

118. Synthesis of Polyaza Macrocyclic Ligands Incorporating Pyridine Units

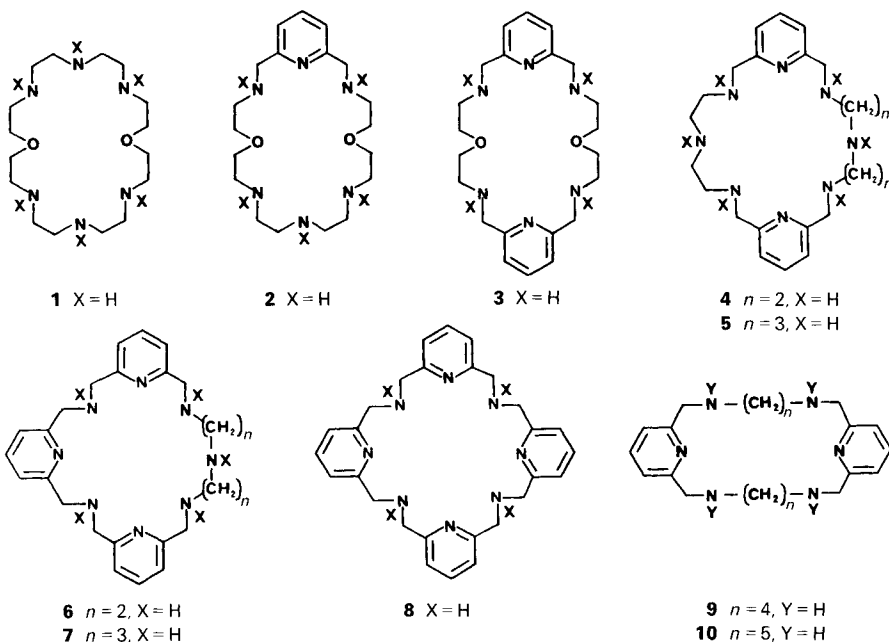
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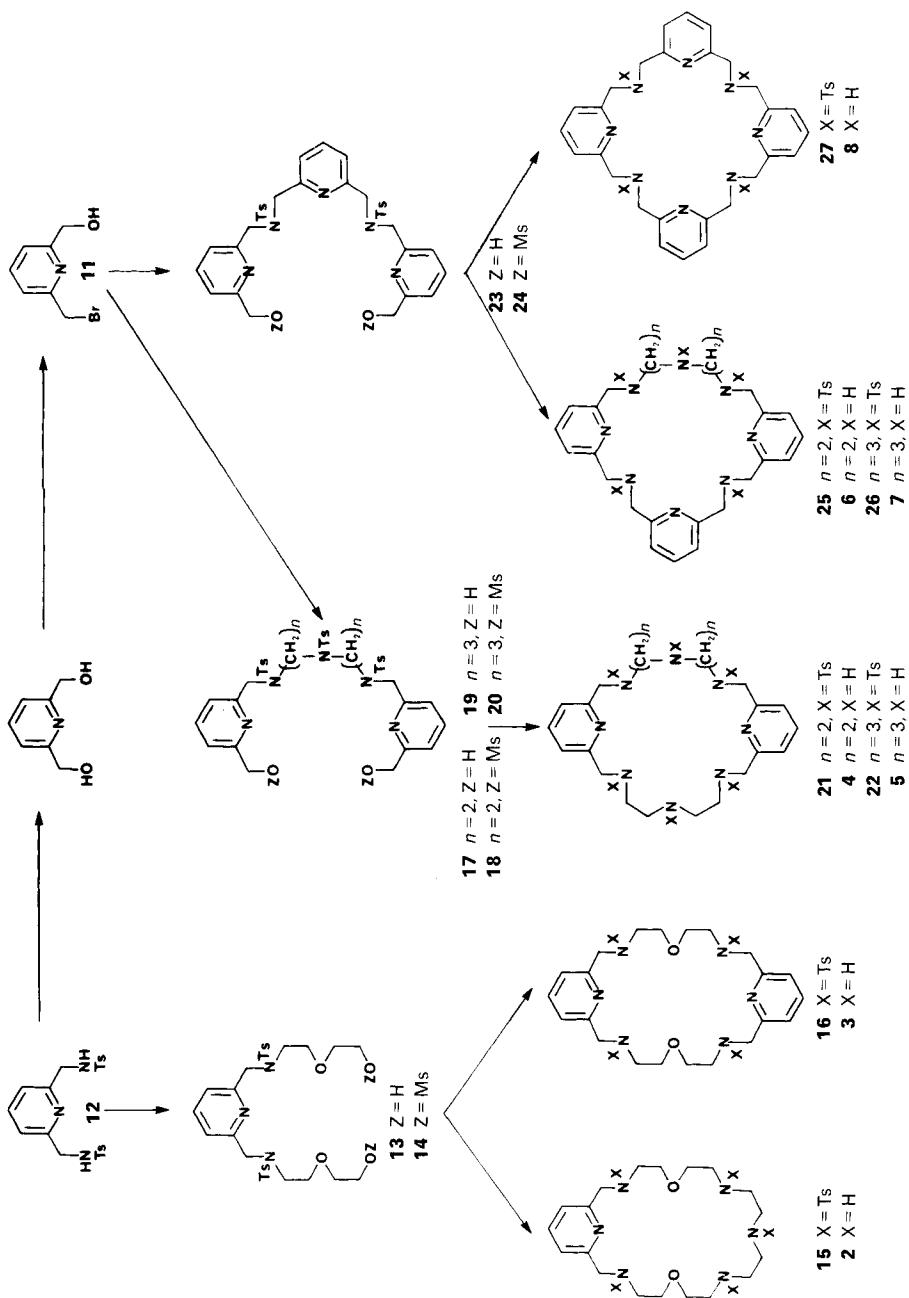
The synthesis of nine macrocyclic polyamines **2–10** containing pyridine units is described. These compounds are 22- (**9**), 24- (**2–4**, **6**, **8**, **10**), or 26- (**5**, **7**) membered hexaaza (**2**, **3**, **9**, **10**) or octaaza (**4–7**) macrocycles in which one to four pyridine units are incorporated. Compounds **3**, **4**, **9**, and **10** are homoditopic ligands, whereas **2** and **5** are heteroditopic and **6–8** multitopic receptors. Compounds **2–10** are potential ligands for metal cations as well as, in their protonated forms, for anions. Protonated macrocycles **2–10** are also potential catalysts for the hydrolysis of nucleotides and polyphosphates.

Introduction. – Receptor-incorporating amine functionalities are particularly interesting ligands, since, depending on their protonation state, they either form complexes with transition metals (when unprotonated) [1–4] or bind negatively charged anionic species (when protonated) by electrostatic interactions and H-bonding between positively



¹⁾ URA 0422 of the CNRS.

Scheme 1



charged ammonium sites and negatively charged centers on anions [5–10]. Macro-(poly)cyclic polyamines, depending on their size and the location of their binding sites, form a variety of mono-, di-, and polynuclear complexes with transition-metal cations [10–13]. On the other hand, when protonated, they bind organic, inorganic as well as biologically important anions [5–10] [14–20]. Moreover, partial protonation leads to the co-existence of both amine and ammonium sites allowing the simultaneous binding of anions and transition-metal cations [21] [22]. The rich variety of properties displayed by the ditopic hexamine macrocycle $[24]N_6O_2$ (**1**) illustrates nicely this dual ability to bind both cations and anions. Indeed, unprotonated **1** yields dinuclear Cu [23–25], Ni [25], Zn [25], Co [25] [26], and Rh complexes [27]. Protonated polycationic macrocycle **1** forms in aqueous solution a variety of stable complexes with nucleotides and polyphosphates, and shows marked selectivity patterns between them [28] [29]. Interestingly, it catalyses the hydrolysis of nucleotide polyphosphates [28] [30] [31], as well as phosphorylation processes of phosphate and phosphate-containing biologically important substrates [32] [33].

Recently, we described the synthesis of a series of macrocyclic polyamines structurally related to compound **1** and studied their ability to bind nucleotides and to catalyse phosphoryl-transfer processes [32] [34] [35]. We wish to report here the synthesis of nine macrocyclic polyamines, **2–10**, containing pyridine units which may be considered as structural analogues of $[24]N_6O_2$ (**1**).

Design of Macrocyclic Polyamines Incorporating Pyridine Units. – The syntheses of a number of macrocycles containing pyridine units have already been reported [36–44]. Macrocycles **2–10** may be considered as analogues of compound **1**. In compounds **2** and **3**, one or both of the two $NHCH_2CH_2NHCH_2CH_2NH$ binding subunits are replaced by a 2,6-bis(aminomethyl)pyridine unit. The synthesis of compounds **2** [40] and **3** [37] [44] using other synthetic routes has been reported.

Whereas in the model compound **1** the two triamino binding subunits are linked together by $CH_2CH_2OCH_2CH_2$ chains, in compound **4**²⁾, they are linked by 2,6-bis-(methyl)pyridine units. The same holds for compound **5** which, in addition, contains one $NH(CH_2)_3NH(CH_2)_3NH$ and one $NHCH_2CH_2NHCH_2CH_2NH$ subunits and for compound **6** in which one of the subunits is replaced by 2,6-bis(aminomethyl)pyridine. In compound **7**, the $NH(CH_2)_3NH(CH_2)_3NH$ and the 2,6-bis(aminomethyl)pyridine units are bridged by 2,6-dimethylpyridine. In the tetrapyridine compound **8**, both subunits are replaced by 2,6-bis(aminomethyl)pyridine which are linked together by two 2,6-dimethylpyridine units. This compound may also be considered as analogue of $[24]N_8$. Finally, in compound **9** and **10** [45], the binding subunits are two 2,6-bis(aminomethyl)pyridine, bridged by tetra- or pentamethylene chains.

