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Synthesis of chiral 18-crown-6 ethers containing lipophilic chains and their enantiomeric recognition of chiral ammonium picrates

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Abstract—Four new chiral 18-crown-6 ethers have been prepared to be used in enantiomeric recognition and extraction. The influence of the lipophilic character and bulkiness of the substituents on the complexation of different chiral ammonium picrates in CD_3CN has been evaluated. Racemic aqueous solutions of the ammonium salts have been enriched in one enantiomer after extraction experiments, and the enantiomeric excesses have been calculated.

1. Introduction

The study of enantiomeric recognition of primary alkylammonium salts by chiral macrocyclic receptors is useful in developing new methods of asymmetric synthesis and chromatographic resolution of enantiomers.[1] Among these macrocycles, optically active 18-crown-6 ethers (18C6) have been well investigated.[2] These 18C6 derivatives are obtained by attachment of the appropriate substituents to the aliphatic carbons of the polyether ring. Interaction between the ring and the ammonium group anchors the guest molecule, and the steric interactions between the 18C6 side chains and the guest species results in enantiomeric recognition.

For a long time, we have been interested in the development of crown ether based allosteric systems, in which cation complexing or extraction properties could be regulated by conformational changes. This led us to the synthesis of a cyclohexane substituted 18C6 derivative, whose conformation of the crown ether moiety is dependent on the pH of the medium.[3] One drawback of this compound is its relatively high solubility in water, which makes its use in extraction experiments difficult. On the other hand, although the molecule is chiral, it is obtained as a racemic mixture, which is not easy to resolve by conventional methods (crystallization or chromatographic resolution). It would thus be very interesting to obtain this compound (or a related one) enantiomerically pure. One way of addressing both problems could be by attaching two chiral lipophilic chains to the 18C6 ring.

As part of these ongoing studies, we herein report the synthesis and characterization of new chiral 18C6 derivatives containing lipophilic chains, **1**–**4** (Fig. 1), and their binding constants and extraction properties with two different chiral ammonium salts. For comparison purposes, we also prepared and studied the macrocyclic polyethers **5** and **6**, whose enantiomers had been previously synthesized by others.[4]

2. Results and discussion

2.1. Synthesis of the ligands

The procedure for the synthesis of related chiral crown ethers with C_2- and D_2-symmetry is well established in the literature[4,5] and relies on the choice of appropriate carbohydrate derivatives, with the terminal OH groups usually protected as acetals or benzyl ethers. We selected (−)-2,3-*O*-isopropylidene-D-threitol **7**, which is commercially available enantiomerically pure, as a convenient source of chirality.

The syntheses of lipophilic ligands **1**–**4** as well as the 18C6 derivatives **5** and **6** are shown in Schemes 1 and 2. The key intermediates are the C_2-symmetric triethylene glycol derivatives **11a**,**b**, which upon condensation

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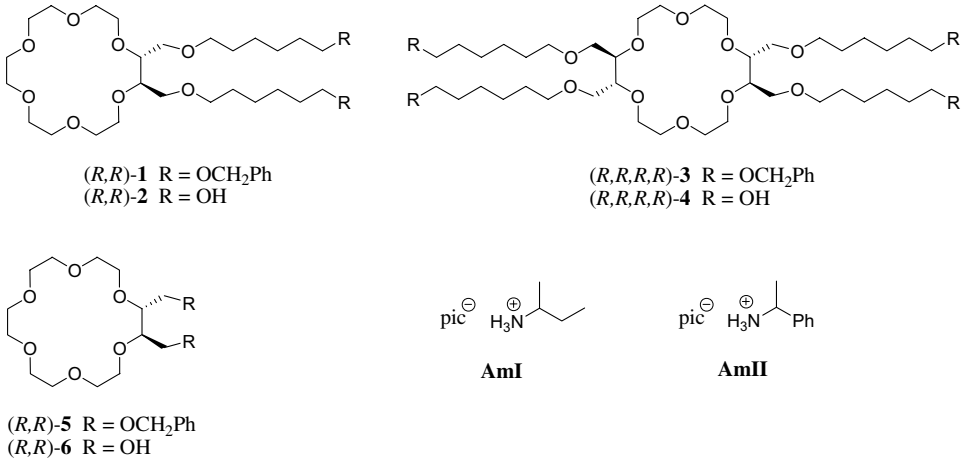
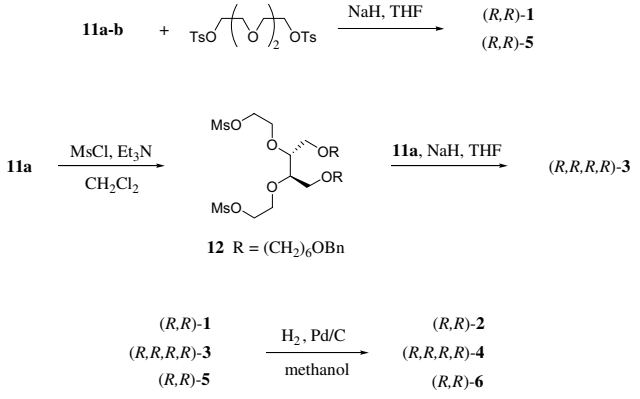


