FULL PAPER

Dalton
www.rsc.org/dalton

Synthesis of C_2-symmetric aza- and azaoxa-macrocyclic ligands derived from (1*R*,2*R*)-1,2-diaminocyclohexane and their applications in catalysis †

Sonia Pulacchini,[a] Kevin F. Sibbons,[a] Kirtida Shastri,[a] Majid Motevalli,[a] Michael Watkinson,*[a] Hayley Wan,[b] Andrew Whiting[b] and Andrew P. Lightfoot[c]

[a] *Department of Chemistry, Queen Mary, University of London, Mile End Road, London, UK E1 4NS. E-mail: m.watkinson@qmul.ac.uk*

[b] *Chemistry Department, University of Durham, Science Laboratories, South Road, Durham, UK DH1 3LE. E-mail: andy.whiting@durham.ac.uk*

[c] *GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, UK CM19 5AW*

Received 21st October 2002, Accepted 7th January 2003
First published as an Advance Article on the web 23rd April 2003

Investigations have been undertaken into the synthesis of chiral derivatives of 1,4,7-triazacyclononane and 1,7-diaza-4-oxacyclononane that incorporate the C_2-symmetric (*R*,*R*)-1,2-diaminocyclohexane backbone. The target ligands **17a** and **17b** have been prepared as their hydrochloride salts, the latter of which has been characterized by single crystal X-ray diffraction revealing an extensively hydrogen bonded polymeric network in the solid state. These investigations have shown that the formation of the fused bicyclic system in these ligands *via* standard Richman–Atkins macrocyclisation conditions is extremely difficult, particularly for the intermediate **16a**, when three tosyl amide nitrogen atoms must be accommodated in the macrocyclic ring. In addition to these target ligands the unexpected piperazine **15** as well as the novel binucleating ligand **19** have also been prepared. Preliminary investigation into the coordination chemistry of **17b** resulted in the formation of the copper(II) complex [Cu(**17b**)Cl_2] in which the copper centre exists in the expected square-pyramidal geometry with the two chloride ions and the nitrogen donors occupying the equatorial positions and with the oxygen donor apically situated. The complex has been screened for activity and found to be a potent catalyst for two hetero-Diels–Alder reactions. The first aza-Diels–Alder reaction of imine **20** with Danishefsky's diene **21** proceeds to yield the cycloadduct **22** in 94% yield. The second nitroso-Diels–Alder reaction relies on the *in situ* oxidation of hydroxylamine **23** to dienophile **24**, catalysed by the complex in the presence of *tert*-butyl hydroperoxide, which is then trapped as cycloadduct **25** by cyclohexadiene in 69% yield.

Introduction

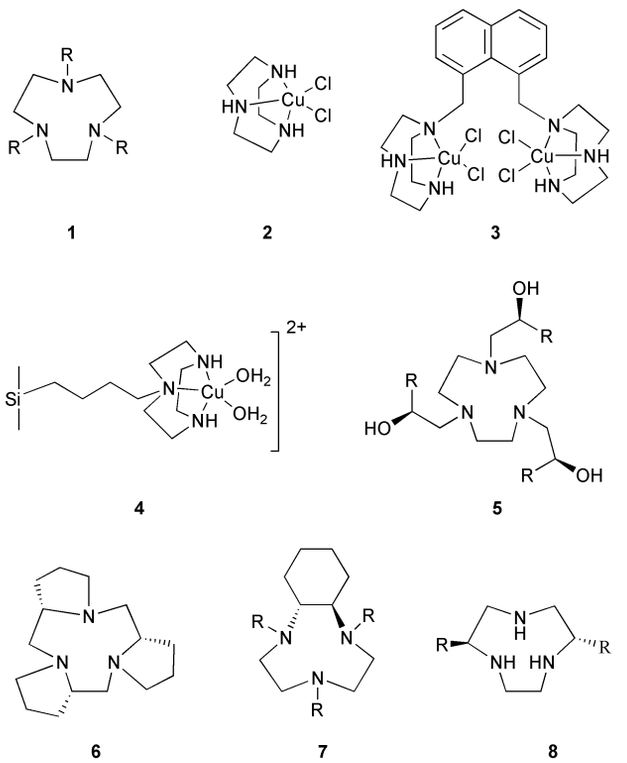
The azamacrocyclic ligand 1,4,7-triazacyclononane or TACN, **1** (R = H), has attracted considerable interest in recent years for its applications in oxidative catalysis. One of its most famous, and also notorious, applications was the Accelerator™ catalyst marketed by Unilever in the early nineties as a low-temperature bleaching additive for washing powders.[1] Excellent bleaching properties were observed, but were unfortunately associated with unwanted fabric damage following prolonged washing cycles. Despite this negative outcome, the potential of this powerful oxidant was soon demonstrated in a synthetic context and examples of the use of manganese complexes, principally of **1** (R = Me), soon appeared. A wide range of substrates has been shown to be effectively oxidised, principally using the environmentally benign oxidant hydrogen peroxide, including benzylic alcohols,[2] sulfides,[3] phenols[4] and even hydrocarbons.[5] Potentially of greatest synthetic utility and interest are the reports of the efficient epoxidation, and most recently *cis*-dihydroxylation, of a range of alkenes.[6] Within this class of oxidative processes the nature of the active species has received considerable attention.[7] Whilst much evidence has been presented to support a binuclear active catalytic species, there are examples of mononuclear solid supported analogues that show activity as oxidative catalysts.[8]

In addition to this impressive array of activity in oxidative catalysis, complexes of **1** (R = H) have also shown considerable efficacy as mimics of hydrolytic enzymes. This activity has principally centred on the copper(II) complex **2**[9] and closely related analogues like **3**.[10] These have been shown to facilitate the hydrolytic cleavage of a range of both activated phosphate esters as well as the kinetically stable phosphate ester systems like RNA and DNA; the key knowledge here being that as for the oxidative manganese systems, it is apparent that the active catalysts can be either mononuclear or binuclear depending on the substrate. This is exemplified by a comparison between two closely related analogues. The solid supported mononuclear analogue **4**,[11] shows activity in the hydrolytic cleavage of bis-(4-nitrophenyl)phosphate. In contrast, the binuclear analogue **3** shows a 300–500 fold enhancement per metal centre in the hydrolytic cleavage of RNA[10] over its mononuclear analogue.

In view of this array of catalytic activity, in particular the recent interest in efficient catalysts for the formation of enantiomerically pure epoxides, it is perhaps a little surprising that examples of chiral analogues of **1** are so limited. Chirality was incorporated into the ligand system through the alkylation of the secondary amine nitrogen atoms in **1** (R = H) to generate the C_3-symmetric analogue **5** (R = Me or Pr^i).[12] Complexes prepared *in situ* using manganese(II) acetate were shown to catalyse the asymmetric epoxidation of a range of olefins with hydrogen peroxide; the highest levels of asymmetric induction were observed for the benchmark *cis*-β-methylstyrene which led to the production of the (1*R*, 2*R*)-*trans*-epoxide with 55% *ee*. At the outset of our investigations, examples of triazacyclononanes with a single stereocentre in the macrocyclic ring were known,[13] however, examples in which the desirable C_2-symmetry element were included were much more limited.[14] Since the start of these investigations Bolm has also reported the application of a second class of C_3-symmetric derivative of **1** in which the chirality was incorporated into the macrocyclic framework by reduction of a tricylic peptide derived from

† Based on the presentation given at Dalton Discussion No. 5, 10–12th April 2003, Noordwijkerhout, The Netherlands.

DOI: 10.1039/b210285d



L-proline, **6**.[15] Although conversions and enantiomeric excesses were moderate the potential of these systems in catalysis was clearly demonstrated.

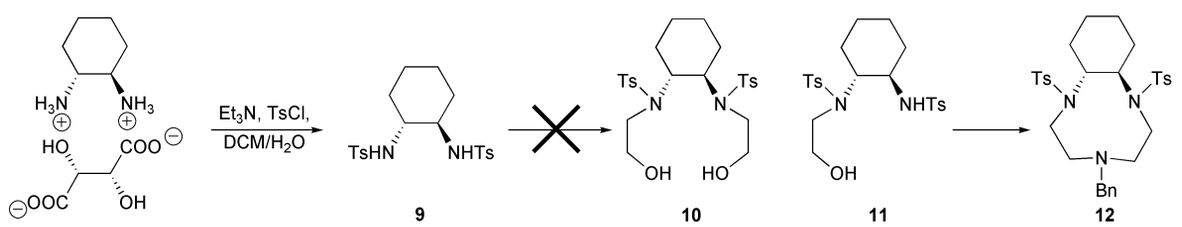
Our interest in this area was therefore initiated by the interesting catalytic properties and the lack of chiral analogues available that might provide extremely efficient asymmetric catalysts. In addition our thoughts and efforts were focussed by the indeterminate nature of the catalytically active species for the manganese systems, as well as on the requirement for both mononuclear and binuclear analogues in the hydrolytic systems. Our initial investigations centred on the synthesis of the previously reported macrocyclic ligand **7**,[14] whose synthesis had appeared in the patent literature. In addition we,[16] and others,[13,17] have recently reported an alternative approach that utilises chiral pool amino acids to generate C_2-symmetric analogues like **8**. Although a report of the synthesis of **7** appeared shortly after we began these investigations,[18] it has still proven to be surprisingly challenging to prepare. Herein we summarise the recent advances that we have made and speculate as to future applications.

