New linked macrocyclic systems derived from selectively protected S_2N_2 macrocycles

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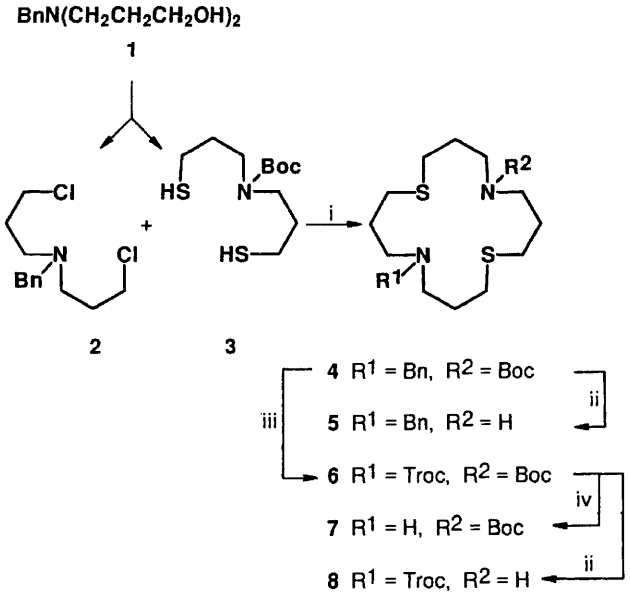
Novel application of a protecting group strategy has enabled a simple and efficient synthesis of the new tri-linked S_2N_2 macrocycles 12, 15, 17 and 20. This strategy involves the introduction of complementary protecting groups (R^1 and R^2) into the precursor macrocycle 4, which can then be manipulated to provide a synthetically versatile set of mono-N-protected S_2N_2 macrocyclic building blocks 5, 7 and 8.

The incorporation of macrocyclic ring systems into larger molecular assemblies has been a notable feature of recent research in supramolecular chemistry.[1] With few exceptions,[2] such studies have involved crown ether moieties, and particularly diazacrown ethers, largely due to their relative ease of synthesis.[3] As a consequence the metal complexation possibilities for the resulting 'super' molecules have often been restricted to hard[4] metal ions such as the alkali and alkaline earth metals.

We describe herein a flexible protecting group strategy designed to allow a wider range of macrocyclic systems—particularly those capable of complexing selected transition and post-transition metal ions—to be incorporated into such assemblies. As an initial example of this approach, we have developed a simple and efficient synthesis of the selectively protected 16-membered S_2N_2 macrocyclic system **4**, based on the strategy outlined in Scheme 1. This strategy, which is



Scheme 1 Bn = benzyl; Boc = *tert*-butoxycarbonyl; Troc = 2,2,2-trichloroethoxycarbonyl. *Reagents and conditions:* i, Cs_2CO_3, DMF, 85 °C, high dilution; ii, 3 mol dm^{-3} HCl, MeOH; iii, Cl_3CCH_2OCOCl, K_2CO_3, PhH, 80 °C; iv, Zn, HOAc.

capable of extension to related ring systems, allows the introduction of complementary protecting groups (R^1 and R^2) into the target macrocycle **4**. In contrast, previous synthetic approaches to this ring system have either lacked generality[5] or do not permit the two ring nitrogens to be easily distinguished.[6]

Results and discussion

In the present study, both of the fragments **2** and **3** used to construct macrocycle **4** were derived from the same starting material, *N*-benzylbis(3-hydroxypropyl)amine **1**[7] (synthesised in the current study by dialkylation of benzylamine with 3-chloropropanol in refluxing acetonitrile over anhydrous sodium carbonate). For **2**,[7] this simply involved chlorination with thionyl chloride. The relatively unstable dithiol **3** was obtained from **1** by the sequence of hydrogenolysis, chlorination, protection as the *tert*-butoxycarbonyl derivative, conversion to the bisthioacetate and cleavage with methanolic NaOMe. Macrocyclisation of **2** and **3** was carried out by the Kellogg procedure.[8] After silica gel chromatography, diprotected macrocycle **4** was isolated in 58% yield.

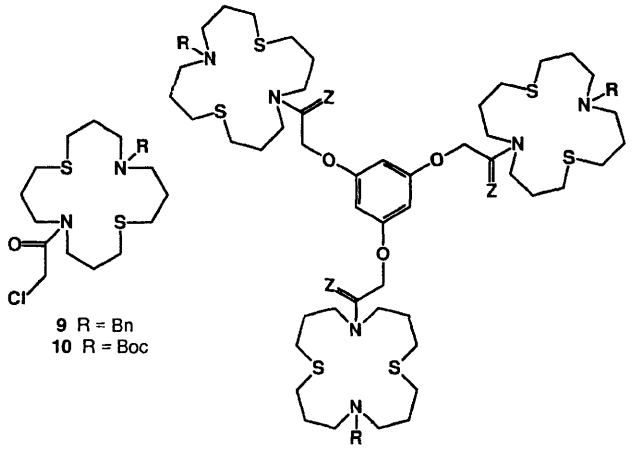
Deprotection of **4** to the *N*-benzyl macrocycle **5** could be achieved in near quantitative yield by hydrolysis in 3 mol dm^{-3} HCl–MeOH. Attempts to debenzylate **4** by conventional hydrogenolysis, transfer hydrogenation[9] or using Pearlman's catalyst[10] were uniformly unsuccessful. Debenzylation could be achieved however, by reaction of **4** with 2,2,2-trichloroethyl chloroformate;[11] the resulting *N*-Boc-*N'*-Troc macrocycle **6** was isolated in 96% yield. In turn, reduction of **6** with zinc dust in glacial acetic acid[12] afforded the *N*-Boc macrocycle **7**, in 72% yield. Cleavage of the *tert*-butoxycarbonyl protecting group of **6** was also easily achieved, providing access to the *N*-Troc macrocycle **8**.

The ^1H (and ^{13}C) NMR spectra of **4–8** clearly confirm the success of these protecting group manipulations. Most diagnostic are the ^1H NMR absorptions due to the protecting group moieties themselves, and characteristic resonances for the ring methylene groups adjacent to nitrogen and sulfur. Each of the Boc-protected derivatives (**4**, **6** and **7**) shows a broad 'singlet' absorption at δ 3.34 ± 0.01 while the Troc-protected compounds **6** and **8** exhibit triplets at δ 3.49 and 3.47, respectively. The remaining methylenes (CH_2S, CH_2NH, CH_2NBn) appear as triplets in the region δ 2.47–2.76.

