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New heterotopic, linked macrocyclic systems derived from selectively protected macrocycles

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Abstract—The use of orthogonally protected cyclam and 1,9-dithia-5,13-diazacyclohexadecane macrocycles, in combination with aza-18-crown-6, has enabled the efficient synthesis of a new heterotritopic macrocyclic ligand incorporating N_4-, N_2S_2- and NO_5-donor sites. A similar strategy has allowed the incorporation of cyclam and 1,9-dithia-5,13-diazacyclohexadecane into a cofacial ligand. Further, the synthesis of novel tetramacrocyclic ligands has been achieved in which the macrocycles are linked in a cyclic arrangement. The availability of different binding sites in the respective products makes the latter suitable candidates for the synthesis of a range of mixed-metal multinuclear complexes.

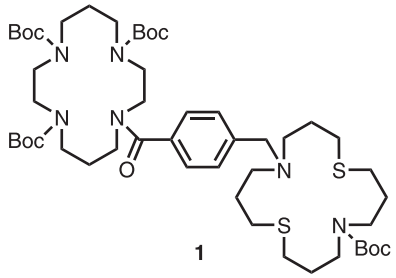
1. Introduction

A major thrust in recent macrocyclic ligand research has been the development of multi-component structures in which individual macrocyclic units are linked.[1–5] Examples of such systems exist that display a range of molecular architectures that include, linear, branched, stacked, and dendritic arrangements of their macrocyclic components. Such nanometre-scale structures have been employed in a range of studies for binding two or more metal ions simultaneously in defined positions with respect to each other.

The majority of the investigations in the above area have involved linked systems incorporating macrocycles of a similar type.[1–5] Examples include linked crown,[6–8] aza-crown,[7,9–16] thiaazacrown[17,18a–c] and porphyrin-derived systems[19,20]—in part, reflecting the ease of synthesis of suitably functionalised derivatives involving these macrocyclic types.

Examples incorporating hetero-macrocyclic rings are much less common even though such compounds have the potential to produce new hetero-metal systems exhibiting unusual properties, including unusual spectral, photoactive and redox properties.[21] Beside their considerable intrinsic interest, linked di- or polynuclear macrocyclic complexes may also serve as models for the charge transfer, electron transport and allosteric behaviour found in many metal-containing biochemical systems.[22,23]

Previously, we have reported the facile synthesis of a number of new linked, homo-[17,24,25] and heteroditopic[26] macrocycles obtained via simple protecting group strategies. For example, in one study, tris(*N*-Boc) cyclam and *N*-Boc protected S_2N_2-donor macrocycles were linked via unsymmetrical linking agents to yield intermediates such as **1**.[26]



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Based on the methodology developed in the above studies, an aim of the investigation now reported was to undertake the synthesis of structurally more elaborate linked species such as the heterotritopic and cofacial derivatives exemplified by **2** and **3**. Motivation for the synthesis of such species included the desire to obtain ligand systems capable of promoting the binding of different metal ions in sterically defined spatial and electronic environments.

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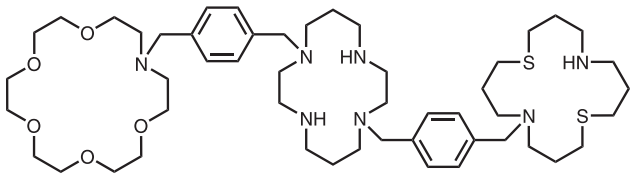

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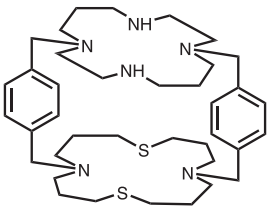

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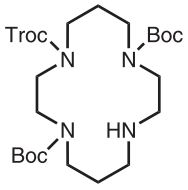
2. Results and discussion

2.1. Protected macrocyclic precursors

The synthesis of **2** and **3** required the N-protection of cyclam with two orthogonal protecting groups such that two (*trans*) nitrogens could be separately functionalised. Protected cyclams of this general type have been reported.[27,28] However, these were not suitable for our purposes since they require somewhat harsh conditions for deprotection and, in any case, the isolation of the starting diprotected macrocycle is not necessarily straightforward. Both of these potential difficulties were satisfactorily circumnavigated by synthesising the trihetero-protected cyclam **4**.



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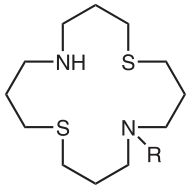
Access to *trans*-diprotected cyclams in large quantities and high yields was made possible via the procedure reported by Guilard et al. for the synthesis of **5**.[29] Subsequently, **5** was reacted with 2 equiv of di-*tert*-butyl dicarbonate and the benzyl groups removed by hydrogenation over palladium catalyst to give **7** (Scheme 1). It appeared not to be possible to use **5** directly for formation of the proposed linked hetero-ring systems as our experience is that removal of benzyl groups by hydrogenation is difficult in the presence of sulfur-containing macrocycles due to poisoning of the catalyst.

The 2,2,2-trichloroethoxycarbonyl (Troc) protecting group was chosen for protection of one of the nitrogens of **7** since this group can be readily removed under mild conditions in the presence of the *tert*-butoxycarbonyl group.[17] Thus, addition of 0.8 equiv of Troc chloride to 1,8-di-Boc(cyclam) **7** gave the required triprotected cyclam **4** in 46% yield (based on **7**) (Scheme 2). This product was readily characterised by ^{1}H NMR, the *t*-butyl singlet at δ 1.46 and Troc methylene resonance at δ 4.75 being diagnostic. Attempts to increase the yield of **4** by using more Troc chloride were unsuccessful and led instead to increased isolation of the di-Troc derivative **8**. The symmetry of **8** allows it to be easily distinguished from **4** by the presence of a single resonance for the ring methylene groups β- to nitrogen (δ 1.83).

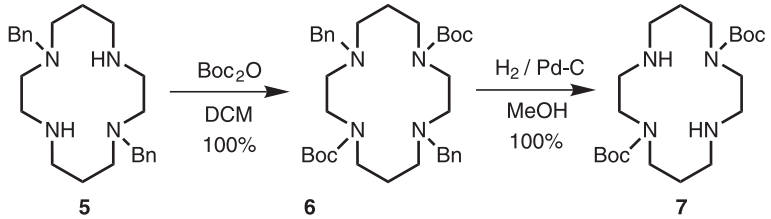
Alternatively, tetra-protected cyclam **8** was obtained in 85% yield by reaction of **7** with excess Troc chloride. After removal of the Boc groups from **8** to give **9** in 95% yield, subsequent reaction with 0.8 equiv of Boc_2O allowed the isolation of the alternative triprotected cyclam **10**, in 78% yield (based on **9**) (Scheme 3). This species, while not used in the current synthesis, represents an alternative trihetero-protected cyclam.[30]

The second macrocyclic component chosen for incorporation into the planned heterotopic systems was the 16-membered S_2N_2-donor macrocycle **11**. Macrocycle **11** was a desirable component for the proposed systems as it provides a very different coordination environment compared to cyclam. The parent (unsubstituted) macrocycle was originally reported by Kaden et al.[31] However, the synthetic approach employed in this previous study was not suitable for our present purpose since it did not allow easy chemical differentiation between the two ring nitrogen sites.



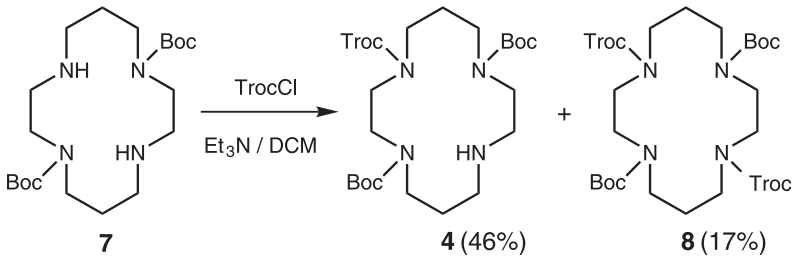
11 R = H
12 R = Boc
13 R = Troc

Incorporation of **11** into linked homotopic systems, including dendrimers, has been demonstrated previously by our group,[17,32] aided by the availability of syntheses for

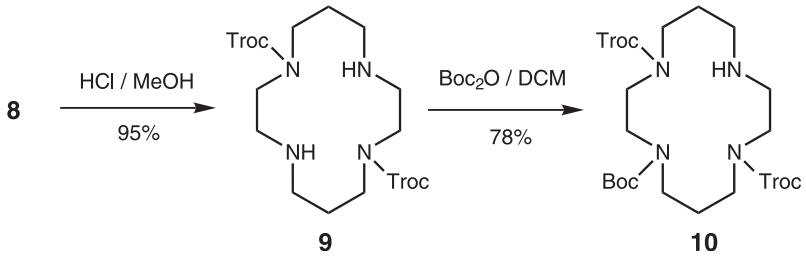


5 6 7

Scheme 1.



Scheme 2.



Scheme 3.

several mono-protected derivatives that include **12** and **13**. The latter species appeared suitable for incorporation into hetero-ring, ditopic systems of the type of interest in the present study.

2.2. Synthesis of orthogonally protected linked intermediates

Since different macrocyclic ring systems were to be linked, a stepwise synthetic approach was employed as we have previously demonstrated that such an approach is generally applicable for obtaining linked hetero-ditopic macrocyclic systems.[26] 4-(Chloromethyl)benzoyl chloride **14** was employed as a difunctional linking reagent in our previous studies,[26] and was again used for the current synthesis. Selectivity tends to be facilitated when using this linking reagent due to the greater tendency for acylation, rather than alkylation, to occur at the secondary amino groups present in the (partially) protected macrocycles of interest.

A solution of triprotected cyclam **4** in dichloromethane containing triethylamine was reacted with 4-(chloromethyl)benzoyl chloride **14** to give chloroamide **15** in 95% yield (Scheme 4). As expected, the signals for the methylene groups α- to the secondary nitrogen in **4** (δ 2.16 and 2.78) are absent from the ^{1}H spectrum of the amide **15**. Instead, these resonances are shifted downfield to ca. δ 3.2 such that they overlap with the signals for the methylene groups α- to carbamate nitrogens. The benzylic protons of **15** appear at δ 4.59.

