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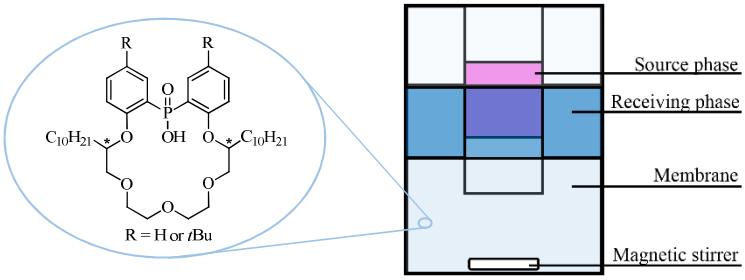

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Synthesis and enantioselective transport studies of both enantiomers of new chiral proton-ionizable crown ethers containing a diarylphosphinic acid unit

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ABSTRACT

The synthesis of four new enantiopure crown ethers containing a diarylphosphinic acid unit has been carried out. As a continuation of our work in this field, the enantioselective transport ability of these ligands for chiral amines has been studied in an aqueous source phase/lipophilic organic bulk liquid membrane/aqueous receiving phase system controlled by the pH of the media. By altering the structures of the carriers we improved the enantioselectivity of the transport.

1. Introduction

The enantiomers of various primary amines have different biological activities, thus their enantiorecognition is of great significance[1]. Primary amines are formed during the degradation of amino acids or serve as neurotransmitters[2]. Primary amines are also very important building blocks of biologically active molecules[1,2]. To be able to understand better the transport process of primary amines through the cell membrane, studying their transport through liquid membrane systems would be helpful. For a long time in transport of biological active compounds (e.g drug delivery, amino acid purification etc.) supramolecular systems have been sucesfully used[3-5]. Optically active crown ethers as carrier molecules have been studied in the enantioselective transport of chiral amines[6-11].

Among carrier molecules, ionophores operating by a "switching mechanism' form a very important group[12]. These ionophores may have a high ion-binding ability at the source phase/lipophilic membrane interface and a low ion binding ability at the lipophilic membrane/receiving phase interface in an aqueous source phase/lipophilic membrane/aqueous receiving phase bulk liquid membrane system. The ion-binding ability of the carriers can be reversible changed by light[13], redox potential[14], temperature[14], or pH gradient[15]. If these factors are set properly in the membrane system the ionophores can perform active transport of ions[12].

In the case of proton-ionizable crown ether carriers, the pH of the media and the pK_a value of the corresponding acid determine the driving force of the transport. These crown ethers are mostly ionized at higher pHs than their pK_a values, which phenomenon increases the stability of the cation–ionophore complex[16-41]. Considering the active transport of amines in the above mentioned membrane system, the pK_a value of the conjugated acid of the counter anion of the protonated amine should be higher than that of the carrier at the source phase/membrane interface, and the receiving phase should be an aqueous solution of a stronger acid than the proton-ionizable ionophore. In this case, the complex formation of the protonated amine with the anion of the carrier is favourable at the source phase/membrane interface, and at the membrane/receiving phase interface the dissociation of the complex is favoured[42,43].

For the successful operation of the transport, the acidic carrier should be lipophilic enough to stay in the lipophilic

membrane in both complexed and uncomplexed forms. Keeping these requirements in mind, we inserted a relatively acidic diarylphosphinic acid unit[44] and two long alkyl chains into the macroring of the crown ether[42,43].

Earlier we synthesized lipophilic crown ethers (*S*,*S*)-**1**, (*R*,*R*)-**1**, (*S*,*S*)-**2** and (*R*,*R*)-**2** (see Figure 1), and studied the transport of metal ions and protonated chiral amines of these ligands. We also investigated the effect of the substitution of the aromatic ring on the enantioselective transport ability[42,43]. These enantio-pure macrocycles showed weak enantio-selectivity for the examined amines.

It was found earlier that the position of the alkyl groups at the chiral centers in the crown ethers can effect the enantiomeric recognition[45].

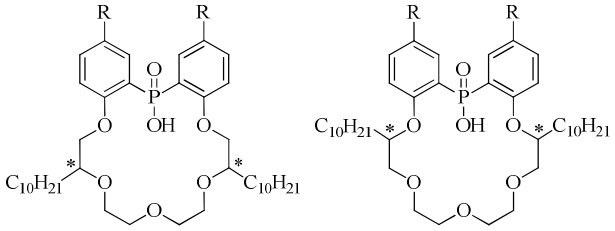


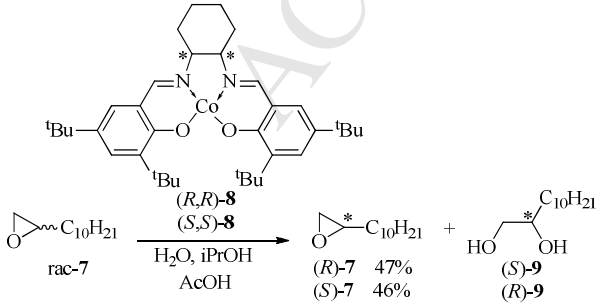
Figure 1. Reported and newly synthesized enantiopure lipophilic proton-ionizable crown ethers.

Herein, we report the synthesis of new macrocycles which contain the lipophilic alkyl chains closer to the diaryl-phosphinic acid unit (*S*,*S*)-**3**, (*R*,*R*)-**3**, (*S*,*S*)-**4** and (*R*,*R*)-**4** (see Fig. 1). These macrocycles were utilized as carrier molecules in the active enantioselective transport of protonated phenylethylamine, phenylglycinol, phenylalaninol, and ephedrine controlled by the pH of the media.

