Synthesis of Bicyclic Polyaza Polycarboxylic Macrocycles Containing a 12-Membered Unit

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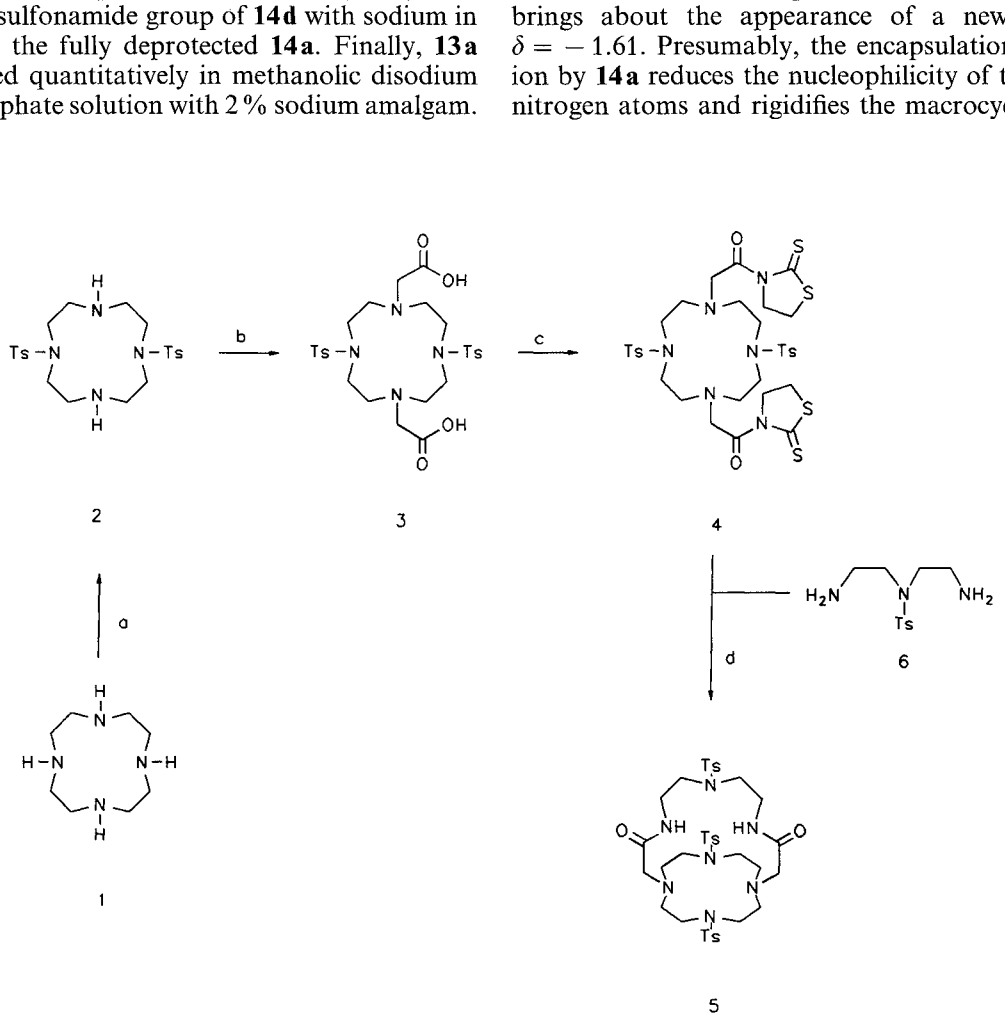
High dilution reactions between a diamine and a diacid activated with 1,3-thiazolidine-2-thione afforded bicyclic polyamines after reduction of the amido moieties with borane. The cyclisation yields ranged between 34 and 84% and presumably depend on the rigidity of the reagents. Selection of the most appropriate procedures for the deprotection of tosylated amino groups and for the addition of carboxylic groups appear to depend on the structure and the cavity size of the macrocycles. For instance, encapsulation of a Na^+ ion as seen by ^{23}Na NMR prevents the substitution of the secondary amino groups of the polyaza ligands by acetate functions.

The 12-membered tetraaza macrocycle **1** proved very useful as starting material for the synthesis of new ligands.[1] Substituting the nitrogen atoms of **1** with carboxylic groups[2], or amide functions,[3] leads to ligands that form thermodynamically very stable and kinetically inert lanthanide chelates.[4] These compounds are particularly effective as contrast agents for magnetic resonance imaging,[5] as enzyme restriction analogues[3,6] or for radiotherapy with labelled antibodies.[7,8] All these applications require the use of exceedingly stable lanthanide chelates either to ensure the low toxicity of the contrast agents or to maintain metal ions fully tethered to an antisens oligomer or to an antibody. Introducing the tetraaza ring **1** as a subunit into polycyclic structures could offer possibilities for enhanced binding, provided the dimensions of the new macrocyclic cavities are commensurate to the ionic size of the metals. The present paper describes the synthesis of new bicyclic ligands featuring only nitrogen heteroatoms and containing cycle **1** as a subunit. So far, only a few all-nitrogen donor cryptands incorporating subunit **1** have been reported.[9,10] In all cases, some of the nitrogen atoms of **1** were substituted with methyl groups and were thus unavailable as reaction sites. Herein, we report on the syntheses of bicyclic derivatives of **1** featuring secondary amino groups and on the preparation of their analogues substituted with carboxylic groups.

The starting material for all the syntheses reported herein is **2**, a compound that is readily prepared in large quantities.[11] The cyclic compound **2** is particularly convenient for obtaining polycyclic ligands substituted with coordinating groups since it features two nitrogen atoms in *trans* position that are specifically protected by the removable *p*-toluenesulfonyl moiety. As shown in Schemes 1–3, two reaction paths were followed to prepare the bicyclic macrocycles **12a–c**. In both approaches, cyclisation was achieved by reacting a diamine with an activated diacid but compound **2** was substituted either with two acid functions (Scheme 1) or with two amino groups (Scheme 2). When possible, the cyclisation step was performed after activating a diacid as a dichloride but in most cases, another activating group was needed because of the reactivity of the tertiary amino groups. Activation of the acid groups of **3** or **9b** with 1,3-thiazolidine-2-thione (TTH) was carried out in the presence of 1,3-dicyclohexylcarbodiimide (DCC) following the general procedure reported by Nagao et al.[12] The formation of the bicyclic diamide **5** was achieved by reacting the activated diacid **4** with monotosylated diethylenetriamine **6**[13] in high dilution conditions. A similar procedure has already been used successfully by Fujita[14] for the synthesis of monocyclic macrolactams, who showed that the production of 16- to 24-membered rings is favoured and that the formation of amide bonds is easily followed because of the disappearance of the yellow colour of the activated acid functions. Furthermore, acids activated with 1,3-thiazolidine-2-thione react rapidly with primary amines and are not sensitive to water or alcohols. The new hexaaza unit formed by reacting **4** with **6** is an 18-membered cycle and activation of **3** with TTH thus seems ideally suited for the preparation of bicyclic compounds such as **5**. In the other synthetic path (see Scheme 2), compounds **7a** and **7b** were obtained from **2** by reaction with either bromoacetamide or acrylamide. Reduction of the diamides **7a** and **7b** with borane in tetrahydrofuran afforded the corresponding diamines in high yields after hydrolysis of the aminoborane derivatives with 6 M hydrochloric acid and extraction from concentrated aqueous solutions of lithium hydroxide with dichloromethane. The Li^+ ion was selected for salting-out in preference to other alkali ions to avoid the formation of poorly extractable metal complexes of the macrocyclic amines. The activated diacid **10a** was obtained by condensing *N*-tosyliminodiacetic dichloride **(9a)**[15] with the thallium salt of TTH.[16] Cyclisation of **10a** with **8a** in high dilution conditions afforded the bicyclic diamide **11a** in good yields (84% after separation by flash chromatography). A lower yield was obtained if the dichloride **9a** was used directly in the cyclisation step instead of the diprotected derivative **10a**. Since the transformation of the diacid **9a** into the bis-thiazolidine derivative **10a** is not quantitative, the overall yields of **11a** are nearly identical whether the cyclisation is performed directly between the diamine **8a** and a diacid dichloride or if the latter is first transformed into a bis-thiazolidinethione. The cyclisation reaction was also carried out with the diamine **8b** which features two propylenic side arms. This reaction gives the larger macrocyclic diamide **11b** with a 44% yield, only presumably because of the greater flexibility of **8b**. One of the aims of the present paper is the preparation of various polyaza di- and tricarboxylic ligands and we thus devised a procedure for the synthesis of macrocycles such as **11c** that feature a tertiary amino group. *N*-Methyliminodiacetic acid was reacted with two equivalents of TTH following the procedure already used for the synthesis of **4**. The crystallisation step leading to macrocycle **11c** is not very effective and a yield of only 34% was obtained after flash chromatography. This poor yield can again be assigned to the higher flexibility of one of the reagents, the methyl group in **10b** being less bulky than the tosyl group in **10a**.

