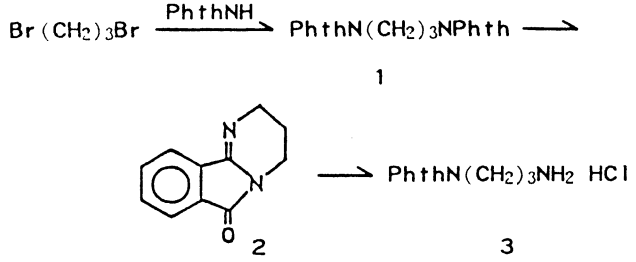
Efficient Synthetic Method for Differentially Protected Naturally Occurring Acyclic Polyamines

Masaaki IWATA* and Hiroyoshi KUZUHARA
RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-01
(Received August 25, 1988)

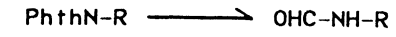
A new systematic route to threefold protected natural polyamines, spermidine, spermine, thermine, and thermospermine, was developed through alternate regioselective manipulation on the terminal primary amino groups, starting from *N,N*-phthaloyl-1,3-propanediamine hydrochloride (**3**). When **3** was tosylated at the amine terminal and the phthaloyl terminal was subjected to transformation to the formamido group followed by substitution at the tosyl terminal with, e.g., *N*-(4-bromobutyl)phthalimide, threefold protected spermidine was obtained in excellent yield. After hydrolysis of the formamido group to amine salt, a sequence of the reactions was satisfactorily repeated to afford various types of threefold protected natural tetramines.

Feasible synthetic methods for differentially protected natural acyclic polyamines play the crucial role in the total synthesis of polyamine conjugates[1] since the polyamine moiety has to be introduced regiospecifically at the proper step of the synthesis. In particular, in unsymmetrical natural polyamine-derived conjugates such as spermidine and thermospermine conjugates, the terminal primary amino groups have to be differentiated essentially for orientated introduction. In the literature survey, practical methods hitherto devised for discrimination of amino group have relied on (i) the reactivity difference in amino groups,[2] (ii) stoichiometric control of reactants in the level of triamine formation,[3] and (iii) the extension of differential protection generated in the level of diamine formation through the traditional way of stepwise synthesis.[4] Since the first method depends on the intrinsic nature of reactivity difference in amino groups of expensive spermidine as a starting material, it is inadequate for a large scale synthesis and for versatile synthetic utility.

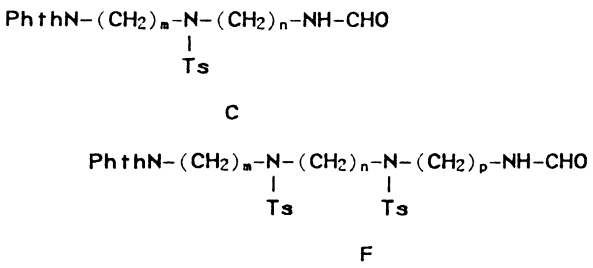
We have recently found the novel transformation reaction[5] specific for *N,N:N′,N′*-diphthaloyl-1,3-propanediamine (**1**). In the transformation reaction *N,N*-phthaloyl-1,3-propanediamine hydrochloride (**3**) is readily obtained quantitatively passing through the fused heterocycle (**2**) prepared in high yield from **1**.[6]



Since the transformation reaction indicates facile discrimination of the terminal primary amino groups in two steps, exemplification of synthetic feasibility of **3** was planned for molecular design of differentially protected polyamines, combining with another transformation reaction of phthalimides to formamides as follows;[7]



