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Synthesis of novel C_2-symmetric chiral crown ethers and investigation of their enantiomeric recognition properties

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ABSTRACT

A series of new C_2-symmetric chiral aza crown ether macrocycles **1**–**4** have been synthesized from (*S*)-3-aryloxy-1,2-propanediol and (*S*)-1,2-propanediol for the enantiomeric recognition of amino acid ester derivatives. These new macrocycles have been shown to be strong complexing agents for primary organic ammonium salts (with K up to 176.93 M^{-1} and ΔG° up to 12.81 kJ mol^{-1}) by ^1H NMR titration. These macrocyclic host exhibited enantioselective bonding toward the D-enantiomer of phenylalanine methyl ester hydrochloride with K_D/K_L up to 6.87 in $CDCl_3$ with 0.25% CD_3OD.

1. Introduction

Chiral crown ethers are among the most efficient enantioselective receptors for amines, amino acids, and their derivatives.[1] Therefore, they can be used as catalysts in asymmetric reactions, enantioselective sensors, and models of biological systems.[2,3] In 1970s the first synthetic chiral crown ethers were prepared by Cram et al.[4] These enantiomerically pure macrocyclic molecules showed significant enantiomeric recognition toward protonated chiral amines and amino acid esters.[5] Since the pioneering work of Cram and co-workers a large number of different chiral crown ethers have been synthesized and studied for enantiomeric recognition toward protonated chiral primary amines, amino acids, and their derivatives.[6,7,1,8,9] The study of the enantioselective recognition of protonated chiral primary amines, amino acids, and their derivatives is of great significance since these compounds are basic building blocks of important biomolecules[1] and useful in developing new methods for asymmetric (synthesized) chromatographic resolution of enantiomers.[1]

Effective enantiomeric recognition requires that a chiral macrocyclic receptor be capable of forming sufficiently stable complexes with substrate enantiomers and that a chiral barrier be present, which reduces the stability of one of the diastereoisomeric complexes thus formed.

In other words, the enantiodifferentiating properties of chiral crown ethers are determined by the stability of complexes with chiral substrates and by the nature of the chiral fragment in the macroring. The complexing power of chiral crown ethers depends on a number of factors, including the nature of the donor groups in the macroring. In many cases, the introduction of nitrogen atoms into the macrocyclic skeleton increases the stability of complexes with ammonium ion and amine and amino acid salts.[10] However, among a large series of chiral crown ethers, aza crown ethers have been studied to the least extent.[11]

The chiral nature of the crown ether, the rigidity of the microenvironment of its cavity, and the quality of the side arm are all expected to play an important role. Azacrown ethers with a side arm attached to the nitrogen atom in the macrocyclic ring may enhance and regulate cation binding properties, as well as the lipophilicity. Crown ethers with heteroatom-containing podand arms are known to have a highly lipophilic character and a unique guest selectivity via macroring-side arm cooperativity.[12,13]

It is known that the symmetry of the macrocyclic ring is crucial for enantiomeric recognition, therefore we focused on the synthesis of C_2-symmetric chiral crown ethers derived from amino alcohols. Our interest has been focused on the enantiomeric recognition of amino acids utilizing a synthetic chiral crown ether. We recently studied the enantiomeric recognition of chiral ammonium salts by an aza crown ether.[14] Herein, we report the synthesis of a new C_2-symmetric chiral receptor 18-crown-6 derivatives and their enantiomeric recognition of different α-amino acid methyl ester hydrochlorides (D-PheAlaOMe, L-PheAlaOMe, D-ValOMe, and L-ValOMe) by ^1H NMR titration method in $CDCl_3$ with 0.25% CD_3OD.

2. Results and discussion

2.1. Synthesis

Initially, phenol and (*S*)-glycidol were transformed into diol **1b**, which was tosylated to generate **2b**. Compounds **2a** and **2b** were reacted with excess (*S*)-α-phenyl ethylamine to obtain **4a** and **4b** in yields of 65% and 63%, respectively (Scheme 1).

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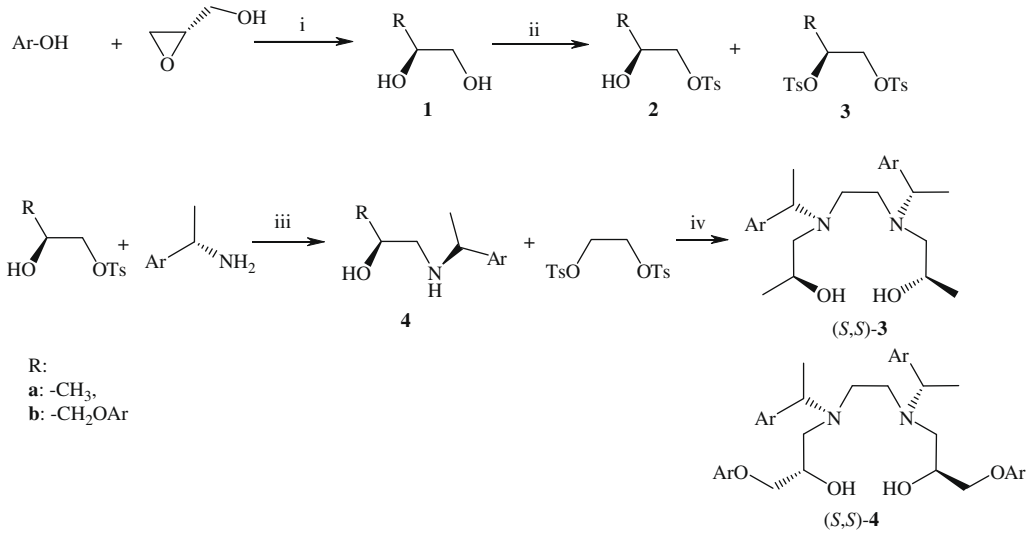


