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Synthesis and Structure of Macrocyclic Bis(hydroxynaphthoic amide)s Connected by an Achiral or Chiral Diamine

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Macrocyclic bis(hydroxynaphthoic amide)s **6**, connected by an achiral or chiral diamine, were synthesized by the tandem Claisen rearrangement. CD spectra, X-ray crystallographic analyses, and variable-temperature NMR measurements of the chiral bis(hydroxynaphthoic amide)s revealed that the two hydroxynaphthalene rings in these macrocycles adopt a twisted conformation both in solution and in the crystalline state because of the steric hindrance between the two hydroxynaphthalene rings and that the chirality of the twisted conformation is generated by that of the chiral linker. Theoretical calculations revealed that the chiral linker works effectively to favor energetically one conformer of the diastereomers, although a flipping process was possible and can be observed to occur on the NMR time scale in variable-temperature experiments.

Introduction

Organic compounds whose chirality arises from their helical structures have been attracting much attention. Many sterically crowded aromatic compounds are well-known to adopt a helical or twisted structure.[1] For example, an alkyl-chain-connected dinaphthalene adopts a twisted structure in the crystalline state,[2] and chiral tether-bridged dinaphthalenes have been used for the preparation of chiral, twisted 1,1′-binaphthyl derivatives.[3] Macrocyclization of a dinaphthalene has also been used to induce a helical arrangement of the naphthyl moieties.[4] Although the highly symmetrical, helical, or twisted structures of these compounds are very fascinating in themselves as fundamental chiral skeletons, most of the compounds lack a reactive functional group that can be used for their transformation into useful materials.

During our research on the tandem Claisen rearrangement,[5] which is a useful method for the synthesis of macrocyclic polyphenols and polynaphthols applicable as hosts[6] for organic guest molecules and ligands[7] for metal ions (Chart 1), it became apparent that some of the macrocycles may adopt a twisted conformation due to the steric hindrance between two hydroxyaryl groups connected by an isobutenylene unit; this linker is not long enough to allow the two hydroxyaryl groups to become coplanar. However, no indication of such twisted conformation in solution has been obtained from the NMR and CD spectra, probably due to the flexibility of the isobutenylene unit allowing rapid conformational change at room temperature. These observations prompted us to

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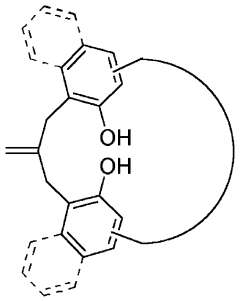

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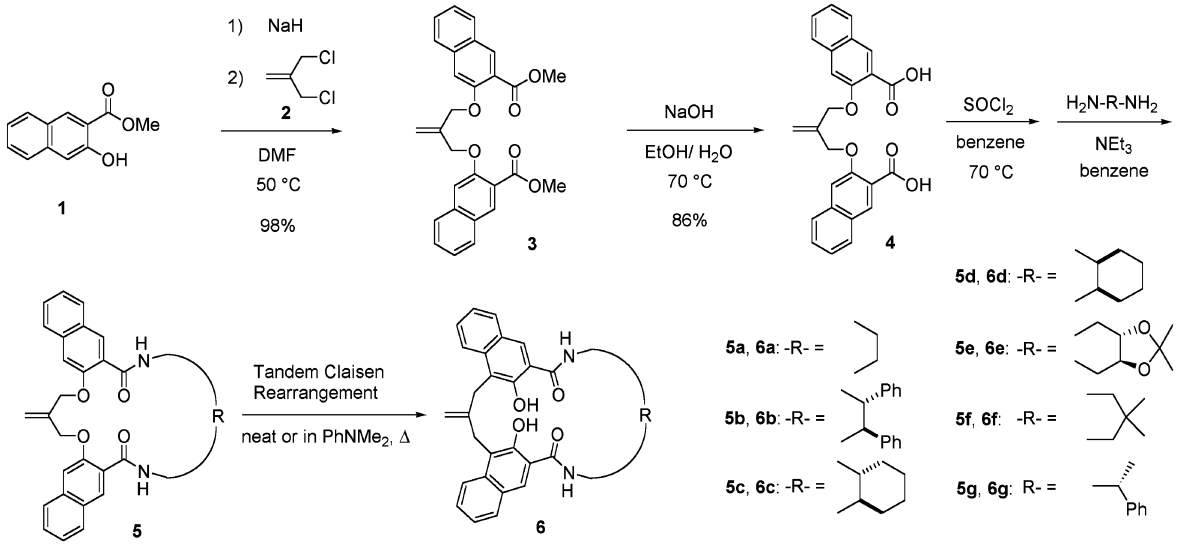


fix the twisted conformation by introducing a chiral group into the macrocyclic system in the expectation that the chiral group would be able to control the direction of the twist and that adjusting the ring to a suitable size would make the transition energy for flipping of the two hydroxyaryl groups high enough to prevent it occurring at room temperature. This macrocyclic system has three distinctive features: (1) the acidic hydroxy groups can contribute to host−guest interaction and/or chelation to metal ions, (2) the C_2 symmetry of the system presents the fascinating possibility of using the system as a chiral ligand for a metal catalyst, because the number of diastereomeric transition states in metal-catalyzed enantioselective processes will be restricted,[8] and (3) the flexibility of the isobutenylene unit allows for dynamic conformational change.

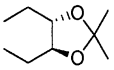
In this paper, we describe both the synthesis of new macrocyclic bis(hydroxynaphthoic amide)s via the tandem Claisen rearrangement and the twisted conformations they adopt, as well as the activation energies for the flipping of these conformations.

