# Chiral Calix[4]arenes Bearing Amino Alcohol Functionality as Membrane Carriers for Transport of Chiral Amino Acid Methylesters and Mandelic Acid

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*ABSTRACT* Novel chiral calix[4]arene derivatives bearing amino alcohol moieties at the lower rim have been synthesized from the reaction of *p-tert*-butylcalix[4]arene diester with various amino alcohols. The transport of amino acid esters (phenylglycine, phenylalanine, and tryptophan methyl esters hydrochloride) and mandelic acid were studied through chloroform bulk liquid membrane system using chiral calix[4]arenes **15–20**. All these receptors have been found to act as carriers for transport of aromatic amino acid methylesters and mandelic acid from the aqueous source phase to the aqueous receiving phase. The influence of calixarene and guest structures upon transport through liquid membrane is discussed. *Chirality 24:129–136, 2012.* 

*KEY WORDS:* chiral calix[4]arene; bulk liquid membrane; amino acid methyl esters; mandelic acid; transport rate

## INTRODUCTION

The production and availability of enantiomerically pure compounds is of great importance for the pharmaceutical industry.[1,2] As most drug effects are due to interactions with chiral biological materials, each stereoisomer of a chiral drug usually exhibit different pharmacological activities due to the stereoselectivity of enzymatic reactions and other biological processes.[3] Therefore, only one enantiomer contribute to its pharmacodynamic behavior, while the other shows no or a much weaker effect or harmful effects.[4] Regulatory agencies such as the U.S. Food and Drug Administration, issued a mandate requiring pharmaceutical companies to evaluate the effects of individual enantiomers and to verify the enantiomeric purity of chiral drugs that are produced.[5,6] Furthermore, even if a drug is to be marketed as a single enantiomer, the pharmaceutical properties and toxicity must be established for both enantiomers.[7,8] Such regulations have greatly encouraged and stimulated the production and sale of single-enantiomer drugs.

A variety of methods are available to obtain enantiopure compounds, for example, from natural sources, fermentation, or asymmetric synthesis, or by resolution of racemates.[9–11] Despite the advances in asymmetric synthesis of pure enantiomers, the separation of racemates is still the most important industrial approach for the preparation of enantiomerically pure compounds. Extractive separation of liquid membrane is widely used in chiral separation process[12–16] due to their cost effectiveness, low energy demand, set-up simplicity, and the possibility to be used in continuous mode.

Amino acids are important naturally occurring compounds assembling into polypeptides with a wide range of vital biological functions and useful building blocks in the production of drug intermediates and protein-based drugs. The complexation and transport of racemic mixtures with chiral receptors has been pointed out as a smooth method for enantiomeric resolution, because it requires low concentrations of the receptor, which can be recovered at the end of the process.[17]

In the literature, various types of chiral receptors bearing cyclodextrins (CDs),[18–20] tartaric acid derivatives,[21] crown ethers,[22–24] chiral complexes of transition metals,[25] carriers with porphyrin or sapphyrin rings,[26] macrocyclic pseudopeptides,[27] chiral phosphoric acids esters,[28,29] guanidine derivatives of sterols,[30,31] or cinchonidine,[32] have been reported on the chiral separation of amino acids. Although many calixarene derivatives have been synthesized as membrane carriers for anions,[33] cations,[34,35] and neutral molecules,[36–38] only a few investigations[39] have been reported for chiral guests.

Our recent studies in this field were mainly dedicated to synthesis of novel chiral receptors containing various functionalities including azacrown ethers,[40] aminonaphthol derivatives,[41,42] and amines[43] as well as their extraction abilities and enantiomeric recognition properties toward chiral carboxylic acids and amino acid derivatives, we herein report the synthesis of novel calix[4]arene derivatives bearing chiral amino alcohol moieties at the lower rim and their potential applications as carriers in transport of amino acids through bulk liquid membrane.

## MATERIALS AND METHODS

### *General*

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary. $^{1}H$ and $^{13}C$ NMR spectra were recorded at room temperature on a Varian 400 MHz spectrometer in $CDCl_3$. Infrared (IR) spectra were obtained on a Perkin Elmer Fourier transform infrared (FTIR) spectrum-100 FTIR spectrometer using KBr pellets. Ultraviolet-visible (UV-Vis) spectra were measured with a Perkin Elmer Lambda 25 spectrometer. Optical rotations were measured on an Atago AP-100

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digital polarimeter. Elemental analyses were performed using a Leco CHNS-932 analyzer.

Analytical thin layer chromatography (TLC) was performed using Merck prepared plates (silica gel 60 $F_{254}$ on aluminum). Flash chromatography separations were performed on a Merck Silica Gel 60 (230–400 mesh). All reactions, unless otherwise noted, were conducted under a nitrogen atmosphere. All starting materials and reagents used were of standard analytical grade from Fluka, Merck and Aldrich and used without further purification. Toluene was distilled from $CaH_2$ and stored over sodium wire. Other commercial grade solvents were distilled, and then stored over molecular sieves. The drying agent used was anhydrous $MgSO_4$.

### Syntheses

The synthesis of **2–5** has been already described by us.[44]

### General Procedure for the Synthesis of Compounds 6 and 7

To a cooled solution of (*R*)-(-)-*N*-(2,3-epoxypropyl)phthalimide **1** (102 mg, 0.50 mmol) in 10 ml of 2-propanol, amine, or amino alcohol (0.6 mmol, 1.2 eq) in 10 ml of 2-propanol was added at 0°C and stirred for 1 h. It was then refluxed for 8 h. After the completion of the reaction, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel ($CHCl_3$/MeOH 1:20 as eluent) to afford **6–7** as solids.

### 2-[(2R)-2-hydroxy-3-indoline-1-yl-propyl]isoindoline-1,3-dione (6)

Yellow solid; yield 64%; mp: 105–108°C; $\alpha_D^{25}$ = + 23.5 (c 1.53, $CHCl_3$). IR (KBr): 3460, 1764, 1698, 1605 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 7.90–7.85 (m, 2H, Ar*H*), 7.76–7.71 (m, 2H, Ar*H*), 7.10–7.05 (m, 2H, Ar*H*), 6.70 (t, *J* = 7.4 Hz, 1H, Ar*H*), 6.56 (d, *J* = 7.8 Hz, 1H, Ar*H*), 4.24-4.18 (m, 1H, OHC*H*), 3.90 (d, *J* = 5.9 Hz, 2H, NC$H_2$CH), 3.51 (q, *J* = 8.6 Hz, 1H, NC$H_2$), 3.35 (q, *J* = 8.6 Hz, 1H, NC$H_2$), 3.18-3.08 (m, 2H, NC$H_2$CH), 3.02–2.98 (m, 2H, NCH$_2$C$H_2$), 2.79 (d, *J* = 4.1 Hz, 1H, O*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 168.9, 152.7, 134.3, 132.2, 130.1, 127.6, 124.8, 123.7, 118.9, 107.8, 68.5, 55.4, 55.2, 42.4, 29.0; Anal. Calcd for $C_{19}H_{18}N_2O_3$ (322.31): C, 70.82%; H, 5.63%; N, 8.72%; Found C, 70.86%; H, 5.66%; N, 8.79%.

