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A practical method for building linear and cyclic triamines from (2-trimethylsilyl)ethanesulfonamides (SES-amides)

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Abstract—SES-chloride has been obtained in higher yield and purity by improving Weinreb's original procedure, allowing efficient access to the primary SES-amide. Linear triamines can be built conveniently from the SES-amide in high yields, with the potential for orthogonal protection. The modified Richman–Atkins cyclisation of SES-amides allows access to novel biologically interesting triazamacrocycles with combinations of three-, four-, five- and six-carbon bridges within the ring. Purification of the free macrocyclic amines by distillation greatly simplifies the workup, increasing the practicability of multi-gram scale synthesis. Although CsF sometimes provided undesirably low yields in the deprotection step, alternative fluoride sources were found to be unsuitable for the deprotection of SES-triazamacrocycles.

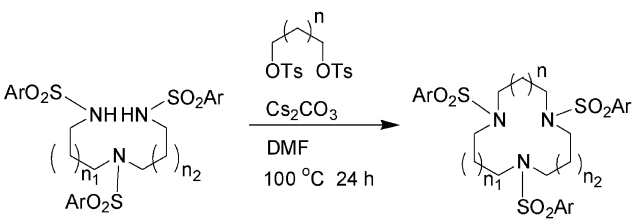
1. Introduction

Polyazamacrocycles have a number of biologically interesting applications, including the ability of their metal complexes to catalyse the hydrolysis of DNA[1] and peptides.[2] The coordination properties and thus the activity of the complexes are affected by the number of nitrogens and the size of the ring.[3] The latter can be varied by changing the length of the carbon chains between the nitrogens. Triazamacrocycles which form metal complexes with larger chelate ring sizes (e.g. 8 and 9-membered rings) are of interest because of the unusual geometry they impart on their coordinated metal ions.[4] Linear triamines with various carbon chain lengths including 4-, 5- and 6-carbon bridges exhibit anti-cancer activity,[5] and also have anti-parasitic and anti-fungal properties.[6] Their synthesis is usually lengthy and/or low yielding, often requiring purification of intermediates by column chromatography.[5]

Polyazamacrocycles are notoriously difficult to synthesize-probably the most common and flexible route is the Richman–Atkins cyclisation.[7] This involves protecting a linear polyamine as a sulfonamide, generating the di-anion (in situ or in a separate step) via a sodium, potassium or caesium salt, and coupling with the ditosylate of a diol followed by intramolecular cyclisation (Scheme 1), giving the polysulfonamide of the macrocyclic polyamine which must be deprotected.

Arylsulfonamides such as *p*-toluenesulfonamides have traditionally been used for the cyclisation. These offer an advantage in reactivity over other nitrogen protecting groups by increasing the acidity of the amide protons, with the aryl sulfonyl group stabilizing the nitrogen anions. The bulky tosyl groups also confer a Thorpe-Ingold-type effect on the transition state, promoting intramolecular cyclisation rather than intermolecular oligomerisation.[8,9] However, the conditions for aryl sulfonamide removal are very harsh and, with the exception of a few commercially-available polyazamacrocycles such as 1,4,7-triazacyclononane (tacn) and 1,4,7,11-triazacyclododecane (cyclen), often not highly effective for these types of compounds. Hydrolysis by heating at reflux in conc. sulfuric acid or HBr/AcOH (with or without phenol), or reduction with lithium or sodium in ammonia, is necessary for even partial deprotection, and sometimes decomposes the macrocycle in the process.[3,10–12] This results in low yields of macrocycles from large-scale cyclisations, and also severely limits the scope for varying the functionality in and around the macrocyclic structure.

Recently Hoye et al. developed the use of 2-trimethylsilylethanesulfonamides for synthesis of a representative range



Scheme 1. Richman–Atkins synthesis of azamacrocycles.

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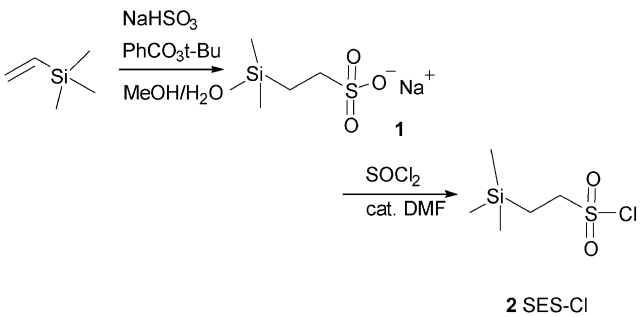
of polyazamacrocycles, but they limited their exploration of alkyl triazamacrocycles to two commercially available compounds, tacn and 1,5,9-triazacyclododecane (tacd).[8] In their procedure, the SES group is used to protect polyamines as sulfonamides for cyclisation. It offers the same advantages as traditional aryl sulfonamides, with some added features. The reaction is carried out at room temperature, with almost no oligomerisation observed. The deprotection is mild enough to allow for the survival of sensitive functionality in the compound, and also leaves the free amine rather than the salt, eliminating the need for conversion from the acid salt into the free base. This conversion often reduces recovered yields due to the solubility of these basic compounds in water.

Here, we report our use of SES-amides in a modular synthesis of triamines and novel triazamacrocycles, including an improved yield in the synthesis of SES-chloride and high purity in the isolated triazamacrocycles.

