Design and Synthesis of Macromonocyclic Polyamines Composed of Natural Methylene Arrays

Masaaki IWATA* and Hiroyoshi KUZUHARA
RIKEN (The Institute of Physical and Chemical Research),
Wako, Saitama 351-01
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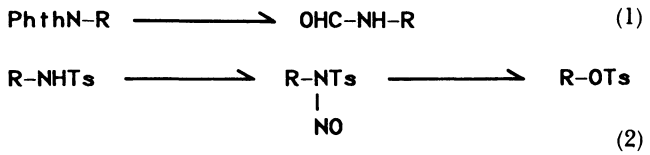
A general synthetic method applicable to acyclic and cyclic polyamines was developed. The methodology was exemplified by systematical synthesis of twelve macromonocyclic polyamines, **1** ([17]N_4) through **12** ([35]N_8), composed of the combination of four natural polyamine segments, spermidine, spermine, thermine, and thermospermine. These twelve designed macrocycles are exhausted numbers of possible structures defined by three arbitrarily chosen criteria concerning with methylene chain arrays and nitrogen content (four to eight). The common elements of the structural characteristics were analyzed and were found to be reduced to readily available three classes of simple *N,N'*-ditosylalkanediamines derived from diamines and triamine. Nitrogen content was increased systematically through the reaction of *N,N'*-ditosylalkanediamine with one of three ω-phthalimidated electrophiles followed by regeneration of the same functionality at symmetrical both terminals as the starting materials via a series of transformation reaction, in excellent yields. Tractable formamide intermediate profits the facile synthesis of acyclic polyamines with long chains. Cyclization was achieved, under high dilution conditions, through the reaction of α,ω-bis(tosylamide) with α,ω-ditosylates in DMF in the presence of cesium carbonate. The cyclization occurred in practical synthetic yields even in the formation of multi-membered ring when the shorter electrophile and the longest α,ω-bis(tosylamide) reacted.

Knowledge of biological importance of natural polyamines as one of substances controlling cell functions[1] has stimulated much interest in intrinsic biological role of amino groups involved in, through the synthesis of selectively modified spermidines[2a] or through the studies on biological activities of polyamine analogues.[2b,c] Ubiquitous natural polyamines, spermidine and spermine, and rare species-specific polyamines, thermine[3a] and thermospermine,[3b] are correlated structurally in a sense of disposition of methylene chain blocks, in which both types of polyamines are composed, mysteriously, of the combination of the contiguous three and/or four methylene chain blocks. Difference lies only in the order of the methylene block disposed along the polyamine chain. Biosynthetically, this implys only the limited numbers of amino acid sources, methionine and ornithine. However, profound nature of their sequence might be concealed in their biological function because of their species-specific beings.

Cyclic polyamines, in which the studies had been initiated based on the interest in complexing reagents with high stability and/or selectivity for metal ions,[4a,b] have extended recently their subject fields in search of functions such as molecule or ion receptors, analogous to but much more different from crown ethers, which effect such functions as recognition, regulation, transport, and catalysis for guest molecules or ions.[4c] Since these functions are highly dependent on the molecular design of the macrocycles, synthetic feasibility of a given molecular architecture is crucial to access for investigation. The strategy in most cases has been to elaborate the substituted acyclic polyamine backbone from a simple amine and then close macrocycle late in the synthesis. Prior derivatization of a polyamine building block has resorted to rather limited methods.[2a,4d,e,f] Presently, the most effective molecular architecture for designed cyclic polyamines has been carried out through four main processes; (a) the synthesis of acyclic polyamines with α,ω-bis(tosylamide)s as nucleophiles, and (b) of electrophiles with electron-withdrawing groups at both terminals, followed by (c) cyclization between nucleophiles and electrophiles, and, finally, (d) deprotection of the protecting groups on the amino groups.[5] All the presently known methods, however, suffer from some synthetic drawback especially, in (a), (b), and (c) steps for efficient and generally adaptable architecture. In (a) step, it is desirable to accommodate every type of methylene chain blocks and to regenerate efficiently the same nucleophilic functionality in the shortest procedure.[2a] In (b) step, it is ideal to accommodate the tosyloxy group at both terminals.[6] In addition, when designed macrocycles might be constructed through several couples of α,ω-nucleophiles and α,ω-electrophiles in (c) step, it is ideal to select readily best couples according to a certain guiding principle.

Recently, we have developed two elemental reactions; the transformation reaction of phthalimides to formamides[7] (Eq. 1) and the rearrangement reaction of *N*-nitroso sulfonamides, which are quantitatively prepared by nitrosation of the corresponding sulfonamides, to tosylate[8] (Eq. 2). Through the



preliminary investigations concerning with applicability of the elemental reactions,[9] a new plan of molecular architecture for macromonocyclic polyamines was emerged. In the plan, firstly, our concern

was to provide cyclic polyamines, in which all the methylene blocks in the ring are composed of natural methylene arrays. This effort might provide functionally unique macrocycles which may reveal the biological significance of mysterious natural methylene arrays and of biological role of primary amino groups. Secondary, our concern was to elongate chain as long as possible, in order to know how much extent the elemental reactions could be tenable in polyamine synthesis. Therefore, most of the problems involved in the conventional methods are expected to be solved through the present study.

Results and Discussion

Concept of Design and Specification: In design of cyclic polyamines, three criteria, concerning with methylene chain arrays and amine content, were defined to limit arbitrariness of the structures and to reduce numbers of targets; i) every two or three contiguous methylene blocks bisected by nitrogen atoms are comparable to one of natural polyamine segments, spermidine, spermine, thermine, and thermospermine, ii) the cycle includes these four natural polyamine arrays at least once in the chain, and iii) four through eight nitrogen atoms exist in the chain. These three criteria generate logically twelve polyamines, **1** ([17]N_4) through **12** ([35]N_8), as exhausted numbers of possible structures to be synthesized. In order to minimize synthetic steps of the defined macrocycles, the common elements of the structural characteristics were analyzed; according to their

