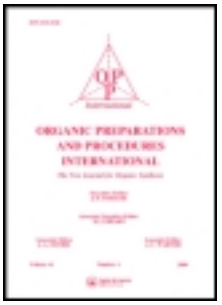

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SYNTHESES OF α- AND β-DIMERS OF LITHOCHOLIC ACID ESTERS

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SYNTHESES OF α- AND β-DIMERS OF LITHOCHOLIC ACID ESTERS

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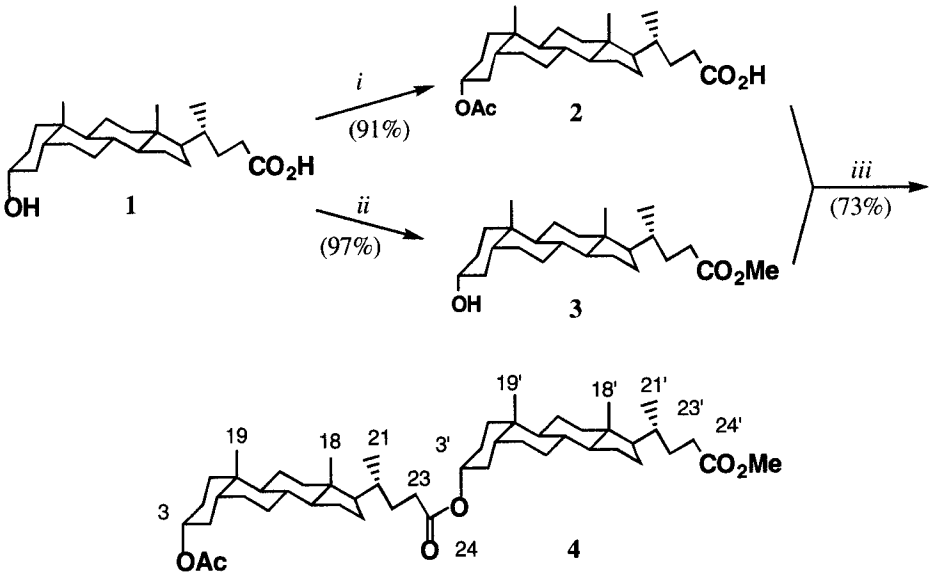
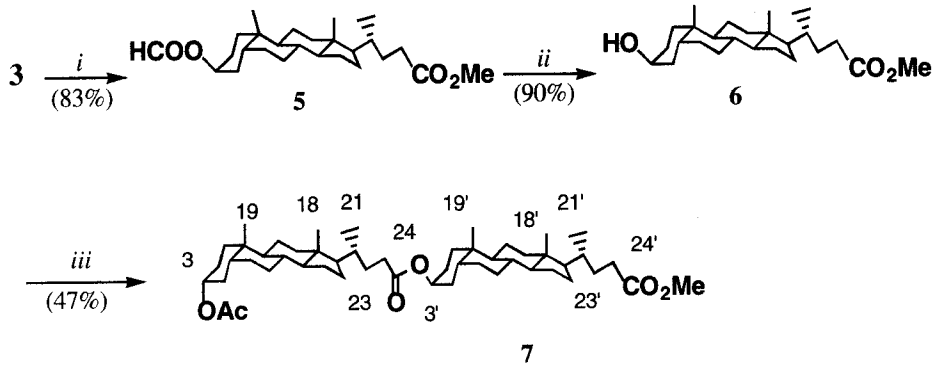
Dimeric steroids were first observed as synthetic by-products,[1] and then discovered in nature.[2] Our interest in the synthesis of dimeric steroids dating back to 1984,[3] was stimulated by the question as to whether two cholic acid molecules or a cholic acid molecule and a cholesterol molecule can form an ester linkage in the gastrointestinal and liver systems of mammals. The synthesis of dimeric and oligomeric bile acid derivatives clearly demonstrates that this is chemically feasible.[4] The potential template and complexing activity of cholaphanes and cyclocholates have stimulated interest in the synthesis of oligomeric cholic acid derivatives.[5] Dimeric steroids have been used as catalysts for some types of reactions.[6] Dimerization of steroids can be a good method for the synthesis of new pharmacologically active steroids.[7] *bis*-Steroids have been used as protecting groups in some important steroids.[7] Lithocholic acid (**1**), which has one functional group at each end of the molecule, can easily be dimerized after protecting one functional group. The interesting structure of lithocholic acid (**1**) and possible applications in pharmaceutical science and other areas led to our interest in the syntheses of these dimers with distinct architectures. The α-dimer is capable of acquiring a folded conformation as demonstrated by the formation of dimeric cyclocholates.[4] The β-dimer, however, should not be capable of acquiring a folded conformation, and we are interested in studying the consequence of this structural modification.

