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A CONVENIENT SYNTHESIS OF 1α- AND 1β-HYDROXYCHOLESTEROL[1]

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Abstract—An efficient procedure for the preparation of 1α-hydroxycholesterol 3-acetate **4** is described, which starts from cholesterol and involves as key steps transannular cyclization of the ten-membered ring containing (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5-one **1** to the oxetane derivative 1α,5-epoxy-5α-cholestan-3β-ol acetate **3**, and opening of the four-membered ether ring in the latter compound. 1β-Hydroxycholesterol diacetate **9** was obtained by oxidation of **4** to the 1-oxo derivative **8**, followed by metal hydride reduction and acetylation.

The recent finding that vitamin D_3, a steroidal hormone, must be hydroxylated at C(25) in liver and subsequently at C(1) in kidney, in order to produce its physiological activity in increased calcium transport, bone mineral mobilization and calcification, has stimulated much interest in the chemical introduction of the hydroxyl group at these two positions. The resulting 1α,25-dihydroxycholecalciferol, which was synthesized chemically first by DeLuca *et al.*[2] by more than 20 steps from *i*-homocholanic acid methyl ether, and later more conveniently by Barton *et al.*,[3] is the most potent metabolite of vitamin D_3.[4] Since the "artificial" 1α-hydroxy analogue of vitamin D_3 exhibits comparable biological activity to 1α,25-dihydroxy-vitamin D_3, and is less expensive and easier to prepare, Holick *et al.*[5] suggested that 1α-hydroxy-vitamin D_3 could be more attractive as a drug for the treatment of renal osteodystrophy and hypoparathyroidism.

In a preliminary communication,[6] some time ago, we described briefly one of the first successful procedures for the preparation of 1α-hydroxycholesterol (in the form of its 3-acetate),‡ an important product since it represents the key intermediate in the majority of syntheses of 1α-hydroxy-vitamin D_3.[5,8]§ Although several ways for obtaining 1α-hydroxycholesterol have been reported subsequently,[8,10] the convenience and overall yield of our synthetic approach, starting from cholesterol, parallel those of the best methods described so far. For that reason, in the present paper, we wish to give more detailed information on our synthesis of 1α-hydroxycholesterol 3-acetate, and also of the new compound 1β-hydroxycholesterol diacetate.

For the introduction of the oxygen function at C(1) the ten-membered ring containing (*E*) - 3β - acetoxy - 5,10 - seco - 1(10) - cholesten - 5 - one **1**[11] was required, which could be readily prepared, in 56% yield, from cholesterol, by the reaction sequence given in Scheme 1.

When **1** was subjected to UV irradiation in acetone solution with a high pressure mercury lamp (TQ 150 Z2), it underwent a transannular Paterno–Büchi reaction (cycloaddition of oxygen of the carbonyl chromophore to C(1)

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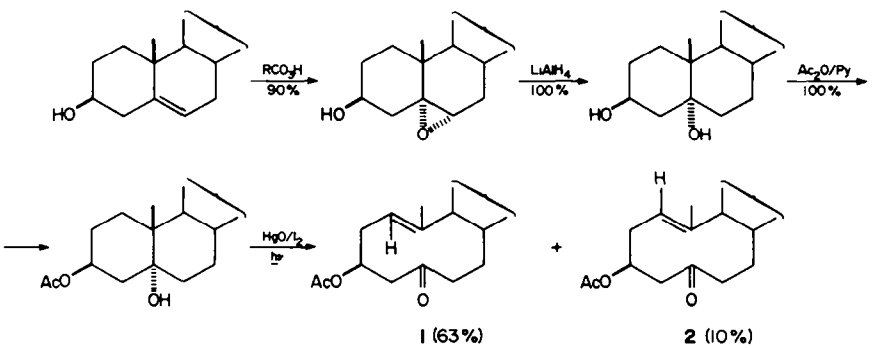
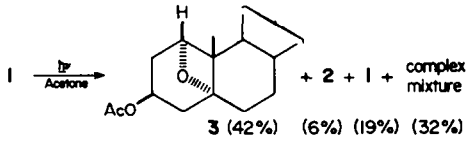
‡The compound described by Pelc and Kodicek[7] as 1α-hydroxycholesterol had physical constants which differed markedly from those reported by other authors.

§To our knowledge, only two synthetic routes leading to 1α-hydroxy-vitamin D_3 do not proceed via 1α-hydroxycholesterol.[9]



Scheme 1.

