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Synthesis of chiral monoaza-15-crown-5 ethers from a chiral amino alcohol and enantiomeric recognition of potassium and sodium salts of amino acids

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Abstract—The enantiomeric recognition of chiral monoaza-crown ethers for amino acids as their sodium and potassium salts has been investigated by UV–vis. The highest discrimination was observed for TrpK (D/L = 6.47). The reversed enantioselectivity of chiral monoaza-crown ether **II** was observed for TrpK.

1. Introduction

Molecular and enantiomeric recognition phenomena play an important role in a variety of physical, chemical, and biological processes. Examples include the determination of concentrations, separation of enantiomers, catalysis reactions, and the incorporation of single enantiomeric forms of amino acids, organic ammonium salts, and in biochemical pathways.[1] Crown ethers, first introduced in 1967 by Pedersen,[2,3] are macrocyclic polyethers, which are able to form stable and selective complexes with alkali, alkaline-earth, and primary ammonium cations. Following this discovery, chemists realized that chiral derivatives of these molecules could serve as models for the study of chiral recognition in enzymatic and other reactions. Since Cram et al. published their pioneering studies on the use of chiral macrocyclic ligands for enantiomeric recognition,[4] a large number of chiral macrocycles have been synthesized and studied.[5–7]

The study of enantiomeric recognition of amines and protonated amines is of great significance since these compounds are basic building blocks for biological molecules. Amino acids are major components of proteins in natural living systems and their versatile abilities to form complexes with a variety of molecules present various types of interaction modes.[8]

Among the various types of compounds studied, such as derivatized amino acids and cyclodextrins, proteins, and carbohydrates, chiral crown ethers have been recognized as the most successful selectors used in LC chiral stationary phases for the resolution of primary amine containing compounds.[9] It has been predicted that chiral macrocyclic compounds will play a major role in future enantiomeric separations.[10]

Bako et al. synthesized a number of monoaza-15-crown-5 ethers from monosaccharides, such as glucose, galactose, and mannitol. They found that most of them can be used as catalysts in asymmetric reactions, such as Michael additions and Darzens condensations.[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 important roles. Azacrown ethers with a side arm attached to the nitrogen of the macrocyclic ring may enhance and regulate the cation-binding properties, as well as lipophilicity. Crown ethers are known to have a highly lipophilic character and unique guest selectivity via the macroring side arm.[12]

There has been continuing interest for the molecular recognition of amino acids derivatives by NMR, UV–vis, extraction and transport experiment.[13–16] Until today, marvelous host–guest combinations systems, which

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show high degrees of chiral recognition, have been developed and their recognition mechanism has been gradually made clear as same combined effects of charge-dipole, hydrogen bonding, hydrophobic, and π–π interaction and steric complementarity etc.[17]

Recently, our interest has concerned monoaza-crown ethers from (*R*)-(−)-2-amino-1-butanol, which is widely used in the production of the antituberculostatic ethembutol and is inexpensive.[18] The interaction of these chiral macrocycles with potassium and sodium salts of amino acids helps us to understand the binding phenomena and their catalytic effects on chiral recognition. Herein, to the enantioselective recognition capabilities of chiral monoaza-15-crown ethers toward potassium and sodium salts of amino acids are compared by UV–vis spectroscopy.

