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Synthesis and optical characterization of novel enantiopure BODIPY linked azacrown ethers as potential fluorescent chemosensors☆

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ABSTRACT

Two novel enantiopure BODIPY linked azacrown ether chemosensors were prepared by reacting 3-chloro-5-methoxyBODIPY with new enantiopure monoaza-18-crown-6 ether ligands bearing two methyl and isobutyl groups on their chiral centres, respectively. The latter compounds were synthesized starting from optically active tetraethylene glycols in six steps. The operation of chemosensors is based on the intramolecular charge transfer (ICT) process. They exhibit pronounced off–on type fluorescent responses to some metal ions and chiral primary aralkyl ammonium ions, in particular to Ca^{2+} and Pb^{2+}. Even in the case of 1:1 ratio of Ca^{2+} and Pb^{2+} ions to the ionophores, the fluorescence intensities and quantum yield values increased more than 10-fold, as well as both the absorption and emission bands were blue-shifted by about 20–30 nm (hipsochromic effect) in acetonitrile. The formation of relatively stable complexes allowed the determination of log K_s values by the mole-ratio method.

1. Introduction

The synthesis and development of sensitive and selective fluorescent sensors for metal ion analysis have gained much research interest due to the great demand for their application in many fields such as environmental chemistry, food industry, medical diagnosis and life sciences.[1] Fluorescence spectroscopy is an attractive tool due to its selectivity, sensitivity and versatility.[2,3] Many fluorescent cation sensors have either a modular structure consisting of a fluorophore and a receptor unit separated by a short alkyl spacer or a structure wherein the receptor is part of the π-electron system of the fluorophore. They work on the basis of photoinduced electron transfer (PET) and internal charge transfer (ICT) processes, respectively. In the absence of analytes such as metal or organic ions, both types of sensor molecules show reduced fluorescence due to the efficient quenching process (PET or ICT) in the excited state. Whereas in PET sensor molecules the binding of the analyte increases the fluorescence intensity to a great extent without spectral shifts, ICT sensor molecules show a moderate increase in their fluorescence intensity with significant shifts in their absorption and fluorescence spectra upon complexation.[4–11] In a wider sense, mostly PET sensor systems besides ICT type ones are extensively studied also in sensing of anions[6,9,12,13] and neutral molecules.[8,9,14] Furthermore, many PET sensors have also been developed exploiting the selective quenching of fluorescence upon interaction with an analyte.[4–7,9,12,13]

Enantiomeric recognition is a widespread and important phenomenon in nature. Examples for its action include the metabolism of single enantiomeric forms of amino acids and saccharides in biosynthetic pathways. Stereostructure of optically active natural ion carriers (ionophores) such as valinomycin, monensin, lasalocid, monactin, dinactin, salinomycin, narasin and nigericin also plays an important role in the selective transport of metal cations through biomembranes.[15,16]

The determination of the enantiomeric composition of organic compounds is of great importance in drug discovery, food industry, pesticide chemistry, biological and separation sciences. Enantiomers may be theoretically distinguished from each other by artificial chiral host molecules such as crown ethers.[17,18] In the past two decades many efforts have been made on the development of fluorescent chiral chemosensors.[19–24] Among them some crown ethers containing various fluorescent units were synthesized and their enantiomeric recognition ability towards amino acid derivatives, amino

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alcohols and primary amines were studied.[25–29] The complexation properties of some chiral fluorescent crown ether based chemosensors towards metal ions were also investigated.[28–30]

Boron-dipyrromethene (BODIPY,[31] 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) derivatives are useful fluorophores for constructing chemosensors, because of their advantageous characteristics such as sharp absorption and fluorescence bands, high molar extinction coefficients, high fluorescence quantum yields, high stability against light and chemical reactions, and also because they can be excited in the visible range of light.[32–35] A number of chemosensors containing boradiazaindacenes such as crown ethers,[36–48] calix[4]crown ethers[49–52] and podands[53] have been synthesized and their selective metal ion binding abilities have been studied. Furthermore, some of them have been applied for the development of molecular logic gates.[44,51]

Herein we report the synthesis of two new enantiopure BODIPY based azacrown ether chemosensors having methyl and isobutyl groups on their chiral centres and also the studies on their complexation properties towards various metal ions (Li^+, Na^+, K^+, Ag^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, Cu^{2+}, Pb^{2+}, Cd^{2+}, Hg^{2+}, Fe^{3+}), NH_4^+ ion and the enantiomers of α-phenylethylammonium perchlorate (PEA) and α-(1-naphthyl)ethylammonium perchlorate (NEA) salts. In addition we report our extended complexation studies towards metal ions in more detail on the achiral analogue described earlier in the literature.[39]

2. Results and discussion

2.1. Synthesis

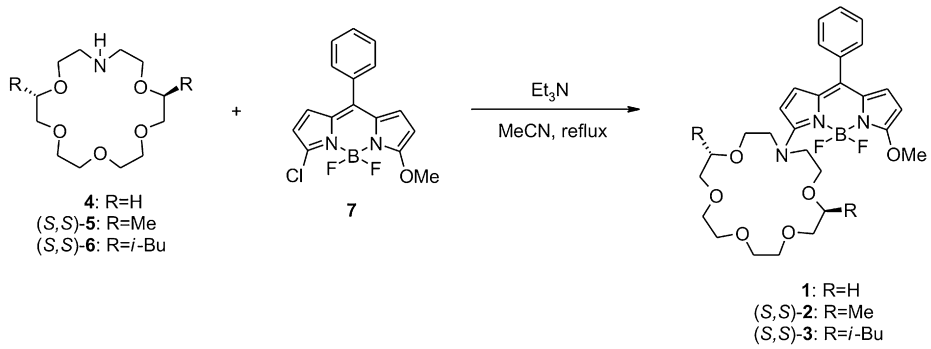
BODIPY linked azacrown ether chemosensor **1** was prepared according to the literature.[39] Enantiopure BODIPY linked monoaza-18-crown-6 ether ligands (*S*,*S*)-**2** and (*S*,*S*)-**3** were obtained by reacting the new chiral monoazacrown ethers (*S*,*S*)-**5** and (*S*,*S*)-**6** with BODIPY derivative **7** in acetonitrile in the presence of triethylamine as a base adopting the procedure[39] described for the synthesis of achiral analogue **1** (Scheme 1). BODIPY derivative **7** was also prepared by following the previously reported method.[39]

The synthesis of enantiopure monoazacrown ethers (*S*,*S*)-**5** and (*S*,*S*)-**6** was started from chiral tetraethylene glycols (*S*,*S*)-**8**[54] and (*S*,*S*)-**9**,[55] which were obtained as described in the literature. First, the latter tetraethylene glycols were elongated with two ethylene glycol units by reacting their disodium derivatives with 2-(benzyloxy)-ethylmethanesulfonate (**10**)[56] in THF to give chiral hexaethylene glycol dibenzyl ethers (*S*,*S*)-**11** and (*S*,*S*)-**12**. Benzyl protecting groups were removed by catalytic hydrogenation in methanol to obtain chiral hexaethylene glycols (*S*,*S*)-**13** and (*S*,*S*)-**14**. The latter glycols were treated with tosyl chloride in triethylamine to produce chiral hexaethylene glycol ditosylates (*S*,*S*)-**15** and (*S*,*S*)-**16**, which were transformed to chiral diiodo derivatives (*S*,*S*)-**17** and (*S*,*S*)-**18** by reacting them with sodium iodide in acetone. Reaction of diiodo derivatives (*S*,*S*)-**17** and (*S*,*S*)-**18** with benzylamine in the presence of potassium carbonate as a base in acetonitrile resulted in the *N*-benzyl derivatives of chiral monoazacrown ethers [(*S*,*S*)-**19** and (*S*,*S*)-**20**)]. Finally, benzyl protecting groups were removed by catalytic hydrogenation in methanol to furnish the desired chiral monoazacrown ethers (*S*,*S*)-**5** and (*S*,*S*)-**6** (Scheme 2).

