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AN EFFICIENT SYNTHESIS OF CHOLANIC ACIDS FROM 20-KETOPREGNANES

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Abstract—An efficient synthesis of 3β-hydroxy-5α-cholanic acid (**8**) and 3β-hydroxy-Δ^5-cholanic acid (**16**) was carried out starting from 5α-dihydropregnenolone (**1**) and pregnenolone (**9**). The monoacetates (**3** and **11**), prepared by Grignard reaction of **1** and **9** with 3,3-ethylenedioxypropylmagnesium bromide followed by acetylation, were dehydrated selectively to give the $\Delta^{20(22)}$-compounds (**4** and **12**) which on hydrogenation followed by acid treatment and Jones oxidation yielded **8** and **16**, respectively.

In the course of our work directed toward the total synthesis of steroids via an intramolecular cycloaddition of *o*-quinodimethanes derived from thermolysis of olefinic benzocyclobutenes,[1] we have succeeded in disclosing a novel transformation of D-aromatic steroids into 20-ketopregnane steroids,[2,3] the latter of which are important types of steroids. So, recently we have focussed our attention to devise an efficient conversion of 20-ketopregnane steroids into the other types of steroids having functionallised side chains.[4,5] Although numerous studies[6–14] about an introduction of steroid side chains have been carried out, only limited informations are available for a conversion of 20-ketopregnanes into cholic acid derivatives which are now important compounds for an investigation of the biological fates of cholesterol and also for the treatment of gallstones. Along with our recent success in the total synthesis of (+)-chenodeoxycholic acid,[15] we have studied the introduction of cholic acid side chains into 20-ketopregnanes.

Here we wish to report a synthesis of 3β-hydroxy-5α-cholanic acid (**8**) and 3β-hydroxy-Δ^5-cholanic acid (**16**) starting from 5α-dihydropregnenolone (**1**) and pregnenolone (**9**), respectively.

Grignard reaction of 5α-dihydropregnenolone (**1**) with 3,3-ethylenedioxypropylmagnesium bromide prepared from the corresponding bromide afforded the diol **2** [*m/e* 405 ($\underline{M}^+$-15)] which on selective acetylation gave the monoacetate **3** [*m/e* 447 ($\underline{M}^+$-15)]. Dehydration of **3** was effected by means of phosphoryl chloride-pyridine to yield the $\Delta^{20(22)}$-compound **4** [*m/e* 444 ($\underline{M}^+$)] selectively, which was then hydrogenated to give the 20(*R*)-compound **5** [*m/e* 446 ($\underline{M}^+$)] in quantitative yield.

The aldehyde **6** [*m/e* 402 ($\underline{M}^+$)] obtained by acid treatment of the acetal **5** was finally converted into 3β-hydroxy-5α-cholanic acid (**8**) by Jones oxidation followed by hydrolysis of the resulting acetate (**7**). The compound **8** thus obtained was identical with the authentic sample in all aspects including IR and NMR spectra and mixed m.p.

The compound **16**, $\Delta^{5(6)}$-analogue of the compound **8** was also synthesised from pregnenolone (**9**) through the same reaction sequences described for **8** and also identified by comparison with the authentic sample.[18]

Thus we could propose one of the most effective ways for the stereo-selective introduction of cholanic acid side chain into 20-ketopregnanes.