The three mono-N-protected macrocycles **5**, **7** and **8** provide a synthetically versatile set of building blocks which will allow incorporation of this S_2N_2 ring system into a variety of supramolecular structures—including tricyclic cage molecules and higher order dendritic structures. This potential is exemplified by the attachment of the *N*-benzyl **5** and *N*-Boc **7** derivatives to two tritopic aromatic cores as outlined in Schemes 2 and 3.

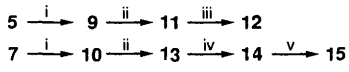
For attachment to the phloroglucinol (1,3,5-trihydroxybenzene) core, **5** and **7** were first acylated with chloroacetyl chloride; the resulting chloromethylamides (**9** and **10** respectively) were used to trialkylate phloroglucinol (Cs_2CO_3, DMF). Subsequent reduction (BH_3·THF) of triamide **11** gave the *N*-benzyl protected trimacrocyclic species **12**, while

deprotection of **13** to **14** followed by a similar reduction afforded the corresponding deprotected species **15** (Scheme 2).



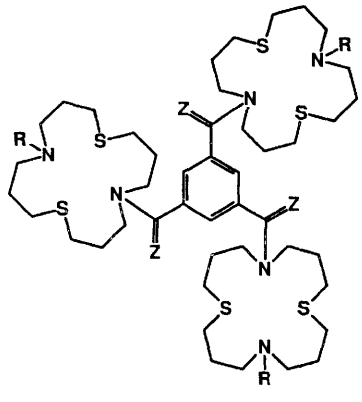
9 R = Bn
10 R = Boc

11 R = Bn, Z = O
12 R = Bn, Z = H, H
13 R = Boc, Z = O
14 R = H, Z = O
15 R = H, Z = H, H

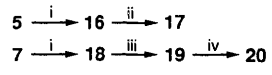


Scheme 2 Bn = benzyl; Boc = *tert*-butoxycarbonyl. *Reagents and conditions:* i, $ClCH_2COCl$, Et_3N, THF; ii, $C_6H_3(OH)_3$, Cs_2CO_3, DMF; iii, BH_3·THF then MeOH–H_2O–conc. HCl (20:5:2); iv, 3 mol dm^{-3} HCl, MeOH; v, BH_3·Me_2S then MeOH–H_2O–conc. HCl (20:5:2).

The 1,3,5-tribenzyl-linked compounds **17** and **20** were obtained in a similar manner, but commencing with direct acylation of **5** and **7** with trimesoyl chloride (Scheme 3).



16 R = Bn, Z = O
17 R = Bn, Z = H, H
18 R = Boc, Z = O
19 R = H, Z = O
20 R = H, Z = H, H



Scheme 3 Bn = benzyl; Boc = *tert*-butoxycarbonyl. *Reagents and conditions:* i, $C_6H_3(COCl)_3$, Et_3N, THF; ii, Bu^i_2AlH, CH_2Cl_2; iii, 3 mol dm^{-3} HCl, MeOH; iv, BH_3·Me_2S then MeOH–H_2O–conc. HCl (20:5:2).

Characterisation of these high molecular weight tri-linked macrocyclic species was not a trivial task—not the least due to their isolation as viscous oils or glasses which retained solvent tenaciously. Nevertheless, in the great majority of cases, elemental composition of chromatographically homogeneous material is supported by high resolution mass spectrometry (EI and ES) or in individual cases, microanalysis. Interpretation of the NMR spectra of many of these compounds was complicated by signal broadening and/or splitting caused by slow interconversion of amide rotamers. This complication is removed in the final reduction products (**12** and **15**, **17** and **20**) which exhibit well-defined NMR spectra supporting the proposed structures. Thus, in the ^1H NMR spectra, diagnostic singlet absorptions are observed for the aromatic core methine groups—at *ca.* δ 6.1 for the phloroglucinol derivatives **12** and **15**, and at *ca.* δ 7.1 for the 1,3,5-tribenzyl linked compounds **17** and **20**. Characteristic ^1H NMR signals also appear for the methylene groups of the 'linker arms' and for the non-equivalent methylene groups of the macrocyclic rings. The latter absorptions are analogous to those of the precursor macrocycles (*e.g.* **5** and **7**) with some minor chemical shift differences. Appropriate ^{13}C NMR resonances were observed in each case and for selected examples, the above ^1H NMR assignments were confirmed by short- and long-range ^1H–^{13}C correlation experiments.

Conclusions

In this report, an efficient protecting group strategy has been exemplified for the preparation of one category of extended macrocyclic-containing system. Clearly, variations of the strategy are applicable to the synthesis of a number of related categories, some of which appear not readily obtainable by other means. Preliminary metal-ion binding and membrane transport studies indicate that both the tri-linked species **12**, **15**, **17**, **20** and their mono-linked analogues (not described here except for **5**), show selective binding for the 'soft' silver(I) ion relative to a number of first-row transition and post-transition ions. The results from these experiments will be reported in due course.

Experimental

General

All reagents were of analytical grade. Reactions were monitored by analytical TLC on cut strips of precoated plastic backed sheets (Merck silica gel 60 F254, 0.25 mm thickness). Vacuum assisted column chromatography was performed using Merck Kieselgel 60 H. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer; δ_H values are relative to Me_4Si, δ_C values are reported relative to $CDCl_3$ at 77.0 ppm and J values are given in Hz. The vast majority of compounds prepared in this study were viscous oils and elemental composition (of chromatographically homogeneous material) is principally supported by high resolution mass spectrometry. Electrospray (ES) ionisation spectra (Bruker BioApex 47e spectrometer) were provided by Bruker Instruments Inc., Billerica MA. Electron impact (EI) spectra (Kraytos MS 25RFA spectrometer) were provided by the Organic Mass Spectrometry Unit, Department of Chemistry, University of Queensland. Microanalyses were performed at James Cook University of North Queensland. DMF was dried over 4 Å and 13 X molecular sieves and then distilled under reduced pressure. Benzene was distilled from sodium wire and THF from sodium benzophenone ketyl. Reactions were carried out under an inert atmosphere of nitrogen. 'Ether' refers to diethyl ether.

N-Benzylbis(3-hydroxypropyl)amine 1

3-Chloropropanol (70.2 g, 0.743 mol) was added to a stirred solution of benzylamine (36.2 g, 0.338 mol) in CH_3CN (1.2 dm^3) containing Na_2CO_3 (78.7 g, 0.743 mol). The mixture was refluxed for 4 days after which the solid was removed by filtration through Celite and the solvent evaporated. The product **1**[7] was isolated as a colourless oil (67.2 g, 95%) which was used without further purification; δ_H($CDCl_3$; 300 MHz) 7.30 (5 H, m, Ar-H), 4.56 (2 H, br s, OH), 3.60 (4 H, t, J 5.8, CH_2OH), 3.52 (2 H, s, $PhCH_2$), 2.56 (4 H, t, J 6.4, NCH_2) and 1.70 (4 H, quin, J 6.3, $NCH_2CH_2CH_2OH$).

