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Pyridine containing chiral macrocycles: synthesis and their enantiomeric recognition for amino acid derivatives

Pınar Deniz, Yılmaz Turgut *, Mahmut Togrul, Halil Hosgoren

University of Dicle, Faculty of Science, Department of Chemistry, TR 21280 Diyarbakir, Turkey

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ABSTRACT

Four novel C_2-symmetric enantiomerically pure, chiral pyridine-18-crown-6 type macrocycles containing lipophilic chains at the stereogenic centers were prepared. The enantioselectivity of the new ligands toward the enantiomers of D-,L-amino acid methyl ester derivatives were also determined by ^{1}H NMR titration method. These novel macrocycles have been showed to be strong complexing agents for D- and L-amino acid methyl ester hydrochloride salts (with K_{ass} up to 13590 M^{-1} and ΔG^0 up to 23.3 kJ mol^{-1} and selectivity ratio: 80:20) by ^{1}H NMR titration methods. These macrocyclic hosts exhibited enantioselective binding towards the D-enantiomer of valine methyl ester hydrochloride with K_D/K_L up to 5.08 in $CDCl_3$ with 0.25% CD_3OD.

1. Introduction

Molecular recognition between molecules plays an important role in biochemical systems. The careful characterization of such synthetic systems could lead to a much improved understanding of natural systems. One area of recent interest is the enantiomeric recognition of organic ammonium cations by chiral macrocyclic ligands. Hence, the design, synthesis, and use of macrocycles capable of selective recognition of other molecules is of great interest in a variety of fields. Various types of natural and synthetic chiral compounds have been used as chiral subunits for constructing optically active crown ethers, and the continuing development of chiral building blocks has resulted in the production of a wide variety of optically active crown ethers exhibiting characteristic chiral recognition behavior.[1] Crown ethers, for example, have indicated excellent enantiodiscrimination for the enantiomers of chiral organic ammonium guests.[2]

Since Cram and et al. prepared their important enantiomeric recognition studies,[3] many different chiral macrocyclic ligands have been prepared for enantiomeric recognition. Some of these ligands include amino acid units,[4] sugar molecules,[1a,5] diaza crown units,[6] and chiral crown ethers containing the pyridine subcyclic unit.[2,7–16] Macrocyclic pyridine-based systems are important in metal chelation and extraction,[17] host–guest systems[18] and enzyme mimics,[19] antibiotics,[20] and natural products, such as marine alkaloids.[21]

Excellent reviews of chiral macrocycles and their interaction with organic ammonium salts have been published.[1d,22–24] A number of synthetic model compounds have been designed and synthesized as a chiral host molecule that help chemists understand the basis of the mechanisms of host–guest complexation and chiral recognitions.[25]

Chiral pyridine-containing macrocycles have been an attractive research area due to their ability for chiral discrimination between chiral organic ammonium salts and amino acid derivatives.[26] The pyridine subunit of these macrocycles were reported to be important for the tripod hydrogen bonding formation with organic ammonium salts, and the π–π interactions with the aromatic moiety of the ammonium guest, and steric repulsion between the bulky groups on the stereogenic centers of the ligand and the substituents of the ammonium salt.[2] In addition, pyridine units as building blocks are incorporated into the ring structure not only providing proton acceptors at the pyridyl nitrogens, but also bringing rigidity into the ring.[27]In many cases, macrocyclic pyridine-based systems are chosen for study because they form thermodynamically stable complexes with chiral primary ammonium cations in a number of solvent mixtures, and they also exhibit appreciable enantiomeric recognition.[7,9–11]

The present paper describes the synthesis of four novel C_2-symmetric chiral pyridine-containing 18-crown-6 macrocycles, each containing pairs of the following substituents: ethyl (**4**), isopropyl (**5**), phenyl (**6**), and benzyl (**7**). The enantiomeric recognition of chiral pyridine-containing 18-crown-6 ligands towards the enantiomers of different α-amino acid methyl ester hydrochlorides (D-PheOMe, L-PheOMe, D-ValOMe, L-ValOMe) by ^{1}H NMR titrations in $CDCl_3$ with 0.25% CD_3OD were studied at 25 °C. These

* Corresponding author. Tel.: +90 412 2488550; fax: +90 412 2488300; e-mail address: yturgut@dicle.edu.tr (Y. Turgut).

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macrocycles have a C_2-symmetry axis and their chirality derives from the D-amino acid derivatives used in their synthesis.

2. Results and discussion

2.1. Synthesis

In the present study, several macrocycles having different alkyl moieties attached to the stereogenic center and containing dipyridine units were synthesized, and effect of the alkyl moieties in the stereogenic center on enantiomeric recognition was investigated.

