ORGANIC LETTERS

2011
Vol. 13, No. 5
1264–1266

# Planar-Chiral Macrocyclic Host Pillar[5]arene: No Rotation of Units and Isolation of Enantiomers by Introducing Bulky Substituents

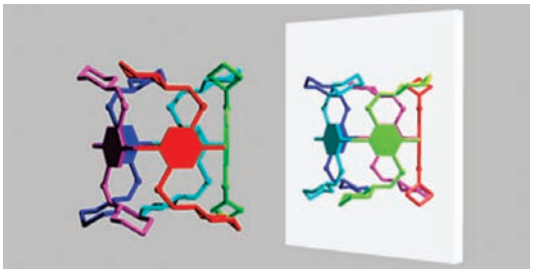
**Tomoki Ogoshi,* Kae Masaki, Ryohei Shiga, Keisuke Kitajima, and Tada-aki Yamagishi**

*Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan*

*ogoshi@t.kanazawa-u.ac.jp*

**Received January 10, 2011**

## ABSTRACT



**Enantiomers of bulky percyclohexylmethyl-substituted pillar[5]arene (Cy-C1-Pillar) were able to be separated by chiral column chromatography, and the separated enantiomers did not racemize. Even though modified with the bulky cyclohexylmethyl-substituents at both rims, Cy-C1-Pillar was able to capture a guest molecule.**

Planar-chiral compounds are interesting from a structural point of view, and are expected to be useful as a framework for functional materials[1] such as chiral discriminators[2a,b] or chiral polymers and supramolecules,[2c,d] or as guest receptors.[2g] Recently, we reported a novel macrocyclic host molecule and named it "pillar[5]arene".[3] The composition of pillar[5]arene is almost the same as that of typical calixarenes.[4] 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 permethylated pillar[5]arene

(1) (a) *Cyclophane Chemistry*; Vögtle, F., Ed.; Wiley: Chichester, 1993. (b) *Modern Cyclophane Chemistry*; Gleither, R., Hopf, H., Eds.; Wiley: Chichester, 2004.

(2) (a) Oi, S.; Miyano, S. *Chem. Lett.* **1992**, 987–990. (b) Hattori, T.; Harada, N.; Oi, S.; Abe, H.; Miyano, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1043–1046. (c) Fiesel, R.; Huber, J.; Scherf, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2113–2116. (d) Fiesel, R.; Huber, J.; Apel, U.; Enkelmann, V.; Hentschke, R.; Scherf, U. *Macromol. Chem. Phys.* **1997**, *198*, 2623–2650. (e) Kanomata, N.; Nakata, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1207–1211. (f) Kanomata, N.; Nakata, T. *J. Am. Chem. Soc.* **2000**, *122*, 4563–4568. (g) Katoono, R.; Kawai, H.; Fujiwara, K.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 8455–8459.

(3) (a) Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022–5023. (b) Ogoshi, T.; Umeda, K.; Yamagishi, T.; Nakamoto, Y. *Chem. Commun.* **2009**, 4874–4876. (c) Ogoshi, T.; Kitajima, K.; Yamagishi, T.; Nakamoto, Y. *Org. Lett.* **2010**, *12*, 636–638. (d) Ogoshi, T.; Kitajima, K.; Aoki, T.; Yamagishi, T.; Nakamoto, Y. *J. Phys. Chem. Lett.* **2010**, *1*, 817–821. (e) Ogoshi, T.; Nishida, Y.; Yamagishi, T.; Nakamoto, Y. *Macromolecules* **2010**, *43*, 3145–3147. (f) Ogoshi, T.; Hashizume, M.; Yamagishi, T.; Nakamoto, Y. *Chem. Commun.* **2010**, 3708–3710. (g) Ogoshi, T.; Kitajima, K.; Aoki, T.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Org. Chem.* **2010**, *75*, 3268–3273. (h) Ogoshi, T.; Nishida, Y.; Yamagishi, T.; Nakamoto, Y. *Macromolecules* **2010**, *43*, 7068–7072. (i) Ogoshi, T.; Aoki, T.; Kitajima, K.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Org. Chem.* **2011**, *76*, 328–331. (j) Ogoshi, T.; Tanaka, S.; Yamagishi, T.; Nakamoto, Y. *Chem. Lett.* **2011**, *40*, 96–98. (k) Ogoshi, T.; Shiga, R.; Yamagishi, T.; Nakamoto, Y. *J. Org. Chem.* **2011**, *76*, 618–622. (l) Cao, D.; Kou, Y.; Liang, J.; Chen, Z.; Wang, L.; Meier, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 9721–9723. (m) Zhang, Z.; Xia, B.; Han, C.; Yu, Y.; Huang, F. *Org. Lett.* **2010**, *12*, 3285–3287.