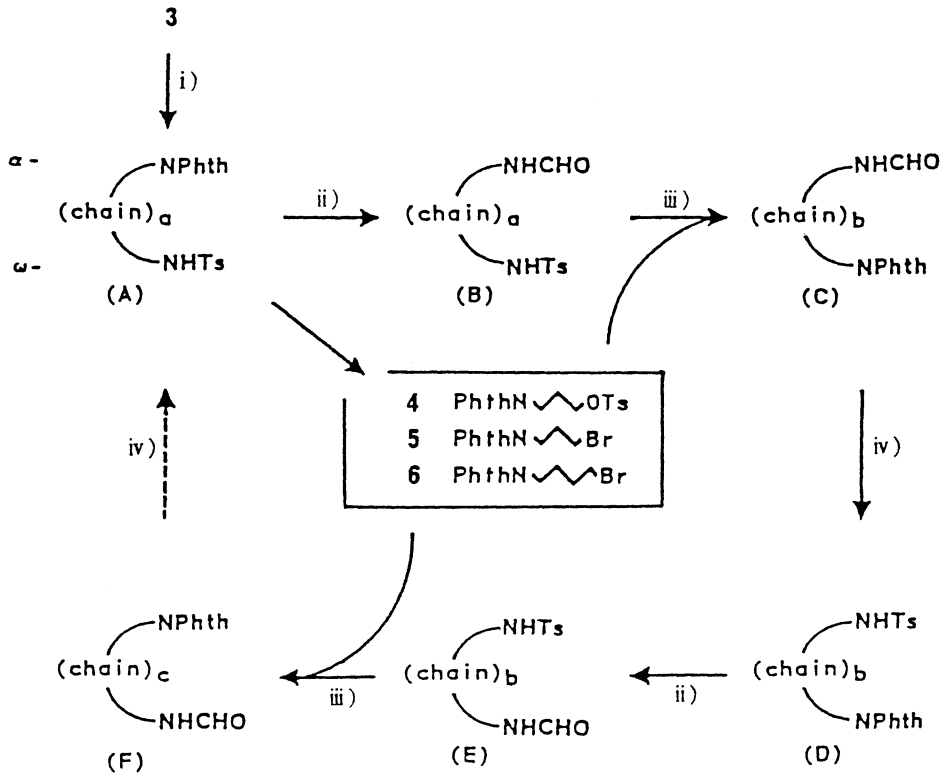
We set synthetic targets of threefold protected triamines (**C**) and tetramines (**F**) with the following types of functional groups;



in which the primary amino groups at both ends are protected differently by the base- and hydrazine-sensitive phthaloyl group and by the acid-sensitive and reducible formyl group, respectively, and the secondary amino groups, by the photo-,[8] alkali metal- and HBr-sensitive tosyl group.[9]

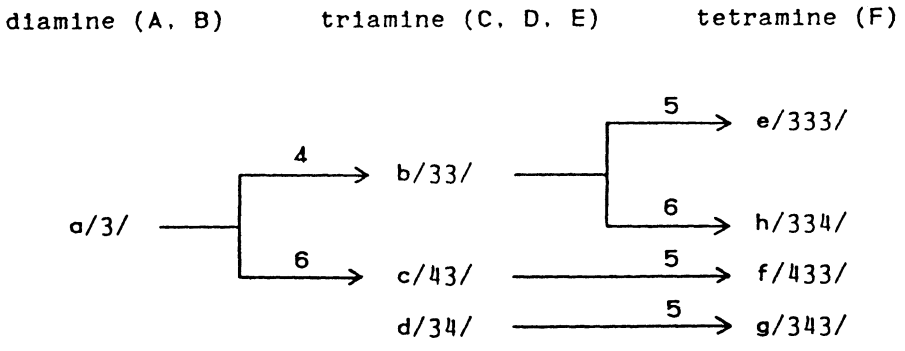
The synthetic plan is shown in Scheme 1, which is characterized by alternate regioselective manipulation on the terminal primary amino groups in a systematic way as follows; to start with tosylation of **3** followed by the transformatlon of the phthalimido group to formamido group (**A**→**B**). Then, the tosylamino group at the other ω-terminus functioning as nucleophile reacts with ω-phthalimidated compounds, either **4**, **5**, or **6** (**B**→**C**). The formamido group is hydrolyzed to give ω-*N,N*-phthaloylated α,ω-diamine hydrochloride, which disposes the same functional groups as those of the starting **3** in a reversed order. Therefore, a series of the reactions will be repeated for construction of tetramines in a similar fashion, disposing the primary amino group outside in (**D**→**E**→**F**). Since there has been no report on nucleophilic reactivity of formamido nitrogen, **A** to **B** or **E** to **F** steps are crucial in the present plan in which the terminus of diamine **B** or **E**, bearing both tosylamino and formamido groups, reacts with ω-phthalimidated compound (**4**).