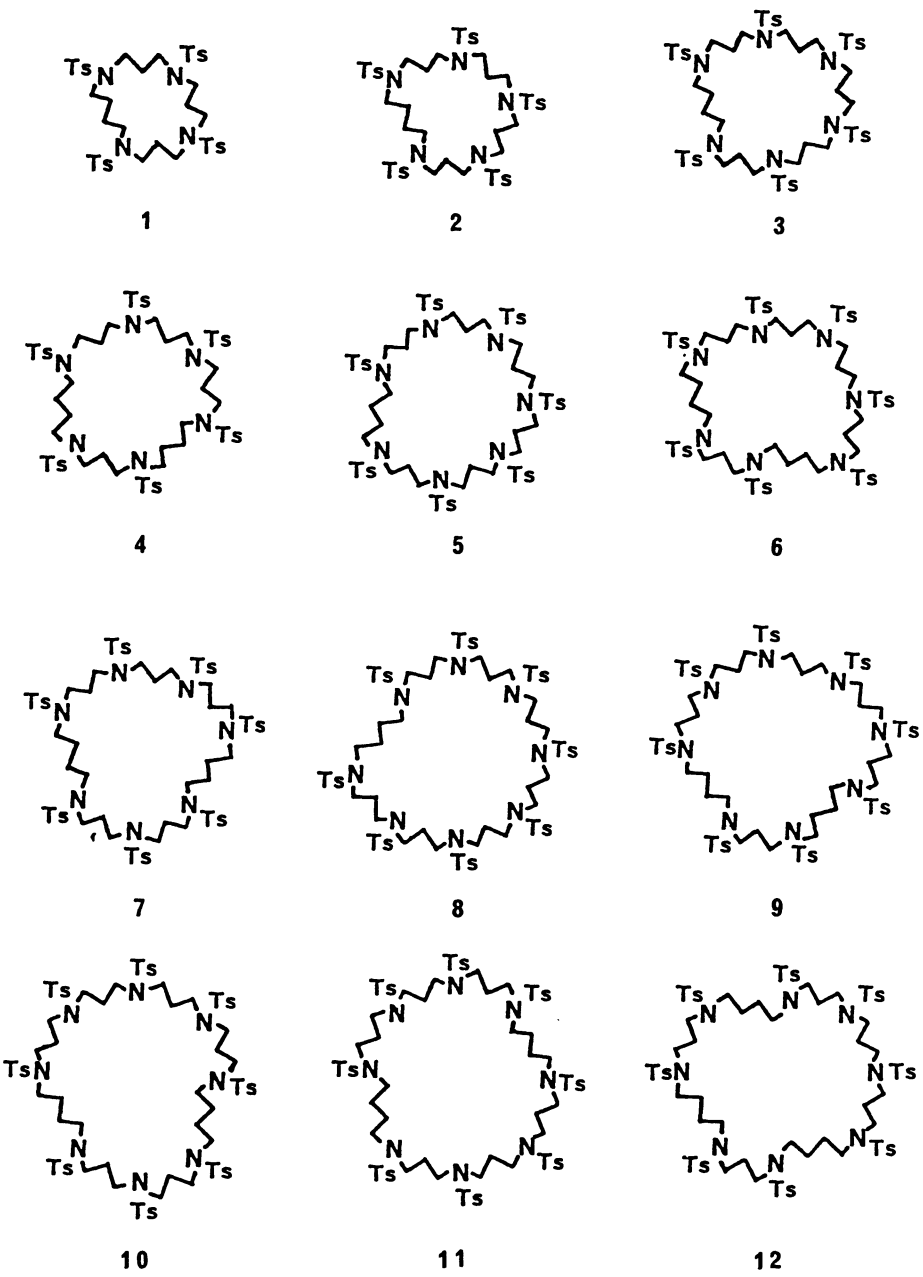
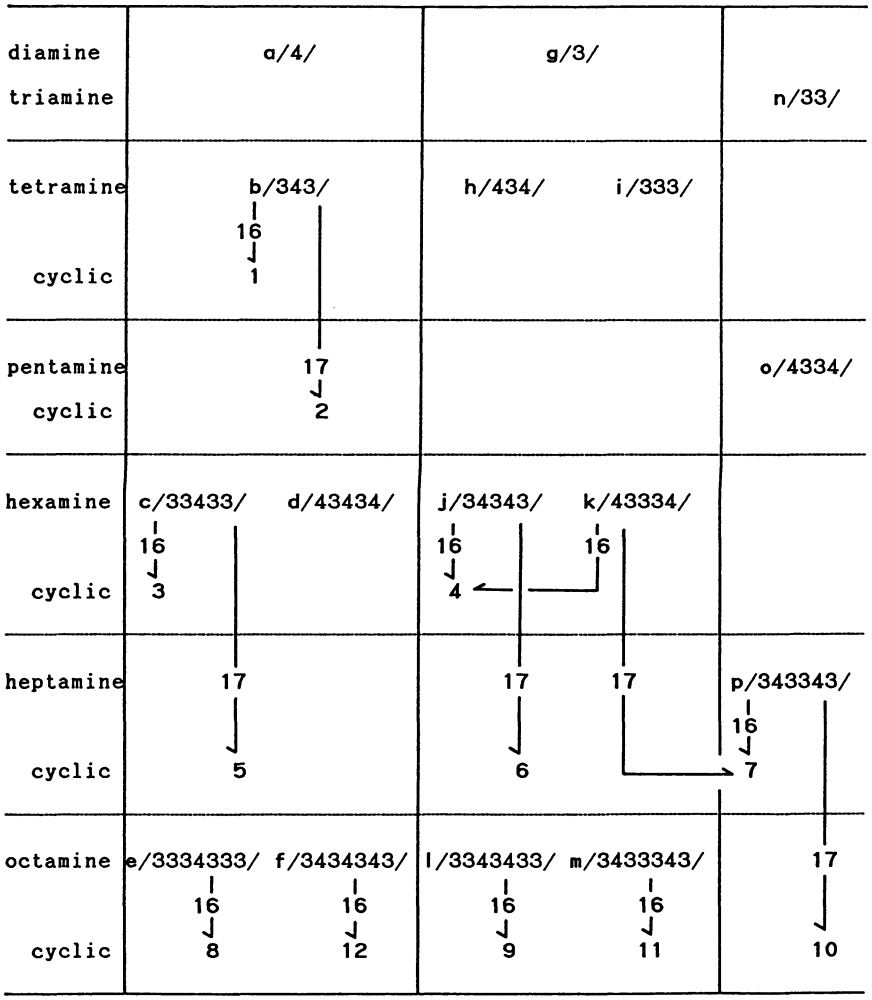


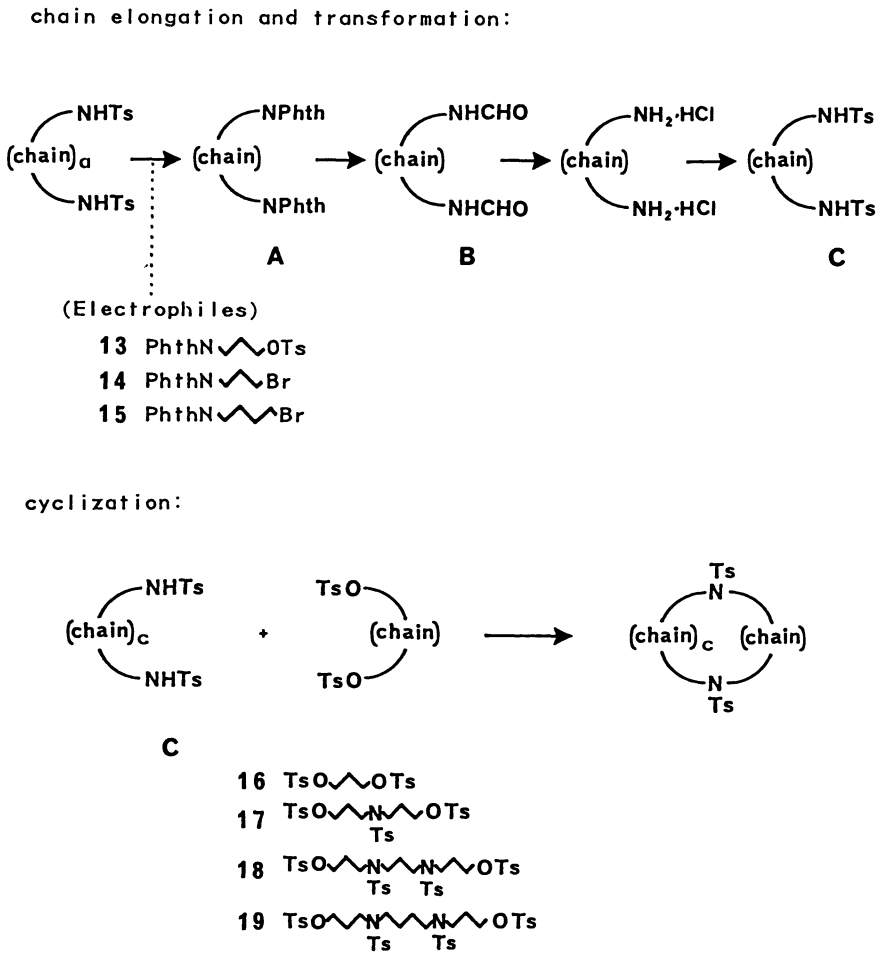
Table 1. The Flow Chart of Hierarchical Synthetic Design of Tosylated Acyclic and Cyclic Polyamines[a)]



a) The chain type is shown by gothic alphabet and the chain composition is indicated by the contiguous methylene chain blocks in Arabic numerals with the default of nitrogen atoms between slant lines. Arrows in Table indicate a formal route from the acyclic to cyclic polyamines by use of α,ω-ditosylates (**16**, **17**) indicated in the arrow intermitted.

molecular symmetry, these twelve macrocycles designed were found to be divided into three classes. Starting from *N*,*N*′-ditosyl-1,4-butanediamine (**a**) as one core chain, six macrocycles, **1**, **2**, **3**, **5**, **8**, and **12** could be derived. Likewise, *N*,*N*′-ditosyl-1,3-propanediamine (**g**) as another core chain emerges four macrocycles, **4**, **6**, **9**, and **11**. N^1,N^7,4-Tritosyl-4-azaheptane-1,7-diamine (**n**) could be the other core for two macrocycles, **7** and **10**. Owing to their molecular symmetry, two macrocycles, **4** and **7**, might be synthesized through alternative combination.

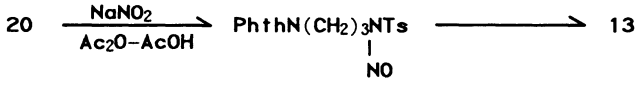
Molecular Architecture: As shown in Table 1, nitrogen content could be increased hierarchically, for synthetic convenience, at both terminals with the same electrophiles. For example, diamine chains (**a**, **g**) will be source for tetramine chains, which, then, be source for hexamine and octamine chains. Thus, heptamine chain (**p**) will be derived from pentamine chain (**o**), which might have been derived from triamine chain (**n**). We expected that chain elongation from the lower to the higher nitrogen content and transformation to regenerate the same functionality at symmetrical both terminals as the starting α,ω-bis(tosylamide)s would be provided through the processes illustrated in Scheme 1; the reaction of α,ω-bis(tosylamide)s, **a**, **g**, or **n**, with ω-phthalimidated electrophiles, **13**, **14**, or **15**, will provide α,ω-diphthalimides (**A**) which then be transformed to α,ω-diformamides (**B**) and subsequently to α,ω-bis(tosylamide)s (**C**) to give **b**, **h**, or **o**, respectively, with the higher nitrogen content. The processes were expected to be recyclizable. Cyclization was expected to be achieved by the conventional process,[6)] using **C** and α,ω-ditosylated electrophiles, **16**, **17**, **18**, or **19**. As a result, in the strategy of our molecular architecture (in Table 1 and Scheme 1),



Scheme 1.

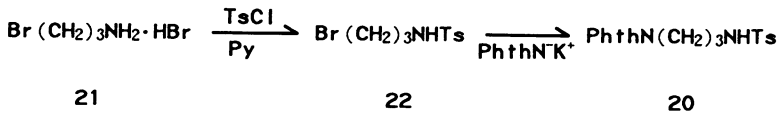
synthetic feasibility will be judged from the efficacy of repeated three reactions, chain elongation, **A** to **C** transformation, and cyclization. Therefore, efficient synthesis of electrophilic synthons, ω-phthalimidated electrophiles (**13**, **14**, **15**) and, α,ω-ditosylates (**16**, **17**, **18**, **19**), required for chain elongation and cyclization, should be the first issue.

