

Multi-Layer Macromonocyclic Polyamines. I. Molecular Design and Synthesis of Component Monocyclic Precursors [#]

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We designed "multi-layer macromonocyclic polyamines" which might be appropriate polymorphismic molecular scaffolds as host-molecules in ionic or molecular interaction with small or large guest ions or molecules. In polymorphismic molecules, several macromonocyclic polyamines with the same and/or different ring sizes and nitrogen contents are connected to each other by alkylene spacers with various length of the chain. Actual target molecules are characterized by possessing methylene chain arrays of natural polyamines, and we have synthesized from simple starting materials fourteen component macromonocycles with various sizes, 12- to 34-membered rings containing three to eight nitrogen atoms, as essential building blocks required for construction of multi-layer molecules. Our method of synthesis was shown to be very efficient. In a final step, the *N*-protecting benzyl group was successfully removed by hydrogenation on 10%-Pd/C under 4 kg cm⁻² H₂ to give the cyclic amine precursors, which could be internal and terminal components in the architecture of the multi-layer molecules. The structures of synthesized compounds were characterized and confirmed by EA, ¹H NMR, SIMS, and FAB(+) mass spectrometry.

We have been intrigued by the possibility of the development of biologically active synthetic polyamines because increasing knowledge of the crucial role of natural polyamines, putrescine, spermidine, and spermine, in cell biology has been stimulating versatile basic and applied research interests. Especially, we have been stimulated by recent interesting topics on natural and synthetic polyamines as reviewed in brain pathology,¹ environmental stress in plant,^{2,3} plant molecular genetic analysis,⁴ African trypanosomes,⁵ spider toxins in therapeutic neurochemistry,^{6,7} chemotherapy of parasitic protozoan diseases,⁸ cancer chemoprevention,^{9,10} and ion channels in the nervous system.^{11–14} In addition, the interaction between polyamine dendritic polymers and DNA,¹⁵ the stimulatory effect of synthetic polyamines on T7 RNA polymerase transcription activity,¹⁶ and the potent anti-HIV activity of synthetic polyamines^{17–21} are very interesting demonstrations of pronounced biological effects of synthetic polyamines. We have been particularly interested in the complexation capability of natural polyamines for many biogenic anion functional groups, such as phosphate, carbon dioxide, carbonate, carboxylate, and nitroxide, and with metal ions. Their flexible complexation capability seems to show that the association potential in complex formation would be controllable by circumstantial conditions such as ring sizes, nitrogen content, kinds of core metals, pH, ionic strength, and temperature.^{22–31} In other word, the association should be soft enough for natural polyamines to behave like manipulative free hands for organizing and/or

binding to biogenic large molecules such as DNA, RNA, or proteins by interaction with these functional groups. Guided by this conceptual hypothesis, we have attempted to design a new molecular system which could be flexible in complexation and soft in association. In the present report, we would like to describe a new molecular system, synthetic strategy, and synthetic method for functionalized macromonocyclic polyamines as important precursors to build up a variety of flexible multi-layer macromonocyclic molecules.

Results and Discussion

A combination of stick(s) and circle(s) such as shown in Fig. 1 inspired us to consider a new system of molecular architecture; in the model, two circles and a stick forming a double-layer would have two ultimate shapes (or morphisms), T1 and T2. By overlapping another set of a circle and a stick, three circles and two sticks forming a triple-layer would have three ultimate shapes, Th1, Th2, and Th3, and by overlapping one more set of a circle and a stick, four circles and three sticks forming a quadruple-layer would have six shapes, F1 through F6. (The mathematical relation between circle number (*n*) and total ultimate shape number (*S*) can be related in a general equation shown in the footnote.)³² In the illustrated models, it is obvious that there are two typical situations in each combination; two contiguous circles are directing toward the same side (interlocked type as in T1) or toward the opposite side (open apart type as in T2). In a poly-circle model, the other typical situations: that every other circle and every two other circles are directing to the same side as in Th1 and F1 and to the opposite side. As a whole, we considered this model as new molecular scaffolds

[#] This work is dedicated to the late Dr. Sakae Emoto and a part of the Japanese patent.

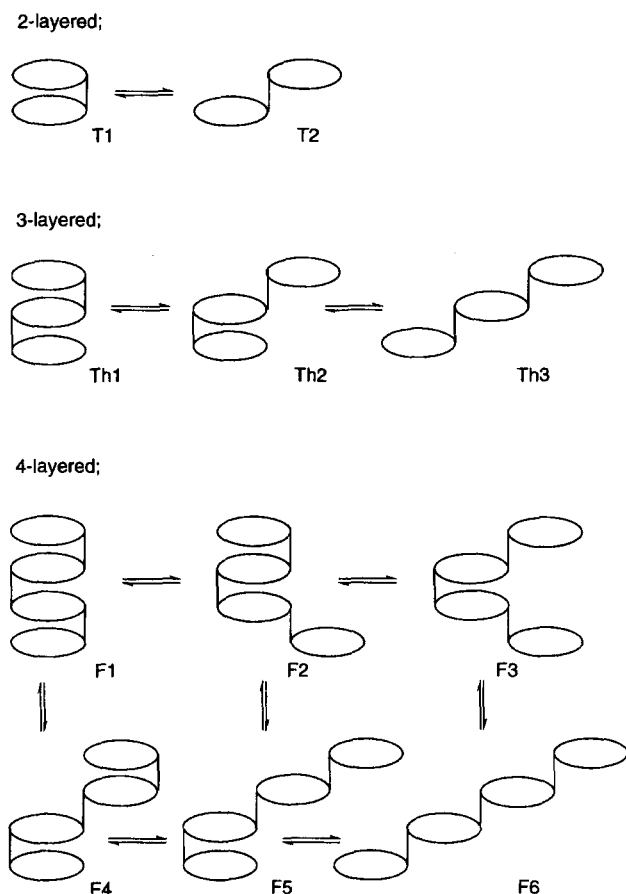


Fig. 1. Typical polymorphism in several homogeneous combination of circles ($=n$) and sticks, indicating the formation of maximum number ($=S$) of inter-locked and open-apart ultimate state models characterized by mutual interaction between the circles; namely, when $n = 1, 2$, and 3 , then $S = 2, 3$, and 6 , respectively (see Ref. 32 for general arithmetic relation between n and S in this type polymorphism).

for the design of self-organizable molecules. Our molecular architecture started on the basis of the idea that we would consider the circle as a macrocycle and the stick as an alkylene chain. There are two possible atoms, carbon and nitrogen, for juncture atoms between circle and stick. In reference to our previous synthetic works on macromonocyclic polyamines,³³ we chose nitrogen atom as a juncture atom.

Referring to our previous works, either application of differential protection method³⁴ or modification of general synthesis of macromonocyclic polyamines³³ seemed to be the first choice of synthetic strategies to construct multi-layer molecules. In several comparative studies on the first several steps, however, the differential protection method suffered from critical synthetic default, especially in the step of formamide formation in the presence of tertiary amino group. As shown in Fig. 2, the present strategy, called block-synthetic method, requires two key building blocks of terminal macrocycles (A) and central macrocycles (B) as components for a variety combination of macromonocycles; a molecule forming a double-layer will be synthesized by the reaction of two terminal cycles. A molecule forming a triple-layer will

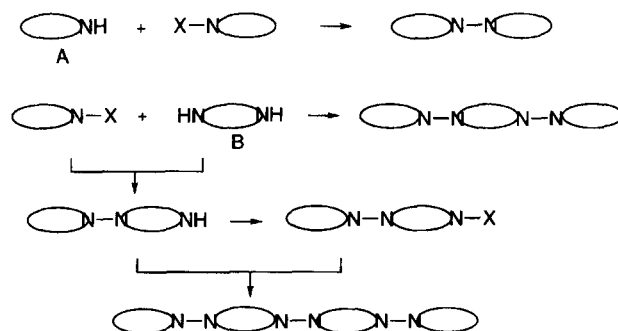
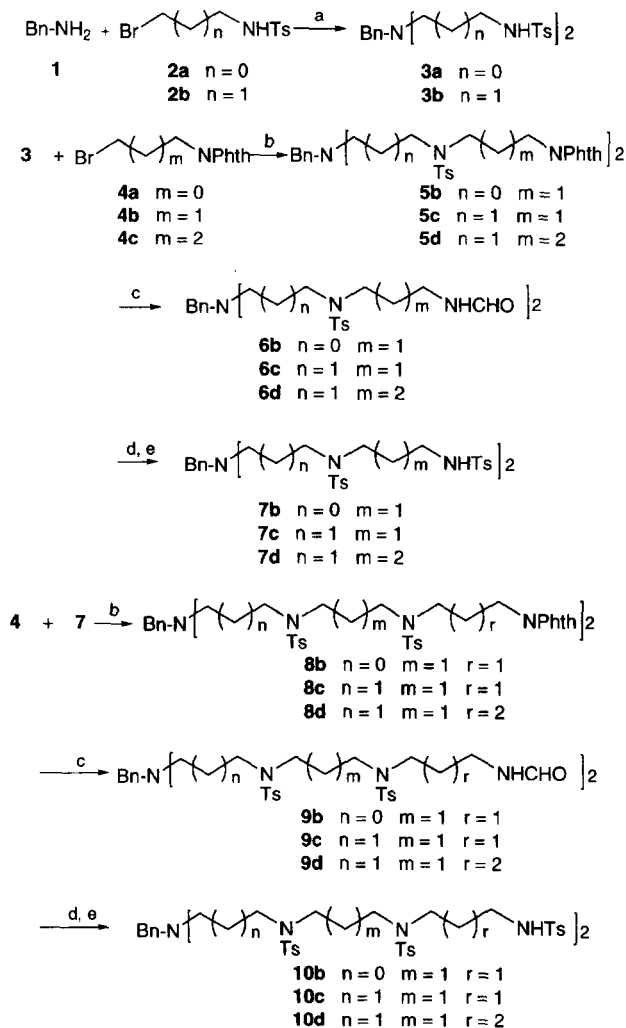


Fig. 2. Block-synthetic method; Principal synthetic strategy building up two to four layer molecules from macromonocyclic monoamines and diamines.

be accommodated in principle by the reaction of a central cycle with two terminal cycles. A molecule of a quadruple-layer consists of two central cycles and two terminal cycles. Therefore, feasibility studies on the synthesis of terminal and central cycles are the first issue for the architecture of multi-layer macromonocyclic polyamines.

