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Planar-Chiral Pillar[5]arene: Chiral Switches Induced by Multiexternal Stimulus of Temperature, Solvents, and Addition of Achiral Guest Molecule

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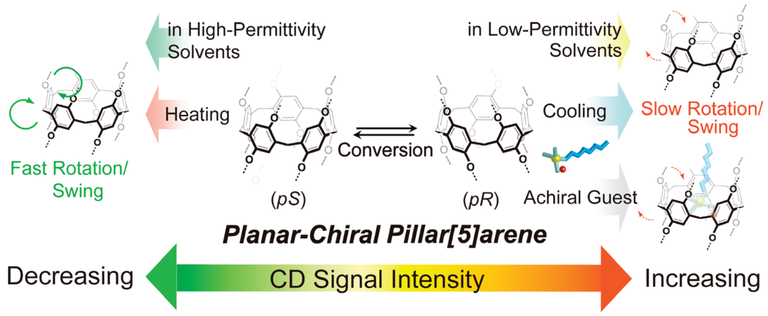

We synthesized chiral-substituents modified pillar[5]arene for the first time. The chiral-substituents modified pillar[5]arene showed planar chirality and interconversion between (*pS*) and (*pR*) forms took place quickly. The planar chirality was switched by temperature, solvents, and addition of achiral guest. As the measurement temperature increased, the diastereomeric excess was decreased. The diastereomeric excesses were high in low-permittivity solvents, while a low diastereomeric excess was observed in high-permittivity solvents. Addition of achiral guest induced an increase of negative CD intensities.

Introduction

Much attention has been recently focused on controlling and switching molecular chirality because it will be applicable to data storage, optical devices, and chiral sensors.[1,2] Chiral switches can change reversibly between two or more stable states under the action of external chemical, electrochemical, photochemical, or thermal input.[2−4] Many chiral switches induced by these external stimuli have been described, but only a few systems showed switching induced by multiexternal stimuli.[4] Herein we demonstrate multiresponsive chiral switches using the planar chirality of novel macrocyclic host "pillar[5]arene",[5] which was first synthesized and named by our group. Figure 1 shows single-crystal and

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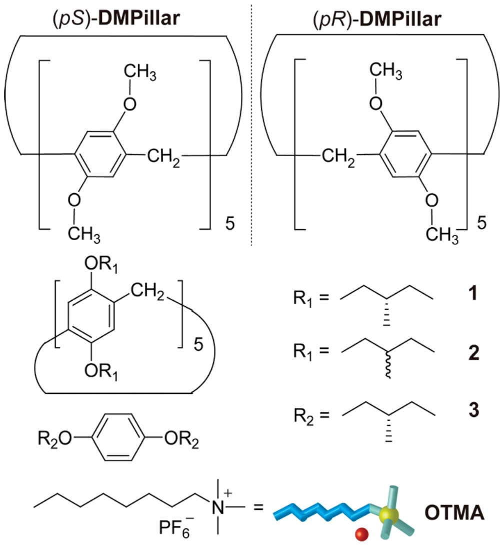

FIGURE 1. Chemical structures of (*pS*)- and(*pR*)-**DMPillar**, **1**, **2**, **3**, and **OTMA**.

chemical structures of dimethoxy-substituted pillar[5]arene (**DMPillar**).

The composition of pillar[5]arene is almost the same as that of typical calixarenes.[6] However, because its repeating units are connected by methylene bridges at the para-position, pillar[5]arene has a unique symmetrical pillar architecture that is different from the basket-shaped structure of the meta-bridged calixarenes. Moreover, crystals of pillar[5]arene are racemic forms: in **DMPillar**, planar-chiral (*pS*)- and (*pR*)-**DMPillar** are mixed in 1:1 proportion. All pillar[5]arenes which have been synthesized are racemic mixtures, thus synthesis and investigation of planar chirality of pillar[5]arene are one of the important research targets. Consequently, in this study, for synthesis of planar-chiral pillar[5]arene we employed a new monomer, 1,4-bis[2(*S*)-methylbutoxy]benzene (**3**, Figure 1), carrying chiral substituents at both rims. In a similar manner to synthesis of **DMPillar**, we successfully obtained a novel pillar[5]arene carrying 2(*S*)-methylbutoxy moieties at both rims (**1**, Figure 1). We investigated planar chirality and chiral switching of **1** by three external stimuli, namely temperature, solvents, and addition of an achiral guest molecule.

