

## SYNTHESES AND PROPERTIES OF CHIRAL TRICYCLIC COMPOUNDS BRIDGED BY CYSTINE UNITS

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**Abstract-** Novel chiral tricyclic compounds were prepared from the reactions of the cystine dimethyl ester and 4-substituted 2,6-bis(chloromethyl)phenol derivatives. The <sup>1</sup>H-NMR and CD spectra showed the existence of chiral twisting of the cyclophane unit, which was induced by the chirality of the cystine moiety.

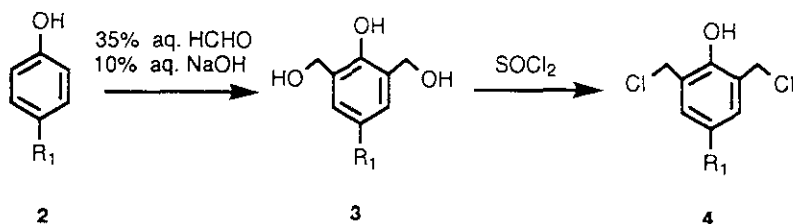
Introducing conformational constraints to the backbone of peptides is a field that has great interest, because the peptidomimetics can make it possible to design simple models for studying biological interactions.<sup>1</sup> Therefore, much effort has been made toward the restriction of the conformational flexibility of peptides by the incorporating templates and S-S linkages.<sup>1,2</sup>

Phenols offer attractive alternatives to the amide bonds of peptides for making hydrogen bonds, because the hydroxyl groups of phenols have proton donor and acceptor properties, and the aromatic ring can be expected to restrict the flexibility of the conformations.

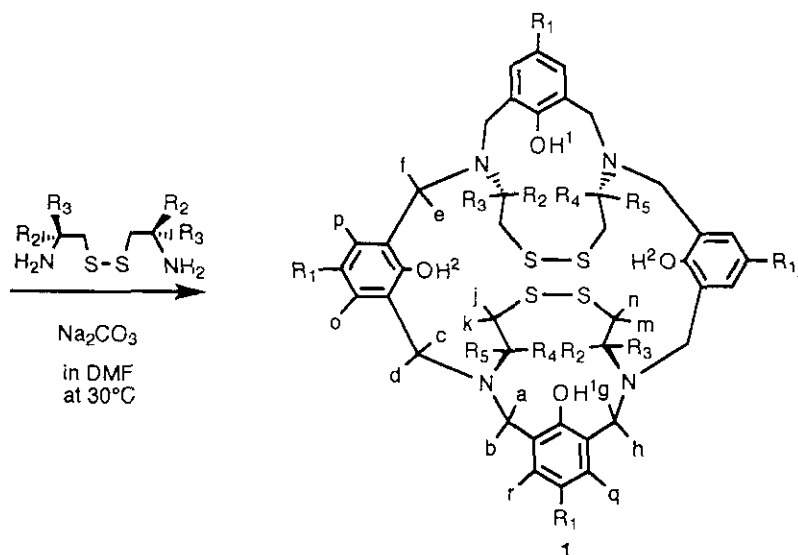
Therefore, we planned to construct a chiral macrocycle from phenol and a cystine unit. We now describe the results.

The cyclization reaction between the (*R,R*)-cystine dimethyl ester and two equimolar amounts of 2,6-bis(chloromethyl)-*p*-cresol (**4a**) in dry DMF at 30°C in the presence of sodium carbonate under a nitrogen atmosphere gave a [2+4] tricyclic compound (**1a**) in 9 % yield. Analogously, reactions using 2,6-bis(chloromethyl)-*p*-substituted phenols (**4b**, **4c**, and **4d**) instead of **4a** afforded the corresponding products (**1b**, **1c** and **1d**) in 8, 7, and 5 % yields, respectively. The enantiomer (**1e**) of **1b** was also prepared from the reaction of **4b** with the (*S,S*)-cystine dimethyl ester under the same reaction conditions in 7 % yield.

The structures of **1** were determined on the basis of the NMR, IR, and MS spectra and elemental analyses. The MALDI-TOF MS spectrum, which is known to give only molecular ion peaks (Figure 1),<sup>3</sup> indicated that the product was constructed from two cystines and four *m*-xylene units. From the MS spectral data, three possible



a:  $R_1=Me$ , b:  $R_1=t-Bu$ , c:  $R_1=o$ -hexyl, d:  $R_1=Ph$



a:  $R_1=Me$ ,  $R_2=R_5=CO_2Me$ ,  $R_3=l$ ,  $R_4=i$   
 b:  $R_1=t-Bu$ ,  $R_2=R_5=CO_2Me$ ,  $R_3=l$ ,  $R_4=i$   
 c:  $R_1=o$ -hexyl,  $R_2=R_5=CO_2Me$ ,  $R_3=l$ ,  $R_4=i$   
 d:  $R_1=Ph$ ,  $R_2=R_5=CO_2Me$ ,  $R_3=l$ ,  $R_4=i$   
 e:  $R_1=t-Bu$ ,  $R_2=l$ ,  $R_3=R_4=CO_2Me$ ,  $R_5=l$

Scheme 1.

planar structures (A, B, and C in Figure 2) can be proposed for the product. The CPK model consideration of the product indicates that the structure C is too hard to construct by the model. In the NOESY experiment of **1** (Figures 5 and 6), the observed NOEs ( $H_x/H_i$  and  $H_j/H_n$ ) are only compatible with structure A. Furthermore, the CPK model consideration of structure A implies that steric repulsion should make the *anti* configuration of the cystine unit more stable than the *syn*-type. Based on the above results, the *anti*-type A is considered to be the correct structure.

