4,5-Dimethoxy-1,2-diiodobenzene. 4,5-Dimethoxy-2-aminobenzoic acid (13.8 g, 70 mmol) in dioxane (200 mL) was added over 1 h to a refluxing solution of iodine (38 g, 150 mmol), isoamyl nitrite (21 g, 180 mmol), and chloroform (1000 mL) and treated as above. After concentration the residue was diluted with ligroin, passed through a pad of silica gel, and concentrated. The residue was recrystallized from heptane to give 2.5 g product (9%): mp 130–132 °C; ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 2), 3.79 (s, 6); ^{13}C NMR ($CDCl_3$) {^{1}H} δ 149.3, 121.6, 96.8, 55.8; IR (KBr) 1490, 1430, 1330, 1315, 1245, 1205, 1180, 1020, 850, 780, 630 cm^{-1}. Anal. Calcd for $C_8H_8I_2O_2$: C, 24.64; H, 2.07. Found: C, 24.75; H, 2.08.

4-Methyl-1,2-diiodobenzene. 5-Methyl-2-aminobenzoic acid (50 g, 330 mmol) in dioxane (600 mL) was added over several hours to a refluxing solution of iodine (92.5 g, 360 mmol), isoamyl nitrite (58 g, 500 mmol), and chloroform (1200 mL) and treated as above. The product was purified by fractional distillation to give 26.4 g (8%): bp 260 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (m, 2), 6.84 (dd, J = 7.7, 1.2 Hz, 2), 2.25 (s, 3); ^{13}C NMR ($CDCl_3$) {^{1}H} δ 139.8, 139.3, 138.7, 130.2, 107.7, 103.6, 20.5; IR (neat) 1450, 1375, 1255, 1090, 1000, 870, 815, 805, 660 cm^{-1}. Anal. Calcd for $C_7H_6I_2$: C, 24.45; H, 1.76. Found: C, 24.74; H, 1.88.

2,3-Diiodonaphthalene. 3-Amino-2-naphthoic acid (25 g, 133 mmol) in dioxane (1500 mL) was added over several hours to a refluxing solution of iodine (35 g, 138 mmol), isoamylnitrite (25 g, 215 mmol), and chloroform (2000 mL) and allowed to react for 18 h. After this time the reaction mixture was neutralized with 10 L of 10% NaOH. The product was extracted with ethyl acetate (2 × 1000 mL), treated with a $Na_2S_2O_3$ solution, and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was dissolved in ligroin and then passed through a column of silica gel, eluting with 1:1 ligroin–dichloromethane. The product was isolated and recrystallized from ethanol to give 1.9 g (0.5%): mp 115.5–117 °C; ^{1}H NMR (DMSO-d_6) δ 8.55 (s, 2), 7.81 (m, 2), 7.52 (m, 2); ^{13}C NMR (DMSO-d_6) {^{1}H} δ 137.9, 133.4, 127.2, 126.6, 105.1; IR (KBr) 1480, 1395, 1300, 1130, 935, 870, 840, 755 cm^{-1}. Anal. Calcd for $C_{10}H_6I_2$: C, 31.61; H, 1.59. Found: C, 31.35; H, 1.63.

Preparation of Imides. For these preparative-scale reactions the following general conditions were used: 3% $PdCl_2L_2$, 2.4 equiv of DBU, DMAc (0.2 M), 115 °C, 90–95 psi of CO, and 1.0–1.1 equiv of *o*-diiodobenzene unless otherwise noted. The following is a representative example. Isolation and characterization data for previously reported phthalimides can be found in the supplementary material.

***N*-(4-Carbomethoxyphenyl)phthalimide (8d).** 4-(Aminomethyl)benzoate (517 mg, 3.42 mmol), *o*-diiodobenzene (500 μL, 3.82 mmol), $PdCl_2L_2$ (72 mg, 0.102 mmol), DMAc (17 mL), and DBU (1.23 mL, 8.20 mmol) were allowed to react at 115 °C under 95 psi CO for 5.5 h. After this time the reaction mixture was concentrated. The solid which crystallized was isolated by filtration and washed with methanol to give 470 mg (49%) of product. The filtrate was concentrated and slurried with methanol, and the solid formed was isolated by filtration and again washed with methanol to give 110 mg more product. The filtrate was again concentrated, dissolved in $CHCl_3$ (50 mL), washed with water (3 × 50 mL), dried over Na_2SO_4, filtered, concentrated, and then subjected to chromatotron purification (3:1, hexanes–ethyl acetate) to give 40 mg more product: total yield 62%; mp 179–180 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 2), 7.94 (m, 2), 7.80 (m, 2), 7.58 (d, J = 8.5 Hz, 2), 3.93 (s, 3); ^{13}C NMR ($CDCl_3$) {^{1}H} δ 166.7, 166.2, 135.8, 134.6, 131.4, 130.3, 129.2, 125.8, 123.8, 52.2; IR (KBr) 2950, 1785, 1715, 1605, 1380, 1275, 1115, 720 cm^{-1}. Anal. Calcd for $C_{16}H_{11}NO_4$: C, 68.33; H, 3.94; N, 4.98. Found: C, 67.96; H, 4.07; N, 4.97.

4-Methyl-*N*-phenylphthalimide (8l): mp 199–201 °C; ^{1}H NMR (DMSO-d_6) δ 7.82 (d, J = 7.6 Hz, 1), 7.77 (s, 1), 7.68 (d, J = 7.6 Hz, 1), 7.48 (m, 2), 7.41 (m, 3), 2.49 (s, 3); ^{13}C NMR (DMSO-d_6) {^{1}H} δ 167.1, 167.0, 145.7, 135.1, 132.0, 131.9, 128.8, 128.0, 127.4, 123.8, 123.4, 21.4; IR (KBr) 1770, 1705, 1490, 1375, 1100, 750, 735 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.00; H, 4.75; N, 5.87.

4,5-Dimethoxy-*N*-phenylphthalimide (8p): mp 242–243.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.47 (m, 4), 7.40 (m, 3), 3.94 (s, 6). ^{13}C NMR (DMSO-d_6) {^{1}H} δ 149.3, 121.6, 96.8, 55.8; IR (KBr) 1775, 1705, 1595, 1500, 1375, 1315, 1220, 1090, 1065, 990, 760 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.43; H, 4.66; N, 4.94.

