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Synthesis and Enantiodifferentiating Properties of Chiral Aza Crown Ethers

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Abstract—Alkylation of 2-substituted (4*S*,5*S*)-4,5-bis(hydroxymethyl)-1,3-dioxolanes with 9-benzyl-1,17-diiodo-3,6,12,15-tetraoxa-9-azaheptadecane afforded new chiral aza and diaza crown ethers as a result of [1 + 1] and [2 + 2] additions. Their catalytic debenzylation gave the corresponding derivatives with a secondary amino group. The reaction of diethyl (+)-tartrate and diethyl (4*S*,5*S*)-1,3-dioxolane-4,5-diacetates with 1,8-diamino-3,6-dioxaoctane led to formation of chiral macrocyclic lactams which were reduced with lithium aluminum hydride. The resulting diaza crown ethers were tested for enantioselectivity in complex formation with L- and D-valine methyl ester by the potentiometric method. In most cases, the aza crown ethers showed better enantioselectivity than their oxygen analogs.

Chiral crown ethers are among the most efficient enantiodifferentiating receptors for amines, amino acids, and their derivatives [1]. Therefore, they can be used as catalysts in asymmetric reactions, enantioselective sensors, enantiodifferentiating agents, and models of biological systems [2, 3]. Effective enantiomeric recognition requires that a chiral macrocyclic receptor be capable of forming sufficiently stable complexes with substrate enantiomers and that a chiral barrier be present, which reduces the stability of one of the diastereoisomeric complexes thus formed [3]. In other words, enantiodifferentiating properties of chiral crown ethers are determined by the satbility of complexes with chiral substrates and by the nature of chiral fragment in the macroring.

Complexing power of chiral crown ethers depends on a number of factors, including the nature of donor groups in the macroring. In many cases, introduction of nitrogen atoms into the macrocyclic skeleton increases the stability of complexes with ammonium ion and amine and amino acid salts [4]. However, among a large series of chiral crown ethers, aza crown ethers have been studied to the least extent [1]. As far as we know, only our early publication [5] described the synthesis and enantiomeric selectivity of several chiral aza crown ethers on the basis of natural (+)-tartaric acid derivatives. In the preceding communication we reported on the synthesis of a series of chiral crown ethers and enantioselectivity of their reaction with L- and D-valine methyl esters [6]. In continuation of these studies we now report on the synthesis and enantiodifferentiating properties of new chiral aza and diaza crown ethers.

As starting compounds we used chiral substituted 1,3-dioxolanes **Ia** and **Ib**. Their condensation with 9-benzyl-1,17-diiodo-3,6,12,15-tetraoxa-9-azaheptadecane in dioxane in the presence of sodium hydride gave previously unknown N-benzyl-substituted aza (**IIa**, **IIb**) and diaza crown ethers (**IIIa**, **IIIb**) which can be regarded, respectively, as [1 + 1] and [2 + 2] condensation products. Catalytic hydrogenation of compounds **IIa**, **IIb**, **IIIa**, and **IIIb** afforded aza crown ethers **IIc** and **IId** and diaza crown ethers **IIIc** and **IIId** (Scheme 1).

We have proposed a convenient procedure for the preparation of chiral amides **V**, **VIa**, and **VIb** by reaction of diethyl (+)-tartrate or 1,3-dioxolanes **IVa** and **IVb** with 1,8-diamino-3,6-dioxaoctane in methyl alcohol in the presence of sodium methoxide. The subsequent reduction of lactams **V**, **VIa**, and **VIb** with lithium aluminum hydride in tetrahydrofuran gave diaza crown ethers **VII**, **VIIIa**, and **VIIIb**, respectively (Scheme 2).