2. Results and discussion

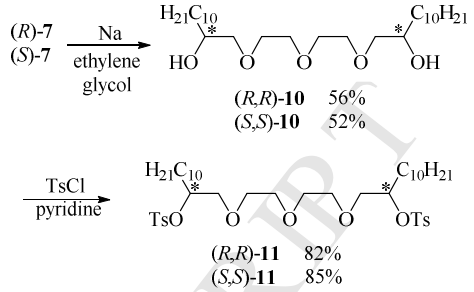
2.1. Synthesis

In order to obtain the new optically active crown ethers, first the chiral key intermediate ditosylates (*R*,*R*)-**11** and (*S*,*S*)-**11** were prepared. The racemic 1,2-epoxydodecane rac-**7** was opened enantioselectively by a Jacobsen's Hydrolytic Kinetic Resolution procedure[46,47] (see Sheme 1) to give enantiopure epoxides. In the case of epoxide (*R*)-**7** catalyst (*R*,*R*)-**8** was used, as we reported earlier[42].



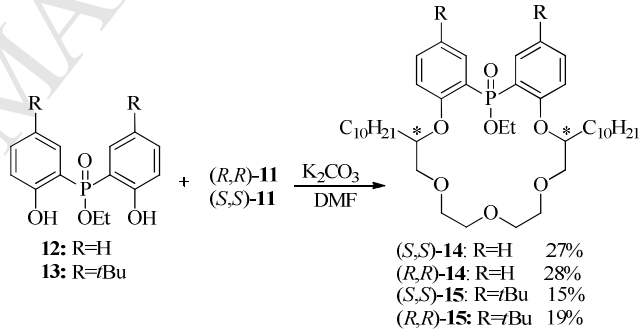
Scheme 1. Preparation of enantiopure epoxides

Analogously, the antipode of the catalyst (*S*,*S*)-**8** was used to obtain epoxide (*S*)-**7**[48]. Epoxide (*R*)-**7** or (*S*)-**7** was reacted with the sodium salt of diethylene glycol to get the corresponding tetraethylene glycol derivative (*R*,*R*)-**10** or (*S*,*S*)-**10**[49,50], which was tosylated to obtain (*R*,*R*)-**11** or (*S*,*S*)-**11** (see Sheme 2).

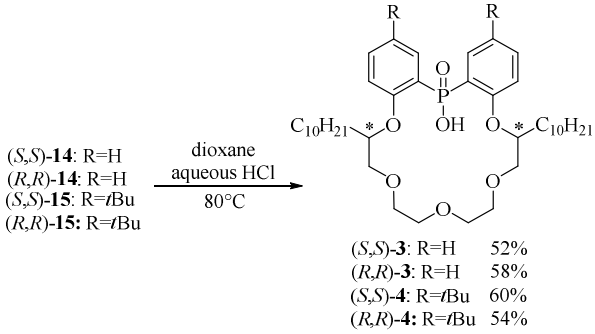


Scheme 2. Preparation of enantiopure key intermediates

Macrocyclization was carried out by the reaction of the reported ethyl phosphinates **12**[51] or **13**[43] and ditosylates (*R*,*R*)-**11** or (*S*,*S*)-**11** at 50°C in DMF using K_2CO_3 as a base (see Sheme 3). Applying these conditions the Williamson type ether formation takes place with total inversion of configuration. Macrocycles (*S*,*S*) -**14**, (*R*,*R*)-**14**, (*S*,*S*)-**15**, and (*R*,*R*)-**15** were hydrolyzed by the reported method[51], using a mixture of dioxane and aqueous HCl solution (see Sheme 4).



Scheme 3. Macrocyclization reaction



Scheme 4. Hydrolysis of crown ethers containing an ethyl diarylphosphinate unit.

2.2. Transport studies

Transport studies were carried out in a bulk liquid membrane cell reported earlier[52] (see Figure 2). The errors for the transported amounts of amines were smaller than 2%, and the errors for the ee values were smaller than 1% (calculated from three independent measurements). The source phase was 2mL of a 1 M aqueous solution of acetate salt of the

racemic mixture of the protonated amine. The membrane was 12 mL of a 1 mM solution of ligand (*S*,*S*)-**3** or (*S*,*S*)-**4** in CH_2Cl_2. The receiving phase was 6 mL of a 2% aqueous HCl solution, unless otherwise indicated.

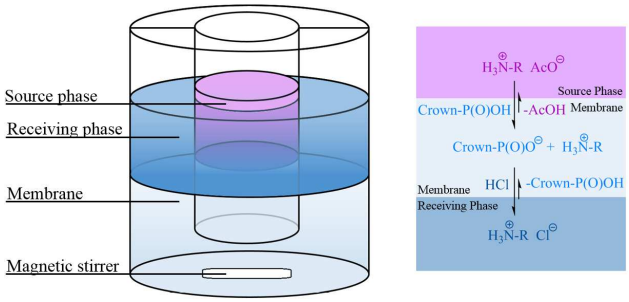


Figure 2. Bulk liquid membrane cell

The effect of the factors on the enantioselective transport of phenylethylamine and phenylglycinol was thoroughly investigated earlier[42], thus now these optimal conditions were used. The transports were carried out at 18°C. In the case of phenylethylamine the time of the transport was 4 h. In other cases this value was 24 h, because the transports of those amines were much slower. The results of the transports of chiral amines are shown in Table 1. For comparison, the previous results using macrocycles (*S*,*S*)-**1** and (*S*,*S*)-**2** are indicated in parentheses[43].

