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The enantiomeric recognition of chiral organic ammonium salts by chiral pyridino-macrocycles bearing aminoalcohol subunits

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ABSTRACT

Pyridine-based macrocycles were prepared by treating 2,6-bis[[2′6′-bis(bromomethyl)-4′-methylphenoxy]methyl]pyridine **3** with the appropriate chiral aminoalcohols. The enantiomeric recognition of these macrocycles bearing aminoalcohol subunits of the pyridinocrown type ligand was evaluated for chiral organic ammonium salts by UV titration. The important differences were observed in the K_a values of (*R*)-Am2 and (*S*)-Am2 for (*S*,*S*,*S*)-**1**, (*S*,*S*,*S*)-**2** and (*S*,*S*,*S*)-**3** hosts, $K_S/K_R = 5.0$, $K_S/K_R = 2.4$ and $K_S/K_R = 5.0$, respectively. There seems to be a general tendency for hosts to recognise (*S*)-enantiomers for both Am1 and Am2.

1. Introduction

Molecular recognition, especially chiral recognition, is one of the most significant processes for diverse physical, chemical and biological phenomena. Therefore, the design, synthesis and use of molecules capable of enantiomeric recognition of other molecules are of great interest to workers in these fields.[1,2] In particular, optically active macrocyclic receptors and their enantioselective recognition of chiral compounds have been attracting much attention.[3] Such model systems have found applications in the development of pharmaceuticals,[4–7] enantioselective catalysis,[8] separation of enantiomers,[9] and the sensing,[10] purification and analysis of enantiomers.[11–13] They can also contribute to a better understanding of biological systems and their functions since chiral recognition is an essential phenomena in living systems. Hence, the study of synthetic modelling for chiral recognition is an area of ever increasing research activity. Continuing efforts creating chiral artificial receptors for enantioselective recognition have been made and the recognition mechanism has been gradually understood as the combined efforts of several non-covalent interactions such as hydrogen bonding, electrostatic interactions, hydrophobic interactions, cation–π interactions, π–π staking interactions and steric complementarity[14,15]

The study of the enantiomeric recognition of amines and protonated amine compounds is of significance since these compounds are the basic building blocks of biological molecules. Amino acids are major components of proteins in natural living systems and their versatile ability to form complexes with a variety of molecules presents various types of interaction modes.[16] The development of new receptors capable of recognising amino acids and their derivatives has attracted more interest in the recent past three decades. After the pioneering research of Cram et al. on the use of chiral macrocyclic ligands in enantiomeric recognition[17] a great number of chiral artificial receptors have been synthesised and studied.[16,18] Recently, a series of chiral artificial receptors, such as the binaphthol dimmers,[19] the chiral macrocycles,[20–22] the chiral crown ethers[23,24] and cyclodextrin derivatives[25,26] have been synthesised for enantioselective recognition of amino acid derivatives. It has been predicted that chiral macrocyclic compounds will play a major role in future enantiomeric separations of amines and protonated amine compounds.[16,27] In particular, pyridine units containing crown ethers (pyridinecrowns) are very useful for the recognition of amine and protonated amine compounds since they form strong complexes with organic amine salts and also show appreciable enantiomeric recognition in certain cases.[1,28–30]

Various methods have been used for determining the chiral recognition of chiral macrocyclic hosts. Examples are the methods of titration UV–vis, extraction/NMR, extraction/polarimetry, titration NMR, variable temperature NMR, NOE, induced circular dichromism, liquid chromatography (LC), transport and capillary electrophoresis.

Recently, our interest has concerned aza-macrocycles and their molecular and enantiomeric recognitions towards amines and protoned amine derivatives.[22–24,31] Herein, we report the synthesis of a series of pyridino-macrocycles bearing amino alcohol subunits and their enantiomeric recognition properties towards alkyl ammonium salts which were investigated by UV–vis spectroscopy.

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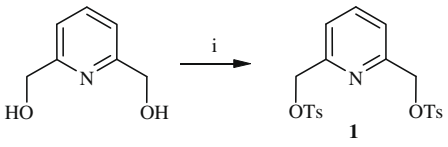
2. Results and discussion

