Synthesis of cholic acid-based molecular receptors: head-to-head cholaphanes

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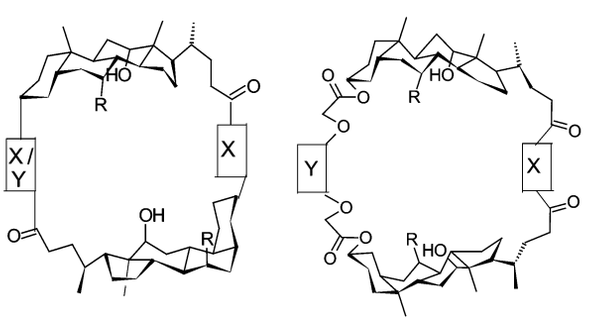
A novel synthetic strategy for the synthesis of head-to-head cholaphanes (**II**) using spacers, ethylenediamine or *m*-xylylenediamine as X and terephthalate as Y, has been reported. The synthesis constitutes the incorporation of different bile acids, *viz.* cholic and deoxycholic acids, thereby manipulating the number of hydroxy groups inside the cavity of cholaphanes. The final cyclization step involving Cs salt methodology leads to the synthesis of cholaphanes **7a**–**c** and **10a**,**b** in high yields.

Introduction

There has been considerable interest in recent years on the synthesis of molecular receptors based on bile acids.[1] The unique features of bile acids such as their chiral and rigid framework, and the different reactivities of their hydroxy groups, have made them attractive molecules for the design of synthetic receptors. Consequently, many cyclic systems consisting of two, three and four steroidal units have been synthesized.[2–11] Some of these cyclic systems, commonly known as cholaphanes, have shown remarkable capability for diastereo- and enantioselective binding of carbohydrate derivatives in organic solvents.[12,13] Most of these systems have involved a head-to-tail arrangement (**I**) of bile acids. The basic approach of their synthetic strategy involved either direct head-to-tail coupling of bile acids using standard methods of macrolactonization or introduction of an amino group at the 3α-position of the steroid followed by amide bond formation between the two ends of the steroids. These strategies have been found to give low yields of the cyclic products.



Type I R = H/ OH **Type II**

Trimeric[14] and dimeric[15] cholaphanes consisting of a head-to-head combination of bile acids (**II**) have also been synthesized using the same cyclization strategy, giving (extremely) low yields of the products, 28 and 11%, respectively. Hence, there was a need for the development of a more efficient method for the synthesis of head-to-head cholaphanes.

Earlier, we reported the synthesis of head-to-head cholaphanes involving Cs salt methodology. In that preliminary report,[16] we described the use of the DCC method for the selective bromoacetylation of the dimeric cholamide at the 3α-positions, which usually gives low yields (35–40%, in 48 h) of the products. Moreover, the difficulty in removing dicyclohexylurea from the products makes this method very unattractive. To overcome this problem, we have modified this step and used bromoacetyl bromide in the presence of anhydrous K_2CO_3, which reacts preferentially at an equatorial 3α-position and gives more than 70% yield (in 10 min) of the desired bis-3α-bromoacetylated cholamides. This modification has made the synthetic strategy much simpler and efficient and led to the synthesis of various head-to-head cholaphanes, which may be used for the study of the supramolecular chemistry of this class of compounds.

Results and discussion

The reaction sequence shown in Scheme 1 has been followed for the synthesis of head-to-head cholaphanes with ethylenediamine and terephthalate as spacers. Treatment of methyl cholate **1a** with a large excess of ethylenediamine at room temperature for 24 h resulted in complete conversion of methyl cholate into the monocholamide **2a**. The ^{1}H NMR spectrum revealed a triplet at δ 2.77 for –CH_2–C**H**$_2$–NH_2 and a multiplet at δ 3.24 for –CH_2–C**H**$_2$–NHCO–, which indicated the formation of amide **2a**. The three steroidal methine protons at the 3-, 7- and 12-position appeared at δ 3.35 (multiplet), 3.76 (broad singlet) and 3.90 (broad singlet), respectively. The characteristic three steroidal methyl protons at the 18-, 19- and 21-position appeared at δ 0.66 (singlet), 0.88 (singlet) and 1.00 (doublet) respectively. The remaining steroidal protons showed a complex pattern of signals between δ 1.05 and 2.50.

Condensation of cholamide **2a** with the succinimido ester of cholic acid, compound **3a**, was carried out in DMF at room temperature. The resulting dicholylethylenediamide **4a**, which was obtained in quantitative yield, showed IR bands at 3400 and 1652 cm^{-1} for OH/NH and carbonyl of amide bonds, respectively. The ^{1}H NMR spectrum revealed a multiplet at δ 3.42 for –NH–C**H**$_2$–C**H**$_2$–NH–. The complete disappearance of the signal at δ 2.77 clearly indicated the formation of the product **4a**. This was supported by the ^{13}C NMR spectrum wherein the C-24 signal appeared at δ_C 175.92. The signal at δ_C 39.27 was attributed to –NH–CH_2–CH_2–NH– methylene carbon atoms. The methine carbons, C-3, C-12 and C-7, appeared at δ_C 72.98, 71.61 and 68.26, respectively. The structure was further confirmed by FAB mass spectroscopy revealing an (M^+ + H) peak at *m*/*z* 841.

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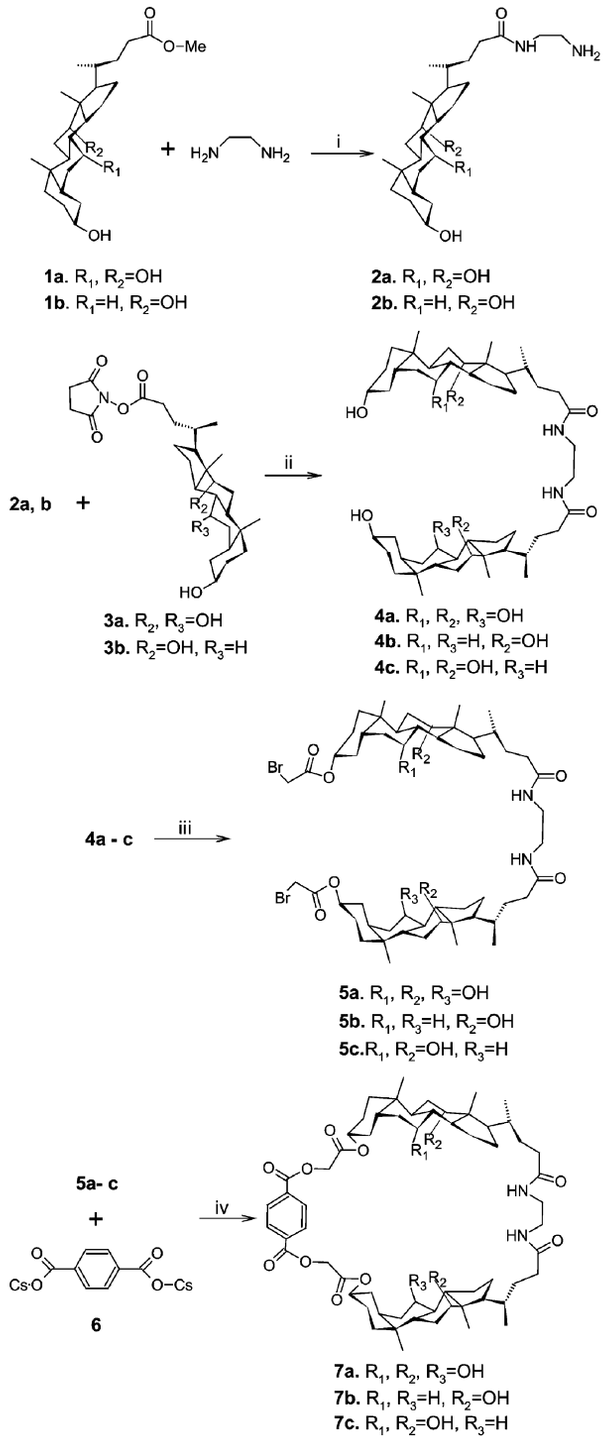


