JOC Article

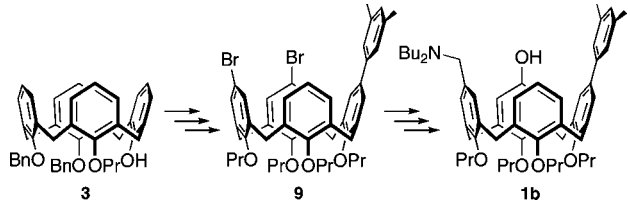
Synthesis and Resolution of a Multifunctional Inherently Chiral Calix[4]arene with an ABCD Substitution Pattern at the Wide Rim: The Effect of a Multifunctional Structure in the Organocatalyst on Enantioselectivity in Asymmetric Reactions

Seiji Shirakawa, Tomohiro Kimura, Shun-ichi Murata, and Shoichi Shimizu*

Department of Applied Molecular Chemistry, College of Industrial Technology, Nihon University, Narashino, Chiba, 275-8575, Japan

s5simizu@cit.nihon-u.ac.jp

Received November 2, 2008



An efficient synthetic route to inherently chiral calix[4]arenes with an ABCD substitution pattern at the wide rim in the cone conformation was developed for the first time. For the synthesis of inherently chiral ABCD-type calix[4]arenes, first 5,11-dibromo-17-(3,5-dimethylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene (**9**) was prepared as a key intermediate. Then, functionalization of the calix[4]arene **9** was examined, and highly regioselective monofunctionalization was achieved via selective monolithiation of bromo groups. Various multifunctionalized inherently chiral ABCD-type calix[4]arenes can be synthesized by using this method; thus, the synthesis of inherently chiral phosphine and carboxylic acid derivatives of ABCD-type calix[4]arene was demonstrated. In addition, the aminophenol derivative **1b** of an ABCD-type calix[4]arene with a 3,5-dimethylphenyl group at the wide rim was synthesized and resolved into optically pure enantiomers. The chiral calix[4]arene **1b** was used as an organocatalyst in asymmetric Michael addition reactions of thiophenols. The effect of the 3,5-dimethylphenyl group at the wide rim of calix[4]arene **1b** on enantioselectivity was examined, and a positive effect of the 3,5-dimethylphenyl group was observed.

Introduction

Calixarenes have been widely used as three-dimensional molecular platforms for the design of artificial molecular receptors, owing to the ready availability of cheap starting materials and the facile modification of the calixarene structure at the wide and narrow rims.[1]

The chemistry of chiral calixarenes has received increasing interest in recent years, as it is important to the development of new chiral receptors for asymmetric recognition and provides potent tools for understanding the stereochemistry of biochemical systems. Hence, many chiral calixarenes containing chiral residues at either the wide or the narrow rim have been prepared as chiral receptors[2] and catalysts.[3] A more challenging and attractive approach to the introduction of chirality is to make the calixarene "inherently" chiral by creating an unsymmetrical array of achiral substituents on the calixarene skeleton.[4] Over the past two decades, many inherently chiral calixarenes have been prepared, and some of them have been resolved into individual enantiomers.[5] In spite of these efforts, only a few

* Corresponding author. Phone: +81 47-474-2568. Fax: +81 47-474-2579.

(1) For representative reviews on calixarenes, see: (a) *Calixarenes: A Versatile Class of Macrocyclic Compounds; Topics in Inclusion Science 3*; Vicens, J., Böhmer,V., Eds.; Kluwer: Dordrecht, The Netherlands, 1991. (b) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933–8968. (c) Takeshita, M.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1088–1097. (d) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713–745. (e) Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon Press: Oxford, UK, 1996; Vol. 2, pp 103−142. (f) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713–1734. (g) Gutsche, C. D. *Caixarenes Revisited; Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, UK, 1998. (h) *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, UK, 2000. (i) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.;Kluwer: Dordrecht, The Netherlands, 2001. (j) Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291–5316.

10.1021/jo8024412 CCC: $40.75 © 2009 American Chemical Society
Published on Web 12/19/2008

examples of enantiomeric recognition[6] and asymmetric catalysis[7] with inherently chiral calixarenes have been reported. These limited results might arise from difficulties associated with both the design of a synthetic route to functionalized inherently chiral calixarenes and separation of the chiral products into optically pure enantiomers.

Recently, we developed an efficient method for the synthesis and optical resolution of a novel inherently chiral calix[4]arene **1a** with dual functionalities (Figure 1).[8] The chiral calix[4]arene **1a** possesses amino and hydroxy groups, which are involved in molecular recognition at proximal positions on the wide rim (ABCC substitution pattern). Also, the conformation of the chiral calix[4]arene **1a** was fixed in the cone conformation, which provides a specific chiral environment. The enantiomeric recognition ability of the chiral calix[4]arene **1a** was examined,

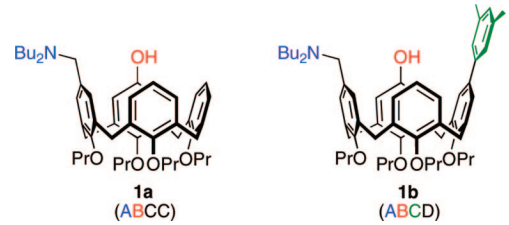


FIGURE 1. Functionalized inherently chiral calix[4]arenes **1**.

and we found that the chiral calix[4]arene **1a** could be used as an organocatalyst[9] in asymmetric Michael addition reactions of thiophenols[10] with high catalytic efficiency. Unfortunately, the observed enantioselectivity of the products was poor. For the design of a more effective chiral catalyst, we introduced additional substituent on the wide rim. Ultimately, we designed an inherently chiral ABCD-type calix[4]arene **1b** containing a 3,5-dimethylphenyl group as a sterically bulky substituent (Figure 1). Such an inherently chiral wide rim ABCD-type calix[4]arene is very rare,[11] and to the best of our knowledge, the synthesis of an ABCD-substituted calix[4]arene with control of the conformation has never been reported. Herein, we wish to report the development of an efficient synthetic route to the inherently chiral wide rim ABCD-type calix[4]arene fixed in a cone conformation, and the beneficial effects of the multifunctional structure on its enantioselectivity as an organocatalyst in asymmetric Michael addition reactions.

Results and Discussion

Synthesis of Key Intermediate 9 for the Synthesis of Inherently Chiral Calix[4]arenes with an ABCD Substitution Pattern at the Wide Rim. For the synthesis of inherently chiral ABCD-substituted calix[4]arenes in the cone conformation, we synthesized 5,11-dibromo-17-(3,5-dimethylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene (**9**) as a key intermediate. The calix[4]arene **9** can be prepared from the already reported calix[4]arene dibenzyl ether **2**,[12] as outlined in Scheme 1. For the regioselective introduction of bromo and 3,5-dimethylphenyl groups onto the wide rim, first, a 3,5-dimethylphenyl group was introduced onto the calix[4]arene. Thus, one of the proximal dihydroxy groups of **2** was selectively transformed to a mono-*O*-alkylated product **3** by treatment with propyl bromide in the presence of Na_2CO_3 as a base. Use of Na_2CO_3 as the base was a key factor in the selective mono-*O*-alkylation of **2**.[12] The para

(2) (a) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522–524. (b) Pinkhassik, E.; Stibor, I.; Casnati, A.; Ungaro, R. *J. Org. Chem.* **1997**, *62*, 8654–8659. (c) Castellano, R. K.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 11156–11163. (d) Prins, L. J.; Jong, F. D.; Timmerman, P.; Reinhoudt, D. N. *Nature* **2000**, *408*, 181–184. (e) Botta, B.; Subissati, D.; Tafi, A.; Della Monache, G.; Filippi, A.; Speranza, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4767–4770. (f) Zheng, Y.-S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189–1192. (g) Sansone, F.; Baldini, L.; Casnati, A.; Chierici, E.; Faimani, G.; Ugozzoli, F.; Ungaro, R. *J. Am. Chem. Soc.* **2004**, *126*, 6204–6205. (h) Cherenok, S.; Vovk, A.; Muravyova, I.; Shivanyuk, A.; Kukhar, V.; Lipkowski, J.; Kalchenko, V. *Org. Lett.* **2006**, *8*, 549–552. (i) Bonini, C.; Chiummiento, L.; Funicello, M.; Teresa Lopardo, M.; Lupattelli, P.; Laurita, A.; Cornia, A. *J. Org. Chem.* **2008**, *73*, 4233–4236.

(3) (a) Arnott, G.; Heaney, H.; Hunter, R.; Page, P. C. B. *Eur. J. Org. Chem.* **2004**, 5126–5134. (b) Gaeta, C.; De Rosa, M.; Fruilo, M.; Soriente, A.; Neri, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2333–2340. (c) Arnott, G.; Hunter, R. *Tetrahedron* **2006**, *62*, 992–1000. (d) Quintard, A.; Darbost, U.; Vocanson, F.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1926–1933. (e) Marson, A.; Freixa, Z.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **2007**, 4587–4591. (f) Bozkurt, S.; Durmaz, M.; Yilmaz, M.; Sirit, A. *Tetrahedron: Asymmetry* **2008**, *19*, 618–623.

(4) (a) Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 17–39. (b) Otsuka, H.; Shinkai, S. *Supramol. Sci.* **1996**, *3*, 189–205. (c) Dalla Cort, A.; Mandolini, L.; Pasquini, C.; Schiaffino, L. *New J. Chem.* **2004**, *28*, 1198–1199.

