The synthesis of C_2-symmetric 1,4,7-triazacyclononane ligands derived from chiral aziridines

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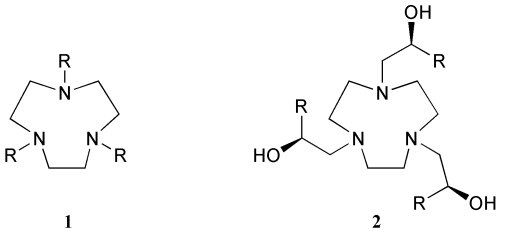
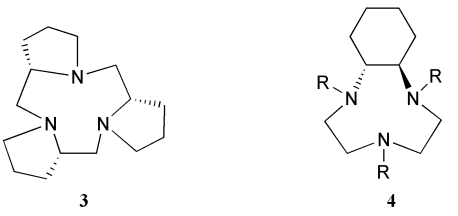
An efficient synthetic route for the synthesis of C_2-symmetric derivatives of 1,4,7-triazacyclononanes **14** from chiral pool amino acids has been developed. These investigations have shown that competitive formation of piperazines **7** occurs when inappropriate nitrogen protecting groups are employed. It is apparent that the formation of the piperazines occurs as a result of an intramolecular nucleophilic attack followed by a β-elimination. This appears to only be relevant for the formation of the [9]-N_3 ring, as the larger [12]-N_4 macrocycle, **11**, is formed *via* a Richman–Atkins cyclisation in the presence of the same benzylic protected nitrogen atom. The single crystal X-ray structures of piperazine **7a** and 1,4,7-triazacyclononanes **14a** both reveal that weak intermolecular C–H···O=S interactions occur in the solid state in these systems.

Introduction

Manganese complexes of a number of derivatives of 1,4,7-triazacyclononane or TACN, **1** (R = H), have been shown to be extremely potent oxidation catalysts. Arguably the most famous, and also notorious, example was the Accelerator™ catalyst marketed by Unilever in the early nineties as a low-temperature bleaching additive for washing powders.[1] Although excellent bleaching properties were observed, these were associated with unwanted fabric damage following prolonged washing cycles. Despite this negative outcome, the potential of this powerful oxidant was soon demonstrated in a synthetic context and examples of the use of manganese complexes, principally of **1** (R = Me), soon appeared. A wide range of substrates has subsequently been shown to be effectively oxidised, principally using the environmentally benign oxidant hydrogen peroxide, including benzylic alcohols,[2] sulfides,[3] phenols[4] and even hydrocarbons.[5] Potentially of greatest synthetic utility and interest are the reports of the efficient epoxidation, and most recently *cis*-dihydroxylation, of a range of alkenes.[6]

In view of this array of activity and the recent interest in efficient catalysts for the formation of enantiomerically pure epoxides, it is perhaps a little surprising that examples of chiral analogues of **1** are so limited. The first reports of chiral analogues of **1** appeared in patents,[7] with the first example of an application in asymmetric synthesis being reported by Bolm.[8] In this case chirality was incorporated into the ligand system through the alkylation of the secondary amine nitrogen atoms in **1** to generate the C_3-symmetric analogue **2** (R = Me or Pr^i). Complexes prepared *in situ* using manganese(II) acetate were shown to catalyse the asymmetric epoxidation of a range of olefins with hydrogen peroxide; the highest levels of asymmetric induction were observed for the benchmark *cis*-β-methylstyrene which led to the production of the 1*R*,2*R*-*trans*-epoxide with 55% *ee*. More recently Bolm has also reported the application of a second class of C_3-symmetric derivative of **1** in which the chirality was incorporated into the macrocyclic framework by reduction of a tricylic peptide derived from L-proline, **3**.[9] Although conversions and enantiomeric excesses were moderate the potential of these systems in catalysis was clearly demonstrated.





Our interest in this area has focussed on the preparation of C_2-symmetric analogues. Our initial investigations[10] centred on the application of the previously reported macrocyclic ligand **4**,[11] however, due to the difficulties associated with its synthesis and the general lack of easily accessible vicinal diamines, we decided to adopt an alternative approach utilising chiral pool amino acids. Although our initial investigations in this area have only just appeared,[12] a recent related account[13] prompts us to now report our other efforts in this area.†

Results and discussion

We have recently reported an extremely selective means of effecting the selective ring-opening of *N*-tosyl activated aziri-

† Note added in proof: a further related study appeared after submission of this manuscript: G. Argouarch, C. L. Gibson, G. Stones and D. C. Sherrington, *Tetrahedron Lett.*, 2002, **43**, 3795.