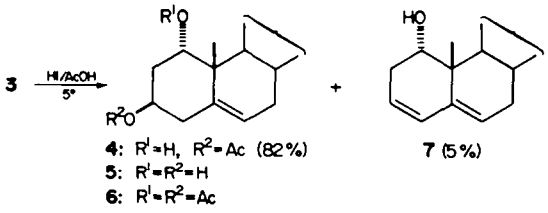
of the olefinic double bond) to give, as shown in Scheme 2, a photoproduct with an oxetane structure, i.e. 1α,5 - epoxy - 5α - cholestan - 3β - ol acetate 3,† in 42% yield; the other products isolated from the irradiated mixture were (Z) - 3β - acetoxy - 5,10 - seco - 1(10) - cholesten - 5 - one 2 (6%), starting material 1 (19%) and a complex mixture (32%) which was not further investigated. A more detailed study of this photolytic reaction has shown that



Scheme 2.

UV irradiation of 1 in dioxane, acetone, benzene, methanol or isopropanol solution leads in all cases to the intramolecular Paterno–Büchi reaction and predominant formation of the oxetane derivative 3, but the highest chemical yield of this photoproduct was obtained when irradiation was performed in acetone for 3.5 h. Prolonged irradiation until complete disappearance of the starting seco-ketone 1 caused the amount of the oxetane product 3 to decrease and that of the complex mixture to increase.

Treatment of the oxetane derivative 3 with hydriodic acid in glacial acetic acid at 5° resulted in the opening of the four-membered ether ring and formation (Scheme 3) of 1α-hydroxycholesterol 3-acetate 4 in high yield (82%), accompanied by a small amount (5%) of 1α-hydroxy-3,5-cholestadiene 7.‡ The structures of both 1α-hydroxy compounds 4 and 7 were confirmed by their spectral data and, in the case of product 4, by hydrolysis to 1α-hydroxycholesterol 5 and catalytic hydrogenation of the latter compound to the known 5α-cholestane-1α,3β-diol.[12] The overall yield of 4, starting from cholesterol, amounts to about 20%.



Scheme 3.

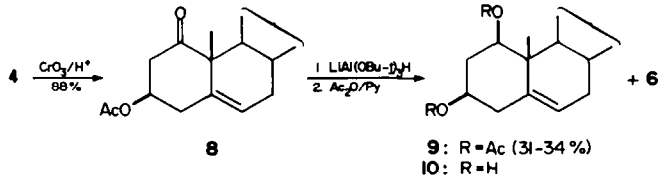
For further transformation into 1α-hydroxy-vitamin D_3,[8a,8b,8c] the monoacetate 4 was converted to the diacetate 6 which, upon bromination at C(7) and dehydrobromination[13] followed by chromatographic separation on silica gel-silver nitrate, afforded 19% of 4,6- and 28% of 5,7 - cholestadiene - 1α,3β - diol diacetate. UV irradiation of the latter compound produced 1α-hydroxy-previtamin D_3 diacetate which, upon refluxing in cyclohexane, careful saponification and chromatography on silica gel, gave 1α-hydroxy-vitamin D_3.

Jones oxidation of the monoacetate 4 afforded 3β-acetoxy - 5 - cholesten - 1 - one (8, Scheme 4) in 88% yield. When this ketone 8 was reduced with lithium tri(t-butoxy)aluminium hydride in tetrahydrofuran (at 0–5°) it gave, in nearly quantitative yield, a 1:2.5 mixture of 1α- and 1β-hydroxycholesterol 3-acetates,§ from which, upon acetylation and chromatography on silica gel, the pure 1β-hydroxycholesterol diacetate 9 was obtained (in 31–34% yield, based on 8).¶ Hydrolysis of 9 gave quantitatively 1β-hydroxycholesterol 10.

Further work is in progress in order to investigate the possibility of transforming the diacetate 9 into 1β-hydroxy-vitamin D_3.

