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Synthesis and chiral recognition abilities of new calix[6]arenes bearing amino alcohol moieties

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Abstract—Herein the synthesis and recognition abilities towards amino acids and amino alcohols of new D-/L-phenylalaninol substituted *p-tert*-butylcalix[6]arenas are reported. These compounds, **6** and **7** have been synthesized via nucleophilic substitution reactions involving 5,11,17,23,29,35-*tert*-butyl-37,38-dimethoxy-39,40,41,42-(*p*-tosylethoxy)calix[6]arene **5** with D-/L-phenylalaninol in dry THF. The extraction properties of **6** and **7** towards some selected amino acid methylesters and amino alcohols have been studied by liquid–liquid extraction. These results show that chiral calix[6]arene derivatives exhibit a good affinity towards all amino acids and amino alcohols.

1. Introduction

A macrocyclic compound forms a stable complex with a guest molecule by entrapping it into its cavity. Since the 1980s, calixarene, which is formed by the condensation between *p*-alkyl phenol and formaldehyde under basic conditions, has attracted much attention as a macrocyclic platform. The scaffold of calix[*n*]arenes can be modified by introducing many kinds of functional groups and/or structural groups, to create a specific interaction to a target guest molecule. A number of books have been published concerning the synthesis, structural features and host–guest interactions.[1] More specifically, the subject of chemical recognition and separation of ions was addressed in several publications.[2] On the other hand, only a few reviews concerning calixarenes for biochemical recognition are available, for example, on peptido- and glycoconjugates and the role of hydrogen-bonding interactions,[3] on neoglycoconjugates with large rigidified cavities[4] and on synthetic receptors.[5] Molecular recognition, and in particular chiral recognition, is one of the most fundamental and significant processes in living systems.[6] Chiral recognition can contribute to the understanding of biochemical systems and offer new perspectives for the development of pharmaceuticals, enantioselective sensors, catalysts and other molecular devices.[7] Among the several kinds of host molecule for recognition, calixarenes offer a number of advantages in terms of selectivity and efficiency of binding.[8] The introduction of an amino acid or an amino alcohol could lead to chirality in the artificial receptors. Due to the important role played by amino acid and amino alcohol units in several recognition processes of natural and artificial systems,[9] chiral discrimination[10] and stereoselective synthesis, synthetic calix[4]arenes containing amino acid have been extensively studied.[11] Readily available calix[6]arenes could constitute as ideal platforms for the design of such enantioselective endo-receptors.[1,12] In fact, their cavity is large enough for the deep inclusion of organic molecules. Surprisingly, examples of enantiomerically pure calix[6]arenes are rare[13] and their host–guest properties towards chiral guests have not been investigated much. This is mainly due to the fact that calix[6]arenes suffer from their reputation as highly flexible molecules, which is not compatible with efficient syntheses and good host properties. Recently we reported that the synthesis of two chiral calix[4]arenes bearing an (*RS*)-phenyl ethylamine moiety and evaluation of their extraction ability towards some amino acid methylesters.[14] Herein, we report on the synthesis of some new chiral calix[6]arene amine derivatives bearing a D-/L-phenylalaninol group and on their use as ligands in amino acid and amino alcohol recognition studies.

2. Results and discussion

2.1. Synthesis

We were interested in the synthesis of calix[6]arene-based ionophores having chiral binding sites in order to under-