Synthesis of Electrophiles: Elongative introduction of three methylene chain would be accommodated by *N*-(3-tosyloxypropyl)phthalimide (**13**) or *N*-(3-bromopropyl)phthalimide (**14**), and four methylene chain would be accommodated by *N*-(4-bromobutyl)phthalimide (**15**). It should be noted, as pointed previously,[9a] that the tosyloxy group is about five-fold more reactive than the bromo group. Thus, efficient synthesis of **13** was pursued. According to *N*-nitroso sulfonamide–sulfonate rearrangement reaction,[8a] *N*-(3-tosylaminopropyl)phthalimide (**20**) could be a precursor for **13**. Compound **20** was prepared via independent two routes; one route was via tosylation of commercially available 3-bromopropylamine hydrobromide (**21**) followed by condensation with potassium phthalimide (route A). The other route started with diphthalimidation of commercially available 1,3-dibromopropane (**23**) followed by treatment with hydrazine hydrate to afford a unique heterocycle, 3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoindol-6-one (**25**).[10] After hydrolysis of **25**, tosylation in the presence of triethylamine gave **20** in quantitative yield (route B). Both routes proceeded in excellent yields. In economical point of view, compound **21** is expensive. Nitrosation of **20** proceeded quantitatively[8b] and the nitrosated product was rearranged in hot benzene to give **13** in 80% conversion yield. For the pur-



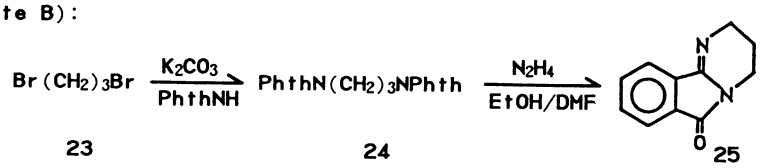
pose of reactivity comparison with **13**, compound **14** was prepared in 88% yield through the modification of the Gabriel method[11a] via the reaction of 1,3-dibromopropane with phthalimide. Since *N*-(4-tosyloxybutyl)phthalimide (**27**) has been unavailable in practical scale,[12] *N*-(4-bromobutyl)phthalimide (**15**), employed for accommodation of four methylene block throughout, was prepared in 68% yield through

(route A):

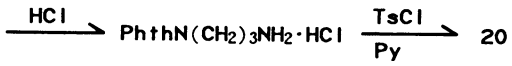


21 22 20

(route B):



23 24 25



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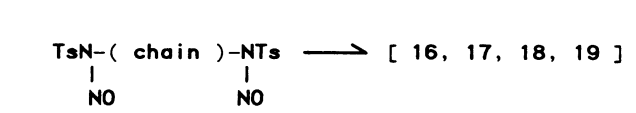
modification of the Gabriel method[11b] via the reaction of 1,4-dibromobutane (**28**) with phthalimide.

α,ω-Ditosylates, **16**, **17**, **18** and **19**, were prepared from the corresponding α,ω-bis(tosylamide)s, **Cg**, **Cn**, **Ci**, and **Cb**, respectively, through the nitrosation[8b] followed by the rearrangement reaction.[8a]



Chain Elongation and Transformation: Presently, three methods have been available for the condensation of electrophiles with α,ω-tosylamides (**C**) in synthetic polyamine chemistry; conventional use of potassium carbonate as base trigger in *N*,*N*-dimethylformamide (DMF), activation of α,ω-bis(tosylamino) groups via the formation of the corresponding Na salt,[6] and use of cesium carbonate[13] in DMF. When cesium carbonate was employed for the reaction of **Ca** with **13** in DMF at ambient temperature, the product **Ab** was obtained almost quantatively though the reaction proceeded very slowly (a day long). When the reaction temperature was elevated up to 80 °C for acceleration of the condensation, the reaction was not accelerated but decomposition of **13** turned out remarkable.

In preliminary experiments, tosylates were found to be decomposed considerably during the slow condensation reaction with potassium carbonate, probably due to the prolonged reaction time. When the reaction temperature was elevated, decomposition of the tosylate was accelerated as well as in the case of the use of cesium carbonate, resulting in marked decrease in product yield. When the Na salt of tosylamide of **Ca** reacted with **13** in DMF, the condensation occurred rapidly but yield of **Ab** never exceeded 40% in several runs. Therefore, in sacrifice of the reaction time, cesium carbonate was employed as a base for chain elongation throughout the present study. In addition, difference in reactivity between the tosyloxy group and the bromo group was not apparent due, probably, to mild reaction conditions. Thus, both **13** and **14** were employed for introduction of three methylene chains without intention and **15**, for accommodation of four methylene chains. Since the bromo group is more tough against base than the tosyloxy group, in a general sense, and more feasible in scaled-up synthesis, compound **14** was employed more often than **13**. Furthermore, it was an idea that ω-phthalimidated electrophile was added in slight excess amount so as to supply its amount lost by its decomposition during prolonged reaction time.

The transformation reaction of phthalimides to formamides[7] was applied satisfactorily to the conversion of α,ω-diphthalimides (**A**) to α,ω-diformamides (**B**) without exception and the yield of **B** became optimal when 20 mol equiv hydrazine hydrate to **A** was employed in hot DMF. Compound **B** was hydrolyzed with hot 2 M HCl (1 M=1 mol dm^{-3}) to give the corresponding hydrochloride salt. It was optional to isolate hydrochloride salt mostly as crystals. However, for the present purpose, the hydrochloride was treated, without neutralization, directly with tosyl chloride in pyridine in the presence of triethylamine to afford α,ω-bis(tosylamide) (**C**).

These series of reactions were found to be repeated successfully without decrease in product yields even if the chain was elongated to octamines. The results in repeated manipulation, **A** through **C**, are summarized in Table 2. Tractable formamide intermediate (**B**) profits greatly the facile synthesis of acyclic poly-

amines. In addition, operationally simplified tosylation by in situ neutralization of hydrochloride salt with triethylamine was found to be advantageous for increased yields of tosylamide (**C**) and decreased decomposition of unstable free amine.

Macrocyclization: The same three methods as those shown in the section of chain elongation and transformation have been available for cyclization reaction of the electrophiles with nucleophiles. Since the product yield in the chain elongation turned out optimal when cesium carbonate was used as a base, the same base seemed to be the best choice upon macrocyclization as well. Under high dilution conditions, α,ω-bis(tosylamide) and α,ω-ditosylate (1.2 mol equiv) reacted in the presence of cesium carbonate (2.5 mol equiv) in DMF (a day long). The results obtained are listed in Table 3. Compound **1** ([17]N_4) and **2** ([21]N_5) were obtained almost quantitatively. Since compound **1** had been prepared previously in 56% yield by the reaction of **Ci** with 1,4-dibromobutane in the presence of potassium carbonate in DMF at 120 °C,[13] the present method turned out to improve the product yield of cyclization to great extent. The difference in yields suggests how important the choice of base, reaction time, and types of electrophiles is for macrocyclization. The other cyclic polyamines, **3** through **12** containing six to eight nitrogens in the ring, were prepared in rather excellent yields for such large ring sizes. There was no by-product in any case. Unreacted nucleophile **C** was retrieved. However, α,ω-ditosylated electrophile was not retrieved but decomposed completely. This implys that conversion yield based on nucleophile **C** was quantitative in all cases. Thus, it is suggestive as for the conditions of optimal cyclization that yield will be elevated further if α,ω-ditosylated electrophile is added intermittently in a suitable time during the reaction.

Compounds **7** ([30]N_7), **9** ([33]N_8), and **11** ([34]N_8) were prepared, for comparison, by two sets of electrophile and nucleophile. The results reveal that a coupling of the electrophile with the shortest chain length and the nucleophile with the longest chain

Table 2. Product Yields (%) of α,ω-Diphthalimides (**A**), α,ω-Diformamides (**B**), and α,ω-Bis(tosylamide)s (**C**) in the Chain Elongation and Transformation Reactions (in Scheme 1)

Terminal groups → NPhth Chain type[a]	NPhth (**A**)	NHCHO (**B**)	NHTs (**C**)
a/4/	—	—	67
b/343/	99	83	98
c/33433/	88	74	84
d/43434/	96	78	83
e/3334333/	99	78	89
f/3434343/	92	85	90
g/3/	—	—	70
h/434/	98	92	82
i/333/	99	92	93
j/34343/	99	86	90
k/43334/	80	91	90
l/3343433/	95	80	90
m/3433343/	93	74	97
n/33/	95	98	94
o/4334/	98	79	78
p/343343/	89	80	69

a) The chain type is shown by gothic alphabet and the chain composition is indicated by the contiguous methylene chain blocks in Arabic numerals with the default of nitrogen atoms between slant lines.

