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Preparation of Both Antipodes of Enantiopure Inherently Chiral Calix[4]crowns

Yu-Dong Cao, Jun Luo, Qi-Yu Zheng,* Chuan-Feng Chen, Mei-Xiang Wang, and Zhi-Tang Huang*

Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China

huangzt@public.bta.net.cn

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Abstract: Both antipodes of enantiopure inherently chiral calix[4]crown derivatives were successfully obtained through separation of their BINOL diastereomeric derivatives of corresponding racemates using preparative TLC instead of conventional HPLC methods. Such a result provides a basis for future study of chiral recognition and asymmetric catalysis with inherently chiral calixrene derivatives.

Calix[4]arenes have been extensively studied for host−guest chemistry.[1] Because of their unique cavity-shaped architecture and preorganized binding sites, calix[4]-arenes are frequently used as construction platforms of molecular receptors for complexation of ions or neutral molecules. For two decades, there has been increasing interest focused on the synthesis of inherently chiral calix[4]arenes due to their potential to realize chiral discrimination and asymmetric catalysis.[2] A general approach to such types of compounds involves asymmetric arrangement of several achiral substituents on the lower rims of conformationally rigid calix[4]arenes.[3] The evidence for the existence of inherent chirality can be deduced from their sophisticated NMR in the absence or presence of a chiral shift reagent,[4] and in some cases it also can be attested through CD symmetric images of a pair of enantiomers.[5] Optical resolution is usually achieved via HPLC using a chiral column. Due to the difficulty of obtaining optically pure inherently chiral calixarenes, most research results reported are limited in the scope of separation of enantiopure inherently chiral calix[4]-arenes through HPLC in spite of more and more synthesis methods found.[6] So far there has been only one report each about chiral discrimination[7] and catalysis[8] of inherently chiral calix[4]arenes. Here, we describe a convenient approach to enantiopure antipodes of the AABH-type inherently chiral calix[4]arenes by the reaction of racemic calix[4]crown derivatives with (*S*)-BINOL followed by the separation of the diastereomers formed using preparative TLC methods and the cleavage of the (*S*)-BINOL auxiliary.

As illustrated in Scheme 1, the symmetric calix[4]-crowns underwent O-monoalkylation reaction with ethyl bromoacetate in the presence of 1 equiv of Cs_2CO_3 in dry DMF.[9] Saponification of **2** led to the formation of racemic acid **3**. The structure of acid **3** was confirmed by its spectroscopic data, and particularly the cone conformation of **3** was evidenced by the observation of bridging methylene carbon signals at ca. 32 ppm in ^{13}C NMR spectra.[10] Both racemates of **2a** and **3a** were resolved into a pair of enantiomers through an HPLC method using a Chiralcel OD or Chiralcel AD column with hexane/isopropyl alcohol (9:1, v/v) as the mobile phase at 0.8 mL/min flow rate. The enantiomer ratio of **2a** is approved to be 50:50 while for **3a** it is 47:50.

In a previous report, it was mentioned that analytical separation of diastereomeric salts of inherently chiral calixarene phosphoric acids can be realized using HPLC on achiral columns (Separon SGX C18 or Partisil 5 ODS 3).[11] Encouraged by the formation and optical resolution of inherently chiral calix[4]crown derivatives, we then attempted the preparation of both antipodes of enantiopure inherently chiral calix[4]crowns through chromatographic separation methods. To take advantage of the carboxylic acid group appended to the low rim of calix[4]crown, we conducted derivation of racemic **3a** with a number of chiral auxiliaries such as L-menthol, L-cinchonidine, and L-amino acid esters. No easy separation of the diastereomers resulting from these chiral reagents was attained on TLC. Finally, we found that the esterification of **3a** with (*S*)-BINOL led to the formation of a pair of diastereomers which were readily separated using TLC on a preparative scale.

