Research Article

Wen-Shan Liu*, Hong-Ying Li, Hai-Xia Zhang, Xiu-Yuan Han, Xi-Chun Guo, Chuan-Hua Ding*

Bridging chiral de-*tert*-butylcalix[4]arenes: Optical resolution based on column chromatography and structural characterization

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Abstract: As the third-generation supramolecular main structure, calixarenes, especially chiral calixarenes, have been applied to various fields. In this study, the bridging chiral de-*tert*-butylcalix[4]arene derivatives with an amide group attached to a chiral point was synthesized for the first time, which provided a new group for its structural derivation at the bridging chiral position. The racemic compound **2** was optically resolved by column chromatography on silica gel with the aid of the chiral auxiliary (1*S*)-(+)-10-camphorsulfonyl chloride, and finally a pair of optically pure bridging chiral de-*tert*-butylcalix[4]arene derivatives **4a** and **4b** were obtained. The results of experimental and calculated ECD showed that compounds **4a** and **4b** were a pair of enantiomers, and their absolute configurations were designated *S* and *R*, respectively. This study provides new idea for the derivatization of specific chiral groups based on bridging chiral calix[4]arenes and their chiral resolution.

Keywords: de-*tert*-butylcalix[4]arene, (1*S*)-(+)-10-camphorsulfonyl chloride, synthesis, chiral resolution, ECD

Graphical abstract

1 Introduction

With its unique three-dimensional cavity structure, calixarene has become the third-generation supramolecular host molecule after crown ether and cyclodextrin. Calixarenes derivatives are widely used in biomedicine [1], nanoscience [2], and chemical sensors [3]. In particular, the application of chiral calixarenes derivatives in chiral recognition [4,5] and molecular asymmetric catalysis [6–8] has broad application prospects.

Intrinsically chiral calixarenes contain two major family members: inherently chiral calixarenes [9,10] and bridging chiral calixarenes [11–13]. Inherently chiral calixarenes are derived from asymmetric substitution only on the phenyl rings and (or) oxygen atom. The bridging chiral calixarenes exhibit asymmetric substitution on the bridged methylene group. Figure 1 takes de-*tert*-butylcalix[4]arenes as an example to show its two intrinsically chiral structures. Although inherently chiral calixarenes have been studied for decades and applied to many fields, its chiral recognition ability and asymmetric catalytic efficiency are often not satisfactory. The exciting thing is that the unique bridging chiral calixarenes will provide a platform for the construction of specific chiral hosts and catalysts and will point out a new direction for future development. However, there are two main reasons that limit the further application of bridging chiral calixarenes, one is the problem of optical purification of bridging chiral calixarenes, and the other is the

* **Corresponding author: Wen-Shan Liu**, Department of Pharmacy, Shandong Key Laboratory of Clinical Applied Pharmacology, Affiliated Hospital of Weifang Medical University, Weifang 261041, Shandong Province, China, e-mail: liuwenshan@wfmc.edu.cn

* **Corresponding author: Chuan-Hua Ding**, Department of Pharmacy, Shandong Key Laboratory of Clinical Applied Pharmacology, Affiliated Hospital of Weifang Medical University, Weifang 261041, Shandong Province, China, e-mail: dchh422@163.com

Hong-Ying Li, Hai-Xia Zhang, Xiu-Yuan Han, Xi-Chun Guo: Department of Pharmacy, Shandong Key Laboratory of Clinical Applied Pharmacology, Affiliated Hospital of Weifang Medical University, Weifang 261041, Shandong Province, China

Figure 1: Intrinsically chiral calix[4]arenes: (a) shows inherently chiral calixarenes and (b) shows bridging chiral calixarenes.

lack of further derivable groups on the chiral structure, such as amide, amino, or carboxyl groups. Here, we focus on the derivation of amide group. As an important derivative group, amide can be modified to the required groups through reduction reaction, Hoffman degradation reaction, and so on.

In this study, we introduced an amide group on the chiral group of the chiral calixarenes for the first time and used chiral auxiliary (1*S*)-(+)-10-camphorsulfonyl chloride to perform optical resolution on it by column chromatography. The absolute configurations of the enantiomers **4a** and **4b** were determined by electron circular dichroism (ECD) experiment and calculation. This study provides a new method for the structure derivation and chiral resolution of bridging chiral calix[4]arenes.

