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Bifurcated, modular syntheses of chiral annulet triazacyclononanes

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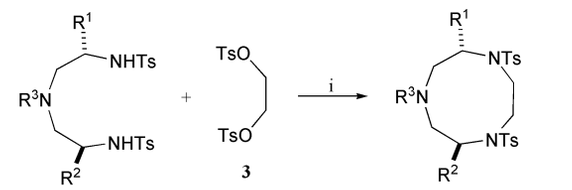
Three chiral 2,6-disubstituted tri-*N*-methyl azamacrocycles have been prepared by modular methods. These macrocycles were accessed from three chiral 1,4,7-triazaheptanes intermediates that were prepared by two independent routes. The first of these routes involved the benzylamine opening of chiral tosyl aziridines followed by debenzylation but was problematic on solubility grounds. A second, more effective, route was developed which avoided debenzylation by using ammonia in the nucleophilic opening of chiral tosyl aziridines.

Introduction

The continued interest in the synthesis of 1,4,7-triazacyclononane derivatives is maintained by the use of transition metal complexes of these azamacrocycles to catalyse a variety of processes. Transition metal complexes of 1,4,7-triazacyclononane derivatives have been investigated as biomimetics of manganese catalase,[1,2] Photosystem II,[1,3] and hemocyanin.[4] These metal complexes have also been used to catalyse organic transformations such as the hydrolytic cleavage of RNA,[5] DNA[6] and peptides[7] as well as the oxidation of sulfides,[8] alcohols,[9] alkanes[10] and alkenes.[11] In particular, the epoxidation of alkenes has generated considerable interest and stereoselective[12] as well as enantioselective processes have been described using chiral analogues of 1,4,7-triazacyclononane by Beller *et al.*,[13] Bolm *et al.*[14,15] and ourselves.[16]

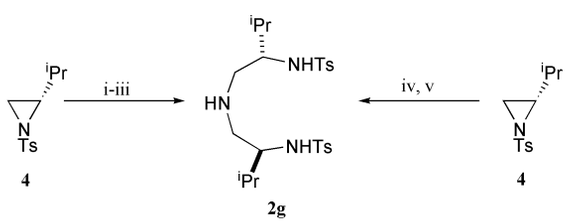
Despite the great interest in triazacyclononanes and their synthesis, the preparation of chiral variants where the stereochemistry is associated with the carbon backbone are less common. Thus, chiral triazacyclononanes with one,[17] two (C-2,3)[18] and three[15] stereocentres on the macrocyclic ring, have been prepared. Recently, ourselves (**1a**–**c**),[16] Kim *et al.* (**1e**)[19] and Watkinson and co-workers (**1b**,**d**)[20] have reported the preparation of 2,6-disubstituted triazacyclononanes **1a**–**e**. These three independent reports utilised the Richman–Atkins cyclisation of chiral 4-substituted 1,7-ditosyl-1,4,7-triazaheptanes **2a**–**e** with ethylene glycol ditosylate **3** in the key macrocyclisation step (Scheme 1). The key intermediate 4-substituted 1,7-ditosyl-1,4,7-triazaheptanes **2a**–**e** were prepared from 1,7-ditosyl-1,4,7-triazaheptanes **2f**–**h** which, in turn, were accessed by nitrogen based nucleophilic opening of the chiral tosyl aziridines *e.g.* **4** (Scheme 2). While Kim *et al.* used azide opening of chiral tosyl aziridine **4**, we and Watkinson and co-workers opted to use benzylamine. In our hands, the subsequent debenzylation of **2i**–**k** and analogues was problematic because of solubility problems. Herein, we report full experimental details of our syntheses of azamacrocycles **1a**–**c** and their detosylation and *N*-methylation from our previous communication.[16] In addition, an alternative route of choice, avoiding the debenzylation problems involving the opening of chiral tosyl aziridines with ammonia is described. In some cases, this alternative route leads to improved overall yields in comparison with the use of benzylamine aziridine opening and subsequent debenzylation.



2a $R^1 = R^2 = Me$ $R^3 = Ts$
2b $R^1 = R^2 = {}^iPr$ $R^3 = Ts$
2c $R^1 = Me$ $R^2 = {}^iPr$ $R^3 = Ts$
2d $R^1 = R^2 = {}^sBu$ $R^3 = Ts$
2e $R^1 = R^2 = {}^iPr$ $R^3 = CBZ$
2f $R^1 = R^2 = Me$ $R^3 = H$
2g $R^1 = R^2 = {}^iPr$ $R^3 = H$
2h $R^1 = Me$ $R^2 = {}^iPr$ $R^3 = H$
2i $R^1 = R^2 = Me$ $R^3 = Bn$
2j $R^1 = R^2 = {}^iPr$ $R^3 = Bn$
2k $R^1 = Me$ $R^2 = {}^iPr$ $R^3 = Bn$

1a $R^1 = R^2 = Me$ $R^3 = Ts$
1b $R^1 = R^2 = {}^iPr$ $R^3 = Ts$
1c $R^1 = Me$ $R^2 = {}^iPr$ $R^3 = Ts$
1d $R^1 = R^2 = {}^sBu$ $R^3 = Ts$
1e $R^1 = R^2 = {}^iPr$ $R^3 = CBZ$

Scheme 1 *Reagents and conditions*: $CsCO_3$, DMF, 80 °C or NaH, DMF.



Scheme 2 *Reagents and conditions*: i, NaN_3; ii, H_2, Pd–C, MeOH; iii, **4**; iv, 0.5 equiv. $BnNH_2$, MeOH; v, H_2, $Pd(OH)_2$, MeOH.

Results and discussion

The synthesis of chiral azamacrocycles **1a**–**c** began with the conversion of alaninol **5a** and valinol **5b** into the known tosyl aziridines **6**[21] and **4**[22] *via* tosylation and cyclisation through a modification of the method of Moberg and co-workers (Scheme 3).[23] It had been shown that sulfonamide aziridines could be opened with primary amines to give bis(adducts) under the appropriate conditions.[22a,24] This nucleophilic attack generally occurs at the least substituted carbon. Thus, reaction of tosyl aziridines **6** and **4** with 0.5 of an equivalent of benzylamine in methanol afforded the bis(adducts) **2i** and **2j** in 86 and 67%, respectively.[25,26] Alternatively, treatment of tosyl aziridine **6** with excess benzylamine in methanol at room temperature afforded the mono adduct **7** in 85% yield. Concomitantly with our communication,[16] Watkinson and co-workers[25] reported a similar approach to the mono adduct **7** (56%) and analogues

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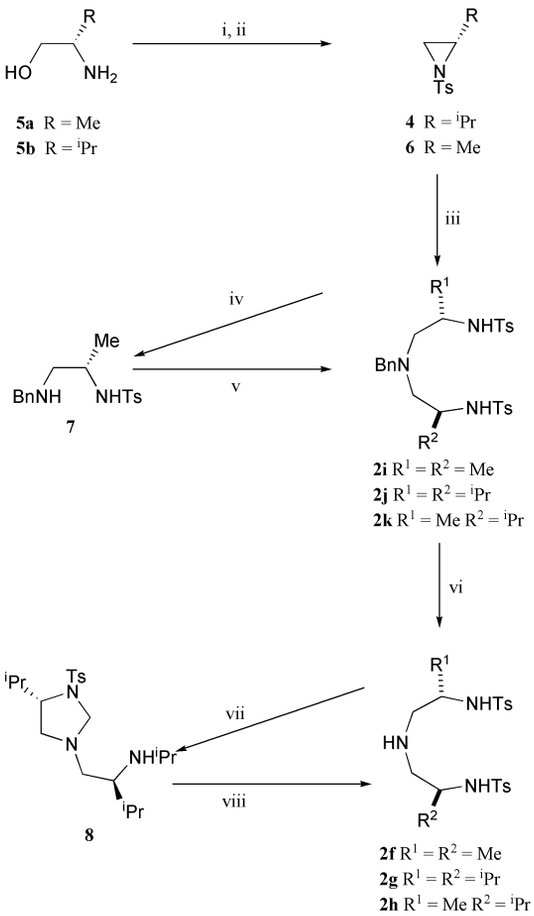
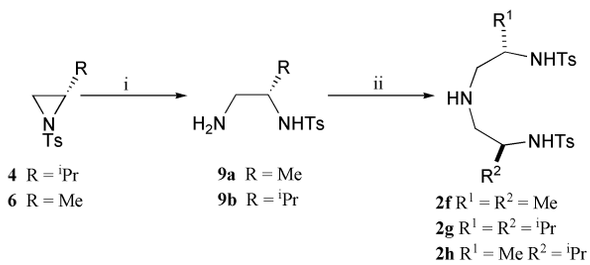


Scheme 3 *Reagents and conditions*: i, TsCl, pyr; ii, NaH, THF; iii, 0.5 equiv. $BnNH_2$, MeOH; iv, excess $BnNH_2$, MeOH; v, **6** MeOH; vi, H_2, $Pd(OH)_2$, MeOH or H_2, Pd–C, AcOH; vii, H_2, $Pd(OH)_2$, MeOH–CH_2Cl_2; viii, 3 M HCl, MeOH.

using acetonitrile at reflux. The subsequent reaction of mono adducts such as **7** with alternative tosyl aziridines was an attractive prospect because it might allow a divergent approach to C_1 symmetric chiral precursors. Accordingly, reaction of mono adduct **7** with tosyl aziridine **4** in methanol afforded the non-symmetrical bis(adduct) **2k** in 45% yield.

Ourselves and Watkinson and co-workers have shown that **2i**[16] and **2j**,[20] respectively, are not appropriate substrates for Richman–Atkins cyclisation because of nucleophilic interference by the benzyl protected amine. Accordingly, hydrogenolytic removal of the benzyl group from **2i** and **2j** using palladium hydroxide in methanol afforded the free amines **2f** and **2g** in 86 (65.2% overall from **5a**) and 71% yield (42.9% overall from **5b**), respectively. However, solubility problems were experienced in these debenzylation procedures. Indeed, in larger scale (*ca*. 1 g) debenzylation of **2g**, solubility problems were acute and required the addition of dichloromethane as co-solvent which afforded the novel imidazolidine **8** in 78% yield. Subsequent, acid hydrolysis of imidazolidine **8** afforded an alternative synthesis of amine **2g** (43.3% overall yield from **5b**). These solubility issues were severe for the debenzylation of **2k** and this deprotection was unsuccessful using palladium hydroxide in methanol. This process was achieved using palladium on charcoal with acetic acid as the solvent which afforded the non symmetric amine **2h** in 40% yield (13.5% overall from **5a**).

The above problems with solubility in the debenzylations of benzylamines **2i**–**k** forced us to re-evaluate routes to amines **2f**–**h**. The use of ammonia to open tosyl aziridines can yield mixtures of mono, bis and tris(adducts).[23,26] However, Taylor and co-workers have developed a two step process for the selective preparation of bis(adducts) *via* the mono ammonia opened tosyl aziridines.[22a,27] Accordingly, treatment of tosyl aziridine **6** with ammonia saturated methanol at 0 °C afforded the mono adduct **9a** in 95% yield (Scheme 4). Subsequent reaction of **9a** with tosyl aziridine **6** in toluene at reflux provided an alternative route to **2f** in 61% yield (51.1% overall from **5a**). Analogously, ammonia opening of tosyl aziridine **4** afforded the mono adduct **9b** in 89% which then reacted with tosyl aziridine **4** to provide **2g** in 56% (44.9% overall from **5b**).[22a,27] The non-symmetric amine **2h** was accessed by reaction of mono adduct **9a** with tosyl aziridine **4** in 88% yield (73.7% overall from **5a**). These alternative routes to the amines **2f**–**h** *via* the mono adducts **9** (Scheme 4) were the methods of choice as there were no solubility issues making the syntheses much easier. Moreover, the route using ammonia opening of aziridine was significantly more efficient than the route using benzylamine (Scheme 3) in the case of **2h** (70.3 *vs*. 13.5 % overall from **5a**).