Two diastereomers of **4a-1** and **4a-2** show a marked difference in ^1H NMR spectra. The proton of the phenolic

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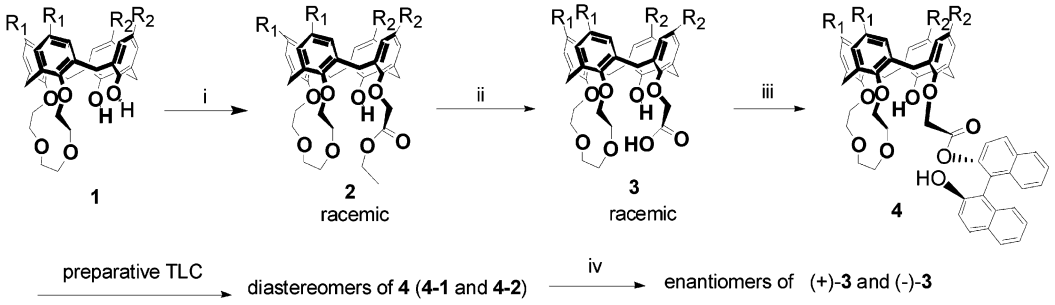
SCHEME 1 [a]



a: $R_1 = R_2 = H$; **b**: $R_1 = t$-Bu, $R_2 = H$.

[a] Reagents: (i) $BrCH_2COOEt$, Cs_2CO_3, DMF; (ii) NaOH, $EtOH/H_2O$; (iii) (*S*)-BINOL, DCC, DMAP, DCM; (iv) NaOH, $EtOH/H_2O$.

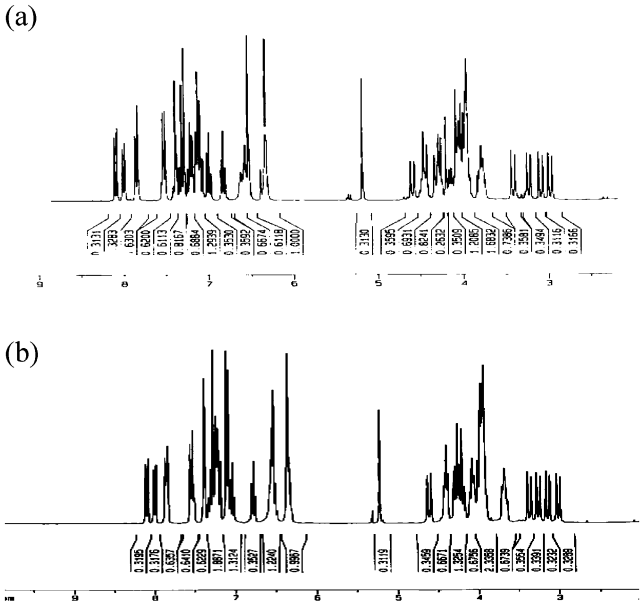


FIGURE 1. ^1H NMR spectra of **4a-1** (a) and **4a-2** (b) in $CDCl_3$.

hydroxy group of **4a-1** resonates at 5.18 ppm, while that of **4a-2** resonates at 5.23 ppm. Such a difference may be attributed to the interaction between binaphthyl moiety and calix[4]arene inherent chirality, which results in the micro-environment difference of the hydrogen bond between carbonyl and hydroxy groups. Moreover, the chemical shifts of bridging methylene show fine splitting patterns with four pairs of AX systems. Interestingly, the relative chemical shifts of bridging methylene protons of **4a-2** move toward lower fields compared with those of **4a-1**. The phenomena may be the result of distortion of calix[4]arene backbones for the steric arrangement attributed to the existence of outer chiral centers. As could be unambiguously deduced from the ^1H NMR and ^{13}C NMR spectra, compounds of **4a** adopt a cone conformation (Figure 1).

Hydrolysis of diastereomers under alkaline conditions yielded optical active calix[4]crown derivatives (+)-**3a**, (−)-**3a**, (+)-**3b,** or (−)-**3b** in high yields with enantiomeric purity as high as 99.9% (HPLC analysis). Circular dichroism (CD) spectroscopy shows an excellent mirror image between (+)-**3a** ($[\alpha]_D$ 40) and (−)-**3a** ($[\alpha]_D$ − 40), indicating clearly the inherent chirality of (+)-**3a** and (−)-**3a**.[12] Here, (+)-**3a** was tentatively assigned as the P-enantiomer (Figure 2).

