Syntheses of Cholesta-5,7-diene-3β,25-diol and Cholesta-5,7-diene-1α,3β,25-triol

Yoji TACHIBANA,* Shinji YOKOYAMA, and Masahiro TSUJI
Central Research Laboratory, Nisshin Flour Milling Co., Ltd.,
Tsurugaoka, Ooimachi, Irumagun, Saitama 354
(Received February 25, 1989)

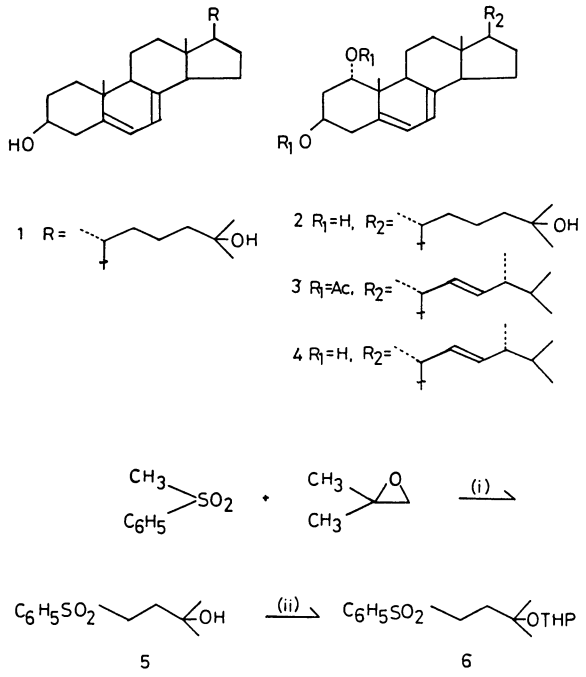
Adducts of 3β-acetoxy- and 1α,3β-diacetoxy-23,24-dinorchola-5,7-dien-22-al (**7** and **14**) with 4-phenyl-3*H*-1,2,4-triazole-3,5-dione prepared by the ozonolysis of the corresponding adducts of ergosteryl acetate and 1α-acetoxyergosteryl acetate were transformed into 22-bromo-3β-tetrahydropyranyloxy- and 22-iodo-1α,3β-bis-(tetrahydropyranyloxy)-23,24-dinorchola-5,7-diene (**11** and **26**). The halide derivatives (**11** and **26**) were coupled with 2-methyl-4-phenylsulfonyl-2-(tetrahydropyranyloxy)butane (**6**) to afford 23-phenylsulfonyl-3β,25-bis(tetrahydropyranyloxy)- and 23-phenylsulfonyl-1α,3β,25-tris(tetrahydropyranyloxy)cholesta-5,7-diene (**12** and **27**). The reductive desulfonylation and deprotection of the tetrahydropyranyl group of **12** and **27** provided the title compounds, cholesta-5,7-diene-3β,25-diol (**1**) and cholesta-5,7-diene-1α,3β,25-triol (**2**).

It has been reported that vitamin D_3 must be metabolized to 25-hydroxyvitamin D_3 (25-OH-D_3) in the liver, and subsequently to 1α,25-dihydroxyvitamin D_3 (25-$(OH)_2$-D_3) in the kidney, before eliciting its hormonal activity.[1] Many workers have reported the syntheses of cholesta-5,7-diene-3β,25-diol (**1**)[2] and cholesta-5,7-diene-1α,3β,25-triol (**2**),[3-5] the precursors of 25-(OH)-D_3 and 1α,25-$(OH)_2$-D_3. Concerning the syntheses of **1** and **2**, any process of preparing them utilizing cholest-5-ene-3β,25-diol[6] and cholest-5-ene-1α,3β,25-triol[7] as key intermediates generally gives poor yields of **1** and **2** due to the side reactions involving the formation of a considerable amount of undesired 4,6-diene isomers.

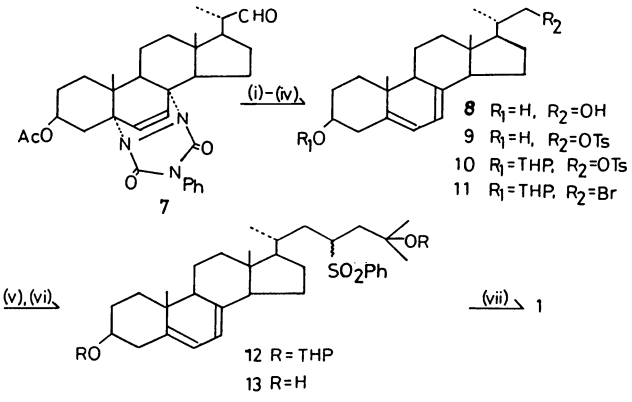
We previously reported the synthesis of 1α-acetoxyergosteryl acetate (**3**) and 1α-hydroxyergosterol (**4**).[8] The C-22 aldehyde or alcohol readily obtainable from **3** and **4** seemed to be a good synthon for the preparation of 1α-hydroxylated steroidal 5,7-diene derivatives. In the present paper, the alternative syntheses of **1** and **2**, by the coupling of the corresponding steroidal 5,7-diene part and the side chain moiety, is described.

