Preparation of Large Macrocyclic Tetra-amines Consisting of a Methylene Backbone and a Cyclophane Type Skeleton

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Efficient synthetic routes to 1,10,19,28-tetraazacyclohexatriacontane, a 36-membered ring compound with a methylene backbone, and bis(*N,N'*-octamethylene-4,4'-diaminodiphenylmethane), a 38-membered tetra-amine with a cyclophane skeleton, have been developed *via* reduction of tetralactam and *via* a double condensation reaction, respectively. Overall yields are 51% with 5 steps for the former, and 46% with 6 steps for the latter, while the corresponding 2 + 2 cyclization gave the cyclic compounds in poor yields, 9% and 4%, respectively, for the 36-membered tetra-aza ring and for the 38-membered cyclophane derivative.

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In the course of our extensive studies on the interaction between organic materials and metal ions, we have previously reported anticancer platinum pyrimidine greens [3-5], and ferredoxin model compounds with macrocycles [6-8]. As is well known, there are many biological materials where particular metals are stoichiometrically involved; for example, metalloenzymes, hemoglobin, blue copper, chlorophyll and so on [9]. Among them non-heme iron-sulfur proteins are widely distributed in living organisms from bacteria to mammals [10,11], taking very important roles in various biological redox reactions especially as electron transfers. They are related to many fundamental reactions such as photosynthesis, biosynthesis of steroidal hormones, metabolism of fatty acids and sulfur, nitrogen fixation reactions, and so on [10,11]. It has been shown that the active site Fe-S cores in high-potential proteins are surrounded by the proteins consisting of largely hydrophobic amino acids [12,13]. Therefore, in order to examine the environmental effect on the Fe-S core using macrocyclic tetrathiol ligands, development of convenient

