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Synthesis of a 24-Epimeric Mixture of 4α,14α,24-Trimethyl-9(11)-cholesten-3-one

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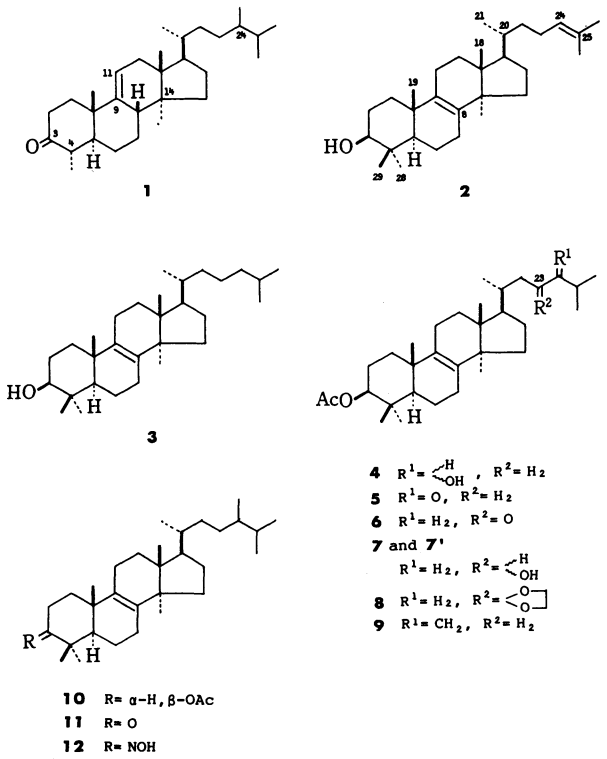
A 24-epimeric mixture of 4α,14α,24-trimethyl-9(11)-cholesten-3-one was synthesized from lanosterol through 4α,14α,24-trimethyl-8-cholesten-3β-ol and 4α,14α,24-trimethyl-7,11-dioxocholestan-3β-yl acetate as key intermediates.

A triterpene mixture (ca. 4 mg) was obtained from the plant fossil (ca. 50 g) collected at the Ningyo-toge area on the border between Tottori and Okayama Prefectures.[1] Preparative gas chromatographic separation of the mixture afforded three components, **a** ($C_{29}H_{48}O$), **b** ($C_{29}H_{50}O$), and **c** ($C_{30}H_{50}O$), which weighed about hundreds μg, respectively. Spectral examination suggested that the component **c** is a mixture of two unsaturated tetracyclic triterpene ketone and one of them might be 4α,14α,24ξ-trimethyl-9(11)-cholesten-3-one. However, a paucity of the material prevented us from the further confirmation of the proposed structure. This paper describes a preparation of a 24-epimeric mixture of 4α,14α,24-trimethyl-9(11)-cholesten-3-one (**1**)[2] from lanosterol (**2**) as an authentic sample, whose ^{1}H NMR and mass spectra are compared with those of the natural specimen.

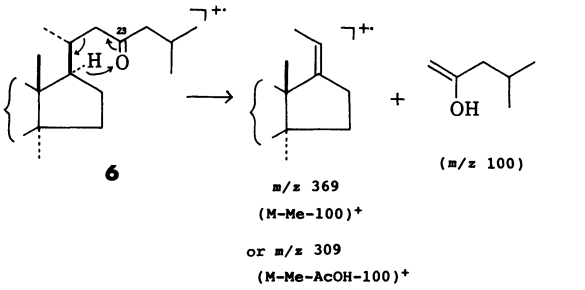
A commercial lanosterol containing ca. 45% dihydrolanosterol (=8-lanosten-3β-ol) (**3**) was acetylated and subjected to hydroboration using diborane in tetrahydrofuran (THF) to afford a mixture of 24-hydroxy-8-lanosten-3β-yl acetate (**4**) and dihydrolanosteryl acetate, the former of which, after separation, was oxidized with Jones reagent to yield 24-oxo-8-lanosten-3β-yl acetate (**5**).

When the hydroboration was effected in situ with diborane generated by sodium borohydride and boron trifluoride etherate in THF, and oxidation with sodium dichromate was followed without isolation of 24-hydroxy-8-lanosten-3β-yl acetate (**4**), the hydroboration-oxidation reaction[3] was found to give a mixture of two ketones, one of which was shown to be identical with **5** by GLC examination and ^{1}H NMR spectrum. The mixture was treated with sodium borohydride to afford a mixture of three hydroxy acetates, one of which was identical with 24-hydroxy-8-lanosten-3β-yl acetate (**4**). The other two showed similar IR, ^{1}H NMR, and MS spectra to those of **4**, and were inferred to be epimeric secondary alcohols (**7** and **7'**), because they gave almost the same ^{1}H NMR spectra each other and the same peak area at δ 3.8 due to *H*-C-OH as that at δ 4.5 due to *H*-C-OAc, respectively. Therefore, the epimeric alcohols (**7** and **7'**) were oxidized with Jones reagent, respectively, to give the same acetoxy ketone (**6**), which showed fragment peaks at *m/z* 369 ([M−Me−100]$^+$) and *m/z* 309 ([M−Me−AcOH−100]$^+$). Since the appearance of these peaks indicates a loss of $C_6H_{12}O$ (*m/z* 100) derived from McLafferty rearrangement,[4] the location of the carbonyl group was deduced to be at C-23 (Scheme 1). This conclusion was confirmed by characteristic fragment peaks at *m/z* 471 and *m/z* 129 observed in the mass specrtum of ethylene acetal (**8**) of the ketone (**6**) (Scheme 2). From these findings, the ketone (**6**) could be formulated as 23-oxo-8-lanosten-3β-yl acetate. Since the absence of 23-ene in the starting material was certified by the ^{1}H NMR examination, the formation of **6** is inexplicable. Further investigation on the formation mechanism is under way.