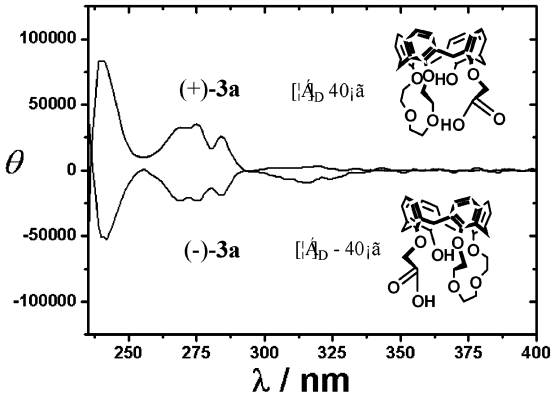


FIGURE 2. CD spectra of (+)-**3a** and (−)-**3a** in DCM.

In summary, we have developed the synthesis of racemic inherently chiral calix[4]crown derivatives by the O-monoalkylation of calix[4]crowns. The optical resolution of inherently chiral calix[4]crown acids was achieved through their esterification using (*S*)-BINOL followed by diastereomer separation using preparative TLC. The method provides a convenient approach to both antipodes of enantiopure inherently chiral calix[4]crown derivatives. The current investigation also provides a basis for the study of chiral recognition with inherently chiral calix[4]arenes, which is being actively pursued in this laboratory.

Experimental Section

2a (Racemic Mixture). To a stirred mixture of **1a**[13] (1.076 g, 2 mmol) and Cs_2CO_3 (652 mg, 2 mmol) in dry DMF (20 mL) was added $BrCH_2COOEt$ (334 mg, 2 mmol), and the reaction mixture was heated at 60−70 °C for 5 h under nitrogen. Then a small amount of 10% HCl was added to quench the reaction. The solvent was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$. Compound **2a** was isolated by column chromatography (petroleum ether/acetone, 6:1 v/v) as a white solid: 876 mg (yield 70%); mp 57−59 °C; ^1H NMR ($CDCl_3$) δ 7.22, 7.14 (2t, 4H, J = 7.1 Hz), 7.04 (t, 1H, J = 7.3 Hz), 6.83 (t, 1H, J = 7.5 Hz), 6.58−6.54 (m, 3H), 6.39 (s,

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3H), 5.37 (s, 1H), 4.68, 4.60, 4.59, 4.48 (4d, 4H, J = 13 Hz), 4.44−3.75 (m, 14H), 4.08 (q, 2H), 3.41, 3.35, 3.31, 3.27 (4d, 4H, J = 13 Hz), 1.36 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 170.2, 157.5, 155.5, 154.2, 153.7, 137.8, 137.6, 135.0, 133.7, 133.6, 133.1, 131.6, 130.3, 130.2, 130.1, 129.7, 129.5, 129.3, 129.0, 128.9, 128.8, 124.9, 124.2, 124.1, 120.0, 75.9, 73.6, 73.0, 72.7, 71.0, 70.5, 70.0, 62.0, 32.0, 31.9, 31.7, 30.9, 15.2; MALDI-TOF MS m/z 625 ([M + H]$^+$), 647 ([M + Na]$^+$), 663 ([M + K]$^+$); IR (KBr) 3444, 2915, 1756, 1589, 1459. Anal. Calcd for $C_{38}H_{40}O_8$: C, 73.06; H, 6.45. Found: C, 73.04; H, 6.57.

