Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2013, **11**, 2827

Conformational analysis and synthetic approaches to polydentate perhydro-diazepine ligands for the complexation of gallium(III)†

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Received 7th February 2013,
Accepted 6th March 2013

DOI: 10.1039/c3ob40287h

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Synthetic approaches are reported to polydentate ligands based on 6-phenyl-6-amino-perhydro-1,4-diazepine. The synthetic route devised averts ring-opening reactions, allowing the exocyclic N-substituent to be introduced separately and involves a nitro-Mannich condensation, prior to chemoselective RANEY® nickel reduction. Comparison of the solid-state structures of four synthetic intermediates reveals that the seven-membered ring adopts a preferred twist-chair conformer in the solid state. Solution state NMR experiments highlight a conformational preference for the bulky aryl groups to adopt an equatorial site, pre-disposing the ligand to metal binding, by adoption of a conformation that creates a facial array of the ligand nitrogen atoms. This ligand conformation averts the formation of less stable metal complexes with differing ligation modes, notably in the binding of Ga^{3+} to related ligands, where a *C*-methyl substituent replaces the phenyl group at the quaternary centre.

Introduction

Finding ligands that bind metal ions rapidly yet form kinetically stable complexes for safe use *in vivo* remains a challenging task.[1] Recently we have reported the behaviour of certain hexadentate ligands that bind ^{68}Ga rapidly over the pH range 4–7 yet form kinetically stable complexes suitable for use *in vivo*.[2] Here, we describe the details of the synthetic approach to such ligands, highlighting competitive ring-opening reactions. In addition we assess their solution and solid-state conformations in detail, in order to explain their favourable metal-ion binding characteristics.

Generally, acyclic systems possess fast forward rates of metal binding, but are more susceptible to dissociation pathways. On the other hand, macrocyclic ligands usually form more kinetically inert metal complexes but their higher binding stability constants are often associated with slower rates of complexation and more particularly dissociation.[3] These issues are of particular importance in molecular imaging involving labelling of ligands by metallic radioisotopes, especially with short-lived radionuclides, such as the positron emitters ^{68}Ga($t_{1/2}$ 68 min), ^{64}Cu($t_{1/2}$ 12.8 h), ^{52}Fe($t_{1/2}$ 8.2 h) and ^{55}Co($t_{1/2}$ 17.5 h). The over-riding need to avoid premature metal dissociation *in vivo* has meant that macrocyclic ligand systems have often been preferred, especially those that are sensibly matched in coordination number and donor type to the given metal ion and are pre-organised to the required coordination geometry. The hexadentate ligands NOTA[4] **1**, and the triphosphinate analogues, **2**,[5,6] have therefore attracted attention for labelling with ^{67}Ga(γ, 7.8 h), ^{68}Ga and ^{111}In(γ, $t_{1/2}$ 68 h).[7] These ions, like Fe^{3+}, Co^{3+} and Zn^{2+} prefer an octahedral coordination environment with 'hard' donor atoms. The radiolabelled complexes resist acid catalysed dissociation *in vivo*[8,9] but can be rather slow to label at ambient pH and temperature. The rate-limiting step in metal ion binding in aqueous media is likely to be associated with N-deprotonation of the ligand, a process which tends to be inhibited by the conformational rigidity of the 1,4,7-triazacyclononane ligand, where there is a tendency to conserve the square [333] conformation. These issues are most acute with ^{68}Ga labelling, owing to its short half-life and the propensity of the aqua ion to hydrolyse above pH 5.

The 7-ring heterocycle derivate 6-amino-6-methyl perhydro-1,4-diazapine, **3a**, is isomeric with 1,4,7-triazacyclononane, **4**, and like the unsubstituted analogue, **3b**, (DAZA) it has attracted attention as a ligand scaffold, as N-substitution readily allows formation of heptadentate and hexadentate ligands.[10–13] However, the conformational flexibility of saturated, heterocyclic seven-membered rings is well documented.[14–17] Several low-energy conformations are populated, of which the twisted-chair (TC) conformations are usually lowest in energy (Scheme 1). In addition, in **3a–3c**, the

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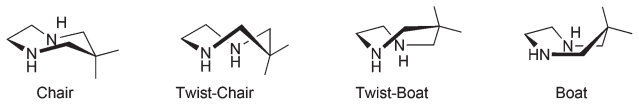
†Electronic supplementary information (ESI) available. CCDC 911245 and 911246. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob40287h



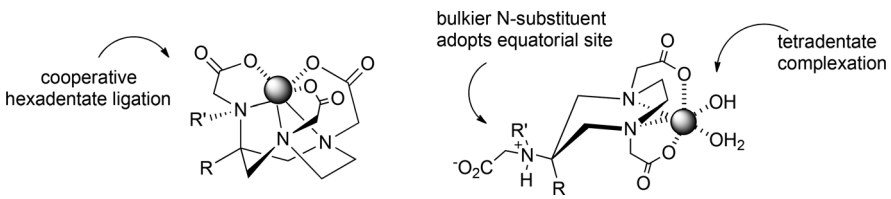
Scheme 1

conformational equilibrium interconverts the axial and equatorial sites, with the more bulky 6-substituent preferring the latter position.

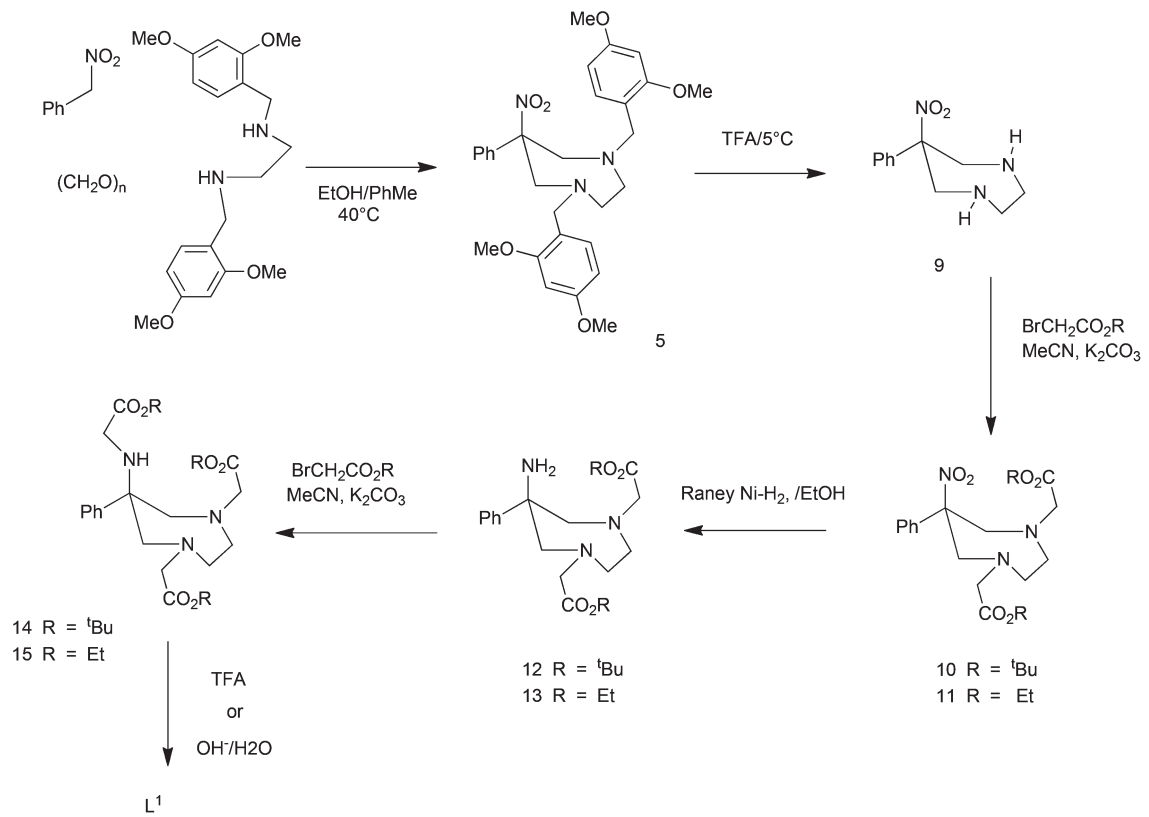
In order for these ligands to present a facing-capping array of three nitrogen donors, the 6-amino group needs to adopt an axial position. This is preferred when the other 6-substituent is more bulky. Consideration of literature '*A*' values suggests that an aryl ring at this site is preferred over a simple alkyl group (Ph: 12 kJ mol^{-1}; Me 7 kJ mol^{-1}; NH_2/NH_3^+ 6–7 kJ mol^{-1}; $HN(CH_2R)_2$ 10 kJ mol^{-1}) and can be readily derivatised for subsequent conjugation. Accordingly, we set out to prepare **3c**, and create hexadentate aza-carboxylate ligands, L^1–L^3, based on this scaffold that were more pre-organised towards metal ion complexation, than ligands such as L^5, L^{4a} or L^{4b} (AAZTA)[11] (Scheme 2). Furthermore, we needed to develop a versatile synthetic route that allowed the exocyclic and endocyclic N-substituents to be differentiated easily, thereby permitting opportunities for selective conjugation *via* the exocyclic nitrogen substituent.