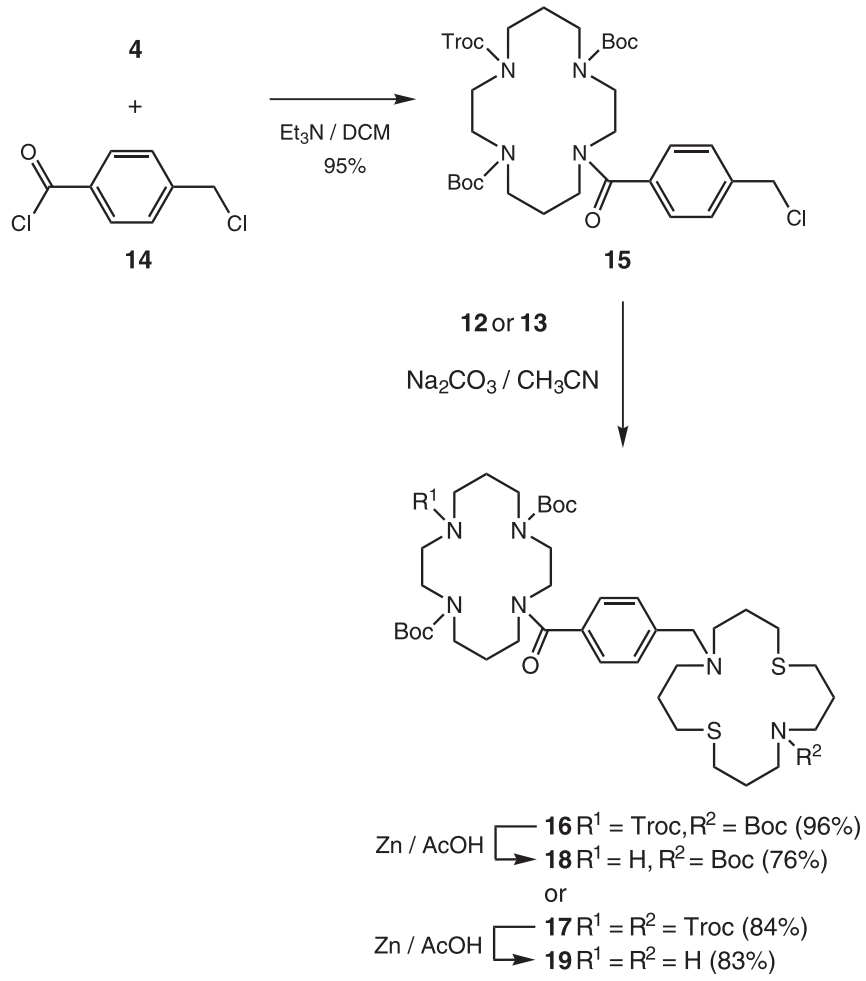
For the synthesis of the heterotritopic ligand **2**, it was necessary that the protecting group on the S_2N_2-donor macrocycle be orthogonal to the Troc group of the cyclam moiety in order to facilitate further functionalisation of the latter. Thus, the *N*-Boc-S_2N_2-derivative **12** was alkylated with **15** to give the tris(Boc)-Troc-protected amide **16** (Scheme 4). The reaction was carried out in refluxing acetonitrile in the presence of sodium carbonate over a period of 24 h and **16** was isolated in 96% yield. The ^{1}H NMR spectrum of the product was in accord with the expected product; in particular, the benzylic proton signal of **15** (δ 4.59) was replaced by a singlet at δ 3.51, characteristic of a benzylamine derivative. The Troc-protected S_2N_2-donor macrocycle **13** was alkylated with **15** under the same conditions; the corresponding linked amide **17** was obtained in 84% yield after chromatography (Scheme 4).

Selective removal of the Troc group of **16** was achieved by zinc reduction in glacial acetic acid to give **18** in 76% yield (Scheme 4). As expected, deprotection was accompanied by the disappearance of the Troc methylene resonance at δ 4.75 in the ^{1}H spectrum of **16**. Removal of the Troc protecting groups from **17** was again effected by treatment with zinc/glacial acetic acid, with the desired product **19** being isolated in 83% yield (Scheme 4).

2.3. Synthesis of a heterotritopic ligand

The selective Troc-deprotection of **16** enabled functionalisation of the resulting secondary amine ring of intermediate **18**. Thus, acylation of **18** with **14** (triethylamine/dichloromethane) gave the chloroamide **20** in 93% yield (Scheme 5).

Based on the success of the above procedures, it was decided to attempt the synthesis of a heterotritopic system in which a third macrocycle was incorporated that had different coordination characteristics to those of either the (essentially) soft-donor character of the S_2N_2-donor macrocycles or the intermediate character of the N_4-donor set of cyclam. The monoaza crown ether macrocycle 1-aza-18-crown-6 **21**, with its five hard ether donors, appeared to be an ideal precursor for the third ring. This system also had the advantage that it contains a single secondary amine linkage site without the need to protect other amino groups. Accordingly, **21** was alkylated with **20** in acetonitrile in the presence of sodium carbonate to give **22** in 50% yield after chromatography on silica gel (Scheme 5). A second, lower R_f component with a similar ^{1}H NMR spectrum to that of **22** was also isolated from the chromatography. This lower R_f



Scheme 4.

component was much less soluble in chloroform. The only discernable difference in the ^{1}H NMR spectra of the respective fractions was associated with proton signals arising from the azacrown moiety.[33] In view of this, it was concluded that the lower R_f compound was likely the sodium adduct of **22**, with the sodium ion originating from the sodium carbonate used in the synthesis. The chromatography of sodium adducts of azacrowns has been performed previously by our group.[34]

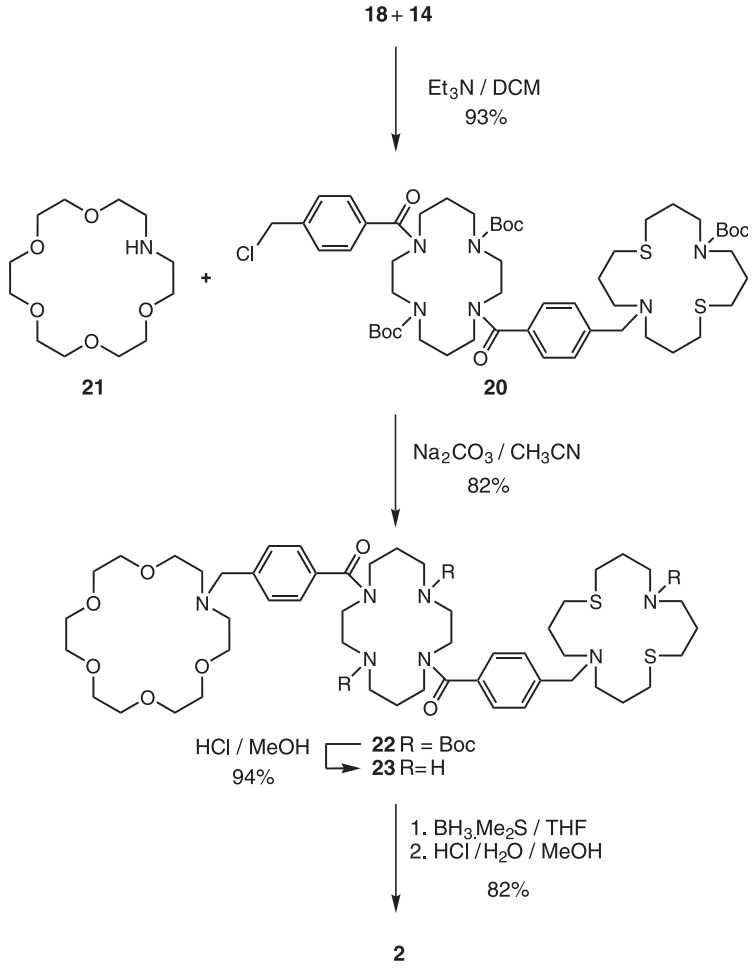
The suspected sodium adduct was converted to the metal-free product by partitioning it between chloroform and water and continuously extracting the organic phase with water (using a continuous extractor for liquid–liquid extraction by upward displacement) over 3 days. The material in the organic layer then ran at an identical R_f to the initial crop of **22** and also displayed an identical ^{1}H NMR spectrum to it. Combining the two fractions gave an overall yield of **22** of 82%. This combined product was dried by azeotropic distillation of a toluene solution (rather than over sodium sulfate).

A two-step deprotection/reduction protocol (Scheme 5) was used to obtain the target heterotritopic ligand **2** (even though it has been reported that in a related synthesis both steps could be accomplished simultaneously).[35] In our case, the two step procedure had the advantage that it made the intermediate diamide **23** available for possible future metal coordination studies. This latter product was obtained by deprotection of **22** with methanolic hydrochloric acid. Work-up involved basifying the reaction mixture with aqueous ammonium hydroxide, instead of sodium or potassium hydroxide, to avoid alkali metal adduct contamination.

The final step in the synthesis of **2**, the reduction of the amide groups of **23** by borane–dimethylsulfide complex in tetrahydrofuran, was achieved in 82% yield (Scheme 5) and corresponded to the disappearance of the amide carbon resonance (δ 171.7) originally present in the ^{13}C NMR spectrum of **23**. Likewise, a strong absorption at 1621.8 cm^{-1} in the infrared spectrum of **23**, consistent with an amide stretching frequency, was absent in the corresponding spectrum of **2**. HRMS data also supported the proposed structure.[†]

The ^{1}H NMR spectrum of **2** is noticeably sharper than that of **23** reflecting the absence of amide rotamers in the

[†] A preliminary metal-ion coordination study led to isolation of a dinuclear copper(II) complex whose microanalysis corresponded to $[Cu_2L](ClO_4)_4\cdot H_2O$ (L=2). This complex was then treated with sodium perchlorate to give the sodium derivative, analysing as $[Cu_2NaL](ClO_4)_4\cdot 5H_2O$ (L=2)].



