34. Synthesis of Macrobicyclic Polyamines by Direct Macrobicyclisation *via* Tripode-Tripode Coupling

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The synthesis of five macrobicyclic polyamines **1–5** is described following a route in which the macrobicycle is formed by the coupling of two tripodal subunits. Such a sequence is appreciably shorter than the stepwise construction *via* a macrocycle, and may give higher yields, as illustrated by the case of bis-tren **3**, which has been synthesized following both routes.

Introduction. – The very active current research in macrocyclic chemistry has led to the development of numerous procedures for effecting macrocyclization, thus giving access to a great number of new macrocyclic molecules (for recent reviews, see *e.g.* [1] [2]). Extension into the macropolycyclic manifold requires consideration of synthetic strategies for the construction of multibridged frameworks [3]. The first representatives of the simplest category of macropolycycles were the diaza-macrobicycles $N[(CH_2)_n]_3N$ ($n > 7$) [4] and the diazapolyoxa-macrobicyclic cryptands [5] [6]. These two types of compounds were obtained by a sequential, two-step pathway involving first synthesis of a macrocycle followed by bridging of the latter, both cyclization steps being effected under high dilution conditions. Although, principally, such conditions *must* favour macrocyclization, methods have been sought which would afford acceptable yields in less dilute conditions; this has been realized in particular by using C–N bond formation through (C–X + tosylamine) reaction as closure process [7–9].

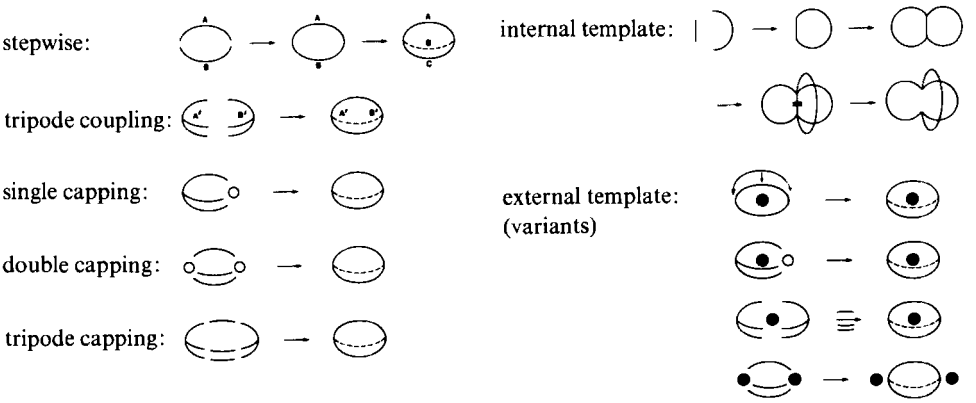

Figure. *Some synthetic strategies giving access to macrobicyclic molecules.* The circles represent groups retained in the final product; the black dots represent external templates temporarily used for construction purposes.

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Several other synthetic strategies may be devised for the construction of macrobicyclic systems, depending on the number of steps, on the nature and number of groups to be condensed, on the use of an internal or of an external template, *etc.* The *Figure* gives a schematic presentation of several approaches to macrobicycle generation [10].

The *stepwise* process requires two cyclization reactions, (each forming two bonds) but generates an intermediate macrocycle, which may also present interesting properties, and allows to introduce three different bridges A, B, and C.

The *tripode coupling* process is a 'one-pot' procedure but could suffer from extensive side reactions since it requires formation of three bonds in a single condensation step; it gives access to 'left-right' dissymetric macrobicycles when two different tripodal subunits A and B, are employed; these compounds conserve a threefold symmetry axis through the bridgehead atoms.

The latter *macrobicyclization* process is the more direct one, provided reagents, reactions, and conditions can be found which give sufficiently high yields. Several such cases have been described, concerning the synthesis of triply bridged cyclophanes [11–15], triphenylmethane [16], and 1,3,5-triazine [17], these reactions are usually of the 'tripode coupling' variety. The cyclotrimerisation of terminal diacetylenes on a *Ziegler* catalyst [11] is of the 'external template – two center' type (*Fig.*, last case, bottom). Twelve-center reactions forming six bonds in a single step, which belong to the 'tripode-capping' type *(Fig.)* afford macrobicyclic cryptands [18a] and templated capping gives sepulchrates [18b]. Triple bridging of C_3 cyclotriveratrylene (CTV) derivatives leads to bis-CTV [19] and speleand [20] macropolycyclic cages.

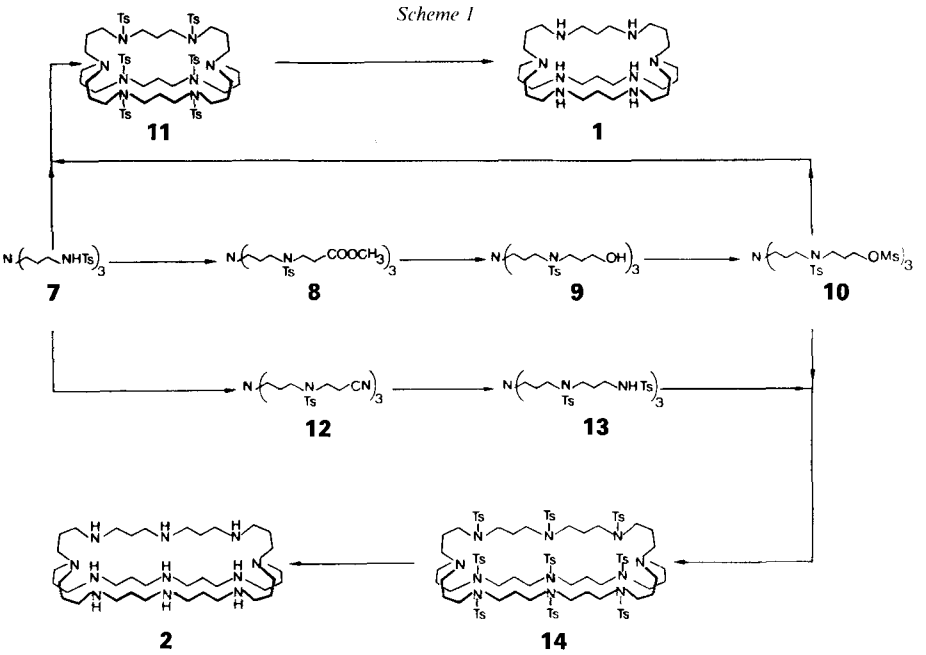
We report here the synthesis of five macrobicyclic polyamine cryptands **1**–**5** by coupling of two tripodal subunits *via* triple C–N bond formation through (C-OMs + tosylamine) reactions and without recourse to high-dilution conditions. Compound **3** (bis-tren) has already been synthesized earlier in a stepwise fashion [21]; a similar route has been used for the preparation of related macrobicyclic compounds [22].

Synthesis of the Macrobicycles 1–5. – The reaction sequences followed for synthesizing the macrobicyclic polyamines **1**–**5** are represented in *Schemes 1* and *2*. The key macrobicyclization steps involved the condensation of a tris-terminal tosylamine tripodal subunit with a tris-terminal tripodal mesylate; they were performed in hot dimethylformamide (DMF) in presence of a large excess of $CsCO_3$ [23] or K_2CO_3 and afforded the macrobicyclic polytosylamines **11**, **14**, **22**, **28** and **34** in yields from 20% up to 50%. The preparation of the tripodal reagents, the tosylamines (**7**, **13**, **17**) and the mesylates (**10**, **21**, **27**, **33**), followed a straightforward reaction sequence (*Schemes 1* and *2*). The final detosylation step was effected in high yield affording the macrobicycles **1**–**5**.

The interest of the macrobicyclization procedure employed here becomes apparent when the overall yields of the synthesis of bis-tren **3** from commercially available starting materials are compared: 11% for direct macrobicyclization and 4% for the step-by-step sequence described earlier [21]. The former has also the distinct advantage of requiring fewer individual steps than the latter, only nine as compared to fifteen.