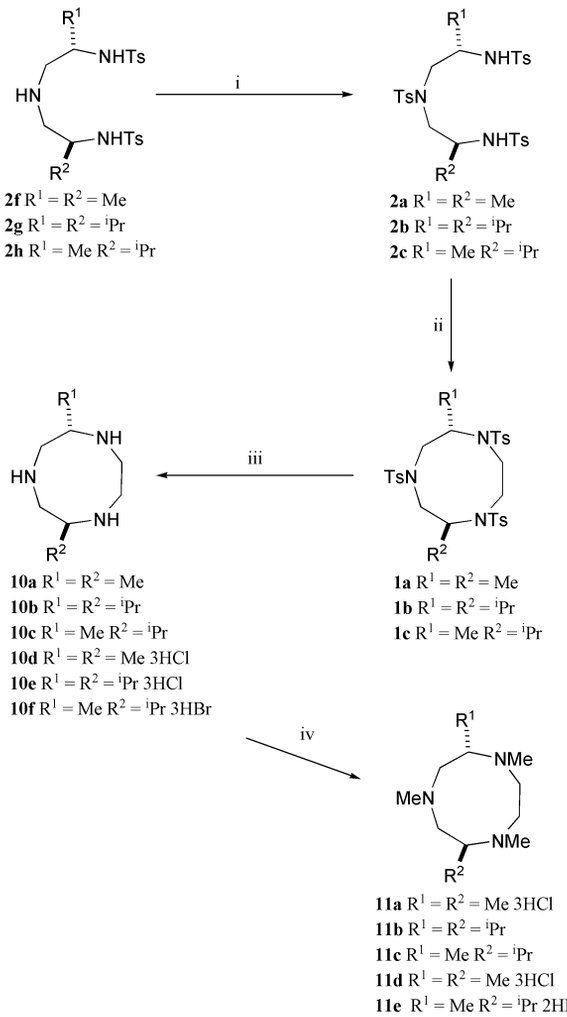


Scheme 4 *Reagents and conditions*: i, NH_3, MeOH, 0 °C; ii, **4** or **6**, $C_6H_4CH_3$, Δ.

With effective routes to the secondary amine tosamides **2f**–**h** in hand we turned our attention to facilitating macrocyclisation which required suppressing the nucleophilicity of the central amine function. In Richman–Atkins macrocyclisations,[28,29] the amino functionalities are commonly protected as their sulfonamide derivatives. Accordingly, treatment of amines **2f**–**h** with tosyl chloride in pyridine furnished the fully protected tristosamides **1a**–**c** (Scheme 5).

Richman–Atkins cyclisations to form aza crowns generally involve the reaction of the dianion of a bissulfonamide with a bistosylate ester in anhydrous DMF. The sodium dianion of the bissulfonamide is commonly prepared prior to cyclisation with sodium hydride in DMF or sodium ethoxide in ethanol.[28,29] Alternatively, the caesium salt can be generated *in situ* using caesium carbonate in DMF. We have generally found that the use of sodium hydride in DMF is a more effective procedure to carry out the macrocyclisations to afford C-substituted 1,4,7-triazacyclononane tristosamides.[30] Therefore, macrocyclisation of the tristosamides **2a**–**c** with sodium hydride in DMF with ethylene glycol ditosylate **3** smoothly afforded the triazacyclononane tristosamides **1a**–**c** in over 70% yield.

The subsequent steps from tristosamides **1a**–**c** required the removal of the *N*-tosyl protecting groups and subsequent *N*-alkylation. *N*-Tosyl groups have been removed from C-alkyl substituted triazacyclononanes by three popular deprotection procedures. Thus, Mason *et al.* and Weatherburn *et al.* have used hydrobromic acid in glacial acetic acid at reflux to deprotect a C-methyl substituted triazacyclononane tristosamide.[17a,d] However, we have found that this method gives incomplete deprotection of C-alkyl triazacyclononane tristosamides, forming instead a mixture of mono and bistosamide macrocycles.[30] Alternatively, Parker and co-workers have removed the tosyl protecting groups in a 2-(4-benzamidobutyl)-1,4,7-triazacyclononane tristosamide by lithium in ammonia or by heating in concentrated sulfuric acid.[17e] We have found that the lithium in ammonia reductive deprotection to be very efficient in the case of C-alkyl macrocycles.[30] Accordingly, lithium in ammonia detosylation of tosamides **1a**–**c** provided the free amines **10a**–**c**. In the case of **10b** and **10c** the process was reasonably efficient with the formation of products in 66 and 87% yield, respect-



2f $R^1 = R^2 = Me$
2g $R^1 = R^2 = {}^iPr$
2h $R^1 = Me\ R^2 = {}^iPr$

2a $R^1 = R^2 = Me$
2b $R^1 = R^2 = {}^iPr$
2c $R^1 = Me\ R^2 = {}^iPr$

10a $R^1 = R^2 = Me$
10b $R^1 = R^2 = {}^iPr$
10c $R^1 = Me\ R^2 = {}^iPr$
10d $R^1 = R^2 = Me$ 3HCl
10e $R^1 = R^2 = {}^iPr$ 3HCl
10f $R^1 = Me\ R^2 = {}^iPr$ 3HBr

1a $R^1 = R^2 = Me$
1b $R^1 = R^2 = {}^iPr$
1c $R^1 = Me\ R^2 = {}^iPr$

11a $R^1 = R^2 = Me$ 3HCl
11b $R^1 = R^2 = {}^iPr$
11c $R^1 = Me\ R^2 = {}^iPr$
11d $R^1 = R^2 = Me$ 3HCl
11e $R^1 = Me\ R^2 = {}^iPr$ 2HBr

Scheme 5 *Reagents and conditions*: i, TsCl, Pyr; ii, **3**, NaH, DMF, 80 °C; iii, Li, NH_3, EtOH; iv, CH_2O, HCO_2H, Δ.

ively. The deprotection of the dimethyl substituted macrocycle **1a** was achieved in a disappointing yield of 13% and was a function of the water solubility of triamine **10a**. The C_2 symmetric macrocycles **10a** and **10b** were additionally characterised as their respective hydrochloride salts **10d** and **10e** while the non-symmetric macrocycle **1c** was also characterised as the hydrobromide salt **10f**. The use of sulfuric acid deprotection was investigated in the case of deprotection of the non-symmetric macrocycle **1c** which afforded a lower yield of the free amine **10c** (63%).

The final step in our syntheses required the *N*-methylation of macrocycles **10a**–**c**. After a brief model study of the methylation of 1,4,7-triazacyclononane using butyllithium and methyl iodide[31] (45%) or Eschweiler–Clarke (82%)[32] it was decided to use the later *N*-methylation procedure on the grounds of efficiency and purity of the product. Furthermore, the use of Eschweiler–Clarke *N*-methylation proved to be particularly advantageous in the case of dimethyl macrocycle **10a**. In this case simply taking the crude aqueous extract after lithium in ammonia detosylation of **1a** and subjecting it to these *N*-methylation conditions afforded the dimethyl macrocycle **11a** in 44% over two steps. As water solubility was not an issue with **10b** and **10c**, Eschweiler–Clarke *N*-methylation of the isolated macrocycles gave the requisite novel macrocycles **11b** and **11c** in 66 and 90% yields, respectively. The *N*-methyl macrocycles **11a** and **11c** were additionally characterised as their salts **11d** and **11e**, respectively. The crystalline nature of hydrobromide salt **11e** allowed an X-ray analysis to be carried out and allowed both the stereochemistry and the absolute structure to be confirmed unequivocally by single crystal diffraction (Fig. 1).

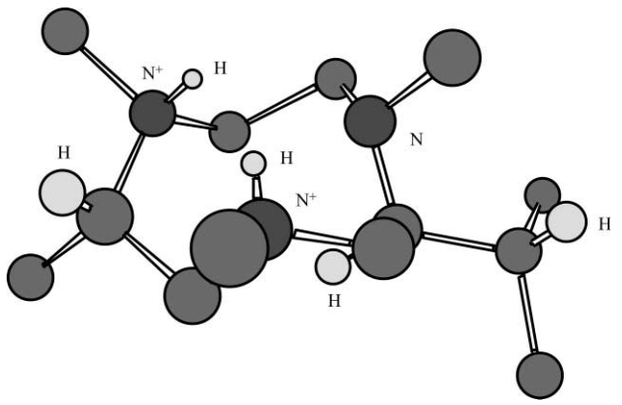


Fig. 1 Chem3D representation of the molecular structure of **11e** with only the key hydrogen atoms included for clarity.

Unexpectedly, this material was the dihydrobromide salt **11e** rather than the anticipated trihydrobromide salt. The dihydrobromide salt **11e** results from protonation of the less sterically encumbered N1 and N4 while N7, adjacent to the isopropyl group remains as the free base.

Conclusions

Two independent and modular routes have been developed for the syntheses of chiral 1,4,7-triazaheptanes as intermediates in the preparation of chiral 1,4,7-triazamacrocycles. The first modular route to 1,4,7-triazaheptanes involved the benzylamine nucleophilic opening of chiral tosyl aziridines followed by hydrogenolytic debenzylation. Solubility problems in the debenzylation step were overcome by developing an alternate route that avoided the need for this deprotection step. These more amenable routes involved the nucleophilic opening of chiral tosyl aziridines with ammonia, which led, in some cases, to increased efficiencies. The highly modular nature of these routes readily allowed the preparation of C_2 symmetric and dissymmetric 1,4,7-triazaheptanes. These key intermediates were then used in the preparation of three chiral 2,6-disubstituted 1,4,7-trimethyl triazamacrocycles in 8–9 steps overall and 12.77–29.9% overall yields.

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 . The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and the concentrations are given 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, KBr discs or as a 1–2% solution (CCl_4). 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.

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.*[33] using silica gel (230–400 mesh).

Experimental procedures

(2*S*)-2-Methyl-1-[(4-methylphenyl)sulfonyl]aziridine 6. Using (*S*)-alaninol **5a** and the method of Moberg and co-workers,[23] the title compound was obtained as an off white solid (4.4 g, 20.8 mmol, 88%); mp 60–62 °C (lit.[21] mp 58–59 °C); Found C, 56.87; H, 6.1; N, 6.61; S, 15.48%; MH^+ *m/z* 212.0736; Calculated for $C_{10}H_{14}NO_2$: C, 56.85; H, 6.2; N, 6.63; S, 15.17%; *m/z* 212.0659; $[a]_D$ +30.3 (*c* = 1.02, $CHCl_3$) (lit.[21] +29.6 (*c* = 1.02, $CHCl_3$)); ν_{max} (KBr, cm^{-1}) 3049 (w, C_6H_4), 2962 (s, CH), 2928 (m, CH), 2873 (w, CH), 1319 (s, SO_2NH), 1159 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 1.26 (d, *J* 5.6, 3H, –CH_3), 2.02 (d, *J* 5.8, 1H, TsNCH_2), 2.45 (s, 3H, –C_6H_4–CH_3), 2.62 (d, *J* 7.0, 1H, TsNCH_2), 2.82 (m, 1H, TsNCH), 7.34 (d, *J* 8.0, 2H, –C_6H_4–CH_3), 7.82 (d, *J* 8.0, 2H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 17.0 (–CH$_3$), 21.8 (–C_6H_4–CH$_3$), 35.0 (TsNCH$_2$), 36.1 (TsNCH), 128.0 (Ar–CH), 129.9 (Ar–CH), 136.6 (Ar–C), 144.6 (Ar–C).

