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# Chiral lariat ethers as membrane carriers for chiral amino acids and their sodium and potassium salts

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ABSTRACT

Four chiral lariat ethers **8**–**11** containing a (*p*-methoxyphenoxy) methyl side arm were used for chiral discrimination of amino acids in their zwitterionic form or as potassium and sodium salts in transport across a bulk chloroform membrane with satisfactory selectivity. The carriers that were employed exhibited different transport selectivity relative to the amino acids and their salts under study. The D/L selectivity strongly depends on the amino acids or their salts, and in some cases reverse selectivity has been obtained. The best selectivity was obtained in the case of tyrosine and its potassium salts for all carriers. The transport rates of amino acids and their salts were found to be controlled by factors such as the structure of the carriers and amino acids or their salts. Among these factors, it was also found that the side arm of the lariat ethers plays an important role in the transport process. As a consequence, the main goal of our investigation was to separate the chiral amino acids through liquid membranes.



## 1. Introduction

The enantiomeric discrimination of chiral organic molecules has attracted considerable attention over the past two decades due to an urgent need to develop analytical tools for monitoring the enantiomeric purity of chiral species of biochemical, pharmaceutical, and agrochemical relevance, as well as the methodology for separating enantiomers for commercial purposes. Amino acids are important bioactive substances. A study on transport selectivity and the kinetics of amino acids through the liquid membrane would be helpful for separation and in understanding the transport process of amino acids through the cell membrane.

Supramolecular chemistry is principally based on the concept of molecular recognition, which is defined as a process of selective binding and selection of substrates by a receptor. A new system of recognition and separation could take advantage of the functional features (binding and selections) of supramolecular species.[1] Many studies were focused on the design and synthesis of a great variety of functionalized macrocycles such as crown ethers, aza crown ethers, cryptands, and calixarenes, which are able to recognize and/or exhibit catalytic activities on biologically interesting ammonium guests (amino acids, biogenic amines, and peptides).[2–8] The attractive properties of synthetic macrocyclic receptors that are able to form complexes with various compounds by non-covalent interactions are used in understanding the phenomenon of biochemical specificity, especially in the area of molecular recognition. The chiral nature of crown ethers, the rigidity of the microenvironment of their cavity, and the quality of the side arm are all expected to play an important role in enantiomeric recognition. The attachment of a side arm with potential cation coordination sites produces complexing agents called lariat ethers.[9] For some lariat ethers, the presence of a flexible side arm with an electron donor site is known well to enhance the binding ability of the ligand by the participation of this additional donor group in the complexation, providing three dimensional cavities.

Several studies have been reported on the transport of amino acids using crown ethers by different techniques.[10–15] Calix[*n*]arenas have been employed for the selective transport of amino acid methylesters[16,17] and amines, amino acids, and peptides.[18] Gokel et al. have reported the first enantioselective transport of Z-amino acid and dipeptide $K^+$ carboxylates through a bulk chloroform membrane.[19] Mendoza et al. reported the enantioselective transport of amino acids by guanidinium receptors.[20] Amino acids and their sodium and potassium salts have been transported enantioselectively through a liquid membrane by using chiral crown ether derived from methyl α-D-mannose[10,21] and chiral diazacrown ethers having arene side arm,[22] respectively. In continuation with our interest in this subject, we used one 15-crown-5 **8** chiral lariat ether and three 18-crown-6 **9**–**11** chiral lariat ethers incorporating flexible donating side arm (*p*-methoxyphenoxy) methyl as a chiral auxiliary, chosen due to its donor groups. Macrocycles **8**–**11** have been synthesized by ring closure of chiral subunit diol **1** prepared from (*S*)-glycidol and *p*-methoxyphenol, as described in our previous report, that exhibited good chiral recognition properties toward amino acid methyl esters.[8] Macrocycles **10** and **11** bear

