Syntheses of Linear Dimeric and Cyclic Oligomeric Cholate Ester Derivatives

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Received 7 August 1996; revised 14 October 1996

One-step syntheses of cyclic trimer **2** and tetramer **3** of lithocholate were achieved from the cycloesterification of lithocholic acid **(1)** by using 2-chlorobenzoyl chloride and 4-dimethylaminopyridine (DMAP). The tetramer **5** of 7,12-diacetyl-24-norcholic acid **(4)** was synthesized by a similar method. These results suggest that the cyclotrimer is the preferred cycle size for the cholic acid system and that the cyclotetramer is the preferred cycle size for the 24-norcholic acid system. Cyclotetramerization of lithocholic acid is preferred over cyclodimerization. The structure of tetramer **3** was verified by a multistep synthesis. The structures and stereochemistry of all dimers, oligomers, and intermediate products were determined by means of spectroscopic analyses.

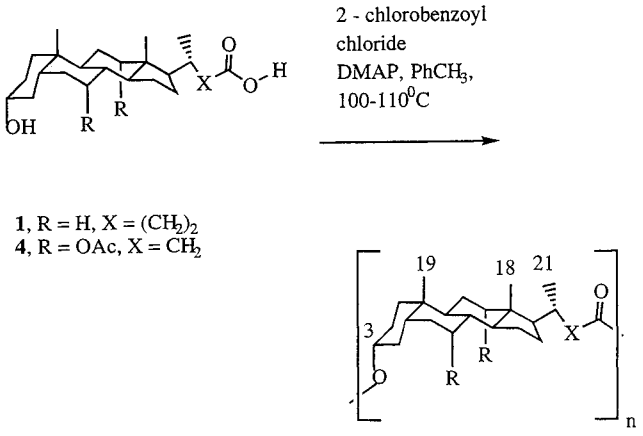
The potential template and complexing activity of cyclocholates has stimulated interest in the syntheses of oligomeric cholic acid derivatives.[1-9] This work has explored the use of cholic acid as a chiral building block to construct artificial receptors and has led to related molecular recognition studies. Bonar-Law and co-workers reported a multistep synthesis of a tetrameric derivative of cholic acid by coupling the appropriate dimer.[3] A similar synthetic strategy was used for the multistep synthesis of tetrameric forms of lithocholic acid derivatives in this work. Compared to cholic acid, lithocholic acid **(1)** is prone to fewer side reactions because of less steric hindrance and fewer reaction sites. The macrolactonization of lithocholic and 24-norcholic acids are reported here for the first time. The striking difference between the oligomerization of lithocholic and 24-norcholic acids can be seen in this work. Lithocholic acid and (*S*)-phenylalanine were used in the synthesis of a steroidal cyclopeptide having a lipophilic cavity.[10] We expect that cyclocholate oligomers formed from lithocholic acid units would also have a lipophilic cavity while cyclocholate oligomers derived from cholic acid units would have a hydrophilic cavity.

We also have long standing interest in the molecular architecture of bile acid dimeric and oligomeric derivatives.[11,12] It is well known that deoxycholic acid forms 1:1 molecular inclusion complexes by co-crystallization because its crystal structure has channels that can accommodate insertion of some molecules. We expect crystal structures of the cyclic trimers and tetramers of cholic acid to have additional empty space. The porous crystals of cyclotrimer **2**, cyclotetramer **3** and cyclotetramer **5** have the potential of resolving racemates by selective inclusion of one enantiomer. These and other structural studies require efficient and flexible syntheses of oligomeric bile acid derivatives and this is the primary motivation for this work. A communication by Davis and Walsh[7] reports that cyclotrimerization of a 23,24-dinorcholic acid derivative is preferred over cyclotetramerization.

The trimer **2** and tetramer **3** were synthesized from lithocholic acid **(1)** in one step as shown in Scheme 1. These two oligomers were prepared by Yamaguchi macrolactonization[2,13] using 2-chlorobenzoyl chloride as the coupling agent. This coupling agent has less steric hindrance than 2,6-dichlorobenzoyl chloride or 2,4,6-trichlorobenzoyl chloride and was used because it was already available in our laboratory and we were interested in probing the consequence of this difference in steric hindrance. The yields of trimer **2** and tetramer **3** are 32% and 4%, respectively, [the starting material (37%) and other product mixture (9%) were also obtained]. The tetramer **5** was synthesized by a similar method (Scheme 1) from 7,12-diacetyl 24-norcholic acid **(4)** in 12% yield [the starting material (25%), the ester of 7,12-diacetyl 24-norcholic acid and 2-chlorobenzoyl chloride (38%), and other product mixture (8%) were also obtained]. Dilute solutions (4 mM) were used to favor the formation of cyclic compounds **(2,3,5)**.