### 2-[(2R)-3-(dibenzylamino)-2-hydroxy-propyl]isoindoline-1,3-dione (7)

White solid; yield 84%; mp: 142–144°C; $\alpha_D^{25}$ = + 19.7 (c 1.32, $CHCl_3$). IR (KBr): 3468, 1771, 1704, 1613 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 7.75 (dd, *J* = 3.1, 5.5 Hz, 2H, Ar*H*), 7.62 (dd, *J* = 3.1, 5.5 Hz, 2H, Ar*H*), 7.26–7.11 (m, 10H, Ar*H*), 3.99–3.93 (m, 1H, NCH$_2$C*H*OH), 3.69–3.63 (m, 3H, NC$H_2$CH and NC$H_2$Ar), 3.55 (dd, *J* = 7.3, 14.1 Hz, 1H, NC$H_2$CH), 3.43 (d, *J* = 13.3 Hz, 2H, NC$H_2$Ar), 2.49 (d, *J* = 6.6 Hz, 2H, CHC$H_2$N), 2.25–2.19 (m, 1H, O*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm 168.7, 139.3, 132.4, 130.5, 128.4, 127.9, 127.2, 123.7, 66.4, 61.5, 58.9, 55.2, 45.9; Anal. Calcd for $C_{25}H_{24}N_2O_3$ (400.18): C, 74.98%; H, 6.04%; N, 7.00%; Found C, 75.06%; H, 6.05%; N, 7.03%.

### General Procedure for the Synthesis of Compounds 8–13

To a solution of **2–7** (1.0 mmol) in ethanol (10 ml) was added $N_2H_4.H_2O$ (0.5 ml), and the mixture was refluxed for 8 h. After the completion of the reaction, the solvent was removed under reduced pressure and residue was dissolved in $CHCl_3$ (15 ml) and washed with saturated aq $NaHCO_3$ (2 × 5 ml). The aqueous layer was extracted three times with $CHCl_3$, and the combined organic solutions were evaporated to obtain **8–13**, as yellow oils.

### (2S)-1-amino-3-[[(1S)-1-phenylethyl]amino]propan-2-ol (8)

Viscous yellow oil; yield 84%; $\alpha_D^{25}$ = −22.23 (c 1.44, $CHCl_3$). IR (KBr): 3091 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 7.34–7.20 (m, 5H, Ar*H*), 3.75 (q, *J* = 6.6 Hz, 1H, $CH_3$C*H*), 3.60 (ddd, *J* = 11.9, 7.4 Hz, 3.6 Hz, 1H, C*H*OH), 2.71 (dd, *J* = 11.9, 3.5 Hz, 1H, NH$_2$C$H_2$CH (AB spin system)), 2.58 (dd, *J* = 12.7, 3.7 Hz, 2H, NHC$H_2$CH), 2.35 (dd, *J* = 11.9, 3.5 Hz, 1H, NH$_2$C$H_2$CH (AB spin system)), 2.20 (bs, 4H, N$H_2$ and O*H*), 1.35 (d, *J* = 6.6 Hz, 3H, NHCHC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 145.2, 128.8, 127.3, 126.8, 70.0, 58.2, 51.0, 45.4, 24.5; Anal. Calcd for $C_{11}H_{18}N_2O$ (194.14): C, 68.01%; H, 9.34%; N, 14.42%; Found C, 68.07%; H, 9.35%; N, 14.45%.

### (2S)-1-amino-3-[[(1R)-2-hydroxy-1-phenylethyl]amino]propan-2-ol (9)

Viscous yellow oil; yield 91%; $\alpha_D^{25}$ = + 20.74 (c 1.88, $CHCl_3$). IR (KBr): 3093 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 7.30–7.05 (m, 5H, Ar*H*), 3.74–3.48 (m, 4H, C*H*Ar and C*H*OH and CHC$H_2$OH), 2.77–2.20 (m, 4H, NH$_2$C$H_2$CH and NHC$H_2$CH), 1.97 (bs, 5H, N$H_2$ and N*H* and O*H* and O*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 138.6, 128.7, 127.8, 127.1, 73.9, 65.2, 64.9, 50.6, 45.9; Anal. Calcd for $C_{11}H_{18}N_2O_2$ (210.14): C, 62.83%; H, 8.63%; N, 13.32%; Found C, 62.88%; H, 8.64%; N, 13.35%.

### ((2R)-2-[[(2S)-3-amino-2-hydroxy-propyl]amino]butan-1-ol (10)

Viscous yellow oil; yield 76%; $\alpha_D^{25}$ = −19.34 (c 0.93, $CHCl_3$). IR (KBr): 3088 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.78–3.62 (m, 1H, C*H*OH), 3.58–3.48 (m, 3H, NHC*H* and CHC$H_2$OH), 2.77–2.55 (m, 4H, NH$_2$C$H_2$CH and NHC$H_2$CH), 1.74 (bs, 5H, NH2 and OH and OH and NH), 1.53–1.37 (m, 2H, CHC$H_2$CH$_3$), 0.90 (t, *J* = 7.3 Hz, 3H, CHCH$_2$C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 74.1, 64.2, 62.8, 51.4, 47.8, 22.1, 10.9; Anal. Calcd for $C_7H_{18}N_2O_2$ (162.14): C, 51.82%; H, 11.18%; N, 17.27%; Found C, 51.83%; H, 11.18%; N, 17.30%.

### ((1R,2S)-1-[[(2S)-3-amino-2-hydroxy-propyl]amino]indan-2-ol (11)

Viscous yellow oil; yield 73%; $\alpha_D^{25}$ = + 24.56 (c 1.14, $CHCl_3$). IR (KBr): 3095 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 7.14–7.05 (m, 4H, Ar*H*), 4.20–3.95 (m, 4H, NHC*H*Ar, CHC*H*OH and C*H*OH), 2.92–2.73 (m, 4H, NH$_2$C$H_2$CH and NHC$H_2$CH), 2.49–2.21 (m, 2H, C$H_2$ ), 2.05 (bs, 4H, N$H_2$, N*H* and O*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 143.8, 139.7, 128.1, 126.4, 126.4, 124.5, 74.7, 74.2, 72.6, 50.9, 47.4, 37.6; Anal. Calcd for $C_{12}H_{18}N_2O_2$ (222.28): C, 64.84%; H, 8.16%; N, 12.60%; Found C, 64.89%; H, 8.16%; N, 12.63%.

### ((2S)-1-amino-3-indolin-1-yl-propan-2-ol (12)

Viscous yellow oil; yield 92%; $\alpha_D^{25}$ = + 24.85 (c 1.69, $CHCl_3$). IR (KBr): 3086 $cm^{-1}$; $^1$H NMR (400 MHz,$CDCl_3$): $\delta_H$ (ppm) 6.98 (m, 2H, Ar*H*), 6.60 (t, *J* = 7.4 Hz, 1H, Ar*H*), 6.44 (d, *J* = 7.8 Hz, 1H, Ar*H*), 3.76 (sep, *J* = 4.11, 3.66 Hz, 1H, C*H*OH), 3.40 (q, *J* = 8.4 Hz, 1H, NC$H_2$CH$_2$), 3.22 (q, *J* = 8.7 Hz, 1H, NC$H_2$CH$_2$), 3.06 (dd, *J* = 5.7, 7.8 Hz, 1H, NCH$_2$C$H_2$), 2.94–2.78 (m, 3H, NCH$_2$C$H_2$ and CHC$H_2$NH$_2$), 2.70–2.50 (m, 5H, CHC$H_2$NH$_2$ and N$H_2$ and CHC$H_2$N and OH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 153.7, 129.8, 126.8, 125.4, 121.7, 106.9, 70.2, 63.4, 56.8, 47.5, 28.9; Anal. Calcd for $C_{11}H_{16}N_2O$ (192.26): C, 68.72%; H, 8.39%; N, 14.57%; Found C, 68.81%; H, 8.40%; N, 14.59%.

### (2S)-1-amino-3-(dibenzylamino)propan-2-ol (13)

Viscous yellow oil; yield 89%; $\alpha_D^{25}$ = + 44.66 (c 1.03, $CHCl_3$). IR (KBr): 3092 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 7.38–7.07 (m, 10H, Ar*H*), 3.77–3.56 (m, 3H, C*H*OH and C$H_2$Ar), 3.41 (d, *J* = 13.4 Hz, 2H, C$H_2$Ar), 2.63 (dd, *J* = 3.6, 12.9 Hz, 1H, CHC$H_2$), 2.53–2.33 (m, 3H, CHC$H_2$ and NH$_2$C$H_2$CH), 2.10 (bs, 3H, O*H* and N$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 138.9, 129.2, 128.6, 127.5, 68.9, 59.0, 57.0, 45.7; Anal. Calcd for $C_{17}H_{22}N_2O$ (270.37): C, 75.52%; H, 8.20%; N, 10.36%; Found C, 75.63%; H, 8.21%; N, 10.41%.

