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Enantioseparation of protonated primary arylalkylamines and amino acids containing an aromatic moiety on a pyridino-crown ether based new chiral stationary phase

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Abstract—This paper reports the preparation and testing of a new pyridino-18-crown-6 ether based chiral stationary phase (CSP). The chiral crown ether was covalently bound to silica gel. Circular dichroism (CD) spectroscopy was used for probing the complex formation of the chiral crown ether with the enantiomers of protonated primary arylalkylamines. The (*S*,*S*)-dimethylpyridino-18-crown-6 ether selector having a terminal double bond was first transformed to a triethoxysilyl derivative by regioselective hydrosilylation, and then heated with spherical HPLC quality silica gel to obtain the CSP. The discriminating power of the HPLC column filled with the above CSP was tested by using the hydrogenperchlorate salts of racemic α-(1-naphthyl)ethylamine (1-NEA), α-(2-naphthyl)ethylamine (2-NEA) and the hydrochloride salts of aromatic α-amino acids and α-amino acids containing different aromatic side-chain protecting groups.

1. Introduction

Enantiomeric recognition is an important phenomenon in nature. Examples include the metabolism of single enantiomeric forms of amino acids and sugars in biosynthetic pathways. Enantiomers are expected to have different biological and physiological properties. Therefore, efficient analytical methods are needed to determine the enantiomeric purity of drug candidates and synthetic intermediates. One of the most frequently used methods for the determination of enantiomeric compositions and enantioseparations of mixtures of enantiomers is chromatography on chiral stationary phases (CSPs). Over the past few decades there has been great interest in designing new CSPs.[1–5] Chiral crown ethers immobilized on a solid matrix are promising packing materials, which can be used in chiral liquid chromatography (CLC). In the late seventies, Cram et al. reported the attachment of substituted bis(binaphthyl)-22-crown-6 ligands to both silica gel[6] and polymer resin.[7] Using these CSPs, they separated several racemic organic ammonium salts, mainly protonated amino acid esters. Since their pioneering work, a great number of researchers have prepared CSPs for CLC containing different chiral crown ethers as selectors and used them for the determination of enantiomeric compositions and enantioseparations of enantiomeric mixtures of protonated primary amines and amino acid derivatives.[8–15] Enantiomerically pure chiral pyridino-18-crown-6 ether type ligands and their discrimination between the enantiomers of protonated primary amines and amino acid derivatives have been thoroughly studied using calorimetric titration,[16,17] ^{1}H NMR spectroscopy,[16,18] MS spectrometry[19,20] and X-ray crystallography.[21] Circular dichroism (CD) spectroscopy was also used for studying enantiomeric recognition of chiral aralkyl ammonium salts[22,23] by the latter ligands. CD studies have revealed that chiral pyridino-18-crown-6 hosts including (*S*,*S*)-**1** (see Fig. 1) discriminate not only between enantiomers of chiral aralkylammonium salts but also between the enantiomers of protonated aromatic amino acid esters.[22] Chiral dimethyl-, diphenyl- and di-*tert*-butylpyridino-18-crown-6 ligands were attached to ordinary silica gel and these CSPs (*S*,*S*)-CSP-**2**,

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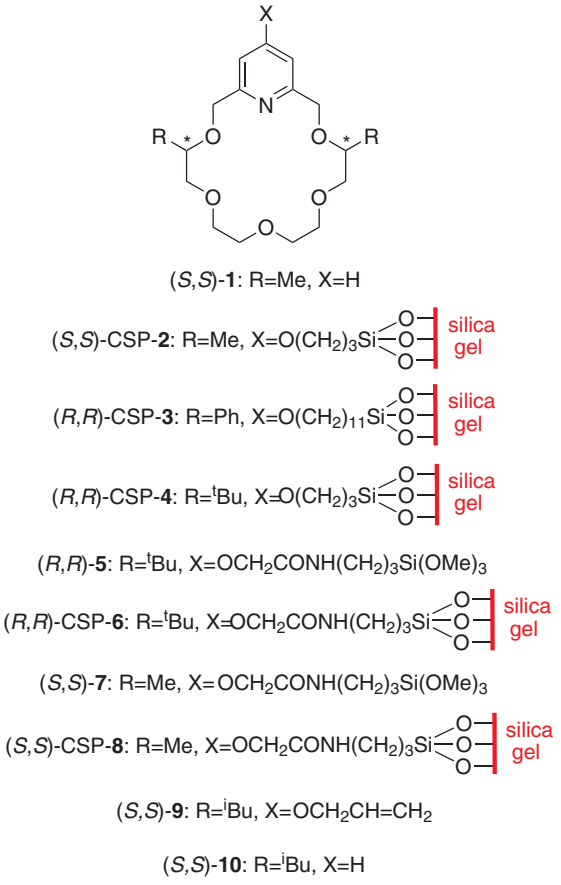