We first examined the synthesis of **1**. The C 5 synthon to constitute C (23)—C (27) side chain part was prepared as shown in Scheme 1. Methyl phenyl sulfone was treated with 2,2-dimethyloxirane in the presence of sodium hydride to give phenylsulfonyl alcohol (**5**). The hydroxyl group of **5** was protected as a tetrahydropyranyl ether (**6**) in the usual manner.

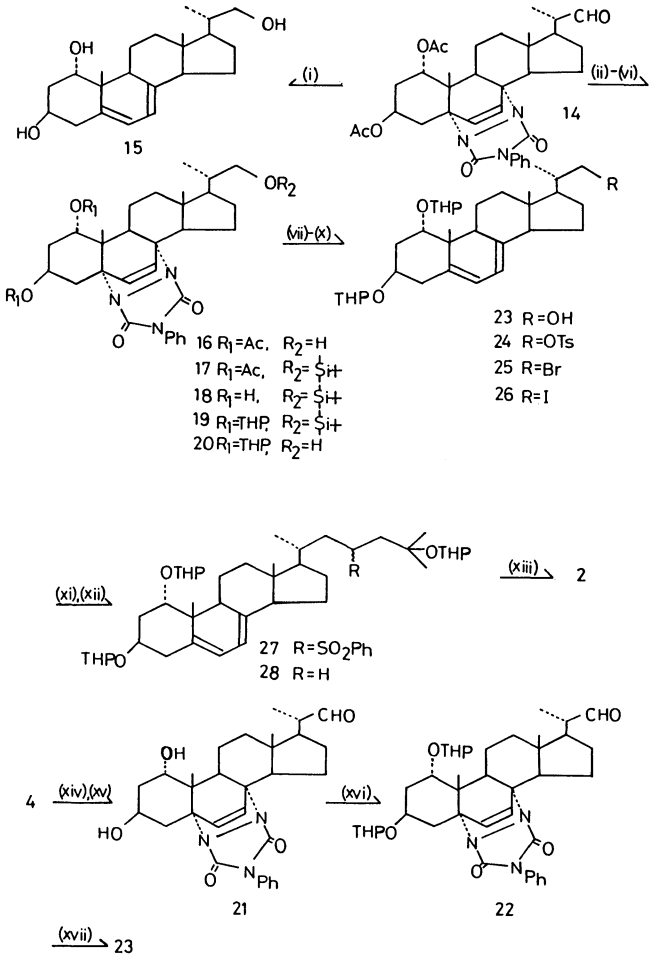
Ergosterol was converted into the known C-22 aldehyde (**7**) via route involving the protection of the 5,7-diene with 4-phenyl-3*H*-1,2,4-triazole-3,5-dione (PTAD) and ozonolysis according to the procedure described by Barton et al.[9] The aldehyde (**7**) was reduced with $LiAlH_4$ to afford the diol (**8**), which was treated with an equimolar amount of *p*-toluenesulfonyl chloride to give C-22 tosylate (**9**) selectively. After the hydroxyl group of **9** was protected as a tetrahydropyranyl ether, the resulting **10** was converted to C-22 bromide (**11**) by treatment with lithium bromide.[10] The bromide (**11**) was condensed with



Scheme 1. (i) NaH, (ii) DHP-PPTS.



Scheme 2. (i) $LiAlH_4$, (ii) TsCl-Py, (iii) DHP-PPTS, (iv) LiBr-Li_2CO_3, (v) BuLi/**6**, (vi) PPTS/EtOH, (vii) Na-Hg.



Scheme 3. (i) $LiAlH_4$, (ii) $NaBH_4$, (iii) *t*-$BuMe_2SiCl$-imidazole, (iv) KOH/EtOH, (v) DHP-PPTS, (vi) Bu_4NF/THF, (vii) $LiAlH_4$, (viii) TsCl-Py, (ix) LiBr-Li_2CO_3, (x) NaI, (xi) BuLi/**6**, (xii) Na-Hg, (xiii) PPTS/EtOH, (xiv) 4-Phenyl-3*H*-1,2,4-triazole-3,5-dione (xv) O_3-Me_2S, (xvi) DHP-PPTS, (xvii) $LiAlH_4$.

the C 5 alcohol derivative (**6**) in the presence of BuLi to provide the 23-phenylsulfonyl derivative (**12**). The deprotection of the tetrahydropyranyl group of **12** under acidic conditions, followed by the reductive desulfonylation[11] of the diol (**13**) with sodium amalgum led to the target compound (**1**) (Scheme 2).