Scheme 5.

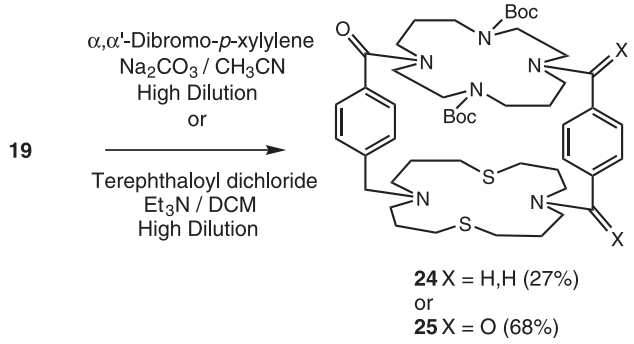
former;[26] nevertheless, numerous chemical shift overlaps were evident. The three types of protons for macrocyclic ring methylene groups not adjacent to heteroatoms appear as a complex multiplet between δ 1.6 and 1.9. When the spectrum was run at 333 K, three resonances were just resolved in this region, with the other spectral resonances remaining largely unchanged. A complex multiplet in the region δ 2.4–2.8 is assigned to a combination of the macrocyclic ring methylene protons adjacent to the sulfur and amino groups. The complex multiplet between δ 3.5 and 3.8 corresponds to the methylene protons adjacent to oxygen as well as to the benzylic protons. The aromatic protons occur as a broad multipet in the region δ 7.3–7.5.

2.4. Synthesis of a hetero-ring cofacial ligand

Conversion of the linked bis(macrocycle) species **19** to its cofacial analog required intramolecular linking of its two secondary amino groups. The cyclisation involved the simultaneous addition of **19** and α,α'-dibromo-*p*-xylylene by means of a dual syringe pump to a suspension of sodium carbonate in refluxing acetonitrile over 110 h under high dilution conditions (Scheme 6). After chromatography, the desired 1 + 1 cyclisation product **24** was obtained in 27% yield, with HRMS supporting the target structure.

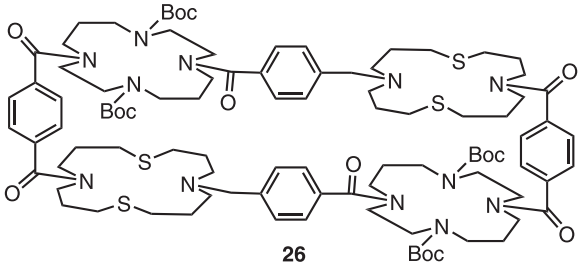
In light of the initial low yield obtained for the cyclised product, a further attempt was made to effect the cyclisation via a bis-acylation reaction employing terephthaloyl dichloride. Thus, addition of **19** and terephthaloyl dichloride via the dual syringe pump to a solution of triethylamine in dichloromethane under high dilution was carried out over 110 h (Scheme 6). After chromatography, the desired tricyclic ligand **25** was this time isolated in 68% yield.

A small amount (11% yield) of a product was also isolated during the above chromatographic procedure which had a



Scheme 6.

HRMS corresponding to a 2+2 cyclisation product. Isomers are possible for such stoichiometry, the most likely of which are given by **26** and **27**. It is assumed that neither one of these products would be favoured under the reaction conditions employed. Nevertheless, only one component was observed by TLC analysis using a variety of mobile phases.[36] As might be predicted, due to severe spectral overlap the NMR spectra of the product were uninformative with respect to possible isomeric composition. It is noted that while a catenane consisting of two interlocked 1+1 cyclisation products would also yield the same mass, it appears unlikely that such a product would form in preference to products of type **26** and **27**.



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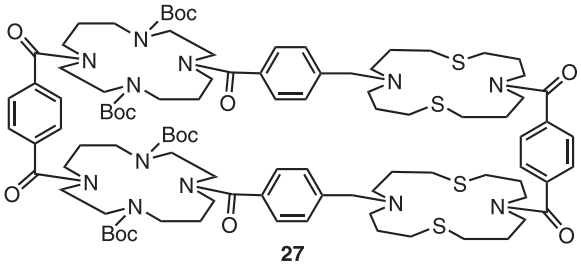


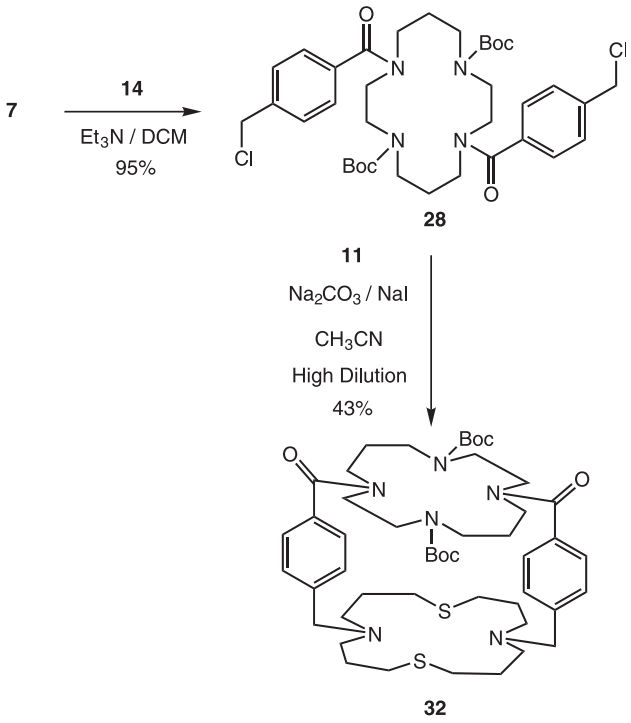
27

2.5. Synthesis of a cofacial ligand from a di-functionalised cyclam

The use of 4-(chloromethyl)benzoyl chloride **14** as a difunctional linking reagent was again used for bis-acylation of **7** to produce **28** in 95% yield after chromatography (Scheme 7).

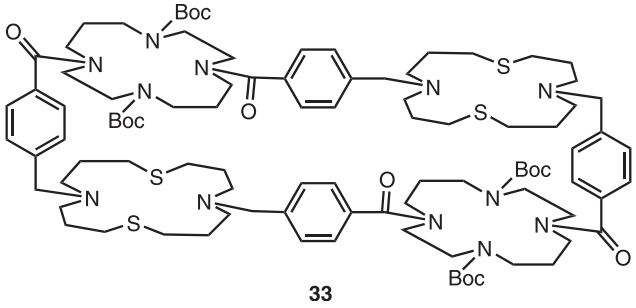
The possibility of bis-N-alkylation of the parent 16-membered S_2N_2-donor macrocycle **11** by the benzyl chloride functionalities present in **28** was also explored. The preparation of **11** was originally reported by Kaden et al.[31] However, in the present study a synthesis of **11** was devised which employed intermediates already prepared in the authors' laboratory.[17] Thus, cyclisation of *N*-Boc-dichloride **29** and *N*-Boc-dithiol **30** afforded the di-*N*-Boc macrocycle **31** in 60% yield (Scheme 8). Complete deprotection of **31** with trifluoroacetic acid in dichloromethane subsequently gave the desired macrocycle **11** in 96% yield.

Once again, using high-dilution conditions, macrocycle **11** and the bis(chloroamide) **28** were added simultaneously via a dual syringe pump to a suspension of potassium carbonate and sodium iodide in a large volume of refluxing acetonitrile over 110 h (Scheme 7). After workup and chromatography, the desired cofacial ligand **32** was isolated in 43% yield. Interestingly, a second, lower R_f component was isolated in 11% yield from the chromatographic procedure employed.



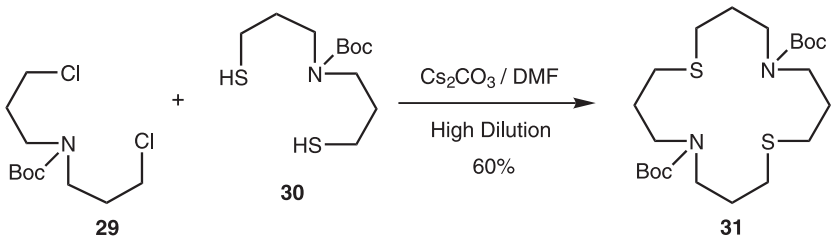
Scheme 7.

The ES-HRMS was in accord with this species being the 2+2 cyclisation product **33**.



