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The enantiomeric recognition of chiral organic ammonium salts by chiral monoaza-15-crown-5 ether derivatives

Yılmaz Turgut,* Elif Şahin, Mahmut Toğrul and Halil Hoşgören

Faculty of Science, Department of Chemistry, University of Dicle, 21280 Diyarbakır, Turkey

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Abstract—Novel chiral monoaza-15-crown-5 ether derivatives **1** and **2** were prepared from L-phenylalaninol and L-leucinol, respectively. The effect of the substituent at the stereogenic center on chiral recognition and enantioselectivity were investigated. Binding constant (K), free-energy changes ($-\Delta G_0$), enthalpy change (ΔH), and entropy change (ΔS) values were determined with enantiomers of organic ammonium salts by a titration UV–vis method in $CHCl_3$.

1. Introduction

Host–guest chiral recognition is important in a variety of physical, chemical, and biological processes including sensing, purification, and resolution of enantiomers, asymmetric catalysis reactions, and single enantiomeric forms of amino acids and sugars.[1] Hence, the design, synthesis, and the use of molecules capable of enantiomeric recognition of other molecules are of great interest to workers in these fields. In particular, optically active macrocyclic receptors and their enantioselective recognition of chiral compounds have been attracting much attention.[2] Cram et al. first described in 1973 the syntheses and characterization of a number of chiral crown ethers capable of enantiomeric recognition toward primary ammonium salts.[3,4] The rapid development in the field of molecular recognition as applied to macrocycles was recognized by the awarding of Nobel Prizes in 1987 to three of its pioneers, Pedersen,[5] Lehn,[6] and Cram.[7] Since their pioneering work, enantiomeric recognition of chiral organic ammonium salts by chiral crown ethers has received much attention[8] while complexation studies of these macrocycles have been reviewed.[9–13]

Chirality derived from the readily accessible α-amino acids has been incorporated into the side chains of aza and diaza macrocyclic polyethers. Among the chiral macrocycles crown ethers, several azacrown ethers were synthesized from amino acids[14] and their enantiomeric recognition properties studied.[15,16]

We report herein the synthesis of chiral amino alcohol precursors from L-phenylalanine and L-leucine and two chiral monoaza-15-crown-5 ether derivatives. The host–guest interactions involving these chiral ligand and chiral organic ammonium salts were characterized. K_a, $-\Delta G_0$, ΔH, and ΔS values for these host–guest interactions are also reported.

2. Result and discussion

2.1. Synthesis

The syntheses of L-phenylalaninol and L-leucinol were accomplished in one step from L-phenylalanine and L-leucine according to procedures described in the literature.[17] The conversion of **1a** and **1b** to *N*-benzyl amino alcohol derivatives was carried out using our previously reported method.[18] The conversion of **2a** and **2b** to **3a** and **3b** was carried out at −20 °C, as shown in Scheme 1.

(*R*)- and (*S*)-enantiomers of $PhCH(CH_3)NH_3^+ClO_4^-$ and $1\text{-}NapCH(CH_3)NH_3^+ClO_4^-$ were prepared from $PhCH(CH_3)NH_2$ and $1\text{-}NapCH(CH_3)NH_2$, respectively. Tosylates were prepared according to a procedure previously reported.[19] Chiral host **1** was prepared from **3a** and tosylate, using sodium hydride as a base in THF. Host **2** was synthesized in the same way starting from **3b**. To obtain the product in a solid state (for easier

* Corresponding author. Tel.: +90-412-2488550; fax: +90-412-24880-39; e-mail: yturgut@dicle.edu.tr

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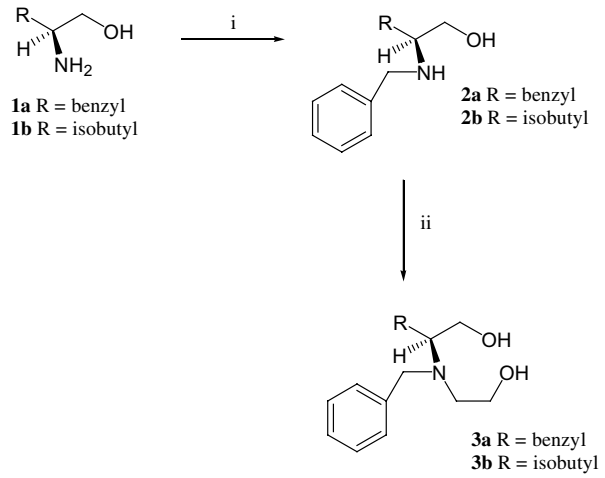


