Designer ligands. Part 4.[1] Synthesis of acyclic and macrocyclic platinum group metal-specific ligands

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Synthetic pathways to a range of novel, polydentate, sulfur-containing, mono-amide ligands, designed to coordinate platinum group metals, have been developed. Access to the tetradentate systems was facilitated by the extensive use of disulfide linkages as a protection strategy.

Solvent extraction processes, using metal-specific ligands, are now typically applied to separate the valuable platinum group metals (PGM) from base metals such as iron, copper, nickel and cobalt.[2] Particular interest in platinum-specific ligands has been promoted by the discovery of the anti-tumour platinum complexes, cisplatin[3] and carboplatin.[4] The dose-limiting nephrotoxicity of cisplatin is attributed to the complexation of platinum with sulfur-rich enzymes and proteins in the kidney, and attention has been given to the use of various ligands as "rescue agents" to remove platinum from these biomolecules.[5] Kimura *et al.*[6] have reported macrocyclic N_2S_2 and N_2S_3 ligands whose complexation with Pt(II) and Pd(II) involves initial coordination to the soft sulfur donors followed by PGM-selective deprotonation of the amide groups and formation of M–N bonds. More recently, Archer *et al.*[7] have prepared a somewhat analogous series of *acyclic* NS_3H_3 ligands containing terminal thiol groups, which were expected to enhance the stability of complexes with the radioisotope, technetium-99.

Our own research has been concerned with the development of novel, PGM-specific ligands which incorporate the design features illustrated in Fig. 1; these include: (i) an aromatic ring to enhance lipophilicity for solvent extraction applications, or for linkage to an inert polymeric matrix; (ii) an amide function for PGM-specificity;[6] (iii) side-chains to accommodate additional sulfur donors; (iv) *ortho*-*N*,*S*-disubstitution to permit the formation of 5-membered chelates; and (v) a *para*-substituent to "fine-tune" electron density at the amide nitrogen. In this paper, we describe the synthesis of a range of tetradentate ligands which, on preliminary examination, exhibit significant PGM-specifity.

Extension of the side-chains (iii; Fig. 1) to include additional sulfur donors requires appropriate protection of reactive thiol groups in reagents and intermediates. The benzyl protecting group is readily attached to the thiol function[7,8] and has found use in the synthesis of sulfur-containing peptides.[9] In a previous communication[1] we reported the preparation of the intermediate **3** by reaction of 2-aminobenzenethiol **1** with the benzyl sulfide reagent **2** (Scheme 1). While acetylation of the intermediate **3** gave the tridentate, monoamide ligand **4** in good yield (73%), initial attempts to extend this approach to the synthesis of the tetradentate ligands **5** and **8** proved unsuccessful.† However, when the intermediate **3** was reacted with *S*-benzylthioacetic acid **6** in the presence of the coupling agent, 1,1′-carbonyldiimidazole (CDI), the tetradentate ligand **8** was

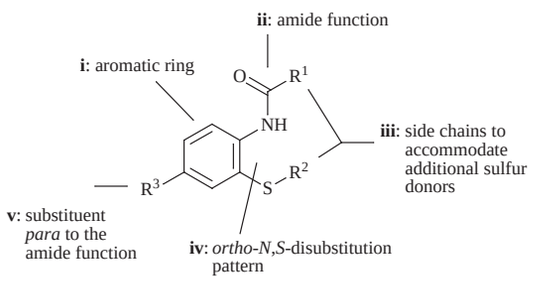


Fig. 1 Design features of novel PGM-specific ligands.

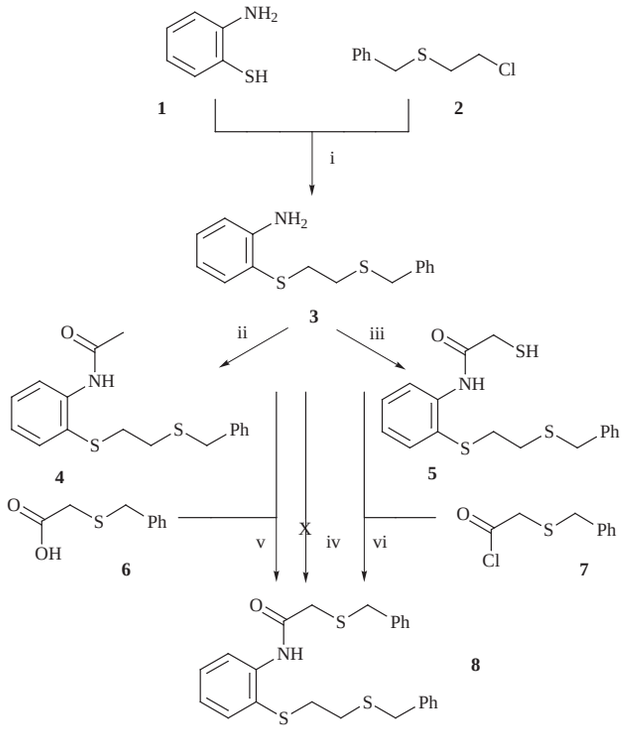
obtained in 60% yield; in a preferred variation, direct acylation using the acid chloride **7** gave the product in higher yield. Attempted removal of the benzyl protecting groups in **8** by reductive cleavage using sodium in liquid ammonia[10] afforded, unexpectedly, a complex mixture of products. Examination of the literature revealed precedents for: desulfurisation;[11] the reduction of aliphatic sulfides to thiols and hydrocarbons;[12] and the cleavage aryl thioethers.[13] Consequently, attention was turned to the application of an unusual protection strategy, involving the use of disulfide linkages.

In essence, the protection strategy is to treat disulfides as masked mercaptans; the target molecule acts as its own protecting group, final fission of the disulfide linkage affording two equivalents of product. Thus, bis(2-chloroethyl) disulfide **11**, prepared as outlined in Scheme 2, was reacted with the *o*-aminobenzenethiolates **12a**,**b** to give the intermediate disulfides **13a**,**b** in almost quantitative yield and in sufficient purity to proceed without purification. Acetylation of the amines **13a**,**b** with acetic anhydride afforded the crystalline amido disulfides **14a**,**b**, selective reduction of which was expected to yield the desired tridentate ligands **15a**,**b**. Treatment of the disulfide **14a** with sodium borohydride–aluminium trichloride, a reducing system reported to reduce disulfides[14] but not amides,[15] gave both the expected amide **15a** (25%) and the corresponding amine **16** (29%),‡ while use of triphenylphosphine[17] in methanol containing aqueous perchloric acid, afforded the amide **15a** (28%) together with the hydrolysed product **17** (33%). The desired reduction of the disulfides **14a**,**b** to the target ligands **15a**,**b** was finally achieved, in acceptable yield, using triphenylphosphine in aqueous methanol (1 : 10), the reaction being conducted under nitrogen to inhibit oxidation back to the disulfides.