Synthesis of Macrocycles 2–10. For the macrocyclic polyamines **2–8**, the key step, the cyclisation, was achieved by condensation of *N,N'*-ditosyl-2,6-bis(aminomethyl)pyridine (**12**) or of $TsN(CH_2CH_2N(Ts)H)_2$ with α,ω -dimesyloxy derivatives in hot DMF.

Macrocycles 2 and 3 (Scheme 1). Compound **12** was obtained in 94% yield by tosylation with $TsCl$ of 2,6-bis(aminomethyl)pyridine [46] prepared in the three steps from 2,6-bis(hydroxymethyl)pyridine [42]. The reaction of **12** with excess 2-(2-chloroethoxy)ethanol in DMF in the presence of K_2CO_3 gave, in 72% yield, the diol **13** which

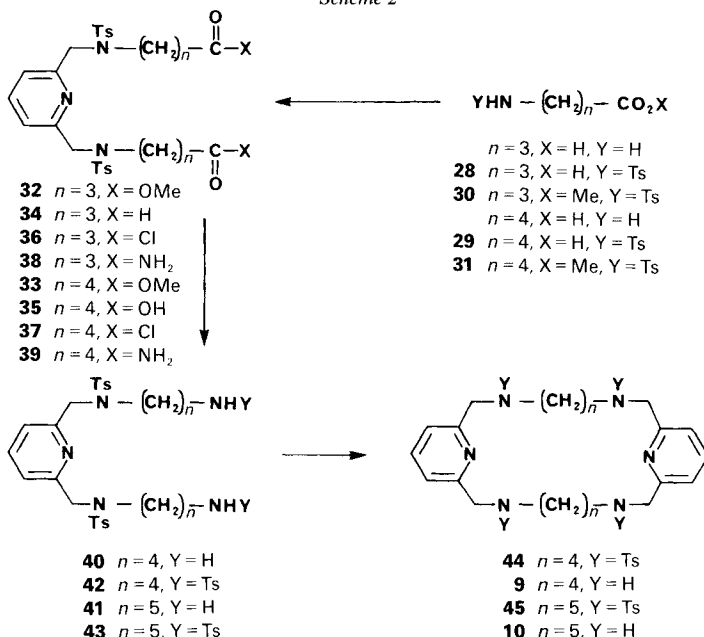
²⁾ The macrobicyclic tris(pyridine) analogue of compound **4** has been obtained [41b] by reduction of the corresponding hexamine [41a].

was converted, in quantitative yield, into its di(mesyloxy) derivative **14** by treatment with MsCl in CH_2Cl_2 in the presence of Et_3N . This compound was the common starting material for the synthesis of macrocycles **2** and **3**. Condensation of **14** with the disodium salts of $\text{TsN}(\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$ [**24**] or of **12**, prepared by treatment with Na in MeOH , led to the penta- and tetratosyl macrocycles **15** and **16** in 30–35% yield. Compound **15** was also prepared, in 30% yield, by condensation of $\text{TsN}((\text{CH}_2)_2\text{N}(\text{Ts})(\text{CH}_2)_2\text{O}-(\text{CH}_2)_2\text{OMs})_2$ [**32**] with **12** in the presence of Cs_2CO_3 following the procedures developed for the synthesis of polyazamacro(poly)cycles [**17**] [**32**] [**34**] [**47**] [**48**]. Removal of the Ts groups was achieved by treatment with 33% HBr in AcOH at 80° in the presence of phenol, yielding the hydrobromide salts of **2** and **3**. The free macrocyclic polyamines **2** and **3** were obtained by passing their HBr salts over a *Dowex IX8* resin in its basic form; they should be stored under N_2 or kept as their hexaammonium salts.

Macrocycles 4–8 (Scheme 1). Compound **11** was prepared according to published procedure [**36**]. The reaction of the disodium salts of $\text{TsN}(\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$ [**24**] or $\text{TsN}(\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$ [**47**] with **12** gave the diols **17** and **19**, respectively, in 50–54% yields, which were converted into their di(mesyloxy) derivatives **18** and **20**, respectively, in quantitative yields. The reaction of **11** with the disodium salt of **12** gave the diol **23**, which was further transformed into its di(mesyloxy) derivative **24**. These compounds were the common intermediates for the synthesis of macrocycles **4–8**. Condensation of **18** with $\text{TsN}(\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$ in the presence of Cs_2CO_3 led to the macrocycle **21** (30% yield). The reaction of the disodium salt of $\text{TsN}(\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$ with **20** gave the hexatosyl macrocycle **22** (35% yield), whereas its condensation with **24** led to the pentatosyl macrocycle **25** (35% yield). Condensation of the disodium salt of **12** with **20** led to the pentatosyl macrocycle **26** (35% yield), whereas its condensation with **24** gave the tetrapyridine macrocycle **27** (40% yield). Removal of the Ts groups was achieved by treatment with $\text{HBr}/\text{AcOH}/\text{phenol}$ for **21** and **22**. Compounds **25–27** were detosylated by treatment with concentrated H_2SO_4 at 100° . All final macrocyclic polyamines should be stored under N_2 or as their ammonium salts.

Synthesis of Macrocycles 9 and 10 (Scheme 2). For the synthesis of macrocycles **9** and **10**, the cyclisation was achieved by condensation of an α,ω -di(*p*-toluenesulfonamide) with 2,6-bis(bromomethyl)pyridine in DMF [**46**]. 4-Aminobutyric acid or 5-aminovaleric acid were tosylated in 90% yield with TsCl in H_2O at 90° in the presence of KOH or NaOH , affording the starting materials **28** and **29**. These two acids were esterified in 90% yield with MeOH/HCl yielding the methyl esters **30** and **31**. The sodium salts of **30** and **31** were generated by treatment with Na in MeOH and then reacted in DMF at 100° with 2,6-bis(bromomethyl)pyridine [**49**] giving the diesters **32** and **33** (80% yield) which, after saponification, gave the diacids **34** and **35** in 80–85% yields. Treatment of **34** and **35** with SOCl_2 yielded the diacid-chloride derivatives **36** and **37** which were treated with NH_3 in THF at 0° affording, in 90–95% yields, the amide derivatives **38** and **39**. Reduction of **38** and **39** with B_2H_6 to the diamines **40** and **41** was followed by their tosylation in 80–85% yields, affording the two cyclisation partners **42** and **43**. The disodium salts of **42** and **43**, prepared by treatment with Na in MeOH , were condensed in DMF at 100° with 2,6-bis(bromomethyl)pyridine affording the macrocyclic compounds **44** and **45** in 70 and 60% yields, respectively. Removal of the Ts groups (conc. H_2SO_4 , 100°) afforded the free macrocycles **9** and **10** (65–75% yield).

Scheme 2



Properties of the Macrocycles 2–10. – It has been shown that compound (**2**) forms dinuclear Pd, Pt, and Rh complexes [40], and that compound **3** binds two Co cations [44]. Ditopic macrocyclic compounds **9** and **10** form dinuclear Cu complexes [46]. On the other hand, protonated compound **2** like **1** binds ATP^{4-} and ADP^{3-} and catalyses their hydrolysis [50]. The binding of both transition-metal cations and anions by macrocycles **2–10** as well as their ability to catalyse phosphoryl-transfer processes are under current investigation and will be reported elsewhere.

Experimental Part

General. M.p.: uncorrected. $^1\text{H-NMR}$: Varian A-60, Varian EM-360A, or Bruker-Sy200 spectrometer. $^{13}\text{C-NMR}$: Varian XL-100 or Bruker Sy-200 spectrometer. Chemical shifts (δ) are given in ppm with TMS as internal standard in CDCl_3 , or *t*-BuOH in D_2O . MS: performed by the 'Service de Spectrométrie de Masse', Strasbourg. Microanalyses were performed by the 'Service de Microanalyse', Strasbourg.

2,6-Bis{[N-(5-hydroxy-3-oxapentyl)-N-tosylamino]methyl}pyridine (13**).** In a 250-ml flask, 2,6-Bis{[N-tosylamino]methyl}pyridine (**12**; 10 g, 22.44 mmol), K_2CO_3 (12.41 g, 89.76 mmol), 2-(2-chlorethoxy)ethanol (11.18 g, 89.78 mmol), and DMF (100 ml) were stirred and heated to 85° for 24 h. The mixture was allowed to cool to r.t., and stirring was continued for another 24 h. The solid was filtered and washed with DMF (50 ml), the solns. were combined and evaporated to dryness, the orange residue was taken up in CH_2Cl_2 (250 ml), washed with brine (100 ml), dried (MgSO_4), and evaporated to dryness leaving 16.17 g of an oil. Pure **13** (10 g, 72%) was obtained as a colorless liquid after chromatography (SiO_2 ; CH_2Cl_2 /1%–2.5% MeOH). $^1\text{H-NMR}$ (CDCl_3): 2.44 (s, 2 CH_3); 3.26 (t, 2 CH_2N); 3.41 (s, 4 CH_2O); 3.50 (t, 2 CH_2OH); 4.11 (br., 2 OH); 4.61 (s, 2 PyCH_2N); 7.26–7.75 (m, 11 arom. H). $^{13}\text{C-NMR}$ (CDCl_3): 21.5 (CH_3); 47.6 (CH_2N); 53.8, 61.5 (CH_2O); 69.8 (CH_2OH); 72.4 (PyCH_2N); 121.4 (Py); 127.2, 129.8 (Ts); 137.4 (Py); 137.9, 143.5 (Ts); 156.9 (Py). Anal. calc. for $\text{C}_{29}\text{H}_{39}\text{N}_3\text{O}_8\text{S}_2 \cdot 2 \text{ MeOH}$ (685.84): C 54.29, H 6.90, N 6.12; found: C 54.51, H 6.35, N 6.61.