Macrobicycle [11.11.11]-N_8 **1** *(Scheme 1)*. The tricyano compound $N(CH_2CH_2CN)_3$ **6** was easily obtained by mixing NH_4OAc with acrylonitrile in $MeOH/H_2O$ [24]. Reduction of **6** with $LiAlH_4$ in the presence of $AlCl_3$ in THF [25] followed by *in-situ* conversion of the three primary amines to tosylamines afforded compound **7** which was the starting

Scheme 1

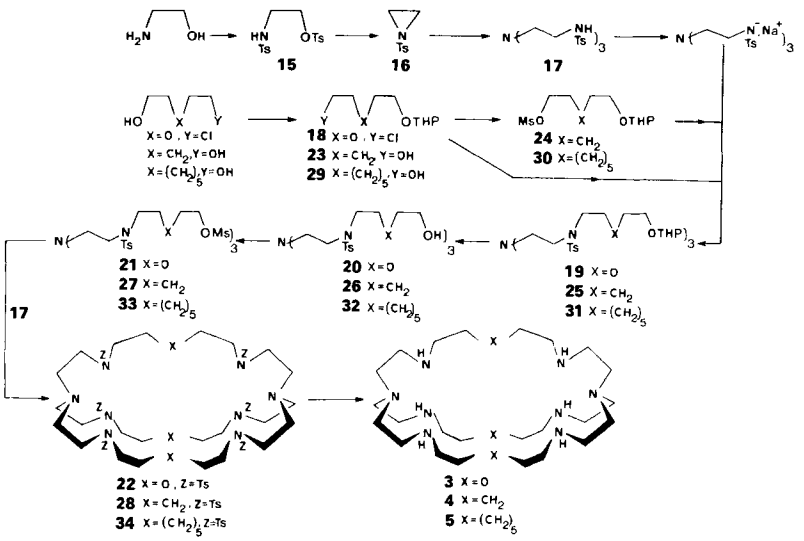


material for the synthesis of the two macrobicycles **1** and **2**. The *Michael* addition of methyl acrylate to tritosylamine **7** gave the triester **8** which was reduced to the triol **9** and then converted into the trimesylate **10**. The latter tripode was condensed with tripode **7** at 95° in DMF in the presence of Cs_2CO_3, yielding the hexatosyl-macrobicycle **11** in 50% yield. The tosyl groups of **11** were removed by a treatment with 30% HBr in AcOH in the presence of a large excess of phenol [26] giving **1**·8 HBr. The free macrobicyclic octaamine **1** was obtained by passing **1**·8 HBr over a *Dowex 1* × *8* resin in its basic form. Compound **1** should be stored under N_2 or kept as its polyammonium salt; the same holds for the other macrobicycles **2**–**5**.

Macrobicycle [15.15.15]-N_{11} **2** *(Scheme 1)*. The *Michael* addition of acrylonitrile to compound **7** in DMF in presence of K_2CO_3 gave the trinitrile **12**. Reduction of **12** with diborane [27] led to the corresponding triamine which was converted into the hexatosylamine **13**. Bicyclization between **13** and the trimesylate **10** was achieved at 80° in DMF in presence of a large excess of Cs_2CO_3 yielding the nonatosyl macrobicycle **14** in 27% yield. Removal of the tosyl groups of **14** with HBr/AcOH/phenol as described above gave the hydrobromide salt which may be converted into another salt by anion exchange or into the parent macrobicycle **2**.

Macrobicycle [11.11.11]-N_8O_3 **3** *(Scheme 2)*. Treatment of 2-aminoethanol with tosyl chloride [28] gave compound **15** which was converted to tosylaziridine **16** in the presence of KOH in toluene [29]. The reaction of **16** with NH_4OAc in a mixture of toluene/MeCN 1:1 at 70° afforded compound **17** which was the starting material for the synthesis of macrobicycle **3**–**5**. Treatment of 'monochloro-diethyleneglycol' with dihydropyran [30] gave the protected alcohol **18** which was condensed with the tris(sodium salt) of **17** leading to **19**. Removal of the tetrahydropyranyl group was achieved in the presence of TsOH in EtOH/H_2O 95:5 under reflux [31]. The triol **20** was converted into the trime-

Scheme 2



sylate **21**. Bicyclization of **17** and **21** was performed in hot DMF in presence of Cs_2CO_3 in large excess, yielding the hexatosyl-macrobicycle **22** in 31% yield. The tosyl groups were removed as described above to give **3**.

Macrobicycles [11.11.11]-N_8–C_3 **4** *and [15.15.15]-N_8–C_9* **5** *(Scheme 2).* Monoprotection of 1,5-pentanediol or 1,9-nonanediol with dihydropyran [30] [32] yielded **23** and **29** which were converted into the mesylates **24** and **30**, respectively. Reaction of the tris(sodium salt) of **17** with **24** or **30** in DMF gave **25** and **31**. Deprotection in EtOH/H_2O 95:5 in the presence of TsOH afforded **26** and **32** which were converted into the trimesylates **27** and **33**. Bicyclization was achieved in DMF as described above leading to the hexatosyl-macrobicycles **28** and **34** in 45% and 23% yield, respectively. Deprotection of **28** and **34** was achieved as described above yielding the macrobicyclic polyamines **4** and **5**, which were kept as their polyammonium salts.

Properties of the Macrobicycles 1–5. – Compounds **1–5** are macrobicyclic diamines related both to the polyaza-cryptands [33] and to the macrocyclic polyamines [34] studied earlier. The structures indicated agree with the spectral and analytical data. Furthermore, compound **3** is identical with the same macrobicycle obtained by stepwise synthesis [21].

Structures **1–5** depict the macrobicycles in their *in,in* form, where the bridgehead N-atom sites are directed towards the interior of the molecule. Of course, since nitrogen inversion at an amine center is fast, these compounds are actually present as a rapidly interconverting equilibrium mixture of forms with the bridgeheads directed either *in* or *out*.

Being polyamines, macrobicycles **1–5** may act as ligands either for metal ions when unprotonated or for anions when protonated. Indeed, bis-tren **3** has been shown to form dinuclear cryptates with transition metal ions [21] [35]; on the other hand, its hexaprotonated form binds anions strongly and selectively giving anion cryptates [36]. Similarly, the macrobicycles **1**, **2**, **4**, and **5** present characteristic cation- and anion-binding properties [37]. Such results will be published later.

Experimental Part

General. Melting points (m.p.) are uncorrected. ^{1}H-NMR spectra were recorded on a *Varian A60, Varian EM 360A* or *Bruker SY 200* spectrometer and ^{13}C-NMR on a *Varian XL 100* or *Bruker SY 200* spectrometer. Chemical shifts δ are given in ppm with TMS as the standard. Mass spectra (MS) were performed by the 'Service de spectrométrie de masse', Strasbourg. Microanalysis were performed by the 'Service de microanalyse', Strasbourg.

3,3',3''-Nitrilotripropiononitril (**6**). NH_4OAc (308 g, 4 mol), acrylonitrile (212 g, 4 mol), MeOH (400 ml), and H_2O (400 ml) were refluxed for 20 h. The mixture was concentrated to 600 ml and extracted with CH_2Cl_2 (600 ml). The CH_2Cl_2 soln. was washed with 2N NaOH (100 ml) and H_2O (100 ml), and dried ($MgSO_4$). Evaporation left a viscous oil which was taken up in 1 l of hot EtOH. As the soln. cooled, **6** (232.3 g, 33%) crystallized as colourless needles, m.p. 59° ([24]: 57–58°). ^{1}H-NMR ($CDCl_3$): 2.53 (*t*, 3 CH_2N); 2.94 (*t*, 3 CH_2CN). ^{13}C-NMR ($CDCl_3$): 118.5 (CN); 49.4 (CH_2CH_2CN); 17.2 (CH_2–CH_2–CN). Anal. calc. for $C_9H_{12}N_4$ (176.21): C 61.34, H 6.86, N 31.79; found: C 61.32, H 6.99, N 31.72.