EXPERIMENTAL

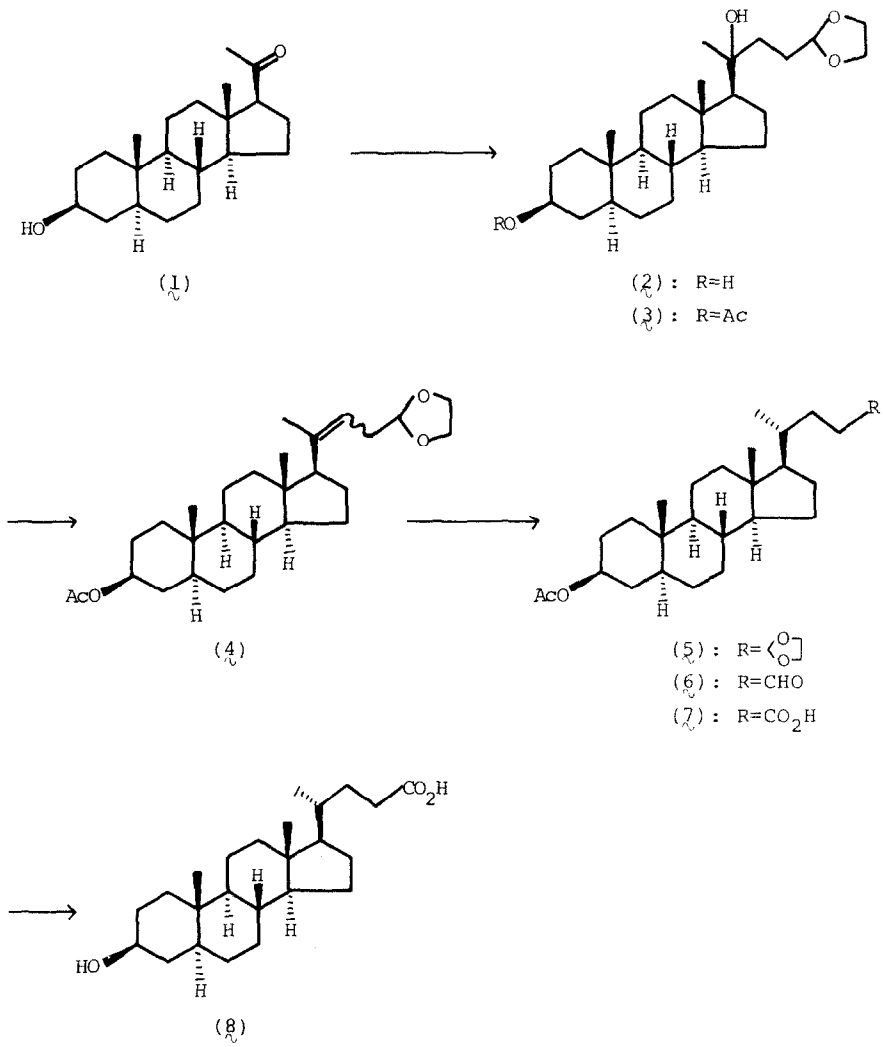
General. M.ps were taken with a Yanagimoto micro-apparatus (MP-52). IR spectra were obtained with a Hitachi 215 recording spectrophotometer and NMR spectra with a JEOL JNM-PMX 60 spectrometer.

Chemical shifts are reported as δ values relative to internal TMS. Mass spectra were recorded on a Hitachi M-52G spectrometer. All optical rotations were measured in $CHCl_3$ soln, otherwise stated, at 20° on a JASCO-PIP-SL polarimeter using 1 dm cell.

24,24-*ethylenedioxy*-5α-*chol*-3β,20-*diol* (**2**). To a stirred soln of **1** (400 mg) in anhyd THF (20 ml) was added a soln of Grignard reagent [prepared from Mg (150 mg) and 3,3-ethylenedioxypropyl bromide (1.2 g) in anhyd THF (30 ml)] at room temp. After being stirred for 1 h under N_2, water (100 ml) was added to the mixture and the resulting mixture was extracted three times with 100 ml portions of EtOAc. The organic layer was washed with NaClaq and dried (Na_2SO_4). Evaporation of the solvent afforded a crude product which was chromatographed on silica gel (15 g) using $CHCl_3$ as eluent to give **2** (497 mg, 94.0%) as colourless needles (from EtOAc), m.p. 172–174° (Found: C, 73.80; H, 10.66. $C_{26}H_{44}O_4$ requires: C, 74.24; H, 10.54%); IR ν_{max} ($CHCl_3$) 3600 cm^{-1} (OH); MNR ($CDCl_3$) δ 0.82 (6H, s, 2×Me), 1.23 (3H, s, Me), 3.23–4.20 (5H, m, 3α-H and $-OCH_2CH_2O-$) and 4.80 (1H, t, J = 3Hz, $-CH\langle^{O-}_{O-}$); MS *m/e* 405 ($\underline{M}^+$-15).

