Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2087–2099

TETRAHEDRON: *ASYMMETRY*

Enantioseparation of racemic organic ammonium perchlorates by a silica gel bound optically active di-*tert*-butylpyridino-18-crown-6 ligand

Zoltán Köntös,[a] Péter Huszthy,[b,*] Jerald S. Bradshaw [c] and Reed M. Izatt [c]

[a] *Institute for Organic Chemistry, Technical University Budapest, H-1521 Budapest, Hungary*
[b] *Research Group for Alkaloid Chemistry, Hungarian Academy of Sciences, H-1521 Budapest, Hungary*
[c] *Department of Chemistry, Brigham Young University, Provo, Utah 84602, USA*

Received 31 March 1999; accepted 27 April 1999

Abstract

Both enantiomers of the novel chiral di-*tert*-butylpyridino-18-crown-6 ligand (*R*,*R*)-**7** and (*S*,*S*)-**7** containing an allyloxy group on the pyridine subcyclic unit were prepared by the reaction of 4-allyloxy-2,6-pyridinedimethyl ditosylate **9** and the enantiomers of di-*tert*-butyl-substituted tetraethylene glycol (*R*,*R*)-**8** and (*S*,*S*)-**8** in the presence of a strong base. One of them, (*R*,*R*)-**7**, was covalently attached to silica gel, and this chiral stationary phase (CSP) separated four selected racemic organic ammonium perchlorates into their enantiomers by column chromatography.

1. Introduction

Enantiomeric resolution using a chiral stationary phase (CSP) has been an expanding field of research during the last two decades in order to meet the strong demand for the determination of enantiomeric composition and in the separation of racemic mixtures of drugs, pesticides and other fine chemicals of importance.[1–6]

Enantiomeric recognition in chromatographic terms means preferential interaction of one enantiomer of a racemic mixture with the CSP which can lead to chromatographic resolution.[7,8] In the last quarter of a century there has been great interest in designing new CSPs capable of resolving different classes of compounds.[5–8] The study of enantiomeric separations of amines and protonated amines (amino acids and their derivatives, for example) is of significance since these compounds are basic building blocks of biomolecules.

* Corresponding author. E-mail: huszthy.szk@chem.bme.hu

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00163-9

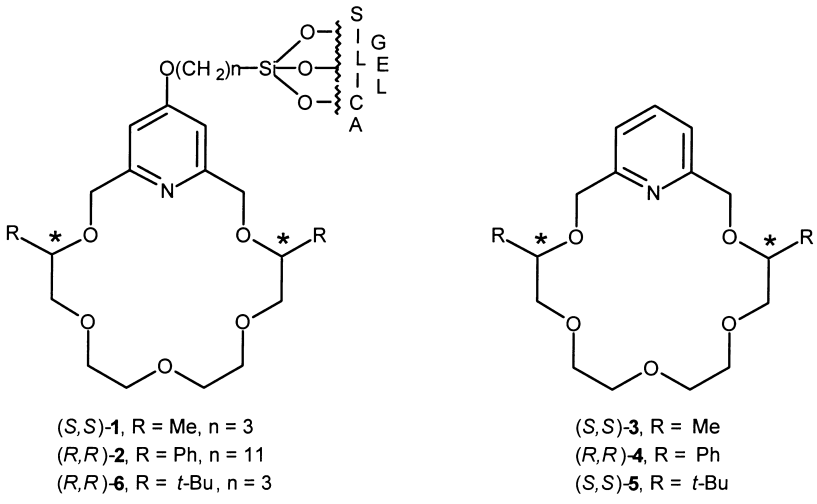


Figure 1. Chiral pyridino-18-crown-6 ligands and CSPs based on enantiomerically pure chiral pyridino-18-crown-6 ligands covalently attached to silica gel

Among several types of compounds studied, such as amino acids (native and derivatized), peptides, cyclodextrins (native or derivatized) and linear derivatized carbohydrates (cellulose or amylose), chiral crown ethers containing the dinaphthyl moiety as a chiral barrier have been used as successful selectors for CSPs in determinations of the enantiomeric compositions and in separations of amine and protonated amine compounds.[9–21]

Recently we reported the enantioseparation of racemic [α-(1-naphthyl)ethyl]ammonium perchlorate (NapCH(Me)$NH_3^+ClO_4^-$) using CSPs (*S*,*S*)-**1** and (*R*,*R*)-**2** containing pyridino-18-crown-6 ligands as chiral selectors.[22] As expected from previous studies,[7,9] the degree of enantiomeric recognition of the parent ligands (*S*,*S*)-**3** and (*R*,*R*)-**4** (see Fig. 1) expressed in the difference of the Gibbs free energies, $\Delta(\Delta G)$ for the complexation of (*S*)- and (*R*)-NapCH(Me)$NH_3^+ClO_4^-$ in the same solvent as the eluent (MeOH), paralleled very well the effectiveness of enantiomeric separation on CSPs (*S*,*S*)-**1** and (*R*,*R*)-**2**. Our previous studies also showed that (*S*,*S*)-**5** containing the bulky *tert*-butyl groups at the stereogenic centers had the highest enantioselectivity among stable pyridino-18-crown-6 ligands.[23,24] The other advantage of using ligand (*S*,*S*)-**5** as a selector for enantioseparation of racemic NapCH(Me)$NH_3^+ClO_4^-$ and other racemic organic ammonium salts is not only that the $\Delta(\Delta G)$ value is large, but also that the individual ΔG values (see Table 1) are relatively small which also favors enantioseparations on a CSP.[7]

In this paper we report the preparation of CSP (*R*,*R*)-**6** and its use for enantioseparation of selected racemic organic ammonium salts.

