Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Maitra, Uday , D'souza, Lawrence J. and Kumar, P. Vijay(1998) 'Synthesis and Cation Binding Properties of New Bile Acid-based Crown Ethers', Supramolecular Chemistry, 10: 1, 97 — 106
To link to this Article: DOI: 10.1080/10610279808055400
URL: http://dx.doi.org/10.1080/10610279808055400

SUPRAMOLECULAR CHEMISTRY, Vol. 10, pp. 97–106
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Synthesis and Cation Binding Properties of New Bile Acid-based Crown Ethers

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(Received 22 December 1997; Revised 15 April 1998)

A series of bile acid-based crown ethers (7a–c, 12 and 13) were easily constructed from readily available precursors. Measurement of association constants (K_a) with alkali metal picrates in $CHCl_3$ showed that azacrown ethers 7a–c and *Chola-Crowns* 12 and 13 show greater binding towards Rb^+ and K^+. The presence of the aromatic moieties showed subtle changes in the binding properties. Insight II minimized structures show very different conformations of aromatic units in 7a–b and 13.

Keywords: Crown ether, bile acid, cation binding

INTRODUCTION

Almost three decades after the serendipitous discovery of the cation binding properties of macrocyclic polyethers by Pederson [1], the literature today is still abound with new developments and applications of crown ethers [2] in diverse fields of chemistry such as phase transfer catalysis [3], ion transport [4], chromatography [5], chromogenic reagents [6], photoresponsive crown ethers [7] *etc.*

A special class of polyether macrocycles-the *Lariat ethers*-were developed by Gokel [8] in which covalently linked sidearms were positioned to interact with a macrocycle-bound metal ion to improve the binding. These crown ethers are flexible and dynamic, properties which the natural ionophores possess. When the side arm is lipophilic, as in cholesterol-derived crown ethers, the molecules can assemble into aggregates (bilayers/micelles/vesicles) [9] of significant size and stability. Considering the importance of steroidal crown ethers in various aspects of supramolecular chemistry such as in liquid crystals [10], membrane mimics [11], chiral recognition [12], and the use of crown ethers as chiral catalysts [13], we decided to exploit the unusual structural aspects of bile acids [14] to construct cation receptors with pendant aromatic units. Bile acids with their bipolar surfaces and well spaced hydroxyl groups of different reactivities offer an ideal scaffold to synthesize lariat type ethers. In this paper, we present the synthesis and metal ion binding properties of new bile acid based crown ethers.

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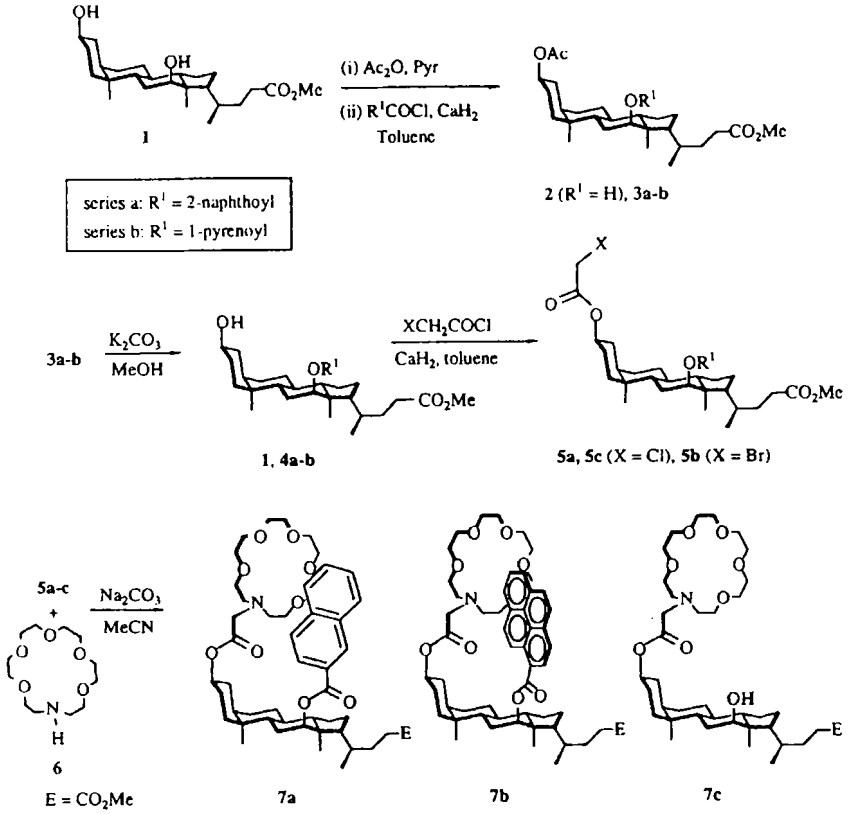
RESULTS AND DISCUSSIONS