Scheme 1. Reagents and conditions: (i) $PhCH_2Cl$, Na_2CO_3, 110 °C, (ii) ethylene oxide.

isolation) $NaClO_4 \cdot H_2O$ (toxic) was added to macrocycle crown **1** and **2**. These macrocycles were then recovered from their complex form by column chromatography to give yellow oils in 46% and 61% yield, respectively, as shown in Scheme 2. Our previous studies[20] on the factors governing enantiomeric recognition of chiral organic ammonium salt by chiral aza-15-crown-5 ethers showed that the highest enantioselectivity can be expected when a host involving a benzo unit is on the ring. As a result, we turned to the synthesis of chiral aza-15-crown-5, **1**, and **2**, ethers starting from L-phenylalaninol and L-leucinol with effect of the substituent at the stereogenic center. The structures proposed for these chiral macrocycles and amino alcohols are consistent with data obtained from ^1H NMR, ^{13}C NMR, IR spectra, and elemental analyses.

2.2. Molecular recognition and UV–vis

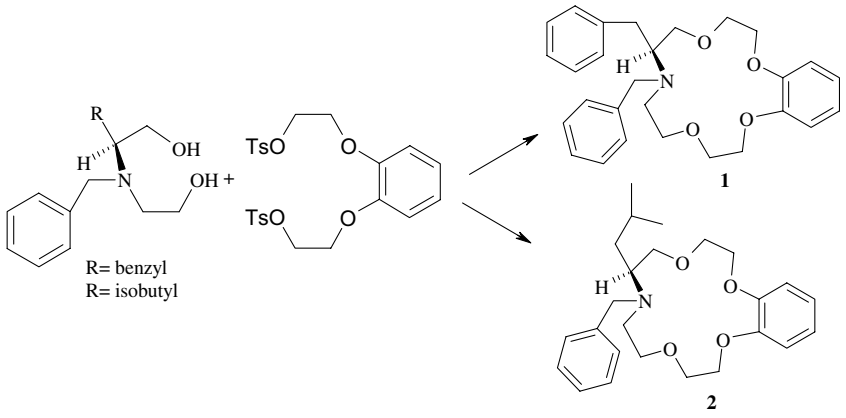
The main purpose of synthesizing these receptors is to study their molecular recognition for guest molecules. Molecular recognition can be characterized by various spectroscopic methods, such as ultraviolet visible (UV–vis), NMR, fluorescence, and infrared (IR), which are powerful tools used for the examination of the recognition ability of new chiral macrocycles.[1,21–23] UV–vis spectroscopy is a convenient and widely used method for the study of binding phenomena. When the receptor (or substrate) absorbs light at different wavelengths in the free and complexed states, the differences in the UV–vis spectra may suffice for the estimation of molecular recognition thermodynamics. In UV spectroscopic titration experiments, the addition of a varying concentration of guest molecules results in a gradual increase or decrease of characteristic absorptions of the host molecules. With the assumption of a 1:1 stoichiometry, the complexation of ammonium cations (G) with chiral azacrown ether type molecular (H) is expressed by Eq. 1:

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

Under the conditions employed herein, chiral organic ammonium perchlorate salts were selected as the guest molecules. The association constants of the supramolecular systems formed were calculated according to the modified Benesi–Hilderbrand equation, Eq. 2,[24] where $[H]_0$ and $[G]_0$ refer to the total concentration of crown ether and organic ammonium salt, respectively, $\Delta\varepsilon$ is the change in molar extinction co-efficient between the free and complexed crown ether and ΔA denotes the absorption changes of crown ether on the addition of organic ammonium salts.

$$[H]_0[G]_0/\Delta A = 1/K_a\Delta\varepsilon + [G]_0/\Delta\varepsilon \tag{2}$$

For all guest molecules examined, plots of calculated $[H]_0[G]_0/\Delta A$ values as a function of $[G]_0$ values gave excellent linear relationships, supporting the 1:1 complex formation. The binding constants (K_a) and free-energy changes ($-\Delta G^0$) of these hosts with guest molecules obtained from usual curve fitting analyses ($R > 0$, 9834) of observed absorbance changes are summarized in Table 1. The binding constant, K_a of the complexes of crown ethers **1** and **2** with organic ammonium salts were determined by the Benesi–Hilderbrand equation on the basis of the UV–vis spectrum of the complexes in $CHCl_3$ collected at four different temperatures. The thermodynamic parameters, ($-\Delta G^0$), (ΔH), and (ΔS) for the complex formation were determined from the van't Hoff plots of the K_a values with changes summarized in Table



Scheme 2. Reagents and conditions: NaH, THF, reflux, 50 h.