Table 3. Macromonocyclization by the Reaction of α,ω-Ditosylates with α,ω-Bis(tosylamide)s (**C**)

Product		Reactants		Yield/%
Compd.	Type[a]	α,ω-Ditosyl ester[b]	**C**[b]	
1	(17)N4	**16**/3/	**b**/343/	99
2	(21)N5	**16**/3/	**q**/3433/	98
3	(25)N6	**16**/3/	**c**/33433/	61
4	(26)N6	**16**/3/	**j**/34343/	56
5	(29)N7	**17**/33/	**c**/33433/	55
6	(30)N7	**17**/33/	**j**/34343/	64
7	(30)N7	**17**/33/	**k**/43334/	66
		19/343/	**q**/3433/	47
8	(33)N8	**16**/3/	**e**/3334333/	75
9	(34)N8	**16**/3/	**l**/3343433/	86
		18/333/	**j**/34343/	37
10	(34)N8	**17**/33/	**p**/343343/	53
11	(34)N8	**16**/3/	**m**/3433343/	64
		19/343/	**c**/33433/	38
12	(35)N8	**16**/3/	**f**/3434343/	48

a) Ring size in the parentheses and nitrogen content in Arabic numerals are shown. b) The chain type is shown by gothic Arabic numerals or alphabet and the chain composition is indicated by the contiguous methylene chain blocks in Arabic numerals with the default of nitrogen atoms between slant lines.

length gives far better yield in each case.

Spectral Characteristics: Chemical shifts in ^{1}H NMR spectra are summarized in Tables 4 through 7. Table 4 includes all protons for macrocycles, **1** through **12**. Table 5 includes protons in the methylene region for α,ω-diphthalimide (**A**). Table 6 includes protons in the methylene region and the formamido group for typical α,ω-diformamide (**B**). Table 7 includes protons in the methylene region and tosylamino group for α,ω-bis(tosylamide) (**C**). All signals were perfectly assigned by ^{1}H–^{1}H spin decoupling technique.

^{1}H NMR spectra provide certain information about the ring flexibility in cyclic polyamines since FIN- and TIN-protons[15] indicate marked dependence on

Table 4. Chemical Shifts of All Protons in ^{1}H NMR Spectra for Cyclic Polyamines, **1** through **12**[a] (δ/ppm, in $CDCl_3$)

	Ring	FIN	TIN	FOU	TOU	ArMe	ArHme	ArHs
1	(17)N4	1.68	1.96	3.06	3.09, 3.13	2.43, 2.428	7.31, 7.32	7.64, 7.66
2	(21)N5	1.68	1.95, 1.96	3.09	3.13, 3.15, 3.16	2.40, 2.43	7.31	7.65, 7.66, 7.67
3	(25)N6	1.62	1.94, 1.97, 2.01	3.09	3.11, 3.13, 3.17	2.41, 2.42	7.28, 7.29, 7.30	7.63, 7.65
4	(26)N6	1.62	1.93	3.09	3.11, 3.13	2.407, 2.41	7.28, 7.29, 7.30	7.64
5	(29)N7	1.57	1.90	3.09	3.11	2.41	7.28, 7.29	7.64
6	(30)N7	1.58	1.89	3.10	3.11	2.41	7.28	7.64
7	(30)N7	1.57	1.89	3.09	3.10, 3.11	2.41	7.28, 7.29	7.64
8	(33)N8	1.53	1.89	3.08	3.11	2.40	7.28	7.63
9	(34)N8	1.54	1.88	3.08	3.10, 3.11	2.40	7.27	7.63
10	(34)N8	1.54	1.87	3.08	3.10	2.40	7.28, 7.29	7.63
11	(34)N8	1.54	1.88	3.07	3.09, 3.10	2.40, 2.40	7.27, 7.28	7.63, 7.64
12	(35)N8	1.54	1.86	3.08	3.08	2.40	7.28	7.64, 7.65

a) See Ref. 15 for the significance of abbreviated designation.

Table 5. Chemical Shifts of Methylene Protons in ^{1}H NMR Spectra for α,ω-Diphthalimides (**A**)[a] (δ/ppm, in $CDCl_3$)

	Compd	C1	C2	C3	C4	FIN	TIN	FOU	TOU
b	343	3.69	1.90	3.18		1.60		3.12	
c	33433	3.67	1.89	3.16		1.56	1.89	3.12	3.10
d	43434	3.65	1.64	1.55	3.11	1.54	1.84	3.11	3.11
e	3334333	3.67	1.89	3.16		1.53	1.86	3.10	3.10
f	3434343	3.66	1.83	3.15		1.55	1.86	3.10	3.10
h	333	3.70	1.90	3.20			1.98		3.15
i	434	3.67	1.67	1.56	3.11		1.85		3.10
j	34343	3.67	1.87	3.15		1.56	1.85	3.10	3.12
k	43334	3.65	1.64	1.55	3.11		1.87, 1.92		3.11, 3.13, 3.14
l	3343433	3.67	1.86	3.16		1.54	1.87	3.10	3.10
m	3433343	3.66	1.86	3.12		1.54	1.86	3.09	3.09, 3.12, 3.13
n	33	3.70	1.95	3.22					
o	4334	3.66	1.66	1.56	3.12		1.88		3.12
p	343343	3.66	1.86	3.15		1.55	1.86	3.10	3.11, 3.13

a) See Ref. 15 for the significance of abbreviated designation.

Table 6. Chemical Shifts of Main Protons in ^{1}H NMR Spectra for α,ω-Diformamides (**B**)[a] (δ/ppm, in $CDCl_3$)

	Compd	C1	C2	C3	C4	FIN	TIN	FOU	TOU	NH	CHO
b	343	3.40	1.77	3.13		1.58		3.09		6.38	8.20
c	33433	3.37	1.78	3.13		1.60	1.88	3.10	3.12	6.44	8.15
d	43434	3.30	1.57	1.63	3.07	1.63	1.90	3.14	3.11, 3.12	6.24	8.13
h	333	3.40	1.79	3.12			1.79		3.12	6.52	8.18
i	434	3.32	1.59	1.62	3.07		1.90		3.14	6.17	8.17
j	34343	3.36	1.77	3.12		1.58	1.88	3.10	3.11	6.43	8.16
k	43334	3.30	1.57	1.63	3.06		1.93, 1.94		3.11, 3.14, 3.17	6.30	8.12
n	33	3.40	1.80	3.15						6.29	8.19
o	4334	3.31	1.59	1.63	3.06		1.93		3.17	6.20	8.15

a) See Ref. 15 for the significance of abbreviated designation.

Table 7. Chemical Shifts of Main Protons in ^{1}H NMR Spectra for α,ω-Bis(tosylamide)s (**C**)[a] (δ/ppm, in $CDCl_3$)

	Compd	C1	C2	C3	C4	FIN	TIN	FOU	TOU	NH
b	343	2.98	1.77	3.12		1.53		3.07		5.31
c	33433	2.97	1.77	3.12		1.60	1.85	3.09	3.08, 3.09	5.40
d	43434	2.90	1.52	1.60	3.04	1.64	1.88	3.12	3.11, 3.13	5.16
e	3334333	2.95	1.77	3.09		1.56	1.86, 1.87	3.10	3.10	5.41
f	3434343	2.95	1.74	3.09		1.53	1.84	3.09	3.09	5.37
h	333	2.99	1.79	3.09			1.85		3.14	5.36
i	434	2.93	1.55	1.67	3.08		1.92		3.14	5.18
j	34343	2.96	1.75	3.11		1.55	1.86	3.08	3.09	5.34
k	43334	2.89	1.53	1.63	3.04		1.93, 1.98		3.11, 3.16	5.25
l	3343433	2.95	1.72	3.08		1.52	1.88, 1.89	3.04, 3.06	3.10, 3.11	5.39
m	3433343	2.95	1.75	3.10		1.54	1.89	3.06, 3.07	3.11	5.39
n	33	2.96	1.72	3.11						5.13
o	4334	2.91	1.54	1.64	3.06		1.94		3.12, 3.16	5.14
p	343343	2.95	1.74	3.10		1.54	1.89	3.06, 3.07	3.11	5.39

a) See Ref. 15 for the significance of abbreviated designation.

the ring size. In comparison of **1** and **12**, the difference in chemical shift values between them is 0.14 for FIN-protons and 0.1 for TIN-protons, respectively (Table 4). Since chemical shift values for all protons in **12** are almost the same as those for open-chain polyamines (**A**) to (**C**), compound **1** is fairly a rigid molecule. In viewpoint of the ring flexibility on the basis of chemical shift value, cyclic polyamines, **6** and **7** with thirty-membered ring, are the boundary ring size whether or not the ring is flexible. Thus, the macrocycles, **2** through **5**, are rather rigid molecules in comparison with the macrocycles, **8** through **12**. It is reasonable to predict that the trend observed is related closely to the nitrogen function in the molecule; that is, latent amine nitrogens involved in the polyamines, **8** through **12**, might behave equivalently, while each of those in polyamines, **1** through **5**, would function differently. Averaged chemical shift values for the terminal tosylamide proton (NHTs) in **C**, and the formamide proton (NHCHO) and the formyl proton in **B** are δ 5.30, 6.33, and 8.16, respectively.