Design

We recently reported the construction of a rigid *"Chola-Crown"* on cholic acid and studied its cation binding properties [15]. The yield of the crown ether was low, which was attributed to side-reactions involving the side-chain ester under the reaction conditions. In this paper we report the synthesis and binding properties of two types of crown ethers using the bile acid backbone. The first type has an aza-crown ether positioned at the C-3 position of methyl 7-deoxycholate (**1**), whereas the second type, belonging to the class of *'Chola-Crown'*, is built on the 24-norcholane skeleton (no side-chain ester) using the hydroxyls at C-3 and C-7. In both types pendant *aromatic* units were attached at C-12 since we reasoned that these crown ethers with pendant aromatic units might be useful prototypes for the design of ionic devices [16–18]. Such systems could also be designed to study cation–π interactions systematically [19].

Synthesis

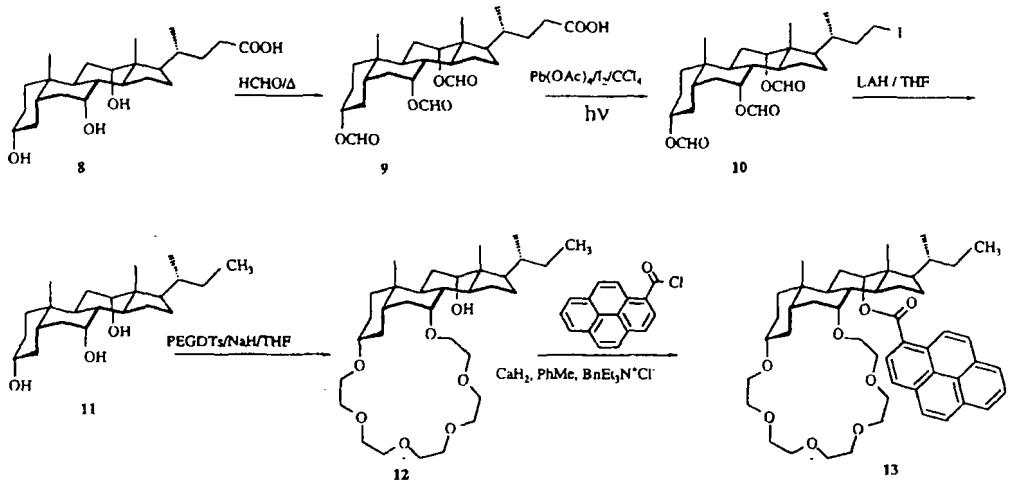
Compound **2** (obtained by the selective acetylation of **1** with Ac_2O/pyridine) [20] was esterified [21] with 2-naphthoyl and 1-pyrenoyl chlorides to the corresponding esters **3a–b** in 90 and 91% yields. Methanolysis (K_2CO_3/MeOH) of the C-3 ester of **3a–b** afforded free 3-hydroxy esters **4a–b** (95 and 96%). Esterification of **4a–b** and **1** with haloacetyl chloride afforded haloacetyl esters **5a–b** (92 and 94%) and **5c** (75%), respectively (Scheme 1). The desired steroidal



SCHEME 1

ethers **7a–c** were obtained by refluxing **5a–c** with monoaza 18-Crown-6 (**6**) [22] in the presence of Na_2CO_3 in CH_3CN in 53–75% yield.

Cholic acid **8** was converted to triformylcholic acid **9** [23] in 95% yield. Iodo-decarboxylation of compound **9** using Barton's method ($Pb(OAc)_4/I_2/h\nu$) gave 23-iodo-24-norcholane derivative **10** in 85% yield [24]. $LiAlH_4$ reduction of **10** in refluxing THF yielded **11** in 85% yield. *'Chola-Crown'* **12** was made from **11** by reacting it with pentaethylene glycolditosylate (**PEGDTs**) in the presence of NaH (isolated yield 30%). Compound **12** was converted to its pyrenoyl derivative **13** using Oppenauer esterification procedure (Scheme 2).



SCHEME 2

Properties

Binding measurements were performed in $CHCl_3$ using Cram's method [25] using the metal picrates [26] and the data are presented in Table I. Compounds **7a** and **7c** were found to be slightly more selective for Rb^+ and the binding constants decreased in the order $Rb^+ > K^+ > Na^+ > Cs^+ > Li^+$. Hosts having the aromatic units at C-12 showed a measurable increase in the binding constants of Rb^+ and K^+. Another interesting observation is that crown **7a** having a 12α-naphthoate binds Rb^+ more tightly than **7b** having a 12α-pyrenoate moiety. Unlike compounds **7a** and **7c** which belong to 18-Crown-6-class, chola-crowns **12** and **13** which belong to the 21-Crown-6-showed comparable binding of K^+ and Rb^+. The binding decreased in the order $K^+ > Rb^+ > Na^+ > Cs^+ > Li^+$ for compound **12**, but the presence of pyrene at C-12 in Compound **13** resulted in increased binding of Cs^+ compared to Na^+.

