Synthetic Studies of Vitamin D_3 Analogues from Bile Acids. Part 2.[1] Syntheses of Cholesta-1,4-dien- and -1,4,6-trien-3-ones having a 24- and/or 25-Hydroxylated Side Chain from Lithocholic Acid

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Syntheses of 3α-hydroxy-5β-cholestanes having a 25-, 24*R*-, or 24*S*-hydroxy group [(13), (6a and b)] or a 24,25-dihydroxy group [(14)] from lithocholic acid (1) are described. These hydroxylated cholestanes were converted to the 1,4-dien-3-ones (15), (10a and b), and (16), and then to the 1,4,6-trien-3-ones (18), (11a and b), and (19) by normal dehydrogenation procedures without affecting the side chains.

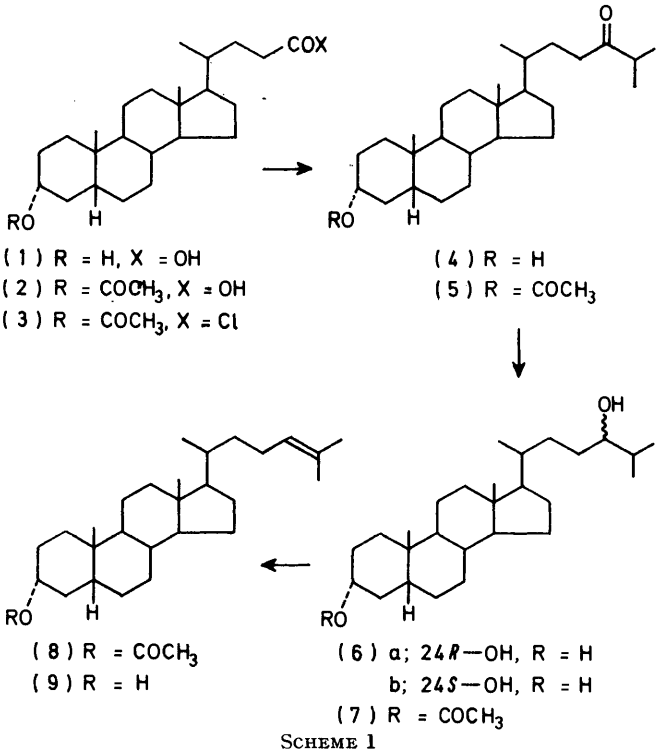
THE importance of cholesta-1,4-dien- and -1,4,6-trien-3-ones with an appropriately hydroxylated side chain as intermediates for the syntheses of naturally produced cholecalciferol metabolites and their synthetic analogues has been well documented.[2]

In this report, we describe a general synthesis of 3α-hydroxy-5β-cholestanes having four kinds of hydroxylated side chains from lithocholic acid (1),† one of the principal constituents of bile acids, and their subsequent conversions into the corresponding 1,4-dien-3-ones and 1,4,6-trien-3-ones. Our method was elaborated during a retrosynthesis of the title compounds. (i) Addition of a three carbon unit to an appropriate C_{24} steroid may give a 24-oxygenated derivative whose 24-oxygen function provides a means for modifying the side chain and (ii) the derived steroids with an appropriately hydroxylated side chain are then dehydrogenated to the 1,4-dien- or 1,4,6-trien-3-ones by alteration of some functional groups present in the original C_{24} steroid.

Lithocholic acid appears to be the ideal choice as a starting material for the above strategy, since the carboxy function allows the formation of the 24-oxygenated derivative from which the desired side chains can be created and the hydroxy group may be used for the introduction of the unsaturated functions in the A and/or B rings.

Elaboration of the C-17 side chain of (1) into an eight carbon unit was performed by use of the ketone synthesis devised originally by Blaise and Maire.[4] Thus, the acid chloride (3) derived from the acetate (2) was transformed to 3α-hydroxy-5β-cholestan-24-one (4) in *ca.* 50% overall yield from (1) by treatment with di-isopropylcadmium followed by hydrolysis. The acetate (5) was smoothly reduced by calcium borohydride at below −10 °C to the 24-ol (7) without affecting the 3-acetoxy function.