10.1021/ol200062j 
**Published on Web 02/02/2011**

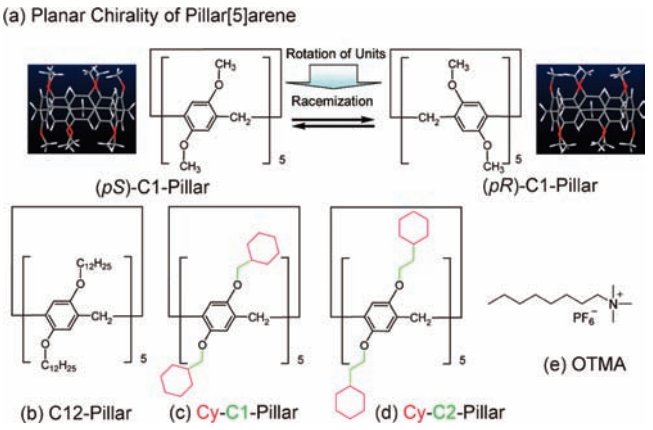



**Figure 1.** (a) Planar chirality of **C1-Pillar**. Chemical structures of (b) **C12-Pillar**, (c) **Cy-C1-Pillar**, (d) **Cy-C2-Pillar**, and (e) **OTMA**.

(**C1-Pillar**, Figure 1a), planar-chiral (*pS*)- and (*pR*)-**C1-Pillar** are mixed in a 1:1 proportion. Thus synthesis and investigation of pillar[5]arenes with planar chirality are an important research target. However, all pillar[5]arenes that have been synthesized are racemic mixtures; racemization takes place by rotation of units, and isolation of planar-chiral pillar[5]arene enantiomers has not been accomplished. To isolate planar-chiral pillar[5]arene from racemic mixtures, inhibiting the rotational motion is necessary. However, even by introducing long dodecyl chains at both rims (**C12-Pillar**, Figure 1b) rotation of the units took place.[3g] Consequently, with the objective of isolating planar-chiral pillar[5]arene, in the present study we synthesized novel pillar[5]arenes carrying more bulky cyclohexyl substituents at both rims. Percyclohexylmethyl- (**Cy-C1-Pillar**, Figure 1c) and percyclohexylethyl-pillar[5]arenes (**Cy-C2-Pillar**, Figure 1d) were prepared. Their synthetic procedures and characterization by $^1$H NMR, $^{13}$C NMR, $^1$H−$^1$H COSY, HSQC, mass and elemental analysis are shown in the Supporting Information. Their rotational and planar-chiral properties were investigated by variable-temperature $^1$H NMR and chiral HPLC measurements.

Figure 2 shows variable-temperature partial $^1$H NMR spectra of these pillar[5]arenes. In both cases, the proton signal from the methylene moieties adjacent to the O atoms (peak b) was split into two groups of peaks in 1:1 integration ratio at 20 °C. Due to the planar chirality of pillar[5]arene the methylene protons are diastereomeric. Such split proton resonances were observed in **C12-Pillar** and the split signals coalesced at 1 °C.[3g] Due to the rotation of the units, the methylene protons are not diastereomeric at that temperature. Thus, the split proton resonances are a

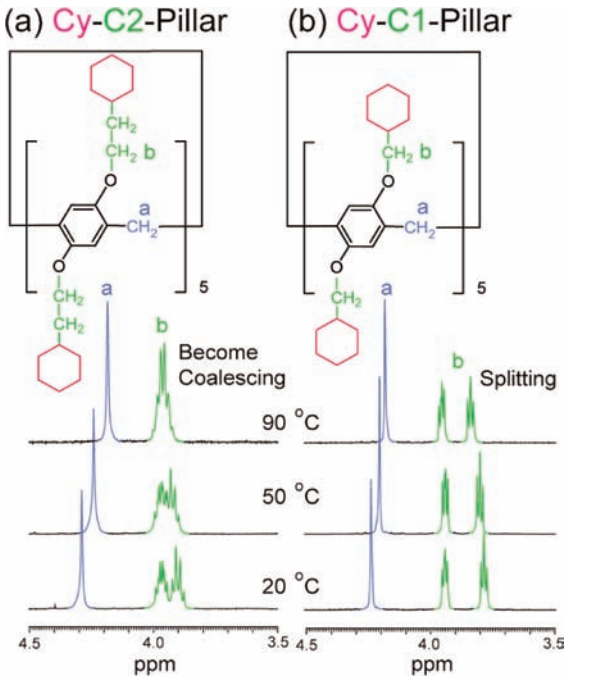



**Figure 2.** Variable-temperature partial $^1$H NMR spectra of (a) **Cy-C2-Pillar** and (b) **Cy-C1-Pillar** in toluene-$d_8$.