1) Stepwise Differential Manipulation at the Terminal Groups.



i) $TsCl/Py/NEt_3$, ii) N_2H_4 H_2O/DMF, iii) Cs_2CO_3/DMF, iv) 2M-HCl then i).

2) Correlation Diagram of the Methylene Chain Array with Nitrogen Content Involved in A through F Compounds.



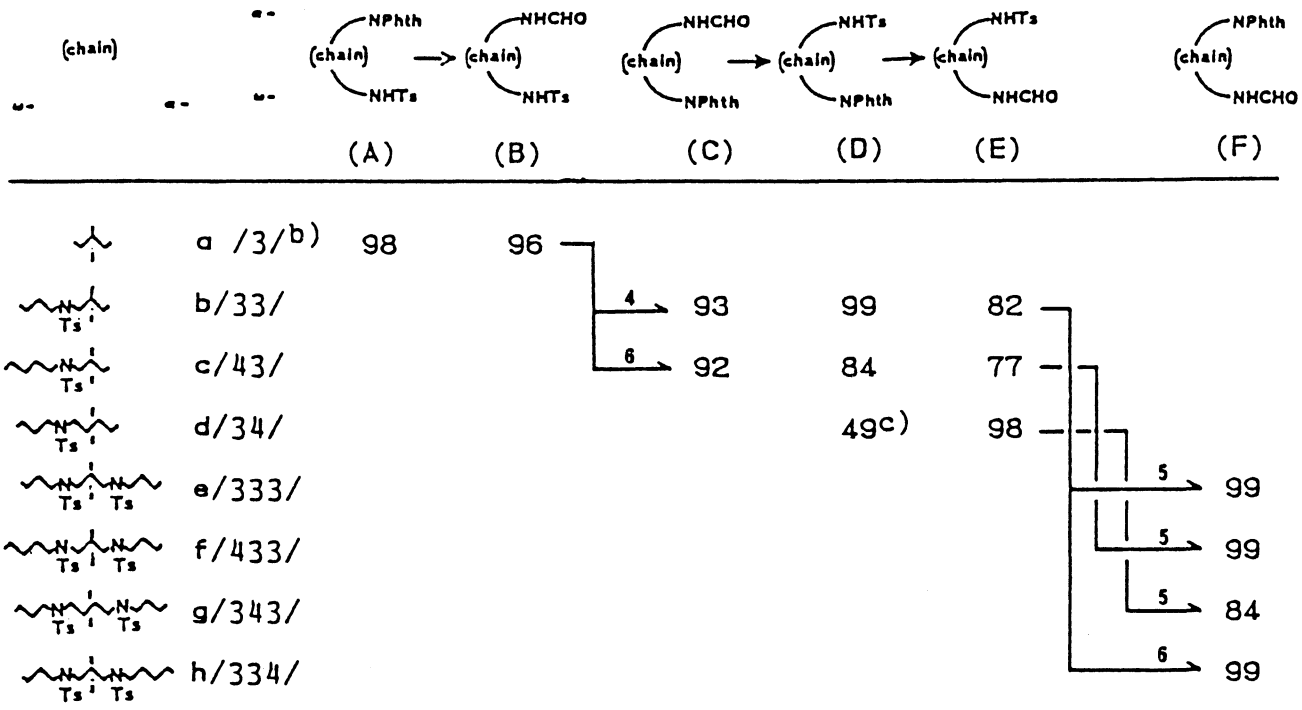
Scheme 1.

