Supplementary Material for Organic & Biomolecular Chemistry

Synthesis of Nitrogen and Sulfur Macrocycles With *Cis* Exogenous Oxygen and Sulfur Donor Atoms

Vivienne A. White,[a] Nicholas J. Long[*a] and Neil Robertson[*b]

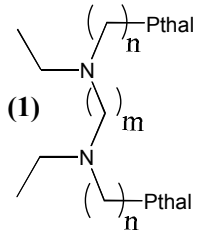
[a]*Department of Chemistry, Imperial College of Science Technology and Medicine, South Kensington, London SW7 2AY, UK. Fax: +44 020 759457804; Tel: +44 020 75945781; E-mail:n.long@imperial.ac.uk*
[b]*School of Chemistry, University of Edinburgh, King's Buildings, Edinburgh EH9 3JJ, UK. Fax: +44 1316504743; Tel: +44 131 6504755; E-mail: neil.robertson@ed.ac.uk*

Supplementary Information

Synthesis and Characterisation of Phthalimide-protected intermediates (1a-c)

The series of diprotected diamines in Table S1 was synthesised via the optimised conditions presented below. Compounds **1a-c** were characterised by both positive ion FAB mass spectrometry and ^{1}H NMR. The molecular ion for each compound is given in the table. Neither the expected fragmentation peaks from loss of phthalimide groups nor peaks corresponding to monoprotected diamine fragments were observed and absence of the latter was indicative of compound purity.

Table S1: Phthalimide protected diamine series

	n value	M value	Molecular ion	Compound label
(1) 	2	2	m/z = 463	**1a**
	2	3	m/z = 477	**1b**
	3	2	m/z = 491	**1c**

1a 1,4-(N-ethyl-phthalimide)-N,N'diethylethanediamine
Sodium carbonate (1.06 g, 10 mmol) and N-(2-bromoethyl)-phthalimide (2.82 g, 11 mmol) were placed together in a Schlenk tube and dry acetonitrile (4 mL) was added. The suspension was stirred and heated to reflux. N,N'-diethylethylenediamine (0.72 mL, 5 mmol) was then added slowly drop-wise followed by dry acetonitrile (0.75 mL). The mixture was allowed to reflux (at 70-80°C) for a further 2-3 days. After cooling, the carbonate and NaBr precipitates were filtered off with addition of dry acetonitrile (10 mL) to wash the precipitate. The filtrate was reduced to a half volume, heated till clear and left to stand under N_2. Any unreacted N-(2-bromoethyl)-phthalimide rapidly formed fine white needle-like crystals that were removed by filtration. The filtrate volume was then further reduced by a third, heated till clear and left to stand under N_2. In the absence of crystallisation at room temperature, the solution was frozen then allowed to thaw slowly to yield 1,4-(N-ethyl-phthalimide)-N,N'diethylethanediamine (1.12 g, 2.41 mmol, 48 %) as a cream coloured microcrystalline powder.

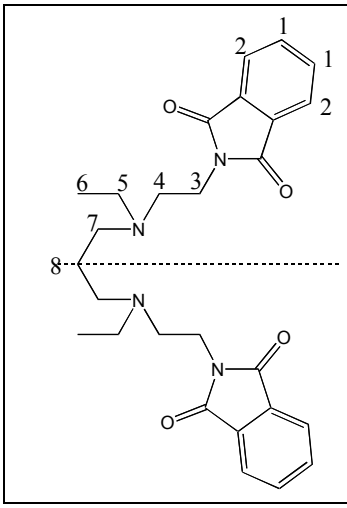
^{1}H NMR δ($CDCl_3$) ppm: 0.89 (t, 6H, CH_2CH_3), 2.46 (s, 4H, NCH_2CH_2N), 2.48 (q, 4H, $NHCH_2CH_3$), 2.64 (t, 4H, NCH_2CH_2phthal), 3.69 (t, 4H, CH_2CH_2phthal), 7.67 & 7.79 (m, 2 x 4H, benz).
($^+$ve FAB) *m/z:* 463 $(M)^+$, 245, 231, 174