useful marker to determine whether rotation of the units takes place on the NMR time scale. On heating, the methylene peaks of **Cy-C2-Pillar** moved toward each other and coalesced (Figure 2a). This indicates that rotation of the units in **Cy-C2-Pillar** occurred on the NMR time scale at the elevated temperatures. By contrast, in **Cy-C1-Pillar** the methylene proton resonances hardly changed even on heating (Figure 2b). This result indicates that rotation of the units in **Cy-C1-Pillar** either did not take place or occurred extremely slowly on the NMR time scale in the temperature range investigated.

To further investigate the rotational motion in **Cy-C1-Pillar**, chiral HPLC measurements were carried out (Figures 3a and b). Upon injection of **Cy-C1-Pillar** onto an appropriate chiral HPLC column, two peaks of equal area were observed (Figure 3a). The fractions were collected separately then the first fraction was reinjected. The original first peak was found but the second peak from the paired enantiomer was not observed (Figure 3b, blue line). In addition, even by holding at 40 °C for 18 h, the second peak was not detected (Figure 3b, red line). The same trends were also observed in reinjection of the second fraction (Supporting Information). These data indicate that **Cy-C1-Pillar** enantiomers did not racemize. Figures 3c and d show UV−vis and CD spectra of each fraction. The CD spectra of the fractions were mirror images, indicating isolation of enantiopure (*pS*)- and (*pR*)-**Cy-C1-Pillar**.

The results of variable-temperature $^1$H NMR and chiral HPLC measurements can be summarized as follows (Figure 4). In variable-temperature $^1$H NMR measurements of **Cy-C2-Pillar**, rotation of the units took place on

(4) (a) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer Academic: Dordrecht, 1991. (c) Atwood, J. L.; Dalgarno, S. J.; Hardie, M. J.; Raston, C. L. *Chem. Commun.* **2005**, 337–339. (d) Castro, R.; Godinez, L. A.; Criss, C. M.; Kaifer, A. E. *J. Org. Chem.* **1997**, *62*, 4928–4935. (e) Cacciapaglia, R.; Casnati, A.; Mandolini, L.; Peracchi, A.; Reinhoudt, D. N.; Salvio, R.; Sartori, A.; Ungaro, R. *J. Am. Chem. Soc.* **2007**, *129*, 12512–12520.

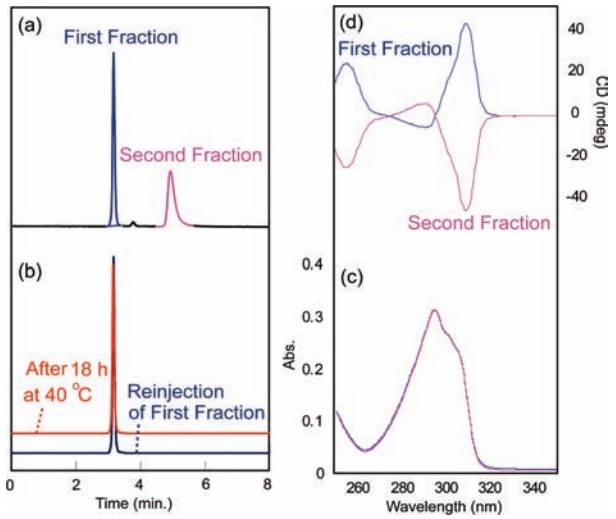



**Figure 3.** (a) Chiral HPLC traces of **Cy-C1-Pillar** and (b) the first fraction of **Cy-C1-Pillar** by holding at 40 °C for 18 h. Hexane/EtOH = 97/3 (vol %) was used as eluent. (c) UV−vis and (d) CD spectra of the first and second fractions (14 $\mu$L mol$^{-1}$cm$^{-1}$) in hexane at 25 °C.