The transport of phenylethylamine was much faster by macrocycle (*S*,*S*)-**2** than (*S*,*S*)-**1**, but the enantioselectivity was lower in the former case. Compared to this, crown ethers (*S*,*S*)-**3** and (*S*,*S*)-**4** transported phenylethylamine as fast as (*S*,*S*)-**1**, but with no enantioselectivity. The highest enantioselectivity was obtained for the transport of phenylglycinol. Marcocycle (*S*,*S*)-**3** showed bigger enantiomeric discrimination than (*S*,*S*)-**1**, but crown ethers (*S*,*S*)-**4** and (*S*,*S*)-**2** had almost the same enantioselectivity values. The enantioselectivities for the transports of phenylalaninol and ephedrine by (*S*,*S*)-**3** and (*S*,*S*)-**4** are fairly low.

In the cases of macrocycles with an (*S*,*S*)-configuration were used as a carrier, (*R*)-phenylglycinol and (*R*)-phenylalaninol were enriched in the receiving phase. As it can be expected, the (*S*) enantiomers of the amines were in excess in the receiving phase when crown ethers with an (*R*,*R*)-configuration were used. This means a preference for heterochiral complex formation, contrary to the case of the earlier synthesized crown ethers (*S*,*S*)-**1** and (*S*,*S*)-**2**[43].

Table 1. Transports of different chiral amines for 4h or 24h

Amine (*AcOH)	Ligand	Amount (%)	ee (%)
Phenylethyl-amine (4 h)	(*S*,*S*)-**3** [(*S*,*S*)-**1**]	13 [14]	0 [13]
	(*S*,*S*)-**4** [(*S*,*S*)-**2**]	15 [31]	0 [4]
Phenylglycinol (24 h)	(*S*,*S*)-**3** [(*S*,*S*)-**1**]	22 [24]	20 [12]
	(*S*,*S*)-**4** [(*S*,*S*)-**2**]	19 [24]	18 [17]
Phenylalaninol (24 h)	(*S*,*S*)-**3**	21	8
	(*S*,*S*)-**4**	22	4
Ephedrine (24 h)	(*S*,*S*)-**3**	29	2
	(*S*,*S*)-**4**	38	0

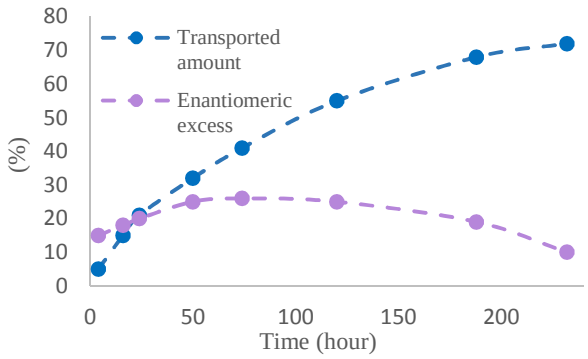
In the case of macrocycle (*S*,*S*)-**3** (1*S*,2*R*)-(+)-ephedrine was enriched in the receiving phase and for (*S*,*S*)-**4** we did not experienced any enantioselectivity. Considering these results, we can conclude, that the outcome of the transport depends very much on the structure of the ligand and the transported amine as well.

Time dependence of the transports for phenylglycinol and phenyalaninol has also been examined using (*S*,*S*)-**3** as a carrier (see Table 2, Diagram 1, Table 3). Kinetics of the transports confirm that these transport processes work against concentration gradient with decreasing transport speed, the same behavior, which we reported earlier in the case of phenyletylamine using (*S*,*S*)-**1** as a carrier[43]. Unexpectedly, increasing the time of the transport led to an increase in the enantiomeric excess until 50 h of transport time. Somewhere between 120 h and 172 h transport times, the enantiomeric excess started to decrease. To clarify this unexpected result we ran an experiment with racemic protonated phenylglycinol acetate in the source phase and without carrier (*S*,*S*)-**3** in the membrane phase, otherwise in same circumstances. We observed that some racemic protonated phenylglycinol appeared in the receiving phase, but this leakage was slowlier than the transport of the preferred enantiomer by the carrier. Because the leakage of the racemic mixture and later on the mixture enriched in the less preferred enantiomer of the protonated phenylglycinol acetate, and the enantioselective transport by the carrier are counterproductive processes, we assume that these can cause this unexpected result.

Table 2. Transport of phenylglycinol using (*S*,*S*)-**3** as a carrier.

Time (h)	Amount (%)	ee (%)
4	5	15
16	15	18
24	21	20
50	32	25
74	40	26
120	56	25
172	68	19
232	72	10

Diagram 1. Time dependence diagram for transport of phenylglycinol using (*S*,*S*)-**3** as a carrier.



In the case of phenylalaninol the enantiomeric excess was 8% and did not change during the time of the experiment. Changing the membrane (1,2-dichlorobenzene), temperature (14°C), and source phase concentration (0.5 M) did not increase the enantiomeric excess.

Table 3. Transport of phenylalaninol using (*S*,*S*)-**3** as a carrier.

