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Enantiomeric Recognition of D- and L-Amino Acid Methyl Ester Hydrochlorides by New Chiral *Bis*-pyridino-18-crown-6 Substituted with Urea, and Diphenyl Groups

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Abstract

The article reports the synthesis and chiral recognition properties of a new chiral *bis*-pyridino-18-crown-6 (**7**), having urea, diphenyl, and allyloxy groups. The chiral *bis*-pyridino-18-crown-6 was prepared by a thirteen-steps procedure from the commercially available (*S*)-(+)-mandelic acid and chelidamic acid. The association constants (K_a) (1.33×10^3–3.20×10^3) for enantiomeric recognition of D- and L-amino acid methyl ester hydrochlorides using the chiral *bis*-pyridino-18-crown-6 have been examined by ^{1}H-NMR titration method in $CDCl_3$ at 25 °C. The chiral *bis*-pyridino-18-crown-6 showed higher association constants for the D-series amino acid methyl ester (D-AlaOMe, D-LeuOMe, D-MetOMe) hydrochlorides as compared to the corresponding L-series (L-AlaOMe, L-LeuOMe, L-MetOMe) hydrochlorides.

Introduction

Molecular recognition exists in many biochemical procedures including antibody–antigen interactions, biocatalysis reactions, the DNA double helix, and the use of single enantiomeric forms of amino acids and sugars in metabolic pathways. Therefore, the chiral macrocyclic ligands capable of the selective recognition of other species have been of great interest for the investigations of catalysis [1, 2], separations [3, 4], enzyme mimics [5–7], and other areas involving chiral molecular recognition [8]. Much attention has been paid to the study of enantiomeric recognition of amines and protonated amines by chiral macrocyclic ligands since many of these compounds are basic building blocks of biological molecules [9]. In 1973, Cram *et al*. first described the syntheses and characterization of a number of chiral crown ethers capable of enantiomeric recognition toward primary ammonium salts [10]. Since the pioneering work of Pedersen [11], Lehn [12], and Cram [13], enantiomeric recognition of chiral organic ammonium salts by chiral crown ethers has received much attention [9, 14, 15].

Our interest has been focused on the enantiomeric recognition of amino acids utilizing synthetic chiral crown ether. We report herein the synthesis of a new chiral receptor (*S*,*S*)-**7**, *bis*-pyridino-18-crown-6, substituted with urea, diphenyl, and allyloxy groups, and its enantiomeric recognition of different α-amino acid methyl ester hydrochlorides (D-AlaOMe, L-AlaOMe, D-LeuOMe, L-LeuOMe, D-MetOMe, L-MetOMe) by ^{1}H-NMR titration method in $CDCl_3$ at 25 °C.

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Experimental

General information

^{1}H-NMR, and ^{13}C-NMR spectra were recorded on Varian Unity Plus 5 (500 MHz), and Varian Gemimi 200 (200 MHz). Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 mass spectrometer under fast atom bombardment (FAB) conditions with NBA as the matrix in the Korea Basic Science Institute (Daegu, Korea). Flash column chromatography was performed using E. Merk silica gel (60, particle size 0.040–0.063 mm). All reactions were carried out under an argon atmosphere with dry solvent under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), and diethyl ether were distilled from sodium/benzophenone ketyl immediately prior to use and methylene chloride (CH_2Cl_2) was dried from calcium

hydride. All chemicals were reagent grade unless otherwise specified.

The 7-{[2,6-*bis*(iodomethyl)-4-pyridinyl]-oxy}heptanenitrile (**14**) and diethyl 4-(alloxy)-2,6-pyridinedicaboxylate (**9**) were prepared using our previously reported methods [16, 17]. The D-, and L-amino acid methyl ester hydrochlorides were obtained from Aldrich Chemical Co. and used without purification in this study: D-alanine methyl ester hydrochloride (D-AlaOMe), L-alanine methyl ester hydrochloride (L-AlaOMe), D-leucine methyl ester hydrochloride (D-LeuOMe), L-leucine methyl ester hydrochloride (L-LeuOMe), D-methionine methyl ester hydrochloride (D-MetOMe), L-methionine methyl ester hydrochloride (L-MetOMe).

