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Larger Groups, Smaller Enantioselectivity? Two Anthracene-Containing, Pyridino-Crown Ether-Based Fluorescent Sensor Molecules

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Abstract

(*R,R*)- and (*S,S*)-enantiomers of anthracene-containing pyridino-18-crown-6 ether having *tert*-butyl groups at the stereogenic centers were prepared with the aim of achieving higher enantioselectivity than for the reported (*S,S*)-analogue having isobutyl groups. The enantiomeric recognition abilities of the new sensor molecules toward chiral protonated primary amines and amino acid esters were studied in acetonitrile by UV–vis and fluorescence spectroscopies. The pK_a values of these pyridino-crown ethers and their reported (*S,S*)-analogues having methyl or isobutyl groups have also been determined in acetonitrile.

Keywords

anthracene, crown ether, enantiomeric discrimination, fluorescence spectroscopy, Suzuki–Miyaura coupling

1 Introduction

Fluorescent molecular sensors have an enormous significance as they can be applied in environmental science, drug research or diagnostics [1–3], due to the advantageous properties of fluorescence spectroscopy: high sensitivity and selectivity [4]. Since enantiomeric purity requirements in the pharmaceutical industry are becoming stricter [5, 6], sensor molecules among them fluorescent ones which enable selective and sensitive recognition of enantiomers received much research interest [2, 7, 8].

Previously, numerous optically active crown ether-based fluorescent chemosensors have been developed [9–14]. Those macrocycles which were prepared and studied in our research group so far contained acridine, phenazine, acridone, BODIPY, anthracene, benzothiazole, pyrene, 1,8-naphthalimide, and disubstituted 1,2,3-triazoles as fluorescent signaling units [9–14]. Among the anthracene-containing ones [12, 15], two pyridino-crown ether-based chemosensors (*S*,*S*)-**1** and (*S*,*S*)-**2** (Fig. 1) were synthesized, which showed appreciable or moderate enantiomeric recognition toward chiral primary ammonium salts, the discrimination for protonated 1-(1-naphthyl)ethylamine being greater in the case of ligand (*S*,*S*)-**2** bearing isobutyl groups [15]. We wondered how we could increase the enantiomeric recognition ability of these type of sensor molecules.

Pyridino-crown ethers having *tert*-butyl groups at the stereogenic centers [16–21] have been reported to have a greater enantioselectivity than the ones containing other groups such as methyl [17, 20, 21], isobutyl [17, 20], and phenyl [21]. Furthermore, chiral stationary phases based on the latter type crown ethers having *tert*-butyl groups revealed good enantioseparation abilities toward chiral organic ammonium salts [22–25].

Therefore, replacing the methyl or isobutyl groups with *tert*-butyl ones seemed appealing. In this work, we present the synthesis, characterization, and enantiomeric recognition studies of two new fluorescent *tert*-butyl-substituted pyridino-crown ethers containing an anthracene moiety [(*R*,*R*)-**3** and (*S*,*S*)-**3**, Fig. 1].

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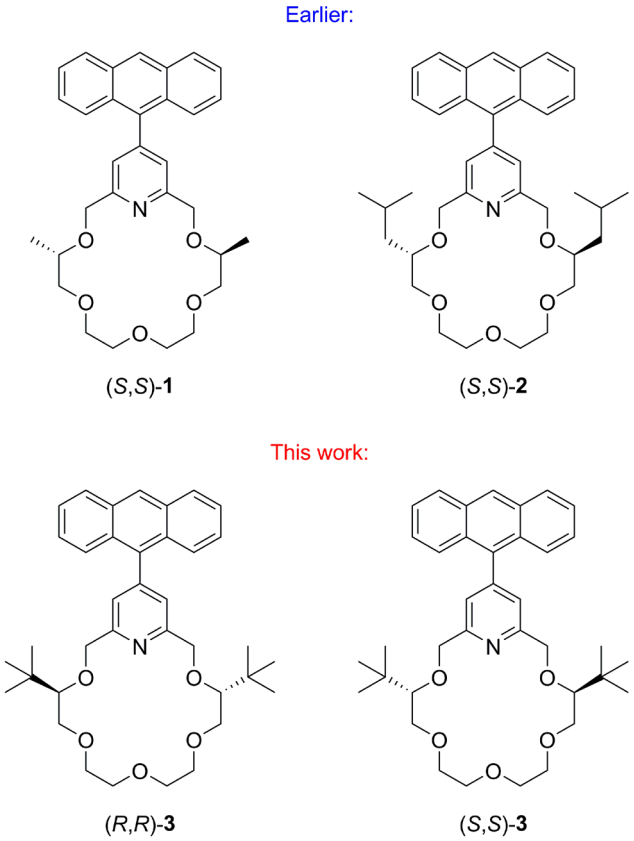