Results and Discussion

By reacting **3** and paraformaldehyde in the presence of boron trifluoride diethyl etherate [$BF_3O(C_2H_5)_2$], we prepared a mixture of polymer and **1**. Using silica gel column chromatography, we successfully isolated **1** (yield 10%). As for **1**, a control compound pillar[5]arene derivative (**2**, Figure 1) was prepared from 1,4-bis(2-methylbutoxy)benzene by a similar pathway (yield 13%). The structures of **1** and **2** were completely characterized by ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H COSY, TOCSY, HSQC, FAB-mass measurements, and elemental analysis (Supporting Information).

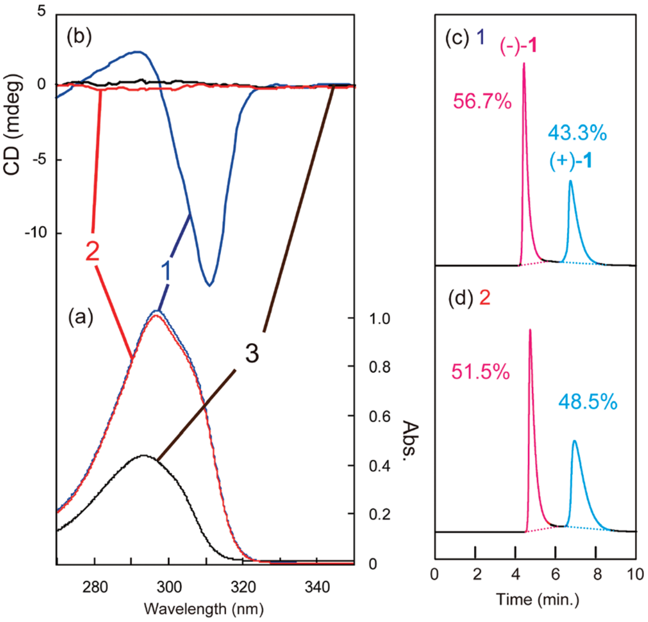

FIGURE 2. (a) UV−vis and (b) CD spectra of **1** (blue line, 4.10 × 10^{-5} L mol^{-1}cm^{-1}), **2** (red line, 4.10 × 10^{-5} L mol^{-1}cm^{-1}), and **3** (black line, 2.03 × 10^{-4} L mol^{-1}cm^{-1}) in chloroform at 25 °C. Chiral HPLC traces of (c) **1** and (d) **2** at 0 °C. Hexane was used as eluent.

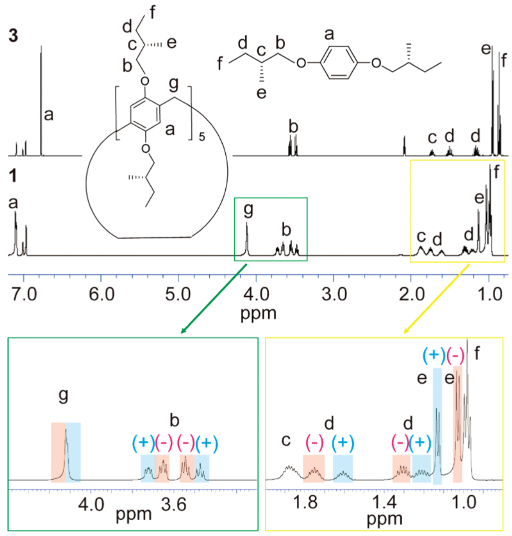

FIGURE 3. ^{1}H NMR spectra of **1** and **3** in toluene-d_8 at 25 °C.