The enantioselectivity of complex formation of aza crown ethers **IIa**–**IId**, **IIIa**–**IIId**, **V**, **VIa**, **VIb**, **VII**, **VIIIa**, and **VIIIb** with L- and D-valine methyl

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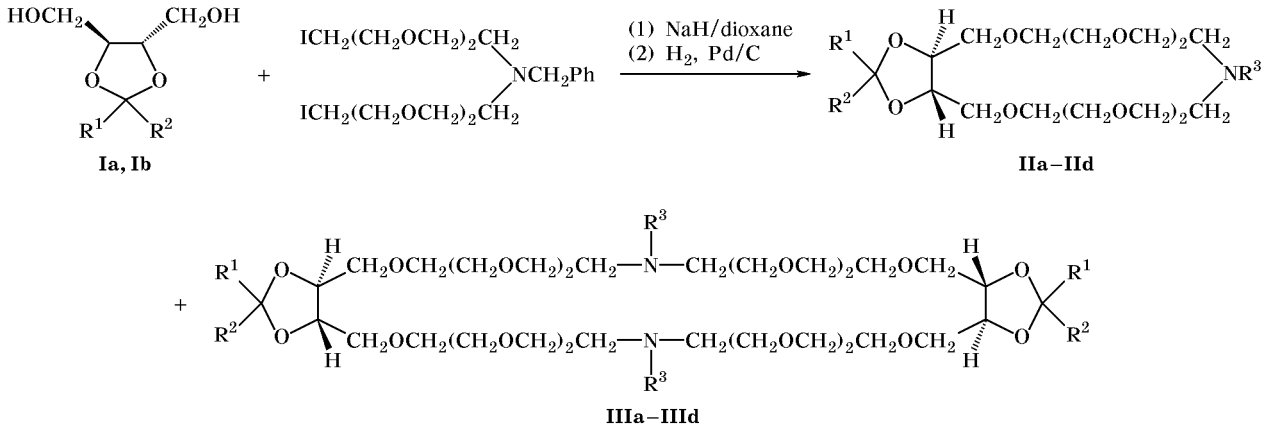
Scheme 1.