24,24-*ethylenedioxy*-Δ^5-*chol*-3β,20-*diol* (**10**). The compound **10** was obtained from **9** by the procedure described for the synthesis of **2** in 98.2% yield as a colourless powder (Found: C, 74.13; H, 10.08. $C_{26}H_{42}O_4$ requires: C, 74.60; H, 10.11%); IR ν_{max} ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.85 (3H, s, Me), 1.00 (3H, s, Me), 1.11, 1.25 (each 3H, each s, Me), 3.20–3.80 (1H, m, 3α-H), 3.90 (4H, d, J = 2Hz, $-OCH_2CH_2O-$), 4.86 (1H, t, J = 4Hz, $CH\langle^{O-}_{O-}$) and 5.31 (1H, br s, olefinic H); MS *m/e* 403 ($\underline{M}^+$-15).

24,24-*ethylenedioxy*-20-*hydroxy*-5α-*chola*-3β-*acetate* (**3**). To a soln of **2** (450 mg) in pyridine (10 ml) was added Ac_2O (1 g) at room temp under N_2 and the mixture was stirred for 14 h at room temp. The mixture was poured into water (100 ml) and extracted three times with 50 ml portions EtOAc. The organic extract was washed with $NaHCO_3$aq, $KHSO_4$aq, and NaClaq and dried (Na_2SO_4). Evaporation of the solvent afforded a crude product



(1)

(2): R=H
(3): R=Ac

(4)

(5): R=
(6): R=CHO
(7): R=CO_2H

(8)

Scheme 1.

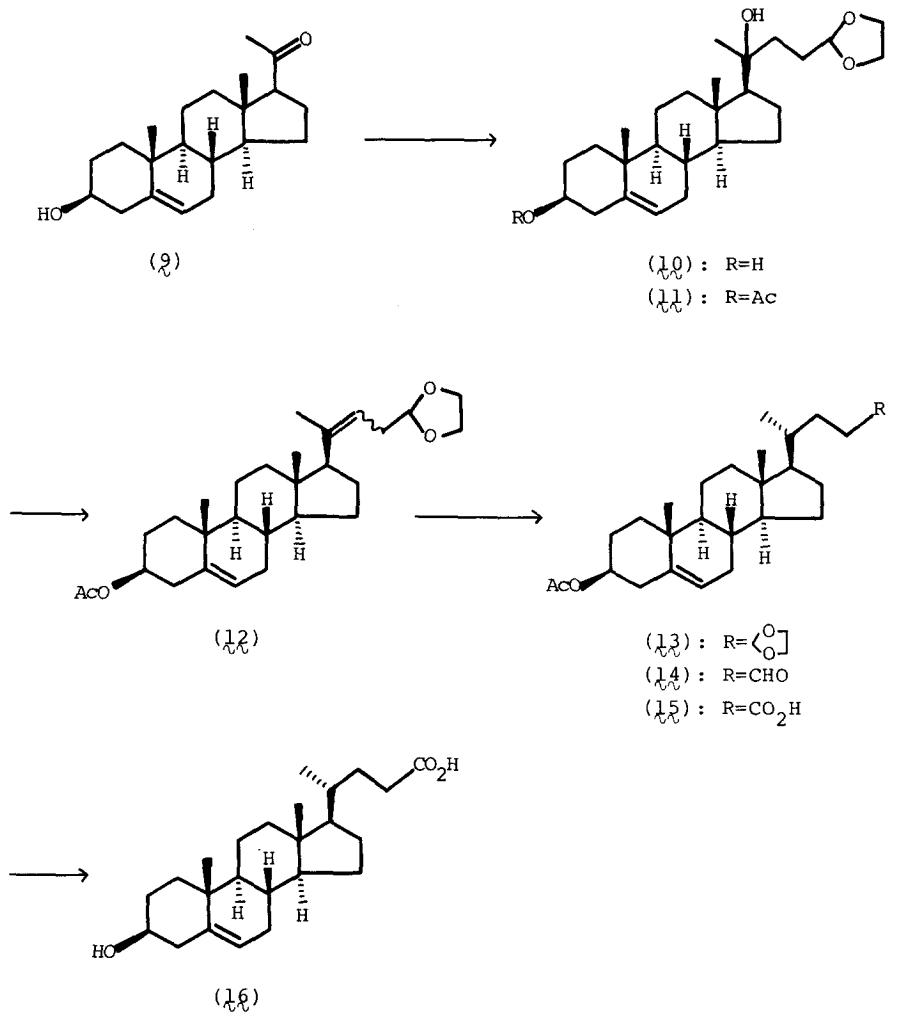
which was chromatographed on silica gel (10 g) using $CHCl_3$ as eluent to give **3** (440 mg, 89.0%) as colourless needles (from hexane), m.p. 134–136° (Found: C, 72.39; H, 10.10. $C_{28}H_{46}O_5$ requires: C, 72.69; H, 10.02%); IR ν_{max} ($CHCl_3$) 3600 cm^{-1} (OH) and 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.80 (6H, s, 2 × Me), 1.21 (3H, s, Me), 1.98 (3H, s, Me), 3.85 (4H, d, J = 2Hz, $-OCH_2CH_2O-$), 4.30–4.90 (1H, m, 3α-H), and 4.77 (1H, t, J = 3Hz, $-CH\langle^{O-}_{O-}\rangle$); MS *m/e* 447 ($M^+$-15).