2. Results and discussion

2.1. Synthesis of SES-chloride

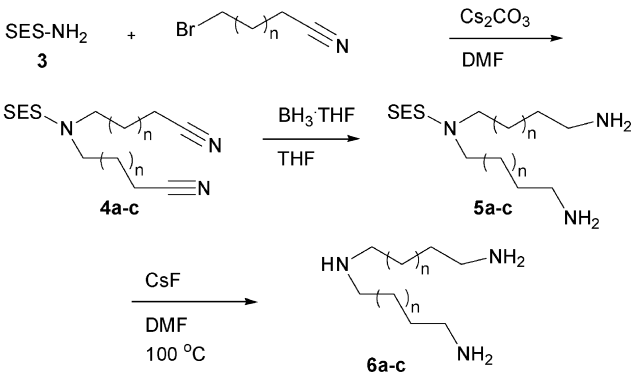
The synthesis of SES-chloride from vinyltrimethylsilane (Scheme 2) was improved to give better yield and purity. We found that by using 10 times as much DMF as previously reported,[13] we could obtain exclusively the sulfonyl chloride **2** (free from sulfonic anhydride) in 86% yield (compared to ~68–77% yield, after distillation from residual sulfonic anhydride, for the published procedure). This eliminates the need for purification other than solvent removal and filtration, and increases the overall yield from vinyltrimethylsilane to greater than 70%. The yield is an improvement on previously published procedures,[13] but importantly, so is the practicability of the production of laboratory scale amounts of **2** for general use as a sulfonamide protecting group.



Scheme 2. Route to SES-chloride.

2.2. Preparation of triamines

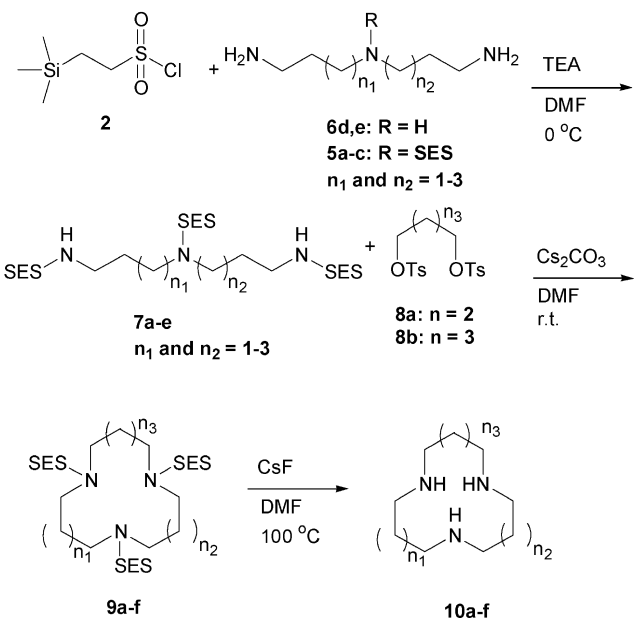
We have used this simple access to SES-chloride to build triamines for the synthesis of triazamacrocycles. Non-commercially available triamines **6a** and **6b** were built from SES-amide as shown in Scheme 3, and yields are given in Table 1. **6c** was also built from SES-amide for comparison. The primary amines were then protected with SES-chloride and the sulfonamides were cyclised as shown in Scheme 4. The mono-SES-protected triamines could be deprotected in



Scheme 3. Preparation of linear triamines. Yields are given in Table 1.

Table 1. Yields for linear triamine synthesis

n	R=CN (%)	R=CH_2NH_2 (%)	Free triamine	Over 3 steps (%)	Rept. yield (%)
1	**4a**: 96	**5a**: 96	**6a**: 84	77	60[14]
2	**4b**: 76	**5b**: 95	**6b**: 84	61	42[5]
3	**4c**: 73	**5c**: 97	**6c**: 46	32	11[15,16]



Scheme 4. Triazamacrocycle synthesis. Cyclisation and deprotection yields and carbon chain lengths n_1–n_2 are given in Table 2.

the same manner as the triazamacrocycles, providing the triamines **6a**-**b** in higher yields than previously reported.[5] Before the deprotection, the secondary SES-amide allows for orthogonal protection of the primary amines if desired.

2.3. Synthesis and deprotection of triazamacrocycles

Compounds **9a**-**f** were prepared and deprotected (Scheme 4), and the free amines were purified by Kugelrohr distillation. **10b**, **c**, **e** and **f** are novel compounds. **10a** and **10d** have not previously been reported as the free bases, only as acid salts.[4,17] The yields of cyclisation and deprotection are reported in Table 2. The macrocycles exhibited no

Table 2. Triazamacrocycle structural details and yields

n_1, n_2, n_3	Ring size	Cyclisation yield (%)	Deprotection yield (%)
1,1,3	[3,3,5]	**9a**: 54	**10a**: 62
2,2,1	[4,4,3]	**9b**: 41	**10b**: 33
1,2,3	[3,4,5]	**9c**: 47	**10c**: 39
2,2,2	[4,4,4]	**9d**: 29	**10d**: 67
3,3,2	[5,5,4]	**9e**: 29	**10e**: 33
4,4,2	[6,6,4]	**9f**: 21	**10f**: 31

appreciable oligomerisation during cyclisation. We also found that the use of dry DMF was not necessary for the cyclisation—in fact, the yields of cyclised products as reported here were slightly higher when DMF containing 1–2% water was used. Yields of all the cyclisations were comparable to typical Richman–Atkins cyclisation results. The SES-protected triamines **7a-d** could be purified by crystallization from methanol/water or isopropanol. While the deprotection yields were variable, very high purities (as indicated by ^{1}H and ^{13}C NMR spectroscopy) were obtained in the purification by Kugelrohr distillation.

The occasionally low isolated yields in the deprotection appeared to be the result of chelation of the free macrocycle with Cs^+ residues. Upon Kugelrohr distillation, some amount of pure amine was obtained, but a significant amount of yellow oil remained in the original flask. It was not possible to distill this material even at temperatures exceeding 250°C and pressures below 0.1 mm Hg. ^{1}H NMR spectroscopy of the yellow material showed it still appeared to contain mostly the macrocyclic amine. However, slight chemical shift changes indicated that the free amine may have complexed to residual Cs^+ ions. Small macrocyclic heterocycles are known to chelate to alkali metal ions, e.g. 18-crown-6 forms a strong complex with K^+. Also, a 'perfect fit' between ion size and macrocycle cavity is not necessary for complexation to occur.[18] Attempts to free the parent amine using EDTA, or forming the HCl salt, were not successful.