EXPERIMENTAL[‖]

All m.ps are uncorrected. Optical rotations were measured in $CHCl_3$ soln. NMR spectra were obtained at 100 MHz with a Varian HA-100-D spectrometer in $CDCl_3$ soln, using TMS as internal standard; chemical shifts are reported in δ values (abbreviations: s singlet, d doublet, t triplet, q quartet, m multiplet). IR spectra were determined on Perkin–Elmer instruments, models 221 and 337. UV absorption spectra were recorded with a Perkin–Elmer 137 UV spectrophotometer. Mass spectra were taken on an Atlas CH4 mass spectrometer. Irradiations were carried out in a cylindrical flask fitted with a central water-cooled immersion well for the light source. The separation of products was monitored by TLC on silica gel (Stahl) with benzene–EtOAc (9:1 or 7:3), detection being effected with 50% H_2SO_4. Silica gel (0.05–0.2 mm) or $AgNO_3$-impregnated silica gel[14] (0.05–0.2 mm) were used for column chromatography. Light petroleum refers to the fraction boiling at 40–60°.



Scheme 4.

†The structure and stereochemistry of the oxetane photoproduct 3 were established on the basis of IR, NMR and mass spectral data, and chemical behaviour.[6] The possible mechanism of formation of 3 from 1 was discussed previously.[6]

‡When this experiment was run without temperature control, opening of the oxetane ring in 3 with acetic acid elimination to give the diene 7, was the preferred reaction path.

§This ratio was estimated from the NMR spectrum (relative intensities of the signals for AcO-1 and Me-19) of the mixture of diacetates 6 and 9, obtained by acetylation of the crude reduction product. In a similar way, it was found that reduction of 8 with lithium aluminium hydride in diethyl ether (at 20°) and sodium borohydride in methanol (at 5°) gave the 1α- and 1β-epimeric alcohols in ratios of 1:1.5 and 1:2, respectively.

¶It should be noted that controlled acetylation (lesser excess of acetic anhydride and shorter reaction time) of the reduction mixture leaves about 47% of the epimeric 1α- and 1β-hydroxycholesterol 3-acetates unchanged and that these can be re-oxidized to ketone 8, thus providing the possibility to increase the actual yield of diacetate 9 (see Experimental, Procedure B).

‖We wish to thank Dr. R. Tasovac (Microanalytical Laboratory, Faculty of Science, Belgrade) for carrying out elemental microanalyses. Spectral determinations were performed at Ciba-Geigy AG, Basle, Switzerland (direction Dr. H. Hürzeler and Dr. H. Fuhrer) and at the Faculty of Science, Belgrade (direction Prof. D. Jeremić).

5,6α-Epoxy-5α-cholestan-3β-ol. Cholesterol (60 g) in CH_2Cl_2 (225 ml) was treated with 85% *m*-chloroperbenzoic acid (34 g in 340 ml CH_2Cl_2) at room temp. for 30 min. The mixture was worked up in the usual way to give 5,6α - epoxy - 5α - cholestan - 3β - ol (56 g, 90%), which was recrystallized from aqueous acetone, m.p. 142–143° (lit.[15] 141–143°).

4α-Cholestane-3β,5-diol 3-acetate. 5,6α-Epoxy-5α-cholestan-3β-ol (50 g) was reduced with $LiAlH_4$ in the usual way to give 5α-cholestane-3β,5-diol[16] (50 g, 100%). This diol, without further purification, was acetylated with Ac_2O-pyridine, affording 5α-cholestane-3β,5-diol 3-acetate (55.5 g, 100%), which was recrystallized from acetone, (53 g, 95.5%), m.p. 185° (lit.[16] 185°).

Fragmentation of 5α-cholestane-3β,5-diol 3-acetate. A stirred suspension of 5α-cholestane-3β,5-diol 3-acetate (20 g), yellow mercuric oxide (30 g) and iodine (30 g) in CCl_4 (400 ml) was irradiated for 2 h at room temp. with a 500 W tungsten lamp placed in a central air-cooled tube.† The solid was removed by filtration and the filtrate washed successively with aq $Na_2S_2O_3$, aq $NaHCO_3$ and H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was crystallized from acetone-MeOH, giving (*E*) - 3β - acetoxy - 5,10 - seco - 1(10) - cholesten - 5 - one **1** (12.5 g, 63%), which was recrystallized from the same solvent mixture (12.1 g, 61%), m.p. 136° (lit.[11a] 136°). The mother liquors from these crystallizations were combined and evaporated *in vacuo* to dryness, and the residue (about 10 g) was chromatographed on 200 g of silica gel. The benzene and benzene–ether (99:1) eluates afforded (*Z*) - 3β - acetoxy - 5,10 - seco - 1(10) - cholesten - 5 - one **2** (2.1 g, 10.5%), which was twice recrystallized from acetone (1.4 g, 7%), m.p. 138° (lit.[11a] 138°).

