April 1993 Notes Chem. Pharm. Bull. 41(4) 763—765 (1993) 763

Potential Bile Acid Metabolites. XXI.
A New Synthesis of Allochenodeoxycholic and Allocholic Acids[1)]

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Received September 28, 1992

A new method for the preparation of allochenodeoxycholic and allocholic acids is described. The key steps in the synthesis are 1) simultaneous oxidation–dehydrogenation reaction of 3α-hydroxy 5β-bile acid formyl esters with iodoxybenzene catalyzed by benzeneseleninic anhydride, 2) reductive allomerization at C-5 of the 1,4-dien-3-oxo hydroxy acids with lithium/liq. ammonia, and 3) subsequent reduction of the resulting 3-oxo 5α-compounds with K-Selectride.

Keywords 3α,7α-dihydroxy-5α-cholanoic acid; 3α,7α,12α-trihydroxy-5α-cholanoic acid; bile acid

Allochenodeoxycholic (**1a**) and allocholic (**1b**) acids, historically of key importance in the elucidation of the structural and stereochemical relationships between the 5α-(A/B-*trans*; "allo") and 5β-(A/B-*cis*; normal) bile acids, are products isolated from some vertebrates[2)] and from human biologic fluids[3)] and are also attractive starting materials for the synthesis of various 5α-bile alcohols present in lower vertebrates.[4)] However, **1a** and **1b**, although known for many years and with a number of reported methods for preparation,[5)] are still not easily available. We now report a new synthesis of **1a** and **1b**, which proceeds through easily prepared, well defined intermediates and affords pure products in good yields.

The desired compounds **1a** and **1b** were synthesized from the methyl esters (**2a** and **2b**) of the respective parent 5β-bile acids, chenodeoxycholic and cholic acids, according to the route shown in Chart 1. It seemed to us that the most feasible route, starting from the readily available **2a** and **2b**, to the corresponding 5α-analogs (**1a** and **1b**), through the inversion of the configuration at C-5 (allomerization), would be a better way to obtain intermediary 4-en-3-oxo or 1,4-dien-3-oxo hydroxy acids.[6)] In our recent paper,[7)] we have reported an easy and high yield (64—80%) one-step conversion of various methyl 3-hydroxy acetoxy cholanoates to the corresponding 1,4-dien-3-ones by treatment in boiling toluene with iodoxybenzene catalyzed benzeneseleninic anhydride. In fact, our preliminary experiment indicated that the direct oxidation–dehydrogenation reaction of methyl 3α-hydroxy-7α,12α-diacetoxy-5-β-cholanoate proceeds cleanly (isolated yield, 73%), when the hydroxyl groups at C-7 and/or C-12 are protected by an acetyl group. However, attempted hydrolysis of the resulting methyl 3-oxo-7α,12α-diacetoxy-1,4-choladienoate in the subsequent step under the usual conditions (refluxed in 10% methanolic potassium hydroxide for 8 h) resulted in the easy elimination of the acetoxyl group at C-7 to form the 3-oxo-1,4,6-trienoic acid. Consequently, we could prepare the key intermediates, 1,4-dien-3-oxo hydroxy acids **6a** and **6b**, from methyl chenodeoxycholate 7-formate **4a** and methyl cholate 7,12-diformate **4c**, respectively, *via* the 1,4-dien-3-oxo formyl esters (**5a** and **5c**), because the formyl group as a protecting group is much more easily eliminated than the acetyl group under mild conditions.[8)] Compounds **4a** and **4c** were obtained in two steps from **2a** and **2b**, respectively, as follows: 1) formylation of **2a** and **2b** with 99% formic acid containing a catalytic amount of perchloric acid gave the performylated esters (**3a** and **3c**) and 2) subsequent partial deformylation at C-3 was effected by using saturated methanolic ammonia at room temperature for 30 min,

