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New heteroditopic, linked macrocyclic systems derived from selectively protected N_2S_2-, N_3O_2- and N_4-donor macrocycles

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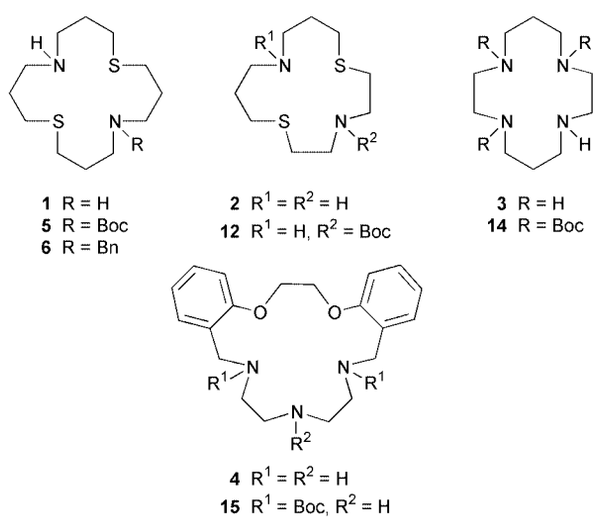
The use of selectively *tert*-butoxycarbonyl protected derivatives of 1,9-dithia-5,13-diazacyclohexadecane **1**, 1,7-dithia-4,11-diazacyclotetradecane **2**, 1,4,8,11-tetraazacyclotetradecane **3** and 2,5-dioxa-8,11,14-triaza-1,6(1,2)-dibenzenacyclopentadecaphane **4** has enabled the efficient synthesis of new linked heteroditopic macrocyclic systems incorporating combinations of N_2S_2- and N_4- or N_3O_2-donor sites. Incorporation of two types of binding sites in the respective products makes them suitable candidates for the synthesis of a range of mixed-metal, di- and oligo-nuclear metal complexes.

There is a continuing interest in the synthesis of covalently linked macrocyclic systems[1,2] capable of simultaneously binding two (or more) metal ions. Such ligands may give rise to metal complexes exhibiting unusual electronic, catalytic and/or redox properties and, for example, be of interest as models for the charge transfer and electron transport behaviour found in a range of metal-containing biochemical systems.

The majority of studies in the area have involved ligands incorporating linked macrocycles of a similar type.[1–4] Examples include linked crowns,[5] azacrowns,[5–7] and thiazacrowns.[8,9] However, examples of this type incorporating hetero-macrocyclic rings are much less common,[2] even though such compounds have the potential to produce new hetero-metal systems exhibiting unusual properties, including unusual redox properties.

In this paper we describe the use of protecting group chemistry to synthesise new linked macrocyclic systems incorporating combinations of the 16- and 14-membered N_2S_2-donor systems of type **1** and **2**, the 14-membered N_4-donor (cyclam) ring **3** and the 17-membered N_3O_2-donor system **4**. These rings were selected because of their tendency to exhibit a wide range of metal-ion binding behaviour towards individual first-row transition and post-transition metal ions. Thus many studies[10–14] have shown that N_2S_2-donor systems related to systems of type **1** and **2** have a strong affinity for 'soft' ions such as copper(I), silver(I), palladium(II) and platinum(II), whereas **4** and related dibenzo N_3O_2-donor rings have been documented to coordinate well to a range of metals of intermediate hardness, including manganese(II), nickel(II), copper(II), zinc(II), cadmium(II) and lead(II); although these rings also bind soft silver(I) relatively strongly.[15] Similarly, cyclam **3** and its derivatives are well known for their rich transition and post-transition ion chemistry.[16]

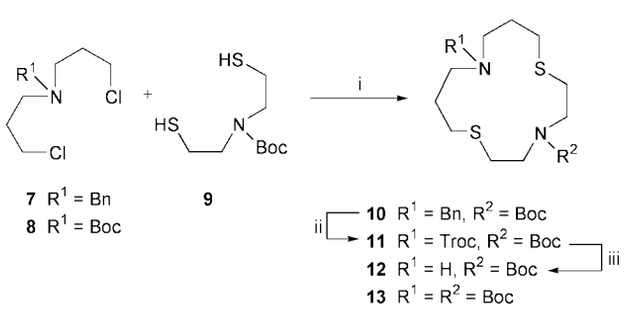
A motivation for the synthesis of the present ligands was the desire, in the context of the design of redox-controlled molecular switches, to obtain ligand systems capable of promoting the binding of hetero-metal ions in (at least) approximately defined spatial and electronic environments.



Results and discussion

Synthesis of protected macrocyclic precursors

Mono-*N*-protected derivatives of the 16-membered 1,9-dithia-5,13-diazacyclohexadecane ring **1**—for example, the *tert*-butoxycarbonyl and benzyl derivatives (**5** and **6**, respectively)—were available *via* the Kellogg procedure[17] reported previously by us.[8] In the present work, this procedure was again used to prepare the analogous *N*-Boc derivative, **12**, of the new 14-membered N_2S_2-donor macrocycle **2** (Scheme 1). While



Scheme 1 Bn = benzyl; Boc = *tert*-butoxycarbonyl; Troc = 2,2,2-trichloroethoxycarbonyl. *Reagents and conditions*: i, Cs_2CO_3, KI, DMF, 85 °C, high dilution; ii, Cl_3CCH_2OCOCl, K_2CO_3, PhH, 80 °C; iii, Zn, HOAc.

a number of 14-membered N_2S_2 macrocycles have been reported,[13,14] of the two possible *trans* isomers, only **2** has the required symmetry around the nitrogen atoms to ensure that cyclisation of its precursors yields a single product. Although

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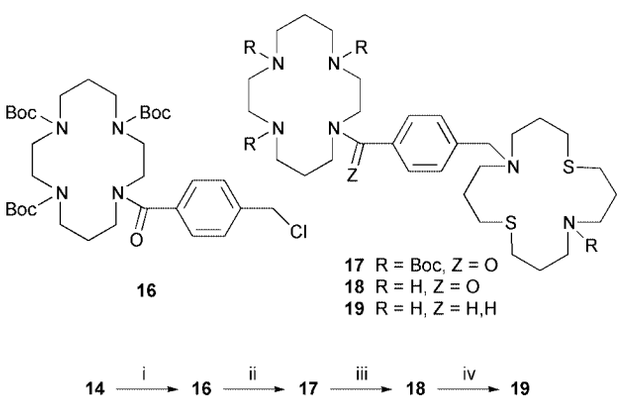
the parent macrocycle **2** could be prepared by hydrolysis of **12**, a more efficient route proceeded *via* the bis(*N*-Boc) derivative **13** which was obtained in 62% yield from an analogous cyclisation employing the *N*-Boc starting material **8** instead of the benzyl derivative **7**. The ^{1}H and ^{13}C NMR spectra together with the ESI-MS confirmed the structure of **2**.

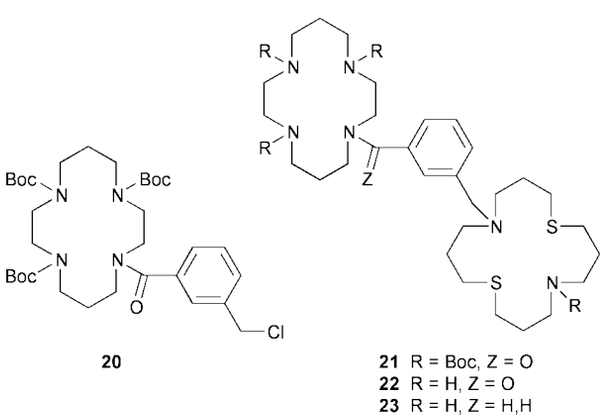
Tris(*N*-Boc) cyclam **14**[18] and the bis(*N*-Boc) derivative **15**[19] of 2,5-dioxa-8,11,14-triaza-1,6(1,2)-dibenzenacyclopentadecaphane **4** were prepared by essentially the same method—namely, acylation of the parent macrocycles (**3** and **4**) with sub-stoichiometric quantities of di-*tert*-butyl dicarbonate followed by chromatographic separation of the mixture of *tert*-butoxycarbonyl derivatives formed.