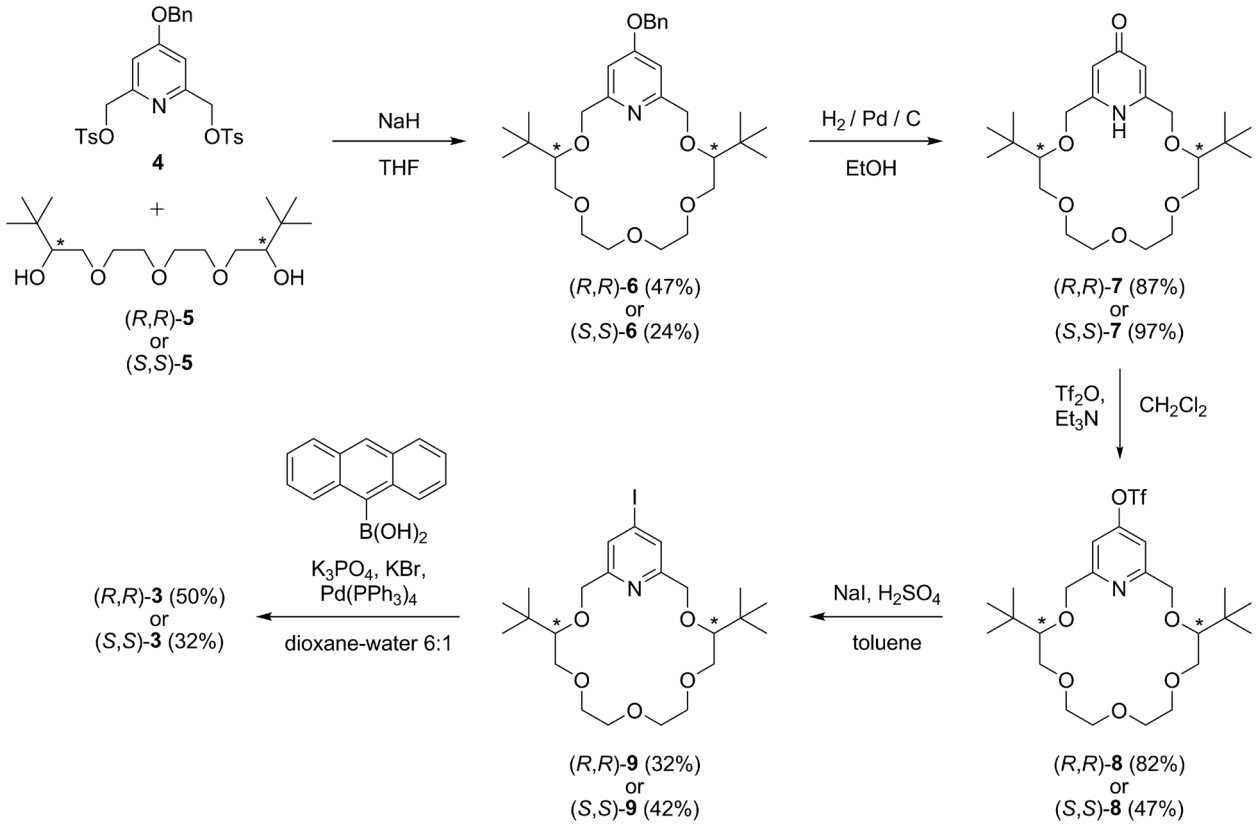
Fig. 1 Enantiopure pyridino-18-crown-6 ethers containing an anthracene fluorophore unit

2 Results and discussion

2.1 Synthesis

Benzyl-protected ditosylate **4** was prepared from chelidonic acid in five steps by methods reported in the literature [26]. Enantiopure *tert*-butyl-substituted tetraethylene glycols (*R*,*R*)-**5** and (*S*,*S*)-**5** were obtained from pinacolone and diethylene glycol in six steps according to literature procedures [22]. The synthesis of sensor molecules (*R*,*R*)-**3** and (*S*,*S*)-**3** from precursors **4** and (*R*,*R*)-**5** or (*S*,*S*)-**5** (Scheme 1) was performed in a similar way as their isobutyl [(*S*,*S*)-**2**] [15] or methyl [(*S*,*S*)-**1**] [15, 27, 28] analogues.