In the IR spectra, the OH stretching vibrational absorption of **1** was observed in the range of 3280-3260  $cm^{-1}$ . Two kinds of OH proton signals of the hydroxyl groups were observed in the range of 9.09-9.47 ppm and 9.87-10.24 ppm, respectively. These values indicate that the hydrogen of the hydroxyl group of **1** forms strong

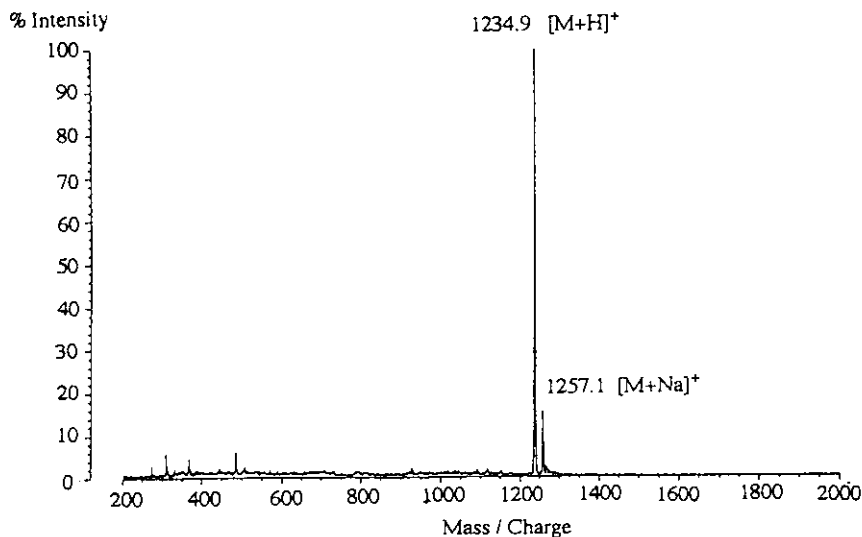


Figure 1. MALDI-TOF MS spectrum of **1b**.

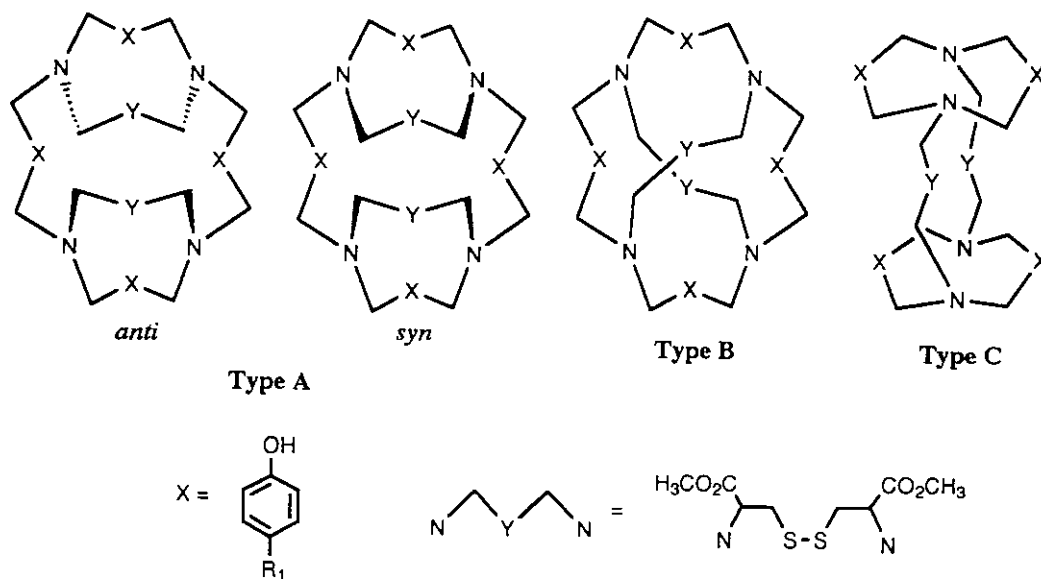


Figure 2.

hydrogen bonding.

The methylene protons of **1** appeared as four pairs of doublets due to the geminal coupling between  $H_{exo}$  and  $H_{endo}$  at room temperature. These pairs did not coalesce at 55 °C in  $CDCl_3$ , indicating that the tricyclic compounds form a rigid structure. The  $\Delta\delta$  values ( $\Delta\delta H_{xy} = \delta H_x - \delta H_y$ ) of the  $ArCH_2Ar$  methylene protons are expected to be sensitive to the dihedral angle between the plane of the aromatic ring and the adjacent methylene protons (Figure 7).<sup>4</sup>

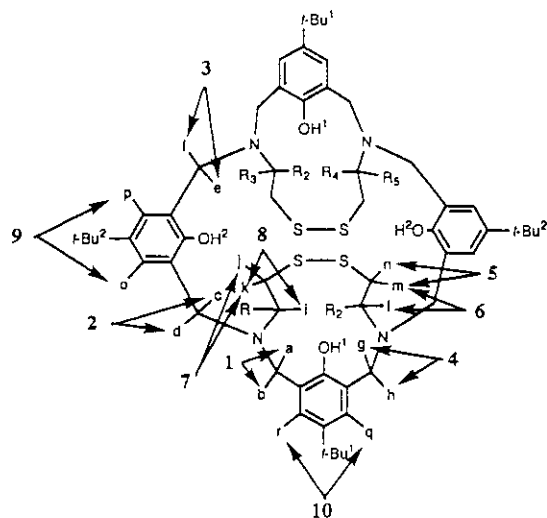


Figure 3. Correlations observed in  $^1\text{H}$ - $^1\text{H}$  COSY experiment of **1b**.