The lower synthetic yield of tetramer **5** (compared to **2**) is consistent with the 7,12-diacetyl groups and the shorter 17-sidechain creating more steric hindrance. Starting from lithocholic acid **(1)**, the major product is cyclotrimeric (Scheme 1). Starting from 7,12-diacetyl-24-norcholic acid **(4)**, the major product is cyclotetrameric (Scheme 1). We suggest that this is because the longer 17-sidechain is more conducive to the formation of cyclotrimer and the shorter sidechain more favorable to the formation of cyclotetramer for steric reasons.

In the one-step syntheses of oligomers from lithocholic acid (Scheme 1), the major cycloproduct is the trimer **2**.



Scheme 1

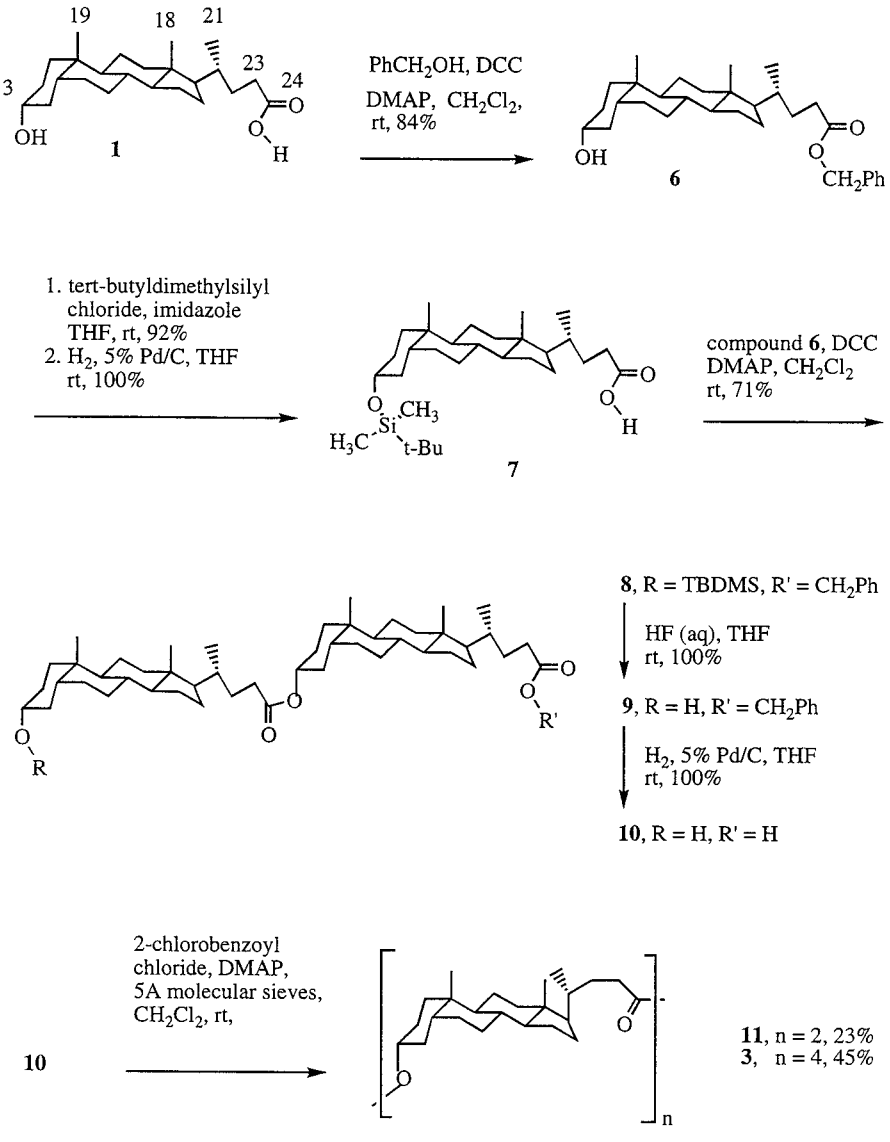
The tetramer **3** was synthesized from lithocholic acid **(1)** in seven steps as shown in Scheme 2. In the first step, the carboxyl group of lithocholic acid **(1)** was protected as the corresponding benzyl ester via reaction with benzyl alcohol by using DCC and DMAP.[14] Then the 3-hydroxyl group was protected with *tert*-butyldimethylsilyl chloride.[15] To synthesize dimer **8**, compound **7** was reacted with benzyl lithocholate **(6)**. The dimer **10** was produced by cleaving the TBDMS group of dimer **8** with aqueous HF[16] and cleaving the benzyl group via catalytic hydrogenation.[17] Finally the tetramer **3** was synthesized by cycloesterification of dimer **10** using 2-chlorobenzoyl chloride and DMAP.[3] The overall yield is 24% (45% in the last step). This last step also yielded 23% cyclodimer **11**. Thus, cyclotetramerization is preferred to cyclodimerization by a factor of 2:1, even though the former requires two reaction steps and the latter requires only one intramolecular reaction step from **10**.

