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The synthesis of an isopropyl substituted 1,4,7-triazacyclononane *via* an *in situ* sequential macrocyclisation method

Graham Stones, Gilles Argouarch,† Alan R. Kennedy, David C. Sherrington and Colin L. Gibson *

Department of Pure & Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, UK G1 1XL. E-mail: c.l.gibson@strath.ac.uk

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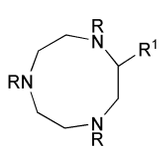
Using L-valine methyl ester hydrochloride as starting material, the synthesis of (2*S*)-2-isopropyl-1,4,7-trimethyl-1,4,7-triazacyclononane is described. Various standard Richman–Atkins cyclisation methods gave only poor yields in the key macrocyclisation step. Efficient macrocyclisation yields were, however, realised when an *in situ* sequential cyclisation method was developed.

Introduction

Currently, there is significant interest in the synthesis and chemistry of polyazamacrocycles because of the ability of these ligands to form kinetically and thermodynamically stable metal ion complexes.[1] The ability of 1,4,7-triazacyclononane **1a** together with *N*-alkyl derivatives **1b**, and analogues thereof, to stabilise high oxidation states of metal ions is particularly noteworthy. The ability of ligands such as **1** to stabilise high metal ion oxidation states has led to their use as biomimetics of manganese enzymes including manganese catalyse and Photosystem II.[2] These biomimetic studies on **1b** led Hage *et al.* to develop manganese complexes of this macrocycle as catalysts for low temperature bleaching with hydrogen peroxide.[3] Hage *et al.* also used these manganese complexes as epoxidation catalysts. Subsequently, there followed much interest in the use of azamacrocycle derivatives of **1** in conjunction with manganese ions as epoxidation catalysts. One drawback of the use of macrocycle **1a** and manganese(II) as an epoxidation system is the pronounced catalyse activity resulting in the decomposition of hydrogen peroxide. However, De Vos *et al.* have developed a method for overcoming the problem of hydrogen peroxide disproportionation by carrying out epoxidations at 0 °C in acetone.[4] Subsequently, using complexes generated *in situ* from manganese(II) and **1b** both De Vos *et al.*[5] and Berkessel *et al.*[6] have described stereoselective epoxidations of unfunctionalised alkenes using hydrogen peroxide in the presence of oxalate or ascorbate co-additives. This considerable interest led to the development of enantioselective epoxidations being carried out using chiral non racemic analogues of **1b** by Beller *et al.*,[7] Bolm *et al.*[8,9] and ourselves.[10]

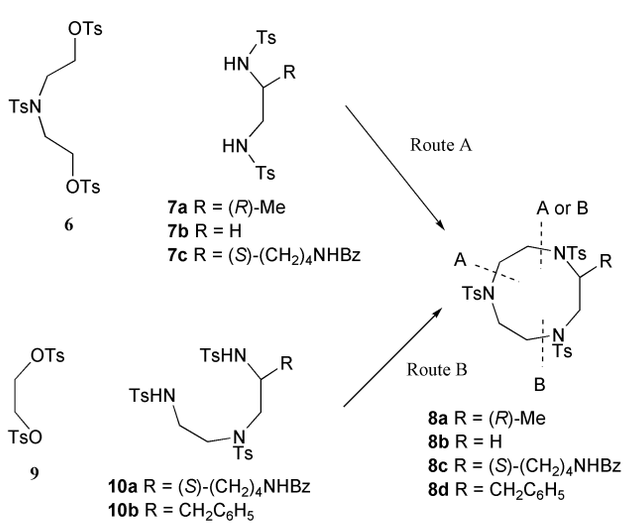
Despite the above interest in triazacyclononanes there are few examples of the synthesis of chiral analogues where the stereochemistry is directly associated with the macrocyclic ring itself. At the outset of our studies only macrocycles **2**,[11] **3**[12] and **4**[13] with one stereocentre on the macrocyclic ring had been reported. Subsequently, triazacyclononanes possessing two (C-2,3[14] and C-2,6[10,15,16]) and three stereocentres[9] on the macrocyclic ring were reported. However, the synthesis of chiral triazacyclononanes is far from trivial as evidenced from our early studies in the area.[17] In this context, we initially focused on the synthesis of chiral monosubstituted triazacyclononanes, even here there were obvious problems with the synthesis of these molecules. Therefore, the challenge that we set ourselves was the preparation of the novel sterically demanding isopropyl substituted triazacyclononane **5** (Fig. 1).



1a R = R^1 = H
1b R = Me R^1 = H
2 R = H R^1 = (*R*)-Me
3 R = H R^1 = (*S*)-(CH$_2$)$_4$NHBz
4 R = H R^1 = (±)-CH$_2$Ph
5 R = Me R^1 = (*S*)-^{i}Pr

Fig. 1

The first reported synthesis of a chiral triazacyclononane with a stereocentre on the ring annulus was the (*R*)-2-methyl-1,4,7-triazacyclononane **2** by Mason and Peacock who investigated the chiroptical properties of the cobalt(III) complex.[11a] Their synthesis (Route A, Scheme 1) involved a Richman–Atkins cyclisation[19] of a 1,2-ditosamide **7a** and tritosyl diethanolamine **6** which afforded the tristosamide **8a**. Subsequent studies by Graham and Weatherburn showed that Richman–Atkins cyclisation of racemic 1,2-ditosamide **7a** and tritosyl diethanolamine **6** in dimethyl sulfoxide only gave a 20% yield of the tristosamide **8a** in the macrocyclisation step.[19] The failure of Route A to afford efficient yields of macrocycle was rationalised by Searle and Geue in the synthesis of tristosamide **8b** in terms of inhibition of the first substitution step because of steric and/or electronic factors from the bis anion of bistosamide **7b**.[20]



Scheme 1

Failure of Route A to furnish efficient yields in the macrocyclisation step for both mono and unsubstituted macrocycles led to the investigation of alternative disconnections. The

† *Present address*: UMR CNRS 6509, Organometalliques et Catalyse, University de Rennes, Campus de Beaulieu, 35042 Rennes, France

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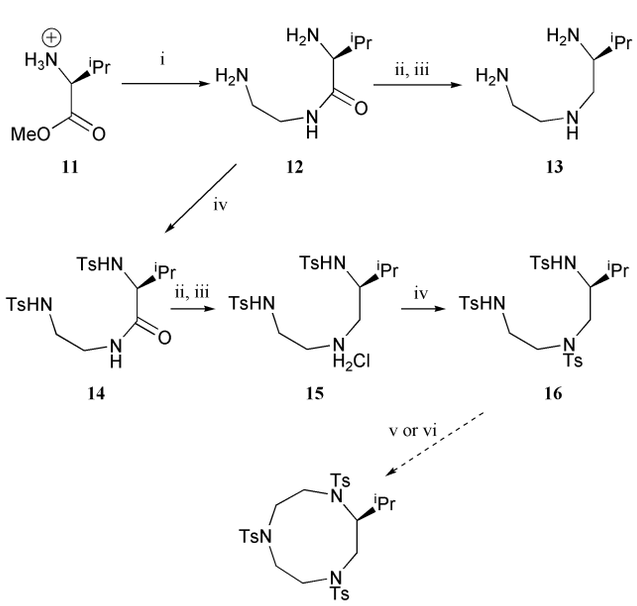
alternate approach (Route B, Scheme 1), first developed by Cox *et al.* for the mono substituted macrocycle **8c**, involved the Richman–Atkins cyclisation of a tristosylate **10a** with ethylene glycol ditosylate **9**.[12] Such an approach afforded the macrocycle **8c** in 71% yield while the method using **7c** and **6** (Route A) afforded only 35% yield. Subsequently, Koek *et al.* used Route B in the synthesis of the racemic benzyl substituted azamacrocycle **8d** from tristosamide **10b** and bistosylate **9**.[13]

With these observations in mind, we set about investigating the preparation of the novel sterically demanding isopropyl macrocycle **5** and its use as an epoxidation catalyst. In this paper we describe our studies which showed that even using approach B can be problematic and present a solution to this problem.