Figure 1. Structures of enantiopure chiral pyridino-18-crown-6 ethers and CSPs based on those derivatives covalently bound to silica gel.

(*R*,*R*)-CSP-**3** and (*R*,*R*)-CSP-**4** separated the enantiomers of selected chiral aralkylammonium perchlorates.[24–26] The preparation of an enantiopure di-*tert*-butylpyridino-18-crown-6 ether based chiral selector containing an amide bond and a trimethoxysilyl group, (*R*,*R*)-**5** and also its attachment to HPLC quality silica gel to obtain (*R*,*R*)-CSP-**6** (Fig. 1) was also reported.[27] The latter CSP separated the enantiomers of the hydrogenperchlorate salts of racemic α-(1-naphthyl)ethylamine (1-NEA) and α-phenylethylamine (PEA) by HPLC.[27] However, (*R*,*R*)-CSP-**6** could not separate the enantiomers of amino acid derivatives containing aromatic moieties, although the chromatographic conditions were systematically changed to a great extent.[28] As we thought that the main reason for this failure is the low stability of the diastereomeric complexes formed by the bulky *tert*-butyl group containing selector and the analytes,[16] we decided to prepare the dimethyl-substituted analogue, which was supposed to form more stable complexes with protonated primary aralkyl amines and amino acid derivatives.[16] It should be noted here that the preparation of the dimethyl-substituted analogue of (*R*,*R*)-**5**, that is, (*S*,*S*)-**7** (see Fig. 1) is much easier, more economical and needs less time than that of (*R*,*R*)-**5**, especially regarding that (*S*,*S*)-**7** can be obtained by using a novel procedure, superior to the one reported[27] for obtaining (*R*,*R*)-**5**. Herein, we report on the novel procedure for obtaining the new compound (*S*,*S*)-**7**, attachment of the latter to spherical HPLC quality silica gel, and on testing this new chiral stationary phase (*S*,*S*)-CSP-**8** with a variety of protonated primary aralkylamines and amino acid derivatives.