Synthesis

*4-(Allyloxy)-2,6-bis({[(2S)-2-(methoxymethoxy)-2-phenylethyl]oxy}methyl)pyridine (**3**)*

To a stirred mixture of NaH (2.26 g, 60% suspension in mineral oil, 47.19 mmol) and DMF (10 ml) at 0 °C under Ar was added dropwise (2*S*)-2-(methoxymethoxy)-2-phenylethaol (**2**) (6.53 g, 15.73 mmol) dissolved in DMF (30 ml). The mixture was stirred at room temperature for 10 min, and then heated at 90 °C for 3 h. The mixture was cooled to 0 °C and treated with 4-(allyloxy)-2,6-*bis*(iodomethyl)pyridine (**13**) (5.73 g, 31.47 mmol) dissolved in DMF (60 ml). The mixture was stirred for 10 min at 0 °C, for 10 min at room temperature, and then for 24 h at 90 °C. The mixture was extracted with ethyl acetate (3×80 ml) and water (50 ml). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give **3** (4.5 g, 61%) as a pale brown oil (R_f 0.29, SiO_2, EtOAc–Hexane = 1:1). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.4 (s, 6H), 3.62 (d, 2H, J = 6.59 Hz), 3.68 (d, 2H, J = 8.2 Hz), 3.75 (d, 2H, J = 6.59 Hz), 3.84 (d, 2H, J = 8.2 Hz), 4.50–4.74 (m, 4H), 4.80–4.92 (m, 4H), 5.29 (d, 1H J = 6.9 Hz), 5.37 (d, 1H, J = 11.5 Hz), 5.96–6.06 (m, 1H), 6.80 (s, 2H), 7.10–7.37 (m, 10H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 55.47, 68.5, 70.6, 74.6, 79.9, 95.5, 102.3, 116.7, 125.1, 127.2, 127.9, 132.8, 142.3, 159.5, 164.5; HRMS (FAB, NBA) calcd 524.2648 for $C_{30}H_{38}NO_7$ $(M + H)^+$, found 524.2654.

*(1S)-2-{[4-(Allyloxy)-6({[(2S)-2-hydroxy-2-phenylethyl]oxy-}methyl)-2-pyridinyl]methoxy}-1-Phenylethanol (**4**)*

To a stirred solution of compound **3** (1.8 g, 3.32 mmol) in THF (40 ml) was added 10% aquous HCl (5 ml) at room temperature. The reaction mixture was heated at 50 °C for 5 h. The resulting suspension was treated with saturated aqueous $NaHCO_3$ solution (20 ml), and extracted with CH_2Cl_2 (3×60 ml). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give **4** (0.9 g, 62%) as white solids (R_f 0.25, SiO_2, EtOAc-Hexane = 1:1). Mp: 131 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.65 (d, 2H, J = 7.9 Hz), 3.83 (d, 2H, J = 7.9 Hz), 4.57 (d, 2H, J = 3.3 Hz), 4.64–4.99 (m, 6H), 5.02 (d, 2H, J = 1.6 Hz), 5.38 (d, 1H, J = 6.9 Hz), 5.43 (d, 1H, J = 11.5 Hz), 5.96–6.02 (m, 1H), 6.69 (s, 2H), 7.22–7.40 (m, 10H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 68.4, 72.5, 73.6, 74.2, 102.7, 118.2, 126.3, 127.5, 128.7, 135.4, 143.5, 159.2, 164.69; HRMS (FAB, NBA) calcd 436.2124 for $C_{26}H_{30}NO_5$ $(M + H)^+$, found 436.2124.

*7-{[(5S,15S)-21-(Allyloxy)-5,15-diphenyl-3,6,14,17-tetraoxa-23,24-diazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8(24),9,11,19,21-hexaen-10-yl]oxy}heptanenitrile (**5**)*