2. Results and discussion

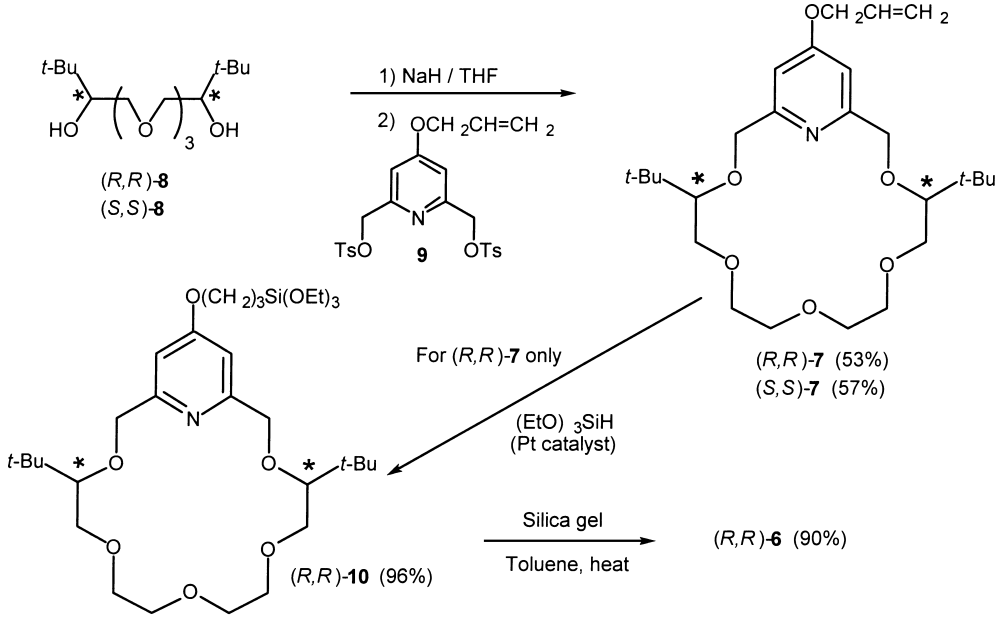
The two enantiomers of the new di-*tert*-butyl pyridino-18-crown-6 ligand (*R*,*R*)-**7** and (*S*,*S*)-**7** (see Scheme 1) were prepared from the two enantiomers of the di-*tert*-butyl-substituted tetraethylene glycol [(*R*,*R*)-**8** and (*S*,*S*)-**8**] and 4-allyloxy-2,6-pyridinedimethyl ditosylate **9** in THF using a strong base NaH in a similar manner as we described earlier[22,25–27] for obtaining analogous crown ethers. It can also be seen in Scheme 1 how one of the enantiomers [(*R*,*R*)-**7**] was attached covalently to silica gel to obtain CSP (*R*,*R*)-**6**. The first step of this procedure was a highly regioselective hydrosilylation reaction using triethoxysilane and a commercially available Pt catalyst to obtain chiral crown-substituted triethoxysilane

Table 1
ΔG (kJ/mol) and $\Delta(\Delta G)$ values for the interactions of enantiomerically pure chiral pyridine-containing ligands with the enantiomers of [α-(1-naphthyl)ethyl]ammonium perchlorate (NapCH(Me)$NH_3^+ClO_4^-$) at 25°C

Ligand	Cation	ΔG[a]	$\Delta(\Delta G)$	Method	Solvent	Ref.[a]
(*S*,*S*)-**3**	(*R*)-NapCH(Me)NH_3^+	-17.1		calorimetry	CH_3OH	23
	(*S*)-NapCH(Me)NH_3^+	-15.8	-1.3	calorimetry	CH_3OH	23
(*R*,*R*)-**4**	(*S*)-NapCH(Me)NH_3^+	-17.7		^{1}H NMR	CD_3OD	25
	(*R*)-NapCH(Me)NH_3^+	-16.7	-1.0	^{1}H NMR	CD_3OD	25
(*S*,*S*)-**5**	(*R*)-NapCH(Me)NH_3^+	-7.6		^{1}H NMR	$CD_3OD/CDCl_3$ (1/9)	25
	(*S*)-NapCH(Me)NH_3^+	-3.5	-4.1	^{1}H NMR	$CD_3OD/CDCl_3$ (1/9)	25

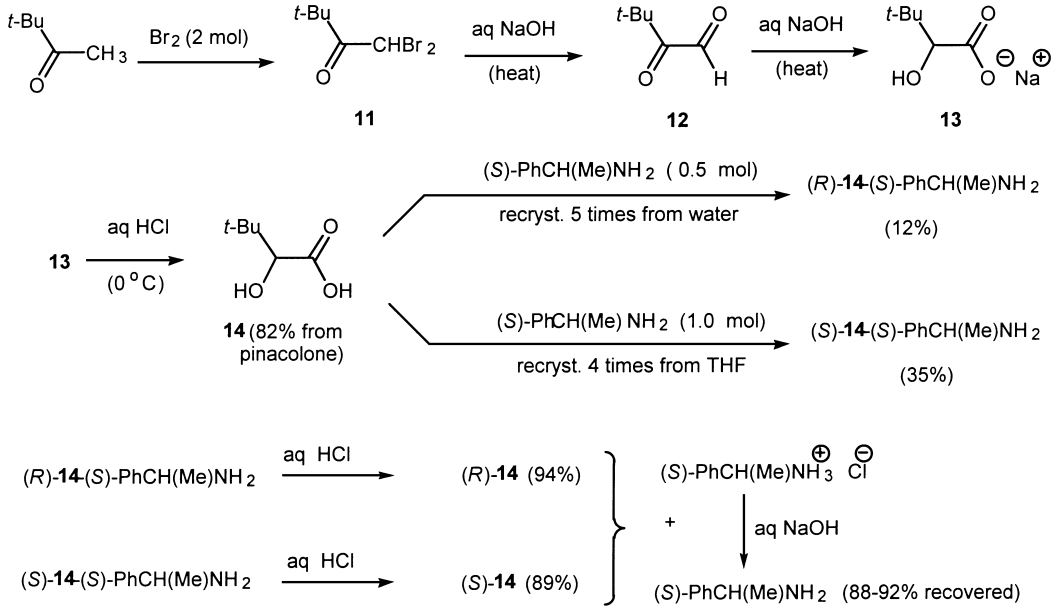
[a] ΔG values were calculated from log*K* data given in references 23 and 25.

(*R*,*R*)-**10**. The latter was then heated with silica gel using toluene as a solvent in a similar manner as described by us earlier for the preparation of CSPs (*S*,*S*)-**1**[27] and (*R*,*R*)-**2**.[22] The silica gel CSP (*R*,*R*)-**6** contained approximately 0.43 mmol of chiral crown per gram as determined by elemental analysis. 4-Allyloxy-2,6-pyridinedimethyl ditosylate **9**[27,28] needed for the synthesis of both enantiomers of the new crown ether (*R*,*R*)-**7** and (*S*,*S*)-**7** was prepared as reported.[27] Although we described the synthesis of one enantiomer of di-*tert*-butyl-substituted tetraethylene glycol (*S*,*S*)-**8**[25] earlier, that procedure was not a convenient one for large scale preparation. Here we report a straightforward preparation of both enantiomers (*R*,*R*)-**8** and (*S*,*S*)-**8** in multigram quantities (see Schemes 2 and 3).

