Facile Syntheses of Homothia- and Homoazacalixarenes

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Decahomotetrathiacalix[6]arenes were conveniently prepared from the 2:2 cyclization reactions of bis(chloromethyl)phenol-formaldehyde trimers with 1,2-ethanedithiol in high yields. In contrast, the similar reactions of the trimers with 1,3-propanedithiol instead of 1,2-ethanedithiol gave 1:1 macrocycles, hexahomodithiacalix[3]arenes, in good yields. Homoazacalixarenes were also prepared from the analogous reactions using piperazines. These macrocycles adopt a cone-like form as a preferable conformation in solution.

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Introduction.

Calixarenes have attracted much interest as potential host compounds, because of their easy modification and their large variety [1]. Most derivatives of calixarene are obtained by attaching functional groups to the phenol units. In contrast, our interest was focused on the modification of the methylene moiety of calixarenes, which were built up by changing the methylene unit to other group such as carbonyl, sulfur, and amino acids [2].

Recently, Miyano *et al.* reported a convenient and easy synthesis of thiacalix[4]arene in a satisfactory yield by simply heating phenol with elemental sulfur in the presence of a base [3]. After this useful synthetic method of thiacalix[4]arene was reported, the increasing interest in the development of thiacalix[4]arenes is certainly due to the unique properties of the sulfur atom in the macrocyclic ring [4].

This situation inspired us to synthesize homothiacalixarenes, which also possess sulfur atom in the macrocyclic ring [5]. Therefore, we investigated the syntheses of homothiacalixarenes through the reactions of bis(chloromethyl)phenol-formaldehyde oligomers with alkanedithiols, and found the facile formation of decahomotetrathiacalix[6]arenes and hexahomodithiacalix[3]arenes in good yields. Furthermore, we also investigated the syntheses of homoazacalixarenes incorporating a piperazine unit into the macrocyclic ring [6]. We now report the results.

Results and Discussion.

Decahomotetrathiacalix[6]arenes **1** were synthesized as follows. A solution of 1,2-ethanedithiol in dry *N,N*-dimethylformamide and a solution of bis(chloromethyl)phenol-formaldehyde trimer **8c**, which was derived from the chlorination of the corresponding alcohol **7c** (Scheme 1), in dry *N,N*-dimethylformamide were added simultaneously to a suspension of sodium carbonate in dry *N,N*-dimethylformamide over a period of 1 hour with stirring under nitrogen atmosphere at 30° and then the mixture was further stirred for 2 hours. After usual workup, we obtained a 2:2 macrocycle **1a**, decahomotetrathiacalix[6]arene, in 90% yield. Similar reactions using **8d** and **8e** instead of **8c** gave the corresponding macrocycles **1b** and **1c** in 55 and 89% yields, respectively. In contrast, the analogous reactions using the corresponding bis(chloromethyl)phenol-formaldehyde monomer **8a**, dimer **8b**, and tetramer **8f** did not isolate any macrocyclic compound except polymeric materials. Reactions of bis(chloromethyl)trimers **8c-8e** with 1,3-propanedithiol instead of 1,2-ethanedithiol gave 1:1 macrocycles **2a-2c**, hexahomodithiacalix[3]arenes, in 73, 56, and 43% yields, respectively. In this case, we did not obtain the corresponding 2:2 macrocycles.

The reaction of piperazine with bis(chloromethyl) dimer **8b** in chloroform in the presence of triethylamine at 20° gave the 2:2 macrocyclic compound **3a** in 64% yield. The similar reaction using *trans*-2,5-dimethylpiperazine instead of piperazine also gave the corresponding 2:2 macrocycle **3b** in 13% yield. In contrast, the reactions of piperazines with bis(chloromethyl)trimer **8c** and tetramer **8f** gave 1:1 macrocycles **4a**, **4b** and **5a** in 32, 6, and 19% yields, respectively.

The structure of the macrocycles **1-5** was accomplished on the bases of their nmr, mass spectra and elemental analyses. The OH proton signals of the phenol unit were observed at the range of δ 8.39-12.30 ppm, indicating the existence of the intramolecular hydrogen bonding.

The $ArCH_2Ar$ and $ArCH_2S$ methylene proton signals of homothiacalixarenes **1a** and **2a** were observed as singlets at ambient temperature. When the spectra were measured at -60° in deuteriochloroform, two pairs of doublets were observed in the methylene proton region (Figure 1). The doublets with the larger chemical shift difference are assigned to the methylene protons of the $ArCH_2Ar$, and the other pair of doublets are ascribed to the $ArCH_2S$ protons by using COSY and NOESY experiments at -60°. The difference of the chemical shifts (Δδ) between the high- and low-field resonances arising from the $ArCH_2Ar$ methylene protons was at the range of 0.63-0.68 ppm, indicating that the adjacent aryl rings adopt a *syn* orienta-

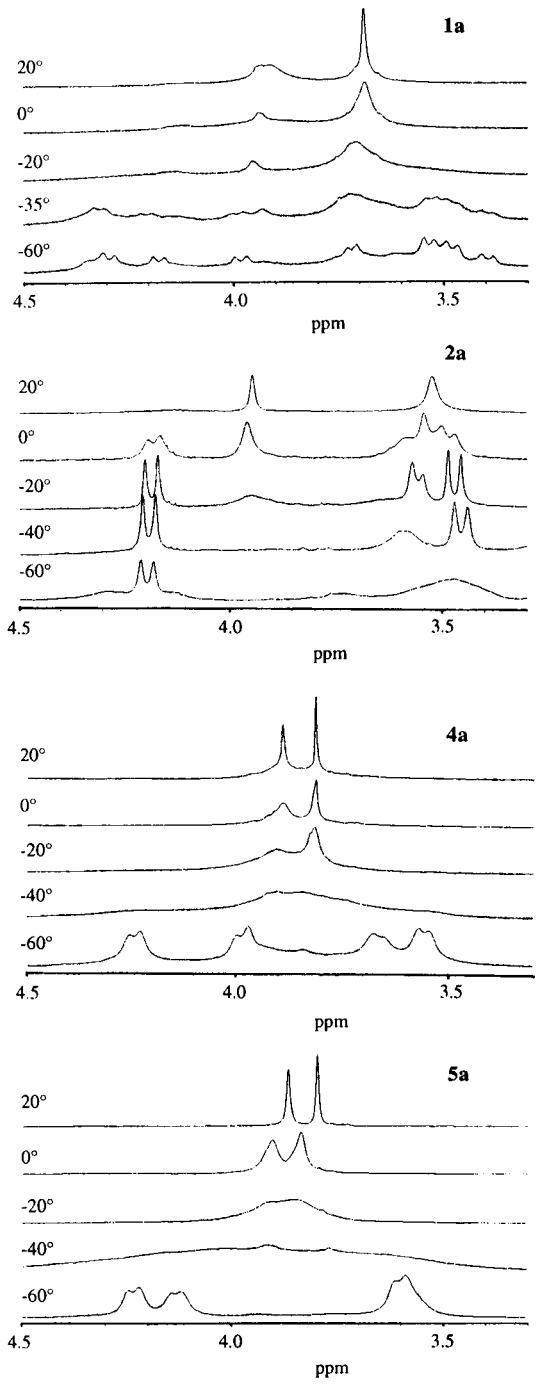


Figure 1. Partial ^1H nmr spectra of methylene protons in macrocycles **1a**, **2a**, **4a**, and **5a** in deuteriochloroform at variable temperatures at 500 MHz.

