Stereocontrolled Conversion of Hyodeoxycholic Acid into Chenodeoxycholic Acid and Ursodeoxycholic Acid

Wei-Shan Zhou,* Zhong-Qi Wang, and Biao Jiang
Shanghai Institute of Organic Chemistry, Academic Sinica, Shanghai, China

The first conversion of methyl hyodeoxycholanate into methyl chenodeoxycholanate and ursodeoxycholic acid in a stereocontrolled manner, by means of a 1,2-carbonyl transposition.

Ursodeoxycholic acid (**1**) and chenodeoxycholic acid (**2a**) are used in the clinical treatment of biliary disease. Although ursodeoxycholic acid (**1**) has been synthesized from chenodeoxycholic acid (**2a**)[1] or cholic acid,[2] the synthesis of (**1**) or (**2a**) from hyodeoxycholic acid (**3a**) has not yet been reported. In connection with our previous work on the synthesis of ursodeoxycholic acid (**1**) and chenodeoxycholic acid (**2a**) from hyodeoxycholic acid (**3a**),[3] we were interested in the stereocontrolled construction of the common 5β-3α,7α(7β)-dihydroxy structural unit. We report the use of a 1,2-carbonyl transposition process to attain our aim.

Methyl hyodeoxycholanate (**3b**) was oxidized selectively with pyridinium dichromate (PDC) to afford (**4**) in 62% yield.[4] Compound (**4**) was then treated with trimethylsilyl chloride in the presence of LDA to afford the enol silyl ether (**5**) regioselectively. The enol silyl ether[5] was then oxidized with *m*-chloroperbenzoic acid or ozone to give the methyl 3α,7α-dihydroxy-6-oxo-5β-cholan-24-oate (**6a**) in 93% yield [91% overall in two steps from (**4**)]. The 5β-configuration of (**6a**) was confirmed by c.d.[4] The hydrazide (**7**) obtained by reaction of (**6a**) with benzenesulphonic acid hydrazide was then reduced with sodium borohydride[5] to yield [in 46% overall yield in two steps from (**6a**)] methyl chenodeoxycholanate (**2b**), identical in all aspects with an authentic sample.[6,7] Methyl chenodeoxycholanate (**2b**) was synthesized, starting from the methyl hyodeoxycholanate (**3b**), in 25% overall yield in 5 steps. For the synthesis of ursodeoxycholic acid (**1**), (**2b**) was oxidized with Jones' reagent to give, in 86% yield, the 5β-methyl-3,7-dioxocholanate which was then reduced with lithium–liquid ammonia to furnish (**1**) in 68% yield, which was identical in all aspects with an authentic sample.[8] The overall yield was 15% over 7 steps starting from the methyl hyodeoxycholanate (**3b**).