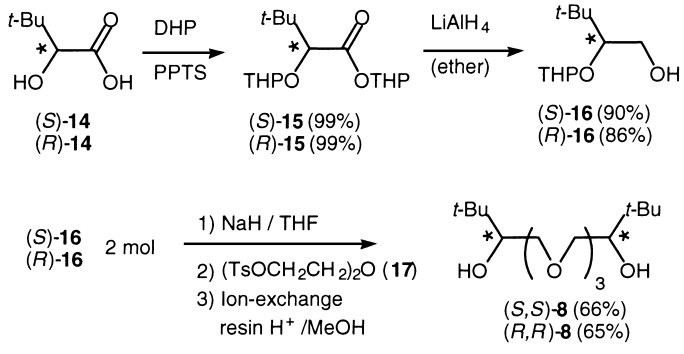


Scheme 1. Preparation of chiral allyloxypyridino-crowns (*R*,*R*)-**7** and (*S*,*S*)-**7**, and silica gel bound chiral crown (*R*,*R*)-**6**

The preparation of the enantiomerically pure chiral hydroxy acid precursors (*R*)-**14** and (*S*)-**14** is outlined in Scheme 2. Van Draanen et al.[29] described a 'one pot' synthesis for racemic hydroxy acid



Scheme 2. Preparation and resolution of racemic hydroxy acid **14**



Scheme 3. Preparation of chiral di-*tert*-butyl-substituted tetraethylene glycol (*R,R*)-**8** and (*S,S*)-**8**

14 starting from pinacolone and gaseous Cl_2. We found that using Br_2 instead of Cl_2 and making other minor modifications, a more convenient laboratory procedure could be developed for obtaining **14** (see Scheme 2).

Dibromination of pinacolone in acidic conditions gave **11** which was heated with aqueous NaOH solution. The α-oxo-aldehyde **12** first formed underwent an internal Cannizzaro reaction in this strong basic medium resulting in sodium salt **13** which after acidification gave hydroxy acid **14**. Racemic acid **14** was resolved into its enantiomers (*R*)-**14** and (*S*)-**14** using (*S*)-1-phenylethylamine [(*S*)-PhCH(Me)NH_2] (see Scheme 2). Masamune et al.[30] described the preparation of the diastereomeric salt (*S*)-**14**-(*S*)-PhCH(Me)NH_2 from 1 mol of **14** and 1 mol of resolving agent (*S*)-PhCH(Me)NH_2 using isopropanol (three times) and an ethanol–ether mixture (once) as solvents for recrystallization. As using the latter solvents for recrystallization did not give satisfactory results in our hands, we used other systems. When we used 0.5 mol of resolving agent (*S*)-PhCH(Me)NH_2 for 1 mol of racemic acid **14** and water as a solvent of recrystallization, the diastereomeric salt (*R*)-**14**-(*S*)-PhCH(Me)NH_2 was obtained. Using 1 mol of (*S*)-PhCH(Me)NH_2 for 1 mol of **14** and THF as a solvent of recrystallization, the diastereomeric salt (*S*)-**14**-(*S*)-PhCH(Me)NH_2 was obtained. Both enantiomers of hydroxy acid **14**, i.e. (*R*)-**14** and

(*S*)-**14** were obtained by acidification of diastereomeric salts (*R*)-**14**-(*S*)-PhCH(Me)NH_2 and (*S*)-**14**-(*S*)-PhCH(Me)NH_2 with diluted aqueous HCl followed by extraction with ether. From the aqueous phases containing (*S*)-PhCH(Me)$NH_3^+Cl^-$, the resolving agent [(*S*)-PhCH(Me)NH_2] was recovered by using aqueous NaOH followed by extraction with ether in good yields (see Scheme 2).

The preparation of the enantiomers of di-*tert*-butyl-substituted tetraethylene glycol (*R,R*)-**8** and (*S,S*)-**8** from enantiomerically pure hydroxy acids (*R*)-**14** and (*S*)-**14** is shown in Scheme 3.

Hydroxy acids (*R*)-**14** and (*S*)-**14** were first treated with an excess of dihydropyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS) catalyst to give the bis-tetrahydropyranyl (THP) derivatives (*R*)-**15** and (*S*)-**15** which were then reduced to give mono-THP-blocked alcohols (*R*)-**16** and (*S*)-**16**. Two moles of alcohols (*R*)-**16** and (*S*)-**16** were deprotonated using NaH in THF and the alkoxides formed were reacted with one mole of diethylene glycol di-*p*-tosylate **17** to obtain bis-THP-blocked derivatives of (*R,R*)-**8** and (*S,S*)-**8** which were then deblocked with strong acidic ion-exchange resin (H^+ form) in methanol to give the two enantiomers of tetraethylene glycol (*R,R*)-**8** and (*S,S*)-**8**.

The separations of racemic organic ammonium perchlorates using new silica gel CSP (*R,R*)-**6** are shown in Fig. 2 [α-(1-naphthyl)ethylamine hydrogen perchlorate salt, NapCH(Me)$NH_3^+ClO_4^-$, **18**]; Fig. 3 [1-phenylethylamine hydrogen perchlorate salt, PhCH(Me)$NH_3^+ClO_4^-$, **19**]; Fig. 4 [methyl phenylalaninate hydrogen perchlorate salt, PhAla$NH_3^+ClO_4^-$, **20**]; and Fig. 5 [methyl phenylglycinate hydrogen perchlorate salt, PhGly$NH_3^+ClO_4^-$, **21**]. These separation studies were carried out in a manner similar to that reported.[22,27] Very concentrated methanol/dichloromethane solutions of the racemic ammonium salts **18**–**21** were placed on a column containing CSP (*R,R*)-**6** and then the enantiomers of the ammonium salts **18**–**21** were eluted with different mixtures of methanol and dichloromethane (see Experimental). We found that among many solvents and solvent mixtures the different ratios of methanol and dichloromethane allowed good separations of enantiomers. The amounts of (*R*)- and (*S*)-salts in each fraction were determined by polarimetry using calibration curves (see Experimental).

Because (*R,R*)-**6** interacts more strongly with (*S*)-salts,[22,27] (*R*)-salts pass through the column first and the (*S*)-salts last as observed in Figs. 2–5. Studies on using other racemic organic ammonium salts and improving separations by the change of solvent systems, loading and flow rates are in progress. The results of these studies will be published later.

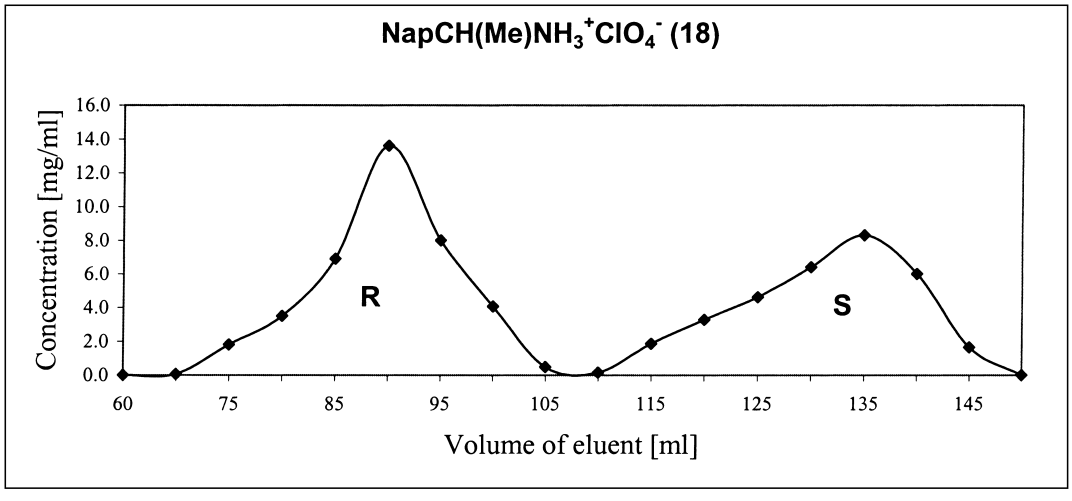


Figure 2.