tion [1a]. This is further supported by the resonance for the pertinent carbon atoms in the range of 30.8-31.4 ppm, in fairly good agreement with the rule proposed by de Mendoza for the determination of the calixarene conformation. The coalesence temperatures (T_c) of the $ArCH_2Ar$ methylene protons are -35° for **1a** and 40° for **2a**, which correspond to free energy barriers ($\Delta G^{\ddagger}$) of 10.6 and 10.9 kcal/mole, respectively [7].

The conformational properties of homoazacalixarenes **3a**, **4a**, and **5a** were also investigated by using ^1H and ^{13}C nmr spectroscopy. In the variable temperature spectra of **3a**, the signals of the $ArCH_2Ar$ methylene protons were observed as singlets at room temperature and did not split at -60° in deuteriochloroform. In contrast, the ^1H nmr spectrum of **4a** at -60° gave four pairs of doublets in the methylene region, which were ascribed to two $ArCH_2Ar$ and two $ArCH_2N$ methylene protons as summarized in Table 2. At -60°, we also observed three OH proton signals (δ 8.98, 10.30, and 14.30 ppm) with equal intensities. Considering the nitrogen atom is a good proton acceptor, the OH proton signal observed at the lowest magnetic field is assigned to the OH proton adjacent to the amine moiety, which forms hydrogen bonding not only with hydroxy groups but also with nitrogen atom as shown in Figure 2. The *syn* orientation of the phenol units is corroborated by the Δδ values (0.58 and 0.69 ppm) of the $ArCH_2Ar$ methylene protons and the resonances (δ 31.0 ppm) of the relevant carbon atom in the nmr spectra. From the coalescence data (T_c = -20°) of the $ArCH_2Ar$ methylene protons, a barrier of 11.5 kcal/mole was calculated for the inversion process [7]. Macrocycle **5a** displays in the ^1H nmr two broad signals (δ 3.50 and 4.12 ppm) for the $ArCH_2N$ protons and two singlets (δ 3.52 and 3.93 ppm) for the $ArCH_2Ar$ protons. Upon cooling the temperature, the $ArCH_2N$ methylene signals was obseved as a pair of doublet (δ 3.46 and 4.19 ppm) at -40°, however, the $ArCH_2Ar$ methylene proton did not completely decoalesced at -60° in deuteriochloroform. In the ^1H nmr spectrum at -60° four signals for hydroxy groups (δ 8.27, 9.33, 11.76, and 14.00 ppm) in an integral ratio of 1:1:1:1 were observed, indicating that the frozen hydrogen bonding array of **5a** is similar to that of **4a** as shown in Figure 2. The methylene carbon resonances (δ 31.1 and 31.9 ppm) of the $ArCH_2Ar$ moieties imply that the preferable conformation of **5a** is a cone form in solution.

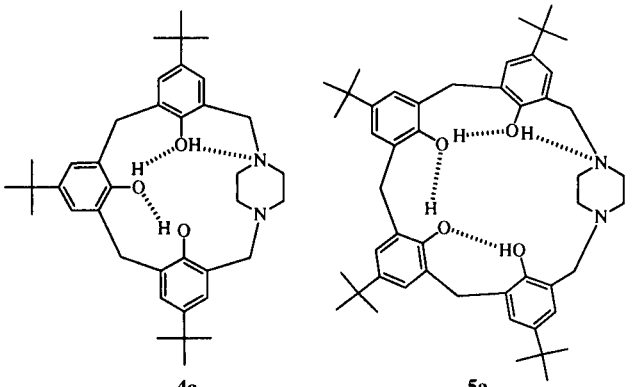


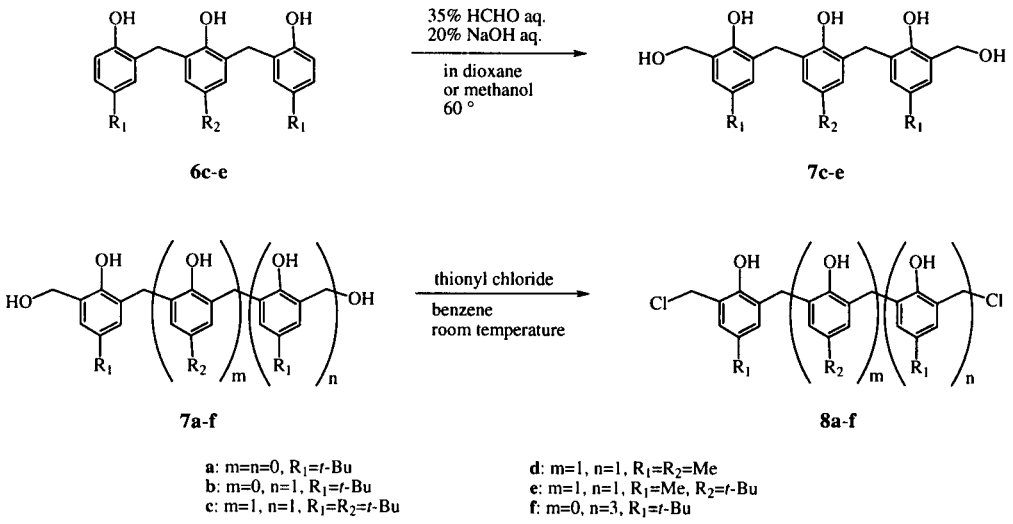
Figure 2.

In conclusion, we found facile syntheses of homothiacalixarenes **1** and **2** through the cyclization reactions between bis(chloromethyl)phenolformaldehyde trimers and alkanedithiols, and elucidated that the length of alkyl chain of alkanedithiols and the number of the phenol units of the phenol-formaldehyde oligomers play an important role in the formation of the macrocycles.