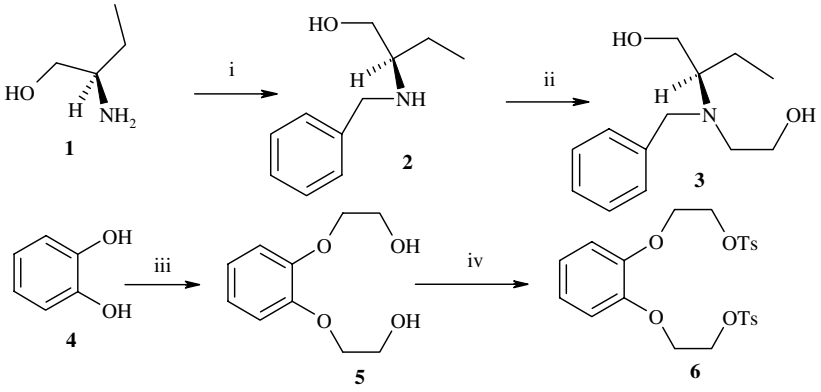
2. Results and discussion

2.1. Synthesis

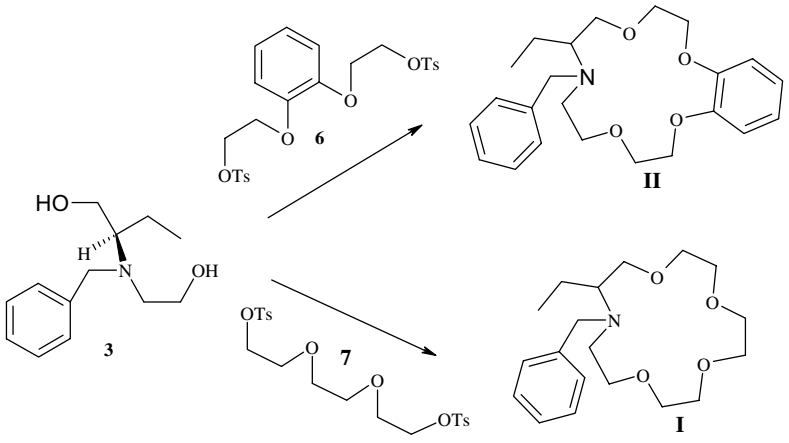
The versatile building block for crown ether synthesis was prepared as shown in Scheme 1. A single step reaction of catechol with ethylene oxide in the presence of a catalyst was used, at mild temperature gave **5** in high yield. In the reaction, two catalysts were used, diethylene amine hydrochloride, and piperidine hydrochloride, but the yield of product was similar.[19] The conversion of (*R*)-2-amino-1-butanol **1** to *N*-benzyl aminoalcohol derivatives **2** was carried out by our previous method.[20] The conversion of **2** to **3** was carried out at −20 °C, as shown in Scheme 1. Chiral macrocycles **I** and **II** were prepared in the 65% and 69% yields, respectively, as shown in Scheme 2. After the cyclization reaction, sodium perchlorate ($NaClO_4 \cdot H_2O$) was added to crude product, and the macrocycles obtained as $NaClO_4 \cdot H_2O$ complexes. The free ligand was recovered by column chromatograph. The structure of the free ligand was determined by NMR and X-ray analysis.[20]

2.2. UV–vis

UV–vis spectroscopy is a convenient and widely used method for the study of binding phenomena.[21] When the receptor (or substrate) absorbs light at different wavelengths in the free and complexed states, the differences in ultraviolet spectrophotometry may be enough for the estimation of molecular and enantiomeric recognition. The binding constants (K_a) of the inclusion complexes of monoaza-15-crown-5 ethers with amino acids



Scheme 1. Reagents and conditions: (i) $PhCH_2CI$, Na_2CO_3, 110 °C; (ii) ethylene oxide, MeOH, −20 °C; (iii) ethylene oxide, MeOH, 40 °C; (iv) TsCl, pyridine, −10 °C.



Scheme 2. Reagents and conditions: NaH, THF, reflux, 5 days.

potassium and sodium salts were determined on the basis of the differential absorption spectra. UV spectrometry was measured in a solution of CH_3CN (HPLC grade)–H_2O (50:2, differential absorption spectra were obtained directly using the instrument according to its normal procedures. The quartz cells were kept at a constant temperature (25 ± 0.1 °C) with a thermostated cell compartment.

In the UV spectroscopic titration experiments, the addition of varying concentrations of amino acid salts (guest) molecules resulted in either a gradual increase or decrease of characteristic absorptions of the host molecules. With the assumption of a 1:1 stoichiometry, the complexation of amino acid salts (G) with chiral macrocycles (H) is expressed by Eq. 1:

$$H + G \leftrightarrows H \cdot G \quad (1)$$

$$[H]_o \cdot [G]_o/\Delta A = 1/K_a\Delta\varepsilon + [G]_o/\Delta\varepsilon \quad (2)$$