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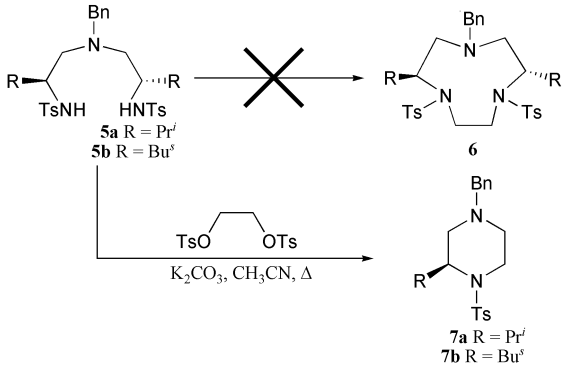
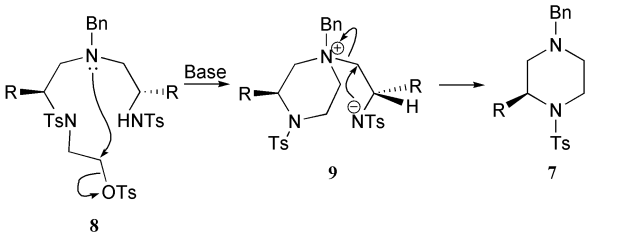


Scheme 1 The synthesis of piperazines **7**.



Scheme 2 Proposed mechanism for the formation of piperazines **7** *via* an intramolecular elimination reaction.

dines, to selectively yield single and double ring-opened materials.[12] The double ring-opened materials **5** were of particular interest to us as we expected that they could be used directly in the synthesis of new analogues of **1** using standard Richman–Atkins conditions,[14] Scheme 1. A particularly appealing feature of this synthetic route lay in the generation of the unsymmetrically substituted triazacyclononane **6** which might lead to novel binucleating ligands following the removal of the benzylic protecting group.[15] Unfortunately the reaction did not proceed as hoped under a range of standard cyclisation conditions and piperazines **7** were isolated. Piperazine formation is presumably thermodynamically driven by the creation of the six-membered ring, as has previously been observed in related polyamine systems.[16] We believe that this reaction proceeds as depicted in Scheme 2 *via* an intramolecular elimination of the *N*-tosylaziridine. It is noteworthy that in the related report,[13] formation of larger polyamine macrocycles could be effected in the presence of a *p*-methoxybenzene protected nitrogen atom, but that an amide protecting group was required when the 1,4,7-triazacyclononane ring system was synthesised.

We were able to obtain crystals of **7a** suitable for single crystal X-ray diffraction, Table 1. These crystals revealed that the piperazine ring adopts the expected chair-like conformation, which is slightly flattened by the almost planar sulfonamide nitrogen atom, Fig. 1; the sum of the angles about this atom being 358.3° [C(8)–N(1)–C(11) = 114.7(3)°, C(8)–N(1)–S(1) = 121.9(3)°, C(11)–N(1)–S(1) = 121.7(2)°]. The nitrogen sulfur bond length of S(1)–N(1) = 1.600(3) Å is slightly shorter than those observed in structurally related piperazines.[17] Finally the tetrahedral sulfur atom shows slight asymmetry in the sulfur oxygen bonds, S(1)–O(1) = 1.424(3) Å and S(1)–O(2) = 1.433(3) Å. In contrast to the nine other related structures which all exist as discrete monomers, the piperazine rings in **7a** are linked into polymeric arrays *via* interactions between C(9)–H and O(2) of the next molecule of 3.488(5) Å as shown in Fig. 1.

In view of this outcome we wondered whether such an intramolecular elimination reaction could be used as a direct route towards *C*-chiral macrocycles, **10**. We therefore investigated this possibility for **5a**, Scheme 3, in which an analogous intramolecular elimination reaction would lead to the *C*-chiral analogue, **10**. In this case however, the elimination reaction did not occur and only the 12-membered N_4-macrocycle **11** that would be expected to form *via* a classical Richman–Atkins cyclisation[14] could be isolated. This and the related report[13]

Table 1 Details of crystal structures and refinement for **7a** and **14a**

	7a	**14a**
Empirical formula	$C_{21}H_{28}N_2O_2S$	$C_{33}H_{45}N_3O_6S_3$
Formula weight	372.51	675.90
Temperature/K	293(2)	160(2)
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions/Å	$a = 8.180(5)$	$a = 11.261(2)$
	$b = 23.468(8)$	$b = 13.805(3)$
	$c = 10.149(4)$	$c = 21.546(4)$
Volume/Å^3	1948.4(16)	3349.5(11)
Z	4	4
$\rho_{calc.}$/mg m^{-3}	1.270	1.340
Absorption coefficient/mm^{-1}	0.184	0.270
$F(000)$	800	1440
Crystal size/mm	$0.4 \times 0.4 \times 0.2$	$0.20 \times 0.15 \times 0.10$
θ range/°	1.74 to 24.99	1.75 to 24.99
Index ranges	$-2 \leqslant h \leqslant 9$, $-2 \leqslant k \leqslant 27$, $-5 \leqslant l \leqslant 12$	$-2 \leqslant h \leqslant 13$, $-7 \leqslant k \leqslant 16$, $-10 \leqslant l \leqslant 25$
Reflections collected	2031	3415
Independent reflections	1977 [R(int) = 0.0053]	3319 [R(int) = 0.0047]
Completeness to $\theta = 24.99°$ (%)	99.9	99.9
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	1977/0/214	3319/1/413
Goodness-of-fit on F^2	1.106	1.037
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0384$, $wR_2 = 0.1116$	$R_1 = 0.0569$, $wR_2 = 0.1036$
R indices (all data)	$R_1 = 0.0506$, $wR_2 = 0.1288$	$R_1 = 0.1912$, $wR_2 = 0.1327$
Absolute structure parameter	−0.04(16)	0.18(19)
Largest diff. peak and hole/e Å^{-3}	0.337 and −0.391	0.481 and −0.440