Experimental

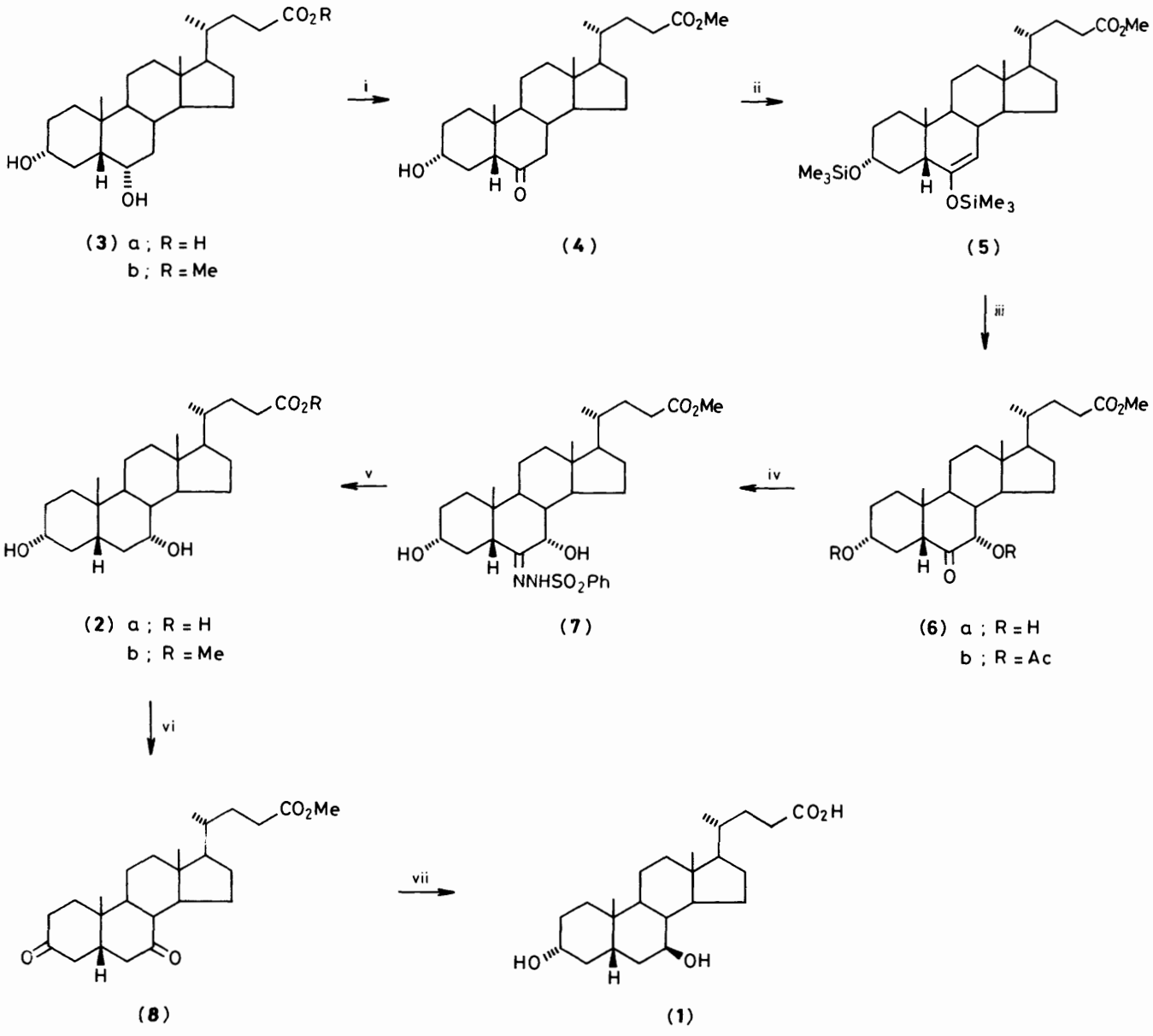
The silica gel used for the chromatography was 200—300 mesh in size. T.l.c. was carried out using silica gel GF254, plates were developed with Vanillin. M.p.s are uncorrected. Optical rotations were measured on an Autopol III polarimeter. I.r. spectra were recorded as KCl discs or films on a Zeiss-75 spectrometer. ^{1}H N.m.r. spectra were recorded in p.p.m. on a Varian XL-200 spectrometer using TMS as an internal standard. Mass spectra were run on Finnigan 4021 instruments. Elemental analyses were performed by the Analytical Department of this Institute. Light petroleum refers to the fraction boiling within the range 60—90 °C throughout.

Methyl 3α,6-*Bis*(*trimethylsilyloxy*)-5β-*chol*-6-*en*-24-*oate* (**5**).— To a solution of di-isopropylamine (0.9 ml, 6.4 mmol) and trace amounts of triphenylmethane in dry tetrahydrofuran (THF) (3 ml) was added BuLi (1.6M in hexane; 4 ml) at 0 °C under N_2 with stirring. The reaction was kept at 0 °C for 30 min and then allowed to warm to room temperature for a further 30 min until an orange–yellow solution was formed. This LDA solution was cooled to −78 °C and freshly distilled trimethylsilyl chloride (1 ml) was added dropwise; the mixture was then stirred for 5 min. A solution of (**4**) (404 mg, 1 mmol) in dry THF (4 ml) was added dropwise and the mixture stirred for 30 min at −78 °C. Triethylamine (2 ml) was then added dropwise and the solution was stirred for 1 h at the same temperature. The mixture was then allowed to warm to −20 °C when saturated $NaHCO_3$ (2 ml) was added. After extraction with EtOAc, the organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give an oil, which was suitable for the next step without purification.