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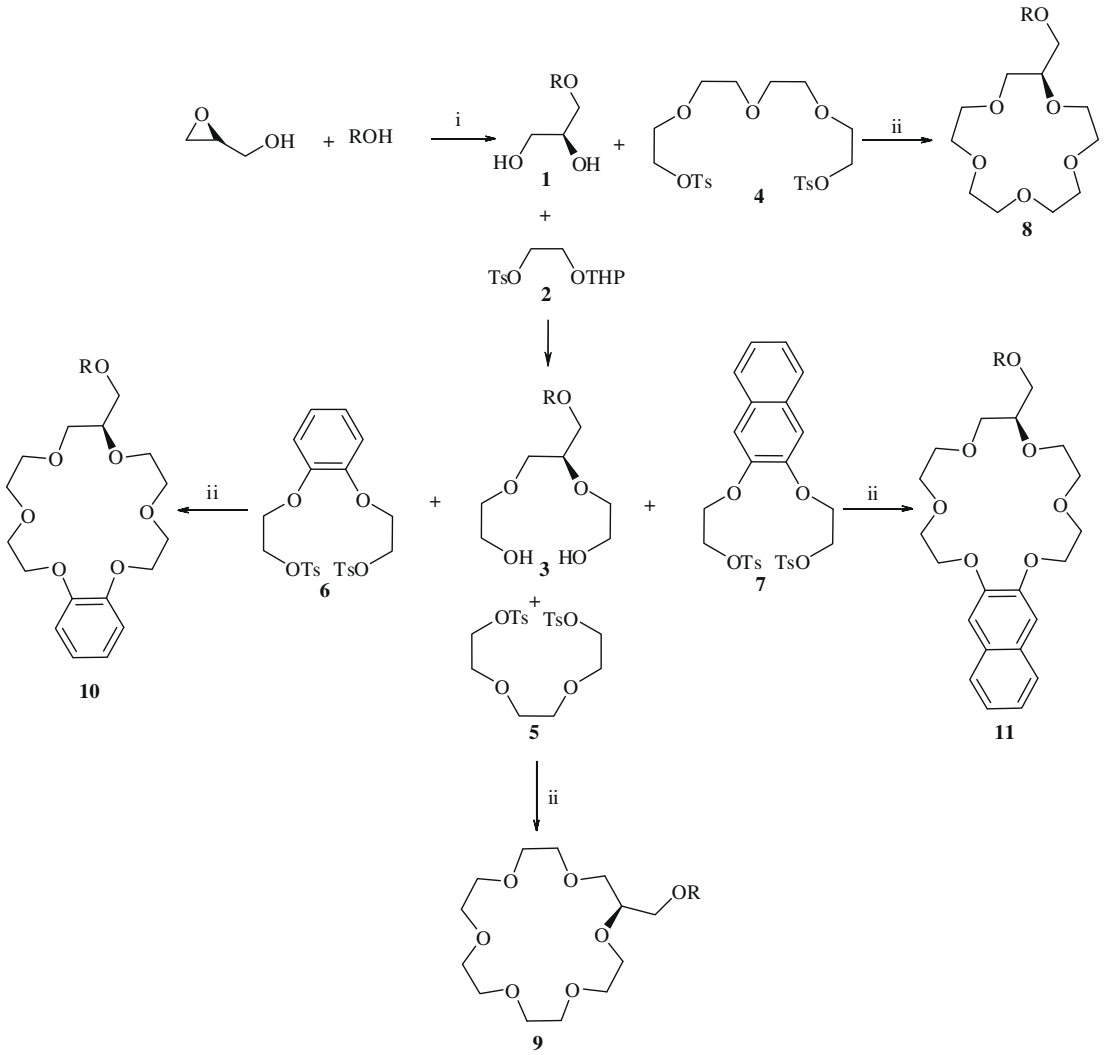


**Scheme 1.** R: *p*-MeOPh–, Reagents and condition: (i) piperidine hydrochloride, 70–80 °C, 4 h., (ii) NaH, THF, reflux, 56 h.

benzo and naphtho units as rigid and lipophilic groups, respectively. The lariat crown ethers used in this study are shown in Scheme 1.

## 2. Results and discussion

In this study, chiral lariat hosts **8**–**11** have been prepared from key intermediates **1** and **3** as shown in Scheme 1. Chiral subunit diol **1** was synthesized by regioselective ring-opening reaction of chiral glycidol, *p*-methoxyphenol, and catalytic amount of piperidine hydrochloride in high enantiopurity. Chiral building block diol **3** was prepared by the reaction of diol **1** and tosylate **2**, which was obtained via monoprotection of ethylene glycol. Employed chiral lariat hosts **8**–**11** were synthesized by a ring closure reaction of chiral diols **1** and **3** and appropriate ditosylates **4**–**7** under high-dilution conditions as described.[8]

Table 1 presents a set of transport data for phenylalanine, phenylglycine, tyrosine, and tryptophan, and their sodium and potassium salts, respectively. Four chiral lariat ethers bearing (*p*-methoxyphenoxy) methyl moiety, 15-crown-5 **8**, 18-crown 6 **9**, benzo-18-crown-6 **10**, and naphtho-18-crown-6 **11** have been employed as carriers in the chloroform membrane phase. The concentration of transported species was measured in the receiving phase within 72 h.

