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Highly Selective Cyclotrimerization of Lithocholic Acid by DCC/DMAP Reagent

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Synthesis of cyclolithocholates by using dicyclohexylcarboimide (DCC) and 4-dimethylaminopyridine (DMAP) is described. Cyclotrimerization is the principal reaction route for lithocholic acid system. These reaction conditions were less successful in the cyclization of 12-oxolithocholic acid.

INTRODUCTION

Recently, the synthesis of taylor-made dimeric and oligomeric steroids has become of interest because of their possible application as biochemical/cellular membrane models and as components in molecular engineering.[1,2] Cyclocholates are bile acid-based macrocycles capable of binding other biologically important substances.[1] Some of them have been used as a chiral building block to construct artificial receptors and led to related molecular recognition studies.[3] The peptide conformations influenced by a subtle change in the molecular structure of the steroid is also reported recently.[4] The syntheses of cyclocholates were achieved from the cycloesterification of appropriately prepared monomeric hydroxy acids by using 2,6-dichlorobenzoyl chloride (DCBC) and 4-dimethylaminopyridine (DMAP) refluxing in toluene (Yamaguchi macrolactonization)[5–7] or by transesterification under thermodynamic, equilibrating conditions using a potassium methoxide-crown ether complex.[8] In this paper, we report a unique macrolactonization of lithocholic acid using DCC and DMAP and the isolation of cyclodilithocholate (**2a**), cyclotrilithocholate (**2b**), and cyclotetralithocholate (**2c**).

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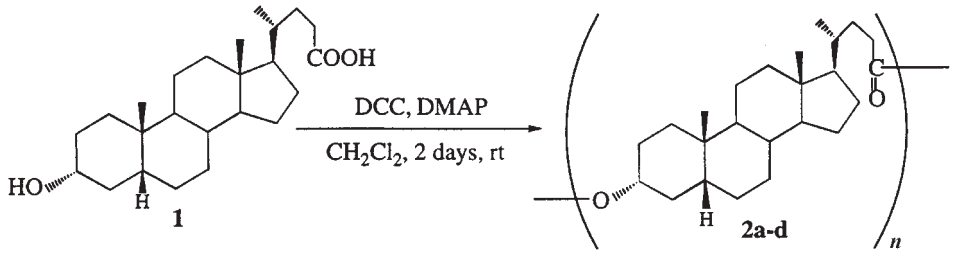
RESULTS AND DISCUSSION

Cyclization: The cyclolithocholates were first prepared from lithocholic acid **1** by Yamaguchi macrolactonization[6,7] and confirmed later (Scheme 1). Cyclotrimerization is preferred over cyclodimerization, cyclotetramerization and cyclopentamerization. However, the dimerizations of lithocholic acid derivatives were acomplished by DCC and DMAP.[9] We successfully applied this milder reaction in the cyclization of lithocholic acid and obtained three cyclooligomers (from dimer to tetramer). Cyclotrimerization is still principle reaction route (52.5%). Since competitive benzoylation of the 3α-OH is absent in this reaction compared the Yamaguchi reaction, higher yields are obtained. However, the same reaction was less successful on 12-oxolithocholic acid. Small amounts of cyclotrimer were detected by TLC (EtOAc: cyclohexane=1:2) compared with the standard.[5] This is possibly due to a side reaction between DCC and 12-oxo.



	n=2	*n*=3	*n*=4	*n*=5
Compd	**2a**	**2b**	**2c**	**2d**
Yields[6]	–	32%	4%	–
Yields[7]	29.8%	34.4%	8.4%	11.5%
Yields	2.1%	52.5%	4%	–

Scheme 1

^{13}C NMR Spectra: The assignments of the ^{13}C NMR resonances are based on the previous data on the methyl 3α-(acetyloxy)-5β-cholan-oate.[10] The 17-sidechain of **2a–2c** undergoes a major change in flexibility and molecular tension as the cycle size goes from cyclodimer to cyclotetramer. The largest ^{13}C NMR chemical shift differences with changes in cycle size occur in the C-17 and C-20 to C-24 carbons.[6] In comparison of the ^{13}C NMR, significant deshielding of the C-17 (52.58, 54.77 and 56.28 ppm), C-18 (11.88, 12.01 and