The α-dimer **4** was synthesized from lithocholic acid (**1**) in three steps (overall yield 64%) as shown in Scheme 1. In the first step, the 3α-hydroxyl group was protected as the corresponding acetate via reaction with acetic anhydride.[8] Methyl lithocholate (**3**) was prepared by reacting lithocholic acid (**1**) with acetyl chloride and methanol at room temperature.[9] Finally α-dimer **4** was produced from the reaction of methyl lithocholate (**3**) and acetyl lithocholic acid (**2**) by using dicyclohexylcarboimide (DCC) and 4-dimethylaminopyridine (DMAP) at room temperature in 73% yield. To synthesize β-dimer **7** (Scheme 2), the 3α-OH group of methyl lithocholate (**3**) was converted to a 3β-formate of opposite configuration by the Mitsunobu reaction.[10,11] The β-alcohol **6** was acquired by removing the formate-group with CH_3ONa in CH_3OH at room temperature.[10,11] The β-dimer **7** was synthesized by the esterification of β-alcohol **6** with acetyl lithocholic acid (**2**) in 47% yield.



i) Ac_2O, pyridine, rt ii)MeOH, AcCl, rt iii)DCC, DMAP, CH_2Cl_2, rt

Scheme 1



i)Ph_3P, DEAD, HCOOH, THF, rt ii)MeONa, MeOH, rt iii)compound **2**, DCC, DMAP, CH_2Cl_2, rt

Scheme 2

The lower yield is consistent with the axial hydroxyl group being more sterically hindered than the equatorial hydroxyl group.

The multiplicity and chemical shifts of 3α-H and 3β-H are characteristic. For comparison, the ^1H NMR data of acetyl lithocholic acid (**2**), 3α-alcohol **3**, α-dimer **4**, methyl 3β-formoxy-

cholanoate (**5**), 3β-alcohol **6**, and β-dimer **7** are listed in Table 1. From this table, we can see: 1) the equatorial hydrogen geminal to the 3β-OH has higher chemical shift value than the axial hydrogen geminal to the 3α-OH. 2) Conversion of the 3-alcohol to the 3-ester results in a deshielding of the geminal 3-hydrogen. 3) The axial 3β–hydrogen gives a multiplet, and the equatorial 3α-hydrogen gives a singlet in the NMR spectrum.

TABLE 1. Partial ^{1}H NMR Data for Compounds **2**, **3**, **4**, **5**, **6** and **7**

	Compound					
Proton	**2**	**3**	**4**	**5**	**6**	**7**
H-3β	4.73 (m, 1H)	3.65 (m, 1H)	4.72 (m, 2H)			4.72 (m, 1H)
H-3α				5.20 (s, 1H)	4.08 (s, 1H)	5.07 (s, 1H)

The partial ^{1}H NMR data for α-dimer **4** and β-dimer **7** are listed in Table 2. Because one 3β-H is converted to 3α-H in β-dimer **7**, two peaks appear (3β-H: 4.72 PPM; 3α-H: 5.07 PPM). The inversion of the configuration at the position-3 also causes an increase in the separation of two C21-H peaks and the separation of two C18-H peaks.