In a manner similar to that described above, the synthesis of **2** was achieved as outlined in Scheme 3. The C-22 aldehyde (**14**) was synthesized by the ozonolysis of the adduct of **3** with PTAD.[12] As described in the synthesis of **1**, we attempted the selective tosylation for the hydroxyl group (at C-22) of the triol (**15**) prepared by the reduction of the aldehyde (**14**) with $LiAlH_4$. However, in contrast to the tosylation of **8**, the reaction of **15** with *p*-toluenesulfonyl chloride gave mixtures. Thus, the aldehyde (**14**) was subjected to reduction with $NaBH_4$ to produce the C-22 alcohol (**16**). The acetyl groups of **16** seemed to be unstable under the basic conditions employed here, and therefore, they were converted to tetrahydropyranyl groups as follows.[13] The protection of the hydroxyl group at C-22 as *t*-butyldimethylsilyl ether and the successive hydrolysis of the acetyl groups afforded the 1,3-diol (**18**). The protection of the hydroxyl groups of **18** as tetrahydropyranyl ether followed by the removal of the *t*-butyldimethylsilyl group with Bu_4NF provided the C-22 alcohol (**20**). The alcohol (**20**) was then treated with $LiAlH_4$ to give bis(tetrahydropyranyloxy) C-22 alcohol (**23**).

Alternatively, the alcohol (**23**) was obtained from 1α-hydroxyergosterol (**4**). The Diels-Alder adduct of **4** with PTAD was ozonized to yield the C-22 aldehyde (**21**). No epimerization of **21** (at C-20) was observed at this stage.[9] The protection of the 1,3-diol of **21** as tetrahydropyranyl ether and the subsequent reduction with $LiAlH_4$ produced the 5,7-diene (**23**). Subsequently, the alcohol (**23**) was reacted with *p*-toluenesulfonyl chloride to afford C-22 tosylate (**24**). The bromide (**25**) derived from **24** proved to be rather unreactive toward **6**. Accordingly, the tosylate (**24**) was converted to the corresponding iodide (**26**) by means of reaction with sodium iodide in boiling acetone.[13]

The iodide (**26**) was condensed with the sulfone (**6**) under the same conditions described above to yield the 23-phenylsulfonyl derivative (**27**). The reductive elimination of the phenylsulfonyl group with Na-Hg and the subsequent cleavage of the tetrahydropyranyl groups furnished the desired compound, cholesta-5,7-diene-1α,3β,25-triol (**2**).

Since 1α-hydroxylated C-22 alcohol (**23**) is obtainable from 1α-acetoxyergosteryl acetate or 1α-hydroxyergosterol, the procedure described here will provide a convenient synthetic method for the preparation of 1α-hydroxylated provitamin D derivatives.

Experimental

Melting points are uncorrected. UV spectra were taken on a Hitachi 320 spectrometer. ^1H NMR spectra were recorded in $CDCl_3$ on a JEOL JNF-FX200 spectrometer with TMS as an internal standard. Mass spectra were measured on a Hitachi M-80 mass spectrometer. Solvents were removed under reduced pressure.

2-Methyl-4-phenylsulfonyl-2-(tetrahydropyranyloxy)-butane (6). A dimethyl sulfoxide solution (70 ml) containing methyl phenyl sulfone (21.8 g) and sodium hydride (3.4 g) was heated at 70 °C for 1.5 h and then the solution was diluted with tetrahydrofuran (THF) (70 ml). To the solution, isobutylene oxide (14.0 g) in 35 ml of THF was added dropwise at 0 °C. The mixture was allowed to react for 3 h at 0 °C. After THF was removed, the residue was extracted with benzene. The benzene solution was washed with brine, dried over sodium sulfate and concentrated to dryness. The residue was purified by silica-gel chromatography. Elution with ethyl acetate/hexane (1/4, v/v) gave 2-methyl-4-phenylsulfonyl-2-butanol (**5**).[11] 20.7 g (65%).

A dichloromethane solution (250 ml) of **5** (8.0 g), dihydropyran (4.4 g), and pyridinium *p*-toluenesulfonate

(PPTS) (0.9 g) was reacted at room temperature for 6 h. The solution was washed with brine, dried (sodium sulfate) and evaporated. The residue was crystallized from ethyl acetate to afford **6**. 8.3 g (76%); mp 80—82 °C (lit,[11] 84—85 °C).

23,24-Dinorchola-5,7-diene-3β,22-diol (8). To a THF (60 ml) solution of $LiAlH_4$ (3.0 g) was added dropwise the solution of **7** (2.9 g in 50 ml of THF). The mixture was refluxed for 3 h. After decomposition of the excess $LiAlH_4$ with water, the solution was filtered on Celite. The residue after the evaporation of THF was crystallized from chloroform-methanol to yield **8**. 1.3 g (73%); mp 195—197 °C; *m/z* 330 (M^+); ^1H NMR δ=5.40, 5.58 (2H, m, H-6, H-7), 3.65 (2H, m, H-22), 3.40 (1H, m, H-3). Found: C, 79.65; H, 10.40%. Calcd for $C_{22}H_{34}O_2$; C, 79.95; H, 10.37%.

