Synthesis and Cation Binding Properties of a Novel "Chola-Crown"

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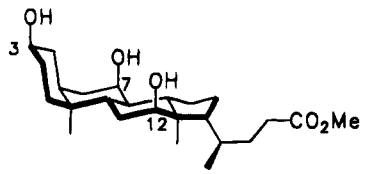
Since Pederson's discovery in 1967,[1] a large number of crown ethers have been synthesized for studying their cation-binding properties.[2] Many crown ether derivatives have been examined for enantioselective binding of appropriate guest molecules.[3] Crown ether-based biomimetic systems have also been investigated by various groups.[4] We report a *one-step* synthesis of a novel cholic acid derived chiral 21-crown-6 with a built-in handle for the attachment of additional functionality and our preliminary results of its cation binding properties.

Chiral crown ethers have been synthesized from a variety of natural products bearing OH groups;[2,5] however, no attempt has so far been made to utilize the uniquely disposed hydroxyl groups of bile acids for this purpose. In recent years bile acids have attracted considerable attention for asymmetric synthesis,[6] molecular recognition,[7] drug delivery,[8] etc. We felt that it should be possible to construct crown ethers using the 3 and the 7 hydroxyl groups of cholic acid, which have a 1,5 relationship. The 12-OH could then be utilized for appropriate modification to create a variety of functionalized chiral crown ethers.

In view of the known[9] reactivity of the three hydroxyl groups of cholic acid toward acylation (3 ≫ 7 > 12) we reasoned that the treatment of *unprotected* methyl cholate (**1**) with penta(ethylene glycol) ditosylate ($PEGTs_2$)



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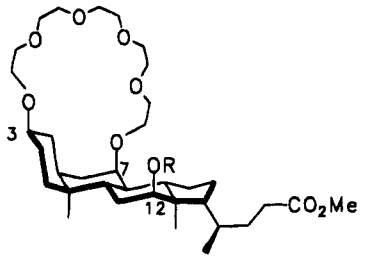
in the presence of a base should lead to the formation of the desired 21-C-6 involving the 3 and the 7 hydroxyl groups of cholic acid. Assuming the first alkylation to go to C-3, and considering the template effect of the metal ion (Na^+) during cyclization, the formation of the crown ether between C-3 and C-7 should be much more facile than the one between C-3 and C-12.[10] Indeed, refluxing methyl cholate with sodium hydride and $PEGTs_2$ in THF for 3 days followed by reesterification of the side chain (HCl/MeOH) yielded compound **2** in ca. 10% yield.[11] Even



2: R = H
3: R = 2-Naphthoyl

though **2** is produced in low yield, its one-step construction from inexpensive reactants is appealing. Compound **2** was purified as the 12-(2-naphthoate) **3** and was characterized spectroscopically. The most notable feature of the ^{1}H-NMR spectrum of **3** is the presence of a singlet at δ 5.39 with the shape (apparent triplet) and line width expected for the 12-H,[12] thus providing strong support for the structure shown.

Association constant measurements of cations with **3** were carried out in chloroform at 25 °C using Cram's picrate extraction method.[13] The results are as follows (M^+, log K_a): Na^+, 4.31; K^+, 5.43; Rb^+, 5.17; Cs^+, 4.64; ^{t}Bu-NH_3^+, 3.55.

The binding constants show moderately high binding affinity for K^+ and Rb^+. We believe that the incorporation of the 1,5 diol (cholic acid part) in the crown ether has led to the distortion of the macrocycle with nonoptimal orientation of the ether oxygens toward a bound cation. This is supported by computer modeling studies.[14] We find that in the energy-minimized structure (Figure 1) the ethylene glycol moiety directly attached to C-7 adopts a transoid geometry making one of the oxygens "exodentate",[15] whereas a gauche-type conformation is required for the oxygen lone pairs to orient toward the center the macrocycle. Nevertheless, the appreciable

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(10) The distance between the hydroxyl groups in the C-3 and C-12 is 6.32 Å and that between C-3 and C-7 is 5.02 Å as seen in the X-ray structure of cholic acid. (See: Johnson, P. L.; Schaefer, J. P. *Acta Crystallogr.* **1972**, *B28*, 3083.)
(11) Cyclization of a side chain-reduced and trityl-protected cholic acid derivative with $PEGTs_2$ gave the corresponding 21-C-6 derivative in ca. 20% yield.
(12) 7-H is coupled to *three* vicinal hydrogens with coupling constants on the order of 3 Hz, whereas 12-H is coupled to *two* vicinal hydrogens with ca. 3 Hz coupling (these J values are estimated from the energy-minimized (MMX) strucure of cholic acid using PCMODEL. In high resolution ^{1}H-NMR, 7-H and 12-H appear as an apparent quartet and triplet, respectively.
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(14) Modeling studies were done on a Silicon Graphics Workstation using the **Insight II** program (version 2.2.0). The "21-C-6" on the steroid was built starting from the crystal structures of cholic acid and 18-C-6. Molecular mechanics calculations were done in the DISCOVER module using the CVFF forcefield.
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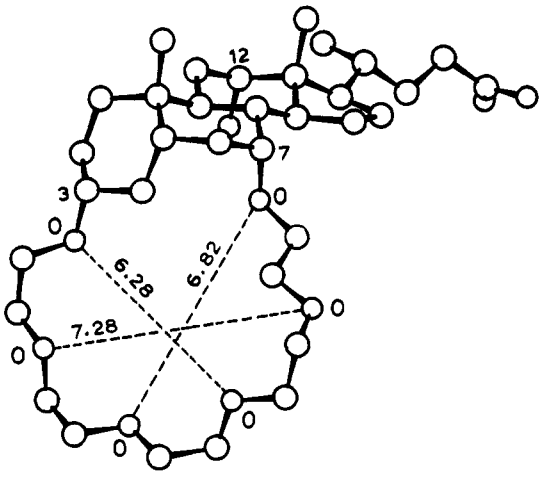