TABLE I

^{13}C NMR ($CDCl_3$) of 3α-Hydroxy-5β-cholan-24-oic Acid Derivatives

Assignment	$C_{27}H_{44}O_4$[a]	**2a**	**2b**	**2c**
C-18	11.7	11.88	12.01	12.31
C-21	18.0	19.54	18.42	18.19
*CH_3*CO	21.0	–	–	–
C-11	21.1	20.70	20.86	20.87
C-19	23.0	23.32	23.35	23.28
C-15	24.4	24.08	24.21	24.39
C-7	26.7	26.44	26.42	26.20
C-6	27.3	26.75	26.75	26.58
C-16	28.4	27.21	27.06	27.00
C-2	26.4	28.08	28.14	28.44
C-23	(31.1)	28.63	30.14	31.23
C-22	(31.3)	31.11	30.57	32.03
C-4	32.2	32.02	32.45	32.14
C-10	34.8	34.69	34.56	34.52
C-20	35.6	(34.69)	34.94	34.97
C-1	35.1	35.20	35.17	35.30
C-8	36.1	36.03	35.59	35.78
C-12	40.5	39.67	40.27	40.33
C-9	40.6	40.33	40.39	40.57
C-5	42.0	41.77	41.92	41.67
C-13	43.0	42.76	42.70	42.88
OCH_3	51.6	–	–	–
C-17	56.5	52.58	54.77	56.28
C-14	56.7	56.53	56.59	56.83
C-3	74.4	74.13	74.06	73.99
CH_3*CO*	169.4	–	–	–
C-24	175.2	175.28	173.89	173.34

[a]Methyl 3α-(acetyloxy)-5β-cholan-oate.

12.31 ppm) and C-23 (28.63, 30.14 and 31.23 ppm) carbons occurred in the cyclodimer 2**a** relative to the cyclotrimer 2**b** and the cyclotetramer **2c**. The shielding chemical shifts for C-21 (19.54, 18.42 and 18.19 ppm), C-3 (74.13, 74.06 and 73.99 ppm), and C-24 (175.28, 173.89 and 174.34 ppm) and the chemical shifts for C-14 and C-13 are well separated from the other ^{13}C NMR peaks.

EXPERIMENTAL SECTION

Column chromatography was carried out using Grade 62 (60–200 mesh) silica gel and eluted by hexane-ethyl acetate solvent system. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured at 250 MHz and 63 MHz (Bruker) in $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on a VG20–253 or VGZAB-HS Spectrometer.

Cyclization of lithocholic acid: To a stirred solution of lithocholic acid (1.5 g, 3.98 mmol) in dry CH_2Cl_2 (125 mL), DMAP (1.72 g, 14.1 mmol) and DCC (2.72 g, 13.2 mmol) was added. The reaction mixture was then stirred for two days at room temperature. The reaction mixture was filtered and the filtrate washed with dilute HCl (1.0 M), satd $NaHCO_3$, brine, dried by Na_2SO_4 and the solvent was evaporated to dryness. The residue was flash chromatographed on a silica gel column with 5:1 hexane/EtOAc and the cyclooligomers eluted in the order listed below.

Cyclodimer ***2a****:* m.p. 309–311 °C [Ref. 6: 298–300 °C; Ref. 7: 255 (decomp.)], yield: 2.1%. ^{1}H NMR ($CDCl_3$) δ/ppm: 0.64 (s, 3H, 18-H_3); 0.92–0.93 (m, 6H, 19-H_3, 21-H_3); 2.24 (t, 2H, 23-H_2); 4.75 (m, 1H, 3β-H). FAB/MS (3-NBA) *m/z*: 717.7 $[M+1]^+$.

Cyclotrimer ***2b****:* m.p. 300–302 °C [Ref. 6: 300–302 °C (corrected); Ref. 7: 217–222 °C], yield: 52.5%. ^{1}H NMR ($CDCl_3$) δ/ppm: 0.64 (s, 3H, 18-H_3); 0.93 (s, 6H, 19-H_3, 21-H_3); 2.26 (m, 2H, 23-H_2); 4.77 (m, 1H, 3β-H). FAB/MS (3-NBA+LiI) *m/z*: 1081.9 $[M+Li]^+$.

Cyclotetramer ***2c****:* m.p. 240–242 °C [Ref. 6: 248–250 °C; Ref. 7: 214–218 °C], yield: 9.8%. ^{1}H NMR ($CDCl_3$) δ/ppm: 0.67 (s, 3H, 18-H_3); 0.92 (s, 6H, 19-H_3, 21-H_3); 2.27 (m, 2H, 23-H_2); 4.72 (m, 1H, 3β-H). FAB/MS (3-NBA+LiI) *m/z*: 1440.3 $[M+Li]^+$.

CONCLUSION

Three lithocholic acid cyclooligomer analogs have been synthesized by DCC coupling and characterized by ^{1}H NMR, ^{13}C NMR, MS spectroscopy. Under these reaction conditions, cyclotrimer is the major product. This is probably because the linear trimer has two choices – either add on another lithocholic unit or intramolecularly cyclize, but in the accumulation, say 50%, of linear trimer, the concentration of monomer has also been reduced to the point where cyclotrimerization is sufficiently competitive.

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SAŽETAK

Visoko selektivna ciklotrimerizacija litokolne kiseline pomoću DCC/DMAP reagensa

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Opisana je sinteza ciklolitokolata primjenom dicikloheksilkarbodiimida (DCC) i 4-dimetilaminopiridina (DMAP). Ciklotrimerizacija glavni je reakcijski put za litokolnu kiselinu. Ti su reakcijski uvjeti bili manje uspješni pri ciklizaciji 12-okso-litokolne kiseline.