Insight II (DISCOVER, CVFF forcefield) minimized structures of **7a–b** and **13** show different spatial dispositions of the C-12 aromatic units with respect to the crown moiety (Fig. 1). The surface of the aromatic units in azacrowns **7a–b** is more or less parallel to the mean crown ether plane, whereas in **13** it is perpendicular. This results in complete blocking of one face of the crown ether in chola-crown **13**. Even though these

TABLE I Association Constants (Log K_a) of alkali metal ions with hosts in $CHCl_3$ at 25°C by Cram's method

Metal Ions	7a	7b	7c	12	13	18-C-6
Li^+	5.95	5.79	5.99	4.66	4.17	5.63
Na^+	6.55	6.58	6.63	5.18	4.56	6.11
K^+	6.96	7.06	6.70	5.63	5.68	>11
Rb^+	7.36	7.04	6.90	5.47	5.54	10.57
Cs^+	6.39	6.52	6.32	5.07	4.83	–

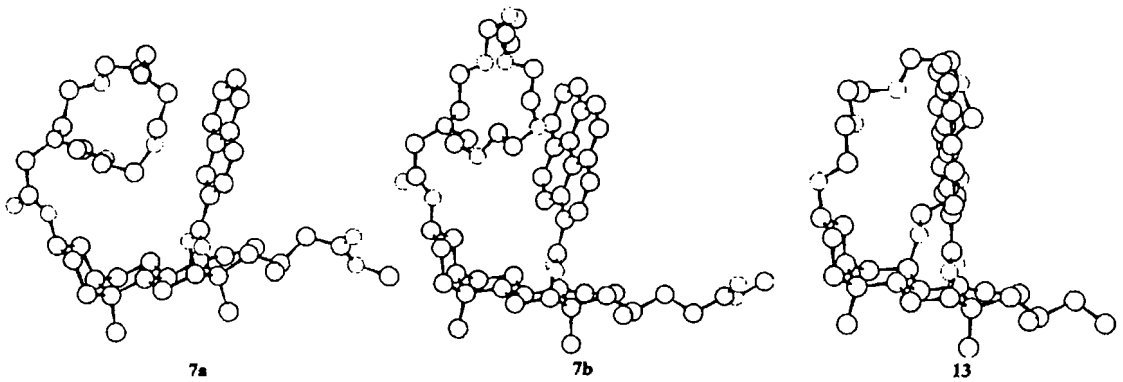


FIGURE 1 Minimized (gas-phase) structures of **7a–b** and **13**. The hydrogen atoms have been omitted for clarity. (See Color Plate).

are gas phase structures, the different relative orientations of the aromatic surfaces is striking.

CONCLUSIONS

The newly synthesized steroidal crown ethers offer attractive opportunities not only for systematically studying the interaction of a bound metal ion with a pendant ligand attached at C-12, but also for the design and construction of novel ionic devices. Our protocol provides a convenient strategy to position a crown ether (or a different receptor) and another (interacting) group in close proximity in space. We believe that the analysis of the crystal structures of the metal ion complexes of **7a**, **7b** and **13** will be of considerable interest of understanding the nature of the interaction of the metal ion with the aromatic unit. A detailed examination of the properties of some of these crown ethers are being investigated in our laboratory, and the results will be reported in due course.

EXPERIMENTAL

General

Melting points were recorded in open capillaries and are uncorrected. Proton spectra were recorded on 90, 200, 270 and 400 MHz spectrometers. Unless otherwise stated ^{1}H NMR were recorded in $CDCl_3$ using $CHCl_3$ as the internal standard ($\delta = 7.270$). For ^{13}C spectra the peak at 77.0 ppm arising from $CDCl_3$ was used as the internal reference. Optical rotations were measured in appropriate solvents using sodium D light. Microanalyses were done on an automated C/H/N/S analyzer. LRMS implies EI-LRMS unless otherwise mentioned. FAB mass were recorded using argon/xenon (6 kV, 10 mA) as the FAB gas using *m*-nitrobenzyl alcohol as a matrix. Infrared spectra were taken in $CHCl_3$, as a thin film on NaCl plates (neat) [27] or in Nujol. All reactions were conducted under dry nitrogen and stirred magnetically unless otherwise stated. Reaction temperatures refer to external or bath temperatures, unless indicated otherwise. Thin layer chromatography was performed using precoated plates (silica gel 60F-254) purchased from Sigma. These plates were stained either with iodine vapor or with 5–10% phospomolybdic acid in ethanol or Lieberman-Bucchardt reagent. Purification of the products were usually done using gravity columns.

Solvents

All solvents were purified and distilled before use. Toluene, benzene and tetrahydrofuran was distilled from sodium/benzophenone ketyl. Methanol was distilled from magnesium methoxide.