UV irradiation of (E) - 3β - *acetoxy* - 5,10 - *seco* - 1(10) - *cholesten* - 5 - *one* **1**. A soln of **1** (1.0 g) in acetone (250 ml) was irradiated with a high pressure mercury lamp TQ 150 Z2 (Hanau) at room temp. for 3.5 h. It was then evaporated *in vacuo* and the oily residue chromatographed on silica gel (30 g). Benzene–ether (99:1) eluted **2** (60 mg, 6%), m.p. 138° (acetone). Benzene–ether (98:2) eluates gave 190 mg (19%) of unchanged **1**, m.p. 136° (acetone–MeOH). Benzene–ether (97:3 and 96:4) eluted 1α,5 - epoxy - 5α - cholestan - 3β - ol acetate[6] **3** (420 mg, 42%), which was twice recrystallized from acetone (344 mg, 34.5%), m.p. 101–102°. $[\alpha]_D^{20}$ +20° ± 2° (*c* = 1.0); IR (CH_2Cl_2): ν_{max} 1732, 1238, 1025 cm^{-1}; NMR: δ 0.66 (Me-19, s), 0.84 (Me-18, s), 0.86 (Me-26 and Me-27, d), 0.90 (Me-21, d), 2.01 (AcO, s), 3.94 (H-1, d), 4.20 (H-3, m); MS: *m/e* 444 (M). (Found: C, 78.18; H, 10.87. $C_{29}H_{48}O_3$ requires: C, 78.32; H, 10.88%).

Further elution with more polar solvents afforded a complex mixture (320 mg, 32%), which was not further investigated.

Similar UV irradiation of **1** (1.0 g) in different solvents (250 ml) at room temp gave the following results. In dioxane after 4 h: 3% of **2**, 10% of **1**, 34% of **3**, 55% of the complex mixture; in benzene after 25 h: 2% of **2**, 58% of **1**, 25% of **3**, 15% of the complex mixture; in MeOH after 4 h: 1% of **2**, 5% of **1**, 25% of **3**, 65% of the complex mixture; in isopropanol after 3 h: 1% of **2**, 20% of **1**, 28% of **3**, 50% of the complex mixture.

Opening of the ether ring in 1α,5 - *epoxy* - 5α - *cholestan* - 3β - *ol acetate* **3**. The oxetane derivative **3** (3.40 g) was dissolved in glacial AcOH (70 ml) and cooled to 5°. To this semi-solid soln a cooled soln of hydriodic acid (1.45 ml of 57% HI aq) in glacial AcOH (45 ml) was added portionwise. The resulting mixture was left at 5° for 20 min, diluted with H_2O and extracted with ether. The ethereal extract was washed with H_2O, saturated aq $NaHCO_3$ and H_2O, dried over $MgSO_4$ and evaporated *in vacuo* to dryness, leaving a crystalline solid which was chromatographed on silica gel (125 g). Elution with benzene afforded 162 mg (5%) of 3,5 - cholestadien - 1α - ol[6] **7**, which was recrystallized from MeOH (136 mg, 4.5%), m.p. 95–96°. IR (KBr): ν_{max} 3360, 1640 cm^{-1}; UV (MeOH): λ_{max} 228 (ε 18,500), 236 (ε 20,400), 244 nm (ε 12,800). (Found: C, 81.03; H, 11.32. $C_{27}H_{44}O \cdot CH_3OH$ requires: C, 80.71; H, 11.61%).

Benzene–ether (96:4 and 95:5) eluates gave 2.81 g (82.5%) of 1α-hydroxycholesterol 3-acetate[6] **4**, which was recrystallized from acetone (2.58 g, 76%), m.p. 166–168°. $[\alpha]_D^{20}$ −41° (*c* = 0.70); IR (KBr): ν_{max} 3460, 1715, 1272 cm^{-1}; NMR: δ 0.66 (Me-18, s), 0.85 (Me-26 and Me-27, d), 0.90 (Me-21, d), 1.02 (Me-19, s), 1.99 (AcO, s), 3.82 (H-1, m), 5.00 (H-3, m), 5.58 (H-6, m). (Found: C, 78.31; H, 10.69. $C_{29}H_{48}O_3$ requires: C, 78.32; H, 10.88%).

