Steroid-based receptors with tunable cavities; stepwise and direct syntheses of a C_3-symmetrical prototype

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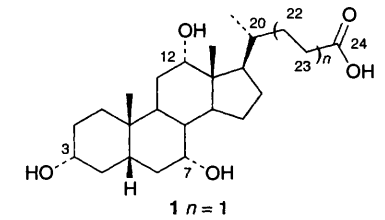
The highly preorganised 'cyclocholamide' 12 serves as prototype for a new series of receptors 4 bearing inward-directed polar functional groups; 12 has been synthesized by cyclotrimerisation of a monomer unit, and also by a stepwise route adaptable to the preparation of non-C_3-symmetrical analogues.

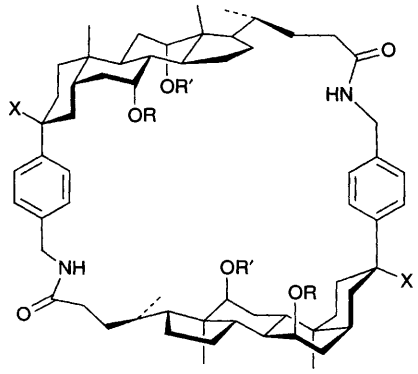
The bile acids, such as cholic acid **1**, are now well-established as 'engineering components' for supramolecular chemistry.[1] The rigid steroidal framework can be used to organise an array of functional groups, and is readily incorporated in macrocyclic structures with potential as synthetic receptors *etc.* However, while these structures generally have quite well-defined 3-dimensional geometries, there is usually an element of flexibility arising from the C(22)–C(24) steroidal side-chain. For example the 'cholaphanes' **3**, reported previously from this laboratory,[1a,c–e] can adopt a range of distinct conformations, not all of which have open cavities.[1d] Although this need not destroy their recognition properties (*e.g.* as carbohydrate receptors),[2] it severely hampers attempts to rationalise their behaviour using computational methods, limits the selectivity attainable, and should also reduce the strength of binding to well-matched guests.

In response to this problem, we have been exploring the synthesis of less flexible macrocyclic frameworks derived from cholic acid. We now present a new design strategy which has been used to generate a range of functionalised hosts, several of which have enforced cavities with strictly limited conformational freedom. The approach is noteworthy in allowing tuning of molecular properties, such as size and rigidity, without undue synthetic effort.

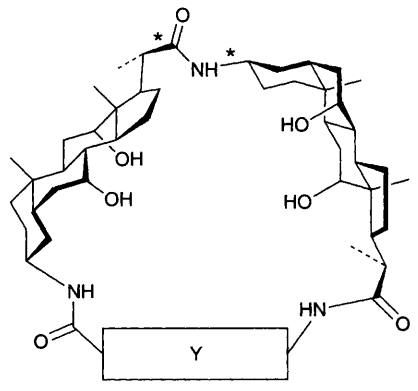
The general design is represented by **4**,[3] a macro-tri-lactam composed of two steroidal moieties and a third, variable fragment. To reduce flexibility, the steroidal units in these 'cyclocholamides'† are derived from bis-nor cholic acid **2**, and thus lack the C(22) and C(23) side chain methylene groups. Rotation about the two starred bonds allows the angle between the steroid skeleta to vary, but there is limited scope for other movement in this region of the macrocycle. Provided the third unit 'Y' is suitably rigid, the macrocyclic framework may have very few conformational options. By variation of 'Y' one may control the size of the cavity and the flexibility of the framework, and may incorporate additional functionality with recognition, catalytic and/or solubilising properties. This report describes the synthesis of the dimeric 'roof' of this structure,