(5) (a) Pappalardo, S.; Caccamese, S.; Giunta, L. *Tetrahedron Lett.* **1991**, *32*, 7747–7750. (b) Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Iwamoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2429–2434. (c) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, *115*, 3997–4006. (d) Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 4271–4275. (e) Jin, T.; Monde, K. *Chem. Commun.* **1998**, 1357–1358. (f) Browne, J. K.; McKervey, M. A.; Pitarch, M.; Russell, J. A.; Millership, J. S. *Tetrahedron Lett.* **1998**, *39*, 1787–1790. (g) Morohashi, N.; Iki, N.; Onodera, T.; Kabuto, C.; Miyano, S. *Tetrahedron Lett.* **2000**, *41*, 5093–5097. (h) Caccamese, S.; Bottino, A.; Cunsolo, F.; Parlato, S.; Neri, P. *Tetrahedron: Asymmetry* **2000**, *11*, 3103–3112. (i) Hesek, D.; Inoue, Y.; Drew, M. G. B.; Beer, P. D.; Hembury, G. A.; Ishida, H.; Aoki, F. *Org. Lett.* **2000**, *2*, 2237–2240. (j) Cao, Y.-D.; Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Wang, M.-X.; Huang, Z.-T. *J. Org. Chem.* **2004**, *69*, 206–208. (k) Narumi, F.; Hattori, T.; Yamabuki, W.; Kabuto, C.; Kameyama, H. *Tetrahedron: Asymmetry* **2005**, *16*, 793–800. (l) Miao, R.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *J. Org. Chem.* **2005**, *70*, 7662–7671. (m) Boyko, V. I.; Shivanyuk, A.; Pyrozhenko, V. V.; Zubatyuk, R. I.; Shishkin, O. V.; Kalchenko, V. I. *Tetrahedron Lett.* **2006**, *47*, 7775–7778. (n) Yakovenko, A. V.; Boyko, V. I.; Danylyuk, O.; Suwinska, K.; Lipkowski, J.; Kalchenko, V. I. *Org. Lett.* **2007**, *9*, 1183–1185. (o) Xu, Z.-X.; Zhang, C.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2007**, *9*, 4447–4450. (p) Boyko, V. I.; Yakovenko, A. V.; Matvieiev, Y. I.; Kalchenko, O. I.; Shishkin, O. V.; Kalchenko, V. I. *Tetrahedron* **2008**, *67*, 7567–7573. (q) Narumi, F.; Matsumura, N.; Sasagawa, N.; Natori, K.; Kajiwara, T.; Hattori, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1470–1475. (r) Xu, Z.-X.; Zhang, C.; Yang, Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2008**, *10*, 477–479. (s) Paletta, M.; Klaes, M.; Neumann, B.; Stammler, H.-G.; Grimme, S.; Mattay, J. *Eur. J. Org. Chem.* **2008**, 555–562.

(6) (a) Araki, K.; Inada, K.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 72–74. (b) Narumi, F.; Hattori, T.; Matsumura, N.; Onodera, T.; Katagiri, H.; Kabuto, C.; Kameyama, H.; Miyano, S. *Tetrahedron* **2004**, *60*, 7827–7833. (c) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2005**, *61*, 8517–8528.

(7) Inherently chiral calixarenes containing other chiral residue were applied to asymmetric reactions as chiral ligands or catalysts, see: (a) Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, 2508–2517. (b) Xu, Z.-X.; Li, G.-K.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2008**, *67*, 8668–8675.

(8) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117–3119.

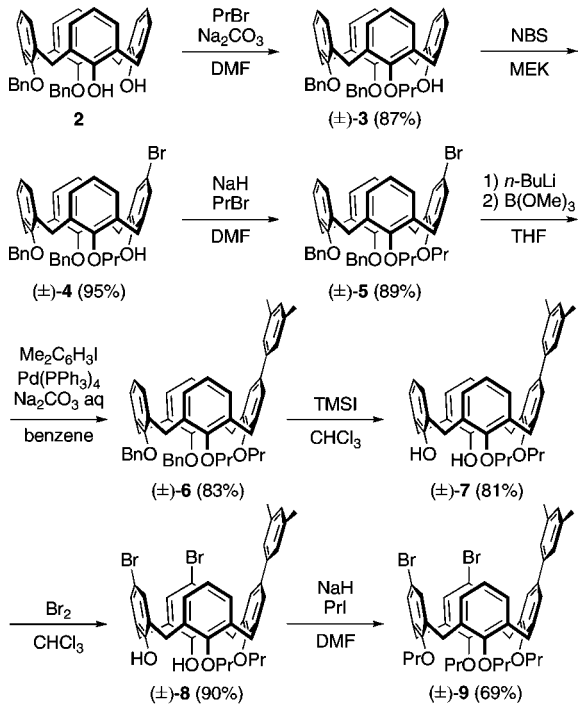
(9) For representative reviews on organocatalysts, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724. (c) Berkssel, A.; Göger, H. *Asymmetric Organocatalysis-From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Willy-VCH: Weinheim, Germany, 2005. (d) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Willy-VCH: Weinheim, Germany, 2007.

(10) For catalytic asymmetric Michael addition reactions of thiophenols, see: (a) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417–430. (b) Suzuki, K.; Ikegami, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277–3282. (c) Wang, F.; Tada, M. *Agric. Biol. Chem.* **1990**, *54*, 2989–2992. (d) Ito, A.; Konishi, K.; Aida, T. *Tetrahedron Lett.* **1996**, *37*, 2585–2588. (e) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043–4044. (f) Ostendorf, M.; van der Neut, S.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 105–113. (g) Ostendorf, M.; Dijkink, J.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 115–124. (h) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589–9594. (i) Skarzewski, J.; Zielinska-Blajet, M.; Turowska-Tryk, I. *Tetrahedron: Asymmetry* **2001**, *12*, 1923–1928. (j) McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338–340. (k) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603–606.

(11) (a) Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200–3205. (b) Zetta, L.; Wolff, A.; Vogt, W.; Platt, K.-L.; Böhmer, V. *Tetrahedron* **1991**, *47*, 1911–1924.

(12) Shimizu, S.; Moriyama, A.; Kito, K.; Sasaki, Y. *J. Org. Chem.* **2003**, *68*, 2187–2194.

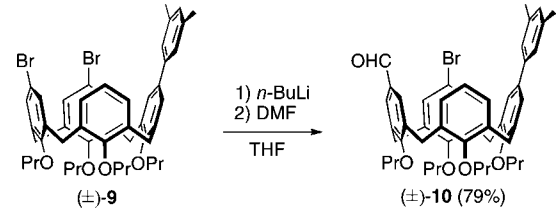
SCHEME 1. Synthesis of Calix[4]arene 9 as a Key Intermediate



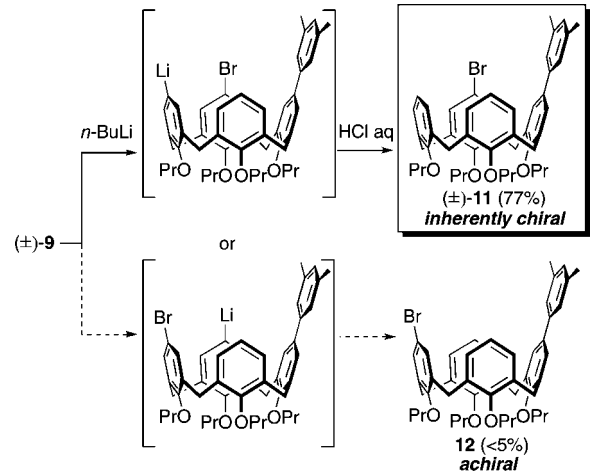
position of the free phenolic ring of tri-*O*-alkylated calix[4]arene **3** was selectively brominated to afford **4**. After *O*-propylation of **4**, the tetraalkoxycalix[4]arene **5** was treated with *n*-BuLi and the resulting lithiation compound was transformed to the boronate by treatment with $B(OMe)_3$. Then, the 3,5-dimethylphenyl group was installed by using a Suzuki−Miyaura coupling reaction[13] between the boronate of calix[4]arene and 1-iodo-3,5-dimethylbenzene to afford the calix[4]arene **6**. The selective dealkylation of the benzyl groups at the narrow rim of **6** was performed by treatment with 2.3 equiv of trimethylsilyl iodide to afford the dialkoxycalix[4]arene **7**. After regioselective dibromination on the para positions of the free phenolic rings in calix[4]arene **7**, the resulting dibromo calix[4]arene **8** was *O*-alkylated with propyl iodide in the presence of NaH to yield the desired calix[4]arene **9** fixed in the cone conformation.

Regioselective Functionalization of the Calix[4]arene 9. Next, we focused on the regioselective functionalization of the proximally disubstituted bromo groups of the calix[4]arene **9**. For the synthesis of calix[4]arene **1b**, monoformylation of **9** was performed as follows. The calix[4]arene **9** was treated with 1.1 equiv of *n*-BuLi and, subsequently, with *N*,*N*-dimethylformamide. As a result of regioselective lithiation, the monoformylated calix[4]arene **10** was obtained in 79% yield (Scheme 2). The position of the formyl group in **10** was confirmed by treatment with aqueous HCl after lithiation (Scheme 3). We knew that if the bromine−lithium exchange reaction occurred selectively at the distal position of the 3,5-dimethylphenyl group, then the inherently chiral calix[4]arene **11** would be obtained as the result of protonation by aqueous HCl. On the other hand, we knew that if the reaction occurred at the proximal position of the 3,5-dimethylphenyl group, the achiral calix[4]arene **12** would be obtained. After the monolithiation of **9** shown in

SCHEME 2. Regioselective Formylation of 9



SCHEME 3. Confirmation of the Lithiated Position for Selective Functionalization



Scheme 3, ^1H and ^{13}C NMR analyses of the obtained product clearly indicated that the product possessed an inherent chirality derived from product **11**. Thus, the ^1H NMR spectrum of **11** showed a set of four AB systems for methylene bridges of calix[4]arene, at 4.48, 4.46, 4.43, and 4.40 ppm for axial protons and at 3.22, 3.17, 3.15, and 3.10 ppm for equatrial protons. The ^{13}C NMR spectrum showed peaks at 31.11, 30.99, 30.97, and 30.84 ppm for the four pertinent carbons. The ^1H and ^{13}C NMR spectra observed exhibited patterns characteristic of inherently chiral calix[4]arenes in a cone conformation.[14] The origin of regioselectivity for the lithiation of **9** is presumably due to the steric hindrance of the 3,5-dimethylphenyl group.

Other regioselective functionalization was also possible by using the present method (Scheme 4). After monolithiation of **9**, the resulting lithiated compound was treated with either chlorodiphenylphosphine or CO_2, and gave either the corresponding phosphine[15,16] or the carboxylic acid derivatives **13** and **14**. This synthetic procedure offers an efficient method for the synthesis of various inherently chiral wide rim ABCD-type calix[4]arenes.

Synthesis and Optical Resolution of a Multifunctional Inherently Chiral Calix[4]arene 1b. Synthesis of the inherently

(13) For reviews on Suzuki−Miyaura coupling reactions, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.

(14) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sánchez, C. *J. Org. Chem.* **1991**, *56*, 3372–3376.