2. Results and discussion

2.1. Synthesis

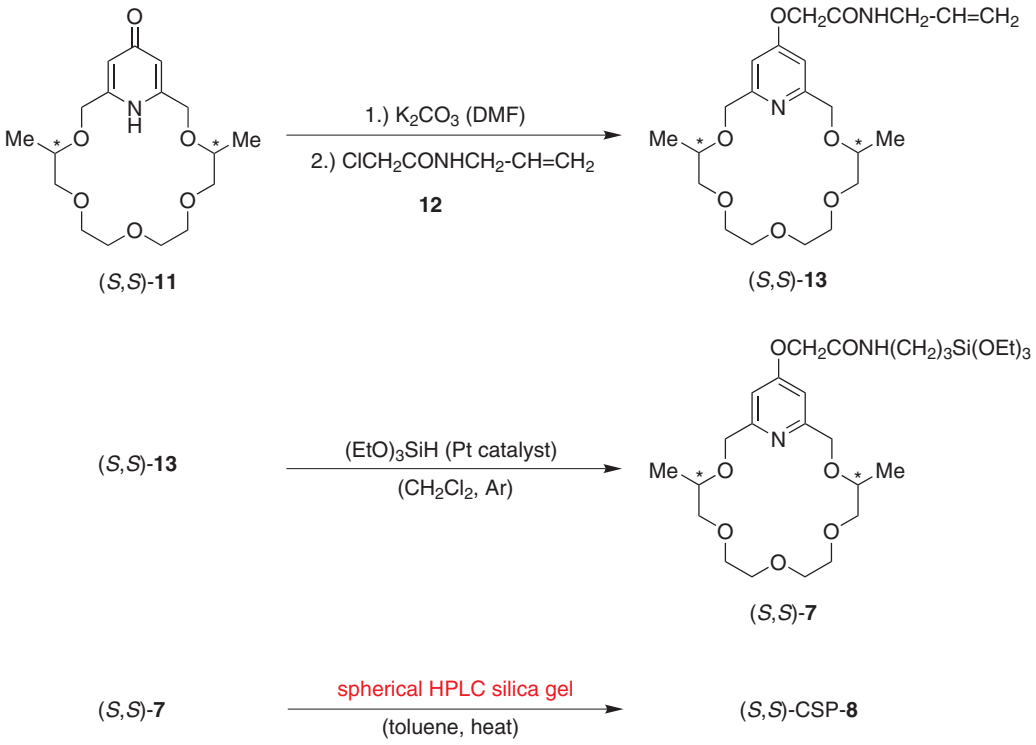
The enantiopure dimethyl-substituted pyridino-18-crown-6 ether (*S*,*S*)-**13** containing a terminal double bond (see Scheme 1) was prepared from the reported dimethylpyridono-18-crown-6 ligand (*S*,*S*)-**11**[29] and *N*-allyl-chloroacetamide **12**[30] using K_2CO_3 as a base in DMF. Regioselective hydrosilylation of ligand (*S*,*S*)-**13** was carried out with triethoxysilane in CH_2Cl_2 using a commercially available Pt catalyst to obtain the chiral crown-substituted triethoxysilane (*S*,*S*)-**7**. To prepare (*S*,*S*)-CSP-**8**, (*S*,*S*)-**7** was then heated with spherical HPLC quality silica gel using toluene as a solvent in a similar manner as described by us earlier for the preparation of ordinary silica gel bound chiral stationary phases (*S*,*S*)-CSP-**2**,[24] (*R*,*R*)-CSP-**3**[25] and (*R*,*R*)-CSP-**4**.[26]

2.2. CD spectroscopy

According to previous CD spectroscopic studies, the parent chiral pyridino crown ether (*S*,*S*)-**1** (see Fig. 1) has the power to discriminate between the enantiomers of arylalkyl ammonium salts 1-NEA·$HClO_4$ and PEA·$HClO_4$.[22,23] The CD spectra of the heterochiral [(*S*,*S*)-host+(*R*)-guest] and homochiral [(*S*,*S*)-host+(*S*)-guest] complexes differ from the sum spectra ($\Delta\varepsilon_{host}+\Delta\varepsilon_{guest}$) but the spectral effect of complexing is more significant in the heterochiral case. Contrary to this, the difference in the spectral changes is less significant for the hydrochloride or hydrogenperchlorate salts of phenylalanine methyl ester (PAMA) and phenylglycine methyl ester (PGMA).[22] Substitution by an alkoxy group at the γ-position of the pyridine ring improves the complexing ability and discriminating power of the pyridino-18-crown-6 ether.[23] As shown in Figure 2, the spectral response of (*S*,*S*)-**9** (R = *i*-Bu, X = OCH_2–CH=CH_2) to complexing enantiomers of 1-NEA·$HClO_4$ is dramatically enhanced as compared to that of (*S*,*S*)-**10** (R = *i*-Bu, X = H). This is likely due to the increased ^1L_a electric transition moment of the γ-substituted pyridine ring.[23]

2.3. High performance liquid chromatography

An HPLC column filled with (*S*,*S*)-CSP-**8** was used for separating the enantiomers of the test compounds listed in Figure 3, Tables 1 and 2. Gradient elution was applied with solvent systems A [4% acetic acid (AcOH) in methanol (MeOH)] and B_1 [1% triethylamine (TEA) in MeOH] (Table 1) or B_2 [1% TEA in a 1:1 mixture of MeOH/water]. Optimum analysis times and effective resolutions were achieved with the above eluents and a flow rate of 1.2 mL/min. Acidic modifier (AcOH) in the mobile phase is necessary to form the protonated primary amino group of the analytes.[12] Triethylamine (TEA) in the mobile phase



Scheme 1. Preparation of the new chiral stationary phase (*S*,*S*)-CSP-8 based on enantiopure dimethylpyridino-18-crown-6 ligand covalently attached to silica gel.