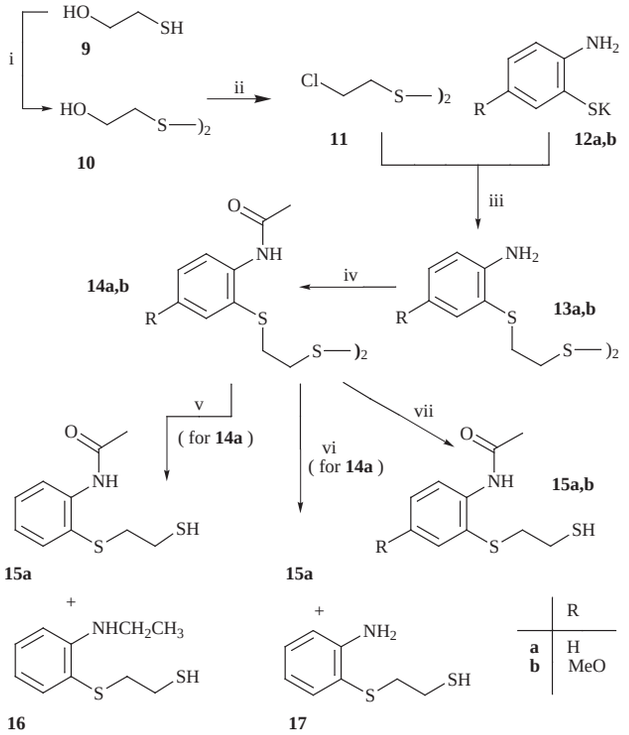
Having successfully applied the disulfide protection strategy to the preparation of the tridentate ligands **15a,b**, the method-

† Heating **3** with mercaptoacetic acid for 8 hours under a stream of dry nitrogen (to prevent disulfide formation) gave **5** in negligible yield (4%), while treatment of **3** with chloroacetyl chloride and phenylmethanethiol in triethylamine gave none of the *S*-benzylated analogue **8**.

‡ A later report (see ref. 16) indicated that this reagent reduces tertiary but not primary amides.



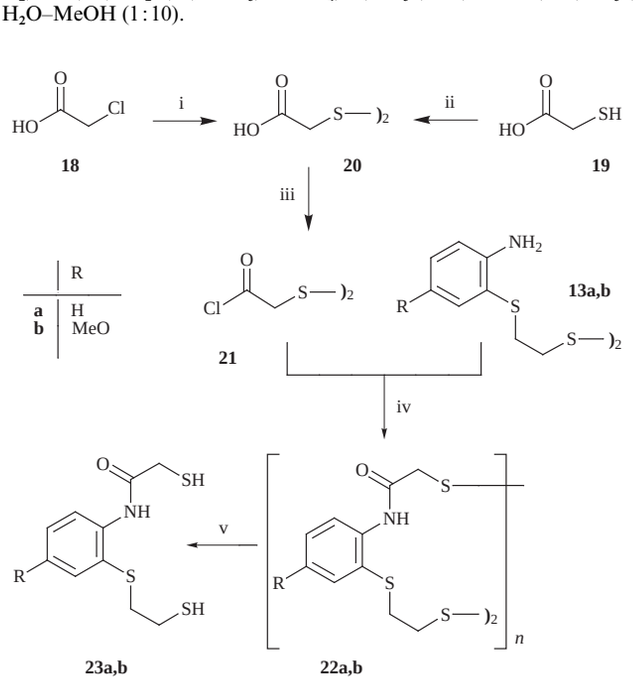
Scheme 1 *Reagents and conditions*: i, KOH, MeOH; ii, Ac_2O, H_2SO_4; iii, $HSCH_2CO_2H$, N_2, heat; iv, $ClCH_2COCl$, Et_3N, $PhCH_2SH$; v, CDI; vi, Et_3N.



Scheme 2 *Reagents and conditions*: i, H_2O_2; ii, conc. HCl; iii, MeOH, N_2, heat; iv, Ac_2O; v, $AlCl_3$, $NaBH_4$; vi, Ph_3P, H^+, MeOH; vii, Ph_3P, H_2O–MeOH (1 : 10).

ology was extended to the synthesis of tetradentate analogues by using disulfide linkages to protect *both* side-arms. Bis[(chloroformyl)methyl] disulfide **21** (obtained in two ways, as outlined in Scheme 3) was reacted with the disulfides **13a** and **13b** to give the corresponding polymeric products **22a** and **22b**, apparently quantitatively. The size and structure of the polymers were not considered to be critical since reductive cleavage of *all* disulfide linkages was expected to afford, in each case, the target ligand (**23a** or **23b**) *as the sole monomeric unit*. In the case of the parent system, reduction of the polymer **22a** with triphenylphosphine in aqueous methanol afforded the expected tetradentate ligand **23a** in 60–70% yield. The methoxy analogue **23b**, however, was obtained in much lower yields (5–10%)—a result attributed, at least partially, to the relative insolubility of the polymeric material **22b** and the presence of a contaminating polymer **25** which, upon reduction, affords the lactam **26** (Scheme 4).§ The precursor **24** of the contaminating polymer **25** appears to be formed during, or after, isolation of 2-amino-5-methoxybenzenethiol, used as the potassium salt **12b** in the preparation of the disulfide **13b** (Scheme 2). These complications were addressed by: i, ensuring that subsequent preparation of the disulfide **13b** did not involve *isolation* of the benzenethiol precursor; and ii, using a benzoyl protecting group in conjunction with the disulfide moiety. Thus, reaction of the *p*-methoxy disulfide **13b** with *S*-benzoylthioacetic acid **27**, in the presence of CDI, gave the intermediate **29** in 20% yield; an alternative approach using the acid chloride **28**, however, resulted in an almost quantitative conversion (Scheme 5). Deprotection of the intermediate **29**, which contained *both* disulfide *and* benzoyl groups, was effected using triphenylphosphine in aqueous methanol followed by aqueous potassium hydroxide, and the desired tetradentate ligand **23b** was finally isolated in >90% yield.

With the tetradentate ligands **23a**,**b** in hand, the preparation of their macrocyclic derivatives **30a**,**b** was investigated. Using a

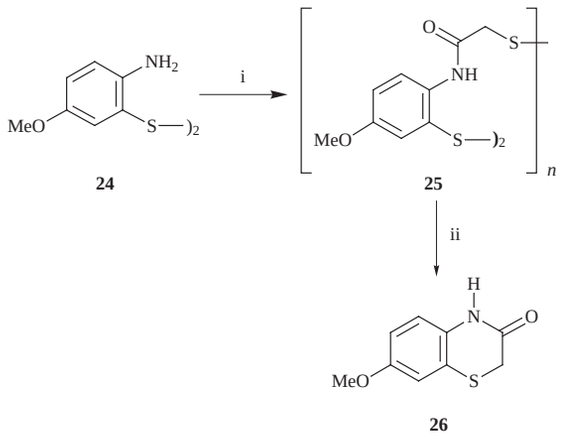


Scheme 3 *Reagents and conditions*: i, $Na_2S_2O_3$, Na_2CO_3, I_2; ii, I_2, KI; iii, $SOCl_2$; iv, Et_3N; v, Ph_3P, H_2O–MeOH (1 : 10).