Using precision made Dreiding models that were optimally arranged on a flat surface, we made two different measurements. The approximate spacing between the centers of two adjacent lithocholate *C*-rings for the cyclodimer, cyclotrimer, cyclotetramer, and linear dimer were determined to be 6, 11, 12.5, and 14.2 Å, respectively. The approximate diameters for the cyclotrimer and cyclotetramer were determined to be 13 and 17 Å, respectively, and the average approximate diameter for the cyclodimer (6 and 11 Å) is 9 Å.

For comparison, the ^{1}H NMR data of dimer **11**, trimer **2**, tetramer **3** and tetramer **5** are listed in Table 1. From this table, it can be seen that: 1) the chemical shifts of the four compounds are individually distinguishable; 2) the doublet arising from H-21 of dimer **11**, tetramer **3** and tetramer **5** has a chemical shift intermediate to the chemical shifts for the C-18 and C-19 methyl groups, with the latter being most deshielded.

The ^{1}H NMR data of dimer **8**, dimer **9**, and dimer **10** are listed in the experimental section. From this section, it can be seen that: 1) the chemical shift of the 3′-H is higher than that of 3-H; 2) the separation of 18-H and 18′-H can be seen in dimer **8** and dimer **9**.

Table 2 lists the ^{13}C NMR (proton decoupled) data of dimer **11**, trimer **2**, tetramer **3** and tetramer **5**. The as-



Scheme 2

Table 1. Partial ^{1}H NMR (250 MHz) Data for Cyclic Dimer **11**, Trimer **2**, Tetramer **3** and Tetramer **5**

Proton	Compound			
	Cyclic dimer **11**	Cyclic trimer **2**	Cyclic tetramer **3**	Cyclic tetramer **5**
H-12				5.09 (s, 4H)
H-7				4.92 (m, 4H)
H-3	4.75 (m, 2H)	4.77 (m, 3H)	4.72 (m, 4H)	4.67 (m, 4H)
H-23	2.22 (m, 4H)	2.25 (m, 6H)	2.27 (m, 8H)	–
H-22				2.40 (m, 8H)
12-OCOMe				2.12 (s, 12H)
7-OCOMe				2.07 (s, 12H)
H-19	0.94 (s, 6H)	0.93 (s, 9H)	0.93 (s, 12H)	0.91 (s, 12H)
H-21	0.92 (d, 6H)	0.93 (s, 9H)	0.92 (d, 12H)	0.84 (d, 12H)
H-18	0.64 (s, 6H)	0.65 (s, 9H)	0.67 (s, 12H)	0.77 (s, 12H)

Table 2. ^{13}C NMR (63 MHz, proton decoupled) Data for Cyclic Dimer **11**, Trimer **2**, Tetramer **3** and Tetramer **5**

Assignment	Compound			
	Cyclic dimer **11**	Cyclic trimer **2**	Cyclic tetramer **3**	Cyclic tetramer **5**
C-24	175.22	173.94	173.25	
12-O*CO*Me				170.12
7-O*CO*Me				169.88
C-3	74.12	74.06	73.90	73.08
C-14	56.53	56.59	56.74	43.90
C-17	52.60	54.71	56.19	48.54
C-13	42.79	42.69	42.79	45.13
C-5	41.79	41.91	41.58	42.03
C-9	40.39	40.39	40.48	27.07
C-12	39.72	40.24	40.24	75.51
C-4	36.03	35.85	35.70	37.66
C-8	35.23	35.17	35.21	40.66
C-1	34.72	34.59	34.88	40.66
C-20	34.72	34.59	34.42	34.42
C-10	32.08	32.44	32.04	34.03
C-22	31.12	30.57	31.95	33.08
C-23	28.63	30.09	31.15	172.65
C-2	28.08	28.14	28.35	29.04
C-16	27.21	27.06	26.91	25.52
C-6	26.75	26.75	26.50	31.18
C-7	26.44	26.42	26.12	70.76
C-15	24.08	24.24	24.31	21.59
C-19	23.29	23.35	23.17	22.34
C-11	20.71	20.85	20.80	22.65
12-, 7-OCO*Me*				21.34
C-21	19.53	18.44	18.11	18.14
C-18	11.83	12.01	12.22	12.37