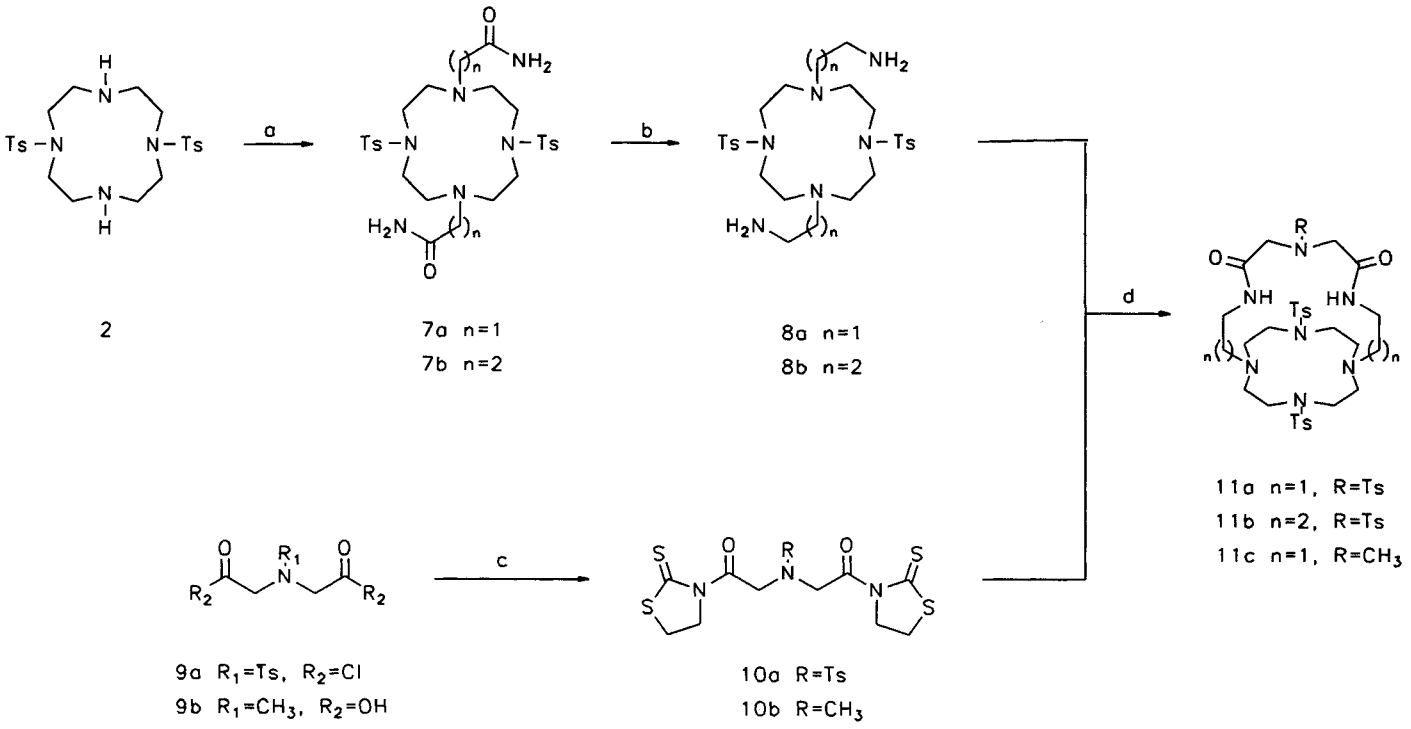
The diamides **11a–c** were reduced with solutions of borane in tetrahydrofuran (see Scheme 3). The heptaaza ligands **12a–c** could have been transformed directly into tetra- or pentaacids but we decided to prepare di- and tricarboxylic ligands instead, since we intend to study the properties of electrically neutral or positively charged lanthanide chelates. The polyamines **12a–c** were thus methylated with formaldehyde/formic acid mixtures and several approaches were tested for the deprotection of the tosylated amino groups. Removal of the protecting groups of **13a** in hot concentrated sulfuric acid during 5 days yielded a mixture of the fully deprotected amine **14a** and of compound **14d** that had lost only the tosyl groups in the 12-membered unit (yields determined by NMR: 25% and 48%, respectively). The same treatment gave the larger macrocycle **14b** from **13b** in 48 h and in 75% yield and no monotosylated derivative was isolated. One could thus assume that the removal of the two tosyl groups in the tetraaza cycle of **13a** and the subsequent protonation of the deprotected amine functions cause a rigidification of the macrocycle and prevent the protonation[17] of the remaining tosylated nitrogen atom because of electrostatic repulsions. Reductive hydrolysis of the remaining sulfonamide group of **14d** with sodium in butanol led to the fully deprotected **14a**. Finally, **13a** was deprotected quantitatively in methanolic disodium hydrogen phosphate solution with 2% sodium amalgam. The same technique was also applied successfully in the case of **13b**.