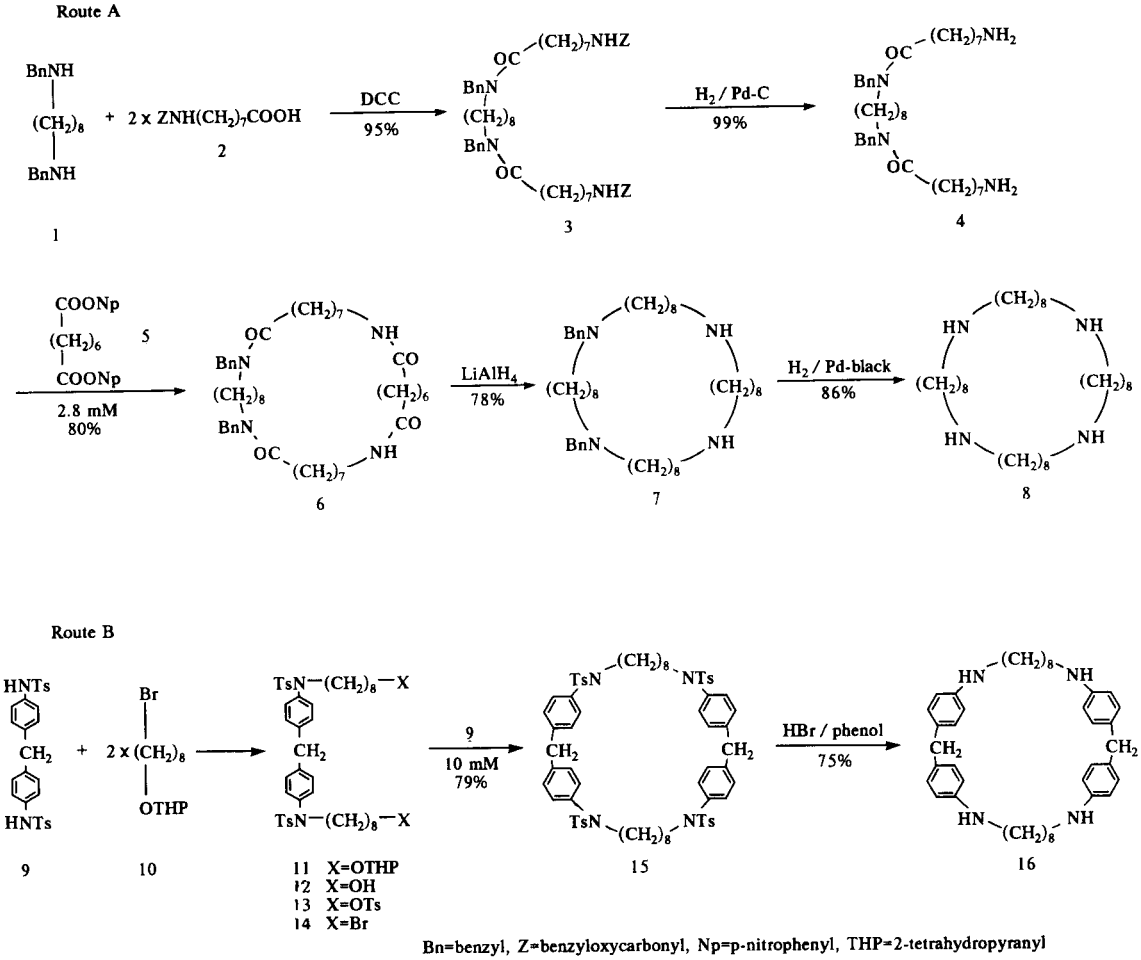

Figure 1. Macrocycles via 2 + 2 Addition.

methods for preparing tetra-aza macrocycles as key compounds which provide intramolecular hydrophobic domains is highly desired. Consequently we describe here an efficient synthesis of macrocyclic tetra-amines with a 36- and a 38-membered ring consisting of a methylene backbone and cyclophane type macrocycle.

Synthetic Route to 36-Membered Cyclic Tetra-amine with a Methylene Backbone *via* Tetralactam.

The most general procedures to obtain a cyclic tetra-amine as a key intermediate compound involve a reduction reaction of the corresponding tetralactam. Not only limited examples were known for the formation of tetralactams, which utilize a silyl compound as a template [14], and intramolecular cyclization reaction [15], but also there was little precedent for synthesizing tetralactams with rings larger than 30 members. Intramolecular cyclization of a tetrapeptide derived from an ω-amino acid gave only 40% of the corresponding cyclic compound with a high dilution condition (3.1×10^{-4} *M*), which is impractical [16]. While intermolecular cyclization *via* double condensation between diamine and dicarboxylic acid derivatives gave an increased yield (70%) [17], the subsequent reduction of the tetralactam into a cyclic tetra-amine was inefficient (up to 10% yield). Since the main problem seemed to be its poor solubility in most of the common organic solvents, the corresponding tetralactam protected partly with a benzyl group **6** was postulated. Compound **4** was synthesized from **1** and **2** *via* **3** according to Route A in Figure 1. The cyclization between **4** and **5** yielded the dibenzyl derivative of a 36-membered tetra-amide **6**. Compound **6** was obtained in 80 and 63% yields with 2.8 and 5.0 m*M* concentration, respectively, in a DMF-methanol (40:1) solution. However decreased yields were observed in a tetrahydrofuran solution (2.8 m*M*, 34%), and the use of DMF gave preferable results for the cyclization. Compound **6** was converted to cyclic dibenzyl tetra-amine derivative **7** by a reduction reaction at four amide groups simultaneously with lithium aluminum hydride in 78% yield. Then the 36-membered cyclic tetra-amine **8** was obtained without difficulty after removal of the benzyl groups from **7** by palladium-black under hydrogen (86%).

Thus **8** can be synthesized in 51% overall yield from **1** and **2** in 5 steps by Route A. This is slightly better than the previous method which gave the same compound in 46% overall yield in 6 steps *via* a double condensation reaction [8,18].

Synthesis of a 38-membered Cyclic Tetra-amine with a Cyclophane Type Skeleton **16**.