Synthesis of ligands L^1–L^3

The key intermediate in the synthesis of L^1–L^3 proved to be the nitro-compound **9**[3] (Scheme 3). Prior work in the analogous series of 6-methyl-substituted ligands had centred on a two-step synthesis of **3a** *via* co-condensation of nitromethane, formaldehyde and *N*,*N*-dibenzylethylenediamine, followed by reductive hydrogenolysis using Pearlman's catalyst.[11a] Such a strategy was inappropriate here, as *C*-benzylic cleavage occurs simultaneously, leading to ring-opening. Therefore, the acid-labile 2,4-dimethoxybenzyl analogue was used, as it can be



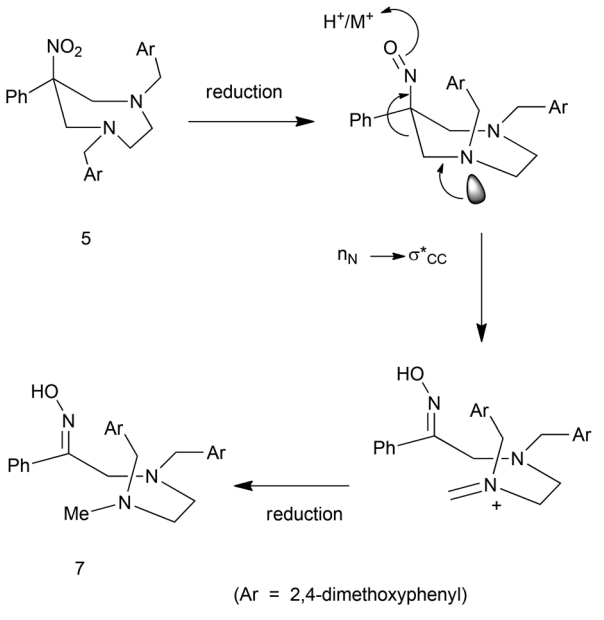
Scheme 2



Scheme 3 Synthesis of L^1.

cleaved selectively by TFA under ambient conditions.[18] The nitro-Mannich reaction was undertaken initially in aqueous EtOH at 80 °C but under these conditions, solvolysis of the product **5** also occurred at the benzylic site, leading to the undesired tertiary alcohol, **6**. At elevated temperatures and in this polar solvent, it is assumed that an S_N1 reaction is favoured. Such nitro/hydroxyl substitution reactions are rare but have previously been reported at tertiary nitroalkane sites.[19] By reducing both solvent polarity (50 : 50, PhMe–EtOH) and the reaction temperature (40 °C), this substitution reaction was suppressed, allowing the desired nitro-compound, **5** to be isolated in moderate yield.

Reductive deprotection of **5** using tin, zinc or iron in HCl was compromised by concomitant solvolysis of the nitro-group, and both direct or transfer (HCO_2NH_4 or N_2H_4) hydrogenolysis over various palladium on carbon catalysts failed to give the desired triamine **3c** in significant yield. An attempt was therefore made to employ the conditions used by Ganem for selective nitro-group reduction using NiB_2/BH_4^- generated *in situ* from $NaBH_4$ and $NiCl_2$.[20] However, a reductive ring opening reaction occurred instead, leading to exclusive formation of the *N*-methylated oxime, **7**. The same product was observed following reduction with $LiAlH_4$ in Et_2O. This unusual reaction is presumably proceeding *via* a *C*-nitroso intermediate (Scheme 4), in which the endocyclic nitrogen lone-pair is antiperiplanar to the cleaving carbon–carbon bond in a Grob fragmentation, assisted by the favourable σ_N–σ^*_{CC} interaction. The successful selective reduction of the nitro group in **5** was finally undertaken using hydrogenation over RANEY® nickel in ethanol at room temperature, as reported by Go and co-workers.[21] The monoamine was converted into the carbamate derivate **8** directly, to facilitate chromatographic purification. Subsequent treatment with TFA in CH_2Cl_2 cleaved the electron rich benzyl groups and afforded the triamine **3c**.



Scheme 4

This sequence of transformations from **5** was not high yielding and an alternative route was explored that also allowed selective functionalisation of the exocyclic nitrogen. Removal of the dimethoxybenzyl groups using TFA gave the diamine (**9**) followed by selective *N*-alkylation with an α-bromoacetate ester (R = Et or ^{t}Bu). This process allowed the diesters **10** and **11** to be obtained in reasonable yield (Scheme 3). Subsequent nitro-reduction using hydrogenation over RANEY® nickel generated the amines **12** and **13** which could by *N*-alkylated again with the appropriate α-bromo ester to give the triesters **14** and **15**. Formation of the tetra-*N*-alkylated products was inhibited by the steric bulk of the phenyl group and required more forcing conditions to give the tetra-ester, **10**.

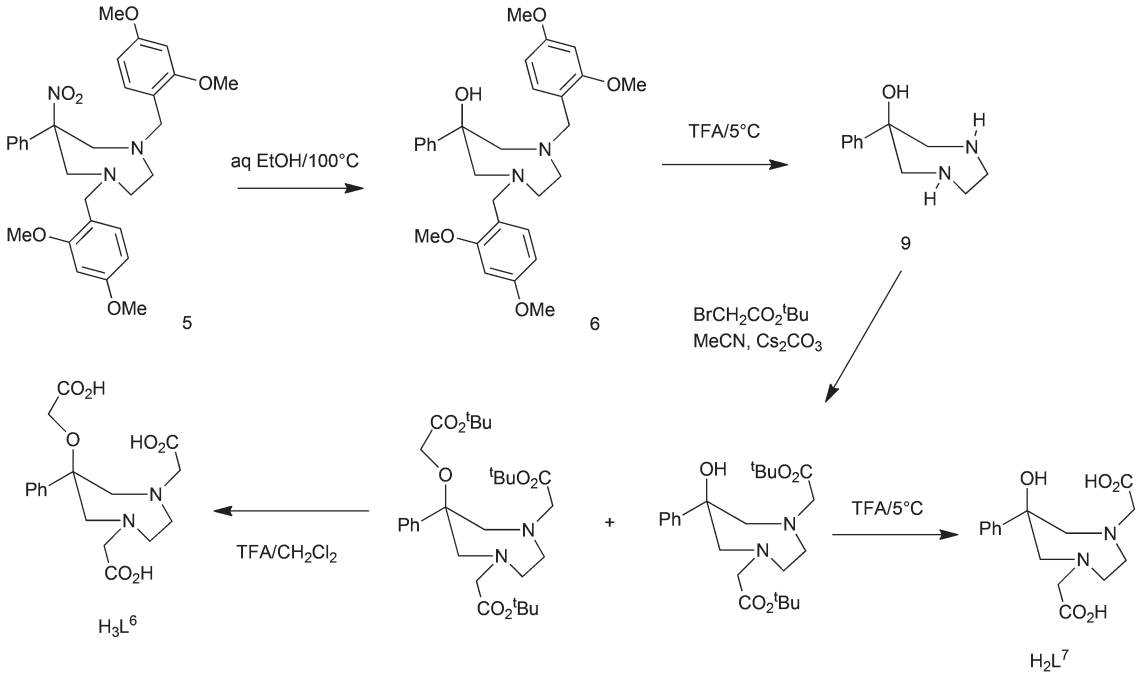
Acidic deprotection (TFA/CH_2Cl_2) or aqueous base hydrolysis in THF of **14** or **15** gave rise to the target ligand L^1. In the case of the deprotection of **14**, concomitant lactamisation of the product was observed – as had been noted earlier in the *C*-methyl series[13,2] – but to a much lesser extent. Therefore, the preferred sequence to L^1 involves the use of ethyl bromoacetate, as the base hydrolysis reaction conditions inhibit the undesired intramolecular cyclisation.

The lactamisation reaction noted with L^1 is impossible with a tertiary amine at the exocyclic site. Therefore, *N*-methylation of **14** (MeI/MeCN) gave **17**, followed by TFA treatment to offer the ligand L^2, without any problems. Similarly, the use of (*R*)-ethyl-2-trifluoromethylsulfonyl-propionate in place of $BrCH_2CO_2Et$, in this sequence allowed the synthesis of (*SSS*)-L^3 to be undertaken *via* compounds **18**, **19** and **20**. In this case, the lactamisation reaction does not occur at all when L^3 is in acidic aqueous media.

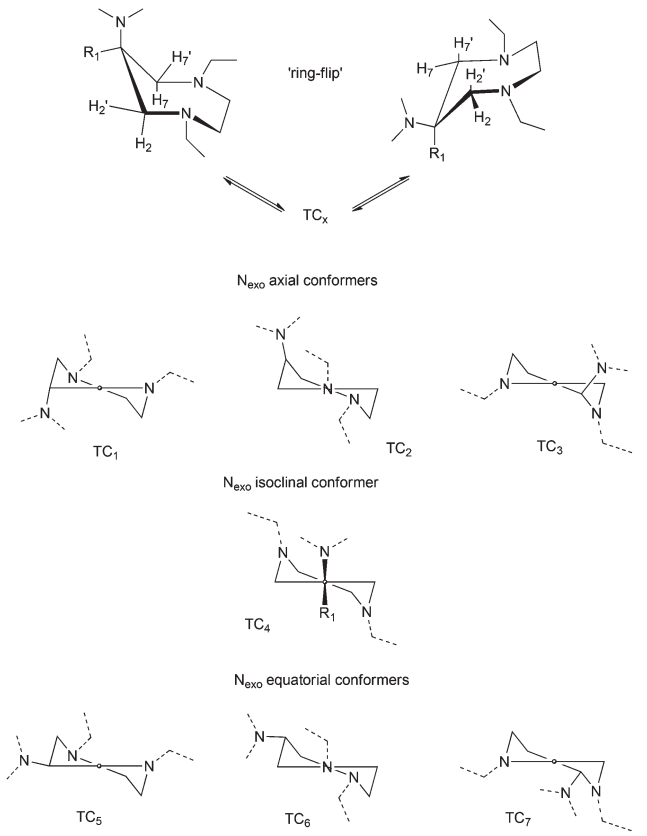
The unexpected formation of the tertiary alcohol **6**, *via* solvolysis of the nitro compound **5**, permitted the synthesis of the hexadentate ligand L^6. In this compound, the alkoxy substituent may be estimated to have an '*A*' value of about 2.5 kJ mol^{-1}, and hence the conformational bias in favour of the preferred geometry for metal ion binding is slightly greater than with L^1. Solvolysis of **5** in boiling aqueous ethanol afforded **6**, and following removal of the substituted *N*-benzyl groups (TFA/CH_2Cl_2), the resultant diamine **21** was alkylated with *tert*-butyl bromoacetate to afford the triester **22**, as well as the diester **23**. Cleavage of the ester groups in **23** and **22** with TFA led to formation of the pentadentate ligand, L^7 and the hexadentate compound L^6 (Scheme 5). These are new ligand types that will be the subject of further investigation in due course.