2.2. UV–vis and fluorescence spectroscopic characterization

The UV–vis spectrophotometric and fluorescence emission properties of chemosensors **1**–(*S*,*S*)-**3** as well as their metal ion and NH_4^+ complexes are summarized in Table 1. The absorption spectra of compounds **1**–(*S*,*S*)-**3** in acetonitrile show similar characteristics to BODIPY chromophores described in the literature.[32–35] An intense band in the 400–600 nm region with a maximum at 527–529 nm and a shoulder at the shorter wavelength side can be attributed to a strong S_0–S_1 transition. Less intense absorption bands (S_0–S_2) can also be observed at about 350 nm. The absorption spectra of BODIPY crown ethers **1**–(*S*,*S*)-**3** are significantly red-shifted (ca. 30 nm) compared to the reference compound **7** (λ_{max}=498 nm) due to an extended conjugation of the π-system of the fluorophore with the imino group of the crown ether. Furthermore, the absorption bands of ionophores **1**–(*S*,*S*)-**3** are considerably wider and their absorption coefficients are smaller than those of the reference compound **7** (ε=47,700 M^{-1} cm^{-1}). The alkyl groups on the chiral centres of crown ethers (*S*,*S*)-**2** and (*S*,*S*)-**3** hardly influence their spectrophotometric properties. Bathochromic shifts (5 nm) can be seen in the absorption spectra of **1**–(*S*,*S*)-**3** in dichloromethane containing 1% methanol compared to those recorded in acetonitrile.

Similar trends can be observed in the fluorescence behaviour of BODIPY linked crown ethers **1**–(*S*,*S*)-**3** (Table 1). They show red-shifted (ca. 50 nm) and wider emission bands in acetonitrile compared to the reference compound **7** (λ_{max}=525 nm). The quantum yields of **1**–(*S*,*S*)-**3** are only two times lower than that of **7** (Φ_f=0.0088). The low quantum yield values of **1**–(*S*,*S*)-**3** can be attributed to an intramolecular charge transfer (ICT) process in the excited state leading to a strong quenching of the fluorescence.[4–7,9,36–40,44–47,50] Whereas the BODIPY derivative having methyl substituents at position 1,3,5,7 and a phenyl group at the *meso* position of the BODIPY core has a relatively large quantum yield (Φ_f=0.6 in acetonitrile),[36,37] our reference compound **7** has quite a low quantum yield value compared to the former one. On the one hand this can be explained by the lack of the steric hindrance of the methyl groups at position 1 and 7 in compound **7**, which results in a more extended π-system leading to fluorescence reduction.[34] On the other hand, it has been found that the quantum yields tended to be reduced by electron donating substituents at position 3 and 5 relative to unsubstituted BODIPYs.[34,57,58] It is important to note that the measured

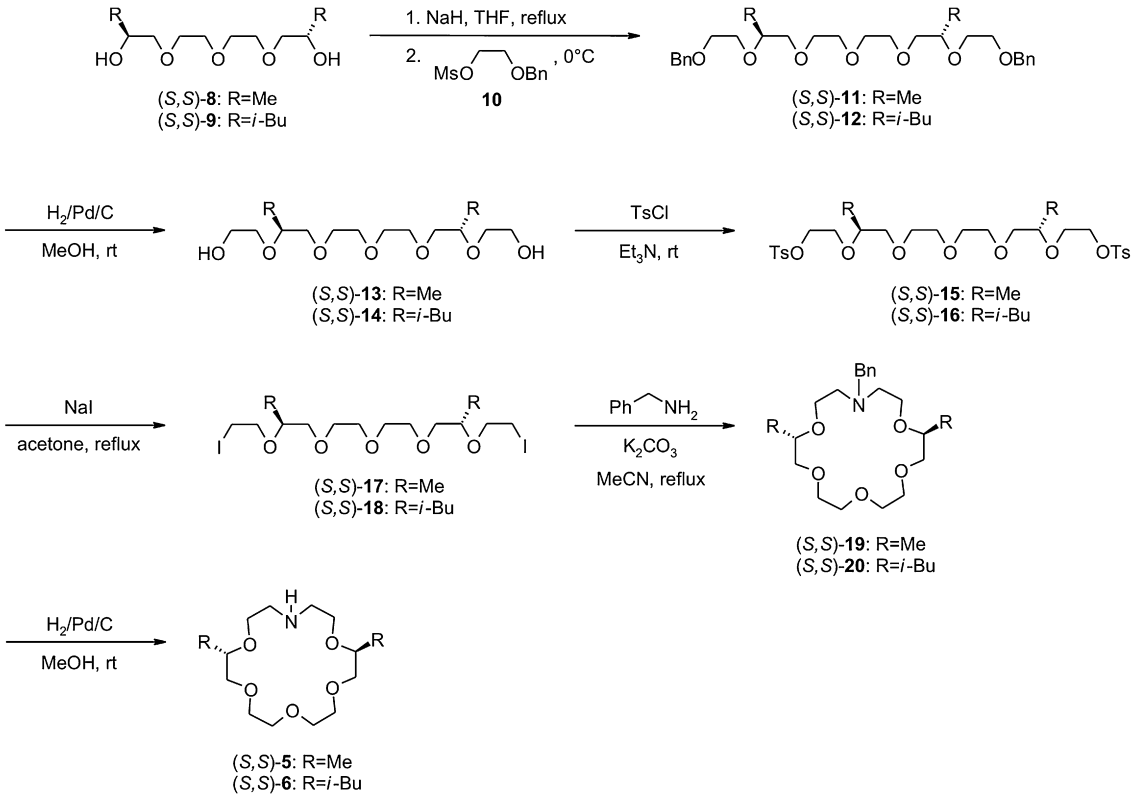


4: R=H
(*S*,*S*)-**5**: R=Me
(*S*,*S*)-**6**: R=*i*-Bu

7

1: R=H
(*S*,*S*)-**2**: R=Me
(*S*,*S*)-**3**: R=*i*-Bu

Scheme 1. Preparation of chiral BODIPY linked azacrown ether chemosensors (*S*,*S*)-**2** and (*S*,*S*)-**3** and achiral analogue **1**.



Scheme 2. Preparation of chiral monoazacrown ethers (*S*,*S*)-**5** and (*S*,*S*)-**6**.

Table 1
Absorption and emission data of **1**–(*S*,*S*)-**3** and their metal ion and NH_4^+ complexes in MeCN

	1				(*S*,*S*)-**2**				(*S*,*S*)-**3**				
	λ (abs) nm	ε^a	λ (em) nm	Φ_f	λ (abs) nm	ε^a	λ (em) nm	Φ_f	λ (abs) nm	ε^a	λ (em) nm	Φ_f	M^{n+}/L
Free	529	2.96	571	0.0049	527	2.96	572	0.0049	527	2.95	572	0.0045	—
Ca^{2+}	510	3.13	553	0.050	509	3.53	550	0.051	508	3.34	550	0.047	2
Pb^{2+}	507	3.01	546	0.056	509	3.37	548	0.053	507	3.30	546	0.054	2
Hg^{2+}	419	2.23	532	0.020	418	2.29	535	0.039	416	2.59	541	0.013	2
Cu^{2+}	475	1.26	534	0.0029	476	1.53	532	0.0066	475	1.40	534	0.0011	2
Fe^{3+}	478	0.85	537	0.0015	479	1.61	534	0.0040	478	1.36	538	0.0010	20
Ag^+	529	2.95	570	0.0048	525	2.93	572	0.0047	527	2.98	572	0.0045	20
Mg^{2+}	510	2.74	553	0.039	512	2.84	552	0.0099	509	2.95	551	0.015	200
Zn^{2+}	512	2.51	557	0.014	510	2.90	555	0.013	513	2.69	561	0.010	200
Cd^{2+}	537	3.28	571	0.011	537	3.08	575	0.0080	537	3.28	574	0.010	200
Li^+	531	3.01	571	0.0052	528	2.98	574	0.0048	528	2.97	571	0.0045	200
Na^+	531	2.99	569	0.0055	529	3.11	570	0.0064	531	3.13	568	0.0048	200
K^+	505	3.30	542	0.036	510	3.08	574	0.0062	526	3.13	572	0.0044	200
NH_4^+	527	2.66	562	0.0072	527	2.97	564	0.0055	526	2.97	565	0.0047	200

[a] $\times 10^4\ M^{-1}\ cm^{-1}$.

spectrophotometric data (absorption and emission maxima as well as fluorescence quantum yield) of achiral analogue **1** were found to be very similar to those determined by Baruah et al. (λ_{abs}=529 nm, λ_{em}=565 nm, Φ_f=0.006).[39]

2.3. Stoichiometry and stability of ionophore–metal ion complexes

Based on the previous results of Baruah et al.[39] achiral analogue **1** was proved to be K^+ selective over other alkaline ions (Li^+, Na^+, Cs^+) in acetonitrile. We extended the complexation studies in more detail on achiral ligand **1** and compared the binding properties of chiral analogues (*S*,*S*)-**2** and (*S*,*S*)-**3** towards metal ions (Li^+, Na^+, K^+, Ag^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, Cu^{2+}, Pb^{2+}, Cd^{2+}, Hg^{2+}, Fe^{3+}) and NH_4^+ ion to those obtained for chemosensor **1**. The stability constants and stoichiometries of ionophore–metal ion complexes determined by the mole-ratio[59] or Benesi–Hildebrand[60–62] method are shown in Table 2.