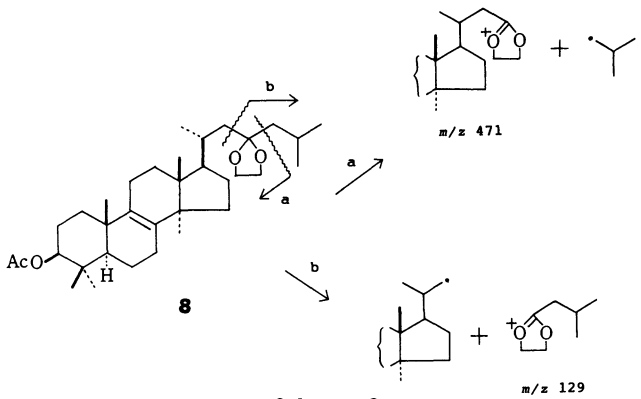


24-Oxo-8-lanosten-3β-yl acetate (**5**) was converted into 24-methylene derivative (**9**) by Wittig reaction, which was subjected to hydrogenation to yield a 24-epimeric mixture of 24-methyl-8-lanosten-3β-yl acetate (**10**)†. 4β-Demethylation of **10** was carried out by

†All 24-methyl derivatives obtained by the preparation described below in this paper are 24-epimeric mixtures, respectively.



Scheme 1.

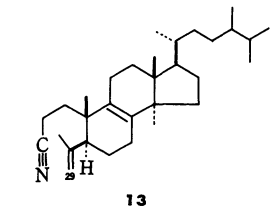


Scheme 2.

the same procedure as described in the previous paper;[1] hydrolysis of 24-methyl-8-lanosten-3β-yl acetate (**10**) followed by Jones oxidation gave a ketone (**11**), which was converted into the corresponding oxime (**12**), a seconitrile (**13**), and then a nitrile epoxide (**14**). On a treatment with boron trifluoride etherate, **14** afforded the demethylation product, 4α,14α,24-trimethyl-8-cholesten-3-one (=24-methyl-29-nor-8-lanosten-3-one) (**15**) in about 6.1% yield from **10**.

4α,14α,24-Trimethyl-8-cholesten-3β-yl acetate (**16**), $C_{32}H_{54}O_2$ [*m/z* 470.4159 determined by high resolution mass spectrometry (HR-MS)] derived from **15** was subjected to an allylic oxidation with chromium trioxide[5] in acetic acid-hexane to afford 4α,14α,24-trimethyl-7,11-dioxo-8-cholesten-3β-yl acetate (**17**), $C_{32}H_{50}O_4$ (*m/z* 498.3709) in 55% yield. An absorption band due to the unsaturated carbonyl group was observed at 1680 cm^{-1} in the IR spectrum. On heating with zinc dust in acetic acid,[5] **17** afforded a saturated dione acetate (**18**), $C_{32}H_{52}O_4$ (*m/z* 500.3896), in 66% yield.

Selective decarbonylation at C-7 was examined using 7,11-dioxolanostan-3β-yl acetate (**19**)[6] as a model compound. Wolff-Kishner reduction of **19** under standard conditions afforded a 7-deoxo derivative (**20**) in 41% yield accompanied with a 7,11-dideoxo derivative, lanostan-3β-ol (**21**), in 18% yield. The formation of **21** was reduced by removing the excess hydrazine at reduced pressure after hydrazone formation.[7] However, this modification could not improve the yield of **20**. Next, the reduction of a tosylhydrazone (**22**) of **19** with sodium (cyano-*C*)trihydroborate[8] was investigated, but the tosylhydrazone (**22**) could not be prepared in a good yield in ethanol nor in acetic acid.[9]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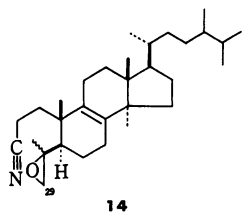
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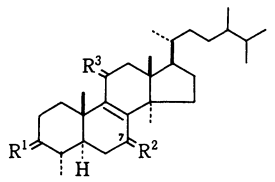
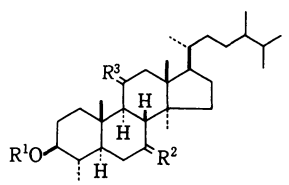
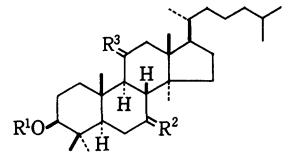
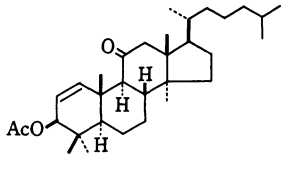

15 R^1= O, R^2= R^3= H_2
16 R^1= α-H, β-OAc, R^2= R^3= H_2
17 R^1= α-H, β-OAc, R^2= R^3= O


18 R^1= Ac, R^2= R^3= O
26 R^1= Ac, R^2=  , R^3= O
27 R^1= Ac, R^2= H_2, R^3= O
29 R^1= H, R^2= H_2, R^3= α-H,β-OH
30 R^1= Ac, R^2= H_2, R^3= α-H,β-OH