TABLE **2.** Partial ^{1}H NMR (250 MHz) Data for α-Dimer **4** and β-Dimer **7**

	Compound	
Proton	α-dimer **4**	β-dimer **7**
H-3α		5.07 (s, 1H)
H-3β	4.72 (m, 2H)	4.72 (m, 1H)
H-25'	3.66 (s, 3H)	3.66 (s, 3H)
H-23	2.25 (m, 4H)	2.27 (m, 4H)
H-26	2.03 (s, 3H)	2.03 (s, 3H)
H-19	0.93 (s,6H)	0.91 (s, 6H)
H-21	0.91 (d, 6H)	0.90 (d, 3H)
H-21'		0.88 (d, 3H)
H-18	0.65 (s, 6H)	0.65 (s, 3H)
H-18'		0.64 (s, 3H)

Table 3 lists the ^{13}C NMR data of α-dimer **4** and β-dimer **7.** These two spectra were assigned through comparisons with closely related compounds tabulated by Blunt and Stothers.[12] The inversion of one of two 3β-H to 3α-H causes the following changes: 1) the chemical shift of C-3' is changed to 70.39 PPM from 74.03 PPM. 2) The chemical shifts of some carbons in the range of 50 to 20 PPM are also changed. 3) Because of its lower symmetry the β-dimer **7** has more peaks (40 peaks) than α-dimer **4** (29 peaks).

The data of FAB/MS (3-NBA + NaI) spectra of the α- and β-dimers are distinctive in the *m/z* range between 650 to 400 daltons. While both spectra have the same metalated molecular ion

peak, the α-dimer has two fragment peaks at 589.6 and 413.4, and the β-dimer has two additional prominent ion peaks given in Figure 1.