Linked systems

The synthesis of the linked systems **19**, **23**, **27**, **30**, **33**, **36** and **40**, **43** was achieved using closely related procedures. Since *different* macrocyclic systems were being linked, a stepwise approach was employed, as illustrated in Scheme 2 for the



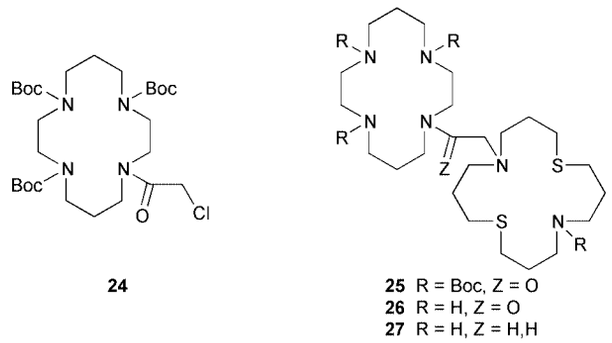
Scheme 2 Bn = benzyl; Boc = *tert*-butoxycarbonyl; Troc = 2,2,2-trichloroethoxycarbonyl. *Reagents and conditions*: i, $ClCH_2ArCOCl$, Et_3N, DCM; ii, Na_2CO_3, NaI, CH_3CN; iii, TFA, PhSMe, DCM; iv, $BH_3{\cdot}SMe_2$, THF then MeOH–H_2O–conc. HCl (4 : 1 : 1).

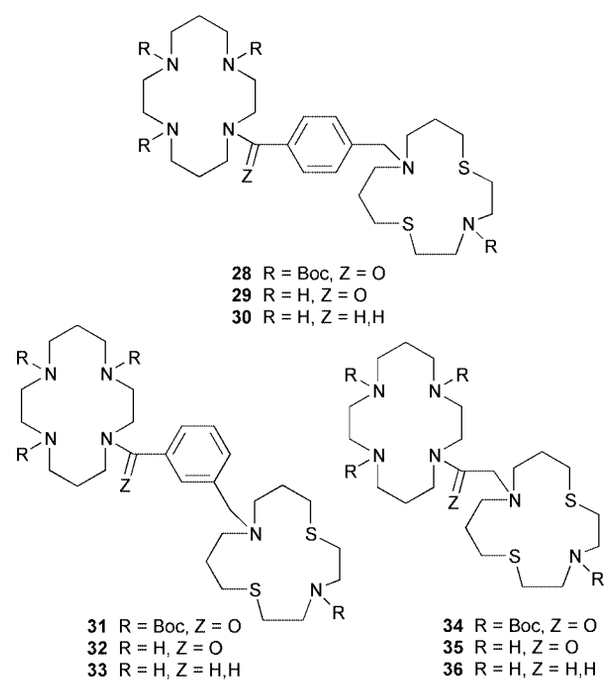


para-xylyl linked system **19** incorporating cyclam and a 16-membered S_2N_2 macrocyclic moiety.

Thus, acylation of tris(*N*-Boc) cyclam **14** with 4-(chloromethyl)benzoyl chloride readily generated the chloromethylbenzamide **16** which was used in the alkylation (sodium carbonate–sodium iodide–acetonitrile) of the *N*-Boc-S_2N_2 derivative **5**. Deprotection (TFA–thioanisole–DCM) of the resulting linked amide **17** to give **18**, followed by reduction with $BH_3{\cdot}SMe_2$ in THF furnished the desired heterotopic linked macrocyclic system **19**. Exactly analogous chemistry allowed linkage of the two macrocycles through *meta*-xylyl and ethano bridging groups, as in **23** and **27**, respectively. The relevant intermediates for these latter syntheses are **20**–**22** and **24**–**26**, respectively.

In a parallel series of experiments, the key chloroamides **16**, **20** and **24** were used to link cyclam to the 14-membered macrocycle **2**, leading to an analogous series of compounds **30**, **33** and **36**.



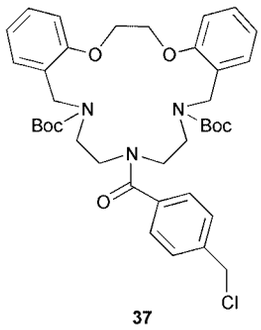


The generality of the above synthetic approach was further illustrated by the successful linking of the S_2N_2 macrocycle **1** to the central nitrogen of the N_3O_2 macrocycle **4** *via* the *para*-xylyl linker. Again, this involved initial acylation [of the bis(*N*-Boc) derivative **15**] to give the chloromethylbenzamide **37**, with subsequent use of this material to alkylate **5**, followed by the normal deprotection and reduction steps. In this manner, linked system **40** was obtained in an acceptable overall yield. Replacement of **5** in this sequence with the benzyl derivative **6** furnished the corresponding *N*-benzyl linked system **43**.

Characterisation of the linked systems described above relied on high resolution electrospray mass spectrometry for determination of elemental composition, since the compounds were all glasses or viscous oils which tenaciously retained the last traces of solvent. Their ^{1}H and ^{13}C NMR spectra were consistent with the proposed structures, but involved considerable spectral overlap arising from the inherently similar chemical environment of the ring methylene groups of the constituent macrocycles. Interpretation of these spectra was also complicated by signal broadening and/or splitting caused by slow interconversion of rotamers of acylated intermediates. This situation is improved somewhat in the final products after deprotection and amide reduction. For all the xylyl linked compounds, the benzylic protons appear as sharp singlets at δ 3.5 ± 0.1.

Conclusions

The present paper describes the facile syntheses of a number of



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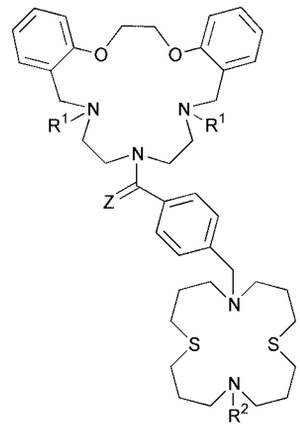

38 R^1 = Boc, R^2 = Boc, Z = O
39 R^1 = H, R^2 = H, Z = O
40 R^1 = H, R^2 = H, Z = H,H
41 R^1 = Boc, R^2 = Bn, Z = O
42 R^1 = H, R^2 = Bn, Z = O
43 R^1 = H, R^2 = Bn, Z = H,H

new linked, heterotopic macrocycles *via* simple protecting group strategies. Based on the known metal-ion chemistry of the single ring types,[16] each of the present macrocycles 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 for future study. Our efforts in this direction will be reported in due course.

Experimental

General

All reagents were of analytical grade. 2,5-Dioxa-8,11,14-triaza-1,6(1,2)-dibenzenacyclopentadecaphane **4**,[20] 5-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane **5**,[8] 5-benzyl-1,9-dithia-5,13-diazacyclohexadecane **6**,[8] *N*-benzylbis(3-chloropropyl)amine **7**,[8] *N*-*tert*-butoxycarbonylbis(3-chloropropyl)-amine **8**,[8] 1,4,8-tris(*tert*-butoxycarbonyl)-1,4,8,11-tetraaza-cyclotetradecane **14**,[18] were synthesised as described previously; the selectively protected 8,14-bis(*tert*-butoxycarbonyl)-2,5-dioxa-8,11,14-triaza-1,6(1,2)-dibenzenacyclopentadecaphane **15** was prepared by reaction of the parent N_3O_2-macrocycle with 1.7 equivalents of Boc_2O followed by separation of the required product by column chromatography on silica gel (ethyl acetate–hexane as eluent).[19] NMR spectra were recorded on Bruker AC-200 and AM-300 spectrometers; δ_H values are relative to Me_4Si and δ_C values are relative to $CDCl_3$ at 77.0 ppm and *J* values are given in hertz. The majority of compounds prepared in this study were viscous oils and elemental composition (of chromatographically homogeneous materials) is supported mainly by high resolution mass spectrometry.

