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On the Synthesis of Unsymmetrical Bis(Macrocyclic) Ligands

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Abstract: The syntheses of novel three and four carbon-bridged unsymmetrical bis(macrocyclic) ligands have been investigated. Suitable functionalization of a selectively protected 1,4,7-triazacyclononane macrocycle allows for the coupling of this well-studied ligand to either 1,4-diazacyclononane or 4,7-diaza-1-oxacyclononane.

INTRODUCTION

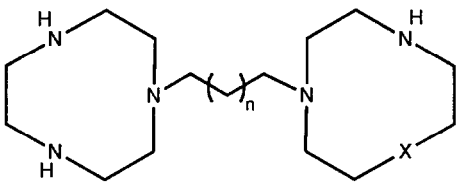
The synthesis and metal complexation properties of ligand systems containing two covalently-linked crown units have been extensively studied in recent years.[1-7] These ligands, known as "bis(macrocycles)", are capable of coordinating either one or two metal ions. The uncomplexed bis(macrocycles) have been studied as hosts for both cationic[1] and anionic[2] substrates and in the formation of mono-layer lipid membranes (bola-amphisomes).[3] The resulting dinuclear metal complexes have been probed in the study of multi-electron redox processes,[4] as agents for the activation of small molecules,[5] receptors for organic substrates,[6] and models for the active sites of polynuclear metal-containing proteins.[7]

One such protein is hemerythrin (Hr),[8] a non-heme iron-containing respiratory protein found in several phyla of marine worms. The active site is composed of a μ-oxobis(μ-carboxylato)diiron unit capped at one face by three imidazole ligands from histidine residues and at the other face by two imidazole ligands from histidine residues. The unsymmetrical coordination of the triply-bridged diiron core provides a vacant coordination site at one iron center for the binding of dioxygen. Because this functional center is considered prototypical of that found in other non-heme iron-containing proteins[8] which are not as well understood (e.g. ribonucleotide reductase, purple acid phosphatase, methane monooxygenase, etc.), it has been an attractive target for model studies.[9]

To date, the vast majority of model compounds are coordinatively saturated diiron species. Though these systems accurately mimic the salient structural and spectroscopic features of the Hr active site, the lack of a vacant coordination site generally limits their utility.[10] Thus, our interest in unsymmetrical bis(macrocycles) (i.e. molecules that contain two *different* covalently-linked macrocycles) stems from their potential ability to both stabilize a Hr-like, μ-oxobis(μ-carboxylato)diiron core and provide a vacant, or weakly coordinated site for the binding of dioxygen. In addition, other dinuclear metal complexes (e.g. Ni(II), Cu(II)) derived from such

ligands may be of interest as multi-electron redox agents in which the two metal ions are in distinct ligand environments.[4h]

The bis(macrocycles) reported to date can be placed into two categories: symmetrical (containing identical covalently-linked macrocycles) and unsymmetrical (containing different covalently-linked macrocycles). To our knowledge, with only three exceptions,[1j,1k,4h] all of the bis(macrocycles) fall into the symmetrical category. Their relative ease of synthesis is undoubtedly a contributing factor to this discrepancy. As a result, short, high yielding synthetic routes to unsymmetrical bis(macrocyclic) ligands are needed to facilitate the study of their ligating properties. We report here two such routes which result in the formation of novel three and four carbon-bridged bis(macrocycles) containing the versatile 1,4,7-triazacyclononane moiety[11] (TACN) coupled to either 1,4-diazacyclononane[12] (DACN) or 4,7-diaza-1-oxacyclononane[13] (ODACN).