N-Benzylbis(3-chloropropyl)amine 2

To a solution of *N*-benzylbis(3-hydroxypropyl)amine **1** (34.6 g, 0.165 mol) in CH_2Cl_2 (600 cm^3) at 0 °C was added thionyl chloride (98.5 g, 0.828 mol). The reaction mixture was allowed to gradually warm to room temperature overnight and then refluxed for 2 h. Excess thionyl chloride was destroyed by careful addition of MeOH, the solvent was evaporated and the residue partitioned between 10% aqueous NaOH (400 cm^3) and CH_2Cl_2 (400 cm^3). The aqueous layer was extracted with a further 400 cm^3 of CH_2Cl_2 and the combined organic layers dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate–hexanes as eluent) to give **2** [7] as a yellow–brown oil (37.0 g, 92%); δ_H($CDCl_3$; 300 MHz) 7.27 (5 H, m, Ar-H), 3.53 (4 H, t, *J* 6.5, CH_2Cl), 3.51 (2 H, s, $PhCH_2$), 2.54 (4 H, t, *J* 6.7, NCH_2) and 1.88 (4 H, quin, *J* ~6.5, $NCH_2CH_2CH_2Cl$).

Synthesis of dithiol 3

(a) Bis(3-hydroxypropyl)amine. *N*-Benzylbis(3-hydroxypropyl)amine **1** (20.0 g, 0.096 mol) and MeOH (10 cm^3) were added to a glass pressure hydrogenation vessel under a stream of N_2. 10% Palladium on charcoal (1 g) was carefully added to the solution in the vessel. The mixture was then agitated under H_2 (3 atm) for 2 h. The catalyst was removed by filtration through Celite and the MeOH evaporated under reduced pressure. The resulting bis(3-hydroxypropyl)amine [13] (11.76 g, 92%) was used without further purification; δ_H($CDCl_3$; 300 MHz) 3.75 (4 H, t, *J* 5.7, CH_2OH), 3.29 (2 H, br s, OH), 2.82 (4 H, t, *J* 6.1, CH_2N) and 1.72 (4 H, quin, *J* ~6, $NCH_2CH_2CH_2OH$).

(b) Bis(3-chloropropyl)amine. Thionyl chloride (183 g, 1.538 mol) was added slowly to a solution of bis(3-hydroxypropyl)amine (51.2 g, 0.385 mol) in CH_2Cl_2 (500 cm^3) at 0 °C. The reaction mixture was allowed to gradually come to room temperature overnight and then refluxed for 2 h. Excess thionyl chloride was destroyed by careful addition of MeOH, the solvent was evaporated and the residue partitioned between 10% aqueous NaOH (450 cm^3) and CH_2Cl_2 (450 cm^3). The aqueous layer was extracted with a further 450 cm^3 of CH_2Cl_2 and the combined organic layers dried (Na_2SO_4) and evaporated under reduced pressure. Bis(3-chloropropyl)amine [13] (52.1 g, 80%) was isolated as a yellow oil and used without further purification; δ_H($CDCl_3$; 300 MHz) 3.63 (4 H, t, *J* 6.4, CH_2Cl), 2.79 (4 H, t, *J* 6.8, CH_2N) and 1.96 (4 H, quin, *J* 6.6, $NCH_2CH_2CH_2Cl$).

(c) *N*-*tert*-Butoxycarbonylbis(3-chloropropyl)amine. A solution of bis(3-chloropropyl)amine (52.1 g, 0.306 mol) in CH_2Cl_2 (300 cm^3) was rapidly stirred with 10% aqueous NaOH (250 cm^3). Di-*tert*-butyl dicarbonate (66.84 g, 0.306 mol) in CH_2Cl_2 (200 cm^3) was added slowly to the stirred mixture from a dropping funnel over a period of 2 h. The mixture was rapidly stirred for a further 4 h after which the phases were separated, the organic layer dried (Na_2SO_4) and evaporated under reduced pressure. N-tert-*butoxycarbonylbis*(3-*chloropropyl*)-*amine* was isolated as a clear oil (63.7 g, 77%) which was used without further purification [Found: M^+, 269.0932 (EI). $C_{11}H_{21}NO_2Cl_2$ requires M^+, 269.0949]; δ_H($CDCl_3$; 300 MHz) 3.58 (4 H, t, *J* 6.4, CH_2Cl), 3.35 (4 H, t, *J* 7.0, CH_2NBoc), 2.01 (4 H, quin, *J* ~6.5, $NCH_2CH_2CH_2Cl$) and 1.46 [9 H, s, $C(CH_3)_3$]; δ_C($CDCl_3$; 75 MHz) 155.5, 79.9, 45.2, 42.4, 31.4 and 28.4.

(d) *N*-*tert*-Butoxycarbonylbis(3-thioacetoxypropyl)amine. To a solution of *N*-(*tert*-butoxycarbonyl)bis(3-chloropropyl)amine (18.84 g, 69.7 mmol) in DMF (120 cm^3) was added solid potassium thioacetate (19.9 g, 174 mmol) and the mixture stirred at room temperature for 2 days. The DMF was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (100 cm^3) and water (100 cm^3). The organic layer was washed with a further 100 cm^3 of water, dried (Na_2SO_4) and the CH_2Cl_2 removed under reduced pressure. The residue was purified by column chromatography (eluting with ethyl acetate–hexanes, 1:9) to give N-tert-*butoxycarbonylbis*(3-*thioacetoxypropyl*)-*amine* as a brown oil (15.36 g, 80%) (Found: C, 52.0; H, 7.9; N, 3.5. $C_{15}H_{27}NO_4S_2$ requires C, 51.6; H, 7.8; N, 4.0%); R_f(ethyl acetate–hexanes, 1:3) 0.45; δ_H($CDCl_3$; 300 MHz) 3.22 (4 H, br s, CH_2NBoc), 2.86 (4 H, t, *J* 7.2, CH_2SCOCH_3), 2.33 (6 H, s, $SCOCH_3$), 1.79 (4 H, quin, *J* ~7, $NCH_2CH_2CH_2SCOCH_3$) and 1.46 [9 H, s, $C(CH_3)_3$]; δ_C($CDCl_3$; 75 MHz) 195.5, 155.3, 79.6, 46.0, 45.9, 30.5, 28.3 and 26.3.

