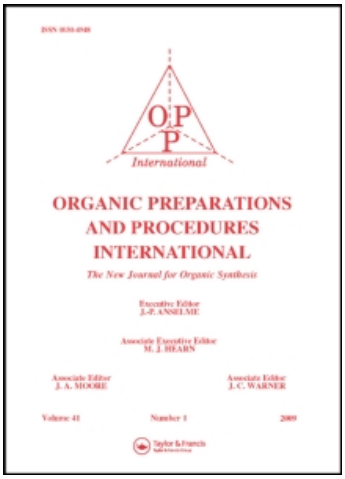

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SELECTIVE REDUCTION OF THE FORMYLATED BILE ACIDS TO THE CORRESPONDING FORMYLATED BILE ALCOHOLS ANALOGS

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SELECTIVE REDUCTION OF THE FORMYLATED BILE ACIDS TO THE CORRESPONDING FORMYLATED BILE ALCOHOLS ANALOGS

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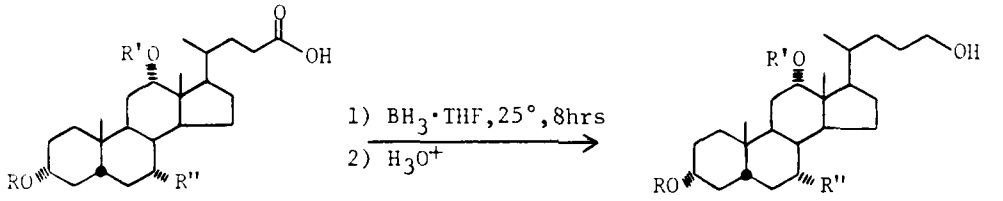
In our study on the development of steroid-based emulsifying agents for synthetic blood,[1] we developed a new method to synthesize formylated bile acid alcohol derivatives (2a and 2b) by selective reduction of the side-chain carboxylic acid function in formylated bile acids with borane/tetrahydrofuran complex (BH_3·THF). Selective reduction of the mixed anhydride of 3α,7α,12α-tris(acetyloxy)cholic acid (1e) and ethyl chloroformate with sodium borohydride has been reported by Hoshita and coworkers.[2] Their method has certain drawbacks: (1) a two-step 24-hour reduction at 0° is required, and (2) the product isolated was a syrup; extension of this method to tris(formyloxy)cholic acid (1a) led to a complex mixture of products, and a difficult chromatographic separation was required to

Scheme 1



1

a) R,R' = (C=O)H; R" = O(C=O)H
b) R,R' = (C=O)H; R" = H
b) R,R' = H; R" = OH
d) R,R',R" = H
e) R,R' = $(C=O)CH_3$; R" = $O(C=O)CH_3$

2

a) R,R' = (C=O)H; R"= O(C=O)H
b) R,R' = (C=O)H; R"= H
c) R,R' = H; R"= OH
d) R,R',R" = H
e) R,R' = $(C=O)CH_3$; R"= $O(C=O)CH_3$
f) R = H; R'= (C=O)H; R"= O(C=O)H
g) R,R" = H; R'= (C=O)H

isolate pure 2a as a syrupy material.[3] This paper describes a simple, high-yield procedure for the syntheses of crystalline formylated bile acid alcohol derivatives, 2a and 2b, and an extension of this reaction to the syntheses of simple bile acid alcohol derivatives, 2c and 2d.

After formylated bile acids 1a and 1b were synthesized in high yield,[4,7] isolate pure 2a as a they were converted to the corresponding alcohols 2a and 2b. A solution of 1a in THF reacted with 1.1 equivalent of BH_3·THF complex in THF at room temperature for 8 hrs to give a mixture of products consisting mostly of 2a (ca. 85%) and 2f (ca. 12%). Flash chromatography of this mixture over silica gel gave the desired product 2a and the major side product 2f in 82% and 10% yields, respectively. The presence of the formyloxy groups in 2a was confirmed by the NMR spectrum which showed formyl protons[5] as a set of singlets at δ 8.14, 8.09 and 8.01 and the methine protons at δ 5.26 (C_{12}-H), 5.05 (C_7-H) and 4.70 (C_3-H).