14 n = 1, X = O
15 n = 1, X = CH_2
24 n = 2, X = O
25 n = 2, X = CH_2

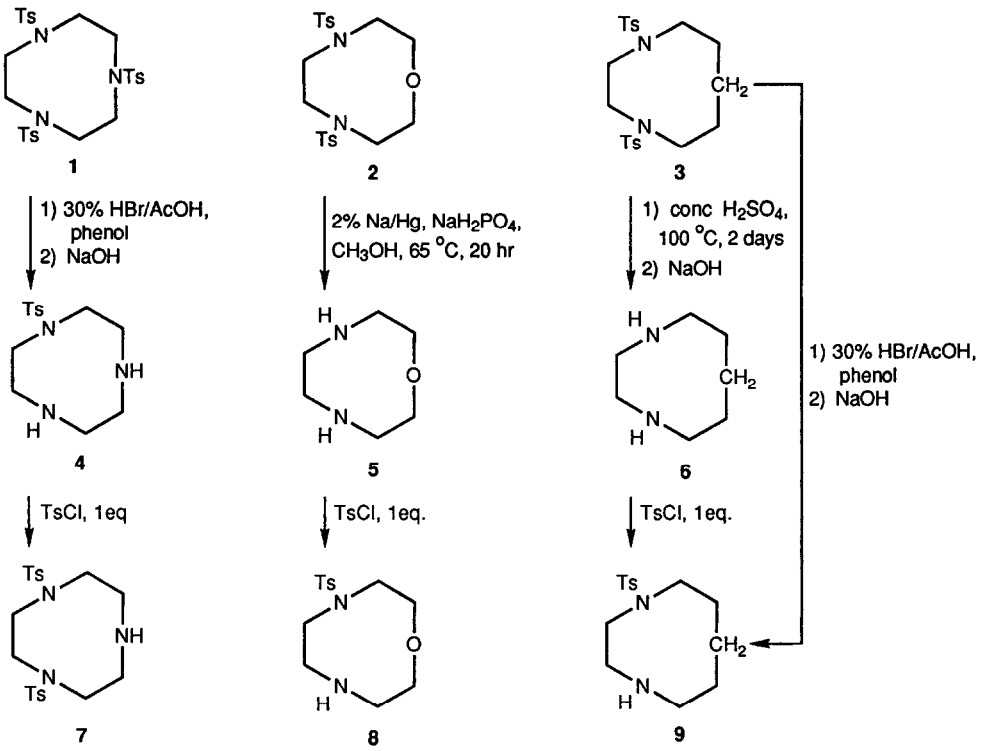
RESULTS AND DISCUSSION

As shown in Scheme 1, the first step toward the synthesis of ligands **14**, **15**, **24**, and **25** is the selective protection of the three nine-membered macrocycles 1,4,7-triazacyclononane, 4,7-diaza-1-oxacyclononane, and 1,4-diazacyclononane. As we described in an earlier report,[7a] treatment of **1** with 30% HBr/AcOH in the presence of phenol selectively removes only two tosyl groups in over 90% yield and, following a neutralization step, gives **4**.[14] The unprecedented partial detosylation is attributed to the insolubility of the N-tosyl-1,4,7-triazacyclononane dihydrobromide salt in acetic acid. The next step involves the addition of one equivalent of TsCl to produce N,N'-ditosyl-1,4,7-triazacyclononane, **7**.

In our hands, the detosylation of the known compound N,N'-ditosyl-4,7-diaza-1-oxacyclononane **2** to give the free amine, **5**,[13a,13b,15] was complicated by the ether functionality. Under the acidic conditions required to hydrolyze the tosylamide groups, the ether linkage was prone to cleavage, resulting in a mixture of products. However, using a reductive detosylation procedure (2% Na/Hg),[16] pure **5** was isolated as a colorless oil in slightly over 40% yield. The lack of any starting material or partially deprotected material (i.e. **8**) in the reaction mixture is an indication that the somewhat hydrophilic **5** was not completely recovered during purification. Despite the relatively low yield, however, the ease of obtaining *pure* **5** using Na/Hg makes it an attractive alternative for the deprotection of this macrocycle. Once deprotected, **5** was converted to the desired target **8** by the addition of 1 equivalent of TsCl.

Using methods similar to that developed by Richman and Atkins,[17] the disodium salt of ditosylethylenediamine was condensed with 1,5-dibromopentane to form N,N'-ditosyl-1,4-diazacyclononane, **3**. This complex was deprotected via two different pathways. One tosyl group was removed by treatment of **3** with 30% HBr/AcOH at 90 °C. Here, in contrast to what is observed during the synthesis of **4**, **9** does not

Scheme 1



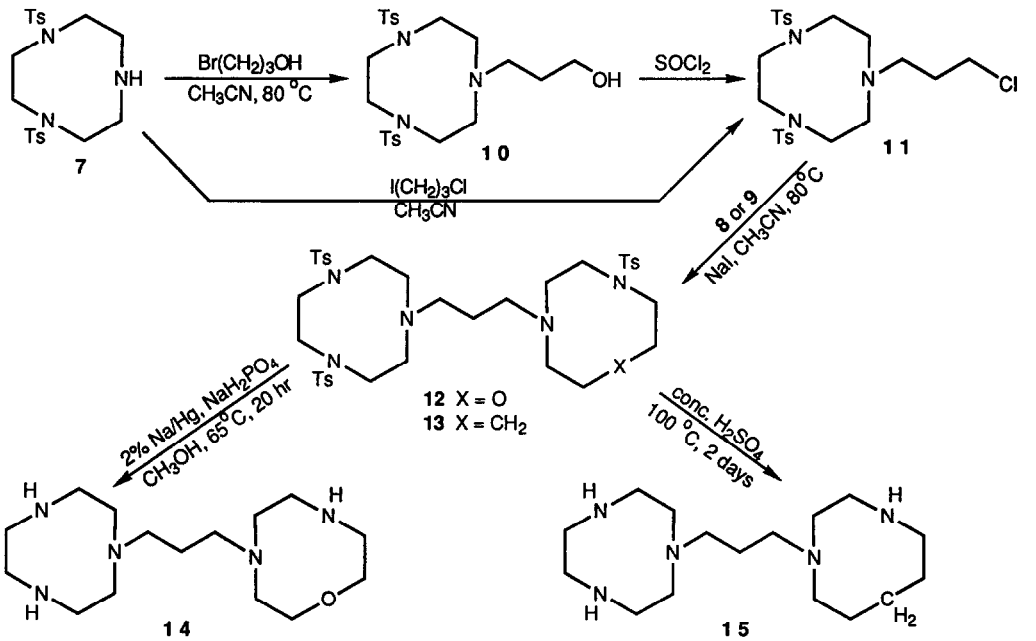
precipitate from the HBr/AcOH reaction. As a result extensive chromatography is needed to separate **9** from the significant amounts of both **3** and **6** present in the reaction mixture. Alternatively, complete deprotection of **3** can be achieved in ≥ 90% yield when conc. H_2SO_4 at 100 °C is used for 2 days. Following the addition of 1 eq. of TsCl to **6**, **9** is produced in high yield. For this particular macrocycle, the partial deprotection reaction is both laborious and poor in yield; thus, complete deprotection followed by the stoichiometric addition of TsCl is the preferred route.

An appropriate propyl-appended derivative of TACN containing a point of attachment for **8** and **9** is considered next. As shown in Scheme 2, **7** was reacted with one equivalent of 3-chloro-1-iodopropane to produce **11**. This reaction also produces a small amount of 1,3-bis(N,N'-ditosyl-1,4,7-triaza-1-cyclononyl)propane[7c] by attack of **7** on each of the terminal carbon atoms of the propane moiety. Yields, however, are typically poor (30%) for this reaction. A more efficient route is the reaction of **7** and 3-bromo-1-propanol to produce **10**. Following treatment with thionyl chloride, pure **11** was obtained in 77% yield (based on **7**).

Both **8** and **9** were then attached to **11** by heating in acetonitrile at reflux to produce the protected bis(macrocycles), **12** and **13**, respectively. Deprotection of **13** was achieved by hydrolysis in concentrated H_2SO_4 at 100 °C for 2 days, and, following a neutralization step, resulted in the unsymmetrical ligand, **15**.