Preparation of Compounds 17, 19, and 23. The disodium salts of $\text{TsN}(\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$, $\text{TsN}(\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$, or **12** were prepared as follows: in a 250-ml flask, Na was first dissolved in dry MeOH, then the desired tosylamide derivative was added and the mixture refluxed under Ar for 2 h. The mixture was allowed to cool to r.t., and the solvent was removed. The disodium salts were obtained as white solids and were dried for 4 h under vacuum before use.

The disodium salt of $\text{TsN}(\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$ or $\text{TsN}(\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$, or of compound **12** was dissolved in DMF and heated to 90° . To this stirred soln. was added dropwise (1 h) a soln. of **11** in DMF, and stirring at 90° was continued for further 5 h. The mixture was allowed to cool to r.t. and evaporated to dryness. The residue obtained was taken up in CH_2Cl_2 (200 ml), washed with 2.5N NaOH (100 ml), dried (MgSO_4), and the solvent removed. Pure **17**, **19**, and **23** were obtained after chromatography (SiO_2 ; CH_2Cl_2 /0–1.5% MeOH).

1,9-Bis[6-(hydroxymethyl)pyridin-2-yl]-2,5,8-tritosyl-2,5,8-triazanonane (17). From $\text{TsN}(\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$ (8.40 g, 14.85 mmol); Na (0.717 g, 31.19 mmol), MeOH (50 ml); $\text{TsN}(\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{Na})_2$ (9.05 g, 14.85 mmol) in DMF (60 ml), **11** (6.00 g, 29.70 mmol) in DMF (70 ml). Yield: 6.50 g (54%). $^1\text{H-NMR}$ (CDCl_3): 2.34 (s, CH_3); 2.38 (s, 2 CH_3); 2.98 (br. m, 2 CH_2N); 3.24 (br. m, 2 CH_2N); 4.20 (br., 2 OH); 4.39 (s, 2 PyCH_2N); 4.62 (s, 2 CH_2OH); 7.16–7.71 (m, 18 arom. H). $^{13}\text{C-NMR}$ (CDCl_3): 20.90, 20.94 (CH_3); 47.5, 48.2 (CH_2N); 54.0 (PyCH_2N); 68.3 (CH_2OH); 119.2, 121.0 (Py); 126.5, 126.8, 129.2, 129.3 (Ts); 134.5 (Py); 135.2, 137.1, 143.2 (Ts); 154.8, 159.3 (Py). Anal. calc. for $\text{C}_{39}\text{H}_{45}\text{N}_5\text{O}_8\text{S}_3 \cdot 0.5 \text{CH}_2\text{Cl}_2$ (850.46): C 57.78, H 5.45, N 8.23; found: C 56.70, H 5.40, N 8.44.

1,11-Bis[6-(hydroxymethyl)pyridin-2-yl]-2,6,10-tritosyl-2,6,10-triazaundecane (19). From $\text{TsN}(\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{H})_2$ (16.99 g, 28.61 mmol); Na (1.38 g, 60.09 mmol), MeOH (70 ml); $\text{TsN}(\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{Na})_2$ (18.25 g, 28.61 mmol) in DMF (200 ml), **11** (11.56 g, 57.23 mmol) in DMF (100 ml). Yield: 12 g (50%). $^1\text{H-NMR}$ (CDCl_3): 1.48 (q, 2 $\text{CH}_2\text{CH}_2\text{CH}_2$); 2.39 (s, CH_3); 2.41 (s, 2 CH_3); 2.84 (t, 2 CH_2N); 3.13 (t, 2 CH_2N); 4.14 (br. s, 2 OH); 4.37 (s, 2 PyCH_2N); 4.65 (s, 2 CH_2OH); 7.16–7.69 (m, 18 arom. H). $^{13}\text{C-NMR}$ (CDCl_3): 21.3 (CH_3); 27.8 ($\text{CH}_2\text{CH}_2\text{CH}_2$); 46.3, 46.9 (CH_2N); 53.7 (PyCH_2N); 64.0 (CH_2OH); 119.4, 121.2 (Py); 126.8, 127.1, 129.5, 129.6, 135.6, 135.8 (Ts); 137.5 (Py); 143.2, 143.4 (Ts); 155.8, 159.0 (Py). Anal. calc. for $\text{C}_{41}\text{H}_{49}\text{N}_5\text{O}_8\text{S}_3$ (836.05): C 58.90, H 5.91, N 8.38; found: C 58.84, H 5.85, N 8.22.

2,6-Bis[6-(hydroxymethyl)pyridin-2-yl]methoxy-N-tosylamino methylpyridine (23). From **12** (4.80 g, 10.77 mmol); Na (0.52 g, 22.62 mmol), MeOH (50 ml); disodium salt of **12** (5.27 g, 10.85 mmol) in DMF (70 ml); **11** (4.35 g, 21.55 mmol) in DMF (60 ml). Yield: 3.78 g (51%). $^1\text{H-NMR}$ (CDCl_3): 2.38 (s, 2 CH_3); 4.37 (s, 2 CH_2N); 4.45 (s, 2 CH_2N); 4.52 (s, 2 CH_2OH); 7.0–7.69 (m, 17 arom. H). $^{13}\text{C-NMR}$ (CDCl_3): 21.3 (CH_3); 53.3, 53.4 (CH_2N); 63.8 (CH_2O); 119.0, 121.1 (Py); 127.1, 129.4 (Ts); 136.8 (Py); 136.9 (Ts); 137.0 (Py); 143.3 (Ts); 155.2, 155.7, 158.6 (Py). Anal. calc. for $\text{C}_{35}\text{H}_{37}\text{N}_5\text{O}_6\text{S}_2 \cdot 0.5 \text{CH}_2\text{Cl}_2$ (730.33): C 58.38, H 5.24, N 9.59; found: C 57.88, H 5.30, N 9.58.

Preparation of Compounds 14, 18, 20, and 24. In a 250-ml flask, to the diol **13**, **17**, **19**, or **23** dissolved in dry CH_2Cl_2 (100 ml), Et_3N was added, and the mixture was stirred and cooled in an ice-bath. To this was added dropwise (15 min) a soln. of MsCl in CH_2Cl_2 (100 ml), the mixture was further stirred for 3 h at r.t., before it was rapidly washed with H_2O /ice (50 ml), 10% HCl (50 ml), sat. soln. of NaHCO_3 (50 ml), and brine (50 ml). The org. layer was dried (MgSO_4) and evaporated to dryness under vacuum at r.t. yielding oils which were not further purified.

2,6-Bis[6-(mesyloxy)-3-oxapentyl]-N-tosylamino methylpyridine (14). From **13** (9.25 g, 15.31 mmol); Et_3N (6.4 ml, 45.93 mmol); MsCl (4.38 g, 38.28 mmol). Yield: 11.69 g (98%). $^1\text{H-NMR}$ (CDCl_3): 2.40 (s, 2 CH_3 (Ts)); 3.0 (s, 2 CH_3 (Ms)); 3.48 (br., 2 CH_2N , 4 CH_2O); 4.15 (br. m, 2 CH_2OMs); 4.43 (br. s, 2 PyCH_2N); 7.16–7.90 (m, 11 arom. H). $^{13}\text{C-NMR}$ (CDCl_3): 21.3 (CH_3 (Ts)); 37.3 (CH_3 (Ms)); 48.2 ($\text{CH}_2\text{CH}_2\text{N}$); 54.2 (PyCH_2N); 68.3, 68.8, 69.2 (CH_2O); 120.8 (Py); 127.0, 129.6 (Ts); 137.4 (Ts); 138.3 (Py); 143.4 (Ts); 156.6 (Py). Anal. calc. for $\text{C}_{31}\text{H}_{43}\text{N}_3\text{O}_{12}\text{S}_4 \cdot 0.5 \text{CH}_2\text{Cl}_2$ (777.93): C 46.11, H 5.40, N 5.12; found: C 46.51, H 4.40, N 5.23.