Scheme 1. Reagents and conditions: (i) piperidine hydrochloride, 75 °C; (ii) tosyl chloride, dichloromethane: pyridine, −25 °C, and (iii, iv) Na_2CO_3, 14 h, 120 °C.

The C_2-symmetric chiral amino alcohols (*S,S*)-**3** and (*S,S*)-**4** were synthesized from the ditosylate with excess **4a** and **4b** in the presence of Na_2CO_3 in yields of 46% and 48%, respectively.

Chiral C_2-symmetric crowns **1**–**4** were synthesized for the enantiomeric recognition of α-amino acid methyl ester hydrochlorides. The syntheses of the designed chiral crown ethers **1**–**4** are summarized in Schemes 2 and 3, respectively. Cyclization of the appropriate ditosylate with (*S,S*)-**3** and (*S,S*)-**4** using NaH as a base in dry and freshly prepared THF afforded **3** and **4**.

2.2. Enantiomeric recognition by ^{1}H NMR of host–guest complexes

NMR spectroscopy is one of the most common methods employed for the analysis of chiral compounds.[15] Enantiomerically pure derivatizing reagents can be used to prepare diastereomeric compounds that have differences in their NMR spectra. Alternatively, enantiomerically pure or enriched compounds can be used as chiral solvating agents to form diastereomeric complexes that associate through non-covalent interactions.

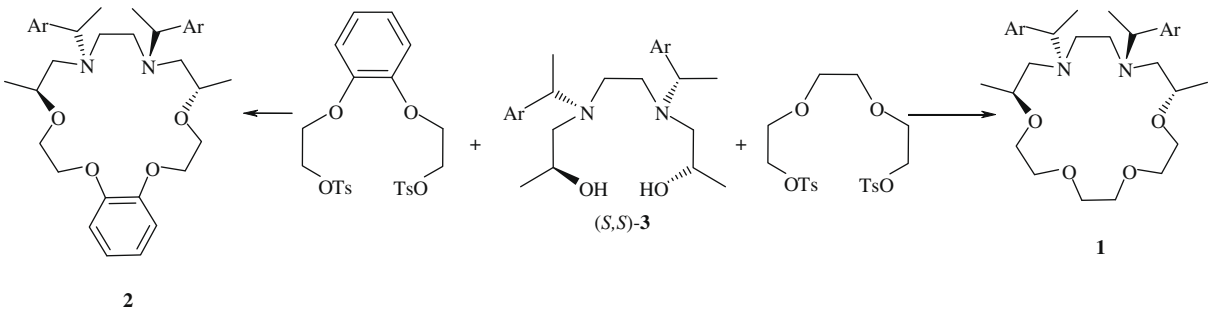
The NMR titration method has proven to be effective in determining the bonding constant value for chiral crown ether-chiral ammonium cation interaction, especially for systems in which both host and guest molecules contain aromatic groups. The advantage of the ^{1}H NMR method are that the experiment can be carried out in a wide variety of solvents and that useful structural information can often be obtained.

Crown ethers are important families of cavity compounds that have found rather widespread application as chiral NMR solvating agents. Crown ethers, which usually involve compounds with an 18-crown-6 unit, are known for their ability to bond to protonated primary ammonium cations[16] via a three-point (tripod) hydrogen bond interaction. Studies on the binding of amino acid carboxylates by multiple hydrogen bonding receptors have gained increasing importance in recent years. Examples of chiral recognition involving chiral 18-crown-6 type ligands and chiral primary ammonium cations have already been shown by us and others.[17,18]