### General Procedure for the Synthesis of Compounds 15–20

An appropriate primary amine (20.0 mmol) was dissolved in 1:2 toluene/MeOH mixture (30 ml) and added dropwise to a solution of 5,11,17,23-tetra-*tert*-butyl-25,27-diethoxycarbonylmethoxy-26,28-dihydroxycalix[4]arene **14** (328 mg, 0.4 mmol) in 10 ml toluene with continuous stirring at room temperature for about 30 min. Then, the reaction mixture was refluxed, and the reactions were monitored by TLC. After the substrate had been consumed, the solvent was evaporated under

reduced pressure, and the residue was triturated with MeOH to give a crude product. The crude products were purified by flash chromatography ($SiO_2$, $CHCl_3$/MeOH 15:1) and recrystallized from $CHCl_3$/MeOH.

### *25,27-Bis(N-[-[(2R)-2-hydroxy-3-[[(1S)-1-phenylethyl]amino]propyl]asetamide))-26,28-dihydroxy-5,11,17,23-tetra(tert-butyl)calix[4]arene (15)*

Reaction mixture was refluxed for 3 days. White solid; yield 62%; mp: 104–107°C; $\alpha_D^{25}$ = −38.5 (c 1.35, $CHCl_3$). IR (KBr): 3325, 2962, 1666 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 9.01 (t, *J* = 5.5 Hz, 2H, N*H*), 7.66 (s, 2H, O*H*), 7.29–7.19 (m, 10H, Ar*H*), 7.10 (s, 4H, Ar*H*), 6.90 (s, 4H, Ar*H*), 4.61 (d, *J* = 15.0 Hz, 2H, OC$H_2$CO), 4.50 (d, *J* = 14.9 Hz, 2H, OC$H_2$CO), 4.14 (dd, *J* = 13.3, 6.3 Hz, 4H, ArC$H_2$Ar), 3.84 (sep, *J* =3.8, 7.5 Hz, 2H, C*H*OH), 3.63 (q, *J* = 6.6 Hz, 2H, $CH_3$C*H*), 3.52–3.37 (m, 8H, ArC$H_2$Ar and CONHC$H_2$CH), 3.05 (bs, 4H, N*H* and O*H*), 2.60 (dd, *J* = 8.4, 3.9 Hz, 2H, CHC$H_2$NHCH), 2.44 (dd, *J* = 7.9, 4.0 Hz, 2H, CHC$H_2$NHCH and NHC$H_2$CH), 1.32 (d, *J* = 6.7 Hz, 6H, C$H_3$CH), 1.29 (s, 18H, CC$H_3$), 1.03 (s, 18H, CC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 169.7, 149.7, 149.6, 148.6, 145.2, 143.4, 132.5, 132.4, 128.7, 127.6, 127.5, 127.2, 126.8, 126.5, 126.3, 125.9, 125.8, 75.0, 69.4, 58.1, 50.7, 44.0, 32.4, 34.3, 31.9, 31.2, 24.4; Anal. Calcd for $C_{70}H_{92}N_4O_8$ (1117.51): C, 75.22%; H, 8.33%; N, 5.04%; Found C, 75.28%; H, 8.34%; N, 5.09%.

### *25,27-Bis(N-[[(2R)-2-hydroxy-3-[[(1R)-2-hydroxy-1-phenylethyl]amino]propyl]asetamide))-26,28-dihydroxy-5,11,17,23-tetra(tert-butyl)calix[4]arene (16)*

Reaction mixture was refluxed for 4 days. White solid; yield 69%; mp: 110–113°C; $\alpha_D^{25}$ = + 29.75 (c 1.21, $CHCl_3$). IR (KBr): 3319, 2959, 1657 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 9.26 (t, *J* = 5.1 Hz, 2H, N*H*), 7.74 (s, 2H, O*H*), 7.40-7.20 (m, 10H, Ar*H*), 7.11–7.09 (m, 4H, Ar*H*), 6.92–6.89 (m, 4H, Ar*H*), 4.74 (d, *J* = 15.3 Hz, 2H, OC$H_2$CO), 4.49 (d, *J* = 15.0 Hz, 2H, OC$H_2$CO), 4.17 (dd, *J* = 13.1, 6.8 Hz, 4H, ArC$H_2$Ar), 3.94 (sep, *J* = 6.1, 5.7, 4.7 Hz, 2H, NHC*H*C$H_2$OH), 3.78–3.36 (m, 14H, OHC*H* and CONHC$H_2$CH and CHC$H_2$NHCH and ArC$H_2$Ar), 3.20–2.95 (m, 6H, NH and CHO*H* and C$H_2$O*H*), 2.60 (d, *J* = 5.7 Hz, 4H, CHC$H_2$OH), 1.28 (s, 18H, CC$H_3$), 1.03 (s, 18H, CC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 170.3, 149.7, 149.6, 148.5, 143.5, 140.3, 132.6, 132.5, 128.9, 127.8, 127.7, 127.4, 126.8, 126.6, 126.3, 125.9, 125.7, 75.0, 69.1, 67.4, 64.6, 50.2, 44.1, 34.4, 32.4, 31.9, 31.2; Anal. Calcd for $C_{70}H_{92}N_4O_{10}$ (1149.50): C, 73.14%; H, 8.07%; N, 4.87%; Found C, 73.19%; H, 8.08%; N, 4.91%.

### *25,27-Bis(N-[[(2R)-2-hydroxy-3-[[(1R)-1-(hydroxymethyl)propyl]amino]propyl]asetamide))-26,28-dihydroxy-5,11,17,23-tetra(tert-butyl)calix[4]arene (17)*

Reaction mixture was refluxed for 4 days. White solid; yield 58%; mp: 175–178°C; $\alpha_D^{25}$ = + 64.9 (c 1.17, $CHCl_3$). IR (KBr): 3350, 2956, 1650 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 8.62 (t, *J* = 5.2 Hz; 2H, N*H*), 7.81 (s, 2H, ArO*H*), 7.07–6.99 (m, 4H, Ar*H*), 6.72 (s, 4H, Ar*H*), 4.56–4.43 (m, 4H, OC$H_2$CO), 4.32–4.16 (m, 6H, ArC$H_2$Ar, C*H*OH), 3.93 (dd, *J* = 12.3, 17.8 Hz, 2H, NHC*H*), 3.76–3.63 (m, 4H, C$H_2$OH), 3.36–2.99 (m, 16H, NHC$H_2$ and NHC$H_2$ and ArC$H_2$Ar and C$H_2$CH$_3$), 2.12–2.02 (m, 6H, N*H* and O*H* and O*H*), 1.28 (s, 18H, CC$H_3$), 0.97 (t, *J* = 8.0 Hz, 6H, CH$_2$C$H_3$), 0.92 (s, 18H, CC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 169.4, 151.4, 150.6, 143.0, 142.7, 126.7, 126.2, 125.9, 125.7, 125.9, 124.2, 75.9, 70.2, 64.6, 50.9, 44.3, 34.7, 34.5, 32.5, 31.7, 31.4, 31.1, 21.3; Anal. Calcd for $C_{62}H_{92}N_4O_{10}$ (1053.41): C, 70.69%; H, 8.80%; N, 5.32%; Found C, 70.75%; H, 8.82%; N, 5.35%.