Conformational analysis of selected ligand intermediates

Earlier studies of the conformational analysis of 1,4-diazepine derivative revealed a preference for a twisted-chair conformer.[14] In the case of 6-substituted derivatives, there are seven such low energy conformations (Scheme 6). It is the presence of unfavourable eclipsing interactions in the NCH_2CH_2N moiety that disfavours population of alternative chair and boat conformers (Scheme 1). Amongst the seven twist-chair (TC_n) conformers, one has the exocyclic N-substituent in an isoclinal



Scheme 5



Scheme 6

position (TC_4) and two sets of three place it either axial (TC_{1-3}) or equatorial (TC_{5-7}). Crystal structures of the protonated salts of **3a** and **3b**, reveal population of TC_6 (H_3**3b**$^{3+}$), and TC_4/TC_7 (H_3**3a**$^{3+}$),[10] whilst in metal complexes of **3b** and substituted ligands derived from these triamines a chair conformation is preferred as it allows a facial N_3 array to be created, notwithstanding the concomitant unfavourable eclipsing interaction in the NCH_2CH_2N moiety[10,11b,12,22,23] and the need to place the N substituent in an axial site.

In the series of ligands defined herein, the metal-binding conformation (Scheme 6) is in equilibrium with an alternate chair, in which the N-substituent is equatorial. Exchange between these high-energy conformers occurs *via* the preferred TC_n conformations, and the relative steric bulk of the C_6 substituents in particular will determine the position of the equilibrium and the energy barrier to conformer exchange. Information concerning the ring conformation has been obtained for selected ligand intermediates by crystallographic analysis and by solution state ^{1}H NMR nOe spectroscopy.

A set of three intermediates **10**, **23** and **24**, gave crystals suitable for X-ray analysis, and their structures were solved at 120 K and compared to that of compound **5**.[2] In each structure, the seven-membered ring adopts a twist-chair conformation (Fig. 1). An alternate view taken along the C_4–C_5 bond illustrates the isoclinal orientation of the substituents at the quaternary centre. In each case, this corresponds to a TC_4 conformer (Scheme 6), and the compounds crystallised as a pair of enantiomers, related *via* a puckering of the ring. The NCH_2–CH_2N torsion angles were 56.9, 57.6, 54.7 and 49.3° for **5**, **10**, **23** and **24**, respectively; such values are close to the ideal 60° angle.

Proton NMR NOESY experiments provided information about the mutual spatial orientation of ligand protons in solution. In the ethyl esters **25** and **20**, with *C*-Me and *C*-Ph groups at the quaternary centre, the pairs of methylene

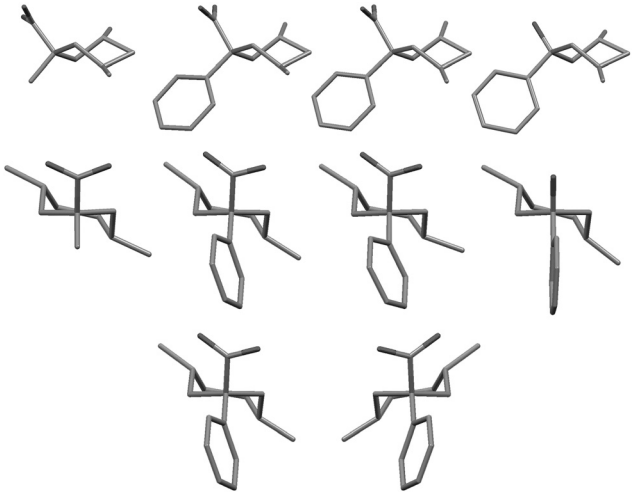


Fig. 1 Views (from the left) of the intermediates **24**, **5**, **10** and **23** in the solid-state (120 K): *upper*: showing the twist-chair conformation (TC_4); *centre*: view showing the isoclinal orientation of the substituents at the quaternary centre; *lower*: illustrating the enantiomeric conformers for **5**. Endocyclic N-substituents and H-atoms are removed for clarity.

protons are diastereotopic and anisochronous. The NOESY experiment allowed relative nOe enhancements to be assessed, in each case (Fig. 2 and Table 1). Strong nOe correlations were observed for **25**, between the exocyclic NCH proton (labelled H_a) and two endocyclic methylene protons, with a very weak correlation between the quaternary *C*-Me groups (labelled H_b) and this pair of protons. On the other hand, a very strong correlation was observed between H_b and the other pair of protons at C_2 and C_7 (Scheme 7). Thus, the methyl protons have through-space interactions with an 'axial' orientated proton on one carbon and an 'equatorial' proton on the other, whilst for the NC*H*Me proton (quartet at 3.41 ppm) the other pair of protons are close in space. Such correlations can tentatively be rationalised in terms of the preferred population of a TC_4 conformer (Scheme 7). The nearest neighbour distances in the X-ray analyses of **24** accord with this interpretation.

With the *C*-Ph triester, **20**, fewer strong nOe correlations were observed. NOE-correlations were found between the *ortho*-phenyl protons, H_b and each proton at C_2 and C_7, but only a weak nOe enhancement (4%) was measured between the NC*H*Me proton and one H_2 proton. Such behaviour is consistent with the adoption of a major solution conformer in which the exocyclic N-substituent adopts a more well-defined 'axial' position, with the phenyl ring equatorial and closer to the plane of the heterocyclic ring. As a consequence, the 'through space' distance between the NC*H*Me proton and the 'axial/equatorial' proton pairs at C_2 and C_7 increases, as is observed comparing relevant distances in the X-ray structures of **24** and **5**.

Comparative solution NMR behaviour of the protonated ligands L^{4a} and L^1

The sequence of protonation of the aza-carboxylate ligands L^{4a} (*C*-Me) and L^1(*C*-Ph) has been assessed by following the

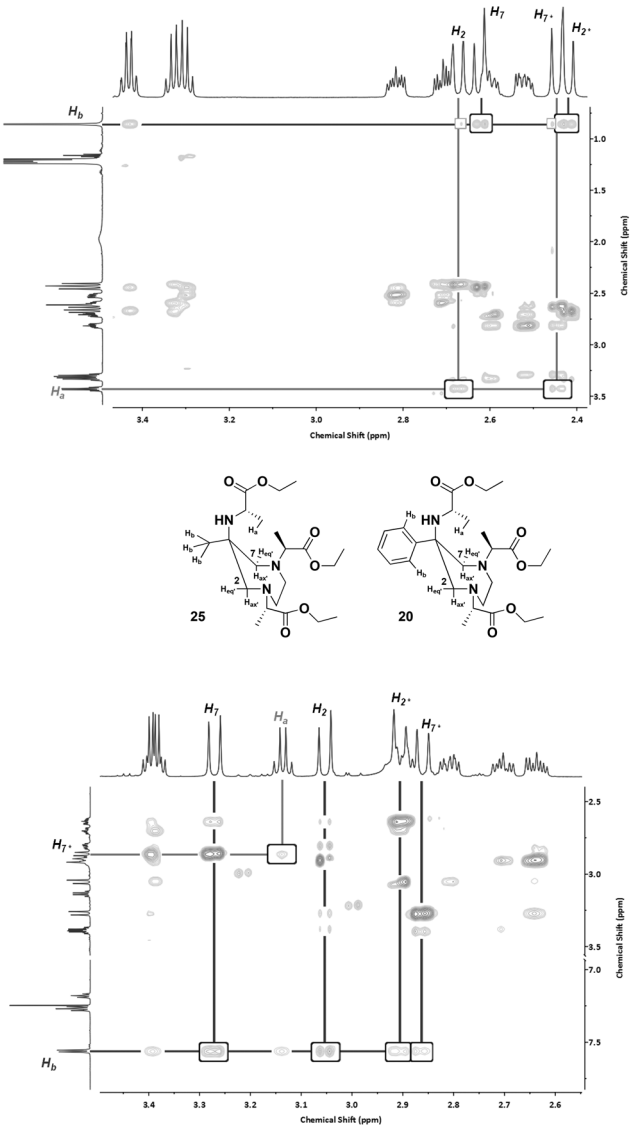
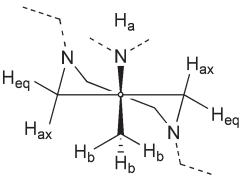


Fig. 2 2D-NOESY spectra (600 MHz, 298 K, $CDCl_3$): *upper*, for **25** showing nOe correlations between *C*-Me protons (H_b) and methylene hydrogens; *lower*, for **20** showing correlations between the *C*-Ph *ortho* hydrogens (H_b) and methylene protons; *centre*, schematic showing the numbering system used.