Figure 1.

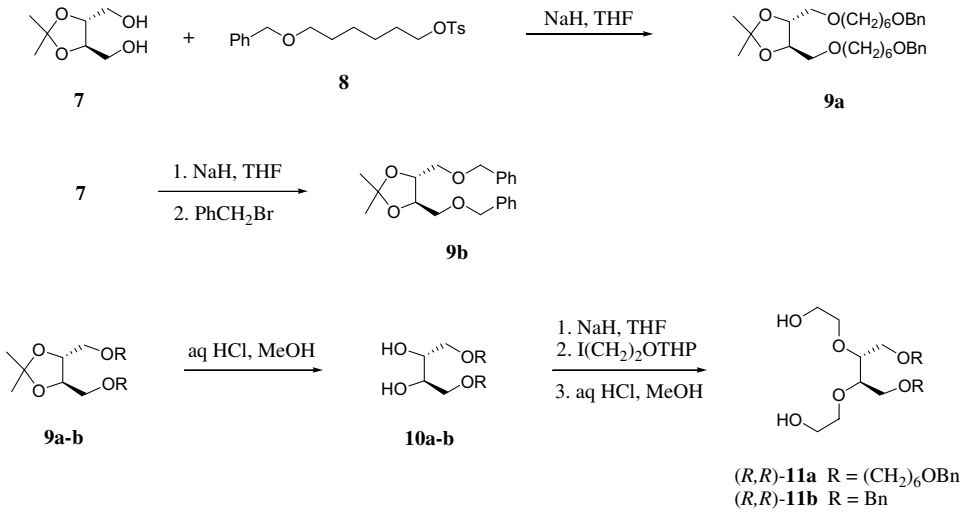
with appropriate tosylated or mesylated triethylene glycols under high dilution conditions, afford the desired crown ethers.

Alkylation of diol **7** by the *p*-toluenesulfonate derivative **8** was carried out with NaH in refluxing THF, to yield acetal **9a** (91%), which was hydrolyzed to diol **10a** with aq HCl in methanol at room temperature (Scheme 1). Similarly, benzylation of **7** with benzyl bromide in the presence of NaH in THF, followed by acidic hydrolysis of the acetal moiety led to 1,4-di-*O*-benzyl-D-threitol **10b** in 90% overall yield.[6] Chiral triethylene glycol derivatives **11a**,**b** were obtained by alkylation of diols **10a**,**b** with THP-protected 2-iodoethanol and subsequent hydrolysis of the protective group with hydrochloric acid in methanol.

Reaction of **11a** with triethylene glycol di-*O*-tosylate in the presence of NaH in THF at reflux for 2 days led to the C_2-symmetric crown ether (*R*,*R*)-**1** in 25% yield after column chromatography (Scheme 2). On the other hand, the cyclic polyether (*R*,*R*)-**5** was obtained in 40% yield by condensation of diol **11b** with triethylene glycol di-*p*-tosylate in a similar manner.[4] For the preparation of the D_2-symmetric crown ether **3**, diol **11a** was first mesylated with mesyl chloride and Et_3N in dichloromethane (87%), and then allowed to react with 1 equiv of **11a** in the presence of NaH in THF under reflux. (*R*,*R*,*R*,*R*)-**3** was thus obtained in 20% yield after



Scheme 2.



Scheme 1.