Treatment of (7) with phosphoryl chloride in pyridine afforded 5β-cholest-24-en-3α-yl acetate (8) which was hydrolysed to 5β-cholest-24-en-3α-ol (9). The overall yield of (9) from (1) is *ca.* 30%. Compounds (4) and (9) are the key intermediates in this synthesis. Thus, compound (4) serves as the precursor of 24*R*- and 24*S*-hydroxy steroids, while (9) is used for the syntheses of 25-hydroxy- and 24,25-dihydroxy-steroids.



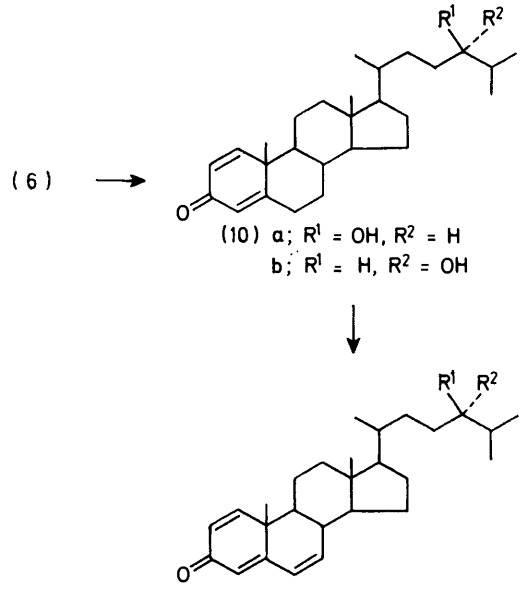
SCHEME 1

Syntheses of 24R- *and* 24S-*Hydroxycholesta*-1,4-*dien- and* -1,4,6-*trien*-3-*ones from* 3α-*Hydroxy*-5β-*cholestan*-24-*one* (4).—Reduction of (4) with sodium borohydride afforded a diastereoisomeric mixture of 5β-cholestane-3α,24-diol (6), showing two spots on t.l.c. Column chromatography over alumina afforded two crystalline compounds (6a and b) in 1 : 1 ratio. Since each showed a single spot on t.l.c. and exhibited almost the same spectral properties, it is clear that (6a and b) are the 24-diastereoisomers. Treatment of each compound with dichlorodicyanobenzoquinone (DDQ) afforded the corresponding 1,4-dien-3-ones (10a and b) in *ca.* 40% yield.‡

† Lithocholic acid is isolated commercially from pig and ox bile and gallstones [3a] and also prepared from cholic acid or from deoxycholic acid.[3b]

‡ It is well known [5] that while dehydrogenation of 5-en-3-ols with DDQ affords 1,4,6-trien-3-ones, the corresponding dehydrogenation of saturated 3-ols affords only 1,4-dien-3-ones.

Both dienones were then transformed to the corresponding trienones (11a and b) * in *ca.* 30% yield by the application of the well known bromination–dehydrobromination procedure.[7] These compounds were compared with the trienones obtained from 24*R*- and 24*S*-hydroxycholesterols [8] by dehydrogenation with DDQ and as a result, (11a) was identified as 24*R*-hydroxycholesta-1,4,6-trien-3-one, and (11b) with 24*S*-hydroxy isomer. Therefore, it is evident that (6a) and (10a) have a 24*R*- and (6b) and (10b) a 24*S*-hydroxy group.



