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Synthesis and enantiomeric recognition studies of dialkyl-substituted 18-crown-6 ethers containing an acridine fluorophore unit

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ABSTRACT

Selectivity of the reported dimethyl-substituted (*R,R*)-**1**, the diisobutyl-substituted (*R,R*)-**2** acridino-18-crown-6 ethers and the newly synthesized acridino-crown ether (*S,S*)-**3** containing the methyl groups one carbon–carbon bond further away from the acridine unit was studied towards the enantiomers of the hydrogen perchlorate salts of α-phenylethylamine, α-(1-naphthyl)ethylamine, phenylglycine methyl ester and phenylalanine methyl ester using fluorescence.

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1. Introduction

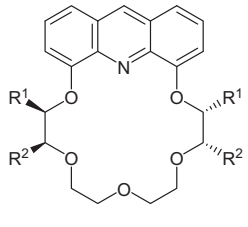
Enantiomeric recognition, as a special case of molecular recognition, is a widespread and important phenomenon in Nature. Examples of its action include the anabolism and catabolism of single enantiomeric forms of amino acids and sugars in biosynthetic pathways. Since the individual enantiomers of a biologically active compound have different toxicological and pharmacological properties, the determination of the enantiomeric composition of organic compounds has great importance in pharmaceutical, cosmetic and pesticide industries as well as in environmental analysis.

Primary amines, amino acids and their derivatives are very important molecules of biological relevance. Amino acids are the building blocks of proteins, and primary amines are formed during the degradation of amino acids or serve as neurotransmitters. Therefore, the development of synthetic receptors for their enantioselective recognition is also of great importance.[1]

Sensor molecules capable of enantiomeric recognition can be built into potentiometric membrane electrodes,[2–9] optodes,[10,11] amperometric biosensors,[6,8,12] voltammetric electrodes,[8] immunosensors[6,8] and enantioselective sensors with molecularly imprinted polymers.[6,8]

Fluorescence spectroscopy offers a sensitive, selective and versatile detection method.[13,14] Over the past two decades, numerous fluorescent sensor molecules were investigated for chiral recognition,[15–21] including some crown ethers,[22–29] too. The enantiomeric recognition abilities of the latter macrocycles containing various fluorescent units towards the enantiomers of amino acid derivatives, amino alcohols and primary amines were studied.

Earlier studies on the complexation properties of crown ethers containing a pyridine subcyclic unit showed excellent complexation properties towards protonated primary amines and amino acids.[30] Complexation studies of the enantiomerically pure pyridino-crown ethers with protonated primary aralkyl amines and amino acids proved that the enantioselectivity is based on three independent interactions: tripodal hydrogen bonding, π–π stacking and steric repulsion. To enhance π–π interactions, we previously prepared crown ethers containing an acridine subcyclic unit.[9,31,32] The latter crown ethers, which contain an acridine unit instead of a pyridine one are not only more rigid, which improves selectivity, but they



(*R,R*)-**1**: R^1=Me, R^2=H
(*R,R*)-**2**: R^1=iBu, R^2=H
(*S,S*)-**3**: R^1=H, R^2=Me

Figure 1. Schematics of enantiopure crown ethers containing an acridine unit.

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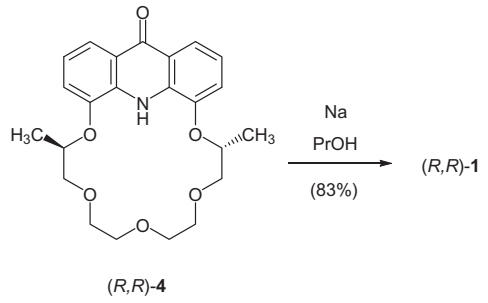
are also fluorogenic, so their complexation properties can be studied using the sensitive fluorescence spectroscopy.

Herein we report the complexation studies of the dimethyl-substituted (*R*,*R*)-**1**,[31] diisobutyl-substituted (*R*,*R*)-**2**[9] and the new dimethyl-substituted (*S*,*S*)-**3** acridino-18-crown-6 ethers (Fig. 1) towards the enantiomers of protonated primary amines and amino acid methyl esters using fluorescence spectroscopic method.