The cyclophane tetra-amine **16** was efficiently prepared by the double condensation method employing **9** and **10** *via* Route B. The dibromide **14** (95% from **13**) was derived from **9** and the monobromoalcohol **10**, *via* compounds **11** (95%), **12** (95%) and **13** (90%). Namely formation of **11** and the subsequent deprotection reaction to yield **12** were readily achieved. Tosylation reaction of **12** with tosyl chloride was unsuccessful under ordinary reaction conditions with pyridine. However, the reaction proceeded very smoothly in the presence of DMAP (*N,N'*-dimethylamino-

Table 1
Synthesis of **15** by Double Condensation Reaction

Run	Base	Reaction Temp, °C	[9] m*M*	Yield %
1	K_2CO_3	120	10.0	67
2	Cs_2CO_3	120	10.0	79
3	Cs_2CO_3	60	10.0	59
4	Cs_2CO_3	120	20.0	56
5	Cs_2CO_3	120	40.0	29

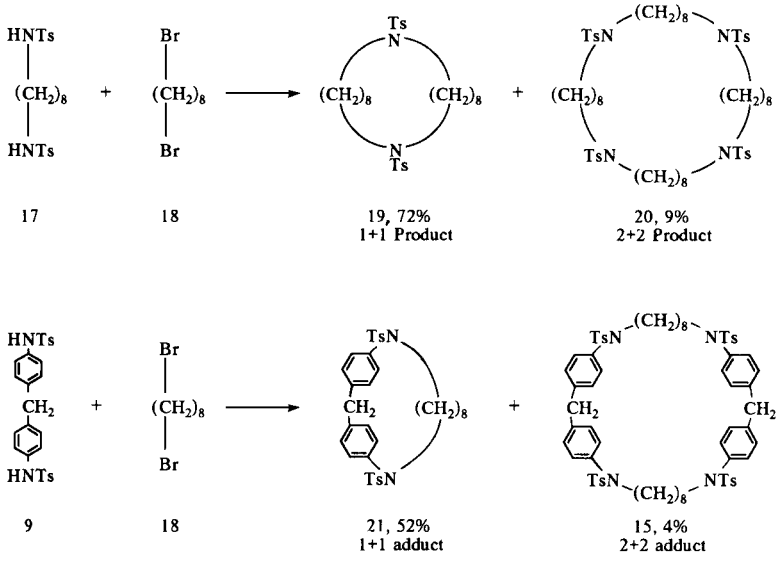

Figure 2. Synthetic Routes to Large Macrocyclic Tetraamines.

pyridine) in dichloromethane. The tosyl derivative **13** was then converted to the dibromide **14** with lithium bromide in acetone. By an intermolecular double condensation reaction with **9** and **14**, a 38-membered tetratosylamide compound **15** was obtained with remarkably high efficiency. Even in higher concentrations, still reasonable yields were resulted. The favorable effects of the cesium ion on the cyclization have been observed as well. These are summarized in Table 1. The corresponding 2 + 2 cyclization [19,20] gave very poor yields; for example, 9 and 4% for **20** and **15**, respectively, while the corresponding 1 + 1 adducts **19** and **21** were obtained in 72 and 52% yields as shown in Figure 2.

EXPERIMENTAL

General Methods.

Melting points are uncorrected. Flash chromatographic separations were carried out as described [21] on 230-400-mesh silica gel 60. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl; DMF, acetonitrile, dichloromethane, benzene, hexane and chloroform were distilled from calcium hydride. Ethanol and methanol were distilled from Mg, and ethyl acetate and acetone were purified by distillation. *N,N'*-Dimethylaminopyridine (DMAP) was recrystallized from benzene-hexane. Other materials were purchased from appropriate sources and used as received. Absorption spectra were recorded on a Cary 219 spectrophotometer. The ^{1}H-nmr spectra were determined on a JEOL JMN GX-270 or a JEOL FX-100 spectrometer, and chemical shifts are relative to TMS as the internal reference. Mass spectra were measured on a JEOL JMS-D300 spectrometer. *N,N'*-Dibenzyl-1,8-octadiamine (**1**) [22], 8-bromo-1-(2-tetrahydropyranyloxy)octane (**10**) [23], and *N,N'*-bis(*p*-tolylsulfonyl)-4,4'-diaminodiphenylmethane (**9**) [24] were prepared according to literature procedures.

Route A: Synthesis of **8**.

8-Benzyloxycarbonylamidooctanoic Acid **2**.