Finding the best method for the addition of carboxylic groups to **14a** was not straightforward and we were unable to obtain good yields despite several attempts by different procedures. Reacting the polyamines with sodium bromoacetate, ethyl bromoacetate or ethyl 2-(trifluoromethylsulphonyloxy)propionate[18] in methanol, acetonitrile or dimethylformamide in the presence of sodium carbonate gave untractable mixtures. Replacing sodium carbonate by caesium carbonate yielded deep brown reaction mixtures out of which we could not isolate the desired compound.[19] Use of methyl bromoacetate/diisopropylethylamine mixture was not more effective. It appears that our attempts at synthesizing polyacids in the presence of a sodium-containing base were thwarted by the complexation of the Na^+ ion by macrocycle **14a**. Indeed, sodium hydroxide is extracted from aqueous solutions by **14a** in dichloromethane. Moreover, the ^{23}Na NMR spectra of the organic phase clearly indicate that the sodium ion is encapsulated by the ligand since the addition of **14a** to aqueous sodium chloride solution brings about the appearance of a new ^{23}Na peak $\delta = -1.61$. Presumably, the encapsulation of the Na^+ ion by **14a** reduces the nucleophilicity of the secondary nitrogen atoms and rigidifies the macrocyclic cage thus



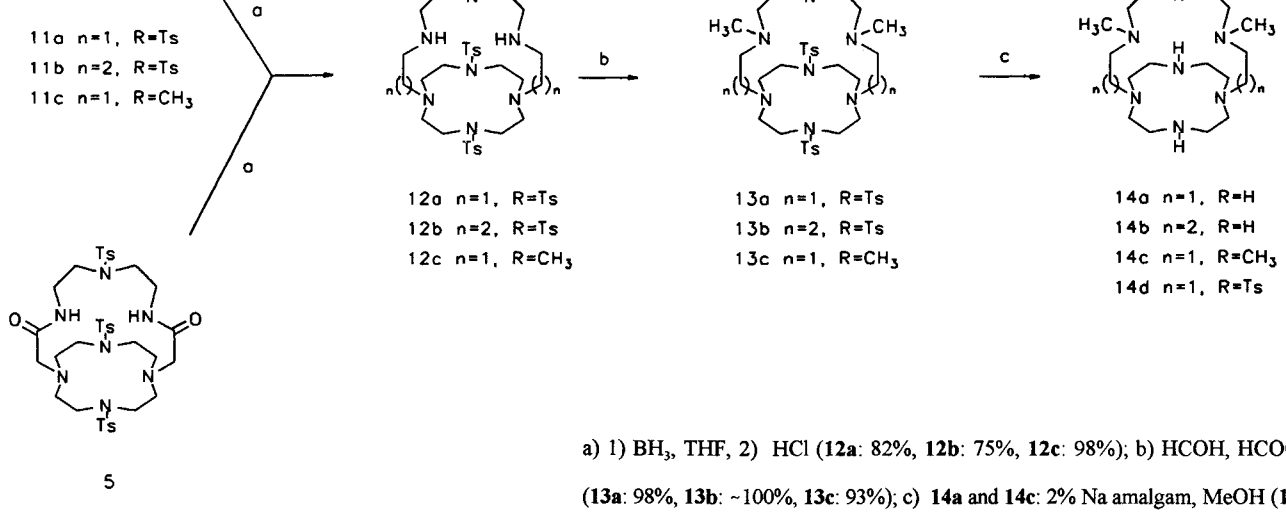
a) TsCl, pyridine (90%)[11]; b) $BrCH_2COOK$, Na_2CO_3, MeOH (87%); c) 1,3-thiazolidine-2-thione, DCC, DMAP, CH_2Cl_2 (55%).

Scheme 1



a) **7a**: $BrCH_2CONH_2$, Na_2CO_3, MeOH (86%), **7b**: CH_2=CHCONH$_2$, MeOH (67%); b) BH_3, THF (**8a**: 85%, **8b**: ~100 %); c) **10a**: Tl(I) 1,3-thiazolidine-2-thiolate, THF (74%), **10b**: 1,3-thiazolidine-2-thione, DCC, DMAP, CH_2Cl_2 (90%); d) **11a** from **9a** and **8a**, Et_3N, CH_2Cl_2 (60%), **11a** from **8a** and **10a**, CH_2Cl_2 (84%), **11b**from **8b** and **10a** CH_2Cl_2 (44%), **11c** from **8a** and **10b**, CH_2Cl_2 (34%)

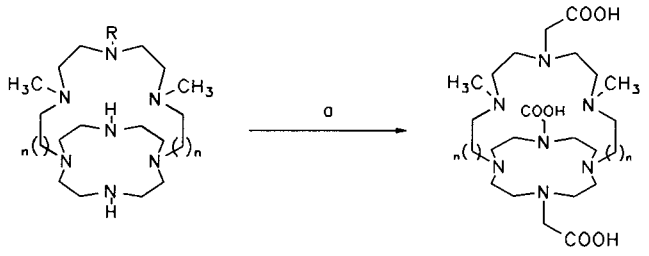
Scheme 2



a) 1) BH_3, THF, 2) HCl (**12a**: 82%, **12b**: 75%, **12c**: 98%); b) HCOH, HCOOH (**13a**: 98%, **13b**: ~100%, **13c**: 93%); c) **14a** and **14c**: 2% Na amalgam, MeOH (**14a**: ~100%, **14c**: 95%), **14b**: conc. H_2SO_4 (75%).

Scheme 3

making the NH groups less available for reaction with a haloester. None of the other alkali metal hydroxides is extracted by **14a** into an organic phase. In keeping with the extraction experiments and the NMR measurements, the polyaza polycarboxylic macrocycles **15a–b** were obtained by reacting the polyamines **14a–c** with neutralized bromoacetic acid in methanol suspensions of an excess of potassium carbonate (Scheme 4). Despite our efforts, the yields of the reaction remained rather low (**15a**: 60%, **15b**: 55%).



14a n=1, R=H
14b n=2, R=H

15a n=1
15b n=2

$BrCH_2COOK$, MeOH, K_2CO_3, 65°C (**15a**: 60%, **15b**: 36%)

Scheme 4

Studies of the protonation processes of the bicyclic polyamines and of their polycarboxylate derivatives as well as investigations of the complexation of metal ions by these ligands are in progress.

All solvents were dried using common techniques and all reactions were carried out under N_2. High dilution reactions were performed in a locally built instrument.[20] All reagents were added at a rate of 1 mL/min. Column chromatography was performed using silica gel (70–230 mesh, 60 Å for column chromatography, Aldrich, and grade 9385, Merck, for flash chromatography). Melting points are uncorrected. Compounds **11a–c** and **14a–d** gave C,H,N analyses ± 0.5%. Elemental analyses of **14a–d** were performed after an overnight treatment of the amine hydrochlorides with a $CHCl_3$ solution saturated with NH_3. The inorganic salts were filtered and the solvent was evaporated to yield colorless waxes. Mass spectra were obtained on a Fisons VG Platform (electrospray, ES) or a Fisons Autospec mass spectrometer (fast atom bombardment, FAB, in 3-nitrobenzyl alcohol, NOBA, or in glycerol). ^1H and ^{13}C spectra were recorded on a Bruker AM400 spectrometer.

1,7-Dicarboxymethyl-4,10-di(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane (3):
A solution of KOH (0.55 g, 9.8 mmol) in absolute MeOH (6 mL) was cooled to 0 °C and carefully added to a solution of bromoacetic acid (1.36 g, 9.8 mmol) in absolute MeOH (10 mL) in such a way that the temperature never rose above 5 °C. This solution was then added to a mixture of **2**[11] (2.09 g, 4.3 mmol) and of anhydr. Na_2CO_3 (1.037 g, 9.8 mmol) in absolute MeOH (50 mL). The suspension was heated first at 45 °C during 6 h and then at 65 °C overnight. MeOH was evaporated under reduced pressure and the residue was dissolved in H_2O (50 mL). The solution was filtered and the filtrate acidified to pH 1 with 6 M HCl. The precipitated **3** was filtered, washed with chilled H_2O (25 mL) and dried; yield: 2.23 g (87%); mp 182–185 °C.