SCHEME 2

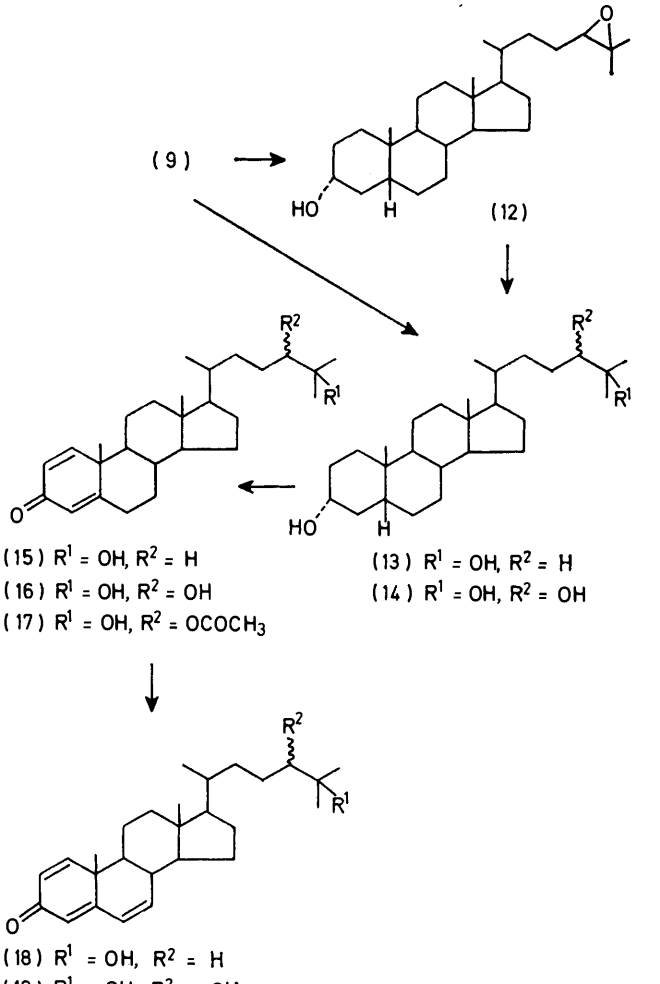
It should be noted that the isomers a and b of compounds (7), (10), and (11) exhibited almost identical properties on t.l.c. and column chromatography, and therefore, effective separation of the isomers is only possible with the diols (6).

Syntheses of 25-*Hydroxy- and* 24ξ,25-*Dihydroxycholesta*-1,4-*dien- and* -1,4,6-*trien*-3-*ones from* 5β-*Cholest*-24-*en*-3α-*ol* (11).—The 3α-hydroxy function in (9) does not require any protection during the side chain modifications. This led to a much simplified procedure and significantly higher overall yields for the preparation of our target compounds.

Oxidation of (9) with *m*-chloroperbenzoic acid afforded 24,25-epoxy-5β-cholestan-3α-ol (12), which, by reduction with lithium aluminium hydride, gave the expected 5β-cholestane-3α,25-diol (13). Alternatively, the same diol was also obtained by oxymercuriation (by mercury trifluoroacetate–demercuration † in a yield comparable to that above).

Epoxide (12) was hydrolysed in aqueous dioxan in the presence of sulphuric acid to give 5β-cholestane-3β,24ξ,25-triol (14), in 56% overall yield from (9). Though the same triol was also obtained directly from (9) by oxidation using either osmium tetraoxide or performic acid, the yields of (14) were less than that in the above indirect method.

With the side chains now fully elaborated, dehydrogenation of compounds (13) and (14) with DDQ in dioxan as in the case of the conversion of (6) into (10), led to the desired 1,4-dien-3-ones (15) and (16) again in satisfactory yield (*ca.* 40%). These dienones were then dehydrogenated to the trienones (18) and (19) by the bromination–dehydrobromination procedure used in the synthesis of (11a and b), in yields of 20—30%. It should be noted that the yield (*ca.* 20%) of (19) is somewhat increased (*ca.* 30%) if the 24-hydroxy group of (16) is protected by acetylation prior to dehydrobromination.



SCHEME 3

In Part 3, we report the synthesis of various side chain hydroxylated analogues of 1α-hydroxycholecalciferol

* Though both trienones were previously synthesized, their physical properties were not fully described.[6]

† This reaction was successfully employed in the syntheses of 25-hydroxycholesterol by Morisaki *et al.*,[9a] and of 25-hydroxy-3-epicholesterol by us.[9b] In both cases, the Δ⁵-function did not react with mercury trifluoroacetate.

using dienones and trienones obtained here in which the unsaturated functions in the A and/or B rings are utilized successfully for the introduction of the 1α-hydroxy function.