Macrocyclization reactions of ditosylate **4** and tetraethylene glycol (*R*,*R*)-**5** or (*S*,*S*)-**5** in THF in the presence of sodium hydride yielded benzyl-protected crown ether (*R*,*R*)-**6** or (*S*,*S*)-**6**. Macrocycles (*R*,*R*)-**6** and (*S*,*S*)-**6** were debenzylated by catalytic hydrogenation in ethanol to render pyridono-crown ethers (*R*,*R*)-**7** and (*S*,*S*)-**7**, the former of which is known from the literature [23], but here we prepared them in a different route. These pyridono-crown ethers were transformed to triflates (*R*,*R*)-**8** and (*S*,*S*)-**8** with trifluoromethanesulfonic anhydride in dichloromethane using triethylamine as a base. The triflates were reacted with sodium iodide in toluene using a catalytic amount of sulfuric acid. Crown ethers (*R*,*R*)-**9** and (*S*,*S*)-**9** were used to prepare sensor molecules (*R*,*R*)-**3** and (*S*,*S*)-**3** by Suzuki–Miyaura coupling.



Scheme 1 Synthesis of sensor molecules (*R*,*R*)-**3** and (*S*,*S*)-**3**

2.2 Enantiomeric recognition studies

We have investigated the enantiomeric recognition abilities of macrocycles (*R*,*R*)-**3** and (*S*,*S*)-**3** toward the enantiomers of 1-phenylethylamine hydrogen perchlorate (PEA), 1-(1-naphthyl)ethylamine hydrogen perchlorate (NEA), phenylglycine methyl ester hydrogen perchlorate (PGME), and phenylalanine methyl ester hydrogen perchlorate (PAME) (Fig. 2) with UV–vis and fluorescence spectroscopies in acetonitrile.

When adding the enantiomers of PEA and NEA to macrocycles (*R*,*R*)-**3** and (*S*,*S*)-**3**, moderate absorption changes occurred (Fig. 3 (a)), which showed a partial (ca. 30%) protonation process based on the comparison with the effect of sulfuric acid (Fig. 3 (c)). It should be noted here that sensor molecules (*S*,*S*)-**1** and (*S*,*S*)-**2** exhibited practically no absorption changes on addition of PEA and NEA (under the same experimental conditions) [15]. These negligible changes indicated no protonation, because the UV–vis spectra of protonated (*S*,*S*)-**1** and (*S*,*S*)-**2** induced by sulfuric acid are similar to that of protonated (*S*,*S*)-**3** (Fig. 3 (c)). In Fig. 3 (a), the small differences in the spectral changes (e.g., at 331, 354.5, and 375 nm) in contrast to Fig. 3 (c) can refer to the presence of two concomitant processes: complexation and protonation, of which the latter causes significant absorption changes, while the former only induces little (negligible) ones.

However, the corresponding fluorescence titration spectra of crown ethers (*R*,*R*)-**3** and (*S*,*S*)-**3** (their fluorescence quantum yields in acetonirile were 0.62 and 0.61, respectively) with PEA and NEA revealed large fluorescence quenching (Fig. 4). This can mainly be attributed to the complexation processes, and in some degree to

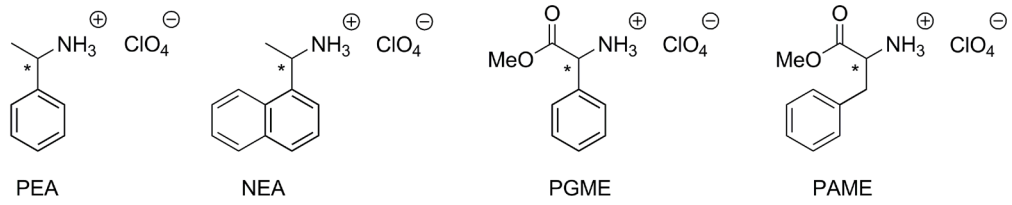


Fig. 2 Chiral primary ammonium salts used in the enantiomeric recognition studies