The extent of removal of the formyl groups was directly dependent on the amount of reducing agent used. When an exact stoichiometric amount of BH_3·THF complex (3 equivalents of hydride) in THF was used, a much cleaner reaction with negligible cleavage (4%) of the formyloxy groups occurred. However, the reduction was incomplete and only a 70% conversion of the acid to alcohol was observed. When a large excess of BH_3·THF complex in THF was used, much greater loss of formyl groups was observed, including formation of 5β-cholan-3α,7α,12α,24-tetrol (2c) and other partially cleaved formyloxycholan-24-ols. Reduction at a lower temperature gave a slower reaction; after 6 days at 5° only a 83% conversion of the acid to alcohol was observed. A slight improvement in the ratio of 2a to 2f (88:12) was observed, but this improvement was offset by the unsatisfactory conversion (83%) and the inconvenience of carrying out the reaction at 5° for 6 days. Cleavage of the formyloxy group from C-3 was indicated by the NMR spectrum which showed the disappearance of the formyl proton signal at δ 8.01 and

shift of the methine proton C_3-H from δ 4.70 to δ 3.55. The conditions developed for 2a were applied to the synthesis of 2b. Reduction of 1b with 1.1 equivalent of BH_3·THF complex in THF at room temperature provided the desired product 2b and the side product 2g in 82% and 17% yields, respectively.

We have extended the above reaction to the synthesis of 5β-cholan-3α,-7α,12α,24-tetrol (2c) and 5β-cholan-3α,12α,24-triol (2d). Cholic acid (1c) and deoxycholic acid (1d) were reduced with an excess of BH_3·THF complex in THF at room temperature to provide the corresponding alcohols 2c and 2d in 90% and 85% yields, respectively. An excess of BH_3·THF complex in THF was employed to compensate for the hydride lost in removal of the hydroxyl protons of the bile acids. The progress of the reaction was monitored by following the disappearance of the C=O stretching vibration at 1716 cm^{-1} in the infrared spectrum. The advantage of our method in contrast to that reported in the literature[2,6] for the synthesis of bile acid alcohol derivatives lies in its simplicity and excellent yields of the isolated products. The above procedure provides easy access not only to simple bile acid alcohols derivatives, but also to formylated bile acid alcohol derivatives because of selectivity of the BH_3·THF for reaction with the acid. The relative ease of removal of the formyl groups recommends this method as a simple entry to the C_{24}-transformed bile acid alcohol derivatives.[7]

EXPERIMENTAL SECTION

The melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The infrared spectra were obtained on a Perkin-Elmer Model 1750 Infrared Fourier Transform Spectrometer. Only principal, sharply defined peaks are reported. The proton NMR and the carbon NMR spectra were recorded on a Magnachem Model 200, 200 MHz, Fourier Transform NMR Spectrometer. Thin layer chromatography (TLC) was performed on precoated TLC plates (silica gel 60, F-254, layer thickness 0.2mm) manufactured by E. Merck and Co. Elemental analyses were carried out by Galbraith Laboratories, Inc. Tetrahydrofuran (THF) was dried and distilled over sodium/benzophenone. The term "brine" means a saturated sodium chloride solution in water. Glassware used was dried in an oven, assembled, and flame-dried under argon.

Anal. Calcd. for $C_{27}H_{42}O_7$: C, 67.76; H, 8.85

Found: C, 68.04; H, 8.90

3α-Hydroxy-7α,12α-bis(formyloxy)-5β-cholan-24-ol (2f).- The title compound was isolated as a colorless syrup with the following properties, TLC (70% benzene/acetone): R_F 0.24; IR (thin film): 3350, 2950, 2850, 1725, 1175 and 1050 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.13 [s, 1H, C_{12}-O(C=O)H], 8.07 [s, 1H, C_7-O(C=O)H], 5.23 (peak, 1H, C_{12}-H], 5.00 (peak, 1H, C_7-H), 3.58 (br m, 3H, J = 6.0 Hz, C_3-H + C_{24}-H_2), 0.91 (s, C_{19}-H_3) and 0.74 (s, C_{18}-H_3).

