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Inherently Chiral Biscalix[4]arenes: Design and Syntheses

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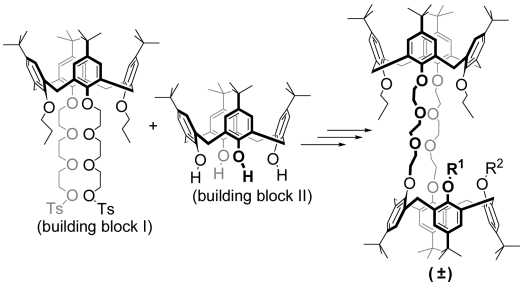

Inherently chiral biscalix[4]arenes have been designed and synthesized by covalently assembling two calix[4]arene building blocks in a 1,3-position linking with 1,2-position pattern at the lower rims via two triethylene glycol bridges

The study of chiral calixarenes is a robust and lasting development stage in calixarene chemistry, for the prospect of obtaining efficient calix-based chiral sensors and catalysts.[1−7] Generally, two strategies have been applied to endowing parent calix[4]arene with chirality. The first strategy introduces stereogenic center(s) directly onto the calix platform. In this regard, the relatively simple and most widely used method involves anchoring various chiral fragments to the calix skeleton by reacting calix[4]arene with corresponding chiral electrophiles under basic conditions.[1] A newly developed and intriguing method utilizes a direct asymmetric reaction on properly functionalized calixarene to produce chiral calix[4]arenes.[2] The second strategy creates "inherent chirality", a phenomenon that is related to the presence of molecular curvature,[3] by the asymmetric array of achiral substituent(s) onto the nonplanar 3-dimensional calix skeleton. Generating inherent chirality without using chiral reagents results in a racemic mixture of both enantiomers, which could be optically resolved through chiral HPLC[4] or by chemical resolution method[5] in some cases. Stereoselective approaches to inherently chiral calix[4]arenes have also been developed recently.[6] So far, there have been examples of inherently chiral calix[4]arenes with diversified substitution patterns (upper and/or lower rim, meta-position[5e,g,j,6c,d,7]) and conformations (cone, partial cone,[4e,5c−5e] 1,2-alternate,[8] and 1,3-alternate[9]), all of which were based on one calix platform. The versatility of calixarene provides much room for the design of calix-based hosts of more sophisticated structures and, hopefully, superior properties. Conceptually, the marriage of inherent chirality and biscalixarene gives birth to inherently chiral biscalixarene, whose merits may include (i) spacious chiral environment; (ii) possible synergistic effect of the two calix cavities, and (iii) more deployable binding sites compared with monocalix-based inherently chiral entity. Herein we report on the design and syntheses of inherently chiral biscalix[4]arenes.

The design of singly bridged inherently chiral biscalix-[4]arene seems rather straightforward. The strategy is to treat one calix unit as the parent and the other calix unit as one of the substituents which form an asymmetric array on the skeleton of the parent calixarene. However, the orientation of the two calix components may be undefined due to the free rotation along the bridging covalent single bond (eq 1). Such

(1) For representative examples, see: (a) Kubo, Y.; Maeda, S. Y.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522. (b) Zheng, Y.-S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189. (c) Sansone, F.; Baldini, L.; Casnati, A.; Chierici, E.; Faimani, G.; Ugozzol, F.; Ungaro, R. *J. Am. Chem. Soc.* **2004**, *126*, 6204. (d) Becker, T.; Goh, C. Y.; Jones, F.; Mclldowie, M. J.; Mocerino, M.; Ogden, M. I. *Chem. Commun.* **2008**, 3900. (e) Demirtas, H. N.; Bozkurt, S.; Durmaz, M.; Yilmaz, M.; Sirit, A. *Tetrahedron* **2009**, *65*, 3014.

(2) Bonini, C.; Chiummiento, L.; Funicello, M.; Lopardo, M. T.; Lupattelli, P.; Laurita, A.; Cornia, A. *J. Org. Chem.* **2008**, *73*, 4233.