Time (h)	Amount (%)
4	9
16	16
24	22
50	34
74	42

3. Conclusion

In conclusion, new enantiopure lipophilic proton-ionizable crown ethers (*S*,*S*)-**3**, (*R*,*R*)-**3**, (*S*,*S*)-**4**, and (*R*,*R*)-**4** were synthesized. These molecules are suitable carriers for the active transport of protonated phenylethylamine, phenylglycinol, phenylalaninol, and ephedrine controlled by the pH of the media. According to our results, chiral carriers form heterochiral complexes more favourable than homochiral ones. We should emphasize that in the case of these new carriers the degree of enantioselectivity was modest, and depends very much on the structure of the ligand and the transported amine as well. In the transport of phenylglycinol we could enhance the enantiomeric discrimination of these type of crown ethers by modification of the structure. Thus we hope that in the future by further modification in the structure of the carriers the enantioselectivity can continue to improve.

4. Experimental Section

4.1. General

All starting materials were purchased from Sigma–Aldrich Corporation unless otherwise noted. Compounds (*R*)-**7**, (*S*)-**7**, **12** and **13** were prepared as reported[42,43,48,51]. All reactions were monitored by TLC and visualized by UV lamp (254 nm). Silica gel 60 F_{254} (Merck) plates were used for TLC. Silica gel 60 (70–230 mesh, Merck) was 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[55]. Evaporations were carried out under reduced pressure. Melting points were taken on a Boetius micro-melting point apparatus and are uncorrected. Optical rotations were taken on a Perkin–Elmer 241 polarimeter that was calibrated by measuring the optical 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 (75.5 MHz) NMR spectra were taken on a Bruker 300 Avance spectrometer and it is indicated in each individual case. ^{31}P (121.5 MHz, reference: H_3PO_4) NMR spectra were recorded on a Brucker 300 Avance spectrometer. Mass spectra were recorded on an Agilent 1200 Series coupled Agilent 6130 Series Quadrupole LC-MS instrument in electrospray ionization (ESI) mode. HRMS analyses were performed on a Thermo Velos Pro Orbitrap Elite (Thermo Fisher Scientific, Bremen, Germany) system. The ionization method was ESI and operated in positive ion mode. The protonated molecular ion peaks were fragmented by CID at a normalized collision energy of 35%. The samples were solved in methanol. Data acquisition and analysis were accomplished with Xcalibur software version 2.2 (Thermo Fisher Scientific). Enantiomeric excesses of phenylethylamine and phenylglycinol were determined on an Agilent 1100 liquid chromatography system equipped with a vacuum degasser, a quaternary pump, a thermostated autosampler, a column temperature controller and a diode array detector, (Agilent Technologies, Palo Alto, CA, USA). ChemStation B.04.03 was used for data acquisition and analysis. Chiral chromatographic analysis of phenylethylamine and phenylglycinol was performed on a CROWNPAK CR(-) column (150 x 4.0 mm, 5 µm) (Däicel Corp, France). Isocratic elution was applied. In the case of phenylethylamine, measurements were carried out at 25 °C, with a mobile phase flow rate of 0.9 mL/min, using aqueous perchloric acid (pH=1.5) as eluent. Retention times: 13.3 minutes for (*R*)-enantiomer and 17.2 minutes for (*S*)-enantiomer. In the case of phenylglycinol the measurements were carried out at 20 °C, with a mobile phase flow rate of 0.6 mL/min, using aqueous perchloric acid (pH=2.0) as eluent. Retention times: 7.9 minutes for (*R*)-enantiomer and 9.3 minutes for (*S*)-enantiomer. Chiral separation of the ephedrine and phenylalaninol enantiomers were carried out on a PerkinElmer Series 200 liquid chromatography system equipped with a vacuum degasser, a binary pump, an autosampler, a column temperature controller and a UV/VIS detector, (PerkinElmer, Inc, Shelton, CT, USA). TotalChrom Workstation v. 6.3.1 was used for data acquisition and analysis. Chromatographic analysis was performed on a Lux® Amylose-2 column (250 × 4.6 mm, 5µm) (Phenomenex Inc., USA). Isocratic elution was applied. In case of ephedrine, measurements were carried out at 20 °C, with a mobile phase flow rate of 0.8 mL/min, using a 90:10 mixture of hexane and ethanol as eluent. Retention times: 7.4 minutes for (*R*,*S*)-enantiomer and 8.6 minutes for (*S*,*R*)-enantiomer. In case of phenylalaninol, measurements were carried out at 20 °C, with a mobile phase flow rate of 0.8 mL/min, using a 85:15 mixture of hexane and ethanol as eluent. Retention times: 8.7 minutes for (*S*)-enantiomer and 10.1 minutes for (*R*)-enantiomer.

4.2. Synthesis

4.2.1. (1*S*,11*S*)-1,11-Didecyl-3,6,9-trioxaundecane-1,11-diol (*S*,*S*)-10

(*S*)-Epoxydodecane ((*S*)-**7**) was prepared from racemic 1,2-epoxydodecane by the procedure of Jaconbsen[46]. Diethylene glycol (2.19 g, 207 mmol) was placed in a three necked flask fitted with a stirrer, dropping funnel, and a dry acetone condenser. After a catalytic amount of sodium (70 mg) was added and dissolved, the stirred mixture was heated at 100 °C. (*S*)-Epoxydodecane ((*S*)-**7**) (8.00g, 43,4 mol) was added in half an hour. The reaction mixture was stirred at 100 °C for one day, then it was allowed to cool down to room temperature, and saturated aqueous sodium bicarbonate solution (20 mL) was added. Diethyl ether (50 mL) was added to the cooled mixture, and the solution was shaken with 75 mL of brine. The brine layer was extracted with 100 ml of ether two times. The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to obtain a yellow oil. This crude product was purified by chromatography on silica gel using acetone-hexane mixtures (polarity raised from 1:10 to 1:4) as eluents to obtain the product as a colorless oil. It was crystallised