Electrospray ionization mass spectra (ESI-MS) were obtained on a Bruker BioApex 47e ICR mass spectrometer. In some cases the most abundant peak in the spectra corresponded to the sodium adduct. Microanalyses were performed at James Cook University.

1,7-Dithia-4,11-diazacyclotetradecane 2

TFA (0.062 cm^3, 0.80 mmol) was added slowly to a solution of bis(*N*-Boc) macrocycle **13** (0.435 g, 1.0 mmol) and thioanisole (1.24 g, 10 mmol) in DCM (2 cm^3). The solution was stirred at RT for 2 h after which excess acid was neutralised with 10% aqueous sodium hydroxide (5 cm^3) and the aqueous layer extracted with DCM (3 × 50 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the resulting material was achieved by recrystallisation from petroleum ether. *1,7-Dithia-4,11-diazacyclotetradecane* **2** was isolated as a white crystalline solid (0.14 g, 60%). An analysis sample was recrystallised twice more from petroleum ether to give colourless needles, mp 98.5–99.5 °C [Found: C, 51.4; H, 9.4; N, 11.7; S, 27.6. $C_{10}H_{22}N_2S_2$ requires C, 51.24; H, 9.46; N, 11.95; S, 27.35%. Found M + H^+, 235.1298 (ES). $C_{10}H_{22}N_2S_2$ requires M + H^+, 235.1297]; δ_H ($CDCl_3$; 300 MHz) 1.82 (4 H, quin, $CH_2CH_2CH_2$), 2.7–2.9 (16 H, complex m, NCH_2, SCH_2); δ_C ($CDCl_3$; 75 MHz) 27.6, 27.7, 32.5, 46.3, 46.4.

Synthesis of *N*-*tert*-butoxycarbonylbis(2-thioethyl)amine 9

(a) Bis(2-chloroethyl)amine hydrochloride. To a stirred solution of bis-(2-hydroxyethyl)amine (105.1 g, 0.5 mol) in dry DCM (500 cm^3) at 0 °C was added thionyl chloride (178.5 g, 1.5 mol) slowly over a 2 h period. The reaction mixture was allowed to gradually warm to RT and left to stir for 12 h. Excess thionyl chloride was destroyed with methanol, and the majority of the solvent removed under reduced pressure. The product was precipitated by addition of diethyl ether and isolated by vacuum filtration, a second crop being obtained from the mother liquor by removing the solvent under reduced pressure and addition of diethyl ether. The resulting bis(2-chloroethyl)-amine hydrochloride (73.2 g, 82%) was used without further purification [Found $(M - Cl)^+$, 142.0189 (ES). $C_4H_9NCl_2$ requires $(M - Cl)^+$, 142.0185]; δ_H ($CDCl_3$; 300 MHz) 3.50 (4 H, t, *J* 6.0, CH_2N), 4.05 (4 H, t, *J* 6.0, CH_2Cl), 10.01 (2 H, br s, NH_2); δ_C ($CDCl_3$; 125 MHz) 38.5, 49.3.

(b) *N*-*tert*-Butoxycarbonylbis(2-chloroethyl)amine. A suspension of bis(2-chloroethyl)amine hydrochloride (35.70 g, 0.2 mol) in DCM (300 cm^3) was rapidly stirred with 10% aqueous sodium hydroxide (200 cm^3), to which di-*tert*-butyl dicarbonate (43.65 g, 0.2 mol) in DCM (200 cm^3) was added. The reaction mixture was allowed to stir for 12 h at RT after which DCM (200 cm^3) was added and the organic and aqueous layers separated. The aqueous layer was re-extracted with a further portion of DCM (200 cm^3) and the combined organic fractions dried (Na_2SO_4) and evaporated under reduced pressure. The resulting *N-tert-butoxycarbonylbis(2-chloroethyl)amine* (38.8 g, 80%) was used without further purification [Found M + Na^+, 264.0530 (ES). $C_9H_{17}Cl_2NO_2$ requires M + Na^+, 264.0528]; δ_H ($CDCl_3$; 300 MHz) 1.45 (9 H, s, ^{t}Bu), 3.4–3.7 (8 H, m, CH_2N, CH_2Cl); δ_C ($CDCl_3$; 125 MHz) 27.7, 41.3, 41.5, 50.0, 50.2, 79.9, 154.1.

(c) *N*-*tert*-Butoxycarbonylbis(2-thioacetoxyethyl)amine. To a solution of *N*-*tert*-butoxycarbonylbis(2-chloroethyl)amine (48.43 g, 0.2 mol) in DMF (250 cm^3) was added solid potassium thioacetate (57.11 g, 0.5 mol) and the mixture stirred at RT for three days. The DMF was removed *in vacuo* and the residue partitioned between DCM (500 cm^3) and water (200 cm^3). The organic layer was washed with a further portion of water (200 cm^3) and the combined aqueous layers re-extracted with DCM (2 × 500 cm^3). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting with EtOAc–hexanes, 1 : 9) to give *N-tert-butoxycarbonylbis(2-thioacetoxyethyl)amine* as a red-brown oil (53.0 g, 82%) [Found M + Na^+, 344.0959 (ES). $C_{13}H_{23}NO_4S_2$ requires M + Na^+, 344.0961]; δ_H ($CDCl_3$; 300 MHz) 1.49 (9 H, s, ^{t}Bu), 2.32 (6 H, s, $SCOCH_3$), 3.00 (4 H, br s, CH_2S), 3.35 (4 H, t, CH_2N); δ_C ($CDCl_3$; 125 MHz) 27.2, 27.7, 28.2, 30.5, 47.2, 47.4, 80.1, 155.0, 194.9, 195.4.

The above bisthioacetate (32.15 g, 0.1 mol) was stirred in a solution of sodium methoxide (120 cm^3, 1.9 mol dm^{-3}) at RT for 5 min, after which the solvent was removed *in vacuo* and the residue partitioned between 10% aqueous sodium hydroxide (300 cm^3) and DCM (500 cm^3). The aqueous layer was extracted with a further portion of DCM (500 cm^3) and then acidified to pH 2 with concentrated hydrochloric acid, while the

organic extract was discarded. The aqueous layer was extracted with DCM (3 × 250 cm^3), the combined organic layers dried (Na_2SO_4) and the solvent removed under reduced pressure to yield *N-tert-butoxycarbonylbis(2-thioethyl)amine* **9** as a red–brown oil (16.95 g, 72%), which was used immediately to minimise loss by disulfide formation [Found M + Na^+, 260.0754 (ES). $C_9H_{19}NO_2S_2$ requires M + Na^+, 260.0755]; δ_H ($CDCl_3$; 300 MHz) 1.44 (9 H, s, ^{t}Bu), 2.6–2.7 (4 H, br m, CH_2S), 3.3–3.45 (4 H, br m, CH_2N), 1.32 (2 H, br s, SH); δ_C ($CDCl_3$; 125 MHz) 23.2, 28.3, 51.5, 80.2, 155.1.