Table 1 ^{1}H NMR NOESY correlations and relative enhancements observed for **25** and **20** (600 MHz, 298 K) between protons at C_2 and C_7 and the *C*-Me (H_b) or *C*-Ph (*ortho*, H_b) protons, as well as the NC*H*Me proton (H_a)

NOESY correlation		Relative nOe enhancement (%)
25	H_b–$H_{2'}$	39
	H_b–H_7	27
	H_a–H_2	21
	H_a–$H_{7'}$	11
	H_b–H_2 and H_b–$H_{7'}$	$\leq$2
20	H_b–$H_{2'}$ and H_b–$H_{7'}$	31[a,b]
	H_b–H_7	36
	H_b–H_2	23
	H_a–$H_{7'}$	4

[a] Note that there are two *ortho* phenyl hydrogens (H_b) rotating rapidly about the *C*-Ph bond. [b] Signals were too close to separate individual enhancements.



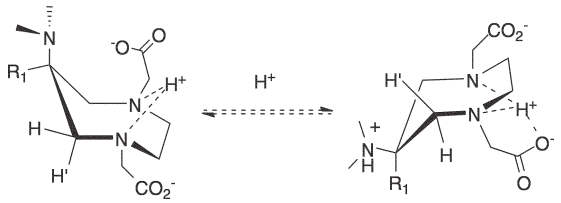
the proton H_a refers to a proton on the N-substituent

Scheme 7

changes in the chemical shift of the ^{1}H NMR ligand resonances as a function of pH. Earlier work has shown that the first pK_a of L^{4a} (and by inference L^1) lies above pH 10.5[13b,2] and can be ascribed to protonation of the endocyclic nitrogen to form a stable, bridged H-bond that rigidifies the structure. The second protonation will then occur at the exocyclic nitrogen (Scheme 8). This protonation step may be accompanied by a change in ligand conformation, as both Coulombic repulsion and the increased steric demand of an N-protonated substituent dictate that the exocyclic N-substituent may prefer an equatorial site. The pK_a value for H_2L^{4a} was measured to be 5.70 (±0.10) (295 K, I = 0.1 M NaCl)[2] and parallel experiments with H_2L^1 gave a value of 5.58 (±0.10) (ESI†).

Proton NMR NOESY experiments were undertaken with H_2L^{4a} at pH 2.0 (pD 2.4) 5.0 and pH 7. In the more acidic solution, the strongest nOe correlation was observed between the quaternary methyl group and the 2 protons at C_2/C_7 resonating to lower frequency (Fig. 3). The *N–Me* and proximate NCH_2 groups showed a strong nOe correlation to the higher frequency protons at C_2/C_7. In contrast, at pH 7, each of these correlations was reversed and the *C*-Me group must then be closer in space to the higher frequency protons, with the NMe and NCH_2C groups closer to the pair of protons resonating to lower frequency. Such behaviour accords with a protonation process in which the *C*-Me site occupies an axial site at lower pH and the bulkier protonated N-substituent prefers to adopt the equatorial position. At higher pH, these site preferences are reversed. In contrast, parallel NOESY experiments with L^1 in D_2O showed no significant pH dependence of the nOe correlations in the pH range 2 to 7, strongly suggesting that the bulkier phenyl ring adopted the equatorial position constantly.

The behaviour of the protonated ligand $[H_2L^{4a}]^{2+}$ at pD 2.4 was also examined by variable temperature ^{1}H NMR spectroscopy. A series of spectra was recorded at 5 °C intervals from 298 K to 363 K (ESI†). The endocyclic methylene protons at C_2 and C_7 resonate as a simple AB spin system, separated by



Scheme 8

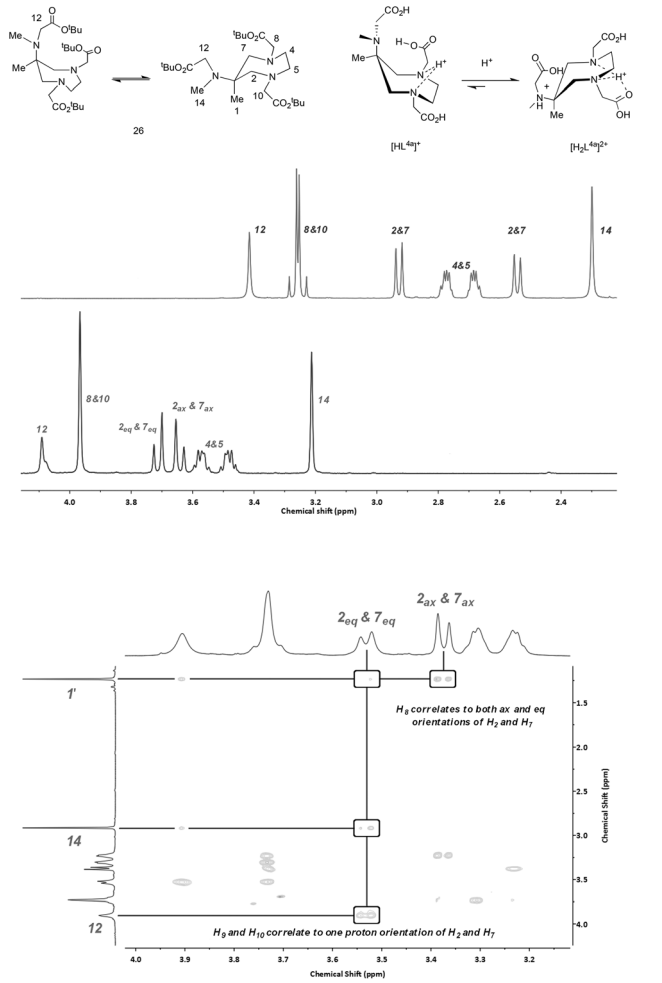


Fig. 3 Partial ^{1}H NMR spectra (700 MHz, 298 K) for the triester, **26** ($CDCl_3$), and for $[H_2L^{4a}]^{2+}$ (D_2O, pD 2.4) showing the spectral assignments; *lower* 2D-NOESY NMR spectrum (700 MHz, pD 2.4, 298 K) for $[H_2L^{4a}]^{2+}$ showing observed correlations.

0.14 ppm with a coupling constant of −16 Hz at 298 K. As the temperature increased, a coalescence phenomenon was observed with T_c estimated to be 360 K. An estimate of the activation energy associated with this dynamic exchange process, based on a conventional two-site Eyring analysis, gave a free energy of activation of 74 (±2) kJ mol^{-1}. This relatively high energy barrier to interconversion of the major solution conformers can be attributed to the difficulty of exchanging chair or twisted chair conformers in which the quaternary substituents exchange sites. This process exchanges the axial/equatorial positions of the observed, methylene protons (Scheme 8).

Conclusions

These 2D-NOESY and dynamic NMR experiments offer a simple explanation for the pH-dependent ligand speciation of the series of ligands, L^1–L^4, and their behaviour in binding Ga^{3+} at pH 2, 3 and 5.[2] It was found that the *C*-Me series of ligands, L^{4a}/L^{4b} bound ^{68}Ga quickly, but gave rise to more than

one type of radiolabelled complex, over the whole pH range, of differing relative stability. In contrast, the *C*-Ph series of ligands, L^1–L^3, bind ^{68}Ga rapidly at pH ≥ 3.5 to produce one major stable solution species, and only at lower pH gave rise to additional species of inferior kinetic stability. Thus, if the forward rate of Ga complexation is fast with respect to the rate of interconversion of the major ligand solution conformers, 'kinetically trapped' metal complexes of lower stability will form, by binding to the isolated EDDA or NDA moieties (EDDA: ethylenediaminediacetate; NDA-aminodiacetate) (Scheme 2).

Therefore, the ligands L^1–L^3, populating a preferred major solution conformer that reduces the likelihood of formation of the less stable metal complexes lacking cooperative N_3O_3 ligation, are excellent candidates for the rapid radiolabelling of Ga^{3+} and related small tripositive metal ions that are similar in size. Crystal structures of the Ga^{3+} complexes of L^1, L^3 and L^{4a} [3,24] have revealed formation of the expected N_3O_3 binding polyhedron, in which the seven-membered ring adopts a chair conformation. Detailed analysis of this structural work has been reported elsewhere.[27]

We thank the Association of Commonwealth Universities for a Scholarship (BPW), and thank Dr Dmitry Yufit (X-ray) and Dr Juan Aguilar for help with X-ray and NMR analyses.

Experimental

General experimental details for reagents, solvents, chromatography and spectroscopy have been reported in ref. 2 (ESI†).

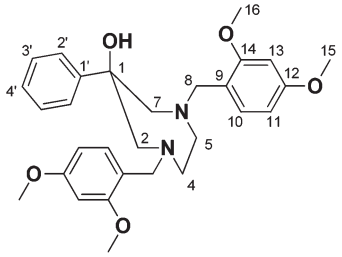
Crystallography

The single crystal X-ray data were collected at 120 K on a Agilent Gemini Ultra (compound **10**), a Bruker SMART 1000 (compound **23**) and a Bruker SMART 6000 (compound **24**) diffractometers (graphite monochromators, λMoK_α, λ = 0.70073 Å) equipped with Cryostream (Oxford Cryosystems) open-flow nitrogen cryostats. Each structure was solved by direct methods and refined by full-matrix least squares on F^2 for all data using Olex2[25] and SHELXTLγ[26] software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms in structure **23** and **24** were located on the difference map and refined isotropically, H atoms in structure **10** and the methyl group of molecule **24** were placed in the calculated positions and refined in "riding" mode. The atoms of disordered over two positions tertiary butyl groups in molecule **10** were refined isotropically with fixed SOF = 0.5. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 906040, 911245, 911246 and 906039 (compounds **5**, **10**, **23** and **24** respectively). The structures of compounds **24** and **5** have been reported earlier[3] and are compared here (CCDC 906039 and CCDC 906040).

