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Preparation of a new chiral acridino-18-crown-6 ether-based stationary phase for enantioseparation of racemic protonated primary aralkyl amines

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Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract—Starting from commercially available and relatively cheap chemicals first enantiopure dimethyl-substituted monoaza-18-crown-6 ether (*R*,*R*)-**21** containing a diphenylamine unit was prepared, which was then transformed to dimethyl-substituted acridino-18-crown-6 ligand (*R*,*R*)-**19** having an *N*-allyl-carbamoyl linker by several steps. The terminal double bond of the latter made possible to attach (*R*,*R*)-**19** to γ-mercaptopropyl-functionalized spherical HPLC quality silica gel obtaining a new chiral stationary phase (*R*,*R*)-CSP-**37**. Based on electronic circular dichroism (ECD) studies the *N*-allyl-carbamoyl group attached to the acridine ring of the chiral host (*R*,*R*)-**19** does weaken exciton interaction between the host and guest molecules, but does not destroy the discriminating power of the chiral host. An HPLC column filled with (*R*,*R*)-CSP-**37** was tested for the enantioseparation of racemic 1-(1-naphthyl)- and 1-(2-naphthyl)ethylamine hydrogenperchlorates using isocratic conditions.

1. Introduction

It is well known that the enantiomers of chiral biogen amines, amino acids and their derivatives have different biological and physiological properties. Therefore, efficient methods for their enantiomeric separation and determination of their enantiomeric compositions are essential.

Among the various methods available, liquid chromatography (LC) on chiral stationary phases (CSPs) has been proved to be the most precise and efficient means of separating the two enantiomers and of determining the enantiomeric compositions.[1] CSPs having crown ether selectors have been most successfully utilized in enantiomeric separation of primary amines, amino acids and their derivatives for both analytical and preparative purposes.[2,3]

Cram and co-workers were the first who prepared and utilized CSPs containing chiral crown ethers for the resolution of primary amines, amino acids and amino acid esters. They immobilized optically active bis(1,1′-binaphthyl)-22-crown-6 ethers on silica gel[4] and polystyrene resin.[5]

In 1987 Shinbo and co-workers were dynamically coating (3,3′-diphenyl-1,1′-binaphthyl)-20-crown-6 ether[6] and 5 years later (6,6′-dioctyl-3,3′-diphenyl-1,1′-binaphthyl)-20-crown-6 ether[7] on octadecylsilica gel. The latter CSPs were successfully applied for the resolution of various racemic compounds containing a primary amino group.

In 2001 Hyun and co-workers using suitable side chains attached a (3,3′-diphenyl-1,1′-binaphthyl)-20-crown-6 derivative covalently to silica gel, and this CSP proved to be very useful in the resolution of various racemic α-amino acids,[8] non-cyclic and cyclic amines, amino alcohols[9] and aryl α-amino ketones.[10]

Application of (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid as a chiral selector for liquid chromatographic CSPs

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was first reported by Machida[11] and Hyun[12] in 1998. The latter two research groups used the same chiral crown ether as a selector, but with different modes of attachments to obtain the CSPs.

Especially Hyun and co-workers have been very successful in developing new CSPs containing (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid for the resolution of a great variety of racemic amino compounds and their derivatives.[13–18]

Recently Hirose and co-workers reported the preparation and the successful application of several CSPs where the optically active pseudo-18-crown-6 ethers as selectors were covalently bound to silica gel.[19–22] These CSPs separated the enantiomers of racemic amines, amino alcohols, amino acids and amino acid esters with great efficiency.

In 1993 Bradshaw and co-workers reported the preparation of the first CSP [(*S*,*S*)-CSP-**1**, see Fig. 1] containing an optically active pyridino-18-crown-6 ether as a chiral selector. They attached an enantiopure dimethylpyridino-18-crown-6 ether derivative to ordinary silica gel by covalent bonds, and using first an acetone–methanol mixture as an eluent they could not get a good enantiomeric separation of racemic 1-(1-naphthyl)ethylamine hydrogenperchlorate (1-NEA) at atmospheric pressure.[23] However, using the same CSP [(*S*,*S*)-CSP-**1**], but applying pure methanol as an eluent they obtained an almost baseline separation of 1-NEA at atmospheric pressure.[24]

The latter research group also attached a diphenylpyridino-18-crown-6 ether to ordinary silica gel by covalent bonds, but this CSP [(*R*,*R*)-CSP-**2**, see Fig. 1] was less efficient in the enantioseparation of 1-NEA than (*S*,*S*)-CSP-**1**.[24]

An enantiopure di-*tert*-butylpyridino-18-crown-6 ether derivative was first attached to ordinary silica gel, and the CSP so obtained [(*R*,*R*)-CSP-**3**, see Fig. 1] separated well the enantiomers of racemic 1-NEA, 1-phenylethylamine hydrogenperchlorate (PEA), phenylalanine methyl ester hydrogenperchlorate (PAME) and phenylglycine methyl ester hydrogenperchlorate (PGME) at atmospheric pressure.[25,26] For the purpose of improving enantiomeric separation, another optically active di-*tert*-butylpyridino-18-crown-6 ether derivative was attached to HPLC quality silica gel by covalent bonds and this CSP [(*R*,*R*)-CSP-**4**, see Fig. 1] separated the enantiomers of racemic 1-NEA and PEA under high pressure with great efficiency.[27]

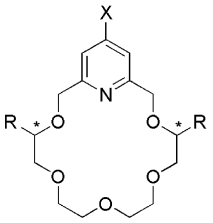
Very recently an optically active dimethylpyridino-18-crown-6 ether derivative was immobilized on spherical HPLC quality silica gel and the CSP so obtained [(*S*,*S*)-CSP-**5**, see Fig. 1] separated very well the enantiomers of racemic 1-NEA, 1-(2-naphthyl)ethylamine hydrogenperchlorate (2-NEA), aromatic α-amino acids and aliphatic α-amino acids containing different aromatic side-chain protecting groups applying high pressure.[28]

It was reported a few years ago that optically active dimethylacridino-18-crown-6 ether (*R*,*R*)-**6** (see Fig. 2) showed higher enantioselectivity towards 1-NEA and PEA than its pyridino analogue (*S*,*S*)-**7** (see Fig. 2).[29]

The higher enantioselectivity was rationalized by the stronger π–π interaction of the extended π system of the acridine unit and the more rigid conformation of host molecule (*R*,*R*)-**6**.[29]

This observation initiated and motivated us to prepare a CSP based on an optically active dimethylacridino-18-crown-6 ether derivative as a chiral selector.

Studying the reports connected with our plan in the literature we found that Charbonniere and Ziessel described the preparation of the monoaza-18-crown-6 ligand **8** (see Fig. 3)



(*S*,*S*)-CSP-**1**: R=Me, X=O(CH$_2$)$_3$Si– ordinary silica gel

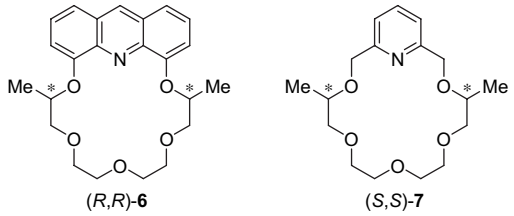
(*R*,*R*)-CSP-**2**: R=Ph, X=O(CH$_2$)$_{11}$Si– ordinary silica gel

(*R*,*R*)-CSP-**3**: R=^{t}Bu, X=O(CH$_2$)$_3$Si– ordinary silica gel

(*R*,*R*)-CSP-**4**: R=^{t}Bu, X=OCH$_2$CONH(CH$_2$)$_3$Si– HPLC quality silica gel

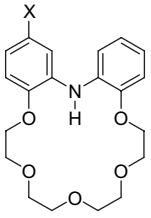
(*S*,*S*)-CSP-**5**: R=Me, X=OCH$_2$CONH(CH$_2$)$_3$Si– spherical HPLC silica gel

Figure 1. Schematics of reported CSPs based on enantiopure pyridino-18-crown-6 ethers as selectors.



