Synthesis of 5α-Cholestan-6-one Derivatives with Some Substituents at the C-1, C-2, or C-3 Position

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In order to investigate the regioselectivity of Baeyer-Villiger oxidation, thirty 5α-cholestan-6-one derivatives with various substituents (methyl, hydrogen, acetoxymethyl, methoxy, acetyloxy, benzoxyloxy, trifluoroacetoxy, p-toluenesulfonyloxy) at the C-1, C-2, or C-3 position were synthesized from cholesterol. The 6-oxo functional group of 5α-cholestan-6-one derivatives was introduced via hydroboration. The 3α-derivatives were readily obtained by using the native 3α-hydroxyl group of cholesterol. The 3β-isomers were obtained by inversion of the configuration of the 3β-tosylate 24 with tetra-n-butylammonium acetate in refluxing 2-butanone. The 2β-isomers were derived from the 2-ene 43 by bromohydration, LiAlH₄ reduction, and esterification. The 2β- to 2α-hydroxyl group inversion was achieved by Birch reduction of the 2-oxo steroid 51. The 1αderivatives were derived from the known 6β-acetoxy-1α-hydroxy-5α-cholest-2-ene (57).

Keywords—Baeyer-Villiger oxidation; regioselectivity; 5α-cholestan-6-one derivative; hydroboration; configuration inversion; methoxymethyl group

In Baeyer-Villiger oxidation, the migratory aptitude of alkyl groups with retention of configuration is in the order of tertiary > secondary > primary, as expected from their relative abilities to stabilize an electron-deficient, tetrahedral transition state. It was reported that upon the oxidation of 5α-cholestan-6-one-6 (1) with peracid, the 6-oxalactone 3 was obtained as a major product and its regioisomeric 7-oxalactone 2 as a minor product.¹ On the other hand, in the case of 3β-acetoxy-5α-cholestan-6-one (4) the major product was not the 6-oxalactone 6 but the 7-oxalactone 5.¹ During the course of our synthesis of brassinolide (7) and castasterone (8), naturally occurring plant growth hormonal steroids, we also observed a similar unusual phenomenon in the Baeyer-Villiger oxidation of (22R,23R,24S)-2α,3α,22,23-tetraacetoxy-5α-ergostan-6-one (10); the C-7 carbon migrated more readily than the C-5 carbon, affording the 7-oxalactone 9 with ca. 90% regioselectivity.² This high regioselectivity, which can be ascribed to the effect of not only the 3α-acetoxy but also the 2α-acetoxy group, prompted us to investigate the regioselectivity of the Baeyer–Villiger oxidation of 5α-cholestan-6-one derivatives in more detail. We have prepared thirty 5α-cholestan-6-one derivatives with various substituents at the C-1, C-2, or C-3 position from cholesterol (11) and reported the regioselectivity of Baeyer–Villiger oxidation of them.³ In this paper, we present details of the synthesis of the 5α-cholestan-6-one derivatives (4, 13—16, 18—20, 22, 26—30, 32, 38, 41, 42, 46, 47, 49, 50, 53—56, 60—63). The 5α-cholestan-6-one derivatives (4, 13—16) with substituents at the 3β-position were prepared from the known 3β-tetrahydropranyloxy-5α-cholestan-6-one (12).⁴ Acid hydrolysis of 12 gave 3β-hydroxy-5α-cholestan-6-one (13), which was converted into the corresponding acetate 4, the benzoate 14, the trifluoroacetate 15, and the tosylate 16. 3β-Methoxy-5α-cholestan-6-one (22) was synthesized from cholesterol methyl ether (21) as follows. Hydroboration of 21 with BH₃-tetrahydrofuran (THF) complex, followed by
alkaline H₂O₂ oxidation gave 6α-hydroxy-3β-methoxy-5α-cholestane, which, without purification, was oxidized with Jones reagent. The 6-ketone 22 was obtained in 80% yield after chromatography.

The next target compounds were 5α-cholestan-6-one (18), 2α,3α-dihydroxy-5α-cholestan-6-one (19), and 2α,3α-diacetoxy-5α-cholestan-6-one (20). These 6-oxo steroids were prepared from the tosylate 16 according to our procedure used for the synthesis of brassinolide (7).³ Thus, treatment of 16 with lithium bromide in refluxing dimethylformamide gave the 2-ene 17 in 95% yield. Hydrogenation provided 5α-cholestan-6-one (18), quantitatively. Stereoselective α-face hydroxylation of 17 was carried out with a catalytic amount of osmium tetroxide and an excess of N-methylmorpholine N-oxide in tert-BuOH-THF-H₂O (10:3:1) to afford the alkaline H₂O₂ oxidation gave 6α-hydroxy-3β-methoxy-5α-cholestane, which, without purification, was oxidized with Jones reagent. The 6-ketone 22 was obtained in 80% yield after chromatography.