Results and discussion

The incorporation of the 1,2-diaminocyclohexane moiety into a 1,4,7-triazacyclononane macrocyclic ligand was particularly appealing to us, as it is an inexpensive starting material and both enantiomers are readily available. Moreover, this chiral framework has been included in a number of ligands that have been successfully applied in a range of asymmetric catalytic processes, most notably by Jacobsen and co-workers in metallosalen complexes.[19] Although there are now two reports of the synthesis of **7**,[14,18] we were keen to exploit our recently reported procedure for the synthesis of unsymmetrically substituted 1,4,7-triazacyclononanes in the synthesis of derivatives of **7**[20] in view of the possible utility of binuclear catalysts (*vide supra*). The synthesis of **12** was therefore attempted employing this efficient cyclisation protocol (Scheme 1). This strategy was essential as statistical deprotection/reprotection strategies that have been previously employed for achiral variants *viz.* **1** would be of little utility for **7**.

The planned synthesis of the macrocyclic ligand **12** required enantiomerically pure (*R*,*R*)-1,2-diaminocyclohexane. Although a number of procedures have been reported for the resolution of this diamine,[21] the extraction of the free amine following neutralisation of the diastereomeric tartrate salt always proved relatively inefficient in our hands. We therefore wondered whether it might be possible to effect direct functionalisation of the chiral substrate through the *in situ* decomposition of the monotartrate salt in the presence of *p*-toluenesulfonyl chloride. The monotartrate salt of the diamine was thus dissolved in the minimum amount of water and a large excess of triethylamine. A solution of *p*-toluenesulfonyl chloride in dichloromethane was then added to the aqueous solution and this biphasic mixture stirred vigorously for a few hours (Scheme 1). Evaporation of the solvents, trituration with dilute hydrochloric acid followed by recrystallisation of the crude material gave **9** in 99% yield.

The main problem encountered in the synthetic pathway depicted in Scheme 1 was unexpected as we were unable to effect the desired alkylation of the sulfonamide **9**, despite a range of experimental conditions being investigated (Table 1).



Scheme 1 Attempted alkylation of (1*R*,2*R*)-1,2-diaminocyclohexane.

Table 1 Experimental conditions employed for the attempted alkylation of **9**

Entry	Base	Electrophile	Solvent	*T*/°C	*t*/h	Yield (%)
1	K_2CO_3	2-chloroethanol	MeCN	reflux	12	0
2	K_2CO_3	2-chloroethanol	DMF	100	72	traces[a]
3	NaOH	2-chloroethanol	CH_2Cl_2/H_2O	20	12	0
4	KOH	ethylene carbonate	–	180	48	0[b]
5	K_2CO_3	ethylene carbonate	DMF	reflux	36	mixture[c]
6	Cs_2CO_3	ethylene oxide	EtOH	20	6	0
7	K_2CO_3	ethylene oxide	EtOH	20	6	0
8	K_2CO_3	ethylene oxide	EtOH	20	6	0[d]

[a] The reaction was carried out in a sealed tube. [b] The substrate and the electrophile were fused together following a reported procedure.[23] [c] The crude product was purified by column chromatography. An inseparable mixture of mono- and di-substituted products was isolated. [d] The reaction was carried out in the presence of montmorillonite K10.[24]

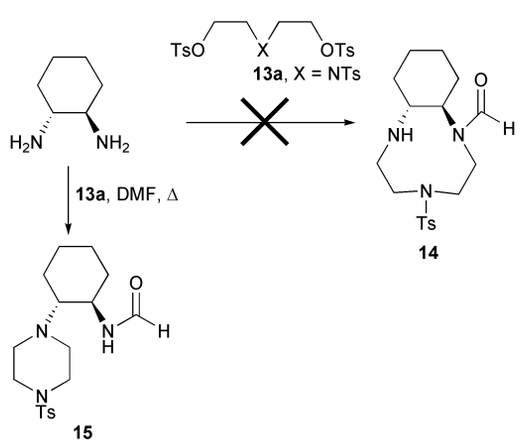
Table 2 Experimental conditions employed for the attempted alkylation of (*R*,*R*)-1,2-diaminocyclohexane

Entry	Base	Electrophile	Solvent	*T*/°C	Yield (%)
1	K_2CO_3	ethylene carbonate	DMF	100	0
2	NaOH	2-chloroethanol	H_2O	20	0
3	–	ethylene oxide	THF	20	0[a]

[a] The yield remained 0 when the reaction was carried out in the presence of montmorillonite K10.[24]

In most cases only starting materials were recovered, although in one case (Table 1, entry 5) an inseparable mixture of di- **10** and mono-alkylated **11** products could be recovered in low yield. Unfortunately the complex reaction mixture proved impossible to separate by column chromatography, although it was possible to identify **10** and **11** with reasonable confidence by ^{1}H NMR and mass spectrometry (FAB HRMS: **10** [M + Na]$^+$ found 533.1739. $C_{24}H_{34}N_2O_6S_2Na^+$ requires 533.1756; **11** [M + Na]$^+$ found 489.1505. $C_{22}H_{30}N_2O_5S_2Na^+$ requires 489.1494). The reasons for our failure to alkylate **9** under these standard conditions[22–24] were unclear, especially in the light of a related report in which it has been alkylated in moderate yield with 3-bromopropan-1-ol.[22] We thus decided to investigate the alkylation of the free diamine directly under similar conditions. To our surprise and disappointment, no reaction occurred and in all cases only the starting diamine could be recovered (Table 2). Even an adaptation of a very efficient procedure that has been reported for the alkylation of achiral derivatives, in which the diamine and 2-chloroethanol were reacted in an aqueous solution of sodium hydroxide (Table 2, entry 2) failed.[25] Disappointing results were also obtained when ethylene oxide was employed as the alkylating agent (Table 2, entry 3).

Despite these unsuccessful results we decided to investigate the reactivity of other electrophiles with the diamine. In view of the sterically restricted nature of tosylamide **9**, we attempted to achieve a direct macrocyclisation reaction by reacting the free diamine with **13a** (Scheme 2). It initially appeared from the ^{1}H- and ^{13}C-NMR spectra of the major product from the complex crude reaction mixture (24% yield) that the desired macrocycle had been formed, with the exception that one amino group had reacted with the solvent DMF to form an amide derivative; a reaction that has precedent.[26] Therefore macrocycle **14** was anticipated and its formation was supported by mass spectrometry (see Experimental section). Crystals suitable for X-ray diffraction were obtained by slow evaporation of an ethanolic solution and the crystal structure revealed that piperazine **15** had in fact formed, Fig. 1.



Scheme 2 Attempt to form the target macrocycle directly from (1*R*,2*R*)-1,2-diaminocyclohexane.

The crystal structure reveals that both six-membered rings in **15** have ideal chair conformations and standard C–C and C–N bond distances are observed. The N(1)–S(1) bonds length of 1.617(11) Å reflects a degree of double bond character of the

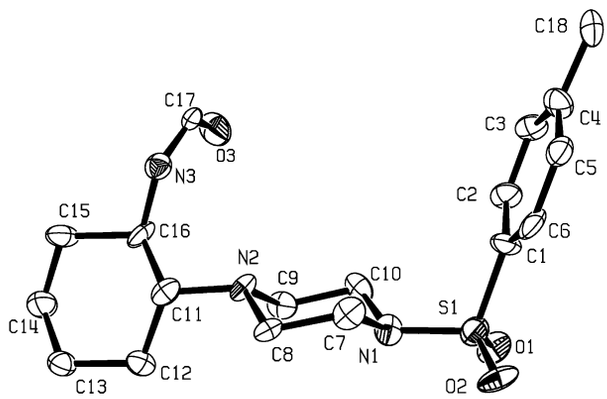


Fig. 1 ORTEP representation of the asymmetric unit of **15**. Hydrogen atoms have been omitted for clarity.

N–S bond, which is further corroborated by the inequivalent S–O bond lengths of 1.428(9) and 1.465(8) Å in the sulfonyl group. This behaviour is consistent with other related piperazines.[16a] It is interesting to note that the distances between N(2)–C(8) and N(2)–C(9) are almost identical [1.453(15) and 1.455(14) Å, respectively] whereas the bond lengths N(1)–C(7) and N(1)–C(10) show considerable asymmetry [1.520(15) and 1.455(14) Å, respectively]. This elongation for the N(1)–C(7) distance is probably due to the steric effect of the bulky tosyl group on the nitrogen atom. A significant shortening of the N(3)–C(17) bond is also observed (1.344(17) Å) reflecting a degree of delocalisation of the lone pair of N(3) into the amide bond.

Although **15** behaves as a 1 : 3 mixture of two conformers in solution at room temperature due to the restricted rotation about the N(3)–C(17) amide bond (see Experimental section), only one conformer is present in the unit cell. The reason for this appears to lie in the intricate polymeric hydrogen bonding network that forms in the unit cell as a result of interactions between the hydrogen atoms attached to the nitrogen of the amido group N(3) and the oxygen atom O(3a) of an amido group in a neighbouring molecule (Fig. 2).