In synthetic macrocyclic polyamine chemistry, preparation of open chain starting materials is often more difficult than subsequent ring closure reactions. Indeed, access to important open chain polyamines and diamino ethers by shorter and more convenient methods has been elaborated.^{35–40} In our molecular design, it is required that the amino groups of terminal and central cyclic polyamines at the juncture points are protected by a group different from the nitrogen protecting groups at the other ring nitrogen atoms. We chose in the protocol the *N*-benzyl protecting group for the formers and the *N*-tosyl protecting group for the latters. Architecture of the methylene chain arrays in this design was consistent with the previous idea,³³ except for the less-than-16-membered ring; cyclic polyamines must contain at least once a methylene chain array of natural acyclic polyamine, spermidine, spermine, thermine, or thermospermine. The synthetic strategy will be useful to clarify fine structural factors governing relationships between physico-chemical or biological properties and fine molecular composition.

Building units for the construction of central and terminal macrocycles were prepared by the processes shown in Schemes 1 and 2. Synthesis of *N*-benzyl- α,ω -bis(*p*-toluenesulfonylamide)s, **3**, **7**, and **10**, is shown in Scheme 1. *N*-Alkylation with *N*-(ω -bromoalkyl)tosylamides, **2**, took place, slowly but in high yield, by treatment of benzylamine in acetonitrile in the presence of sodium hydrogen carbonate. Chain elongation continued smoothly by the method reported previously.^{33,34} There was no synthetic problem in the transformation reaction of phthalimides, **5** or **8**, to formamides, **6** or **9**, even in the presence of the tertiary amine functional group. In addition, it was a new finding that quaternization of tertiary amino group rarely occurs in the steps of *N*-alkylations, as in the cases of the reactions of benzylamine **1** with **2**, **3** with **4**, and **7** with **4**. Determination of product structure was straightforward with measurements of IR and ¹H NMR spectra. In the IR spectra, changes in ter-



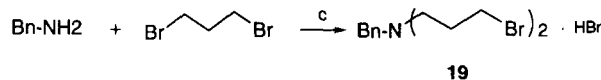
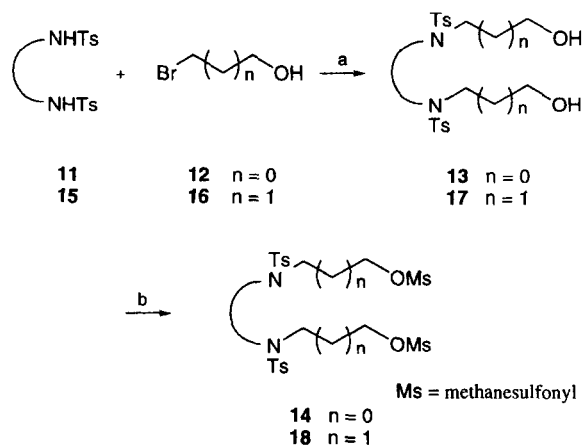
Bn = benzyl, Ts = *p*-toluenesulfonyl, Phth = Phthaloyl

a NaHCO₃, CH₃CN, 70 °C, 4 d; b K₂CO₃, DMF, r.t., 4 d;
c N₂H₄·H₂O, DMF, 75 °C, 2 d; d 2 M-HCl, CHCl₃, 65 °C, 5 h;
e TsCl, pyridine, NEt₃, r.t., overnight

Scheme 1. Synthesis of *N*-benzyl- α,ω -bis(*p*-toluenesulfonylamide)s.

minimal functional groups such as sulfonamide, phthalimide, or formamide groups were traceable; thus the product structures were strongly supported by the presence or absence of these characteristic absorption bands before and after the reaction. By the measurements of ¹H NMR spectra, interior methylene groups were completely assignable through the spin-spin decoupling technique. In addition, terminal methylene protons distinctive from the interior methylene protons were perfectly assigned by the sequential decoupling with the terminal proton in the functional group. Proton assignments are listed in Table 1.⁴¹

α,ω -Bis(methanesulfonate)s, **14** and **18**, as the synthetic blocks for the terminal macrocycles, were prepared in quantitative yields by the reaction of α,ω -bis(*p*-toluenesulfonylamide)s, **11**^{42,43} and **15**,^{42,43} with ω -bromoalkan-1-ol, **12** and **16**, followed by the mesylation of the resulting α,ω -diols, **13** and **17** (Scheme 2 and Chart 1). The product structures



a K₂CO₃, DMF, r.t., 4 d; b MsCl, CH₂Cl₂, NEt₃, r.t., 2 h;
c NaHCO₃, CH₃CN, 70 °C, 24 h

Scheme 2. Synthesis of building blocks for cyclization.

were supported by the appearance of the functional groups on IR spectra, and confirmed by the complete proton assignments on ¹H NMR spectra shown in Table 2. The synthetic block for the central counter part, *N,N*-bis(3-bromopropyl)-benzylamine **19**, was prepared as crystals in moderate yield by the reaction of benzylamine with 1,3-dibromopropane, followed by addition of hydrobromic acid in acetic acid and evaporation.

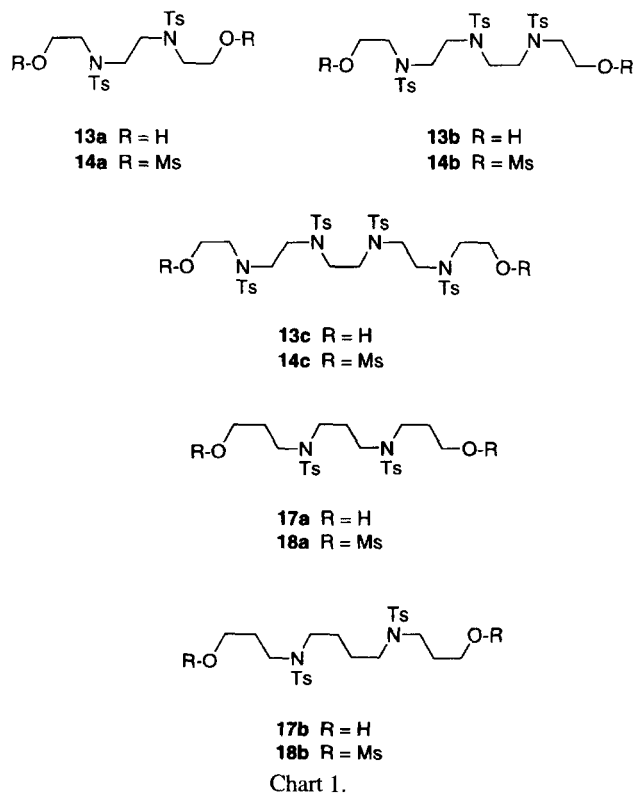


Table 1. ^1H NMR Spectral Data (δ /ppm, in CDCl_3 , TMS, 500 MHz)^{a)}

Compd	C-1	C-2	C-3	C-4	TW	TIN	TOU	ArMe	ArHme	ArHs	NHTs	NHCHO	CHO	$\text{CH}_2\text{C}_6\text{H}_5$
3a	2.91	2.51						2.41	7.27	7.71	5.11			3.42
3b	2.93	1.65	2.41					2.42	7.31	7.70	5.70			3.43
5b	3.60	1.77	3.11		2.75, 3.14			2.39	7.23	7.61				3.62
5c	3.66	1.86	3.15			1.72	2.39, 3.10	2.39	7.24	7.62				3.45
5d	3.64	1.64	1.52	3.09		1.72	2.38, 3.09	2.38	7.24	7.64				3.53
6b	3.31	1.63	3.08		2.69, 3.12			2.43	7.30	7.63		6.28	8.13	3.61
6c	3.37	1.72	3.10			1.69	2.39, 3.10	2.42	7.30	7.64		6.45	8.17	3.46
6d	3.28	1.55	1.55	3.05		1.69	2.42, 3.10	2.42	7.29	7.64		6.14	8.13	3.48
7b	2.91	1.64	3.08		2.64, 3.11			2.41	7.27	7.60	5.26			3.58
								2.42		7.70				
7c	2.94	1.72	3.10				2.36, 3.06	2.41	7.24	7.62	5.38			3.42
								2.42	7.28	7.72				
7d	2.90	1.50	1.57	3.04		1.68	3.09	2.41	7.26	7.63	4.97			3.46
										7.71				
8b	3.64	1.82	3.12		2.71, 3.17	1.80	3.04, 3.05	2.38	7.25	7.61				3.64
								2.39		7.62				
8c	3.66	1.86	3.15			1.68, 1.84	2.38, 3.09	2.38	7.25	7.62				3.45
							3.10	2.39						
8d	3.63	1.63	1.52	3.08		1.80, 1.82	3.08, 3.09	2.37	7.25	7.63				3.46
								2.39	7.26					
9b	3.35	1.71	3.08		2.71, 3.15	1.76	3.03, 3.06	2.41	7.28	7.63		6.41	8.15	3.62
								2.42	7.30	7.62				
9c	3.37	1.76	3.11			1.67, 1.84	3.09, 3.11	2.41	7.27	7.62		6.42	8.15	3.45
									7.29	7.64				
9d	3.27	1.54	1.62	3.05		1.67, 1.85	2.41, 3.10	2.41	7.28	7.63		6.21	8.11	3.44
10b	3.01	1.82	3.06		2.67, 3.13	1.73	3.02, 3.04	2.37	7.24	7.61	5.55			3.61
								2.38	7.26	7.62				
10c	2.93	1.74	3.09			1.60, 1.81	3.04, 3.06	2.39	7.27	7.62	4.80			3.50
							3.07	2.40		7.71				
								2.41						
10d	2.89	1.49	1.57	3.02		1.68, 1.84	3.10	2.39	7.25	7.62	5.07			3.44
								2.40	7.26	7.63				
									7.27	7.70				

a) See Ref. 41 for the significance of the abbreviation of the proton assignment.