### *25,27-Bis(N-[[(2R)-2-hydroxy-3-[[(1R,2S)-2-hydroxyindan-1-yl]amino]propyl]asetamide))-26,28-dihydroxy-5,11,17,23-tetra(tert-butyl)calix[4]arene (18)*

Reaction mixture was refluxed for 3 days. White solid; yield 52%; mp: 175–178°C; $\alpha_D^{25}$ = + 25.4 (c 1.73, $CHCl_3$). IR (KBr): 3346, 2956, 1664 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 9.04 (t, *J* = 4.9 Hz, 2H, N*H*), 7.58 (s, 2H, O*H*), 7.22–7.19 (m, 2H, Ar*H*), 7.18–7.09 (m, 6H, Ar*H*), 7.00–6.97 (m, 4H, Ar*H*), 6.81 (s, 4H, Ar*H*), 4.56 (d, *J* = 15.1 Hz, 2H, OC$H_2$CO), 4.47 (d, *J* = 15.0 Hz, 2H, OC$H_2$CO), 4.28–4.25 (m, 2H, C*H*OH), 4.14 (dd, *J* = 12.3, 5.1 Hz, 4H, ArC$H_2$Ar), 3.91–3.86 (m, 2H, C*H*OH), 3.81 (d, *J* = 6.1 Hz, 2H, C*H*NH), 3.49–3.30 (m, 14H, ArC$H_2$Ar and CONHC$H_2$CH and N*H* and O*H*), 2.92–2.82 (m, 8H, CHC$H_2$NHCH and CHCHC$H_2$), 1.17 (s, 18H, CC$H_3$), 0.94 (s, 18H, CC$H_3$); $^{13}$C NMR (100 MHz,$CDCl_3$) $\delta_C$ (ppm) 170.2, 149.6, 148.5, 143.5, 142.2, 140.9, 132.5, 132.4, 128.2, 127.6, 127.0, 126.5, 126.3, 125.9, 125.8, 125.6, 124.6, 75.0, 72.1, 70.1, 66.5, 52.0, 44.1, 39.8, 34.1, 32.4, 31.8, 31.1; Anal. Calcd for $C_{72}H_{92}N_4O_{10}$ (1173.52): C, 73.69%; H, 7.90%; N, 4.77%; Found C, 73.74%; H, 7.91%; N, 4.80%.

### *25,27-Bis(N-[[(2S)-2-hydroxy-3-indolin-1-yl-propyl]asetamide))-26,28-dihydroxy-5,11,17,23-tetra(tert-butyl)calix[4]arene (19)*

Reaction mixture was refluxed for 4 days. White solid; yield 71%; mp: 118–121°C; $\alpha_D^{25}$ = + 45.1 (c 0.93, $CHCl_3$). IR (KBr): 3332, 2955, 1659 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 9.05 (t, *J* = 5.5 Hz, 2H, N*H*), 7.64 (s, 2H, O*H*), 7.01 (s, 4H, Ar*H*), 6.97 (d, *J* = 7.2 Hz, 2H, Ar*H*), 6.91 (t, *J* = 7.9 Hz, 2H, Ar*H*), 6.83 (s, 4H, Ar*H*), 6.59 (t, *J* = 7.4 Hz, 2H, Ar*H*), 6.35 (d, *J* = 7.9 Hz, 2H, Ar*H*), 4.50 (dd, *J* = 2.9, 5.1 Hz, 4H, OC$H_2$CO), 4.09 (d, *J* = 13.3 Hz, 4H, ArC$H_2$Ar), 4.04–3.98 (m, 2H, C*H*OH), 3.67 (qd, *J* = 2.9, 5.1 Hz, 2H, NHC$H_2$CH), 3.42 (qd, *J* = 2.4, 5.7 Hz, 2H, NC$H_2$CH$_2$), 3.36–3.30 (m, 6H, NHC$H_2$CH and NC$H_2$CH and NC$H_2$CH$_2$), 3.14 (q, *J* = 8.8 Hz, 2H, NC$H_2$CH), 3.08 (dd, *J* = 7.7, 6.0 Hz, 2H, ArC$H_2$Ar), 2.99 (dd, *J* = 4.9, 8.6 Hz, 2H, ArC$H_2$Ar), 2.85 (t, *J* = 8.2 Hz, 4H, NCH$_2$C$H_2$Ph), 1.55 ( bs, 2H, O*H*), 1.20 (s, 18H, CC$H_3$), 0.96 (s, 18H, CC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 169.4, 152.8, 149.6, 149.5, 148.6, 143.4, 132.5, 130.1, 127.6, 127.5, 126.5, 126.4, 125.9, 125.8, 124.7, 118.5, 107.6, 75.1, 69.4, 55.0, 54.9, 43.9, 32.4, 34.3, 31.8, 31.2, 29.0; Anal. Calcd for $C_{70}H_{88}N_4O_8$ (1113.47): C, 75.51%; H, 7.97%; N, 5.03%; Found C, 75.56%; H, 7.98%; N, 5.05%.

### *25,27-Bis(N-[[(2S)-3-(dibenzoylamino)-2-hydroxy-propyl]asetamide))-26,28-dihydroxy-5,11,17,23-tetra(tert-butyl)calix[4]arene (20)*

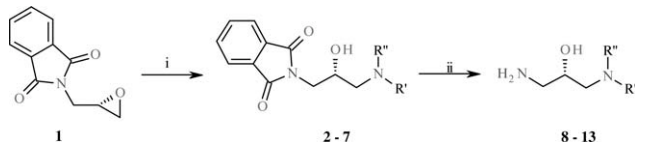
Reaction mixture was refluxed for 3 days. White solid; yield 76%; mp: 165–168°C; $\alpha_D^{25}$ = + 19.4 (c 1.44, $CHCl_3$). IR (KBr): 3336, 2953, 1665 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ (ppm) 8.95 (t, *J* = 5.4 Hz, 2H, N*H*), 7.58 (s, 2H, O*H*), 7.39–7.17 (m, 20H, Ar*H*), 7.08 (s, 4H, Ar*H*), 6.88 (s, 4H, Ar*H*), 4.48 (dd, *J* = 15.0, 34.9 Hz, 4H, OC$H_2$CO), 4.22–4.00 (m, 4H, ArC$H_2$Ar), 3.98–3.86 (m, 2H, C*H*OH), 3.61 (d, *J* = 13.6 Hz, 4H, NC$H_2$Ar), 3.53 (ddd, *J* = 3.6, 5.1, 13.6 Hz, 2H, CHC$H_2$NH), 3.47–3.39 (m, 6H, NC$H_2$Ar and CHO*H*), 3.38–3.27 (m, 6H, CHC$H_2$NH and ArC$H_2$Ar), 2.71–2.40 (m, 4H, CHC$H_2$N), 1.28 (s, 18H, CC$H_3$), 1.03 (s, 18H, CC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ (ppm) 169.4, 149.8, 149.6, 148.4, 143.2, 138.8, 132.5, 132.4, 129.2, 128.6, 127.6, 127.4, 127.3, 126.4, 126.3, 125.8, 125.7, 67.7, 58.5, 57.4, 43.9, 34.3, 34.1, 32.4, 32.2, 31.9, 31.2, 14.4; Anal. Calcd for $C_{82}H_{100}N_4O_8$ (1269.69): C, 77.61%; H, 7.93%; N, 4.41%; Found C, 77.64%; H, 7.94%; N, 4.45%.

## RESULTS AND DISCUSSION

### *Design and Synthesis of the New Hosts*

Amino alcohols are known to be very useful substances in the total synthesis of a variety of natural products, being widely used in asymmetric synthesis, as building elements for heterocycles, and used as reagents or catalytic agents in organic chemistry. It was expected that chiral calix[4]arene derivatives bearing both an amino group and a hydroxyl group can be used as membrane carriers for the enantioselective transport of chiral amino acids and mandelic acid. To the best of our knowledge, there are few examples[45,46] of chiral calixarenes known to date as enantioselective carriers in transport of amino acid esters and mandelic acid through bulk liquid membrane.

