EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201101769

Synthesis and Preliminary Structural and Binding Characterization of New Enantiopure Crown Ethers Containing an Alkyl Diarylphosphinate or a Proton-Ionizable Diarylphosphinic Acid Unit

György Székely,[a] Barbara Csordás,[b] Viktor Farkas,[b] József Kupai,[a] Peter Pogány,[c] Zsuzsanna Sánta,[d] Zoltán Szakács,[d] Tünde Tóth,[a,e] Miklós Hollósi,[b] József Nyitrai,[a][†] and Péter Huszthy*[a,e]

Keywords: Molecular recognition / Host–guest systems / Crown compounds / Phosphorus / Circular dichroism / NMR titration / DFT calculations

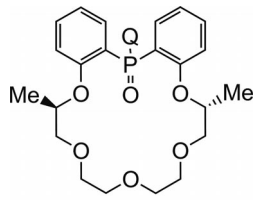
New enantiopure crown ethers containing either an ethyl diarylphosphinate moiety [(*S*,*S*)-**4** to (*S*,*S*)-**7**] or a proton-ionizable diarylphosphinic acid unit [(*S*,*S*)-**8** to (*S*,*S*)-**11**] have been synthesized. Electronic circular dichroism (ECD) studies on the complexation of these new enantiopure crown ethers with the enantiomers of α-(1-naphthyl)ethylammonium perchlorate (1-NEA) and with α-(2-naphthyl)ethylammonium perchlorate (2-NEA) were also carried out. These studies showed appreciable enantiomeric recognition with heterochiral [(*S*,*S*)-crown ether plus either (*R*)-1- or (*R*)-2-NEA] preference. Theoretical calculations found three significant intermolecular hydrogen bonds in the complexes of (*S*,*S*)-**9**. Furthermore, preference for heterochiral complexes was also observed, in good agreement with ECD results. Complex formation constants were determined by NMR titration for four selected crown ether/NEA pairs.

Introduction

Optically active crown ethers have received a great deal of attention in many fields of chemistry because these chiral host molecules can be very effective enantioselective sensors and selectors for the different enantiomers of various guest molecules.[1–3] These optically active receptors can discriminate between the enantiomers of protonated primary organic amines,[4,5] which are the basic building blocks of biomolecules. Primary organic amines are also formed during the degradation of amino acids or serve as neurotransmitters. The enantiomers of biogenic amines can have different pharmacological and toxicological effects, so their enantioselective sensing and separation are of great importance in the pharmaceutical, food, pesticide, and cosmetics industries, as well as in environmental analysis.[6]

Since Cram and co-workers synthetized the first optically active crown ethers containing binaphthyl units[7] – which displayed excellent enantiomeric recognition capabilities for protonated primary organic amines,[8] leading to effective enantioseparation techniques[9–11] – a great number of different enantiopure crown ethers have been prepared for similar purposes. These research activities have been well documented.[1–6,12–1]

Recently the synthesis and characterization (IR, ^{1}H, ^{13}C, and ^{31}P NMR, as well as MS) of a new family of chiral crown ethers containing either an alkyl diarylphosphinate component or a proton-ionizable diarylphosphinic acid unit have been described (see Figure 1). ECD spectroscopic



(*R*,*R*)-**1**: Q = OMe
(*R*,*R*)-**2**: Q = OEt
(*R*,*R*)-**3**: Q = OH

Figure 1. Reported enantiopure crown ethers containing either an alkyl diarylphosphinate or a proton-ionizable diarylphosphinic acid unit.

[a] Department of Organic Chemistry and Technology, Budapest University of Technology and Economics,
Szent Gellért tér 4, PO Box 91, 1111 Budapest, Hungary
Fax: +36-1-4633297
E-mail: huszthy@mail.bme.hu
[b] Protein Modelling Group of the Hungarian Academy of Sciences, Eötvös Loránd University,
Pázmány Péter sétány 1/A, PO Box 32, 1518 Budapest, 112, Hungary
[c] Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics,
Szent Gellért tér 4, 1111 Budapest, Hungary
[d] Spectroscopic Research Division,
Gedeon Richter Plc., Gyömrői út 19–21, PO Box 27,
1475 Budapest 10, Hungary
[e] Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences,
Szent Gellért tér 4, PO Box 91, 1521 Budapest, Hungary
[†] Deceased August 25, 2011

studies on the enantiopure chiral crown compounds (*R*,*R*)-**1**, (*R*,*R*)-**2**, and (*R*,*R*)-**3** were also reported.[15]

ECD spectra of the crown ether (*R*,*R*)-**1**, containing the methyl phosphinate unit, were measured in solvents of different polarities: 2,2,4-trimethylpentane (isooctane, iOc), MeCN, MeOH, and 2,2,2-trifluoroethanol (TFE).[15] The characteristic feature of the ECD spectra in all four solvents is a negative ^1B_b exciton couplet. ECD spectra of the proton-ionizable crown ether (*R*,*R*)-**3** were measured in H_2O, MeOH, MeCN, and TFE [(*R*,*R*)-**3** is not soluble in iOc]. A similar negative ^1B_b exciton couplet was found only in H_2O and MeOH, whereas in MeCN and TFE a strong asymmetric positive band appears below 230 nm in the far-UV region.

The unique ECD spectrum of the crown ether (*R*,*R*)-**3**, containing the phosphinic acid unit, in MeCN[15] prompted us to consider the possibility of dimerization of the crown ether through the POOH groups. X-ray crystallographic studies on the parent achiral crown ether [with hydrogen atoms instead of methyl groups in the macro ring of (*R*,*R*)-**3**] confirmed dimer formation by (*R*,*R*)-**3**.[16]

According to ECD measurements, crown ether (*R*,*R*)-**1**, containing the methyl phosphinate unit, interacts with α-(1-naphthyl)ethylammonium perchlorate (abbreviated as 1-NEA) but does not discriminate between its enantiomers. ECD spectra also clearly show that crown ether (*R*,*R*)-**3**, containing the phosphinic acid unit, does not bind 1-NEA at a 1:1 molar ratio and does not discriminate between its enantiomers.

In an attempt to explore the complexing capabilities and enantiomer discriminating power of crown ethers containing either a phosphinate or a phosphinic acid unit, 18-crown-6 ethers and 21-crown-7 ethers containing methyl or octyl substituents at positions 6/16 and 7/15, respectively [(*S*,*S*)-**4**, (*S*,*S*)-**5**, (*S*,*S*)-**6**, (*S*,*S*)-**7** (Scheme 1; for nomenclature see Figure 2, a) and (*S*,*S*)-**8**, (*S*,*S*)-**9**, (*S*,*S*)-**10**, (*S*,*S*)-**11** (Scheme 2; for nomenclature see Figure 2, b)] were synthesized. The discriminating capabilities of the new crown ethers (*S*,*S*)-**4** to (*S*,*S*)-**11** were probed by ECD spectroscopy with 1-NEA and α-(2-naphthyl)ethylammonium perchlorate (2-NEA) in MeCN solution. No estimates for the binding constants emerged from ECD experiments, so these were determined for selected systems by ^1H NMR titration. Four titrations were performed, allowing investigation of the chiral discrimination of (*S*,*S*)-**9** with regard to the enantiomers of 1-NEA and study of the possible roles of phosphinic acid and ethyl ester groups in complexation

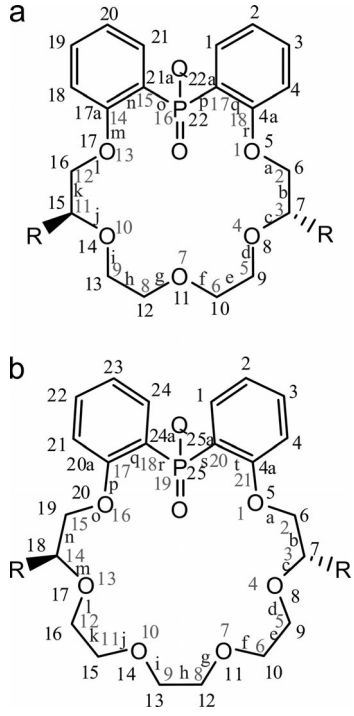
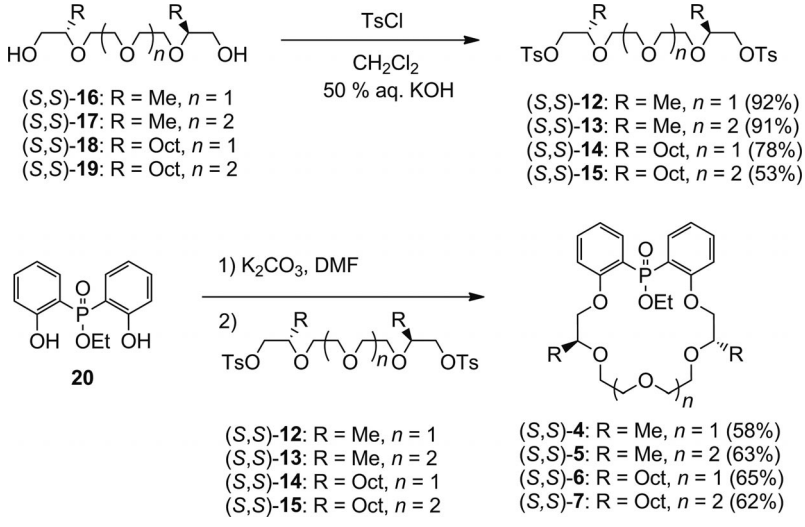
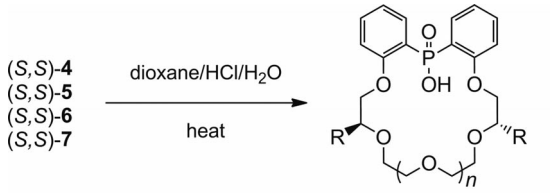


Figure 2. a) Nomenclature of 18-crown-6 ethers containing a phosphinate or a phosphinic acid unit, respectively. b) Nomenclature of 21-crown-7 ethers containing a phosphinate or a phosphinic acid unit, respectively.



Scheme 1. Preparation of new macrocycles containing diarylphosphinic acid ethyl ester moieties.

in titrations of (*R*)-1-NEA with (*S*,*S*)-**9** and (*S*,*S*)-**5**. Guest-sided regioselectivity could also be examined from titrations of (*S*,*S*)-**9** with 1- and 2-NEA.



(*S*,*S*)-**8**: R = Me, *n* = 1 (52%)
(*S*,*S*)-**9**: R = Me, *n* = 2 (69%)
(*S*,*S*)-**10**: R = Oct, *n* = 1 (60%)
(*S*,*S*)-**11**: R = Oct, *n* = 2 (59%)

Scheme 2. Preparation of new proton-ionizable crown ethers containing diarylphosphinic acid units.

Results and Discussion

Synthesis

The new enantiopure dialkyl-substituted macrocycles (*S*,*S*)-**4** to (*S*,*S*)-**7** were prepared as shown in Scheme 1.

The corresponding oligoethylene glycol ditosylate derivatives (*S*,*S*)-**12** to (*S*,*S*)-**15** (see Scheme 1) were synthesized from the previously reported enantiopure dimethyl-substituted oligoethylene glycols (*S*,*S*)-**16**[17] and (*S*,*S*)-**17**[18] and from the previously reported enantiopure dioctyl-substituted oligoethylene glycols (*S*,*S*)-**18**[17] and (*S*,*S*)-**19**[17] by treatment with tosyl chloride in a CH_2Cl_2/H_2O mixture in the presence of the strong base KOH. This procedure was based on the previously described synthesis of the dioctyl-substituted tetraethylene glycol ditosylate (*S*,*S*)-**14**.[19]

The enantiopure ligands (*S*,*S*)-**4** and (*S*,*S*)-**5** (see Scheme 1) were then prepared from the reported ethyl bis(2-hydroxyphenyl)phosphinate (**20**)[20] and enantiopure dimethyl-substituted tetraethylene glycol ditosylate (*S*,*S*)-**12** or enantiopure dimethyl-substituted pentaethylene glycol ditosylate (*S*,*S*)-**13**, respectively, at 50 °C in DMF in the presence of K_2CO_3 as a base by the procedure[15] described for the synthesis of the similar macrocycles (*R*,*R*)-**1** and (*R*,*R*)-**2** (see Figure 1). The enantiopure macrocycles (*S*,*S*)-**6** and (*S*,*S*)-**7** (see Scheme 1) were prepared in a similar manner from **20**[20] and dioctyl-substituted tetraethylene glycol ditosylate (*S*,*S*)-**14** or enantiopure dioctyl-substituted pentaethylene glycol ditosylate (*S*,*S*)-**15**.

