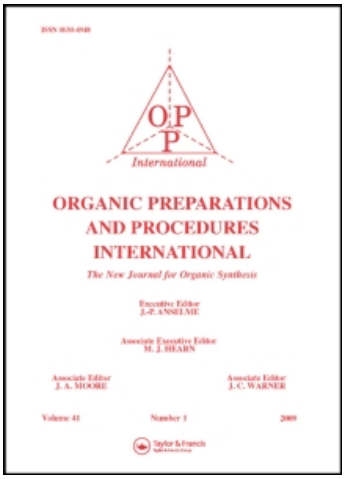

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SELECTIVE PROTECTION OF THE SIDE CHAIN HYDROXY GROUP IN BILE ALCOHOL DERIVATIVES

A. A. Malik[a]; R. J. Cormier[a]; C. M. Sharts[a]
[a] Department of Chemistry, San Diego State University, San Diego, CA

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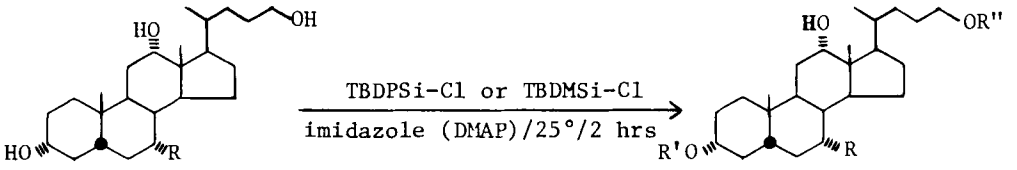
SELECTIVE PROTECTION OF THE SIDE CHAIN HYDROXY GROUP IN BILE ALCOHOL DERIVATIVES

A. A. Malik, R. J. Cormier and C. M. Sharts*

Department of Chemistry
San Diego State University, San Diego, CA 92182-0328

During our investigation on the syntheses of steroid-based emulsifying agents for synthetic blood,[1] we needed a protecting group with the following two properties: (1) stability to n-butyllithium and (2) ability to preferentially protect primary hydroxyl groups in the presence of secondary hydroxyl groups. The silyl ethers tert-butyldimethylsilyl (TBDMSi) ether[2,3] and tert-butyldiphenylsilyl (TBDPSi) ether[4] were prime candidates because they are easily formed, are compatible with various organometallic reagents and are easily cleaved.[2] This report describes TBDPSi-chloride as a preferred reagent for selective silylation of the primary hydroxyl group of bile alcohol derivatives.

Scheme 1



1 R = OH

2 R = H

3 R = OH; R' = H; R" = TBDMSi

5 R = OH; R' = H; R" = TBDPSi

11 R, R' = H; R" = TBDPSi

4 R = OH; R', R" = TBDMSi

6 R = OH; R', R" = TBDPSi

12 R = H; R', R" = TBDPSi

Our initial reactions were carried out with 5β-cholan-3α,7α,12α,24-tetrol (1) and TBDMSi-chloride (Scheme 1). Treatment of a solution of 1 in DMF with 1.20 equivalents of TBDMSi-chloride in the presence of 2.25 equivalents of imidazole at 25° for 2 hours, gave 45.8% of monosubstituted 3 and 12.0% of the disubstituted product 4 (Table, entry 1). The lack of selectivity observed with TBDMSi-chloride led us to use the sterically larger TBDPSi-chloride. 5β-Cholan-3α,7α,12α,24-tetrol reacted with 1.20 equivalents of TBDPSi-chloride in the presence of imidazole at 25° for 2 hrs (entry 2) to give monosubstituted 5 in 92% yield. Less than 1% of the disubstituted product (6) was observed. As shown in the Table, the yield of 5 and the ratio of mono:di (5:6) were dependent on the reaction conditions. When the reaction was carried out at a higher temperature (entries 3 and 4) or for a long period at 25° (entries 5 and 6), a much lower yield