UV−vis and CD spectra are shown in Figure 2. **1**, **2**, and **3** showed absorption bands at about 290 nm in the range of the $\pi-\pi^*$ transition of benzene (Figure 2a). Even though **3** has two asymmetric carbon atoms, an induced CD signal was not observed in that region, because the asymmetric carbon atoms are far from the benzene. By contrast, **1** showed a negative Cotton effect in the region. That observation indicates that the negative Cotton effect observed in **1** can be ascribed to planar chirality. Cotton bands were not observed for **2**. Hence introduction of the chiral substituents at both rims afforded planar-chiral pillar[5]arene. To investigate the diastereomeric excess of **1**, chiral HPLC measurements were carried out (Figure 2c). In **1**, two peaks were clearly found; from the peak integration the (−)-**1**/(+)-**1** ratio was 56.7/43.3

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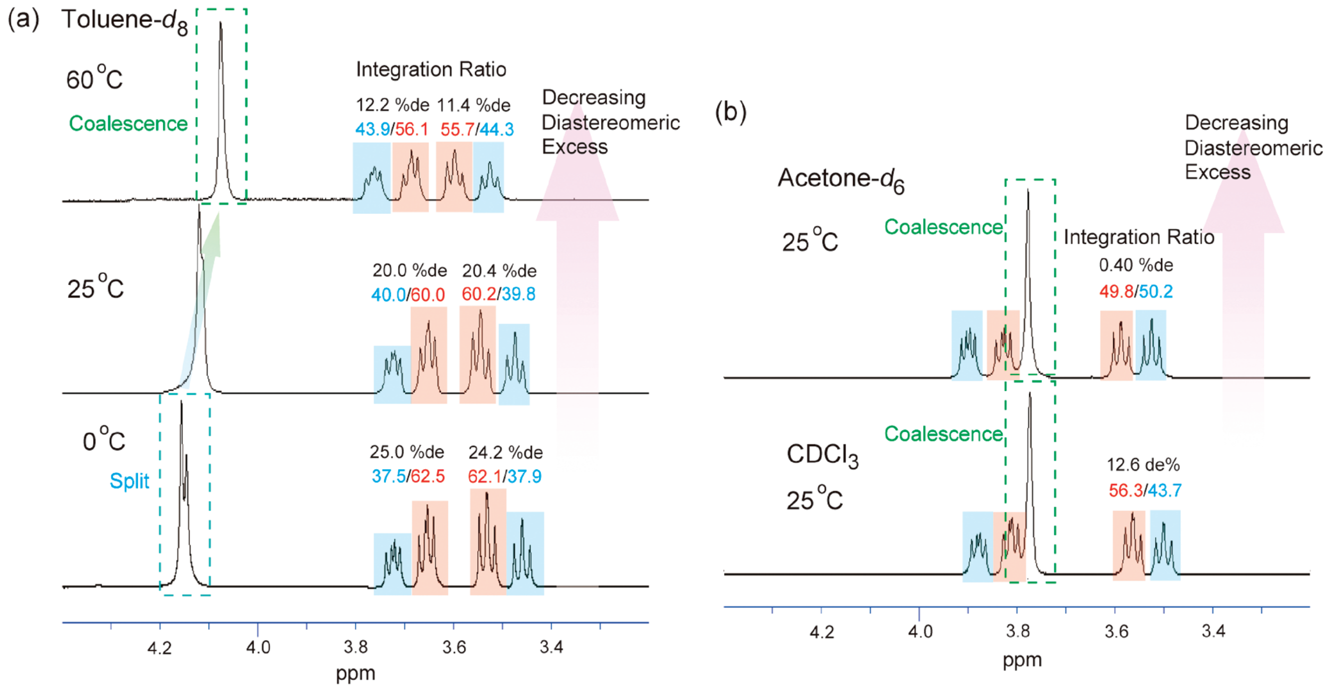

FIGURE 4. (a) Variable-temperature partial ^{1}H NMR spectra of **1** in toluene-d_8. (b) Partial ^{1}H NMR spectra of **1** in acetone-d_6 and $CDCl_3$ at 25 °C.

