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Synthesis of polyaza macropolycyclic ligands

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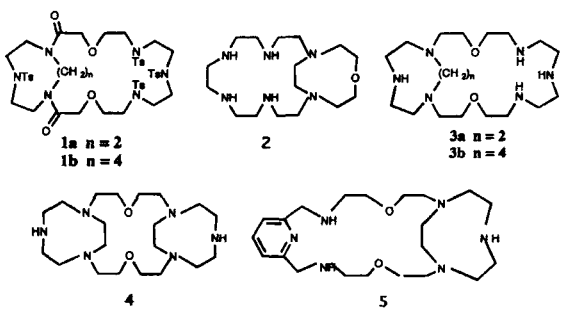
General routes to macropolycycles containing small rings and pyridine are described. The routes utilize macrocyclic lactams as precursors with diphenylphosphoryl azide (DPPA) as an activating agent for the dicarboxylic acids. In bridged lactams, traditional methods of total deprotection (HBr-HOAc in the presence of phenol or concentrated H_2SO_4) are not successful, because the deprotection in the smaller rings is incomplete. Small rings can be totally deprotected using sodium metal. In the case of pyridine-containing macrocycles with small rings, the use of sodium is undesirable; hence, initial benzyl protection of the small cyclononane ring, allows for deprotection by the traditional HBr-HOAc method. The synthesis of four different macropolycyclic lactams, their reduction and deprotection are described.

Synthetic strategies for polyaza macrocyclic compounds have been avidly sought for a number of years, in order to obtain macrocycles which complex metal ions as well as to achieve receptors of other substrates such as organic and inorganic anions and cations. The cyclization is a crucial step in these reactions, often requiring high dilution techniques and resulting in low yields. Recently we reported a convenient method of preparing macrocyclic lactams **1** as precursors to polycyclic polyaza macrocycles. The method, which consists of using diphenylphosphoryl azide (DPPA) as an activating agent of dicarboxylic acids, simplifies the synthesis of macropolycyclic lactams.[1] While the desired macrocyclic product is usually the totally reduced and deprotected macrocycle, in the bridged lactams traditional methods of total deprotection (HBr-HOAc in the presence of phenol or concentrated H_2SO_4) are not successful. Herein are reported general methods for the reduction and deprotection of midsized cyclic and polycyclic lactams including both bi- and tricyclic compounds **2–5**.



1a n = 2
1b n = 4

2

3a n = 2
3b n = 4

4

5

RESULTS AND DISCUSSION

The bicycle with the monooxadiazacyclononane ring (**2**) was obtained as shown in Scheme 1. The reaction of ditosylethylenediamine (**6**) with diethylene glycol ditosylate (**7**) in the presence of K_2CO_3 gave a mixture of 1 + 1 and 2 + 2 adducts, **8** and **10** in 53% and 20% yield, respectively. The mixture was easily isolated by recrystallization in CH_2Cl_2-ethanol. The macrobicycle was then formed by reacting the diacid **14** with the cyclononane, **8**. Reduction of the resulting lactam **15**, followed by detosylation in HBr-HOAc in the presence of phenol gave a mixture because of partial decomposition, so reductive cleavage was carried out using metallic sodium.

The bicycles **3a** and **b** were synthesized from the previously reported macrocyclic lactams **1a** and **1b** (Scheme 2). Reduction of the lactams **1a** and **b** with borane gave good yields of **17a** and **b**, respectively. Compounds **17**, however, gave the monotosylated compounds **18** in the presence of HBr-HOAc/phenol. With concentrated H_2SO_4, **17b** could be converted into the totally detosylated **3b**, while **17a** still retained one tosyl group. The monotosylated compounds could be deprotected using sodium metal, however. This difficulty in detosylation is probably related to steric hindrance in the small rings. It was therefore desirable to design a one step general methodology for detosylation of difficult compounds and, in particular, to achieve more compli-

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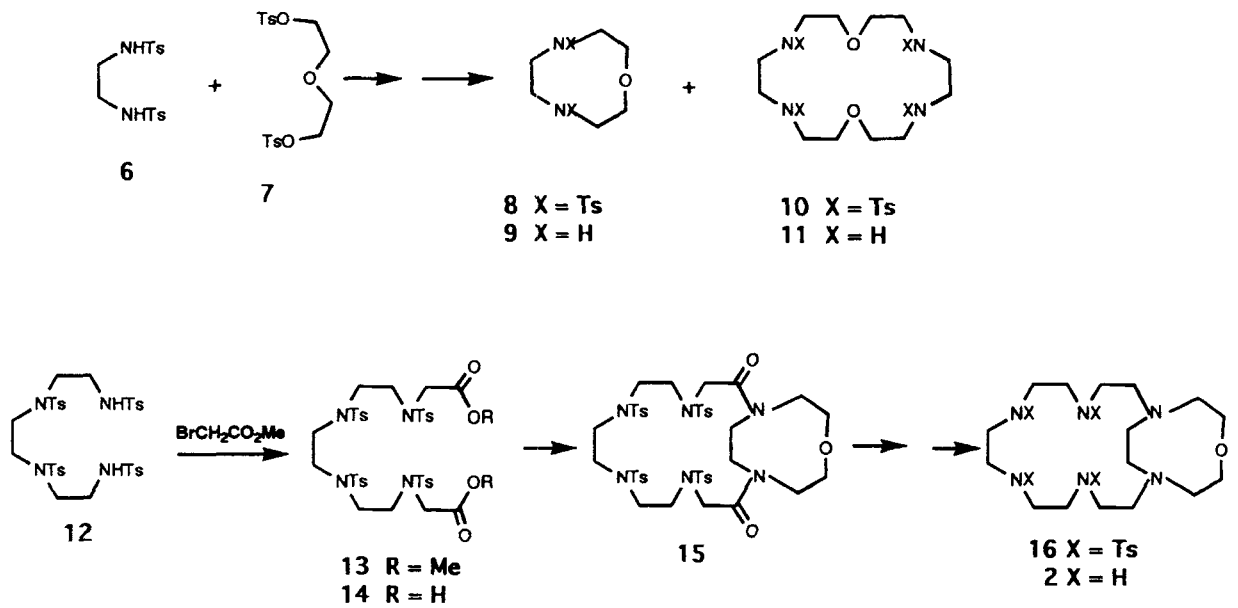
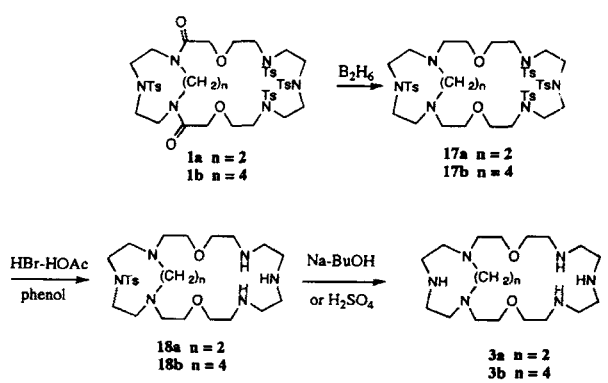


Scheme 1

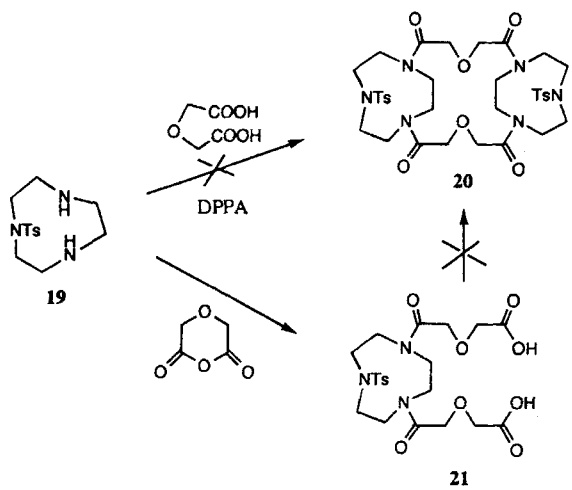
cated sterically constrained tricyclic compounds such as **4** using simple methods.

The initial attempt at obtaining the tricylic compound **20** was not successful and employed the direct reaction of monotosylated triazacyclononane with diglycolic acid in the presence of a dehydrating agent, DPPA (Scheme 3). Treatment of monotosylated triazacyclononane with diglycolic acid anhydride readily afforded the diacid **21**, but the reaction of **21** with triazacyclononane under DPPA did not give **20**. This failure probably is because the small cyclononane ring limits free rotation of the first amide bonds formed, which makes additional amide formation more difficult.

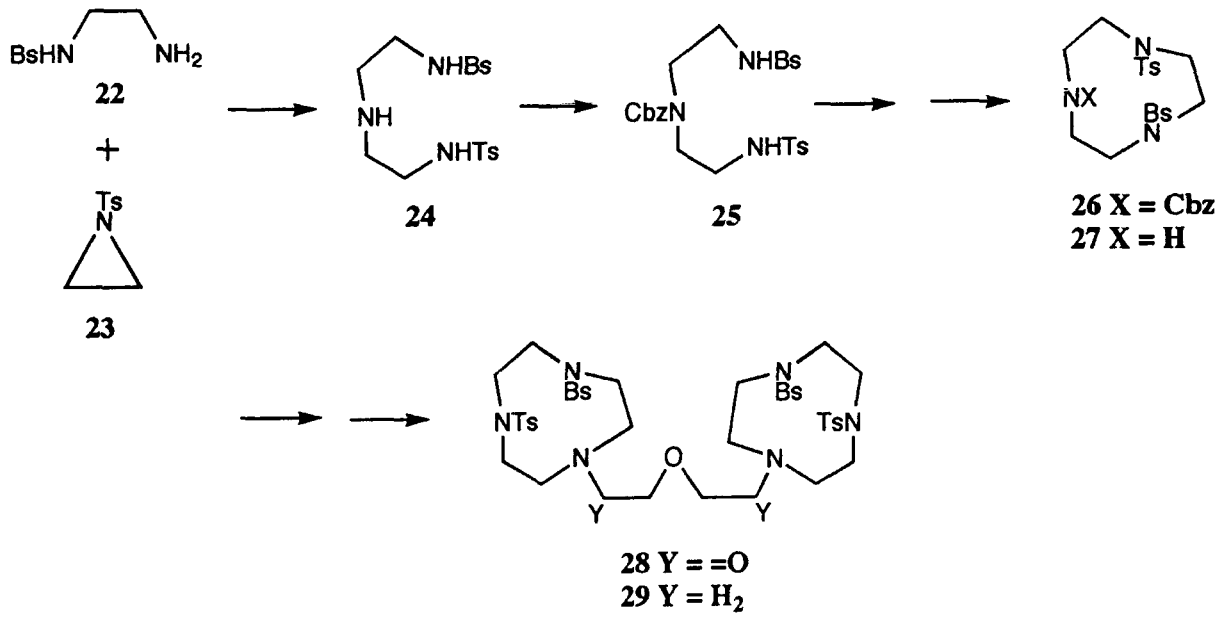
Scheme 4 was then devised in which different protective groups were employed. The rationale was based on an early report[2] in which a benzylsulfonyl moiety was found to be easily removed under hydrogenolysis in the presence of Raney nickel, while tosyl groups were impervious under the same conditions. Monobenzylsulfonylethylenediamine (**22**) was prepared by a method similar to that used for the synthesis of monotosylethylenediamine.[3] Treatment of **22** with tosylaziridine (**23**) in acetonitrile[4] gave **24** with two different protective groups. The remaining free amine of **24** was protected using a benzylcarboxyl (Cbz) group, to give **25** with three different protective groups. Reaction of **25** with ethylene glycol ditosylate in the presence of base in DMF gave the fully protected triazacyclononane **26**, from which the benzylcarboxylate could be readily removed in acidic media to afford **27**. Treatment of **27** with diglycolic acid dichloride in CH_2Cl_2 in the presence of Et_3N gave the amide **28**, which was readily reduced to