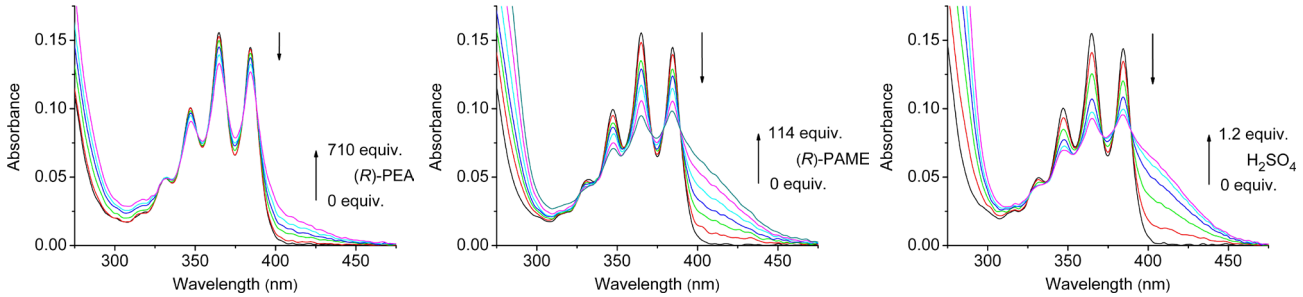


Fig. 3 Series of UV–vis absorption spectra of (*S,S*)-**3** (20 μM) upon titration with (*R*)-PEA (0, 10, 30, 90, 210, 710 equiv.) (a), with (*R*)-PAME (0, 0.5, 1, 2, 5, 14, 114 equiv.) (b), and with H_2SO_4 (0, 0.24, 0.50, 0.74, 1.0, 1.2 equiv.) (c) in MeCN

Fig. 4 Series of fluorescence emission spectra upon titration of (*R*,*R*)-**3** (20 μM) with (*S*)-NEA (0, 2, 4, 8, 14, 20, 30, 50, 90, 130, 190, 310, 710, 1510, 3110 equiv.) in MeCN, λ_{ex} = 337 nm (a). Titration curves of (*R*,*R*)-**3** with the enantiomers of NEA (0, 2, 4, 8, 14, 20, 30, 50, 90, 130, 190, 310, 710 equiv.) at 408 nm (b)

protonation (protonation of all anthracene-containing pyridino-crown ethers with sulfuric acid also quenched the fluorescence). The evaluation of the fluorescence titration data showed that the series of spectra could be fitted satisfactorily assuming 1:1 complexation and neglecting protonation (Table 1). In accordance with the fact that the larger *tert*-butyl group has a stronger steric repulsive effect than both the isobutyl and methyl groups [17, 21], these complex stability constants (Table 1) are significantly – ca. two orders of magnitude or more – smaller than those of ligands (*S*,*S*)-**2** and (*S*,*S*)-**1** [15] (Fig. 5).

The different behavior of crown ethers (*R*,*R*)-**3** and (*S*,*S*)-**3** can be attributed to their significantly weaker complex formation ability (Table 1) compared to ligands (*S*,*S*)-**1** and (*S*,*S*)-**2** [15], while the competing acid–base equilibria are similar for all ligands based on the similar pK_a (MeCN) values of their protonated forms (Table 2). Therefore, the protonation process could become more dominant in the cases of crown ethers (*R*,*R*)-**3** and (*S*,*S*)-**3**. For comparison, the pK_a (MeCN) values of PEA and NEA

Table 1 Stability constants for complexes of (*R*,*R*)-**3** and (*S*,*S*)-**3** with the enantiomers of primary ammonium salts and the degrees of enantiomeric discrimination in MeCN[a]

	(*R*,*R*)-**3**		(*S*,*S*)-**3**	
	log*K*	Δlog*K*	log*K*	Δlog*K*
(*R*)-PEA	2.47 ± 0.03	0.00	2.49 ± 0.02	0.05
(*S*)-PEA	2.47 ± 0.02		2.44 ± 0.02	
(*R*)-NEA	2.63 ± 0.03	–0.24	2.85 ± 0.03	0.23
(*S*)-NEA	2.87 ± 0.03		2.62 ± 0.03	
(*R*)-PGME	[b]	[b]	[b]	[b]
(*S*)-PGME	[b]		[b]	
(*R*)-PAME	[b]	[b]	[b]	[b]
(*S*)-PAME	[b]		[b]	

[a] Complex stability constants (*K*) are given in M^{-1}.
[b] Total protonation of the host molecules took place.

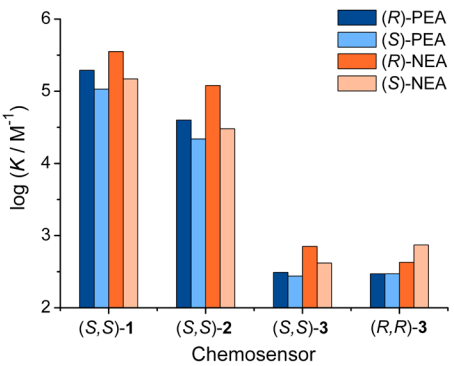


Fig. 5 Stability constants (*K*) for complexes of (*S*,*S*)-**1**, (*S*,*S*)-**2** (data were taken from [15]), (*S*,*S*)-**3**, and (*R*,*R*)-**3** (Table 1) with the enantiomers of PEA and NEA in MeCN. Degrees of enantiomeric recognition: $\Delta\log K = \log K_{(R)} - \log K_{(S)}$.