1b 1,5-(N-ethyl-phthalimide)-N,N'diethylpropanediamine
Sodium carbonate (1.06 g, 10 mmol), N-(2-bromoethyl)-phthalimide (2.80 g, 11 mmol) and N,N'-diethylpropandiamine (0.8 mL, 5 mmol) were reacted as described for compound **1a**. Slow recrystallisation from dry acetonitrile at room temperature under nitrogen yielded pale yellow rhombic crystals of 1,5-(N-ethyl-phthalimide)-N,N'diethylpropanediamine (1.05 g, 2.2 mmol, 44 %) in 2 crops.
^{1}H NMR δ($CDCl_3$) ppm: 0.90 (t, 6H, NCH_2CH_3), 1.48 (m, 2H, $CH_2CH_2CH_2$), 2.39 (t, 4H, $NCH_2(CH_2)_2N$), 2.48 (q, 4H, $NHCH_2CH_3$) 2.63 (t, 4H, NCH_2CH_2phthal), 3.71 (t, 4H, NCH_2CH_2phthal), 7.68 & 7.81 (m, 2 x 4H, benz).
($^+$ve FAB) *m/z:* 477 $(M)^+$, 231, 174, 131

1c 1,4-(N-propyl-phthalimide)-N,N'diethylethanediamine
Sodium carbonate (1.06 g, 10 mmol), N-(3-bromopropyl)-phthalimide (2.95 g, 11 mmol) and N,N'-diethylethylenediamine (0.72 mL, 5 mmol) were reacted as described for compound **1a**. Slow crystallisation from dry acetonitrile at room temperature under nitrogen yielded pale yellow rhombic crystals of 1,4-(N-propyl-phthalimide)-N,N'diethylethanediamine (1.21 g, 2.47 mmol, 49.5 %).
^{1}H NMR δ($CDCl_3$) ppm: 0.96 (t, 6H, CH_2CH_3), 1.81 (m, 4H, $CH_2CH_2CH_2$), 2.48 (m, 12H, $NHCH_2CH_3$), 3.70 (t, 4H, CH_2CH_2phthal), 7.69 & 7.81 (m, 2 x 4H, benz).
($^+$ve FAB) *m/z:* 491 $(M)^+$, 259, 245

The ^{1}H NMR spectra of the series were simplified by symmetry, as indicated by the dotted line in the structural diagram of compound **1b** in Table S2. The ^{1}H NMR peaks listed in normal typescript in Table S2 were present for all three compounds in the series with only slight shifts in ppm values. For compound **1b** there was a clear distinction between the chemical shifts and multiplicities of its NCH_2 protons in the 2.4-2.7 ppm region, unlike for the C2 bridged species (**1a** and **c**), where the symmetry rendered the C2 bridging protons chemically equivalent, producing a singlet peak that overlapped with the other NCH_2 peaks. The main difference between the ^{1}H NMR spectra of the compounds in the series lay in the presence, position and integration value of the $NCH_2CH_2CH_2N$ peak at ~1.5 ppm (in *italics* in Table S2) – absent in **1a**, with an integral value of 2H for **1b** and 4H for **1c**.

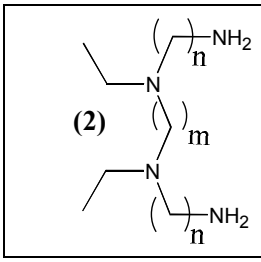
Table S2: ^{1}H NMR assignments for compound 1b

	**δ / ppm**	**multiplicity**	**Integral**	**Assignment**
	0.90	Triplet	6H	6
	1.46	*quintet*	*2H*	*8*
	2.39	Triplet	4H	7
	2.48	Quartet	4H	5
	2.63	Triplet	4H	4
	3.71	Triplet	4H	3
	7.68	Multiplet	4H	1
	7.81	Multiplet	4	2

Compounds **1a-c** were all crystalline in nature although **1a** required cooling to crystallise. Whilst second crops of crystals could often be obtained from the mother liquor, yields decreased for reactions using more than 7.5mmols of diamine starting material.

Synthesis and Characterisation of Deprotected diamine intermediates (2a-c)

Table S3: Tetraamine precursor series

	n value	m value	Molecular ion	Compound label
	2	2	*m/z* = 203	**2a**
	2	3	*m/z* = 217	**2b**
	3	2	*m/z* = 231	**2c**

2a 4,7-diethyl-1,4,7,10-tetraazadecane
Using standard Schlenk techniques throughout, 1,4-(N-ethyl-phthalimide)-N,N'diethylethanediamine (**1a**) (470 mg, 1.01 mmol) was suspended in degassed absolute ethanol (5 mL) and heated to reflux. Hydrazine monohydrate (0.1 mL, 2 mmol) was added drop-wise over 10 minutes as a degassed, 50% ethanolic solution. The mixture was refluxed for a further 3 hours during which the solution rapidly became clear then generated a creamy suspension. Concentrated hydrochloric acid (1.5 mL) was added to the suspension, followed by a further 40 minutes reflux. After cooling and stirring overnight, the volume of ethanol was reduced to ~½ ml on a vacuum line. Degassed distilled water (25 mL) was added and the mixture stirred vigorously for an hour. The aqueous solution was removed by cannular filtration and the filtrate volume reduced to 5-10 mL then basified to pH12 with sodium hydroxide pellets. An oil formed on the surface and was extracted into degassed diethyl ether (3x20 mL) *in situ*. The ethereal fractions were collected by cannular transfer, combined and dried over powdered KOH overnight.