was used for the deactivation of the free silanol groups.[31] The elution order of the enantiomers was determined by the injection of standard (separately available) authentic enantiomers. It was found that the (*S*)-enantiomer eluted with a shorter retention time than that of its antipode. This behaviour is in full agreement with our observation using CSPs containing similar pyridino-crown ethers as chiral selectors attached to ordinary silica gel[24–26] or Merrifield resin[29] at atmospheric pressure. The observed elution order can be explained by the generally observed higher stability of the heterochiral complexes [i.e., (*R*,*R*)-crown ether-(*S*)-aralkylammoniun salt or (*S*,*S*)-crown ether-(*R*)-aralkylammonium salt] compared to that of homochiral complexes [i.e., (*S*,*S*)-crown ether-(*S*)-aralkylammonium salt or (*R*,*R*)-crown ether-(*R*)-aralkylammonium salt].[16,23]

It is very promising that in addition to the aromatic primary ammonium salts such as 1- and 2-NEA·$HClO_4$ and some aromatic amino acids such as Phe, Tyr and Trp, derivatives of nonaromatic amino acids with aromatic protecting groups (*S*-benzyl-homocysteine, *O*-benzyl-serine and ε-*N*-benzyloxycarbonyl-lysine) could also be separated on (*S*,*S*)-CSP-**8** (Fig. 4).

Chiral separations on our new CSP are affected by several properties of the analytes. The steric effect of the 'side-chain' groups is an important factor. By comparing the resolution data of 2-NEA·$HClO_4$, and 1-NEA·$HClO_4$, it can be seen that the decrease of the retention (k'), separation (α) and resolution (R_s) factors (Table 1) is due to an unfavourable position of the naphthalene ring in the complex.[23]

In the case of the amino acids, which have an aromatic side-chain group (Trp, Phe and Tyr), the differences between the sizes of the aromatic groups have no significant effect on the elution profiles. Trp is more retained than Phe and Tyr. Under the conditions investigated, the CSP was unable to discriminate between Phe and Tyr (Table 1). Interestingly, the most retained analyte among our model compounds is the *S*-benzyl-homocysteine, but the enantioselectivity achieved is lower than in the case of Phe. The distance of the aromatic ring from the chiral centre does not correlate very well with the retention and separation data (Table 1). By using a water–methanol mixture as eluent the retention times and the resolution factors decreased, and the value of enantioselectivity (α) increased (Table 2). This effect on the separation factor (α) is difficult to explain. It is clear that the enantiomer separation of this pyridino-18-crown-6 ether based CSP is more efficient when the mobile phase is more hydrophilic.

3. Conclusion

CD spectroscopy proved to be an efficient tool for testing the discriminating potential of chiral pyridine-18-crown-6 ligands in solution and for designing CSPs with improved chromatographic parameters. Synthetic studies are currently in progress in order to increase the capacity (the attached amount, mmol crown ether/g silica) of CSP and to monitor the structural features of chiral selectors which are needed for improving enantioseparation on a pyridine-18-crown-6 ether-based CSP.