2.1. Synthesis

Tosylate **1** was prepared by the procedure given in the literature, as shown in Scheme 1.[32] A tetra-bromide building block for macrocycle synthesis from 4-methylphenol was prepared as shown in Scheme 2. The conversion of 4-methylphenol to 2,5-dihydroxymethyl-4-methylphenol was carried out by our modified previous method.[33] The conversion of 2,5-dihydroxymethyl-4-methylphenol to **2** and **3** was carried out according to the reported procedure.[29] Chiral macrocycles of (*S*,*S*,*S*)-**1**, (*S*,*S*,*S*)-**2** and (*S*,*S*,*S*)-**3** were obtained in 29%, 32% and 37% yields, respectively, as shown in Scheme 3. The syntheses of macrocycles (*S*,*S*,*S*)-**1**, (*S*,*S*,*S*)-**2** and (*S*,*S*,*S*)-**3** are of special interest. The reaction of tetrabromide **3** with various amino alcohols was expected to afford (*S*,*S*,*S*,*S*)-**1**, (*S*,*S*,*S*,*S*)-**2** and (*S*,*S*,*S*,*S*)-**3**, respectively. However, the main products obtained were (*S*,*S*,*S*)-**1**, (*S*,*S*,*S*)-**2** and (*S*,*S*,*S*)-**3,** respectively. By using either excess or equivalent amount of amino alcohols, we obtained the same products. As can be seen from Figure 1, the molecular dynamics calculations for (*S*,*S*,*S*)-**3** showed that when the first cyclisation reaction occurs, the other two side arms of the molecules become far from each other, and therefore, the second cyclisation reaction cannot occur. These results show that the pyridine nitrogen has a template role for the cyclisation reaction.



Scheme 1. Reagents and condition: (i) TsCl, KOH, −10 °C.

The structures proposed for these new chiral macrocycles are consistent with the data obtained from ^{1}H, ^{13}C NMR, IR and elemental analyses.

2.2. Enantiomeric recognition studies using a UV-titration method

The main purpose of synthesising these receptors is to study their enantiomeric recognition for guest molecules. The enantiomeric recognition can be characterised by various spectroscopic methods, such as NMR, ultraviolet visible (UV–vis), fluorescence and infrared (IR), which are powerful tools used for examining the recognition ability of new chiral macrocycles.[1,11,12] UV–vis spectroscopic method is a convenient and a widely used method for the study of binding phenomena, and there are now hundreds of reports where UV-titration has been used to measure intermolecular association.[21] When the macrocycles absorb light at different wavelengths in free and complexed states, the differences in the UV–vis spectra may suffice for the estimation of molecular and enantiomeric recognition thermodynamics. In UV spectroscopic titration experiments, the addition of varying concentrations of guest molecules results in a gradual increase or decrease of the characteristic absorption of the host molecules. The complexation of ammonium cations [*G*] with chiral macrocycles [*H*] is expressed by Eq. 1:

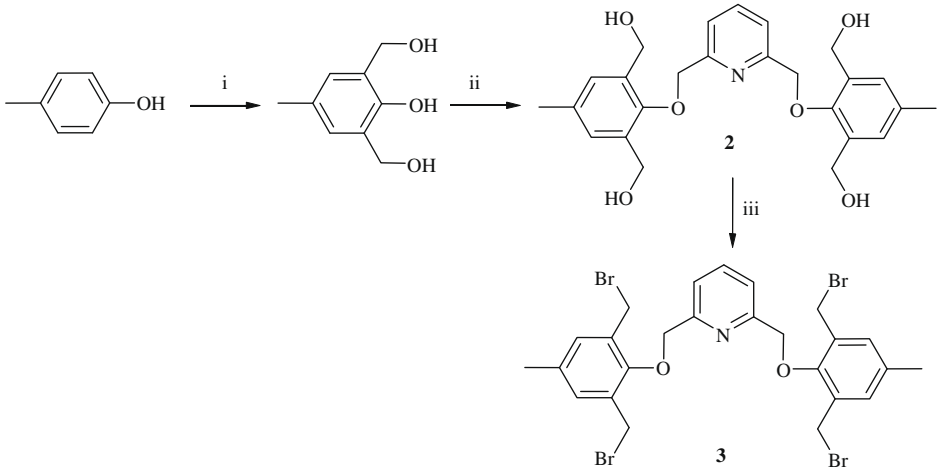
$$H + G \overset{K}{\leftrightarrows} H \cdot G \tag{1}$$

Under the conditions employed herein, chiral organic ammonium hydrochloride salts were selected as the guest molecules (Scheme 3). The binding constant (association constant) of the supramolecular system formed can be calculated according to modified Benesi–Hildebrand equation, (Eq. 2), where $[H]_o$ and $[G]_o$ refer to the total concentration of the pyridine-macrocycles and organic ammonium salts, respectively. Moreover, $\Delta\varepsilon$ is the difference between the molar extinction coefficient for the free and complexed chiral macrocycle host; ΔA denotes the change in absorption of the host on adding alkyl ammonium salts (guest). The original Benesi–Hildebrand experiment concerned an optical spectroscopy study of the association of iodine with aromatic hydrocarbons.[34] The key feature of this method is that by working with a large excess of component *H*, the concentration of uncomplexed *H* can be set equal to the initial concentration, $[H = H_o]$. For all of the guests examined, plots of calculated $[H]_o \cdot [G]_o/\Delta A$ values as a function of $[G]_o$ values gave an excellent linear relationship ($R > 0.9992$) with a slope $1/\Delta\varepsilon$ and intercept $1/K_a \cdot \Delta\varepsilon$ thus supporting the 1:1 complex formation.