4-*tert*-Butoxycarbonyl-11-benzyl-1,7-dithia-4,11-diazacyclotetradecane 10

A solution of *N*-benzylbis(3-chloropropyl)amine **7** (16.40 g, 63.0 mmol) and dithiol **9** (16.95 g, 71.0 mmol) in dry DMF (500 cm^3) was added over a period of 36 h to a stirred suspension of caesium carbonate (46.27 g, 142 mmol) and potassium iodide (1.05 g, 6.3 mmol) in dry DMF (2.3 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 DCM and the solids removed by filtration through Celite. Evaporation of the solvent under reduced pressure gave a brown oil/crystalline solid that was purified by column chromatography on silica gel (eluting with EtOAc–hexanes, 1:9). *4-tert-Butoxycarbonyl-11-benzyl-1,7-dithia-4,11-diazacyclotetradecane* **10** was obtained as a low melting solid (17.65 g, 66%) [Found M + H^+, 425.2282 (ES). $C_{22}H_{36}N_2O_2S_2$ requires M + H^+, 425.2296]; δ_H ($CDCl_3$; 300 MHz) 1.42 (9 H, s, ^{t}Bu), 1.7–1.9 (4 H, m, CH_2CH_2-NCH_2Ph), 2.4–2.6 (8 H, m, CH_2S), 2.7–2.8 (4 H, m, CH_2NCH_2Ph), 3.3–3.5 (4 H, m, CH_2NBoc), 3.46 (2 H, s, CH_2Ph), 7.2–7.3 (5 H, m, PhH); δ_C ($CDCl_3$; 75 MHz) 28.3, 28.4, 28.9, 29.6, 30.7, 31.2, 48.9, 49.7, 52.5, 53.0, 59.5, 126.9, 128.1, 128.6, 128.8, 139.5, 155.1.

4-*tert*-Butoxycarbonyl-11-(2,2,2-trichloroethoxycarbonyl)-1,7-dithia-4,11-diazacyclotetradecane 11

Potassium carbonate (15.6 g, 112.5 mmol) was added to a solution of *N*-benzyl-*N′*-Boc-macrocycle **10** (19.11 g, 45.0 mmol) and 2,2,2-trichloroethyl chloroformate (19.1 g, 90.0 mmol, 12.4 cm^3) in dry benzene (400 cm^3), and the mixture refluxed for 12 h. The solvent was evaporated and the residue dissolved in DCM (600 cm^3) and washed with water (2 × 200 cm^3). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a colourless oil. Purification of this material was achieved by column chromatography on silica gel (eluting with EtOAc–hexanes, 1:9) to yield *11-(2,2,2-trichloroethoxycarbonyl)-4-tert-butoxycarbonyl-1,7-dithia-4,11-diazacyclotetradecane* **11** as a white, low melting solid (17.3 g, 97%) [Found M + H^+, 509.0849 (ES). $C_{22}H_{36}N_2O_2S_2$ requires M + H^+, 509.0863]; δ_H ($CDCl_3$; 300 MHz) 1.44 (9 H, s, ^{t}Bu), 1.9–2.0 (4 H, br m, CH_2CH_2NTroc), 2.59 (4 H, m, NCH_2CH_2-CH_2S), 2.71 (4 H, m, NCH_2CH_2S), 3.4–3.6 (8 H, m, CH_2NTroc, CH_2NBoc), 4.76 (2 H, s, Cl_3CCH_2OCO); δ_C ($CDCl_3$; 125 MHz) 28.2, 29.1, 29.6, 30.1, 30.3, 47.8, 48.5, 49.1, 74.8, 79.8, 95.5, 154.3, 154.6.

4-*tert*-Butoxycarbonyl-1,7-dithia-4,11-diazacyclotetradecane 12

N-Troc-*N′*-Boc-macrocycle **11** (16.30 g, 32.0 mmol) was dissolved in glacial acetic acid (400 cm^3) and stirred with activated zinc dust (20.9 g) at RT for 2 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 (500 cm^3) and DCM (250 cm^3) at 0 °C. The layers were separated and the aqueous layer re-extracted with DCM (2 × 200 cm^3). The combined DCM 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 2–8% MeOH–DCM gradient elution) to give *4-tert-butoxycarbonyl-1,7-dithia-4,11-diazacyclotetradecane* **12** as a clear oil (8.03 g, 75%) [Found M + H^+, 335.1826 (ES). $C_{22}H_{36}N_2O_2S_2$ requires M + H^+, 335.1821]; δ_H ($CDCl_3$; 300 MHz) 1.44 (9 H, s, ^{t}Bu), 1.65–1.75 (4 H, m, CH_2CH_2N), 2.5–2.85 (12 H, br m, CH_2NH, CH_2S), 3.42 (4 H, br t, CH_2NBoc); δ_C ($CDCl_3$; 125 MHz) 28.1, 28.3, 29.9, 30.1, 30.8, 31.0, 46.1, 47.0, 48.1, 49.0, 79.3, 79.5, 154.8.

4,11-Bis(*tert*-butoxycarbonyl)-1,7-dithia-4,11-diazacyclotetradecane 13

Prepared as for **10** from dichloro compound **8** (12.0 g, 46.0 mmol), dithiol **9** (10.9 g, 46.0 mmol), caesium carbonate (33.8 g, 104 mmol) and potassium iodide (0.76 g, 4.6 mmol) to give *4,11-bis(tert-butoxycarbonyl)-1,7-dithia-4,11-diazacyclotetradecane* **13** as a low melting solid (12.4 g, 62%) [Found M + H^+, 435.2334 (ES). $C_{20}H_{38}N_2O_2S_2$ requires M + H^+, 45.2346]; δ_H ($CDCl_3$; 300 MHz) 1.43, 1.44 (total 18 H, 2 × ^{t}Bu), 1.9 (4 H, m, $CH_2CH_2CH_2$), 2.53 (4 H, m, $NCH_2CH_2CH_2S$), 2.68 (4 H, m, NCH_2CH_2S), 3.25–3.5 (8 H, br m, CH_2N); δ_C ($CDCl_3$; 75 MHz) 28.3, 29.4, 29.7, 30.1, ~45–50 (broad overlapping signals), 79.4, 79.6, 154.5, 155.4.

Chloromethylbenzamide 16

1,4,8-Tris(*tert*-butoxycarbonyl)cyclam **14** (7.8 g, 15.6 mmol) was dissolved in dry DCM (20 cm^3). Triethylamine (2.5 g, 25 mmol) and then 4-(chloromethyl)benzoyl chloride (4.4 g, 23.4 mmol) were added by syringe. The reaction mixture was stirred at RT for 1 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 3% MeOH–DCM. *Chloromethylbenzamide* **16** was isolated as a colourless oil (9.15 g, 90%) [Found M + H^+, 653.3708 (ES). $C_{33}H_{53}N_4O_7Cl$ requires M + H^+, 653.3675]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27 H, br s, ^{t}Bu), 1.7–1.9 (4 H, br m, $CH_2CH_2CH_2N$), 3.1–3.7 (16 H, br m, CH_2N), 4.59 (2 H, br s, CH_2Cl), 7.2–7.5 (4 H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 28.2, 45.3, ~45–50 (broad overlapping signals), 79.5, 126.5, 128.4, 136.3, 138.4, 155.3, 171.0.

Tetrakis(*N*-Boc) amide 17

5-*tert*-Butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane **5** (2.06 g, 5.69 mmol) was dissolved in dry acetonitrile (20 cm^3) and added to a refluxing mixture of chloromethylbenzamide **16** (3.38 g, 5.17 mmol), sodium carbonate (0.66 g, 6.21 mmol) and sodium iodide (0.08 g, 0.52 mmol) in acetonitrile (10 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 DCM (50 cm^3) and water (20 cm^3). The aqueous layer was extracted with DCM (3 × 50 cm^3), the combined organic layers were dried (Na_2SO_4), and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). *Tetrakis(N-Boc) amide* **17** was isolated as a colourless oil (3.80 g, 75%) [Found M + H^+, 979.5978 (ES). $C_{50}H_{86}N_6O_9S_2$ requires M + H^+, 979.5970]; δ_H ($CDCl_3$; 300 MHz) 1.45 (36 H, s, ^{t}Bu), 1.7–2.0 (12 H, br m, $CH_2CH_2CH_2N$), 2.4–2.7 (12 H, m, CH_2S, CH_2NCH_2Ar), 3.2–3.7 (20 H, br m, CH_2NBoc), 3.50 (2 H, s, $ArCH_2N$), 7.25–7.35 (4 H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.4, 28.2, 29.3, 29.6, ~45–50 (broad overlapping signals), 47.2, 52.5, 58.6, 79.1, 79.6, 126.1, 128.5, 134.9, 140.9, 155.3, 171.7.