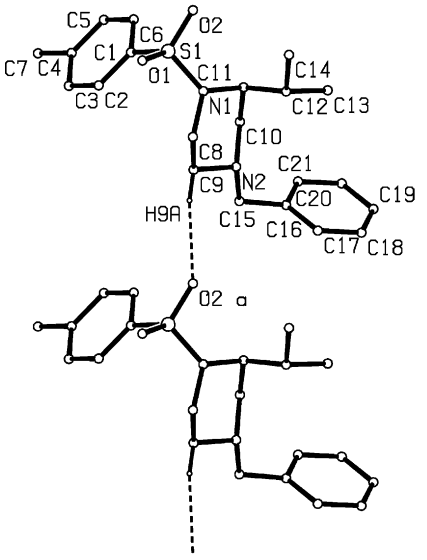


Fig. 1 Single crystal structure of **7a** showing the polymeric network with selected bond lengths (Å) and angles (°) [a = $-1+x$, y, z]: S(1)–O(1) 1.424(3), S(1)–O(2) 1.433(3), S(1)–N(1) 1.600(3), N(1)–C(8) 1.477(5), N(1)–C(11) 1.497(5), N(2)–C(9) 1.466(5), N(2)–C(10) 1.467(5), C(8)–C(9) 1.507(6), C(10)–C(11) 1.510(5); O(1)–S(1)–O(2) 120.18(19), O(1)–S(1)–N(1) 106.53(18), O(2)–S(1)–N(1) 107.01(17), O(1)–S(1)–C(1) 106.76(16), O(2)–S(1)–C(1) 106.75(17), N(1)–S(1)–C(1) 109.32(17), C(8)–N(1)–C(11) 114.7(3), C(8)–N(1)–S(1) 121.9(3); C(9)···O(2a) 3.488(3).

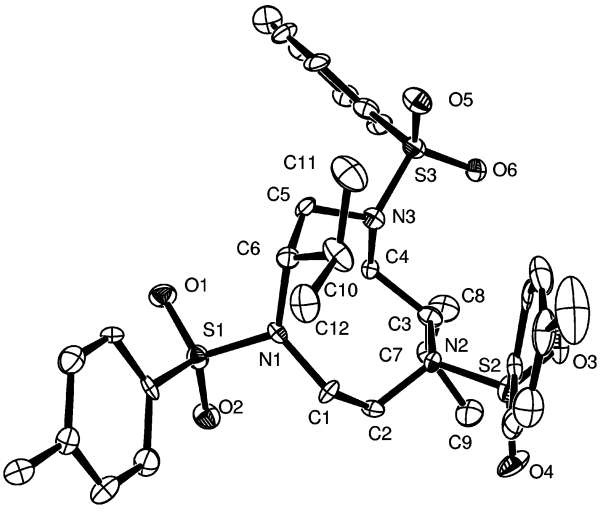
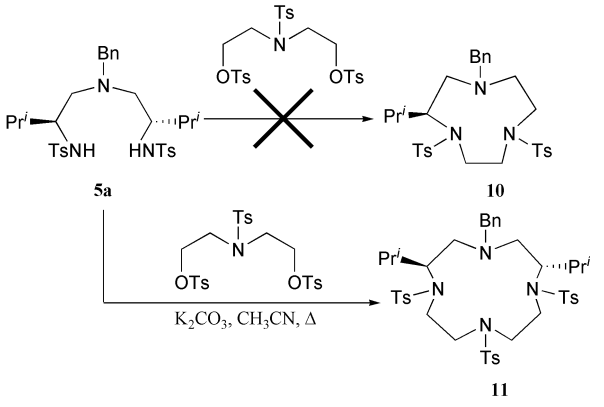


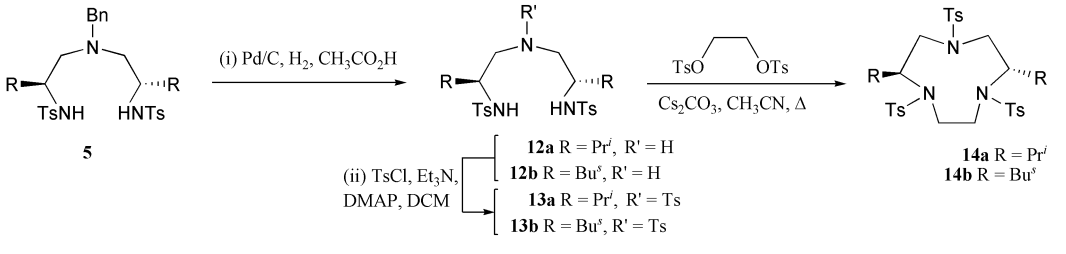
Fig. 2 The single crystal structure of **14a** with selected bond lengths (Å) and angles(°): S(1)–O(2) 1.436(6), S(1)–O(1) 1.438(6), S(1)–N(1) 1.621(7), S(2)–O(4) 1.438(7), S(2)–O(3) 1.439(6), S(2)–N(2) 1.633(7), S(3)–O(5) 1.438(7), S(3)–O(6) 1.438(6), S(3)–N(3) 1.649(7), N(1)–C(1) 1.473(10), N(1)–C(6) 1.514(10), N(2)–C(2) 1.481(10), N(2)–C(3) 1.481(10), N(3)–C(5) 1.482(10), N(3)–C(4) 1.485(10), C(1)–C(2) 1.550(12); C(1)–N(1)–C(6) 122.8(7), C(1)–N(1)–S(1) 115.5(6), C(6)–N(1)–S(1) 118.0(6), C(2)–N(2)–C(3) 118.0(7), C(2)–N(2)–S(2) 116.4(6), C(3)–N(2)–S(2) 119.6(6), C(5)–N(3)–C(4) 113.6(6), C(5)–N(3)–S(3) 114.7(5), C(4)–N(3)–S(3) 114.0(5); C(18)···O(2a) 3.2571.