Enantiopure proton-ionizable ligands (*S*,*S*)-**8** to (*S*,*S*)-**11**, each containing a diarylphosphinic acid unit, were prepared from the corresponding dimethyl- and dioctyl-substituted macrocycles (*S*,*S*)-**4** to (*S*,*S*)-**7**, each containing an ethyl phosphinate moiety, by acidic hydrolysis at elevated temperature in the presence of a dioxane/10% aqueous HCl (1:1) mixture (see Scheme 2) in a procedure based on that described[15] for the synthesis of (*R*,*R*)-**3** (see Figure 1).

Electronic Circular Dichroism (ECD) Spectroscopy

The new crown ethers (*S*,*S*)-**4** to (*S*,*S*)-**7** and (*S*,*S*)-**8** to (*S*,*S*)-**11**, containing either an ethyl phosphinate unit or a phosphinic acid moiety, respectively, were characterized by ECD spectroscopy similarly to the previously reported 6,16-dimethyl-substituted chiral crown ethers (*R*,*R*)-**1** and (*R*,*R*)-**2**.[15] The opposite sign of the spectra of the crown ethers (*S*,*S*)-**4** to (*S*,*S*)-**7** is the consequence of the (*S*,*S*) configuration of the chirality centers; the intensities of the bands of the positive ^1B_b couplets are similar. The spectral characteristics of the dioctyl-substituted crown ethers, regardless of the different cavity sizes (18-crown-6 or 21-crown-7 ether), are also similar.

Crown ethers (*S*,*S*)-**8** to (*S*,*S*)-**11** were intended for use for the transport of metal ions and enantiomers of protonated primary arylalkylamines through a water/dichloromethane/water bulk liquid membrane system. Effective transport requires lipophilic side chains such as octyl groups. The rationale behind the choice of methyl and octyl side chains was investigation of the effects of their different lipophilicities on the ECD spectra. The 7,15-dioctyl-substituted 18-crown-6-type crown ether (*S*,*S*)-**6** has a spectrum that is the mirror image of that of (*R*,*R*)-**2**.[15] Compounds (*S*,*S*)-**4** (R = Me) and (*S*,*S*)-**6** (R = Oct) each feature a weak ^1B_b couplet with a rather strong positive ^1L_a band (Figure 3).

The oligoethylene glycol moieties of the 21-crown-7-type molecules [(*S*,*S*)-**5** and (*S*,*S*)-**7**] have flexible conformations. The ECD spectra are determined by the aromatic chromophores and the chiral centers at positions 7 and 18.

The ECD spectrum of 7,18-dimethyl-substituted 18-crown-6-type crown ether (*S*,*S*)-**8**, containing a phosphinic acid unit, is similar to the spectrum of (*R*,*R*)-**3**[15] but the sign of the bands is positive because of the (*S*,*S*) configuration of the chiral centers (Figure 4, a,b). The spectrum is marked by one strong positive band centered between 205 nm and 210 nm, whereas the other crown ethers (*S*,*S*)-**9**, (*S*,*S*)-**10**, and (*S*,*S*)-**11** containing the phosphinic acid unit show three bands below 210 nm and a broad negative ^1L_a band at about 227 nm (Figure 3, c,d). The three short-wavelength bands are of low intensity. Crown ethers (*S*,*S*)-**9**, (*S*,*S*)-**10**, and (*S*,*S*)-**11** might exist in MeCN as mixtures of dimers (Figure 4, a,b) and monomers showing a negative band near 200 nm (Figure 4).

If the spectra of the complexes of enantiomers are significantly different, enantiomer discrimination is very probable. If the spectra are the same or similar, enantiomer discrimination can be ruled out. ECD spectra should be measured at different host/guest molar ratios. The chiral discriminating capabilities of crown ethers (*S*,*S*)-**4** to (*S*,*S*)-**7**, each containing an ethyl phosphinate moiety, and of crown ethers (*S*,*S*)-**8** to (*S*,*S*)-**11**, each containing a phosphinic acid unit, were tested with α-(1-naphthyl)ethylammonium perchlorate (1-NEA) and α-(2-naphthyl)ethylammonium perchlorate (2-NEA). The solvent was MeCN and the experiments were carried out at 1:1 molar ratios of the crown ether and 1- or 2-NEA.

Disubstituted 18-crown-6-type ligands (*S*,*S*)-**4** and (*S*,*S*)-**6** form complexes with (*R*)- and (*S*)-1-NEA and with (*R*)- and (*S*)-2-NEA at 1:1 crown ether/NEA ratios. On the basis of band intensities, the spectra of the heterochiral [(*S*,*S*)-

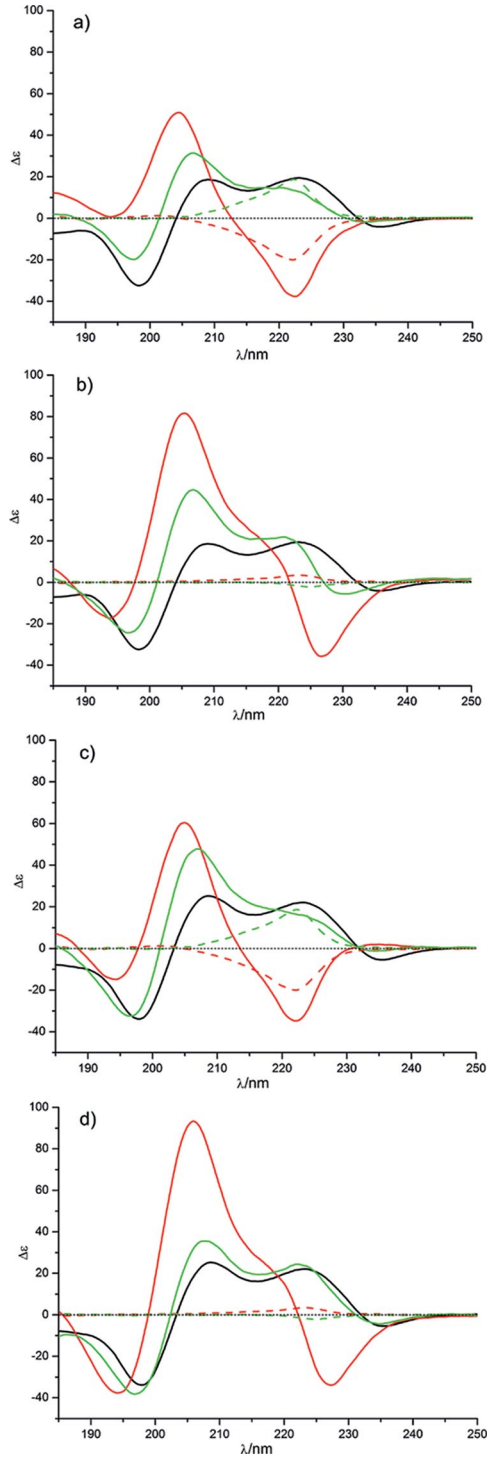


Figure 3. a) ECD spectra of the ethyl phosphinate (*S*,*S*)-**4** in MeCN (black), (*S*,*S*)-**4** plus (*R*)-1-NEA complex (red), (*S*,*S*)-**4** plus (*S*)-1-NEA complex (green), (*R*)-1-NEA (dashed red line), (*S*)-1-NEA (dashed green line). b) ECD spectra of (*S*,*S*)-**4** in MeCN (black), (*S*,*S*)-**4** plus (*R*)-2-NEA complex (red), (*S*,*S*)-**4** plus (*S*)-2-NEA complex (green), (*R*)-2-NEA (dashed red line), (*S*)-2-NEA (dashed green line). c) ECD spectra of ethyl phosphinate (*S*,*S*)-**6** in MeCN (black), (*S*,*S*)-**6** plus (*R*)-1-NEA complex (red), (*S*,*S*)-**6** plus (*S*)-1-NEA complex (green), (*R*)-1-NEA (dashed red line), (*S*)-1-NEA (dashed green line). d) ECD spectra of (*S*,*S*)-**6** in MeCN (black), (*S*,*S*)-**6** plus (*R*)-2-NEA complex (red), (*S*,*S*)-**6** plus (*S*)-2-NEA complex (green), (*R*)-2-NEA (dashed red line), (*S*)-2-NEA (dashed green line).

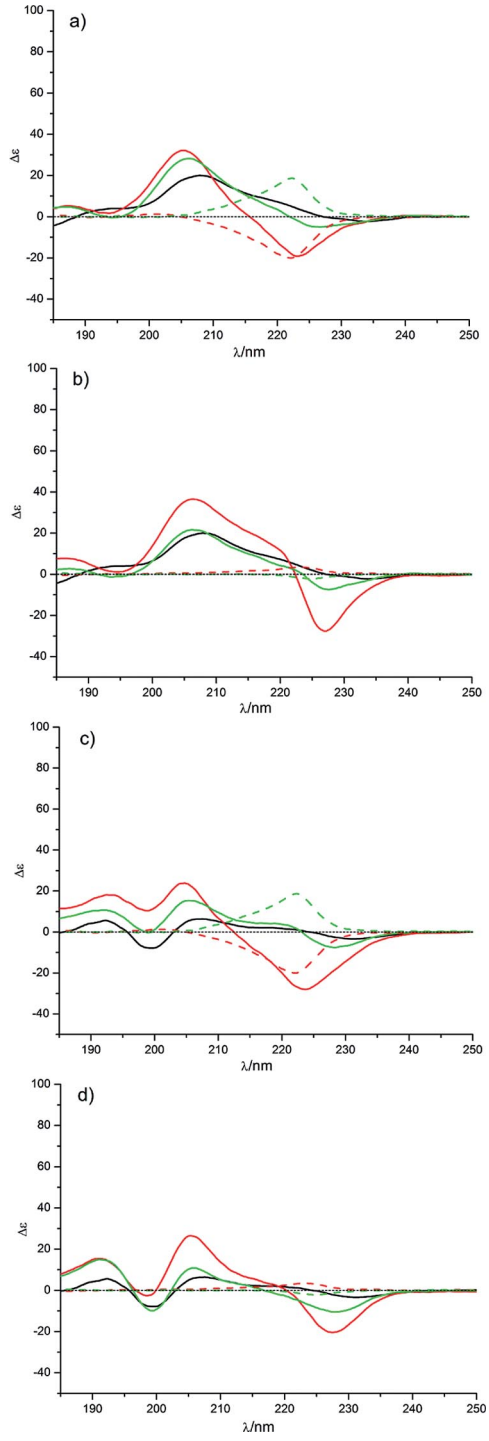


Figure 4. a) ECD spectra of phosphinic acid (*S*,*S*)-**8** in MeCN (black), (*S*,*S*)-**8** plus (*R*)-1-NEA complex (red), (*S*,*S*)-**8** plus (*S*)-1-NEA complex (green), (*R*)-1-NEA (dashed red line), (*S*)-1-NEA (dashed green line). b) ECD spectra of crown ether (*S*,*S*)-**8** in MeCN (black), crown ether (*S*,*S*)-**8** plus (*R*)-2-NEA complex (red), crown ether (*S*,*S*)-**8** plus (*S*)-2-NEA complex (green), (*R*)-2-NEA (dashed red line), (*S*)-2-NEA (dashed green line). c) ECD spectra of phosphinic acid (*S*,*S*)-**9** in MeCN (black), (*S*,*S*)-**9** plus (*R*)-1-NEA complex (red), (*S*,*S*)-**9** plus (*S*)-1-NEA complex (green), (*R*)-1-NEA (dashed red line), (*S*)-1-NEA (dashed green line). d) ECD spectra of (*S*,*S*)-**9** in MeCN (black), crown ether (*S*,*S*)-**9** plus (*R*)-2-NEA complex (red), crown ether (*S*,*S*)-**9** plus (*S*)-2-NEA complex (green), (*R*)-2-NEA (dashed red line), (*S*)-2-NEA (dashed green line).

crown ether plus either (*R*)-1- or (*R*)-2-NEA] complexes differ more from the spectra of the (*S*,*S*)-crown ethers **4** and **6** than those of the homochiral [(*S*,*S*)-crown ether plus either (*S*)-1- or (*S*)-2-NEA] ones. The most intense short-wavelength bands appear in the spectra of the heterochiral complexes of 2-NEA (Figure 3).