To a mixture of water (1 ml) and 97% sulfuric acid (22 ml), cyclooctanone oxime [25] (10 g, 70.8 mmoles) was added portionwise at 115°, and stirred for 1.5 hours at 110°. The mixture was then poured into water (170 ml), and refluxed for 7 hours in the presence of active charcoal (430 mg). The solution was filtered, neutralized with 50% sodium hydroxide solution, and decolorized again by refluxing with charcoal (400 mg). After filtration, benzyloxycarbonyl chloride (11.2 g, 65.6 mmoles) and 50% sodium hydroxide solution (5 ml) were added to the filtrate at 0°, and stirred vigorously. After 4 hours, the mixture was diluted with 1 ℓ of water, washed with ether (500 ml x 2), acidified with 2*N* hydrochloric acid, and then extracted with ethyl acetate (250 ml x 2). Recrystallization from ethyl acetate-petroleum ether gave colorless leaflets (16.6 g, 80%), mp 62-62.5°; ir (nujol): 3300, 1680-1700 and 1530 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.32-1.62 (m, 10H), 2.34 (t, 2H, J = 7.1 Hz), 3.08-3.21 (m, 2H), 4.76 (br, 1H), 5.10 (s, 2H), 7.35 (s, 5H).

Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.54; H, 8.06; N, 4.80.

1,26-Dibenzyloxycarbonylamido-8,19-dioxo-9,18-dibenzyldiazahexacosane **3**.

To a mixture of the above acid **2** (1.7 g, 5.80 mmoles) and DCC (1.3 g, 6.30 mmoles) in dichloromethane (20 ml) at 0° was added **1** (0.9 g, 2.8 mmoles) [22] in dichloromethane (20 ml), and stirred at 0° for 2 hours, then at room temperature overnight. The precipitated urea was filtered off, and the filtrate was washed subsequently with 1*N* hydrochloric acid, 10% sodium hydroxide solution and brine. A pale yellow oil (2.3 g, 95%) was obtained after a column chromatography over silica gel eluted with *n*-hexane-ethyl acetate (2:1); ir (neat): 3300, 1710, 1640 and 1250 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.24-1.71 (m, 32H), 2.24-2.39 (m, 4H), 3.13-3.36 (m, 8H), 4.55 (d, 4H, J = 15.1 Hz), 4.79 (br, 2H), 5.09 (s, 4H), 7.19-7.46 (m, 20H).

Anal. Calcd for $C_{54}H_{74}N_4O_6$: C, 74.11; H, 8.52; N, 6.40. Found: C, 73.84; H, 8.57; N, 6.59.

1,26-Diamino-8,19-dibenzyldiazahexacosane **4**.

Treatment of **3** (8.34 g, 9.56 mmoles) with 10% palladium on charcoal (600 mg) in methanol (50 ml) for 3 hours under hydrogen afforded a pale yellow oil (5.75 g, 99%) after a silica gel column eluted with ethyl acetate; ir (neat): 3350, 3250 and 1640 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.25-1.51 (m, 32H), 1.98 (s, 4H), 2.26-2.40 (m, 4H), 2.72-2.82 (m, 4H), 3.16-3.35 (m, 4H), 4.56 (d, 4H, J = 6.6 Hz), 7.20-7.30 (m, 10H).

Anal. Calcd. for $C_{38}H_{66}N_4O_2$: C, 75.19; H, 10.30; N, 9.23. Found: C, 74.94; H, 10.39; N, 9.04.

Di-*p*-nitrophenyl octanedionate **5**.

To a solution of *p*-nitrophenol (4.30 g, 30.9 mmoles) and pyridine (2.50 g, 31.6 mmoles) in dichloromethane (12 ml) was added octane dionyl chloride [3.20 g, 15.2 mmoles; prepared from subenic acid and thionyl chloride, $bp_{0.5}$ 114°; ir (neat): 1790 cm^{-1}] in dichloromethane dropwise at 0°, and stirred for 3 hours. The mixture was washed subsequently with 2*N* hydrochloric acid, saturated sodium bicarbonate solution and brine, and dried (sodium sulfate). Recrystallization from ethyl acetate-ether gave pale yellow leaflets (4.60 g, 73%), mp 110.5-111°; ir (nujol): 1750, 1620 and 1590 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.49-1.85 (m, 8H), 2.62 (t, 4H, J = 7.3 Hz), 7.21, 7.30, 8.20, 8.27 (ABq, 8H, J = 8.0 Hz).

Anal. Calcd. for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.71; H, 4.69; N, 6.56.

18,27-Dibenzyl-8,17,28-trioxo-9,18,27-triazapentatriacontane Lactam **6**.