Scheme 2



Scheme 3



Scheme 4

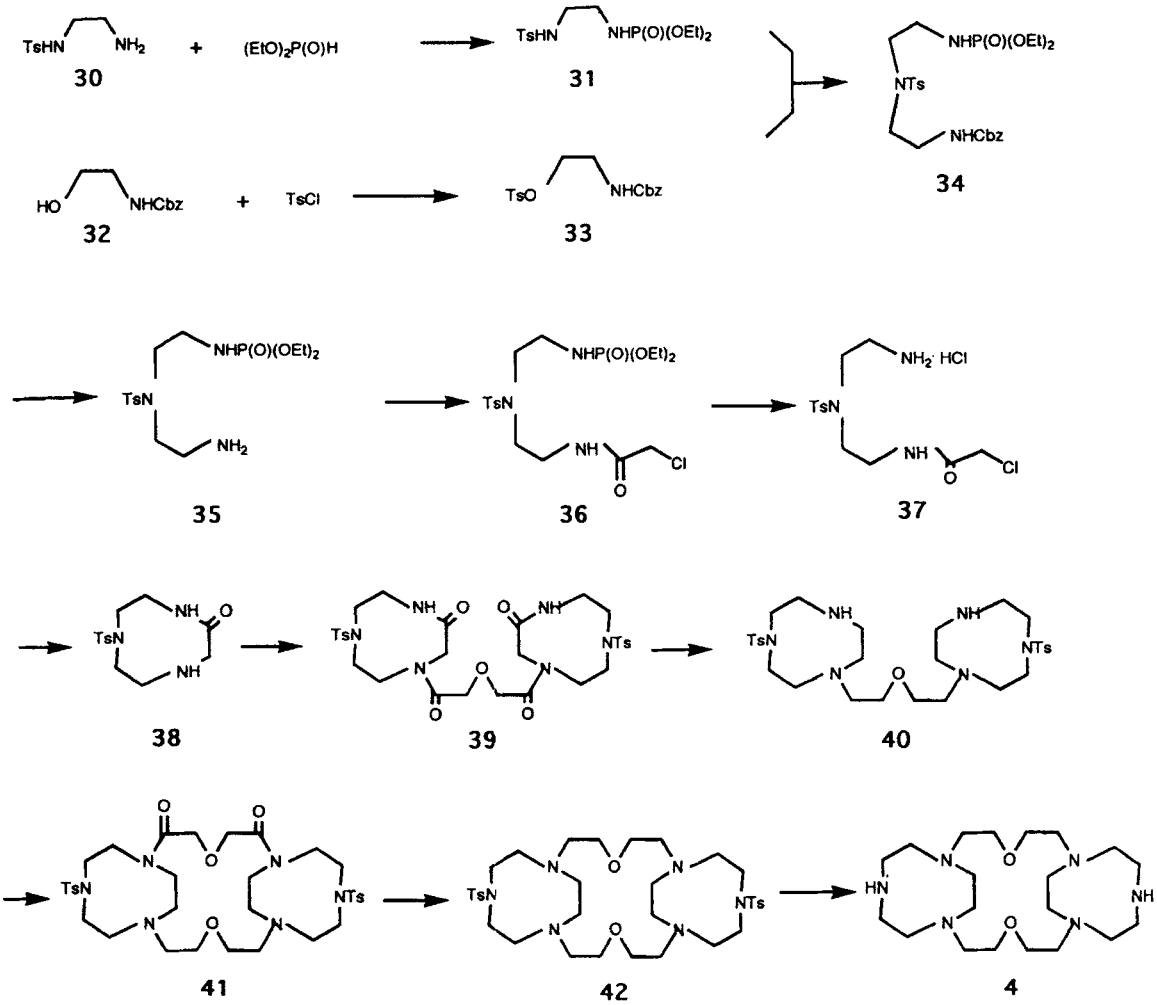
the amine **29** using borane. Unfortunately, the benzylsulfonyl moiety could not be removed using Raney nickel either in refluxing ethanol or in the presence of H_2 at room temperature. More vigorous conditions (at elevated temperatures and longer time in the case of H_2 atmosphere) simply resulted in the decomposition of the starting material.

The synthetic route was therefore modified as a result of the difficulty in removing the benzylsulfonyl group. Successful synthesis of the small macrocycle **38** was achieved using Cbz as a protective group (Scheme 5, compound **34**). The Cbz group was removed by hydrogenolysis using palladium-charcoal as catalyst, and replaced with a chloroacetyl group. An attempt to cyclize **36** in the presence of NaH in DMF resulted in very low yields. Cyclization was readily accomplished, however, after removal of the phosphoryl group which gave **38** in good yield. The bicyclic tetraamide **39** was readily obtained by treatment of **38** with diglycolic acid dichloride. The amides were then reduced with borane to give the free base **40**. Treatment of **40** with diglycolic acid in DMF in the presence of DPPA gave the macrotricycle **41** in reasonable yield, and reduction with borane followed by detosylation using sodium in butanol gave the final product **4**.

The inherent problem with small multicyclic macrocyclic ring systems such as **2**, **3**, and **4** is the harsh reaction conditions required to remove the tosyl groups, i.e., metallic sodium. In the synthesis of macrocycles containing a pyridyl subunit such as **5** (Scheme 6), the use of sodium is undesirable since it can reduce and possibly cleave the aromatic ring. Fortunately, by using benzyl protection, this problem could be circumvented. Furthermore, the benzyl group is easily removed under acidic conditions. Thus, in order to obtain the desired benzyl-protected macrocycle **45**, **43** was reduced using borane, followed by reductive cleavage of tosyl groups using sodium in butanol.

A minor problem was encountered in the initial steps in the synthesis of the "western" pyridine-containing portion of the macrocycle. Oxidation of N-tosylaminoethoxyethanol (**46**) (Scheme 6) with pyridinium-chlorochromate (PCC) in CH_2Cl_2 gave mainly the morphilinone **47** rather than the corresponding aldehyde. The ring of **47** was easily broken, however, in HCl-methanol solution at room temperature or in refluxing methanol in the presence of a small quantity of concentrated H_2SO_4. An attempt to oxidize the diol **49** after condensation with bis(chloromethyl)pyridine using Jone's reagent gave the corresponding lactone rather than acid **51**. The acid could be obtained, however, by reaction of 2,6-bis(chloromethyl)pyridine with **48** in DMF giving the dicarboxylate, **50**, which could then be hydrolyzed to the corresponding acid, **51**, in good yield. As expected, the free amine **5** was obtained by deprotection in one step in concentrated H_2SO_4 or in HBr-HOAc.

In conclusion, routes leading to the synthesis of new selectively protected triazacyclononanes have been developed. These methods are suitable for other midsize cyclic compounds, all of which are of great interest for constructing various ligands and receptors. Additionally, the methodology developed for the synthesis of macrobicycles and macrotricycles in this work is generally applicable.



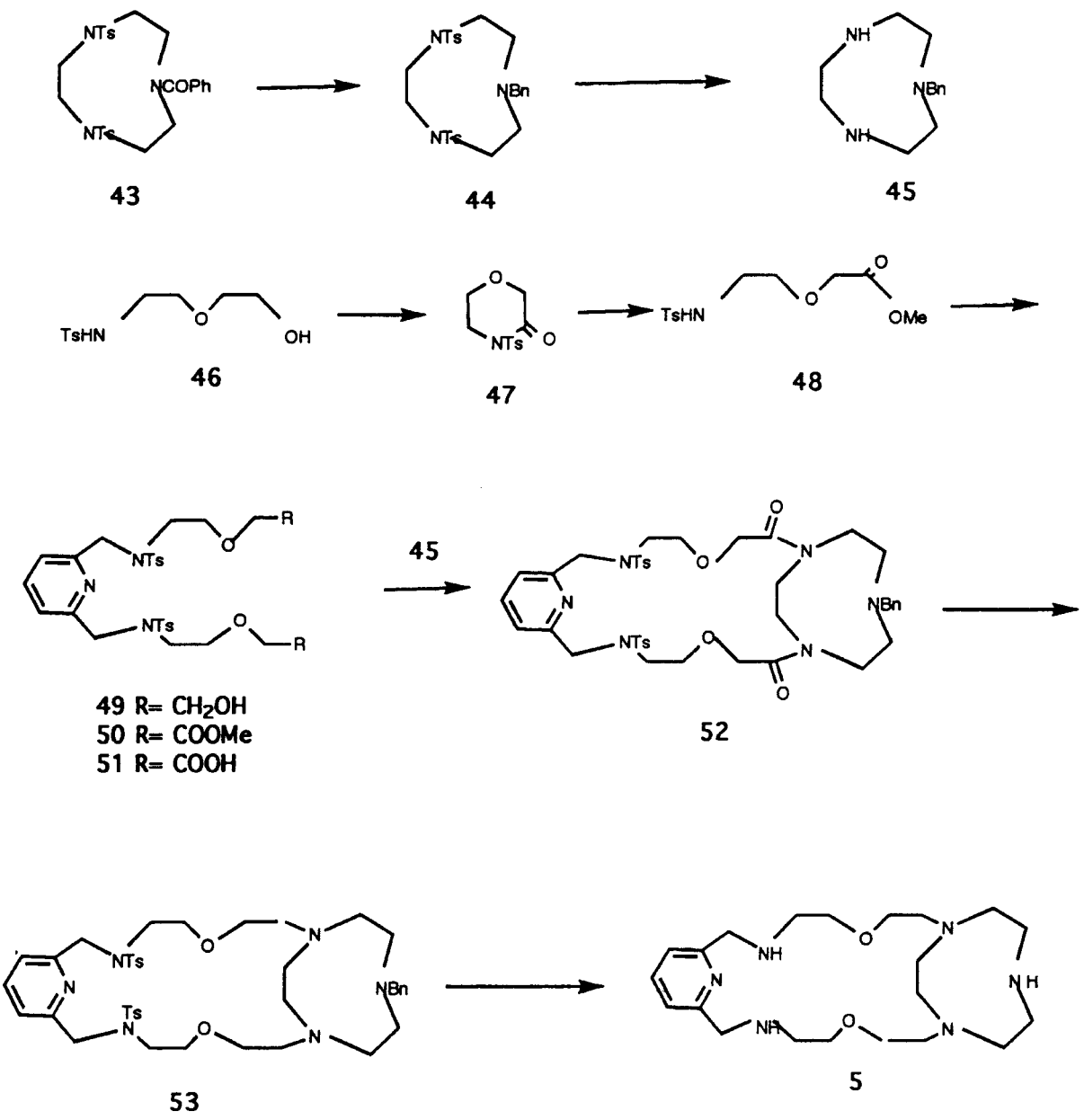
Scheme 5

EXPERIMENTAL SECTION

1,4-bis(*p*-tolysulfonyl)-1,4-diazabutane (**6**),[5] 1,4,7,10-tetrakis(*p*-tolylsulfonyl)-1,4,7,10-tetraaminedecane (**12**),[6] 1-(*p*-tolylsulfonyl)-1,4,7-triazacyclononane (**19**),[1] 1-tosylaziridine (**23**),[7] 1-(*p*-tolylsulfonyl)-1,4-diazabutane (**30**),[5] 4-benzoyl-1,7-bis(*p*-tolylsulfonyl)triazaheptane,[8] and bis-2-chloromethylpyridine[9] were synthesized as previously described. All other reagents were commercially available. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-300 at 300 and 75.43 MHz, respectively. Mass spectral data were obtained by Dr. Todd Williams of the Mass Spectrometry Laboratory at the University of Kansas. Elemental analysis for carbon, hydrogen, and nitrogen were performed at the Microanalytical Laboratory, University of Kansas by Dr. Tho Nguyen. Melting points were measured using capillary tubes without calibration.