^1H NMR (D_2O + NaOH): δ = 2.41 (s, 6H, $ArCH_3$), 2.90 (br, 8H, ring CH_2), 3.10 (s, 4H, CH_2CO_2H), 3.21 (br, 8H, ring CH_2), 7.42 (d, J = 7.4 Hz, 4 H_{arom}), 7.71 (d, J = 7.4 Hz, 4 H_{arom}).

^{13}C NMR (D_2O + NaOH): δ = 23.4, 50.2, 55.2, 60.0, 129.9, 132.7, 135.5, 147.6, 181.4.

1,7-Di(1′-*N*-acetyl-1,3-thiazolidine-2-thione)-4,10-di(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane (4):
To a suspension of acid **3** (2.23 g, 3.74 mmol) in CH_2Cl_2 (30 mL) was added solid 1,3-thiazolidine-2-thione (0.99 g, 8.3 mmol) in one portion. After cooling to 0 °C, DCC (1.87 g, 9 mmol) and 4-(*N*,*N*-dimethyl)aminopyridine (DMAP) (0.1 g) were added. The mixture was stirred for 1 h at 0 °C and overnight at r.t. *N*,*N*′-Dicyclohexylurea formed was filtered and the solution was extracted with H_2O (2 × 15 mL). The organic phases were dried ($MgSO_4$), filtered and the solvent was evaporated in vacuum. The oily residue was dissolved in $CHCl_3$ (10 mL) and **4** was isolated by precipitation following the addition to the solution of a large volume of Et_2O (250 mL). Compound **4** was collected by filtration and dried overnight in vacuum; yield: 1.56 g (55%).

^1H NMR ($CDCl_3$): δ = 2.40 (s, 6H, $ArCH_3$), 3.02 (br t, 8H, ring CH_2), 3.18 (br t, 8H, ring CH_2), 3.34 (t, 4H, J = 7.5 Hz, CH_2S), 4.36 (s, 4H, CH_2CO), 4.54 (t, 4H, J = 7.5 Hz, NCH_2CH_2S), 7.28 (d, J = 8.2 Hz, 4 H_{arom}), 7.63 (d, J = 8.2 Hz, 4 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 21.3, 28.9, 49.5, 54.9, 55.6, 60.2, 127.2, 129.5, 134.8, 143.2, 173.2, 201.4.

3,11-Dioxo-7,16,21-tri(*p*-toluenesulfonyl)-1,4,7,10,13,16,21-heptaazabicyclo[11.5.5]tricosane (5):
Solutions of **4** (0.80 g, 1.0 mmol) in CH_2Cl_2 (250 mL) and of **6**[13] (0.27 g, 1.05 mmol) in CH_2Cl_2 (250 mL) were prepared and added simultaneously to CH_2Cl_2 (1 L) under vigorous stirring. The stirring was continued for 1 h after the addition and the solvent was evaporated under reduced pressure. Compound **5** was isolated from the solid residue by chromatography (silica gel, EtOAc), as a pale yellow amorphous solid; yield: 0.450 g (55%); TLC (silica gel, EtOAc): 1,3-thiazolidine-2-thione (0.71), **5** (0.38).

^1H NMR ($CDCl_3$): δ = 2.33 (s, 3H, $ArCH_3$), 2.36 (s, 6H, $ArCH_3$), 2.86, 3.10, 3.16 (br, 24H, ring + bridge CH_2), 3.38, 3.63 (2 d, 2 × 2H, NCH_2CO), 7.20 (d, J = 8.2 Hz, 2 H_{arom}), 7.27 (d, J = 7.9 Hz, 4 H_{arom}), 7.50 (d, J = 8.2 Hz, 2 H_{arom}), 7.58 (d, J = 7.9 Hz, 4 H_{arom}), 7.82 (t, 2H, J = 4 Hz, N*H*CO).

^{13}C NMR ($CDCl_3$): δ = 21.2, 21.3, 37.9, 49.5, 50.4, 54.5, 58.6, 126.9, 127.6, 129.6, 129.7, 132.4, 134.7, 143.4, 143.9, 170.5.

1,7-Di(carbamoylmethyl)-4,10-di(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane (7a):
To a solution of **2** (2.06 g, 4.3 mmol) in absolute MeOH (80 mL) were added bromoacetamide (1.21 g, 8.8 mmol) and anhydr. Na_2CO_3 (0.93 g, 8.8 mmol) and the resulting suspension was refluxed for 20 h. The solvent was evaporated in vacuum and the remaining solid was shaken with $CHCl_3$ (80 mL) during 1 h. The precipitate was filtered, washed with $CHCl_3$ (20 mL) and taken up in H_2O (40 mL). The suspension was stirred for 1 h. Diamide **7a** was filtered, washed with water (20 mL) and dried in vacuum; yield: 2.20 g (86%); mp 243–244 °C.

^1H NMR (DMSO-d_6): δ = 2.38 (s, 6H, $ArCH_3$), 2.83 (br, 8H, ring CH_2), 3.10 (s, 4H, CH_2CO), 3.13 (br, 8H, ring CH_2), 7.08 (s, 2H, NH), 7.33 (s, 2H, NH), 7.40 (d, J = 7.9 Hz, 4 H_{arom}), 7.66 (d, J = 7.9 Hz, 4 H_{arom}).

^{13}C NMR (DMSO-d_6): δ = 21.0, 48.4, 54.1, 56.4, 127.1, 129.9, 134.9, 143.3, 172.6.

MS (FAB in NOBA): m/z = 595 (MH^+).

1,7-Di(3′-propanamide)-4,10-di(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclodecane (7b):
The diprotected **2** (1.202 g, 2.5 mmol) was mixed with acrylamide (0.355 g, 5 mmol) and absolute MeOH (1.5 mL). This slurry was heated at 75 °C for 72 h while taking care that the solvent did not completely evaporate. MeOH was removed under reduced pressure and the residue was stirred in $CHCl_3$ (30 mL) in order to dissolve the unreacted **2**. The insoluble pale yellow solid **7b** was filtered, washed with $CHCl_3$ and dried in vacuum; yield: 1.04 g (67%); mp 213–214 °C.

^{1}H NMR (DMSO-d_6): δ = 2.11 (t, J = 7.0 Hz, 4H, NCH_2CH$_2$CO), 2.38 (s, 6H, ArCH_3), 2.64 (br, 12H, ring CH$_2$ + CH$_2$CO), 3.33 (br, 8H, ring CH$_2$), 6.76 (s, 2H, CONH$_2$), 7.31 (s, 2H, CONH$_2$), NH$_2$), 7.41 (d, J = 8.1 Hz, 4H$_{arom}$), 7.67 (d, J = 8.1 Hz, 4H$_{arom}$).

^{13}C NMR (DMSO-d_6): δ = 21.0, 32.1, 47.8, 49.9, 53.3, 127.1, 129.9, 135.3, 143.2, 173.3.

MS (FAB in glycerol): m/z = 623 (MH$^+$).

1,7-Di(2′-aminoethyl)-4,10-di(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane (8a):

Diamide **7a** (5.55 g, 9.3 mmol) was dissolved under N$_2$ in a 1 M solution of BH$_3$ in THF (100 mL). The solution was refluxed overnight before neutralizing the excess BH$_3$ by dropwise addition of H$_2$O. The solvents were evaporated under reduced pressure. The remaining solid was dissolved in 6 M HCl (100 mL) and the resulting solution was refluxed for 16 h. The reaction mixture was brought to dryness in a Rotavapor and the solid residue was suspended in H$_2$O (20 mL). The pH was brought to 12 by the addition of a 2 M LiOH solution and the mixture was extracted with CH$_2$Cl$_2$ (3 × 100 mL). The combined organic phases were washed with H$_2$O (2 × 50 mL) and dried (MgSO$_4$). Evaporation of the solvent afforded **8a** as a colourless oil; yield: 4.48 g (85%). An analytical sample of **8a** was obtained by dissolution in EtOH followed by the precipitation of the hydrochloride salt with concentrated HCl. The isolated salt was then crystallized from H$_2$O/EtOH.