To a stirred mixture of NaH (0.16 g, 60% suspension mineral oil, 3.30 mmol) in THF (30 ml) at 0 °C under Ar was added diol **4** (0.5 g, 1.10 mmol) in THF (40 ml). The reaction mixture was stirred for 10 min at room temperature, and refluxed at 80 °C for 3 h under argon. After stirring for 3 h, the mixture was cooled to 0 °C, and treated with 7-{[2,6-*bis*(iodomethyl)-4-pyridinyl]oxy}heptanenitrile (**14**) [11] (0.53 g, 1.10 mmol) in THF (40 ml) over 1 h. After stirring at 0 °C for 1 h, and at room temperature for 48 h, the reaction mixture was concentrated under reduced pressure, and diluted with methylene chloride (60 ml) and water (20 ml) and extracted with methylene chloride (3×60 ml). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give **5** (0.35 g, 48%) as a yellow oil (R_f 0.27, SiO_2, 5% MeOH–CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24–1.76 (m, 8H), 2.37 (t, 2H, J = 6.9 Hz), 3.63 (d, 2H, J = 13.1 Hz), 3.69–3.94 (m, 4H), 4.04 (t, 2H, J = 6.9 Hz), 4.36 (d, 2H, J = 13.1 Hz), 4.40–4.78 (m, 8H), 5.02 (d, 2H, J = 1.6 Hz), 5.38 (d, 1H, J = 6.9 Hz), 5.43 (d, 1H, J = 11.5 Hz), 5.96–6.02 (m, 1H), 6.69 (s, 2H), 7.22–7.40 (m, 10H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ 16.7, 24.1, 25.7, 28.4, 28.9, 29.7, 67.9, 73.3, 75.2, 77.8, 78.5, 102.5, 107.0, 118.5, 125.8, 127.8, 128.3, 132.8, 139.3, 157.2, 160.2, 168.2; HRMS (FAB, NBA) calcd 677.8284 for $C_{41}H_{48}N_3O_6$ $(M + H)^+$, found 677.8257.

*6-{[(5S,15S)-21-(Allyloxy)-5,15-diphenyl-3,6,14,17-tetraoxa-23-azatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8(24),9,11,19,21-hexaen-10-yl]oxy}-1-hexanamine (**6**)*

To a stirred solution of 0.32 g (0.48 mmol) of nitrile compound **5** in of CH_2Cl_2 (5 ml) at 0 °C under Ar was added, drop by drop, 0.016 g (0.42 mmol) of $LiAlH_4$ in dry diethyl ether (10 ml). After addition, the mixture was stirred for 2 h at room temperature. The resulting mixture was quenched by saturated aqueous NH_4Cl (10 ml) at 0 °C, and extracted with diethyl ether (3×40 ml). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced

pressure. The residue was purified by flash chromatography to give **6** (0.18 g, 56%) as a colorless oil (R_f 0.27, SiO_2, 15% MeOH–CH_2Cl_2). ^{1}H-NMR (200 MHz, DMSO-d_6) δ1.23–1.73 (m, 8H), 2.83 (t, 2H, J = 6.9 Hz), 3.65 (d, 2H, J = 13.1 Hz), 3.73–3.97 (m, 4H), 4.39 (d, 2H, J = 13.1 Hz), 4.45–4.82 (m, 8H), 5.33 (d, 1H, J = 6.9 Hz), 5.45 (d, 1H, J = 11.5 Hz), 5.98–6.03 (m, 1H), 6.59 (s, 2H), 6.86 (s, 2H), 7.26–7.34 (m, 10H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 25.3, 27.4, 28.8, 29.6, 34.6, 42.5, 68.1, 68.9, 73.4, 75.4, 76.6, 77.9, 102.7, 107.9, 118.7, 126.2, 127.9, 128.9, 132.4, 140.2, 158.3, 160.5, 168.6; HRMS (FAB, NBA) calcd 668.3525 for $C_{40}H_{50}N_2O_6$ (M + H)$^+$, found 668.3548.

N-(7-{[(5S,15S)-21-(Allyloxy)-5,15-diphenyl-3,6,14,17-tetraoxa-23,24-diazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8(24),9,11,19,21-hexaen-10-yl]oxy}heptyl)-N′-ethylurea (**7**)

