42**)*

*(i) From methylation of **41***

Sodium hydride (80% dispersion in oil; 159 mg, 5.29 mmol) was added in portions to a stirred solution of **41** (452 mg, 0.84 mmol) and iodomethane (1.5 mL, 24 mmol) in anhydrous tetrahydrofuran (25 mL) under an argon atmosphere. The mixture was stirred at room temperature overnight and added cautiously to water (25 mL). The tetrahydrofuran was removed and the residue was extracted with ether (50 mL, 2 × 25 mL). The combined ethereal layers were washed with water (2 × 15 mL), dried (Na_2SO_4), and concentrated. The residual oil (488 mg) was flash chromatographed on silica gel (2 × 13 cm) with chloroform–hexanes (85:15 v/v) as eluent to give **42** (412 mg, 89%) as a colorless oil that resisted crystallization; ir λ_{max}: 6.12 (w) μm; ^{1}H nmr δ: 0.73 (s, C-18 Me), 1.03 (s, C-19 Me), 2.70 (dd, J = 12, 4 Hz, 1H), 3.10 (s, 3H), 3.73 (br m) and 3.87 (s) (4H), 4.60 (s, 2H), 7.37 (m, 5H); ms m/z: 551 (1), 460 (95), 91 (100). *Anal.* calcd. for $C_{36}H_{57}O_3N$: C 78.35, H 10.41, N 2.54; found: C 78.30, H 10.27, N 2.55.

*(ii) From methylation of **40***

Treatment of **40** (31 mg, 0.06 mmol) with NaH (80% dispersion in oil; 25 mg, 0.83 mmol) and iodomethane (0.20 mL, 3.2 mmol) in anhydrous tetrahydrofuran (3 mL) for 12 h and work-up as in (*i*) gave a colorless oil (32 mg), shown by ^{1}H nmr spectroscopy to be **42**.

*Reaction of **29** with methylmagnesium iodide. Formation of 6α-methyl-5α-cholestane-3β,6β-diol (**44**) and 4aξ-methyl-*A*-homo-*B*-nor-5β-cholestane-3β,4aξ-diol (**45**)*

An ethereal solution of methylmagnesium iodide was prepared by the addition of a solution of freshly distilled iodomethane (10.1 mL, 162 mmol) in anhydrous ether (4 mL) to a stirred mixture of purified magnesium turnings[8] (0.802 g, 33.0 mmol) in anhydrous ether (1 mL) under a nitrogen atmosphere. Grignard formation was self-initiated and the mixture was stirred at room temperature for 3 h. Anhydrous ether

[8]Magnesium turnings were washed with aqueous 2 *M* HCl (25 mL), water (×5), ethanol (×10), and anhydrous ether (×5), and pumped under high vacuum overnight.

(10 mL) was added, and the resulting slightly cloudy, grey mixture was transferred via cannula to an addition funnel, added dropwise over a period of 1 h to a stirred solution of **29** (2.48 g, 6.17 mmol) in a mixture of anhydrous benzene (25 mL) and ether (15 mL) under a nitrogen atmosphere, and heated at reflux. Following the addition, solvent (20 mL) was removed by distillation at atmospheric pressure, bp 40–51°C, and the residual solution was heated under reflux for a further 9 h. The resulting colorless, slightly cloudy reaction mixture was poured into ice, and saturated aqueous NH_4Cl was added. The organic phase was separated and washed with aqueous 5% $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated to give a white solid (2.56 g). The ^1H nmr spectrum of the product indicated the presence of two major components, **44** and **45**, in a ~60:40 ratio. The solid was triturated with acetone, and **44** was obtained as the residual white powder, mp 184–186°C (lit. (42) mp 194°C); ir λ_{max}: 2.82 (sh, w), 2.95 (br, w) μm; ^1H nmr δ: 0.67 (s, C-18 Me), 1.02 (s, C-19 Me), 1.15 (s), 1.57 (m, OH, absent after treatment with D_2O), 3.53 (br m, $W_{1/2}$ = 20 Hz, 1H); ms *m/z*: 418 (3), 403 (100), 400 (68). *Accurate Mass* calcd. for $C_{27}H_{47}O_2$ (M − CH_3), $C_{28}H_{48}O$ (M − H_2O): 403.3576, 400.3705; found: 403.3563, 400.3698.