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Next, we synthesized 5α-cholestan-6-one derivatives substituted at the 3α-position. Attempted inversion reaction of the 3β-tosylate 16 with various reagents (AcOK or AcONa/dimethylformamide (DMF) or dimethyl sulfoxide (DMSO), BzONa/DMF or DMSO, KO₃/18-crown-6/DMF-DMSO) and the Mitsunobu reaction of the 3β-ol 13 turned out to be fruitless because of the low yield of the inversion product. Therefore, we adopted the reported method,⁴ which involves the inversion reaction of the 3β-tosyl-6β-ol 24 with tetra-n-butylammonium acetate. The substrate 24 was obtained as follows. Reduction of 13 with lithium aluminum hydride and recrystallization from ethyl acetate gave crystalline 3β,6β-dihydroxy-5α-cholestan-6-one (23) in 75% yield. Other stereoisomers were removed by recrystallization. Treatment of 23 with 1.14 eq of p-toluenesulfonyl chloride and pyridine gave the 3β-monotosylate 24 in 91% yield. Heating of 24 with tetra-n-butylammonium acetate and 2-butanol at reflux temperature gave the inversion product 25, which was then oxidized with Jones reagent to afford 3α-acetoxy-5α-cholestan-6-one (26) in 50% yield. Saponification of 26 with 5% KOH/MeOH gave the 3α-ol 27, which was converted into the benzoate 28, the trifluoroacetate 29, and the tosylate 30. Refluxing of 24 with methanol also gave the inversion product 31. Jones oxidation of 31 gave 3α-methoxy-5α-cholestan-6-one (32) in 50% yield.
The 3β-methyl, 3α- and 3β-acetoxy methyl derivatives 38, 41, 42 of 5α-cholestan-6-one were next synthesized. Acetylation of 23 gave the 3β,6β-diacetate 33. Selective saponification of the 3β-acetyl group followed by Jones oxidation provided the known 6β-acetoxy-5α-
cholestan-3-one (34)\(^4\) in 76\% yield. After exchange of the acetyl group in 34 with a methoxymethyl (MOM) group, the 3-oxo compound 35 was submitted to Wittig reaction with methylenetriphenylphosphorane to give the olefin 36 in 73\% yield from 34. Hydrogenation of 36 provided the saturated compound 37 as a single product. The 3β-configuration was expected from the less hindered, \(\beta\)-face attack of hydrogen. Removal of the MOM group with conc. HCl was followed by Jones oxidation to give 3β-methyl-5β-cholestan-6-one (38) in 90\% yield. Hydroboration of 36, followed by alkaline \(\text{H}_2\text{O}_2\) oxidation yielded, after acetylation, two separable products. Chromatographic separation gave the less polar 3α compound 40 and the more polar 3β compound 39, in 50 and 27\% yields, respectively. These were converted, as described for 38, into the corresponding 3α-6-oxo steroid 42 (\(\delta_H\) 4.04 (2H, d, \(J=8\) Hz, –CH\(_2\)–OAc)) and 3β-6-oxo steroid 41 (\(\delta_H\) 3.90 (2H, d, \(J=5\) Hz, –CH\(_2\)–OAc)), respectively. The stereochemical assignment of 41 and 42 was based on the relative chemical shift due to the
acetoxy methylene in the proton nuclear magnetic resonance (\(^1\)H-NMR) spectra. The 3\(\alpha\)-isomer should have lower chemical shift than the 3\(\beta\)-isomer because of the 1,3-diaxial interaction between the acetoxymethyl and 1\(\alpha\)- and 5\(\alpha\)-hydrogens.