The ECD spectra of the complexes of 7,18-dimethyl and 7,18-dioctyl-substituted 21-crown-7-type ligands (*S*,*S*)-**5** and (*S*,*S*)-**7** are similar to those of the complexes of the smaller ring size 18-crown-6 ligands (*S*,*S*)-**4** and (*S*,*S*)-**6** but the band intensities are smaller. The longer-wavelength band (near 220 nm) of the 21-crown-7 ethers (*S*,*S*)-**5** and (*S*,*S*)-**7** shows more definite changes upon complex formation (spectra not shown).

The short-wavelength regions of the ECD spectra of the heterochiral 2-NEA complexes of (*S*,*S*)-**4** and (*S*,*S*)-**6** are each marked by an asymmetric positive exciton couplet at about 200 nm (Figure 3).

The spectra of 1-NEA and 2-NEA complexes with crown ether phosphinic acids feature weak bands. The ECD spectra of the homochiral [(*S*,*S*)-crown ether plus (*S*)-1-NEA] and heterochiral [(*S*,*S*)-crown ether plus (*R*)-1-NEA] complexes of phosphinic acids (*S*,*S*)-**8** and (*S*,*S*)-**9** (R = Me) are similar below 210 nm but differ significantly above 220 nm (Figure 4). The spectra of the homochiral 1-NEA complexes of phosphinic acids (*S*,*S*)-**10** and (*S*,*S*)-**11** (R = Oct) are similar to the ECD spectra of the uncomplexed ligands (spectra not shown). The heterochiral complexes show significantly different ECD spectra marked by one positive ^1B_b band below 210 nm and a strong ^1L_a band above 220 nm. The ECD spectra of the homochiral 2-NEA complexes of ligands (*S*,*S*)-**8** to (*S*,*S*)-**11** are also similar to the spectra of the uncomplexed crown compounds (Figure 4). In contrast, the ECD spectra of the heterochiral 2-NEA complexes differ significantly [see the spectrum of (*S*,*S*)-**9** and (*R*)-2-NEA].

We measured ECD spectra of (*S*,*S*)-**8** in MeCN, MeOH, and H_2O (Figure 5). The spectrum in H_2O shows an intense short-wavelength positive couplet, similarly to the spectra of 6,16-dimethyl-substituted (*R*,*R*)-**3**.[15] The spectrum in MeOH also has a low-wavelength couplet but its intensity is lower than in H_2O (Figure 5). The spectrum measured in MeCN shows a broad positive band. Crown ethers (*S*,*S*)-**9**, (*S*,*S*)-**10**, and (*S*,*S*)-**11** also show strong solvent dependence.

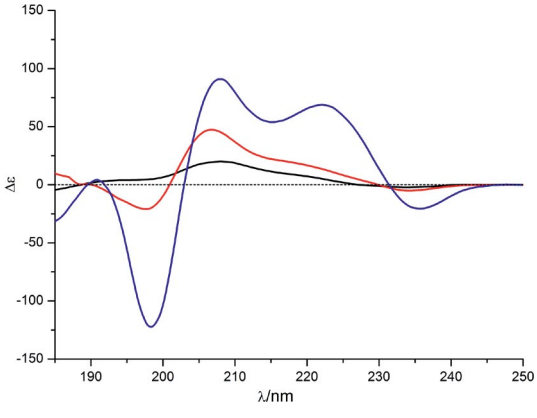


Figure 5. Far-UV ECD spectra of (*S*,*S*)-**8** in H_2O (blue), MeOH (red), and MeCN (black).

Computational Results

The goal of the computations was to determine the main binding characteristics of (*S*,*S*)-**9** with all four guests (*R*)- and (*S*)-1-NEA and (*R*)- and (*S*)-2-NEA. Calculations showed the 2-NEA complexes to be more stable than those of 1-NEA; the energy differences between the two *R* enantiomers and between the two *S* enantiomers were both 9–10 kJ mol^{-1}. Three important hydrogen bonding interactions were found in the complexes. One hydrogen bond is formed between one R-NH_3^+ hydrogen and the phosphanyl oxygen (P=O); the other two hydrogen atoms of R-NH_3^+ are bound to O^{11} and O^{17}, respectively (see Figure 6a–d). The intermolecular hydrogen bonding between the phosphanyl hydroxyl group (P–OH) and either O^5 or O^8 of (*S*,*S*)-**9** strains the structure, so these structures are 10–20 kJ mol^{-1} higher in energy than the ground state geometry of the given configuration. The hydrogen bonds of the most stable structures are given in Table 1. The stability order of the complexes was found to change in the following order: (*S*)-1-NEA/(*S*,*S*)-**9** < (*R*)-1-NEA/(*S*,*S*)-**9** and (*S*)-2-NEA/(*S*,*S*)-**9** < (*R*)-2-NEA/(*S*,*S*)-**9**. In the case of 1-NEA slightly greater discrimination was found than for 2-NEA, although this difference is negligible, with significant uncertainty caused by multiple factors both in the complex structure and the structural differences of the different stereoisomers of NEA. Note that this relates to isolated molecules without consideration of the solvent effects.

Table 1. Calculated hydrogen bonds in the ground state structures (values given in Å).

Structure	N–H(1)···O=P	N–H(2)···O^{11}	N–H(3)···O^{17}
(*R*)-1-NEA/(*S*,*S*)-**9**	1.58	1.95	1.96
(*S*)-1-NEA/(*S*,*S*)-**9**	1.59	1.92	1.89
(*R*)-2-NEA/(*S*,*S*)-**9**	1.70	1.96	1.99
(*S*)-2-NEA/(*S*,*S*)-**9**	1.76	1.86	1.96

NMR Titrations

^{1}H NMR titration is a powerful tool for characterization of complex formation[24] between a crown ether (CE) and a guest (G), yielding the association constant of the presumed 1:1 complex (K = [G·CE][G]$^{-1}$[CE]$^{-1}$). Because of the amounts of materials available, a single NMR sample of the host was prepared and a 10× concentrated guest solution in the same solvent was gradually added to this NMR tube to minimize dilution of the host. ^{1}H NMR spectra were recorded to observe the effects of complex formation on the chemical shifts of both constituents. To assign the highly overlapping host phenyl and guest naphthyl proton signals and the host aliphatic protons, 2D TOCSY spectra were also run at each titration point. The observed chemical shift versus total concentration ratio c_G/c_{CE} datasets of the most responsive host and guest protons are plotted in Figures 7, 8, 9, and 10.

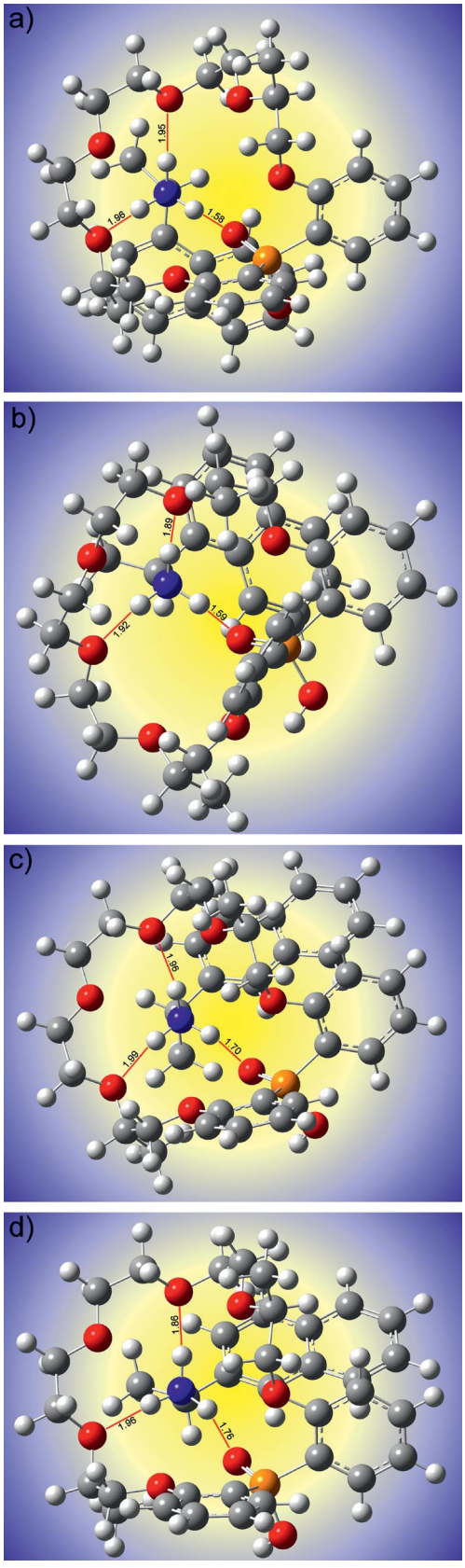


Figure 6. Predictions of typical host–guest interactions between the novel crown ethers and the NEA ligands based on DFT calculations: a) (*S*,*S*)-**9** with (*R*)-1-NEA; b) (*S*,*S*)-**9** with (*S*)-1-NEA; c) (*S*,*S*)-**9** with (*R*)-2-NEA; d) (*S*,*S*)-**9** with (*S*)-2-NEA.

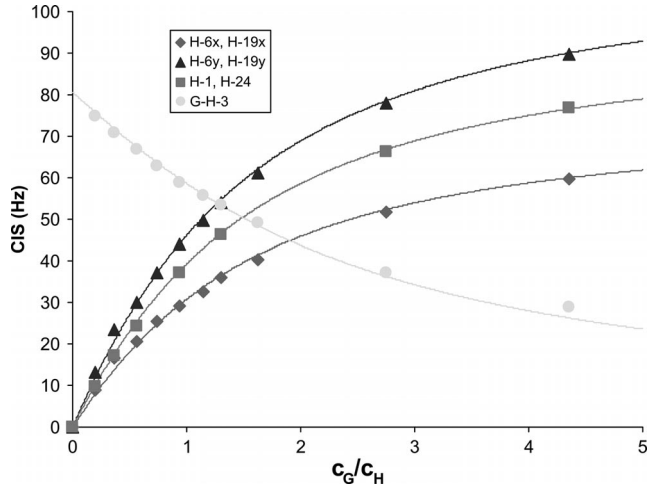


Figure 7. Chemical shift changes upon complexation ($\Delta\delta$) as functions of the guest/host concentration ratio for selected protons of (*S*,*S*)-**9** host and (*R*)-1-NEA guest (abs. values); CIS: chemically induced shift.