Results and Discussion

Macrocyclic bis(hydroxynaphthoic amide)s **6a**−**f** were synthesized from methyl 3-hydroxy-2-naphthoate (**1**) in four steps as shown in Scheme 1. Compound **1** was treated successively with sodium hydride and isobutenylene dichloride (**2**) to give bis(aryl ether) **3**. After hydrolysis of **3**, the resultant dicarboxylic acid **4** was converted to the diacyl halide by treatment with thionyl chloride and then allowed to react with either an achiral or a chiral diamine under high dilution conditions. All of the reactions proceeded very smoothly, and the macrocyclic diamides **5** were obtained in acceptable yields. The results are listed in Table 1.

Macrocyclic bis(hydroxynaphthoic amide)s **6** were obtained by the tandem Claisen rearrangement of macrocyclic diamides **5**. At first, the tandem Claisen rearrangements were performed in the molten state; for those macrocyclic diamides **5** melting rapidly at a temperature lower than 220 °C (Table 1, entries 2, 3, 7, and 8),

TABLE 1. Conditions and Yields of the Cyclization and Rearrangement Reactions

entry	-R-	cyclization product	cyclization yield/%	condition of rearrangement	rearrangement product	rearrangement yield/%
1		**5a**	43	$PhNMe_2$ 180 °C	**6a**	20
2		(*R*,*R*)-**5b**	30	neat 180 °C	(*R*,*R*)-**6b**	60
3		(*S*,*S*)-**5b**	38	neat 180 °C	(*S*,*S*)-**6b**	80
4		(*R*,*R*)-**5c**	30	$PhNMe_2$ 180 °C	(*R*,*R*)-**6c**	62
5		(*S*,*S*)-**5c**	35	$PhNMe_2$ 180 °C	(*S*,*S*)-**6c**	55
6		**5d**	66	$PhNMe_2$ 180 °C	**6d**	32
7		(*S*,*S*)-**5e**	52	neat 160 °C	(*S*,*S*)-**6e**	88
8		**5f**	83	neat 160 °C	**6f**	43

rearrangement in the molten state gave **6** in satisfactory yields, whereas the rearrangement gave only poor results with macrocyclic diamides **5** which did not melt easily at a temperature lower than 220 °C (Table 1, entries 1, 4, 5, and 6). For such macrocyclic diamides **5**, the rearrangements were carried out in solution in *N*,*N*-dimethylaniline, which had previously been reported to be a good solvent for the Claisen rearrangement.[9] In

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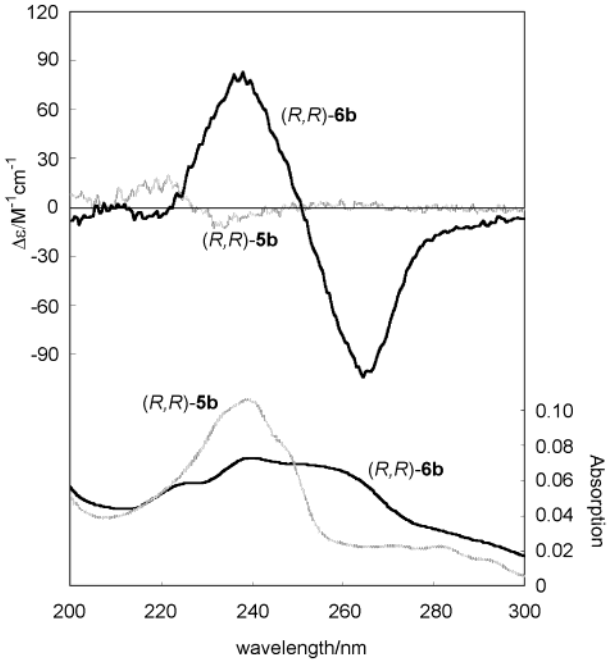

FIGURE 1. CD and UV spectra of (*R*,*R*)-**5b** and (*R*,*R*)-**6b** in acetonitrile.

general, the yields of the rearranged products were higher when the rearrangements were carried out in the molten state, when possible.

The CD and UV spectra of macrocyclic diamide **5b** and bis(hydroxynaphthoic amide) **6b** are shown in Figure 1. (1*R*,2*R*)-1,2-Diphenylethylenediamine-linked (*R*,*R*)-**5b** showed a very weak Cotton effect centered at 220 nm, which can be ascribed to the chirality of the 1,2-diphenylethylenediamine unit. The Cotton effects of (1*S*,2*S*)-1,2-diphenylethylenediamine-linked (*S*,*S*)-**5b**, (1*R*,2*R*)-1,2-cyclohexanediamine-linked (*R*,*R*)-**5c**, (1*S*,2*S*)-1,2-cyclohexanediamine-linked (*S*,*S*)-**5c**, and (2*S*,3*S*)-2,3-isopropylidenedioxy-1,4-butanediamine-linked (*S*,*S*)-**5e** were essentially the same as that of (*R*,*R*)-**5b**, except for differences in the signs of the first and second Cotton effects; the observed Cotton effect arises from the chiral diamine components. These results indicate that there is no contribution of the naphthalene rings to the Cotton effects for the unrearranged macrocycles **5**. On the other hand, the rearranged product, the (1*R*,2*R*)-1,2-diphenylethylenediamine-linked bis(hydroxynaphthoic amide) (*R*,*R*)-**6b**, showed a large Cotton effect centered at 250 nm. Since the UV absorption at 250 nm is caused by the transition of the long axes of the hydroxynaphthalene rings, this Cotton effect must be induced by the two hydroxynaphthalene rings, i.e., by the chirality arising from distortion of the long axes of the hydroxynaphthalene rings (a twisted conformation) in solution. The difference in CD spectral behavior between the unrearranged compound **5b** and the rearranged compound **6b** arises from their structural features; in the case of **5b**, the naphthalene rings are connected by a long and flexible isobutenylenedioxo group and there are no steric interactions inside the macrocycle, while the hydroxynaphthalene rings of **6b** are linked by the obviously shorter and rather rigid isobutenylene group, making the flipping of the twisted conformation hard due to the steric