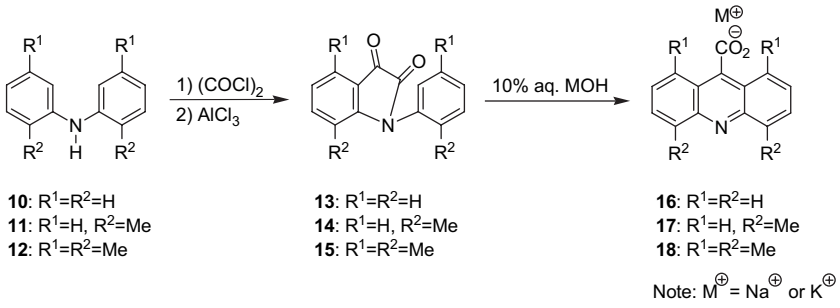
(*R*,*R*)-**6** (*S*,*S*)-**7**

Figure 2. Structures of enantiopure dimethyl-substituted acridino- and pyridino-18-crown-6 ligands.



8: X=H
9: X=Cl

Figure 3. Reported monoaza-18-crown-6 ether type ligands containing a diphenylamine unit.



Scheme 1. Reported preparation of acridine-9-carboxylic acid alkali metal salts from diphenylamines.[32–34]

containing a diphenylamine unit.[30] It should be noted here that Ágai and co-workers earlier reported the synthesis of the chloro-substituted derivative of the latter macrocycle, i.e., **9** (see Fig. 3).[31]

It was also reported that some diphenylamines (**10**–**12** for example, see Scheme 1) had been transformed to *N*-arylisatins (**13**–**15**) then to acridine-9-carboxylic acid alkali metal salts (**16**–**18**) as outlined in Scheme 1.[32–34]

Based on these observations we prepared the enantiopure dimethylacridino-18-crown-6 ether with a potassium carboxylate unit at position 9 of the acridine moiety, transformed it to an *N*-allyl-carbamoyl derivative, immobilized the latter on spherical HPLC quality silica gel and tested the new CSP so obtained for enantiomeric separation of racemic protonated primary amines containing an aromatic moiety. The synthesis of *N*-allyl-carbamoyl derivative of the parent achiral acridino-18-crown-6 ether, the complexation of the latter and its enantiopure dimethyl-substituted analogue with the enantiomers of protonated primary amines using CD spectroscopy are also reported here.

2. Results and discussion

2.1. Synthesis

The synthesis of enantiopure dimethylacridino-18-crown-6 ether derivative (*R*,*R*)-**19** (see Scheme 2) containing an *N*-allyl-carbamoyl side chain, which makes possible the covalent attachment of the chiral selector to silica gel, and the preparation of its achiral analogue **20** are shown in Scheme 2.

As for a model reaction, presumably useful in the case of the preparation of its enantiopure dimethyl-substituted analogue (*R*,*R*)-**21** (see Scheme 2), first we studied the reaction leading to the reported[30] macrocycle **8**. Charbonniere and Ziessel reported a 55% yield for ligand **8** obtained by macrocyclization of diol **22** and ditosylate **23** in the presence of Cs_2CO_3 in acetonitrile at 80 °C. Unfortunately no other reaction conditions were given.[30] We changed the other reaction parameters in wide ranges, but could not reach better yields at 80 °C than 44%. We observed, however, that substitution of Cs_2CO_3 with the much cheaper K_2CO_3 did not affect the yield of macrocycle **8**.

Our research group reported that the reactions of different phenols with enantiopure secondary tosylates in the presence of K_2CO_3 using different dipolar solvents can lead to some extent of racemization when carried out at higher temperatures than 50 °C, thus to secure total inversion of configuration the reaction temperature was always kept at 50 °C.[35–37]

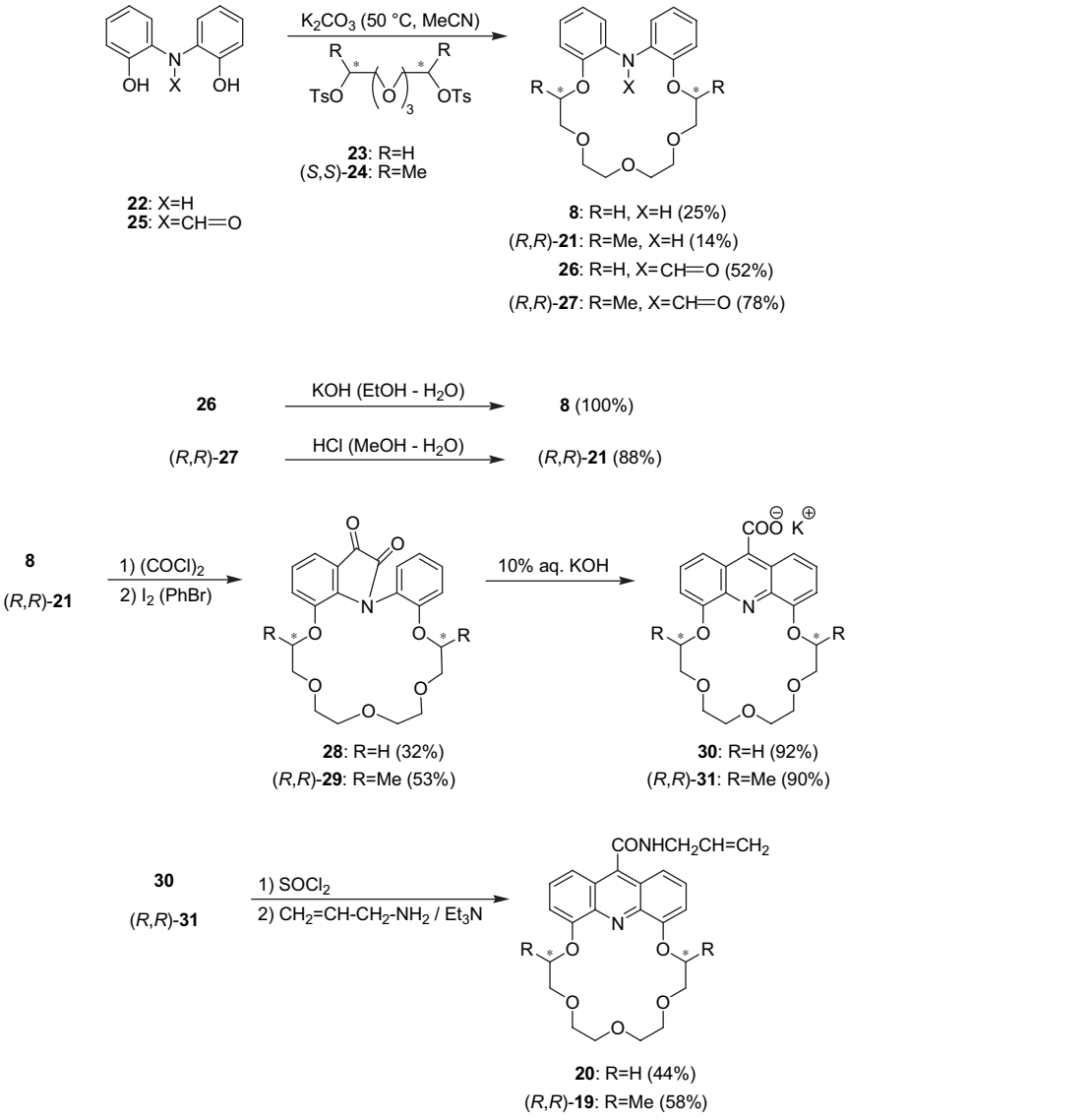
As we should carry out the reaction at 50 °C for obtaining its enantiopure analogue (*R*,*R*)-**21** from diol **22** and ditosylate (*S*,*S*)-**24**, the preparation of achiral ligand **8** was also performed at this temperature in otherwise the same conditions than getting the highest yield at 80 °C. When we carried out the reaction of diol **22** and ditosylate **23** at 50 °C we obtained achiral ligand **8** unfortunately only in 25% yield.