The acetone solution from the trituration was concentrated, and the residual solid was crystallized from ethyl acetate to give **45** (0.14 g, 5%) as white crystals, mp 86.5–88.5°C; ir λ_{max}: 2.83 (sh, w), 2.93 (br, w) μm; ^1H nmr δ: 0.67 (s, C-18 Me), 0.98 (s, C-19 Me), 1.22 (s), 1.90 (m, OH, absent after treatment with D_2O), 3.98 (nar m, $W_{1/2}$ = 12 Hz, 1H); ms *m/z*: 418 (5), 87 (100). *Accurate Mass* calcd. for $C_{28}H_{50}O_2$: 418.3811; found: 418.3787.

Reaction of ***4b*** *with lithium dimethylcuprate. Formation of 5,6β-epoxy-5β-cholestan-3β-yl 3-oxobutyrate (**49**) and 5,6β-epoxy-5β-cholestan-3β-ol (**29**)*

A stirred suspension of CuI (147 mg, 0.77 mmol) in anhydrous ether (10 mL) under a nitrogen atmosphere and cooled in an ice–salt bath was treated dropwise with a solution of methyllithium–LiBr complex in ether (1.2 *M*; 1.25 mL, 1.50 mmol). To the ethereal solution of lithium dimethylcuprate, a solution of **4*b*** (172 mg, 0.39 mmol) in anhydrous ether (5 mL) was added dropwise over a period of 15 min. A yellow precipitate slowly began to fall from solution, and the mixture was stirred in the ice–salt bath for 3 h. The resulting yellow suspension was treated with saturated aqueous NH_4Cl (10 mL), and the two-phase mixture was stirred at room temperature overnight. The ethereal layer was separated, washed with saturated aqueous $Na_2S_2O_3$ and water, dried ($MgSO_4$), and concentrated to give a white solid (130 mg). The ^1H nmr spectrum of the product evidenced a ~40:60 mixture of **49** and **29**. An ethereal solution of the solid was applied to a 1-mm silica gel plate, and the plate was eluted with ether. The upper band (R_f 0.66) gave **49** (40 mg, 21%) as a white solid; ir λ_{max}: 5.73, 5.81 μm; ^1H nmr (100 MHz) δ: 0.64 (s, C-18 Me), 1.00 (s, C-19 Me), 2.25 (s, 3H), 3.07 (d, *J* = 3 Hz, 1H), 3.42 (br s, exchanges slowly with D_2O, 2H), 4.84 (br m, $W_{1/2}$ = 24 Hz, 1H); ms *m/z*: 486 (2), 384 (100). The lower band (R_f 0.41) gave **29** (65 mg, 42%) as a white solid.

*6-Nitrocholesteryl acetate (**50**)*

Nitration of cholesteryl acetate (**1**) (49) gave **50** in 68% yield as white needles, mp 103.5°C–105°C (from methanol) (lit. (49) mp 102.5–103°C); ir λ_{max}: 5.75, 6.62 (m) μm; ^1H nmr δ: 0.70 (s, C-18 Me), 1.15 (s, C-19 Me), 2.02 (s), 4.60 (br m, $W_{1/2}$ = 18 Hz, 1H); ms *m/z*: 473 (6), 413 (100).