Scheme 3 The synthesis of the [12]-N_4 C_2-symmetric ligand **11**.

strongly suggest that polyamine macrocycles, with the exception of 1,4,7-triazacyclononanes, are available *via* this methodology, but that an alternative strategy is required for the synthesis of the nine-membered triaza ring.

As a result of this finding we were faced with two choices. The first was to reinvestigate the ring opening of *N*-tosylaziridines with alternative less nucleophilic amines that might prevent intramoleculear attack as in **8**, Scheme 2, occurring. The second was to remove the benzylic protecting groups in **5** and to reprotect the nitrogen atoms with an alternative protecting group that suppressed the nitrogen nucleophilicity sufficiently to prevent intramolecular cyclisation occurring. We decided to investigate the latter approach and found that the benzylic protecting group could be readily removed in almost quantitative yield giving **12** as shown in Scheme 4. We elected to use the tosyl protecting group to protect the secondary nitrogen atoms in **12** as we were confident **13** would undergo the desired cyclisation reaction. This indeed proved to be the case and the new C_2-symmetric macrocycles **14** were prepared in good yield. Crystals of **14a** suitable for single crystal X-ray diffraction confirmed the structure and absolute stereochemistry of **14a**, Table 1 and Fig. 2. The structure reveals that the two sulfonamide groups adjacent to the stereogenic centres N(1) and N(2) are similar with comparable sulfur–nitrogen bond lengths [S(1)–N(1) = 1.621(7)Å and S(2)–N(2) = 1.633(7) Å] and relatively planar geometries; the sum of the angles about each nitrogen being 356.3° and 354.0°, Table 1. The third sulfonamide centre is slightly different with a slightly longer bond length between the sulfur and nitrogen atoms of 1.649(7) Å and a greater deviation from planarity; the sum of the angles about nitrogen is 342.3°. This is comparable with our observations in the related macrocyclic system **4** (R = Ts) in which the sulfonamide nitrogen atoms adjacent to the stereogenic centres remain essentially planar, whilst the third sulfonamide nitrogen deviates markedly from planarity.[10] In both cases we assume that



Scheme 4 The synthesis of the target C_2-symmetric azamacrocyclic ligands **14**.

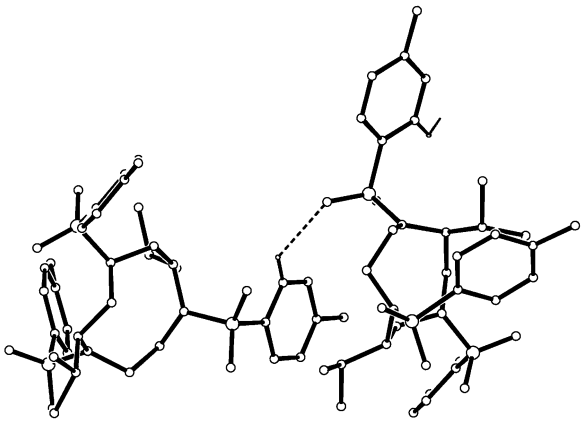


Fig. 3 The polymeric array in **14a**.

this is a steric effect resulting from an effort to reduce ring strain, the magnitude of which is greater in the fused bicyclic system **4**. As was observed for piperazine **7a**, a polymeric array exists in the solid state (Fig. 3). The monomer units are joined by long interactions between the sulfonamide oxygen atom O(2)a and the H(18) atom of a neighbouring sulfonamide group O(2)a···C(18) = 3.2571 Å. The interaction is clearly restricted to the solid state as none of the shielding effects in the ^{1}H NMR of **7a** that we have observed in related sulfonamide systems[10] are seen in this case.

Conclusion

We have developed a new synthetic route for the synthesis of C_2-symmetric macrocyclic 1,4,7-triazacyclononane ligands, **14**, derived from chiral pool amino acids. We are currently actively engaged in an investigation of their coordination chemistry and their application in asymmetric catalysis.