(3) For review and opinion on inherently chiral calixarenes, see: (a) Vysotsky, M.; Schmidt, C.; Böhmer, V. *Adv. Supramol. Chem.* **2000**, *7*, 139. (b) Dalla Cort, A.; Mandolini, L.; Pasquini, C.; Schiaffino, L. *New J. Chem.* **2004**, *28*, 1198.

(4) (a) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, *115*, 3997 (Corrigendum: 1993, 115, 12228). (b) Ferguson, G.; Gallagher, J. F.; Giunta, L.; Neri, P.; Pappalardo, S.; Parisi, M. *J. Org. Chem.* **1994**, *59*, 42. (c) Arnaud-Neu, F.; Caccamese, S.; Fuangswasdi, S.; Pappalardo, S.; Parisi, M. F.; Petringa, A.; Principato, G. *J. Org. Chem.* **1997**, *62*, 8041. (d) Jin, T.; Monde, K. *Chem. Commun.* **1998**, 1357. (e) Hesek, D.; Inoue, Y.; Drew, M. G. B.; Beer, P. D.; Hembury, G. A.; Ishida, H.; Aoki, F. *Org. Lett.* **2000**, *2*, 2237. (f) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Eur. J. Org. Chem.* **2008**, 5957. (g) Shirakawa, S.; Shimizu, S. *Eur. J. Org. Chem.* **2009**, 1916. (h) Shirakawa, S.; Kimura, T.; Murata, S.; Shimizu, S. *J. Org. Chem.* **2009**, *74*, 1288.

(5) (a) Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, 2508. (b) Cao, Y.-D.; Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Wang, M.-X.; Huang, Z.-T. *J. Org. Chem.* **2004**, *69*, 206. (c) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2005**, *61*, 8517. (d) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Chem.—Eur. J.* **2005**, *11*, 5917. (e) Miao, R.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *J. Org. Chem.* **2005**, *70*, 7662. (f) Yakovenko, A. V.; Boyko, V. I.; Danylyuk, O.; Suwinska, K.; Lipkowski, J.; Kalchenko, V. I. *Org. Lett.* **2007**, *9*, 1183. (g) Xu, Z.-X.; Zhang, C.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2007**, *9*, 4447. (h) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117. (i) Boyko, V. I.; Yakovenko, A. V.; Matvieiev, Y. I.; Kalchenko, O. I.; Shishkin, O. V.; Kalchenko, V. I. *Tetrahedron* **2008**, *64*, 7567. (j) Xu, Z.-X.; Li, G.-K.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2008**, *64*, 8668. (k) Kliachyna, M. A.; Yesypenko, O. A.; Pirozhenko, V. V.; Shishkina, S. V.; Shishkin, O. V.; Boyko, V. I.; Kalchenko, V. I. *Tetrahedron* **2009**, *65*, 7085.

(6) (a) Browne, J. K.; McKervey, M. A.; Pitarch, M.; Russell, J. A.; Millership, J. S. *Tetrahedron Lett.* **1998**, *39*, 1787. (b) Boyko, V. I.; Shivanyuk, A.; Pyrozhenko, V. V.; Zubatyuk, R. I.; Shishkin, O. V.; Kalchenko, V. I. *Tetrahedron Lett.* **2006**, *47*, 7775. (c) Xu, Z.-X.; Zhang, C.; Yang, Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2008**, *10*, 477. (d) Herbert, S. A.; Arnott, G. E. *Org. Lett.* **2009**, *11*, 4986.

(7) (a) Reddy, P. A.; Gutsche, C. D. *J. Org. Chem.* **1993**, *58*, 3245. (b) Verboom, W.; Bodewes, P. J.; van Essen, G.; Timmerman, P.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron* **1995**, *51*, 499. (c) Ikeda, A.; Yoshimura, M.; Lhotak, P.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1945. (d) Barton, O. G.; Neumann, B.; Stammler, H.-G.; Mattay, J. *Org. Biomol. Chem.* **2008**, *6*, 104.