To a mixture of diamine **4** (2.80 g, 4.61 mmoles), triethylamine (933 mg, 9.22 mmoles) and imidazole (314 mg, 4.61 mmoles) in DMF (1.6 ℓ) was added the active ester **5** (1.98 g, 4.61 mmoles) in dichloromethane (400 ml) dropwise over a period of 8 hours, and stirred overnight. After evaporation of the solvent, the residue was dissolved in ethyl acetate, and washed subsequently with 1*N* hydrochloric acid, 10% sodium hydroxide solution, and brine. A pale yellow oil (2.23 g, 80%) was obtained after chromatography over silica gel eluted with chloroform-methanol (1:40); ir (neat): 3300 and 1640 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.27-1.64 (m, 40H), 2.15-2.41 (m, 8H), 3.19-3.39 (m, 8H), 4.56 (d, 4H, J = 12.2 Hz), 7.14-7.37 (m, 10H); ms: EI-HR Observed, 744.5560 (Calcd. 744.5536).

Anal. Calcd. for $C_{46}H_{72}N_4O_4$: C, 74.15; H, 9.74; N, 7.54. Found: C, 73.97; H, 9.75; N, 7.82.

1,10-Dibenzyl-18,29-tetraazacyclohexatriacontane **7**.

A tetrahydrofuran (200 ml) solution of **6** (14 g, 18.8 mmoles) was added dropwise into a suspension of lithium aluminum hydride (7.1 g, 18.7 mmoles) in tetrahydrofuran (400 ml), and refluxed for 5.5 hours under argon. Water (11 ml) was added at 0°, and the mixture was stirred for 14 hours at room temperature. Then 25% sodium hydroxide solution (3.5 ml) and water (3 ml) were added, and stirred for 30 minutes. The precipitate was removed by filtration, and tetrahydrofuran was evaporated off. The residue was then dissolved in chloroform, washed with brine, dried over sodium sulfate, and evaporated. Pale yellow oil (10.1 g, 78%) was obtained after alumina column chromatography with methanol-chloroform (1:8); ir (neat): 3250 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.28 (br, 48H), 2.38 (t, 8H, J = 7.1 Hz), 2.60 (t, 8H, J = 6.6 Hz), 3.53 (s, 4H), 7.23-7.35 (m, 10H).

Anal. Calcd. for $C_{46}H_{80}N_4$: C, 80.17; H, 11.70; N, 8.13. Found: C, 80.42; H, 11.56; N, 7.92.

1,10,19,28-Tetraazacyclohexatriacontane **8**.

Dibenzyltetraamide **7** (3.0 g, 4.3 mmoles) in 40 ml of water-methanol (4:1) and 2 ml of concentrated hydrochloric acid was stirred for 24 hours at room temperature in the presence of palladium-black (600 mg) under hydrogen. After removal of the catalyst and evaporation of the solvent, recrystallization from methanol gave pure colorless cyclic tetraamine as amorphous solid (2.4 g, 86%). Data for the free amine are given below, mp 63-65°; ir (Nujol): 3300 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.32 (br, 36H), 1.46 (br, 16H), 2.59 (t, 16H, J = 7.1 Hz); ms: EI-HR Observed, 508.5415 (Calcd. for $C_{32}H_{68}N_4$: 508.5428).

Data for the hydrochloride salt are as follows: mp >300°.

Anal. Calcd. for $C_{32}H_{72}N_4Cl_4$: C, 58.70; H, 11.08; N, 8.56, Cl, 21.66. Found: C, 58.51; H, 10.92; N, 8.50; Cl, 21.56.

Route B. Synthesis of **16**.

N,N'-Bis(*p*-tolylsulfonyl)-*N,N'*-bis[8-(2-tetrahydropyraloxy)octanyl]-4,4'-diaminodiphenylmethane **11**.