N,N',N''-*Tritosyl-3,3',3''-nitrilotripropylamine* (**7**). $AlCl_3$ (51 g, 0.24 mol) was dissolved in dry THF (500 ml) while stirring and cooling (ice bath). This soln. was added to a mixture of $LiAlH_4$ (12 g, 0.31 mol) and dry THF (200 ml), while cooling (ice bath) and stirring mechanically. To this soln. was added dropwise over 30 min compound **6** (20 g, 0.12 mol) in 200 ml of dry THF. Stirring was continued for another 75 h at r.t. While cooling (ice bath), H_2O (400 ml) was added, cautiously, followed by H_2O (300 ml) sat. with Na_2SO_4. $Al(OH)_3$ was removed by filtration and the solid was washed with 1.5 l of H_2O. To the filtrate was added K_2CO_3 (90 g), and the soln. was heated to 70° with stirring. An excess TsCl (80 g) was added, and stirring at 70° continued for another 75 h. After cooling, the aq. layer was decanted, and the brown residual oil was dissolved in CH_2Cl_2 (500 ml) and washed with H_2O (500 ml); the aq. layer was extracted with CH_2Cl_2 (1.5 l), and the org. layers were combined and dried ($MgSO_4$). Evaporation left a brown oil (50 g). Pure **7** (34 g, 46%) was obtained after chromatography on alumina (700 g) with 2.5% MeOH/$CHCl_3$; it was crystallized from hot EtOH, m.p. 126°. ^{1}H-NMR ($CDCl_3$): 1.55 (br., 3 $CH_2CH_2CH_2$); 2.25 (br., 3 CH_2N); 2.40 (*s*, 3 CH_3); 2.90 (br., 3 CH_2NTs); 5.9 (br., 3 NH); 7.28, 7.77 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.9, 137.4, 130.3, 127.7 (arom. C); 52.7 (CH_2N); 42.8 (CH_2NTs); 26.5 ($CH_2CH_2CH_2$); 22.0 (CH_3). Anal. calc. for $C_{30}H_{63}N_4O_6S_3$ (650.80): C 55.36, H 6.50, N 8.61; found: C 55.29, H 6.49, N 8.50.

Trimethyl 4,4',4''-Tritosyl-7,7',7''-nitrilotri(4-azaheptanoate) (**8**). Compound 7 (10 g, 0.015 mol), methyl acrylate (5 ml), K_2CO_3 (7 g), and DMF (130 ml) were stirred at r.t. for 24 h. After filtration of the white solid, the filtrate was partionned between CH_2Cl_2 (250 ml), H_2O (250 ml), and brine (80 ml). The aq. layer was extracted with CH_2Cl_2 (200 ml) and the org. layers were combined and dried $MgSO_4$. Evaporation left 15 g of a mixture of 3 compounds. Pure **8** (10.5 g, 75%) was obtained as an oil after chromatography on alumina (350 g) with CH_2Cl_2/Et_2O 1:1. ^{1}H-NMR ($CDCl_3$): 1.65 (br., 3 $CH_2CH_2CH_2$); 2.35 (*s*, 3 CH_3); 2.68 (*m*, 3 CH_2CO); 3.3 (*m*, 9 CH_2N); 3.57 (*s*, 3 CH_3); 7.3, 7.75 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 171.5 (CO); 143.3, 136.6, 129.8, 127.1 (arom. C); 51.5, 51.0, 47.4, 44.2 (CH_2N, CH_3); 34.2 (CH_2CO); 26.4 ($CH_2CH_2CH_2$); 21.3 (CH_3). Anal. calc. for $C_{42}H_{60}N_4O_{12}S_3$ (909.10): C 55.48, H 6.65, N 6.17; found: C 55.31, H 6.66, N 6.07.

4,4',4''-Tritosyl-7,7',7''-nitrilotri(4-azaheptanol) (**9**). $LiAlH_4$ (3.6 g, 0.092 mol) and dry THF (100 ml) were stirred under Ar at 0°. A soln. of **8** (10.5 g, 0.012 mol) in dry THF (100 ml) was added dropwise within 20 min. The mixture was allowed to come to r.t. and stirred for a further 40 h. A sat. soln. of Na_2SO_4 (100 ml) was added cautiously while cooling (ice bath), the $Al(OH)_3$ was removed by filtration and washed with THF (500 ml). The filtrates were combined and evaporated leaving a viscous oil which was taken up in CH_2Cl_2 (200 ml) and dried ($MgSO_4$). Evaporation left 8 g of yellowish oil. Pure **9** (7.45 g, 78% yield) was obtained as an oil after chromatography on alumina (200 g) with 2.5% MeOH/CH_2Cl_2. ^{1}H-NMR ($CDCl_3$): 1.8 (br., 6 $CH_2CH_2CH_2$); 2.45 (*s*, 3 CH_3); 2.88 (br., 3 OH); 3.2 (*m*, 9 CH_2N); 3.75 (*t*, 3 CH_2OH); 7.3, 7.8 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.6, 136.5, 129.9, 127.3 (arom. C); 59.4 (CH_2OH); 51.6, 47.9, 46.0 (CH_2N); 32.0, 26.6 ($CH_2CH_2CH_2$); 21.6 (CH_3). Anal. calc. for $C_{39}H_{60}N_4O_9S_3$ (825.07): C 56.77, H 7.33, N 6.79; found: C 55.71, H 7.27, N 6.66.

4,4',4''-Tritosyl-7,7',7''-nitrilotri(4-azaheptyl) Tris(methanesulfonate) (**10**). Compound **9** (7.42 g, 9 mmol), Et_3N (8.5 ml), and dry CH_2Cl_2 (200 ml) were stirred at 0°. MsCl (2.4 ml, 30 mmol) in dry CH_2Cl_2 (60 ml) was added dropwise over 30 min. The mixture was allowed to come to r.t., and stirring was continued for another 24 h. The orange soln. was washed rapidly with cooled H_2O (150 ml), cooled 1N HCl (100 ml), $NaHCO_3$ (100 ml), and then dried ($MgSO_4$). Evaporation gave **10** (9.04 g, 95%) as a pale yellow oil sufficiently pure to be used directly for the cyclisation reactions. Compound **10** is rather unstable; it should be stored below 0° and used within 1 or 2 days. ^{1}H-NMR ($CDCl_3$): 1.8 (br., 6 $CH_2CH_2CH_2$); 2.35 (*s*, 3 CH_3); 3.0 (*s*, 3 CH_3); 3.1 (br., 9 CH_2N); 4.25 (*t*, 3 CH_2O); 7.35, 7.7 (*m*, 12 arom. H). Anal. calc. for $C_{42}H_{66}N_4O_{15}S_6$ (1059.33): C 47.61, H 6.28; found: C 46.68, H 6.27.

5,9,17,21,28,32-Hexatosyl-1,5,9,13,17,21,28,32-octaazabicyclo-[11.11.11]pentatriacontane (**11**). Compound **7** (4.85 g, 7.4 mmol), $CsCO_3$ (30 g) and DMF (400 ml) were stirred and heated to 95°. To this mixture was added

dropwise over 40 min **10** (7.9 g, 7.4 mmol) in DMF (200 ml). Stirring was continued for another 70 h. The mixture was allowed to come to r.t.; the solid was removed by filtration, and the residue was washed with CH_2Cl_2 (200 ml). The org. layers were combined, evaporated to dryness and the viscous yellow oil was taken up in CH_2Cl_2 (400 ml), washed with 1N NaOH (200 ml). The aq. layer was extracted 3× with CH_2Cl_2 (200 ml). The org. layers were combined and dried ($MgSO_4$). Evaporation left a colored solid. Pure **11** (5.3 g, 50%) was obtained as a solid after chromatography on alumina (400 g) with 1% MeOH/CH_2Cl_2 and recrystallized from CH_2Cl_2/MeOH/EtOH as fine white needles, m.p. 110°. ^{1}H-NMR ($CDCl_3$): 1.75 (br., 9 $CH_2CH_2CH_2$); 2.34 (*s*, 6 CH_3); 3.08 (br., 18 CH_2N); 7.3, 7.7 (*m*, 24 arom. H). ^{13}C-NMR ($CDCl_3$): 143.5, 136.2, 129.9, 127.4 (arom. C); 51.9, 47.8, 47.2 (CH_2N); 29.4, 27.1 ($CH_2CH_2CH_2$); 21.6 (CH_3). MS: 1420 (M^+), 1265 (M^+ – Ts). Anal. calc. for $C_{69}H_{96}N_8O_{12}S_6 \cdot CH_2Cl_2$ (1506.80): C 55.79, H 6.55, N 7.74; found: C 55.86, H 6.79, N 7.73.