Under the conditions employed, the concentration of the host (1.01×10^{-5} mol dm^{-3}) is much lower that of amino acid salts, that is $[H]_o \ll [G]_o$. Therefore, the binding constant of the supramolecular system formed can be calculated according to modified Hildebrand–Benesi equation,[22] Eq. 2, where $[H]_o$ represents the total concentration of host; $[G]_o$ denotes the total concentration of guest amino acid salts; $\Delta\varepsilon$ is the difference between the molar extinction coefficient for the free and complexed chiral monoaza-15crown-5 ether; ΔA denotes the changes in the absorption of the host on adding aminoacid salts. For all the guest molecules examined, plots of calculated $[H]_o \cdot [G]_o/\Delta A$ values as a function of $[G]_o$ values gave an excellent linear relationship ($R > 0.9952$) supporting the 1:1 complex function. The typical UV spectral changes upon the addition of L-PhAlaNa salt to **II** are shown in Figure 1, while a typical plot is shown for the complexation of compound host **II** with guest L-PhAlaNa in Figure 2.

The properties of macrocycle **I** deserve special interest. Macrocycle **I** did not give any absorbance in a mixture of CH_3CN–H_2O, but gave good absorbance in $CHCl_3$ at 241.7 nm. However in this case, the solubility problem of the amino acid salts arises. Macrocycle **II** gives good absorbance in $CHCl_3$ at 242 and 276 nm but in CH_3CN–H_2O mixture (50:2) just one absorbance at 242.3 nm was observed.

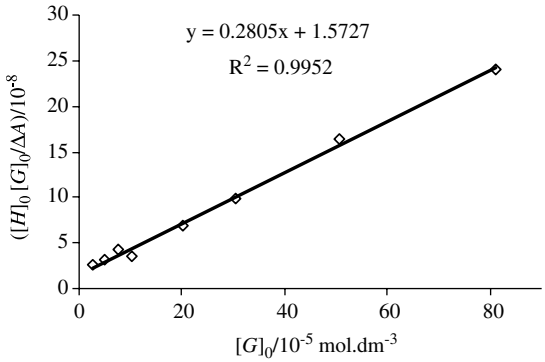


Figure 2. Typical plot of $[H]_o \cdot [G]_o/\Delta A$ versus $[G]_o$ for the host–guest complexation of **II** and L-PhAlaNa salt in CH_3CN–H_2O (50:2).

The binding constant (K_a) and the free-energy changes (ΔG_o) of this host with guest molecules obtained from usual curve fitting analyses ($R > 0.9952$) of observed K_a values and $-\Delta G_o$ changes are summarized in Table 1, along with enantioselectivity K_D/K_L or $\Delta\Delta G_o$ calculated from $-\Delta G_o$ for the complexation of D/L-amino acid potassium and sodium salts by this host. The amino acid may interact in different ways to form stable complexes. In a neutral solution, the amino acid may be complexed in its neutral form (coordination of the amino group and hydrogen bonding of the acid part), or more generally, in its zwiterionic form for which thermodynamic studies have been undertaken, complexation being weak; in acidic medium the amino acid is bound through the ammonium ion. In the basic medium it was complexed through the carboxylate function.[23] It should therefore be equally true that the variation of guest structure will also effect the extent of enantiomeric recognition displayed by a given ligand and stability of the complex formed between the guest and the given ligand (Scheme 3). Ion pair[24] receptors to date have been based on

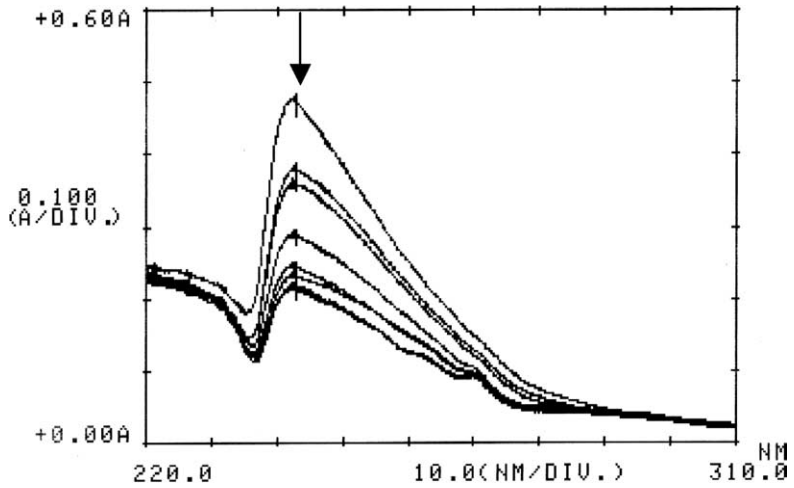
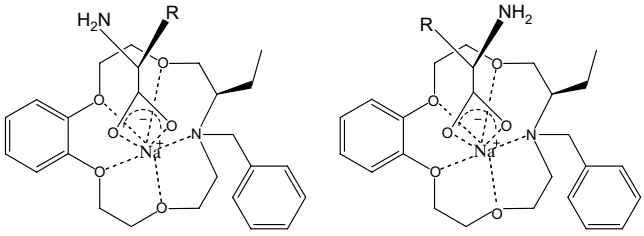