2. Results and discussion

2.1. Synthesis

Enantiopure dimethyl-substituted (*R*,*R*)-**1**[31] and diisobutyl-substituted (*R*,*R*)-**2**[9] acridino-crown ethers (Fig. 1) were prepared according to the literature. Dimethyl-substituted macrocycle (*R*,*R*)-**1** was also synthesized starting from the reported acridono-crown ether (*R*,*R*)-**4**[33] using sodium metal in propanol (Scheme 1) as described for the reduction of previously reported similar acridono-crown ethers.[9]



Scheme 1. New synthesis of dimethyl-substituted crown ether (*R*,*R*)-**1**.

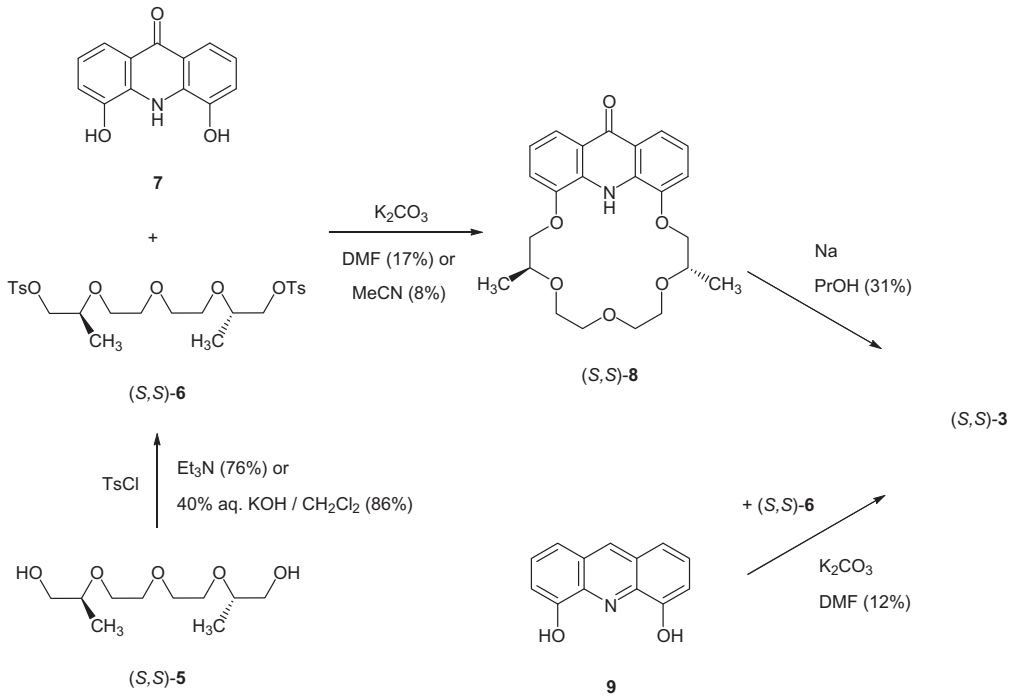
New enantiopure dimethyl-substituted macrocycle (*S*,*S*)-**3** was prepared as outlined in Scheme 2. The reported enantiopure tetraethylene glycol (*S*,*S*)-**5**[34] was treated with tosyl chloride in triethylamine and in 40% aqueous potassium hydroxide–dichloromethane mixture, respectively, to obtain ditosylate (*S*,*S*)-**6** in good yield. 4,5-Dihydroxyacridin-9(10*H*)one **7**[35] was then reacted with ditosylate (*S*,*S*)-**6** in the presence of a weak base potassium carbonate in DMF or in acetonitrile according to the procedure described for the synthesis of the parent achiral acridono-crown ether[35] to give ligand (*S*,*S*)-**8**. Acridono-crown ether (*S*,*S*)-**8** was then reduced with sodium metal in propanol to give acridino-crown ether (*S*,*S*)-**3** as described for the reduction of the previously reported similar acridono-crown ethers.[9] Macrocycle (*S*,*S*)-**3** was also prepared starting from acridine-4,5-diol **9**[9] and ditosylate (*S*,*S*)-**6** in the presence of potassium carbonate in DMF according to the procedure described for the synthesis of acridino-crown ether (*R*,*R*)-**1**.[31]

2.2. Enantiomeric recognition studies

The enantiomeric recognition abilities of acridino-crown ethers (*R*,*R*)-**1**, (*R*,*R*)-**2** and (*S*,*S*)-**3** (Fig. 1) were studied in acetonitrile towards the enantiomers of α-phenylethylamine hydrogen perchlorate (PEA), α-(1-naphthyl)ethylamine hydrogen perchlorate (NEA), phenylglycine methyl ester hydrogen perchlorate (PGME) and phenylalanine methyl ester hydrogen perchlorate (PAME) salts (Fig. 2).

