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First bile acid-derived chiral dendritic species with nanometric dimensions

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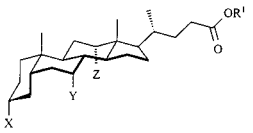
This paper describes the first synthesis of branched bile acid oligomers.

The chemistry of dendrimers has been a dominating theme in chemical sciences in recent years. Chiral dendritic species[1] also appeared in the chemical literature shortly after the first achiral version was reported.[2] Apart from their potential applications in asymmetric catalysis and chiral recognition,[3] chiral dendritic species have been of considerable interest because of a search towards *macromolecular asymmetry*.[4] A dendrimer possesses three distinct regions, *viz.* the core, the branching units and the end groups, and the incorporation of chirality in the dendrimer can in general be achieved by choosing one or more such components to be chiral.[1b] Molecules from the natural chiral pool, *e.g.* amino acids,[1a] nucleic acids,[5] sugars[6] and tartaric acid,[4e,f] have been employed to design chiral dendrimers. Bile acids, forming another class of the naturally occurring group of chiral molecules, have been extensively used in supramolecular chemistry including the synthesis of cyclic and linear polymers.[7] Bile acids (*e.g.* **1**–**3**) offer a carboxy group and multiple



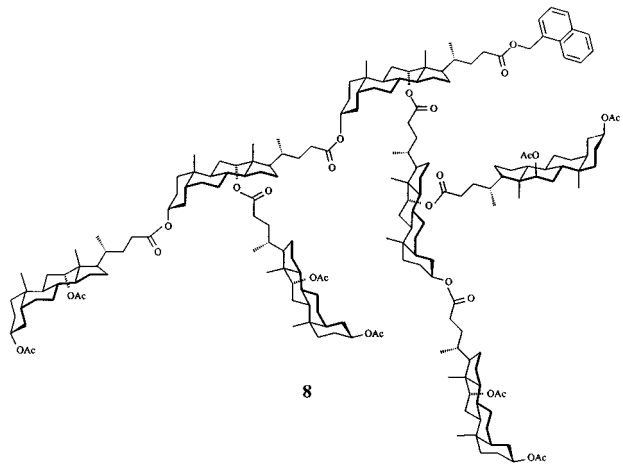
1 Lithocholic acid	X = OH, Y = Z = H, R^1 = H
2 Deoxycholic acid	X = Z = OH, Y = H, R^1 = H
3 Cholic acid	X = Y = Z = OH, R^1 = H
4 Deoxycholic acid, 3,12-diacetate	X = Z = OAc, Y = H, R^1 = H
5 1-Naphthylmethyl deoxycholate	X = Z = OH, Y = H, R^1 = 1-CH_2Np
6 Cholic acid, 3,7,12-triacetate	X = Y = Z = OAc, R^1 = H
7 1-Naphthylmethyl cholate	X = Y = Z = OH, R^1 = 1-CH_2Np

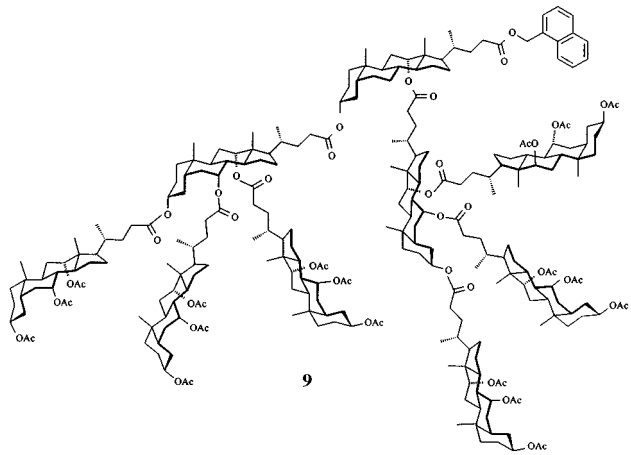
hydroxy groups (up to three) and are versatile AB_2 or AB_3 building blocks for dendritic construction. We report here the synthesis of the *first* bile acid-based chiral dendrons **8** and **9**, a heptamer and a nonamer, respectively. These relatively small oligomers of large chiral building blocks are of nanometric dimensions.

We adopted *Fréchet's* convergent strategy[8] to accomplish the synthesis of **8** and **9**. Orthogonal protection of deoxycholic acid **2** with acetate and 1-naphthylmethyl groups[9] generated steroids **4** (Ac_2O, Et_3N, DMAP, 92%) and **5** (1-naphthylmethyl chloride/DBU/DMF, 79%), respectively. In an analogous manner cholic acid **3** was converted to **6** (45%) and **7** (77%).