Scheme 1 *Reagents and conditions (and yields)*: i, CH_3OH, rt, 48 h, (98%); ii, DMF, rt, 24 h, **4a** (96%), **4b** (95%), **4c** (96%); iii, $BrCH_2COBr$, anhydrous K_2CO_3, $CHCl_3$, 55–60 °C, 10 min, **5a** (70%), **5b** (75%), **5c** (73%); iv, DMF, 12 h, rt, **7a** (95%), **7b** (85%), **7c** (87%).

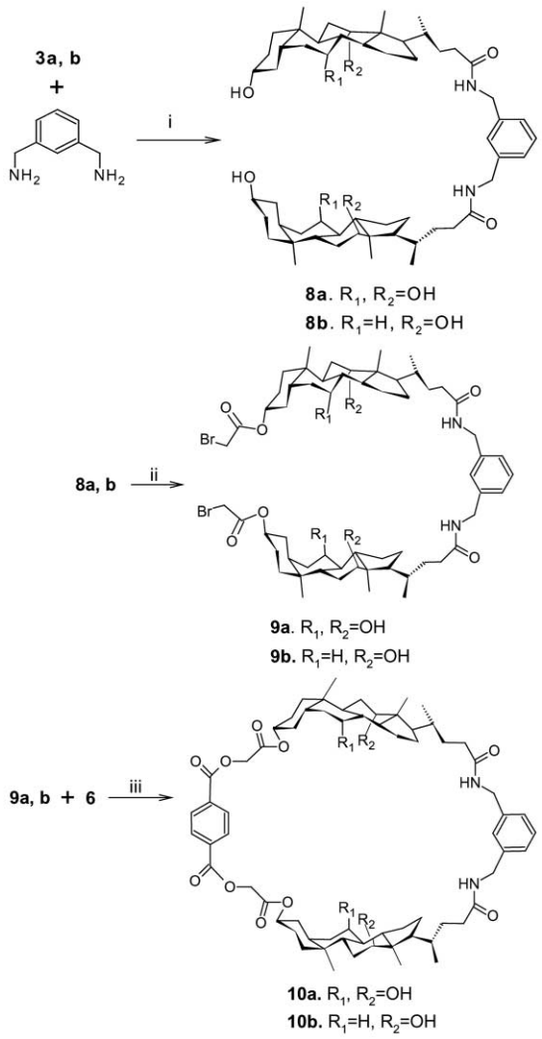
The selective bromoacetylation of the bis-cholamide **4a** at the 3α-position was effected by treatment of **4a** with two equivalents of bromoacetyl bromide in chloroform in the presence of anhydrous K_2CO_3 at 55–60 °C. Since the 3α-OH group, being equatorial, is known to be more reactive than the 12α- and 7α-OH groups, it was possible to obtain 3α-bromoacetyl derivative **5a** preferentially in 70% yield. The compound was easily purified by column chromatography. The IR spectrum of **5a** revealed bands at 3420, 1733 and 1653 cm^{-1} for OH/NH, ester and amide carbonyl bonds, respectively. In the ^1H NMR spectrum, a distinct singlet at δ 3.71 for bromoacetyl protons was observed. In addition, there was a downfield shift for the 3β-proton, which appeared at δ 4.57 as a broad multiplet, while 7β and 12β protons appeared at their original positions at δ 3.79 and 3.92, respectively, thus confirming that the reaction had taken place only at the 3α-position.

These dimeric systems have been cyclized using Kellogg's Cs salt methodology.[17] Numerous examples of its application in the synthesis of various macrocyclic compounds have been documented[18] including the cyclization of very flexible starting materials. In the case of steroidal systems, which are less flexible, better results were expected.

Thus, treatment of bis-bromoacetylcholamide **5a** with an equivalent amount of dicaesium terephthalate **6** in dry DMF resulted in the formation of the cholaphane **7a** in about 95% yield. The formation of the cyclic product was established on the basis of its IR, ^1H NMR and FAB mass spectra. The IR spectrum showed bands at 3408, 1734 and 1652 cm^{-1} for OH/NH, ester and amide carbonyl bonds, respectively. In addition to usual steroidal signals, the ^1H NMR spectrum revealed broad singlets at δ 3.29, 4.74, and 8.09 due to –NH–C**H**$_2$–C**H**$_2$–NH, –CO–CH_2–O and aromatic protons, respectively. The appearance of the signals at δ 4.74 and 8.09 and the complete disappearance of the signal at δ 3.71 for –$COCH_2$Br established the formation of the cyclic compound **7a**, which was further confirmed by its FAB mass spectrum revealing the (M^+ + H) peak at *m*/*z* 1087. The ^{13}C NMR spectrum showed three signals at δ_C 175.75, 167.21 and 165.14 ppm, which were attributed to carbonyl carbons, –CONH–, –**O**C**O**Ar and –**O**C**O**CH_2–, respectively. The four aromatic CH carbons appeared as an overlapped signal at δ_C 129.80 whereas the quaternary carbons (phenyl) appeared at δ_C 133.27, which was confirmed by its disappearance in a DEPT $^{13}C\{^1H\}$ 135-NMR spectrum. It is noteworthy that the methine C-3 carbon of the bis-cholamide undergoes a downfield shift from δ_C 72.98 (in **4a**) to 76.57 in the case of cholaphane **7a**. The methylene carbon atoms –$OCOCH_2$– and –NH–CH_2–CH_2–NH– were found to resonate at δ_C 61.61 and 39.29, respectively.

The deoxycholaphane **7b** was synthesized following a similar reaction scheme as described for the cholaphane **7a** by the reaction of bis-(3α-*O*-bromoacetyldeoxycholamide) **5b** with dicaesium terephthalate **6**. The cholaphane **7c** having two different types of steroidal units, *viz.* cholic and deoxycholic acids, was also synthesized. For this purpose, the cholamide **2a** was condensed with the succinimido ester of deoxycholic acid under conditions similar to those described earlier to give the cholic deoxycholic ethylenediamide **4c**. This was then bromoacetylated at the 3α-position with bromoacetyl bromide and the resulting bis-(3α-bromoacetyl) cholic deoxycholic ethylenediamide **5c** was cyclized with dicaesium terephthalate to give the cholic deoxycholic cycloproduct **7c** in 87% yield. The cholaphanes were characterized on the basis of their elemental analyses and IR, NMR and FAB mass spectra.