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

(9) Sharma, S. K.; Gutsche, C. D. *J. Org. Chem.* **1999**, *64*, 3507.

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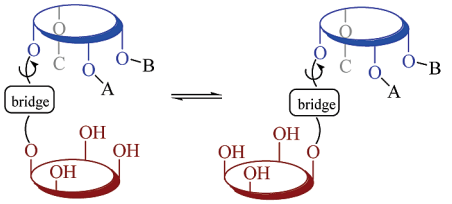
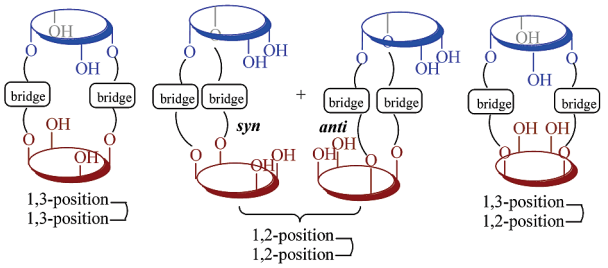
a disadvantage could be circumvented by covalently connecting two calix units with two bridges. There are three patterns to link two calix[4]arene building blocks as cone conformers via two identical bridges at the lower rims to form a doubly bridged biscalix[4]arene: (i) 1,3-position linking with 1,3-position, (ii) 1,2-position linking with 1,2-position, and (iii) 1,3-position linking with 1,2-pisition (eq 2). In the first scenario, where two bridges link the two calix units distally, it would be difficult to generate inherent chirality due to the C_{2v} symmetry plane that always exists. The second scenario, where two bridges link the two calix units proximally, may result in a mixture of *syn* and *anti* isomers. By contrast, the third scenario, where two bridges connect the two calix units distally at one rim and proximally at the other, allows both simpler products and further modification for creation of inherent chirality at the lower rims and therefore is the strategy of choice.



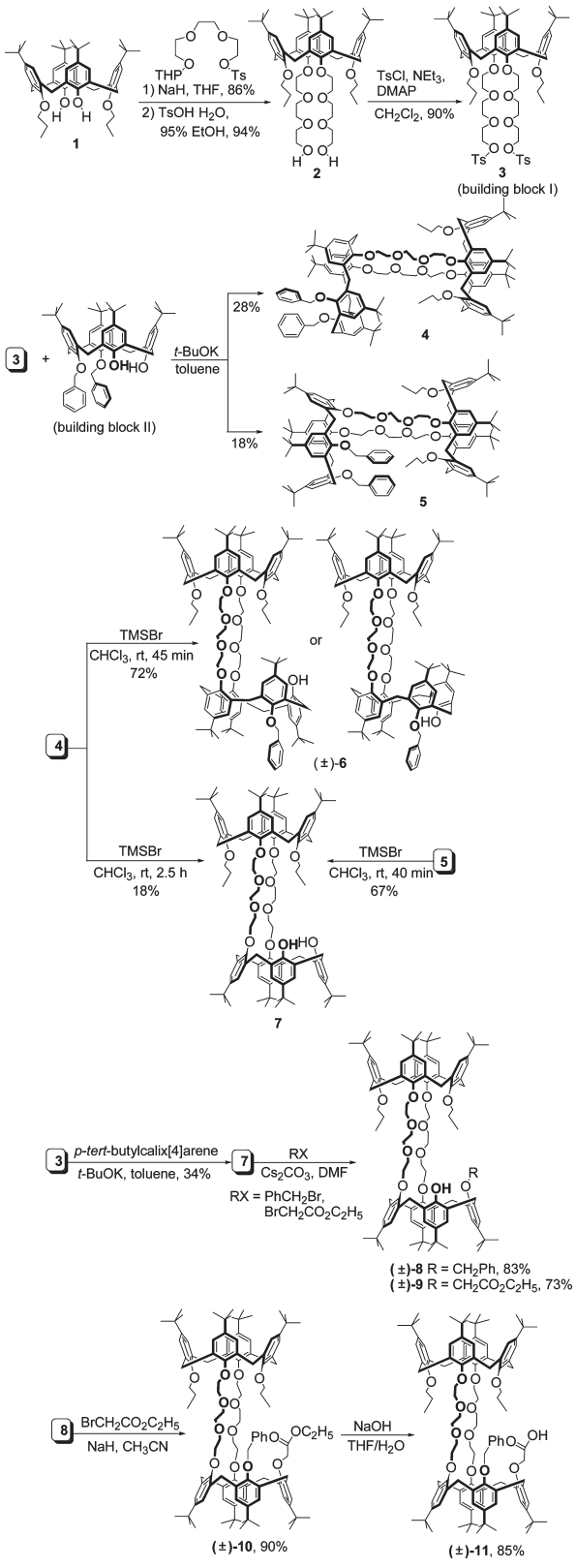
(1)