Figure 1. UV–vis spectra of **II** (1.01×10^{-5} mol dm^{-3}) in the presence of L-PhAlaNa salt (2.5×10^{-5}–8.1×10^{-4} mol dm^{-3}) in CH_3CN–H_2O (50:2).

Table 1. Binding constants (K_a), free-energy changes ($-\Delta G_o$), enantioselectivities K_L/K_D and $\Delta\Delta G_o$ calculated from $-\Delta G_o$, for complexation for 1:1 of L/D-amino acids potassium and sodium salts with chiral host **II** in CH_3CN–H_2O at 25 °C[a]

Entry	Host	Guest[b]	K_a ($dm^3\ mol^{-1}$)	K_D/K_L	$-\Delta G_o$ (kJ mol^{-1})	$\Delta\Delta G_o$ (kJ mol^{-1})[c]
1	**II**	L-PhAlaNa	$(1.5 \pm 0.040) \times 10^4$	3.27	23.83	2.93
2	**II**	D-PhAlaNa	$(4.9 \pm 0.038) \times 10^4$		26.76	
3	**II**	L-PhAlaK	$(1.8 \pm 0.042) \times 10^4$	1.17	24.28	0.38
4	**II**	D-PhAlaK	$(2.1 \pm 0.048) \times 10^4$		24.66	
5	**II**	L-PhGlyNa	$(2.0 \pm 0.051) \times 10^4$	2.75	24.54	2.51
6	**II**	D-PhGlyNa	$(5.5 \pm 0.033) \times 10^4$		27.05	
7	**II**	L-PhGlyK	$(1.8 \pm 0.036) \times 10^4$	1.56	24.28	1.10
8	**II**	D-PhGlyK	$(2.8 \pm 0.040) \times 10^4$		25.38	
9	**II**	L-TrpNa	$(1.7 \pm 0.041) \times 10^3$	1.12	18.43	0.28
10	**II**	D-TrpNa	$(1.9 \pm 0.055) \times 10^3$		18.71	
11	**II**	L-TrpK	$(1.7 \pm 0.048) \times 10^3$	6.47	18.43	4.63
12	**II**	D-TrpK	$(1.1 \pm 0.04) \times 10^4$		23.06	

[a] Concentration of the receptor (1.01×10^{-5} M).
[b] PhAlaNa(K): phenylalanine sodium or potassium salts, PhGlyNa(K): phenylglycine sodium or potassium salts, TrpNa(K): tryptophan sodium or potassium salts.
[c] $\Delta\Delta G_o$: $-(\Delta G_{o(L)} - \Delta G_{o(D)})$.



Scheme 3. The enantiomeric recognition mode of amino acid sodium or potassium salts by host **II**.

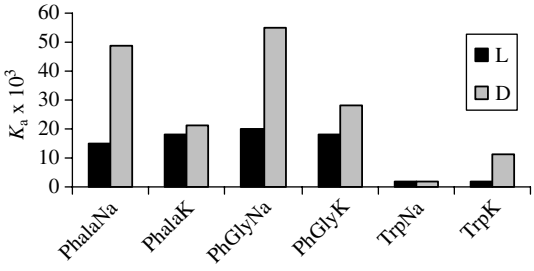


Figure 3. Bar plot of enantioselective recognition of L,D-PhAla, PhGly, and tryptophan Na or K salts for **II**.