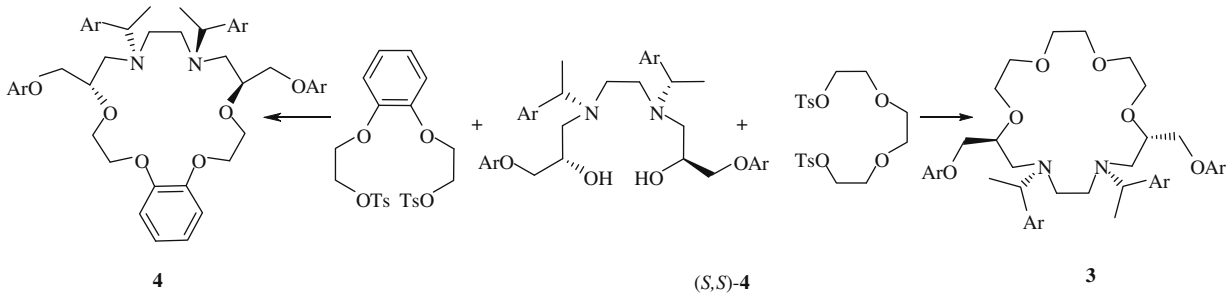
The association constants of the supramolecular systems formed were calculated according to the modified Benesi–Hildebrand equation.[19] All the binding constants of the complexes were obtained by the non-linear least-squares method on the basis of the ^{1}H NMR spectra data using the same methyl peak of the chiral guest.[20]

The enantiomeric recognition for the hydrogen chloride salts of D-, L-PheAlaOMe, D-, L-ValOMe by chiral crown ethers **1**–**4** have been characterized by ^{1}H NMR titration method. Figure 2 shows the spectroscopic changes of the ^{1}H NMR methine proton signals of D- and L-phenylalanine methyl ester hydrochloride (5.6 mM) in the absence and presence of chiral crown ethers **4** (2.23–17.8 mM) in $CDCl_3$ with 0.25% CD_3OD at 298 K. Before adding any host, the methine proton of guest showed one triplet peak at around 4.35 ppm. When the host and guest interact in a solution forming a 1:1 complex, this singlet peak was shifted downfield. The binding constant of the complex was obtained using these peaks.

As shown in Table 1 and Figure 2, all amino acid methyl ester hydrochlorides form a stable complex with chiral crown ethers **1**–**4**. The association constants of the chiral crown ether **1** with



Scheme 2. Synthesis of chiral crown macrocycles. Reagents and conditions: (1) NaH/THF, reflux, 2 h; (2) ditosylate/THF, 50 h.



Scheme 3. Synthesis of chiral crown macrocycles. Reagents and conditions: (1) NaH/THF, reflux, 2 h; (2) ditosylate/THF, 50 h.

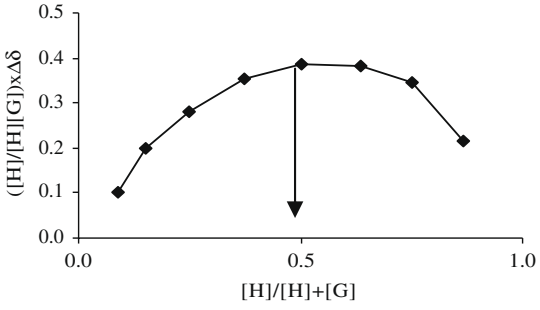


Figure 1. Job Plots for D-ValOMe·HCl and host **4**.

the D- and L-enantiomers of PheAlaOMe were found to be 34.82 and 25.45, respectively, The D-form is 1.37 times more stable than the L-form ($K_D/K_L = 1.37$), as shown in Table 1. In the same way, crown **2** exhibited chiral recognition toward the enantiomers of a PheAlaOMe salt by forming a complex with the D-form of the guest, which was 2.27 times more stable than that formed with the L-form and $-\Delta G^\circ = 9.61$ kJ mol^{-1}.

Host **1** differed from **3** in that the methyl substituent on **1** is replaced by an aryloxy group in **3**. From our earlier study;[14] it was found that the highest enantioselectivity can be obtained when the host contains a benzo unit on the ring of the chiral macrocycles as seen in **3**. From Table 1, host **3**, the D-form of PheAlaOMe is 6.87 times more stable than the L-form ($K_D/K_L = 6.87$ and $-\Delta G^\circ = 12.81$ kJ mol^{-1}). These results demonstrate that the substituent on the stereogenic center plays a very important role on the chiral recognition. It is also known that for enantiomeric recognition, the steric repulsion between the substituent on the stereogenic center (e.g., alkyl-group) and the substituent of the amino acid ester has been found to be an important factor.[21] The high enantioselectivity of the macrocycles might be due to its pseudo 18-crown-6 frame work, which seems to provide a good environment for noncovalent interactions (e.g., ion pairing, hydrogen bonding, cation–π interaction and aromatic face-to-face or/and edge π–π interaction). On the other hand, the macrocyclic **4** exhibits stronger binding and better enantioselectivity for the amino acid esters containing an aliphatic group than for those possessing an aromatic group. This result can be explained by the bulkiness of the valine group compared to the phenylalanine group of the amino acids.