Next we describe the synthesis of 5\(\alpha\)-cholestan-6-one derivatives with C-2 substituents. Reduction of 5\(\alpha\)-cholest-2-en-6-one (17) with lithium aluminum hydride was followed by protection of the resulting 6\(\alpha\)-ol as the MOM ether to give 43. Bromohydrination of 43 with N-bromosuccinimide/H\(_2\)O followed by reduction with lithium aluminum hydride provided the 2\(\beta\)-ol 44 (\(\delta_H\) 4.10 (1H, m, \(W_{1/2} = 8\) Hz, 2\(\alpha\)-H)) in 50\% yield from 17. The reaction possibly proceeded via the 2\(\beta\),3\(\beta\)-epoxide, which suffered further reduction in trans-diaxial fashion. Acetylation of 44, removal of the MOM group, and oxidation with pyridinium chlorochromate in the presence of sodium acetate gave 2\(\beta\)-acetoxy-5\(\alpha\)-cholestan-6-one (46) in 79\% yield. Saponification of 46 with 5\% KOH/MeOH under reflux provided the less polar 5\(\alpha\) compound 47 (19\%, \(\delta_H\) 4.15 (1H, m, \(W_{1/2} = 8\) Hz, 2\(\alpha\)-H)) and the more polar 5\(\beta\) compound 48 (69\%, \(\delta_H\) 3.78 (1H, m, \(W_{1/2} = 24\) Hz, 2\(\alpha\)-H)). 2\(\beta\)-Hydroxy-5\(\alpha\)-cholestan-6-one (47) was converted into the trifluoroacetate 49 and the tosylate 50.

The 2\(\alpha\)-isomers 53—56 were prepared as follows. Jones oxidation of 44 gave the 2-oxo compound 51. This was treated with Li/NH\(_3—\)EtOH and subsequently quenched with dry ammonium chloride to afford, after acetylation, the 2\(\alpha\)-acetate 52 (\(\delta_H\) 4.90 (1H, m, \(W_{1/2} = 24\) Hz, 2\(\beta\)-H)) as a single product in 86\% yield from 44. Regeneration of the 6-oxo functionality gave 2\(\alpha\)-acetoxy-5\(\alpha\)-cholestan-6-one (53) in 95\% yield. 2\(\beta\)-Hydroxy-5\(\alpha\)-cholestan-6-one (54), obtained by saponification of 53, was converted into the trifluoroacetate 55 and the tosylate 56.

The 6-oxo steroids with 1\(\alpha\)-substituents were prepared from the known 6,6-acetoxy-1\(\alpha\)-hydroxy-5\(\alpha\)-cholest-2-ene (57), which was obtained from 34 according to the reported method. Hydrogenation of 57 gave 6\(\alpha\)-acetoxy-1\(\alpha\)-hydroxy-5\(\alpha\)-cholestan-6-one (58). Protection of the 1\(\alpha\)-hydroxyl group of 58 as the MOM ether was followed by saponification to provide the 6\(\alpha\)-ol 59. This was submitted to Jones oxidation and then acid hydrolysis to afford 1\(\alpha\)-hydroxy-5\(\alpha\)-cholestan-6-one (60) in 80\% overall yield. The alcohol 60 was converted into the acetate 61, the trifluoroacetate 62, and the tosylate 63.

### Experimental

Melting points were determined with a hot-stage microscope and are uncorrected. Infrared (IR) spectra were taken with a Hitachi 260-10 spectrometer in chloroform solution. \(^1\)H-NMR spectra were taken with a Hitachi R-24A (60 MHz) or JEOL PS-100 (100 MHz) spectrometer in deuteriochloroform solution with tetramethylsilane as an internal standard. Column chromatography was done on Kieselgel 60 F\(_{254}\) (Merck, 70-230 mesh) and analytical thin layer chromatography (TLC) was carried out on precoated Kieselgel 60 F\(_{254}\) (Merck, 0.25 mm thickness). Work-up refers to dilution with water, extraction with the organic solvent indicated in parenthesis, washing of the extract to neutrality, drying over anhydrous magnesium sulfate, filtration, and removal of the solvent under reduced pressure. The following abbreviations are used: ether, diethyl ether; MeOH, methanol; EtOAc, ethyl acetate; CHCl\(_3\), chloroform; CH\(_2\)Cl\(_2\), dichloromethane.