The ethereal product was then collected by cannular filtration into a pre-weighed dry Schlenk tube and reduced to dryness on a vacuum line to yield 4,7-diethyl-1,4,7,10-tetraazadecane (206 mg, 1.03 mmol, 102 %) as an oil. The excess yield was due to absorption of water and carbon dioxide upon accidental exposure to the atmosphere.
^{1}H NMR δ($CDCl_3$) ppm: 0.99 (t, 6H, NCH_2CH_3), 1.58 (br, H_2O), 2.4-2.5 (m, 12H NCH_2CH_2), 2.70 (t, 4H, $NH_2CH_2CH_2$).
($^+$ve FAB) *m/z:* 281 (M^++2H_2O+CO_2), 267 (M^++H_2O+CO_2), 281 (M^++H_2O), 203 $(M)^+$, 172 (M^+-2NH_2), 113/115 (M^+-2$(CH_2)_2$N)).

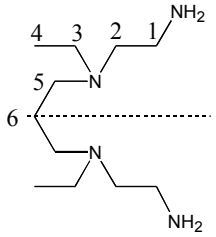
2b 4,8-diethyl-1,4,8,11-tetraazaundecane
1,5-(N-ethyl-phthalimide)-N,N'diethylpropanediamine (**1b**) (480 mg, 1 mmol) was deprotected with hydrazine monohydrate (0.1 mL, 2 mmol) as described for compound **2a** to yield pure 4,8-diethyl-1,4,8,11-tetraazaundecane (204 mg, 0.94 mmol, 94 %) as a carbon dioxide sensitive and deliquescent clear oil.
^{1}H NMR δ($CDCl_3$) ppm: 0.95 (t, 6H, NCH_2CH_3), 1.27 (br, 2H, N*H*), 1.52 (m, 2H, $CH_2CH_2CH_2$), 2.3-2.5 (m, 12H NCH_2CH_2), 2.67 (t, 4H, $NH_2CH_2CH_2$).
($^+$ve FAB) *m/z:* 217 $(M)^+$, 186 (M^+-2NH_2), 133 (M^+-2$(CH_2)_2$N)), 129 (M^+-$NH_2(CH_2)_2NCH_2CH_3$), 101 ($N(CH2)_3NCH_2CH_3$), 71 ($N(CH2)_3N$).

2c 5,8-diethyl-1,5,8,12-tetraazadodecane
1,4-(N-propyl-phthalimide)-N,N'diethylethanediamine (**1c**) (605 mg, 1.25 mmol) was deprotected with hydrazine monohydrate (0.13 mL, 2.6 mmol) as described for compound **2a** to yield pure 4,8-diethyl-1,4,8,11-tetraazaundecane (236 mg, 1.02 mmol, 82 %) as a carbon dioxide sensitive and deliquescent clear oil.
^{1}H NMR δ($CDCl_3$) ppm: 0.93 (t, 6H, NCH_2CH_3), 1.50 (m, 4H, $CH_2CH_2CH_2$), 2.3-2.5 (m, 12H NCH_2CH_2), 2.64 (t, 4H, $NH_2CH_2CH_2$).
($^+$ve FAB) *m/z:* 231 $(M)^+$, 129 (M^+-$NH_2(CH_2)_3NCH_2CH_3$), 115 (M^+-2$(CH_2)_2NH_2$)), 86 ($N(CH2)_2NCH_2CH_3$), 71 ($N(CH2)_3N$).

The molecular ion for each compound is given in Table S3. Fragmentation peaks corresponding to loss of 2NH_2 and 2$(CH_2)_nNH_2$ were observed, i.e. for **2b**: *m/z* = 217 (M^+), 186 (M^+-2NH_2) and 129 (M^+- 2$(CH_2)_2NH_2$). As for compounds **1a-c**, the absence of peaks corresponding to mono-N-substituted diamine fragments was indicative of compound purity.