Diethylene glycol ditosylate (7). To a solution of diethylene glycol (10.6 g, 0.1 mol) and triethylamine (5.4 g, 0.25 mol) in CH_2Cl_2 (100 mL) was added dropwise a solution of tosyl chloride (40 g, 0.21 mol) in CH_2Cl_2 (100 mL) over a period of 0.5 h with stirring in an ice-bath. The mixture was stirred overnight at room temperature, and then washed with H_2O (100 mL), HCl (50 mL, 2 M), saturated $NaHCO_3$ and brine. The solution was dried (Na_2SO_4), concentrated, and the solid was recrystallized from ethanol: yield 40.5 g (98%), mp 92.5–93.5 °C. ^{1}H NMR ($CDCl_3$) 7.79, 7.37 (4 H each, d, Ts), 4.11, 3.62 (4 H each, m, CH_2), 2.47 (3 H, s, CH_3) ppm. ^{13}C NMR ($CDCl_3$) 144.91, 132.75, 129.84, 127.85, 68.97, 68.63, 21.57 ppm.

1,4-Bis(*p*-tolylsulfonyl)-1,4-diaza-7-oxacyclonane (8) and 1,4,10,13-tetrakis(*p*-tolylsulfonyl)-7.16-dioxa-1,4,10,13-tetraazacyclo-octadecane (10). The mixture of ditosylate **7** (8.28 g, 0.02 mol), 1,4-bis(*p*-tolylsulfonyl)-1,4-diazabutane (**6**) (7.36 g, 0.02 mol) and K_2CO_3 (27.60 g, 0.2 mol) in DMF (400 mL) was stirred for 16 h at 80 °C. The DMF was then concentrated in vacuo. The residue was diluted with CH_2Cl_2 (200 mL),



Scheme 6

washed with water, and dried (Na_2SO_4). The CH_2Cl_2 solution was concentrated to about 20 mL, and 20 mL of ethanol was added to crystallize the products (**8** and **10**): yield 6.8 g (78%). The solid was redissolved into CH_2Cl_2 (30 mL) and the insoluble 2:2 cyclization product **10** was isolated: yield 3.51 g (20%), mp 243–248 °C. The filtrate was collected and concentrated to give **8**, which was recrystallized from CH_2Cl_2-ethanol: yield 4.6 g (53%), mp 195-196 °C. **8**: ^{1}H NMR ($CDCl_3$) 7.72, 7.34 (4 H each, d, Ts), 3.92 (4 H, t, CH_2O), 3.48 (4 H, s, CH_2N), 3.26 (4 H, t, CH_2N), 2.44 (6 H, s, CH_3) ppm. ^{13}C NMR 143.57, 135.12, 129.73, 127.22, 71.86, 51.97, 51.74, 21.41 ppm. CIMS (NH_3) (rel intens) 439 $(M + 1H)^+$ (62), 283 $(M - Ts)^+$ (82). Anal. Calcd for $C_{20}H_{26}N_2O_5S_2$: C, 54.77; H, 5.98; N, 6.39. Found: C, 54.40; H, 6.00; N, 6.18. **10**: ^{1}H NMR ($CDCl_3$) 7.72, 7.33 (8 H each, d, Ts), 3.55 (8 H, t, CH_2O), 3.33 (8 H, s, CH_2N), 3.23 (8 H, t, CH_2N), 2.45 (12 H, s, CH_3) ppm. ^{13}C NMR 143.56, 135.73, 129.80, 127.28, 71.58, 50.50, 50.15, 21.52 ppm. FABMS (rel intens) 877 $(M + 1H)^+$ (38), 723 (60), 567 (25), 439 (40), 215 (100).

1,4-Diaza-7-oxacyclononane (9). A mixture of the tosylated cyclononane **8** (6.922 g, 0.016 mol) and phenol (6.9 g, 0.073 mol) in HBr-HOAc (90 mL, 32%) was

stirred at 80°C for 72 h under N_2, and then cooled to room temperature. Ether (250 mL) was poured to precipitate the salt. The solid was collected and washed with hot ethanol: yield 3.7 g (80%). ^{1}H NMR (D_2O) 4.07 (4 H, t, CH_2O), 3.79 (4 H, s, CH_2N), 3.54 (4 H, t, CH_2N) ppm. ^{13}C NMR 68.90, 49.28, 47.20 ppm. Anal. Calcd for $C_6H_{14}N_2O{\cdot}2HBr$: C, 24.68; H, 5.52; N, 9.59. Found: C, 24.30; H, 5.80; N, 9.60.

7,16-Dioxa-1,4,10,13-tetraazacyclooctadecane (11). A mixture of the tosylated macrocycle **10** (1.8 g, 2.1 mmol) and phenol (1.8 g, 19 mmol) in HBr-HOAc (15 mL, 32%) was stirred at 80 °C for 3 d. After cooling, ether (100 mL) was poured to precipitate the product. The solid was collected and recrystallized from water-ethanol: yield 0.96 g (78%). ^{1}H NMR (D_2O) 3.68 8 H, t, CH_2O), 3.56 (8 H, br. s, CH_2N), 3.37 (8 H, t, CH_2N) ppm. ^{13}C NMR 68.76, 68.69, 51.19, 47.93, 47.88 ppm. EIMS (rel intens) 261 $(M + 1H)^+$ (48), 204(80). Anal. Calcd for $C_{12}H_{28}N_4O_2{\cdot}4HBr$: C, 24.68; H, 5.52; N, 9.59. Found: C, 24.74; H, 5.80; N, 9.38.

Dimethyl 3,6,9,12-tetrakis(p-tolylsulfonyl)-3,6,9,12-tetraazatetra-decanedioate (13). A mixture of the tetrakistosylamide (**12**) (7.62 g, 10 mmol), methyl bromoacetate (6.12 g, 40 mmol) and K_2CO_3 (6.9 g, 50 mmol) in DMF (30 mL) was stirred at 60–65 °C for 6 h. The mixture was then poured into water (200 mL), and the solid was collected by suction and dried (air). The product was recrystallized from ethanol: yield 7.5 g (83%), mp 154-155 °C. ^{1}H NMR ($CDCl_3$) 7.74 (8 H, d, Ts), 7.34, 7.31 (4 H each, d, Ts), 4.09 (4 H, s, CH_2CO), 3.60 (6 H, s, CH_3O), 3.46 (4 H, t, CH_2N), 3.40 (4 H, t, CH_2N), 3.32 (4 H, s, CH_2N), 2.45, 2.43 (6 H each, s, CH_3) ppm. ^{13}C NMR 169.35, 143.82, 143.70, 135.66, 134.71, 129.91, 129.68, 127.45, 52.10, 49.87, 49.33, 49.06, 48.55, 21.52. Anal. Calcd for $C_{40}H_{50}N_4O_{12}S_4$: C, 52.96; H, 5.56; N, 6.18. Found: C, 52.94; H, 5.80; N, 6.49.

3,6,9,12-Tetrakis(*p*-tolylsulfonyl)-3,6,9,12-tetraazatetradecanedioic acid (14). To a solution of the ester **13** (4.53 g, 5 mmol) in ethanol (50 ml) was added aqueous KOH (4 mL, 50%). The mixture was refluxed for 16 h, and the ethanol was removed. The residue was taken up in water (100 mL) and acidified with concentrated HCl to pH 3. The solid was collected and rinsed with water and dried (air). The product was recrystallized from ethanol-water: yield 3.4 g (77%), mp 208–209 °C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 7.76, 7.74, 7.36, 7.33 (4 H, d, Ts), 4.01 (4 H, s, CH_2CO), 3.42 (8 H, s, CH_2N), 3.30 (4 H, s, CH_2N), 2.47, 2.44 (6 H, s, CH_3) ppm. ^{13}C NMR 170.07, 143.29, 143.07, 129.44, 129.20, 126.91, 126.87, 49.46, 48.57, 48.33, 47.98, 21.02 ppm. Anal. Calcd for $C_{38}H_{46}N_4O_{12}S_4{\cdot}2H_2O$: C, 49.88; H, 5.51; N, 6.12. Found: C, 49.96; H, 5.78; N, 6.50.

4,7,10,13-Tetrakis(*p*-tolylsulfonyl)-2,15-dioxo-19-oxa-1,4,7,10,13,16,-hexaazabicyclo[14,5,$2^{1,16}$]tricosane (15). A mixture of diacid **14** (0.878 g, 1 mmol), and the dihydrobromide of **9** (0.292 g, 1 mmol), DPPA (1.1 g, 4 mmol) and triethylamine (1.5 g, 15 mmol) in DMF (100 mL) was stirred under N_2 at room temperature for 20 h. The DMF was removed in vacuo and the residue was taken up in CH_2Cl_2 (50 mL), and washed with water (50 mL) and aqueous $NaHCO_3$ (50 mL). The mixture, after evaporation, was isolated by chromatography (SiO_2, CH_2Cl_2-MeOH, 100:5) to give **15** as a foam: yield 0.55 g (57%). ^{1}H NMR ($CDCl_3$) 7.80-7.69, 7.37-7.28 (8 H each, m, Ts), 4.5-3.10 (28 H, m, CH_2), 2.46, 2.42 (6 H each, s, CH_3) ppm. ^{13}C NMR 169.41, 168.63(*C*O); 143.87, 143.81, 143.57, 143.47, 135.65, 135.01, 134.82, 134.02, 129.83, 129.78, 129.73, 129.28, 128.20, 127.52, 127.29 (arom.); 74.15 (OCH_2); 51.83, 51.43, 51.03, 50.81, 50.39, 50.27, 50.00, 49.25, 48.27, 47.78 (CH_2N); 21.46 (CH_3) ppm. FABMS (rel intens) 973 $(M + 1H)^+$ (55), 819 (100), 663 (50), 507 (14). Anal. Calcd for $C_{44}H_{56}N_6O_{11}S_4$: C, 54.30; H, 5.80; N, 8.64. Found: C, 54.30; H, 5.80; N, 8.40.

4,7,10,13-Tetrakis(*p*-tolylsulfonyl)-19-oxa-1,4,7,10,13,16,-hexaaza-bicyclo[14,5,$2^{1,16}$]tricosane (16). To a solution of the amide **15** (1.47 g, 1.5 mmol) was added borane-THF (10 mL, 1M) under N_2 at room temperature. The mixture was then refluxed for 10 H and the excess borane was decomposed cautiously by adding 4 M HCl (3 mL) at 0 °C and refluxing for 1 h. The solution was concentrated in vacuo and neutralized with 10% NaOH followed by extraction with CH_2Cl_2 (3 × 20 mL) and drying (K_2CO_3). The product was purified by chromatography (SiO_2, CH_2Cl_2-MeOH, 100:10) and isolated as a foam: yield 0.78 g (55%). ^{1}H NMR ($CDCl_3$) 7.76-7.72, 7.37-7.31 (8 H, m, Ts), 3.58-3.22 (20 H, m, CH_2O and CH_2N), 2.73 (12 H, m, CH_2N) 2.45, 2.43 (6 H each, s, CH_3) ppm. ^{13}C NMR 143.52, 143.03, 135.91, 134.39, 129.57, 129.44, 127.13, 126.85, 71.13, 56.53, 55.65, 54.32, 49.99, 49.72, 47.58, 47.29, 21.17, 21.11 ppm. FABMS (rel intens) 945 $(M + 1H)^+$ (100), 791 (8), 253 (22). Anal. Calcd for $C_{44}H_{60}N_6O_9S_4{\cdot}0.5CH_2Cl_2{\cdot}H_2O$: C, 52.83; H, 6.28; N, 8.31. Found: C, 53.08; H, 6.50; N, 8.18.