In order to investigate the effect of rigidity in the system, a *m*-xylylenediamine spacer was introduced instead of ethylenediamine and the cholaphanes **10a**,**b** were synthesized following a slighty modified synthetic strategy[19] (Scheme 2). For this, two equivalents of activated esters of cholic and deoxycholic acids were directly condensed with one equivalent of *m*-xylylenediamine in DMF at room temperature to give the corresponding dicholic *m*-xylylenediamides **8a**,**b**. The IR spectrum for **8a** showed bands at 3399 and 1653 cm^{-1} for OH/NH and carbonyl of amide bond, respectively. The ^1H NMR spectrum showed a broad singlet at δ 7.21 for aromatic protons and a multiplet at δ 4.37 for HN–C**H**$_2$–C_6H_4. The methine protons at the 7β- and 12β-position were observed as broad singlets at δ 3.80 and 3.91, respectively, whereas the proton at the 3β-position appeared at δ 3.21 as a multiplet. The ^{13}C NMR spectrum showed that, on changing the spacer from ethylenediamine to *m*-xylyenediamine, the carbonyl carbon C-24 shifted upfield from δ_C 175.92 (in **4a**) to 174.71. A minor chemical-shift difference was observed in the case of C-3, C-12 and C-7 carbons



Scheme 2 *Reagents and conditions (and yields)*: i, DMF, rt, 10 h, **8a** (88%), **8b** (87%); ii, $BrCH_2COBr$, anhydrous K_2CO_3, 55–60 °C, 10 min, **9a** (71%), **9b** (76%); iii, DMF, 12 h, rt, **10a** (81%), **10b** (75%).

which appeared at δ_C 72.82, 71.38 and 68.06, respectively. The FAB mass spectrum showed peaks at 918 (M^+ + H) and 940 (M^+ + Na).

Selective bromoacetylation at the 3α-position was achieved similarly with bromoacetyl bromide in chloroform. Cyclization of the bis-3α-*O*-bromoacetylated cholamides **9a**,**b** with dicaesium terephthalate under conditions similar to those described earlier afforded the cholaphanes **10a**,**b**. The appearance of the expected bands in the IR spectra and the characteristic signals in the ^{1}H NMR spectra, particularly broad singlets in the region δ 4.82–4.83 for $–COCH_2O–$ and 8.14–8.15 for terephthalic protons, established the formation of the cholaphanes **10a**,**b**. The ^{13}C NMR spectrum of **10a** revealed an overlapped signal for quaternary carbons of *m*-xylylenediamine at δ_C 138.70. The other phenyl carbons were found to resonate at δ_C 128.55 and 126.38, respectively. The methylene carbons $–OCOCH_2–$ and $–CH_2NH–$, appeared at δ_C 61.46 and 43.02, respectively. The rest of the carbon signals appeared at almost the same chemical shifts as those of cholaphane **7a**. The FAB mass spectra showed the (M^+ + H) peaks at 1165 and 1131 for **10a** and **10b**, respectively. All the cholaphanes have been found to be fairly soluble in chloroform.

Conclusion

The preferential bromoacetylation at the 3α-position of bile acids with bromoacetyl bromide in the presence of anhydrous K_2CO_3 and highly efficient macrocyclization by the Cs salt method have led to the synthesis of various cholaphanes in high yields. This method can incorporate different types of bile acids, thereby increasing their potential for molecular recognition and supramolecular chemistry.

Experimental

General

Melting points are uncorrected. IR spectra were recorded on a Nicolet Protégé 460 Spectrometer, using potassium bromide pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin DPX 300. Tetramethylsilane was used as internal reference and the chemical shifts are expressed as displacement (δ) in ppm downfield from tetramethylsilane. Mass spectra were recorded on a JEOL SX 102/DA-6000 Mass Spectrometer using argon/xenon as the FAB gas and *m*-nitrobenzyl alcohol as the matrix. The accelerating voltage was 10 kV and the spectra were recorded at room temperature. Elemental analyses were taken on a Perkin-Elmer 240C Elemental Analyzer. Column chromatography was carried out using Qualigens silica gel 60–120 mesh. The solid compounds were dried under vacuum in the presence of P_2O_5.

***N*-Cholylethylenedimine 2a.** Methyl cholate **1a** (10 g, 23.66 mmol) was treated with an excess of ethylenediamine (15 ml) in methanol (50 ml). The reaction mixture was stirred at room temperature for 48 h, then poured over ice-cold water (400 ml); the solid obtained was filtered off, dried, and purified by recrystallization from chloroform–methanol to give the pure *product* **2a** (9.9 g, 98%); mp 175–177 °C; IR ν_{max} (KBr)/cm^{-1} 3390, 1663, 1622, 1571; δ_H (300 MHz; $CDCl_3$–CD_3OD) 3.90 (br s, 1H, 12β-H), 3.76 (br s, 1H, 7β-H), 3.35 (m, 1H, 3β-H), 3.24 (m, 2H, $NHCH_2$), 2.77 (t, J = 6 Hz, 2H, CH_2NH_2), 250–1.05 (24H, steroidal H), 1.00 (d, J = 6 Hz, 3H, 21-Me), 0.88 (s, 3H, 19-Me) 0.66 (s, 3H, 18-Me).

***N*-Deoxycholylethylenediamine 2b.** Methyl deoxycholate **1b** (4.06 g, 10 mmol) was treated with ethylenediamine (8 ml) in methanol (30 ml) following the same procedure described for the preparation of *N*-cholylethylenediamine **2a** to give title *amide* **2b** (3.9 g, 98%); mp 115–117 °C; IR ν_{max} (KBr)/cm^{-1} 3368, 1636, 1558; δ_H (300 MHz; $CDCl_3$–CD_3OD) 3.95 (br s, 1H, 12β-H), 3.56 (m, 1H, 3β-H), 3.27 (m, 2H, $NHCH_2$), 2.80 (m, 2H, CH_2NH_2), 2.10–1.20 (25H, steroidal H), 0.99 (br s, 3H, 21-Me), 0.90 (s, 3H, 19-Me), 0.67 (s, 3H, 18-Me).

Succinimido cholate 3a. Cholic acid (8.50 g, 20.8 mmol) was dissolved in dry DMF (30 ml). To this was added *N*-hydroxysuccinimide (2.87 g, 24.9 mmol). The mixture was stirred for 10 min at room temperature and then DCC (6 g, 29.12 mmol) was added. After 15 h, the mixture was filtered to remove the precipitated solid, dicyclohexylurea. The filtrate was mixed with ice–water (500 ml) and the white solid obtained was filtered off, washed with ice–water, and dried in vacuum. The dried white solid was purified by column chromatography [5% (v/v) MeOH in $CHCl_3$] (R_f 0.55) to give *product* **3a** as a white crystalline solid (9.8 g, 90%); mp 110–112 °C; IR ν_{max} (KBr)/cm^{-1} 3314, 1814, 1784, 1736; δ_H (300 MHz; $CDCl_3$) 3.98 (br s, 1H, 12β-H), 3.85 (br s, 1H 7β-H), 3.45 (m, 1H, 3β-H), 2.84 (s, 4H, $–CH_2–CH_2–$), 2.50–1.10 (24H, steroidal H), 1.00 (d, J = 6 Hz, 3H, 21-Me), 0.89 (s, 3H, 19-Me), 0.70 (s, 3H, 18-Me).