Methyl 3α-Acetoxy-12α-(2-naphthoyl) oxy-5β-cholan-24-oate (3a)

To a solution of **2** (1.2 g, 2.7 mmol) in toluene (10 mL), CaH_2 (0.674 g, 16 mmol), tetrabutylammonium iodide (0.5 g, 1.4 mmol) and 2-naphthoyl chloride (0.76 g, 3.9 mmol) were added and the resulting mixture was stirred at 110°C for 24 h. After filtration and washing the residue with EtOAc, the organic layer was washed with 7% $NaHCO_3$ solution, water, brine and finally dried over anhyd Na_2SO_4 and filtered. The solvent was removed in vacuo to yield the crude product, which was purified by column chromatography on silica gel (100–200 mesh, 15 cm × 2.4 cm, 20 g) using 5% EtOAc/hexanes as the eluent. The title compound was obtained in 90% (1.44 g) yield. Mp 65–67°C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.85 (s, 6H), 0.96 (s, 3H), 1.0–2.20 (m, steroidal CH and CH_2 and acetyl), 1.8 (s, 3H), 3.6 (s, 3H), 4.20–4.80 (br m, 1H), 5.44 (s, 1H), 7.48–7.68 (m, 2H), 7.84–8.20 (m, 4H), 8.60 (s, 1H); $[\alpha]_D^{25}$: +39° (*c* 2.1, $CHCl_3$); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 12.6, 17.6, 21.1, 23.0, 23.5, 26.0, 26.9, 27.4, 30.8, 32.2, 33.9, 34.7, 35.8, 41.7, 45.5, 47.9, 50.2, 51.2, 73.8, 76.0, 76.5, 77.4, 78.8, 125.1, 126.6, 127.8, 128.2, 129.4, 130.8, 132.5, 135.4, 165.9, 170.2, 174.2; MS 602 (M^+, 12), 370 (100), 315 (100), 255 (100).

Methyl 3α-(Acetoxy)-12α-(1-pyrenoyl) oxy-5β-cholan-24-oate (3b)

This compound was prepared in 91% yield following the procedure for **3a**; mp 183–185°C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.96 (d, 3H, J = 6.5 Hz), 0.98 (s, 3H), 1.12–2.40 (m, steroidal CH and CH_2), 1.76 (s, 3H), 3.58 (s, 3H), 4.60–4.70 (br m, 1H), 5.59 (s, 1H), 8.04–8.30 (m, 7H), 8.62 (d, 1H, J = 8.1 Hz), 9.20 (d, 1H, J = 9.5 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 12.8, 17.9, 21.3, 23.1, 23.6, 25.9, 26.2, 26.5, 26.9, 27.6, 30.8, 30.9, 32.3, 34.2, 34.8, 34.9, 41.8, 45.6, 48.1, 50.2, 50.5, 73.9, 76.7, 76.9, 77.3, 124.4, 124.9, 125.1, 126.0, 126.2, 126.3, 127.2, 127.9, 129.5, 129.7, 130.5, 130.8, 131.2, 134.2, 167.7, 170.5, 174.6; $[\alpha]_D^{24}$ +74°, (*c* 3.308, $CHCl_3$); HRMS: Calc. for $C_{44}H_{52}O_6$: 676.3788 Found: 676.3764.

Methyl 3α-Hydroxy-12α-((2-naphthoyl) oxy)-5β-cholan-24-oate (4a)

A mixture of **3a** (1.3 g, 2.1 mmol) and K_2CO_3 (0.29 g, 2.1 mmol) in dry MeOH (15 mL) was stirred at rt for 3 h. The reaction was quenched by adding AcOH (1 mL), the volatiles were removed on a rotavapor and the residue was dissolved in EtOAc (25 mL). The organic layer was washed with 7% $NaHCO_3$ solution, water, brine and finally dried over anhyd Na_2SO_4 and filtered. The solvent was removed in vacuo to yield the crude product, which was purified by column chromatography on silica gel (100–200 mesh, 13 cm × 2 cm, 10 g) using 5–10% EtOAc/hexanes as the eluent. The pure material was obtained in 95% (1.06 g) yield. Mp 79–80°C; 1H NMR (90 MHz, $CDCl_3$) δ 0.84 (m, 6H), 0.94 (s, 3H), 1.0–2.0 (m, steroidal CH and CH_2), 2.20 (m, 2H), 3.50 (br m, 1H), 3.60 (s, 3H), 5.40 (s, 1H), 7.48–7.60 (br s, 2H), 7.84–8.08 (m, 4H), 8.60 (s, 1H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 12.5, 17.3, 23.1, 23.5, 26.0, 27.0, 27.3, 30.2, 30.7, 33.9, 34.6, 35.8, 36.1, 41.8, 45.4, 47.8, 50.0, 51.3, 71.2, 77.5, 78.7, 124.9, 126.6, 127.6, 128.0, 128.3, 129.4, 130.8, 132.4, 135.4, 166.0, 174.3; HRMS: Calc for $C_{36}H_{48}O_5$: 560.3464 Found: 560.3502.