In summary, we have obtained a variety of side chain hydroxylated cholesta-1,4-dien-3-ones (10a and b), (15), and (16) and -1,4,6-trien-3-ones (11a and b), (18), and (19) from lithocholic acid (1). This and the previous work [1] demonstrate the applicability of lithocholic acid (1) and related bile acids as starting materials for the syntheses of polar metabolites of vitamin D_3.

EXPERIMENTAL

M.p.s were measured with a Yanagimoto microapparatus, i.r. spectra with a Hitachi 285 spectrometer, n.m.r. spectra with a Perkin-Elmer R-20A spectrometer (60 MHz; tetramethylsilane as internal standard), optical rotations with a Perkin-Elmer 241 polarimeter, and u.v. spectra with a Hitachi 124 spectrometer (ethanol as solvent). Extracts were dried over anhydrous $MgSO_4$. Kieselgel 60 F-254 (Merck) was used for t.l.c. and Wakogel C-200 (silica gel) and alumina (Wako Pure Chemical Industries) for column chromatography. Mass spectra were run with a Shimadzu LKB-9000 computer system. All compounds showed the expected M^+ ions.

3α-Hydroxy-5β-cholestan-24-one (4).—To the solution of isopropylmagnesium bromide prepared as in the usual manner from magnesium (13.4 g) and isopropyl bromide (60 ml) in dry ether (600 ml), cadmium bromide (75 g) was added portionwise at room temperature. The resulting dark solution was refluxed gently for 1 h. After addition of dry benzene (200 ml), most of the ether was evaporated. To this solution, the chloride (3) in dry benzene (200 ml), prepared from the acetate (2) (30 g) by the usual method, was added dropwise for 20 min, and the mixture was stirred for 1 h at 20 °C. To the cooled mixture, 5% aqueous hydrochloric acid was added and the separated organic layer was washed with water, dried, and evaporated. Treatment of the residue with potassium hydroxide solution in methanol gave an oil, which was chromatographed on silica gel to yield the *24-one* (4) (16.6 g), m.p. 123—125° (from methanol) (Found: C, 80.2; H, 11.5. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%), $[\alpha]_D^{25}$ +34.4° (*c* 1, chloroform), $\nu_{max.}$ (KBr) 3 540 (OH) and 1 702 cm^{-1} (C=O), δ($CDCl_3$) 0.64, 1.02, 1.14 (each 3 H, s), 0.92 (6 H, s), and 3.63 (1 H, m).

Usual acetylation with pyridine and acetic anhydride gave *3α-acetoxy-5β-cholestan-24-one* (5) in a quantitative yield, m.p. 96—98° (from ethanol) (Found: C, 78.2; H, 10.65. $C_{29}H_{48}O_3$ requires C, 78.35; H, 10.9%), $[\alpha]_D^{25}$ +44.0° (*c* 1, chloroform), δ($CDCl_3$) 2.03 (3 H, s, $COCH_3$) and 4.75 (1 H, m).

3α-Acetoxy-5β-cholestan-24ξ-ol (7).—The acetate (5) (852.0 mg) was reduced with sodium borohydride (at 0 °C) or with calcium borohydride (at −10 °C) for 1 h. The usual work-up gave the 3α-acetoxy-24ξ-ol (7) as an oil, δ($CDCl_3$) 0.64, 0.87, 0.93, 0.96 (each 3 H, s), 2.02 (3 H, s, $COCH_3$), 3.3, and 4.65 (each 1 H, m).

5β-Cholestan-24-en-3α-ol (9).—To the solution of compound (7) (701.7 mg) in pyridine (10 ml), phosphoryl chloride (1.5 ml) was added, and the mixture was allowed to stand overnight at 25 °C. The mixture was poured into ice–water and extracted with ether. The extract was washed with diluted hydrochloric acid and then water, dried, and evaporated to give 5β-cholestan-24-en-3α-yl acetate (8) as an oil, δ($CDCl_3$) 1.58 and 1.68 (each 3 H, s, vinyl methyl), 2.02 (3 H, s, $COCH_3$), and 4.5—5.3 (2 H, m, 3- and 24-H), *m/e* 428 (M^+), 413, 368, 353, 344, 315, 285, 255, and 215.