A mixture of **9** (15.7 g, 31.0 mmoles) [24], **10** (20.0 g, 68.3 mmoles) [23] and potassium carbonate (8.6 g, 62.2 mmoles) in DMF (400 ml) was heated at 120° for 5 hours under argon. Excess potassium carbonate was removed by filtration, and DMF was distilled off. The residue dissolved in ethyl acetate (500 ml) was washed with brine, and purified on a silica gel column eluted with ethyl acetate:hexane (1:3) to afford pale yellow oil (27.5 g, 95%); ^{1}H-nmr (deuteriochloroform): 2.42 (s, 6H), 3.33-3.86 (m, 12H), 3.95 (s, 2H), 4.56 (t, 2H, J = 2.6 Hz), 6.96 (d, 4H, J = 8.4 Hz), 7.11 (d, 4H, J = 8.4 Hz), 7.25 (d, 4H, J = 8.1 Hz), 7.48 (d, 4H, J = 8.4 Hz).

Anal. Calcd. for $C_{53}H_{74}N_2O_8S_2$: C, 68.35, H, 8.01; N, 3.01; S, 6.89. Found: C, 68.18; H, 8.01; N, 3.20; S, 6.91.

N,N'-Bis(*p*-tolylsulfonyl)-*N,N'*-bis(8-hydroxyoctanyl)-4,4'-diaminodiphenylmethane **12**.

Compound **11** (14.0 g, 15.0 mmoles) was treated with toluene sulfonic acid (6.3 g, 33.1 mmoles) in methanol (800 ml) at room temperature for 40 minutes. Methanol was removed by evaporation, and the residue dissolved in ethyl acetate was washed with saturated sodium bicarbonate solution and water. Purification by a silica gel column gave pale yellow oil (10.9 g, 95%) eluted with ethyl acetate:hexane (1:2); ir (neat): 3350 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.41 (s, 6H), 3.48 (t, 4H, J = 6.8 Hz), 3.61 (t, 4H, J = 6.6 Hz), 3.96 (s, 2H), 6.97 (d, 4H, J = 8.4 Hz), 7.11 (d, 4H, J = 8.8 Hz), 7.25 (d, 4H, J = 8.1 Hz), 7.43 (d, 4H, J = 8.4 Hz); ms: EI-HR Observed, 762.3754 (Calcd. 762.3739).

Anal. Calcd. for $C_{43}H_{58}N_2O_6S_2$: C, 67.68; H, 7.66; N, 3.67; S, 8.40. Found: C, 67.52; H, 7.60; N, 3.45; S, 8.38.

N,N'-Bis(*p*-tolylsulfonyl)-*N,N'*-bis[8-(*p*-tolylsulfonyloxy)octanyl]-4,4'-diaminodiphenylmethane **13**.

To a mixture of **12** (19.6 g, 25.7 mmoles), triethylamine (8.6 ml, 61.7 mmoles) and DMAP (31.3 g, 257 mmoles) in dry dichloromethane (800 ml) was added tosyl chloride (14.7 g, 77.2 mmoles), and stirred at room temperature for 30 minutes. The solution was successively washed with 5% hydrochloric acid, saturated sodium bicarbonate solution and brine, and dried (sodium sulfate). A colorless oil (24.9 g, 90%) was obtained after column chromatography over silica gel eluted with ethyl acetate:hexane (1:1); ^{1}H-nmr (deuteriochloroform): 2.42 (s, 6H), 2.44 (s, 6H), 3.46 (t, 4H, J = 6.8 Hz), 3.97 (t, 4H, J = 6.4 Hz), 3.99 (s, 2H), 6.96 (d, 4H, J = 8.4 Hz), 7.11 (d, 4H, J = 8.1 Hz), 7.25 (d, 4H, J = 8.1 Hz), 7.34 (d, 4H, J = 7.7 Hz), 7.46 (d, 4H, J = 8.4 Hz), 7.78 (d, 4H, J = 8.4 Hz).

Anal. Calcd. for $C_{57}H_{70}N_{20}O_{10}S_4$: C, 63.90; H, 6.59; N, 2.62; S, 11.97. Found: C, 63.73; H, 6.53; N, 2.50; S, 11.88.

N,N'-Bis(*p*-tolylsulfonyl)-*N,N'*-bis(8-bromooctanyl)-4,4'-diaminodiphenylmethane **14**.