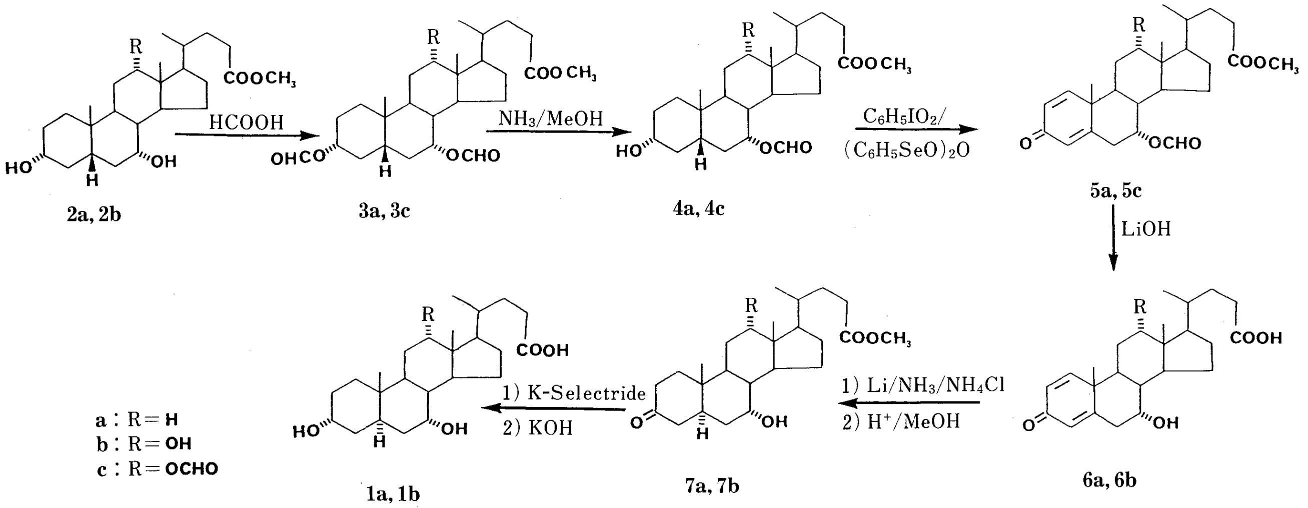

Chart 1

without disturbing the C-7 and C-12 formyloxy groups and the C-24 ester group. This procedure is therefore preferable to the hazardous and toxic diazomethane method[9] for the large scale preparation of **4a** and **4c**.

When the iodoxybenzene–benzeneseleninic anhydride reaction mentioned above was applied to **4a** and **4c**, the compounds were smoothly converted to the 1,4-dien-3-oxo formyl esters **5a** (yield, 77%) and **5c** (yield, 70%). (In this reaction, iodoxybenzene and benzeneseleninic anhydride may be replaced by *m*-iodoxybenzoic acid and diphenyl diselenide, respectively[9]). Subsequent treatment of **5a** and **5c** with lithium hydroxide in aqueous methanol under mild conditions (1.5 h at room temperature) resulted in deformylation at both C-7 and C-12, together with hydrolysis of the ester group at C-24, providing **6a** and **6b** almost quantitatively.

The use of metallic lithium in liq. ammonia as a reducing agent was found to be much preferred to that of the catalytic hydrogenation reported recently by Zhu and co-workers[9] in the allomerization of **6a** and **6b**. Thus, the lithium–ammonia reduction of **6a** and **6b**, without the addition of a proton donor,[10] and subsequent reesterification successfully achieved the intended transformation, avoiding the formation of by-products resulting from the reductive allomerization, and raised the isolated yield of the allomerized 3-oxo 5α-esters (**7a** and **7b**) to 60—65%.