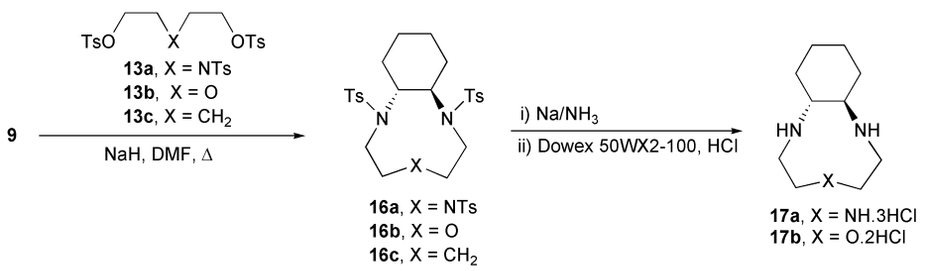
Despite being disappointed by the isolation of **15** in low yield we were nonetheless encouraged that we had been able to effect any alkylation! The previously reported syntheses of **7** (R = H)[14,18] were therefore investigated, *via* **16a**, as well as the synthesis of the mixed hetero-donor macrocyclic analogue **16b** (Scheme 3). We initially attempted to reproduce the results that had been reported for the synthesis of **7**. Unfortunately our meticulous repetition of both procedures on several occasions never resulted in the intermediate to the target macrocycle **16a**, being isolated in yields greater than 23% and 20% respectively (Table 3, entries 1 and 2).

As the only other materials that could be identified in the crude reaction mixture were the starting materials **9** and **13**, a thorough investigation was undertaken in order to optimise the yield of the cyclisation reaction (Table 3).

The previously reported procedures were not improved on by the use of potassium *tert*-butoxide as a base (Table 3, entry 3) or by the use of stronger bases like lithium diisopropylamide (LDA) and ^{n}BuLi (Table 3, entries 4 and 5), apparently due to the insolubility of the lithium salts of **9** in THF, and starting

Table 3 Experimental conditions examined for the synthesis of **16a**

Entry	Base	Solvent	*T*/°C	*t*/h	Conc./ M	Yield (%)
1	MeONa	MeOH/DMF	100	12	0.237	23[14]
2	K_2CO_3	DMF	50	168	0.048	20[18]
3	^{t}BuOK	DMF	140	72	0.079	14
4	LDA	THF	reflux	12	0.059	0
5	^{n}BuLi	THF	reflux	12	0.059	21
6	NaH	THF	reflux	12	0.053	0
7	NaH	DMF	100	12	0.148	46



Scheme 3 Formation of the target macrocyclic ligands.

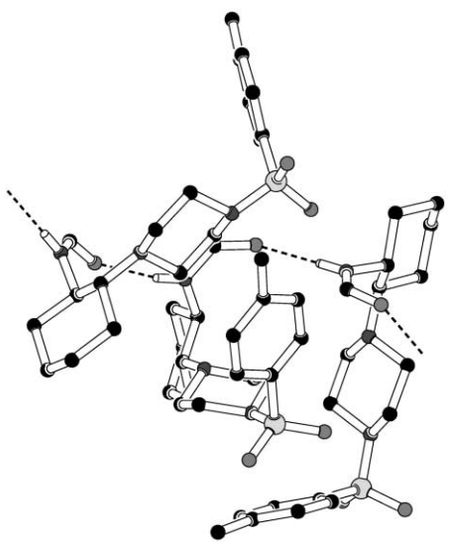


Fig. 2 The polymeric hydrogen bonding array in **15**. Hydrogen bond length with e.s.d.s (Å) N(3)–H ··· O(3a) 2.830(14). Symmetry transformations used to generate equivalent atoms: #1 $-y + 1$, $x + 1$, $z + 1/4$.

materials were recovered. The most effective base proved to be sodium hydride, however, the outcome of the reaction proved to be extremely sensitive to the solvent, the temperature and the concentration of the reaction mixture. The choice of solvent proved to be essential with moderate yields of **16a** only being obtained in DMF, in which the sodium salt of **9** is fairly soluble. In spite of this the desired product **16a** could only be isolated at best in 46% yield (Table 3, entry 7). A slight increase in the concentration to 0.158 M resulted in the yield dropping, presumably as a consequence of the reduced solubility of the disodium salt. Similarly a reduction in concentration to 0.118 M also resulted in a lower yield of the desired product.

The effect of the temperature was also investigated. Although it is clear that this parameter must be carefully controlled, it is apparent that concentration has a more significant effect than temperature. In addition to these parameters the work-up procedure also has a significant impact on the isolated yield of **16a**. Optimum yields (entry 7) were obtained by triturating the crude reaction mixture with boiling ethanol (after the removal of solvent DMF) and sparingly soluble **16a** could be easily isolated by filtration. In contrast extraction of the crude reaction product into dichloromethane followed by washing of the organic phase with dilute hydrochloric acid resulted in a dramatrically lower yield. The former convenient work-up procedure was therefore always adopted. We were both disappointed and a little puzzled by this result, in particular the presence of an unexpected signal in the ^{1}H NMR of **16a** between 4.71 and 4.92 ppm. Therefore the synthesis of the related azaoxamacrocyclic ligand, **16b**, was investigated and a detailed NMR and molecular modelling study of both **16a** and **16b** undertaken which will be reported elsewhere.[27]

We first decided to investigate whether the low yield in the cyclisation step resulted from electrophile **13a** being too sterically demanding. The cyclisation reaction using **13b** as the electrophile was thus investigated. As for **16a** a range of reaction conditions was investigated and the optimisation of these led to the isolation of **16b** in 62% yield. To the best of our knowledge this represents the first report of this ligand. We believe that the lower yield obtained for **16a** is likely to be due to the difficulties associated with the formation of the fused bicyclic framework incorporating three nearly planar *N*-sulfonyl groups.[27] When **13b** is employed the intramolecular cyclisation can occur more effectively because the backbone of the electrophile is more flexible due to the sp^3 hybridised heteroatom in the centre of its structure. The sodium cation might also act as a more effective template for cyclisation as a result of the presence of the harder oxygen donor.

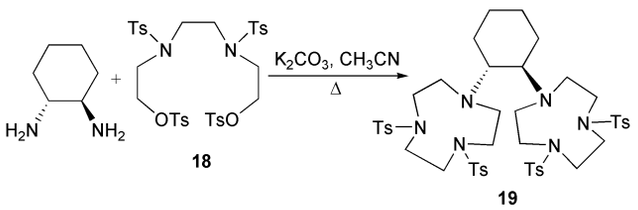
To establish whether such a templating effect was occurring, a related cyclisation reaction was briefly investigated using **13c** as the electrophile. In this case the framework of the macrocycle would be similar to **16b** inasmuch as only sp^3 atoms would be present in the nine-membered ring. Performing the cyclisation reaction under the optimised conditions for **16a** and **16b**, resulted in the desired macrocycle **16c** only being recovered in 7% yield. The unsatisfactory yield of this cyclic product thus supports the templating role of the sodium cation in the formation of **16b**.

Deprotection of the macrocyclic compounds **16a** and **16b** using classical deprotection methodologies[14,18,28] were examined. The most effective method proved to be dissolving metal reduction of sodium in liquid ammonia for both ligands, although the work-up proved problematical. In both cases our attempts to isolate the free amines were low yielding and it proved more convenient to recover their hydrochloride salts by ion exchange chromatography on Dowex 50WX2-100 giving the desired products **17a**·3HCl and **17b**·2HCl in 70% and 82% yield respectively.

Slow evaporation of an aqueous solution of **17b**·2HCl resulted in the formation of crystals suitable for single crystal

diffraction. These revealed the expected structure for the macrocyclic ligand in which the six-membered ring adopts a perfect chair conformation, Fig. 3, and the asymmetric unit is completed by the two chloride ions and a water molecule in which all C–C, C–O and C–N bonds are unexceptional. Two short hydrogen bonding interactions of 2.724(4) Å between N(1)–H(01) ··· O(1) and 2.884(5) between N(2)–H(05) ··· O(1) within the macrocycle are then supplemented by an extensive hydrogen bonding network between the ammonium nitrogen atoms N(1) and N(2) the two chloride ions Cl(1) and Cl(2), as well as the water molecule of crystallisation, as shown in Fig. 4. The roles of the two chloride ions in the network are distinct with Cl(1) acting as a direct bridge between two macrocyclic moieties as well as linking to a third *via* a water molecule of crystallisation. The second chloride ion, in contrast, appears to essentially serve to template the macrocyclic ligand into the conformation observed *via* hydrogen bonding interactions with N(1)–H(01) and N(2)–H(05), this then enables O(1) to also interact *via* hydrogen bonds with one of these hydrogen atoms. The second chloride ion also links to other macrocyclic moieties *via* the water molecules of crystallisation.

In the light of our failure to access a satisfactory route towards binucleating ligands containing the *trans*-diaminocyclohexane backbone *via* our desired route (Scheme 1), we wondered whether it might be possible to employ the efficient synthetic procedure we recently reported for the direct synthesis of a range of binucleating analogues of **1** from diamines[29] to prepare **19** (Scheme 4). Although this was not the ideal ligand architecture to prepare, as it would not enable us to effect direct comparisions with mononucleating **17a** in catalytic systems, we felt that it presented the opportunity to prepare a most interesting and potentially useful new ligand. The reaction of the diamine with **18** under these optimised reaction conditions was therefore investigated and the diamine was found to react smoothly with **18** to yield the novel binucleating ligand **19** in 72% yield, thereby providing a route to a binucleating ligand derived from the diamine.



Scheme 4 One-pot synthesis of novel binucleating ligand **19**.

Having prepared these new ligands we were keen to investigate the application of their complexes in catalysis. Our preliminary investigations into the coordination chemistry of the new azaoxamacrocyclic ligand **17b** with copper(II) enabled us to isolate blue crystals of a copper complex [Cu(**17b**)Cl_2] in 42% yield. Single crystal X-ray diffraction revealed them to be a mononuclear five-coordinate complex (Fig. 5). To the best of our knowledge this represents not only the first report of the synthesis of this C_2-symmetric azaoxa ligand but also the first single crystal X-ray structure of any coordinatively unsaturated mononuclear copper(II) complex with a single [9]aneN_2O-macrocyclic ligand.