Homoazacalixarenes **3**, **4**, and **5** incorporating a piperazine unit into the macrocyclic ring were also prepared by a similar method. In this case, the yields of the macrocycles decreased with increasing the number of the phenol unit of the bis(chloromethyl)compounds.

From the ^{1}H and ^{13}C nmr experiment, these macrocycles adopt a cone conformation in solution. The ring inversion energies ($\Delta G^{\ddagger}$ =10.6 kcal/mole for **1a**, 10.9 kcal/mole for **2a**, 11.6 kcal/mole for **4a**) of the macrocycles obtained indicate that the introduction of alkanedithiol and piperazine unit into the macrocyclic ring causes the ring fluctuation ($\Delta G^{\ddagger}$: values of calix[*n*]arenes; 15.7 kcal/mole (*n*=4), 13.2 kcal/mole (*n*=5)) [la].

Scheme 1

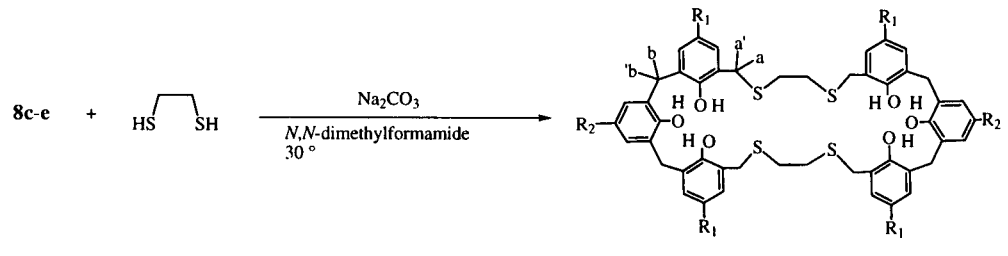


6c-e **7c-e**

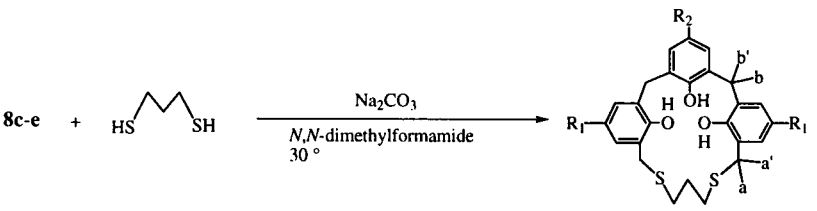
7a-f **8a-f**

a: m=n=0, R_1=*t*-Bu
b: m=0, n=1, R_1=*t*-Bu
c: m=1, n=1, R_1=R_2=*t*-Bu
d: m=1, n=1, R_1=R_2=Me
e: m=1, n=1, R_1=Me, R_2=*t*-Bu
f: m=0, n=3, R_1=*t*-Bu

Scheme 2



1a: R_1=R_2=*t*-Bu
1b: R_1=*t*-Bu, R_2=Me
1c: R_1=R_2=Me



2a: R_1=R_2=*t*-Bu
2b: R_1=*t*-Bu, R_2=Me
2c: R_1=R_2=Me

Scheme 3

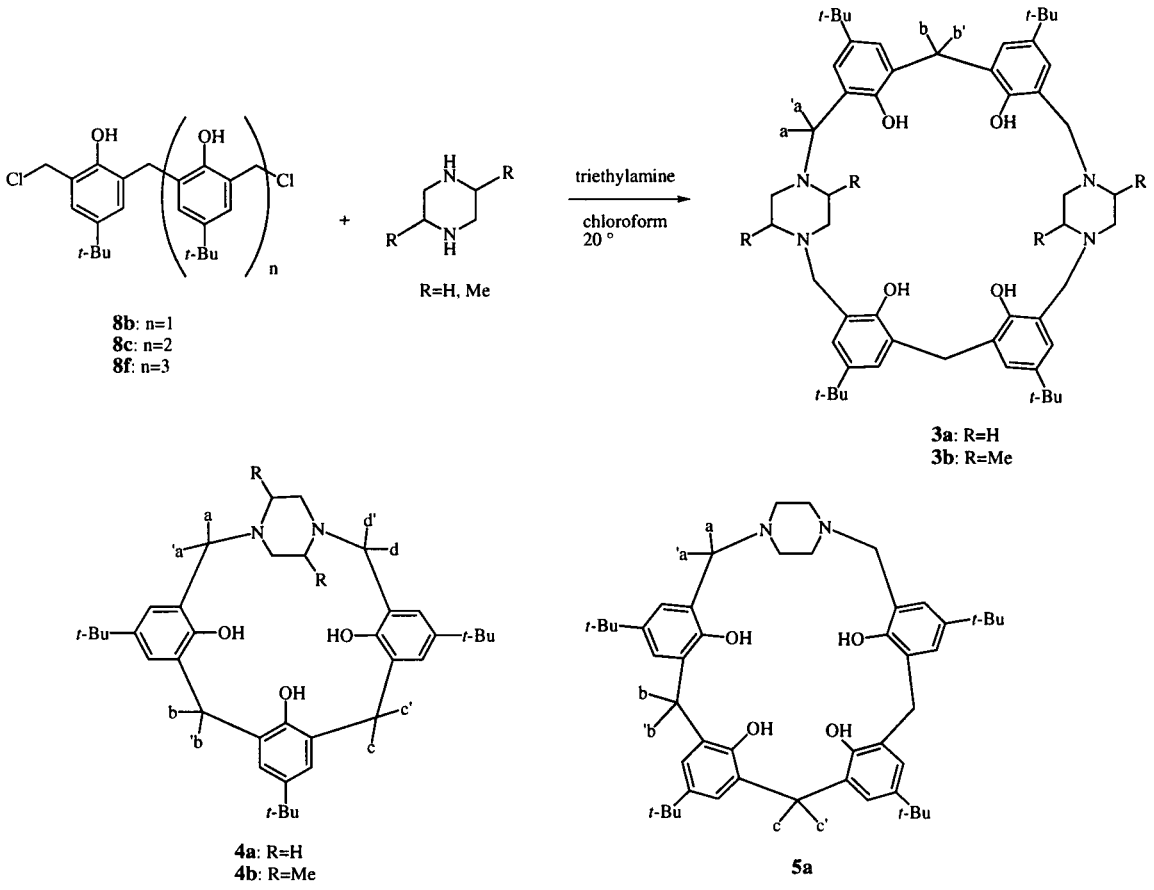


Table 1

Hydroxyl Proton Chemical Shift Values and the Chemical Shift Values of the $ArCH_2Ar$ Methylene Carbon Atoms in Deuteriochloroform (^1H for 500 MHz, ^{13}C for 125 MHz)