3a (Racemic Mixture). To a solution of NaOH (160 mg, 4 mmol) in EtOH/H_2O (10 mL/10 mL) was added **2a** (500 mg, 0.8 mmol), and the reaction mixture was refluxed for 2 h. After removal of the solvent under reduced pressure, 10% HCl was added. After filtration, the solid was partitioned between water and CH_2Cl_2. Compound **3a** was isolated by column chromatography (CH_2Cl_2/CH_3OH, 20:1 v/v) as a colorless crystal (416 mg, yield 87%): mp 120−122 °C; ^{1}H NMR ($CDCl_3$) δ 8.12 (s, 1H), 7.13−6.71 (m, 12H), 4.92, 4.90, 4.39, 4.34 (4d, 4H, J = 13.3 Hz), 4.26−3.81 (m, 14H), 3.51, 3.41, 3.37, 3.36 (4d, 4H, J = 13.7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.1, 155.2, 153.1, 152.2, 152.0, 135.6, 135.4, 135.1, 134.5, 133.1, 132.8, 129.6, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 125.2, 124.8, 124.0, 120.2, 75.4, 74.0, 71.6, 70.6, 70.2, 69.8, 69.2, 32.0, 31.5, 31.1, 29.4; MALDI-TOF MS m/z 597 ([M + H]$^+$), 619 ([M + Na]$^+$); IR (KBr) 3410, 2922, 1621, 1461. Anal. Calcd for $C_{36}H_{36}O_8$, H_2O: C, 70.34; H, 6.23. Found: C, 70.10; H, 6.09.

4a-1 and 4a-2 (Diastereomers). A solution of **3a** (894 mg, 1.5 mmol), (*S*)-BINOL (472 mg, 1.65 mmol), DCC (310 mg, 1.5 mmol), and DMAP (18 mg, 0.15 mmol) in CH_2Cl_2 (50 mL) was stirred at rt for 7 h. During this period, a large amount of insoluble DCU was formed which was removed by filtration. After removal of solvent, the residue was purified by column chromatography (petroleum ether/ethyl acetate, 4:1 v/v) to afford **4a-1** and **4a-2** as a white solid of diastereomeric mixture (978 mg in total, yield 76%) which was then subjected to preparative TLC using $CHCl_3$/ethyl acetate (6:1, v/v) as eluent. The two dispatched bands (UV−vis) were collected, respectively, and soaked in acetone for several hours (decomposed slightly). Then each was eluted with acetone through short column chromatography. After evaporation of acetone, each was further purified by column chromatography (petroleum ether/ethyl acetate, 4:1 v/v) to afford **4a-1** and **4a-2** as pure enantiomers, respectively (**4a-1**, 354 mg, yield 36%; **4a-2**, 390 mg, yield 40%).

4a-1: mp 158−159 °C; ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1H, J = 8.9 Hz), 7.99 (d, 1H, J = 8.8 Hz), 7.86 (dd, 2H, J = 9.1 Hz), 7.56−7.49 (m, 2H), 7.41−7.37 (m, 2H), 7.33−7.26 (m, 3H), 7.22−7.10 (m, 5H), 6.99 (t, 1H, J = 7.2 Hz), 6.83 (t, 1H, J = 7.3 Hz), 6.68−6.26 (m, 7H), 5.18 (s, 1H), 4.60, 4.47, 4.45, 4.32 (4d, 4H, J = 13.8 Hz, $ArCH_2Ar$), 4.26−3.75 (m, 14H), 3.43, 3.24, 3.10, 2.98 (4d, 4H, J = 13.5 Hz, $ArCH_2Ar$); ^{13}C NMR ($CDCl_3$) δ 168.1, 156.4, 154.3, 153.2, 152.5, 152.2, 147.2, 137.1, 136.5, 133.9, 133.6, 132.9, 132.4, 132.2, 132.1. 131.9, 130.6, 130.4, 130.2, 129.4, 129.3, 129.1, 128.9, 128.8, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.2, 126.7, 126.1, 126.0, 124.6, 124.2, 124.0, 123.5, 123.4, 123.3, 121.6, 119.1, 118.3, 114.1, 74.7, 72.2, 71.5, 71.2, 69.6, 69.2, 68.2, 31.1, 30.7, 30.6, 29.9; MALDI-TOF MS m/z 887.6 ([M + Na]$^+$), 903.5 ([M + K]$^+$); IR (KBr) 3443, 2918, 1782, 1621, 1591, 1459. Anal. Calcd for $C_{56}H_{48}O_9$·0.5H_2O: C, 76.96; H, 5.65. Found: C, 77.14; H, 6.05;