24,24-*ethylenedioxy*-20-*hydroxy*-Δ^5-*chola*-3β-*acetate* (**11**). Compound **11** was obtained from **10** by the procedure described for **3** in 94.1% yield as a colourless powder (Found: C, 72.54; H, 9.75. $C_{28}H_{44}O_5$ requires: C, 73.00; H, 9.63%); IR ν_{max} ($CHCl_3$) 3600 cm^{-1} (OH) and 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.85 (3H, s, Me), 1.01 (3H, s, Me), 1.64 (3H, s, Me), 2.00 (3H, s, Me), 3.86 (4H, d, J = 2Hz, $-OCH_2CH_2O-$), 4.33–4.85 (1H, m, 3α-H), 4.80 (1H, t, J = 4Hz, $-CH\langle^{O-}_{O-}\rangle$) and 5.33 (1H, br s, olefinic H); MS *m/e* 445 (M^+-15).

3β-*acetoxy*-24,24-*ethylenedioxy*-5α-*chola*-$\Delta^{20(22)}$-*ene* (**4**). A mixture of **3** (1.25 g), pyridine (4.5 ml) and $POCl_3$ (1.5 ml) was stirred for 16 h at room temp under N_2. The mixture was poured into water (50 ml) and extracted three times with 50 ml portions EtOAc. The organic layer was washed with $KHSO_4$aq, sat $NaHCO_3$aq, and sat NaClaq, and dried (Na_2SO_4). Removal of the solvent afforded a crude product which was chromatographed on silica gel (20 g) using $CHCl_3$ as eluent to give **4** (810 mg, 67.5%) as a colourless oil (Found: C, 75.26; H, 9.84. $C_{28}H_{44}O_4$ requires: C, 75.63; H, 9.97%); IR ν_{max} ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.51, 0.52 (each 3H, each s, Me), 0.80 (3H, s, Me), 1.63 (3H, s, Me), 1.97 (3H, s, Me), 3.85 (4H, d, J = 2Hz, $-OCH_2CH_2O-$), 4.30–4.95 (1H, m, 3α-H), 4.80 (1H, t, J = 7Hz, olefinic H); MS *m/e* 444 (M^+).

3β-*acetoxy*-24,24-*ethylenedioxychol*-$\Delta^{5,20(22)}$-*diene* (**12**). Compound **12** was obtained from **11** by the procedure described for **4** in 88.5% yield as a colourless powder (Found: C, 75.68; H, 9.57. $C_{28}H_{42}O_4$ requires: C, 75.97; H, 9.56%); IR ν_{max} ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.57, 0.58 (each 3H, each s, Me), 1.02 (3H, s, Me), 1.67 (3H, br s, Me), 2.02 (3H, s, Me), 3.89 (4H, d, J = 2Hz, $-OCH_2CH_2O-$), 4.25–4.90 (1H, m, 3α-H), 4.86 (1H, t, J = 4Hz, $-CH\langle^{O-}_{O-}\rangle$), 5.23 (1H, t, J = 7Hz, C_{22}-H), and 5.38 (1H, br s, olefinic H); MS *m/e* 442 (M^+).

24,24-*ethylenedioxy*-5α-*chola*-3β-*acetate* (**5**). A mixture of **4** (810 mg) and PtO_2 (80 mg) in EtOH (50 ml) was stirred under H_2 at room temp. Hydrogenation proceeded smoothly within 3 h. The soln was then filtered to remove the catalyst, which was washed with EtOH. The filtrate and washing were combined and evaporated to yield a crude product which was chromatographed on silica gel (20 g) using $CHCl_3$ as eluent to give **5** (790 mg, 97%) as a colourless powder (Found: C, 75.50; H, 10.64. $C_{28}H_{46}O_4$ requires: C, 75.29; H, 10.38%); $[\alpha]_D$ + 12.2° (c = 0.278); IR ν_{max}



Scheme 2.