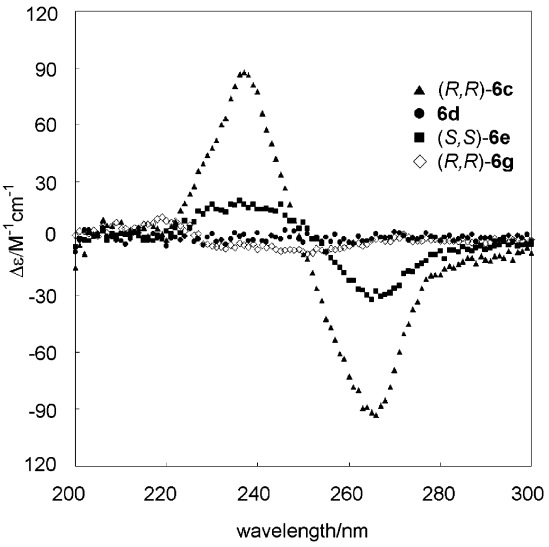

FIGURE 2. CD spectra of **6c**−**e**,**g** in acetonitrile.

hindrance between the two hydroxynaphthalene groups. Moreover, the fact that the CD spectrum of acyclic (*R*,*R*)-**6g**, a ring-opened analogue of macrocyclic (*S*,*S*)-**6b**, did not show any remarkable Cotton effect strongly supports the conclusion that the Cotton effect of **6b** results not from the chirality of the amine moiety, but rather from the twisted conformation of the hydroxynaphthalene rings, and that the macrocyclic structure is essential for this chirality to be induced (Figure 2). The Cotton effect of (1*R*,2*R*)-1,2-cyclohexanediamine-linked (*R*,*R*)-**6c** was almost the same as that of (1*R*,2*R*)-1,2-diphenylethylenediamine-linked (*R*,*R*)-**6b** (Figure 2), indicating that the conformation of the two hydroxynaphthalene rings in the rearranged product **6c** is very similar to the twisted conformation of **6b** in solution. Moreover, (*S*,*S*)-**6b** and (*S*,*S*)-**6c** gave Cotton effects that were mirror images of those of (*R*,*R*)-**6b** and (*R*,*R*)-**6c**, respectively. These results clearly indicate that the chiral diamine components do indeed control the direction of the twist. (2*S*,3*S*)-2,3-Isopropylidenedioxy-1,4-butanediamine-linked (*S*,*S*)-**6e** showed a Cotton effect that was clearly weaker than those of (*R*,*R*)-**6b** and (*R*,*R*)-**6c**, even though in this case too the Cotton effect arose from a twisted conformation of the two hydroxynaphthalene rings, the enlargement of the ring size (from the fifteen-membered rings of (*R*,*R*)-**6b** and (*R*,*R*)-**6c** to the 17-membered ring of (*S*,*S*)-**6e**) makes the twist of the hydroxynaphthalene rings smaller, diminishing the Cotton effect. In contrast, *cis*-1,2-cyclohexanediamine-linked **6d** showed no Cotton effect, as expected for a meso form. These CD spectral observations indicate that the chirality arising from the twisted conformation is induced by the chiral diamine component of macrocyclic bis(hydroxynaphthoic amide)s **6**.

X-ray crystallographic analyses were performed for bis(hydroxynaphthoic amide)s (*R*,*R*)-**6b**, (*R*,*R*)-**6c**, (*S*,*S*)-**6e**, and **6f**. As can be seen from Figure 3, in all cases, the two hydroxynaphthalene rings are twisted due to the steric hindrance between them to generate a C_2 axis through the C═C bond of the isobutenylene moiety. Thus, the isobutenylenedinaphthyl moiety becomes chiral. The crystal of (1*R*,2*R*)-1,2-diphenylethyleneamine-linked (*R*,*R*)-