Taking into account the transport experiments, it is clear that the flux of D-phenylglycine was found to be higher than that of the L-enantiomer, except in the case of host **11** for phenylglycine (Figs. 2–5). Conversely, with phenylalanine, hosts **9** and **10** enantioselectively transport L-phenylalanine over D-phenylalanine (Figs. 3 and 4). However, the flux of D-phenylalanine was found to be higher than that of the L-enantiomer for host **11** (Fig. 5). A high D/L selectivity was also found for phenylalanine, but a low and reverse selectivity was found for its sodium and potassium salts with the host **8** (Fig. 2). The reverse selectivity may be attributed to the influence of the cation involved.

There is a good linearity between the selectivity for the D-enantiomers of tyrosine, over the L-enantiomers for all hosts that were investigated (Figs. 2–5). Not only are these regular correlations of enantiomeric discrimination for tyrosine, but also the high flux values were obtained in the case of tyrosine. The tyrosine case deserves particular attention, the highest enantiomeric discrimination was obtained for tyrosine and its potassium salt for all hosts (Figs. 2–5). The much more pronounced enantioselectivity of tyrosine may be assessed with the three hydrogen bonding complexes of tyrosine which contains the appropriate steric interactions that cause specific conformational binding including the favorable π–π interaction between flexible side arm of hosts and aromatic moiety of guests. Many studies have reported the solid-state structures of

**Table 1**
Transport data through liquid membrane[a,b]

| Amino acid | 8 | | 9 | | 10 | | 11 | |
|---|---|---|---|---|---|---|---|---|
| | $J_{72} \times 10^8$ (mol m$^{-2}$ s$^{-1}$) | $\alpha_T$ | $J_{72} \times 10^8$ (mol m$^{-2}$ s$^{-1}$) | $\alpha_T$ | $J_{72} \times 10^8$ (mol m$^{-2}$ s$^{-1}$) | $\alpha_T$ | $J_{72} \times 10^8$ (mol m$^{-2}$ s$^{-1}$) | $\alpha_T$ |
| L-PhGly | 4.23 | 2.18 | 14.84 | 1.41 | 3.64 | 2.78 | 35.87 | 1.94 |
| D-PhGly | 9.24 | | 20.94 | | 10.12 | | 18.48 | |
| L-PhGlyNa | 6.58 | 1.57 | 3.83 | 3.74 | 5.70 | 2.64 | 8.94 | 2.39 |
| D-PhGlyNa | 10.32 | | 14.35 | | 15.04 | | 21.33 | |
| L-PhGlyK | 3.54 | 5.14 | 2.45 | 4.49 | 2.95 | 12.29 | 6.59 | 2.25 |
| D-PhGlyK | 18.18 | | 11.01 | | 36.27 | | 14.84 | |
| L-PhAla | 31.26 | 3.49 | 36.07 | 3.31 | 35.58 | 2.68 | 8.75 | 2.87 |
| D-PhAla | 8.95 | | 10.91 | | 13.27 | | 25.16 | |
| L-PhAlaNa | 4.92 | 2.66 | 20.74 | 1.31 | 34.99 | 1.65 | 9.63 | 2.68 |
| D-PhAlaNa | 13.07 | | 15.83 | | 21.13 | | 25.85 | |
| L-PhAlaK | 11.21 | 1.27 | 25.56 | 2.10 | 24.67 | 1.38 | 12.98 | 2.08 |
| D-PhAlaK | 14.25 | | 12.19 | | 17.89 | | 27.03 | |
| L-Tyr | 3.05 | 13.73 | 11.01 | 3.45 | 7.96 | 4.86 | 2.56 | 15.55 |
| D-Tyr | 41.87 | | 38.04 | | 38.73 | | 39.81 | |
| L-TyrNa | 34.40 | 1.41 | 46.39 | 1.04 | 16.81 | 2.87 | 48.36 | 1.00 |
| D-TyrNa | 48.36 | | 48.26 | | 48.26 | | 48.46 | |
| L-TyrK | 4.62 | 8.30 | 10.81 | 3.48 | 7.18 | 5.22 | 2.75 | 14.12 |
| D-TyrK | 38.34 | | 37.65 | | 37.45 | | 38.83 | |
| L-Trp | 3.54 | 1.09 | 5.03 | 1.13 | 6.59 | 1.05 | 13.07 | 1.55 |
| D-Trp | 3.24 | | 4.42 | | 6.29 | | 8.45 | |
| L-Trp Na | 50.23 | 1.74 | 44.72 | 1.67 | 44.53 | 1.80 | 50.03 | 1.54 |
| D-TrpNa | 28.80 | | 26.74 | | 24.77 | | 32.54 | |
| L-Trp K | 39.32 | 1.01 | 28.60 | 1.07 | 39.61 | 1.02 | 39.90 | 1.11 |
| D-Trp K | 38.83 | | 30.57 | | 40.30 | | 44.33 | |