As expected, with K-Selectride (potassium tri-*sec*-butylborohydride) as a reducing agent, the 3-oxo group of **7a** and **7b** could be reduced stereoselectively to the axial-oriented 3α-hydroxyl group[11] to give the desired esters of **1a** and **2a** in excellent isolated yields (86 and 91%) without formation of the corresponding 3β-epimers. The esters were then hydrolyzed by the usual methanolic potassium hydroxide method to afford the corresponding acids **1a** and **1b**. Thus, the overall yield of good quality of **1a** and **1b** from **2a** and **2b** was at least *ca.* 30%.

Experimental

Cholic acid was purchased from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan). Chenodeoxycholic acid was kindly supplied from Tokyo Tanabe Co. (Tokyo, Japan). Melting points (mp) were determined on an electric micro hot stage and are uncorrected. Infrared (IR) specta were obtained on a Perkin-Elmer 1600 series FTIR as KBr disk. Ultraviolet (UV) spectra were determined in ethanol solution using a Shimadzu UV-265FS UV-visible recording spectrophotometer. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a JEOL FX-90Q instrument at 90 MHz; chemical shifts are expressed in δ (ppm) relative to Me_4Si. High- and low-resolution mass spectra (MS) were recorded on JEOL JMS-AX500 and DX-303 mass spectrometers, respectively, at 70 eV.

Methyl 3α,7α-Diformyloxy-5β-cholanoate (3a) A solution of methyl chenodeoxycholate (**2a**; 10.0 g) in 99% formic acid (40 ml) containing 10 drops of 60% perchloric acid was stirred at 50 °C for 1.5 h. Acetic anhydride (30 ml) was added slowly with an ice-bath cooling, and the mixture was poured into water. The precipitated solid was filtered, washed with water, and recrystallized from aqueous acetone as colorless needles: yield, 10.36 g (91%); mp 80—82 °C. IR ν_{max} cm^{-1}: 1728 (C=O), 1183 (C–O). ^{1}H-NMR δ: 0.66 (s, 3H, 18-Me), 0.93 (d, 3H, *J*=5.4 Hz, 21-Me), 0.95 (s, 3H, 19-Me), 3.66 (s, 3H, COOMe), 4.73 (br m, 1H, 3β-H), 5.04 (m, 1H, 7β-H), 8.02 (s, 1H, 3α-CHO), 8.08 (s, 1H, 7α-CHO). *Anal.* Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 69.87; H, 8.99.

Methyl 3α,7α,12α-Triformyloxy-5β-cholanoate (3c) Methyl cholate (**2b**, 10.0 g) was converted to its performate **3c** by the method described for the preparation of **3a**. Recrystallization from aqueous ethanol afforded the title compound as colorless thin plates: yield, 10.33 g (86%); mp 133—135 °C. IR ν_{max} cm^{-1}: 1744 (C=O), 1166 (C–O). ^{1}H-NMR δ: 0.76 (s, 3H, 18-Me), 0.85 (d, 3H, *J*=5.4 Hz, 21-Me), 0.95 (s, 3H, 19-Me), 3.66 (s, 3H, COOMe), 4.79 (br m, 1H, 3β-H), 5.08 (m, 1H, 7β-H), 5.27 (m, 1H, 12β-H), 8.03 (s, 1H, 3α-CHO), 8.11 (s, 1H, 7α-CHO), 8.17 (s, 1H, 12α-CHO). *Anal.* Calcd for $C_{28}H_{42}O_8$: C, 66.38; H, 8.36. Found: C, 66.40; H, 8.43.