Methyl 3α-Hydroxy-12α-((1-pyrenoyl) oxy)-5β-cholan-24-oate (4b)

This compound was prepared from compound **3b** in 96% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (m, 6H), 0.97 (s, 3H), 1.03–2.30 (m, steroidal CH and CH_2), 3.45–3.56 (br m, 1H), 3.57 (s, 3H), 5.58 (s, 1H), 8.06–8.60 (m, 7H), 8.62 (d, 1H, J = 8.10 Hz), 9.22 (d, 1H, J = 9.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 17.5, 23.0, 23.4, 25.7, 26.0, 26.9, 27.2, 30.4, 30.6, 30.8, 34.0,

34.6, 34.9, 35.7, 36.1, 41.8, 45.3, 47.8, 49.8, 51.2, 71.4, 76.7, 124.3, 124.6, 126.1, 127.0, 127.6, 129.4, 131.0, 132.0, 133.5, 167.5, 174.5; $[\alpha]_D^{21}$: +52° (*c* 0.536, $CHCl_3$); HRMS: Calc. for $C_{42}H_{50}O_5$: 634.3651 Found: 634.3658.

Methyl 3α-((Chloroacetyl)oxy)-12α-((2-naphthoyl) oxy)-5β-cholan-24-oate (5a)

Compound **4a** (0.15 g, 0.27 mmol) was dissolved in dry toluene (1 mL) and CaH_2 (0.068 g, 1.6 mmol), tetrabutylammonium iodide (0.038 g, 0.11 mmol) and chloroacetyl chloride (0.031 g, 0.34 mmol) were added. The mixture was stirred under N_2 atmosphere overnight. The crude product was obtained by aqueous work up after filtering the reaction mixture through celite and washing the residue with EtOAc (20 mL). Chromatography on silica gel using 10% EtOAc/hexanes as the eluent gave the pure material in 92% (0.156 g) yield. Mp 158–159°C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.84 (m, 6H), 0.96 (s, 3H), 1.0–2.0 (m, steroidal CH and CH_2), 2.20 (m, 2H), 3.60 (s, 3H), 3.68 (d, 2H), 4.4–4.88 (br m, 1H), 5.40 (s, 1H), 7.40–7.68 (m, 2H), 7.80–8.21 (m, 4H), 8.60 (s, 1H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 12.6, 17.6, 22.9, 23.6, 26.0, 26.8, 27.4, 32.0, 34.0, 34.7, 35.8, 41.0, 41.6, 45.5, 47.9, 50.2, 51.2, 76.0, 76.5, 77.4, 78.8, 125.1, 126.7, 127.7, 128.2, 129.4, 130.8, 132.53, 135.5, 165.8, 166.5, 174.3; $[\alpha]_D^{24}$: +41° (*c* 0.757, $CHCl_3$); Anal. Calc. for $C_{38}H_{49}ClO_6$: C: 71.62, H: 7.75 Found: C: 71.88, H: 7.78.

Methyl 3α-((Bromoacetyl)oxy)-12α-((1-pyrenoyl)oxy)-5β-cholan-24-oate (5b)

This was prepared in 94% yield from **4b** and bromoacetyl bromide as described for **5a**. mp 129–130°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.99 (m, 6H), 1.10–2.20 (m, steroidal CH and CH_2), 3.62 (s, 3H), 3.68 (d, 2H, *J* = 6 Hz), 4.7–4.9 (br m, 1H, 5.59 (s, 1H), 8.20–8.40 (m, 7H), 8.63 (d, 1H, *J* = 8.2 Hz), 9.21 (d, 1H, *J* = 9.5); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.6, 17.6, 22.9, 23.5, 25.7, 26.0, 26.2, 26.7, 27.3, 30.7, 30.9, 31.9, 34.0, 34.6, 34.7, 34.8, 35.7, 40.9, 41.6, 45.4, 47.9, 50.0, 51.3, 76.1, 76.9, 124.7, 126.0, 126.3, 127.1, 127.8, 128.4, 129.3, 129.5, 130.1, 130.3, 130.8, 131.0, 133.5, 134.1, 166.5, 167.4, 174.5 $[\alpha]_D^{24}$: +93° (*c* 0.442, $CHCl_3$); MS: 756 ($M^+/^{81}$Br, 32), 754 ($M^+/^{79}$Br, 31), 710 (80), 465 (18), 371 (100), 246 (85), 229 (87).