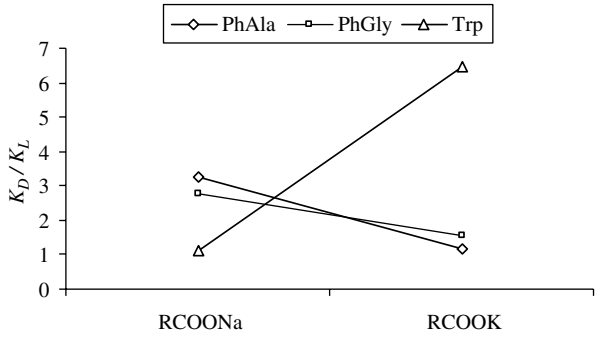


Figure 4. Enantiomeric differentiation of salts of amino acid by macrocycle **II**.

hydrogen bonding. Positively charged or Lewis acid groups coordinate the anion crown moieties to bind the cation. These types of host molecules generally exhibit cooperative and allosteric effects, whereby the association of one ion alters the binding affinity of the counterion. This cooperative behavior can be positive or negative depending on whether the binding affinity is enhanced or reduced, respectively. Cooperative behavior can result from several factors, such as through-space or through-space electrostatic interactions between ions or conformational changes induced by binding.

Table 1 shows the binding constant (K_a) and the free energy changes $-\Delta G_o$ for phenylalanine, phenylglycine, and tryptophan as their sodium and potassium salts, respectively. The experimental result shows that the D-enantiomer of PhAlaNa, PhAlaK, PhGlyNa, PhGlyK, TrpNa, TrpK were better recognized than their L-enantiomer (Fig. 3). Although both enantiomers of PhAlaNa, PhAlaK, PhGlyNa, and PhGlyK give more stable complexes than TrpNa and TrpK; the highest discrimination was observed for TrpK (Fig. 4).

Taking into account the host employed, the observed enantioselectivity could be attributed to the different modes of some functional groups of amino acids with the chiral macrocycle. In general, the highest discrimination was observed with TrpK D/L for the macrocycle. This could be the result of strong steric interactions of the indolic group relative to the phenyl one with an arene unit on the macrocycle. The effect of the cation involved in the enantiomeric recognition is probably dependent on the structure of the crown ether employed. It is well known that variations in Na^+/K^+ selectivity are primarily due to the degree of interaction of the pendant arm with Na^+ and K^+. Gokel et al. used a lariat ether receptor system to obtain clear evidence for cation–π interactions between Na^+ or K^+ and benzene, phenol, and indole.[25] The complex of K^+ with lariat ether is the most remarkable owing to its previously

reported apical–π interaction.[26] In our system, substituting the arene unit on the macroring could probably lead to formation of apical–π interactions with K^+. This result was observed in the case of TrpK. In general, the observed chiral discrimination can be achieved by the repulsive noncovalent steric interaction with the chiral barrier on the ring, side arm of macrocycle and the functional groups of the amino acids.

3. Experimental

3.1. General remarks

All chemicals were reagent grade unless otherwise specified. Amino acid was purchased from Fluka chemical company. Silica gel 60 (Merck, 0.040–0.063 mm) and silica gel/TLC-cards (F254) were used for flash column chromatography and TLC. Melting points were determined with a Gallenkamp Model apparatus with open capillaries. Infrared spectra were recorded on a MIDAC-FTIR Model 1700 spectrophotometer. Elemental analyses were obtained with a Carlo-Erba 1108 model apparatus. Optical rotations were taken on a Perkin–Elmer 341 model polarimeter. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 High Performance Digital FT-NMR Spectrometer. Refraction indexes were measured using an Atago Abbe refractometer.

3.2. Absorption spectra measurements

The abilities of crown ethers to coordinate to amino acid salts were investigated using UV spectroscopic titration.[21] The UV–vis spectra were measured at 25 ± 0.1 °C with a thermostated cell compartment with a Shimadzu 160 UV spectrometer. The same concentration of guest solution was added to the sample cell and reference cell. The maximum wavelength is 242.3 nm for **2**. CH_3CN–H_2O (50:2) was used as the solvent. The concentration of the hosts was 1.01×10^{-5} mol dm^{-3} with an increasing concentration of the added guest.