Table 2. ^1H NMR Spectral Data (δ /ppm, in CDCl_3 , TMS, 500 MHz)^{a)}

Compd	C-1	C-2	C-3	TW	TIN	TOU	FIN	FOU	ArMe	ArHme	ArHs	CH_3SO_3	OH
13a	3.82	3.25		3.41					2.44	7.33	7.71		2.67
13b	3.80	3.24		3.37, 3.93					2.43	7.32	7.72		2.50
									2.45	7.34	7.73		
13c	3.78	3.24		3.36, 3.37					2.43, 2.45	7.31, 7.33	7.71, 7.74		2.55
				3.39									
14a	4.39	3.45		3.41					2.45	7.36	7.74	3.06	
14b	4.40	3.45		3.36, 3.37					2.44, 2.45	7.35, 7.36	7.74, 7.75	3.05	
14c	4.40	3.45		3.31, 3.33					2.43, 2.44	7.33, 7.35	7.76, 7.77	3.03	
				3.43									
17a	3.73	1.77	3.21		1.90	3.15			2.43	7.31	7.67		2.30
17b	3.72	1.75	3.21				1.59	3.12	2.43	7.31	7.68		2.31
18a	4.30	2.03	3.20		1.89	3.15			2.44	7.33	7.67	3.05	
18b	4.30	2.03	3.19				1.59	3.11	2.44	7.32	7.67	3.05	

a) See Ref. 41 for the significance of the abbreviation of the proton assignment.

Terminal macrocycles including mono-*N*-benzyl substituent, **20**–**26** (Chart 2), were prepared by the reaction of 1,3-dibromopropane or methanesulfonates, **14** or **18**, with α,ω -disulfonamides, **3**, **7**, or **10**, according to the method reported previously for the preparation of per-*N*-tosylated macromonomers (Scheme 3).^{33,44} Product yields were rather

high for these sizes of macromonomers, and no by-product was detected. This implies that no quarternization occurred at the highly nucleophilic tertiary amino group that is benzylated. Product structures were simply supported by their IR spectra, which indicate the absence of any NH vibration band for each starting α,ω -disulfonamide. Analyses of

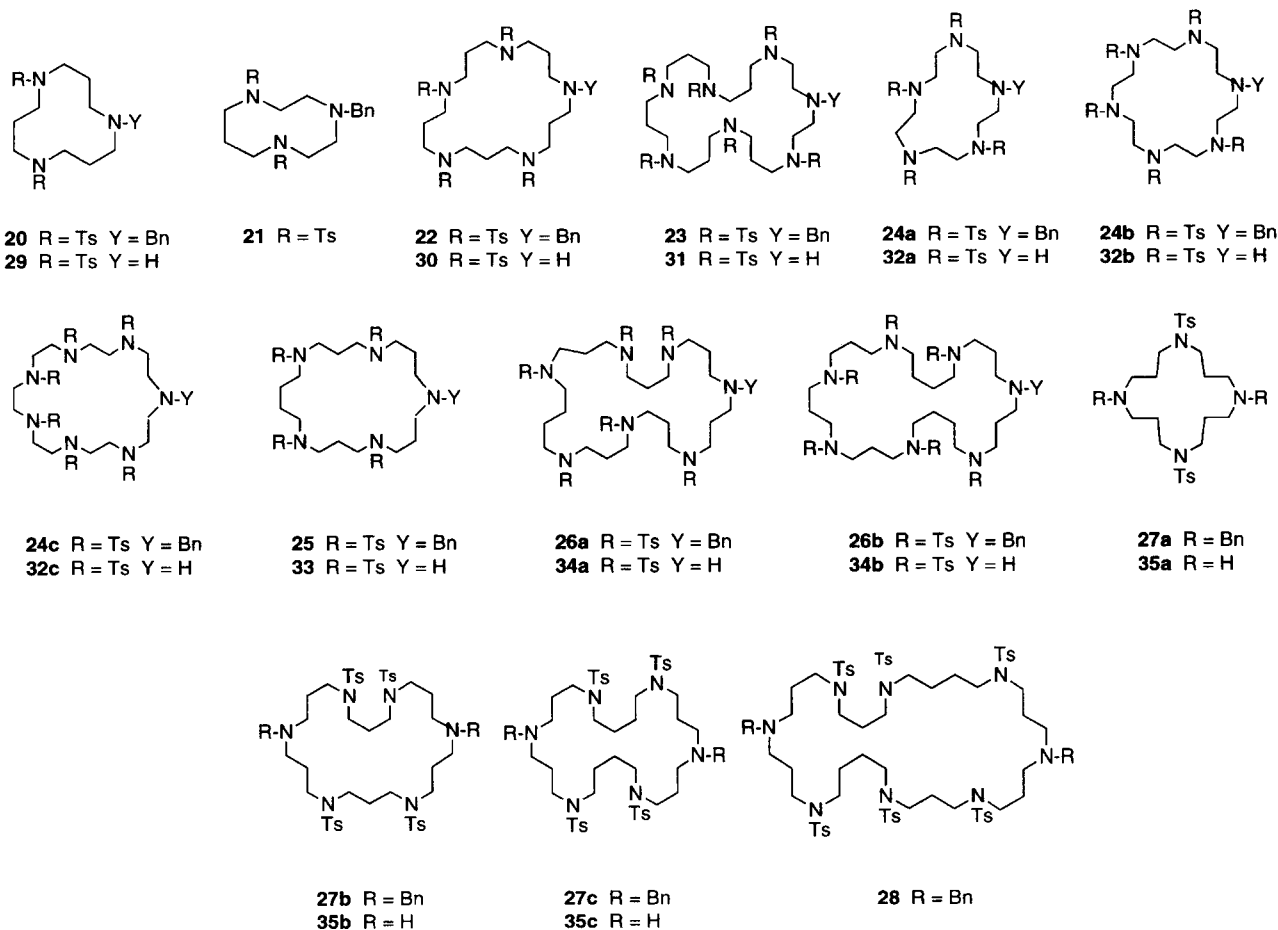
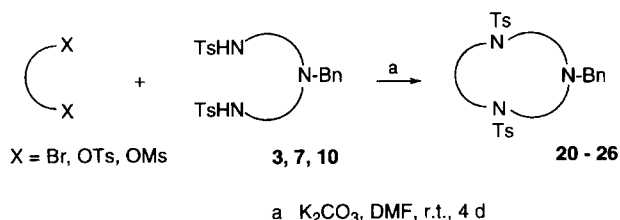
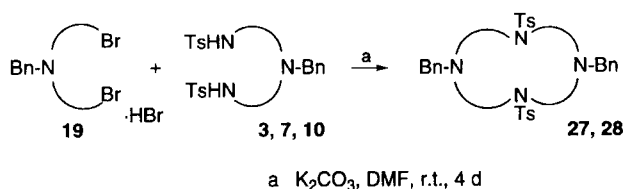


Chart 2.

Scheme 3. Synthesis of *N*-monobenzyl cyclic polyamines.

1H NMR and secondary ion mass spectroscopy (SIMS) spectra gave precise information about their structures. All the macromonocycles synthesized here have a symmetry plane through the *N*-benzyl group. This feature was a good guide to confirm exactly the molecular structure in every case based on the NMR spectrum.

Central parts of macromonocyclic compounds, **27** and **28** (Chart 2), including *N,N'*-dibenzyl group were synthesized by the reaction of α,ω -bis(tosylamide)s, **3**, **7**, or **10**, with **19** under the conditions similar to the preparation of terminal macromonocycles mentioned above (Scheme 4). The structures were perfectly confirmed through 1H NMR (Table 3), SIMS spectrometry, and X-ray crystallography; a crystal structure of **27c** indicated the special molecular characteristic as the largest metal-free ring ever reported;⁴⁵ the real molecule seems to be such a shape possessing two outer wide spaces connected by a central narrow space just like

Scheme 4. Synthesis of *N,N'*-dibenzyl cyclic polyamines.

the structure drawn here as **27c**. The benzyl and the tolyl aromatic rings at N(5) and N(14) in **27c** lie out of the 26-membered ring, respectively. The tolyl group at N(9), however, covers over the ring in the region of the wider space stated above. The disposition of the *N*-substituents seems to make space available for trapping a small molecule among two tolyl groups and the macrocyclic ring.