Methyl 3α-((Chloroacetyl)oxy)-12α-hydroxy-5β-cholan-24-oate (5c)

This was prepared from **1** and chloroacetyl chloride in 75% yield. mp 134–135°C; ^{1}H NMR (90 MHz, $CDCl_3$), δ 0.73 (s, 3H), 0.96 (s, 3H), 1.0 (d, 3H, *J* = 6.4 Hz), 1.04–2.0 (m, steroidal CH and CH_2), 2.30 (m, 2H), 3.68 (s, 3H), 4.04 (s, 3H), 4.80 (br m, 1H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 12.8, 17.2, 23.0, 26.3, 26.9, 27.4, 28.7, 31.0, 33.6, 34.1, 34.9, 35.1, 36.0, 41.2, 46.4, 47.0, 48.1, 51.4, 72.7, 76.0, 76.5, 78.8, 166.7, 174.5; $[\alpha]_D^{25}$: +51° (*c* 0.848, $CHCl_3$); Anal. Calc. for $C_{27}H_{43}ClO_5$ C: 67.13, H: 8.97 Found: C: 66.66, H: 9.06.

Methyl 3α-(1-((1-Aza-4,7,10,13,16-pentaoxa)cyclooctadecylacetyl)oxy)-12α-((2-naphthoyl)oxy)-5α-cholan-24-oate (7a)

To a suspension of **5a** (0.146 g, 0.23 mmol) in CH_3CN (2 mL), Na_2CO_3 (0.03 g, 0.28 mmol) and **6** (0.06 g, 0.23 mmol) were added and the mixture was refluxed under N_2 for 24 h. The crude product was filtered and the residue was washed with EtOAc. The combined organic layer was washed with 7% $NaHCO_3$ solution, water, brine and finally dried over anhyd $MgSO_4$ and filtered. The solvent was removed in vacuo to yield the crude product. Chromatography on silica using 2–5% MeOH/CH_2Cl_2 gave the pure material in 65% (0.128 g) yield. Mp 48–50°C; ^{1}H NMR (270 MHz, $CDCl_3$,) δ 0.84 (br s, 6H), 0.95 (s, 3H), 1.03–2.38 (m, steroidal CH and CH_2), 2.60 (m, 4H), 3.27–3.70 (m, 25H), 4.65 (br m, 1H), 5.41 (s, 1H), 7.60 (m, 2H), 7.90–8.20 (m, 4H), 8.62

(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 17.4, 23.1, 23.6, 25.8, 26.1, 26.6, 26.9, 27.4, 30.8, 30.9, 32.3, 34.1, 34.7, 35.8, 41.9, 45.6, 50.0, 51.3, 54.0, 67.6, 68.5, 69.7, 70.4, 70.5, 74.7, 125.1, 126.8, 127.8, 128.0, 128.3, 129.3, 130.8, 132.5, 135.5, 166.0, 174.4; $[\alpha]_D^{25}$: +25° (*c* 2.0, $CHCl_3$); MS (886 (M^+ + Na, 78), 864 (M^+, 20), 344 (95), 95 (85), 55 (100).

Methyl 3α-(1-((1-Aza-4,7,10,13,16-pentaoxa)cyclooctadecylacetyl)oxy)-12α-((1-pyrenoyl)oxy)-5α-cholan-24-oate (7b)

To a suspension of **5b** (0.11 g, 0.145 mmol) in CH_3CN (2 mL), Na_2CO_3 (0.05 g, 0.47 mmol) and **6** (0.0488 g, 0.185 mmol) were added and the mixture was refluxed under N_2 for 24 h. The crude reaction mixture was filtered, the residue washed with EtOAc and the combined organic layer was washed with 7% $NaHCO_3$ solution, water, brine and finally dried over anhyd $MgSO_4$ and filtered. Volatiles were removed in vacuo to yield the crude product. Chromatography on silica with 2–5% MeOH/CH_2Cl_2 gave the pure material in 53% (0.0725 g) yield. Mp 60–62°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.94 (d, 3H, J = 6.4Hz), 0.97 (s, 3H), 1.01–2.27 (m, steroidal CH and CH_2), 2.30–2.45 (m, 4H), 3.05–3.70 (m, 25H), 4.60–4.70 (br m, 1H), 5.56 (s, 1H), 8.08–8.30 (m, 7H), 8.68 (d, 1H, J = 8.7 Hz), 9.30 (d, 1H, J = 9.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 17.7, 22.9, 23.6, 25.7, 26.2, 26.3, 26.8, 27.4, 30.8, 31.0, 32.0, 34.1, 34.8, 34.9, 35.0, 35.8, 41.8, 45.6, 48.0, 50.4, 51.4, 54.7, 55.0, 67.2, 69.2, 69.3, 69.4, 69.8, 70.2, 70.4, 70.5, 75.0, 77.4, 124.3, 124.4, 124.6, 124.9, 126.2, 126.4, 126.5, 126.6, 127.3, 128.2, 129.5, 129.8, 130.4, 131.0, 131.1, 134.3, 167.4, 172.1, 175.0; $[\alpha]_D^{25}$: +51° (*c* 5.7, $CHCl_3$); HRMS Calc. for $C_{56}H_{75}NO_{11}$: 938.5418 Found: 938.5424.