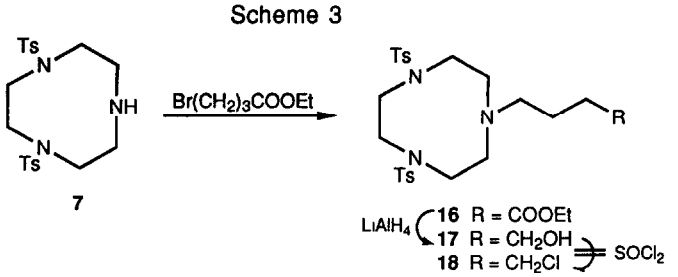
Because **12** contains an ether functionality, susceptible to acid hydrolysis, 2% Na/Hg was used as the detosylating agent. This afforded **14** as a colorless oil in over 90% yield.

Scheme 2



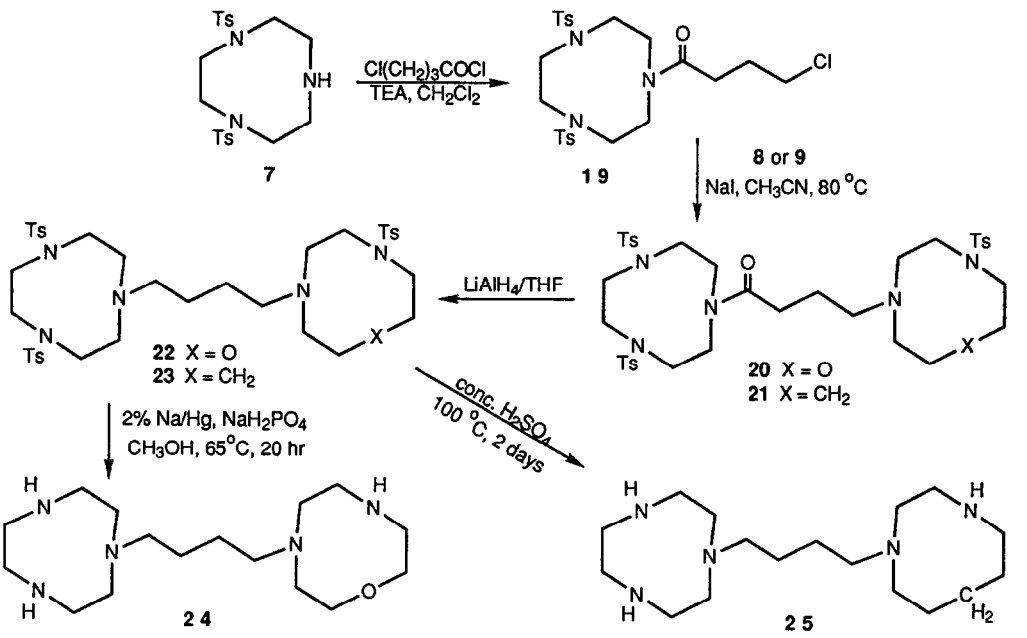
The synthesis of the butyl-bridged analogs to **14** and **15** is discussed next. As shown in Scheme 3, efforts to prepare the "chloro-butyl"-appended TACN, **18**, using a method similar to that described above proved unsuccessful. The reaction of **7** with ethyl 4-bromobutyrate produced the ester **16**. Reduction of the ester to the alcohol, **17**, was accomplished in quantitative yield by reaction with $LiAlH_4$. Treatment of **17** with thionyl chloride, however, did not produce the desired product. Instead, we presume that an intramolecular attack of the tertiary amine on the alkyl chloride functionality consumes the putative species **18**. Formation of a highly strained four-membered ring prevents a similar quaternization reaction from occurring in **11**.

Scheme 3



A successful approach to the synthesis of **24** and **25** began with the reaction of **7** and 4-chlorobutyryl chloride to form **19** (Scheme 4). The amide functionality prevents the intramolecular attack of the TACN "N" atom on the terminal carbon atom of the butyl group. The macrocyles **8** and **9** were then linked to **19** to afford **20** and **21**, respectively. Reduction of the amide groups was accomplished using $LiAlH_4$ to give the protected butyl-bridged bis(macrocycles) **22** and **23**, respectively. Deprotection of **23** in an acidic medium (conc. H_2SO_4, 100 °C, 2 days) resulted in the formation of **25**; whereas **22** was detosylated using 2% Na/Hg to give **24**.

Scheme 4



CONCLUSION

We have established a four-step synthetic sequence to three and four carbon bridged, unsymmetrical bis(macrocyclic) ligands with overall yields (based on **7**) of 50-60%. Provided the appropriate selectively protected macrocycle is available, this route should also allow for the facile synthesis of a variety of unsymmetrical bis(macrocycles), including those containing the well-studied cyclam and cyclen rings. Indeed, suitable derivatives of cyclam (N,N',N"-tris(*p*-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane)[4f] and cyclen (N,N',N"-tris(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane)[1f] have already been reported. The present work thus sets the stage for the study of possible dinuclear metal complexes prepared from ligands **14**, **15**, **24** and **25** and could provide a new approach to the preparation of diiron complexes relevant to the problem of obtaining improved models for hemerythrin.

EXPERIMENTAL

Materials and Apparatus. N,N'-bis(*p*-toluenesulfonyl)-1,4,7-triazacyclononane,[7a,7c] **7**, and N,N'-bis(*p*-toluenesulfonyl)-4,7-diaza-1-oxacyclononane,[13] **2**, were prepared according to literature procedures. All other reagents and solvents were of reagent grade quality, obtained from commercial suppliers, and used without further purification. Melting points are uncorrected. Proton and carbon NMR spectra were recorded on a General Electric QE-300 (300 MHz) spectrometer. Routine low resolution mass spectra were measured with either a Finnigan-MAT 4023 or Bell and Howell 21-491 spectrometer. Fast atom bombardment (FAB) and CI mass spectra were determined using a Finnigan-MAT TSQ-70 instrument.