Upon titration of ligands (*R*,*R*)-**1**, (*R*,*R*)-**2** and (*S*,*S*)-**3** with the enantiomers of the optically active salts, the absorption spectra hardly changed, since only a slight bathochromic shift (5–10 nm) could be observed (Fig. 3). However, the fluorescence emission spectra showed a relatively large decrease upon addition of the salts, which means that the fluorescence was significantly quenched in the complexes (Figs. 4–6). The latter fluorescence changes were used to determine the stability constants of the complexes (Table 1) and the degree of enantiomeric differentiation ($\Delta \log K = \log K_{(S)} - \log K_{(R)}$, Table 2). All of the titration series of the spectra could be fitted satisfactorily using a complex form with 1:1 stoichiometry.

The results in Table 2 represent that macrocycles (*R*,*R*)-**1** and (*R*,*R*)-**2** having methyl and isobutyl groups on their stereogenic centres, respectively, showed similar and appreciable enantiomeric



Scheme 2. Preparation of new dimethyl-substituted crown ether (*S*,*S*)-**3**.

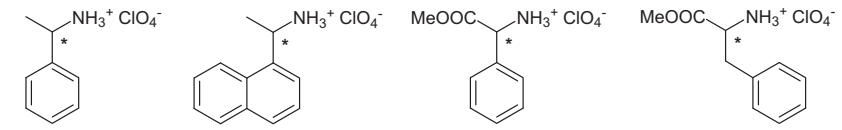


Figure 2. Optically active salts used in the enantiomeric recognition studies.

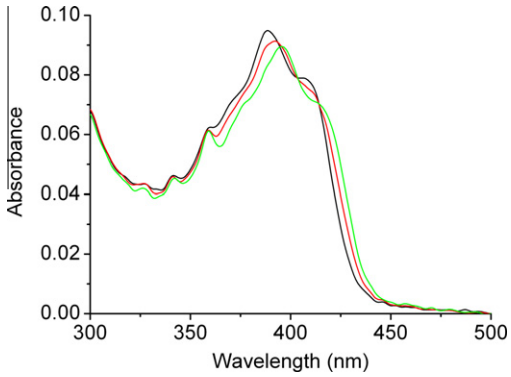


Figure 3. Absorption spectral changes of (*R*,*R*)-**2** (20 μM) on increasing addition of (*S*)-PEA (0–8 equiv) in MeCN.

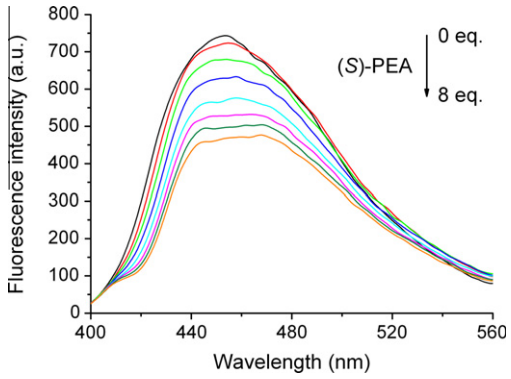


Figure 4. Fluorescence emission series of spectra upon titration of (*R*,*R*)-**2** (20 μM) with (*S*)-PEA (0–8 equiv) in MeCN, λ_{ex} = 380 nm.

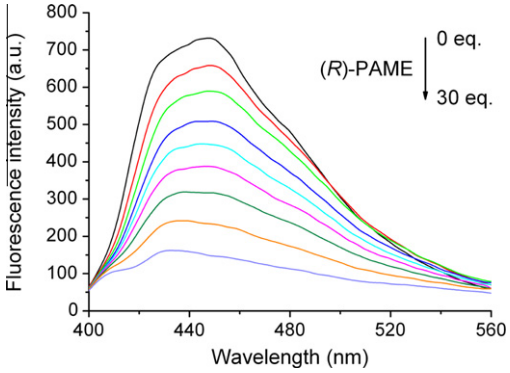


Figure 6. Fluorescence emission series of spectra upon titration of (*S*,*S*)-**3** (20 μM) with (*R*)-PAME (0–30 equiv) in MeCN, λ_{ex} = 380 nm.