1,5,9,13,17,21,28,32-Octaazabicyclo[11.11.11]pentatriacontane (**1**). Compound **11** (0.73 g, 0.5 mmol), phenol (2 g), and 60 ml of a 33% HBr/AcOH were heated to 80° for 16 h under a well ventilated hood. After evaporation, the colored residue was taken up in Et_2O (100 ml), and **1**·8 HBr was isolated as a yellow solid after filtration. This solid was dissolved in H_2O (20 ml) and passed over *Dowex 1 × 8* resin (basic form). The aq. soln. of the free base was acidified to pH 2 with conc. HCl, and the H_2O evaporated. The solid obtained was dissolved in the minimum of H_2O/EtOH 1:1 and abs. EtOH was added until the soln. became cloudy. Crystallization occured after 20 min giving the very hygroscopic **1**·8 HCl (0.32 g, 90%), m.p. > 250°. ^{1}H-NMR (D_2O): 2.40 (br., 9 $CH_2CH_2CH_2$); 3.1 (*m*, 12 $CH2NH_2^+$); 3.3 (*m*, 6 CH_2NH^+). ^{13}C-NMR (D_2O): 52.1, 45.6 (CH_2N); 23.9, 21.9 ($CH_2CH_2CH_2$). Anal. calc. for $C_{27}H_{60}N_8 \cdot 8\,HCl \cdot H_2O$ (806.51): C 40.20, H 8.75, N 13.89; found: C 40.40, H 8.61, N 13.65.

The salt **1**·8 TsOH was obtained by addition of TsOH (1.3 g, 6.8 mmol) to the free base (0.33 g, 0.66 mmol) in soln. in H_2O. After evaporation, the residue was dissolved in MeOH/EtOH 1:1 and Et_2O was added until the soln. became cloudy, m.p. > 250°. ^{1}H-NMR (D_2O): 2.03 (br., 3 $CH_2CH_2CH_2$); 2.27 (br., 6 $CH_2CH_2CH_2$); 2.43 (*s*, 8 CH_3); 3.13, 3.45 (br., 18 CH_2N); 7.4, 7.7 (*m*, 32 arom. H). ^{13}C-NMR (D_2O): 144.2, 139.0, 131.1, 126.8 (arom. C); 52.2, 45.5, 45.2 (CH_2N); 22.3, 22.0, 21.9 ($CH_2CH_2CH_2$). Anal. calc. for $C_{83}H_{124}N_8O_{24}S_8$ (1874.36): C 53.18, H 6.67, N 5.98; found: C 52.79, H 7.06, N 5.88.

4,4',4''-Tritosyl-7,7',7''-nitrilotri(4-azaheptanenitrile) (**12**). The mixture of **7** (5 g, 7.7 mmol), acrylonitrile (1.65 ml, 25.4 mmol), K_2CO_3 (3.5 g, 25.4 mmol), and 50 ml of DMF was stirred for 64 h at r.t. H_2O (300 ml) and CH_2Cl_2 (200 ml) were added, and the aq. phase was washed with CH_2Cl_2 (3 × 50 ml). The combined org. layers were dried (Na_2SO_4) and concentrated to 20 ml. This soln. was passed over an alumina column with CH_2Cl_2: **12** (5.8 g, 95%) as a viscous oil. ^{1}H-NMR ($CDCl_3$): 1.80 (br., 3 $CH_2CH_2CH_2$); 2.41 (*s*, 3 CH_3); 2.2–3.0 (br. *m*, 3 NCH_2, 3 CH_2CN); 3.3 (br., 6 CH_2NTs); 7.34, 7.74 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 144.6, 136.1, 130.6, 127.9 (arom. C); 118.5 (CN); 51.6 (NCH_2); 48.7, 45.3 (CH_2NTs); 27.4 ($CH_2CH_2CH_2$); 22.0 (CH_3); 19.5 (CH_2CN). Anal. calc. for $C_{39}H_{51}N_7O_6S_3 \cdot CH_2Cl_2$ (810.03): C 53.68, H 5.97, N 10.96; found: C 54.08, H 5.83, N 11.10.

N,N',N'',4,4',4''-Hexatosyl-7,7',7''-nitrilotri(4-azaheptylamine) (**13**). Trinitrile **12** (6 g, 7.4 mmol) and a soln. of B_2H_6 in THF (150 ml, 1.0M) were heated to reflux for 12 h under N_2. After cooling to r.t., MeOH (20 ml) was added carefully to destroy excess B_2H_6, and the solvents were evaporated. The residue was dissolved in 2.5M HCl/MeOH (200 ml) and refluxed for 3 h. The soln. was evaporated, the residue partitioned between CH_2Cl_2 (150 ml) and 1N NaOH (100 ml), and the aq. layer was further extracted with CH_2Cl_2 (2 × 100 ml) and the org. layers combined, dried (Na_2SO_4), and evaporated giving the crude tetraamine as a viscous oil. To this oil in THF (100 ml)/CH_2Cl_2 (10 ml)/Et_3N (12 ml, 86 mmol), TsCl (4.8 g, 25 mmol) in 10 ml THF was added over 10 min, and the mixture stirred for 12 h at r.t. The solvents were evaporated. The residue was partitioned between CH_2Cl_2 and H_2O. The aq. layer was further extracted with CH_2Cl_2 (2 × 100 ml), and the org. layers were combined, dried (Na_2SO_4) and evaporated leaving the crude **13** as an oil. This oil was chromatographed over alumina (150 g) with CH_2Cl_2 affording pure **13** (5.1 g, 52%) as an oil. ^{1}H-NMR ($CDCl_3$): 1.75 (br., 6 $CH_2CH_2CH_2$); 2.35 (br., 3 NCH_2); 2.40 (*s*, 6 CH_3); 3.05 (br., 9 CH_2NTs); 5.6 (br., 3 NH); 7.3, 7.7 (*m*, 24 arom. H). ^{13}C-NMR ($CDCl_3$): 144.1, 143.8, 137.5, 130.4, 127.6 (arom. C); 51.7 (NCH_2); 48.3, 46.8, 40.9 (CH_2NTs); 29.9, 27.2 ($CH_2CH_2CH_2$); 22.1 (CH_3). Anal. calc. for $C_{60}H_{81}N_7O_{12}S_6$ (1284.66): C 56.02, H 6.35, N 7.63; found: C 55.90, H 6.36, N 7.45.

5,9,13,21,25,29,36,40,44,-Nonatosyl-1,5,9,13,17,21,25,29,36,40,44-undecaazabicyclo[15.15.15]heptatetracontane (**14**). A mixture of **10** (1.95 g, 1.8 mmol), **13** (2.3 g, 1.8 mmol), Cs_2CO_3[3]) (20 g, 62 mmol), and DMF (150 ml) was stirred at 80° for 48 h. The solvent was evaporated. The residue was partitioned between CH_2Cl_2 (100 ml) and 1N NaOH (100 ml). The aq. layer was further extracted with CH_2Cl_2 (3 × 100 ml). The org. layers were combined, dried (Na_2SO_4) and evaporated. The residue was passed over an alumina column (120 g), with CH_2Cl_2/toluene 1:1 to give **14** (1 g, 27%) as a viscous oil. ^{1}H-NMR ($CDCl_3$): 1.83 (br., 12 $CH_2CH_2CH_2$); 2.38 (*s*, 9 CH_3); 3.12 (br., 24

[3]) The same reaction performed using K_2CO_3 gave only 19% yield.

CH_2N); 7.1, 7.8 (*m*, 36 arom. H). ^{13}C-NMR ($CDCl_3$): 143.4, 136.7, 130.0, 127.4 (arom. C); 51.15, 47.6, 46.8 (CH_2N); 29.3, 26.5 ($CH_2CH_2CH_2$); 21.6 (CH_3). MS: 2057 (M^+), 1902 ($M^+ - Ts$). Anal. calc. for $C_{99}H_{135}N_{11}O_{18}S_9 \cdot C_6H_5CH_3$ (2055.68): C 59.27, H 6.71, N 7.17; found: C 59.62, H 6.62, N 7.29.