**3\(\beta\)-Hydroxy-5\(\alpha\)-cholestan-6-one (13)** — The crude 3\(\beta\)-tetrahydropranyloxy-5\(\alpha\)-cholestan-6-one (31 g) obtained from cholesterol (11) according to the reported method was treated with 6 M HCl (50 ml) and THF (400 ml) at room temperature for 1 h. Work-up (ether) and chromatography on silica gel (150 g) with benzene—EtOAc (10:1) gave the 3\(\beta\)-ol 13 (22.4 g, 75\% from 11), mp 142-144 °C (MeOH). IR \(\nu_{\text{max}}\) cm\(^{-1}\): 1710. \(^1\)H-NMR \(\delta_H\): 0.66 (3H, s, 18-H\(_3\)), 0.74 (3H, s, 19-H\(_3\)), 0.85 (6H, d, \(J = 6\) Hz, 26-H\(_3\), 27-H\(_3\)), 3.54 (1H, m, 3-H). Anal. Calcd for C\(_{27}\)H\(_{46}\)O\(_2\): C, 80.54; H, 11.52. Found: C, 80.60; H, 11.54.

**3\(\beta\)-Acetoxy-5\(\alpha\)-cholestan-6-one (4)** — The 3\(\beta\)-ol 13 (225 mg, 0.498 mmol) in pyridine (1 ml) was treated with acetic anhydride (1 ml) at room temperature overnight. Work-up (EtOAc) and chromatography on silica gel (20 g) with benzene—EtOAc (10:1) gave the 3\(\beta\)-ole (13, 225 mg, 0.498 mmol) in pyridine (1 ml) was treated with acetic anhydride (1 ml) at room temperature overnight. Work-up (EtOAc) and chromatography on silica gel (20 g) with benzene gave the acetate 4 (182 mg, 82\%), mp 129—130 °C (MeOH). \(^1\)H-NMR \(\delta_H\): 0.67 (3H, s, 18-H\(_3\)), 0.80 (3H, s, 19-H\(_3\)), 0.85 (6H, d, \(J = 6\) Hz, 26-H\(_3\), 27-H\(_3\)), 2.00 (3H, s, acetyl), 4.83 (1H, m, 3-H). Anal. Calcd for C\(_{29}\)H\(_{48}\)O\(_3\): C, 78.32; H, 10.88. Found: C, 78.56; H, 10.85.

**3\(\beta\)-Benzyloxy-5\(\alpha\)-cholestan-6-one (14)** — The 3\(\beta\)-ol 13 (320 mg, 0.796 mmol) in pyridine (2 ml) was treated with benzyol chloride (0.2 ml) at room temperature overnight. Work-up (EtOAc) and chromatography on silica gel (20 g)
with benzene gave the benzotate 14 (368 mg, 94%), mp 172—174 °C (MeOH). 1H-NMR δ: 0.67 (3H, s, 18-H3), 0.81 (3H, s, 19-H3), 0.85 (6H, d, J = 6 Hz, 26-H3, 27-H3), 4.85 (1H, m, 3-H), 7.30—7.60 (3H, m, benzoyl), 7.90—8.10 (2H, m, benzoyl). Anal. Calcd for C34H52O4S: C, 73.34; H, 9.41. Found: C, 73.46; H, 9.50.

3β-Trifluoroacetoxy-5α-cholestan-6-one (15)—The 3β-ol 13 (402 mg, 1.0 mmol) in CHCl3—pyridine (1:1, 2 ml) was treated with trifluoroacetic anhydride (0.3 ml) at room temperature overnight. Work-up (EtOAc) and chromatography on silica gel (20 g) with benzene gave the trifluoroacetate 15 (403 mg, 84%), mp 143—145 °C (CHCl3—MeOH). 1H-NMR δ: 0.66 (3H, s, 18-H3), 0.79 (3H, s, 19-H3), 0.86 (6H, d, J = 6 Hz, 26-H3, 27-H3), 4.86 (1H, m, 3-H). Anal. Calcd for C34H52O6F3: C, 69.85; H, 9.10. Found: C, 69.77; H, 8.98.

3β-p-Toluenesulfonyloxy-5α-cholestan-6-one (16)—The 3β-ol 13 (4.02 g, 10.0 mmol) in pyridine (30 ml) was treated with p-toluenesulfonyl chloride (30 mg) under a hydrogen atmosphere at room temperature overnight. Work-up (EtOAc) and chromatography on silica gel (100 g) with benzene gave the tosylate 16 (5.0 g, 90%), mp 175—177 °C (MeOH). 1H-NMR δ: 0.63 (3H, s, 18-H3), 0.71 (3H, s, 19-H3), 0.85 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.90 (3H, d, J = 6 H2, 21-H3), 2.45 (3H, s, tosyl), 4.50 (1H, m, 3-H), 7.40 (2H, d, J = 8 Hz, tosyl), 7.90 (2H, d, J = 8 Hz, tosyl). Anal. Calcd for C34H52O4S: C, 74.06; H, 10.02. Found: C, 74.03; H, 9.94.