1 $n = 1$
2 $n = 0$



3 X = H or $CH(CN)_2$



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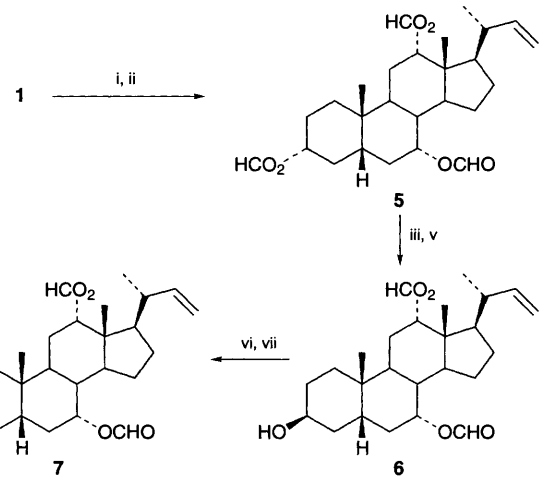
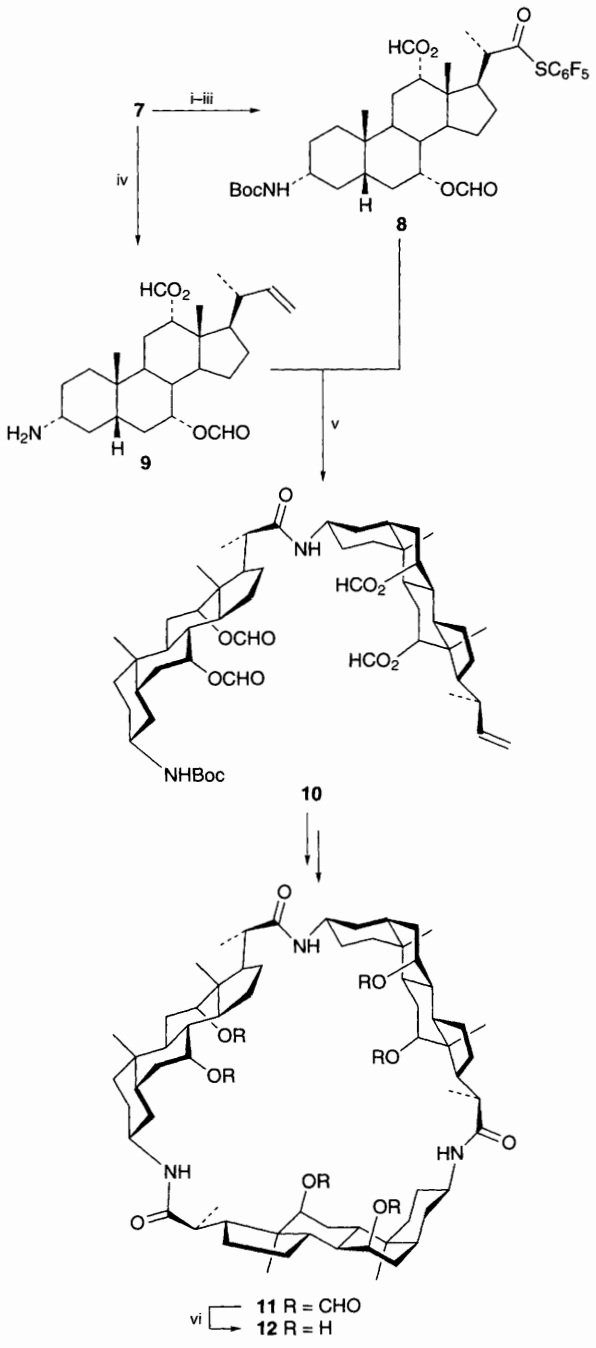


Scheme 1 *Reagents and conditions*: i, HCO_2H, $HClO_4$ (cat.), 95%; ii, $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine, 76%; iii, NaOAc, MeOH, *ca*, 100%, iv, Ph_3P, HCO_2H, DEAD, THF, 96%; v, NaOAc, MeOH, 99%; vi, $MeSO_2Cl$, py, $(Pr^i)_2NEt$, CH_2Cl_2, 93%; vii, NaN_3, DMPU, 96%

and its elaboration into the C_3-symmetrical cyclocholamide **12** by incorporation of a third steroidal unit. The extension of this work to give macrocycles of lower symmetry is reported in the communication following this one.[4]

The key synthetic intermediates for this programme are the steroidal azide **7** (Scheme 1) and the linear dimeric species **10** (Scheme 2). In both molecules a C(22,23) alkene serves as a masked carboxy group. This unit was accessed directly from the natural side-chain by oxidative decarboxylation (**1** → **5** Scheme 1)[5] and could be degraded when needed to a C(22) carboxylic acid using the Ruthenium-catalysed oxidation developed by Sharpless and coworkers.[6] Conversion of **5** to **6** proceeded through 3α-deformylation, Mitsunobu inversion with formate as nucleophile, and cleavage of the 3β formate. The deformylations were highly selective, remarkably so in the second case given the axial disposition of all three formyloxy groups. Mesylation and substitution with azide ion completed the sequence to **7**, which was prepared in 61% overall yield from **1**.