(15) For reviews on phosphine-substituted calixarenes, see: (a) Wieser, C.; Dieleman, C. B.; Matt, D. *Coord. Chem. Rev.* **1997**, *165*, 93–161. (b) Harvey, P. D. *Coord. Chem. Rev.* **2002**, *233−234*, 289–309. (c) Jeunesse, C.; Armspach, D.; Matt, D. *Chem. Commun.* **2005**, 5603–5614.

(16) For wide rim phosphine-substituted calixarenes, see: (a) Hamada, F.; Fukugaki, T.; Murai, K.; William, G.; Atwood, J. L. *J. Incl. Phenom.* **1991**, *10*, 57–61. (b) Wieser-Jeunesse, C.; Matt, D.; De Cian, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2861–2864. (c) Shimizu, S.; Shirakawa, S.; Sasaki, Y.; Hirai, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1256–1259. (d) Shirakawa, S.; Shimizu, S.; Sasaki, Y. *New J. Chem.* **2001**, *25*, 777–779. (e) Vézina, M.; Gagnon, J.; Villeneuve, K.; Drouin, M.; Harvey, P. D. *Organometallics* **2001**, *20*, 273–281. (f) Takenaka, K.; Obora, Y.; Hong Jang, L.; Tsuji, Y. *Organometallics* **2002**, *21*, 1158–1166. (g) Lejeune, M.; Sémeril, D.; Jeunesse, C.; Matt, D.; Peruch, F.; Lutz, P. J.; Ricard, L. *Chem. Eur. J.* **2004**, *10*, 5354–5360.

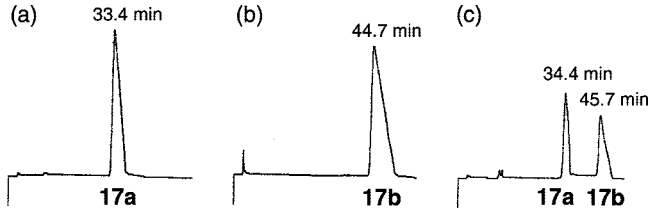
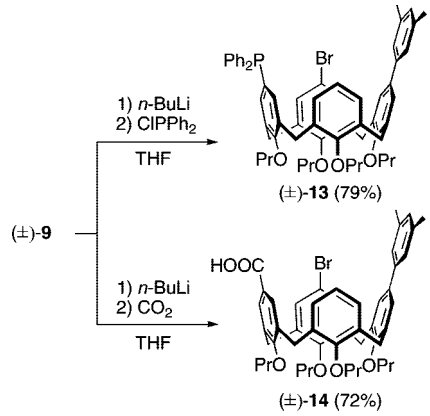
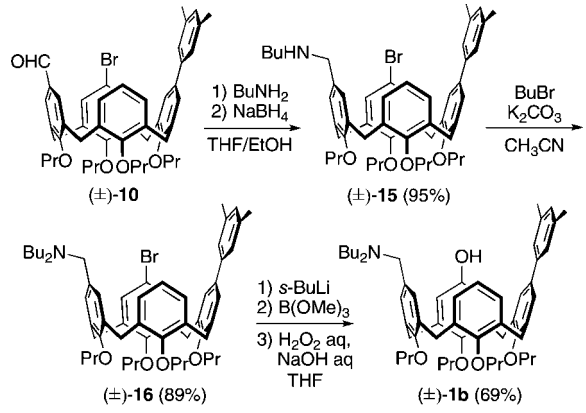


FIGURE 2. HPLC chromatograms of **17a** (a), **17b** (b), and a mixture of **17a** and **17b** (c) [column: SUMICHIRAL OA-2000 (0.46 cm × 25 cm); eluent: $CHCl_3$; flow rate: 1.0 mL/min].

SCHEME 4. Other Examples of Regioselective Functionalization



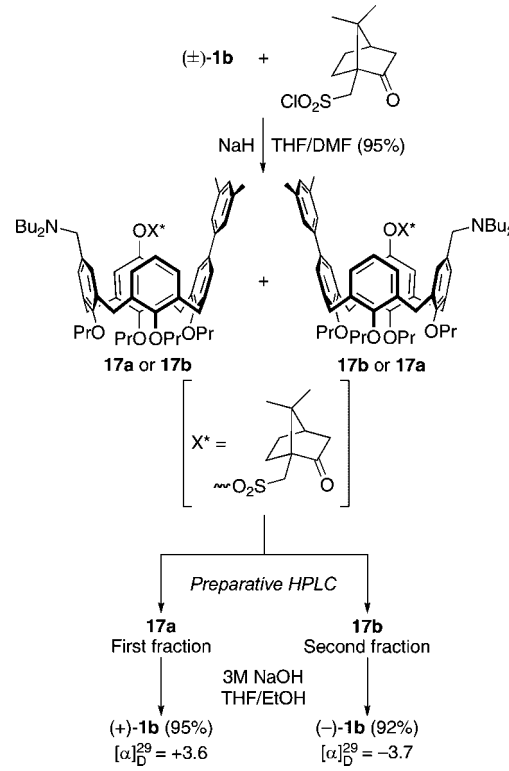
SCHEME 5. Synthesis of Inherently Chiral Calix[4]arene 1b



chiral calix[4]arene **1b** was achieved from **10** in a manner similar to the previously described synthesis of **1a** (Scheme 5).[8] Thus, the reductive amination of the formyl group of **10** with *n*-butylamine gave the secondary amine **15** in 95% yield. Compound **15** was transformed with *n*-butyl bromide to the tertiary amine **16** in 89% yield. Lithiation of the bromine substituent on **16** and the trapping of the resulting anion with $B(OMe)_3$ gave the corresponding boronate. The boronate was oxidized by H_2O_2 with use of a one-pot method, giving the target calix[4]arene **1b** as racemates in 69% yield.[17]

The efficient resolution of inherently chiral calix[4]arene **1b** could be achieved by preparative HPLC after conversion into the diastereomeric (1*S*)-camphorsulfonyl esters **17a** and **17b** (Scheme 6). Thus, treatment of racemic calix[4]arene **1b** with (1*S*)-10-camphorsulfonyl chloride in the presence of NaH gave

SCHEME 6. Optical Resolution of Inherently Chiral Calix[4]arene 1b



a ∼1:1 mixture of the diastereomers **17a** and **17b**. The diastereomeric mixture (200 mg) of **17a** and **17b** was loaded onto the preparative HPLC column, and diastereomerically pure **17a** (∼65 mg) and **17b** (∼35 mg) were obtained.

In the ^{1}H NMR spectra of diastereomers **17a** and **17b** (Figure S1, Suporting Information), there was a significant difference in the chemical shift of the protons next to the sulfonyl group. The protons of SO_2CH_2 in the camphorsulfonyl moieties showed a set of two doublets for **17a** (3.66, 2.94 ppm) and **17b** (3.61, 3.03 ppm). Comparison of the spectra for the diastereomerically pure **17a** and **17b** and their mixture clearly indicates that perfect separation of the diastereomers **17a** and **17b** was achieved by using preparative HPLC. The diastereomeric purity of **17a** and **17b** was also confirmed with HPLC analyses (Figure 2).

Finally, hydrolysis of **17a** and **17b** with NaOH for removal of the camphorsulfonyl group afforded the optically pure calix[4]arenes (+)-**1b** and (−)-**1b**, respectively (Scheme 6). The optical rotations for (+)-**1b** and (−)-**1b** showed similar values with opposite signs, and the circular dichroism (CD) spectra of the enantiomers of **1b** showed mirror images (Figure 3), which proved they were indeed a pair of enantiomers. This is the first example of the separation of enantiomers of an inherently chiral calix[4]arene with an ABCD substitution pattern at the wide rim.

Asymmetric Michael Addition Reactions Catalyzed by an Inherently Chiral Calix[4]arene 1b. Previously, we have reported that the use of a wide rim ABCC-type chiral calix[4]arene **1a**[18] as an organocatalyst efficiently promoted the Michael addition reaction of thiophenol with low enantioselectivity (15% ee, Scheme 7).[8] Although the observed enantioselectivity of the product was low, it was noteworthy that, for the

(17) The target calix[4]arene (±)-**1b** was prepared from **2** in 12 steps and 14% overall yield.

(18) The signs of (−)-**1a** were assigned from the CD spectrum at λ_{max} (295 nm). For the CD spectrum of (−)-**1a**, see ref 8.

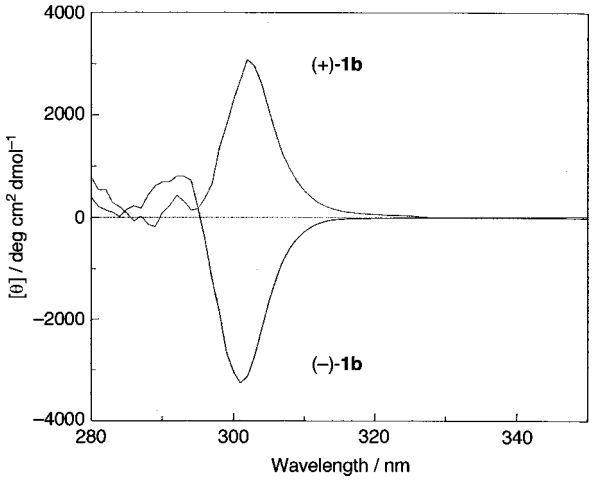
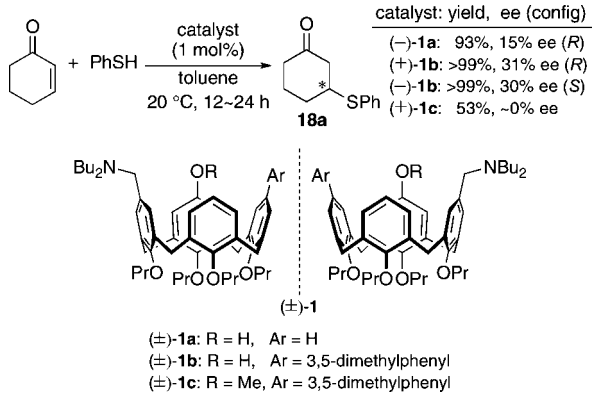


FIGURE 3. CD spectra of enantiomers of an inherently chiral calix[4]arene **1b** in $CHCl_3$.