Methyl 3α-(1-((1-Aza-4,7,10,13,16-pentaoxa)cyclooctadecylacetyl)oxy)-12α-hydroxy-5β-cholan-24-oate (7c)

Sodium carbonate (0.13 g, 1.2 mmol) was taken in MeCN (3 mL) and **6** (0.22 g, 0.84 mmol) was added. After stirring for 1 h under N_2, **5c** (0.3 g, 0.62 mmol) was added and the mixture was heated to 80°C. After 24 h the reaction mixture was filtered and the residue was washed with EtOAc. The combined organic layer was washed with 7% $NaHCO_3$ solution, water, brine and finally dried over anhydrous Na_2SO_4 and filtered. The solvent was removed in vacuo to yield the crude product, which was purified by column chromatography on silica gel using 2–3% MeOH/CH_2Cl_2 as eluent. The title compound was obtained in 75% (0.33 g) yield as a viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.68 (s, 3H), 0.92 (s, 3H), 0.97 (d, 3H, J = 6.3 Hz), 1.0–2.0 (m, steroidal CH and CH_2), 2.17–2.44 (m, 2H), 2.88 (m, 4H), 3.30–3.44 (br s, 2H), 3.50–3.80 (m, 23H), 3.95 (s, 1H), 4.85 (br m, 1H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 12.7, 17.3, 23.0, 23.6, 26.0, 26.4, 27.0, 27.4, 28.7, 29.6, 30.9, 31.0, 32.1, 33.6, 34.1, 34.8, 35.0, 35.6, 36.0, 41.9, 46.5, 47.2, 48.2, 54.4, 55.7, 68.1, 69.7, 70.6, 73.0, 75.1, 171.9, 174.6; $[\alpha]_D^{24}$: +34° (*c* 7.68, $CHCl_3$); MS 711 ($M + H^+$, 1.2), 678 (4.4), 452 (10), 322 (15), 277 (100), 246 (24), 100 (31).

3α,7α,12α-Triformyloxy-5β-cholan-24-oic acid (9)

This was made using a literature procedure in 95% yield [24]. mp: 206°C (lit. 208°C) IR (Nujol): 1710 (s), 1460 (s), 1370 (m), 1180(m) cm^{-1}. ^{1}H-NMR, (90 MHz, $CDCl_3$), δ: 0.77 (s, 3H), 0.82 (d, 6.0 Hz, 3H), 0.96 (s, 3H), 1.0–2.0 (m, steroidal CH and CH_2), 4.68 (s, 1H), 5.04 (s, 1H), 5.25 (s, 1H), 8.00 (s, 1H), 8.08 (s, 1H), 8.17 (s, 1H). $[\alpha]_D^{24}$ +45.7°, (*c* 3.152, $CHCl_3$)

3α,7α,12α-Triformyloxy-5β-23-iodo-24-norcholane (10)

A solution of **9** (5.0 g, 10.2 mmol) in carbon tetrachloride (50 mL) was taken in a 250 mL three necked rb flask fitted with a reflux condenser, an argon bladder and a pressure

equalizing addition funnel. Lead tetraacetate (9.0 g, 20.29 mmol) was added under argon and the mixture was allowed to boil for 5 min. The flask was irradiated with a 200 Watt tungsten lamp while I_2 (3.8g, 14.96 mmol in CCl_4) was added dropwise, while stirring the reaction mixture vigorously. When the colour of I_2 persisted (3–4 h) the addition of I_2 was stopped and the mixture was allowed to reflux for 1 h. After cooling, the mixture was filtered to separate lead oxide. The residue washed with CCl_4 (2 × 10 mL). The organic layer was washed with 5% aq. $Na_2S_2O_3$, water and brine. After removal of volatiles the solid was chromatographed on a column of silica gel with 10% ethyl acetate/hexanes. The pure product was obtained in 85% yield (5 g). Mp: 154°C. IR (Neat): 2800–3000 (s), 1730 (s), 1370 (m), 1230 (s), 1020 (m), 750 (m)cm^{-1}. ^{1}HNMR (90 MHz, $CDCl_3$), δ: 0.75–0.95 (m, 6H), 0.95 (s, 3H), 1.0–2.0 (m, steroidal CH and CH_2), 3.20 (m, 2H), 4.70 (m, 1H), 5.05 (m, 1H), 5.27 (m, 1H), 8.05 (s, 1H), 8.15 (s, 1H), 8.20 (s, 1H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 11.94, 16.75, 22.22, 22.48, 25.34, 26.38, 27.03, 28.33, 31.06, 34.05, 36.26, 37.43, 39.64, 40.56, 42.77, 44.85, 46.80, 70.34, 73.46, 74.89, 160.21. $[\alpha]_D^{24}$ +63.5°, (*c* 10.8, $CHCl_3$).