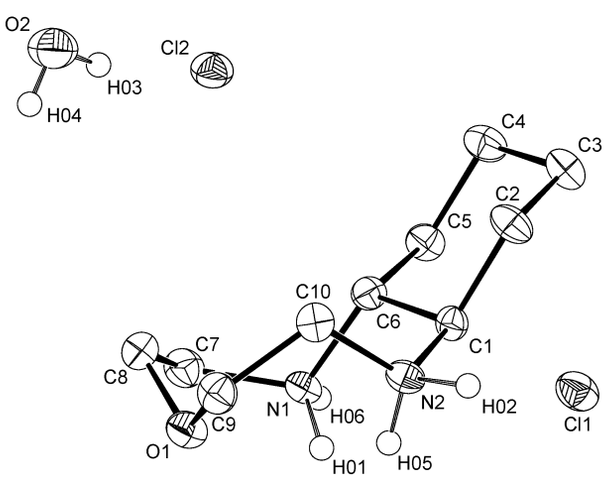


Fig. 3 ORTEP representation of the asymmetric unit of **17b**·2HCl·H_2O. Only hydrogen atoms located in the difference map have been included for clarity.

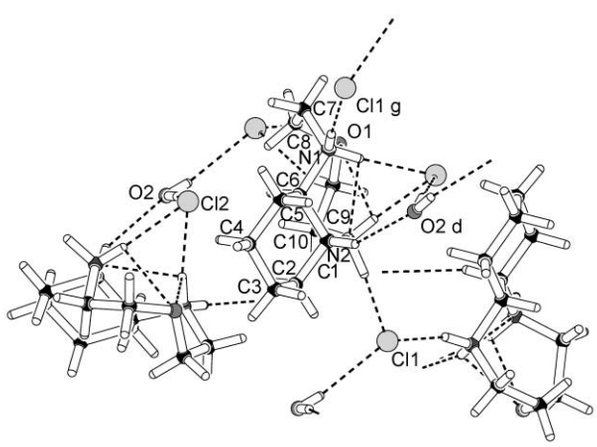


Fig. 4 The polymeric hydrogen bonding array in **17b**·2HCl·H_2O. Hydrogen bond lengths with e.s.d.s (Å) N(1)–H(06) ··· Cl(1) 3.099(4), N(1)–H(01) ··· Cl(2) 3.185(4), N(1)–H(01) ··· N(2) 3.043(5), N(1)–H(01) ··· O(1) 2.724(4), N(2)–H(02) ··· Cl(1)#1 3.103(4), N(2)–H(05) ··· Cl(2) 3.108(3), N(2)–H(05) ··· O(1) 2.884(5), O(2)–H(04) ··· Cl(1) 3.271(4), O(2)–H(03) ··· Cl(2)#2 3.217(4). Symmetry transformations used to generate equivalent atoms: #1 $-x + 1/2, -y, z - 1/2$. #2 $x - 1/2, -y + 1/2, -z$.

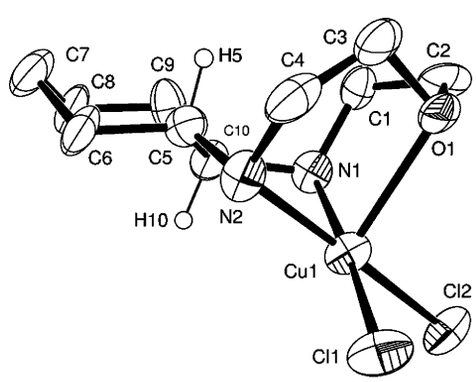
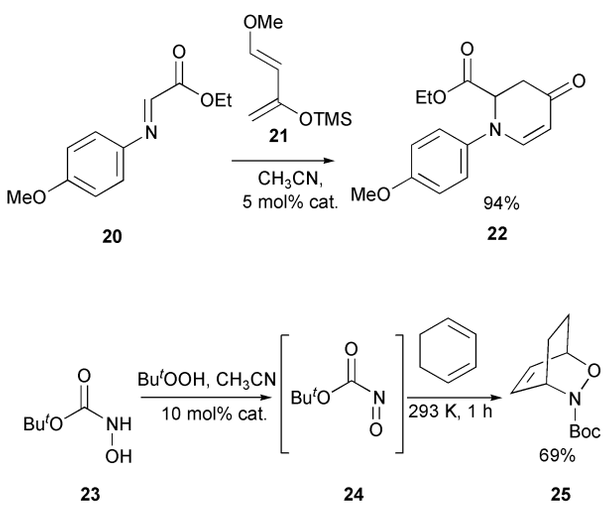


Fig. 5 ORTEP representation of the structure of [Cu(**17b**)Cl_2]. All hydrogen atoms with the exception of H(5) and H(10) are omitted for clarity. Note that there are two molecules in the asymmetric unit but that selected bond distances (Å) and angles (°) are given for one of these: Cu(1)–N(1) 2.03(3), Cu(1)–N(2) 2.02(2), Cu(1)–O(1) 2.343(17), Cu(1)–Cl(1) 2.303(11), Cu(1)–Cl(2) 2.244(8); N(1)–Cu(1)–N(2) 84.8(11), N(1)–Cu(1)–Cl(2) 92.1(7), N(2)–Cu(1)–Cl(2) 176.0(9), N(1)–Cu(1)–Cl(1) 172.8(7), N(2)–Cu(1)–Cl(1) 88.0(9), Cl(2)–Cu(1)–Cl(1) 95.1(4), N(1)–Cu(1)–O(1) 81.2(9), N(2)–Cu(1)–O(1) 79.7(8), Cl(2)–Cu(1)–O(1) 102.3(5), Cl(1)–Cu(1)–O(1) 97.8(7).

The structure reveals the geometry about the copper(II) centre to be essentially square-based pyramidal with the basal plane being made up of the two nitrogen donors of the macrocyclic ligand and the two chloride anions; the copper ion deviating by only 0.0426 Å from this plane. The oxygen donor of the macrocycle occupies the apical position and the Cu–O bond length of 2.34(2) Å is slightly shorter than the equivalent interaction in the related 'sandwich' complex [Cu([9]-ane$N_2O)_2$]$^{2+}$ of 2.3690(18) Å.[30] All other bond lengths and angles are comparable with those observed in the related copper(II) complex of 1,4,7-triazacyclononane.[31]

We were particularly encouraged by the geometry about the metal in [Cu(**17b**)Cl_2], in particular the position of H10 which suggested that the complex might provide a catalytic pocket capable of inducing reasonable levels of asymmetric induction. Although we had become interested in this ligand system for other reasons, our recent interest in the asymmetric aza-Diels–Alder and nitroso-Diels–Alder reactions,[32] led us to test this new catalyst in two such reactions that we routinely screen as part of this programme. The first of these centred on the reaction of *N*-arylimine, **20**, with Danishefsky's diene, **21**,[33] which was found to be efficiently catalysed by [Cu(**17b**)Cl_2], yielding the cycloadduct **22** in 94% yield after twelve hours at room temperature (Scheme 5). Although no *ee* was detected, the exceptional rate enhancement of this reaction by this catalyst represents an extremely promising result and indicates that this type of catalyst may have considerable potential for this class of reaction. ‡



Scheme 5 The catalytic activity of [Cu(**17b**)Cl_2] in hetero-Diels–Alder reactions.

In addition we have been actively searching for new asymmetric metal catalyst-based hydroxamic acid oxidation systems in which the metal catalyst could not only achieve efficient oxidation to the nitrosos derivative, but could also control a subsequent asymmetric nitroso-cycloaddition reaction. We have therefore been screening a range of chiral metal complexes, in the presence of various oxidising agents for their ability to catalyse the *in situ* oxidation of *N*-Boc hydroxylamine **23** to nitroso dienophile **24** and its subsequent cycloaddition to give cycloadduct **25** (Scheme 5). We were pleased to find that [Cu(**17b**)Cl_2] acted as a potent catalyst for this process, being slightly more efficient than the ruthenium(II)–(IV) system recently reported by us.[32b] As for **22**, however, no asymmetric induction was observed by chiral HPLC and racemic hetero-Diels–Alder adduct **25** was isolated in 69% yield. ‡ This result also parallels our previous findings and suggests that the intermediate acyl nitroso compound rapidly dissociates from the metal once generated and reacts thermally with the diene.[34] In this case, copper(II) presumably also releases the dienophile to undergo thermal cycloaddition and hence produce a racemic cycloadduct.

‡ A referee has suggested that the reactions may be catalysed as a result of $CuCl_2$ dissociation from the macrocyclic ligand which then acts as the catalyst. Although $CuCl_2$ does catalyse these processes effectively it is for this reason that we became interested in screening chiral complexes of copper(II) as potential asymmetric catalysts. We believe that the macrocyclic effect will prevent such dissociation of the metal from the ligand occurring on the timescale of the reactions and that the reasons for the lack of asymmetric induction will be addressed by second generation ligand systems currently under investigation.