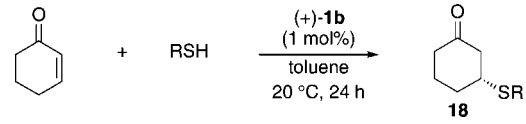
SCHEME 7. Effect of Catalyst Structure in the Michael Addition Reaction



first time, an inherently chiral calixarene with no chiral residue was successfully used in asymmetric catalysis. For the improvement of enantioselectivity, we employed an ABCD-type chiral calix[4]arene **1b** containing a 3,5-dimethylphenyl group at the wide rim for a Michael addition reaction of thiophenol. Pleasingly, a positive effect of the additional 3,5-dimethylphenyl group was observed and the product **18a** was obtained in 31% ee with excellent yield (Scheme 7). In addition, the chiral calix[4]arene **1c**,[19] which is masked with a methyl group on the hydroxy group, was tested as a catalyst in the reaction. The catalyst **1c** promoted the Michael addition reaction moderately with almost no enantioselectivity. These results clearly indicate that both the amino and hydroxy groups of catalyst **1b** are important for both reactivity and selectivity in the Michael addition reaction of thiophenols. Although the details of the mechanism of the asymmetric Michael addition reaction are not yet clear, it is expected that the amino group of catalyst **1b** activates thiophenol and forms the ammonium thiolate complex, and that the hydroxy group of catalyst **1b** activates cyclohexenone via a hydrogen bond between the carbonyl group of the substrate and the hydroxy group of the catalyst.[10] Moreover, the 3,5-dimethylphenyl group of catalyst **1b** may selectively block the one of the enantio-face of cyclohexenone, and the thiolate anion attacks to the cyclohexenone from the opposite face. So, this hypothesis indicates the direction that design of more efficient inherently chiral calixarene catalysts should take.

(19) The signs of (+)-**1c** were assigned from the CD spectrum at λ_{max} (300 nm). For the CD spectrum of (+)-**1c**, see the Supporting Information, Figure S2.

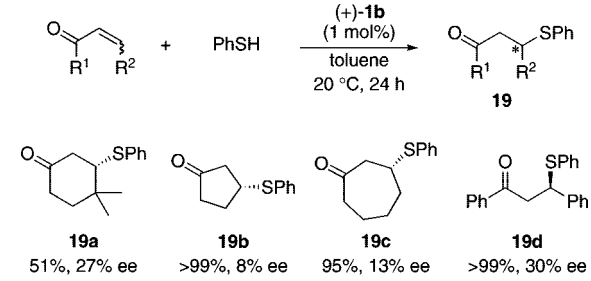
TABLE 1. Catalytic Asymmetric Michael Addition Reactions of 2-Cyclohexen-1-one Catalyzed by (+)-1b



entry	R	% yield[a]	% ee[b] (config)[c]
1	Ph	>99(**18a**)	31(*R*)
2	2-naphthyl	97(**18b**)	22(*R*)
3	4-*t*-BuC_6H_4	97(**18c**)	25(*R*)
4	4-MeOC_6H_4	96(**18d**)	24(*R*)
5	4-ClC_6H_4	>99(**18e**)	16(*R*)
6	$PhCH_2$	18 (**18f**)	~0

[a] Isolated yield. [b] Determined by HPLC. [c] Determined by comparison with the literature values of optical rotations.[10]

SCHEME 8. Catalytic Asymmetric Michael Addition Reactions of Thiophenol Catalyzed by (+)-1b



The results of the Michael addition reactions of 2-cyclohexen-1-one catalyzed by calix[4]arene (+)-**1b** are summarized in Table 1. Various substituted thiophenols could be applied to the reaction system, to give the product in excellent yields with low to moderate enantioselectivities (entry 1−5). When alkyl thiols, such as benzyl mercaptan, were used, the product was obtained in low yield with low enantioselectivity (entry 6).

Furthermore, this reaction system could be applied to other cyclic and acyclic enones (Scheme 8). Substituted cyclohexenone gave the product **19a** with a degree of enantioselectivity comparable to that observed for the reaction of 2-cyclohexen-1-one. Other cyclic enones with different ring sizes gave the products **19b** and **19c** in lower enantioselectivities. The reaction of chalcone, which is an acyclic enone, afforded the product **19d** in excellent yield with moderate enantioselectivity.

Conclusions

In the present study, we developed an efficient synthetic route to new inherently chiral calix[4]arenes with an ABCD substitution pattern at the wide rim in the cone conformation. The synthetic method shows potential for the synthesis of inherently chiral ABCD-type calix[4]arenes. For instance, the inherently chiral calix[4]arene **1b** containing both a 3,5-dimethylphenyl group and an aminophenol structure was synthesized and resolved into optically pure enantiomers. The effect of the 3,5-dimethylphenyl group of **1b** in the asymmetric Michael addition reactions was examined, and a positive effect on enantioselectivity was observed. The asymmetric induction observed for the Michael addition reaction was still moderate. However, we believe that this result indicates the direction that the design of more efficient inherently chiral calixarene catalysts should take.

Experimental Section

25,26-Dibenzyloxy-27-hydroxy-28-propoxycalix[4]arene [(±)-3]. To a mixture of 25,26-dibenzyloxy-27,28-dihydroxycalix-[4]arene[12] (20 mmol) and Na_2CO_3 (600 mmol) in DMF (150 mL) was added *n*-propyl bromide (300 mmol), and the mixture was heated at 80 °C for 15 h. The reaction mixture was cooled to room temperature, and was then quenched with water. After the removal of solvents by distillation, the organic materials were dissolved in $CHCl_3$ (150 mL). The organic solution was washed with H_2O, and dried over $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/hexane = 3/2 as eluent) afforded **3** in 87% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.38 (m, 10H), 7.04−7.13 (m, 4H), 6.91 (t, J = 7.4 Hz, 1H), 6.75 (t, J = 7.4 Hz, 1H), 6.36−6.49 (m, 6H), 5.46 (s, 1H), 5.13 (d, J = 11.9 Hz, 1H), 5.09 (d, J = 11.9 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.68 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 13.8 Hz, 1H), 4.35 (d, J = 13.7 Hz, 1H), 4.30 (d, J = 13.1 Hz, 1H), 4.08 (d, J = 13.1 Hz, 1H), 3.63−3.72 (m, 2H), 3.32 (d, J = 13.7 Hz, 1H), 3.16 (d, J = 13.2 Hz, 1H), 3.12 (d, J = 13.7 Hz, 1H), 2.94 (d, J = 13.2 Hz, 1H), 1.64−1.84 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 154.2, 153.9, 153.4, 137.6, 137.4, 136.9, 133.6, 133.5, 133.1, 132.7, 131.0, 130.6, 130.2, 129.1, 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.91, 127.85, 127.60, 127.59, 123.3, 123.1, 119.2, 77.6, 77.4, 75.8, 31.2, 31.1, 31.0, 23.1, 10.6 ppm; IR 3526, 3063, 3030, 2963, 2920, 2874, 1459, 1249, 1200, 1089, 967, 762, 700 cm^{-1}. Anal. Calcd for $C_{45}H_{42}O_4$: C, 83.56; H, 6.54. Found: C, 83.18; H, 6.66.

25,26-Dibenzyloxy-5-bromo-28-hydroxy-27-propoxycalix[4]-arene [(±)-4]. To a solution of **3** (12 mmol) in 2-butanone (180 mL) was added *N*-bromosuccinimide (12.6 mmol), and the yellow solution was stirred at room temperature for 24 h. After evaporation of the solvent, trituration of the solid residue with MeOH gave **4** in 95% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.38 (m, 12H), 7.12 (dd, J = 1.5, 7.4 Hz, 1H), 7.06 (dd, J = 1.5, 7.5 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.44−6.50 (m, 6H), 5.59 (s, 1H), 5.11 (d, J = 11.8 Hz, 1H), 5.07 (d, J = 11.8 Hz, 1H), 4.68 (s, 2H), 4.34 (d, J = 13.7 Hz, 1H), 4.28 (d, J = 13.0 Hz, 1H), 4.25 (d, J = 13.4 Hz, 1H), 4.07 (d, J = 13.1 Hz, 1H), 3.59−3.71 (m, 2H), 3.26 (d, J = 13.7 Hz, 1H), 3.16 (d, J = 13.2 Hz, 1H), 3.02 (d, J = 13.7 Hz, 1H), 2.95 (d, J = 13.2 Hz, 1H), 1.65−1.80 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 154.1, 153.7, 152.6, 137.5, 137.15, 137.09, 136.7, 133.7, 133.6, 132.9, 132.4, 132.2, 131.8, 130.7, 130.6, 130.1, 129.1, 128.9, 128.7, 128.36, 128.35, 128.30, 128.0, 127.9, 127.8, 127.6, 123.5, 123.2, 111.0, 77.7, 77.5, 75.8, 31.1, 30.9, 30.7, 23.0, 10.6 ppm; IR 3524, 3064, 3030, 2963, 2922, 2875, 1458, 1250, 1200, 1087, 966, 763, 699 cm^{-1}. Anal. Calcd for $C_{45}H_{41}BrO_4$: C, 74.48; H, 5.69. Found: C, 74.56; H, 5.49.

25,26-Dibenzyloxy-5-bromo-27,28-dipropoxycalix[4]arene [(±)-5]. To a mixture of **4** (15 mmol) and NaH (45 mmol, 60% dispersion in paraffin liquid) in DMF (150 mL) was added *n*-propyl bromide (45 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with 1 N HCl aq (30 mL). After the removal of solvents by distillation, the organic materials were dissolved in $CHCl_3$ (150 mL). The organic solution was washed with H_2O, and dried over $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/hexane = 1/1 as eluent) afforded **5** in 89% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.40 (m, 10H), 6.70−6.81 (m, 6H), 6.61 (t, J = 7.5 Hz, 1H), 6.45−6.48 (m, 2H), 6.36−6.41 (m, 2H), 4.93 (d, J = 11.9 Hz, 1H), 4.89 (d, J = 11.8 Hz, 1H), 4.83 (s, 2H), 4.40 (d, J = 13.5 Hz, 1H + 1H), 4.18 (d, J = 13.5 Hz, 1H), 4.16 (d, J = 13.5 Hz, 1H), 3.89−3.98 (m, 2H), 3.70−3.76 (m, 2H), 3.10 (d, J = 13.6 Hz, 1H + 1H), 2.98 (d, J = 13.5 Hz, 1H), 2.95 (d, J = 13.6 Hz, 1H), 1.78−1.95 (m, 4H), 0.97 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 155.4, 155.2, 155.0, 137.8, 137.6, 136.9, 136.7, 136.2, 135.9, 135.3, 135.1, 134.51, 134.48, 130.45, 130.38, 129.7, 129.0, 128.8, 128.3, 128.1, 127.90, 127.85, 127.81, 127.79, 127.77, 122.5, 122.4, 122.1, 114.7, 76.7, 76.6, 76.5, 76.1, 31.11, 31.08, 30.9, 23.21, 23.16, 10.4, 10.1 ppm; IR 3060, 3032, 2963, 2874, 1457, 1248, 1209, 1193, 1084, 1005, 974, 766, 756, 698 cm^{-1}. Anal. Calcd for $C_{48}H_{47}BrO_4$: C, 75.09; H, 6.17. Found: C, 74.79; H, 6.07.