^{1}H NMR (CDCl$_3$): δ = 2.49 (s, 6H, ArCH_3), 2.60 (t, 4H, J = 1.6 Hz, CH_2CH$_2$NH$_2$), 2.88 (m, 12H, ring CH$_2$ + CH$_2$NH$_2$), 3.25 (t, 8H, J = 4.2 Hz, ring CH$_2$), 7.38 (d, J = 8.0 Hz, 4H$_{arom}$), 7.72 (d, J = 8.0 Hz, 4H$_{arom}$).

^{13}C NMR (CDCl$_3$): δ = 21.3, 38.8, 49.4, 55.0, 57.1, 127.2, 129.5, 134.4, 143.3.

MS (FAB in glycerol): m/z = 567 (MH$^+$).

1,7-Di(3′-propylamine)-4,10-di(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane (8b):

This reduction was carried out as described for **8a** starting from **7b** (3.11 g, 4.9 mmol) in a 1 M solution of BH$_3$ in THF (50 mL). Diamine **8b** was isolated as a colourless vitreous solid; yield: 2.97 g (~100%).

^{1}H NMR (CDCl$_3$): δ = 1.53 (m, 4H, bridge CH$_2$), 2.39 (s, 6H, ArCH$_3$), 2.45 (t, 4H, J = 7.2 Hz, bridge CH$_2$), 2.67 (t, 4H, J = 7.2 Hz, bridge CH$_2$), 2.73 (t, 8H, J = 4.9 Hz, ring CH$_2$), 3.18 (t, 8H, J = 4.9 Hz, ring CH$_2$), 7.27 (d, J = 8.2 Hz, 4H$_{arom}$), 7.63 (d, J = 8.2 Hz, 4H$_{arom}$).

^{13}C NMR (CDCl$_3$): δ = 21.3, 29.9, 40.2, 48.3, 52.3, 54.2, 127.2, 129.8, 135.2, 143.1.

MS (FAB in glycerol): m/z = 595 (MH$^+$), 440 (MH$^+$-Ts)

1,5-Di[oxo-3-(*p*-toluenesulfonyl)-3-azapentane-1,5-diyl] bis(1,3-thiazolidine-2-thione (10a):

N-Tosyliminodiacetyl dichloride[15] (4.50 g, 13.9 mmol) was dissolved in anhydr. THF (135 mL). The solution was stirred for 5 min and the thallium(I) salt of 1,3-thiazolidine-2-thione[16] (9.90 g, 30.6 mmol, 2.2 equiv) was added in one portion. The resulting suspension was stirred for 2 d. The precipitate of TlCl was filtered and washed with THF (25 mL). Removal of the solvent by evaporation under reduced pressure afforded a yellow oil. The title compound was isolated by crystallization from CH$_2$Cl$_2$ that gave two crops of crystals. An additional crop was obtained when adding the remaining CH$_2$Cl$_2$ solution to Et$_2$O (150 mL). All crops were combined and used without further purification; yield: 5.04 g (74%); mp 147–148 °C.

^{1}H NMR (CDCl$_3$): δ = 2.40 (s, 3H, ArCH_3), 3.33 (t, 4H, J = 4.0 Hz, CH$_{2\,thiazol}$), 4.49 (t, 4H, J = 4.0 Hz, CH$_{2\,thiazol}$), 5.07 (s, 4H, CH$_2$), 7.27 (d, J = 8.2 Hz, 2H$_{arom}$), 7.70 (d, J = 8.2 Hz, 2H$_{arom}$).

^{13}C NMR (CDCl$_3$): δ = 21.4, 29.1, 53.7, 55.7, 127.3, 129.4, 136.4, 143.6, 170.0, 201.5.

MS (FAB in NOBA): m/z = 490 (MH$^+$).

3-*N*-Methyliminodiacetyl-1,3-thiazolidine-2-thione (10b):

Compound **9b** (3 g, 20.4 mmol) was added to a solution of 1,3-thiazolidine-2-thione (4.86 g, 40.8 mmol) in CH$_2$Cl$_2$ (60 mL). This suspension was cooled to 0 °C. DCC (8.42 g, 40.8 mmol) and DMAP (0.10 g) were added to the mixture. Stirring was continued for 2 d at r.t. Dicyclohexylurea formed was filtered and washed with CH$_2$Cl$_2$ (2 × 15 mL). The filtrate and the washings were evaporated under reduced pressure to give a yellow solid that still contained the three reactants. The solid was suspended in a 1 M NaOH solution (20 mL) for 8 h. It was filtered, washed with H$_2$O (2 × 15 mL) and dried in vacuum. The yellow solid was used for the cyclisation step without further purification; yield: 90% (estimated by ^{1}H NMR).

^{1}H NMR (CDCl$_3$): δ = 2.44 (s, 3H, CH$_3$N), 2.52 (s, 4H, CH$_2$CO), 3.31 (t, 4H, J = 7.6 Hz, CH$_{2\,thiazol}$), 4.55 (t, 4H, J = 7.6 Hz, CH$_{2\,thiazol}$).

^{1}C NMR (CDCl$_3$): δ = 29.8, 43.1, 56.6, 63.1, 173.4, 202.1.

5,9-Dioxo-7,16,21-tri(*p*-toluenesulfonyl)-1,4,7,10,13,16,21-heptaazabicyclo[11.5.5]tricosane (11a):

Method A:

Two solutions containing respectively a) **8a** (1.21 g, 2.14 mmol) and Et$_3$N (1.5 mL, 10.8 mmol) in anhydr. CH$_2$Cl$_2$ (250 mL), and b) **9a** (0.73 g, 2.25 mmol, 1.05 equiv) in anhydr. CH$_2$Cl$_2$ (250 mL) were added simultaneously to vigorously stirred anhydr. CH$_2$Cl$_2$ (1.5 L). The mixture was stirred for 1 h after the end of the addition that was carried out at a 1 mL/min rate. Removal of the solvent afforded a yellow residue that was shaken with H$_2$O (75 mL) for 16 h. The insoluble material was filtered, washed with H$_2$O (25 mL) and dried in vacuo. Product **11a** was purified by chromatography (silica gel, CHCl$_3$/MeOH, 9:1) and isolated as a pale yellow wax; yield: 1.05 g (60%).

Method B:

Compounds **10a** (3.02 g, 6.17 mmol) and **8a** (3.49 g, 6.17 mmol) were separately dissolved in CH$_2$Cl$_2$ (250 mL). These two solutions were added simultaneously to a vigorously stirred large volume of CH$_2$Cl$_2$ (1.5 L). Stirring was continued for 1 h after the end of the addition and the solvent was evaporated under reduced pressure. The yellow solid was eluted on silica gel [flash chromatography, CH$_2$Cl$_2$, CH$_2$Cl$_2$/MeOH (98:2) for eluting TTH, CH$_2$Cl$_2$/MeOH (96:4) for eluting **11a**] to afford the title compound as a pale yellow solid wax; yield: 4.24 g (84%).