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stand their recognition ability towards amino acid methylesters and amino alcohols via the two phase solvent extraction systems. The synthesis of **1**–**7** depicted in Figure 4 have been carried out as follows: After compounds **1** and **2** have been synthesized according to previous literature methods,[15,16] compound **2** was reacted with ethylbromoacetate in dry acetone in the presence of potassium carbonate at reflux for 2.5 days in order to obtain **3** in 63% yield. This compound has been characterized by a combination of ^{1}H NMR, IR and elemental analysis. The IR spectra shows an ester band at 1766 cm^{-1}, and ^{1}H NMR exhibits three singlets at 3.09, 3.20 and 3.35 ppm corresponding to the four ester groups. Subsequent reduction of these ester groups of **3** by lithium aluminium hydride yielded alcohol derivative **4** in 65% yield. Completion of the reaction was followed by FTIR-spectroscopy, which showed the disappearance of the band due to ester groups at 1766 cm^{-1} and appearance of the band due to alcohol hydroxyl groups at 3490 cm^{-1}. ^{1}H NMR spectra confirmed the reduction due to observing new peaks at 3.13–3.36 and 3.40 ppm, which correspond to the alcohol groups. After compound **4** had been characterized by ^{1}H NMR, it was treated with *p*-toluenesulfonyl chloride at −4 °C and tosylate derivative **5** has been obtained in 74% yield. Conversion of the alcohol groups into tosylate groups has been confirmed by FTIR, which showed the disappearance of the alcohol band at 3490 cm^{-1} and appearance of the 921 cm^{-1} (S=O), 741 and 823 cm^{-1} (S–O) bands. Consequently compound **5** has been reacted with D-/L-phenylalaninol in dry THF at room temperature for 5 h to obtain chiral calix[6]arene derivatives **6** and **7** in 51% and 45% yields, respectively. Compounds **6** and **7** have been characterized by a combination of ^{1}H NMR, IR and elemental analysis. IR spectra of **6** and **7** show the amine bands at 3102 cm^{-1} and 3105 cm^{-1}, respectively. Compounds **6** and **7** are asymmetric due to the formation of chiral sub-units onto the lower rim of calix[6]arene. The splitting patterns of protons (see Experimental) reflect the presence of the chiral moieties in the molecules.[12]

2.2. Two-phase solvent extraction studies

The present work is focused in order to elaborate the strategic requirements for the two-phase extraction measurements, therefore, the binding abilities of parent *p-tert*-butylcalix[4]arene **1**, its ester derivative **3**, its alcohol derivative **4** and the synthesized chiral calix[6]arenes **6** and **7** towards some selected amino acids and amino alcohols, have been evaluated by means of solvent extraction of their ammonium picrates and the results have been summarized in Tables 1 and 2. These data have been obtained by using dichloromethane solution of the ligands to extract ammonium picrates from aqueous solution. The equilibrium concentration of ammonium picrate in an aqueous phase was then determined spectrophotometrically. From the extraction data given in Tables 1 and 2, it has been observed that parent *p-tert*-butylcalix[6]arene **1** and ester derivative **3** transfer both amino acids and amino alcohols from aqueous phase into the organic phase in trace amounts, alcohol derivative **4** displays a noteworthy extraction ability towards these species, and chiral calix[6]arenes **6** and **7** recognize both amino acids and amino alcohols in high yields. According to our experience and knowledge from our previous study and the other studies,[14,17] increasing the extraction properties of chiral calix[6]arene amines **6** and **7** can be explained by multiple hydrogen bonding between chiral calix[6]arene amines and amino acids or amino alcohols. In addition, the guests are stabilized by CH–π interactions with the aromatic walls of the hydrophobic cavity of the chiral calix[6]arenes **6** and **7**. Also although they are small, similar interactions have been observed for alcohol derivative **4** due to its hydroxyl groups. An expectation of this study is also to observe chiral discrimination between amino acids or amino alcohols by using these new chiral calix[6]arene amines as a ligand. From the results, this goal is relatively true, especially for phenylglycinols because of their extraction abilities being different according to each other, when compared to other species.

Table 1. Extraction percentage of selected amino acid methylesters with **3**, **4**, **6** and **7**[a]

Ligand	L-AlaOMe	D-AlaOMe	L-PheOMe	D-PheOMe	D-TrpOMe	L-TrpOMe
1[b]	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
3	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
4	17.4	16.9	16.1	16.5	15.8	16.3
6	91.4	89.1	90.3	90.7	87.5	93.2
7	84.3	89.6	87.2	82.5	85.4	89.8

[a] Aqueous phase, [ammonium picrate] = 2.0×10^{-5} M; organic phase, dichloromethane, [ligand] = 1.0×10^{-3}; at 25 °C, for 1 h.
[b] Chloroform was used as organic phase.