[a] Transport experiments were obtained from three replicates, and estimated errors are <12%.
[b] $J_{72}$ = Flux of transported amino acids after 72 h (mol m$^{-2}$ s$^{-1}$); $\alpha_T$ = ratio of fluxes: higher/lower flux; PhGly = phenylglycine; PhAla = phenylalanine; Tyr = tyrosine; Trp = tryptophan.

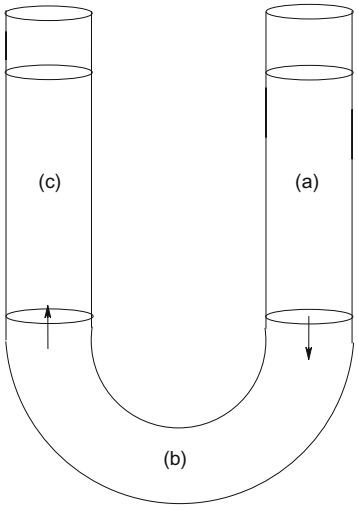


**Figure 1.** Transport apparatus and detailed experimental conditions. (a) Source phase (2 mL): amino acid or its salts ($4 \times 10^{-3}$ M) (by adding NaOH or KOH ($4 \times 10^{-3}$ M). (b) Organic carrier phase (2 mL): chloroform; carrier: lariat crown ethers (**8**–**11**) ($2 \times 10^{-3}$ M). (c) Receiving phase (2 mL): pure water.

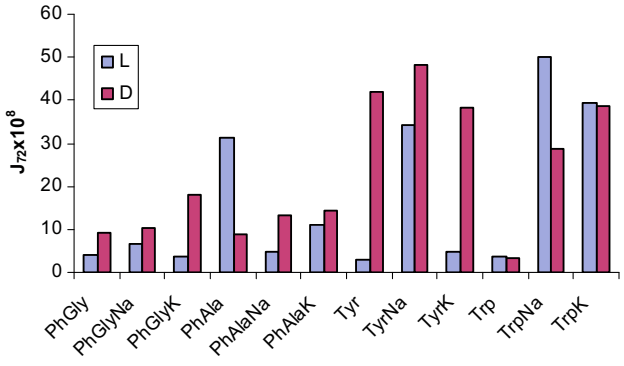


**Figure 2.** Bar plots of fluxes of amino acids and their salts for host **8**.

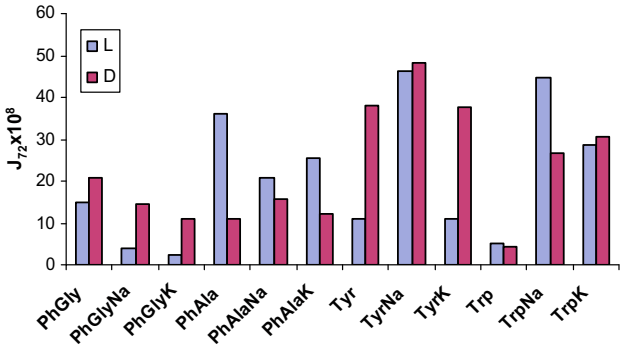


**Figure 3.** Bar plots of fluxes of amino acids and their salts for host **9**.

lariat ether complexes in which the cation is π-coordinated by phenyl,[18,19] phenol, or indoles[20] with $K^+$; few data have been reported for the $Na^+$ arene interaction. In general, the higher enantioselectivity of potassium salts can be explained by apical-π or a sandwich-type supramolecular complex which also causes specific conformational binding as mentioned for tyrosine due to its larger size. The tyrosine sodium salt is probably transported as a counterion of phenolate ion in which the stereogenic center of tyrosine salt orientated out of the complex; therefore, in this case the enantioselectivity cannot be observed.