3α,7α,12α-Trihydroxy-5β-24-nor-cholane (11)

Compund **10** (3.0 g, 5.2 mmol) was dissolved in THF (20 mL) and LAH (0.7 g, 18.4 mmol) was added and stirred at 50°C for 6 h. The reaction mixture was cooled to room temperature and quenched with 20% aq. sodium potassium tartarate (40 mL), extracted with ethyl acetate (3 × 25 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and volatiles were removed in vacuo. The solid residue was chromatographed on a silica gel column with 50% ethyl acetate/hexanes. The pure product was obtained in 85% yield (1.51 g). mp: 185°C. IR (Neat): 3000–3600 (br), 2600–3000 (s), 1460 (m), 1370 (m), 1080 (m), 750 (s) cm^{-1}. ^{1}HNMR (270 MHz, $CDCl_3$), δ: 0.69 (s, 3H), 0.85 (t, 7.3 Hz, 3H), 0.97 (d, 6.4 Hz, 3H), 1.0–2.0 (m, steroidal CH and CH_2), 3.48 (m, 1H), 3.88 (br s, 1H), 4.01 (br s, 1H). ^{13}CNMR (22.5 MHz, $CDCl_3$) δ 10.69, 12.53, 17.18, 22.60, 23.36, 26.39, 27.58, 28.34, 30.29, 34.85, 35.50, 37.12, 39.61, 41.67, 46.44, 47.09, 68.54, 72.01, 73.31.

24-Nor-chola-21-crown-6 (12)

A suspension of NaH (50%, 0.32 g, 6.96 mmol) in dry THF (95 mL) was taken in a rb fitted a pressure equilizing addition funnel and reflux condenser under argon. The addition funnel was charged with **11** (0.5 g, 1.37 mmol) and pentaethyleneglycol ditosylate (PEGDTs) (1.0 g, 1.88 mmol) dissolved in dry THF (45 mL), and was added at a rate of approximately 1 mL/h to the refluxing NaH/THF mixture. The reaction was continued for 12 h, cooled to rt and volatiles were removed in vacuo. The residue suspended in $CHCl_3$ (50 mL) acidified with acetic acid (3 mL), washed with water and dried over anhyd. $MgSO_4$. After the removal of volatiles the oily residue was chromatographed on silica gel (100–200 mesh) using 50% EtOAc/hexanes. The pure product was obtained in 30% yield. IR (Neat): 3000–3600 (br), 2800–3000 (s), 1450 (m), 1190 (s) cm^{-1}. ^{1}HNMR (200 MHz $CDCl_3$), δ: 0.67 (s, 3H), 0.96 (s, 3H), 1.00 (d, 6.2 Hz, 3H), 1.0–2.0 (m, steroidal CH and CH_2), 3.0–3.35 (m, 3H), 3.45–3.9 (m, 20H), 3.96 (m, 1H). MS 566 (M^+, 1), 548 (2), 311 (100), 253 (80), 239 (50), 195 (20).

12α-(1-pyrenoyloxy)-24-nor-chola-21-crown-6 (13)

Compound **12** (0.050 g, 0.088 mmol) was taken in a 5 mL rb flask fitted with a reflux condenser. Dry toluene (0.5 mL), CaH_2 (100 mg, 2.38 mmol) and benzyltriethylammonium chloride (10 mg, 0.044 mmol) were added and refluxed for 10 min. To the refluxing mixture 1-pyrenoyl chloride (40 mg, 0.15 mmol) in toluene (1 mL) was added and refluxed for 24 h. The mixture

was filtered through a pad of celite, washed with EtOAc (3×2 mL). The combined organic layer was washed with 7% $NaHCO_3$ solution, water, brine and finally dried over anhyd Na_2SO_4 and filtered. The solvent was removed in vacuo to yield the crude product which was purified on a silica gel column (20 g, 100–200 mesh, 20 cm × 1.0 cm) using 50% of EtOAc/hexanes as the eluent. The pure product was obtained in 43% yield (30 mg). IR (Neat) : 2800–3000 (s), 1700 (s), 1450 (s), 1260 (m), 1100 (m) cm^{-1}. ^{1}HNMR (270 MHz, $CDCl_3$), δ : 0.86 (s, 1H), 0.90–0.96 (m, 6H), 1.0–2.0 (m, steroidal CH and CH_2), 3.10 (m, 1H), 3.2–3.9 (m, 28H), 5.59 (br s, 1H), 8.06 (t, 10 Hz, 1H), 8.10–8.40 (m, 6H), 8.60 (d, 11 Hz, 1H), 9.18 (d, 11 Hz, 1H). HRMS: Calc. for $C_{50}H_{66}O_8$: 794.4757 Found: 794.4764. UV (λ_{max}, logϵ): (10% $CHCl_3/CH_3CN$ v/v) 350 (4.41), 280 (4.42), 243 (4.72).

Acknowledgments

Support of this work by the Department of Science and Technology (Grant # SP/S1/G09/91 and SP/S1/G08/95) is gratefully acknowledged. The Sophisticated Instruments Facility at this campus is thanked for recording high-field NMR spectra. L. J. D. and V. K. P. thank the U. G. C. for financial support.

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