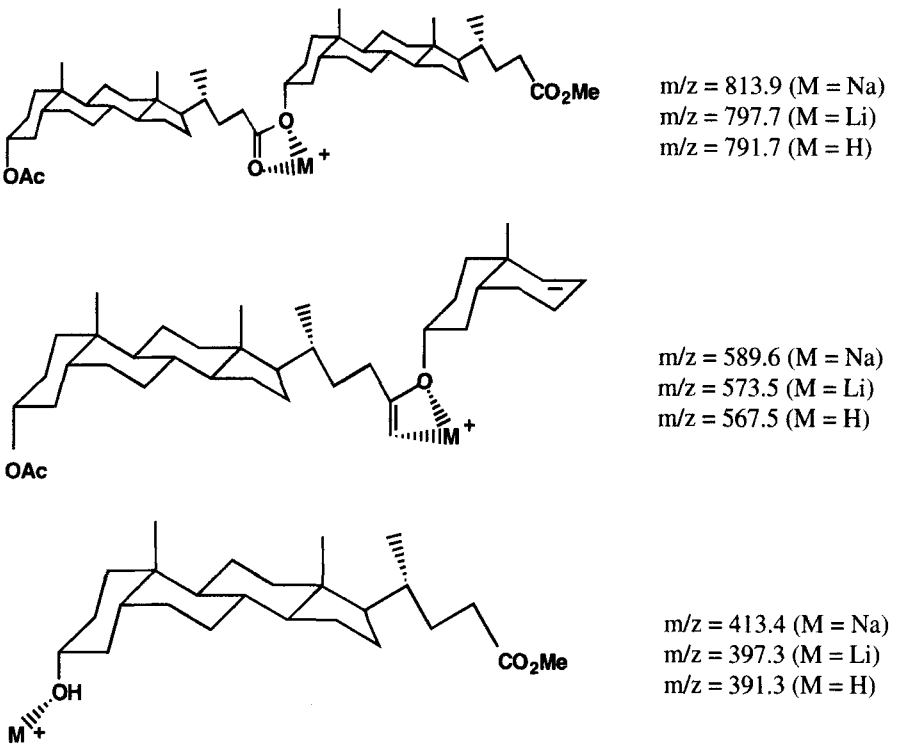


Fig. 1 Partial Assignment of FAB/MS of α-Dimer **4**

EXPERIMENTAL SECTION

Materials were obtained from commercial suppliers and used without further purification. Methanol, methylene chloride and THF were dried with 3A molecular sieves. Column chromatography was carried out using Grade 62 (60-200 mesh) silica gel and eluting with hexane-ethyl acetate solvent systems. Reactions and chromatography fractions were analyzed using Fisher 250 micron silica gel G (5 X 20 cm) TLC plates. All R_f values of TLC were determined with 4:1 hexane-ethyl acetate. Visualization was done by spraying the plates with $Ce(SO_4)_2 + H_2SO_4$ 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 peak intensities were recorded as w (weak), m (medium) and s (strong). ^1H and ^{13}C NMR spectra of α-dimer **4** and β-dimer **7** were measured at 250 MHz (Bruker). ^1H NMR of other samples were recorded on a EM-390 90 MHz NMR spectrometer. All NMR samples were measured in $CDCl_3$ using TMS as the internal standard.

Acetyl Lithocholic Acid (2).- A mixture of 0.7332 g (1.95 mmol) of lithocholic acid (**1**), 1.5 mL of pyridine, and 0.75 mL (0.8100 g, 7.9333 mmol) of acetic anhydride was heated on the steam bath for 0.5 hour and diluted extensively with water. The precipitated granular product was collected, washed

well with water, and dried. The crude product was purified by recrystallization from hexane-ethyl acetate; yield 0.7906 g (97%) of **2**, mp. 210-212°, lit.[13], 164-167°; R_f: 0.24. Partial ^{1}H NMR: δ 8.58 (m, 1H, COOH), 4.73 (m, 1H, 3β-H), 2.30 (m, 2H, 23-CH_2), 2.02 (s, 3H, CH_3CO), 0.93 (s, 6H, 19-CH_3, 21-CH_3), 0.66 (s, 3H, 18-CH_3). IR: 3450 (s), 2960 (s), 2890 (s), 1730 (s), 1705 (s), 1450 (m), 1380 (m), 1365 (m), 1250 (s), 1175 (w), 1035 (m) cm^{-1}.

TABLE 3. ^{13}C NMR (65 MHz) Data for α-Dimer **4** and β-Dimer **7**

	Compound			Compound	
Proton	α-dimer **4**	β-dimer **7**	Proton	α-dimer **4**	β-dimer **7**
C-24	174.59	174.58	C-20'		34.62
C-24'	173.65	173.68	C-10	32.30	32.30
C-25	170.47	170.46	C-22	31.75	31.82
C-3	74.34	74.33	C-22'		31.22
C-3'	74.03	70.39	C-23	31.07	31.03
C-14	56.56	56.56	C-23'		30.84
C-17	56.13	56.14	C-2	28.17	29.68
C-17'	56.13	56.01	C-2'		28.17
C-25'	51.35	51.34	C-16	27.03	27.03
C-13	42.76	42.80	C-6	26.66	26.66
C-5	41.93	41.95	C-6'		26.54
C-9	40.48	40.49	C-7	26.34	26.36
C-12	40.19	40.19	C-7'		26.17
C-4	35.82	39.94	C-15	24.18	24.18
C-4'		37.46	C-19	23.32	23.87
C-8	35.30	35.82	C-19'		23.33
C-8'		35.70	C-26	21.38	21.38
C-1	35.08	35.30	C-11	20.84	20.85
C-1'		35.09	C-21	18.29	18.26
C-20	34.60	34.84	C-18	12.05	12.04