Table 2 The pK_a values of protonated (*S*,*S*)-**1**–(*S*,*S*)-**3** and (*R*,*R*)-**3** in MeCN[a]

	(*S*,*S*)-**1**	(*S*,*S*)-**2**	(*S*,*S*)-**3**	(*R*,*R*)-**3**
pK_a	14.19 ± 0.03	13.74 ± 0.05	13.84 ± 0.05	13.80 ± 0.02

[a] The pK_a values were determined with UV–vis spectrophotometric titrations by adding saccharin as a titrant acid to the sensor molecules.

can be estimated slightly higher than that of protonated benzyl amine (16.91 [29]). Furthermore, the less basic character of amino acid esters than primary amines (e.g., ca. 2.5–2.7 pK_a unit difference for phenylalanine methyl ester [30] and 1-phenylethylamine [31, 32] in water) together with the low complex forming affinity of crown ethers (*R*,*R*)-**3** and (*S*,*S*)-**3** with primary ammonium ions, resulted in that PGME and PAME protonated ligands (*R*,*R*)-**3** and (*S*,*S*)-**3** (Fig. 3 (b), (c)) instead of complexation. Thus, enantiomeric recognition abilities could not be examined in these cases.

Owing to the mentioned larger steric repulsion of the *tert*-butyl groups, larger enantiomeric discrimination was also expected, based on the previous studies with the parent pyridino-crown ethers having no anthracene unit [17, 20]. These experiments in methanol by calorimetry and ^{1}H NMR spectroscopy [17] and in acetonitrile by CD spectroscopy [20] showed an increasing enantioselectivity toward NEA in the order of methyl, isobutyl, and *tert*-butyl groups. Here, to our surprise, sensor molecules (*R*,*R*)-**3** and (*S*,*S*)-**3** revealed moderate and no enantiomeric differentiation to NEA and PEA, respectively (Table 1), which are significantly smaller than the appropriate enantiomeric recognition abilities of ligands (*S*,*S*)-**2** and even (*S*,*S*)-**1** [15] (Fig. 5). Previously, we reported that the presence of isobutyl groups in crown ether (*S*,*S*)-**2** and the extended π–π interaction between NEA and the host were needed for achieving the highest and remarkable selectivity ($\Delta\log K = 0.60$) [15]. Interestingly, the presence of *tert*-butyl groups in the macroring and a large anthracene unit at position 4 of the pyridine ring does not favor a high enantioselectivity.

It should be noted here that the mentioned enantiomeric recognition abilities were determined at room temperature; however, the change of the temperature has an effect on the extent of enantioselectivity, and even can reverse it at an isoenantioselective temperature [33–36]. The latter phenomenon (i.e. temperature-dependent reversal of enantioselectivity) was experienced in the case of an analogous 4-azophenolic pseudo-18-crown-6 ether having *tert*-butyl groups at the stereogenic centers, when examined with the enantiomers of chiral amines [33, 34].

3 Conclusion

We synthesized new anthracene-containing sensor molecules (*R*,*R*)-**3** and (*S*,*S*)-**3** in a similar way as their reported [15] analogues. These showed greater extent of protonation upon addition of all chiral salts than analogous compounds (*S*,*S*)-**1** and (*S*,*S*)-**2** [15]. This is due to the significantly less ability of ligands (*R*,*R*)-**3** and (*S*,*S*)-**3** to form complexes with the ammonium guests, therefore the acid–base reaction became more dominant between the two concurrent processes, complexation and protonation. Unexpectedly, in this anthracene–pyridino-crown ether fluorescent sensing system the change of isobutyl groups [(*S*,*S*)-**2**] to *tert*-butyl ones [(*R*,*R*)-**3** and (*S*,*S*)-**3**] did not manifest in higher enantiomeric recognition of chiral ammonium guests.

4 Experimental

4.1 General

Starting materials were purchased from Sigma–Aldrich unless otherwise noted. Aluminum oxide 60 F_{254} neutral type E and silica gel 60 F_{254} plates (Merck) were used for thin-layer chromatography (TLC). Aluminum oxide (neutral, activated, Brockmann 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.

Optical rotations were taken on a PerkinElmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. IR spectra were recorded on a Bruker Alpha-T Fourier transform infrared (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 (75.5 MHz) NMR spectra were taken on a Bruker 300 Avance spectrometer. HRMS analyses were performed on a Waters Q-TOF Premier mass spectrometer or a Thermo Velos Pro Orbitrap Elite system in positive ESI mode. Enantiomeric excess (*ee*) values of (*R*,*R*)-**3** and (*S*,*S*)-**3** were determined with a PerkinElmer Series 200 HPLC system, using ethanol–hexane 1:99 mixture as an eluent in isocratic elution (0.8 mL/min, 20 °C) on a Phenomenex Lux® Amylose-2 column (250 × 4.6 mm, 5 μm). Detector wavelength: 254 nm. Retention times: 11.1 min for (*R*,*R*)-**3** and 12.6 min for (*S*,*S*)-**3**.