25,26-Dibenzyloxy-5-(3,5-dimethylphenyl)-27,28-di-propoxycalix[4]arene [(±)-6]. To a solution of **5** (10 mmol) in THF (70 mL) was added *n*-BuLi (13 mmol, 1.5 M in hexane) at −78 °C under argon atmosphere, and the mixture was stirred for 30 min at this temperature. $B(OMe)_3$ (20 mmol) was then added, and the mixture was stirred for 1 h at −78 °C. The mixture was then warmed to room temperature and stirred for an additional 1 h. The reaction was quenched with 1 N HCl aq (30 mL). After removal of THF by evaporation, the organic materials were extracted with $CHCl_3$ (2 × 50 mL). The organic solution was washed with water and dried over $MgSO_4$. The solvent was evaporated to obtain the crude boronic acid derivative. To a mixture of the crude boronic acid, 1-iodo-3,5-dimethylbenzene (20 mmol), and $Pd(PPh_3)_4$ (0.40 mmol) in benzene (150 mL) was added 2 M Na_2CO_3 aq (50 mL). The reaction mixture was refluxed for 20 h under argon atmosphere. After completion of the reaction, the reaction mixture was extracted with $CHCl_3$ (2 × 50 mL). The organic solution was washed with water and dried over $MgSO_4$. Evaporation of solvents and purification of the residue by silica gel column chromatography ($CHCl_3$/hexane = 2/3 as eluent) afforded **6** in 83% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.34 (m, 10H), 6.88−6.90 (m, 3H), 6.76−6.78 (m, 2H), 6.50−6.67 (m, 8H), 6.41 (t, J = 7.5 Hz, 1H), 4.87−4.91 (m, 4H), 4.49 (d, J = 13.4 Hz, 1H), 4.37 (d, J = 13.4 Hz, 1H), 4.36 (d, J = 13.4 Hz, 1H), 4.15 (d, J = 13.4 Hz, 1H), 3.85−3.91 (m, 4H), 3.20 (d, J = 13.5 Hz, 1H), 3.10 (d, J = 13.6 Hz, 1H), 3.06 (d, J = 13.6 Hz, 1H), 2.94 (d, J = 13.5 Hz, 1H), 2.33 (s, 6H), 1.88−1.97 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 156.1, 155.3, 141.6, 137.90, 137.87, 137.7, 135.4, 135.28, 135.26, 135.23, 135.10, 135.08, 135.07, 135.05, 129.5, 129.4, 128.32, 128.26, 128.22, 128.1, 127.95, 127.94, 127.86, 127.75, 127.03, 127.00, 125.0, 122.3, 122.0, 76.7, 76.6, 76.4, 31.25, 31.22, 31.14, 31.12, 23.33, 23.28, 21.4, 10.34, 10.31 ppm; IR 3062, 3036, 2962, 2916, 2874, 1458, 1213, 1192, 1005, 968, 759, 698 cm^{-1}. Anal. Calcd for $C_{56}H_{56}O_4$: C, 84.81; H, 7.12. Found: C, 84.52; H, 7.02.

5-(3,5-Dimethylphenyl)-25,26-dihydroxy-27,28-dipropoxy-calix[4]arene [(±)-7]. To a solution of **6** (10 mmol) in $CHCl_3$ (80 mL) was added dropwise trimethylsilyl iodide (23 mmol) under argon atmosphere. The mixture was stirred for 48 h at 45 °C and then the reaction was quenched with water (20 mL). The organic materials were extracted with $CHCl_3$ (2 × 50 mL). The combined organic solution was washed with 2 M Na_2SO_3 aq and water. The solution was dried over $MgSO_4$, and the solvent was evaporated. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$/hexane = 3/2 as eluent) to obtain (±)-**7** in 81% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.92 (s, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.17 (d, J = 2.2 Hz, 1H), 7.08 (dd, J = 1.5, 7.6 Hz, 1H), 6.91−7.03 (m, 8H), 6.77 (t, J = 7.6 Hz, 1H), 6.63 (t, J = 7.5 Hz, 1H), 6.62 (t, J = 7.5 Hz, 1H), 4.58 (d, J = 12.4 Hz, 1H), 4.38 (d, J = 12.4 Hz, 1H), 4.36 (d, J = 13.4 Hz, 1H), 4.35 (d, J = 12.4 Hz, 1H), 4.04−4.18 (m, 2H), 3.86−3.97 (m, 2H), 3.46 (d, J = 12.8 Hz, 1H + 1H), 3.39 (d, J = 12.8 Hz, 1H), 3.36 (d, J = 13.4 Hz, 1H), 2.32 (s, 6H), 2.08−2.21 (m, 4H), 1.17 (t, J = 7.4 Hz, 3H + 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 153.0, 151.6, 151.1, 141.0, 138.1, 138.0, 135.2, 134.45, 134.37, 134.2, 129.6, 129.40, 129.37, 129.33, 129.1, 128.9, 128.8, 128.7, 128.3, 128.14, 128.08, 127.9, 125.1, 124.8, 120.9, 120.5, 78.5, 78.4, 32.4, 31.96, 31.93, 30.3, 23.5, 23.4, 21.5, 10.5, 10.4 ppm; IR 3322, 3024, 2965, 2931, 2876, 1465, 1387, 1219, 1096, 988, 846, 753 cm^{-1}. Anal. Calcd for $C_{42}H_{44}O_4$: C, 82.32; H, 7.24. Found: C, 82.20; H, 7.18.

5,11-Dibromo-17-(3,5-dimethylphenyl)-27,28-dihydroxy-25,26-dipropoxycalix[4]arene [(±)-8]. To a solution of **7** (7.5 mmol) in

$CHCl_3$ (300 mL) was added dropwise a solution of Br_2 (15 mmol) in $CHCl_3$ (50 mL) at −20 °C. After complete addition of the Br_2 solution, the reaction was quenched with sat. Na_2SO_3 aq (20 mL). The organic materials were extracted with $CHCl_3$ (2 × 50 mL). The organic solution was washed with H_2O and dried over $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($CHCl_3$/hexane = 2/3 as eluent) afforded **8** in 90% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.81 (s, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.12−7.16 (m, 4H), 7.06−7.08 (m, 2H), 7.02 (s, 2H), 6.94−6.99 (m, 2H), 6.83 (t, J = 7.6 Hz, 1H), 4.54 (d, J = 12.4 Hz, 1H), 4.32 (d, J = 13.5 Hz, 1H), 4.31 (d, J = 12.9 Hz, 1H), 4.28 (d, J = 13.2 Hz, 1H), 4.04−4.18 (m, 2H), 3.86−3.95 (m, 2H), 3.48 (d, J = 12.5 Hz, 1H), 3.42 (d, J = 13.2 Hz, 1H), 3.36 (d, J = 13.0 Hz, 1H), 3.23 (d, J = 13.5 Hz, 1H), 2.35 (s, 6H), 2.07−2.19 (m, 4H), 1.16 (t, J = 7.4 Hz, 3H + 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.6, 150.8, 150.3, 140.6, 138.4, 138.1, 135.0, 134.4, 133.3, 133.1, 131.6, 131.4, 131.3, 131.1, 130.83, 130.75, 130.69, 130.4, 129.3, 129.1, 128.8, 128.2, 128.0, 125.1, 125.0, 112.4, 112.0, 78.54, 78.47, 32.1, 31.7, 31.3, 30.1, 23.3, 23.2, 21.4, 10.35, 10.25 ppm; IR 3312, 2977, 2931, 2876, 1476, 1387, 1266, 1219, 989, 847 cm^{-1}. Anal. Calcd for $C_{42}H_{42}Br_2O_4 \cdot 0.4CHCl_3$: C, 62.26; H, 5.18. Found: C, 62.20; H, 5.11.

5,11-Dibromo-17-(3,5-dimethylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene [(±)-9]. To a mixture of **8** (7.0 mmol) and NaH (105 mmol, 60% dispersion in paraffin liquid) in DMF (150 mL) was added *n*-propyl iodide (105 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 24 h. The reaction was quenched with 1 N HCl aq (30 mL). After the removal of solvents by distillation, the organic materials were dissolved in $CHCl_3$ (300 mL). The organic solution was washed with H_2O and dried over $MgSO_4$. Evaporation of solvents and purification of the residue with silica gel column chromatography ($CHCl_3$/hexane = 2/5 as eluent) afforded **9** in 69% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 2.1 Hz, 1H), 7.17 (s, 2H), 7.15 (d, J = 2.1 Hz, 1H), 7.10 (d, J = 2.3 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 6.95 (s, 1H), 6.57 (t, J = 7.6 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 6.34−6.36 (m, 2H), 6.29 (d, J = 7.5 Hz, 1H), 4.48 (d, J = 13.4 Hz, 1H), 4.42 (d, J = 13.5 Hz, 1H + 1H), 4.36 (d, J = 13.5 Hz, 1H), 3.86−4.01 (m, 4H), 3.67−3.79 (m, 4H), 3.23 (d, J = 13.5 Hz, 1H), 3.16 (d, J = 12.7 Hz, 1H), 3.12 (d, J = 12.9 Hz, 1H), 3.05 (d, J = 13.6 Hz, 1H), 2.39 (s, 6H), 1.83−1.97 (m, 8H), 1.07 (t, J = 7.3 Hz, 3H), 1.06 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 156.7, 155.5, 154.8, 141.0, 138.7, 138.0, 137.7, 136.5, 136.3, 135.5, 135.4, 135.2, 133.8, 132.9, 131.6, 130.9, 130.7, 130.2, 128.3, 128.0, 127.8, 127.5, 127.2, 125.0, 122.5, 115.1, 114.4, 77.0, 76.8, 76.72, 76.68, 31.2, 31.1, 30.9, 30.7, 23.4, 23.3, 23.1, 23.0, 21.5, 10.7, 10.6, 10.0, 9.9 ppm; IR 2963, 2935, 2875, 1457, 1196, 1004, 965, 847 cm^{-1}. Anal. Calcd for $C_{48}H_{54}Br_2O_4$: C, 67.45; H, 6.37. Found: C, 67.28; H, 6.36.

