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A New Approach to Enantiopure Inherently Chiral Calix[4]arenes: Determination of Their Absolute Configurations

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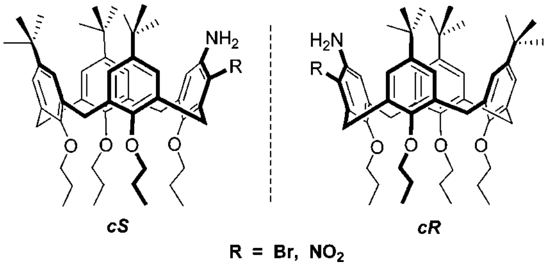
ABSTRACT



A new approach to the synthesis of meta-substituted enantiopure inherently chiral calix[4]arenes by introducing L-Boc-proline as dual functions of the chiral auxiliary has been described. Moreover, the absolute configurations of the enantiomers were determined by CD spectra, X-ray crystallographic analysis, and the chemical derivative method.

Inherently chiral calixarenes[1] whose chiralities originate from the asymmetric array of achiral residues on the calixarene skeletons have attracted much attention for their unique structures and potential applications in chiral recognition[2] and asymmetric catalysis.[3] In the past two decades, several different approaches to inherently chiral calix[4]arenes have appeared in the literature; however, their optical resolution was usually achieved through HPLC methods,[1,4] which was inappropriate for scale-up and thus impeded their practical applications. Recently, we[5] and other groups[6] reported a convenient approach to enantiopure inherently chiral calixarene derivatives by introduction of a chiral auxiliary and then separation of subsquent diastereomers via column chromatography on silica gel, preparative TLC, or even simple crystallization. This approach allows the gram-scale synthesis of the enantiopure inherently chiral calix[4]arenes and further research on their potential applications.[5e]

In 1995, Reinhoudt et al.[7] reported a simple method for the preparation of two functionalized inherently chiral calix[4]arenes by direct introduction of a substituent in *p*-acetoamido-substituted calix[4]arene. We envisaged that if

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(1) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, UK, 1998.

(2) Jin, T.; Monde, K. *Chem. Commun.* **1998**, 1357−1358.

(3) Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, 2508−2517.

(4) Some examples: (a) Caccamese, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Principato, G. *Tetrahedron* **1999**, *55*, 5505−5514. (b) Tairov, M. A.; Vysotsky, M. O.; Kalchenko, O. I.; Pirozhenko, V. V.; Kalchenko, V. I. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1405−1411. (c) Caccamese, S.; Bottino, A.; Cunsolo, F.; Parlato, S.; Neri, P. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3103−3112. (d) Hesek, D.; Inoue, Y.; Drew, M. G. B.; Beer, P. D.; Hembury, G. A.; Ishida, H.; Aoki, F. *Org. Lett.* **2000**, *2*, 2237−2240. (e) Xu, B.; Carroll, P. J.; Swager, T. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2094−2097.

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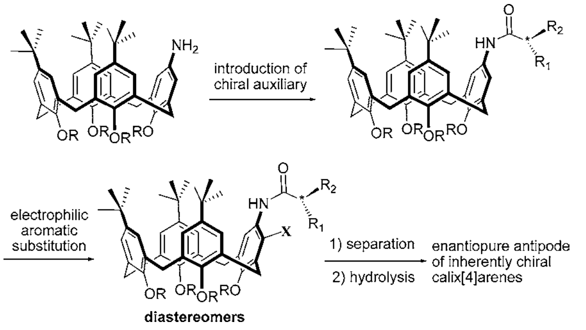
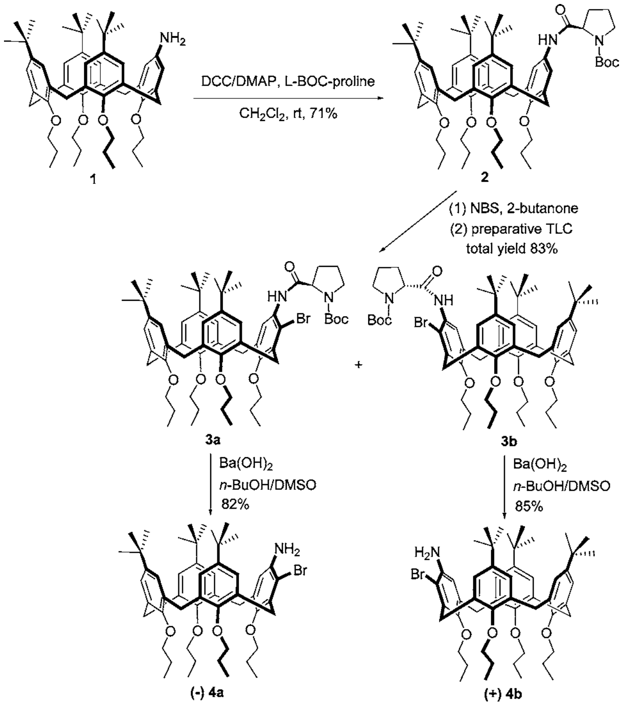
a chiral amide was used instead of the acetoamide, it would perform as not only an activating group but also a chiral resolving auxiliary. Consequently, enantiopure inherently chiral calix[4]arenes could be obtained by the electrophilic aromatic substitution, separation of the diastereomers, and then hydrolysis (Scheme 1). Here, we report a new approach to enantiopure inherently chiral calix[4]arenes by introducing L-Boc-proline as dual functions of the chiral auxiliary, which appears to be more efficient than those we reported previously.[5] Moreover, their absolute configurations can also be determined by CD spectra, X-ray crystallographic analysis, and the chemical derivative method.