Table 2. Extraction percentage of selected amino alcohols with **3**, **4**, **6** and **7**[a]

Ligand	D-Phegly	L-Phegly	(*R*)-Hyd-Me-Pyr	(*S*)-Hyd-Me-Pyr
1[b]	<1.0	<1.0	<1.0	<1.0
3	<1.0	<1.0	<1.0	<1.0
4	16.8	14.1	15.9	16.3
6	92.3	72.5	89.1	90.4
7	83.5	87.6	84.4	91.2

[a] Aqueous phase, [ammonium picrate] = 2.0×10^{-5} M; organic phase, dichloromethane, [ligand] = 1.0×10^{-3}; at 25 °C, for 1 h.
[b] Chloroform was used as organic phase.

The extraction data for **6** has been analyzed by a classical slope analysis method. Assuming the extraction of an ammonium cation ($R–NH_3^+$) by the receptor **6** according to the following equilibrium:

$$[R–NH_3^+]_{aq} + [Pic^-]_{aq} + x[L]_{org} \rightleftharpoons [R–NH_3Pic(L)_x]_{org}$$

The extraction constant K_{ex} is defined by

$$K_{ex} = \frac{[R–NH_3Pic(L)_x]}{[R–NH_3^+][Pic^-][L]^x} \quad (1)$$

Eq. (1) can be rewritten as

$$\log D_A = \log K_{ex}Pic + x \log[L] \quad (2)$$

where the distribution ratio D_A is defined as ratio of the concentrations of the ammonium cation ($R–NH_3^+$) in the two phases:

$$D_A = [R–NH_3Pic(L)_x]_{org}/[R–NH_3^+]_{aq} \quad (3)$$

Consequently a plot of $\log D_A$ versus log[L] leads to a straight line, whose slope allows the stoichiometry of the extracted species to be determined.

Figure 1 shows the extraction into dichloromethane at different concentrations of **6** for the ammonium ion. A linear relationship between $\log D_A$ versus log[L] is observed with a slope for ammonium ion by **6**, which equals 2.14, suggesting that **6** forms a 2:1 complex with an ammonium cation. The analytical data of **6** shows that the complexation reaction takes place according to the following equilibrium:

$$2(L)_{org} + (R–NH_3^+Pic^-)_{aq} \overset{K_{ext}}{\rightleftharpoons} (L_2, R–NH_3^+Pic^-)_{org}$$

According to the experimental data, if the Eq. 2 rearrangement for **6**, $\log K_{ex}$ has the value 7.24 ± 0.2.

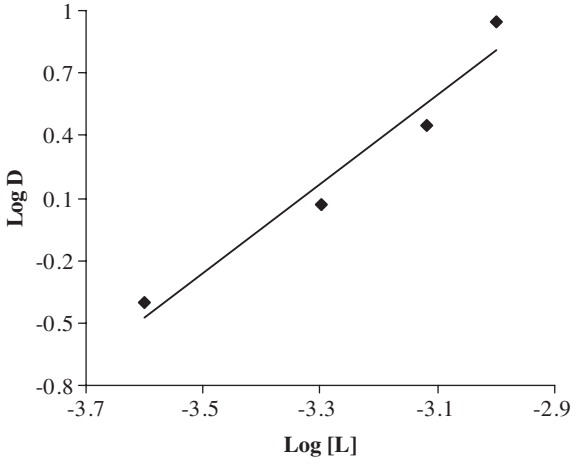

Figure 1. Log D versus log[L] for the extraction of D-PEA by **6** from an aqueous phase into dichloromethane phase at 25 °C.

3. Conclusions

A *p-tert*-butylcalix[6]arene was modified with chiral amino alcohol groups in order to examine the extraction and chiral discrimination ability towards some selected amino acids and amino alcohols. Although the chiral calix[6]arene derivatives **6** and **7** were excellent extractants for all the amino acids and amino alcohols used, the chiral discrimination between the amino acids and amino alcohols could be obtained. It should be noted that the hydrophobic cavity of chiral calix[6]arenes and hydrogen bonding led us to recognize these amino acids and amino alcohols. This work should be useful with regards to the synthesis of chiral and enantioselective receptors.