Succinimido deoxycholate 3b. Deoxycholic acid (6 g, 15.31 mmol) and *N*-hydroxysuccinimide (2.07 g, 18 mmol) were dissolved in dry DMF (40 ml). To this solution was added DCC (3.75 g, 18.17 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was worked up as described earlier. The product obtained was purified by column chromatography [5% (v/v) MeOH in $CHCl_3$] (R_f 0.64) to give a

colourless crystalline *solid* **3b** (7.3 g, 94%); mp 145–146 °C; IR ν_{max} (KBr)/cm^{-1} 3314, 1814, 1783, 1735; δ_H (300 MHz; $CDCl_3$) 3.98 (br s, 1H, 12β-H), 3.61 (m, 1H, 3β-H), 2.82 (s, 4H, –CH_2–CH_2–), 2.50–1.03 (25H, steroidal H), 1.00 (d, J = 6 Hz, 3H, 21-Me), 0.91 (s, 3H, 19-Me), 0.69 (s, 3H, 18-Me).

***N*,*N*′-Dicholylethylenediamine 4a.** *N*-Cholylethylenediamine **2a** (901 mg, 2 mmol) and succinimido cholate **3a** (1.01 g, 2 mmol) were dissolved in dry DMF (15 ml) and the solution was stirred at room temperature for 24 h. The reaction mixture was then poured over ice–water (500 ml). Brine was added and the white solid precipitated was filtered off, washed with cold water, and dried under vacuum. The compound was purified by column chromatography [10% (v/v) MeOH in $CHCl_3$] (R_f 0.35) to give *product* **4a** as a white crystalline solid (1.62 g, 96%); mp 160–162 °C (Found: C, 69.81; H, 10.01; N, 3.06%. Calc. for $C_{50}H_{84}N_2O_8 \cdot H_2O$: C, 69.89; H, 10.08; N, 3.26%); IR ν_{max} (KBr)/cm^{-1} 3400, 1652; δ_H (300 MHz; $CDCl_3$–CD_3OD) 3.96 (br s, 2H, 2 × 12β-H), 3.84 (br s, 2H, 2 × 7β-H), 3.24 (m, 2H, 2 × 3β-H), 3.42 (m, 4H, 2 × CH_2NHCO), 2.19–1.20 (48H, steroidal H), 0.99 (br s, 6H, 2 × 21-Me), 0.89 (s, 6H, 2 × 19-Me), 0.67 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 175.92 (C, C-24), 72.98 (CH, C-3), 71.61 (CH, C-12), 68.26 (CH, C-7), 39.27 (CH_2, –NHCH_2CH_2NH–), 35.25 (CH_2, C-23), 31.72 (CH_2, C-22); *m*/*z* (FAB) 863 (M^+ + Na, 40%), 841 (M^+ + H, 60), 805 (5), 787 (5), 733 (10), 661 (17), 527 (7), 509 (6), 479 (7), 451 (15), 415 (12), 397 (36), 371 (22), 355 (45), 337 (50), 289 (18), 271 (62), 253 (72), 227 (30), 199 (35), 171 (34), 119 (67), 107 (100).

***N*,*N*′-Bisdeoxycholylethylenediamine 4b.** Compound **4b** was prepared from succinimido deoxycholate **3b** (979 mg, 2 mmol) and *N*-deoxycholylethylenediamine **2b** (869 mg, 2 mmol) following the same procedure as for the preparation of bis-cholamide **4a**. Purification of the crude product was achieved by column chromatography [8% (v/v) MeOH in $CHCl_3$] (R_f 0.40) to give *product* **4b** (1.5 g, 95%); mp 152–153 °C (Found: C, 71.83; H, 10.34; N, 3.70%. Calc. for $C_{50}H_{84}N_2O_6 \cdot 1.5H_2O$: C, 71.81; H, 10.48; N, 3.34%); IR ν_{max} (KBr)/cm^{-1} 3334, 1659; δ_H (300 MHz; $CDCl_3$–CD_3OD) 3.95 (br s, 2H, 2 × 12β-H), 3.55 (m, 2H, 2 × 3β-H), 3.37 (m, 4H, 2 × CH_2NHCO), 2.40–1.10 (50H, steroidal H), 0.98 (d, J = 6 Hz, 6H, 2 × 21-Me), 0.90 (s, 6H, 2 × 19-Me), 0.67 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 175.92 (C, C-24), 72.92 (CH, C-3), 71.30 (CH, C-12), 39.27 (CH_2, –NH–CH_2–CH_2NH–), 35.25 (CH_2, C-23), 31.62 (CH_2, C-22); *m*/*z* (FAB) 832 (M^+ + Na, 20%), 810 (M^+ + H, 100), 792 (10), 773 (5), 489 (5), 460 (9), 435 (7), 417 (6), 399 (10), 382 (8), 357 (7), 289 (18), 255 (7), 176 (5), 136 (64), 107 (17).

***N*-Cholyl-*N*′-deoxycholylethylenediamine 4c.** *N*-Cholylethylenediamine **2a** (450 mg, 1 mmol) and succinimido deoxycholate **3b** (489 mg, 1 mmol) were dissolved in DMF (10 ml) and the reaction mixture was stirred at room temperature for 24 h. The compound obtained after work-up was purified by chromatography [10% (v/v) MeOH in $CHCl_3$] (R_f 0.41) to give *product* **4c** (795 mg, 96%) as a white crystalline solid; mp 151–153 °C (Found: C, 72.17; H, 9.96; N, 3.77%. Calc. for $C_{50}H_{84}N_2O_7 \cdot 0.5H_2O$: C, 71.98; H, 10.26; N, 3.35%); IR ν_{max} (KBr)/cm^{-1} 3391, 1653; δ_H (300 MHz; $CDCl_3$–CD_3OD) 3.96 (br s, 2H, 2 × 12β-H), 3.83 (br s, 1H, 7β-H), 3.57 (m, 2H, 2 × 3β-H), 3.38 (m, 4H, 2 × CH_2NHCO), 2.50–1.01 (49H, steroidal H), 0.99 (br s, 2H, 2 × 21-Me), 0.90 (s, 6 H, 2 × 19-Me), 0.67 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 175.92 (C, C-24), 175.75 (C, C-24′), 72.95 (CH, C-3, -3′), 71.54 (CH, C-12), 71.42 (CH, C-12′), 68.24 (CH, C-7), 39.27 (CH_2, CH_2NHCO), 35.26 (CH_2, C-23, -23′), 31.63 (CH_2, C-22, -22′), 27.05 (CH_2, C-7′); *m*/*z* (FAB) 825 (M^+ + H, 34%), 807 (4), 661 (33), 460 (15), 391 (30), 371 (25), 289 (32), 273 (4), 207 (8), 165 (5), 107 (16).