23,24-Dinorchola-5,7-diene-3β,22-diol 22-*p*-Toluenesulfonate (9). **8** (740 mg) and *p*-toluenesulfonyl chloride (635 mg) in a pyridine solution (10 ml) were reacted at room temperature for 6 h. The solution was then extracted with chloroform, washed with 10% hydrochloric acid, brine, and saturated sodium bicarbonate, dried (sodium sulfate), and evaporated. The residue was purified by means of chromatography on silica gel. Elution with chloroform/hexane (3/2, v/v) and crystallization of the crude product from ethyl acetate-hexane afforded **9**. 650 mg (60%); mp 163—165 °C; *m/z* 484 (M^+), 466 (M^+-H_2O); ^1H NMR δ=7.79 (2H d, *J*=8.4 Hz, aryl), 7.34 (2H, d, *J*=8.4 Hz, aryl), 5.56, 5.38 (2H, m, H-6, H-7), 3.97 (1H, m, H-22), 3.81 (1H, m, H-22), 3.64 (1H, m, H-3), 2.45 (3H, s, CH_3 (tosyl)). Found: C, 71.56; H, 8.49%. Calcd for $C_{29}H_{40}O_4S$: C, 71.70; H, 8.52%.

3β-Tetrahydropyranyloxy-23,24-dinorchola-5,7-dien-22-ol *p*-Toluenesulfonate (10). The tosylate (**9**) (600 mg) was dissolved in dichloromethane (10 ml). Dihydropyran (155 mg) and PPTS (30 mg) were added to the solution and the mixture was stirred at room temperature for 4 h. The solution was washed with brine and dried (sodium sulfate). The residue after the evaporation of solvent was crystallized from methanol to afford **10**. 470 mg (67%); mp 148—149 °C; *m/z* 568 (M^+), 484 (M^+—DHP); ^1H NMR δ=7.79 (2H, d, *J*=8.4 Hz, aryl), 7.34 (2H, d, *J*=8.4 Hz, aryl), 5.35, 5.55 (2H, m, H-6, H-7), 4.70 (1H, m, CH(THP)), 3.90 (1H, m, CH_2(THP)), 3.82, 3.70 (2H, m, H-22), 3.50 (1H, m, CH_2(THP)), 2.45 (3H, s, CH_3 (tosyl)). Found: C, 71.49; H, 8.48%. Calcd for $C_{34}H_{48}O_5S$: C, 71.79; H, 8.48%.

22-Bromo-3β-tetrahydropyranyloxy-23,24-dinorchola-5,7-diene (11). A *N,N*-dimethylformamide solution (5 ml) of the tosylate (**10**) (470 mg), lithium carbonate (58 mg) and lithium bromide (330 mg) was heated at 70 °C for 1 h. The mixture was extracted with chloroform, washed with brine, dried (sodium sulfate) and concentrated to dryness. The residue was chromatographed on silica gel (eluted with 5% ethyl acetate in hexane) to yield, **11**. 305 mg (77%); mp 146—149 °C (crystallized from ethyl acetate). ^1H NMR δ=5.37, 5.55 (2H, m, H-6, H-7), 4.75 (1H, m, CH(THP)), 3.81 (1H, m, CH_2 (THP)), 3.63 (1H, m, H-3), 3.52 (2H, m, H-22, CH_2(THP)), 3.36 (1H, m, H-22). Found: C, 67.67; H, 8.63%. Calcd for $C_{27}H_{41}O_2Br$: C, 67.91; H, 8.65%.

23-(Phenylsulfonyl)cholesta-5,7-diene-3β,25-diol (13). The sulfone derivative (**6**) (213 mg) was dissolved in THF (5 ml) and cooled to −20 °C. To the solution, was added dropwise 10% BuLi hexane solution (0.4 ml) and then the mixture was reacted with stirring at −20 °C for 1 h. To the solution was added the 22-bromide (**11**) (65 mg) in a mixture solution of HMPA (0.1 ml) and THF (0.5 ml). The mixture solution was stirred at −20 °C for 3 h. After the addition of sat ammonium chloride, the mixture was extracted with chloroform, washed with brine, dried (sodium sulfate) and evaporated. The residue was purified by chromatography on silica gel. Elution with 10% ethyl acetate in hexane afforded (**12**) (100 mg). The crude product was dissolved in ethanol (5 ml) and PPTS (16 mg) was added. The mixture solution was reacted at 50 °C for 3 h and extracted with chloroform. The solution was washed with brine, dried (sodium sulfate) and concentrated to dryness. The residue was chromatographed on silica gel (eluted with 20% ethyl acetate in hexane) to give **13**. 38 mg (51%) (amorphous powder); *m/z* 540 (M^+); ^1H NMR δ=7.91—7.95 (2H, m, aryl), 7.54—7.70 (2H, m, aryl), 5.57, 5.35 (2H, m, H-6, H-7), 3.70 (1H, m, H-3), 3.45 (1H, m, H-23).