4. Experimental

4.1. Materials and general methods

Melting points were determined on a Gallenkamp apparatus in a sealed capillary and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 250 MHz spectrometer in $CDCl_3$ with TMS as the internal standard. IR spectra were recorded on a Perkin Elmer 1605 FTIR spectrometer as KBr pellets. UV–vis spectra were obtained on a Shimadzu 160A UV–visible recording spectrophotometer. FAB-MS spectra were taken on a Varian MAT 312 spectrometer. Elemental analyses were performed on a Leco CHNS-932 analyzer. Specific rotations were measured on A Krüss Optronic polarimeter.

Analytical TLC was performed on precoated silica gel plates (SiO_2, Merck PF_{254}), while silica gel 60 (Merck, particle size 0.040–0.063 mm, 230–240 mesh) was used for preparative column chromatography. Generally, solvents were dried by storing them over molecular sieves (Aldrich; 4 Å, 8–12 mesh). Acetone and CH_2Cl_2 were distilled from $CaSO_4$ and $CaCl_2$, respectively. Dry THF was distilled from sodium and benzophenone. All aqueous solutions were prepared with deionized water that had been passed through a Millipore Milli-Q Plus water purification system.

The following amino acid methylester hydrochlorides and amino alcohols obtained from Aldrich or Merck at the highest commercially available purity were used in this study: L-phenylalanine methylester hydrochloride (L-PheOMe), D-phenylalanine methylester hydrochloride (D-PheOMe), L-alanine methylester hydrochloride (L-AlaOMe), D-alanine methylester hydrochloride (D-AlaOMe), L-tryptophan methylester hydrochloride (L-TrpOMe), D-tryptophan methylester hydrochloride (D-TrpOMe), L-phenylglycinol (L-Phegly), D-phenylglycinol (L-Phegly), (*R*)-(5)-(hydroxymethyl)-2-pyrolidinone [(*R*)-Hyd-Me-Pyr], (*S*)-(5)-(hydroxymethyl)-2-pyrolidinone [(*S*)-Hyd-Me-Pyr] (Figs. 2 and 3).

Figure 4 illustrates the successive synthetic steps of the extractants (**1**–**7**) used. Compounds **1** and **2** were prepared according to the literature methods.[15,16] Other compounds (**3**–**7**) were synthesized by adapting known synthetic procedures.

4.2. Syntheses

4.2.1. 5,11,17,23,29,35-*tert*-Butyl-37,38-dimethoxy-39,40,41,42-(methoxycarbonylmethoxy)calix[6]arene 3. To a mixture of **2** (7 g, 7.00 mmol) and K_2CO_3 (3.86 g,

28.00 mmol) in acetone (400 mL), ethylbromoacetate (2.6 mL, 28.0 mmol) was added and the reaction mixture was stirred at reflux for 2.5 days. After cooling, the solvent was removed under reduced pressure. The remaining solid was taken up CH_2Cl_2 (250 mL) and washed with 1 M HCl (2 × 250 mL) and water (250 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a white powder. The product was crystallized from methylene chloride and hexane to obtain pure **3** (63%). IR (KBr): 1766 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 1.14, 1.18, 1.23 (s, 18H), 3.09 (s, 6H), 3.20 (br s, 4H), 3.35 (s, 2H), 3.69 (s, 2H), 3.74 (s, 4H), 3.60 (br s, 6H), 3.92 (br s, 8H), 3.98 (br s, 6H), 7.02 (br s, 6H), 7.14 (br s, 2H), 7.21 (br s, 4H). mp: 138–140 °C. FAB-MS *m/z*: (1312.7) $[M+Na]^+$ (calcd 1312.7). Calculated for $C_{80}H_{104}O_{14}$ (1289.67): C, 74.50; H, 8.13. Found: C, 74.54; H, 8.24.

