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The synthesis of unsymmetrically N-substituted chiral 1,4,7-triazacyclononanes†

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A number of chiral unsymmetrically N-substituted 1,4,7-triazacyclononane ligands have been prepared by modular methods. The key step in the synthesis centres on the macrocyclisation of three tertiary amide precursors under standard Richman–Atkins conditions which allows for subsequent N-functionalisation.

Introduction

There continues to be great interest in macrocyclic polyamines because of their rich and robust coordination chemistry,[1] resulting in many applications of their complexes as biomimetics, in medicine and in catalysis. In particular, those derived from 1,4,7-triazacyclononane (TACN), **1a** (Fig. 1) (*e.g.* its N-alkyl derivatives such as **1b**) constitute a privileged class of ligand for a variety of cations. Transition metal complexes of **1** have found application as sensors,[2] metalloenzyme biosite models (*e.g.* of manganese containing enzymes[3] and of dioxygen activation in iron[4] and copper enzymes[5]) as well as hydrolytic agents capable of the non-oxidative cleavage of a range of substrates, including activated esters,[6] RNA[7] and even DNA.[8] Arguably greatest interest has been generated by the activity of manganese complexes of **1b** in oxidative catalysis. This followed the initial disclosure by Hage *et al.*[9] that a range of manganese complexes of **1b**, including the remarkable complex **2** first reported by Wieghardt *et al.*,[10] were potent low-temperature bleaching catalysts for domestic laundry applications. Subsequent reports detailing the application of manganese complexes in the catalytic oxidation of alcohols,[11] sulfides,[12] alkanes[13] and alkenes[14] have appeared, although it is alkene epoxidation; the first reports of which were also presented in the seminal study of Hage *et al.*,[9] that has attracted greatest interest. Given this interest, and the continued requirement for a generic catalytic asymmetric epoxidation system, it is somewhat surprising that examples of applications of enantiomerically pure analogues of 1,4,7-triazacyclononanes in the epoxidation of alkenes are limited to reports from Beller *et al.*,[15] Bolm *et al.*,[16] and Gibson and co-workers.[17] However, the apparently simple macrocyclic structures, like **3**–**5**, belie the underlying synthetic challenge, as recently noted by Kopac and Hall[18] as well as Gibson and co-workers,[17b] and there remain very few examples of chiral analogues of **1** in which the stereochemistry is included within the carbon skeleton of the macrocyclic ring.[19]

We,[20] along with others,[17,21,22] are currently engaged in a programme developing efficient routes to 1,4,7-triazacyclononane ligands bearing two stereocentres (C-2,6) derived from chiral pool amino acids, like **5a**, with a view to applying them in asymmetric catalysis. Our investigations have followed broadly similar lines to those of Kim *et al.*[21] as well as Gibson and co-workers,[17,22] in contrast to these studies, however, a principal goal for us has been to develop convenient routes towards unsymmetrically N-substituted enantiomerically pure ligand systems like **5b** ($R^1 \neq R^2$). We believe that such frameworks will be of interest in catalysis because of the efficacy of binuclear metal complexes in certain catalytic applications[7a] and also the uncertainty surrounding the active catalytic species in the manganese oxidation systems.[9] Herein we present the first example of a concise route towards a number of such ligands.

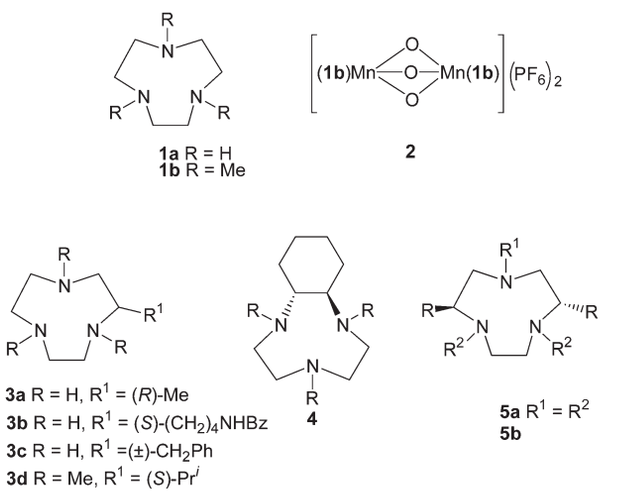

Fig. 1

Results and discussion

Unfortunately the conventional synthetic routes that are used to prepare unsymmetrically N-substituted derivatives of **1**,[23] such as statistical alkylation of **1** or the selective derivitisation of its orthoamide,[24] are not applicable to chiral analogues, as complex mixtures of products would result. It is therefore necessary to incorporate the desymmeterisation of the N-substituents prior to (route A), or during (route B), the macrocyclisation step (Scheme 1).

We have previously successfully adopted the latter approach in the direct synthesis of unsymmetrically N-substituted analogues of **1** (from **8**: R = H, R^2 = Ts, R^1 = Bn)[23] but subsequently found it impossible to apply this procedure to the synthesis of unsymmetrically N-substituted analogues of **4**.[19j] Unfortunately

† Electronic supplementary information (ESI) available: Molecular modelling methodology. Figs. S1–S4: Lowest energy conformation calculated for the protonated form of **6b**, **6b**·HOAc, the protonated form of **6a** and **6a**·HOAc. Figs. S5 and S6: Charge distribution calculated for the protonated forms of **6a** and **6b**. See http://www.rsc.org/suppdata/ob/b4/b409259g/

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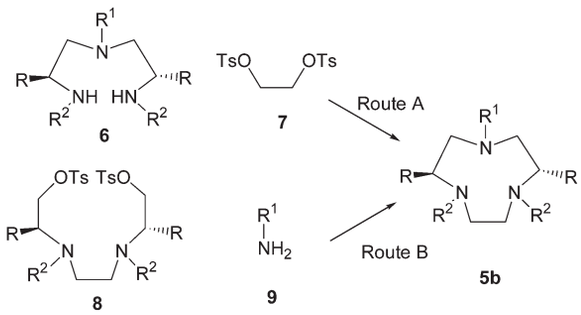
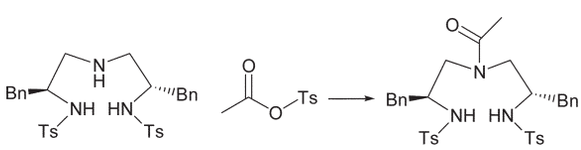