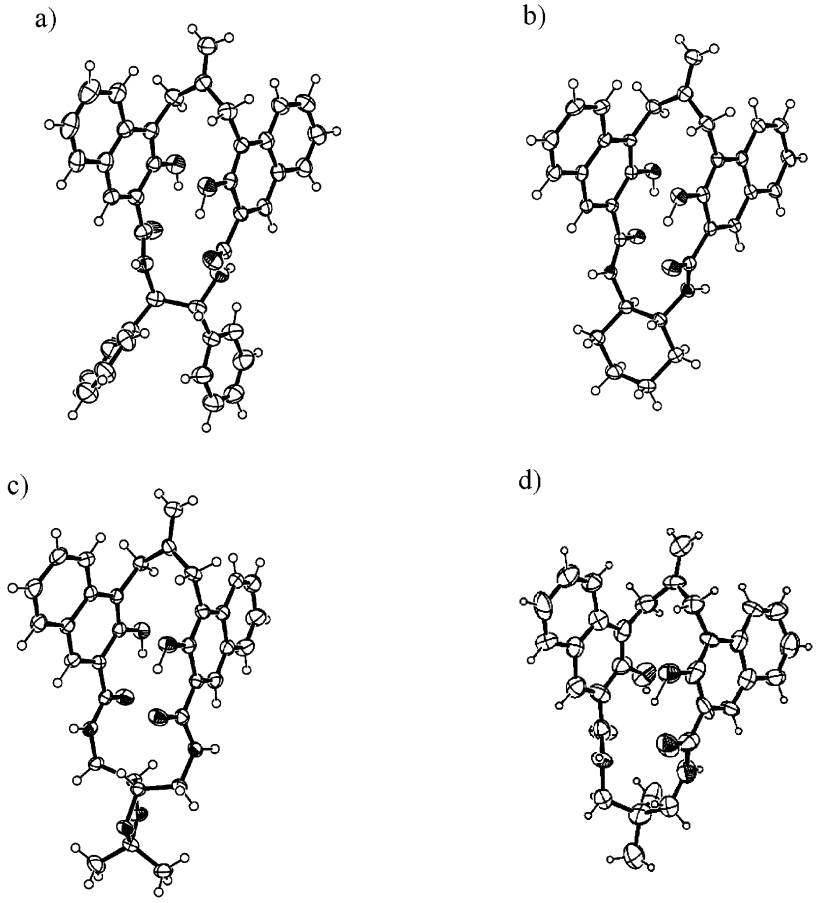

FIGURE 3. Crystal structures of (a) (*R*,*R*)-**6b**, (b) (*R*,*R*)-**6c**, (c) (*S*,*S*)-**6e**, and (d) **6f**. Solvent molecules are omitted for clarity.

6b belongs to the space group $P2_12_12_1$, indicating that it consists of molecules of a single diastereomer and that the absolute configuration of the twisted isobutenylenedinaphthyl moiety is fixed to be *M* because of the chirality of the (1*R*,2*R*)-diphenylethylenediamine component. The crystal structures of (1*R*,2*R*)-1,2-cyclohexanediamine-linked (*R*,*R*)-**6c** and (2*S*,3*S*)-2,3-isopropylidenedioxy-1,4-butanediamine-linked (*S*,*S*)-**6e** are very similar to that of (*R*,*R*)-**6b**; the twisted conformation is fixed to be *M*. These results strongly suggest that the absolute configuration of the isobutenylenedinaphthyl moiety in the macrocyclic bis(hydroxynaphthoic amide)s linked with a chiral diamine is determined by the absolute configuration of the substituents on the chiral diamine component. Even the two hydroxynaphthalene rings of achiral 2,2-dimethyl-1,3-propanediamine-linked **6f** also adopt a twisted conformation in the crystalline state as do chiral **6b**,**c**,**e**, although its crystal includes both *P* and *M* twisted conformations.

The CD exciton chilarity method[10] is known to be useful for explaining the relationship between two excitons in solution. As shown in Figures 1 and 2, each of (*R*,*R*)-**6b,** (*R*,*R*)-**6c**, and (*S*,*S*)-**6e** showed a negative primary Cotton effect and a positive secondary Cotton effect. This means that the long axes of the two hydroxynaphthalene rings in these macrocyclic bis(hydroxynaphthoic amide)s connected by a chiral diamine are twisted counterclockwise. The X-ray crystal structures of (*R*,*R*)-**6b**, (*R*,*R*)-**6c**, and (*S*,*S*)-**6e** also showed that their hydroxynaphthalene rings takes up a counterclockwise twisted conformation (Figure 3). These observations indicate that the conformations of (*R*,*R*)-**6b**, (*R*,*R*)-**6c**, and (*S*,*S*)-**6e** in solution and in the crystalline state are similar to each other and that locking of the twisted conformation is governed by the chiral diamine component in these macrocyclic bis(hydroxynaphthoic amide)s.

Variable-temperature NMR measurements were carried out for the macrocyclic bis(hydroxynaphthoic amide)s **6**. The NMR spectrum of ethylenediamine-linked, 15-membered **6a** at 30 °C showed two sets of split signals corresponding to the methylene protons of the isobutenylene and ethylenediamide parts, and these signals became broader on raising the temperature, as shown in Figure 4. At 70 °C, the signals of the methylene protons of the isobutenylene part fused to a singlet, and the signals of the methylene protons of the ethylenediamide part became extraordinarily broad, the signal being hard to distinguish from the baseline. At 80 °C, the signals of the methylene protons of the ethylenediamide part coalesced. Upon further raising the temperature, each of the two methylene signals reappeared as a singlet. On the other hand, the signals of the methylene protons of 16-membered **6f** were broad singlets even at −10 °C (Figure 5). Lowering the temperature led to

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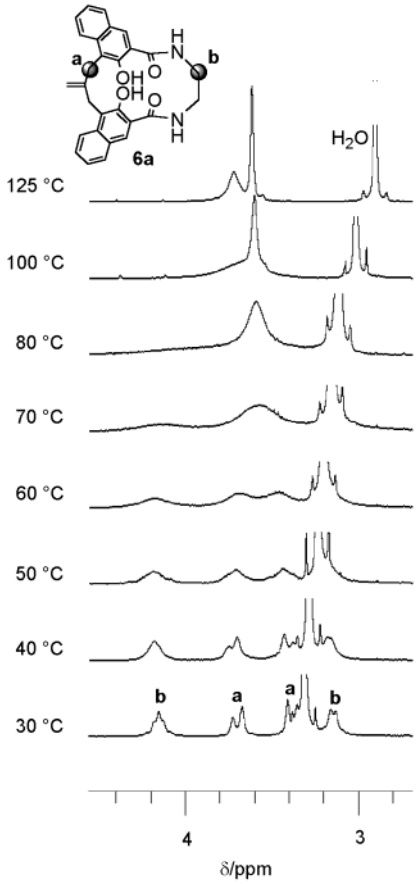

FIGURE 4. Vt NMR spectra of **6a** in DMSO-d_6 (300 MHz).