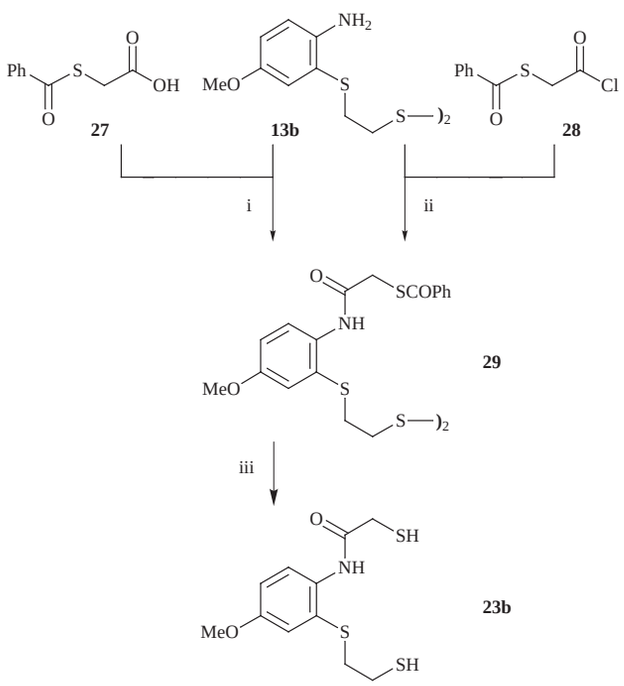
simulated high-dilution technique,[19] solutions of 1,2-dibromoethane and the dimercapto compound (**23a** or **23b**) in dry *N*,*N*-dimethylformamide were added *slowly* and *simultaneously*, at *ca*. 45 min intervals during 12 h, to a solution of caesium carbonate in dry DMF under nitrogen (Scheme 6), the base being chosen to exploit the "caesium effect".[20] Work-up and flash chromatography yielded the crystalline macrocycles **30a** (31%) and **30b** (17%), which were fully characterised by elemental and spectroscopic analysis.

In summary, synthetic pathways to a range of customised ligands have been established. Preliminary studies, using selected ligands, have clearly indicated their ability to complex platinum(II) and palladium(II),[21] and future research will be

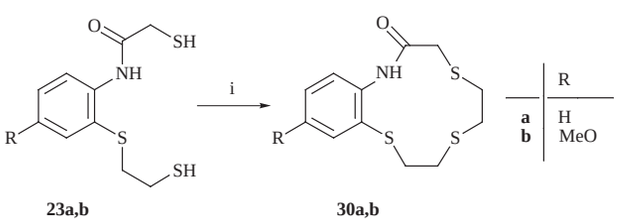
§ A precedent for cyclisation to the 7-methoxy lactam **26** is provided by the somewhat analogous formation of the "parent" lactam in up to 75% yield (see ref. 18).



Scheme 4 *Reagents and conditions*: i, $(ClCOCH_2S)_2$, Et_3N; ii, Ph_3P, H_2O–MeOH (1 : 10).



Scheme 5 *Reagents and conditions*: i, CDI; ii, Et_3N; iii, Ph_3P, H_2O–MeOH (1 : 10), then KOH.



Scheme 6 *Reagents and conditions*: i, Cs_2CO_3, $BrCH_2CH_2Br$, DMF.

directed towards quantifying their PGM-extraction potential and elucidating the associated coordination chemistry.

Experimental

Infrared spectra were recorded on Perkin-Elmer 2000 and Perkin-Elmer 180 spectrophotometers; NMR spectra were recorded on a Bruker AMX 400 spectrometer and chemical shifts are reported relative to the solvent peaks. Low resolution mass spectra were obtained on a Hewlett-Packard 5988A mass spectrometer and high resolution analyses on a Kratos MS8ORF double-focusing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit). Literature methods were used to prepare the known alkylating and acylating agents **2**,[22] **6**,[23] **7**,[24] **11**,[25] **27**[26] and **28**;[1] preparation of the intermediate ligand **3** has also been described previously.[1] [**CAUTIONARY NOTE**. Synthesis of bis(2-chloroethyl) disulfide **11** *via* chlorination of bis(2-hydroxyethyl) disulfide **10** is expected to preclude formation of bis(2-chloroethyl) sulfide (mustard gas). Nevertheless, appropriate precautions are recommended.]

2′-(5-Phenyl-1,4-dithiapentyl)acetanilide 4

Conc. H_2SO_4 (5 drops) was added to a solution of 2-(5-phenyl-1,4-dithiapentyl)aniline **3** (2.29 g, 8.31 mmol) in Ac_2O (46 mL). The mixture was stirred for 5 h at room temperature, and then poured into warm water (200 mL). The aqueous mixture was extracted with EtOAc (3 × 40 mL) and the combined extracts were dried (anhyd. $MgSO_4$). Removal of the solvent *in vacuo* afforded a brown oil (3.7 g) which was purified by flash chromatography [elution with EtOAc–hexane (2 : 8)] to afford, as a white solid, *2-(5-phenyl-1,4-dithiapentyl)acetanilide* **4** (1.94 g, 73%), mp 48–49 °C (from EtOAc–hexane) (Found: C, 64.1; H, 6.1; N, 4.2; M^+, 317.0910. $C_{17}H_{19}NOS_2$ requires C, 64.3; H, 6.0; N, 4.4%; *M*, 317.0908); ν_{max}(KBr)/cm^{-1} 3340 (NH) and 1690 (CO); δ_H(400 MHz; $CDCl_3$) 2.11 (3H, s, $COCH_3$), 2.44 (2H, m, CH_2S), 2.75 (2H, m, $ArSCH_2$), 3.56 (2H, s, $ArCH_2S$), 6.90–7.38 (8H, m, ArH), 8.32 (1H, d, ArH) and 8.49 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.8, 30.7, 36.0 and 36.1 (C-2′, C-3′, C-5′ and CH_3), 120.2, 121.2, 123.9, 127.1, 128.5, 128.6, 130.0, 135.5, 137.7 and 140.0 (ArC) and 168.3 (CO).

N-(2-Mercaptoethanoyl)-2-(5-phenyl-1,4-dithiapentyl)aniline 5

A melt of 2-(5-phenyl-1,4-dithiapentyl)aniline **3** (5.23 g, 19.0 mmol) and 2-mercaptoacetic acid (1.75 g, 19.0 mmol) was heated at 110–120 °C in a stream of dry N_2. After heating for 5 h, TLC indicated the formation of a small amount of product. The components of the melt were separated by flash chromatography [elution with EtOAc–hexane (1 : 9)] to afford *N-(2-mercaptoethanoyl)-2-(5-phenyl-1,4-dithiapentyl)aniline* **5** (0.29 g, 4%); δ_H(400 MHz; $CDCl_3$) 1.98 (1H, t, *J* 8.9 Hz, SH), 2.52 (2H, m, CH_2S), 2.83 (2H, m, $ArSCH_2$), 3.38 (2H, d, *J* 8.9 Hz, $COCH_2S$), 3.61 (2H, s, $ArCH_2S$), 6.98–7.51 (8H, m, ArH), 8.41 (1H, d, ArH) and 9.70 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 29.7, 30.7, 35.8 and 36.2 (C-2′, C-3′, C-5′ and $COCH_2S$), 119.9, 124.4, 127.0, 128.4, 128.6, 128.7, 130.0, 135.7, 137.9 and 139.5 (ArC) and 167.3 (CO).