Conclusion

Synthetic availability of the recently developed transformation reaction of phthalimides to formamides[7] and tosylamides to tosylates via *N*-nitrosotoluenesulfonamide intermediates[8] for polyamine synthesis was investigated through molecular architecture for designed polyamines with natural methylene arrays. Since chain elongation, transformation, and cyclization reactions proceeded very effectively, the present route provides a new adaptable method generally applicable to polyamine synthesis. Several problems involved in the traditional synthetic processes for cyclic polyamines has now been overcome perfectly. In addition, a guiding principle for the choice of better couple of nucleophiles and electrophiles upon cyclization has now been discovered. In the present synthesis, all the amino nitrogens are protected by the tosyl group, which makes it advantageous to monitor the proceeding reaction and isolation as well. Since effective detosylation methods are available for *N*-tosylated polyamines,[5,16] formal synthesis of acyclic and cyclic polyamines has now been established.

Experimental

The ^{1}H NMR spectra were recorded on JEOL GSX-500S (500 MHz) instrument with Me_4Si as the internal standard in $CDCl_3$ unless otherwise mentioned; chemical shifts (δ) and coupling constants (J) are in parts per million and hertz, respectively. Infrared spectra (IR) were obtained on a Shimadzu IR-27 apparatus. 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, 20×20 cm), for thin-layer chromatography (TLC). Product spots on TLC were detected either with UV-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).

Materials. *N*,*N*-Dimethylformamide (DMF) was dried over Molecular Sieves (Type A). Phthalimide, 3-bromopropylamine hydrobromide (**21**), 1,3-dibromopropane (**23**), and 1,4-dibromobutane (**28**) are commercially available. Potassium phthalimide was prepared according to the described method.[17] 1,3-Diphthalimidopropane (**24**)[11a] was prepared by the reaction of **23** with phthalimide in the presence of potassium carbonate in DMF. 3,4-Dihydro-2*H*-pyrimido[2,1-*a*]isoindol-6-one (**25**) was prepared from **24** through newly developed method.[10] *N*-(3-Bromopropyl)phthalimide (**14**) and *N*-(4-bromobutyl)phthalimide (**15**) were prepared by the reaction of **23** and **28**, respectively, with phthalimide in 88 and 68% yields respectively;[11] **14**, mp 73—75 °C (lit,[11a] mp 72—73 °C); **15**, mp 81—82 °C (lit,[11b] mp 80.5 °C). Synthesis of α,ω-

ditosylates, **16**, **17**, **18**, and **19**, from the corresponding α,ω-bis(tosylamide)s will be described elsewhere. *N,N'*-Ditosyl-1,4-butanediamine (**a**) and *N,N'*-ditosyl-1,3-propanediamine (**g**) were prepared from the correspoding diamines via the method previously reported.[18]

Synthesis of *N*-(3-Tosylaminopropyl)phthalimide (20). Route A; compound **21** (15 g, 69 mmol) and tosyl chloride (29.6 g, 1.5 mol equiv) pyridine (150 mL) was stirred at 0—5 °C for 2 h. The mixture was poured into water and extracted with chloroform. The chloroform layer was washed several times with 2 M HCl and, then, dried over $MgSO_4$. Chloroform was removed and the residue was chromatographed on a silica-gel column eluted with chloroform–acetone (95:5 v/v) to give 11.92 g (99% yield) of *N*-tosyl-3-bromopropylamine (**22**). A mixture of **22** (2.93 g, 10 mmol) and potassium phthalimide in DMF (50 mL) was heated at 80 °C for 3 h. The mixture was poured into brine and resulting precipitate was collected by filtration. The precipitate was recrystallized from ethanol to give 2.665 g (74% yield) of **20**.

Route B; compound **25** (1.23 g, 6.6 mol) was heated with 2 M HCl (28 mL) containing ethanol (5 mL) at 75 °C for 5 h. Solvents were removed under reduced pressure and the residue was recrystallized from ethanol to give 1.55 g (98% yield) of *N*-(3-aminopropyl)phthalimide hydrochloride (**26**); mp 192—194 °C. Calcd for $C_{11}H_{13}O_2N_2Cl$; C, 54.89; H, 5.44; N, 11.64; Cl, 14.73%. Found; C, 54.79; H, 5.45; N, 11.48; Cl, 15.02%. IR (KBr) ν 2400—2800 (NH_3^+), 1780 and 1710 (C=O) cm^{-1}.

Compound **26** (1.5 g, 6.2 mmol) and tosyl chloride (1.54 g, 1.3 mol eguiv to **26**) in pyridine (45 mL) and triethylamine (1 mL) were stirred at ambient temperature for 4 h. Solvents were removed and the residue was chromatographed on a silica-gel column eluted with chloroform–acetone (9:1 v/v) to afford 1.46 g (98% yield) of **20**; mp 170—171 °C. Calcd for $C_{18}H_{18}O_4N_2S$: C, 60.32; H, 5.06; N, 7.82; S, 8.95%. Found: C, 60.13; H, 5.08; N, 7.71; S, 8.91%. IR (KBr) ν 3290 (NH), 1770, 1705 (C=O), 1340, 1160 (SO_2) cm^{-1}. ^1H NMR; δ=1.83 (2H, quin, J=6.35, phthN-CH_2-$C\underline{H}_2$-), 2.40 (3H, s, ArMe[15]), 3.74 (2H, t, J=6.35, phthN-$C\underline{H}_2$-CH_2-), 3.93 (2H b-m, -CH_2-$C\underline{H}_2$-NHTs), 5.25 (1H, b-t, N$\underline{H}$Ts), 7.27 (2H, d J=8.30, ArHme[15]), 7.75 (2H, d, J=8.30, ArHs[15]), 7.73 (2H, m, aromatic protons meta to phthaloyl carbonyl), 7.82 (2H, m, aromatic protons ortho to phthaloyl carbonyl).

Synthesis of *N*-(3-Tosyloxypropyl)phthalimide (13). Compound **20** (1.5 g, 4.2 mmol) was treated with sodium nitrite (0.713 g, 2 mol equiv to **20**) in a mixture of acetic anhydride (15 mL) and acetic acid (3 mL) at below 5 °C for 3 h. The mixture was poured into water and the resulting crystalline precipitate was collected by filtration. After dried in Drierite desiccator, the nitrosated compound was heated with benzene (80 mL) at 80 °C for 20 h. Solvent was removed and the residue was chromatographed on a silica-gel column eluted with chloroform–acetone (95:5 v/v) to give 0.87 g (59% yield) of **13**; mp 92—94 °C. Calcd for $C_{18}H_{17}O_5NS$: C, 60.15; H, 4.77; N, 3.90; S, 8.92%. Found: C, 60.15; H, 4.78; N, 4.25; S, 8.68%. IR (KBr) ν 1773, 1710 (C=O), 1357, 1188, 1175 (SO_2) cm^{-1}. ^1H NMR; δ=2.06 (2H, quin, J=6.83, phthN-CH_2-$C\underline{H}_2$-), 2.44 (3H, s, ArMe[15]), 3.74 (2H, t, J=6.83, phthN-$C\underline{H}_2$-CH_2-), 4.11 (2H, t, -CH_2-$C\underline{H}_2$-OTs), 7.33 (2H, d, J=8.30, ArHme[15]), 7.78 (2H, d, J=8.30, ArHs[15]), 7.72 (2H, m, aromatic protons meta to phthaloyl carbonyl), and 7.83 (2H, m, aromatic protons ortho to phthaloyl carbonyl).

General Procedure for the Synthesis of α,ω-Diphthalimides (A) by the Reaction of α,ω-Tosylamides (C) with ω-Phthalimidated Electrophilies (13,14,15). A mixture of α,ω-bis(tosylamide) (**C**), one of ω-phthalimidated electrophiles (**13,14,15**) (2.2 mol equiv to **C**), and cesium carbonate (2.5 mol equiv to **C**) in DMF was stirred at ambient temperature for two days. The mixture was filtered through Celite and, then, the solvent was removed under reduced pressure. The residue was chromatographed on a silica-gel column eluted with chloroform–acetone (95:5 v/v) to give α,ω-diphthalimide (**A**).

General Procedure for the Synthesis of α,ω-Diformamides (B) from α,ω-Diphthalimides (A). To a solution of α,ω-diphthalimide (**A**) in DMF, hydrazine hydrate (20 mol equiv to **A**) was added and the mixture was heated at 75 °C for 23 h. After removal of DMF, the residue was chromatographed on a silica-gel column eluted with chloroform–methanol (9:1 v/v) to give α,ω-diformamide (**B**).

General Procedure for the Synthesis of α,ω-Bis(tosylamide)s (C) from α,ω-Diformamides (B). To a solution of α,ω-diformamide (**B**) in a small amount of ethanol, 2 M hydrochloric acid was added and heated at 80 °C for 4 h. Solvents were removed and the residue was stirred with tosyl chloride (2.6 mol equiv to **B**) in pyridine containing a small amount of triethylamine at ambient temperature for 4 h. Solvents were evaporated under reduced pressure and the residue was chromatographed on a silica-gel column eluted with chloroform–acetone (9:1 v/v) to give α,ω-bis(tosylamide)s (**C**).