33

The identification of **32** by electrospray mass spectrometry is complicated by the fact that this method may produce dimers during the ionisation process. A singly protonated dimer of **32** would give the same *m/z* parent ion as a singly protonated molecular ion of **33**, with an identical isotopic distribution. However, it is suggested that this did not occur as the mass spectra of **32** and **33** were dissimilar under the same ionisation conditions. The spectrum of **32** is unequivocal, with $[M+H]^+$ and $[M+Na]^+$ ions at *m/z* 895.5200 and 917.4958, respectively, with each peak displaying the predicted isotopic distribution. Neither $[2M+2H]^{2+}$ nor $[2M+H]^+$ ions were observed. For **33** $[M+H]^+$ and $[M+Na]^+$ ions at *m/z* 1789.9126 and 1811.8831 were observed; peaks at this *m/z* were not observed for **32** under the same ionisation conditions. Also, a peak occurs at *m/z* 895.5177 for **33**, with an isotopic distribution corresponding to that of a doubly protonated ion, consistent with the presence of $[M+2H]^+$. Other parent molecular ions corresponding to $[M+H+Na]^{2+}$ and

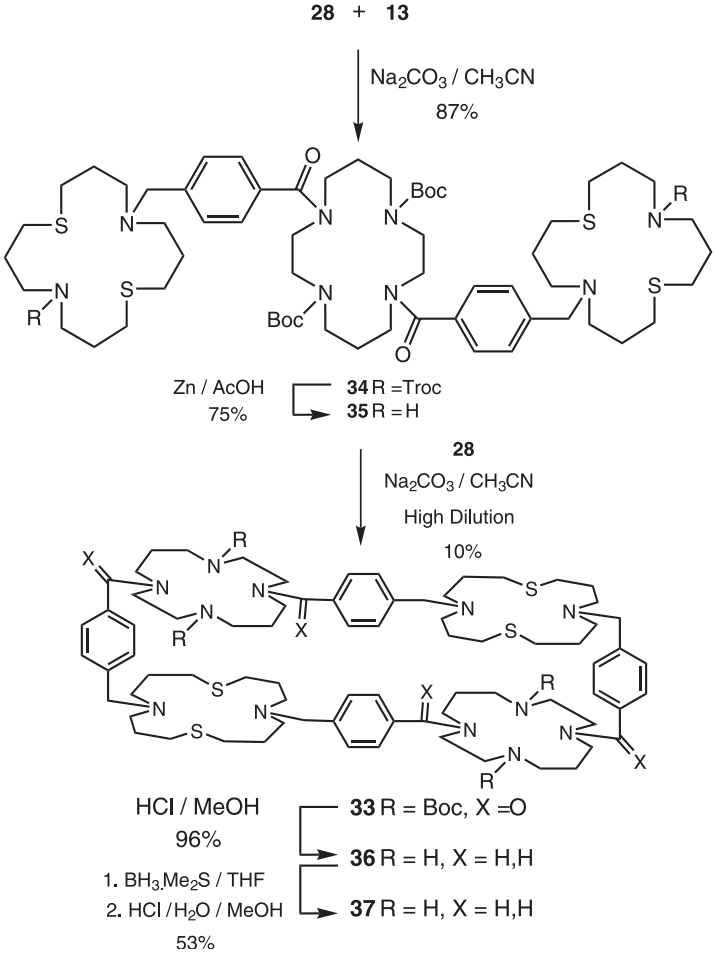


Scheme 8.

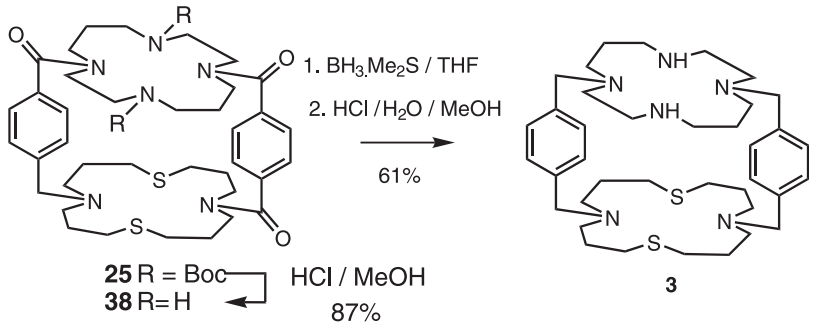
$[M+2Na]^{2+}$ were also observed, at *m*/*z* values of 906.5088 and 917.5900, respectively.

The ^{1}H NMR of **32** suffers from extreme broadening, most likely due to slow rotation of the amide rotamers.[26] The Boc singlet at δ 1.46 is broader than the analogous resonance for the linear bis(macrocycles) described above. Two broad signals at δ 1.74 and 1.89 are assigned to the macrocyclic ring methylenes not adjacent to a heteroatom. Two broad overlapping signals are found at δ 2.41 and 2.59 which are due to the ring methylenes adjacent to sulfur or a benzylamino group. A number of overlapping broad signals occur in the region δ 3.2–3.8 for the ring methylenes adjacent to amide nitrogens and the benzylic protons. Finally, two broad signals at δ 7.34 and 7.39 are due to the aromatic protons. The ^{1}H NMR spectrum of **33** in the present study was not able to be distinguished from that of **32**. The small chemical shift differences that might be expected between these two compounds are presumably masked by the broadness of the spectra.

The serendipitous isolation of the novel tetramacrocycle species **33** described above encouraged an attempt to synthesise this compound by means of a more considered (and hopefully higher yielding) strategy. To this end, the bis-alkylating agent **28** was reacted with two equivalents of the mono-Troc-protected macrocycle **13** to give the hetero-protected species **34** in 86% yield (Scheme 9). Removal of the Troc groups from **34** was performed with zinc in glacial acetic acid in 75% yield to give the tris(macrocyclic) species **35** containing two terminal NH groups.



Scheme 9.



Scheme 10.

Subsequent reaction of **28** with **35** under high dilution conditions was successful in affording the tetra-macrocyclic species **33**, but in the disappointingly low yield of 10% (Scheme 9). This low yield (and presumably also that for the product from the reaction of **28** with **11**) is attributed to the relatively large distance between the reacting termini of **35**, which lowers the prospect of ring closure but increases the tendency for oligomerisation. Obviously, this procedure is less than satisfactory for obtaining significant quantities of **33**.

2.6. Completion of target syntheses

Deprotection of **33** was accomplished in hydrochloric acid/methanol to give the tetraamide **36** in 96% yield (Scheme 9) while the bis(Boc) cofacial ligand **25** was also readily deprotected to give the cofacial amide **38** in 87% yield (Scheme 10). Reduction of the respective amides was performed with borane dimethyl sulfide complex in tetrahydrofuran. Reduction of **36** gave **37** in 53% yield (Scheme 9). To obtain the unsubstituted cofacial derivative **3**, amide **38** was reduced with borane dimethyl sulfide complex to yield **3** in 67% yield (Scheme 10).[37]

In contrast to the observations made for the linear tritopic ligand **2**, final reduction of the amide groups of **38** did not lead to the expected sharpening of the ^{1}H NMR spectrum of the reduced product **3**—possibly a result of the cyclic nature of **3** restricting bond rotation to an intermediate rate on the NMR time scale. Obtaining the spectrum at higher temperatures did not result in a significant improvement. Nevertheless, the spectrum could be reasonably assigned in terms of the types of protons present. The macrocyclic ring methylene protons not adjacent to a heteroatom give a broad resonance at δ 1.74 while the remaining ring methylene resonances are found at δ 2.4–2.8 (as broad overlapping signals). Two distinct singlets at δ 3.50 and δ 3.68 are assigned to the two types of non-equivalent benzylic protons. The aromatic protons give rise to a multiplet spanning δ 7.1–7.3. Under the conditions employed, the ^{1}H NMR spectrum of **37** was essentially indistinguishable from that of **3**.

In gauging the success of the various strategies for synthesising **3**, two aspects deserve comment. These are (i) the yield of the cyclisation step, and (ii) the ease of synthesis of the precursors required for this cyclisation. While **25** can be formed in a superior yield of 68%, the synthesis of the precursor **19** represents an involved procedure. Conversely, **32** was synthesised in the lower yield of 43%, but its precursor **28** is synthesised in three fewer steps. Further, the high-dilution conditions required for **25** (room temperature, dichloromethane) are perhaps preferred over those for **32** (refluxing acetonitrile). On balance, the synthesis of **3** is most efficiently achieved via **32**; however, of course, this route can not be applied to systems with unsymmetrical linkers.

3. Conclusions

The present paper describes the facile synthesis of new heterotopic macrocyclic ligands, including a heterotritopic tris(macrocyclic) ligand and a heteroditopic cofacial ligand. This has been achieved via the development of new orthogonal protecting group strategies enabling the selective linking of different macrocyclic components—including the linkage of four macrocycles incorporating two different donor sets, in a cyclic arrangement. Based on the known metal-ion chemistry of the constituent macrocycles, the described ligands incorporate sites that will clearly exhibit different affinities for particular metal ions. The new derivatives thus lead the way for the synthesis of a range of new hetero-metal complexes. Our efforts in this direction will be reported in due course.

4. Experimental

4.1. General

Where available, all reagents were of analytical grade. 1,4,8,11-Tetraazacyclotetradecane (cyclam),[38a,b] *N*-*tert*-butoxycarbonylbis(3-chloropropyl)amine **29**,[17] *N*-*tert*-butoxycarbonylbis(3-mercaptopropyl)amine **30**,[17] 1,8-dibenzyl-1,4,8,11-tetraazacyclotetradecane **5**,[29] 5-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane **12**,[17] 5-(2,2,2-trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane **13**[17] and 1-aza-18-crown-6 **21**[39] were synthesised as described previously. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Acetonitrile and dichloromethane were distilled from calcium hydride. All reactions were carried out under an inert atmosphere of dry nitrogen. NMR spectra were recorded on a Bruker AM-300 spectrometer. Chemical shifts are quoted in δ units (ppm) relative to the residual proton signal in $CDCl_3$ (δ_H 7.26) or to $CDCl_3$ (δ_C 77.0). The majority of compounds prepared in this study were viscous

oils and elemental composition (of chromatographically homogeneous materials) is mainly supported by high-resolution mass spectrometry (HRMS). High-resolution electrospray ionisation mass spectra (ESI-MS) were obtained on a Bruker BioApex 47e FTICR mass spectrometer. In some cases, the most abundant peak in the spectra corresponded to the sodium adduct.

4.1.1. 1,8-Dibenzyl-4,11-bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 6. To a solution of 1,8-dibenzyl-1,4,8,11-tetraazacyclotetradecane **5** (27.4 g, 0.072 mol) in dichloromethane was added di-*tert*-butyl dicarbonate (39.3 g, 0.18 mol) in dichloromethane and the mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the resulting oily residue purified by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless oil (41.8 g, 100%). [Found $(M+H)^+$, 581.4067 (ES). $C_{34}H_{52}N_4O_4$ requires $(M+H)^+$, 581.4061]; δ_H ($CDCl_3$; 300 MHz) 1.38 (18H, br s, ^tBu), 1.77 (4H, br m, $CH_2CH_2CH_2NH$), 2.4–2.7 (8H, br m, $ArCH_2NCH_2$), 3.2–3.6 (8H, br m, CH_2NBoc), 3.55 (4H, s, $ArCH_2$), 7.30 (10H, br s, ArH).