3.2.1. 1,2-Bis-(2-hydroxy ethoxy)benzene 5. This compound was prepared according to the procedure recorded in the literature[19] from catechol (11.0 g, 100 mmol) diethylamine hydrochloride (as a catalyst) and ethylene oxide (9.8 mL, 200 mmol) to give 18.8 g, 95%; mp 81–83 °C.

3.2.2. 1,2-Bis-(2-*p*-tolylsulfonylethoxy)benzene 7. This compound was prepared according to the procedure recorded in the literature[19] from 1,2-bis-(2-hydroxy ethoxy)benzene **5** (26.73 g, 135 mmol), pyridine (110 mL) at −10 °C and *p*-toluenesulfonylchloride (51.43 g, 270 mmol) to give 66 g, 96%; mp 95–95.5 °C.

3.2.3. (*R*)-(−)-*N*-Benzyl-2-amino-1-butanol 2. (*R*)-(−)-Amino-1-butanol **1** (71.2 g, 0.8 mol), benzyl chloride (25.3 g, 0.2 mol) and Na_2CO_3 (20 g, 0.18 mol) were placed in a 250 mL two-necked round bottomed flask equipped with an addition Dean Stark apparatus. The mixture was stirred at 100 °C for 8 h under dry N_2. Then the mixture was cooled and $CHCl_3$ (100 mL) was added to the mixture and refluxed for 1 h. The $CHCl_3$ layer was separated from the solid phase. The remaining solid was then re-extracted with $CHCl_3$ (3×25 mL).The combined $CHCl_3$ layers were dried over Na_2SO_4 and evaporated. The product was distilled at reduced pressure to give 33 g (94%), $[\alpha]_D^{20} = -25.6$ (*c* 0.08, EtOH). Bp 98–100 °C/0.1 mmHg, mp 71–72 °C. Mw 179 g (found: C, 73.67; H, 9.63; N, 7.74; $C_{11}H_{17}NO$ requires: C, 73.70; H, 9.56; N, 7.80); IR (KBr): 3287, 3076, 2931, 2836, 1467, 1361, 1068 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.98 (3H, t, $J = 7.48$ Hz), 1.48–1.63 (2H, m), 2.64–2.68 (1H, m), 3.38–3.85 (2H, ddd), 3.75–3.85 (2H, dd), 7.29–7.39 (5H, m); ^{13}C NMR ($CDCl_3$): δ 10.73, 24.64, 51.48, 60.21, 63.05, 127.45, 128.86, 140.83.

3.2.4. (*R*)-(−)-*N*-Benzyl-4-hydroxymethyl-3-azahexane-1-ol 3. A solution of 47 g (260 mmol) of **2** in 100 mL of methanol was cooled to −20 °C in a 250 mL flask. 11.52 g (260 mmol) of ethylene oxide in 50 mL of methanol was added to the solution dropwise at the same temperature. After addition the mixture was stirred for 12 h at −20 °C and then for 24 h at +4 °C. The mixture was kept for one day at room temperature. Methanol was then evaporated in vacuo. The product was purified by distillation under reduced pressure at 155 °C/0.1 mmHg to give 56 g (94%) of **2**. $\eta_i^{20} = 1.524$; $[\alpha]_D^{20} = -14.9$ (*c* 0.08, EtOH). Mw 223 g (found: C, 66.76; H, 9.04; N, 6.08, $C_{13}H_{21}NO_2$ requires: C, 66.90; H, 9.07; N, 6.00); IR (neat film): 3368, 3085, 3061, 3026, 2957, 2876, 1602, 1494, 1453, 1372, 1115, 1054, 729, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t, $J = 7.47$ Hz), 1.22–1.29 (1H, m), 1.60–1.67 (1H, m), 2.59–2.64 (1H, dt), 2.71–2.85, (2H, m), 3.41 (2H, t, $J = 10.28$), 3.45–3.56 (2H, ddd), 3.62–3.84 (4H, dd), 7.22–7.37 (5H, m); ^{13}C NMR ($CDCl_3$): δ 12.23, 19.72, 51.87, 55.32, 60.52, 61.90, 63.41, 127.41, 128.76, 129.16, 140.52.