19 R^1= Ac, R^2= R^3= O
20 R^1= H, R^2= H_2, R^3= O
21 R^1= H, R^2= R^3= H_2
22 R^1= Ac, R^2= NNHTs, R^3= O
23 R^1= Ac, R^2=  , R^3= O
24 R^1= Ac, R^2= H_2, R^3= O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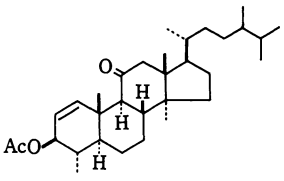
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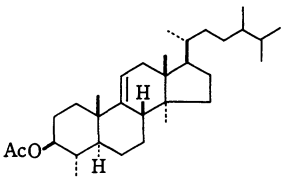
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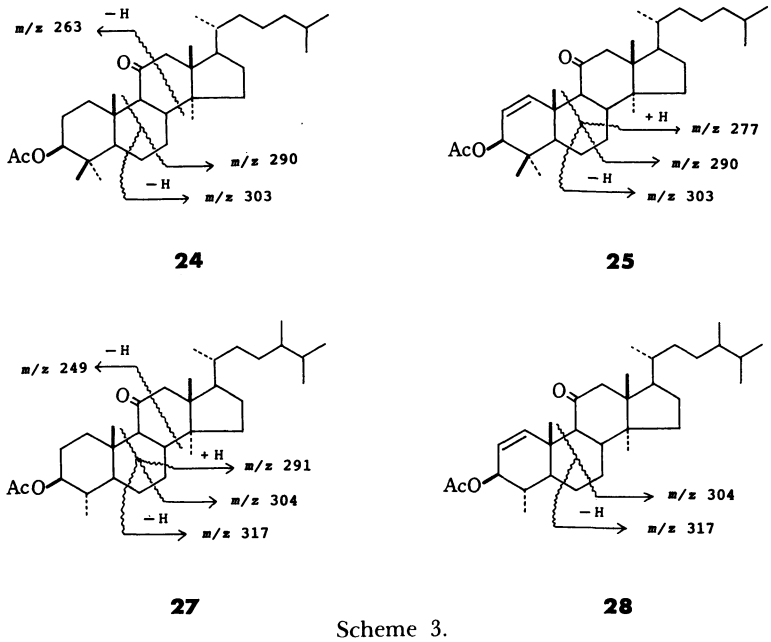
Then the 7,11-dione (**19**) was converted into 7,7-ethylenedithio-11-oxolanostan-3β-yl acetate (**23**), which was treated with Raney nickel W2[10] in dioxane to afford the desired 7-deoxo derivative (**24**) in 86% yield from **19**.[11] Thioacetalization and desulfurization in a large scale, however, afforded a mixture of **24** and an olefin (**25**), latter of which was inferred to be 11-oxo-1-lanosten-3β-yl acetate by ^1H NMR spectrum and GC-MS examination (Scheme 3).[12,13] This was supported by hydrogenation of the mixture (**24** and **25**) giving rise to the single product, **24**.

According to the procedures described above, 4α,14α,24-trimethyl-7,11-dioxocholestan-3β-yl acetate (**18**) was converted into a 7,7-ethylenedithio derivative (**26**), which was treated with Raney nickel W2.[10] The reaction product was also found to consist of two com-



Scheme 3.

pounds by GLC examination. The ^{1}H NMR spectrum of the mixture showed two singlet signals due to acetoxyl groups at δ 2.03 and 2.04 and a couple of doublet signals due to vicinal olefinic protons at δ 5.47 and 5.72, respectively. These findings and the mass spectrum revealed that the mixture consisted of the desired 11-oxo derivative (**27**) together with an olefinic by-product (**28**), whose double bond was confirmed to be 1-ene from the fragment ions at *m/z* 304 and *m/z* 317 (Scheme 3).[12,13] The mixture was hydrogenated to afford the single product, which was identical with **27**. The formation mechanism of **25** and **28** was not made clear yet.

The introduction of a double bond between C-9 and C-11 was achieved by usual manner; 4α,14α,24-trimethyl-11-oxocholestan-3β-yl acetate (**27**) was reduced with lithium aluminium hydride (LAH) to afford a 3β,11β-diol (**29**), which, after a partial acetylation, was treated with phosphoryl chloride, 4α,14α,24-trimethyl-9(11)-cholesten-3β-yl acetate (**31**), mp 119—120 °C (lit,[2] mp 123—125 °C; lit,[14] mp 117.5—118.5 °C), being obtained. Hydrolysis of **31** followed by Jones oxidation gave 4α,14α,24-trimethyl-9(11)-cholesten-3-one (**1**). In the ^{1}H NMR spectrum of **1**, an olefinic proton at C-11 was observed at δ 5.35 and two singlet signals due to C-18 and C-19 methyl groups appeared at δ 0.69 and 1.23, respectively. The ^{1}H NMR spectral data of acetate (**31**) and ketone (**1**) are compatible with 9(11)-ene structure.[1,2,15]

The synthetic 24-epimeric mixture of 4α,14α,24-trimethyl-9(11)-cholesten-3-one (**1**) exhibited the same ^{1}H NMR spectrum at 270 MHz and the same fragment pattern in the mass spectrum as those of the natural specimen obtained from the plant fossil. However, the absolute configuration at C-24 of the natural specimen could not be determined unequivocally from only this finding.

Experimental[16]

24-Oxo-8-lanosten-3β-yl Acetate (5). A mixture (1.0 g) of lanosteryl acetate and dihydrolanosteryl acetate in a ratio of 5:4 was prepared from a commercial lanosterol (**2**) (E. Merck) and dissolved in THF (20 ml). To the solution kept at 1—2 °C, diborane in THF (1.1 mmol ml^{-1}; 1.2 ml) was added with stirring. The stirring was continued for 5.5 h at room temperature, and further for 1.5 h after addition of water (0.13 ml). The solution was cooled to 2—4 °C and 3 M (1 M=1 mol dm^{-3}) sodium hydroxide solution (0.33 ml) and 30% hydrogen peroxide (0.2 ml) were added with stirring. After stirring was continued at room temperature and then at 40—60 °C for 3.5 h, the usual work-up and chromatographic separation on silica gel (12 g) eluted with 10—40% ether in hexane gave dihydrolanosteryl acetate (283 mg) and 24-hydroxy-8-lanosten-3β-yl acetate (**4**; 256 mg).

A cold solution of 24-hydroxy-8-lanosten-3β-yl acetate (**4**; 204 mg) in acetone (15 ml) was treated with Jones reagent (0.25 ml) and the solution was stirred for 5 min. 2-Propanol (0.5 ml) was added and the usual work-up gave a residue, which was crystallized from ether-methanol to afford 24-oxo-8-lanosten-3β-yl acetate (**5**; 118 mg), mp 128—129.5 °C.