2 Results and discussion

Using *de-tert*-butylcalix[4]arenes as the starting material, bridging chiral *de-tert*-butylcalix[4]arene derivative 1 mono-bridge-substituted with an equatorial *N,N'*-dimethylformamyl group could be prepared through a homologous anionic ortho-Fries rearrangement in high yield [9]. As shown in the synthetic route of Figure 2, first, the *N,N'*-dimethylformamide group was hydrolyzed in toluene under the action of strong acid methanesulfonic acid and formed an unstable lactone structure with the phenol hydroxyl group on the ortho-benzene of the chiral center. The reaction solution did not require posttreatment, and ammonia water was added at 0°C to obtain the bridging chiral *de-tert*-butylcalix[4]arene with an equatorial amide

Figure 2: Reagents and conditions: (a) methanesulfonic acid, toluene, 120°C; (b) $\text{NH}_3 \cdot \text{H}_2\text{O}$, 0°C; (c) (1*S*)-(+)-10-camphorsulfonyl chloride, Cs_2CO_3 , CH_3CN , rt; and (d) NaOH , $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 80°C.

group 2. Subsequently, (1*S*)-(+)-10-camphorsulfonyl chloride was used as a chiral auxiliary, and under the action of Cs_2CO_3 in CH_3CN at room temperature, a nucleophilic substitution reaction occurred with the phenolic hydroxyl group on compound **2** to obtain a pair of diastereomeric mixtures **3a** and **3b**. The molar ratio between the chiral auxiliary and compound **2** was 1:1. Fortunately, the R_f values of the diastereomers **3a** and **3b** were 0.46 and 0.40, respectively, with visible separation points. They could be successfully separated through silica gel column chromatography, with the total yield reaching 86% (**2a**, 45%; **2b**, 41%). Finally, the chiral auxiliary (1*S*)-(+)-10-camphorsulfonyl group on the diastereomers **3a** and **3b** was removed to obtain a pair of enantiomers **4a** ($[\alpha]_D^{25} = -7.7$) and **4b** ($[\alpha]_D^{25} = +7.8$) under alkaline conditions.

The theoretical ECD spectra of **4a** and **4b** were calculated by quantum chemistry method, according to the relative spatial relationship between the bridging center and propyl group, and compared with those of methanol. As shown in Figure 3a, at room temperature, the experimental ECD spectra of **4a** and **4b** in MeOH at a concentration of 1.0×10^{-4} g/L showed a pair of excellent mirror images, proving that they were a pair of enantiomers. As shown in Figure 3b, the ECD spectra of compounds **4a** and **4b** calculated at TD-B3LYP/6-31G(d)//B3LYP/6-31G(d) level showed an acceptable fit with their experimental spectra in terms of band form and sign with respect to wavelength. According to the results of ECD experiment and calculation, the absolute configurations of compounds **4a** and **4b** could be assigned as *S* and *R*, respectively.

In the process of hydrolyzing *N,N*-dimethylformamide in compound **1**, we tried many hydrolysis reagents, including strong acids such as *p*-toluenesulfonic acid, concentrated hydrochloric acid, concentrated sulfuric acid, and trifluoroacetic acid, as well as some strong bases. However, these hydrolysis reagents were difficult to react. In the end, under our continuous attempts and efforts to replace the reaction solvent, we found that methane sulfonic acid had a good hydrolysis effect on the *N,N*-dimethylformamide group of compound **1**. Compared with several strong acids tried before, methanesulfonic acid is more acidic, resulting in the hydrolysis of *N,N*-dimethylformamide. Interestingly, when analyzing the structure of compound **2**, we were pleasantly surprised to find that during the hydrolysis of compound **1**, a propoxy group in the structure was also hydrolyzed to a phenolic hydroxyl group, which had been confirmed by ^1H NMR spectrum and high-resolution mass spectrometry. As shown in Figure 4, according to the intermolecular hydrogen bond (H-bond) interaction, the phenolic hydroxyl group after the hydrolysis of the propoxy group and the phenolic hydroxyl group on the two ortho-benzene rings, respectively, formed intramolecular H-bond

Figure 3: (a) Experimental ECD spectra of **4a** (black line) and **4b** (red line) in MeOH and (b) calculated ECD spectra of **4a** (blue line) at the TD-B3LYP/6-31G(d)//B3LYP/6-31G(d) level.