Acknowledgment. We would like to thank D. Margevich for FTIR spectra, J. Lugert for GC–MS results, and P. Keogh for help in their subsequent interpretation.

Supplementary Material Available: A full description of experimental procedures and physical and spectral properties of all phthalimides synthesized as well as mass spectral data of the products in Scheme II (9 pages). Ordering information is given on any current masthead page.

Cyclodextrin-Induced Conformational Enantiomerism of Dinaphthylmethanes

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Pamoic acid (4,4′-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid]) included in the γ-cyclodextrin (γ-CDx) cavity shows an extremely strong, bisignate Cotton effect on its circular dichroism (CD) spectrum, suggesting that (*R*)-helix pamoic acid is selectively bound to γ-CDx. 2,2′-Dihydroxy-1,1′-dinaphthylmethane also exhibits the (+) to (−) bisignate CD signals in aqueous γ-CDx solution but the CD intensities are much weaker than those of pamoic acid–γ-CDx complex. The CD intensities are correlated with the stabilities of the inclusion complexes. A larger binding constant for the pamoic acid–γ-CDx complex (K = 4100 dm^3 mol^{-1}) may be ascribed to a hydrogen-bonding interaction between a carboxylate anion of the guest and a secondary hydroxyl group of the host. The ^{1}H NMR spectroscopic measurements suggest a plausible structure of the pamoic acid–γ-CDx complex where a naphthalene moiety of pamoic acid is situated inside of the γ-CDx cavity and another naphthalene ring is located at the rim of the primary hydroxyl group side of the γ-CDx cavity. Although the hydrogen-bonding interaction is not essential for conformational enantiomerism of dinaphthylmethane derivatives, it seems to enhance the chiral recognition by cyclodextrins.

Introduction

Cyclodextrins (CDx) are cyclic oligosaccharides composed of several glucopyranose units and can include organic compounds and inorganic anions into their hydrophobic cavities.[1] Since cyclodextrins are chiral host molecules, attempts have been made to achieve optical resolution using CDxs. Sulfinyl compounds,[2] phenyl-

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alanine, α-methylbenzylamine,[3] and phosphinate compounds[4] are known as guest molecules whose enantiomers are partially resolved by CDxs. The following factors have been considered as prerequisites for optical resolution of sulfinyl compounds via β-CDx inclusion complexes: (1) inclusion of a hydrophobic part of the guest molecule in a CDx cavity, (2) hydrogen-bonding interaction between the host and guest molecules, and (3) steric hindrance due to a bulky group of the guest and CDx.[2] This speculation has been developed as a "three-point attachment model" for stereoselective complexation.[5] Enantioselective complexation by CDxs has been utilized in separation of enantiomers by liquid chromatography.[6] In most cases, hydrogen-bonding interactions have been assumed to play an important role for chiral recognition by CDxs.

Cyclodextrins also induce conformational enantiomerism of guest molecules. Exciton-coupling theory of circular dichroism (CD) spectroscopy[7] reveals that (*S*)-helix bilirubin is selectively formed in complexation with α-, β-, and γ-CDxs.[8] Recently, it has been shown that an enantioselective complexation of bilirubin with CDxs is realized by hydrogen-bond formation between the host and guest molecules.[9] On the basis of circularly polarized fluorescence (CPF) spectroscopic data, it has been concluded that a pyrene excimer formed in the γ-CDx cavity is optically active.[10] In this case, there is no possibility of the hydrogen bonding. The CD or CPF spectroscopy also reveals the selective complexation of conformational enantiomers of fluorescein,[11] an acridine orange dimer,[12] 4-helicene, and biphenyl[13] with CDxs.

Recently we found that heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMe-β-CDx) prefers (*S*)-1,1′-bi-2-naphthol and its related compounds as the guests while β-CDx itself shows a very weak ability to recognize the chirality of these binaphthyl derivatives.[14] Although the contribution of the hydrogen bonding cannot be excluded, it may be more reasonable to consider that a steric factor dominates the enantioselectivity. In the present work, we studied the CDx-induced conformational enantiomerism of 4,4′-methylenebis(3-hydroxy-2-naphthalenecarboxylic acid)

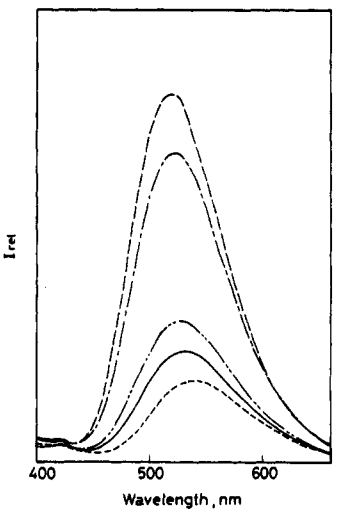
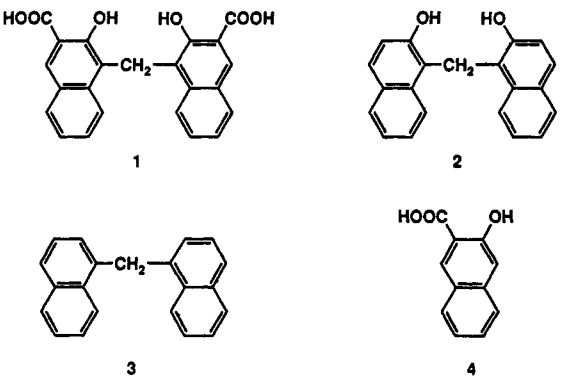


Figure 1. Fluorescence spectra of 1 (2×10^{-6} mol dm^{-3}) in water at pH 10.8 in the absence and the presence of CDx (1×10^{-2} mol dm^{-3}): —, H_2O and α-CDx; -·-·-, β-CDx; - - -, γ-CDx; – –, DMe-β-CDx, -·-, TMe-β-CDx.

(pamoic acid, **1**), 2,2′-dihydroxy-1,1′-dinaphthylmethane (**2**), and 1,1′-dinaphthylmethane (**3**) by means of CD, fluorescence, and ^{1}H NMR spectroscopies. Since these



dinaphthylmethanes are not optically active in solutions and are bichromophoric, the absolute configurations of these guests included in the CDx cavity can easily be determined from the bisignate CD signals. **1** and **2** can interact with CDxs through hydrogen bonding while **3** does not. Therefore, we expect to learn whether the hydrogen-bonding interaction is the prerequisite for chiral recognition by CDxs or not. The aim of the present work is to understand one of the detailed mechanisms for chiral recognition by CDxs in aqueous solutions.