^{1}H NMR (CDCl$_3$): δ = 2.37 (s, 6H, ArCH_3), 2.40 (s, 3H, ArCH_3), 2.57–3.30 (5 m, 24H, ring CH$_2$ + bridge CH$_2$), 3.79 (s, 4H, NCH$_2$CO), 7.18 (br, 2H, NHCO), 7.29 (2 d, J = 8.2 Hz, 6H$_{arom}$), 7.62 (d, J = 8.2 Hz, 4H$_{arom}$), 7.72 (d, J = 8.2 Hz, 2H$_{arom}$).

^{13}C NMR (CDCl$_3$): δ = 21.3, 21.4, 37.9, 48.5, 53.2, 54.3, 54.8, 127.3, 127.9, 129.6 (2 ×), 133.7, 134.1, 143.5, 144.2, 167.9.

MS (FAB in glycerol): m/z = 819 (MH$^+$).

6,10-Dioxo-8,18,23-tri(*p*-toluenesulfonyl)-1,5,8,11,15,18,23-heptaazabicyclo[13.5.5]pentaicosane (11b):

Bismacrocycle **11b** was synthesized according to the high dilution technique used for the preparation of **5**. Diamine **8b** (2.96 g, 4.98 mmol) dissolved in CH$_2$Cl$_2$ (250 mL) and diacid **10a** (2.44 g, 4.98 mmol) dissolved in CH$_2$Cl$_2$ (250 mL) were added simultaneously to a large volume of CH$_2$Cl$_2$ (1 L). Elution of the residue after workup on a silica gel column (CH$_2$Cl$_2$, CH$_2$Cl$_2$/MeOH, 9:1 for eluting TTH, 8:2 for eluting **11b**) afforded **11b** as a white amorphous solid; yield: 1.85 g (44%).

^{1}H NMR (CDCl$_3$): δ = 1.90 (br, 4H, bridge CH$_2$), 2.36 (s, 3H, ArCH_3), 2.40 (s, 6H, ArCH_3), 3.3–3.5 (24H, ring CH$_2$ + bridge CH$_2$), 4.00 (s, 4H, NCH$_2$CO), 7.26 (d, J = 8.1 Hz, 2H$_{arom}$), 7.31 (d, J = 8.1 Hz, 4H$_{arom}$), 7.59 (d, J = 8.2 Hz, 4H$_{arom}$), 7.75 (d, J = 8.2 Hz, 2H$_{arom}$).

^{13}C NMR (CDCl$_3$): δ = 21.4, 21.7, 31.0, 36.7, 45.7, 53.4 (2 ×), 54.2, 127.5, 127.6, 129.8, 130.1, 131.0, 134.5, 144.1, 145.1, 170.4.

MS (FAB in glycerol): m/z = 847 (MH$^+$), 692 (MH$^+$-Ts).

7-Methyl-5,9-dioxo-16,21-di(*p*-toluenesulfonyl)-1,4,7,10,13,16,21-heptaazabicyclo[11.5.5]tricosane (11c):
Two solutions, containing respectively **8a** (1.72 g, 3.03 mmol) and **10b** (1.68 g, ~ 3 mmol) in CH_2Cl_2 (250 mL) were added simultaneously to a vigorously stirred large volume of CH_2Cl_2 (1 L). The workup procedure was the same as the one used for the other macrocyclisations (see **11a**). The product was isolated by flash chromatography on silica gel (CH_2Cl_2, CH_2Cl_2/MeOH, 99:1, 98:2 and 8:2) as a pale yellow solid wax; yield: 0.691 g (34%).

^{1}H NMR ($CDCl_3$): δ = 2.13 (s, 3H, CH_3N), 2.41 (s, 6H, ArCH_3), 2.59 (t, 4H, J = 7.1 Hz, bridge CH_2), 2.73 (m, 8H, ring CH_2), 2.98 (m, 4H, bridge CH_2), 3.36 (m, 8H, ring CH_2), 3.40 (s, 4H, CH_2CO), 7.31 (m, 4H_{arom} + 2NHCO), 7.60 (d, J = 8.2 Hz, 4H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 22.4, 37.3, 44.7, 48.5, 54.2, 54.4, 63.8, 128.2, 130.8, 135.0, 144.8, 170.6.

MS (FAB in NOBA): m/z = 678 (MH^+), 522 (MH^+-Ts).

7,16,21-Tri(*p*-toluenesulfonyl)-1,4,7,10,13,16,21-heptaazabicyclo-[11.5.5]tricosane (12a):
From **11a**: The bismacrocyclic diamide **11a** (4.11 g, 5.02 mmol) was added to a 1 M solution of BH_3 in THF (100 mL) and the title compound was isolated as described above for the preparation of **8a**. Polyamine **12a** is a glassy solid; yield: 3.25 g (82%).

From **5**: The same procedure afforded **12a**; yield: 80%.

^{1}H NMR ($CDCl_3$): δ = 2.36, 2.39 (2 s, 9H, ArCH_3), 2.48, 2.68 (2 m, 2 × 4H, bridge CH_2), 2.84, 2.92, 3.13, 3.18 (4 m, 24H, ring CH_2 + bridge CH_2), 7.25 (m, 6H_{arom}), 7.62 (m, 6H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 21.5 (2 peaks), 46.7, 49.1, 49.8, 50.2, 54.5, 54.8, 127.4, 127.7, 129.6, 129.8, 134.2, 135.4, 143.2, 143.5.

MS (FAB in NOBA): m/z = 790 (MH^+), 635 (MH^+-Ts).

8,18,23-Tri(*p*-toluenesulfonyl)-1,5,8,11,15,18,23-heptaazabicyclo-[13.5.5]pentaicosane (12b):
Diamide **11b** (1.87 g, 2.2 mmol) was dissolved in a 1 M solution of BH_3 in THF (50 mL) and the reaction was carried out exactly as for the synthesis of **8a** and **12a**; yield: 1.35 g (75%) of a colourless vitreous solid.

^{1}H NMR ($CDCl_3$): δ = 1.64 (m, 4H, bridge CH_2), 2.38, 2.40 (2 s, 9H, ArCH_3), 2.44 (m, 4H, bridge CH_2), 2.68 (m, 16H, ring CH_2 + bridge CH_2), 2.80, 3.18 (2 m, 12H, ring CH_2 + bridge CH_2), 7.28 (m, 6H_{arom}), 7.63 (m, 6H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 21.3 (2 ×), 27.3, 47.9, 48.9, 49.3, 50.5, 53.4, 54.2, 127.1, 127.3, 129.5 (2 ×), 134.9, 135.1, 143.3 (2 ×).

MS (FAB in NOBA): m/z = 818 (MH^+), 663 (MH^+-Ts).

7-Methyl-16,21-di(*p*-toluenesulfonyl)-1,4,7,10,13,16,21-heptaazabicyclo[11.5.5]tricosane (12c):
Diamide **11c** (0.70 g, 1.03 mmol) was dissolved in a 1 M solution of BH_3 in THF (21 mL). The resulting solution was treated the same way as in the synthesis of **12a** affording the bismacrocyclic polyamine **12c** as a white solid; yield: 0.656 g (98%).