Taking into account the transport experiments of tryptophan and its salts, it is clear that the flux of L-trptophan is somewhat higher than that of the D-enantiomer for all hosts, opposite to its potassium salt for host **11,** where the situation is reversed. As in the case of reversed situation of tyrosine, the enantiomeric discrimination of tryptophan sodium salt was obtained moderately higher than that of tryptophan and its potassium salt, which were

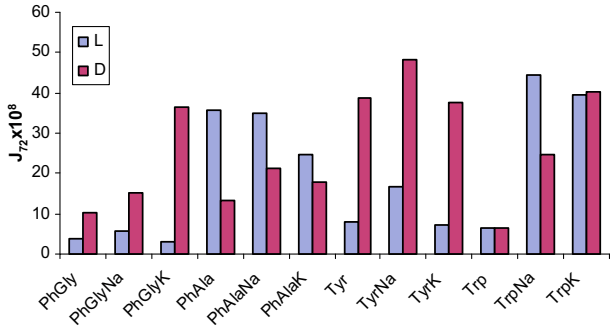


**Figure 4.** Bar plots of fluxes of amino acids and their salts for host **10**.

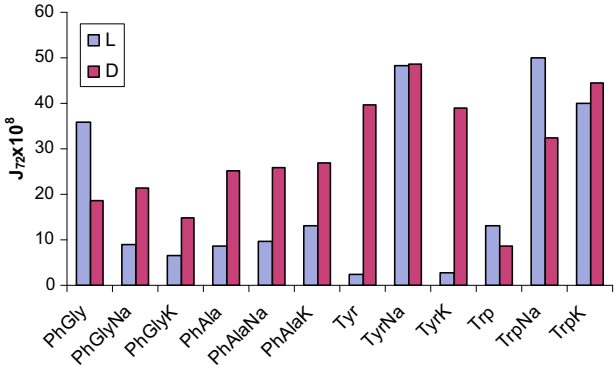


**Figure 5.** Bar plots of fluxes of amino acids and their salts for host **11**.

found to be quite low for all hosts. Noteworthy results were also obtained for tryptophan when compared with its sodium and potassium salts (Figs. 2–5). The lowest transport rate of tryptophan indicated that intra-molecular hydrogen bonding or ion-dipole interaction of zwitterionic form of tryptophan lead to no supramolecular complexation between hosts **8**–**11**. However, the sodium and potassium salts of tryptophan were probably transported as the counterion of non-specific conformational binding complexes between the metal cation and hosts that also include more favorable π–π interactions as mentioned above for the tyrosine sodium salt than in the cases of the phenylglycine and phenylalanine.

There are many factors that favor the complexation strength, such as (i) solvent polarity, (ii) a good size correspondence between guest and host, (iii) lack of strain in the host, and (iv) the presence of donor groups in the host and in the side arm which are appropriate for the guest. Although the potassium and sodium ions form stronger complexes with 18-crown-6 and 15-crown-5, respectively, there is unlikely to be a correlation between the cation size and enantioselectivity. This result is in agreement with those of a previous report.[21] The results also show that no significant π–π interaction exists between the aromatic residue of the amino acid and receptors **10** and **11,** having benzo and naphtho units related to hosts **8** and **9**. However, benzo- and naphtho-18-crown-6 **10** and **11** generally have a better flux of phenylglycine or its salts than hosts **8** and **9**. This indicates a strong π–π stacking interaction. The investigated carrier systems exhibited satisfactory transport rates and enantiomeric discriminations for all amino acids and their salts when compared with the previously reported data.[10,21,22] It is difficult to say that the transport rates depend on the hydrophobicity of the amino acids as the opposite statement was reported by the previous report.[17] These results significantly indicate the influence of side arm which might be providing steric hindrance, and cation–π and π–π stacking interactions by its electron donor capacity. These results are also in agreement with those observations of solid-state lariat ether complexes including side arm participation in metal–cation complexation,[23–25] and increased stability constant in solution compared with corresponding crown ether ligands.[9] Thus, the highly selective transport of amino acids and their salts was achieved as zwitterionic forms via the three hydrogen bonds of the protonated ammonium and the charge interactions of metal carboxylate with chiral lariat ethers **8**–**11**, respectively.