Results and discussion

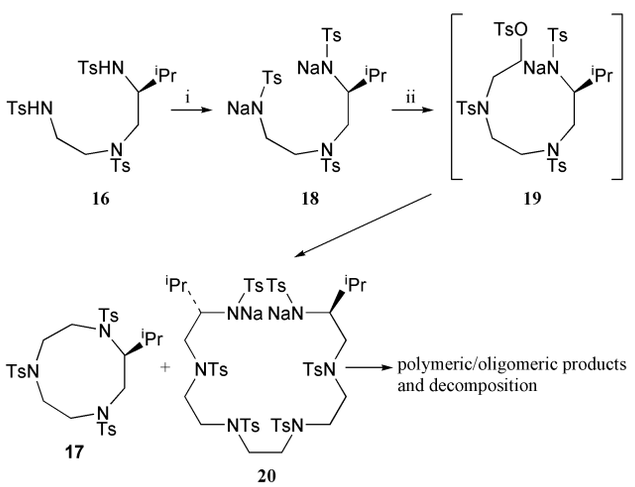
Our exploratory studies in this area with racemic 1,2-ditosamide **7a** and tritosyl diethanolamine **6** confirmed the observations of Graham and Weatherburn[19] in that Route A was not a synthetically viable approach. In this case, macrocyclisation was carried out in DMF and gave racemic **8a** in only 10–15% yield as impure material.

Thus, the synthesis of isopropyl substituted macrocycle **5** was investigated based on the approach of Cox *et al.* for **3**.[12] In this context, L-valine methyl ester hydrochloride **11** was reacted neat with ethylene diamine which afforded the amide **12** (89%) (Scheme 2). Reduction of the amide **12** with borane–THF complex followed by acid hydrolysis proved to be problematic with only low yields of the triamine **13** being isolated. Therefore, an alternative sequential procedure was developed for the preparation of a protected form of the triamine **13**. This alternative sequence involved initial reaction of amide **12** with 4-toluenesulfonyl chloride in pyridine which afforded the bistosamide **14** in 71% yield. Reduction of bistosamide **14** with borane–dimethyl sulfide complex followed by acid hydrolysis gave the hydrochloride salt **15** (63%). Protection of the central nitrogen in **15** was accomplished by reaction with 4-toluenesulfonyl chloride in pyridine which smoothly afforded the tristosamide **16** (72%).



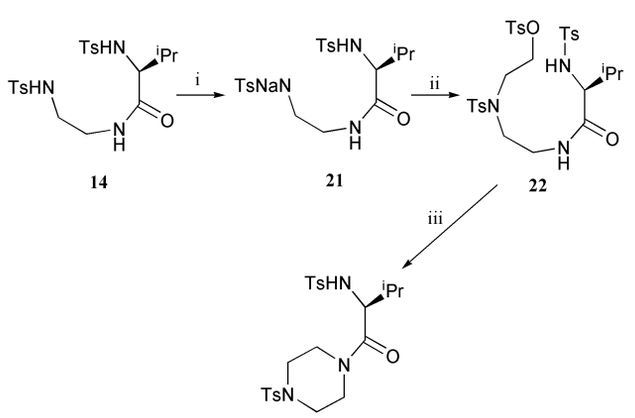
Scheme 2 *Reagents and conditions*: i, $(CH_2NH_2)_2$, 120 °C; ii, $H_3B{\cdot}SMe_2$, THF, Δ; iii, 6 M HCl, Δ; iv, TsCl, pyr; v, 2 equiv. NaH, **9**, DMF, 80 °C; vi, $CsCO_3$, **9**, DMF, 80 °C.

The planned synthesis of macrocycle **5** required the macrocyclisation of tristosamide **16** using a Richman–Atkins cyclisation. In general, the Richman–Atkins macrocyclisation[18] involves the reaction of ethylene glycol ditosylate **9** with the bis sodium salt of a suitable tosamide derivative. Alternatively, the caesium salt formed *in situ* from the tosamide and caesium carbonate can be used. Slow addition of the electrophilic tosylate ester to the sodium or caesium salt in DMF at 80 °C generally gives the macrocycle. However, all such approaches using bistosamide **16** proved to be very inefficient with low yields of the macrocycle **17** being formed together with decomposition and polymeric products. It was speculated that the isopropyl group in tristosamide **16** was detrimental to the cyclisation by inhibiting the reactivity of the adjacent tosamide anion. This steric hindrance would result in the less hindered tosamide anion of dianion **18** displacing one *O*-tosyl ester group in ethylene glycol ditosylate **9** to give the mono substitution product **19** (Scheme 3). The low yield of cyclisation product **17** suggested that the intramolecular cyclisation of **19** was hindered, probably by the C-2 isopropyl group. Consequently, a less sterically demanding pathway from **19** may involve intermolecular substitution to give the dimer **20**. The dimeric product **20** could then react further to give oligomeric and/or polymeric products.



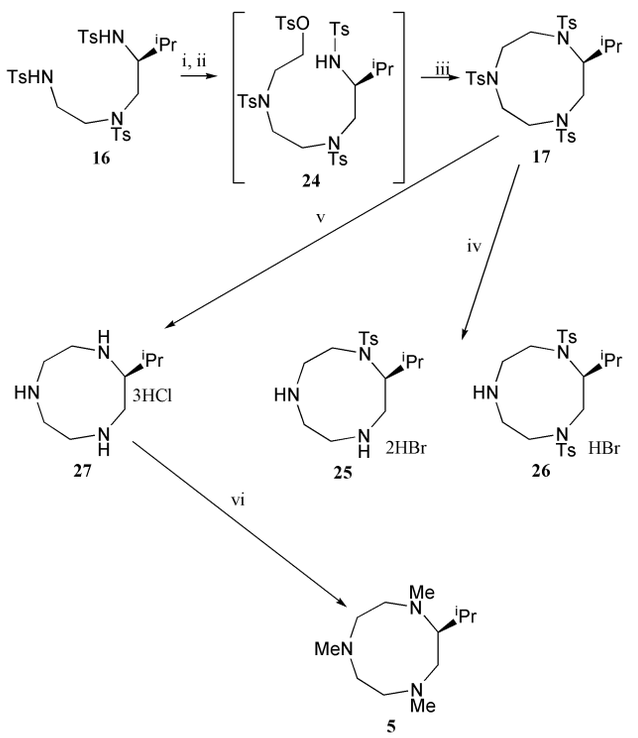
Scheme 3 *Reagents and conditions*: i, 2 equiv. NaH, DMF, 60 °C; ii, **9**.

In order that the problems of decomposition and/or oligomerisation *via* **19** could be avoided it was decided to try a sequential cyclisation process. Accordingly, the bistosamide **14** was reacted with one equivalent of sodium hydride in DMF to form the monosodium salt **21** followed by reaction with ethylene glycol ditosylate **9** (Scheme 4). This happily afforded the mono alkylated product **22** which had alkylated at the least hindered tosamide function. Subsequent treatment of **22** with a further equivalent of sodium hydride in DMF afforded the piperazine **23** rather than macrocyclisation. The piperazine **23** was a consequence of the amide nitrogen in the sodium salt of



Scheme 4 *Reagents and conditions*: i, 1 equiv. NaH, DMF, 0 °C; ii, **9**, RT; iii, 1 equiv. NaH, DMF, 80 °C.