Scheme 1



Starting from the aminocalix[4]arene **1**,[8] compound **2** was prepared in 71% yield by the reaction of **1** and L-Boc-proline in the presence of DCC and DMAP. Bromination of **2** with an excess of NBS in 2-butanone at room temperature gave the diastereomers **3a** and **3b** as a mixture in 83% total yield, which could then be readily separated by preparative TLC (Scheme 2). MALDI-TOF MS of both **3a** and **3b** showed peaks at *m/z* 1052.4 for M^+, 1075.4 for $[M + Na]^+$, and 1091.4 for $[M + K]^+$.[9] But different ^{1}H NMR spectral properties of **3a** and **3b** were observed (Figure 1). While well-defined proton signals of **3b** in $CDCl_3$ at room temperature or in DMSO-d_6 at 350 K were observed, the protons of **3a** showed quite broadened signals in both $CDCl_3$ and DMSO-d_6 (Figure 1a,b) at room temperature, which might be due to the conformations of the proline moiety and its rate of cis−trans isomerization.[9,10] At 350 K, sharpened proton signals of **3a** could be observed in DMSO-d_6 (Figure 1c).

Scheme 2



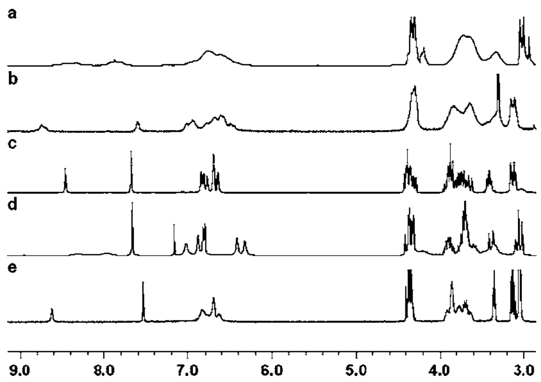


Figure 1. Partial ^{1}H NMR spectra (300 MHz) of **3a** and **3b**: (a) **3a** in $CDCl_3$, (b) **3a** in DMSO-d_6, (c) **3a** in DMSO-d_6 at 350 K, (d) **3b** in $CDCl_3$, and (e) **3b** in DMSO-d_6 at 350 K.

We tried the amide hydrolysis of **3a** and **3b** under different acidic and basic conditions, and finally found that the hydrolysis with $Ba(OH)_2 \cdot 8H_2O$ in *n*-butanol and DMSO proved to be successful. Consequently, a pair of antipodes **4a** and **4b** could be obtained in 82% and 85% yield,

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[5] (a) Cao, Y.-D.; Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Wang, M.-X.; Huang, Z.-T. *J. Org. Chem.* **2004**, *69*, 206−208. (b) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Chem. Eur. J.* **2005**, *11*, 5917−5928. (c) Li, S.-Y.; Zheng, Q.-Y.; Chen C.-F.; Huang, Z.-T. *Tetrahedron*: *Asymmetry* **2005**, *16*, 641−645. (d) Mao, R.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *J. Org. Chem.* **2005**, *70*, 7662−7671. (e) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2005**, *61*, 8517−8528.

[6] (a) Yakovenko, A. V.; Boyko, V. I.; Danylyuk, O.; Suwinska, K.; Lipkowski, J.; Kalchenko, V. I. *Org. Lett.* **2007**, *9*, 1183−1185. (b) Narumi, F.; Hattori, T.; Yamabuki, W.; Kabuto, C.; Kameyama, H. *Tetrahedron*: *Asymmetry* **2005**, *16*, 793−800. (c) Narumi, F.; Hattori, T.; Matsumura, N.; Onodera, T.; Katagiri, H.; Kabuto, C.; Kameyama, H.; Miyano, S. *Tetrahedron* **2004**, *60*, 7827−7833. (d) Boyko, V. I.; Shivanyuk, A.; Pyrozhenko, V. V.; Zubatyuk, R. I.; Shishkin, O. V.; Kalchenko, V. I. *Tetrahedron Lett.* **2006**, *47*, 7775−7778.