It is well known that *N*-benzyl group is more resistant to reductive debenzylation than *O*-benzyl group under the same conditions. *O*-Benzyl protecting group in carbohydrate chemistry, for example, is eliminated easily by treatment with 1 kg cm^{-2} hydrogen gas at ambient temperature in the presence of 10% Pd-C catalyst. These conditions, however, don't work for the removal of *N*-benzyl protecting group. We found a consistent procedure that secures quantitative removal of *N*-benzyl protecting group by use of a pressure-resistant reaction vessel made from stainless steel. When an acetic acid solution of *N*-monobenzyl or *N,N'*-di-

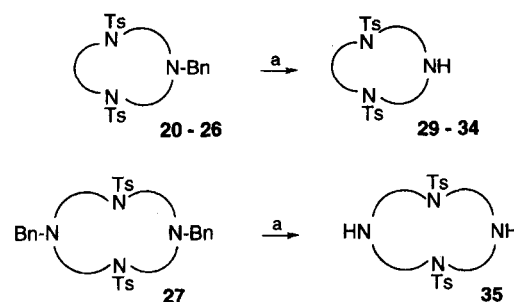
Table 3. ^1H NMR Spectral Data (δ/ppm , in CDCl_3 , TMS, 500 MHz)^{a)}

Compd	TW	TIN	TOU	FIN	FOU	ArMe	ArHme	ArHs	$\text{CH}_2\text{C}_6\text{H}_5$
20		1.72, 1.92	2.43, 3.12, 3.25			2.43	7.30	7.66	3.43
21	2.94, 3.02	2.42	3.22			2.42	7.30	7.65	3.70
22		1.63, 1.69, 1.92	3.09, 3.11, 3.14			2.40, 2.43	7.28, 7.32	7.60, 7.67	3.41
23	2.73, 3.07	1.87, 1.94, 1.96	3.11, 3.13, 3.15			2.39, 2.41	7.22, 7.29	7.54, 7.63	3.62
						2.42	7.31	7.65	
24a	2.60, 2.63, 3.12					2.40, 2.42	7.24, 7.27	7.58, 7.59	3.58
	3.27, 3.32					2.45, 2.46	7.33, 7.34	7.70, 7.72	
24b	2.63, 3.13, 3.27					2.40, 2.44	7.24, 7.33	7.58, 7.70	3.58
	3.32, 3.42					2.45	7.35	7.74	
24c	2.64, 3.14, 3.27					2.42, 2.43	7.30, 7.33	7.68, 7.71	3.60
	3.29					2.44		7.72	
25		1.69, 1.87	3.09, 3.13	1.65	3.10	2.40, 2.43	7.24, 7.31	7.60, 7.67	3.41
26a		1.65, 1.89	3.09, 3.10	1.59	3.09	2.39, 2.40	7.24, 7.28	7.61, 7.63	3.39
						2.41	7.29	7.65	
26b		1.65, 1.89, 1.92	2.34, 3.06, 3.10	1.57	3.07	2.39, 2.41	7.23, 7.29	7.61, 7.64	3.41
			3.13			2.42	7.30	7.65	
27a		1.69	2.39, 3.06			2.41	7.27	7.58	3.48
27b		1.72, 1.92	2.42, 3.08, 3.13			2.40	7.26	7.62	3.46
27c		1.58, 1.68	2.37, 3.08, 3.09			2.40	7.25	7.62	3.44
28		1.66, 1.82	2.35, 2.37, 3.06	1.60	3.06	2.40	7.25, 7.27	7.61, 7.62	3.42
								7.64	

a) See Ref. 41 for the significance of the abbreviation of the proton assignment.

benzyl compounds, **20**–**26** or **27**, in the presence of 10% Pd-C was hydrogenated with around 4.5 kg cm^{-2} at around 75°C in the stainless steel vessel overnight, the corresponding debenzylated compound, **29**–**34** or **35** respectively, was obtained quantitatively as colorless amorphous powder after usual work-up (Scheme 5). The product structure was confirmed straightway by the appearance of NH vibrational absorption band around 3400 cm^{-1} on IR spectrum and by the disappearance of characteristic proton signal of the benzyl group on ^1H NMR spectrum. All the other structural features stated above for molecular symmetry were reflected on the ^1H NMR spectra of the debenzylated compounds as well (Table 4).

As a consequence of the most important part of synthetic works to construct multi-aligned macromonocyclic

a) $\text{H}_2/10\% \text{ Pd-C}$, 4 kg/cm^2 , 3 dScheme 5. Reductive debenzylation with $\text{H}_2/10\% \text{ Pd-C}$.

polyamines, a new synthetic route was developed toward

Table 4. ^1H NMR Spectral Data (δ/ppm , in CDCl_3 , TMS, 500 MHz)^{a)}

Compd	TW	TIN	TOU	FIN	FOU	ArMe	ArHme	ArHs
29		1.72, 1.91	2.68, 3.17, 3.19			2.43	7.31	7.67
31	2.89, 3.08	1.96, 1.98	3.15			2.41	7.30	7.65, 7.69
32a	2.83, 3.14, 3.28					2.44	7.32, 7.33	7.66, 7.72
	3.35, 3.36							
32b	2.73, 3.16, 3.29					2.43	7.30, 7.31, 7.33	7.67, 7.68, 7.72
	3.35, 3.42							
32c	2.80, 3.20, 3.22					2.38, 2.42, 2.44	7.26, 7.28, 7.31	7.61, 7.67, 7.73
	3.24, 3.25, 3.32, 3.41							
33		1.97, 1.99	2.93, 3.14, 3.17	1.70	3.11	2.41, 2.43	7.30, 7.31	7.66
34a		1.62, 1.92, 1.95	3.12, 3.18			2.41, 2.42	7.30, 7.31	7.64, 7.66
34b		1.92, 2.00	2.97, 3.05, 3.09	1.62	3.07, 3.09	2.41, 2.42	7.29, 7.30, 7.31	7.65, 7.66
			3.13					
35b		1.90, 1.98	2.75, 3.13			2.42	7.30	7.64
35c		2.09	2.90, 3.10	1.57	3.12	2.43	7.30	7.63

a) See Ref. 41 for the significance of the abbreviation of the proton assignment.

fourteen, in total, terminal and internal parts of macromonocyclic monoamines and diamines. Among the processes, it is the most striking feature that the presence of the tertiary amino group with benzyl protecting group won't interfere with chain elongation, transformation reaction, and macrocyclization processes by the formation of quaternary ammonium salt. Furthermore, successful synthesis of *N,N*-bis(ω -bromoalkyl)benzylamines was likely to allow us to develop general synthetic route to *N,N'*-dibenzyl macrocyclic polyamines as precursors for internal macrocycles. In addition, one marked improvement is that the *N*-benzyl protecting group is consistently removable in quantitative yield by elevated-pressure catalytic hydrogenation. In consequence, highly useful macromonocyclic building-blocks were made available for alignment of macrocycles in a variety of manners.

Experimental

General: The ^1H NMR spectra were recorded on a JEOL GSX-500S (500 MHz) spectrometer with Me_4Si as an internal standard in CDCl_3 unless otherwise mentioned; chemical shifts (δ) and coupling constants (J) are in parts per million (ppm) and hertz (Hz), respectively. Signal assignments were performed by aid of ^1H - ^1H decoupling method. IR spectra were obtained on a Shimadzu IR-27 and Shimadzu FT-IR 8100M spectrophotometers. Merck silica-gel 60 (Art. 7734, 0.063–0.02) was used for column chromatography, and fragmented Merck precoated silica-gel 60 F_{254} plates (Art. 5715, 20×5 cm), for TLC. Product spots on TLC were detected either under a UV-light lamp or in an iodine vapor bath. The uncorrected melting points were measured in a bilayered coverglass (18 m/m, thickness 0.13–0.17 mm) with a micro-melting point apparatus (Yanagimoto Seisakusho, Serial No. 2647). Secondary ion mass spectra (SIMS) were measured with a Hitachi M-80, and FAB(+)-MS and electron spray ionization mass spectra (ESI-MS), with JEOL JMS-HX110 spectrometers. Elemental analyses were performed in the micro analysis laboratory of this Institute.

Materials: *N*-(2-Bromoethyl)-*p*-toluenesulfonamide (**2a**) and *N*-(3-bromopropyl)-*p*-toluenesulfonamide (**2b**) were prepared by the previous method.³³ *N*-(2-Bromoethyl)phthalimide (**4a**), *N*-(3-bromopropyl)phthalimide (**4b**), and *N*-(4-bromobutyl)phthalimide (**4c**) were prepared by the Gabriel method.⁴⁶ *N,N'*-Ditosyl-1,2-ethanediamine (**11a**), *N*¹,*N*³,*N*⁵-tritosyl-3-aza-1,5-pentanediamine (**11b**), *N*¹,*N*³,*N*⁶,*N*⁸-tetratosyl-3,6-diaza-1,8-octanediamine (**11c**), *N,N'*-ditosyl-1,3-propanediamine (**15a**), and *N,N'*-ditosyl-1,4-butanediamine (**15b**) were prepared by the previous method.^{42,43}

***N*⁴-Benzyl-*N*¹,*N*⁷-ditosyl-4-aza-1,7-heptanediamine (**3b**):** In acetonitrile (80 mL), benzylamine (**1**, 1.2 g) and *N*-tosyl-3-bromopropylamine (**2b**, 7.53 g, 2.3 mol equiv to **1**) were stirred in the presence of sodium hydrogen carbonate (9.41 g, 10 mol equiv to **1**) at 70 °C for 70 h. After filtration, the solvent was removed under reduced pressure, and the residue was chromatographed on a silica-gel column with chloroform–acetone (4 : 1 v/v) to give 5.89 g of **3b** (99% yield) as viscous liquid. Calcd for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_4\text{S}_2$: C, 61.22; H, 6.66; N, 7.93; S, 12.11%. Found: C, 60.87; H, 6.55; N, 7.67; S, 12.19%. IR (neat) ν 3290 (NH), 1320 and 1150 (SO_2) cm^{-1} . ^1H NMR (CDCl_3), shown in Table 1.

***N*³-Benzyl-*N*¹,*N*⁵-ditosyl-3-aza-1,5-pentanediamine (**3a**):** was obtained by the reaction of **1** with *N*-tosyl-2-bromoethylamine (**2a**) in 99% yield as viscous liquid. Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_4\text{S}_2$: C, 59.85; H, 6.23; N, 8.38; S, 12.78%. Found: C, 59.46; H, 6.12; N, 8.12;

S, 13.02%. IR (neat) ν 3290 (NH), 1320 and 1155 (SO_2) cm^{-1} . ^1H NMR (CDCl_3), shown in Table 1.