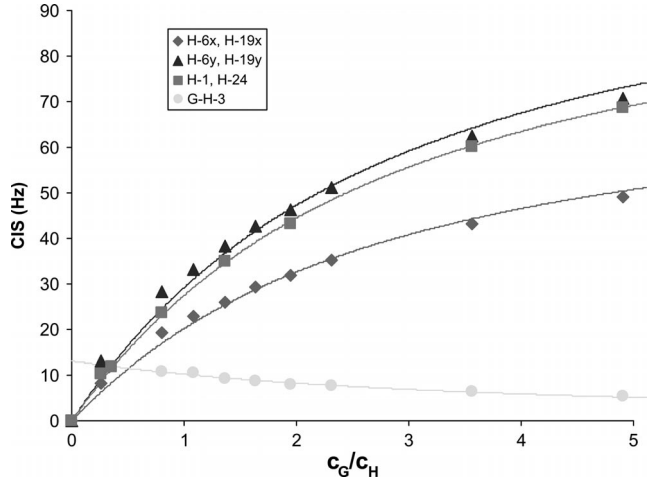


Figure 8. Chemical shift changes upon complexation ($\Delta\delta$) as functions of the guest/host concentration ratio for selected protons of (*S*,*S*)-**9** host and (*S*)-1-NEA guest (abs. values).

For better visualization and comparison, $\Delta\delta$ values (the observed chemical shift minus that of the uncomplexed host or guest, recorded in a separate experiment) are depicted. These datasets were evaluated by simultaneous nonlinear curve fitting (see Experimental for details) to yield the binding constant and the maximum changes of chemical shifts upon complexation, the so-called limiting chemical shift displacements ($\Delta\delta_{max}$; see Figure 11, values given in ppb). These latter correspond to "plateaus" in Figure 7–Figure 10 that could be reached with a large excess of the guest ensuring 100% complexation (experimentally inaccessible because of solubility limitations).

Most previous complexation studies on crown ethers have been performed in $CDCl_3$, because this inert solvent enhances the intermolecular association (through hydrogen bonds of the ammonium group in our case). However, the solubilities of our 1-NEA and 2-NEA ligands required the

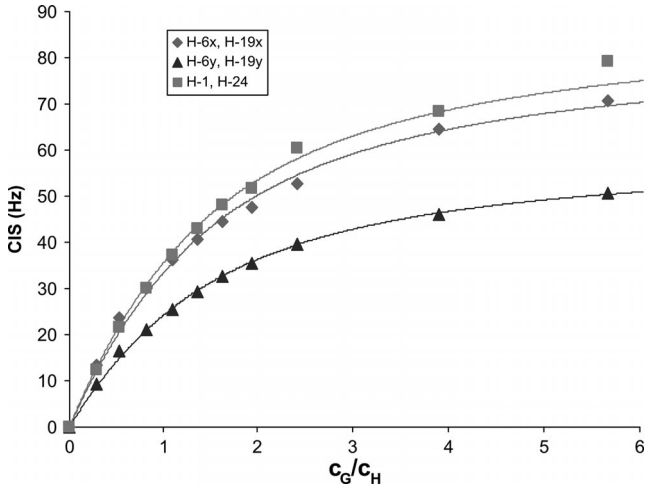


Figure 9. Chemical shift changes upon complexation ($\Delta\delta$) as functions of the guest/host concentration ratio for selected protons of (*S*,*S*)-**9** host and (*R*)-2-NEA guest (abs. values).

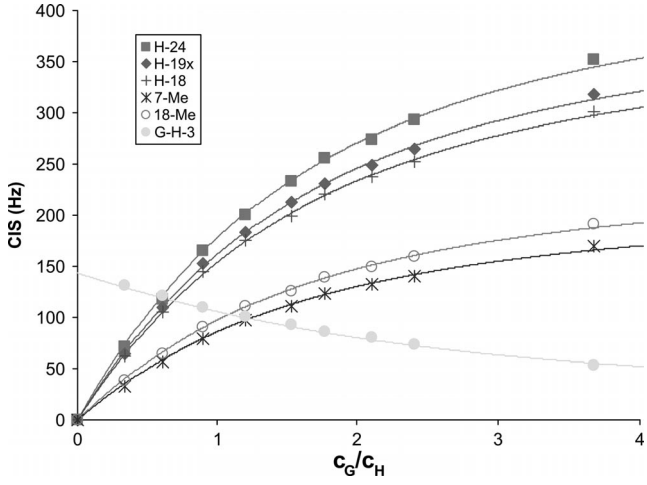


Figure 10. Chemical shift changes upon complexation ($\Delta\delta$) as functions of the guest/host concentration ratio for selected protons of (*S*,*S*)-**5** host and (*R*)-1-NEA guest (abs. values).

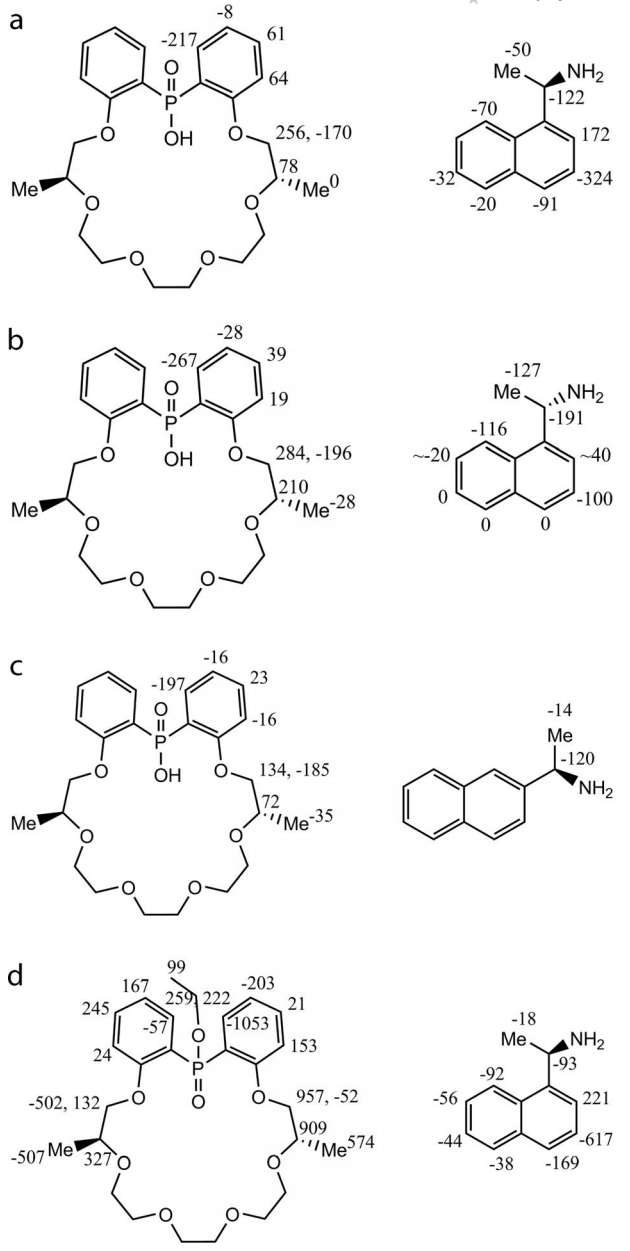


Figure 11. Chemical shift changes upon full complexation ($\Delta\delta_{max}$) in ppb for selected protons of a) (*S*,*S*)-**9** host and (*R*)-1-NEA guest; b) (*S*,*S*)-**9** host and (*S*)-1-NEA guest; c) (*S*,*S*)-**9** host and (*R*)-2-NEA guest; d) (*S*,*S*)-**5** host and (*R*)-1-NEA guest.

use of CD_3OD (10% v/v) as a cosolvent. This is known to decrease the binding constants, but their magnitudes remained in the range measureable by NMR titration.[25]

In the case of the crown ether (*S*,*S*)-**9**, three titrations were performed with the following ligands: (*R*)-1-NEA, (*S*)-1-NEA, and (*R*)-2-NEA. (*R*)-1-NEA showed a binding affinity ($K = 167 \pm 8$) more than more than double that of its *S* enantiomer ($K = 70 \pm 3$). This can be explained in terms of the generally observed higher stabilities of the heterochiral complexes [i.e., (*R*,*R*)-crown ether/(*S*)-arylalkylammonium salt or (*S*,*S*)-crown ether/(*R*)-arylalkylammonium salt] in relation to those of homochiral complexes [i.e., (*S*,*S*)-crown ether/(*S*)-arylalkylammonium salt or (*R*,*R*)-crown ether/(*R*)-arylalkylammonium salt].[14,26] The significantly different $\Delta\delta_{max}$ values found for both host and guest protons (see Figure 11, a) might be indicative of differing binding geometries of the two enantiomers.

During titration of (*R*)-2-NEA with (*S*,*S*)-**9**, extremely closely overlapping aromatic signals were observed for the guest at 500 MHz, so chemical shifts could be analyzed only for its aliphatic methine and methyl protons. These aliphatic nuclei showed $\Delta\delta_{max}$ values similar to those for (*R*)-1-NEA. From the crown ether perspective, though, $\Delta\delta_{max}$ for the phenyl proton *ortho* to the oxygen (H-4, H-21) differs considerably and the crown ether methyl signal here shows $\Delta\delta_{max} = -35$ ppb, whereas practically no change was observed in complexation with (*R*)-1-NEA. These differences indicate different orientations of the regioisomeric guests within the host cavity, which is also reflected by the larger binding constant for (*R*)-2-NEA ($K = 216 \pm 14$).

The two sides of the (*S*,*S*)-**5** host molecule become diastereotopic, leading to the potential inequivalence of all carbon-bound protons and thus to the doubling of most resonance signals. This is expected because the phosphorus atom here is a prochiral center, whereas in the phosphinic acid analogue (*S*,*S*)-**9** its =O and –OH substituents are quasi-equivalent, due either to fast proton exchange even in an aprotic solvent such as $CDCl_3$ or to the formation of a hypothesized homodimer.[15] Nevertheless, 2D TOCSY allowed its almost complete ^{1}H NMR assignment and, interestingly, three- to fivefold increases in $\Delta\delta_{max}$ values in relation to (*S*,*S*)-**9** were found. However, the affinity towards the same guest (*R*)-1-NEA remained virtually the same ($K = 171 \pm 3$). This contrasts with the ECD results, in which the ester host was a stronger binder than the phosphinic acid in acetonitrile, but the use of a different, CD_3OD-containing solvent mixture in NMR might influence both the binding preferences and the propensity to homodimer formation.

Conclusions

The synthesis and characterization of a new type of chiral crown ethers containing either an alkyl diarylphosphinate moiety [(*S*,*S*)-**4** to (*S*,*S*)-**7**] or a diarylphosphinic acid unit [(*S*,*S*)-**8** to (*S*,*S*)-**11**] have been achieved.

Because of the presence of the aryl substituents the ECD spectra are rich in bands in the ^1B_b, ^1L_a, and ^1L_b regions (190–250 nm and 260–330 nm, respectively). In MeCN their heterochiral complexes [(*S*,*S*)-crown ether plus (*R*)-1- or (*R*)-2-NEA] show more intense spectra than their homochiral [(*S*,*S*)-crown ether plus (*S*)-1- or (*S*)-2-NEA] counterparts. The band intensities of the 18-crown-6-type complexes are greater than those of the 7,18-dimethyl- and 7,18-dioctyl-substituted 21-crown-7-type complexes.

The ECD spectra and the chiral discriminating capabilities of the crown ethers (*S*,*S*)-**8** to (*S*,*S*)-**11**, each containing a phosphinic acid moiety, differ notably from those of the crown ethers (*S*,*S*)-**4** to (*S*,*S*)-**7**, each containing an ethyl phosphinate moiety. All of the ligands (*S*,*S*)-**8** to (*S*,*S*)-**11** have low-intensity ECD spectra in MeCN. They show strong solvent dependence (Figure 5). This is a clear sign of the dimer- or aggregate-forming capabilities of the POOH groups of crown ethers (*S*,*S*)-**8** to (*S*,*S*)-**11**, as described[15] earlier for (*R*,*R*)-**3**.

Theoretical calculations showed that three important hydrogen bonds are formed between (*S*,*S*)-**9** and the enantiomers of 1-NEA and 2-NEA. Steric effects play important roles in the final structures. The heterochiral [(*R*)-NEA plus (*S*,*S*)-**9**] complexes proved to be more stable than the homochiral ones.