Scheme 1

both ourselves[20] and Gibson and co-workers,[17a] have previously demonstrated that for the former approach (route A), the presence of the synthetically convenient benzylic tertiary amine in **6** (R^1 = Bn, R^2 = Ts) is not compatible with the formation of the desired nine-membered macrocyclic ring **5b** (R^1 = Bn, R^2 = Ts). The approach that we both adopted towards the first-generation macrocycles was thus to reveal the secondary amines **6** (R^1 = H, R^2 = Ts) by catalytic hydrogenation and then to re-protect them as their sulfonamides **6** (R^1 = R^2 = Ts) which then underwent facile macrocyclisation under standard Richman–Atkins conditions. Whilst Gibson and co-workers have subsequently moved away from this approach due to solubility issues during the debenzylations,[22] we have continued to use this method and, in one case, were intrigued by the regular isolation of **11a** under these reaction conditions for some time (Scheme 2). We assumed that **11a** had formed as a result of the *in situ* reaction of the secondary amine **6a** with anhydride **10**, following reaction of TsCl with a stoichiometric quantity of the acetate anion, and were able to support this postulate by a control experiment on the free amine **6a** which also yielded amide **11a** (see Experimental section).



Scheme 2

This was rather puzzling, as the standard work-up used in all hydrogenation reactions in this series involved neutralisation with KOH to liberate the secondary amine; moreover, we never observed this phenomenon in the other cases (**6b**: R = Pr^i, R^1 = H, R^2 = Ts; **6c**: R = Bu^s, R^1 = H, R^2 = Ts). We thus postulated that **6a** formed a particularly stable ammonium salt in the presence of acetic acid as a result of a major conformational change predicted by molecular modelling (see also ESI†).

Our attempts to substantiate this by NMR titration proved fruitless, although they did result in our isolation of single crystals of free amine **6b** whose structure appeared consistent with the modelling (Fig. 2). A subsequent reinvestigation of the procedure revealed nothing untoward as free amine **6a** could be routinely isolated. Nonetheless this proved to be a fortuitous result as we were aware that benzamides had previously been employed by Bulkowski and co-workers[25] and Parker and co-workers[19e,26] in the synthesis of selectively N-functionalised polyamine macrocyclic ligands under standard Richman–Atkins conditions, including derivatives of **1**; furthermore, the selective removal of the benzamide group to generate unsymmetrically N-substituted macrocycles was demonstrated. We viewed the procedure of Parker and co-workers,[19e,26] in which detosylation could be accomplished using concentrated sulfuric acid whilst leaving the benzamide intact, as a particularly appealing strategy and speculated whether this would be applicable to acetamide **11a**, as this would provide a direct route towards our target generic unsymmetrically N-substituted ligand **5b**. We were

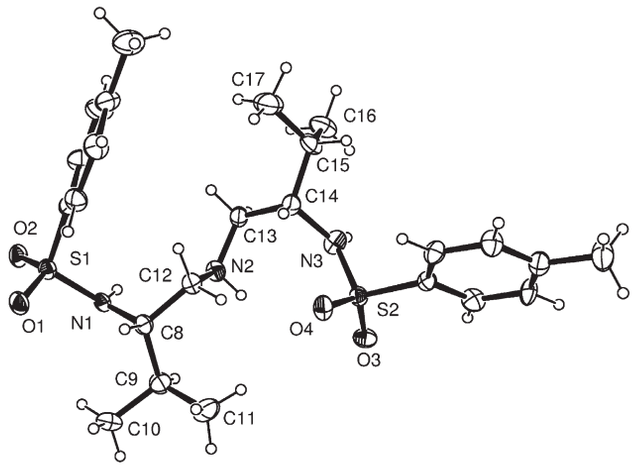


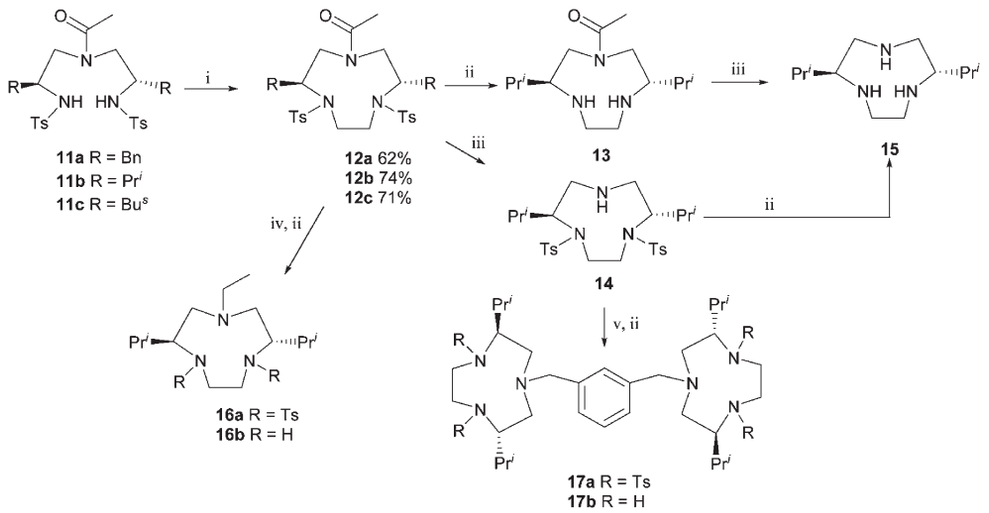
Fig. 2 ORTEP plot of the single crystal X-ray structure of **6b** with 50% probability ellipsoids.

delighted to find that **11a** underwent macrocyclisation cleanly under conventional Richman–Atkins conditions to yield **12a** (Scheme 3).

As a result of this successful outcome we were able to develop this procedure (now using acetic anhydride to prepare acetamides **11**, see Experimental section) towards the synthesis of other related azamacrocyclic precursors **12**, the structure of **12b** being corroborated by single crystal X-ray diffraction (Fig. 3).