***N,N'*-Bis(3-phthalimidopropyl)-*N,N'*-ditosyl-1,4-butanediamine (Ab).** By the reaction of **a** with either **13** or **14**, compound **Ab** was obtained as crystals; mp 201—202 °C (recryst. from ethanol–acetone). Calcd for $C_{40}H_{42}O_8N_4S_2$: C, 62.32; H, 5.49; N, 7.27; S, 8.32%. Found: C, 62.11; H, 5.47; N, 7.18; S, 8.36%. IR (KBr) ν 1770, 1720 (C=O), 1340, 1155 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

***N,N'*-Bis(3-formamidopropyl)-*N,N'*-ditosyl-1,4-butanediamine (Bb).** By the reaction of **Ab** with N_2H_4 in DMF, compound **Bb** was obtained as viscous liquid; Calcd for $C_{26}H_{38}O_6N_4S_2$: C, 55.10; H, 6.76; N, 9.89; S, 11.32%. Found: C, 54.99; H, 6.72; N, 9.98; S, 11.11%. IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 6.

***N,N'*-Bis[3-(tosylamino)propyl]-*N,N'*-ditosyl-1,4-butanediamine (Cb).** Through treatment of **Bb** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Cb** was obtained as viscous liquid; Calcd for $C_{38}H_{50}O_8N_4S_4$: C, 55.72; H, 6.15; N, 6.84; S, 15.66%. Found: C, 55.71; H, 6.29; N, 6.70; S, 15.55%. IR (KRS) ν 3280 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

4,8,13,17-Tetratosyl-N^1,N^1:N^{20},N^{20}-diphthaloyl-4,8,13,17-tetraazaeicosane-1,20-diamine (Ac). By the reaction of **Cb** with either **13** or **14**, compound **Ac** was obtained as amorphous powder; Calcd for $C_{60}H_{68}O_{12}N_6S_4$: C, 60.34; H, 5.74; N, 7.04; S, 10.75%. Found: C, 60.14; H, 5.84; N, 6.87; S, 10.52%. IR (KBr) ν 1770, 1720 (C=O), 1340, 1155 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

4,8,13,17-Tetratosyl-N^1,N^{20}-diformyl-4,8,13,17-tetraazaeicosane-1,20-diamine (Bc). By the reaction of **Ac** with N_2H_4 in DMF, compound **Bc** was obtained as amorphous

powder; Calcd for $C_{46}H_{64}O_{10}N_6S_4$: C, 55.84; H, 6.52; N, 8.50; S, 12.97%. Found: C, 56.10; H, 6.43; N, 8.73; S, 12.87%. IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 6.

N^1,N^{20},4,8,13,17-Hexatosyl-4,8,13,17-tetraazaeicosane-1,20-diamine (Cc). Through treatment of **Bb** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Cc** was obtained as amorphous powder; Calcd for $C_{58}H_{76}O_{12}N_6S_6$: C, 56.10; H, 6.17; N, 6.77; S, 15.50%. Found: C, 55.92; H, 6.15; N, 6.53; S, 15.36%. IR (KRS) ν 3290 (NH), 1330, 1155 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

5,9,14,18-Tetratosyl-N^1,N^1:N^{22},N^{22}-diphthaloyl-5,9,14,18-tetraazadocosane-1,22-diamine (Ad). By the reaction of **Cb** with **15**, compound **Ad** was obtained as viscous liquid; Calcd for $C_{62}H_{72}O_{12}N_6S_4$: C, 60.96; H, 5.94; N, 6.88; S, 10.50%. Found: C, 60.72; H, 5.86; N, 7.16; S, 10.36%. IR (KBr) ν 1770, 1710 (C=O), 1340, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

5,9,14,18-Tetratosyl-N^1,N^{22}-diformyl-5,9,14,18-tetraazadocosane-1,22-diamine (Bd). By the reaction of **Ad** with N_2H_4 in DMF, compound **Bd** was obtained as viscous liquid; Calcd for $C_{48}H_{60}O_{10}N_6S_4$: C, 56.67; H, 6.74; N, 8.26; S, 12.61%. Found: C, 56.78; H, 6.74; N, 8.04; S, 12.75%. IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 6.

N^1,N^{22},5,9,14,18-Hexatosyl-5,9,14,18-tetraazadocosane-1,22-diamine (Cd). Through treatment of **Bd** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Cd** was obtained as amorphous powder; Calcd for $C_{60}H_{80}O_{12}N_6S_6$: C, 56.75; H, 6.35; N, 6.62; S, 15.15%. Found: C, 56.61; H, 6.22; N, 6.56; S, 15.04%. IR (KBr) ν 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

4,8,12,17,21,25-Hexatosyl-N^1,N^1:N^{28},N^{28}-diphthaloyl-4,8,12,17,21,25-hexaazaoctacosane-1,28-diamine (Ae). By the reaction of **Cc** with **14** compound **Ae** was obtained as amorphous powder; Calcd for $C_{80}H_{94}O_{16}N_8S_6$: C, 59.46; H, 5.86; N, 6.94; S, 11.91%. Found: C, 59.34; H, 5.79; N, 6.68; S, 11.75%. IR (KBr) ν 1770, 1710 (C=O), 1340, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

4,8,12,17,21,25-Hexatosyl-N^1,N^{28}-diformyl-4,8,12,17,21,25-hexaazaoctacosane-1,28-diamine (Be). By the reaction of **Ae** with N_2H_4 in DMF, compound **Be** was obtained as amorphous powder; IR (KBr) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}.

N^1,N^{28},4,8,12,17,21,25-Octatosyl-4,8,12,17,21,25-hexaazaoctacosane-1,28-diamine (Ce). Through treatment of **Be** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Ce** was obtained as amorphous powder; Calcd for $C_{78}H_{102}O_{16}N_8S_8$: C, 56.29; H, 6.18; N, 6.73; S, 15.42%. Found: C, 55.95; H, 6.15; N, 6.54; S, 15.30%. IR (KBr) ν 3290 (NH), 1330, 1155 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

4,9,13,18,22,27-Hexatosyl-N^1,N^1:N^{30},N^{30}-diphthaloyl-4,9,13,18,22,27-hexaazatriacontane-1,30-diamine (Af). By the reaction of **Cd** with **14**, compound **Af** was obtained as amorphous powder; Calcd for $C_{82}H_{98}O_{16}N_8S_6$: C, 59.90; H, 6.01; N, 6.82; S, 11.70%. Found: C, 59.60; H, 5.96; N, 6.86; S, 11.49%. IR (KBr) ν 1770, 1710 (C=O), 1340, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

4,9,13,18,22,27-Hexatosyl-N^1,N^{30}-diformyl-4,9,13,18,22,27-hexaazatriacontane-1,30-diamine (Bf). By the reaction of **Af** with N_2H_4 in DMF, compound **Bf** was obtained as amorphous powder; IR (KBr) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}.

N^1,N^{30},4,9,13,18,22,27-Octatosyl-4,9,13,18,22,27-hexaazatriacontane-1,30-diamine (Cf). Through treatment of **Bf** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Cf** was obtained as amorphous powder; IR (KBr) ν 3290 (NH), 1330, 1155 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

***N*,*N*′-Bis(3-phthalimidopropyl)-*N*,*N*′-ditosyl-1,3-propanediamine (Ah).** By the reaction of **g** with either **13** or **14**, compound **Ah** was obtained as amorphous powder; Calcd for $C_{39}H_{40}O_8N_4S_2$: C, 61.89; H, 5.33; N, 7.40; S, 8.47%. Found: C, 61.76; H, 5.36; N, 7.20; S, 8.37%. IR (KBr) ν 1770, 1710 (C=O), 1335, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

***N*,*N*′-Bis(3-formamidopropyl)-*N*,*N*′-ditosyl-1,3-propanediamine (Bh).** By the reaction of **Ah** with N_2H_2 in DMF, compound **Bh** was obtained as viscous liquid; Calcd for $C_{25}H_{36}O_6N_4S_2$: C, 54.32; H, 6.57; N, 10.14; S, 11.60%. Found: C, 54.10; H, 6.67; N, 9.97; S, 11.40%. IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 6.

***N*,*N*′-Bis[3-(tosylamino)propyl]-*N*,*N*′-ditosyl-1,3-propanediamine (Ch).** Through treatment of **Bh** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Ch** was obtained as viscous liquid; Calcd for $C_{37}H_{48}O_8N_4S_4$: C, 55.20; H, 6.01; N, 6.96; S, 15.93%. Found: C, 55.56; H, 5.98; N, 6.93; S, 15.97%. IR (KRS) ν 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

***N*,*N*′-Bis(4-phthalimidobutyl)-*N*,*N*′-ditosyl-1,3-propanediamine (Ai).** By the reaction of **g** with **15**, compound **Ai** was obtained as amorphous powder; Calcd for $C_{41}H_{44}O_8N_4S_2$: C, 62.73; H, 5.65; N, 7.14; S, 8.17%. Found: C, 62.59; H, 5.68; N, 7.06; S, 8.14%. IR (KBr) 1770, 1710 (C=O), 1335, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

***N*,*N*′-Bis(4-formamidobutyl)-*N*,*N*′-ditosyl-1,3-propanediamine (Bi).** By the reaction of **Ai** with N_2H_4 in DMF, compound **Bi** was obtained as viscous liquid; Calcd for $C_{27}H_{40}O_6N_4S_2$: C, 55.84; H, 6.94; N, 9.65; S, 11.04%. Found: C, 55.61; H, 6.83; N, 9.57; S, 10.78%. IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 6.