To achieve the desired goal, *p-tert*-butylcalix[4]arene diester **14** was chosen as the precursor, and the synthetic route is shown in Scheme 1 and 2 for the synthesis of chiral



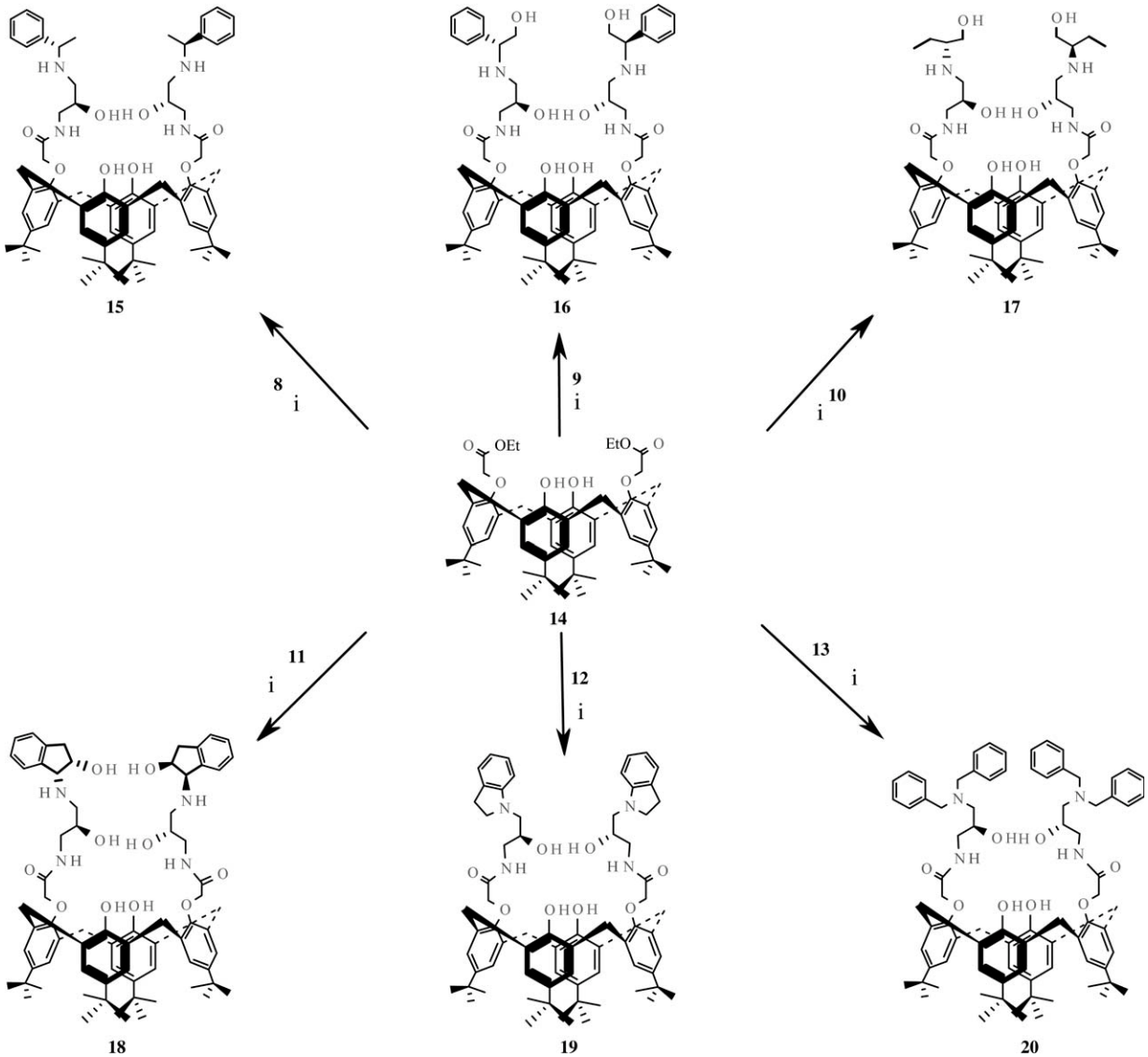
**Scheme 1.** (**i**) Appropriate chiral amine or amino alcohol, 2-propanol, reflux, 64%–84% (**ii**) $NH_2NH_2.H_2O$, ethanol, reflux.

calix[4]arene derivatives **15–20**. Thus, following the literature procedure,[44] chiral subunits **8–13** were readily prepared by the regioselective ring opening of the (*R*)-*N*-(2,3-epoxypropyl)phthalimide with (*S*)-phenyl ethylamine, (*R*)-2-phenyl glycinol, (*R*)-2-amino-1-butanol, (1*R*, 2*S*)-cis-1-amino-2-indanol, indoline and dibenzylamine and subsequent cleavage of chiral phthalimides **8–13** with hydrazine hydrate by refluxing in ethanol.

Then, coupling of the amino alcohols **8–13** with the calix[4]arene diester by refluxing in toluene/MeOH (1:1) mixture led to the formation of the chiral calix[4]arene derivatives **15–20** in moderate to good yields. The products were characterized by a combination of $^1$H NMR, $^{13}$C NMR, FTIR, and elemental analysis. With an efficient synthetic scheme for the synthesis of chiral calix[4]arenes in hand, we turned our attention to their transport abilities of these receptors as enantioselective carriers toward mandelic acid and aromatic amino acid esters through liquid membranes. To take advantage of both amine and alcohol group in these calix[4]-arene derivatives, the enantiomers of phenylglycine (PhGlyOMe.HCl), phenylalanine (PheOMe.HCl) and tryptophan methyl ester hydrochloride (TrpOMe.HCl) and mandelic acid (MA) were chosen as guest molecules.

### *Liquid Membrane Transport of Amino Acid Methyl Esters and Mandelic Acid*

Facilitated transport studies were performed at room temperature in a U-type glass tube, consisting of a chloroform phase separating two aqueous sources and receiving phases. The transport apparatus and detailed experimental conditions are shown in Figure 1. The experiments were performed in all cases at least twice under strict similar conditions due to the many factors influencing transport



**Scheme 2.** (**i**) Chiral β hydroxy amine **8–13**, MeOH/toluene (1:1), reflux, 52%–76%.

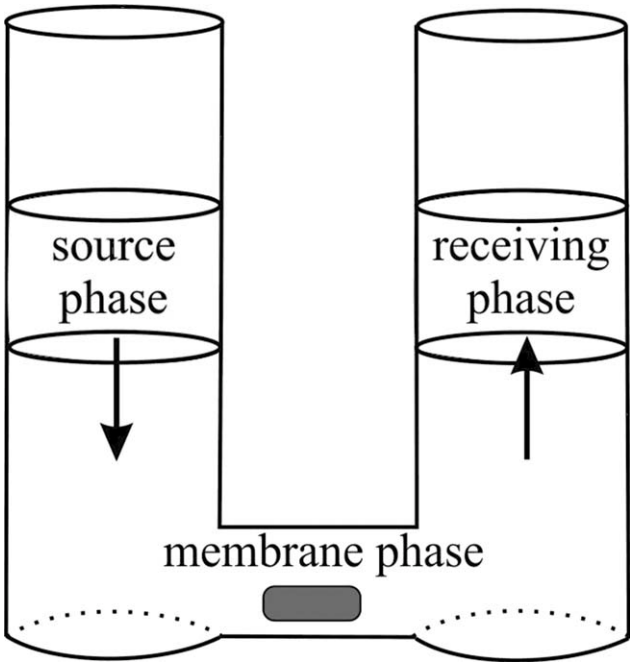



**Fig. 1.** Transport apparatus and detailed experimental conditions. (**a**) Source phase (5 ml): amino acid methyl esters hydrochloride (pH = 5.5) or mandelic acid (pH = 2.0) ($2 \times 10^{-4}$ or $7 \times 10^{-3}$ M). (**b**) Organic carrier phase (10 ml): $CHCl_3$; carrier: chiral calix[4]arene derivatives (**15–20**) ($2 \times 10^{-4}$ M). (**c**) Receiving phase (5 ml): pure water (pH = 1.5 for amino acid methyl esters hydrochloride and pH = 8.0 for mandelic acid).

rates and enantioselectivities. The estimated errors (<10%) are consistent with those reported in the literature.[47] A blank experiment using the organic solvent without the carrier indicated that the enantioselectivity of amino acids was negligible. The feed phase was an aqueous solution (5 ml) of amino acid methyl ester hydrochloride $2.0 \times 10^{-4}$ or $7.0 \times 10^{-3}$ M at pH = 5.5 value obtained by adding HCl or LiOH. The receiving phase was a solution (5 ml) of HCl (pH = 1.5). The membrane phase, 10 ml of chiral calix[4] arenes of $2.0 \times 10^{-4}$ M in chloroform was introduced in the tube.[48] The membrane phase was stirred at 300 rpm by a magnetic stirrer.