Table 1. Binding constants (K), the Gibbs free-energy changes ($-\Delta G_0$), enantioselectivities K_R/K_S, and $-\Delta G_0$ calculated from $-\Delta G_0$ for the complexation of (*RS*)-guest with the chiral host **1** and host **2** in $CHCl_3$ at 25 °C

Host	Guest[a]	K ($dm^3\ mol^{-1}$)	K_R/K_S	$-\Delta G_0$ ($kJ\ mol^{-1}$)	$\Delta\Delta G_0$[b] ($kJ\ mol^{-1}$)
1	(*R*)-PhEt	1.97×10^4	1.40	24.50	−0.83
	(*S*)-PhEt	1.41×10^4		23.67	
	(*R*)-NapEt	9.22×10^3	0.51	22.60	1.70
	(*S*)-NapEt	1.82×10^4		24.30	
2	(*R*)-PhEt	9.53×10^3	4.76	22.71	−1.73
	(*S*)-PhEt	4.77×10^3		20.98	
	(*R*)-NapEt	4.00×10^3	1.33	20.52	−0.32
	(*S*)-NapEt	3.00×10^3		20.20	

[a] PhEt: α-phenylethylamine perchlorate salts. NapEt: α-(-1-naphthyl)ethylamine perchlorate salts.
[b] $\Delta\Delta G_0 = -\Delta G_{0(R)} - \Delta G_{0(S)}$.

1. The typical UV spectral changes upon the addition of (*S*)-$PhCH(CH_3)NH_3^+ClO_4^-$ salt to **2** are shown in Figure 1 while typical plots are shown for the complexation of **2** with (*S*)-$PhCH(CH_3)NH_3^+ClO_4^-$ salt in Figure 2.

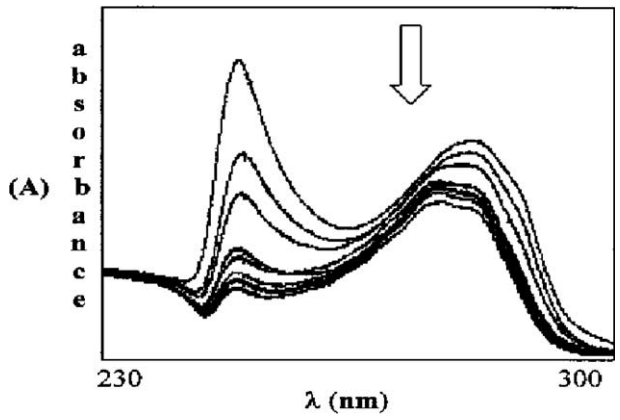


Figure 1. UV–vis spectra of **2** (2.0×10^{-4} mol dm^{-3}) in the presence of (*S*)-$PhCH(CH_3)NH_3^+ClO_4^-$ salt (5.0×10^{-5}–7.5×10^{-4} mol dm^{-3}).

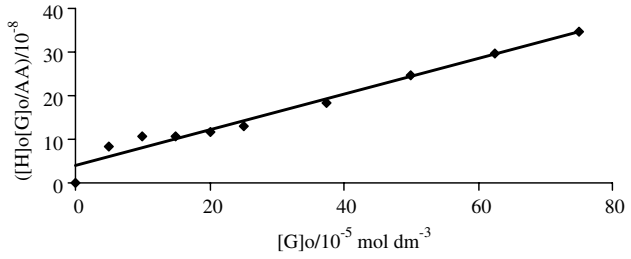


Figure 2. Typical plot of $[H]_0[G]_0/\Delta A$ versus $[G]_0$ for the host–guest complexation of **2** and (*S*)-$PhCH(CH_3)NH_3^+ClO_4^-$ salt in $CHCl_3$.