To circumvent the problem of metal ion chelation, alternative fluoride sources were investigated. Although tetraalkylammonium fluorides (e.g. TBAF, TEAF, TMAF) and KF/18-crown-6 did successfully remove the SES-groups, it was not possible to separate their by-products from the desired amines by Kugelrohr distillation. Other fluoride sources (polymer-supported fluoride, NH_4F_2, NH_4F, HF/pyridine, 40% aqueous HF) were unsuccessful at deprotecting the sulfonamides even under harsh conditions, e.g. reflux, microwave irradiation, and sonication.

3. Conclusions

The modular synthesis of triamines from SES-amide offers convenient access to linear and cyclic amines with control over the carbon-bridge architecture. The improved efficiency achieved in the production of SES-chloride greatly increases the practicality of the use of this protecting group. Further studies of the complexation properties of the novel macrocycles are in progress, as is the biological evaluation of their ability to act as unnatural polyamine analogues.

4. Experimental

Air- and/or moisture-sensitive experiments were carried out under an atmosphere of N_2 or Ar with glassware oven-dried and N_2 cooled. Chemicals were purchased from Aldrich Chemical Company (Gillingham, Dorset, UK) or Lancaster Synthesis Ltd (Morecambe, Lancs, UK) and used without further purification. DMF was dried by three times sequential drying over 3 Å molecular sieves.[19] 'Wet DMF' was used as purchased and not dried. Melting points were measured with a Gallenkamp apparatus and are uncorrected. R_f values are reported from silica gel thin-layer chromatography. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer, with chemical shift values reported on the δ scale (TMS=0) relative to residual chloroform (δ_H=7.27 or δ_C=77.2) as internal standards unless otherwise stated. Coupling constants (J) are reported in Hertz (Hz). Mass spectrometry was performed on a JEOL JMS-700 spectrometer, and infrared spectra were obtained either via solution phase (in $CDCl_3$), or diamond anvil (Golden Gate) IR using an FT-IR spectrophotometer.

4.1. 2-(Trimethylsilylethane)sulfonyl chloride (2)

2-(Trimethylsilyl)ethane sodium sulfonate (**1**) was prepared according to the procedure of Weinreb et al.,[13] except the reaction was allowed to proceed for 72 h, the salt was dried on a rotary evaporator at 60°C for 4 h, and yields obtained were 85–92%. The preparation of sulfonyl chloride was modified as follows:

The sulfonate salt (30.8 g, 0.151 mol) was crushed to a fine powder in a round-bottom flask with a large stir bar. The solid was cooled to 0°C on an ice bath, and thionyl chloride (175 mL, 0.340 mol) was added dropwise via pressure-equalising dropping funnel fitted with an oil bubbler, causing evolution of SO_2 gas. It was essential to maintain strong magnetic stirring throughout the addition of the thionyl chloride to ensure even cooling and dispersion of the sulfonate salt. Upon completion of thionyl chloride addition, the dropping funnel was removed and *N*,*N*-dimethylformamide (4.3 mL, 5.5 mmol) was added dropwise. The oil bubbler was fitted to the flask and the mixture stirred while allowing it to warm to room temperature. After 24 h, the excess thionyl chloride was removed by rotary evaporation (with the vacuum protected by a base trap). Hexane (2×50 mL) was added to assist in the removal of residual thionyl chloride. The resulting yellow paste was stirred with hexane (250 mL) for 15 min, then filtered through a pad of Celite, washing with more hexane (approximately 200 mL). The hexane was removed by rotary evaporation to give pure 2-(trimethylsilyl)ethanesulfonyl chloride as a yellow oil (25.7 g, 85% yield). Spectroscopic data were identical to those reported in the literature.[13]

4.1.1. 2-(Trimethylsilyl)ethanesulfonamide (3). Ammonia gas, produced by gentle warming (30–40°C) of 8 M aqueous ammonia solution, was bubbled through a stirred solution of **2** (11.0 g, 55 mmol) in dichloromethane (100 mL) at 0°C. After 2 h the reaction mixture was filtered,

washed with water, dried ($MgSO_4$) and concentrated to give **3** as a cream crystalline solid (8.73 g, 88% yield) mp=85–88°C; IR: ν_{max} (Golden Gate) 1147, 1271, 1327, 1547, 2900 and 2952 cm^{-1}; ^1H NMR: δ_H ($CDCl_3$) 0.07 (9H, s), 1.06–1.10 (2H, m), 3.03–3.07 (2H, m), 4.82 (2H, s); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 11.2, 51.9; MS: *m/z* (CI^+ mode) 182.12 ($[M+H]^+$, 5%), 166.09 (100), 154.09 (7), 138.06 (11), 122.12 (5), 101.14 (10), 85.14 (11), 71.09 (10). Found $[M+H]^+$ 182.0669, $C_5H_{16}O_2NSiS$ requires 182.0671.

4.2. Typical procedure for the synthesis of 4a-c

4.2.1. *N*-(2-(Trimethylsilyl)ethanesulfonyl)-bis-(3-cyanopropyl)amine (4a). Compound **3** (2.00 g, 11.0 mmol), dissolved in DMF (30 mL) with caesium carbonate (33.0 mmol), was treated with 4-bromobutyronitrile (3.27 g, 22.1 mmol) and stirred at room temperature for 24 h. The DMF was removed by rotary evaporation under high vacuum and the residue taken up in dichloromethane (50 mL), which was washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4 and evaporated to give the crude substituted sulfonamide (no purification necessary) as a beige oil (3.35 g, 96% yield); IR: ν_{max} (Golden Gate) 1138, 1167, 1250, 1327, 1421, 1460, 1672, 2247 and 2953 cm^{-1}; ^1H NMR: δ_H ($CDCl_3$) 0.07 (9H, s), 0.98–1.04 (2H, m), 1.95–2.03 (4H, quintet, *J*=7.1 Hz), 2.44–2.48 (4H, t, *J*=7.1 Hz), 2.84–2.96 (2H, m), 3.32–3.36 (4H, t, *J*=7.1 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 11.6, 15.0, 47.9, 48.4, 119.2; MS: *m/z* (FAB+ mode) 338.1 ($[M+Na]^+$, 100%), 271.1 (10), 73.8 (30). Found $[M+Na]^+$ 338.1335, $C_{13}H_{25}O_2N_3SiSNa$ requires 338.1334.