(2)

The synthetic pathway of the doubly bridged inherently chiral biscalix[4]arenes is depicted in Scheme 1. 25,27-Dipropoxy-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arene **1**[10] was treated with 1-tosyl-10-(tetrahydropyran-2-yl)-1,4,7,10-tetraoxadecane[11] in the presence of NaH to afford the tetra-*O*-alkylated intermediate, the THP protecting groups of which were subsequently removed with $TsOH \cdot H_2O$ to give the diol compound **2** in 81% yield for the two steps. Tosylation of **2** afforded **3** as building block I in 90% yield. Reacting **3** with 25,26-dibenzyloxy-27,28-dihydroxy-*p*-*tert*-butylcalix[4]arene,[12] which served as building block II, in the presence of *t*-BuOK in toluene at 70 °C furnished biscalix[4]arenes **4** and **5** as a mixture of two conformational isomers (the less polar cone−1,2-alternate conformer and the more polar cone−cone conformer) in a ratio of ca. 1.5:1. In an attempt to debenzylate **4** and **5** respectively, trimethylsilyl bromide (TMSBr) proved to be a relatively more efficient reagent compared with Pd/C-catalyzed hydrogenation or $AlCl_3$. In the case of **4**, reaction with TMSBr (2.0 equiv) in

SCHEME 1. Syntheses of Inherently Chiral Biscalix[4]arenes



$CHCl_3$ at room temperature for 45 min led to **6** as a major product in 72% yield, which was suggested by ESI-MS *m*/*z* 1723.2 [M + Na^+] as the monodebenzylated compound and therefore is an inherently chiral biscalix[4]arene. In principle,

(10) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955.
(11) Asakawa, M.; Ashton, P. R.; Balzani, V.; Boyd, S. E.; Credi, A.; Mattersteig, G.; Menzer, S.; Montalti, M.; Raymo, F. M.; Ruffilli, C.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *Eur. J. Org. Chem.* **1999**, 985.
(12) Groenen, L. C.; Ruel, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, P.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, *32*, 2675.

the free phenolic hydroxyl in **6** might pass the annulus by rotation, leading to two possible conformers (the cone−partial cone and the cone−1,2-alternate conformers as indicated in Scheme 1). However, NMR spectra ($CDCl_3$, 25 °C) suggested that a simple compound was formed as could be seen from the two sextets (1.95 and 1.82 ppm, J = 7.5 Hz) for the $ArOCH_2CH_2CH_3$ protons in the ^1H NMR spectrum as well as two sets of signals (23.50, 23.38, 10.73, and 10.58 ppm) for the $ArOCH_2CH_2CH_3$ carbons in the ^{13}C NMR spectrum. For the moment, there has been no absolute evidence for the unambiguous determination of the structure of **6**. By extension of the reaction time (2.5 h) and increase of the amounts of TMSBr (4.0 equiv), we obtained the fully debenzylated product **7** in 18% yield along with other complicated side products. By contrast, it was easier to fully debenzylate the cone−cone conformer **5**. When **5** was subjected to TMSBr (2.0 equiv) in $CHCl_3$ at room temperature for 40 min, **7** was formed in 67% yield. The structure of **7** was confirmed by its spectroscopic data (see the Experimental Section). Notably, in its ^1H NMR spectrum, the singlet appearing at 8.70 ppm corresponds to the phenolic hydroxy groups. As expected, the triplets appearing at 1.10 and 1.00 ppm correspond to the methyl protons of the two propyl groups, which is also consistent with the two groups of signals for the propyl carbons in the ^{13}C NMR spectrum.