Synthesis

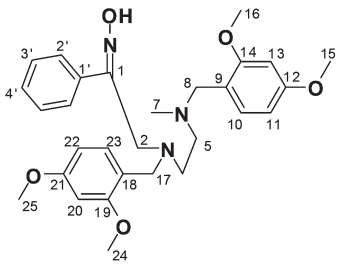
Details of the synthesis of compounds **9**, **11–13**, **15**, **18–20** and ligands H_3L^1 and H_3L^3 were given in the ESI† of the related preliminary communication.[2]

1,4-Bis(2,4-dimethoxybenzyl)-6-phenyl-1,4-diazepan-6-ol, 6.



The nitro-compound, **5**, (0.05 g, 0.10 mmol) was dissolved in ethanol (20 mL) and the solution boiled under reflux. The solvolysis reaction was monitored using TLC (hexane : ethyl acetate; 65 : 35). Once the precursor (R_f = 0.55) had been consumed, solvent was removed under reduced pressure and the resulting oil re-dissolved in chloroform (50 mL) and washed successively with aqueous potassium carbonate solution (2 × 50 mL, 0.1 M) and water (50 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by silica gel column chromatography (hexane → 50% ethyl acetate) yielded a yellow oil (0.017 g, 34%). R_f = 0.45 (hexane : ethyl acetate; 50 : 50). δ_H ($CDCl_3$, 700 MHz): 2.53 (2H, m, $H^{4,5}$); 2.76 (2H, d, *J* 13, $H^{2,7}$); 2.80 (2H, m, $H^{4,5}$); 3.18 (2H, d, *J* 13, $H^{2,7}$); 3.67 (2H, d, *J* 4, H^8); 3.74 (2H, d, *J* 4, H^8); 3.78 (6H, s, H^{16}); 3.79 (6H, s, H^{15}); 6.41 (2H, d, *J* 9, H^{11}); 6.44 (2H, s, H^{13}); 7.16 (2H, d, *J* 9, H^{10}); 7.20 (1H, t , *J* 8, $H^{4'}$); 7.30 (2H, t, *J* 8, $H^{3'}$); 7.48 (2H, d, *J* 8, $H^{2'}$). δ_C($CDCl_3$, 176 MHz): 54.0 ($C^{4/5}$); 55.3 (C^{16}); 55.3 (C^{15}); 56.8 (C^8); 67.6 ($C^{2,7}$); 74.7 ($C^{1'}$); 98.5 (C^{13}); 103.7 (C^{11}); 120.0 (C^9); 124.6 ($C^{2'}$); 126.4 ($C^{4'}$); 127.9 ($C^{3'}$); 131.0 (C^{10}); 146.1 (C^1); 158.8 (C^{12}); 160.0 (C^{14}). HRMS ES+ (*m*/*z*): found: 493.2724 $[M + H]^+$; $C_{29}H_{37}N_2O_5$ requires 493.2702.

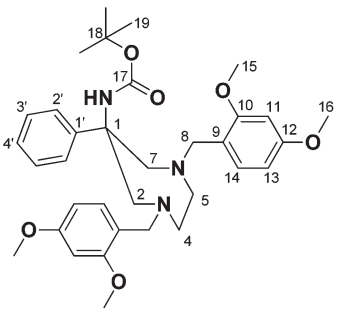
***tert*-Butyl 1,4-bis(2,4-dimethoxybenzyl)-6-phenyl-1,4-diazepan-6-yl carbamate, 7.**



Sodium borohydride (0.013 g, 0.58 mmol) was added portionwise to a solution of nickel(II)chloride hexahydrate (0.025 g, 0.11 mmol) in anhydrous methanol (20 mL) cooled in an ice-bath, and the mixture stirred for 30 min. The protected amine **5** (0.10 g, 0.19 mmol) dissolved in anhydrous methanol (2 mL) was added to the reaction mixture, followed by sodium borohydride (0.028 g, 0.74 mmol) added in portions. The reaction mixture was allowed to warm to room temperature. The reaction was monitored by TLC, and once complete the mixture

was filtered through Celite®, and the insoluble borate salts washed with ice-cold methanol. The filtrates were combined, and the solvent removed under reduced pressure. The resulting residue was re-dissolved in chloroform (40 mL) and washed successively with aqueous potassium carbonate solution (2 × 30 mL, 0.1 M) and water (30 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by silica gel column chromatography (hexane → 20% ethyl acetate) afforded a colourless oil (0.075 g, 78%). R_f = 0.35 (hexane : ethyl acetate; 50 : 50). δ_H ($CDCl_3$, 500 MHz): 2.16 (3H, s, H^7); 2.66 (2H, m, H^5); 2.74 (2H, m, H^4); 3.46 (2H, s, H^8); 3.67 (2H, s, H^{17}); 3.75 (6H, s, $H^{15/16,24/25}$); 3.79 (6H, s + s, $H^{15/16,24/25}$); 3.86 (2H, s, H^2); 6.41 (4H, m, $H^{13,14,22,23}$); 7.08 (1H, d, *J* 8, H^{20}); 7.18 (1H, d, *J* 8, H^{11}); 7.33 (3H, m, $H^{3',4'}$); 7.59 (2H, m, $H^{2'}$). δ_C ($CDCl_3$, 125 MHz): 42.52 (C^7); 51.24 (C^4); 53.23 (C^{17}); 53.43 (C^2); 54.34 (C^5); 55.40 ($C^{15/16,24/25}$); 55.50 ($C^{15/16,24/25}$); 55.77 (C^8); 98.64 ($C^{13/14/22/23}$); 98.71 ($C^{13/14/22/23}$); 104.09 ($C^{13/14/22/23}$); 104.28 ($C^{13/14/22/23}$); 117.15 (C^{18}); 119.16 (C^9); 126.31 ($C^{2'}$); 128.52 ($C^{3'/4'}$); 128.99 ($C^{3'/4'}$); 131.82 (C^{11}); 132.46 (C^{20}); 136.52 ($C^{1'}$); 154.26 (C^1); 159.03 (C^{10}); 159.34 (C^{19}); 160.24 ($C^{12/21}$); 161.01 ($C^{12/21}$). HRMS ES+ (*m*/*z*): found 508.2818 $[M + H]^+$; $C_{29}H_{38}N_3O_5$ requires 508.2811.

(*E*)-2-((2,4-Dimethoxybenzyl)(2-((2,4-dimethoxybenzyl)(methyl)-amino)ethyl)amino)-1-phenylethanone oxime, 8.

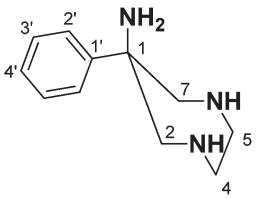


The synthesis of the NHBoc-protected primary amine, **8**, was carried out in two steps, involving reduction of the nitro-functionality, followed by Boc-protection.

An aqueous slurry of RANEY® nickel (0.010 g) was washed with methanol (3 × 25 mL) and ethanol added (10 mL). The suspension was then transferred into a solution of **5** (0.050 g, 0.096 mmol) in ethanol (25 mL). The flask was evacuated and back-filled with hydrogen gas using four vacuum-purge cycles, and the mixture stirred at 298 K under an atmosphere of hydrogen. The reaction was monitored by TLC for formation of the primary amine. Once complete (~3 h), the solution was decanted, and the solid washed with methanol (3 × 20 mL). The washings and decanted solution were combined, removed under reduced pressure and re-dissolved in methanol (25 mL). Remaining RANEY® nickel and insoluble by-products where removed by filtration through a base washed Celite® filter, and the solvent was then removed under reduced pressure. The resulting oil was re-dissolved in chloroform : isopropanol (80 : 20; 20 mL) and washed successively with aqueous sodium hydroxide (2 × 20 mL, 0.5 M) and water (15 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure to yield a colourless oil.

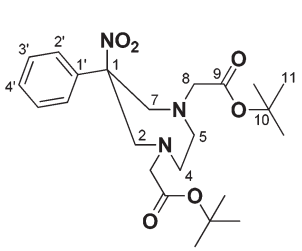
Di-*tert*-butyl dicarbonate (0.042 g, 0.19 mmol) was added gradually, to a solution of the amine and triethylamine (0.029 g, 0.29 mmol) in chloroform (15 mL), and the mixture stirred at room temperature. The reaction was monitored by LS-ES MS, to follow consumption of starting material. Once complete, solvent was removed and the residue re-dissolved in chloroform (15 mL) and washed successively with aqueous sodium hydroxide (2 × 15 mL, 0.5 M) and water (3 × 10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield a colourless oil. Purification by silica gel column chromatography (hexane → 60% ethylacetate) afforded a colourless oil (0.005 g, 9%). R_f = 0.35 (hexane : ethylacetate, 50 : 50). δ_H ($CDCl_3$, 700 MHz): 1.36 (3H, s, H^{19}); 2.48 (4H, s, H^8); 2.72 (2H, m, $H^{4,5}$); 3.35 (2H, m, $H^{4,5}$); 3.46 (2H, d, *J* 13, $H^{2,7}$); 3.59 (2H, d, *J* 13, $H^{2,7}$); 3.73 (6H, s, $H^{15/16}$); 3.78 (6H, s, $H^{15/16}$); 6.37 (2H, d, *J* 8, H^{11}); 6.41 (2H, s, H^{13}); 7.14 (4H, m, $H^{3',4',10}$); 7.35 (4H, m, $H^{2'}$). δ_C ($CDCl_3$, 176 MHz): 28.25 (C^{19}); 55.33 ($C^{15/16}$); 55.53 ($C^{15/16}$); 57.19 (C^8); 57.33 ($C^{2/7}$); 57.84 (C^1); 68.77 ($C^{4/5}$); 78.61 (C^{18}); 98.65 (C^{11}); 103.73 (C^{13}); 120.21 (C^9); 125.17 ($C^{2'}$); 125.75 ($C^{3'}$); 125.92 ($C^{4'}$); 131.12 (C^{14}); 146.19 (C^{17}); 159.46 (C^{12}); 159.76 (C^{10}). HRMS ES+ (*m*/*z*): found 592.3406 $[M + H]^+$; $C_{34}H_{46}N_3O_6$ requires 592.3387; found 614.3221 $[M + Na]^+$; $C_{34}H_{45}N_3NaO_6$ requires 614.3206.