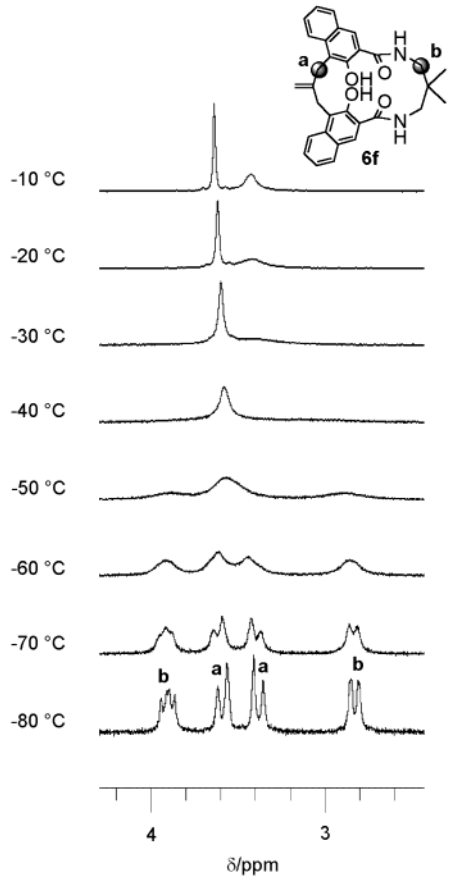

FIGURE 5. Vt NMR spectra of **6f** in CD_2Cl_2 (300 MHz).

splitting of the signals of two sets of methylene protons. At −50 °C, two signals were observed for the methylene protons of the diamide part, and the signal of the methylene protons of the isobutenylene part split at −60 °C. Even though the X-ray crystallographic analysis of achiral macrocyclic bis(hydroxynaphthoic amide) **6f** showed that the isobutenylenedinaphthyl moiety has a twisted conformation, the NMR spectral change observed for **6f** indicates that fast flipping of the two naphthalene rings takes place at room temperature in solution.

On the basis of these NMR spectral observations, the activation energies for flipping of the twist conformations ($\Delta G^{\ddagger}$) were estimated to be 16.5 kcal mol^{-1} for 15-membered **6a** and 10.8 kcal mol^{-1} for 16-membered **6f** (Table 2).[11] In contrast, in the cases of chiral macrocyclic bis(hydroxynaphthoic amide)s, 15-membered **6b** and **6c** and even 17-membered **6e** showed no coalescence of any signals at a temperature of up to 180 °C.

To clarify the behavior of the NMR signals in the series **6b**, **6c**, and **6e**, we performed theoretical calculations for the flipping of **6b**. (*R*,*R*)-**6b** can exist as two diastereomers, (*M*)-(*R*,*R*)-**6b** and (*P*)-(*R*,*R*)-**6b**, for which the absolute configurations of the two hydroxynaphthalene groups are *M* and *P*, respectively. Each geometry was optimized at the B3LYP/3-21g* level of theory, and the structures determined are displayed in Figure 6.[12] The calculated dihedral angles between the $C_{amide}-N_{amide}-C_{chiral\ center}$ plane and the $C_{phenyl}-C_{chiral\ center}-N_{amide}$ plane are 166.3° and −83.5° for (*P*)-(*R*,*R*)-**6b** and (*M*)-(*R*,*R*)-**6b**, respectively, and (*M*)-(*R*,*R*)-**6b** is calculated to be 7.9 kcal mol^{-1} more stable than (*P*)-(*R*,*R*)-**6b**. The calculated structure for (*M*)-(*R*,*R*)-**6b** is very similar to actually found for (*M*)-(*R*,*R*)-**6b** in the crystalline state. The geometry of the 1,2-diphenyldiamine, optimized using the same method, is quite similar to that of the chiral linker part in (*P*)-(*R*,*R*)-**6b**. This structural information leads us to the conclusion that lowering the strain of the twisted conformation of the hydroxynaphthalene rings dominates the overall stability of (*M*)-(*R*,*R*)-**6b**, even though there is an accompanying loss in stability due to the less favorable conformation of the chiral diamine. However, the absolute energy difference (7.9 kcal mol^{-1})

TABLE 2. Activation Energies for Flipping

entry	substrate	T_c/K	$\delta\nu^a$/Hz	J^a/Hz	$\Delta G^{\ddagger}_{Tc}{}^b$/kcal mol^{-1}
1	**6a**	343	159	16.2	16.5 ± 0.2
2	(*R*,*R*)-**6b**	*c*	135	16.5	
3	(*R*,*R*)-**6c**	*c*	142	16.8	
4	**6e**	*c*	65.1	15.3	
5	**6f**	223	58.2	16.2	10.8 ± 0.2

[a] The $\delta\nu$ and J values for the methylene protons of the isobutenylene part are listed. [b] The activation energy was calculated from the following equation: $\pi SQR[(\delta\nu^2+6J^2)/2] = RT_c \exp(-\Delta G^{\ddagger}_{Tc}/RT_c)/Nh$.[11] [c] No coalescence of the signals was observed up to a temperature of 180 °C.

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(12) All theoretical calculations were performed employing Beck's exchange and Lee−Yang−Parr's 3parameter correlation functionals with 3-21g* basis sets using a Gaussian 98 package.