Experimental Section

Materials. All cyclodextrins (Nacalai Tesque) and the sodium salt of **1** (Aldrich) were purchased and used without further purification except for heptakis(2,6-di-*O*-methyl)-β-CDx (DMe-β-CDx). DMe-β-CDx was precipitated by heating its aqueous solution and was collected by filtration. **1** (Aldrich) was purified by recrystallization from pyridine. **2** and **3** were prepared and purified according to the procedures described in the literature.[15,16] 3-Hydroxy-2-naphthoic acid (**4**, Nacalai Tesque) was recrystallized from ethanol.

Spectroscopic Measurements. The absorption and uncorrected fluorescence spectra were measured with a Shimadzu UV-2100 spectrophotometer and a Hitachi 650-60 spectrofluorometer, respectively. The CD spectra were taken on a Jasco J-500A spectropolarimeter. The 400-MHz ^{1}H NMR spectra in D_2O were measured on a JEOL GX-400 spectrometer at 23 ± 1

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Table I. Binding Constants (K) of Inclusion Complexes of 1, 2, and 4 with CDxs in Aqueous Solutions at 25 °C

CDx	K, dm^3 mol^{-1}		
	1[a]	2[b]	4[b]
β-CDx	210 ± 2	180 ± 10	1073 ± 1
γ-CDx	4100 ± 700	210 ± 30	126 ± 10
DMe-β-CDx	340 ± 10	90 ± 1	4429 ± 300
TMe-β-CDx	250 ± 10	140 ± 5	457 ± 3

[a] The binding constants were determined in aqueous alkaline solutions (pH 10.8). No appreciable changes in the K values were obtained in water at pH 5.5. [b] The binding constants were determined in water (pH 5.5).

°C. The chemical shifts were determined by using sodium 3-(trimethylsilyl)-1-propanesulfonate (Merck) as an external standard.

Results and Discussion

Binding Constants. Inclusion phenomena of the 1-CDx systems can be studied by measuring fluorescence spectra. Figure 1 shows the fluorescence spectra of 1 in aqueous alkaline solutions at pH 10.8 (NaOH) with and without CDxs. 1 in water fluoresces (λ_{max} = 532 nm). α-CDx does not affect the fluorescence spectrum because the size of the α-CDx cavity is too small to include 1. Addition of β-CDx, DMe-β-CDx, or TMe-β-CDx causes a blue shift of the fluorescence maximum accompanied by an increase in fluorescence yield. γ-CDx, however, reduces the yield of a red-shifted fluorescence. The fluorescence behavior of 1 at pH 5.5 is the same as that at pH 10.8. The binding constants (K) for the 1–CDx complexes were determined by Benesi–Hildebrand plots[17] for the fluorescence intensity changes. 1 was excited at an isosbestic point observed in the absorption spectroscopic change of 1 upon addition of CDx. Linear Benesi–Hildebrand plots indicate the formation of 1:1 host–guest complexes. The results are summarized in Table I, together with the K values obtained for 2 and 4. The K value for the 1–γ-CDx complex is much larger (K = 4100 ± 700 dm^3 mol^{-1}) than that for the 2–γ-CDx complex (K = 210 ± 30 dm^3 mol^{-1}). The pH titration monitored by absorption spectroscopy suggests that pK_1 of 1 due to dissociation of the carboxyl group is below 3 and pK_2 due to the dissociation of the hydroxyl group is above 13. The pK_1 value could not be determined accurately because of precipitation of 1 in the free carboxylic acid form (–COOH) in water at lower pH. The lower pK_1 (<3) compared with 2-naphthoic acid (pK_a = 4.16) and the higher pK_2 (>13) compared with 2-naphthol (pK_a = 9.2) should be interpreted in terms of hydrogen-bond formation between the carboxylate anion and the adjacent hydroxyl group of 1. The large stability of the 1–γ-CDx complex may be ascribed to the hydrogen-bonding interaction between the carboxylate anion of 1 and the secondary hydroxyl group of γ-CDx (vide infra). The K value for the 4–γ-CDx complex is much smaller than that of the 4–β-CDx complex. The size of the γ-CDx cavity may be too large to form a stable inclusion complex of 4 having a smaller molecular size. Matching the size of the guest with the size of the CDx cavity is very important to stabilize the inclusion complex through van der Waals interactions.[18,19] The proposed hydrogen-bonding interaction may not be effective in stabilizing the inclusion complex when the size of guest does not fit inside the host. At the present stage, we cannot explain the reason for an extremely large K value of the 4–DMe–β-CDx complex. Low solubility of 3 in water prevented the determination of K.

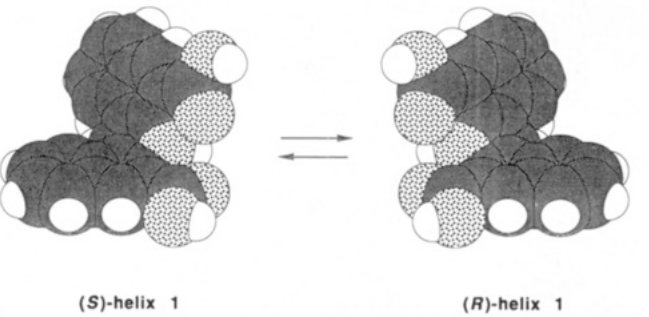

Figure 2. Enantiomeric conformers of 1.

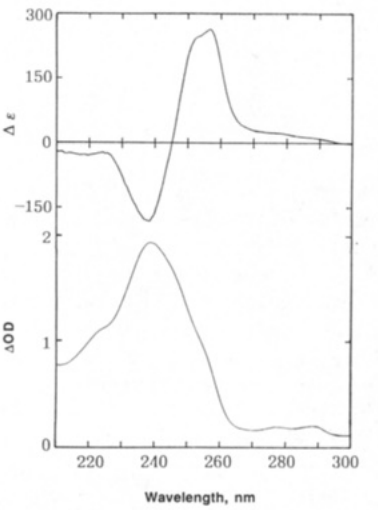

Figure 3. Absorption and CD spectra of 1 (2×10^{-5} mol dm^{-3}) in the aqueous γ-CDx (1×10^{-2} mol dm^{-3}) solution at pH 10.8.