4.2.2. *N*-(2-(Trimethylsilyl)ethanesulfonyl)-bis-(4-cyanobutyl) amine (4b). Using 5-bromovaleronitrile (2.68 g, 16.54 mmol) and **3** (1.5 g, 8.27 mmol), **4b** was prepared as above and purified by column chromatography (EtOAc, silica) to give a yellow oil (2.16 g, 76% yield); R_f (EtOAc)=0.64; IR: ν_{max} (Golden Gate) 1140, 1167, 1250, 1329, 2249 and 2952 cm^{-1}; ^1H NMR: δ_H ($CDCl_3$) 0.06 (9H, s), 0.97–1.01 (2H, m), 1.68–1.81 (8H, m), 2.42–2.45 (4H, t, *J*=6.6 Hz), 2.85–2.90 (2H, m), 3.24–3.28 (4H, t, *J*=6.8 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 10.7, 17.1, 22.6, 47.8, 48.0, 119.6; MS: *m/z* (CI^+ mode) 344.3 ($[M+H]^+$, 35%), 316.2 (9), 280.3 (2), 252.2 (30), 226.2 (4), 211.2 (3), 180.2 (2), 138.2 (1), 111.1 (1), 73.1 (3), 57.1 (100). Found $[M+H]^+$ 344.1827, $C_{15}H_{30}O_2N_3SiS$ requires 344.1828.

4.2.3. *N*-(2-(Trimethylsilyl)ethanesulfonyl)-bis-(cyanopentyl)amine (4c). Using 6-bromocapronitrile (2.91 g, 16.54 mmol) and **3** (1.5 g, 8.27 mmol), **4c** was purified by column chromatography (EtOAc, silica) to give a yellow oil (2.26 g, 73% yield); R_f (EtOAc)=0.61; IR: ν_{max} (Golden Gate) 1139, 1250, 1327 and 2951 cm^{-1}; ^1H NMR: δ_H ($CDCl_3$) 0.06 (9H, s), 0.97–1.02 (2H, m), 1.45–1.53 (4H, m), 1.61–1.74 (8H, m), 2.35–2.39 (4H, t, *J*=7.0 Hz), 2.84–2.88 (2H, m), 3.19–3.22 (4H, t, *J*=7.5 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 10.7, 17.5, 25.3, 26.1, 29.0, 48.2, 48.3, 119.85; MS: *m/z* (FAB+ mode) 372.4 ($[M+H]^+$, 12%), 280.4 (92), 226.2 (12), 197.2 (12), 149.1 (28), 73.7 (100), 56.0 (9). Found $[M+H]^+$ 372.2153, $C_{17}H_{34}O_2N_3SiS$ requires 372.2141.

4.3. General procedure for the synthesis of 5a-c

4.3.1. 6-(2-(Trimethylsilyl)ethanesulfonyl)-1,6,11-triazaundecane (5a). Compound **4a** (3.28 g, 10.4 mmol) was dissolved in anhydrous THF (20 mL) in an oven-dried flask. Borane–THF (1 M in THF, 8 equiv.) was added via syringe and the solution heated at reflux for 2 h. The excess borane was quenched with 6 M HCl and methanol. The resulting borate esters and excess solvent were removed by rotary evaporation. The remaining aqueous solution was basified to pH 13–14 and extracted with dichloromethane (5×50 mL). The organic layers were combined, dried with Na_2SO_4 and concentrated to give **5a** as a clear oil (3.24 g, 96% yield); IR: ν_{max} (Golden Gate) 1136, 1165, 1215, 1252, 1323, 1458, 1560, 2341, 2360 and 2943 cm^{-1}; ^1H NMR: δ_H ($CDCl_3$) 0.06 (9H, s), 0.98–1.04 (2H, m), 1.42–1.49 (4H, m), 1.60–1.68 (4H, m), 2.71–2.73 (4H, t, *J*=7.0 Hz), 3.20–3.24 (4H, t, *J*=7.7 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 10.7, 26.9, 31.1, 42.1, 48.4, 48.9; MS: *m/z* (FAB+ mode) 324.2 ($[M+H]^+$, 50%), 253.1 (10), 226.1 (5), 136.1 (6), 101.4 (5), 73.8 (100) and 70.9 (23). Found $[M+H]^+$ 324.2147, $C_{13}H_{34}O_2N_3SiS$ requires 324.2141.

4.3.2. 7-(2-(Trimethylsilyl)ethanesulfonyl)-1,7,13-triazatridecane (5b). Using **4b** (2.10 g, 6.11 mmol), **5b** was prepared as a clear oil (2.05 g, 95% yield); IR: ν_{max} (Golden Gate) 1167, 1248, 1327, 1560, 2862 and 2927 cm^{-1}; ^1H NMR: δ_H ($CDCl_3$) 0.06 (9H, s), 0.98–1.02 (2H, m), 1.24–1.51 (12H, m), 1.56–1.64 (4H, quintet, *J*=7.1 Hz), 2.68–2.72 (4H, t, *J*=7.1 Hz), 2.83–2.88 (2H, m), 3.18–3.22 (4H, t, *J*=7.6 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.7, 10.7, 24.3, 29.3, 33.6, 42.3, 48.1, 48.3; MS: *m/z* (FAB+ mode) 352.5 ($[M+H]^+$ 100%), 226.2 (7), 169.2 (3), 84.6 (24), 73.7 (95). Found $[M+H]^+$ 352.2452, $C_{15}H_{38}O_2N_3SiS$ requires 352.2454.