		δ_{OH} (relative intensity) / [ppm]	$\delta ArCH_2Ar$ / [ppm]
1a	20°	8.77	31.3
	-60°	9.04	
1b	20°	8.57	30.8
1c	20°	8.59	31.4
2a	20°	8.50, 8.70 (2:1)	31.4
	-60°	8.74, 8.91 (2:1)	
2b	20°	8.40, 8.62 (2:1)	30.9
2c	20°	8.39, 8.61 (2:1)	31.4
3a	20°	10.6	29.2
	-60°	11.2	
3b	20°	10.7	29.3
4a	20°	8.38	31.0
	-60°	8.98, 10.30, 14.30 (1:1:1)	
4b	20°	8.39	30.9
5a	20°	8.58, 12.30 (1:1)	31.1, 31.9
	-60°	8.27, 9.33, 11.76, 14.00 (1:1:1:1)	

Table 2

The Difference Between H_{exo} and H_{endo} Proton of the Methylene Moiety at 500 MHz in Deuteriochloroform

Macrocycle	Temperature	$ArCH_aH_{a'}$ (J, Hz; Δδ, ppm)	$ArCH_bH_{b'}Ar$ (J, Hz; Δδ, ppm)	$ArCH_cH_{c'}Ar$ (J, Hz; Δδ, ppm)	$ArCH_dH_{d'}$ (J, Hz; Δδ, ppm)
1a	20°	3.79	3.87	-	-
	-60°	3.66,3.98(12.5,0.32)	3.56,4.24(12.5,0.68)	-	-
1b	20°	3.73	3.81	-	-
1c	20°	3.74	3.84	-	-
2a	20°	3.75	3.85	-	-
	-60°	3.60,4.13(13.5,0.53)	3.60,4.23(13.5,0.63)	-	-
2b	20°	3.79	3.83	-	-
2c	20°	3.74	3.83	-	-
3a	20°	3.70	3.96	-	-
	-60°	3.72	3.95	-	-
3b	20°	3.14,4.43(13.0,1.29)	3.98	-	-
4a	20°	3.90	3.67	-	-
	-60°	3.52,3.71(11.5,0.19)	3.47,4.16(15.0,0.69)	3.38,3.96(15.0,0.58)	3.52,4.28(14.5,0.76)
4b	20°	3.26,4.20(13.0,0.94)	3.90	-	-
5a	20	3.50, 4.12	3.52	3.93	-
	-40°	3.46,4.19(15.0,0.73)	-[a]	-[a]	-[a]

[a] too broad to assign the signals

EXPERIMENTAL

All of the melting points were uncorrected. ^1H and ^{13}C nmr spectra were obtained on Varian Mercury 200, Varian INOVA 500, and JEOL EX-270 spectrophotometers using tetramethyl silane as an internal standard. Ir spectra were taken on HORIBA FT-200 spectrophotometer. Fab-mass (*m*-nitrobenzylalcohol as a matrix) and ei-mass (70 eV) spectra were collected by JEOL JMS AX-505HA spectrometer. Column chromatography was performed using silica gel (Kieselgel 60, 63-299 μm, 70-230 mesh, Merck). *N,N*-Dimethylformamide was stored in molecular seives 4A and distilled from calcium hydride before used. Triethyl amine was distilled from NaOH under a nitrogen atmosphere. All other chemicals were reagent grade and used without further purification. 2-[3-(5-*tert*-Butylsalicyl)-5-*tert*-butylsalicyl]-4-*tert*-butylphenol (**6c**) [11], 2-[3-(5-methylsalicyl)-5-methylsalicyl]-4-methylphenol (**6d**) [12], 3-[3-[3-(hydroxymethyl)-5-*tert*-butylsalicyl]-5-*tert*-butylsalicyl]-2-hydroxy-5-*tert*-butylbenzylalcohol (**7c**) [13], 3-[3-[3-(hydroxymethyl)-5-methylsalicyl]-5-methylsalicyl]-2-hydroxy-5-methylbenzylalcohol (**7d**) [14], 3-[3-[3-[3-(hydroxymethyl)-5-*tert*-butylsalicyl]-5-*tert*-butylsalicyl]-5-*tert*-butylsalicyl]-2-hydroxy-5-*tert*-butylbenzylalcohol (**7f**) [13], 4-*tert*-butyl-2,6-bis(chloromethyl)phenol (**8a**) [16], 2-[3-[3-(chloromethyl)-5-*tert*-butylsalicyl]-5-*tert*-butylsalicyl]-6-(chloromethyl)-4-*tert*-butylphenol (**8c**) [15], were prepared by reported methods in literature.

Preparation of 2-[3-(5-Methylsalicyl)-5-*tert*-butylsalicyl]-4-methylphenol (**6e**).

A mixture of *p*-cresol (8.86 g, 82 mmoles), 4-*tert*-butyl-2,5-bis(hydroxymethyl)phenol (1.72 g, 8.2 mmoles), *p*-toluenesulfonic acid (0.05 g, 0.26 mmole) in benzene (50 ml) was refluxed for 2 hours. Removal of excess *p*-cresol by steam distillation gave a white powder, which was recrystallized from benzene to give **6e** (2.01 g, 63%) as colorless crystals, mp 231-232° (from benzene); ^1H nmr (deuteriochloroform): δ 1.29 (s, 9H, *t*-Bu), 2.23 (s, 6H, CH_3 x 2), 3.85 (s, 4H, $ArCH_2Ar$ x 2), 6.68 (d, 2H, Ar-H x 2, J = 8.0 Hz), 6.87 (dd, 2H, Ar-H x 2, J = 2.2, 8.0 Hz), 7.06 (d, 2H, Ar-H x 2, J = 2.2 Hz), 7.16 (s, 2H, Ar-H x 2); ^{13}C nmr (deuteriochloroform: DMSO-d_6, 4:1): δ 19.3, 29.9, 30.5, 32.7, 114.1, 124.4, 125.8, 126.0, 126.5, 127.6, 129.7, 141.3, 148.3, 150.4; ms: m/z 390 (M^+).

Anal. Calcd. for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74. Found: C, 80.02; H, 7.70.

Synthesis of 3-[3-[3-(Hydroxymethyl)-5-methylsalicyl]-5-*tert*-butylsalicyl]-2-hydroxy-5-methylbenzyl Alcohol (**7e**).

