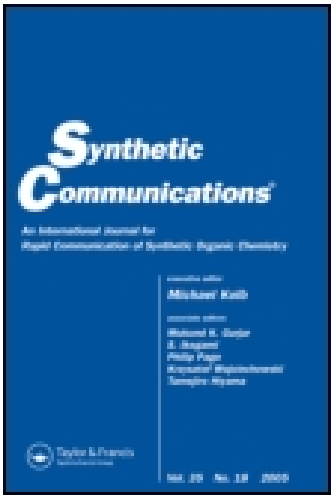

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# SYNTHESES OF NOVEL CHIRAL CALIX[4]CROWN: LARIAT CALIX[4]-1,3-AZA-CROWNS WITH CHIRAL AMINO ACID GROUPS AS BRANCHED CHAINS

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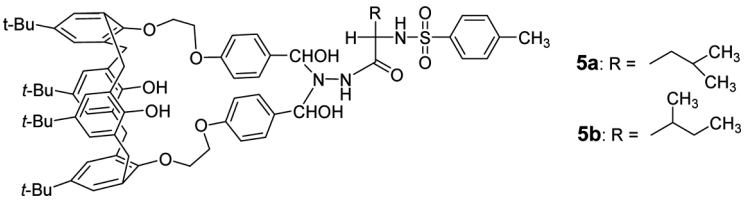
## GRAPHICAL ABSTRACT




**Abstract** *The first examples of lariat calix[4]-1,3-aza-crowns with chiral amino acid groups as branched chains (**5a** and **5b**) were designed and synthesized via a 1 + 1 addition reaction of calix[4]-1,3-substituted benzaldehyde derivative (**4**) and amino acid hydrazide derivatives (**3a** and **3b**) in yields of 70% and 75%, respectively. The preliminary extraction experiments suggested that hosts **5a** and **5b** possessed good complexation abilities for α-amino acids.*

**Keywords** Amino acid; aza; calix[4]crown; chiral; lariat

## INTRODUCTION

Calixarenes are important supramolecular building blocks, which can be modified by introducing suitable functional groups and/or structural groups to create a specific interaction and target guest molecules.[1,2] In particular, the chiral recognition of calixarene derivatives has attracted increasing research interest because of potential applications in enantiomer discrimination processes.[3–5] To obtain chiral calixarenes, the facile methods introduced chiral units on calix rims. Therefore, a large number of chiral calixarenes have been synthesized using chiral units as functional groups, such as amino acids,[6] amino alcohol,[7] peptides,[8] alkaloids,[9] chiral amines,[10] pinene-like units,[11] glycidyl,[12] and guanidinium

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groups.[13] On the other hand, some chiral calix[4]crowns were reported using chiral spacers as bridging chains, such as binaphthyl amine,[11] diphenyl amine,[14] dinaphthol ether,[5,15] and glucoside,[16] From these reports, it could be concluded that the enantiomer recognition capabilities depended on the species, structures, and conformations of chiral calix[4]arenene. In this article, we report the facile synthesis of a novel chiral calix[4]crown: the lariat calix[4]-1,3-aza-crown with chiral amino acid groups as branched chains.

The synthetic route is shown in Figure 1. L-leucine and L-Isoleucine were converted to their ester derivatives **1a** and **1b**. Reacting compounds **1a** and **1b** with p-toluene sulfonyl chloride afforded compounds **2a** and **2b**. Then, by ammonolysis of compounds **2a** and **2b** with hydrazine hydrate, amino acid hydrazide derivatives **3a** and **3b** were prepared in ideal yields.[17] By reacting *p-tert*-butylcalix[4]arene with *p*-tosyloxyethoxyl-benzaldehyde (mol. ratio = 1:2) in a $K_2CO_3$/MeCN system for 48 h, calix[4]-1,3-substituted benzaldehyde derivative **4** was obtained.[18] By stirring compound **4** with **3** in $CHCl_3$-EtOH ($V/V$ 1:1) at room temperature, novel chiral calix[4]crown **5a** and **5b** were prepared via $1+1$ addition. They were purified conveniently by crystallization in $CHCl_3$-MeOH in yields of 70% and 75%, respectively. It was interesting that no Schiff base (containing C=N bonds) condensation products were obtained in this reaction condition under any molar ratio of compounds **4** and **3**. when these reactions were performed under refluxing conditions, the reaction results became complicated and no purified compounds were separated successfully. To obtain Schiffbase condensation product, we also tried to react compound **1** with **4** directly, but no condensation reaction happened under any kind of reaction conditions, which might be attributed to the low reaction activities of amino groups in compound **1**. To the best of our knowledge, compounds **5a** and **5b** were the first examples of lariat calix[4]-1,3-aza-crowns with chiral amino acid groups as branched chains.