***N*,*N*′-Bis[4-(tosylamino)buty]-*N*,*N*′-ditosyl-1,3-propanediamine (Ci).** Through treatment of **Bi** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Ci** was obtained as viscous liquid; Calcd for $C_{39}H_{52}O_8N_4S_4$: C, 56.22; H, 6.29; N, 6.73; S, 15.40%. Found: C, 55.94; H, 6.24; N, 6.76; S, 15.15%. IR (KRS) ν 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

4,9,13,18-Tetratosyl-N^1,N^1:N^{21},N^{21}-diphthaloyl-4,9,13,18-tetraazaheneicosane-1,21-diamine (Aj). By the reaction of **Ci** with either **13** or **14**, compound **Aj** was obtained as amorphous powder; Calcd for $C_{61}H_{70}O_{12}N_6S_4$: C, 60.67; H, 5.84; N, 6.96; S, 10.62%. Found: C, 60.59; H, 5.77; N, 6.56; S, 10.39%. IR (KBr) ν 1770, 1710 (C=O), 1335, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

4,9,13,18-Tetratosyl-N^1,N^{21}-diformyl-4,9,13,18-tetraazaheneicosane-1,21-diamine (Bj). By the reaction of **Aj** with N_2H_4 in DMF, compound **Bj** was obtained as amorphous powder; Calcd for $C_{47}H_{66}O_{10}N_6S_4$: C, 56.26; H, 6.63; N, 8.38; S, 12.78%. Found: C, 55.92; H, 6.73; N, 8.57; S, 12.66%. IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 6.

N^1,N^{21},4,9,13,18-Hexatosyl-4,9,13,18-tetraazaheneicosane-

1,21-diamine (Cj). Through treatment of **Bi** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Cj** was obtained as amorphous powder; Calcd for $C_{59}H_{78}O_{12}N_6S_6$: C, 56.43; H, 6.26; N, 6.69; S, 15.32%. Found: C, 56.71; H, 6.19; N, 6.54; S, 15.29%. IR (KBr) ν 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

5,9,13,17-Tetratosyl-N^1,N^1:N^{21},N^{21}-diphthaloyl-5,9,13,17-tetraazaheneicosane-1,21-diamine (Ak). By the reaction of **Ch** with **15**, compound **Ak** was obtained as viscous liquid; Calcd for $C_{61}H_{70}O_{12}N_6S_4$: C, 60.67; H, 5.84; N, 6.96; S, 10.62%. Found: C, 60.40; H, 5.83; N, 6.93; S, 10.56%. IR(KRS) ν 1770, 1710 (C=O), 1335, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

5,9,13,17-Tetratosyl-N^1,N^{21}-diformyl-5,9,13,17-tetraazaheneicosane-1,21-diamine (Bk). By the reaction of **Ak** with N_2H_4 in DMF, compound **Bk** was obtained as viscous liquid; Calcd for $C_{47}H_{66}O_{10}N_6S_4$: C, 56.26; H, 6.63; N, 8.38; S, 12.78%. Found: C, 55.98; H, 6.63; N, 8.19; S, 12.76%. IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 6.

N^1,N^{21},5,9,13,17-Hexatosyl-5,9,13,17-tetraazaheneicosane-1,21-diamine (Ck). Through treatment of **Bk** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Ck** was obtained as amorphous powder; Calcd for $C_{59}H_{78}O_{12}N_6S_6$: C, 56.43; H, 6.26; N, 6.69; S, 15.32%. Found: C, 56.38; H, 6.05; N, 6.40; S, 15.37%. IR (KBr) 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

4,8,13,17,22,26-Hexatosyl-N^1,N^1:N^{29},N^{29}-diphthaloyl-4,8,13,17,22,26-hexaazanonacosane-1,29-diamine (Al). By the reaction of **Cj** with **14**, compound **Al** was obtained as amorphous powder; Calcd for $C_{81}H_{96}O_{16}N_8S_6$: C, 59.68; H, 5.94; N, 6.88; S, 11.80%. Found: C, 59.60; H, 5.80; N, 6.79; S, 11.52%. IR (KBr) ν 1770, 1710 (C=O), 1335, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

4,8,13,17,22,26-Hexatosyl-N^1,N^{29}-diformyl-4,8,13,17,22,26-hexaazanonacosane-1,29-diamine (Bl). By the reaction of **Al** with N_2H_4 in DMF, compound **Bl** was obtained as viscous liquid; IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. It was very hard to obtain analytically pure sample by chromatography. Thus, the sample was directly subjected to the next reaction.

N^1,N^{29},4,8,13,17,22,26-Octatosyl-4,8,13,17,22,26-hexaazanonacosane-1,29-diamine (Cl). Through treatment of **Bl** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Cl** was obtained as amorphous powder; Calcd for $C_{79}H_{104}O_{16}N_8S_8$: C, 56.54; H, 6.25; N, 6.68; S, 15.29%. Found: C, 56.80; H, 6.09; N, 6.48; S, 15.17%. IR (KBr) ν 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

4,9,13,17,21,26-Hexatosyl-N^1,N^1:N^{29},N^{29}-diphthaloyl-4,9,13,17,21,26-hexaazanonacosane-1,29-diamine (Am). By the reaction of **Ck** with **14**, compound **Am** was obtained as amorphous powder; Calcd for $C_{81}H_{96}O_{16}N_8S_6$: C, 59.68; H, 5.94; N, 6.88; S, 11.80%. Found: C, 59.55; H, 5.82; N, 6.73; S, 11.88%. IR (KBr) ν 1770, 1710 (C=O), 1335, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

4,9,13,17,21,26-Hexatosyl-N^1,N^{29}-diformyl-4,9,13,17,21,26-hexaazanonacosane-1,29-diamine (Bm). By the reaction of **Al** with N_2H_4 in DMF, compound **Bm** was obtained as viscous liquid; IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. It was very hard to obtain analytically pure sample by chromatography. Thus, the sample was directly subjected to the next reaction.

N^1,N^{29},4,9,13,17,21,26-Octatosyl-4,9,13,17,21,26-hexaazanonacosane-1,29-diamine (Cm). Through treatment of **Bm** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Cm** was obtained as amorphous powder; Calcd for $C_{79}H_{104}O_{16}N_8S_8$: C, 56.54; H, 6.25; N, 6.68; S, 15.29%. Found: C, 56.47; H, 6.18; N, 6.50; S, 15.49%. IR (KBr) ν 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

N^1,N^1:N^7,N^7-Diphthaloyl-4-tosyl-4-azaheptane-1,7-diamine (An). By the reaction of **13** with **20** in the presence of cesium carbonate, compound **An** was obtained as crystals; mp 227—228 °C (recryst. from ethanol). Calcd for $C_{29}H_{27}O_6N_3S$: C, 63.84; H, 4.99; N, 7.70; S, 5.88%. Found: C, 63.85; H, 4.99; N, 7.66; S, 5.91%. IR (KBr) ν 1770, 1710 (C=O), 1335, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

N^1,N^7-Diformyl-4-tosyl-4-azaheptane-1,7-diamine (Bn). By the reaction of **Al** with N_2H_4 in DMF, compound **Bm** was not obtained and, thus, was prepared via the separate path; the reaction of *N*-formyl-*N'*-tosyl-1,3-propanediamine[7] with **14** in the presence of cesium carbonate in DMF gave N^1-formyl-N^7-phthaloyl-N^4-tosyl-4-azaheptane-1,7-diamine in 93% yield, which was, then, treated with hydrazine hydrate in DMF to afford **Bn** in 98% yield; viscous liquid. Calcd for $C_{15}H_{23}O_4N_3S$: C, 52.76; H, 6.79; N, 12.31; S, 9.39%. Found: C, 52.81; H, 6.87; N, 12.20; S, 9.21%. IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 6.

N^1,N^7,4-Tritosyl-4-azaheptane-1,7-diamine (Cn). Through treatment of **Bn** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Cn** was obtained as amorphous powder; Calcd for $C_{27}H_{35}O_6N_3S_3$: C, 54.61; H, 5.94: N, 7.08; S, 16.20%. Found: C, 54.29; H, 5.99; N, 7.03; S, 16.04%. IR (KBr) ν 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

5,9,13-Tritosyl-N^1,N^1:N^{17},N^{17}-diphthaloyl-5,9,13-triazaheptadecane-1,17-diamine (Ao). By the reaction of **Cn** with **15**, compound **Ao** was obtained as amorphous powder; Calcd for $C_{51}H_{57}O_{10}N_5S_3$: C, 61.48; H, 5.77; N, 7.03; S, 9.66%. Found: C, 61.66; H, 5.71; N, 7.06; S, 9.55%. IR (KBr) ν 1770, 1710 (C=O), 1335, 1150 (SO_3) cm^{-1}. ^1H NMR, shown in Table 5.

5,9,13-Tritosyl-N^1,N^{17}-diformyl-5,9,13-triazaheptadecane-1,17-diamine (Bo). By the reaction of **Ao** with N_2H_4, compound **Bo** was obtained as viscous liquid; Calcd for $C_{37}H_{53}O_8N_5S_3$: C, 56.11; H, 6.75; N, 8.84; S, 12.15%. Found: C, 55.90; H, 6.78; N, 8.79; S, 11.99%. IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 6.