19-Oxa-1,4,7,10,13,16,-hexaazabicyclo[14,5,$2^{1,16}$]tricosane (2). Butanol (100 mL) was poured into a solution of the tosylated compound **16** (0.631 g, 0.668 mmol) in THF (50 mL), and the mixture was heated to 70 °C. To this solution was added sodium (4.7 g, 0.2 mol) gradually with vigorous stirring, and the mixture was refluxed until the sodium disappeared. The solution was concentrated, water (100 mL) was added, and the solution was again concentrated until a solid formed. CH_2Cl_2 (200 mL) was added, and the resulting solution was refluxed for 1h and cooled to room temperature. The solid was filtered and washed with CH_2Cl_2 (100 mL). The combined filtrates were extracted with dilute HCl (2 M, 3 × 20 mL). The HCl solution was concentrated in vacuo to dryness, and the residue was refluxed in MeOH (20 mL) to form a clear solution. Ether was added to

precipitate the salt of **2**, which was collected by filtration: yield 0.19 g (52%). ^{1}H NMR (D_2O) 4.12 (4 H, t, CH_2O), 3.79-3.47 (24 H, m, CH_2N), 3.38 (3 H, s, CH_3OH), 3.23 (4 H, br. s, CH_2N) ppm. ^{13}C NMR 70.20, 54.88, 54.63, 54.06, 49.10 (CH_3OH), 44.39, 44.03, 44.14, 43.62 ppm. FABMS 329 $(M + 1H)^+$ (28), 201 (35), 185 (100). Anal. Calcd for $C_{16}H_{36}N_6O{\cdot}5HCl{\cdot}MeOH$: C, 37.61; H, 8.37; N, 15.48. Found: C, 37.30; H, 9.08; N, 15.56.

4,13,16,19-Tetrakis(*p*-tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazabicyclo[17,5,2^{1,7}]hexacosane (17a). To a solution of the amide **1a** (415 mg, 0.4 mole) in anhydrous THF (10 mL) was added a solution of 1 M diborane-THF (3 mL) under nitrogen. The mixture was refluxed for 12 h. The excess diborane was cautiously decomposed by addition of 4 M HCl (2 mL) after cooling to 0°C in an ice bath. The solution was then refluxed for 1 h and evaporated in vacuo to give a semisolid. Water (10 mL) was added to this residue, and the solution was made alkaline by addition of 10% NaOH and extracted with CH_2Cl_2 (3 × 20 mL). The extract was dried (K_2CO_3) and concentrated. Chromatography (Al_2O_3, CH_2Cl_2-MeOH, 50:1) gave a foam: yield 320 mg (81%). ^{1}H NMR ($CDCl_3$) 7.61 (8 H, m, Ts), 7.26 (8 H, m, Ts), 3.49-2.93 (36 H, m, CH_2O, CH_2N), 2.59 (8 H, br s, CH_2N), 2.36 (9 H, s, CH_3), 2.34 (3 H, s, CH_3) ppm. ^{13}C NMR ($CDCl_3$) 143.63, 143.47, 142.97, 136.01, 135.91, 135.45, 129.80, 129.64, 127.43, 127.16, 126.99, 69.90, 69.74, 56.43, 55.48, 54.65, 50.46, 50.12, 49.59, 49.32, 21.53, 21.48 ppm. CIMS (NH_3) m/e (rel. intens.) 989 (M + 1H)$^+$ (25), 833 (M-Ts)$^+$ (20). Anal. Calcd for $C_{46}H_{64}N_6O_{10}S_4{\cdot}H_2O$: C, 54.85; H, 6.60; N, 8.34. Found: C, 54.87; H, 6.37; N, 8.21.

4-(*p*-Tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazabicyclo-[17,5,2^{1,7}]hexacosane (18a). A mixture of **17a** (300 mg, 0.303 mmol) and phenol (400 mg, 4.26 mmol) in 32% HBr-acetic acid (12 mL) was stirred at 80 °C under nitrogen for 3 d. After cooling, anhidrous ether was added to precipitate the salt, which was collected by filtration, washed with ether (3 × 10 mL) and dissolved in water (10 mL). The aqueous solution was extracted with ether, and evaporated to about 2 mL. The free amine was obtained by passing the salt solution through a Dowex-50 ion exchange resin (OH-form): yield 107 mg (67%). ^{1}H NMR ($CDCl_3$) 7.69, 7.32 (2 H each, d, Ts), 3.52 (8 H, br t, CH_2O), 3.29, 3.10 (4 H each, m, CH_2N), 2.82-2.71 (20 H, m, CH_2N), 2.44 (3 H, s, CH_3), 2.2 (3 H, br s, N*H*) ppm. ^{13}C NMR ($CDCl_3$) 142.90, 135.88, 129.54, 127.06, 70.07, 69.86, 57.36, 56.04, 55.67, 50.75, 49.34, 49.29, 49.21, 21.40 ppm. EIMS m/e 527 (M + 1H)$^+$, 452, 371 (M-Ts)$^+$. HRMS Calcd for $C_{25}H_{46}N_6O_4S$ + 1H: 527.3377. Found: 527.3350.

10,22-Dioxa-1,4,7,13,16,19-hexaazabicyclo[17,5,2^{1,7}]-hexacosane (3a). To a solution of **18a** (200 mg, 0.38 mmol) in butanol (10 mL) was added sodium (0.6 g, 26 mmol). When the reaction subsided, the mixture was refluxed until the sodium disappeared (about 4 h). The solvent was then removed in vacuo, and the residue was taken up into water (5 mL) and acidified with 4 M HCl. The solution was extracted with ether (3 × 20 mL). The aqueous solution was made basic with 10% NaOH and extracted with CH_2Cl_2 (4 × 10 mL). Evaporation and drying (solid KOH) of the extract gave an oil: yield 120 mg (85%). ^{1}H NMR($CDCl_3$) 3.59 (8 H, t, CH_2O), 2.88-2.78 (24 H, m, CH_2N), 3.31 (4 H, br s, N*H*), 2.72 (4 H, s, CH_2N) ppm. ^{13}C NMR ($CDCl_3$) 70.14, 69.78, 56.02, 53.61, 51.56, 48.97, 48.93, 48.67, 46.04 ppm. EIMS m/e (rel. intens.) 373 $(M + 1H)^+$ (25), 342 (15), 328 (15), 129 (78). HRMS Calcd for $C_{18}H_{40}N_6O_2$: 372.3213. Found: 372.3203. The free amine was converted to the HCl salt by adding 4 M HCl and evaporating to dryness. The salt was recrystallized in methanol-ether. Anal. Calcd for $C_{18}H_{40}N_6O_2{\cdot}6HCl{\cdot}2CH_3OH{\cdot}2H_2O$: C, 34.94; H, 8.50; N, 12.23. Found: C, 35.01; H, 9.00; N, 12.38.

4,13,16,19-Tetrakis(*p*-tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazabicyclo[17,5,4^{1,7}]octacosane (17b). To a solution of the amide **1b** (290 mg, 0.278 mmole) in anhydrous THF (10 mL) was added a solution of 1M diborane-THF (2 mL) under nitrogen. The mixture was refluxed overnight and the reaction was quenched with 4 M HCl (1 mL). The solution was then refluxed for 1 h and evaporated in vacuo to give a semisolid. Water (10 mL) was added to this residue and the solution was made alkaline by addition of 10% NaOH followed by extraction with CH_2Cl_2 (3 × 20 mL). The extract was dried (K_2CO_3) and concentrated. Chromatography (SiO_2, CH_2Cl_2: MeOH, 10:1 containing several drops of triethylamine) and evaporation gave the product **17b** as a foam: yield 270 mg (95%). ^{1}H NMR ($CDCl_3$) 7.69, 7.31 (8 H each, m, Ts), 3.80-2.57 (36 H, m, CH_2O, CH_2N), 2.43 (12 H, s, CH_3), 1.42 (4 H, br s, CH_2CH_2N) ppm. ^{13}C NMR 143.39, 143.24, 142.62, 135.81, 135.26, 135.02, 69.36, 68.79, 53.26, 52.77, 51.86, 49.51, 49.33, 49.30, 49.02, 22.66, 21.24 ppm. CIMS (NH_3) m/e 1017 $(M + 1H)^+$, 861 $(M\text{-}Ts)^+$. Anal. Calcd for $C_{48}H_{68}N_6O_{10}S_4{\cdot}1.5CH_2Cl_2$: C, 51.41; H, 6.25; N, 7.34. Found: C, 51.68; H, 6.00; N, 7.20.

4-(*p*-Tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazabicyclo-[17,5,4^{1,7}]octacosane (18b). A mixture of **17b** (260 mg, 0.256 mmol) and phenol (260 mg, 2.77 mmol) in 32% HBr-acetic acid (2 mL) was stirred at 80 °C under nitrogen for 3 d. After cooling, anhydrous ether was added to precipitate the salt, which was collected by filtration, washed with ether (3 × 10 mL) and dissolved in water (10 mL). The aqueous solution was extracted with ether, and evaporated to about 2 mL. The free amine **18b** was obtained by passing the salt solution through a Dowex-50 ion exchange resin (OH-form): yield 105 mg (74%). ^{1}H NMR ($CDCl_3$) 7.72, 7.32 (2 H each, d, Ts), 3.53 (8 H, br t, CH_2O), 3.24 (4 H, t, CH_2N), 2.87-2.66 (24 H, m, CH_2N), 2.44 (3 H, s, CH_3), 1.90 (3 H, br s, N*H*), 1.63 (4 H, br s, $CH_2CH_2CH_2$) ppm. ^{13}H NMR

($CDCl_3$) 142.70, 135.53, 129.33, 127.24, 70.06, 68.65, 55.08, 53.06, 52.94, 49.62, 49.23, 48.66, 23.73, 21.30 ppm. CIMS (NH_3) m/e (rel. intens.) 555 $(M + 1H)^+$ (54), 399 $(M\text{-}Ts)^+$ (45). HRMS Calcd for $C_{27}H_{50}N_6O_4S$+ 1H 555.3692. Found 555.3679. Anal. Calcd for $C_{27}H_{50}N_6O_4S{\cdot}5\ HCl{\cdot}H_2O$: C, 42.95; H, 7.61; N, 11.13. Found: C, 43.24; H, 8.10; N, 11.10.

10,22-Dioxa-1,4,7,13,16,19-hexaazabicyclo-[17,5,4^{1,7}]-octacosane (3b). The tosylated compound **4** (230 mg, 0.226 mmol) was dissolved in 98% H_2SO_4 (3 mL) and heated at 110 °C for 3 d with stirring in a sealed flask. After cooling, precooled absolute ethanol (10 mL) was cautiously added, followed by ether (20 mL) to precipitate the product. The solid was collected, washed with ether and then dissolved in water (10 mL). The aqueous solution was extracted with ether (3 × 10 mL) and concentrated to about 2 mL. The residue was passed through a Dowex-50 ion exchange resin (OH-form) column to obtain the free amine as an oil: yield 60 mg (66%). ^{1}H NMR ($CDCl_3$) 3.60-3.55 (8 H, m, CH_2O), 3.20 (4 H, m, CH_2N), 2.83-2.59 (28 H, m, CH_2N, NH), 1.60 (4 H, br s, $NCH_2(CH_2)_2CH_2$) ppm. ^{13}C NMR ($CDCl_3$) 70.26, 69.22, 54.61, 53.87, 53.40, 49.85, 49.75, 49.53, 45.82, 24.76 ppm. CIMS (NH_3) m/e (rel intens) 401 $(M + 1H)^+$ (76%). HRMS m/e for $C_{20}H_{44}N_6O_2$ requires: 400.353. Found: 400.353. The free amine was converted to the HCl salt and recrystallized from ethanol. Anal. Calcd for $C_{20}H_{42}N_6O_2{\cdot}6HCl{\cdot}EtOH{\cdot}2H_2O$: C, 37.78; H, 8.36; N, 12.01. Found: C, 37.70; H, 8.40; N, 11.68.