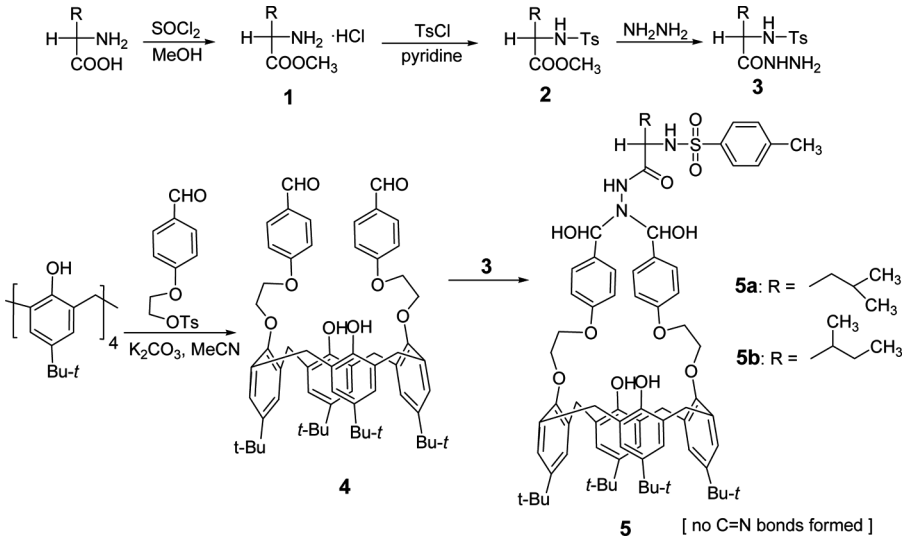


**Figure 1.** The synthetic route of the title compounds.

**Table 1.** Extracting percentages (%E) of α-amino acids from water into $CHCl_3$

| Amino acids | Gly | Trp | His | Lys | Ile | Arg | Pro | Thr |
|---|---|---|---|---|---|---|---|---|
| **5a** | 15.3 | 48.3 | 17.6 | 24.8 | 26.4 | 10.9 | 18.2 | 23.3 |
| **5b** | 13.1 | 56.8 | 23.4 | 18.6 | 23.3 | 14.2 | 13.7 | 24.6 |

The structures and conformations of novel chiral calix[4]arenes **5a** and **5b** were characterized by electrospray ionization–mass spectrometry (ESI-MS) infrared (IR) spectra, $^1$H NMR, and elemental analyses. The ESI-MS spectra of compound **5a** and **5b** showed clearly molecular base peaks at 1282.0 ($MK^+$) and 1243.3 ($M^+$), respectively, which indicated that these reactions were $1+1$ intermolecular addition reactions, not Schiffbase condensation. This deduction was also supported by the IR spectra of **5a** and **5b**, in which the C=O absorption peak of compound **4** at 1694 $cm^{-1}$ disappeared, but no C=N (Schiffbases) absorption peak appeared. In the $^1$H NMR spectra of compounds **5a** and **5b**, all $^1$H NMR signals were assigned to protons properly. Two singlets (1:1) for the *tert*-butyl groups, and one AB system for the methylene bridges of the calix[4]arene skeleton indicated that the calix[4]arene moiety adopted the cone conformation.[9–11,17]

To evaluate the complexation abilities of novel hosts **5a** and **5b**, the preliminary extraction experiments for α-amino acids were studied. The results are summarized in Table 1. It can be seen that compounds **5a** and **5b** exhibited reasonable extraction abilities toward tested α-amino acids. Moreover, both **5a** and **5b** showed good extraction selectivity for tryptophan. The extraction percentage of host **5b** for tryptophan was as high as 56.8%. The similar complexation abilities of **5a** and **5b** might be attributed to their similar "pre-organized" bridging-crown structures. Further complexation studies, such as enantiomer discrimination, are under investigation.

## EXPERIMENTAL

Melting points are uncorrected. $^1$H NMR spectra were recorded in $CDCl_3$ on a Bruker-ARX 500 instrument at room temperature, using tetramethylsilane (TMS) as an internal standard. ESI-MS spectra were obtained on a DECAX-30000 LCQ Deca XP mass spectrometer. Elemental analyses were performed on a Vario EL III Elemental Analyzer. IR spectra were recorded on a Perkin-Elmer 1605 Fourier transform (FT)–IR spectrometer as KBr pellets. Calix[4]-1,3-substituted benzaldehyde derivative **4**[18] and the hydrazide derivatives of L-leucine and L-*iso*-leucine (**3a** and **3b**),[19] were prepared according to the published procedures. All solvents were purified by standard procedures.