Repeating the titration experiment with K^+ in the case of chemosensor **1**, our result was in good agreement with that described in the literature,[39] namely the absorption and emission spectra of ionophore **1** have been considerably changed upon addition of an excess of K^+. This means that chemosensor **1** forms a relatively stable complex with K^+. In contrast, the absorption and fluorescence spectra of ligand (*S*,*S*)-**3** bearing isobutyl groups on its chiral centres remained unchanged under the same experimental conditions (Fig. 1). Therefore complexation with K^+ does not occur at all in this case, which can be explained by the conformational changes of the crown ether ring owing to the bulky isobutyl groups.

Table 2
Stability constants and stoichiometries of metal ion and NH_4^+ complexes of **1**–(*S*,*S*)-**3** in MeCN[a–c]

	1		(*S*,*S*)-**2**		(*S*,*S*)-**3**	
	log K_s	L:M^{n+}	log K_s	L:M^{n+}	log K_s	L:M^{n+}
Ca^{2+}	12.82	2:1	11.07	2:1	11.92	2:1
Pb^{2+}	7.20	1:1	6.68	1:1	6.32	1:1
Pb^{2+}	—	2:1	12.30	2:1	14.61	2:1
Hg^{2+}	5.84	1:1	5.95	1:1	5.82	1:1
Mg^{2+}	3.18	1:1	2.34	1:1	2.08	1:1
Zn^{2+}	2.86	1:1	2.05	1:1	1.58	1:1
Cd^{2+}	2.28	1:1	3.05	1:1	2.14	1:1
K^+	3.17	1:1	2.03	1:1	—	—
NH_4^+	2.79	1:1	—	—	—	—

[a] No complexation could be observed in the case of Li^+, Na^+ and Ag^+. The stability constants of complexes with Cu^{2+} and Fe^{3+} could not be calculated because of their complicated behaviour.
[b] In the case of 2:1 stoichiometric complexes, K_s denotes the overall equilibrium constant β defined as $[ML_2]/[M][L]^2$.
[c] In the case of Ca^{2+}, Pb^{2+} and Hg^{2+}, the stability constants could be determined by the mole-ratio method and those of other ligand–metal ion complexes were calculated from the Benesi–Hildebrand plots valid for 1:1 stoichiometry.

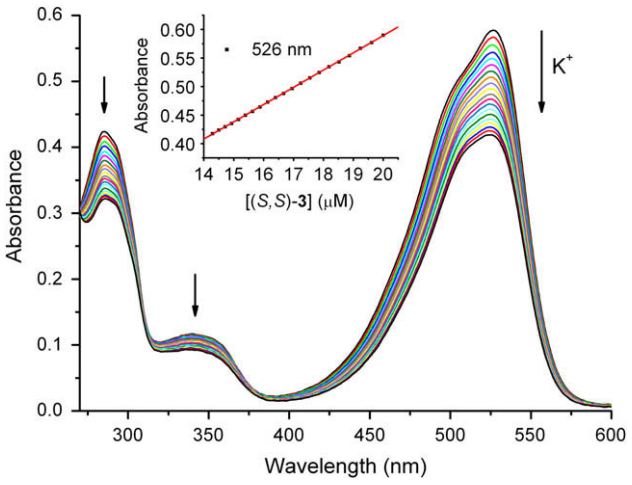


Figure 1. UV–vis titration spectra of (*S*,*S*)-**3** (20 μM, 2.5 mL) on increasing addition of 0.1 M K^+ solution (0–40 mM, 0–1 mL) in MeCN.

Addition of Ca^{2+}, Pb^{2+}, Mg^{2+}, Zn^{2+}, Hg^{2+}, Cu^{2+} ions causes remarkable changes in the absorption and emission spectra of all the three ligands. The most significant effects appear in the case of Ca^{2+}, Pb^{2+}, Hg^{2+} and Cu^{2+} (Figs. 2 and 3).

Addition of 1 equiv of Ca^{2+} and Pb^{2+} ions induced more than 10-fold fluorescence enhancement in acetonitrile. Both absorption and emission bands were blue-shifted by about 18–26 nm (hipsochromic effect, Fig. 2 and Table 1). The formation of relatively stable complexes allowed the calculation of log K_s values by the mol-ratio method.[59] (The log K_s values of other ligand–metal ion complexes were determined from the Benesi–Hildebrand plots[60–62] valid for 1:1 stoichiometry.) Unlike the expected 1:1 ligand to metal ion ratio,[39] the complex stoichiometries of ionophores **1**–(*S*,*S*)-**3** with Ca^{2+} and Pb^{2+} were found to be 2:1. The only exception was the ligand **1**–Pb^{2+} complex, which has 1:1 stoichiometry (Table 2). Nevertheless, increasing concentration of Pb^{2+} shifts the chemical equilibrium to the formation of 1:1 stoichiometric complexes in the case of (*S*,*S*)-**2** and (*S*,*S*)-**3** as well and therefore the titration curves contain two breaking points (not shown). Because of the unexpected stoichiometry of the complexes with Ca^{2+}, the equilibrium constants were also determined by fitting the data using the nonlinear least-squares regression program SPECFIT. The values of overall stability constants (log β=11.81–12.89) are essentially the same as the ones obtained by the mole-ratio method. Comparing the stepwise stability constants, the values of log $K_{s1:1}$ (2.36–3.71) are significantly smaller than those of log $K_{s2:1}$ (9.12–10.53). Therefore on the speciation distribution diagrams (not shown) the complexes with 1:1 stoichiometry could not be practically observed.

A considerable blue-shift of the absorption and emission bands with large fluorescence intensity decrease can be observed upon the addition of Cu^{2+} (0–2 equiv) to ionophores **1**–(*S*,*S*)-**3** (Fig. 3 and Table 1). The spectral characteristics of Cu^{2+} in excess cannot be identified on the UV–vis titration series of spectra as compared to the absorption spectrum of $Cu(ClO_4)_2$ in acetonitrile (3.5 mM $Cu(ClO_4)_2$ in acetonitrile, A=0.07 at 763 nm). Two breaking (equivalent) points appear on the titration curves in the range of 0–2 metal ion to ligand ratio (Fig. 3). At first glance, the fluorescence quenching and the blue-shift of the emission spectra can be explained by the effect of paramagnetic Cu^{2+} ions and the deconjugation of the crown ether nitrogen from the BODIPY moiety, respectively. Our attempt to determine stability constants using nonlinear regression analysis by means of the SPECFIT program was unsuccessful. This can be interpreted by the structural changes of the sensor molecules upon interaction with Cu^{2+}. Probably at higher excess, Cu^{2+} may bind to the dipyrromethene unit by displacement of the BF_2 group.[38] In the same experimental conditions (0–2 equiv) both absorption and emission bands of ionophores **1**–(*S*,*S*)-**3** were significantly blue-shifted [110 nm and 40 nm (λ_{ex}=488 nm), respectively] with an increase of the emission intensities by the effect of Hg^{2+} (not shown). The UV–vis and fluorescence titration experiments of