3α,12α-Bis(formyloxy)-5β-cholan-24-ol-(2b).- Using the above procedure, treatment of a solution of 0.490 g (1.09 mmol) of 1b in 20 mL of THF gave after work-up, a residue consisting of 2b and 2g. Flash chromatography of the residue over silica (200-400 mesh) using 85% benzene/acetone as an eluent gave 0.385 g (81%) of 2b, and 0.075 g (17%) of 2g. Recrystallization of 2b from hexane/ether/methanol (few drops), provided 2b as white needles, mp. 107-108°; TLC (70% benzene/acetone): R_F 0.66; IR (KBr): 3380, 2942, 2869, 1723, 1175 and 1059 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.13 [s, 1H, C_{12}-O(C=O)H], 8.03 [s, 1H, C_3-O(C=O)H], 5.26 (peak, 1H, C_{12}-H), 4.83 (hump, 1H, C_3-H), 3.60 (t, J = 6.25 Hz, 2H, C_{24}-H_2), 0.93 (s, C_{19}-H_3), 0.85 (d, J = 6.6 Hz, C_{21}-H_3) and 0.75 (s, C_{18}-H_3); ^{13}C NMR ($CDCl_3$): δ 160.64 [C_{12}-O(C=O) H], 160.54 [C_3-O(C=O)H], 76.08 (C_{12}), 74.08 (C_3) and 63.37 (C_{24}).

Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74

Found: C, 71.76; H, 9.56

3α-Hydroxy-12α-formyloxy-5β-cholan-24-ol (2g).- The title compound was isolated as a white solid with the following properties, mp. 173-175°; TLC (70% benzene/acetone): R_F 0.26; IR (KBr): 3350, 2940, 2860, 1720, 1170 and 1055 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.10 [s, 1H, C_{12}-O(C=O)H], 5.25 (peak, 1H, C_{12}-H), 3.55 (br m, J = 6.0 Hz, 3H, C_3-H + C_{24}-H_2), 0.89 (s, C_{19}-H_3) and 0.73 (s, C_{18}-H_3).

3α,12α-Bis(formyloxy)-5β-cholan-24-oic acid (1b).- The method described by Tsereng et al.[4] gave the title product with the following partially reported properties, mp. 193.5-195°, lit.[4] mp. 195-196°; TLC (70% benzene/acetone): R_F 0.51; IR (KBr): 3450-2450, 1730, 1715, 1100-1250 and 970 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.97 [br s, 1H, $-CO_2\underline{H}$], 7.96 [s, 1H, C_{12}-O-(C=O)$\underline{H}$], 7.86 [s, 1H, C_3-O(C=O)$\underline{H}$], 5.12 (peak, 1H, C_{12}-$\underline{H}$), 4.73 (hump, 1H, C_3-$\underline{H}$), 0.89 (s, C_{19}-$\underline{H}_3$) and 0.73 (s, C_{18}-$\underline{H}_3$).