(13.4%de). In the case of **2** (Figure 2d), two peaks were also observed and the integration ratio was 51.5/48.5, indicating that **2** was the racemic form. To ascertain whether or not interconversion between (−)-**1** and (+)-**1** takes place, we collected first and second fractions and then sequentially reinjected the fractions (Supporting Information) at 25 °C. In both cases, two peaks derived from (−)-**1** and (+)-**1** were observed and the peak integration ratio was similar to the ratio of the original injected sample. Thus interconversion between (−)-**1** and (+)-**1** occurred at 25 °C and separation of the two diastereomers is difficult.

Figure 3 shows ^{1}H NMR spectra of **1** and **3**. In contrast to **3**, a new peak from methylene bridge protons (peak g) at 4.1 ppm was observed in **1**. The other signals were complex compared with those of **3**, indicating that **1** was a mixture of (−)-**1** and (+)-**1**. To assign these complex signals, we carried out ^{1}H−^{1}H COSY and TOCSY analyses of **1**. From these analyses, two separated spin systems (Figure 3, blue and red squares) were identified. The peaks from the two different spin systems were thus assigned a (−)-**1** and (+)-**1**.

Figure 4a shows partial variable-temperature ^{1}H NMR spectra of **1** in toluene-d_8. At 0 °C, the peak from the methylene bridge protons was clearly split (blue dash square), and on heating the split signal coalesced (green dash square). Due to fast rotation and swing movements of the units, the magnetic condition of the methylene bridge protons between (−)-**1** and (+)-**1** could not be distinguished. From the integration ratio of the methylene proton signals adjacent to O atoms of (−)-**1** and (+)-**1**, we calculated the diastereomeric excess. The integration ratio in **1** at 25 °C was found to be 60.2/39.8 (Figure 4a, 20.4% de): in **2** at 25 °C the integration ratio was 51.3/48.7 (Supporting Information), indicating that **2** is the racemic form. At 0 °C (Figure 4a), the (−)-**1**/(+)-**1** ratio was 62.1/37.9 (24.2% de), and at 60 °C the ratio was 55.7/44.3 (11.4% de). Thus as the measurement temperature increased, the (−)-**1**/(+)-**1** ratio decreased. Figure 5b shows variable-temperature CD spectra of **1** in hexane. On heating, a decrease in negative CD intensity was observed. From these data, it is apparent that the (−)-**1**/(+)-**1** ratios were strongly dependent on temperature and decreased upon heating. Since swing and rotational motions of **1** are fast at high temperatures the diastereomeric excess should decrease.

Reversibility of the thermally responsive chiral switching was investigated (Figure 5c). After heating, the sample was cooled to 0 °C at which temperature the CD intensity recovered and reverted to that of the pristine state. It was possible to perform at least six switching cycles, indicating that the thermally responsive CD intensity change is reversible.

The effect of solvents on the planar chirality of **1** was investigated. The methylene bridge protons of **1** at 25 °C in toluene-d_8 were split (Figure 4a), while they were coalesced in $CDCl_3$ and acetone-d_6 at 25 °C (Figure 4b). From the peak integration ratio, diastereomeric excesses in different solvents at 25 °C were determined. In low-permittivity solvents toluene-d_8 and $CDCl_3$ the diastereomeric excesses were found to be 20.4% de and 12.6% de, respectively (Figure 4, parts a and b). On the other hand, in high-permittivity solvent acetone-d_6, a low diastereomeric excess (0.40% de, Figure 4b) was observed. CD spectra of **1** in hexane−THF mixed solvents (Supporting Information) showed that as the ratio of low-permittivity solvent hexane to high-permittivity solvent THF decreased, a decrease of negative CD intensities was observed. These results indicated that the diastereomeric excess largely depended on solvent permittivity. Due to the fast swing and rotational motion in high-permittivity solvents, the CD intensity should decrease in such solvents, as observed.