Macrocyclization of diol **22** and ditosylate (*S*,*S*)-**24** in the presence of K_2CO_3 rendered the very stable potassium tosylate complex of (*R*,*R*)-**21**, which could not be decomplexed by chromatography on silica gel. Decomplexation was performed by chromatography on neutral alumina obtaining the free ligand (*R*,*R*)-**21** in 14% yield calculated for the precursors **22** and (*S*,*S*)-**24**.

We note here that the very stable potassium tosylate complex of dimethylacridino-18-crown-6 ligand (*R*,*R*)-**6** (see Fig. 2) was reported and chromatography on neutral alumina was also used to obtain the free macrocycle.[35]

Ágai and co-workers reported that for the preparation of ligand **9** (see Fig. 3) they treated *N*-(5-chloro-2-hydroxyphenyl)-*N*-(2-hydroxyphenyl)formamide with 1,11-dichloro-3,6,9-trioxaundecane using K_2CO_3 as a base in cyclohexanone followed by removal of the formyl group from the nitrogen. In these conditions Ágai and co-workers reached a 51% yield for ligand **9**.[31]

Although starting from diol **25** and carrying out the macrocyclization in the latter conditions we hardly reached 15% yield for ligand **26**, but by using ditosylate **23** instead of the dichloro-oligoether and substituting cyclohexanone with acetonitrile, we obtained 52% yield for macrocycle **26** (see Scheme 2). We obtained higher (78%) yield for enantiopure ligand (*R*,*R*)-**27** with total inversion of configuration of ditosylate (*S*,*S*)-**24** applying the latter reaction conditions. Removal of the formyl group from the nitrogen of macrocycle **26** went excellently (100% yield) using potassium hydroxide in aqueous ethanol. In the case of macrocycle (*R*,*R*)-**27**, because of the very strong potassium cation complexation tendency of ligand (*R*,*R*)-**21** (see above), we did not want to use any alkali metal hydroxide, so we removed the formyl group from the nitrogen with hydrochloric acid in aqueous methanol obtaining a good yield (88%). In the



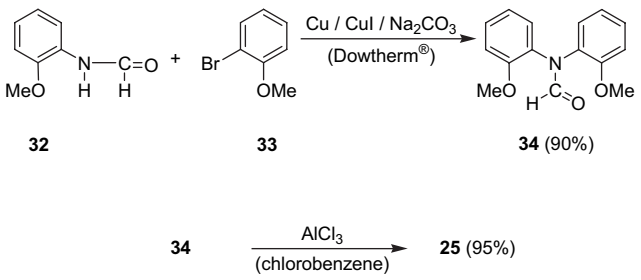
Scheme 2. Preparation of enantiopure dimethylacridino-18-crown-6 ether derivative (*R*,*R*)-**19** and its achiral analogue **20** containing an *N*-allyl-carbamoyl side chain.

latter case we used aqueous tetramethylammonium hydroxide solution for neutralization to obtain the free ligand (*R*,*R*)-**21**.

Achiral macrocycle **8** was first treated with oxalyl chloride to obtain the monoamide monoacid chloride intermediate {6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo-[*n*,*q*][1,4,7,10,13,16]pentaoxazacyclooctadecine-22-yl]-(oxo)acetyl chloride}, which was transformed to isatin derivative **28** without isolation and purification. Using aluminium chloride as a catalyst for this Friedel–Crafts type acylation we obtained only a 7% yield of isatin derivative **28**, but applying iodine instead of aluminium chloride we reached a 32% yield of it. Isatin derivative **28** was heated with diluted aqueous potassium hydroxide to render the achiral ligand **30** containing a potassium carboxylate unit in a very good yield (92%, see Scheme 2). Starting from chiral ligand (*R*,*R*)-**21** and following the procedure applied for its achiral analogue **8**, we obtained enantiopure isatin derivative (*R*,*R*)-**29** in a 53% yield and ligand (*R*,*R*)-**31** containing the potassium carboxylate unit in a 90% yield. Potassium salts **30** and (*R*,*R*)-**31** were first treated with thionyl chloride to obtain the relevant acid chlorides, then the latters were reacted without isolation and purification with allylamine using triethylamine as a base to gain ligands **20** and (*R*,*R*)-**19** containing an *N*-allyl-carbamoyl side chain in acceptable yields (44% and 58%, respectively).

The preparation of *N*,*N*-bis(2-hydroxyphenyl)formamide (**25**) needed for the synthesis of macrocycles **20** and (*R*,*R*)-**19** is shown in Scheme 3. Formamide derivative **25** was obtained by a modification of the procedure reported for the preparation of *N*-(5-chloro-2-hydroxyphenyl)-*N*-(2-hydroxyphenyl)formamide.[38] First *N*-(2-methoxyphenyl)formamide (**32**)[39] was treated with 2-bromoanisole (**33**) in Dowtherm® A using copper powder and cuprous iodide as catalysts in the presence of sodium carbonate then the unreported formamide derivative **34** was demethylated with anhydrous aluminium chloride in chlorobenzene to obtain *N*,*N*-bis(2-hydroxyphenyl)formamide (**25**). It should be mentioned

here that the melting point of diol **25** is reported in a patent,[40] but no more information of it is given.



Scheme 3. Preparation of *N*,*N*-bis(2-hydroxyphenyl)formamide (**25**).

The new CSP [(*R*,*R*)-CSP-**37**] was prepared by a modification of the reported procedure described by Gasparrini and co-workers for another compound containing a terminal double bond,[41] and is outlined in Scheme 4. First spherical HPLC quality silica gel was heated with γ-mercaptopropyl-trimethoxysilane (**35**) then this γ-mercaptopropyl-functionalized silica gel (**36**) was reacted with chiral ligand (*R*,*R*)-**19** containing the terminal double bond in the presence of free radical initiator azoisobutyronitrile (AIBN) to form (*R*,*R*)-CSP-**37**.

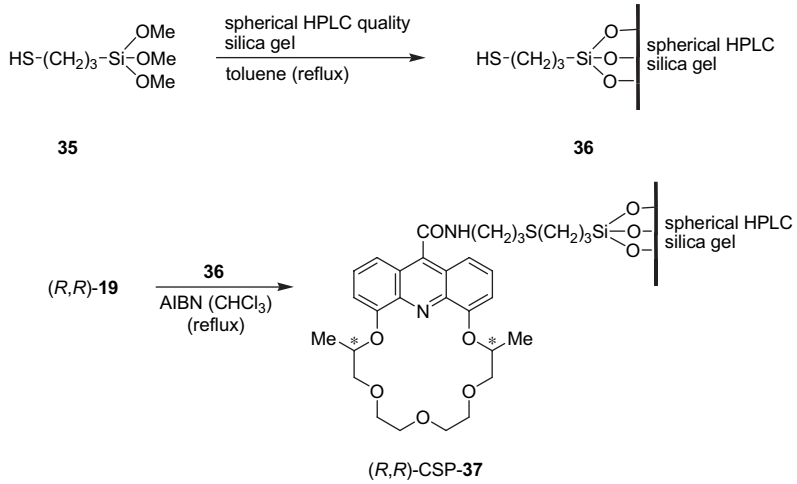
2.2. Electronic circular dichroism (ECD) spectroscopy

In an attempt to probe the effect of a linker group on the enantiomer discriminating potential of acridino-18-crown-6 ligands, ECD spectra of the complexes with (*R*)- and (*S*)-NEA of chiral (*R*,*R*)-**6** and its achiral parent crown ether {2,5,8,11,14-pentaoxa-26-azatetracyclo[13.9.3.0.^{19,27}0^{21,25}]-heptacosa-15,17,19,21,22,24(1),26-heptaene} as well as their *N*-allyl-carbamoyl derivatives [(*R*,*R*)-**19** and **20**, respectively] were measured in acetonitrile. The chiroptical properties of acridino-18-crown-6 ligands and their (*R*)- and (*S*)-NEA complexes were reported earlier.[42] The ECD spectra of the complexes reflected exciton interaction.[42] The ECD spectra of the (*S*)-NEA complexes of the *N*-allyl-carbamoyl derivatives of both the chiral and achiral hosts [(*R*,*R*)-**19** and **20**, respectively] also showed an exciton couplet in the $^{1}B_{b}$ region of the spectra (Fig. 4). The (*R*)-NEA complex of the achiral host **20** showed a mirror image exciton spectrum with oppositely signed bands, while the band intensities and the amplitude of the couplet in the spectrum of the homochiral (*R*)-NEA complex of the chiral host (*R*,*R*)-**19** were much smaller than those of the (*S*)-NEA complex. As shown in Figure 4, the homochiral complex (*R*,*R*)-**19**/(*R*)-NEA showed practically no exciton splitting.