23-Oxo-8-lanosten-3β-yl Acetate (6). Sodium borohydride (30 mg) was added to a solution of the mixture (1 g) of lanosteryl acetate and dihydrolanosteryl acetate in THF (5 ml) under a nitrogen atmosphere and the solution was kept at 25—30 °C. Boron trifluoride etherate (0.03 ml) in THF (0.12 ml) was added and the solution was stirred for 6 h. After addition of water (0.15 ml), a solution of sodium dichromate in sulfuric acid [prepared by dissolving $Na_2Cr_2O_7 \cdot 2H_2O$ (0.33 g) in concd sulfuric acid (0.25 ml) and water (ca. 1.2 ml)] was added dropwise. The usual work-up afforded a residue, which was chromatographed on silica gel (55 g). Elution with 10—25% ether in hexane afforded a mixture (224 mg) of 24-one (**5**) and 23-one (**6**), the ratio of which was found to be 2:3 by GLC examination.

The mixture (120 mg) of **5** and **6** in ethanol was reduced with sodium borohydride (22 mg) for 32 h and the usual work-up afforded a residue, which was subjected to separation by preparative TLC developed with 40% ether in hexane twice to afford (23*S* or *R*)-23-hydroxy-8-lanosten-3β-yl acetate (**7**; 28 mg), 24-hydroxy derivative (**4**; 35 mg), and (23*R* or *S*)-23-hydroxy derivative (**7'**; 14 mg). The 24-hydroxy derivative, mp 142—143 °C, was completely identical with the authentic sample (**4**) derived by hydroboration of lanosteryl acetate. **7**: Mp 171—172 °C (colorless needles from ether-methanol); IR (Nujol) 3570, 1730, and 1270 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.72 (3H, s; 18-Me), 0.88—1.00 (Me's), 2.03 (3H, s; AcO), 3.78 (1H, m; 23-H), and 4.50 (1H, m; 3α-H); MS *m/z* (%) 486 (M^+; 34), 471 (54), 453 (40), 411 (100), 393 (62), 369 (25), 311 (19), and 309 (23). **7'**: Mp 152—153 °C (colorless needles from ether-methanol); IR (Nujol) 3300, 1740, and 1240 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.70 (3H, s; 18-Me), 0.88—1.00 (Me's), 2.03 (3H, s; AcO), 3.78 (1H, m; 23-H), and 4.49 (1H, m; 3α-H); MS *m/z* (%) 486 (M^+; 19), 471 (33), 453 (32), 411 (100), 393 (60), 369 (18), 311 (25), and 309 (26).

A solution of an epimeric alcohol (**7**; 44 mg) in acetone (3 ml) was treated with Jones reagent (0.05 ml) at 0 °C with stirring for 5 min and 2-propanol (0.3 ml) was added to the reaction mixture. The usual work-up gave a residue, which was separated by silica-gel chromatography (C-200, 2 g). 23-Oxo-8-lanosten-3β-yl acetate (**6**; 31 mg) was eluted with 10—30% ether in hexane, mp 135—136 °C (colorless needles from methanol); IR (Nujol) 1720, 1710, 1265, 1035, and 980 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=0.72 (3H, s; 18-Me), 0.84—1.00 (Me's), 2.03 (3H, s; AcO), and 4.50 (1H, m; 3α-H); MS *m/z* (%) 484 (M^+; 31), 469 (76), 424 (8), 409 (100), 369 (48), and 309 (79). The other epimer (**7'**; 17 mg), on oxidation, afforded the same ketone (**6**; 13 mg).

23,23-Ethylenedioxy-8-lanosten-3β-yl Acetate (8). To a solution of a ketone (**6**; 23 mg) in benzene (8 ml), ethylene glycol (0.75 ml) and a small amount of *p*-toluenesulfonic acid were added, and the solution was heated under reflux using a Dean-Stark separator containing Molecular Sieves 4A 1/16 for 10 h. After addition of 10% sodium hydroxide solution, an organic layer was separated and worked up as usual. A residue was purified by silica-gel chromatography (C-200, 3 g, elution with 10—30% ether in hexane) to afford 23,23-ethylenedioxy-8-lanosten-3β-yl acetate (**8**), MS *m/z* 528 (M^+), 513, 471, and 129 (base peak).

24-Methylene-8-lanosten-3β-yl Acetate (9). To the Wittig reagent prepared from methyltriphenylphosphonium bromide (1.41 g) in THF (30 ml) and butyllithium in hexane (10 w/v %, 2.5 ml), a solution of 24-oxo-8-lanosten-3β-yl acetate (**5**; 1.81 g) in THF (7 ml) was added under nitrogen. After reflux for 17 h, solvents were removed and the residue was dissolved in a mixture of ether-water (1 : 1; 60 ml). The ethereal layer was separated and the aqueous layer was extracted with ether three times (each 20 ml). The organic layer and extracts were combined and worked up as usual to afford a residue. Chromatographic separation on silica gel (elution with 2—40% ether in hexane) yielded 24-methylene-8-lanosten-3β-yl acetate (**9**; 1.02 g) together with the starting material (**5**; 197 mg). **9**: Colorless plates (from ether-methanol) sublimes on heating; IR (Nujol) 1720, 1640, 1250, and 890 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.70 (3H, s), 0.89—1.06 (Me's), 2.04 (3H, s; AcO), ca. 4.4 (1H, m; *H*-C-OAc), 4.67 and 4.72 (each 1H, br s; H_2C=C); MS *m/z* (%) 482 (M^+; 33), 467 (85), 407 (59), and 155 (100).

24-Methyl-8-lanosten-3β-yl Acetate (10). 24-Methylene derivative (**9**; 772 mg) in ether (60 ml) was hydrogenated in the presence of platinum oxide (81 mg) under atmospheric pressure for 48 h to afford 24-methyl-8-lanosten-3β-yl acetate (**10**; 780 mg), mp 127—128.5 °C; IR (Nujol) 1720 and 1245 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.69 (3H, s), 1.00 (3H, s), 2.03 (3H, s; AcO) and 4.51 (1H, m; *H*-C-OAc); MS *m/z* (%) 484 (M^+; 22), 469 (98), and 409 (100).