Scheme 2 *Reagents and conditions*: i, Ph_3P, THF, MeOH, H_2O, then $(Boc)_2O$, $(Pr^i)_2NEt$, 85%; ii, $NaIO_4$, $RuCl_3$ (cat.), CCl_4, MeCN, H_2O, 90%; iii, C_6F_5SH, DCC, CH_2Cl_2, 93%; iv, Zn, AcOH, 95%; v, $(Pr^i)_2NEt$, DMAP, CH_2Cl_2, 85%; vi, Cs_2CO_3, MeOH, 93%

The coupling of two monomeric units to give dimer **10** (Scheme 2) was accomplished using the pentafluorothiophenyl (PFTP) active ester protocol reported in an earlier communication.[7] Acyl donor **8** was prepared from **7** by (i) azide reduction (Ph_3P, H_2O) followed by *in situ* *N*-protection (as Boc), (ii) alkene oxidation (see above), and (iii) active ester formation (DCC, C_6F_5SH). An alternative reduction (Zn, AcOH) was used for conversion of **7** to amine **9**. The combination of **8** and **9** in the presence of DMAP and $(Pr^i)_2NEt$ gave **10** in 85% yield, 60% overall from **7** *via* **8**. Repetition of the last three steps converted **10** into the analogous trimer, and a third oxidation-activation sequence gave the corresponding PFTP ester (overall yield 59%). Removal of the *N*-Boc protection [TFA, CH_2Cl_2) and treatment with DMAP/$(Pr^i)_2NEt$ under high dilution in CH_2Cl_2 gave the hexaformylated cyclocholamide **11** in 35% yield. Finally, deformylation with Cs_2CO_3 in methanol gave hexol **12** in a 93% yield.‡

Although this stepwise route was useful in establishing general methodology for our programme, it was found (not surprisingly) to be less efficient than a direct cyclotrimerisation. Thus, *N*-deprotection of **8** and subjection of the resulting amine salt to the cyclisation conditions gave **11** in a yield of 40%. The overall yield of **12** from cholic acid **1**, employing this direct route, may be calculated as 16%.

Molecular mechanics calculations§ on **12** indicate that it is highly preorganised for binding polar organic molecules. The macrocyclic framework appears to be restricted to a single conformation, shown in Fig. 1, all other minima being higher in energy by at least 30 KJ mol^{-1}. The cavity is large enough to accept small organic molecules such as carbohydrates, and is bounded by a total of nine inward-directed polar functional groups (6 × OH and 3 × amide NH). Despite its rigidity and polar functionality **12** is soluble in $CDCl_3$ to a level of *ca.* 1 mmol dm^{-3}, and should thus be suitable for studies of molecular recognition by hydrogen bonding in this convenient, non-polar organic solvent.

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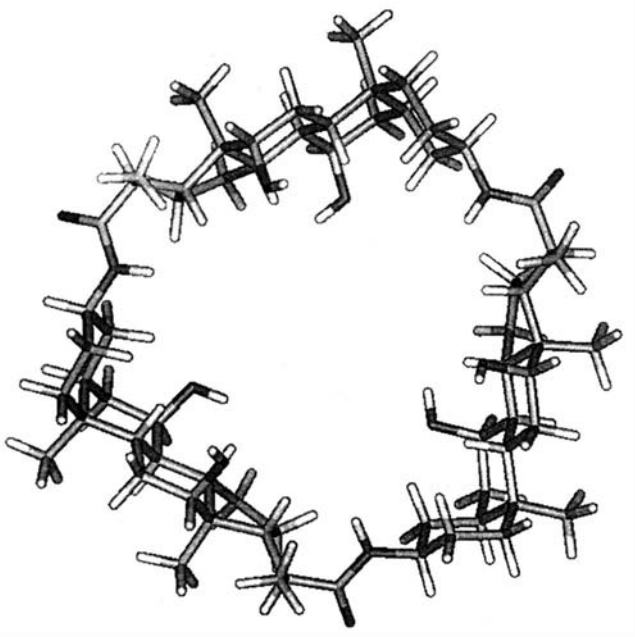

Fig. 1 Structure of **12** generated by molecular modelling (see text). The cavity is bounded by 6 hydroxy groups forming two equilateral triangles, with O···O distances of 6.78 Å [C(7)–OH] and 7.75 Å [C(12)–OH].