22 participating in the nucleophilic ring closure. Ourselves[10] and Watkinson and co-workers[16] had observed analogous problems of a central nucleophilic nitrogen participating in attempted macrocyclisations for the preparation of disubstituted systems. The solution to this problem required a reduction of the nucleophilicity of the amide nitrogen in **22**. Accordingly, a sequential *in situ* alkylation and cyclisation protocol was developed. Thus, tristosamide **16** was treated with one equivalent of sodium hydride in DMF at 0 °C followed by the addition of ethylene glycol ditosylate **9** (Scheme 5). Presumably, this afforded the mono alkylated product **24**. Slow addition of the final equivalent of sodium hydride was carried out and this afforded the desired macrocycle **17** in a welcome 78% yield.



Scheme 5 *Reagents and conditions*: i, 1 equiv. NaH, DMF, 0 °C; ii, **9**, RT; iii, Slow addn of 1 equiv. NaH, 80 °C; iv, HBr-AcOH, Δ, 48 h; v, Li, NH_3, EtOH, THF; vi, HCO_2H, HCHO.

The spectral properties of **17** were in full accord with the structure, however, the crystalline nature of **17** allowed both the stereochemistry and the absolute structure to be confirmed unequivocally by single crystal X-ray diffraction. The solid-state structure (Fig. 2) indicated that as expected the isopropyl group adopts a pseudo-equatorial position on the ring. The ring puckering is dominated by the three sp^2 N centers. These are oriented so that two have the same directionality (N1 and N3 in the crystal structure) and hold their substituent tosyl groups on the opposite face of the 9-membered ring from the isopropyl group. Only the third tosyl group furthest from the isopropyl, is on the same face as it. All three N centers show considerable deviations from planarity (N1, N2 and N3 lie −0.320, 0.211 and − 0.104 Å respectively from the planes defined by the atoms bonded to them). The tosylate on N3 (adjacent to isopropyl) is twisted so that the phenyl ring lies over one face of the 9-membered ring whilst the other tosyl groups point away from the main body of the molecule. (Ct–N3–S3–C24 is 2.8°, where Ct is the 9-membered rings centroid and C24 is the *ipso* C atom whilst the equivalent torsions for the other tosyl groups are 140.5 and 175.5°). Surprisingly for a structure with no obviously strong intermolecular contacts, there are large channels running parallel to the crystallographic *c* direction. Careful examination of electron-density syntheses showed no evidence for the presence of disordered solvent in these.

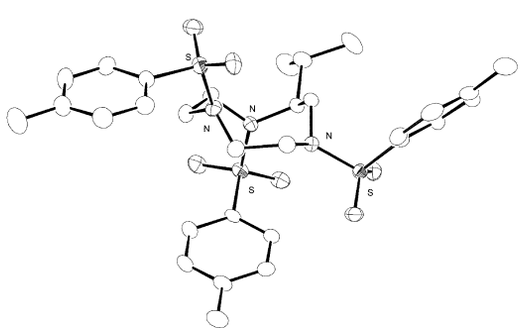


Fig. 2 Molecular structure of **17** with 40% displacement ellipsoids. H atoms have been omitted for clarity.

The remaining sequence for the preparation of **5** required the detosylation of **17** followed by *N*-methylation. Using the detosylation conditions of Weatherburn and Graham of hydrobromic acid in acetic acid afforded the mono **25** and bistosamide **26** derivatives in 28 and 47% yields, respectively. Complete detosylation was achieved with lithium in ammonia reduction of **17** which afforded the deprotected macrocycle **27** as the hydrochloride salt (53%). Subsequent, Eschweiler–Clarke *N*-methylation of the freebase of **27**, formed *in situ*, gave the required isopropyl macrocycle **5** in 72% yield.

In situ epoxidations were carried out using macrocycle **5** by application of the stereoselective method of Berkessel and Sklorz[6] involving manganese(II) acetate with an ascorbate/ascorbic acid co-ligand system. In the case of dodecene, a 36% yield of the racemic epoxide was obtained while for styrene, a 31% yield of (*R*)-styrene oxide was isolated with a 16% ee.

Conclusions

The synthesis of (2*S*)-2-isopropyl-1,4,7-trimethyl-1,4,7-triazacyclononane was carried out in 7 steps and 8.5% overall yield from L-valine methyl ester hydrochloride. Standard Richman–Atkins cyclisation procedures gave only low yields of the macrocyclisation product. This inefficient cyclisation was attributed to a detrimental steric hindrance of the 2-isopropyl substituted nucleophilic component in the macrocyclisation step. Consequently, a sequential *in situ* macrocyclisation method was developed which gave a cyclisation yield of 78%. The macrocycle was used as a ligand in the *in situ* epoxidation of alkenes with manganese(II) and hydrogen peroxide in the presence of an ascorbate/ascorbic acid co-ligand system.

Experimental

Instrumentation

Melting points were determined on a Reichert 7905 hot stage and are uncorrected. Specific rotations were measured at 20 °C in a 1 cm^3 cell with a pathlength of 10 cm using a Perkin-Elmer 341 polarimeter. Specific rotations were measured at 20 °C, the values are given in 10^{-1} deg cm^2 g^{-1} and the concentrations are quoted in g 100 cm^{-3}. ^{1}H-NMR spectra were recorded on Bruker WM-250, JEOL 270, or Bruker AMX-400 spectrometers in the indicated solvents operating at 250, 270 or 400 MHz, respectively. ^{13}C-NMR spectra were obtained on the same instruments operating at 62.89, 67.80, and 100 MHz, respectively. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dq, doublet of quartets; sep, septet. Coupling constants were recorded in Hz. Infra red (IR) spectra were recorded on a Nicolet Impact 400D FTIR spectrometer either as liquid films or as KBr discs. Mass spectra were recorded on a JEOL JMS AX505 spectrometer at Strathclyde or at the EPSRC National

Mass Spectrometry service, Swansea. Microanalyses were performed by the microanalytical service at Strathclyde. HPLC analysis of styrene oxide was performed using an Applied Chromatography Systems (ACS) Model 351 isocratic pump in conjunction with a Daicel Chiralcel OD column (250 × 4.6 mm) with 0.25% propanol in hexane (1 cm^3 min^{-1}) as the eluant. The peaks were detected with an ACS Model 750/12 UV detector set at 254 nm and an ACS Chiramonitor. The data were collected on a Viglen computer fitted with a SUMMIT data card and the chromatograms were integrated using COMUS SUMMIT software.

General methods

Anhydrous reactions were carried out under an atmosphere of nitrogen in oven dried glassware (140 °C). Anhydrous solvents were obtained using standard procedures: ethanol ($Mg(OEt)_2$), pyridine (predried over KOH, distilled from CaH_2), THF (K metal), toluene (Na metal) and triethylamine (CaH_2). All other reagents were used as supplied. Flash column chromatography was performed according to the procedure of Still *et al.*[21] using silica gel (230–400 mesh).

Experimental procedures

(2*S*)-2-Amino-*N*-(2-aminoethyl)-3-methylbutanamide 12. To ethylene diamine (50 cm^3, 747 mmol) at room temperature under a nitrogen atmosphere was added, portionwise, methyl (2*S*)-2-amino-3-methylbutanoate **11**[22] (1.00 g, 5.96 mmol) over 10 min. The homogeneous mixture was brought to 120 °C for 6 h. The resulting reaction mixture was allowed to cool to room temperature and the volatiles were evaporated to afford the title compound as a viscous yellow oil without purification, (840 mg, 5.30 mmol, 89%). Found: MH^+ 160.1445. $C_7H_{17}N_3O$ requires: 160.1372; $[\alpha]_D$ +6.8 (c = 0.22, methanol); υ_{max} (liquid film, cm^{-1}) 3350 (br, NH), 3293 (br, NH), 2959 (s, CH), 2920 (s, CH), 2850 (s, CH), 1649 (s, C=O); δ_H (250 MHz, $CDCl_3$) 0.76 (d, J 6.8, 3H, –CH_3), 0.83 (d, J 6.8, 3H, –CH_3), 2.24 (m, 1H, CH(CH_3)$_2$), 2.76 (m, 2H, –C$H_2$$NH_2$), 3.17 (m, 2H, –C$H_2$$NH_2$), 3.25 (m, 1H, NHCOC$H$); δ_C (100 MHz, $CDCl_3$) 15.0, 18.6 (–$C$$H_3$), 29.8 (–$C$H($CH_3$)$_2$), 40.8 (–$C$$H_2$$NH_2$), 43.9 (–$CHNH_2$), 59.2 (CONH$C$H).