UV–vis spectra were taken on a Unicam UV4-100 spectrophotometer. Quartz cuvettes with path length of 1 cm were used. Fluorescence emission spectra were recorded on a PerkinElmer LS 50B luminescent spectrometer and were corrected by the spectrometer software. Quartz cuvettes with path length of 1 cm were used. Fluorescence quantum yields were determined relative to quinine sulfate (Φ_f = 0.53 in 0.1 M H_2SO_4) [4]. Enantiomers of PEA, NEA, PGME, and PAME were prepared as reported [22] in our laboratory. The pK_a value of saccharin in MeCN (14.57) was taken from the literature [38]. The concentrations of the sensor molecules were 20 μM during all titrations. In order to determine the equilibrium constants by global nonlinear regression analysis, the SPECFIT/32™ software was used.

4.2 (4*R*,14*R*)-19-(Anthracen-9-yl)-4,14-di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene [(*R*,*R*)-3]

A mixture of iodopyridino-crown ether (*R*,*R*)-**9** (74 mg, 0.14 mmol), anthracen-9-ylboronic acid (43 mg, 4.5 mmol), KBr (21 mg, 0.18 mmol), powdered K_3PO_4 (52 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) in peroxide-free dioxane–water 6:1 (2.6 mL) was stirred at 90 °C under Ar for a day. The volatile components were removed, and the residue was partitioned between dichloromethane (10 mL) and water (10 mL). The aqueous phase was further extracted with dichloromethane (2 × 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on alumina using 1,2-dimethoxyethane–hexane 1:100 mixture as an eluent. The product obtained this way was subsequently recrystallized from diisopropyl ether, then dissolved in toluene, the solution was filtered through cotton, and evaporated to give (*R*,*R*)-**3** (41 mg, 50%) as white crystals.

R_f: 0.24 (alumina TLC, EtOH–toluene 1:80); mp: 185–188 °C; *ee* > 99%; $[\alpha]_{436}^{25}$ = +37.0 (*c* = 1.00, toluene); IR (KBr) $\tilde{\nu}_{max}$ (cm^{-1}) 3044, 2963, 2868, 1625, 1601, 1555, 1520, 1479, 1447, 1411, 1396, 1363, 1334, 1297, 1262, 1246, 1139, 1126, 1109, 1077, 1043, 1017, 971, 916, 889, 868, 795, 746, 693, 624, 559, 542; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.91 (s, 18H), 3.37 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 3.47–3.76 (m, 10H), 3.71 (dd, J_1 = 11 Hz, J_2 = 2 Hz, 2H), 4.97–5.08 (m, 4H), 7.34–7.45 (m, 2H), 7.42 (s, 2H), 7.45–7.55 (m, 2H), 7.69 (d, *J* = 9 Hz, 2H), 8.08 (d, *J* = 8 Hz, 2H), 8.55 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 26.62, 34.85, 70.85, 71.39, 72.85, 74.89, 85.91, 123.14, 125.48, 125.97, 126.59, 127.45, 128.64, 129.73, 131.50, 134.90, 148.12, 159.15; HRMS *m/z* $(M+H)^+$ found 586.3518, $C_{37}H_{48}NO_5^+$ requires 586.3527.

4.3 (4*S*,14*S*)-19-(Anthracen-9-yl)-4,14-di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene [(*S*,*S*)-3]

Sensor molecule (*S*,*S*)-**3** was prepared in the same way as (*R*,*R*)-**3** from iodopyridino-crown ether (*S*,*S*)-**9** (250 mg, 0.59 mmol). Yield: 111 mg, 32%; *ee* > 99%; $[\alpha]_{436}^{25} = -37.0$ (*c* = 1.00, toluene). Spectral data and other physical properties of (*S*,*S*)-**3** were the same as those of (*R*,*R*)-**3** reported above.

4.4 (4*R*,14*R*)-19-Benzyloxy-4,14-di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene [(*R*,*R*)-6]

Into a three-necked, flame-dried round-bottom flask (equipped with a stirring bar, an Ar inlet, a dropping funnel, and a condenser), pure and dry THF (32 mL) was added under Ar, followed by NaH (3.02 g, 75.5 mmol, 60% in mineral oil dispersion). To this stirred mixture a solution of tetraethylene glycol (*R*,*R*)-**5** [22] (5.27 g, 17.2 mmol) in pure and dry THF (80 mL) was added dropwise at 0 °C, followed by refluxing for 4 h. The mixture was cooled to –75 °C, and a solution of ditosylate **4** [26] (9.52 g, 17.2 mmol) in pure and dry THF (300 mL) was added to it under Ar. The mixture was then allowed to warm up to rt and stirred for 3 days. The volatile components were removed, and the residue was partitioned between diethyl ether (200 mL) and ice-water (300 g). The aqueous phase was further extracted with diethyl ether (3 × 200 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on alumina using ethanol–toluene 1:200 mixture as an eluent to give (*R*,*R*)-**6** (4.17 g, 47%) as a yellow oil.