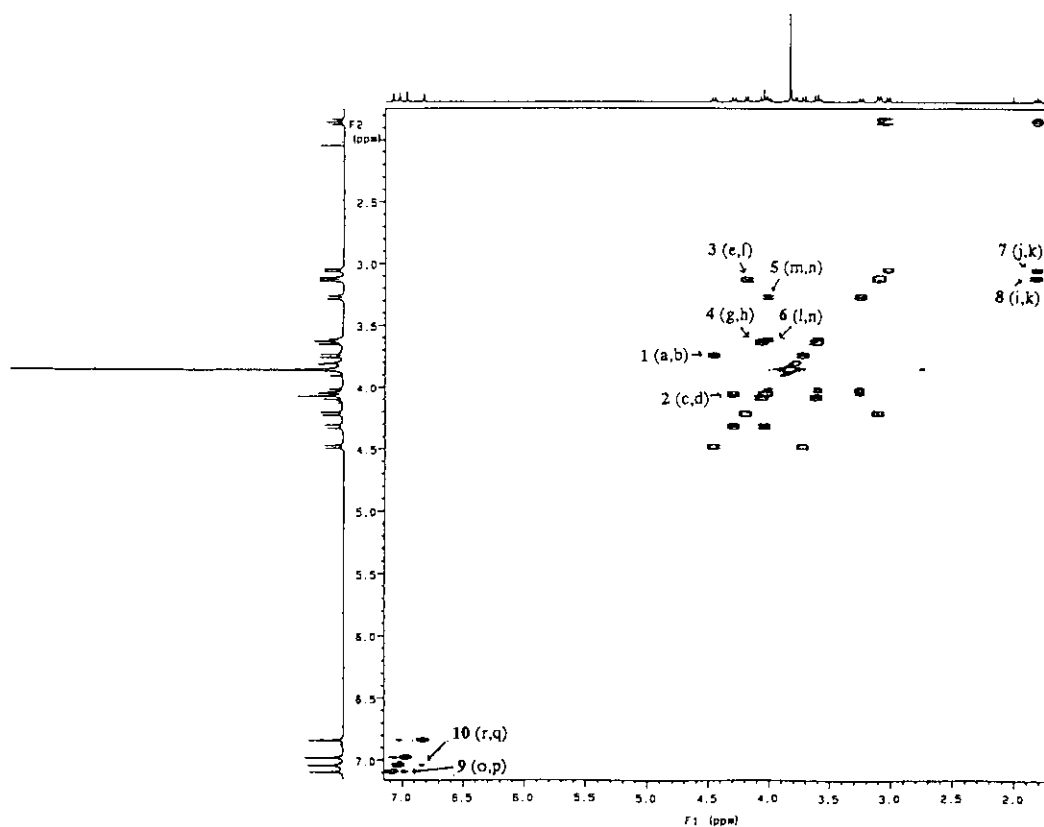


Figure 4.  $^1\text{H}$ - $^1\text{H}$  COSY spectrum (500 MHz) of **1b** in  $\text{CDCl}_3$  at 20  $^\circ\text{C}$ .

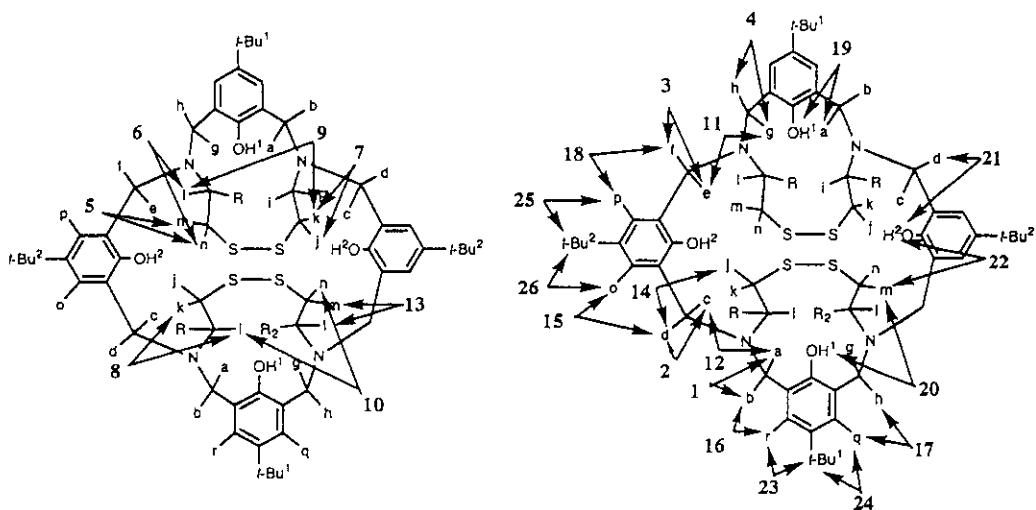


Figure 5. Correlations observed in NOESY experiment of **1b**.