***N*,*N*′-Bis(3α-*O*-bromoacetylcholyl)ethylenediamine 5a.** Bischolamide **4a** (420 mg, 0.5 mmol) was stirred at 55–60 °C in dry $CHCl_3$ (20 ml) until it completely dissolved. Anhydrous K_2CO_3 (139 mg, 1 mmol) was then added. To this was added 10 ml of a solution of bromoacetyl bromide in $CHCl_3$ 1% (v/v) (202 mg, 1 mmol) dropwise. After 10 min, the heating was stopped, ice-cold water (20 ml) was added, and the organic layer was separated. After drying (anhydrous Na_2SO_4) and evaporation of the solvent, the brown sticky mass was chromatographed on silica gel [0–5% (v/v) MeOH in $CHCl_3$] [R_f 0.68 in 10% (v/v) MeOH in $CHCl_3$] to give bis-3α-bromoacetyl *derivative* **5a** as a semi-solid (379 mg, 70%); IR ν_{max} (KBr)/cm^{-1} 3420, 1733, 1653; δ_H (300 MHz; $CDCl_3$) 4.57 (m, 2H, 2 × 3β-H), 3.92 (br s, 2H, 2 × 12β-H), 3.79 (br s, 2H, 2 × 7β-H), 3.71 (s, 4H, 2 × CH_2Br), 3.29 (m, 4H, 2 × CH_2NH), 2.30–1.00 (48H, steroidal H), 0.92 (br s, 6H, 2 × 21-Me), 0.84 (s, 6H, 2 × 19-Me), 0.62 (s, 6H, 2 × 18-Me).

***N*,*N*′-Bis(3α-*O*-bromoacetyldeoxycholyl)ethylenediamine 5b.** Bis-bromoacetyl-deoxycholamide derivative **5b** was prepared by reaction of bisdeoxycholamide **4b** (650 mg, 0.80 mmol) with bromoacetyl bromide (323 mg, 1.6 mmol) in the presence of anhydrous K_2CO_3 (221 mg, 1.6 mmol) in dry $CHCl_3$ (10 ml). The product was isolated and purified by column chromatography [0–3% (v/v) MeOH in $CHCl_3$] [R_f 0.55 in 8% (v/v) MeOH in $CHCl_3$] to yield *compound* **5b** as a sticky solid (633 mg, 75%); IR ν_{max} (KBr)/cm^{-1} 3400, 1730, 1652; δ_H (300 MHz; $CDCl_3$) 4.71 (m, 2H, 2 × 3β-H), 3.93 (br s, 2H, 2 × 12β-H), 3.73 (s, 4H, 2 × CH_2Br), 3.31 (m, 4H, 2 × CH_2NH), 2.40–1.00 (50H, steroidal, H), 0.93 (d, J = 6 Hz, 6H, 21-Me), 0.86 (s, 6H, 19-Me), 0.62 (s, 6H, 18-Me).

3α,3α′*O*-Bis(bromoacetyl)cholyl(deoxycholyl)ethylenediamine 5c. The procedure followed was the same as that described for other bromoacetyl derivatives by taking cholyldeoxycholamide **4c** (550 mg, 0.66 mmol), bromoacetyl bromide (267 mg, 1.32 mmol) and anhydrous K_2CO_3 (183 mg, 1.32 mmol) in dry $CHCl_3$ (10 ml), which yielded *compound* **5c** as a sticky solid (519 mg, 73%); IR ν_{max} (KBr)/cm^{-1} 3425, 1735, 1655; δ_H (300 MHz; $CDCl_3$) 4.77 and 4.68 (m, 2H, 3β-H and 3′β-H), 3.98 (br s, 2H, 2 × 12β-H); 3.85 (br s, 1H, 7β-H), 3.78 (s, 4H, 2 × CH_2Br), 3.36 (m, 4H, 2 × CH_2NH), 2.40–1.20 (49H, steroidal H), 1.00 (br s, 6H, 21-Me), 0.91 (s, 6H, 19-Me), 0.68 (s, 6H, 18-Me).

Dicaesium terephthalate 6. Terephthalic acid (830 mg, 5 mmol) was dissolved in dry DMF (8 ml) and to this was added an equivalent amount (1.62 g, 5 mmol) of caesium carbonate. After stirring for 3 h (complete neutralization), the solid obtained was filtered off, washed with acetone, and dried under vacuum (1.85 g, 95%); IR ν_{max} (KBr)/cm^{-1} 1580; δ_H (DMSO-d_6) 7.85 (br s, Ar–H).

Bis(3α-*O*-hydroxyacetylcholyl)ethylenediamine cyclic terephthalate (cholaphane) 7a. Bis-bromoacetylcholamide **5a** (217 mg, 0.20 mmol) was dissolved in dry DMF (6 ml) and to this was added an equivalent amount of dicaesium terephthalate **6** (89 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for 12 h, then was filtered and the filtrate was poured into ice-cold brine (20 ml). The solid obtained was filtered off and dried under vacuum. The compound was purified by column chromatography [0–5% (v/v) MeOH in $CHCl_3$] [R_f 0.53 in 10% (v/v) MeOH in $CHCl_3$] to give the *cholaphane* **7a** as a white crystalline solid (205 mg, 95%); mp 185–188 °C (Found: C, 64.96; H, 8.43; N, 2.41. Calc. for $C_{62}H_{90}N_2O_{14} \cdot 3H_2O$: C, 65.24; H, 8.47; N, 2.45%); IR ν_{max} (KBr)/cm^{-1} 3408, 1734, 1652; δ_H (300 MHz; $CDCl_3$–CD_3OD) 8.09 (br s, 4H, Ar-H), 4.74 (br s, 4H, 2 × $COCH_2O$), 4.56 (m, 2H, 2 × 3β-H), 3.93 (br s, 2H, 2 × 12β-H), 3.73 (br s, 2H, 2 × 7β-H), 3.29 (br s, 4H, 2 × CH_2-NHCO), 2.50–1.00 (48H, steroidal H), 0.92 (br s, 6H, 2 × 21-Me), 0.83 (s, 6H, 2 × 19-Me), 0.60 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 175.75 (C, C-24), 167.21 (C, OCOAr), 165.14 (C, $OCOCH_2$), 133.27 (C, Ar–C), 129.80 (CH, Ar–CH),

76.57 (CH, C-3), 72.77 (CH, C-12), 67.90 (CH, C-7), 61.61 (CH_2, $OCOCH_2$), 39.29 (CH_2, CH_2NHCO), 34.66 (CH_2, C-23), 32.85 (CH_2, C-22); *m*/*z* (FAB) 1109 (M^+ + Na, 4%), 1087 (M^+ + H, 12), 1069 (3), 966 (3), 615 (8), 436 (13), 397 (9), 380 (12), 355 (5), 337 (12), 279 (12), 253 (19), 225 (22), 119 (53), 105 (70).