3α,3β-Dihydroxy-5α-cholestan-6-one (17)—The 2-ene 17 (10.0 g, 26 mmol) in dimethylformamide (70 ml) was treated with anhydrous lithium bromide (10 g, 115 mmol) under reflux for 1 h. Work-up (EtOAc) and chromatography on silica gel (100 g) with benzene gave the 2-ene 17 (16.4 g, 95%), mp 97—98 °C (MeOH). IR νmax cm⁻¹: 1710. 1H-NMR δ: 0.66 (3H, s, 18-H3), 0.84 (3H, s, 19-H3), 0.86 (6H, d, J = 6 Hz, 26-H3, 27-H3), 1.99 (3H, s, acetyl), 2.08 (3H, s, acetyl), 2.56 (1H, dd, J = 22 Hz, 26-H3), 4.92 (1H, m, W1/2 = 22 Hz, 26-H3), 5.36 (1H, m, W1/2 = 7 Hz, 3β-H). Anal. Calcd for C29H43O4: C, 80.58; H, 9.95. Found: C, 80.68; H, 9.93.

3α,3β-Diacetoxy-5α-cholestan-6-one (18)—The 3α,3β-diol 19 (7.96 g, 91%) in EtOAc (30 ml) was treated with 3% Pd-C (30 mg) under a hydrogen atmosphere at room temperature overnight. Filtration and removal of the solvent gave 3α,3β-cholestan-6-one (18) (300 mg, 0.78 mmol) in EtOAc (20 ml) was treated with 5% Pd-C (30 mg) under a hydrogen atmosphere at room temperature overnight. Work-up (CH2Cl2) and chromatography on silica gel (30 g) with benzene—EtOAc (1:2) gave the 2a,3α-diol 19 (0.97 g, 89%), mp 206—207 °C (CHCl3—MeOH).

3α,3β-Diacetoxy-5α-cholestan-6-one (19)—The 2-ene 17 (3.0 g, 26 mmol) in tert-BuOH—THF—H2O (10 : 3 : 1, 10 ml) was treated with osmium tetroxide (20 mg) and N-methylmorpholine N-oxide (750 mg, 6.4 mmol) at room temperature overnight. Work-up (CH2Cl2) and chromatography on silica gel (30 g) with benzene—EtOAc (1:2) gave the 2a,3α-diol 19 (0.87 g, 85%), mp 120—122 °C (CHCl3—MeOH).

3α-Methoxy-5α-cholestan-6-one (20)—The 3α,3β-diol 19 (400 mg, 0.957 mmol) in pyridine (5 ml) was treated with acetic anhydride (4 ml) at 60 °C overnight. Work-up (EtOAc) and chromatography on silica gel (30 g) with benzene—EtOAc (1:2) gave the diacetate 20 (470 mg, 98%), mp 152—153 °C (MeOH). 1H-NMR δ: 0.68 (3H, s, 18-H3), 0.88 (3H, s, 19-H3), 0.86 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.92 (3H, d, J = 6 Hz, 21-H3), 1.99 (3H, s, tosyl), 2.08 (3H, s, acetyl), 2.56 (1H, dd, J = 6 Hz, 3-H), 4.92 (1H, m, W1/2 = 22 Hz, 26-H3), 5.36 (1H, m, W1/2 = 7 Hz, 3β-H). Anal. Calcd for C29H45O4: C, 84.31; H, 11.53. Found: C, 84.37; H, 11.33.