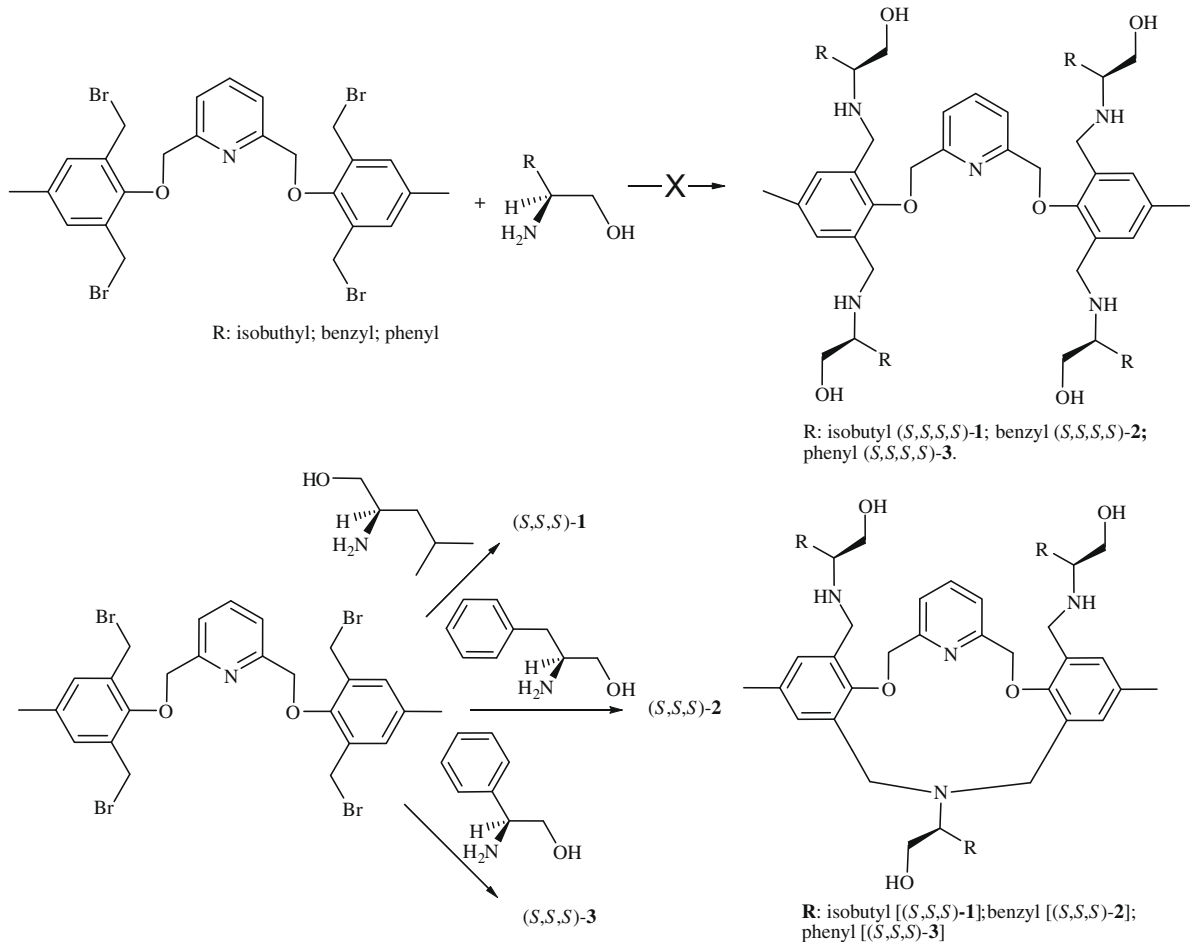
$$[H]_o \cdot [G]_o/\Delta A = 1/K_a \cdot \Delta\varepsilon + [G]_o/\Delta\varepsilon \tag{2}$$

where $\Delta A = (A_H - A_{obs})$, and $\Delta\varepsilon = (\varepsilon_H - \varepsilon_{H.G})$.

It is well-known that crown ethers form very stable complexes with ammonium salts by means of a hydrogen-bonding network, thus making them useful in many applications;[35] in particular, those bearing stereogenic centres and a bulky substituent on their ring core are of great interest in stereoselective applications.[16] The model compound, easily synthesised as compared to crown ethers, might be considered to be a cyclic pyridine possessing crown



Scheme 2. Reagents and conditions: (i) HCHO, NaOH, 40 °C; (ii) **1**, Cs_2CO_3, acetone; (iii) PBr_3, THF.