Conclusion

Despite this success it had become apparent that the synthetic difficulties associated with **17a** and **17b**, in particular the low yielding formation of the fused-bicyclic framework, were insurmountable. It was also clear that the limited availability of vicinal diamines[35] would hamper the synthesis of a wide range of ligands in this way. Therefore libraries capable of providing sufficient structural modularity to develop these systems further in a range of asymmetric catalytic applications were an unlikely prospect. We thus became interested in a different approach involving the use of aziridines derived from chiral pool amino acids. Although our preliminary findings,[16] as well as those of others,[13,17] have only recently appeared, we have continued to develop the design and synthesis of these ligands further. As a result we are now able to prepare a broad range of azamacrocyclic ligands by careful selection of the aziridine ring-opening strategy. In addition, our very recent findings suggest that the longstanding goal of generic but related mononucleating and dinucleating analogues are now a viable goal. We are therefore in a position whereby modular and systematic changes in the structure of the ligands as well as the nuclearity of the complexes can be made. This will enable us to assess the effect of these changes on catalyst behaviour and the systematic screening of asymmetric catalysts should soon be a reality. We are currently actively engaged in the process of screening these ligand sets for activity using diversity methods, in a number of processes of interest to us. Of particular interest is the development of the highly active catalyst [Cu(**17b**)Cl_2] that we have discovered for the aza-Diels–Alder and nitroso-Diels–Alder reactions presented herein. Investigations are currently underway in our laboratories to establish the role of the copper catalyst in this reaction and to prepare improved analogues of this complex capable of inducing asymmetric induction in these important hetero-Diels–Alder reactions.

Experimental

General remarks

All reagents were purchased from either Aldrich or Lancaster and were used without further purification unless otherwise stated. Starting materials **13a**,[18] **13b**,[35] **13c**,[36] **16c**,[37] **18**[20] and **20**[32a,38] were prepared according to the reported procedures. Solvents that were required to be anhydrous were dried as follows: DMF was refluxed overnight with 4 Å molecular sieves and was then distilled under reduced pressure from triphenylchlorosilane in an atmosphere of nitrogen. Acetonitrile was refluxed overnight with calcium hydride in an atmosphere of nitrogen and then distilled from calcium hydride. THF, diethyl ether and toluene were distilled from sodium benzophenone in an atmosphere of nitrogen. Dicholoromethane was distilled from calcium hydride in an atmosphere of nitrogen. Petroleum spirit (bp 40–60 °C) was redistilled before use. Nitrogen for inert atmosphere use was purified by passing it through anhydrous manganese(II) oxide, 3 Å molecular sieves and highly reduced chromium adsorbed onto a silica support. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (Merck). Flash chromatography was performed on silica gel 60 F_{254}, 230–400 mesh (Merck). Ion-exchange chromatography was performed on Dowex 50WX2-100 acidic cation-exchange resin. Ninhydrin was used in order to visualise aliphatic amines not UV visible. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Optical rotations were determined using an Optical Activity LTD, AA-1000 polarimeter with a path length of 5 cm and concentrations are reported in g per 100 cm^{-3}. Elemental analyses were obtained using a Carlo Erba 1106 elemental analyser. ^{1}H-NMR and ^{13}C-NMR spectra were recorded as $CDCl_3$ solutions on a JEOL JNM-EX spectrometer at 270 MHz and at 67.9 MHz respectively, unless otherwise stated,

and were referenced to residual chloroform as the internal standard. *J* values are given in Hz. IR spectra were recorded on a Perkin-Elmer 1720X FT-IR spectrometer with a solid state ATR attachment. UV spectra were recorded on a Hewlett-Packard 8453 diode array UV spectrophotometer. Mass spectra were recorded on a VG Instruments ZAB-SE using xenon gas at 8 kV in a matrix of 3-nitrobenzyl alcohol (mNBA) and sodium iodide (FAB) or on a V.G. BIO-Q instrument (CI, NH_3). Screening of catalytic activity was undertaken as previously reported[32,34] (10 mol% catalyst, 100 mol% *tert*-butyl hydroperoxide (TBHP), MeCN, RT, 1 h) and the cycloadduct analysed by HPLC (ChiralCel OD column, 254 nm UV detector, propan-2-ol (IPA) : hexane as eluent. R_f 27.7 and 39.6 min for **22** (eluent 3 : 7) and R_f = 7 and 9 min for **25** (eluent 1 : 9)).

Synthesis of (1*R*,2*R*)-cyclohexane-1,2-di-4-methylbenzenesulfonamide, 9

To a solution of (*R*,*R*)-1,2-diammoniumcyclohexane tartrate salt[21] (500 mg, 1.89 mmol) in water (3 cm^3) was added triethylamine (1.16 cm^3, 8.32 mmol) and the mixture was stirred at room temperature until the solution became clear. After 10 minutes, a solution of *p*-toluenesulfonyl chloride (790 mg, 4.16 mmol) in dichloromethane (15 cm^3) was added and the biphasic system vigorously stirred at room temperature overnight. A 10% aqueous solution of hydrochloric acid (10 cm^3) was added and, after stirring for few minutes, the two layers were separated. The aqueous layer was extracted with dichloromethane (2 × 15 cm^3) and the combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude material was recrystallised from hot ethanol to give **9** (790 mg, 99%) as white crystals whose analytical and spectroscopic data were consistent with those previously reported.[39]

Synthesis of (1*R*,2*R*)-2-piperazin-1-ylcyclohexylacetamide, 15

A mixture of (*R*,*R*)-1,2-diaminocyclohexane (65 mg, 0.57 mmol) and **13a** (355 mg, 0.63 mmol) in dry DMF (10 cm^3) was stirred at 100 °C for 4 days in an atmosphere of nitrogen. After cooling to room temperature, the solvent was evaporated under reduced pressure. The solid obtained was purified by flash chromatography on silica gel (ethyl acetate–petroleum spirit (bp 40–60 °C), 2 : 1 + 1% triethylamine) to give a yellow solid. This impure material was recrystallised from hot ethanol to give **15** (50 mg, 24%) as white crystals and as a 1 : 3 mixture of two conformers at room temperature in solution. mp 196–99 °C; $\tilde{\nu}_{max}$/cm^{-1} 3269 (NH), 1647 (CO), 1554 (NH), 1346 (SO_2), 1162 (SO_2); δ_H 0.99–1.42 (4H, m, CH_2–CH_2–CHN), 1.58–2.30 (4H, m, CH_2–CH_2–CHN), 2.32–2.54 (6H, m, CH_3–Ar, CH_2–CH_2–C*H*N and N–(H)CH_{eq}–CH_2–NTs), 2.60–2.85 (2H, m, N–(H)CH_{ax}–CH_2–NTs), 2.92–3.08 (4H, m, N–CH_2–CH_2–NTs), 3.09–3.71 (1H, m, CH_2–C*H*–NH–CHO), 5.64–6.62 (1H, m, N*H*–CHO), 7.33 (2H, d, *J* 8.1, CH_3C–C*H*), 7.52–7.72 (2H, m, SO_2C–C*H*), 8.06 (1H, br s, NH–C*H*O); δ_C 21.6, 23.0, 23.2, 24.3, 24.5, 24.8, 25.2, 32.8, 33.3, 46.3, 46.5, 47.2, 49.1, 50.8, 67.0, 67.7, 127.7, 127.8, 129.7, 129.9, 132.0, 132.6, 143.6, 144.0, 161.0, 163.2; δ_C(100 MHz, $C_2D_2Cl_4$, 393K) 21.2, 23.9, 24.6, 25.2, 33.4, 46.3, 47.8, 52.4, 61.7, 67.7, 127.6, 129.8, 134.7, 143.7, 161.4; *m*/*z* (FAB) 388 (M + Na$^+$, 2%), 366 (M + H$^+$, 100); HRMS (M + H)$^+$ $C_{18}H_{28}N_3O_3S$ requires 366.1851. Found 366.1864.

Macrocycle (4a*R*,11a*R*)-5,8,11-tris(4-methylbenzenesulfonyl)-dodecahydro-5,8,11-triazabenzocyclononene, 16a

Tosylamide **9** (2.0 g, 4.73 mmol) was added to a suspension of sodium hydride (450 mg of a 60% dispersion in mineral oil, 11.36 mmol) in freshly distilled DMF (20 cm^3) in an atmosphere of nitrogen and the mixture was heated at 100 °C. After one hour, a solution of **13a** (2.96 g, 5.21 mmol) in DMF (12 cm^3) was added dropwise and the mixture was stirred at 100 °C overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the residue triturated with a 10% aqueous solution of hydrochloric acid (40 cm^3). A white precipitate was separated by filtration, dried *in vacuo* and triturated with boiling ethanol. Analytically pure **16a** was separated by filtration as a white solid (1.40 g, 46%). mp 294–95 °C; $[\alpha]_D^{28}$ = −53.9 (*c* 2.7 in dichloromethane) (Found C, 56.4; H, 6.1; N, 6.2; S, 14.7. $C_{31}H_{39}N_3O_6S_3 \cdot H_2O$ requires C, 56.1; H, 6.2; N, 6.3; S 14.5%); $\tilde{\nu}_{max}$/cm^{-1} 1597, 1494, 1447, 1314 (SO_2), 1151 (SO_2), 1088, 985, 818, 709, 692; δ_H 0.90–1.36 (4H, m, CH_2–CH_2–CHN), 1.40–1.59 (1H, m, CH_2–(H)CH_{eq}–CHN), 1.60–1.79 (1H, m, CH_2–(H)CH_{eq}–CHN), 1.94–2.16 (1H, m, CH_2–(H)CH_{ax}–CHN), 2.17–2.43 (10H, m, CH_2–(H)CH_{ax}–CHN and CH_3–Ar), 2.44–2.66 (1H, m, (H)C*H*–NTs), 2.92–3.56 (7H, m, CH_2–NTs and NTs–(H)C*H*–CH_2–NTs), 3.58–3.80 (1H, m, NTs–(H)C*H*–CH_2–NTs), 4.71–4.92 (1H, m, C*H*–NTs), 7.07–7.35 (6H, m, CH_3C–C*H*), 7.59 (2H, d, *J* 8.1, SO_2C–C*H*), 7.73 (2H, d, *J* 8.1, SO_2CC*H*), 7.94 (2H, bd, *J* 7.7, SO_2C–C*H*); δ_C 21.5, 24.5, 25.8, 28.8, 30.0, 46.9, 52.1, 54.7, 55.6, 59.9, 67.9, 127.1, 127.6, 128.4, 129.5, 129.7, 129.8, 134.8, 137.2, 138.0, 143.3, 143.4, 144.0; *m*/*z* (FAB) 668 (M + Na$^+$, 66%), 646 (M + H$^+$, 31), 490 (M$^+$ − Ts, 59), 334 (M$^+$ − 2Ts − H), 59), 227 (100); HRMS (M + H)$^+$. $C_{31}H_{40}N_3O_6S_3$ requires 646.2079. Found 646.2062.

