Synthesis of Large Macrocyclic Tetraaza Compounds with A Methylene Backbone: Cyclo[-NH- $(CH_2)_n$-]$_4$, (n = 6, 7, 8, 9 and 10). The Formation of 28-, 32-, 36-, 40- and 44-Membered Rings.

Takenori Tomohiro, Kouichi Uoto [1], and Hiroaki (Yohmei) Okuno*

National Chemical Laboratory for Industry (NCLI), Tsukuba, Ibaraki 305, Japan

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A series of macrocyclic tetraamines with 28-, 32-, 36-, 40- and 44-membered rings have been efficiently prepared from the corresponding ditosylamide and monobromoalcohol derivatives in 6 steps *via* a double condensation reaction. Overall yields were: 41, 41, 46, 29, and 33%, respectively, for 1,8,15,22-tetraazacyclooctacontane (**11a**), 1,9,17,25-tetraazacyclodotriacontane (**11b**), 1,10,19,28-tetraazacyclohexatriacontane (**11c**), 1,11,21,31-tetraazacyclotetracontane (**11d**) and 1,12,23,34-tetraazacyclotetratetracontane (**11e**).

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Novel biologically active materials have been derived through the interaction between organic compounds and metal ions. Typical examples include the metalloenzymes [2], bleomycin and cisplatin [3]. In the past we have been interested in anticancer platinum pyrimidines [4] as well as iron-sulphur protein analogues with macrocyclic tetrathiolate ligands where the 4Fe-4S cubane core is embedded in an intramolecular hydrophobic environment [5]. Nonheme-containing iron-sulphur proteins are found in a wide distribution of living organisms, from bacteria to mammals [6], and assume a very important role in various biological redox reactions - especially as agents for electron transfer. These high-potential proteins [7-9] exhibited redox potentials (1-/2-) near +0.35 volts *vs.* NHE at *p*H 7 in water. The structure of the 4Fe-4S active site of these proteins is very similar to that of low-potential 4Fe-4S ferredoxins, which exhibit redox potentials in their most stable forms (2-/3-) near -0.4 to -0.6 volts [6,10,11]. Since the active site cores in these high-potential proteins are surrounded by proteins which are composed largely of hydrophobic amino acids [12,13], the contribution of a hydrophobic environment may be important for stabilizing the 4Fe-4S cores, especially for the high-potential proteins. We sought to examine the environmental effects on the Fe_4S_4 core using macrocyclic tetrathiol ligands which provide intramolecular hydrophobic domains instead of the conventional small alkyl- and arylthiolate ligands, and also investigate their ability to fix carbon dioxide [14]. In order to do this, an efficient preparation of the key compounds, a series of cyclic tetraamines containing 28-, 32-, 36-, 40-,

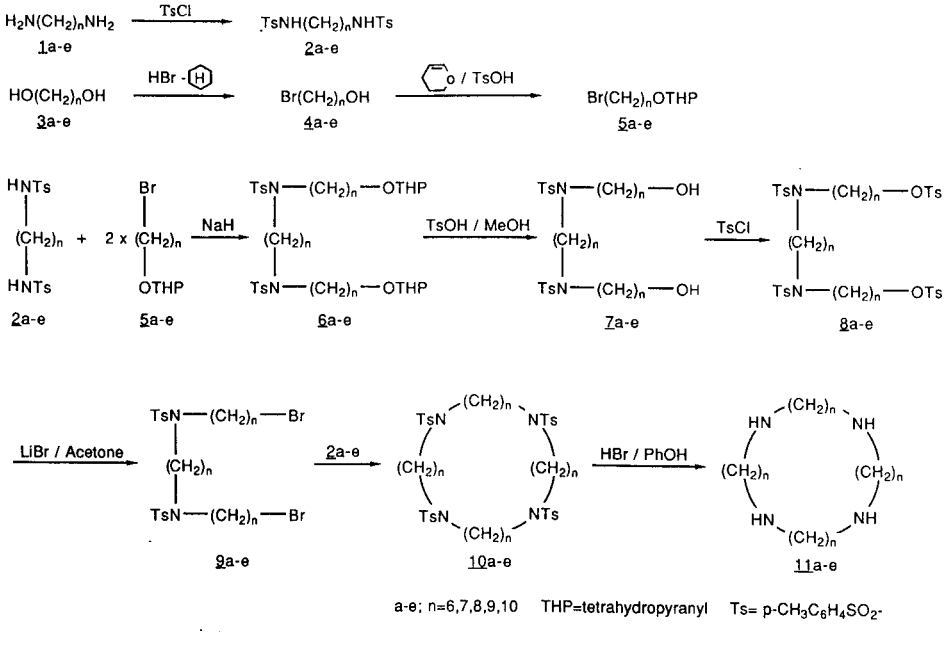

Figure 1. Synthetic Route to Macrocyclic Tetraamines.

and 44-membered rings, was highly desired. There was, however, little precedent available in the literature for the synthesis of such large macrocyclic tetraamines. We reported in a previous work a new facile synthetic route to 36- and 38-membered ring tetraaza macrocycles consisting of a methylene backbone and a cyclophane-type skeleton [15,16]. We describe in the present work a successful application of this synthetic method to the preparation of large macrocyclic tetraamine derivatives with 28- and 44-membered rings which involves a double condensation reaction [17].

Previously reported methods to obtain cyclic tetraamine compounds utilized reductions of the corresponding tetralactams, or featured a direct formation starting with the appropriate amine derivatives. Only limited examples are known, for the preparation of large-ring tetralactams. These are made using silyl compounds as templates [18], and also by intramolecular cyclization reactions [19].

In our earlier reports we gave an account of the synthesis of 36-membered tetralactam rings from the corresponding linear amides *via* an intramolecular azide [20], or *via* a double condensation of a diamine with dicarboxylic acid derivatives [15]. The subsequent reduction of the tetralactams into cyclic tetraamines, however, proved unsatisfactory ($\leq 10\%$ yield). We report in the present work a direct formation of tetraamide derivatives **10** by a double condensation reaction between ditosylamide **2** and dibromo compounds **9** as shown in Figure 1.