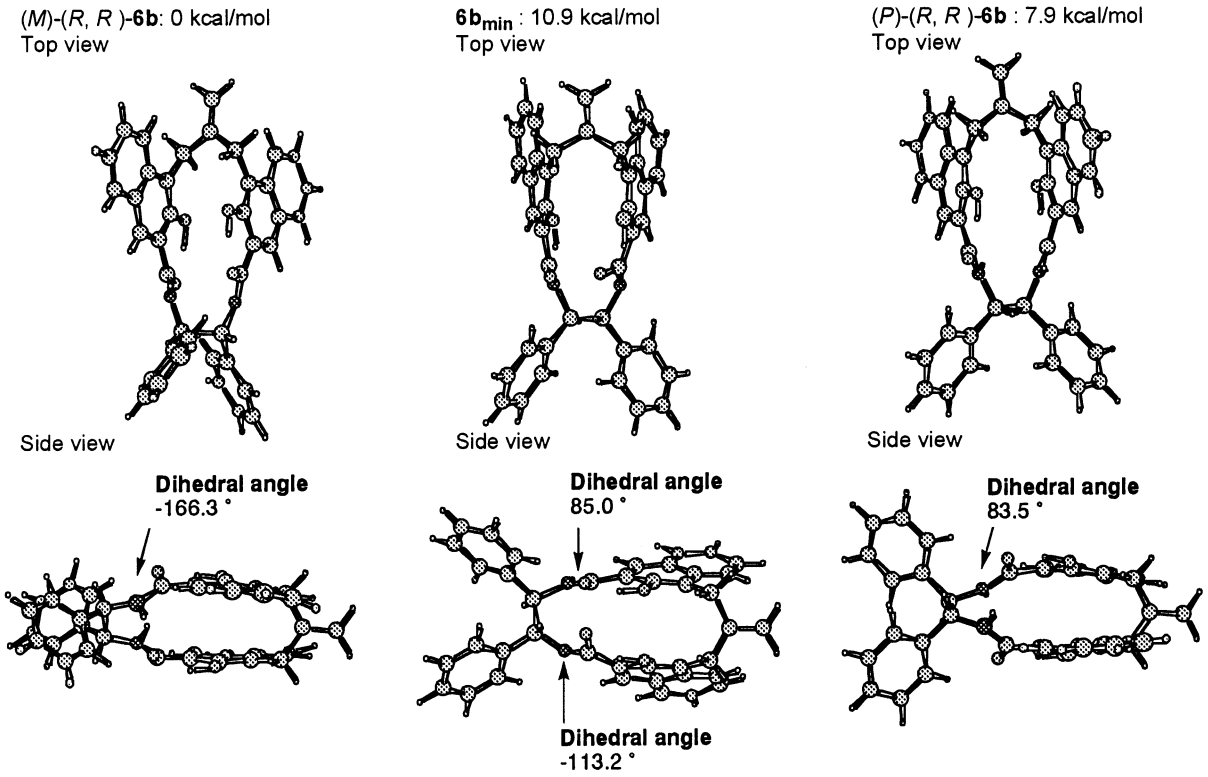

FIGURE 6. Two diastereomers of (*R*,*R*)-**6b** and an intermediate optimized with B3LYP/3-21g*. Dihedral angles are in degrees.

is obviously small enough to allow the existence of not only (*M*)-(*R*,*R*)-**6b** but also (*P*)-(*R*,*R*)-**6b** under the conditions of the present NMR study. A minimum energy intermediate structure ((*R*,*R*)-**6b$_{min}$**) was also found on the flipping path. The direction of sliding of the two hydroxynaphthalene rings governs the conformation of the isobutenylenedinaphthyl moiety in the product. The dihedral angles of (*R*,*R*)-**6b$_{min}$** corresponding to those in (*M*)-(*R*,*R*)-**6b** and (*P*)-(*R*,*R*)-**6b** are 113.2° and −85.2°. The energy of (*R*,*R*)-**6b$_{min}$** is 10.9 mol^{-1} higher than (*M*)-(*R*,*R*)-**6b** and 3.0 kcal mol^{-1} higher than (*P*)-(*R*,*R*)-**6b**. If the coalescence of (*R*,*R*)-**6b** occurs at greater than 180 °C, then the activation barrier ($\Delta G^{\ddagger}$) is estimated to be greater than 22.0 kcal/mol. However, the energy of the intermediate (*R*,*R*)-**6b$_{min}$** is not that high compared to those of (*M*)-(*R*,*R*)-**6b** and (*P*)-(*R*,*R*)-**6b**. So, the transition states for flipping likely lie at an absolute energy level difference of less than 22 kcal mol^{-1}. These theoretical calculations and considerations suggest that flipping occurs under the conditions of the NMR spectral study, and that the coalescence cannot be detected in a NMR time scale. However, the equilibrium is largely shifted toward the more stable diastereomer (*M*)-(*R*,*R*)-**6b**, since the chiral linker makes the hydroxynaphthalene rings of the other diastereomer (*P*)-(*R*,*R*)-**6b** highly distorted.

Conclusion

Macrocyclic bis(hydroxynaphthoic amide)s connected by either an achiral or a chiral diamine were synthesized. X-ray crystal analyses revealed that the macrocylclic bis(hydroxynaphthoic amide)s had a twisted conformation in the crystalline state because of the steric hindrance between the two hydroxynaphthalene rings and that the absolute configuration of the twist was determined by the absolute configuration of the substituents on the chiral diamine component. CD spectra and variable-temperature NMR spectra of the chiral macrocyclic bis(hydroxynaphthoic amide)s, and a theoretical study on **6b** showed that chiral linker works effectively to favor one diastereoisomer enegetically, although the flipping process occurred within the NMR temperature range.

Experimental Section

The general procedure is listed in the Supporting Information. The melting points are uncorrected. ^{1}H NMR (300 or 500 MHz) spectra were measured with Me_4Si as an internal standard when $CDCl_3$ was used as solvent; otherwise, residual protiated solvent was used as an internal standard; the δ and J values are given in ppm and Hz, respectively. The IR spectra are recorded in units of cm^{-1}.

Methyl 2-[[2-[2-[3-(Methoxycarbonyl)naphthoxy]methyl]allyl]oxy]-3-naphthoate (3). Sodium hydride (7.2 g, 0.3 mol) and potassium iodide (100 mg) were added in succession at rt to a solution of methyl 3-hydroxy-2-naphthoate (**1**) (50.5 g, 0.25 mol) in DMF (200 mL). To this yellow suspension was added 3-chloro-2-chloromethyl-1-butene (**2**) (15.6 g, 0.125 mol) at 70 °C, and the mixture was stirred for 3 h. The mixture was concentrated under reduced pressure and then extracted with CH_2Cl_2. After the usual workup, **3** was obtained as a brownish amorphous mass (56.2 g, 0.123 mol, 98%), which was used in the following reactions without further purification.