### Novel Chiral Calix[4]crowns 5a and 5b

Under an $N_2$ atmosphere, the mixture of compound **4** (1 mmol, 0.94 g) and amino acid derivative **3** (1.1 mmol, 0.33 g) was stirred in 40 mL $CHCl_3$-EtOH ($V/V$ 1:1) at room temperature for 24 h. Thin-layer chromatography (TLC) detection showed the disappearance of materials. After distilling off the solvent under reduced pressure at room temperature, the residue was treated with 15 mL MeOH. The yellow

precipitation was then separated out. The precipitation was recrystallized by $CHCl_3$-MeOH, novel chiral calix[4]crowns **5a** and **5b** were then obtained in the yields of 70% and 75%, respectively.

**Compound 5a.** Mp 243–245 °C; $[\alpha]_D^{27} = +3.7$ (*c* 0.20, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 1.0 [s, 18 H, $C(CH_3)_3$], 1.03–1.09 [m, 6 H, $C(CH_3)_2$], 1.28 [s, 18 H, $C(CH_3)_3$], 2.20–2.45 (m, 4 H, $ArCH_3$ and $CHMe_2$), 1.38–1.46 (m, 2 H, $CCH_2C$), 3.30 (d, $J = 16.5$ Hz, 4 H, $ArCH_2Ar$), 3.33 (bs, 1 H, CHCO), 4.20 – 4.30 (m, 10 H, $OCH_2$ and ArCH), 4.36 (d, $J = 16.5$ Hz, 4 H, $ArCH_2Ar$), 6.75 – 7.95 (m, 20 H, ArH), 8.38 (bs, 2 H, OH), 8.90 (bs, 2 H, OH), 9.78 (s, 1 H, NH), 9.83 (s, 1 H, NH); IR (KBr) ν: 3429 (OH and NH), 1602 (CONH) $cm^{-1}$; MS *m/z* (%): 1282.0 ($MK^+$, 100). Anal. calcd. for $C_{75}H_{93}O_{11}N_3S$: C, 72.38; H, 7.53; N, 3.37. Found: C,72.29; H, 7.62; N, 3.49.

**Compound 5b.** Mp 228–231 °C; $[\alpha]_D^{27} = +3.1$ (*c* 0.20, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 1.01 [s, 18 H, $C(CH_3)_3$], 1.04–1.10 [m, 6 H, $C(CH_3)_2$], 1.29 [s, 18 H, $C(CH_3)_3$], 1.18–1.27 (m, 2 H, $CH_2Me$), 2.18–2.43 (m, 4 H, $ArCH_3$ and CHMe), 3.31 (d, $J = 16.0$ Hz, 4 H, $ArCH_2Ar$), 3.30 (bs, 1 H, CHCO), 4.18–4.30 (m, 10 H, $OCH_2$ and ArCH), 4.35 (d, $J = 16.0$ Hz, 4 H, $ArCH_2Ar$), 6.71 – 7.92 (m, 20 H, ArH), 8.37 (bs, 2 H, OH), 8.88 (bs, 2 H, OH), 9.72 (s, 1 H, NH), 9.94 (s, 1 H, NH); IR (KBr) ν: 3430 (OH and NH), 1604 (CONH) $cm^{-1}$; MS *m/z* (%): 1243.3 ($M^+$, 100). Anal. calcd. for $C_{75}H_{93}O_{11}N_3S$: C, 72.38; H, 7.53; N, 3.37. Found: C, 72.27; H, 7.59; N, 3.47.

### The Extraction Experiments of α-Amino Acids

According to the reported methods[20,21], 3 mL of chloroform solution containing calixarene derivative ($1.0 \times 10^{-4}$ M) and 3 mL of aqueous solution containing amino acids ($1.0 \times 10^{-4}$ M) were placed in a flask. The mixture was shaken for 5 min and stored for 2 h at room temperature. The extraction ability was not affected by further shaking, indicating that the equilibrium had been attained within 2 h. The concentrations of amino acids after extraction were assessed by classical ninhydrin tests.[22] The extracting percentage (E%) was determined by the decrease of the amino acid concentration in the aqueous phase: $E\% = \{([Pic]_{blank} - [Pic]_{water})/[Pic]_{blank}\} \times 100$, where $[Pic]_{blank}$ denoted the amino acid concentrations in the aqueous phase after extraction with pure chloroform and $[Pic]_{water}$ denoted the amino acid concentrations in the aqueous phase after extraction with chloroform solution containing calixarene derivatives as extractants. An average of two independent experiments was carried out. The measuring error for amino acid extraction test data was less than 2%. Control experiments showed that the extraction percentages for amino acids were less than 0.3% in the absence of the calixarene derivatives.

## ACKNOWLEDGMENTS

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