Acetate (8) was hydrolysed in a 5% potassium hydroxide solution in methanol, yielding *24-en-3α-ol* (9) (489.3 mg), m.p. 117—118° (from hexane) (Found: C, 83.75; H, 11.85. $C_{27}H_{46}O$ requires C, 83.85; H, 12.0%), $[\alpha]_D^{25}$ +32.4° (*c* 1, chloroform), δ($CDCl_3$) 1.59 and 1.68 (each 3 H, s, vinyl methyl), 3.7 (1 H, m, 3-H), and 5.1 (1 H, m, 24-H).

24,25-Epoxycholestan-3α-ol (12).—To the solution of the 24-en-3α-ol (9) (1.02 g) in chloroform (10 ml), *m*-chloroperbenzoic acid (1.02 g) was added at 0 °C and the mixture was stirred for 14 h at 5 °C. The mixture was washed with potassium carbonate solution (5%) and then water, dried, and evaporated. The residue was chromatographed on silica gel. Elution with chloroform gave at first the recovered 24-ene (9) and then the 24,25-epoxide (12) (893 mg), m.p. 137—140° (from methanol) (Found: C, 78.45; H, 11.1. Calc. for $C_{27}H_{46}O_2$,1/2H_2O: C, 78.8; H, 11.5%), $[\alpha]_D^{25}$ +27.2° (*c* 2, chloroform), δ(CCl_4) 0.64, 1.20, 1.23 (each 3 H, s), 0.91 (6 H, s), 3.50 (1 H, m, 3-H), and 4.12br (1 H, s, 24-H).

5β-Cholestane-3α,25-diol (13).—(a) *From the 24,25-epoxide* (12). To a solution of the 24,25-epoxide (12) (808 mg) in dry tetrahydrofuran (20 ml), lithium aluminium hydride (0.4 g) was added portionwise and the mixture was refluxed gently for 30 min. After cooling, excess of reagent was decomposed with aqueous acetone and after removal of the precipitate by filtration, the filtrate was extracted with ether. The extract was washed with water, dried, and evaporated to give a solid. Recrystallization from ethanol afforded the *3α,25-diol* (13) (612.6 mg), m.p. 184—185° (Found: C, 80.1; H, 11.7. $C_{27}H_{48}O_2$ requires C, 80.15; H, 11.95%), $[\alpha]_D^{25}$ +32.6° (*c* 1, chloroform), δ($CDCl_3$) 0.62, 1.20 (each 3 H, s), 0.92 (6 H, s), and 3.60 (1 H, m, 3-H).

(b) *From the 24-ene* (9). The 24-ene (9) (130.1 mg) was dissolved in the mixture of tetrahydrofuran (1 ml) and dimethylformamide (1 ml), and mercury trifluoroacetate (215.4 mg) and water (0.5 ml) were added. The mixture was stirred for 7 h at 20 °C. To the mixture, 3N-sodium hydroxide (1 ml) was added and the demercuriation was carried out by addition of sodium borohydride (0.1 g). After removal of the precipitate by filtration, the filtrate was extracted with ether, washed with water, dried, and evaporated. The residue was chromatographed on silica gel (chloroform) to give a solid. Recrystallization from ethanol afforded the 3α,25-diol (13) (53.7 mg), identical (i.r. and mixed m.p.) with the foregoing sample.

5β-Cholestane-3α,24ξ,25-triol (14).—(a) *From the 24,25-epoxide* (12). To the solution of the 24,25-epoxide (12) (160.2 mg) in aqueous dioxan (6 ml), a drop of 10% sulphuric acid was added, and the mixture was stirred for 4 h at 25 °C. The mixture was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was purified by chromatography on silica gel (5% methanol–chloroform), yielding the triol (14) (93.6 mg), m.p. 152—154° (from ethanol) (Found: C, 75.35; H, 11.3. Calc. for $C_{27}H_{48}O_3$,1/2H_2O: C, 75.55; H, 11.5%), $[\alpha]_D^{25}$ +28.1° [*c* 0.5, chloroform–methanol (1 : 1)], *m/e* 402 (100%, $M^+ - 18$). Treatment of (14) with acetone in the presence of an acid catalyst afforded the acetonide, m.p. 130—135°.