The flux ($J$) of each enantiomer was calculated by:[49–51]

$$J = \frac{V_r \Delta C_r}{At} \tag{1}$$

where $t$ is the time over which the concentration difference, $\Delta C_r$, is measured in the receiving phase, $V_r$ the receiving volume, and $A$ is the effective membrane area. This is the flux from the start of the experiment till time $t$.

The enantioselectivity was calculated in terms of the flux ratio ($\alpha$), corresponds to the flux of the one enantiomer with respect to the other enantiomer.

$$\alpha = \frac{J_D}{J_L} \tag{2}$$

To determine the concentration of transported guests, corresponding samples were periodically withdrawn from the aqueous receiving phases in each experiment and the amounts of amino acid esters were measured by UV-Vis spectroscopy (Fig. 2).

Transport data shown in Table 1 and Figure 3, indicate that chiral carriers **15–20** showed relatively good transport abilities for the enantiomers of PhGlyOMe.HCl. The transport sequence of PhGlyOMe.HCl has been found that the order of carriers is **20** > **16** > **18** > **15** > **19** > **17**. The enantiomer designated L form had a relatively higher flux in all cases investigated. This means that chiral carriers preferentially recognize L-PhGlyOMe.HCl relating to D-enantiomer. The highest L/D selectivity was observed with hosts **19** and **20**, affording $K_L/K_D$ of 1.74 and 2.05, respectively.

As can be seen from Table 1, all macrocyclic carriers showed significantly lower transport rates for the enantiomers of tryptophan methyl ester hydrochloride than other amino acid esters. The flux of D-tryptophan ester was found to be higher than that of the L-enantiomer in each case, except in the case of host **17**, which enantioselectively transport L-enantiomer over D-antipode (Fig. 4). The highest enantioselectivity was found with the host **16**, affording $K_D/K_L$ of 3.29.

Among all the amino acid esters studied, phenylalanine showed the highest transport efficiency with chiral calix[4]-arene derivatives. This can attributed to the favorable π-π interaction between the phenyl group in PheOMe.HCl and the aromatic moieties in carriers as well as hydrophobicity and hydrogen bonding. With macrocycles **15**, **17,** and **18**, the fluxes of D-PheOMe.HCl were found to be higher than that of the L-enantiomer, but the highest and reverse selectivities were found with the host **16**, **19,** and **20**, affording $K_L/K_D$ of 1.32, 3.18, and 1.61 respectively (Fig. 5).

The facilitated transport of mandelic acid through a liquid membrane was also studied in the presence of chiral calix[4]-arene derivatives. The feed phase contains 5 ml of aqueous mandelic acid solution at pH = 2 present in one arm whereas the aqueous receiving phase, 5 ml (pH = 8) is present in the other arm. The membrane phase, 10 ml of chiral calix[4]arenes of $2.0 \times 10^{-4}$ M in chloroform was introduced in the tube. The aqueous and organic phases were stirred at 300 rpm at room temperature for 24 h. The experimental data of

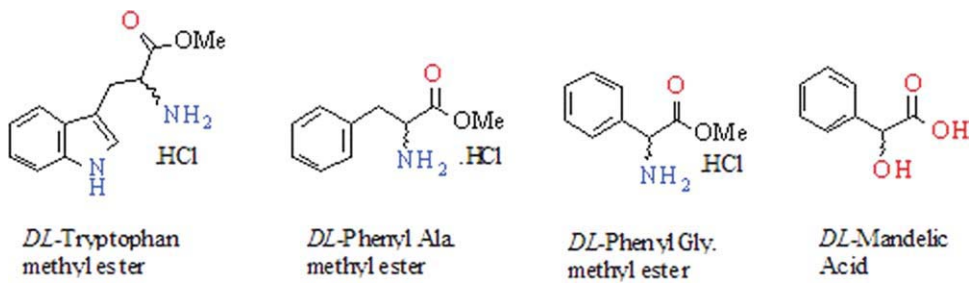



**Fig. 2.** Chemical structures of the guests studied. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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

| Guest | 15 | | 16 | | 17 | | 18 | | 19 | | 20 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $J_{24} \times 10^{-9}$ | α | $J_{24} \times 10^{-9}$ | α | $J_{24} \times 10^{-9}$ | α | $J_{24} \times 10^{-9}$ | α | $J_{24} \times 10^{-9}$ | α | $J_{24} \times 10^{-9}$ | α |
| D-PheOMe | 319.43 | 1.34 (D) | 275.05 | 1.32 (L) | 201.26 | 1.23 (D) | 432.70 | 2.11 (D) | 159.97 | 3.18 (L) | 230.80 | 1.61 (L) |
| L-PheOMe | 237.90 | | 362.00 | | 163.33 | | 204.87 | | 508.69 | | 372.19 | |
| D-TrpOMe | 10.51 | 1.56 (D) | 15.79 | 3.29 (D) | 5.81 | 1.05 (L) | 11.48 | 1.50 (D) | 13.76 | 1.88 (D) | 11.50 | 1.48 (D) |
| L-TrpOMe | 6.72 | | 4.81 | | 6.12 | | 7.66 | | 7.34 | | 7.78 | |
| D-PhGlyOMe | 214.03 | 1.60 (L) | 248.09 | 1.68 (L) | 179.58 | 1.01 (L) | 281.89 | 1.37 (L) | 193.26 | 1.74 (L) | 224.87 | 2.05 (L) |
| L-PhGlyOMe | 343.30 | | 417.35 | | 181.13 | | 384.97 | | 337.23 | | 460.18 | |
| D-MA | 15.34 | 1.35 (L) | 17.07 | 1.65 (L) | 10.57 | 1.30 (L) | 14.01 | 1.68 (L) | 12.98 | 1.75 (L) | 14.17 | 1.42 (L) |
| L-MA | 20.73 | | 28.16 | | 13.79 | | 23.56 | | 22.76 | | 20.15 | |

[a]Data obtained from three independent transport experiments, estimated errors are <10%.
[b]$J_{24}$ = Flux of transported amino acid methyl esters or mandelic acid after 24 h (mol $(m^2\ s)^{-1}$); $\alpha_T$ = ratio of fluxes: higher/lower flux; TrpOMe.HCl = Tryptophan methyl ester hydrochloride; PheOMe.HCl = Phenylalanine methyl ester hydrochloride; PhGlyOMe.HCl = Phenylglycine methyl ester hydrochloride; MA = Mandelic acid. D or L indicates the preferential form of enantiomers.