R_f: 0.32 (alumina TLC, EtOH–toluene 1:80); $[\alpha]_D^{25} = -5.1$ (*c* = 1.05, EtOH); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3063, 3034, 2952, 2904, 2868, 1597, 1577, 1497, 1479, 1453, 1395, 1361, 1340, 1320, 1253, 1221, 1198, 1149, 1091, 1044, 1017, 1001, 991, 926, 863, 844, 735, 696, 626, 592, 527; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.95 (s, 18H), 3.24 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 3.43–3.56 (m, 10H), 3.66 (dd, J_1 = 11 Hz, J_2 = 2 Hz, 2H), the diastereotopic benzylic type $-CH_2-$ protons give an AB quartet: δ_A 4.78 and δ_B 4.84 (J_{AB} = 14 Hz, 4H), 5.14 (s, 2H), 6.92 (s, 2H), 7.31–7.46 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 26.45, 34.57, 69.72, 70.51, 70.94, 72.46, 74.21, 85.18, 106.80, 127.59, 128.28, 128.73, 136.12, 160.46, 165.82; HRMS *m/z* $(M+H)^+$ found 516.3326, $C_{30}H_{46}NO_6^+$ requires 516.3320.

4.5 (4*S*,14*S*)-19-Benzyloxy-4,14-di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene [(*S*,*S*)-6]

Crown ether (*S*,*S*)-**6** was prepared in the same way as (*R*,*R*)-**6** from tetraethylene glycol (*S*,*S*)-**5** [22] (2.35 g, 7.68 mmol). Yield: 949 mg, 24%; $[\alpha]_D^{25} = +6.3$ (*c* = 1.02, EtOH). Spectral data and other physical properties of (*S*,*S*)-**6** were the same as those of (*R*,*R*)-**6** reported above.

4.6 (4*R*,14*R*)-4,14-Di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-dien-19(21*H*)-one [(*R*,*R*)-7]

Benzyloxy derivative (*R*,*R*)-**6** (623 mg, 1.21 mmol) was hydrogenated in ethanol (25 mL) in the presence of Pd/C catalyst (63 mg, 10% Pd on activated charcoal). After the reaction was complete, the flask was flushed with Ar, and the catalyst was filtered over diatomaceous earth, and washed with ethanol. The filtrate was evaporated to give (*R*,*R*)-**7** (447 mg, 87%) as a greyish yellow oil. Crown ether (*R*,*R*)-**7** obtained this way had the same physical and spectroscopic properties as previously reported [23].

4.7 (4*S*,14*S*)-4,14-Di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-dien-19(21*H*)-one [(*S*,*S*)-7]

Macrocycle (*S*,*S*)-**7** was prepared in the same way as (*R*,*R*)-**7** from benzyloxy derivative (*S*,*S*)-**6** (797 mg, 1.55 mmol). Yield: 634 mg, 97%; greyish yellow oil; R_f: 0.37 (alumina TLC, EtOH–toluene 1:15); $[\alpha]_D^{25} = +38.3$ (*c* = 0.91, CH_2Cl_2). All spectroscopic data of (*S*,*S*)-**7** were identical to those of (*R*,*R*)-**7** [23].

4.8 (4*R*,14*R*)-4,14-Di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-trien-19-yl trifluoromethanesulfonate [(*R*,*R*)-8]

Into a two-necked, round-bottom flask (equipped with a stirring bar, a septum, and an Ar inlet) was placed pyridono-crown ether (*R*,*R*)-**7** (509 mg, 1.20 mmol), dry dichloromethane (5 mL), and triethylamine (380 µL, 276 mg, 2.73 mmol) under Ar. The reaction mixture was cooled to 0 °C, and trifluoromethanesulfonic anhydride (400 µL, 672 mg, 2.38 mmol) was added slowly to it using a syringe. The mixture was stirred at 0 °C for 5 min, then at rt for 1 h. The reaction mixture was poured into a mixture of ice-water (50 g) and 25% aqueous Me_4NOH solution (2 mL) (the pH was adjusted to 12), and it was extracted with dichloromethane (3 × 40 mL). The combined organic phase was dried

over anhydrous $MgSO_4$, filtered, and evaporated. The brown crude product was purified by column chromatography on silica gel using acetone–toluene 1:10 mixture as an eluent to give (*R*,*R*)-**8** (438 mg, 82%) as a pale yellow oil.