1,9-Bis[6-(mesyloxy)methylpyridin-2-yl]methyl-2,5,8-tritosyl-2,5,8-triazanonane (18). From **17** (6.45 g, 7.98 mmol); Et_3N (4.45 ml, 31.93 mmol); MsCl (2.74 g, 23.95 mmol). Yield: 7.18 g (93%). $^1\text{H-NMR}$ (CDCl_3): 2.41 (s, CH_3 (Ts)); 2.43 (s, 2 CH_3 (Ts)); 3.04 (s, 2 CH_3 (Ms)); 3.08 (m, 2 $\text{CH}_2\text{CH}_2\text{N}$); 3.32 (m, 2 $\text{CH}_2\text{CH}_2\text{N}$); 4.42 (s, 2 PyCH_2N); 5.20 (s, 2 CH_2O); 7.20–7.80 (m, 18 arom. H). $^{13}\text{C-NMR}$ (CDCl_3): 21.0 (CH_3 (Ts)); 37.4 (CH_3 (Ms)); 47.95, 48.5 (CH_2N); 54.1 (PyCH_2N); 70.8 (CH_2O); 120.6, 122.4 (Py); 126.6, 126.9, 129.3 (Ts); 134.5 (Py); 135.3, 137.5, 143.3 (Ts); 153.1, 155.9 (Py). Anal. calc. for $\text{C}_{41}\text{H}_{49}\text{N}_5\text{O}_{12}\text{S}_5$ (964.11): C 51.07, H 5.12; found: C 51.66, H 5.20.

1,11-Bis[6-(mesyloxy)methylpyridin-2-yl]methyl-2,6,10-tritosyl-2,6,10-triazaundecane (20). From **19** (9.40 g, 11.24 mmol); Et_3N (6.23 ml, 44.97 mmol); MsCl (3.86 g, 33.73 mmol). Yield: 11.15 g (100%). $^1\text{H-NMR}$ (CDCl_3): 1.80 (q, 2 $\text{CH}_2\text{CH}_2\text{CH}_2$); 2.40 (s, CH_3 (Ts)); 2.42 (s, 2 CH_3 (Ts)); 2.89 (t, 2 CH_2N); 3.05 (s, 2 CH_3 (Ms)); 3.16 (t, 2 CH_2N); 4.38 (s, PyCH_2N); 5.17 (s, 2 CH_2); 7.25–7.73 (m, 18 arom. H). $^{13}\text{C-NMR}$ (CDCl_3): 21.3 (CH_3

(Ts)); 27.8 (CH₂CH₂CH₂); 37.8 (CH₃ (Ms)); 48.4, 48.9 (CH₂N); 53.6 (PyCH₂N); 71.1 (CH₂O); 120.9, 122.5 (Py); 126.8, 127.0, 129.5, 129.6 (Ts); 135.8 (Py); 136.7, 137.8, 143.2, 143.4 (Ts); 153.0, 158.8 (Py). Anal. calc. for C₄₃H₅₃N₅O₁₂S₅·0.5 CH₂Cl₂ (1043.68): C 50.49, H 5.26, N 6.76; found: C 50.60, H 5.77, N 6.60.

2,6-Bis{N-{{6-[(*mesyloxy*)methyl]pyridin-2-yl}methyl}-N-tosylamino}methylpyridine (**24**). From **23** (8.05 g, 11.70 mmol); Et₃N (4.89 ml, 35.11 mmol); MsCl (4.02 g, 35.11 mmol). Yield: 9.73 g (98%). ¹H-NMR (CDCl₃): 2.40 (s, 2 CH₃ (Ts)); 3.05 (s, 2 CH₃ (Ms)); 4.39 (s, 2 CH₂N); 4.47 (s, 2 CH₂N); 5.06 (s, 2 CH₂O); 7.11–7.66 (m, 17 arom. H). ¹³C-NMR (CDCl₃): 20.9 (CH₃ (Ts)); 37.4 (CH₃ (Ms)); 52.6, 53.0 (CH₂N); 70.7 (CH₂O); 120.4, 121.3, 122.1 (Py); 126.8, 129.2 (Ts); 135.8 (Py); 137.8, 143.2 (Ts); 152.5, 154.9, 155.7 (Py). Anal. calc. for C₃₇H₄₁N₅O₁₀S₄ (844.00): C 52.65, H 4.90, N 8.30; found: C 51.49, H 5.00, N 8.07.

Preparation of the Macrocycles 15, 16, and 21. Compound **15** was prepared by two different methods: *i*) in a 1-l flask, compound **12** (8.49 g, 19.07 mmol), K₂CO₃ (31.06 g, 95.35 mmol), and DMF (500 ml) were stirred and heated to 90°. To this, a soln. of TsN(CH₂CH₂N(Ts)CH₂CH₂OCH₂CH₂OMs) (17.11 g, 19.07 mmol) in DMF (200 ml) was added dropwise (2 h), the mixture was further stirred at 90° for 24 h, before it was allowed to cool to r.t. The solid was removed by filtration, and the mixture was evaporated to dryness under vacuum. The brown residue was taken up in CH₂Cl₂ (300 ml), washed with brine (200 ml), the aq. layer further extracted with CH₂Cl₂ (4 × 200 ml). The org. layers were combined, dried (MgSO₄), and evaporated to dryness leaving 24 g of a mixture. Compound **15** was obtained as a glass in 30% yield (6.70 g) after chromatography (SiO₂; CH₂Cl₂/0–0.5% MeOH).

ii) In a 250-ml flask, Na (0.124 g, 5.4 mmol) was dissolved in dry MeOH (50 ml), TsN(CH₂CH₂N(Ts)H)₂ (1.145 g, 2.57 mmol) was added, and the mixture refluxed for 2 h. The solvent was removed and the solid dried under vacuum for 3 h. The disodium salt (1.53 g, 2.57 mmol) was dissolved in DMF (70 ml), the soln. stirred and heated to 90°. To this, a soln. of **14** (2 g, 2.57 mmol) in DMF (60 ml) was added dropwise (2 h), and stirring at 90° was further continued for 15 h, before the mixture was allowed to cool to r.t. The soln. was poured onto crushed ice, the solid filtered and washed with H₂O (200 ml). It was dissolved in CH₂Cl₂ (150 ml) and washed further with H₂O (70 ml). The org. layer was dried (MgSO₄) and evaporated to dryness leaving 2.38 g of a mixture. Compound **15** was obtained after chromatography in 35% yield (0.89 g).

3,9,12,15,21-Pentatosyl-3,9,12,15,21,27-hexaaza-6,18-dioxabicyclo[21.3.1]heptaicos-1(27),23,25-triene (15). ¹H-NMR (CDCl₃): 2.40, 2.41, 2.41 (3s, 5 CH₃); 3.07 (t, 2 CH₂N); 3.23 (m, 4 CH₂N); 3.36 (m, 4 CH₂O); 3.43 (t, 2 CH₂N); 4.38 (s, 2 PyCH₂N); 7.23–7.65 (m, 23 arom. H). ¹³C-NMR (CDCl₃): 21.4, 21.5 (CH₃); 48.3, 49.1, 49.2 (CH₂N); 54.7 (PyCH₂N); 70.1, 70.2 (CH₂O); 120.8 (Py); 127.1, 127.2, 127.3, 129.6, 129.8, 135.2 (Ts); 135.7 (Py); 137.0, 137.2, 143.3, 143.6 (Ts); 156.7 (Py). MS: 1151 ([M + H]⁺); 995 ([M + H]⁺ – Ts); 840 ([M + H]⁺ – 2 Ts); 685 ([M + H]⁺ – 3 Ts). Anal. calc. for C₅₄H₆₆N₆O₁₂S₅ (1151.45): C 56.33, H 5.78, N 7.30; found: C 56.54, H 5.56, N 7.29.

3,9,17,23-Tetratosyl-3,9,17,23,29,30-hexaaza-6,20-dioxatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11(30),12,14,25,27-hexaene (16). In a 1-l flask, **12** (6.41 g, 13.79 mmol), Cs₂CO₃ (27 g, 82.70 mmol), and DMF (500 ml) were stirred and heated to 85°. To this mixture, a soln. of **14** (10.73, 13.79 mmol) in DMF (200 ml) was added dropwise (4 h). The mixture was further stirred at 85° for 48 h, before it was allowed to cool to r.t. The solid was removed by filtration and the solvent evaporated to dryness under vacuum leaving an orange residue which was taken up in warm CH₂Cl₂ (500 ml). The suspension was filtered and the solvent removed leaving 18 g of an orange liquid. Pure **16** was obtained after chromatography (SiO₂; CH₂Cl₂) and recrystallized from CH₂Cl₂/hexane. Yield: 4.50 g (32%). M.p. 185°. ¹H-NMR (CDCl₃): 2.42 (s, 4 CH₃); 3.18 (br. s, 8 CH₂N, 4 CH₂O); 4.31 (s, 4 PyCH₂N); 7.23–7.64 (m, 22 arom. H). ¹³C-NMR (CDCl₃): 21.4 (CH₃); 48.0 (CH₂N); 54.3 (PyCH₂N); 69.5 (CH₂O); 121.1 (Py); 127.1, 129.6 (Ts); 137.0 (Py); 137.2, 143.4 (Ts); 156.6 (Py). MS: 1031 ([M + H]⁺); 875 ([M + H]⁺ – Ts); 721 ([M + H]⁺ – 2 Ts). Anal. calc. for C₅₀H₅₈N₆O₁₀S₄ (1031.28): C 58.23, H 5.67, N 8.15; found: C 58.06, H 5.63, N 8.16.