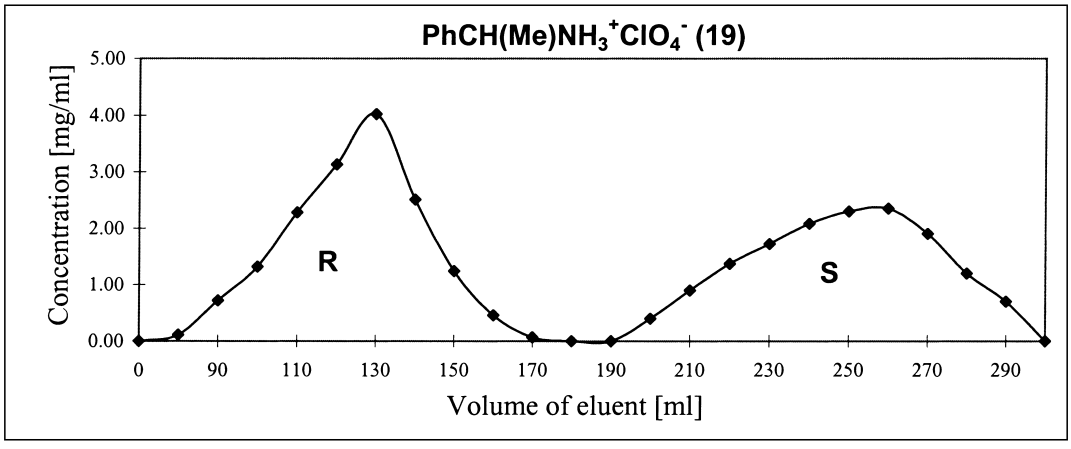


Figure 3.

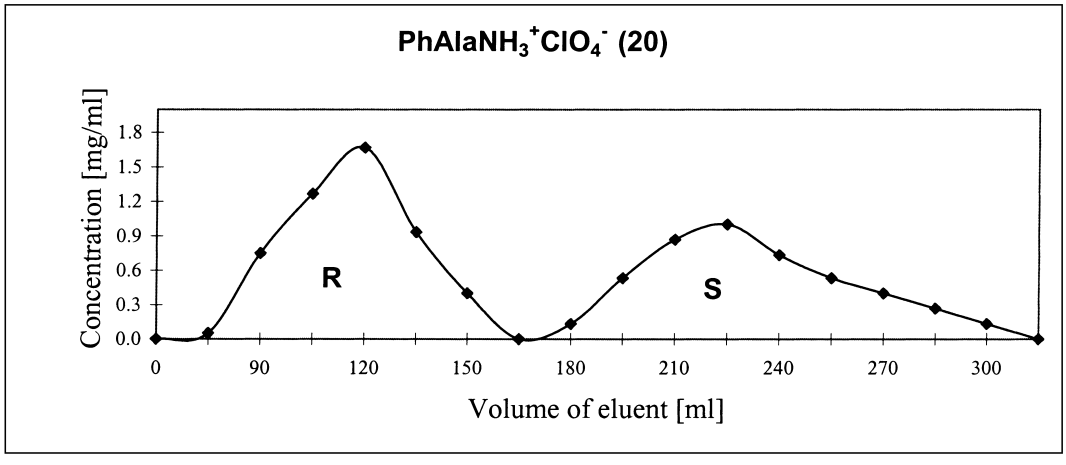


Figure 4.

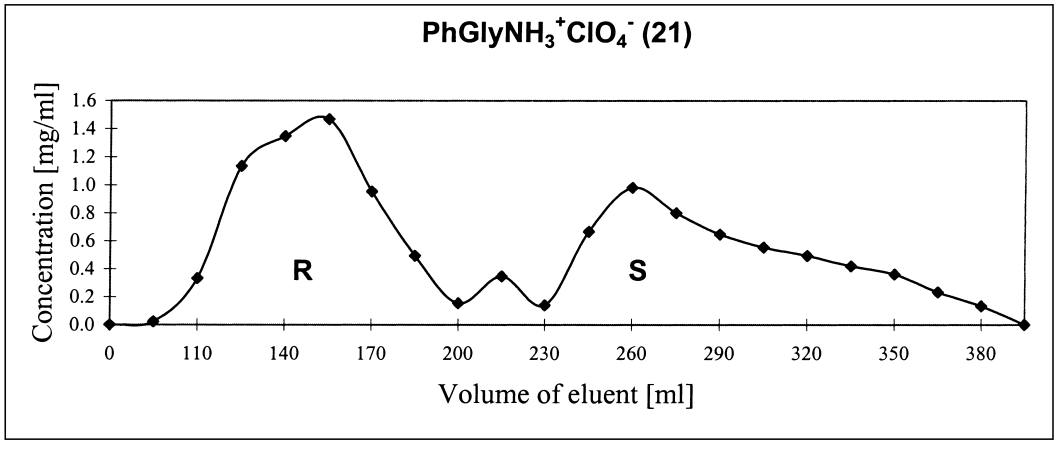


Figure 5.

3. Experimental

3.1. General

Infrared spectra were obtained 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 and ^{1}H (80 MHz) NMR spectra were obtained on a Brucker AW-80 spectrometer in $CDCl_3$ unless otherwise indicated. Molecular weights were determined by a VG-ZAB-2 SEQ reverse geometry mass spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic 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 aluminum oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminum 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[31] methods. Evaporations were carried out under reduced pressure unless otherwise stated.