Results and Discussion

In the presence of triethylamine, **3** was tosylated with tosyl chloride in pyridine to give **Aa**,[10] which was treated with hydrazine hydrate in DMF to afford **Ba**. Alternatively, nitrosation of **Aa** followed by the rearrangement reaction in benzene gave **4**.[6,11] Condensation of **Ba** with **4** was best carried out by the use of cesium carbonate in DMF[6] to give the aimed threefold protected **Cb** exclusively. This reveals that the formamido nitrogen is far less reactive as nucleophile than the tosylamino nitrogen. Likewise, threefold protected spermidine (**Cc**) was obtained by the reaction of **Ba** with **6**. Hydrolysis of **C** in a mixed solvent of ethanol and 2 M HCl was completed at 75 °C for 3 h to yield the corresponding hydrochloride salts, which

were satisfactorily tosylated with tosyl chloride in pyridine in the presence of triethylamine to afford **D**. Since the present strategy is started with **3**, it is impossible to prepare **Dd** which bears the same functional groups at each primary amines in the opposite order to those of **Dc**. Therefore, **Dd** was supplied by the reaction of *N*,*N*′-ditosyl-1,4-butanediamine with **4**. All the **D** series of compounds were subjected to the transformation with hydrazine hydrate in DMF,[7] in the same way as **A** to **B** conversion, to afford **E** series. At this stage, we were ready to carry out the *N*-alkylation at the α-terminus with ω-phthalimidated compounds, **5** and **6**, to construct the second series of threefold protected natural tetramines (**F**). Symmetrical thermine derivative,[12a] **Fe**, was prepared by the reaction of **Eb** with **5** in DMF in the presence of cesium carbonate. Likewise, two isomers of unsymmetrical thermospermine derivatives,[12b] **Ff** and **Fh**, were prepared by the

Table 1. Product Yield(%) of Systematic Differential Protection of Amino Groups[a]



a) The transformation/substitution products are correlated by the arrow, the number on which corresponds to a electrophile employed in Scheme 1. b) the abbreviated chain symbol in the second column stands for the contiguous methylene chain blocks in Arabic numerals with default of nitrogen atoms between slant lines. In the first column, ω-terminus is placed at the left side and α-terminus, at the right side. These termini were arbitrarily chosen, independent of the nomenclature rule. c) **Dd**, obtained as by-product in the separate route (see Experimental).

Table 2. Chemical Shifts of Methylene Protons in ^{1}H NMR Spectra for Differentially Protected Polyamines, **B** through **F**.[a] (δ/ppm, in $CDCl_3$)

Compd		C1	C2	C3	C5	C6	C7	C8	C9	C10	C11	C12
Ba	3	3.40	1.70	2.96								
Cb	33	3.48	1.82	3.17	3.19	1.90	3.70					
Cc	43	3.44	1.77	3.16	3.14	1.56	1.66	3.66				
Db	33	3.67	1.84	3.15	3.15	1.84	3.10					
Dc	43	3.05	1.76	3.14	3.10	1.51	1.63	3.64				
Dd	34	3.78	1.87	3.15	3.04	1.71	1.60	2.99				
Eb	33	3.35	1.75	3.12	3.14	1.78	3.00					
Ec	43	3.03	1.78	3.13	3.08	1.55	1.55	3.31				
Ed	34	3.41	1.78	3.13	3.06	1.61	1.52	2.93				
Fe	333	3.43	1.82	3.16	3.12	1.88	3.15		3.16	1.94	3.71	
Ff	433	3.71	1.89	3.17	3.13	1.96	3.16		3.09	1.67	1.60	3.35
Fg	343	3.42	1.80	3.16	3.13	1.59	1.59	3.15		3.15	1.88	3.67
Fh	334	3.43	1.81	3.15	3.11	1.87	3.13		3.11	1.55	1.66	3.67

a) See Ref. 13 for the significance of abbreviated designation.