from hexane, to obtain (*S*,*S*)-**10** (5.36g, 52%) as a white powder. R_f (acetone-hexane 1:4) 0.27; $[\alpha]_D^{29}$=-11.5 (*c* 1.05, CH_2Cl_2); mp. 55-57 °C; ν_{max} (neat) 3424, 2955, 2922, 2850, 1465, 1378, 1345, 1311, 1162, 1149, 1125, 1090, 1063, 1049, 998, 982, 958, 908, 885, 842, 728, 720, 622, 542 cm^{-1}; δ_H (125 MHz $CDC1_3$) 0.86 (6H, t, *J* = 7 Hz, C<u>H</u>$_3$); 1.23-1.46 (m, 36H, C<u>H</u>$_2$); 3.26-3.30 (m, 2H, OC<u>H</u>$_2$); 3.50-3.54 (m, 2H, OC<u>H</u>$_2$); 3.60-3.68 (m, 10H, OC<u>H</u>$_2$, O<u>H</u>); 3.73–3.78 (2H, br m, OC<u>H</u>). δ_C (125 MHz, $CDCl_3$) 14.11 (<u>C</u>H$_3$); 22.68; 25.63; 29.34; 29.59; 29.64; 29.74; 31.92; 32.88 (<u>C</u>H$_2$); 70.08; 70.35; 70.44; 76.23 (O<u>C</u>H, O<u>C</u>H$_2$). HRMS: MH^+ found 475.43562; $C_{28}H_{58}O_5$ requires: 475.42842.

4.2.2. (1*R*,11*R*)-1,11-Didecyl-3,6,9-trioxaundecane-1,11-diol (*R*,*R*)-10

Diol (*R*,*R*)-**10** was prepared in the same way as described above for (*S*,*S*)-**10** starting from (*R*)-epoxydedodecane (*R*)-**7** (11.0 g, 59.72 mmol). Yield: 7.93 g (56 %). $[\alpha]_D^{26}$=+12.1 (*c* 1.08, CH_2Cl_2). Other physical and spectroscopic data of (*R*,*R*)-**10** concurred with those of diol (*S*,*S*)-**10**.

4.2.3. (1*S*,11*S*)-1,11-Didecyl-3,6,9-trioxaundecane-1,11-diyl-bis(4-methylbenzenesulfonate) (*S*,*S*)-11

Tosyl chloride (3.41 g, 17.89 mmol) and pyridine (10 ml) was placed under Ar in a three necked flask fitted with a stirring bar and dropping funnel. The mixture was cooled to 0 °C, and (*S*,*S*)-**10** (2.50 g, 5.27 mmol) dissolved in pyridine (30mL) was added dropwise. After addition, the mixture was allowed to warm up to room temperature. The mixture was stirred for two days, and then the pyridine was removed. 10 % Aqueous HCl solution (15 mL) and dichloromethane (30 mL) were added to the residue. The resulting phases were shaken thoroughly, and then they were separated. The aqueous phase was shaken with 20 mL portions of dichloromethane three times. The combined organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed. The crude product was purified by column chromatography on silica gel using first dichloromethane-methanol (200:1) and then ethyl acetate-hexane (8:1) as eluents to get (*S*,*S*)-**11** (3.39 g, 82 %) as a colourless oil. R_f (ethyl acetate-hexane 1:4) 0.14; $[\alpha]_D^{22}$=+5.3 (*c* 1.00, CH_2Cl_2); ν_{max} (neat) 2922, 2853, 1598, 1496, 1458, 1401, 1359, 1306, 1291, 1188, 1175, 1119, 1097, 1019, 906, 813, 778, 664, 576, 553, 458 cm^{-1}; δ_H (125 MHz $CDC1_3$) 0.90 (t, *J* = 7 Hz, 6H, C<u>H</u>$_3$); 1.13-1.33 (m, 32H, C<u>H</u>$_2$); 1.60-1.65 (m, 4H, C<u>H</u>$_2$); 2.46 (s, C<u>H</u>$_3$); 3.49-3.61 (m, 12H, OC<u>H</u>$_2$); 4.60-4.65 (m, 2H, OC<u>H</u>); 7.34 (d, *J* = 8 Hz, 4H, Ar<u>H</u>); 7.82 (d, *J* = 8.4 Hz, 4H, Ar<u>H</u>). δ_C (125 MHz, $CDCl_3$) 14.16 (<u>C</u>H$_3$); 21.66; 22.72; 24.78; 29.28; 29.36; 29.43; 29.53; 29.63; 31.47; 31.97 (<u>C</u>H$_2$); 70.47; 70.85; 72.17; 81.99 (O<u>C</u>H, O<u>C</u>H$_2$); 127.89; 129.63; 134.46; 144.44 (Ar<u>C</u>). HRMS: MH^+ found 783.45407; $C_{42}H_{70}O_9S_2$ requires: 782.44613.

4.2.4. (1*R*,11*R*)-1,11-Didecyl-3,6,9-trioxaundecane-1,11-diyl-bis(4-methylbenzenesulfonate) (*R*,*R*)-11

Ditosylate (*R*,*R*)-**11** was prepared in the same way as described above for (*S*,*S*)-**11** starting from diol (*R*,*R*)-**10** (3.20 g, 6.75 mmol). Yield: 7.93 g (85 %). $[\alpha]_D^{25}$=-5.6 (*c* 1.05, CH_2Cl_2). Other physical and spectroscopic data of ditosylate (*R*,*R*)-**11** concurred with those of (*S*,*S*)-**11**.