CD Spectra. Exciton coupling theory[7] can be used to determine the absolute configuration of a chiral, bichromophoric compound. When the orientation of the transition dipoles of the two chomophores takes an (*R*)-helix configuration, the CD spectrum is split into two bands due to an exciton coupling interaction at the wavelength region of electronic transition, where positively and negatively signed CD signals appear at longer and shorter wavelengths, respectively. The opposite Cotton effect is observed for an (*S*)-helix compound. 1 is composed of two naphthalene moieties which are linked with a methylene bridge. A Corey–Pauling–Koltun (CPK) molecular model suggests two conformational enantiomers of 1 (Figure 2). Of course, no optical activity was measured for 1 in water. HPLC using a chiral column (Sumichiral QA-2500I), which can completely separate the enantiomers of 1,1′-bi-2-naphthol, showed one peak, suggesting that interconversion between the conformational enantiomers of 1 takes place readily at room temperature.

Figure 3 shows the absorption and CD spectra of 1 in an aqueous γ-CDx solution at pH 10.8 (NaOH). A very intense (+) to (–) bisignate CD spectrum ($\Delta\epsilon$ = +267.7 and −186.9 dm^{3}mol^{-1} cm^{-1} at 256 and 238 nm, respectively) was observed, indicating that 1 bound to γ-CDx selectively assumes an (*R*)-helix configuration. The CD spectroscopic data obtained for complexation of 1 are listed in Table II, together with the data for other CDxs. (*S*)-1,1′-Bi-2-naphthol (100% optical purity), which has an (*R*)-helix configuration, is an analogue of (*R*)-helix 1 and shows a

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Table II. CD Spectroscopic Data for 1 (2×10^{-5} mol dm^{-3}) in CDx (1×10^{-2} mol dm^{-3}) Solutions at pH 10.8 and 5.5[a]

CDx	pH	$\Delta\epsilon_1$ (λ_{ext}, nm)	$\Delta\epsilon_2$ (λ_{ext}, nm)
α-CDx	10.8	no CD signal	
α-CDx	5.5	no CD signal	
α-CDx	2.2	no CD signal	
β-CDx	10.8	11.6 (249)	−7.1 (234)
β-CDx	5.5	11.8 (249)	−7.6 (235)
β-CDx	2.2	no CD signal	
γ-CDx	13.2	176.8 (257)	−121.2 (238)
γ-CDx	10.8	267.7 (256)	−186.9 (238)
γ-CDx	5.5	272.7 (256)	−186.8 (238)
γ-CDx	2.2	15.2 (260)	−7.6 (239)
DME-β-CDx	10.8	−2.5 (258)	10.1 (237)
DMe-β-CDx	5.5	−4.6 (257)	7.6 (239)
DMe-β-CDx	2.2	−125.8 (257)	101.5 (238)
TMe-β-CDx	10.8	23.2 (255)	−19.2 (235)
TMe-β-CDx	5.5	19.3 (254)	−18.2 (237)
TMe-β-CDx	2.2	−151.5 (258)	125.8 (246)

[a] The CD spectra were measured at 20 °C. $\Delta\epsilon$ denotes the molar circular dichroism ($\Delta\epsilon = [\theta]/3300$ dm^3 mol^{-1} cm^{-1}).

(+) to (−) bisignate Cotton effect having $\Delta\epsilon = \pm 152$ dm^3 mol^{-1} cm^{-1} at the ^1B_b transition band in water. It has been shown that a strong bisignate Cotton effect is found in complexation of bilirubin with human serum albumin.[20] Bilirubin is preferentially bound to human serum albumin in an (*R*)-helix configuration ($\Delta\epsilon$ = ca. ±50 dm^3 mol^{-1} cm^{-1}).[20b] Bilirubin bound to α-, β-, or γ-CDx also exhibits the (−) to (+) bisignate Cotton effect where the absolute value of $\Delta\epsilon$ is less than 10 dm^3 mol^{-1} cm^{-1}.[8,9] Comparing our data with these reported $\Delta\epsilon$ values, it can be said that γ-CDx induces an extremely strong bisignate Cotton effect for 1. The relative CD intensity of 1 bound to γ-CDx to the CD intensity of the 1–β-CDx complex is 23, which corresponds to the relative binding constant ($K_{\gamma\text{-CDx}}/K_{\beta\text{-CDx}}$ = 20). Table II also reveals that the CD spectroscopic data obtained in aqueous alkaline solution (pH 10.8) are the same as those in water (pH 5.5). At the pH range between 5.5 and 10.8, 1 is in a dianion form (–COO$^-$ form) in bulk solution. At pH 2.2 (HCl) where 1 is in a free carboxylic acid form (–COOH form), the CD intensities dramatically decrease (see Table II). These results clearly indicate a strong interaction between the carboxylate anion(s) of 1 and the hydroxyl group(s) of γ-CDx. Hydrogen bonding, –COO$^-$···HO–, may participate in the conformational enantiomerism of 1 in the γ-CDx cavity at higher pH. There are two classes of the hydroxyl groups in γ-CDx: namely the primary and secondary hydroxyl groups. The pK_a of the secondary hydroxyl group of γ-CDx has been reported to be 12.081 at 25 °C.[21] Then we measured the CD spectrum of 1 in the γ-CDx solution at pH 13.2. The intensities of the (+) to (−) bisignate CD signals ($\Delta\epsilon$ = +176.8 and −121.2 dm^3 mol^{-1} cm^{-1} at 257 and 238 nm, respectively) are significantly reduced at pH 13.2 where a secondary hydroxyl group of γ-CDx dissociates and the carboxyl group of 1 in the vicinity of the secondary hydroxyl group of γ-CDx may also dissociate. Electrostatic repulsion between the carboxylate anion of 1 and the hydroxylate anion of γ-CDx seems to lower the stability of the 1–γ-CDx complex. On the basis of these observations, it may be reasonable to speculate that the secondary hydroxyl group of γ-CDx interacts with the carboxylate anion of 1 through hydrogen bonding.