Cholesta-5,7-diene-3β,25-diol (1). A solution of the sulfone derivative (**13**) (38 mg) in methanol (15 ml) saturated with Na_2HPO_4 was treated with 5% Na-Hg (2.5 g) at 35 °C for 4 h. After the separation of Hg by filtration, the solution was extracted with chloroform, washed with brine, and dried (sodium sulfate). Evaporation of the solvent left solid, which was crystallized from chloroform-hexane to provide **1**. 14 mg (50%); mp 182—183 °C. (lit,[2] 185—187 °C). UV λ_{max} 282 nm (ε=11900, ethanol).

22-Hydroxy-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-23,24-dinorchol-6-ene-1α,3β-diol 1,3-Diacetate (16). To a ethanol solution (10 ml) of sodium borohydride (0.6 g) was added a solution of **14** (2.0 g) in chloroform (50 ml) and the mixture was reacted with stirring at 0 °C for 30 min. The solution was washed with 50% acetic acid, sat sodium hydrogencarbonate and brine, dried (sodium sulfate) and evaporated. Crystallization of the residue from chloroform-hexane afforded **16**. 1.8 g, (90%); mp 196—198 °C; *m/z* 370 (M^+—triazolidine—CH_3COOH); ^1H NMR δ=7.26—7.52 (5H, m, aryl), 6.45, 6.34 (2H, ABq, *J*=8.0 Hz, H-6, H-7), 5.91 (1H, m, H-3), 5.11 (1H, brs, H-1), 3.21—3.38 (2H, m, H-22), 2.01, 2.03 (6H, s, $COCH_3$). Found: C, 66.94; H, 7.15; N, 6.82%. Calcd for $C_{34}H_{43}O_7N_3$: C, 67.42; H, 7.15; N, 6.94%.

22-(*t*-Butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-23,24-dinorchol-6-ene-1α,3β-diol 1,3-Diacetate (17). To a solution of **16** (1.8 g) in *N,N*-dimethylformamide (5 ml) was added *t*-butyldimethylsilyl chloride (0.9 g) and imidazole (0.9 g). The mixture was warmed at 40 °C for 30 min and extracted with ether, washed with brine and evaporated. Purification on silica gel (eluted with ethyl acetate/hexane (3/7, v/v)) afforded **17**. 1.8 g (amorphous powder) (84%); *m/z* 484 (M^+—triazolidine—CH_3COOH); ^1H NMR δ=7.25—7.52 (5H, m, aryl), 6.45, 6.32 (2H, ABq, *J*=8.0 Hz, H-6, H-7), 5.88 (1H, m, H-3), 5.12 (1H, brs, H-1), 3.58 (1H, m, H-9), 3.28 (2H, m, H-22), 2.01, 2.03 (6H, s, $COCH_3$).

22-(*t*-Butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazoline-1,2-diyl)-23,24-dinorchol-6-ene-1α,3β-diol (18). A methanol solution (50 ml) of **17** (1.7 g) and potassium carbonate (0.4 g) was heated at 60 °C for 1 h. After methanol was removed, the residue was extracted with chloroform, washed with brine and concentrated. The residue was crystallized from methanol-benzene to provide **18**. 1.3 g (85%); mp 222—224 °C; *m/z* 460 (M^+—triazolidine); ^1H NMR δ=7.23—7.39 (5H, m, aryl), 6.35, 6.18 (2H, ABq,

J=8.0 Hz, H-6, H-7), 4.80 (1H, m, H-3), 3.69 (1H, brs, H-1), 3.61 (1H, m, H-9), 3.05—3.29 (2H, m, H-22). Found: C, 67.50; H, 8.50; N, 6.36%. Calcd for $C_{36}H_{53}N_3O_5Si$: C, 67.97; H, 8.41; N, 6.61%.

22-(*t*-Butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazoline-1,2-diyl)-1α,3β-bis(tetrahydropyranyloxy)-23,24-dinorchol-6-ene (19). The bis(silyl ether) (**18**) (1.2 g) was dissolved in dichloromethane (20 ml). To the solution, dihydropyran (350 mg) and PPTS (70 mg) were added. The mixture solution was reacted under reflux for 4 h. The solution was washed with brine, dried (sodium sulfate) and evaporated. The residue was purified by silica-gel chromatography. Elution with ethyl acetate/hexane (1/4, v/v) gave **19** as an amorphous powder. 1.1 g (75%); m/z 442 (M^+−triazolidine−2DHP−H_2O); ^{1}H NMR δ=7.20—7.50 (5H, m, aryl), 6.35, 6.49 (2H, ABq, J=8.0 Hz, H-6, H-7), 4.85 (2H, s, CH(THP)), 4.95 (1H, m, H-3), 3.40—3.92 (7H, m, CH_2(THP), H-1, H-9, H-22), 3.15—3.28 (1H, m, H-22). Found: C, 68.47; H, 8.65; N, 5.16%. Calcd for $C_{46}H_{70}N_3O_7$: C, 68.60; H, 8.78; N, 5.22%.