Synthesis of macrocycle (4a*R*,11a*R*)-5,11-bis(4-methylbenzenesulfonyl)dodecahydro-8-oxa-5,11-diazabenzocyclononene, 16b

Tosylamide **9** (4.0 g, 9.47 mmol) was added to a suspension of sodium hydride (830 mg of a 60% dispersion in mineral oil, 20.83 mmol) in freshly distilled DMF (60 cm^3) in an atmosphere of nitrogen and the mixture was heated at 140 °C. After two hours, **13b** (4.32 g, 10.41 mmol) was added portionwise within 1 hour and the mixture was stirred at 140 °C overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the residue triturated with a 10% aqueous solution of hydrochloric acid (60 cm^3). A white precipitate was separated by filtration, washed with water (2 × 40 cm^3) and dried *in vacuo*. The white solid obtained was recrystallised from hot ethanol to give **16b** (2.89 g, 62%) as white crystals. mp 205–207 °C; $[\alpha]_D^{28}$ = −6.8 (*c* 1 in chloroform) (Found C, 57.7; H, 6.7; N, 5.6; S, 12.9. $C_{24}H_{32}N_2O_5S_2 \cdot \frac{1}{2}H_2O$ requires C, 57.5; H, 6.6; N, 5.6; S 12.8%); $\tilde{\nu}_{max}$/cm^{-1} 1331 (SO_2), 1132 (SO_2), 1115 (COC); δ_H 0.90–1.18 (2H, m, (H)CH_{eq}–CH_2–CHN), 1.20–1.45 (2H, m, (H)CH_{ax}–CH_2–CH–N), 1.50–1.64 (1H, br s, CH_2–(H)CH_{eq}–CHN), 1.65–1.82 (1H, br s, CH_2–(H)CH_{eq}–CHN), 1.98–2.16 (1H, m, CH_2–(H)CH_{ax}–CHN), 2.42 (7H, br s, CH_2–(H)CH_{ax}–CHN and 2 × CH_3–Ar), 2.88–3.41 (6H, bm), 3.60–4.03 (3H, bm), 4.78–5.02 (1H, br s, C*H*–NTs), 7.30 (4H, d, *J* 8.1, CH_3CC*H*), 7.82 (2H, br s, SO_2CC*H*), 8.01 (2H, br s, SO_2CC*H*); δ_C 21.5, 24.5, 25.9, 28.8, 30.0, 46.0, 51.2, 59.8, 66.9, 75.6, 127.6, 128.4, 129.5, 137.5, 138.1, 143.2; δ_C(100 MHz, $C_2D_2Cl_4$, 393K) 21.4, 25.3, 29.6, 58.4, 61.6, 75.7, 127.9, 129.5, 138.1, 143.3; *m*/*z* (FAB) 515 (M + Na$^+$, 100%), 493 (M + H$^+$, 48), 337 (M$^+$ − Ts, 45); HRMS (M + Na)$^+$$C_{24}H_{32}N_2O_5S_2Na$ requires 515.1650. Found 515.1639.

Synthesis of (8a*R*,12a*R*)-1,8-bis(4-methylbenzenesulfonyl)tetradecahydrobenzo[*b*][1,4]diazecine, 16c

Tosylamide **9** (1.0 g, 2.37 mmol) was added to a suspension of sodium hydride (230 mg of a 60% dispersion in mineral oil, 5.68 mmol) in freshly distilled DMF (10 cm^3) in an atmosphere of nitrogen and the mixture was heated at 140 °C. After one hour, a solution of **13c** (1.07 g, 2.60 mmol) in DMF (12 cm^3) was added dropwise and the mixture was stirred at 140 °C overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the residue triturated with a 10% aqueous solution of hydrochloric acid (20 cm^3). A white precipitate was separated by filtration, dried *in vacuo* and

purified by flash chromatography on silica gel (petroleum spirit (bp 40–60 °C)–ethyl acetate, 2 : 1) to give **16c** (80 mg, 7%) as a white solid. mp 199–201 °C; $\tilde{\nu}_{max}$/cm^{-1} 1325 (SO_2), 1149 (SO_2); δ_H(400 MHz, $C_2D_2Cl_4$, 393K) 1.20–1.27 (2H, m, (H)CH_{eq}–CH_2–CHN), 1.44 (4H, br s, (H)CH_{ax}–CH_2–CHN and NTsCH_2–CH_2–CH_2), 1.65–1.83 (8H, m, CH_2–CH_2–CH_2N and NTs–CH_2–CH_2–CH_2), 2.44 (6H, s, CH_3–Ar), 3.06–3.16 (4H, m, NTs–CH_2–CH_2–CH_2), 3.82 (2H, br s, C*H*–NTs), 7.31 (4H, d, *J* 8.2, CH_3C–C*H*), 7.90 (4H, d, *J* 8.2, SO_2C–C*H*); δ_C(100 MHz, $C_2D_2Cl_4$, 393K) 17.5, 21.2, 25.8, 30.4, 44.2, 61.3, 128.2, 129.3, 138.8, 142.9; *m*/*z* (FAB) 513 (M + Na^+, 100%), 491 (M + H^+, 56), 335 (M^+ − Ts, 54); HRMS (M + H)$^+$. $C_{25}H_{35}N_2O_4S_2$ requires 491.2038. Found 491.2052.

Synthesis of (4a*R*,11a*R*)-dodecahydro-5,8,11-triazoniabenzocyclononene trihydrochloride, 17a·3HCl

To a mixture of **16a** (4.98 g, 7.71 mmol) in dry THF (180 cm^3) at −78 °C were added liquid ammonia (150 cm^3) and sodium (3.19 g, 138.79 mmol). The deep blue mixture was stirred at −78 °C for two hours and water was then carefully added dropwise. The dry ice bath was removed and the flask was left open overnight in a fume cupboard in order to let the ammonia evaporate. Then resultant mixture was acidified with a 10% aqueous solution of hydrochloric acid (200 cm^3) and the solution concentrated under reduced pressure. The solid obtained was washed with toluene (3 × 150 cm^3), ethyl acetate (2 × 100 cm^3) and diethyl ether (2 × 100 cm^3) in an atmosphere of nitrogen. The brown solid obtained was purified by ion exchange chromatography on Dowex 50WX2-100 acidic cation-exchange resin (1 M hydrochloric acid was used as eluent). The solid obtained was triturated with ethanol and the insoluble material separated by filtration. The filtrate was concentrated to give **17a**·3HCl (1.58 g, 70%) as a light brown powder. mp 240 °C decomp.; $[\alpha]_D^{28}$ = −55.6 (*c* 0.41 in water); $\tilde{\nu}_{max}$/cm^{-1} 2934 (NH_2^+), 1583 (NH_2^+); δ_H(D_2O) 1.35–1.87 (4H, m, CH_2–CH_2–CHN), 1.90–2.09 (2H, m, CH_2–(H)CH_{eq}–CHN), 2.11–2.33 (2H, m, CH_2–(H)CH_{ax}–CHN), 3.13–3.35 (2H, m, C*H*–NH), 3.35–3.84 (8H, m, CH_2–N); δ_C(D_2O) 22.9, 28.3, 41.6, 55.8, 62.8; *m*/*z* (FAB) 184 (M^+ − H_2Cl_3, 100%); HRMS $(M)^+$ − H_2Cl_3. $C_{10}H_{22}N_3$ requires 184.1814. Found 184.1803.