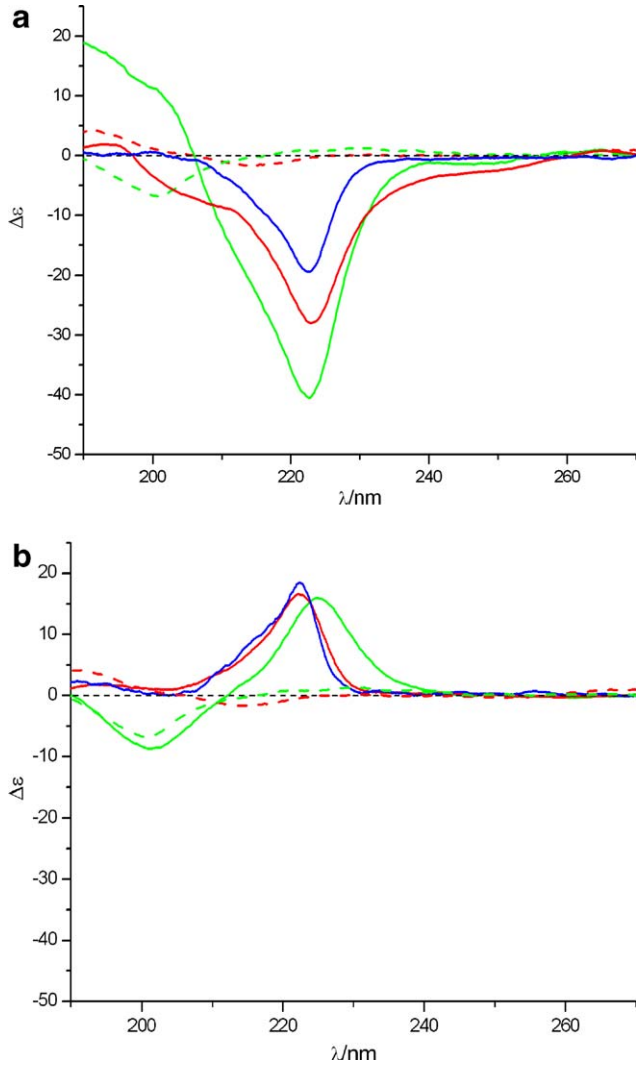


Figure 2. CD spectra of (a) heterochiral complex of (*S*,*S*)-**9** (– – –) with (*R*)-1-NEA (——) and (*S*,*S*)-**10** (– – –) with (*R*)-1-NEA (——) compared to (*R*)-1-NEA (——); (b) homochiral complex of (*S*,*S*)-**9** (– – –) with (*S*)-1-NEA (——) and (*S*,*S*)-**10** (– – –) with (*S*)-1-NEA (——) compared to (*S*)-1-NEA (——).

4. Experimental

4.1. General

Infrared (IR) 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 taken on a Bruker DRX-500 Avance spectrometer. Molecular masses were determined by a ZQ2000 (Waters Corp.) mass spectrometer using electrospray ionization. Elemental analyses were performed in the Microanalytical Laboratory at the Department of Organic Chemistry, L. Eötvös University, Budapest, Hungary. 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. Solvents were dried and purified according to the well-established methods.[32] Evaporations were carried out under reduced pressure.

4.2. Preparation and characterization of (*S*,*S*)-CSP-8

4.2.1. 2-[(4*S*,14*S*)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-trien-19-yloxy]-*N*-(3-triethoxysilylpropyl)acetamide (*S*,*S*)-7. A solution of crown ether derivative (*S*,*S*)-**13** (200 mg, 0.456 mmol) and triethoxysilane (0.36 mL, 0.32 g, 2.32 mmol freshly distilled under argon) in pure and dry CH_2Cl_2 was stirred at room temperature under argon in a 5 mL one-necked flask equipped with a rubber septum. Pt catalyst (SIP 6830.0, CAS No. 68478-92-2, ABCR, Kalsruhe, Germany) (three drops) was added through the rubber septum using a syringe and a needle. After stirring the reaction mixture for 5 days at room temperature, ^{1}H and ^{13}C NMR spectra of a small aliquot showed that the signals of the olefin protons [5.17–5.26 (m, 2H) and 5.83–5.92 (m, 1H)] and carbons [117.05 and 133.64] had disappeared. The volatile compounds were removed from the reaction mixture (0.005 mmHg) giving (*S*,*S*)-**7**, which was used for the next step without further purification. IR (neat) ν_{max}: 3320, 2976, 2952, 2888, 1676, 1600, 1540, 1456, 1392, 1348, 1264, 1084, 960, 888, 800 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.53 (tr, $J = 8$ Hz, 2H), 1.06 (d, $J = 6$ Hz, 6H), 1.11 (tr, $J = 7$ Hz, 9H), 1.56–1.59 (m, 2H), 3.23–3.56 (m, 14H) 3.69–3.75 (m, 8H), 4.43 (s, 2H), 4.67 (s, 4H), 6.60 (br s, NH, 1H), 6.72 (s, 2H); ^{13}C (125 MHz, $CDCl_3$): δ 1.02, 17.11, 18.00, 18.23, 41.41, 58.47, 59.12, 70.68, 70.85, 71.67, 73.80, 76.14, 106.46, 160.98, 164.33, 166.99.