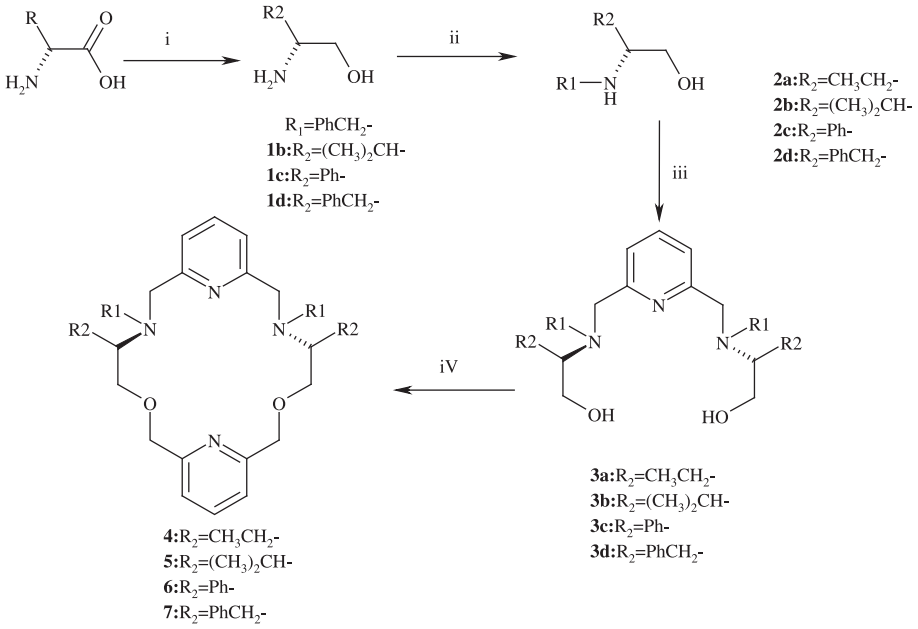
In this study, since the chiral amino alcohols used as a chirality source are expensive, they were not used directly, instead their cheaper amino acid forms were purchased, which were reduced with proper procedures[28] to obtain the corresponding amino alcohols in high yields (Scheme 1). As a source of chirality, D-valine, D-glycine, and D-phenyl alanine were reduced with $NaBH_4$-I_2 and the corresponding amino alcohols D-valinol **1b** (91%, lit.[28] 94%), D-glycinol **1c** (90%, lit.[28] 91%) and D-phenylalaninol **1d** (77%, lit.[28] 72%) were obtained. (*R*)-(−)-2-Amino-1-butanol (98%) was purchased and used without further purification.

prepared compounds were purified by appropriate methods and characterized by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR, MS and when necessary ^{1}H–^{1}H NMR, ^{1}H–^{13}C NMR), and were then employed in enantiomeric recognition. The cyclization is observed with [1+1] ratio according to MS spectra of 4, 5, 6, and 7.

2.2. Enantiomeric recognition

Systems having strong interactions or good chiral recognition allow for further investigation of their structural properties. The chiral ligands studied in laboratories contain 18-membered macrocycles and pyridine subunits. The choice of 18-membered macrocycles is generally based on the fact that they form more stable complexes with primary amines and ammonium cations in solvents than other crown ethers with larger or smaller ring size.[26,29]

It is accepted that insertion of pyridine subunits into the macrocycle has two positive effects: first, $N^+H\cdots N$ hydrogen bond interaction with the pyridine nitrogen are generally much more stable than $N^+-H\cdots O$ bonds.[30] Second, if ammonium cation contains an aromatic moiety, then the pyridine ring enables further interactions between the cation and the ligand due to π–π in-



Scheme 1. Synthesis of chiral amino alcohols and chiral macrocycles. Reagent and conditions: (i) $NaBH_4/I_2$/THF (ii) 1. benzaldehyde, 2. $NaBH_4$, (iii) 2,6-bis(bromomethyl)pyridine, 110 °C (iv) 1. NaH/THF, reflux, 2. 2,6-bis(bromomethyl)pyridine/THF, 58 h.

Compound **1a** and reduced products **1b**–**d** were treated with benzaldehyde in methanol under argon atmosphere at reflux temperature to give their imines, which were then reduced with $NaBH_4$ in the same reaction medium to synthesize the corresponding *N*-benzyl derivatives **2a** (91%), **2b** (94%), **2c** (96%), and **2d** (93%) (Scheme 1).

Compound **2a**–**d** were the reacted with 2,6-bis(bromomethyl) pyridine (using catalytic amount of KI) under Ar atmosphere in the presence of Na_2CO_3 and refluxed at 100 °C for 12 h to give **3a**–**d** having C_2-symmetric pyridine units and which will be used as precursors for crown ethers in 73, 66, 68, and 69% yield, respectively.