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Footnotes

† This usage, for macrolactams linked through nitrogen atoms directly bound to bile acid nuclei, is consistent with that of 'cyclocholate' for the corresponding lactones.[1a,b] On this basis the macrocycle derived from lithocholic acid, reported recently by Albert and Feigl,[1f] would also be a cyclocholamide. A cyclocholate derived from three bis-nor-cholanoyl units, and thus closely related to compound **12**, has been synthesized by Dr R. P. Bonar-Law and Dr J. K. M. Sanders (personal communication).

‡ *Selected spectroscopic data* for **11**: FABMS 1252 (MH^+); δ_H ($CDCl_3$, 300 MHz) 0.77 (9 H, s, 18-Me), 0.94 (9 H, s, 19-Me), 1.01 (9 H, d, 21-Me), 3.56 (3 H, m, 3β-H), 4.87 (3 H, m, 7β-H), 5.13 (3 H, m, 12β-H), 5.93 (3 H, m, NH) and 8.06, 8.34 (2 × 3 H, s, OCOH). For **12**: δ_H ($CDCl_3$, 300 MHz) 0.70 (9 H, s, 18-Me), 0.90 (9 H, s, 19-Me), 1.23 (9 H, d, 21-Me), 3.63 (3 H, m, 3β-H), 3.86 (3 H, m, 7β-H), 3.94 (3 H, m, 12β-H) and 5.48 (3 H, m, NH). ^{13}C NMR spectra of both **11** and **12** ($CDCl_3$, 75.5 MHz) confirmed the C_3-symmetry.

§ Calculations were performed using the Monte Carlo search-minimisation routine and MM2 force field, as implemented in MacroModel V4.0 running on a Silicon Graphics 4D25TG workstation. See: F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.

References

1 (*a*) A. P. Davis, *Chem. Soc. Rev.*, 1993, **22**, 243, and references cited therein. For recent developments see: (*b*) L. G. Mackay, R. P. Bonar-Law, and J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. I*, 1993, 1377; (*c*) R. P. Bonar-Law and A. P. Davis, *Tetrahedron*, 1993, **49**, 9829; (*d*) R. P. Bonar-Law and A. P. Davis, *Tetrahedron*, 1993, **49**, 9854; (*e*) R. P. Bonar-Law, A. P. Davis and B. J. Dorgan, *Tetrahedron*, 1993, **49**, 9855; (*f*) D. Albert and M. Feigl, *Tetrahedron Lett.*, 1994, **35**, 565; (*g* R. Boyce, G. Li, H. P. Nestler, T. Suenaga and W. C. Still, *J. Am. Chem. Soc.*, 1994, **116**, 7955; (*h*) D. Roy and D. M. Birney, *Synlett*, 1994, 798; (*i*) P. Venkatesan, Y. Cheng, and D. Kahne, *J. Am. Chem. Soc.*, 1994, **116**, 6955; (*j*) U. Maitra and L. J. D'Souza, *J. Chem. Soc., Chem. Commun.*, 1994, 2793; (*k*) H.-P. Hsieh, J. G. Muller and C. J. Burrows, *J. Am Chem. Soc.*, 1994, **116**, 12 077; (*l*) R. P. Bonar-Law and J. K. M. Sanders, *J. Am Chem. Soc.*, 1995, **117**, 259.

2 (*a*) R. P. Bonar-Law, A. P. Davis, and B. A. Murray, *Angew. Chem.*, 1990, **102**, 1497; *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1407; (*b*) K. M. Bhattarai, R. P. Bonar-Law, A. P. Davis and B. A. Murray, *J. Chem. Soc., Chem. Commun.*, 1992, 752.

3 The potential of this architecture is mentioned briefly in ref. 1(*a*).

4 A. P. Davis, S. Menzer, J. J. Walsh and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1996, 453.

5 G. L. Carlson, D. T. E. Belobaba and A. F. Hofmann, *Steroids*, 1977, **30** 787.

6 P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.

7 A. P. Davis and J. J. Walsh, *Tetrahedron Lett.*, 1994, **35**, 4865.

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