The "triamino-analogue" of methyl allocholate; a rigid, functionalised scaffold for supramolecular chemistry†

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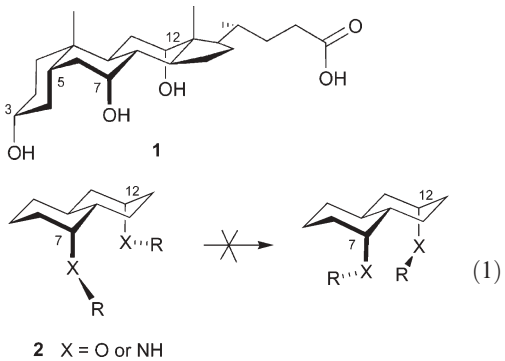
Cholic acid 1 has been converted into triamine 5 with the all-*trans* polycyclic allocholanoyl skeleton and co-directed, axial amino groups; the potential of this system as a scaffold is illustrated by conversion to a preorganised anion receptor.

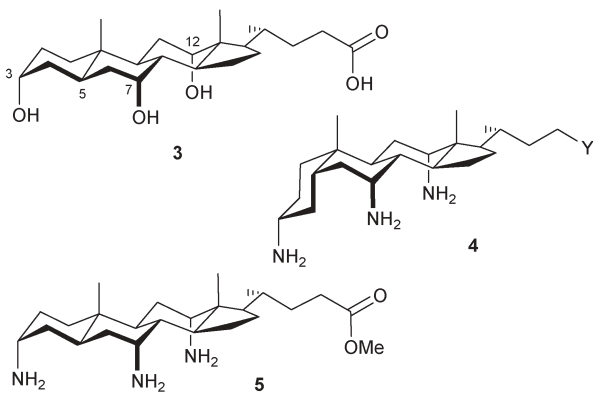
The bile acids, such as cholic acid **1**, have been widely exploited as scaffolds for supramolecular, medicinal and combinatorial chemistry.[1] Their extended, rigid frameworks may be employed to create large preorganised structures, while their co-directed functionality may be transformed to control recognition, amphiphilic and self-assembly properties. The axially-disposed 7,12 substitution is also useful. In derivatives of form **2**, groups R cannot rotate beneath the body of the steroid due to 1,3-diaxial interactions (Eq. 1).[2] The XR units are thus held in place, preorganised for recognition and other purposes.



2 X = O or NH

The common bile acids possess the 5β configuration, as in **1**, and most functional derivatives have shared this stereochemistry. However the 5α skeleton, as in *allo*cholic acid **3**, provides an interesting and complementary alternative. It is slightly longer, increasing the spacing between the functionalised positions. Also, the all-*trans* structure confers a flatter profile, changing the relationship between the substituents. Thus in **3**, the 3-, 7- and 12-C–O bonds are angled at ~ 90° with respect to the plane of the three carbon atoms. For **1**, the corresponding angle is ~ 70°. Finally, *all three* substituents in the allocholyl system are axial, and thus restricted as in **2**. Scaffolds derived from **3** could thus impart almost perfect preorganisation to podand-type molecular architectures.

Amino-substituted bile acids are especially useful as facial amphiphiles,[1f,3] and as starting materials for anion receptors[1d,2] and combinatorial libraries.[4] We[5] and others[6] have described several preparations of triamines **4**, derived from **1**, but 5α analogues such as **5** are unknown.[7] We now report the synthesis of **5**, the first "triaza-analogue" of an allocholic acid derivative. We also show how this scaffold can be employed in the construction of anion receptors, exploiting the increased preorganisation afforded by all-axial substitution.



Triamine **5** was prepared from cholic acid **1** as shown in Scheme 1. Enone **6** was available in ~ 52% overall yield *via* classical procedures (formylation, 3-deformylation, oxidation + 4-bromination, HBr elimination). Reduction of the enone unit with Li/NH_3/*t*-BuOH gave triol **7**,[8] establishing the 5α stereochemistry. Oxidation gave triketone **8**, and treatment with hydroxylamine gave the corresponding trioxime. This compound was subjected to a two-stage reduction procedure (H_2/Pt then Zn) which we had previously used to generate axial amino groups in the 5β series.[5b,c] In this case the transformation was axial-selective in all three centres, giving **5** in ~ 60% yield. The triamine was protected and characterised as tris-Boc derivative **9**. The relative stereochemistry at carbons 3, 5, 7 and 12 was confirmed by X-ray crystallography (Fig. 1).[9] The crystal structure also illustrates the preorganisation of the C–NH–CO units, all of which are held with their CO groups directed outwards and NH inwards. Distances between the NH hydrogens are 3.5 Å (7,12), 4.8 Å (3,7) and 5.8 Å (3,12). The binding site thus created is occupied in the crystal by a *t*-butoxycarbonyl unit from a neighbouring molecule, with intermolecular hydrogen bonds from "host" 7,12-N*H* to "guest" *t*-BuO–C=*O*.