To a stirred solution of amine **6** (1.10 g, 1.65 mmol) in methylene chloride (10 ml) 0 °C under Ar was added ethyl isocyanate (0.35 g, 1.65 mmol) in methylene chloride (5 ml). The mixture was stirred at room temperature for 8 h, and concentrated under reduced pressure. The residue was purified by flash chromatography to give **7** (0.70 g, 57%) as a colorless oil (R_f 0.34, SiO_2, 10% MeOH–CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.10–1.14 (m, 3H), 1.27–1.36 (m, 4H), 1.44 (m, 2H), 1.43–1.47 (m, 2H), 1.48–1.50 (m, 2H), 1.75–1.77 (m, 2H), 3.14–3.21 (m, 4H), 3.69 (d, 2H, J = 7.9 Hz), 3.91–3.97 (m, 4H), 4.31 (d, 2H, J = 10.9 Hz), 4.57 (d, 2H, J = 10.9 Hz), 4.61–4.67 (m, 6H), 4.68 (s, 2H), 5.47–5.34 (dd, 2H, J = 8.8, 15 Hz), 6.07–6.17 (m, 1H), 6.67 (s, 1H), 6.87 (s, 1H), 7.47–7.34 (m, 10H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 15.5, 25.7, 26.72, 28.7, 28.9, 30.1, 35.1, 40.3, 67.8, 68.6, 71.2, 73.2, 75.1, 79.7, 107.36, 118.3, 126.9, 127.8, 128.5, 132.1, 138.92, 158.48, 159.71, 165.89, 166.16; HRMS (FAB, NBA) calcd 739.3993 for $C_{43}H_{55}N_4O_7$ (M + H)$^+$, found 739.3925.

4-(Allyloxy)-2,6-bis(hydroxymethyl)pyridine (**11**)

A solution of diethyl 4-(allyloxy)-2,6-pyridinedicarboxylate (**9**) (1.01 g, 3.40 mmol) in ethanol (40 ml) was added dropwise to a suspension of $NaBH_4$ (0.38 g, 10.21 mmol) at 0 °C under Ar. The reaction mixture at 0 °C was treated with $CaCl_2$ (0.37 g, 3.40 mmol) over 20 min. After stirring at room temperature for 4 h, the reaction mixture was diluted with ethyl acetate (70 ml) and water (50 ml) and the aqueous phase was extracted with ethyl acetate (3×70 ml). The combined organic layer was washed with brine (40 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give **11** (0.45 g, 67%) as white solids (R_f 0.25, SiO_2, EtOAc–Hexane = 1:1). Mp: 97 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.47–4.51 (m, 2H), 4.70 (m, 4H), 5.24 (d, 1H, J = 6.9 Hz), 5.35 (d, 1H, J = 11.5 Hz), 5.95–6.05 (m, 1H), 7.20 (s, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 63.2. 68.4, 103.5, 117.5, 131.5, 158.7, 165.2; MS (FAB, NBA) m/z 196.18 (M + H)$^+$, calcd 196.09.

4-(Allyloxy)-2,6-bis(iodomethyl)pyridine (**13**)