1,5,9,13,17,21,25,29,36,40,44-Undecaazabicyclo[15.15.15]heptatetracontane (**2**). The mixture of **14** (0.5 g, 0.25 mmol), phenol (2 g, 21 mmol), and 30 ml of 33% HBr/AcOH was heated at 80° for 14 h. After evaporation, the colored residue was dissolved in 50 ml H_2O and the soln. was extracted with CH_2Cl_2 (4 × 50 ml). The aq. phase was concentrated to 5 ml and was passed over *Dowex 1 × 8* resin (basic form). The free amine soln. was treated with an excess of HCl. After evaporation of the H_2O, crystallization of **2**·11 HCl was performed in abs. EtOH (210 mg, 80%), m.p. > 250°. This salt is very hygroscopic. ^{13}C-NMR (D_2O): 51.8, 45.9, 45.7 (CH_2N); 23.7, 22.0 ($CH_2CH_2CH_2$). Anal. calc. for $C_{36}H_{92}Cl_{11}N_{11} \cdot 20\ H_2O$ (1429.48): C 30.25, H 9.31, N 10.78; found: C 30.06, H 9.35, N 10.82.

The salt **2**·11 HCl (50 mg) was dissolved in 5 ml H_2O and passed over a *Dowex 1 × 8* resin (basic form). The free amine was treated with 2,4,6-trimethylbenzenesulfonic acid. H_2O was evaporated, the residue dissolved in MeOH (0.5 ml) and the salt precipitated as a white powder by addition of Et_2O/toluene 1:1. Anal. calc. for $C_{135}H_{213}O_{33}N_{11}S_{11} \cdot 11\ H_2O$ (3069.09): C 52.83, H 7.72, N 5.02; found: C 52.79, H 7.96, N 4.75.

By a similar procedure, **2**·11 TsOH was obtained. Anal. calc. for $C_{113}H_{169}O_{33}N_{11}S_{11} \cdot 8\ H_2O$ (2562.2): C 50.16, H 6.58, N 5.69; found: C 49.80, H 6.65, N 5.38.

2-(Tosylamino)ethyl p-*Toluenesulfonate* (**15**) was synthesized by the procedure described in [28]. To a stirred suspension of TsCl (802.6 g, 4.2 mol) in pyridine (500 ml) cooled to −40° was added dropwise a soln. (cooled to 0°) of 2-aminoethanol (122.2 g, 2 mol) in pyridine (200 ml). After the addition was completed, the temp. was maintained for 1 h at −10° and overnight at 0°. Crushed ice was added, the solid was filtered, washed with H_2O and dissolved in $CHCl_3$ (1 l), and this solution was washed 3× with H_2O, dried (Na_2SO_4) and evaporated. The solid was dissolved in hot CCl_4 (1.5 l), and **15** crystallized on cooling (550 g, 75%), m.p. 87–88° ([28]: 86–87°). ^{1}H-NMR ($CDCl_3$): 2.43 (*s*, 2 CH_3); 3.20 (*q*, CH_2N); 4.06 (*t*, CH_2O); 5.33 (*t*, NH); 7.35, 7.75 (*m*, 8 arom. H).

N-*Tosylaziridine* (**16**) was synthesized according to the procedure given in [29]. Compound **15** (228 g, 0.61 mol) was suspended in toluene (2 l). To this vigorously stirred mixture, a soln. of KOH (156 g, 2.8 mol) in H_2O (800 ml) was added within 1 h. The stirring was maintained for 2 more h, the mixture decanted, and the org. layer washed 3× with H_2O, dried (Na_2SO_4), and evaporated affording pure **16** (110 g, 99%) as a solid. This compound was used directly for the following step, m.p. 63° ([29]: 63–64°). ^{1}H-NMR ($CDCl_3$): 2.36 (*s*, 2 CH_2); 2.46 (*s*, CH_3); 7.4, 7.9 (*m*, 4 arom. H).

N,N′,N″-*Tritosyl-2,2′,2″-nitrilotriethylamine* (**17**). Aziridine **16** (110 g, 0.56 mol) was dissolved in a toluene/MeCN 1:1 (400 ml). NH_4OAc (11 g, 0.143 mol) was added to this soln. The mixture was stirred and heated to 70° for 24 h. After evaporation, **17** crystallized from a toluene soln. (80.4 g, 92%), m.p. 108° ([38]: 105–108°). ^{1}H-NMR ($CDCl_3$): 2.4 (*s* + br., 3 CH_3, 3 CH_2NHTs); 2.85 (br., 3 CH_2N); 5.85 (br., 3 N*H*Ts); 7.3, 7.85 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.1, 136.7, 129.6, 127.0 (arom. C); 53.9 (CH_2N); 40.7 (CH_2NHTs); 21.3 (CH_3). Anal. calc. for $C_{27}H_{36}N_4O_6S_3$ (608.8): C 53.27, H 5.96, N 9.20; found: C 53.09, H 6.06, N 9.13.

*1-Chloro-5-(tetrahydro-2*H*-pyran-2-yloxy)-3-oxopentane* (**18**) was synthesized according to the procedure given in [30]. To monochlorodiethyleneglycol (56 g, 0.45 mol) and CH_2Cl_2 (150 ml), a soln. of freshly distilled 2*H*-dihydropyran (44.8 g, 0.53 mol) in CH_2Cl_2 (50 ml) was added within 30 min while stirring. After the addition was completed, 12 drops of conc. HCl were added, and the soln. was heated for 1 h at 40°. After cooling, K_2CO_3 (10 g) was added, the solvent was evaporated, and the residue dried for 12 h on a vacuum pump giving **18** as an oil (quant. yield). It was used directly for the next step. ^{1}H-NMR ($CDCl_3$): 1.65 (br., 3 CH_2); 3.5–4.15 (br. *m*, $ClCH_2$, 4 OCH_2); 4.7 (br., OCHO).

N,N,N-*Tris[8-(tetrahydro-2*H*-pyran-2-yl)oxy-3-tosyl-6-oxa-3-azaoctyl]amine* (**19**). To dry MeOH (200 ml), Na (9.6 g, 0.42 mol) was slowly added in small portions under Ar. When all Na had reacted, **17** (85 g, 0.139 mol) was added, the mixture heated at 50° for 2 h, the solvent evaporated, and the residue dried on a vacuum pump. The Na salt was suspended in dry DMF (400 ml). To this suspension, a soln. of **18** (118 g, 0.56 mol) in DMF (200 ml) was added within 1 h. After addition of K_2CO_3 (10 g), the mixture was heated at 110° for 8 h, the solvent evaporated under vacuum, and the residue taken in CH_2Cl_2 (500 ml) and washed with H_2O (1 l). The aq. layer was further extracted 3× with CH_2Cl_2. The org. layers were combined, dried (Na_2SO_4), then K_2CO_3 (5 g) was added to maintain a basic medium. After evaporation, the crude mixture was triturated 4× with 500 ml of hexane in order to eliminate unreacted **18**. The residue was dissolved in toluene/hexane 1:1 and passed over an alumina column (1 kg) with toluene. Pure **19** (106 g, 68%) was obtained as a viscous oil. ^{1}H-NMR ($CDCl_3$): 1.65 (br., 9 CH_2); 2.45 (*s*, 3 CH_3); 2.85 (br., 3 NCH_2); 3.0–4.0 (br. *m*, 6 CH_2NTs, 12 CH_2O); 4.6 (br., 3 OCHO); 7.3, 7.8 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.2, 137.0, 129.7, 127.2 (arom. C); 99.0 (OCHO); 70.4, 70.1,

66.6, 62.3 (CH_2O); 54.0, 48.9, 47.7 (CH_2N), 30.6, 25.5 (CH_2); 21.5 (CH_3); 19.6 (CH_2). Anal. calc. for $C_{54}H_{84}N_4O_{15}S_3 \cdot ½\ C_6H_5CH_3$ (1125.4): C 58.91, H 7.51, N 4.79; found: C 58.96, H 7.38, N 4.81.