Table 1. Complexation constants ($\log K$) and enantioselectivity in complexation determined in CD_3CN by ^1H NMR titration

Picrate	(*R*,*R*)-**1**	(*R*,*R*)-**2**	(*R*,*R*,*R*,*R*)-**3**	(*R*,*R*,*R*,*R*)-**4**	(*R*,*R*)-**5**	(*R*,*R*)-**6**
(*R*)-(−)-**AmI**	4.61	4.91	4.06	3.96	2.15	1.93
(*S*)-(+)-**AmI**	2.55	2.27	2.11	2.07	2.03	2.09
$\log(K_R/K_S)$	2.06	2.64	1.95	1.89	0.12	0.15
(*R*)-(+)-**AmII**	5.42	5.08	3.17	2.98	2.11	2.01
(*S*)-(−)-**AmII**	2.24	2.65	2.04	2.05	2.06	2.06
$\log K_R/K_S$	3.23	2.43	1.13	0.93	0.05	−0.05

chromatography as a pale yellow oil. Finally, the benzyl groups in **1**, **5** and **3** were removed by catalytic hydrogenolysis over 10% palladium–carbon in methanol solution to give diols (*R*,*R*)-**2**, (*R*,*R*)-**6** and (*R*,*R*,*R*,*R*)-**4** in almost quantitative yields.

2.2. Complexation studies

The complexation capability of receptors **1**–**6** towards two different chiral alkylammonium picrates, (+)-(*S*)- and (−)-(*R*)-*sec*-butylammonium picrate **AmI** and (+)-(*R*)- and (−)-(*S*)-α-methylbencylammonium picrate **AmII** was evaluated by ^1H NMR studies in CD_3CN as solvent. Table 1 contains the $\log K$ values for these chiral ligands calculated using the method developed by Mernyi.[7] The data in Table 1 clearly show that ligands (*R*,*R*)-**1** and (*R*,*R*)-**2** exhibit enantiomeric recognition in CD_3CN. Thus (*R*,*R*)-**1** favoured (*R*)-**AmI** over (*S*)-**AmI** and (*R*)-**AmII** over (*S*)-**AmII** by a $\Delta\log K$ of 2.06 and 3.23, respectively. Similar results were observed with (*R*,*R*)-**2** with $\Delta\log K = 2.64$ and 2.43 for **AmI** and **AmII**, respectively. These results indicated that the presence of the phenyl rings in ligand (*R*,*R*)-**1** not only gives rise to higher complexation constants with (*R*)-**AmII** than with (*R*)-**AmI** ($\log K = 5.42$ and 4.61, respectively) but also increases the enantiomeric recognition ($\Delta\log K = 2.06$ for **AmI** and 3.23 for **AmII**). The observed differences could be related to the presence of a phenyl group in **AmII** that could interact with the aromatic rings in the ligand. In addition, the observed differences shown by (*R*,*R*)-**2** in ammonium salts complexation corroborate the influence of the phenyl group in the recognition process. Structures estimated by molecular mechanics by using PCModel (v. 8.0)[8] for the complexes formed between ligand (*R*,*R*)-**1** and (*R*)- and (*S*)-**AmII** (Fig. 2) show different interactions between the phenyl rings depending on the stereochemistry.[9] The complex formed with (*R*)-**AmII** shows a π-staking interaction that is not observed with (*S*)-**AmII**. This type of interaction could be responsible for the higher complexation constant and enantiomeric recognition observed with this ligand.[10]

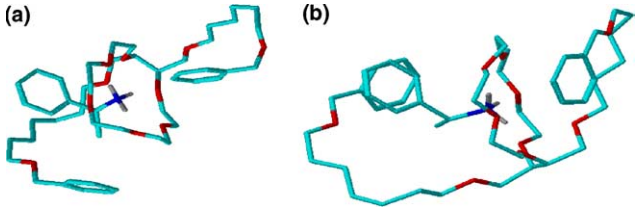


Figure 2. Structures estimated by molecular mechanics by using PCModel (v. 8.0)[8] for the complexes formed between ligand (*R*,*R*)-**1** and (a) (*S*)-**AmII**, (b) (*R*)-**AmII**.

On the other hand, the results observed with ligands (*R*,*R*,*R*,*R*)-**3**, (*R*,*R*,*R*,*R*)-**4**, (*R*,*R*)-**5** and (*R*,*R*)-**6** demonstrate that the presence of the two hydrophobic chains in ligands (*R*,*R*)-**1** and (*R*,*R*)-**2** give rise to the best environment not only for complexation, but also for enantiomeric recognition. Among the factors that should be considered to understand these results, the lipophilic effect of the chains seems to be very important because complexation constants with ligands (*R*,*R*)-**5** and (*R*,*R*)-**6** were clearly lower than with the other described ligands. In addition, the effect was stronger in the complexation of the (*R*)-enantiomer than in the (*S*)-enantiomer. Moreover, a smaller enantiomeric recognition was observed for these two ligands (see Table 1). Another effect to be considered in chiral complexation is the bulkiness of the chiral substituents that also seems to be important in this case.[11] Thus, side chains in ligands (*R*,*R*)-**5** and (*R*,*R*)-**6** are too short to have strong influence in complexation. By contrast, the four chains present in (*R*,*R*,*R*,*R*)-**3** and (*R*,*R*,*R*,*R*)-**4** seem to prevent the formation of complexes with the enantiomers and a lower chiral recognition was observed. This behaviour was very clearly observed by comparing the complexation of (*R*)-**AmII** with (*R*,*R*)-**1** and (*R*,*R*,*R*,*R*)-**3** where $\log K = 5.42$ for the former ligand and 3.17 for the later.