3α,7α,12α-Tris(formyloxy)-5β-cholan-24-ol (2a).- A three-necked, round-bottomed flask fitted with a rubber septum, a magnetic stirring bar and an argon inlet/outlet was charged with 0.500 g (1.01 mmol) of 1a and 20 mL of anhydrous THF. To the stirred solution, was added 1.20 mL of 1.0M BH_3·THF complex in THF dropwise via a syringe over a period of 10 mins and the resulting mixture stirred at room temperature for 8 hrs. The reaction mixture was quenched with 5 mL of 0.5N HCl and extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with 0.5N HCl (1 x 75 mL), water (1 x 75 mL), 10% Na_2CO_3 (3 x 75 mL), water (1 x 75 mL) and brine (1 x 75 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to provide a colorless syrupy material. Flash chromatography of this residue over silica (200-400 mesh) using benzene/acetone (7:3) mixture as an eluent, afforded 0.40 g (82%) of 2a and 0.047 g (10%) of 2f. Recrystallization of the crude 2a from hexane/ether/methanol afforded pure 2a as white needles, mp. 147.5-148.5°; TLC (70% benzene/acetone): R_F 0.61; IR (KBr): 3470, 2938, 2874, 1723 and 1179 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.14 [s, 1H, C_{12}-O(C=O)$\underline{H}$], 8.09 [s, 1H, C_7-O(C=O)$\underline{H}$], 8.01 [s, 1H, C_3-O(C=O)$\underline{H}$] 5.26 (peak, 1H, C_{12}-$\underline{H}$), 5.05 (peak, 1H, C_7-$\underline{H}$), 4.70 (hump, 1H, C_3-$\underline{H}$), 3.58 (t, 2H, J = 6.2 Hz, C_{24}-$\underline{H}_2$), 0.93 (s, C_{19}-$\underline{H}_3$), 0.85 (d, J = 6.6 Hz, C_{21}-$\underline{H}_3$) and 0.75 (s, C_{18}-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$): δ 160.54 [-O($\underline{C}$=O)H], 75.34 (C_{12}), 75.74 (C_3), 70.67 (C_7) and 63.32 (C_{24}).

5β-Cholan-3α,7α,12α,24-tetrol (2c).- In a manner similar to that described for the preparation of 1a, a solution of 1.0 g (2.5 mmol) of cholic acid in 25 mL of THF was reacted at room temperature with 21 mL (11 mmol) of 0.5M BH_3·THF complex in THF. The mixture was allowed to stir at room temperature for 8 hrs after which the reaction was quenched by adding 10 mL of 0.5N HCl. After stirring at room temperature for 1 hr, the mixture was diluted with 20 mL of water and 50 mL of THF/diethyl ether (1:1) mixture. The organic layer was separated and the aqueous layer extracted with two 30 mL portions of THF/ether (1:1) mixture. The combined organic layers were then washed with brine (2 x 125 mL), 1.5N KOH (2 x 125 mL), and brine (2 x 125 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to provide 0.93 g of 2c. Recrystallization of the crude product from methanol afforded 0.86 g (89%) of 2c as a white crystalline solid, mp. 228-229.5°, lit.[2] mp. 234.5-235.5°; TLC (80% methanol/CH_2Cl_2): R_F 0.87; IR (KBr): 3300, 2950, 2855, 1090, 1060 and 1020 cm^{-1}; ^1H NMR (pyridine-d_5): δ 4.13 (peak, 1H, C_{12}-H), 4.00 (peak, 1H, C_7-H), 3.75 (t, J= 6.0 Hz, 2H, C_{24}-H_2), 3.63 (hump, 1H, C_3-H), 0.89 (s, C_{19}-H_3) and 0.73 (s, C_{18}-H_3); ^{13}C NMR (CD_3OD): δ 74.19 (C_{12}), 72.98 (C_3), 69.23 (C_7) and 63.73 (C_{24}); mass spectrum, m/z: 376 (M^+-H_2O), 358 (M^+-$2H_2O$), 340 (M^+-$3H_2O$), 289 (M^+-H_2O-side chain), 271 (M^+-$2H_2O$-side chain) and 253 (M^+-$3H_2O$-side chain).

5β-Cholan-3α,7α,24-triol (2d).- Prepared in 85% yield by following the procedure described for 2c. The crude product was recrystallized from ethyl acetate, mp. 121-123°, lit.[6] mp. 123°; TLC (75% CH_2Cl_2/methanol): R_F 0.80; IR (KBr): 3354, 2937, 2865, 1069 and 1044 cm^{-1}; ^1H NMR (pyridine-d_5): δ 4.25 (peak, 1H, C_{12}-H), 3.92 (br m, J = 6.0 Hz, 3H, C_3-H + C_{24}-H_2); ^{13}C (pyridine-d_5): δ 72.38 (C_{12}), 71.31 (C_3) and 62.84 (C_{24}); mass spectrum, m/z: 360 (M^+-H_2O), 342 (M^+-$2H_2O$), 273 (M^+-H_2O-side chain) and 255 (M^+-$2H_2O$-side chain).

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