***N*⁸-Benzyl-1,15-diphthalimido-*N*⁴,*N*¹²-ditosyl-4,8,12-triazapentadecane (**5c**):** In DMF (45 mL), **3b** (1.76 g) *N*-(3-bromopropyl)phthalimide (**4b**, 3.3 g; 3 mol equiv to **3b**) and potassium carbonate (6.9 g, 15 mol equiv to **3b**) were stirred at r.t. for 6 d. After filtration, the solvent was removed under reduced pressure, and the residue was chromatographed on a silica-gel column with chloroform–acetone (95 : 5 (300 mL) to 9 : 1 (300 mL) v/v) to give 3.00 g of **5c** (99% yield) as viscous liquid. Calcd for $\text{C}_{49}\text{H}_{53}\text{N}_5\text{O}_8\text{S}_2$: C, 65.09; H, 5.91; N, 7.75; S, 7.09%. Found: C, 64.96; H, 5.85; N, 7.74; S, 7.15%. IR (neat) ν 1771 and 1710 (C=O), 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 1.

***N*⁷-Benzyl-1,13-diphthalimido-*N*⁴,*N*¹⁰-ditosyl-4,7,10-triazatridecane (**5b**)** was obtained by the reaction of **3a** with **4b** in 99% yield as viscous liquid. Calcd for $\text{C}_{47}\text{H}_{49}\text{N}_5\text{O}_8\text{S}_2$: C, 64.44; H, 5.64; N, 8.00; S, 7.32%. Found: C, 64.52; H, 5.48; N, 8.06; S, 7.33%. IR (neat) ν 1770 and 1710 (C=O), 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 1.

***N*⁹-Benzyl-1,17-diphthalimido-*N*⁵,*N*¹³-ditosyl-5,9,13-triazaheptadecane (**5d**)** was obtained by the reaction of **3b** with *N*-(4-bromobutyl)phthalimide (**4c**) in 99% yield as viscous liquid. Calcd for $\text{C}_{51}\text{H}_{57}\text{N}_5\text{O}_8\text{S}_2$: C, 65.71; H, 6.16; N, 7.51; S, 6.88%. Found: C, 65.40; H, 5.96; N, 7.26; S, 6.85%. IR (neat) ν 1770 and 1710 (C=O), 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 1.

***N*⁸-Benzyl-*N*¹,*N*¹⁵-diformyl-*N*⁴,*N*¹²-ditosyl-4,8,12-triaza-1,15-pentadecanediamine (**6c**):** In DMF (60 mL), **5c** (2.97 g) and hydrazine hydrate (3 mL, 20 mol equiv to **5c**) were stirred at 75 °C for 2 d. The solvents were removed under reduced pressure and chloroform was added to the residue. The resulting precipitate was removed by filtration. The filtrate was evaporated and chromatographed on a silica-gel column with chloroform–methanol (93 : 7 v/v) to give 1.74 g (76% yield) of **6c** as viscous liquid. Calcd for $\text{C}_{35}\text{H}_{49}\text{N}_5\text{O}_6\text{S}_2$: C, 60.06; H, 7.06; N, 10.01; S, 9.16%. Found: C, 60.22; H, 7.00; N, 10.12; S, 9.02%. IR (neat) ν 3300 (NH), 1670 (C=O), 1330 and 1155 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 1.

***N*⁷-Benzyl-*N*¹,*N*¹³-diformyl-*N*⁴,*N*¹⁰-ditosyl-4,7,10-triaza-1,13-tridecanediamine (**6b**)** was obtained by the reaction of **5b** with hydrazine in 95% yield as viscous liquid. Calcd for $\text{C}_{33}\text{H}_{45}\text{N}_5\text{O}_6\text{S}_2$: C, 58.99; H, 6.75; N, 10.43; S, 9.55%. Found: C, 58.62; H, 6.73; N, 10.31; S, 9.62%. IR (neat) ν 3300 (NH), 1670 (C=O), 1330 and 1155 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 1.

***N*⁹-Benzyl-*N*¹,*N*¹⁷-diformyl-*N*⁵,*N*¹³-ditosyl-5,9,13-triaza-1,17-heptadecanediamine (**6d**)** was obtained by the reaction of **5d** with hydrazine in DMF in 90% yield as viscous liquid. Calcd for $\text{C}_{37}\text{H}_{53}\text{N}_5\text{O}_6\text{S}_2$: C, 61.04; H, 7.34; N, 9.62; S, 8.81%. Found: C, 61.09; H, 7.35; N, 9.38; S, 8.54%. IR (neat) ν 3300 (NH), 1670 (C=O), 1330 and 1155 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 1.

***N*⁸-Benzyl-*N*¹,*N*⁴,*N*¹²,*N*¹⁵-tetratosyl-4,8,12-triaza-1,15-pentadecanediamine (**7c**):** To **6c** (1.70 g) in chloroform (5 mL) was added 6 M HCl (10 mL, 1 M = 1 mol dm^{-3}) and the mixture was stirred at 70 °C for 4 h. The reaction mixture was evaporated to dryness under reduced pressure. To the residue were added pyridine (60 mL) and tosyl chloride (1.16 g, 2.5 mol equiv to **6c**) and the mixture was stirred at r.t. for 12 h. After evaporation, the residue was chromatographed on a silica-gel column with chloroform–acetone (9 : 1 (300 mL) then 4 : 1 (300 mL) v/v) to afford 1.27 g (55% yield) of **7c** as viscous liquid. Calcd for $\text{C}_{47}\text{H}_{61}\text{N}_5\text{O}_8\text{S}_4$: C, 59.28; H, 6.46; N, 7.36; S, 13.47%. Found: C, 58.95; H, 6.43; N, 7.27;

S, 13.45%. IR (neat) ν 3290 (NH), 1330 and 1155 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*⁷-Benzyl-*N*¹,*N*⁴,*N*¹⁰,*N*¹³-tetratosyl-4, 7, 10- triaza- 1, 13- tridecanediamine (7b) and *N*⁹-Benzyl-*N*¹,*N*⁵,*N*¹³,*N*¹⁷-tetratosyl-5,9,13-triaza-1,17-heptadecanediamine (7d)** were obtained as viscous liquids in 51 and 69% yields, respectively.

7b: IR (neat) ν 3290 (NH), 1320 and 1155 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

7d: Calcd for $\text{C}_{49}\text{H}_{65}\text{N}_5\text{O}_8\text{S}_4$: C, 60.03; H, 6.68; N, 7.15; S, 13.08%. Found: C, 59.77; H, 6.56; N, 6.92; S, 13.21%. IR (neat) ν 3260 (NH), 1330 and 1155 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*¹¹-Benzyl-1,21-diphthalimido-*N*⁴,*N*⁸,*N*¹⁴,*N*¹⁸-tetratosyl-4,8, 11,14,18-pentaazaheneicosane (8b)** was prepared by the method similar to that of preparation of **5** by the reaction of tosylamides **3** with **4**; thus, the reaction of tosylamide **7b** with **4b** afforded **8b** as amorphous powder in 91% yield. Calcd for $\text{C}_{67}\text{H}_{75}\text{N}_7\text{O}_{12}\text{S}_4$: C, 61.97; H, 5.82; N, 7.55; S, 9.88%. Found: C, 61.88; H, 5.80; N, 7.36; S, 9.82%. IR (KBr) ν 1770 and 1710 (C=O), 1330 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*¹²-Benzyl-1,23-diphthalimido-*N*⁴,*N*⁸,*N*¹⁶,*N*²⁰-tetratosyl-4,8, 12,16,20-pentaazatricosane (8c)** was prepared by the reaction of tosylamide **7c** with **4b** as viscous liquid in 85% yield. Calcd for $\text{C}_{69}\text{H}_{79}\text{N}_7\text{O}_{12}\text{S}_4$: C, 62.47; H, 6.00; N, 7.39; S, 9.67%. Found: C, 62.30; H, 6.15; N, 7.35; S, 9.45%. IR (neat) ν 1770 and 1710 (C=O), 1330 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*¹³-Benzyl-1,25-diphthalimido-*N*⁵,*N*⁹,*N*¹⁷,*N*²¹-tetratosyl-5,9, 13,17,21-pentaazapentacosane (8d)** was prepared by the reaction of tosylamide **7c** with **4c** as amorphous powder in 95% yield. Calcd for $\text{C}_{71}\text{H}_{83}\text{N}_7\text{O}_{12}\text{S}_4$: C, 62.95; H, 6.18; N, 7.24; S, 9.47%. Found: C, 62.71; H, 6.10; N, 7.17; S, 9.60%. IR (KBr) ν 1770 and 1710 (C=O), 1330 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*¹¹-Benzyl-*N*¹,*N*²¹-diformyl-*N*⁴,*N*⁸,*N*¹⁴,*N*¹⁸-tetratosyl-4,8,11, 14,18-pentaaza-1,21-heneicosanediamine (9b)** was prepared from **8b** by the method similar to that of preparation of **6** from phthalimides **5** with hydrazine hydrate; 88% yield as viscous liquid. Calcd for $\text{C}_{53}\text{H}_{71}\text{N}_7\text{O}_{10}\text{S}_4$: C, 58.16; H, 6.54; N, 8.96; S, 11.72%. Found: C, 57.91; H, 6.34; N, 8.84; S, 11.71%. IR (neat) ν 3300 (NH), 1670 (C=O), 1330 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*¹²-Benzyl-*N*¹,*N*²³-diformyl-*N*⁴,*N*⁸,*N*¹⁶,*N*²⁰-tetratosyl-4,8,12, 16,20-pentaaza-1,23-tricosanediamine (9c)** was prepared from **8c**; 90% yield as viscous liquid. Calcd for $\text{C}_{55}\text{H}_{75}\text{N}_7\text{O}_{10}\text{S}_4$: C, 58.85; H, 6.74; N, 8.74; S, 11.43%. Found: C, 58.57; H, 6.70; N, 8.82; S, 11.05%. IR (neat) ν 3300 (NH), 1670 (C=O), 1330 and 1142 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*¹³-Benzyl-*N*¹,*N*²⁵-diformyl-*N*⁵,*N*⁹,*N*¹⁷,*N*²¹-tetratosyl-5,9,13, 17,21-pentaaza-1,25-pentacosanediamine (9d)** was prepared from **8d**; 90% yield as viscous liquid. Calcd for $\text{C}_{57}\text{H}_{79}\text{N}_7\text{O}_{10}\text{S}_4$: C, 59.50; H, 6.92; N, 8.52; S, 11.15%. Found: C, 59.39; H, 6.88; N, 8.38; S, 11.13%. IR (neat) ν 3400 (NH), 1670 (C=O), 1330 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*¹¹-Benzyl-*N*¹,*N*⁴,*N*⁸,*N*¹⁴,*N*¹⁸,*N*²¹-hexatosyl-4,8,11,14,18-pentaaza-1,21-heneicosanediamine (10b)** was prepared from **9b** by the method similar to that of preparation of tosylamides **7** from formamide **6** through several processes described above; 93% yield as amorphous powder. Calcd for $\text{C}_{65}\text{H}_{83}\text{N}_7\text{O}_{12}\text{S}_6$: C, 57.97; H, 6.21; N, 7.28; S, 14.29%. Found: C, 58.07; H, 6.22; N, 6.93; S, 11.59%. IR (KBr) ν 3290 (NH), 1330 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*¹²-Benzyl-*N*¹,*N*⁴,*N*⁸,*N*¹⁶,*N*²⁰,*N*²³-hexatosyl-4,8,12,16,20-pentaaza-1,23-tricosanediamine (10c)** was prepared from **9c**; 95% yield as amorphous powder. Calcd for $\text{C}_{67}\text{H}_{87}\text{N}_7\text{O}_{12}\text{S}_6$: C, 58.53; H, 6.38; N, 7.13; S, 13.99%. Found: C, 58.57; H, 6.16; N, 7.29; S, 13.67%. IR (KBr) ν 3290 (NH), 1325 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*¹³-Benzyl-*N*¹,*N*⁵,*N*⁹,*N*¹⁷,*N*²¹,*N*²⁵-hexatosyl-5,9,13,17,21-pentaaza-1,25-pentacosanediamine (10d)** was prepared from **9d**; 77% yield as amorphous powder. Calcd for $\text{C}_{69}\text{H}_{91}\text{N}_7\text{O}_{12}\text{S}_6$: C, 59.07; H, 6.54; N, 6.99; S, 13.71%. Found: C, 58.97; H, 6.44; N, 6.89; S, 13.76%. IR (KBr) ν 3290 (NH), 1330 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 1.