(2*S*)-3-Methyl-2-{[(4-methylphenyl)sulfonyl]amino}-*N*-(2-{[(4-methylphenyl)sulfonyl]amino}ethyl)butanamide 14. To a solution of (2*S*)-2-amino-*N*-(2-aminoethyl)-3-methylbutanamide **12** (4.90 g, 30.70 mmol) in pyridine (70 cm^3) at 0 °C under a nitrogen atmosphere was added *p*-toluenesulfonyl chloride (14.66 g, 76.9 mmol) in batches over 30 min. The orange solution was allowed to come to room temperature and stirred for a further 6 h at room temperature. The black reaction mixture, was quenched with ice (~300 g) and conc. HCl (80 cm^3). This mixture was washed with dichloromethane (×2, 100 cm^3), and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The resulting brown red oil was crystallised (methanol–water) to afford the title compound as colourless needles (10.1 g, 21.7 mmol, 71%); mp 163–164 °C. Found: C, 53.9; H, 6.3; N, 9.0; S, 13.7: MH^+ 468.2016. $C_{21}H_{29}O_5S_2N_3$ requires: C, 54.2; H, 6.2; N, 8.7; S, 13.7%: 468.1990. $[\alpha]_D$ −34.5 (c = 1, $CHCl_3$). υ_{max} (KBr, cm^{-1}) 3339 (s, NHTs), 3263 (s, NHCO), 2962 (m, CH), 2929 (m, CH), 2877 (m, CH), 1655 (s, C=O), 1328 (s, SO_2NH), 1159 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.77 (d, J 6.8, 3H, –CH_3), 0.80 (d, J 6.8, 3H, –CH_3), 2.06 (m, 1H, CH(CH_3)$_2$), 2.44 (s, 3H, –C_6H_4–CH_3), 2.46 (s, 3H, –C_6H_4–CH_3), 3.03 (m, 2H, –NCH_2), 3.35 (m, 2H, TsNCH_2), 3.51 (m, 1H, TsNCH), 5.61 (s, 1H, CONH), 5.7 (d, J 7.7, 1H, TsNH), 6.96 (s,1H, TsNH), 7.73–7.8 (m, 8H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 17.5 (–$C$$H_3$), 19.3 (–$C$$H_3$), 21.7 (2 × –$C_6H_4$–$C$$H_3$), 31.0 ($C$H($CH_3$)$_2$), 39.7 (TsN$C$$H_2$–), 42.8 ($C$$H_2$NHCO), 62.7 (CO$C$HNTs), 127.3 (2 × Ar–$C$H), 127.7 (2 × Ar–$C$H), 129.9 (2 × Ar–$C$H), 130.1 (2× Ar–$C$H), 136.3 (Ar–$C$), 137.0 (Ar–$C$), 143.8 (Ar–$C$), 144.2 (Ar–$C$), 171.8 ($C$=O).

4-Methyl-*N*-{2-[(2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butylamino]ethyl}benzenesulfonamide 15. To a solution of (2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}-*N*-(2-{[(4-methylphenyl)sulfonyl]amino}ethyl)butanamide **14** (1.80 g, 3.80 mmol) in THF (25 cm^3) was added borane–dimethyl sulfide complex (1.10 cm^3, 11.40 mmol). The reaction was heated to reflux for 24 h. On cooling, the reaction was quenched with methanol (20 cm^3) and the volatiles were evaporated under reduced pressure. To the resulting residue was added 2 M HCl (25 cm^3) and the system was heated to reflux for a further 24 h. On cooling the resulting aqueous solution was extracted with dichloromethane (×2, 25 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to afford a pale yellow oil which subsequently solidified to give a colourless solid. Recrystallisation from EtOAc afforded the titled compound as colourless crystals (1.2 g. 2.4 mmol, 63%); mp 147–149 °C; Found C, 51.6; H, 6.6; N, 8.4; S, 13.2; Cl, 7.1; MH^+ 454.1850. $C_{21}H_{32}O_4S_2N_3Cl$ requires: C, 51.6; H, 6.4; N, 8.6; S, 13.0; Cl, 7.3%; 454.1841. $[\alpha]_D$ −26.1 (c = 1, $CHCl_3$). υ_{max}(KBr, cm^{-1}) 3272 (s, NHTs), 3200–2600 (br, N^+H(Cl)), 2964 (s, CH), 2880 (s, CH), 2790 (s, CH), 1325 (s, SO_2NH), 1175 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.67 (m, 6H, –CH_3), 1.72 (m, 1H, CH(CH_3)$_2$), 2.21 (br, 1H, NH), 2.37 (s, 3H, –C_6H_4–CH_3), 2.39 (s, 3H, –C_6H_4–CH_3), 3.13 (m, 2H, C$H_2$$N^+$), 3.38 (m, 2H, C$H_2$NTs), 3.40 (m, 2H, C$H_2$$N^+$), 3.56 (m, 1H, C$H$NTs), 7.27 (m, 4H, –$C_6H_4$–$CH_3$), 7.80 (d, J 8.2, 2H, –C_6H_4–CH_3), 7.87 (d, J 8.2, 2H, –C_6H_4–CH_3), 8.75 (br, 1H, NH); δ_C (100 MHz, $CDCl_3$) 18.6, 18.7 (–$C$$H_3$), 21.7 (–$C_6H_4$–$C$$H_3$), 21.8 (–$C_6H_4$–$C$$H_3$), 30.5 ($C$H($CH_3$)$_2$), 42.7 (N$C$$H_2$), 48.3 (N$C$$H_2$), 49.7 (TsN$C$$H_2$), 59.1 (TsN$C$H), 127.3 (2 × Ar–$C$H), 127.6 (2 × Ar–$C$H), 129.9 (4 × Ar–$C$H), 136.5 (Ar–$C$), 137.2 (Ar–$C$), 138.2 (Ar–$C$), 143.5 (Ar–$C$).