Bis(3α-*O*-hydroxyacetyldeoxycholyl)ethylenediamine cyclic terephthalate (deoxycholaphane) 7b. Bis-bromoacetyl-deoxycholamide **5b** (244 mg, 0.23 mmol) was dissolved in dry DMF (6 ml) and treated with dicaesium terephthalate (102 mg, 0.23 mmol). The work-up procedure followed was as described for the cholaphane **7a**. The residue obtained on concentration *in vacuo* was purified by column chromatography [0–4% (v/v) MeOH in $CHCl_3$] [R_f 0.59 in 10% (v/v) MeOH in $CHCl_3$] to give the *deoxycholaphane* **7b** (207 mg, 85%) as a white crystalline solid; mp 196–199 °C (Found: C, 68.86; H, 8.73; N, 2.33%. Calc. for $C_{62}H_{90}N_2O_{12}\cdot H_2O$: C, 69.31; H, 8.63; N, 2.60%); IR ν_{max} (KBr)/cm^{-1} 3410, 1735, 1648; δ_H (300 MHz; $CDCl_3$–CD_3OD) 8.17 (br s, 4H, Ar–H), 4.83 (br s, 6H, 2 × $COCH_2O$ and 2 × 3β-H), 3.98 (br s, 2H, 2 × 12β-H), 3.34 (br s, 4H, 2 × C*H*$_2$NHCO), 2.40–1.03 (50H, steroidal H), 0.98 (br s, 6H, 2 × 21-Me), 0.91 (s, 6H, 2 × 19-Me), 0.67 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 175.35 (C, C-24), 167.12 (C, OCOAr), 165.19 (C, $OCOCH_2$), 133.37 (C, Ar–C), 129.90 (CH, Ar–CH), 76.05 (CH, C-3), 72.84 (CH, C-12), 61.66 (CH_2, $OCOCH_2$), 39.54 (CH_2, CH_2NHCO), 31.96 (CH_2, C-23), 31.57 (CH_2, C-22); *m*/*z* (FAB) 1078 (M^+ + Na, 33%), 1056 (M^+ + H, 52), 1036 (17), 993 (10), 958 (11), 935 (100), 919 (17), 891 (9), 857 (11), 813 (16), 796 (36), 778 (12), 738 (28), 715 (10), 662 (70), 632 (14), 604 (40), 600 (15), 578 (76), 552 (38), 521 (12), 493 (18), 460 (18), 439 (12), 413 (32), 382 (60), 357 (16), 339 (40), 289 (80), 279 (22), 255 (40), 207 (50), 119 (64), 107 (95).

3α-*O*-Hydroxyacetylcholyl-3α′-*O*-hydroxyacetyldeoxycholylethylenediamine cyclic terephthalate (cholaphane) 7c. Bis-bromoacetylcholic-deoxycholamide **5c** (190 mg, 0.17 mmol) was dissolved in dry DMF (5 ml) and treated with dicaesium terephthalate (76 mg, 0.17 mmol) at room temperature for 12 h. The usual work-up gave *compound* **7c**, which was purified by column chromatography [0–5% (v/v) MeOH in $CHCl_3$] [R_f 0.57 in 10% (v/v) MeOH in $CHCl_3$] (165 mg, 87%); mp 215 °C (decomp.) (Found: C, 64.99; H, 8.59; N, 2.94%. Calc. for $C_{62}H_{90}N_2O_{13}\cdot 4H_2O$: C, 65.12; H, 8.63; N, 2.45%); IR ν_{max} (KBr)/cm^{-1} 3410, 1735, 1650; δ_H (300 MHz; $CDCl_3$–CD_3OD) 8.17 (br s, 4H, Ar–H), 4.83 (br s, 4H, 2 × $COCH_2O$), 4.60 (m, 2H, 2 × 3β-H), 3.97 (br s, 2H, 2 × 12β-H), 3.83 (br s, 1H, 7β-H), 3.36 (br s, 4H, 2 × C*H*$_2$NHCO), 2.25–1.02 (49H, steroidal H), 0.99 (br s, 6H, 2 × 21-Me), 0.91 (br s, 6H, 2 × 19-Me), 0.67 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 175.39 (C, C-24), 167.12 (C, OCOAr), 165.19 (C, $OCOCH_2$), 133.36 (C, Ar–C), 129.89 (CH, Ar–CH), 76.06 (CH, C-3), 72.84 (CH, C-12), 67.99 (CH, C-7), 61.69 (CH_2, $OCOCH_2$), 39.60 (CH_2, CH_2NHCO), 31.93 (CH_2, C-23), 26.86 (CH, C-7′); *m*/*z* (FAB) 1071 (M^+ + H, 20%), 1018 (3), 951 (4), 811 (3), 735 (6), 460 (7), 399 (10), 382 (16), 355 (6), 337 (14), 289 (63), 273 (22), 120 (50), 107 (95).

***N*,*N*′-Dicholyl-*m*-xylylenediamine 8a.** Succinimido cholate **3a** (2.22 g, 4.3 mmol) was dissolved in DMF (10 ml) and to this was added *m*-xylylenediamine (299 mg, 2.15 mmol). The reaction mixture was stirred under nitrogen atmosphere at room temperature for 10 h. The turbid mixture was then filtered. The clear filtrate was mixed with ice-cold brine (400 ml). The white solid that separated was filtered off, washed with cold water, and dried under vacuum. The dried solid was purified by column chromatography [10% (v/v) MeOH in $CHCl_3$] (R_f 0.40) to yield the pure *product* **8a** (1.78 g, 88%) as a white crystalline solid; mp 153–155 °C (Found: C, 71.81; H, 9.80; N, 3.07%. Calc. for $C_{56}H_{88}N_2O_8\cdot H_2O$: C, 71.91; H, 9.69; N, 2.99%); ν_{max} (KBr)/cm^{-1} 3399, 1653; δ_H (300 MHz; $CDCl_3$–CD_3OD) 7.21 (br s, 4H, Ar–H), 4.37 (m, 4H, 2 × C*H*$_2$NH), 3.91 (br s, 2H, 2 × 12β-H), 3.80 (br s, 2H, 2 × 7β-H), 3.21 (m, 2H, 2 × 3β-H), 2.25–1.10 (48H, steroidal H), 0.98 (br s, 6H, 2 × 21-Me), 0.86 (s, 6H, 2 × 19-Me), 0.66 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 174.71 (C, C-24), 138.61 (C, Ar–C), 128.51 (CH, Ar–CH), 126.77 (CH, Ar–CH), 72.82 (CH, C-3), 71.38 (CH, C-12), 68.06 (CH, C-7), 43.01 (CH_2, CH_2NHCO), 32.36 (CH_2, C-23), 31.46 (CH_2, C-22); *m*/*z* (FAB) 940 (M^+ + Na, 43%), 918 (M^+ + H, 43), 900 (8), 809 (8), 637 (11), 615 (11), 577 (10), 555 (10), 525 (8), 501 (9), 473 (9), 436 (13), 355 (8), 337 (25), 289 (20), 271 (25), 253 (32), 225 (31), 199 (12), 176 (17), 119 (35), 105 (77).