5α,8α-(4-Phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-1α,3β-bis(tetrahydropyranyloxy)-23,24-dinorchol-6-en-22-ol (20). To a THF solution (50 ml) of **19** (1.0 g) was added 2.5 ml of 1 M (1 mol dm^{-3}) tetrabutylammonium fluoride THF solution. The solution was stirred at room temp for 2 h and then extracted with ethyl acetate, washed with brine and evaporated. The residue was chromatographed on silica gel. Elution with ethyl acetate/hexane (3/7, v/v) afforded **20** (amorphous solid). 0.8 g (95%); m/z 514 (M^+−triazolidine); ^{1}H NMR δ=7.21—7.49 (5H, m, aryl), 6.29, 6.43 (2H, ABq, J=8.0 Hz, H-6, H-7), 4.79—4.86 (2H, m, CH(THP)), 3.90 (2H, m, CH_2(THP)), 3.30—3.76 (6H, m, H-1, H-9, H-22, CH_2(THP)).

1α,3β-Dihydroxy-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-23,24-dinorchol-6-en-22-al (21). 1α-Hydroxyergosterol (**4**) (270 mg) was dissolved in acetone (50 ml). To the solution was added PTAD by portion until the red color of the solution persisted. Removal of solvent and crystallization from acetone afforded 1α-hydroxy-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl) ergosterol. 270 mg (87%); mp 237—238 °C; m/z 412 (M^+−triazolidine); ^{1}H NMR δ=7.28—7.41 (5H, m, aryl), 6.23, 6.39 (2H, m, H-6, H-7), 5.20 (2H, m, H-22, H-23), 4.84 (1H, m, H-3), 3.80 (1H, m, H-1). Found: C, 73.42; H, 8.38; N, 6.93%. Calcd for $C_{36}H_{49}O_4N_3$: C, 73.56; H, 8.40; N, 7.15%.

A 1% pyridine-dichloromethane solution (150 ml) of the adduct (200 mg) was ozonized at −60 °C (ozonizer E0-301, Okano Works Ltd.) until almost all the starting material was consumed (monitored by thin-layer chromatography). After argon gas was passed through the vessel, dimethyl sulfide (1 ml) was added. The solution was warmed slowly to room temperature, washed with brine, dried (sodium sulfate) and evaporated. The residue was chromatographed on silica gel. Elution with ethyl acetate/chloroform (1/4, v/v) gave **21** (amorphous powder) 140 mg (79%); m/z 344 (M^+−triazolidine); ^{1}H NMR δ=9.57 (1H, d, J=3.4 Hz, H-22), 7.29—7.40 (5H, m, aryl), 6.24, 6.36 (2H, ABq, J=8.1 Hz, H-6, H-7), 4.76 (1H, m, H-3), 3.76 (1H, m, H-1).

5α,8α-(4-Phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-1α,3β-bis(tetrahydropyranyloxy)-23,24-dinorchol-6-en-22-al (22). To a solution of the 22-aldehyde (**21**) (135 mg) in dichloromethane (10 ml) were added dihydropyran (108 mg) and PPTS (20 mg). The mixture was allowed to react at room temperature for 12 h. The solution was washed with brine, dried (sodium sulfate) and evaporated. The residue was purified by silica-gel chromatography (eluted with ethyl acetate/hexane (1/9, v/v)) to provide **22** ((108 mg (61%)) along with 5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-3β-tetrahydropyranyloxy-23,24-dinorchol-6-en-22-al (42 mg (20%)). m/z 326 (M^+−triazolidine−2DHP−H_2O); ^{1}H NMR δ=9.56 (1H, d, J=3.4 Hz, H-22), 7.30—7.45 (5H, m, aryl), 6.36 (2H, m, H-6, H-7), 4.92 (1H, m, H-3), 4.80—4.85 (2H, m, CH(THP)), 3.89 (2H, m, CH_2(THP)), 3.70 (1H, brs, H-1), 3.50 (2H, m, CH_2(THP)).