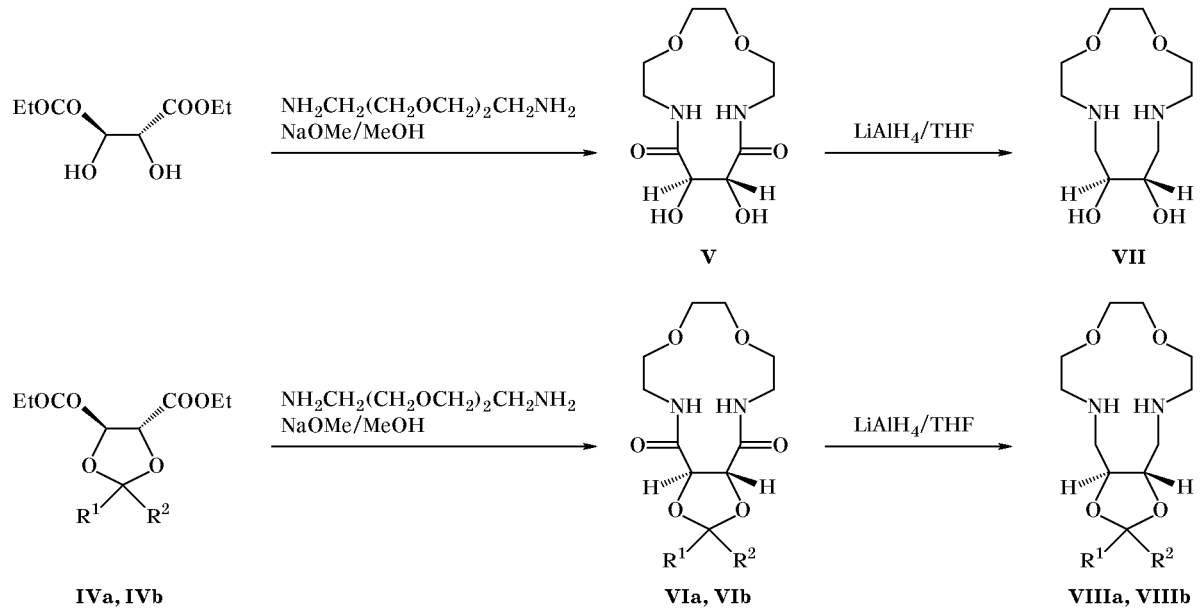


I, R^1 = Me, R^2 = *t*-Bu (**a**); R^1 = H, R^2 = Ph (**b**); **II**, R^1 = Me, R^2 = *t*-Bu, R^3 = Bzl (**a**); R^1 = H, R^2 = Ph, R^3 = Bzl (**b**); R^1 = Me, R^2 = *t*-Bu, R^3 = H (**c**); R^1 = R^3 = H, R^2 = Ph (**d**); **III**, R^1 = Me, R^2 = *t*-Bu, R^3 = Bzl (**a**); R^1 = H, R^2 = Ph, R^3 = Bzl (**b**); R^1 = Me, R^2 = *t*-Bu, R^3 = H (**c**); R^1 = R^3 = H, R^2 = Ph (**d**).

ester hydrochlorides was estimated by the potentiometric enantioselectivity coefficients K_{LD} [7]. The K_{LD} values (averaged from 5–7 measurements) are given in table. These coefficients characterize preference of complex formation between aza crown ether and one enantiomer of the substrate: when K_{LD} is equal to unity, enantioselectivity in complex formation is absent; K_{LD} values larger or lesser than unity indicate predominant complex formation of aza crown ether with L- or D-valine methyl ester, respectively.

All the examined aza crown ethers reacted preferentially with L-valine methyl ester hydrochloride, and their enantioselectivity was considerably higher than that of the oxygen analogs [6] (except for amides **V**, **VIa** and **VIb**). Presumably, increased enantioselectivity in the complex formation with chiral aza crown ethers is explained by greater stability of complexes with amino acid esters, as compared to similar complexes derived from nitrogen-free crown ethers. Aza crown ethers **IIc**, **IId**, **IIIc**, and **IIId** are characterized

Scheme 2.



IV, **VI**, **VIII**, R^1 = Me, R^2 = *t*-Bu (**a**); R^1 = H, R^2 = Ph (**b**).

by higher K_{LD} values (1.82–1.98) than their *N*-benzyl derivatives **IIa**, **IIb**, **IIIa**, **IIIb** (K_{LD} 1.55–1.73). This may be due to additional stabilization of the complexes via hydrogen bonding. The maximal enantioselectivity was observed for diaza crown ethers **VIIIa** and **VIIIb** (K_{LD} 2.07 and 2.12, respectively).

On the whole, our results indicate that search for new ligands exhibiting high enantioselectivity is more promising in the series of aza crown ethers containing (+)-tartaric acid moieties.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-250 instrument (250 MHz) in DMSO-d_6 using TMS as internal reference. The molecular weights were determined from the mass spectra which were obtained on Varian MAT-112 and MKh-1321 mass spectrometers with direct sample admission into the ion source (energy of ionizing electrons 70 eV). The optical rotations ($[\alpha]_D^{20}$) were measured on a Perkin–Elmer 241 MC polarimeter. GLC analysis was performed on a Chrom-5 chromatograph equipped with a flame-ionization detector; glass column, 1200 × 3 mm; stationary phase SE-30 (5%) on Inerton AW-DMCS (0.100–0.125 mm); carrier gas helium. Glass plates with a fixed layer of neutral aluminum oxide (L 5/40 μm) were used for TLC; eluent chloroform–benzene–methanol–2-propanol, 8 : 3 : 0.3 : 0.3; development with iodine vapor; also, Silufol plates were used (eluent chloroform–methanol–acetone, 2 : 1 : 1; development with a solution of ninhydrin in diethyl ether). Preparative liquid chromatography was performed in glass columns charged with neutral aluminum oxide (L 40/250 μm; eluent chloroform–benzene–methanol–2-propanol, 8 : 3 : 0.3 : 0.3) or silica gel (L 40/100 μm; eluent chloroform–methanol–acetone, 2 : 1 : 1). Compounds **Ia**, **Ib**, **IVa**, and **IVb** [6] and 1,8-diamino-3,6-dioxaoctane [8] were prepared by known methods.