11-Bromo-5-(3,5-dimethylphenyl)-17-formyl-25,26,27,28-tetrapropoxycalix[4]arene [(±)-10]. To a solution of **9** (5.0 mmol) in THF (70 mL) was added *n*-BuLi (5.5 mmol, 1.5 M in hexane) at −78 °C under argon atmosphere and the mixture was stirred for 20 min at this temperature. Dry *N*,*N*-dimethylformamide (7.5 mmol) was then added, and the mixture was stirred for 15 min at −78 °C. The reaction was quenched with 0.2 N HCl aq (40 mL). After removal of THF by evaporation, the organic materials were extracted with $CHCl_3$ (2 × 50 mL). The organic solution was washed with water and dried over $MgSO_4$. Evaporation of solvents and purification of the residue with silica gel column chromatography ($CHCl_3$/hexane = 1/2 to 2/1 as eluent) afforded **10** in 79% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.11−7.13 (m, 3H), 6.96 (s, 1H), 6.57 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 2.3 Hz, 1H), 6.36 (d, J = 6.9 Hz, 1H), 6.33 (d, J = 2.2 Hz, 1H), 6.26 (d, J = 7.4 Hz, 1H), 4.51 (d, J = 13.6 Hz, 1H), 4.48 (d, J = 13.9 Hz, 1H), 4.45 (d, J = 14.0 Hz, 1H), 4.43 (d, J = 13.5 Hz, 1H), 3.69−4.12 (m, 8H), 3.29 (d, J = 13.7 Hz, 1H), 3.24 (d, J = 12.9 Hz, 1H), 3.21 (d, J = 13.2 Hz, 1H), 3.16 (d, J = 13.7 Hz, 1H), 2.39 (s, 6H), 1.85−1.97 (m, 8H), 1.08 (t, J = 7.4 Hz, 3H), 1.07 (t, J = 7.4 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H + 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 163.4, 156.9, 155.5, 154.8, 140.8, 138.1, 137.4, 136.5, 136.4, 135.5, 135.2, 135.1, 133.9, 132.7, 130.9, 130.8, 130.21, 130.17, 128.3, 128.1, 127.6, 127.5, 127.1, 124.8, 122.6, 115.1, 77.0, 76.91, 76.85, 76.7, 31.1, 30.99, 30.97, 30.8, 23.4, 23.3, 23.2, 23.1, 21.4, 10.63, 10.56, 9.96, 9.94 ppm; IR 2962, 2923, 2874, 1691, 1458, 1196, 1126, 1003, 964 cm^{-1}. Anal. Calcd for $C_{49}H_{55}BrO_5$: C, 73.21; H, 6.90. Found: C, 73.30; H, 6.37.[20]

5-Bromo-11-(3,5-dimethylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene [(±)-11]. To a solution of **9** (0.50 mmol) in THF (10 mL) was added *n*-BuLi (0.55 mmol, 1.5 M in hexane) at −78 °C under argon atmosphere, and the mixture was stirred for 20 min at this temperature. The reaction was quenched with 0.2 N HCl aq (10 mL). After removal of THF by evaporation, organic materials were extracted with $CHCl_3$ (2 × 10 mL). The organic solution was washed with water and dried over $MgSO_4$. Evaporation of solvents and purification of the residue with silica gel column chromatography ($CHCl_3$/hexane = 1/10 to 1/3 as eluent) afforded **11** in 77% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H), 7.02 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 6.94 (s, 1H), 6.80 (d, J = 7.4 Hz, 1H), 6.75 (d, J = 6.3 Hz, 1H), 6.58−6.64 (m, 2H), 6.54 (d, J = 2.3 Hz, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.46 (d, J = 7.4 Hz, 1H), 6.41 (d, J = 7.0 Hz, 1H), 4.48 (d, J = 13.4 Hz, 1H), 4.46 (d, J = 13.4 Hz, 1H), 4.43 (d, J = 13.4 Hz, 1H), 4.40 (d, J = 13.4 Hz, 1H), 3.75−3.94 (m, 8H), 3.22 (d, J = 13.5 Hz, 1H), 3.17 (d, J = 13.5 Hz, 1H), 3.15 (d, J = 13.5 Hz, 1H), 3.10 (d, J = 13.5 Hz, 1H), 2.37 (s, 6H), 1.85−1.96 (m, 8H), 1.04 (t, J = 7.4 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 156.6, 156.0, 155.3, 141.3, 137.9, 136.8, 136.7, 136.1, 136.0, 135.1, 134.9, 134.3, 134.2, 130.5, 130.4, 128.7, 128.2, 128.1, 127.9, 127.8, 127.5, 126.9, 125.0, 122.2, 122.1, 114.7, 76.8, 76.7, 76.6, 31.1, 30.99, 30.97, 30.8, 23.3, 23.2, 23.13, 23.10, 21.4, 10.52, 10.45, 10.1 ppm; IR 2961, 2930, 2873, 1456, 1195, 1006, 965, 762 cm^{-1}. Anal. Calcd for $C_{48}H_{55}BrO_4 \cdot 0.2CHCl_3$: C, 72.41; H, 6.93. Found: C, 72.66; H, 6.97.

11-Bromo-5-(3,5-dimethylphenyl)-17-diphenylphosphino-25,26,27,28-tetrapropoxycalix[4]arene [(±)-13]. To a solution of **9** (0.50 mmol) in THF (10 mL) was added *n*-BuLi (0.55 mmol, 1.5 M in hexane) at −78 °C under argon atmosphere and the mixture was stirred for 20 min at this temperature. A solution of chlorodiphenylphosphine (1.0 mmol) in THF (3 mL) was then added to the reaction mixture, and the mixture was stirred for 0.5 h at −78 °C. The reaction mixture was then warmed to room temperature and stirred for an additional 1 h. The reaction was quenched with sat. NH_4Cl aq (10 mL). After removal of THF by evaporation, the organic materials were extracted with $CHCl_3$ (2 × 10 mL). The organic solution was washed with water and dried over $MgSO_4$. Evaporation of solvents and purification of the residueby column chromatography on silica gel ($CHCl_3$/hexane = 1/2 as eluent) afforded **13** in 79% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.40 (m, 14H), 7.09 (dd, J = 1.8, 7.9 Hz, 1H), 6.96−6.99 (m, 2H), 6.52 (t, J = 7.6 Hz, 1H), 6.26 (d, J = 2.3 Hz, 1H), 6.22 (d, J = 7.4 Hz, 1H), 6.19 (d, J = 2.3 Hz, 1H), 6.10 (d, J = 7.1 Hz, 1H), 4.48 (d, J = 13.5 Hz, 1H), 4.42 (d, J = 13.6 Hz, 1H + 1H), 4.36 (d, J = 13.4 Hz, 1H), 3.94−4.07 (m, 4H), 3.58−3.73 (m, 4H), 3.24 (d, J = 13.6 Hz, 1H), 3.15 (d, J = 13.6 Hz, 1H), 3.09 (d, J = 13.4 Hz, 1H), 3.01 (d, J = 13.5 Hz, 1H), 2.41 (s, 6H), 1.79−1.99 (m, 8H), 1.09 (t, J = 7.0 Hz, 3H), 1.07 (t, J = 7.0 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 157.4, 155.2, 154.5, 141.0, 138.2, 137.6, 137.5, 137.2, 136.7, 136.6, 136.2, 135.9, 135.5, 135.4, 135.2, 135.0, 134.5, 134.3, 133.5, 133.32, 133.26, 132.9, 130.4, 130.1, 128.6, 128.5,

(20) A formylated calix[4]arene **10** was somewhat unstable compared with other calixarenes.

128.44, 128.39, 127.8, 127.5, 127.4, 127.2, 124.9, 122.4, 115.0, 77.0, 76.8, 76.7, 76.5, 31.2, 31.1, 30.9, 30.8, 23.5, 23.4, 23.1, 23.0, 21.5, 10.8, 10.7, 9.9, 9.8 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ −6.3 (s) ppm; IR 3017, 2969, 2927, 2878, 1738, 1456, 1374, 1217 cm^{-1}. Anal. Calcd for $C_{60}H_{64}BrO_4P$: C, 75.06; H, 6.72. Found: C, 74.80; H, 6.83.

11-Bromo-5-carboxy-17-(3,5-dimethylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene [(±)-14]. To a solution of **9** (0.50 mmol) in THF (10 mL) was added *n*-BuLi (0.55 mmol, 1.5 M in hexane) at −78 °C under argon atmosphere and the mixture was stirred for 20 min at this temperature. Then, CO_2 gas was bubbled via a needle for 15 min at −78 °C. The reaction was quenched with 0.2 N HCl aq (10 mL). After removal of THF by evaporation, organic materials were extracted with $CHCl_3$ (2 × 10 mL). The organic solution was washed with water and dried over $MgSO_4$. Evaporation of solvents and purification of the residue with silica gel column chromatography ($CHCl_3$/AcOEt = 20/1 to 5/1 as eluent) afforded **14** in 72% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.22−7.24 (m, 3H), 6.96 (s, 1H), 6.53 (t, J = 7.6 Hz, 1H), 6.32 (d, J = 2.3 Hz, 1H), 6.24−6.27 (m, 2H), 6.19 (d, J = 7.5 Hz, 1H), 4.50 (d, J = 13.6 Hz, 1H), 4.49 (d, J = 13.4 Hz, 1H), 4.44 (d, J = 13.4 Hz, 1H), 4.43 (d, J = 13.4 Hz, 1H), 3.95−4.16 (m, 4H), 3.67−3.77 (m, 4H), 3.30 (d, J = 13.7 Hz, 1H), 3.25 (d, J = 13.2 Hz, 1H), 3.21 (d, J = 13.4 Hz, 1H), 3.17 (d, J = 13.7 Hz, 1H), 2.40 (s, 6H), 1.83−1.99 (m, 8H), 1.11 (t, J = 6.7 Hz, 3H), 1.09 (t, J = 6.7 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 163.1, 157.3, 155.3, 154.6, 140.8, 138.2, 137.1, 137.0, 136.2, 136.0, 135.1, 135.0, 133.4, 132.6, 131.5, 130.9, 130.6, 130.2, 128.4, 127.9, 127.8, 127.5, 127.2, 124.8, 122.7, 122.6, 115.2, 77.0, 76.9, 76.8, 76.7, 31.2, 31.0, 30.9, 23.5, 23.4, 23.2, 23.0, 21.5, 10.8, 10.7, 9.9 ppm; IR 2963, 2931, 2876, 1681, 1459, 1426, 1307, 1210, 1003, 964 cm^{-1}. Anal. Calcd for $C_{49}H_{55}BrO_6$: C, 71.78; H, 6.76. Found: C, 71.64; H, 6.60.