3.2.5. (*R*)-(−)-2-Ethyl-*N*-benzyl-4,7,10,13-tetraoxa-1-azacyclopentadecane I. To a solution of NaH (80% in mineral oil) 3.57 g (120 mmol) in dry THF (100 mL) in an N_2 atmosphere, (*R*)-(−)-*N*-benzyl-4-hydroxymethyl-3-azahexzan-1-ol **3** 6.62 g (30 mmol) in THF (100 mL) was added slowly at 0 °C. The mixture was heated slowly to 30–40 °C. The mixture was then kept at this temperature for 1.5 h. Then triethylene glycol ditosylate **7** 14.95 g (33 mmol) in THF (200 mL) was added slowly to the mixture. The mixture was stirred at 80 °C for 5 days. THF extract was evaporated and water (50 mL) added to the remaining residue. The organic phase was extracted with $CHCI_3$ (3×50 mL) and the combined organic phase dried over $MgSO_4$ and evaporated. The product was dissolved in ethyl acetate (5 mL) and $NaClO_4H_2O$ 4.20 g (30 mmol) in ethyl acetate (5 mL) was added. The product was recrystallized from ethyl acetate to yield 9.20 g (65%), mp 132–133 °C. $[\alpha]_D^{20} = -28.8$ (*c* 0.04, EtOH). Mw 459.5 g (found: C, 49.57; H, 6.74; N, 3.05, $C_{19}H_{31}NO_4{\cdot}NaClO_4$ requires: C, 49.62; H, 6.75; N, 2.98). IR (KBr): 3478, 3062, 3027, 1479, 1454, 1246, 1121, 741 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.86 (3H, t, $J = 7.21$ Hz); 1.16 (1H,

br s); 1.56 (1H, br s); 2.80–4.10 (21H, m); 7.25–7.35 (5H, m). ^{13}C NMR ($CDCl_3$): δ 12.05, 17.92, 68.51, 68.76, 68.96, 69.91, 127.31, 128.78, 128.94. The free ligand was recovered by passing the complex through a column on basic AI_2O_3. Triethyl amine–ethyl acetate–petroleum ether [(40–60), 3:30:67, respectively] as oil.

3.2.6. (*R*)-(−)-2-Ethyl-*N*-benzyl-4,7,10,13-tetraoxa-8,9-benzo-1-azacyclopentadec-8-ene II. To a solution of NaH (80% in mineral oil) 3.57 g (120 mmol) in dry THF (100 mL) under a N_2 atmosphere, (*R*)-(−)-*N*-benzyl-4-hydroxymethyl-3-azahexzan-1-ol **3** 6.62 g (30 mmol) in THF (100 mL) was added slowly at 0 °C. The mixture was heated slowly to 30–40 °C. The mixture was then kept at this temperature for 1.5 h. 1,2-Bis-(2-*p*-tolylsulfonylethoxy)benzene **6** (16.7 g, 33 mmol) in THF (100 mL) was added dropwise to the mixture in 2 h. The mixture was stirred at 80 °C for 5 days. THF extract was evaporated and water (50 mL) added to the remaining residue. The organic phase was extracted with $CHCl_3$ (3×50 mL) and the combined organic phase dried using $MgSO_4$ and evaporated. The product was dissolved in ethyl acetate (5 mL) and $NaClO_4 \cdot H_2O$ 4.20 g (30 mmol) in ethyl acetate (5 mL) was then added. The product was recrystallized from ethyl acetate to yield 10.50 g (69%), mp 152–154 °C. $[\alpha]_D^{20} = -2.2$ (*c* 0.04, EtOH). Mw 507.5 g (found: C, 54.45; H, 6.18; N, 2.72, $C_{23}H_{31}NO_4$-$NaClO_4$ requires: C, 54.38; H, 6.10; N, 2.75); IR (KBr): 3061, 3024, 2968, 2876, 1593, 1503, 1455, 1250, 1199, 1117, 1028, 928, 748, 702, 623 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.94 (3H, t, $J = 7.32$ Hz), 1.63 (1H, br s), 1.56 (1H, br s), 2.86–4.31 (17H, m), 6.75–7.31 (9H, m); ^{13}C NMR ($CDCl_3$): δ 12.51, 18.23, 66.79, 68.30, 68.67, 70.75, 113.02, 122.45, 127.55, 128.77, 129.36, 147.13.

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