As for the **1a-c** series, the ^{1}H NMR spectra of the **2a-c** series were simplified by the indicated symmetry (Table S4). The ^{1}H NMR peaks listed in normal typescript in Table S4 were present for all three compounds in the series with only slight shifts in ppm values. The NCH_2 proton peaks in the 2.3-2.5 ppm region generally overlapped too much to allow separate assignments. In an expected reflection of their **1a-c** precursors, the main difference between the ^{1}H NMR spectra of the compounds in the **2a-c** series lay in the presence, position and integration value of the $NCH_2CH_2CH_2N$ peak at ~1.5 ppm (in *italics* in Table S4) – absent in 2**a**, with an integral value of 2H for **2b** and 4H for **2c**.

Table S4: ^{1}H NMR assignments for compound 2b

	**δ / ppm**	**multiplicity**	**integral**	**assignment**
	0.90	triplet	6H	4
	1.27	broad	2H	NH
	1.57	*multiplet*	*2H*	*6*
	2.3-5	multiplet	12H	2,3 and 5
	2.7	triplet	4H	1

Synthesis and Characterisation of 10b,c and 11b,c

10b 2,3-dioxo-7,11-dithia-1,4-diazacyclotridecane and
11b 2,3,15,16-tetraoxo-7,11,20,24-tetrathia-1,4,14,17-tetraazacyclo26ane
Applying standard Schlenk techniques, 1,11-diamino-4,8-dithiaundecane (422 mg, 2.2 mmol) was dissolved in degassed ethanol (120 mL) and placed in an appropriate flask via cannular transfer. Dimethyl oxalate (265 mg, 2.2 mmol) was dissolved in degassed ethanol (120 mL). A pool of stirring degassed ethanol (250 mL) was then heated to reflux prior to the simultaneous drop-wise addition of the two reactant solutions via peristaltic pump at 40rpm (or monitored cannular transfer) until addition was complete. The mixture was allowed to continue refluxing for a further 12 hours then cooled and allowed to stir at 35°C for 48 hours. The ethanol was removed and recycled. The white residue was extracted into hot chloroform and any insoluble polymeric material was filtered off. The chloroform filtrate was evaporated to dryness and partial separation of the products was achieved by column chromatography (silica / ethyl acetate). 7,11-diethyl-2,3-dioxo-1,4,7,11-tetraazacyclo-tridecane (**10b**) was eluted as the second fraction and 2,3,15,16-tetraoxo-7,11,20,24-tetrathia-1,4,14,17-tetraazacyclo26ane (**11b**) as the third fraction. Both co-eluted with a by-product and were creamy white powders upon removal of the solvent (191 mg, ~35 %).
10b (impure) ^{1}H NMR δ($CDCl_3$) ppm: 1.36 (t, by-product), 1.67 (m, 2H, $CH_2CH_2CH_2$), 2.48 (t, 4H, SCH_2CH_2N), 2.84 (t, 4H, $SCH_2CH_2CH_2$), 3.48 (dt, 4H, $C(O)NHCH_2CH_2$), 4.33 (q, by-product), 7.76 (br, 2H, N*H*amide).
(Ammonia CI) *m/z*: 266 $(M+NH_4)^+$, 249 $(M)^+$; ($^+$ve FAB) *m/z:* 663, 249 $(M)^+$.
IR (KBr disk, cm^{-1}): 3402m, 3006w, 2931w, 1699m, 1680s, 1508s, 1457w, 1361w, 1261w, 1098w, 1015w, 846s.
11b: (impure) ^{1}H NMR δ($CDCl_3$) ppm: 1.67, 1.95 (m, 4H, $CH_2CH_2CH_2$), 2.48, 2.68 (t, 8H, SCH_2CH_2N), 2.84, 2.74 (t, 8H, $SCH_2CH_2CH_2$), 3.48, 3.55 (dt, 8H, $C(O)NHCH_2CH_2$), 7.76, 8.45 (br, 2H, N*H*amide).
(Ammonia CI) *m/z* : 266 $(M+NH_4)^+$, 249 $(M)^+$; ($^+$ve FAB) *m/z:* 663, 497 (M(**11b**))$^+$, 395 (M(**10b**)Cs)$^+$, 250 (M(**10b**))$^+$, 144.