^{1}H NMR ($CDCl_3$): δ = 2.06 (s, 3H, CH_3N), 2.37 (s, 6H, ArCH_3), 2.53 (m, 4H, bridge CH_2), 2.6–2.9 (m, 16H, ring CH_2 + bridge CH_2), 2.92 (m, 4H, bridge CH_2), 3.17 (m, 8H, ring CH_2), 7.26 (d, J = 8.2 Hz, 4H_{arom}), 7.64 (d, J = 8.2 Hz, 4H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 22.3, 41.0 (br), 128.4, 130.6, 135.4, 144.4.

MS (FAB in NOBA): m/z = 650 (MH^+), 495 (MH^+-Ts).

4,10-Dimethyl-7,16,21-tri(*p*-toluenesulfonyl)-1,4,7,10,13,16,21-heptaazabicyclo[11.5.5]tricosane (13a):
Bismacrocycle **12a** (1.83 g, 2.31 mmol) was dissolved in concentrated formic acid (25 mL) and the temperature was raised to 70°C before the addition of a large excess of solid paraformaldehyde (0.4 g). This mixture was stirred overnight at 70°C. Removal of the solvent afforded an oily product that was dissolved in H_2O (~ 5 mL). A sat. aq solution of Na_2CO_3 was then slowly poured in with stirring until the pH became strongly basic (~ 12). The precipitated **13a** was filtered, washed with H_2O (25 mL) and dried in vacuum; yield: 1.85 g of a colourless glassy solid (98%).

^{1}H NMR ($CDCl_3$): δ = 2.39, 2.40 (2 s, 9H, ArCH_3), 2.09 (s, 6H, NCH_3), 2.45–2.52 (m, 12H, bridge CH_2), 2.85 (t, 8H, J = 5.0 Hz, ring CH_2), 3.16 (t, 8H, J = 5.0 Hz, ring CH_2), 3.30 (t, 4H, J = 7.0 Hz, bridge CH_2), 7.26 (m, 6H_{arom}), 7.61 (d, J = 8.2 Hz, 4H_{arom}), 7.66 (d, J = 8.2 Hz, 2H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 22.4 (2 peaks), 43.4, 47.5, 50.5, 54.6, 55.9, 57.2, 58.0, 127.9, 128.1, 130.5, 130.6, 135.7, 137.8, 144.0, 144.3.

MS (FAB in glycerol): m/z = 818 (MH^+), 663 (MH^+-Ts).

5,11-Dimethyl-8,18,23-tri(*p*-toluenesulfonyl)-1,5,8,11,15,18,23-heptaazabicyclo[13.5.5]pentaicosane (13b):
Paraformaldehyde (0.200 g) was added at 70°C to a solution of **12b** (0.53 g, 0.65 mmol) in conc. formic acid (15 mL). The reaction was performed as described for **13a** except that **13b** separated from the aqueous phase as a viscous oil that was extracted with CH_2Cl_2 (2 × 50 mL). The organic phases were dried ($MgSO_4$) and the solvent evaporated in vacuum to afford **13b** as a colourless vitreous solid; yield: 0.55 g (~ 100%).

^{1}H NMR ($CDCl_3$): δ = 1.57 (br, 4H, bridge CH_2), 2.21 (s, 6H, NCH_3), 2.29 (s, 3H, ArCH_3), 2.34 (s, 6H, $ArCH_3$), 2.43 (m, 8H, ring CH_2 + bridge CH_2), 2.57 (m, 4H, ring CH_2 + bridge CH_2), 2.78 (m, 8H, ring CH_2 + bridge CH_2), 3.15 (m, 12H, ring CH_2 + bridge CH_2), 7.20 (d, J = 8.2 Hz, 2H_{arom}), 7.24 (d, J = 8.2 Hz, 4H_{arom}), 7.56 (d, J = 8.2 Hz, 4H_{arom}), 7.61 (d, J = 8.2 Hz, 2H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 21.3, 24.0, 41.8, 46.8, 47.9, 52.4, 53.8, 55.3, 56.3, 127.0, 127.3, 129.5, 129.6, 134.5, 135.1, 143.1, 143.5.

MS (FAB in glycerol): m/z = 846 (MH^+), 691 (MH^+-Ts).

4,7,10-Trimethyl-16,21-di(*p*-toluenesulfonyl)-1,4,7,10,13,16,21-heptaazabicyclo[11.5.5]tricosane (13c):
The procedure was the same as for the synthesis of **13a** starting from **12c** (0.598 g, 0.92 mmol) in conc. formic acid (10 mL). The titled compound was isolated after the usual workup procedure (see **13a**) as a slightly brown vitreous solid; yield: 0.377 g (93%).

^{1}H NMR ($CDCl_3$): δ = 2.12 (s, 6H, ArCH_3), 2.19 (m, 4H, bridge CH_2), 2.39 (s, 9H, CH_3N), 2.47 (m, 12H, bridge CH_2), 2.82 (m, 8H, ring CH_2), 3.17 (m, 8H, ring CH_2), 7.26 (d, J = 8.1 Hz, 4H_{arom}), 7.61 (d, J = 8.1 Hz, 4H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 22.3, 43.7, 44.2, 46.7, 50.5, 54.5, 55.7, 56.4, 56.9, 128.3, 130.5, 135.8, 144.1.

MS (FAB in NOBA): m/z = 678 (MH^+).

4,10-Dimethyl-1,4,7,10,13,16,21-heptaazabicyclo[11.5.5]tricosane (14a):
Solid Na_2HPO_4 (1.1 g) and 2% sodium amalgam (21.2 g) were added to a solution of **13a** (0.96 g, 1.2 mmol) in absolute MeOH (20 mL). The suspension was refluxed for 20 h. H_2O (40 mL) was carefully added after cooling while stirring. The solution was decanted and the remaining mercury was washed with H_2O (3 × 20 mL). All the aqueous phases were gathered, filtered and concentrated in vacuum until the volume was decreased to 15 mL. This solution was extracted with CH_2C_2 (3 × 75 mL) and the organic phases were evaporated under reduced pressure to yield **14a** as a colourless oil. It was purified by dissolution in EtOH (20 mL) and addition of conc. HCl. Evaporation of the solvents under reduced pressure was followed by an overnight reflux of the solid suspended in absolute EtOH (20 mL). The insoluble hydrochloride was filtered under N_2 and dried in vacuum; yield: ~ 100%.

^{1}H NMR (D_2O): δ = 3.02 (m, 4H, CH_2), 3.15 (s, 6H, NCH_3), 3.21 (m, 8H, CH_2), 3.33 (m, 4H, CH_2), 3.65 (m, 4H, CH_2), 3.75 (m, 4H, CH_2), 3.92 (m, 8H, CH_2).

^{13}C NMR (D_2O): δ = 43.8, 44.9, 45.2, 51.3, 52.2, 57.1, 57.6.

MS (FAB in NOBA): m/z = 356 (MH^+).

5,11-Dimethyl-1,5,8,11,15,18,23-heptaazabicyclo[13.5.5]pentaicosane (14b):
Bismacrocycle **13b** (0.630 g, 0.74 mmol) was dissolved in conc. H_2SO_4 (20 mL). The resulting dark mixture was heated at 100°C for 48 h. The cold solution was added dropwise to cold Et_2O (75 mL) under vigorous stirring. The precipitate that formed immediately was filtered under N_2 and dissolved in H_2O (~ 25 mL). The Et_2O

that remained trapped in the precipitate was removed by boiling the solution for 1 h. A 1 M LiOH solution was added until the pH became higher than 12. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL) and H_2O was evaporated in vacuum. The solid residue was suspended in CH_2Cl_2 (25 mL) and the mixture was stirred overnight. The inorganic salts were filtered and washed with CH_2Cl_2 (2 × 10 mL). Product **14b** was isolated by removal of the solvent under reduced pressure; yield: 0.213 g (75%).