4.2.2. Chiral stationary phase (*S*,*S*)-CSP-8. The pyridino crown ether derivate containing the triethoxysilyl group [(*S*,*S*)-**7**] (253 mg, 0.42 mmol) in pure and dry toluene (30 mL) was stirred (mechanical stirring) with HPLC quality spherical silica gel (Superspher® Si 60, Cat. No. 119609, Merck) (2.6 g) under argon using an oil bath (bath temperature: 120 °C) for 4 days. The silica gel was filtered and washed with 50% ethanol in toluene (3 × 30 mL), ethanol (1 × 30 mL), 50% methanol in CH_2Cl_2 (2 × 30 mL) and CH_2Cl_2 (3 × 30 mL). The filtrate and washings were evaporated to give 31 mg of a thick oil. The silica gel containing the bound crown ether was dried in a vacuum oven at 80 °C for 14 h. A sample of blank silica gel was dried the same way and it gave a combustion analysis of C, 1.1; H, 1.55; N, 0.00. The combustion analysis of (*S*,*S*)-CSP-**8** gave C, 4.95; H, 2.04; N, 0.39. This result shows that each gram of (*S*,*S*)-CSP-**8** contained 0.15 mmol (by C%), 0.14 mmol (by H%) and 0.14 mmol (by N%) of chiral crown ether.

4.2.3. *N*-Allyl-chloroacetamide 12. This compound was prepared as reported.[30] Bp: 46–48 °C (0.05 mmHg); reported[30] bp: 110–112 °C (14 mmHg); n_D^{20}: 1.4891, reported[30] $n_D^{19.5}$: 1.4892. IR (neat) ν_{max} 3296, 3088, 1664, 1540, 1420, 1240, 1264, 992, 924, 768, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.93–3.94 (m, 2H), 4.07 (s, 2H), 5.17–5.25 (m,2H), 5.82–5.89 (m, 1H), 6.1 (br s, NH, 1H); ^{13}C (125 MHz, $CDCl_3$): δ 42.22, 42.70, 116.99, 133.40, 165.96.

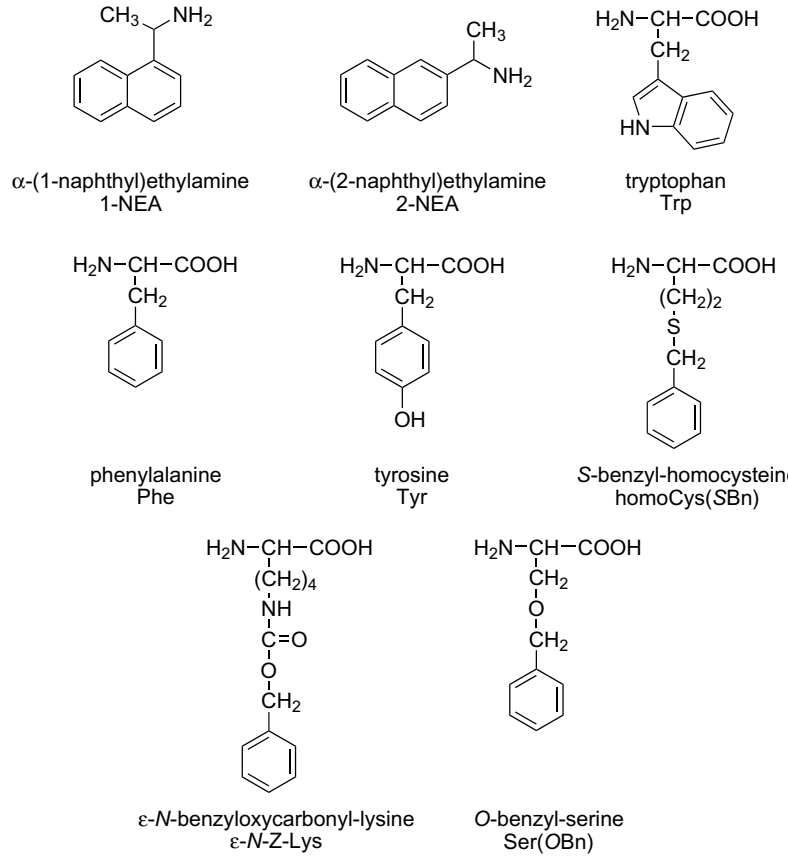


Figure 3. Structures of the analytes.

