Synthesis of steroidal triply-bridged cyclophanes

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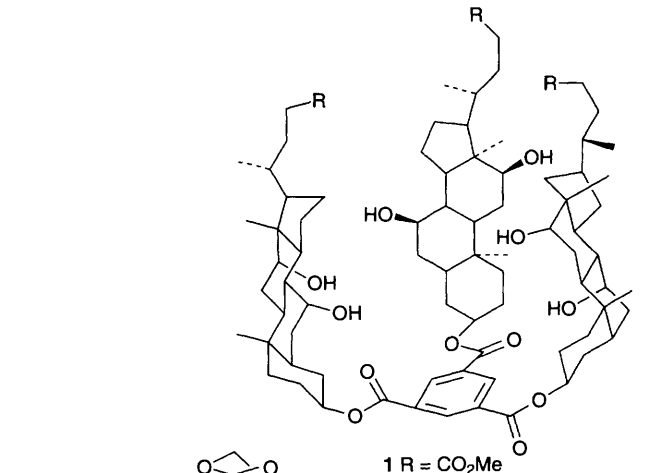
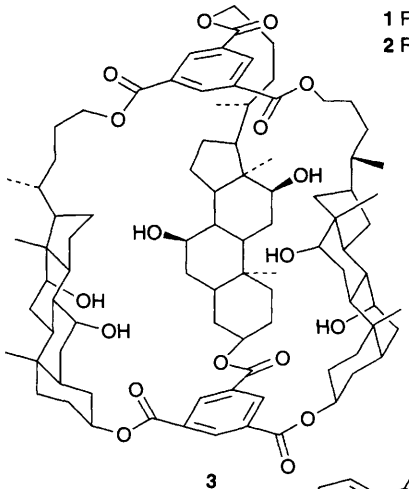
Steroidal triply-bridged cyclophanes are synthesised using cholic acid derivatives as bridge units; cyclophane 3 moderately binds to organic guest molecules and enantioselectively binds to *N*-*Z*-phenylalanine.

Vögtle's type macro bicyclic compounds,[1] which contain two spacer units linked by three long bridges, are good t molecules as the inner binding sites on the bridges, direct towards the centre of the cavity. For efficient binding of guest molecules, the bridge unit should be a rigid molecule and the outer surface of the bridge should be lipophilic and its inner surface should be hydrophilic or *vice versa*. From these view points, cholic acid, a steroidal bile acid, is a suitable candidate for the bridge unit of a Vögtle's type compound. Moreover, its *cis* A–B ring junction is appropriate for the construction of cyclic compounds. Owing to its unique structural features, lipophilic on one side and hydrophilic on the other side of the steroidal backbone, cholic acid has recently been investigated as a host molecule for molecular crystals,[2] a spacer unit for cyclophanes (cholaphanes)[3] and a component of some other cyclic compounds.[4] Here we report the first synthesis of a steroidal triply-bridged cyclophane, a Vögtle's type compound with three steroidal bridge units. Methyl cholate was treated with trimesoyl chloride (1,3,5-benzenetricarbonyl trichloride) in toluene under reflux with DMAP to give tripodant **1** in 60% yield.† The most reactive hydroxy groups at the 3-position were selectively esterificated. Selective reduction of the methyl ester to the alcohol was carried out by DIBAL-H in THF at room temperature to afford **2** (62%).† Ring closure of **2** with trimesoyl chloride was performed under high dilution conditions. To refluxing toluene, a THF solution of **2** with DMAP and a toluene solution of trimesoyl chloride were added simultaneously using two syringes with the aid of a syringe pump over 20 h. Separation of the product was carried out by flash column chromatography on silica gel to give **3** in 28% yield.† Cyclophane **4** was prepared in 5% yield from **2** and 1,3,5-tris[3-(2-chlorocarbonylethyl)phenyl]benzene. A one-step synthesis of **3** from petromyzonol and trimesoyl chloride was attempted but proved inefficient and gave only a trace amount of **3** along with insoluble polymeric materials.

The triply-bridged cyclophane **3** possesses a hydrophilic cavity in which six hydroxy groups direct towards the centre of the cavity. A preliminary binding study of **3** was carried out for 10 organic guest compounds. The binding constants for these molecules are shown in Table 1. Job plots[5] suggested that two molecules of *p*-nitrophenol were bound to one molecule of **3**. The 1 : 2 (**3** : guest) ratio was also observed for *m*-nitrophenol. The rest of the guest molecules formed 1 : 1 complexes with **3**. The observation of upfield shifts for benzene ring protons of nitrophenols (δ 0.37 and 0.22 for *p*-nitrophenol when 2 equiv. were added) indicated that nitrophenols were included inside the cavity of **3**. The hydroxy groups (the 7- and 12-positions) were confirmed to be the binding sites from the downfield shifts of protons at the 7- and 12-positions δ 0.02 and 0.06 respectively when 2 equiv. of *p*-nitrophenol were added. The binding constants were calculated by non-linear least-square regression[6] on the data obtained from the titration measured by ^{1}H NMR in $CDCl_3$. For 1 : 2 (host : guest) complex formation, a