4.2.5. (6*S*,16*S*)-6,16-didecyl-22-ethoxy-6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo[n,q][1,4,7,10,13,16]pentaoxa-λ^5-phosphacyclooctadecin-22-one (*S*,*S*)-14

Ethyl bis(2-hydroxyphenyl)phosphinate (**12**)[51] (0.59 g, 2.11 mmol), dodecyl-substituted tetraethylene glycol ditosylate (*R*,*R*)-**11** (1.50 g, 1.91 mmol) and finely powdered anhydrous K_2CO_3 (5 g, 36 mmol) were mixed with vigorous stirring in dry DMF (50 mL) under Ar. The temperature of the vigorously stirred reaction mixture was raised to 50 °C and kept at this temperature until TLC analysis showed the total consumption of the starting materials (15 days). The solvent was removed at 40 °C, then the residue was dissolved in water (150 mL) and dichloromethane (80 mL). The aqueous phase was shaken with 80 mL dichloromethane three times. The combined organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed. The crude product was purified by coulumn cromatography on silica gel using ethyl acetate–hexane mixtures (polarity raised from 1:4 to 1:1) as eluents to give (*S*,*S*)-**14** (0.37 g, 27 %) as a colourless oil; R_f (CH_2Cl_2-MeOH 15:1) 0.88; $[\alpha]_D^{22}$=-39.1 (*c* 0.74, CH_2Cl_2); ν_{max} (neat) 3065, 2922, 2853, 1590, 1577, 1473, 1444, 1367, 1278, 1243, 1220, 1142, 1088, 1040, 948, 754, 709, 566, 552, 514 cm^{-1}; δ_H (125 MHz, $CDCl_3$) 0.80 (t, *J*=6 Hz, 6H, C<u>H</u>$_3$); 1.17-1.29 (m, 35H, C<u>H</u>$_2$, C<u>H</u>$_3$); 1.35-1.42 (m, 4H, C<u>H</u>$_2$); 2.52-2.58 (m, 1H, OC<u>H</u>$_2$); 2.82-2.99 (m, 5H, OC<u>H</u>$_2$); 3.22-3.25 (m, 6H, OC<u>H</u>, OC<u>H</u>$_2$); 3.78-4.16 (m, 2H, OC<u>H</u>$_2$); 4.30-4.33 (m, 2H, OC<u>H</u>$_2$); 6.84-6.98 (m, 4H, Ar<u>H</u>); 7.26-7.37 (m, 2H, Ar<u>H</u>); 7.77-8.14 (m, 2H, Ar<u>H</u>). δ_C (125 MHz, $CDCl_3$) 14,32 (d, *J*=1 Hz, <u>C</u>H$_3$); 16.50 (d, *J*=7 Hz, <u>C</u>H$_3$); 22.65; 25.15; 25.21; 29.29; 29.31; 29.45; 29.53; 29.58; 29.62; 29.66; 31.87; 31.39; 32.09 (<u>C</u>H$_2$); 59.84 (d, *J*=5 Hz, O<u>C</u>H$_2$); 70.77; 70.89; 70.93; 71.34; 72.84; 73.43 (O<u>C</u>H$_2$); 75.60; 76.68 (OCH); 111.71 (d, *J*=8 Hz, Ar<u>C</u>); 112.29 (d, *J*=8 Hz, Ar<u>C</u>); 119.41 (d, *J*=4 Hz, Ar<u>C</u>); 119.57 (d, *J*=5 Hz, Ar<u>C</u>); 120.58 (d, *J*=84 Hz, Ar<u>C</u>); 122.46 (d, *J*=99 Hz, Ar<u>C</u>); 132.67 (d, *J*=2 Hz, Ar<u>C</u>), 133.15 (d, *J*=2 Hz, Ar<u>C</u>); 133.37 (d, *J*=4 Hz, Ar<u>C</u>); 136.61 (d, *J*=7 Hz, Ar<u>C</u>), 159.40 (d, *J*=4 Hz, Ar<u>C</u>); 160.39 (d, *J*=5 Hz, Ar<u>C</u>). δ_P (121.5 MHz, $CDCl_3$) 25.46. HRMS: MH^+ 717.48525; $C_{42}H_{69}O_7P$ requires: 717.47809.

4.2.6. (6*R*,16*R*)-6,16-didecyl-22-ethoxy-6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo[n,q][1,4,7,10,13,16]pentaoxa-λ^5-phosphacyclooctadecin-22-one (*R*,*R*)-14

Crown ether (*R*,*R*)-**14** was prepared in the same way as described above for (*S*,*S*)-**14** starting from ditosylate (*S*,*S*)-**11** (1.50 g, 1.91 mmol). Yield: 0.38 g (28 %). $[\alpha]_D^{25}$=+38.5 (*c* 0.77, CH_2Cl_2). Other physical and spectroscopic data of (*R*,*R*)-**14** concurred with those of crown ether (*S*,*S*)-**14**.