(2*S*)-2-Isopropyl-1-[(4-methylphenyl)sulfonyl]aziridine 4. Analogously, (*S*)-valinol **5b** afforded the title compound as an off white solid (3.3 g, 13.6 mmol, 90%); mp 85–87 °C (lit.[27] 75–77 °C); Found C, 60.5; H, 7.2; N, 5.8; S, 13.4%; MH^+ *m/z* 240.1051; Calculated for $C_{12}H_{27}O_2SN$: C, 60.2; H, 7.2; N, 5.9; S, 13.4%; *m/z* 240.1058; $[a]_D$ +15.9 (*c* = 0.95, $CHCl_3$) (lit.[27] +12.2 (*c* = 1.2, $CHCl_3$)); ν_{max} (KBr, cm^{-1}) 3049 (w, C_6H_4), 2962 (s, CH), 2928 (m, CH), 2873 (w, CH), 1319 (s, SO_2NH), 1159 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.80 (d, *J* 6.7, 3H, –CH_3), 0.90 (d, *J* 6.7, 3H, –CH_3), 1.42 (m, 1H, CH(CH_3)$_2$), 2.10 (d, *J* 4.6, 1H, TsNCH_2), 2.45 (s, 3H, –C_6H_4–CH_3), 2.52 (m, 1H, TsNCH), 2.61 (d, *J* 8.0, 1H, TsNCH_2), 7.34 (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, $CDCl_3$) 19.2 (–CH$_3$), 19.7 (–CH$_3$), 21.8 (–C_6H_4–CH$_3$), 30.3 (CH(CH_3)$_2$), 32.9 (TsNCH$_2$), 46.4 (TsNCH$_2$); 128.3 (Ar–CH), 129.7 (Ar–CH), 135.4 (Ar–C), 144.6 (Ar–C).

***N*-{(1*S*)-2-[Benzyl((2*S*)-{(4-methylphenyl)sulfonyl]amino}-propyl)amino]-1-methylethyl}-4-methylbenzenesulfonamide 2i.** To a solution of (2*S*)-2-methyl-1-[(4-methylphenyl)sulfonyl]-aziridine **6** (1.8 g, 8.53 mmol) in methanol (20 cm^3) was added benzylamine (456 mg, 4.26 mmol). The solution was stirred for 4 days at room temperature, upon completion of this period the solvent was evaporated to give a crude brown solid. Purification by column chromatography on silica (hexane : EtOAc from 2 : 1 to 1 : 1) afforded a colourless solid (1.94 g, 3.67 mmol, 86%); mp 129 °C (lit. for hemi hydrate[25] 91–92 °C). Found C, 60.84; H, 6.46; N, 7.74%; MH^+ *m/z* 530.2153; Calculated for $C_{27}H_{35}O_4S_2N_3$: C, 61.22; H, 6.66; N, 7.94%; *m/z* 530.2147; $[a]_D$ −13.8 (*c* = 1.00, $CHCl_3$) (lit. for hemi hydrate[25] −43.2 (*c* = 0.5, $CHCl_3$)); ν_{max} (KBr, cm^{-1}) 3450–3100 (bm, NHTs), 3064 (w, ArH), 3030 (w, ArH), 2970, 2930, 2820 (all w, CH), 1332 (s, NSO_2), 1162 (s, NSO_2), 1094 (s), 815 (m, ArH); δ_H (250 MHz, $CDCl_3$) 0.91 (d, *J* 6.3, 6H, –CH_3), 2.15–2.41 (m, 4H, NCH_2), 2.33 (s, 6H, –C_6H_4–CH_3), 3.08 (d, *J* 13.5, 1H, NC$H_a$$H_b$), 3.36 (m, 2H, NC$H$), 3.47 (d, *J* 13.5, 1H, NC$H_a$$H_b$), 5.24 (bs, 2H, SO_2NH), 7.02–7.05 (m, 2H, ArH), 7.19–7.31 (m, 7H, ArH), 7.76 (d, *J* 8.1, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 19.8 (–CH$_3$), 21.6 (–C_6H_4CH$_3$), 47.1 (NCH_2), 57.9 (NCH$_2$), 59.6 (TsNCH), 127.2, 127.4, 128.5, 129.3, 129.7 (all Ar–CH), 137.5, 138.1, 143.3 (all Ar–C).

((1*S*)-1-{[Benzyl((2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)amino]methyl}-2-methylpropyl)-4-methylbenzenesulfonamide 2j. The title compound was obtained in an analogous fashion to **2i** using (2*S*)-2-isopropyl-1-[(4-methylphenyl)sulfonyl]aziridine **4** (2.2 g, 14.2 mmol) and benzylamine (492 mg, 4.60 mmol). Purification by column chromatography on silica (hexane : ethyl acetate 2 : 1) followed by recrystallisation (hexane : dichloromethane 2 : 1) afforded a colourless solid (1.8 g, 3.08 mmol, 67%); mp 123–125 °C (lit.[25] 135–136 °C); Found MH^+ *m/z* 586.2773; Calculated for $C_{31}H_{43}O_4S_2N_3$ *m/z* 586.2773; $[a]_D$ −12.2 (*c* = 1.00, $CHCl_3$) (lit.[25] −37.6 (*c* = 0.5, $CHCl_3$)); ν_{max} (KBr, cm^{-1}) 3266 (s, *NH*Ts), 3034 (w, C_6H_4), 2966 (s, CH), 2927 (m, CH), 2876 (w, CH), 1325 (s, SO_2NH), 1160 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.65 (d, *J* 8.2, 6H, –CH_3), 0.67 (d, *J* 7.0, 6H, –CH_3), 1.89 (m, 2H, CH(CH_3)$_2$), 2.30 (d, *J* 5.7, 2H, CH_2N), 2.34 (d, *J* 5.7, 2H, CH_2N), 2.41 (s, 6H, –C_6H_4–CH_3) 2.48 (m, 2H, NCH_2), 3.47 (m, 2H, TsNHCH), 7.23 (m, 5H, –C_6H_5) 7.28 (m, 4H, –C_6H_4–CH_3), 7.81 (d, *J* 8.3, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 17.5 (–CH$_3$), 18.0 (–CH$_3$), 21.7 (2 × –C_6H_4–CH$_3$), 29.9 (CH(CH_3)$_2$), 54.3 (2 × NCH$_2$), 56.2 (NCH$_2$), 58.6 (2 × TsNCH), 127.1 (2 × Ar–CH), 127.4 (2 × Ar–CH), 128.5 (2 × Ar–CH), 129.6 (2 × Ar–CH), 129.7 (2 × Ar–CH), 137.9 (2 × Ar–C), 139.0 (2 × Ar–C), 143.1 (Ar–C).

***N*-[(1*S*)-2-(Benzylamino)-1-methylethyl]-4-methylbenzenesulfonamide 7.** To a solution of (2*S*)-2-methyl-1-[(4-methylphenyl)sulfonyl]aziridine **6** (422 mg, 2 mmol) in methanol (10 cm^3) was added benzylamine (1 g, 9.34 mmol). The solution was stirred for 2 days at room temperature, upon completion of this period the solvent was evaporated. Purification by column chromatography on silica (hexane : EtOAc from 1 : 4) afforded a colourless oil (542 mg, 1.70 mmol, 85%); Found C, 63.72; H, 6.91; N, 9.2; S, 10.18%; MH^+ *m/z* 319.1482; Calculated for $C_{17}H_{22}O_2SN_2$ C, 64.12; H, 6.69; N, 8.8; S, 10.07%; *m/z* 319.1480; $[a]_D$ +2.6 (*c* = 0.70, $CHCl_3$) (lit.[25] −4.8 (*c* = 0.5, $CHCl_3$)); ν_{max} (CCl_4, cm^{-1}) 3710–3460 (bw, NH), 3460–3130 (s, SO_2NH), 3080, 3060, 3030 (all s, ArH), 2975, 2930, 2870, 2850 (all s, CH), 1600, 1490, 1450 (all s, Ar), 1320 (s, SO_2N), 1150 (s, SO_2N), 1095 (s), 820 (s), 740 (s), 700 (s); δ_H (250 MHz, $CDCl_3$) 1.06 (d, *J* 6.5, 3H, –CH_3), 2.36 (s, 3H, –C_6H_4–CH_3), 2.38–2.57 (m, 2H, NCH_2), 3.23 (m, 1H, TsNHCH), 3.53 (s, 2H, NCH_2), 7.15–7.32 (m, 7H, ArH), 7.70 (d, *J* 8, 2H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 20.0 (–CH$_3$), 21.9 (–C_6H_4–CH$_3$), 49.2 (NCH$_2$), 53.6 (NCH$_2$), 54.1 (2 × TsNCH), 127.6 (Ar–CH), 127.7 (Ar–CH), 128.4 (Ar–CH), 128.9 (Ar–CH), 130.1 (Ar–CH), 138.0 (Ar–C), 140.2 (Ar–C), 143.7 (Ar–C).

***N*-{(1*S*)-2-[Benzyl((2*S*)-3-methyl-2-{[(4-methylphenyl)-sulfonyl]amino}butyl)amino]-1-methylethyl}-4-methylbenzenesulfonamide 2k.** To a solution of (2*S*)-2-isopropyl-1-[(4-methylphenyl)sulfonyl]aziridine **4** (433 mg, 1.81 mmol) in methanol (10 cm^3) was added *N*-[(1*S*)-2-(benzylamino)-1-methylethyl]-4-methylbenzenesulfonamide **7** (576 mg, 1.81 mmol). The solution was stirred for 4 days at RT and the solvent was evaporated. The crude product was purified by column chromatography on silica (hexane : EtOAc 3 : 1) to give the unreacted aziridine **4** in a first fraction (206 mg, 0.86 mmol, 48%) and in a second fraction the title compound as a colourless solid (452 mg, 0.81 mmol, 45%); mp 143–145 °C; Found C, 62.54; H, 7.16; N, 7.39%; MH^+ *m/z* 558.2444; $C_{29}H_{39}N_3O_4S_2$ requires C, 62.45; H, 7.05; N, 7.54%; *m/z* 558.2460; $[a]_D$ = −12.8 (*c* = 0.50, $CHCl_3$); ν_{max} (KBr, cm^{-1}) 3270 (s, SO_2NH), 3060 and 3030 (w, ArH), 2960 and 2930 (m, CH), 1600 (w, Ar), 1445 (s), 1320 (s, SO_2N), 1160 (s, SO_2N), 810 (m, ArH), 750 (m, ArH), 700 (m, ArH); δ_H (400 MHz, $CDCl_3$) 0.64 (d, *J* 6.8, 3H, –CH_3), 0.67 (d, *J* 6.9, 3H, –CH_3), 1.04 (d, *J* 6.3, 3H, –CH_3), 1.81 (m, 1H, CH(CH_3)$_2$), 2.27–2.32 (m, 2H, CH_2N), 2.39 (s, 3H, –C_6H_4–CH_3), 2.42 (s, 3H, –C_6H_4–CH_3), 2.43–2.49 (m, 2H, CH_2N), 3.19 (d, *J* 13.3, 1H, C$H_a$$H_b$Ph), 3.43 (m, 1H, TsNHC$H$), 3.53 (m, 1H, TsNHC$H$), 3.68 (d, *J* 13.3, 1H, C$H_a$$H_b$Ph), 4.85 (bs, 1H, TsN$H$CH), 5.48 (bs, 1H, TsN$H$CH), 7.16–7.30 (m, 9H, ArH), 7.80–7.85 (m, 4H, ArH); δ_C (100 MHz, $CDCl_3$) 17.5 (–CH$_3$),

18.0 (–CH_3), 20.0 (–CH_3), 21.6 (–C_6H_4–CH_3), 21.7 (–C_6H_4–CH_3), 30.1 ($CH(CH_3)_2$), 47.0 (NCH_2), 54.6 (NCH_2), 56.2 (NCH_2), 58.3 (TsNCH), 59.7 (TsNCH), 127.1 (Ar–CH), 127.2 (Ar–CH), 127.4 (Ar–CH), 128.5 (Ar–CH), 129.5 (Ar–CH), 129.6 (Ar–CH), 129.7 (Ar–CH), 137.6 (Ar–C), 138.4 (Ar–C), 138.8 (Ar–C), 143.2 (Ar–C), 143.3 (Ar–C).