3.2. Silica gel bound chiral crown (R,R)-6 (Scheme 1)

The hydrosilylation reaction of crown ether (*R,R*)-**7** with triethoxysilane, and the attachment of the resulting triethoxysilyl-derivative (*R,R*)-**10** were carried out in a similar manner as reported by us[22,27] for analogous macrocycles. A mixture of (*R,R*)-**7** (9.0 g, 19.3 mmol) and triethoxysilane (5.5 mL, 4.9 g, 29.0 mmol, freshly distilled under Ar) was stirred vigorously at rt in a 50 mL one-necked flask equipped with a rubber septum. Pt catalyst (SIP 6830.0, ABCR, Karlsruhe, Germany) (10 drops) was added through the rubber septum. After stirring the reaction mixture for 5 days at rt, the ^{1}H NMR spectrum of a small aliquot showed that the olefin protons of (*R,R*)-**7** had disappeared. The volatile compounds were removed from the reaction mixture (0.02 mmHg) giving (*R,R*)-**10** (10.04 g, 96%); ^{1}H NMR (500 MHz) δ 0.77 (t, *J*=8 Hz, 2H), 0.96 (s, 18H), 1.24 (t, *J*=7 Hz, 9H), 1.84 (m, 2H), 3.45–3.67 (m, 12H), 3.61–3.67 (m, 2H), 4.00 (m, 2H), 4.78–4.85 (m, 4H), 6.83 (s, 2H); ^{13}C NMR (125 MHz) δ 18.50, 26.63, 26.74, 34.75, 34.77, 58.64, 69.84, 70.70, 71.10, 72.65, 85.34, 88.77, 148.14, 160.40, 166.40. Triethoxysilyl-derivative (*R,R*)-**10** (10.0 g, 18.5 mmol) was stirred (mechanical stirring) with silica gel (41.0 g Davisil™, grade 646, 35–60 mesh, 150 Å) in toluene (680 mL) at 90°C for 5 days. The silica gel was filtered and washed with 50% toluene in methanol (3×100 mL) and then with methanol (3×100 mL). The filtrate and washings were evaporated to give 1.9 g of unreacted organic material. This means that 8.1 g (17.3 mmol, 90%) of (*R,R*)-**7** was attached to the silica gel. The silica gel containing the bound crown (*R,R*)-**6** was dried in a vacuum oven at 60°C for 3 h. A sample of blank silica gel was dried the same way and it gave a combustion analysis of C, 0.00; H, 0.60; N, 0.00. The combustion analysis of (*R,R*)-**6** gave C, 6.44; H, 1.36; N, 0.59. This means that each gram of (*R,R*)-**6** contained 0.42 mmol (by %C) or 0.43 mmol (by %H) of the chiral crown.

3.3. 19-Allyloxy-(4R,14R)-(+)-4,14-di-tert-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (R,R)-7 (Scheme 1)

To a well stirred suspension of NaH (5.51 g, 138 mmol, 60% dispersion in mineral oil) in THF (90 mL) was added dropwise under Ar at 0°C (*R,R*)-**8** (14.84 g, 48.4 mmol) dissolved in THF (460 mL). The

mixture was stirred at 0°C for 10 min, at rt for 30 min and at reflux temperature for 3 h. The reaction mixture was cooled to −10°C and **9** (24.8 g, 49.2 mmol) dissolved in THF (520 mL) was added dropwise. The resulting mixture was stirred at −10°C for 20 min and then at rt for 4 days. After the reaction had been completed, the solvent was removed. The residue was taken up in a mixture of ether (900 mL), ice (400 g) and water (400 mL). The resulting mixture was mixed well and separated. The aqueous phase was shaken with ether (2×600 mL). The combined organic phase was dried ($MgSO_4$), filtered, and the solvent was removed. The residue was purified by column chromatography on neutral alumina using 1% EtOH in toluene as an eluent to give pure (*R*,*R*)-**7** (12.0 g, 53%) as an oil; R_f=0.55 (silica TLC, 17% EtOH in toluene); $[\alpha]_D^{25}$=+19.2 (*c* 1.223, benzene); IR (neat) ν 2960, 2930, 2900, 2870, 1590, 1575, 1470, 1450, 1440, 1390, 1360, 1330, 1310, 1100, 1030, 980, 910, 850 cm^{-1}; ^1H NMR (500 MHz) δ 0.96 (s, 18H), 3.48–3.55 (m, 12H), 3.63–3.68 (m, 2H), 4.60 (d, *J*=5 Hz, 2H), 4.76–4.86 (m, 4H), 5.32–5.45 (m, 2H), 6.01–6.09 (m, 1H), 6.86 (s, 2H); ^{13}C NMR (125 MHz) δ 26.47, 34.60, 68.50, 70.57, 70.95, 72.50, 74.22, 85.18, 106.70, 118.40, 132.45, 160.40, 165.70; MS (FAB, glycerol matrix) 466 $[M+H]^+$. Anal. calcd for $C_{20}H_{43}NO_6$: C, 67.07; H, 9.31; N, 3.01. Found: C, 66.98; H, 9.34; N, 3.10.

*3.4. 19-Allyloxy-(4*S*,14*S*)-(−)-4,14-di*-tert-*butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (*S,S*)-**7** (Scheme 1)*

Compound (*S*,*S*)-**7** was prepared and purified in the same way as described above for (*R*,*R*)-**7** starting from (*S*,*S*)-**8** (5.57 g, 24.0 mmol) to give (*S*,*S*)-**7** (6.48 g, 57%); $[\alpha]_D^{25}$=−19.0 (*c* 1.15, benzene). All other physical properties and spectral data were identical to those of (*R*,*R*)-**7**. Anal. calcd for $C_{20}H_{43}NO_6$: C, 67.07; H, 9.31; N, 3.01. Found: C, 66.88; H, 9.44; N, 3.15.

*3.5. (*R,R*)-(−)-1,11-Di*-tert-*butyl-3,6,9-trioxaundecane-1,11-diol (*R,R*)-**8** (Scheme 3)*

To a well stirred suspension of NaH (21.6 g, 544 mmol, 60% dispersion in mineral oil) in THF (100 mL) was added dropwise at 0°C and under Ar alcohol (*R*)-**16** (60.4 g, 298 mmol) dissolved in THF (400 mL). The reaction mixture was stirred at 0°C for 10 min, at rt for 20 min and at reflux temperature for 3 h. The reaction mixture was cooled to 0°C and diethylene glycol di-*p*-tosylate **17** (60.0 g, 290 mmol) dissolved in THF (110 mL) was added dropwise. Stirring was continued at 0°C for 10 min then at rt for 4 days. The solvent was removed and the residue was taken up in a mixture of ice (200 g), water (260 mL) and ether (800 mL). The mixture was shaken well and separated. The aqueous phase was extracted with ether (2×300 mL). The combined organic phase was shaken with saturated brine (500 mL), dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (148.2 g) was stirred with Amberlite® IR-120 strong acidic ion-exchange resin (H^+ form, 26.0 g) in methanol (3.2 L) at rt for 18 h. After deblocking had been completed the resin was filtered, washed with methanol (3×30 mL) and the solution was evaporated. The residue was taken up in a mixture of water (140 mL), methanol (560 mL) and hexane (360 mL). The mixture was shaken well and separated. The aqueous methanol phase was extracted with hexane (3×100 mL). The combined hexane phase was shaken with 1:4 (v/v) water:methanol (200 mL). The combined aqueous methanol solution was evaporated. The residue was taken up in toluene (60 mL) and the solvent was removed. The latter procedure was repeated two more times to remove water. The crude product was purified by distillation to give (*R*,*R*)-**8** (30.2 g, 66%); bp: 108–110°C (0.1 mmHg); R_f=0.45 (silica TLC, 9% EtOH in toluene); $[\alpha]_D^{25}$=−38.2 (*c* 2.08, benzene) (lit.[25] $[\alpha]_D^{25}$=+38.0 (*c* 2.08, benzene) for the other enantiomer (*S*,*S*)-**8**). All other physical properties and spectral data were identical to those reported[25] for (*S*,*S*)-**8**.