The pyridino C_2-symmetric **3a**–**d** having ethyl-, isopropyl-, phenyl-, and benzyl-moieties in their side arms were converted into the corresponding alcoholates with NaH in dried THF using a quite dilute medium and then they were cyclised in a one to one ratio with 2,6-bis(bromomethyl)pyridine. The chiral macrocycles possessing dipyridine units obtained by column chromatography, **5** (43%), **6** (37%), **7** (38%) and **8** (46%) are shown in Scheme 1. All the

teractions. For enantiomeric recognition, binding constants (K_{ass}), Gibbs free energy change (ΔG^0) and ratio of enantioselectivity (K_D/K_L) for host macrocycles **4**, **5**, **6**, and **7** with D-, L-Valine (ValOMe) and phenyl alanine (PheOMe) methyl ester hydrochloride salts were calculated using the ^{1}H NMR titration technique (Table 1).

Amino acid ester salts are widely used in enantiomeric recognition studies for three reasons: (i) ammonium salts make stronger hydrogen bonds than the amines, which increases enantioselectivity, (ii) ammonium salts containing an aromatic moiety enable cation–π interactions, (iii) the ester moiety in amino acid ester salts contributes to the strength of hydrogen bonding due to its acceptor property and if a proton exists in the macrocycle it also contributes enantiomeric recognition by forming a hydrogen bond with it. To compare the binding constants, the triplet signal of pyridine in the macrocycle the chemical shift of which is δ 7.725 ppm was chosen.

In the ^{1}H NMR titrations, concentrations of the host macrocycle ligands were kept constant at 8.18 mM and increasing concentrations of (0–18.2 mM) guest were added. An illustrative

Table 1
Association constants (K_{ass}), the Gibbs free energy changes ($-\Delta G^0$) and enantioselectivites K_D/K_L for the complexation of D-/L- guest with the **4**,**5**,**6**, and **7** in $CDCl_3$ with 0.25% CD_3OD

Entry	Host	Guests	K_{ass} (M^{-1})	K_D/K_L	$-\Delta G^0$ (kJ mol^{-1})[a]	$-\Delta\Delta G^0$ (kJ mol^{-1})[b]
1	4	D-PheOMe·HCl	1785	2.04	18.3	1.80
2	4	L-PheOMe·HCl	875		16.5	
3	4	D-ValOMe·HCl	2325	2.63	18.9	2.30
4	4	L-ValOMe·HCl	885		16.6	
5	5	D-PheOMe·HCl	2580	1.22	19.2	0.5
6	5	L-PheOMe·HCl	2105		18.7	
7	5	D-ValOMe·HCl	13,590	5.08	23.3	4.00
8	5	L-ValOMe·HCl	2675		19.3	
9	6	D-PheOMe·HCl	395	0.77 (K_L/K_D=1.29)	14.6	0.60
10	6	L-PheOMe·HCl	510		15.2	
11	6	D-ValOMe·HCl	32	0.33 (K_L/K_D=3.00)	8.5	2.80
12	6	L-ValOMe·HCl	96		11.3	
13	7	D-PheOMe·HCl	1190	1.21	17.3	0.50
14	7	L-PheOMe·HCl	983		16.8	
15	7	D-ValOMe·HCl	660	0.72 (K_L/K_D=1.38)	15.8	0.8
16	7	L-ValOMe·HCl	914		16.6	

[a] $\Delta G^0 = -2.303\ RTLog\ K$.
[b] $\Delta\Delta G^0 = -(\Delta G^0_D - \Delta G^0_L)$ or $\Delta\Delta G_0 = -(\Delta G^0_L - \Delta G^0_D)$.

change in the chemical shift of the signal at δ 7.725 ppm in the host depending on increasing guest concentration for L-ValOMe salts of macrocycle **5** is presented in Fig. 1. Furthermore, the stoichiometry of the host–guest complex was calculated in terms of chemical shift of this signal. The stoichiometry was found to be 1:1 according to Job plot method (Fig. 2). Typical plots are shown for the complexation of compound **5** with L-PheOMe·HCl in Fig. 3.