Table 1
Stability constants for complexes of (*R*,*R*)-**1**, (*R*,*R*)-**2** and (*S*,*S*)-**3** with the enantiomers of PEA, NEA, PGME and PAME in MeCN

	log *K*		
	(*R*,*R*)-**1**	(*R*,*R*)-**2**	(*S*,*S*)-**3**
(*R*)-PEA	5.10	4.93	5.35
(*S*)-PEA	5.40	5.18	5.29
(*R*)-NEA	5.11	4.92	5.64
(*S*)-NEA	5.52	5.28	5.67
(*R*)-PGME	5.64	5.17	4.61
(*S*)-PGME	5.56	4.93	4.87
(*R*)-PAME	4.67	4.95	4.38
(*S*)-PAME	4.75	5.15	4.35

recognition abilities towards the enantiomers of PEA and NEA (Figs. 4 and 5). However, in the case of the latter optically active salts, little to no enantiomeric discrimination could be found with ligand (*S*,*S*)-**3**, which contains two methyl groups on its stereogenic centres one carbon–carbon bond further away from the acridine moiety. This demonstrates that the positions of the stereogenic centres with the methyl groups in the ligand have a considerable effect on the degree of enantiomeric recognition. This is in good

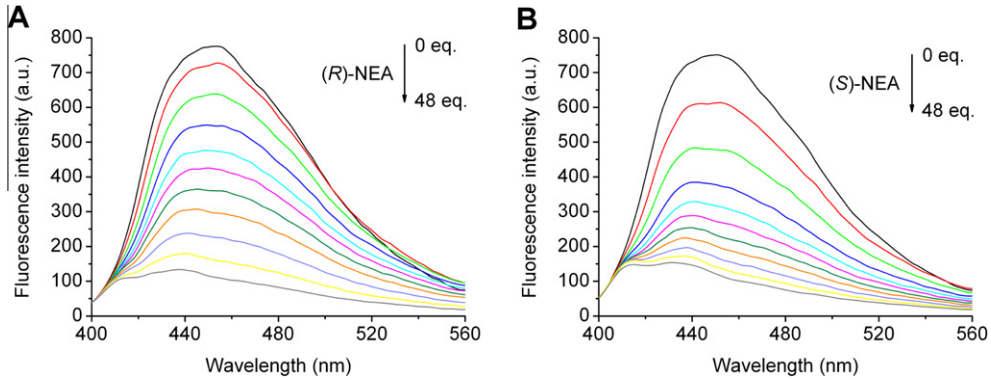


Figure 5. Fluorescence emission series of spectra upon titration of (*R*,*R*)-**2** (5 μM) with NEA [A: (*R*)-NEA, 0–48 equiv, B: (*S*)-NEA, 0–48 equiv] in MeCN, λ_{ex} = 380 nm.

Table 2
Enantioselectivity of (*R,R*)-**1**, (*R,R*)-**2** and (*S,S*)-**3** towards the enantiomers of PEA, NEA, PGME and PAME in MeCN

	Δ log *K*		
	(*R,R*)-**1**	(*R,R*)-**2**	(*S,S*)-**3**
(*R*)-PEA (*S*)-PEA	0.30[a]	0.25[b]	−0.06
(*R*)-NEA (*S*)-NEA	0.41[a]	0.36	0.03
(*R*)-PGME (*S*)-PGME	−0.08	−0.24	0.26
(*R*)-PAME (*S*)-PAME	0.08	0.20	−0.03

[a] Enantioselectivity values of 0.70 and 0.72 were reported earlier for the complexation of (*R,R*)-**1** with the enantiomers of PEA and NEA, respectively, in MeCN.[22]
[b] In the case of ligand (*R,R*)-**2**, the selectivity for the enantiomers of PEA in MeCN is the same as in water assessed by potentiometry using the enantiomers of α-phenylethylamine hydrochloride (K_S/K_R = 1.79, Δ log *K* = 0.25).[9]

agreement with the results reported earlier for the ester type pyridino-crown ethers containing phenyl groups in the macroring examined for PEA and NEA salts.[36] Similar effects could be experienced in the case of (*R,R*)-**2** and an analogous crown ether containing octyl groups at the same positions as the methyl substituents in ligand (*S,S*)-**3**.[9] Furthermore, ligand (*R,R*)-**2** showed a reasonable enantiomeric recognition towards the enantiomers of PGME and PAME, too, while its dimethyl analogue (*R,R*)-**1** showed poor enantioselectivity with these salts. In the case of crown ether (*S,S*)-**3**, enantiomeric recognition was only observed with the enantiomers of PGME.