Synthesis of (4a*R*,11a*R*)-dodecahydro-8-oxa-5,11-diazoniabenzocyclononene dihydrochloride 17b·2HCl

To a solution of **16b** (4.98 g, 10.11 mmol) in dry THF (100 cm^3) at −78 °C were added liquid ammonia (150 cm^3) and sodium (2.79 g, 121.31 mmol). The deep blue mixture was stirred at −78 °C for two hours then water was carefully added dropwise. The dry ice bath was removed and the flask was left open overnight in a fume cupboard in order to let the ammonia evaporate. Then resultant mixture was acidified with a 10% aqueous solution of hydrochloric acid (250 cm^3) and the solvents were removed under reduced pressure. The solid obtained was washed with toluene (3 × 150 cm^3), ethyl acetate (2 × 100 cm^3) and diethyl ether (2 × 100 cm^3) in an atmosphere of nitrogen. The brown solid obtained was purified by ion exchange chromatography on Dowex 50WX2-100 acidic cation-exchange resin (1 M hydrochloric acid was used as eluent). The solid obtained was triturated with ethanol and the insoluble material separated by filtration. The filtrate was concentrated to give **17b**·2HCl (2.09 g, 82%) as a light brown powder. mp 270 °C decomp.; $[\alpha]_D^{25}$ = −43.8 (*c* 0.83 in water); $\tilde{\nu}_{max}$/cm^{-1} 2949 (NH_2^+), 1610 (NH_2^+), 1111 (COC); δ_H(D_2O) 1.24–1.47 (2H, m, (H)CH_{eq}–CH_2–CHN), 1.54–1.97 (4H, m, (H)CH_{ax}–CH_2–CHN and CH_2–(H)CH_{eq}–CHN), 2.12–2.33 (2H, m, CH_2–(H)CH_{ax}–CHN), 3.24–3.37 (2H, m, NH–CH_2–CH_2–O), 3.46–3.65 (2H, m, CH_2–CH_2–O), 3.68–3.83 (2H, m, C*H*N), 3.88–4.05 (4H, m, NH–CH_2–CH_2–O); δ_C(D_2O) 23.0, 28.4, 41.1, 55.2, 62.1; *m*/*z* (FAB) 185 (M^+ − HCl_2, 100%); HRMS $(M)^+$ − HCl_2. $C_{10}H_{21}N_2O$ requires 185.1654. Found 185.1651.

(*R*,*R*)-1,2-Bis[*N*,*N*′-bis(4-methylbenzenesulfonyl)-1,4,7-triaza-1-cyclonon-1-ylmethyl]cyclohexane, 19

To a stirred suspension of compound **18** (2.00 g, 2.61 mmol) and potassium carbonate (1.08 g, 7.82 mmol) in dry acetonitrile (20 cm^3) was added (*R*,*R*)-1,2-diaminocyclohexane (0.15 cm^3, 1.3 mmol) dropwise under nitrogen. The resultant mixture was heated at 85 °C under reflux for 3 days and the course of the reaction was monitored by TLC (2 : 1, diethyl ether : CH_2Cl_2). The inorganic salts were removed by filtration and the solvent evaporated *in vacuo* to yield the crude product as an off-white solid. The product **19** was purified by column chromatography (2 : 1 ethyl acetate : petroleum spirits (bp 40–60 °C)) (0.15 g, 72%). mp 142–145 °C. $[\alpha]_D^{28}$ = +3.8 (*c* 1.0 in chloroform); $\tilde{\nu}_{max}$/cm^{-1} 2929, 1673, 1597, 1446, 1325 $(SO_2)_{NTs}$, 1152 $(SO_2)_{NTs}$,1088, 980, 813, 710, 689; δ_H 1.00–1.18 (2H, bm, (H)CH_{eq}–CH_2–CHN), 1.19–1.38 (2H, bm, (H)CH_{ax}–CH_2–CHN), 1.63–1.80 (2H, bm, CH_2–(H)CH_{eq}–CHN), 1.85–2.00 (2H, bm, CH_2–(H)CH_{ax}–CHN), 2.42 (12H, s, CH_3–Ar), 2.45–2.60 (2H, br s, CH_2–CH_2–C*H*–NTs), 2.90–3.03 (4H, br s, N–CH_2–CH_2–TsN), 3.10–3.35 (4H, br s, N–CH_2–CH_2–NTs), 3.38–3.62 (4H, s, TsN–CH_2–CH_2–NTs), 7.30 (8H, d, *J* 8.3, CH_3C–C*H*), 7.63 (8H, d, *J* 8.3, SO_2C–C*H*); δ_C 21.5, 26.1, 29.9, 52.3, 52.5, 64.4, 127.4, 129.8, 135.2, 143.4; *m*/*z* (FAB) 955 (M + H, 33%) 799 (M − Ts, 46), 518 ($C_{26}H_{37}N_3O_4S_2$ − H, 100), 437 ($C_{20}H_{27}N_3O_4S_2$, 19); HRMS (M + H)$^+$ $C_{49}H_{61}N_6O_8S_4$ requires 955.3590. Found 955.3625.

Synthesis of copper(II) complex [Cu(17b)Cl_2]

The copper(II) complex [Cu(**17b**)Cl_2], was prepared in 42% yield by adaptation of a reported procedure.[31] mp 195 °C decomp.; λ_{max}/nm 265 (2600), 679 (26); $\tilde{\nu}_{max}$/cm^{-1} 1084 (COC); *m*/*z* (FAB) 282 (M − Cl, 41%); HRMS $C_{10}H_{20}CuN_2O$ requires 247.0872. Found 247.0878. Slow evaporation of an aqueous solution led to crystals suitable for single crystal X-ray diffraction.

X-Ray crystallography

The intensity data were collected on a CAD-4 diffractometer using Mo-Kα radiation (λ = 0.71069 Å) with ω–2θ scans for **15** and [Cu(**17b**)Cl_2]. The unit cell parameters were determined by least-squares refinement on diffractometer angles [**15** $9.29 \le \theta \le 11.71°$; [Cu(**17b**)$Cl_2$] $8.23 \le \theta \le 12.78°$] for 23 and 25 automatically centred reflections for **15** and [Cu(**17b**)Cl_2] respectively.[40] All data were corrected for absorption by empirical methods (ψ scan)[41] and for Lorentz-polarization effects by XCAD4.[42] The structures were solved by the heavy-atom method using the programs SHELXS-97,[43] and DIRDIF[44] and refined anisotropically (non-hydrogen atoms) by full-matrix least-squares on F^2 using SHELXL-97.[43] The H-atom positions were calculated geometrically and refined with a riding model. Data for **15** were corrected for absorption using an isotropic non-hydrogen model with the programme DIFABS.[45] In the final stage of refinement for [Cu(**17b**)Cl_2] data were corrected for absorption with DIFABS.[45]

For **17b** intensity data were collected using an Enraf-Nonius Kappa CCD area detector on an Enraf-Nonius FR591 rotating anode generator at 120(2) K. Graphite monochromated Mo-K_α radiation (λ = 0.71073 Å) was used with ϕ and ω to fill the Ewald sphere. Data collection, cell refinement and data reduction were carried out using the DENZO[46] and COLLECT[47] packages. Preliminary absorption correction was carried out by multiple scans using SORTAV.[48] The structure was solved by direct methods using DIRDIF[44] and developed by difference Fourier techniques with subsequent refinement on F^2 by full matrix least squares using SHELXL-97.[43] Data were corrected for absorption using an isotropic non-hydrogen model with the

programme XABS2.[49] The H atoms on the NH_2^+ moieties and the water molecule were located in the difference map and refined without geometric constraints. All other H atoms were refined in their calculated geometric positions and refined using an atom riding model. Anisotropic thermal parameters were refined for all non-hydrogen atoms.

The programs ORTEP-3,[50] and PLATON[51] were used for graphical representations and WINGX[52] was used to prepare material for publication for all structures.

Crystal data for **15**. $C_{18}H_{27}N_3O_3S$, M = 365.49, tetragonal, a = 11.164(2), b = 11.164(2), c = 14.910(3) Å, U = 1858.3(6) Å^3, T = 180(2) K, space group $P4_1$, Z = 4, μ(Mo-K$_\alpha$) = 0.196 mm^{-1}, 1553 reflections measured, 1351 unique (R_{int} = 0.0364) which were used in all calculations. The final wR [$I>2\sigma(I)$] was 0.1382.

Crystal data for **17b**·2HCl·H_2O. $C_{10}H_{24}Cl_2N_2O_2$, M = 275.21, orthorhombic, a = 7.9736(4), b = 12.2913(6), c = 14.1517(9) Å, U = 1386.95(13) Å^3, T = 120(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo-K$_\alpha$) = 0.459 mm^{-1}, 3042 reflections measured, 1778 unique (R_{int} = 0.0877) which were used in all calculations. The final wR [$I>2\sigma(I)$] was 0.0830.

Crystal data for [Cu(**17b**)Cl_2]. $C_{10}H_{18}Cl_2CuN_2O$, M = 316.70, tetragonal, a = 26.629(4), b = 26.629(4), c = 7.506(2) Å, U = 5322.5(18) Å^3, T = 293(2) K, space group $I4_1$,§ Z = 16, μ(Mo-K$_\alpha$) = 2.024 mm^{-1}, 2688 reflections measured, 2521 unique (R_{int} = 0.0197) which were used in all calculations. The final wR [$I>2\sigma(I)$] was 0.1524 (all data).

CCDC reference numbers 188705, 195733 and 195734.

See http://www.rsc.org/suppdata/dt/b2/b210285d/ for crystallographic data in CIF or other electronic format.

Acknowledgements

We are grateful to Queen Mary, University of London for a studentship (S. P.) and also to the EPSRC for a studentship (K. F. S., GR/R19182/01), EPSRC and Warwick International Limited for a CASE award for New Academics (K. S.) (Award No. 00800316) and GlaxoSmithKline for an Industrial CASE studentship (H. W.) (Ref. No. 9931546X). We are indebted to The University of London Research Instruments Service (ULRIS) for mass spectra (London School of Pharmacy) and for NMR spectra at 400 MHz (Queen Mary). We also thank the EPSRC National X-ray service (University of Southampton) for the collection of data for **17b**·2HCl·H_2O. In addition we thank The University of London Central Research Fund, The Nuffield Foundation and The Royal Society for financial support and Dr I. Abrahams for final refinements of two of the X-ray structures.

§ The Patterson map could not be refined using the $I4_{1a}$ space group.