An analytical sample was recrystallized from hexane/diethyl ether (10/1) to give a yellow solid: mp 98.3−98.7 °C; IR (KBr) 1730, 1630, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (6H, s), 4.93 (4H, s), 5.59 (2H, s), 7.30 (2H, s), 7.44 (2H, t, J = 7.5), 7.51 (2H, t, J = 7.5), 7.71 (2H, d, J = 8.4), 7.83 (2H, d, J = 8.5), 8.34 (2H, s). Anal. Calcd for $C_{28}H_{24}O_6$: C, 73.67; H, 5.30. Found: C, 73.67; H, 5.43.

2-[[2-[2-[3-(Methoxycarbonyl)naphthoxy]methyl]allyl]oxy]-3-naphthoic Acid (4). An aqueous solution (10 mL) of sodium hydroxide (370 mg, 9.3 mmol) was added at rt to a

solution of **3** (1.06 g, 2.32 mmol) in ethanol/THF (4/1) (20 mL). The mixture was stirred for 4 h at 70 °C. A yellow precipitate was obtained by adjusting the pH of the mixture to ~3 by adding concentrated aqueous HCl. Recrystallization of the precipitate from THF/H_2O (4/1) gave **4** as yellow needles (850 mg, 1.98 mmol, 86%): mp 221−225 °C; IR (KBr) 3000, 1680; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.90 (4H, s), 5.51 (2H, s), 7.40 (2H, t, J = 7.6), 7.47 (2H, s), 7.53 (2H, t, J = 7.6), 7.80 (2H, d, J = 8.2), 7.94 (2H, d, J = 8.1), 8.27 (2H, s), 12.96 (2H, s). Anal. Calcd for $C_{26}H_{20}O_6$: C, 72.89; H, 4.71. Found: C, 72.73; H, 4.97.

Synthesis of Macrocycle 5. The synthetic procedure for **5a** is representative for the preparation of all the other compounds **5**. Compound characterization data for **5b**−**g** are listed in the Supporting Information.

Macrocycle 5a. To a suspension of **4** (1.71 g, 4.00 mmol) in benzene (40 mL) was added thionyl chloride (9.5 g, 80 mmol) at rt. The mixture was stirred for 10 h at 60 °C to afford a yellow solution. The solution was concentrated under reduced pressure to give a yellow solid that was dried under vacuum at 60 °C. After the solid had been dissolved in benzene (200 mL), triethylamine (1.6 g, 16 mmol) was added at rt. Ethylenediamine (240 mg, 4.00 mmol) in benzene (200 mL) was added dropwise over 2 h at 50 °C to this solution. After being stirred for an additional 2 h, the mixture was concentrated under reduced pressure and then extracted with CH_2Cl_2. After the usual workup, **5a** was obtained as a white solid (873 mg, 1.70 mmol, 43%): mp 209−211 °C; IR (KBr) 3400, 1640; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (4H, dd, J = 2.9, 3.0), 4.88 (4H, s), 5.78(2H, s), 7.25 (2H, s), 7.42 (2H, t, J = 7.7), 7.53 (2H, t, J = 7.5), 7.72 (2H, d, J = 8.1), 7.92 (2H, d, J = 8.1), 8.29 (2H, s), 8.77 (2H,s). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.17; H, 5.32; N, 6.12.

Macrocycle (*R*,*R*)-5b. (*R*,*R*)-**5b** was obtained from **4** (428 mg, 1.00 mmol) and (1*R*,2*R*)-diphenylethylenediamine (212 mg, 1.00 mmol) as a white solid (182 mg, 0.301 mmol, 30%) after purification by PTLC ($CHCl_3$ × 5).

Macrocycle (*S*,*S*)-5b. (*S*,*S*)-**5b** was obtained from **4** (435 mg, 1.01 mmol) and (1*S*,2*S*)-diphenylethylenediamine (214 mg, 1.01 mmol) as a white solid (234 mg, 0.387 mmol, 38%) after purification by PTLC ($CHCl_3$ × 5).

Macrocycle (*R*,*R*)-5c. (*R*,*R*)-**5c** was obtained from **4** (857 mg, 2.00 mmol) and (1*R*,2*R*)-1,2-cyclohexanediamine (228 mg, 2.00 mmol) as a white solid (300 mg, 0.592 mmol, 30%) after purification by column chromatography ($CHCl_3$).

Macrocycle (*S*,*S*)-5c. (*S*,*S*)-**5c** was obtained from **4** (233 mg, 0.544 mmol) and (1*S*,2*S*)-1,2-cyclohexanediamine (62 mg, 0.543 mmol) as a white solid (95 mg, 0.189 mmol, 35%) after purification by column chromatography ($CHCl_3$).

Macrocycle 5d. 5d was obtained from **4** (857 mg, 2.00 mmol) and *cis*-1,2-cyclohexanediamine (228 mg, 2.00 mmol) as a white foam (666 mg, 1.31 mmol, 66%) after purification by column chromatography ($CHCl_3$).

Macrocycle (*S*,*S*)-5e. (*S*,*S*)-**5e** was obtained from **4** (857 mg, 2.00 mmol) and (2*S*,3*S*)-2,3-isopropylidenedioxy-1,4-butanediamine (320 mg, 2.00 mmol), which was prepared according to the literature methods,[14−16] as a white foam (580 mg, 1.05 mmol, 52%) after purification by column chromatography ($CHCl_3$/ethyl acetate (4/1)).