Linked amide 18

Tetrakis(*N*-Boc) amide **17** (3.66 g, 3.74 mmol) was dissolved in DCM (3 cm^3) to which thioanisole (4.65 g, 37.4 mmol) was added. TFA (17.06 g, 149.6 mmol) was added slowly with initial rapid evolution of carbon dioxide. The solution was stirred at

RT for 2 h after which excess TFA was removed under reduced pressure. The residue was treated with 10% aqueous sodium hydroxide (50 cm^3) and the aqueous layer extracted with DCM (3 × 100 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel eluting with 5% MeOH–DCM with 1% saturated NH_3 solution. *Linked amide* **18** was isolated as a colourless oil (1.54 g, 71%) [Found M + H^+, 579.3874 (ES). $C_{30}H_{54}N_6OS_2$ requires M + H^+, 579.3873]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.8 (12 H, m, $CH_2CH_2CH_2N$), 2.4–2.8 (20 H, m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.3–3.8 (4 H, br m, CH_2CO), 3.52 (2 H, s, $ArCH_2N$), 7.25–7.35 (4 H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.2, 27.1, 28.2, 28.7, 29.2, 29.4, 45.1, 46.9, 47.2, 47.5, 48.2, 52.1, 58.5, 67.5, 126.0, 128.2, 135.2, 140.7, 171.6.

Heteroditopic linked macrocycle 19

Linked amide **18** (1.8 g, 3.10 mmol) was dissolved in dry THF (10 cm^3). A solution of BH_3·SMe_2 (31.0 cm^3, 2.0 mol dm^{-3}, 62.0 mmol) in THF was added slowly and then heated at reflux for 40 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–conc. HCl (4 : 1 : 1; 60 cm^3) for 1 h. The methanol was removed under reduced pressure and the resulting solution partitioned between 10% aqueous sodium hydroxide (100 cm^3) and DCM (200 cm^3). The aqueous layer was extracted with DCM (2 × 100 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). *Heteroditopic linked macrocycle* **19** was isolated as a colourless oil (1.33 g, 76%) [Found M + H^+, 565.4081 (ES). $C_{30}H_{56}N_6S_2$ requires M + H^+, 565.4081]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.8 (12 H, m, $CH_2CH_2CH_2N$), 2.4–2.8 (32 H, m, CH_2N, CH_2S), 3.49 (2 H, s, $ArCH_2N$), 3.55 (2 H, s, $ArCH_2N$), 7.24 (4 H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.6, 27.1, 27.7, 28.8, 29.3, 29.5, 46.9, 47.0, 47.3, 48.5, 48.8, 49.0, 50.3, 52.1, 53.0, 53.8, 57.2, 58.5, 128.2, 128.7, 136.8, 138.0.

Chloromethylbenzamide 20

Prepared as for **16** from 1,4,8-tris(*tert*-butoxycarbonyl)cyclam **14** (7.8 g, 15.6 mmol), triethylamine (2.5 g, 25.0 mmol) and 3-(chloromethyl)benzoyl chloride (4.4 g, 23.4 mmol) to give *chloromethylbenzamide* **20** as a colourless oil (9.15 g, 90%) [Found M + Na^+, 675.3476 (ES). $C_{33}H_{53}N_4O_7Cl$ requires M + Na^+, 674.3495]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27 H, br s, ^tBu), 1.7–1.9 (4 H, br m, $CH_2CH_2CH_2N$), 3.1–3.7 (16 H, br m, CH_2N), 4.59 (2 H, br s, CH_2Cl), 7.2–7.5 (4 H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 28.3, 45.3, ~45–50 (broad overlapping signals), 79.6, 125.9, 126.4, 128.6, 129.2, 137.1, 137.6, 155.4, 171.1.

Tetrakis(*N*-Boc) amide 21

Prepared as for **17** from 5-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane **5** (2.48 g, 7.4 mmol), **20** (4.40 g, 6.7 mmol), sodium carbonate (0.86 g, 8.1 mmol) and sodium iodide (0.10 g, 0.67 mmol) to give *tetrakis(N-Boc) amide* **21** as a colourless oil (4.17 g, 65%) [Found M + H^+, 979.5958 (ES). $C_{50}H_{86}N_6O_9S_2$ requires M + H^+, 979.5970]; δ_H ($CDCl_3$; 300 MHz) 1.38 (36 H, s, ^tBu), 1.6–1.9 (12 H, br m, $CH_2CH_2CH_2N$), 2.35–2.55 (12 H, m, CH_2S, CH_2NCH_2Ar), 3.1–3.6 (20 H, br m, CH_2NBoc), 3.45 (2 H, s, $ArCH_2N$), 7.1–7.4 (4 H, br m, ArH); δ_C ($CDCl_3$; 125 MHz) 27.4, 28.3, 29.5, 29.8, ~45–50 (broad overlapping signals), 47.3, 52.5, 58.7, 79.3, 79.7, 124.7, 126.7, 128.2, 129.6, 136.3, 139.9, 155.5, 171.8.

Linked amide 22

Prepared as for **18** from **21** (3.06 g, 3.12 mmol), TFA acid (9.6 cm^3, 124.8 mmol) and thioanisole (3.88 g, 31.2 mmol) to give *linked amide* **22** as a colourless oil (1.61 g, 89%) [Found M + H^+, 503.3561 (ES). $C_{30}H_{54}N_6OS_2$ requires M + H^+, 503.3560]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.8 (12 H, m, $CH_2CH_2CH_2N$), 2.4–2.9 (20 H, m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.3–3.8 (4 H, br m, CH_2CO), 3.51 (2 H, s, $ArCH_2N$), 7.2–7.5 (4 H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.2, 27.1, 28.1, 28.8, 29.3, 29.5, 45.1, 47.0, 47.2, 47.6, 48.3, 52.1, 58.7, 67.6, 124.6, 126.4, 127.9, 129.2, 136.7, 139.9, 171.7.

Heteroditopic linked macrocycle 23

Prepared as for **19** from **22** (1.60 g, 2.76 mmol) and BH_3·SMe_2 (28.0 cm^3, 2.0 mol dm^{-3}, 56.0 mmol) to give *heteroditopic linked macrocycle* **23** as a colourless oil (1.10 g, 71%) [Found M + H^+, 565.4104 (ES). $C_{30}H_{56}N_6S_2$ requires M + H^+, 565.4081]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.9 (12 H, m, $CH_2CH_2CH_2N$), 2.4–2.8 (32 H, CH_2N, CH_2S), 3.50 (2 H, s, $ArCH_2N$), 3.57 (2 H, s, $ArCH_2N$), 7.1–7.3 (4 H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.1, 26.5, 27.3, 28.5, 28.8, 29.0, 46.5, 46.6, 48.0, 48.3, 49.6, 51.6, 52.2, 53.2, 57.0, 58.5, 126.7, 127.0, 127.1, 128.8, 137.5, 138.6.

Chloroacetamide 24

Prepared as for **16** from 1,4,8-tris(*tert*-butoxycarbonyl)cyclam **14** (1.12 g, 2.2 mmol), triethylamine (0.27 g, 2.7 mmol) and chloroacetyl chloride (0.305 g, 2.7 mmol) to give *chloroacetamide* **24** as a yellow–brown oil (1.05 g, 83%) [Found M + H^+, 577.3362 (ES). $C_{27}H_{49}N_4O_7Cl$ requires M + H^+, 577.3362]; δ_H ($CDCl_3$; 300 MHz) 1.45 (br s, ^tBu), 1.7–1.9 (4 H, br m, $CH_2CH_2CH_2N$), 3.2–3.6 (16 H, br m, CH_2N), 4.09 (br s, $COCH_2Cl$); δ_C ($CDCl_3$; 75 MHz) 28.1, 41.1, ~45–50 (broad overlapping signals), 79.8, 155.6, 166.2.