3,6,9,17,20,23-Hexatosyl-3,6,9,17,20,23,29,30-octaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11(30),12,14,25,27-hexaene (21). In a 500-ml flask, TsN(CH₂CH₂N(Ts)H)₂ (4.20 g, 7.43 mmol), Cs₂CO₃ (12 g, 37.15 mmol), and DMF (100 ml) were stirred and heated to 90°. To this, a soln. of **18** (7.16 g, 7.43 mmol) in DMF (100 ml) was added dropwise (1 h). Stirring at 90° was further continued for 24 h, before the mixture was allowed to cool to r.t. The solid was removed by filtration, and the orange soln. was poured onto crushed ice, the solid was filtered and taken up in CH₂Cl₂ (400 ml), washed with H₂O (100 ml) dried (MgSO₄), and the soln. evaporated to dryness. Pure **21** was obtained as a white solid after chromatography (SiO₂; CH₂Cl₂) and was recrystallized from CH₂Cl₂/hexane/DMF. Yield: 3.13 g (33%). M.p. 142°. ¹H-NMR (CDCl₃): 2.35 (s, 4 CH₃); 2.40 (s, 2 CH₃); 3.07 (m, 4 CH₂N); 3.20 (m, 4 CH₂N); 4.31 (s, 4 PyCH₂N); 7.14–7.62 (m, 30 arom. H). ¹³C-NMR (CDCl₃): 21.4 (CH₃); 47.7, 48.3, 53.7 (CH₂N); 121.9 (Py); 127.3, 129.7, 136.1 (Ts); 137.4 (Py); 143.5 (Ts); 155.9 (Py). MS: 1337 ([M + H]⁺); 1181 ([M + H]⁺ – Ts); 1027 ([M + H]⁺ – 2 Ts); 871 ([M + H]⁺ – 3 Ts). Anal. calc. for C₆₄H₇₄N₈O₁₂S₆·1.5 CH₂Cl₂ (1467.10): C 53.62, H 5.29, N 7.63; found: C 53.20, H 5.08, N 7.63.

Preparation of Protected Macrocycles 22–27. In a 250-ml flask, the sodium salt of TsN(CH₂CH₂N(Ts)H)₂, TsN(CH₂CH₂CH₂N(Ts)H)₂, or **12** prepared as described (see preparation of **17**, **19**, and **23**) was dissolved in DMF, the mixture was stirred and heated to 90°. A soln. of **14**, **18**, **20**, or **24** in DMF was added dropwise (2 h). The mixture was further stirred at 90° for 2–3 h, before it was allowed to cool to r.t. It was then poured onto crushed ice. The solid was filtered and washed with H₂O (200 ml). The solid residue was taken up in CH₂Cl₂ (300 ml) and further washed with H₂O (200 ml), the org. layer was dried (MgSO₄) and evaporated to dryness. The residues were purified by chromatography (SiO₂, CH₂Cl₂/0–1% MeOH).

3,6,9,17,21,25-Hexatosyl-3,6,9,17,21,25,31,32-octaazatriacyclo[25.3.1.1^{1,15}]dotriaconta-1(31),11(32),12,14,27,29-hexaene (22). From TsN(CH₂CH₂N(Ts)Na)₂ (3.42 g, 5.62 mmol) in DMF (70 ml); **20** (5.57 g, 5.62 mmol) in DMF (70 ml). Yield: 2.45 g (32%). ¹H-NMR (CDCl₃): 1.55 (*q*, 2 CH₂CH₂CH₂); 2.40 (*br. s*, 6 CH₃); 2.83 (*br. m*, 4 CH₂N); 3.20 (*br. m*, 4 CH₂N); 4.25 (*s*, 2 PyCH₂N); 4.34 (*s*, 2 PyCH₂N); 7.20–7.72 (*m*, 30 arom. H). ¹³C-NMR (CDCl₃): 21.5 (CH₃); 27.0 (CH₂CH₂CH₂); 45.8, 46.4, 47.5, 48.6 (CH₂N); 52.7, 54.7 (PyCH₂N); 121.2, 122.2 (Py); 126.9, 127.1, 127.4, 129.7, 129.8, 129.9 (Ts); 135.5 (Py); 136.6, 137.6, 143.3, 143.6 (Ts); 155.4, 157.1 (Py). MS: 1365 ([*M* + H]⁺); 1209 ([*M* + H]⁺ – Ts); 1055 ([*M* + H]⁺ – 2 Ts); 899 ([*M* + H]⁺ – 3 Ts). Anal. calc. for C₆₆H₇₆N₈O₁₂S₆·CH₂Cl₂ (1450.71): C 55.47, H 5.41, N 7.72; found: C 55.81, H 5.61, N 7.69.

3,6,9,17,25-Pentatosyl-3,6,9,17,25,31,32,33-octaazatetracyclo[25.3.1.1^{11,15}.1^{19,23}]tritiaconta-1(31),11(32),12,14,19(33),20,22,27,29-nonaene (25). From TsN(CH₂CH₂N(Ts)Na)₂ (4.33 g, 7.11 mmol) in DMF (100 ml); **24** (6.00 g, 7.11 mmol) in DMF (60 ml). Yield: 2.99 g (35%). M.p. 188–189°. ¹H-NMR (CDCl₃): 2.38 (*br. s*, 5 CH₃); 2.97 (*br. m*, 2 CH₂N); 3.18 (*br. m*, 2 CH₂N); 4.13 (*s*, 2 PyCH₂N); 4.40 (*s*, 2 PyCH₂N); 4.42 (*s*, 2 PyCH₂N); 7.10–7.57 (*br. m*, 29 arom. H). ¹³C-NMR (CDCl₃): 21.4 (CH₃); 47.2, 48.1 (CH₂N); 52.9, 53.4, 53.5 (PyCH₂N); 120.6, 121.5, 122.0 (Py); 127.1, 127.2, 127.3, 129.4, 129.6, 129.7 (Ts); 135.9 (Py); 137.1, 137.3, 143.1, 143.4, 143.5 (Ts); 155.3, 156.1, 156.3 (Py). MS: 1217 ([*M* + H]⁺); 1063 ([*M* + H]⁺ – Ts); 907 ([*M* + H]⁺ + 2 Ts); 751 ([*M* + H]⁺ – 3 Ts). Anal. calc. for C₆₀H₆₄N₈O₁₀S₅ (1217.52): C 59.19, H 5.30, N 9.20; found: C 58.99, H 5.42, N 8.99.

3,7,11,19,27-Pentatosyl-3,7,11,19,27,33,34,35-octaazatetracyclo[27.3.1.1^{5,9}.1^{13,17}.1^{21,25}]pentatriaconta-1(33),13(34),14,16,21(35),22,24,29,31-nonaene (26). From disodium salt of **12** (2.74 g, 5.62 mmol) in DMF (70 ml); **20** (5.57 g, 5.62 mmol) in DMF (70 ml). Yield: 2.50 g (36%). ¹H-NMR (CDCl₃): 1.42 (*q*, 2 CH₂CH₂CH₂); 2.35, 2.40 (2*s*, 5 CH₃); 2.79 (*t*, 2 CH₂N); 3.03 (*t*, 2 CH₂N); 4.12, 4.37, 4.38 (3*s*, 6 PyCH₂N); 7.07–7.60 (*m*, 29 arom. H). ¹³C-NMR (CDCl₃): 21.5 (CH₃); 27.5 (CH₂CH₂CH₂); 46.3, 46.5 (CH₂N); 52.9, 53.2 (PyCH₂N); 121.1, 121.4, 121.5 (Py); 127.0, 127.1, 129.4, 129.6, 137.2, 143.0 (Ts); 155.6, 155.8, 156.1 (Py). MS: 1245 ([*M* + H]⁺); 1089 ([*M* + H]⁺ – Ts); 935 ([*M* + H]⁺ – 2 Ts); 779 ([*M* + H]⁺ – 3 Ts); 623 ([*M* + H]⁺ – 4 Ts). Anal. calc. for C₆₀H₆₈N₈O₁₀S₅·0.5 CH₂Cl₂ (1288.03): C 58.28, H 5.40, N 8.70; found: C 58.28, H 5.40, N 9.03.

3,11,19,27-Tetratosyl-3,11,19,27,33,34,35,36-octaazapentacyclo[27.3.1.1^{5,9}.1^{13,17}.1^{21,25}]hexatriaconta-1(33),5(34),6,8,13(35),14,16,21(36),22,24,29,31-dodecaene (27). From disodium salt of **12** (2.16 g, 4.42 mmol) in DMF (100 ml); **24** (3.73 g, 4.42 mmol). Yield: 1.57 g (35%). M.p. > 260°. ¹H-NMR (CDCl₃): 2.39 (*s*, 4 CH₃); 4.26 (*s*, 8 CH₂N); 7.05–7.50 (*m*, 29 arom. H). ¹³C-NMR (CDCl₃): 21.5 (CH₃); 53.2 (CH₂N); 121.1 (Py); 127.1, 129.5 (Ts); 137.1 (Py); 143.5 (Ts); 155.7 (Py). MS: 1097 ([*M* + H]⁺); 943 ([*M* + H]⁺ – Ts); 787 ([*M* + H]⁺ – 2 Ts); 629 ([*M* + H]⁺ – 3 Ts); 473 ([*M* + H]⁺ – 4 Ts). Anal. calc. for C₅₆H₅₆N₈O₈S₄ (1097.35): C 61.29, H 5.14, N 10.21; found: C 61.09, H 5.23, N 10.12.