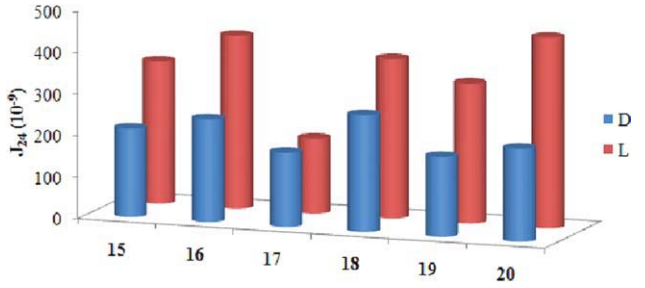



**Fig. 3.** Bar plots of fluxes of PhGly-OMe for hosts **15–20**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the transport shown in Table 1 and Figure 6 indicated that the fluxes of both enantiomers were relatively low when compared with the amino acid esters investigated. All chiral carriers displayed similar enantioselectivity and preferentially transported the D-enantiomers.

It is clear that, the fluxes of both enantimers linearly increased and the enantioselectivity reached a maximum during the first 90 min of transport experiments. After this time, the fluxes and the enantioselectivities decreased down. This is probably due to the loss of chiral carrier from the liquid membrane leading to reduced enantioselectivities and lower fluxes as reported.

From the results shown in Table 1, it can be concluded that the structure of calixarene derivative is one of the most important factor for recognition of amino acid esters. The chiral carriers **15–20** are broadly similar in that all contain hydrogen bonding sites defined by carbonyl oxygen, amide nitrogen, and hydroxy groups at roughly similar positions with respect to the phenoxy oxygen, chiral and achiral end groups capable of additional hydrogen bonding (secondary and tertiary amine or hydroxy group), and alkyl or aryl groups. With macrocycle **17**, the lowest transport rates and

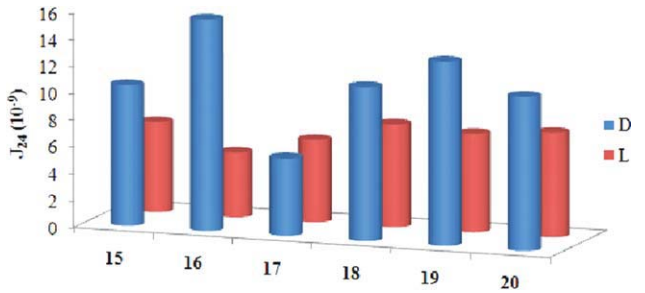



**Fig. 4.** Bar plots of fluxes of Trp-OMe for hosts **15–20**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

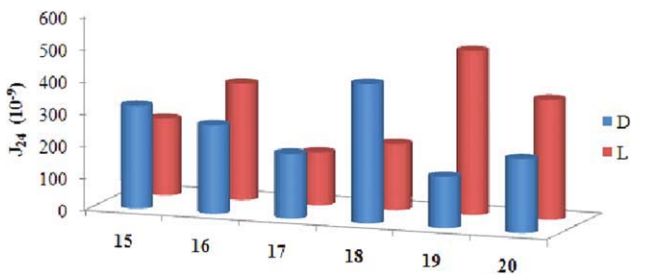



**Fig. 5.** Bar plots of fluxes of PheOMe for hosts **15–20**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

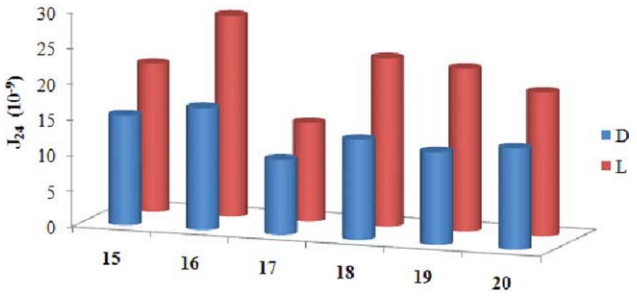



**Fig. 6.** Bar plots of fluxes of mandelic acid for hosts **15–20**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

selectivities were observed for amino acid esters and mandelic acid. This might be related the lack of π-π stacking between aromatic moieties and the weak steric interactions of those substituents with the amino acid ester molecule. As in the case of receptor **16**, the introduction of a phenyl group instead of the ethyl group affects the transport rate and enantioselectivity. This could be attributed to the favorable π-π interactions between the phenyl moiety of the carrier and the aromatic fragment of amino acid esters and mandelic acid. Similarly, chiral receptors **15**, **18–20** containing bulky aromatic groups have also considerable higher transport rates and stereoselectivities because of the same reason.

The transport mechanism of amino acid esters through the bulk liquid membrane containing chiral calix[4]arenes as carriers can be explained by the model described previously.[46] The protonated amino acid ester in the source phase at pH = 5.5 diffuses to the interface and a complex occurs via an interaction of the basic nitrogen atom in the chiral receptor and the quaternary ammonium cation in the amino acid ester. The complex diffuses toward the opposite interface through the bulk liquid membrane phase. The stripping reaction takes place with hydrogen ions at the interface in the receiving phase (pH = 1.5) and the chiral carrier is regenerated.

In the case of mandelic acid, the interaction between the acidic proton of the mandelic acid and the basic nitrogen atoms of the chiral receptor may form an ion pair complex at the interface and can be extracted to the organic phase. The complex is then transported to the receiving solution at pH = 8 and mandelic acid is released.

## CONCLUSION

In this study, novel chiral calix[4]arene derivatives containing amino alcohol moieties were synthesized by the reaction of diester derivative of *p-tert*-butylcalix[4]arene with various amino alcohols. The transport abilities of these receptors toward amino acid esters and mandelic acid have been studied by UV-Vis spectroscopy. The receptors exhibited different chiral recognition abilities towards the enantiomers of racemic guests. The receptors having aromatic end groups showed considerable higher transport rates and stereoselectivities. The results indicate that the multiple hydrogen bonding, steric hindrance, structural rigidity or flexibility, and π-π stacking between the aromatic groups may be responsible for the enantiomeric recognition.