Tetrakis(*N*-Boc) amide 25

Prepared as for **17** from 5-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane **5** (0.689 g, 1.9 mmol), **24** (1.16 g, 2.0 mmol), sodium carbonate (0.26 g, 2.4 mmol) and sodium iodide (0.03 g, 0.2 mmol) to give *tetrakis(N-Boc) amide* **25** as a colourless oil (1.37 g, 80%) [Found M + H^+, 903.5631 (ES). $C_{44}H_{82}N_6O_9S_2$ requires M + H^+, 903.5657]; δ_H ($CDCl_3$; 300 MHz) 1.45 (36 H, s, ^tBu), 1.6–1.9 (12 H, br m, $CH_2CH_2CH_2N$), 2.5–2.8 (12 H, m, CH_2S, CH_2NCH_2CO), 3.2–3.5 (22 H, br m, CH_2N-Boc, CH_2CO); δ_C ($CDCl_3$; 75 MHz) 27.6, 28.4, 29.3, 29.6, ~45–50 (broad overlapping signals), 47.4, 47.5, 48.8, 53.2, 79.7, 79.8, 155.6.

Linked amide 26

Prepared as for **18** from **25** (0.65 g, 0.71 mmol), TFA (3.24 g, 28.4 mmol) and thioanisole (0.88 g, 7.1 mmol) to give *linked amide* **26** as a colourless oil (0.236 g, 66%) [Found M + H^+, 503.3561 (ES). $C_{24}H_{50}N_6OS_2$ requires M + H^+, 503.3560]; δ_H ($CDCl_3$; 300 MHz) 1.6–2.0 (12 H, m, $CH_2CH_2CH_2N$), 2.5–3.1 (20 H, m, CH_2S, CH_2NH, CH_2NCH_2CO), 3.25 (2 H, br s, CH_2CO), 3.5–3.8 (4 H, br m, CH_2CO); δ_C ($CDCl_3$; 75 MHz) 24.9, 26.0, 27.3, 27.7, 28.7, 29.4, 29.9, 42.6, 44.2, 44.7, 45.0, 45.4, 45.7, 47.0, 47.6, 47.8, 48.6, 49.0, 49.8, 50.1, 53.3, 53.6, 54.3, 57.2, 57.4, 58.2, 58.8, 170.7.

Heteroditopic linked macrocycle 27

Prepared as for **19** from **26** (0.20 g, 0.40 mmol) and BH_3·SMe_2 (4.0 cm^3, 2.0 mol dm^{-3}, 8.0 mmol) to give *heteroditopic linked macrocycle* **27** as a colourless oil (0.138 g, 71%) [Found M + H^+, 489.3769 (ES). $C_{24}H_{52}N_6S_2$ requires M + H^+, 489.3767]; δ_H ($CDCl_3$; 300 MHz) 1.6–2.0 (12 H, m, $CH_2CH_2CH_2N$), 2.4–2.8 (32 H, m, CH_2N, CH_2S); δ_C ($CDCl_3$; 75 MHz) 27.3, 27.5, 27.8, 29.1, 29.5, 29.8, 47.3, 47.4, 48.5, 49.1, 50.3, 50.8, 51.5, 53.0, 53.7, 54.4.

Tetrakis(*N*-Boc) amide 28

Prepared as for **17** from 4-*tert*-butoxycarbonyl-1,7-dithia-4,11-diazacyclohexadecane **12** (1.90 g, 5.69 mmol), **16** (3.38 g, 5.17 mmol), sodium carbonate (0.09 g, 6.21 mmol) and sodium iodide (0.08 g, 0.52 mmol) to give *tetrakis(N-Boc) amide* **28** as a colourless oil (3.69 g, 75%) [Found M + H^+, 951.5612 (ES). $C_{48}H_{82}N_6O_9S_2$ requires M + H^+, 951.5657]; δ_H ($CDCl_3$; 300 MHz) 1.45 (36 H, s, ^{t}Bu), 1.7–1.9 (8 H, br m, $CH_2CH_2CH_2N$), 2.4–2.8 (12 H, m, CH_2S, CH_2NCH_2Ar), 3.2–3.8 (20 H, br m, CH_2NBoc), 3.50 (2 H, s, $ArCH_2N$), 7.35 (4 H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 28.3, 29.5, 30.7, 31.1, ~45–50 (broad overlapping signals), 48.8, 49.6, 52.5, 52.8, 59.2, 79.8, 126.3, 128.6, 135.0, 141.0, 155.1, 171.7.

Linked amide 29

Prepared as for **18** from **28** (5.56 g, 3.74 mmol), TFA (17.1 g, 149.6 mmol) and thioanisole (4.65 g, 37.4 mmol) to give *linked amide* **29** as a colourless oil (1.52 g, 74%) [Found M + H^+, 551.3577 (ES). $C_{28}H_{50}N_6OS_2$ requires M + H^+, 551.3560]; δ_H ($CDCl_3$; 300 MHz) 1.7–1.8 (8 H, m, $CH_2CH_2CH_2N$), 2.4–2.9 (20 H, m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.3–3.8 (4 H, br m, CH_2CO), 3.50 (2 H, s, $ArCH_2N$), 7.25–7.35 (4 H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.2, 26.6, 28.1, 32.1, 44.9, 46.0, 47.0, 47.4, 48.1, 51.5, 58.2, 62.4, 125.9, 128.1, 135.0, 140.6, 171.6.

Heteroditopic linked macrocycle 30

Prepared as for **19** from **29** (1.7 g, 3.09 mmol) and $BH_3{\cdot}SMe_2$ (31.0 cm^3, 2.0 mol dm^{-3}, 62.0 mmol) to give *heteroditopic linked macrocycle* **30** as a colourless oil (1.20 g, 73%) [Found M + H^+, 537.3776 (ES). $C_{28}H_{52}N_6S_2$ requires M + H^+, 537.3768]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.9 (12 H, m, $CH_2CH_2CH_2N$), 2.4–2.9 (32 H, m, CH_2N, CH_2S), 3.47 (2 H, s, $ArCH_2N$), 3.57 (2 H, s, $ArCH_2N$), 7.24 (4 H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.6, 26.9, 27.5, 28.7, 28.9, 32.6, 46.7, 47.0, 47.4, 48.7, 49.0, 49.3, 50.4, 51.8, 53.3, 53.7, 57.4, 58.2, 128.6, 129.2, 136.9, 138.5.

Tetrakis(*N*-Boc) amide 31

Prepared as for **17** from 4-*tert*-butoxycarbonyl-1,7-dithia-4,11-diazacyclohexadecane **12** (2.48 g, 7.41 mmol), **20** (4.4 g, 6.74 mmol), sodium carbonate (0.10 g, 8.1 mmol) and sodium iodide (0.09 g, 0.67 mmol) to give *tetrakis(N-Boc) amide* **31** as a colourless oil (4.17 g, 65%) [Found M + H^+, 951.5645 (ES). $C_{48}H_{82}N_6O_9S_2$ requires M + H^+, 951.5657]; δ_H ($CDCl_3$; 300 MHz) 1.45 (36 H, s, ^{t}Bu), 1.7–1.8 (8 H, br m, $CH_2CH_2CH_2N$), 2.4–2.8 (12 H, m, CH_2S, CH_2NCH_2Ar), 3.2–3.7 (20 H, br m, CH_2NBoc), 3.51 (s, $ArCH_2N$), 7.2–7.4 (4 H, br m, ArH); δ_C ($CDCl_3$; 125 MHz) 28.3, 29.5, 30.7, 31.1, ~45–50 (broad overlapping signals), 48.8, 49.6, 52.4, 52.8, 59.2, 79.8, 124.6, 126.8, 128.2, 129.6, 136.3, 140.1, 155.1, 171.8.