The following consequences can be drawn from the results of the ECD experiments:

(i) As reported earlier,[42] the (*R*,*R*)-dimethylacridino-18-crown-6 ether host (*R*,*R*)-**6** has a significant enantiomer discriminating potential on the basis of the amplitudes of the exciton couplet in the spectra of heterochiral and homochiral complexes.

(ii) The presence of the *N*-allyl-carbamoyl linker group decreases the amplitude of the exciton couplet in the spectrum of the heterochiral complex [(*R*,*R*)-**19**/(*S*)-NEA]. In the spectrum of the homochiral complex [(*R*,*R*)-**19**/(*R*)-NEA] the intensity of the oppositely signed bands is much lower but the significant difference between the measured spectrum of the homochiral complex and the sum spectrum [(*R*,*R*)-**19**+(*R*)-NEA at 1:1 M ratio] still reflects significant interaction. It should be emphasized here that there is no direct correlation between the stability of the heterochiral and homochiral complexes and the amplitude of the exciton couplet in their ECD spectra. A complex with a large log *K* (*K* is the stability constant) value may give rise to an exciton couplet with small amplitude (and vice versa) if the geometric factors (distance and relative orientation) of the interacting chromophore systems are not favourable. The long wavelength shoulder at ~280 nm in the UV spectra of the heterochiral and homochiral complexes of (*R*,*R*)-**19** may be a sign of π–π interaction between the aromatic chromophores of the complex and the double bond of the allyl group. (A definite shoulder is not seen in the spectra of the complexes of the linker-containing achiral host **20**.)



Scheme 4. Preparation of γ-mercaptopropyl-functionalized spherical HPLC quality silica gel **36** and immobilization of chiral selector (*R*,*R*)-**19** on it to form the new CSP [(*R*,*R*)-CSP-**37**].

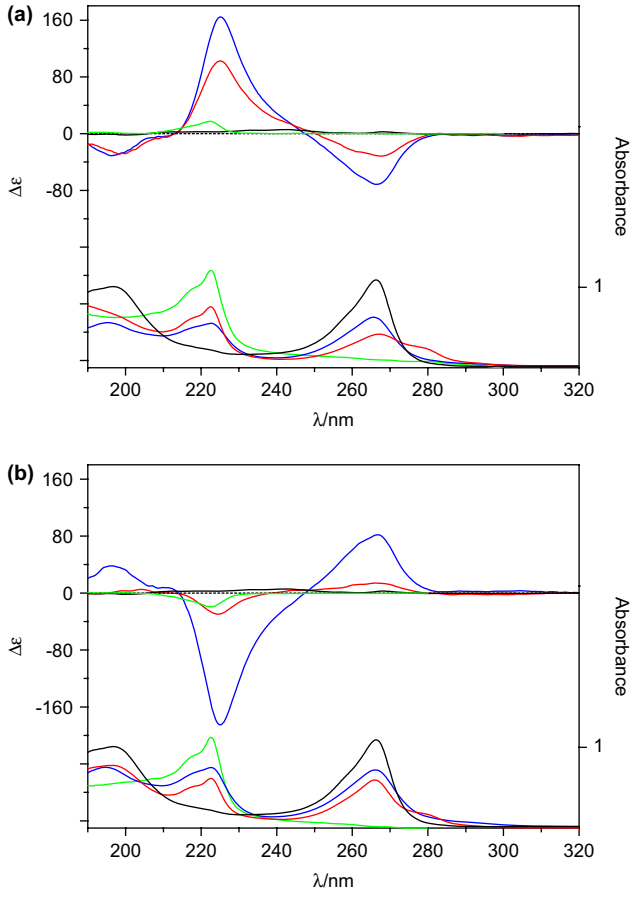


Figure 4. ECD spectra (top) and UV spectra (bottom) of (a) heterochiral complex of (*R*,*R*)-**19** (—) with (*S*)-1-NEA (—) and **20** with (*S*)-1-NEA (—) compared to (*S*)-1-NEA (—); (b) homochiral complex of (*R*,*R*)-**19** (—) with (*R*)-1-NEA (—) and **20** with (*R*)-1-NEA (—) compared to (*R*)-1-NEA (—).

(iii) The achiral acridino-18-crown-6 host not having a linker group forms complexes with the (*S*)- and (*R*)-NEA showing mirror image spectra.[42] The amplitude of the couplet of the (*S*)-NEA or (*R*)-NEA complex is identical and comparable to that in the spectrum of the (*R*,*R*)-**19**/(*S*)-NEA heterochiral complex, but it is much larger than the amplitude of the couplet of the homochiral (*R*,*R*)-**19**/(*R*)-NEA complex.

Based on the ECD studies discussed above the *N*-allylcarbamoyl group attached to the acridine ring of the chiral host [(*R*,*R*)-**19**] does weaken exciton interaction between the host and guest molecules but does not destroy the discriminating power of the chiral host.

2.3. High performance liquid chromatography

After successful filling with (*R*,*R*)-CSP-**37**, the HPLC column was tested for the enantioseparation of racemic 1-NEA and 2-NEA using isocratic conditions. In our previous studies in the case of pyridino-18-crown-6 ether selector the chromatographic enantioseparations were performed by using acetic acid as an acidic modifier.[28] Because of the relatively low basicity and the stronger complex formation tendency[29] of the acridino ligand, acceptable analysis times and effective resolutions were achieved only by using 100 mM

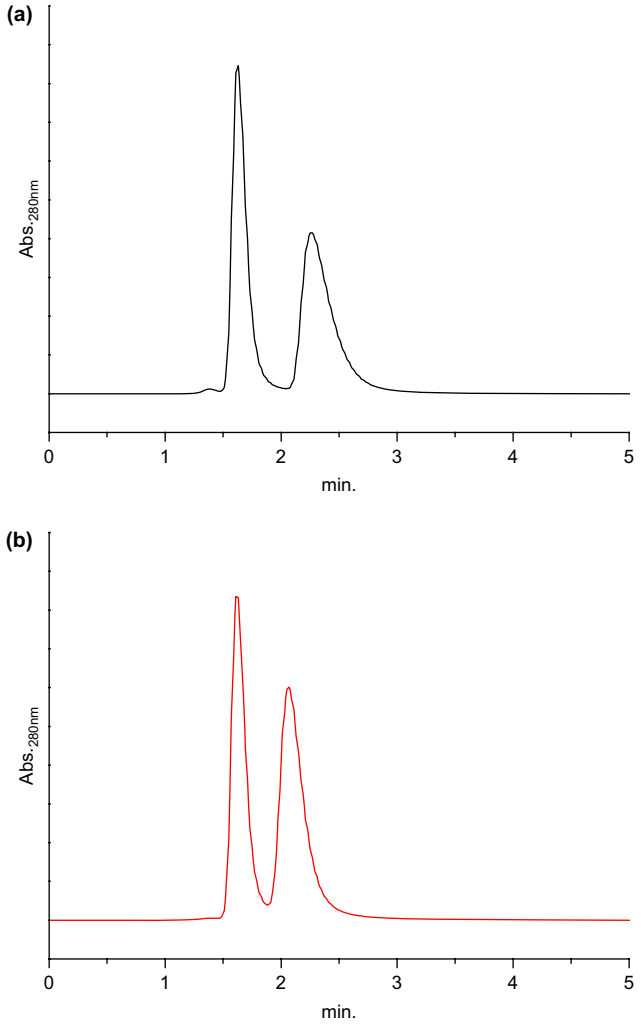


Figure 5. Chromatograms of enantioseparations of racemic (a) 1-NEA and (b) 2-NEA using (*R*,*R*)-CSP-**37**. Isocratic condition: 20% 100 mM aqueous $HClO_4$ solution in methanol (flow rate: 1.2 mL/min).