## LITERATURE CITED

1. Breuer M, Ditrich K, Habicher T, Hauer B, Kesseler M, Sturmer R, Zelinski T. Industrial methods for the production of optically active intermediates. Angew Chem Int Ed Engl 2004;43:788–824.
2. Verkuijl BJV, Minnaard AJ, Vries JG, Feringa BL. Chiral separation of underivatized amino acids by reactive extraction with palladium-binap complexes. J Org Chem 2009;74:6526–6533.
3. Afonso CAM, Crespo JG. Recent advances in chiral resolution through membrane-based approaches. Angew Chem Int Ed Engl 2004;43:5293–5295.
4. Caner H, Groner E, Levy L. Agranat, I. Trends in the development of chiral drugs. Drug Discov Today 2004;9:105–110.
5. Stinson CS. Fine chemicals. Chem Eng News 2001;79:65–84.
6. Armstrong DW, Han SM. Enantiomeric separations in chromatography. Crit Rev Anal Chem 1988;19:175–224.
7. Hinze DL. Applications of cyclodextrins in chromatographic separations and purification methods. Sep Purif Methods 1981;10:159–237.
8. Armstrong DW. Optical isomer separation by liquid chromatography. Anal Chem 1987;59:84A–91A.
9. Sheldon RA. Chirotechnology; industrial synthesis of optically active compounds. New York: Marcel Dekker Inc.; 1993. p 423.
10. Sheldrake GN, Crosbyb J, Collins AN. Chirality in industry II. New York: Wiley; 1997. p 411.
11. Steensma M, Kuipers NJM, Haan ABD, Kwant G. Identification of enantioselective extractants for chiral separation of amines and aminoalcohols. Chirality 2006;18:314–328.
12. Maier NM, Franco P, Lindner W. Separation of enantiomers: needs, challenges, perspectives. J Chromatogr A 2001;906:3–303.
13. Xie R, Chu LY, Deng JG. Membranes and membrane processes for chiral resolution. Chem Soc Rev 2008;37:1243–1263.
14. Jirage KB, Martin CR. New developments in membrane-based separations. Trends Biotechnol 1999;17:197–200.
15. Gumi T, Minguillon C, Palet C. Separation of propranolol enantiomers through membranes based on chiral derivatized polysulfone. Polymer 2005;46:12306–12312.
16. Yang L, Chen XQ, Jiao FP. Extractive resolution of racemic mandelic acid through a bulk liquid membrane containing binary chiral carrier. J Braz Chem Soc 2009;20:1493–1498.
17. Mutihac L, Lee JH, Kim JS, Vicens J. Recognition of amino acids by functionalized calixarenes. Chem Soc Rev 2011;40:2777–2796.
18. Armstrong DW, Ward TJ, Armstrong RD, Beesley TE. Separation of drug stereoisomers by the formation of β-cyclodextrin complexes. Science 1986;232:1132–1135.
19. Ferreira Q, Coelhoso IM, Ramalhete N, Marques HMC. Resolution of racemic propranolol in liquid membranes containing TA-beta-cyclodextrin. Sep Sci Technol 2006;41:3553–3568.
20. Wang HD, Chu LY, Song H, Yang JP, Xie R, Yang M. Preparation and enantiomer separation characteristics of chitosan/b-cyclodextrin composite membranes. J Membr Sci 2007;297:262–270.
21. Abe Y, Shoji T, Kobayashi M, Qing W, Asai N, Nishizawa H. Enantioselective distribution of amino-alcohols in a liquid-liquid two-phase system containing dialkyl L-tartarate and boric acid. Chem Pharm Bull 1995;43:262–265.
22. Newcomb M, Toner JL, Helgeson RC, Cram DJ. Host-guest complexation. 20. Chiral recognition in transport as a molecular basis for a catalytic resolving machine. J Am Chem Soc 1979;101:4941–4947.
23. Demirel N, Bulut Y, Hosgoren H. Enantioselective transport and liquid-liquid extraction of amino acids as their potassium and sodium salts by optically active diaza-18-crown-6 ethers. Chirality 2004;16:347–350.
24. Kozbial M, Pietraszkiewicz M, Pietraszkiewicz O. Chiral discrimination of amino acids by an optically active crown ether studied by hplc, extraction and a liquid membrane transport experiments. J Incl Phenom Macrocycl Chem 1998;30:69–77.
25. Tsukube H, Shinoida S, Uenishi J, Kanatani T, Itoh H, Shiode M, Iwachido T, Yonemitsu O. Molecular recognition with lanthanide(III) tris(β-diketonate) complexes: extraction, transport, and chiral recognition of unprotected amino acids. Inorg Chem 1998;37:1585–1591.
26. Sessler JL, Andrievsky A. Efficient transport of aromatic amino acids by sapphyrin-lasalocid conjugates. Chem Eur J 1998;4:159–167.
27. Miyake H, Yamashita T, Kojima Y, Tsukube H. Enantioselective transport of amino acid ester salts by macrocyclic pseudopeptides containing *N, N'*-ethylene-bridged-dipeptide units. Tetrahedron Lett 1995; 36:7669–7672.
28. Dzygiel P, Wieczorek P, Jonsson J, Milewska M, Kafarski P. Separation of amino acid enantiomers using supported liquid membrane extraction with chiral phosphates and phosphonates. Tetrahedron 1999;55:9923–9932.

29. Dzygiel P, Wieczorek P, Kafarski P. Supported liquid membrane separation of amines and amino acid derivatives with chiral esters of phosphoric acids as carriers. J Sep Sci 2003;26:1050–1056.
30. Baragana B, Blackburn AG, Breccia P, Davis AP, Mendoza J, Padron-Carrillo JM, Prados P, Riedner J, Vries JG. Enantioselective transport by a steroidal guanidinium receptor. Chem Eur J 2002;8: 2931–2936.
31. Breccia P, Gool MV, Fernández RP, Santamaría SM, Gago F, Prados P, Mendoza J. Guanidinium receptors as enantioselective amino acid membrane carriers. J Am Chem Soc 2003;125:8270–8284.
32. Stella D, Calzado JA, Girelli AM, Canepari S, Bucci R, Palet C, Valiente M. Liquid membranes for chiral separations. Application of cinchonidine as a chiral carrier. J Sep Sci 2002;25:229–238.
33. Beer PD, Gale PA. Anion recognition and sensing: the state of the art and future perspectives. Angew Chem Int Ed Engl 2001;40:486–516.
34. Ludwig R. Fresenius J. Calixarenes in analytical and separation chemistry. Anal Chem 2000;367:103–128.
35. Iqbal KSJ, Cragg PJ. Trans membrane ion transport by calixarenes and their derivatives. Dalton Trans 2007;26–32; doi:10.1039/B613867P.
36. Mutihac L, Buschmann HJ, Diacu E. Calixarene derivatives as carriers in liquid membrane transport. Desalination 2002;148:253–256.
37. Mutihac L, Mutihac R. Liquid–liquid extraction and transport through membrane of amino acid methylesters by calix[n]arene derivatives. J Incl Phenom Macrocycl Chem 2007;59:177–181.
38. Mutihac L. Calix[n]arenes as synthetic membrane transporters. Anal Lett 2010;43:1355–1366.
39. Sirit A, Yilmaz M. Chiral calixarenes. Turk J Chem 2009;33:159–200.
40. Demirtas HN, Bozkurt S, Durmaz M, Yilmaz M, Sirit A. Synthesis of new chiralcalix[4]azacrowns for enantiomeric recognition of carboxylic acids. Tetrahedron:Asymmetry 2008;19:2020–2025.
41. Durmaz M, Bozkurt S, Naziroglu HN, Yilmaz M, Sirit A. Chiral calix[4]arenes bearing aminonaphthol moieties as membrane carriers for amino acid methyl esters and mandelic acid. Tetrahedron:Asymmetry 2011;22: 791–796.
42. Durmaz M, Yilmaz M, Sirit A. Synthesis of chiral calix[4]arenes bearing aminonaphthol moieties and their use in the enantiomeric recognition of carboxylic acids. Org Biomol Chem 2011;9:571–580.
43. Naziroglu HN, Durmaz M, Bozkurt S, Sirit A. Application of l-proline derivatives as chiral shift reagents for enantiomeric recognition of carboxylic acids. Chirality 2011;23:463–471.
44. Bozkurt S, Durmaz M, Naziroglu HN, Yilmaz M, Sirit A. Amino alcohol based chiral solvating agents: synthesis and applications in the NMR enantiodiscrimination of carboxylic acids. Tetrahedron:Asymmetry 2011;22:541–549.
45. Okada Y, Kasai Y, Nishimura J. The selective extraction and transport of amino acids by calix[4]arene-derived esters. Tetrahedron Lett 1995;36:555–558.
46. Oshima T, Inoue K, Furusaki S, Goto M. Liquid membrane transport of amino acids by a calix[6]arene carboxylic acid derivative. J Membr Sci 2003;217:87–97.
47. Aydin I, Aral T, Karakaplan M, Hosgören H. Chiral lariat ethers as membrane carriers for chiral amino acids and their sodium and potassium salts. Tetrahedron:Asymmetry 2009;20:179–183.
48. Kim L, Hamdi A, Stancu AD, Souane R, Mutihac L, Vicens J. Selective membrane transport of amino acids by functionalised calix[4]arenes. J Incl Phenom Macrocycl Chem 2010;66:55–59.
49. Jiao F, Chen X, Hu W, Yang L, Huang K. Enantioselective transport of R-Clenbuterol through a bulk liquid membrane containing O,O'-dibenzoyl-(2S, 3S)-tartaric acid. J Braz Chem Soc 2007;18:804–809.
50. Krieg HM, Lotter J, Keizer K, Breytenbach JC. Enrichment of chlorthalidone enantiomers by an aqueous bulk liquid membrane containing β-cyclodextrin. J Membr Sci 2000;167:33–45.
51. Raizada P, Vyas V, Sharma U. Liquid membrane extraction and transport of amino acids using calix[6]arene. Indian J Chem Tech 2010;17:267–273.