The similar results were obtained for the 1–β-CDx system, though the intensities of the bisignate CD signals

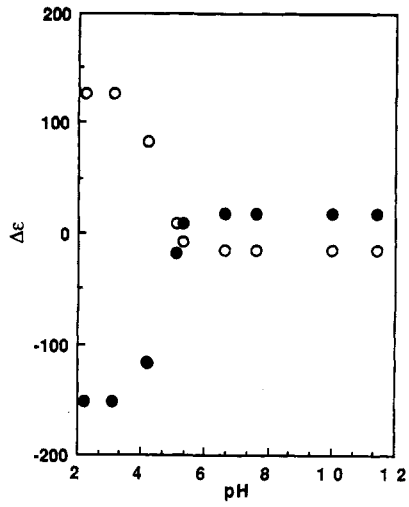

Figure 4. pH dependency of the bisignate CD signals of 1 (2×10^{-5} mol dm^{-3}) in aqueous TMe-β-CDx (1×10^{-2} mol dm^{-3}): ●, monitored at 250 (pH > 6.6), 253 (pH = 5.3), and 258 nm (pH < 5.1); ○, monitored at 238 nm.

Table III. CD Spectroscopic Data for 2 (1×10^{-5} mol dm^{-3}) in CDx (1×10^{-2} mol dm^{-3}) Solutions at pH 5.5

CDx	$\Delta\epsilon_1$ (λ_{ext}, nm)	$\Delta\epsilon_w$ (λ_{ext}, nm)
α-CDx	no CD signal	
β-CDx	11.1 (227)	
γ-CDx	49.0 (235)	−29.3 (225)
DMe-β-CDx	−23.2 (236)	20.2 (224)
TMe-β-CDx	65.2 (234)	−37.9 (224)

are much weaker than those of the 1–γ-CDx complex formed at pH above 5.5. The cavity size of β-CDx seems to be too small to include 1 ($K = 210 \pm 2$ dm^3 mol^{-1}) while 4 can form a stable axial complex of β-CDx ($K = 1073 \pm 1$ dm^3 mol^{-1}). No CD signal was measured at pH 2.2.

In a hydrogen-bond formation, TMe-β-CDx can act as a hydrogen acceptor, not a hydrogen donor. Therefore, TMe-β-CDx cannot interact with 1 in the dianion form through hydrogen bonding. Indeed, the stability of the 1–TMe-β-CDx complex ($K = 340 \pm 10$ dm^3 mol^{-1} at pH 5.5) is much lower than that of 1–γ-CDx complex. The 1–TMe-β-CDx complex, however, shows the (+) to (−) bisignate Cotton effect at pH 5.5 and 10.8 ($\Delta\epsilon$ = ca. ±20 dm^3 mol^{-1} cm^{-1}, Table II), which suggests that the hydrogen bonding between the carboxylate anion of 1 and the hydroxyl group of CDx is not essential for enantioselective complexation of 1 with CDx. A dramatic change was found in the CD spectrum when the pH was lowered to 2.2. An oppositely signed and very intense CD spectrum ($\Delta\epsilon$ = −151.5 and +125.8 dm^3 mol^{-1} cm^{-1} at 258 and 238 nm, respectively) was observed for 1 in aqueous TMe-β-CDx solution at pH 2.2. This result is in contrast to the case of β-CDx where the CD signal disappears at pH 2.2. Figure 4 shows the pH dependence of the CD intensities of 1 in aqueous TMe-β-CDx. The signs of the bisignate Cotton effect is inverted at pH 5. Although the *K* value in an acidic medium cannot be determined because of low solubility of 1 in the –COOH form, the increase in lipophilicity of the guest may enhance the inclusion of 1 in the hydrophobic cavity of TMe-β-CDx. At the present stage, the reason why TMe-β-CDx recognizes (*S*)-helix 1 in the –COOH form as a preferable guest is not clear. From the results shown in Figure 4, the apparent pK_1 value of 1 included in TMe-β-CDx is evaluated to be 4.6, which is higher than that in bulk water (pK_1 < 3). A (−) to (+) bisignate CD signal having very high intensities was also observed for 1 included in DMe-β-CDx at pH 2.2. At

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Table IV. CD Spectroscopic Data for 3 (1×10^{-5} mol dm^{-3}) in CDx (1×10^{-2} mol dm^{-3}) Solutions at pH 5.5

CDx	$\Delta\epsilon_1$ (λ_{ext}, nm)	$\Delta\epsilon_2$ (λ_{ext}, nm)
α-CDx	no CD signal	
β-CDx	8.1 (226)	
γ-CDx	12.4 (234)	
DMe-β-CDx	−16.7 (230)	23.3 (224)
TMe-β-CDx	−45.5 (230)	38.9 (223)

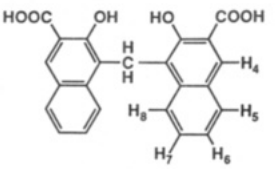
higher pH, the 1-DMe-β-CDx complex exhibits considerably weaker (−) to (+) Cotton effect.

Table III summarizes the CD data for **2**, which does not have the −COOH group, in the aqueous CDx solutions at pH 5.5. α-CDx does not interact with **2**. Although **2** is bound to β-CDx ($K = 180 \pm 10$ dm^3 mol^{-1}), the guest exists as a racemic mixture in the β-CDx solution. Despite the increase in lipophilicity of the guest relative to **1**, the **2**–γ-CDx complex ($K = 210 \pm 30$ dm^3 mol^{-1}) is much more unstable than the **1**–γ-CDx complex ($K = 4100 \pm 700$ dm^3 mol^{-1}). This supports the **1**–γ-CDx complex stabilized by hydrogen bonding between the carboxylate anion of **1** and the hydroxyl group of γ-CDx. The **2**–γ-CDx complex shows a (+) to (−) bisignate CD signal having relatively weak intensities. Similar to the case of **1**, DMe-β-CDx and TMe-β-CDx prefer (*S*)- and (*R*)-helix **2**, respectively, as the guests.