The single-crystal X-ray structure of **12b** is comparable to other closely related structures that have been recently reported.[17b,19j,20] The triazamacrocyclic ring adopts a chair-boat-like conformation with the sulfonamide groups pseudo-equatorial, situated on the opposite face of the ring to the isopropyl groups adjacent to them. The two sulfonamide groups, N(1) and N(2), are similar with comparable nitrogen–sulfur bond lengths (S(1)–N(1) = 1.6272(18) Å, S(2)–N(2) = 1.6292(18) Å). Although both sulfonamide nitrogen atoms deviate from planarity, N(1) 0.0940 and N(2) −0.0556, this deviation is smaller than that observed by Gibson and co-workers in the related (2*S*)-2-isopropyl-1,4,7-tris[(4-methylphenyl)sulfonyl]-1,4,7-triazacyclononane.[17b] In contrast the acetamide group lies parallel to the ring system, with oxygen O(5), nitrogen N(3) and carbon C(24) along with the adjacent carbon atoms C(16), C(17) and C(25) forming a plane (the distances of these atoms from a calculated plane of least squares are: C(16) −0.0135(21); C(17) −0.0766(23); C(24) 0.0066(23); C(25) −0.0652(27); N(3) 0.0766(19) and O(5) 0.0079(17)). The single-crystal X-ray structure also reveals significant differences in the environments of the Pr^i side chains. Whilst the Pr^i group attached to C(18) is situated underneath the π-system of the sulfonamide group, that attached to C(15) is considerably further away from the π-system of the other sulfonamide group. The conformation observed in the crystal structure accounts for the loss of C_2-symmetry observed in the ^{13}C and ^1H NMR spectra, particularly the differences observed for the Pr^i signals, which appear to indicate that the solid and solution state structures of **12b** are the same.

With extra confidence in the structural integrity of **12b** we embarked upon the application of Parker's conditions for the selective removal of the sulfonamide groups. To our delight this could be effected cleanly and in high yield using concentrated sulfuric acid to yield unsymmetrically N-substituted macrocycle **13**. Similarly an ethanolic solution of hydrochloric acid led to the facile removal of the acetamide group to furnish macrocycle **14**;[21] we believe this route to provide a superior synthetic procedure as it provides greater synthetic flexibility in protecting group chemistry allowing selective removal of either group. Subsequent removal of the remaining protecting groups in **13** and **14** could then be readily achieved, using the appropriate conditions (see Scheme 3) to yield **15**,[21,22] although we have



Scheme 3 *Reagents and conditions*: i, **7**, Cs_2CO_3, CH_3CN, Δ; ii, H_2SO_4 (conc.), Δ; iii, EtOH, HCl, Δ, 2 d.; iv, $LiAlH_4$, THF, Δ; v, 1,3-bis(bromomethyl)benzene, Cs_2CO_3, CH_3CN, Δ, 3 d.

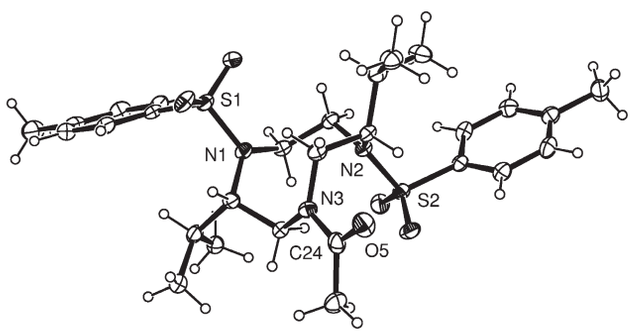


Fig. 3 ORTEP plot of the single-crystal X-ray structure of **12b** with 50% probability displacement ellipsoids.

found that the yield and purity of **15** to be superior when the acetamide is removed first *i.e. via* **14**.

We have also been able to develop this synthetic strategy further to provide reliable routes towards new ligands of this type. Firstly we were readily able to effect the reduction of the tertiary amide **12b** using $LiAlH_4$ to yield the ethyl substituted macrocyclic tertiary amine **16a**. Although the selective N-alkylation of **1** is known, the reported methods are not readily applicable to these chiral analogues. We therefore believe that this approach will prove particularly useful in the development of active catalysts, as it provides an expedient means for steric and electronic fine-tuning of ligand frameworks to be undertaken through the incorporation of alternative tertiary amides prior to the macrocyclisation step. We have also been able to use the unsymmetrically N-substituted intermediate **14** to produce the novel binucleating ligand **17b**, albeit in low yield. Similarly achiral binucleating ligands like **17** derived from **1** are well known, and of considerable current interest, but the synthetic routes towards them are again inappropriate to the preparation of chiral analogues.[27]

In summary, we have developed an efficient and modular synthetic route towards unsymmetrically N-substituted chiral 1,4,7-triazacyclononane ligands. In addition this route allows us to access potentially important binucleating ligand structures like **17b**. To the best of our knowledge this represents the first report of ligand systems like **12**, **13**, **16** and **17**.

Experimental

General remarks

All reagents were purchased from either Aldrich, Lancaster or Avocado and were used without further purification unless otherwise stated. Starting materials **6** were prepared according to the reported procedures.[28] Solvents that were required to be anhydrous were dried as follows: Acetonitrile was refluxed for 5 h with calcium hydride in an atmosphere of nitrogen and then distilled from calcium hydride. THF was distilled from sodium and benzophenone ketyl in an atmosphere of nitrogen. Nitrogen for inert atmosphere use was purified by passing it through anhydrous manganese(II) oxide, 3 Å 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. Optical rotations were determined using an Optical Activity LTD, AA-1000 polarimeter and concentrations are reported in g/100 cm^3. Elemental analyses were obtained using a Carlo Erba 1106 elemental analyser. ^1H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions, unless otherwise stated, on a JEOL JNM-EX270 spectrometer at 270 and at 67.9 MHz, respectively, and were referenced to residual chloroform as the internal standard; *J* values are given in Hertz. IR spectra were recorded on a Perkin-Elmer 1720X FT-IR spectrometer with a solid-state ATR attachment, with the exception of **16a** and **16b** which were recorded as dichloromethane solutions using KBr discs on a Shimadzu FTIR 8300 spectrometer. Mass spectra were either 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) (University of London Research Instruments Service, School of Pharmacy, University of London) or a Waters ZQ4000 or a MAT 900XLT (ESI) (EPSRC National Mass Spectrometry Service Centre, Chemistry Department, University of Wales, Swansea).