11-Bromo-5-(*N*-butylaminomethyl)-17-(3,5-dimethylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene [(±)-15]. To a solution of **10** (4.0 mmol) in a mixture of THF (30 mL) and EtOH (20 mL) was added *n*-butylamine (20 mmol) at room temperature, and the mixture was stirred for 12 h. $NaBH_4$ (4.0 mmol) was then added, and the mixture was stirred for 30 min. The reaction was quenched with sat. NH_4Cl aq. After removal of THF and ethanol by evaporation, the organic materials were extracted with $CHCl_3$ (2 × 50 mL). The organic solution was washed with water and dried over $MgSO_4$. Evaporation of solvents and purification of the residue with silica gel column chromatography ($CHCl_3$/MeOH = 20/1 to 10/1 as eluent) afforded **15** in 95% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 2.0 Hz, 1H), 7.17 (s, 2H), 7.15 (d, J = 2.0 Hz, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 6.87 (s, 1H), 6.53 (t, J = 7.6 Hz, 1H), 6.38 (d, J = 2.1 Hz, 1H), 6.30−6.34 (m, 2H), 6.26 (d, J = 7.4 Hz, 1H), 4.48 (d, J = 13.4 Hz, 1H), 4.44 (d, J = 13.4 Hz, 1H), 4.43 (d, J = 13.4 Hz, 1H), 4.38 (d, J = 13.4 Hz, 1H), 3.86−4.02 (m, 4H), 3.69−3.76 (m, 4H), 3.61 (s, 2H), 3.23 (d, J = 13.5 Hz, 1H), 3.15 (d, J = 13.5 Hz, 1H), 3.14 (d, J = 13.5 Hz, 1H), 3.08 (d, J = 13.5 Hz, 1H), 2.58 (t, J = 7.3 Hz, 2H), 2.39 (s, 6H), 1.83−1.98 (m, 8H), 1.46−1.54 (m, 2H), 1.31−1.40 (m, 2H), 1.08 (t, J = 7.3 Hz, 3H), 1.06 (t, J = 7.3 Hz, 3H), 0.88−0.94 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 156.5, 155.5, 154.8, 140.9, 138.0, 136.7, 136.4, 136.2, 136.1, 135.7, 135.4, 134.8, 133.7, 133.6, 133.4, 130.3, 130.2, 128.9, 128.3, 127.59, 127.56, 127.0, 124.8, 122.3, 114.8, 76.9, 76.7, 76.6, 76.5, 53.6, 48.9, 32.0, 31.1, 31.0, 30.9, 30.8, 23.4, 23.3, 23.03, 23.00, 21.5, 20.5, 14.0, 10.7, 10.6, 9.9 ppm; IR 3424, 2960, 2926, 2873, 1456, 1221, 1195, 1006, 965 cm^{-1}. Anal. Calcd for $C_{53}H_{66}BrNO_4 \cdot H_2O$: C, 72.42; H, 7.80; N, 1.59. Found: C, 72.68; H, 7.73; N, 1.64.

11-Bromo-5-(*N*,*N*-dibutylaminomethyl)-17-(3,5-dimethylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene [(±)-16]. To a mixture of **15** (4.0 mmol) and K_2CO_3 (8.0 mmol) in CH_3CN (80 mL) was added *n*-butyl bromide (12 mmol), and the mixture was refluxed for 12 h. The reaction mixture was cooled to room temperature and was then quenched with water. After the removal of CH_3CN by evaporation, the organic materials were extracted with $CHCl_3$ (2 × 50 mL), and the organic solution was dried over $MgSO_4$. Evaporation of solvents and purification of the residue from column chromatography on silica gel ($CHCl_3$/AcOEt = 20/1 to 10/1 as eluent) afforded **16** in 89% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.27 (m, 4H), 7.00 (s, 1H), 6.96 (s, 1H), 6.94 (s, 1H), 6.49 (dt, J = 2.5, 7.6 Hz, 1H), 6.18−6.30 (m, 4H), 4.49 (d, J = 13.4 Hz, 1H), 4.44 (d, J = 13.4 Hz, 1H), 4.43 (d, J = 13.4 Hz, 1H), 4.38 (d, J = 13.4 Hz, 1H), 3.88−4.05 (m, 4H), 3.66−3.74 (m, 4H), 3.44 (s, 2H), 3.23 (d, J = 13.5 Hz, 1H), 3.16 (d, J = 13.4 Hz, 1H), 3.14 (d, J = 13.5 Hz, 1H), 3.08 (d, J = 13.4 Hz, 1H), 2.43 (t, J = 7.5 Hz, 4H), 2.40 (s, 6H), 1.82−1.98 (m, 8H), 1.43−1.49 (m, 4H), 1.26−1.36 (m, 4H), 1.05−1.11 (m, 6H), 0.87−0.93 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 156.6, 155.3, 154.6, 140.9, 138.1, 137.0, 136.3, 136.1, 135.94, 135.85, 135.3, 134.7, 133.5, 133.3, 130.3, 130.1, 129.9, 129.3, 128.3, 127.6, 127.4, 127.0, 124.8, 122.3, 114.9, 76.9, 76.7, 76.54, 76.53, 58.1, 53.5, 31.2, 31.0, 30.9, 30.8, 29.0, 23.5, 23.3, 23.0, 21.4, 20.7, 14.1, 10.75, 10.67, 9.90, 9.86 ppm; IR 2958, 2930, 2872, 1456, 1220, 1195, 1006, 965 cm^{-1}. Anal. Calcd for $C_{57}H_{74}BrNO_4 \cdot H_2O$: C, 73.21; H, 8.19; N, 1.50. Found: C, 73.58; H, 8.08; N, 1.35.

5-(*N*,*N*-Dibutylaminomethyl)-17-(3,5-dimethylphenyl)-11-hydroxy-25,26,27,28-tetrapropoxycalix[4]arene [(±)-1b]. To a solution of **16** (3.0 mmol) in THF (60 mL) was added *sec*-BuLi (4.5 mmol, 1.0 M in hexane) at −78 °C under argon atmosphere, and the mixture was stirred for 45 min at this temperature. $B(OMe)_3$ (6.6 mmol) was then added, and the mixture was stirred for 30 min at −78 °C. To the resulting reaction mixture was added 30% H_2O_2 aq (10 mL) and 3 N NaOH aq (10 mL), then the mixture was warmed to room temperature. After being stirred for 1 h at room temperature, the reaction was quenched with 0.5 M $Na_2S_2O_3$ aq (70 mL) and the mixture was stirred for 30 min. After removal of THF by evaporation, organic materials were extracted with $CHCl_3$ (2 × 50 mL). The organic solution was washed with 0.1 N HCl aq and sat. $NaHCO_3$ aq. The solution was dried over $MgSO_4$, and the solvent was evaporated. The resulting residue was purified by using silica gel column chromatography ($CHCl_3$/AcOEt = 3/1 to 1/2 as eluent) to obtain (±)-**1b** in 69% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.21 (m, 4H, Ar-*H*), 6.89−6.94 (m, 3H, Ar-*H*), 6.40 (t, J = 7.5 Hz, 1H, Ar-*H*), 6.25−6.33 (m, 2H, Ar-*H*), 5.73−5.75 (m, 2H, Ar-*H*), 4.49 (d, J = 13.3 Hz, 1H, ArCH_2Ar), 4.45 (d, J = 13.2 Hz, 1H, ArCH_2Ar), 4.43 (d, J = 13.3 Hz, 1H, ArCH_2Ar), 4.38 (d, J = 13.2 Hz, 1H, ArCH_2Ar), 3.92−3.99 (m, 4H, OCH_2CH$_2$), 3.65−3.76 (m, 4H, OCH_2CH$_2$), 3.41 (s, 2H, ArCH_2N), 3.21 (d, J = 13.4 Hz, 1H, ArCH_2Ar), 3.13 (d, J = 13.4 Hz, 1H, ArCH_2Ar), 3.12 (d, J = 13.4 Hz, 1H, ArCH_2Ar), 3.05 (d, J = 13.4 Hz, 1H, ArCH_2Ar), 2.38 (s, 6H, ArCH_3), 2.35−2.42 (m, 4H, NCH_2CH$_2$), 1.84−1.99 (m, 8H, OCH$_2$CH_2CH$_3$), 1.41−1.48 (m, 4H, NCH$_2$CH_2CH$_2$), 1.23−1.32 (m, 4H, NCH$_2$CH$_2$CH_2CH$_3$), 1.04−1.10 (m, 6H, NCH$_2$CH$_2$CH$_2$CH_3), 0.87−0.93 (m, 12H, OCH$_2$CH$_2$CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 156.7, 155.6, 150.2, 149.5, 141.0, 138.0, 136.6, 136.4, 136.0, 135.9, 134.7, 134.54, 134.49, 133.8, 133.7, 129.7, 129.6, 128.2, 127.7, 127.5, 127.2, 127.1, 124.8, 121.8, 114.3, 114.2, 76.9, 76.8, 76.6, 76.5, 57.9, 53.2, 31.2, 31.1, 31.0, 30.9, 28.5, 23.42, 23.37, 23.04, 23.02, 21.5, 20.7, 14.1, 10.71, 10.69, 10.0, 9.9 ppm; IR 3399, 2959, 2930, 2872, 1463, 1217, 1008 cm^{-1}. Anal. Calcd for $C_{57}H_{75}NO_5 \cdot H_2O$: C, 78.49; H, 8.90; N, 1.61. Found: C, 78.58; H, 8.91; N, 1.42.