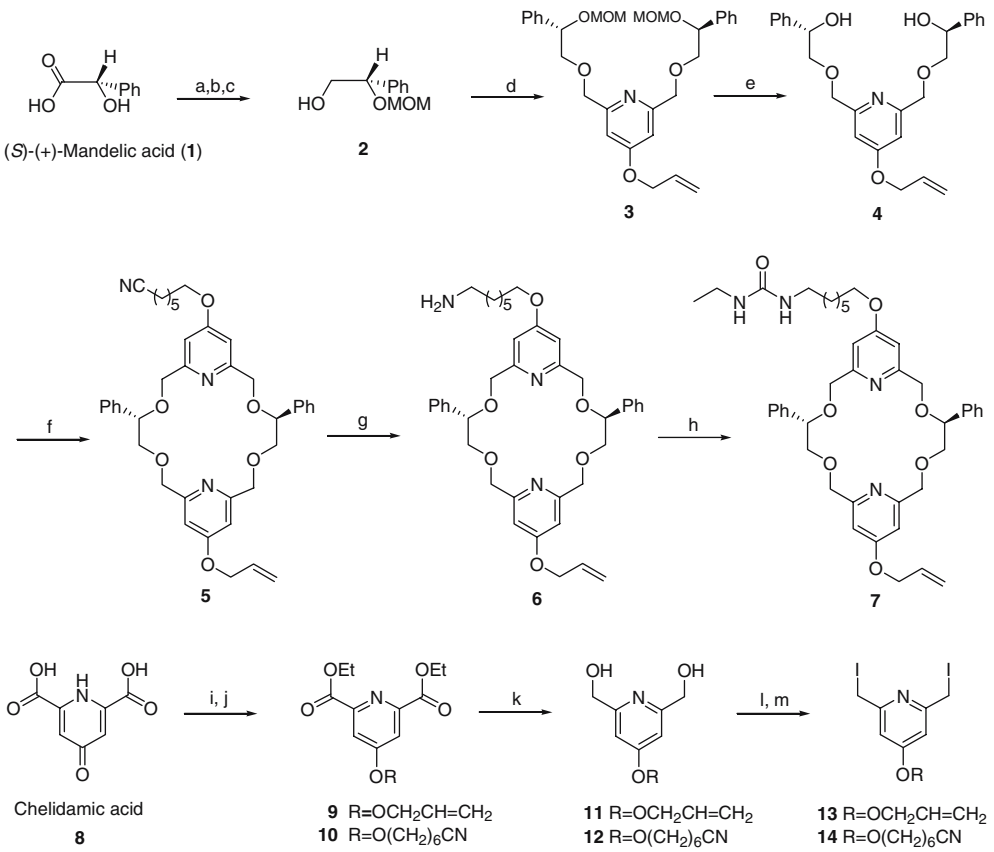
To a stirred solution of 4-(Allyloxy)-2,6-*bis*(hydroxylmethyl)pyridine (**11**) (18 g, 92.26 mmol)) in methylene chloride (50 ml) at 0 °C under Ar was added thionyl chloride (65.2 g, 548.03 mmol). The reaction mixture was heated at 70 °C for 5 h. After cooling to room temperature, excess amount of thionyl chloride was removed under reduced pressure. Crushed ice was added to the concentrate and the resulting suspension was neutralized with 10% aqueous Na_2CO_3 solution, diluted with ethyl acetate (200 ml) and water (80 ml), and extracted with ethyl acetate (2×200 ml). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 4-(allyloxy)-2,6-*bis*(chloromethyl)-pyridine (17 g, 79%) as white solids (R_f 0.29, SiO_2, EtOAc–Hexane = 1:2). Mp: 110 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.68 (m, 5H), 5.35 (d, 1H, J = 5.39 Hz), 5.45 (d, 1H, J = 5.39 Hz), 5.88–6.06 (m, 1H), 6.82 (s, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 47.9, 69.2, 108.5, 117.6, 132.7, 159.0, 164.5; FAB-MS m/z 232.16 (M + H)$^+$, calcd 232.02; HRMS calcd 232.0296 for $C_{10}H_{11}Cl_2NO$ (M + H)$^+$, found 232.0259.

To a stirred solution of 4-(allyloxy)-2,6-*bis*(chloromethyl)pyridine (3.3 g, 13.05 mmol) in acetone (50 ml) at room temperature under Ar was added sodium iodide (5.87 g, 39.16 mmol). The reaction mixture was stirred at 80 °C for 24 h. After concentration under reduced pressure, the reaction mixture was diluted with methylene chloride (150 ml) and water (50 ml), and the aqueous phase was extracted with methylene chloride (3×100 ml). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give **13** (4.3 g, 80%) as a yellow solids (R_f 0.28, SiO_2, EtOAc–Hexane = 1:2). Mp: 113 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) **13** (4.3 g, 80%) as yellow solids (R_f 0.28) δ 4.44 (s, 4H), 4.59 (d, 1H, J = 5.39 Hz), 5.25 (d, 1H, J = 6.9 Hz), 5.38 (d, 1H, J = 11.5 Hz), 5.88–6.00 (m, 1H), 6.82 (s, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 17.9, 68.2, 102.5, 117.8, 132.6, 159.2, 165.9; HRMS calcd 415.9008 for $C_{10}H_{12}Cl_2NO$ (M + H$^+$), found 415.9015.

Results and discussion

Synthesis

Chiral *bis*-pyridino-18-crown-6 (**7**), having urea, diphenyl, and allyloxy groups was synthesized for the enantiomeric recognition of α-amino acid methyl ester hydrochlorides. The synthesis of the designed chiral crown ether (*S,S*)-**7** are summarized in Scheme 1. The chiral crown ether (*S,S*)-**7** was prepared by a thirteen-steps procedure. The chiral subunit alcohol **2** was prepared from (*S*)-(+)-mandelic acid using our previously reported route [16]. Alcohol **2** was coupled with the diiodide **13** by using sodium hydride to generate