4-Methyl-*N*-((1*S*)-2-methyl-1-{[(4-methylphenyl)sulfonyl](2-{[(4-methylphenyl)sulfonyl]amino}ethyl)amino]methyl}propyl)-benzenesulfonamide 16. To a solution of 4-methyl-*N*-((1*S*)-2-methyl-1-{[(4-methylphenyl)sulfonyl]amino}ethyl)amino]-methyl}propyl)benzenesulfonamide hydrochloride **15** (1.50 g, 3.10 mmol) in pyridine (20 cm^3) at 0 °C under a nitrogen atmosphere was added *p*-toluenesulfonyl chloride (583 mg, 3.10 mmol) in batches over 30 min. The orange solution was allowed to come to room temperature and stirred for a further 6 h at room temperature. The now black reaction mixture was quenched with ice (~100 g) and conc. HCl (25 cm^3). This mixture was extracted with dichloromethane (×2, 25 cm^3), and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated to afford a crude dark brown oil. Purification by column chromatography on silica (hexane–EtOAc–CH_2Cl_2 3 : 2 : 5) afforded a light yellow solid which subsequently solidified to a colourless solid (1.4 g, 2.23 mmol, 72%); mp 78–80 °C; Found: C, 55.3; H, 5.9; N, 6.7; S, 15.6; MH^+ 608.1930. $C_{28}H_{37}O_6S_3N_3$ requires: C, 55.3; H, 6.1; N, 6.9; S, 15.8%; 608.1923; $[\alpha]_D$ −46.4 (c = 1, $CHCl_3$). υ_{max}(KBr, cm^{-1}) 3284 (s, NHTs), 3059 (w, C_6H_4), 2962 (s, CH), 2910 (s, CH), 2875 (m, CH), 1331 (s, SO_2NH), 1156 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.78 (d, J 6.8, 3H, –CH_3), 0.82 (d, J 6.8, 3H, –CH_3), 1.77 (m, 1H, CH(CH_3)$_2$), 2.39 (s, 3H, –C_6H_4–CH_3), 2.46 (s, 6H, –C_6H_4–CH_3), 2.55 (m, 2H, CH_2NTs), 2.77 (m, 2H, CH_2NTs), 3.64 (m, 2H, CH_2NTs), 3.67 (m, 1H, CH_2NTs), 7.25 (d, J 8.1, 3H, –C_6H_4–CH_3), 7.34 (d, J 8.1, 3H, –C_6H_4–CH_3), 7.71 (d, J 8.1, 1H, –C_6H_4–CH_3), 7.77 (d, J 8.1, 1H, –C_6H_4–CH_3), 7.88 (d, J 8.1, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 18.4, 18.7 (–$C$$H_3$), 21.6 (–$C_6H_4$–$C$$H_3$), 21.8 (2× –$C_6H_4$–$C$$H_3$), 31.1 ($C$H($CH_3$)$_2$), 48.2 (TsN$C$$H_2$), 48.8 (TsN$C$$H_2$), 49.3 (TsN$C$$H_2$), 58.7 (TsN$C$H), 127.2 (3× Ar–$C$H), 128.4 (3× Ar–$C$H), 129.8 (3× Ar–$C$H), 136.8 (3× Ar–$C$H), 138.0 (2× Ar–$C$), 143.5 (2× Ar–$C$), 145.2 (2× Ar–$C$).

{2-[((2*S*)-3-Methyl-2-{{(4-methylphenyl)sulfonyl]amino}-butanoyl)amino]ethyl}[(4-methylphenyl)sulfonyl]amino}ethyl-4-methylbenzene sulfonate 22. To a solution of (2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}-*N*-(2-{[(4-methylphenyl)-sulfonyl]amino}ethyl)butanamide **14** (1.00 g, 2.10 mmol) in DMF (10 cm^3) at 0 °C was added a suspension of NaH (51 mg, 2.14 mmol) in DMF (2 cm^3) over 1 h. The suspension was allowed to come to room temperature and stirred for a further 1 h. Ethylene glycol ditosylate **9** (583 mg, 2.10 mmol) in DMF (1 cm^3) was added dropwise over 30 min to the solution. The reaction was stirred overnight and at the completion of this period the reaction was quenched by the addition of water (10 cm^3). The DMF was removed under reduced pressure (12 mmHg) and the residue was dissolved in EtOAc (15 cm^3). The organic layer was washed with water (×2, 20 cm^3), dried (Na_2SO_4), filtered and evaporated to give a brown solid. Purification by column chromatography on silica (hexane–EtOAc–CH_2Cl_2 4 : 1 : 5) afforded a white solid (798 mg, 1.2 mmol, 57%); mp 132–134 °C; Found: C, 55.3; H, 5.9; N, 6.7; S, 15.6; MH^+ 666.1953. $C_{30}H_{39}O_8S_3N_3$ requires: C, 55.3; H, 6.1; N, 6.9; S, 15.8%; 666.1977. $[a]_D$ −24.1 (*c* = 1, $CHCl_3$). υ_{max}(KBr, cm^{-1}) 3334 (s, *NH*Ts), 3254 (s, *NH*CO), 3080 (w, C_6H_4), 2960 (s, CH), 2920 (s, CH), 2810 (m, CH), 1649 (s, C=O), 1350 (s, SO_2NH), 1180 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.82 (d, *J* 6.8, 3H, –C*H*$_3$), 0.90 (d, *J* 6.8, 3H, –C*H*$_3$), 2.1 (m, 1H, C*H*$(CH_3)_2$), 2.26 (s, 3H, –C_6H_4–C*H*$_3$), 2.37 (s, 3H, –C_6H_4–C*H*$_3$), 2.47 (s, 3H, –C_6H_4–C*H*$_3$), 3.01 (m, 2H, C*H*$_2$N), 3.14 (m, 2H, C*H*$_2$N), 3.28 (m, 2H, C*H*$_2$NTs), 3.51 (d, *J* 4.7, 1H, C*H*NTs), 4.19 (m, 2H, C*H*$_2$OTs), 5.32 (br, 1H, CONH), 7.25 (d, *J* 8.0, 2H, –C_6H_4–CH_3), 7.32 (d, *J* 8.0, 2H, –C_6H_4–CH_3), 7.38 (d, *J* 8.3, 2H, –C_6H_4–CH_3), 7.64 (d, *J* 8.3, 2H, –C_6H_4–CH_3), 7.75 (d, *J* 8.3, 2H, –C_6H_4–CH_3), 7.79 (d, *J* 8.3, 2H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 17.3, 19.3 (–*C*H_3), 21.7 (3 × –C_6H_4–*C*H_3), 31.4 (*C*H$(CH_3)_2$), 38.8 (N*C*H$_2$), 48.6 (TsN*C*H$_2$), 49.5 (TsN*C*H$_2$), 62.2 (TsN*C*H), 69.1 (TsO*C*H$_2$), 127.4 (2× Ar–*C*H), 127.6 (2× Ar–*C*H), 128.1 (2 × Ar–*C*H), 129.2 (2 × Ar–*C*H), 130.2 (2 × Ar–*C*H), 132.4 (Ar–*C*H), 135.2 (Ar–*C*H), 137.0 (2× Ar–*C*), 143.7 (2× Ar–*C*), 144.3 (Ar–*C*), 145.5 (Ar–*C*), 171.1 (C=O).