Table. Reaction of Bile Alcohol Derivatives and Substituted Silyl Chlorides

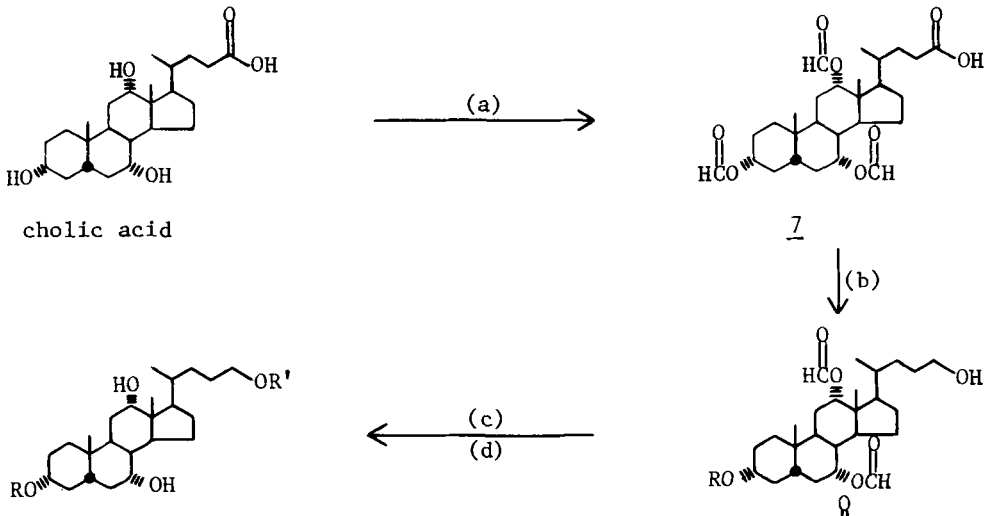
Entry	Silyl Chloride	Bile Alcohol Analog	Base	Temp (°C)	Time[5] (hrs)	Yield mono (%)	Yield di (%)	Ratio mono:di
1	TBDMSi-Cl	1	imidazole	25	2	45.8	12.0	79:21
2	TBDPSi-Cl	"	"	"	2	92.1	0.8	> 99
3	"	"	DMAP	40	19	5.6	1.8	75:25
4	"	"	imidazole	40	19	6.3	2.1	75:25
5	"	"	"	25	19	40.6	2.7	94:6
6	"	"	DMAP	25	19	28.7	1.2	96:4
7	"	"	imidazole	4	144	87.3	0.7	99:1
8	"	"	"	25	8	77.3	1.2	98:2
9	"	"	DMAP	25	2	82.0	-[a]	> 99
10	"	"	"	25	1	89.7	-[a]	> 99
11	"	2	imidazole	25	2	94.5	-[a]	> 99

[a] Amount of disilylated product isolated was less than 0.5%

of 5 resulted. On the other hand, when the reaction was carried out at a lower temperature (entry 7) or for a shorter period of time at 25° (entries 2, 8, 9 and 10),[5] a much higher yield of 5 was obtained. Similarly, the formation of 6 was also dependent on time and temperature. Higher temperature and longer reaction time favored the formation of the disubstituted product 6. For example, when the reaction was carried out at 25° for 2 hrs, a ratio of 5:6 in excess of 99:1 was observed (entry 2). However, when the temperature was increased to 40° and the reaction time extended to 19 hrs (entry 4), a ratio of 5:6 as low as 75:25 was observed.

The position of the silyl group in 5 was confirmed by comparing 5 with product 10a obtained by an alternate route (Scheme 2). Formylation of

Scheme 2



cholic acid

7

10a R = H; R' = TBDPSi

10b R,R' = TBDPSi

8a R = CH

8b R = H

(a) $HCOH/HClO_4/55°/Ac_2O$

(b) $BH_3 \cdot THF/THF/25°$

(c) $TBDPSiCl/DMAP/CH_2Cl_2/25°$

(d) $nBuLi/THF/25°$

cholic acid,[6] followed by selective reduction[7] of the acid function in 7, gave 8a in 74% yield.[8] Silylation of 8a with TBDPSi-chloride, followed by the cleavage of the formyloxy protecting groups with n-butyllithium,[9] provided the desired product 10a in an overall yield of 57%. Comparison of 10a with 5 by TLC, mixture melting point, ^{1}H NMR, and infrared spectroscopy, indicated that the products, 10a and 5, were identical in all respects.

The need for imidazole or some other base catalyst for silylation has been demonstrated by Ogilivee.[3] We chose 4-dimethylaminopyridine (DMAP) as a substitute for imidazole. When DMAP was used instead of imidazole with time of reaction unchanged, lower yields of 5 were obtained as indicated by comparison of entries 2 and 9, 3 and 4, and 5 and 6. However, when the reaction time was shortened (compare entries 9 and 10), 5 was obtained in a yield (90%) comparable with that obtained with imidazole (92%). We find DMAP gives yields comparable to imidazole in a shorter time.

The conditions developed for 5 were applied to the synthesis of 11. Treatment of a solution of 5β-cholan-3α,12α,24-triol (2) in DMF with 1.20 equivalents of TBDPSi-chloride in the presence of 2.25 equivalents of imidazole at room temperature for 2 hrs gave the desired product 11 in 94% yield (Table, entry 11). The amount of the disubstituted product (12) isolated was less than 0.5%.