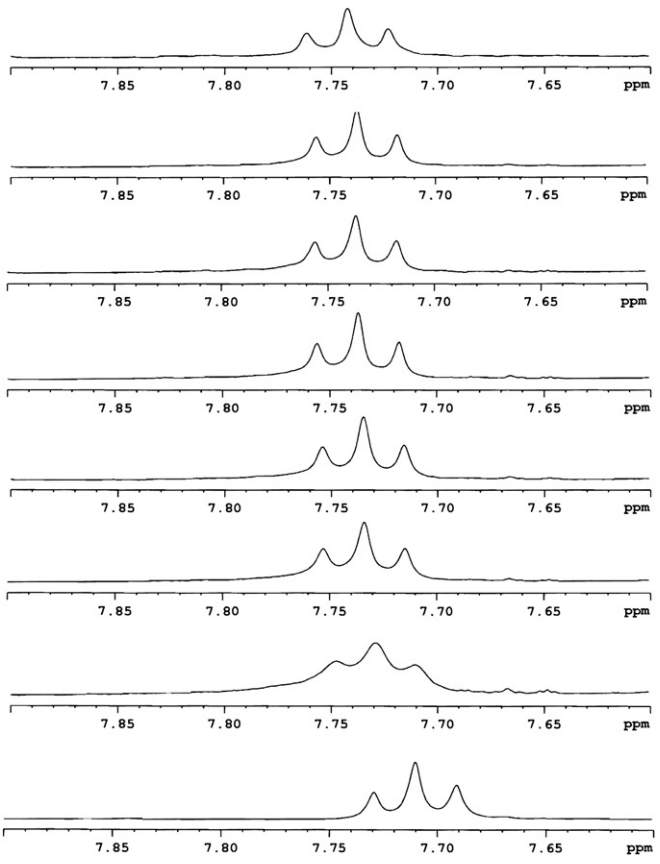


Fig. 1. ^1H NMR spectral changes of chiral crown ether 5(8.18 mM) in the presence of L-ValOMe (0–18.2 mM) in $CDCl_3$ with 0.25% CD_3OD at 25 °C.

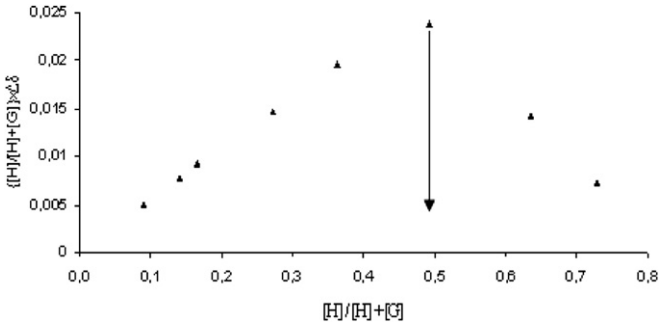


Fig. 2. Job plot for L-PheOMe·HCl and host **5**.

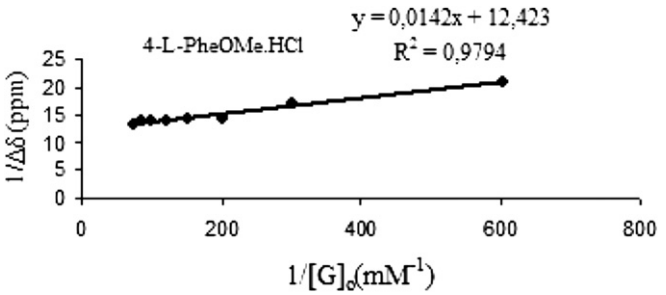


Fig. 3. Typical plot of $1/\Delta\delta$ versus $1/[G]_o$ for host–guest complexion of host 5 and L-PheOMe·HCl.

Considering the values in Table 1, it can be *noted* that macrocycle **4** containing the ethyl moiety forms makes stronger complexes with D-forms of both phenyl alanine methyl ester hydrochloride and valine methyl ester hydrochloride, and that D-ValOMe is better in terms of the enantioselectivity of amino acid ester salts (enantioselectivity ratio for D-, L-PheOMe, K_D/K_L=2.04; that for D-, L-ValOMe, K_D/K_L=2.63). Binding constants for D-PheOMe and D-ValOMe are 1785 M^{-1} and 2325 M^{-1}, respectively, showing that the steric effect of the guests, which contain no aromatic moiety and in which there exists no π–π interaction is an important factor for good enantioselectivity. This is in agreement with the concept that repulsive interactions of chiral macrocyclic receptors decreases complexation stability of an enantiomer significantly and give the chance to form a remarkably stable complex of the guest with the host, a basic requisite for enantiomeric recognition.

In the case of macrocycle **5** possessing an isopropyl moiety of the stereogenic center, binding constants with D-PheOMe and L-PheOMe are 2580 M^{-1} and 2105 M^{-1}, those with D-ValOMe and L-ValOMe are 13590 M^{-1} and 2675 M^{-1}, respectively. It is observed that macrocycle **5** forms excellent complexes with both D- and L-PheOMe but it does not show a high enantioselectivity between these guests (K_D/K_L=1.22). On the other hand, this macrocycle shows five times higher enantioselectivity for D-ValOMe than the L-form (K_D/K_L=5.08), which implies that besides a steric repulsion between the isopropyl moiety in the stereogenic center and that of the guest molecule, the host makes a stronger interaction with spatial orientation of D-form of the amino acid. These results suggest that the steric effect of ammonium guest is important for good enantioselectivity when no aromatic group is available for π–π interactions.

In considering the moieties in the stereocenters of macrocycles **4** and **5**, which contain ethyl and isopropyl moieties, respectively, the guests having no π–π interaction and containing no aromatic moiety makes stronger complexes and show higher enantioselectivity with the macrocycles (Table 1, entries: 3, 4, 7, and 8).