Determination of K values for chiral host–guest interactions provides information about the capability of the chiral hosts to recognize enantiomers of the chiral host under given sets of conditions. The correlation of the degree of recognition with the structural features of recognition with the structural features of the host–guest complexes is essential in understanding the origin of the chiral recognition. The thermodynamic data in Table 2 provides information that makes possible the identification and evaluation of the relationship between the chiral ligand and the ammonium cation structures and the degree of chiral recognition. Therefore, determination of ΔH and ΔS for crown ether-chiral ammonium salt interactions is desirable. A general trend among these values is that both ΔH and ΔS favor the formation of the complex, if one enantiomer of the guest is favored over the other by the chiral host in terms of both ΔH (more negative in value) and ΔS (less negative in value). Sometimes, the entropic contribution seemed to be more important than the enthalpy contribution. Among chiral host–guest systems, the ideal candidates would be those that showed relatively strong interaction and yet are sufficiently simple that synthetic modifications can be made easily. The choice of such systems should allow us to examine in a systematic manner the effect on the enantiomeric recognition of altering various structural features and environmental factors. We have shown that **1** and **2** azacrown ethers formed complexes of appreciable stability with primary ammonium cations and displayed good chiral recognition toward enantiomers of these guests. It has been found that[20] the highest enantioselectivity can be seen when the host containing a benzo unit on the ring of the chiral aza-15-crown-5 ethers. As a result, we synthesized the chiral aza-15-crown-5 ethers **1** and **2**, which include a benzo unit on the ring starting from L-phenylalaninol and L-leucinol, respectively. Macrocycle **1** differed from **2** in that the benzyl substituent on **1** is replaced by an isobutyl in **2**. From Table 1 and Figure 3, both 1-$NapCH(CH_3)NH_3^+ClO_4^-$ and $PhCH(CH_3)NH_3^+ClO_4^-$ salts form stable complexes with **1**. The stability constants of **1** with the (*R*)- and (*S*)-enantiomers of $PhCH(CH_3)NH_3^+ClO_4^-$ were found to be 1.97×10^4 and 1.41×10^4, respectively, the (*R*) form, 1.40 times more

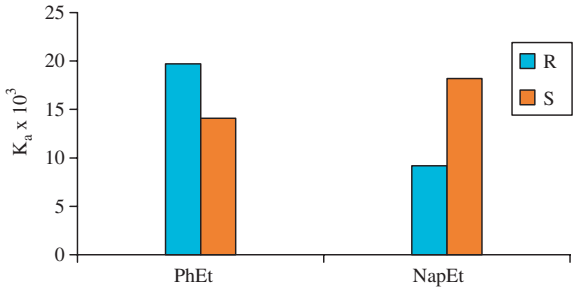


Figure 3. Bar plots of enantioselective recognition of $PhCH(CH_3)NH_3^+ClO_4^-$(PhEt) and 1-$NapCH(CH_3)NH_3^+ClO_4^-$ (NapEt) for **1**.

stable than the (*S*)-PhCH(CH_3)$NH_3^+ClO_4^-$ (K_R/K_S = 1.40). In the same way, **1** exhibited chiral recognition toward the enantiomers of 1-NapCH(CH_3)$NH_3^+ClO_4^-$ salt by forming a complex with the (*S*)-form of the guest, which was 0.51 times more stable than that formed with the (*R*) and $\Delta\Delta G_0 = 1.70\,kJ\,mol^{-1}$ in $CHCl_3$. In the case of **2**, from Table 1 and Figure 4, it can be seen that **2** has a greater enantioselectivity toward (*R*)-PhCH(CH_3)$NH_3^+ClO_4^-$ than (*S*)-PhCH(CH_3)$NH_3^+ClO_4^-$, which was 4.76 times more stable than that formed with the (*S*)- form ($\Delta\Delta G_0 = -1.73\,kJ\,mol^{-1}$). This discrimination could be due to the different interaction modes of the substituent on the guest with chiral barriers on the host.

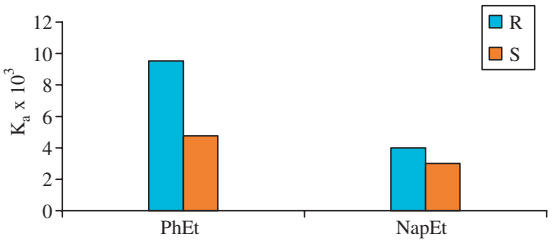


Figure 4. Bar plots of enantioselective recognition of PhCH(CH_3)$NH_3^+ClO_4^-$ (PhEt) and 1-NapCH(CH_3)$NH_3^+ClO_4^-$ (NapEt) for **2**.