Preparation of N,N'-bis(p-toluenesulfonyl)-1,4-diazacyclononane (3) Under a nitrogen atmosphere, N,N'-bis(*p*-toluenesulfonyl)ethylenediamine (3.68 g; 10.0 mmol) and NaH (0.528 g; 22.0 mmol) were stirred in 150 mL DMF at 90 °C for 1 hour. To this solution was added, dropwise, 1,5-dibromopentane (2.30 g; 10 mmol) dissolved in 125 mL DMF. The reaction was stirred and kept at 90 °C under N_2 for 24 hours. The volume of the solution was reduced to approximately 20% of the original volume and poured into 1L of ice water. The resulting pale brown precipitate was filtered, dissolved in methylene chloride, and dried over $MgSO_4$. The product was purified by column chromatography on silica gel (CH_2Cl_2 as eluent) to afford **21** (2.53 g) as a white solid: yield 58%; mp 265-267 °C; ^{1}H NMR ($CDCl_3$): δ 1.92 (2 H, quintet, $NCH_2CH_2CH_2CH_2CH_2N$), 2.05 (4 H, br, $NCH_2CH_2CH_2$), 2.42 (6 H, s, CH_3Ar), 3.24 (4 H, t, $NCH_2CH_2CH_2$), 3.29 (4 H, s, NCH_2CH_2N), 7.31 (4 H, d, aromatic), 7.64 (4 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.5, 25.3, 27.1, 51.5, 51.5, 127.0, 129.7, 135.3, 143.4; CI MS m/e 437 (MH^+), 281 (M-Ts).

Preparation of 1-oxa-4,7-diazacyclononane (5).[13] Compound **2** (2.44 g, 5.57 mmol), anhydrous disodium phosphate (3.5 g), and 2% Na amalgam (65 g) were placed in 35 mL of dry methanol. The mixture was heated at reflux under N_2 for 20 hours while stirring rapidly. After cooling to room temperature, the resulting slurry was decanted into water and extracted three times with chloroform. The organic layers were combined and dried over $MgSO_4$. The $MgSO_4$ was filtered and the solvent removed *in vacuo* to yield **5** (290 mg) as a colorless oil: yield 40%; ^{1}H NMR ($CDCl_3$): δ 2.79-2.85 (8 H, m, NCH_2), 3.66 (4 H, t, OCH_2); ^{13}C NMR ($CDCl_3$): δ 49.9, 50.0, 74.9; CI MS m/e 131 (MH^+).

Preparation of 1,4-diazacyclononane (6) The synthesis of this macrocycle has been reported previously via the di-isobutylaluminum hydride cleavage of an appropriate aminal precursor.[12]

The ditosyl derivative, **3**, (3.48 g; 7.98 mmol) was dissolved in concentrated H_2SO_4 (15 mL) and heated at 90 °C under a nitrogen atmosphere for 48 h. The resulting brown solution was cooled in an ice bath and basified to a solution pH > 12 by the cautious addition of 15 N NaOH. It was then extracted with $CHCl_3$ (3 X 250 mL). The resulting organic layers were combined and dried over $MgSO_4$. Following removal of solvent, **6** was obtained as a tan solid (954 mg): yield 93%; ^{1}H NMR ($CDCl_3$): δ 1.42-1.54 (6 H, m, $NCH_2CH_2CH_2CH_2CH_2N$), 2.61 (4 H, s, NCH_2CH_2N), 2.67 (4 H, t, $NCH_2CH_2CH_2CH_2CH_2N$), 4.80 (2 H, br, *NH*); ^{13}C NMR ($CDCl_3$): δ 24.8, 29.7, 48.5, 48.8; EI MS m/e 128 (M^+).

Preparation of N-(p-toluenesulfonyl)-4,7-diaza-1-oxacyclononane (8). To a room temperature, stirred suspension of **5** (0.533 g; 4.10 mmol) in 12 mL of 7.5 N NaOH was added TsCl (0.778 g; 4.08 mmol) dissolved in 150 mL of ethyl ether over a period of 3 hours. The solvent was removed on a rotary evaporator, and the resulting white solid was taken up in chloroform, washed with water, and the organic layer dried over

$MgSO_4$. Pure **8** (0.802 g) was obtained by column chromatography on silica gel (5% $CH_3OH/CHCl_3$ as eluent): yield 69%; mp 81-82 °C; ^1H NMR ($CDCl_3$): δ 1.64 (1 H, br, N*H*), 2.42 (3 H, s, C*H*$_3$Ar), 2.92 (2 H, t, ArNCH$_2$C*H*$_2$NH), 3.13 (2 H, t, OCH$_2$C*H*$_2$NH), 3.20 (2 H, t, ArNC*H*$_2$CH$_2$NH), 3.23 (2 H, t, ArNC*H*$_2$CH$_2$O), 3.76 (2 H, t, OC*H*$_2$CH$_2$NH), 3.88 (2 H, t, ArCH$_2$C*H*$_2$O), 7.31 (2 H, d, aromatic), 7.66 (2 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.4, 49.3, 49.8, 52.2, 53.1, 72.8, 75.2, 127.1, 129.7, 143.2; FAB MS m/e 285 (MH^+).

Preparation of N-(p-toluenesulfonyl)-1,4-diazacyclononane (9). (a) To a stirred suspension of **6** (0.626 g; 4.89 mmol) in 10 mL 7.5 N NaOH was added, dropwise, *p*-toluenesulfonyl chloride (0.926 g; 4.86 mmol) dissolved in ethyl ether (75 mL) over a period of 3 hours at room temperature. The ether was removed on a rotary evaporator and the resultant crude material was extracted with $CHCl_3$. Pure **9** (994 mg) was obtained as a white solid following column chromatography on silica gel (5% $CH_3OH/CHCl_3$): yield 72%.