Macrocycle 5f. 5f was obtained from **4** (857 mg, 2.00 mmol) and 2,2-dimethyl-1,3-propanediamine (204 mg, 2.00 mmol) as a white foam (821 mg, 1.65 mmol, 83%) after purification by column chromatography ($CHCl_3$).

(*R*,*R*)-*N*-1-Phenylethyl 2-[[2-[2-[3-(*N*-1-phenylethylcarbamoyl)naphthoxy]methyl]allyl]oxy]-3-naphthoic Amide ((*R*,*R*)-5g). (*R*,*R*)-**5g** was obtained from **4** (860 mg, 2.01 mmol) and *R*-α-phenylethylamine (484 mg, 3.99 mmol) as a white solid (1.17 g, 1.84 mmol, 92%).

Synthesis of Macrocyclic Naphthol 6. Compound characterization data for **6b**−**g** are listed in the Supporting Information.

Macrocyclic Naphthol 6a. 5a (150 mg, 0.331 mmol) was dissolved in *N*,*N*-dimethylaniline (5 mL) at 150 °C. The solution was heated at 180 °C for 2 h to afford a yellow precipitate. The precipitate was collected by filtration and washed with CH_2Cl_2 to give **6a** (30 mg, 0.066 mmol, 20%) as a yellow powder: mp 325−326 °C; IR (KBr) 3320, 1640; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.14 (2H, d, J = 7.8), 3.38 (2H, d, J = 16.8), 3.70 (2H, d, J = 15.6), 4.15 (2H, s), 5.43 (2H, s), 7.31 (2H, t, J = 7.8), 7.50 (2H, t, J = 7.7), 7.80 (2H, d, J = 8.1), 8.02 (2H, d, J = 8.4), 8.20 (2H, s), 8.82 (2H, s), 11.35 (2H, s). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.55; H, 5.46; N, 6.15.

Macrocyclic Naphthol (*R*,*R*)-6b. (*R*,*R*)-**5b** (70 mg, 0.116 mmol) was melted at 220 °C by using a glass tube oven equipped with a vacuum pump. The melt was heated at 180 °C for 1 h. Purification by PTLC ($CHCl_3$×2) gave (*R*,*R*)-**6b** (43 mg, 0.071 mmol, 60%) as a yellow solid. A crystal suitable for X-ray analysis was obtained from a CH_2Cl_2 solution by the vapor diffusion method.

Macrocyclic Naphthol (*S*,*S*)-6b. (*S*,*S*)-**5b** (75 mg, 0.124 mmol) was melted at 220 °C by using a glass tube oven equipped with a vacuum pump. The melt was heated at 180 °C for 1 h. Purification by PTLC ($CHCl_3$ × 2) gave (*S*,*S*)-**6b** (60 mg, 0.099 mmol, 80%) as a yellow solid.

Macrocyclic Naphthol (*R*,*R*)-6c. According to the procedure given for the preparation of **6a**, (*R*,*R*)-**6c** was obtained from (*R*,*R*)-**5c** (150 mg, 0.296 mmol) as a yellow solid (93 mg, 0.184 mmol, 62%) after purification by PTLC ($CHCl_3$). A crystal suitable for X-ray analysis was obtained from a DMSO solution.

Macrocyclic Naphthol (*S*,*S*)-6c. According to the procedure given for the preparation of **6a**, (*S*,*S*)-**6c** was obtained from (*S*,*S*)-**5c** (116 mg, 0.228 mmol) as a yellow solid (64 mg, 0.126 mmol, 55%) after purification by PTLC ($CHCl_3$).

Macrocyclic Naphthol 6d. According to the procedure given for the preparation of **6a**, **6d** was obtained from **5d** (123 mg, 0.243 mmol) as a yellow solid (39 mg, 0.077 mmol, 32%) after purification by PTLC ($CHCl_3$×2). A crystal suitable for X-ray analysis was obtained from a DMSO solution.

Macrocyclic Naphthol (*S*,*S*)-6e. (*S*,*S*)-**5e** (51 mg, 0.092 mmol) was heated at 160 °C for 2 h by using a glass tube oven equipped with a vacuum pump. Purification by PTLC ($CHCl_3$/ethyl acetate (2/1) × 2) gave (*S*,*S*)-**6e** (45 mg, 0.081 mmol, 88%) as a yellow solid. A crystal suitable for X-ray analysis was obtained from a DMSO solution.

Macrocyclic Naphthol 6f. According to the procedure given for the preparation of (*S*,*S*)-**6e**, **6f** was obtained from **5f** (63 mg, 0.127 mmol) as a yellow solid (27 mg, 0.055 mmol, 43%) after purification by PTLC ($CHCl_3$ × 3). A crystal suitable for X-ray analysis was obtained from a CH_2Cl_2 solution.

(*R*,*R*)-*N*-1-Phenylethyl-2-hydroxy-1-[2-[1-[2-hydroxy-3-(*N*-1-phenylethylcarbamoyl)naphthyl]methyl]allyl]-3-naphthoic Amide ((*R*,*R*)-6g). According to the procedure given for the preparation of (*S*,*S*)-**6e**, (*R*,*R*)-**6g** was obtained from (*R*,*R*)-**5g** (153 mg, 0.241 mmol) as a yellow solid (104 mg, 0.164 mmol, 68%) after purification by PTLC (benzene/ethyl acetate (95/5) × 3).

Supporting Information Available: Crystallographic data for (*R*,*R*)-**6b**, (*R*,*R*)-**6c**, **6d**, (*S*,*S*)-**6e**, and **6f**, compound characterization data for **5b**−**g** and **6b**−**g**, and ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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