9-Benzyl-1,17-diiodo-3,6,12,15-tetraoxa-9-azaheptadecane. A mixture of 69.2 g (370 mmol) of 1,8-dichloro-3,6-dioxaoctane, 4.9 g (46 mmol) of benzylamine, and 12.2 g (115 mmol) of sodium carbonate was stirred for 8 h at 120°C. The mixture was cooled, dissolved in 200 ml of methanol, and filtered, and the precipitate was washed with methanol (2 × 20 ml). The filtrate was combined with the washings and evaporated, and the residue was subjected to column chromatography on neutral Al_2O_3 to isolate 12.5 g (67%) of 9-benzyl-1,17-dichloro-3,6,12,15-tetraoxa-9-azaheptadecane as a colorless oily liquid. ^{1}H NMR spectrum, δ, ppm: 2.59 t (4H, NCH_2), 3.48–3.62 m (22H, OCH_2, $ClCH_2$, C**H**$_2$Ph), 7.10–7.19 m (5H, Ph). Found, %: C 55.97; H 7.80; N 3.31; Cl 17.44. $C_{19}H_{31}Cl_2NO_4$. Calculated, %: C 55.88; H 7.65; N 3.43; Cl 17.36.

Enantioselectivity coefficients of aza crown ethers **IIa**–**IId**, **IIIa**–**IIId**, **V**, **VIa**, **VIb**, **VII**, **VIIIa**, and **VIIIb**

Compound no.	K_{LD}	Compound no.	K_{LD}
IIa	1.68	**IIId**	1.86
IIb	1.73	**V**	1.28
IIc	1.92	**VIa**	1.38
IId	1.98	**VIb**	1.35
IIIa	1.55	**VII**	1.64
IIIb	1.58	**VIIIa**	2.07
IIIc	1.82	**VIIIb**	2.12

A solution of 6.5 g (16 mmol) of 9-benzyl-1,17-dichloro-3,6,12,15-tetraoxa-9-azaheptadecane and 7.2 g (48 mmol) of sodium iodide in 15 ml of anhydrous acetonitrile was heated for 14 h under reflux with vigorous stirring. The mixture was cooled and filtered, the precipitate was washed with two 10-ml portions of acetonitrile, and the solvent was distilled off under reduced pressure. The residue was dissolved in 15 ml of diethyl ether, the solution was filtered, and the filtrate was evaporated to obtain 9.1 g (97%) of 9-benzyl-1,17-diiodo-3,6,12,15-tetraoxa-9-azaheptadecane as a light yellow oily liquid. ^{1}H NMR spectrum, δ, ppm: 2.65 t (4H, NCH_2), 3.05 q (4H, OCH_2), 3.44–3.64 m (18H, OCH_2, CH_2Ph), 7.05–7.11 m (5H, Ph). Found, %: C 38.72; H 5.34; I 42.76; N 2.42. $C_{19}H_{31}I_2NO_4$. Calculated, %: C 38.60; H 5.29; I 42.93; N 2.37.