N-[2-(Benzylthio)ethanoyl]-2-(5-phenyl-1,4-dithiapentyl)aniline 8

Method 1. A solution of 2-(benzylthio)ethanoyl chloride **7** (3.28 g, 16.3 mmol) in dry THF (30 mL) was added dropwise, using a syringe, to a stirred solution of 2-(5-phenyl-1,4-dithiapentyl)aniline **3** (4.49 g, 16.3 mmol) and dry triethylamine (2.51 mL, 18.0 mmol) in dry THF (30 mL). The mixture was stirred at room temperature for 2 h before adding H_2O (30 mL). The THF was evaporated *in vacuo* and the aqueous residue was extracted with EtOAc (3 × 30 mL); the EtOAc extracts were combined and dried (anhyd. $MgSO_4$). Evaporation of the solvent yielded a brown solid which was recrystallised twice from EtOH–EtOAc (9 : 1) to afford, as white crystals, *N-[2-(benzylthio)ethanoyl]-2-(5-phenyl-1,4-dithiapentyl)aniline* **8** (4.34 g, 60%), mp 81–81.5 °C (from EtOH–EtOAc) (Found: C, 65.3; H, 5.85; N, 3.1; M^+, 439.1086. $C_{24}H_{25}NOS_3$ requires C, 65.6; H, 5.7; N, 3.2%; *M*, 439.1098); ν_{max}(KBr)/cm^{-1} 3270 (NH) and 1675 (CO); δ_H(400 MHz; $CDCl_3$) 2.53–2.57 (2H, m, SCH_2), 2.84–2.88 (2H, m, $ArSCH_2$), 3.28 (2H, s, $COCH_2S$), 3.63 (2H, s, $ArCH_2S$), 3.76 (2H, s, $ArCH_2S$), 7.03–7.49 (13H, m, ArH), 8.41 (1H, d, ArH) and 9.78 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 30.7, 35.8, 36.1, 36.5 and 37.0 (C-2′, C-3′, C-5′ and $COCH_2SCH_2$), 120.0, 122.2, 124.3, 127.1, 127.4, 128.5, 128.6, 128.7, 129.0, 129.9, 135.5, 136.5, 137.9 and 139.5 (ArC) and 166.8 (CO).

Method 2. A solution of 2-(benzylthio)ethanoic acid **6** (3.85 g, 16.9 mmol) in dry THF (40 mL) was added dropwise, using a cannula, to a solution of 1,1′-carbonyldiimidazole (CDI) (2.92 g, 18.0 mmol) in dry THF (30 mL) under dry N_2. The mixture was stirred for 20 minutes before the dropwise addition of a solution of 2-(5-phenyl-1,4-dithiapentyl)aniline **3** (4.50 g, 16.9 mmol) in THF (40 mL). The mixture was stirred for a further 1.5 h before adding H_2O (30 mL). The THF was removed *in vacuo* and the aqueous residue was extracted with EtOAc (3 × 30 mL); the EtOAc extracts were combined and dried (anhyd. $MgSO_4$). Removal of the solvent *in vacuo*, followed by flash chromatography [elution with EtOAc–hexane (1:9)] afforded *N*-[2-(benzylthio)ethanoyl]-2-(5-phenyl-1,4-dithiapentyl)aniline **8** (4.48 g, 60%).

1,8-Bis(2-aminophenyl)-1,4,5,8-tetrathiaoctane 13a

A solution of bis(2-chloroethyl) disulfide **11**¶ (4.88 g, 25.5 mmol) in MeOH (50 mL) was added dropwise to a stirred solution of 2-aminobenzenethiol (6.39 g, 51.1 mmol) and KOH (2.86 g, 51.1 mmol) in MeOH (100 mL) under N_2. The resulting mixture was boiled under reflux for 2 h; then H_2O (30 mL) was added and the MeOH removed *in vacuo*. The aqueous residue was extracted with $CHCl_3$ and the combined $CHCl_3$ extracts were washed (brine) and dried (anhyd. $MgSO_4$). Evaporation of the $CHCl_3$ *in vacuo* afforded, as a dark yellow oil, *1,8-bis(2-aminophenyl)-1,4,5,8-tetrathiaoctane* **13a** (9.59 g, 100%) [(Found: M^+, 368.0504. $C_{16}H_{20}N_2S_4$ requires *M*, 368.0509); ν_{max}(thin film)/cm^{-1} 3360 (NH); δ_H(60 MHz; $CDCl_3$) 2.70–3.40 (8H, m, SCH_2CH_2S), 4.51 (4H, s, NH_2) and 6.72–7.70 (8H, m, ArH)], which was used without further purification.

1,8-Bis(2-amino-5-methoxyphenyl)-1,4,5,8-tetrathiaoctane 13b

A mixture of 2-amino-6-methoxybenzothiazole[1] (3.80 g, 21.1 mmol) in 50% aqueous KOH (50 mL) was boiled under reflux for 12 h in an atmosphere of dry N_2. The solution was then cooled to room temperature and a solution of bis(2-chloroethyl) disulfide **11** (2.01 g, 10.5 mmol) in MeOH (40 mL) was added with vigorous stirring. The resulting mixture was stirred under N_2 for 3 h and then extracted with $CHCl_3$ (3 × 30 mL). The combined $CHCl_3$ extracts were washed (brine) and dried (anhyd. $MgSO_4$). The $CHCl_3$ was removed *in vacuo* to afford, as a black oil, *1,8-bis(2-amino-5-methoxyphenyl)-1,4,5,8-tetrathiaoctane* **13b** (4.87 g, 100%) [ν_{max}(thin film)/cm^{-1} 3360 (NH); δ_H(400 MHz; $CDCl_3$) 2.73–2.76 (4H, m, CH_2SSCH_2), 2.97–3.01 (4H, m, $ArSCH_2$), 3.71 (6H, s, OCH_3), 4.05 (4H, br s, NH_2), 6.62–6.74 (4H, m, ArH) and 6.94 (2H, d, ArH); δ_C(100 MHz; $CDCl_3$) 33.8 and 38.1 (C-2, C-3, C-6 and C-7), 55.8 (OCH_3) and 116.1, 116.5, 117.4, 120.3, 142.3 and 152.1 (ArC)], which was used without further purification.