The tedious protection−deprotection procedure and low yields prompted us to seek direct access to compound **7**, which is a useful achiral precursor for the construction of inherently chiral biscalix[4]arenes. Previous literatures[13] have adequately proven that *t*-BuOK as a base in toluene generally favors the formation of proximally substituted calixbiscrowns as a mixture of cone and 1,2-alt conformers upon treatment of either parent calix[4]arene with 2 equiv of polyethylene glycol ditosylates or calix[4]monocrown with 1 equiv of polyethylene glycol ditosylates. Enlightened by this, we treated *p-tert*-butylcalix[4]arene (as building block II) with 1 equiv of calix[4]arene ditosylate **3** (building block I) in the presence of *t*-BuOK in toluene and obtained the proximally linked product **7** in yield up to 34%. Further monoalkylation of **7** with suitable electrophiles (BnBr and ethyl bromoacetate) in the presence of Cs_2CO_3 in DMF furnished corresponding inherently chiral biscalix[4]arene derivatives **8** and **9** as racemates, respectively. Alkylation of the remaining phenolic hydroxyl of **8** by reaction with ethyl bromoacetate in the presence of NaH in CH_3CN provided compound **10**, which was further converted into corresponding carboxylic acid derivative **11** by hydrolysis under basic condition.

As expected, the NMR spectra of all the inherently chiral biscalix[4]arenes are quite complicated due to the complex splitting patterns and overlapping of the signals. Still, some details of the structural features are discernible. For example, in the ^1H NMR spectrum of **9** (Figure 1), the signals arising from the aromatic rings of the two calix moieties appear in the region of 7.18−6.49 ppm, where two singlets at 7.16 (4H) and 6.49 ppm (4H) are attributable to the aromatic protons of the 1,3-bridged calix unit and the four pairs of doublets at 7.17 and 7.16 ppm (1H each, J = 2.7 Hz, partly overlapped), 7.12 and 7.09 ppm (1H each, J = 2.7 Hz), 6.67 and 6.66 ppm (1H each, J = 2.7 Hz), and 6.54 and 6.53 ppm (1H each, J = 2.7 Hz) are attributable to the aromatic protons of the 1,2-bridged calix unit. The singlet appearing at 5.76 ppm corresponds to the phenolic hydroxyl proton. In the region of 3.41−3.14 ppm, six doublets at 3.33, 3.31, 3.30, 3.24, 3.18, and 3.16 ppm (1H, 1H, 1H, 1H, 3H, 1H, J = ca. 13.0 Hz) are assignable to the eight equatorial protons of the $ArCH_2Ar$ methylene groups. The two triplets appearing at 1.12 (3H, J = 7.5 Hz) and 0.98 ppm (3H, J = 7.5 Hz) correspond to the methyl protons of the two sets of propyl groups. In the ^{13}C NMR spectrum of **9**, the carbon signal arising from $ArCH_2Ar$ methylene groups at around 31.0 ppm is consistent with its cone−cone conformation. As a proof of the inherent chirality, ^1H NMR spectra of compounds (±)-**9**−**11** were measured in the presence of excess (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's reagent) and several signals showed obvious splitting in all cases, presumably due to the formation of the diastereomeric complexes.