Hydrolysis of 1α-*hydroxycholesterol* 3-*acetate* **4**. The acetate **4** (420 mg) was hydrolyzed with 5% methanolic KOH at room temp and worked up in the usual way to give 1α-hydroxycholesterol[6] **5** (380 mg, 100%), which was recrystallized from acetone (351 mg, 92.5%), m.p. 162–164°‡ (lit.[8,10] m.ps ranging from 154° to 163°). $[\alpha]_D^{20}$ −32° (*c* = 1.0) (lit.[8,10] rotations: ranging from −28° to −38°); IR (KBr): ν_{max} 3460 cm^{-1}; NMR: δ 0.69 (Me-18, s), 0.86 (Me-26 and Me-27, d), 0.90 (Me-21, d), 1.04 (Me-19, s), 3.83 (H-1, m), 4.05 (H-3, m),§ 5.50 (H-6, m). (Found: C, 80.30; H, 11.31. $C_{27}H_{46}O_2$ requires: C, 80.54; H, 11.52%).

Catalytic hydrogenation of 1α-*hydroxycholesterol* (**5**). The diol **5** (110 mg) was hydrogenated with pre-reduced PtO_2 (10 mg) in EtOAc (20 ml + 1 drop of $HClO_4$) to give 5α-cholestane-1α,3β-diol, which was recrystallized from MeOH (94 mg, 85%), m.p. 154–156°, undepressed by admixture with an authentic sample,[12] m.p. 155–156° (lit.[12] m.p. 155–156°). $[\alpha]_D^{20}$ +38° (*c* = 1.0) (lit.[12] +36.9°).

Acetylation of 1α-*hydroxycholesterol* 3-*acetate* **4**. To a soln of **4** (2.0 g) in pyridine (20 ml), Ac_2O (20 ml) was added and the mixture left 24 h at room temp. Working up in the usual way gave 1α-hydroxycholesterol diacetate[6] **6** (2.2 g), which was recrystallized from acetone–MeOH (2.01 g, 92%), m.p. 98–100° (lit.[8b] 98–99°). $[\alpha]_D^{20}$ −15° ±2° (*c* = 0.38) (lit.[8b] −14°); IR (CH_2Cl_2): ν_{max} 1735, 1235 cm^{-1}; NMR: δ 0.64 (Me-18, s), 0.84 (Me-26 and Me-27, d), 0.88 (Me-21, d), 1.06 (Me-19, s), 1.97 (AcO-3, s), 2.03 (AcO-1, s), 4.90 (H-3, m), 5.02 (H-1, t), 5.50 (H-6, m). (Found: C, 76.34; H, 10.18. $C_{31}H_{50}O_4$ requires: C, 76.50; H, 10.36%).

Oxidation of 1α-*hydroxycholesterol* 3-*acetate* **4**. To a cooled (0–5°) soln of **4** (1.15 g) in 150 ml of acetone a slight excess of Kiliani's chromic acid solution[18] was added with constant stirring. After 10 min ice-cold H_2O was added, the precipitate was filtered off, and washed thoroughly with H_2O and air-dried to give 1-oxocholesterol acetate[6] (3β - acetoxy - 5 - cholesten - 1 - one) **8** (1.1 g, 96.5%), which was recrystallized from acetone–MeOH (1.0 g, 88%), m.p. 146–148°. $[\alpha]_D^{20}$ −13° (*c* = 0.2); IR (CCl_4): ν_{max} 1740, 1708, 1232 cm^{-1}; NMR: δ 0.67 (Me-18, s), 0.85 (Me-26 and Me-27, d), 0.89 (Me-21, d), 1.25 (Me-19, s), 2.00 (AcO, s) 4.90 (H-3, m), 5.62 (H-6, m). (Found: C, 78.53; H, 10.38. $C_{29}H_{46}O_3$ requires: C, 78.68; H, 10.47%).