The above bisthioacetate (22.26 g, 81 mmol) was stirred in a solution of NaOMe in MeOH (100 cm^3, 1.7 mol dm^{-3}) for 5 min, after which the solvent was removed under reduced pressure. The residue was then partitioned between 10% aqueous NaOH (200 cm^3) and CH_2Cl_2 (200 cm^3). The aqueous layer was extracted with CH_2Cl_2 (200 cm^3) and then carefully acidified with conc. HCl to pH 2. The aqueous layer was extracted with CH_2Cl_2 (200 cm^3 × 3) and the combined organic layers dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The product, N-tert-*butoxycarbonylbis*(3-*thiopropyl*)*amine* **3** (15.85 g, 74% yield), was isolated as a red–brown oil and was used immediately to minimise loss by disulfide formation; δ_H($CDCl_3$; 300 MHz) 3.29 (4 H, br s, CH_2NBoc), 2.52 (4 H, q, *J* 7.3, CH_2CH_2SH), 1.83 (4 H, quin, *J* ~7, $CH_2CH_2CH_2SH$), 1.58 (2 H, s, SH) and 1.46 [9 H, s, $C(CH_3)_3$]; δ_C($CDCl_3$, 75 MHz) 155.5, 79.7, 46.0, 35.9, 28.5 and 28.0.

5-Benzyl-13-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane 4

A solution of dichloro compound **2** (11.99 g, 46.1 mmol) and dithiol **3** (12.23 g, 46.1 mmol) in dry DMF (500 cm^3) was added over a period of 12 h to a stirred suspension of Cs_2CO_3 (33 g, 101 mmol) in dry DMF (1.3 dm^3) at 85 °C. The reaction mixture was stirred at this temperature for a further 24 h. The DMF was removed *in vacuo*, the residue taken up in CH_2Cl_2 and the Cs_2CO_3 removed by filtration through Celite. Evaporation of the solvent gave a brown oil that was purified by chromatography on silica gel using 10% ethyl acetate–hexanes as eluent. *Diprotected macrocycle* **4** was obtained as a clear viscous oil (12.07 g, 58%) [Found: M + H^+, 453.2594 (ES). $C_{24}H_{40}N_2O_2S_2$ requires M + H^+, 453.2609]; δ_H($CDCl_3$; 300 MHz) 7.35–7.20 (5 H, m, Ph), 3.51 (2 H, s, $PhCH_2$), 3.34 (4 H, br s, CH_2NBoc), 2.58, 2.52, 2.47 (12 H, overlapping t, SCH_2, $PhCH_2NCH_2$), 1.91 (4 H, quin, *J* 6.5, CH_2CH_2NBoc), 1.73 (4 H, quin, *J* 7.2, $CH_2CH_2NCH_2Ph$) and 1.45 [9 H, s, $C(CH_3)_3$]; δ_C($CDCl_3$; 75 MHz) 155.7, 139.6, 128.8, 128.1, 126.7, 79.4, 59.1, 52.9, 47.5, 29.6, 29.5, 28.5 and 27.7.

5-Benzyl-1,9-dithia-5,13-diazacyclohexadecane 5

Macrocycle **4** (2.47 g, 5.4 mmol) was dissolved in a solution of 3 mol dm^{-3} HCl in MeOH (25 cm^3) and stirred at room temperature for 1 h. The MeOH was removed under reduced pressure and the residue basified with 10% aqueous NaOH and extracted with CH_2Cl_2 (100 cm^3 × 3). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil. This material was purified by chromatography on silica gel using 4% MeOH–CH_2Cl_2 as eluent to give *macrocycle* **5** as a yellow oil (1.83 g, 96%) [Found: C, 64.4; H, 9.25; N, 7.7. $C_{19}H_{32}N_2S_2$ requires C, 64.75; H, 9.15; N, 7.95%. Found: M + H^+, 352.1997 (ES). $C_{19}H_{32}N_2S_2$ requires M + H^+, 352.2007]; δ_H($CDCl_3$; 300 MHz) 7.30–7.22 (5 H, m, Ph), 3.52 (2 H, s, $PhCH_2$), 2.76 (4 H, t, *J* 6.0, CH_2NH), 2.67 (4 H, t, *J* 7.2, CH_2S), 2.56 (4 H, t, *J* 7.2, CH_2S), 2.49 (4 H, t, *J* 6.7, CH_2NCH_2Ph) and 1.83–1.72 (8 H, m, CH_2CH_2N); δ_C($CDCl_3$; 75 MHz) 139.7, 128.7, 128.1, 126.8, 59.2, 52.5, 47.3, 29.9, 29.7, 29.1 and 27.5.

5-*tert*-Butoxycarbonyl-13-(2,2,2-trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane 6

Potassium carbonate (1.16 g, 8.4 mmol) was added to a solution of macrocycle **4** (2.53 g, 5.6 mmol) and 2,2,2-trichloroethyl chloroformate in dry benzene (60 cm^3) and the mixture *refluxed*

for 12 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (120 cm^3), washed with H_2O (40 cm^3 × 2), dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless oil. Purification of this material was achieved by chromatography on silica gel (eluting with EtOAc–hexanes, 1:9) to yield *macrocycle* **6** as an amorphous solid (2.90 g, 96%) [Found: M + H^+, 536.1103 (ES). $C_{20}H_{35}N_2O_4S_2Cl_3$ requires M + H^+, 536.1104]; δ_H($CDCl_3$; 300 MHz) 4.75 (2 H, s, Cl_3CCH_2OCO), 3.49 (4 H, t, *J* 7.2, CH_2NTroc), 3.53 (4 H, br s, CH_2NBoc), 2.59 (4 H, t, *J* 6.5, CH_2S), 2.56 (4 H, t, *J* 6.6, CH_2S), 2.0–1.8 (8 H, m, $SCH_2CH_2CH_2N$) and 1.45 [9 H, s, $C(CH_3)_3$]; δ_C($CDCl_3$; 75 MHz) 155.4, 154.2, 95.6, 79.4, 74.8, 48.0, 47.2, 29.8, 29.7, 28.8, 28.3 and 28.0.