1-Benzylsulfonyl-1,4-diazabutane (22). To a solution of ethylenediamine (12 g, 0.2 mol) in benzene (60 mL) and hexane (30 mL) was added a solution of benzylsulfonyl chloride (7.6 g, 0.04 mol) in benzene (20 mL) at 0 °C with vigorous stirring under inert atmosphere over a period of 0.5 h. After the addition was complete, the mixture was stirred at 25 °C for 3 h, followed by evaporation to yield a solid. Hot water (20 mL) was added to the solid, and it was filtered and washed with hot water (3 × 20 mL). The combined filtrates were concentrated to about 20 mL and allowed to stand at room temperature. The resulting crystals were collected, washed with cold water, and recrystallized from ethanol-ether to give pure product, **22**: yield 4.7 g (55%), mp 94-98 °C. For elemental analysis the free base was converted into the HCl salt, which was recrystallized from ethanol-ether. ^{1}H NMR ($CDCl_3$) 7.40 (5 H, s, Bs), 4.26 (2 H, s, phCH_2), 2.96 (2 H, t, CH_2), 2.67 (2 H, t, CH_2) ppm. ^{13}C NMR 130.64, 129.60, 128.71, 128.58, 58.48, 45.65, 41.70 ppm. EIMS m/e (rel intens) 215 $(M + 1H)^+$ (21), 121 (63), 91 (82). HRMS m/e for $C_9H_{14}N_2O_2S$ requires 214.0776. Found: 214.0780. Anal. Calcd for $C_9H_{14}N_2O_2S{\cdot}HCl$: C, 43.12; H, 5.63; N, 11.17. Found: C, 43.23; H, 5.70; N, 10.99.

1-Benzylsulfonyl-7-(*p*-tolylsulfonyl)-1,4,7-triazaheptane (24). To a solution of **22** (4.28 g, 0.02 mol) in refluxing acetonitrile (100 mL) was added dropwise a solution of 1-tosylaziridine (3.94 g, 0.02 mol) in acetonitrile (100 mL) with stirring. The addition was complete in 2 h, and the mixture was refluxed for an additional 2 h. Evaporation in vacuo gave a residue, which was chromatographed (SiO_2, CH_2Cl_2-MeOH, 100:5) to give **24** as liquid: yield 5.01 g (61%). ^{1}H NMR ($CDCl_3$) 7.75 (2 H, d, Ts), 7.37 (5 H, m, Bs), 7.31 (2 H, d, Ts), 4.29 (2H, s, phCH_2), 4.20 (3 H, br s, NH), 2.95 (4 H, m, CH_2N), 2.58 (2H, t, CH_2N), 2.54 (2 H, t, CH_2N), 2.42 (3 H, s, CH_3) ppm; ^{13}C NMR 143.30, 136.59, 130.67, 129.66, 129.39, 128.65, 128.50, 126.99, 58.63, 48.51, 47.59, 42.95, 42.44, 21.41 ppm; CIMS (NH_3) m/e (rel intens) 412 $(M + 1H)^+$ (25), 258 (12), 227 (28), 215 (28), 91 (82); HRMS m/e for $C_{18}H_{25}N_3O_4S_2$ + 1H requires: 412.1365. Found: 412.1356.

1-Benzylsulfonyl-4-benzyloxycarbonyl-7-(*p*-tolylsulfonyl)-1,4,7-triazaheptane (14). To a solution of **24** (5 g, 0.012 mol) in CH_2Cl_2 (70 mL) and Et_3N (1.5 g, 0.015 mol) was added dropwise a solution of benzyl chloroformate (2.18 g, 95%, 0.012 mol) in CH_2Cl_2 (30 mL) at 0 °C with stirring. After completion of addition, the mixture was stirred for an additional 5 h at room temperature. The solution was then washed in turn with dilute HCl, $NaHCO_3$ and brine, and dried (Na_2SO_4). The residue, after evaporation, was passed through a short column (SiO_2, CH_2Cl_2-MeOH, 10:1) to give **25** as a viscous liquid: yield 6.5 g (99%). ^{1}H NMR ($CDCl_3$) 7.72 (2 H, m, Ts), 7.33 (10 H, m, Ph, Bs), 7.22 (2H, m, Ts), 6.01, 5.93 (1 H, NH), 5.66, 5.53 (1 H, s, NH), 5.05 (2 H, s, phCH_2O), 4.23, 4.18 (2 H, s, phCH_2SO_2), 3.34, 3.03 (4 H each, m, CH_2N), 2.34 (3 H, s, CH_3) ppm. ^{13}C NMR 156 (*C*O); 142.87, 136.36, 128.11, 127.31 (Ts); 135.84, 129.29, 127.59, 126.51 (benzyloxy); 130.30, 128.96, 128.23, 127.87 (benzylsulfonyl); 66.92 (phCH_2O); 58.07, 57.90 (phCH_2SO_2); 48.47, 48.04, 47.83, 47.57 (CH_2NSO_2); 41.64, 41.57, 41.27 (CH_2NCO); 20.98 (CH_3) ppm. EIMS m/e 546 $(M + 1H)^+$, 502, 464, 438, 390, 374, 346. HRMS m/e for $C_{26}H_{31}N_3O_6S_2$ + 1H requires: 546.1732. Found: 546.1732.

1-Benzyloxycarbonyl-4-benzylsulfonyl-7-(*p*-tolylsulfonyl)-1,4,7-triazacyclononane (15). A mixture of **25** (545 mg, 1 mmol), ethylene glycol ditosylate (370 mg, 1 mmol) and Cs_2CO_3 (1.63 g, 5 mmol) in DMF (50 mL) was stirred at 70 °C for 10 h. The solution was concentrated in vacuo, diluted with CH_2Cl_2 (30 mL), washed with H_2O and brine, and dried (Na_2SO_4). Concentration gave a residue, which was purified by chromatography (SiO_2, CH_2Cl_2-MeOH, 100:1) to afford **26**: yield 300 mg (53%), mp 209-210 °C. ^{1}H NMR ($CDCl_3$) 7.68, 7.60 (2 H, d d, Ts), 7.41-7.31 (12 H, m, Ph, Bs, Ts), 5.17, 5.14 (2 H, phCH_2O), 4.34, 4.32 (2 H, phCH_2SO_2), 3.67-3.16 (12 H, m, CH_2N), 2.45, 2.44 (3 H, CH_3) ppm. ^{13}C NMR (DMSO) 155.38, 155.32 (*C*O); 143.59, 143.55, 136.75, 136.68, 134.37, 134.23, 130.90, 129.92, 129.35, 128.46, 128.39, 128.29, 127.80, 127.66, 127.59,

127.27, 127.13 (arom), 66.54 (phCH_2O); 54.23, 54.06 (phCH_2SO_2); 52.50, 52.11, 51.66, 50.98, 50.70, 50.26, 50.00, 49.80, 49.29, 48.91 (CH_2N); 20.98 (CH_3) ppm. CIMS (NH_3) m/e 572 $(M + 1H)^+$, 438 $(M - Cbz)^+$, 418, 416 (M-Ts or Bs)$^+$. HRMS m/e for $C_{28}H_{33}N_3O_6S_2$ + 1H requires: 572.1889. Found: 572.1882. Anal. Calcd for $C_{28}H_{33}N_3O_6S_2$: C, 58.83; H, 5.82; N, 7.35. Found: C, 58.78; H, 5.52; N, 7.10.

1-Benzylsulfonyl-4-(*p*-tolylsulfonyl)-1,4,7-triazacyclononane (27). Compound **26** (0.1 g, 2 mmol) was dissolved in trifluoroacetic acid (10 mL) and H_2O (0.5 mL). The mixture was heated at 120 °C for 2 h, and the solvent was evaporated in vacuo to give a residue, which was diluted with H_2O (10 mL). The solution was neutralized with 10% NaOH and extracted with CH_2Cl_2 (4 × 10 mL). The extract was dried (K_2CO_3) and concentrated, and passed through a short column (SiO_2, CH_2Cl_2-MeOH, 100:10) to give **27**: yield 0.85g (97%), mp 138–139°C. ^{1}H NMR ($CDCl_3$) 7.68, 7.65 (2 H, b, Ts), 7.42-7.32 (7 H, m, Bs, Ph, Ts), 4.33 (2H, s, PhCH_2SO_2), 3.34, 3.12 (12 H, m, CH_2N), 2.45 (3 H, s, CH_3) ppm. 13C NMR ($CDCl_3$) 143.56, 134.87, 130.58, 129.71, 128.85, 128.82, 128.66, 127.08 (arom), 56.14, 53.94, 53.85, 53.39, 53.02, 48.68, 48.59 (CH_2N), 21.42 (CH_3) ppm. CIMS (NH_3) m/e 438 $(M + 1H)^+$, 282 (M - Ts)$^+$. Anal. Calcd for $C_{20}H_{27}N_3O_4S_2 \cdot CH_3OH$: C, 53.70, H, 6.65, N, 8.95. Found: C, 54.15, H, 6.58, N, 8.80.

1,4-Bis[4-benzylsulfonyl-7-(*p*-tolylsulfonyl)-1,4,7-triazacyclononyl]-diglycolamide (28). To a solution of **27** (0.895 g, 2.05 mmol) in CH_2Cl_2 (80 mL) and Et_3N (0.35 g, 3.5 mmol) was added dropwise a solution of diglycolic acid dichloride (0.175 g, 1.02 mmol) in CH_2Cl_2 (20 mL) at 0 °C with stirring, stirring was continued after the completion of addition for 2 h at 25 °C. The solution was washed with dilute HCl, saturated $NaHCO_3$ and brine in turn, and was dried (Na_2SO_4). Evaporation gave a residue, which was passed short column (SiO_2, CH_2Cl_2-MeOH, 100:10) to obtain the product **28** as a foam: yield 0.935 g (94%). ^{1}H NMR ($CDCl_3$) 7.56 (4 H, m, Ts), 7.27-7.14 (14 H, m, Bs, Ts), 4.38, 4.29 (4H, phCH_2SO_2), 4.18, 4.16 (4 H, OCH_2), 3.51-3.00 (24 H, m, CH_2N), 2.34, 2.33, 2.29 (6 H, CH_3) ppm. ^{13}C NMR 170.01, 169.95, 169.87 (CO); 143.67, 143.55, 143.50, 134.10, 133.52, 130.46, 130.40, 130.33, 130.27, 129.59, 129.52, 128.64, 128.55, 128.09, 127.16, 126.98, 126.93 (arom); 69.80, 69.54, 69.38 (CH_2O); 55.24, 55.11, 54.60, 54.38 (phCH_2SO_2); 53.17, 52.83, 52.77, 52.57, 52.39, 51.39, 50.45, 50.18, 49.99, 49.68, 49.57, 49.23, 48.53 (CH_2N); 21.20 (CH_3) ppm. CIMS (NH_3) m/e 974, 973 $(M + 1H)^+$, 818 (M - Ts or Bs)$^+$, 664. Anal. Calcd for $C_{44}H_{56}N_6O_{11}S_4 \cdot 0.5\ CH_2Cl_2$: C, 52.63; H, 5.66; N, 8.27. Found: C, 52.88; H, 5.48; N, 8.20.

2,2'-Bis[4-benzylsulfonyl-7-(*p*-tolylsulfonyl)-1,4,7-triazacyclononyl]-diethylether (18). The amide **28** (243 mg, 0.25 mol) was reduced with borane (3 mL, 1 M), in refluxing THF (6 mL). The reaction was quenched by adding 4N HCl (3 mL) and refluxing until all of the solid was dissolved. The THF was evaporated in vacuo and the residue was neutralized with 10% NaOH. The mixture was extracted with CH_2Cl_2 (20 mL) and dried (K_2CO_3). Evaporation gave a residue pure enough to proceed to the next step: yield 0.223 g (94%), ^{1}H NMR ($CDCl_3$) 7.64 (4 H, d, Ts), 7.38 (10 H, m, Bs), 7.29 (4 H, d, Ts), 4.27 (4 H, s, phCH_2SO_2), 3.48 (4 H, m, CH_2O), 3.38, 3.07, 2.86, 2.81, 2.68 (28 H, m, CH_2N), 2.40 (6 H,s, CH_3) ppm. ^{13}C NMR 143.13, 135.08, 130.48, 129.51, 128.77, 128.58, 128.45, 126.88 (arom); 69.31 (CH_2O); 56.13, 55.98, 55.94, 55.83, 52.52, 52.36, 51.24, 51.18 (CH_2N and phCH_2SO_2); 21.25 (CH_3) ppm. FABMS 945 $(M + 1H)^+$ (100), 791, 789.