24-Methyl-8-lanoten-3-one (11). 24-Methyl-8-lanosten-3β-yl acetate (**10**; 91 mg) was hydrolyzed with potassium hydroxide (0.2 g) in boiling ethanol to afford 24-methyl-8-lanosten-3β-ol (83 mg), mp 156—158 °C (colorless needles from ether-methanol); IR (Nujol) 3300 and 3200 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=ca. 3.2 (1H, m; *H*-C-OH); MS *m/z* (%) 442 (M^+; 23), 427 (100), and 409 (48).

24-Methyl-8-lanosten-3β-ol (620 mg) in acetone (70 ml) was oxidized with Jones reagent (2 ml) at 0 °C. The usual work-up and chromatographic separation on silica gel (elution with 5—10% ether in hexane) gave 24-methyl-8-lanosten-3-one (**11**; 350 mg), mp 109—111 °C; IR 1720 cm^{-1}; MS *m/z* (%) 440 (M^+; 18) and 425 (100).

Demethylation of 24-Methyl-8-lanosten-3-one (11). A mixture of ketone (**11**; 1.12 g), potassium acetate (4.9 g), and hydroxylamine hydrochloride (97%, 2.6 g) in methanol (490 ml) was refluxed for 3 h. The reaction product was crystallized from ether-methanol to give the corresponding oxime (**12**; 1.07 g), mp 200—203 °C (colorlsee needles); IR (Nujol) 3270, 950, and 930 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=3.03 and 3.20 (total 1H); MS *m/z* (%) 455 (M^+; 13), 440 (90), 424 (23), and 69 (100); Found: *m/z* 455.4116. Calcd for $C_{31}H_{53}NO$: M, 455.4126.

A mixture of oxime (**12**; 1.05 g) and *p*-toluenesulfonyl chloride (recrystallized from hexane; 1.66 g) in pyridine (17 ml) was refluxed for 3 h under nitrogen. Ether (85 ml) was added and the mixture was washed with 2 M hydrochloric acid three times (each 85 ml). The organic layer was washed with a saturated sodium hydrogencarbonate solution and then brine. Chromatographic separation on silica gel (elution with 1—3% ether in hexane) yielded a crude 24-methyl-3,4-seco-4(29),8-lanostadiene-3-nitrile[17] (**13**; 826 mg) as a pale yellow oil, IR (neat) 2250 and 1640 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.77 (Me), 4.67 (1H), and 4.90 (1H); MS *m/z* (%) 437 (M^+; 82), 422 (83), 394 (22), and 383 (100); Found: *m/z* 437.4003. Calcd for $C_{31}H_{51}N$: M, 437.4020.

m-Chloroperbenzoic acid (80%, 609 mg) was added to a solution of the crude seconitrile (**13**; 732 mg) in dichloromethane (150 ml) kept at 0 °C and the mixture was allowed to stand for 72 h at this temperature. The usual work-up gave a residue, which was subjected to column chromatography on silica gel. Elution with 10—30% ether in hexane yielded 4,29-epoxy-24-methyl-3,4-seco-8-lanostene-3-nitrile[17] (**14**; 359 mg) as a colorless oil, IR (neat) 2250 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=2.67 (2H, s; H_2C  C); MS *m/z* (%) 453 (M^+; 5), 438 (27), 420 (8), 410 (7), 399 (16), 381 (10), 370 (5), 86 (100); Found: *m/z* 453.3953. Calcd for $C_{31}H_{51}NO$: M, 453.3969.

The epoxy nitrile (**14**; 404 mg) in toluene (47 ml) was heated with boron trifluoride etherate (0.8 ml) for 3 h under nitrogen and the heating was continued for 1 h after addition of 4 M hydrochloric acid (27 ml). The organic layer was separated and worked up as usual. Purification by column

chromatography on silica gel (elution with 5% ether in hexane) followed by crystallization from ether-methanol afforded 4α,14α,24-trimethyl-8-cholesten-3-one (**15**; 113 mg), mp 109—113 °C; IR (Nujol) 1710 cm^{-1}; MS *m/z* (%) 426 (M^+; 17) and 411 (100); Found: *m/z* 426.3783. Calcd for $C_{30}H_{50}O$: M, 426.3860.

4α,14α,24-Trimethyl-8-cholesten-3β-yl Acetate (16). 4α,14α,24-Trimethyl-8-cholesten-3-one (**15**; 113 mg) was treated with LAH (66 mg) in ether to afford a 3β-alcohol, mp 156—158 °C; IR (Nujol) 3350 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=ca. 3.1 (1H, m; *H*-C-OH); MS *m/z* (%) 428 (M^+; 17), 413 (100), and 395 (26). This alcohol (70 mg) was acetylated with acetic anhydride (1.4 ml) and pyridine (2.8 ml) to yield 4α,14α,24-trimethyl-8-cholesten-3β-yl acetate (**16**) quantitatively, mp 119—121 °C (colorless needles from methanol); IR (Nujol) 1740 and 1245 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.70 (3H, s; 18-Me), 0.74—0.98 (Me's), 2.05 (3H, s; AcO), and 4.38 (1H, dt, *J*=5 and 10 Hz; 3α-H); MS *m/z* (%) 470 (M^+; 39), 455 (100), 410 (5), and 395 (51); Found: *m/z* 470.4159. Calcd for $C_{32}H_{54}O_2$: M, 470.4124.