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[8] Alemi, A. A.; Shaabani, B.; Dilmaghani, K. A.; Ganjali, S. T. *Molecules* **2001**, *6*, 417−423.

[9] See the Supporting Information.

[10] (a) Halab, L.; Lubell, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 2474−2484. (b) Ghasparian, A.; Moehle, K.; Linden, A.; Robinson, J. A. *Chem. Commun.* **2006**, 174−176.

respectively (Scheme 2). Circular dichroism (CD) spectroscopy (Figure 2) showed an excellent mirror image between

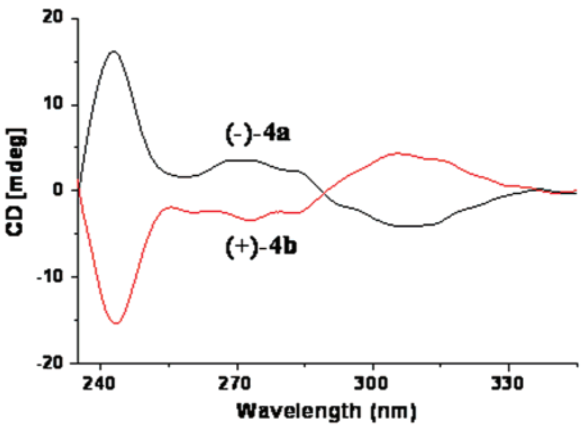


Figure 2. CD spectra of (−)-**4a** and (+)-**4b** in CH_2Cl_2 at 25 °C.

(−)-**4a** ($[\alpha]^{25}_D$ −15.9) and (+)-**4b** ($[\alpha]^{25}_D$ +15.9), indicating their inherent chirality.

The absolute configurations of **4a** and **4b** were further determined by a single-crystal X-ray diffraction study. Thus, a suitable crystal was obtained by diffusion of *n*-pentane into **4a** in THF and MeOH (v/v, 1:1).[11] As shown in Figure 3, the macrocyclic framework adopts the usual shape for a calix[4]arene in the cone conformation, with angles between the opposite phenoxy rings of 3.98° and 94.70°, respectively. Because the Br group is located at the C-6 position[12] of the inherently chiral calix[4]arene **4a**, its absolute configuration can be designated as *cS*.[13] On the basis of the result of **4a**, we can further assign the absolute configurations of **3a**, **3b**, and **4b** to be *cS*, *cR*, and *cR*, respectively.

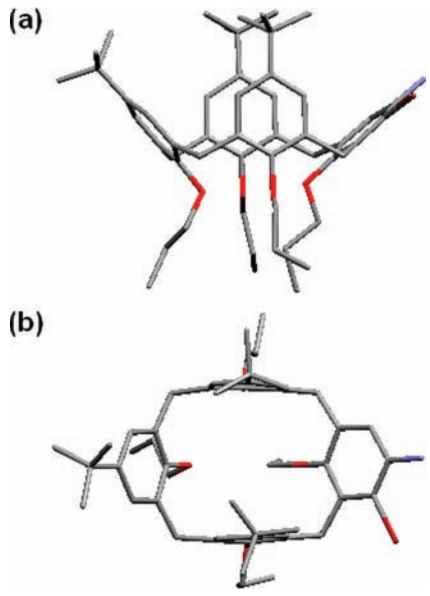
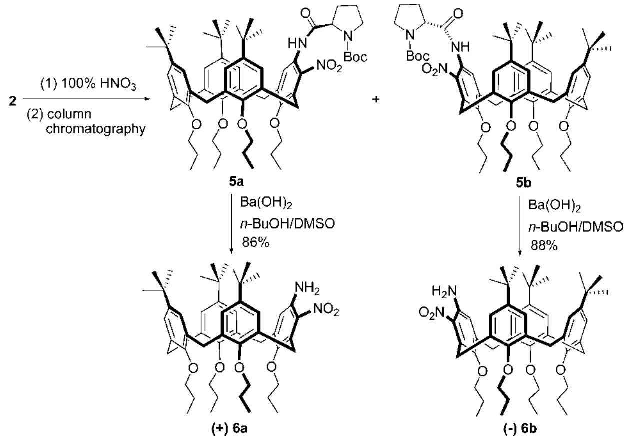


Figure 3. Side view (a) and top view (b) of the crystal structure of compound **4a**. Hydrogen atoms are omitted for clarity.