Table 3. Chemical Shifts of Miscellaneous Protons in ^{1}H NMR Spectra for Differentially Protected Polyamines, **B** through **F**.[a] (δ/ppm, in $CDCl_3$)

Compd	ArMe	NH-Ts	NH-CHO	CHO	ArHme	ArHs	PhthH
Ba 3	2.43	5.45	6.02	8.16	7.31	7.74	
Cb 33	2.42		6.37	8.21	7.29	7.65	7.73, 7.84
Cc 43	2.40		6.38	8.21	7.29	7.66	7.73, 7.84
Db 33	2.43	5.36			7.31	7.64, 7.76	7.72, 7.84
Dc 43	2.41, 2.43	5.35			7.29, 7.31	7.65, 7.77	7.72, 7.86
Dd 34	2.42, 2.43	5.15			7.30, 7.31	7.65, 7.75	7.73, 7.82
Eb 33	2.43	5.30	6.24	8.16	7.31, 7.32	7.65, 7.74	
Ec 43	2.43, 2.44	4.97	6.36	8.20	7.32, 7.33	7.67, 7.77	
Ed 34	2.43	5.37	5.80	8.18	7.31	7.65, 7.75	
Fe 333	2.42		6.45	8.20	7.31, 7.32	7.64, 7.66	7.75, 7.84
Ff 433	2.42, 2.43		6.17	8.17	7.31	7.65	7.73, 7.84
Fg 343	2.42, 2.43		6.41	8.19	7.30, 7.32	7.64, 7.67	7.73, 7.86
Fh 334	2.40, 2.43		6.42	8.20	7.29, 7.33	7.64, 7.66	7.72, 7.84

a) See Ref. 13 for the significance of abbreviated designation.

reaction of **Ec** with **5** and **Eb** with **6**, respectively. Threefold protected spermine derivative, **Fg**, was prepared from **Ed** and **5** as well. Relationshlp between starting materials and products are shown together with all the product yields in Table 1. Tables 2 and 3 are implicated to chemical shifts of all the protons in ^{1}H NMR spectra for **B** through **F** series of compounds.

In viewpoint of regioselectivity of the chain elongation and transformation and excellent product yields in each step, the present method for differential protection provides a new synthetic approach to polyamine conjugates. According to the present method, natural polyamines differentially modifiable at each terminus are supplied in a large scale from the cheap starting materials.

Experimental

General: The ^{1}H NMR spectra were recorded on JEOL GSX-500S (500 MHz) instrument 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 and hertz, respectively. Infrared spectra (IR) were obtained on a Shimadzu IR-27 apparatus. Merck sllica 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). Pyridine, triethylamine, tosyl chloride, hydrazine hydrate, anhydrous cesium carbonate, and sodium nitrite are purchased and employed without further puriflcation. The preparation of *N,N:N′,N′*-diphthaloyl-1,3-propanediamine (**1**) and its transformation to 3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoindol-6-one (**2**) have been reported recently.[5] Hydrolysis of **2** to *N,N*-phthaloyl-1,3-propanediamine hydrochloride (**3**) and its tosylation to give *N,N*-phthaloyl-*N′*-tosyl-1,3-propanediamine (**Aa**) have been described in the preceding report.[6] ω-Phthalimidated electrophiles, **4**, **5**, and **6**, were prepared by the method in the preceding report.[6,11] N^1,N^1-Phthaloyl-4,N^8-ditosyl-4-azaoctane-1,8-diamine (**Dd**) was prepared as by-product in the following procedure; to a stirred mixture of Na-salt of *N,N′*-ditosyl-1,4-butanediamine[14] in DMF, **4** (2.6 mol equiv) in DMF was added dropwise at 80 °C. After workup, the residue was chromatographed on a silica-gel column to give *N,N′*-bis(3-phthalimidopropyl)-*N,N′*-ditosyl-1,4-butanediamine as a crystal in 44% yield[6] and **Dd** in 49% yield as viscous liquid; **Dd**, Found: C, 59.40; H, 5.71; N, 7.17; S, 10.71%. Calcd for $C_{29}H_{33}O_6N_3S_2$: C, 59.67; H, 5.70; N, 7.20; S, 10.99%. IR (KRS), ν 3290 (NH), 1770 and 1710 (CO), and 1330 and 1150 (SO_2) cm^{-1}.