Scheme 3. Reagents and conditions: Cs_2CO_3, CH_3CN, reflux, 1 day.

ethers such as rings, and are predicted to behave in a similar way to accommodate ammonium salts. In addition, because they possess pyridine units on their rings, they are expected to be superior to crown ethers. The determination of K values for chiral host–guest interactions provides information about the capability of the chiral hosts to recognise enantiomers of the chiral guest under given sets of conditions. The correlation of the degree of recognition with the structural features of the host guest complexes is essential in understanding the origin of chiral recognition.

We examined the binding properties of the novel pyridine-macrocycles (*S*,*S*,*S*)-**1,** (*S*,*S*,*S*)-**2** and (*S*,*S*,*S*)-**3** towards the enantiomers of Am1 and Am2 (Scheme 4) by using UV-titration. The concentration of the host was fixed to 3.33×10^{-5} M in $CHCl_3$. The UV–vis spectrum at λ_{max} 239 and 272 nm was monitored, with the addition of various concentrations (1.33×10^{-5}–6.67×10^{-4} M) of guests.

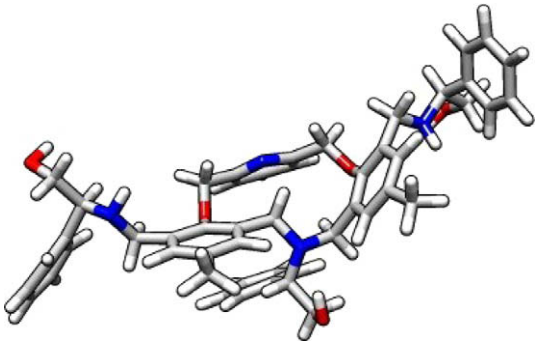
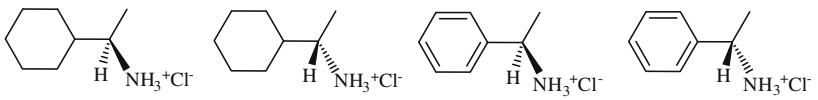


Figure 1. Molecular dynamics calculations for (*S*,*S*,*S*)-**3** by AMBER v9.

The typical UV spectral changes upon the addition of (*R*)-Am1 salt [(*R*)-α-(−) phenyl-ethylammonium hydrochloride] to (*S*,*S*,*S*)-**2** are shown in Figure 2, while a typical plot is shown for the complexation of compound (*S*,*S*,*S*)-**2** with guest (*R*)-Am1 in Figure 3. The Job's plot based on the UV-spectroscopic changes which supported the 1:1 stoichiometry of host–guest complexes is shown in Figure 4.

The binding constant (K_a) of the inclusion complexes of pyridine-macrocycles bearing amino alcohol subunits (*S*,*S*,*S*)-**1**, (*S*,*S*,*S*)-**2** and (*S*,*S*,*S*)-**3**, with organic ammonium salts was determined by the Benesi–Hildebrand equation on the basis of the UV–vis spectrum of the complexes in $CHCl_3$ collected at 25 ± 1 °C. The binding constant (K_a) and the Gibbs free energy changes ($-\Delta G_o$) of these hosts with guest molecules obtained from usual curve fitting analyses ($R > 0.9992$) of observed absorbance changes are summarised in Table 1, along with enantioselectivity K_S/K_R or $\Delta\Delta G_o$ calculated from $-\Delta G_o$ for the complexation of (*R*/*S*)-organic ammonium salts by the given hosts.

Significant differences were observed in the K_a values of (*R*)-Am2 and (*S*)-Am2 for (*S*,*S*,*S*)-**1**, (*S*,*S*,*S*)-**2** and (*S*,*S*,*S*)-**3** hosts, $K_S/K_R = 5.0$, $K_S/K_R = 2.4$ and $K_S/K_R = 5.0$, $\Delta\Delta G_o = 3.99$, 2.16 and 3.99 kJ mol^{-1}, respectively, as shown in Table 1. On the other hand, differences in the K_a values of (*R*)-Am1 and (*S*)-Am1 for (*S*,*S*,*S*)-**1**, (*S*,*S*,*S*)-**2**, (*S*,*S*,*S*)-**3** hosts, were moderate, $K_S/K_R = 2.0$, $K_S/K_R = 0.9$ and $K_S/K_R = 2.1$, $\Delta\Delta G_o = 1.63$, −0.26 and 1.80 kJ mol^{-1}, respectively.



Scheme 4. Ammonium hydrochloride salts used as a guest.