[(1*S*)-2-Amino-1-methylethyl]-4-methylbenzenesulfonamide 9a. To a saturated solution of ammonia in methanol (300 cm^3) at 0 °C was added, dropwise, with stirring a solution of (2*S*)-2-methyl-1-[(4-methylphenyl)sulfonyl]aziridine **6** (4.8 g, 22.77 mmol) in methanol (100 cm^3) over a period of 2 h. Ammonia was bubbled continuously through the reaction mixture during addition and for 30 min after it was completed. The solution flask was stoppered and allowed to stand for 24 h. The volatiles were evaporated under reduced pressure to afford the title compound as a colourless solid (4.95 g, 21.69 mmol, 95%) (toluene); mp 128–130 °C; Found C, 52.8; H, 7.38; N, 12.17; S, 14.36%; MH^+ *m*/*z* 229.0994; $C_{10}H_{16}N_2O_2S$ requires C, 52.61; H, 7.06; N, 12.27; S, 14.04%; *m*/*z* 229.1011; $[a]_D$ 14.9 (*c* = 1, $CHCl_3$); ν_{max} (KBr, cm^{-1}) 3350 (s, NH_2), 3290 (m, NHTs), 3055 (s, C_6H_4), 2980 (s, CH), 2878 (s, CH), 2626 (s, CH), 1600 (s), 1493 (s), 1457 (s), 1311 (s, SO_2NH), 1156 (s, SO_2NH), 1097 (s), 815 (s, C_6H_4); δ_H (400 MHz, $CDCl_3$) 0.99 (d, *J* 6.6, 3H, –CH_3), 2,40 (s, 3H, C_6H_4–CH_3), 2.49 (dd, *J* 13, 6.97, 1H, CH_2NH_2), 2.66 (dd, *J* 13, 4.49, 1H, CH_2NH_2), 3.14–3.22 (m, 1H, CHNHTs), 7.27 (d, *J* 7.98, 2H, –C_6H_4–CH_3), 7.75 (d, *J* 7.98, 2H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 18.99 (–CH_3), 21.64 (–C_6H_4–CH_3), 47.31 (CH_2NH_2), 51.87 (TsNCH), 127.19 (2 × Ar–CH), 129.81 (2 × Ar–CH), 138.13 (Ar–C), 143.36 (Ar–C).

[(1*S*)-1-(Aminomethyl)-2-methylpropyl]-4-methylbenzenesulfonamide 9b. Compound **9b** was prepared in an analogous fashion to **9a** using (2*S*)-2-isopropyl-1-[(4-methylphenyl)-sulfonyl]aziridine **4** (1.4 g, 5.8 mmol) which afforded a colourless solid (1.35 g, 5.2 mmol, 89%); mp 85–87 °C (lit.[22a] 87–88 °C); Found MH^+ *m*/*z* 257.1334; $C_{12}H_{20}O_2SN_2$ requires *m*/*z* 257.1323; $[a]_D$ −15.9 (*c* = 1, $CHCl_3$) (lit.[22a] +12.0 *c* = 1, C_6H_6); ν_{max} (KBr, cm^{-1}) 3396 (s, NH_2), 3357 (s, NH_2), 3297 (s, *NH*Ts), 3070 (s, C_6H_4), 2959 (s, CH), 2873 (s, CH), 2778 (m, CH), 1311 (s, SO_2NH), 1148 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.79 (d, *J* 6.9, 3H, –CH_3), 0.81 (d, *J* 6.9, 3H, –CH_3), 1.77 (m, 1H, CH(CH_3)$_2$), 2.42 (s, 3H, –C_6H_4–CH_3), 2.58 (dd, *J* 13.2, 4.7, 1H, –CH_2NH_2), 2.67 (dd, *J* 13.2, 6.0, 1H, –CH_2NH_2), 2.96 (m, 1H, CHNHTs), 7.29 (d, *J* 8.0, 2H, –C_6H_4–CH_3), 7.78 (d, *J* 8.0, 2H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 18.7 (–CH_3), 18.9 (–CH_3), 30.0 (–C_6H_4–CH_3), 30.4 ($CH(CH_3)_2$), 42.5 (CH_2NH_2) 61.2 (TsNCH), 127.2 (2 × Ar–CH), 129.7 (2 × Ar–CH), 138.4 (Ar–C), 143.3 (Ar–C).

4-Methyl-*N*-{(1*S*)-1-methyl-2-[((2*S*)-2-{[(4-methylphenyl)-sulfonyl] amino]propyl)amino]ethyl}benzenesulfonamide 2f. *Method (a), via* debenzylation of *N-{(1S)-2-[benzyl((2S)-{(4-methylphenyl)sulfonyl]amino}propyl)amino]-1-methylethyl}-4-methylbenzenesulfonamide* ***2i***. *N*-{(1*S*)-2-[Benzyl((2*S*)-{(4-methylphenyl)sulfonyl]amino}propyl)amino]-1-methylethyl}-4-methylbenzenesulfonamide **2i** (1.62 g, 3.06 mmol) and $Pd(OH)_2$ (163 mg, 10 mol% Pd) in MeOH (30 cm^3) under 1 atm H_2 at RT. After 1 h, the hydrogenation was complete and the solvent was evaporated. Purification of the crude product on silica (EtOAc) gave a colourless solid (1.15 g, 2.62 mmol, 86%); mp 131°C; Found C, 54.56; H, 6.63; N, 9.46%; MH^+ *m*/*z* 440.1673; $C_{20}H_{29}N_3O_4S_2$ requires C, 54.65; H, 6.65; N, 9.56%; *m*/*z* 440.1678; $[a]_D$ = −15.4 (*c* = 1, $CHCl_3$); ν_{max} (KBr, cm^{-1}) 3260 (s, SO_2NH), 3060 and 3039 (w, ArH), 2970, 2930 and 2870 (all s, CH), 1600 (m, Ar), 1460 (s), 1440 (s), 1320 (s, SO_2N), 1150 (s, SO_2N), 820 (s, ArH); δ_H (400 MHz, $CDCl_3$) 0.95 (d, *J* 6.6, 6H, –CH_3), 2.30–2.38 (m, 4H, –CH_2NH), 2.40 (s, 6H, –C_6H_4–CH_3), 3.23 (m, 2H, –CHTsN), 5.20 (bs, 2H, TsNH), 7.29 (d, *J* 7.9, 4H, –C_6H_4–CH_3), 7.77 (d, *J* 7.9, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 19.4 (–CH_3), 21.6 (–CH_3), 49.1 (NCH_2), 54.1 (NCH), 127.2 (Ar–CH), 129.9 (Ar–CH), 137.9 (Ar–C), 143.4 (Ar–C).

Method (b), via ring opening of *(2S)-2-methyl-1-[(4-methylphenyl)sulfonyl]aziridine* ***6*** *with [(1S)-2-amino-1-methylethyl]-4-methylbenzenesulfonamide* ***9a***. A solution of [(1*S*)-2-amino-1-methylethyl]-4-methylbenzenesulfonamide **9a** (1.5 g, 6.6 mmol) in anhydrous toluene (25 cm^3) was heated to reflux under an inert atmosphere. To this solution was added (2*S*)-2-methyl-1-[(4-methylphenyl)sulfonyl]aziridine **6** (1.4 g, 6.6 mmol) dropwise over a 2 h period. The reaction mixture was heated at reflux temperature for an additional 48 h. On completion of this period the toluene was removed under reduced pressure and the residue was dissolved in dichloromethane (10 cm^3). The dichloromethane extract was washed with 3 M HCl (×2, 15 cm^3) dried (Na_2SO_4), filtered and evaporated to give a light brown solid. Purification by column chromatography on silica (hexane : EtOAc : CH_2Cl_2 2 : 3 : 5) afforded a colourless solid (1.9 g, 4.0 mmol, 60%) with identical spectroscopic data to that recorded above.

4-Methyl-*N*-((1*S*)-2-methyl-1-{[((2*S*)-3-methyl-2{[(4-methylphenyl)sulfonyl]amino}butyl)amino]methyl}propyl)benzenesulfonamide 2g. *Method (a), via* debenzylation of *((1S)-1-{[benzyl-((2S)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)-amino]methyl}-2-methylpropyl)-4-methylbenzenesulfonamide* ***2j***. Debenzylation of ((1*S*)-1-{[benzyl((2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)amino]methyl}-2-methylpropyl)-4-methylbenzenesulfonamide **2j** (1 g, 1.79 mmol) in an analogous fashion to the preparation of **2f** followed by column chromatography on silica (hexane : EtOAc : CH_2Cl_2 2 : 3 : 5) gave the title compound as a colourless solid (695 mg, 1.4 mmol, 78%); mp 121–123 °C (lit.[22a] 121–122 °C); Found MH^+ *m*/*z* 496.2317; $C_{24}H_{37}O_4S_2N_3$ requires *m*/*z* 496.2304; $[a]_D$ −21.8 (*c* = 0.5, $CHCl_3$) (lit.[27] −17.0 (*c* = 1.1, $CHCl_3$)); ν_{max} (KBr, cm^{-1}) 3289 (s, *NH*Ts), 3230 (s, NH), 2957 (s, CH), 2810 (m, CH), 1322 (s, SO_2NH), 1159 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.65 (m, 12H, –CH_3), 1.66 (m, 2H, CH(CH_3)$_2$), 2.33 (m, 2H, CH_2NH), 2.41 (s, 6H, –C_6H_4–CH_3), 2.45 (m, 2H, CH_2NH), 3.02 (m, 2H, CHNH), 4.96 (br, 1H, NH), 7.29 (d, *J* 8.0, 4H, –C_6H_4–CH_3), 7.76 (d, *J* 8.0, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 18.5 (–CH_3), 18.7 (–CH_3), 21.6 (2 × –C_6H_4–CH_3), 30.4 ($CH(CH_3)_2$), 49.7 (2 × NCH_2), 58.8 (2 × TsNCH), 127.2 (4 × Ar–CH), 129.8 (4 × Ar–CH), 138.4 (2 × Ar–C), 143.3 (2 × Ar–C).