4-Methyl-*N*-[(1*S*)-2-methyl-1-({4-[(4-methylphenyl)sulfonyl]-1-piperazinyl}carbonyl)propyl]benzenesulfonamide 23. NaH (18 mg, 0.75 mmol) in DMF (1 cm^3) was added dropwise to a solution of {2-[((2*S*)-3-methyl-2-{{(4-methylphenyl)sulfonyl]-amino}butanoyl)amino]ethyl}[(4-methylphenyl)sulfonyl]amino}-ethyl-4-methylbenzene sulfonate **22** (500 mg, 0.75 mmol) in DMF (8 cm^3) at 80 °C. The resulting solution was stirred at 80 °C overnight. During this period the colour of the solution changed from colourless to brown and at completion the reaction was quenched by addition of water (10 cm^3). The DMF was removed under reduced pressure (12 mmHg) and the residue was dissolved in EtOAc (15 cm^3). The organic layer was washed with water (×2, 20 cm^3), dried (Na_2SO_4), filtered and evaporated to give a brown solid. Purification by column chromatography on silica (hexane–EtOAc–CH_2Cl_2 3 : 2 : 5) afforded a colourless solid (192 mg, 0.39 mmol, 52%); mp 184–185 °C; Found: MH^+ 494.1751; $C_{23}H_{31}O_5S_2N_3$ requires: 494.1783; $[a]_D$ +99.8 (*c* = 1, $CHCl_3$). υ_{max}(KBr, cm^{-1}) 3285 (m, *NH*Ts), 3064 (w, C_6H_4), 2980 (m, CH), 2950 (m, CH), 2840 (m, CH), 1639 (s, C=O), 1335 (s, SO_2NH), 1170 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.79 (d, *J* 6.7, 3H, –C*H*$_3$), 0.95 (d, *J* 6.7, 3H, –C*H*$_3$), 1.72 (m, 1H, C*H*$(CH_3)_2$), 2.25 (s, 3H, –C_6H_4–C*H*$_3$), 2.46 (s, 3H, –C_6H_4–C*H*$_3$), 2.52 (m, 2H, C*H*$_2$N), 2.7 (m, 2H, C*H*$_2$N), 3.31 (m, 2H, C*H*$_2$NTs), 3.46 (m, 2H, C*H*$_2$NTs), 3.83 (m, 1H, C*H*NTs), 7.05 (d, *J* 8.0, 2H, –C_6H_4–CH_3), 7.38 (d, *J* 8.0, 2H, –C_6H_4–CH_3), 7.58 (d, *J* 8.2, 2H, –C_6H_4–CH_3), 7.64 (d, *J* 8.2, 2H, –C_6H_4–CH_3), δ_C (100 MHz, $CDCl_3$) 16.8, 19.8 (–*C*H_3), 21.5 (–C_6H_4–*C*H_3), 21.7 (–C_6H_4–*C*H_3), 31.5 (*C*H$(CH_3)_2$), 41.5 (N*C*H$_2$), 45.0 (N*C*H$_2$), 45.3 (TsN*C*H$_2$), 45.7 (2× TsN*C*H$_2$), 57.7 (TsN*C*H), 127.5 (2× Ar–*C*H), 127.9 (2× Ar–*C*H), 129.5 (2× Ar–*C*H), 130.2 (2× Ar–*C*H), 133.0 (Ar–*C*), 136.9 (Ar–*C*), 143.7 (Ar–*C*), 144.5 (Ar–*C*), 169.3 (C=O).

(2*S*)-2-Isopropyl-1,4,7-tris[(4-methylphenyl)sulfonyl]-1,4,7-triazacyclononane 17. To a solution of 4-methyl-*N*((1*S*)-2-methyl-1-{[[(4-methylphenyl)sulfonyl](2-{[(4-methylphenyl)-sulfonyl]amino}ethyl)amino]methyl}propyl)benzenesulfonamide **16** (1.00 g, 1.63 mmol) in DMF (10 cm^3) at 0 °C was added a suspension of washed NaH (39 mg, 1.63 mmol) in DMF (1 cm^3) over 30 min. The suspension was allowed to come to room temperature and stirred for a further 1 h. Ethylene glycol ditosylate **9** (603 mg, 1.63 mmol) in DMF (1 cm^3) was added dropwise over 30 min to the solution. The temperature was raised to 80 °C and the final equivalent of NaH (39 mg, 1.63 mmol) in DMF (1 cm^3) was added by slow addition over 2 h. The solution was maintained at 80 °C overnight and at completion was quenched by the addition of water (10 cm^3). The DMF was removed under reduced pressure (12 mmHg) and the residue was dissolved in EtOAc (15 cm^3). The organic layer was washed with water (×2, 20 cm^3), dried (Na_2SO_4), filtered and evaporated to give a brown solid. Purification by column chromatography on silica (hexane–EtOAc–CH_2Cl_2 4 : 1 : 5) afforded a colourless solid (815 mg, 1.28 mmol, 78%); mp 178–180 °C; Found: MH^+ 634.2079. $C_{30}H_{39}O_6S_3N_3$ requires: 634.2089; $[a]_D$ −34.4 (*c* = 1, $CHCl_3$). υ_{max} (KBr, cm^{-1}) 3034 (w, C_6H_4), 2918 (m, CH), 2910 (m, CH), 2850 (w, CH), 1338 (s, SO_2NH), 1158 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.68 (d, *J* 6.7, 3H, –C*H*$_3$), 1.05 (d, *J* 6.7, 3H, –C*H*$_3$), 1.25 (m, 1H, C*H*$(CH_3)_2$), 2.39 (s, 3H, –C_6H_4–C*H*$_3$), 2.43 (s, 3H, –C_6H_4–C*H*$_3$), 2.44 (s, 3H, –C_6H_4–C*H*$_3$), 3.07 (m, 4H, C*H*$_2$NTs), 3.47 (m, 4H, C*H*$_2$NTs), 3.80 (m, 2H, C*H*$_2$NTs), 4.36 (m, 1H, C*H*NTs), 7.3 (m, 6H, –C_6H_4–CH_3), 7.58 (d, *J* 8.0, 2H, –C_6H_4–CH_3), 7.70 (d, *J* 8.0, 2H, –C_6H_4–CH_3), 7.83 (d, *J* 8.0, 2H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 20.6 (–*C*H_3), 21.72 (3× –C_6H_4–*C*H_3), 21.7 (*C*H$(CH_3)_2$), 46.1 (TsN*C*H$_2$), 47.8 (TsN*C*H$_2$), 46.3 (TsN*C*H$_2$), 51.3 (TsN*C*H$_2$), 52.1 (TsN*C*H$_2$), 53.9 (TsN*C*H$_2$), 127.5 (2 × Ar–*C*H), 128.0 (4 × Ar–*C*H), 128.1 (2 × Ar–*C*H), 130.1 (2 × Ar–*C*H), 130.2 (2 × Ar–*C*H), 143.5 (2 × Ar–*C*), 144.0 (2 × Ar–*C*), 144.3 (2 × Ar–*C*).

X-Ray crystallographic study of (2*S*)-2-isopropyl-1,4,7-tris-[(4-methylphenyl)sulfonyl]-1,4,7-triazacyclononane 17‡. Colourless crystals of **17** were grown from ethyl acetate solution. Crystal data for **17**, $C_{30}H_{39}N_3O_6S_3$; Measurements were made at 150 K on a colourless fragment cut from a larger crystal using a Rigaku AFC7S diffractometer. Hexagonal, space group $P6_5$, $a = b = 19.555(3)$, $c = 15.475(4)$ Å, $V = 5125.2(17)$ $Å^3$, $Z = 6$, Mo-Kα radiation, $\lambda = 0.71069$ Å, $\mu = 0.260$ mm^{-1}. Final refinement to convergence on F^2 gave $R = 0.0460$ (5086 obs. data only), $R_w = 0.1292$ (all 7639 unique data) and GOF = 1.024. Refinement of a Flack parameter to 0.00(8) indicates that the absolute structure is as shown.

(2*S*)-2-Isopropyl-1-[(4-methylphenyl)sulfonyl]-1,4,7-triaza-cyclononane 25 and (2*S*)-2-isopropyl-1,4-bis[(4-methylphenyl)-sulfonyl]-1,4,7-triazacyclononane 26. To a solution of HBr (48%, 1.6 cm^3) and glacial acetic acid (0.9 cm^3) was added (2*S*)-2-isopropyl-1,4,7-tris[(4-methylphenyl)sulfonyl]-1,4,7-triaza-cyclononane **17** (0.20 g, 0.32 mmol) to give a suspension. The reaction was heated to reflux upon which the suspension dissolved. The reaction was continued for a 48 h period. On completion, the reaction was cooled and ether (15 cm^3) was added to the reaction. The precipitate that formed was removed by filtration. The supernatant was washed with 2 M NaOH (×2, 15 cm^3), dried (Na_2SO_4), filtered and evaporated to give a brown solid. Purification by column chromatography on silica

‡ CCDC reference numbers 206761. See http://www.rsc.org/suppdata/ob/b3/b302887a/ for crystallographic data in .cif or other electronic format.