1 R = CO_2Me
2 R = CH_2OH



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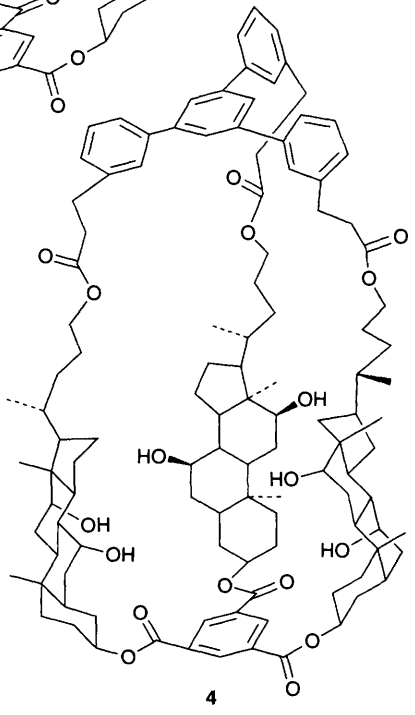

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Table 1 Binding constants of organic guest molecules to **3** in $CDCl_3$ at 24 °C

Guest molecules	Binding constant/ $dm^3\ mol^{-1}$	
	K_1[a]	K_2[b]
p-nitrophenol	220 ± 1	55 ± 1
m-nitrophenol	191 ± 1	48 ± 1
triethanolamine	1266 ± 159	
diethylene glycol	245 ± 55	
N-Z-D-alanine	215 ± 6	
N-Z-L-alanine	286 ± 14	
N-Z-D-phenylalanine	40 ± 6	
N-Z-L-phenylalanine	268 ± 22	
octyl-α-D-glucopyranoside	293 ± 20	
octyl-β-D-glucopyranoside	245 ± 55	

[a] Binding constants for 1:1 complexes. [b] Binding constants for 1:2 (**3**:guest) complexes.

published equation for NMR data analysis[3a] was employed. A moderate enantioselectivity was observed for *N*-Z-phenylalanine. The $\Delta\Delta G$ (the difference in free energy of formation of molecular complexes) between D- and L-enantiomer was found to be 4.7 kJ mol^{-1} at 24 °C.

Footnote

† *Selected spectroscopic data* for **1**: mp 196–197 °C; ν_{max}(KBr)/cm^{-1} 3564, 2940, 2872, 1726 and 1242; δ_H (400 MHz; $CDCl_3$) 0.71 (9 H, s), 0.94 (9 H, s), 0.98 (9 H, d, *J* 7.0 Hz), 3.68 (9 H, s), 1.09–2.56 (m), 3.88 (3 H, br s), 4.00 (3 H, br s), 4.88 (3 H, m) and 8.78 (3 H, s) [Found: MH^+, 1461.8579. $C_{84}H_{126}O_{18}K$ (MK^+) requires 1461.8581]. For **2**: mp 233–234 °C; ν_{max}(KBr)/cm^{-1} 3542, 2940, 2868, 1710 and 1246; δ_H (400 MHz; $CDCl_3$ with three drops of CD_3OD) 0.71 (9 H, s), 0.96 (9 H, s), 0.99 (9 H, d, *J* 7.0 Hz), 2.60–1.04 (m), 3.57 (6 H, td, *J* 6.7 and 1.8 Hz), 3.86 (3 H, br s), 3.99 (3 H, br s), 4.89 (3 H, m) and 8.74 (3 H, s) [Found: MH^+, 1339.9183. $C_{81}H_{127}O_{15}$ (MH^+) requires 1339.9175]. For **3**: mp 269–270 °C; ν_{max}(KBr)/cm^{-1} 3448, 2940, 2868, 1730 and 1242; δ_H (400 MHz; $CDCl_3$) 0.69 (9 H, s), 0.92 (9 H, s), 1.00 (9 H, d, *J* 6.9 Hz), 1.07–2.38 (m), 3.83 (3 H, br s), 3.93 (3 H, br s), 4.19 (3 H, ddd, *J* 9.7, 8.6 and 4.4 Hz), 4.59 (3 H, m), 4.60 (3 H, m), 8.26 (3 H, s) and 8.83 (3 H, s); δ_C (125 MHz; $CDCl_3$) 12.53 (q), 17.76 (q), 22.40 (q), 23.00 (t), 24.23 (t), 26.23 (t), 26.79 (d), 27.22 (t), 28.42 (t), 31.49 (t), 34.11 (t), 34.55 (d), 34.64 (t), 34.67 (t), 39.59 (d), 40.88 (d), 41.85 (d), 46.14 (d), 46.31 (s), 66.17 (t), 68.13 (d), 72.64 (d), 77.10 (d), 131.46 (d), 131.92 (d), 133.36 (d), 134.49 (d), 165.06 (s) and 166.54 (s), one steroidal backbone resonance was not detected or degenerated (ref. R. P Bonar-Law, A. P. Davis and B. J. Dorgan, *Tetrahedron*, 1993, **49**, 9855) [Found: MH^+, 1495.9034. $C_{90}H_{127}O_{18}$ (MH^+) requires 1495.9022].

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