The tetraamine **11** was synthesized as follows. Treatment of **2** with two equivalents of **5** in the presence of sodium hydride, and dimethylformamide gave **6**. After removal of the tetrahydropyranyl groups, the resulting **7** was subsequently, treated with tosyl chloride to give **8**. The dibromo compound **9** was synthesized by treatment of **8** with lithium bromide. The double condensation reaction [15] between **9** and **2** proceeded smoothly in DMF in the presence of sodium hydride to afford **10**. The reaction could be carried out at a 10 mmole concentration without high-dilution techniques to give the corresponding macrocycle in excellent yields. The tosylate **10** was then converted into the free tetraamine **11** in a phenolic solution of hydrogen bromide. Thus, **11a-e** were obtained in 41, 41, 46, 29 and 33% overall yields, respectively, for **11a**, **11b**, **11c**, **11dc** and **11e** in six steps starting from **2** and **5**. The yields for each step are summarized in Table 1. The corresponding 2 + 2 cyclization [21,22] gave very poor yields. For example, compound **10c** was obtained in only 9% yield while the corresponding 1 + 1 adduct was isolated in 72% yield [17].

Table 1

Synthesis of Macrocyclic Tetraamines

Compound	Yield (%) of 6	7	8	9	10	11	Overall yield, %	[Ring size]
a (n = 6)	97	94	96	98	70	68	40.8	[28]
b (n = 7)	93	99	92	98	66	74	40.5	[32]
c (n = 8)	92	92	91	85	77	91	45.9	[36] [a]
d (n = 9)	69	quant	95	95	63	75	29.4	[40]
e (n = 10)	84	quant	92	91	59	80	33.2	[44]

[a] Data from ref 5.

EXPERIMENTAL

Melting points are uncorrected. Flash chromatographic separations were carried out on 230-400 mesh silica gel 60. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl; dimethylformamide, methylene chloride, acetonitrile benzene, hexane and chloroform were distilled over calcium hydride. Ethanol and methanol were distilled over magnesium. Ethyl acetate and acetone were purified by simple distillation. *N,N'*-Dimethylaminopyridine (DMAP) was recrystallized from benzene-hexane. Other materials were purchased from appropriate sources and used as received. Infrared spectra were obtained with a JASCO IRA-2. The nmr spectra were determined on a JEOL JMN GX-270 or a JEOL FX-100 spectrometer, and chemical shifts are relative to TMS as an internal reference. Mass spectra were measured on a JEOL JMS-D300 spectrometer. Synthesis of the 36-membered ring compound (c series) has been described elsewhere [5].

N,N'-Bis-*p*-toluenesulfonyl-1,6-hexanediamine (**2a**).

1,6-Hexanediamine (5.0 g, 43 mmoles), triethylamine (9.1 g, 90 mmoles) and *N,N'*-dimethylaminopyridine (11.0 g, 90 mmoles) were dissolved in 150 ml of dry dichloromethane. To this solution was added 17.2 g (90 mmoles) of *p*-toluenesulfonyl chloride in 50 ml of dichloromethane at 0° and it was stirred for 3 hours at room temperature. The reaction mixture was washed with 3*N* hydrochloric acid, saturated aqueous sodium bicarbonate and brine. The organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness *in vacuo*. Recrystallization from methanol afforded colorless needles in 96% yield (17.5 g), mp 152-153° (methanol); ir (Nujol): 3250 cm^{-1}; ^1H-nmr (deuteriochloroform): ppm 1.0-1.6 (m, 8H, $-CH_2-$), 2.42 (s, 6H, CH_3-Ph), 2.86 (d of t, 4H, J = 6.4 Hz, N_α-CH_2), 4.86 (t, 2H, J = 6.5 Hz, deuterium oxide exchangeable, NH), 7.31 (d, 4H, J = 8.3 Hz, arom), 7.77 (d, 4H, J = 8.3 Hz, arom).

Anal. Calcd. for $C_{20}H_{28}N_2O_4S_2$: C, 56.57; H, 6.64; N, 6.59. Found: C, 56.47; H, 6.65; N, 6.54.

The following compounds were similarly prepared:

N,N'-Bis-*p*-toluenesulfonyl-1,7-heptanediamine (**2b**).

With 1,7-heptanediamine (5.0 g, 38 mmoles), triethylamine (8.2 g, 81 mmoles) and (9.9 g, 81 mmoles) in 150 ml of dry dichloromethane; 15.4 g (81 mmoles) of *p*-toluenesulfonyl chloride in 50 ml of dichloromethane; colorless needles were obtained (15.5 g, 92%), mp 141.5-142.5° (methanol); ir (Nujol): 3240 cm^{-1}; ^1H-nmr (deuteriochloroform): ppm 1.0-1.6 (m, 10H, $-CH_2-$), 2.41 (s, 6H, CH_3-Ph), 2.86 (d of t, 4H, J = 6.4 Hz, N_α-CH_2), 4.97 (t, 2H, J = 6.5 Hz, deuterium oxide exchangeable, NH), 7.28 (d, 4H, J = 8.3 Hz, arom), 7.75 (d, 4H, J = 8.3 Hz, arom).

Anal. Calcd. for $C_{21}H_{30}N_2O_4S_2$: C, 57.50; H, 6.89; N, 6.38. Found: C, 57.40; H, 6.93; N, 6.35.

N,N'-Bis-*p*-toluenesulfonyl-1,9-nonanediamine (**2d**).

1,9-Nonanediamine (5.0 g, 32 mmoles), triethylamine (6.7 g, 66 mmoles) and *N,N'*-dimethylaminopyridine (8.1 g, 66 mmoles) in 120 ml of dry dichloromethane (12.6 g, 66 mmoles) of *p*-toluenesulfonyl chloride in 30 ml of dichloromethane gave colorless leaflets, 13.9 g (94%); mp 92-93° (methanol/*n*-hexane); ir (Nujol): 3230 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.0-1.6 (m, 14H, $-CH_2-$), 2.41 (s, 6H, CH_3-Ph), 2.89 (d of t, 4H, J = 6.4 Hz, N_α-CH_2), 4.85 (t, 2H, J = 6.5 Hz, deuterium oxide exchangeable, NH), 7.30 (d, 4H, J = 8.3 Hz, arom), 7.76 (d, 4H, J = 8.3 Hz, arom).

Anal. Calcd. for $C_{38}H_{54}N_2O_4S_2$: C, 59.20; H, 7.34; N, 6.00. Found: C, 59.15; H, 7.47; N, 5.94.

N,N'-Bis-*p*-toluenesulfonyl-1,10-decanediamine (**2e**).