Reaction of ***50*** *with lithium dimethylcuprate. Formation of 3α,5-cyclo-5α-cholestan-6-one (*E*)-oxime (**51**), 3β-acetoxy-5α-cholestan-6-one (*E*)-oxime (**55**), and 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (**10**)*

An ethereal solution of lithium dimethylcuprate was prepared by the dropwise addition of a solution of methyllithium–LiBr complex in ether (1.7 *M*; 17.4 mL, 29.6 mmol) to a stirred suspension of purified (75) CuI (2.93 g, 15.4 mmol) in anhydrous ether (125 mL) under an argon atmosphere and cooled in an ice bath. A solution of **50** (1.39 g, 2.94 mmol) in anhydrous ether (15 mL) was added dropwise over a period of 30 min, and the resulting yellow suspension was stirred at 0°C for 3 h and subsequently added via cannula to a stirred solution of saturated aqueous NH_4Cl (250 mL) buffered to pH 8 with aqueous 28% NH_3. The two-phase mixture was stirred overnight, and the blue aqueous layer was extracted with ether (3 × 50 mL). The combined ethereal layer and extracts were washed with saturated aqueous NaCl (4 × 10 mL), dried (Na_2SO_4), and concentrated to give a yellow oil (1.32 g). Preparative thin-layer chromatography of the oil (134 mg) on silica gel with hexanes – ethyl acetate (4:1 v/v) gave **51** (77 mg, 65%) as a white solid. Crystallization from aqueous ethanol gave white crystals, mp 126–126.5°C (lit. (76) mp 125–126°C). A mixture mp taken with a sample of **51**, mp 124.5–125.5°C, prepared by oximination of ketone **52** (*vide infra*) was 125–126°C. Compound **51**: ir λ_{max}: 2.78 (sh, m), 3.06 (br, m), 6.07 (w) μm; ^1H nmr δ: 0.49 (m, 1H), 0.68 (s, C-18 Me), 0.91(s, C-19 Me), 3.30 (br d, *J* = 11 Hz, 1H), 8.67 (v br m, OH, 1H); ms *m/z*: 399 (12), 135 (100). *Accurate Mass* calcd. for $C_{27}H_{45}ON$: 399.3501; found: 399.3505. *Anal.* calcd. for $C_{27}H_{45}ON$: C 81.14, H 11.35, N 3.50; found: C 80.79, H 11.31, N 3.55.

A portion (411 mg) of the crude oil was purified by medium pressure liquid chromatography on a 3 × 25-cm silica gel column (Merck) with hexanes – ethyl acetate (85:15 v/v) as eluent. Compound **51** (176 mg, 48%) was eluted first, and further elution gave a white solid (46 mg) and a colorless oil (22 mg). Flash silica gel chromatography of the solid with dichloromethane – ethyl acetate (9:1 v/v) gave a mixture (30 mg) of **55** and **10** as a white solid; ir λ_{max}: 2.88 (sh, w), 3.06 (br, w), 5.79, 6.20 (w) μm; ^1H nmr δ: 0.63 (s, C-18 Me), 0.75 (s, C-19 Me, **55**), 0.80 (s, C-19 Me, **10**), 2.00 (s), 3.33 (br d, *J* = 11 Hz, **55** 7β-H), 4.67 (br m, **55** C*H*OAc), 5.05 (br m, **10** C*H*OAc); ^{13}C nmr (δ > 60 ppm) δ: 70.8, 73.4, 80.3, 159.8, 170.6, 171.0, 212.2; ms *m/z*: 460 (10), 459 (5), 43 (100).

Hydrolysis of ***51***. *Formation of 3α,5-cyclo-5α-cholestan-6-one (**52**)*

A mixture of **51** (58 mg, 0.15 mmol) and $NaHSO_3$ (311 mg) in absolute ethanol (14 mL) and water (2.7 mL) was stirred and heated under reflux for 3 h. The mixture was allowed to cool and the ethanol was removed. The residue was extracted with ether (25 mL, 3 × 10 mL), and the ethereal extract was washed with saturated aqueous $NaHCO_3$ (10 mL) and water, dried (Na_2SO_4), and concentrated to give **52** (49 mg, 87%) as a white solid. Crystallization from methanol gave white crystals, mp 97–98°C (lit. (77) mp 97.2–97.6°C). A mixture mp taken with a sample of **52**, mp 99–99.5°C, prepared by oxidation of **54** (*vide infra*) was 97.5–99.5°C. Ketone **52**: ir λ_{max}: 5.94 μm; ^1H nmr δ: 0.70 (s, C-18 Me), 1.00 (s, C-19 Me); ms *m/z*: 384 (100). *Accurate Mass* calcd. for $C_{27}H_{44}O$: 384.3392; found: 384.3398.