Method (b), via hydrolysis of *N-[(1S)-1-({(4S)-4-isopropyl-3-[(4-methylphenyl)sulfonyl]imidazolidinyl}methyl)-2-methylpropyl]-4-methylbenzenesulfonamide* ***8***. ((1*S*)-1-{[Benzyl((2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)amino]-methyl}-2-methylpropyl)-4-methylbenzenesulfonamide **2j** (3.0 g, 5.3 mmol) and $Pd(OH)_2$ (285 mg, 10 mol% Pd) were placed in MeOH (50 cm^3) and dichloromethane (50 cm^3) under 1 atm H_2. After 3 h there was no further uptake of hydrogen and the reaction was stopped. The solvent was evaporated and the crude material was purified by column chromatography on silica (hexane : EtOAc : CH_2Cl_2 2 : 3 : 5) to afford *N*-[(1*S*)-1-({(4*S*)-4-isopropyl-3-[(4-methylphenyl)sulfonyl]imidazol-idinyl}methyl)-2-methylpropyl]-4-methylbenzenesulfonamide **8** as a colourless solid (1.8 g, 3.6 mmol, 68%); mp 110–111 °C; Found MH^+ *m*/*z* 508.22816; $C_{25}H_{38}O_4S_2N_3$ requires *m*/*z* 508.23038; $[a]_D$ = −31.0 (*c* = 1, $CHCl_3$). ν_{max} (KBr, cm^{-1}) 3285 (s, *NH*Ts), 2969 (s, CH), 2823 (m, CH), 1342 (s, SO_2NH), 1162 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.6 (d, *J* 6.9, 3H, –CH_3), 0.65 (d, *J* 6.9, 3H, –CH_3), 0.84 (d, *J* 6.7, 3H, –CH_3), 0.65 (d, *J* 6.7, 3H, –CH_3), 1.60 (m, 1H, CH(CH_3)$_2$), 2.01 (m, 1H, CH(CH_3)$_2$), 2.02 (m, 2H, CH_2N), 2.41 (s, 6H, –C_6H_4–CH_3), 2.47 (m, 2H, CH_2NTs), 2.83 (m, 1H, CH_aH$_b$NTs), 3.51 (m, 1H, CH$_a$$H_b$NTs), 3.62 (d, *J* 8.4, 1H, CHNTs), 4.0 (d, *J* 8.4, 1H, CHNTs), 7.29 (m, 4H, –C_6H_4–CH_3), 7.76 (m, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 16.50 (–CH_3), 17.7 (–CH_3), 17.9 (–CH_3), 19.3 (–CH_3), 29.0 (2 × –C_6H_4–CH_3), 31.4 ($CH(CH_3)_2$), 53.4 (NCH_2), 53.7

(NCH_2), 57.4 (TsN*C*H), 63.8 (TsN*C*H) 71.5 (TsN*C*H_2N), 127.3 (2 × Ar–*C*H), 127.9 (2 × Ar–*C*H), 129.8 (2 × Ar–*C*H), 129.9 (2 × Ar–*C*H), 135.3 (Ar–*C*), 137.9 (Ar–*C*), 143.5 (Ar–*C*), 143.9 (Ar–*C*).

To a solution of *N*-[(1*S*)-1-({(4*S*)-4-isopropyl-3-[(4-methylphenyl)sulfonyl]imidazolidinyl}methyl)-2-methylpropyl]-4-methylbenzenesulfonamide **8** (130 mg, 0.26 mmol) in methanol (5 cm^3) was added 3 M aqueous hydrochloric acid (5 cm^3) and the reaction was stirred for 7 h. The reaction was cooled to 0 °C and neutralised to pH 10 with 2 M aqueous sodium hydroxide and extracted with dichloromethane (×2, 10 cm^3). The combined organic extracts were concentrated under reduced pressure and the residue taken up in ethanol (5 cm^3). To the resulting solution was added solid sodium hydroxide (256 mg, 6.4 mmol, 25 equiv.) and this mixture was heated to reflux for 22 h. At the completion of this period the volatiles were removed under reduced pressure. The residue was suspended in water (10 cm^3) and this was acidified to pH 8 with 12 M aqueous hydrochloric acid. The aqueous phase was extracted with dichloromethane (×3, 10 cm^3) then dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography on silica (hexane : EtOAc : CH_2Cl_2 2 : 3 : 5) gave 4-methyl-*N*-((1*S*)-2-methyl-1-{[((2*S*)-3-methyl-2{[(4-methylphenyl)sulfonyl]amino}butyl)amino]methyl}propyl)benzenesulfonamide **2g** as a colourless solid (116.7 mg, 0.24 mmol, 92%); Found C, 58.25; H, 7.60; N, 8.25; S, 13.09%; MH^+ *m*/*z* 496.2295; $C_{24}H_{37}N_3O_4S_2$ requires C, 58.15; H, 7.52; N, 8.48; S, 12.94%; *m*/*z* 496.2304. The remaining spectroscopic data was identical to that recorded above.

Method (c), via ring opening of *(2S)-2-isopropyl-1-[(4-methylphenyl)sulfonyl]aziridine* ***4*** *with (1S)-1-(aminomethyl)-2-methylpropyl]-4-methylbenzenesulfonamide* ***9b***. The title compound was obtained in an analogous fashion to the preparation of compound **2f** using [(1*S*)-1-(aminomethyl)-2-methylpropyl]-4-methylbenzenesulfonamide **9b** (1.3 g, 5 mmol) and (2*S*)-2-isopropyl-1-[(4-methylphenyl)sulfonyl]aziridine **4** (1.2 g, 5 mmol) followed by purification by column chromatography on silica (hexane : EtOAc : CH_2Cl_2 2 : 3 : 5) gave the title compound as a white solid (1.4 g, 2.8 mmol, 56%) with spectroscopic data identical to that recorded above.

4-Methyl-*N*-{(1*S*)-1-methyl-2-[((2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)amino]ethyl}benzenesulfonamide 2h. *Method (a), via* debenzylation of *N-{(1S)-2-[benzyl((2S)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)amino]-1-methylethyl}-4-methylbenzenesulfonamide* ***2k***. *N*-{(1*S*)-2-[Benzyl((2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}-butyl)amino]-1-methylethyl}-4-methylbenzenesulfonamide **2k** (300 mg, 0.54 mmol) and palladium on charcoal (57 mg, 10 mol% Pd) in AcOH (5 cm^3) were hydrogenated under 1 atm H_2 at RT for 12 h. After evaporation of the solvent, the crude product was filtered through a short pad of silica (EtOAc: EtOH 1 : 1). After evaporation of the solvent, 2 M aqueous sodium hydroxide was added to the amine which was then extracted with EtOAc, washed with 2 M NaOH and brine, and dried over $MgSO_4$. Purification by flash column chromatography on silica (EtOAc) gave an oil (100 mg, 0.21 mmol, 40%); Found MH^+ *m*/*z* 468.1981; Calculated for $C_{22}H_{34}N_3O_4S_2$ *m*/*z* 461.1991; $[\alpha]_D = -13.8$ (*c* = 1.00; $CHCl_3$); ν_{max} (CCl_4, cm^{-1}) 3275 (s, NH), 3064 and 3043 (w, ArH). 2965 (s, CH), 2933 (m, CH), 2878 (m, CH), 1463 (s), 1492 (s), 1326 (s, SO_2NH), 1161 (s, SO_2NH), 815 (m, ArH); δ_H (400 MHz, $CDCl_3$) 0.74 (d, *J* 6.9, 3H, CH_3), 0.76 (d, *J* 6.9, 3H, CH_3), 0.96 (d, *J* 6.5, 3H, CH_3), 1.67 (m, 1H, C*H*(CH_3)$_2$), 2.29–2.46 (m, 4H, CH_2NH), 2.41 (s, 6H, –C_6H_4–CH_3), 3.02 (m, 1H, C*H*NH), 3.22 (m, 1H, C*H*NH), 5.05 (bs, 2H, N*H*), 7.28–7.32 (m, 4H, –C_6H_4–CH_3), 7.75–7.78 (m, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 18.4 (–*C*H_3), 18.7 (–*C*H_3), 19.5 (–*C*H_3), 21.6 (2 × –C_6H_4–*C*H_3), 30.6 (*C*H(CH_3)$_2$), 49.0 (N*C*H_2), 49.5 (N*C*H_2), 54.4 (TsN*C*H), 58.9 (TsN*C*H), 127.2 (Ar–*C*H), 127.3)Ar–*C*H), 129.8 (Ar–*C*H), 129.9 (Ar–*C*H), 138.0 (Ar–*C*), 138.3 (Ar–*C*), 143.4 (Ar–*C*), 143.5 (Ar–*C*).

Method (b), via ring opening of *(2S)-2-isopropyl-1-[(4-methylphenyl)sulfonyl]aziridine* ***4*** *with [(1S)-2-amino-1-methylethyl]-4-methylbenzenesulfonamide* ***9a***. The title compound was obtained in an analogous fashion to compound **2f** using [(1*S*)-2-amino-1-methylethyl]-4-methylbenzenesulfonamide **9a** (1.458 g, 6.396 mmol) and (2*S*)-2-isopropyl-1-[(4-methylphenyl)-sulfonyl]aziridine **4** (1.526 g, 6.38 mmol) and flash column chromatography on silica (CH_2Cl_2 : MeOH 92 : 8) afforded a colourless gum (2.621 g, 5.61 mmol, 88%); mp 30–32.5 °C; Found MH^+ *m*/*z* 468.2018; $C_{22}H_{34}N_3O_4S_2$ requires *m*/*z* 468.1991; $[\alpha]_D = -10.2$ (*c* = 1.01; $CHCl_3$); ν_{max} (CCl_4, cm^{-1}) 3275 (s, NH) 3064 and 3043 (w, ArH), 2965 (s, CH), 2933 (m, CH), 2878 (m, CH), 1463 (s), 1429 (s), 1326 (s, SO_2NH), 1161 (s, SO_2NH), 815 (m, ArH); δ_H (400 MHz, $CDCl_3$) 0.72 (d, *J* 6.9, 3H,–CH_3), 0.75 (d, *J* 6.9, 3H,–CH_3), 0.93 (d, *J* 6.5, 3H,–CH_3), 1.66 (m, 1H, C*H*(CH_3)$_2$), 2.35 (m, 4H, –CH_2NH), 2.40 (s, 6H, –C_6H_4–CH_3), 3.00 (m, 1H, C*H*NHTs), 3.21 (m, 1H, C*H*NHTs), 7.28 (m, 4H, –C_6H_4–CH_3), 7.76 (m, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 18.4 (–*C*H_3), 18.7 (–*C*H_3), 19.5 (–*C*H_3), 21.6 (2 × –C_6H_4–*C*H_3), 30.5 (*C*H(CH_3)$_2$), 48.97 (N*C*H_2), 49.4 (N*C*H_2), 54.4 (TsN*C*H), 58.8 (TsN*C*H), 127.2 (Ar–*C*H), 127.3)Ar–*C*H), 129.8 (Ar–*C*H), 129.9 (Ar–*C*H), 138.0 (Ar–*C*), 138.4 (Ar–*C*), 143.4 (Ar–*C*), 143.4 (Ar–*C*).

4-Methyl-*N*-{(1*S*)-1-methyl-2-[[(4-methylphenyl)sulfonyl]-((2*S*)-2-{[(4-methylphenyl)sulfonyl]amino}propyl)amino]ethyl}-benzenesulfonamide 2a. To a solution of 4-methyl-*N*-{(1*S*)-1-methyl-2-[((2*S*)-2-{[(4-methylphenyl)sulfonyl]amino]propyl)-amino]ethyl}benzenesulfonamide **2f** (1.3 g, 2.8 mmol) in pyridine (20 cm^3) at 0 °C under a nitrogen atmosphere was added *p*-toluenesulfonyl chloride (550 mg, 2.8 mmol) in batches over 30 min. The orange solution was allowed to come to room temperature and stirred for a further 6 h whereby the colour changed from orange to red. The reaction 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 4 : 1 : 5) afforded a yellow solid (1.5 g, 2.5 mmol, 89%); mp 68–70 °C; Found C, 54.5; H, 5.9; N, 6.8%; MH^+ *m*/*z* 594.1760; $C_{27}H_{35}O_6S_3N_3$ requires C, 54.6; H, 5.9; N, 7.1%; *m*/*z* 594.1766; $[\alpha]_D$ −42.3 (*c* = 1, $CHCl_3$); ν_{max} (KBr, cm^{-1}) 3275 (s, N*H*Ts), 3034 (w, C_6H_4), 2977 (m, CH), 2926 (m, CH), 2874 (m, CH), 1331 (s, SO_2NH), 1159 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.96 (d, *J* 6.6, 6H, –CH_3), 2.46 (s, 6H, –C_6H_4–CH_3), 2.48 (s, 3H, –C_6H_4–CH_3), 2.84 (dd, *J* 14.8, 6.2, 2H, –CH_2NTs), 3.16 (dd, *J* 14.8, 6.2, 2H, –CH_2NTs), 3.40 (m, 2H, –C*H*NHTs), 7.31 (d, *J* 8.3, 4H, –C_6H_4–CH_3), 7.36 (d, *J* 8.3, 2H, –C_6H_4–CH_3), 7.69 (d, *J* 8.3, 2H, –C_6H_4–CH_3), 7.77 (d, *J* 8.3, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 19.2 (2 × –*C*H_3), 21.7 (–C_6H_4–*C*H_3), 21.7 (2 × –C_6H_4–*C*H_3), 48.7 (2 × TsN*C*H_2), 60.6 (2 × TsN*C*H), 127.3 (2 × Ar–*C*H), 127.6 (4 × Ar–*C*H), 129.9 (4 × Ar–*C*H), 130.2 (4 × Ar–*C*H), 135.21 (2 × Ar–*C*), 137.8 (2 × Ar–*C*), 143.7 (Ar–*C*), 144.3 (Ar–*C*).