We also investigated chemically induced chiral switching. When **1** was mixed with octyltrimethyl ammonium hexafluorophosphate (**OTMA**, Figure 1) in $CDCl_3$ at 25 °C, a new set of peaks from complexed and free species of **OTMA** was

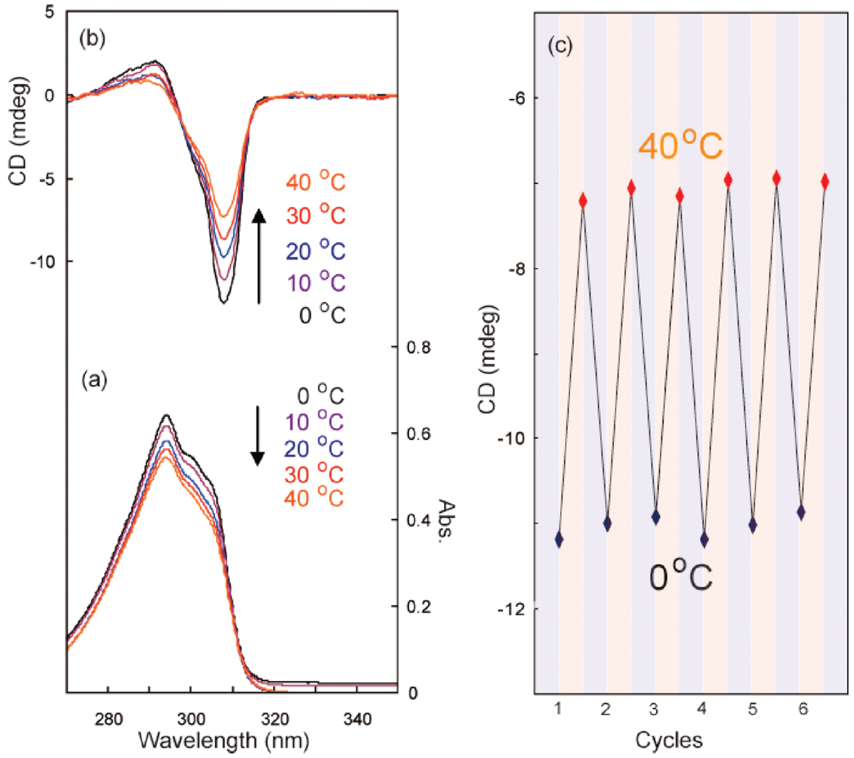

FIGURE 5. Variable-temperature (a) UV−vis and (b) CD spectra of **1** (2.10×10^{-5} L mol^{-1}cm^{-1}) in hexane. (c) Change in CD intensity for **1** (2.10×10^{-5} L mol^{-1}cm^{-1}) in hexane by repetitive heating and cooling.