Preparation of Compounds 2–5. Compounds **15–16** or **21–22** were heated at 90° in HBr/AcOH (33%, 100 ml) in the presence of phenol during 20 h. The mixture was allowed to cool to r.t., the solid formed was filtered, washed with Et₂O (200 ml), and dried under vacuum. The purple solid was dissolved in H₂O and passed over a basic exchange column (Dowex 1X8), the free polyamines were collected and acidified with conc. HCl (pH 1), the solvent was removed, and the desired hydrochloride salts were taken up in EtOH, evaporated (3 × 20 ml) to remove H₂O, and dried under vacuum for 24 h.

3,9,12,15,21,27-Hexaaza-6,18-dioxabicyclo[21.3.1]heptaconta-1(27),23,25-triene (2). From **15** (4.94 g, 4.29 mmol); phenol (5.0 g). Yield: 2.49 g (97%). M.p. 150° (very hygroscopic). ¹H-NMR (D₂O): 3.47 (*br. m*, 2 CH₂N); 3.57 (*br. m*, 2 CH₂N); 3.64 (*br. m*, 4 CH₂N); 3.96 (*br. m*, 2 CH₂O); 4.02 (*br. m*, 2 CH₂O); 4.59 (*s*, 2 PyCH₂N); 7.56 (*d*, 2 arom. H); 8.02 (*t*, 1 arom. H). ¹³C-NMR (D₂O): 45.6, 46.1, 49.3, 49.8, 52.7 (CH₂N); 67.2, 67.4 (CH₂O); 125.1, 141.3, 152.6 (Py). Anal. calc. for C₁₉H₃₆N₆O₂·5 HCl·1 MeOH (594.86): C 40.38, H 7.62, N 14.13; found: C 39.96, H 7.84, N 13.84.

3,9,17,23,29,30-Hexaaza-6,20-dioxatriacyclo[23.3.1.1^{11,15}]triaconta-1(29),11(29),12,14,25,27-hexaene (3). From **16** (4.31 g, 4.18 mmol); phenol (4.50 g). Yield: 2.28 g (90%). M.p. 160° (very hygroscopic). ¹H-NMR (D₂O): 3.54 (*t*, 4 CH₂N); 4.02 (*t*, 4 CH₂O); 4.55 (*s*, 4 PyCH₂N); 7.50 (*d*, 4 arom. H); 7.96 (*t*, 2 arom. H). ¹³C-NMR (D₂O): 49.3 (CH₂N); 52.6 (PyCH₂N); 67.5 (CH₂O); 124.9, 141.2, 152.5 (Py). Anal. calc. for C₂₀H₃₄N₆O₂·6 HCl·2 EtOH (725.46): C 43.05, H 7.22, N 11.58; found: C 43.61, H 6.94, N 12.24.

3,6,9,17,20,23,29,30-Octaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11(30),12,14,25,27-hexaene (4). From **21** (1.40 g, 1.05 mmol); phenol (1.50 g). Yield: 0.62 g (94%). M.p. 228°. ¹H-NMR (D₂O): 3.79, 3.81 (2 br. s, 8 CH₂N); 4.65 (s, 4 PyCH₂N); 7.55 (d, 4 arom. H); 8.02 (t, 2 arom. H). ¹³C-NMR (D₂O): 45.7, 46.5 (CH₂N); 53.3 (PyCH₂N); 125.2, 141.7, 152.3 (Py). Anal. calc. for C₂₂H₃₄N₈·8 HCl, 4 H₂O (776.27): C 34.04, H 6.49, N 14.43; found: C 34.43, H 6.97, N 14.01.

3,6,9,17,21,25,31,32-Octaazatricyclo[25.3.1.1^{11,15}]dotriaconta-1(31),11(32),12,14,27,29-hexaene (5). From **22** (2.03 g, 1.48 mmol). Yield: 0.97 g (90%). M.p. 250° (dec.). ¹H-NMR (D₂O): 2.37 (q, 2 CH₂CH₂CH₂); 3.45 (br. m, 4 CH₂N); 3.78 (br. s, 4 CH₂N); 4.56, 4.62 (2s, 4 PyCH₂N); 7.54 (d, 4 arom. H); 8.00 (t, 2 arom. H). ¹³C-NMR (D₂O): 24.7 (CH₂CH₂CH₂); 45.2, 46.0, 46.1, 46.7 (CH₂N); 52.9 (PyCH₂N); 124.8, 125.0, 141.4, 152.5 (Py). Anal. calc. for C₂₄H₄₀N₈·6 HCl·2 MeOH (723.44): C 43.16, H 6.67, N 15.48; found: C 43.01, H 7.18, N 15.00.

Preparation of Macrocycles 6–8. In a 100-ml flask, **25**, **26**, or **27** in conc. H₂SO₄ (25 ml) was heated at 100° during 6 h (**24** and **25**) or 2 h (**26**). The mixture was allowed to cool to r.t., then poured into a soln. of 40% NaOH (150 ml) cooled in an ice-bath. The basic aq. soln. was extracted with CHCl₃ (5 × 100 ml), the org. layer dried (MgSO₄), and evaporated to dryness. The residue was dissolved in abs. EtOH (15 ml) and acidified to pH 1 with conc. HCl. The solvent was removed and the residue co-evaporated with anh. MeOH (3 × 20 ml) and abs. EtOH (3 × 20 ml) yielding the hydrochloride salts of **6–8** as white solids which were further dried under vacuum for 12 h.

3,6,9,17,25,31,32,33-Octaazatetracyclo[25.3.1.1^{11,15}.1^{19,23}]tritiaconta-1(31),11(32),12,14,19(33),20,22,27,29-nonaene (6). From **25** (2.45 g, 2.0 mmol). Yield: 1.19 g (78%). M.p. 196° (dec.). ¹H-NMR (D₂O): 3.73 (br. s, 4 CH₂N); 4.61, 4.66 (2s, 6 PyCH₂N); 7.42–7.62 (m, 6 arom. H); 7.96–8.05 (m, 3 arom. H). ¹³C-NMR (D₂O): 45.5, 46.5 (CH₂N); 52.6, 53.0 (PyCH₂N); 124.6, 124.9, 125.2, 141.2, 152.2, 152.4 (Py). Anal. calc. for C₂₅H₃₄N₈·6 HCl·2 EtOH (757.49): C 45.98, H 6.91, N 14.79; found: C 45.30, H 6.21, N 14.67.

3,7,11,19,27,33,34,35-Octaazatetracyclo[27.3.1.1^{13,17}.1^{21,25}]pentatriaconta-1(33),13(34),14,16,21(35),22,24,29,31-nonaene (7). From **26** (2.21 g, 1.83 mmol). Yield: 1.07 g (83%). M.p. 190° (dec.). ¹H-NMR (D₂O): 2.29 (q, 2 CH₂CH₂CH₂); 3.34 (t, 2 CH₂N); 3.38 (t, 2 CH₂N); 4.55, 4.62, 4.66 (3s, 6 PyCH₂N); 7.55 (d, 3 arom. H); 7.57 (d, 3 arom. H); 8.02 (t, 3 arom. H). ¹³C-NMR (D₂O): 24.4 (CH₂CH₂CH₂); 45.7, 46.4 (CH₂N); 52.7 (PyCH₂N); 125.1, 125.4, 141.4, 152.3, 152.6, 152.7 (Py). Anal. calc. for C₂₇H₃₈N₈·6 HCl·1 MeOH (725.46): 46.35, H 6.66, N 15.44; found: C 45.71, H 6.99, N 15.22.

3,11,19,27,33,34,35,36-Octaazapentacyclo[27.3.1.1^{5,9}.1^{13,17}.1^{21,25}]hexatriaconta-1(33),5(34),6,8,13(35),14,16,21(36),22,24,29,31-dodecaene (8). From **27** (2.03 g, 1.85 mmol). Yield: 1.10 g (90%). M.p. > 260°. ¹H-NMR (D₂O): 4.63 (s, 8 CH₂); 7.52 (d, 8 H, Py); 7.98 (t, 4 H, Py). ¹³C-NMR (D₂O): 52.4 (CH₂); 125.0, 141.3, 152.4 (Py). Anal. calc. for C₂₈H₃₂N₈·5 HCl (662.92): C 50.73, H 5.62, N 16.90; found: C 50.67, H 5.76, N 16.43.

Preparation of Compounds 28 and 29. In a 500-ml flask, to a H₂O soln. (150 ml) of 4-aminobutyric acid or 5-aminovaleric acid, solid KOH or NaOH was added, and the soln. stirred and heated to 90°. To this, TsCl was added in batches over ca. 15 min, and the mixture was further stirred at 90° for 3 h, and then allowed to cool to r.t. 6N HCl was added until pH 5 was reached, the solid filtered, washed with H₂O and dried.

4-(Tosylamino)butyric Acid (**28**). From 4-aminobutyric acid (10.3 g, 100 mmol); KOH (13 g, 230 mmol); TsCl (20 g, 105 mmol). Yield: 23 g (90%). M.p. 135°. ¹H-NMR (NaOD): 1.70 (m, CH₂CH₂N); 2.20 (m, CH₂CO₂); 2.35 (s, CH₃); 2.80 (m, CH₂N); 7.29, 7.67 (2d, 4 arom. H). Anal. calc. for C₁₁H₁₃NO₄S (257.30): C 51.36, H 5.84, N 5.45; found: C 51.27, H 5.60, N 5.51.