1-(Diethylphosphoryl)-4-(*p*-tolylsulfonyl)-1,4-diazabutane (31). A solution of diethyl phosphite (69 g, 50 mmol) in CCl_4 (10 mL) was added dropwise with stirring to a mixture of the monotosylated ethylenediamine (**30**) (10.7 g, 50 mmol), K_2CO_3 (13.8 g, 0.1 mol), $KHCO_3$ (10.0 g, 0.1 mol), CH_2Cl_2 (40 mL) and NBu_4Br (0.8 g, 2.5 mmol) at room temperature. Stirring was continued overnight. The inorganic salts were filtered and washed with CH_2Cl_2. The filtrate was evaporated in vacuo to give the crude phosphoramidate which was recrystallized from ethyl acetate-hexane to give the pure product: yield 9.1 g (52%), mp 97°C. ^{1}H NMR ($CDCl_3$) 7.76, 7.29 (2 H each, d, Ts), 6.35 (1 H, br s, TsN*H*), 4.03 (4 H, m, OCH_2CH_3), 3.85 (1 H, br s, HNP), 3.01 (4 H, m, CH_2N), 2.42 (3 H, s, CH_3), 1.29 (6 H, t, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$) 144.48, 138.66, 130.95, 128.36, 64.00, 63.93, 45.79, 42.35, 22.80, 17.51, 17.42 ppm. Anal. Calcd for $C_{13}H_{23}N_2O_5PS$: C, 44.56; H, 6.62; N, 8.00. Found: C, 44.89; H, 6.80; N, 8.32.

2-Benzyloxycarbonylaminoethyl-*p*-tolylsulfonate (33). A solution of N-benzyloxycarbonylethanolamine (**32**) (19.5 g, 0.1 mol) and Et_3N (12.1 g, 0.12 mol) in CH_2Cl_2(100 mL) was added to a solution of tosyl chloride (20 g, 0.105 mol) in CH_2Cl_2 (100 mL) at 0°C with stirring over a period of 1 h. The mixture was stirred at room temperature overnight, and then washed with dilute HCl (1 M, 100 mL), saturated $NaHCO_3$ (100 mL) and brine, and dried (Na_2SO_4). Evaporation of the solution gave a solid which was washed with ether and dried (air): yield 28.5 g (82%), mp 79-80°C. ^{1}H NMR ($CDCl_3$) 7.76 (2 H, d, J = 8.2 Hz, Ts), 7.31 (5 H, s, Ph), 7.28 (2 H, d, Ts), 5.40 (1 H, br s, N*H*), 5.04 (2 H, s, phCH_2O), 4.07 (2 H, t, J = 4.9 Hz, CH_2O), 3.41 (2 H, br s, CH_2N), 2.40 (3 H, s, CH_3) ppm. ^{13}C NMR 156.12 (CO); 144.91, 132.37, 129.80, 127.71 (Ts); 136.14, 128.34, 127.97, 127.79 (ph); 68.91, 66.63 (CH_2O); 39.97 (CH_2N); 21.43 (CH_3) ppm.

1-Benzyloxycarbonyl-4-(*p*-tolylsulfonyl)-7-(diethylphosphoryl)-1,4,7 triazaheptane (34) A mixture of **31** (70 g, 0.2 mol), **33** (69.8 g, 0.2 mol) and K_2CO_3 (138 g, 1 mol) in DMF (500 mL) was stirred at 70 °C

overnight. The inorganic solids were filtered, the solution was evaporated in vacuo, and the residue was diluted with CH_2Cl_2 (400 mL), washed with water and dried (Na_2SO_4). Evaporation and chromatography (SiO_2, CH_2Cl_2:MeOH 100:2) gave an oily product: yield 66.5 g (63%). ^1H NMR ($CDCl_3$) 7.67 (2 H, d, Ts), 7.33-7.28 (7 H, m, Ph, Ts), 6.02 (1 H, br s, NHCO), 5.09 (2 H, s, OCH_2ph), 4.05 (4 H, m, OCH_2CH_3), 3.61 (1 H, br s, NHP), 3.37 (2 H, br s, CH_2N), 3.20-3.15 (6 H, m, CH_2N), 2.41 (3 H, s, $TsCH_3$), 1.28 (H, m, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$) 156.71, 143.63, 136.53, 135.32, 129.76, 128.34, 127.84, 127.15, 66.52, 62.52, 62.44, 51.23, 51.17, 49.56, 40.45, 40.34, 21.37, 16.12, 16.02 ppm. EIMS (CH_2Cl_2) m/e (rel. intens.) 528 $(M + 1H)^+$ (45), 421, 420 $(M\text{-}phCH_2O)^+$. Anal. Calcd for $C_{23}H_{34}N_3O_7PS$: C, 52.36; H, 6.50; N, 7.96. Found: C, 52.21; H, 6.67; N, 8.01.

1-(Diethylphosphoryl)-4-(*p*-tolylsulfonyl)-1,4,7-triazaheptane (35). Compound **34** (2.64 g, 5 mmol) in ethanol (20 mL) was treated to hydrogenolysis under H_2 (20 psi) with 5% palladium-charcoal at room temperature for 10 h. The catalyst was filtered, and the filtrate was evaporated in vacuo to give a viscous liquid, which was chromatographed (Al_2O_3, CH_2Cl_2-MeOH, 10:1): yield 1.73 g (88%). ^1H NMR ($CDCl_3$) 7.72 (2 H, d, Ts), 7.35 (2 H, d, Ts), 4.88 (1 H, br s, NH), 4.07 (4 H, m, OCH_2CH_3), 3.16 (6 H, m, CH_2N), 2.93 (2 H, t, CH_2NH_2), 2.4 (3 H, s, $TsCH_3$), 1.64 (2 H, br s, NH_2), 1.33 (6 H, t, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$) 142.74, 134.92, 129.14, 126.42, 61.40, 61.33, 51.88, 50.25, 50.17, 40.23, 40.11, 20.67, 15.52, 15.43 ppm. EIMS (NH_3) m/e 394 $(M + 1H)^+$ (60), 363 (20), 238 $(M - Ts)^+$ (25), 227 (75). HRMS m/e for $C_{15}H_{28}N_3O_5SP$ + 1H requires: 394.1565. Found: 349.1577.

1-Chloroacetyl-4-(*p*-tolylsulfonyl)-7-diethylphosphoryl)-1,4,7-triazaheptane (36). A solution of **35** (7.86 g, 0.02 mol) and Et_3N (2.12 g, 0.021 mol) in CH_2Cl_2 (80 mL) was cooled to 0°C in an ice bath. A solution of chloroacetyl chloride (2.26 g, 0.02 mol) in CH_2Cl_2 (30 mL) was added dropwise with stirring over a period of 0.5 h. After addition was complete, stirring was continued at 0°C for another 0.5 h. The solution was washed with cold dilute HCl (1 M, 20 mL), saturated $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation gave a viscous oil: yield 9.3 g (99%). ^1H NMR ($CDCl_3$) 8.05 (1 H, br s, NHCO), 7.70 (2 H, d, Ts), 7.33 (2 H, d, Ts), 4.18-4.10 (7 H, m, NHP, OCH_2CH_3 and CH_2Cl), 3.54 (2 H, t, CH_2N), 3.24-3.11 (6 H, m, CH_2N), 2.43 (3 H, s, $TsCH_3$), 1.34 (6 H, t, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$) 166.74, 143.37, 134.78, 129.47, 126.84, 62.10, 62.03, 51.17, 51.11, 48.68, 42.18, 39.99, 39.04, 21.04, 15.85, 15.75 ppm. FABMS 470 $(M + 1H)^+$ (100). Anal. Calcd for $C_{17}H_{29}N_3ClO_6PS$: C, 43.45; H, 6.22; N, 8.94. Found: C, 43.18; H, 6.48; N, 8.80.

1-Chloroacetyl-4-(*p*-tolylsulfonyl)-1,4-diazabutane (37). To a solution of **36** (6.8 g, 0.0145 mol) in THF (40 mL) was introduced gaseous HCl at 0°C until saturated. After sitting at room temperature for 2 h, the THF was removed in vacuo, ether (100 mL) was added, and the mixture was stored in a refrigerator overnight. The solid was collected by suction and recrystallized with ethanol-ether to give crystalline product: yield 5.2 g (97%), mp 182-183°C. ^1H NMR (D_2O) 7.55 (2 H, d, Ts), 7.28 (2 H, d, Ts), 3.87 (2 H, s, CH_2Cl), 3.33 (2 H, t, CH_2N), 3.31-3.20 (4 H, m, CH_2N), 3.10 (2 H, t, CH_2N), 2.24 (3 H, s, $TsCH_3$) ppm. ^{13}C NMR (D_2O) 172.73, 148.33, 136.30, 133.01, 129.80, 51.37, 49.28, 44.95, 41.09, 40.99, 23.44 ppm. Anal. Calcd for $C_{13}H_{20}N_3ClO_3S$·HCl: C, 42.17; H, 5.72; N, 11.34. Found: C, 42.18; H, 6.32; N, 11.00.

5-(*p*-Tolylsulfonyl)-2,5,8-triazacyclononanone (38). To a suspension of Na_2CO_3 (3.0 g, 0.0283 mol) in ethanol (500 mL) at 60°C with stirring was added dropwise a solution of **37** (5.0 g, 0.0135 mol) in ethanol (200 mL) over a period of 2 h. After the addition was complete, the mixture was stirred overnight. The inorganic chemicals were filtered, and the ethanol was concentrated in vacuo to afford a solid. The crude product was recrystallized from ethanol to obtain **38**: yield 2.7 g (68%). ^1H NMR ($CDCl_3$) 8.07 (1 H, s, NHCO), 7.68 (2 H, s, NHCO), 7.68 (2 H, d, Ts), 7.31 (2 H, d, Ts), 3.83-2.61 (10 H, m, CH_2N), 2.42 (3 H, s, $TsCH_3$), 2.07 (1 H, br s, NH) ppm. ^{13}C NMR ($CDCl_3$) 178.68, 143.77, 135.06, 129.84, 127.24, 53.46, 53.08, 50.96, 50.83, 40.47, 21.48 ppm. EIMS m/e (rel. intens.) 298 $(M + 1H)^+$ (1.5), 155 (4.5), 142 $(M - Ts)^+$ (48), 113 (43), 85 (70). HRMS for $C_{13}H_{19}N_3O_3S$ + 1H requires: 298.1224. Found: 298.1228. Anal Calcd for $C_{13}H_{19}N_3O_3S$: C, 52.51; H, 6.44; N, 14.13. Found: C, 52.29; H, 6.78; N, 14.30.

1,4-Bis[7-(*p*-tolylsulfonyl)-3-oxo-1,4,7-triazacyclononane]diglycol-amide (39). Compound **38** (1.485 g, 5 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and Et_3N (0.6 g, 6 mmol) and then cooled to −70°C in dry ice-isopropyl alcohol. A solution of diglycolic acid dichloride (0.45 g, 2.63 mmol) in CH_2Cl_2 (10 mL) was added dropwise under nitrogen with stirring over a period of 0.5 h. After addition was complete, the resultant solution was stirred for 2 h allowing the temperature to rise to room temperature. The solution was washed with dilute HCl (1 M, 10 mL), saturated $NaHCO_3$ (10 mL) and dried (Na_2SO_4). Evaporation and recrystallization from ethanol gave the solid **39**: yield 1.72 g (99%), mp 280-283°C. ^1H NMR (DMSO-d_6) 7.69, 7.41 (8 H, m, Ts), 4.41-2.88 (24 H, m, CH_2), 2.39 (6 H, s, CH_3) ppm. ^{13}C NMR (DMSO-d_6) 170.6-168.2 (CO); 143.20, 143.17, 135.8, 134.7, 129.8, 126.94, 126.85 (Ts); 70.1-68.9 (CH_2O); 55.6-48.6 (CH_2N); 41.5 (CH_2N), 20.9 (CH_3) ppm. CIMS (NH3) m/e 693 $(M + 1H)^+$. Anal. Calcd for $C_{30}H_{40}N_6O_9S_2$·0.5CH_2Cl_2: C, 49.83; H, 5.62; N, 11.43. Found: C, 50.00; H, 5.51; N, 11.18.