It can also be seen in Table 2 that in most cases, the heterochiral [(*R,R*)–(*S*) or (*S,S*)–(*R*)] complexes were more stable, while in the case of PGME, the homochiral complexes had higher stabilities. It is important to note that the latter statement is based on nomenclature, but considering that the spatial arrangement of the amino group, the aromatic moiety (phenyl or benzyl) and the third group (methyl or methoxycarbonyl) is similar in (*R*)-PEA, (*R*)-NEA, (*S*)-PGME and (*S*)-PAME, it can be stated that PAME had an exceptional behaviour rather than PGME. This is because in the more stable complexes of PAME, the enantiomer of the salt had the opposite spatial arrangement than in the more stable complexes of PEA, NEA and PGME. The different behaviour of PAME may be explained by its structural difference compared to the other salts, namely that the aromatic ring is separated from the stereogenic centre by a methylene unit. It was also observed that the stability constants of the complexes of (*R,R*)-**2** are smaller than those for the complexes of (*R,R*)-**1**, which can be attributed to the bulkiness of the isobutyl groups. The exception here is again the PAME, which formed more stable complexes with ligand (*R,R*)-**2** rather than ligand (*R,R*)-**1**.

3. Conclusion

A new procedure has been elaborated for the preparation of the dimethyl-substituted acridino-crown ether (*R,R*)-**1**. The synthesis of new chiral crown ethers (*S,S*)-**8** and (*S,S*)-**3** containing an acridone and an acridine unit, respectively, has been achieved. A new efficient procedure has been worked out for the preparation of dimethyl-substituted tetraethylene glycol ditosylate (*S,S*)-**6**.

We examined the enantiomeric recognition properties of ligands (*R,R*)-**1**, (*R,R*)-**2** and (*S,S*)-**3** towards the enantiomers of protonated primary amines and amino acid derivatives. We have demonstrated that the type and position of the alkyl groups in the crown ether ring have a considerable effect on the degree of enantiomeric recognition.

4. Experimental

4.1. General

Starting materials were purchased from Sigma–Aldrich Corporation unless otherwise noted. Silica Gel 60 F_{254} (Merck) and aluminium oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminium oxide (neutral, activated, Brockman I) and Silica Gel 60 (70–230 mesh, Merck) were used for column chromatography. Ratios of solvents for the eluents are given in volumes (mL/mL). Solvents were dried and purified according to well established methods.[37] Evaporations were carried out under reduced pressure unless otherwise stated.

Melting points were taken on a Boetius micro-melting point apparatus and are uncorrected. Optical rotations were taken on a Perkin Elmer 241 polarimeter, which was calibrated by measuring the specific rotations of both enantiomers of menthol. Infrared spectra were recorded on a Bruker Alpha-T FT-IR spectrometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained on a Bruker 300 Avance spectrometer. Mass spectra were recorded on a Finningan-MAT 95 XP MS instrument (reference compound: heptacosafluorotributylamine) using EI (70 eV) method. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary.

UV–vis spectra were taken on a Unicam UV4-100 spectrophotometer. Fluorescence spectra were recorded on a Perkin Elmer LS 50B luminescence spectrometer and on an Edinburgh Instruments FLS920 spectrofluorimeter. Both the emission and excitation spectra were corrected by the spectrometer software. Quartz cuvettes with a path length of 1 cm were used. Enantiomers of PEA, NEA, PGME and PAME were prepared in our laboratory.[38] The concentrations of ligands were 20 μM in general, but 5 μM when titrated with NEA. The stability constants of complexes were determined by global nonlinear regression analysis using SPECFIT/32™ programme.