5α-Cholestan-6-one (21)—The 3α-ol 21 (10 g, 22.5 mmol) in THF (50 ml) was treated with p-toluenesulfonyl chloride (3.5 g, 20.0 mmol) at room temperature overnight. Work-up (CH2Cl2) and chromatography on silica gel (30 g) with benzene—EtOAc (1:2) gave the 3α-tosylate 21 (14.5 g, 69%), mp 135—136 °C. 1H-NMR δ: 0.69 (3H, s, 18-H3), 0.86 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.90 (3H, d, J = 6 Hz, 21-H3), 1.01 (3H, s, 19-H3), 2.03 (3H, s, acetyl), 3.71 (1H, m, W1/2 = 7 Hz, 6β-H), 5.08 (1H, m, W1/2 = 7 Hz, 3β-H). This product 25 (3.2 g, 7.17 mmol) in acetone (100 ml) was treated with 1 eq of Jones reagent at room temperature for 10 min. Work-up (ether) and chromatography on silica gel (100 g) with benzene—EtOAc (1:2) gave the 3α-tosylate 21 (14.5 g, 69%), mp 135—136 °C. 1H-NMR δ: 0.69 (3H, s, 18-H3), 0.75 (3H, s, 19-H3), 0.86 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.90 (3H, d, J = 6 Hz, 21-H3), 2.04 (3H, s, acetyl), 2.54 (1H, dd, J = 11 Hz, 5Hz, 5α-H), 5.09 (1H, m, W1/2 = 7 Hz, 3β-H). Anal. Calcd for C28H42O4S: C, 78.32; H, 10.88. Found: C, 78.52; H, 10.95.

3α-Hydroxy-5α-cholestan-6-one (22)—The acetate 26 (2.34 g, 5.04 mmol) in MeOH (50 ml) was treated with...
5\% KOH/MeOH (20 ml) at room temperature for 3 h. Work-up (ether) and chromatography on silica gel (30 g) with benzene−EtOAc (50 : 1) gave the 3α-ol (1.5 g, 72\%), mp 158−160 °C (ether−MeOH) (lit. 39 mp 160 °C). IR νmax cm⁻¹: 1712. 1H-NMR δ: 0.64 (3H, s, 18-H3), 0.71 (3H, s, 19-H3), 0.85 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.89 (3H, d, J = 6 Hz, 21-H3), 4.12 (1H, m, W1/2 = 8 Hz, 3β-H).

3α-Benzoyloxy-5α-cholestan-6-one (28) — The 3α-ol (300 mg, 0.746 mmol) was converted, as described for 14, into the benzoate 28 (374 mg, 98\%), mp 137−138 °C (ether−MeOH). 1H-NMR δ: 0.66 (3H, s, 18-H3), 0.79 (3H, s, 19-H3), 0.85 (6H, d, J = 6 Hz, 26-H3, 27-H3), 2.67 (1H, dd, J = 11, 5 Hz, 5α-H), 5.36 (1H, m, W1/2 = 8 Hz, 3β-H), 7.30−7.60 (3H, m, benzoyl), 7.90−8.10 (2H, m, benzoyl). Anal. Calc'd for C24H30O5: C, 80.58; H, 9.95. Found: C, 80.57; H, 9.92.

3α-Trifluoroacetoxyl-5α-cholestan-6-one (29) — The 3α-ol (270 mg, 0.746 mmol) was converted, as described for 15, into the trifluoroacetate 29 (324 mg, 87\%), mp 105−106 °C (CHCl3−MeOH). 1H-NMR δ: 0.68 (3H, s, 18-H3), 0.78 (3H, s, 19-H3), 0.84 (6H, d, J = 6 Hz, 26-H3, 27-H3), 2.54 (1H, dd, J = 10, 6 Hz, 5α-H), 5.33 (1H, m, W1/2 = 8 Hz, 3β-H). Anal. Calc'd for C23H32F3O3: C, 69.85; H, 9.10. Found: C, 70.10; H, 8.87.

3α-Methoxy-5α-cholestan-6-one (30) — The mixture of the tosylate 24 (1.0 g, 1.79 mmol) and MeOH (50 ml) was refluxed for 2 d. Work-up (ether) and chromatography on silica gel (20 g) with benzene−EtOAc (20 : 1) gave the 3α-methoxy-6α-ol 31 (390 mg, 54\%), oil. 1H-NMR δ: 0.68 (3H, s, 18-H3), 0.85 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.90 (3H, s, 19-H3), 2.39 (3H, s, tosyl), 2.54 (1H, dd, J = 10, 6 Hz, 5α-H), 5.33 (1H, m, W1/2 = 8 Hz, 3β-H). Anal. Calc'd for C24H30O3S: C, 78.34; H, 10.88. Found: C, 78.32; H, 10.88.