***N*³,*N*⁶-Ditosyl-3,6-diaza-1,8-octanediol (13a):** A mixture of *N*,*N*'-ditosyl-1,2-ethanediamine (**11a**, 5.011 g), 2-bromoethanol (**12**, 3.909 g; 2.3 mol equiv to **11a**), and anhydrous potassium carbonate (18.796 g, 10 mol equiv to **11a**) was heated in DMF (120 mL) at 75 °C for 2 d. The reaction mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was recrystallized by addition of methanol and 5.289 g (85% yield) of **13a** was obtained as colorless crystals; mp 150–152 °C. Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_6\text{S}_2$: C, 52.61; H, 6.18; N, 6.14; S, 14.05%. Found: C, 52.93; H, 6.20; N, 6.21; S, 13.93%. IR (KBr) ν 3350 (OH), 1325 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 2.

***N*³,*N*⁶,*N*⁹-Tritosyl-3,6,9-triaza-1,11-undecanediol (13b)** was prepared by the reaction of *N*¹,*N*³,*N*⁵-tritosyl-3-aza-1,5-pentanediamine (**11b**) with 2-bromoethanol (**12**) in the presence of anhydrous potassium carbonate in DMF; 99% yield, as viscous liquid. Calcd for $\text{C}_{29}\text{H}_{39}\text{N}_3\text{O}_8\text{S}_2$: C, 53.27; H, 6.01; N, 6.43; S, 14.71%. Found: C, 52.84; H, 6.02; N, 6.40; S, 14.57%. IR (neat) ν 3530 (OH), 1325 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 2.

***N*³,*N*⁶,*N*⁹,*N*¹²-Tetratosyl-3,6,9,12-tetraaza-1,14-tetradecanediol (13c)** was prepared by the reaction of *N*¹,*N*³,*N*⁶,*N*⁸-tetratosyl-3,6-diaza-1,8-octanediamine (**11c**) with 2-bromoethanol (**12**) in the presence of anhydrous potassium carbonate in DMF; 70% yield, as colorless crystals from methanol; mp 195–197 °C. Calcd for $\text{C}_{38}\text{H}_{50}\text{N}_4\text{O}_{10}\text{S}_4$: C, 53.62; H, 5.92; N, 6.58; S, 15.07%. Found: C, 53.35; H, 5.87; N, 6.58; S, 14.92%. IR (KBr) ν 3410 (OH), 1330 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 2.

***N*,*N*'-Bis(2-mesyloxyethyl)-*N*,*N*'-ditosyl-1,2-ethanediamine (14a):** A mixture of **13a** (3.0 g), mesyl chloride (1.27 mL, 2.5 mol equiv to **13a**), and triethylamine (3.17 mL, 2.5 times in volume to MsCl volume) in dichloromethane (80 mL) was stirred at r.t. for 90 min. The solvents were removed under reduced pressure and the residue was recrystallized from methanol to give 3.4 g (84%) of **14a** as colorless crystals; mp 144–145 °C. Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_{10}\text{S}_4$: C, 43.12; H, 5.26; N, 4.57; S, 20.93%. Found: C, 43.28; H, 5.22; N, 4.47; S, 20.83%. IR (KBr) ν 1340, 1330 and 1150 cm^{-1} (SO_2). A single crystal obtained from chloroform-methanol as colorless plates was analyzed by X-ray crystallography.⁴⁷ $^1\text{H NMR}$ (CDCl_3), shown in Table 2.

***O*¹,*O*¹¹-Dimesyl-*N*³,*N*⁶,*N*⁹-tritosyl-3,6,9-triaza-1,11-undecanediol (14b)** was prepared by the reaction of **13b** with mesyl chloride in the presence of triethylamine in dichloromethane; 90% yield, as amorphous powder. Calcd for $\text{C}_{31}\text{H}_{43}\text{N}_3\text{O}_{12}\text{S}_5$: C, 45.96; H, 5.35; N, 5.19; S, 19.79%. Found: C, 45.78; H, 5.26; N, 4.96; S, 19.76%. IR (KBr) ν 1340, 1330 and 1150 cm^{-1} (SO_2). $^1\text{H NMR}$ (CDCl_3), shown in Table 2.

***O*¹,*O*¹⁴-Dimesyl-*N*³,*N*⁶,*N*⁹,*N*¹²-tetratosyl-3,6,9,12-tetraaza-1, 14-tetradecanediol (14c)** was prepared by the reaction of **13c** with mesyl chloride in the presence of triethylamine in dichloromethane; 99% yield, as amorphous powder. Calcd for $\text{C}_{40}\text{H}_{54}\text{N}_4\text{O}_{14}\text{S}_6$: C, 47.69; H, 5.40; N, 5.56; S, 19.01%. Found: C, 47.41; H, 5.34; N,

5.38; S, 18.94%. IR (KBr) ν 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 2.

N^4,N^8 -Ditosyl-4,8-diaza-1,11-undecanediol (17a): A mixture of **15a** (4.30 g), 3-bromo-1-propanol (**16**, 3.59 g; 2.3 mol equiv to **15a**), and potassium carbonate (15.53 g, 10 mol equiv to **15a**) in DMF (140 mL) was stirred at 70 $^\circ\text{C}$ for a day. After filtration through Celite, the filtrate was evaporated under reduced pressure, and the residue was chromatographed on a silica-gel column with chloroform–acetone (8 : 2 v/v) (300 mL) followed by chloroform–methanol (9 : 1 v/v) (300 mL) to give 5.60 g (99% yield) of **17a** as pale yellow viscous liquid. Calcd for $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_6\text{S}_2$: C, 55.40; H, 6.87; N, 5.62; S, 12.86%. Found: C, 55.36; H, 6.87; N, 5.52; S, 12.70%. IR (neat) ν 3530 (OH), 1330 and 1155 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 2.

N^4,N^9 -Ditosyl-4,9-diaza-1,12-dodecanediol (17b) was prepared by the reaction of **15b** with **16** in DMF in the presence of potassium carbonate to give **17b** in 87% yield as colorless crystals (recryst. from methanol); mp 126–127 $^\circ\text{C}$. Calcd for $\text{C}_{24}\text{H}_{36}\text{N}_2\text{O}_6\text{S}_2$: C, 56.22; H, 7.08; N, 5.47; S, 12.51%. Found: C, 56.20; H, 7.09; N, 5.38; S, 12.36%. IR (KBr) ν 3550 (OH), 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 2.

O^1,O^{11} -Dimesyl- N^4,N^8 -ditosyl-4,8-diaza-1,11-undecanediol (18a): A mixture of **17a** (6.88 g), mesyl chloride (2.70 mL, 2.5 mol equiv to **17a**), and triethylamine (6.67 mL, 2.5 times in volume to MsCl volume) in dichloromethane (90 mL) was stirred at r.t. for 90 min. The solvents were removed under reduced pressure and the residue was chromatographed on a silica-gel column with chloroform–acetone (93 : 7 v/v) (200 mL) followed by (9 : 1 v/v) (200 mL) to give 6.32 g (70% yield) of **18a** as pale yellow viscous liquid. Calcd for $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_{10}\text{S}_4$: C, 45.85; H, 5.85; N, 4.28; S, 19.59%. Found: C, 45.50; H, 5.74; N, 4.02; S, 19.50%. IR (KBr) ν 1340, 1320, 1170, and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 2.