5-*tert*-Butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane 7

Macrocycle **6** (1.54 g, 3.0 mmol) was dissolved in glacial acetic acid (20 cm^3) and stirred with Zn dust (5.7 g) at room temperature for 2 h. The reaction mixture was poured into 10% aqueous NaOH (300 cm^3) at 0 °C and the resultant suspension extracted with CH_2Cl_2 (200 cm^3 × 3). The combined organic layers were dried (Na_2SO_4) and evaporated to give a brown oil that was purified by chromatography on silica gel with 2–8% MeOH–CH_2Cl_2 gradient elution. *Macrocycle* **7** was isolated as a clear oil (0.77 g, 72%) [Found: M + H^+, 362.2065 (ES). $C_{17}H_{34}N_2O_2S_2$ requires M + H^+, 362.2062]; δ_H($CDCl_3$; 300 MHz) 3.33 (4 H, br s, CH_2NBoc), 2.76 (4 H, t, *J* 6.0, CH_2NH), 2.70 (4 H, t, *J* 6.9, CH_2S), 2.55 (4 H, t, *J* 6.8, CH_2S), 2.09 (1 H, br s, NH), 1.89 (4 H, quin, *J* ~7, $SCH_2CH_2CH_2N$), 1.80 (4 H, quin, *J* ~6.5, $SCH_2CH_2CH_2N$) and 1.45 [9 H, s, $C(CH_3)_3$]; δ_C($CDCl_3$; 75 MHz) 155.5, 79.3, 47.4, 47.1, 29.5, 29.4, 28.7, 28.4 and 27.6.

5-(2,2,2-Trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane 8

Macrocycle **6** (0.113 g, 0.2 mmol) was dissolved in a solution of 3 mol dm^{-3} HCl in MeOH (10 cm^3) and stirred at room temperature for 1 h. The methanol was removed under reduced pressure and the residue basified with 10% aqueous NaOH and extracted with CH_2Cl_2 (50 cm^3 × 3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow glass. This material was purified by chromatography on silica gel (eluting with MeOH–CH_2Cl_2, 1:19) to give *macrocycle* **8** as a yellow oil (0.083 g, 90%) [Found: M + H^+, 436.0578 (ES). $C_{15}H_{27}N_2O_2S_2Cl_3$ requires M + H^+, 436.0580]; δ_H($CDCl_3$; 300 MHz) 4.75 (2 H, s, Cl_3CCH_2OCO), 3.47 (4 H, t, *J* 7.2, CH_2NTroc), 2.74 (4 H, t, *J* 6.0, CH_2NH), 2.70 (4 H, t, *J* 6.9, CH_2S), 2.58 (4 H, t, *J* 6.7, CH_2S), 1.96 (4 H, m, $SCH_2CH_2CH_2NTroc$), 1.79 (4 H, quin, *J* ~6.5, $SCH_2CH_2CH_2NH$) and 1.49 (1 H, br s, NH); δ_C($CDCl_3$; 75 MHz) 154.2, 95.6, 74.9, 47.8, 47.3, 47.1, 30.2, 29.6, 29.4, 28.7, 28.5 and 27.9. The ^{13}C NMR spectrum of this compound shows doubling of certain signals, presumably due to slow interconversion of carbamate rotamers. Such splitting and/or broadening is observed, to a greater or lesser extent, in the ^1H and/or ^{13}C NMR spectra of all subsequent compounds which are 'acylated' on at least one nitrogen of the constituent macrocyclic ring(s).

5-Benzyl-13-chloroacetyl-1,9-dithia-5,13-diazacyclohexadecane 9

Macrocycle **5** (1.02 g, 2.9 mmol) was dissolved in dry THF (40 cm^3). Triethylamine (0.32 g, 3.2 mmol) and then chloroacetyl chloride (0.36 g, 3.2 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue partitioned between CH_2Cl_2 (200 cm^3) and water (50 cm^3). The organic layer was washed with a further 50 cm^3 of water, dried (Na_2SO_4) and evaporated under reduced pressure. *Macrocycle* **9** was isolated as a yellow–brown oil (1.10 g, 89%) after purification by chromatography on silica gel (eluting with ether–hexanes, 1:1) [Found: M^+, 428.1725 (EI). $C_{21}H_{33}N_2OS_2Cl$ requires M^+, 428.1723]; δ_H($CDCl_3$; 300 MHz) 7.31–7.28 (5 H, m, Ph), 4.09 (2 H, s, $NCOCH_2Cl$), 3.52 (4 H, t, *J* 7.7, CH_2NCOCH_2Cl), 3.51 (2 H, s, $PhCH_2$), 2.6–2.5 (12 H, m, CH_2SCH_2, CH_2NCH_2Ph), 1.98 (4 H, quin, *J* ~7, $CH_2CH_2NCOCH_2Cl$) and 1.74 (4 H, quin, *J* ~6.5, $CH_2CH_2NCH_2Ph$); δ_C($CDCl_3$; 75 MHz) 155.6, 139.5, 128.9, 128.2, 127.0, 77.2, 59.4, 53.0, 48.3, 46.1, 41.2, 30.0, 29.5, 28.0 and 27.5.

5-*tert*-Butoxycarbonyl-13-chloroacetyl-5,13-diazacyclohexadecane 10

Macrocycle **7** (0.98 g, 2.7 mmol) was dissolved in dry THF (20 cm^3). Triethylamine (0.30 g, 3.0 mmol) and then chloroacetyl chloride (0.33 g, 3.0 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue partitioned between CH_2Cl_2 (200 cm^3) and water (50 cm^3). The organic layer was then washed with a further 50 cm^3 of water, dried (Na_2SO_4) and evaporated under reduced pressure. *Macrocycle* **10** was isolated as a clear oil (1.15 g, 97%) after purification by chromatography on silica gel (eluting with ethyl acetate–hexanes, 1:3) [Found: M^+, 438.1777 (EI). $C_{19}H_{35}N_2O_3S_2Cl$ requires M^+, 438.1778]; δ_H($CDCl_3$; 300 MHz) 4.11 (2 H, s, $NCOCH_2Cl$), 3.58 (4 H, t, *J* 7.4, CH_2NCOCH_2Cl), 3.35 [4 H, t, *J* 6.6, $CH_2NCO_2C(CH_3)_3$], 2.66–2.48 (8 H, m, CH_2SCH_2), 1.97–1.88 (8 H, m, $SCH_2CH_2CH_2N$) and 1.45 [9 H, s, $C(CH_3)_3$]; δ_C($CDCl_3$; 75 MHz) 155.6, 155.5, 79.5, 77.2, 48.1, 47.6, 47.2, 46.2, 30.0, 29.5, 28.8, 28.4 and 27.4.