Aza crown ethers IIa, IIb, IIIa, and IIIb. A solution of 2.5 g (~12 mmol) of 1,3-dioxolane **Ia** or **Ib** in 230 ml of anhydrous dioxane was added dropwise with stirring under argon to a suspension of 2.9 g (120 mmol) of sodium hydride in 170 ml of anhydrous dioxane. The mixture was stirred for 1 h at 50–60°C, and a solution of 7.1 g (12 mmol) of 9-benzyl-1,17-diiodo-3,6,12,15-tetraoxa-9-azaheptadecane in 230 ml of anhydrous dioxane was added. The mixture was stirred for 16 h at 70–80°C, cooled, and poured into 200 ml of ice water. The products were extracted into chloroform (5 × 100 ml), the extract was dried over Na_2SO_4, and the solvent was distilled off under reduced pressure. Pure products **IIa**, **IIb**, **IIIa**, and **IIIb** were isolated as colorless oily substances by column chromatography on neutral aluminum oxide.

(1*S*,23*S*)-12-Benzyl-25-(*tert*-butyl)-25-methyl-3,6,9,15,18,21,24,26-octaoxa-12-azabicyclo[21.3.0]-hexacosane (IIa). Yield 3.4 g (52%). $[\alpha]_D^{20}$ = –4.2°

(*c* = 3.0, CH_3OH). ^1H NMR spectrum, δ, ppm: 0.98 s (9H, *t*-Bu), 1.30 s (3H, CH_3), 2.66 t (4H, NCH_2), 3.52–3.74 m (26H, OCH_2, C**H**$_2$Ph), 3.82–4.06 m (2H, OCH), 7.07– 7.14 m (5H, Ph). Found, %: C 64.61; H 9.19; N 2.57. M^+ 539. $C_{29}H_{49}NO_8$. Calculated, %: C 64.54; H 9.15; N 2.60. *M* 539.71.

(1*S*,23*S*)-12-Benzyl-25-phenyl-3,6,9,15,18,21,24,-26-octaoxa-12-azabicyclo[21.3.0]hexacosane (IIb). Yield 3.6 g (56%). $[\alpha]_D^{20}$ = +8.4° (*c* = 3.0, CH_3OH). ^1H NMR spectrum, δ, ppm: 2.70 t (4H, NCH_2), 3.54–3.76 m (26H, OCH_2, C**H**$_2$Ph), 3.90–3.98 m (2H, OCH), 5.98 s (1H), 7.16–7.42 m (10H, Ph). Found, %: C 59.95; H 7.88; N 2.61. M^+ 545. $C_{30}H_{43}NO_8$. Calculated, %: C 66.03; H 7.94; N 2.57. *M* 545.67.

(1*S*,23*S*,27*S*,49*S*)-12,38-Dibenzyl-25,51-di-*tert*-butyl-25,51-dimethyl-3,6,9,15,18,21,24,26,29,32,35,-41,44,47,50,52-hexadecaoxa-12,38-diazatricyclo-[47.3.0.0^{23,27}]dopentacontane (IIIa). Yield 1.3 g (10%). $[\alpha]_D^{20}$ = –3.8° (*c* = 3.0, CH_3OH). ^1H NMR spectrum, δ, ppm: 0.98 s (18H, *t*-Bu), 1.30 s (6H, CH_3), 2.64 t (8H, NCH_2), 3.50–3.72 m (52H, OCH_2, C**H**$_2$Ph), 3.76–3.96 m (4H, OCH), 7.06–7.15 m (10H, Ph). Found, %: C 64.48; H 9.09; N 2.64. M^+ 1078. $C_{58}H_{98}N_2O_{16}$. Calculated, %: C 64.54; H 9.15; N 2.60. *M* 1079.42.

(1*S*,23*S*,27*S*,49*S*)-12,38-Dibenzyl-25,51-diphenyl-3,6,9,15,18,21,24,26,29,32,35,41,44,47,50,52-hexadecaoxa-12,38-diazatricyclo[47.3.0.0^{23,27}]dopentacontane (IIIb). Yield 0.91 g (7%). $[\alpha]_D^{20}$ = +4.2° (*c* = 3.0, CH_3OH). ^1H NMR spectrum, δ, ppm: 2.68 t (8H, NCH_2), 3.50–3.62 m (52H, OCH_2, C**H**$_2$Ph), 3.86–3.92 m (4H, OCH), 5.97 s (2H), 7.12–7.46 m (20H, Ph). Found, %: C 65.98; H 8.00; N 2.61. M^+ 1090. $C_{60}H_{86}N_2O_{16}$. Calculated, %: C 66.04; H 7.94; N 2.57. *M* 1091.34.