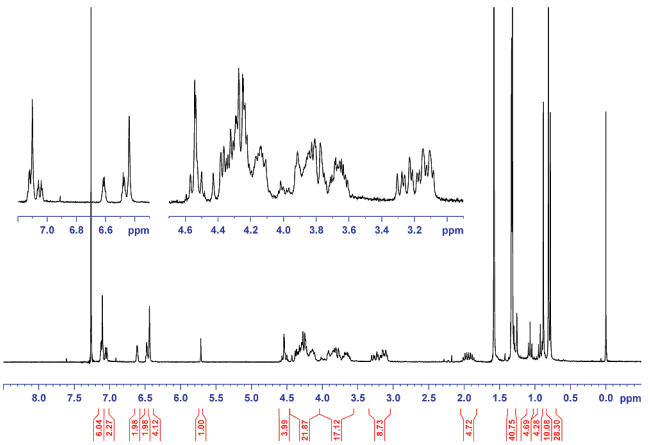


FIGURE 1. ^1H NMR spectrum (300 MHz, 25 °C) of inherently chiral biscalix[4]arene (±)-**9** in $CDCl_3$.

At the current stage, attempts to optically resolve inherently chiral biscalix[4]arene carboxylic acid racemates (±)-**11** by chemical resolution method with chiral auxiliaries such as (*S*)-BINOL and (*R*)-1-phenylethylamine (in the presence of DCC and DMAP in CH_2Cl_2) failed. In both cases, the reaction was quite slow (presumably due to the steric hindrance of **11**) and the diastereomers formed appeared as one spot on the analytic TLC plate. However, optical resolution of (±)-**11** was achieved by semi-preparative HPLC with a CHIRACEL OD-H column. The CD spectra of the separated enantiomers showed mirror images of each other (Figure 2).

In summary, we have offered an approach to inherently chiral biscalix[4]arenes, which were covalently assembled by two calix[4]arene building blocks in a 1,3-position linking with 1,2-position pattern at the lower rims via two triethylene glycol bridges. The achiral intermediate **7**, which has only one symmetry plane, may provide an excellent platform for the construction of inherently chiral biscalix[4]arene derivatives.

Experimental Section

Reaction of Compound 3 (Building Block I) with *p-tert*-Butylcalix[4]arene (Building Block II) for the Preparation of Biscalix[4]arenes 7. To a suspension of *p-tert*-butylcalix[4]arene (1.00 g, 1.54 mmol) in toluene (200 mL) was added *t*-BuOK

(13) (a) Arduini, A.; Domiano, L.; Pochini, A.; Secchi, A.; Ungaro, R.; Ugozzoli, F.; Struck, O.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1997**, *53*, 3767. (b) Ferguson, G.; Lough, A. J.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Petringa, A. *J. Org. Chem.* **1998**, *63*, 9703.

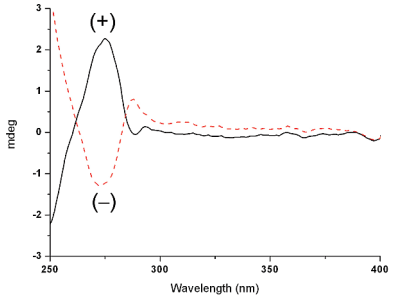


FIGURE 2. The CD spectra of the enantiomers of inherently chiral biscalix[4]arene **11** in $CHCl_3$ at 25 °C. The black solid line and the red dotted line denote the (+)-**11** and (−)-**11** which were separated by chiral HPLC.