(b) Compound **3** and phenol (4.30 g) were heated at 90 °C in 30% HBr/AcOH (70 mL) for 36 hours. The resulting solution was brought to room temperature and, then, basified with 15 N NaOH and extracted with $CHCl_3$. The organic layers were combined and dried over $MgSO_4$. Pure **9** (758 mg) was obtained as a pale orange solid following column chromatography on silica gel (the concentration of CH_3OH in $CHCl_3$ for the eluent was increased gradually from 0% to 20% with the largest fraction that absorbed UV light (as monitored by TLC) being collected): yield 30%; mp 90 °C; ^1H NMR ($CDCl_3$): δ 1.54 (1 H, br, N*H*), 1.73 (4 H, m, NCH$_2$C*H*$_2$C*H*$_2$CH$_2$CH$_2$NTs), 1.95 (2 H, quintet, NCH$_2$CH$_2$CH$_2$C*H*$_2$CH$_2$NTs), 2.39 (3 H, s, C*H*$_3$Ar), 2.85 (2 H, t, TsNCH$_2$CH$_2$NC*H*$_2$), 2.94 (2 H, t, TsNCH$_2$C*H*$_2$N), 3.00 (2 H, t, TsNC*H*$_2$CH$_2$CH$_2$), 3.15 (2 H, t, TsNC*H*$_2$CH$_2$N), 7.28 (2 H, d, aromatic), 7.65 (2 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.4, 25.9, 26.3, 26.8, 49.4, 49.7, 51.5, 52.2, 127.2, 129.5, 143.0; CI MS m/e 283 (M^+), 127 (M-Ts).

Preparation of 3-[N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononyl]-1-propanol (10). 3-Bromo-1-propanol (289 μL; 3.20 mmol) was added via a syringe needle to an acetonitrile solution (100 mL) containing **7** (1.316 g; 3.01 mmol) and triethylamine (1 mL). The reaction was stirred and heated at reflux under a nitrogen atmosphere for 24 hours. The solvent was then removed on a rotary evaporator. The residue was taken up in $CHCl_3$ and washed with aqueous base (pH > 12). The organic layer was separated and dried over $MgSO_4$. Pure **10** (1.43 g) was obtained as a white semi-solid following column chromatography on silica gel (3% $CH_3OH/CHCl_3$, eluent): yield 96%; ^1H NMR ($CDCl_3$): δ 1.68 (2 H, quintet, NCH$_2$C*H*$_2$CH$_2$OH), 2.43 (6 H, s, CH_3Ar), 2.79 (2 H, t, NC*H*$_2$CH$_2$CH$_2$OH), 2.99 (4 H, t, (C*H*$_2$)$_2$NCH$_2$CH$_2$CH$_2$OH), 3.24 (4 H, br, (CH$_2$)$_2$NCH$_2$C*H*$_2$NTs), 3.40 (4 H, s, TsNC*H*$_2$C*H*$_2$NTs), 3.80 (2 H, t, NCH$_2$CH$_2$C*H*$_2$OH), 7.32 (4 H, d, aromatic), 7.65 (4 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.5, 29.5, 51.6, 52.9, 54.4, 54.8, 61.6, 127.1, 129.8, 135.1, 143.6; CI MS m/e 496 (MH^+), 340 (M-Ts).

Preparation of 1-[N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononyl]-3-chloropropane (11). (a) To an acetonitrile solution (60 mL) containing **7** (1.06 g; 2.43 mmol) and triethylamine (1 mL) was added 3-chloro-1-iodopropane (261 μL; 2.43 mmol) via a syringe needle. The reaction was stirred and heated at reflux under a nitrogen atmosphere for 18 hours. The solvent was then removed on a rotary evaporator. The residue was taken up in $CHCl_3$ and washed with aqueous base (pH > 12). The organic layer was separated and dried over $MgSO_4$. Pure **11** (400 mg) was obtained as a white solid following column chromatography on silica gel (3% $CH_3OH/CHCl_3$, eluent): yield 32%.

(b) To a chloroform solution (50 mL) containing **10** (1.21 g; 2.44 mmol) was added, dropwise, freshly distilled thionyl chloride (5 mL). After stirring overnight at room temperature under a nitrogen atmosphere, the reaction was quenched by the careful addition of water and basified to a pH > 12 with NaOH. The organic layer was then separated and dried over $MgSO_4$. Pure **11** (1.00 g) was obtained as a white solid following column chromatography on silica gel (3% $CH_3OH/CHCl_3$, eluent): yield 80%; mp 147-148 °C; ^1H NMR ($CDCl_3$): δ 1.69 (2 H, quintet, $NCH_2CH_2CH_2Cl$), 2.39 (6 H, s, CH_3Ar), 2.70 (2 H, t, $NCH_2CH_2CH_2Cl$), 2.84 (4 H, t, $(CH_2)_2NCH_2CH_2CH_2Cl$), 3.16 (4 H, br, $(CH_2)_2NCH_2CH_2NTs$), 3.47 (4 H, s, $TsNCH_2CH_2NTs$), 3.69 (2 H, t, $NCH_2CH_2CH_2Cl$), 7.29 (4 H, d, aromatic), 7.65 (4 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.4, 30.2, 43.1, 51.5, 52.8, 53.5, 55.7, 127.1, 129.7, 135.1, 143.4; CI MS m/e 514 (MH^+), 359 (M-Ts).