As shown in Table 1, steric repulsion will give one of the possible explanations of the D-form of all amino acid methyl ester hydrochlorides higher binding constant as compared to that of the L-series. Even though it is quite difficult to extract any clear

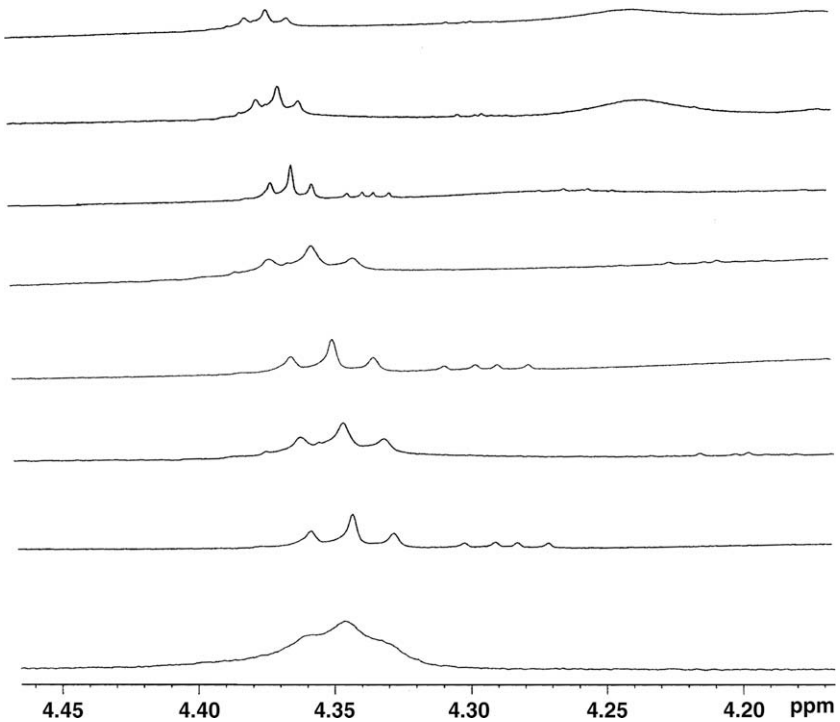


Figure 2. ^{1}H NMR spectral changes of chiral crown ether **4** in the presence of phenyl alanine methyl ester hydrochloride (methine signal) in $CDCl_3$ with 0.25% CD_3OD.

Table 1
Binding constants (K_a), the Gibbs free energy changes ($-\Delta G^\circ$) and enantioselectivites K_D/K_L for the complexation of D-/L-guest with the hosts (**1**–**4**) in $CDCl_3$ with 0.25% CD_3OD

Host	Guest	K_a ($dm^3\ mol^{-1}$)	K_D/K_L	$-\Delta G^\circ$ ($kJ\ mol^{-1}$)
1	D-PheAlaOMe·HCl	34.82 ± 0.012	1.37	8.78 ± 0.018
	L-PheAlaOMe·HCl	25.45 ± 0.021		8.01 ± 0.018
	D-ValOMe·HCl	0.50 ± 0.039	1.45	7.47 ± 0.032
	L-ValOMe·HCl	6.43 ± 0.008		6.92 ± 0.018
2	D-PheAlaOMe·HCl	48.44 ± 0.014	2.27	9.61 ± 0.014
	L-PheAlaOMe·HCl	21.38 ± 0.028		7.58 ± 0.011
	D-ValOMe·HCl	4.80 ± 0.031	1.36	7.95 ± 0.030
	L-ValOMe·HCl	8.30 ± 0.007		7.20 ± 0.008
3	D-PheAlaOMe·HCl	176.93 ± 0.016	6.87	12.81 ± 0.018
	L-PheAlaOMe·HCl	25.76 ± 0.018		8.04 ± 0.019
	D-ValOMe·HCl	9.04 ± 0.038	1.50	9.64 ± 0.030
	L-ValOMe·HCl	2.66 ± 0.018		8.63 ± 0.020
4	D-PheAlaOMe·HCl	46.19 ± 0.019	2.13	9.49 ± 0.020
	L-PheAlaOMe·HCl	21.71 ± 0.022		7.62 ± 0.021
	D-ValOMe·HCl	36.48 ± 0.014	8.50	12.17 ± 0.012
	L-ValOMe·HCl	6.06 ± 0.017		6.87 ± 0.016

reason for this trend, the hydrogen bonding of the ammonium cation of the guest with the oxygen and nitrogen of the macrocycle could play important roles in enantiomeric recognition. Therefore, the hydrogen bonding between the host and the guests may lead to the formation of the complex, while steric interaction contributes to enantiomeric recognition. In general, a N–H···N hydrogen bond is stronger than a N–H···O bond.[22] Thus, the typical tripod hydrogen bond involving nitrogen on the macrocycle and two alternate oxygen atoms of the macrocycle and three hydrogen atoms of the ammonium cation is possible.

3. Conclusions

In conclusion, we have developed a series of new C_2-symmetric chiral amino alcohol and crown macrocycles **1**–**4** and their enantiomeric recognition properties toward D- and L-amino acid methyl ester hydrochlorides using NMR titration have been studied. Crown macrocycle **3** exhibited the highest enantioselectivity toward D-phenylalanine methyl ester hydrochloride with K_D/K_L equal to 6.87. The structure–binding relationship studies showed that the π–π interaction between the phenyl group of the ammonium guest and benzo unit and aryloxy subunit of the macrocycle host is important for high enantioselectivity.