14b · HCl:

^{1}H NMR (D_2O): δ = 2.08 (m, 4H, bridge CH_2), 2.61 (m, 4H), 2.85 (m, 4H), 2.96 (m, 4H), 2.98 (s, 6H, NCH_3), 3.17 (m, 4H), 3.31 (m, 4H), 3.40 (m, 4H), 3.73 (br, 8H).

^{13}C NMR (D_2O): δ = 26.7, 43.4, 44.6 (2), 44.8, 51.2, 52.2, 60.0.

^{1}H NMR ($CDCl_3$): δ = 1.61 (q, 4H, J = 5.6 Hz, bridge CH_2), 2.19 (s, 6H, NCH_3), 2.35 (t, 4H, J = 7.6 Hz, bridge CH_2), 2.43 (t, 4H, J = 7.6 Hz, bridge CH_2), 2.49 (m, 12H, ring CH_2 + bridge CH_2), 2.58 (m, 12H, ring CH_2 + bridge CH_2).

^{13}C NMR ($CDCl_3$): δ = 26.5, 43.1, 46.6, 47.1, 53.2, 54.1, 55.8, 57.2.

MS (FAB in glycerol): m/z = 384 (MH^+).

4,7,10-Trimethyl-1,4,7,10,13,16,21-heptaazabicyclo[11.5.5]tricosane (14c):

Compound **14c** was prepared following the procedure reported for the synthesis of **14a**. Bismacrocycle **13c** (0.535 g, 0.79 mmol) was dissolved in absolute MeOH (12 mL) and treated with a 2% sodium amalgam (18.15 g) and anhydr. Na_2HPO_4 (0.896 g). The reaction and the usual workup afforded the hydrochloride of **14c** as a white solid; yield: 0.359 g (95%).

14c · HCl:

^{1}H NMR (D_2O): δ = 3.14, 3.18 (2 s, 9H, CH_3N), 3.22, 3.28, 3.39, 3.50, 3.70, 4.15 (6 m, 32H, ring CH_2 + bridge CH_2).

^{13}C NMR (D_2O): δ = 43.3, 43.9, 44.8, 45.3, 49.4, 50.5, 52.1, 53.8, 55.6, 57.9.

MS (FAB in NOBA): m/z = 370 (MH^+).

7,16,21-Tricarboxymethyl-4,10-dimethyl-1,4,7,10,13,16,21-heptaazabicyclo[11.5.5]tricosane (15a):

A chilled solution of KOH (0.142 mg, 2.538 mmol) in absolute MeOH (4 mL) was added dropwise to a cooled (0°C) solution of bromoacetic acid (0.321 g, 2.307 mmol) in absolute MeOH (10 mL) taking care that the temperature never rose above 5°C. This solution was poured onto a mixture of 300 mg of the hydrochloride salt of **14a** (~ 0.70 mmol) and anhydr. K_2CO_3 (0.966 g, 7 mmol, 10 equiv.) in absolute MeOH (25 mL). The resulting suspension was stirred for 6 h at 45°C and for 16 h at 65°C. The solvent was removed under reduced pressure and the solid residue was taken up in absolute MeOH (20 mL). After stirring for 1 h, the precipitated inorganic salts were filtered and washed with EtOH (2 × 5 mL). The filtrates were evaporated in vacuum and the remaining viscous solid was dissolved in MeOH (10 mL). Acetone was then carefully added on the top of the methanolic solution until two distinct phases of equal volumes (~ 15 mL) were obtained. The precipitate of inorganic salts that formed upon standing overnight at 0°C was filtered and washed with acetone. The filtrate and the acetone washings were evaporated and the residue was dissolved in absolute EtOH (10 mL). Conc. HCl was added and the solvents were removed in vacuum. The solid was taken up in absolute EtOH (10 mL) and the suspension refluxed overnight. The hygroscopic white hydrochloride was filtered under N_2 and dried in vacuum; yield: ~ 60%, mp 254–256°C (dec.). Molecular weight determined by pH-metry: 661, **15a** · $(HCl)_3$ · $(H_2O)_{1.2}$ requires 660.7.

15a – *Potassium salt:*

^{1}H NMR (D_2O): δ = 3.02, 3.04 (2 s, 6H, NCH_3), 3.25–3.60 (br, 24H, ring CH_2 + bridge CH_2), 3.65 (br, 2H, CH_2CO_2H), 3.74 (br, 2H, CH_2CO_2H), 4.13 (br, 8H, ring CH_2 and/or bridge CH_2).

^{13}C NMR (D_2O): spectrum too broad to be assigned.

MS (FAB in NOBA): m/z = 530 (MH^+), 472 (M-CH_2CO_2 + H^+), 414 (M-2CH_2CO_2 + H^+).

8,18,23-Tricarboxymethyl-5,11-dimethyl-1,5,8,11,15,18,23-heptaazabicyclo[13.5.5]pentaicosane (15b):

Bismacrocycle **15b** was synthesized according to the technique developed for the synthesis of **15a**. Bromoacetic acid (0.196 g, 1.408 mmol) in absolute MeOH (6 mL) neutralised by KOH (0.087 g, 1.55 mmol) in absolute MeOH (3 mL) was added to a solution of **14b** (0.200 g, 0.44 mmol) and of anhydr. K_2CO_3 (0.607 g, 10 equiv.) in absolute MeOH (25 mL). When the reaction was completed, enough acetone (~ 10 mL) was added to the filtered solution to obtain a cloudy mixture that was stored overnight at 0°C. The solid was filtered, dissolved in EtOH (~ 10 mL) and conc. HCl (5 mL), was added. The solvents were removed in vacuum and the residue was suspended in EtOH (10 mL). Refluxing the suspension for 1 h followed by filtration under N_2 afforded the title compound **15b** as its hygroscopic solid hydrochloride salt; yield: 0.106 g (36%). Molecular weight determined by pH-metry: 694, **15b** $(HCl)_3(H_2O)_{1.5}$ requires 694.1.

15b – *Potassium Salt:*

^{1}H NMR (D_2O, 328 K): δ = 2.17 (br, m, 4H, bridge CH_2), 2.71 (br s, 6H, NCH_3), 2.8 to 3.3 (2 broad unresolved bands, 18H, ring CH_2 + bridge, CH_2), 3.34 (br s, 2H, CH_2CO_2H), 3.45 (br s, 2H, CH_2CO_2H), 3.65 (br, 4H, ring or bridge CH_2).

^{13}C NMR (D_2O): spectrum too broad to be assigned.

MS (FAB in NOBA): m/z = 559 (MH^+), 501 (M-CH_2CO_2 + H^+), 442 (M-2CH_2CO_2 + H^+).

MS (ES in MeCN/H_2O 50/50: m/z = 559 (MH^+), 279.8 (MH_2^{2+}/2), 500 (M-CH_2CO_2 + H^+), 250.3 [(M-CH_2CO_2 + 2H)$^{2+}$/2], 442 (M-2CH_2CO_2 + H^+), 221.8 [(M-2CH_2CO_2 + H)$^{2+}$/2].

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