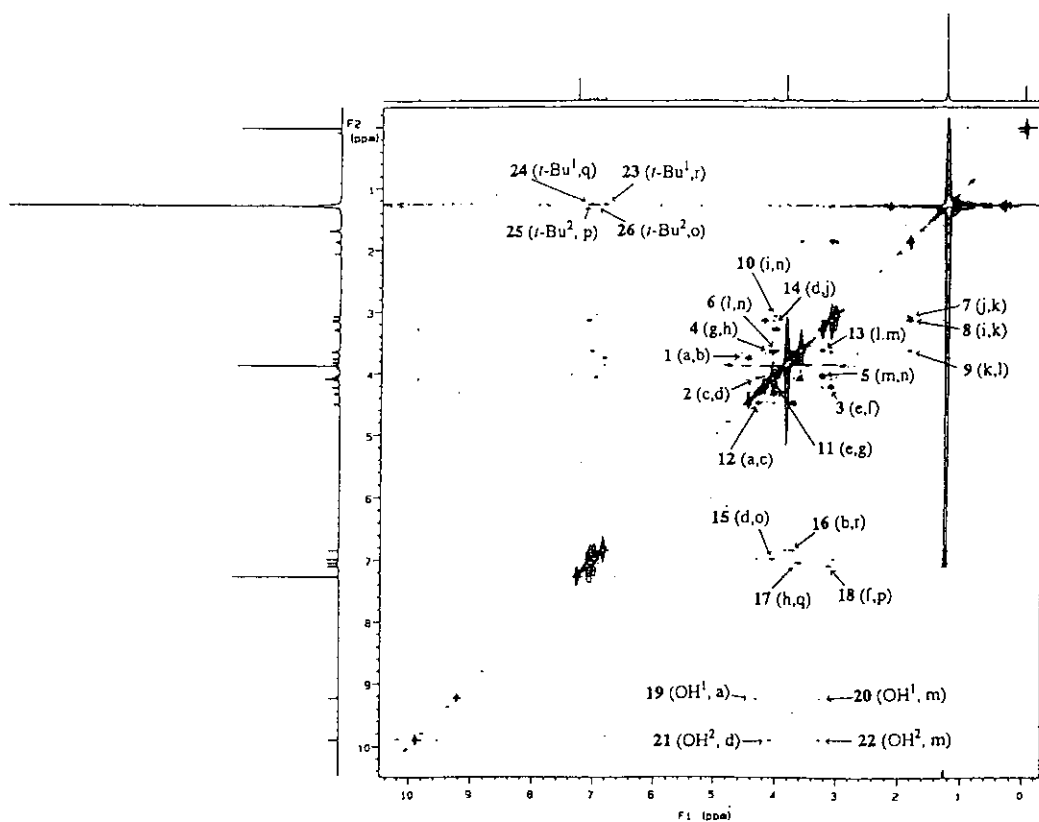
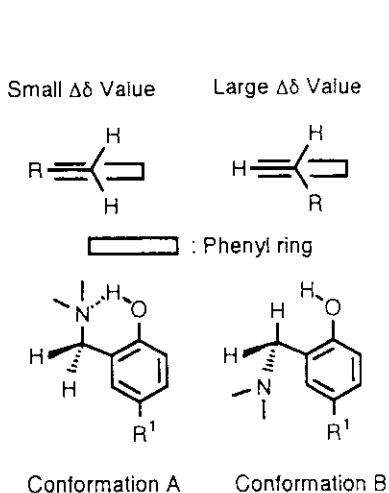


Figure 6. NOESY spectrum (0.30 ms mixing time at 500 MHz) of **1b** in  $\text{CDCl}_3$  at 20 °C.

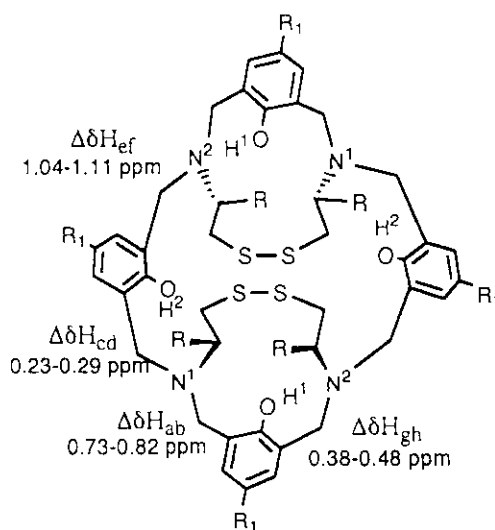
Therefore, the different  $\Delta\delta$  values observed imply that each *m*-xylene unit adopts a twisted form. Since the smallest  $\Delta\delta$  values are verified to be the  $H_cH_d$  methylene protons, it is reasonable to assume that the  $OH^2$  hydroxyl proton forms a strong hydrogen bonding with the  $N^1$  nitrogen atom. This speculation was supported by the chemical shift of the  $CH_cH_d$  carbon atoms (ca.  $\delta$  60 ppm), which were observed at the lowest magnetic field. The circular dichroism (CD) spectra of **1** were clearly observed at the absorption due to the phenol chromophore (**1a**:  $\lambda_{ext}$  237 nm ( $\theta$ , -40300), **1b**: 237 nm ( $\theta$ , -45900), **1c**: 237 nm ( $\theta$ , -28400), **1d**: 253 nm ( $\theta$ , -60900)) in hexane at 20 °C, supporting the assumption that the phenols are chiral.<sup>4</sup> The CD spectrum of **1e**, which is the corresponding enantiomer of **1b**, gave a mirror image spectrum (Figure 9). These observations clearly indicate that the chirality of the cyclophane moiety is induced by the chirality of the cystine unit.

**Table 1.**  $\Delta\delta$  values ( $\Delta\delta H_{xy} = \delta H_x - \delta H_y$ ) of  $ArCH_2Ar$  methylene protons, chemical shifts of OH protons (500 MHz for  $^1H$ ), and chemical shifts of  $ArCH_2Ar$  carbon atoms (125 MHz for  $^{13}C$ ) in  $CDCl_3$  at 20 °C.