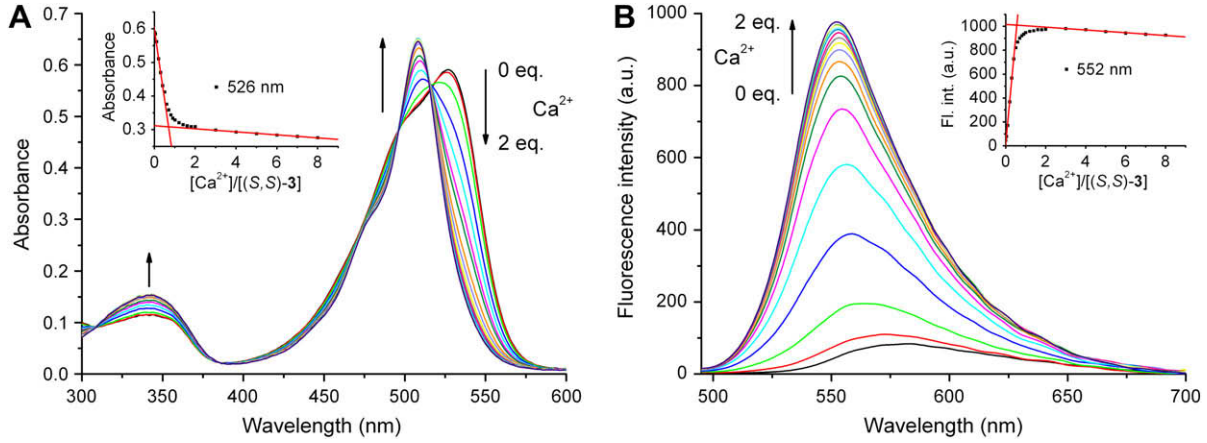


Figure 2. Absorption (**A**) and emission (**B**) series of spectra of (*S*,*S*)-**3** (20 μM) on increasing addition of Ca^{2+} (0–2 equiv) in MeCN, λ_{ex}=488 nm. Insets: titration curves (0–8 equiv) at 526 nm (**A**) and 552 nm (**B**).

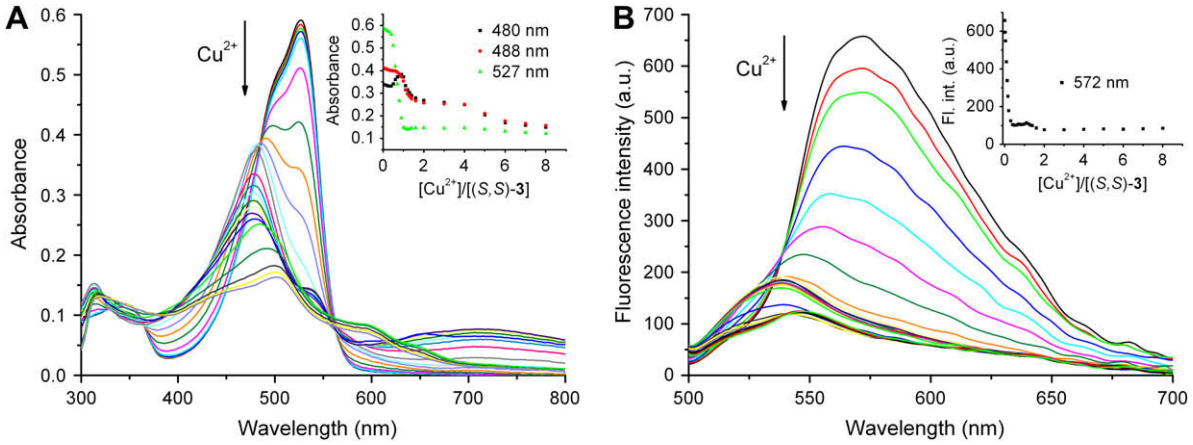


Figure 3. Absorption (**A**) and emission (**B**) series of spectra of (*S*,*S*)-**3** (20 μM) on increasing addition of Cu^{2+} (0–8 equiv) in MeCN, λ_{ex}=488 nm. Insets: titration curves at 480, 488 and 527 nm (**A**) and 572 nm (**B**).

ionophores **1**–(*S*,*S*)-**3** with Fe^{3+} (0–20 equiv) afford similar series of spectra to those with Cu^{2+} (not shown).

In the case of Mg^{2+} and Zn^{2+} ions, approximately 500 and 1000-fold, respectively, higher metal ion concentration was needed to generate similar changes in the absorption and emission spectra than for Ca^{2+} or Pb^{2+} (Table 1). No changes of the spectrophotometric properties could be observed in the case of Li^{+}, Na^{+} and Ag^{+}.

Upon complexation with Ca^{2+}, Pb^{2+}, Mg^{2+}, Zn^{2+} and Hg^{2+} ions, the maxima of both absorption and emission bands are considerably blue-shifted (about 15–40 nm) and large fluorescence enhancement (4–12-fold) is observed with respect to the free ionophores. These indicate that the interaction of metal ions with the nitrogen atom of the crown ether decreases the conjugation of the latter with the π-system of the fluorophore and efficiently suppresses the ICT process in the excited state. Cu^{2+} ions are capable of facilitating the charge transfer (ICT) mechanism thereby resulted in quenching of fluorescence as seen in the cases of several photoinduced electron transfer (PET) sensor molecules.[4–7,9] Comparison of the complex stability constants of ligands **1**–(*S*,*S*)-**3** with a selected metal ion shows that the stability of complexes depends on the conformation of the ionophores changed by the alkyl groups via decreasing the effective diameter of the crown ether ring. The most pronounced effect can be observed in the case of K^{+} and NH_4^{+} (Table 2). It is noteworthy to mention that the introduction of alkyl groups in (*S*,*S*)-**2** and (*S*,*S*)-**3** enhances their selectivity towards Ca^{2+} and Pb^{2+} compared to achiral ligand **1** (Fig. 4 and Table 2).

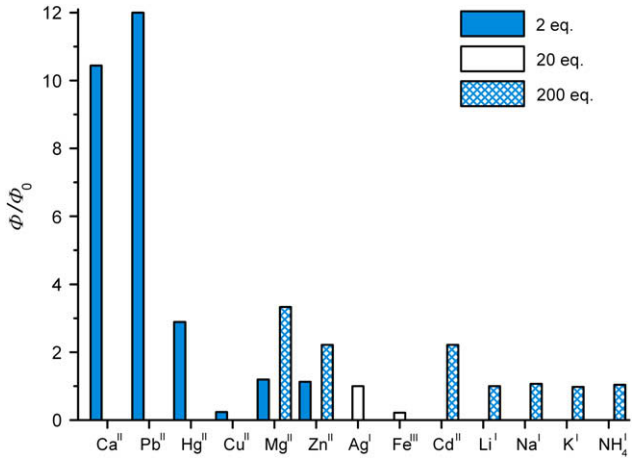


Figure 4. Fluorescence response of (*S*,*S*)-**3** in the presence of various cations in MeCN.

2.4. Enantiomeric recognition of ionophores

Two of the three ionophores studied [(*S*,*S*)-**2** and (*S*,*S*)-**3**] are optically active bearing methyl and isobutyl groups on their chiral centres, respectively. Therefore enantiomers may be theoretically distinguished from each other by these enantiopure ligands. Thus the complexation properties of (*S*,*S*)-**2** and (*S*,*S*)-**3** towards the enantiomers of primary aralkyl ammonium perchlorate (PEA and NEA) salts were also examined.

No changes in both absorption and emission spectra were detected, when the titration experiments were carried out in acetonitrile. Using dichloromethane containing 1% methanol instead of acetonitrile, however, a significant blue-shift of the absorption and emission spectra (ca. 15–25 nm) and fluorescence enhancement could be observed upon addition of the enantiomers of PEA and NEA. The spectrophotometric signals reached a constant value after addition of an excess of the enantiomers of ammonium ions. This means that complexation between the ligands and these organic ammonium ions takes place, but the complexes have relatively small stability constants (Table 3).[25,28] It can be suggested that the spectrophotometric properties of the optically active ligands have not been altered to the same extent by the enantiomers of the organic ammonium salts. However, these differences in the spectrophotometric properties (absorption and emission maxima of complexes, molar absorption coefficients, quantum yields and stability constants) are not suitable for practical applications (Fig. 5 and Table 3). In our opinion, the lack of enantioselectivity or the poor one may be attributed to the relatively high flexibility of chiral ligands (*S*,*S*)-**2** and (*S*,*S*)-**3**. The isobutyl groups in ligand (*S*,*S*)-**3** considerably decreased the stability of complexes formed with the enantiomers of both PEA and NEA compared to achiral analogue **1**. The methyl substituted ligand (*S*,*S*)-**2** is able to discriminate between PEA and NEA in terms of stability of their complexes indicating that the steric hindrance of aromatic rings in the guest molecules also plays an important role besides the alkyl substitution of the host molecule.