Complex formation constants were determined for four selected crown ether/NEA systems by NMR titrations, and these also affirmed the preference of the formation of heterochiral complexes over homochiral ones (ca. twofold difference in *K*, equals $\Delta K = 0.38$). The experimental results are in accordance with the results of the theoretical calculations predicting the 2-NEA to be a stronger binder than 1-NEA. On comparison of the results for the analogous phosphinic acid and phosphinate ester crown ethers, the observed changes in chemical shifts are much larger in the ester case, but the binding constants turned out to be nearly the same.

Experimental Section

General: Infrared spectra were recorded with a Zeiss Specord IR 75 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter that was calibrated by measurement of the optical rotations of both enantiomers of menthol. NMR spectra were recorded at 298 K either with a Bruker DRX 500 Avance spectrometer or with an Agilent (Varian) NMRS 500 fitted with a HCN PFG Triple Resonance ^{13}C-Enhanced Cold Probe, both operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C, or with a Bruker 300 Avance spectrometer (operating at 300 MHz for ^{1}H, 75.5 MHz for ^{13}C, and 121.5 MHz for ^{31}P). The chemical shifts were referenced to TMS (for ^{1}H, ^{13}C) or H_3PO_4 (for ^{31}P).

Mass spectra were recorded with a ZQ 2000 MS instrument (Waters Corp.) by the ESI method. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute of Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were measured with a Boetius micro-melting point apparatus. Starting materials were purchased from Sigma–Aldrich Corporation unless otherwise noted. Silica gel (Merck, 60 F_{254}) and aluminium oxide plates (Merck, 60 F_{254} neutral type E) 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 by well-established[27] methods. Concentration was carried out under reduced pressure unless otherwise stated. Electronic circular dichroism measurements were performed with a Jasco Dichrograph J-810 instrument at room temperature and a 0.02 cm quartz cell for measurements between 185 and 250 nm and a 0.1 cm cell between 250 and 330 nm. The spectra were averages of five scans. The concentration of crown ethers was 0.5 mM.

Quantum chemical calculations focusing on geometry optimization were carried out with use of the Becke3–Lee–Yang–Parr exchange-correlation functional[21,22] in conjunction with the 6–31G** basis set. The starting structure of (*S*,*S*)-**9** was built up by modification of the available Cartesian coordinates obtained by X-ray diffraction study of (*R*,*R*)-**1**.[16] All the quantum chemical calculations were performed with the Gaussian 03 program.[23] The computed geometries were visualized with the aid of the GaussView 3.09 program.

The NMR titrations were performed with the VNMRS-500 spectrometer described above in a CD_3Cl/CD_3OD (9:1 v/v) solvent mixture (both >99.8% deuterium, Merck, Germany). In each titration series, the initial concentration of the 600 μL crown ether solution was accurately set to around 5 mM; on addition of the guest solution (50 mM) to this NMR tube with analytical pipettes [100 or 1000 μL, Eppendorf (Hamburg, Germany)] with ±0.1 to 1 μL precision, the ligand concentration was varied between 0 and 20–25 mM. The temperature within the RF coil was controlled with an accuracy of ±0.5 °C and a precision of ±0.1 °C during the titrations. The ^{1}H spectra were recorded by collection of 64–128 k data points over a spectral width of 16 ppm, with use of a recycling delay (at+d1) of >6 s and co-addition of eight transients. Spectrum

processing included no apodization and zero filling to 512 k yielded a digital resolution of 0.01 Hz. ^{1}H NMR chemical shifts were calibrated to the signal of internal TMS (δ =0.00 ppm). Standard 2D TOCSY and if necessary also 2D HSQC and HMBC spectra were also recorded with VnmrJ 3.1 software and use of Chempack to confirm signal assignments.

Evaluation of the recorded ^{1}H NMR chemical shift titration curves is based on the following principles.[25] With the assumption of a simple 1:1 stoichiometry, the complex formation is characterized by the binding (association) constant $K = [G{\cdot}CE][G]^{-1}[CE]^{-1}$. If the kinetics of complexation are rapid on the chemical shift timescale, the observed chemical shift ($\delta^{CE,i}$) of the i^{th}carbon-bound proton of the crown ether varies gradually between its limiting values for the free host (δ^i_{CE}) and the complex ($\delta^i_{G{\cdot}CE}$).

$$\delta^{CE,i} = x_{CE}\delta^i_{CE} + x_{G{\cdot}CE}\delta^i_{G{\cdot}CE} = \frac{\delta^i_{CE} + K[G]\delta^i_{G{\cdot}CE}}{1 + K[G]} \qquad (1)$$

where x denotes molar fraction. The measured chemical shift change upon addition of a certain amount of the ligand is called the *chemical shift displacement* ($\Delta\delta^{CE,i} = \Delta\delta^{CE,i} - \delta^i_{CE}$), whereas its limiting value for an infinite excess of the ligand is the *limiting chemical shift displacement* ($\Delta\delta^{CE,i}_{\infty}$[28] $= \delta^i_{G{\cdot}CE} - \delta^i_{CE}$); $\delta^{CE,i}$ is determined at the starting point of titration (no guest added).

Similar relationships and definitions hold for the observed chemical shift of the j^{th} guest proton:

$$\delta^{G,j} = x_G\delta^j_G + x_{G{\cdot}CE}\delta^j_{G{\cdot}CE} = \frac{\delta^j_G + K[CE]\delta^j_{G{\cdot}CE}}{1 + K[CE]} \qquad (2)$$

The chemical shift change of the j^{th}guest proton upon full complexation is $\Delta\delta^{G,j}_{\infty} = \delta^j_{G{\cdot}CE} - \delta^j_G$

$\delta^{G,i}$ is determined from the ^{1}H spectra of the guest stock solution in a separate experiment.

The equilibrium concentrations [G] and [CE] are calculated for each titration point from the total (analytical) concentrations c_G and c_{CE} by solving the mass balance equation,

$C_G = [G] + [G{\cdot}CE] = [G](1+ K)[CE]$ (3)

$C_{CE} = [CE] + [G{\cdot}CE] = [CE](1+ K)[G]$ (4)

Input data for the multivariate data evaluation were the total concentrations c_{CE} and c_G (their ratio was checked from the integrals of the non-overlapping methyl doublets of CE and G), chemical shifts of the free components ($\delta^{G,i}$ and $\delta^{CE,i}$ in Hz) and the observed chemical shift values in Hz for the host and guest protons most influenced by complexation (these are plotted in Figure 7–Figure 10). The OPIUM program[29] was used to perform least-squares fitting of Eqs. (1) and (2) to these datasets to determine the common parameter K as well as the complex-specific chemical shift $\delta^{G{\cdot}CE}_i$ (or $\delta^{G{\cdot}CE}_j$) for each nucleus involved in the calculation. The obtained binding constant was fixed and multiple linear regression was carried out with the same program to determine $\delta^{G{\cdot}CE}_i$ for the less responsive nuclei.

22-Ethoxy-7,15-dimethyl-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*)-4]: See Scheme 1. Ethyl bis(2-hydroxyphenyl)phosphinate (**20**, 7.46 g, 26.8 mmol), dimethyl-substituted tetraethylene glycol ditosylate (*S*,*S*)-**12** (14.5 g, 27.3 mmol),[30] and finely powdered anhydrous K_2CO_3 (26.0 g, 188 mmol) were mixed with vigorous stirring in dry DMF (330 mL) at room temp. under Ar. After the reaction mixture had been stirred at room temp. for 10 min, the flask was immersed in an oil bath and the temperature of the reaction mixture was raised to 50 °C and kept at this temperature with vigorous stirring until TLC analysis showed the total consumption of the starting ditosylate (*S*,*S*)-**12** (11 d). The solvent was removed at 40 °C and the residue was taken up in a mixture of ice/water (350 mL) and CH_2Cl_2 (500 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 200 mL). The combined organic phase was shaken with H_2O (300 mL), dried with $MgSO_4$, and filtered, and the solvent was removed. The crude product was purified by chromatography on silica gel with a dioxane/hexane (1:3) mixture as eluent to give (*S*,*S*)-**4** (7.22 g, 58%) as a viscous oil. R_f = 0.25 (aluminium oxide TLC, EtOH/toluene 1:40), R_f = 0.30 (silica gel TLC, dioxane/hexane 1:3). $[\alpha]^{26}_D$ = –0.95 (*c* = 2.21, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.97 (d, $J_{H,H}$ = 6 Hz, 3 H) and 0.99 (d, $J_{H,H}$ = 6 Hz, 3 H, CH_3 groups attached to the macro ring), 1.29 (t, $J_{H,H}$ = 7 Hz, 3 H, *O*-ethyl CH_3), 2.91–3.04 (m, 3 H, OCH_2), 3.04–3.12 (m, 1 H, OCH_2), 3.24–3.40 (m, 5 H, OCH_2), 3.43–3.50 (m, 1 H, OCH_2), 3.67–3.70 (m, 1 H, OCH_2), 3.75–3.77 (m, 1 H, OCH_2), 3.86–3.96 (m, 1 H, OCH), 4.04–4.10 (q, 2 H, ethyl OCH_2), 4.12–4.19 (m, 1 H, OCH), 6.94–6.98 [m, 2 H, ArC(4)H, ArC(18)H], 6.99–7.06 [m, 2 H, ArC(2)H, ArC(20)H], 7.39–7.46 [m, 2 H, ArC(3)H, ArC(19)H], 7.87–7.91 [m, 1 H, ArC(1)H, ArC(21)H], 8.02–8.06 [m, 1 H, ArC(1)H, ArC(21)H] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 16.70 (d, *J* = 6.8 Hz, O-ethyl CH_3), 17.30, 17.87 (CH_3 groups attached to the macro ring), 60.55 (d, *J* = 5.7 Hz, O-ethyl CH_2), 69.70, 70.00, 71.13, 71.37, 72.74, 72.78 (OCH_2 groups), 75.59, 75.68 (OCH groups), 112.53 (d, *J* = 7.5 Hz, ArC_4, ArC^{18}), 112.80 (d, *J* = 8.1 Hz, ArC^4, ArC^{18}), 120.28 (d, *J* = 12.2 Hz, ArC^2, ArC^{20}), 120.34 (d, *J* = 13.0 Hz, ArC^2, ArC^{20}), 120.68 (d, *J* = 136.5 Hz, ArC^{21a}, ArC^{22a}), 121.59 (d, *J* = 147.7 Hz, ArC^{21a}, ArC^{22a}), 133.17 (d, *J* = 1.4 Hz, ArC^3, ArC^{19}), 133.48 (d, *J* ≈ 5.6 Hz, ArC^1, ArC^{21}), 133.53 (d, *J* ≈ 2.0 Hz, ArC^3, ArC^{19}), 135.46 (d, *J* = 7.4 Hz, ArC^1, ArC^{21}), 160.55 (d, *J* = 3.5 Hz, ArC^{4a}, ArC^{17a}), 161.02 (d, *J* = 5.0 Hz, ArC^{4a}, ArC^{17a}) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$, 25 °C): δ = 26.72 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3440, 3093, 3062, 2977, 2931, 2872, 1591, 1576, 1474, 1444, 1375, 1281, 1232, 1222, 1210, 1164, 1142, 1133, 1102, 1089, 1021, 945, 807, 777, 758, 567 cm^{-1}. MS: *m*/*z* = 464.50 [M + 1]$^+$. $C_{24}H_{33}O_7P$ (464.49): calcd. C 62.06, H 7.16, P 6.67; found C 61.80, H 7.17, P 6.52.