Methyl 7α-Formyloxy-3α-hydroxy-5β-cholanoate (4a) A stirred suspension of the ester **3a** (8.0 g) in methanol (150 ml) was bubbled with ammonia gas at room temperature for 5 min to saturate the solution; the solution bacame clear within a few minutes. After further stirring at room temperature for 30 min, water (150 ml) was added, and the mixture, with an ice-water cooling, was acidified with 10% H_2SO_4 with stirring. The precipitated solid was filtered, washed with water, and recrystallized from aqueous methanol as colorless thin plates: yield, 6.80 g (91%); mp 75—77 °C. IR ν_{max} cm^{-1}: 1724 (C=O), 3426 (OH), 1180 (C–O). ^{1}H-NMR δ: 0.65 (s, 3H, 18-Me), 0.92 (d, 3H, *J*=5.4 Hz, 21-Me), 0.93 (s, 3H, 19-Me), 3.49 (br m, 1H, 3β-H), 3.66 (s, 3H, COOMe), 5.03 (m, 1H, 7β-H), 8.08 (s, 1H, 7α-CHO). *Anal.* Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.77; H, 9.75.

Methyl 7α,12α-Diformyloxy-3α-hydroxy-5β-cholanoate (4c) The ester **3a** (8.0 g), hydrolyzed with saturated ammonia in methanol by the procedure described for the preparation of **4a**, gave nearly quantitatively the ester **4c**, which resisted crystallization attempts. IR ν_{max} cm^{-1}: 1720 (C=O), 3422 (OH), 1182 (C–O). ^{1}H-NMR δ: 0.75 (s, 3H, 18-Me), 0.84 (d, 3H, *J*=5.4 Hz, 21-Me), 0.93 (s, 3H, 19-Me), 3.48 (br m, 1H, 3β-H), 3.66 (s, 3H, COOMe), 5.04 (m, 1H, 7β-H), 5.25 (m, 1H, 12β-H), 8.10 (s, 1H, 7α-CHO), 8.14 (s, 1H, 12α-CHO). High-resolution MS: 433.2935 (M^+ −2HCOOH, $C_{26}H_{41}O_5$ requires 433.2954).

Methyl 7α-Formyloxy-3-oxo-1,4-choladienoate (5a) To a solution of the ester **4a** (6.0 g) in toluene (200 ml) were added freshly prepared iodoxybenzene (12.0 g) and benzeneseleninic anhydride (1.2 g). The suspension was vigorously stirred under refluxing for 3 h; the reaction was monitored by TLC. The homogeneous solution was cooled to room temperature, and the organic layer was washed with water, dried over Drierite, and evaporated to give a light brown oil. The oil, which consisted essentially of a single component as judged by TLC, was chromatographed on a column of silica gel (150 g). Elution with benzene–EtOAc (1 : 1, v/v) afforded a homogeneous oil (4.53 g, 77%) which could not be crystallized (lit. mp 131—132 °C[6]), but was identified as the desired ester **5a** by the following data. IR ν_{max} cm^{-1}: 1735 (C=O), 1188 (C–O), 1666, 1628, 1601 ($\Delta^{1,4}$-3-oxo). UV λ_{max} nm (ε): 243.1 (14000). ^{1}H-NMR δ: 0.75 (s, 3H, 18-Me), 0.93 (d, 3H, *J*=5.4 Hz, 21-Me), 1.26 (s, 3H, 19-Me), 3.66 (s, 3H, COOMe), 5.21 (m, 1H, 7β-H), 6.03 (br s, 1H, 4-H), 6.26 (dd, 1H, *J*=9.9, 1.8 Hz, 2-H), 7.09 (d, 1H, *J*=9.9 Hz, 1-H), 8.03 (s, 1H, 7α-CHO). High-resolution MS: 428.2561 (M^+, $C_{26}H_{36}O_5$ requires 428.2563).