Tertiary amides **11a**–**c** were all prepared in an identical manner as exemplified by the synthesis of **11b**.

Synthesis of (2*S*,6*S*)-4-acetyl-1,7-di-*p*-toluenesulfonyl-2,6-dibenzyl-1,4,7-triazaheptane 11a

Amide **11a** was initially isolated due to the adventitious formation of anhydride **10** *in situ.* To support this postulate, amide **11a** was prepared as outlined below; however, it can be routinely prepared on a large scale in the same manner as that detailed for **11b**.

Glacial acetic acid (0.134 g, 2.24 mmol) and (2*S*,6*S*)-1,7-di-*p*-toluenesulfonyl-2,6-dibenzyl-1,4,7-triazaheptane, **6a** (1.02 g, 1.72 mmol) were dissolved in CH_2Cl_2 (9 cm^3). DMAP (0.042 g, 0.344 mmol), triethylamine (0.520 g, 5.15 mmol) and *p*-toluenesulfonyl chloride (0.390 g, 2.05 mmol) were added and the reaction mixture was stirred under nitrogen for 18 h. The solvent was removed under reduced pressure and the remaining slightly yellow oil was stirred with water (9 cm^3) for 30 min. The water was decanted off and the remaining off-white solid was recrystallised from ethanol to yield **11a** (750 mg, 69%) as colourless crystals,

mp 198–200 °C; $[\alpha]_D^{25}$ +2.4 (*c* 0.5, $CHCl_3$). Found C, 64.6; H, 6.3; N, 6.6. $C_{34}H_{39}N_3O_5S_2$ requires C, 64.4; H 6.2; N, 6.5%; $\tilde{\nu}_{max}$/cm^{-1} 3259, 2915, 1606, 1493, 1446, 1416, 1314, 1257, 1150, 1096, 807, 743, 695; δ_H 1.81 (3H, s, CH_3CON), 2.30 (1H, dd, *J* 13.9 and 7.3, ArCH_2CH), 2.37 (6H, s, ArCH_3), 2.52 (1H, dd, *J* 13.9 and 6.3, ArCH_2CH), 2.62 (1H, dd, *J* 13.3 and 7.6, ArCH_2CH), 2.79–2.85 (3H, m, ArCH_2CH and NCH_2CH(CH$_2$)), 3.10–3.31 (2H, m, NCH_2CH(CH$_2$) and CH$_2$CH(CH$_2$)N), 3.45–3.66 (2H, m, NCH_2CH(CH$_2$) and CH$_2$CH(CH$_2$)N), 4.82 (1H, d, *J* 7.2, CH(CH$_2$)NHSO$_2$), 5.60 (1H, d, *J* 6.1, CH(CH$_2$)NHSO$_2$), 6.74–6.77 (2H, m, Ar-*H*), 7.01–7.24 (12H, m, Ar-*H*), 7.37 (2H, d, *J* 8.3, Ar-*H*), 7.55 (2H, d, *J* 8.3, Ar-*H*); δ_C 21.6, 39.2, 40.8, 48.8, 52.4, 54.0, 54.5, 126.7, 126.8, 126.9, 128.6, 128.9, 129.3, 129.7, 135.9, 137.0, 137.2, 137.9, 143.1, 143.4, 173.0; *m*/*z* (FAB): 656 (31%, MNa$^+$), 634 (73, MH$^+$), 592 (66); (HRMS Found: (MH$^+$) 634.2430. $C_{34}H_{40}N_3O_5S_2$ requires 634.2409).

Synthesis of (2*S*,6*S*)-4-acetyl-1,7-di-*p*-toluenesulfonyl-2,6-di(1-methylethyl)-1,4,7-triazaheptane 11b

Acetic anhydride (0.65 g, 6.32 mmol) was added to (2*S*,6*S*)-1,5-di-*p*-toluenesulfonyl-2,6-di(methylethyl)-1,4,7-triazaheptane **6b** (2.85 g, 5.75 mmol) and the resultant solution heated at reflux for 4 h. The dark red–brown solid was then recrystallised from hot methanol to yield **11b** (2.40 g, 78%) as a white crystalline solid, mp 176–178 °C; $[\alpha]_D^{25}$ −27.6 (*c* 0.5, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} 3247, 2959, 1453, 1417, 1320, 1288, 1159, 1092, 812; δ_H 0.69 (3H, d, *J* 6.9, (CH_3)$_2$CH), 0.73–0.81 (9H, m, (CH_3)$_2$CH), 1.61–1.82 (2H, m, (CH$_3$)$_2$CH), 1.88 (3H, s, CH_3CON), 2.40 (6H, s, ArCH_3), 2.57 (1H, dd, *J* 14.0 and 2.9, NCH_2CH(CH)), 2.91 (1H, dd, *J* 15.1 and 6.6, NCH_2CH(CH)), 3.05 (1H, dd, *J* 15.1 and 7.7, NCH_2CH(CH)) 3.13–3.22 (2H, m, CH$_2$CH(CH)NHSO$_2$), 3.50–3.60 (1H, m, NCH_2CH(CH)), 4.68 (1H, d, *J* 9.1, CH(CH)NHSO$_2$), 5.43 (1H, d, *J* 6.9, CH(CH)NHSO$_2$), 7.26 (2H, d, *J* 8.0, Ar-*H*), 7.28 (2H, d, *J* 8.0, Ar-*H*), 7.67 (2H, d, J 8.2, Ar-*H*) 7.68 (2H, d, J 8.2, Ar-*H*); δ_C 16.8, 17.6, 18.4, 19.0, 21.6, 45.6, 50.1, 57.3, 58.0, 127.0, 129.6, 129.9, 137.6, 138.6, 143.2, 143.8, 173.1; *m*/*z* (FAB): 560 (44%, MNa$^+$), 538 (100, MH$^+$), 496 (69), 367 (42); (HRMS Found: (MH$^+$) 538.2395. $C_{22}H_{40}N_3O_5S_2$ requires 538.2409).