5-(Tosylamino)pentanoic Acid (**29**). From 5-aminovaleric acid (14 g, 120 mmol); NaOH (10 g, 250 mmol); TsCl (23 g, 120 mmol). Yield: 29 g (90%). M.p. 95°. ¹H-NMR (NaOD): 1.52 (m, CH₂CH₂CH₂N); 2.18 (m, CH₂CO₂); 2.43 (s, CH₃); 2.80 (m, CH₂N); 7.46, 7.80 (2d, 4 arom. H). Anal. calc. for C₁₂H₁₇NO₄S (271.33): C 53.14, H 6.27, N 5.17; found: C 53.20, H 6.39, N 5.18.

Preparation of Compounds 30 and 31. In a 500-ml flask, to a soln. of **28** or **29** in MeOH (300 ml), 12N HCl (3 ml) was added and the mixture refluxed for 3 h. The solvent was removed, the residue was taken up in CH₂Cl₂ (200 ml), and washed with 4N soln. of Na₂CO₃. The org. layer was dried (Na₂SO₄) and evaporated to dryness. Pure **29** and **30** were obtained after crystallization from CH₂Cl₂/hexane and CH₂Cl₂/Et₂O, respectively.

Methyl 4-(Tosylamino)butyrate (**30**). From **28** (20 g, 78 mmol). Yield: 12 g (90%). M.p. 92–93°. ¹H-NMR (CDCl₃): 1.80 (m, CH₂CH₂N); 2.30 (m, CH₂CO₂); 2.45 (s, CH₃); 3.0 (m, CH₂N); 3.70 (s, CH₃O); 7.39, 7.88, (2d, 4 arom. H). Anal. calc. for C₁₂H₁₇NO₄S (271.33): C 53.14, H 6.27, N 5.17; found: C 53.06, H 6.38, N 5.26.

Methyl 5-(Tosylamino)pentanoate (**31**). From **29** (27 g, 100 mmol). Yield: 26 g (90%). M.p. 54°. ¹H-NMR (CDCl₃): 1.58 (m, CH₂CH₂CH₂N); 2.30 (m, CH₂CO₂); 2.50 (s, CH₃); 2.95 (m, CH₂N); 3.70 (s, CH₃O); 7.43, 7.91 (2d, 4 arom. H). Anal. calc. for C₁₃H₁₉O₄NS (285.36): C 54.74, H 6.67, N 4.91; found: C 54.63, H 6.55, N 4.98.

Preparation of Compounds 32 and 33. In a 500-ml flask, to a soln. of Na in MeOH (300 ml), **30** or **31** was added and the mixture refluxed for 1 h. The solvent was removed and the salt dissolved in DMF. To this stirred soln., 2,6-bis(bromomethyl)pyridine was added and the mixture heated to 100° for 2 h. The residue obtained after

evaporation of DMF was taken up in CH_2Cl_2 (200 ml), washed with 1N HCl (3×50 ml), dried and the solvent removed. The residue was dissolved in toluene and filtered through SiO_2 yielding **32** and **33** as colorless liquids.

2,6-Bis{[N-(3-(methoxycarbonyl)propyl)-N-tosylamino]methyl}pyridine (= Dimethyl δ,δ' -Ditosylpyridine-2,6-di(δ -azaheptanoate); **32**). From Na (1.36 g, 59 mmol); **30** (16 g, 59 mmol) DMF (300 ml). Yield: 15 g (80%). $^1\text{H-NMR}$ (CDCl_3): 1.72 (m, $\text{CH}_2\text{CH}_2\text{N}$); 2.20 (m, 2 CH_2CO_2); 2.45 (s, 2 CH_3); 3.22 (m, 2 CH_2N); 3.65 (s, 2 CH_3O); 4.40 (s, 2 PyCH_2N); 7.20–7.80 (m, 11 arom. H). Anal. calc. for $\text{C}_{31}\text{H}_{39}\text{N}_3\text{O}_8\text{S}_2$ (645.78): C 57.65, H 6.09, N 6.51; found: C 57.66, H 6.07, N 6.47.

2,6-Bis{[N-(4-(methoxycarbonyl)butyl)-N-tosylamino]methyl}pyridine (= Dimethyl ϵ,ϵ' -Ditosylpyridine-2,6-di(ϵ -azaheptanoate); **33**). From Na (1.64 g, 71 mmol); **31** (20 g, 70 mmol); DMF (250 ml). Yield: 19 g (80%). $^1\text{H-NMR}$ (CDCl_3): 1.47 (m, 2 $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$); 2.23 (m, 2 CH_2CO_2); 2.43 (s, 2 CH_3); 3.25 (m, 2 CH_2N); 3.66 (s, 2 CH_3O); 4.42 (s, 2 PyCH_2N); 7.32–7.80 (m, 11 arom. H). Anal. calc. for $\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_8\text{S}_2$ (673.84): C 58.82, H 6.49, N 6.24; found: C 58.79, H 6.39, N 6.23.

Preparation of Compounds 34 and 35. In a 500-ml flask, to a soln. of **32** or **33** in THF (300 ml), 4N HCl (60 ml) was added and the mixture refluxed for 5 h. After evaporation to dryness, NaOH 20% (300 ml) was added to the residue and the soln. extracted with CH_2Cl_2 . The aq. layer was acidified to pH 6 with HCl. In the case of **34**, acidification yielded an oil which was recrystallized from cold MeOH/ H_2O . For **35**, after acidification to pH 6, the aq. layer was further extracted with CHCl_3 , the org. layer dried and evaporated to dryness yielding a colorless glass.

2,6-Bis{[N-(3-carboxypropyl)-N-tosylamino]methyl}pyridine (= δ,δ' -Ditosylpyridine-2,6-di(δ -azaheptanoic acid); **34**). From **32** (15 g, 23.3 mmol). Yield: 12.2 g (85%). M.p. 152–153°. $^1\text{H-NMR}$ (NaOD): 1.80 (br. m, 2 $\text{CH}_2\text{CH}_2\text{N}$); 2.10 (br. m, 2 CH_2CO_2); 2.25 (s, 2 CH_3); 2.90 (br. m, 2 CH_2N); 4.20 (br. s, 2 PyCH_2N); 7.10–7.70 (br. m, 11 arom. H). Anal. calc. for $\text{C}_{29}\text{H}_{35}\text{N}_3\text{O}_8\text{S}_2$ (671.73): C 56.39, H 6.80, N 5.71; found: C 56.44, H 6.90, N 5.74.

2,6-Bis{[N-(4-carboxybutyl)-N-tosylamino]methyl}pyridine (= ϵ,ϵ' -Ditosylpyridine-2,6-di(ϵ -azaheptanoic acid); **35**). From **33** (16 g, 24.7 mmol). Yield: 12 g (80%). $^1\text{H-NMR}$ (CDCl_3): 1.43 (m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$); 2.25 (m, CH_2CO_2); 2.42 (s, 2 CH_3); 3.20 (m, 2 CH_2N); 4.45 (s, 2 PyCH_2N); 7.32–7.80 (m, 11 arom. H). Anal. calc. for $\text{C}_{31}\text{H}_{39}\text{N}_3\text{O}_8\text{S}_2$ (645.78): C 57.65, H 6.09, N 6.51; found: C 56.70, H 6.27, N 6.61.

Preparation of Compounds 36 and 37. A 250-ml flask containing **34** or **35** was cooled in an ice bath, and SOCl_2 (30 ml) was added and the mixture stirred until complete dissolution of the diacid. Stirring was further continued for 30 min, then the mixture was evaporated to dryness, and the diacid dichlorides obtained were used in the next step without further purification.

2,6-Bis{[N-(3-(chloroformyl)propyl)-N-tosylamino]methyl}pyridine (= δ,δ' -Ditosylpyridine-2,6-di(δ -azaheptanoyl chloride); **36**). From **34** (10 g, 16.2 mmol). $^1\text{H-NMR}$ (CDCl_3): 1.80 (m, 2 $\text{CH}_2\text{CH}_2\text{N}$); 2.50 (s, 2 CH_3); 2.90 (t, 2 CH_2CO); 3.30 (t, CH_2N); 5.0 (s, 2 PyCH_2N); 7.34, 7.74 (2d, 8 arom. H (Ts)); 8.05–8.46 (m, 3 arom. H (Py)).

2,6-Bis{[N-(4-(chloroformyl)butyl)-N-tosylamino]methyl}pyridine (= ϵ,ϵ' -Ditosylpyridine-2,6-di(ϵ -azaheptanoyl chloride); **37**). From **35** (10 g, 15.5 mmol). $^1\text{H-NMR}$ (CDCl_3): 1.55 (m, 2 $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$); 2.48 (s, 2 CH_3); 2.90 (m, CH_2CO); 3.32 (m, CH_2N); 5.10 (s, PyCH_2N); 7.49, 7.90 (2d, 8 arom. H (Ts)); 8.25–8.60 (m, 3 arom. H (Py)).

Preparation of Compounds 38 and 39. To a 500-ml flask containing 350 ml of dry THF saturated with NH_3 and cooled in an ice-bath, a soln. of **36** or **37** in dry THF (100 ml) was added dropwise over a period of 1 h. After evaporation to dryness, the residue was taken up in H_2O (150 ml) and extracted with CH_2Cl_2 (3×50 ml). The org. layer was evaporated to dryness. In the case of **38**, the residue was passed over an Al_2O_3 column eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1 and then crystallized from MeOH/ Et_2O . In the case of **39**, the pure compound was obtained by crystallization of the residue from MeOH/ Et_2O .