4.2.7. (6*S*,16*S*)-2,20-Di-tert-butyl-6,16-didecyl-22-ethoxy-6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo[n,q][1,4,7,10,13,16] pentaoxa-λ^5-phosphacyclo-octadecin-22-one (*S*,*S*)-15

Crown ether (*S*,*S*)-**15** was prepared in the same way as described above for (*S*,*S*)-**14** starting from ditosylate (*R*,*R*)-**11** (1.50 g, 1.91 mmol) and ethyl bis(5-*tert*-butyl-2-hydroxyphenyl)-phosphinate (**13**)[43] (0.83 g, 2.11 mmol). Yield: 0.24 g (15 %). The product is a colourless oil. R_f (CH_2Cl_2-MeOH 15:1) 0.81; $[\alpha]_D^{22}$=+22.7 (*c* 1.02, CH_2Cl_2); ν_{max} (neat) 2953, 3032, 2922, 2854, 1599, 1487, 1466, 1394, 1362, 1294, 1264, 1220, 1164, 1126, 1086, 1041, 948, 879, 813, 669, 545, 503 cm^{-1}; δ_H (125 MHz, $CDCl_3$) 0.86-0.90 (m, 6H, C<u>H</u>$_3$); 1.21-1.52 (m, 63H, C<u>H</u>$_2$, C<u>H</u>$_3$); 2.44-2.49 (m, 1H, OC<u>H</u>$_2$); 2.87-2.88 (m, 2H, OC<u>H</u>$_2$); 2.93-2.96 (m, 1H,

OC$\underline{H}_2$); 3.00-3.06 (m, 2H, OC$\underline{H}_2$); 3.26-3.52 (m, 6H, OC$\underline{H}$, OC$\underline{H}_2$); 3.89-3.96 (m, 1H, OC$\underline{H}_2$); 4.20-4.27 (m, 1H, OC$\underline{H}_2$); 4.32-4.38 (m, 2H, OC$\underline{H}_2$); 6.85-6.89 (m, 2H, Ar$\underline{H}$); 7.36-7.44 (m, 2H, Ar$\underline{H}$); 7.88-7.92 (m, 1H, Ar$\underline{H}$); 8.14-8.17 (m, 1H, Ar$\underline{H}$). δ_C (125 MHz, $CDCl_3$) 14.11 (d, *J*=2 Hz, $\underline{C}H_3$); 16.55 (d, *J*=7 Hz, $\underline{C}H_3$); 22.67; 25.26; 25.37; 29.31; 29.33; 29.49; 29.59; 29.65; 29.70; 31.59; 31.69; 31.89; 32.03; 32.31 ($\underline{C}H_2$, $\underline{C}H_3$); 34.18; 34.29 ($\underline{C}(CH_3)_3$); 59.80 (d, *J*=5 Hz, O$\underline{C}H_2$); 70.63; 70.76; 70.81; 71.47; 72.52; 73.58 (O$\underline{C}H_2$); 75.46; 76.68 (OCH); 111.18 (d, *J*=8 Hz, Ar$\underline{C}$); 111.82 (d, *J*=9 Hz, Ar$\underline{C}$); 120.32 (d, *J*=119 Hz, Ar$\underline{C}$); 121.44 (d, *J*=133 Hz, Ar$\underline{C}$); 129.66 (d, *J*=3 Hz, Ar$\underline{C}$); 129.71 (d, *J*=4 Hz, Ar$\underline{C}$); 130.03 (d, *J*=1 Hz, Ar$\underline{C}$); 132.63 (d, *J*=7 Hz, Ar$\underline{C}$); 141.78 (d, *J*=11 Hz, Ar$\underline{C}$); 142.19 (d, *J*=12 Hz, Ar$\underline{C}$), 157.14 (d, *J*=4 Hz, Ar$\underline{C}$); 158.19 (d, *J*=5 Hz, Ar$\underline{C}$). δ_P (121.5 MHz, $CDCl_3$) 26.28. HRMS: MH^+ found 829.61015; $C_{50}H_{85}O_7P$ requires: 829.60329.

4.2.8. (6*R*,16*R*)-2,20-Di-tert-butyl-6,16-didecyl-22-ethoxy-6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo [n,q][1,4,7,10,13,16] pentaoxa-λ^5-phosphacyclo-octadecin-22-one (*R*,*R*)-15

Crown ether (*R*,*R*)-**15** was prepared in the same way as described above for (*S*,*S*)-**14** starting from ditosylate (*S*,*S*)-**11** (1.50 g, 1.91 mmol) and ethyl bis(5-*tert*-butyl-2-hydroxyphenyl)-phosphinate (**13**)[45] (0.83 g, 2.11 mmol). Yield: 0.30 g (19 %). $[\alpha]_D^{26}$=-24.0 (*c* 0.83, CH_2Cl_2). Other physical and spectro-scopic data of (*R*,*R*)-**15** concurred with those of crown ether (*S*,*S*)-**15**.

4.2.9. (6*R*,16*R*)-6,16-didecyl-22-hydroxy-6,7,9,10,12,13, 15,16-octahydro-22*H*-dibenzo[n,q][1,4,7,10,13,16] pentaoxa-λ^5-phosphacyclooctadecin-22-one (*S*,*S*)-3