(b) *From the 24-ene* (9). Osmium tetraoxide (44.8 mg) was added to the solution of the 24-ene (9) (62 mg) in dry ether (5 ml). The mixture was stirred at 25 °C for 16 h,

evaporated, and the resulted osmate was decomposed by refluxing for 2 h with sodium sulphite (0.3 g) in aqueous ethanol (7.5 ml). After removal of the precipitate by filtration, the filtrate was extracted with ether. The extract was washed with water, dried, and evaporated to give a solid. Recrystallization from ethanol afforded the triol (14) (35 mg), identical (i.r. and mixed m.p.) with the foregoing sample.

Oxidation of (9) (161.5 mg) using performic acid for 20 h at 5 °C, followed by hydrolysis of the resulted formate also gave the triol (14) (77.2 mg).

5β-*Cholestane*-3α,24-*diol* (6a *and* b). *Separation of the Diastereoisomers*.—The crystalline diastereoisomeric mixture of the 3α,24ξ-diol (6) obtained by the reduction of the 24-one (4) (187.3 mg) with sodium borohydride (90 mg) in methanol was chromatographed on alumina. The fraction eluted first with chloroform afforded pure 24S-*isomer* (6b) (70 mg), m.p. 123—124.5° (Found: C, 80.0; H, 11.75. $C_{27}H_{48}O_2$ requires C, 80.15; H, 11.95%), $[\alpha]_D^{28}$ +20.4° (*c* 0.5, chloroform), δ($CDCl_3$) 0.65, 0.87, 0.92, 0.96 (each 3 H, s), and 3.50 (2 H, m, 3- and 24-H). A mixture (37 mg) was next eluted. Further elution with chloroform afforded pure 24R-*isomer* (6a) (75 mg), m.p. 143.5—144.5° (Found: C, 80.0; H, 11.85%), $[\alpha]_D^{28}$ +40.0° (*c* 0.5, chloroform). The i.r., n.m.r., and mass spectra of each isomer were almost identical.

25-*Hydroxycholesta*-1,4-*dien*-3-*one* (15).—To the solution of the 3α,25-diol (13) (510 mg) in dry dioxan (10 ml), DDQ (998 mg) was added and the mixture was refluxed for 16 h. After removal of the precipitate by filtration, the mixture was evaporated and the residue was chromatographed on alumina. The fraction which was eluted with chloroform was largely the desired 1,4-diene. Recrystallization of this fraction from ether afforded pure 1,4-*diene* (15) (227 mg), m.p. 151—153° (Found: C, 81.25; H, 10.55. $C_{27}H_{42}O_2$ requires C, 81.35; H, 10.6%), $[\alpha]_D^{25}$ +27.6° (*c* 1, chloroform), $\lambda_{max.}$ 247 nm, δ($CDCl_3$) 0.73 (3 H, s), 0.95br (9 H, s), 5.98br (1 H, s, 4-H), 6.13, and 6.95 (each 1 H, d, *J* 10 Hz, 1- and 2-H).

24ξ,25-*Dihydroxycholesta*-1,4-*dien*-3-*one* (16).—The same treatment of the triol (14) (349.4 mg) with DDQ (661 mg) as described above afforded the 1,4-diene (16) (162.8 mg), m.p. 165—167° (from ether) (Found: C, 78.15; H, 10.35. Calc. for $C_{27}H_{42}O_3$: C, 78.2; H, 10.2%), $[\alpha]_D^{25}$ +27.5° (*c* 0.3, chloroform), δ($CDCl_3$) 0.73, 0.95 (each 3 H, s), 1.19 (6 H, s), 6.11br (1 H, s, 4-H), 6.25, and 7.10 (1 H, d, *J* 10 Hz, 1- and 2-H).