Preparation of 1-[N,N'-bis(p-toluenesulfonyl)-1,4,7-triaza-1-cyclononyl]-3-[N-(p-toluenesulfonyl)-4,7-diaza-1-oxa-4-cyclononyl]propane (12). Compound **8** (0.614 g; 2.16 mmol), **11** (1.11 g; 2.17 mmol), sodium iodide (approx. 50 mg), and triethylamine (0.5 mL) were added together in acetonitrile (125 mL) and heated at reflux for 24 hours under a nitrogen atmosphere. The solvent was then removed on a rotary evaporator. The resultant thick brown oil was partitioned between $CHCl_3$ and 1 N NaOH. The organic layer was separated and dried over $MgSO_4$. Pure **12** was obtained as a white foamy solid (1.50 g) following column chromatography on silica gel (3% $CH_3OH/CHCl_3$, eluent): yield 91%; mp 75-78 °C; ^1H NMR ($CDCl_3$): δ 1.62 (2 H, quintet, $NCH_2CH_2CH_2N$), 2.37 (3 H, s, $CH_3ArNCH_2CH_2O$), 2.39 (6 H, s, $CH_3ArNCH_2CH_2NArCH_3$), 2.57-2.63 (4 H, m, $NCH_2CH_2CH_2N$), 2.72 (2 H, t, $CH_2CH_2CH_2NCH_2$), 2.88 (6 H, m, $CH_2CH_2CH_2NCH_2$), 3.20 (8 H, m, $TsNCH_2$), 3.47 (4 H, s, $TsNCH_2CH_2NTs$), 3.69 (2 H, t, $OCH_2CH_2N(CH_2)_2$), 3.88 (2 H, t, OCH_2CH_2NTs), 7.29 (6 H, d, aromatic), 7.64 (6 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.5, 26.2, 50.5, 51.5, 52.6, 55.3, 55.7, 55.9, 72.8, 72.9, 127.1, 127.2, 129.6, 129.7, 135.2, 135.8, 143.1, 143.4; CI MS m/e 762 (MH^+).

Preparation of 1-[N,N'-bis(p-toluenesulfonyl)-1,4,7-triaza-1-cyclononyl]-3-[N-(p-toluenesulfonyl)-1,4-diaza-1-cyclononyl]propane (13). Using the same procedure as described for the synthesis of **12**, **9** (0.531 g; 1.87 mmol) and **11** (0.965 g; 1.88 mmol) were combined to produce pure **13** (0.993 g) as a white foamy solid following column chromatography on silica gel (2% $CH_3OH/CHCl_3$, eluent): yield 70%; mp 75-78 °C; ^1H NMR ($CDCl_3$): δ 1.55 (2 H, quintet, $CH_2CH_2CH_2CH_2CH_2$), 1.72 (4 H, br, $CH_2CH_2CH_2$), 1.98 (2 H, br quintet, $CH_2CH_2CH_2$), 2.39 (3 H, s, CH_3Ar), 2.42 (6 H, s, CH_3Ar), 2.47 (2 H, t, NCH_2), 2.54-2.62 (4 H, m, NCH_2), 2.69 (2 H, t, NCH_2), 2.85 (4 H, t, NCH_2), 3.01 (2 H, t, $TsNCH_2$), 3.15 (6 H, br, $TsNCH_2$), 3.46 (4 H, s, $TsNCH_2$), 7.24-7.33 (6 H, m, aromatic), 7.61-7.68 (6 H, m, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.3(6), 21.4(0), 26.1, 26.4, 26.7, 27.2, 51.3, 51.9, 52.4, 55.3, 55.5, 55.7, 56.8, 57.3, 127.0, 127.1, 129.4, 129.7, 135.2, 135.7, 142.7, 143.3; CI MS m/e 761 (MH^+), 605 (M-Ts), 297 (M-3Ts).

Preparation of 1-(1,4,7-triaza-1-cyclononyl)-3-(4,7-diaza-1-oxa-4-cyclononyl)propane (14). Compound **12** (507 mg, 0.666 mmol), anhydrous disodium phosphate (1.0 g), and 2% Na amalgam (32 g) were placed in 20 mL of dry methanol. The mixture was heated at reflux under N_2 for 20 hours while stirring rapidly. After cooling to room temperature, the resulting slurry was decanted into water and extracted three times with chloroform. The organic layers were combined and dried over $MgSO_4$. The $MgSO_4$ was filtered and the solvent removed *in vacuo* to yield **14** (181 mg) as a colorless oil: yield 91%; ^1H NMR ($CDCl_3$): δ 1.62 (2 H, quintet, $NCH_2CH_2CH_2N$), 2.49-2.63 (6 H, m, CH_2N), 2.63-2.75 (12 H, m, CH_2N), 2.75-2.88 (6 H, m, CH_2N), 3.58-3.88 (7 H, m, CH_2O, *NH* (exchangeable with D_2O)); ^{13}C NMR ($CDCl_3$): δ 26.6, 46.4, 46 6,

48.0, 49.3, 53.0, 55.2, 55.6, 56.0, 56.3, 73.0, 73.3; CI MS m/e 300 (MH^+); HR MS m/e 300.2754 (MH^+) (calcd for $C_{15}H_{34}N_5O$, m/e 300.2763).

Preparation of 1-(1,4,7-triaza-1-cyclononyl)-3-(1,4-diaza-1-cyclononyl)propane (15). Using the same procedure as in the synthesis of **6**, the tritosyl derivative, **13**, (1.01 g; 1.33 mmol) was deprotected to produce pure **15** as a pale yellow oil (0.364 g): yield 92%; ^1H NMR ($CDCl_3$): δ 1.36-1.56 (8 H, m, $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2$), 2.27-2.69 (24 H, m, NCH_2); ^{13}C NMR ($CDCl_3$): δ 20.7, 24.7, 25.7, 26.2, 45.8, 46.3(7), 46.4(3), 46.6, 51.9, 52.2, 52.8, 55.4, 55.6; EI MS m/e 297 (M^+); HR MS m/e 297.2897 (M^+) (calcd for $C_{16}H_{35}N_5$, m/e 297.2892).

Preparation of ethyl 4-[N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononyl]butyrate (16). Compound **7** (3.06 g; 7 mmol) and ethyl 4-bromobutyrate (1.37 g; 7 mmol) were added to a solution of triethylamine (1.5 mL) dissolved in acetonitrile (100 mL). The reaction was heated at reflux while stirring under a nitrogen atmosphere for 24 hours. After removal of the solvent on a rotary evaporator, the reaction mixture was partitioned between $CHCl_3$ and aqueous base (pH > 12). The organic layer was dried over $MgSO_4$. Pure **16** (2.86 g) was obtained as a white solid following column chromatography on silica (2% $CH_3OH/CHCl_3$, eluent): yield 74%; ^1H NMR ($CDCl_3$): δ 1.19 (3 H, t, CH_3CH_2O), 1.75 (2 H, quintet, $NCH_2CH_2CH_2$), 2.34 (2 H, t, $C(O)CH_2$), 2.41 (6 H, s, CH_3Ar), 2.57 (2 H, t, $NCH_2CH_2CH_2$), 2.88 (4 H, t, $TsNCH_2CH_2N$), 3.16 (4 H, br t, $TsNCH_2CH_2N$), 3.47 (4 H, s, $TsNCH_2CH_2NTs$), 4.09 (2 H, q, OCH_2), 7.30 (4 H, d, aromatic), 7.65 (4 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 14.1, 21.3, 22.8, 31.6, 51.2, 52.3, 55.3, 56.1, 60.1, 127.0, 129.6, 135.2, 143.3, 173.5; CI MS m/e 552 (MH^+), 396 (M-Ts).