6-Phenyl-1,4-diazepan-6-amine, 3c.



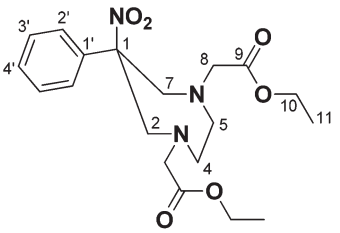
Trifluoroacetic acid (1 mL) was added to a solution of the protected triamine **8** (0.010 g, 0.017 mmol) in dichloromethane (1 mL), and the mixture stirred at room temperature. The reaction was monitored using LC-ESI MS, and once complete, the solvent was removed by lyophilisation. Excess trifluoroacetic acid was removed through repeated addition and removal of dichloromethane (3 × 2 mL) and subsequently methanol (3 × 2 mL), to afford a white solid (0.004 g). δ_H (CD_3OD, 600 MHz): 3.37 (2H, m, $H^{4,5}$); 3.42 (2H, d, *J* 15, $H^{2,7}$); 3.56 (2H, m, $H^{4,5}$); 3.70 (2H, d, *J* 15, $H^{2,7}$); 7.29 (1H, t, $H^{4'}$); 7.35 (2H, t, $H^{2'}$); 7.38 (2H, d, $H^{2'}$). δ_C (CD_3OD, 151 MHz): 43.77 ($C^{4,5}$); 53.13 ($C^{2,7}$); 65.88 (C^1); 124.76 ($C^{2'}$); 125.00 ($C^{4'}$); 129.48 ($C^{3'}$). HRMS ES+ (*m*/*z*): found 192.1485 $[M + H]^+$; $C_{11}H_{18}N_3$ requires 192.1501.

***tert*-Butyl 2,2′-(6-nitro-6-phenyl-1,4-diazepane-1,4-diyl)diacetate, 10.**



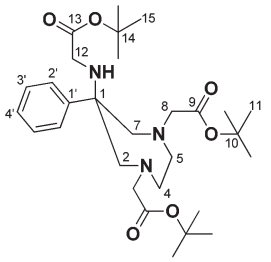
tert-Butyl bromoacetate (0.10 g, 0.52 mmol) was added dropwise to a mixture of potassium carbonate (0.072 g, 0.52 mmol) and **9** (0.029 g, 0.13 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at 35 °C for 24 h, and solvent removed under reduced pressure. The resulting oil was re-dissolved in chloroform (20 mL) and washed successively with aqueous potassium carbonate solution (2 × 20 mL, 0.1 M) and water (20 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by silica gel column chromatography (hexane : ethyl acetate, 95 : 5) yielded a white solid (0.036 g, 62%). R_f = 0.49 (hexane : ethyl acetate; 65 : 35). m.p. 78–90 °C. δ_H ($CDCl_3$, 700 MHz): 1.44 (18H, s, H^{11}); 2.93 (2H, m, $H^{4,5}$); 3.03 (2H, m, $H^{4,5}$); 3.38 (2H, d, *J* 17, H^8); 3.56 (2H, d, *J* 17, H^8); 3.63 (2H, d, *J* 15, $H^{2,7}$); 3.96 (4H, d, *J* 15, $H^{2,7}$); 7.24 (2H, d, *J* 8, $H^{2'}$); 7.31 (2H, m, $H^{3',4'}$). δ_C ($CDCl_3$, 176 MHz): 28.20 (C^{11}); 55.93 ($C^{4,5}$); 60.33 (C^8); 62.87 ($C^{2,7}$); 81.15 (C^{10}); 97.99 ($C^{1'}$); 124.62 ($C^{2'}$); 128.52 ($C^{4'}$); 128.81 ($C^{3'}$); 138.68 (C^1); 170.90 (C^9). HRMS ES+ (*m*/*z*): found: 450.2612 $[M + H]^+$; $C_{23}H_{36}N_3O_6$ requires 450.2604. The structure of **7** was confirmed by single crystal X-ray diffraction: $C_{23}H_{35}N_3O_6$, M_r = 449.54, monoclinic ($P2_1/c$); *a* = 21.3378(19) Å, *b* = 11.5579(10) Å, *c* = 10.3203(9) Å, *V* = 2503.9(4) Å^3, β = 100.329(9)°, *Z* = 4; μ = 0.086 mm^{-1}, $D_{calc.}$ = 1.192 mg mm^{-3}, *T* 120(2) K; 5463 independent reflections (R_{int} = 0.1564), R_1 = 0.0899, ωR_2 = 0.1741 ($I > 2\sigma(I)$). CCDC 911245.

Diethyl 2,2′-(6-nitro-6-phenyl-1,4-diazepane-1,4-diyl)diacetate, 11.



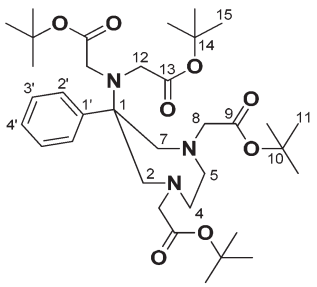
Ethyl bromoacetate (0.061 g, 0.52 mmol) was added dropwise to a stirred solution of potassium carbonate (0.072 g, 0.52 mmol) and **9** (0.029 g, 0.13 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at 35 °C for 24 h, and solvent removed under reduced pressure. The resulting oil was re-dissolved in chloroform (20 mL) and washed successively with aqueous potassium carbonate solution (2 × 20 mL, 0.1 M) and water (20 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by silica gel column chromatography (hexane → 20% ethyl acetate) yielded a yellow oil (0.034 g, 66%). R_f = 0.27 (hexane : ethyl acetate, 65 : 35). δ_H ($CDCl_3$, 700 MHz): 1.26 (6H, t, *J* 7, H^{11}); 2.96 (2H, m, $H^{4,5}$); 3.04 (2H, m, $H^{4,5}$); 3.49 (2H, d, *J* 18, H^8); 3.64 (2H, d, *J* 15, $H^{2,7}$); 3.67 (2H, d, *J* 18, H^8); 3.97 (2H, d, *J* 15, $H^{2,7}$); 7.24 (2H, d, *J* 8, $H^{2'}$); 7.32 (2H, m, $H^{3',4'}$). δ_C ($CDCl_3$, 176 MHz): 14.26 (C^{11}); 55.85 ($C^{4,5}$); 59.41 (C^8); 60.40 (C^{10}); 62.70 ($C^{2,7}$); 97.76 ($C^{1'}$); 124.63 ($C^{2'}$); 128.62 ($C^{4'}$); 128.84 ($C^{3'}$); 138.41 (C^1); 171.53 (C^9). HRMS ES+ (*m*/*z*): found: 394.1968 $[M + H]^+$; $C_{19}H_{28}N_3O_6$ requires 394.1978.

***tert*-Butyl 2,2′-(6-(2-*tert*-butoxy-2-oxoethylamino)-6-phenyl-1,4-diazepane-1,4-diyl)diacetate, 14.**



tert-Butyl-bromoacetate (0.29 g, 1.6 mmol) was added to a solution of **12** (0.050 g, 0.3 mmol) and potassium carbonate (0.31 g, 2.1 mmol) in acetonitrile (30 mL), and the mixture stirred for 18 h at 40 °C under argon. The solvent was removed under reduced pressure and the resulting oil re-dissolved in chloroform (20 mL) and washed successively with aqueous potassium carbonate solution (2 × 20 mL, 0.1 M) and water (20 mL), dried over magnesium sulphate, filtered and solvent removed under reduced pressure. Purification by silica gel column chromatography (hexane → 5% ethyl acetate) yielded a yellow oil (0.051 g, 32%). R_f = 0.60 (hexane : ethyl acetate; 65 : 35). δ_H ($CDCl_3$, 700 MHz): 1.37 (18H, s, H^{11}); 1.38 (9H, s, H^{15}); 1.89 (1H, br. s, NH); 2.83 (2H, d, *J* 15, $H^{4,5}$); 2.87 (4H, s, $H^{2,7}$); 3.04 (2H, s, H^{12}); 3.27 (2H, d, *J* 15, $H^{4,5}$); 3.33 (4H, s, H^8); 7.14 (1H, t, *J* 7, $H^{4'}$); 7.24 (2H, t, *J* 7, $H^{3'}$); 7.45 (2H, d, *J* 7, $H^{2'}$). δ_C ($CDCl_3$, 176 MHz): 28.10 (C^{11}); 28.21 (C^{15}); 45.57 (C^{12}); 56.44 ($C^{2,7}$); 61.62 (C^8); 62.08 ($C^{1'}$); 65.54 ($C^{4,5}$); 80.88 ($C^{10,14}$); 126.51 ($C^{2'}$); 126.67 ($C^{4'}$); 128.26 ($C^{3'}$); 144.48 (C^1); 171.01 (C^9); 171.75 (C^{13}). HRMS ES+ (*m*/*z*): found: 534.3556 $[M + H]^+$; $C_{29}H_{48}N_3O_6$ requires 534.3543.