4.2.2. 5,11,17,23,29,35-*tert*-Butyl-37,38-dimethoxy-39,40,41,42-(hydroxyethoxy)calix[6]arene 4. $LiAlH_4$ (0.5 g) was added to a solution of **3** (2 g, 1.55 mmol) in anhydrous diethyl ether at −4 °C over a 5 min period. The solution began refluxing. The solution was allowed to remain undisturbed until it returned to ambient temperature. Heat was applied, and the solution refluxed for 16 h. Any excess $LiAlH_4$ was destroyed by the addition of cold HCl (8 mL, 2 M), and the organic layer separated. The ether layer was further washed with HCl (2 × 50 mL), brine and then dried over $MgSO_4$. A white solid residue was obtained after evaporation of the ether under reduced pressure. Trituration of this solid residue with boiling hexane gave the product as white feathery crystals. Yield, 65% (1.2 g); mp: 175–180 °C. IR (KBr): 3490 cm^{-1} (OH). ^1H NMR ($CDCl_3$): δ 1.10, 1.28 (s, 27H), 3.13–3.36 (m, 14H), 3.40 (s, 4H), 3.53 (br s, 6H), 3.85 (br s, 8H), 3.91 (br s, 6H), 6.74–6.99 (m, 6H), 7.02–7.21 (m, 2H), 7.21 (br s, 4H). FAB-MS *m/z*: (1200.6) $[M+Na]^+$ (calcd 1200.6). Calculated for $C_{76}H_{104}O_{10}$ (1177.63): C, 77.51; H, 8.90. Found: C, 77.73; H, 9.10.

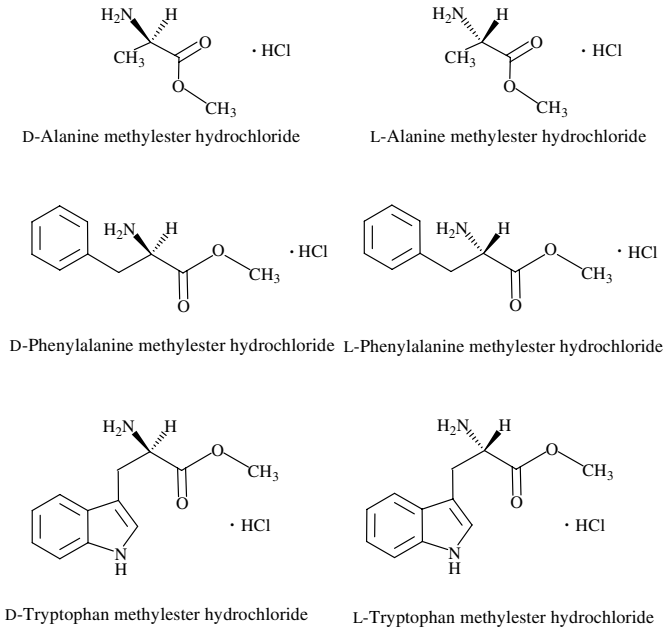

Figure 2. The chemical structures of some selected amino acid methylesters used in experiments.

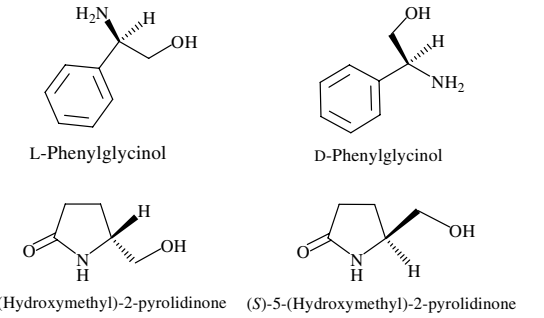

Figure 3. The chemical structures of some selected amino alcohols used in experiments.