4. Experimental

4.1. Reagents and general methods

All chemicals were reagent grade unless otherwise specified. (*S*)-α-Phenyl ethylamine was purchased from Fluka. The D- and L-amino acid methyl ester hydrochlorides were obtained from Aldrich Chemical Co. Silica Gel 60 (Merck, 0.040–0.063 mm) and silica gel/TLC-cards (F254) were used for flash column chromatography and TLC. All reactions were carried out under an N_2 atmosphere with a dry solvent under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use and methylene chloride (CH_2Cl_2) was dried from calcium hydride. Melting points were determined with a Gallenkamp Model apparatus with open capillaries. Elemental analyses were performed with a Carlo-Erba 1108 model apparatus. Optical rotations were taken on a Perkin Elmer 341 model polarimeter. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 High Performance Digital FT-NMR Spectrometer. The chemical shifts (δ) and coupling constants (J) are expressed in parts per million and hertz.

4.2. Syntheses

4.2.1. (*S*)-(+)-2-Hydroxypropyl *p*-toluenesulfonate 2a

To a stirred solution of (*S*)-2-propanediol (5.18 g, 68.06 mmol) in dichloromethane/pyridine (10:10 V/V) at −25 °C under argon was added dropwise *p*-toluenesulfonylchloride (12.97 g, 68.06 mmol) dissolved in 10 mL CH_2Cl_2 over a period of 2 h. The mixture was stirred at −25 °C for 4 h and then rt for 2 h. After the reaction was completed, 150 mL of CH_2Cl_2 were added and the mixture was shaken successively with ice-cold water, 1 M 40 mL aqueous HCl, 75 mL water, saturated $NaHCO_3$, and water, respectively. The organic phase was dried with $MgSO_4$ and filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography over silica gel using toluene/EtOAc (5/1) to give **2a** (9 g, 58%) as white crystals. Mp 33–35 °C (lit.[23] 34–35 °C), $[\alpha]_D^{25}$ − 12.05 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ (ppm) 1.17 (d, 3H, J = 7.2 Hz), 2.12 (s, 1H), 2.47 (s, 3H), 3.84–3.89 (m, 1H), 3.99–4.08 (m, 2H), 7.37 (d, 2H, J = 8.0 Hz), 7.82 (d, 2H, J = 8.0 Hz).

4.2.2. (*S*)-1-(*p*-Toluenesulfonate)-3-phenoxy-2-propanole 2b

To a stirred solution of (*S*)-3-phenoxypropane-1,2-diol[24] (5.00 g, 29 mmol) in dichloromethane/pyridine (10:10 V/V) at −25 °C under argon was added dropwise *p*-toluenesulfonylchloride (5.67 g, 29 mmol) dissolved in 20 mL of CH_2Cl_2 over a period of 2 h. The mixture was stirred at −25 °C for 4 h and then kept at rt for 2 h. After the reaction was completed, 150 mL of CH_2Cl_2 were added and the mixture was shaken successively with ice-cold water, 1 M of 40 mL aqueous HCl, 75 mL of water, saturated $NaHCO_3$, and water. The organic phase was dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography over silica gel using toluene/EtOAc (5/1) to give **2b** (7 g, 75%) as white crystals. Mp: 83–84 °C $[\alpha]_D^{25} = -10.0$ (*c* 1, MeOH); ^1H NMR ($CDCl_3$): δ (ppm) 2.50 (s, 3H), 4.16 (d, 2H, J = 4.9 Hz), 4.23–4.29 (m, 3H), 6.94 (d, 2H, J = 9.6 Hz), 7.35 (d, 2H, J = 8.4 Hz), 7.81 (d, 2H, J = 8.4 Hz), 8.20 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 21.54, 68.00, 68.80, 69.80, 114.64, 125.84, 127.94, 129.98, 132.85, 142.33, 145.30, 163.00. Anal. Calcd for $C_{16}H_{18}SO_5$: C, 59.63; H, 5.59; S, 9.94. Found: C, 59.64; H, 5.60; S, 7.01.

4.2.3. (*S*)-1-[*N*-(*S*)-α-Phenyl ethyl]amino-2-propanole 4a

(*S*)-α-Phenylethylamine (18.97 g, 156.52 mmol), (*S*)-(+)-2-hydroxypropyl *p*-toluenesulfonate (9 g, 39.13 mmol) and Na_2CO_3 (4.77 g, 45.00 mmol) were stirred at 110 °C for 12 h under argon. The mixture was cooled after which 100 mL of $CHCl_3$ were added to the mixture and refluxed for 2 h. The organic phase was separated from the solid phase. The remaining solid was re-extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ layers were dried with Na_2SO_4 and the organic phase was removed under reduced pressure. The excess (*S*)-α-phenyl ethylamine was distilled at 90–95 °C/1 mmHg and the product was distilled at 140–141 °C/1 mmHg to give **4a** (4.52 g, 65%) as an oil. $[\alpha]_D^{34} = +25.4$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 1.10 (d, 3H, J = 4 Hz), 1.40 (d, 3H, J = 4 Hz), 2.26 (q, 1H, J = 4.0 Hz), 2.52 (br s, 2H), 2.47 (q, 1H, J = 8.0 Hz), 3.82 (q, 2H, J = 4.0 Hz), 7.25 (m, 5H). ^{13}C NMR ($CDCl_3$): δ (ppm) 20.41, 24.46, 54.40, 57.68, 65.79, 126.54, 129.09, 128.56, 144.98. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.74; H, 9.49; N, 7.82. Found: C, 74.00; H, 9.70; N, 7.80.