To a solution of ethyl phosphinate ((*S*,*S*)-**14**) (0.34 g, 0.47 mmol) in dioxane (10 mL) was added 10 % aqueous HCl solution (10 mL) at room temperature. The temperature of the vigorously stirred reaction mixture was raised to 80°C and kept at this temperature until TLC analysis showed the total consumption of the starting material (17 days). The solvent was removed at 40 °C. The residue was dissolved in a mixture of water (20 mL) and dichloromethane (15 mL). The phases were shaken well and separated. The aqueous phase was shaken with dichloromethane (10 mL) two times. The combined organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed. The residue was purified by PLC using methanol-dichloromethane (1:20) as an eluent to give (*S*,*S*)-**3** (0.17 g, 52%) as a pale brown oil.; R_f (CH_2Cl_2-MeOH 15:1) 0.30; $[\alpha]_D^{24}$=-36.4 (*c* 0.74, MeOH); ν_{max} (neat) 3064, 2921, 2852, 1664, 1587, 1574, 1469, 1440, 1378, 1269, 1234, 1134, 1095, 1029, 942, 802, 753, 703, 563, 522 cm^{-1}; δ_H (125 MHz, CD_3OD) 0.92 (t, *J*=6 Hz, 6H, C$\underline{H}_3$); 1.21-1.37 (m, 32H, C$\underline{H}_2$, C$\underline{H}_3$); 1.41-1.53 (m, 4H, C$\underline{H}_2$); 3.23-3.64 (m, 12H, OC$\underline{H}$, OC$\underline{H}_2$); 4.40-4.52 (m, 2H, OC$\underline{H}_2$); 6.92-7.06 (m, 4H, Ar$\underline{H}$); 7.35-7.40 (m, 2H, Ar$\underline{H}$); 7.80-7.93 (m, 2H, Ar$\underline{H}$). δ_C (75.5 MHz, CD_3OD, 318K) 13,05 ($\underline{C}H_3$); 22.31 ($\underline{C}H_3$); 25.03; 29.04; 29.20; 29.34; 31.15; 31.67 ($\underline{C}H_2$); 70.12; 70.19; 72.26; (O$\underline{C}H_2$); 76.29 (OCH); 112.71; 119.70; 131.20; 133.96; 159.14 (Ar$\underline{C}$). δ_P (121.5 MHz, CD_3OD) 15.61 (br). HRMS: MH^+ found 689.45385; $C_{40}H_{65}O_7P$ requires: 689.44679.

4.2.10. (6*S*,16*S*)-6,16-didecyl-22- hydroxy-6,7,9,10,12, 13,15,16-octahydro-22*H*-dibenzo[n,q][1,4,7,10,13,16] pentaoxa- λ^5-phosphacyclooctadecin-22-one (*R*,*R*)-3

Proton-ionizable crown ether (*R*,*R*)-**3** was prepared in the same way as described above for (*S*,*S*)-**3** starting from ethyl phosphinate (*R*,*R*)-**14** (0.22 g, 0.30 mmol). Yield: 0.12 g (28 %). $[\alpha]_D^{24}$=+37.5 (*c* 0.77, MeOH). Other physical and spectroscopic data of (*R*,*R*)-**3** concurred with those of proton-ionizable crown ether (*S*,*S*)-**3.**

4.2.11. (6*R*,16*R*)-2,20-Di-tert-butyl-6,16-didecyl-22-hydroxy-6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo [n,q][1,4,7,10,13,16] pentaoxa- λ^5-phosphacyclo-octadecin-22-one (*S*,*S*)-4

Proton-ionizable crown ether (*S*,*S*)-**4** was prepared in the same way as described above for (*S*,*S*)-**3** starting from ethyl phosphinate (*S*,*S*)-**15** (0.29 g, 0.35 mmol). Yield: 0.17 g (60 %). The product is a pale yellow oil. R_f (CH_2Cl_2-MeOH 15:1) 0.36; $[\alpha]_D^{22}$=+17.5 (*c* 1.05, CH_2Cl_2); ν_{max} (neat) 3030, 2952, 2922, 2853, 1597, 1574, 1484, 1466, 1393, 1360, 1291, 1261, 1241, 1191, 1146, 1124, 1091, 1034, 941, 877, 810, 721, 669, 580, 547, 506 cm^{-1}; δ_H (125 MHz, $CDCl_3$) 0.92 (t, *J*=7 Hz 6H, C$\underline{H}_3$); 1.22-1.56 (m, 60H, C$\underline{H}_2$, C$\underline{H}_3$); 3.33-3.74 (m, 12H, OC$\underline{H}$, OC$\underline{H}_2$); 4.45-4.55 (m, 2H, OC$\underline{H}_2$); 6.96-7.03 (m, 2H, Ar$\underline{H}$); 7.47-7.49 (m, 2H, Ar$\underline{H}$); 7.85-7.95 (m, 2H, Ar$\underline{H}$). δ_C (125 MHz, CD_3OD, 318K) 13.03 ($\underline{C}H_3$); 22.30; 25.13; 29.01; 29.14; 29.31; 29.35; 30.69; 31.66 ($\underline{C}H_2$, $\underline{C}H_3$); 33.75 ($\underline{C}(CH_3)_3$); 69.65; 69.88; 72.10; (O$\underline{C}H_2$); 76.62 (OCH); 112.56; 128.14; 130.58; 142.57; 157.74 (Ar$\underline{C}$). δ_P (121.5 MHz, $CDCl_3$) 21.39 (br). HRMS: MH^+ found 801.57904; $C_{48}H_{81}O_7P$ requires: 801.57199.

4.2.12. (6*S*,16*S*)-2,20-Di-tert-butyl-6,16-didecyl-22-hydroxy-6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo [n,q][1,4,7,10,13,16] pentaoxa-λ^5-phosphacyclo-octadecin-22-one (*R*,*R*)-4

Proton-ionizable crown ether (*R*,*R*)-**4** was prepared in the same way as described above for (*S*,*S*)-**3** starting from ethyl phosphinate (*R*,*R*)-**15** (0.24 g, 0.29 mmol). Yield: 0.13 g (54 %). $[\alpha]_D^{24}$=-15.6 (*c* 1.01, CH_2Cl_2). Other physical and spectroscopic data of (*R*,*R*)-**4** concurred with those of proton-ionizable crown ether (*S*,*S*)-**4**.

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