Compound **13** (24.9 g, 23.3 mmoles) and lithium bromide (6.1 g, 69.8 mmoles) in acetone (600 ml) were refluxed for 4 hours. The precipitated salts were filtered off, and acetone was evaporated. The residue dissolved in ethyl acetate was washed with water, and dried (sodium sulfate). Chromatographic purification with silica gel afforded colorless crystals from dichloromethane petroleum ether, mp 60-62° (19.6 g, 95%) eluted with ethyl acetate:hexane (1:1); ^{1}H-nmr (deuteriochloroform): 1.82 (m, 4H), 2.42 (s, 6H), 3.38 (t, 4H, J = 6.8 Hz), 3.48 (t, 4H, J = 6.7 Hz), 3.96 (s, 2H), 6.98 (d. 4H, J = 8.4 Hz), 7.11 (d, 4H, J = 8.4 Hz), 7.25 (d, 4H, J = 8.1 Hz), 7.48 (d, 4H, J = 8.4 Hz); ms: FI [m/z (relative intensity)]: 886 (M^+, 56.7%), 888 (M^++2, 100%), 8.90 (M^++4, 56.5%), 842 (M^+-46, 73.4%), 8.06 (M^+-80, 56.4%).

Anal. Calcd. for $C_{43}H_{56}N_2O_4S_2Br_2$: C, 58.10; H, 6.35; N, 3.15; S, 7.22; Br, 17.98. Found: C, 58.04; H, 6.42; N, 3.16; S, 7.15; Br, 18.09.

Bis-[*N,N'*-bis(*p*-tolylsulfonyl)-*N*-*N'*-octamethylene-4,4'-diaminodiphenylmethane] **15**.

To a mixture of **9** (1.42 g, 2.80 mmoles) and cesium carbonate (1.83 g, 5.62 mmoles) in DMF (280 ml) was added dropwise a DMF solution (110 ml) of **14** (2.5 g, 2.81 mmoles) over a period of 2 hours, and then heated at 120° for 4 hours. DMF was evaporated *in vacuo*, and water (20 ml) was poured into the residue. The resulted colorless solid was extracted into dichloromethane. The combined extracts were washed with brine, dried (magnesium sulfate), and evaporated. The residue was solidified by triturating with petroleum ether, purified by a silica gel column eluted with dichloromethane ethyl acetate = 25 = 1, and recrystallized from chloroform-ethanol to yield colorless crystals (2.73 g, 79%), mp 246-248°; ^{1}H-nmr (deuteriochloroform): 2.42 (s, 12H), 3.45 (t, 8H, J = 6.6 Hz), 3.94 (s, 4H), 6.93 (d, 8H, J = 8.4 Hz), 7.06 (d, 8H, J = 8.4 Hz), 7.24 (d, 8H, J = 8.1 Hz), 7.46 (d, 8H, J = 8.1 Hz); ms: FD [m/z (relative intensity)]: 1232 (M^+, 97.2%), 1080 (M^+-152, 89.5%), 1079 (M^+-153,

100%), 1078 (M^+-154, 99.5%), 924 (M^+-308, 57.9%), 617 (M^+-615, 50.6%).

Anal. Calcd. for $C_{70}H_{80}N_4O_8S_4$: C, 68.15; H, 6.54; N, 4.54; S, 10.40. Found: C, 67.92; H, 6.57; N, 4.43; S, 10.52.

Bis(*N*,*N'*-octamethylene-4,4'-diaminodiphenylmethane) **16**.

A mixture of **15** (2.0 g, 1.62 mmoles), phenol (3.8 g, 40.4 mmoles) and 48% hydrobromic acid (78 ml) was refluxed for 8 hours. The precipitates were collected by filtration, and washed with ether and ethanol. The solid was dissolved in 20% sodium hydroxide solution (60 ml) and refluxed for 1 hour. The precipitates were again collected by filtration, washed with water and ethanol, and purified by recrystallization from chloroform-ethanol to give pale red needles (0.75 g, 75%), mp 147-149°; ir (nujol): 3250 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.52-1.59 (m, 8H), 3.06 (t, 8H, J = 7.0 Hz), 3.45 (s, 4H), 3.74 (s, 4H), 6.51 (d, 8H, J = 8.4 Hz), 6.96 (d, 8H, J = 8.4 Hz).

Anal. Calcd. for $C_{42}H_{56}N_4/½H_2O$: C, 80.66; H, 9.02; N, 8.95. Found: C, 80.95; H, 9.13; N, 8.99.

Conclusively, we have developed efficient synthetic routes to large macrocyclic tetra-amine compounds with methylene and cyclophane skeletons.

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