N^1,N^{17},5,9,13-Pentatosyl-5,9,13-triazaheptadecane-1,17-diamine (Co). Through treatment of **Bo** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Co** was obtained as amorphous powder; Calcd for $C_{49}H_{65}O_{10}N_5S_5$: C, 56.35; H, 6.27; N, 6.71; S, 15.35%. Found: C, 56.30; H, 6.15; N, 6.64; S, 15.36%. IR (KBr) ν 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

4,9,13,17,22-Pentatosyl-N^1,N^1:N^{25},N^{25}-diphthaloyl-4,9,13,17,22-pentaazapentacosane-1,25-diamine (Ap). By the reaction of **Co** with **14**, compound **Ap** was obtained as amorphous powder; Calcd for $C_{71}H_{83}O_{14}N_7S_5$: C, 60.10; H, 5.90; N, 6.91; S, 11.30%. Found: C, 60.33; H, 6.06; N, 6.76; S, 11.18%. IR (KBr) ν 1770, 1710 (C=O), 1335, 1150 (SO_2) cm^{-1}. ^1H NMR, shown in Table 5.

4,9,13,17,22-Pentatosyl-N^1,N^{25}-diformyl-4,9,13,17,22-penta-

azapentacosane-1,25-diamine (Bp). By the reaction of **Ap** with N_2H_4, compound **Bp** was obtained as viscous liquid; IR (KRS) ν 3350 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}. It was very hard to obtain analytically pure sample by chromatography. Thus, the sample was directly subjected to the next reaction.

***N*¹,*N*²⁵,4,9,13,17,22-Heptatosyl-4,9,13,17,22-pentaazapentacosane-1,25-diamine (Cp).** Through treatment of **Bp** with 2 M hydrochloric acid and, then, with tosyl chloride, compound **Cp** was obtained as amorphous powder; Calcd for $C_{79}H_{104}O_{16}N_8S_8$: C, 56.49; H, 6.25; N, 6.68; S, 15.30%. Found: C, 56.47; H, 6.10; N, 6.66; S, 15.28%. IR (KBr) 3290 (NH), 1330, 1160 (SO_2) cm^{-1}. ^1H NMR, shown in Table 7.

General Procedure for the Synthesis of Macromonocyclic Polyamines, (1) through (12). A mixture of α,ω-bis(tosylamide) (**C**), α,ω-ditosylate (**16**, **17**, **18**, or **19**) (1.2 mol equiv to **C**), and cesium carbonate (2.5 mol equiv to **C**) in DMF was stirred at ambient temperature for a day or two. The mixture was filtered through Celite and the solvent was, then, evaporated under reduced pressure. The residue as chromatographed on a silica-gel column eluted with chloroform–acetone (95:5 v/v) to afford cyclic polyamine.

1,5,9,13-Tetratosyl-1,5,9,13-tetraazacycloheptadecane (1): [17]N_4. By the reaction of **16** with **Cb**, compound **1** was obtained as amorphous powder. Compound **1** had been prepared via alternative route in less yield.[14] IR (KBr) ν 1335 and 1150 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,17-Pentatosyl-1,5,9,13,17-pentaazacycloheneicosane (2): [21]N_5. By the reaction of **16** with *N*¹,*N*¹⁶,4,8,13-pentatosyl-4,8,13-triazahexadecane-1,16-diamine (**Cq**), which was derived from tosylated spermidine in similar series of procedure to those for **Co** preparation from **An**, compound **2** was obtained as amorphous powder; Calcd for $C_{51}H_{67}O_{10}N_5S_5$: C, 57.22; H, 6.31; N, 6.54; S, 14.98%. Found: C, 56.89; H, 6.27; N, 6.32; S, 15.23%. Amorphous powder. IR (KBr) ν 1335 and 1150 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,17,21-Hexatosyl-1,5,9,13,17,21-hexaazacyclopentacosane (3): [25]N_6. By the reaction of **16** with **Cc**, compound **3** was obtained as amorphous powder; Calcd for $C_{61}H_{80}O_{12}N_6S_6$: C, 57.16; H, 6.29; N, 6.56; S, 15.01%. Found: C, 57.18; H, 6.29; N, 6.46; S, 15.08%. IR (KBr) ν 1335 and 1150 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,18,22-Hexatosyl-1,5,9,13,18,22-hexaazacyclohexacosane (4): [26]N_6. By the reaction of **16** with **Cj**, compound **4** was obtained as amorphous powder; Calcd for $C_{62}H_{82}O_{12}N_6S_6$: C, 57.47; H, 6.38; N, 6.49; S, 14.85%. Found: C, 57.63; H, 6.40; N, 6.12; S, 14.52%. IR (KBr) ν 1335 and 1155 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,17,21,25-Heptatosyl-1,5,9,13,17,21,25-heptaazacyclononacosane (5): [29]N_7. By the reaction of **17** with **Cc**, compound **5** was obtained as amorphous powder; Calcd for $C_{71}H_{93}O_{14}N_7S_7$: C, 57.11; H, 6.28; N, 6.57; S, 15.03%. Found: C, 57.21; H, 6.30; N, 6.42; S, 14.85%. IR (KBr) ν 1335 and 1155 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,17,22,26-Heptatosyl-1,5,9,13,17,22,26-heptaazacyclotriacontane (6): [30]N_7. By the reaction of **17** with **Cj**, compound **6** was obtained as amorphous powder; Calcd for $C_{72}H_{95}O_{14}N_7S_7$: C, 57.38; H, 6.35; N, 6.51; S, 14.90%. Found: C, 57.12; H, 6.42; N, 6.21; S, 14.64%. IR (KBr) ν 1335 and 1155 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,18,22,26-Heptatosyl-1,5,9,13,18,22,26-heptaazacyclotriacontane (7): [30]N_7. In order to examine the effect on cyclization yield by changing in a couple of electrophile and nucleophile, two couples were tested; by the reaction of **17** with **Co**, compound **7** was obtained as amorphous powder in 66% yield. Alternatively, by the reaction of **19** with **Cq**, compound **7** was obtained in 47% yield. Calcd for $C_{72}H_{95}O_{14}N_7S_7$: C, 57.38; H, 6.35; N, 6.51; S, 14.90%. Found: C, 57.52; H, 6.68; N, 6.14; S, 14.58%. IR (KBr) ν 1335 and 1155 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,17,21,25,29,-Octatosyl-1,5,9,13,17,21,25,29-octaazacyclotritriacontane (8): [33]N_8. By the reaction of **16** with **Ce**, compound **8** was obtained as amorphous powder; Calcd for $C_{81}H_{106}O_{16}N_8S_8$: C, 57.08; H, 6.27; N, 6.58; S, 15.05%. Found: C, 57.14; H, 6.35; N, 6.31; S, 14.78%. IR (KBr) ν 1335 and 1155 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,17,21,26,30-Octatosyl-1,5,9,13,17,21,26,30-octaazacyclotetratriacontane (9): [34]N_8. In order to examine the effect on cyclization yield by changing in a couple of electrophile and nucleophile, two couples were tested; by the reaction of **16** with **Cl**, compound **9** was obtained as amorphous powder in 86% yield. Alternatively, by the reaction of **18** with **Cj**, compound **9** was obtained in 37% yield. Calcd for $C_{82}H_{108}O_{16}N_8S_8$: C, 57.31; H, 6.34; N, 6.52; S, 14.93%. Found: C, 56.98; H, 6.36; N, 6.18; S, 14.54%. IR (KBr) ν 1335 and 1155 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,17,22,26,30-Octatosyl-1,5,9,13,17,22,26,30-octaazacyclotetratriacontane (10): [34]N_8. By the reaction of **17** with **Cp** compound **10** was obtained as amorphous powder; Calcd for $C_{82}H_{108}O_{16}N_8S_8$: C, 57.31; H, 6.34; N, 6.52; S, 14.93%. Found: C, 56.99; H, 6.34; N, 6.26; S, 14.92%. IR (KBr) ν 1335 and 1155 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,18,22,26,30-Octatosyl-1,5,9,13,18,22,26,30-octaazacyclotetratriacontane (11): [34]N_8. In order to examine the effect on cyclization yield by changing in a couple of electrophile and nucleophile, two couples were tested; by the reaction of **16** with **Cm**, compound **11** was obtained as amorphous powder in 64% yield. Alternatively, by the reaction of **19** with **Cc**, compound **11** was obtained in 38% yield. Calcd for $C_{82}H_{108}O_{16}N_8S_8$: C, 57.31; H, 6.34; N, 6.52; S, 14.93%. Found: C, 56.99; H, 6.38; N, 6.34; S, 14.62%. IR (KBr) ν 1335 and 1155 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

1,5,9,13,18,22,27,31-Octatosyl-1,5,9,13,18,22,27,31-octaazacyclopentatriacontane (12): [35]N_8. By the reaction of **16** with **Cf**, compound **12** was obtained as amorphous powder; Calcd for $C_{83}H_{110}O_{16}N_8S_8$: C, 57.54; H, 6.40; N, 6.47; S, 14.81%. Found: C, 57.45; H, 6.46; N, 6.29; S, 14.78%. IR (KBr) ν 1335 and 1155 (SO_2) cm^{-1}. ^1H NMR data, listed in Table 4.

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