The presence of a benzyl substituent on the stereogenic center as in the case of macrocycle **1**, results in recognition of (*R*)-PhCH(CH_3)$NH_3^+ClO_4^-$, (*S*)-PhCH(CH_3)$NH_3^+ClO_4^-$, and (*S*)-1-NapCH(CH_3)$NH_3^+ClO_4^-$ salts in good order but the observed enantioselectivity was low. The observed enantioselectivity toward (*R*)-PhCH(CH_3)$NH_3^+ClO_4^-$ increases in the case isobutyl substituent. In conclusion, it has been demonstrated that the substituent on the stereogenic center play a very important effect on the chiral recognition. It is also known that for enantiomeric recognition, the steric repulsion between the substituent on the stereogenic center and the substituent of ammonium cation has been found to be an important factor.[25] It is expected that the extent of enantiomeric recognition could be improved upon due to the bulkiness of the substituent at the stereogenic center.[1]

Thermodynamic parameters (ΔH, ΔS, $\Delta_{R-S}\Delta H$, and $\Delta_{R-S}\Delta S$) for the interaction of (*RS*)-α-phenylethylamine perchlorate and α-(1-naphthyl)ethylamine perchlorate salts with **1** and **2** in $CHCl_3$ are given in Table 2. Complexation of the chiral ammonium salts with **1** and **2** was exothermic in each case while the ΔS value was negative except in the case of (*R*)-PhCH(CH_3)$NH_3^+ClO_4^-$ for **1**, (*R*)-PhCH(CH_3)$NH_3^+ClO_4^-$, (*S*)-PhCH(CH_3)$NH_3^+ClO_4^-$, and (*S*)-1-NapCH(CH_3)$NH_3^+ClO_4^-$ for **2**. These facts indicate that the interaction of (*S*)-PhCH(CH_3)$NH_3^+ClO_4^-$ ($\Delta_{R-S}\Delta H = 15.22$), (*RS*)-1-NapCH($CH_3$)$NH_3^+ClO_4^-$ ($\Delta_{R-S}\Delta H = 8.60$) with the **1** are enthalpy driven. The enthalpy discrimination values for **2** can be seen in Table 2, and are as follows: $\Delta_{R-S}\Delta H$ of (*RS*)-PhCH(CH_3)$NH_3^+ClO_4^-$ 7.97 and $\Delta_{R-S}\Delta H$ of (*RS*)-1-NapCH(CH_3)$NH_3^+ClO_4^-$ $-17.37\,kJ\,mol^{-1}$ for **2**. These results indicate that the increased negative enthalpy discrimination arises from the interaction between **2** and guest cations. On the other hand, both enthalpy and entropy changes contribute to the increased (*R*)-1-NapCH(CH_3)$NH_3^+ClO_4^-$ binding constant with **2**, the much larger negative ΔH values probably arise from a strong interaction between guest and the nitrogen atoms of the hosts.

The reason behind entropy values being positive with certain guests while negative with others can be explained by the reaction enthalpy. As the difference between enthalpy increases, the reaction entropy will become negative. As for enantiomeric recognition, both enthalpy and entropic changes contribute. In the case of host **1**, the entropy for the formation of the complexes is negative in the most cases, indicating unfavorable entropic contribution to the formation of complexes. As in the case of host **2**, the entropy for the formation of the complexes is positive in the most cases, indicating favorable entropic contribution to the formation of complexes.

3. Experimental

3.1. General information

All chemicals were reagent grade unless otherwise specified. L-Phenylalanine, L-leucine, and (*RS*)-α-phenyl ethylamine and α-(1-naphthyl)ethylamine were purchased from Fluka chemical company. Silica gel 60 (Merck, 0.040–0.063 mm) and silica gel/TLC-cards

Table 2. Thermodynamic parameters for complexation of host **1** and host **2** with (*RS*)-guest in $CHCl_3$

Host	Guest[a]	ΔH ($kJ\,mol^{-1}$)	$\Delta_{R-S}\Delta H$[b]	ΔS ($J\,mol^{-1}K^{-1}$)	$\Delta_{R-S}\Delta S$[c]
1	(*R*)-PhEt	−9.69	15.22	49.58	53.74
	(*S*)-PhEt	−24.91		−4.16	
	(*R*)-NapEt	−31.79	8.60	−30.54	23.30
	(*S*)-NapEt	−40.39		−53.84	
2	(*R*)-PhEt	−19.67	−5.40	10.13	−5.74
	(*S*)-PhEt	−14.27		15.87	
	(*R*)-NapEt	−23.00	−17.37	−8.21	−57.11
	(*S*)-NapEt	−5.63		48.90	

[a] Same as a in Table 1.
[b] $\Delta_{R-S}\Delta H = \Delta H_R - \Delta H_S$.
[c] $\Delta_{R-S}\Delta S = \Delta S_R - \Delta S_S$.

(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 Mattson 1000 FTIR model spectrometer. Elemental analyses were performed 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.