Experimental

General methods

All reagents were commercially available and were used without further purification, unless otherwise stated. CH_3CN was heated under reflux overnight with CaH_2 in an atmosphere of nitrogen and then distilled from CaH_2. CH_2Cl_2 was distilled from P_2O_5. Triethylamine was distilled from KOH pellets prior to use. Nitrogen for inert atmosphere use was purified by passing it through anhydrous manganese(II) oxide, 3Å molecular sieves and highly reduced chromium adsorbed onto a silica support. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (Merck). Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were obtained using a Carlo Erba 1106 elemental analyser. All ^{1}H-NMR and ^{13}C-NMR spectra were recorded as $CDCl_3$ solutions on a JEOL JNM-EX spectrometer at 270 MHz and at 67.9 MHz respectively unless otherwise stated. All spectra were referenced to residual $CHCl_3$ as the internal standard with J values given in Hertz. IR spectra were recorded on a Perkin-Elmer 1720X FT-IR spectrometer with a solid state ATR attachment. Fast atom bombardment (FAB) mass spectra were recorded on a VG Instruments ZAB-SE using xenon gas at 8 kV in a matrix of 3-nitrobenzyl alcohol (MNBA) and sodium iodide (FAB). Optical rotations were recorded on an Optical Activity Ltd AA1000 polarimeter using the sodium D line (589 nm) and are given in units of 10^{-1} deg dm^2 g^{-1}. All samples were homogeneous by TLC.

(*S*)-4-Benzyl-2-(1-methylethyl)-1-(4-methylbenzenesulfonyl)-piperazine 7a

Tertiary amine **5a** (3.00 g, 5.09 mmol), ethylene glycol 1,2-ditolyl-4-sulfonic acid ester (2.45 g, 6.62 mmol) and potassium carbonate (2.11 g, 15.27 mmol) were dissolved in acetonitrile (60 cm^3) and refluxed for 3 d. The resulting white solid was removed by filtration and washed with acetonitrile (60 cm^3). The solvent was removed from the combined filtrates and the resulting yellow semi-solid purified by column chromatography (eluents: petroleum spirits (bp 40–60 °C)–ethyl acetate, 3:1) to give the piperazine **7a** (1.13 g, 60%) as colourless crystals, mp 141–142 °C (from acetonitrile); $[\alpha]_D^{25}$ +32.6 (*c* 0.5 in $CHCl_3$); Found: C, 68.0; H, 7.5; N, 7.7. $C_{21}H_{28}N_2O_2S$ requires C, 67.7; H, 7.53; N, 7.68 %; ν_{max}/cm^{-1} 2966, 2361, 1596, 1454, 1319, 1305, 1235, 1156, 1092, 978, 921, 887, 814, 755, 745, 726, 677, 662, 599, 561, 543, 501, 449; δ_H 0.75 (3H, d, *J* 6.4, CH(C*H*$_3$)$_2$), 0.91 (3H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 1.66–1.78 (2H, m, C*H*(CH$_3$)$_2$ and piperazine ring-*H*), 2.32–2.40 (1H, m, piperazine ring-*H*), 2.42 (3H, s, Ar-C*H*$_3$), 2.49–2.54 (1H, m, piperazine ring-*H*), 2.69 (1H, d, *J* 11.9, piperazine ring-*H*), 3.16 (1H, d, *J* 13.1, Ar-C*H*$_2$-N), 3.18–3.43 (2H, complex m, piperazine ring-*H*), 3.36 (1H, d, *J* 13.1, Ar-C*H*$_2$-N), 3.67–3.74 (1H, m, piperazine ring-*H*), 7.18–7.28 (7H, m, Ar-*H*), 7.69 (2H, d, *J* 8.4, Ar-*H*); δ_C 19.9, 20.0, 21.6, 26.2, 41.6, 52.0, 52.4, 60.6, 63.0, 127.1, 127.2, 128.3, 128.9, 129.7, 138.1, 139.3, 142.9; *m*/*z* (FAB): 373 (54%, M + H), 217 (100, M − Ts) (Found: (M + H) 373.1958. $C_{21}H_{29}N_2O_2S$ requires 373.1950).

(*S*)-4-Benzyl-2-(1-methylpropyl)-1-(4-methylbenzenesulfonyl)-piperazine 7b

7b was prepared in an identical manner to **7a** and was isolated as a waxy solid (200 mg, 67%), mp = 59–62 °C (from ethanol); $[\alpha]_D^{25}$ +33.2 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 2966, 2964, 2362, 2238, 1596, 1451, 1377, 1340, 1326, 1275, 1149, 1116, 1095, 1015, 963, 917, 812, 751, 740, 702, 642, 598, 562, 552, 540; δ_H 0.70 (3H, d, *J* 6.7, C*H*$_3$-CH(CH)-CH$_2$), 0.87 (3H, t, *J* 7.3, CH$_2$-C*H*$_3$), 0.94–1.10 (1H, m, C*H*$_2$-CH$_3$), 1.59–1.76 (3H, m, piperazine ring-*H* and C*H*$_2$-CH$_3$), 2.01–2.18 (1H, m, CH$_3$-C*H*(CH)-CH$_2$), 2.42 (3H, s, Ar-C*H*$_3$), 2.47–2.52 (1H, m, piperazine ring-*H*), 2.69 (1H, d, *J* 11.9, piperazine ring-*H*), 3.15 (1H, d, *J* 13.0, Ar-C*H*$_2$-N), 3.19–3.29 (1H, m, piperazine ring-*H*), 3.35 (1H, d, *J* 13.0, Ar-C*H*$_2$-N), 3.41–3.56 (1H, m, piperazine ring-*H*), 3.66–3.72 (1H, m, piperazine ring-*H*), 7.19–7.28 (7H, m, Ar-*H*), 7.68 (2H, d, *J* 8.2, Ar-*H*); δ_C 11.4, 15.7, 21.6, 25.4, 32.4, 41.7, 51.9, 52.3, 59.2, 63.0, 127.1, 127.2, 128.3, 129.0, 129.7, 137.9, 139.3, 143.0; *m*/*z* (FAB): 387 (52%, M + H, 231) 231 (100%, M − Ts) (Found: (M + H) 387.2106. $C_{22}H_{30}N_2O_2S$ requires 387.2094).