Synthesis of (2*S*,6*S*)-4-acetyl-1,7-di-*p*-toluenesulfonyl-2,6-di(1-methylpropyl)-1,4,7-triazaheptane 11c

Amide **11c** was prepared from (2*S*,6*S*)-1,7-di-*p*-toluenesulfonyl-2,6-di(1-methylpropyl)-1,4,7-triazaheptane **6c** in an identical manner to **11b** and was isolated as colourless crystals (6.76 g, 70%), mp 182–184 °C (from ethanol); $[\alpha]_D^{25}$ +12.4 (*c* 0.5, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} 3297, 2967, 2885, 1614, 1441, 1417, 1324, 1288, 1158, 1092, 809; δ_H 0.69 (3H, d, *J* 6.9, CH_3CH(CH$_2$)), 0.76–0.85 (9H, m, CH_3CH(CH$_2$) and CH_3CH$_2$CH(CH)), 0.92–1.05 (2H, m, CH$_3$CH_2CH(CH)), 1.17–1.24 (2H, m, CH$_3$CH_2CH(CH)), 1.26–1.36 (1H, m, CH$_2$CH(CH)), 1.44–1.53 (1H, m, CH$_2$CH(CH)), 1.87 (3H, s, CH_3CON), 2.39 (6H, s, ArCH_3), 2.39–2.45 (1H, m, NCH_2CH(CH)), 2.75 (1H, dd, *J* 15.3 and 4.8, NCH_2CH(CH)), 2.94 (1H, dd, *J* 15.4 and 9.4, NCH_2CH(CH)), 3.19–3.32 (2H, m, CH$_2$CH(CH)NH), 3.66–3.73 (1H, m, NCH_2CH(CH)), 5.51 (1H, d, *J* 8.8, CH(CH)NHSO$_2$), 5.76 (1H, m, *J* 6.6, CH(CH)NHSO$_2$), 7.26 (2H, d, *J* 8.3, Ar-*H*), 7.26 (2H, d, *J* 8.3, Ar-*H*), 7.66 (2H, d, *J* 8.3, Ar-*H*), 7.67 (2H, d, *J* 8.3, Ar-*H*); δ_C 12.0, 12.1, 13.8, 21.6, 25.0, 26.1, 37.4, 38.9, 44.4, 48.6, 56.3, 56.5, 129.6, 127.0, 129.6, 129.8, 137.9, 138.4, 143.2, 143.6, 173.0; *m*/*z* (FAB): 588 (48%, MNa$^+$), 566 (100, MH$^+$), 524 (73), 395 (51), 283 (55); (HRMS Found: (MH$^+$) 566.2745. $C_{28}H_{44}N_3O_5S_2$ requires 566.2722).

Macrocycles **13a**–**c** were prepared in an identical manner which is exemplified by the synthesis of **12b**.

Synthesis of (2*S*,6*S*)-4-acetyl-2,6-diphenyl-1,7-di-*p*-toluenesulfonyl-1,4,7-triazacyclononane 12a

Macrocycle **12a** was prepared in an identical manner to **12b** from **11a** to yield colourless crystals (8.37 g, 62%), mp 125–126 °C (from acetonitrile); $[\alpha]_D^{25}$ −41.2 (*c* 0.5, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} 2927, 1647, 1597, 1494, 1450, 1420, 1333, 1286, 1152, 1088, 1033, 1011, 955, 910, 861, 815, 730, 713, 695, 668, 654, 602, 543, 521, 493; δ_H 1.98 (3H, s, NCOCH_3), 2.18–2.50 (4H, m, ArCH_2CH), 2.39 (3H, s, ArCH_3), 2.42 (3H, s, ArCH_3), 3.41–3.93 (6H, m, tacn-*H*), 4.07–4.16 (1H, m, tacn-*H*), 4.19–4.48 (3H, m, tacn-*H*), 6.94–6.98 (2H, m, Ar-*H*), 7.07–7.35 (12H, m, Ar-*H*), 7.64 (2H, d, *J* 8.3, Ar-*H*), 7.79 (2H, d, *J* 8.3, Ar-*H*), δ_C 21.6, 21.8, 36.3, 36.6, 45.2, 46.2, 46.4, 48.3, 58.1, 59.7, 126.6, 127.1, 127.2, 127.2, 128.6, 128.9, 129.0, 130.0, 130.2, 136.9, 143.8, 144.3, 171.5; *m*/*z* (FAB): 682 (12%, MNa$^+$), 660 (100%, MH$^+$), 568 (25%, M − (CH$_3$Ar)), 504 (13%, M − Ts), 463 (17%, M − (Ts and CH$_2$CO)); (HRMS Found: (MH$^+$) 660.2540. $C_{36}H_{42}N_3O_5S_2$ requires 660.2566).

Synthesis of (2*S*,6*S*)-4-acetyl-2,6-di(1-methylethyl)-1,7-di-*p*-toluenesulfonyl-1,4,7-triazacyclononane 12b

Amide **11b** (5.00 g, 9.30 mmol), **7**[25] (4.48 g, 12.09 mmol) and caesium carbonate (9.09 g, 27.90 mmol) were dissolved in dry acetonitrile (100 cm^3) and heated at reflux under nitrogen for 6 d. The resulting white solid was filtered off and washed with acetonitrile (100 cm^3). The solvent was removed from the combined filtrates and the resulting yellow semi-solid was recrystallised from acetonitrile to yield macrocycle **12b** (3.86 g, 74%) as colourless crystals, mp 173–175 °C (from acetonitrile); $[\alpha]_D^{25}$ +147.8 (*c* 0.5, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} 2965, 1650, 1434, 1419, 1386, 1335, 1284, 1144, 1089, 814, 714; δ_H 0.24 (3H, d, *J* 6.7, (CH_3)$_2$CH), 0.64 (3H, d, *J* 6.9, (CH_3)$_2$CH), 0.79–0.83 (6H, m, (CH_3)$_2$CH), 1.41–1.49 (1H, m, (CH$_3$)$_2$CH), 1.72–1.79 (1H, m, (CH$_3$)$_2$CH), 2.18 (3H, s, CH_3CO), 2.40 (3H, s, ArCH_3), 2.41 (3H, s, ArCH_3), 3.26 (1H, dd, *J* 15.1 and 10.6, tacn-*H*), 3.41–3.97 (8H, m, tacn-*H*), 4.42 (1H, dd, J 15.1 and 2.7, tacn-*H*) 7.25–7.30 (4H, m, Ar-*H*), 7.65–7.71 (4H, m, Ar-*H*); δ_C 18.3, 19.3, 20.3, 20.8, 21.6, 22.5, 29.7, 30.7, 42.2, 45.3, 46.4, 46.9, 62.3, 63.1, 127.3, 127.4, 129.7, 129.8, 137.8, 138.0, 143.6, 143.8, 171.4; *m*/*z* (FAB): 564 (100%, MH$^+$), 522 (41), 408 (51), 366 (20); (HRMS Found: (MH$^+$) 564.2588. $C_{28}H_{42}N_3O_5S_2$ requires 564.2566).