$(CHCl_3)$ 1720 cm^{-1} (C=O); NMR $(CDCl_3)$ δ 0.65 (3H, s, Me), 0.80 (3H, s, Me), 0.92 (3H, d, J = 8Hz, Me), 1.97 (3H, s, Me), 3.83 (4H, d, J = 2Hz, $-OCH_2CH_2O-$), 4.25–4.90 (1H, m, 3α-H) and 4.73 (1H, t, J = 4Hz, $-CH\langle^{O-}_{O-}\rangle$), MS *m/e* 446 ($M^+$).

24,24-*ethylenedioxy*-Δ^5-*chola*-3β-*acetate* (**13**). Compound **13** was obtained from **12** by the procedure described for **5** in 96.8% yield as colourless needles (from MeOH), m.p. 114–117° (Found: C, 75.34; H, 10.07. $C_{28}H_{44}O_4$ requires: C, 75.63; H, 9.97%); $[\alpha]_D$-38.1° (c = 0.194); IRν_{max} $(CHCl_3)$ 1720 cm^{-1} (C=O); NMR $(CDCl_3)$ δ 0.67 (3H, s, Me), 0.93 (3H, d, J = 7Hz, Me), 1.00 (3H, s, Me), 1.99 (3H, s, Me), 3.87 (4H, d, J = 2Hz, $-OCH_2CH_2O-$), 4.30–4.80 (1H, m, 3α-H), 4.78 (1H, t, J = 4Hz, $-CH\langle^{O-}_{O-}\rangle$) and 5.35 (1H, br s; olefinic H); MS *m/e* 384 (M^+–60).

3β-*acetoxy*-5α-*cholanic aldehyde* (**6**). To a soln of **5** (480 mg) in acetone (5 ml) was added 10% HClaq (5 drops) and the mixture was stirred for 3 h at room temp. The solvent was removed by evaporation and the residue was diluted with water (50 ml) and extracted three times with 50 ml portions EtOAc. This extract was washed with sat $NaHCO_3$aq and dried (Na_2SO_4). Removal of the solvent afforded the crude product which was chromatographed on silica gel (10 g) using $CHCl_3$ as eluent to give **6** (450 mg, 99.5%) as colourless needles (from acetone), m.p. 140–142° (Found: C, 77.96; H, 10.87. $C_{26}H_{42}O_3$ requires: C, 77.56; H, 10.52%); $[\alpha]_D$ + 17.5° (c = 0.252); IRν_{max} $(CHCl_3)$ 1720 cm^{-1} (C=O); NMR $(CDCl_3)$ δ 0.66 (3H, s, Me), 0.81 (3H, s, Me), 0.90 (3H, d, J = 7Hz, Me), 2.00 (3H, s, Me), 4.40–4.98 (1H, m, 3α-H), and 9.73 (1H, br s, CHO); MS *m/e* 402 (M^+).

3β-*acetoxy*-Δ^5-*cholenic aldehyde* (**14**). Compound **14** was obtained from **13** by the procedure described for **6** in 91.7% yield as colourless needles (from MeOH), m.p. 95–97° (Found: C, 78.13; H, 9.99. $C_{26}H_{40}O_3$ requires: C, 77.95; H, 10.07%); $[\alpha]_D$ −42.9°C (c = 0.238); IRν_{max} $(CHCl_3)$ 1720 cm^{-1} (C=O); NMR $(CDCl_3)$ δ 0.69 (3H, s, Me), 0.94 (3H, d, J = 7Hz, Me), 1.01 (3H, s, Me), 2.00 (3H, s, Me), 4.23–4.86 (1H, m, 3α-H), 5.34 (1H, br s, olefinic H) and 9.71 (1H, t, J = 2Hz, CHO); MS *m/e* 340 (M^+-60).