3.6. (S,S)-(+)-1,11-Di-tert-butyl-3,6,9-trioxaundecane-1,11-diol (S,S)-**8** (Scheme 3)

Compound (*S,S*)-**8** was prepared in the same way as described above for (*R,R*)-**8** starting from (*S*)-**16** (15.1 g, 74.5 mmol). The crude product was purified by distillation to give (*S,S*)-**8** (7.2 g, 65%); bp: 108–110°C (0.1 mmHg); R_f=0.45 (silica TLC, 9% EtOH in toluene); $[\alpha]_D^{25}$=+37.9 (*c* 2.08, benzene) (lit.[25] $[\alpha]_D^{25}$=+38.0 (*c* 2.08, benzene)). All other physical properties and spectral data were identical to those reported.[25]

3.7. 4-Allyloxy-2,6-pyridinedimethyl ditosylate **9** (Scheme 1)

Compound **9** was prepared from 4-allyloxy-2,6-pyridinedimethanol and tosyl chloride using powdered KOH in THF as reported;[27] (yield: 86%), R_f=0.6 (silica gel TLC, 9% 2-butanone in toluene); mp: 80–81°C (MeOH–1,2-dichloroethane) (lit.[27] mp: 79–81°C (MeOH–1,2-dichloroethane)). All other physical properties and spectral data were identical to those reported.[27]

3.8. (±)-2-Hydroxy-3,3-dimethylbutanoic acid **14** (Scheme 2)

Compound **14** was prepared in a similar manner to that reported.[29] The main difference was that we used bromine instead of chlorine. To a stirred mixture of pinacolone (75 mL, 60 g, 0.6 mol) and two drops of concentrated aqueous HBr was added dropwise under Ar in an ice–salt bath bromine (62 mL, 194 g, 0.775 mol). After adding about 70% of the bromine the reaction mixture solidified, so the temperature was increased to 75°C, and the rest of the bromine was added at this temperature. After stirring the reaction mixture at 80°C for another 1 h, 20% aqueous NaOH solution (720 mL) was slowly added. The resulting mixture was stirred overnight, then cooled to 0°C, and the unreacted pinacolone was removed by shaking with ether (300 mL). The pH of the aqueous phase was adjusted with concentrated aqueous HCl to 2, then the solution was shaken with ether (1×600 mL and 3×300 mL). The combined organic phase was dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was recrystallized from 1,2-dichloroethane to give pure **14** (65.0 g, 82%); R_f=0.45 (silica gel TLC, 1:2:7 acetic acid:ethyl acetate:hexane); mp: 86–87°C (lit.[29] mp: 87–88°C (benzene)). All other physical properties and spectral data were identical to those reported.[29]

3.9. (S,R)-(+)-1-Phenylethylammonium 2-hydroxy-3,3-dimethylbutanoate [(R)-**14**-(S)PhCH(Me)NH_2] (Scheme 2)

To a stirred solution of hydroxy acid **14** (51.4 g, 389 mmol) in water (296 mL) was added at 0°C and under Ar (*S*)-1-phenylethylamine (23.6 g, 25 mL, 194.5 mmol). After addition the reaction mixture was refluxed until a clear solution formed, then it was stored at rt for 6 h and in a refrigerator overnight. The crude diastereomeric salt was filtered off, dried and recrystallized five times from water (6 mL of water for each gram of salt) to give optically pure (*R*)-**14**-(*S*)-PhCH(Me)NH_2 salt (12.5 g, 12%); mp: 147–149°C; $[\alpha]_D^{25}$=+18.2 (*c* 2.01, ethanol); IR (KBr) ν 3650–2400 (broad), 1700, 1670, 1630, 1600, 1540, 1500, 1400, 1300, 1200, 1060, 1000, 750, 735, 680 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 0.88 (s, 9H), 1.46 (d, *J*=6 Hz, 3H), 3.23 (s, 1H), 4.30 (q, *J*=6 Hz, 1H), 7.17 (s, disappeared in D_2O, 4H), 7.38–7.59 (m, 5H). Instead of racemic hydroxy acid **14**, the partially resolved **14** which was later recovered from the mother liquors (THF) of recrystallization of (*S*)-**14**-(*S*)-PhCH(Me)NH_2 (see below) can also be used.

3.10. (S,S)-(−)-1-Phenylethylammonium 2-hydroxy-3,3-dimethylbutanoate [(S)-**14**-(S)-PhCH(Me)NH_2] (Scheme 2)

To a stirred solution of hydroxy acid **14** (25.7 g, 195 mmol) in THF (400 mL) was added at 0°C and under Ar (*S*)-1-phenylethylamine (23.6 g, 25 mL, 195 mmol). After addition the reaction mixture was refluxed until a clear solution formed, then it was stored at rt for 6 h and in a refrigerator overnight. The crude diastereomeric salt was filtered off, dried and recrystallized from THF (35 mL of THF for each gram of salt) to give optically pure (*S*)-**14**-(*S*)-PhEtNH_2 (18.0 g, 35%); mp: 170–172°C (lit.[30] mp: 171–172°C (ethanol–ether)); $[\alpha]_D^{25}$=−30.9 (*c* 2.0, ethanol) (lit.[30] $[\alpha]_D^{20}$=−33.1 (*c* 2.00, ethanol)). Instead of racemic hydroxy acid **14**, the partially resolved **14** which was later recovered from the aqueous mother liquors of recrystallization of (*R*)-**14**-(*S*) PhEtNH_2 (see above) can also be used. All other physical properties and spectral data were identical to those reported.[30]

3.11. (R)- and (S)-2-Hydroxy-3,3-dimethylbutanoic acid (R)-(−)-(**14**), (S)-(+)-(**14**) (Scheme 2)

To a well stirred mixture of optically pure diastereomeric salt (*R*)-**14**-(*S*)-PhEtNH_2 or (*S*)-**14**-(*S*)-PhEtNH_2 (50.2 g, 198.2 mmol), ether (500 mL) and water (70 mL) was added dropwise at 0°C 3 M aqueous HCl until the pH of the aqueous phase remained 2 (about 65 mL). The phases were separated and the aqueous one was extracted with ether (2×150 mL). The combined organic phase was shaken with saturated brine (500 mL), dried ($MgSO_4$), filtered and the solvent was removed. The crude acids were recrystallized from isopropyl ether–hexane to give pure (*R*)-(−)-**14** (24.7 g, 94%) or (*S*)-(+)-**14** (23.3 g, 89%); mp: 53–54°C for (*R*)-**14** and 52–53°C for (*S*)-**14** (lit.[30] mp: 51–52°C for (*S*)-**14**); $[\alpha]_D^{25}$=4.3 (*c* 4.0, water) for (*R*)-**14** or $[\alpha]_D^{25}$=+4.3 (*c* 4.0, water) for (*S*)-**14** (lit.[30] $[\alpha]_D^{25}$=+4.45 (*c* 4.0, water) for (*S*)-**14**).