	$\Delta\delta H_{ab}$	$\Delta\delta H_{cd}$	$\Delta\delta H_{ef}$	$\Delta\delta H_{gh}$	$\delta OH^1$	$\delta OH^2$	$\delta CH_{ab}$	$\delta CH_{cd}$	$\delta CH_{ef}$	$\delta CH_{gh}$
<b>1a</b>	0.82	0.29	1.11	0.41	9.13	9.87	54.7	60.1	51.9	53.3
<b>1b</b>	0.73	0.27	1.09	0.48	9.09	9.85	54.8	60.5	52.3	53.6
<b>1c</b>	0.77	0.27	1.08	0.42	9.17	9.91	54.7	60.3	52.0	53.4
<b>1d</b>	0.78	0.23	1.04	0.38	9.47	10.24	54.9	60.4	52.1	53.6
<b>1b</b> (50°C)	0.73	0.27	1.09	0.48	-	-	-	-	-	-
<b>1b</b> (-60°C)	0.79	0.29	1.01	0.29	9.33	10.49	-	-	-	-



**Figure 7.**



**Figure 8.**

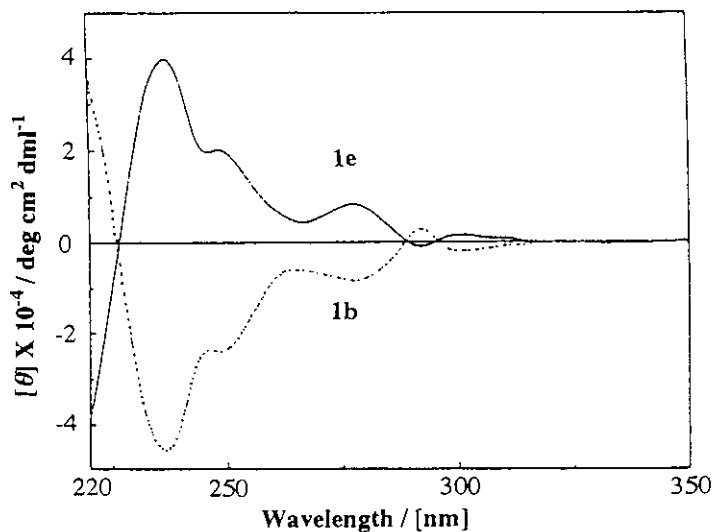


Figure 9. CD spectra of chiral tricyclic compounds (1b) and (1e) in hexane at 20 °C.

In conclusion, we prepared chiral tricyclic compounds by the cyclization reactions between the cystine dimethyl ester and bis(chloromethyl)phenols. The NMR and CD spectra revealed that the chirality of the cystine unit induced the chirality of the cyclophane moiety.

## EXPERIMENTAL

Melting points were measured by Yanagimoto melting point apparatus and were uncorrected. Varian unity INOVA 500 instrument was employed for  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , H-H and C-H COSY, and NOESY experiments. IR and UV spectra were taken on Horiba FT-200 and Hitachi 228A spectrophotometers, respectively. FAB MS spectra were obtained by JEOL JMS AX-505HA spectrometer using *m*-nitrobenzyl alcohol as a matrix. MALDI-TOF mass spectrum was obtained by Kratos Kompact MALDI using 2,5-dihydroxybenzoic acid as a matrix. CD spectra were collected by Jasco J720W1 spectrophotometer. All chemicals were reagents grade and were used without further purification. Dry benzene was distilled from sodium under  $\text{N}_2$ . DMF was stored in molecular sieve 4A and then was distilled from  $\text{CaH}_2$ . 4-Substituted 2,6-bis(hydroxymethyl)phenols (**3**) were prepared according to the methods reported in literatures. **3a**: mp 124-125 °C (lit, 130.5 °C).<sup>5</sup> **3b**: mp 72-73 °C (lit, 74.5 °C).<sup>6</sup> **3c**: mp 107-108 °C (lit, 106-107 °C).<sup>7</sup> **3d**: mp 118-119 °C (lit, 110-111.5°C).<sup>7</sup> 4-Substituted 2,6-bis(chloromethyl)phenols (**4**) were prepared by improved method as follow.

**Preparation of 2,6-Bis(chloromethyl)-4-substituted Phenol Derivatives (4).** To a solution of **3** (5 mmol) in dry benzene (30 mL) was slowly added a solution of thionyl chloride (2.38 g, 20 mmol) in dry benzene

(10 mL) at 20 °C over 1 h. After the addition was completed, the mixture was stirred at 20 °C for 5 h. The solvent and excess thionyl chloride were removed by evaporator keeping the temperature below 30 °C. The resulting white solid was washed with hexane several times. Recrystallization of the solid from benzene gave **4** as colorless crystals in 80~90 % yield. **4a**: mp 85-86 °C (lit., 87 °C).<sup>8</sup> **4b**: mp 81-82 °C (lit., 82 °C).<sup>8</sup> **2,6-Bis(chloromethyl)-4-cyclohexyl phenol (4c)** : colorless oil. FAB-MS 273 ([M+H]<sup>+</sup>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.20-1.90

(m, CH<sub>2</sub> x 4, 10H), 2.42 (m, CH, 1H), 4.68 (s, CH<sub>2</sub>Cl x 2, 4H), 5.59 (br s, Ar-OH, 1H), 7.12 (s, Ar-H x 2, 2H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ 26.0 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 34.5 (CH<sub>2</sub>), 42.7 (CH<sub>2</sub>Cl), 43.5 (CH), 124.4 (C), 129.4 (CH), 140.9 (C), 151.1 (COH). Anal. Calcd for C<sub>14</sub>H<sub>18</sub>OCl<sub>2</sub>, C, 61.55; H, 6.64. Found C, 61.77; H, 6.41.