A mixture of **6e** (1.01 g, 2.6 mmoles), 25 % potassium hydroxide aqueous solution (5 ml), and 1,4-dioxane (5 ml) was added 35% formaline (20 ml, 230 mmoles) at 0° over 30 minutes. After the addition was complete, the mixture was allowed to stir at 60° for 20 hours. After cooling to room temperature, the mixture was acidified by 10% hydrochloric acid aqueous solution to give white precipitates, which was dissolved in chloroform. The organic layer was washed with water three times and dried over anhydrous sodium sulfate. Removal of chloroform gave a colorless oily residue, which was subjected to column chromatography on silica gel using hexane:ethyl acetate 2:1 as an eluent to give **7e** (0.62 g, 53% yield) as colorless crystals, mp 144-146° (from ethyl acetate-hexane); ^1H nmr (deuteriochloroform): δ 1.27 (s, 9H, *t*-Bu), 2.19 (s, 6H, CH_3 x 2), 3.85 (s, 4H, $ArCH_2Ar$ x 2), 4.68 (s, 4H, $ArCH_2OH$ x 2), 6.66 (d, 2H, Ar-H x 2, J = 2.0 Hz), 6.98 (d, 2H, Ar-H x 2, J = 2.0 Hz), 7.13 (s, 2H, Ar-H x 2); ^{13}C nmr (deuteriochloroform): δ 20.4, 31.4, 31.5, 34.0, 63.7, 125.5, 125.9, 127.0, 127.1, 127.7, 129.7, 130.5, 144.1, 147.4, 149.9; (FAB) ms: m/z 451 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{34}O_5$: C, 74.64; H, 7.61. Found: C, 74.88; H, 7.72.

General Procedure for the Preparation of Bis(chloromethyl)-phenol-formaldehyde Oligomers (**8**).

To a solution or suspension of **7** (1.1 mmoles) in dry benzene (10 ml) was added a solution of thionyl chloride (1.0 g, 8.0 mmoles) in dry benzene (10 ml) over 30 minutes. After the addition was complete, the mixture was allowed to stir at room temperature for 3 hours. Removal of benzene and excess thionyl chloride below 25° under a reduced pressure gave bis-(chloromethyl)phenol-formaldehyde oligomer as a colorless

powder, which was recrystallized from benzene to give pure crystals.

2-[3-(Chloromethyl)-5-*tert*-butylsalicyl]-6-(chloromethyl)-4-*tert*-butylphenol (**8b**).

The yield of **8b** was 90% as colorless crystals, mp 125-126° (from benzene); ^{1}H nmr (deuteriochloroform): δ 1.27 (s, 18H, *t*-Bu x 2), 3.95 (s, 2H, $ArCH_2Ar$), 4.67 (s, 4H, $ArCH_2Cl$ x 2), 7.12 (d, 2H, Ar-H x 2, J = 2.0 Hz), 7.31 (d, 2H, Ar-H x 2, J = 2.0 Hz); ^{13}C nmr (deuteriochloroform): δ 31.2, 31.4, 34.1, 43.6, 123.4, 125.6, 127.4, 128.5, 144.2, 149.3; (FAB) ms: m/z 409 $(M+H)^+$.

Anal. Calcd. for $C_{23}H_{30}Cl_2O_2$: C, 67.48; H, 7.39. Found: C, 67.74; H, 7.55.

2-[3-[3-(Chloromethyl)-5-methylsalicyl]-5-methylsalicyl]-6-(chloromethyl)-4-methylphenol (**8d**).

The yield of **8d** was 95% as colorless crystals, mp 110-111° (from benzene); ^{1}H nmr (deuteriochloroform): δ 2.23 (s, 3H, CH_3), 2.24 (s, 6H, CH_3 x 2), 3.84 (s, 4H, $ArCH_2Ar$ x 2), 4.62 (s, 4H, CH_2Cl x 2), 6.92 (d, 2H, Ar x 2, J = 2.0 Hz), 6.94 (s, 2H, Ar-H x 2), 7.07 (d, 2H, Ar-H, J = 2.0 Hz), 7.12 (bs, 2H, OH x 2), 9.00 (bs, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 20.4, 20.5, 31.2, 43.2, 123.9, 127.1, 128.0, 128.3, 129.0, 129.2, 129.7, 132.1, 147.3, 149.3; (FAB) ms: m/z 445 $(M+H)^+$.

Anal. Calcd. for $C_{25}H_{26}Cl_2O_3$: C, 67.42; H, 5.88. Found: C, 67.44; H, 5.99.

2-[3-[3-(Chloromethyl)-5-methylsalicyl]-5-*tert*-butylsalicyl]-6-(chloromethyl)-4-methylphenol (**8e**).

The yield of **8e** was 90% as colorless crystals, mp 134° (dec., from benzene); ^{1}H nmr (deuteriochloroform): δ 1.27 (s, 9H, *t*-Bu), 2.19 (s, 6H, CH_3 x 2), 3.85 (s, 4H, $ArCH_2Ar$ x 2), 4.67 (s, 4H, $ArCH_2Cl$ x 2), 6.65 (d, 2H, Ar-H x 2, J = 2.2 Hz), 6.98 (d, 2H, Ar-H x 2, J = 2.2 Hz), 7.13 (s, 2H, Ar-H x 2); ^{13}C nmr (deuteriochloroform): δ 20.4, 30.5, 31.6, 34.1, 43.2, 123.9, 126.2, 126.6, 128.0, 129.2, 130.7, 132.1, 144.5, 147.4, 149.4; (FAB) ms: m/z 487 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{32}Cl_2O_3$: C, 68.99; H, 6.62. Found: C, 68.87; H, 6.82.

2-[3-[3-[3-(Chloromethyl)-5-*tert*-butylsalicyl]-5-*tert*-butylsalicyl]-5-*tert*-butylsalicyl]-6-(chloromethyl)-4-*tert*-butylphenol (**8f**).

The yield of **8f** was 85% as colorless crystals, mp 214° (dec., from benzene); ^{1}H nmr (deuteriochloroform): δ 1.25 (s, 18H, *t*-Bu x 2), 1.26 (s, 18H, *t*-Bu x 2), 3.87 (s, 2H, $ArCH_2Ar$), 3.90 (s, 4H, $ArCH_2Ar$ x 2), 4.68 (s, 4H, $ArCH_2Cl$ x 2), 7.12 (d, 2H, Ar x 2, J = 2.0 Hz), 7.14 (s, 4H, Ar-H), 7.31 (d, 2H, Ar-H x 2, J = 2.0 Hz); ^{13}C nmr (deuteriochloroform): δ 31.3, 31.4, 31.7, 32.1, 33.9, 34.0, 43.7, 123.5, 125.5, 125.8, 125.9, 126.9, 127.2, 128.0, 128.6, 144.1, 144.4, 147.1, 149.2; (FAB) ms: m/z 797 $(M+H)^+$.