Linked amide 32

Prepared as for **18** from **31** (3.63 g, 3.81 mmol), TFA (17.38 g, 152.4 mmol) and thioanisole to give *linked amide* **32** as a colourless oil (1.7 g, 80%) [Found M + H^+, 475.3243 (ES). $C_{28}H_{50}N_6OS_2$ requires M + H^+, 475.3247]; δ_H ($CDCl_3$; 300 MHz) 1.65–1.85 (8 H, m, $CH_2CH_2CH_2N$), 2.4–3.0 (20 H, m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.3–3.8 (4 H, br m, CH_2CO), 3.50 (2 H, s, $ArCH_2N$), 7.2–7.4 (4 H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.2, 26.6, 28.3, 32.2, 45.1, 46.3, 47.3, 47.5, 48.2, 51.6, 58.0, 67.5, 124.4, 126.4, 127.8, 129.0, 136.7, 139.8, 171.5.

Heteroditopic linked macrocycle 33

Prepared as for **19** from **32** (1.70 g, 3.09 mmol) and $BH_3{\cdot}SMe_2$ (31.0 cm^3, 2.0 mol dm^{-3}, 62.0 mmol) to give *heteroditopic linked macrocycle* **33** as a colourless oil (1.19 g, 72%) [Found M + H^+, 537.3773 (ES). $C_{28}H_{52}N_6S_2$ requires M + H^+, 537.3768]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.9 (8 H, m, $CH_2CH_2CH_2N$), 2.4–2.9 (32 H, m, CH_2N, CH_2S), 3.44 (2 H, s, $ArCH_2N$), 3.53 (2 H, s, $ArCH_2N$), 7.1–7.3 (4 H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.4, 26.2, 27.8, 28.0, 31.9, 46.6, 47.1, 48.1, 48.3, 49.8, 51.2, 52.2, 53.7, 57.0, 58.0, 126.6, 126.9, 127.2, 128.9, 137.6, 138.5.

Tetrakis(*N*-Boc) amide 34

Prepared as for **17** from 4-*tert*-butoxycarbonyl-1,7-dithia-4,11-diazacyclohexadecane **12** (0.55 g, 1.65 mmol), **24** (0.86 g, 1.50 mmol), sodium carbonate (0.19 g, 1.8 mmol) and sodium iodide (0.02 g, 0.15 mmol) to give *tetrakis(N-Boc) amide* **34** as a colourless oil (0.94 g, 72%) [Found M + H^+, 875.5364 (ES). $C_{42}H_{78}N_6O_9S_2$ requires M + H^+, 875.5344]; δ_H ($CDCl_3$; 300 MHz) 1.45 (36 H, s, ^{t}Bu), 1.7–1.8 (8 H, br m, $CH_2CH_2CH_2N$), 2.5–2.8 (12 H, m, CH_2S, CH_2NCH_2CO), 3.2–3.5 (22 H, br m, CH_2NBoc, CH_2CO); δ_C ($CDCl_3$; 75 MHz) 28.3, 29.4, 30.5, 31.0, ~45–50 (broad overlapping signals), 48.4, 49.3, 53.0, 53.6, 79.7, 155.1.

Linked amide 35

Prepared as for **18** from **34** (0.875 g, 1.0 mmol), TFA (4.56 g, 40.0 mmol) and thioanisole (1.24 g, 10.0 mmol) to give *linked amide* **35** as a colourless oil (0.284 g, 68%) [Found M + H^+, 475.3243 (ES). $C_{22}H_{46}N_6OS_2$ requires M + H^+, 475.3247]; δ_H ($CDCl_3$; 300 MHz) 1.6–2.0 (8 H, m, $CH_2CH_2CH_2N$), 2.6–3.0 (20 H, m, CH_2S, CH_2NH, CH_2NCH_2CO), 3.25 (2 H, br s, CH_2CO), 3.5–3.7 (4 H, br m, CH_2CO); δ_C ($CDCl_3$; 75 MHz) 25.7, 25.9, 27.2, 27.8, 29.0, 32.7, 43.3, 44.7, 45.0, 45.7, 46.8, 47.3, 47.8, 48.6, 49.1, 49.4, 49.6, 49.9, 52.6, 56.1, 57.2, 170.6.

Heteroditopic linked macrocycle 36

Prepared as for **19** from **35** (0.20 g, 0.42 mmol) and $BH_3{\cdot}SMe_2$ (4.0 cm^3, 2.0 mol dm^{-3}, 8.0 mmol) to give *heteroditopic linked macrocycle* **36** as a colourless oil (0.136 g, 70%) [Found M + H^+, 461.3460 (ES). $C_{22}H_{48}N_6S_2$ requires M + H^+, 461.3454]; δ_H ($CDCl_3$; 300 MHz) 1.6–2.0 (8 H, m, $CH_2CH_2CH_2N$), 2.4–2.8 (32 H, m, CH_2N, CH_2S); δ_C ($CDCl_3$; 75 MHz) 27.1, 27.4, 27.7, 29.1, 29.3, 29.7, 47.3, 47.5, 48.6, 49.3, 50.2, 50.7, 51.6, 53.0, 53.6, 54.5.

Chloromethylbenzamide 37

Prepared as for **16** from 8,14-bis(*tert*-butoxycarbonyl)-2,5-dioxa-8,11,14-triaza-1,6(1,2)-dibenzenacyclopentadecaphane **15** (0.174 g, 0.32 mmol), triethylamine (0.052 g, 0.51 mmol) and 4-(chloromethyl)benzoyl chloride (0.091 g, 0.48 mmol) to give *chloromethylbenzamide* **37** as a colourless oil (0.200 g, 90%) [Found M + Na^+, 716.3059 (ES). $C_{38}H_{48}ClN_3O_7$ requires M + Na^+, 716.3073]; δ_H ($CDCl_3$; 200 MHz) 1.2–1.5 (18 H, br s, ^{t}Bu), 3.1–3.6 (8 H, br m, NCH_2CH_2N), 4.37 (4 H, s, CH_2O), 4.4–4.6 (4 H, br s, NCH_2ArO), 4.56 (2 H, s, CH_2Cl), 6.9–7.0 (4 H, m, H-4′, H-5′), 7.2–7.4 (8 H, m, COArH, H-3′, H-6′); δ_C ($CDCl_3$; 50 MHz) 28.4, 44.3, 44–46 (broad overlapping signals), 47.2, 67.0, 80.1, 111.2, 121.4, 126.0, 127.0, 128.5, 136.8, 138.7, 155.9, 156.3, 172.1.

Tris(*N*-Boc) amide 38

Prepared as for **17** from **37** (0.491 g, 0.71 mmol), sodium carbonate (0.090 g, 0.85 mmol) sodium iodide (0.010 g, 0.07 mmol) and **5** (0.092 g, 0.26 mmol) to give *tris(N-Boc) amide* **38** as a colourless oil (0.670 g, 92%) [Found M + Na^+, 1042.5367 (ES). $C_{55}H_{81}N_5O_9S_2$ requires M + Na^+, 1042.5317]; δ_H ($CDCl_3$; 200 MHz) 1.2–1.5 (27 H, br s, ^{t}Bu), 1.7–1.9 (8 H, br m, $NCH_2CH_2CH_2S$), 2.46 (8 H, m, CH_2S), 2.67 (4 H, t, $ArCH_2NCH_2CH_2CH_2S$), 3.1–3.6 (12 H, br m, NCH_2CH_2N, $BocNCH_2CH_2CH_2S$), 3.50 (2 H, s, $COArCH_2N$), 4.37 (4 H, s, CH_2O), 4.3–4.6 (4 H, br s, NCH_2ArO), 6.9–7.0 (4 H, m, H-4′, H-5′), 7.1–7.3 (8 H, m, COArH, H-3′, H-6′); δ_C ($CDCl_3$; 50 MHz) 27.6, 28.4, 29.6, 29.9, 43–45 (broad overlapping signals), 47.4, 52.7, 58.8,

67.0, 79.4, 80.0, 111.1, 121.4, 126.0, 126.6, 128.3, 128.4, 128.6, 140.6, 141.1, 155.6, 156.2, 172.1.