Methyl 3α,7α-*Dihydroxy*-6-*oxo*-5β-*cholan*-24-*oate* (**6a**).—(A) *Using* m-*chloroperbenzoic acid.* To a solution of (**5**) (230 mg) in dry CH_2Cl_2 (10 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (200 mg) in dry CH_2Cl_2 (10 ml) at 5 °C with stirring. The mixture was then allowed to warm to room temperature when it was stirred for 26 h. The mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was then chromatographed on silica gel using acetone–light petroleum (2:8) as eluant to give an oily compound (**6a**) [164 mg, 93% overall yield from (**4**)]; $[\alpha]_D^{13}$ −7.4° (*c* 0.5 in $CHCl_3$); $\nu_{max.}$(film) 3 400, 1 735, and 1 705 cm^{-1}; δ_H 0.66 (3 H, s, 18-CH_3), 0.83 (3 H, s, 19-CH_3), 0.93 (3 H, d, *J* 6 Hz, 21-CH_3), 3.66 (3 H, s, OCH_3), 3.75 (1 H, br, 3β-H), and 3.95 (1 H, d, *J* 5 Hz, 7β-H); *m/z* 420 (M^+).

(B) *Using ozone.* Ozone was passed into a solution of (**5**) (400 mg) in pyridine (0.5 ml) and CH_2Cl_2 (20 ml) at −78 °C, until the solution became blue. After purging the excess of ozone with N_2, the solution was washed with 10% HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel to give (**6a**) as an oil [280 mg, 91% overall yield from (**4**)]; $[\alpha]_D^{20}$ −7.8° (*c* 0.87 in $CHCl_3$); $\nu_{max.}$(film) 3 445, 1 725, and 1 705 cm^{-1}; δ_H 0.63 (3 H, s, 18-CH_3), 0.82 (3 H, s, 19-CH_3), 0.94 (3 H, d, *J* 6 Hz, 21-CH_3), 3.59 (1 H, br, 3β-H), 3.62 (3 H, s, OCH_3), and 3.81 (1 H, d, *J* 4 Hz, 7β-H); *m/z* (420 (M^+).

Methyl 3α,7α-*Diacetoxy*-6-*oxo*-5β-*cholan*-24-*oate* (**6b**).— Compound (**6a**) (60 mg) dissolved in pyridine (1 ml) and Ac_2O (0.5 ml) was allowed to stand at room temperature for 24 h and then poured into water and extracted with EtOAc. The organic layer was washed with 10% HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel using acetone–light petroleum (1:9) as eluant gave (**6b**) (65 mg, 90%) (Found: C, 69.05; H, 8.95. $C_{29}H_{44}O_7$ requires C, 69.02; H, 8.79%); m.p. 149—150 °C (from acetone–light petroleum); $[\alpha]_D^{30}$ 62.3° (*c* 0.62 in $CHCl_3$); $\nu_{max.}$(KCl) 1 742, 1 707, and 1 205 cm^{-1};



Scheme 1. *Reagents:* i, PDC–CH_2Cl_2; ii, LDA, TMSCl, THF; iii, *m*-CPBA, CH_2Cl_2, or O_3, Py–CH_2Cl_2; iv, $C_6H_5SO_2NHNH_2$, 0.5% HCl–MeOH; v, $NaBH_4$, HAc; vi, Jones' reagent; vii, Li–NH_3

δ_H 0.66 (3 H, s, 18-CH_3), 0.86 (3 H, s, 19-CH_3), 0.94 (3 H, d, *J* 6 Hz, 21-CH_3), 2.04 (3 H, s, 3-$COCH_3$), 2.12 (3 H, s, 7-$COCH_3$), 3.67 (3 H, s, OCH_3), 4.58 (1 H, br, 3β-H), and 4.89 (1 H, d, *J* 3.5 Hz, 7β-H); *m/z* 505 ($M^+ + 1$); C.D. $\lambda_{max.}$(MeOH) 212 nm, $\Delta\varepsilon = -3.96$.

Methyl Chenodeoxycholanate (**2b**).—To a solution of the (**6a**) (180 mg) in 0.5% HCl–MeOH (35 ml) was added benzenesulphonohydrazide (130 mg) and the resulting mixture stirred at 5 °C for 24 h. The solution was washed with saturated aqueous $NaHCO_3$ and then concentrated under reduced pressure. The residue was extracted with EtOAc and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give (**7**) (260 mg). The crude compound was dissolved in acetic acid (10 ml) and $NaBH_4$ (200 mg) was added portionwise at room temperature during 4 h with stirring. The solution was then neutralized with cold saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was then chromatographed on silica gel with acetone–light petroleum (2:8) as eluant to give (**2b**) (180 mg, 46% overall yield in two steps) (Found: C, 73.8; H, 10.55. $C_{25}H_{42}O_4$ requires C, 73.85; H, 10.41%); m.p. 98—100 °C (from ethyl acetate); $[\alpha]_D^{21}$ +12.4° (*c* 0.5 in $CHCl_3$) {lit.,[6,7] $[\alpha]_D^{25}$ +13° ($CHCl_3$)}; δ_H 0.66 (3 H, s, 18-CH_3), 0.90 (3 H, s, 19-CH_3), 0.92 (3 H, d, *J* 7 Hz, 21-CH_3), 3.50 (1 H, br, 3β-H), 3.66 (3 H, s, OCH_3), and 3.85 (1 H, d, *J* 4 Hz, 7β-H).