2,2'-Bis[4-(*p*-tolylsulfonyl)-1,4,7-triazacyclononyl] diethyl ether (40). The amide **39** (1.69 g, 2.44 mmol)

was suspended in THF (50 mL) under argon, and 1M borane-THF (20 mL) was added by syringe. The mixture was refluxed for 10 h. The boron complex was decomposed cautiously by adding dilute HCl (4 M, 3 mL) and refluxing for 1 h. The solution was evaporated in vacuo, and the residue was made alkaline with 10% NaOH. The product was extracted with CH_2Cl_2 (3 × 20 mL) and dried (K_2CO_3). Evaporation and chromatography (SiO_2, CH_2Cl_2-MeOH, 100:3) gave **40** as an oil: yield 1.55 g (99%). ^{1}H NMR ($CDCl_3$) 7.68 (4 H, d, Ts), 7.31 (4 H, d, Ts), 3.52 (4 H, t, C*H*$_2$O), 3.32 (2 H, br s, N*H*), 3.21-2.77 (28 H, m, C*H*$_2$N), 2.43 (6 H, s, C*H*$_3$) ppm. ^{13}C NMR (*C*DCl_3) 143.24, 135.40, 129.64, 127.16, 69.69, 56.64, 55.45, 55.28, 51.54, 48.69, 47.54, 21.44 ppm. CIMS (NH_3) m/e (rel. intens.) 637 $(M + 1H)^+$ (70), 481 $(M - Ts)^+$ (15). The free amine was converted to the HCl salt by adding aqueous HCl, evaporating to dryness, and recrystallizing from ethanol. Anal. Calcd for $C_{30}H_{48}N_6O_5S_2$·4HCl: C, 46.04; H, 6.70; N, 10.74. Found: C, 46.35; H, 6.90; N, 10.60.

4,16-Bis(*p*-tolylsulfonyl)-8,12-dioxo-10,22-dioxa-1,4,7,13,16,19-hexaaza tricyclo[17.5.2^{1,7}.2^{13,19}]octacosane (41). A solution of the amine **40** (1.63 g, 2.56 mmol) in THF (750 mL) was mixed with a solution of diglycolic acid (0.345 g, 2.57 mmol) in DMF (50 mL). To the resulting mixture was added Et_3N (0.87 g, 8.6 mmol) and DPPA (2.11 g, 7.68 mmol) at room temperature, followed by stirring for 16 h. The THF and DMF were removed in vacuo, and the residue was taken up into CH_2Cl_2 (100 mL), washed with saturated $NaHCO_3$, and dried (Na_2SO_4). Evaporation and chromatography (Al_2O_3, CH_2Cl_2-MeOH: 100:5) gave **41** as a foam: yield 1.149g (61%). ^{1}H NMR ($CDCl_3$) 7.63 (4 H, m, Ts), 7.28 (4 H, m, Ts), 4.50-2.60 (36 H, m, C*H*$_2$), 2.42 (6 H, s, C*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$) 170.20, 169.61, 169.0, 167.91(*C*O); 143.59, 143.52, 143.46, 135.0, 134.90, 134.69, 129.65, 129.63, 127.21, 127.08 (arom); 71.2-67.8 (*C*H$_2$O); 57.40-48.04 (*C*H$_2$N); 21.4 (*C*H$_3$) ppm. FABMS m/e (rel. intens.) 735 $(M + 1H)^+$ (100), 579 $(M - Ts)^+$ (28). Anal. Calcd for $C_{34}H_{50}N_6O_8S_2$·0.5 CH_2Cl_2: C, 53.31; H,6.60; N, 10.81. Found: C, 53.30; H, 6.9; N, 11.10.

4,16-Bis(*p*-tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazatricyclo-[17.5.2^{1,7}.2^{13,19}]octacosane (42). To a solution of the amide **41** (70 mg, 0.095 mmol) in THF (2 mL) under argon was added a solution of borane-THF (1.5 mL, 1M, 1.5 mmol). The solution was refluxed for 10 h and quenched by cooling to 0°C and adding dilute HCl (1mL, 4 M). The resulting solution was refluxed for 1 h, and the THF was removed in vacuo. The residue was neutralized by adding NaOH (10%), and extracted with CH_2Cl_2 (3 × 10 ml), dried (K_2CO_3), and concentrated in vacuo yielding **42** in pure form: yield 65 mg (97%), m.p.147–149°C. ^{1}H NMR ($CDCl_3$) 7.59 (4 H, d, Ts), 7.22 (4 H, d, Ts), 3.40 (8 H, t, C*H*$_2$O), 3.16 (8 H, br s, C*H*$_2$N), 2.99 (8 H, br s, C*H*$_2$N), 2.73 (8 H, s, C*H*$_2$N), 2.69 (8 H, t, J = 4.4 Hz, C*H*$_2$N), 2.34 (6 H, s, C*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$) 142.64, 135.87, 129.32, 126.84, 69.66, 56.86, 55.62, 55.56, 50.25, 21.24 ppm. CIMS (NH_3) m/e (rel. intens.) 707 $(M + 1H)^+$ (20), 551 $(M - Ts)^+$ (25) 354 (20), 310 (55), 241 (80). Anal. Calcd for $C_{34}H_{54}N_6O_6S_2$·H_2O: C, 55.33; H, 7.79; N, 11.59. Found: C, 56.70; H, 7.90; N, 11.38.

10,22-Dioxa-1,4,7,13,16,19-hexaazatricyclo-[17.5.2^{1,7}.2^{13,19}]octacosane (4). The tosylamide **42** (210 mg, 0.3 mmol) was dissolved in butanol (40 mL) by heating, and sodium was added in two portions (0.6 g each). When the reaction subsided, the solution was heated at 115–120°C and stirred until the sodium disappeared (about 1 h), followed by concentration to remove the most of butanol. Water (20 mL) was added and the solution was concentrated again. The residue was acidified with 1N of HCl to pH 1 and was extracted with CH_2Cl_2 (3 × 20 mL) to remove the thiol and impurities. The aqueous solution was basified with 10% NaOH, extracted with CH_2Cl_2 (5 × 20 mL), and dried (K_2CO_3). The product **4** was obtained as an oil by concentrating the CH_2Cl_2, and was shown by NMR to be almost pure: yield 100 mg (84%). Further purification was accomplished by converting the free amine into the HCl salt and recrystallizing from methanol-ethanol. ^{1}H NMR (D_2O) 3.87 (8 H, br s, C*H*$_2$O), 3.62 (1 H, q, HOC*H*$_2$CH$_3$), 3.47, 3.43 (8 H, each, br s, C*H*$_2$N), 3.30 (16 H, br s, C*H*$_2$N), 1.15 (1.5 H, t, HOCH$_2$C*H*$_3$) ppm. ^{13}C NMR (D_2O) 68.42, 60.17 (HO*C*H$_2$CH$_3$), 58.93, 52.49, 52.04, 44.61, 19.55 (HOCH$_2$*C*H$_3$) ppm. EIMS m/e (rel. intens.) 398 (M^+, 30), 383 (20), 368 (35), 353 (30), 342 (50), 328 (30), 269 (75), 255 (75), 241 (78), 227 (79), 212 (80). HRMS for $C_{20}H_{42}N_6O_2$ requires 398.3369. Found: 398.3359. Anal. Calcd for $C_{20}H_{42}N_6O_2$·6HCl·0.5 EtOH·4H_2O: C, 35.40; H, 8.35; N, 11.80. Found: C, 35.70; H, 8.30; N, 11.98.

4-Benzoyl-1,7-bis(*p*-tolylsulfonyl)-1,4,7-triazacyclononane (43). A solution of 4-benzoyl-1,7-bis(*p*-tolylsulfonyl)-1,4,7-triazaheptane[6] (6.8 g, 13.2 mmol) in DMSO (60 mL) was added dropwise to a suspension of NaH (0.67 g, 27.7 mmol, freshly washed in hexane) in DMSO (40 mL) at room temperature while stirring. The resulting solution was warmed to 60–70°C and 1,4-bis(*p*-tolylsulfonyl)-1,4-diazabutane (4.1 g, 13.2 mmol) in DMSO (100 mL) was added dropwise over 1 h. The mixture was stirred an additional 2 h, and poured into an ice-water bath. The solid was collected by suction filtration, washed with water and chromatographed (SiO, hexane-ethyl acetate, 2:1) to give pure **43**: yield 7.3 g (99.8%). ^{1}H NMR 7.69, 7.63 (4 H, d d, Ts), 7.51-7.39 (5 H, m, Ph), 7.32 (4 H, m, Ts), 3.92 (2 H, s, NHC*H*$_2$), 3.76 (2 H, s, NHC*H*$_2$), 3.51-3.39 (8 H, m, NHC*H*$_2$), 2.43 (6 H, s, C*H*$_3$) ppm. ^{13}C NMR 144.12, 143.92, 136.63, 134.73, 134.05, 129.92, 129.42, 128.56, 127.39, 127.23, 126.91,

53.49, 53.33, 53.21, 52.82, 49.15, 47.59, 21.53 ppm. EIMS m/e 543 (M + 1H)+, 386 (M - Ts)$^+$. HRMS for $C_{27}H_{31}N_3O_5S_2$ requires 541.1703. Found: 541.1696.

4-Benzyl-1,7-bis(*p*-tolylsulfonyl)-1,4,7-triazacyclononane (44). 4-Benzoyl-1,7-bis(*p*-tolylsulfonyl)-1,4,7-triazacyclononane, **43**, (6.5 g, 0.012 mol) was reduced with borane-THF. The crystalline product was isolated from CH_2Cl_2-MeOH: yield 4.7 g (74%), mp 144-146°C. ^{1}H NMR ($CDCl_3$) 7.65 (4 H, d, J = 8.2 Hz, Ts), 7.38-7.20 (9 H, m, ph and Ts), 3.75 (2 H, s, phCH_2), 3.48 (4 H, s, NHCH_2), 3.13 (4 H, s, NHCH_2), 2.99 (4 H s, NHCH_2), 2.40 (6 H, s, CH_3) ppm. ^{13}C NMR 143.35, 139.31, 135.33, 129.68, 129.01, 128.21, 127.08, 126.95, 61.14, 54.60, 52.33, 51.42, 21.41 ppm. Anal. Calcd for $C_{27}H_{33}N_3O_4S_2$: C, 61.45; H, 6.30; N, 7.96. Found: C, 61.22; H, 6.40; N, 7.80.

1-Benzyl-1,4,7-triazacyclononane (45). The tosylated compound **44** (4.0 g, 7.6 mmol) was dissolved in butanol (200 mL) by heating. To this solution sodium was added in portions (6.0 g, 0.26 mol), and the mixture was stirred at 100–110°C until the sodium disappeared. The butanol was evaporated in vacuo, and water (100 mL) was added. The resulting solution was concentrated to yield a solid which was taken up with 20 mL of H_2O and extracted with ether (3 × 50 mL). The ether solution was concentrated, and the residue was diluted with 2 M HCl solution (20 mL). The acidic solution was extracted with CH_2Cl_2 (3 × 20 mL), and the aqueous portion was concentrated to dryness to obtain **45** as a solid, which was recrystallized from ethanol: yield 1.4 g (56%). ^{1}H NMR (D_2O) 7.49 (5 H, s, ph), 3.97 (2 H, s, phCH_2), 3.67 (4 H, s, CH_2), 3.27 (4 H, t, NHCH_2), 3.09 (4 H t, NHCH_2) ppm. ^{13}C NMR (D_2O) 137.83, 133.01, 131.57, 131.10, 61.78, 50.30, 46.22, 44.87 ppm. Anal. Calcd for $C_{13}H_{21}N_3$·3HCl·0.5H_2O: C, 46.23; H, 7.46; N, 12.44. Found: C, 46.80; H, 7.80; N, 12.40.