1,8-Bis(2-acetamidophenyl)-1,4,5,8-tetrathiaoctane 14a

Conc. H_2SO_4 (19 drops) was added to a solution of 1,8-bis(2-aminophenyl)-1,4,5,8-tetrathiaoctane **13a** (9.59 g, 29.9 mmol) in Ac_2O (190 mL) and the mixture was stirred at room temperature for 30 minutes. The excess Ac_2O was hydrolysed by pouring the solution into warm H_2O (400 mL) and stirring the solution for 30 minutes. (The temperature of this solution was kept below 90 °C by the addition of cold water when necessary.) The aqueous solution was cooled (ice), and the pale pink precipitate was filtered off and recrystallised from EtOH–H_2O to afford, as colourless crystals, *1,8-bis(2-acetamidophenyl)-1,4,5,-8-tetrathiaoctane* **14a** (4.90 g, 40%), mp 125–127 °C (from aqueous EtOH) (Found: C, 52.6; H, 5.4; N, 5.8. $C_{20}H_{24}N_2O_2S_4$ requires C, 53.1; H, 5.35; N, 6.2%); ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1650 (CO); δ_H(400 MHz; $CDCl_3$) 2.22 (6H, s, $COCH_3$), 2.69 (4H, m, CH_2SSCH_2), 3.01 (4H, m, $ArSCH_2$), 7.03 (2H, m, ArH), 7.32 (2H, m, ArH), 7.49 (2H, dd, ArH), 8.37 (2H, d, ArH) and 8.45 (2H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.9 and 35.2 (C-2, C-3, C-6 and C-7), 37.4 (CH_3), 120.5, 121.5, 124.1, 130.2, 135.4 and 140.0 (ArC) and 169.0 (CO).

1,8-Bis(2-acetamido-5-methoxyphenyl)-1,4,5,8-tetrathiaoctane 14b

The experimental procedure employed for the synthesis of 1,8-bis(2-acetamidophenyl)-1,4,5,8-tetrathiaoctane **14a** was followed, using 1,8-bis(2-amino-5-methoxyphenyl)-1,4,5,8-tetrathiaoctane **13b** (2.66 g, 6.71 mmol), Ac_2O (100 mL) and conc. H_2SO_4 (10 drops). The crude precipitate was purified by recrystallising twice from EtOH–H_2O (2:1) to afford *1,6-bis(2-acetamido-5-methoxyphenyl)-1,4,5,8-tetrathiaoctane* **14b** (1.36 g, 40%), mp 131–133 °C (from EtOH–H_2O) (Found: C, 51.2; H, 5.6; N, 5.4; M^+, 512.0918. $C_{22}H_{28}N_2O_4S_4$ requires C, 51.55; H, 5.5; N, 5.5%; *M*, 512.0932); ν_{max}(KBr)/cm^{-1} 3290 (NH) and 1655 (CO); δ_H(400 MHz; $CDCl_3$) 2.20 (6H, s, $COCH_3$), 2.71 (4H, m, CH_2SSCH_2), 3.04 (4H, m, $ArSCH_2$), 3.77 (6H, s, OCH_3), 6.86 (2H, dd, *J* 2.6 and 9.0 Hz, ArH), 7.02 (2H, d, *J* 2.7 Hz, ArH), 8.12 (2H, br s, NH) and 8.18 (2H, d, *J* 9.0 Hz, ArH); δ_C(100 MHz; $CDCl_3$) 24.7 ($CO\mathit{C}H_3$), 34.9 and 37.4 (C-2, C-3, C-6 and C-7), 55.6 (OCH_3), 114.9, 119.8, 122.4, 123.3, 133.0 and 156.0 (ArC) and 168.1 (CO); *m*/*z* 512 (M^+, 18%) and 196 (100).

2′-[(2-Mercaptoethyl)thio]acetanilide 15a

A mixture of 1,8-bis(2-acetamidophenyl)-1,4,5,8-tetrathiaoctane **14a** (0.50 g, 1.2 mmol) and Ph_3P (0.36 g, 1.4 mmol) in aqueous MeOH (1:10; 100 mL) was stirred in an atmosphere of N_2 for 3 h, at 60 °C. H_2O (10 mL) was added and the MeOH was removed *in vacuo*. Benzene (30 mL) and then NaOH pellets (2.0 g) were added to the aqueous residue, and the mixture was stirred vigorously until the NaOH pellets had dissolved. The phases were separated and the aqueous phase was extracted with benzene (40 mL). The aqueous solution was acidified with 16% aq. HCl, extracted with benzene (3 × 30 mL), and the combined benzene extracts were washed (brine) and dried (anhyd. $MgSO_4$). The benzene was evaporated *in vacuo,* and the solid residue was purified by flash chromatography [elution with EtOAc–hexane (3:7)] to afford, as a white solid, *2′-[(2-mercaptoethyl)thio]acetanilide* **15a** (0.33 g, 65%), mp 58.5–59.5 °C (from EtOAc–hexane) (Found: C, 52.7; H, 5.75; N, 6.0; M^+, 227.0421. $C_{10}H_{13}NOS_2$ requires C, 52.85; H, 5.8; N, 6.2%; *M*, 227.0439); ν_{max}(KBr)/cm^{-1} 3295 (NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 1.62 (1H, t, *J* 7.9 Hz, SH), 2.22 (3H, s, $COCH_3$), 2.59–2.65 (2H, m, $C\mathit{H}_2SH$), 2.91–2.95 (2H, m, $ArSCH_2$), 7.02 (1H, t, ArH), 7.32 (1H, t, ArH), 7.49 (1H, d, ArH), 8.38 (1H, d, ArH) and 8.52 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.1 (CH_3), 24.9 and 39.9 (SCH_2CH_2S), 120.3, 124.0, 130.1, 130.8, 135.5 and 139.9 (ArC) and 168.3 (CO); *m*/*z* 227 (M^+, 9.4%) and 125 (100).

2′-[(2-Mercaptoethyl)thio]-4′-methoxyacetanilide 15b

The experimental procedure employed for the synthesis of 2′-[(2-mercaptoethyl)thio]acetanilide **15a** was followed, using 1,8-bis(2-acetamido-5-methoxyphenyl)-1,4,5,8-tetrathiaoctane **14b** (0.35 g, 1.4 mmol) and Ph_3P (0.43 g, 1.6 mmol) in aqueous MeOH (1:10; 140 mL). Purification by flash chromatography [elution with EtOAc–hexane (4:6)] afforded, as pale yellow crystals, *2′-[(2-mercaptoethyl)thio]-4′-methoxyacetanilide* **15b** (0.28 g, 40%), mp 78–79.5 °C (from EtOAc–hexane) (Found: C, 51.0; H, 6.1; N, 5.5; M^+, 257.0528. $C_{11}H_{15}NO_2S_2$ requires C, 51.35; H, 5.9; N, 5.45%; *M*, 257.0544); ν_{max}(KBr)/cm^{-1} 3290

¶ CAUTION! During rotary evaporation to remove water from the reaction mixture containing the bis(2-hydroxyethyl) disulfide precursor **10**, the flask shattered, presumably due to thermal decomposition of residual hydrogen peroxide. In subsequent preparations, excess hydrogen peroxide was reduced with potassium permanganate prior to rotary evaporation.

(NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 1.62 (1H, t, *J* 8.0 Hz, SH), 2.19 (3H, s, $COCH_3$), 2.61–2.66 (2H, m, CH_2SH), 2.93–2.97 (2H, m, $ArSCH_2$), 3.76 (3H, s, OCH_3), 6.86 (1H, dd, *J* 2.8 and 9.0 Hz, ArH), 7.02 (1H, d, *J* 2.7 Hz, ArH) and 8.19–8.21 (2H, m, ArH and NH); δ_C(100 MHz; $CDCl_3$) 24.1 ($CO\mathit{C}H_3$), 24.7 and 39.7 ($SCH_2\mathit{C}H_2S$), 55.5 (OCH_3), 115.0, 120.0, 122.2, 123.1, 133.0 and 155.7 (ArC) and 168.1 (CO); *m*/*z* 257 (M^+, 12.6%) and 155 (100).

N-Ethyl-2-[(2-mercaptoethyl)thio]aniline 16

1,8-Bis(2-acetamidophenyl)-1,4,5,8-tetrathiaoctane **14a** (0.50 g, 1.2 mmol) was added to a slurry of $NaBH_4$ (0.38 g, 9.9 mmol) and $AlCl_3$ (0.63 g, 4.7 mmol) in dry THF (50 mL), and the mixture was stirred overnight, at room temperature, in an atmosphere of dry N_2. The mixture was cooled (<8 °C) and quenched by the cautious, sequential addition of 1 M NaOH (5 mL) and 3 M HCl (20 mL). The THF was removed *in vacuo* and the aqueous residue was extracted with benzene. The benzene extracts were combined, washed (brine) and dried (anhyd. $MgSO_4$), and the benzene was evaporated *in vacuo*. Purification by flash chromatography [elution with EtOAc–hexane (1:9)] afforded two fractions, *viz*., (i) as white crystals, 2′-[(2-mercaptoethyl)thio]acetanilide **15a** (0.12 g, 25%) and (ii) as an oil, *N-ethyl-2-[(2-mercaptoethyl)thio]aniline* **16** (0.14 g, 30%); δ_H(400 MHz; $CDCl_3$) 1.24 (3H, t, $C\mathit{H}_3CH_2$), 1.59 (1H, t, SH), 2.54–2.59 (2H, m, $C\mathit{H}_2SH$), 2.80–2.84 (2H, m, $ArSCH_2$), 3.13 (2H, q, NCH_2), 4.94 (1H, br s, NH), 6.53–6.57 (2H, m, ArH), 7.16 (1H, dt, *J* 1.7 and 8.0 Hz, ArH) and 7.34 (1H, dd, *J* 1.7 and 8.0 Hz, ArH); δ_C(100 MHz; $CDCl_3$) 14.6 (CH_3), 24.4, 38.1 and 38.4 (SCH_2CH_2S, and NCH_2) and 110.0, 115.6, 116.3, 130.4, 136.5 and 149.3 (ArC).

2-[(2-Mercaptoethyl)thio]aniline 17

A mixture of 1,8-bis(2-acetamidophenyl)-1,4,5,8-tetrathiaoctane **14a** (0.50 g, 1.2 mmol) and Ph_3P (0.36 g, 1.4 mmol) in aqueous MeOH (1:10; 0.1 M in $HClO_4$; 100 mL) was boiled under reflux for 3 h in an atmosphere of N_2. The mixture was then cooled; H_2O (10 mL) was added and the MeOH removed *in vacuo*. Benzene (20 mL) and then NaOH pellets (2.0 g) were added to the aqueous residue and the heterogeneous mixture was stirred vigorously for 10 minutes. The phases were separated and the basic aqueous phase was washed with benzene (20 mL) before acidification with 16% HCl. The acidic, aqueous solution was extracted with benzene and the combined benzene extracts were washed (brine) and dried (anhyd. $MgSO_4$), and the benzene was evaporated *in vacuo*. Purification by flash chromatography [elution with EtOAc–hexane (1:9)] afforded two fractions, *viz*., (i) 2′-[(2-mercaptoethyl)thio]acetanilide **15a** (0.14 g, 28%), and (ii) as an oil, *2-[(2-mercaptoethyl)thio]aniline* **17** (0.16 g, 33%); δ_H(400 MHz; $CDCl_3$) 1.68 (1H, t, *J* 7.7 Hz, SH), 2.60–2.68 (2H, m, $C\mathit{H}_2SH$), 2.89–2.93 (2H, m, $ArSCH_2$), 4.30 (2H, br s, NH_2), 6.66–6.71 (2H, m, ArH), 7.10–7.15 (1H, m, ArH) and 7.37 (1H, dd, *J* 1.5 and 7.6 Hz, ArH); δ_C(100 MHz; $CDCl_3$) 24.3 and 38.2 (SCH_2CH_2S), 114.8, 116.0, 118.2, 129.9, 136.1 and 148.3 (ArC).

Bis[(chloroformyl)methyl] disulfide 21

Thionyl chloride (13.3 mL, 0.182 mol) was added dropwise to bis(carboxymethyl) disulfide **20**[27] (6.68 g, 36.7 mmol) with stirring. After the addition, the flask was fitted with a reflux condenser with a $CaCl_2$ drying tube, and the mixture stirred at room temperature for 2 days. Unreacted thionyl chloride was removed *in vacuo* and the remaining oil was distilled *in vacuo* (with difficulty and some decomposition) to afford bis[(chloroformyl)methyl] disulfide **21** (6.75 g, 84%), bp 110 °C/0.02 mmHg [δ_H(400 MHz; $CDCl_3$) 4.07 (4H, s, CH_2); δ_C(100 MHz; $CDCl_3$) 52.0 (SCH_2) and 169.7 (CO)], which was used without further purification.

Polymeric disulfide 22a

A solution of bis[(chloroformyl)methyl] disulfide **21** (2.38 g, 10.9 mmol) in dry THF (50 mL) was added, under N_2, to a stirred solution of 1,8-bis(2-aminophenyl)-1,4,5,8-tetrathiaoctane **13a** (4.00 g, 10.9 mmol) and dry triethylamine (2.42 g, 23.8 mmol) in dry THF (100 mL). After stirring under N_2 for 3 h, the THF was evaporated *in vacuo.* The residue was triturated with H_2O, filtered, and washed with H_2O to afford, as a light brown solid, the polymeric disulfide **22a** (5.71 g, 100%), which was used without further purification.

Polymeric disulfide 22b

The experimental procedure employed for the synthesis of the polymeric disulfide **22a** was followed, using bis[(chloroformyl)-methyl] disulfide **21** (1.24 g, 5.66 mmol), 1,8-bis(2-amino-5-methoxyphenyl)-1,4,5,8-tetrathiaoctane **13b** (2.24 g, 5.65 mmol) and dry triethylamine (1.26 g, 12.5 mmol). The brown solid was washed with H_2O and dried *in vacuo* to afford the polymeric disulfide **22b** (3.71 g, 100%), which was used without further purification.