3. Conclusion

The synthesis and characterization of two new enantiopure BODIPY linked azacrown ethers (*S*,*S*)-**2** and (*S*,*S*)-**3** have been achieved. The preparation of their several unreported precursors is also performed. BODIPY linked chemosensor (*S*,*S*)-**3** having isobutyl groups on its chiral centres shows significant changes in the absorption and fluorescence spectra upon complexation with Ca^{2+} and Pb^{2+} ions. The isobutyl groups cause improved selectivity

Table 3
Stability constants of complexes of **1**–(*S*,*S*)-**3** with the enantiomers of aralkyl ammonium ions in CH_2Cl_2/MeOH (99:1, v/v)

	1		(*S*,*S*)-**2**		(*S*,*S*)-**3**	
	UV–vis	Fluorescence	UV–vis	Fluorescence	UV–vis	Fluorescence
(*S*)-PEA	4.67±0.13	4.77±0.10	4.60±0.04	4.72±0.04	3.99±0.35	4.09±0.05
(*R*)-PEA	4.83±0.13	4.83±0.15	4.60±0.02	4.71±0.03	4.15±0.32	4.23±0.09
(*S*)-NEA	4.85±0.08	4.82±0.08	4.17±0.12	4.10±0.03	3.98±0.28	4.14±0.14
(*R*)-NEA	4.77±0.06	4.75±0.06	4.12±0.13	3.97±0.01	4.04±0.26	4.06±0.12

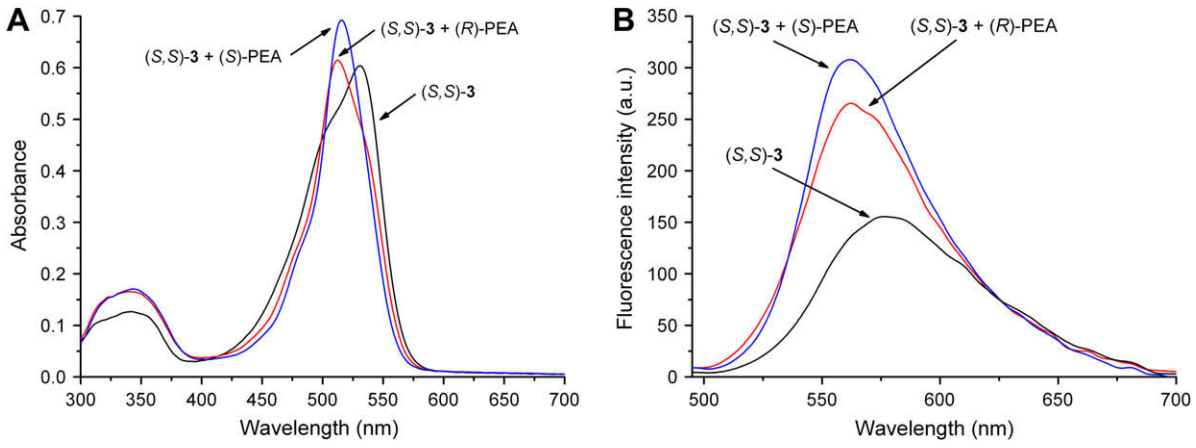


Figure 5. Absorption (**A**) and emission (**B**) spectra of free ligand (*S*,*S*)-**3** (20 μM) and its complexes with (*R*)- and (*S*)-PEA (200 equiv) in CH_2Cl_2/MeOH (99:1, v/v), λ_{ex}=488 nm.

towards the latter ions compared to achiral analogue **1** by changing the conformation of the crown ether ring. As the presence of isobutyl groups in the molecule enhances its lipophilicity as well, this ligand can be a good candidate for a sensing unit of an optode membrane. It shows only moderate enantioselectivity towards the enantiomers of α-phenylethylammonium perchlorate (PEA), which may be attributed to the relatively high flexibility of chiral ligand (*S*,*S*)-**3**. A more rigid system containing fluorescent signalling moiety is expected to show a higher degree of enantiomeric recognition making suitable for practical applications.

4. Experimental

4.1. General

Infrared spectra (neat unless otherwise indicated) were recorded on a Zeiss Specord IR 75 spectrometer. Optical rotations were taken on a Perkin–Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. NMR spectra were recorded in $CDCl_3$ either on a Bruker DRX-500 Avance spectrometer (at 500 MHz for ^1H and 125.8 MHz for ^{13}C spectra) or on a Bruker 300 Avance spectrometer (at 300 MHz for ^1H and 75.5 MHz for ^{13}C spectra) and it is indicated in each individual case. Mass spectra were recorded on a ZQ2000 MS instrument (Waters Corp.) using ESI method. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute of Chemistry, L. Eötvös University, Budapest, Hungary. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminium oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Silica gel 60 (70–230 mesh, Merck) and aluminium oxide (neutral, activated, Brockman I) were used for column chromatography. Ratios of solvents for the eluents are given in volumes (mL/mL). Romil Ltd (Cambridge, UK) SuperPurity Solvent grade THF stored under argon was used as purchased. All other solvents were dried and purified according to well-established methods.[63] Evaporations were carried out under reduced pressure.

UV–vis spectra were taken on a UNICAM UV4-100 spectrophotometer controlled by VISION 3.4 software (ATI UNICAM, Cambridge, UK). Fluorescence spectra were recorded on a Perkin–Elmer LS 50B luminescent spectrometer supplied with a FL WinLab 3.0™ software (Perkin–Elmer Corp., USA). Both the emission and excitation spectra were corrected by the spectrometer software. Quartz cuvettes with path length of 1 cm were used. Fluorescence quantum yields were determined relative to Rhodamine 6 G (Φ_f=0.76 in water, λ_{ex}=488 nm).[64] Spectrophotometric titrations were carried out according to the literature.[65] Titrant metal ions in MeCN or chiral primary aralkyl ammonium ions in CH_2Cl_2/MeOH (99:1, v/v) were employed for the log K_s determination of the ionophore complexes. Perchlorate salts of ions were used in general with the exception of KSCN, $AgNO_3$, $FeCl_3$ and NH_4SCN. All of metal ion salts were of analytical grade. Chiral aralkyl ammonium perchlorate salts were prepared in our laboratory.[28] The concentration of titrant ions was 0.001 M (Ca^{2+}, Pb^{2+}, Mg^{2+}, Zn^{2+}, Hg^{2+}, Cu^{2+}) or 0.01 M (Ag^+, Fe^{3+} and chiral aralkyl ammonium ions) or 0.1 M (Li^+, Na^+, K^+, NH_4^+, Mg^{2+}, Zn^{2+}, Cd^{2+}). The titrant was added with a Hamilton syringe to a 2.5 mL ionophore containing (20 μM) MeCN or CH_2Cl_2/MeOH (99:1, v/v) solution in a quartz cell. If the spectrophotometric signals reached a constant value only after addition of a considerable excess of titrant ions, the Benesi–Hildebrand evaluation[60–62] was applied for the calculation of the log K_s values. For the determination of some of the stability constants by nonlinear regression analysis, SPECFIT/32™ program was used.

4.2. General procedure for the synthesis of chiral BODIPY linked monoazacrown ethers (*S*,*S*)-2 and (*S*,*S*)-3

Ligands (*S*,*S*)-**2** and (*S*,*S*)-**3** were synthesized according to the procedure described in the literature[39] for the achiral analogue **1** with the exception that the molar ratio of crown ethers (*S*,*S*)-**5** and (*S*,*S*)-**6**, respectively, to BODIPY derivative **7** was 1:1 instead of 1.5:1. The crude products were purified as described below for each compound.