4.3.3. 8-(2-(Trimethylsilyl)ethanesulfonyl)-1,8,15-triazapentadecane (5c). Using **4c** (2.24 g, 6.03 mmol), **5c** was prepared as a clear oil (2.22 g, 97% yield); IR: ν_{max} (Golden Gate) 1165, 1250, 1325, 1464, 1572, 2856 and 2929 cm^{-1}; ^1H NMR: δ_H ($CDCl_3$) 0.04 (9H, s), 0.97–1.01 (2H, m), 1.21–1.48 (16H, m), 1.54–1.61 (4H, quintet, *J*=7.2 Hz), 2.68 (4H, t, *J*=7.2 Hz), 2.82–2.86 (2H, m), 3.18 (4H, t, *J*=6.7 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 10.7, 26.9, 26.9, 29.4, 33.9, 42.3, 48.1, 48.3; MS: *m/z* (FAB+ mode) 380.5 ($[M+H]^+$ 72%), 288.4 (3), 226.2 (4), 185.3 (4), 98.5 (16), 73.7 (100). Found $[M+H]^+$ 380.2773, $C_{17}H_{42}O_2N_3SiS$ requires 380.2767.

4.4. Typical procedure for the synthesis of 6a-c

4.4.1. 1,6,11-Triazaundecane (6a). Compound **5a** (3.24 g, 10.0 mmol) was dissolved in dry DMF (100 mL) and the solution was added via syringe to a flask with caesium fluoride (10 equiv., previously dried under vacuum for 3 h at ~200°C). The suspension was heated to 100°C overnight while stirring, checking evaporated aliquots by ^1H NMR spectroscopy for disappearance of SES peaks. Upon completion (48 h), MeOH was added (2–5 mL) and the solvent was removed by rotary evaporation under high vacuum. The residue was taken up in dichloromethane, filtered through a small pad of Celite, and the solution evaporated to give **6a** as a beige oil (1.34 g, 84%); ^1H and

^{13}C NMR spectra agreed with literature values.[14] ^{1}H NMR: δ_H ($CDCl_3$) 1.39–1.52 (8H, m), 2.57 (4H, t, J=6.9 Hz), 2.66 (4H, t, J=6.7 Hz); ^{13}C NMR: δ_C ($CDCl_3$) 27.8, 31.8, 42.4, 50.1.

4.4.2. 1,7,13-Triazatridecane (6b). Using **5b** (0.200 g, 0.569 mmol), **6b** was prepared to give an oil (0.089 g, 84% yield); ^{1}H and ^{13}C NMR agreed with literature values.[5] ^{1}H NMR: δ_H ($CDCl_3$) 1.34–1.61 (10H, m), 2.62 (4H, t, J=7.2 Hz), 2.71 (4H, t, J=6.9 Hz); ^{13}C NMR: δ_C ($CDCl_3$) 25.1, 30.4, 34.1, 42.5, 50.4.

4.4.3. 1,8,15-Triazapentadecane (6c). Using **5c** (1.45 g, 3.82 mmol), **6c** was prepared to give an oil (0.38 g, 46% yield); ^{1}H and ^{13}C NMR agreed with literature values.[15] ^{1}H NMR: δ_H ($CDCl_3$) 1.33–1.55 (12H, m), 2.60 (4H, t, J=7.2 Hz), 2.69 (4H, t, J=6.9 Hz); ^{13}C NMR: δ_C ($CDCl_3$) 27.2, 27.7, 30.6, 34.2, 42.5, 50.4.

4.5. Typical procedure for the synthesis of 7a-e

4.5.1. 1,5,9-Tris-2(trimethylsilyl)ethanesulfonyl-1,5,9-triazanonane (7a). Dipropylenetriamine (0.820 g, 6.23 mmol) was dissolved in dry DMF (12 mL) in an oven-dried, N_2-cooled 3-neck round-bottom flask with stir bar, pressure-equalising dropping funnel and internal thermometer. Triethylamine (5 equiv.) was added and the mixture was cooled to 0°C in an immersion-cooler cold bath. Neat SES-Cl (4 equiv.) was added dropwise, sufficiently slowly to keep the internal temperature below 10°C (in order to minimise decomposition of the sulfonyl chloride in the presence of triethylamine). The mixture was stirred overnight while being held at 0°C, then the DMF was removed by rotary evaporation under high vacuum. The residue was taken up in water (50 mL) and dichloromethane (50 mL). The organic layer was washed with brine (25 mL), dried with Na_2SO_4 and concentrated to give **7a**, which was purified by column chromatography (9:1 DCM/EtOAc, silica) to give a cream solid (2.77 g, 71.1% yield); mp=100.2–101.5°C (lit. 106.5–107.5°C[8]); NMR and IR data agreed with literature values.[8]

4.5.2. 1,5,10-Tris-2(trimethylsilyl)ethanesulfonyl-1,5,10-triazadecane (7b). Using spermidine (2.60 g, 36.1 mmol), **7b** was prepared and purified by recrystallisation from MeOH/H_2O (1:1) to give a cream powder (10.0 g, 87% yield); mp=104–106°C; IR: ν_{max} ($CDCl_3$ solution cell) 1142, 1169, 1254, 1327, 1383, 1468, 2900, 2956, 3294 and 3394 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) 0.06 (27H, s), 0.98–1.04 (6H, m), 1.57–1.64 (2H, quintet, J=6.8 Hz), 1.69–1.76 (2H, quintet, J=6.8 Hz), 1.82–1.88 (2H, quintet, J=6.0 Hz), 2.87–2.96 (6H, m), 3.12–3.37 (8H, m), 4.64 (1H, t, J=6.8 Hz), and 5.17 (1H, t, J=6.8 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.60, 10.9, 26.5, 27.7, 30.6, 40.3, 43.0, 46.1, 47.7, 49.0; MS: m/z (FAB+ mode NaI) 660.1 ([M+Na]$^+$, 100%), 494.2 (11.5), 330.2 (6.5), 273.1 (7), 147.1 (5), 73.8 (98), and 60.0 (8). Found [M+Na]$^+$ 660.2457, $C_{22}H_{55}O_6N_3Si_3S_3Na$ requires 660.2459.