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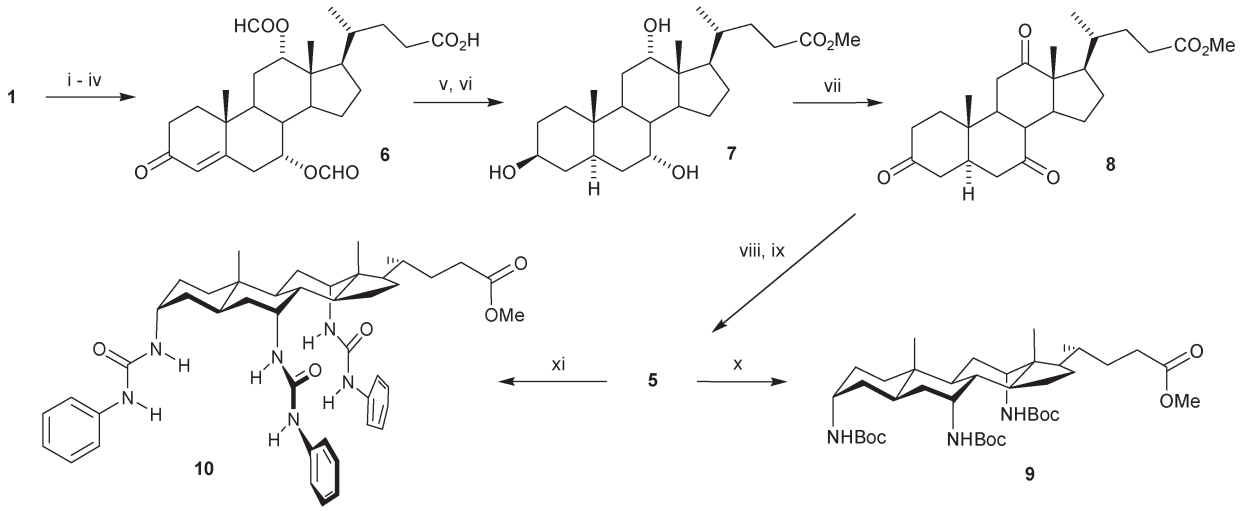
† Electronic supplementary information (ESI) available: Details of synthetic procedures and X-ray crystallography, including packing diagrams. See DOI: 10.1039/b602415g



Scheme 1 Synthesis of triamine **5** and derivatives from cholic acid **1**. *Reagents and conditions*: (i) HCO_2H, $HClO_3$ cat., Ac_2O; (ii) NaOH, acetone; (iii) *N*-bromosuccinimide, *t*-butanol; (iv) semicarbazide hydrochloride, $NaHCO_3$, *t*-butanol, then pyruvic acid, H_2O; (v) NaOH aq.; (vi) Li, NH_3, THF, *t*-butanol, then MeOH, H_2SO_4; (vii) $Ca(OCl)_2$, AcOH; (viii) $H_2NOH{\cdot}HCl$, NaOAc, MeOH; (ix) H_2, Pt cat., AcOH, then Zn, AcOH; (x) $(Boc)_2O$, THF, $NaHCO_3$ aq.; (xi) PhNCO, THF.

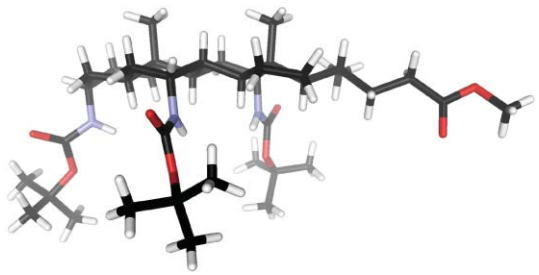


Fig. 1 The structure of **9** in the crystal.

To highlight the potential of **5** we considered its application in the field of anion recognition. We have previously shown that 5β analogues **4** can be used to prepare powerful electroneutral anion receptors, termed "cholapods".[1d,2] Conversion of the amino groups to ureas, sulfonamides *etc.* creates a variety of binding sites with convergent H-bond donors. Although these systems can be very effective, they possess one disadvantage. As shown in Fig. 2, rotation about the C3–N bond allows an H-bond acceptor atom X to approach donors attached to position 7. The resulting conformations are incapable of anion binding. In most cases the H-bonds are quite long and probably relatively weak, but they must lower affinities to some extent. No such problem occurs for analogues derived from **5**. We therefore prepared tris-urea **10** as the first example of an "allocholapod" anion receptor. **10** was available in a single step from **5** through treatment with phenyl isocyanate (Scheme 1). Binding constants to anions, as tetraethylammonium salts, were measured using the extraction protocol previously applied to the cholapods.[2b,10] Briefly, the procedure involves the partition of substrate $Et_4N^+X^-$ between water and chloroform in the presence of the receptor and the measurement of an extraction constant K_e. The binding constant is given by the formula $K_a = K_e/K_d$, where K_d is the distribution constant for partition of the substrate between the phases in the absence of receptor. The method is especially useful for powerful receptors in non-polar media, as there is essentially no upper limit to the binding constants which can be measured.