4.2.3. 5,11,17,23,29,35-*tert*-Butyl-37,38-dimethoxy-39,40,41,42-(*p*-tosylethoxy)calix[6]arene 5. A solution of **4** (1 g, 0.85 mmol) in pyridine (25 mL) was treated with *para*-toluenesulfonyl chloride (1.96 g) at −4 °C. The mixture was stirred for 5 min to ensure a homogeneous solution. The solution was then kept at −4 °C for 5 days. To this solution was added HCl (25 mL, 2 M) and a precipitate formed. This precipitate was filtered, and then dissolved in methylene chloride. This solution was washed with HCl (2 × 10 mL, 2 M), brine (2 × 50 mL) and then dried over $MgSO_4$. Evaporation of the solution gave a white solid residue, which was crystallized from a mixture of methylene chloride and hexane to give product **5** in 74% yield. mp: 145–150 °C. IR (KBr): 921 cm^{-1} (S=O), 741, 823 cm^{-1} (S–O).

4.2.4. Preparation of chiral *p-tert*-butyl-calix[6]arene amines with D/L-phenylalaninol. The preparation of compounds **6** and **7** is carried out following the general procedure: D/L-phenylalaninol (0.92 mmol) was added to a solution of **5** (0.22 mmol) dissolved in dry THF (50 mL). After the mixture was stirred at room temperature for 5 h, distilled water (15 mL) was added to the solution. The mixture was extracted with dichloromethane, washed with distilled water (2 × 50 mL), brine (2 × 50 mL) and then dried with aqueous magnesium sulfate. The solvent was evaporated under vacuo, and recrystallized with dichloromethane to give **6/7** as white crystals. For compound **6**, yield: 51%, mp: 209 °C. $[\alpha]_D^{22} = -3.9$ (*c* 3.3, $CHCl_3$); IR (KBr): 3102 cm^{-1} (NH), 3414 cm^{-1} (OH); ^1H NMR ($CDCI_3$): δ 1.15 (br s, 54H), 2.67 (dd, $J = 9$ Hz, 4H), 2.87 (dd, $J = 4.5$ Hz, 4H), 3.30–3.51 (m, 16H), 3.57 (d, $J = 8.5$ Hz, 8H), 3.67 (t, $J = 6.5$ Hz, 8H), 4.37 (br s, 8H), 5.00 (br s, 6H), 6.77 (s, 4H), 6.90–7.11 (m, 32H), 7.66 (d, $J = 8$ Hz, 4H). FAB-MS *m/z*: (1733.4) $[M+Na]^+$ (calcd 1733.4). Calculated for $C_{112}H_{148}N_4O_{10}$ (1710.39): C, 78.65; H, 8.72; N, 3.27. Found: C, 78.81; H, 9.01, N, 3.25.

For compound **7**, yield: 45%, mp: 213 °C. $[\alpha]_D^{22} = +4.2$ (*c* 3.3, $CHCl_3$); IR (KBr): 3105 cm^{-1} (NH), 3420 cm^{-1} (OH); ^1H NMR ($CDCI_3$): δ 1.11 (br s, 54H), 2.78 (m, 8H), 3.28–3.52 (m, 16H), 3.53 (d, $J = 8.5$ Hz), 3.64 (t, $J = 6.5$ Hz), 4.39 (br s, 8H), 5.05 (br s, 6H), 6.76 (s, 4H), 6.90–7.17 (m, 32H), 7.65 (d, $J = 8$ Hz, 4H). FAB-MS