6,6',6''-Tritosyl-8,8',8''-nitrilotri(3-oxa-6-azaoctanol) (**20**). Compound **19** (106 g, 0.094 mol) was treated with conc. HCl (50 ml) in AcOH (800 ml). The mixture was heated at 50° for 12 h, during which the soln. turned dark. After evaporation, toluene was added (3×) and evaporated to eliminate all the acids. The residue was dissolved in CH_2Cl_2 (500 ml), and K_2CO_3 (10 g) was added. After stirring for 12 h, filtration and evaporation of the solvent, the triacetate derivative was obtained as an oil (87 g, 93%): This crude compound was treated by a soln. containing 1N NaOH (150 ml) in MeOH (500 ml). The mixture was heated at 50° for 1 h until TLC showed that all the acetate was saponified. After evaporation, H_2O (200 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 200 ml). The solvent was partially removed and the soln. filtered through 100 g of silica gel with 2% MeOH/CH_2Cl_2. After evaporation, the residue was chromatographed on alumina (1.5 kg). Compound **20** was eluted with 1% MeOH/CH_2Cl_2 as a viscous oil. ^{1}H-NMR ($CDCl_3$): 2.42 (*s*, 3 CH_3); 2.85 (br., 3 NCH_2); 3.1–3.8 (br. *m*, 6 CH_2NTs, 9 CH_2O); 7.33, 7.76 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.4, 136.9, 129.8, 127.3 (arom. C); 72.7, 70.3, 61.7 (CH_2O); 53.8, 49.1, 47.6 (CH_2N); 21.5 (CH_3). Anal. calc. for $C_{39}H_{60}N_4O_{12}S_3$ (872.18): C 53.66, H 6.88, N 6.42; found: C 53.90, H 6.94, N 6.15.

6,6',6''-Tritosyl-8,8',8''-nitrilotri(3-oxa-6-azaoctyl) Tris(methanesulfonate) (**21**). To a stirred soln. of **20** (7.7 g, 8.8 mmol), and Et_3N (22 ml, 160 mmol) in CH_2Cl_2 (300 ml) at 0°, MsCl (2.8 ml, 36 mmol) was slowly added. The mixture was stirred for 1 h at 0° and 2 h at r.t. The soln. was washed successively with 1N HCl (50 ml), 1N NaOH (50 ml), and H_2O (50 ml), dried (Na_2SO_4), and evaporated. The residue was dried on vacuum pump for a few h. The yellow oil **21** (9.7 g, 98%) was used directly for the cyclization step. ^{13}C-NMR ($CDCl_3$): 144.1, 137.1, 130.4, 127.7 (arom. C); 70.5, 69.5, 69.3 (CH_2O); 54.4, 49.4, 48.3 (CH_2N); 38.1 (CH_3Ms); 22.0 ($CH_3C_6H_4$).

4,10,16,22,27,33-Hexatosyl-7,19,30-trioxa-1,4,10,13,16,22,27,33-octaazabicyclo[11.11.11]pentatriacontane (**22**). The mixture of **21** (10.95 g, 9.9 mmol), **17** (6.05 g, 9.9 mmol), DMF (500 ml), and K_2CO_3 (50 g, 360 mmol) was well stirred and heated at 80° for 30 h. After cooling, the mixture was filtered, the solid residue washed with CH_2Cl_2, and the filtrate evaporated. The residue was treated with CH_2Cl_2 (300 ml) and 1N NaOH (100 ml). The org. layer was washed with H_2O, dried ($MgSO_4$), and evaporated. Chromatography of the residue over an alumina column (400 g) with CH_2Cl_2/toluene 3:1 gave pure **22** (4.34 g, 31%) as an amorphous solid which did not crystallize. ^{1}H-NMR ($CDCl_3$): 2.4 (*s*, 6 CH_3); 2.72 (br., 6 CH_2N); 3.24 (br., 12 CH_2NTs); 3.46 (br., 6 CH_2O); 7.30, 7.68 (*m*, 24 arom. H). ^{13}C-NMR ($CDCl_3$): 143.5, 136.9, 130.0, 127.2 (arom. C); 70.45 (CH_2O); 53.60, 48.90, 47.95 (CH_2N); 21.5 (CH_3). Anal. calc. for $C_{66}H_{90}N_8O_{15}S_6$ (1427.79): C 55.52, H 6.35, N 7.85; found: C 55.28, H 6.30, N 7.95. Compound **22** was identical (^{1}H-NMR, ^{13}C-NMR, TLC) with the hexatosylated compound obtained earlier in this laboratory *via* step-by-step synthesis [21].

7,19,30-Trioxa-1,4,10,13,16,22,27,33-octaazabicyclo[11.11.11]pentatriacontane (**3**). A mixture of **22** (2.6 g, 1.8 mmol), phenol (4 g, 34 mmol), and 33% HBr/AcOH (70 ml) was heated at 80° for 16 h. After cooling, the soln. was evaporated, the residue taken up in H_2O (50 ml) and CH_2Cl_2 (100 ml), and the aq. phase extracted with CH_2Cl_2 (4 × 100 ml) to eliminate the phenol, evaporated, and dried at the vacuum pump for 12 h. The residue was passed over a *Dowex 1 × 8* resin (basic form). The aq. phase of the free octaamine was evaporated giving **3** (87%) which turned yellow rapidly. It was transformed into polyammonium salts by addition of the appropriate acid. Several such salts have already been described and studied: *e.g.* the chloride, bromide, and perchlorate. ^{1}H-NMR (D_2O; perchlorate salt): 2.9 (br. *t*, 6 NCH_2CH_2); 3.35 (br., $NCH_2CH_2NHCH_2CH_2O$); 3.9 (*t*, 6 CH_2O). ^{13}C-NMR (D_2O; chloride salt): 66.25 (CH_2O); 50.30 (NCH_2); 48.30, 45.55 ($NCH_2CH_2NHCH_2CH_2O$).

5-[(Tetrahydro-2H-pyran-2-yl)oxy]pentanol (**23**). To a stirred mixture of 1,5-pentanediol (100 g, 0.96 mol) and conc. HCl (30 drops), 3,4-dihydro-2*H*-pyran (26.92 g, 0.32 mol) was added dropwise. The mixture was stirred at r.t. for 48 h. The mono- and diprotected alcohol was extracted into toluene (350 ml), washed with H_2O (100 ml), dried ($MgSO_4$) and evaporated. Pure **23** (26 g, 14.4%) was obtained as an oil after chromatography on silica gel with AcOEt/hexane 4:6. ^{1}H-NMR ($CDCl_3$): 1.6 (br., 2 $CH_2CH_2CH_2$); 2.25 (br., OH); 3.65 (*m*, 3 CH_2O); 4.60 (br., OCHO). ^{13}C-NMR ($CDCl_3$): 98.9 (OCHO); 67.5, 62.7, 62.4 (CH_2O); 32.5, 30.8, 29.5, 25.5, 22.5, 19.7 ($CH_2CH_2CH_2$). Anal. calc. for $C_{10}H_{20}O_3$ (188.26): C 63.80, H 10.70; found: C 63.99, H 10.69.

5-[(Tetrahydro-2H-pyran-2-yl)oxy]pentyl Methanesulfonate (**24**). A soln. of **23** (25.52 g, 0.135 mol) in dry CH_2Cl_2 (250 ml) was cooled to −18° and Et_3N (28.5 ml) was added. To the stirred solution, MsCl (11.6 ml) in dry CH_2Cl_2 (120 ml) was added dropwise within 1 h. The mixture was allowed to warm to r.t., and stirring was continued for 2 h. The mixture was washed successively with ice-water (100 ml), cold 10% HCl (100 ml), sat. aq. $NaHCO_3$ (100 ml), and brine (100 ml). The CH_2Cl_2 layer was dried ($MgSO_4$) and evaporated to give **24** as an oil (95%) which was used without further purification for the following step. ^{1}H-NMR ($CDCl_3$): 1.65 (br., 2 $CH_2CH_2CH_2$); 3.05 (*s*, CH_3); 3.62 (*m*, 2 CH_2O); 4.25 (*t*, CH_2OMs); 4.60 (br., OCHO). ^{13}C-NMR ($CDCl_3$): 98.8

(OCHO); 70.1, 67.0, 62.3 (CH_2O); 37.1 (CH_3); 30.7, 29.0, 28.9, 25.4, 22.3, 19.6 (CH_2). Anal. calc. for $C_{11}H_{22}O_5S$ (266.35): C 49.60, H 8.32; found: C 49.76, H 8.38.