4.1.2. 1,8-Bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 7. 1,8-Dibenzyl-4,11-bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane **6** (20.9 g, 36.0 mmol) was dissolved in methanol (100 cm^3) and glacial acetic acid (2 cm^3, 36.0 mmol) in a pressure hydrogenation vessel under a stream of N_2. Palladium on charcoal (10%) (3.8 g, 3.6 mmol) was carefully added to the solution and the mixture was then agitated under H_2 (3 atm) for 12 h. The catalyst was removed by filtration through Celite and the solvent was evaporated under reduced pressure. The residue was partitioned between 10% aqueous sodium hydroxide (100 cm^3) and dichloromethane (300 cm^3) then the aqueous layer was re-extracted with dichloromethane (2×250 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give an oily residue, which was purified by column chromatography on silica gel (eluting with 5% MeOH–DCM). The title compound was isolated as colourless oil (14.4 g, 100%). The ^1H NMR spectrum was as previously reported.[40]

4.1.3. 1,8-Bis(*tert*-butoxycarbonyl)-4-(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 4. 1,8-Bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane **7** (2.27 g, 5.67 mmol) was dissolved in dry dichloromethane (80 cm^3). Triethylamine (0.69 g, 6.8 mmol) and then 2,2,2-trichloroethyl chloroformate (0.96 g, 4.54 mmol) in dichloromethane (30 cm^3) were added. The reaction mixture was stirred at room temperature for 12 h. The organic layer was washed with water (2×50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a yellow oil (1.50 g, 72%). [Found $(M+Na)^+$, 597.2014 (ES). $C_{23}H_{41}N_4O_6Cl_3$ requires $(M+Na)^+$, 597.1984]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^tBu), 1.71 (2H, br m, $BocNCH_2CH_2CH_2NH$), 1.95 (2H, br m, $BocNCH_2CH_2CH_2NBoc$), 2.61 (2H, br m, $CH_2CH_2CH_2NH$), 2.78 (2H, br m, $BocNCH_2CH_2NH$), 3.2–3.6 (12H, br m, CH_2NBoc), 4.73 (2H, s, Cl_3CCH_2OCO); δ_C ($CDCl_3$; 75 MHz) 28.5, 29.6, 30.8, ~45–50 (broad overlapping signals), 75.1, 79.6, 95.7, 155.4, 156.2.

4.1.4. 1,8-Bis(*tert*-butoxycarbonyl)-4,11-bis(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 8. 1,8-Bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane **7** (1.00 g, 2.50 mmol) was dissolved in dry dichloromethane (50 cm^3). Triethylamine (0.76 g, 7.5 mmol) and then 2,2,2-trichloroethyl chloroformate (1.32 g, 6.25 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 2 h. The organic layer was then washed with water (2×30 cm^3), dried (sodium sulfate) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a yellow oil (1.59 g, 85%). [Found $M+Na^+$, 771.1008 (ES). $C_{26}H_{42}N_4O_8Cl_6$ requires $M+H^+$, 771.1026]; δ_H ($CDCl_3$; 300 MHz) 1.45 (18H, br s, ^tBu), 1.83 (4H, br m, $CH_2CH_2CH_2$), 3.3–3.5 (16H, br m, CH_2NCO), 4.74 (4H, s, Cl_3CCH_2OCO); δ_C ($CDCl_3$; 75 MHz) 28.3, ~45–50 (broad overlapping signals), 75.0, 80.1, 95.3, 154.0, 155.8.

4.1.5. 1,8-Bis(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 9. Tetra-substituted cyclam **8** (3.50 g, 4.66 mmol) was dissolved in methanol (80 cm^3) and stirred with concentrated hydrochloric acid (4.7 cm^3, 365 g/L, 47 mmol) at room temperature for 2 h. The methanol was removed in vacuo and the residue partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (100 cm^3). The layers were separated and the aqueous layer re-extracted with dichloromethane (2× 100 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure to give the title compound as a yellow oil; this product was used without further purification (2.20 g, 85%). [Found $M+H^+$, 549.0148 (ES). $C_{16}H_{26}N_4O_4Cl_6$ requires $M+H^+$, 549.0158]; δ_H ($CDCl_3$; 300 MHz) 1.84 (4H, br m, CH_2CH_2N), 2.73 (4H, br m, $CH_2CH_2CH_2NH$), 2.88 (4H, br m, $TrocNCH_2CH_2NH$), 3.4–3.6 (8H, br m, CH_2NTroc), 4.75 (2H, s, Cl_3CCH_2OCO); δ_C ($CDCl_3$; 75 MHz) 28.9, ~45–50 (broad overlapping signals), 74.7, 95.5, 154.5.

4.1.6. 4-*tert*-Butoxycarbonyl-1,8-bis(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 10. Bis(Troc)-cyclam **9** (2.10 g, 3.81 mmol) was dissolved in dry dichloromethane (40 cm^3) to which was added di-*tert*-butyl dicarbonate (0.67 g, 3.05 mmol) in dry dichloromethane (20 cm^3) and the reaction mixture was stirred for 12 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless oil [1.94 g, 78% (based on **9**)]. [Found $M+Na^+$, 671.0493 (ES). $C_{21}H_{34}N_4O_6Cl_6$ requires $M+Na^+$, 671.0502]; δ_H ($CDCl_3$; 300 MHz) 1.46 (9H, br s, ^tBu), 1.77 (2H, br m, $TrocNCH_2CH_2CH_2NH$), 2.05 (2H, br m, $TrocNCH_2CH_2CH_2NBoc$), 2.65 (2H, br m, $CH_2CH_2CH_2NH$), 2.87 (2H, br m, $TrocNCH_2CH_2NH$), 3.2–3.6 (12H, br m, CH_2NBoc), 4.76 (2H, s, Cl_3CCH_2OCO); δ_C ($CDCl_3$; 75 MHz) 28.2, 29.4, ~45–50 (broad overlapping signals), 74.7, 79.4, 95.6, 154.0, 155.1.

4.1.7. 1,8-Bis(*tert*-butoxycarbonyl)-4-[4-(chloromethyl)-benzoyl]-11-(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 15. Bis(Boc)-Troc-cyclam **4** (1.96 g, 3.40 mmol) was dissolved in dry dichloromethane (80 cm^3). Triethylamine (0.45 g, 4.42 mmol) and then 4-(chloromethyl)benzoyl chloride **14** (0.775 g, 4.08 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 12 h. The organic layer was washed with water (2×50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (2.40 g, 95%). [Found $(M+Na)^+$, 749.2037 (ES). $C_{31}H_{46}N_4O_7Cl_4$ requires $(M+Na)^+$, 749.2013]; δ_H ($CDCl_3$; 300 MHz) 1.47 (18H, br s, ^{t}Bu), 1.6–2.0 (4H, br m, $CH_2CH_2CH_2N$), 3.1–3.7 (16H, br m, CH_2NBoc), 4.58 (2H, s, $ArCH_2Cl$), 4.75 (2H, s, Cl_3CCH_2OCO), 7.3–7.5 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 28.4, 45.3, ~45–50 (broad overlapping signals), 75.1, 80.2, 95.3, 126.6, 128.6, 136.3, 138.5, 154.2, 155.8, 171.2.

4.1.8. 5-*tert*-Butoxycarbonyl-13-(4-{[4,11-bis(*tert*-butoxycarbonyl)-8-(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-1,9-dithia-5,13-diazacyclohexadecane 16. 5-*tert*-Butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane **12** (1.24 g, 3.43 mmol) was dissolved in dry acetonitrile (15 cm^3) and added to a refluxing mixture of chloroamide **15** (2.08 g, 2.86 mmol), sodium carbonate (0.455 g, 4.29 mmol) and sodium iodide (0.086 g, 0.57 mmol) in dry acetonitrile (5 cm^3). The reaction was allowed to reflux for 24 h after which the solvent was removed under reduced pressure and the residue partitioned between dichloromethane (50 cm^3) and water (20 cm^3). The aqueous layer was extracted with dichloromethane (3×50 cm^3), the combined organic layers were dried (Na_2SO_4), then evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (2.90 g, 96%). [Found $(M+H)^+$, 1053.4485 (ES). $C_{48}H_{79}N_6S_2O_9Cl_3$ requires $(M+H)^+$, 1053.4488]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27H, br s, ^{t}Bu), 1.74 (4H, br m, $CH_2CH_2NCH_2Ar$), 1.89 (8H, br m, $CH_2CH_2CH_2NCO$), 2.3–2.6 (12H, m, CH_2S, CH_2NCH_2Ar), 3.1–3.7 (16H, br m, CH_2NCO), 3.52 (2H, s, $ArCH_2N$), 4.75 (2H, s, Cl_3CCH_2OCO), 7.3–7.4 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.5, ~45–50 (broad overlapping signals), 47.5, 52.8, 58.9, 75.2, 79.4, 80.1, 95.4, 126.3, 128.7, 135.0, 141.1, 154.3, 155.6, 171.7.

4.1.9. 5-(4-{[4,11-Bis(*tert*-butoxycarbonyl)-8-(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-13-(2,2,2-trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane 17. 5-(2,2,2-Trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane **13** (0.29 g, 0.66 mmol) was dissolved in dry acetonitrile (5 cm^3) and this solution was added to a refluxing mixture of chloroamide **15** (0.40 g, 0.55 mmol), sodium carbonate (0.09 g, 0.83 mmol) and sodium iodide (0.02 g, 0.11 mmol) in dry acetonitrile (5 cm^3). The reaction mixture was heated at reflux for 24 h after which the solvent was removed under reduced pressure and the residue partitioned between dichloromethane (30 cm^3) and water (10 cm^3). The aqueous layer was extracted with dichloromethane (3×50 cm^3), the combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (0.52 g, 84%). [Found $(M+H)^+$, 1127.2973 (ES). $C_{46}H_{72}N_6S_2O_9Cl_6$ requires $(M+H)^+$, 1127.3006]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.75 (4H, br m, $CH_2CH_2NCH_2Ar$), 1.97 (8H, br m, $CH_2CH_2CH_2NCO$), 2.4–2.7 (12H, m, CH_2S, CH_2NCH_2Ar), 3.1–3.8 (22H, br m, CH_2NCO, $ArCH_2N$), 4.76 (4H, s, Cl_3CCH_2OCO), 7.2–7.4 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.5, 29.2, 29.6, 29.7, 30.0, ~45–50 (broad overlapping signals), 47.5, 48.2, 52.8, 58.9, 75.0, 80.2, 94.4, 95.7, 126.3, 128.7, 135.0, 141.0, 154.3, 156.0, 171.7.