N-(2-Mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]aniline 23a

A mixture of the polymeric disulfide **22a** (1.00 g, 3.88 mmol) and Ph_3P (1.12 g, 4.27 mmol) in aqueous MeOH (1:10; 150 mL) was stirred for 2 h under N_2. The MeOH was evaporated *in vacuo* and H_2O (15 mL), benzene (30 mL) and NaOH pellets (3.0 g) were added sequentially, and the resulting mixture was stirred for 5 min. The phases were separated, and the aqueous phase was washed with benzene before being acidified with 16% aq. HCl. The acidic aqueous phase was extracted with benzene (3 × 30 mL) and the combined benzene extracts were washed (brine) and dried (anhyd. $MgSO_4$). The benzene was evaporated *in vacuo* and the residue was purified by flash chromatography [elution with EtOAc–hexane (3:7)] to afford *N-(2-mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]aniline* **23a** (0.50 g, 50%), mp 45–46 °C (from EtOAc–hexane) (Found: C, 46.4; H, 5.0; N, 5.4; M^+, 259.0127. $C_{10}H_{13}NOS_3$ requires C, 46.3; H, 5.1; N, 5.4%; *M*, 259.0159); ν_{max}(KBr)/cm^{-1} 3280 (NH) and 1675 (CO); δ_H(400 MHz; $CDCl_3$) 1.65 (1H, t, *J* 8.1 Hz, SH), 2.07 (1H, t, *J* 9.2 Hz, $COCH_2S\mathit{H}$), 2.62–2.68 (2H, m, $C\mathit{H}_2SH$), 2.95–2.99 (2H, m, $ArSCH_2$), 3.46 (2H, d, *J* 9.2 Hz, $COCH_2S$), 7.07 and 7.35 (2H, dt, *J* 1.4 and 7.8 Hz, 4-H and 5-H), 7.53 (1H, dd, *J* 1.4 and 7.8 Hz, 3-H), 8.41 (1H, d, *J* 8.2 Hz, 6-H) and 9.75 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.2, 29.7 and 39.9 (SCH_2CH_2S and $CO\mathit{C}H_2S$), 120.1, 124.5, 130.2 and 135.7 (C-3, C-4, C-5 and C-6), 122.0 and 139.4 (C-1 and C-2) and 167.3 (CO); *m*/*z* 259 (M^+, 4.4%) and 152 (100).

N-(2-Mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]-4-methoxyaniline 23b

Method 1. A solution of the disulfide **29** (0.53 g, 0.68 mmol) and Ph_3P (0.23 g, 0.88 mmol) in acetone (50 mL) and aqueous MeOH (1:10; 100 mL) was boiled under reflux for 3 h in an atmosphere of N_2. The mixture was cooled to room temperature and KOH pellets (2.0 g) and H_2O (10 mL) were added. The mixture was stirred until the KOH pellets had dissolved and the MeOH and acetone were then removed *in vacuo*. The aqueous residue was washed with benzene (2 × 20 mL) and adjusted to pH 6 with 16% aq. HCl before being extracted with benzene (3 × 20 mL). The combined benzene extracts were washed (brine) and dried (anhyd. $MgSO_4$), and the benzene was evaporated *in vacuo* to afford the crude product (0.36 g, 93%), which was purified by flash chromatography [elution with EtOAc–hexane (4:6)] to afford *N-(2-mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]-4-methoxyaniline* **23b**, mp 69–71 °C (from EtOAc–hexane) (Found: C, 45.8; H, 5.2; N, 4.8; M^+, 289.0261. $C_{11}H_{15}NO_2S_3$ requires C, 45.7; H, 5.2; N, 4.8%; *M*, 289.0265); ν_{max}(KBr)/cm^{-1} 3290 (NH), 2560 (SH) and 1655 (CO); δ_H(400

MHz; $CDCl_3$) 1.65 (1H, t, *J* 8.0 Hz, SH), 2.05 (1H, t, *J* 9.2 Hz, $COCH_2SH$), 2.63–2.69 (2H, m, CH_2SH), 2.97–3.01 (2H, m, $ArSCH_2$), 3.44 (2H, d, *J* 9.2 Hz, $COCH_2S$), 3.78 (3H, s, OCH_3), 6.79 (1H, dd, *J* 2.8 and 9.0 Hz, 5-H), 7.05 (1H, d, *J* 2.8 Hz, 3-H), 8.24 (1H, d, *J* 9.0 Hz, 6-H) and 9.45 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.2, 29.5 and 39.6 (SCH_2CH_2S and $COCH_2S$), 55.5 (OCH_3), 115.0, 120.2 and 121.7 (C-3, C-5 and C-6), 123.8, 132.5 and 156.0 (C-1, C-2 and C-4) and 166.9 (CO); *m*/*z* 289 (M^+, 30%) and 182 (100).

Method 2. A solution of the polymeric disulfide **22b** (1.00 g, 3.48 mmol) and Ph_3P (1.00 g, 3.83 mmol) in aqueous MeOH (1:10; 150 mL) and acetone (20 mL) was heated (60 °C) for 2 h under N_2. The mixture was filtered while still hot, and the MeOH and acetone were evaporated from the filtrate *in vacuo*. H_2O (15 mL), benzene (30 mL) and NaOH pellets (3 g) were added sequentially to the aqueous residue, which was vigorously stirred for 5 minutes. The phases were separated and the basic aqueous phase was washed with benzene before acidification with 16% aq. HCl. The acidic, aqueous phase was extracted with benzene and the combined benzene extracts were washed (brine) and dried (anhyd. $MgSO_4$). The benzene was evaporated *in vacuo* to yield crude *N*-(2-mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]-4-methoxyaniline **23b** (0.14 g).

Polymeric disulfide 25

A solution of bis[(chloroformyl)methyl] disulfide **21** (1.75 g, 8.02 mmol) in dry THF (40 mL) was added dropwise, through a cannula, to a mixture of bis(2-amino-5-methoxyphenyl) disulfide **24** (3.18 g, 14.0 mmol) and dry triethylamine (1.78 g, 17.6 mmol) in dry THF (50 mL). The mixture was stirred overnight and the THF was evaporated *in vacuo*. The residual brown solid was triturated with H_2O, filtered, washed with H_2O and dried *in vacuo* to afford the polymeric disulfide **25** (4.08 g).

Lactam 26

A mixture of the polymeric disulfide **25** (1.00 g, 4.40 mmol) and Ph_3P (1.00 g, 3.83 mmol) in aqueous MeOH (1:10) was heated (60 °C) under reflux in an atmosphere of N_2. After cooling, the mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography [elution with EtOAc–hexane (4:6)] to afford, as an orange solid, the lactam **26** (0.28 g, 28%), mp 172–175 °C (from EtOAc–hexane) (Found: M^+ 195.0402. Calc. for $C_9H_9NO_2S$ *M*, 195.0354); ν_{max}(KBr)/cm^{-1} 3180 (NH) and 1675 (CO); δ_H(400 MHz; $CDCl_3$) 3.41 (2H, s, CH_2), 3.77 (3H, s, OCH_3), 6.72 (1H, dd, *J* 2.6 Hz and 8.7 Hz, ArH), 6.81 (1H, d, ArH), 6.84 (1H, d, *J* 2.6 Hz, ArH) and 8.82 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 30.1 (CH_2), 55.7 (OCH_3), 112.6, 113.5, 118.3, 121.2, 130.0 and 155.9 (ArC) and 165.8 (CO); *m*/*z* 195 (M^+, 100%).