*4.2.1. (2S,12S)-16-{(2Z)-2-[[1-(Difluoroboryl)-5-methoxy-1H-pyrrol-2-yl](phenyl)methylene]-2H-pyrrol-5-yl}-2,12-dimethyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane [(S,S)-**2**].* The crude product was purified by column chromatography on silica gel using 1:2 acetone/hexane as an eluent to give (*S*,*S*)-**2** (32 mg, 20%) starting from (*S*,*S*)-**5** (80 mg, 0.276 mmol), **7** (92 mg, 0.276 mmol), triethylamine (1 mL) and MeCN (40 mL). Reddish violet oil. R_f=0.21 (silica gel TLC, 1:2 acetone/hexane); $[\alpha]_D^{25}$ −163 (*c* 0.240, CH_2Cl_2); IR (KBr) ν_{max} 3472, 3072, 2958, 2932, 2872, 1564, 1512, 1460, 1401, 1354, 1309, 1264, 1208, 1152, 1110, 1088, 1032, 991, 971, 882, 851, 722, 703 cm^{-1}; ^1H NMR (500 MHz) δ 1.10 (d, *J*=6 Hz, 6H), 1.69 (s, br, complexed H_2O), 3.41–3.51 (m, 4H), 3.56–3.73 (m, 10H), 3.78–3.86 (m, 2H), 3.90–4.01 (m, 2H), 3.98 (s, 3H), 4.01–4.10 (m, 2H), 4.10–4.27 (m, 2H), 5.64 (d, *J*=4 Hz, 1H), 6.26 (d, *J*=4 Hz, 1H), 6.34 (d, *J*=5 Hz, 1H), 6.71 (d, *J*=5 Hz, 1H), 7.38–7.48 (m, 5H); ^{13}C NMR (75.5 MHz) δ 16.83, 53.91, 58.27, 68.67, 71.01, 71.13, 75.49, 75.73, 93.31, 113.10, 120.23, 125.56, 128.12, 128.77, 130.79, 131.32, 133.32, 133.86, 135.32, 160.46, 162.15; MS: 588 $(M+1)^+$. Anal. Calcd for $C_{30}H_{40}BF_2N_3O_6\cdot H_2O$: C, 59.51; H, 6.99; N, 6.94. Found: C, 59.42; H, 7.03; N, 6.86.

*4.2.2. (2S,12S)-16-{(2Z)-2-[[1-(Difluoroboryl)-5-methoxy-1H-pyrrol-2-yl](phenyl)methylene]-2H-pyrrol-5-yl}-2,12-diisobutyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane [(S,S)-**3**].* The crude product was purified by column chromatography on silica gel using 1:3 acetone/hexane as an eluent to give (*S*,*S*)-**3** (33 mg, 18%) starting from (*S*,*S*)-**6** (104 mg, 0.276 mmol), **7** (92 mg, 0.276 mmol), triethylamine (1 mL) and MeCN (40 mL). Reddish violet oil. R_f=0.43 (silica gel TLC, 1:2 acetone/hexane); $[\alpha]_D^{25}$ −185 (*c* 0.275, CH_2Cl_2); IR ν_{max} 3585, 3137, 3058, 2955, 2928, 2870, 1574, 1505, 1466, 1402, 1359, 1312, 1268, 1233, 1159, 1112, 1091, 1023, 994, 969, 885, 847, 737, 709 cm^{-1}; ^1H NMR (500 MHz) δ 0.81 (d, *J*=7 Hz, 6H), 0.82 (d, *J*=7 Hz, 6H), 1.00–1.10 (m, 2H), 1.30–1.40 (m, 2H), 1.56–1.68 (m, 2H), 1.75 (s, br, complexed H_2O), 3.25–3.67 (m, 14H), 3.81–3.89 (m, 4H), 3.90 (s, 3H), 3.93–4.02 (m, 2H), 4.07–4.17 (m, 2H), 5.55 (d, *J*=3 Hz, 1H), 6.17 (d, *J*=3 Hz, 1H), 6.31 (d, *J*=5 Hz, 1H), 6.62 (d, *J*=5 Hz, 1H), 7.31–7.40 (m, 5H); ^{13}C NMR (75.5 MHz) δ 22.61, 23.45, 24.83, 40.94, 54.01, 58.23, 69.30, 71.05, 71.10, 74.87, 78.22, 93.06, 113.66, 119.79, 125.52, 128.10, 128.70, 130.81, 130.93, 133.12, 133.95, 135.42, 160.26, 162.36; MS: 672 $(M+1)^+$. Anal. Calcd for $C_{36}H_{52}BF_2N_3O_6\cdot H_2O$: C, 62.70; H, 7.89; N, 6.09. Found: C, 62.62; H, 7.80; N, 5.95.

4.3. General procedure for the synthesis of chiral monoazacrown ethers (*S,S*)-5 and (*S,S*)-6

Hydrogenation of *N*-benzyl-blocked dimethyl-substituted monoazacrown ether (*S*,*S*)-**19** (801 mg, 2.1 mmol) or *N*-benzyl-blocked diisobutyl-substituted monoazacrown ether (*S*,*S*)-**20** (978 mg, 2.1 mmol) was carried out in MeOH (40 mL) over Pd/C catalyst (98 mg, 10% palladium on charcoal, activated) in a similar way as described above for dibenzyl-protected oligoethers (*S*,*S*)-**13** and (*S*,*S*)-**14** to give the desired monoazacrown ethers (*S*,*S*)-**5** and (*S*,*S*)-**6**. The crude products were either purified by column chromatography or used without purification as described below for each compound.

*4.3.1. (2S,12S)-2,12-Dimethyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane [(S,S)-**5**].* The crude product was purified by column chromatography on alumina using 1:20 EtOH/toluene as an eluent to give (*S*,*S*)-**5** (263 mg, 43%) as a colourless oil. R_f=0.21 (alumina TLC, 1:10 EtOH/toluene); $[\alpha]_D^{25}$ +35.7 (*c* 2.01, EtOH); IR ν_{max} 3504, 3345, 3072, 2872, 1648, 1624, 1584, 1456, 1376, 1352, 1320, 1248, 1128, 1016, 1000, 852, 836 cm^{-1}; ^1H NMR (500 MHz) δ 1.05 (d, *J*=6 Hz, 6H), 2.70–2.79 (m, 4H), 2.92 (s, br, 1H), 3.35–3.45 (m, 4H), 3.49–3.71 (m, 14H); ^{13}C NMR (75.5 MHz) δ 16.34, 49.66, 68.02, 70.77, 71.19, 74.70, 75.60. Anal. Calcd for $C_{14}H_{29}NO_5$: C, 57.71; H, 10.03; N, 4.81. Found: C, 57.59; H, 10.14; N, 4.73.

*4.3.2. (2S,12S)-2,12-Diisobutyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane [(S,S)-**6**].* Yield: 726 mg (92%). Colourless oil. R_f=0.41 (alumina TLC, 1:10 EtOH/toluene); $[\alpha]_D^{25}$ +3.1 (*c* 2.00, EtOH); IR ν_{max} 3501, 3342, 2957, 2888, 2872, 1649, 1619, 1581, 1456, 1376, 1352, 1312, 1251, 1129, 1014, 1002, 851, 834 cm^{-1}; ^1H NMR (300 MHz) δ 0.90 (d, *J*=7 Hz, 12H), 1.07–1.21 (m, 2H), 1.37–1.50 (m, 2H), 1.58–1.78 (m, 2H), 2.62–2.91 (m, 4H), 3.01 (s, br, 1H), 3.36–3.76 (m, 18H); ^{13}C NMR (75.5 MHz) δ 22.76, 23.29, 24.69, 24.82, 40.61, 49.81, 68.74, 70.83, 71.29, 74.77. Anal. Calcd for $C_{20}H_{41}NO_5$: C, 63.97; H, 11.00; N, 3.73. Found: C, 63.88; H, 11.17; N, 3.62.

4.4. General procedure for the synthesis of chiral hexaethylene glycol dibenzyl ethers (*S,S*)-11 and (*S,S*)-12

A solution of dimethyl-substituted tetraethylene glycol (*S*,*S*)-**8**[54] (3.73 g, 16.8 mmol) or diisobutyl-substituted tetraethylene glycol (*S*,*S*)-**9**[55] (5.15 g, 16.8 mmol) in dry THF (50 mL) was added dropwise under Ar at rt to a well stirred suspension of NaH (2.15 g, 53.8 mmol, 60% dispersion in mineral oil) in dry THF (20 mL). After the addition was completed, the mixture was stirred at reflux temperature for 2 h. The reaction mixture was cooled down to −5 °C and a solution of mesylate **10**[56] (8.51 g, 37.0 mmol) in dry THF (80 mL) was added dropwise, and then it was allowed to warm up to rt. Stirring was continued at rt for 4 days. The solvent was removed and the unreacted NaH was destroyed by addition of ice (20 g) and water (10 mL) to the residue. The mixture was stirred vigorously for 15 min. Ether (80 mL) was added to the mixture and the phases were mixed well and separated. The aqueous phase was extracted with ether (3×40 mL). The combined organic phase was shaken with saturated brine (1×60 mL), dried over $MgSO_4$, filtered and the solvent was evaporated. The crude products were purified as described below for each compound.