The results of the CD measurements for **3**, which does not have any hydrogen-bonding site, are listed in Table IV. Simple induced CD spectra were observed for **3** in the β- and γ-CDx solutions. The interconversion between the conformational enantiomers of **3** is expected to occur much more easily than that of **1** or **2** because of the absence of the hydroxyl groups at the 2 and 2′ positions. The interconversion may occur even in the γ-CDx cavity. The methylated β-CDxs provide the (−) to (+) bisignate Cotton effects. **3** seems to be included tightly in these methylated β-CDxs, leading to restriction of the conformational change of **3**. The results obtained for the **3**-methylated β-CDx systems clearly reveal that hydrogen-bonding interaction is not essential for the conformational enantiomerism of the dinaphthylmethane derivatives.

^{1}H NMR Spectra. ^{1}H NMR spectra were measured to deduce the structure of the **1**-γ-CDx complex. Figure 5 shows the 400-MHz ^{1}H NMR spectroscopic change of **1** (1×10^{-2} mol dm^{-3}) upon addition of γ-CDx. The singlet signal due to the H_4 protons at 8.30 ppm in D_2O shifts to lower magnetic field in the presence of γ-CDx (8.40 ppm in the presence of 1×10^{-2} mol dm^{-3} γ-CDx). In contrast, the doublet signal due to the H_5 protons at 7.99 ppm shifts to higher magnetic field upon complexation (7.79 ppm in the presence of 1×10^{-2} mol dm^{-3} γ-CDx). The chemical shifts of the H_7 and H_8 protons are scarcely affected by γ-CDx. Judging from the CPK molecular model, it seems that only one naphthalene moiety of **1** can be included in the γ-CDx cavity. Figure 6 shows a plausible model for the **1**–γ-CDx complex. One of the naphthalene moieties of **1** is incorporated into the γ-CDx cavity and another naphthalene ring is located around the rim of the primary hydroxyl group side of the CDx cavity where a part of the naphthalene moiety sticks out from the cavity. In this model, both protons at the 4 and 5 positions of a naphthalene ring of **1** contact with the inside wall of the γ-CDx cavity, and the protons at the 7 and 8 positions of **1** are situated at the outside of the cavity.

Each proton signal of γ-CDx (1×10^{-2} mol dm^{-3}) is also shifted upon addition of **1** (Figure 7). The most remarkable shifts were observed for the H-5 and H-6 protons of γ-CDx. In D_2O without **1**, the signals due to H-5 and H-6 are overlapped to show a broad singlet at 3.84 ppm.



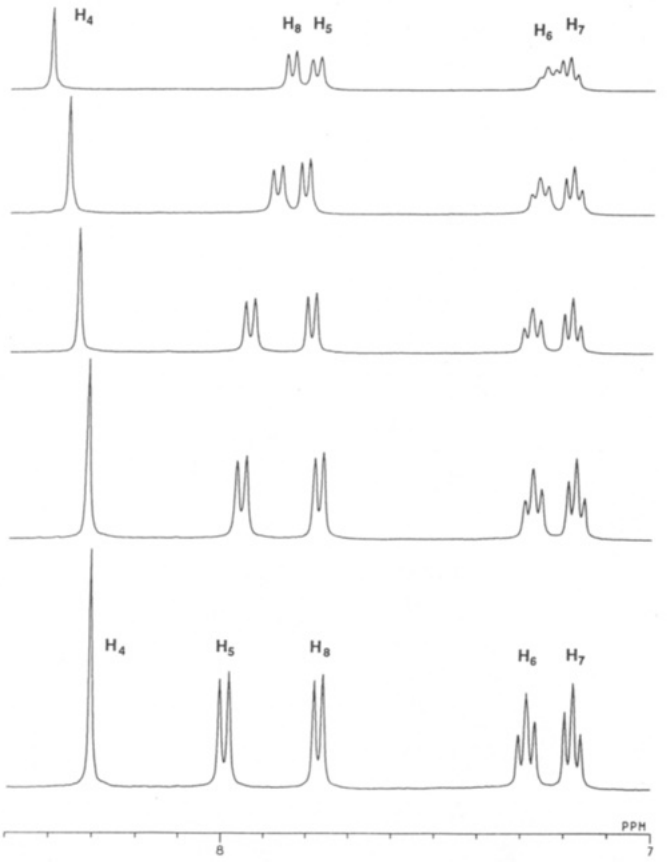


Figure 5. 400-MHz ^{1}H NMR spectra of **1** (1×10^{-2} mol dm^{-3}) in D_2O in the absence and the presence of γ-CDx ([γ-CDx] = (0, 0.13, 0.25, 0.50, 1.00) $\times 10^{-2}$ mol dm^{-3} from the bottom) at 23 °C.

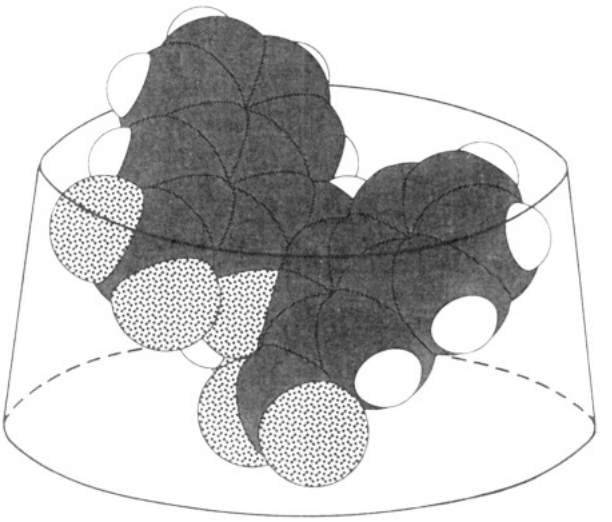


Figure 6. A plausible structure of the **1**–γ-CDx inclusion complex in water. In this model, one of the naphthalene moieties of **1** is located inside of the γ-CDx cavity where a carboxylate anion of **1** forms a hydrogen bond with a secondary hydroxyl group of γ-CDx. Another naphthalene moiety is situated at the primary hydroxyl group side of γ-CDx where a part of the naphthalene ring sticks out from the cavity.