**2,6-Bis(chloromethyl)-4-phenylphenol (4d)** : mp 136-138 °C (from benzene). FAB-MS 267 ([M+H]<sup>+</sup>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 4.76 (s, CH<sub>2</sub>Cl x 2, 4H), 5.80 (br s, Ar-OH, 1H), 7.30-7.58 (m, Ph and Ar-H, 7H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ 42.4 (CH<sub>2</sub>Cl), 125.1 (C), 126.7 (CH), 127.2 (C), 128.8 (CH), 129.7 (CH), 134.4 (C), 139.6 (C), 152.6 (COH). Anal. Calcd for C<sub>14</sub>H<sub>12</sub>OCl<sub>2</sub>, C, 62.94; H, 4.53. Found C, 63.14; H, 4.83.

#### General Procedure of the Syntheses of Chiral Macrocycles (1).

To a suspension of sodium carbonate (0.64 g, 6.0 mmol) in 50 mL of dry DMF were added a solution of 4-substituted bis(chloromethyl)phenol derivative (**4**) (2.0 mmol) in 50 mL of dry DMF and a solution of cystine dimethyl ester dihydrochloride (0.34 g, 1.0 mmol) in 50 mL of dry DMF at 30 °C over 6 h under a nitrogen atmosphere. After the addition was completed, the mixture was stirred at 30 °C for 12 h. Removal of DMF under a reduced pressure gave a pale yellow oily residue, which was dissolved with dichloromethane (100 mL). The solution was washed 3 times with water (100 mL) and dried over anhydrous sodium sulfate. Removal of dichloromethane gave a yellow oily residue, which was subjected to column chromatography on silica gel using hexane: ethyl acetate (1:3) as an eluent to give **1** as a white powder.

**1a**: mp 198-203 °C (from dichloromethane-hexane).  $[\alpha]_D^{20} = -181^\circ$  (c=0.1, CHCl<sub>3</sub>). FAB-MS 1065 ([M+H]<sup>+</sup>). IR (CHCl<sub>3</sub>) 3268 (ν<sub>OH</sub>), 1732 (ν<sub>CO</sub>) cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.92 (dd, *J* = 10.0 and 11.0 Hz, H<sub>x</sub>, 2H), 2.21 (s, CH<sub>3</sub>, 6H), 2.23 (s, CH<sub>3</sub>, 6H), 3.07 (d, *J* = 10.0 Hz, H<sub>i</sub>, 2H), 3.08 (d, *J* = 11.5 Hz, H<sub>f</sub>, 2H), 3.14 (d, *J* = 11.0 Hz, H<sub>j</sub>, 2H), 3.25 (dd, *J* = 2.5 and 14.0 Hz, H<sub>m</sub>, 2H), 3.62 (d, *J* = 12.5 Hz, H<sub>b</sub>, 2H), 3.63 (d, *J* = 14.0 Hz, H<sub>n</sub>, 2H), 3.64 (dd, *J* = 2.5, 11.0 Hz, H<sub>i</sub>, 2H), 3.84 (s, CO<sub>2</sub>CH<sub>3</sub>, 6H), 3.85 (s, CO<sub>2</sub>CH<sub>3</sub>, 6H), 4.02 (d, *J* = 13.0 Hz, H<sub>d</sub>, 2H), 4.04 (d, *J* = 14.0 Hz, H<sub>g</sub>, 2H), 4.06 (dd, *J* = 11.0 and 14.0 Hz, H<sub>n</sub>, 2H), 4.18 (d, *J* = 11.5 Hz, H<sub>e</sub>, 2H), 4.31 (d, *J* = 13.0 Hz, H<sub>c</sub>, 2H), 4.43 (d, *J* = 12.5 Hz, H<sub>s</sub>, 2H), 6.63 (d, *J* = 2.0 Hz, H<sub>r</sub>, 2H), 6.82 (br s, H<sub>o</sub> and H<sub>q</sub>, 4H), 6.83 (d, *J* = 2.0 Hz, H<sub>p</sub>, 2H), 9.13 (br s, OH<sup>1</sup>, 2H), 9.87 (br s, OH<sup>2</sup>, 2H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ 20.3 (ArCH<sub>3</sub>), 20.5 (ArCH<sub>3</sub>), 40.1 (SCH<sub>2</sub>), 45.0 (SCH<sub>2</sub>), 51.6 (CO<sub>2</sub>CH<sub>3</sub>), 51.7 (CO<sub>2</sub>CH<sub>3</sub>), 51.9 (NCH<sub>2</sub>), 53.3 (NCH<sub>2</sub>), 54.7 (NCH<sub>2</sub>), 59.7 (CHCO<sub>2</sub>CH<sub>3</sub>), 60.1 (NCH<sub>2</sub>), 64.7 (CHCO<sub>2</sub>CH<sub>3</sub>), 122.1 (C), 123.6 (C), 123.8 (C), 123.9 (C), 128.1 (C), 128.2 (C), 131.0 (CH), 131.1 (CH x 2), 132.5 (CH), 153.8 (COH),



154.3 (COH), 170.8 (CO), 171.1 (CO). Anal. Calcd for  $C_{52}H_{64}N_4O_{12}S_4$ , C, 58.63; H, 6.06; N, 5.26. Found C, 58.94; H, 6.25; N, 5.00.