Methyl 3,7-*Dioxo*-5β-*cholan*-2-*oate* (**8**).—To a solution of (**2b**) (70 mg) in acetone (2 ml) at 10 °C was added dropwise the Jones' reagent (0.2 ml) for 30 min with stirring. The mixture was then quenched with propan-2-ol and concentrated under reduced pressure. The residue was extracted with EtOAc and the organic layer was first washed with saturated aqueous

$NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude compound was recrystallized from acetone–light petroleum to give (**8**) (60 mg, 86%), m.p. 157—159 °C; $[\alpha]_D^{20}$ −38.9° (*c* 0.55 in $CHCl_3$) {lit.,[7] m.p. 152—155 °C, $[\alpha]_D$ −36° (*c* 0.2 in $CHCl_3$), lit.,[6] m.p. 163—166 °C}; $\lambda_{max.}$(MeOH 278 nm ($\Delta\varepsilon$ = −0.32).

Ursodeoxycholic Acid (**1**).—To a solution of liquid ammonia (100 ml) (dried with Na) at −50 °C was added a solution of (**8**) (1 g) in dry THF (10 ml) and methanol (0.6 ml), and then lithium (250 mg), the reaction mixture was then stirred for 1 h. After quenching with MeOH (5 ml), the liquid ammonia was evaporated and 15% HCl was added. The mixture was then extracted with EtOAc, and the organic layer separated, washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a residue. This was chromatographed on silica gel with acetone–light petroleum (3:7) as eluant to give (**1**) (680 mg, 68%) (Found: C, 73.85; H, 10.55. $C_{24}H_{40}O_4$ requires C, 73.45; H, 10.25%); m.p. 204—205 °C (from ethyl acetate); $[\alpha]_D^{25}$ +58° (*c* 1.0 in EtOH), {lit.,[8] m.p. 203 °C, $[\alpha]_D^{25}$ +57° (*c* 2.0 in EtOH)}.

References

1 (*a*) I. A. MacDonald, Y. P. Rochon, D. M. Hutchison, and L. V. Holdeman, *Appl. Environ. Microbiol.*, 1982, **44**, 1187; (*b*) Tokyo Tanabe Co. Ltd. Jpn., *Kokai Tokyo Koho Jpn.* 82.56497 (*Chem. Abstr.*, 1982, **97**, 127928s); (*c*) K. Saito, K. Shimomura, and M. Sakamaki, Jap. P. 77 07950 (*Chem. Abstr.*, 1977, **87**, 168274n); (*d*) G. Armand, G.P. 2 950 481 (*Chem. Abstr.*, 1981, **94**, 15996u); (*e*) M. Faba and D. Eusebio, Span. P. 489661 (*Chem. Abstr.*, 1982, **96**, 20375m); (*f*) C. Badia and J. Maria, Span. P. 499525 (*Chem. Abstr.*, 1982, **97**, 145149t).

2 T. Iida and F. C. Chang, *J. Org. Chem.*, 1982, **47**, 2966.

3 Z. Q. Wang, H. Q. Que, L. Z. Jiang, W. S. Zhou, and Youji Huaxue, unpublished work.

4 W. S. Zhou and W. S. Tian, *Acta Chim. Sin.*, 1984, **42**, 1173.

5 T. Iida, T. Tamura, T. Matsumoto, and F. C. Chang, *Synthesis*, 1984, 957.

6 E. Hauser, E. Baumgartner, and K. Meyer, *Helv. Chim. Acta*, 1960, **43**, 1595.

7 E. Mappus and Cl. Y. Cuilleron, *Steroids*, 1979, **33**, 693.

8 L. F. Fieser and M. Fieser, 'Steroids,' Reinhold Publishing Corporation, New York, 1959, p. 422.

Received 4*th October* 1988; *Paper* 8/03950J