(hexane–EtOAc–CH_2Cl_2 2 : 3 : 5) afforded two fractions. The more mobile **26** as an off white solid (72 mg, 0.15 mmol, 47%); mp 104–106 °C; Found: MH^+ 480.2009; $C_{23}H_{34}O_4S_2N_3$ requires 480.1991; υ_{max} (KBr, cm^{-1}) 3323 (s, NH), 3052 (w, C_6H_4), 2964 (m, CH), 2848 (m, CH), 1325 (s, SO_2NH), 1162 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.83 (d, *J* 7.0, 6H, CH_3), 2.15 (m, 1H, $((CH_3)_2CH)$, 2.27 (m, 4H, CH_2N), 2.44 (s, 3H, $-C_6H_4-CH_3$), 2.52 (s, 3H, $-C_6H_4-CH_3$), 2.90 (m, 2H, CH_2NTs), 3.12 (m, 1H, CH_aH_bNTs), 3.28 (m, 2H, CH_2NTs), 3.46 (m, 1H, CH_aH_bNTs), 3.75 (m, 1H, CHNTs), 5.16 (br, 1H, NH), 7.24 (d, *J* 8.2, 2H, $-C_6H_4-CH_3$), 7.41 (d, *J* 8.2, 2H, $-C_6H_4-CH_3$), 7.75 (d, *J* 8.2, 2H, $-C_6H_4-CH_3$), 7.85 (d, *J* 8.2, 2H, $-C_6H_4-CH_3$); δ_C (100 MHz, $CDCl_3$) 16.6 ($-CH_3$), 18.2 ($-CH_3$), 21.7 ($C_6H_4-CH_3$), 21.8 ($C_6H_4-CH_3$), 29.3 ($(CH_3)_2CH$), 45.9 (2× NCH_2), 52.2 ($TsNCH_2$), 55.1 ($TsNCH_2$), 55.0 ($TsNCH_2$), 56.1 (TsNCH), 127.3 (2× Ar–CH), 127.9 (2× Ar–CH), 129.7 (2× Ar–CH), 130.0 (2× Ar–CH), 132.6 (Ar–C), 137.5 (Ar–C), 143.5 (Ar–C), 144.2 (Ar–C).

The more polar fraction gave yellow sticky solid **25** (29 mg, 0.09 mmol, 28%); mp 161–163 °C; Found: MH^+ 326.1923; $C_{16}H_{28}O_2SN_3$ requires 326.1902. υ_{max}(KBr, cm^{-1}) 3356 (w, NH), 3068 (w, C_6H_4), 2958 (m, CH), 2872 (m, CH), 1326 (s, SO_2NH), 1157 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.86 (d, *J* 6.0, 3H, CH_3), 0.90 (d, *J* 6.0, 3H, CH_3), 2.08 (m, 1H, $((CH_3)_2CH)$, 2.12 (m, 4H, CH_2N), 2.14 (m, 1H, CH_aH_bNTs), 2.27 (m, 1H, CH_aH_b-NTs), 2.40 (s, 3H, $-C_6H_4-CH_3$), 2.60 (m, 2H, CH_2N), 2.79 (m, 2H, CH_2NTs), 3.05 (m, 1H, CHNTs), 7.24 (d, *J* 8.2, 2H, $-C_6H_4-CH_3$), 7.41 (d, *J* 8.2, 2H, $-C_6H_4-CH_3$), 7.31 (d, *J* 8.1, 2H, $-C_6H_4-CH_3$), 7.74 (d, *J* 8.1, 2H, $-C_6H_4-CH_3$); δ_C (100 MHz, $CDCl_3$) 16.6 (CH_3), 18.6 (CH_3), 21.9 ($-C_6H_4-CH_3$), 29.4 (NCH), 46.1 (NCH_2), 46.5 (NCH_2), 54.3 (NCH_2), 55.1 ($TsNCH_2$), 56.9 (TsNCH), 127.6 (2 × Ar–CH), 129.8 (2 × Ar–CH), 137.6 (Ar–C), 143.6 (Ar–C).

(2*S*)-2-Isopropyl-1,4,7-triazacyclononane trihydrochloride 27. To a solution of (2*S*)-2-isopropyl-1,4,7-tris[(4-methylphenyl)-sulfonyl]-1,4,7-triazacyclononane **17** (350 mg, 0.55 mmol) in THF (25 cm^3) and EtOH (1.40 cm^3, 30 mmol) was condensed dry NH_3 (150 cm^3) at −78 °C. To this solution was added lithium metal (189 mg, 27 mmol) in small portions to give an intense blue color. The reaction mixture was allowed to warm to room temperature overnight. Water was added (10 cm^3) and the solution was acidified (pH 1) with conc HCl (1 cm^3). The aqueous solution was extracted with dichloromethane (×2, 10 cm^3). The aqueous phase was made basic (pH 14) by addition of solid NaOH (~500 mg). The basic solution was extracted with dichloromethane (×4, 10 cm^3), EtOAc (×2, 10 cm^3) and the combined organic phases were dried (Na_2SO_4), filtered and evaporated to give light yellow oil (72 mg, 0.42 mmol, 76%). To a solution of this oil (72 mg, 0.42 mmol) in EtOH (2 cm^3) was added conc. HCl (0.12 cm^3) at room temperature with rapid stirring. To this solution was added ether (10 cm^3) and the colourless precipitate that formed was removed by filtration and dried under reduced pressure to give the hydrochloride salt (89 mg, 0.29 mmol, 69%); mp 142–144 °C; Found: MH^+ 172.1813. $C_9H_{21}N_3$ requires 172.1811; $[a]_D$ +29.7 (*c* = 1, MeOH). υ_{max}(KBr, cm^{-1}) 3440 (w, NH), 2957 (s, CH), 2762 (s, CH); δ_H (400 MHz, D_2O) 1.00 (d, *J* 6.8, 3H, $-CH_3$), 1.08 (d, *J* 6.8, 3H, $-CH_3$), 1.94 (m, 2H, $CH(CH_3)_2$), 3.10 (m, 2H, $NHCH_2$), 3.41 (m, 6H, $NHCH_2$), 3.63 (m, 1H, NHCH); δ_C (100 MHz, D_2O) 18.2 ($-CH_3$), 19.0 ($-CH_3$), 30.9 ($CH(CH_3)_2$), 41.5 ($NHCH_2$), 41.8 ($NHCH_2$), 43.1 ($NHCH_2$), 43.1 ($NHCH_2$), 46.1 (NHCH), 59.1 (NHCH).

(2*S*)-2-Isopropyl-1,4,7-trimethyl-1,4,7-triazacyclononane 5. A stirred solution of (2*S*)-2-isopropyl-1,4,7-triazacyclononane **27** (110 mg, 0.64 mmol) and formaldehyde (37%, 0.4 cm^3, 5.9 mmol) and formic acid (90%, 0.60 cm^3, 13.9 mmol) was heated to reflux (bath temp. 90 °C) under a nitrogen atmosphere for 20 h. After cooling to room temperature the reaction was acidified (pH 1) with conc. HCl (1 cm^3) and the volatiles were removed under reduced pressure. The aqueous solution was extracted with dichloromethane (×2, 10 cm^3). The aqueous phase was made basic (pH 14) by addition of solid NaOH (~500 mg). The basic solution was extracted with dichloromethane (×4, 10 cm^3), and the combined organic phases were dried (Na_2SO_4), filtered and evaporated to give a light brown oil (98 mg, 0.46 mmol, 72%); Found: MH^+ 214.2286; $C_{12}H_{27}N_3$ requires 214.2283. $[a]_D$ +12.3 (*c* = 1, $CHCl_3$); υ_{max}(CCl_4, cm^{-1}) 2950 (m, CH), 2870 (m, CH); δ_H (400 MHz, $CDCl_3$) 0.84 (d, *J* 6.9, 3H, $-CH_3$), 0.86 (d, *J* 6.9, 3H, $-CH_3$), 1.66 (m, 1H, $CH(CH_3)_2$), 2.31 (m, 2H, NCH_2), 2.34 (s, 3H, NCH_3), 2.35 (s, 3H, NCH_3), 2.38 (s, 3H, NCH_3), 2.58 (m, 4H, NCH_2), 2.60 (m, 2H, NCH_2) 2.72 (m, 2H, NCH_2), 3.09 (m, H, NCH); δ_C (100 MHz, $CDCl_3$) 20.8 ($-CH_3$), 21.2 ($-CH_3$), 30.2 ($CH(CH_3)_2$), 37.8 (NCH_3), 46.7 (NCH_3), 47.6 (NCH_3), 56.1 (NCH_2), 56.3 (NCH_2), 57.2 (NCH_2), 57.3 (NCH_2), 57.4 (NCH_2), 69.2 (NCH).