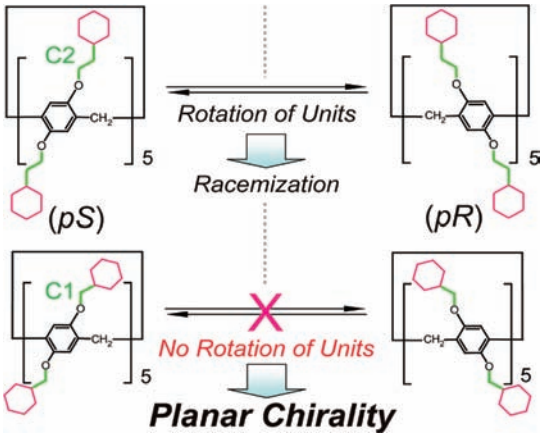



**Figure 4.** Schematic representation of the rotation movements of bulky percyclohexyl-substituted pillar[5]arenes.

the NMR time scale, whereas the units of **Cy-C1-Pillar** did not rotate (or rotated extremely slowly) on the NMR time scale. Chiral HPLC measurements exhibited no racemization of **Cy-C1-Pillar**, indicating inhibition of rotation of the units. It is very interesting to note that the length of the methylene linker (**C1** or **C2**) between pillar[5]arene and cyclohexyl groups strongly affected the rotational motion.

We also investigated the host−guest properties of **Cy-C1-Pillar**. When **Cy-C1-Pillar** was mixed with octyltrimethyl ammonium hexafluorophosphate (**OTMA**, Figure 1e) in $CDCl_3$ at 25 °C, the peaks of **Cy-C1-Pillar** became broadening and a new set of peaks from complexed (green peaks) and free (read peaks) species of **OTMA** was observed (Figure 5c). This indicates formation of a host−guest complex between **Cy-C1-Pillar** 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 830 M$^{-1}$ (Supporting Information).

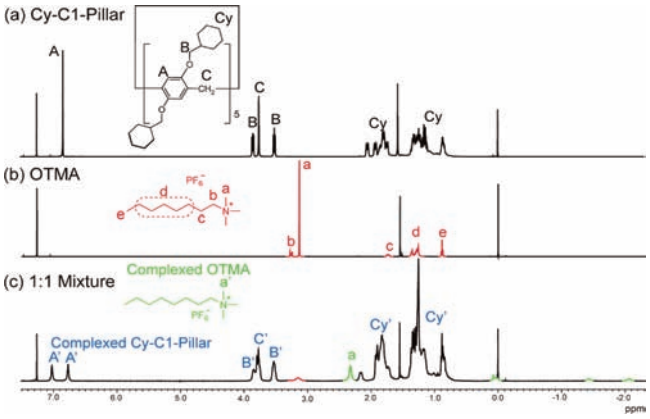



**Figure 5.** $^1$H NMR spectra of (a) **Cy-C1-Pillar**, (b) **OTMA**, and (c) the 1:1 mixture of **Cy-C1-Pillar** and **OTMA** in 10 mM in $CDCl_3$ at 25 °C.

In conclusion, we were able to inhibit rotation of the units in pillar[5]arene by modification with cyclohexylmethyl groups. Since the units did not rotate, we successfully isolated each (*pS*)- and (*pR*)-form pillar[5]arene enantiomer. To the best of our knowledge, inhibition of the rotation and isolation of the enantiomers of pillar[5]arene are the first example. To introduce chirality into host molecules, a typical approach is modification of asymmetric carbons in host molecules.[5] Cyclodextrins show chirality because they have many asymmetric carbons.[5b,c] However, in the present study we successfully obtained chiral host pillar[5]arene by inhibition of rotation of the units. While various kinds of host molecules have been developed, planar-chiral host molecules are little known. Surprisingly, despite the introduction of the 10 bulky cyclohexylmethyl groups at both rims, **Cy-C1-Pillar** is able to capture a guest molecule. On the basis of the host−guest property, planar-chiral host **Cy-C1-Pillar** enantiomers will be used as chiral guest receptors, building blocks for planar-chiral supramolecular architectures.

**Acknowledgment.** This work was supported by a Grant-in-Aid for Young Scientists (WAKATE B-1975011) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

**Supporting Information Available.** Experimental section, characterization data of all new pillar[5]arenes, chiral HPLC traces of the reinjected second fraction, Job's plots and association constant for the complex between **Cy-C1-Pillar** and **OTMA**. This material is available free of charge via the Internet at http://pubs.acs.org.

(5) (a) Castellano, R. K.; Kim, B. H.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 12671–12672. (b) Lynam, C.; Jennings, K.; Nolan, K.; Kane, P.; McKervey, M. A.; Diamond, D. *Anal. Chem.* **2002**, *74*, 59–66. (c) Kanagaraj, K.; Suresh, P.; Pitchumani, K. *Org. Lett.* **2010**, *12*, 4070–4073. (d) Miyauchi, M.; Takashima, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* **2005**, *127*, 2984–2989.