For recovering the resolving agent (*S*)-PhCH(Me)NH_2, the aqueous solution containing (*S*)-PhCH(Me)$NH_3^+Cl^-$ was made basic with 20% aqueous NaOH and it was extracted with ether (1×400 mL and 2×100 mL). The combined organic phase was shaken with saturated brine (2×300 mL), dried ($MgSO_4$) and the solvent was removed. The residue was purified by distillation (bp: 71–73°C (12 mmHg)) (lit.[32] bp: 73°C (12 mmHg)) to give pure (*S*)-PhCH(Me)NH_2 (21–22 g, 88–92%); $[\alpha]_D^{22}$=−40.2 (neat) (lit.[32] $[\alpha]_D^{22}$=−40.3 (neat)).

3.12. Tetrahydropyranyl 2-(R)-(+)-(tetrahydropyranyloxy)-3,3-dimethylbutanoate (R)-**15** (Scheme 3)

To a well stirred mixture of (*R*)-**14** hydroxy acid (44.3 g, 0.335 mol) and dihydropyran (DHP) (98 mL, 90 g, 1.07 mol) was added in an ice–salt bath and under Ar pyridinium *p*-toluenesulfonate (PPTS) catalyst (3.0 g) and one drop of pyridine. After stirring the reaction mixture in the ice–salt bath for 10 min and at rt for 1 day, the excess DHP was evaporated. The residue was taken up in a mixture of CH_2Cl_2 (500 mL), ice (100 g) and water (100 mL). The phases were mixed well and separated. The organic phase was shaken with water (2×50 mL), dried ($MgSO_4$), filtered and the solvent was removed to give crude (*R*)-**15** (100.0 g, 99%), which was used without further purification; R_f=0.8, 0.9 (silica gel TLC, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25}$=+11.3 (*c* 2.17, THF); IR (neat) ν 2970, 2920, 2890, 2870, 1730, 1490, 1440, 1400, 1370, 1280, 1220, 1170, 1120, 1030, 980, 940, 900, 880, 820 cm^{-1}; ^1H NMR (80 MHz) δ 0.90 (s, 4.5H), 0.98 (s, 4.5H), 1.16–2.00 (m, 12H), 3.28–4.03 (m, 5H), 4.63–4.82 (m, 1H), 5.95–6.03 (m, 1H).

3.13. Tetrahydropyranyl 2-(S)-(−)-(tetrahydropyranyloxy)-3,3-dimethylbutanoate (S)-**15** (Scheme 3)

Compound (*S*)-**15** was prepared in the same way as described above for (*R*)-**15** starting from (*S*)-**14** (15.7 g, 119 mmol). The crude (*S*)-**15** (35.4 g, 99%) was used without further purification; R_f=0.8, 0.9

(silica gel TLC, 25% ethyl acetate in toluene); $[\alpha]_D^{25}=-30.1$ (*c* 2.1, THF); IR (neat) ν 2980, 2930, 2880, 2860, 1730, 1480, 1450, 1410, 1360, 1270, 1210, 1180, 1130, 1030, 1010, 990, 950, 910, 870, 810 cm^{-1}; ^1H NMR (80 MHz) δ 0.96 (s, 4.5H), 1.04 (s, 4.5H), 1.21–1.98 (m, 12H), 3.36–4.05 (m, 5H), 4.52–4.71 (m, 1H), 5.98–6.06 (m, 1H).

*3.14. 2-(*R*)-(+)-(Tetrahydropyranyloxy)-3,3-dimethylbutanol (*R*)-**16** (Scheme 3)*

To a well stirred suspension of $LiAlH_4$ (19.0 g, 500 mmol) in ether (350 mL) under Ar at 0°C was slowly added (*R*)-**15** (100.6 g, 335 mmol) dissolved in ether (300 mL). The mixture was stirred at 0°C for 30 min, at rt for 10 min, and at reflux temperature for 48 h. When the reduction had been completed, the mixture was cooled in an ice–salt bath and saturated NH_4Cl (19 mL) and 5% NaOH solution (38 mL) were added very slowly. The resulting mixture was stirred at rt for 4 h, at reflux temperature for 14 h and at rt again for 6 h. The precipitate was filtered and washed with ether (3×30 mL). The filtrate and washings were combined and shaken with 5% aqueous Na_2CO_3 solution (1×50 mL) and water (3×100 mL) to remove pentane-1,5-diol. The ethereal solution was shaken with saturated brine, dried ($MgSO_4$), filtered and the solvent was removed. The crude product was purified by distillation to give (*R*)-**16** (61.0 g, 90%); bp: 64–66°C (0.2 mmHg); R_f=0.5, 0.3 (silica TLC, 9% 2-butanone in toluene); $[\alpha]_D^{25}=+14.6$ (*c* 3.0, THF); IR (neat) ν 3450 (broad), 2970, 2960, 2940, 2890, 2870, 1490, 1440, 1400, 1370, 1270, 1170, 1130, 1080, 1020, 1000, 980, 920, 900, 870, 800 cm^{-1}; ^1H NMR (80 MHz) δ 0.92 (s, 4.5H), 0.99 (s, 4.5H), 1.35–1.91 (m, 6H), 2.83 (broad s, disappeared with D_2O, 1H), 3.05–4.01 (m, 5H), 4.43–4.68 (m, 1H).

*3.15. 2-(S)-(−)-(Tetrahydropyranyloxy)-3,3-dimethylbutanol (S)-**16** (Scheme 3)*

Compound (*S*)-**16** was prepared in the same way as described above for (*R*)-**16** starting from (*S*)-**15** (35.4 g, 119 mmol). The crude product was purified by distillation to give (*S*)-**16** (20.6 g, 86%); bp: 64–66°C (0.2 mmHg); R_f=0.5, 0.3 (silica TLC, 9% 2-butanone in toluene); $[\alpha]_D^{25}=-14.5$ (*c* 3.0, THF); IR (neat) ν 3540 (broad), 3010, 2990, 2970, 2940, 2890, 2870, 1480, 1440, 1390, 1330, 1270, 1200, 1170, 1130, 1110, 1070, 1020, 1000, 950, 920, 900, 870, 850, 800 cm^{-1}; ^1H NMR (80 MHz) δ 0.95 (s, 4.5H), 1.04 (s, 4.5H), 1.28–1.97 (m, 6H), 2.45 (broad s, disappeared with D_2O, 1H), 3.11–4.21 (m, 5H), 4.28–4.98 (m, 1H).