4-Methyl-*N*-[(1*S*)-2-methyl-1-({((2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)[(4-methylphenyl)sulfonyl]-amino}methyl)propyl]benzenesulfonamide 2b. Compound **2b** was prepared in an identical manner to **2a** using 4-methyl-*N*-((1*S*)-2-methyl-1-{[((2*S*)-3-methyl-2{[(4-methylphenyl)-sulfonyl]amino}butyl)amino]methyl}propyl)benzenesulfonamide **2g** (1.4 g, 2.8 mmol). Purification by column chromatography on silica (hexane : EtOAc : CH_2Cl_2 4 : 1 : 5) afforded a yellow solid (1.5 g, 2.3 mmol, 82%); mp 209–211 °C (lit.[20] mp 205–207 °C); Found C, 57.3; H, 6.7; N, 6.5; S, 14.8%; MH^+ *m*/*z* 650.2404; $C_{31}H_{43}O_6S_3N_3$ requires C, 57.3; H, 6.8; N, 6.2; S, 14.7%; *m*/*z* 650.2405; $[\alpha]_D$ −73.1 (*c* = 1, $CHCl_3$) (lit.[20] −30.4

(c = 0.5, $CHCl_3$)); ν_{max} (KBr, cm^{-1}) 3250 (s, *NH*Ts), 3044 (w, C_6H_4), 2961 (m, CH), 2928 (m, CH), 2874 (m, CH), 1325 (s, SO_2NH), 1162 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.58 (d, J 6.9, 6H, –CH_3), 0.74 (d, J 6.9, 6H, –CH_3), 1.84 (m, 2H, CH(CH_3)$_2$), 2.42 (s, 6H, –C_6H_4–CH_3), 2.46 (s, 3H, –C_6H_4–CH_3), 3.01 (m, 4H, –CH_2NHTs), 3.18 (m, 2H, –CHNHTs), 5.00 (d, J 8.0, 2H, NHTs), 7.28 (d, J 8.0, 4H, –C_6H_4–CH_3), 7.36 (d, J 8.0, 2H, –C_6H_4–CH_3), 7.67 (d, J 8.3, 2H, –C_6H_4–CH_3), 7.74 (d, J 8.3, 4H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 16.6 (2 × −CH_3), 17.9 (2 × −CH_3), 21.7 (3 × –C_6H_4–CH_3), 28.5 (2 × CH(CH_3)$_2$), 51.0 (2 × TsNCH_2), 57.2 (2 × TsNCH), 127.4 (2 × Ar–CH), 127.7 (3 × Ar–CH), 129.7 (3 × Ar–CH), 130.2 (3 × Ar–CH), 134.8 (2 × Ar–C) 137.7 (2 × Ar–C), 143.5 (2 × Ar–C).

4-Methyl-*N*-((1*S*)-1-methyl-2-{((2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)[(4-methylphenyl)sulfonyl]amino}ethyl)benzenesulfonamide 2c. Compound **2c** was prepared in an identical manner to **2a** using 4-methyl-*N*-{(1*S*)-1-methyl-2-[((2*S*)-3-methyl-2-{[(4-methyl-phenyl)sulfonyl]amino}butyl)-amino]ethyl}benzenesulfonamide **2h** (1.916 mg, 4.1 mmol). Purification by silica flash column chromatography (CH_2Cl_2 : EtOAc 94 : 6) afforded a colourless solid (1.838 g, 2.96 mmol, 72%); mp 165–166 °C; Found C, 55.77; H, 6.12; N, 6.66; S, 15.65%; MH^+ *m/z* 622.2112; $C_{29}H_{40}N_3O_6S_3$ requires C, 56.02; H, 6.32; N, 6.76; S, 15.47%; *m/z* 622.2079; $[\alpha]_D$ −67 (c = 0.505, $CHCl_3$); ν_{max} (CCl_4, cm^{-1}) 3281 (w, NHTs), 2965, 2927 and 2873 (m, all CH), 1164 (w, SO_2N), 908 (s), 739 (s); δ_H (400 MHz, $CDCl_3$) 0.51 (d, J 6.9, 3H, –CH_3), 0.69 (d, J 6.9, 3H, –CH_3), 0.95 (d, J 6.5, 3H, –CH_3), 1.74 (m, 1H, CH(CH_3)$_2$), 2.39 (s, 3H, –C_6H_4–CH_3), 2.41 (s, 3H, –C_6H_4–CH_3), 2.43 (s, 3H, –C_6H_4–CH_3), 2.70 (dd, J 14.9, 6.2, 1H, –CHHNHTs), 2.91 (dd, J 14.1, 6.2, 1H, –CHHNHTs), 3.12 (m, 3H, –CHNHTs), 3.35 (m, 1H, –CHNHTs), 5.08 (d, J 6.2, 1H, NHTs), 5.44 (bs, 1H, NHTs), 7.27 (m, 6H, –C_6H_4–CH_3), 7.69 (m, 12H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 16.15 (–CH_3), 18.42 (–CH_3), 19.43 (–CH_3), 21.66 (2 × –C_6H_4–CH_3), 21.70 (–C_6H_4–CH_3) 28.25 (CH(CH_3)$_2$), 48.99 (TsNCH_2), 51.50 (TsNCH_2), 55.27 (TsNCH), 56.97 (TsNCH), 127.4, 127.37, 127.72, 129.82, 129.88 and 130.15 (all Ar–CH), 134.86, 137.55, 137.86 (all Ar–C), 143.52, 143.69, 144.30 (all Ar–C).

(2*S*,6*S*)-2,6-Dimethyl-1,4,7-tris[(4-methylphenyl)sulfonyl]-1,4,7-triazacyclononane 1a. Hexane washed NaH (42 mg, 1.7 mmol) in DMF (1 cm^3) was added to a solution of 4-methyl-*N*-{(1*S*)-1-methyl-2-[[(4-methylphenyl)sulfonyl]((2*S*)-2-{[(4-methylphenyl) sulfonyl]amino}propyl)amino]ethyl}benzene-sulfonamide **2a** (500 mg, 0.84 mmol) in DMF (8 cm^3) at room temperature. The resulting solution was heated to 80 °C and a solution of ethyleneglycol ditosylate **3** (343 mg, 0.92 mmol) in DMF (2 cm^3) was added dropwise over 1 h. During this period the colour of the solution changed from brown to black. The reaction was stirred overnight at 80 °C and at completion was quenched by addition of water (10 cm^3). The DMF was removed under reduced pressure (12 mmHg) and the residue 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 (374 mg, 0.60 mmol, 71%); mp 209–211 °C; Found C, 56.0; H, 6.0; N, 6.5%; MH^+ *m/z* 620.1926; $C_{29}H_{37}O_6S_3N_3$ requires C, 56.2; H, 6.0; N, 6.8%; *m/z* 620.1923; $[\alpha]_D$ +95.3 (c = 1, $CHCl_3$); ν_{max} (KBr, cm^{-1}) 3064 (w, C_6H_4), 2924 (w, CH), 1335 (s, SO_2NH), 1155 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.69 (d, J 6.5, 6H, –CH_3), 2.43 (s, 6H, –C_6H_4–CH_3), 2.46 (s, 3H, –C_6H_4–CH_3), 3.24 (d, J 13.8, 2H, –CH_2NTs), 3.52 (m, 6H, –CH_2NTs), 4.15 (m, 2H, –CHNTs), 7.30 (d, 8.0, 4H, –C_6H_4–CH_3), 7.35 (d, J 8.0, 2H, –C_6H_4–CH_3), 7.65 (d, J 8.3, 4H, –C_6H_4–CH_3), 7.78 (d, J 8.3, 2H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 14.9 (–CH_3), 21.7 (3 × –C_6H_4–CH_3), 45.6 (4 × TsNCH_2), 53.8 (2 × TsNCH), 127.2 (3 × Ar–CH), 127.7 (3 × Ar–CH), 129.9 (3 × Ar–CH), 130.0 (3 × Ar–CH), 137.1 (2 × Ar–C), 143.6 (2 × Ar–C), 143.9 (2 × Ar–C).

(2*S*,6*S*)-2,6-Diisopropyl-1,4,7-tris[(4-methylphenyl)sulfonyl]-1,4,7-triazacyclononane 1b. Compound **1b** was prepared in an identical manner to **1a** from 4-methyl-*N*-[(1*S*)-2-methyl-1-({((2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)-[(4-methylphenyl)sulfonyl]amino}methyl)propyl]benzene-sulfonamide **2b** (800 mg, 1.2 mmol) and washed sodium hydride (103 mg, 2.5 mmol). Purification by column chromatography on silica (hexane : EtOAc : CH_2Cl_2 4 : 1 : 5) afforded a colourless solid (514 mg, 0.87 mmol, 73%); mp 210–212 °C (lit.[20] mp 214–215 °C); Found MH^+ *m/z* 676.2540; $C_{33}H_{46}O_6S_3N_3$ requires *m/z* 676.2549; $[\alpha]_D$ = −76.1 (c = 1, $CHCl_3$) (lit.[20] $[\alpha]_D$ = −7.4 (c = 0.5, $CHCl_3$)); ν_{max} (KBr, cm^{-1}) 2972 (w, CH), 2880 (w, CH), 2720 (w, CH), 1338 (s, SO_2NH), 1172 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.38 (br, 6H, –CH_3), 0.88 (d, J 6.2, 6H, –CH_3), 1.01 (m, 2H, CH(CH_3)$_2$), 2.40 (s, 6H, –C_6H_4–CH_3), 2.47 (s, 3H, –C_6H_4–CH_3), 3.21 (m, 4H, –CH_2NTs), 3.40 (m, 2H, –CHNTs), 3.66 (m, 4H, –CH_2NTs), 3.78 (m, 2H, –CHNTs), 7.28 (d, J 8.0, 4H, –C_6H_4–CH_3), 7.37 (d, J 8.0, 2H, –C_6H_4–CH_3), 7.73 (m, 6H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 20.2 (2 × –CH_3), 20.6 (2 × –CH_3), 21.6 (3 × –C_6H_4–CH_3), 21.7 (2 × CH(CH_3)$_2$), 45.7 (4 × TsNCH_2), 64.6 (2 × TsNCH), 127.7 (4 × Ar–CH), 128.2 (4 × Ar–CH), 129.8 (4 × Ar–CH), 129.9 (2 × Ar–C), 143.6 (2 × Ar–C), 144.1 (2 × Ar–C).