25-Ethoxy-7,18-dimethyl-6,7,9,10,12,13,15,16,18,19-decahydro-25*H*-dibenzo[*q*,*t*][1,4,7,10,13,16,19]hexaoxa-λ^5-phosphacyclohenicosin-25-one [(*S*,*S*)-5]: See Scheme 1. Optically active ligand (*S*,*S*)-**5** was prepared in the same way as described above for its analogue (*S*,*S*)-**4** by starting from ethyl bis(2-hydroxyphenyl)phosphinate (**20**, 5.32 g, 19.1 mmol), dimethyl-substituted pentaethylene glycol ditosylate (*S*,*S*)-**13** (11.0 g, 19.1 mmol), finely powdered anhydrous K_2CO_3 (26.0 g, 188 mmol), and pure DMF (300 mL). White viscous oil; yield 6.14 g (63%). R_f = 0.30 (aluminium oxide TLC, EtOH/toluene 1:40), R_f = 0.18 (silica gel TLC, dioxane/hexane 1:3). $[\alpha]^{25}_D$ = –6.15 (*c* = 1.56, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.01 (d, $J_{H,H}$ = 6 Hz, 3 H, 7-Me), 1.06 (d, $J_{H,H}$ = 6 Hz, 3 H, 18-Me), 1.30 (t, $J_{H,H}$ = 7 Hz, 3 H, *O*-ethyl CH_3), 3.02–3.22 (m, 4 H, OCH_2, 2 × OCH), 3.25–3.33 (m, 3 H, OCH_2), 3.37–3.44 (m, 2 H, OCH_2), 3.46–3.51 (m, 5 H, OCH_2), 3.64–3.67 (m, 1 H, H_x-19), 3.73–3.77 (m, 1 H, H_x-6), 3.86–3.96 (m, 1 H, O-ethyl CH_2), 3.97–4.03 (m, 2 H, H_y-6, H_y-19), 4.11–4.19 (m, 1 H, O-ethyl CH_2), 6.88–6.97 [m, 2 H, ArC(4)H, ArC(21)H], 7.01–7.11 [m, 2 H, ArC(2)H, ArC(23)H], 7.39–7.50 [m, 2 H, ArC(3)H, ArC(22)H], 7.92 [dd, 1 H, ArC(1)H], 8.03 [dd, $^3J_{P,H}$ = 14.5, $J_{H\ ortho}$ = 7.6 Hz, 1 H, ArC(24)H] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 16.50 (d, *J* = 6.8 Hz, O-ethyl CH_3), 17.53 (7-Me), 17.84 (18-Me), 60.70 (d, $^2J_{P,C}$ = 5.7 Hz, O-ethyl CH_2), 69.00, 69.09, 70.71,

70.94, 71.01, 71.07 (OCH_2), 72.36 (C-19), 72.85 (C-6) 74.40 (C-18), 74.75 (C-7), 112.19 (d, $^3J_{P,C}$ = 7.5 Hz, ArC^{21}), 112.52 (d, $^3J_{P,C}$ = 8.3 Hz, ArC^4), 120.13 (d, $^1J_{P,C}$ = 137.0 Hz) and 121.02 (d, $^1J_{P,C}$ = 148.2 Hz, ArC^{24a}, ArC^{25a}), 120.51 (d, $^3J_{P,C}$ = 12.1 Hz) and 120.60 (d, $^3J_{P,C}$ = 13.1 Hz, ArC^2, ArC^{23}), 133.30 (d, $^4J_{P,C}$ = 2.0 Hz, ArC^3), 133.44 (d, $^2J_{P,C}$ = 4.9 Hz, ArC^1), 133.61 (d, $^4J_{P,C}$ = 1.8 Hz, ArC^{22}), 135.33 (d, $^2J_{P,C}$ = 7.6 Hz, ArC^{24}), 160.20 (d, $^2J_{P,C}$ = 3.5 Hz) and 160.67 (d, $^2J_{P,C}$ = 5.1 Hz, ArC^{4a}, ArC^{20a}) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$, 25 °C): δ = 27.25 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2970, 2929, 2869, 1590, 1474, 1441, 1375, 1280, 1235, 1214, 1135, 1090, 1023, 950, 817, 756 cm^{-1}. MS: *m*/*z* = 508.55 $[M + 1]^+$. $C_{26}H_{37}O_8P$ (508.55): calcd. C 61.41, H 7.33, P 6.09; found C 61.13, H 7.28, P 5.82.

22-Ethoxy-7,15-dioctyl-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*)-6]: See Scheme 1. Optically active ligand (*S*,*S*)-**6** was prepared in the same way as described above for its analogue (*S*,*S*)-**4** by starting from ethyl bis(2-hydroxyphenyl)phosphinate (**20**, 169 mg, 0.586 mmol), dioctyl-substituted tetraethylene glycol ditosylate (*S*,*S*)-**14** (426 mg, 0.586 mmol), finely powdered anhydrous K_2CO_3 (0.81 g, 5.86 mmol), and pure DMF (11 mL). The crude product was purified by chromatography first on aluminium oxide with EtOAc/hexane (1:5) as eluent followed by chromatography on silica gel with dioxane/toluene (1:6) as eluent to give (*S*,*S*)-**6** (252 mg, 65%) as a pale yellow oil. R_f = 0.48 (Al_2O_3 TLC, EtOAc/hexane 1:2 + 5% HCl). $[\alpha]_D^{25}$ = –5.6 (*c* = 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.88 (t, $J_{H,H}$ = 7 Hz, 3 H) and 0.89 (t, $J_{H,H}$ = 7 Hz, 3 H, octyl CH_3 groups), 1.11–1.42 (m, 31 H, 14 octyl CH_2, O-ethyl CH_3), 2.67–2.81 (m, 2 H, OCH_2), 2.99–3.15 (m, 2 H, OCH_2), 3.20–3.40 (m, 5 H, OCH_2), 3.45–3.54 (m, 1 H, OCH_2), 3.66–3.74 (m, 1 H, OCH_2), 3.74–3.83 (m, 1 H, OCH_2), 3.85–3.96 (m, 1 H, OCH), 4.02–4.11 (m, 2 H, O-ethyl CH_2), 4.11–4.20 (m, 1 H, OCH), 6.88–6.98 [m, 2 H, ArC(4)H, ArC(18)H], 6.98–7.09 [m, 2 H, ArC(2)H, ArC(20)H], 7.37–7.50 [m, 2 H, ArC(3)H, ArC(19)-H], 7.84–7.94 [m, 1 H, ArC(1)H, ArC(21)H], 7.99–8.11 [m, 1 H, ArC(1)H, ArC(21)H] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 14.16 (octyl CH_3 groups), 16.53 (d, *J* = 6.8 Hz, O-ethyl CH_3), 22.72, 25.30, 25.37, 29.32, 29.35, 29.59, 29.72, 29.81, 31.91, 31.94, 32.04, 32.81 (octyl CH_2 groups), 60.35 (d, *J* = 5.7 Hz, O-ethyl CH_2), 70.59, 70.89, 71.07, 71.31, 71.80, 71.90 (OCH_2 groups), 79.98, 80.11 (OCH groups), 112.35 (d, *J* = 7.4 Hz, ArC^4, ArC^{18}), 112.76 (d, *J* = 8.2 Hz, ArC^4, ArC^{18}), 120.59 (d, *J* = 146.2 Hz, ArC^{21a}, ArC^{22a}), 120.22 (d, *J* = 12.5 Hz, ArC^2, ArC^{20}), 121.55 (d, *J* = 147.9 Hz, ArC^{21a}, ArC^{22a}), 132.99 (d, *J* = 1.6 Hz, ArC^3, ArC^{19}), 133.15 (d, *J* = 4.6 Hz, ArC^1, ArC^{21}), 133.40 (d, *J* = 1.6 Hz, ArC^3, ArC^{19}), 135.26 (d, *J* = 7.5 Hz, ArC^1, ArC^{21}), 160.47 (d, *J* = 3.5 Hz, ArC^{4a}, ArC^{17a}), 160.96 (d, *J* = 5.0 Hz, ArC^{4a}, ArC^{17a}) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$, 25 °C): δ = 26.62 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3069, 2924, 2855, 1578, 1475, 1443, 1390, 1378, 1350, 1280, 1239, 1219, 1162, 1141, 1091, 1036, 948, 822, 804, 754, 711, 680, 610, 566 cm^{-1}. MS: *m*/*z* = 660.88 $[M + 1]^+$. $C_{38}H_{61}O_7P$ (660.87): calcd. C 69.06, H 9.30, P 4.69; found C 68.82, H 9.09, P 4.95.

25-Ethoxy-7,18-dioctyl-6,7,9,10,12,13,15,16,18,19-decahydro-25*H*-dibenzo[*q*,*t*][1,4,7,10,13,16,19]hexaoxa-λ^5-phosphacyclohenicosin-25-one [(*S*,*S*)-7]: See Scheme 1. Optically active ligand (*S*,*S*)-7 was prepared in the same way as described above for its analogue (*S*,*S*)-**4** by starting from ethyl bis(2-hydroxyphenyl)phosphinate (**20**, 1.8 g, 6.48 mmol), dioctyl-substituted pentaethylene glycol ditosylate (*S*,*S*)-**15** (5.0 g, 6.48 mmol), finely powdered anhydrous K_2CO_3 (25.0 g, 0.181 mol), and pure DMF (160 mL). The crude product was purified by chromatography first on aluminium oxide with EtOAc/hexane (1:2.5) as eluent followed by chromatography on silica gel with MeCN/EtOH/toluene (1:2:40) as eluent to give (*S*,*S*)-**7** (2.8 g, 62%) as a pale yellow oil. R_f = 0.52 (Al_2O_3 TLC, EtOAc/hexane 1:2 + 5% HCl). $[\alpha]_D^{25}$ = –19.54 (*c* = 1.71,CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.88 (t, $J_{H,H}$ = 7 Hz, 3 H) and 0.89 (t, $J_{H,H}$ = 7 Hz, 3 H, octyl CH_3 groups), 1.12–1.41 (m, 31 H, 14 octyl CH_2, O-ethyl CH_3), 2.92–3.05 (m, 2 H, OCH_2), 3.11–3.29 (m, 4 H, OCH_2), 3.31–3.40 (m, 2 H, OCH_2), 3.40–3.51 (m, 6 H, OCH_2), 3.66–3.73 (m, 1 H, OCH_2), 3.76–3.83 (m, 1 H, OCH_2), 3.84–3.92 (m, 1 H, OCH), 3.93–4.02 (m, 2 H, O-ethyl CH_2), 4.08–4.18 (m, 1 H, OCH), 6.85–6.96 [m, 2 H, ArC(4)H, ArC(21)H], 6.98–7.10 [m, 2 H, ArC(2)H, ArC(23)H], 7.37–7.50 [m, 2 H, ArC(3)H, ArC(22)-H], 7.86–7.96 [m, 1 H, ArC(1)H, ArC(24)H], 8.01–8.11 [m, 1 H, ArC(1)H, ArC(24)H] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 14.31 (octyl CH_3 groups), 16.64 (d, *J* = 6.9 Hz, O-ethyl CH_3), 22.87, 25.44, 25.63, 29.49, 29.52, 29.79, 29.84, 29.98, 32.07, 32.09, 32.57, 32.95 (octyl CH_2 groups), 60.48 (d, *J* = 5.6 Hz, O-ethyl CH_2), 70.40, 70.62, 70.75, 70.97, 71.22, 71.38, 71.56, 72.45 (OCH_2 groups), 78.90, 79.15 (OCH groups), 112.18 (d, *J* = 7.5 Hz, ArC^4, ArC^{21}), 112.61 (d, *J* = 8.0 Hz, ArC^4, ArC^{21}), 120.57 (d, *J* = 13.0 Hz, ArC^2, ArC^{23}),120.70 (d, *J* = 135.9 Hz, ArC^{24a}, ArC^{25a}), 121.63 (d, *J* = 150.8 Hz, ArC^{24a}, ArC^{25a}), 133.34 (d, *J* = 2.1 Hz, ArC^3, ArC^{22}), 133.51 (d, *J* = 4.6 Hz, ArC^1, ArC^{24}), 133.73 (d, *J* = 1.9 Hz, ArC^3, ArC^{22}), 135.56 (d, *J* = 7.5 Hz, ArC^1, ArC^{24}), 160.28 (d, *J* = 3.6 Hz, ArC^{4a}, ArC^{20a}), 160.79 (d, *J* = 5.0 Hz, ArC^{4a}, ArC^{20a}) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$, 25 °C): δ = 26.09 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2922, 2854, 1590, 1578, 1467, 1442, 1389, 1378, 1349, 1324, 1280, 1240, 1220, 1161, 1135, 1090, 1036, 947, 875, 825, 804, 755, 713, 609, 567 cm^{-1}. MS: *m*/*z* = 704.93 $[M + 1]^+$. $C_{40}H_{65}O_8P$ (704.92): calcd. C 68.15, H 9.29, P 4.39; found C 67.92, H 9.09, P 4.55.