Synthesis of (2*S*,6*S*)-4-acetyl-2,6-di(1-methylpropyl)-1,7-di-*p*-toluenesulfonyl-1,4,7-triazacyclononane 12c

Macrocycle **12c** was prepared from **11c** in an identical manner to **12b** to yield colourless crystals (2.62 g, 71%), mp 198–200 °C (from acetonitrile); $[\alpha]_D^{25}$ +152.0 (*c* 0.5, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} 1648, 1449, 1333, 1220, 1180, 1034, 714; δ_H 0.27–0.42 (1H, m, CH(CH$_3$)CH$_2$), 0.51–0.94 (11H, m, CH(CH_3)CH$_2$), CHCH_2CH$_3$, CH$_2$CH_3) 0.58 (3H, t, *J* 6.9, CH$_2$CH_3), 0.97–1.16 (2H, m, CHCH_2CH$_3$), 1.38–1.45 (1H, m, CH(CH$_3$)CH$_2$), 2.15 (3H, s, NCOCH_3), 2.39 (3H, s, ArCH_3), 2.40 (3H, s, ArCH_3), 3.23 (1H, dd, *J* 15.1 and 10.7, tacn-*H*), 3.34–4.05 (8H, m, tacn-*H*), 4.39 (1H, dd, *J* 15.1 and 2.6, tacn-*H*), 7.25 (2H, d, *J* 8.0, Ar-*H*), 7.27 (2H, d, *J* 8.0, Ar-*H*), 7.64 (2H, d, *J* 8.3, Ar-*H*), 7.69 (2H, d, *J* 8.3, Ar-*H*); δ_C 11.8, 11.9, 14.8, 15.5, 21.6, 22.5, 26.5, 27.6, 36.6, 37.8, 42.0, 45.1, 46.7, 61.3, 62.0, 127.3, 127.4, 129.6, 129.8, 137.8, 138.0, 143.7, 143.9, 171.1; *m*/*z* (FAB): 614 (12%, MNa$^+$), 592 (100, MH$^+$), 436 (49); (HRMS Found: (MH$^+$) 592–2887. $C_{30}H_{46}N_3O_5S_2$ requires 592.2879).

Synthesis of (2*S*,6*S*)-4-acetyl-2,6-di(1-methylethyl)-1,4,7-triazacyclononane 13

Macrocycle **12b** (600 mg, 1.07 mmol) was suspended in concentrated sulfuric acid (5 cm^3) and stirred at 95 °C for 16 h. The dark brown solution was cooled on ice and slowly added to ice-cold diethyl ether (250 cm^3). The resulting light brown precipitate was collected, redissolved in water (10 cm^3) and carefully neutralised with solid potassium hydroxide pellets. The resulting aqueous solution was extracted with dichloromethane (3 × 50 cm^3). The organic phases were combined dried over anhydrous magnesium sulfate and the solvents removed under reduced pressure to give **13** (80 mg, 52%) as a colourless oil, $[\alpha]_D^{25}$ +13.2 (*c* 0.65, $CHCl_3$), $\tilde{\nu}_{max}$/cm^{-1} 2955, 2871, 1630, 1467,

1416, 1361, 1292, 1038, 732; δ_H 0.63–0.72 (12H, m, $(CH_3)_2CH$), 1.32–1.44 (2H, m, $CH(CH_3)_2$), 1.90 (3H, s, $NCOCH_3$), 2.09–2.31 (3H, m, tacn-*H*), 2.52–2.80 (3H, m, tacn-*H*), 2.94–3.14 (3H, m, tacn-*H*), 3.33 (1H, dd, *J* 2.5 and 12.9, tacn-*H*); δ_C18.3, 18.4, 19.4, 19.6, 22.7, 31.9, 32.5, 50.3, 51.4, 53.5, 55.5, 60.2, 60.6, 172.0; *m*/*z* (ES): 256.1 (100%, MH^+); (HRMS Found: (MH^+) 256.2379. $C_{14}H_{30}N_3O$ requires 256.2389).

Synthesis of (2*S*,6*S*)-2,6-di(1-methylethyl)-1,7-di-*p*-toluenesulfonyl-1,4,7-triazacyclononane 14

To a solution of macrocycle **12b** (3.00 g, 5.33 mmol) in ethanol (40 cm^3) was added concentrated hydrochloric acid solution (40 cm^3) and the mixture was heated under reflux for 4 d. The solution was cooled on ice and neutralised using solid potassium hydroxide pellets. The volume was reduced by half under reduced pressure and the remaining solution was extracted with dichloromethane (3 × 30 cm^3). The organic phases were combined, dried over anhydrous magnesium sulfate and the solvents removed under reduced pressure to leave **14** (1.76 g, 63%) as a colourless solid. All spectroscopic data were consistent with those previously reported.[21] In addition the following data are reported: $\tilde{\nu}_{max}$/cm^{-1} 2963, 2874, 1465, 1324, 1291, 1148, 1089, 814; δ_H 0.29 (6H, d, *J* 6.6, $(CH_3)_2CH$), 0.75 (6H, d, *J* 6.3, $(CH_3)_2CH$), 1.34–1.47 (2H, m, $CH(CH_3)_2$), 2.37 (6H, s, $ArCH_3$), 2.93 (2H, dd, *J* 14.0 and 6.9, $NCH_2CH(CH)$), 3.11 (2H, dd, *J* 14.0 and 3.9, $HNCH_2CH(CH)$), 3.28–3.34 (2H, m, $CH_2CH(CH)NSO_2$), 3.42 (2H, d, *J* 14.6, NCH_2CH_2N), 3.61 (2H, d, *J* 14.9, NCH_2CH_2N), 7.23 (4H, d, *J* 8.0, Ar-*H*), 7.65 (4H, d, *J* 8.3, Ar-*H*); *m*/*z* (FAB): 522 (100%, MH^+), 366 (38); (HRMS Found: (MH^+) 522.2441. $C_{26}H_{40}N_3O_4S_2$ requires 522.2460).