signments of these spectra are made through comparisons with closely related compounds tabulated by Blunt and Stothers,[18] a closely related compound published by Bonar-Law and Davis,[19] and from spectra resulting from ongoing work currently in progress in our laboratory. From this table, it is noted that most of the chemical shifts of tetramer **5** are larger than those of dimer **11**, trimer **2**, and tetramer **3** for the same positions which is clearly due to the effect of the 8 acetate groups present in **5**. The ^{13}C chemical shift trends for the sequence of cyclic dimer **11**, trimer **2**, and tetramer **3** (in that order) are particularly revealing: C-17 ($\Delta\delta = +3.6$ ppm), C-20 ($\Delta\delta = -0.3$ ppm), C-21 ($\Delta\delta = -1.42$ ppm), C-22 ($\Delta\delta = +1.4$ ppm), C-23 ($\Delta\delta = +2.5$ ppm), and C-24 ($\Delta\delta = -2.0$ ppm). The carbons associated with the 17-sidechains experience the largest change in chemical shifts as the size of the cyclic system changes from dimeric to tetrameric. The 17-sidechain tether undergoes a major change in flexibility and molecular tension.

Table 3 lists the ^{13}C NMR (proton decoupled) data of dimer **8**, dimer **9** and dimer **10**. From this table, we note: 1) The chemical shift of 24-C is higher than that of 24′-C; 2) the chemical shift of 3′-C is higher than that of 3-C; 3) the chemical shifts of the three compounds are distinct.

Table 3. ^{13}C NMR (63 MHz, proton decoupled) Data for Dimer **8**, Dimer **9** and Dimer **10**

Assignment	Compound		
	Dimer **8**	Dimer **9**	Dimer **10**
C-24	174.01	174.13	
C-24′	173.82	173.83	
Ph	128.58	128.58	
Ph	128.21	128.23	
C-3′	74.09	74.12	73.69
C-3	72.89	71.92	70.48
Ph*CH*$_2$	66.11	66.11	
C-14, C-14′	56.49	56.53	56.25
C-17, C-17′	56.10	56.53	55.81
C-13, C-13′	42.76	42.76	42.52
C-5, C-5′	42.33	42.15	41.85
C-9, C-9′	41.91	41.91	41.60
C-12, C-12′	40.45	40.46	39.22
C-4, C-4′	40.21	40.21	36.26
C-8, C-8′	36.98	36.51	35.66
C-1	35.63	35.90	35.30
C-1′	35.36	35.36	
C-20	35.11	35.11	35.00
C-20′	34.33	34.63	
C-10, C-10′	32.33	32.33	34.38
C-22, C-22′	31.78	31.78	31.48
C-23	31.36	31.36	30.83
C-23′	31.06	31.06	
C-2′	30.57		
C-2	28.21	28.21	30.33
C-16	27.35	27.24	27.96
C-16′	27.05	27.05	
C-6, C-6′	26.70	26.70	27.11
C-7, C-7′	26.44	26.33	26.33
t-Bu	26.33		
t-Bu	26.02		
C-15, C-15′	24.22	24.24	23.96
C-19, C-19′	23.39	23.40	23.27
C-11, C-11′	20.86	20.87	20.61
C-21, C-21′	18.32	18.32	18.15
C-18, C-18′	12.07	12.11	11.95
Si(CH_3)$_2$	−4.55		

The peaks arising from the carbonyls in dimer **10** were not seen because of poor solubility coupled with background noise.

The data of FAB/MS (3-NBA + LiI) spectra of trimer **2** and tetramer **3** are distinctive in the *m/z* range above 400 daltons. The trimer **2** has a peak at 721.6 daltons, and the tetramer **3** has three peaks at 521.4, 711.5 and 837.7 daltons. The data of FAB/MS (3-NBA + LiI) spectra of dimer **8**, dimer **9**, dimer **10** and cyclic dimer **11** are also individually characteristic. In addition to having different lithiated molecular ion peaks, they reveal distinctive daughter ion peaks in the *m/z* range between 200 to 500 daltons.