When macrocycle **6**, containing a phenyl moiety of the stereogenic center is compared with **4** and **5**, it can be easily seen that it

does not make strong complexes with phenyl alanine and valine methyl ester salts, nor does it exhibit much enantioselectivity between the enantiomers. By comparing binding constants for macrocycle **6** with guests, it can be shown that it has a greater binding constant and a weak selectivity for PheOMe salts containing an aromatic moiety compared with ValOMe salts containing aliphatic moiety (K_D/K_L=0.77 for PheOMe, K_D/K_L=0.33 for ValOMe) (Table 1, entries: 9–12). This means that there may be a π–π interaction between the phenyl moiety present in the stereogenic centers of the macrocycle and the amino acid ester salts containing aromatic moiety.

In the case of macrocycle **7** containing a benzyl moiety in the stereogenic center, it was found that there was merely 1.21-fold enantioselectivity between D-PheOMe and L-PheOMe, and that the L-form exhibited a higher enantioselectivity than the D-form (K_D/K_L=0.72, K_L/K_D=1.37).

When **6** and **7**, which have phenyl and benzyl moieties, respectively, are compared with each other, it can be seen that **7** makes stronger complexes with both PheOMe and ValOMe salts, but its enantioselectivity is not so different from **6**. Macrocycles **4** and **5** displayed higher enantioselectivity for D-forms of both phenyl alanine methyl ester and valine methyl ester hydrochloride salts than L-forms. It was shown that **6** made stronger complexes with L-forms of both amino acids, while **7** made stronger complexes with D-PheOMe and L-ValOMe salts.

3. Conclusions

1. In view of binding constants and enantioselectivities, **5** exhibited the highest enantioselectivity as well as quite strong complexation with D- and L-ValOMe guest. This supports the opinion that the nitrogen atom in the macrocycle makes better three points hydrogen bonding with the $-^{+}NH_3$ moiety of ammonium cations of the guest and increases binding strength.[31]
2. When **4** and **5** are compared with **6** and **7**, as shown in Table 1, compound **4** and **5**, which have ethyl and isopropyl moieties at the stereogenic center, respectively, not only make stronger complexes, but also exhibit higher selectivity (Table 1, entries: 1–8) Binding and enantioselectivity for **6** and **7**, which possess phenyl and benzyl moieties at the stereogenic center, respectively, are low and medium level, which may be attributed to prevention of the phenyl and benzyl moieties from approaching the cation in the guest.
3. It can be said that for **6** and **7**, which have phenyl and benzyl moieties at the stereogenic center, respectively, stronger complexation especially with the amino acid methyl ester salts having an aromatic moiety is due to the cavity of the host, hydrogen bonding between the host and the guest combined with π–π interactions.

4. Experimental

4.1. General information

All chemicals were reagent grade unless otherwise specified. D-Amino acids were purchased from Sigma–Aldrich or Fluka chemical company. 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 (F_{254}) were used for column chromatography and TLC. All reactions were carried out under Nitrogen or Argon atmosphere with dry solvent under anhydrous conditions, unless other 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. Specific 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. The chemical shifts (δ) and coupling constants (J) were expressed in parts per million and hertz.

Mass spectrometry analysis was performed on an autoflex III MALDI-TOF/TOF-MS system (Bruker Daltonics, Bremen, Germany).

4.2. Synthesis

*4.2.1. (2R)-2-{Benzyl[(6-{[benzyl(2R)-(1-hydroxybutan-2-yl)amino] methyl]pyridin-2-yl)methyl]amino}-butane-1-ol (**3a**).* (2*R*)-2-(Benzylamino)butan-1-ol **2a** (6.0 g, 33.5 mmol), 2,6-bis-(bromomethyl) pyridine (4.5 g, 16.7 mmol), sodium carbonate (5.33 g, 50.0 mmol), and KI (50 mg) in EtOH (50 mL) were stirred at 100 °C for 12 h under Argon. Then the mixture was cooled and $CHCl_3$ (100 mL) was added to the mixture and refluxed for 2 h. The solution was filtered, EtOH was removed in vacuo and $CHCl_3$ (50 mL) was added to the residue. The solution was washed with water and brine (50 mL) twice. The aqueous solution was extracted with $CHCl_3$ (2×50 mL). The combined $CHCl_3$ phases were dried over anhydrous Na_2SO_4. The solvent was concentrated and crude product was purified by column chromatography over silica gel using toluene/EtOAc/TEA (30/3/1) to afford **3a** (5.65 g, 73%) as a yellow oil, TLC R_f=0.25. $[\alpha]_D^{27}$ −10.8 (*c* 1, EtOH); IR: ν 3288, 3072, 3031, 2978, 2935, 1606, 1496, 1458, 1162, 1079, 912, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm) 0.95 (t, 6H, *J*=8.0 Hz), 1.28–1.35 (m, 2H), 1.74–1.81 (m, 2H), 2.80–2.86 (m, 2H), 3.53–3.74 (m, 8H), quartet of AB spin system δ_A: 3.86ve δ_B: 3.97 (4H, *J*=12.0 Hz), 5.07 (br s, 2H), 6.98 (d, 2H, *J*=8.0 Hz) 7.16–7.32 (m, 10H), 7.46 (t, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ (ppm) 11.85, 19.34, 54.48, 54.91, 61.64, 63.26, 121.21, 126.93, 128.20, 128.92, 136.89, 139.62, 159.61. Anal. Calcd for $C_{29}H_{39}N_3O_2$: C, 75.48; H, 8.46; N, 9.11. Found: C, 75.60; H, 8.58; N, 9.12.