Methyl 7α,12α-Diformyloxy-3-oxo-1,4-choladienoate (5c) The ester **4c** (6.0 g) was subjected to the oxidation–dehydrogenation reaction with iodoxybenzene and benzeneseleninic anhydride and processed as described for the preparation of **4a**. The oil was chromatographed on a silica gel column (150 g) and eluted with benzene–EtOAc (3 : 7, v/v). Crystallization of the product from EtOAc–hexane gave the title compound **5c** as colorless crystals: yield, 4.12 g (70%); mp 178—180 °C (lit. mp 180—182 °C[6] and 183—184 °C[9]). IR ν_{max} cm^{-1}: 1720 (C=O), 1174 (C–O), 1659, 1622, 1603 ($\Delta^{1,4}$-3-oxo). UV λ_{max}. nm (ε): 243.3 (15500). ^{1}H-NMR δ: 0.84 (s, 3H, 18-Me), 1.25 (s, 3H, 19-Me), 3.66 (s, 3H, COOMe), 5.26 (m, 2H, 7β- and 12β-H), 6.04 (br s, 1H, 4-H), 6.25 (dd, 1H, *J*=9.9, 1.8 Hz, 2-H), 6.95 (d, 1H, *J*=9.9 Hz, 1-H), 8.05, 8.06 (s, each 1H, 7α-, 12α-CHO). *Anal.* Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.58; H, 7.65.

7α-Hydroxy-3-oxo-1,4-choladienoic Acid (6a) To a stirred solution of the ester **5a** (4.0 g) in methanol (160 ml) was added dropwise 2 M LiOH solution (65 ml), and the mixture was stirred at room temperature for 1.5 h. The solvent was evaporated, and the residue was redissolved in water, cooled in an ice-bath, and acidified with 10% H_2SO_4 with stirring. The precipitated solid was filtered, washed with water, and recrystallized from aqueous methanol as colorless needles: yield, 3.46 g (95%); mp 262—264 °C. IR ν_{max} cm^{-1}: 1725 (C=O), 3460 (OH), 1655, 1590 ($\Delta^{1,4}$-3-oxo). UV λ_{max}. nm (ε): 244.6 (14800). ^{1}H-NMR ($CDCl_3$+20% DMSO-d_6) δ: 0.74 (s, 3H, 18-Me), 0.93 (d, 3H, *J*=5.4 Hz, 21-Me), 1.23 (s, 3H, 19-Me), 3.99 (m, 1H, 7β-H), 6.07 (br s, 1H, 4-H), 6.17 (dd, 1H, *J*=9.9, 1.8 Hz, 2-H), 7.11 (d, 1H, *J*=9.9 Hz, 1-H). *Anal.* Calcd for $C_{24}H_{34}O_4$: C, 74.57; H. 8.87. Found: C, 74.33; H, 8.79.

7α,12α-Dihydroxy-3-oxo-1,4-choladienoic Acid (6b) The ester **5c** (4.0 g), hydrolyzed with 2 M LiOH solution and worked up as described for the preparation of **6a**, yielded the crude acid. Recrystallization from aqueous methanol gave **6b** as colorless crystals: yield, 2.98 g (87%); mp 249—252 °C. IR ν_{max} cm^{-1}: 1712 (C=O), 3416 (OH), 1660, 1603 ($\Delta^{1,4}$-3-oxo). UV λ_{max} nm (ε): 243.3 (13900). ^{1}H-NMR ($CDCl_3$+20% DMSO-d_6) δ: 0.74

(s, 3H, 18-Me), 0.99 (d, 3H, $J=6.3$ Hz, 21-Me), 1.21 (s, 3H, 19-Me), 3.96 (m, 2H, 7β-, 12β-H), 6.07 (br s, 1H, 4-H), 6.18 (dd, 1H, $J=9.9$, 1.8 Hz, 2-H), 7.09 (d, 1H, $J=9.9$ Hz, 1-H). *Anal.* Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.71; H. 8.63.