2.3. Extraction experiments

The influence that the enantiomeric recognition exhibited by ligands **1**–**6** has in extraction experiments was evaluated by using the method reported by Cram.[12] Extraction experiments were carried out between chloroform and an aqueous phase. The calculated extraction constants are shown in Table 2. Racemic picrates of *sec*-butylammonium (±)-**AmI** and α-methylbenzylammonium (±)-**AmII** were used in the aqueous solution with the corresponding ligands **1**–**6** dissolved in the organic phase. Determination of the extraction constants were carried out by using UV-spectroscopy. The obtained results demonstrate that under these conditions the extraction of α-methylbenzylammonium picrate **AmII** was higher than the extraction of *sec*-butylammonium picrate **AmI** with all the ligands prepared. This behaviour could be related to the higher lipophilic character of **AmII**. On the other hand, even though ligands (*R*,*R*)-**5** and (*R*,*R*)-**6** show higher extraction properties than the other studied ligands, they do not give rise to chiral discrimination, as shown by measuring the specific rotation of the resulting aqueous solutions after the extraction experiments.

Table 2. Extraction constants ($CHCl_3/H_2O$) and ee in the aqueous phase after extraction experiments

Picrate		(*R*,*R*)-**1**	(*R*,*R*)-**2**	(*R*,*R*,*R*,*R*)-**3**	(*R*,*R*,*R*,*R*)-**4**	(*R*,*R*)-**5**	(*R*,*R*)-**6**
(±)-**AmI**	Log K_e	2.64	2.86	2.16	2.12	2.27	1.84
	$[\alpha]_D^{20}$	+2.6	+2.8	+2.4	+2.45	0.00	0.00
	ee (%)	25	27	23	23	0	0
(±)-**AmII**	Log K_e	3.64	3.21	3.89	3.66	4.92	4.76
	$[\alpha]_D^{20}$	−2.35	−2.4	−1.7	—	0.00	0.00
	ee (%)	33	33	24	—	0	0

Enantiomeric excess were determined by optical rotation measurements.

Conversely, ligands (*R*,*R*)-**1**, (*R*,*R*)-**2**, (*R*,*R*,*R*,*R*)-**3** and (*R*,*R*,*R*,*R*)-**4** show a moderate chiral discrimination in extraction experiments being the (*R*)-enantiomer of both picrates preferentially extracted. Data in Table 2 also indicate that the number of chains on the crown ether seems to have only small influence on extraction. Finally, the results observed with both ammonium salts, (±)-**AmI** and (±)-**AmII**, suggest that the structure of the ammonium salts is not too important in these type of experiments.

3. Experimental

3.1. General

Column chromatography was performed with silica gel 60 (230–400 mesh, Merck). Silica gel 60 F_{254} (Merck) plates were used for TLC. Optical rotations were taken on a Perkin–Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded on either Bruker Avance 300 or 400 MHz spectrometers, with the deuterated solvent as the lock and residual solvent as the internal reference. Electronic impact high-resolution mass spectra (HRMS) were recorded in the positive ion mode on a VG-AUTOSPEC. UV–vis spectra were recorded on a double beam Shimadzu UV-2102 PC spectrophotometer using a 1 cm pathlength quartz UV-cell. All measurements were carried out at 293 K (thermostated). All commercially available reagents were used without further purification. THF was distilled from Na/benzophenone under Ar prior to use.