(*S*,*S*)-4-Benzyl-2,6-bis(1-methylpropyl)-1,7,10-tris(4-methylbenzenesulfonyl)-1,4,7,10-tetraazacyclododecane 11

Tertiary amine **5a** (1.00 g, 1.71 mmol), *N*,*O*,*O*′-tris(4-methylbenzenesulfonyl)diethanolamine (1.26 g, 2.22 mmol) and caesium carbonate (1.67 g, 5.13 mmol) were dissolved in dry acetonitrile (50 cm^3) and refluxed for 6 d under N_2. The white solid was filtered off and washed with acetonitrile (50 cm^3). The filtrates were combined, the solvent was removed and the resulting product purified by column chromatography (eluents: petroleum spirits–ethyl acetate, 75:25) to give macrocycle **11** (463 mg, 34%) as colourless crystals, mp 108–110 °C; $[\alpha]_D^{25}$ +24.2 (*c* 0.5, $CHCl_3$); Found: C, 61.1; H, 6.7; N, 6.6. $C_{42}H_{56}N_4O_6S_3.H_2O$ requires: C, 61.0; H, 7.1; N, 6.8 %; ν_{max}/cm^{-1}: 2961, 2360, 2341, 1597, 1494, 1454, 1322, 1262, 1154, 1089, 1019, 942, 912, 890, 814, 722, 699, 661, 582, 571, 548, 515, 486, 461; δ_H 0.70 (6H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.82 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.82–1.91 (2H, m, C*H*(CH$_3$)$_2$), 2.39 (6H, s, Ar-C*H*$_3$), 2.42 (3H, s, Ar-C*H*$_3$), 2.94–2.98 (2H,

m, ring N-CH_n), 3.26–3.84 (14H, m, ring N-CH_n), 7.10–7.35 (11H, m, Ar-*H*) 7.60–7.65 (2H, m, Ar-*H*), 7.73 (4H, d, *J* 8.4, Ar-*H*); δ_C 20.0, 21.6, 21.8, 30.8, 46.1, 50.7, 57.5, 64.3, 66.2, 127.2, 127.8, 128.0, 128.2, 129.7, 129.8, 130.4, 134.3, 136.5, 137.8, 143.3, 144.0; *m*/*z* (FAB): 809 (23%, M + H), 653 (55, M − Ts) (Found: (M + H) 809.3466. $C_{42}H_{57}N_4O_6S_3$ requires 809.3448).

N-(1-{*N*′-[(2-{4-methylbenzenesulfonylamino}-3-methylbutyl]-aminoethyl}-2-methylpropyl-4-methylbenzenesulfonamide 12a

To a solution of **5a** (3.00 g, 5.13 mmol) in glacial acetic acid (60 cm^3) was added palladium dispersion on carbon (280 mg, 10% w/w) and the reaction was stirred under an atmosphere of hydrogen for 18 hours. The solid was removed by filtration and the solid washed with ethanol (60 cm^3) and ethyl acetate (60 cm^3). The organic phases were combined and the solvents removed under reduced pressure to yield a yellow oil. The oil was redissolved in CH_2Cl_2 and stirred with potassium hydroxide solution (60 cm^3, 1 M) for 30 min. The layers were seperated and the aqueous layer washed with CH_2Cl_2 (2×30 cm^3). The organic phases were combined, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield an off-white solid (2.48 g, 97.5%). All spectroscopic data were consistent with those previously reported.[18] In addition HRMS, found (M + H) 496.2311. $C_{24}H_{38}N_3O_4S_2$ requires 496.2304.

N-(1-{*N*′-[(2-{4-methylbenzenesulfonylamino}-3-methylpentyl]-aminoethyl}-2-methylbutyl-4-methylbenzenesulfonamide 12b

12b was prepared in an identical manner to **12a** to yield a yellow solid (4.84 g, 95%), mp 99–101 °C; $[\alpha]_D^{25}$ −2.2 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1}: 3291, 3168, 2360, 2338, 1596, 1457, 1419, 1326, 1156, 1092, 1076, 1017, 952, 856, 816, 700, 655, 571, 547, 496, 436; δ_H 0.70 (6H, d, *J* 6.9, CH_3-CH(CH)-CH_2), 0.77 (6H, t, *J* 7.3, CH_2-CH_3), 0.83–1.07 (2H, m, CH-CH(CH_2)-CH_3), 1.18–1.31 (2H, m, CH-CH(CH_2)-CH_3), 1.33–1.50 (2H, m, CH-C*H*(CH_2)-CH_3), 2.18 (2H, dd, *J* 12.6 and *J* 4.0, NH-CH_2-CH(CH)), 2.34 (2H, dd, *J* 12.9 and *J* 7.9, NH-CH_2-CH(CH)), 2.41 (6H, s, Ar-CH_3), 3.02–3.08 (2H, m, CH_2-C*H*(CH)-$NHSO_2$), 7.28 (4H, d, *J* 8.1, Ar-*H*), 7.75 (4H, d, *J* 8.1, Ar-*H*); δ_C 11.8, 14.4, 21.6, 25.7, 37.1, 48.2, 56.8, 127.2, 129.7, 138.1, 143.3; *m*/*z* (FAB): 524 (100%, M + H); (Found: M + H 524.2631. $C_{26}H_{42}N_3O_4S_2$ requires 524.2617).