R_f: 0.36 (alumina TLC, EtOH–toluene 1:80); $[\alpha]_D^{25}$ = +15.1 (*c* = 0.60, CH_2Cl_2); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3364, 2956, 2906, 2871, 2323, 2102, 2030, 2018, 2003, 1967, 1953, 1597, 1581, 1480, 1427, 1397, 1363, 1351, 1335, 1296, 1243, 1212, 1139, 1014, 993, 967, 876, 820, 765, 731, 696, 666, 606, 571, 515, 465; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.97 (s, 18H), 3.28 (dd, J_1 = 8 Hz J_2 = 2 Hz, 2H), 3.38–3.52 (m, 10H), 3.67 (dd, J_1 = 11, J_2 = 2 Hz, 2H), the diastereotopic benzylic type –CH_2– protons give an AB quartet: δ_A 4.89 and δ_B 4.93 (J_{AB} = 14 Hz, 4H), 7.25 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 26.57, 34.67, 70.76, 71.35, 72.78, 73.68, 86.10, 112.12, 120.13, 157.50, 163.18; HRMS *m/z* $(M+H)^+$ found 558.2352, $C_{24}H_{39}F_3NO_8S^+$ requires 558.2343.

4.9 (4*S*,14*S*)-4,14-Di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-trien-19-yl trifluoromethanesulfonate [(*S*,*S*)-8]

Triflate (*S*,*S*)-**8** was prepared in the same way as (*R*,*R*)-**8** from pyridono-crown ether (*S*,*S*)-**7** (643 mg, 1.49 mmol). Yield: 438 mg, 47%; $[\alpha]_D^{25}$ = –15.7 (*c* = 0.60, CH_2Cl_2). Spectral data and other physical properties of (*S*,*S*)-**8** were the same as those of (*R*,*R*)-**8** reported above.

4.10 (4*R*,14*R*)-19-Iodo-4,14-di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene [(*R*,*R*)-9]

To a solution of triflate (*R*,*R*)-**8** (877 mg, 1.97 mmol) in toluene (20 mL), NaI (1.48 g, 9.85 mmol), and 2 drops of 96% H_2SO_4 were added. The mixture was stirred under Ar at rt for a day. The volatile components were removed. Ice-water (100 g) and 10% aqueous NaOH solution (2 mL) were added to the residue to adjust the pH to 12. The mixture was extracted with dichloromethane (3 × 80 mL). The combined organic phase was washed with 5% aqueous $Na_2S_2O_3$ solution (50 mL), and this aqueous phase was also extracted with dichloromethane (30 mL). The organic phases were combined again, and extracted with water (2 × 30 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on alumina using ethanol–toluene 1:100 mixture as an eluent to give (*R*,*R*)-**9** (267 mg, 32%) as yellowish brown crystals.

R_f: 0.49 (alumina TLC, EtOH–toluene 1:80); mp: 66–67 °C; $[\alpha]_D^{25}$ = +22.6 (*c* = 2.00, CH_2Cl_2); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2961, 2898, 2866, 2748, 1735, 1567, 1473, 1459, 1394, 1381, 1364, 1346, 1329, 1261, 1221, 1195, 1136, 1115, 1083, 1063, 1039, 1018, 936, 924, 899, 880, 865, 857, 841, 816, 801, 754, 734, 702, 652, 636, 531; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.96 (s, 18H), 3.23 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 3.40–3.60 (m, 10H), 3.66 (dd, J_1 = 11 Hz, J_2 = 2 Hz, 2H), the diastereotopic benzylic type –CH_2– protons give an AB quartet: δ_A 4.79 and δ_B 4.82 (J_{AB} = 14 Hz, 4H), 7.68 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 26.46, 34.61, 70.55, 71.04, 72.57, 73.88, 85.91, 106.34, 129.36, 159.64; HRMS *m/z* $(M+H)^+$ found 536.1869, $C_{23}H_{39}INO_5^+$ requires 536.1867.

4.11 (4*S*,14*S*)-19-Iodo-4,14-di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene [(*S*,*S*)-9]

Crown ether (*S*,*S*)-**9** was prepared in the same way as (*R*,*R*)-**9** from triflate (*S*,*S*)-**8** (1.05 g, 1.96 mmol). Yield: 440 mg, 42%; $[\alpha]_D^{25}$ = –21.8 (*c* = 2.00, CH_2Cl_2). Spectral data and other physical properties of (*S*,*S*)-**9** were the same as those of (*R*,*R*)-**9** reported above.

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