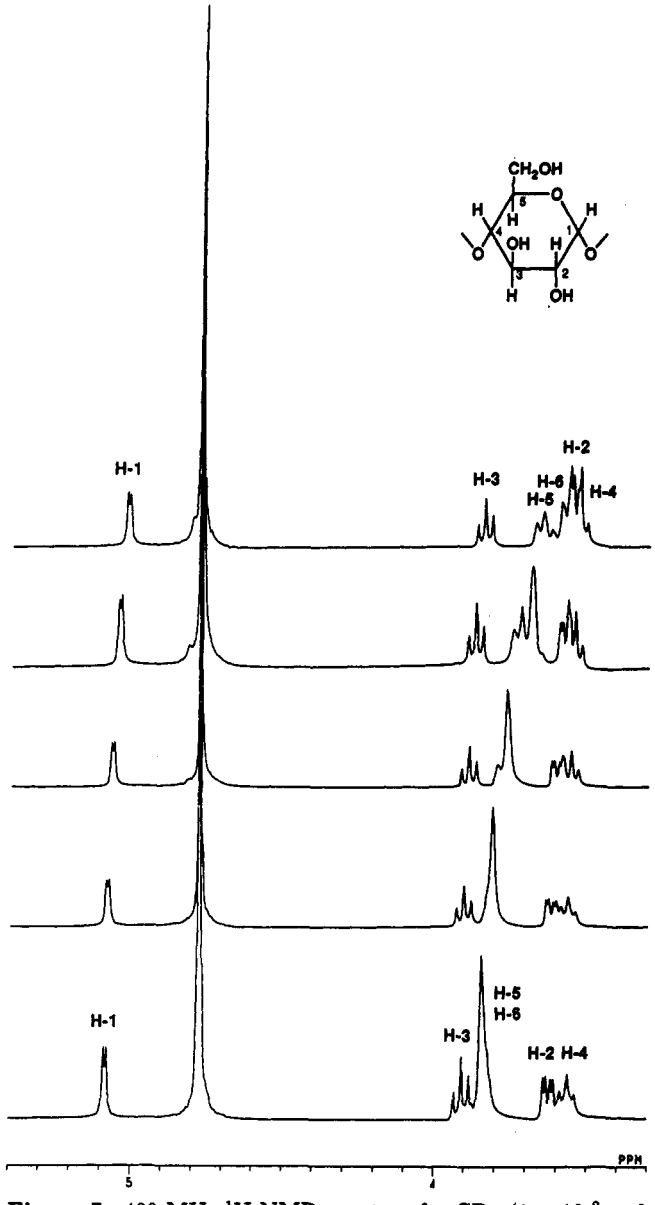


Figure 7. 400-MHz ^1H NMR spectra of γ-CDx (1×10^{-2} mol dm^{-3}) in D_2O in the absence and the presence of 1 ([1] = (0, 0.13, 0.25, 0.50, 1.00) $\times 10^{-2}$ mol dm^{-3} from the bottom) at 23 °C.

In the presence of 1×10^{-2} mol dm^{-3} 1, these signals are separated from each other to be observed at 3.65 and 3.59 ppm for the H-5 and H-6 protons, respectively. The assignment of the H-5 and H-6 proton signals was carried out by a proton–proton correlated 2D NMR (COSY) measurement. The H-3 proton signal at 3.91 ppm in D_2O also shifts to lower magnetic field in the presence of 1 (3.84 ppm in the presence of 1×10^{-2} mol dm^{-3} 1). Small shifts were measured for the H-1, H-2, and H-4 protons which are located outside of the CDx cavity. These results also support the proposed model shown in Figure 6.

The NOE difference spectrum (NOESY) was mesaured for an equimolar mixture of 1 and γ-CDx (1×10^{-2} mol dm^{-3}) in D_2O to confirm the model. The correlations were clearly observed between H_5 and H-3, H_5 and H-5, and H_7 and H-6 protons. In the model shown in Figure 6, a carboxylate anion of a naphthalene moiety of 1 is located at the rim of the secondary hydroxyl group side of γ-CDx and interacts with a secondary hydroxyl group of γ-CDx through hydrogen bonding. The H_5 proton of a naphthalene ring of 1 included in the γ-CDx cavity can contact with both H-3 and H-5 protons of γ-CDx and the H_7 protons of 1 are in the vicinity of the H-6 protons of γ-CDx. The results of the NOESY measurement are also explained reasonably by the model demonstrated in Figure 6.

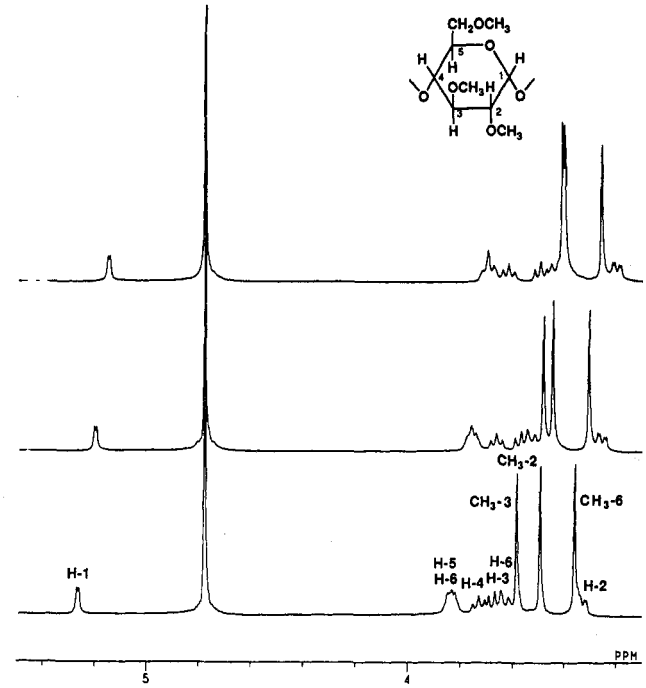


Figure 8. 400-MHz ^1H NMR spectra of TMe-β-CDx (1×10^{-2} mol dm^{-3}) in D_2O in the absence and the presence of 1 ([1] = (0, 0.5, 1.0) $\times 10^{-2}$ mol dm^{-3} from the bottom) at 23 °C.

Similar NMR spectroscopic behavior was observed in the complexation of 1 with β-CDx. The overlapped singlet signals due to the H-5 and H-6 protons of β-CDx at 3.85 ppm in D_2O shift to 3.68 ppm without separation of these two signals. The 1 molecule seems also to be included in the β-CDx cavity in the similar manner as the case of the 1–γ-CDx system.