3.2. UV spectral measurements

The abilities of crown ethers to coordinate to chiral organic ammonium salts were investigated using UV spectroscopic titration.[26] The UV–vis spectra were measured at 288, 298, 308, and 318 K with a thermostated cell compartment by Shimadzu 160 UV spectrometer. The same concentrations of guest solution were added to the sample cell and reference cell. The maximum wavelength was 242 and 277 nm for **1** and **2** in $CHCl_3$. The concentrations of the host are 2.0×10^{-4} mol dm^{-3} with the increasing concentration of the added guest.

3.3. (*S*)-*N*-Benzyl-2-amino-3-phenyl-1-propanol 2a

(*S*)-Phenylalaninol (33 g, 0.218 mol), benzyl chloride (6.96 g, 0.055 mol), and anhydrous Na_2CO_3 (5.8 g, 0.055 mol) were placed in a 250 mL two-necked round bottomed flask. The mixture was stirred at 110 °C for 12 h under dry N_2. The mixture was then cooled and $CHCI_3$ (150 mL) added to the mixture and refluxed for 2 h. The $CHCl_3$ layer was separated from the solid phase. The solid phase was re-extracted with $CHCI_3$ (3×150 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated. The product was then distilled under reduced pressure and the residue recrystallized from toluene to give 10 g of **2a** (77%), bp 165–167 °C/0.8 mmHg, mp 54–56 °C; $[\alpha]_D^{20} = -11.1$ (*c* 1.2, MeOH); IR (KBr) 3355, 3289, 3084, 3057, 3026, 2919, 1495, 1451, 1379, 1344, 1114, 1060, 1028, 959, 919, 885, 854, 742, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (br, 2H), 2.76–3.00 (m, 3H), 3.35–3.80 (m, 4H), 7.17–7.34 (m,10H); ^{13}C NMR ($CDCl_3$) δ 38.51, 51.55, 59.84, 62.95, 126.85, 127.50, 128.44, 128.88, 128.99, 129.62, 138.92, 140.42. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 79.60; H, 7.80; N, 5.78.

3.4. (*S*)-*N*-Benzyl-2-amino-4-methyl-1-pentanol 2b

This compound was prepared as described above for **2a**, using **1b** (21 g, 0.181 mol), benzyl chloride (5.72 g, 0.045 mol), and anhydrous Na_2CO_3 (4.65 g, 0.045 mol). The product was distilled and crystallized from petroleum ether–benzene to give 8 g of **2b** (88%), bp 123–125 °C/0.8 mmHg, mp 72–73 °C; $[\alpha]_D^{20} = +33.5$ (*c* 1, MeOH); IR (KBr) 3294, 3070, 3024, 2960, 2928, 2909, 1503, 1464, 1387, 1348, 1271, 1208, 1092, 1060, 1022, 970, 880, 841, 783, 746, 707, 617 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90–0.96 (dd, 6H), 1.25–1.31 (m, 1H), 2.40–1.67 (m, 2H), 2.76–2.78 (m,1H) 3.28–3.70 (m, 2H), 3.77–3.85 (dd, 2H), 7.26–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.13, 25.37, 41.65, 56.62, 63.58, 77.81, 77.46, 127.53, 128.56, 128.90, 140.46. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.44; H, 10.20; N, 6.60. Found: C, 75.36; H, 10.36; N, 6.76.

3.5. (*S*)-*N*-Benzyl-4-benzyl-3-aza-1,5-propanediol 3a

A solution of **2a** (10 g, 0.04 mol) in 250 mL methanol was cooled to −20 °C in a 100 mL flask. Ethylene oxide (2 mL, 0.04 mol) in 10 mL of methanol at 20 °C was added to the solution dropwise at −20 °C. The mixture was kept at −20 °C during addition in deepfreeze. After addition the mixture was stirred for 24 h at −20 °C and a further 24 h at +4 °C. The mixture was kept for 1 day at room temperature in a closed flask. Methanol was evaporated in rotary evaporator. The product was purified by distillation under reduced pressure to give 11 g of **3a** (94%), bp 188–192 °C/0.8 mmHg; $[\alpha]_D^{20} = -13.2$ (*c*1, MeOH); IR (KBr) 3363, 3087, 3064, 3026, 2941, 1602, 1491, 1453, 1369, 1135, 1033, 916, 869, 745, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.46–3.92 (m, 11H), 7.14–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 33.31, 51.40, 55.67, 60.46, 61.77, 63.35, 126.63, 127.64, 128.93, 128.99, 129.26, 129.51, 139.92, 140.18. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.70; H, 8.00; N, 4.89. Found: C, 75.79; H, 8.07; N, 4.91.