3.2. 6-(Benzyloxy)hexan-1-ol *p*-methylbenzenesulfonate 8

Pyridine (1.12 mL, 13.4 mmol) and *p*-toluenesulfonyl chloride (2.18 g, 11.4 mmol) were added to a solution of 6-(benzyloxy)hexan-1-ol[13] (1.40 g, 6.7 mmol) in $CHCl_3$ (10 mL). The solution was stirred at 0 °C for 2 h and then at room temperature for 2 h. Diethyl ether (25 mL) and water (10 mL) were added. The organic phase was separated and washed with HCl (2 M), then with $NaHCO_3$ (5%) and finally with water, dried over anhydrous Na_2SO_4 and concentrated. The resulting oil was purified by column chromatography on silica gel (hexane/ethyl acetate 1:1 as eluent) to yield **8** as a colourless oil (2.38 g, 98%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, $J = 10.0$ Hz, 2H), 7.36–7.33 (m, 7H), 4.48 (s, 2H), 4.10 (t, $J = 8.6$ Hz, 2H), 3.42 (t, $J = 8.6$ Hz, 2H), 2.44 (s, 3H), 1.64–1.56 (m, 4H), 1.34–1.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.2$, 131.1, 127.2, 75.7, 69.8, 61.4, 29.6, 27.6, 26.6, 26.3, 20.9.

3.3. 1,4-Bis-*O*-(6-benzyloxyhexyl)-2,3-*O*-isopropylidene-D-threitol 9a

2,3-*O*-Isopropylidene-D-threitol (**7**; 359 mg, 2.2 mmol) in THF (10 mL) was added to a stirred suspension of NaH (60% in mineral oil, 270 mg, 6.8 mmol) in THF (35 mL) under an argon atmosphere. The mixture was stirred for 1 h at room temperature and then for 1 h at 80 °C. The reaction mixture was cooled at 0 °C after which **8** (1.92 g, 5.3 mmol) in THF (15 mL) added. After stirring under argon at 80 °C for 3 days, the reaction mixture was cooled at 0 °C and a satd aq NH_4Cl (30 mL) was added. The organic solvent was removed and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was subjected to column chromatography on silica gel (hexane/CH_2Cl_2 9:1) to afford **9a** as a pale yellow oil (1.09 g, 91%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.33 (m, 10H), 4.49 (s, 4H), 3.96 (t, $J = 3.9$ Hz, 2H); 3.55 (t, $J = 3.9$ Hz, 4H); 3.44 (t, $J = 8.6$ Hz, 8H); 1.64–1.57 (m, 8H), 1.55–1.26 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 129.3, 127.6, 109.6, 72.8, 71.8, 71.5, 70.4, 60.4, 29.5, 27.0, 25.9, 21.0, 14.1.

3.4. 1,4-Di-*O*-benzyl-2,3-*O*-isopropylidene-D-threitol 9b

Reaction of diol **7** (1.04 g, 6.4 mmol), NaH (19.3 mmol) and benzyl bromide (1.68 mL, 14.2 mmol) at 80 °C for 24 h, as described above for **9a**, gave compound **9b**[6] (2.08 g, 95%) as a pale yellow oil after column chromatography (silica gel; hexane/ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 10H), 4.56 (s, 4H), 4.23–3.50 (m, 6H); 1.41 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.8, 128.1, 110.1, 73.9, 71.1, 27.4.

3.5. 1,4-Bis-*O*-(6-benzyloxyhexyl)-D-threitol 10a

To a solution of **9a** (1.17 g, 2.2 mmol) in methanol (25 mL) at 0 °C, 10% aqueous HCl (8 mL) was added dropwise. The mixture was stirred for 4 h at rt, then it was cooled again at 0 °C and neutralized with satd aq $NaHCO_3$. The solution was then extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel (hexane/ethyl acetate) affording **10a** (1.0 g, 90%) as a colourless oil. $[\alpha]_D^{23} = +2.4$ (*c* 1.72, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.26 (m, 10H), 4.49 (s, 4H), 3.96 (t,

$J = 3.8$ Hz, 2H), 3.55 (t, $J = 3.8$ Hz, 4H), 3.44 (t, $J = 8.6$ Hz, 8H), 1.66–1.56 (m, 8H), 1.37–1.35 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 129.3, 127.6, 127.5, 72.8, 71.8, 71.5, 70.4, 60.4, 29.5, 27.0, 25.9, 21.0.

3.6. 1,4-Di-*O*-benzyl-D-threitol 10b

This compound was prepared from ketal **9b** (2.28 g, 6.7 mmol) and hydrochloric acid in methanol as described above for **10a**. Crude **10b** was obtained as a white solid (1.90 g, 94%) and was used without further purification. $[\alpha]_D^{23} = +6.2$ (c 1.44, $CHCl_3$) [lit.:[6] $[\alpha]_D^{24} = +6.16$ (c 3.83, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 10H), 4.55 (s, 4H), 3.89–3.86 (m, 2H), 3.62–3.58 (m, 4H), 2.94 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 128.8, 128.2, 74.0, 72.4, 71.0.