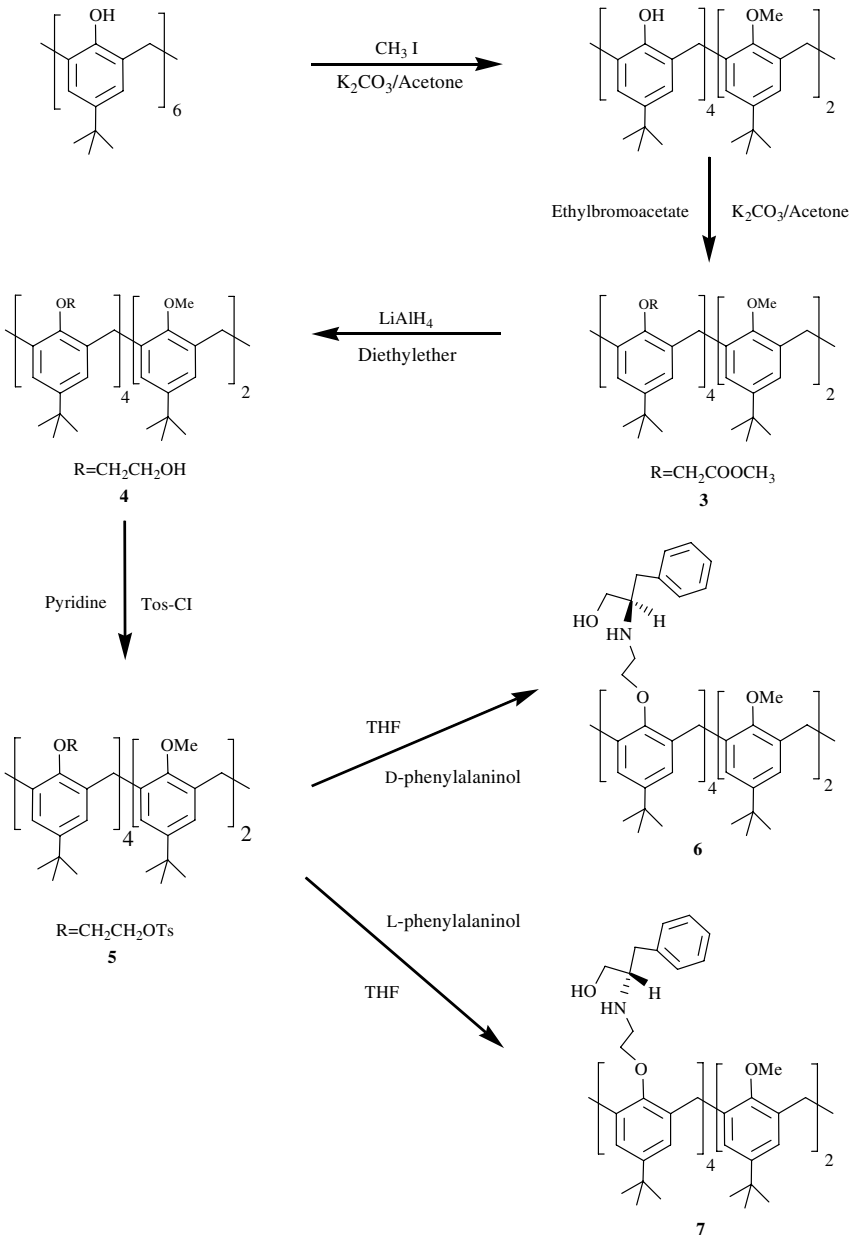

Figure 4. Schematic representation of synthesis of chiral calix[6]arene derivatives **6** and **7**.

m/z: (1733.4) $[M+Na]^+$ (calcd 1733.4). Calculated for $C_{112}H_{148}N_4O_{10}$ (1710.39): C, 78.65; H, 8.72; N, 3.27. Found: C, 78.84; H, 8.91, N, 3.26.

4.3. Analytical procedure

Picrate extraction experiments were performed following Pedersen's procedure.[18] A 10 mL of a 2.0×10^{-5} M aqueous picrate (the picrate solutions were prepared as our previous study[14]) and 10 mL of 1×10^{-3} M solution of calixarene **6** or **7** in CH_2Cl_2 were vigorously agitated in a stoppered glass tube with a mechanical shaker for 2 min, then magnetically stirred in a thermostated water-bath at 25 °C for 1 h, and finally left standing for an additional 30 min. The concentration of the picrate ion, which remained in the aqueous phase was then determined spectrophotometrically. Blank experiments showed that no picrate extraction occurred in the absence of calixarene. The percent extraction (E%) has been calculated as:

$$(E\%) = (A_0 - A/A_0) \times 100 \quad (4)$$

where A_0 and A are the initial and final concentrations of the metal picrate before and after the extraction, respectively.

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