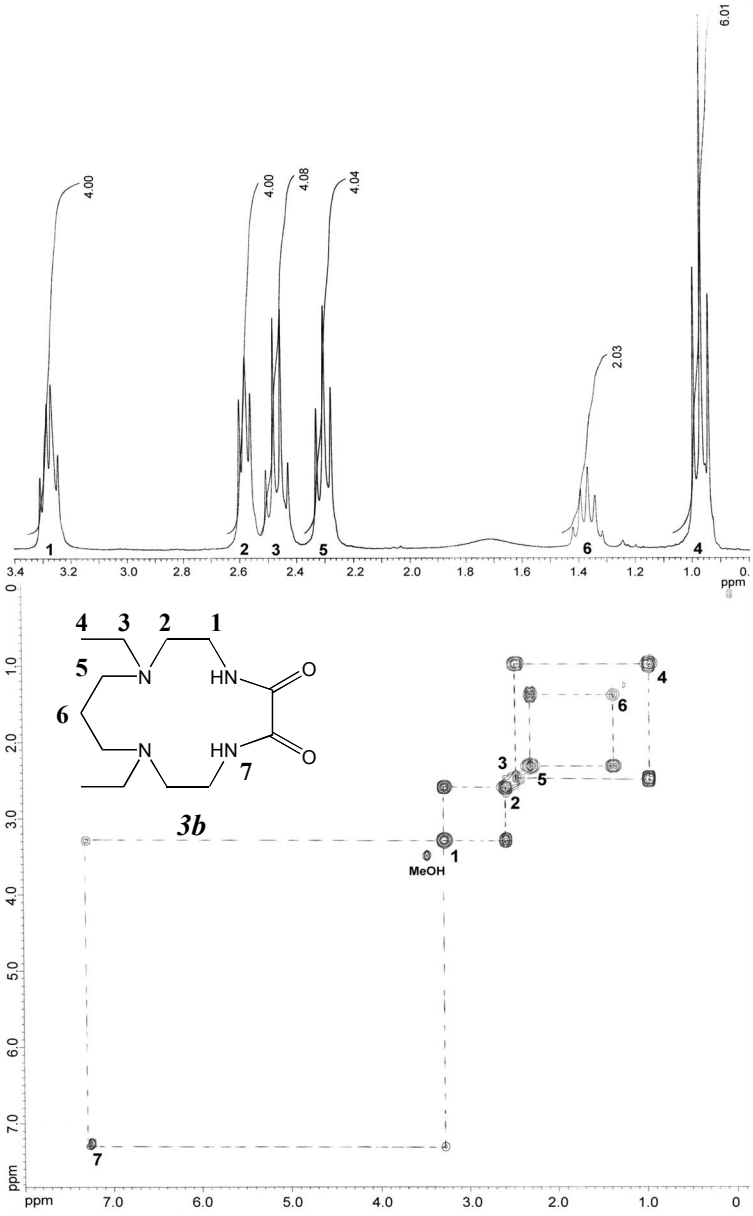
10c 2,3-dioxo-8,11-dithia-1,4-diazacyclotetradecane and

11c 2,3,16,17-tetraoxo-8,11,22,25-tetrathia-1,4,15,18-tetraazacyclo[28]ane
Applying standard Schlenk techniques, 1,12-diamino-5,8-dithiadodecane (250 mg, 1.2mmol) was dissolved in degassed chloroform (100 mL) and placed in a jacketed Schlenk tube via cannular transfer. Oxalyl chloride (0.105 mL, 1.2mmol) was dissolved in water-cooled degassed chloroform (100 mL) in a jacketed Schlenk tube. Caesium carbonate (780 mg, 2.4 mmol) suspended in degassed chloroform (200 mL) was cooled to 0°C in an ice bath prior to the simultaneous drop-wise addition with stirring of the two reactant solutions via monitored cannular transfer (teflon tubing) over 5½ hours until addition was complete. The mixture was then allowed to gradually return to room temperature and stirred at room temperature overnight. The caesium salts precipitated were filtered off and the filtrate washed with distilled water (3 x 50 mL) and brine (50 mL). The chloroform phase was then dried over anhydrous magnesium sulphate, filtered and the solvent removed. Separation by column chromatography (silica / ethyl acetate) co-eluted 2,3-dioxo-8,11-dithia-1,4-diazacyclotetradecane and a by-product at rf 0.65 (186 mg, ~59 %).
^{1}H NMR δ($CDCl_3$) ppm: 1.36 (t, by-product), 1.86 (m, 4H, $CH_2CH_2CH_2$), 2.58 (t, 4H, SCH_2CH_2), 2.71 (s, 4H, SCH_2CH_2S), 3.45 (dt, 4H, $C(O)NHCH_2CH_2$), 4.33 (q, by-product), 7.36 (br, 2H, N*H*amide).
($^{+}$ve FAB) *m/z:* 409 (by product), 395 $(MCs)^{+}$, 158 (by product)
IR (KBr disk, cm^{-1}): 3415m, 3014m, 2942w, 1733m, 1702s, 1529m, 1446w, 1373w, 1306m, 1274m, 1209s, 1096w, 1014w, 872m.