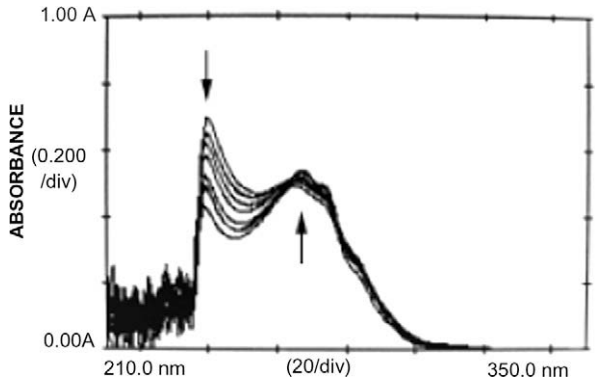


Figure 2. UV–vis spectra of (*S*,*S*,*S*)-**2** (3.33×10^{-5} mol dm^{-3}) in the presence of (*R*)-AM1 (1.33×10^{-5}–3.33×10^{-4}) mol dm^{-3}).

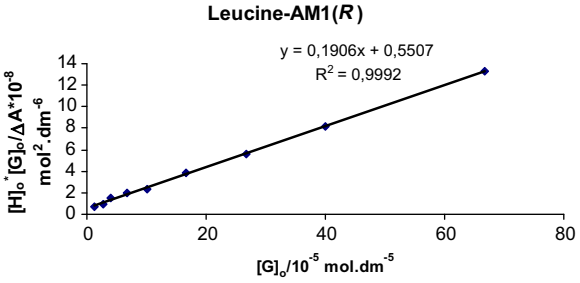


Figure 3. Typical plot of $[H]_o{\cdot}[G]_o/\Delta A$ versus $[G]_o$ for host–guest complexation of (*S*,*S*,*S*)-**2** and (*R*)-α-(−)phenyl-ethylammonium hydrochloride salt [(*R*)-AM1].

Figure 4. Job plot for pyridine-macrocycle (*S*,*S*,*S*)-**2** (*R*)-AM1.

The result indicates that all hosts form very stable complexes with Am1 and Am2 salts with relatively similar binding constants ($\sim 10^4$ M^{-1}) except for host (*S*,*S*,*S*)-**2** which has larger binding constants ($\sim 10^5$ M^{-1}) for Am1 salts, The hosts exhibit a preference for enantiomers with an absolute configuration of (*S*) for both amine salts (guests Am1 and Am2). However, the hosts bearing phenyl and bulky isobutyl process a better discrimination ability compared to those bearing benzyl groups. The hosts bearing phenyl and isobutyl groups form more stable complexes with the (*S*)-configuration of the enantiomer of the guests of both Am1 and Am2.

Table 1
Binding constant (K_a), the Gibbs free energy changes ($-\Delta G_o$), enantioselectivities K_S/K_R or $\Delta\Delta G_o$ for including the *R*/*S* guest with the chiral host macrocyles in $CHCl_3$ at 25 °C

Host	Guest[a]	K_a (M^{-1})	K_S/K_R	$-\Delta G_o$ (kJ mol^{-1})	$\Delta\Delta G_o$[b] (kJ mol^{-1})
(*S*,*S*,*S*)-**1**					
	(*R*)-AM1	$(2.0 \pm 0.23) \times 10^4$	2.0	24.62	1.63
	(*S*)-AM1	$(4.0 \pm 0.34) \times 10^4$		26.25	
	(*R*)-AM2	$(1.0 \pm 0.42) \times 10^4$	5.0	22.82	3.99
	(*S*)-AM2	$(5.0 \pm 0.36) \times 10^4$		26.81	
(*S*,*S*,*S*)-**2**					
	(R)-AM1	$(2.0 \pm 0.31) \times 10^5$	0.9	30.24	−0.26
	(S)-AM1	$(1.8 \pm 0.38) \times 10^5$		29.98	
	(R)-AM2	$(1.67 \pm 0.19) \times 10^4$	2.4	24.09	2.16
	(S)-AM2	$(4.0 \pm 0.43) \times 10^4$		26.25	
(*S*,*S*,*S*)-**3**					
	(R)-AM1	$(1.5 \pm 0.26) \times 10^4$	2.1	23.82	1.80
	(S)-AM1	$(3.1 \pm 0.18) \times 10^4$		25.62	
	(R)-AM2	$(1.0 \pm 0.34) \times 10^4$	5.0	22.82	3.99
	(S)-AM2	$(5.0 \pm 0.46) \times 10^4$		26.81	

[a] AM1: α-phenylethylamine hydrochloride salts. AM2: cyclohexylethylamine hydrochloride salts.
[b] $\Delta\Delta G_o = -\Delta G_{o(R)} - \Delta G_{o(S)}$.