## 3. Conclusion

In conclusion, liquid membranes are often used to simulate the membrane transport of organics of biological interest (amino acids, organic acids, nucleotides, etc.) by employing macrocyclic receptors, lipophilic charged carriers, or chiral receptors (for enantioselective separations) as selective carriers. These membranes display a high selectivity due to a specific complexation (hydrogen bonding, electrostatic or hydrophobic interactions) of a solute by the selective carriers. We have shown that lariat ethers **8**–**11** with a flexible side arm not only increase the fluxes of amino acids, in both zwitterionic and metal carboxylate forms, but also provide a satisfactory enantiomeric discrimination as well. It is essential that the complexation should occur from the more sterically hindered side of the macrocyclic rings to effect steric discrimination interactions between chiral auxiliary and the chiral guest molecules.

## 4. Experimental

### 4.1. Apparatus

Melting points were determined with GALLENKAMP Model (UK) apparatus with open capillaries. Infrared spectra were recorded on a MİDAC-FTIR Model 1700 (Costa Mesa, CA, USA) spectrophotometer. The elemental analyses were performed with CARLO-ERBA Model 1108 (Rodano, Milan, Italy) apparatus. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a BRUKER DPX-400 high-performance digital FT-NMR (Bremen, Germany) spectrometer, with tetramethysilane as the internal standard solution in deuteriochloroform. Optical rotations were recorded by using PERKIN ELMER Model 341 (Beaconsfield, Bocks, UK) polarimeter. UV analysis for transport experiments were performed with PERKIN ELMER Lambda 35 UV (Beaconsfield, Bocks, UK) spectrometer. All chemicals were of reagent grade unless otherwise specified. THF was dried (on sodium benzophenone ketyl) and distilled prior to use.

### 4.2. Synthesis

Compounds **1**–**7** were synthesized as described in our previous report.[8]

#### 4.2.1. (*S*)-2-[(4-Methoxyphenoxy)methyl]-15-crown-5 8

To a suspension of 0.88 g (29.00 mmol 80% in mineral oil) of NaH in 150 mL of the dry THF at 0 °C was added a solution of (*S*)-3-(*p*-methoxyphenoxy)-1,2-propanediol **1** (1.30 g, 6.56 mmol) in 250 mL of THF. The reaction mixture was refluxed for 2 h. After cooling to 0 °C, a solution of tetra (ethylene glycol) di-(*p*-toluenesulfonate) (3.29 g, 6.56 mmol) in 250 mL of THF was slowly added. The suspension was refluxed for 48 h. The solvent was evaporated after adding 100 mL of water to the residue. The mixture was extracted with $CH_2Cl_2$ (4 × 20 mL), and the combined organic layers were washed with 50 mL of water and dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by column chromatography (eluent: EtoAc/hexane/triethylamine: 5/5/1) to yield 0.91 g (39%) of pure product as a viscous oil. $[\alpha]_D^{30} = -14.0$ (*c* 7.0, $CHCl_3$). $^1$H NMR $\delta$ (ppm): 3.64–4.03 (m, 24H); 6.81–6.88 (m,

4H); $^{13}$C NMR $\delta$ (ppm): 153.89, 153.06, 115.60, 114.60, 78.17, 76.72, 71.09, 70,83, 70,79, 70.56, 70.54, 70.48, 70.41, 68.97, 68.42, 55.73. IR $\nu$ (cm$^{-1}$): 3043, 2940, 2874, 1602, 1509, 1463, 1233, 1133, 1041, 941, 829, 743. Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.87. Found: C, 60.45; H, 7.95.

#### 4.2.2. (*S*)-2-[(4-Methoxyphenoxy)methyl]-18-crown-6 9

Compound **9** was prepared in a manner similar to that described for the preparation of (*S*)-**8** by using diol **3** (1.45 g, 5.00 mmol) and tri (ethylene glycol) di(*p*-toluenesulfonate) (2.80 g, 5.00 mmol) to give 0.35 g, (18%) of pure **9**. $[\alpha]_D^{30} = -8.8$ (*c* 4.66, $CHCl_3$). $^1$H NMR $\delta$ (ppm): 6.71–6.78 (m, 4H); 3.54–3.97 (m, 28H) $^{13}$C NMR $\delta$ (ppm): 153.84, 152.99, 115.53, 114.55, 77.82, 77.74, 77.34, 71.31, 70.96, 70.85, 70.83, 70.72, 70.69, 70.65, 70.10, 68.67, 67.90, 55.68. IR $\nu$ (cm$^{-1}$): 3049, 2937, 2871, 1602, 1516, 1470, 1358, 1290, 1238, 1120, 1041, 988, 948, 829,750. Anal. Calcd for $C_{20}H_{32}O_8$ : C, 60.0; H, 8.00. Found: C, 59.87; H, 8.11.