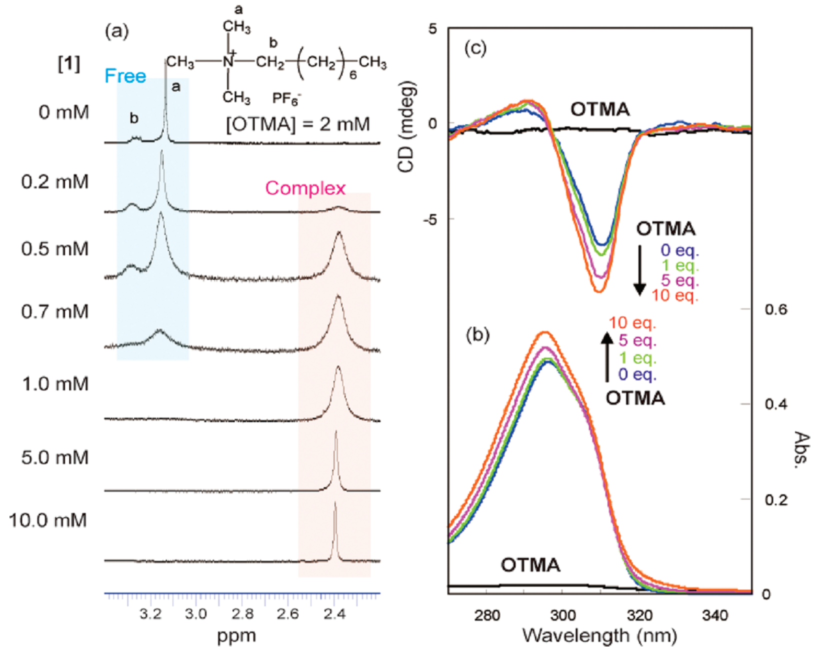

FIGURE 6. (a) Partial ^{1}H NMR spectra of **OTMA** (2 mM) with **1** (0−10 mM). (b) UV−vis and (c) CD spectra of **1** (21.5 μL mol^{-1} cm^{-1}) upon addition of **OTMA** (0−10 equiv to **1**).

observed (Figure 6a). This indicates formation of a host−guest complex between **1** and **OTMA**, and the complexation process was slow on the NMR time scale at 25 °C. From Job plots the stoichiometry of the host−guest complex was 1:1 and the association constant of the complex was found to be 1300 M^{-1} (Supporting Information). Parts b and c of Figure 6 show UV−vis and CD spectra of **1** with **OTMA**. Upon addition of **OTMA**, an increase of negative CD intensities was observed. In this spectral region there were no absorption bands or Cotton effect for **OTMA**. Even though **OTMA** is an achiral compound, the CD intensity increased with increasing **OTMA** content. Addition of **OTMA** induced broadening of the ^{1}H NMR spectrum of **1** (Supporting Information). The foundation indicates that the inclusion of **OTMA** into the cavity of **1** slowed conformational flexibility of **1**, which led to an increase of the CD intensity with increasing **OTMA** content.

Conclusions

We synthesized chiral-substituents modified pillar[5]arene (**1**) for the first time. **1** showed planar chirality and interconversion between (*pS*)-**1** and (*pR*)-**1** took place. The diastereomeric excess of **1** was relatively small, thus introduction of more bulky chiral substituents and/or many asymmetric carbons at the both rims should enhance the diastereomeric excess. By using the interconversion between (*pS*)-**1** and (*pR*)-**1**, we have demonstrated multiexternal stimuli-responsive chiral switching of **1**. It is interesting to note that the molecular recognition event of the achiral guest increased the CD intensity of **1**. To the best of our knowledge, chiral switching by complexation of an achiral guest is little known, while chiral guest-induced chiral switching has been reported.[2,3] Pillar[5]arene is able to capture guest molecules and thus should be expected to be an interesting platform compared with other planar-chiral compounds.

Experimental Section

1,4-Bis[2(*S*)-methylbutoxy]benzene (**3**), 1,4-bis(2-methylbutoxy)-benzene, and octylammonium perfluorophosphate (OTMA) were synthesized according to literature procedures.[7,8]