Scheme 1. Reaction conditions: (a) CH_3I, DBU, room temp., 3 h; (b) CH_3OCH_2Br, $(CH_3)_2NC_6H_5$, CH_2Cl_2, room temp., 5 h; (c) $LiAlH_4$, diethyl ether, 0 °C to room temp., 4 h; (d) **13**, NaH, DMF, reflux, 90 °C, 24 h; (e) 10 % HCl, THF, room temp. to 50 °C, 5 h; (f) **14**, NaH, THF, 90 °C to room temp., 48 h; (g) $LiAlH_4$, CH_2Cl_2/diethyl ether, 0 °C to room temp., 2 h ; (h) ethyl isocyanate, CH_2Cl_2, room temp., 8 h; (i) EtOH, *conc.* H_2SO_4 (*cat.*), reflux, 80 °C, 24 h; (j) $BrCH_2CH=CH_2$, K_2CO_3, acetone, room temp. to 80 °C, 15 h; (k) $NaBH_4$, $CaCl_2$ EtOH, 0 °C to room temp., 4 h ; (l) $SOCl_2$, CH_2Cl_2, 0–70 °C, 5 h; (m) NaI, acetone, reflux, 80 °C, 24 h.

compound **3**. The diiodides **13** was prepared from chelidamic acid (**8**) by the same procedure for the preparation of diiodide **14** [16]. Esterification of chelidamic acid (**8**), by using ethanol and sulfuric acid, followed by alkylation with allylbromide provided compound **9** [17]. Compound **9** was reduced using sodium borohydride in ethanol to generate the diol **11**, which was converted to the diiodides **13**, by using $SOCl_2$, followed by NaI. The MOM-protecting group of compound **3** was removed by using 10% aqueous HCl to afford the diol **4**, the southern part of the macrocycle. The generated diol **4** was coupled with the diiodide **14**, the northern part of the macrocycle, by using sodium hydride in THF under high dilution condition to afford the macrocycle **5**. The nitrile of the macrocycle **5** was reduced by using lithium aluminum hydride to generate the amine **6**. The generated amine **6** was treated with ethyl isocyanate to afford the final macrocycle **7**. After purification by using column chromatography (CH_2Cl_2:MeOH = 93:7), the structure of the new chiral crown ether (*S*,*S*)-**7** was identified by using ^{1}H-NMR (500: MHz), ^{1}H-^{1}H COSY (500 MHz), ^{13}C-NMR, and FAB MS.

The new chiral crown ether (*S*,*S*)-**7** was designed and synthesized in such a way that the interaction options available for the incoming chiral amino acid are limited. As shown in Figure 1, the complex is possible to have tripod hydrogen bonding between the one nitrogen and two oxygens of the host and three hydrogen atoms of the ammonium cation of the guest. In addition to this, another hydrogen bonding interactions between urea hydrogens of the host and ester oxygen of the guest could be possible to exist. With these possible hydrogen bonding interactions between the chiral crown ether (*S*,*S*)-**7** and the amino acid methyl ester hydrochloride, the complex with the D-amino acid methyl ester hydrochloride will have less severe steric repulsion between the alkyl group on the chiral carbon of the guest and the phenyl group of the host. This steric repulsion will give one of the possible explanations of the higher binding constant in case of D-AlaOMe and D-LeuOMe, and D-MetOMe as compared to that of L-series. The higher binding constants of the D-enantiomers as compared to those of the L-enantiomers could also be utilized in the preparation of the chiral stationary phase (CSP) for HPLC. For this future purpose, the allyloxy group was introduced in one of the pyridine group on the chiral crown ether (*S*,*S*)-**7**.

^{1}H-NMR titration studies

The enantiomeric recognition for the hydrogen chloride salts of D-, L-AlaOMe, D-, L-LeuOMe, and