Methyl 7α-Hydroxy-3-oxo-5α-cholanoate (7a) To a blue colored suspension of metallic lithium (600 mg) dissolved in liq. ammonia (250 ml) was added a solution of the acid **6a** (3.0 g) in tetrahydrofuran (THF) (40 ml), and the mixture was stirred at room temperature for 20 min with a dry-ice condenser. The reaction was quenched by adding an excess of ammonium chloride, then most of the ammonia was evaporated. The light gray residue, dissolved in water, was acidified with 10% H_2SO_4 and extracted with EtOAc. The combined extracts were washed with saturated brine, dried over Drierite, and evaporated to dryness. The residue was then esterified in the usual manner. The methylated product, which was shown by TLC to consist essentially of a single component, was purified by a short column of neutral alumina (activity III, 70 g). Elution with benzene–EtOAc (3 : 7, v/v) afforded **7a** which was recrystallized from aqueous acetone as colorless needles: yield, 1.89 g (60%); mp 137—139 °C (lit. mp 137—138 °C[12)] and 143—144 °C[13)]). IR ν_{max} cm^{-1}: 1741 (C=O), 3510, 1035 (OH). ^{1}H-NMR δ: 0.69 (s, 3H, 18-Me), 0.93 (d, 3H, $J=5.4$ Hz, 21-Me), 1.01 (s, 3H, 19-Me), 3.66 (s, 3H, COOMe), 3.86 (m, 1H, 7β-H). *Anal.* Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.05; H, 9.93.

Methyl 7α,12α-Dihydroxy-3-oxo-5-α-cholanoate (7b) The acid **6b** (3.0 g) was subjected to a reduction reaction with metallic lithium/liq. ammonia/ammonium chloride, followed by esterification and worked up as described for the preparation of **6a**. The crude product was purified on a short column of neutral alumina (activity III, 70 g) and eluted with EtOAc–methanol (98 : 2, v/v). Crystallization of the purified product from acetone–hexane gave **7b** as colorless crystals: yield, 2.04 g (65%); mp 149—151 °C (lit. mp 150—152 °C,[9)] 152—154 °C,[14)] 156—157 °C[15)]). IR ν_{max} cm^{-1}: 1716 (C=O), 3400, 1035 (OH). ^{1}H-NMR δ: 0.71 (s, 3H, 18-Me), 0.99 (s, 3H, 19-Me), 3.66 (s, 3H, COOMe), 3.86 (m, 1H, 7β-H), 3.98 (m, 1H, 12β-H). *Anal.* Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.08; H, 9.58.

3α,7α-Dihydroxy-5α-cholanoic Acid (1a) To a stirred solution of the 3-oxo ester **7a** (1.0 g) in dry THF (10 ml), at −20 °C under N_2, was added dropwise a 1 M solution of K-Selectride in THF (5 ml). After the mixture was further stirred at −20 °C for 3 h, 3 N NaOH solution (5 ml) and then 30% H_2O_2 (5 ml) were added slowly to the solution, and the reaction product was extracted with EtOAc (×3). The combined extracts were washed with 10% HCl and saturated brine, dried over Drierite, and evaporated to give an oily residue. The oil was reesterified in the usual manner, and the methylated product, which showed almost a single spot on TLC, was further purified by a short column of neutral alumina (activity II, 30 g). Elution with benzene–EtOAc (2 : 3, v/v) afforded the methyl ester of the title compound **1a** which was recrystallized from aqueous acetone as colorless crystals: yield, 865 mg (86%), mp 125—127 °C (lit. mp 126.5—127.5 °C,[5)] 125—126 °C,[13)] 116—118 °C[14)]). IR ν_{max} cm^{-1}: 1741 (C=O), 3378, 1030, 1004 (OH). ^{1}H-NMR δ: 0.66 (s, 3H, 18-Me), 0.78 (s, 3H, 19-Me), 0.92 (d, 3H, $J=5.4$ Hz, 21-Me), 3.66 (s, 3H, COOMe), 3.83 (m, 1H, 7β-H), 4.05 (m, 1H, 3β-H). MS m/z (relative intensity): 406 (3, M^+), 388 (73, $M-H_2O$), 373 (17, $M-H_2O-CH_3$), 370 (19, $M-2H_2O$), 355 (12, $M-2H_2O-CH_3$), 273 (66, $M-H_2O-$side chain (S. C.)), 264 (29, M−S.C.−part of ring D), 249 (32, M−S.C.−ring D), 246 (37, $M-H_2O-$S.C.−part of ring D), 228 (32, $M-2H_2O-$S.C.−part of ring D), 213 (40, $M-2H_2O-$S.C.−ring D), 55 (100). *Anal.* Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.55; H, 10.42.