Supplementary Material for Organic & Biomolecular Chemistry

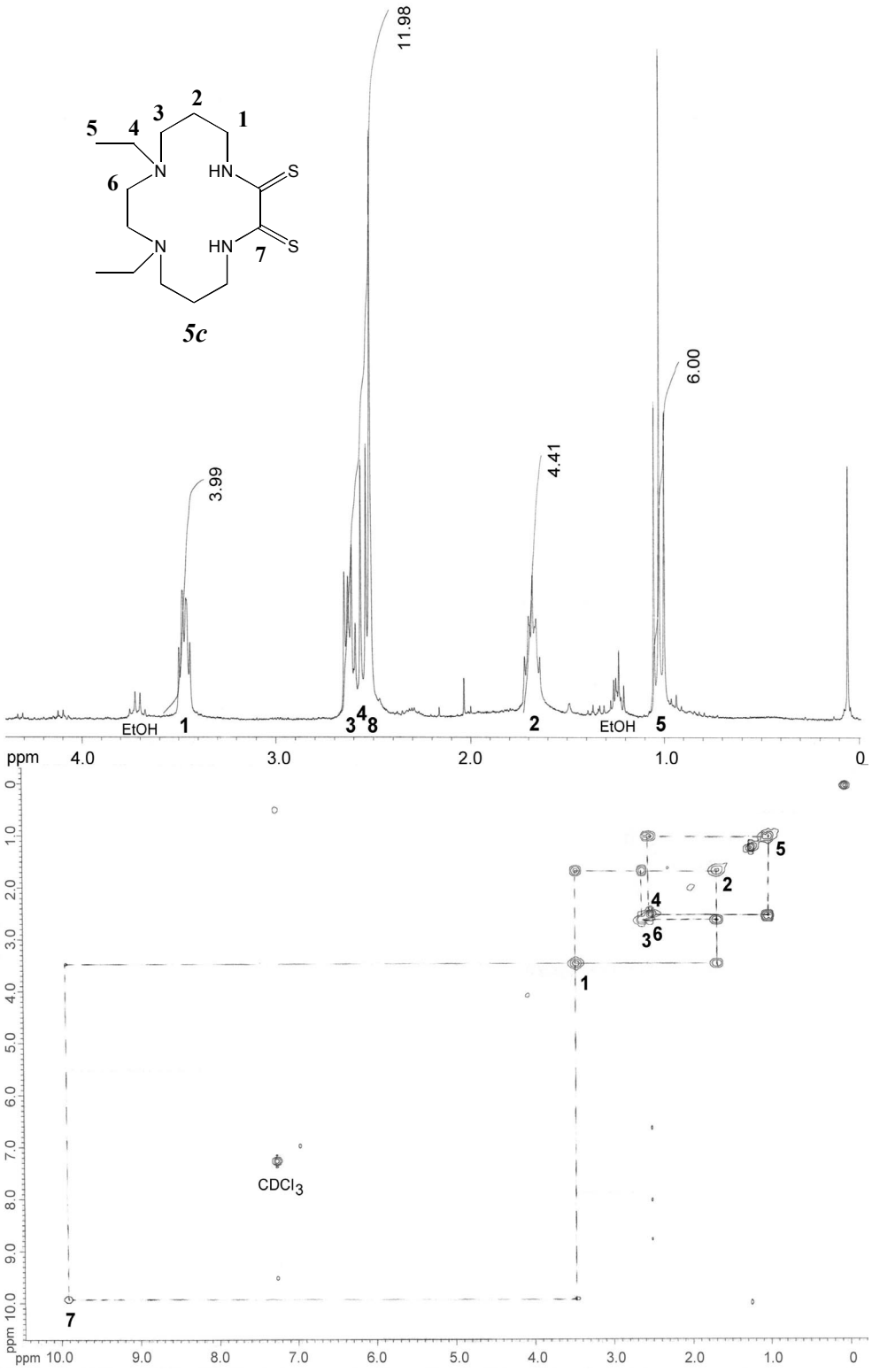
Further NMR Characterisation of Macrocycles:

^{1}H NMR and COSY NMR of **3b**



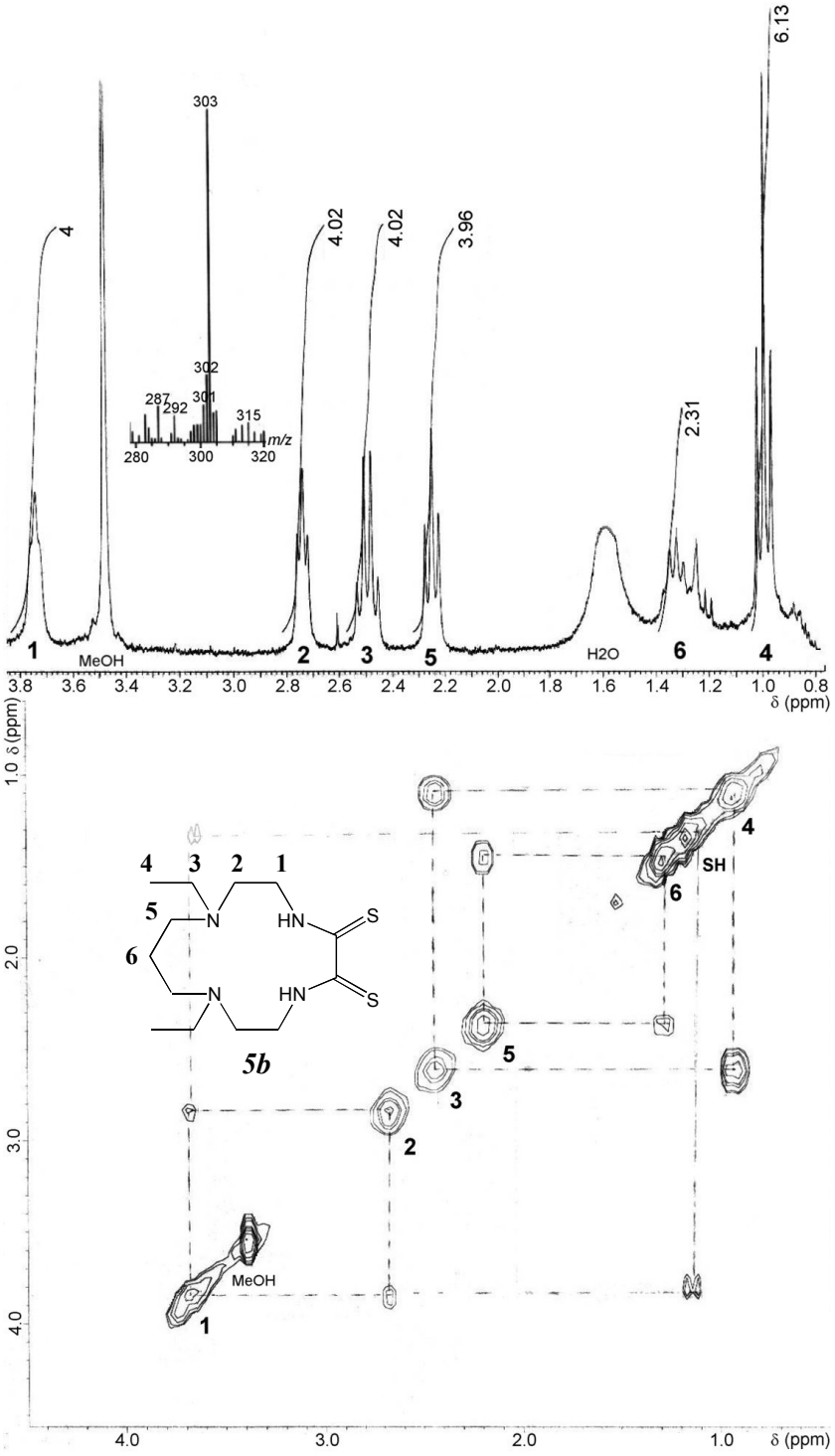
Supplementary Material for Organic & Biomolecular Chemistry