1-(*p*-tolylsulfonyl)morphilin-2-one (47). To a solution of pyridinium chlorochromate (10.7 g, 0.05 mol) in CH_2Cl_2 (30 mL) was added a solution of N-tosylaminoethoxyethanol (**46**) (2.59 g, 0.01 mol) in CH_2Cl_2 (10 mL) at room temperature with vigorous stirring. After stirring overnight, ether (100 mL) was added to precipitate the product, and the solution was decanted. The solid was washed with ether (2 × 30 mL), and the combined solution was concentrated. The residue was purified by recrystallization from CH_2Cl_2-ether to yield **47**: yield 2.2 g (86%), mp 137-138°C. ^{1}H NMR ($CDCl_3$) 7.97 (2 H, d, Ts), 7.37 (2 H, d, Ts), 4.15 (2 H, s, CH_2O), 3.98 (4 H, br s, NCH_2CH_2O), 2.48 (3 H, s, CH_3) ppm. ^{13}C NMR 166.43, 145.39, 135.16, 129.45, 128.73, 68.70, 64.37, 45.85, 21.63 ppm. Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.48; H, 5.08; N, 5.80.

Methyl 2-(2-(*p*-tolylsulfamido)ethoxy)acetate (48). To a suspension of the lactam **47** (1.0 g, 3.9 mmol) in methanol (10 mL) at 0°C was introduced dry gaseous HCl until saturation was achieved. The resulting solution was sealed and allowed to remain at room temperature for 10 h, at which time it was poured into ice-water which contained an excess of $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2 (2 × 20 mL) and dried (Na_2SO_4). Evaporation of the solution gave **48** as an oil: yield 1.08 g (96%). The oil could be crystallized by dissolving in ether (10 mL) and storing in a refrigerator: mp 58°C. ^{1}H NMR ($CDCl_3$) 7.76 (2 H, d, Ts), 7.30 (2 H, d, Ts), 5.31 (1 H, t, N*H*), 4.03 (2 H, s, OCH_2CO), 3.75 (3 H, s, OCH_3), 3.59 (2 H, t, CH_2O), 3.14 (2 H, q, CH_2N), 2.42 (3 H, s, CH_3) ppm. ^{13}C NMR 170.83, 143.27, 136.81, 129.56, 127.03, 70.11, 67.99, 51.91, 42.84, 21.40 ppm. CIMS m/e (rel intens) 288 (M + 1H)$^+$ (77), 184 (26), 155 (72), 132 (74). Anal. Calcd for $C_{12}H_{17}NO_5S$: C, 50.16; H, 5.96; N, 4.87. Found: C, 50.30; H, 6.18; N, 4.99.

Dimethyl 6,12-bis(*p*-tolylsulfonyl)-8,10-pyridyl-3,15-dioxa-6,9,12-triaza-heptadecanedioate (50). A mixture of 2,6-bis(chloromethyl)pyridine (3.52 g, 0.02 mol), **48** (11.48 g, 0.04 mol), and K_2CO_3 (45 g, 0.33 mol) in DMF (100 mL) was stirred at 90°C overnight. The mixture was then cooled to room temperature, poured into water (500 mL), and extracted with CH_2Cl_2 (100 mL). The organic layer was washed with water (2 × 50 mL) and dried (Na_2SO_4). After evaporating the solvent, the residue was chromatographed (SiO_2, ethyl acetate-hexane, 1:1) to give **50** as an oil: 12.5 g (92%). ^{1}H NMR ($CDCl_3$) 7.72-7.61 (5 H, m, Ts, 4-py), 7.34 (2 H, d, py), 7.28 (4 H, d, Ts), 4.46 (4 H, s, pyCH_2), 3.88 (4 H, s, OCH_2CO), 3.68 (6 H, s, OCH_3), 3.58 (4 H, t, OCH_2), 3.43 (4 H, t, NHCH_2), 2.40 (6 H, s, CH_3) ppm. ^{13}C NMR 170.00, 156.12, 142.97, 136.97, 136.35, 129.22, 126.90, 120.71, 69.42, 67.61, 53.72, 51.31, 47.56, 21.06 ppm. FABMS m/e (rel intens) 678 (M + 1H)$^+$ (100), 522 (M - Ts)$^+$ (36), 407 (20). Anal. Calcd for $C_{31}H_{39}N_3O_{10}S_2$: C, 54.93; H, 5.80; N, 6.20. Found: C, 54.98; H, 6.10; N, 6.38.

6,12-bis(*p*-tolylsulfonyl)-8,10-pyridyl-3,15-dioxa-6,9,12-triazaheptadecane dioic acid (51). To a solution of the ester **50** (1.68g, 2.48 mmol) in methanol (10 mL) was added a solution of 1 M KOH in methanol (10 mL) at room temperature, followed by stirring overnight. After evaporation in vacuo to dryness, water (10 mL) was poured into the residue and the solution was refluxed for 1 h and cooled to room temperature. The solution was then acidified to pH 4 using 1 M HCl, extracted with CH_2Cl_2 (3 × 20 mL) and dried (Na_2SO_4). Evaporation gave **51** as a solid, which was recrystallized from ethanol: yield 1.37 g (85%), mp 144-145°C. ^{1}H NMR ($CDCl_3$) 10.88 (2 H, br s, O*H*), 7.82 (1 H, t, 4-py), 7.70 (4 H, d, Ts), 7.54 (2 H, d, py), 7.30 (4 H, d, Ts), 4.57 (4 H, s, pyCH_2), 3.79 (4 H, s, OCH_2CO), 3.50 (4 H, t, J = 4.8 Hz, CH_2O), 3.40 (4 H, t, CH_2N), 2.41 (6 H, s, CH_3)

ppm. ^{13}C NMR 172.93, 155.85, 143.80, 139.61, 136.05, 129.82, 127.13, 122.28, 69.69, 67.97. 52.74, 48.04, 21.44 ppm. FABMS m/e (rel intens) 650 $(M + 1H)^+$ (100), 494 $(M - Ts)^+$ (13). Anal. Calcd for $C_{29}H_{35}N_3O_{10}S_2$: C, 53.61; H, 5.43; N, 6.47. Found: C, 53.33; H, 5.48; N, 6.78.

16-Benzyl-7,25-bis(*p*-tolylsulfonyl)-12,20-dioxo-10,22-dioxa-7,13,16,19,25, 27-hexaazatricyclo[21.3-.$1^{1,5}$.$2^{13,19}$]-nonacosa-1(27),2,4-triene (52). A mixture of the diacid **51** (1.298 g, 2 mmol), 1-benzyltriazacyclononane **45** (0.656 g, 2 mmol), triethylamine (1.5 g, 15 mmol) and DPPA (1.65 g, 6 mmol) in DMF (200 mL) was stirred at room temperature for 24 h. The DMF was evaporated in vacuo, and the residue was taken up into CH_2Cl_2 (50 mL), and washed with saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$). After concentration the residue was chromatographed (SiO_2, CH_2Cl_2-MeOH, 100:2) to give the product as a foam: yield 0.85 g (51%). ^1H NMR ($CDCl_3$) 7.73-7.65 (5 H, m, Ts, py), 7.42-7.20 (11 H, m, Ts, Ph and py), 4.43, 4.40 (2 H each, s, pyCH_2), 4.0-2.67 (26 H, m, CH_2NH, CH_2O and phCH_2), 2.44, 2.42 (3 H each, s, TsCH_3) ppm. ^{13}C NMR ($CDCl_3$) 169.84, 169.41 (*C*O), 159.59, 155.85, 139.00, 121.91, 121.57 (py), 143.45, 143.35, 136.32, 136.11, 129.67, 129.64, 127.18 (Ts), 137.57, 128.84, 128.49, 127.29 (ph), 70.60, 69.66, 69.61, 68.43 (CH_2O), 62.02 (phCH_2), 59.17 (pyCH_2), 54.45, 54.07, 52.91, 51.19, 48.88, 48.15, 47.67, 46.93 (CH_2N), 21.45 (CH_3) ppm. FABMS m/e (rel intens) 833 $(M + 1H)^+$ (100), 677 $(M - Ts)^+$ (22). Anal. Calcd for $C_{42}H_{52}N_6O_8S_2 \cdot H_2O$: C, 59.27; H, 6.40; N, 9.88. Found: C, 59.54; H, 6.38; N, 10.20.

16-Benzyl-7,25-bis(p-tolylsulfonyl)-10,22-dioxa-7,13,16,19,25,27-hexaaza tricyclo[21.3.$1^{1,5}$.$2^{13,19}$]nonacosa-1(27),2,4-triene (53). The amide **52** (0.8g, 0.96 mmol) was treated with borane (2 mL, 1M in THF) as described for compound **16**. The product was isolated by column chromatography (Al_2O_3, CH_2Cl_2-MeOH: 100:5) as a foam: yield 0.58 g (75%). ^1H NMR ($CDCl_3$) 7.70-7.62 (5 H, m Ts, py), 7.36-7.21 (11 H, m, Ts, py, ph), 4.52 (4 H, s, pyCH_2), 3.59 (2 H, s, phCH_2), 3.46 (8 H, m, CH_2O), 3.27 (4 H, t, CH_2NH), 2.78 (4 H, s, CH_2NH), 2.63 (8 H, s, CH_2NH), 2.52 (4 H, t, CH_2NH), 2.42 (6 H, s, TsCH_3) ppm. ^{13}C NMR 156.62, 143.09, 140.04, 137.03, 136.65, 129.41, 128.73, 127.86, 126.90, 126.48, 120.33, 69.96, 69.60, 63.01, 57.14, 56.04, 55.71, 55.01, 54.28, 48.16, 21.27 ppm. FABMS m/e (rel intens) 805 $(M + 1H)^+$ (100), 649 $(M - Ts)^+$ (10). Anal. Calcd for $C_{42}H_{56}N_6O_6S_2 \cdot 1.5\ H_2O$: C, 60.63; H, 7.15; N, 10.09. Found: C, 60.43; H, 7.50; N, 9.78.

10,22-Dioxa-7,13,16,19,25,27-hexaazatricyclo-[21.3.$1^{1,5}$.$2^{13,19}$]nona-cosa-1(27),2,4-triene (5). The tosylated compound **53** (0.5 g, 0.62 mmol) in concentrated H_2SO_4 (1 mL) was stirred at 110°C in a sealed vial for 36 h. The mixture was then poured into ice (ca. 10 g). The aqueous solution was extracted with ether (2 × 10 mL), made basic with 10% NaOH, and extracted with CH_2Cl_2 (3 × 20 mL). The CH_2Cl_2 layer was dried (solid KOH) and evaporated to give **5** as an oil: yield 183 mg (73%). ^1H NMR ($CDCl_3$) 7.56 (1 H, t, py), 7.12 (2 H, d, py), 3.89 (4 H, s, pyCH_2), 3.58 (4 H, t, CH_2O), 3.53 (4 H, t, CH_2O), 2.86-2.69 (23 H, m, CH_2N, N*H*) ppm. ^{13}C NMR ($CDCl_3$) 158.98, 136.56, 120.77, 70.34, 69.91, 55.78, 54.99, 53.71, 51.75, 48.95, 46.41 ppm. FABMS m/e (rel intens) 407 $(M + 1H)^+$ (100). HRMS for $C_{21}H_{38}N_6O_2$ + 1H requires: 407.3132. Found: 407.3120. For elemental analysis the free amine was converted into the HCl salt, which was recrystallized from ethanol. Anal. Calcd for $C_{21}H_{38}N_6O_2 \cdot 6HCl \cdot EtOH$: C, 41.14; H, 7.51; N, 12.52. Found: C, 41.80; H, 8.00; N, 12.91.

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