This observation for the host bearing isobutyl groups was confirmed by an ERF (enantiomer recognition factor) of 2.0 and 5.0 (K_S/K_R), which corresponds to approximately 33% and 67% ees for Am1 and Am2, respectively. For the host bearing a phenyl with an ERF of 2.1 and 5.0 (K_S/K_R) it corresponds to approximately 36% and 67% ees for Am1 and Am2, respectively. These findings clearly indicate that the complex host bearing phenyl and isobutyl are more stable with an (*S*)-configuration of the enantiomer of guests of both Am1 and Am2; fits better than the one with an (*R*)-configuration because the phenyl and cyclohexyl groups in the former is placed opposite to the isobutyl and phenyl side chains in the cavity of the host, whereas in the latter, these groups are located in the same face, causing unfavourable steric interactions. These chiral ligands exhibit enantiomeric recognition for the chiral forms of various organic ammonium salts. This is evident from the differences in the K_a values as shown in Table 1. All hosts examined, formed kinetically more stable complexes with an (*S*)-configuration enantiomer than with (*R*)-configuration of both Am1 and Am2. There seems to be a general tendency for hosts to recognise the (*S*)-enantiomers for both Am1 and Am2. The host bearing benzyl (*S*,*S*,*S*)-**2**, binds the guest of Am1 approximately 10 times strongly than that of Am2. However, enantiomeric discrimination is lower than the other hosts. The results show that the structures of host and guests, hydrogen bonding, π–π staking, π–charge interaction and steric complementarity, may be responsible for the enantioselective recognition.

3. Experimental

3.1. General information

Melting points were determined with a GALLENKAMP Model apparatus with open capillaries and are uncorrected. Infrared

spectra were recorded on a MIDAC-FTIR Model 1700 spectrometer. The elemental analyses were obtained with CARLO-ERBA Model 1108 apparatus. Optical rotations were taken on a Perkin–Emler 341 Model polarimeter. ^{1}H (400 MHz), ^{13}C (100 MHz) ^{1}H NMR titration and two dimensional NMR (DEPT, COSY, HETCOR, HMQC, HMBC) spectra were recorded on a BRUKER DPX-400 High Performance Digital FT-NMR spectrometer in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards.

All chemicals were of reagent grade and were purchased from either Aldrich or Fluka, and used without further purification unless specified. All solvents were dried before use following standard procedures. All reactions were performed under an atmosphere of dry nitrogen.

3.2. Synthesis of aminoalcohols

L-Glycinol was purchased from Fluka, and used without further purification. The synthesis of L-leucinol and L-phenylalanilol was accomplished in one step from L-leucine and L-phenylalanine according to procedures described in the literature.[36]

3.3. 2,6-[(Tosyloxy)methyl]pyridine 1

This reaction was carried out according to the modified procedure in the literature.[32] A solution of 2,6-bis(hydroxymethyl)pyridine (8.48 g, 61 mmol) in 200 mL CH_2Cl_2 was added to a 40% aqueous solution of KOH (200 mL). The reaction mixture was cooled at 0 °C and stirred for 30 min, after which a solution of *p*-toluene sulphonyl chloride (23.25 g, 122 mmol) was added to it in one portion. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature until silica gel TLC using 1/4 (v/v) methanol/toluene as an eluent showed complete conversion of the starting materials and only one main spot for the product (R_f 0.75). The mixture was washed in a separatory funnel with water and CH_2Cl_2 (200 mL of each). The resulting mixture was shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3×200 mL), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. The residue was triturated with dry and pure methanol to give **1** as a white crystal (25.18 g, 91%); mp 121–122 °C. IR (KBr, cm^{-1}): 3070, 3031, 3001, 2962, 2893, 1601, 1361, 1196, 1117, 964, 880, 607, 551 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 6H), 5.07 (s, 4H), 7.34–7.83 (m, 11H) ppm.

3.4. 2,6-Bis[2′,6′-bis(hydroxymethyl)-4′-methylphenoxymethyl]pyridine 2

A solution of 4-methyl-2,6-bis(hydroxymethyl)phenol (7.06 g, 42 mmol) and K_2CO_3 (6.21 g, 45 mmol) in 200 mL of acetone was refluxed for 30 min. Next, 2,6-[(tosyloxy)methyl]pyridine (10.10 g, 23 mmol) was added to the reaction mixture and rinsed with 80 mL of acetone. The reaction mixture was heated at reflux for 16 h. Then, H_2O (100 mL) was added, and the reaction mixture was filtered hot. The volume of the filtrate was reduced to 140 mL on a rotary evaporator. The analytically pure product precipitated on standing at 4 °C to give **2** as a white crystal (8.73 g, 89%); mp 180–181 °C; IR (KBr, cm^{-1}) 3411, 2960, 2914, 1601, 1486,1239,1158, 1024, 873, 619 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 2.51 (s, 6H), 4.58 (s, 8H), 4.97 (s, 4H) 5.29 (br s, 4H), 7.19 (s, 4H), 7.67 (d, 2H, J = 8.1 Hz), 8.00 (t, 1H, J = 8.1 Hz); ^{13}C NMR (DMSO-d_6) 25.94, 63.34, 81.32, 125.87, 133.21, 137.98, 139.90, 143.24, 156.45, 161.98. Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 7.47; N, 3.19. Found: C, 68.18; H, 7.49; N, 3.13.