aqueous $HClO_4$ solution as an acidic modifier (see Fig. 5). The shorter retention time of 2-NEA is due to the unfavourable position of the naphthalene ring therefore smaller the stability constant of the complex. The elution order of the enantiomers was determined by injection of standard authentic (*R*)-enantiomers. It was shown in both cases that the (*R*)-enantiomer eluted with a shorter retention time than that of its antipode. This demonstrates the generally observed higher stability of heterochiral complexes [(*R*,*R*)-crown ether-(*S*)-ammonium salt] compared to that of homochiral complexes [(*R*,*R*)-crown ether-(*R*)-ammonium salt]. This behaviour is in full agreement with our observation using the (*S*,*S*)-CSP-**5** containing a dimethyl-substituted pyridino crown ether derivative as a chiral selector attached to spherical HPLC quality silica gel.[28]

3. Conclusion

We have shown that using bis(2-hydroxyphenyl)formamide (**25**) instead of bis(2-hydroxyphenyl)amine (**22**) for the macrocyclization with tetraethylene glycols **23** and (*S*,*S*)-**24** raises the yields appreciably. We found that crown ethers **8** and

(*R*,*R*)-**21** containing a diphenylamine unit could be transformed to isatin derivatives **28** and (*R*,*R*)-**26** in significantly better yields if we used iodine instead of aluminium chloride as a catalyst, although the latter has been reported to be applied widely in similar reactions. We have demonstrated that the terminal double bond of the *N*-allyl-carbamoyl linker is a very useful unit for attaching a selector covalently to γ-mercaptopropyl-functionalized spherical HPLC quality silica gel. The ECD studies have shown that the *N*-allyl-carbamoyl group attached to the acridine ring of the chiral host (*R*,*R*)-**19** weakens exciton interaction between the host and guest molecules, but it does not destroy enantioselectivity. We demonstrated that the new chiral stationary phase (*R*,*R*)-CSP-**37** separated the enantiomers of racemic 1- and 2-NEA efficiently. Experiments are in progress to apply this new CSP for the enantioseparation of selected racemic protonated primary amines, amino acids and their derivatives.

4. Experimental

4.1. General

Infrared spectra were recorded on a Zeiss Specord IR 75 spectrometer. Optical rotations were taken on a Perkin–Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer. Mass spectra were recorded on a Finningan-MAT 95 XP MS instrument (reference compound: heptacosafluorotributylamine) using EI (70 eV) method. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro-melting point apparatus and were uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminium oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminium oxide (neutral, activated, Brockman I) and silica gel 60 (70–230 mesh, Merck) were used for column chromatography. Ratios of solvents for the eluents are given in volumes (mL/mL). Solvents were dried and purified according to well-established[43] methods. Evaporations were carried out under reduced pressure unless otherwise stated.

Electronic circular dichroism measurements were performed on a Jasco Dichrograph J-810 at room temperature in quartz cell with 0.02 cm path length. The spectra were averaged of five scans in the region between 190 and 320 nm in acetonitrile. The concentration of crown ethers was 0.5 mM.

4.2. Synthesis

4.2.1. 6,7,9,10,12,13,15,16-Octahydro-22*H*-dibenzo[*n*,*q*]-[1,4,7,10,16]pentaoxazacyclooctadecine (8) from 22 and 23. Diol **22** (2.1 g, 10.4 mmol), ditosylate **23** (6.1 g, 12.1 mmol) and finely powdered anhydrous K_2CO_3 (13.1 g, 95 mmol) were mixed with vigorous stirring in anhydrous acetonitrile (200 mL) at room temperature (rt) under Ar. 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 materials (2 days). The solvent was removed and the residue was taken up in a mixture of water (80 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was shaken with water (30 mL), dried over $MgSO_4$, filtered and the solvent was removed. The crude product was purified by chromatography on silica gel using CH_2Cl_2–EtOAc (10:1) mixture as an eluent.

The white crystals took up a mole of water on standing. Yield: 0.98 g (25%). Mp: 136–137 °C (acetonitrile); R_f: 0.3 (silica gel TLC, toluene–EtOAc 1:1); IR (KBr) ν_{max} 3536, 3520, 3496, 3400, 3232, 3040, 1648, 1584, 1536, 1520, 1496, 1456, 1336, 1288, 1248, 1208, 1116, 1088, 948, 744 cm^{-1}; ^{1}H and ^{13}C NMR spectra of our compound **8** were slightly different than the ones reported[30] for **8**. ^{1}H NMR ($CDCl_3$) δ 3.70 (br s, NH, 1H), 3.76 (s, 8H), 3.94–3.96 (m, 4H), 4.21–4.23 (m, 4H), 4.36 (br s, complexed H_2O, 2H), 6.90–6.94 (m, 6H), 7.43–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 68.09, 69.92, 70.94, 71.26, 111.94, 117.13, 121.15, 121.47, 131.93, 148.97. Anal. Calcd for $C_{20}H_{25}NO_5 \cdot H_2O$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.65; H, 7.19; N, 3.57.

4.2.1.1. Macrocycle 8 from *N*-formyl-derivative 26. To a vigorously stirred boiling solution of *N*-formyl-derivative **26** (3.9 g, 10 mmol) in EtOH (120 mL) was added under Ar a solution of KOH (3.4 g, 52 mmol) in water (13.5 mL) dropwise. After addition of the aqueous KOH solution the reaction mixture was stirred at boiling temperature for 30 min and then it was let to cool down to rt. The crystals were filtered, washed with water (2×20 mL) then with EtOH (2×20 mL) and air-dried to get macrocycle **8** as a monohydrate (3.78 g, 100%), which was identical in every respect to that prepared by the procedure described above.

4.2.2. (6*R*,16*R*)-6,16-Dimethyl-6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxazacyclooctadecine [(*R*,*R*)-21] from 22 and (*S*,*S*)-24. Diol **22** (1.06 g, 5.3 mmol), ditosylate (*S*,*S*)-**24**[35,36] (2.8 g, 5.3 mmol) and finely powdered anhydrous K_2CO_3 (7.28 g, 5.3 mmol) were mixed with vigorous stirring in anhydrous acetonitrile (100 mL) at rt under Ar. 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 materials (50 h). After the reaction was completed the solvent was removed and the residue was taken up in a mixture of water (80 mL) and CH_2Cl_2 (80 mL). The aqueous phase was shaken with CH_2Cl_2 (3×40 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed.

The crude product was purified by flash-chromatography on silica gel using CH_2Cl_2–EtOAc (20:1) mixture as an eluent to obtain the potassium tosylate complex of (*R*,*R*)-**21** (0.58 g, 18%); R_f: 0.45 (silica gel TLC, CH_2Cl_2–EtOAc 3:1); $[\alpha]_D^{25}$ −40.8 (*c* 0.34, CH_2Cl_2); IR (neat) ν_{max} 3416, 1600, 1528, 1496, 1352, 1244, 1176, 1120, 924, 744, 654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, *J*=6.5 Hz, 6H), 2.45 (s, 3H), 3.69–3.71 (m, 4H), 3.74–3.84 (m, 8H), 4.71–4.73 (m, 2H),

6.85–6.94 (m, 6H), 7.10 (br s, NH, 1H), 7.33 (d, J=8 Hz, 2H), 7.39 (d, J=7.5 Hz, 2H), 7.81 (d, J=8 Hz, 2H).