Methyl Lithocholate (3).- To a cooled solution of 0.5001 g (1.33 mmol) of lithocholic acid (**1**) in 6 mL (4.7568 g, 148.5 mmol) dry CH_3OH, 0.5 mL (0.5525 g, 7.038 mmol) acetyl chloride was added. After the mixture had stood at room temperature overnight, cold water was added until just turbid. The product was filtered, washed with water, and dried. The crude product was recrystallized from hexane-ethyl acetate; yield 0.4720 g (91%) of **3**, mp. 123-125°, lit.[13] 126-128°; R_f: 0.25. Partial ^{1}H NMR: δ 3.63 (s, 3H, OCH_3), 3.56 (m, 1H, 3β-H), 2.24 (m, 2H, 23-CH_2), 0.90 (s, 6H, 19-CH_3, 21-CH_3), 0.63 (s, 3H, 18-CH_3). IR: 3360 (s), 2930 (s), 2850 (s), 1760 (s), 1450 (m), 1380 (m), 1330 (w), 1315 (w), 1250 (m), 1220 (m), 1175 (m), 1075 (w), 1050 (m) cm^{-1}.

α-Dimer 4.- To a stirred solution of 0.4180 g (1.0 mmol) acetyl lithocholic acid (**2**) in 15 mL dry CH_2Cl_2, 0.0183 g (0.15 mmol) DMAP and 0.4290 g (1.1 mmol) methyl lithocholate (**3**) were added. Then 0.3399 g (1.65 mmol) DCC was added to the reaction mixture which was stirred for two days at room temperature in a sealed flask. The reaction mixture was diluted with 20 mL CH_2Cl_2 and filtered. The filtrate is washed with 5% aqueous HCl, saturated $NaHCO_3$, and water, dried by $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography and recrystallized from ethyl acetate-chloroform to yield α-dimer **4** with yield 0.5767 g (73%), mp. 212-214°; R_f: 0.69. Partial ^1H NMR: δ 4.72 (m, 2H, 3β-H, 3β'-H), 3.66 (s, 3H, OCH_3), 2.25 (m, 4H, 23-CH_2), 2.03 (s, 3H, 3α-OAc), 0.93 (s, 6H, 19-CH_3 , 19'-CH_3), 0.91 (d, 6H, 21-CH_3, 21'-CH_3), 0.65 (s, 6H, 18-CH_3, 18'-CH_3). ^{13}C NMR: δ 174.59, 173.65, 170.47, 74.34, 74.03, 56.56, 56.13, 51.35, 42.76, 41.93, 40.48, 40.19, 35.82, 35.30, 35.08, 34.60, 32.30, 31.75, 31.07, 28.17, 27.03, 26.66, 26.34, 24.18, 23.32, 21,38, 20.84, 18.29, 12.05. IR: 2935 (s), 2870 (s), 1735 (s), 1475 (m), 1455 (m), 1425 (w), 1390 (m), 1366 (m), 1338 (w), 1250 (m), 1182 (m), 1120 (w), 1040 (m), 990 (w) cm^{-1}. FAB/MS (3-NBA): 791.7 $(MH)^+$, 705.6 (5), 567.6 (15), 373.4 (40), 289.1 (19), 154.1 (100). FAB/MS (3-NBA + NaI): 813.9 $(MNa)^+$, 589.6 (15), 413.4 (47), 322.9 (27), 242.0 (9), 172.9 (100).

Anal. Calcd for $C_{51}H_{82}O_6$: C, 77.42; H, 10.45. Found: C, 77.98; H, 10.77

Methyl 3β-Formyloxycholanoate (5).- See references 10 and 11. A mixture of 0.3900 g (1.0 mmol) methyl lithocholate (**3**), 1.0492 g (4.0 mmol) Ph_3P and 8 mL dry THF was stirred to dissolve. To this solution was added 0.096 g (2.0 mmol) HCOOH and 0.6968 g (4.0 mmol) diethyl azodicarboxylate (DEAD). After the solution was stirred for 2 days at room temperature. The solvents were evaporated. The crude product was purified by column chromatography and recrystallization from hexane-ethyl acetate; yield 0.3449 g (83%) of **5**, mp. 110-112°, lit.[10] 114-116°; R_f: 0.77. Partial ^1H NMR: δ 8.08 (s, 1H, CHO), 5.20 (s, 1H, 3α-CH), 3.63 (s, 3H, OCH_3), 2.22 (m, 2H, 23-CH_2), 0.97 (s, 3H, 19-CH_3), 0.94 (d, 3H, 21-CH_3), 0.67 (s, 3H, 18-CH_3). IR: 2940 (s), 2870 (s), 1735 (s), 1720 (s), 1450 (s), 1390 (m), 1310 (w), 1280 (w), 1230 (m), 1175 (s), 1050 (m), 1010 (w), 970 (w), 920 (w), 890 (w) cm^{-1} .