The above ester, hydrolyzed by the usual methanolic KOH method, gave nearly quantitatively the corresponding acid **1a**: mp, 245—246 °C (colorless prisms from EtOAc) (lit. mp 245—247 °C[5)], 245—246 °C[13)]). IR ν_{max} cm^{-1}: 1702 (C=O), 3402, 1030, 1003 (OH). ^{1}H-NMR ($CDCl_3$ + 20% DMSO-d_6) δ: 0.65 (s, 3H, 18-Me), 0.76 (s, 3H, 19-Me), 0.92 (d, 3H, $J=5.4$ Hz, 21-Me), 3.75 (m, 1H, 7β-H), 3.97 (m, 1H, 3β-H). *Anal.* Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.17; H, 10.36.

3α,7α,12α-Trihydroxy-5α-cholanoic Acid (1b) The 3-oxo ester **7b** (1.0 g) was reduced with K-Selectride, followed by reesterification as described for the preparation of **1a**. After being processed analogously, the crude product, which was found by TLC to consist essentially of a single component, was further purified by a short column of neutral alumina (activity III, 30 g). Elution with CH_2Cl_2–methanol (97 : 3, v/v) gave the methyl ester of the title compound **1b** which was recrystalized from acetone–hexane as colorless crystals: yield, 885 mg (88%); mp 228—230 °C (lit. mp 226—228 °C[9)], 225—226 °C[14,15)]). IR ν_{max} cm^{-1}: 1740 (C=O), 3386, 1030, 1010 (OH). ^{1}H-NMR δ: 0.68 (s, 3H, 18-Me), 0.77 (s, 3H, 19-Me), 0.98 (d, 3H, $J=5.4$ Hz, 21-Me), 3.66 (s, 3H, COOMe), 3.83 (m, 1H, 7β-H), 3.95 (m, 1H, 12β-H), 4.05 (m, 1H, 3β-H). MS m/z (relative intensity): 404 (1, $M-H_2O$), 386 (69, $M-2H_2O$), 371 (8, $M-2H_2O-CH_3$), 289 (15, $M-H_2O-$S.C.), 271 (100, $M-2H_2O-$S.C.), 253 (19, $M-3H_2O-$S.C.). *Anal.* Calcd for $C_{25}H_{42}O_5$: C, 71.05; H, 10.02. Found: C, 70.83; H, 10.06.

The above ester, hydrolyzed in the usual manner, afforded almost quantitatively the corresponding acid **1b**: mp 254—257 °C (colorless crystals from aqueous acetone) (lit. mp 239—241 °C[12)], 250—251 °C[13)]). IR ν_{max} cm^{-1}: 1709 (C=O), 3400, 1031, 1011 (OH). ^{1}H-NMR ($CDCl_3$ + 20% DMSO-d_6) δ: 0.66 (s, 3H, 18-Me), 0.74 (s, 3H, 19-Me), 0.98 (d, 3H, $J=6.3$ Hz, 21-Me), 3.71 (m, 1H, 7β-H), 3.86 (m, 1H, 12β-H), 3.95 (m, 1H, 3β-H). *Anal.* Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.56; H, 9.64.

Acknowledgements We thank the staff of the Central Analytical Laboratory of the Pharmaceutical Institute, Tohoku University, for elemental analyses and mass spectral measurements. We are also grateful to Tokyo Tanabe Co., Ltd. (Tokyo, Japan) for a generous supply of chenodeoxycholic acid. One (T. I.) of the authors thanks the Koriyama Area Technopolis Promotion Organization for a grant.

References and Notes

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