^{1}H NMR and COSY NMR of macrocycle **5c**



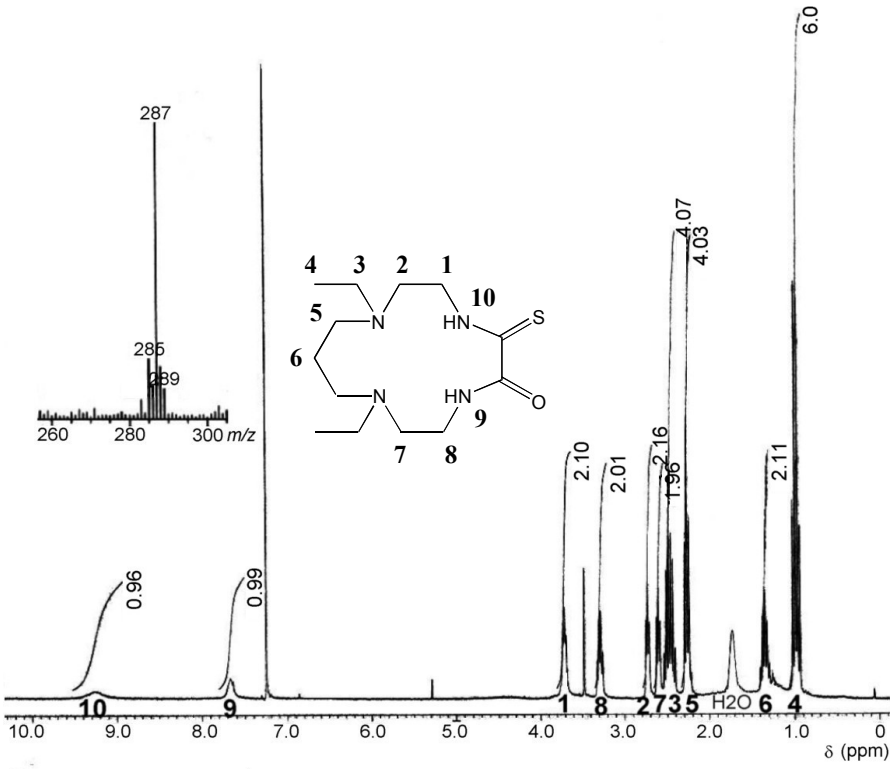
5c

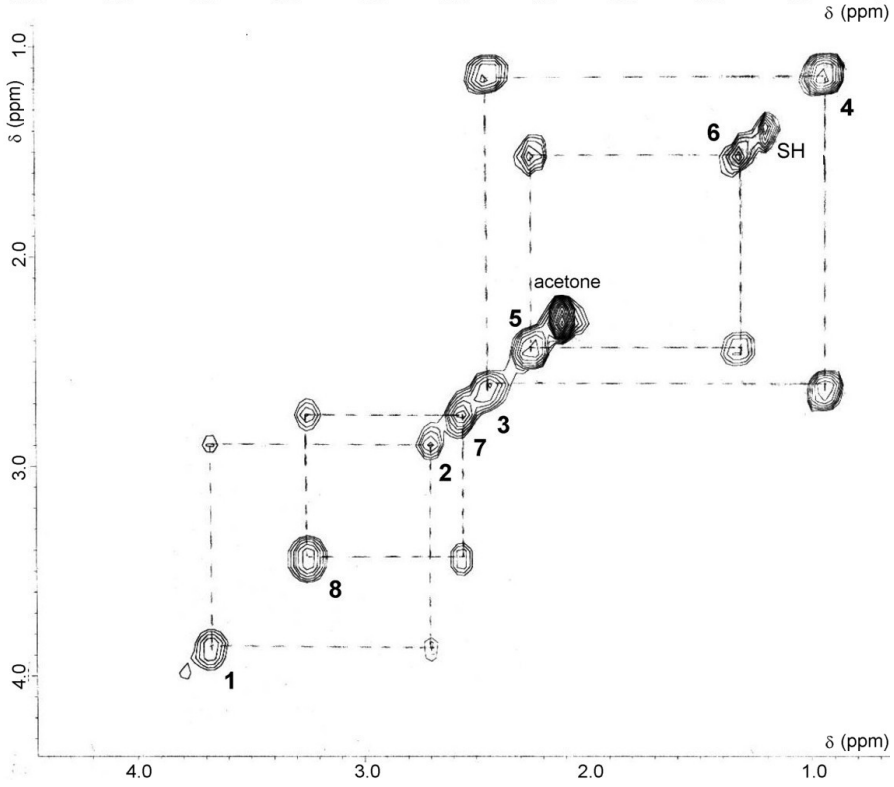
^{1}H NMR and COSY NMR of macrocycle **5b**



Supplementary Material for Organic & Biomolecular Chemistry

^{1}H NMR and COSY NMR of macrocycle **7b**





^{1}H NMR and COSY NMR of macrocycle **10c** (SP= side product)