1,3,5-Tris[(13-benzyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)-carbonylmethoxy]benzene 11

Chloromethylamide **9** (2.23 g, 5.2 mmol) was added to a solution of phloroglucinol (1,3,5-trihydroxybenzene) (0.20 g, 1.58 mmol) in dry DMF (10 cm^3) containing Cs_2CO_3 (1.8 g, 5.5 mmol) and the mixture stirred at room temperature for 12 h. The DMF was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (100 cm^3) and water (50 cm^3). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The product *triamide* **11** was isolated as a yellow glass (1.80 g, 87%) after purification by chromatography on silica gel (gradient elution, 0.5–2.5% MeOH–CH_2Cl_2) [Found: M + H^+, 1303.6268 (ES). $C_{69}H_{102}O_6N_6S_6$ requires M + H^+, 1303.6263]; δ_H($CDCl_3$; 300 MHz) 7.34–7.28 (15 H, m, Ph), 6.23 (3 H, s, core ArH), 4.63 (6 H, s, CH_2CON), 3.54–3.50 (18 H, m, CH_2NCO, $PhCH_2$), 2.65–2.45 (36 H, m, CH_2SCH_2, CH_2NCH_2Ph), 1.96 (12 H, br m, $CH_2CH_2NCH_2Ph$) and 1.72 (12 H, br m, CH_2CH_2NCO); δ_C($CDCl_3$; 75 MHz) 167.3, 159.7, 139.5, 128.9, 128.2, 127.0, 95.0, 67.3, 59.2, 53.0, 52.8, 47.5, 46.0, 29.9, 29.3, 29.0, 27.8, 27.6 and 27.4.

1,3,5-Tris[2-(13-benzyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)-ethoxy]benzene 12

Triamide **11** (1.80 g, 1.37 mmol) was dissolved in dry THF (20 cm^3). A 1.0 mol dm^{-3} solution of BH_3·THF (41 cm^3) was added slowly and the solution then refluxed for 12 h. The solution was allowed to cool and the excess borane destroyed by careful addition of MeOH. The THF was removed under reduced pressure and the residue hydrolysed in refluxing MeOH–H_2O–conc. HCl (20:5:2; 54 cm^3) for 1 h. The MeOH was removed under reduced pressure and the resulting solution partitioned between 10% aqueous NaOH (100 cm^3) and CH_2Cl_2 (100 cm^3). The aqueous layer was extracted with CH_2Cl_2 (100 cm^3 × 2) and the combined organic layers dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using 2% MeOH–CH_2Cl_2 as eluent. *Triether* **12** was isolated as a clear viscous oil (1.49 g, 86%) (Found: C, 65.8; H, 8.45; N, 6.8. $C_{57}H_{108}N_6O_3S_6$ requires C, 65.65; H, 8.65; N, 6.65%); δ_H($CDCl_3$; 300 MHz) 7.36–7.28 (15 H, m, Ph), 6.08 (3 H, s, core ArH), 3.98 (6 H, t, *J* 5.8, NCH_2CH_2O), 3.50 (6 H, s, NCH_2Ph), 2.84 (6 H, t, *J* 5.8,

NCH_2CH_2O), 2.61–2.55 (36 H, m, CH_2SCH_2, CH_2NCH_2-CH_2O), 2.46 (12 H, t, *J* 6.1, CH_2NCH_2Ph), 1.77–1.71 (24 H, m, CH$_2$CH_2CH_2); δ_C(CDCl$_3$; 75 MHz) 160.7, 139.7, 128.8, 128.1, 126.8, 93.9, 66.5, 59.5, 53.6, 53.5, 52.7, 30.1, 30.0, 27.8 and 27.7.

1,3,5-Tris[(13-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)carbonylmethoxy]benzene 13

Chloromethylamide **10** (7.86 g, 17.92 mmol) was added to a suspension of Cs_2CO_3 (6.4 g, 19.7 mmol) in dry DMF (20 cm^3). The reaction mixture was heated to 65 °C and phloroglucinol (1,3,5-trihydroxybenzene) (0.68 g, 5.4 mmol) was then added. After stirring for 10 h the DMF was removed *in vacuo* and CH_2Cl_2 (100 cm^3) added to the residue. The solid was removed by filtration through Celite and the filtrate dried (Na_2SO_4) and evaporated. The crude reaction material was purified by column chromatography on silica gel (eluent CH_2Cl_2–MeOH, 49:1) to give *protected triamide* **13** as a glass (5.6 g, 78%) (Found: C, 54.55; H, 8.15; N, 6.05. $C_{63}H_{108}N_6O_{12}S_6$·3$H_2O$ requires C, 54.5; H, 8.3; N, 6.05%); R_f(MeOH–CH_2Cl_2, 1:19) 0.54; δ_H(CDCl$_3$; 300 MHz) 6.21 (3 H, s, core ArH), 4.62 (6 H, s, OCH_2CON), 3.49 (12 H, t, *J* 7.4, CH_2NCOCH$_2$), 3.34 [12 H, br s, CH_2NCO$_2$C(CH$_3$)$_3$], 2.96–2.88 (24 H, m, CH$_2$SCH_2), 1.91–1.86 (24 H, m, NCH$_2$CH_2-CH$_2$S) and 1.45 [27 H, s, C(CH_3)$_3$]; δ_C(CDCl$_3$; 75 MHz) 167.2, 159.8, 155.5, 95.0, 79.5, 67.1, 47.2, 45.9, 30.1, 29.7, 29.2, 28.4 and 27.4.

1,3,5-Tris[(1,9-dithia-5,13-diazacyclohexadec-5-yl)carbonylmethoxy]benzene 14

Protected triamide **13** (0.48 g, 0.36 mmol) was stirred in a solution of 3 mol dm^{-3} HCl–MeOH (10 cm^3) at room temperature for 1.5 h. The MeOH was removed under reduced pressure and the aqueous residue basified with 10% aqueous NaOH (50 cm^3). The basic solution was extracted with CH_2Cl_2 (50 cm^3 × 3) and the combined organic layers dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting with CH_2Cl_2–MeOH, 19:1 with 1% saturated NH_3 solution) to give *triamide* **14** as a viscous oil (0.33 g, 89%); R_f(CH_2Cl_2–MeOH, 9:1 with 1% saturated NH_3 solution) 0.37; δ_H(CDCl$_3$; 300 MHz) 6.21 (3 H, s, ArH), 4.62 (6 H, s, OCH_2CON), 3.49 (12 H, t, *J* 7.7, CH_2NCOCH$_2$), 2.73–2.64 (24 H, m, CH$_2$SCH_2), 2.57 (12 H, t, *J* 5.8, CH_2NH), ~1.95 (12 H, br m, CH_2CH$_2$NCOCH$_2$) and 1.78 (12 H, quin, *J* 5.8, CH_2CH$_2$NH); δ_C(CDCl$_3$, 75 MHz) 167.2, 159.8, 94.9, 67.3, 59.8, 53.4, 47.5, 47.2, 45.7, 45.5, 29.8, 29.2, 28.8 and 27.1.