#### 4.2.3. (*S*)-12-[(4-Methoxyphenoxy)methyl]-2,3-benzo-18-crown-6 10

Compound **10** was prepared in a manner similar to that described for the preparation of (*S*)-**8** by using diol **3** (1.00 g, 3.50 mmol) and 2,3-bis-[2-(*p*-tolylsulfonyl)ethoxy]benzene (1.77 g, 3.50 mmol) to give 0.20 g (12%) of pure **10** as a viscous oil, which was purified by silica gel column chromatography (eluent: petroleum ether (60–80)/EtOAc/triethylamine: 80/17/3). $[\alpha]_D^{30} = -2.7$ (*c* 2.0, $CHCl_3$). $^1$H NMR $\delta$ (ppm): 3.71–3.84 (m, 12H); 3.89–4.01 (m, 8H); 4.15–4.20 (m, 4H); 6.78–6.85 (m, 4H); 6.90–6.94 (m, 4H). $^{13}$C NMR $\delta$ (ppm): 152.96, 151.94, 149.43, 121.63, 114.31, 113.85, 113.38, 73.80, 71.93, 70.95, 70.42, 70.02, 69.97, 69.88, 69.32, 67.52, 67.34, 66.82, 54.20. IR $\nu$ (cm$^{-1}$): 3069, 2924, 2871, 1615, 1509, 1451, 1233, 1133, 1041, 935, 829, 750. Anal. Calcd for $C_{24}H_{32}O_8$: C, 64.28; H, 7.14. Found: C, 64.38; H, 7.24.

#### 4.2.4. (*S*)-12-[(4-Methoxyphenoxy)methyl]-2,3-naphtho-18-crown-6 11

Compound **11** was prepared in a manner similar to that described for the preparation of (*S*)-**9** by using diol **3** (1.45 g, 5.00 mmol) and 2,3-bis-[2-(*p*-tolylsulfonyl)ethoxy]naphthalene **4** (2.72 g, 5.00 mmol) to give 0.30 g (12%) of pure **11** as a white solid, which was purified by crystallization in ethanol, mp 88–89 °C. $[\alpha]_D^{30} = -8.6$ (*c* 3.76, $CHCl_3$). $^1$H NMR $\delta$ (ppm): 7.58–7.56 (dd, 2H); 7.16–7.25 (dd, 2H); 7.01–7.02 (d, 2.8 Hz, 2H); 6.60–6.69 (m, 4H); 4.12–4.20 (m, 4H); 3.80–3.94 (m, 8H); 3.59–3.75 (m, 12H). $^{13}$C NMR $\delta$ (ppm): 153.83, 152.97, 149.12, 149.10, 129.33, 129.31, 126.33, 124.18, 115.48, 106.87, 78.01 71.59, 71.32, 71.13, 71.03, 70.23, 69.55, 69.41, 68.80, 68.68, 68.46, 55.66. IR $\nu$ (cm$^{-1}$): 3056, 2931, 2884, 1610, 1516, 1457, 1240, 1120, 1060, 941, 823, 743. Anal. Calcd for $C_{28}H_{34}O_8$: C, 67.46; H, 6.82. Found: C, 67.05; H, 6.42.

### 4.3. Transport experiments

Transport experiments were run at 25 °C in the custom-made, U-shaped glass apparatus of 10 mm diameter for 72 h. The bulk liquid membrane consisted of 2 mL of chloroform containing the crown ethers **8**–**11** at a concentration of $2 \times 10^{-3}$ M. The membrane was stirred magnetically at 300 rpm. The source phase (2 mL) contained the amino acid, or its salt at a concentration of $4 \times 10^{-3}$ M. The receiving phase was 2 mL of pure water. Blank tests indicated that the transport of amino acids was negligible. The concentration of the amino acids and their salts in the receiving phase and the source phase was assessed by UV spectrophotometer. The transport apparatus and detailed experimental conditions are shown in Figure 1.

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