interactions, which marked the chemical shift of the phenol hydroxyl group after the hydrolysis of propoxy group larger, and the peak shaped wider and shorter. This indicated that the activity of phenolic hydroxyl group after hydrolysis of propoxy group was significantly higher than that of phenolic hydroxyl group on two ortho-benzene rings, which was conducive to the hydrolysis of *N,N*-dimethylformamide and the formation of lactone. In addition, according to the hydrogen spectrum structure of compound **3a**, it was found that after the resolution reagent reacted with the phenolic hydroxyl group, the broad and low peak disappeared, which further indicated that the resolution reagent reacted with the phenolic hydroxyl group after the hydrolysis of propoxy group.

3 Conclusion

As the main structure of the third-generation supramolecular, calixarenes have been widely used in various

Figure 4: The chemical shift and peak characteristics of hydroxyl functional groups in compounds **2** and **3a**: (a) shows the structure of compound **2**, (b) shows the hydroxyl peak in compound **2**, (c) shows the structure of compound **3a**, and (d) shows the hydroxyl peak in compound **3a**.

fields. This study focused on the structure of bridging chiral de-*tert*-butylcalix[4]arene and obtained the first bridging chiral de-*tert*-butylcalix[4]arene with an amide group attached to the chiral point. Using the chiral auxiliary (1S)-(+)-10-camphorsulfonyl chloride, the racemic compound **2** was optically resolved to obtain a pair of optically pure bridging chiral calix[4]arene derivatives **4a** and **4b**, and the experimental and calculated results of ECD spectra proved that they were a pair of enantiomers. This study provides a new method for the derivatization and resolution of bridging chiral calixarenes.

4 Experimental section

General information: All chemicals were purchased from commercial sources and used without further purification. ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded at 300 MHz (^1H) and at 75.5 MHz (^{13}C). CDCl_3 (δ 7.26 ppm) or TMS (δ 0.00 ppm) was used as an internal standard for ^1H NMR spectra, and CDCl_3 (δ 77.00 ppm) or TMS (δ 0.00 ppm) was used as an internal standard for ^{13}C NMR spectra. The following abbreviations are used to indicate the multiplicity in NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and J indicates the NMR coupling constant measured in Hertz. The courses of the reactions were monitored by thin layer chromatography (TLC) using TLC aluminium sheets with Silica gel 60 GF254. The column chromatography was performed

using Silica gel 60. Optical rotations were measured using a polarimeter with a 1 dm path length. Experimental circular dichroism spectra were recorded in a quartz cuvette of 1 mm optical path length. High-resolution mass spectra (HRMS) were measured on a mass spectrometer equipped with a time of flight (TOF) system and an electrospray ionization (ESI) ion source.

Compound 2. A mixture of compound **1** (3.00 g, 5.06 mmol) and methanesulfonic acid (1.64 mL, 25.30 mmol) in toluene (100 mL) was stirred at 110°C for 3 h. After the reaction was completed by TLC analysis, the heating device was removed, and the reaction temperature was reduced to 0°C under the condition of ice bath. A 25% aqueous ammonia solution (40 mL) was slowly added dropwise, and the reaction was stopped after stirring for 1 h. The mixture was extracted with CH_2Cl_2 (3 mL $\times$ 60 mL) and washed with saturated NaCl solution (3 mL $\times$ 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (PE:EA = 3:1) to obtain the intermediate **2** (1.65 g, 62% yield).

Compound 2: White solid. M.p. 196.5–198.2°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.14 (s, 1H), 8.72 (s, 1H), 8.63 (s, 1H), 7.49 (t, 2H), 7.31 (d, J = 7.2 Hz, 1H), 7.07–7.21 (m, 6H), 6.92 (dd, J = 1.6 Hz, J = 7.2 Hz, 1H), 6.83 (t, 1H), 6.61–6.68 (m, 2H), 6.55–6.60 (t, 1H), 5.57 (s, 1H), 4.14–4.24 (m, 2H), 4.10 (d, J = 13.6 Hz, 1H), 4.01–4.07 (m, 1H), 3.88–3.97 (m, 1H), 3.58 (d, J = 13.2 Hz), 3.47 (s, J = 12.8 Hz,