Aza crown ethers IIc, IId, IIIc, and IIId. A stream of hydrogen was passed under stirring over a period of 2 h through a suspension of 100 mg of palladium black in 20 ml of anhydrous methanol, and 0.65 g (~1.2 mmol) of aza crown ether **IIa** or **IIb** or 1.3 g (~1.2 mmol) of diaza crown ether **IIIa** or **IIIb** was added. The mixture was stirred while passing hydrogen for 8 h (compounds **IIa** and **IIb**) or 16 h (**IIIa** and **IIIb**). The precipitate was filtered off and washed with methanol (2 × 10 ml), the filtrate was combined with the washings, and the solvent (methanol and toluene formed during the reaction) was distilled off on a rotary evaporator. Almost pure aza crown ethers **IIc**, **IId**, **IIIc**, and **IIId** were thus isolated as colorless oily substances.

(1*S*,23*S*)-25-*tert*-Butyl-25-methyl-3,6,9,15,18,21,-24,26-octaoxa-12-azabicyclo[21.3.0]hexacosane (IIc). Yield 0.53 g (98%). $[\alpha]_D^{20}$ = –2.2° (*c* = 1.0, CH_3OH). ^1H NMR spectrum, δ, ppm: 0.98 s (9H, *t*-Bu), 1.30 s (3H, CH_3), 2.36 br.s (1H, NH), 2.78–2.88 m (4H, NCH_2), 3.50–3.62 m (24H, OCH_2), 3.80–4.02 m (2H, OCH). Found, %: C 58.84; H 5.60; N 3.16. M^+ 449. $C_{22}H_{43}NO_8$. Calculated, %: C 58.78; H 5.56; N 3.12. *M* 449.58.

(1*S*,23*S*)-25-Phenyl-3,6,9,15,18,21,24,26-octaoxa-12-azabicyclo[21.3.0]hexacosane (IId). Yield 0.52 g (97%). $[\alpha]_D^{20}$ = +6.3° (*c* = 1.0, CH_3OH). ^1H NMR spectrum, δ, ppm: 2.40 br.s (1H, NH), 2.90–3.04 m (4H, NCH_2), 3.54–3.64 m (24H, OCH_2), 3.86–3.92 m (2H, OCH), 5.98 s (1H), 7.35–7.50 m (5H, Ph). Found, %: C 60.60; H 8.14; N 3.11. M^+ 455. $C_{23}H_{37}NO_8$. Calculated, %: C 60.64; H 8.19; N 3.08. *M* 455.55.

(1*S*,23*S*,27*S*,49*S*)-25,51-Di-*tert*-butyl-25,51-dimethyl-3,6,9,15,18,21,24,26,29,32,35,41,44,47,50,52-hexadecaoxa-12,38-diazatricyclo[47.3.0.0^{23,27}]dopentacontane (IIIc). Yield 1.0 g (93%). $[\alpha]_D^{20}$ = +8.1° (*c* = 5.0, CH_3OH). ^1H NMR spectrum, δ, ppm: 0.96 s (18H, *t*-Bu), 1.31 s (6H, CH_3), 2.52 br.s (2H, NH), 2.84–2.96 m (8H, NCH_2), 3.52–3.68 m (48H, OCH_2), 3.77–3.98 m (4H, OCH). Found, %: C 58.73; H 9.70; N 3.07. M^+ 898. $C_{44}H_{86}N_2O_{16}$. Calculated, %: C 58.78; H 9.64; N 3.12. *M* 899.17.