4.2.4. (*S*)-1-[*N*-(*S*)-α-Phenyl ethyl]amino-3-phenoxy-2-propanole 4b

(*S*)-α-Phenylethylamine (3.75 g, 31.05 mmol), (*S*)-1-(*p*-toluenesulfonate)-3-phenoxy-2-propanole **2b** (2.00 g, 6.21 mmol) and Na_2CO_3 (0.65 g, 6.13 mmol) were stirred at 110 °C for 12 h under argon. Then the mixture was cooled and 50 mL $CHCl_3$ was added to the mixture and refluxed for 2 h. The organic phase was separated from the solid phase. The remaining solid was re-extracted

with $CHCl_3$ (3 × 25 mL). The combined $CHCl_3$ layers were dried with Na_2SO_4 and organic phase was removed under reduced pressure. The excess (*S*)-α-phenylethylamine was distilled at 90–95 °C/1 mmHg and the residue was purified by chromatography over silica gel using EtOAc/*n*-hexane/Et_3N (7/5/1) to give **4b** (1.00 g, 63%) as a yellow oil. $[\alpha]_D^{34} = +35.4$ (*c* 1.68, $CHCl_3$); IR: *v* 3326, 3058, 3031, 2967, 2929, 2877, 1741, 1606, 1587, 1490, 1452, 1375, 1297, 1247, 1170, 1085, 1047, 881, 815, 752, 694 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) 1.44 (d, 3H, *J* = 7.0 Hz), 2.63 (br s, 2H, NH ve OH) 2.73 (m, 2H), 3.83 (q, 1H, *J* = 7.0 Hz) 3.97 (m, 3H), 6.95 (m, 3H), 7.39 (m, 10H). ^{13}C NMR ($CDCl_3$): δ (ppm) 24.23, 50.12, 58.74, 68.95, 70.61, 115.65, 121.07, 126.69, 127.15, 128.61, 129.53, 145.15, 158.72. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.27; H, 7.75; N, 5.16. Found: C, 75.25; H, 7.59; N, 5.18.

4.2.5. (2*S*,9*S*)-4,7-[*N*-(*S*)-α-Phenyl ethyl]diaza-2,9-decanediol (*S*,*S*)-3

(*S*)-1-[*N*-(*S*)-α-Phenyl ethyl] amino-2-propanole (9 g, 50.28 mmol), ethylene glycol ditosylate (3.10 g, 8.38 mmol), and Na_2CO_3 (1.5 g, 14.15 mmol) were stirred at 120 °C for 14 h under Argon. Then the mixture was cooled and 100 mL $CHCl_3$ was added to the mixture and refluxed for 2 h. The organic phase was separated from the solid phase. The remaining solid was re-extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ layers were dried with Na_2SO_4 and the organic phase was removed under reduced pressure. The excess (*S*)-1-[*N*-(*S*)-α-phenyl ethyl] amino-2-propanole was distilled at 140–141 °C/1 mmHg. The residue was purified by chromatography over silica gel using EtOAc/hexane/Et_3N (10/30/2) to give (*S*,*S*)-**3** (1.50 g, 46.00%) as a yellow oil. $[\alpha]_D^{25} = -72.9$ (*c* 3.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ (ppm) 1.12 (d, 6H, *J* = 8.0 Hz), 1.48 (d, 6H, *J* = 8.0 Hz), 2.24 (t, 4H, *J* = 12.0 Hz), 2.43 (q, 2H, *J* = 4.0 Hz), 2.71–2.76 (m, 2H), 3.76–3.80 (m, 4H). 3.76–3.80 (m, 4H), 4.78 (br s, 2H), 7.18–7.37 8 m, 10H). ^{13}C NMR ($CDCl_3$): δ (ppm) 18.67, 20.25, 48.70, 58.56, 59.48, 63.57, 127.24, 128.18, 141.08. Anal. Calcd for $C_{24}H_{36}O_2N_2$: C, 75.00; H, 9.37; N, 7.29. Found: C, 75.20; H, 9.45; N, 7.18.