22-Hydroxy-7,15-dimethyl-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*)-8]: See Scheme 2. Aqueous HCl solution (10% w/w, 214 mL) was added at room temp. to a vigorously stirred solution of optically active macrocycle (*S*,*S*)-**4** (2.6 g, 5.6 mmol), containing the ethyl diarylphosphinate moiety, in freshly distilled dioxane (214 mL). The flask was immersed in an oil bath and the temperature of the reaction mixture was raised to 80 °C and kept at this temperature with vigorous stirring until TLC analysis show the total consumption of the starting material (4 d). After the reaction was complete, the volatile components were removed by distillation at 30 °C. The residue was taken up in toluene (50 mL) and the solvent was removed. This procedure was repeated and the crude product was dried with KOH pellets under reduced pressure. The white solid material was recrystallized from dibutyl ether with addition of charcoal to give pure (*S*,*S*)-**8** (1.27 g, 52%) as white crystals; m.p. 265–269 °C (dibutyl ether). R_f = 0.48 (silica gel TLC, MeOH/$ClCH_2CH_2Cl$ 1:4). $[\alpha]_D^{25}$ = +46.45 (*c* = 0.92, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 1.10 (d, $J_{H,H}$ = 6 Hz, 6 H, CH_3 groups attached to the macro ring), 3.26–3.34 (m, 1 H, OCH_2), 3.54–3.70 (m, 5 H, OCH_2), 3.70–3.79 (m, 2 H, OCH_2), 3.79–3.88 (m, 2 H, OCH_2), 3.88–3.99 (m, 2 H, OCH_2), 4.03–4.16 (m, 2 H, OCH), 6.88–7.04 [m, 4 H, ArC(2)H, ArC(4)H, ArC(18)-H, ArC(20)H], 7.29–7.44 [m, 2 H, ArC(3)H, ArC(19)H], 7.50–7.69 [m, 2 H, ArC(1)H, ArC(21)H] ppm. ^{13}C NMR (75.5 MHz, [D$_6$]-DMSO, 25 °C): δ = 15.75 (CH_3 groups attached to the macro ring), 68.03, 70.51, 73.50 (OCH_2 groups), 75.78 (OCH groups), 114.79 (d, *J* = 8.0 Hz, ArC^4, ArC^{18}), 122.23 (d, *J* = 12.2 Hz, ArC^2, ArC^{20}), 129.91 (d, *J* = 132.2 Hz, ArC^{21a}, ArC^{22a}), 132.96 (d, *J* = 1.9 Hz, ArC^3, ArC^{19}), 134.74 (d, *J* = 8.2 Hz, ArC^1, ArC^{21}), 161.24 (d, *J* = 2.4 Hz, ArC^{4a}, ArC^{17a}) ppm. ^{31}P NMR (121.5 MHz, [D$_6$]DMSO, 25 °C): δ = 15.82 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3401, 2976, 2935, 2880, 1712, 1589, 1576, 1480, 1440, 1375, 1342, 1275, 1244, 1182, 1135, 1093, 1046, 1033, 995, 979, 940, 818, 761, 713, 649, 581 cm^{-1}. MS:

m/*z* = 436.20 [M + 1]$^+$. $C_{22}H_{29}O_7P$ (436.44): calcd. C 60.54, H 6.70, P 7.10; found C 60.35, H 6.81, P 7.02.

25-Hydroxy-7,18-dimethyl-6,7,9,10,12,13,15,16,18,19-decahydro-25*H*-dibenzo[*q*,*t*][1,4,7,10,13,16,19]hexaoxa-λ^5-phosphacyclohenicosin-25-one [(*S*,*S*)-9]: See Scheme 2. Proton-ionizable macrocycle (*S*,*S*)-**9** was obtained by starting from ethyl ester (*S*,*S*)-**5** (4.0 g, 7.86 mmol) and following the procedure described above for the acid hydrolysis of macrocycle (*S*,*S*)-**4**; yield 2.6 g (69%) white crystals; m.p. 157–158 °C (dibutyl ether). R_f = 0.41 (silica gel TLC, acetic acid/$ClCH_2CH_2Cl$ 1:2). $[\alpha]_D^{24}$ = +33.15 (*c* = 1.03, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.11 (d, $J_{H,H}$ = 6.5 Hz, 6 H, CH_3 groups attached to the macro ring), 3.52–3.66 (m, 12 H, OCH_2), 3.66–3.73 (m, 2 H, OCH), 3.94–4.00 (d_{AB}, J_{gem} = 9.6 Hz, 2× 2 H, OCH_2-6, OCH_2-19), 6.86–6.95 [dd, $^4J_{P,H}$ = 5.6, $J_{H\ ortho}$ = 8.0 Hz, 2 H, ArC(4)H, ArC(21)H], 6.95–7.04 [m, 2 H, ArC(2)H, ArC(23)H], 7.41–7.52 [m, 2 H, ArC(3)H, ArC(22)H], 7.66–7.78 [ddd, $^3J_{P,H}$ = 15.0, $J_{H\ ortho}$ = 7.4, $J_{H\ meta}$ = 1.2 Hz, 2 H, ArC(1)H, ArC(24)H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.12 (CH_3), 68.88, 70.94, 71.12 (C-9,10,12,13,15,16), 72.90 (C-6, C-19), 74.42 (C-7, C-18), 112.21 (d, $^3J_{P,C}$ = 7.2 Hz, ArC^4, ArC^{21}), 120.76 (d, $^3J_{P,C}$ = 13.3 Hz, ArC^2, ArC^{23}), 122.26 (d, $^1J_{P,C}$ = 142.9 Hz, ArC^{24a}, ArC^{25a}), 133.53 (ArC^3, ArC^{22}), 134.15 (d, $^2J_{P,C}$ = 8.4 Hz, ArC^1, ArC^{24}), 160.37 (ArC^{4a}, ArC^{20a}) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$, 25 °C): δ = 28.16 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3350, 2873, 1591, 1577, 1480, 1441, 1392, 1374, 1353, 1337, 1281, 1247, 1122, 1085, 1044, 992, 972, 950, 886, 833, 757, 737, 725, 697, 643, 576 cm^{-1}. MS: *m*/*z* = 481.20 [M + 1]$^+$. $C_{24}H_{33}O_8P$ (480.49): calcd. C 59.99, H 6.92, P 6.45; found C 59.80, H 6.81, P 6.33.

22-Hydroxy-7,15-dioctyl-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*)-10]: See Scheme 2. Proton-ionizable macrocycle (*S*,*S*)-**10** was obtained by starting from ethyl ester (*S*,*S*)-**6** (155 mg, 0.23 mmol) and following the procedure described above for the acid hydrolysis of macrocycle (*S*,*S*)-**4**. The crude product was purified by chromatography on silica gel with MeCN/EtOH/toluene (2:5:20) as eluent to give (*S*,*S*)-**10** (97 mg, 60%) as a brown oil. R_f = 0.50 [silica gel TLC, MeCN/EtOH/toluene (2:5:20)]. $[\alpha]_D^{27}$ = +27.60 (*c* = 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, $J_{H,H}$ = 6 Hz, 6 H, octyl CH_3), 1.18–1.52 (m, 28 H, 14 octyl CH_2), 3.32–3.49 (m, 2 H, OCH_2), 3.49–3.71 (m, 8 H, OCH_2), 3.88–4.11 (m, 4 H, OCH_2, OCH), 6.83–6.94 [m, 2 H, ArC(4)H, ArC(18)H], 6.94–7.07 [m, 2 H, ArC(2)H, ArC(20)H], 7.38–7.52 [m, 2 H, ArC(3)H, ArC(19)H], 7.59–7.73 [m, 2 H, ArC(1)H, ArC(21)H], 8.01 (brs, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 14.33 (octyl CH_3 groups), 22.88, 25.72, 29.48, 29.75, 29.89, 31.60, 32.08 (octyl CH_2 groups), 70.17, 71.16, 71.71 (OCH_2 groups), 78.76 (OCH groups), 111.81 (d, *J* = 8.0 Hz, ArC^4, ArC^{18}), 120.69 (d, *J* = 13.1 Hz, ArC^2, ArC^{20}), 121.50 (d, *J* = 137.9 Hz, ArC^{21a}, ArC^{22a}), 133.64 (d, *J* = 1.3 Hz, ArC^3, ArC^{19}), 134.31 (d, *J* = 8.1 Hz, ArC^1, ArC^{21}), 160.44 (ArC^{4a}, ArC^{17a}) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$, 25 °C): δ = 27.9 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3066, 2923, 2854, 1701, 1661, 1618, 1591, 1577, 1476, 1441, 1395, 1375, 1346, 1337, 1280, 1241, 1140, 1090, 1044, 1021, 942, 825, 788, 753, 702, 613, 598, 554 cm^{-1}. MS: *m*/*z* = 632.80 [M + 1]$^+$. $C_{36}H_{57}O_7P$ (632.82): calcd. C 68.33, H 9.08, P 4.89; found C 68.04, H 8.95, P 4.73.

25-Hydroxy-7,18-dioctyl-6,7,9,10,12,13,15,16,18,19-decahydro-25*H*-dibenzo[*q*,*t*][1,4,7,10,13,16,19]hexaoxa-λ^5-phosphacyclohenicosin-25-one [(*S*,*S*)-11]: See Scheme 2. Proton-ionizable macrocycle (*S*,*S*)-**11** was obtained by starting from ethyl ester (*S*,*S*)-**7** (250 mg, 0.35 mmol) and following the procedure described above for the acid hydrolysis of macrocycle (*S*,*S*)-**4**; yield 140 mg (59%) as a pale yellow oil. R_f = 0.23 [silica gel TLC, MeCN/EtOH/toluene (1:2:20)]. $[\alpha]_D^{25}$ = +10.14 (*c* = 1.04, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.82–0.97 (m, 6 H, octyl CH_3 groups), 1.15–1.51 (m, 28 H, octyl CH_2 groups), 3.06–3.23 (m, 2 H, OCH_2), 3.23–3.65 (m, 12 H, OCH_2), 3.79–3.92 (m, 2 H, OCH_2), 3.92–4.10 (m, 2 H, OCH), 6.83–7.10 [m, 4 H, ArC(2)H, ArC(4)H, ArC(21)H, ArC(23)H], 7.36–7.52 [m, 2 H, ArC(3)H, ArC(22)H], 7.72–7.91 [m, 2 H, ArC(1)H, ArC(24)H], 8.43 (brs, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 14.33 (octyl CH_3 groups), 22.89, 25.62, 29.50, 29.81, 29.89, 31.65, 32.09 (octyl CH_2 groups), 70.02, 70.85, 71.28, 72.07 (OCH_2 groups), 78.82 (OCH groups), 112.22 (d, *J* = 8.7 Hz, ArC^4, ArC^{21}), 120.68 (d, *J* = 13.6 Hz, ArC^2, ArC^{23}), 122.27 (d, *J* = 143.3 Hz, ArC^{24a}, ArC^{25a}), 133.40 (ArC^3, ArC^{22}), 134.08 (d, *J* = 7.4 Hz, ArC^1, ArC^{24}), 160.46 (d, *J* = 3.0 Hz, ArC^{4a}, ArC^{20a}) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$, 25 °C): δ = 29.09 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2922, 2853, 1591, 1577, 1477, 1466, 1442, 1378, 1349, 1280, 1241, 1137, 1089, 1044, 1021, 942, 800, 753, 713, 682, 613, 557 cm^{-1}. MS: *m*/*z* = 676.40 [M + 1]$^+$. $C_{38}H_{61}O_8P$ (676.87): calcd. C 67.43, H 9.08, P 4.58; found C 67.23, H 8.81, P 4.65.