N,*N*-Bis(2-[4-methylbenzenesulfonylamino]-3-methylbutyl)-4-methylbenzenesulfonamide 13a

p-Toluenesulfonyl chloride (462 mg, 2.42 mmol) and **12a** (1.00 g, 2.02 mmol) were dissolved in dry CH_2Cl_2 (20 cm^3) under nitrogen. Triethylamine (613 mg, 6.06 mmol) and DMAP (49 mg, 0.4 mmol) were added and the yellow solution stirred for 12 h. The solvent was removed under reduced pressure and the resulting yellow oil stirred with H_2O (20 cm^3) for 1 h. The water was decanted and the remaining yellow semi-solid recrystallised from EtOH to give **13a** (1.00 g, 76%) as colourless crystals, mp 205–207 °C (from ethanol), $[\alpha]_D^{25}$ −30.4 (*c* 0.5, $CHCl_3$); Found C, 57.8; H, 6.8; N, 6.5. $C_{31}H_{43}N_3O_6S_3$ requires C, 57.3; H 6.7; N, 6.5%; ν_{max}/cm^{-1} 3244, 2958, 1597, 1454, 1353, 1320, 1160, 1127, 1092, 1037, 1019, 964, 891, 813, 737, 665, 617, 587, 553, 513, 460; δ_H 0.55 (6H, d, *J* 7.2, CH(CH_3)$_2$), 0.71 (6H, d, *J* 6.9, CH(CH_3)$_2$), 1.65–1.85 (2H, m, C*H*(CH_3)$_2$), 2.39 (6H, s, Ar-CH_3), 2.43 (3H, s, Ar-CH_3), 2.87–3.02 (4H, m, SO_2N-CH_2-CH(CH)), 3.08–3.19 (2H, m, CH_2-C*H*(CH)-$NHSO_2$), 5.07 (2H, d, *J* 6.6, CH-N*H*-SO_2), 7.25 (4H, d, *J* 8.0, Ar-*H*), 7.33 (2H, d, *J* 8.0, Ar-*H*), 7.65 (2H, d, *J* 8.3, Ar-*H*), 7.72 (4H, d, *J* 8.3, Ar-*H*); δ_C 16.5, 17.9, 21.6, 28.4, 51.0, 57.1, 127.3, 127.6, 129.7, 130.1, 134.6, 137.5, 143.5, 144.3; *m*/*z* (FAB) 650 (13.5%, M + H); (Found: M + H 650.2373. $C_{31}H_{44}N_3O_6S_6$ requires 650.2392).

N,*N*-Bis(2-[4-methylbenzenesulfonylamino]-3-methylpentyl)-4-methylbenzenesulfonamide 13b

13b was prepared in an identical manner to **13a** to yield colourless crystals (5.11 g, 88%), mp 191–192 °C (from ethanol); $[\alpha]_D^{25}$ −10.4 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 3255, 2957, 2920, 2367, 1596, 1453, 1351, 1325, 1306, 1163, 1092, 1039, 1020, 967, 903, 812, 744, 688, 666, 603, 555, 548, 521; δ_H 0.59 (6H, d, *J* 7.2 CH_3-CH(CH)-CH_2), 0.77–0.94 (8H, m, CH_3-CH_2 and CH(CH)-CH_2-CH_3), 1.08–1.24 (2H, m, CH(CH)-CH_2-CH_3), 1.55–1.65 (2H, m, CH_3-C*H*(CH)-CH_2), 2.39 (6H, s, Ar-CH_3), 2.43 (3H, s, Ar-CH_3), 2.70 (2H, dd, *J* 14.8 and *J* 5.0, SO_2NH-CH_2-CH(CH)), 3.04 (2H, dd, *J* 14.6 and *J* 8.8, SO_2NH-CH_2-CH(CH)), 3.11–3.22 (2H, m, CH_2-C*H*(CH)-$NHSO_2$), 5.02 (2H, d, *J* 6.1, CH(CH)-N*H*-SO_2), 7.25 (4H, d, *J* 8.0, Ar-*H*), 7.35 (2H, d, *J* 8.2, Ar-*H*), 7.50–7.69 (6H, m, Ar-*H*); δ_C 12.2, 13.8, 21.6, 24.8, 36.1, 48.0, 55.5, 127.3, 127.5, 129.7, 130.3, 135.6, 137.7, 143.5, 144.4; *m*/*z* (FAB): 700 (16%, M + Na), 678 (52, M + H) (Found: M + H 678.2694. $C_{33}H_{48}N_3O_6S_3$ requires 678.2705)