The results of the measurements on allocholapod receptor **10** are summarised in Table 1. Also shown are published data for 5β-analogue **11**.[2b,11] The switch from 5β to 5α causes a general increase in binding constants while affecting selectivity to some extent. Although not large, the effects may be attributed to the adjustment of the H-bond donor array and, in particular, the improved preorganisation resulting from the axial 3-substituent.

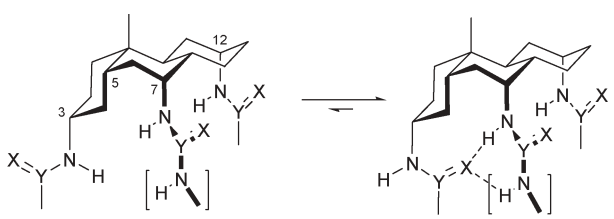
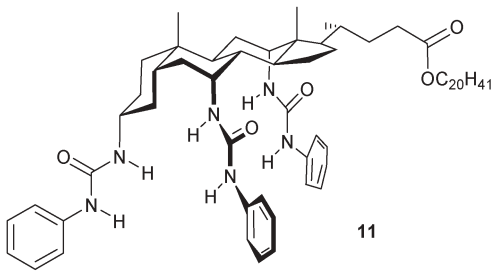


Fig. 2 Intramolecular hydrogen bonding in anion receptors derived from 5β triamines **4**. The groups in positions 3, 7 and 12 may be amides, sulfonamides, ureas or thioureas.

Table 1 Binding constants (K_a, M^{-1}) for $Et_4N^+X^-$ to tris-urea receptors **10** and **11** in water-saturated $CHCl_3$[a]

X^-	**10**	**11**[b]	Ratio **10/11**
AcO^-	7.5×10^8	1.4×10^8	5.4
$EtSO_3^-$	5.5×10^8	2.2×10^8	2.5
Cl^-	8.0×10^8	2.7×10^8	3.0
Br^-	3.1×10^8	1.4×10^8	2.2
NO_3^-	3.2×10^8	1.6×10^8	2.0
I^-	9.4×10^7	2.2×10^7	4.3
ClO_4^-	2.3×10^7	6.0×10^6	3.8

[a] Measured by extraction of the salts from water into $CHCl_3$. For details of the method see ref. 2*b*. [b] Data from ref. 2*b*.



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In conclusion, we have shown that cholic acid **1** can be converted into a triamino scaffold based on the all-*trans*, allocholanoyl framework. Stereochemistry is controlled at 4 centres to give a co-directed, triaxial arrangement of substituents. The system complements the 5β analogue **4**, possessing the same general features but with subtle geometrical and conformational differences. The scaffold has potential for anion recognition, and should have applications in other areas which require rigid polyfunctionalised platforms. Future work will focus on the differential protection of the three amino groups,[12] increasing the scope for library synthesis, receptor design and pharmaceutical discovery.

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9 Crystal data: **9**: $C_{41}H_{73}N_3O_9$, M = 752.02, hexagonal, a = 27.007(4), c = 11.473(2) Å, V = 7247(2) Å^3, T = 173(2) K, space group $P6_5$, Z = 6, μ = 0.072 mm^{-1}, R_{int} = 0.1962 (for 51131 measured reflections), R_1 = 0.0843 [for 2107 unique reflections with > 2$\sigma(I)$], wR_2 = 0.2260 (for all 3343 unique reflections). CCDC 299145. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b602415g Interestingly, the packing involves spiral arrays of steroid molecules surrounding asymmetrical channels. For diagrams, see Supplementary Information. Similar structures with channels up to 14 Å diameter have been observed for some 5β cholapods (see: A. L. Sisson, V. del Amo Sanchez, G. Magro, A. M. E. Griffin, S. Shah, J. P. H. Charmant and A. P. Davis, *Angew. Chem., Int. Ed.*, 2005, **44**, 6878). In the present case the channel diameter is smaller, at *ca.* 5 Å.

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11 Although **10** and **11** are different in 2 respects (configuration at C5, and ester group), it is the former which is significant. To confirm this point, the methyl ester analogue of **11**[5c] was tested against a more limited series of anions. The binding constants were the same as those for **11** to within experimental error. For further details see Supporting Information.

12 We have already differentiated between positions 3 and 7/12, through selective protection of the equatorial 3β-OH in intermediate **7**. Further transformations led to an analogue of **9** with the 3α-N protected as azide.