4.1.10. 5-*tert*-Butoxycarbonyl-13-(4-{[4,11-bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-1,9-dithia-5,13-diazacyclohexadecane 18. Tris(Boc)-Troc amide **16** (2.90 g, 2.75 mmol) was dissolved in glacial acetic acid (30 cm^3) and stirred with activated zinc dust (9.0 g, 140 mmol) at room temperature for 12 h. The reaction mixture was filtered through Celite with excess glacial acetic acid; the acid was then removed in vacuo. The residue was partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (50 cm^3) at 0 °C. The layers were separated and the aqueous layer was re-extracted with DCM (2×20 cm^3). The combined dichloromethane extract was dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil. This material was purified by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless glass (1.84 g, 76%). [Found $(M+H)^+$, 879.5458 (ES). $C_{45}H_{78}N_6S_2O_7$ requires $(M+H)^+$, 879.5446]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27H, br s, ^{t}Bu), 1.73 (6H, br m, $CH_2CH_2NCH_2Ar$, $CH_2CH_2CH_2NH$), 1.90 (6H, br m, $CH_2CH_2CH_2NCO$), 2.4–2.8 (16H, m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.2–3.7 (16H, br m, CH_2NCO), 3.51 (2H, s, $ArCH_2N$), 7.2–7.4 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.5, 29.7, 29.9, ~43–50 (broad overlapping signals), 47.4, 52.7, 58.8, 79.2, 79.4, 79.6, 126.4, 128.6, 135.4, 141.0, 154.5, 171.7.

4.1.11. 5-(4-{[4,11-Bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-1,9-dithia-5,13-diazacyclohexadecane 19. Bis(Boc)-bis(Troc) amide **17** (3.50 g, 3.10 mmol) was dissolved in glacial acetic acid (20 cm^3) and stirred with activated zinc dust (6.5 g, 100 mmol) at room temperature for 2 h. The reaction mixture was filtered through Celite with excess glacial acetic acid; the acid was then removed in vacuo. The residue was partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (50 cm^3) at 0 °C. The layers were separated and the aqueous layer was re-extracted with dichloromethane (2×50 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure to give a brown oil. This material was purified by column chromatography on silica gel (eluting with 5% MeOH–DCM). The title compound was isolated as a colourless glass (2.0 g, 83%). [Found $(M+H)^+$, 779.4888 (ES). $C_{40}H_{70}N_6S_2O_5$ requires $(M+H)^+$, 779.4921]; δ_H ($CDCl_3$; 300 MHz) 1.48 (18H, br s, ^{t}Bu), 1.6–1.9 (8H, br m,

CH_2CH_2S), 2.13 (4H, br m, $CH_2CH_2CH_2NCO$), 2.3–2.9 (20H, m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.2–3.8 (12H, br m, CH_2NCO), 3.51 (2H, s, $ArCH_2N$), 7.2–7.4 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.8, 27.5, 28.4, 28.5, 29.7, 30.0, ~45–50 (broad overlapping signals), 45.6, 52.5, 58.7, 79.7, 126.6, 128.8, 135.1, 140.7, 155.8, 171.8.

4.1.12. 5-*tert*-Butoxycarbonyl-13-[4-({4,11-bis(*tert*-butoxycarbonyl)-8-[4-(chloromethyl)benzoyl]-1,4,8,11-tetraazacyclotetradecan-1-yl}carbonyl)benzyl]-1,9-dithia-5,13-diazacyclohexadecane 20. Tris(Boc) amide **18** (1.82 g, 2.07 mmol) was dissolved in dry DCM (30 cm^3). Triethylamine (0.27 g, 2.7 mmol) and then 4-(chloromethyl)benzoyl chloride (0.470 g, 2.48 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 12 h. The organic layer was then washed with water (2×20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless glass (1.99 g, 93%). [Found $(M+H)^+$, 1031.5491 (ES). $C_{31}H_{46}N_4O_7Cl_4$ requires $(M+H)^+$, 1031.5475]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27H, br s, ^{t}Bu), 1.74 (4H, br m, $CH_2CH_2CH_2NCH_2Ar$), 1.90 (8H, br m, $CH_2CH_2CH_2NCO$), 2.2–2.6 (12H, m, CH_2S, CH_2NCH_2Ar), 3.0–3.8 (20H, br m, CH_2NCO), 3.51 (2H, s, $ArCH_2N$), 4.58 (2H, s, $ArCH_2Cl$), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.4, 28.2, 29.4, 29.6, ~45–50 (broad overlapping signals), 45.2, 47.2, 52.6, 58.6, 79.1, 79.7, 126.0, 126.4, 128.4, 134.7, 136.2, 138.3, 140.9, 154.2, 170.9, 171.5.

4.1.13. 16-(4-{[4,11-Bis(*tert*-butoxycarbonyl)-8-{4-[(13-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecan-5-yl)methyl]benzoyl}-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 22. 1-Aza-18-crown-6 **21** (0.38 g, 1.44 mmol) was dissolved in dry acetonitrile (20 cm^3) and added to a refluxing mixture of chloroamide **20** (1.24 g, 1.20 mmol), sodium carbonate (0.190 g, 1.80 mmol) and sodium iodide (0.036 g, 0.24 mmol) in dry acetonitrile (10 cm^3). The reaction mixture was heated at reflux for 24 h after which the solids were filtered off and washed with dichloromethane (3×50 cm^3). The filtrate and washings were combined and the solvent removed under reduced pressure. The resulting residue was partitioned between chloroform (50 cm^3) and water (20 cm^3) and continuously extracted with water (using a continuous liquid-liquid extractor, by upward displacement) for 3 days. The organic layer was separated, and evaporated to give a colourless oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The product was dried by azeotropic distillation involving toluene. The title compound was isolated as a colourless glass (1.20 g, 80%). [Found $(M+H)^+$, 1258.7474 (ES). $C_{67}H_{107}N_7S_2O_{13}$ requires $(M+H)^+$, 1258.7440]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27H, br s, ^{t}Bu), 1.74 (4H, br m, $CH_2CH_2NCH_2Ar$), 1.90 (8H, br m, $CH_2CH_2CH_2NCO$), 2.4–2.6 (12H, m, CH_2S, CH_2NCH_2Ar), 2.84 (4H, br m, NCH_2CH_2O), 3.1–3.8 (44H, br m, CH_2NCO, $ArCH_2N$, CH_2O), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.6, 28.3, 28.4, 29.6, 29.8, ~45–50 (broad overlapping signals), 47.4, 52.7, 54.1, 68.2, 99.9, 70.2, 70.3, 79.3, 80.1, 126.2, 126.3, 128.6, 129.4, 135.0, 141.0, 155.4, 171.6.

4.1.14. 16-[4-({8-[4-(1,9-Dithia-5,13-diazacyclohexadecan-5-ylmethyl)benzoyl]-1,4,8,11-tetraazacyclotetradecan-1-yl}carbonyl)benzyl]-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 23. Tris(Boc) diamide **22** (0.90 g, 0.71 mmol) was dissolved in methanol (15 cm^3) and stirred with concentrated HCl (2.1 mL, 365 g/L, 21 mmol) at room temperature for 2 h. The methanol was removed in vacuo and the residue partitioned between saturated aqueous ammonia solution (20 cm^3) and dichloromethane (50 cm^3). The layers were separated and the aqueous layer re-extracted with dichloromethane (2×50 cm^3). The combined dichloromethane extract was dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a colourless oil that was used without further purification (0.64 g, 94%). [Found $(M+H)^+$, 958.5848 (ES). $C_{50}H_{83}N_7S_2O_7$ requires $(M+H)^+$, 958.5868]; δ_H ($CDCl_3$; 300 MHz) 1.4–2.0 (12H, br m, $CH_2CH_2CH_2$), 2.4–3.0 (30H, br m, CH_2S, CH_2NH, CH_2NCH_2Ar, NCH_2CH_2O), 3.2–3.8 (32H, br m, CH_2NCO, $ArCH_2N$, CH_2O), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.2, 28.9, 29.4, 29.6, ~45–50 (broad overlapping signals), 47.0, 52.3, 53.5, 58.6, 59.3, 69.5, 69.9, 70.3, 70.5, 126.0, 128.2, 135.1, 140.7, 171.7.

4.1.15. 16-[4-({8-[4-(1,9-Dithia-5,13-diazacyclohexadecan-5-ylmethyl)benzyl]-1,4,8,11-tetraazacyclotetradecan-1-yl}methyl)benzyl]-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 2. Diamide **23** (0.64 g, 0.67 mmol) was dissolved in dry THF (5 cm^3). A 2.0 mol dm^{-3} solution of $BH_3 \cdot SMe_2$ (5 mL, 10 mmol) was added slowly and the solution then heated to reflux for 24 h. The solution was allowed to cool and the excess borane destroyed by careful addition of methanol. The THF was removed under reduced pressure and the residue hydrolysed in refluxing MeOH–H_2O–concentrated HCl (20:10:10; 30 cm^3) for 1 h. The methanol was removed under reduced pressure and the resulting solution partitioned between saturated aqueous ammonia (20 cm^3) and dichloromethane (50 cm^3). The aqueous layer was extracted with dichloromethane (2×50 cm^3) and the combined organic layers dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the resulting material was achieved by column chromatography on silica gel (eluting with 5% MeOH–DCM with 1% saturated NH_3 solution). The title compound was isolated as a colourless oil (0.51 g, 82%). [Found $(M+H)^+$, 930.6258 (ES). $C_{50}H_{87}N_7S_2O_5$ requires $(M+H)^+$, 929.6282]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.9 (12H, br m, $CH_2CH_2CH_2$), 2.4–2.8 (36H, br m, CH_2S, CH_2NH, CH_2NCH_2Ar, NCH_2CH_2O), 3.5–3.8 (28H, br m, CH_2NCO, $ArCH_2N$, CH_2O), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 24.6, 27.5, 28.9, 29.6, 29.9, 47.2, 47.4, 48.1, 50.3, 51.1, 52.5, 53.6, 58.6, 58.8, 59.4, 69.7, 70.1, 70.5, 70.6, 128.5, 128.6, 129.2, 135.6, 135.7, 138.4, 138.6.