Table 1. Chromatographic data for the separation of racemic perchlorate or hydrochloride salts on (*S*,*S*)-CSP-**8**

Analytes	*t* (*S*)	*t* (*R*)	*k*′ (*R*)	α	R_s
1-NEA	4.77	8.65	5.65	2.12	2.73
2-NEA	4.74	7.00	4.38	1.66	1.97
Trp	3.70	5.03	2.87	1.55	1.38
Phe/Tyr	3.13	4.42	2.40	1.70	1.56
HomoCys(*S*Bn)	6.62	9.22	6.09	1.49	1.62
ε-*N*-*Z*-Lys	4.43	5.85	3.50	1.45	1.45
Ser(*O*Bn)	5.25	5.85	3.50	1.15	0.32

Gradient elution: 5–0% eluent B_1 over 15 min (flow rate: 1.2 mL/min).

Table 2. The effect of water: chromatographic data for the separation of racemic perchlorate or hydrochloride salts on (*S*,*S*)-CSP-**8**

Analytes	*t* (*S*)	*t* (*R*)	*k*′ (*R*)	α	R_s
1-NEA	2.33	4.13	2.18	2.75	2.75
2-NEA	2.35	3.45	1.65	2.05	1.85
Trp	2.57	3.27	1.52	1.55	1.05
HomoCys(*S*Bn)	3.60	4.82	2.71	1.53	1.19

Gradient elution: 5–0% eluent B_2 over 15 min (flow rate: 1.2 mL/min).

4.2.4. 2-[(4*S*,14*S*)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-trien-19-yloxy]-*N*-(2-propenyl)-acetamide (*S*,*S*)-13. To a solution of dimethylpyridono-18-crown-6 ether (*S*,*S*)-**11** (1.0 g, 2.9 mmol) in pure and dry DMF (30 mL) was added first finely powdered anhydrous K_2CO_3 (1.2 g, 8.7 mmol) followed by *N*-allylchloroacetamide **12** (1.11 g, 8.3 mmol), and the resulting mixture was stirred at room temperature under argon for 3 days. After this time TLC analysis (Al_2O_3, eluent: 5% ethanol in toluene, R_f [(*S*,*S*)-**11**]: 0.1; R_f [(*S*,*S*)-**13**]: 0.25), showed total consumption of the starting material (*S*,*S*)-**11** and formation of a new product [(*S*,*S*)-**13**].