3.7. 1,4-Bis-*O*-(6-benzyloxyhexyl)-2,3-bis-*O*-(2-hydroxyethyl)-D-threitol 11a

Diol **10a** (346 mg, 0.7 mmol) in dry THF (10 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 116 mg, 2.9 mmol) in dry THF (15 mL). The resulting suspension was stirred at 80 °C for 2 h under argon. The reaction mixture was cooled to 0 °C and *O*-(2′-tetrahydropyranyl)-2-yodoethanol (653 mg, 2.6 mmol) in dry THF (10 mL) then added dropwise. The resulting mixture was stirred under argon at 80 °C for 2 days. This was then cooled to 0 °C and a satd aq NH_4Cl (20 mL) added with stirring. The organic solvent was removed and the aqueous phase extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford a pale yellow oil (184 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.23 (m, 10H), 4.63 (t, $J = 3.9$ Hz, 2H), 4.49 (s, 4H), 4.24–4.17 (m, 4H), 3.85–3.40 (m, 22H), 1.83–1.35 (m, 28H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 128.3, 127.6, 127.5, 98.8, 98.7, 79.2, 72.8, 71.4, 70.7, 70.4, 66.9, 62.1, 62.0, 30.6, 29.7, 26.0, 25.4, 19.4, 19.3.

To a solution of the previous bis(tetrahydropyranyl) derivative (156 mg, 0.2 mmol) in ethanol (10 mL), concd HCl (0.4 mL) was added, and the mixture refluxed for 3 h. The solution was cooled to 0 °C and neutralized with solid Na_2CO_3. The suspension was filtered and the solvent was evaporated. The resulting crude was subjected to column chromatography on silica gel (CH_2Cl_2/methanol) to yield **11a** as a pale yellow oil (102 mg, 91%). $[\alpha]_D = -4.8$ (c 1.0, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.23 (m, 10H), 4.49 (s, 4H), 3.85–3.40 (m, 22H), 1.83–1.35 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 128.3, 127.6, 127.5, 79.8, 73.2, 72.9, 71.8, 70.3, 62.3, 29.7, 29.4, 26.0, 25.9.

3.8. 2,3-Bis-*O*-(2-hydroxyethyl)-1,4-di-*O*-benzyl-D-threitol 11b

In a similar way, the reaction of diol **10b** (1.91 g, 6.3 mmol), NaH (21.8 mmol) and THP-protected yodoethanol (4.97 g, 19.4 mmol) yielded the bis(tetrahydropyranyl)ether derivative as a pale yellow oil (1.34 g, 38%) after column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.22 (m, 10H), 4.61–4.60 (m, 2H), 4.52 (s, 4H), 3.87–3.48 (m, 18H), 1.79–1.50 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 128.3, 127.6, 127.5, 98.8, 98.7, 79.2, 72.8, 71.4, 70.7, 70.4, 66.9, 62.1, 62.0, 30.6, 29.7, 26.0.

Acidic hydrolysis of the above THP-protected diol (650 mg, 1.2 mmol) followed by column chromatography led to **11b** [reference] as a colourless oil (466 mg, 91%). $[\alpha]_D = -2.5$ (c 1.06, $CHCl_3$) {lit.:[4] $[\alpha]_D^{24} = +2.5$ (c 2.2, $CHCl_3$)}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.22 (m, 10H), 4.51 (s, 4H), 3.72–3.48 (m, 14H), 2.75 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 128.3, 127.6, 79.8, 73.2, 72.9, 71.8, 70.3, 62.3.

3.9. Crown ether (*R*,*R*)-1

To a suspension of NaH (60% dispersion in mineral oil, 0.23 g, 5.8 mmol) in THF (5 mL) **11a** (526 mg, 0.9 mmol) in THF (15 mL) was added dropwise under argon. The resulting suspension was stirred at 80 °C for 2 h. Triethylene glycol di-*p*-tosylate (476 mg, 1.0 mmol) in THF (30 mL) was slowly added dropwise (ca. 75 min) at 60 °C. Once the addition was over, the suspension was stirred at 80 °C for 2 days. The reaction mixture was cooled to 0 °C and aq satd NH_4Cl (20 mL) added. The organic solvent was evaporated and the resulting aqueous phase extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated. The resulting oil was purified by column chromatography on silica gel (hexane/ethyl acetate) to give (*R*,*R*)-**1** as a pale yellow oil (159 mg, 25%). $[\alpha]_D = -4.7$ (c 1.6, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.23 (m, 10H), 4.50 (s, 4H), 3.64–3.41 (m, 34H), 1.61–1.35 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 128.3, 127.6, 127.4, 72.8, 71.4, 71.3, 70.7, 70.6, 70.4, 70.0, 29.8, 29.7, 29.6, 26.0, 25.9; HRMS calcd for $C_{40}H_{64}O_{10}$: 704.450; found: 704.446.