General Procedure for Formation of Formamides (B and E) from Phthalimides (A and D): To a solution of phthalimide (**A** or **D**) in DMF, hydrazine hydrate (10 mol equiv) was added and the mixture was heated at 75 °C for more than 18 h. After removal of DMF under reduced pressure, the residue was chromatographed on a silica-gel column eluting with chloroform–methanol (9 : 1 v/v) to give formamide (**B** or **E**).

General Procedure for the Chain Elongation Reaction from ω-Formyl-α-*p*-toluenesulfonamides (B and E) to ω-Formyl-α-phthalimides (C and E): A mixture of formamidated *p*-toluenesulfonamide (**B** or **E**), one of appropriate ω-phthalimidated electrophile (**4**, **5**, or **6**) (1.1 mol equiv to **B** or **E**), and cesium carbonate (1.2 mol equiv) in DMF was stirred at ambient temperature for two days. The mixture was filtered through Celite, then the solvent was removed under reduced pressure. The residue was chromatographed on a silica-gel column eluting with chloroform–acetone (95 : 5 v/v) to give formamidated phthalimide (**C** or **F**).

General Procedure for Hydrolysis and Tosylation of α-Formy-ω-phthalimide (C) to Form α-Tosylamino-ω-phthalimide (D): To a solution of **C** in a small amount of ethanol, 2 M hydrochloric acid was added and heated at 80 °C for 4 h. The solvents were removed under reduced pressure and the residue was stirred with tosyl chloride (1.5 mol equiv to **C**) in pyridine containing a small amount of triethylamine at ambient temperature for 4 h. The solvents were evaporated under reduced pressure and the residue was chromatographed on a silica-gel column eluting with chloroform–acetone (9 : 1 v/v) to afford **D**.

N^1-Formyl-N^3-tosyl-1,3-propanediamine (Ba); viscous

liquid. Found: C, 51.55; H, 6.35; N, 10.94; S, 12.30%. Calcd for $C_{11}H_{16}O_3N_2S$: C, 51.54; H, 6.29; N, 10.93; S, 12.51%. IR (KRS) ν 3360, 3270 (NH), 1660, 1525, 1440 (C=O), 1320, 1150 (SO_2) cm^{-1}.

N^1-Formyl-N^7,N^7-phthaloyl-4-tosyl-4-azapheptane-1,7-diamine (Cb); mp 129—130 °C (spont. cryst.). Found: C, 59.32; H, 5.71; N, 9.53; S, 6.92%. Calcd for $C_{22}H_{25}O_5N_3S$: C, 59.58; H, 5.68; N, 9.48; S, 7.23%. IR (KBr) ν 3400 (NH), 1770, 1710 (C=O), 1670, 1520, 1435, (NHCHO), 1345, 1155 (SO_2) cm^{-1}.

N^7,N^7-Phthaloyl-N^1,4-ditosyl-4-azaheptane-1,7-diamine (Db); amorphous powder. Found: C, 59.05; H, 5.49; N, 7.17; S, 11.13%. Calcd for $C_{28}H_{31}O_6N_3S_2$: C, 59.03; H, 5.49; N, 7.38; S, 11.26%. IR (KBr) ν 3290 (NH), 1765, 1710 (C=O), 1330, 1155 (SO_2) cm^{-1}.