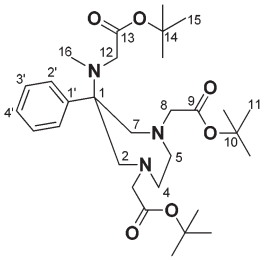
***tert*-Butyl 2,2′-(1,4-bis(2-*tert*-butoxy-2-oxoethyl)-6-phenyl-1,4-diazepan-6-ylazanediyl)diacetate, 16.**



tert-Butyl-bromoacetate (0.14 g, 0.72 mmol) was added to a solution of **12** (0.050 g, 0.12 mmol) and potassium carbonate (0.13 g, 0.96 mmol) in acetonitrile (20 mL), and the mixture stirred for 18 h at 50 °C under argon. The solvent was removed under reduced pressure and the resulting oil re-dissolved in chloroform (20 mL) and washed successively with aqueous potassium carbonate solution (2 × 20 mL, 0.1 M) and water (2 × 20 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by silica gel column chromatography (hexane → 5% ethyl acetate) afforded the title compound as a yellow oil (0.009 g, 12%). R_f = 0.75 (hexane : ethyl acetate; 65 : 35). δ_H ($CDCl_3$, 700 MHz): 1.42 (18H, s, $H^{11/15}$);

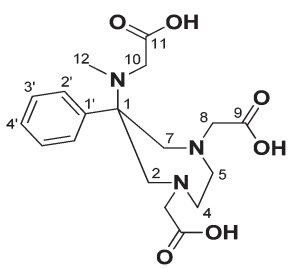
1.43 (18H, s, $H^{11/15}$); 2.72 (2H, m, $H^{4,5}$); 2.84 (2H, m, $H^{4,5}$); 3.11 (2H, d, *J* 15, $H^{2,7}$); 3.29 (4H, d + d, $H^{2,7+8}$); 3.36 (2H, d, *J* 17, H^{8}); 3.59 (4H, s, H^{12}); 7.17 (1H, t, *J* 8, $H^{4'}$); 7.27 (2H, t, *J* 8, $H^{3'}$); 7.73 (2H, d, *J* 8, $H^{2'}$). δ_C ($CDCl_3$, 176 MHz): 28.08 ($C^{11/15}$); 28.19 ($C^{11/15}$); 53.66 (C^{12}); 59.12 ($C^{4,5}$); 62.04 (C^{8}); 65.41 ($C^{2,7}$); 67.37 (C^{1}); 80.06 ($C^{10/14}$); 80.84 ($C^{10/14}$); 126.46 ($C^{4'}$); 127.08 ($C^{2'}$); 128.05 ($C^{3'}$); 147.73 ($C^{1'}$); 170.54 (C^{9}); 172.13 (C^{13}). HRMS ES+ (*m*/*z*): found 648.4227 $[M + H]^+$; $C_{35}H_{58}N_3O_8$ requires 648.4224; found 670.4058 $[M + Na]^+$; $C_{35}H_{57}N_3NaO_8$ requires 670.4043.

***tert*-Butyl 2,2′-(6-((2-*tert*-butoxy-2-oxoethyl)(methyl)amino)-6-phenyl-1,4-diazepane-1,4-diyl)diacetate, 17.**



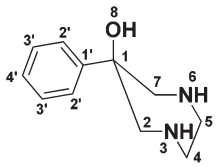
Methyl iodide (0.032 g, 0.023 mmol) was added to a solution of **14** (0.03 g, 0.056 mmol) and potassium carbonate (0.032 g, 0.023 mmol) in acetonitrile (30 mL), and the mixture stirred for 24 hours at 30 °C, under argon. The solvent was removed under reduced pressure and the resulting oil re-dissolved in chloroform (20 mL) and washed successively with aqueous potassium carbonate solution (2 × 20 mL, 0.1 M) and water (20 mL), dried over potassium carbonate, filtered and solvent removed under reduced pressure. Purification by silica gel column chromatography (hexane → 5% ethyl acetate) yielded a yellow oil (0.01 g, 45%). R_f = 0.60 (SiO_2, hexane : ethyl acetate; 65 : 35). δ_H ($CDCl_3$, 700 MHz): 1.38 (18H, s, H^{11}); 1.39 (9H, s, H^{15}); 2.23 (3H, s, H^{16}); 2.70 (2H, m, $H^{4,5}$); 2.80 (4H, m, $H^{4,5}$); 3.06 (2H, d, *J* 15, $H^{2,7}$); 3.13 (2H, d, *J* 15, $H^{2,7}$); 3.26 (2H, d, *J* 17, H^{8}); 3.30 (2H, d, *J* 17, H^{8}); 3.47 (2H, s, H^{12}); 7.11 (1H, t, *J* 8, $H^{4'}$); 7.21 (2H, t, *J* 8, $H^{3'}$); 7.63 (2H, d, *J* 8, $H^{2'}$). δ_C ($CDCl_3$, 176 MHz): 28.12 (C^{11}); 28.20 (C^{15}); 45.57 (C^{12}); 38.40 (C^{16}); 54.73 (C^{12}); 58.84 ($C^{4,5}$); 62.19 (C^{8}); 64.11 ($C^{2,7}$); 66.55 ($C^{1'}$); 80.10 (C^{14}); 80.84 (C^{10}); 126.27 ($C^{4'}$); 126.94 ($C^{2'}$); 127.96 ($C^{3'}$); 148.05 (C^{1}); 170.63 (C^{9}); 172.37 (C^{13}). HRMS ES+ (*m*/*z*): found: 548.3704 $[M + H]^+$; $C_{30}H_{50}N_3O_6$ requires 548.370.

2,2′-(6-((Carboxymethyl)(methyl)amino)-6-phenyl-1,4-diazepane-1,4-diyl)diacetic acid, H_3L^2.



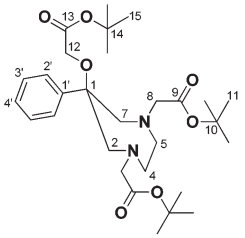
The triester **14** (0.050 g, 0.091 mmol) was dissolved in trifluoroacetic acid–dichloromethane (1 : 1; 2 mL) and left to stir for 2 d at room temperature. The solvent was removed under reduced pressure, the residue re-dissolved in dichloromethane : methanol (1 : 1; 2 mL) and evaporated. This procedure was repeated twice, and with methanol. The resulting solid was dissolved in water (10 mL) and washed with dichloromethane (10 mL). Removal of solvent under reduced pressure and drying *in vacuo* afforded a white solid (0.039 g, 71%). δ_H (D_2O, pD = 2.6, 600 MHz): 2.62 (3H, s, H^{12}); 3.15 (2H, m, $H^{4,5}$); 3.44 (2H, m, $H^{4,5}$); 3.44 (2H, d, *J* 14, $H^{2,7}$); 3.67 (3H, m, $H^{4/5,10}$); 3.83 (3H, m, $H^{4/5,8}$); 3.88 (2H, d, *J* 14, $H^{2,7}$); 7.30 (1H, m, $H^{4'}$); 7.35 (2H, m, $H^{3'}$); 7.40 (2H, m, $H^{2'}$). δ_C (D_2O, pD = 2.6, 151 MHz): 32.60 (C^{12}); 51.89 ($C^{4/5}$); 53.19 ($C^{4/5}$); 58.73 (C^{10}); 59.00 (C^{8}); 63.00 ($C^{2,7}$); 71.85 (C^{1}); 128.87 ($C^{4'}$); 129.05 ($C^{3'}$); 129.44 ($C^{2'}$); 170.04 (C^{9}); 172.80 (C^{11}). HRMS ES+ (*m*/*z*): found 380.1818 $[M + H]^+$; $C_{18}H_{26}N_3O_6$ requires: 380.1822. Found: C, 43.2; H, 4.33; N, 6.84%. $[C_{18}H_{25}N_3O_6]\cdot 2CF_3COOH$ requires: C, 43.5; H, 4.48; N, 6.92%.

6-Phenyl-1,4-diazepan-6-ol, 21.



3,6-Bis(2,4-dimethoxybenzyl)-1-phenyl-3,6-diazepan-1-ol (0.100 g, 0.52 mmol) was dissolved in trifluoroacetic acid–dichloromethane (1 : 1, 2 mL) and left to stir for 2 days at room temperature. The solvent was removed under reduced pressure, the residue re-dissolved in dichloromethane and evaporated. This procedure was repeated twice. The residue was recrystallised from methanol–dichloromethane (1 : 1) to afford a white solid (0.029 g, 76%). δ_H (CD_3OD, 700 MHz): 2.83 (2H, d, *J* 14, $H^{2,7}$); 2.92 (2H, m, $H^{4,5}$); 3.07 (2H, m, $H^{4,5}$); 3.19 (2H, d, *J* 14, $H^{2,7}$); 7.20 (1H, t, *J* 8, $H^{4'}$); 7.37 (2H, t, *J* 8, $H^{3'}$); 7.45 (2H, d, *J* 8, $H^{2'}$). δ_C (CD_3OD, 176 MHz): 48.6 ($C^{4,5}$); 58.9 ($C^{2,7}$); 76.2 (C^{1}); 124.3 ($C^{2'}$); 126.6 ($C^{4'}$); 127.8 ($C^{3'}$); 145.4 ($C^{1'}$). HRMS ES+ (*m*/*z*): found: 193.1271 $[M + H]^+$; calculated for $C_{11}H_{17}N_2O$: 193.1341.