4.5.3. 1,6,11-Tris-2(trimethylsilyl)ethanesulfonyl-1,6,11-triazaundecane (7c). Using **5a** (1.27 g, 3.97 mmol) in DMF (10 mL) and **2** (2.00 g, 9.94 mmol), **7c** was prepared and purified by column chromatography to give a white solid (1.33 g, 52% yield); mp=145.5–146.8°C; IR: ν_{max} (Golden Gate) 1036, 1072, 1109, 1130, 1171, 1244, 1267, 1284, 1311, 1421, 2954 and 3278 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) 0.07 (27H, s), 0.98–1.03 (6H, m), 1.60–1.67 (4H, m), 1.74–1.80 (4H, m), 2.86–2.97 (6H, m), 3.14–3.20 (4H, q, J=6.2 Hz), 3.23–3.27 (4H, t, J=7.2 Hz), 4.93–4.96 (2H, t, J=6.2 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 10.5, 10.9, 26.5, 27.6, 43.0, 47.6, 48.7, 49.2; MS: m/z (FAB+ mode NaI) 674.1 ([M+Na]$^+$, 56%), 560.2 (13), 486.1 (10), 305.1 (22), 136.0 (9), 73.3 (100). Found [M+Na]$^+$ 674.2609, $C_{23}H_{57}O_6N_3Si_3S_3Na$ requires 674.2615.

4.5.4. 1,7,13-Tris-2(trimethylsilyl)ethanesulfonyl-1,7,13-triazatridecane (7d). Using **5b** (2.00 g, 5.69 mmol) and **2** (2.86 g, 14.2 mmol), **7d** was recrystallised from isopropanol/water (~2:1) to give a cream solid (2.42 g, 62% yield); mp=95–99°C; IR: ν_{max} (Golden Gate) 1171, 1246, 1315 and 2951 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) 0.05 (9H, s), 0.06 (18H, s), 0.97–1.03 (6H, m), 1.39–1.45 (4H, m), 1.57–1.67 (8H, m), 2.84–2.88 (2H, m), 2.91–2.95 (4H, m), 3.12 (4H, q, J=6.3 Hz), 3.20 (4H, t, J=7.4 Hz), 4.49 (2H, t, J=6.3 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 10.7, 11.0, 23.8, 29.0, 30.3, 43.4, 48.0, 48.4, 49.0, 138.4; MS: m/z (FAB+ mode NaI) 702.6 ([M+Na]$^+$ 38%), 664.5 (5), 616.6 (6), 588.6 (18), 516.5 (22), 514.5 (18), 333.4 (18), 279.3 (9), 215.2 (8), 136.1 (20), 73.4 (99). Found [M+Na]$^+$ 702.2898, $C_{25}H_{61}N_3O_6Si_3S_3Na$ requires 702.2928.

4.5.5. 1,8,15-Tris-2(trimethylsilyl)ethanesulfonyl-1,8,15-triazapentadecane (7e). Using **5c** (2.20 g, 5.79 mmol) and **2** (3.02 g, 15.0 mmol), **7e** was purified by column chromatography to give white crystals (2.67 g, 65%); mp=89–91°C; IR: ν_{max} (Golden Gate) 1173, 1246, 1284, 1313, 1460, 2856 and 2929 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) 0.05 (9H, s), 0.06 (18H, s), 0.97–1.03 (6H, m), 1.35–1.44 (8H, m), 1.54–1.63 (8H, m), 2.83–2.88 (2H, m), 2.91–2.95 (4H, m), 3.11 (4H, q, J=6.4 Hz), 3.19 (4H, t, J=7.5 Hz), 4.50 (2H, t, J=6.4 Hz); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 1.4, 10.7, 11.0, 26.3, 29.3, 30.7, 43.5, 48.1, 48.3, 49.0; MS: m/z (FAB+ mode NaI) 730.7 ([M+Na]$^+$ 12%), 616.7 (4), 542.5 (3), 293.3 (1), 226.2 (1), 147.1 (2), 73.3 (100), 44.1 (12). Found [M+Na]$^+$ 730.3224, $C_{27}H_{65}N_3O_6Si_3S_3Na$ requires 730.3241.

4.6. Typical procedure for synthesis of 9a-f

4.6.1. 1,5,9-Tris-(2-(trimethylsilyl)ethanesulfonyl)-1,5,9-triazacyclotetradecane [3,3,5] (9a). Compound **7a** (2.00 g, 3.20 mmol) and caesium carbonate (3 equiv.) were combined in wet DMF (30 mL). **8b**[11] (1.32 g, 3.20 mmol) in wet DMF (10 mL), was dripped in slowly via pressure-equalising dropping funnel. The mixture was stirred vigorously for 3–7 days, checking daily for disappearance of ditosylate by TLC of an evaporated aliquot. Upon completion (6 days), the DMF was removed by rotary evaporation under high vacuum and the residue taken up in dichloromethane (100 mL) which was washed with water and brine (50 mL each), dried with Na_2SO_4, and concentrated to give crude **9a**, which was purified by column chromatography (20:1 DCM/EtOAc, silica) to give a white solid (1.21 g, 54% yield); mp=175.0–177.3°C; IR: ν_{max} ($CDCl_3$ solution cell) 1142, 1167, 1254, 1333, 1381, 1464, 2866, 2902 and 2956 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) 0.06

(27H, s), 0.96–1.04 (6H, m), 1.57–1.64 (2H, m), 1.67–1.72 (4H, m), 1.90–1.97 (4H, m), 2.84–2.89 (6H, m), 3.23–3.40 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 10.4, 10.6, 23.7, 29.4, 31.0, 45.8, 46.9, 48.5, 48.7, 50.7; MS: *m/z* (FAB+ mode NaI) 714.1 ($[M+Na]^+$, 15%), 548.2 (4), 526.2 (4), 362.2 (3), 360.2 (2.9), 268.2 (1), 210.1 (5), 98.5 (5) and 73.8 (100). Found $[M+Na]^+$ 714.2930, $C_{26}H_{61}O_6N_3Si_3S_3Na$ requires 714.2928.