(1*S*,23*S*,27*S*,49*S*)-25,51-Diphenyl-3,6,9,15,18,21,-24,26,29,32,35,41,44,47,50,52-hexadecaoxa-12,38-diazatricyclo[47.3.0.0^{23,27}]dopentacontane (IIId). Yield 1.0 g (94%). $[\alpha]_D^{20}$ = –14.3° (*c* = 5.0, CH_3OH). ^1H NMR spectrum, δ, ppm: 2.48 br.s (2H, NH), 2.94–3.05 m (8H, NCH_2), 3.52–3.66 m (48H, OCH_2), 3.89–3.98 m (4H, OCH), 5.98 s (2H), 7.38–7.52 m (10H, Ph). Found, %: C 60.70; H 8.14; N 3.12. M^+ 910. $C_{46}H_{74}N_2O_{16}$. Calculated, %: C 60.65; H 8.19; N 3.08. *M* 911.09.

Aza crown ethers V, VIa, and VIb. Diethyl (+)-tartrate, 2.1 g (10 mmol), or dioxolane **IVa** or **IVb**, 2.9 g (~10 mmol), and 1,8-diamino-3,6-dioxaoctane, 1.5 g (10 mmol), were added to a solution of 0.023 g (1 mmol) of metallic sodium in 200 ml of anhydrous methanol. The mixture was heated with stirring for 6 h under reflux in an argon atmosphere, concentrated, and cooled, and the crude product (brown crystals) was filtered off. Compounds **V**, **VIa**, and **VIb** were purified by column chromatography on silica gel, followed by recrystallization from anhydrous ethanol. The products were colorless hygroscopic crystalline substances.

(9*R*,10*R*)-9,10-Dihydroxy-1,4-dioxa-7,12-diazacyclotetradecane-8,11-dione (V). Yield 0.95 g (35%). mp 161–162°C. $[\alpha]_D^{20}$ = +28.4° (*c* = 2.5, CH_3OH).

^{1}H NMR spectrum, δ, ppm: 3.34–3.41 m (4H, NCH_2), 3.48–3.60 m (8H, OCH_2), 4.12–4.29 m (2H, OCH), 4.82 br.s (2H, OH), 7.52–7.76 m (2H, NH). Found, %: C 45.87; H 7.02; N 10.74. M^+ 262. $C_{10}H_{18}N_2O_6$. Calculated, %: C 45.80; H 6.92; N 10.68. *M* 262.26.

(1*R*,14*R*)-16-*tert*-Butyl-16-methyl-6,9,15,17-tetraoxa-3,12-diazabicyclo[12.3.0]heptadecane-2,13-dione (VIa). Yield 1.5 g (42%). mp 126–127°C. $[\alpha]_D^{20}$ = +16.5° (*c* = 2.5, CH_3OH). ^{1}H NMR spectrum, δ, ppm: 0.96 s (9H, *t*-Bu), 1.31 s (3H, CH_3), 3.30–3.40 m (4H, NCH_2), 3.50–3.64 m (8H, OCH_2), 4.18–4.62 m (2H, OCH), 7.17–7.37 m (2H, NH). Found, %: C 55.72; H 8.21; N 8.07. M^+ 344. $C_{16}H_{28}N_2O_6$. Calculated, %: C 55.80; H 8.19; N 8.13. *M* 344.41.

(1*R*,14*R*)-16-Phenyl-6,9,15,17-tetraoxa-3,12-diazabicyclo[12.3.0]heptadecane-2,13-dione (VIb). Yield 1.4 g (40%). mp 142–143°C. $[\alpha]_D^{20}$ = –10.4° (*c* = 2.5, CH_3OH). ^{1}H NMR spectrum, δ, ppm: 3.35–3.42 m (4H, NCH_2), 3.48–3.60 m (8H, OCH_2), 4.56–4.62 m (2H, OCH), 5.97 s (1H), 7.05–7.58 m (7H, NH, Ph). Found, %: C 58.33; H 6.28; N 7.92. M^+ 350. $C_{17}H_{22}N_2O_6$. Calculated, %: C 58.28; H 6.33; N 7.99. *M* 350.37.