3β-*acetoxy*-5α-*cholanic acid* (**7**). To a soln of **6** (430 mg) in THF (10 ml) was added 8 N soln of chromic acid [prepared from CrO_3 (26.72 g), conc H_2SO_4 (23 ml), and enough water to make the total volume of 100 ml] (8 drops) at 0° and stirring was continued for 10 min at the same temp. The mixture was diluted with water (50 ml) and extracted three times with 50 ml portions EtOAc. The combined organic layer was washed with NaClaq and dried (Na_2SO_4). Removal of the solvent afforded the crude product which was chromatographed on silica gel (5 g) using $CHCl_3$ as eluent to give **7** (245 mg, 54.8%) as colourless needles (from EtOAc–hexane), m.p. 161–163° (Found: C, 74.47; H, 10.43. $C_{26}H_{42}O_4$ requires: C, 74.60; H, 10.11%), $[\alpha]_D$ + 21.7° (c = 0.286); IRν_{max} $(CHCl_3)$ 1720 cm^{-1} (C=O) and 1700 cm^{-1} (C=O); NMR $(CDCl_3)$ δ 0.66 (3H, s, Me), 0.82 (3H, s, Me), 0.94 3H, d, J = 7 Hz. Me), 2.00 (3H, s, Me), 4.30–5.00 (1H, m, 3α-H) and 10.30–11.00 (1H, m, CO_2H); MS *m/e* 418 (M^+).

3β-*acetoxy*-Δ^5-*cholenic acid* (**15**). Compound **15** was obtained from **14** by the procedure described for **7** in 74.2% yield as

colourless needles (from acetone), m.p. 161–163° (Found: C, 74.92; H, 9.88. $C_{26}H_{40}O_4$ requires: C, 74.96: H, 9.68%); $[\alpha]_D$ −37.3° ($c = 0.268$); IR ν_{max} ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.68 (3H, s, Me), 0.93 (3H, d, $J = 7$Hz, Me), 1.00 (3H, s, Me), 2.01 (3H, s, Me), 4.26–4.90 (1H, m, 3α-H), 5.34 (1H, br s, olefinic H) and 10.30–10.80 (1H, m, CO_2H); MS *m/e* 356 ($\underline{M}^+$–60).

3β-hydroxy-5α-cholanic acid (**8**). A mixture of **7** (210 mg) in MeOH (20 ml) and 10% NaOHaq (5 drops) was stirred for 4 h at room temp. After evaporation of the solvent, the residue was treated with 10% HClaq (2 ml) and extracted three times with 50 ml portions of EtOAc. The extract was washed with NaClaq and dried (Na_2SO_4). Evaporation of the solvent afforded a crude product which was chromatographed on silica gel (5 g) using $CHCl_3$–EtOAc (4:1) as eluent to give **8** (165 mg, 87.3%) as colourless needles, which was identical with the authentic sample obtained by purification of commercially available (+)-3β-hydroxy-5α-cholanic acid in its IR ($CHCl_3$), NMR ($CDCl_3$) and mass spectra, including optical rotation and mixed, m.p. 208–211° (from acetone) (Found: C, 76.33; H, 10.46. $C_{24}H_{20}O_3$ requires: C, 76.55; H, 10.71%); $[\alpha]_D$ +33.3° ($c = 0.12$, EtOH); IR ν_{max} ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$–MeOH) δ 0.69 (3H, s, Me), 0.81 (3H, s, Me), 0.95 (3H, d, $J = 6$Hz, Me) and 3.20–3.75 (1H, m, 3α-H); MS *m/e* 376 ($\underline{M}^+$).

3β-hydroxy-Δ⁵-cholenic acid (**16**). Compound **16** was obtained from **15** by the procedure described for **8** in 89.6% yield as colourless needles (from EtOAc), m.p. 218–221° (Found: C, 77.26; H, 10.39. $C_{24}H_{38}O_3$ requires C, 76.96; H, 10.23%); $[\alpha]_D$ −36.0° ($c = 0.116$, EtOH); IR ν_{max} ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$–MeOH) δ 0.71 (3H, s, Me), 0.96 (3H, d, $J = 6$Hz, Me), 1.02 (3H, s, Me), 3.20–3.75 (1H, m, 3α-H), and 5.20–5.45 (1H, br s, olefinic H); MS *m/e* 374 ($\underline{M}^+$), which was identical with the authentic sample obtained by purification of commercially available (−)-3β-hydroxy-Δ⁵-cholenic acid by comparison of its IR, NMR and Mass spectra.

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