4.6.2. 1,5,10-Tris-(2-trimethylsilyl)ethanesulfonyl)-1,5,10-triazacyclotetradecane [4,4,3] (9b). Using **7b** (2.00 g, 3.13 mmol) and **8a**[11] (1.25 g, 3.13 mmol) in DMF (40 mL), **9b** was purified by column chromatography to give a white solid (0.90 g, 41%); mp=145.0–147.6°C; IR: ν_{max} ($CDCl_3$ solution cell) 1142, 1167, 1254, 1333, 1379, 1460, 2866, 2922 and 2956 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) 0.05 (27H, s), 0.97–1.03 (6H, m), 1.76 (8H, bs), 1.99–2.05 (2H, m), 2.83–2.88 (6H, m), 3.20–3.30 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 10.37, 10.42, 27.5, 27.6, 32.8, 45.9, 49.0, 50.4, 51.6; MS: *m/z* (FAB+ mode NaI) 714.1 ($[M+Na]^+$, 27%), 548.2 (6), 362.2 (5), 360.2 (4), 305.2 (1), 210.1 (5), 142.1 (2), 84.5 (10), 73.8 (100), and 59.9 (5). Found $[M+Na]^+$ 714.2926, $C_{26}H_{61}O_6N_3Si_3S_3Na$ requires 714.2928.

4.6.3. 1,5,10-Tris-(2-(trimethylsilyl)ethanesulfonyl)-1,5,10-triazacyclopentadecane [3,4,5] (9c). Using **7b** (5.00 g, 7.82 mmol) and **8b** (3.23 g, 7.82 mmol), **9c** was purified by column chromatography to give a white glassy solid (2.41 g, 47% yield); mp=95.2–97.5°C; IR: ν_{max} ($CDCl_3$ solution cell) 1140, 1167, 1254, 1333, 1377, 1464, 2868, 2902 and 2956 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) 0.06 (27H, s), 0.96–1.03 (6H, m), 1.55–1.65 (10H, m), 1.94–1.98 (2H, m), 2.84–2.89 (6H, m), 3.20–3.34 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) −1.67, −1.63, −1.59, 10.4, 10.5, 10.6, 23.6, 27.1, 27.6, 28.6, 28.7, 31.5, 46.0, 46.7, 47.2, 47.3, 47.4, 48.6, 49.3, 49.4, 49.5 and 50.9; MS: *m/z* (FAB+ mode NaI) 728.1 ($[M+Na]^+$, 93%), 654.1 (1.5), 562.2 (17), 540.2 (4), 490.2 (1), 420.2 (1), 398.2 (11), 376.2 (2.5), 341.2 (1), 210.1 (5), 177.2 (1.5), 84.7 (6.5) and 73.8 (100). Found $[M+Na]^+$ 728.3083, $C_{27}H_{63}O_6N_3Si_3S_3Na$ requires 728.3085.

4.6.4. 1,6,11-Tris-(2-(trimethylsilyl)ethanesulfonyl)-1,6,11-triazacyclopentadecane [4,4,4] (9d). Using **7c** (0.940 g, 1.45 mmol) and **8a** (0.580 g, 1.45 mmol), **9d** was purified by column chromatography to give a white solid (0.294 g, 29% yield); mp=133.2–135.0°C; IR: ν_{max} (Golden Gate) 1045, 1105, 1134, 1167, 1211, 1248, 1325, 1376, 1417, 1456, 2952 and 3020 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) −0.07 (27H, s), 0.80–0.93 (6H, m), 1.58 (12H, broad s), 2.66–2.81 (6H, m), 3.11 (12H, broad s); ^{13}C NMR: δ_C ($CDCl_3$) −1.59, 10.5, 27.3, 46.2, 50.1; MS: *m/z* (FAB+ mode NaI) 728.3 ($[M+Na]^+$, 70%), 690.2 (13), 642.3 (15), 540.3 (60), 476.3 (6), 376.2 (42), 374.2 (27), 210.0 (31), 142.1 (10). Found $[M+Na]^+$ 728.3054, $C_{27}H_{63}O_6N_3Si_3S_3Na$ requires 728.3084.

4.6.5. 1,6,12-Tris-(2-(trimethylsilyl)ethanesulfonyl)-1,6,12-triaza-cycloheptadecane [5,5,4] (9e). Using **7d** (1.80 g, 2.64 mmol) and **8a** (0.97 g, 2.64 mmol), **9e** was purified by column chromatography to give a white solid (0.56 g, 29% yield); mp=120–124°C; IR: ν_{max} (Golden Gate) 1136, 1165, 1250, 1327 and 2951 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) 0.05 (27H, s), 0.97–1.02 (6H, m), 1.40–1.47 (4H, m), 1.59–1.69 (12H, m), 2.84–2.88 (6H, m), 3.18–3.24 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 1.4, 10.6, 10.7, 23.6, 27.6, 29.4, 30.1, 47.3, 47.7, 48.6, 49.6, 49.7; MS: *m/z* (FAB+ mode) 734.8 ($[M+H]^+$ 2%), 718.7 (2), 670.8 (4), 614.7 (4), 568.6 (6), 404.5 (6), 402.5 (4), 210.2 (6), 147.1 (3), 73.7 (100). Found $[M+H]^+$ 734.3541, $C_{29}H_{68}O_6N_3Si_3S_3$ requires 734.3578.

4.6.6. 1,6,13-Tris-(2-trimethylsilanyl-ethanesulfonyl)-1,6,13-triaza-cyclononadecane [6,6,4] (9f). Using **7e** (2.60 g, 3.66 mmol) and **8a** (1.34 g, 3.66 mmol), **9f** was purified by column chromatography to give a white solid (0.59 g, 21% yield); mp=129–134°C; IR: ν_{max} (Golden Gate) 1167, 1248, 1327, 2860 and 2929 cm^{-1}; ^{1}H NMR: δ_H ($CDCl_3$) 0.05 (27H, s), 0.97–1.01 (6H, m), 1.37–1.44 (8H, m), 1.62–1.68 (12H, m), 2.83–2.88 (6H, m), 3.16–3.23 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) −1.6, 1.3, 10.5, 26.3, 26.3, 27.1, 29.7, 29.9, 46.7, 46.9, 49.3, 49.9, 50.0; MS: *m/z* (FAB+ mode) 762.8 ($[M+H]^+$ 2%), 746.8 (3), 698.8 (7), 642.7 (6), 596.7 (17), 432.6 (13), 430.6 (11), 210.2 (6), 147.1 (3) 73.7 (100). Found $[M+H]^+$ 762.3885, $C_{15}H_{30}O_2N_3SiS$ requires 762.3891.