4.1.16. Bis(Boc)-tricyclic amide 24. Bis(Boc) amide **19** (0.413 g, 0.53 mmol) in dry acetonitrile (50 cm^3) and α,α-dibromo-*p*-xylene (0.14 g, 0.53 mmol) in dry acetonitrile (50 cm^3) were added simultaneously by syringe pump to a suspension of potassium carbonate (0.73 g, 5.3 mmol) in dry acetonitrile (2900 cm^3) at reflux over a period of 110 h. The reaction mixture was refluxed for a further 72 h and then the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (80 cm^3) and then

washed with water (2×20 cm^3), dried (sodium sulfate) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 3% MeOH–DCM). The product was isolated as a colourless glass (0.128 g, 27%). [Found $(M+H)^+$, 881.5394 (ES). $C_{48}H_{76}N_6S_2O_5$ requires $(M+H)^+$, 881.5391] (difference between isotope peaks 1.0 amu); δ_H ($CDCl_3$; 300 MHz) 1.2–1.5 (18H, br s, ^{t}Bu), 1.5–2.0 (12H, br m, $CH_2CH_2CH_2$), 2.0–2.9 (20H, m, CH_2S, CH_2NCH_2Ar), 3.0–3.8 (18H, br m, CH_2NCO, $ArCH_2N$), 7.2–7.6 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.6, 28.6, 29.1, 29.6, 30.0, ~45–50 (broad overlapping signals), 52.7, 58.7, 75.2, 80.3, 95.5, 126.1, 128.6, 135.1, 141.2, 154.5, 171.7.

4.1.17. Bis(Boc)-tricyclic triamide 25. Bis(Boc) amide **19** (0.617 g, 0.79 mmol) in dry dichloromethane (50 cm^3) and terephthaloyl dichloride (0.161 g, 0.79 mmol) in dry dichloromethane (50 cm^3) were added simultaneously by syringe pump to a solution of triethylamine (0.40 g, 3.96 mmol) in dry dichloromethane (2900 cm^3) over a period of 110 h at room temperature. The reaction mixture was stirred for a further 36 h at room temperature and then concentrated to a volume of approximately 50 cm^3 under reduced pressure. The organic layer was then washed with water (2×20 cm^3), dried (sodium sulfate) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 3% MeOH–DCM). The title compound was isolated as a colourless glass (0.49 g, 68%). [Found $(M+Na)^+$, 931.4785 (ES). $C_{48}H_{72}N_6S_2O_7$ requires $(M+Na)^+$, 931.47796]; δ_H ($CDCl_3$; 300 MHz) 1.44 (18H, br s, ^{t}Bu), 1.5–2.1 (12H, br m, $CH_2CH_2CH_2$), 2.2–2.7 (12H, m, CH_2S, CH_2NCH_2Ar), 3.1–3.8 (20H, br m, CH_2NCO), 3.48 (2H, s, $ArCH_2N$), 7.2–7.6 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.5, 29.2, 29.7, 30.0, ~43–50 (broad overlapping signals), 52.8, 58.9, 75.0, 80.2, 95.7, 126.3, 128.7, 135.0, 141.0, 154.3, 155.9, 171.7.

A small amount of lower R_f material isolated from this chromatography was identified as 2+2 cyclisation products (0.08 g, 11%). [Found $(M+2H)^{2+}$, 909.5000 (ES). $C_{96}H_{144}N_{12}S_4O_{14}$ requires $(M+2H)^{2+}$, 909.4977]. The NMR spectra were indistinguishable from those of **25**.

4.1.18. 1,8-Bis(*tert*-butoxycarbonyl)-4,11-bis[4-(chloromethyl)benzoyl]-1,4,8,11-tetraazacyclotetradecane 28. To a solution of 1,8-bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane **7** (1.91 g, 4.77 mmol) and triethylamine (1.25 g, 12.4 mmol) in dry dichloromethane (50 cm^3) was added a solution of 4-(chloromethyl)benzoyl chloride **14** (2.16 g, 11.4 mmol) in dry DCM (20 cm^3). The reaction mixture was stirred at room temperature for 12 h after which the reaction mixture was washed with water (2×50 cm^3), dried (sodium sulfate) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (3.20 g, 95%). [Found $(M+Na)^+$, 727.2997 (ES). $C_{36}H_{50}N_4O_6Cl_2$ requires $(M+Na)^+$, 727.3000]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.7–2.1 (4H, br m, $CH_2CH_2CH_2$), 3.2–3.8 (16H, br m, CH_2NCO), 4.58 (4H, s, $ArCH_2Cl$), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 28.5, 30.1, 45.5, ~45–50 (broad overlapping signals), 80.4, 126.7, 128.6, 136.3, 138.7, 155.7, 171.4.

4.1.19. 1,9-Dithia-5,13-diazacyclohexadecane 11. (a) A solution of dichloro compound **29**[17] (6.0 g, 23.0 mmol) and dithiol **30**[17] (6.1 g, 23.0 mmol) in dry *N*,*N*-dimethylformamide (500 cm^3) was added over a period of 36 h to a stirred suspension of caesium carbonate (16.9 g, 51.8 mmol) in dry *N*,*N*-dimethylformamide (2.3 dm^3) at 85 °C. The reaction mixture was stirred at this temperature for a further 24 h. The solvent was removed in vacuo, the residue taken up in dichloromethane and the solids removed by filtration through Celite. Evaporation of the solvent under reduced pressure gave a brown oily crystalline solid that was purified by column chromatography on silica gel (eluting with EtOAc–petroleum ether, 1:9). 5,13-Bis(*tert*-butoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane **31** was obtained as a low melting solid (6.4 g, 60%). δ_H ($CDCl_3$, 300 MHz) 1.38 (18H, s, ^{t}Bu), 1.79 (8H, quin, $CH_2CH_2CH_2$), 2.48 (8H, t, CH_2S), 3.27 (8H, br s, CH_2N). δ_C ($CDCl_3$, 75 MHz) 28.3, 29.7, 47.2, 79.3. This material was used without further characterisation as described below.

(b) Trifluoroacetic acid (0.91 g, 8.0 mmol) was added slowly to di-*N*-Boc macrocycle **31** (0.463 g, 1.0 mmol) in wet dichloromethane. The solution was stirred for 2 h after which excess acid was neutralised with 10% aqueous sodium hydroxide (25 cm^3) and the aqueous layer extracted with dichloromethane (3×50 cm^3). The combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure. Purification of the residue was achieved by column chromatography on silica gel (eluting with 5% MeOH–DCM) to give the title compound as a colourless oil (0.25 g, 95%). The ^{1}H NMR spectrum was as previously reported.[31]

4.1.20. Bis(Boc)-tricyclic diamide 32. Bis(chloroamide) **28** (1.31 g, 1.86 mmol) in dry acetonitrile (50 cm^3) and 1,9-dithia-5,13-diazacyclohexadecane **11** (0.487 g, 1.86 mmol) in dry dichloromethane (50 cm^3) were added simultaneously by syringe pump to a suspension of potassium carbonate (2.6 g, 18.56 mmol) in dry refluxing acetonitrile (2900 cm^3) over a period of 110 h. The reaction mixture was refluxed for a further 60 h and the solvent removed under reduced pressure. The residue was partitioned between dichloromethane (50 cm^3) and water (20 cm^3) and the aqueous layer was extracted with dichloromethane (3×20 cm^3). The combined organic layers were dried (sodium sulfate), and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (0.72 g, 43%). [Found $(M+H)^+$, 895.5200; $(M+Na)^+$, 917.4958 (ES). $C_{48}H_{74}N_6S_2O_6$ requires $(M+H)^+$, 895.5189; $(M+Na)^+$, 917.5009]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.74 and 1.89 (12H, 2×br s, $CH_2CH_2CH_2$), 2.41 and 2.59 (16H, 2×br s, CH_2S, $ArCH_2NCH_2$), 3.2–3.8 (20H, br m, CH_2NCO, $ArCH_2N$), 7.34 and 7.39 (8H, 2×br s, ArH); δ_C ($CDCl_3$; 75 MHz) 28.5, 30.0, 46.5, ~45–50 (broad overlapping signals), 52.6, 59.4, 80.3, 126.7, 128.6, 136.3, 138.7, 155.7, 171.4.

A small amount of the [2+2] reaction product **33** was also isolated (0.19 g, 11%). [Found $(M+2H)^{2+}$, 895.5177 (ES). $C_{96}H_{148}N_{12}S_4O_{12}$ requires $(M+2H)^{2+}$, 895.5189. Other parent ions were observed at *m/z* 1789.9126 $(M+H)^+$, 1811.8831 $(M+Na)^+$, 906.5088 $(M+H+Na)^{2+}$, and 917.5900 $(M+2\ Na)^{2+}$]; the ^1H and ^{13}C NMR spectra were indistinguishable from those of **32**.