1α,3β-Bis(tetrahydropyranyloxy)-23,24-dinorchola-5,7-dien-22-ol (23). (a) (from **20**). A THF solution containing $LiAlH_4$ (0.7 g) was added dropwise the THF solution (50 ml) of **20** (0.7 g). The mixture was reacted under reflux for 1 h. After decomposition of excess $LiAlH_4$, the solution was filtered on Celite. The solution was concentrated and the residue was extracted with ethyl acetate. The solution was washed with brine and evaporated. The residue was purified by silica-gel chromatography. Elution with ethyl acetate/hexane (1/3, v/v) gave **23** (amorphous powder). 0.5 g (95%); ^{1}H NMR δ=5.37, 5.64 (2H, m, H-6, H-7), 4.65—4.80 (2H, m, CH(THP)), 4.13 (1H, m, H-3), 3.89 (2H, m, CH_2(THP)), 3.75 (1H, brs, H-1), 3.65 (1H, m, H-22), 3.52—3.88 (3H, m, CH_2(THP), H-22).

(b) (from **22**). To a THF solution (20 ml) of $LiAlH_4$ (300 mg) was added **22** (100 mg) in THF (20 ml). The mixture was refluxed with stirring for 1 h. After the decomposition of the excess $LiAlH_4$, the solution was filtered on Celite. After the removal of the solvent, the residue was extracted with ethyl acetate. The solution was washed with brine, dried (sodium sulfate) and evaporated. The residue was chromatographed on silica gel. Elution with ethyl acetate/chloroform (1/9, v/v) yielded **23**. 48 mg (63%); the ^{1}H NMR spectrum agreed with that of **23** obtained from **20**.

22-Iodo-1α,3β-bis(tetrahydropyranyloxy)-23,24-dinorchola-5,7-diene (26). To a pyridine solution (5 ml) of **23** (400 mg) was added *p*-toluenesulfonyl chloride (600 mg). The mixture was reacted with stirring at room temperature for 1 h. The solution was extracted with ether, washed with 10% hydrochloric acid, sodium hydrogencarbonate and brine and dried (sodium sulfate). After evaporation of ether, the residue was purified on silica gel. Elution with ethyl acetate/hexane (1/9, v/v) provided 1α,3β-bis(tetrahydropyranyloxy)-23,24-dinorchola-5,7-dien-22-ol *p*-toluenesulfonate (**24**). 450 mg (89%); ^{1}H NMR δ=7.29 (2H, d, J=8.0 Hz, aryl), 7.24 (2H, d, J=8.0 Hz, aryl), 5.35, 5.63 (2H, m, H-6, H-7), 4.68—4.80 (2H, m, CH(THP)), 4.15 (1H, m, H-3), 3.75—4.05 (7H, m, H-1, H-22, CH_2(THP)), 2.25 (3H, s, CH_3(tosyl)).

An acetone solution (5 ml) of the tosylate (**24**) (400 mg) and sodium iodide (540 mg) was heated under reflux for 1 h. The residue after evaporation of acetone was chromatographed on silica gel (eluted ethyl acetate/hexane (1/9, v/v) to give **26** (amorphous powder). 324 mg (85%); m/z 624 (M^+), 540 (M^+−DHP); ^{1}H NMR δ=5.36, 5.64 (2H, m, H-6, H-7), 4.67—4.78 (2H, m, CH(THP)), 4.12 (1H, m, H-3), 3.80—3.98 (2H, m, CH_2(THP)), 3.75 (1H, brs, H-1), 2.45—2.67 (2H, m, CH_2(THP)), 2.20—2.40 (2H, m, H-22). Found: C, 60.99; H, 7.62%; Calcd for $C_{32}H_{49}IO_4$; C, 61.52; H, 7.92%.

23-Phenylsulfonyl-1α,3β,25-tris(tetrahydropyranyloxy)-cholesta-5,7-diene (27). A THF solution (10 ml) of **6** (910

mg) was cooled −20 °C. To the solution was added dropwise a 10% BuLi hexane solution (1.8 ml). The mixture was stirred at −20 °C for 30 min. To the mixture solution was added dropwise a solution of **26** (570 mg in 5 ml of THF and 0.5 ml of HMPA). The mixture was allowed to react for 30 min at −20 °C and for 1 h at 0 °C. After the reaction was stopped by adding sat. ammonium chloride, the mixture was extracted with ethyl acetate, washed with brine, dried (sodium sulfate) and evaporated. The residue was purified by chromatography on silica gel. Elution with ethyl acetate/hexane (1/4, v/v) yielded **27**. 700 mg (95%); *m/z* 706 (M^+−DHP−H_2O; ^{1}H NMR δ=7.50—7.97 (5H, m, aryl), 5.35, 5.62 (2H, m, H-6, H-7), 4.81 (3H, brs, CH(THP)), 4.14 (1H, m, H-3), 3.80—4.00 (3H, m, CH_2(THP)), 3.76 (1H, brs, H-1), 3.35—3.50 (3H, m, CH_2(THP)).