Reduction of 1-*oxocholesterol acetate* **8** *and preparation of* 1β-*hydroxycholesterol diacetate* **9**. *Procedure A.* To a cooled (0°) and stirred soln of **8** (2.59 g) in anhydrous THF (40 ml) a cooled (0–5°) suspension of lithium tri(*t*-butoxy)aluminium hydride (3.0 g) in anhydrous THF (40 ml) was added and the reaction mixture stirred at 0–5° for 15 min. It was then decomposed with 5% AcOH aq (250 ml) and extracted with ether. The ethereal layer was washed with $NaHCO_3$ aq and H_2O, dried (Na_2SO_4) and evaporated *in vacuo* to dryness, to give a mixture of 1α- and 1β-hydroxycholesterol 3-acetates (2.35 g, 90.5%), which was treated with Ac_2O (25 ml) in pyridine (25 ml) for 24 h at room temp and worked up in the usual way. The resulting mixture of 1α,3β- and 1β,3β-diacetates, **6** and **9** (2.58 g, 100%), in ratio about 1:2.5 (estimated from the relative intensities of the NMR signals at δ 2.03 for 1α-OAc in **6** and δ 1.99 for 1β-OAc in **9**), was chromatographed on silica gel (260 g). Benzene–ether (96:4) eluted first 1β-hydroxycholesterol diacetate **9** (1.12 g, 43.5%), which was twice recrystallized from acetone–MeOH (0.93 g, 36%), m.p. 96–98°. $[\alpha]_D^{20}$ −13° (*c* = 0.2); IR (CCl_4): ν_{max} 1740, 1230 cm^{-1}; NMR: δ 0.68 (Me-18, s), 0.87 (Me-26 and Me-27, d), 0.90 (Me-21, d), 1.12 (Me-19, s), 1.97 (AcO-3, s), 1.99 (AcO-1, s), about 4.65 (H-1 and H-3, m), 5.65 (H-6, m). (Found: C, 76.66; H, 10.41. $C_{31}H_{50}O_4$ requires: C, 76.50; H, 10.36%).

The next fractions eluted with benzene–ether (96:4) contained a 1:1 mixture (0.98 g, 38%) of **6** and **9** (estimated from NMR data;

†In the original procedure[11b] larger amounts of HgO and I_2 were used, but in that case a considerably lower yield of **1** was obtained.

‡A somewhat lower m.p. (138–140°) of **5** was reported in our previous publication.[6]

§The signal of the axial 3α-proton in **5** is displaced downfield (relative to the signal of the equatorial 1β-proton) because of the influence of the *syn*-axial 1α-hydroxyl group.[17]

see above). The final benzene–ether (96:4 and 95:5) eluates gave 1α-hydroxycholesterol diacetate **6** (430 mg, 16.5%) (NMR: AcO-1 at δ 2.03), which after two crystallizations from acetone–MeOH (242 mg, 9.5%) melted at 98–100° (see above).

Procedure B. Ketone **8** (2.01 g) was reduced as described in Procedure A. The resulting mixture (1.90 g, 94%) of 1α- and 1β-hydroxycholesterol 3-acetates was dissolved in pyridine (8 ml), treated with Ac_2O (2.15 ml) at room temp. for 5 hr and worked up in the usual way, affording a mixture (2.04 g) which contained the diacetates **6** and **9** and unchanged 1α- and 1β-hydroxycholesterol 3-acetate, and which was chromatographed on silica gel (200 g). Benzene–ether (96:4) eluted first **9** (726 mg, 35%), which was recrystallized from acetone–MeOH (674 mg, 32.5%), m.p. 96–98°. The next benzene–ether (96:4) eluates contained a mixture (148 mg, 7%) of **6** and **9**, in ratio about 1:4 (estimated from NMR data; see above). Elution with benzene–ether (90:10) gave a 1:1 mixture (890 mg, 47%) of 1α- and 1β-hydroxycholesterol 3-acetates (NMR: δ 1.02 (Me-19, s), 3.82 (H-1, m), 5.00 (H-3, m) for the 1α-hydroxy isomer, and δ 1.26 (Me-19, s), 3.51 (H-1, m), 4.62 (H-3, m) for the 1β-hydroxy epimer). This mixture was reoxidized to the starting ketone **8** as described above.

Hydrolysis of 1β-hydroxycholesterol diacetate **9**. The diacetate **9** (200 mg) was hydrolyzed with 5% methanolic KOH at room temp. and worked up in the usual way, to give 1β-hydroxycholesterol **10** (170 mg, 100%), which was recrystallized from acetone–MeOH (140 mg, 85%), m.p. 181–182°. $[\alpha]_D^{29}$ −38.5 ($c = 0.2$); IR (KBr): ν_{max} 3320 cm^{-1}; NMR (CD_3SOCD_3): δ 0.64 (Me-18, s), 0.84 (Me-26 and Me-27, d), 0.88 (Me-21, d), 1.16 (Me-19, s), about 4.40 (H-1 and H-3, m), 5.40 (H-6, m). (Found: C, 80.77; H, 11.50. $C_{27}H_{46}O_2$ requires: C, 80.54; H, 11.52%).

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