4.2. (7*R*,17*R*)-7,17-Dimethyl-6,9,12,15,18-pentaoxa-25-azatetracyclo[21.3.1.0^{5,26}.0^{19,24}]heptacosa-1(26),2,4,19,21,23(27),24-heptaene (*R,R*)-1

To a boiling solution of acridono-crown ether (*R,R*)-**4**[33] (113 mg, 0.28 mmol) in propanol (4.5 mL) was added sodium (200 mg, 8.70 mmol) in 5 portions under Ar, and the mixture was refluxed for 1 h. Water (10 mL) was added to the cooled reaction mixture, and the pH was adjusted to 7 with 10% aqueous HCl solution. The solvent was removed, and the residue was taken up in a mixture of water (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was shaken with water (25 mL), dried over $MgSO_4$, filtered and the solvent was removed. The crude product was purified by chromatography on alumina using EtOH–toluene mixture (1:50) as an eluent to give macrocycle (*R,R*)-**1** (99 mg, 83%) as yellow crystals. Crown ether (*R,R*)-**1** had the same physical properties and spectroscopic data as previously reported.[31]

4.3. (8*S*,16*S*)-8,16-Dimethyl-6,9,12,15,18-pentaoxa-25-azatetracyclo[21.3.1.0^{5,26}.0^{19,24}]heptacosa-1(26),2,4,19,21,23(27),24-heptaene (*S,S*)-3

4.3.1. Starting from macrocycle (*S,S*)-8

Macrocycle (*S,S*)-**3** was prepared as described above for (*R,R*)-**1** starting from acridono-crown ether (*S,S*)-**8** (35 mg, 0.0846 mmol),

sodium (80.4 mg, 3.50 mmol) and propanol (2 mL). Chromatography on alumina using EtOH–acetone mixture (1:10) as an eluent gave crown ether (*S,S*)-**3** (10.5 mg, 31%) as a yellow oil. R_f: 0.37 (alumina TLC, EtOH–acetone 1:10); $[\alpha]_D^{25} = +7.7$ (*c* 0.36, CH_2Cl_2); IR (KBr) ν_{max} 3419, 2963, 2926, 2855, 1720, 1639, 1468, 1461, 1397, 1262, 1099, 1022, 865, 801, 725, 531 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 1.31 (d, J = 6 Hz, 6H), 3.55–3.76 (m, 8H), 4.25–4.29 (m, 4H), 4.33–4.36 (m, 2H), 7.16 (d, J = 8 Hz, 2H), 7.51 (t, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 8.89 (s, 1H); ^{13}C NMR (75.5 MHz, CD_3CN) δ 16.53, 67.08, 71.20, 72.83, 73.65, 109.75, 121.75, 127.72, 129.33, 137.69, 141.81, 154.87. Anal. Calcd for $C_{25}H_{33}NO_5 \cdot H_2O$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.27; H, 6.97; N, 3.15. MS Calcd for $C_{23}H_{27}NO_5$: 397.19. Found $(M+1)^+$: 398.17.

4.3.2. Starting from acridine-4,5-diol 9

A mixture of acridine-4,5-diol **9**[9] (0.203 g, 0.874 mmol), ditosylate (*S,S*)-**6** (0.512 g, 0.961 mmol) and finely powdered anhydrous K_2CO_3 (1.33 g, 8.74 mmol) was stirred in dry and pure DMF (15 mL) vigorously under Ar at rt for 10 min then at 50 °C for five days. The solvent was removed, and the residue was taken up in a mixture of water (30 mL) and EtOAc (60 mL). The phases were shaken well and separated. The aqueous phase was extracted with EtOAc (4 × 40 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The crude product was purified by chromatography on alumina using EtOH–acetone mixture (1:10) as an eluent to give macrocycle (*S,S*)-**3** (48 mg, 12%) as a pale yellow oil. Crown ether (*S,S*)-**3** had the same physical properties and spectroscopic data as the one prepared above starting from acridono-crown ether (*S,S*)-**8**.

4.4. (2*S*,2′*S*)-2,2′-Oxybis[(ethane-2,1-diyloxy)propane-2,1-diyl] bis(4-methylbenzenesulfonate) [(*S,S*)-6]