3.6. (*S*)-*N*-Benzyl-4-hydroxymethyl-3-aza-6-methyl-heptane-1-ol 3b

Prepared as described for **3a**, using **2b** (10 g, 0.049 mol), ethylene oxide (2.2 mL, 0.049 mol). Yield 10 g (83%), bp 168–170 °C/0.8 mmHg; $[\alpha]_D^{20} = +35.6$ (*c* 1, MeOH), IR (KBr) 3358, 3060, 3024, 2960, 1599, 1496, 1478, 1458, 1362, 1162, 1112, 1066, 918, 867, 732, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88–0.92 (dd, 6H), 1.08–1.13 (m, 1H), 1.38–1.44 and 1.52–1.56 (m, 2H), 2.54–2.58 (m, 1H), 2.77–2.87 (m, 2H), 3.37–3.59 (m, 6H) 7.28–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.77, 24.06, 25.82, 35.60, 51.42, 55.19, 59.14, 60.50, 62.37, 127.57, 128.86, 129.24, 140.37. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.71; H, 9.96; N, 5.58. Found: C, 71.70; H, 9.89; N, 5.60.

3.7. (*S*)-2-Benzyl-*N*-benzyl-4,7,10,13-tetraoxa-8,9-benzo-1-azacyclopentadec-8-ene 1

To a suspension of NaH (1.46 g, 0.048 mol, %80 in mineral oil) in 100 mL dry THF at 0 °C was added a solution of diol **3a** (3.5 g, 0.012 mol) in 250 mL of THF. The reaction mixture was refluxed for 2 h. After the reaction had cooled to 0 °C, a solution of tosylate (6.19 g, 0.012 mol) in 250 mL of THF was slowly added. The suspension was refluxed for 50 h. The solvent was evaporated and 100 mL of water was added to the residue. The mixture was extracted with CH_2Cl_2 (3×150). The combined organic layers were washed with 100 mL

of water again, dried on anhydrous Na_2SO_4, and the solvent evaporated. The crude product was purified by flash column chromatography on silica gel (eluent: triethylamine/ethyl acetate/petroleum ether 60–80 = 3:17:80) to give 2.5 g (46%) of an oil; $[\alpha]_D^{20} = -33$ (*c* 1, $CHCl_3$), IR: *v* 3064, 3030, 2926, 2865, 1649, 1601, 1497, 1458, 1370, 1251, 1133, 1045, 927, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81–2.93 (m, 3H), 3.15–3.28 (m, 2H), 3.63–3.91 (m, 10H), 4.15–4.21 (m, 4H), 6.95–6.99 (m, 4H) 7.19–7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) 34.52, 50.66, 57.01, 62.35, 69.13, 69.82, 69.93, 70.04, 72.02, 72.86, 120.53, 121.69, 126.16, 127.03, 128.49, 128.62, 128.87, 129.77, 141.06, 141.34. Anal. Calcd for $C_{28}H_{33}NO_4$: C, 75.00; H, 7.43; N, 3.30. Found: C, 75.02; H, 7.62; N, 3.34.

3.8. (*S*)-2-Isobutyl-*N*-benzyl-4,7,10,13-tetraoxa-8,9-benzo-1-azacyclopentadec-8-ene 2

This compound was prepared in similar manner to **1** using NaH (2.15 g, 0.0715 mol), **3b** (4 g, 0.021 mol), and tosylate (10.62 g, 0.021 mol). The crude product was purified by flash column chromatography on silica gel (eluent: triethylamine/ethyl acetate/petroleum ether 60–80 = 3:17:80), yield was obtained as an oil 4 g (61%); $[\alpha]_D^{20} = -11.6$ (*c* 1.4, $CHCl_3$), IR: *v* 3070, 3031, 2940, 2877, 1592, 1503, 1458, 1362, 1259, 1227, 1131, 1053, 938, 783, 739, 707 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88–0.95 (m, 6H), 1.21–1.81 (m, 3H), 2.86–3.13 (m, 3H), 3.62–3.88 (m, 10H), 4.12–4.20 (m, 4H), 6.90–6.98 (m, 4H), 7.22–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.99, 23.71, 25.39, 38.47, 50.63, 55.99, 58.34, 69.32, 69.88, 69.97, 70.95, 71.93, 73.80, 113.85, 121.63, 126.99, 128.48, 129.00, 141.71, 149.43. Anal. Calcd for $C_{25}H_{35}NO_4$: C, 72.64; H, 8.47; N, 3.30. Found: C, 72.40; H, 8.10; N, 3.10.