1,10-Decanediamine (5.0 g, 29 mmoles), triethylamine (6.2 g, 61 mmoles) and *N,N'*-dimethylaminopyridine (7.4 g, 61 mmoles) in 120 ml of dry dichloromethane 11.6 g (61 mmoles) or *p*-toluenesulfonyl chloride in 30 ml of dichloromethane gave colorless needles, 11.9 g (86%), mp 122-123.5° (methanol); ir (Nujol): 3270 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.0-1.6 (m, 16H, $-CH_2-$), 2.42 (s, 6H, CH_3-Ph), 2.93 (d of t, 4H, J = 6.4 Hz, N_α-CH_2), 4.87 (t, 2H, J = 6.5 Hz, deuterium oxide exchangeable, NH), 7.30 (d, 4H, J = 8.3 Hz, arom), 7.78 (d, 4H, J = 8.3 Hz, arom).

Anal. Calcd. for $C_{24}H_{36}N_2O_4S_2$: C, 59.97; H, 7.55; N, 5.83. Found: C, 60.00; H, 7.62; N, 5.78.

6-Bromo-1-hexanol (**4a**).

According to the slightly modified procedure described by Babler and Invergo [23], a mixture of 1,6-hexanediol (12.0 g, 0.10 mole), 48% hydrobromic acid (383 ml), and water (117 ml) was heated at 70° for 50 hours while being continuously extracted with cyclohexane. The extract was dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and the residue was chromatographed on silica gel with *n*-hexane-ethyl acetate (3:2). A colorless oil was obtained in 70% yield (12.8 g); ir (chloroform): 3620, 3300 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.2-2.1 (m, 8H, $-CH_2-$), 3.42 (t, 2H, J = 6.3 Hz, Br-CH_2), 3.66 (t, 2H, J = 6.0 Hz, O-CH_2), 5.27 (s, 1H, deuterium oxide exchangeable, OH).

Similarly the following compounds were obtained.

7-Bromo-1-heptanol (**4b**).

1,7-Heptanediol (13.2 g, 0.10 mole), 48% hydrobromic acid (383 ml), and water (117 ml) was heated at 70° for 65 hours with cyclohexane and chromatographed on silica gel with *n*-hexane-ethyl acetae (1:1) to give 16.5 g (85%) as a colorless liquid; ir (chloroform): 3600, 3350 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.2-2.1 (m, 10H, $-CH_2-$), 3.40 (t, 2H, J = 6.3 Hz, Br-CH_2), 3.64 (t, 2H, J = 6.3 Hz, O-CH_2), 5.27 (s, 1H, deuterium oxide exchangeable, OH).

Anal. Calcd. for $C_7H_{15}BrO$: C, 43.09; H, 7.75. Found: C, 43.36; H, 7.73.

9-Bromo-1-nonanol (**4d**).

1,9-Nonanediol (16.0 g, 0.10 mole), 48% hydrobromic acid (383 ml), and water (117 ml) was heated at 70° for 60 hours with cyclohexane and chromatographed on silica gel with *n*-hexane-ethyl acetate (3:1) to give 17.7 g (80%) as a colorless liquid; ir (chloroform): 3520, 3450, 1720 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.2-2.1 (m, 14H, $-CH_2-$), 2.33 (s, 1H, deuterium oxide exchangeable, OH), 3.39 (t, 2H, J = 6.8 Hz, Br-CH_2), 3.63 (t, 2H, J = 6.2 Hz, O-CH_2).

Anal. Calcd. for $C_9H_{19}BrO$: C, 48.44; H, 8.58. Found: C, 48.23; H, 8.64.

10-Bromo-1-decanol (**4e**).

1,10-Decanediol (17.4 g, 0.10 mole), 48% hydrobromic acid (383 ml), and water (117 ml) was heated at 70° for 40 hours with cyclohexane and chromatographed on silica gel with *n*-hexane-ethyl acetate (3:1) to afford 17.6 g (74%) as a colorless liquid; ir (chloroform): 3600 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.2-2.0 (m, 16H, $-CH_2-$), 2.68 (s, 1H, deuterium oxide exchangeable, OH), 3.40 (t, 2H, J = 6.5 Hz, Br-CH_2), 3.63 (t, 2H, J = 6.3 Hz, O-CH_2).

Anal. Calcd. for $C_{10}H_{21}BrO$: C, 50.64; H, 8.92. Found: C, 50.57; H, 9.05.

6-Bromo-1-(2-tetrahydropyranyloxy)hexane (**5a**).

A mixture of 6-bromo-1-hexanol (12.0 g, 66 mmoles), 2,3-dihydropyran (6.7 g, 80 mmoles) in dry ether (80 ml) containing *p*-toluene sulfonic acid monohydrate (0.25 g, 1.3 mmoles) was stirred for 12 hours at room temperature. Ether (200 ml) was added to the mixture, and the organic layer was washed successively with 1*N* aqueous sodium hydroxide, water and brine. After removal of the solvent, the residue was fractionally distilled to give 16.7 g (95%) of a colorless liquid, bp 125°/0.14 mm Hg; ir (chloroform): 1720 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.3-2.1 (m, 14H, $-CH_2-$), 3.41 (t, 2H, J = 6.9 Hz, Br-CH_2), 3.5-4.2 (m, 4H, O-CH_2), 4.5-4.7 (m, 1H, O-CH-O).

Anal. Calcd. for $C_{11}H_{21}BrO_2$: C, 49.82; H, 7.98. Found: C, 50.11; H, 8.07.

Similarly the following analogues were synthesized.

7-Bromo-1-(2-tetrahydropyranyloxy)heptane (**5b**).

7-Bromo-1-heptanol (15.0 g, 77 mmoles), 2,3-dihydropyran (7.1 g, 84 mmoles) in dry ether (100 ml), *p*-toluene sulfonic acid monohydrate (0.29 g, 1.5 mmoles) were stirred for 14 hours at room temperature. Ether (200 ml) was added to the mixture, and the same work-up yielded 20.3 g (95%) of a colorless liquid, bp 125°/0.1 mm Hg; ir (chloroform): 1720 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.2-2.1 (m, 16H, $-CH_2-$), 3.40 (t, 2H, J = 6.5 Hz, Br-CH_2), 3.5-4.1 (m, 4H, O-CH_2), 4.5-4.7 (m, 1H, O-CH-O).

Anal. Calcd. for $C_{12}H_{23}BrO_2$: C, 51.61; H, 8.30. Found: C, 51.57; H, 8.39.

9-Bromo-1-(2-tetrahydropyranyloxy)nonane (**5d**).

9-Bromo-1-nonanol (17.0 g, 76 mmoles), 2,3-dihydropyran (7.7 g, 92 mmoles) in dry ether (100 ml), *p*-toluenesulfonic acid monohydrate (0.29 g, 1.5 mmoles) were stirred for 14 hours at room temperature and gave 22.0 g (94%) of a colorless liquid, bp 157-158°/0.6 mm Hg; ir (chloroform): 1710 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-2.1 (m, 20H, $-CH_2-$), 3.40 (t, 2H, J = 6.7 Hz, Br-CH_2), 3.5-4.0 (m, 4H, O-CH_2), 4.5-4.7 (m, 1H, O-CH-O).