Figure 1. Perspective view of the energy-minimized (INSIGHT II) structure of compound **2** (shown in the free acid form). Hydrogen atoms have been removed for clarity.

association constants exhibited by this novel crown ether and the ready availability of a well-positioned hydroxyl group makes this system very attractive for the construction of biomimetic systems[4a,b] in which a bound substrate/metal ion will be able to interact with a C-12 substituent (e.g., a catalytic arm or a coordinating ligand). Additionally, the attachment of a fluorophore or an electrophore at C-12 might lead to metal ion sensors.[16] *The rigid nature of our steroidal crown ether (with respect to the binding and the functionalization sites) makes it an ideal template for constructing such molecular devices.* Many of these possibilities are now being examined in our laboratory, and the results of these investigations will be reported in due course.

Experimental Section

A solution of methyl cholate (0.15 g, 0.35 mmol) and penta(ethylene glycol) distosylate (0.24 g, 0.44 mmol) in dry THF (10 mL) wastreated with sodium hydride (0.18 g, 4.5 mmol), stirred at rt for 7 min, and then refluxed for 61 h with magnetic stirring. The volatiles were removed in vacuo, and the crude product was diluted with 6 mL of chloroform, acidified with 1 mL of glacial acetic acid, diluted further with 50 mL of chloroform, and equilibrated with 20 mL of distilled water. The organic layer was separated, and the aqueous layer was extracted with chloroform (10 mL × 2). The combined organic layer was washed with distilled water (25 mL × 2) and dried over anhyd $MgSO_4$. Volatiles were removed under reduced pressure, and the crude product was reesterified with 2% HCl in methanol at rt (24–25 °C) for 11 h. After removal of the solvent the crude product was initially purified by column chromatography on silica (6 g, 14 × 1.2 cm) using ethyl acetate as the eluant and then purified further on a chromatotron using ethyl acetate as the mobile phase. The isolated product (0.020 g, 9.4%; recovered **1**, 10%) was directly converted to the 12-(2-naphthoate) by refluxing with 2-naphthoyl chloride in the presence of triethylamine and DMAP in toluene for 2 days. Usual workup and purification afforded compound **3** as a glass in 56% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.61 (s, 1 H), 8.07 (dd, J = 8.5 Hz, 1.3 Hz, 1 H), 8.01 (d, J = 7.0 Hz, 1 H), 7.95 (d, J = 8.5 Hz, 1 H), 7.89 (d, J = 7.5 Hz, 1 H), 7.61–7.53 (m, 2 H), 5.39 (s, 1 H, 12-H), 3.90–3.33 (m), 3.58 (s, 3 H), 3.31–3.28 (m, 1 H), 3.02 (br s, $w_{1/2}$ = 21 Hz, 1 H), 2.50–0.71 (m), 0.91 (s, 3 H), 0.84 (d, 6.5 Hz, 3 H), 0.81 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 174.54, 166.24, 135.59, 132.63, 130.97, 129.55, 128.38, 128.06, 127.71, 126.55, 125.16, 79.47, 76.38, 71.35, 71.25, 70.92, 70.80, 70.58, 70.51, 70.35, 69.29, 66.84, 51.35, 47.86, 45.36, 43.56, 41.76, 39.43, 35.09, 34.95, 34.82, 34.73, 30.89, 30.79, 28.99, 28.61, 27.37, 26.88, 25.88, 23.12, 22.68, 17.53, 12.28. UV: λ_{max} 281.2 (ϵ 10 420), 334.0 (ϵ 1970) in 1% $CHCl_3$/MeOH. IR (neat): 2905 (s), 2845 (s), 1725 (s), 1702 (s), 1440 (m), 1350 (m), 1280 (s), 1225 (s), 1192 (s), 1092 (s), 1005 (m) cm^{-1}. HRMS (FAB): 779.4739 (MH^+), calcd for $C_{46}H_{67}O_{10}$ 779.4734. $[\alpha]^{24}_D$: +12.7° (*c* 3.39, $CHCl_3$).

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Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra of **3** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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