3.5. 2,6-Bis[2′,6′-bis(bromomethyl)-4′-methylphenoxymethyl]pyridine 3

A 1.0 M solution of PBr_3 in CH_2Cl_2 (35 mL) was added to a solution of **2** (3.80 g, 8.7 mmol) in dry THF (250 mL) under a nitrogen atmosphere at 0 °C over a period of 30 min. Stirring was continued at 0 °C for 3 h. The reaction mixture was evaporated under vacuum. The residue was added to a mixture of ice-water (130 mL) and CH_2Cl_2 (110 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated under vacuum. The crude product was recrystallised from $ClCH_2CH_2Cl$/MeOH to give **3** as a white solid (3.89 g, 65%); mp 157–158 °C; IR (KBr, cm^{-1}) 3058, 3024, 2969, 1601, 1485, 1226, 1200, 983, 887, 717, 563 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 2.35 (s, 6H), 4.63 (s, 8H), 5.31 (s, 4H) 7.24 (s, 4H), 7.72 (d, 2H, J = 8.1 Hz), 7.93 (t, 1H, J = 8.1 Hz); ^{13}C NMR (DMSO-d_6) 20.68, 27.97, 77.01, 120.89, 131.79, 132.91, 135.10, 137.90, 153.05, 156.55 Anal. Calcd for $C_{25}H_{25}Br_4NO_2$: C, 43.44; H, 3.64; N, 2.03. Found: C, 43.41; H, 3.71; N, 1.98.

3.6. Macrocyclic (*S*,*S*,*S*)-1

A 1 L four-necked, round-bottomed flask, fitted with a two-faced condenser, was charged with 250 mL acetonitrile and Cs_2CO_3 (3.9 g, 12 mmol). The solution was refluxed vigorously while 2,6-bis[2′,6′-bis(bromomethyl)-4′-methylphenoxymethyl] pyridine **3** (2.0 g, 2.9 mmol) in dry acetonitrile (50 mL) and L-leucinol (1.40 g, 12 mmol) in dry acetonitrile (50 mL) were added dropwise at the same rate under dry nitrogen atmosphere. After the addition was complete, the reaction mixture was refluxed overnight. The solution was filtered hot. The volume of filtrate was reduced to 120 mL on a rotary evaporator. Cs_2CO_3 was precipitated on standing at 4 °C. Then the mixture was filtered and the solvent was evaporated. The crude product was washed with hot ether several times to remove excess amino alcohols. The product was crystallised in $CHCl_3$/petroleum ether (2:1) to give (*S*,*S*,*S*)-**1** as a white solid (0.71 g, 33%); mp 124–126 °C; $[\alpha]_D^{35} = +6.8$ (*c* 0.7, CH_2Cl_2). IR (KBr, cm^{-1}): 3405, 3084, 2954, 2931, 2873, 1601, 1469, 1369, 1199, 1141, 1034, 983, 872; ^{1}H NMR (400 MHz) in $CDCl_3$ δ, 0.76–0.94 (18H, m), 1.20–1.22 (4H, m), 1.24–1.26 (2H, m), 1.27–1.29 (1H, m), 1.39–1.45 (2H, m), 2.30 (6H, s), 3.32–5.13 (21H, m), 6.99–7.09 (4H, m), 7.45–7.81 (2H, m); ^{13}C NMR (100 MHz) in $CDCl_3$ δ, 20.91, 21.05, 22.03, 22.17, 22.90, 23.32, 23.64, 23.78, 23.95, 24.91, 25.42, 25.47, 25.56, 30.32, 34.45, 34.61, 47.09, 47.18, 49.12, 56.44, 57.80, 61.71, 63.45 65.84, 77.33, 78.30, 123.44, 129.41, 129.71, 130.88, 131.01, 132.06, 132.99, 133.04, 133.39, 137.50, 137.54, 155.26, 155.82, 156.61, 156.74, 156.99. Anal. Calcd for $C_{43}H_{66}N_4O_5$: C, 71.77; H, 9.25; N, 7.79. Found: C, 71.74; H, 9.25; N, 7.76.