Anal. Calcd. for $C_{14}H_{27}BrO_2$: C, 54.72; H, 8.86. Found: C, 54.94; H, 8.96.

10-Bromo-1-(2-tetrahydropyranyloxy)decane (**5e**).

10-Bromo-1-decanol (16.0 g, 67 mmoles), 2,3-dihydropyran (6.2 g, 74 mmoles) in dry ether (90 ml), *p*-toluenesulfonic acid monohydrate (0.26 g, 1.4 mmoles) were stirred for 19 hours at room temperature and after fractional distillation gave 16.9 g (78%) which was chromatographed on silica gel with *n*-hexane-ethyl acetate (10:1) giving 12.2 g (56%) of a colorless liquid, bp 160°/0.9 mm Hg; ir (chloroform): 1720 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.2-2.1 (m, 22H, $-CH_2-$), 3.40 (t, 2H, J = 6.9 Hz, Br-CH_2), 3.5-4.0 (m, 4H, O-CH_2), 4.5-4.7 (m, 1H, O-CH-O).

N,N'-Bis[6-(2-tetrahydropyranyloxy)hexyl]-*N,N'*-di-*p*-toluenesulfonyl-1,6-hexanediamine (**6a**).

To a solution of **2a** (5.0 g, 11.8 mmoles) in dry DMF (60 ml) was added sodium hydride (0.66 g, 27.5 mmoles) in DMF (20 ml). The mixture was stirred at 60° for 30 minutes under reduced pressure (20-25 mm Hg) to evacuate the hydrogen produced, followed by the addition of **5a** (6.6 g, 24.9 mmoles) in DMF (20 ml). The solution was stirred at 60° for 3 hours, and the colorless solid was filtered off over Celite. After evaporation of the solvent *in vacuo*, the residue was dissolved in ethyl acetate, washed with brine twice, dried over anhydrous magnesium sulfate, and chromatographed on silica gel with *n*-hexane-ethyl acetate (1:1) to afford 9.1 g (97%) of a colorless liquid, ir (chloroform): 1595, 1325, 1140 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.9 (m, 36H, $-CH_2-$), 2.42 (s, 6H, CH_3-Ph), 3.09 (t, 8H, J = 7.4 Hz, $N_\alpha-CH_2$), 3.2-4.0 (m, 8H, O-CH_2), 4.5-4.6 (m, 2H, O-CH-O), 7.30 (d, 4H, J = 8.5 Hz, arom), 7.70 (d, 4H, J = 8.5 Hz, arom).

Anal. Calcd. for $C_{42}H_{68}N_2O_8S_2$: C, 63.60: H, 8.64; N, 3.53. Found: C, 63.28; H, 8.69; N, 3.38.

The related compounds were prepared similarly.

N,N'-Bis[7-(2-tetrahydropyranyloxy)heptyl]-*N,N'*-di-*p*-toluenesulfonyl-1,7-heptanediamine (**6b**).

With **2b** (5.0 g, 11.4 mmoles) in dry DMF (60 ml) and sodium hydride (0.66 g, 27.5 mmoles) in DMF (20 ml), **5b** (6.7 g, 24 mmoles) in DMF (20 ml) was stirred at 60° for 3 hours, silica gel with *n*-hexane-ethyl acetate (1:1) to give 8.9 g (93%) of a colorless liquid; ir (chloroform): 1595, 1330, 1145 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.9 (m, 42H, $-CH_2-$), 2.41 (s, 6H, CH_3-Ph), 3.08 (t, 8H, J = 7.5 Hz, $N_\alpha-CH_2$), 3.2-4.1 (m, 8H, O-CH_2), 4.5-4.7 (m, 2H, O-CH-O), 7.30 (d, 4H, arom), 7.70 (d, 4H, J = 8.3 Hz, arom).

Anal. Calcd. for $C_{45}H_{74}N_2O_8S_2$: C, 64.71; H, 8.93; N, 3.35. Found: C, 64.74; H, 8.98; N, 3.25.

N,N'-Bis[9-(2-tetrahydropyranyloxy)nonyl]-*N,N'*-di-*p*-toluenesulfonyl-1,9-nonanediamine (**6d**).

With **2d** (5.0 g, 10.7 mmoles) in dry DMF (100 ml) and sodium hydride (0.6 g, 25.0 mmoles) in DMF (10 ml), **5d** (6.9 g, 22.5 mmoles) in DMF (10 ml) was stirred at 60° for 3 hours, silica gel with *n*-hexane-ethyl acetate (1:1) to give 6.8 g (69%) of a colorless liquid; ir (chloroform): 1595, 1330, 1145 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.9 (m, 48H, $-CH_2-$), 2.41 (s, 6H, CH_3-Ph), 3.09 (t, 8H, J = 6.8 Hz, $N_\alpha-CH_2$), 3.2-4.0 (m, 8H, O-CH_2), 4.5-4.7 (m, 2H, O-CH-O), 7.29 (d, 4H, J = 9.0 Hz, arom), 7.70 (d, 4H, J = 9.0 Hz, arom).

Anal. Calcd. for $C_{51}H_{86}N_2O_8S_2$: C, 66.63; H, 9.43; N, 3.05. Found: C, 66.51; H, 9.52; N, 3.00.

N,N'-Bis[10-(2-tetrahydropyranyloxy)decyl]-*N,N'*-di-*p*-toluenesulfonyl-1,10-decanediamine (**6e**).

With **2e** (3.6 g, 7.5 mmoles) in dry DMF (40 ml) and sodium hydride (0.43 g, 18.0 mmoles) in DMF (5 ml), **5e** (5.0 g, 16 mmoles) in DMF (15 ml) was stirred at 60° for 3 hours, then chromatographed on silica gel with *n*-hexane-ethyl acetate (2:1) to give 6.0 g (84%) of a colorless liquid; ir (chloroform): 1595, 1330, 1150 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.0-1.9 (m, 60H, $-CH_2-$), 2.41 (s, 6H, CH_3-Ph), 3.10 (t, 8H, J = 7.5 Hz, $N_\alpha-CH_2$), 3.3-4.0 (m, 8H, O-CH_2), 4.5-4.7 (m, 2H, O-CH-O), 7.30 (d, 4H, J = 8.3 Hz, arom), 7.70 (d, 4H, J = 8.3 Hz, arom).