3.10. Crown ether (*R*,*R*)-5

Condensation of **11b** (313.4 mg, 0.8 mmol) with triethylene glycol di-*p*-tosylate (423.1 mg, 0.9 mmol), as described above for compound (*R*,*R*)-**1**, yielded (*R*,*R*)-**5** (161 mg, 40%) as a pale yellow oil. $[\alpha]_D = -4.8$ (c 1.60, $CHCl_3$) {lit.:[4] $[\alpha]_D^{24} = +5.0$ (c 2.1, $CHCl_3$)}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.25 (m, 10H), 4.51 (s, 4H), 3.85–3.46 (m, 26H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.3, 127.6, 127.4, 79.7, 73.2, 71.3, 71.0, 70.5, 70.2, 69.9; HRMS calcd for $C_{28}H_{40}O_8$: 504.272; found: 504.267.

3.11. 1,4-Bis-*O*-(6-benzyloxyhexyl)-2,3-bis-*O*-(2-hydroxyethyl)-D-threitol dimethanesulfonate 12

Mesyl chloride (0.50 mL, 3.75 mmol) in CH_2Cl_2 (6 mL) was added dropwise to a 0 °C solution of **11a** (456 mg, 0.8 mmol) and triethylamine (0.8 mL, 4.56 mmol) in CH_2Cl_2 (25 mL) and the solution stirred under argon at 0 °C for 3 h. The mixture was washed with cooled water, dried over anhydrous Na_2SO_4 and concentrated

to yield an oil, which was purified by column chromatography on silica gel (CH_2Cl_2/hexane). Compound **12** (520 mg, 87%) was isolated as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.23 (m, 10H), 4.50 (s, 4H), 4.33–4.31 (m, 4H), 3.95–3.40 (m, 18H), 3.04 (s, 6H), 1.77–1.34 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 128.8, 128.0, 127.9, 73.3, 70.7, 70.4, 69.8, 69.6, 38.0, 30.0, 29.5, 26.5.

3.12. Crown ether (*R*,*R*,*R*,*R*)-3

NaH (60% dispersion in mineral oil, 339 mg, 8.5 mmol) was added to a solution of **11a** (470.2 mg, 0.84 mmol) in THF (22 mL). The resulting suspension was stirred under argon at 80 °C for 2 h. Compound **12** (672 mg, 0.9 mmol) in THF (35 mL) was slowly added dropwise at 60 °C during 75 min and the mixture was stirred at 80 °C for 3 days. The reaction mixture was cooled to 0 °C and satd aq NH_4Cl (20 mL) added. The organic solvent was removed and the aqueous phase extracted with ethyl acetate. The resulting organic phase was dried over Na_2SO_4, filtered and evaporated. The resulting oil was subjected to column chromatography on silica gel (hexane/ethyl acetate) to yield (*R*,*R*,*R*,*R*)-**3** as a pale yellow oil (192 mg, 20%). $[\alpha]_D = -2.6$ (*c* 11.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.24 (m, 20H), 4.50 (s, 8H), 3.80–3.43 (m, 44H), 1.61–1.36 (m, 32H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 128.7, 127.9, 72.8, 71.4, 71.3, 70.7, 70.6, 70.4, 70.0, 30.1, 26.5; HRMS calcd for $C_{68}H_{104}O_{14}$: 1144.743; found = 1144.712.

3.13. Crown ether (*R*,*R*)-2

A mixture of (*R*,*R*)-**1** (150 mg, 0.21 mmol) and a catalytic amount of 10% Pd(C) in methanol (40 mL) was stirred for 24 h in the presence of an H_2 atmosphere (53 psi). The mixture was then filtered through Celite and the solvent evaporated to afford diol (*R*,*R*)-**2** as a yellow oil (105 mg, 95%). $[\alpha]_D = -4.7$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64–3.41 (m, 34H), 2.13 (s, 2H), 1.61–1.35 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.8, 71.4, 71.3, 70.7, 70.6, 70.4, 70.0, 29.8, 29.7, 29.6, 26.0, 25.9; HRMS calcd for $C_{26}H_{52}O_{10}$: 524.356; found: 524.350.