The cleavage of the TBDPSi ether has been reported in the literature[2-4] to occur under a variety of conditions. In our laboratory we have been able to cleave the TBDPSilyl ether linkage in 5 using 5% HCl in methanol (25°, 12 hrs, 74%), 10% KOH in methanol (reflux, 10 hrs, 76%), and 1.0 M tetra-n-butylammonium fluoride solution in THF (25°, 12 hrs, 75%).

The high yield and selectivity observed in the protection of the primary hydroxyl group in the side chain of bile alcohol analogs make this a useful reaction for the syntheses of C-24 protected bile alcohols analogs.

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 Fourier Transform Infrared Spectrometer. Only principal, sharply defined peaks are reported. The proton nuclear magnetic resonance spectra (^{1}H NMR) and the carbon nuclear magnetic resonance spectra (^{13}C NMR) 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 0.2 mm) manufactured by E. Merck and Co. Flash chromatography was performed on 200-400 mesh silica gel purchased from Aldrich Chemical Co. The elemental analyses were carried out by Galbraith Laboratories. Dimethylformamide (DMF) was dried and distilled over calcium hydride. Tetrahydrofuran (THF) was dried and distilled over sodium/benzophenone. n-Butyllithium (2.6M in hexane), BH_3·THF complex (1.0M in THF), 4-dimethylaminopyridine (DMAP) and tert-butyldiphenylsilyl chloride (TBDPSi-Cl) were purchased from Aldrich Chemical Co. The term "brine" means a saturated sodium chloride solution in water. 5β-Cholan-3α,7α,12α,24-tetrol (1) and 5β-cholan-3α-12α,24-triol (2) and 3α,7α,12α-tris (formyloxy)-5β-cholan-24-ol (8a) were prepared by a literature procedure.[8]

3α,7α,12α-Trihydroxycholan-24-ol-tert-butyldiphenylsilyl ether (5).-A two-necked, round-bottomed flask fitted with rubber septums, a magnetic stirring bar and an argon inlet/outlet was charged with 0.350 g (0.89 mmol) of 5β-cholan-3α,7α,12α,24-tetrol (1), 0.136 g (2.00 mmol) of imidazole and 4.5 mL of DMF. The mixture was heated (ca. 50°) to effect solution, cooled to room temperature and treated with 0.30 mL (0.32 g, 1.16 mmol) of TBDPSi-chloride. After stirring at room temperature for 2 hrs, the mixture was diluted with diethyl ether (40 mL) and the contents poured into a beaker containing 40 mL of 1N HCl. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 25 mL). The ethereal layers were combined and washed with 1N HCl (1 x 75 mL), water (2 x 75 mL) and brine (2 x 75 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to provide a yellow oil. Flash chromatography of the residue over silica gel (200-400 mesh) using 75% ethyl acetate/hexane mixture as an eluent, furnished 0.518 g (92%) of 5 as a chromatographically pure, colorless oil and ca. 6 mg (0.8%) of 6.[7] Crystallization of the oil from hexane provided 0.497 g (88.4%) of 5 as a white solid. An analytical sample was prepared by recrystallization from hexane/

ethyl acetate mixture, mp. 155-156°; TLC (80% ethyl acetate/hexane): R_F 0.24; IR (KBr): 3400, 3075, 3050, 2940, 2860, 1580, 1060-1130 and 1050 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.64 (m, 4H, ArH), 7.38 (m, 6H, ArH), 3.97 (peak, 1H, C_{12}-H), 3.84 (peak, 1H, C_7-H), 3.63 (t, J = 6.1 Hz, 2H, C_{24}-H_2), 3.43 (m, 1H, C_3-H), 1.04 (s, 9H, t-butyl), 0.87 (s, 3H, C_{19}-H_3) and 0.65 (s, 3H, C_{18}-H_3); ^{13}C NMR ($CDCl_3$): δ 135.58, 134.17, 129.45, and 127.55 (aromatic carbons), 73.17 (C_{12}), 71.90 (C_3), 68.50 (C_7) and 64.46 (C_{24}); Mass spectra, m/z: 557 (M^+-H_2O-t-butyl), 555 (M^+-C_6H_5), 539 (M^+-$2H_2O$-t-butyl) and 537 (M^+-H_2O-C_6H_5).