O^1,O^{12} -Dimesyl- N^4,N^9 -ditosyl-4,9-diaza-1,12-dodecanediol (18b) was prepared by the reaction of **17b** with mesyl chloride in the presence of triethylamine in dichloromethane to give **18b** in 75% yield as pale yellow amorphous powder. Calcd for $\text{C}_{26}\text{H}_{40}\text{N}_2\text{O}_{10}\text{S}_4$: C, 46.69; H, 6.03; N, 4.19; S, 19.18%. Found: C, 46.33; H, 5.95; N, 4.17; S, 19.15%. IR (KBr) ν 1340, 1325, 1170, and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 2.

N,N -Bis(3-bromopropyl)benzylamine Hydrobromide (19): A mixture of benzylamine (1.56 g), 1,3-dibromopropane (14.73 g, 5 mol equiv to benzylamine), and sodium hydrogen carbonate (3.67 g, 3 mol equiv to benzylamine) in acetonitrile (80 mL) was heated and stirred at 60 $^\circ\text{C}$ for 22 h. After filtration through Celite, the solvents were removed under reduced pressure and the residue was chromatographed on a silica-gel column with chloroform–acetone (95 : 5 v/v, 200 mL) followed by (9 : 1 v/v, 200 mL) to give colorless salt-free **19** in 37% yield. SIMS (NBA matrix); m/z 348, 350 (M^+H) (Fw = 349.1 for $\text{C}_{13}\text{H}_{19}\text{Br}_2\text{N}$). ^1H NMR (CDCl_3) δ = 2.60 (4H, b-s, $\text{BnN}-\text{CH}_2$), 2.02 (4H, b-s, $\text{BnN}-\text{CH}_2-\text{CH}_2-$), and 3.45 (4H, t, J = 6.5 Hz, CH_2-Br). By addition of 25%-hydrobromic acid in acetic acid to the pure fraction of salt-free **19** collected during column chromatography, the corresponding hydrobromide was obtained as crystals after evaporation of the solvents.

General Procedure for the Synthesis of N -Mono- and N,N' -Dibenzylmacromonocyclic Polyamines (20) through (28). A mixture of N -benzyl- α,ω -bis(tosylamide), **3**, **7**, or **10**, and 1,3-dibromopropane or α,ω -bis(methanesulfonate), **14** or **18**, (1.2 mol equiv to α,ω -bis(tosylamide)) in DMF in the presence of anhydrous potassium carbonate (10 mol equiv to α,ω -bis(tosylamide)) was stirred at ambient temperature for 4 to 7 d. The reaction mixture was

filtered through Celite, and the solvent was removed under reduced pressure. The residue was chromatographed on a silica-gel column eluted with chloroform–acetone (in the variable range from 93 : 7 to 4 : 1 v/v) to afford N -monobenzyl macromonocyclic polyamines (**20**–**26**). Through the similar procedure and molar ratios, N,N' -dibenzyl macromonocyclic polyamines (**27**, **28**) were prepared by the reaction of N -monobenzyl- α,ω -ditosylamides (**3**, **7**, or **10**) with N,N -bis(3-bromopropyl)benzylamine hydrobromide (**19**).

N^1 -Benzyl- N^5,N^9 -ditosyl-1,5,9-triazacyclododecane (20). By the reaction of **3b** with 1,3-dibromopropane, **20** was obtained in 52% yield as colorless crystals (recryst. from methanol); mp 201–203 $^\circ\text{C}$. SIMS (NBA matrix), m/z 570 (M^+H). Calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{O}_4\text{S}_2$ (Fw 569.8): C, 63.24; H, 6.90; N, 7.38; S, 11.26%. Found: C, 63.04; H, 6.88; N, 7.10; S, 11.15%. IR (KBr) ν 1330 and 1160 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 3.

N^4 -Benzyl- N^1,N^7 -ditosyl-1,4,7-triazacyclodecane (21). By the reaction of **3a** with 1,3-dibromopropane, **21** was obtained in 39% yield as colorless amorphous powder. Calcd for $\text{C}_{28}\text{H}_{35}\text{N}_3\text{O}_4\text{S}_2$ (Fw 541.7): C, 62.08; H, 6.51; N, 7.76; S, 11.84%. Found: C, 62.24; H, 6.39; N, 7.50; S, 11.82%. IR (KBr) ν 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 3.

N^1 -Benzyl- N^5,N^9,N^{13},N^{17} -tetraatosyl-1,5,9,13,17-pentaazacycloeicosane (22). By the reaction of **7c** with 1,3-dibromopropane, **22** was obtained in 78% yield as colorless amorphous powder. Calcd for $\text{C}_{50}\text{H}_{67}\text{N}_5\text{O}_8\text{S}_4$ (Fw 994.3): C, 60.39; H, 6.79; N, 7.04; S, 12.90%. Found: C, 60.40; H, 6.56; N, 6.80; S, 12.67%. IR (KBr) ν 1330 and 1160 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 3.

N^4 -Benzyl- $N^1,N^7,N^{11},N^{15},N^{19},N^{23}$ -hexatosyl-1,4,7,11,15,19,23-heptaazacyclohexacosane (23). By the reaction of **10b** with 1,3-dibromopropane, **23** was obtained in 58% yield as colorless amorphous powder. Calcd for $\text{C}_{68}\text{H}_{87}\text{N}_7\text{O}_{12}\text{S}_6$ (Fw 1386.8): C, 58.89; H, 6.32; N, 7.07; S, 13.87%. Found: C, 58.78; H, 6.20; N, 6.74; S, 13.77%. IR (KBr) ν 1330 and 1155 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 3.

N^1 -Benzyl- N^4,N^7,N^{10},N^{13} -tetraatosyl-1,4,7,10,13-pentaazacyclo-pentadecane (24a). By the reaction of **14a** with **3a**, **24a** was obtained in 36% yield as colorless amorphous powder. Calcd for $\text{C}_{45}\text{H}_{55}\text{N}_5\text{O}_8\text{S}_4$ (Fw 922.2): C, 58.61; H, 6.01; N, 7.60; S, 13.91%. Found: C, 58.56; H, 5.94; N, 7.35; S, 14.10%. SIMS (NBA matrix) m/z 922 (M^+H). IR (KBr) ν 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 3.

N^1 -Benzyl- $N^4,N^7,N^{10},N^{13},N^{16}$ -pentatosyl-1,4,7,10,13,16-hexaazacyclooctadecane (24b). By the reaction of **14b** with **3a**, **24b** was obtained in 41% yield as colorless amorphous powder. Calcd for $\text{C}_{54}\text{H}_{66}\text{N}_6\text{O}_{10}\text{S}_5$ (Fw 1119.4): C, 57.93; H, 5.94; N, 7.51; S, 14.32%. Found: C, 57.74; H, 5.80; N, 7.37; S, 14.21%. SIMS (NBA matrix) m/z 1120 (M^+H). IR (KBr) ν 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 3.

N^1 -Benzyl- $N^4,N^7,N^{10},N^{13},N^{16},N^{19}$ -hexatosyl-1,4,7,10,13,16,19-heptaazacycloheneicosane (24c). By the reaction of **14c** with **3a**, **24c** was obtained in 37% yield as colorless amorphous powder. Calcd for $\text{C}_{63}\text{H}_{77}\text{N}_7\text{O}_{12}\text{S}_6$ (Fw 1316.7): C, 57.46; H, 5.90; N, 7.45; S, 14.61%. Found: C, 57.35; H, 5.87; N, 7.35; S, 14.56%. SIMS (NBA matrix) m/z 1316 (M^+H). IR (KBr) ν 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 3.

N^9 -Benzyl- N^1,N^5,N^{13},N^{17} -tetraatosyl-1,5,9,13,17-pentaazacycloheneicosane (25). By the reaction of **18b** with **3b**, **25** was obtained in 58% yield as colorless amorphous powder. Calcd for $\text{C}_{51}\text{H}_{67}\text{N}_5\text{O}_8\text{S}_4$ (Fw 1006.4): C, 60.87; H, 6.71; N, 6.96; S, 12.75%. Found: C, 60.47; H, 6.67; N, 6.93; S, 12.59%. SIMS (NBA matrix) m/z 1006 (M^+H). IR (KBr) ν 1330 and 1150 cm^{-1} (SO_2). ^1H NMR (CDCl_3), shown in Table 3.

***N*¹³-Benzyl-*N*¹,*N*⁵,*N*⁹,*N*¹⁷,*N*²¹,*N*²⁵-hexatosyl-1,5,9,13,17,21,25-heptaazacyclononacosane (26a).** By the reaction of **18b** with **7c**, **26a** was obtained in 52% yield as colorless amorphous powder. Calcd for C₇₁H₉₃N₇O₁₂S₆ (Fw 1428.9): C, 59.68; H, 6.56; N, 6.86; S, 13.47%. Found: C, 59.88; H, 6.56; N, 6.79; S, 13.15%. SIMS (NBA matrix) *m/z* 1428 (M⁺H). IR (KBr) ν 1330 and 1150 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 3.

***N*²²-Benzyl-*N*¹,*N*⁵,*N*⁹,*N*¹³,*N*¹⁸,*N*²⁶-hexatosyl-1,5,9,13,18,22,26-heptaazacyclotriacontane (26b).** By the reaction of **18a** with **7d**, **26a** was obtained in 41% yield as colorless amorphous powder. Calcd for C₇₂H₉₅N₇O₁₂S₆ (Fw 1442.9): C, 59.93; H, 6.64; N, 6.80; S, 13.33%. Found: C, 59.67; H, 6.66; N, 6.49; S, 13.33%. SIMS (NBA matrix) *m/z* 1442 (M⁺H). IR (KBr) ν 1330 and 1155 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 3.

***N*¹,*N*⁹-Dibenzyl-*N*⁵,*N*¹³-ditosyl-1,5,9,13-tetraazacyclohexadecane (27a).** By the reaction of **19** with **3b**, **26a** was obtained in 40% yield as colorless crystals (recryst. from chloroform-methanol); mp 123–124 °C. Calcd for C₄₀H₅₂N₄O₄S₂ (Fw 717.0): C, 67.00; H, 7.31; N, 7.82; S, 8.95%. Found: C, 67.16; H, 7.34; N, 7.93; S, 8.93%. IR (KBr) ν 1330 and 1155 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 3.