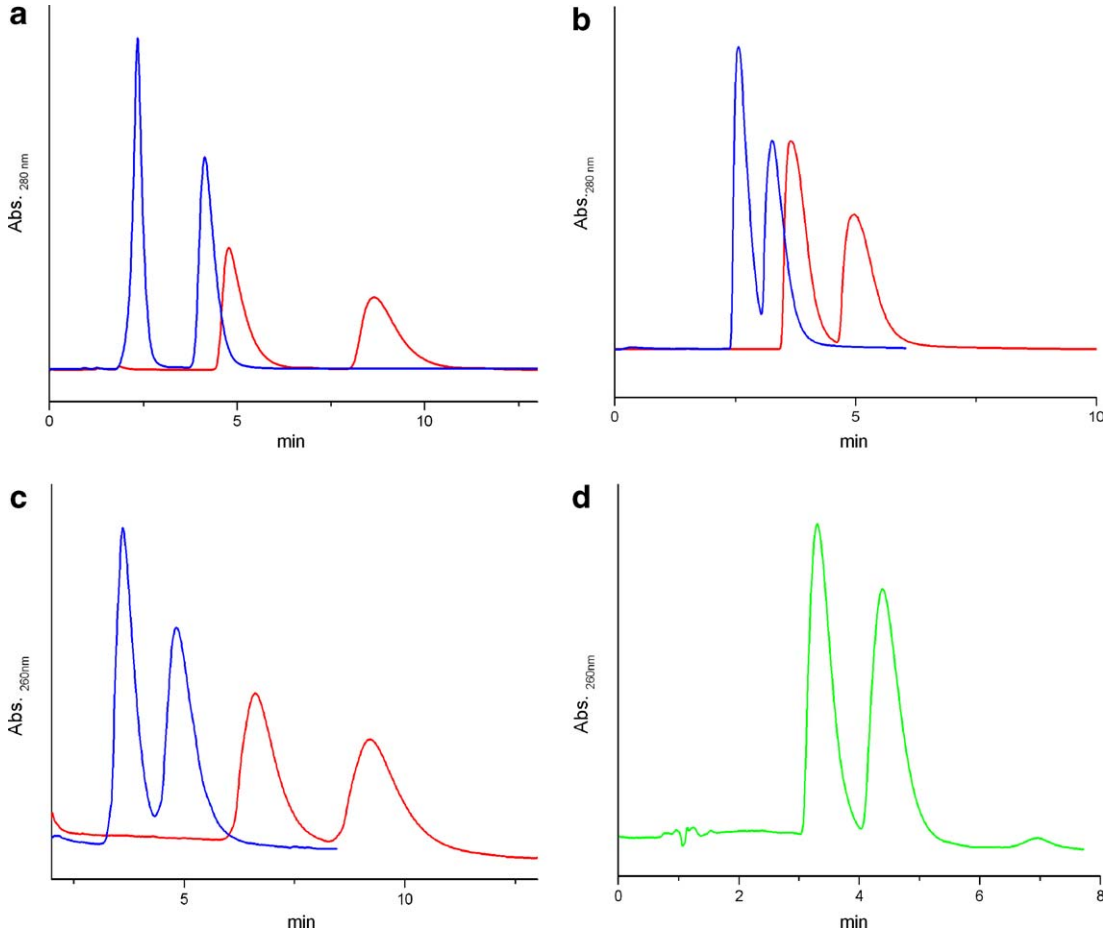


Figure 4. Selected chromatograms of (a) 1-NEA, (b) Trp, (c) homoCys(*S*Bn) and (d) ε-*N*-*Z*-Lys. Red line: 5–0% eluent B_1 over 15 min (flow rate: 1.2 mL/min); blue line: 5%–0% eluent B_2 over 15 min (flow rate: 1.2 mL/min); green line: 3%–0% eluent B_1 over 7 min (flow rate: 1.5 mL/min).

The solvent was evaporated and the residue dissolved in a mixture of CH_2Cl_2 (100 mL) and water (100 mL). The phases were shaken well and separated. The aqueous phase was shaken with CH_2Cl_2 (3×50 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent removed. The residue was purified by column chromatography on alumina using 2.5% ethanol in toluene as an eluent to give 0.95 g (76%) of pure (*S*,*S*)-**13** as a very thick oil. $[\alpha]_D^{25} = +12.7$ (*c* 0.84, CH_2Cl_2); IR (neat) ν_{max} 3296, 3080, 2968, 2872, 1740, 1676, 1600, 1564, 1544, 1452, 1352, 1252, 1112, 992, 924, 856 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.18 (d, $J = 6$ Hz, 6H), 3.45–3.65 (m, 12H), 3.79–3.85 (m, 2H), 3.96–4.02 (m, 2H), 4.58 (s, 2H), 4.79 (s, 4H), 5.17–5.26 (m, 2H), 5.83–5.92 (m, 1H), 6.60 (br s, NH, 1H), 6.84 (s, 2H); ^{13}C (125 MHz, $CDCl_3$): δ 17.20, 41.55, 66.82, 70.76, 70.91, 71.72, 73.91, 76.21, 106.67, 117.05, 133.64, 161.06, 164.38, 167.09; MS 439 $(M+1)^+$. Anal. Calcd for $C_{22}H_{34}N_2O_7$: C, 60.26; H, 7.81; N, 6.39. Found: C, 60.14; H, 7.92; N, 6.25.

4.3. Chromatography

The chiral column was prepared by packing (*S*,*S*)-CSP-**8** into a 150×4.6 mm stainless steel empty HPLC column using the slurry packing method. The packing was performed by using a Haskel-pump at 350 bar.

Chromatography was performed on a Shimadzu HPLC system, involving a SPD-6AV UV-detector, two LC-6A pumps, a SIL-6B autosampler and a SCL-6B system controller. Chromatograms were obtained by using (A) 4% acetic acid in methanol, (B_1) 1% triethylamine in methanol and (B_2) 1% triethylamine in 50% methanol–50% water as eluents.

Acknowledgements

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