(2*S*,6*S*)-2,6-Bis(1-methylethyl)-1,4,7-tris(4-methylbenzenesulfonyl)-1,4,7-triazacyclononane 14a

Tosylamide **13a** (4.50 g, 6.93 mmol), ethylene glycol 1,2-ditolyl-4-sulfonic acid ester (3.34 g, 9.01 mmol) and caesium carbonate (6.77 g, 20.79 mmol) were dissolved in dry acetonitrile (10 cm^3) and refluxed under nitrogen for 6 d. The resulting white solid was filtered off and washed with acetonitrile (10 cm^3). The solvent was removed from the combined filtrates and the resulting yellow semisolid was recrystallised from acetonitrile to yield macrocycle **14a** (3.00 g, 64%) as colourless crystals, mp 214–215 °C (from acetonitrile); $[\alpha]_D^{25}$ −7.4 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 2964, 2360, 1597, 1452, 1395, 1336, 1305, 1154, 1089, 1018, 972, 909, 843, 815, 730, 714, 697, 665, 649, 633, 574, 549; δ_H 0.35 (6H, br s, CH(CH_3)$_2$), 0.85 (6H, d, *J* 6.0, CH(CH_3)$_2$), 0.93–1.16 (2H, bm, C*H*(CH_3)$_2$), 2.38 (6H, s, Ar-CH_3), 2.45 (3H, s, Ar-CH_3), 3.04–3.29 (4H, m, ring-CH_n), 3.30–3.48 (2H, m, ring-CH_n), 3.53–3.88 (4H, m, ring-CH_n), 7.26 (4H, d, *J* 8.3, Ar-*H*), 7.35 (2H, d, *J* 8.3, Ar-*H*), 7.67–7.72 (6H, m, Ar-*H*); δ_C (Bruker AMX400, 100.6 MHz) 20.0, 20.4, 21.8, 28.2, 45.6, 51.7, 64.5, 127.2, 127.6, 128.1, 129.7, 129.8, 143.4, 143.9; *m*/*z*: 698 (52, M + Na), 676 (65, M + H), 520 (69%, M − Ts) (Found: M + H 676.2575. $C_{33}H_{46}N_3O_6S_3$ requires M + H 676.2549).

(2*S*,6*S*)-2,6-Bis(1-methylpropyl)-1,4,7-tris(toluene-4-sulfonyl)-1,4,7-triazacyclononane 14b

13b was prepared in identical manner to **13a** to give colourless crystals of **14b** (4.40 g, 53%), mp 95–97 °C (from acetonitrile); $[\alpha]_D^{25}$ +24.1 (*c* 0.5, $CHCl_3$); Found: C, 59.8; H, 7.0; N, 6.0. $C_{35}H_{49}N_3O_6S_3$ requires: C, 59.7; H, 7.0; N, 6.0%; ν_{max}/cm^{-1} 3203, 2963, 2931, 1596, 1453, 1381, 1340, 1303, 1112, 1151, 1112, 1088, 979, 962, 891, 855, 816, 736, 715, 696, 664, 649, 631, 574, 544; δ_H 0.55–0.64 (8H, m), 0.77–0.80 (8H, m), 0.91–1.06 (2H, m, CH_3-C*H*(CH)-CH_2), 2.39 (6H, s, Ar-CH_3), 2.44 (3H, s, Ar-CH_3), 3.19–3.72 (8H, m, ring-CH_n), 3.75–3.92 (2H, bm, ring-CH_n) 7.25 (4H, d, *J* 8.3, Ar-*H*), 7.34 (2H, d, *J* 8.0, Ar-*H*), 7.73–7.66 (6H, m, Ar-*H*); δ_C 11.6, 15.7, 21.6, 26.7, 35.8, 46.1, 48.7, 63.3, 127.5, 127.8, 129.8, 129.9, 137.7, 143.6, 143.7; *m*/*z* (FAB): 726 (32%, M + Na), 704 (39, M + H) (Found M + H 704.2850. $C_{35}H_{50}N_3O_6S_3$ requires 704.2862).

X-Ray crystallography

The intensity data were collected on a CAD-4 diffractometer using MoKα radiation (λ 0.71069 Å) with ω–2θ scans. The unit cell parameters were determined by least-squares refinement on diffractometer angles [(Piperazine **7a**) $10.22 \leqslant \theta \leqslant 12.41°$ and (Macrocycle **14a**) $8.23 \leqslant \theta \leqslant 12.78°$] for 25 automatically centred reflections.[19] All data were corrected for absorption by empirical methods (Ψ scan)[20] and for Lorentz-polarization effects by XCAD4.[21] The structures were solved by the heavy-atom method using the programs SHELXS-97[22] and DIRDIF-99[23] and refined anisotropically (non-hydrogen atoms) by full-matrix least-squares on F^2 using SHELXL-97.[22] The H atom positions were calculated geometrically and refined with a riding model. In the final stage of refinement data were correct for absorption by DIFABS.[24] The programs ORTEP-3,[25] PLATON[26] were used for drawing the molecules and WINGX[27] was used to prepare material for publication.

CCDC reference numbers 185531 (**14a**) and 185532 (**7a**).

See http://www.rsc.org/suppdata/nj/b2/b204818c/ for crystallographic data in CIF or other electronic format.

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