Anal. Calcd. for $C_{45}H_{58}Cl_2O_4$: C, 73.65; H, 7.97. Found: C, 73.55; H, 7.89.

General Procedure for the Preparation of Homothiacalixarenes (**1** and **2**).

To a suspension of sodium carbonate (212 mg, 2.0 mmoles) in dry *N,N*-dimethylformamide (5 ml) was added a solution of bis(chloromethyl)phenol-formaldehyde trimer (**8c**, **8d**, or **8e**) (0.5 mmole) in dry *N,N*-dimethylformamide (5 ml) and a solution of 1,2-ethanedithiol or 1,3-propanedithiol (0.5 mmole) in *N,N*-dimethylformamide (5 ml) over 1 hour. After the addition was complete, the mixture was allowed to stir at 30° for 2 hours. Removal of the solvent gave a pale yellow oily residue, which was subjected to column chromatography on silica gel using hexane: ethyl acetate, 4:1 as an eluent to give **1** as a white powder.

5,11,22,28,34,45-Hexa-*tert*-butyl-15,18,38,41-tetrathiaheptacyclo[41.3.1.1^{3,7}.1^{9,13}.1^{20,24}.1^{26,30}.1^{32,36}]dopentaconta-1(46),3-(48),4,6,9(49),10,12,20(50),21,23,25(51),27,29,32(52),33,35,43-(47),44-octadecaene-47,48,49,50,51,52-hexaol (**1a**).

The yield of **1a** was 90% as colorless crystals, mp 105-110° (from dichloromethane-hexane); ^{1}H nmr (deuteriochloroform): δ 1.23 (s, 36H, *t*-Bu x 4), 1.29 (s, 18H, *t*-Bu x 2), 2.82 (s, 8H, SCH_2 x 4), 3.79 (s, 8H, $ArCH_2S$ x 4), 3.87 (s, 8H, $ArCH_2Ar$ x 4), 6.85 (d, 4H, Ar-H x 4, J = 2.4 Hz), 7.17 (s, 4H, Ar-H x 4), 7.19 (d, 4H, Ar-H x 4, J = 2.4 Hz), 8.77 (bs, 6H, OH x 6); ^{13}C nmr (deuteriochloroform): δ 31.3, 31.4, 31.6, 32.5, 33.9, 34.2, 123.8, 125.4, 125.9, 126.6, 126.9, 127.5, 143.5, 144.1, 147.2, 149.1; (FAB) ms: m/z 1185 $(M+H)^+$.

Anal. Calcd. for $C_{72}H_{96}O_6S_4$: C, 72.93; H, 8.16. Found: C, 72.99; H, 8.22.

5,11,22,28,34,45-Hexamethyl-15,18,38,41-tetrathiaheptacyclo-[41.3.1.1^{3,7}.1^{9,13}.1^{20,24}.1^{26,30}.1^{32,36}]dopentaconta-1(46),3-(48),4,6,9(49),10,12,20(50),21,23,25(51),27,29,32-(52),33,35,43(47),44-octadecaene-47,48,49,50,51,52-hexaol (**1b**).

The yield of **1b** was 55% as colorless crystals, mp 140-145° (from dichloromethane-hexane); ^{1}H nmr (deuteriochloroform): δ 2.16 (s, 12H, CH_3 x 4), 2.26 (s, 6H, CH_3 x 2), 2.74 (s, 8H, SCH_2 x 4), 3.73 (s, 8H, $ArCH_2S$ x 4), 3.81 (s, 8H, $ArCH_2Ar$ x 4), 6.68 (d, 4H, Ar-H x 4, J = 2.4 Hz), 6.94 (d, 4H, Ar-H x 4, J = 2.4 Hz), 6.96 (s, 4H, Ar-H x 4), 8.47 (bs, 4H, OH x 4), 8.59 (bs, 2H, OH x 2); ^{13}C nmr (deuteriochloroform): δ 20.4, 20.5, 30.8, 32.1, 33.0, 124.7, 127.2, 127.8, 129.1, 129.6, 130.3, 130.5, 130.7, 147.5, 149.0; (FAB) ms: m/z 933 $(M+H)^+$.

Anal. Calcd. for $C_{54}H_{60}O_6S_4$: C, 69.49; H, 6.48. Found: C, 69.71; H, 6.32.

5,28-Di-*tert*-butyl-11,22,34,45-tetramethyl-15,18,38,41-tetrathiaheptacyclo[41.3.1.1^{3,7}.1^{9,13}.1^{20,24}.1^{26,30}.1^{32,36}]dopentaconta-1(46),3(48),4,6,9(49),10,12,20(50),21,23,25(51),27,29,32-(52),33,35,43(47),44-octadecaene-47,48,49,50,51,52-hexaol (**1c**).

The yield of **1c** was 89% as colorless crystals, mp 130-140° (from dichloromethane-hexane); ^{1}H nmr (deuteriochloroform): δ 1.33 (s, 18H, *t*-Bu x 2), 2.15 (s, 12H, CH_3 x 4), 2.75 (s, 8H, SCH_2 x 4), 3.74 (s, 8H, $ArCH_2S$ x 4), 3.84 (s, 8H, $ArCH_2Ar$ x 4), 6.67 (d, 4H, Ar-H x 4, J = 2.4 Hz), 6.94 (d, 4H, Ar-H x 4, J = 2.4 Hz), 7.17 (s, 4H, Ar-H x 4), 8.47 (bs, 4H, OH x 4), 8.59 (bs, 2H, OH x 2); ^{13}C nmr (deuteriochloroform): δ 20.4, 31.4, 31.5, 32.3, 33.1, 34.0, 124.8, 126.0, 126.6, 127.8, 129.0, 130.3, 130.6, 144.0, 147.6, 148.9; (FAB) ms: m/z 1017 $(M+H)^+$.

Anal. Calcd. for $C_{60}H_{72}O_6S_4$: C, 70.83; H, 7.13. Found: C, 70.89; H, 7.33.

5,11,23-Tri-*tert*-butyl-15,19-dithiatetracyclo[19.3.1.1^{3,7}.1^{9,13}]-heptacosa-1(24),3(26),4,6,9(27),10,12,21(25),22-nonaene-25,26,27-triol (**2a**).