(2*S*,6*S*)-2-Isopropyl-6-methyl-1,4,7-tris[(4-methylphenyl)-sulfonyl]-1,4,7-triazacyclonane 1c. Compound **1c** was prepared in an identical manner to **1a** from 4-methyl-*N*-((1*S*)-1-methyl-2-{((2*S*)-3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}butyl)-[(4-methylphenyl)sulfonyl]amino}ethyl)benzenesulfonamide **2c** (820.6 mg, 1.32 mmol) and washed sodium hydride (108.6 mg, 2.71 mmol). Purification by column chromatography on silica (EtOAc : CH_2Cl_2 2 : 98) afforded a colourless solid (618 mg, 0.955 mmol, 72%), an analytical sample was obtained by purification on alumina (CH_2Cl_2) mp 105–106 °C; Found C, 57.14; H, 6.40; N, 6.41; S, 15.15%; MH^+ *m/z* 648.2260; $C_{31}H_{41}N_3O_6S_3$ requires C, 57.47; H, 6.38; N, 6.49; S, 14.85%; *m/z* 648.2236; $[\alpha]_D$ = 80.8 (c = 0.505 $CHCl_3$)); ν_{max} (KBr, cm^{-1}) 3063 (w, ArH), 3029 (w, ArH), 2967 (m, CH), 1452 (m), 1392 (m), 1336 (s, SO_2N), 1155 (s, SO_2N), 1089 (s), 982 (s), 822 (m, ArH); δ_H (400 MHz, $CDCl_3$) 0.33 (d, J 6.8, 3H, –CH_3), 0.63 (d, J 6.8, 3H, –CH_3), 0.89 (d, J 6.5, 3H, –CH_3), 1.47 (m, 1H, CH(CH_3)$_2$), 2.41 (s, 3H, –C_6H_4–CH_3), 2.43 (s, 3H, –C_6H_4–CH_3), 2.47 (s, 3H, –C_6H_4–CH_3), 3.37 (m, 5H, 2 ×–CH_2NTs + –CHNTs), 3.72 (m, 4H, 2 × –CH_2NHTs), 4.20 (bs, 1H, CHNTs), 7.29 (m, 4H, –C_6H_4–CH_3), 7.36 (d, J 8, 2H, –C_6H_4–CH_3), 7.67 (m, 4H, –C_6H_4–CH_3), 7.76 (d, J 8, 2H, –C_6H_4–CH_3); δ_C (100 MHz, $CDCl_3$) 15.22 (–CH_3), 20.19 (–CH_3), 20.55 (–CH_3), 21.66 (2 × –C_6H_4–CH_3), 21.69 (–C_6H_4–CH_3), 29.3 (CH(CH_3)$_2$), 44.60 (TsNCH_2), 47.06 (TsNCH_2), 53.81 (TsNCH_2) 64.6 (2 × TsNCH), 127.23 (Ar–CH), 127.63 (Ar–CH), 127.75 (Ar–CH), 129.81 (Ar–CH), 130.02 (Ar–CH), 137.18 (Ar–C), 143.60 (Ar–C), 143.75 (Ar–C), 143.88 (Ar–C).

(2*S*,6*S*)-2,6-Dimethyl-1,4,7-triazacyclononane 10a. To a solution of (2*S*,6*S*)-2,6-dimethyl-1,4,7-tris[(4-methylphenyl)-sulfonyl]-1,4,7-triazacyclononane **1a** (912 mg, 1.5 mmol) in THF (25 cm^3) and EtOH (4.5 cm^3, 80 mmol) was condensed dry NH_3 (200 cm^3) at −78 °C. To this solution was added lithium metal (514 mg, 74 mmol) in small portions to give an intense blue colour. 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 a light yellow oil (38 mg, 0.24 mmol, 16%); Found MH^+ *m/z* 158.1654; $C_8H_{19}N_3$ requires *m/z* 158.1657; $[a]_D$ +41.3 (*c* = 1, $CHCl_3$); ν_{max} (CCl_4, cm^{-1}) 3291 (br, w, NH), 2872 (s, CH), 2809 (s, CH); δ_H (400 MHz, $CDCl_3$) 1.13 (d, *J* 6.5, 6H, –CH_3), 2.69 (m, 2H, NHCH_2), 2.95 (m, 6H, NHCH_2), 3.01 (m, 2H, NHC*H*), 3.51 (br, 3H, N*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (2 × –CH_3), 42.5 (2 × NHCH_2), 50.7 (NHCH_2), 51.9 (NHCH_2), 53.6 (2 × NHCH).

(2*S*,6*S*)-2,6-Dimethyl-1,4,7-triazacyclononane trihydrochloride 10d. To a solution of (2*S*,6*S*)-2,6-dimethyl-1,4,7-triazacyclononane **10a** (38 mg, 0.14 mmol) in EtOH (2 cm^3) was added conc. HCl (0.08 cm^3) at room temperature with rapid stirring. To this solution was added ether (10 cm^3) and the white precipitate that formed was removed by filtration and dried under reduced pressure to give the hydrochloride salt as a colourless solid (49 mg, 0.19 mmol, 79%); mp 133–135 °C; Found MH^+ *m/z* 158.1654; $C_8H_{19}N_3$ requires *m/z* 158.1657; $[a]_D$ +33.1 (*c* = 1, MeOH); ν_{max} (KBr, cm^{-1}) 2963 (s, CH), 2871 (s, CH), 2805 (s, CH); δ_H (400 MHz, CD_3OD) 1.33 (d, *J* 6.6, 6H, –CH_3), 2.94 (m, 2H, NHCH_2), 3.19 (dd, *J* 14.6, 4.2 2H, NHCH_2), 3.31 (m, 2H, NHCH_2), 3.47 (m, 2H, NHCH_2), 3.68 (m, 2H, NHC*H*); δ_C (100 MHz, CD_3OD) 16.1 (–CH_3), 17.8 (–CH_3), 40.9 (2 × NHCH_2), 51.6 (2 × NHCH_2), 57.8 (2 × NHCH).

(2*S*,6*S*)-2,6-Diisopropyl-1,4,7-triazacyclononane 10b. Compound **10b** was prepared in an identical fashion to **10a** using (2*S*,6*S*)-2,6-diisopropyl-1,4,7-tris[(4-methylphenyl)sulfonyl]-1,4,7-triazacyclononane **1b** (400 mg, 0.59 mmol), EtOH (1.8 cm^3, 32 mmol) and lithium metal (206 mg, 29 mmol) to give a light yellow oil (92 mg, 0.43 mmol, 72%); Found MH^+ *m/z* 214.2283; $C_{12}H_{27}N_3$ requires *m/z* 214.2283; $[a]_D$ +79.2 (*c* = 1, $CHCl_3$); ν_{max} (CCl_4, cm^{-1}) 3316 (w, NH), 2958 (m, CH), 2871 (m, CH); δ_H (400 MHz, $CDCl_3$) 0.88 (d, *J* 6.7, 6H, –CH_3), 0.96 (d, *J* 6.7, 6H, –CH_3), 1.56 (m, 2H, C*H*(CH_3)$_2$), 2.44 (m, 4H, NHCH_2), 2.64 (m, 2H, NHCH_2), 2.76 (m, 2H, NHCH_2), 3.01 (d, *J* 8.9, 2H, NHC*H*), 3.25 (br, 3H, NH); δ_C (100 MHz, $CDCl_3$) 19.7 (2 × –CH_3), 19.9 (2 × –CH_3), 31.9 (2 × C*H*(CH_3)$_2$), 43.9 (2 × NHCH_2), 48.7 (2 × NHCH_2), 58.9 (2 × NHC*H*).

(2*S*,6*S*)-2,6-Diisopropyl-1,4,7-triazacyclononane monohydrochloride 10e. Compound **10e** was prepared in an analogous fashion to **10d** using (2*S*,6*S*)-2,6-diisopropyl-1,4,7-triazacyclononane **10b** (92 mg, 0.43 mmol) to afford a colourless solid (98 mg, 0.39 mmol, 90%); mp 136–138 °C; Found MH^+ *m/z* 214.2283; $C_{12}H_{27}N_3$ requires *m/z* 214.2283; $[a]_D$ +58.7 (*c* = 1, MeOH); ν_{max} (KBr, cm^{-1}) 3416 (w, NH); 2963 (s, CH), 2766 (s, CH), 2650 (s, CH); δ_H (400 MHz, D_2O) 0.94 (d, *J* 6.8, 6H, –CH_3), 1.99 (m, 2H, C*H*(CH_3)$_2$), 2.98 (m, 2H, NHCH_2), 3.31 (m, 2H, NHCH_2), 3.48 (m, 6H, NHCH_2), 3.48 (m, 2H, NHC*H*); δ_C (100 M, D_2O) 18.1 (2 × –CH_3), 19.0 (2 × –CH_3), 29.6 (2 × C*H*(CH_3)$_2$), 40.9 (2 × NHCH_2), 45.5 (2 × NHCH_2), 60.3 (2 × NHCH).

(2*S*,6*S*)-2-Isopropyl-6-methyl-1,4,7-triazacyclononane 10c. Compound **10c** was prepared in an analogous fashion to **10a** using(2*S*,6*S*)-2-isopropyl-6-methyl-1,4,7-tris[(4-methylphenyl)-sulfonyl]-1,4,7-triazacyclonane **1c** (559.7 mg, 0.865 mmol), EtOH (2.74 cm^3) and lithium wire (242.7 mg, 34.97 mmol) to afford a light yellow oil (140.1 mg, 0.756 mmol, 87%); Found MH^+ *m/z* 186.1968; $C_{10}H_{24}N_3$ requires *m/z* 186.1970; ν_{max} (liq. film, cm^{-1}) 3630–3055 (bm, NH), 2953 (s, CH), 2921 (s, CH), 2870 (s, CH), 1466 (m), 1370 (m), 1160 (m), 1121 (m); δ_H (400 MHz, $CDCl_3$) 0.89 (d, *J* 6.7, 3H, –CH_3), 0.95 (d, *J* 6.7, 3H, –CH_3), 1.01 (d, *J* 6.6, 3H, –CH_3), 1.54 (sep, *J* 6.7, 1H, C*H*(CH_3)$_2$), 2.20 (bs, 3H, 3 × N*H*), 2.40 (m, 3H, 3 × C*H*N), 2.58 (m, 2H, 2 × C*H*N), 2.83 (m, 4H, 4 × C*H*N), 2.91 (m, 1H, C*H*N); δ_C (100 MHz, $CDCl_3$) 17.51 (–CH_3), 19.36 (–CH_3), 19.41 (–CH_3), 31.94 (C*H*(CH_3)$_2$), 40.46 (CH_2N), 44.85 (CH_2N), 49.03 (CH_2N), 49.55 (CH_2N), 49.90 (C*H*N), 58.36 (C*H*N).

(2*S*,6*S*)-2-Isopropyl-6-methyl-1,4,7-triazacyclononane trihydrobromide 10f. To a stirred solution of (2*S*,6*S*)-2-isopropyl-6-methyl-1,4,7-triazacyclonane **10c** (38.6 mg, 0.209 mmol) in ether (2 cm^3) at 0 °C was added hydrobromic acid (48%, 0.1 cm^3, 0.883 mmol) to give a tan coloured solid. The solid was washed with ether (×3, 3 cm^3) followed by azeotropic removal of water by evaporation of added toluene (×4, 5 cm^3). The residue was twice precipitated from EtOH (1 cm^3) by the addition of ether (2 cm^3) which gave a cream solid (58.9 mg, 0.138 mmol, 66%) mp 195–198 °C; Found C, 27.03; H, 5.85; N, 9.02%; $C_{10}H_{25}N_3$·3HBr·H_2O requires C, 26.93; H, 6.33; N, 9.42%; $[a]_D$ +30.4 (*c* = 0.565, MeOH); ν_{max} (KBr, cm^{-1}) 3645–3200 (sbr, NH), 2961 (s, CH), 2766 (s), 2651 (s); δ_H (400 MHz, D_2O) 0.99 (d, *J* 6.8, 3H, –CH_3), 1.08 (d, *J* 6.8, 3H, –CH_3), 1.33 (d, *J* 6.68, 3H, –CH_3), 1.97 (sep, *J* 6.8, 1H, C*H*(CH_3)$_2$), 3.02 (m, 2H, 2 × C*H*NH), 3.23–3.71 (m, 7H, 7 × C*H*NH), 3.91 (m, 1H, C*H*NH); δ_C (100 MHz, D_2O) 14.68 (–CH_3), 18.31 (–CH_3), 19.11 (–CH_3), 30.87 (C*H*(CH_3)$_2$), 38.29 (CH_2N), 42.75 (CH_2N), 46.41 (CH_2N), 46.86 (CH_2N), 51.8 (C*H*N), 58.65 (C*H*N).