1,3,5-Tris[2-(1,9-dithia-5,13-diazacyclohexadec-5-yl)ethoxy]-benzene 15

BH_3·Me_2S complex (2.0 mol dm^{-3} solution in THF; 4.8 cm^3, 9.7 mmol) was added slowly by syringe to a solution of triamide **14** (0.24 g, 0.32 mmol) in dry THF. The solution was refluxed for 12 h after which the excess borane was destroyed by careful addition of MeOH. The THF was evaporated and the resulting white powder hydrolysed in refluxing MeOH–H_2O–conc. HCl (20:5:2; 13.5 cm^3) for 1.5 h. The MeOH was removed under reduced pressure and the aqueous residue basified with 10% aqueous NaOH (50 cm^3). The basic solution was then extracted with CH_2Cl_2 (50 cm^3 × 3), the combined extracts dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with CH_2Cl_2–MeOH, 19:1 with 1% saturated NH_3 solution) to give *triether* **15** as a clear oil (0.23 g, 71%) [Found: M + H$^+$, 991.555 (ES). $C_{48}H_{90}N_6O_3S_6$ requires M + H$^+$, 991.548]; δ_H(CDCl$_3$; 300 MHz) 6.04 (3 H, s, ArH,), 3.96 (6 H, t, *J* 5.8, OCH_2CH$_2$N), 2.83 (6 H, t, *J* 5.8, OCH$_2$CH_2N), 2.72 (12 H, t, *J* 6.0, CH_2NH), 2.7–2.6 (36 H, overlapping t, CH_2NCH$_2$CH$_2$O, CH$_2$S) and 1.81–1.73 (24 H, m, SCH$_2$CH_2CH$_2$N); δ_C(CDCl$_3$; 75 MHz) 160.3, 155.5, 93.6, 66.2, 53.1, 47.1, 29.6, 29.5, 28.9 and 27.4.

1,3,5-Tris[(13-benzyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)-carbonyl] benzene 16

Trimesoyl chloride (benzene-1,3,5-tricarbonyl trichloride) (0.46 g, 1.7 mmol) was added to a solution of macrocycle **5** (2.01 g, 5.7 mmol) and triethylamine (0.61 g, 6.0 mmol) in dry THF (20 cm^3). The reaction mixture was stirred at room temperature for 4 h, after which the THF was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 (150 cm^3) and water (100 cm^3). The organic phase was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel (eluting with CH_2Cl_2–MeOH, 39:1) to yield *triamide* **16** (2.0 g, 95%) (Found: C, 64.2; H, 8.05; N, 6.4. $C_{66}H_{96}N_6O_3S_6$·H_2O requires C, 64.35; H, 8.0; N, 6.8%); R_f(CH_2Cl_2–MeOH, 19:1) 0.34; δ_H(CDCl$_3$; 300 MHz) 7.34 (3 H, s, core ArH), 7.31–7.24 (15 H, m, Ph), 3.67, 3.40 (total 12 H, br m, CH$_2$NCOAr), 3.51 (6 H, s, CH$_2$Ph), 2.7–2.3 (total 36 H, overlapping m, CH$_2$SCH$_2$, CH_2NCH$_2$Ph), 2.0, 1.9 (total 12 H, br m, CH_2CH$_2$NCOAr) and 1.75 (12 H, br m, CH_2CH$_2$NCH$_2$Ph); δ_C(CDCl$_3$; 75 MHz) 169.9, 139.5, 137.7, 128.9, 128.1, 126.9, 125.6, 59.1, 52.7, 49.1, 45.0, 30.0, 29.8, 29.2, 28.9, 27.6 and 27.3. Broadening and splitting of signals in the NMR spectra of this compound is particularly pronounced.

1,3,5-Tris[(13-benzyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)-methyl]benzene 17

A solution of diisobutylaluminium hydride (1.0 mol dm^{-3} in CH_2Cl_2; 26 cm^3, 26 mmol) was added to triamide **16** (2.0 g, 1.65 mmol) in CH_2Cl_2 (20 cm^3). The solution was heated at reflux for 10 h, after which the excess diisobutylaluminium hydride was carefully destroyed by the addition of MeOH. The solvent was evaporated and the residue partitioned between ether (200 cm^3) and water (200 cm^3). The aqueous layer was extracted with further ether (200 cm^3 × 2) and the combined organic layers dried (Na_2SO_4) and evaporated. The crude reaction product was purified by column chromatography on silica gel (eluting with CH_2Cl_2–MeOH, 79:1 with 0.25% saturated NH_3) to give *compound* **17** as a clear oil (0.95 g, 47%); R_f(CH_2Cl_2–MeOH, 9:1) 0.41; δ_H(CDCl$_3$; 300 MHz) 7.32–7.30 (15 H, m, Ph), 7.13 (3 H, s, core ArH), 3.54 (12 H, s, CH$_2$Ph, CH$_2$Ar core), 2.56 (24 H, t, *J* 7.0, CH$_2$N), 2.48 (24 H, t, *J* 6.6, CH$_2$SCH$_2$) and 1.77 (24 H, quin, *J* 6.9, NCH$_2$CH_2CH$_2$S); δ_C(CDCl$_3$; 75 MHz) 139.7, 139.4, 128.8, 128.2, 126.9, 59.4, 52.6, 30.1, 30.0, 27.7 and 27.6.

1,3,5-Tris[(13-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadec-5-yl)carbonyl]benzene 18

Trimesoyl chloride (benzene-1,3,5-tricarbonyl trichloride) (0.14 g, 0.51 mmol) was added to a stirred solution of macrocycle **7** (0.59 g, 1.6 mmol) and triethylamine (0.18 g, 1.8 mmol) in dry THF (20 cm^3) at room temperature. After 2.5 h the THF was evaporated and the residue partitioned between CH_2Cl_2 (100 cm^3) and water (50 cm^3). The organic layer was washed with water (50 cm^3), dried (Na_2SO_4) and evaporated. The crude material was purified by column chromatography on silica gel (eluting with CH_2Cl_2–MeOH, 49:1) to yield *protected triamide* **18** as a clear glass (0.58 g, 92%); R_f(CH_2Cl_2–MeOH, 19:1) 0.44; δ_H(CDCl$_3$; 300 MHz) 7.40 (3 H, s, ArH), 3.63, 3.35 (total 24 H, br m, CH$_2$NBoc, CH$_2$NCOAr), 2.63, 2.54, 2.39 (total 24 H, br m, CH$_2$SCH$_2$), 2.0, 1.9 (total 24 H, br m, CH_2CH$_2$N) and 1.46 [27 H, s, C(CH$_3$)$_3$]; δ_C(CDCl$_3$; 75 MHz) 169.8, 155.5, 137.5, 125.3, 79.5, 48.9, 47.2, 45.0, 30.3, 30.0, 29.6, 29.1, 28.4 and 27.4; *m/z* (LSIMS) 1242 (M + H$^+$). Broadening and splitting of signals in the NMR spectra of this compound is particularly pronounced.