N,N'-Bis(6-hydroxyhexyl)-*N,N'*-di-*p*-toluenesulfonyl-1,6-hexanediamine (**7a**).

To a solution of **6a** (8.0 g, 10 mmoles) in methanol (540 ml) was added *p*-toluenesulfonic acid monohydrate (4.0 g, 21 mmoles), and stirred at room temperature for 30 minutes. After evaporation of the solvent, saturated aqueous sodium bicarbonate was poured into the residue, and extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with *n*-hexane-ethyl acetate (1:4) to afford 6.0 g (94%) of a colorless solid. Recrystallization from dichloromethane-petroleum ether gave colorless needles, mp 92-93° (dichloromethane-ether); ir (chloroform): 3580, 3500, 1595, 1325, 1145 1080 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.8 (m, 26H, $-CH_2-$ + OH), 2.42 (s, 6H, CH_3-Ph), 3.09 (t, 8H, J = 6.9 Hz, $N_\alpha-CH_2$), 3.62 (t, 4H, J = 6.3 Hz, O-CH_2), 7.31 (d, 4H, J = 7.5 Hz, arom), 7.70 (d, 4H, J = 7.5 Hz. arom).

Anal. Calcd. for $C_{32}H_{52}N_2O_6S_2$: C, 61.50; H, 8.38; N, 4.48. Found: C, 61.32; H, 8.44; N, 4.43.

Similarly the following derivatives were obtained.

N,N'-Bis(7-hydroxyheptyl)-*N,N'*-di-*p*-toluenesulfonyl-1,7-heptanediamine (**7b**).

Compound **6b** (8.0 g, 9.6 mmoles) in methanol (510 ml) and *p*-toluenesulfonyl chloride (3.8 g, 20 mmoles) were stirred at room temperature for 30 minutes, extracted with ethyl acetate silica gel with *n*-hexane-ethyl acetate (1:4) to afford 6.3 g (99%) of colorless needles, mp 92-93° (dichloromethane-ether); ir (chloroform): 3600, 3420, 1595, 1325, 1145, 1085 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.8 (m, 32H, $-CH_2-$ + OH), 2.41 (s, 6H, CH_3-Ph), 3.08 (t, 8H, J = 6.9 Hz, $N_\alpha-CH_2$), 3.63 (t, 4H, J = 6.3 Hz, O-CH_2), 7.30 (d, 4H, J = 7.8 Hz, arom), 7.69 (d, 4H, J = 7.8 Hz, arom).

Anal. Calcd. for $C_{35}H_{58}N_2O_6S_2$: C, 63.03; H, 8.77. N, 4.20. Found: C, 62.98; H, 8.84; N, 4.11.

N,N'-Bis(9-hydroxynonyl)-*N,N'*-di-*p*-toluenesulfonyl-1,9-nonanediamine (**7d**).

Compound **6d** (6.8 g, 7.4 mmoles) in methanol (380 ml) and *p*-toluenesulfonyl chloride (2.9 g, 15 mmoles) were stirred at room temperature for 20 minutes, extracted with ethyl acetate and chromatographed on silica gel with *n*-hexane-ethyl acetate (1:4) to give 5.6 g (quantitative) of colorless needles, mp 92-93°; ir (chloroform): 3600, 3500, 1595, 1345, 1150, 1085 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.7 (m, 36H, $-CH_2-$), 1.87 (s, 2H, deuterium oxide exchangeable, OH), 2.41 (s, 6H, CH_3-Ph), 3.09 (t, 8H, J = 7.2 Hz, $N_\alpha-CH_2$), 3.63 (t, 4H, J = 6.3 Hz, O-CH_2), 7.30 (d, 4H, J = 8.1 Hz, arom), 7.71 (d, 4H, J = 8.1 Hz, arom).

Anal. Calcd. for $C_{41}H_{70}N_2O_6S_2$: C, 65.56; H, 9.39; N, 3.73. Found: C, 65.59; H, 9.50; N, 3.62.

N,N'-Bis(10-hydroxydecyl)-*N,N'*-di-*p*-toluenesulfonyl-1,10-decanediamine (**7e**).

Compound **6e** (6.0 g, 6.2 mmoles) in methanol (330 ml) and *p*-toluene sulfonic acid (2.5 g, 13 mmoles) were stirred at room temperature for 20 minutes, then extracted with ethyl acetate. It was chromatographed on silica gel with *n*-hexane-ethyl acetate (1:4) to provide 5.0 g (quantitative) of a colorless liquid; ir (chloroform): 3600, 3520, 1595, 1325, 1145, 1085 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.8 (m, 50H, $-CH_2-$ + OH), 2.41 (s, 6H, CH_3-Ph), 3.09 (t, 8H, J = 5.6 Hz, $N_\alpha-CH_2$), 3.63 (t, 4H, J = 6.1 Hz, O-CH_2), 7.29 (d, 4H, J = 7.8 Hz, arom), 7.70 (d, 4H, J = 7.8 Hz,

arom).

Anal. Calcd. for $C_{44}H_{76}N_2O_6S_2$: C, 66.63; H, 9.66; N, 3.53. Found: C, 66.37; H, 9.60; N, 3.40.

N,N'-Di-*p*-toluenesulfonyl-*N,N'*-bis[6-(*p*-toluenesulfonyloxy)hexyl]-1,6-hexanediamine (**8a**).

To a mixture of **7a** (5.0 g, 8.0 mmoles), triethylamine (1.7 g, 17 mmoles) and *N,N'*-dimethylaminopyridine (2.1 g, 17 mmoles) in dry dichloromethane (150 ml) was added dropwise *p*-toluenesulfonic acid (3.2 g, 17 mmoles) in dichloromethane (50 ml), and the solution was stirred for 3 hours at room temperature. Then the reaction mixture was washed successively with 3*N* hydrochloric acid, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo*. Column chromatography on silica gel with benzene-ethyl acetate (10:1) afforded 7.2 g (96%) of a colorless solid. Recrystallization from methanol gave colorless leaflets, mp 93.5-94.5° (methanol); ir (chloroform): 1595, 1350, 1330, 1145, 1085 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.7 (m, 24H, -CH_2-), 2.41 (s, 6H, CH_3-Ph), 2.44 (s, 6H, CH_3-Ph), 3.07 (t, 8H, J = 7.3 Hz, N_α-CH_2), 4.02 (t, 4H, J = 6.0 Hz, O-CH_2), 7.30 (d, 4H, J = 7.5 Hz, arom), 7.38 (d, 4H, J = 7.5 Hz, arom), 7.68 (d, 4H, J = 8.8 Hz, arom), 7.80 (d, 4H, J = 8.8 Hz, arom).