Synthesis of 1. To a solution of 1,4-bis[2(*S*)-methylbutoxy]-benzene (**3**, 3.80 g, 15.2 mmol) in 1,2-dichloroethane (30 mL) was added paraformaldehyde (0.46 g, 15.2 mmol) under nitrogen atmosphere. Then, boron trifluoride diethyl etherate [$BF_3 \cdot O(C_2H_5)_2$, 1.9 mL, 15.2 mmol] was added to the solution and the mixture was stirred at 30 °C for 3 h. The solution was poured into methanol and the resulting precipitate was collected by filtration. The obtained solid was purified by silica gel column chromatography to yield 0.38 g of **1** as a yellow solid: R_f 0.50 (dichloromethane/hexane = 33%/67%); yield 10%; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 6.85 (s, 10H, phenyl protons), 3.91−3.75, 3.61−3.46 (m, 20H, PhOCH_2CH−), 3.77 (s, 10H, methylene bridge protons), 1.97−1.82 (m, 10H, methine protons), 1.76−1.52, 1.40−1.20 (m, 20H, −CH(CH_3)C$H_2$$CH_3$), 1.20−0.83 (m, 60H, methyl protons); ^{13}C NMR ($CDCl_3$, 400 MHz, ppm) δ 149.8, 128.2, 114.9 (C of phenyl), 73.6 (PhO$C$$H_2$CH−), 35.3 (C of methine groups), 29.3 (C of methylene bridge), 26.4 (−CH(CH_3)$C$$H_2$$CH_3$), 16.9 (−CH($C$$H_3$)$CH_2$$CH_3$), 11.5 (−CH-($CH_3$)$CH_2$$C$$H_3$); MS (FAB) calcd for $C_{85}H_{130}O_{10}$ [M]$^+$ 1310.97, found 1311. Anal. Calcd for $C_{85}H_{130}O_{10}$: C, 77.82; H, 9.99. Found: C, 77.86; H, 10.06. $[\alpha]^{25}{}_{365}$ −87.3 (*c* 0.3 in $CHCl_3$).

Synthesis of 2. To a solution of 1,4-bis(2-methylbutoxy)-benzene (3.80 g, 15.2 mmol) in 1,2-dichloroethane (30 mL) was added paraformaldehyde (0.46 g, 15.2 mmol) under nitrogen atmosphere. Then, boron trifluoride diethyl etherate [$BF_3 \cdot O(C_2H_5)_2$, 1.9 mL, 15.2 mmol] was added to the solution and the mixture was stirred at 30 °C for 3 h. The solution was poured into methanol and the resulting precipitate was collected by filtration. The obtained solid was purified by silica gel column chromatography to yield 0.53 g of **2** as a white solid: R_f 0.50 (dichloromethane/hexane = 33%/67%); yield 13%; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 6.84 (s, 10H, phenyl protons), 3.92−3.74, 3.61−3.48 (m, 20H, PhOCH_2CH−), 3.78 (s, 10H, methylene bridge protons), 1.97−1.91 (m, 10H, methine protons), 1.74−1.51, 1.36−1.24 (m, 20H, −CH(CH_3)C$H_2$$CH_3$), 1.14−0.85 (m, 60H, methyl protons); ^{13}C NMR ($CDCl_3$, 400 MHz, ppm) δ 149.9, 128.2, 114.9 (C of phenyl), 73.6 (PhO$C$$H_2$CH−), 35.3 (C of methine groups), 29.3 (C of methylene bridge), 26.4 (−CH(CH_3)$C$$H_2$$CH_3$), 16.9 (−CH($C$$H_3$)$CH_2$$CH_3$), 11.5 (−CH-($CH_3$)$CH_2$$C$$H_3$). Anal. Calcd for $C_{85}H_{130}O_{10}$: C, 77.82; H, 9.99. Found: C, 77.89; H, 10.36. Calcd for $C_{85}H_{130}O_{10}$ [M]$^+$ 1310.97, found 1311. $[\alpha]^{25}{}_{365}$ −4.0 (*c* 0.3 in $CHCl_3$).

Determination of Association Constant between 1 and OTMA. The ^{1}H NMR spectra of mixtures of **1** and **OTMA** in different ratios show two sets of resonances for complexed and uncomplexed OTMA. The association constant K_1 of **1-OTMA** complex was calculated from integrations of complexed and uncomplexed peaks for 1:5 **1-OTMA** stoichiometry.

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Supporting Information Available: NMR spectra of **1** and **2**, chiral HPLC traces of first and second fractions of **1**, and determination of the diastereomeric excess of **2** by ^{1}H NMR measurement, CD spectra of **1** in hexane−THF mixed solvents, Job plots, and determination of association constant, and ^{1}H NMR spectrum of **1** with **OTMA**. This material is available free of charge via the Internet at http://pubs.acs.org.

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