References and notes

1 R. Hage, J. E. Iburg, J. Kerschner, J. H. Koek, E. L. M. Lempers, R. J. Martens, U. S. Racherla, S. W. Russell, T. Swarthoff, M. R. P. van Vliet, J. B. Warnaar, L. van der Wolf and B. Krijen, *Nature (London)*, 1994, **369**, 637.
2 C. Zondervan, R. Hage and B. L. Feringa, *Chem. Commun.*, 1997, 419.
3 D. H. R. Barton, W. Li and J. A. Smith, *Tetrahedron Lett.*, 1998, **39**, 7055.
4 B. C. Gilbert, N. W. J. Kamp, J. R. Lindsay Smith and J. Oakes, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2161.
5 J. R. Lindsay Smith and G. B. Shul'pin, *Tetrahedron Lett.*, 1998, **39**, 4909.
6 See for example: (*a*) V. C. Quee-Smith, L. DelPizzo, S. H. Jureller, J. L. Kerschner and R. Hage, *Inorg. Chem.*, 1996, **35**, 6461; (*b*) D. De Vos and T. Bein, *Chem. Commun.*, 1996, 717; (*c*) D. De Vos, J. L. Meinershagen and T. Bein, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2211; (*d*) A. Berkessel and C. A. Sklorz, *Tetrahedron Lett.*, 1999, **40**, 7965; (*e*) J. Brinksma, L. Schmieder, G van Vliet, R. Boaron, R. Hage, D. De Vos, P. L. Alsters and B. L. Feringa, *Tetrahedron Lett.*, 2002, **43**, 2619.
7 T. H. Bennur, S. Sabne, S. S. Deshpande, D. Srinivas and S. Sivasanker, *J. Mol. Cat. A: Chem.*, 2002, **185**, 71.
8 D. De Vos, S. de Wilderman, B. F. Sels, P. J. Grobet and P. A. Jacobs, *Angew. Chem., Int. Ed.*, 1999, **38**, 980.
9 For recent reviews see for example: (*a*) E. L. Hegg and J. N. Burstyn, *Coord. Chem. Rev.*, 1998, **173**, 133; (*b*) N. H. Williams, B. Takasaki, M. Wall and J. Chin, *Acc. Chem. Res.*, 1999, **32**, 485.
10 M. J. Young and J. Chin, *J. Am. Chem. Soc.*, 1995, **117**, 10577.
11 B. R. Bodsgard and J. N. Burstyn, *Chem. Commun.*, 2001, 647.
12 (*a*) C. Bolm, D. Kadereit and M. Valacchi, *DE Pat.* 19720477, 1997; (*b*) C. Bolm, D. Kadereit and M. Valacchi, *Synlett.*, 1997, 687.
13 G. Argouarch, C. L. Gibson, G. Stones and D. C. Sherrington, *Tetrahedron Lett.*, 2002, **43**, 3795 and references therein.
14 M. Beller, A. Tafesch, R. W. Fischer and B. Scharbert, *DE Pat.* 19523891, 1995.
15 C. Bolm, N. Meyer, G. Raabe, T. Weyhermüller and E. Bothe, *Chem. Commun.*, 2000, 2435.
16 (*a*) J. E. W. Scheuermann, F. Ronketti, M. Motevalli, D. V. Griffiths and M. Watkinson, *New J. Chem.*, 2002, **26**, 1054; (*b*) J. E. W. Scheuermann, G. Ilashenko, D. V. Griffiths and M. Watkinson, *Tetrahedron: Asymmetry*, 2002, **13**, 269.
17 B. M. Kim, S. M. So and H. J. Choi, *Org. Lett.*, 2002, **4**, 949.
18 S. W. Golding, T. W. Hambley, G. A. Lawrance, S. M. Luther, M. Maeder and P. Turner, *J. Chem. Soc., Dalton Trans.*, 1999, 1975.
19 See for example: (*a*) E. N. Jacobsen, *Comprehensive Asymmetric Catalysis Volume II*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin-Heidleberg-New York, 1999, ch. 17, p. 607; (*b*) E. N. Jacobsen and M. H. Wu, *Comprehensive Asymmetric Catalysis Volume II*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin-Heidleberg-New York, 1999, ch. 18.2, p. 649; E. N. Jacobsen and M. H. Wu, *Comprehensive Asymmetric Catalysis Volume III*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin-Heidleberg-New York, 1999, ch. 35, p. 1309.
20 S. Pulacchini and M. Watkinson, *Eur. J. Org. Chem.*, 2001, 4233.
21 (*a*) I. Alfonso, C. Astorga, F. Rebolledo and V. Gotor, *Chem. Commun.*, 1996, 2471; (*b*) F. Galsbol, P. Steenbol and B. S. Sorensen, *Acta Chem. Scand.*, 1972, **26**, 3605; (*c*) D. Gracian and H. P. Schultz, *J. Org. Chem.*, 1971, **36**, 3989.
22 I. Alfonso, F. Rebolledo and V. Gotor, *Tetrahedron: Asymmetry*, 1999, **10**, 367.
23 T. J. Atkins, J. E. Richman and W. F. Oettle, *Org. Synth.*, 1978, **58**, 86.
24 P. Laszlo, *Science*, 1987, **235**, 1473.
25 E. Goss, *Pol. J. Chem.*, 1987, **61**, 605.
26 M. Iwata and H. Kuzuhara, *Chem. Lett.*, 1986, 951.
27 S. Pulacchini, K. F. Sibbons, R. Nasser, G. E. Hawkes, R. T. Kroemer and M. Watkinson, manuscript in preparation.
28 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley and Sons, Oxford, 2nd edn., 1991.
29 S. Pulacchini, K. Shastri, N. C. Dixon and M. Watkinson, *Synthesis*, 2001, 2381.
30 M. Kavana, D. R. Powell and J. N. Burstyn, *Inorg. Chim. Acta*, 2000, **297**, 351.
31 (*a*) K. A. Deal and J. N. Burstyn, *Inorg. Chem.*, 1996, **35**, 2792; (*b*) W. F. Schwindinger, T. G. Fawcett, R. A. Lalancette, J. A. Potenza and H. J. Schugar, *Inorg. Chem.*, 1980, **19**, 1379.
32 (*a*) S. Bromidge, P. Wilson and A. Whiting, *Tetrahedron Lett.*, 1998, **39**, 8905; (*b*) K. R. Flower, A. P. Lightfoot, H. Wan and A. Whiting, *Chem. Commun.*, 2001, 1812; (*c*) A. P. Lightfoot, R. G. Pritchard, H. Wan, J. E. Warren and A. Whiting, *Chem. Commun.*, 2002, 2072.
33 S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, 1974, **96**, 7807.
34 K. R. Flower, A. P. Lightfoot, H. Wan and A. Whiting, *J. Chem. Soc., Perkin Trans. I*, 2002, 2058.
35 D. Lucet, T. Le Gall and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2581.
36 Y. Chen and G. L. Baker, *J. Org. Chem.*, 1999, **64**, 6870.
37 D. H. Busch, D. J. Olszanski, J. C. Stevens, W. P. Schammel, M. Kojima, N. Herron, L. L. Zimmer, K. A. Holter and J. Mocak, *J. Am. Chem. Soc.*, 1981, **103**, 1472.
38 Imine **20** was prepared using the procedure reported for the corresponding methyl ether: S. L. Yao, S. Saaby, R. G. Hazell and K. A. Jörgensen, *Chem. Eur. J.*, 2000, **6**, 2435.
39 H. Takahashi, T. Kawakita, M. Ohno, M. Yoshioka and S. Kobayashi, *Tetrahedron*, 1992, **48**, 5691.
40 Enraf-Nonius CAD-4/PC Software, Version 1.5c, Enraf-Nonius, Delft, The Netherlands, 1994.
41 A. C. T. North, D. C. Phillips and F. S. Mathews, *Acta Crystallogr., Sect. A*, 1968, **24**, 351.
42 K. Harms and S. Wocadlo, XCAD4, CAD Data Reduction, University of Marburg, Marburg, Germany, 1995.

43 G. M. Sheldrick, SHELX-97, Program for solution and Refinement of Crystal Structures, University of Göttingen, Germany, 1997.
44 P. T. Beurskens, G. Beurskens, W. P. Bosman, R. de Gelder, S. Garcia-Granda, R. O. Gould, R. Israel and J. M. M. Smits, DIRDIF-99 program system, Crystallography Laboratory, University of Nijmegen, The Netherlands, 1999.
45 N. Walker and D. Stuart, *Acta. Crystallogr., Sect. A*, 1983, **39**, 158.
46 DENZO Data collection and processing software: Z. Otwinowski and W. Minor, *Methods in Enzymology, Volume 276: Macromolecular Crystallography, Part A*, eds. C.W. Carter, Jr and R.M. Sweet, Academic Press, New York, 1997, pp. 307–326.
47 R. Hooft, COLLECT Data collection and processing user interface, Collect: Data collection software, Nonius B.V., Delft, 1998.
48 SORTAV absorption correction software package: R. H. Blessing, *Acta Crysallogr., Sect. A.*, 1995, **51**, 33; R. H. Blessing, *J. Appl. Crystallogr.*, 1997, **30**, 421.
49 S. Parkin, B. Moezzi and H. Hope, *J. Appl. Crystllogr.*, 1995, **28**, 53.
50 ORTEP-3 for Windows, L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.
51 PLATON/PLUTON, (*a*) A. L. Spek, *Acta Crystallogr., Sect. A*, 1990, **46**, 34; (*b*) A. L. Spek, PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands, 1998.
52 L. J. Farrugia, WinGX- A Windows Program for Crystal Structure Analysis, University of Glasgow, Glasgow, 1998.