Preparation of 4-[N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononyl]butanol (17). To a flame-dried, round-bottomed flask charged with 1 M $LiAlH_4$ in THF (20 mL) was added, dropwise, **16** (2.86 g; 5.2 mmol) dissolved in dry THF at room temperature under a nitrogen atmosphere. After stirring overnight, the reaction was quenched with sodium sulfate decahydrate. Following removal of solvent, the residue was taken up in $CHCl_3$ and washed with aqueous base (pH > 12). The organic layer was dried over $MgSO_4$. After evaporation of the $CHCl_3$ on a rotary evaporator and drying *in vacuo*, **17** was obtained quantitatively as a thick, colorless oil (which solidified upon refrigeration): ^1H NMR ($CDCl_3$): δ 1.57 (2 H, quintet, $NCH_2CH_2CH_2CH_2O$), 1.60 (2 H, quintet, $NCH_2CH_2CH_2CH_2O$), 2.41 (6 H, s, CH_3Ar), 2.60 (2 H, t, $NCH_2CH_2CH_2$), 2.91 (4 H, t, $TsNCH_2CH_2N$), 3.21 (4 H, br t, $TsNCH_2CH_2N$), 3.46 (4 H, s, $TsNCH_2CH_2NTs$), 3.62 (2 H, t, OCH_2), 7.30 (4 H, d, aromatic), 7.65 (4 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.4, 24.3, 30.7, 51.0, 52.3, 54.9, 56.8, 62.5, 127.0, 129.7, 135.1, 143.4; CI MS m/e 510 (MH^+), 354 (M-Ts).

Attempt at the preparation of 1-[N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononyl]-4-chlorobutane (18). Using the same procedure as described for the synthesis of **11**, compound **17** was reacted with thionyl chloride. The reaction produced only one tosylated product which had an R_f value (TLC, 5% $CH_3OH/CHCl_3$) of zero. By comparison to the TLC of **11** (R_f = 0.8, 5% $CH_3OH/CHCl_3$), this product was deemed not to be **18** and, thus, was not characterized further.

Preparation of [(N,N'-bis(p-toluenesulfonyl))-(N''-(4-chlorobutyryl)]-1,4,7-triazacyclononane (19). To a stirred solution of **7** (3.00 g; 6.86 mmol) and triethylamine (1 mL) in dry CH_2Cl_2 (50 mL) was added 4-chlorobutyryl chloride (770 μL; 6.86 mmol). The solution was stirred at room temperature under a nitrogen atmosphere for 15 min, at which time water was added. The organic layer was separated and dried over $MgSO_4$. Pure **19** (3.42 g) was obtained as a white solid following column chromatography on silica gel (2%

$CH_3OH/CHCl_3$, eluent): yield 92%; mp 80-83 °C; ^1H NMR ($CDCl_3$): δ 2.12 (2 H, quintet, $ClCH_2CH_2CH_2$), 2.41 (3 H, s, CH_3Ar), 2.44 (3 H, s, CH_3Ar), 2.72 (2 H, t, $NC(O)CH_2CH_2CH_2Cl$), 3.18 (2 H, br, NCH_2), 3.32-3.52 (6 H, m, NCH_2), 3.58 (2 H, br, NCH_2), 3.62 (2 H, t, $ClCH_2CH_2CH_2$), 3.76 (2 H, br, NCH_2), 7.29 (2 H, d, aromatic), 7.32 (2 H, d, aromatic), 7.60 (2 H, d, aromatic), 7.66 (2 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.4, 28.0, 30.2, 44.6, 49.9, 50.6, 51.2, 52.1, 54.5, 127.2, 127.4, 129.8, 129.9, 133.8, 134.0, 144.0, 173.2; CI MS m/e 542 (MH^+), 386 (M-Ts).

Preparation of 1-[N,N'-bis(p-toluenesulfonyl)-1,4,7-triaza-1-cyclononyl]-4-[N-(p-toluenesulfonyl)-4,7-diaza-1-oxa-4-cyclononyl]butane (22). (a) An acetonitrile solution (50 mL) containing **19** (0.320 g; 0.591 mmol), **8** (0.168 g; 0.591 mmol), triethylamine (1 mL) and NaI (approx. 50 mg) was heated at reflux for 24 hours under a nitrogen atmosphere. The solvent was removed on a rotary evaporator and the resultant product mixture was partitioned between 1 N NaOH and $CHCl_3$. The organic layer was dried over $MgSO_4$. The crude monoamide, **20**, was used without further purification.