4.1.21. Tetrakis(Boc)-pentacyclic tetraamide 33. Bis(-chloroamide) **28** (0.49 g, 0.69 mmol) in dry acetonitrile (50 cm^3) and bis(Boc) diamide **35** (see below) (0.80 g, 0.69 mmol) in dry dichloromethane (50 cm^3) were added simultaneously by syringe pump to a suspension of sodium carbonate (0.37 g, 3.45 mmol) in dry refluxing acetonitrile (2900 cm^3) over a period of 110 h. The reaction mixture was refluxed for a further 60 h and the solvent removed under reduced pressure. The residue was partitioned between dichloromethane (50 cm^3) and water (20 cm^3) and the aqueous layer was extracted with dichloromethane (3× 20 cm^3). The combined organic layers were dried (sodium sulfate), and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (0.12 g, 10%). [Found $(M+2H)^{2+}$, 895.5180 (ES). $C_{96}H_{148}N_{12}S_4O_{12}$ requires $(M+2H)^+$, 895.5189]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.6–2.1 (12H, br m, $CH_2CH_2CH_2$), 2.4–2.7 (16H, br m, CH_2S, $ArCH_2NCH_2$), 3.2–3.8 (20H, br m, CH_2NCO, $ArCH_2N$), 7.3–7.5 (8H, br m, ArH).

4.1.22. 5-(4-{[4,11-Bis(*tert*-butoxycarbonyl)-8-(4-{[13-(2,2,2-trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecan-5-yl]methyl}benzoyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-13-(2,2,2-trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane 34. 5-(2,2,2-Trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane **13** (2.30 g, 5.25 mmol) was dissolved in dry acetonitrile (25 cm^3) and this solution was added to a refluxing mixture of bis(chloroamide) **28** (1.77 g, 2.50 mmol) and sodium carbonate (0.61 g, 5.75 mmol) in dry acetonitrile (50 cm^3). The reaction solution was allowed to reflux for 24 h after which the solvent was removed under reduced pressure and the residue partitioned between dichloromethane (70 cm^3) and water (30 cm^3). The aqueous layer was extracted with dichloromethane (3×50 cm^3), the combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless glass (3.28 g, 87%). [Found $(M+H)^+$, 1505.4798 (ES). $C_{66}H_{102}N_8S_4O_{10}Cl_6$ requires $(M+H)^+$, 1505.4805]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.6–2.1 (20H, br m, $CH_2CH_2CH_2$), 2.4–2.6 (24H, br m, CH_2S, $ArCH_2NCH_2$), 3.2–3.7 (28H, br m, CH_2NCO, $ArCH_2N$), 4.76 (4H, s, Cl_3CCH_2OCO), 7.2–7.4 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.6, 29.3, 30.0, ~45–50 (broad overlapping signals), 48.1, 52.7, 58.7, 75.2, 80.3, 95.4, 126.5, 128.5, 135.0, 141.3, 154.1, 155.9, 171.5.

4.1.23. 5-[4-({4,11-Bis(*tert*-butoxycarbonyl)-8-[4-(1,9-dithia-5,13-diazacyclohexadecan-5-ylmethyl)benzoyl]-1,4,8,11-tetraazacyclotetradecan-1-yl}carbonyl)benzyl]-1,9-dithia-5,13-diazacyclohexadecane 35. Bis(Boc)-bis-(Troc) diamide **34** (1.00 g, 0.66 mmol) was dissolved in glacial acetic acid (30 cm^3) and stirred with activated zinc dust (0.87 g, 1.3 mmol) at room temperature for 12– h. The reaction mixture was filtered through Celite with excess glacial acetic acid, which was then removed in vacuo. The residue was partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (50 cm^3) at 0 °C. The layers were separated and the aqueous layer re-extracted with dichloromethane (2×20 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure to give a brown oil. This material was purified by column chromatography on silica gel (eluting with 5% MeOH–DCM). The title compound was isolated as a colourless glass (0.57 g, 75%). [Found $(M+H)^+$, 1167.28 (ES). $C_{60}H_{100}N_8S_4O_6$ requires $(M+H)^+$, 1157.6721]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.7–2.1 (20H, br m, $CH_2CH_2CH_2$), 2.4–2.8 (32H, br m, CH_2S, $ArCH_2NCH_2$, CH_2NH), 3.2–3.8 (20H, br m, CH_2NCO, $ArCH_2N$), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.5, 28.5, 29.1, 29.9, 46.8, ~45–50 (broad overlapping signals), 52.5, 59.2, 126.9, 128.3, 136.7, 138.5, 155.6, 171.3.

4.1.24. Pentacyclic tetraamide 36. Tetrakis(Boc)-pentacyclic tetraamide **33** (0.10 g, 0.056 mmol) was dissolved in methanol (30 cm^3) and stirred with concentrated hydrochloric acid (5 cm^3, 10 M, 50 mmol) at room temperature for 4 h. The methanol was removed in vacuo and the residue partitioned between 10% aqueous sodium hydroxide (20 cm^3) and dichloromethane (50 cm^3). The layers were separated and the aqueous layer re-extracted with dichloromethane (2×50 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure to give the title compounds as a colourless glass that was used without further purification (0.075 g, 96%). [Found $(M+H)^+$, 1389.8200 (ES). $C_{76}H_{116}N_{12}S_4O_4$ requires $(M+H)^+$, 1389.8197]; δ_H ($CDCl_3$; 300 MHz) 1.4–2.1 (24H, br m, $CH_2CH_2CH_2$), 2.1–3.1 (42H, br m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.1–3.8 (28H, br m, CH_2NCO, $ArCH_2N$), 7.2–7.6 (16H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.6, 28.8, 29.0, 29.8, ~43–50 (broad overlapping signals), 52.7, 53.1, 58.7, 59.1, 126.1, 126.3, 128.4, 135.4, 137.3, 137.5, 137.7, 140.5, 141.0, 170.6, 171.0, 171.7.

4.1.25. Tetramacrocyclic ligand 37. Pentacyclic tetraamide **36** (0.050 g, 0.036 mmol) was dissolved in dry tetrahydrofuran (5 cm^3). A 2.0 M solution of borane dimethylsulfide complex (10 cm^3, 20 mmol) was added slowly and the solution then heated at reflux for 24 h. The solution was allowed to cool and the excess borane was destroyed by careful addition of methanol. The solvent was removed under reduced pressure and the residue was hydrolysed in refluxing methanol–water–concentrated hydrochloric acid (20:10:10; 40 cm^3) for 1 h. The methanol was removed under reduced pressure and the resulting solution was partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (50 cm^3). The aqueous layer was extracted with dichloromethane (2× 25 cm^3) and the combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure.

Purification of the resulting material was achieved by column chromatography on silica gel (eluting with 5% MeOH–DCM containing 1% saturated NH_3 solution). The title compound was isolated as a colourless glass (0.025 g, 53%). [Found $(M+H)^+$, 1333.9001 (ES). $C_{76}H_{124}N_{12}S_4$ requires $(M+H)^+$, 1333.9027]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.9 (24H, m, $CH_2CH_2CH_2N$), 2.4–2.8 (66H, CH_2N, CH_2S), 3.50 (8H, s, $ArCH_2N$), 3.68 (8H, s, $ArCH_2N$), 7.1–7.3 (16H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.8, 27.6, 30.0, 47.5, 49.9, 51.6, 52.5, 53.8, 59.1, 128.4, 128.5, 129.2, 129.3, 135.6, 135.9, 138.2, 138.3.

4.1.26. Tricyclic triamide 38. Bis(Boc)-tricyclic triamide **26** (0.436 g, 0.49 mmol) was dissolved in methanol (80 cm^3) and stirred with concentrated hydrochloric acid (15 cm^3, 10 M, 150 mmol) at room temperature for 6 h. The methanol was removed in vacuo and the residue partitioned between 10% aqueous sodium hydroxide (30 cm^3) and dichloromethane (70 cm^3). The layers were separated and the aqueous layer re-extracted with dichloromethane (2× 50 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with 5% MeOH–DCM containing 1% saturated NH_3 solution). The title compound was isolated as a colourless glass (0.30 g, 87%). [Found $M+H^+$, 709.3919 (ES). $C_{38}H_{56}N_6S_2O_3$ requires $(M+H)^+$, 709.3928]; δ_H ($CDCl_3$; 300 MHz) 1.4–2.1 (12H, br m, $CH_2CH_2CH_2$), 2.1–3.0 (20H, br m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.1–3.8 (14H, br m, CH_2NCO, $ArCH_2N$), 7.2–7.6 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.6, 28.8, 29.0, 29.8, ~43–50 (broad overlapping signals), 52.7, 53.1, 58.7, 59.1, 126.1, 126.3, 128.4, 135.4, 137.3, 137.5, 137.7, 140.5, 141.0, 170.6, 171.0, 171.7.

4.1.27. Cofacial ligand 3. Tricyclic diamide **38** (0.190 g, 0.27 mmol) was dissolved in dry tetrahydrofuran (2 cm^3). A 2.0 mol dm^{-3} solution of borane dimethylsulfide complex (2.7 cm^3, 5.36 mmol) was added slowly and the solution was then heated at reflux for 24 h. The solution was allowed to cool and the excess borane was destroyed by careful addition of methanol. The solvent was removed under reduced pressure and the residue was hydrolysed in refluxing methanol–water–concentrated hydrochloric acid (10:5:5; 20 cm^3) for 1 h. The methanol was removed under reduced pressure and the resulting solution was partitioned between 10% aqueous sodium hydroxide (30 cm^3) and dichloromethane (70 cm^3). The aqueous layer was extracted with dichloromethane (2×25 cm^3) and the combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure. Purification of the resulting material was achieved by column chromatography on silica gel (eluting with 5% MeOH–DCM containing 1% saturated NH_3 solution). The title compound was isolated as a colourless glass (0.12 g, 67%). [Found $(M+H)^+$, 667.4529 (ES). $C_{38}H_{62}N_6S_2$ requires $(M+H)^+$, 667.4550]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.9 (12H, m, $CH_2CH_2CH_2N$), 2.4–2.8 (32H, m, CH_2N, CH_2S), 3.50 (4H, s, $ArCH_2N$), 3.68 (4H, s, $ArCH_2N$), 7.1–7.3 (8H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.8, 27.6, 28.4, 30.0, 47.5, 49.9, 53.8, 128.5, 129.2, 135.9, 138.2.

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