N,N,N-Tris[8-(tetrahydro-2H-pyran-2-yl)oxy-3-tosyl-3-azaoctyl]amine (**25**). A soln. of the tris(sodium salt) of **17** (27 g, 0.040 mol), prepared as described in the preparation of **19**, in DMF (300 ml) was heated at 95°. Then, **24** (32.5 g, 0.122 mol) in DMF (150 ml) was added dropwise and the mixture heated and stirred at 95° for 24 h. After removing the DMF, the crude material was dissolved in CH_2Cl_2 (400 ml), washed with 2N NaOH (200 ml) and brine (200 ml). The org. layer was dried ($MgSO_4$) and evaporated: 55.5 g of a colored oil. Pure **25** (31.8 g, 70%) was obtained as an oil after chromatography on alumina with CH_2Cl_2. ^{1}H-NMR ($CDCl_3$): 1.6 (br., 6 $CH_2CH_2CH_2$); 2.38 (*s*, 3 CH_3); 3.15 (*m*, 9 CH_2N); 3.55 (*m*, 6 CH_2O); 4.55 (br., 3 OCHO); 7.3, 7.75 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.1, 136.9, 129.6, 127.1 (arom. C); 98.9 (OCHO); 67.2, 62.3 (CH_2O); 54.3, 49.5, 46.7 (CH_2N); 30.8, 29.3, 28.7, 25.5, 23.4 (CH_2); 21.4 (CH_3); 19.7 (CH_2). Anal. calc. for $C_{57}H_{90}N_4O_{12}S_3$ (1119.55): C 61.15, H 8.10, N 5.00; found: C 60.96, H 8.30, N 5.30.

6,6',6''-Tritosyl-8,8',8''-nitrilotri(6-azaoctanol) (**26**). A mixture of **25** (28.8 g, 0.026 mol) and TsOH (4.91 g) in EtOH/H_2O 95:5 (350 ml) was refluxed for 43 h. After evaporation, the residue was taken up in CH_2Cl_2 (300 ml) washed with 2N NaOH (150 ml), brine (150 ml), and dried ($MgSO_4$). Evaporation of CH_2Cl_2 left 20 g of an oil. Pure **26** (15.66 g, 70%) was obtained as an oil after chromatography on silica gel with 1 to 3% MeOH/CH_2Cl_2. ^{1}H-NMR ($CDCl_3$): 1.45 (br., 3 $CH_2CH_2CH_2$); 1.95 (br., 3 OH); 2.42 (*s*, 3 CH_3); 2.8 (br. *m*, 3 CH_2N); 3.15 (br. *m*, 6 CH_2NTs); 3.60 (*m*, 3 CH_2O); 7.3, 7.75 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.3, 136.7, 129.7, 127.2 (arom. C); 62.4 (CH_2OH); 54.5, 49.5, 47.0 (CH_2N); 32.1, 28.5, 22.9 (CH_2); 21.4 (CH_3). Anal. calc. for $C_{42}H_{66}N_4O_9S_3$ (867.19): C 58.17, H 7.67, N 6.46; found: C 58.27, H 7.48, N 6.38.

6,6',6''-Tritosyl-8,8',8''-nitrilotri(6-azaoctyl) Tris(methanesulfonate) (**27**) was prepared like **24**, from **26** (10.79 g, 0.0124 mol) in dry CH_2Cl_2 (200 ml), Et_3N (10.5 ml), and MsCl (3.2 ml) in dry CH_2Cl_2 (50 ml; added within 40 min). The oily **27** (13 g, 95%) was used without further purification for the following step. ^{1}H-NMR ($CDCl_3$): 1.45 (br., 3 $CH_2CH_2CH_2$); 2.4 (*s*, 3 CH_3); 3.0 (br. 9 CH_2N, 3 CH_3); 4.15 (*m*, 3 CH_2O); 7.3, 7.72 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.4, 136.7, 129.8, 127.1 (arom. C); 69.8 (CH_2O); 54.3, 49.3, 47.0 (CH_2N); 37.4 (CH_3); 28.6, 28.2, 22.6 (CH_2); 21.4 (CH_3). Anal. calc. for $C_{45}H_{72}N_4O_{15}S_6$ (1101.46): C 49.07, H 6.59, N 5.09; found: C 49.04, H 6.40, N 5.06.

4,10,16,22,27,33-Tosyl-1,4,10,13,16,22,27,33-octaazabicyclo[11.11.11]pentatriacontane (**28**). A mixture of **17** (7.11 g, 0.0117 mol), Cs_2CO_3 (38 g) and DMF (300 ml) was heated under Ar to 95°. To this stirred soln., **27** (12.86 g, 0.0117 mol) in DMF (200 ml) was added dropwise within 1 h. Heating was continued for 67 h. After removing the DMF, the crude material was dissolved in CH_2Cl_2 (500 ml), washing with 2N NaOH (150 ml) produced an emulsion which was dispersed by addition of brine. The org. layer was dried ($MgSO_4$) and evaporated leaving a viscous, colored oil. Pure **28** (7.6 g, 45%) was obtained as a white solid after chromatography on silica gel with 1% MeOH/CH_2Cl_2; and was recrystallized from CH_2Cl_2/EtOH, m.p. 130–132° (dec.). ^{1}H-NMR ($CDCl_3$): 1.45 (br., 3 $CH_2CH_2CH_2$); 2.4 (*s*, 6 CH_3); 3.15 (br., 18 CH_2N); 7.3, 7.75 (*m*, 24 arom. H). ^{13}C-NMR ($CDCl_3$): 143.3, 136.3, 129.8, 127.3 (arom. C); 54.8, 50.2, 47.5 (CH_2N); 29.0 (CH_2CH_2N); 23.9 (CH_2); 21.5 (CH_3). MS: 1421 (M^+), 1264 ($M^+ - Ts$), 1110 ($M^+ - 2\,Ts$), 955 ($M^+ - 3\,Ts$). Anal. calc. for $C_{69}H_{96}N_8O_{12}S_6 \cdot 1.5\,CH_2Cl_2$ (1549.34): C 54.65, H 6.44, N 7.23; found: C 54.60, H 6.51, N 7.44.

1,4,10,13,16,22,27,33-Octaazabicyclo[11.11.11]pentatriacontane Octachloride (**4**·8 HCl). Compound **28** (5 g, 3.5 mmol), phenol (6 g), and 30% HBr/AcOH (250 ml) were heated to 90° for 20 h under a well ventilated hood. After cooling, the purple precipitate was filtered and washed with Et_2O (200 ml). The crude HBr salt was dissolved in H_2O and passed over *Dowex 1 × 8* resin (basic form) with H_2O/EtOH 1:1. The soln. was acidified to pH 1 with conc. HCl and evaporated. The solid obtained was dissolved in the minimum of H_2O and EtOH was added until the soln. became cloudy; **4**·8 HCl crystallized on standing (2.49 g, 90%), m.p. > 250°. ^{1}H-NMR (D_2O): 1.5–1.90 (br., 3 $CH_2CH_2CH_2$); 2.89, 3.16, 3.27 (br., 18 CH_2N). ^{13}C-NMR (D_2O): 51.8, 49.1, 47.1 (CH_2N); 36.1 (CH_2CH_2N); 23.8 (CH_2). Anal. calc. for $C_{27}H_{68}Cl_8N_8 \cdot EtOH \cdot 2H_2O$ (870.61): C 40.00, H 9.03, N 12.87; found: C 39.88, H 9.00, N 12.67.

9-(Tetrahydro-2H-pyrane-2-yl)oxy-1-nonanol (**29**). A mixture of 1,9-nonanediol (60 g, 0.37 mol), THF (20 ml), and conc. HCl (15 drops) was stirred for 15 min. Then, 3,4-dihydro-2*H*-pyran (10.5 g, 0.12 mol) in THF (60 ml) was added dropwise within 30 min. The mixture was stirred at r.t. for 7 h. After evaporation, toluene (300 ml) was added and the mixture heated to 60° until it became homogeneous. The unreacted diol crystallized upon cooling to 4°. The solid was filtered, washed with toluene, and the combined filtrates were washed with H_2O (200 ml), dried ($MgSO_4$) and evaporated. Pure **29** was obtained as an oil after chromatography on silica gel with AcOEt/hexane 2:3. ^{1}H-NMR ($CDCl_3$): 1.50 (br., 10 CH_2); 3.60 (*m*, 3 CH_2O, OH); 4.60 (br., OCHO). ^{13}C-NMR ($CDCl_3$): 98.7 (OCHO); 67.5, 62.4, 62.1 (CH_2O); 32.6, 30.6 (CH_2CH_2O); 29.3, 26.1, 25.7, 25.4, 19.50 (CH_2). Anal. calc. for $C_{14}H_{28}O_3$ (224.36): C 68.80, H 11.54; found: C 68.12, H 10.97.