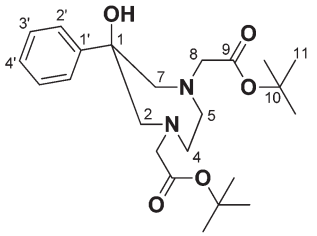
***tert*-Butyl 2,2′-(6-(2-*tert*-butoxy-2-oxoethoxy)-6-phenyl-1,4-diazepane-1,4-diyl)diacetate, 22.**



tert-Butyl-bromoacetate (0.10 g, 0.52 mmol) was added to a solution of **21** (0.02 g, 0.10 mmol) and caesium carbonate (0.10 g, 0.52 mmol) in acetonitrile (15 mL), and the mixture stirred for 18 h at 363 K under argon. The solvent was removed under reduced pressure and the resulting oil re-dissolved in chloroform (15 mL) and washed successively with aqueous potassium carbonate solution (2 × 15 mL, 0.1 M) and water (10 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by silica gel column chromatography

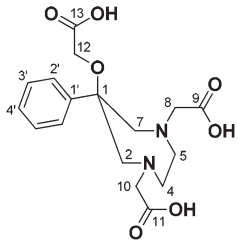
(hexane → 20% ethyl acetate) afforded a colourless oil (0.018 g, 33%). R_f = 0.25 (hexane : ethyl acetate; 50 : 50). δ_H ($CDCl_3$, 700 MHz): 1.42 (18H, s, $H^{11/15}$); 1.43 (9H, s, $H^{11/15}$); 1.46 (9H, s, H^{19}); 1.48 (9H, s, H^{16}); 2.50 (1H, d, *J* 7, $H^{8/12}$); 2.59 (1H, d, *J* 14, $H^{2/7}$); 2.66 (1H, d, *J* 7, $H^{8/12}$); 2.74 (1H, d, *J* 14, $H^{2/7}$); 2.89 (1H, m, $H^{4/5}$); 2.93 (1H, m, $H^{4/5}$); 3.01 (2H, m, $H^{4,5}$); 3.09 (1H, d, *J* 14, $H^{2/7}$); 3.36 (3H, m, $H^{2/7,8,12}$); 7.22 (1H, t, *J* 8, $H^{4'}$); 7.31 (2H, t, *J* 8, $H^{3'}$); 7.50 (1H, d, *J* 8, $H^{2'}$). δ_C ($CDCl_3$, 176 MHz): 28.08 ($C^{11/15/19}$); 28.14 ($C^{11/15/19}$); 28.20 ($C^{11/15/19}$); 37.23 (C^{16}); 55.18 ($C^{4/5}$); 55.47 ($C^{4/5}$); 60.70 (C^8); 63.64 (C^{12}); 64.19 ($C^{2/7}$); 66.37 ($C^{2/7}$); 73.30 (C^1); 80.78 ($C^{10/14/18}$); 81.10 ($C^{10/14/18}$); 81.46 ($C^{10/14/18}$); 82.90 (C^{17}); 124.56 ($C^{2'}$); 126.67 ($C^{4'}$); 128.03 ($C^{3'}$); 145.23 ($C^{1'}$); 170.84 ($C^{9/13}$); 170.91 ($C^{9/13}$). HRMS ES+ (*m*/*z*): found: 535.3362 $[M + H]^+$; $C_{29}H_{47}N_2O_7$ requires 535.3383; found: 557.3192 $[M + Na]^+$; $C_{29}H_{46}N_2NaO_7$ requires 557.3203.

***tert*-Butyl 2,2′-(6-hydroxy-6-phenyl-1,4-diazepane-1,4-diyl)diacetate, 23.**



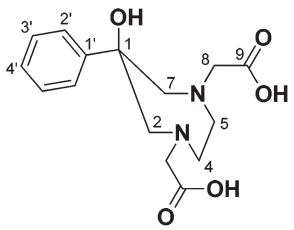
tert-Butyl-bromoacetate (0.20 g, 1.0 mmol) was added dropwise to a mixture of potassium carbonate (0.14 g, 1.0 mmol) and **21** (0.05 g, 0.26 mmol) in acetonitrile (15 mL), and the mixture stirred at 35 °C for 18 h under argon. The solvent was removed under reduced pressure and the resulting oil re-dissolved in chloroform (25 mL) and washed successively with aqueous potassium carbonate solution (2 × 25 mL, 0.1 M) and water (25 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by silica gel column chromatography (hexane → 20% ethyl acetate) yielded white solid (0.084 g, 74%). R_f = 0.15 (hexane : ethyl acetate, 65 : 35). m.p. 88–97 °C. Single crystals of **23** were grown by slow evaporation of saturated ethanol : dichloromethane solution. δ_H ($CDCl_3$, 700 MHz): 1.43 (18H, s, H^{11}); 2.64 (2H, d, *J* 14, $H^{2,7}$); 2.94 (2H, m, $H^{4,5}$); 3.01 (2H, m, $H^{4,5}$); 3.38 (2H, d, *J* 14, $H^{2,7}$); 3.40 (2H, s, H^8); 5.02 (1H, br. s, H^{12}); 7.22 (1H, t, *J* 8, $H^{4'}$); 7.31 (2H, t, *J* 8, $H^{3'}$); 7.50 (2H, d, *J* 8, $H^{2'}$). δ_C ($CDCl_3$, 176 MHz): 28.15 (C^{11}); 54.77 ($C^{4,5}$); 60.67 (C^8); 66.66 ($C^{2,7}$); 73.78 ($C^{1'}$) 81.12 (C^{10}); 124.57 ($C^{2'}$); 126.70 ($C^{4'}$); 128.05 ($C^{3'}$); 145.07 (C^1); 170.87 (C^9). HRMS ES+ (*m*/*z*): found: 421.2714 $[M + H]^+$; $C_{23}H_{37}N_2O_5$ requires 421.2702. The structure of **20** was confirmed by single crystal X-ray diffraction: $C_{23}H_{36}N_2O_5$, M_r = 420.54, triclinic ($P\bar{1}$); *a* = 5.7906(7) Å, *b* = 9.5843(11) Å, *c* = 20.978(2) Å, *V* = 1145.6(2) Å^3, α = 81.025(10)°, β = 87.158(10)°, γ = 85.460(10)°, *Z* = 2; μ = 0.085 mm^{-1}, $D_{calc.}$ = 1.219 mg mm^{-3}, *T* 120(2) K; 5749 independent reflections (R_{int} = 0.0595), R_1 = 0.0563, ωR_2 = 0.1154 ($I > 2\sigma(I)$). CCDC 911246.

2,2′-(6-(Carboxymethoxy)-6-phenyl-1,4-diazepane-1,4-diyl)-diacetic acid, H_3L^6.



The triester **22** (0.020 g, 0.037 mmol) was dissolved in TFA : dichloromethane (1 : 1, 2 mL) and left to stir for 2 days at room temperature. The solvent was removed under reduced pressure, the residue re-dissolved in dichloromethane : methanol (1 : 1; 2 mL) and evaporated. This procedure was repeated twice, and with methanol. The resulting solid was then dissolved in water (10 mL) and washed with dichloromethane (10 mL). Removal of the solvent under reduced pressure afforded, after drying *in vacuo*, a white solid (0.014 g, 81%). δ_H (D_2O, pD = 2.7, 700 MHz): 2.70 (1H, m, $H^{4/5}$); 2.79 (1H, m, $H^{4/5}$); 2.98 (1H, m, $H^{2/7}$); 3.25 (3H, m, $H^{2,7,12}$); 3.36 (2H, m, $H^{2/7,\ 4/5}$); 3.52 (1H, m, $H^{4/5}$); 3.81 (4H, m, $H^{8,10}$); 4.01 (1H, d, H^{12}); 7.30–7.33 (5H, m, Ph H). δ_C (D_2O, pD = 2.7, 176 MHz): 34.18 ($C^{4/5}$); 49.87 ($C^{2/7}$); 55.69 ($C^{4/5}$); 59.38 ($C^{8/10}$); 62.75 (C^{12}); 63.38 ($C^{2/7}$); 72.90 (C^1); 124.42 & 128.46 & 128.91 ($C^{2',3',4'}$) 141.27 ($C^{1'}$); 169.51 & 169.55 ($C^{9/11}$); 175.20 (C^{13}). HRMS ES+ (*m*/*z*): found 389.1337 $[M + Na]^+$; $C_{17}H_{22}N_2NaO_7$ requires 389.1325. Found: C, 47.8; H, 4.97; N, 5.71%. $[C_{17}H_{22}N_2O_7]\cdot CF_3COOH$ requires: C, 47.5; H, 4.83; N, 5.83%.

2,2′-(6-Hydroxy-6-phenyl-1,4-diazepane-1,4-diyl)diacetic acid, H_2L^7.



The diester **23** (0.050 g, 0.12 mmol) was dissolved in trifluoroacetic acid–dichloromethane (1 : 1, 2 mL) and left to stir for 2 days at room temperature. The solvent was removed under reduced pressure, the residue re-dissolved in dichloromethane and evaporated. This procedure was repeated twice, and also with methanol. The resulting solid was dissolved in water (15 mL) and washed with dichloromethane (15 mL). Removal of solvent under reduced pressure afforded a white solid (0.026 g, 51%). δ_H (D_2O, pD 3.58, 700 MHz): 3.44 (2H, d, *J* 14, $H^{2,7}$); 3.72 (2H, m, $H^{4,5}$); 3.84 (2H, m, $H^{4,5}$); 3.89 (4H, s, H^8); 3.89 (2H, d, *J* 14, $H^{2,7}$); 7.33 (1H, m, $H^{4'}$); 7.34 (2H, br. s, $H^{2',3'}$). δ_C (D_2O, pD 3.6, 176 MHz): 51.78 ($C^{4,5}$); 58.75 (C^8); 62.88 ($C^{2,7}$); 71.75 ($C^{1'}$); 124.09 ($C^{2'}$); 128.92 ($C^{4'}$); 129.08 ($C^{3'}$); 140.57 (C^1); 169.54 (C^9). HRMS ES+ (*m*/*z*): found: 309.1450 $[M + H]^+$; $C_{15}H_{21}N_2O_5$ requires 309.1450. Found: C, 48.0; H, 4.84; N,

6.69). $[C_{15}H_{20}N_2O_5]\cdot CF_3COOH$ requires: C, 48.3; H, 5.01; N, 6.63%.

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