4α,14α,24-Trimethyl-7,11-dioxo-8-cholesten-3β-yl Acetate (17). 4α,14α,24-Trimethyl-8-cholesten-3β-yl acetate (**16**; 80 mg) was dissolved in a mixture of acetic acid (6.5 ml) and hexane (1.3 ml) and chromium trioxide (70 mg) in acetic acid (90%, 1 ml) was added to the solution and then the reaction mixture was refluxed for 3 h. After addition of water, the reaction product was extracted with ether and the ethereal extract was worked up as usual to afford a residue, which was chromatographed on silica gel (C-200, 5 g). Elution with 10% ether in hexane gave 4α,14α,24-trimethyl-7,11-dioxo-8-cholesten-3β-yl acetate (**17**; 47 mg), mp 153—155 °C; IR (Nujol) 1740, 1680, and 1240 cm^{-1}; UV (EtOH) 270 nm (ε 7800); ^1H NMR (90 MHz, $CDCl_3$) δ=0.75—0.91 (18H; Me×6), 1.19 (3H, s; Me), 1.31 (3H, s; Me), 2.05 (3H, s; AcO), and 4.40 (1H, dt, *J*=5 and 10 Hz; 3α-H); MS *m/z* (%) 498 (M^+; 100) and 438 (20); Found: *m/z* 498.3709. Calcd for $C_{32}H_{50}O_4$: M, 498.3709.

4α,14α,24-Trimethyl-7,11-dioxocholestan-3β-yl Acetate (18). Zinc dust (420 mg) was added to a boiling solution of 4α,14α,24-trimethyl-7,11-dioxo-8-cholesten-3β-yl acetate (**17**; 81 mg) in acetic acid (4 ml) portionwise and the reaction mixture was refluxed for 5—6 h. After filtration, the filtrate and the washings were evaporated to afford a residue. Water was added to the residue and the reaction product was extracted with ether. The ethereal extract was worked up as usual and a residue was subjected to separation by chromatography on silica gel (C-200, 7.6 g). Elution with 5—20% ether in hexane gave 4α,14α,24-trimethyl-7,11-dioxocholestan-3β-yl acetate (**18**; 54 mg), mp 203 °C (colorless needles from methanol); IR (Nujol) 1730, 1700, and 1260 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.72—0.89 (Me's), 1.23 (3H, s; Me), 1.27 (3H, s; Me), 2.05 (3H, s, AcO), and 4.37 (1H, dt, *J*=5 and 10.5 Hz; 3α-H); MS *m/z* (%) 500 (M^+; 100) and 440 (18); Found: *m/z* 500.3896. Calcd for $C_{32}H_{52}O_4$: M, 500.3866.

Wolff-Kishner Reduction of 7,11-Dioxolanostan-3β-yl Acetate (19) under Standard Conditions. A mixture of dioxo acetate (**19**; 77 mg), diethylene glycol (1.5 ml), and hydrazine hydrate (80%, 1 ml) was refluxed for 1.5 h at 135 °C with stirring. After cooling, potassium hydroxide (0.3 g) was added and the mixture was heated. The excess hydrazine was distilled off until the vapor temperature reached to 200 °C, and then the mixture was refluxed for 2 h. The usual work-up and chromatographic separation on silica gel (C-200, 5 g, elution with 10—40% ether in hexane) afforded lanostan-3β-ol (**21**; 12 mg) and 3β-hydroxylanostan-11-one (**20**; 28 mg), mp 164—164.5 °C.

Wolff-Kishner Reduction of 19 under Modified Conditions. A mixture of **19** (50 mg), diethylene glycol (2.5 ml), and hydrazine hydrate (0.5 ml) was refluxed for 1.5 h at 130 °C with stirring, and then the excess hydrazine was removed off at 65 °C under reduced pressure. Potassium hydroxide (0.1 g) was added and the mixture was refluxed for 3 h. The same work-up afforded **20** (26 mg) and **21** (trace).

A Tosylhydrazone (22) of 7,11-Dioxolanostan-3β-yl Acetate (19). A mixture of diketo acetate (**19**; 20 mg) and *p*-tolylsulfonylhydrazine (52 mg) in ethanol (0.7 ml) was refluxed for 2 h. The solvent was removed to give a residue, which was separated by preparative TLC developed with ethyl acetate-hexane. A small amount of mono-*p*-tosylhydrazone (**22**) was obtained together with the starting material (**19**). **22**; IR (Nujol) 1730, 1700, 1330, 1250, 1170, 1150, and 810 cm^{-1}; UV (EtOH) 225 nm (ε 10960); ^1H NMR (90 MHz, $CDCl_3$) δ=0.65 (3H, s; 18-Me), 0.84—0.91 (Me's), 1.11 (3H, s; Me), 2.05 (3H, s; AcO), 2.44 (3H, s; *p*-CH_3-C_6H_4-), 4.40 (1H, m; 3α-H), 7.26, 7.36, 7.79, and 7.89 (each 1H; aromatic proton). The same reaction was examined in acetic acid as a solvent, but the yield of **22** could not be improved.

7,7-Ethylenedithio-11-oxolanostan-3β-yl Acetate (23). 1,2-Ethanedithiol (1.2 ml) was added to 7,11-dioxolanostan-3β-yl acetate (**19**; 44 mg) in chloroform (3 ml), and the solution was stirred with introducing hydrogen chloride at 0 °C for 4 h. The solvent was removed under reduced pressure and a residue was subjected to separation by column chromatography on silica gel (C-200, 5 g). Elution with 10—25% ether in hexane afforded the ethylenedithio derivative (**23**; 46 mg), mp 174.5—175 °C (colorless needles from ether-methanol); IR (Nujol) 1730, 1700, and 1260 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.83—0.90 (Me's), 1.13 and 1.33 (each 3H, s; Me), 2.04 (3H, s; AcO), 3.26 (4H, s; S-CH_2-CH_2-S), and 4.56 (1H, m; 3α-H); MS *m/z* (%) 576 (M^+; 23), 548 (44), 516 (51), 270 (46), 238 (52), 210 (75), and 185 (100).