**1b:** mp 222-224 °C (from dichloromethane-hexane).  $[\alpha]_D^{20} = -152^\circ$  ( $c = 0.1$ ,  $CHCl_3$ ). FAB-MS 1233 ( $[M+H]^+$ ). IR ( $CHCl_3$ ) 3267 ( $\nu_{OH}$ ), 1732 ( $\nu_{CO}$ )  $cm^{-1}$ .  $^1H$ -NMR ( $CDCl_3$ )  $\delta$  1.11 (s, *t*-Bu, 18H), 1.13 (s, *t*-Bu, 18H), 1.71 (dd,  $J = 10.5$  and  $11.5$  Hz,  $H_k$ , 2H), 2.92 (d,  $J = 11.5$  Hz,  $H_i$ , 2H), 2.99 (d,  $J = 11.5$  Hz,  $H_f$  and  $H_j$ , 4H), 3.14 (dd,  $J = 2.5$  and  $14.0$  Hz,  $H_m$ , 2H), 3.48 (dd,  $J = 2.5$  and  $11.0$  Hz,  $H_l$ , 2H), 3.51 (d,  $J = 14.0$  Hz,  $H_n$ , 2H), 3.61 (d,  $J = 12.5$  Hz,  $H_b$ , 2H), 3.72 (s,  $CO_2CH_3$ , 6H), 3.73 (s,  $CO_2CH_3$ , 6H), 3.90 (dd,  $J = 11.0$  and  $14.0$  Hz,  $H_o$ , 2H), 3.92 (d,  $J = 12.5$  Hz,  $H_d$ , 2H), 3.95 (d,  $J = 14.0$  Hz,  $H_g$ , 2H), 4.07 (d,  $J = 11.5$  Hz,  $H_e$ , 2H), 4.20 (d,  $J = 12.5$  Hz,  $H_c$ , 2H), 4.36 (d,  $J = 12.5$  Hz,  $H_x$ , 2H), 6.70 (d,  $J = 2.0$  Hz,  $H_r$ , 2H), 6.84 (d,  $J = 2.0$  Hz,  $H_s$ , 2H), 6.90 (d,  $J = 2.0$  Hz,  $H_q$ , 2H), 6.95 (d,  $J = 2.0$  Hz,  $H_p$ , 2H), 9.09 (br s,  $OH^1$ , 2H), 9.85 (br s,  $OH^2$ , 2H).  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$  31.4 ( $C(CH_3)$ ), 31.6 ( $C(CH_3)$ ), 33.8 ( $C(CH_3)$ ), 33.8 ( $C(CH_3)$ ), 39.7 ( $SCH_2$ ), 44.7 ( $SCH_2$ ), 51.7 ( $CO_2CH_3$ ), 51.8 ( $CO_2CH_3$ ), 52.3 ( $NCH_2$ ), 53.6 ( $NCH_2$ ), 54.8 ( $NCH_2$ ), 59.6 ( $CHCO_2CH_3$ ), 60.5 ( $NCH_2$ ), 64.7 ( $CHCO_2CH_3$ ), 121.6 (C), 123.1 (C), 123.3 (C), 123.5 (C), 127.0 (CH), 127.2 (CH), 127.6 (CH), 128.8 (CH), 141.8 (C), 141.9 (C), 153.4 (COH), 154.2 (COH), 170.7 (CO), 171.0 (CO). Anal. Calcd for  $C_{64}H_{88}N_4O_{12}S_4$ , C, 62.31; H, 7.19; N, 4.54. Found, C, 62.28; H, 7.33; N, 4.39.

**1c:** 7% yield. mp 207-210 °C (from dichloromethane-hexane).  $[\alpha]_D^{20} = -106^\circ$  ( $c = 0.1$ ,  $CHCl_3$ ). FAB-MS 1337 ( $[M+H]^+$ ). IR ( $CHCl_3$ ) 3280 ( $\nu_{OH}$ ), 1732 ( $\nu_{CO}$ )  $cm^{-1}$ .  $^1H$ -NMR ( $CDCl_3$ )  $\delta$  1.20-1.40 (m, cyclohexyl protons, 12H), 1.65-1.85 (m, cyclohexyl protons and  $H_k$ , 12H), 3.04 (d,  $J = 10.5$  Hz,  $H_i$ , 2H), 3.10 (d,  $J = 11.5$  Hz,  $H_p$ , 2H), 3.11 (d,  $J = 11.0$  Hz,  $H_j$ , 2H), 3.26 (dd,  $J = 2.5$  and  $13.5$  Hz,  $H_m$ , 2H), 3.62 (dd,  $J = 2.5$  and  $11.0$  Hz,  $H_l$ , 2H), 3.63 (d,  $J = 13.5$  Hz,  $H_n$ , 2H), 3.69 (d,  $J = 13.0$  Hz,  $H_b$ , 2H), 3.85 (s,  $CO_2CH_3$ , 6H), 3.86 (s,  $CO_2CH_3$ , 6H), 4.03 (d,  $J = 13.5$  Hz,  $H_d$ , 2H), 4.04 (dd,  $J = 11.0$  and  $13.5$  Hz,  $H_o$ , 2H), 4.05 (d,  $J = 13.5$  Hz,  $H_g$ , 2H), 4.19 (d,  $J = 11.5$  Hz,  $H_c$ , 2H), 4.30 (d,  $J = 13.5$  Hz,  $H_e$ , 2H), 4.45 (d,  $J = 13.0$  Hz,  $H_x$ , 2H), 6.65 (d,  $J = 2.0$  Hz,  $H_r$ , 2H), 6.82 (d,  $J = 2.0$  Hz,  $H_s$ , 2H), 6.85 (d,  $J = 2.0$  Hz,  $H_q$ , 2H), 6.94 (d,  $J = 2.0$  Hz,  $H_p$ , 2H), 9.17 (br s  $OH^1$ , 2H), 9.91 (br s,  $OH^2$ , 2H).  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$  26.1 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 26.9 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 26.9 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub> x 2), 26.9 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub> x 2), 34.1 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 34.1 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 35.0 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 35.1 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 39.8 ( $SCH_2$ ), 43.4 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 43.4 (Ar-CH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 44.8 ( $SCH_2$ ), 51.7 ( $CO_2CH_3$  x 2), 52.0 ( $NCH_2$ ), 53.4 ( $NCH_2$ ), 54.7 ( $NCH_2$ ), 59.7 ( $CHCO_2CH_3$ ), 60.3 ( $NCH_2$ ), 64.8 ( $CHCO_2CH_3$ ), 122.0 (C), 123.5 (C), 123.7 (C), 123.8 (C), 128.3 (CH), 128.6 (CH), 129.0 (CH), 130.1 (CH), 138.8 (C), 138.9 (C), 153.6 (COH), 154.5 (COH), 170.7 (CO), 171.1 (CO). Anal. Calcd for  $C_{72}H_{96}N_4O_{12}S_4$ , C, 64.64; H, 7.23; N, 4.19. Found, C, 64.63; H, 7.28; N, 3.94.