Synthesis of (2*S*,6*S*)-2,6-di(1-methylethyl)-1,4,7-triazacyclononane 15

Macrocycle **15** could be prepared from **13** in an identical fashion to **14** or from **14** in an identical fashion to **13** and isolated routinely in 60–70% yield. All spectroscopic and experimental data were consistent with those previously reported;[21,22] (HRMS Found: (MH^+) 214.2275. $C_{12}H_{28}N_3$ requires 214.2283).

Synthesis of (2*S*,6*S*)-2,6-di(1-methylethyl)-4-ethyl-1,7-di-*p*-toluenesulfonyl-1,4,7-triazacyclononane 16a

To a stirred suspension of lithium aluminium hydride (0.63 g, 15.96 mmol) in dry tetrahydrofuran (60 cm^3) was added dropwise a solution of **12b** (3.00 g, 5.32 mmol) in dry tetrahydrofuran (150 cm^3). The resultant solution was heated at reflux for 18 h under nitrogen and then cooled on ice before potassium hydroxide (1 M, 30 cm^3) was added dropwise causing the previously grey solution to become white. The white gelatinous precipitate was filtered through Celite and then washed with ethyl acetate (100 cm^3). The filtrate was then acidified with 10% hydrochloric acid and the resultant organic layer removed. The aqueous layer was washed with ethyl acetate (3 × 50 cm^3) and the organic layers were combined and washed with brine (3 × 50 cm^3) before being dried over anhydrous magnesium sulfate and concentrated under reduced pressure yielding a dark brown-orange oil (2.37 g, 81%) which was purified upon crystallisation from hot ethanol, yielding **16a** (1.14 g, 39%) as a white crystalline solid. Further yield could be obtained upon concentration of the filtrate (0.36 g, 12%), mp 218–220 °C (from ethanol); $[\alpha]_D^{29}$ +95.5 (*c* 1.0, CH_2Cl_2); $\tilde{\nu}_{max}$/cm^{-1} 1430, 1392, 1335, 1292, 1151, 1087, 714, 695; δ_H 0.22 (3H, d, *J* 6.9, $(CH_3)_2CH$), 0.74 (3H, d, *J* 6.9, $(CH_3)_2CH$), 0.81–0.85 (6H, m, $(CH_3)_2CH$), 1.19–1.28 (1H, m, $(CH_3)_2CH$), 1.42–1.51 (4H, m, CH_3CH_2N and $(CH_3)_2CH$), 2.38 (3H, s, $ArCH_3$), 2.41 (3H, s, $ArCH_3$), 3.04–3.98 (11H, m, NCH_2CHNTs, $TsNCH_2CH_2NTs$, NCH_2CH_3 and $(CH_3)_2CHCH$), 4.81–4.87 (1H, m, $(CH_3)_2CHCH$), 7.28–7.32 (4H, m, Ar-*H*), 7.63 (2H, d, *J* 8.2, Ar-*H*), 7.80 (2H, d, *J* 8.2, Ar-*H*); δ_C 10.0, 18.6, 21.1, 21.6, 21.7, 29.9, 32.0, 45.9, 46.1, 46.3, 49.1, 50.4, 58.0, 58.7, 127.8, 127.9, 130.0, 130.1, 135.6, 137.7, 144.3, 144.9; *m*/*z* (ES): 550.4 (100% MH^+), 584.5 (50); (HRMS Found: (MH^+) 550.2762. $C_{28}H_{44}N_3O_4S_2$ requires 550.2768).

Synthesis of (2*S*,6*S*)-2,6-di(1-methylethyl)-4-ethyl-1,4,7-triazacyclononane 16b

Macrocycle **16a** (250 mg, 0.45 mmol) was suspended in concentrated sulfuric acid (4 cm^3) and stirred at 95 °C for 18 h. The dark brown solution was cooled in ice before being added dropwise to ice-cold diethyl ether (250 cm^3). The ether was decanted off and more ice-cold diethyl ether added to the off-white precipitate. The precipitate was filtered off and the solid obtained dissolved in the minimum amount of distilled water (10 cm^3) before being cooled on ice and basified with solid KOH. The light yellow solution was then extracted with dichloromethane (5 × 20 cm^3), the organic extracts being dried over anhydrous magnesium sulfate before being concentrated under reduced pressure. NMR analysis of this material indicated that incomplete detosylation had occurred, and therefore the cycle was repeated as outlined above to yield **16b** (29.5 mg, 27%) as a light yellow oil, $[\alpha]_D^{31}$ +56.3 (*c* 0.59, CH_2Cl_2), $\tilde{\nu}_{max}$/cm^{-1}: due to the hygroscopic nature of the product IR spectra obtained proved to be meaningless; δ_H 0.76–1.08 (15H, m, $(CH_3)_2CH$ and CH_3CH_2), 1.43–1.55 (2H, m, $(CH_3)_2CH$), 2.24–2.64 (10H, m, NCH_2), 2.72–2.85 (2H, m, $(CH_3)CHCH$); δ_C 12.9, 20.0, 32.2, 44.0, 51.2, 54.7, 59.8; *m*/*z* (ES): 242.2 (100%, MH^+); (HRMS Found (MH^+) 242.2589. $C_{14}H_{32}N_3$ requires 242.2591).