4.4.1. Using Et_3N as a base

To a solution of diol (*S,S*)-**5**[34] (0.99 g, 4.5 mmol) in Et_3N (25 mL) was added tosyl chloride (1.88 g, 9.9 mmol) at rt, and the reaction mixture was stirred vigorously at rt for 5 h. The solvent was removed, and the residue was taken up in a mixture of 5% aqueous HCl solution (50 mL) and CH_2Cl_2 (50 mL). The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic phase was shaken with water (3 × 40 mL), dried over $MgSO_4$, filtered and the solvent was removed. The crude product was purified by chromatography on silica gel using acetone–hexane mixture (1:3) as an eluent to give ditosylate (*S,S*)-**6** (1.79 g, 76%) as a pale yellow oil. R_f: 0.41 (silica gel TLC, acetone–hexane 1:2); $[\alpha]_D^{23} = -6.7$ (*c* 1.2, CH_2Cl_2); IR (neat) ν_{max} 2998, 2943, 2872, 1600, 1496, 1452, 1364, 1296, 1188, 1152, 1096, 988, 816, 800, 668, 552 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.12 (d, J = 6 Hz, 6H), 2.44 (s, 6H), 3.51–3.60 (m, 8H), 3.67–3.70 (m, 2H), 3.91–3.98 (m, 4H), 7.34 (d, J = 8 Hz, 4H), 7.78 (d, J = 8 Hz, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.91, 21.79, 69.05, 70.89, 72.80, 73.65, 128.11, 130.01, 133.15, 144.98.

4.4.2. Using a mixture of 40% aqueous KOH solution and CH_2Cl_2

To a vigorously stirred solution of diol (*S,S*)-**5**[34] (0.27 g, 1.22 mmol) in CH_2Cl_2 (10 mL) were added successively tosyl chloride (0.51 g, 2.68 mmol) and 40% aqueous KOH solution (10 mL) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 5 min and then at rt for one day. Water (20 mL) and CH_2Cl_2 (20 mL) were added to the mixture, and the phases were shaken thoroughly. The phases were separated, and the aqueous phase was shaken with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The crude product was purified by chromatography on silica gel using acetone–hexane mixture (1:3) as an eluent to give ditosylate (*S,S*)-**6** (0.56 g, 86%) as a pale yellow oil. Ditosylate (*S,S*)-**6** had the same physical properties and spectroscopic data as the one prepared above using Et_3N as a base.

4.5. (8*S*,16*S*)-8,16-Dimethyl-6,9,12,15,18-pentaoxa-25-azatetracyclo[21.3.1.0^{5,26}.0^{19,24}]heptacosa-1(26),2,4,19,21,23-hexaene-27-one [(*S,S*)-8]

A mixture of 4,5-dihydroxyacridone monohydrate **7**[35] (0.38 g, 1.55 mmol), ditosylate (*S,S*)-**6** (0.91 g, 1.71 mmol), and finely powdered anhydrous K_2CO_3 (2.15 g, 15.5 mmol) was stirred in either dry and pure DMF (70 mL) or in dry and pure MeCN (70 mL) vigorously under Ar at rt for 10 min and then at 50 °C for six days. The solvent was removed, after which the residue was taken up in a mixture of water (120 mL) and CH_2Cl_2 (120 mL). The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phase was shaken with water (60 mL), dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was purified by chromatography on silica gel using EtOAc–hexane mixture (4:1) as an eluent and then was recrystallized from EtOH to give macrocycle (*S,S*)-**8** (109 mg, 17% using DMF as a solvent or 51 mg, 8% using MeCN as a solvent) as pale yellow crystals. Crown ether (*S,S*)-**8** obtained using either DMF or MeCN as a solvent had the same physical properties and spectroscopic data. Mp: 149–149.5 °C (EtOH); R_f: 0.23 (silica gel TLC, EtOAc–hexane 4:1); $[\alpha]_D^{19} = +54.2$ (*c* 0.25, CH_2Cl_2); IR (KBr) ν_{max} 3424, 2928, 2896, 2872, 1628, 1616, 1600, 1532, 1448, 1424, 1376, 1336, 1272, 1228, 1136, 1120, 1088, 1040, 980, 848, 784, 744, 728, 704, 588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, J = 6 Hz, 6H), 1.96 (broad s, half mol of complexed H_2O, 1H), 3.70–3.86 (m, 8H), 4.07–4.10 (m, 2H), 4.11–4.25 (m, 4H), 7.06 (d, J = 8 Hz, 2H), 7.17 (t, J = 8 Hz, 2H), 8.06 (d, J = 8.5 Hz, 2H), 9.42 (s, NH, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.70, 69.58, 71.13, 73.32, 73.76, 118.74, 120.88, 122.34, 146.86, 178.18. MS Calcd for $C_{23}H_{27}NO_6$: 413.18. Found $(M+1)^+$: 414.38. Anal. Calcd for $C_{23}H_{27}NO_6 \cdot 0.5H_2O$: C, 65.39; H, 6.68; N, 3.32. Found: C, 65.41; H, 6.60; N, 3.27.

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