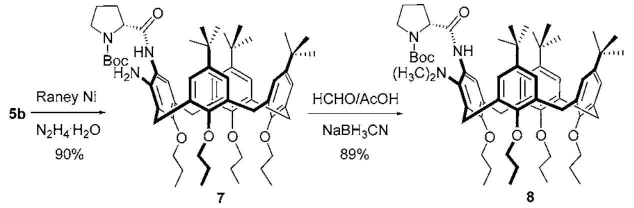
In addition to the bromination, we also studied the nitration of the amidocalix[4]arene derivative **2**. As shown in Scheme 3, a pair of nitro-substituted inherently chiral calix[4]arenes **5a** and **5b** were synthesized by the reaction of **2** with 100% HNO_3, and conveniently resolved by common silica column chromatography. Enantiopure antipode **6a** and **6b** were then obtained by the hydrolysis of **5a** and **5b** with $Ba(OH)_2$ in *n*-BuOH and DMSO. CD spectroscopy[9] also showed an excellent mirror image between (+)-**6a** ($[\alpha]^{25}_D$ +150) and (−)-**6b** ($[\alpha]^{25}_D$ −150), which indicates clearly their inherent chirality.

Scheme 3



Reduction[7] of **5b** by Raney Ni in the presence of hydrazine hydrate gave the aminocalix[4]arene derivative **7**, which was then methylated[14] by HCHO and acetic acid in the presence of $NaBH_3CN$ to give compound **8** in 89% yield (Scheme 4). The X-ray crystal structure of **8**[15] was determined and shown in Figure **4**. Through the chemical derivative method, we could assign the absolute configurations of the nitro-substituted inherently chiral calix[4]arenes. Consequently, we

Scheme 4



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[11] Crystal data for **4a**: $C_{52}H_{72}BrNO_4$, $M = 855.02$, monoclinic, space group $P2_1$, $a = 12.568(7)$ Å, $b = 16.286(9)$ Å, $c = 24.219(14)$ Å, $\beta = 99.468(6)°$, $V = 4890(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.161$ cm^{-3}, Mo Kα radition, $\lambda = 0.71070$ Å, $\mu = 0.883$ mm^{-1}, $T = 113(2)$ K, $R_{int} = 0.0769$, $R_1 = 0.0677$ ($I > 2\sigma(I)$).

[12] About the numbering of carbon atoms in calixarene, see ref 1.

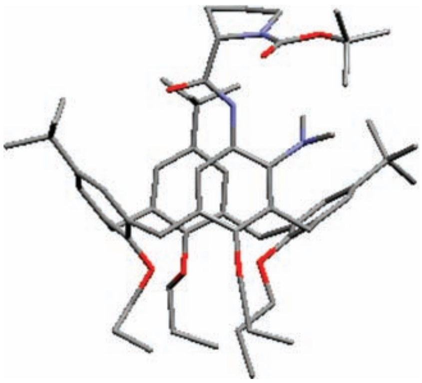

Figure 4. Crystal structure of compound **8**. The methanol molecule and hydrogen atoms are omitted for clarity.

designated the absolute configurations of **5b** and **6b** to be *cR*, in which the nitro group is located at the C-4 position of the calixarene. For **5a** and **6a**, their absolute configurations can be assigned as *cS*.

In summary, we have presented a new approach to the convenient synthesis of two pairs of meta-functionalized inherently chiral calix[4]arenes on the upper rim based on the dual functions of the L-Boc-proline auxiliary, and further assigned their absolute configurations by CD spectra, X-ray crystallographic analysis, and the chemical derivative method. The functionalized inherently chiral calixarenes we described here can be considered as versatile substrates for the preparation of more elaborated inherently chiral calix[4]arenes, which may be applied to chiral recognition and asymmetric catalysis.[16] Further work is now in progress in our laboratory.

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Supporting Information Available: Experimental procedures and characterization of new compounds, CD spectra of (+)-**6a** and (−)-**6b**, and CIF data for the crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Crystal data for **8**: $C_{64.5}H_{95}N_3O_{7.5}$, $M = 1032.44$, monoclinic, space group $P2_1$, $a = 13.7323(6)$ Å, $b = 13.6624(6)$ Å, $c = 32.8806(17)$ Å, $\beta = 96.449(2)°$, $V = 6129.9(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.119$ cm^{-3}, Mo Kα radition, $\lambda = 0.71070$ Å, $\mu = 0.072$ mm^{-1}, $T = 113(2)$ K, $R_{int} = 0.0461$, $R_1 = 0.0597$ ($I > 2\sigma(I)$).

(16) For a more recent example, see: Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117−3119.