Figure 8 shows the ^1H NMR spectrum of TMe-β-CDx in D_2O in the absence and the presence of 1. An assignment of the methyl protons of TMe-β-CDx was carried out according to the literature[22] which describes the complete assignment of NMR spectrum of TMe-β-CDx in $CDCl_3$. The chemical shifts of each protons in D_2O are considerably different from those in $CDCl_3$. All signals shift to higher magnetic fields upon addition of 1. The most remarkable shifts are found for OCH_3 at the 3 position of TMe-β-CDx. Let us define Δδ as the difference in the chemical shifts between signals in the absence and the presence of 1×10^{-2} mol dm^{-3} 1. Δδ for the OCH_3 protons at the 2, 3, and 6 positions are 0.09, 0.18, and 0.10 ppm, respectively. In agreement with a large shift of the signal due to the OCH_3 at the 3 position, the H-3 signal at 3.67 ppm in D_2O shifts to 3.49 ppm in the presence of 1×10^{-2} mol dm^{-3} 1 (Δδ = 0.18 ppm). Probably, the 1 molecule can penetrate the TMe-β-CDx cavity from both sides. The upper side of TMe-β-CDx, which corresponds to the primary hydroxyl group side of β-CDx, is narrower than that of β-CDx. Therefore, 1 may recognize the lower side, which corresponds to the secondary hydroxyl group side of β-CDx, as the preferable binding site. On the contrary, the H-3 proton signal of DMe-β-CDx at 3.95 ppm in D_2O scarcely shifts upon addition of 1 (Δδ = 0.05 ppm) while Δδ for the H-1 proton is 0.10 ppm. This result as well as a small Δδ (0.03 ppm, 3.54 to 3.51 ppm) for the OCH_3 at the 2-position and a relatively large Δδ (0.15 ppm, 3.37 to

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3.22 ppm) for the OCH_3 at the 6-position suggests that the 1 molecule is preferentially bound to DMe-β-CDx from the upper side of the cavity. Since the lower side of the DMe-β-CDx cavity is wider than that of the TMe-β-CDx cavity, the 1 molecule may be bound to the upper side of the DMe-β-CDx cavity to optimize a van der Waals contact.

Although NMR measurements of the 1–TMe-β-CDx system in acidic medium should be essential to know the reason for the inversion of the bisignate CD signals, precipitation of 1 in acidic solution made it impossible to measure NMR spectrum of this complex.

Conclusion

The present paper reports a new conformational enantiomerism in the γ-CDx cavity. We regard the 1–γ-CDx complex as a model for studying the mechanism of chiral recognition by CDxs in aqueous solutions.

The relative enantioselectivities were conveniently evaluated from the intensities of the bisignate CD signals of the inclusion complexes. γ-CDx is the most effective host molecule, where a carboxylate anion of a naphthalene moiety of 1 included in the γ-CDx cavity interacts with a secondary hydroxyl group of γ-CDx through hydrogen bonding and another naphthalene moiety of 1 is located at the rim of the primary hydroxyl group side of γ-CDx. The hydrogen-bonding interaction seems to be achieved when the size of the guest molecule fits well with that of the host to optimize the van der Waals contact. Such cooperative hydrogen bonding and van der Waals interactions give rise to the large stability of the 1-γ-CDx inclusion complex. According to the three-point attachment model,[5] a guest molecule should interact with CDx at, at least, three points in order for chiral recognition to occur. For the 1–γ-CDx system, two points are clarified: namely, (1) hydrogen bonding between the host and guest molecules and (2) tight inclusion of the guest in the host cavity. An additional point seems to be a steric factor. An X-ray crystallographic study indicates that γ-CDx has an almost round shape but is somewhat distorted from the regular octagonal structure.[23]

The present study also reveals that the hydrogen-bonding interaction is not essential for chiral recognition by CDx. Few examples of chiral recognition by CDxs without the aid of hydrogen bonding have been reported.[10,13,14] In the case where hydrogen bonding does not participate, steric factors should dominate the enantioselectivity.

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Registry No. 1, 6640-22-8; 2, 1096-84-0; 3, 607-50-1; 4, 92-70-6; β-CDx, 7585-39-9; γ-CDx, 17465-86-0; DMe-β-CDx, 51166-71-3; TMe-β-CDx, 55216-11-0.

Supplementary Material Available: Analytical data of 1–3, disodium salt of 1, DMe-β-CDx, and TMe-β-CDx and the NOE difference spectrum of the equimolar solution of 1 and γ-CDx in D_2O (3 pages). Ordering information is given on any current masthead page.

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Base-Induced and -Directed Elimination and Rearrangement of Perhydronaphthalene-1,4-diol Monosulfonate Esters. Total Synthesis of (±)-Alloaromadendrane-4β,10α-diol and (±)-Alloaromadendrane-4α,10α-diol

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The total synthesis of (±)-alloaromadendrane-4β,10α-diol (1), supposedly isolated from *Ambrosia peruviana* Willd., is described. The strategically positioned axial hydroxyl group at C(4) played a crucial role in the two key steps of this synthesis (2 and 11 → 3; 4 → 5). Upon treatment with sodium *tert*-amylate in refluxing toluene, both the mesylates 2 and 11 predominantly gave the olefin 3. A mechanism for this regioselective elimination is proposed. The double bond of 3 at C(6)–C(7) was used to introduce a dimethylcyclopropane ring at this position. The intramolecular base-induced rearrangement of 4 proceeded with high selectivity, again guided by the alkoxide at C(4). The resulting exo olefin 5 was converted into diol 1, but its spectral data did not agree with those reported for the natural diol. The epimeric (±)-alloaromadendrane-4α,10α-diol (23) was prepared from 5 via a dehydratation, epoxidation, reduction sequence. Now the spectral data of the natural and the synthetic diol agreed very well and a revision of the structure of the natural product is postulated.

Previous publications[1] from this laboratory demonstrated the base-induced and -directed rearrangement of substituted *trans*-perhydronaphthalene-1,4-diol monosulfonate esters as an effective route to *cis*-perhydroazulene systems with an exocyclic methylene unit. The highly developed understanding of the stereochemistry and conformational analysis of the substituted perhydronaphthalenes makes this rearrangement a very useful one for the synthesis of cis-fused guaianes and other natural products bearing a cis 5,7 fused-ring framework.

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