***N*,*N*′-Bisdeoxycholyl-*m*-xylylenediamine 8b.** Succinimido deoxycholate **3b** (2.45 g, 5.02 mmol) was dissolved in dry DMF (20 ml) and to this was added *m*-xylylenediamine (341 mg, 2.45 mmol). The mixture was stirred at room temperature under nitrogen atmosphere for 10 h. The reaction mixture was worked up as described earlier and the product was purified by column chromatography [10% (v/v) MeOH in $CHCl_3$] (R_f 0.52) to give *compound* **8b** as a white crystalline solid (1.92 g, 87%); mp 145–146 °C (Found: C, 74.29; H, 10.02; N, 2.73%. Calc. for $C_{56}H_{88}N_2O_6\cdot H_2O$: C, 74.46; H, 10.04; N, 3.10%); IR ν_{max} (KBr)/cm^{-1} 3386, 1654; δ_H (300 MHz; $CDCl_3$–CD_3OD) 7.21 (br s, 4H, Ar–H), 4.36 (m, 4H, 2 × C*H*$_2$NH), 3.94 (br s, 2H, 2 × 12β-H), 3.43 (m, 2H, 2 × 3β-H), 2.60–1.00 (50H, steroidal H), 0.95 (d, *J* = 6 Hz, 6H, 2 × 21-Me), 0.89 (s, 6H, 2 × 19-Me), 0.65 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 174.64 (C-24), 138.67 (C, Ar–C), 128.93 (CH, Ar–CH), 126.80 (CH, Ar–CH), 72.92 (CH, C-3), 71.27 (CH, C-12), 43.21 (CH_2, CH_2NHCO), 32.09 (CH_2, C-23), 31.47 (CH_2, C-22), 26.99 (CH_2, C-7); *m*/*z* (FAB) 908 (M^+ + Na, 28%), 886 (M^+ + H, 100), 868 (13), 850 (9), 813 (33), 599 (7), 575 (4), 557 (10), 529 (8), 509 (15), 491 (12), 475 (25), 438 (12), 420 (15), 402 (5), 384 (17), 357 (7), 339 (22), 289 (10), 271 (10), 255 (40), 225 (18), 199 (11), 105 (82).

***N*,*N*′-Bis(3α-*O*-bromoacetylcholyl)-*m*-xylylenediamine 9a.** Dicholyl-*m*-xylylenediamine **8a** (800 mg, 0.87 mmol) was treated with bromoacetyl bromide (351 mg, 1.74 mmol) in the presence of anhydrous K_2CO_3 (241 mg, 1.74 mmol) in dry $CHCl_3$ (20 ml). The procedure was the same as that mentioned for the dimers **5a**–**c** and the crude product was purified by column chromatography [0–5% (v/v) MeOH in $CHCl_3$] [R_f 0.69 in 10% (v/v) MeOH in $CHCl_3$] to give *product* **9a** as a semi-solid (718 mg, 71%); IR ν_{max} (KBr)/cm^{-1} 3325, 1733, 1653; δ_H (300 MHz; $CDCl_3$) 7.18 (br s, 4H, Ar–H), 4.56 (m, 2H, 2 × 3βH), 4.30 (m, 4H, 2 × C*H*$_2$NH), 3.90 (br s, 2H, 2 × 12β-H), 3.76 (br s, 2H, 2 × 7β-H), 3.70 (s, 4H, 2 × CH_2Br), 2.40–1.00 (48H, steroidal H), 0.89 (br s, 6H, 2 × 21-Me), 0.84 (br s, 6H, 2 × 19-Me), 0.60 (s, 6H, 2 × 18-Me).

***N*,*N*′-Bis(3α-*O*-bromoacetyldeoxycholyl)-*m*-xylylenediamine 9b.** This was prepared by taking bis(deoxycholyl)-*m*-xylylenediamine (650 mg, 0.73 mmol), bromoacetyl bromide (295 mg, 1.46 mmol), and anhydrous K_2CO_3 (202 mg, 1.46 mmol) in dry $CHCl_3$ (15 ml) and the crude product obtained after usual work-up was subjected to column chromatography [0–4% (v/v) MeOH in $CHCl_3$] [R_f 0.60 in 8% (v/v) MeOH in $CHCl_3$] to give *product* **9b** as a semi-solid (629 mg, 76%); IR ν_{max} (KBr)/cm^{-1} 3415, 1730, 1652; δ_H (300 MHz; $CDCl_3$) 7.17 (m, 4H, Ar–H), 4.72 (m, 2H, 2 × 3β-H), 4.30 (m, 4H, 2 × C*H*$_2$NH), 3.90 (s, 2H, 2 × 12β-H), 3.74 (s, 4H, 2 × CH_2Br), 2.30–1.03 (50H, steroidal H), 0.91 (d, *J* = 6 Hz, 6H, 2 × 21-Me), 0.86 (s, 6H, 2 × 19-Me), 0.60 (s, 6H, 2 × 18-Me).

Bis(3α-*O*-hydroxyacetylcholyl)-*m*-xylylenediamine cyclic terephthalate 10a. Bis(bromoacetylcholyl)-*m*-xylylenediamine **9a** (300 mg, 0.25 mmol) was dissolved in DMF (8 ml) and to

this solution was added dicaesium terephthalate **6** (113 mg, 0.25 mmol). The mixture was stirred at room temperature for 12 h, filtered, and the filtrate was mixed with ice-cold brine (60 ml). The solid obtained was filtered off, washed with cold water, and dried under vacuum. The crude product was chromatographed on silica gel [0–5% (v/v) MeOH in $CHCl_3$] [R_f 0.55 in 10% (v/v) MeOH in $CHCl_3$] to afford *compound* **10a** as a white crystalline solid (248 mg, 81%); mp 165–168 °C (Found: C, 61.03; H, 8.09; N, 2.19%. Calc. for $C_{68}H_{94}N_2O_{14}\cdot CHCl_3\cdot 3H_2O$: C, 61.08; H, 7.56; N, 2.09%); IR ν_{max} (KBr)/cm^{-1} 3419, 1733, 1653; δ_H (300 MHz; $CDCl_3$–CD_3OD) 8.14 (br s, 4H, Ar–H), 7.19 (br s, 4H, Ar–H), 4.82 (br s, 4H, 2 × $COCH_2O$), 4.68 (m, 2H, 2 × 3β-H), 4.36 (m, 4H, 2 × CH_2NH), 3.90 (br s, 2H, 2 × 12β-H), 3.80 (br s, 2H, 2 × 7β-H), 2.50–1.05 (m, 48H, steroidal H), 0.95 (br s, 6H, 2 × 21-Me), 0.89 (br s, 6H, 2 × 19-Me), 0.65 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 174.55 (C, C-24), 167.01 (C, OCOAr), 164.94 (C, $OCOCH_2$), 138.70 (C, Ar–C), 133.13 (C, Ar–C), 129.68 (CH, Ar–CH), 128.55 (CH, Ar–CH), 126.38 (CH, Ar–CH), 76.03 (CH, C-3), 72.64 (CH, C-12), 67.78 (CH, C-7), 61.46 (CH_2, $OCOCH_2$), 43.02 (CH_2, CH_2NHCO), 32.50 (CH_2, C-23), 31.45 (CH_2, C-22); *m*/*z* (FAB) 1165 (M^+ + 2H, 3%), 1044 (2), 661 (3), 436 (10), 371 (60), 337 (10), 289 (26), 253 (16), 225 (21), 105 (66).