*4.2.2. (2R)-2-{Benzyl[(6-{[benzyl-(2R)-(1-hydroxy-3-methylbutan-2-yl)amino] methyl]pyridin-2-yl)methyl]amino}-3-methylbutan-1-ol (**3b**).* This compound was prepared as described above for **3a** starting from **2b**: (2*R*)-2-(benzylamino)-3-methylbutan-1-ol (5.0 g, 25.9 mmol), 2,6-bis-(bromomethyl)pyridine (3.43 g,12.95 mmol), Na_2CO_3 (4.12 g, 38.85 mmol), and KI (50 mg). The crude product was purified by column chromatography over silica gel using hexane/EtOAc/TEA (60/20/5) to afford **3b** (4.2 g, 66%) as a yellow oil TLC R_f=0.42. $[\alpha]_D^{31}$ +3.5 (*c* 1,$CHCl_3$); IR: ν 3391, 3069, 3030, 2928, 1592, 1458, 1369, 1267, 1157, 1113, 1074, 1016, 912, 797 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm) 0.95 (d, 6H, *J*=8.0 Hz), 1.08 (d, 6H, *J*=8.0 Hz), 1.91–1.99 (m, 2H), 2.62–2.67 (m, 2H), 3.68–4.08 (m, 12H), 5.72 (br s, 2H), 6.91 (d, 2H, *J*=8.0 Hz), 7.15–7.30 (m, 10H), 7.41 (t, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ (ppm) 20.35, 21.96, 28.97, 55.51, 55.62, 60.97, 68.45, 121.45, 126.83, 128.12, 129.04, 136.94, 140.06, 159.51. Anal. Calcd for $C_{31}H_{43}N_3O_2$: C, 76.03; H, 8.85; N, 8.58. Found: C, 76.10; H, 8.86; N, 8.58.

*4.2.3. (2R)-2-{Benzyl[(6-{[benzyl-(2R)-(2-hydroxy-1-phenylethyl) amino]methyl]pyridin-2-yl)methyl]amino}-2-phenylethan-1-ol (**3c**).* This compound was prepared as described above for **3a** starting from **2c**: (2*R*)-2-(benzylamino)-2-phenylethan-1-ol (7.15 g, 31.5 mmol), 2,6-bis-(bromomethyl)pyridine (4.17 g,15.75 mmol), Na_2CO_3 (5.0 gr, 47.2 mmol), and KI (50 mg). The crude product was purified by column chromatography over silica gel using toluene/EtOAc (5/3) to afford **3c** (6.0 g, 68%) as a yellow oil TLC R_f=0.21. $[\alpha]_D^{31}$ −93.2 (*c* 4.1,$CHCl_3$); IR: ν 3338, 3063, 3030, 2928, 2876, 2837, 1600, 1496, 1452, 1361, 1215, 1132, 1066, 1028,758 cm^{-1}. ^{1}H NMR ($CDCl_3$):

δ (ppm) 3.48–3.54 (m, 4H), 3.80–3.89 (m, 4H), 4.12 (q, 2H, *J*=4.0 Hz), 4.23–4.33 (m, 4H), 5.62 (br s, 2H), 7.01 (d, 2H, *J*=8.0 Hz), 7.20–7.45 (m, 20H), 7.50 (t, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ (ppm) 54.64, 55.63, 61.77, 65.43, 121.77, 127.04, 127.71, 128.29, 128.42, 128.49, 128.73, 128.99, 137.24, 139.12, 159.47. Anal. Calcd for $C_{39}H_{43}N_3O_2$: C, 79.97; H, 7.40; N, 7.17. Found: C, 80.00; H, 7.45; N, 7.17.