**1d:** mp 217-222 °C (from dichloromethane-hexane).  $[\alpha]_D^{20} = -144^\circ$  ( $c = 0.1$ ,  $CHCl_3$ ). FAB-MS 1313 ( $[M+H]^+$ ).

IR (CHCl<sub>3</sub>) 3269 ( $\nu_{\text{OH}}$ ), 1732 ( $\nu_{\text{CO}}$ ) cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  2.00 (dd,  $J = 10.0$  and  $12.0$  Hz, H<sub>k</sub>, 2H), 3.18 (d,  $J = 10.0$  Hz, H<sub>i</sub>, 2H), 3.22 (d,  $J = 12.0$  Hz, H<sub>j</sub>, 2H), 3.29 (d,  $J = 12.0$  Hz, H<sub>p</sub>, 2H), 3.34 (dd,  $J = 2.5$  and  $13.5$  Hz, H<sub>m</sub>, 2H), 3.73 (dd,  $J = 2.5$  and  $10.0$  Hz, H<sub>l</sub>, 2H), 3.81 (d,  $J = 12.5$  Hz, H<sub>b</sub>, 2H), 3.83 (d,  $J = 14.0$  Hz, H<sub>n</sub>, 2H), 3.85 (s, CO<sub>2</sub>CH<sub>3</sub>, 6H), 3.89 (s, CO<sub>2</sub>CH<sub>3</sub>, 6H), 4.13 (dd,  $J = 10.0$  and  $13.5$  Hz, H<sub>o</sub>, 2H), 4.21 (d,  $J = 14.0$  Hz, H<sub>g</sub>, 2H), 4.24 (d,  $J = 13.5$  Hz, H<sub>d</sub>, 2H), 4.33 (d,  $J = 12.0$  Hz, H<sub>e</sub>, 2H), 4.47 (d,  $J = 13.5$  Hz, H<sub>c</sub>, 2H), 4.59 (d,  $J = 12.5$  Hz, H<sub>a</sub>, 2H), 7.13 (d,  $J = 2.0$  Hz, aromatic protons, 2H), 7.25-7.58 (m, aromatic protons, 13H), 9.49 (br s, OH<sup>1</sup>, 2H), 10.24 (br s, OH<sup>2</sup>, 2H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  40.1 (SCH<sub>2</sub>), 44.9 (SCH<sub>2</sub>), 51.9 (CO<sub>2</sub>CH<sub>3</sub>), 51.9 (CO<sub>2</sub>CH<sub>3</sub>), 52.1 (NCH<sub>2</sub>), 53.6 (NCH<sub>2</sub>), 55.0 (NCH<sub>2</sub>), 60.0 (CHCO<sub>2</sub>CH<sub>3</sub>), 60.4 (NCH<sub>2</sub>), 64.8 (CHCO<sub>2</sub>CH<sub>3</sub>), 122.7 (C), 124.3 (C), 124.4 (C), 124.5 (C), 126.6 (CH), 126.7 (CH), 126.8 (CH), 128.7 (CH x 2), 129.1 (CH), 129.3 (CH), 129.5 (CH), 130.8 (CH), 132.3 (C), 132.5 (C), 140.3 (C), 140.5 (C), 155.4 (COH), 156.3 (COH), 170.8 (CO), 170.9 (CO). Anal. Calcd for C<sub>72</sub>H<sub>72</sub>N<sub>4</sub>O<sub>12</sub>S<sub>4</sub>, C, 65.83; H, 5.52; N, 4.26. Found C, 65.83; H, 5.58; N, 4.12.

**1e**: mp 220-223 °C (from dichloromethane-hexane).  $[\alpha]_{\text{D}}^{20} = +150^{\circ}$  ( $c = 0.1$ , CHCl<sub>3</sub>). FAB-MS 1233 ([M+H]<sup>+</sup>). Anal. Calcd for C<sub>64</sub>H<sub>88</sub>N<sub>4</sub>O<sub>12</sub>S<sub>4</sub>, C, 62.31; H, 7.19; N, 4.54. Found, C, 62.21; H, 7.28; N, 4.45.

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