6α-Methyl-5α-cholestan-3-one (32) — The mixture of the ketone 35 (2.3 g, 5.16 mmol) in THF (10 ml) was treated with conc HCl (0.2 ml) at 50 °C for 5 h. Work-up (ether) gave a crude product, which was oxidized with Jones reagent to give the 3β-methyl steroid 38 (260 mg, 98\%), mp 102−104 °C (MeOH). 1H-NMR δ: 0.65 (3H, s, 18-H3), 0.68 (3H, s, 19-H3), 0.85 (6H, d, J = 6 Hz, 26-H3, 27-H3). Anal. Calc'd for C24H30O3: C, 83.93; H, 12.07. Found: C, 83.87; H, 12.01.

3- and 3β-Acetoxy-5α-cholestan-6-one (42 and 41) — The olefin 36 (1.0 g, 2.25 mmol) in THF (10 ml) was treated with 1 m BH₃−THF complex solution (6 ml) at room temperature for 1.5 h. Water was carefully added to decompose the excess reagent. Then, 2 m NaOH (3 ml) and 30\% H₂O₂ (3 ml) were added. Stirring was continued at room temperature for 1 h. Work-up (ether) followed by acetylation with acetic anhydride (4 ml) and pyridine (5 ml) at room temperature for 18 h gave two separable products. Work-up (EtOAc) and chromatography on silica gel (50 g) with benzene−EtOAc (100 : 1) gave the less polar product 40 (570 mg, 50\%) and the more polar product 39 (310 mg, 27\%).
The less polar acetate 40 (570 mg) in THF (10 ml) was treated with 6 M HCl (2 ml) at room temperature for 15 h and then treated with Jones reagent in acetone (10 ml). Work-up (ether) and chromatography on silica gel (30 g) with benzene–EtOAc (100:1) gave the 3β-compound 42, mp 68–72 °C (MeOH–ether). 1H-NMR δ: 0.65 (3H, s, 18-H3), 0.74 (3H, s, 19-H3), 0.85 (6H, d, J = 6 Hz, 26-H3, 27-H3), 2.02 (3H, s), 4.04 (2H, d, J = 8 Hz, –CH2–OAc). Anal. Calcd for C30H32O3: C, 77.55; H, 10.99. Found: C, 77.47; H, 10.92.

The more polar acetate 39 (310 mg) was similarly converted into the 6-oxo compound 41 (210 mg, 71%), amorphous solid. 1H-NMR δ: 0.65 (3H, s, 18-H3), 0.70 (3H, s, 19-H3), 0.85 (6H, d, J = 6 Hz, 26-H3, 27-H3), 2.02 (3H, s), acetyl), 3.90 (2H, d, J = 8 Hz, -CH2-OAc).

6β-Methoxymethoxy-5α-cholestan-2-one (43) — 5α-Cholesterol-2-en-6-one (17) (17 g, 44.3 mmol) in THF (300 ml) was treated with lithium aluminum hydride (2.0 g, 52.6 mmol) at room temperature for 1 h. Work-up (ether) and chromatography on silica gel (100 g) with benzene gave the product 43 (15.2 g, 80%), mp 75–76 °C (MeOH). 1H-NMR δ: 0.68 (3H, s, 18-H3), 0.88 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.92 (3H, s, 19-H3), 3.37 (3H, s, –OCH3), 3.66 (1H, m, W1/2 = 8 Hz, 6-H), 4.63 (2H, dd, J = 10, 7 Hz, –OCH2O–), 5.52 (2H, m, 2-H, 3-H). Anal. Calcd for C29H48O3: C, 80.87; H, 11.70. Found: C, 80.94; H, 11.66.

6β-Methoxymethoxy-5α-cholestan-2β-ol (44) — The 2β-ol 44 (8.8 g, 20.5 mmol) in glime–H2O (15:1, 160 ml) was treated with N-bromosuccinimide (5.0 g, 24.5 mmol) at room temperature for 1 h. Work-up (ether) gave a crude product, which in THF (150 ml) was treated with lithium aluminum hydride (1.5 g, 39.5 mmol) under reflux for 2 h. Work-up (ether) and chromatography on silica gel (50 g) with benzene–EtOAc (50:1) gave the 2β-ol 44 (5.5 g, 60%), mp 140–141 °C (MeOH). 1H-NMR δ: 0.69 (3H, s, 18-H3), 0.86 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.91 (3H, s, 19-H3), 3.37 (3H, s, –OCH3), 3.65 (1H, m, W1/2 = 8 Hz, 6-H), 4.15 (1H, m, W1/2 = 9 Hz, 2β-H), 4.62 (1H, m, W1/2 = 8 Hz, 2α-H). Anal. Calcd for C27H46O2: C, 80.54; H, 11.52. Found: C, 80.64; H, 11.55.