The potassium tosylate complex of (*R*,*R*)-**21** (0.58 g, 0.97 mmol) was subjected to chromatography on aluminium oxide using toluene–EtOAc (100:1) mixture as an eluent to obtain the free ligand (*R*,*R*)-**21** (0.29 g, 77%). The overall yield calculated for diol **22** and ditosylate (*S*,*S*)-**24** was 14%. The white crystals took up a mole of water on standing in open air. Mp: 71–74 °C; R_f: 0.27 (aluminium oxide TLC, toluene–EtOAc 100:1); $[\alpha]_D^{25}$ −72.49 (*c* 0.578, CH_2Cl_2); IR (KBr) ν_{max} 3512, 3392, 1640, 1600, 1592, 1584, 1524, 1504, 1496, 1468, 1440, 1356, 1244, 1208, 1096, 948, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (d, J=6 Hz, 6H), 2.01 (br s, complexed H_2O, 2H), 3.66–3.83 (m, 12H), 4.50–4.59 (m, 2H), 6.78 (br s, NH, 1H), 6.80–6.94 (m, 6H), 7.37 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 16.31, 71.34, 71.63, 74.48, 74.76, 114.73, 116.27, 120.06, 121.42, 134.41, 147.10. Anal. Calcd for $C_{22}H_{29}NO_5 \cdot H_2O$: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.31; H, 7.65; N, 3.50.

4.2.2.1. Macrocycle (*R*,*R*)-21 from *N*-formyl-derivative (*R*,*R*)-27. To a stirred solution of *N*-formyl-derivative (*R*,*R*)-**27** (1 g, 2.4 mmol) in MeOH (10 mL) was added 30% aqueous HCl solution (3.0 mL, 28 mmol) and the resulting reaction mixture was stirred at rt for 10 h. To the stirred reaction mixture was added $Me_4NOH \cdot 5H_2O$ (6 g, 33 mmol) dissolved in water (60 mL). Most of the MeOH and about half amount of the water were distilled off, and the aqueous solution was extracted with ether (1×100 and 2×50 mL). The combined organic phase was shaken with water (30 mL), dried over $MgSO_4$, filtered and the solvent was removed. The crude product (*R*,*R*)-**21** (0.86 g, 88%) so obtained was identical in every respect to that prepared by the procedure described above.

4.2.3. 6,7,9,10,12,13,15,16-Octahydro-22*H*-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxazacyclooctadecine-22-carbaldehyde (26). Diol **25** (4.65 g, 22.3 mmol) ditosylate **23** (11.2 g, 22.3 mmol) and finely powdered anhydrous K_2CO_3 (22.0 g, 159 mmol) were mixed in anhydrous acetonitrile (200 mL) with vigorous stirring at rt under Ar. The temperature of the reaction mixture was raised to 50 °C and kept at this temperature for 65 h. The cold reaction mixture was filtered and the precipitate was washed with acetonitrile (3×20 mL). The solvent was removed from the combined acetonitrile solution and the residue was taken up in a mixture of water (20 mL) and CH_2Cl_2 (60 mL). The phases were shaken well and separated. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The crude product was purified by chromatography on silica gel using toluene–EtOAc (first 1:1 then 1:2) mixtures as eluents to obtain macrocycle **26** (4.05 g, 52%) as colourless crystals. Mp: 131 °C; R_f: 0.31 (silica gel TLC, EtOAc); IR (KBr) ν_{max} 1692, 1600, 1504, 1464, 1336, 1280, 1148, 1136, 1128, 1120, 1108, 1088, 1040, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63–3.66 (m, 8H), 3.71–3.73 (m, 2H), 3.80–3.82 (m, 2H), 4.07–4.11 (m, 4H), 6.90–7.25 (m, 8H), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (all the four of the different aliphatic and five of the six different aromatic carbons give double signals in the spectrum) 59.72, 68.60, 68.79, 69.60, 69.90, 70.87, 71.37, 71.59, 114.16, 114.89, 121.16, 126.99, 127.90, 128.65, 128.88, 129.41, 131.28, 153.54, 154.49, 163.28. Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.39; H, 6.46; N, 3.44.

4.2.4. (6*R*,16*R*)-6,16-Dimethyl-6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo[*n*,*q*][1,4,7,10,13]pentaoxazacyclooctadecine-22-carbaldehyde [(*R*,*R*)-27]. Macrocycle (*R*,*R*)-**27** was prepared in the same way as described above for **26** starting from diol **25** (9.35 g, 40.8 mmol), ditosylate (*S*,*S*)-**24** (23.77 g, 44.8 mmol), finely powdered anhydrous K_2CO_3 (47.0 g, 340 mmol) and anhydrous acetonitrile (640 mL). In this case the reaction was complete in 7 days at 50 °C. The crude product was purified by chromatography on silica gel using toluene–EtOAc (first 4:1 then 1:1) mixture as eluents to obtain macrocycle (*R*,*R*)-**27** (13.2 g, 78%) as a thick oil. R_f: 0.18 (silica gel TLC, toluene–EtOAc 1:1); $[\alpha]_D^{25}$ +29.87 (*c* 0.76, CH_2Cl_2); IR (neat) ν_{max} 1692, 1596, 1496, 1456, 1376, 1332, 1272, 1256, 1244, 1124, 1048, 752, 672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, J=6 Hz, 3H), 1.26 (d, J=6 Hz, 3H), 3.22–3.63 (m, 12H), 4.50–4.62 (m, 2H), 6.86–7.37 (m, 8H), 8.5 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (all the five of the different aliphatic and five of the six different aromatic carbons give double signals in the spectrum) 17.00, 17.22, 70.81, 70.86, 71.38, 71.54, 73.20, 73.28, 74.61, 74.74, 114.42, 114.72, 120.37, 120.49, 127.75, 127.93, 128.33, 130.17, 131.62, 152.76, 152.99, 163.89. Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.40; H, 6.81; N, 3.19.

4.2.5. 9,10,12,13,15,16,18,19-Octahydroindolo[7,1-*n*,*o*][1,4,7,10,13,16]benzopentaoxazacyclooctadecine-1,2-dione (28). To a vigorously stirred solution of macrocycle **8** (6.5 g, 18.08 mmol) in dry and pure toluene (20 mL) was added dropwise at rt under Ar oxalyl chloride (3.44 mL, 5.0 g, 39 mmol). The reaction mixture was stirred at rt for 10 min and at 70 °C for 1 h.

The volatile materials were removed and the crude 6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo[*n*,*q*][1,4,7,10,-13,16]pentaoxazacyclooctadecine-22-yl(oxo)acetyl chloride was dissolved in bromobenzene (80 mL). To the latter solution was added iodine at rt with stirring under Ar (0.4 g, 1.58 mmol). The reaction mixture was stirred at reflux temperature for 40 h and the solvent was removed (1 mmHg). The crude product was purified by chromatography on silica gel using CH_2Cl_2–EtOAc (4:1) as an eluent to give **28** (2.4 g, 32%) as red crystals. Mp: 116–118 °C; R_f: 0.34 (silica gel TLC, EtOAc); IR (KBr) ν_{max} 1736, 1608, 1500, 1446, 1368, 1308, 1280, 1112, 784, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09–3.13 (m, 1H), 3.25–3.56 (m, 8H), 3.65–3.73 (m, 4H), 4.03–4.07 (m, 1H), 4.14–4.18 (m, 1H), 4.29–4.34 (m, 1H), 6.98–7.06 (m, 2H), 7.16 (d, J=8 Hz, 1H), 7.21–7.31 (m, 3H), 7.36 (t, J=8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 68.69, 69.07, 70.00, 70.13, 71.05, 71.21, 71.53, 71.61, 113.38, 117.78, 119.19, 120.44, 124.33 (very high, probably two carbon 13 signals together), 125.11, 129.10, 129.88, 140.87, 146.01, 155.40, 158.53, 183.72. Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.72; H, 5.31; N, 3.18.