Disulfide 29

Method 1. A solution of 2-(benzoylthio)ethanoic acid **27** (1.28 g, 6.52 mmol) in dry THF (40 mL) was added to CDI (1.37 g, 8.48 mmol) under dry N_2. The solution was stirred for 20 minutes before the addition of a solution of 1,8-bis(2-amino-5-methoxyphenyl)-1,4,5,8-tetrathiaoctane **13b** (1.19 g, 3.00 mmol) in dry THF (40 mL). The resulting mixture was stirred for 4 h and then quenched by the addition of H_2O (20 mL). The THF was evaporated *in vacuo* and the aqueous residue was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed (brine) and dried (anhyd. $MgSO_4$) and the $CHCl_3$ was evaporated *in vacuo*. Purification of the residue by flash chromatography [elution with EtOAc–hexane (4:6)] afforded the *disulfide* **29** (0.46 g, 20%), mp 86–87 °C (from EtOAc–hexane) (Found: M^+, 784.0888. $C_{36}H_{36}N_2O_6S_6$ requires *M*, 784.0898); ν_{max}(thin film)/cm^{-1} 3290 (NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 2.56–2.59 (4H, m, CH_2SSCH_2), 2.85–2.88 (4H, m, $ArSCH_2$), 3.75 (6H, s, OCH_3), 3.93 (4H, s, $COCH_2S$), 6.85 (2H, dd, *J* 2.9 and 9.1 Hz, 4-H), 7.00 (2H, d, *J* 2.9 Hz, 6-H), 7.46 (4H, t, ArH), 7.59 (2H, t, ArH), 7.98–8.00 (4H, m, ArH), 8.21 (2H, d, *J* 9.1 Hz, 3-H) and 8.95 (2H, br s, NH); δ_C(100 MHz; $CDCl_3$) 33.7, 34.7 and 37.3 (SCH_2CH_2S and $COCH_2S$), 55.6 (CH_3O), 114.9, 120.1, 122.3, 123.9, 127.5, 128.9, 132.6, 134.2, 135.9 and 156.0 (ArC), 166.0 (CON) and 190.9 (COS).

Method 2. 2-(Benzoylthio)ethanoyl chloride **28**[1] (1.45 g, 6.75 mmol) in dry THF (20 mL) was added dropwise, through a cannula, to a solution of 1,8-bis(2-amino-5-methoxyphenyl)-1,4,5,8-tetrathiaoctane **13b** (1.38 g, 3.22 mmol) and dry triethylamine (0.74 g, 7.3 mmol) in dry THF (40 mL). The mixture was stirred overnight under dry N_2; H_2O (20 mL) was then added and the THF evaporated *in vacuo*. The aqueous residue was extracted with $CHCl_3$ and the combined $CHCl_3$ extracts were washed (brine) and dried (anhyd. $MgSO_4$). Evaporation of the $CHCl_3$ *in vacuo* afforded the crude disulfide **29**, which was shown (by TLC) to comprise one component and, consequently, used without further purification.

Macrocyclic ligand 30a

To a stirred suspension of Cs_2CO_3 (1.11 g, 3.39 mmol) in dry DMF (400 mL) in a 2 L round-bottomed flask [fitted with a reflux condenser, an N_2 line and two burettes (entering the flask through septa)] were added, slowly and simultaneously from the burettes, a solution of *N*-(2-mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]aniline **23a** (0.80 g, 3.1 mmol) in dry DMF (100 mL) and a solution of 1,2-dibromoethane (0.58 g, 3.1 mmol) in dry DMF (100 mL). [The reactants were added dropwise, in portions (15 mL), with delays of 45–60 minutes between each portion.] The temperature of the solution was maintained at 30–60 °C. After the addition was complete, stirring was continued for a further 3 h, and the DMF was then removed *in vacuo*. The residue was taken up in CH_2Cl_2 (80 mL) and H_2O (40 mL). The phases were separated and the CH_2Cl_2 extract was dried (anhyd. $MgSO_4$). Removal of the CH_2Cl_2 *in vacuo* afforded an orange–brown solid (0.83 g), which was purified by flash chromatography [elution with EtOAc–hexane (3:7)] to afford, as pale yellow crystals, the *macrocyclic ligand* **30a** (0.27 g, 31%), mp 158–160 °C (from EtOAc–hexane) (Found: C, 50.9; H, 5.15; N, 5.0; M^+, 285.0331. $C_{12}H_{15}NOS_3$ requires C, 50.5; H, 5.3; N, 4.9%; *M*, 285.0316); ν_{max}(KBr)/cm^{-1} 3240 (NH) and 1640 (CO); δ_H(400 MHz; $CDCl_3$) 2.72–3.01 (8H, 4 × m, 4 × SCH_2), 3.58 (2H, s, $COCH_2S$), 7.08 (1H, dt, *J* 1.2 and 7.6 Hz, ArH), 7.36–7.40 (1H, m, ArH), 7.62 (1H, dd, *J* 7.7 and 1.4 Hz, ArH), 8.56 (1H, d, *J* 8.3 Hz, ArH) and 10.34 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 32.2, 32.7, 33.9, 38.3 and 39.1 (SCH_2CH_2S and $COCH_2S$), 119.6, 124.7, 129.8, 130.7, 137.1 and 140.9 (ArC) and 167.4 (CO); *m*/*z* 285 (M^+, 34%) and 152 (100).

Macrocyclic ligand 30b

The experimental procedure employed for the synthesis of the macrocyclic ligand **30a** was followed, using Cs_2CO_3 (0.743 g, 2.28 mmol) in dry DMF (400 mL), *N*-(2-mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]-4-methoxyaniline **23b** (0.60 g, 2.1 mmol) in dry DMF (100 mL) and 1,2-dibromoethane (0.39 g, 2.1 mmol) in dry DMF (100 mL). Flash chromatography [elution with EtOAc–hexane (3:7)] afforded, as white crystals, the *macrocyclic ligand* **30b** (0.11 g, 17%), mp 157–160 °C (from EtOAc–hexane) (Found: C, 49.6; H, 5.4; N, 4.5; M^+, 315.0417. $C_{13}H_{17}NO_2S_3$ requires C, 49.5; H, 5.4; N, 4.4%; *M*, 315.0421); ν_{max}(KBr)/cm^{-1} 3270 (NH) and 1640 (CO); δ_H(400 MHz; $CDCl_3$) 2.72–3.03 (8H, 4 × m, 4 × CH_2S), 3.55 (2H, s, $COCH_2S$), 3.79 (3H, s, OCH_3), 6.94 (1H, dd, *J* 2.9 and 9.2 Hz, ArH), 7.17 (1H, d, *J* 3.0 Hz, ArH), 8.47 (1H, d, *J* 9.2 Hz, ArH) and 10.12 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 32.2, 32.9, 33.8,

38.2 and 39.0 (SCH_2CH_2S and $COCH_2S$), 55.6 (OCH_3), 116.1, 120.9, 121.7, 123.6, 134.3 and 155.9 (ArC) and 166.9 (CO); *m*/*z* 315 (M^+, 35%) and 57 (100).

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