*4.4.1. (6S,16S)-6,16-Dimethyl-1,21-diphenyl-2,5,8,11,14,17,20-heptaoxahenicosane [(S,S)-**11**].* The crude product was purified by column chromatography on silica gel using 2:3 EtOAc/hexane as an eluent to give (*S*,*S*)-**11** (3.13 g, 38%) as a colourless oil. R_f=0.35 (silica gel TLC, 1:1 EtOAc/hexane); $[\alpha]_D^{25}$ +4.9 (*c* 2.01, CH_2Cl_2); IR ν_{max} 3080, 3064, 3048, 3032, 3016, 2980, 2950, 2872, 1648, 1608, 1536, 1496, 1456, 1376, 1280, 1208, 1116, 1056, 1040, 740, 700 cm^{-1}; ^1H NMR (500 MHz) δ 1.19 (d, *J*=6 Hz, 6H), 3.41–3.57 (m, 4H), 3.61–3.78 (m, 18H), 4.60 (s, 4H), 7.25–7.41 (m, 10H); ^{13}C NMR (125.8 MHz) δ 17.42, 68.82, 69.98, 70.81, 70.98, 73.40, 75.26, 75.44, 127.73, 127.90, 128.53, 138.61. Anal. Calcd for $C_{28}H_{42}O_7$: C, 68.55; H, 8.63. Found: C, 68.46; H, 8.71.

*4.4.2. (6S,16S)-6,16-Diisobutyl-1,21-diphenyl-2,5,8,11,14,17,20-heptaoxahenicosane [(S,S)-**12**].* The crude product was purified by column chromatography on silica gel using 2:5 EtOAc/hexane as an eluent to give (*S*,*S*)-**12** (4.34 g, 45%) as a colourless oil. R_f=0.25 (silica gel TLC, 2:5 EtOAc/hexane); $[\alpha]_D^{25}$ −14.6 (*c* 2.01, CH_2Cl_2); IR ν_{max} 3081, 3063, 3032, 3016, 2952, 2944, 2864, 1496, 1456, 1368, 1108, 736, 696, 620, 602 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (d, *J*=7 Hz, 6H), 0.91 (d, *J*=7 Hz, 6H), 1.20–1.27 (m, 2H), 1.41–1.49 (m, 2H), 1.73–1.84 (m, 2H), 3.43–3.69 (m, 20H), 3.80–3.87 (m, 2H), 4.55 (s, 4H), 7.23–7.36 (m, 10H); ^{13}C NMR (75.5 MHz) δ 22.51, 23.56, 24.65, 41.44, 69.69, 70.11, 70.81, 70.98, 73.33, 74.77, 77.75, 127.66, 127.83, 128.47, 138.65. Anal. Calcd for $C_{34}H_{54}O_7$: C, 71.05; H, 9.47. Found: C, 70.97; H, 9.61.

4.5. General procedure for the synthesis of chiral hexaethylene glycols (*S,S*)-13 and (*S,S*)-14

Dibenzyl-blocked dimethyl-substituted hexaethylene glycol (*S*,*S*)-**11** (3.68 g, 7.5 mmol) or dibenzyl-blocked diisobutyl-substituted

hexaethylene glycol (*S,S*)-**12** (4.31 g, 7.5 mmol) was hydrogenated in MeOH (175 mL) in the presence of Pd/C catalyst (0.86 g, 10% palladium on charcoal, activated) until the theoretical volume of hydrogen was consumed. After the reaction was completed, the catalyst was filtered off and the solvent was evaporated to give the desired hexaethylene glycols, which were used without purification.

*4.5.1. (4S,14S)-4,14-Dimethyl-3,6,9,12,15-pentaoxaheptadecane-1,17-diol [(S,S)-**13**].* Yield: 2.14 g (92%). Colourless oil. R_f=0.33 (silica gel TLC, 1:4 MeOH/EtOAc); $[\alpha]_D^{25}$ +26.8 (*c* 2.00, CH_2Cl_2); IR ν_{max} 3400, 2981, 2948, 2872, 1460, 1376, 1352, 1256, 1112, 976, 956, 916, 880 cm^{-1}; ^1H NMR (500 MHz) δ 1.10 (d, *J*=6 Hz, 6H), 3.27 (s, br, 2H), 3.41–3.48 (m, 4H), 3.51–3.58 (m, 2H), 3.60–3.74 (m, 16H); ^{13}C NMR (125.8 MHz) δ 17.05, 62.08, 70.66, 70.77, 70.81, 75.12, 75.52. Anal. Calcd for $C_{14}H_{30}O_7$: C, 54.18; H, 9.74. Found: C, 54.06; H, 9.82.

*4.5.2. (4S,14S)-4,14-Diisobutyl-3,6,9,12,15-pentaoxaheptadecane-1,17-diol [(S,S)-**14**].* Yield: 2.78 g (94%). Colourless oil. R_f=0.75 (silica gel TLC, 1:4 MeOH/EtOAc); $[\alpha]_D^{25}$ +4.1 (*c* 2.12, CH_2Cl_2); IR ν_{max} 3440, 2952, 2888, 2872, 1560, 1536, 1468, 1368, 1116, 972, 940, 908, 884 cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (d, *J*=7 Hz, 6H), 0.93 (d, *J*=7 Hz, 6H), 1.15–1.22 (m, 2H), 1.40–1.48 (m, 2H), 1.68–1.80 (m, 2H), 3.31 (s, br, 2H), 3.42–3.53 (m, 4H), 3.58–3.76 (m, 18H); ^{13}C NMR (75.5 MHz) δ 22.56, 23.50, 24.68, 41.48, 62.43, 70.65, 70.83, 72.08, 74.95, 77.75. Anal. Calcd for $C_{20}H_{42}O_7$: C, 60.88; H, 10.73. Found: C, 60.74; H, 10.85.

4.6. General procedure for the synthesis of chiral hexaethylene glycol ditosylates (*S,S*)-15 and (*S,S*)-16

To stirred dimethyl-substituted hexaethylene glycol (*S,S*)-**13** (2.95 g, 9.5 mmol) or diisobutyl-substituted hexaethylene glycol (*S,S*)-**14** (3.75 g, 9.5 mmol) a solution of tosyl chloride (3.98 g, 20.9 mmol) in dry triethylamine (50 mL) was added dropwise under Ar at rt. After the addition was completed, the reaction mixture was stirred at rt for 2 days. Excess triethylamine was evaporated, and the residue was dissolved in a mixture of ether (100 mL) and water (30 mL). The p*H* of the aqueous phase was adjusted to 2 by addition of 5% aqueous HCl solution and the phases were mixed well and separated. The aqueous phase was extracted with ether (3×50 mL). The combined organic phase was shaken with saturated brine (1×80 mL), dried over $MgSO_4$, filtered and the solvent was removed. The crude products were either purified by column chromatography or used without purification as described below for each compound.

*4.6.1. (4S,14S)-4,14-Dimethyl-3,6,9,12,15-pentaoxaheptadecane-1,17-diyl bis(4-methylbenzenesulfonate) [(S,S)-**15**].* The crude product was purified by column chromatography on silica gel using 1:8 acetone/toluene as an eluent to give (*S,S*)-**15** (2.70 g, 46%) as a colourless oil. R_f=0.40 (silica gel TLC, 1:6 EtOH/toluene); $[\alpha]_D^{25}$ +6.4 (*c* 2.03, CH_2Cl_2); IR ν_{max} 3082, 3058, 3032, 2957, 2882, 2872, 1600, 1568, 1560, 1496, 1456, 1360, 1296, 1176, 1160, 1096, 1016, 920, 816, 776, 664, 552, 540 cm^{-1}; ^1H NMR (500 MHz) δ 1.07 (d, *J*=6 Hz, 6H), 2.44 (s, 6H), 3.34–3.43 (m, 4H), 3.56–3.63 (m, 10H), 3.67–3.76 (m, 4H), 4.13 (t, *J*=5 Hz, 4H), 7.33 (d, *J*=8 Hz, 4H), 7.79 (d, *J*=8 Hz, 4H); ^{13}C NMR (75.5 MHz) δ 17.20, 21.80, 66.98, 69.81, 70.75, 70.95, 75.48, 75.53, 128.15, 129.97, 133.33, 144.90. Anal. Calcd for $C_{28}H_{42}O_{11}S_2$: C, 54.35; H, 6.84. Found: C, 54.20; H, 6.91.