Anal. Calcd. for $C_{46}H_{64}N_2O_{10}S_4$: C, 59.20: H, 6.91; N, 3.00. Found: C, 59.17; H, 7.00; N, 2.95.

In a similar manner, the following compounds were obtained.

N,N'-Di-*p*-toluenesulfonyl-*N,N'*-bis[7-(*p*-toluenesulfonyloxy)heptyl]-1,7-heptanediamine (**8b**).

With **7b** (4.0 g, 6.0 mmoles), triethylamine (1.3 g, 13 mmoles), *N,N*-dimethylaminopyridine (1.5 g, 13 mmoles) in dry dichloromethane (120 ml), *p*-toluenesulfonic acid (2.4 g, 13 mmoles) in dichloromethane (30 ml) was stirred for 2 hours at room temperature, then chromatographed on silica gel with benzene-ethyl acetate (10:1) to give 6.3 g (92%) of a colorless oil; ir (chloroform): 1595, 1350, 1325, 1145, 1085 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.0-1.8 (m, 36H, -CH_2-), 2.41 (s, 6H, CH_3-Ph), 2.44 (s, 6H, CH_3-Ph), 3.08 (t, 8H, J = 7.1 Hz, N_α-CH_2), 4.01 (t, 4H, J = 6.3 Hz, O-CH_2), 7.31 (d, 4H, J = 7.5 Hz, arom), 7.38 (d, 4H, J = 7.8 Hz, arom), 7.71 (d, 4H, J = 7.8 Hz, arom), 7.82 (d, 4H, J = 8.3 Hz, arom).

Anal. Calcd. for $C_{49}H_{70}N_2O_{10}S_4$: C, 60.34; H, 7.23; N, 2.87. Found: C, 60.58; H, 7.35; N, 2.77.

N,N'-Di-*p*-toluenesulfonyl-*N,N'*-bis[9-(*p*-toluenesulfonyloxy)nonyl]-1,9-nonanediamine (**8d**).

With **7d** (5.6 g, 7.5 mmoles), triethylamine (1.6 g, 16 mmoles), *N,N*-dimethylaminopyridine (1.9 g, 16 mmoles) in dry dichloromethane (130 ml), *p*-toluenesulfonic acid (3.0 g, 16 mmoles) in dichloromethane (30 ml) was stirred for 2.5 hours at room temperature, then chromatographed on silica gel with benzene-ethyl acetate (20:1) to afford 7.5 g (95%) of a colorless oil; ir (chloroform): 1595, 1350, 1330, 1150, 1085 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.0-1.8 (m, 36H, -CH_2-), 2.41 (s, 6H, CH_3-Ph), 2.44 (s, 6H, CH_3-Ph), 3.08 (t, 8H, J = 7.1 Hz, N_α-CH_2), 4.01 (t, 4H, J = 6.3 Hz, O-CH_2), 7.31 (d, 4H, J = 7.5 Hz, arom), 7.38 (d, 4H, J = 7.8 Hz, arom), 7.71 (d, 4H, J = 7.8 Hz, arom), 7.82 (d, 4H, J = 8.3 Hz, arom).

Anal. Calcd. for $C_{55}H_{82}N_2O_{10}S_4$: C, 62.35; H, 7.80; N, 2.64. Found: C, 62.40; H, 7.92; N, 2.60.

N,N'-Di-*p*-toluenesulfonyl-*N,N'*-bis[10-(*p*-toluenesulfonyloxy)decyl]-1,10-decanediamine (**8e**).

With **7e** (4.0 g, 5.0 mmoles), triethylamine (1.1 g, 11 mmoles), *N,N*-dimethylaminopyridine (1.3 g, 11 mmoles) in dry dichloromethane (100 ml), *p*-toluenesulfonic acid (2.0 g, 10 mmoles) in dichloromethane (30 ml) was stirred for 2.5 hours at room temperature; then chromatographed on silica gel with benzene-ethyl acetate (20:1) to provide 5.1 g (92%) of a colorless oil; ir (chloroform): 1595, 1350, 1325, 1145, 1185 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.0-1.8 (m, 36H, -CH_2-), 2.41 (s, 6H, CH_3-Ph), 2.44 (s, 6H, CH_3-Ph), 3.08 (t, 8H, J = 7.1 Hz, N_α-CH_2), 4.01 (t, 4H, J = 6.3 Hz, O-CH_2), 7.31 (d, 4H, J = 7.5 Hz, arom), 7.38 (d, 4H, J = 7.8 Hz, arom), 7.71 (d, 4H, J = 7.8 Hz, arom), 7.82 (d, 4H, J = 8.3 Hz, arom).

Anal. Calcd. for $C_{58}H_{88}N_2O_{10}S_4$: C, 63.24; H, 8.05; N, 2.54. Found: C, 63.52; H, 8.31; N, 2.50.

N,N'-Bis(6-bromohexyl)-*N,N'*-di-*p*-toluenesulfonyl-1,6-hexanediamine (**9a**).

A mixture of **8a** (5.0 g, 5.4 mmoles) and lithium bromide (1.4 g, 16 mmoles) in dry acetone (150 ml) was refluxed for 4 hours. After removal of the solid by filtration over celite and evaporation of the solvent, the residue was dissolved in ethyl acetate, washed with brine twice, and dried over anhydrous magnesium sulfate. Chromatography on silica gel with *n*-hexane-ethyl acetate (3:1) afforded 4.0 g (98%) of a colorless solid. Recrystallization gave colorless needles, mp 36-37.5° (ether-petroleum ether); ir (chloroform): 1595, 1325, 1145, 1085 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.7 (m, 20H, -CH_2-), 1.7-2.0 (m, 4H, Br_β-CH_2), 2.42 (s, 6H, CH_3-Ph), 3.09 (t, 8H, J = 6.9 Hz, N_α-CH_2), 3.38 (t, 4H, J = 6.9 Hz, Br-CH_2), 7.31 (d, 4H, J = 8.8 Hz, arom), 7.70 (d, 4H, J = 8.8 Hz, arom).

Anal. Calcd. for $C_{32}H_{50}Br_2N_2O_4S_2$: C, 51.20; H, 6.71; N, 3.73. Found: C, 51.38; H, 6.86; N, 3.70.

The following derivatives were synthesized similarly.

N,N'-Bis(7-bromoheptyl)-*N,N'*-di-*p*-toluenesulfonyl-1,7-heptanediamine (**9b**).