Further elution with the same solvent gave the more polar 5β-steroid 48 (2.86 g, 69%), amorphous solid. 1H-NMR δ: 0.66 (3H, s, 18-H3), 0.86 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.91 (3H, d, J = 6 Hz, 21-H3), 0.92 (3H, s, 19-H3), 3.76 (1H, m, W1/2 = 24 Hz, 2α-H). Anal. Calcd for C29H46O3: C, 78.54; H, 11.52. Found: C, 80.61; H, 11.57.

6β-Trifluoroacetoxy-5α-cholestan-6-one (49) — The 6β-ol 47 (94 mg, 0.234 mmol) was converted, as described for 15, into the trifluoroacetate 49 (105 mg, 80%), mp 176–177 °C (acetone). 1H-NMR δ: 0.64 (3H, s, 18-H3), 0.88 (3H, s, 19-H3), 5.30 (1H, m, W1/2 = 8 Hz, 2α-H). Anal. Calcd for C29H45F3O3: C, 69.85; H, 9.10. Found: C, 70.02; H, 9.14.

2β-p-Toluenesulfonyloxy-5α-cholestan-6-one (50) — The 2β-ol 47 (100 mg, 0.249 mmol) was converted, as described for 16, into the tosylate 50 (115 mg, 83%), mp 153–155 °C (MeOH–ether). 1H-NMR δ: 0.62 (3H, s, 18-H3), 0.85 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.98 (3H, s, 19-H3), 2.40 (3H, s, tosyl), 5.43 (1H, m, W1/2 = 8 Hz, 2α-H), 7.30 (2H, d, J = 8 Hz, tosyl), 7.72 (2H, d, J = 8 Hz, tosyl). Anal. Calcd for C34H32O2S: C, 73.34; H, 9.41. Found: C, 73.28; H, 9.56.

6β-Methoxymethoxy-5α-cholestan-2-one (51) — The 2β-ol 44 (3.0 g, 6.72 mmol) in acetone (50 ml) was treated with 1 eq of Jones reagent at room temperature for 10 min. Work-up (ether) gave the 2-oxo steroid 51 (3.0 g, mp 89–90 °C (MeOH). IR νmax cm⁻¹: 1710. IR-νmax cm⁻¹: 1710. 1H-NMR δ: 0.65 (3H, s, 18-H3), 0.84 (6H, d, J = 6 Hz, 26-H3, 27-H3), 0.89 (3H, s, 19-H3), 3.29 (3H, s, –OCH3), 3.70 (1H, m, W1/2 = 8 Hz, 6-H), 4.55 (2H, d, J = 10, 7 Hz, –OCH2O–). Anal. Calcd for C29H46O3: C, 77.97; H, 11.28. Found: C, 78.15; H, 11.06.

2α-Acetoxy-6β-methoxymethoxy-5α-cholestan-6-one (52) — A solution of the 2-oxo steroid 51 (2.76 g, 6.18 mmol) in THF (80 ml) was added to a solution of liquid ammonia (160 ml) and ethanol (10 ml) at −78 °C under an argon atmosphere. Then, small pieces of lithium (2.0 g) were added portionwise. The mixture was stirred at −78 °C for...
30 min. Then, dry ammonium chloride (50 g) was added portionwise to the reaction mixture at −78 °C. Work-up (ether) gave a crude product, which in pyridine (20 ml) was treated with acetic anhydride (10 ml) at room temperature overnight. Work-up (EtOAc) and chromatography on silica gel (60 g) with benzene gave the 2-acetate 52 (2.62 g, 91%), mp 79–80 °C (MeOH).

1H-NMR: δ: 0.69 (3H, s, 18-H3), 0.86 (6H, d, J = 6 Hz, 26-H3, 27-H3), 1.02 (3H, s, 19-H3), 1.99 (3H, s, acetyl), 3.30 (3H, s, −OCH3), 3.60 (1H, m, W1/2 = 7 Hz, 6z-H), 4.50 (2H, dd, J = 10, 7 Hz, −OCH2O−), 4.85 (1H, m, W1/2 = 24 Hz, 2β-H).

**Anal. Caled for C34H52O4S:** C, 73.34; H, 9.41. Found: C, 73.29; H, 9.43.

### References