Trimer **2**, tetramer **3** and tetramer **5** were synthesized with Yamaguchi macrolactonization. Tetramer **3** was also prepared with a multistep synthesis. Three dimers **(8, 9, 10)** and cyclodimer **11** were produced during the multistep synthesis of tetramer **3**. The ^{13}C chemical shifts of the 17-sidechain show the largest changes with cycle size. Cholates tend to prefer cyclotrimerization and 24-norcholates tend to prefer cyclotetramerization because of their shorter 17-sidechain. This latter conclusion differs with the recent result[7] in which a 23,24-dinorcholic acid derivative preferentially cyclotrimerizes. For the linear dimer of lithocholic acid, cyclotetramerization is preferred over cyclodimerization.

Materials were obtained from commercial suppliers and used without further purification. Toluene was dried with 5A molecular sieves. Column chromatography was carried out using Grade 62 (60–200 mesh) silica gel and eluting with hexane–EtOAc solvent systems. Reactions and chromatography fractions were analyzed using Fisher 250 micron silica gel G (5 × 20 cm) TLC plates. Unless otherwise noted, all TLCs were developed with 10:1 hexane–EtOAc. Visualization was done by spraying the plates with a $Ce(SO_4)_2$ + H_2SO_4 solution and briefly heating. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1320 infrared spectrophotometer as KBr discs. The IR peak intensities were recorded as w (weak), m (medium) and s (strong). ^1H and ^{13}C NMR (proton decoupled) spectra were measured at 250 MHz (Bruker). All NMR samples were measured in $CDCl_3$ using TMS as the internal standard except dimer **10** which was measured in Unisol-D. See the ^1H NMR data for compounds **2**, **3**, **5** and **11** in Table 1, and ^{13}C NMR data for compounds **2**, **3**, **5**, and **8–11** in Tables 2–3.

Cyclic Trimer of Lithocholate 2:

2-Chlorobenzoyl chloride (4.8 mmol) was added to a soln of lithocholic acid (**1**, 1 L, 4 mmol) and DMAP (16 mmol) in anhyd toluene (1000 mL). After stirring at 100–110 °C for 3 days, the mixture was concentrated to 300 mL and filtered. The concd soln was washed with 5% aq HCl (50 mL) sat. $NaHCO_3$ (50 mL), and H_2O (100 mL), then dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography and crystallized from EtOAc–$CHCl_3$. The yield of **2** is 32% [tetramer **3** (4%), the starting material (37%), and other product mixture (9%) were also obtained]; mp 238–240 °C; R_f 0.62.

IR: ν = 1715 (s, C=O stret), 1250 (m, C–O stret), 1160 (m, C–O stret) cm^{-1}.

FAB/MS (3-NBA + LiI): *m/z* = 1081.9 $(MLi)^+$, 367.3 (100).

Anal. Calcd for $C_{72}H_{114}O_6$: C, 80.39; H, 10.68. Found: C, 80.12; H, 10.65.

Cyclic Dimer 11 and Tetramer of Lithocholate 3:

Method 1 (Scheme 1): the same methods of reaction and purification were employed as in those of trimer **2**. The yields of **3** is 4%.

Method 2 (Scheme 2): Dimer **10** (0.16 mmol) was suspended in anhyd CH_2Cl_2 (80 mL). Then DMAP (0.64 mmol) and 5A molecular sieves were added. To the stirred mixture, 2-chlorobenzoyl chloride (0.20 mmol) was added. After stirring for 3 days at r.t. the mixture was filtered and concentrated. The concd soln was washed with 5% aq HCl (50 mL), sat. $NaHCO_3$ (50 mL), and H_2O (100 mL), then dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by column chromatography and crystallized from hexane–EtOAc. The yield of **3** is 45% [the starting material (18%) and cyclodimer **11** (23%) were also obtained].

For **3**: mp 248–250 °C; R_f 0.31.

IR: ν = 1718 (s, C=O stret), 1250 (m, C–O stret), 1170 (m, C–O stret) cm^{-1}.

FAB/MS (3-NBA + LiI): *m/z* = 1440.3 $(MLi)^+$, 521.4 (14), 365.3 (100).

Anal. Calcd for $C_{96}H_{152}O_8$: C, 80.39; H, 10.68. Found: C, 80.05; H, 11.01.

For the cyclodimer **11**: mp 298–300 °C; R_f 0.59.

FAB/MS (3-NBA): *m/z* = 717.7 $(MH)^+$, 359.3 (100), 257.2 (15).