4.2.6. (9*R*,19*R*)-9,19-Dimethyl-9,10,12,13,15,16,18,19-octahydroindolo[7,1-*n*,*o*][1,4,7,10,13,16]benzopentaoxazacyclooctadecine-1,2-dione [(*R*,*R*)-29]. Macrocycle (*R*,*R*)-**29** was prepared in the same way as described above

for **28** starting from (*R*,*R*)-**21** (10.8 g, 27.87 mmol), dry and pure toluene (100 mL) and oxalyl chloride (5.3 mL, 7.71 g, 60.8 mmol). Crude (6*R*,16*R*,)-6,16-dimethyl-6,7,9,10,12,13,15,16-octahydro-22*H*-dibenzo[*n*,*q*][1,4,7,10,13]pentaoxazacyclooctadecine-22-yl(oxo)acetyl chloride, bromobenzene (123 mL) and iodine (0.6 g, 2.37 mmol) were reacted as above. The crude product was purified by chromatography on silica gel using CH_2Cl_2–EtOAc (7:1) as an eluent to give (*R*,*R*)-**29** (6.5 g, 53%) as red crystals. Mp: 137–139 °C; R_f: 0.16 (silica gel TLC, CH_2Cl_2–EtOAc, 7:1); IR (KBr) ν_{max} 1740, 1696, 1608, 1500, 1460, 1372, 1312, 1280, 1240, 1136, 1096, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, J=6 Hz, 3H), 1.16 (d, J=6 Hz, 3H), 3.04–3.15 (m, 2H), 3.34–3.65 (m, 10H), 4.33–4.36 (m, 1H), 4.57–4.60 (m, 1H), 6.98 (t, J=8 Hz, 1H), 7.03 (t, J=8 Hz, 1H), 7.09 (d, J=8 Hz, 1H), 7.25–7.28 (m, 3H), 7.35 (t, J=8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.81, 17.32, 70.88, 71.09, 71.19, 71.37, 74.47, 74.53, 74.82, 74.93, 113.72, 117.53, 119.24, 120.21, 124.25, 125.42, 126.01, 129.79, 129.85, 141.55, 145.20, 154.48, 158.73, 183.86. Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.05; H, 5.95; N, 2.94.

4.2.7. Potassium 6,7,9,10,12,13,15,16-octahydro-1,21-methenobenzo[*n*,*q*][1,4,7,10,13,16]pentaoxazacyclooctadecine-23-carboxylate (30). Isatin derivative **28** (2.4 g, 5.8 mmol) was suspended at rt in 10% aqueous KOH (32 mL) with vigorous stirring and this suspension was heated to reflux and then refluxed for 2 h. The reaction mixture was stored at rt for 3 h and in a refrigerator for a day. The yellow precipitate was filtered off and recrystallized from boiling water to give **30** (2.5 g, 92%) as a bright yellow monohydrate. Mp: >340 °C; IR (KBr) ν_{max} 3496, 1608, 1564, 1504, 1472, 1456, 1424, 1376, 1324, 1280, 1256, 1160, 1104, 956, 744, 616, 512 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.67–3.70 (m, 4H), 3.75–3.78 (m, 4H), 4.03–4.06 (m, 4H), 4.36–4.39 (m, 4H), 7.20 (d, J=8 Hz, 2H), 7.40 (t, J=8 Hz, 2H), 7.70 (d, J=8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 67.80, 67.94, 68.56, 70.33, 107.89, 120.67, 122.25, 124.22, 140.05, 153.28, 156.24, 169.78. Anal. Calcd for $C_{22}H_{22}NO_7K\cdot H_2O$: C, 56.28; H, 5.15; N, 2.98. Found: C, 56.07; H, 5.38; N, 2.81.

4.2.8. Potassium (6*R*,16*R*)-6,16-dimethyl-6,7,9,10,12,13,15,16-octahydro-1,21-methenodibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxazacyclooctadecine-23-carboxylate [(*R*,*R*)-31]. Potassium salt (*R*,*R*)-**31** was prepared in the same way as described above for its achiral analogue **30** starting from (*R*,*R*)-**29** (6.5 g, 14.72 mmol) and 10% aqueous KOH (95 mL). Bright yellow crystals as monohydrates; yield: 6.6 g (90%). Mp: >340 °C; $[\alpha]_D^{25}$ +8.29 (*c* 0.916, MeOH); IR (KBr) ν_{max} 3440, 1596, 1576, 1560, 1472, 1376, 1320, 1272, 1152, 1128, 1100, 956, 748 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (d, J=6 Hz, 6H), 3.62–3.86 (m, 10H), 4.09 (d, J=10 Hz, 2H), 5.05–5.08 (m, 2H), 7.25 (d, J=8 Hz, 2H), 7.38 (t, J=8 Hz, 2H), 7.67 (J=8 Hz); ^{13}C NMR (DMSO-d_6) δ 14.50, 68.77, 70.01, 72.73, 72.81, 109.26, 120.35, 122.40, 124.26, 140.72, 151.81, 152.64, 168.38. Anal. Calcd for $C_{24}H_{26}NO_7K\cdot H_2O$: C, 57.93; H, 5.67; N, 2.81. Found: C, 58.22; H, 5.58; N, 2.62.

4.2.9. *N*-Allyl-6,7,9,10,12,13,15,16-octahydro-1,21-methenodibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxazacyclooctadecine-23-carboxamide (20). To thionyl chloride (30 mL, 48.9 g, 411 mmol) was added with vigorous stirring potassium salt **30** (2.35 g, 5 mmol) in portions at 0 °C. The suspension was stirred at 0 °C for 5 min then the temperature of the reaction was raised to reflux and the mixture was kept boiling for 45 min. The excess thionyl chloride was removed by distillation then dry and pure toluene (10 mL) was added to the residue. The toluene was removed and the residue was treated with toluene (10 mL) as above to remove the traces of thionyl chloride. The crude acid chloride was suspended in pure and dry CH_2Cl_2 (40 mL) and to this suspension was added dropwise at 0 °C a mixture of allylamine (5 mL, 3.81 g, 67 mmol) and triethylamine (10 mL, 7.26 g, 72 mmol) dissolved in pure and dry CH_2Cl_2 (20 mL) under Ar. The reaction mixture was stirred at 0 °C for 5 min then at rt for 1 h. The volatile materials were removed and the solid residue was triturated thoroughly with water (100 mL). The yellow crystals were filtered off, washed with water (3×20 mL) and dried. The crude product was recrystallized from MeOH to give **20** (1.04 g, 44%) as a monohydrate. Mp: 274–6 °C (MeOH); IR (KBr) ν_{max} 3450, 3336,1656, 1624, 1568, 1536, 1472, 1424, 1280, 1112, 924, 744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.69–3.77 (m, 8H), 3.97–4.01 (m, 4H), 4.12–4.15 (m, 2H), 4.32–4.36 (m, 4H), 5.21–5.38 (m, 2H), 6.01–6.10 (m, 1H), 7.21 (d, J=7.0 Hz, 2H), 7.48–7.60 (m, 4H), 9.20 (br s, NH, 1H), (the proton signal of the complexed water molecule merged into the big broad water singlet of DMSO-d_6 centred at 3.43 ppm); ^{13}C NMR (DMSO-d_6) δ 41.46, 68.55, 68.71, 69.26, 70.41, 107.75, 116.07, 116.66, 123.00, 127.19, 134.91, 139.93, 141.01, 154.78, 166.26. MS Calcd for $C_{25}H_{28}N_2O_6$: 452.1942. Found: 452.1921. Anal. Calcd for $C_{25}H_{28}N_2O_6\cdot H_2O$: C, 63.82; H, 6.43; N, 5.95. Found: C, 63.45; H, 6.46; N, 5.71.