The yield of **2a** was 73% as colorless crystals, mp 104-105° (from dichloromethane-hexane); ^{1}H nmr (deuteriochloroform): δ

1.24 (s, 18H, *t*-Bu x 2), 1.33 (s, 9H, *t*-Bu), 1.90 (quintet, 2H, CH_2, J = 7.9 Hz), 2.30 (t, 4H, CH_2 x 2, J = 7.9 Hz), 3.75 (s, 4H, $ArCH_2S$ x 2), 3.85 (s, 4H, $ArCH_2Ar$ x 2), 7.00 (d, 2H, Ar-H x 2, J = 2.6 Hz), 7.20 (d, 2H, Ar-H x 2, J = 2.6 Hz), 7.26 (s, 2H, Ar-H x 2), 8.50 (bs, 2H, OH x 2), 8.70 (bs, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 28.1, 30.0, 31.4, 31.5, 31.7, 33.9, 122.8, 126.0, 126.1, 126.5, 126.6, 126.8, 143.5, 143.9, 147.7, 149.5; (FAB) ms: m/z 607 $(M+H)^+$.

Anal. Calcd. for $C_{37}H_{50}O_3S_2$: C, 73.22; H, 8.30. Found: C, 73.40; H, 8.33.

5,11,23-Trimethyl-15,19-dithiatetracyclo[19.3.1.1^{3,7}.1^{9,13}]heptacosa-1(24),3(26),4,6,9(27),10,12,21(25),22-nonaene-25,26,27-triol (**2b**).

The yield of **2b** was 56% as colorless crystals, mp 143-145° (from dichloromethane-hexane); ^1H nmr (deuteriochloroform): δ 1.83 (quintet, 2H, CH_2, J = 8.0 Hz), 2.22 (s, 6H, CH_3 x 2), 2.25 (t, 4H, CH_2 x 2, J = 8.0 Hz), 2.31 (s, 3H, CH_3), 3.79 (s, 4H, $ArCH_2S$ x 2), 3.83 (s, 4H, $ArCH_2Ar$ x 2), 6.85 (d, 2H, Ar-H x 2, J = 2.0 Hz), 7.03 (d, 2H, Ar-H x 2, J = 2.0 Hz), 7.05 (s, 2H, Ar-H x 2), 8.40 (bs, 2H, OH x 2), 8.62 (bs, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 20.4, 20.5, 28.2, 29.7, 30.9, 123.1, 126.8, 127.1, 129.5, 129.8, 130.1, 130.2, 130.5, 147.7, 149.5; (FAB) ms: m/z 481 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{32}O_3S_2$: C, 69.96; H, 6.71. Found: C, 69.97; H, 6.73.

5,23-Dimethyl-11-*tert*-butyl-15,19-dithiatetracyclo-[19.3.1.1^{3,7}.1^{9,13}]heptacosa-1(24),3(26),4,6,9(27),10,12,21-(25),22-nonaene-25,26,27-triol (**2c**).

The yield of **2c** was 43% as colorless crystals, mp 190.5-194° (from dichloromethane-hexane); ^1H nmr (deuteriochloroform): δ 1.28 (s, 9H, *t*-Bu), 1.82 (quintet, 2H, CH_2, J = 7.9 Hz), 2.18 (s, 6H, CH_3 x 2), 2.30 (t, 4H, CH_2 x 2, J = 7.9 Hz), 3.74 (s, 4H, $ArCH_2S$ x 2), 3.83 (s, 4H, $ArCH_2Ar$ x 2), 6.82 (d, 2H, Ar-H x 2, J = 2.6 Hz), 6.99 (d, 2H, Ar-H x 2, J = 2.6 Hz), 7.22 (s, 2H, Ar-H x 2), 8.39 (bs, 2H, OH x 2), 8.61 (bs, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 20.4, 28.3, 29.7, 30.9, 31.4, 31.6, 34.0, 123.1, 126.3, 126.4, 127.1, 129.5, 130.2, 130.3, 143.9, 147.9, 149.5; (FAB) ms: m/z 523 $(M+H)^+$.

Anal. Calcd. for $C_{31}H_{38}O_3S_2$: C, 71.22; H, 7.33. Found: C, 71.32; H, 7.42.

General Procedure of the Preparation of Homoazacalixarenes (**3**, **4**, and **5**).

To a solution of triethyl amine (0.39 g, 3.9 mmoles) in chlorofrom (130 ml) were added a solution of bis(chloromethyl)phenol-formaldehyde oligomer (1.4 mmoles) in chloroform (30 ml) and a solution of piperazine or *trans*-2,5-dimethylpiperazine (1.4 mmoles) in chloroform (30 ml) at 20° under a nitrogen atmosphere over 10 hours. After the additions were complete, the mixture was further stirred at 20° for 36 hours, and then the reaction mixture was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave a yellow oily residue, which was subjected to column chromatography on silica gel using chloroform as an eluent to give the macrocycles as colorless crystals.

1,15,18,32-Tetraaza-5,11,22,28-tetrakis(*tert*-butyl)heptacyclo[30.2.2.2^{15,18}.1^{3,7}.1^{9,13}.1^{20,24}.1^{26,30}]dotetraconta-3(4),5,7(39),9-(10),11,13(40),20(41),21,23,26(27),28,30(42)-dodecaene-39,40,41,42-tetraol (**3a**).

The yield of **3a** was 64% as colorless crystals, mp 266-271° (from chloroform:acetonitrile, 1:3); ^1H nmr (deuteriochloroform): δ 1.19 (s, 36H, *t*-Bu x 4), 2.20 (br s, 8H, NCH_2 x 4), 2.47 (br s, 8H, NCH_2 x 4), 3.70 (s, 8H, $ArCH_2N$ x 4), 3.96 (s, 4H, $ArCH_2Ar$ x 2), 6.83 (s, 4H, Ar-H x 4), 7.02 (s, 4H, Ar-H x 4), 10.58 (br, 4H, OH x 4); ^{13}C nmr (deuteriochloroform): δ 29.3, 31.6, 52.3, 61.7, 119.5, 123.4, 126.8, 141.4, 153.0; (FAB) ms: m/z 845 $(M+H)^+$.

Anal. Calcd. for $C_{54}H_{76}O_4N_4$: C, 76.74; H, 9.06; N, 6.63. Found: C, 76.84; H, 9.32; N, 6.81.