1,3,5-Tris[(1,9-dithia-5,13-diazacyclohexadec-5-yl)carbonyl]-benzene 19

Protected triamide **18** (0.58 g, 0.47 mmol) was stirred in a solution of 3 mol dm^{-3} HCl–MeOH (20 cm^3) for 1.5 h at room temperature. The MeOH was then evaporated and the aqueous

residue partitioned between 10% aqueous NaOH (100 cm^3) and CH_2Cl_2 (100 cm^3). The aqueous phase was extracted twice more with CH_2Cl_2 (100 cm^3) and the combined organic extracts dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel (eluting with CH_2Cl_2–MeOH, 19:1 with 1% saturated NH_3 solution) to yield *triamide* **19** as a viscous oil (0.43 g, 96%) [Found: M + H^+, 943.439 (ES). $C_{45}H_{78}N_6O_3S_6$ requires M + H^+, 943.454]; R_f(CH_2Cl_2–MeOH, 9:1 with 1% saturated NH_3) 0.39; δ_H($CDCl_3$; 300 MHz) 7.40 (3 H, s, ArH), 3.63, 3.37 (total 12 H, br m, CH_2NCO), 2.7–2.3 (total 36 H, overlapping m, CH_2SCH_2, CH_2NH) and 2.0–1.7 (total 24 H, overlapping m, $CH_2CH_2CH_2$); δ_C($CDCl_3$; 75 MHz) 169.7, 137.4, 125.3, 48.7, 47.3, 44.6, 29.7, 29.2, 28.7, 28.5 and 27.0. Broadening and splitting of signals in the NMR spectra of this compound is particularly pronounced.

1,3,5-Tris[(1,9-dithia-5,13-diazacyclohexadec-5-yl)methyl]-benzene 20

A solution of BH_3·Me_2S complex (2.0 mol dm^{-3}; 10 cm^3, 20.0 mmol) was added to triamide **19** (0.43 g, 0.45 mmol) in dry THF (15 cm^3) at 60 °C. The solution was stirred until no carbonyl absorption was apparent by infrared spectroscopy (*ca.* 7 h). The excess borane was destroyed by careful addition of MeOH and the solvent then evaporated under reduced pressure. The residual white powder was then refluxed in MeOH–H_2O–conc. HCl (20:5:2; 27 cm^3) for 1.5 h. The MeOH was evaporated under reduced pressure and the aqueous residue basified with 10% aqueous NaOH (50 cm^3). The basic solution was extracted with CH_2Cl_2 (100 cm^3 × 3) and the combined organic extracts dried (Na_2SO_4) and evaporated. The resulting oil was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 19:1 with 1% saturated NH_3) to yield *compound* **20** as a clear oil (0.37 g, 91%) [Found: M + H^+, 901.5157 (ES). $C_{45}H_{84}N_6S_6$ requires M + H^+, 901.5160]; δ_H($CDCl_3$; 300 MHz) 7.09 (3 H, s, ArH), 3.51 (6 H, s, $ArCH_2N$), 2.75 (12 H, t, *J* 5.9, CH_2NH), 2.66 (12 H, t, *J* 7.0, CH_2S), 2.55 (12 H, t, *J* 7.2, CH_2S), 2.49 (12 H, t, *J* 6.5, CH_2NCH_2Ar) and *ca.* 1.9–1.75 (24 H, m, $SCH_2CH_2CH_2N$); δ_C($CDCl_3$; 75 MHz) 139.0, 127.6, 58.8, 52.2, 47.0, 29.6, 29.3, 28.9 and 27.2.

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References

1 P. G. Potvin and J.-M. Lehn, *Prog. Macrocyclic Chem.*, 1987, **3**, 167; J.-M. Lehn (Nobel Lecture), *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 89; F. Vögtle, *Supramolecular Chemistry*, Wiley, Chichester, England, 1991; G. Gokel, *Crown Ethers & Cryptands*, Monographs in Supramolecular Chemistry, The Royal Society of Chemistry, Cambridge, England, 1991.

2 J.-M. Lehn, *Pure Appl. Chem.*, 1980, **52**, 2441; A. H. Alberts, J.-M. Lehn and D. Parker, *J. Chem. Soc., Dalton Trans.*, 1985, 2311; C. Seel and F. Vögtle, *Crown Compounds: Towards Future Applications*, ed. S. R. Cooper, VCR, New York, 1992, pp. 191–206; F. Vögtle and E. Weber, *J. Inclusion Phenom.*, 1992, **12**, 75.

3 L. F. Lindoy, *The Chemistry of Macrocyclic Ligand Complexes*, Cambridge University Press, Cambridge, UK, 1989; B. Dietrich, P. Viout and J.-M. Lehn, *Macrocyclic Chemistry. Aspects of Organic and Inorganic Supramolecular Chemistry*, VCH, Weinheim, Germany, 1993; M. Hiraoka, *Crown Ethers and Analogous Compounds*, ed. M. Hiraoka, Elsevier, Amsterdam, The Netherlands, 1992; J. S. Bradshaw, K. R. Krakowiak and R. M. Izatt, *Aza-Crown Macrocycles*, Wiley, New York, 1993.

4 R. G. Pearson, *J. Am. Chem. Soc.*, 1963, **85**, 3533.

5 R. McCrindle, A. J. McAlees and D. K. Stephenson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3070.

6 L. Siegfried and T. Kaden, *Helv. Chim. Acta*, 1984, **67**, 29.

7 F. E. Hahn and S. Rupprecht, *Chem. Ber.*, 1991, **124**, 487.

8 J. Buter and R. M. Kellogg, *J. Chem. Soc., Chem. Commun.*, 1980, 466; J. Buter and R. M. Kellogg, *Org. Synth.*, 1987, **65**, 150.

9 M. K. Anwer and A. F. Spatola, *Synthesis*, 1980, 929.

10 W. M. Pearlman, *Tetrahedron Lett.*, 1967, 1663.

11 M. G. Reinecks and R. G. Daubert, *J. Org. Chem.*, 1973, **38**, 3281; V. H. Rawal, R. J. Jones and M. P. Cava, *J. Org. Chem.*, 1987, **52**, 19.

12 T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 1967, 2555.

13 F. E. Hahn and S. Rupprecht, *Chem. Ber.*, 1991, **124**, 481.

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