*3α,5-Cyclo-5α-cholestan-6β-ol (**54**)*

Cholesteryl *p*-toluenesulfonate (**53**) was treated with a mixture of potassium acetate and acetic anhydride, and the resulting mixture of acetates was hydrolyzed with ethanolic KOH (78) to give **54** (62%) as a white solid, mp 64.5–68°C (lit. (78) 74–75°C); ir λ_{max}: 2.77 (sh, w), 2.90 (br, w) μm; ^1H nmr δ: 0.17–0.57 (m), 0.72 (s, C-18 Me), 1.07 (s, C-19 Me), 1.50 (m, OH, absent after treatment with D_2O), 3.22 (nar m, $W_{1/2}$ = 6 Hz, 1H); ms *m/z*: 386 (1), 368 (100).

Oxidation of ***54***. *Formation of 52*

A stirred suspension of pyridinium chlorochromate (Aldrich: 97 mg, 0.45 mmol) and anhydrous sodium acetate (69 mg, 0.84 mmol) in dichloromethane (1 mL) under a nitrogen atmosphere was treated with a solution of **54** (112 mg, 0.29 mmol) in dichloromethane (1 mL). The mixture was stirred at room temperature for 25 h, and ether (2 mL) was added to the resulting olive-colored suspension. The reaction mixture was applied to a Florisil column (5 g, 2 × 4 cm), and the column was eluted with ether (100 mL). The eluent was concentrated to give **52** (105 mg, 94%) as a white solid. Crystallization from methanol gave white crystals, mp 99–99.5°C (lit. (77) mp 97.2–97.6°C). The spectra of this product were identical to those of **52** prepared by hydrolysis of **51**.

Oximation of ***52***. *Formation of 51*

Compound **52** was treated with hydroxylamine hydrochloride and anhydrous sodium acetate in ethanol to give **51** (91%) as a colorless oil.

Crystallization from aqueous ethanol gave white crystals, mp 124.5–125.5°C (lit. (78) mp 125–126°C). The ir, ^{1}H nmr, ^{13}C nmr, and mass spectra were identical to those of **51** obtained by reaction of **50** with lithium dimethylcuprate.

3β-Acetoxy-5α-cholestan-6-one (56)

Reduction of 6-nitrocholesteryl acetate (**50**) with zinc and acetic acid (54) gave **56** in 88% yield as white needles, mp 128–131.5°C (lit. (54) mp 127–128°C); ir λ_{max}: 5.77, 5.82 μm; ^{1}H nmr δ: 0.68 (s, C-18 Me), 0.80 (s, C-19 Me), 2.03 (s), 4.67 (br m, $W_{1/2}$ = 20 Hz, 1H).

3β-Acetoxy-5α-cholestan-6-one (E)*-oxime (55)*

Compound **56** was treated with hydroxylamine hydrochloride and sodium acetate in ethanol to give **55** (83%) as a white solid. Crystallization from methanol–hexanes gave colorless plates, mp 198–199°C (lit. (79) mp 206–208°C (from methanol)); ir λ_{max}: 2.90 (sh, w), 3.11 (br, w) 5.77, 6.00 (w) μm; ^{1}H nmr δ: 0.67 (s, C-18 Me), 0.75 (s, C-19 Me), 2.00 (s), 3.32 (br d, J = 11 Hz, 1H), 4.65 (br m, $W_{1/2}$ = 22 Hz, 1H), 9.33 (v br m, OH, 1H); ms m/z: 459 (15), 399 (100).

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