Diastereomers 17a and 17b. To a mixture of (±)-**1b** (1.5 mmol) and NaH (4.5 mmol, 60% dispersion in paraffin liquid) in a mixture of THF (20 mL) and DMF (2 mL) was added (1*S*)-10-camphorsulfonyl chloride (4.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h. The reaction was quenched with sat. NH_4Cl aq (20 mL). After the removal of solvents by evaporation, the organic materials were extracted with $CHCl_3$ (2 × 20 mL) and the organic solution was dried over $MgSO_4$. Evaporation of solvents and purification of the residue by using

silica gel column chromatography ($CHCl_3$/AcOEt = 5/1 to 1/1 as eluent) afforded a ~1:1 mixture of diastereomers **17a** and **17b** in 95% yield.

Resolution of Calix[4]arenes 17a and 17b. Resolution of diastereomers **17a** and **17b** was carried out by preparative HPLC, using a SUMICHIRAL OA-2000 column (2.0 cm × 25 cm) with $CHCl_3$ as the eluent. The diastereomeric mixture of **17a** and **17b** (~1:1) (200 mg) was loaded onto the preparative column. The $CHCl_3$ solutions of the separated diastereomers were washed with sat. $NaHCO_3$ aq and pure calix[4]arenes **17a** (first fraction) (~65 mg) and **17b** (second fraction) (~35 mg) were obtained, respectively. The diastereomeric purity of the calix[4]arene **17a** and **17b** was determined with HPLC.

17a: $[\alpha]^{28}_D$ +16.1 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.23 (m, 4H), 6.89−7.00 (m, 3H), 6.39 (t, *J* = 7.2 Hz, 1H), 6.10−6.28 (m, 4H), 4.48 (d, *J* = 13.4 Hz, 1H), 4.46 (d, *J* = 14.4 Hz, 1H), 4.43 (d, *J* = 14.1 Hz, 1H), 4.42 (d, *J* = 13.4 Hz, 1H), 3.87−4.03 (m, 4H), 3.72−3.76 (m, 4H), 3.66 (d, *J* = 15.4 Hz, 1H), 3.44−3.52 (m, 2H), 3.23 (d, *J* = 13.5 Hz, 1H), 3.21 (d, *J* = 13.5 Hz, 1H), 3.16 (d, *J* = 13.4 Hz, 1H), 3.14 (d, *J* = 13.4 Hz, 1H), 2.94 (d, *J* = 15.4 Hz, 1H), 2.39−2.49 (m, 4H), 2.38 (s, 6H), 2.22−2.30 (m, 2H), 1.85−2.01 (m, 10H), 1.42−1.65 (m, 6H), 1.23−1.35 (m, 5H), 1.06−1.10 (m, 9H), 0.85−0.94 (m, 12H), 0.82 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 157.1, 156.7, 155.4, 154.5, 143.3, 140.7, 137.9, 136.6, 136.3, 135.7, 135.4, 135.1, 134.5, 133.8, 133.4, 130.1, 129.5, 128.2, 127.6, 127.4, 127.2, 127.1, 124.7, 122.0, 121.2, 120.8, 76.9, 76.7, 76.6, 76.4, 57.9, 53.1, 47.7, 46.1, 42.5, 41.9, 31.0, 30.92, 30.89, 28.4, 26.5, 24.6, 23.35, 23.29, 23.0, 22.9, 21.4, 20.5, 20.0, 19.6, 14.0, 10.61, 10.55, 9.9 ppm; IR 2959, 2932, 2873, 1748, 1458, 1373, 1220, 1204, 1174, 1007, 982, 966 cm^{-1}. Anal. Calcd for $C_{67}H_{89}NO_8S\cdot H_2O$: C, 74.06; H, 8.44; N, 1.29. Found: C, 74.00; H, 8.23; N, 1.22.

17b: $[\alpha]^{28}_D$ +3.8 (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12−7.16 (m, 4H), 6.84−6.96 (m, 3H), 6.02−6.56 (m, 5H), 4.48 (d, *J* = 13.4 Hz, 1H), 4.47 (d, *J* = 14.5 Hz, 1H), 4.43 (d, *J* = 13.4 Hz, 1H + 1H), 3.87−3.97 (m, 4H), 3.73−3.77 (m, 4H), 3.61 (d, *J* = 15.0 Hz, 1H), 3.41−3.52 (m, 2H), 3.22 (d, *J* = 13.5 Hz, 1H), 3.20 (d, *J* = 13.3 Hz, 1H), 3.18 (d, *J* = 13.4 Hz, 1H), 3.15 (d, *J* = 13.3 Hz, 1H), 3.03 (d, *J* = 15.1 Hz, 1H), 2.37 (s, 6H), 2.33−2.53 (m, 6H), 1.86−2.08 (m, 10H), 1.23−1.58 (m, 11H), 1.04−1.08 (m, 9H), 0.89−0.95 (m, 12H), 0.85 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.1, 156.9, 155.7, 154.7, 143.4, 140.6, 138.0, 136.3, 135.9, 135.0, 134.6, 134.0, 129.8, 128.3, 127.7, 127.3, 126.8, 124.6, 122.1, 121.2, 120.8, 76.9, 76.73, 76.67, 76.58, 58.0, 53.2, 47.8, 46.8, 42.8, 42.4, 31.15, 31.12, 30.9, 29.7, 26.7, 24.9, 23.4, 23.3, 23.0, 21.4, 20.5, 20.0, 19.7, 13.9, 10.6, 10.5, 10.0 ppm; IR 2959, 2931, 2873, 1749, 1461, 1374, 1220, 1174, 1006, 966 cm^{-1}; Anal. Calcd for $C_{67}H_{89}NO_8S\cdot H_2O$: C, 74.06; H, 8.44; N, 1.29. Found: C, 74.33; H, 8.26; N, 1.52.

Hydrolysis of 17a and 17b to Obtain (+)-1b and (−)-1b. Calixarene **17a** or **17b** (0.20 mmol) in a mixture of THF (5 mL) and EtOH (5 mL) was refluxed with 3 M NaOH aq (1.5 mL) for 10 h. The reaction mixture was cooled to 0 °C, and the reaction was then quenched with 1 N HCl aq (6 mL). After the removal of solvents by evaporation, the organic materials were extracted with $CHCl_3$ (2 × 10 mL). The organic solution was washed with 0.1 N HCl aq and sat. $NaHCO_3$ aq, then dried over $MgSO_4$. Evaporation of solvents and purification of the residue with silica gel column chromatography ($CHCl_3$/AcOEt = 2/1 to 1/1 as eluent) afforded (+)-**1b** ($[\alpha]_D^{29}$ +3.6 (*c* 0.90, $CHCl_3$)) or (−)-**1b** ($[\alpha]_D^{29}$ −3.7 (*c* 1.4, $CHCl_3$)) in 95% and 92% yields, respectively.

5-(*N*,*N*-Dibutylaminomethyl)-17-(3,5-dimethylphenyl)-11-methoxy-25,26,27,28-tetrapropoxycalix[4]arene [(+)-1c]. To a mixture of (+)-**1b** (0.20 mmol) and NaH (0.60 mmol, 60% dispersion in paraffin liquid) in a mixture of THF (5 mL) and DMF (0.5 mL) was added methyl iodide (0.60 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with sat. NH_4Cl aq (5 mL). After the removal of solvents by evaporation, the organic materials were extracted with $CHCl_3$ (2 × 5 mL) and the organic solution was dried over $MgSO_4$. Evaporation of solvents and purification of the residue with silica gel column chromatography ($CHCl_3$/AcOEt = 5/1 to 2/1 as eluent) afforded the (+)-**1c**[19] in 62% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06−7.10 (m, 4H), 6.87−6.92 (m, 3H), 6.44−6.52 (m, 3H), 5.96−6.03 (m, 2H), 4.49 (d, *J* = 13.1 Hz, 1H), 4.46 (d, *J* = 13.0 Hz, 1H), 4.45 (d, *J* = 13.0 Hz, 1H), 4.42 (d, *J* = 13.4 Hz, 1H), 3.73−3.92 (m, 8H), 3.53 (s, 2H), 3.45 (s, 3H), 3.21 (d, *J* = 14.2 Hz, 1H), 3.18 (d, *J* = 14.5 Hz, 1H), 3.16 (d, *J* = 13.6 Hz, 1H), 3.13 (d, *J* = 13.6 Hz, 1H), 2.45 (t, *J* = 7.8 Hz, 4H), 2.36 (s, 6H), 1.87−1.99 (m, 8H), 1.50−1.59 (m, 4H), 1.20−1.31 (m, 4H), 1.04 (t, *J* = 7.4 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.89−0.98 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.8, 156.0, 154.0, 150.0, 140.6, 137.9, 136.0, 135.93, 135.88, 135.7, 135.0, 134.9, 134.4, 134.2, 134.1, 130.3, 128.2, 127.9, 127.7, 126.7, 126.6, 124.4, 121.9, 113.0, 112.8, 76.74, 76.69, 76.68, 56.6, 54.9, 52.1, 31.3, 31.11, 31.05, 30.8, 26.6, 23.24, 23.17, 23.08, 21.4, 20.3, 13.8, 10.44, 10.42, 10.1 ppm; IR 2959, 2932, 2873, 1604, 1463, 1210, 1059, 1007, 966 cm^{-1}. Anal. Calcd for $C_{58}H_{77}NO_5\cdot 0.4CHCl_3$: C, 76.61; H, 8.48; N, 1.53. Found: C, 76.33; H, 8.61; N, 1.64.

General Procedure for the Catalytic Asymmetric Michael Addition Reactions Catalyzed by (+)-1b. To a solution of (+)-**1b** (0.0050 mmol) and thiophenol (0.60 mmol) in toluene (1 mL) was added 2-cyclohexen-1-one (0.50 mmol) at 20 °C under argon atmosphere, and the mixture was stirred for 24 h at this temperature. The reaction was quenched with 0.2 N HCl aq (2 mL), and the organic materials were extracted with $CHCl_3$ (2 × 3 mL). The organic solution was washed with water (5 mL) and dried over $MgSO_4$. Evaporation of solvents and purification of the residue with flash chromatography on silica gel afforded a Michael addition product. The enantioselectivity of the product was determined by using chiral HPLC analysis, and the absolute configuration was determined by comparison of the observed optical rotation with the reported values.[10]

Acknowledgment. We thank Yuichi Tanaka for his assistance with this study.

Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR for calixarenes, characterization data, and HPLC chromatograms for Michael addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8024412