1H), 3.42 (d, $J = 13.6$ Hz, 1H), 1.92–2.02 (m, 2H), 1.21 (t, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.7, 150.8, 150.5, 150.4, 148.1, 132.8, 128.1, 128.0, 127.6, 127.6, 127.4 (3C), 127.3, 127.3, 127.1, 126.9, 126.5, 126.5, 125.5, 124.4, 119.8, 118.8, 118.3, 116.9, 77.0, 30.6, 29.8 (2C), 29.2, 21.7, 9.6 ppm. HRMS (ESI): calcd for $\text{C}_{32}\text{H}_{31}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 510.2280; found 510.2278.

Compounds 3a and 3b. To a stirred solution of compound **2** (1.50 g, 2.86 mmol) in dry CH_3CN (80 mL) was slowly added Cs_2CO_3 (2.80 g, 8.58 mmol) under ice-bath. After stirring for 10 min, (1*S*)-10-camphorsulfonyl chloride (1.08 g, 4.29 mmol) was added, the reaction was continued for 2.5 h at room temperature until the reaction was completed and quenched with dilute hydrochloric acid solution. The aqueous layer was extracted with CH_2Cl_2 , extracted twice, and the combined organic layers were washed with saturated NaCl solution and dried over anhydrous Na_2SO_4 . The resulting residue was purified by column chromatography on silica gel (PE: EA = 2:1) to obtain the intermediates **3a** and **3b** (0.93 g, 45% yield for **3a**; 0.85 g, 41% yield for **3b**).

Compound 3a: White solid. M.p. 225.5–227.3°C. ^1H NMR (400 MHz, DMSO- d_6) δ 9.82 (s, 1H), 9.12 (s, 1H), 7.43 (d, $J = 7.8$ Hz, 2H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.05–7.19 (m, 6H), 6.97 (t, 1H), 6.85 (t, 1H), 6.62–6.72 (m, 2H), 5.74 (s, 1H), 4.53 (d, $J = 13.2$ Hz, 1H), 4.17–4.25 (m, 1H), 3.95–4.10 (m, 4H), 3.55–3.66 (m, 2H), 3.51 (d, $J = 14.4$ Hz, 1H), 3.50 (d, $J = 14.4$ Hz, 1H), 2.31–2.47 (m, 2H), 2.17–2.28 (m, 2H), 2.19 (t, 1H), 1.98–2.06 (m, 2H), 1.57–1.67 (m, 1H), 1.44–1.52 (m, 1H), 1.13 (t, 3H), 1.02 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 212.2, 171.1, 151.3, 150.4, 147.8, 141.8, 134.2, 133.4, 132.5, 130.4, 129.3, 129.2, 128.7, 128.2, 128.1, 127.7, 127.7, 127.5, 127.3, 127.2, 126.0, 124.9, 124.5, 124.0, 120.4, 118.6, 77.3, 56.5, 46.8, 46.2, 41.2, 40.9, 29.9, 29.8, 29.2, 28.9, 25.1, 24.0, 21.4, 18.2, 18.0, 8.8 ppm. HRMS (ESI): calcd for $\text{C}_{32}\text{H}_{31}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 724.2944; found 724.2942.

Compound 3b: White solid. M.p. 232.4–234.2°C. ^1H NMR (400 MHz, DMSO- d_6) δ 9.83 (s, 1H), 9.11 (s, 1H), 7.49–7.42 (m, 2H), 7.27 (m, 2H), 7.21–7.04 (m, 6H), 6.98 (t, 1H), 6.92–6.81 (m, 1H), 6.67 (m, 2H), 5.75 (s, 1H), 4.53 (d, $J = 13.1$ Hz, 1H), 4.26–4.15 (m, 2H), 4.05 (d, $J = 2.0$ Hz, 1H), 4.01 (d, $J = 2.1$ Hz, 1H), 3.82 (d, $J = 14.3$ Hz, 1H), 3.68–3.57 (m, 3H), 3.51 (d, $J = 13.6$ Hz, 1H), 2.44–2.34 (m, 2H), 2.28–2.19 (m, 2H), 2.13 (t, $J = 4.5$ Hz, 1H), 2.04–1.96 (m, 2H), 1.68–1.62 (m, 1H), 1.50–1.44 (m, 1H), 1.18–1.08 (m, 6H), 0.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 213.1, 172.0, 152.3, 151.4, 148.9, 143.1, 135.3, 134.5, 133.5, 131.5, 130.2, 130.2, 129.9, 129.3, 129.2, 128.8, 128.8, 128.6, 128.4, 128.2, 127.1, 126.1, 125.6, 125.0, 121.5, 119.7, 78.4, 57.5, 48.0, 46.8, 42.5, 41.9, 31.0, 30.8, 30.4, 30.0, 26.2, 25.4, 22.5, 19.2, 19.1, 9.9 ppm. HRMS (ESI): calcd for $\text{C}_{32}\text{H}_{31}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 724.2944; found 724.2939.