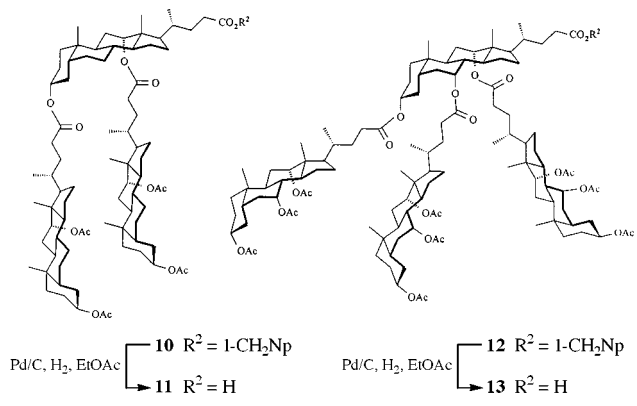
Steroid **4** was converted to the acid chloride, and reacted with **5**, (CaH_2, $BnEt_3N^+Cl^-$, toluene, reflux, 2 d) to generate trimer **10** (70%) which was characterized by IR, ^1H and ^{13}C NMR, UV, HPLC, elemental analysis and MALDI-TOF MS (Scheme 1). The deprotection of **10** to **11** (Pd/C, H_2), conversion to the acid chloride and subsequent reaction with **5** provided heptamer **8** in 75% yield.[10]

The use of cholic acid-based starting materials **6** and **7** led to an increase in the number of branching units, which allowed us to construct tetramer **12** in 69% yield. The deprotection of **12** to **13**, followed by its coupling with **5** generated nonamer **13** (35%).[10] One of the (many possible) conformations of **9** is shown in Fig. 1.





The mobility of these compounds on reversed-phase HPLC shows an interesting pattern (Table 1). With the increase in the oligomeric size, both the polarity (increased number of ester groups) and the lipophilicity (increased number of bile acid



Scheme 1

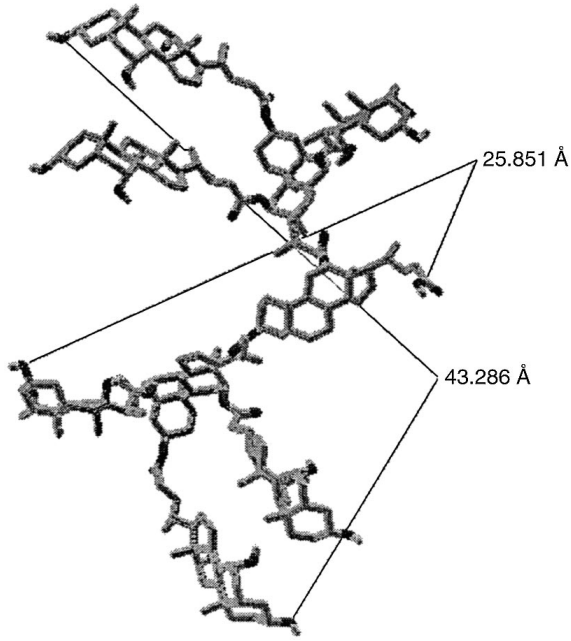


Fig. 1 Representation of one of the many possible conformations of **9**. The 'length' and the 'width' are indicated in Å.

Table 1 HPLC data on bile acid oligomers (25 cm C-18 column, 4.6 mm id)

Steroidal oligomers	Solvent system	Retention time/min
8 (7[a], 15[b])	30% THF–MeOH	14.5
9 (9, 27)	15% THF–MeOH	12.9
10 (3, 7)	15% THF–MeOH	17.1
12 (4, 13)	MeOH	13.8

[a] Number of bile acid moieties present. [b] Number of ester linkages.

units) increase. Experimentally, the order of elution (increasing retention time) on a C-18 column is: **12** < **9** < **10** < **8**. On silica gel TLC a different order is observed; the R_f values increase in the order: **9** < **12** < **8** < **10** (EtOAc–hexanes, 2 : 3 v/v).

The optical rotations of these dendrons are given in Table 2. The molar rotation values show a roughly linear relationship with the number of bile acid units in each dendron (or its molecular weight). This suggests the absence of chiral conformations and local micropolarity which might affect the optical rotation.

These bile acid-based dendrons are of considerable interest because of their shape and nanometric dimensions. The design of larger functionalized dendrimers using analogous repeating units is in progress in our laboratory.

Table 2 Molar and specific rotation values of dendrons in $CHCl_3$

Compound (MW)	Specific rotation	Molar rotation
8 (3116.4)	102.9	3207
9 (4413.9)	84.2	3717
10 (1450.0)	86.6	1256
11 (1309.9)	94.7	1240
12 (2098.8)	80.8	1696
13 (1958.6)	80.6	1579

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9 The 1-naphthylmethyl group was employed for easier identification of the dendrons in the purification steps, and also in the analysis of the sample by UV and HPLC measurements.

10 The MALDI-TOF MS spectrum showed a peak for **8** at *m/z* 3143.0 [expected for $(M+Na)^+$ 3139.4] (Calc. for $C_{195}H_{292}O_{30}$: C, 75.15; H, 9.44%. Found: C, 75.33; H, 9.83%). For **9**, MALDI-TOF MS spectrum showed a peak for at *m/z* 4440.6 [expected for $(M+Na)^+$ = 4436.9] (Calc. for $C_{263}H_{388}O_{54}$: C, 71.57; H, 8.86. Found: C, 71.89; H, 9.26%).

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