2,6-Bis{[N-(3-carbamoylpropyl)-N-tosylamino]methyl}pyridine (= δ,δ' -Ditosylpyridine-2,6-di(δ -azaheptanamide); **38**). From **36** (10 g, 14.5 mmol). Yield: 8.4 g (95%). M.p. 130–132°. $^1\text{H-NMR}$ (CDCl_3): 1.77 (m, 2 $\text{CH}_2\text{CH}_2\text{N}$); 2.13 (m, CH_2N); 2.45 (s, 2 CH_3); 3.25 (m, CH_2CO); 4.40 (s, 2 PyCH_2N); 7.2–7.9 (m, 11 arom. H). Anal. calc. for $\text{C}_{29}\text{H}_{37}\text{N}_5\text{O}_6\text{S}_2$ (615.76): C 56.57, H 6.06, N 11.37; found: C 56.17, H 6.16, N 11.40.

2,6-Bis{[N-(4-carbamoylbutyl)-N-tosylamino]methyl}pyridine (= ϵ,ϵ' -Ditosylpyridine-2,6-di(ϵ -azaheptanamide); **39**). From **37** (9.2 g, 12.8 mmol). Yield: 7.5 g (90%). M.p. 130°. $^1\text{H-NMR}$ (CDCl_3): 1.47 (m, 2 $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$); 2.13 (m, 2 CH_2CO); 2.47 (s, 2 CH_3); 3.21 (m, 2 CH_2N); 4.40 (s, 2 PyCH_2N); 7.32–7.92 (m, 11 arom. H). Anal. calc. for $\text{C}_{31}\text{H}_{41}\text{N}_5\text{O}_6\text{S}_2$ (643.82): C 57.83, H 6.42, N 10.88; found: C 57.69, H 6.37, N 10.90.

Preparation of Compounds 40 and 41. To a soln. of **38** or **39** in dry THF (50 ml), 150 ml of 1M B_2H_6 were added under N_2 and the mixture refluxed during 6 h. After cooling, the excess B_2H_6 was cautiously destroyed with MeOH, then 50 ml of MeOH saturated with HCl were added and the mixture refluxed during 1 h. Evaporation to dryness yielded the HCl salts which were used in the next step without further purification.

2,6-Bis{[N-(4-aminobutyl)-N-tosylamino]methyl}pyridine (**40**). From **38** (8 g, 13 mmol). $^1\text{H-NMR}$ (CDCl_3): 1.38 (br. m, 2 $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$); 2.45 (s, 2 CH_3); 2.58 (m, 2 CH_2NH_2); 3.25 (m, 2 CH_2N); 7.30–7.90 (m, 11 arom. H).

2,6-Bis{[N-(5-aminopentyl)-N-tosylamino]methyl}pyridine (**41**). From **39** (7.5 g, 11.6 mmol).

Preparation of Compounds 42 and 45. Compounds **40** or **41** were dissolved in THF (150 ml), Et₃N (15 ml) and TsCl (5 g, 26 mmol) were added and the mixture was refluxed during 1 h. After filtration of the HCl salt of Et₃N, the solvent was removed. Pure **42** and **43** were obtained after chromatography on Al₂O₃, eluted with CH₂Cl₂, as colorless liquids.

2,6-Bis[{N-tosyl-N-[4-(tosylamino)butyl]amino}methyl]pyridine (42). From **40**. Yield: 9.9 g (85%). ¹H-NMR (CDCl₃): 1.40 (br. *m*, 2 CH₂CH₂CH₂N); 2.43 (*s*, 4 CH₃); 2.82 (br. *m*, 2 CH₂NH); 3.20 (br. *m*, 2 CH₂N); 4.40 (*s*, PyCH₂N); 7.3–7.9 (*m*, 11 arom. H). Anal. calc. for C₄₃H₅₃N₅O₈S₄ (896.16): C 57.63, H 5.96, N 7.82; found: C 57.52, H 6.00, N 7.80.

2,6-Bis[{N-tosyl-N-[5-(tosylamino)pentyl]amino}methyl]pyridine (43). From **41**. Yield: 8.6 g (80%). ¹H-NMR (CDCl₃): 1.25 (br. *m*, 2 CH₂CH₂CH₂CH₂N); 2.30 (*s*, 4 CH₃); 2.77 (*m*, 2 CH₂NH); 3.18 (*m*, 2 CH₂N); 4.40 (*s*, 2 PyCH₂N); 7.25–7.90 (*m*, 11 arom. H).

Preparation of Macrocycles 44 and 45. To a soln. of **42** or **43** in dry EtOH (300 ml), Na was added, the mixture refluxed during 30 min, and then evaporated to dryness. The disodium salt was dissolved in DMF (200 ml), stirred, and heated to 100°. To this was added a soln. of 2,6-bis(bromomethyl)pyridine in DMF (50 ml), and the mixture was further stirred at 100° for another 2 h. After evaporation, H₂O (100 ml) was added to the residue and the desired compound extracted into CH₂Cl₂. The org. phase was dried (Na₂SO₄) and evaporated to dryness. Pure **44** and **45** were obtained by crystallization from CH₂Cl₂/MeOH.

3,8,16,21-Tetratosyl-3,8,16,21,27,28-hexaazatricyclo[21.3.1.1^{10,14}]octaica-1(27),10(28),11,13,23,25-hexaene (44). From **42** (8 g, 8.9 mmol); Na (0.411 g, 17.9 mmol). Yield: 6.25 g (70%). M.p. 206°. ¹H-NMR (CDCl₃): 1.02 (br. *m*, 4 CH₂CH₂N); 2.45 (*s*, 4 CH₃); 3.10 (br. *m*, 4 CH₂N); 4.25 (*s*, 4 PyCH₂N); 7.30–7.90 (*m*, 11 arom. H). Anal. calc. for C₅₀H₅₈N₆O₈S₄ (999.30): C 60.10, H 5.85, N 8.41; found: C 59.93, H 5.84, N 8.49.

3,9,17,23-Tetratosyl-3,9,17,23,29,30-hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11(30),12,14,25,27-hexaene (45). From **43** (8 g, 8.7 mmol); Na (0.4 g, 17.4 mmol). Yield: 5.30 g (60%). M.p. 190°. ¹H-NMR (CDCl₃): 1.0 (*m*, 2 CH₂CH₂CH₂CH₂N); 2.13 (*s*, 4 CH₃); 2.45 (br. *m*, 4 CH₂N); 4.30 (*s*, 4 PyCH₂N); 7.30–7.87 (*m*, 11 arom. H). Anal. calc. for C₅₂H₆₂N₆O₈S₄ (1027.34): C 60.79, H 6.08, N 8.18; found: C 60.70, H 6.01, N 8.23.

Preparation of Compounds 9 and 10. In a 250-ml flask, **44** or **45**, and conc. H₂SO₄ were stirred and heated to 100° during 2 h. The mixture was cooled in an ice-bath, and H₂O (50 ml) was added. The excess acid was neutralized with 50% NaOH and the desired product extracted into CH₂Cl₂. The org. layer was dried (Na₂SO₄) and evaporated to dryness. Pure **9** and **10** were obtained after chromatography on Al₂O₃, eluted with CH₂Cl₂/MeOH: 9:1 as solids. Compound **9** was recrystallized from CH₂Cl₂/hexane; **10** was crystallized as its HCl salt from MeOH/HCl.

3,8,16,21,27,28-Hexaazatricyclo[21.3.1.1^{10,14}]octaica-1(27),10(28),11,13,23,25-hexaene (9). From **44** (6 g, 6 mmol); H₂SO₄ (50 ml); NaOH (200 ml). Yield (75%): 1.72 g. M.p. 122–124°. ¹H-NMR (CDCl₃): 1.61 (*m*, 4 CH₂CH₂N); 2.79 (*m*, 4 CH₂N); 3.92 (*s*, 4 PyCH₂N); 7.05, 7.20, 7.52, 7.60, 7.65, 7.78 (6 *m*, 6 arom. H). ¹³C-NMR (CDCl₃): 28.3 (CH₂CH₂N); 49.5 (CH₂N); 54.8 (PyCH₂N); 120.9, 136.9, 159.2 (arom.). MS: 382 (*M*⁺). Anal. calc. for C₂₂H₃₄N₆ (382.5): C 69.07, H 8.96, N 21.97; found: C 69.24, H 9.01, N 22.15.

3,9,17,23,29,30-Hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11(30),12,14,25,27-hexaene (10). From **45** (2 g, 1.95 mmol); H₂SO₄ (15 ml); NaOH (60 ml). Yield: 0.5 g (65%). ¹H-NMR (CDCl₃): 1.42 (*m*, 2 CH₂CH₂CH₂CH₂N); 2.58 (*m*, 4 CH₂N); 3.90 (*s*, 4 PyCH₂N); 7.08, 7.21, 7.53, 7.65, 7.68, 7.80 (6 *m*, 6 arom. H). ¹³C-NMR (CDCl₃): 24.5 (CH₂CH₂CH₂N); 29.6 (CH₂CH₂N); 48.4 (CH₂N); 54.2 (PyCH₂N); 120.3, 136.2, 158.8 (arom.). Anal. calc. for C₂₄H₃₈N₆·4 HCl·2 H₂O (592.45): C 48.65, H 7.83, N 14.19; found: C 48.42, H 7.85, N 14.39.

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