24-*Hydroxycholesta*-1,4-*dien*-3-*one* (10).—Treatment of the diol (6a and b) with DDQ as described above afforded the 1,4-*diene* (10a), m.p. 120—121° (from ether–hexane) (Found: C, 81.25; H, 10.85. $C_{27}H_{42}O_2$ requires C, 81.35; H, 10.6%), $[\alpha]_D^{25}$ +42.4° (*c* 0.5, chloroform) and the 1,4-*diene* (10b), m.p. 95—96.5° (from ether–hexane) (Found: C, 81.35; H, 10.7%), $[\alpha]_D^{25}$ +38.6° (*c* 0.5, chloroform), each in *ca.* 30% yield. N.m.r. spectra of (10a and b) were practically identical, δ($CDCl_3$) 0.86, 1.22 (each 3 H, s), 0.92 (6 H, d, *J* 6 Hz), 6.07br (1 H, s, 4-H), 6.18, and 7.05 (each 1 H, d, *J* 10 Hz, 1- and 2-H).

25-*Hydroxycholesta*-1,4,6-*trien*-3-*one* (18).—The solution of the 1,4-diene (15) (115.6 mg) in carbon tetrachloride (10 ml) was refluxed for 45 min in the presence of *N*-bromosuccinimide (*ca.* 100 mg; portionwise addition) with irradiation by visible light (300 W tungsten lamp). The reaction was continued until (15) was consumed (t.l.c.). After removal of the precipitate by filtration, the filtrate was evaporated to give the crude 7-bromo derivative as an oil. This crude bromide was refluxed in dimethylformamide (3 ml) in the presence of lithium carbonate (50 mg) and lithium chloride (50 mg) for 2 h. The mixture was extracted with ether. The extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel. The fraction eluted with chloroform was collected and recrystallized from ether to afford (18) (47.9 mg), m.p. 183—184° (lit.,[9] 178—179°) (Found: C, 81.55; H, 10.35. Calc. for $C_{27}H_{40}O_2$: C, 81.75; H, 10.15%).

24,25-*Dihydroxycholesta*-1,4,6-*trien*-3-*one* (19).—Acetylation of the 1,4-diene (16) (162.8 mg) with acetic anhydride and pyridine afforded the 24-acetate (17) (134 mg) as an oil. Bromination and dehydrobromination of (17) as described above gave the 1,4,6-triene 24-acetate as an oil. Hydrolysis with potassium hydroxide in methanol gave the crude material, which was chromatographed on silica gel. The fraction eluted with chloroform was collected and recrystallized to give (19) (40 mg), m.p. 192—195° (from ether) (Found: C, 78.45; H, 9.9. Calc. for $C_{27}H_{40}O_3$: C, 78.6; H, 9.75%), $\lambda_{max.}$ 225, 250, and 299 nm.

24R- (11a) *and* 24S-*Hydroxycholesta*-1,4,6-*trien*-3-*one* (11b).—The 1,4-dienes (10a and b) were converted into the trienones (11a and b), respectively, as described above. *Compound* (11a) was formed in 34% yield, m.p. 152—153.5° (from ether–hexane) (Found: C, 81.45; H, 10.3. $C_{27}H_{40}O_2$ requires C, 81.75; H, 10.15%), o.r.d. (*c* 0.01, chloroform), $[\alpha]^{25}$ −432° (350), 0° (365), +172.8° (386) (peak), +120.2° (400), +11.7° (500), and 0° (600 nm). *Compound* (11b) was formed in 36% yield, m.p. 107—108.5° (from ether–hexane) (Found: C, 81.3; H, 10.35%), o.r.d. (*c* 0.01, chloroform) $[\alpha]^{25}$ −398° (350), 0° (366), +161.3° (386) (peak), +107.6° (400), +0.99° (500), 0° (518), and −2.5° (600 nm). Both the trienones (11a and b) were identical with those obtained from cholest-5-ene-3β,24*R*- and -3β,24*S*-diol by dehydrogenation with DDQ in refluxing dioxan. Spectral properties of both isomers were practically indistinguishable, δ($CDCl_3$) 0.70, 0.86, 0.88 (each 3 H, s), 0.92 (6 H, d, *J* 6 Hz), 3.5—3.9 (1 H, m, 24-H), 5.4—5.9 (4 H, m, 2-, 4-, 6-, and 7-H), and 7.12 (1 H, d, *J* 10 Hz, 1-H).

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