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References and notes

1. Izatt, R. M.; Wang, T.; Hathaway, J. K.; Zhang, X. X.; Curtis, J. C.; Bradshaw, J. S.; Zhu, C. Y. *J. Inc. Phenom. Mol. Recognit. Chem.* **1994**, *17*, 157–175.
2. Zhau, H. W.; Hua, W. T. *J. Org. Chem.* **2000**, *65*, 2933–2938.
3. Kyba, E. P.; Koga, K.; Siegel, M. G.; Sousa, L. R.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692.
4. Stoddart, J. F. Chiral Crown Ethers. In *Topics in Streochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1988; Vol. 17, p 207.
5. Pedersen, C. J. *J. Inc. Phenom.* **1988**, *6*, 337.
6. Lehn, J.-M. *J. Inc. Phenom.* **1988**, *6*, 351.
7. Cram, D. J. *J. Inc. Phenom.* **1988**, *6*, 397.
8. Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313–3361.
9. Pedersen, C. J. In *Synthetic Multidentate Macrocyclic Compounds*; Izatt, R. M., Christensen, J. J., Eds.; Academic: New York, 1978; p 21.
10. Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J.; Sen, P. *Chem. Rev.* **1985**, *85*, 271.
11. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.
12. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2559.
13. Bradshaw, J. S.; Huszthy, P.; Mcdaniel, C. W.; Oue, M.; Zhu, C. Y.; Izatt, R. M. *J. Coord. Chem.* **1992**, *27*, 105–114; Izatt, R.M.; Zhu, C.Y.; Huszthy, P.; Bradshaw, J. S. Enantiomeric Recognition in Macrocycle-Primary Ammonium Cation Systems. In *Crown Ethers: Toward Future Applications*; Cooper. S. R., Ed.; New York, 1993; Chapter 12.
14. Joly, J. P.; Schröder, G. *Tetrahedron Lett.* **1997**, *38*, 8197–8198.
15. Chadwick, D. J.; Cliffe, I. A.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1981**, 992–994.
16. Chadwick, D. J.; Cliffe, I. A.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1707–1717.
17. Marc, J.; McKennon, A.; Meyers, I. *J. Org. Chem.* **1993**, *58*, 3568–3571.
18. Özbey, S.; Hoşgören, H.; Turgut, Y.; Topal, G. *J. Inc. Phenom. Macrocycl. Chem.* **2001**, *39*, 315–320.
19. Topal, G.; Demirel, N.; Toğrul, M.; Turgut, Y.; Hoşgören, H. *J. Heterocycl. Chem.* **2001**, *38*, 281.
20. Turgut, Y.; Hoşgören, H. *Tetrahedron: Asymmetry* **2003**, *14*, 3815–3818.
21. Samu, E.; Huszthy, P.; Horvath, G.; Szöllosy, A.; Neszmelyi, A. *Tetrahedron: Asymmetry* **1999**, *10*, 3615–3626.
22. Pietraszkiewicz, M.; Kozbial, M.; Pietraszkiewicz, O. *J. Membr. Sci.* **1998**, *138*, 109–113.
23. Yuan, Y.; Gao, G.; Jiang, Z.-L.; You, J.-S.; Zhou, Z.-Y.; Yuan, D.-Q.; Xie, R.-G. *Tetrahedron* **2002**, *58*, 8993–8999.
24. (a) Polster, J.; Lachman, H. *Spectrometric Titrations*; VCH: Wienheim, 1989; (b) Connors, K. A. *Binding Constants. The Measurement of Molecular Complex*; Wiley: New York, 1987; (c) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.
25. Davidson, R. B.; Bradshaw, J. S.; Jones, B. A.; Dalley, N. K.; Christensen, J. J.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1984**, *49*, 353.
26. Examples of the UV–vis titremetric method being used in molecular recognition: (a) Pietraszkiewicz, M.; Kozbial, M.; Pietraszkiewicz, O. *J. Membr. Sci.* **1998**, *138*, 109–113; (b) Peng, X.-b; Huang, J.-W.; Li, T.; Ji, L.-N. *Inorg. Chim. Acta* **2000**, *305*, 111–117; (c) Chen, X.; Du, D.-M.; Hua, W.-T. *Tetrahedron: Asymmetry* **2003**, *14*, 999–1007; (d) Yuan, Y.; Gao, G.; Jiang, Z.-L.; You, J.-S.; Zhou, Z.-Y.; Yuan, D.-Q.; Xie, R.-G. *Tetrahedron* **2002**, *58*, 8993–8999, and references cited therein.