3.14. Crown ether (*R*,*R*,*R*,*R*)-4

Hydrogenolysis of (*R*,*R*,*R*,*R*)-**3** (183.3 mg, 0.2 mmol) with 10% Pd(C) in methanol as described above for compound (*R*,*R*)-**2** (40 mL) yielded (*R*,*R*,*R*,*R*)-**4** (134 mg, 92%) as a yellow oil. $[\alpha]_D = -2.6$ (*c* 11.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77–3.20 (m, 48H), 1.58–1.36 (m, 32H);^{13}C NMR (75 MHz, $CDCl_3$): δ 75.5, 72.7, 70.9, 70.1, 68.7, 63.8, 33.2, 30.0, 26.1, 25.7; HRMS calcd for $C_{40}H_{80}O_{14}$: 784.554; found: 784.523.

3.15. Crown ether (*R*,*R*)-6

(*R*,*R*)-**5** (143 mg, 0.28 mmol) was hydrogenolyzed with 10% Pd(C) affording (*R*,*R*)-**6** (84 mg, 92%) as a yellow oil. $[\alpha]_D = -4.2$ (*c* 2.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80–3.46 (m, 26H), 1.81 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 79.6, 73.0, 71.9, 70.6, 70.5, 70.2, 69.7; HRMS calcd for $C_{14}H_{28}O_8$: 324.1784; found: 324.1780.

3.16. General procedure for the synthesis of ammonium picrates

Equimolar proportions of the chiral amine and picric acid were dissolved in ethanol, and the mixture was stirred at rt for 2 h. The solvent was removed and the resulting yellow solid was recrystallized from a toluene/ethanol to afford crystalline ammonium picrates as yellow needles.

sec-Butylammonium picrate, **AmI**: ^{1}H NMR (300 MHz, CD_3CN): δ 8.67 (s, 2H), 3.22–3.26 (m, 1H), 1.56–1.68 (m, 3H), 1.27 (d, $J = 7.0$ Hz, 2H), 0.97 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ 148.7, 126.5, 51.6, 30.8, 21.6, 10.3; (*R*)-**AmI**, $[\alpha]_D = -10.5$ (*c* 1.01, H_2O); (*S*)-**AmI**, $[\alpha]_D = +10.6$ (*c* 1.02, H_2O).

α-Methylbenzylammonium picrate, **AmII**: ^{1}H NMR (300 MHz, CD_3CN): δ 8.68 (s, 2H), 7.34–7.47 (m, 8H), 4.47 (q, $J = 7.0$ Hz, 2H), 1.62 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ 148.7, 126.5, 131.1, 128.9, 46.7, 27.6; (*R*)-**AmII**, $[\alpha]_D = +8.0$ (*c* 0.98, H_2O); (*S*)-**AmII**, $[\alpha]_D = -7.9$ (*c* 1.01, H_2O).

3.17. Complexation experiences

Binding constants of chiral crown ethers **1**–**6** towards chiral ammonium picrates were evaluated by ^{1}H NMR studies. A 0.01 M solution of the ligand in CD_3CN (0.7 mL) was titrated by adding 3 μL aliquots of the appropriate ammonium picrate (0.1 equiv each aliquot) dissolved in a mixture of CD_3CN/CD_3OD 95:5 and registering the ^{1}H NMR spectrum after each addition. $\mathrm{Log}\,K_c$ was calculated using the method reported by Mernyi et al.[7]

3.18. Extraction experiments

Into a 20 mL centrifuge tube was introduced 1 mL of a 0.015 M aqueous solution of ammonium picrate and 1 mL of a 0.045 M solution of the corresponding crown ether in ethanol-free chloroform. The tube was stoppered and shaken at 20 °C for 2 h in a Heidolph REAX 2 shaker. It was then left unshaken for another hour to allow the separation of the aqueous and the organic phase. A 100 μL aliquot of the organic layer was diluted to 2 mL with acetonitrile and transferred into a UV cell. The UV absorption at $\lambda = 295$ nm was measured against a blank experiment. Three repetitions were run for each ligand-salt pair, and concentrations were calculated using the Beer–Lambert's law relationship. Extinction coefficients (ε) in CH_3CN (HPLC-quality grade) on the dynamic range of 10^{-4} to 10^{-5} were determined using a set of standard solutions of different concentrations of each salt. $\mathrm{Log}\,K_e$ were calculated using the model reported by Cram.[12] Enantiomeric excesses of the ammonium picrates after the extractions were evaluated by measuring the optical rotations of the resulting aqueous phases.

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