*4.2.4. (2R)-2-{Benzyl[(6-{[benzyl-(2R)-(1-hydroxy-3-phenylpropan-2-yl)amino] methyl}pyridin-2-yl)methyl]amino}-3-phenylpropan-1-ol (**3d**).* This compound was prepared as described above for **3a** starting from **2d**: (2*R*)-2-(benzylamino)-3-phenylpropan-1-ol (7.41 g, 30.7 mmol), 2,6-bis-(bromomethyl)pyridine (4.06 g,15.35 mmol), Na_2CO_3 (4.87 g, 46.00 mmol), and KI (50 mg). The crude product was recrystallized n-hexane/ethyl acetate (2:1) to afford **3d** (6.2 g, 69%) as a colorless solid mp: 126.5–128 °C; $[\alpha]_D^{31}$ −28.5 (*c* 1, CD_3CN); IR: ν 3402, 3063, 3024, 2922, 2864, 1587, 1496, 1452, 1361, 1132, 1074, 1016, 746, 700 cm^{-1}. ^{1}H NMR (CD_3CN): δ (ppm) 2.55–2.60 (m, 2H), 2.99–3.08 (m, 4H), 3.34–3.36 (m, 2H), 3.62–3.85 (m, 8H), 4.03–4.07 (m, 2H), 4.75 (br s, 2H), 7.07 (d, 2H, *J*=8.0 Hz), 7.18–7.29 (m, 20H), 7.51 (t, 1H, *J*=8.0 Hz). ^{13}C NMR (CD_3CN): δ (ppm) 32.63, 54.14, 54.78, 60.84, 63.51, 121.39, 125.86, 126.75, 128.03, 128.33, 128.88, 129.17, 137.02, 139.97, 140.46, 159.77. Anal. Calcd for $C_{37}H_{39}N_3O_2$: C, 79.68; H, 7.05; N, 7.53. Found: C, 79.70; H, 7.15; N, 7.53.

*4.2.5. (5R,15R)-6,14-Dibenzyl-5,15-diethyl-3,17-dioxa-6,14,23,24-tetraaza tricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12(24)19,21-hexaene (**4**).* To a stirred suspension of NaH (0.176 g, 7.35 mmol 96%) in dry THF (10 mL) under Ar, at 0 °C, was added dropwise to **3a** (1.0 g, 2.1 mmol) dissolved in THF (75 mL). After addition, the mixture was stirred at room temperature for 30 min then refluxed for 2.5 h. The reaction mixture was cooled to 0 °C, and 2,6-bis-(bromomethyl) pyridine (0.556 g, 2.1 mmol) dissolved in 70 mL of THF was added dropwise. After addition, the reaction mixture was stirred at rt for 1 h, and then refluxed for 58 h. After the reaction was completed, the solvent was evaporated under reduced pressure. The residue was thoroughly mixed with ice (10 g) and $CHCl_3$ (100 mL) and the phases were separated. The aqueous phase was washed twice with 100 mL portions of $CHCl_3$. The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was evaporated. The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc/TEA (85/10/5) to afford **4** (0.515 g, 43%) as a yellow oil TLC R_f=0.58. $[\alpha]_D^{30}$ +34.7 (*c* 1.75,$CHCl_3$); MALDI-TOF-MS: *m*/*z*=672.66 $(M+Ag)^+$; IR: ν 3070, 3025, 2962, 2929, 2871, 1600, 1504, 1452, 1361, 1162, 1105, 914, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm) 0.93 (t, 6H, *J*=7.2 Hz), 1.51–1.57 (m, 4H), 2.84–2.86 (m, 2H), 3.58–3.86 (m, 12H), 4.77 (s, 4H), 7.13 (d, 2H, *J*=8.0 Hz), 7.19–7.46 (m, 13H), 7.73 (t, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ (ppm) 11.69, 22.24, 54.75, 55.94, 59.97, 70.52, 73.78, 120.70, 120.95, 126.59, 128.06, 128.78, 136.05, 136.85, 140.82, 158.30, 159.69. Anal. Calcd for $C_{36}H_{44}N_4O_2$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.65; H, 7.95; N, 9.98.

*4.2.6. (4R,14R)-(−)-4,14-Dibenzyl-5,15-bis(propan-2-yl)-3,17-dioxa-6-14-23,24-tetra azatricyclo[17.3.1.1^{8,12}}tetracosa-l(23),8,10,12(24),19,21-hexaene (**5**).* Macrocycle **5** was prepared as described above for macrocycle **4** starting from 2-{benzyl[(6-{[benzyl(1-hydroxy-3-methylbutan-2-yl)amino]methyl]pyridin-2-yl)methyl]amino}-3-methylbutan-1-ol **3b** (1.0 g, 2.04 mmol), NaH (0.172 g, 7.14 mmol), and 2,6-bis-(bromomethyl)pyridine (0.540 g, 2.04 mmol). The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc/TEA (85:10:5) as an eluent to give pure **5** (0.450 g, 37%) as a clear oil TLC R_f=0.53. $[\alpha]_D^{26}$ +36.8 (*c* 3.8, $CHCl_3$); MALDI-TOF-MS: *m*/*z*=700.75 $(M+Ag)^+$; IR: ν 3063, 2961, 2876, 1600, 1458, 1355, 1259, 1151, 1099, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm) 0.91 (d, 6H, *J*=8.0 Hz), 0.96 (d, 6H, *J*=8.0 Hz), 1.86–1.92 (m, 2H), 2.45–2.49 (m, 2H), 3.62–3.93 (m, 12H), quartet of AB spin system δ_A: 4.76 and δ_B: 4.92 (4H, *J*=12.0 Hz), 7.19–7.39 (m, 14H), 7.52 (t, 1H, *J*=8.0 Hz) 7.72 (t, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ (ppm) 20.38, 21.18, 28.69, 55.05, 56.83, 63.55, 68.43, 73.59, 120.92, 120.96, 126.61, 128.06, 128.94, 136.13, 136.83, 140.69, 158.19, 159.52. Anal. Calcd for $C_{38}H_{48}N_4O_2$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.80; H, 8.20; N, 9.50.