N^7-Formyl-N^1,4-ditosyl-4-azaheptane-1,7-diamine (Eb); viscous liquid. Found: C, 54.02; H, 6.35; N, 9.04; S, 13.74%. Calcd for $C_{21}H_{29}O_5N_3S_2$: C, 53.94; H, 6.25; N, 8.99; S, 13.72%. IR (KRS) ν 3380, 3290 (NH), 1670, 1520, 1450 (NHCHO), 1330, 1150 (SO_2) cm^{-1}.

N^1-Formyl-N^8,N^8-phthaloyl-4-tosyl-4-azaoctane-1,8-diamine (Cc); mp 103—104 °C (spont. cryst.). Found: C, 60.12; H, 6.01; N, 9.11; S, 6.88%. Calcd for $C_{23}H_{27}O_5N_3S$: C, 60.37; H, 5.95; N, 9.19; S, 7.01%. IR (KBr) ν 3320 (NH), 1770, 1700 (C=O), 1650, 1535 (NHCHO), 1340, 1160 (SO_2) cm^{-1}.

N^8,N^8-Phthaloyl-N^1,4-ditosyl-4-azaheptane-1,8-diamine (Dc); viscous liquid. Found: C, 59.89; H, 5.54; N, 7.04; S, 11.28%. Calcd for $C_{29}H_{33}O_6N_3S_2$: C, 59.67; H, 5.70; N, 7.20; S, 10.99%. IR (KRS) ν 3290 (NH), 1770, 1710 (C=O), 1330, 1160 (SO_2) cm^{-1}.

N^8-Formyl-N^1,4-ditosyl-4-azaheptane-1,8-diamine (Ec); viscous liquid. Found: C, 54.86; H, 6.49; N, 8.94; S, 13.04%. Calcd for $C_{22}H_{31}O_5N_3S_2$: C, 54.86; H, 6.49; N, 8.73; S, 13.32%. IR (KRS) ν 3370, 3290 (NH), 1665, 1525, 1450 (NHCHO), 1330, 1160 (SO_2) cm^{-1}.

N^1-Formyl-4,N^8-ditosyl-4-azaheptane-1,8-diamine (Ed); viscous liquid. Found: C, 54.67; H, 6.51; N, 8.70; S, 13.04%. Calcd for $C_{22}H_{31}O_5N_3S_2$: C, 54.86; H, 6.49; N, 8.73; S, 13.32%. IR (KRS) ν 3370, 3280 (NH), 1670, 1530, 1450 (NHCHO), 1325, 1155 (SO_2) cm^{-1}.

N^1-Formyl-N^{11},N^{11}-phthaloyl-4,8-ditosyl-4,8-diazaundecane-1,11-diamine (Fe); viscous liquid. Found: C, 58.98; H, 5.94; N, 8.47; S, 6.88%. Calcd for $C_{32}H_{38}O_7N_4S_2$: C, 58.69; H, 5.85; N, 8.56; S, 7.01%. IR (KRS) ν 3380 (NH), 1770, 1710 (C=O), 1670, 1520, 1425 (NHCHO), 1330, 1150 (SO_2) cm^{-1}.

N^{12}-Formyl-,N^1,N^1-phthaloyl-4,8-ditosyl-4,8-diazadodecane-1,12-diamine (Ff); viscous liquid. Found: C, 59.14; H, 6.10; N, 8.33; S, 9.84%. Calcd for $C_{33}H_{40}O_7N_4S_2$: C, 59.26; H, 6.03; N, 8.38; S, 9.59%. IR (KRS) ν 3390 (NH), 1770, 1710 (C=O), 1670, 1520, 1435 (NHCHO), 1335, 1157 (SO_2) cm^{-1}.