Compounds 4a and 4b. To a solution of compound **3a** (or **3b**) (0.5 g, 0.69 mmol) in CH_3CN (30 mL) and water (10 mL) was added NaOH (0.14 g, 3.45 mmol). The reaction mixture was heated to 80°C and stirred for 1 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was neutralized with dilute hydrochloric acid and extracted with CH_2Cl_2 (30 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and evaporated to dryness. The product was further purified by silica gel column chromatography (PE:EA = 3:1) to give **4a** (or **4b**) as a white powder (0.34 g, 94% yield for **4a**; 0.33 g, 92% yield for **4b**).

Compound 4a: White solid. M.p. 192.4–196.3°C. ^1H NMR (400 MHz, DMSO- d_6) δ 9.14 (s, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 7.44–7.56 (m, 2H), 7.30 (d, $J = 6.8$ Hz, 1H), 7.05–7.21 (m, 6H), 6.92 (d, $J = 7.2$ Hz, 1H), 6.83 (t, 1H), 6.61–6.68 (m, 2H), 6.58 (t, 1H), 5.57 (s, 1H), 4.14–4.25 (m, 2H), 4.10 (d, $J = 13.6$ Hz, 1H), 3.99–4.06 (m, 1H), 3.89–3.97 (m, 1H), 3.58 (d, $J = 13.2$ Hz, 1H), 3.39–3.51 (m, 2H), 1.90–2.05 (m, 2H), 1.21 (t, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 173.7, 151.9, 151.6, 151.5, 149.2, 133.9, 129.2, 129.1, 128.7, 128.7, 128.6, 128.5 (3C), 128.4, 128.3, 128.2, 127.9, 127.6, 127.6, 126.5, 125.5, 120.8, 119.9, 119.3, 78.1, 31.6, 30.9, 30.2, 30.0, 22.8, 10.7 ppm. HRMS (ESI): calcd for $\text{C}_{32}\text{H}_{31}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 510.2280; found 510.2277.

Compound 4b: White solid. M.p. 197.7–199.3°C. ^1H NMR (400 MHz, DMSO- d_6) δ 9.10 (s, 1H), 8.67 (d, 2H), 7.45–7.57 (m, 2H), 7.31 (d, $J = 6.8$ Hz, 1H), 7.05–7.20 (m, 6H), 6.92 (d, $J = 7.2$ Hz, 1H), 6.83 (t, 1H), 6.61–6.68 (m, 2H), 6.58 (t, 1H), 5.58 (s, 1H), 4.15–4.26 (m, 2H), 4.10 (d, $J = 13.2$ Hz, 1H), 3.99–4.07 (m, 1H), 3.88–3.98 (m, 1H), 3.58 (d, $J = 13.6$ Hz, 1H), 3.39–3.52 (m, 2H), 1.90–2.05 (m, 2H), 1.21 (t, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 173.8, 151.9, 151.6, 151.5, 149.3, 133.9, 129.2, 129.1, 128.7, 128.7 (2C), 128.5 (3C), 128.4, 128.4, 128.2, 128.0, 127.6, 127.6, 126.6, 125.5, 120.8, 119.9, 119.4, 78.1, 31.6, 30.9, 30.2, 30.0, 22.8, 10.7 ppm. HRMS (ESI): calcd for $\text{C}_{32}\text{H}_{31}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 510.2280; found 510.2278.

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Conflict of interest: The authors report no conflicts of interest in this study.

Ethical approval: The conducted research is not related to either human or animal use.

Data availability statement: The data used to support the findings of this study are included within the supplementary information file.

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