Cyclic Tetramer of 7,12-Diacetyl-24-norcholic Acid 5:

2-Chlorobenzoyl chloride (4.8 mmol) was added to a soln of 7,12-diacetyl-24-norcholic acid (**4**, 1 L, 4 mmol) and DMAP (16 mmol) in anhyd toluene. This mixture was reacted at 100–110 °C for 1 day, and DMAP (16 mmol) and 2-chlorobenzoyl chloride

(9.6 mmol) were added to the mixture in 3 portions over 3 days. On the fourth day, the mixture was concentrated to 300 mL and filtered. The concd soln was washed with 5% aq HCl (50 mL), sat. $NaHCO_3$ (50 mL), and H_2O (100 mL), then dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by column chromatography and crystallized from EtOAc–$CHCl_3$. The yield of **5** is 12% [the starting material (25%), the ester of 7,12-diacetyl-24-norcholic acid and 2-chlorobenzoyl chloride (38%), and other product mixture (8%) were also obtained].

For **5**: mp 263–265°C; R_f (hexane : EtOAc = 1:1) 0.44.

IR: ν = 1725 (s, C=O stret), 1250 (s, C–O stret), 1190 (m, C–O stret), 1175 (m, C–O stret) cm^{-1}.

FAB/MS (3-NBA + NaI): m/z = 1865.2 $(MNa)^+$, 1422.6 (36), 1022.2 (25), 681.6 (100).

Anal. Calcd for $C_{108}H_{160}O_{24}$: C, 70.41; H, 8.75. Found: C, 70.58; H, 9.08.

For the ester of 7,12-diacetyl-24-norcholic acid and 2-chlorobenzoyl chloride: mp 156–158°C; R_f (hexane : EtOAc = 1:1) 0.68.

Partial ^1H NMR: δ = 7.70 (d, 2H, Ph), 7.39 (d, 2H, Ph), 5.09 (m, 1H, 12-CH), 4.92 (m, 1H, 7-CH), 4.67 (m, 1H, 3-CH), 2.37 (m, 2H, 22-CH_2), 2.11 (s, 3H, 12-$OCOCH_3$), 2.06 (s, 3H, 7-$OCOCH_3$), 0.92 (s, 3H, 19-CH_3), 0.86 (d, 3H, 21-CH_3), 0.77 (s, 3H, 18-CH_3).

Benzyl Lithocholate (6):

To a stirred solution of lithocholic acid (**1**, 6 mmol) in anhyd CH_2Cl_2 (8 mL), DMAP (1.2 mmol) and benzyl alcohol (9 mmol) were added. Then DCC (6.6 mmol) was added to the mixture. After being stirred for 1 day at r.t. in a sealed flask, the mixture was diluted with CH_2Cl_2 and filtered. The filtrate was washed with 5% aq HCl (20 mL), sat. $NaHCO_3$ (20 mL), and H_2O (40 mL), then dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by column chromatography and crystallization from hexane–EtOAc. The yield of **6** is 84%; mp 116–118°C; R_f (hexane : EtOAc = 4:1) 0.28.

Partial ^1H NMR: δ = 7.35 (m, 5H, Ph), 5.11 (s, 2H, $PhCH_2$), 3.62 (m, 1H, 3-CH), 2.37 (m, 2H, 23-CH_2), 0.91 (s, 3H, 19-CH_3), 0.90 (d, 3H, 21-CH_3), 0.62 (s, 3H, 18-CH_3).

^{13}C NMR: δ = 174.08, 136.22, 128.54, 128.20, 71.87, 66.11, 56.53, 56.04, 42.79, 42.16, 40.51, 40.22, 36.53, 35.91, 35.38, 34.63, 31.36, 31.05, 30.63, 28.20, 27.24, 26.46, 24.24, 23.41, 20.87, 18.30, 12.07.

IR: ν = 3530 (m, O–H stret), 1717 (s, C=O stret), 1315 (m, C–O stret), 1167 (s, C–O stret), 770 (m, =C–H bend), 715 (m, =C–H bend) cm^{-1}.

Anal. Calcd for $C_{31}H_{46}O_3$: C, 79.78; H, 9.94. Found: C, 79.73; H, 9.92.

***tert*-Butyldimethylsilylbenzyl Lithocholate:**

To a stirred solution of 3.0 mmol benzyl lithocholate **(6)** and imidazole (7.5 mmol) in anhyd THF (6 mL), *tert*-butyldimethylsilyl chloride (3.6 mmol) was added. After being stirred for 1 day at r.t., the mixture was poured into H_2O (100 mL) and extracted with $CHCl_3$ (3 × 30 mL). The organic phase was removed, dried ($MgSO_4$), and evaporated to dryness. The crude product was purified by column chromatography. The yield of this product is 92%; mp 68–70°C; R_f (hexane : EtOAc = 9:1) 0.85.