Compound **8b** (5.0 g, 5.1 mmoles) and lithium bromide (1.3 g, 15 mmoles) in dry acetone (130 ml) were refluxed for 4 hours, then chromatographed on silica gel with *n*-hexane ethyl acetate (3:1) to afford 4.0 g (98%) of a colorless liquid; ir (chloroform): 1595, 1325, 1145, 1085 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.7 (m, 26H, CH_2-), 1.7-2.0 (m, 4H, Br_β-CH_2), 2.41 (s, 6H, CH_3-Ph), 3.08 (t, 8H, J = 7.2 Hz, N_α-CH_2), 3.39 (t, 4H, J = 7.4 Hz, Br-CH_2), 7.29 (d, 4H, J = 8.7 Hz, arom), 7.69 (d, 4H, J = 8.7 Hz, arom).

Anal. Calcd. for $C_{35}H_{56}Br_2N_2O_4S_2$: C, 53.03; H, 7.12; N, 3.53. Found: C, 53.10; H, 7.22; N, 3.47.

N,N'-Bis(9-bromononyl)-*N,N'*-di-*p*-toluenesulfonyl-1,9-nonanediamine (**9d**).

Compound **8d** (4.0 g, 3.8 mmoles) and lithium bromide (0.98 g, 11 mmoles) in dry acetone (100 ml) were refluxed for 3 hours, then chromatographed on silica gel with *n*-hexane-ethyl acetate (4:1) to afford 3.2 g (95%) of a colorless liquid; ir (chloroform): 1595, 1330, 1150, 1085 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.1-1.7 (m, 38H, CH_2-), 1.7-2.0 (m, 4H, Br_β-CH_2), 2.41 (s, 6H, CH_3-Ph), 3.10 (t, 8H, J = 7.5 Hz, N_α-CH_2), 3.40 (t, 4H, J = 6.7 Hz, Br-CH_2), 7.30 (d, 4H, J = 8.5 Hz, arom), 7.71 (d, 4H, J = 8.5 Hz, arom).

Anal. Calcd. for $C_{41}H_{68}Br_2N_2O_4S_2$: C, 56.16; H, 7.82; N, 3.19. Found: C, 56.20; H, 7.91; N, 3.14.

N,N'-Bis(10-bromodecyl)-*N,N'*-di-*p*-toluenesulfonyl-1,10-decanediamine (**9e**).

Compound **8e** (4.0 g, 3.6 mmoles) and lithium bromide (0.95 g, 11 mmoles) in dry acetone (100 ml) were refluxed for 4 hours, then chromatographed on silica gel with *n*-hexane-ethyl acetate (4:1) to afford 3.0 g (91%) of colorless needles, mp 53-54° (ether-petroleum ether); ir (chloroform): 1595, 1330, 1150, 1085 cm^{-1}; ^1H-nmr (deuteriochloroform): ppm 1.1-1.7 (m, 44H, $-CH_2-$), 1.7-2.0 (m, 4H, $Br_{\beta}-CH_2$), 2.40 (s, 6H, CH_3-Ph), 3.09 (t, 8H, J = 7.2 Hz, $N_{\alpha}-CH_2$), 3.39 (t, 4H, J = 6.3 Hz, Br-CH_2), 7.29 (d, 4H, J = 8.1 Hz, arom), 7.69 (d, 4H, J = 8.1 Hz, arom).

Anal. Calcd. for $C_{44}H_{74}Br_2N_2O_4S_2$: C, 57.51; H, 8.12; N, 3.05. Found: C, 57.67; H, 8.23; N, 3.01.

1,8,15,22-Tetra-*p*-toluenesulfonyl-tetraazacyclooctacontane (**10a**).

To a solution of **2a** (283 mg, 0.67 mmole) in dry DMF (60 ml), was added sodium hydride (38.4 mg, 1.6 mmoles) in DMF (7 ml), and the mixture was stirred at 60° for 30 minutes under reduced pressure. A DMF solution (25 ml) of **9a** (500 mg, 0.67 mmole) was then added, and stirred at 60° for 2 hours under nitrogen. After evaporation of the solvent *in vacuo*, 1*N* hydrochloric acid was poured into the residue, extracted with dichloromethane, washed with brine, and dried over anhydrous magnesium sulfate. Chromatography over silica gel eluted with dichloromethane-ethyl acetate (20:1) gave a colorless solid in 70% yield (473 mg). Recrystallization from chloroform-methanol gave colorless leaflets, mp 168-170°; ir (chloroform): 1720 cm^{-1}; ms: FD (m/z) 1013 (MH^+); ^1H-nmr (deuteriochloroform): ppm 1.36 (br s, 16H, CH_2 [skeleton]), 1.4-1.8 (m, 16H, $N_{\beta}-CH_2$), 2.41 (s, 12H, CH_3-Ph), 3.05 (t, 16H, J = 6.8 Hz, $N_{\alpha}-CH_2$), 7.29 (d, 8H, J = 7.6 Hz, arom), 7.67 (d, 8H, J = 7.6 Hz, arom).

Anal. Calcd. for $C_{52}H_{76}N_4O_8S_4$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.22; H, 7.55; N, 5.43.

Following the procedure for **10a**, the following compounds were prepared.

1,9,17,25-Tetra-*p*-toluenesulfonyltetraazacyclodotriacontane (**10b**).

Compound **2b** (277 mg, 0.63 mmole) in dry DMF (40 ml) and sodium hydride (36.6 mg, 1.5 mmoles) in DMF (23 ml) were stirred at 60° for 30 minutes, then **9b** (500 mg, 0.63 mmoles) in DMF (24 ml) was stirred at 60° for 2 hours. Chromatography on silica gel eluted with dichloromethane-ethyl acetate (20:1) provided colorless leaflets, 446 mg (66%), mp 138-139.5° (chloroform-*n*-hexane); ir (chloroform): 1320, 1140 cm^{-1}; ms: FD (m/z) 1069 (MH^+); ^1H-nmr (deuteriochloroform): ppm 1.29 (brs, 24H, CH_2[skeleton]), 1.4-1.7 (m, 16H, $N_{\beta}-CH_2$), 2.41 (s, 12H, CH_3-Ph), 3.05 (t, 16H, J = 7.0 Hz, $N_{\alpha}-CH_2$), 7.30 (d, 8H, J = 8.5 Hz, arom), 7.68 (d, 8H, J = 8.5 Hz, arom).

Anal. Calcd. for $C_{56}H_{84}N_4O_8S_4$: C, 62.88; H, 7.91; N, 5.23. Found: C, 62.68; H, 8.18; N, 5.26.