Methyl 3β-Hydroxycholanoate (6).- See references 10 and 11. β-Formate **5** 0.2926 g (0.7 mmol) was added to a solution of 2.5% CH_3ONa in CH_3OH. After the mixture was stirred for 18 hrs at room temperature, it was concentrated, mixed with 10 mL H_2O, acidified with 5% HCl to pH 3 and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried by $MgSO_4$ and evaporated; yield 0.2457 g (90%) of **6**, mp. 104-106°, lit.[10] 107-109°; R_f: 0.28. Partial ^1H NMR: δ 4.08 (s, 1H, 3α-CH), 3.65 (s, 3H, OCH_3), 2.27 (m, 2H, 23-CH_2), 0.97 (s, 3H, 19-CH_3), 0.92 (d, 3H, 21-CH_3), 0.63 (s, 3H, 18-CH_3). IR: 3430 (s), 2950 (s), 2870 (s), 1735 (s), 1720 (s), 1450 (s), 1390 (m), 1310 (w), 1280 (w), 1230 (m), 1175 (s), 1050 (m), 1010 (w), 970 (w), 920 (w), 890 (w) cm^{-1}.

β-Dimer 7.- Using β-alcohol **6**, the same method was employed as in the synthesis of α-dimer **4**. The yield of **7** is 0.3713 g (47%); mp. 173-175°; R_f: 0.66. Partial ^1H NMR: δ 5.07 (s, 1H, 3α-CH), 4.72 (m, 1H, 3β-CH), 3.66 (s, 3H, OCH_3), 2.27 (m, 4H, 23-CH_2), 2.03 (s, 3H, CH_3CO), 0.91 (s, 6H, 19-CH_3), 0.90 (d, 3H, 21-CH_3), 0.88 (d, 3H, 21'-CH_3), 0.65 (s, 3H, 18-CH_3), 0.64 (s, 3H, 18'-CH_3). ^{13}C NMR: δ 174.584, 173.68, 170.46, 74.33, 70.39, 56.56, 56.14, 56.01, 51.34, 42.80, 41.95, 40.49, 40.19,

39.94, 37.46, 35.82, 35.70, 35.30, 35.09, 34.84, 34.62, 32.30, 31.82, 31.22, 31.03, 30.84, 29.68, 28.17, 27.03, 26.66, 26.54, 26.36, 26.17, 24.18, 23.87, 23.33, 21.38, 20.85, 18.26, 12.04. IR: 2940 (s), 2860 (s), 1730 (s), 1470 (m), 1452 (m), 1383 (m), 1365 (m), 1310 (w), 1247 (s), 1200 (m), 1180 (m), 1167 (m), 1030 (m), 990 (w), 765 (w) cm^{-1}. FAB/MS (3-NBA): 791.7 $(MH)^+$, 705.6 (4), 621.5 (5), 515.5 (5), 442.5 (3), 373.4 (100), 307.2 (9), 257.2 (15), 154.1 (50). FAB/MS (3-NBA + NaI): 813.7 $(MNa)^+$, 648.7 (4), 498.8 (10), 322.8 (21), 241.8 (7), 172.9 (100).

Anal. Calcd for $C_{51}H_{82}O_6$: C,77.42; H,10.45. Found: C,77.43; H,10.60

Acknowledgment.- We gratefully thank Dr. Peter Groner for recording 250 MHz ^1H and ^{13}C NMR. The mass spectra were determined by the Nebraska Center for Mass Spectrometry and the elementary analyses were measured by Galbraith Laboratories Company.

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