(2*S*)-2-Isopropyl-1,4,7-trimethyl-1,4,7-triazacyclononane trihydrobromide. To a solution of (2*S*)-2-isopropyl-1,4,7-trimethyl-1,4,7-triazacyclononane **5** (98 mg, 0.46 mmol) in EtOH (2 cm^3) was added HBr (48%, 0.15 cm^3) at room temperature with rapid stirring. To this solution was added ether (10 cm^3) and the colourless precipitate that formed was removed by filtration and dried under reduced pressure to give the hydrobromide salt (121 mg, 0.37 mmol, 80%); mp 118–120 °C; Found: MH^+ 214.2273; $C_{12}H_{27}N_3$ requires 214.2283; $[a]_D$ +83.2 (*c* = 1, MeOH). υ_{max}(KBr, cm^{-1}) 3407 (s, NH, br), 2968 (m, CH), 2651 (m, CH); δ_H (400 MHz, D_2O) 1.51 (d, *J* 6.7, 3H, $-CH_3$), 1.66 (d, *J* 6.7, 3H, $-CH_3$), 2.65 (m, 1H, $CH(CH_3)_2$), 3.26 (s, 3H, N^+CH_3), 3.64 (m, 3H, N^+CH_3), 3.66 (m, 3H, N^+CH_3), 4.02 (m, 4H, N^+CH_2), 4.11 (m, 2H, N^+CH_2), 4.28 (m, 2H, N^+CH_2), 4.34 (m, 2H, N^+CH_2), 4.48 (m, 1H, N^+CH); δ_C (100 MHz, D_2O) 19.8 ($-CH_3$), 20.0 ($-CH_3$), 29.1 ($CH(CH_3)_2$), 42.8 (N^+CH_3), 45.8 (N^+CH_3), 46.3 (N^+CH_3), 54.4 (2× N^+CH_2), 65.2 (3× N^+CH_2), 69.5 (N^+CH).

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References

1 D. Parker, *Macrocyclic Synthesis A Practical Approach*, Oxford University Press, Oxford, 1996, Ch. 1; J. S. Bradshaw, K. E. Krakowiak and R. M. Izatt, *The Chemistry of Heterocyclic Compounds*, Wiley, New York, 1993, vol. 51; L. F. Lindoy, *The Chemistry of Macrocyclic Ligand Complexes*, CUP, Cambridge, 1989; P. Chadhuri and K. Wieghardt, *Prog. Inorg. Chem.*, 1987, **35**, 329–437.

2 For a review of biomimetic manganese catalysts see: R. Hage, *Recl. Trav. Chim. Pays-Bas.*, 1996, **115**, 385–395.

3 R. Hage, J. E. Iburg, J. Kerschner, J. H. Koek, E. L. M. Lempers, R. J. Martens, U. S. Racherla, S. W. Russell, T. Swathoff, H. R. P. van Vliet, J. B. Warnaar, L. van der Wolf and B. Krijnen, *Nature*, 1994, **369**, 637–638; S. H. Jureller, J. L. Kerschner and R. Humphreys, US Patent, US 5,329,024, 1994; *Chem. Abstr.*, 1995, **122**, 9845z.

4 D. De Vos and T. Bein, *Chem. Commun.*, 1996, 917–918; D. E. De Vos, J. L. Meinershagen and T. Bein, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2211–2213; D. E. De Vos and T. Bein, *J. Organomet. Chem.*, 1996, **520**, 195–200; A. Grenz, S. Ceccarelli and C. Bolm, *Chem. Commun.*, 2001, 1726–1727.

5 D. E. De Vos, B. F. Sels, M. Reynaers, Y. V. Subba Rao and P. A. Jacobs, *Tetrahedron Lett.*, 1998, **39**, 3221–3224.

6 A. Berkesssel and C. A. Sklorz, *Tetrahedron Lett.*, 1999, **40**, 7965–7968.

7 M. Beller, A. Tafesh, R. W. Fischer and B. Scharbert, German Patent, Ger. DE 195 523 890, 1996; *Chem. Abstr.*, 1997, **126**, 74725g; S. W. Golding, T. W. Hambley, G. A. Lawrence, S. M. Luther, M. Maeder and P. Turner, *J. Chem. Soc., Dalton Trans.*, 1999, 1875–1980.
8 C. Bolm, D. Kadereit and M. Valacchi, *Synlett*, 1997, 687–688.
9 C. Bolm, N. Meyer, G. Raabe, T. Weyhermüller and E. Bothe, *Chem. Commun.*, 2000, 2435–2436.
10 G. Argouarch, C. L. Gibson, G. Stones and D. C. Sherrington, *Tetrahedron Lett.*, 2002, **43**, 3795–3798.
11 (*a*) S. F. Mason and R. D. Peacock, *Inorg. Chim. Acta*, 1976, **19**, 75–77; (*b*) A. F. Drake, R. Kuroda and S. F. Mason, *J. Chem. Soc., Dalton Trans.*, 1979, 1095–1100; (*c*) M. Nonoyama, *Trans. Met. Chem.*, 1980, **5**, 269–271.
12 J. P. L. Cox, A. S. Craig, I. M. Helps, K. J. Jankowski, D. Parker, M. A. W. Eaton, A. T. Millican, K. Millar, N. R. A. Beeley and B. A. Boyce, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2567–2576.
13 J. H. Koek, E. W. M. J. Kohlen, S. W. Russell, L. van der Wolf, P. F. ter Steeg and J. C. Hellemons, *Inorg. Chim. Acta*, 1999, **295**, 189–199.
14 M. Beller, A. Tafesh, R. W. Fischer and B. Scharbert, German Patent, Ger. DE 195 23 891, 1995; *Chem. Abstr.*, 1997, **126**, 69346e.
15 B. M. Kim, S. M. So and H. J. Choi, *Org. Lett.*, 2002, **4**, 949–952.
16 J. E. W. Scheuermann, F. Ronketti, M. Motevalli, D. V. Griffiths and M. Watkinson, *New J. Chem.*, 2002, **26**, 1054–1059.
17 A. B. McDonald, B.Sc. Dissertation, University of Strathclyde, 1998.
18 J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.*, 1974, **96**, 2268–2270; T. J. Atkins, J. E. Richman and W. F. Oettlte, *Org. Synth.*, 1955, **Coll Vol III**, 652–662.
19 P. G. Graham and D. C. Weatherburn, *Aust. J. Chem.*, 1983, **36**, 2349–2354.
20 G. H. Searle and R. J. Geue, *Aust. J. Chem.*, 1984, **37**, 959–970.
21 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923–2925.
22 K. Alexander, S. Cook, C. L. Gibson and A. R. Kennedy, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1538–1549; M. Brenner and W. Huber, *Helv. Chim. Acta*, 1953, **36**, 1109–1115.