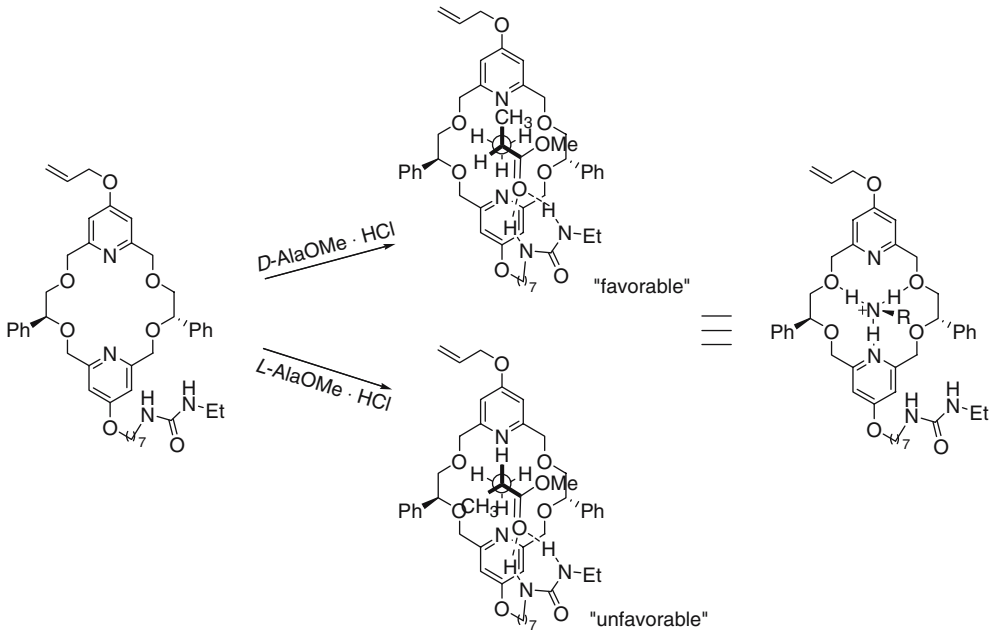


Figure 1. The proposed interaction conformation of chiral crown ether (*S*, *S*)-**7** with D- and L-alanine methyl ester hydrochloride.

D-, L-MetOMe by the chiral crown ether (*S*,*S*)-**7** have been characterized by ^{1}H-NMR titration method. Spectral changes of ^{1}H-NMR (500 MHz) in $CDCl_3$ at 25 °C are shown in Figure 2, where the solution of D-alanine methyl ester hydrochloride (0–0.1 mM) has been consecutively added into the solution of chiral crown ether (*S*,*S*)-**7** (0.02 mM). Before adding any D-alanine methyl ester hydrochloride, the chiral methine protons of the chiral crown ether (*S*,*S*)-**7** showed one broad singlet peak around 4.68 ppm. When D-alanine methyl ester hydrochloride was added, this singlet peak at 4.68 ppm was downfield shifted and split into two peaks at 4.88 and 4.80 ppm as shown in Figure 2. Using these peaks the association constant of the complex in $CDCl_3$ was obtained. All the association constants of the complexes in $CDCl_3$ were obtained by the non-linear least-squares method on the basis of the ^{1}H-NMR spectra data using the same methane peak of the chiral

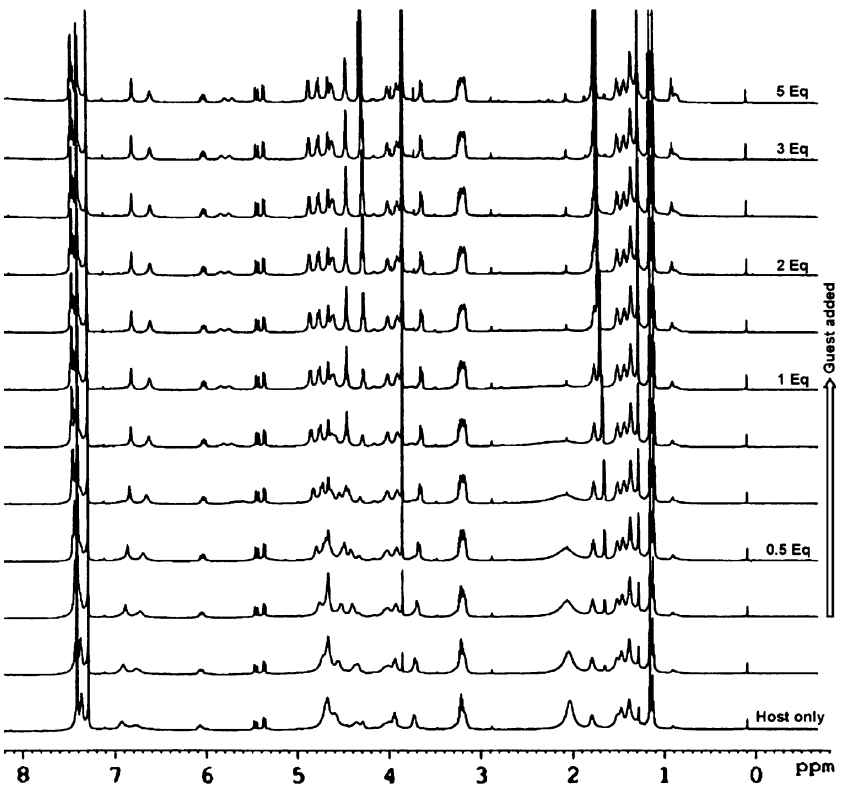


Figure 2. ^{1}H-NMR spectral changes of chiral crown ether (*S*,*S*)-**7** in the presence of D-alanine methyl ester hydrochloride in $CDCl_3$ at 25 °C.