General Procedure for the Preparation of Ditosylates (*S*,*S*)-13 and (*S*,*S*)-15: See Scheme 1. Tosyl chloride (2.0 g, 10.5 mmol) and aqueous KOH (50% w/w, 12 mL) were added successively at 0 °C to a vigorously stirred solution of diol (*S*,*S*)-**17** or (*S*,*S*)-**19** (4.8 mmol) in CH_2Cl_2 (80 mL). The reaction mixture was stirred vigorously at 0 °C for 5 min and then at room temp. for 48 h. Water (90 mL) and CH_2Cl_2 (60 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 (2× 20 mL). The combined organic phase was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed. The crude product was purified as described below for each compound to result in the ditosylates (*S*,*S*)-**13** and (*S*,*S*)-**15**.

(2*S*,13*S*)-2,13-Dimethyl-3,6,9,12-tetraoxatetradecane-1,14-diyl Bis(4-methylbenzenesulfonate) [(*S*,*S*)-13]: See Scheme 1. Ditosylate (*S*,*S*)-**13** was prepared as described above in the General Procedure by starting from diol (*S*,*S*)-**17** (9.0 g, 33.8 mmol), tosyl chloride (15.5 g, 81.8 mmol), and aqueous KOH (50% w/w, 85 mL). The crude product was purified by chromatography on silica gel with acetone/hexane (1:3) as eluent to give ditosylate (*S*,*S*)-**13** (17.6 g, 91%) as a pale yellow oil. R_f = 0.15 (silica gel TLC, acetone/hexane 1:3). $[\alpha]_D^{25}$ = –7.33 (*c* = 1.06, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.12 (d, *J* = 8 Hz, 6 H, CH_3 groups attached to the chiral centers), 2.44 (s, 6 H, $ArCH_3$), 3.53–3.74 (m, 14 H, OCH_2, OCH), 3.89–4.00 (m, 4 H, CH_2OTs), 7.34 [d, *J* = 8 Hz, 4 H, ArC(3)H, ArC(5)H], 7.78 [d, *J* = 8 Hz, 4 H, ArC(2)H, ArC(6)H] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 16.93, 21.81, 69.06, 70.77, 70.85, 72.79, 73.64, 128.12, 130.02, 133.13, 144.98 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2871, 1598, 1452, 1355, 1307, 1292, 1189, 1174, 1095, 1019, 981, 956, 813, 789, 706, 688, 665, 624, 575, 553, 450, 406 cm^{-1}. MS: *m*/*z* = 574.70, [M + 1]$^+$. $C_{26}H_{38}O_{10}S_2$ (574.70): calcd. C 54.34, H 6.66, S 11.16; found C 54.14, H 6.84, S 11.01.

(2*S*,13*S*)-2,13-Dioctyl-3,6,9,12-tetraoxatetradecane-1,14-diyl Bis(4-methylbenzenesulfonate) [(*S*,*S*)-15]: See Scheme 1. Ditosylate (*S*,*S*)-**15** was prepared as described above in the General Procedure by starting from diol (*S*,*S*)-**19** (4.0 g, 8.6 mmol), tosyl chloride (3.62 g, 19.0 mmol), and aqueous KOH (50% w/w, 24 mL). The crude product was purified by chromatography on silica gel with toluene and then EtOAc/hexane (1:3) as eluents to give ditosylate (*S*,*S*)-**15** (7.7 g, 53%) as a pale yellow oil. R_f = 0.15 (silica gel TLC, EtOAc/hexane 1:5). $[\alpha]_D^{25}$ = –4.55 (*c* = 1.01, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, $J_{H,H}$ = 7 Hz, 6 H, octyl CH_3), 1.23–1.43 (m, 28 H, 14 octyl CH_2), 2.44 (s, 6 H, $ArCH_3$), 3.45–3.68 (m,

14 H, OCH_2, OCH), 3.93–4.02 (m, 4 H, CH_2OTs), 7.34 [d, J = 8 Hz, 4 H, ArC(3)H, ArC(5)H], 7.79 [d, J = 8 Hz, 4 H, ArC(2)H, ArC(6)H] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 14.29, 21.83, 22.83, 25.25, 29.41, 29.64, 29.73, 31.55, 32.03, 69.89, 70.75, 70.89, 71.75, 76.81, 128.14, 130.03, 133.12, 144.98 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2928, 2880, 2856, 1960, 1920, 1696, 1600, 1544, 1496, 1484, 1460, 1424, 1364, 1320, 1296, 1224, 1176, 1160, 1096, 1052, 976, 880, 816, 792, 740, 668, 652, 552, 540 cm^{-1}. MS: m/z = 771.10 [M + 1]$^+$. $C_{40}H_{66}O_{10}S_2$ (771.08): calcd. C 62.31, H 8.63, S 8.32; found C 62.12, H 8.88, S 8.14.

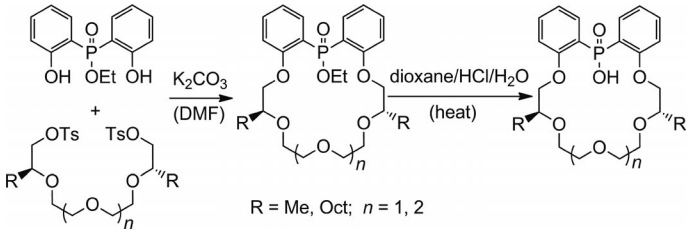
Acknowledgments

Financial support by the Hungarian Scientific Research Fund (OTKA K81127, to P. H.; PD71910, to T. T.; PD71817, to V. F.) and a Szabó Zsuzsa Doctoral Scholarship (to J. K.) is gratefully acknowledged. This work is assocaited with the scientific program of the "Development of quality-oriented and harmonized R+D+I strategy and functional model at BME" project, supported by the New Hungary Development Plan (project ID: TÁMOP-4.2.1/B-09/1/KMR-2010-0002). We wish to express our sincere thanks to Professor Csaba Szántay Jr. for his kind help in the discussion of NMR titrations.

[1] J. F. Stoddart, Chiral Crown Ethers, in: *Topics in Stereochemistry* (Eds.: E. L. Eliel, S. H. Wilen), Wiley-Interscience, New York, **1988**, vol. 17, pp. 207–288.
[2] A. P. Davis, *Chiral Guest Recognition*, in: *Encyclopedia of Supramolecular Chemistry* (Eds.: J. L. Atwood, J. W. Steed), Marcel Dekker, New York, **2004**, pp. 236–244.
[3] J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, 2nd edition, Wiley-Interscience, New York, **2009**, pp. 185–193.
[4] X. X. Zhang, J. S. Bradshaw, R. M. Izatt, *Chem. Rev.* **1997**, *97*, 3313–3361.
[5] A. Späth, B. König, *Beilstein J. Org. Chem.* **2010**, *6*, No. 32.
[6] A. Berthod, *Chiral Recognition in Separation Methods: Mechanism and Applications*, Springer, New York, **2010**.
[7] E. B. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, D. J. Cram, *J. Am. Chem. Soc.* **1973**, *95*, 2692–2693.
[8] E. B. Kyba, J. M. Timko, L. J. Kaplan, F. de Jong, G. W. Gokel, D. J. Cram, *J. Am. Chem. Soc.* **1978**, *100*, 4555–4568.
[9] L. R. Sousa, G. D. Y. Sogah, D. H. Hoffman, D. J. Cram, *J. Am. Chem. Soc.* **1978**, *100*, 4569–4576.
[10] G. D. Y. Sogah, D. J. Cram, *J. Am. Chem. Soc.* **1979**, *101*, 3035–3042.
[11] M. Necomb, J. L. Toner, R. C. Helgeson, D. J. Cram, *J. Am. Chem. Soc.* **1979**, *101*, 4941–4947.
[12] D. J. Cram, *Angew. Chem.* **1988**, *100*, 1041; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009–1020.
[13] R. M. Izatt, C. Y. Zhu, P. Huszthy, J. S. Bradshaw, *Enantiomeric Recognition in Macrocycle–Primary Ammonium Cation Systems*, in: *Crown Compounds: Toward Future Applications* (Ed.: S. R. Cooper), VCH Publishers, New York, **1992**, pp. 207–233.
[14] R. M. Izatt, T. M. Wang, J. K. Hathaway, X. X. Zhang, J. C. Curtis, J. S. Bradshaw, C. Y. Zhu, P. Huszthy, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *17*, 157–175.
[15] P. Huszthy, V. Farkas, T. Tóth, G. Székely, M. Hollósi, *Tetrahedron* **2008**, *64*, 10107–10115.
[16] G. Székely, V. Farkas, L. Párkányi, T. Tóth, M. Hollósi, P. Huszthy, *Struct. Chem.* **2010**, *21*, 277–282.
[17] I. Kovács, P. Huszthy, F. Bertha, D. Sziebert, *Tetrahedron: Asymmetry* **2006**, *17*, 2538–2547.
[18] K. Tsubaki, D. Tanima, M. Nuruzzaman, T. Kusumoto, K. Fuji, T. Kawabata, *J. Org. Chem.* **2005**, *70*, 4609–4616.
[19] J. Kertész, P. Huszthy, A. Kormos, F. Bertha, V. Horváth, G. Horvai, *Tetrahedron: Asymmetry* **2009**, *20*, 2795–2801.
[20] B. Dhawan, D. Redmore, *J. Org. Chem.* **1986**, *51*, 179–183.
[21] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
[22] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
[23] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Gaussian, Inc., Wallingford CT, **2004**.
[24] C. Y. Zhu, J. S. Bradshaw, J. L. Oscarson, R. M. Izatt, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *12*, 275–289.
[25] L. Fielding, *Tetrahedron* **2000**, *56*, 6151–6170.
[26] V. Farkas, L. Szalay, E. Vass, M. Hollósi, G. Horváth, P. Huszthy, *Chirality* **2003**, *15*, S65–S73.
[27] J. A. Riddick, W. B. Bunger, T. K. Sakano, in: *Techniques of Chemistry*, 4th edition (Ed.: A. Weissberger), Wiley-Interscience, New York, **1986**, vol. 2.
[28] G. Tárkányi, *J. Chromatogr. A* **2002**, *961*, 257–276.
[29] M. Kyvala, I. Lukes, OPIUM computer program, **1995**; see: http://web.natur.cuni.cz/~kyvala/opium.html.
[30] J. Kertész, I. Móczár, A. Kormos, P. Baranyai, M. Kubinyi, K. Tóth, P. Huszthy, *Tetrahedron: Asymmetry* **2011**, *22*, 684–689.

Received: December 8, 2011
Published Online: ■

EurJOC European Journal of Organic Chemistry



Enantiopure crown ethers containing either an ethyl phosphinate [(*S*,*S*)-**4** to (*S*,*S*)-**7**] or a phosphinic acid moiety [(*S*,*S*)-**8** to (*S*,*S*)-**11**] were synthesized and complexation with the enantiomers of 1- and 2-NEA was studied. Calculations showed three important hydrogen bonds between (*S*,*S*)-**9** and each enantiomer of 1-NEA and 2-NEA. Appreciable enantiomeric recognition and heterochiral preference were found.

G. Székely, B. Csordás, V. Farkas, J. Kupai, P. Pogány, Z. Sánta, Z. Szakács,, T. Tóth, M. Hollósi, J. Nyitrai, P. Huszthy* 1–13

Synthesis and Preliminary Structural and Binding Characterization of New Enantiopure Crown Ethers Containing an Alkyl Diarylphosphinate or a Proton-Ionizable Diarylphosphinic Acid Unit

Keywords: Molecular recognition / Host–guest systems / Crown compounds / Phosphorus / Circular dichroism / NMR titration / DFT calculations