4.2.6. (1*S*,8*S*)-3,6-[*N*-(*S*)-α-Phenyl ethyl]diaza-1,8-diphenoxymethyl-1,8-decanediol (*S*,*S*)-4

(*S*)-1-[*N*-(*S*)-α-Phenyl ethyl]amino-3-phenoxy–2-propanole **4b** (5.60 g, 20.6 mmol), dibromoethane (1.29 g, 6.90 mmol) and Na_2CO_3 (1.00 g, 9.40 mmol) were stirred at 120 °C for 14 h under argon. Then the mixture was cooled and 100 mL of $CHCl_3$ were added to the mixture and refluxed for 2 h. The organic phase was separated from the solid phase. The remaining solid was re-extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ layers were dried with Na_2SO_4 and the organic phase was removed under reduced pressure. The residue was purified by chromatography over silica gel using EtOAc/petroleum ether/Et_3N (2/12/1) to give (*S*,*S*)-**4** (1.90 g, 48.71%) as a yellow oil. $[\alpha]_D^{34} = -40.5$ (*c* 0.74, $CHCl_3$); IR: *v* 3411, 3070, 3031, 2973, 2935, 2877, 1741, 1697, 1600, 1496, 1452, 1380, 1303, 1247, 1182, 1047, 912, 881, 823, 757 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 1.40 (d, 6H, *J* = 6.9 Hz), 2.51–2.65 (m, 5H), 2.77–2.84 (m, 3H), 3.83–4.07 (m, 8H), 6.93–7.00 (m, 5H), 7.30–7.33 (m, 15H). ^{13}C NMR ($CDCl_3$): δ (ppm) 13.92, 49.76, 53.59, 59.43, 67.63, 70.10, 114.67, 120.92, 127.73, 128.20, 128.33, 129.50, 142.20, 158.88. Anal. Calcd for $C_{36}H_{44}O_4N_2$: C, 76.05; H, 7.75; N, 4.93. Found: C, 76.10; H, 7.85; N, 4.98.

4.2.7. (6*S*,17*S*)-1,4-[*N*-(*S*)-α-Phenylethyl]-diaza-6,17-dimethyl-7,10,13,19-tetraoxacyclooctadecane 1

To a well-stirred suspension of NaH (80 mg, 98%) in 50 mL of dry THF was added dropwise under argon at 0 °C (*S*,*S*)-**3** (400 mg, 1.04 mmol) dissolved in 50 mL of THF. The mixture was stirred at rt for 1 h and at reflux temperature for 2 h. The reaction mixture was cooled to 0 °C and ditosylate (447 mg, 1.04 mmol) dissolved in 50 mL of THF was added dropwise. The resulting mixture was stirred at 0 °C for 30 min and then refluxed for 50 h. After the reaction was complete, the solvent was removed. The residue was taken up in a mixture of ice-water (50 mL) and CH_2Cl_2 (3 × 100 mL). The resulting mixture was mixed well and separated. The combined organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated. The crude product was purified by chromatography on silica gel (eluent: petroleum ether/EtOAc/Et_3N: 90/10/5) to give **1** (120 mg, 20%) as an oil. $[\alpha]_D^{30} = +41$ (*c* 2.5, $CHCl_3$) ^1H NMR ($CDCl_3$): δ (ppm) 0.98 (d, 6H, *J* = 6.0 Hz), 1.31 (d, 6H, *J* = 6.8 Hz), 2.34–2.38 (dd, 2H, *J* = 8.0 Hz), 2.57–2.61 (m, 4H), 2.72 (q, 2H, *J* = 8.0 Hz), 3.51 (q, 2H, *J* = 8.0 Hz), 3.66–3.80 (m, 14H), 7.28–7.31 (m, 10H). ^{13}C NMR ($CDCl_3$): δ (ppm) 15.90, 18.19, 51.55, 56.94, 60.33, 68.21, 71.00, 71.30, 75.47, 126.54, 127.92, 128.34, 144.37. Anal. Calcd for $C_{30}H_{46}N_2O_4$: C, 72.29; H, 4.60; N, 5.62. Found: C, 72.40; H, 4.65; N, 3.50.

4.2.8. (6S,17S)-1,4-[*N*-(*S*)-α-Phenylethyl]-diaza-6,17-dimethyl-11,12-benzo-7,10,13,19-tetraoxacyclooctadec-11-ene 2

Macrocycle **2** was prepared as described above for macrocycle **1** starting from (*S*,*S*)-**3** (400 mg, 1.04 mmol) and 1,2-bis-(2-*p*-tolylsulphonyl ethoxy)benzene (527 mg, 1.04 mmol). The crude product was purified by chromatography on silica gel (eluent: petroleum ether/EtOAc/Et_3N: 67/30/3) to give **2** (120 mg, 22%) as an oil. $[\alpha]_D^{30} = +85$ (*c* 2.5, $CHCl_3$) ^1H NMR ($CDCl_3$): δ (ppm) 1.04 (d, 6H, *J* = 5.6 Hz), 1.30 (d, 6H, *J* = 6.4 Hz), 2.19–2.26 (m, 2H), [AB system: a part of A 2.39, 1H, *J* = 5.59 Hz; a part of B: 2.44, *J* = 7.60, 1H], [AB system: a part of A: 2.52, 1H, *J* = 7.60 Hz; a part of B: 2.53, 1H, *J* = 12.80), 2.66 (dd, 2H, *J* = 5.2 Hz and *J* = 8.0 Hz), 3.40 (q, 2H, *J* = 6.00 Hz), 3.74–3.86 (m, 6H), 4.11 (t, 4H, *J* = 4.00 Hz), 6.97–7.07 (m, 6H), 7.20–7.30 (m, 8H), ^{13}C NMR ($CDCl_3$): δ (ppm) 14.80, 18.43, 50.52, 56.88, 59.59, 67.34, 68.97, 75.77, 115.05, 119.27, 121.42, 124.28, 127.88, 144.18, 149.72. Anal. Calcd for $C_{34}H_{46}N_2O_4$: C, 74.72; H, 8.42; N, 5.13. Found: C, 74.96; H, 8.64; N, 5.14.