Linked amide 39

Prepared as for **18** from **38** (0.655 g, 0.64 mmol), thioanisole (0.60 g, 4.81 mmol) and TFA (2.20 g, 19.26 mmol) to give *linked amide* **39** as a colourless oil (0.376 g, 81%) [Found M + H^+, 720.3999 (ES). $C_{40}H_{57}N_5O_3S_2$ requires M + H^+, 720.3975]; δ_H ($CDCl_3$; 200 MHz) 1.77 (8 H, m, $NCH_2CH_2CH_2S$), 2.48 (4 H, t, $SCH_2CH_2CH_2NH$), 2.55 (4 H, t, $SCH_2CH_2CH_2NCH_2Ar$), 2.67 (4 H, t, $ArCH_2NCH_2CH_2CH_2S$), 2.75 (4 H, t, $NHCH_2CH_2CH_2S$), 2.6–3.0 (4 H, br m, $HNCH_2CH_2N$), 3.4–3.6 (4 H, br m, CH_2NCOAr), 3.51 (2 H, s, $COArCH_2N$), 3.82 (4 H, s, NCH_2ArO), 4.39 (4 H, s, CH_2O), 6.9–7.0 (4 H, m, H-4′, H-5′), 7.1–7.3 (8 H, m, COArH, H-3′, H-6′); δ_C ($CDCl_3$; 50 MHz) 27.4, 29.1, 29.6, 29.9, 46–50 (broad overlapping signals), 47.4, 49.8, 52.5, 58.9, 66.9, 111.4, 121.2, 126.6, 128.3, 128.4, 128.5, 130.3, 135.4, 141.0, 156.6, 172.2.

Heteroditopic linked macrocycle 40

Prepared as for **19** from **39** (0.344 g, 0.48 mmol) and $BH_3{\cdot}SMe_2$ (5.0 cm^3, 2.0 mol dm^{-3}, 10.0 mmol) to give *heteroditopic linked macrocycle* **40** as a colourless oil (0.211 g, 63%) [Found M + H^+, 706.4148 (ES). $C_{40}H_{59}N_5O_2S_2$ requires M + H^+, 706.4183]; δ_H ($CDCl_3$; 200 MHz) 1.77 (8 H, m, $NCH_2CH_2CH_2S$), 2.48 (4 H, t, $SCH_2CH_2CH_2NH$), 2.52 (8 H, m, NCH_2CH_2N), 2.55 (4 H, t, $SCH_2CH_2CH_2NCH_2Ar$), 2.67 (4 H, t, $ArCH_2NCH_2CH_2CH_2S$), 2.75 (4 H, t, $NHCH_2CH_2CH_2S$), 3.18 (2 H, s, $ArCH_2NCH_2CH_2N$), 3.45 (2 H, s, $ArCH_2NCH_2CH_2CH_2S$), 3.72 (4 H, s, NCH_2ArO), 4.46 (4 H, s, CH_2O), 6.9–7.0 (4 H, m, H-4′, H-5′), 7.1–7.3 (8 H, m, COArH, H-3′, H-6′); δ_C ($CDCl_3$; 50 MHz) 27.4, 29.0, 29.5, 29.8, 45.8, 47.2, 50.0, 52.3, 53.6, 56.5, 58.7, 66.6, 110.9, 120.6, 128.1, 128.2, 128.4, 129.0, 131.1, 136.4, 138.1, 156.9.

Bis(*N*-Boc) amide 41

Prepared as for **17** from **37** (0.165 g, 0.24 mmol), sodium carbonate (0.030 g, 0.29 mmol) and sodium iodide (0.003 g, 0.02 mmol) to give *bis(N-Boc) amide* **41** (0.203 g, 84%) [Found M + H_2^{2+}, 505.7782 (ES). $C_{57}H_{79}N_5O_7S_2$ requires M + H_2^{2+}, 505.7783]; δ_H ($CDCl_3$; 200 MHz) 1.2–1.5 (18 H, br s, ^tBu), 1.76 (8 H, m, $NCH_2CH_2CH_2S$), 2.49 (8 H, t, CH_2S), 2.57 (8 H, t, $NCH_2CH_2CH_2S$), 3.1–3.6 (8 H, br m, NCH_2CH_2N), 3.53 (4 H, s, $COArCH_2N$, CH_2Ph), 4.37 (4 H, s, CH_2O), 4.3–4.6 (4 H, br s, NCH_2ArO), 6.9–7.0 (4 H, m, H-4′, H-5′), 7.1–7.3 (13 H, m, COArH, H-3′, H-6′, Ph); δ_C ($CDCl_3$; 50 MHz) 27.5, 27.6, 28.3, 30.0, 44–46 (broad overlapping signals), 52.6, 59.1, 59.4, 67.1, 80.0, 111.1, 121.4, 126.0, 126.6, 126.8, 128.0, 128.1, 128.4, 128.6, 128.8, 136.8, 139.7, 140.9, 155.9, 156.2, 172.1.

Linked amide 42

Prepared as for **18** from **41** (0.233 g, 0.23 mmol), TFA (0.53 g, 4.61 mmol) and thioanisole (0.15 g, 1.19 mmol) to give *linked amide* **42** (0.168 g, 90%) [Found M + H^+, 810.4460 (ES). $C_{47}H_{63}N_5O_3S_2$ requires M + H^+, 810.4445]; δ_H ($CDCl_3$; 200 MHz) 1.76 (8 H, m, $NCH_2CH_2CH_2S$), 2.49 (8 H, t, CH_2S), 2.57 (8 H, t, $NCH_2CH_2CH_2S$), 2.6–3.0 (4 H, br m, $HNCH_2CH_2N$), 3.2–3.6 (4 H, br m, CH_2NCOAr), 3.52 (4 H, s, $COArCH_2N$, CH_2Ph), 3.82 (4 H, s, NCH_2ArO), 4.38 (4 H, s, CH_2O), 6.9–7.0 (4 H, m, H-4′, H-5′), 7.32–7.25 (13 H, m, COArH, H-3′, H-6′, Ph); δ_C ($CDCl_3$; 50 MHz) 27.6, 30.0, 48–50 (broad overlapping signals), 47.4, 48.4, 52.6, 59.4, 66.9, 111.3, 121.1, 126.5, 126.8, 128.0, 128.1, 128.4, 128.6, 128.8, 130.2, 135.4, 139.7, 141.0, 156.6, 172.1.

Heteroditopic linked macrocycle 43

Prepared as for **19** from **42** (0.168 g, 0.21 mmol) and $BH_3{\cdot}SMe_2$ (2.2 cm^3, 2.0 mol dm^{-3}, 4.4 mmol) to give *heteroditopic linked macrocycle* **43** (0.104 g, 71%) [Found M + H^+, 796.4632 (ES). $C_{47}H_{65}N_5O_2S_2$ requires M + H^+, 796.4652]; δ_H ($CDCl_3$; 200 MHz) 1.75 (8 H, m, $NCH_2CH_2CH_2S$), 2.49 (8 H, t, CH_2S), 2.52 (8 H, m, NCH_2CH_2N), 2.57 (8 H, t, $NCH_2CH_2CH_2S$), 3.20 (2 H, s, $ArCH_2NCH_2CH_2N$), 3.46 (2 H, s, $ArCH_2NCH_2CH_2CH_2S$), 3.53 (2 H, s, CH_2Ph), 3.74 (4 H, s, NCH_2ArO), 4.45 (4 H, s, CH_2O), 6.9–7.0 (4 H, m, H-4′, H-5′), 7.2–7.3 (13 H, m, COArH, H-3′, H-6′, Ph); δ_C ($CDCl_3$; 50 MHz) 27.5, 27.6, 29.6, 29.9, 45.8, 50.0, 52.5, 52.6, 53.5, 56.7, 59.0, 59.3, 66.7, 111.1, 120.7, 126.8, 128.0, 128.1, 128.4, 128.5, 128.7, 129.0, 131.2, 136.5, 138.2, 139.6, 156.9.

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