11-Oxolanostan-3β-yl Acetate (24). A crude 7,7-ethylenedithio derivative (**23**) prepared from **19** (25 mg) was dissolved in dioxane (10 ml) and the solution was added to Raney nickel W2[10] (ca. 0.4 g) in a flask. The mixture was refluxed for 6 h and filtered. The filtrate and washings were combined and evaporated to afford a residue. Column chromatography on silica gel (C-200, 2.5 g, elution with 10—25% ether in hexane) afforded 11-oxolanostan-3β-yl acetate (**24**; 21 mg), mp 144—145 °C (colorless needles from ether-methanol). When the desulfurization was carried out in a large scale using **23** prepared from **19** (3.5 g), an inseparable mixture (2.94 g) of 11-oxolanostan-3β-yl acetate (**24**) and 11-oxo-1-lanosten-3β-yl acetate (**25**). Gas chromatography (2% Dexsil 300GC) and ^1H NMR examination revealed that the mixture consisted of **24** and **25** in a ratio of 4:1. A mixture of **24** and **25**; ^1H NMR (90 MHz, $CDCl_3$) δ=0.72—0.91 (Me's), 1.08, 1.10 (Me's), 2.03, 2.04 (total 3H, each s; AcO), 4.49 (1H, m), 5.53, and 5.69 (each 0.2H, d, *J*=10.5 Hz); GC-MS **24**; *m/z* (%) 486 (M^+; 13), 426 (31), 411 (14), 383 (46), 303 (100), 290 (38), and 263 (79). **25**; *m/z* (%) 484 (M^+; 13), 424 (60), 409 (35), 303 (100), 290 (32), and 277 (42).

Hydrogenation of the Mixture of 24 and 25. The mixture (39 mg) of **24** and **25** in a ratio of 4:1 was dissolved in ethanol (8 ml) and hydrogenated in the presence of 10% palladium on carbon (25 mg) at room temperature under

atmospheric pressure for 48 h. The usual work-up and chromatography on silica gel (C-200, 3.8 g, elution with 10—15% ether in hexane) afforded the single product, 11-oxolanostan-3β-yl acetate (**24**; 35 mg), mp 144—145 °C (from ether-methanol); IR (Nujol) 1740, 1700, 1245, and 1030 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.72 (3H, s; Me), 0.83—0.90, 1.07—1.10 (Me's), 2.03 (3H, s; AcO), 2.32, and 2.50 (each 1H, d, J=13.5 Hz; 12-H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ=14.6, 15.9, 16.8, 17.1, 18.4, 21.1, 21.2, 22.5, 22.8, 24.0, 28.0, 28.2, 28.3, 29.2, 33.0, 36.0, 36.4, 36.6, 37.4, 38.2, 39.5, 40.5, 47.9, 48.7, 49.9, 53.0, 55.1, 61.3, 80.7, 170.8, and 211.5; MS m/z (%) 486 (M^+; 31), 426 (36), 411 (8), 383 (20), 303 (100), 290 (24), and 263 (72); Found: m/z 486.4101. Calcd for $C_{32}H_{54}O_3$: M, 486.4073. HR-MS m/z 303.2676 ($C_{21}H_{35}O$), m/z 290.2615 ($C_{20}H_{34}O$), and m/z 263.1683 ($C_{16}H_{23}O_3$).

4α,14α,24-Trimethyl-7,7-ethylenedithio-11-oxocholestan-3β-yl Acetate (26). 1,2-Ethanedithiol (1.5 ml) was added to a solution of 4α,14α,24-trimethyl-7,11-dioxocholestan-3β-yl acetate (**18**; 54 mg) in chloroform (2 ml). The solution was cooled in an ice bath, and hydrogen chloride was introduced with stirring for 3 h. The same work-up as before afforded a residue, which was purified by column chromatography on silica gel (C-200, 4.8 g). Elution with 10—30% ether in hexane gave 4α,14α,24-trimethyl-7,7-ethylenedithio-11-oxocholestan-3β-yl acetate (**26**; 56 mg), mp 195—196 °C (colorless needles from ether-methanol); IR (Nujol) 1730, 1700, and 1255 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.75—0.89 (Me's), 1.07 and 1.38 (each 3H, s; Me), 2.04 (3H, s; AcO), 3.26 (4H, s; S-CH_2-CH_2-S), and 4.42 (1H, dt, J=5 and 10 Hz; 3α-H); MS m/z (%) 576 (M^+; 39), 548 (10), 516 (45), and 284 (100); Found: m/z 576.3700. Calcd for $C_{34}H_{56}O_3S_2$: M, 576.3670.

Desulfurization of 4α,14α,24-Trimethyl-7,7-ethylenedithio-11-oxocholestan-3β-yl Acetate (26). A solution of **26** (56 mg) in dioxane (5 ml) was added to Raney nickel W2[10] (ca. 2 g) and the mixture was refluxed for 5—6 h. The same work-up as before and chromatography on silica gel (C-200, 4 g, elution with 2—15% ether in hexane) yielded an inseparable mixture (42 mg) of 4α,14α,24-trimethyl-11-oxocholestan-3β-yl acetate (**27**) and the corresponding 1-ene derivative (**28**), whose ratio was determined to be ca. 1 : 1 by gas chromatography. The mixture of **27** and **28**; ^1H NMR (90 MHz, $CDCl_3$) δ=0.72—0.89 (Me's), 1.02—1.08 (Me's), 2.03 and 2.04 (total 3H, each s; AcO), 4.36 (1H, m; 3α-H), 5.47, and 5.72 (total 1H, d, J=10.5 Hz; CH=CH); GC-MS **27**; m/z (%) 486 (M^+; 19), 426 (34), 411 (7), 317 (66), 304 (35), 291 (8), and 249 (100). **28**; m/z (%) 484 (M^+; 37), 469 (10), 456 (11), 424 (100), 409 (26), 317 (60), 304 (41), and 290 (52).