1α,3β,25-Tris(tetrahydropyranyloxy)cholesta-5,7-diene (28). A methanol solution (60 ml) (saturated with Na_2HPO_4) of **27** (700 mg) was treated with 5% Na-Hg (8.0 g) at room temperature for 6 h. After Hg was removed by filtration on Celite, the mixture was extracted with ether and washed with brine. The residue after evaporation of ether was chromatographed on silica gel. Elution with ethyl acetate/hexane (1/9, v/v) afforded **28**. 520 mg (90%); *m/z* 584 (M^+−DHP); ^{1}H NMR δ=5.36, 5.64 (2H, m, H-6 H-7), 4.69 (3H, m, CH(THP)), 4.12 (1H, m, H-3) 3.91 (3H, m, CH_2(THP)), 3.74 (1H, brs, H-1), 3.46 (3H, m, CH_2(THP)).

Cholesta-5,7-diene-1α,3β,25-triol (2). A mixture of **28** (400 mg) and PPTS (24 mg) in ethanol (6 ml) was heated at 55 °C for 4 h. The solution was extracted with ether, washed with brine and dried (sodium sulfate). The residue after evaporation of ether was purified by chromatography on silica gel. Elution with ethyl acetate/chloroform (1/3, v/v) gave the crude **2**, which was crystallized from ether-hexane to provide **2** as colorless needles. 205 mg (82%); mp 207—208 °C (lit,[3] 211—213 °C); UV λ_{max} 282 nm (ε=11800, ethanol).

References

1) H. F. DeLuca, H. E. Paaren, and H. K. Schnoes, *Top. Curr. Chem.*, **83**, 1 (1979); H. F. DeLuca and H. K. Schnoes, *Ann. Rep. Med. Chem.*, **19**, 179 (1984).

2) J. A. Campbell, D. M. Squires, and J. C. Babcock, *Steroids*, **13**, 567 (1969).

3) T. Sato, H. Yamauchi, Y. Ogata, T. Kunii, K. Kagei, S. Toyoshima, and T. Kobayashi, *Chem. Pharm. Bull.*, **26**, 2933 (1978).

4) K. Ochi, I. Matsunaga, H. Nagano, M. Fukushima, M. Shindo, C. Kaneko, M. Ishikawa, and H. F. DeLuca, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 165.

5) T. Kametani and H. Furuyama, *Med. Res. Rev.*, **7**, 147 (1987).

6) J. M. Blunt and H. F. DeLuca, *Biochemistry*, **8**, 671 (1969); W. G. Salmond and M. C. Sobala, *Tetrahedron Lett.*, **1977**, 1695; F. J. Sardina, A. Mourino, and L. Castedo, *ibid.*, **24**, 4477 (1983); K. Miyamoto, N. Kubodera, E. Maruyama, K. Ochi, T. Mori, and I. Matsunaga, *Synth. Commun.*, **16**, 513 (1986).

7) D. H. R. Barton, R. H. Hesse, M. Pechet, and E. Rizzardo, *J. Chem. Soc., Chem. Commun.*, **1974**, 103; M. Morisaki, K. Bannai, and N. Ikekawa, *Chem. Pharm. Bull.*, **21**, 1853 (1973); E. J. Semmler, M. F. Holick, H. K. Schnoes, and H. F. DeLuca, *Tetrahedron Lett.*, **1972**, 4147; J. A. Iacobelli and M. R. Uskokovic, *Helv. Chim. Acta*, **57**, 781 (1974).

8) Y. Tachibana, *Bull. Chem. Soc. Jpn.*, **61**, 3915 (1988).

9) D. H. R. Barton, T. Shioiri, and D. A. Widdowson, *J. Chem. Soc. C*, **1971**, 1968; J. W. Morzycki, H. K. Schnoes, and H. F. DeLuca, *J. Org. Chem.*, **49**, 2148 (1984).

10) H. Takayama, M. Ohmori, and S. Yamada, *Tetrahedron Lett.*, **21**, 5027 (1980); S. Yamada, M. Shiraishi, M. Ohmori, and H. Takayama, *ibid.*, **25**, 3347 (1984).

11) A. Fürst, L. Labler, and W. Meier, *Helv. Chim. Acta*, **65**, 1499 (1982).

12) M. Tsuji, Doctral Thesis, University of Tokyo, Tokyo, Japan, 1988.

13) S. K. Dasgupta, K. R. Crump, and M. Gut, *J. Org. Chem.*, **39**, 1658 (1974); Y. Kobayashi, T. Taguchi, S. Mitsuhashi, T. Eguchi, E. Oshima, and N. Ikekawa, *Chem. Pharm. Bull.*, **30**, 4297 (1982); R. R. Sicinski, H. F. DeLuca, H. K. Schnoes, Y. Tanaka, and C. M. Smith. *Bioorg. Chem.*, **15**, 152 (1987); T. Taguchi, R. Namba, M. Nakazawa, M. Nakajima, Y. Nakama, Y. Kobayashi, N. Hara, and N. Ikekawa, *Tetrahedron Lett.*, **29**, 227 (1988).