4.2.9. (6S,17S)-1,4-[*N*-(*S*)-α-Phenylethyl]-diaza-6,17-diphenoxymethyl-7,10,13,19-tetraoxacyclooctadecane 3

Macrocycle **3** was prepared as described above for macrocycle **1** starting from (*S*,*S*)-**4** (500 mg, 0.88 mmol) and triethyleneglycol ditosylate (403 mg, 0.88 mmol). The crude product was purified by chromatography on silica gel (eluent: petroleum ether/EtOAc/triethylamine: 25/5/3) to give **3** (150 mg, 25%) as oil. $[\alpha]_D^{32} = +87$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 1.30 (d, 6H, *J* = 2.4 Hz), 2.50–2.55 (m, 6H), 2.59–2.64 (m, 1H), 2.92–2.97 (m, 1H), 3.64–3.84 (m, 16H), 3.39–4.11 (m, 4H), 6.90–6.98 (m, 5H), 7.21–7.32 (m, 15H). ^{13}C NMR ($CDCl_3$): δ (ppm) 16.84, 50.60, 53.03, 60.15, 68.91, 69.88, 70.83, 70.92, 71.34, 114.62, 120.65, 126.74, 127.89, 128.01, 129.38, 143.15, 158.94. Anal. Calcd for $C_{42}H_{54}N_2O_6$: C, 73.90; H, 7.92; N, 4.11. Found: C, 73.98; H, 8.05; N, 4.20.

4.2.10. (6S,17S)-1,4-[*N*-(S)-α-Phenylethyl]-diaza-6,17-diphenoxymethyl-11,12-benzo-7,10,13,19-tetraoxacyclooctadec-11-ene 4

Macrocycle **4** was prepared as described above for macrocycle **1** starting from (*S*,*S*)-**4** (500 mg, 0.88 mmol) and 1,2-bis-(2-*p*-tolylsulphonyl ethoxy)benzene (445 mg, 0.88 mmol). The crude product was purified by chromatography on silica gel (eluent: petroleum (40–60 °C) ether/EtOAc/Et_3N: 25/5/3) to give **4** (130 mg, 20%). $[\alpha]_D^{30} = +89$ (*c* 2.5, $CHCl_3$) ^1H NMR ($CDCl_3$): δ (ppm) 1.33 (d, 6H, *J* = 6.8 Hz), 2.67–2.78 (m, 6H), 2.86 (d, 2H, *J* = 11.6 Hz), 3.77–3.84 (m, 4H), 3.88–3.98 (m, 4H), 4.09–4.19 (m, 8H), 6.79 (d, 4H, *J* = 8.4 Hz), 6.92–6.96 (m, 6H), 7.22–7.29 (m, 14H). ^{13}C NMR ($CDCl_3$): δ (ppm) 15.87, 51.89, 52.68, 60.54, 69.06, 69.79, 78.70, 93.36, 113.99, 114.51, 120.51, 121.31, 126.75, 127.93, 128.02, 129.28, 143.92, 149.20, 158.85. Anal. Calcd for $C_{46}H_{54}N_2O_6$: C, 75.62; H, 7.39; N, 3.84. Found: C, 76.05; H, 7.40; N, 3.98.

4.3. NMR experiments

4.3.1. Job plots

The stoichiometric of the complex between host-guest was determined by a continuous variation plot (Job's plot) according to a method described in the literature.[20] Equimolar amounts of host and guest compounds were dissolved in $CDCl_3$ with 0.25% CD_3OD. These solutions were distributed among ten NMR tubes, with the molar fraction host and guest in the resulting solutions increased or decreased from 0.1 to 0.9. The Job plots of **4** with D-ValOMeHCl are in Figure 1. Maxima were observed when the molar ratio of the host **4** and D-ValOMeHCl was 1:1(0.5), which indicated that host **4** and the guests formed 1:1 instantaneous complexes.

4.3.2. NMR titrations

The guest compound was dissolved in an appropriate amount of solvent and the resulting solution was evenly distributed among ten NMR tubes. The first tube was sealed only as guest. The host solution was added in increasing amounts to the NMR tubes, so that solutions with the following relative amounts of host versus guest compound.[25] The concentration of the guest was constant (5.6 mM) with the increasing concentration of the added host.

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