Partial ^1H NMR: δ = 7.37 (m, 5H, Ph), 5.11 (s, 2H, 25-CH_2), 3.58 (m, 1H, 3-CH), 2.33 (m, 2H, 23-CH_2), 0.89 (s, 15H, *t*-Bu, 19-CH_3, 21-CH_3), 0.61 (s, 3H, 18-CH_3), 0.06 (s, 6H, $Si(CH_3)_2$).

^{13}C NMR: δ = 174.09, 136.20, 128.54, 128.18, 72.85, 66.07, 56.44, 56.02, 42.74, 42.35, 40.23, 36.97, 35.91, 35.63, 35.34, 34.61, 31.33, 31.04, 28.19, 27.33, 26.43, 26.00, 24.23, 23.41, 20.84, 18.31, 12.03, −4.57.

IR: ν = 1735 (s, C=O stret), 1255 (m, C–O stret), 1175 (m, C–O stret), 1110 (s, Si–OR stret) cm^{-1}.

Anal. Calcd for $C_{37}H_{60}O_3Si$: C, 76.49; H, 10.41. Found: C, 76.42; H, 10.52.

***tert*-Butyldimethylsilyllithocholic acid (7):**

To a soln of *tert*-butylmethylbenzyl lithocholate (2.7 mmol) in THF (27 mL), 5% Pd–C (1.27 g) was added. The mixture was stirred in a H_2 atmosphere for 1 h at r.t. The catalyst was filtered. And the filtrate was evaporated to dryness. The crude product was purified by crystallization from $CHCl_3$–EtOAc. The yield of **7** is 100%; mp 200–202°C; R_f (hexane : EtOAc = 1:1) 0.27.

Partial ^1H NMR: δ = 3.58 (m, 1H, 3-CH), 2.31 (m, 2H, 23-CH_2), 0.89 (s, 15H, *t*-Bu, 19-CH_3, 21-CH_3), 0.64 (s, 3H, 18-CH_3), 0.06 (s, 6H, $Si(CH_3)_2$).

^{13}C NMR: δ = 72.90, 56.46, 56.05, 40.26, 35.36, 34.64, 31.03, 28.20, 27.35, 26.44, 26.02, 24.26, 23.42, 20.86, 18.27, 12.07, −4.55.

IR: ν = 3700–2600 (m, O–H stret), 1690 (s, C=O stret), 1260 (m, C–O stret), 1105 (m, Si–OR stret) cm^{-1}.

Anal. Calcd for $C_{30}H_{54}O_3Si$: C, 73.41; H, 11.09. Found: C, 73.34; H, 11.29.

Dimer 8:

Using compound **7** and compound **6**, the same methods of synthesis and purification were employed as in those of benzyl lithocholate **(6)**. The yield of **8** is 71%; mp 140–142°C; R_f (hexane : EtOAc = 15:1) 0.39.

Partial ^1H NMR: δ = 7.37 (m, 5H, Ph), 5.12 (s, 2H, $PhCH_2$), 4.72 (m, 1H, 3′-CH), 3.58 (m, 1H, 3-CH), 2.31 (m, 4H, 23-CH, 23′-CH), 0.93 (s, 6H, 19-CH_3), 0.90 (s, 15H, t-Bu, 21-CH_3, 21′-CH_3), 0.64 (s, 3H, 18-CH_3), 0.62 (s, 3H, 18′-CH_3), 0.07 (s, 6H, $Si(CH_3)_2$).

IR: ν = 1730 (s, C=O stret), 1255 (m, C–O stret), 1175 (m, C–O stret), 1100 (m, Si–OR stret) cm^{-1}.

FAB/MS (3-NBA + LiI): m/z = 945.6 $(MLi)^+$, 455.3 (38), 357.2 (100), 255.2 (40).

Anal. Calcd for $C_{61}H_{98}O_5Si$: C, 77.98; H, 10.51. Found: C, 77.70; H, 10.90.

Dimer 9:

To a soln of dimer **8** (2.0 mmol) in THF (50 mL), 50% aq HF (7.5 mL) was added. The mixture was stirred for 1 h at r.t., then $CHCl_3/H_2O$ was added. The organic phase was removed, dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by crystallization from hexane–EtOAc. The yield of **9** is 100%; mp 166–168°C; R_f (hexane : EtOAc = 4:1) 0.40.