4a-2: mp 158−160 °C; ^{1}H NMR ($CDCl_3$) δ 8.11 (d, 1H, J = 8.9 Hz), 8.02 (d, 1H, J = 8.8 Hz), 7.85 (dd, 2H, J = 8.9 Hz), 7.56−7.50 (m, 2H), 7.39 (s, 1H), 7.35−7.01 (m, 9H), 6.78 (t, 1H, J = 7.3 Hz), 6.58−6.51 (m, 4H), 6.39−6.32 (m, 3H), 5.23 (s, 1H), 4.61, 4.42, 4.39, 4.29 (4d, 4H, J = 14.3 Hz, $ArCH_2Ar$), 4.24−3.61 (m, 14H), 3.37, 3.26, 3.14, 3.01 (4d, 4H, J = 13.2 Hz, $ArCH_2$-Ar); ^{13}C NMR ($CDCl_3$) δ 167.7, 156.5, 153.6, 153.3, 152.7, 152.2, 147.3, 136.8, 136.7, 133.8, 133.6, 133.5, 132.7, 132.5, 132.3, 132.2, 130.3, 130.2, 130.1, 129.3, 129.2, 129.1, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.2, 126.7, 126.1, 126.0, 124.6, 124.2, 123.9, 123.6, 123.4, 123.3, 121.6, 118.9, 118.4, 114.3, 74.7, 72.0, 71.9, 71.1, 69.6, 69.1, 68.4, 30.9, 30.6, 30.5, 30.1; MALDI-TOF MS m/z 887.4 ([M + Na]$^+$), 903.4 ([M + K]$^+$); IR (KBr) 3447, 2918, 1782, 1622, 1591, 1460. Anal. Calcd for $C_{56}H_{48}O_9$: C, 77.76; H, 5.59. Found: C, 77.58; H, 6.09.

(+)-3a and (−)-3a (Enantiomerically Pure). Hydrolyzing **4a-1** and **4a-2** according to the method of preparing **3** afforded (+)-**3a** and (−)-**3a**, respectively, as white solids with enantiomeric purity ((+)-**3a**, yield 79%; (−)-**3a**, yield 77%). Both have mp, ^{1}H NMR, and ^{13}C NMR data similar to that of racemic mixture **3a**.

(+)-3a: mp 237−239 °C; ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 7.19−6.63 (m, 12H), 4.62, 4.57, 4.37, 4.33 (4d, 4H, J = 14.1 Hz, $ArCH_2$-Ar), 4.30−3.74 (m, 14H), 3.48−3.30 (m, 4H, $ArCH_2Ar$); MALDI-TOF MS m/z 619.5 ([M + Na]$^+$); IR(KBr) 3429, 2925, 1625, 1462; $[\alpha]_D$ +40 (c 0.5, CH_2Cl_2). Anal. Calcd for $C_{36}H_{36}O_8$·H_2O: C, 70.34; H, 6.23. Found: C, 70.34; H, 6.21.

(−)-3a: mp 238−239 °C; ^{1}H NMR ($CDCl_3$) δ 8.91 (s, 1H), 7.24−6.70 (m, 12H), 4.63, 4.58, 4.40, 4.36 (4d, 4H, J = 14.0 Hz, $ArCH_2$-Ar), 4.29−3.78 (m, 14H), 3.52, 3.48, 3.45, 3.36 (4d, 4H, J = 13.0 Hz, $ArCH_2Ar$); MALDI-TOF MS m/z 619.4 ([M + Na]$^+$), 635.4 ([M + K]$^+$); IR (KBr) 3419, 2923, 1620, 1464; $[\alpha]_D$ −40 (c 0.5, CH_2Cl_2). Anal. Calcd for $C_{36}H_{36}O_8$·0.5H_2O: C, 71.39; H, 6.16. Found: C, 71.22; H, 6.22.

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Supporting Information Available: Detailed experimental procedures and spectra of relative compounds **1b**, **2b**, **3b**, **4b-1**, **4b-2**, (+)-**3b**, and (−)-**3b** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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