Synthesis of 1,3-di((3*S*,8*S*)-3,8-di(methylethyl)-4,7-di-*p*-toluenesulfonyl-1,4,7-triazacyclononan-1-ylmethyl)benzene 17a

To a solution of **14** (3.00 g, 5.75 mmol) and 1,3-bis(bromomethyl)benzene (683 mg, 2.59 mmol) in dry acetonitrile (100 cm^3) was added caesium carbonate (2.38 g, 17.25 mmol) and the mixture was heated at reflux for 3 d under nitrogen. The white solid was removed by filtration and washed with acetonitrile (50 cm^3). The organic phases were combined and the solvents removed under reduced pressure giving a yellow solid. This solid was redissolved in ethanol (30 cm^3), poured into ice-cold water (150 cm^3) and the resulting white precipitate collected by suction filtration. The resulting solid was further purified by recrystallisation from ethanol to yield **17a** (1.28 g, 43%) as colourless crystals, mp 108–110 °C (from ethanol); $[\alpha]_D^{25}$ +91.4 (*c* 0.5, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} 2967, 2847, 1463, 1391, 1330, 1243, 1088, 814, 777, 698; δ_H 0.21 (12H, d, *J* 6.3, $(CH_3)_2CH$), 0.54 (12H, d, *J* 6.3, $(CH_3)_2CH$), 1.46–1.53 (4H, m, $(CH_3)_2CH$), 2.38 (12H, s, $ArCH_3$), 2.78 (4H, dd, *J* 14.1 and 2.8, tacn-*H*), 2.99 (4H, dd, *J* 14.6 and 6.6, tacn-*H*), 3.47–3.66 (14H, m, tacn-*H* and $ArCH_2$), 3.93 (2H, d, *J* 12.9, tacn-*H* or $ArCH_2$) 7.23–7.26 (10H, m, Ar-*H*), 7.40–7.43 (2H, m, Ar-*H*), 7.67 (8H, d, *J* 8.0, Ar-*H*); δ_C 20.4, 20.8, 21.6, 28.6, 46.8, 56.1, 59.3, 63.5, 127.4, 129.1, 129.5, 129.8, 137.6, 138.4, 143.1; *m*/*z* (FAB): 1146 (79%, MH^+), 990 (100); (HRMS Found: (MH^+) 1145.5260. $C_{60}H_{85}N_6O_8S_4$ requires 1145.5312).

Synthesis of 1,3-di((3*S*,8*S*)-3,8-di(methylethyl)-1,4,7-triazacyclononan-1-ylmethyl)benzene 17b

This was prepared from **17a** in an identical fashion to **13** and recovered as a brown oil (21 mg, 9%). $\tilde{\nu}_{max}$/cm^{-1} 3397, 2960, 1471, 1368, 1160, 1023, 729, 670, 646, 624, 552, 428; δ_H 0.81 (12H, d, *J* 6.1, $(CH_3)_2CH$), 0.92 (12H, d, *J* 4.4, $(CH_3)_2CH$), 1.46–1.68 (4H, m, $(CH_3)_2CH$), 2.06–3.87 (24H, m, tacn-*H* and $ArCH_2$), 6.97 (1H, s, Ar-*H*), 7.05–7.25 (3H, m, Ar-*H*); δC 20.0, 20.2, 31.9, 53.5, 54.5, 54.5, 61.7, 128.1, 128.6, 138.5, 139.1; *m*/*z* (ES): 529.5 (61%, MH^+), 265.2 (100%, $(M_2H^+)/2$); (HRMS Found: (MH^+) 529.4943. $C_{32}H_{60}N_6$ requires 529.4958).

X-Ray crystallography

The intensity data for **6b** were collected on a CAD4 diffractometer at 160 K. Graphite-monochromated Mo-Kα

radiation (λ = 0.71069 Å) was used with ω–2θ scans. The unit cell parameters were determined by least-squares refinement of 25 automatically centred reflections $9.55 \leq \theta \leq 11.98$. All data were corrected for absorption by empirical methods (ψ scan)[29] and for Lorentz-polarization effects by XCAD4. The structure was solved by direct methods using SHELXS-97[30] and refined anisotropically (non-hydrogen atoms) by full-matrix least-squares on F^2 using SHELXL-97.[30] All H-atoms were calculated geometrically and refined using a riding model.

Crystal data for **6b**: $C_{24}H_{37}N_3O_4S_2$, M = 495.69, orthorhombic, space group $P2_12_12_1$, a = 10.752(4), b = 11.183(5), c = 21.829(10) Å, U = 2624.6(19) Å^3, T = 160(2) K, Z = 4, μ(Mo-Kα) = 0.237 mm^{-1}, 2679 reflections measured, 2622 unique (R_{int} = 0.0053) which were used in all calculations. The final wR [$I > 2\sigma(I)$] was 0.0887 (all data).

The intensity data for **12b** were collected using an Enraf-Nonius Kappa CCD area detector on an Enraf Nonius FR591 rotating anode generator at 120(2) K. Graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) was used with ϕ and ω to fill the Ewald sphere. Data collection, cell refinement and data reduction were carried out using the DENZO[31] and COLLECT[32] packages. A preliminary absorption corrections was carried out by multiple scans using SORTAV.[33] The structures were solved by the heavy-atom method using the program SHELXS-97[30] and refined anisotropically (non-hydrogen atoms) by full-matrix least-squares on F^2 using SHELXL-97.[30] The H-atom positions were calculated geometrically and refined with a riding model. Data were corrected for absorption using an isotropic non-hydrogen model with the program XABS2.[34]

Crystal data for **12b**: $C_{28}H_{41}N_3O_5S_2$, M = 563.76, orthorhombic, space group $P2_12_12_1$, a = 7.47600(10), b = 14.3100(2), c = 26.3880(4) Å, U = 2823.03(7) Å^3, T = 120(2) K, Z = 4, μ(Mo-Kα) = 0.231 mm^{-1}, 25309 reflections measured, 6397 unique (R_{int} = 0.0654) which were used in all calculations. The final wR [$I > 2\sigma(I)$] was 0.0619 (all data).

The program ORTEP-3,[35] was used for graphical representations and WINGX[36] was used to prepare material for publication for both structures.

CCDC reference numbers 214709 and 220376.

See http://www.rsc.org/suppdata/ob/b4/b409259g/ for crystallographic data in CIF or other electronic format.

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