Aza crown ethers VII, VIIIa, and VIIIb. Diamide **V** (0.52 g, 2.0 mmol), **VIa** (0.69 g, 2.0 mmol), or **VIb** (0.70 g, 2.0 mmol) was added in small portions under vigorous stirring in an argon atmosphere to a suspension of 0.15 g (4.0 mmol) of lithium aluminum hydride in 10 ml of anhydrous THF. The mixture was then stirred for 3 h at room temperature, heated for 4 h under reflux, and left overnight. Cold water, 0.15 ml was added, the mixture was filtered, and the precipitate was shaken with 10 ml of THF and filtered off. This procedure was repeated thrice. The filtrates were combined and evaporated under reduced pressure. The residue was dissolved in benzene, and the solution was heated under reflux in a flask equipped with a Dean–Stark trap until water was removed completely. The solvent was distilled off under reduced pressure to isolate diaza crown ether **VII**, **VIIIa**, or **VIIIb** as a colorless oily liquid.

(9*S*,10*S*)-1,4-Dioxa-7,12-diazacyclotetradecane-9,10-diol (VII). Yield 0.29 g (64%). $[\alpha]_D^{20}$ = +8.0° (*c* = 1.0, CH_3OH). ^{1}H NMR spectrum, δ, ppm: 2.73–2.84 m (8H, NCH_2), 3.11 br.s (4H, NH, OH), 3.50–3.62 m (8H, OCH_2), 3.69–3.78 m (2H, OCH). Found, %: C 51.22; H 9.50; N 12.04. M^+ 234. $C_{10}H_{22}N_2O_4$. Calculated, %: C 51.26; H 9.46; N 11.96. *M* 234.29.

(1*S*,14*S*)-16-*tert*-Butyl-16-methyl-6,9,15,17-tetraoxa-3,12-diazabicyclo[12.3.0]heptadecane (VIIIa). Yield 0.49 g (78%). $[\alpha]_D^{20}$ = +22.2° (*c* = 1.0, CH_3OH). ^{1}H NMR spectrum, δ, ppm: 0.92 s (9H, *t*-Bu), 1.23 s (3H, CH_3), 2.33 br.s (2H, NH), 2.85–2.97 m (8H, NCH_2), 3.50–3.60 m (8H, OCH_2), 3.74–3.96 m (2H, OCH). Found, %: C 60.68; H 10.25; N 8.88. M^+ 316. $C_{16}H_{32}N_2O_4$. Calculated, %: C 60.73; H 10.19; N 8.85. *M* 316.44.

(1*S*,14*S*)-16-Phenyl-6,9,15,17-tetraoxa-3,12-diazabicyclo[12.3.0]heptadecane (VIIIb). Yield 0.47 g (72%). $[\alpha]_D^{20}$ = –16.3° (*c* = 1.0, CH_3OH). ^{1}H NMR spectrum, δ, ppm: 2.41 br.s (2H, NH), 2.87–3.02 m (8H, NCH_2), 3.54–3.65 m (8H, OCH_2), 3.90–4.02 m (2H, OCH), 5.96 s (1H), 7.38–7.52 m (5H, Ph). Found, %: C 63.29; H 8.06; N 8.74. M^+ 322. $C_{17}H_{26}N_2O_4$. Calculated, %: C 63.33; H 8.13; N 8.69. *M* 322.40.

Enantioselectivity coefficients of aza crown ethers IIa–IId, IIIa–IIId, V, VIa, VIb, VII, VIIIa, and VIIIb were determined by measuring the membrane potential of an [Ag, AgCl/internal solution// membrane//working solution/Ag, AgCl] cell by the biionic potential technique in 0.01 M aqueous solutions of L- and D-valine methyl ester hydrochlorides, following the procedure described in [6].

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