1,15,18,32-Tetraaza-15,33,35,38-tetramethyl-5,11,22,28-tetrakis(*tert*-butyl)heptacyclo[30.2.2.2^{15,18}.1^{3,7}.1^{9,13}.1^{20,24}.1^{26,30}]dotetraconta-3(4),5,7(39),9(10),11,13(40),20(41),-21,23,26(27),28,30(42)-dodecaene-39,40,41,42-tetraol (**3b**).

The yield of **3b** was 13% as colorless crystals, mp 218-223° (dec., from ethyl acetate:hexane 1:3); ^1H nmr (deuteriochloroform): δ 1.17 (d, 12H, CH_3 x 4, J = 5.6 Hz), 1.22 (s, 36H, *t*-Bu x 4), 2.08 (bs, 4H, CH_2 x 2), 2.55 (bs, 4H, CH x 4), 2.97 (d, 4H, CH_2 x 2, J = 11.8 Hz), 3.14 (d, 4H, ArCHN x 4, J = 13.0 Hz), 3.98 (s, 4H, $ArCH_2Ar$ x 2), 4.43 (d, 4H, ArCHN x 4, J = 13.0 Hz), 6.84 (s, 4H, Ar-H x 4), 7.02 (s, 2H, Ar-H x 2), 7.06 (s, 2H, Ar-H x 2), 10.7 (bs, 4H, OH x 4); ^{13}C nmr (deuteriochloroform): δ 17.2, 29.3, 31.6, 33.9, 56.6, 57.0, 59.3, 119.8, 123.1, 126.6, 127.1, 141.3, 152.9; (FAB) ms: m/z 901 $(M+H)^+$.

Anal. Calcd. for $C_{58}H_{84}O_4N_4$: C, 77.29; H, 9.39; N, 6.22. Found: C, 77.31; H, 9.51; N, 9.45.

1,21-Diaza-5,11,17-tris(*tert*-butyl)pentacyclo[19.2.2.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-3(26),4,6,9(10),11,13(27),15(16),17,19(28)-nonaene-26,27,28-triol (**4a**).

The yield of **4a** was 32% as colorless crystals, mp 268° (dec., from ethyl acetate:hexane 1:4); ^1H nmr (deuteriochloroform): δ 1.11 (s, 18H, *t*-Bu x 2), 1.30 (s, 9H, *t*-Bu), 2.47 (br s, 8H, NCH_2 x 4), 3.67 (s, 4H, $ArCH_2Ar$ x 2), 3.90 (s, 4H, $ArCH_2N$ x 2), 6.80 (s, 2H, Ar-H x 2), 6.87 (s, 2H, Ar-H x 2), 7.26 (s, 2H, Ar-H x 2), 8.38 (bs, 3H, OH x 3); ^{13}C nmr (deuteriochloroform): δ 31.0, 31.4, 31.6, 33.8, 33.9, 52.1, 60.7, 119.8, 123.3, 125.8, 125.9, 127.0, 127.5, 142.2, 142.5, 149.6, 151.2; (FAB) ms: m/z 586 $(M+H)^+$.

Anal. Calcd. for $C_{38}H_{52}O_3N_2$: C, 78.04; H, 8.96; N, 4.79. Found: 77.98; H, 9.01; N, 4.81.

1,21-Diaza-22,24-dimethyl-5,11,17-tris(*tert*-butyl)pentacyclo[19.2.2.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-3(26),4,6,9(10),11,13(27),15-(16),17,19(28)-nonaene-26,27,28-triol (**4b**).

The yield of **4b** was 6% as colorless crystals, mp 208-215° (dec., from ethyl acetate:hexane 1:4); ^1H nmr (deuteriochloroform): δ 0.88 (bs, 6H, CH_3 x 2), 1.06 (s, 18H, *t*-Bu x 2), 1.17 (s, 9H, *t*-Bu), 2.03 (bs, 2H, NCH_2), 2.47 (bs, 2H, NCH x 2), 2.77 (bs, 2H, NCH_2), 3.26 (d, 2H, ArCHN x 2, J = 13.0 Hz), 3.90 (bs, 4H, $ArCH_2Ar$ x 2), 4.20 (d, 2H, ArCHN x 2, J = 13.0 Hz), 6.71 (s, 2H, Ar-H x 2), 6.73 (bs, 2H, Ar-H x 2), 6.99 (s, 2H, Ar-H x 2), 8.39 (bs, 3H, OH x 3); ^{13}C nmr (deuteriochloroform): δ 17.1, 30.9, 31.5, 33.8, 33.9, 57.0, 59.6, 120.3, 125.4, 125.9, 126.7, 127.0, 142.0, 142.7; (FAB) ms: m/z 643 $(M+H)^+$.

Anal. Calcd. for $C_{40}H_{56}O_3N_2$: C, 78.39; H, 9.21; N, 4.57. Found: C, 78.41; H, 9.09; N, 4.66.

1,27-Diaza-5,11,17,23-tetrakis(*tert*-butyl)hexacyclo-[25.2.2.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}]pentatriaconta-3(32),4,6,9(10),11,13(33),15(16),17,19(34),21(22),23,25(35)-dodecaene-32,33,34,35-tetraol (**5a**).

The yield of **5a** was 19% as colorless crystals, mp 251-253° (dec., from ethyl acetate:hexane 1:4); ^1H nmr (deuterio-

chloroform): δ 1.17 (s, 18H, *t*-Bu x 2), 1.29 (s, 18H, *t*-Bu x 2), 2.39 (s, 4H, NCH_2 x 2), 3.05 (s, 4H, NCH_2 x 2), 3.52 (s, 4H, $ArCH_2Ar$ x 2), 3.93 (s, 2H, $ArCH_2Ar$), 3.94 (bs, 4H, NCH_2Ar x 2), 6.72 (d, 2H, Ar-H x 2, J = 1.2 Hz), 6.84 (d, 2H, Ar-H x 2, J = 1.2 Hz), 7.10 (d, 2H, Ar-H x 2, J = 2.5 Hz), 7.27 (d, 2H, Ar-H x 2, J = 2.5 Hz), 8.54 (s, 2H, OH x 2), 12.20 (s, 2H, OH x 2); ^{13}C nmr (deuteriochloroform): δ 29.7, 30.8, 31.4, 31.6, 31.9, 33.9, 52.4, 61.2,119.1, 123.3, 125.4, 125.7, 125.8, 126.3, 126.7, 126.8, 142.2, 142.9, 149.2, 151.3; (FAB) ms: m/z747 $(M+H)^+$.

Anal. Calcd. for $C_{49}H_{66}O_4N_2$: C, 78.78; H, 8.90; N, 3.75. Found: C, 78.95; H, 8.74; N, 3.71.

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