***N*¹,*N*¹³-Dibenzyl-*N*⁵,*N*⁹,*N*¹⁷,*N*²¹-tetratosyl-1,5,9,13,17,21-hexaazacyclotetracosane (27b).** By the reaction of **19** with **7c**, **27b** was obtained in 54% yield as colorless amorphous powder. Calcd for C₆₀H₇₈N₆O₈S₄ (Fw 1139.5): C, 63.24; H, 6.90; N, 7.38; S, 11.26%. Found: C, 63.27; H, 6.72; N, 7.05; S, 11.25%. SIMS (NBA matrix) *m/z* 1140 (M⁺H). IR (KBr) ν 1330 and 1150 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 3.

***N*⁵,*N*¹⁸-Dibenzyl-*N*¹,*N*⁹,*N*¹⁴,*N*²²-tetratosyl-1,5,9,14,18,22-hexaazacyclohexacosane (27c).** By the reaction of **19** with **7d**, **27c** was obtained in 59% yield as colorless crystals (recryst. from chloroform-methanol); mp 184–186 °C. Calcd for C₆₂H₈₂N₆O₈S₄ (Fw 1167.6): C, 63.77; H, 7.08; N, 7.20; S, 10.99%. Found: C, 63.55; H, 7.04; N, 7.04; S, 11.12%. IR (KBr) ν 1330 and 1150 cm⁻¹ (SO₂). A single crystal obtained from chloroform-methanol as colorless column-like crystals was analyzed by X-ray crystallography.⁴⁵ ¹H NMR (CDCl₃), shown in Table 3.

***N*⁵,*N*²²-Dibenzyl-*N*¹,*N*⁹,*N*¹³,*N*¹⁸,*N*²⁶,*N*³⁰-hexatosyl-1,5,9,13,18,22,26,30-octaazacyclotetriacontane (28).** By the reaction of **19** with **10d**, **28** was obtained in 43% yield as colorless amorphous powder. Calcd for C₈₂H₁₀₈N₈O₁₂S₆ (Fw 1590.1): C, 61.93; H, 6.85; N, 7.05; S, 12.10%. Found: C, 61.89; H, 6.73; N, 6.88; S, 12.21%. FAB-MS (NBA matrix) *m/z* 1589 (M⁺H). IR (KBr) ν 1330 and 1155 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 3.

General Procedure in Reductive Debenzylation of *N*-Mono- and *N,N'*-Dibenzylmacromonomocyclic Polyamines, **20 through **27**.** A mixture of *N*-benzylated compound, one of **20** through **27**, and 10% Pd-C (1–1/3 part of weight of that *N*-benzylated compound) in acetic acid (20–30 mL) was sealed and stirred in a specially devised reaction tube made from stainless alloy, and reduced with hydrogen gas under the pressure around 4.0 kg cm⁻² at around 70 °C till cessation of hydrogen up-take (mostly in 3 d; when pressure was decreased during the reaction to less than 2.0 kg cm⁻², hydrogen was refilled to the initial level). The reaction mixture after cooling was filtered and washed several times with methanol through Celite and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica-gel column eluted with chloroform-methanol in the ratio ranging from 95 : 5 to 4 : 1 v/v.

***N*¹,*N*⁵-Ditosyl-1,5,9-triazacyclododecane (29).** By the reductive debenzylation method, **20** afforded **29** as amorphous powder

in 99% yield. Calcd for C₂₃H₃₃N₂O₄S₂ (Fw 479.7): C, 57.59; H, 6.94; N, 8.76; S, 13.37%. Found: C, 57.64; H, 6.75; N, 8.58; S, 13.42%. SIMS (NBA matrix) *m/z* 481 (M⁺H). IR (KBr) ν 3350 (NH), 1330 and 1160 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 4.

***N*¹,*N*⁵,*N*⁹,*N*¹³-Tetratosyl-1,5,9,13,17-pentaazacycloeicosane (30).** By the reductive debenzylation method, **22** afforded **30** as amorphous powder in 89% yield.

***N*¹,*N*⁷,*N*¹¹,*N*¹⁵,*N*¹⁹,*N*²³-Hexatosyl-1,4,7,11,15,19,23-heptaazacyclohexacosane (31).** By the reductive debenzylation method, **23** afforded **31** as amorphous powder in 83% yield. IR (KBr) ν 3400 (NH), 1340 and 1160 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 4.

***N*¹,*N*⁴,*N*⁷,*N*¹⁰-Tetratosyl-1,4,7,10,13-pentaazacyclopentadecane (32a).** By the reductive debenzylation method, **24a** afforded **32a** as amorphous powder in 89% yield. Calcd for C₃₈H₅₉N₅O₈S₄ (Fw 842.2): C, 54.19; H, 7.06; N, 8.32; S, 15.23%. Found: C, 54.04; H, 6.91; N, 8.06; S, 15.08%. IR (KBr) ν 3400 (NH), 1320 and 1145 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 4.

***N*¹,*N*⁴,*N*⁷,*N*¹⁰,*N*¹³-Pentatosyl-1,4,7,10,13,16-hexaazacyclooctadecane (32b).** By the reductive debenzylation method, **24b** afforded **32b** as amorphous powder in 71% yield. Calcd for C₄₇H₆₀N₆O₁₀S₅ (Fw 1029.3): C, 54.84; H, 5.88; N, 8.17; S, 15.58%. Found: C, 54.64; H, 5.98; N, 8.06; S, 15.44%. IR (KBr) ν 3240 (NH), 1330 and 1150 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 4.

***N*¹,*N*⁴,*N*⁷,*N*¹⁰,*N*¹³,*N*¹⁶-Hexatosyl-1,4,7,10,13,16,19-heptaazacycloheptacosane (32c).** By the reductive debenzylation method, **24c** afforded **32c** as amorphous powder in 50% yield. Calcd for C₅₆H₇₁N₇O₁₂S₆ (Fw 1226.6): C, 54.83; H, 5.84; N, 7.99; S, 15.69%. Found: C, 54.63; H, 5.75; N, 7.81; S, 15.40%. IR (KBr) ν 3400 (NH), 1330 and 1150 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 4.

***N*¹,*N*⁵,*N*¹³,*N*¹⁷-Tetratosyl-1,5,9,13,17-pentaazacycloheptacosane (33).** By the reductive debenzylation method, **25** afforded **33** as amorphous powder in 86% yield. Calcd for C₄₄H₆₁N₅O₈S₄ (Fw 916.2): C, 57.68; H, 6.71; N, 7.64; S, 14.00%. Found: C, 57.71; H, 6.54; N, 7.52; S, 14.08%. SIMS (NBA matrix) *m/z* 916 (M⁺H). IR (KBr) ν 3370 (NH), 1330 and 1150 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 4.

***N*¹,*N*⁵,*N*⁹,*N*¹⁷,*N*²¹,*N*²⁵-Hexatosyl-1,5,9,13,17,21,25-heptaazacyclononacosane (34a).** By the reductive debenzylation method, **26a** afforded **34a** as amorphous powder in 75% yield. Calcd for C₆₄H₈₇N₇O₁₂S₆ (Fw 1338.8). SIMS (NBA matrix) *m/z* 1340 (M⁺H). IR (KBr) ν 3370 (NH), 1330 and 1150 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 4.

***N*¹,*N*⁵,*N*⁹,*N*¹³,*N*¹⁸,*N*²⁶-Hexatosyl-1,5,9,13,18,22,26-heptaazacyclotriacontane (34b).** By the reductive debenzylation method, **26b** afforded **34b** as amorphous powder in 75% yield. Calcd for C₆₅H₈₉N₇O₁₂S₆ (Fw 1352.8): C, 57.71; H, 6.63; N, 7.25; S, 14.22%. Found: C, 57.81; H, 6.49; N, 6.94; S, 14.22%. SIMS (NBA matrix) *m/z* 1352 (M⁺H). IR (KBr) ν 3370 (NH), 1330 and 1150 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 4.

***N*¹,*N*⁹-Ditosyl-1,5,9,13-tetraazacyclohexadecane (35a).** By the reductive debenzylation method, **27a** afforded **35a** as amorphous powder in 90% yield. Calcd for C₂₆H₄₀N₄O₄S₂ (Fw 536.7): C, 58.18; H, 7.51; N, 10.44; S, 11.95%. Found: C, 57.93; H, 7.43; N, 10.15; S, 11.80%. IR (KBr) ν 3370 (NH), 1330 and 1150 cm⁻¹ (SO₂). ¹H NMR (CDCl₃), shown in Table 4.

***N*¹,*N*⁵,*N*¹³,*N*¹⁷-Tetratosyl-1,5,9,13,17,21-hexaazacyclotetracosane (35b).** By the reductive debenzylation method, **27b** afforded **35b** as amorphous powder in 86% yield. Calcd for

C₄₆H₆₆N₆O₈S₄ (Fw 959.3): C, 57.90; H, 6.94; N, 8.76; S, 13.37%. Found: C, 57.59; H, 6.83; N, 8.95; S, 13.41%. IR (KBr) ν 3400 (NH), 1330 and 1150 cm⁻¹ (SO₂). ¹HNMR (CDCl₃), shown in Table 4.

N¹,N⁹,N¹⁴,N²²-Tetratosyl- 1, 5, 9, 14, 18, 22-hexaazacyclohexacosane (35c). By the reductive debenzoylation method, **27c** afforded **35c** as amorphous powder in 95% yield. Calcd for C₄₈H₇₀N₆O₈S₄ (Fw 987.4): C, 58.39; H, 7.15; N, 8.51; S, 12.99%. Found: C, 58.11; H, 7.10; N, 8.38; S, 12.78%. IR (KBr) ν 3400 (NH), 1330 and 1150 cm⁻¹ (SO₂). ¹HNMR (CDCl₃), shown in Table 4.

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