N^1-Formyl-N^{12},N^{12}-phthaloyl-4,9-ditosyl-4,9-diazadodecane-1,12-diamine (Fg); viscous liquid. Found: C, 59.48; H, 6.15; N, 8.64; S, 9.25%. Calcd for $C_{33}H_{40}O_7N_4S_2$: C, 59.26; H, 6.03; N, 8.38; S, 9.59%. IR (KRS) ν 3390 (NH), 1770, 1710 (C=O), 1670, 1520, 1432 (NHCHO), 1334, 1155 (SO_2) cm^{-1}.

N^1-Formyl-N^{12},N^{12}-phthaloyl-4,8-ditosyl-4,8-diazadodecane-1,12-diamine (Fh); viscous liquid. Found: C, 59.56; H, 6.12; N, 8.44; S, 9.42%. Calcd for $C_{33}H_{40}O_7N_4S_2$: C, 59.26; H, 6.03; N, 8.38; S, 9.59%. IR (KRS) ν 3390 (NH), 1770, 1710 (C=O), 1670, 1520, 1435 (NHCHO), 1330, 1153 (SO_2) cm^{-1}.

We are indebted to Dr. Hiroshi Yamazaki and his staff in RIKEN for performing elemental analyses and to Dr. Jun Uzawa and Mrs. Tamiko Chijimatsu in RIKEN for measurement of ^1H NMR spectra. M. I. is grateful to the Ministry of Education, Science and Culture for a financial support by a Grant-in-Aid for Scientific Research (No. 62540397).

References

1) B. Ganem, *Acc. Chem. Res.*, **15**, 290 (1982); H. H. Wasserman and J. S. Wu, *Heterocycles*, **17**, 581 (1982); G. B. Henderson, P. Ulrich, A. H. Fairlamb, and A. Cerami, *J. Chem. Soc., Chem. Commun.*, **1986**, 593.

2) K. Chantrapromma, J. S. McManis, and B. Ganem., *Tetrahedron Lett.*, **21**, 2475 (1980).

3) H. Yamamoto and K. Maruoka, *J. Am. Chem. Soc.*, **103**, 6133 (1981).

4) E. Waelchli-Schaer and C. H. Eugster, *Helv. Chim. Acta*, **61**, 928 (1978).

5) Presented in part at the 55th Annual Meeting of the Chemical Society of Japan, Fukuoka, October, 1987, Abstr. No. 1X12.

6) Presented in part at the 57th Annual Meeting of the Chemical Society of Japan, Sendai, September, 1988, Abstr. No. 1F433; M. Iwata and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, **62**, 198 (1989).

7) M. Iwata and H. Kuzuhara, *Chem. Lett.*, **1986**, 951.

8) T. Hamada, A. Nishida, and O. Yonemitsu, *J. Am. Chem. Soc.*, **108**, 140 (1986).

9) T. W. Greene, "Protective Groups in Organic Synthesis," John Wiley and Sons Inc., New York (1981).

10) The notation of the protected polyamines is comprised of the combination of the type of the terminal functional groups in capital letter with the type of the inside chain in small alphabet.

11) M. Iwata and H. Kuzuhara, *J. Chem. Soc., Chem. Commun.*, **1985**, 918; M. Iwata and H. Kuzuhara, *Chem. Lett.*, **1985**, 1941; **1986**, 369.

12) a) T. Ohshima, *Biochem. Biophys. Res. Commun.*, **63**, 1093 (1975). b) *Idem, J. Biol. Chem.*, **254**, 8720 (1979).

13) Cl- through C12-protons are the methylene protons at the position ordered by the nomenclature rule. ArMe-protons designate methyl protons attached to aromatic ring. ArHme-protons designate aromatic protons disposed at position ortho to the methyl group. ArHs-protons designate aromatic protons disposed at position ortho to the sulfonyl group.

14) M. Iwata and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, **55**, 2153 (1982).