Partial ^1H NMR: δ = 7.35 (s, 5H, Ph), 5.11 (s, 2H, $PhCH_2$), 4.72 (m, 1H, 3′-CH), 3.62 (m, 1H, 3-CH), 2.30 (m, 4H, 23-CH_2, 23′-CH_2), 0.91 (s, 6H, 19-CH_3, 19′-CH_3), 0.90 (d, 6H, 21-CH_3, 21′-CH_3), 0.64 (s, 3H, 18-CH_3), 0.615 (s, 3H, 18′-CH_3).

IR: ν = 3540 (m, O–H stret), 1725 (s, C=O stret), 1223 (m, C–O stret), 1180 (m, C–O stret) cm^{-1}.

FAB/MS (3-NBA + LiI): m/z = 831.7 $(MLi)^+$, 455.4 (51), 357.3 (46), 313.1 (100).

Anal. Calcd for $C_{55}H_{84}O_5$: C, 80.05; H, 10.26. Found: C, 79.78; H, 10.70.

Dimer 10:

Using dimer **9**, the same methods of synthesis and purification were employed as in those of compound **7**. The yield of **10** is 100%; mp 253–255°C; R_f (pure EtOAc) 0.31.

Partial ^1H NMR: δ = 4.68 (m, 1H, 3′-CH), 3.49 (m, 1H, 3-CH), 2.24 (m, 4H, 23-CH_2, 23′-CH_2), 0.92 (s, 6H, 19-CH_3, 19′-CH_3), 0.90 (s, 6H, 21-CH_3, 21′-CH_3), 0.64 (s, 6H, 18-CH_3, 18′-CH_3).

IR: 3425 (s, O–H stret), 1730 (s, C=O stret), 1190 (s, C=O stret), 1050 (m, C–O stret) cm^{-1}.

FAB/MS (3-NBA + LiI): m/z = 741.6 $(MLi)^+$, 397.3 (27), 313.1 (100).

Anal. Calcd for $C_{48}H_{78}O_5 \cdot 2H_2O$: C, 74.76; H, 10.72. Found: C, 74.88; H, 10.32.

We gratefully thank Dr. Peter Groner for recording the NMR spectra. The mass spectra were determined by the Nebraska Center for Mass Spectrometry and the elemental analyses were measured by Galbraith Laboratories Company.

(1) Davis, A.P. *Chem. Soc. Rev.* **1993**, 243.
(2) Bonar-Law, R.P.; Sanders, J.K.M. *Tetrahedron Lett.* **1992**, *33*, 2071.

(3) Bonar-Law, R.P.; Mackay, L.G.; Sanders, J.K.M. *J. Chem. Soc., Chem. Commun.* **1993**, 456.
(4) Bonar-Law, R.P.; Sanders, J.K.M. *Tetrahedron Lett.* **1993**, *34*, 1677.
(5) Mackay, L.G.; Bonar-Law, R.P.; Sanders, J.K.M. *J. Chem. Soc., Perkin Tran. I.* **1993**, 1377.
(6) Bonar-Law, R.P.; Sanders, J.K.M. *J. Chem. Soc., Chem. Commun.* **1991**, 574.
(7) Davis, A.P.; Walsh, J.J. *J. Chem. Soc., Chem. Commun.* **1996**, 449.
(8) Davis, A.P.; Menzer, S.; Walsh, J.; Williams, D.J. *J. Chem. Soc., Chem. Commun.* **1996**, 453.
(9) Brady, P.A.; Bonar-Law, R.P.; Rowan, S.J.; Sucking, C.J.; Sander, J.K.M. *J. Chem. Soc., Chem. Commun.* **1996**, 319.
(10) Albert, D.; Feigel, M. *Tetrahedron Lett.* **1994**, *35*, 565.
(11) Li, Y.; Dias, J.R. *Org. Prep. Proced. Int.* **1996**, *28*, 203.
(12) Gao, H.; Dias, J.R. *J. Prakt. Chem.* **1997**, in press.
(13) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(14) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(15) Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(16) Newton, R.F.; Reynolds, D.P. *Tetrahedron Lett.* **1979**, 3981.
(17) Hartung, W.H.; Simowoff, R. *Org. React.* **1953**, *7*, 263.
(18) Blunt, J.W.; Stothers, J.B. *Org. Mag. Reson.* **1977**, *9*, 439.
(19) Bonar-Law, R.P.; Davis, A.P. *Tetrahedron* **1993**, *49*, 9845.