1,11,21,31-Tetra-*p*-toluenesulfonyltetraazacyclotetracontane (**10d**).

Compound **2d** (266 mg, 0.57 mmole) in dry DMF (50 ml) and sodium hydride (32.8 mg, 1.4 mmoles) in DMF (7 ml) was stirred at 60° for 30 minutes, then **9d** (500 mg, 0.57 mmole) in DMF (22 ml) was stirred at 60° for 2 hours. Chromatography on silica gel eluted with dichloromethane-ethyl acetate (30:1) gave colorless needles, 422 mg (63%), mp 119-120° (chloroform-methanol); ir (chloroform): 1320, 1140 cm^{-1}; ms: FD (m/z) 1181 (MH^+); ^1H-nmr (deuteriochloroform): ppm 1.26 (brs, 40H, CH_2[skeleton]), 1.4-1.8 (m, 16H, $N_{\beta}-CH_2$), 2.41 (s, 12H, CH_3-Ph), 3.07 (t, 16H, J = 6.9 Hz, $N_{\alpha}-CH_2$), 7.29 (d, 8H, J = 7.8 Hz, arom), 7.69 (d, 8H, J = 7.8 Hz, arom).

Anal. Calcd. for $C_{64}H_{100}N_4O_8S_4$: C, 65.05; H, 8.53; N, 4.74. Found: C, 64.74; H, 8.69; N, 4.79.

1,12,23,34-Tetra-*p*-toluenesulfonyl-tetraazacyclotetratetracontane (**10e**).

Compound **2e** (790 mg, 0.79 mmole) in dry DMF (160 ml) and sodium hydride (94 mg, 3.9 mmoles) in DMF (2 ml) were stirred at 60° for 30 minutes, then **9e** (1.5 g, 1.6 mmoles) in DMF (63 ml) was stirred at 60° for 2 hours. Chromatography on silica gel eluted with dichloromethane-ethyl acetate (40:1) afforded colorless needles, 1.2 g (59%), mp 67-68.5° (chloroform-*n*-hexane); ir (chloroform): 1320, 1140 cm^{-1}; ms: FD (m/z) 1237 (MH^+); ^1H-nmr (deuteriochloroform): ppm 1.25 (br s, 48H, CH_2 [skeleton]), 1.4-1.8 (m, 16H, $N_{\beta}-CH_2$), 2.40 (s, 12H, CH_3-Ph), 3.07 (t, 16H, J = 7.3 Hz, $N_{\alpha}-CH_2$), 7.29 (d, 8H, J = 8.4 Hz, arom), 7.68 (d, 8H, J = 8.4 Hz, arom).

Anal. Calcd. for $C_{68}H_{108}N_4O_8S_4$: C, 65.98; H, 8.79; N, 4.52. Found: C, 66.49; H, 9.10; N, 4.36.

1,8,15,22-Tetraazacyclooctacontane (**11a**).

A solution of **10a** (1.0 g, 0.99 mmole) and phenol (2.3 g) in 48% hydrobromic acid (46 ml) was refluxed for 8 hours. After evaporation of the solvent at 60-70° *in vacuo*, the residue was poured into chloroform and extracted with 6*N* hydrochloric acid several times. The combined extracts were washed with chloroform twice, made basic with solid sodium hydroxide, and then extracted into chloroform five times. The organic layer was dried over anhydrous magnesium sulfate, evaporated to dryness, and 265 mg (68%) of a pale brown solid was obtained, mp 60-62°; ir (chloroform): 3530 cm^{-1}; ^1H-nmr (deuteriochloroform): ppm 1.2-1.8 (m, 32H, $-CH_2-$), 2.63 (t, 16H, J = 6.9 Hz, $N_{\alpha}-CH_2$).

The following derivatives were synthesized similarly:

1,9,17,25-Tetraazacyclodotriacontane (**11b**).

A solution of **10b** (1.0 g, 0.99 mmole) and phenol (2.2 g) in 48% hydrobromic acid (44 ml) was refluxed for 8 hours. After cooling to room temperature, a small amount of methanol was added to the reaction mixture, and the resulting pale brown solid was collected by filtration followed by washing with ethanol and ether. A suspension of the above solid in 20% aqueous sodium hydroxide (32 ml) was refluxed for 1 hour and the mixture was extracted with dichloromethane four times, dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 313 mg (74%) of a colorless solid, mp 61.5-63°; ir (chloroform): 3530 cm^{-1}; ^1H-nmr (deuteriochloroform): ppm 1.2-1.8 (m, 40H, $-CH_2-$), 2.63 (t, 16H, J = 6.9 Hz, $N_{\alpha}-CH_2$).

1,11,21,31-Tetraazacyclotetracontane (**11d**).

A solution of **10d** (1.0 g, 0.85 mmole) and phenol (2.0 g) in 48% hydrobromic acid (40 ml) was refluxed for 8 hours. After cooling to room temperature, a small amount of methanol was added to the reaction mixture, and the resulting pale brown solid was collected by filtration followed by washing with ethanol and ether. A suspension of the above solid in 20% aqueous sodium hydroxide (29 ml) was refluxed for 1 hour, and the mixture was extracted with dichloromethane five times and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 357 mg (75%) of a colorless solid, mp 70-71°; ir (chloroform): 3530 cm^{-1};

^{1}H-nmr (deuteriochloroform): ppm 1.2-1.7 (m, 56H, -CH_2-), 2.61 (t, 16H, J = 6.3 Hz, N_α-CH_2).

1,12,23,34-Tetraazacyclotetratetracontane (**11e**).

A solution of **10e** (0.5 g, 0.40 mmole) and phenol (1.0 g) in 48% hydrobromic acid (20 ml) was refluxed for 8 hours. After cooling to room temperature, a small amount of methanol was added to the reaction mixture, and the resulting pale brown solid was collected by filtration followed by washing with ethanol and ether. A suspension of the above solid in 20% aqueous sodium hydroxide (14 ml) was refluxed for 1 hour and the mixture was extracted with dichloromethane five times and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 200 mg (80%) of a colorless solid, mp 70-72°; ir (chloroform): 3530 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.2-1.7 (m, 64H, -CH_2-), 2.59 (t, 16H, J = 6.3 Hz, N_α-CH_2).

In conclusion, we have demonstrated the efficient preparation of a series of macrocyclic tetra-amines with 28-, 32-, 36-, 40- and 44-membered rings consisting of a methylene skeleton. These compounds are considered to be suitable as key intermediates for capturing cubane-type 4Fe-4S cluster cores. Related studies including the effects of the environment on the stability of the cores are in progress and will be the subject of future reports.

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