*4.6.2. (4S,14S)-4,14-Diisobutyl-3,6,9,12,15-pentaoxaheptadecane-1,17-diyl bis(4-methylbenzenesulfonate) [(S,S)-**16**].* Yield: 4.27 g (64%). Pale yellow oil. R_f=0.49 (silica gel TLC, 1:6 EtOH/toluene); $[\alpha]_D^{25}$ −10.7 (*c* 2.18, CH_2Cl_2); IR ν_{max} 3080, 3058, 3029, 2960, 2888, 2872, 1600, 1572, 1560, 1496, 1460, 1360, 1296, 1176, 1168, 1120, 1012, 920, 816, 772, 664, 552, 544 cm^{-1}; ^1H NMR (500 MHz) δ 0.84 (d, *J*=7 Hz, 6H), 0.86 (d, *J*=7 Hz, 6H), 1.10–1.17 (m, 2H), 1.29–1.37 (m, 2H), 1.60–1.71 (m, 2H), 2.44 (s, 6H), 3.35–3.63 (m, 14H), 3.64–3.70 (m, 2H), 3.84–3.90 (m, 2H), 4.13 (t, *J*=5 Hz, 4H), 7.33 (d, *J*=8 Hz, 4H), 7.79 (d, *J*=8 Hz, 4H); ^{13}C NMR (125.8 MHz) δ 21.81, 22.37, 23.51, 24.51, 41.12, 67.94, 69.90, 70.76, 70.93, 75.04, 78.02, 128.17, 129.95, 133.36, 144.85. Anal. Calcd for $C_{34}H_{54}O_{11}S_2$: C, 58.10; H, 7.74. Found: C, 58.03; H, 7.82.

4.7. General procedure for the synthesis of chiral hexaethylene glycol diiodo derivatives (*S,S*)-17 and (*S,S*)-18

A mixture of dimethyl-substituted hexaethylene glycol ditosylate (*S,S*)-**15** (1.30 g, 2.1 mmol) or diisobutyl-substituted hexaethylene glycol ditosylate (*S,S*)-**16** (1.48 g, 2.1 mmol), NaI (1.26 g, 8.4 mmol) and dry acetone (20 mL) was stirred under Ar at reflux temperature for 16 h. The solvent was removed and the residue was dissolved in a mixture of ether (80 mL) and water (10 mL). The phases were mixed well and separated. The aqueous phase was extracted with ether (3×40 mL). The combined organic phase was shaken with saturated brine (1×60 mL), dried over $MgSO_4$, filtered and the solvent was removed. The crude products were purified as described below for each compound.

*4.7.1. (4S,14S)-1,17-Diiodo-4,14-dimethyl-3,6,9,12,15-pentaoxaheptadecane [(S,S)-**17**].* The crude product was purified by column chromatography on silica gel using 1:6 acetone/hexane as an eluent to give (*S,S*)-**17** (0.73 g, 66%) as a pale yellow oil. R_f=0.51 (silica gel TLC, 1:6 EtOH/toluene); $[\alpha]_D^{25}$ +3.0 (*c* 2.00, CH_2Cl_2); IR ν_{max} 2968, 2952, 2872, 1560, 1456, 1376, 1344, 1264, 1112, 1000, 924 cm^{-1}; ^1H NMR (500 MHz) δ 1.18 (d, *J*=6 Hz, 6H), 3.21–3.30 (m, 4H), 3.43–3.54 (m, 4H), 3.64–3.74 (m, 10H), 3.81 (t, *J*=7 Hz, 4H); ^{13}C NMR (125.8 MHz) δ 3.84, 17.30, 70.24, 70.63, 70.85, 75.09, 75.40. Anal. Calcd for $C_{14}H_{28}I_2O_5$: C, 31.72; H, 5.32. Found: C, 31.68; H, 5.41.

*4.7.2. (4S,14S)-1,17-Diiodo-4,14-diisobutyl-3,6,9,12,15-pentaoxaheptadecane [(S,S)-**18**].* The crude product was purified by column chromatography on silica gel using 1:7 acetone/hexane as an eluent to give (*S,S*)-**18** (1.02 g, 79%) as a pale yellow oil. R_f=0.61 (silica gel TLC, 1:6 EtOH/toluene); $[\alpha]_D^{25}$ −9.3 (*c* 2.01, CH_2Cl_2); IR ν_{max} 2952, 2944, 2872, 1464, 1408, 1352, 1264, 1116 cm^{-1}; ^1H NMR (300 MHz) δ 0.91 (d, *J*=7 Hz, 6H), 0.92 (d, *J*=7 Hz, 6H), 1.15–1.28 (m, 2H), 1.38–1.51 (m, 2H), 1.73–1.91 (m, 2H), 3.17–3.31 (m, 4H), 3.42–3.52 (m, 4H), 3.52–3.69 (m, 10H), 3.69–3.81 (m, 2H), 3.86–3.98 (m, 2H); ^{13}C NMR (75.5 MHz) δ 4.23, 22.46, 23.61, 24.62, 41.41, 70.88, 71.06, 71.35, 75.21, 77.77. Anal. Calcd for $C_{20}H_{40}I_2O_5$: C, 39.10; H, 6.56. Found: C, 39.01; H, 6.70.

4.8. General procedure for the synthesis of *N*-benzyl derivatives of chiral monoazacrown ethers (*S,S*)-19 and (*S,S*)-20

A mixture of dimethyl-substituted hexaethylene glycol diiodide (*S,S*)-**17** (689 mg, 1.3 mmol) or diisobuyl-substituted hexaethylene glycol diiodide (*S,S*)-**18** (799 mg, 1.3 mmol), benzylamine (139 mg, 1.3 mmol), K_2CO_3 (719 mg, 5.2 mmol) and dry MeCN (15 mL) was stirred under Ar at reflux temperature for 24 h. The solvent was evaporated and the residue was dissolved in a mixture of CH_2Cl_2 (40 mL) and water (40 mL). The phases were mixed well and separated. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The crude products were purified as described below for each compound.

*4.8.1. (2S,12S)-16-Benzyl-2,12-dimethyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane [(S,S)-**19**].* The crude product was purified by column chromatography on alumina using 1:200 EtOH/toluene as an eluent to give (*S,S*)-**19** (263 mg, 53%) as a colourless oil. R_f=0.61

(alumina TLC, 1:20 EtOH/toluene); $[\alpha]_D^{25}$ +5.9 (*c* 2.03, acetone); IR ν_{max} 3081, 3042, 3016, 2964, 2910, 2872, 1624, 1496, 1456, 1376, 1296, 1120, 736, 700 cm^{-1}; ^1H NMR (300 MHz) δ 1.10 (d, *J*=6 Hz, 6H), 2.66–2.90 (m, 4H), 3.37–3.56 (m, 4H), 3.60–3.80 (m, 16H), 7.19–7.39 (m, 5H); ^{13}C NMR (75.5 MHz) δ 17.11, 54.13, 60.21, 67.86, 71.01, 71.05, 74.91, 75.93, 126.80, 128.14, 128.93, 139.88. Anal. Calcd for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25; N, 3.67. Found: C, 65.97; H, 9.39; N, 3.48.

*4.8.2. (2S,12S)-16-Benzyl-2,12-diisobutyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane [(S,S)-**20**].* The crude product was purified by column chromatography on alumina using 1:200 EtOH/toluene as an eluent to give (*S,S*)-**20** (297 mg, 49%) as a colourless oil. R_f=0.82 (alumina TLC, 1:20 EtOH/toluene); $[\alpha]_D^{25}$ −13.9 (*c* 2.01, EtOH); IR ν_{max} 3084, 3046, 3016, 2960, 2907, 2872, 1648, 1564, 1496, 1456, 1368, 1112, 952, 736, 696 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (d, *J*=7 Hz, 6H), 0.89 (d, *J*=7 Hz, 6H), 1.08–1.15 (m, 2H), 1.35–1.42 (m, 2H), 1.63–1.76 (m, 2H), 2.64–2.84 (m, 4H), 3.43–3.84 (m, 20H), 7.16–7.36 (m, 5H); ^{13}C NMR (125.8 MHz) δ 22.51, 23.51, 24.73, 41.29, 54.40, 60.76, 68.94, 71.21, 71.30, 75.66, 77.59, 126.93, 128.26, 129.13, 139.97. Anal. Calcd for $C_{27}H_{47}NO_5$: C, 69.64; H, 10.17; N, 3.01. Found: C, 69.51; H, 10.25; N, 2.98.

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