(2*S*,6*S*)-1,2,4,6,7-Pentamethyl-1,4,7-triazacyclononane 11a. To a solution of (2*S*,6*S*)-2,6-dimethyl-1,4,7-tris[(4-methylphenyl)sulfonyl]-1,4,7-triazacyclononane **1a** (912 mg, 1.5 mmol) in THF (25 cm^3) and EtOH (4.5 cm^3, 80 mmol) was condensed dry NH_3 (200 cm^3) at −78 °C. To this solution was added lithium metal (512 mg, 74 mmol) in small portions to give an intense blue colour. The reaction mixture was allowed to warm to room temperature overnight. Water was added (5 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) and ethyl acetate (×2, 10 cm^3). The resulting aqueous solution was acidified (pH 1) with conc. HCl (1 cm^3) and the volatiles were removed under reduced pressure (2 mmHg). This residue was dissolved in H_2O (1 cm^3) and the solution was neutralised with solid NaOH (168 mg). To this solution was added formaldehyde (37%, 1.1 cm^3, 13.5 mmol) and formic acid (90%, 1.7 cm^3, 30 mmol). The solution 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 light brown oil (131 mg, 0.66 mmol, 44%); Found MH^+ *m/z* 200.2121; $C_9H_{21}N_3$ requires *m/z* 200.2127; $[a]_D$ +42.3 (*c* = 1, $CHCl_3$); ν_{max} (CCl_4, cm^{-1}) 2966 (m, CH), 2777 (m, CH); δ_H (400 MHz, $CDCl_3$) 0.74 (d, *J* 6.1, 6H, –CH_3), 2.05 (d, *J* 10.1, 2H, NCH_2), 2.18 (m, 2H, NCH_2), 2.31 (s, 9H, NCH_3), 2.68 (d, *J* 11.3, 2H, NCH_2), 2.92 (m, 2H, NCH_2), 2.96 (m, 2H, NC*H*); δ_C (100 MHz, D_2O) 11.6 (2 × –CH_3), 41.3 (NCH_3), 45.9 (NCH_3), 51.3 (NCH_3), 53.4 (2 × NCH_2), 54.9 (2 × NCH_2), 60.4 (2 × NCH).

(2*S*,6*S*)-1,2,4,6,7-Pentamethyl-1,4,7-triazacyclononane trihydrochloride 11d. To a solution of (2*S*,6*S*)-1,2,4,6,7-pentamethyl-1,4,7-triazacyclononane **11a** (131 mg, 0.66 mmol) in EtOH (2 cm^3) was added conc. HCl (0.19 cm^3) at room temperature with rapid stirring. To this solution was added ether (10 cm^3) and the white precipitate that formed was removed by filtration and dried under reduced pressure to give the hydrochloride salt (202 mg, 0.65 mmol, 98%); mp 181–183 °C; Found

MH^+ *m/z* 200.2127; $C_{12}H_{27}N_3$ requires *m/z* 200.2126; $[\alpha]_D$ +36.1 (*c* = 1, MeOH); ν_{max} (KBr, cm^{-1}) 3400 (s, NH, br), 2956 (m, CH), 2814 (m, CH); δ_H (400 MHz, D_2O) 1.25 (d, *J* 6.1, 6H, –CH_3), 2.71 (m, 3H, NCH_3), 2.80 (m, 3H, NCH_3), 2.94 (m, 3H, NCH_3), 3.04 (m, 6H, NCH_2), 3.45 (m, 2H, NCH_2), 3.76 (m, 2H, NC*H*), δ_C (100 MHz, D_2O) 9.4 (–CH_3), 11.1 (–CH_3), 37.1 (NCH_3), 41.8 (NCH_3), 44.6 (NCH_3), 45.5 (NCH_2), 51.6 (NCH_2), 53.0 (NCH_2), 55.8 (NCH_2), 58.9 (2 × NCH).

(2*S*,6*S*)-2,6-Diisopropyl-1,4,7-trimethyl-1,4,7-triazacyclononane 11b. A stirred solution of (2*S*,6*S*)-2,6-diisopropyl-1,4,7-triazacyclononane **10b** (91 mg, 0.42 mmol) and formaldehyde (37%, 0.3 cm^3, 3.9 mmol) and formic acid (90%, 0.4 cm^3, 9.2 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 (12 mmHg). 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 light brown oil (73 mg, 0.28 mmol, 66%); Found MH^+ *m/z* 256.2752; $C_{15}H_{33}N_3$ requires *m/z* 256.2753; $[\alpha]_D$ +38.4 (*c* = 0.5, $CHCl_3$); ν_{max} (CCl_4, cm^{-1}) 2955 (m, CH), 2870 (m, CH); δ_H (400 MHz, $CDCl_3$) 0.86 (d, *J* 2.3, 6H, –CH_3), 0.88 (d, *J* 2.3, 6H, –CH_3), 1.64 (m, 2H, CH(CH_3)$_2$), 2.19 (m, 3H, NCH_3), 2.33 (m, 3H, NCH_3), 2.35 (m, 3H, NCH_3), 2.40 (m, 4H, NCH_3), 2.49 (s, 2H, NCH_3), 2.64 (m, 2H, NCH_2), 2.82 (m, 2H, NC*H*); δ_C (100 MHz, $CDCl_3$) 20.9 (2 × –CH_3), 21.2 (2 × –CH_3), 30.7 (2 × CH(CH_3)$_2$), 40.0 (2 × NCH_3), 45.2 (NCH_3), 46.1 (NCH_2), 46.2 (NCH_2), 52.0 (NCH_2), 55.7 (NCH_2), 67.2 (2 × NCH).

(2*S*,6*S*)-2-Isopropyl-1,4,6,7-tetramethyl-1,4,7-triazacyclononane 11c. A stirred solution of (2*S*,6*S*)-2-isopropyl-6-methyl-1,4,7-triazacyclononane **10c** (133.1 mg, 0.718 mmol) and formaldehyde (37%, 0.5 cm^3, 6.67 mmol) and formic acid (90%, 0.67 cm^3, 15.59 mmol) was heated to reflux under a nitrogen atmosphere for 20 h. After cooling to 0 °C, the reaction was acidified (pH 1) *via* the addition of 1 M aqueous HCl (5 cm^3) and concentrated *in vacuo* (1 mmHg). The residue was dissolved in water (15 cm^3) and washed with ether (×3, 15 cm^3) and then basified (pH 14) by the addition of solid NaOH. The basic aqueous solution was extracted with dichloromethane (×4, 15 cm^3) and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated to afford a yellow oil (147.1 mg, 0.647 mmol, 90%); Found MH^+ *m/z* 228.2441; $C_{13}H_{29}N_3$ requires 228.2439; ν_{max} (liq. film, cm^{-1}) 2954 (s), 2928 (s), 2870 (s, all CH), 2835 (s), 2790 (s), 2765 (s), 1450 (m), 1363 (m); δ_H (400 MHz, $CDCl_3$) 0.74 (d, *J* 6.4, 3H, –CH_3), 0.79 (d, *J* 6.7, 6H, –CH_3), 1.57 (m, 1H, CH(CH_3)$_2$), 2.09 (m, 2H, CHN), 2.25 (m, 2H, CHN), 2.28 (s, 6H, NCH_3), 2.41 (s, 3H, NCH_3), 2.46 (m, 1H, CHN), 2.57 (m, 1H, CHN), 2.78 (m, 1H, CHN), 2.85 (m, 1H, CHN), 2.88 (m, 1H, CHN); δ_C (100 MHz, $CDCl_3$) 12.51 (–CH_3), 20.96 (–CH_3), 21.25 (–CH_3), 30.68 (CH(CH_3)$_2$), 41.95 (–CH_3N), 45.67 (–CH_3N), 50.24 (–CH_3N), 54.39 (–CH_2N), 56.30 (–CH_2N), 56.5 (–CHN), 60.6 (–CH_2N), 65.76 (–CHN).

(2*S*,6*S*)-2-Isopropyl-1,4,6,7-tetramethyl-1,4,7-triazacyclononane dihydrobromide 11d. To a stirred solution of (2*S*,6*S*)-2-isopropyl-1,4,6,7-tetramethyl-1,4,7-triazacyclononane **11c** (74 mg, 0.325 mmol) dissolved in ether (3 cm^3) at 0 °C was added hydrobromic acid (48%, 0.165 cm^3, 1.45 mmol) to afford a brown oil. The volatiles were removed and the residue was dissolved in ethanol (1 cm^3) and ether (3 cm^3) was added to afford a cream solid which was recrystallised twice from ethanol to give a colourless solid (77 mg, 0.199 mmol, 61%); mp 250–253 °C; Found C, 39.86; H, 8.26; N, 10.88%; $C_{13}H_{28}N_3 \cdot 2HBr$ requires C, 40.12; H, 8.03; N, 10.8%; $[\alpha]_D$ +34.6 (*c* = 0.52, MeOH); ν_{max} (CCl_4, cm^{-1}) 3625–3170 (bm, NH^+), 3060 (s), 2995 (s, CH), 2980 (s, CH), 2910 (s, CH), 2900–2710 (bs), 1470 (s), 1383 (s), 1341 (s), 1050 (s), 1044 (s), 974 (s); δ_H (400 MHz, D_2O) 1.0 (d, *J* 5.8, 3H, –CH_3), 1.18 (d, *J* 6.0, 3H, –CH_3), 1.42 (d, *J* 6.0, 3H, –CH_3), 2.17 (m, 1H, CH(CH_3)$_2$), 2.70 (s, 3H, NCH_3), 2.92 (m, 1H, NC*H*), 3.06 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 3.25 (m, 3H, NC*H*), 3.48 (m, 3H, NC*H*), 3.74 (m, 1H, NC*H*), 3.86 (m, 1H, NC*H*), 4.08 (m, 1H, NC*H*); δ_C (100 MHz, D_2O) 9.60 (–CH_3), 19.25 (–CH_3), 21.45 (–CH_3), 28.21 (CH(CH_3)$_2$), 36.30 (–CH_3N), 42.25 (–CH_3N), 44.55 (–CH_3N), 47.68 (–CH_2N), 52.02 (–CH_2N), 55.58 (–CH_2N), 57.35 (–CHN), 57.80 (–CHN), 58.37 (–CH_2N), 59.57 (–CHN).

Crystal data for 11e

Measurements were made on a Nonius Kappa CCD diffractometer at 150 K: $C_{13}H_{31}Br_2N_3$, orthorhombic, space group $P2_12_12_1$, *a* = 7.5110(2), *b*= 12.0412(5), *c* = 19.5980(7) Å, *V* = 1772.47(11) $Å^3$, *Z* = 4, MoKα radiation, λ = 0.71073 Å, μ = 4.565 mm^{-1}. Data were corrected for absorption with a multi-scan method. Final refinement to convergence on F^2 and with 177 parameters gave *R* = 0.0349 (3241 observed data), R_w = 0.0685 (all 3844 unique reflections) and GOF = 1.039, Flack parameter −0.030(11).

CCDC reference number 219446.

See http://www.rsc.org/suppdata/ob/b3/b310492c/ for crystallographic data in CIF or other electronic format.

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