4.2.10. (6*R*,16*R*)-*N*-Allyl-6,16-dimethyl-6,7,9,10,12,13,15,16-octahydro-1,21-methenodibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxazacyclooctadecine-23-carboxamide [(*R*,*R*)-19)]. Optically active ligand (*R*,*R*)-**19** was prepared in the same way as described above for its achiral analogue **20** starting from potassium salt (*R*,*R*)-**31** (2.49 g, 5 mmol) and thionyl chloride (30 mL, 48.9 g, 411 mmol). Yellow crystals as monohydrates; yield: 1.45 g (58%). Mp: 178 °C (MeOH); $[\alpha]_D^{25}$ −70.8 (*c* 1.97, CH_2Cl_2); IR (KBr) ν_{max} 3450, 3248, 1656, 1568, 1464, 1376, 1276, 1160, 1144, 1120, 1088, 1080, 940, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7 (br s, complexed H_2O, 2H), 1.45 (d, J=6.5 Hz, 6H), 3.71–4.01 (m, 12H), 4.28–4.31 (m, 2H), 5.11–5.15 (m, 2H), 5.25–5.38 (m, 2H), 6.02–6.10 (m, 1H), 6.60 (br s, NH, 1H), 7.09 (d, J=7 Hz, 2H), 7.41 (t, J=8 Hz, 2H), 7.56 (d, J=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 16.11, 42.41, 71.35 (very high, probably two carbon 13 signals together), 74.58, 75.30, 112.71, 117.34, 117.50, 123.57, 127.14, 133.68, 140.15, 141.50, 153.80, 167.19. MS Calcd for $C_{27}H_{32}N_2O_6$: 480.2255. Found: 480.2246. Anal. Calcd for $C_{27}H_{32}N_2O_6\cdot H_2O$: C, 65.04; H, 6.87; N, 5.62. Found: C, 64.97; H, 6.89; N, 5.43.

4.2.11. *N*,*N*-Bis(2-methoxyphenyl)formamide (34). A mixture of *N*-(2-methoxyphenyl)formamide (**32**) (23.5 g, 0.155 mol), 2-bromoanisole (**33**) (21.5 mL, 32.1 g, 0.172 mol), finely powdered anhydrous Na_2CO_3 (62 g, 0.585 mol), CuI (1.9 g, 0.01 mol) and finely powdered copper (0.8 g, 0.013 mol) was suspended in Dowtherm® (120 mL) with vigorous stirring at rt under Ar. The

temperature of the reaction mixture was raised to 220–225 °C and kept in this range for 8 h. During the reaction, water condensed on the surface of the condenser was removed in every couple of hours. After 8 h 2-bromoanisole (**33**) (5 mL, 7.5 g, 0.04 mol), finely powdered anhydrous Na_2CO_3 (20 g, 0.189 mol), CuI (0.9 g, 0.005 mol) and finely powdered copper (0.5 g, 0.008 mol) were added to the reaction mixture and it was stirred vigorously for 4 h at 220–225 °C under Ar. The brown reaction mixture was cooled to 90 °C, the insoluble materials were filtered off and washed with EtOAc (3×80 mL). Filtrate and washings were combined and all the volatile materials were removed by distillation (first at 5 mmHg then at 0.01 mmHg, in the end using an oil bath of 110 °C). The residue was dissolved in EtOAc (400 mL) and this solution was shaken successively with water (130 mL), 10% aqueous $NaHSO_3$ solution (50 mL) and brine (80 mL). The organic phase was dried over $MgSO_4$, filtered, heated with charcoal for 10 min, filtered again and the solvent was removed. The crude product was triturated with ether and the ethereal solution containing lot of precipitate was stored in a refrigerator overnight. The almost colourless crystals were filtered and recrystallized from a MeOH–ether mixture to give pure **34** (36 g, 90%). Mp: 106–107 °C (MeOH–ether); R_f: 0.47 (silica gel TLC, CH_2Cl_2–acetone, 20:1); IR (KBr) ν_{max} 1696, 1592, 1534, 1450, 1336, 1280, 1240, 1120, 1028, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 3.84 (s, 3H), 6.90–6.99 (m, 4H), 7.22–7.29 (m, 4H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (five aromatic carbons and the methyl carbon give double signals in the spectrum) 56.01, 56.07, 112.41, 112.55, 121.08, 128.73, 128.78, 129.05, 129.20, 129.67, 130.81, 155.07, 155.34, 163.54. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.15; H, 5.80; N, 5.38.

4.2.12. *N,N*-Bis(2-hydroxyphenyl)formamide (25). To a vigorously stirred suspension of anhydrous $AlCl_3$ (107 g, 0.8 mol) in dry and pure chlorobenzene (500 mL) was added *N,N*-bis(2-methoxyphenyl)formamide (**34**) (51.5 g, 0.2 mol) in portions at rt under Ar. The temperature of the reaction mixture was raised to 70 °C and kept at this temperature for 4 h. The reaction mixture was cooled down to rt and it was poured into a vigorously stirred mixture of 37% aqueous HCl (22 mL) and ice-water (1.5 L). Stirring was continued for another hour, the pale yellow crystals were filtered off and washed with water (3×150 mL). The crude product was dried and recrystallized from a mixture of EtOAc and hexane to give pure **25** (43.6 g, 95%). Mp: 159–159.5 °C (EtOAc–hexane). Reported mp: 152–153 °C;[40] R_f: 0.36 (silica gel TLC, CH_2Cl_2–acetone, 10:1); IR (KBr) ν_{max} 3550–2300 (br), 3288, 1654, 1592, 1512, 1492, 1454, 1352, 1272, 1240, 1152, 824, 752 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.78–6.81 (m, 2H), 6.92–6.99 (m, 2H), 7.11–7.18 (m, 4H), 8.29 (s, 1H), 9.74 (br s, OH, 2H); ^{13}C NMR (DMSO-d_6) δ (all the aromatic carbons give double signals in the spectrum) 116.56, 116.65, 119.20, 119.50, 127.71, 128.31, 128.54, 128.58, 129.10, 129.42, 152.78, 153.20, 162.82. Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.32; H, 4.58; N, 6.00.

4.2.13. Preparation of γ-mercaptopropyl-functionalized spherical HPLC quality silica gel (36). A slurry of spherical HPLC quality silica gel (Superspher® Si 60, Merck) (3.0 g) in dry and pure toluene (60 mL) was heated with mechanical stirring at reflux temperature under Ar for 24 h, during which time the water formed was removed azeotropically using a Dean–Stark adapter. After addition of (γ-mercaptopropyl)-trimethoxysilane (0.8 mL, 0.85 g, 4.3 mmol) the mixture was stirred in the above conditions for 2 days. The mixture was cooled down to rt and the modified silica gel was collected by filtration, washed sequentially with toluene (50 mL), CH_2Cl_2 (50 mL), MeOH (50 mL), CH_2Cl_2 (50 mL) and dried at 80 °C under reduced pressure for 14 h. A sample of blank silica gel was dried in the same way and it gave a combustion analysis of C, 1.04; H, 1.14; N, 0.00; S, 0.00. The combustion analysis of modified silica gel **36** gave C, 4.26; H, 1.76; N, 0.00; S, 2.63. This result shows that each gram of **36** contained 0.89 mmol (by C%), 0.86 mmol (by H%) and 0.82 mmol (by S%) of γ-mercaptopropyl-silyl groups.

4.2.14. Chiral stationary phase (*R,R*)-CSP-37. A slurry of γ-mercaptopropyl-functionalized silica gel **36** (2.7 g), macrocycle (*R,R*)-**19** (389 mg, 0.78 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN) (42 mg, 0.26 mmol) in freshly distilled pure and dry $CHCl_3$ (25 mL) was heated with mechanical stirring at reflux temperature under Ar for 2 days; two additional portions of AIBN (42 mg each) were added after 2 and 4 days. After cooling to rt the modified silica gel [(*R,R*)-CSP-**37**] was collected by filtration, washed sequentially with CH_2Cl_2 (60 mL), MeOH (60 mL), CH_2Cl_2 (60 mL) and dried at 80 °C under reduced pressure for 14 h. The combustion analysis of (*R,R*)-CSP-**37** gave C, 8.51; H, 2.24; N, 0.42; S, 2.28. Loading density of macrocycle, based on N: 0.15 mmol/g.

4.3. Chromatography

The chiral column was prepared by packing (*R,R*)-CSP-**37** into a 150× 4.6 mm stainless steel empty HPLC column using a slurry packing method. The packing was performed by using a Haskel-pump at 350 bar.

Chromatography was performed on a Jasco-HPLC instrument. Chromatograms were obtained by using (A) 100 mM aqueous $HClO_4$ solution and (B) methanol as eluents.

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