3.7. Macrocycle (*S*,*S*,*S*)-2

A 1 L four-necked, round-bottomed flask, fitted with a two-faced condenser, was charged with 250 mL acetonitrile and Cs_2CO_3 (3.9 g, 12 mmol). The solution was refluxed vigorously while 2,6-bis[2′,6′-bis(bromomethyl)-4′-methylphenoxymethyl] pyridine **3** (2.0 g, 2.9 mmol) in dry acetonitrile (50 mL) and L-phenylalanilol (1.81 g, 12 mmol) in dry acetonitrile (50 mL) were added dropwise at the same rate under a dry nitrogen atmosphere. After the addition was complete, the reaction mixture was refluxed overnight after which the solution was filtered hot. The volume of filtrate was reduced to 120 mL on a rotary evaporator. Then, Cs_2CO_3 was precipitated on standing at 4 °C. The mixture was filtered and the solvent was evaporated. The crude product was washed with hot ether several times to remove excess amino alcohols. The product was crystallised from $CHCl_3$/petroleum ether (2:1) to give (*S*,*S*,*S*)-**2**

as a solid (0.74 g, 20%); mp 136–138 °C; $[\alpha]_D^{35} = +23.9$ (*c* 0.7, CH_2Cl_2). IR (KBr, cm^{-1}): 3321, 3066, 3027, 2924, 2866, 1601, 1458, 1199, 1130, 1034, 732, 706; ^1H NMR (400 MHz) in $CDCl_3$ δ, 2.18 (6H, s), 2.24–2.32 (6H, AB system), 2.65–4.95 (26H, m), 6.57–7.97 (22H, m);^{13}C NMR (100 MHz) in $CDCl_3$ δ, 20.55, 20.81, 43.12, 43.73, 47.54, 47.91, 48.11, 49.94, 54.16, 57.83, 60.02, 61.13, 61.88, 62.94, 63.56, 68.12, 78.12, 120.67, 123.14, 125.91, 126.28, 127.25, 128.34, 128.98, 129.06, 129,48, 130.58, 131.95, 132.09, 132.85, 133.18, 133,89, 134.07, 136.11, 136.73, 137.59, 137.91, 138.12, 138.45, 140.53, 140.71, 142.70, 146.67, 155.48, 156.78, 157.12. Anal. Calcd for $C_{52}H_{60}N_4O_5$: C, 76.07; H, 7.37; N, 6.82. Found: C, 76.02; H, 7.41; N, 6.78.

3.8. Macrocycle (*S*,*S*,*S*)-3

A 1 L four-necked, round-bottomed flask, fitted with a two-faced condenser, was charged with 250 mL acetonitrile and Cs_2CO_3 (3.9 g, 12 mmol). The solution was refluxed vigorously while 2,6-bis[2′,6′-bis(bromomethyl)-4′-methylphenoxymethyl] pyridine **3** (2.0 g, 2.9 mmol) in dry acetonitrile (50 mL) and L-phenylglycinol (1.64 g, 12 mmol) in dry acetonitrile (50 mL) were added dropwise at the same rate under a dry nitrogen atmosphere. After the addition was complete, the reaction mixture was refluxed overnight after which the solution was filtered hot. The volume of filtrate was reduced to 120 mL on a rotary evaporator. Then, Cs_2CO_3 was precipitated on standing at 4 °C. Then the mixture was filtered and the solvent was evaporated. The crude product was washed with hot ether several times to remove excess amino alcohols. The product was crystallised from $CHCl_3$/petroleum ether (2:1) to give (*S*,*S*,*S*)-**3** as a solid (0.78 g, 35%); mp 142–144 °C; $[\alpha]_D^{35} = -23.7$ (*c* 0.7, CH_2Cl_2). IR (KBr, cm^{-1}): 3338, 3084, 3064, 3030, 2922, 2856, 1601, 1459, 1355, 1201, 1028, 758, 708; ^1H NMR (400 MHz) in $CDCl_3$ δ, 2.23 (6H, s), 2.80–3.89 (22H, m), 4.65–4.85 (4H, AB system), 6.94–7.42 (22H, m); ^{13}C NMR (100 MHz) in $CDCl_3$ δ, 20.77, 20.98, 47.04, 47.61, 49.53, 57.38, 60.74, 63.46, 63.86, 64.37, 65.52, 66.86, 67.90, 78.37, 120.97, 123.37, 126.54, 127.46, 127.61, 128.14, 128.53, 128.59, 128.92, 129.11, 129.45, 129.95, 130.78, 131.93, 132.33, 132.93, 133.41, 133.99, 135.11, 136.05, 137.36, 138.09, 140.53, 140.78, 142.51, 153.77, 155.32, 156.48, 157.03. Anal. Calcd for $C_{49}H_{54}N_4O_5$: C, 75.55; H, 6.99; N, 7.19. Found: C, 75.52; H, 7.02; N, 7.17.

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