(862 mg, 5.0 equiv) and the reaction mixture was stirred at 70 °C for 1 h. Then **3** (2.21 g, 1.1 equiv) was added and the reaction mixture was stirred at 70 °C for 1 d. After removal of the solvent under reduced pressure, the residue was partitioned between H_2O (80 mL) and CH_2Cl_2 (2 × 80 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 20/1) to give **7** as a white solid in 34% yield. Mp 189.1−192.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 2H), 7.13 (s, 4H), 7.01 (d, 2H, J = 2.4 Hz), 6.96 (s, 2H), 6.95 (s, 2H), 6.92 (d, 2H, J = 2.4 Hz), 6.48 (s, 2H), 6.47 (s, 2H), 4.59 (d, 1H, J = 12.6 Hz), 4.44−3.86 (m, 31H), 3.71 (q, 4H, J = 7.8 Hz), 3.34 (d, 4H, J = 13.2 Hz), 3.16 (d, 2H, J = 12.6 Hz), 3.15 (d, 2H, J = 12.6 Hz), 2.07−1.90 (m, 4H), 1.35 (s, 18H), 1.22 (s, 18H), 1.11 (s, 18H), 1.10 (t, 3H, J = 7.5 Hz), 1.00 (t, 3H, J = 7.5 Hz), 0.85 (s, 9H), 0.84 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.3, 152.3, 151.7, 148.9, 146.2, 145.1, 144.0, 143.9, 142.1, 135.49, 135.46, 133.7, 133.4, 131.9, 131.8, 128.6, 127.8, 125.9, 125.47, 125.45, 125.13, 125.06, 124.4, 77.7, 77.6, 74.8, 71.9, 70.8, 70.6, 70.4, 69.6, 34.1, 34.0, 33.8, 33.5, 31.9, 31.7, 31.5, 31.2, 31.1, 31.0, 30.9, 23.6, 23.5, 10.8, 10.7; ESI-MS m/z 1633.2 [M + Na^+]. Anal. Calcd for $C_{106}H_{144}O_{12}$: C 79.06, H 9.01. Found: C 78.97, H 8.86.

Reaction of 7 with Electrophiles. General Procedure for the Preparation of Inherently Chiral Biscalix[4]arenes. A stirred mixture of **7** (869 mg, 0.54 mmol), electrophile (1.2 equiv), and Cs_2CO_3 (211 mg, 0.65 mmol) in DMF (60 mL) was heated at 70 °C for 12 h. The solvent was evaporated under reduced pressure. The residue was partitioned between 1% HCl (50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over $MgSO_4$. The crude product was further purified by column chromatography to give inherently chiral biscalix[4]arene **8** or **9** as a white solid. (±)-**8**: Benzyl bromide (77 μL, 0.65 mmol) was used as the electrophile in the reaction. Column chromatography (SiO_2, hexane/AcOEt = 15/1). Yield 83%. Mp 165.5−168.5 °C (CH_2Cl_2/C_2H_5OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61−7.33 (m, 5H), 7.13 (s, 2H), 7.11 (s, 2H), 7.10 (s, 2H), 7.07 (s, 2H), 6.54 (s, 2H), 6.51 (s, 2H), 6.43 (s, 4H), 5.53 (s, 1H), 4.86 (d, 1H, J = 11.1 Hz), 4.80 (d, 1H, J = 11.1 Hz), 4.52 (d, 1H, J = 12.9 Hz), 4.41 (d, 1H, J = 13.5 Hz), 4.39−3.58 (m, 33H), 3.35−3.25 (m, 4H), 3.18 (d, 1H, J = 12.6 Hz), 3.16 (d, 1H, J = 12.6 Hz), 3.12 (d, 4H, J = 12.6 Hz), 3.10 (d, 1H, J = 12.6 Hz), 1.98 (sextet, 2H, J = 7.5 Hz), 1.88 (sextet, 2H, J = 7.5 Hz), 1.333 (s, 27H), 1.327 (s, 9H), 1.07 (t, 2H, J = 7.5 Hz), 0.91 (t, 2H, J = 7.5 Hz), 0.83 (s, 9H), 0.811 (s, 9H), 0.807 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.7, 154.4, 153.8, 152.4, 151.4, 151.1, 150.7, 145.8, 145.5, 145.4, 145.1, 145.0, 144.0, 143.9, 141.5, 137.5, 135.9, 135.8, 135.6, 135.5, 132.6, 132.2, 131.88, 131.86, 131.84, 131.77, 131.65, 129.4, 129.1, 129.0, 128.5, 128.0, 125.8, 125.53, 125.49, 125.4, 125.1, 125.00, 124.95, 124.92, 124.86, 124.8, 124.5, 124.44, 124.42, 78.2, 77.74, 77.72, 75.0, 72.2, 71.8, 71.3, 71.1, 70.8, 70.5, 70.23, 70.17, 70.0, 69.44, 69.36, 34.11, 34.07, 33.9, 33.67, 33.65, 33.6, 31.8, 31.73, 31.71, 31.7, 31.5, 31.3, 31.13, 31.08, 31.0, 30.9, 23.6, 23.4, 10.8, 10.6; FAB-MS m/z 1723 [M + Na^+]. Anal. Calcd for $C_{113}H_{150}O_{12}$: C 79.82, H 8.89. Found: C 79.41, H 8.79.