Bis(3α-*O*-hydroxyacetyldeoxycholyl)-*m*-xylylenediamine cyclic terephthalate 10b. Bis(bromoacetyldeoxycholyl)-*m*-xylylenediamine **9b** (245 mg, 0.21 mmol) was dissolved in DMF (7 ml) and to this solution was added dicaesium terephthalate **6** (97 mg, 0.21 mmol). The mixture was stirred at room temperature for 12 h. The work-up and purification procedure followed was the same as described for earlier cholaphanes [R_f 0.60 in 10% (v/v) MeOH in $CHCl_3$] and pure *compound* **10b** was obtained as a white crystalline solid (183 mg, 75%); mp 178–180 °C (Found: C, 68.34; H, 7.96; N, 2.43%. Calc. for $C_{68}H_{94}N_2O_{12}\cdot 2H_2O$: C, 68.89; H, 8.33; N 2.36%); IR ν_{max} (KBr)/cm^{-1} 3460, 1735, 1653; δ_H (300 MHz; $CDCl_3$–CD_3OD) 8.15 (br s, 4H, Ar–H), 7.32 (m, 4H, Ar–H), 4.83 (m, 6H, 2 × $COCH_2O$ and 2 × 3β-H), 4.37 (m, 4H, 2 × CH_2NH), 3.96 (br s, 2H, 2 × 12β-H), 2.40–1.10 (m, 50H, steroidal H), 0.98 (br s, 6H, 2 × 21-Me), 0.89 (s, 6H, 2 × 19-Me), 0.65 (s, 6H, 2 × 18-Me); δ_C (75 MHz; $CDCl_3$–CD_3OD) 173.59 (C, C-24), 167.10 (C, OCOAr), 165.19 (C, $OCOCH_2$), 138.99 (C, Ar–C), 133.40 (C, Ar–C), 129.94 (CH, Ar–CH), 129.08 (CH, Ar–CH), 127.02 (CH, Ar–CH), 76.57 (CH, C-3), 73.07 (CH, C-12), 61.73 (CH_2, $OCOCH_2$), 43.49 (CH_2, CH_2NHCO), 32.00 (CH_2, C-23), 31.44 (CH_2, C-22), 26.89 (CH_2, C-7); *m*/*z* (FAB) 1131 (M^+ + H, 20%), 1095 (5), 1010 (5), 871 (3), 813 (11), 757 (3), 661 (10), 475 (17), 391 (7), 339 (13), 289 (22), 255 (20), 207 (10), 105 (48).

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References

1 (*a*) A. P. Davis, *Chem. Soc. Rev.*, 1993, **22**, 243; (*b*) Y. X. Li and J. R. Dias, *Chem. Rev.*, 1997, **97**, 283; (*c*) P. Walliman, T. Marti, A. Furer and F. Diederich, *Chem. Rev.*, 1997, **97**, 1567; (*d*) A. P. Davis and R. S. Wareham, *Angew. Chem., Int. Ed.*, 1999, **38**, 2978.
2 (*a*) R. P. Bonar-Law and A. P. Davis, *J. Chem. Soc., Chem. Commun.*, 1989, 1050; (*b*) R. P. Bonar-Law and A. P. Davis, *Tetrahedron*, 1993, **49**, 9829; (*c*) R. P. Bonar-Law, A. P. Davis and B. J. Dorgan, *Tetrahedron*, 1993, **49**, 9855.
3 (*a*) R. P. Bonar-Law and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1991, 574; (*b*) R. P. Bonar-Law and J. K. M. Sanders, *Tetrahedron Lett.*, 1992, **33**, 2071; (*c*) R. P. Bonar-law, L. G. Mackay and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1993, 456; (*d*) L. G. Mackay, R. P. Bonar-Law and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1377; (*e*) R. P. Bonar-Law and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1995, 3085.
4 A. P. Davis, J. F. Gilmer and J. J. Perry, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1312.
5 (*a*) Y. Li and J. R. Dias, *Synthesis*, 1997, 425; (*b*) H. Gao and J. R. Dias, *Eur. J. Org. Chem.*, 1998, 719; (*c*) H. Gao and J. R. Dias, *New J. Chem.*, 1998, 579.
6 R. P. Bonar-Law and J. K. M. Sanders, *Tetrahedron Lett.*, 1993, **34**, 1677.
7 D. Albert and M. Feigel, *Tetrahedron Lett.*, 1994, **35**, 565.
8 P. A. Brady, R. P. Bonar-Law, S. J. Rowan, C. J. Suckling and J. K. M. Sanders, *Chem. Commun.*, 1996, 319.
9 (*a*) A. P. Davis and J. J. Walsh, *Chem. Commun.*, 1996, 449; (*b*) A. P. Davis, S. Menzer, J. J. Walsh and D. J. Williams, *Chem. Commun.*, 1996, 453.
10 (*a*) A. P. Davis, M. G. Orchard, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1991, 612; (*b*) A. P. Davis and M. G. Orchard, *J. Chem. Soc., Perkin Trans. 1*, 1993, 919.
11 R. P. Bonar-Law, A. P. Davis and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2245.
12 K. M. Bhattarai, R. P. Bonar-law, A. P. Davis and B. A. Murray, *J. Chem. Soc. Chem. Commun.*, 1992, 572.
13 R. P. Bonar-Law, A. P. Davis and B. A. Murray, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1407.
14 S. Kohomoto, D. Fukui, T. Nagashima, K. Kishikawa, M. Yamamoto and K. Yamada, *Chem. Commun.*, 1996, 1869.
15 E. Kolehmainen, J. Tamminen, K. Lappalainen, T. Torkkel and R. Seppala, *Synthesis*, 1996, 1082.
16 P. S. Pandey and R. B. Singh, *Tetrahedron Lett.*, 1997, **38**, 5045.
17 O. Piepers and R. M. Kellogg, *J. Chem. Soc., Chem. Commun.*, 1978, 383.
18 (*a*) W. H. Kruizinga and R. M. Kellogg, *J. Am. Chem. Soc.*, 1981, **103**, 5183; (*b*) R. M. Kellogg, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 782; (*c*) A. G. Talma, P. Jouin, J. G. de Vries, C. B. Troostwijk, G. H. W. Buning, J. K. Waninge, J. Visscher and R. M. Kellogg, *J. Am. Chem. Soc.*, 1985, **107**, 3981.
19 (*a*) C. J. Burrows and R. A. Sauter, *J. Inclusion Phenom.*, 1987, **5**, 117; (*b*) J. F. Kinneary, T. M. Roy, J. S. Albert, H. Yoon, T. R. Wagler, L. Shen and C. J. Burrows, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1989, **7**, 155.