(b) To a flame-dried, 100 mL roundbottomed flask was added a 1 M solution of $LiAlH_4$ in THF (15 mL). The crude monoamide **20** dissolved in dry CH_2Cl_2 (10 mL) was added dropwise while keeping the solution temperature at O °C under N_2. The reaction was allowed to come to room temperature and then stirred overnight. Following quenching with sodium sulfate decahydrate, the solvent was removed on a rotary evaporator. The resulting solid was partitioned between $CHCl_3$ and 1 N NaOH. The organic layer was then separated off and dried over $MgSO_4$. Pure **22** was obtained as a white solid (338 mg) following column chromatography on silica (3% $CH_3OH/CHCl_3$, eluent): yield 74%; mp 69-72 °C; ^1H NMR ($CDCl_3$): δ 1.42 (4 H, br m, $NCH_2(CH_2)_2CH_2N$), 2.36 (3 H, s, CH_3Ar), 2.37 (6 H, s, CH_3Ar), 2.51 (4 H, br t, NCH_2), 2.66 (2 H, t, NCH_2), 2.83 (6 H, m, NCH_2), 3.15 (4 H, m, $TsNCH_2$), 3.22 (4 H, m, $TsNCH_2$), 3.47 (4 H, s, $TsNCH_2CH_2NTs$), 3.64 (2 H, t, NCH_2CH_2O), 3.86 (2 H, t, $TsNCH_2CH_2O$), 7.24 (2 H, d, aromatic), 7.26 (4 H, d, aromatic), 7.62 (2 H, d, aromatic), 7.64 (4 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.3, 25.4, 25.6, 50.2, 51.2, 52.3, 55.6, 57.1, 57.6, 72.6, 126.9, 127.0, 129.4(5), 129.5(4), 135.2, 135.8, 142.9, 143.2; CI MS m/e 776 (MH^+), 620 (M-Ts).

Preparation of 1-[N,N'-bis(p-toluenesulfonyl)-1,4,7-triaza-1-cyclononyl]-4-[N-(p-toluenesulfonyl)-1,4-diaza-1-cyclononyl]butane (23). (a) Compound **19** (1.19 g; 2.20 mmol) and **9** (0.620 g; 2.20 mmol) were added to acetonitrile (125 mL) containing triethylamine (1 mL) and NaI (approx. 50 mg). The reaction was heated at reflux for 24 hours under a nitrogen atmosphere. The solvent was removed on a rotary evaporator and the resultant product mixture was partitioned between 1 N NaOH and $CHCl_3$. The organic layer was dried over $MgSO_4$. Compound **21** was used without further purification.

(b) Using the same procedure as in the synthesis of **22** (step b), **21** (1.25 g; 1.59 mmol) was reacted with $LiAlH_4$ in THF to produce pure **23** following column chromatography on silica (3% $CH_3OH/CHCl_3$, eluent): yield 72%; ^1H NMR ($CDCl_3$): δ 1.42 (4 H, br m, $NCH_2(CH_2)_2CH_2CH_2NTs$), 1.73 (4 H, br, $NCH_2(CH_2)_2CH_2N$), 1.99 (2 H, quintet, $N(CH_2)_3CH_2CH_2NTs$), 2.39 (3 H, s, CH_3Ar), 2.42 (6 H, s, CH_3Ar), 2.43 (2 H, t, NCH_2), 2.53 (2 H, t, NCH_2), 2.60 (2 H, br, NCH_2), 2.69 (2 H, br, NCH_2), 2.85 (4 H, br, NCH_2), 3.02 (2 H, br, $TsNCH_2$), 3.16 (6 H, br, $TsNCH_2$), 3.48 (4 H, s, $TsNCH_2CH_2NTs$), 7.30 (6 H, d, aromatic), 7.65 (6 H, d, aromatic); ^{13}C NMR ($CDCl_3$): δ 21.4, 25.5, 25.9, 26.4, 26.7, 27.3, 51.3, 51.9, 52.3, 52.5, 55.5, 55.6, 57.2, 57.3, 58.7, 126.9(5), 127.0(4), 129.4, 129.6, 135.2, 135.7, 142.7, 143.3; CI MS m/e 774 (MH^+).

Preparation of 1-(1,4,7-triaza-1-cyclononyl)-4-(4,7-diaza-1-oxa-4-cyclononyl)butane (24). Using the same procedure as described for the synthesis of **14**, compound **22** (338 mg, 0.436 mmol) was deprotected by reaction with 2% Na amalgam (40 g) in 20 mL of dry methanol containing anhydrous disodium phosphate (450 mg) to yield **24** (119 mg) as a colorless oil: yield 87%; ^{1}H NMR ($CDCl_3$): δ 1.44 (4 H, br m, $NCH_2CH_2CH_2CH_2N$), 2.48-2.59 (8 H, m, CH_2N), 2.59-2.66 (4 H, m, CH_2N), 2.66-2.88 (12 H, m, CH_2N), 3.39 (3 H, br, N*H*), 3.63 (2 H, t, CH_2O), 3.67 (2 H, t, CH_2O); ^{13}C NMR ($CDCl_3$): δ 25.6, 25.8, 46.0, 46.4, 48.3, 49.5, 52.5, 55.27, 56.0, 57.3, 58.2, 73.2, 73.3; CI MS m/e 314 (MH^+); HR MS m/e 314.2881 (MH^+) (calcd for $C_{16}H_{36}N_5O$, m/e 314.2920), 313.2817 (M^+) (calcd for $C_{16}H_{35}N_5O$, 313.2842).

Preparation of 1-(1,4,7-triaza-1-cyclononyl)-4-(1,4-diaza-1-cyclononyl)butane (25). Using the same procedure as in the synthesis of **6**, the tritosyl derivative, **23**, (1.18 g; 1.53 mmol) was deprotected to produce pure **25** as a pale amber oil (0.436 g): yield 92%; ^{1}H NMR ($CDCl_3$): δ 1.41-1.53 (6 H, m, $NCH_2CH_2CH_2CH_2CH_2N$), 1.62 (4 H, m, $NCH_2CH_2CH_2CH_2N$), 2.44-2.64 (12 H, m, NCH_2), 2.72 (2 H, t, NCH_2), 2.80 (6 H, m, NCH_2), 2.88 (4 H, s, NCH_2), 4.60 (3 H, br, N*H*); ^{13}C NMR ($CDCl_3$): δ 20.4, 24.1, 25.3, 25.7, 44.5, 45.1, 45.4, 45.9, 50.9, 51.0, 51.9, 56.6, 57.0; EI MS m/e 311 (M^+); HR EI MS m/e 311.3039 (M^+) (calcd for $C_{17}H_{37}N_5$, m/e 311.3049).

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