Alkylation of (±)-8 for the Preparation of Compound (±)-10. To a stirred mixture of (±)-**8** (500 mg, 0.294 mmol), NaH (118 mg, 2.94 mmol) in THF (15 mL), and CH_3CN (40 mL) was added ethyl bromoacetate (327 μL, 2.94 mmol) at room temperature. Then the reaction mixture was heated at 70 °C for 1 d. After removal of the solvent under reduced pressure, CH_2Cl_2 (50 mL) was added. The solid residue was removed by passing through a thin layer of Celite. The organic filtrate was evaporated and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate = 15:1) to furnish compound **10** as a white solid in 90% yield. Mp 149.0−151.4 °C (CH_2Cl_2/CH_3CN); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55−7.34 (m, 5H), 7.12 (s, 4H), 6.95 (s, 4H), 6.63 (s, 4H), 6.46 (s, 4H), 4.93 (d, 1H, J = 10.8 Hz), 4.85 (d, 1H, J = 10.8 Hz), 4.82 (d, 1H, J = 16.5 Hz), 4.76 (d, 1H, J = 12.6 Hz), 4.68 (d, 1H, J = 16.5 Hz), 4.60 (d, 1H, J = 13.2 Hz), 4.56 (d, 1H, J = 12.9 Hz), 4.44−3.60 (m, 33H), 3.57−3.38 (m, 2H), 3.19−3.06 (m, 8H), 2.04−1.83 (m, 4H), 1.35 (s, 9H), 1.34 (s, 9H), 1.28 (t, 3H, J = 7.2 Hz), 1.21 (s, 18H), 1.06 (t, 3H, J = 7.5 Hz), 0.97 (s, 18H), 0.94 (t, 3H, J = 7.5 Hz), 0.83 (s, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 154.6, 154.5, 153.8, 153.6, 152.7, 152.6, 152.4, 145.1, 145.0, 144.6, 144.5, 144.0, 143.9, 138.2, 135.54, 135.49, 135.0, 134.6, 134.3, 134.0, 133.3, 133.0, 132.8, 132.7, 131.87, 131.86, 131.8, 129.7, 128.2, 127.9, 125.6, 125.5, 125.4, 125.3, 125.1, 125.0, 124.8, 124.5, 124.4, 77.74, 77.69, 73.6, 72.3, 72.1, 72.0, 71.04, 71.02, 70.9, 70.6, 70.43, 70.35, 70.0, 69.6, 60.3, 34.1, 33.9, 33.7, 33.6, 31.7, 31.64, 31.55, 31.5, 31.4, 31.3, 31.1, 31.0, 30.9, 30.8, 23.53, 23.46, 14.2, 10.7, 10.6; FAB-MS m/z 1809 [M + Na^+]. Anal. Calcd for $C_{117}H_{156}O_{14}$: C 78.66, H 8.80. Found: C 78.53, H 8.94.

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Supporting Information Available: Experimental procedures for compounds **2**, **3**, **4**, **5**, **6**, **9**, and **11**; ^{1}H and ^{13}C NMR spectra of all the new compounds; partial ^{1}H NMR spectra of (±)-**9**−**11** in the absence and presence of Pirkle's reagent; HPLC chromatogram of **11**. This material is available free of charge via the Internet at http://pubs.acs.org.