Anal. Calcd. for $C_{40}H_{60}O_4Si$: C, 75.90; H, 9.55

Found: C, 75.60; H, 9.60

3α,12α-Dihydroxy-cholan-24-ol-24-tert-butyldiphenylsilyl ether (11).-The procedure described for the synthesis of 5 was followed. Flash chromatography of the residue over silica gel using 50% ethyl acetate/hexane as eluent provided 11 as a chromatographically pure white solid (94.5%), mp. 69-70°; TLC (50% ethyl acetate/hexane): R_F 0.64; IR (KBr): 3350, 3060, 3040, 2925, 2850, 1590, 1475, 1460, 1100 and 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.65 (m, 4H, ArH), 7.40 (m, 6H, ArH), 3.98 (peak, 1H, C_{12}-H), 3.63 (br t, J = 5.95 Hz, 3H, C_{24}-H_2 and C_3-H), 1.04 (s, 9H, t-butyl), 0.87 (s, 3H, C_{19}-H_3) and 0.65 (s, 3H, C_{18}-H_3); ^{13}C NMR ($CDCl_3$): δ 135.52, 134.15, 129.43 and 127.48 (aromatic carbons), 73.20 (C_{12}), 71.79 (C_3) and 64.39 (C_{24}); Mass spectra, m/z: 541 (M^+-t-butyl-H_2O), 539 (M^+-C_6H_5), 523 (M^+-t-butyl-$2H_2O$), 343 (M^+-H_2O-TBDPSiO) and 325 (M^+-$2H_2O$-TBDPSiO).

Anal. Calcd. for $C_{40}H_{60}O_3Si$: C, 77.87; H, 9.80

Found: C, 78.05; H, 10.10

3α,7α,12α-Tris(formyloxy)-5β-cholan-24-oic acid (7).-The procedure outlined by Tsereng et al.[6] was followed. Recrystallization of the crude product from 50% ethanol/water provided 7 (89.1%) as white needles, mp. 205-206° (lit. mp. 205-209°,[10] 209-210°[6]); TLC (70% benzene/acetone): R_F 0.44; IR

(KBr): 3600-2500, 1730 (broad), 1100-1250, 1070, 1050 and 1020 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.20 (br s, 1H, $CO_2\underline{H}$), 8.03 [s, 1H, C_{12}-OC(=O)$\underline{H}$], 7.97 [s, 1H, C_7-OC(=O)$\underline{H}$], 7.89 [s, 1H, C_3-O(C=O)$\underline{H}$], 5.15 (peak, 1H, C_{12}-$\underline{H}$), 4.96 (peak, 1H, C_7-$\underline{H}$), 4.63 (m, 1H, C_3-$\underline{H}$), 0.91 (s, C_{19}-$\underline{H_3}$) and 0.73 (s, C_{18}-$\underline{H_3}$).

Alternate Route to 5

Silylation.-A solution of 0.470 g (0.98 mmol) of 8a in 10 mL of dichloromethane containing 0.150 g (1.23 mmol) of DMAP was treated with 0.30 mL (0.32 g, 1.16 mmol) of TBDPSi-Cl. The mixture was stirred at room temperature for 20 hrs. The solvent was removed under reduced pressure and the residue partitioned between equal volumes of diethyl ether and 0.5N HCl. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 25 mL). The combined ethereal layers were washed with 0.5N HCl (150 mL) and brine (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a residue consisting of 9a and t-butyldiphenylsilylhydroxide. The mixture was not separated and was used directly in the next reaction.

Cleavage of Formyloxy Protecting Groups.-The mixture obtained above was dissolved in 15 mL of THF, cooled (ice/water), and treated with excess 2.45M n-butyllithium solution in hexane (5.6 mL, 13.7 mmol). The mixture was allowed to warm to room temperature and stirred at this temperature for 12 hours. The reaction mixture was diluted with diethyl ether and then quenched with 5 mL of 0.5N HCl. Water was added and the organic layer separated. The aqueous layer was extracted with diethyl ether (2 x 25 mL), and the combined ethereal layers were washed in succession with 0.5N HCl (1 x 75 mL), water (2 x 75 mL), 5% Na_2CO_3 (1 x 75 mL), and brine (2 x 75 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow viscous oil. Chromatography of the residue over silica gel (60-200 mesh), using 70% ethyl acetate/hexane as an eluent, afforded 0.481 g (77.7%) of 10a. Recrystallization from

hexane/diethyl ether or hexane/ethyl acetate, afforded 10a as white needles. The product obtained by this route (10a) was compared with 5 (obtained by selective protection of 5β-cholan-3α,7α,12α,24-tetrol). Infrared, TLC, mixture melting point, and ^{1}H and ^{13}C NMR revealed that the products 10a and 5 were identical.

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5. Reduction of reaction time to 1.5 hrs. or less resulted in a lower yield of 5.

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7. Tris(formyloxy) acid was reduced with BH_3·THF to give 82% of 8a and 10% of 8b.[8] The procedure described for 10a gave the disilylated product 10b from 8b. Comparison of 10b with 6, obtained previously as a side-product in the selective protection of 5β-cholan-3α,7α,12α,24-tetrol, confirmed the positions of the silyl groups in 6.

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9. Cleavage of the formyloxy protecting groups was attempted using 10% KOH in methanol. However, due to the competing cleavage of TBDPSi ether, this method was abandoned.

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