Hydrogenation of the Mixture of 27 and 28. The mixture (**27** and **28**; 11 mg) in ethanol was hydrogenated in the presence of 10% palladium on carbon (16 mg) for 64 h under the same conditions as before. Crystallization from ether-methanol yielded 4α,14α,24-trimethyl-11-oxocholestan-3β-yl acetate (**27**; 11 mg), mp 141.5—142.5 °C; IR (Nujol) 1730, 1695, 1250, 1020, and 970 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=0.72—0.89 (Me's), 1.05 and 1.09 (each 3H, s; Me), 2.04 (3H, s; AcO), 2.32 and 2.52 (each 1H, d, J=13.5 Hz; 12-H), 2.74 (1H, dt, J=3 and 13.5 Hz; 1β-H), and 4.36 (1H, dt, J=6 and 10.5 Hz; 3α-H); MS m/z (%) 486 (M^+; 20), 426 (40), 411 (9), 317 (76), 304 (39), 291 (9), and 249 (100); Found: m/z 486.4080. Calcd for $C_{32}H_{54}O_3$: M, 486.4072.

4α,14α,24-Trimethylcholestane-3β,11β-diol (29). 4α,14α,24-Trimethyl-11-oxocholestan-3β-yl acetate (**27**; 41 mg) in ether (8 ml) was refluxed with LAH (28 mg) for 1.5 h under nitrogen. Ethyl acetate (ca. 2 ml) and 2 M hydrochloric acid (13 ml) were added and the reaction product was extracted with ether. By column chromatography on silica gel (C-200, 4.6 g) eluted with 10—20% ethyl acetate in hexane, 4α,14α,24-trimethylcholestane-3β,11β-diol (**29**; 35 mg) was obtained, mp 206—207 °C (colorless needles from ether-methanol); ^1H NMR (90 MHz, $CDCl_3$) δ=0.75—0.93 (Me's), 1.01 and 1.11 (each 3H, s; Me), 3.07 (1H, dt, J=4.5 and 10 Hz; 3α-H), and 4.22 (1H, m; 11α-H); MS m/z (%) 446 (M^+; 2), 428 (53), 413 (100), 410 (19), and 395 (43).

4α,14α,24-Trimethyl-11β-hydroxycholestan-3β-yl Acetate (30). A solution of diol (**29**; 41 mg) in acetic anhydride (0.5 ml) and pyridine (1 ml) was allowed to stand for 19 h at room temperature and the reaction mixture was worked up as usual. The residue was purified by column chromatography on silica gel eluted with 10—30% ether in hexane to give 4α,14α,24-trimethyl-11β-hydroxycholestan-3β-yl acetate (**30**; 39 mg) as colorless needles after crystallization from ether-methanol; ^1H NMR (90 MHz, $CDCl_3$) δ=0.74—0.88 (Me's), 1.00, and 1.12 (each 3H; Me), 2.03 (3H, s; AcO), 4.22 (1H, m), and 4.37 (1H, dt, J=4.5 and 10.5 Hz; 3α-H); MS m/z (%) 488 (M^+; 3), 470 (60), 455 (100), 410 (27), and 395 (83); HR-MS m/z 470.4187. Calcd for $C_{32}H_{56}O_3$ (M−H_2O): m/z 470.4122.

4α,14α,24-Trimethyl-9(11)-cholesten-3β-yl Acetate (31). To a solution of the acetate (**30**; 39 mg) in pyridine (2 ml) was added phosphoryl chloride (0.01 ml) and the mixture was stirred at 90 °C for 3 h. Water was added and the reaction mixture was extracted with ether. The usual work-up gave a residue, which was subjected to column chromatography on silica gel (C-200, 5 g). Elution with 10—20% ether in hexane yielded 4α,14α,24-trimethyl-9(11)-cholesten-3β-yl acetate (**31**; 38 mg) as colorless crystals (from ether-methanol), mp 119—120 °C; ^1H NMR (90 MHz, $CDCl_3$) δ=0.66 (3H, s; Me), 0.76—0.90 (Me's), 1.00 (3H, s; Me), 2.04 (3H, s; AcO), 4.37 (1H, m; 3α-H), and 5.30 (1H, m; 11-H); MS m/z (%) 470 (M^+; 70), 455 (100), 410 (5), and 395 (41); Found: m/z 470.4161. Calcd for $C_{32}H_{54}O_2$: M, 470.4124.

4α,14α,24-Trimethyl-9(11)-cholesten-3-one (1). A solution of the acetate (**31**; 38 mg) in ethanol (5 ml) containing potassium hydroxide (0.1 g) was refluxed for 1.5 h. After the solvent was removed in vacuo, aqueous ammonium chloride solution was added. Extraction with ether and the usual work-up afforded a residue (33 mg), which was purified by crystallization from ether-methanol to give 4α,14α,24-trimethyl-9(11)-cholesten-3β-ol as colorless needles; ^1H NMR (90 MHz, $CDCl_3$) δ=0.66 (3H s; Me), 0.75—1.10 (Me's), 3.07 (1H, m; 3α-H), and 5.28 (1H, m; 11-H); MS m/z (%) 428 (M^+; 3), 413 (14), 410 (41), and 495 (100).

The alcohol (33 mg) above obtained was dissolved in acetone (15 ml) and treated with Jones reagent (3 drops) with stirring at 0 °C. After stirring was continued for 10 min at the same temperature, 2-propanol (10 drops) was added and the reaction mixture was stirred for 10 min. The solvent was evaporated, water (10 ml) was added, and the reaction product was extracted with ether. The extract was washed with a saturated sodium hydrogencarbonate solution and followed by the usual work-up to give a residue, which was chromatographed on silica gel (C-200, 5 g). Elution with 10% ether in hexane afforded 4α,14α,24-trimethyl-9(11)-cholesten-3-one (**1**; 27 mg), mp 143—144 °C (from ether-methanol); $[\alpha]_D^{23}$ 76° (c 0.54, EtOH); IR (Nujol) 1705 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=0.69 (3H, s; 18-Me), 0.74 (3H,

s; Me), 0.77—0.90 (Me's), 1.02 (3H, d, J=7.3 Hz; Me), 1.23 (3H, s; 19-Me), and 5.35 (1H, m; 11-H); MS m/z (%) 426 (M^+; 45), 411 (100), 299 (11), 257 (10), 243 (18), and 251 (21); Found: m/z 426.3899. Calcd for $C_{30}H_{50}O$: M, 426.3861.

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