*4.2.7. (4R,14R)-(−)-4,14-Dibenzyl-5,15-diphenyl-3,17-dioxa-6-14-23,24-tetraaza tricyclo[17.3.1.1^{8,12}}tetracosa-l(23),8,10,12(24),19,21-hexaene (**6**).* Macrocycle **6** was prepared as described above for macrocycle **4** starting from 2-{benzyl[(6-{[benzyl(2-hydroxy-1-phenylethyl)amino]methyl]pyridin-2-yl)methyl}amino}-2-phenylethan-1-ol **3c** (1.0 g, 1.79 mmol), NaH (0.151 g, 6.2 mmol), and 2,6-bis-(bromomethyl)pyridine (0.475 g, 1.79 mmol). The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc/TEA (85:10:5) as an eluent to give pure **6** (0.450 g, 38%) as a clear oil TLC R_f=0.26. $[\alpha]_D^{27}$ −58.2 (*c* 6, $CHCl_3$); MALDI-TOF-MS: *m*/*z*=796.88 $(M+Ag)^+$; IR: ν 3057, 3024, 2934, 1587, 1456, 1458, 1369, 1215, 1099, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm) 3.50–3.54 (m, 2H) quartet of AB spin system δ_A: 3.64 and δ_B: 3.80 (4H, *J*=16.0 Hz), 3.91–3.98 (m, 8H), quartet of AB spin system δ_A: 4.51 and δ_B: 4.68 (4H, *J*=12.0 Hz), 7.20–7.50 (m, 24H), 7.64 (t, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ (ppm) 55.75, 56.32, 63.77, 70.91, 73.72, 120.12, 120.93, 126.82, 127.19, 128.20, 128.73, 128.80, 136.25, 136.79, 139.92, 139.96, 157.98, 159.89. Anal. Calcd for $C_{46}H_{48}N_4O_2$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.21; H, 7.02; N, 8.15.

*4.2.8. (4R,14R)-(−)-5,6,14,15-Tetrabenzyl-3,17-dioxa-6-14-23,24-tetraaza tricyclo[17.3.1.1^{8,12}}tetracosa-l(23),8,10,12(24),19,21-hexaene (**7**).* Macrocycle **7** was prepared as described above for macrocycle **4** starting from 2-{benzyl[(6-{[benzyl(1-hydroxy-3-phenylpropan-2-yl)amino]methyl}pyridin-2-yl)methyl]amino}-3-phenylpropan-1-ol **3d** (1.0 g, 1.71 mmol), NaH (0.144 g, 6 mmol), and 2,6-bis-(bromomethyl)pyridine (0.453 g, 1.79 mmol). The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc/TEA (85:10:5) as an eluent to give pure **7** (0.540 g, 46%) as a clear oil TLC R_f=0.29. $[\alpha]_D^{26}$ +48.3 (*c* 6.3,$CHCl_3$); MALDI-TOF-MS: *m*/*z*=768.76 $(M+Ag)^+$; IR: ν 3057, 3024, 2928, 2857, 1600, 1496, 1452, 1220, 1113, 758 cm^{-1}. ^{1}H NMR (CD_3CN): δ (ppm) quartet of AB spin system (part of A: δ_A: 2.81 and 2.83, dd, 2H, *J*=7.6 Hz), (part of B: δ_B: 2.92 and 2.95, dd, 2H, *J*=7.6 Hz), 3.28–3.35 (m, 2H), 3.64–3.96 (m, 12H) quartet of AB spin system δ_A: 4.73 and δ_B: 4.80 (4H, *J*=12.0 Hz), 6.90 (d, 2H, *J*=8.0 Hz), 7.11 (t, 4H, *J*=4.0 Hz), 7.21–7.30 (m, 20H), 7.71 (t, 1H, *J*=8.0). ^{13}C NMR ($CDCl_3$): δ (ppm) 35.10, 54.75, 55.82, 60.07, 69.77, 73.72, 120.67, 120.90, 125.76, 126.61, 128.06, 128.10, 128.64, 129.44, 136.12, 136.86, 140.30, 140.38, 158.22, 159.37. Anal. Calcd for $C_{44}H_{44}N_4O_2$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.01; H, 6.80; N, 8.50.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.064.

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