Table 1. Association constants (K_a/mol) for host (*S*,*S*)-**7**[a] (0.02 mM)–guest (0–0.1 mM) complexes in $CDCl_3$ at 25 °C

Entry	Guest[b]	K_a	$\alpha[K_a(D)/K_a(L)]$
1	(D)-AlaOMe	3.20×10^3 ($\pm$ 200)	1.75
2	(L)-AlaOMe	1.82×10^3 ($\pm$ 200)	
3	(D)-LeuOMe	2.98×10^3 ($\pm$ 180)	1.50
4	(L)-LeuOMe	1.92×10^3 ($\pm$ 180)	
5	(D)-MetOMe	1.99×10^3 ($\pm$ 140)	1.49
6	(L)-MetOMe	1.33×10^3 ($\pm$ 140)	

[a]The chiral CH proton (-OC*H*Ph-) probe in host (*S*,*S*)-**7** (δ = 4.68 ppm).
[b]AlaOMe: alanine methyl ester hydrochloride, LeuOMe: leucine methyl ester hydrochloride, MetOMe: methionine methyl ester hydrochloride.

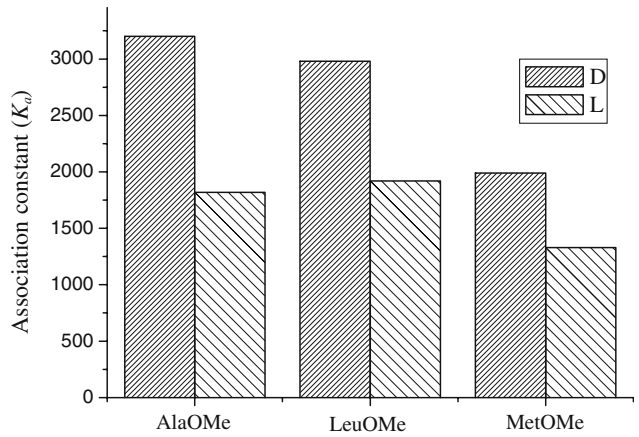


Figure 3. Bar plots of enantioselective recognition of chiral crown ether (*S*,*S*)-**7** (0.02 mM) for AlaOMe, LeuOMe, and MetOMe hydrochloride (0–0.1 mM).

crown ether (*S*,*S*)-7 [18]. As shown in Table 1 and Figure 3, all amino acid methyl ester hydrochlorides form stable complexes with chiral crown ether (*S*,*S*)-**7**. The association constants of the chiral crown ether (*S*,*S*)-**7** with the D-, L-enantiomers of AlaOMe hydrochloride were found to be $3.20\times10^3\ M^{-1}$ ($\pm$ 200) and $1.82\times10^3\ M^{-1}$ ($\pm$ 200), respectively, as shown in Table 1. In the same way, the chiral crown ether (*S*,*S*)-**7** exhibited 1.50, 1.49 times higher association constants with (D)-forms than with (L)-forms of LeuOMe and MetOMe salts. Since it has been known quite well that the *bis*-pyridino-18-crown-6 binds with ammonium salts [19], the synthesized chiral macromolecule **7** should have tripod hydrogen bonding with the ammonium cation of the guests. In addition to this, another hydrogen bonding interactions between urea hydrogens of the host and ester oxygen of the guest may exist. Even though, it is hard to generate any strong hypothesis with only three sets of D/L-amino acid methyl ester hydrochlorides used, the higher association constants with the D-forms may reflect that they encounter less severe steric interaction with the phenyl group of the host.

Conclusions

In conclusion, synthesis of a new chiral *bis*-pyridino-18-crown-6 (**7**), having urea, diphenyl, and allyloxy groups was reported. Enantiomeric recognition of D- and L-amino acid methyl ester hydrochlorides using the chiral crown ether (*S*,*S*)-**7** has been examined by ^{1}H-NMR titration method in $CDCl_3$ at 25 °C.

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