*9-[(Tetrahydro-2*H*-pyran-2-yl)oxy]nonyl Methanesulfonate* (**30**) was prepared, like **24**, from **29** (5.86 g, 0.024 mol) in dry CH_2Cl_2 (60 ml), Et_3N (5 ml), and MsCl (2.04 ml) in dry CH_2Cl_2 (20 ml; added within 20 min; workup: washings with 50 ml each). The oily **30** (98%) was used without further purification for the following step. ^{1}H-NMR ($CDCl_3$): 1.50 (br., 10 CH_2); 3.05 (*s*, CH_3); 3.60 (*m*, 2 CH_2O); 4.25 (*t*, CH_2OMs); 4.60 (br., OCHO). ^{13}C-NMR ($CDCl_3$): 98.7 (OCHO); 70.1, 67.4, 62.1 (CH_2O); 37.1 (CH_3), 30.7, 29.6, 29.2, 28.9, 26.1, 25.4, 25.2, 19.5 (CH_2).

N,N,N-*Tris[12-(tetrahydro-2*H*-pyran-2-yl)oxy-3-tosyl-3-azadodecyl]amine* (**31**). A soln. of the tris(sodium salt) of **17** (21.4 g, 0.031 mol), prepared as described in the above preparation of **19**, in DMF (200 ml) was heated at 95°. Then, **30** (30.9 g, 0.095 mol) in DMF (70 ml) was added dropwise, the mixture was heated and stirred at 95° for 29 h. After the soln. cooled to r.t., an oil separated upon addition of H_2O (200 ml). The supernatant was decanted and the oil taken up in CH_2Cl_2 (300 ml), washed with H_2O (200 ml), and dried ($MgSO_4$). Evaporation left 42.9 g of an oil. Compound **31** (26.31 g, 64%) was obtained as an oil after chromatography on alumina with 0.5% MeOH/$CHCl_3$. ^{1}H-NMR ($CDCl_3$): 1.50 (br., 30 CH_2); 2.45 (*s*, 3 CH_3); 3.4 (*m*, 9 CH_2N, 6 CH_2O); 4.6 (br., 3 OCHO); 7.3, 7.8 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.2, 136.9, 129.7, 127.2 (arom. C); 98.9 (OCHO); 67.7, 62.4 (CH_2O); 54.4, 49.6, 46.7 (CH_2N), 30.8, 29.7, 29.4, 28.8, 26.7, 26.2, 25.5 (CH_2); 21.5 (CH_3); 19.75 (CH_2). Anal. calc. for $C_{69}H_{114}N_4O_{12}S_3$ (1287.81): C 64.34, H 8.92, N 4.35; found: C 64.12, H 9.05, N 4.10.

10,10',10''-Tritosyl-12,12',12''-nitrilotri(10-azadodecanol) (**32**). A mixture of **31** (9.24 g, 7.2 mmol), TsOH (1.37 g) in EtOH/H_2O 95:5 (100 ml) was refluxed for 14 h. After evaporation, the residue was taken in CH_2Cl_2 (250 ml), washed with H_2O (150 ml), and dried ($MgSO_4$). Evaporation left 7.76 g of an oil. Pure **32** (6 g, 80%) was obtained as an oil after chromatography on silica gel with 4 to 5% MeOH/CH_2Cl_2. ^{1}H-NMR ($CDCl_3$): 1.3 (br., 21 CH_2); 2.45 (*s*, 3 CH_3); 2.9 (*m*, 9 CH_2N, 3 OH); 3.6 (*t*, 3 CH_2O); 7.3, 7.8 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.7, 136.8, 129.8, 127.2 (arom. C); 62.9 (CH_2OH); 54.4, 49.6, 46.7 (CH_2N); 32.7, 29.4, 29.3, 29.2, 28.8, 26.6, 25.7 (CH_2); 21.5 (CH_3). Anal. calc. for $C_{54}H_{90}N_4O_9S_3$ (1035.46): C 62.63, H 8.76, N 5.41; found: C 62.39, H 8.78, N 5.31.

10,10',10''-Tritosyl-12,12',12''-nitrilotri(10-azadodecyl) Tris(methanesulfonate) (**33**) was prepared, like **24**, from **32** (4.50 g, 4.3 mmol) in dry CH_2Cl_2 (70 ml), Et_3N (3 ml), and MsCl (1.11 ml) in dry CH_2Cl_2 (20 ml; added within 20 min; workup: washings with 50 ml each). The oily **33** (5.3 g, 96%) was used without further purification for the following step. ^{1}H-NMR ($CDCl_3$): 1.3 (br., 21 CH_2); 2.45 (*s*, 3 CH_3); 3.0 (br., 9 CH_2N, 3 CH_3); 4.25 (*t*, 3 CH_2O); 7.3, 7.8 (*m*, 12 arom. H). ^{13}C-NMR ($CDCl_3$): 143.7, 136.8, 129.9, 127.2 (arom. C); 70.3 (CH_2O); 54.0, 49.8, 46.6 (CH_2N); 37.3 (CH_3); 29.0, 28.9, 28.8, 28.6, 26.5, 25.3 (CH_2); 21.5 (CH_3). Anal. calc. for $C_{57}H_{96}N_4O_{15}S_6 \cdot CH_2Cl_2$ (1354.65): C 51.42, H 7.29, N 4.13; found: C 51.93, H 7.20, N 4.43.

4,14,20,30,35,45-Hexatosyl-1,4,14,17,20,30,35,45-octaazabicyclo[15.15.15]heptatetracontane (**34**). A mixture of **17** (2.39 g, 3.9 mmol), Cs_2CO_3 (11.55 g), and DMF (100 ml) was heated under Ar to 95°. Then, **33** (5 g, 3.9 mmol) in DMF (60 ml) was added dropwise within 30 min under stirring. Heating was continued for 48 h. After removing the DMF, the crude material was dissolved in CH_2Cl_2 (250 ml). Washing with 2N NaOH (100 ml) produced an emulsion which was dispersed by addition of brine. The aq. layer was extracted with further portions of CH_2Cl_2 (2 × 100 ml), and the org. layers were combined and dried ($MgSO_4$). Evaporation left 6.67 g of a solid. Pure **34** (1.43 g, 23%) was obtained as a white foam after chromatography on alumina 1% MeOH/CH_2Cl_2. ^{1}H-NMR ($CDCl_3$): 1.3 (br., 21 CH_2); 2.4 (*s*, 6 CH_3); 3.1 (br. 18 CH_2N); 7.3, 7.8 (*m*, 24 arom. H). ^{13}C-NMR ($CDCl_3$): 143.2, 136.4, 129.7, 127.2 (arom. C); 54.5, 49.9, 47.1 (CH_2N); 29.2, 28.9, 26.5 (CH_2); 21.5 (CH_3). MS: 1590 (M^+), 1434 ($M^+ - Ts$), 1278 ($M^+ - 2$ Ts), 1123 ($M^+ - 3$ Ts), 967 ($M^+ - 4$ Ts), 811 ($M^+ - 5$ Ts). Anal. calc. for $C_{81}H_{120}N_8O_{12}S_6$ (1590.18): C 61.17, H 7.60, N 7.04; found: C 61.12, H 7.44, N 7.24.

*1,4,14,17,20,30,35,45-Octaazabicyclo[15.15.15]heptatetracontane Octa(*p*-toluenesulfonate)* (**5**·8 TsOH). Compound **34** (2.25 g, 1.4 mmol), phenol (5 g), and 33% HBr/AcOH (150 ml) were heated to 90° for 16 h under a well ventilated hood. After cooling, the purple precipitate was filtered and washed with Et_2O (70 ml). The crude HBr salt was dissolved in H_2O and passed over *Dowex 1 × 8* resin (basic form) with H_2O/EtOH 1:1. After evaporation, TsOH 1.24 g was added. The mixture was dissolved in EtOH, and **5**·8 TsOH was precipitated by addition of Et_2O (2.45 g, 85%), m.p. 150° (dec.). ^{13}C-NMR (CD_3OD): 143.5, 142.5, 130.4, 127.3 (arom. C); 51.5, 50.0, 46.6 (CH_2N); 29.5, 29.0, 27.0 (CH_2); 21.6 (CH_3). Anal. calc. for $C_{95}H_{148}N_8O_{24}S_8$ (2042.67): C 55.85, H 7.30, N 5.48; found: C 55.37, H 7.90, N 6.01.

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