4.7. Typical procedure for synthesis of 10a-f

4.7.1. 1,5,9-Triazacyclotetradecane [3,3,5] (10a). Using **9a** (1.21 g, 1.75 mmol), **10a** was prepared according to the typical procedure for **6a-c** and purified by Kugelrohr distillation (0.035 mm Hg/171°C) to give a clear oil (0.216 g, 62% yield); ^{1}H NMR: δ_H ($CDCl_3$) 1.43–1.57 (8H, m), 1.67–1.73 (2H, m), 2.65–2.73 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) 20.9, 25.7, 28.5, 47.2, 47.5, 49.2; MS: *m/z* (EI+ mode) 199.2 ($[M^{\cdot}]^+$, 18%), 198.2 (3), 170.2 (2), 155.1 (5), 141.1 (6), 112.11 (15), 98.1 (48), 82.9 (100), 70.1 (28) and 47.0 (30). Found $[M^{\cdot}]^+$ 199.2049, $C_{11}H_{25}N_3$ requires 199.2048.

4.7.2. 1,5,10-Triazacyclotetradecane [3,4,4] (10b). Using **9b** (0.897 g, 1.28 mmol), **10b** was prepared and purified by Kugelrohr distillation (0.1 mm Hg/170°C) to give a pale yellow oil (0.084 g, 33%); ^{1}H NMR: δ_H ($CDCl_3$) 1.55–1.64 (8H, m), 1.68–1.74 (2H, m), 2.64–2.74 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) 25.2, 25.9, 46.2, 48.2, 49.1; MS: *m/z* (EI+ mode) 199.2 ($[M^{\cdot}]^+$, 19%), 182.2 (3), 154.1 (5), 141.1 (7), 112.1 (15), 98.1 (26), 84.0 (100), 63.0 (51) and 44.1 (23). Found $[M^{\cdot}]^+$ 199.2047, $C_{11}H_{25}N_3$ requires 199.2048.

4.7.3. 1,5,10-Triazacyclopentadecane [3,4,5] (10c). Using **9c** (1.27 g, 1.80 mmol), **10c** was prepared and purified by Kugelrohr distillation (0.1 mm Hg/170°C) to give a pale yellow oil (0.150 g, 39%); ^{1}H NMR: δ_H ($CDCl_3$) 1.49–1.60 (10H, m), 1.64–1.70 (2H, m), 2.61–2.74 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) 23.9, 27.2, 27.9, 28.1, 28.6, 28.8, 47.9, 48.3, 48.6, 49.7, 50.2; MS: *m/z* (EI+ mode) 213.2 ($[M^{\cdot}]^+$, 19%), 196.2 (3), 183.2 (3), 155.2 (6), 141.1 (6), 126.1 (13), 98.1 (53), 84.0 (100), 82.9 (48), 70.1 (36) and 47.0 (34). Found $[M^{\cdot}]^+$ 213.2206, $C_{12}H_{27}N_3$ requires 213.2205.

4.7.4. 1,6,10-Triazacyclopentadecane [4,4,4] (10d). Using **9d** (0.294 g, 0.416 mmol), **10d** was prepared and purified by Kugelrohr distillation (0.05 mm Hg/160°C) to give a pale

tan oil (0.060 g, 67% yield); ^{1}H NMR: δ_H ($CDCl_3$) 1.59 (12H, broad s), 2.68 (12H, broad s); ^{13}C NMR: δ_C ($CDCl_3$) 27.3, 48.7; MS: *m/z* (FAB+ mode) 214.2 ($[M+H]^+$, 100%), 212.2 (11), 126.1 (12), 84.6 (7), 73.7 (10), 48.0 (6). Found $[M+H]^+$ 214.2285, $C_{12}H_{28}N_3$ requires 214.2283.

4.7.5. 1,6,12-Triazacycloheptadecane [5,5,4] (10e). Using **9e** (0.50 g, 0.681 mmol), **10e** was prepared and purified by Kugelrohr distillation (0.05 mm Hg/150°C) to give a clear oil (0.054 g, 33% yield); ^{1}H NMR: δ_H ($CDCl_3$) 1.35–1.59 (19H, m), 2.62–2.66 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) 24.7, 27.7, 29.1, 29.3, 48.7, 49.0, 49.1; MS: *m/z* (EI+ mode) 241.3 ($[M+H]^+$, 14%), 225.3 (2), 200.3 (3), 183.2 (4), 155.2 (11), 140.2 (22), 112.2 (21), 84.1 (100), 70.1 (34), 44.1 (23). Found $[M+H]^+$ 241.2520, $C_{14}H_{31}N_3$ requires 241.2518.

4.7.6. 1,6,13-Triazacyclononadecane [6,6,4] (10f). Using **9f** (0.49 g, 0.643 mmol), **10f** was prepared and purified by Kugelrohr distillation (0.05 mm Hg/165°C) to give a clear oil (0.054 g, 31% yield); ^{1}H NMR: δ_H ($CDCl_3$) 1.38–1.58 (23H, m), 2.62–2.68 (12H, m); ^{13}C NMR: δ_C ($CDCl_3$) 26.5, 26.7, 27.7, 29.4, 29.6, 28.7, 49.0, 49.4; MS: *m/z* (EI+ mode) 269.4 ($[M+H]^+$, 43%), 237.3 (5), 225.3 (6), 211.3 (14), 169.2 (25), 154.2 (23), 126.2 (33), 112.2 (97), 84.1 (100), 70.1 (57), 55.1 (44). Found $[M+H]^+$ 269.2833, $C_{16}H_{35}N_3$ requires 241.2518.

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