*3.16. (R)-(+) and (S)-(−) enantiomers of $NapCH(Me)NH_3^+ClO_4^-$ **18***

The preparation of (*R*)-(+) and (*S*)-(−) enantiomers of **18** was described earlier[23]; R_f=0.8 (silica TLC, 9% MeOH in CH_2Cl_2); (*R*)-(+)-**18**, mp: 184–185°C (lit.[27] 184–185°C); $[\alpha]_{365}^{25}=+21.3$ (*c* 1.0, ethanol) (lit.[27] $[\alpha]_{365}^{22}=+21.3$ (*c* 1.0, ethanol)); (*S*)-(−)-**18**, mp: 184–185°C (lit.[27] 183–184°C); $[\alpha]_{365}^{25}=-21.25$ (*c* 1.0, ethanol) (lit.[27] $[\alpha]_{365}^{22}=-21.1$ (*c* 1.0, ethanol)).

*3.17. (R)-(+) and (S)-(−) enantiomers of $PhCH(Me)NH_3^+ClO_4^-$ **19***

The preparation of (*R*)-(+) and (*S*)-(−) enantiomers of **19** was described earlier.[23] Pure (*R*)-(+) and (*S*)-(−) enantiomers of **19** were obtained by recrystallization from EtOAc:CCl_4 (1:1) (v/v) mixture; R_f=0.7

(silica TLC, 16% MeOH in CH_2Cl_2); (*R*)-(+)-**19**, mp: 96–97°C; $[\alpha]_{365}^{22}$=+16.4 (*c* 1.0, ethanol); (*S*)-(−)-**19**, mp: 96–97°C; $[\alpha]_{365}^{25}$=−16.3 (*c* 1.0, ethanol); IR (KBr) ν 3180, 3080, 2980, 2880, 1640, 1600, 1500, 1450, 1380, 1230, 1150, 1120, 1100, 1030, 760, 700, 630 cm^{-1}; ^1H NMR (80 MHz) δ 2.97 (d, *J*=6 Hz, 3H), 2.81–3.17 (m, 1H), 7.30 (broad s, 3H), 7.82 (broad s, 5H).

*3.18. (R)-(−) and (S)-(+) enantiomers of $PhAlaNH_3^+ClO_4^-$ **20***

The preparation of (*R*)-(−) and (*S*)-(+) enantiomers of **20** was described earlier.[23] Pure (*R*)-(−) and (*S*)-(+) enantiomers of **20** were obtained by recrystallization from an acetonitrile–$CHCl_3$ mixture; R_f=0.55 (silica TLC, 10% MeOH in CH_2Cl_2); (*R*)-(−)-**20**, mp: 173–175°C; $[\alpha]_{365}^{25}$=−86.3 (*c* 1.0, ethanol); (*S*)-(+)-**20**, mp: 175–176°C; $[\alpha]_{365}^{25}$=+86.7 (*c* 1.0, ethanol); IR (KBr) ν 3200, 3180, 3120, 3080, 2950, 2850, 2830, 2680, 2600, 2000, 1730, 1600, 1580, 1570, 1560, 1500, 1460, 1430, 1370, 1350, 1300, 1250, 1150, 1120, 1080, 1030, 1020, 950, 870, 850, 790, 750, 700, 630 cm^{-1}; ^1H NMR (80 MHz, DMSO) δ 3.0–3.4 (m, 2H), 3.71 (s, 3H), 4.15–4.51 (m, 1H), 7.0–7.5 (m, 5H), 8.46 (broad s, 3H).

*3.19. (R)-(−) and (S)-(+) enantiomers of $PhGlyNH_3^+ClO_4^-$ **21***

The (*R*)-(−) and (*S*)-(+) enantiomers of **21** were prepared in the same way as described for (*R*)-(+) and (*S*)-(−)-**20**,[23] starting from 2.00 g (13.23 mmol) of (*R*)-(−) and (*S*)-(+) methyl phenylglycinate. Pure (*R*)-(−) and (*S*)-(+) enantiomers of **21** were obtained by recrystallization from a MeOH–$CHCl_3$ mixture. Yields were 2.97 g (84%) for (*R*)-**21** and 3.07 g (87%) for (*S*)-**21**; R_f=0.4 (silica TLC, 4% MeOH in CH_2Cl_2); (*R*)-(−)-**21**, mp: 118–119°C; $[\alpha]_{365}^{25}$=−90.4 (*c* 1.0, ethanol); (*S*)-(+)- **21**, mp: 120–121°C; $[\alpha]_D^{25}$=+89.85 (*c* 1.0, ethanol); IR (KBr) ν 3180, 3120, 3110, 3080, 3000, 2810, 2680, 2600, 2000, 1720, 1600, 1500, 1460, 1430, 1370, 1300, 1150, 1120, 1100, 1030, 1020, 980, 870, 850, 740, 710, 640 cm^{-1}; ^1H NMR (80 MHz, DMSO) δ 3.73 (s, 3H), 5.31 (s, 1H), 7.5 (s, 5H), 8.92 (broad s, 3H).

*3.20. General procedure for separation of racemic ammonium salts **18–21***

The racemic salt (the amount is indicated in Table 2) was dissolved in 2 mL of the eluent (see Table 2) and was placed onto the top of a column containing 48.0 g of (*R*,*R*)-**6** and eluted with the MeOH–CH_2Cl_2 mixture (see Table 2). The amount of salt was weighed in each 4 mL fraction after evaporation of the solvent. Then the dry salt was dissolved in such a volume of methanol that the concentration of the solution was about 5 mg/mL and the optical rotation was measured. Earlier, a calibration curve was made using methanol as a solvent and the amounts of the enantiomers were calculated relying upon this curve.

The calculated concentrations of (*R*)-(**18**–**21**) and (*S*)-(**18**–**21**) were plotted versus the mL of eluents as shown in the smooth surfaces in Figs. 2–5.

Acknowledgements

Financial support by the Hungarian Scientific Research Fund (OTKA T-14942 and T-25071) and the Office of Naval Research (USA) is gratefully acknowledged.

Table 2
Conditions for chromatographic separation of racemic ammonium salts

	Amount of racemate [mg]	Eluent [MeOH/CH_2Cl_2] (v/v)	Flow rate [mL/min]
(*RS*)-**18**	500	1/7	0.60
(*RS*)-**19**	300	1/20	0.40
(*RS*)-**20**	170	1/30	0.30
(*RS*)-**21**	200	1/35	0.30

References

1. *Chromatographic Chiral Separations*; Zief, M.; Crane, L. J., Eds.; Marcel Dekker: New York, 1988.
2. *Chiral Separations by HPLC: Applications to Pharmaceutical Compounds*; Krstulovic, A. M., Ed.; Ellis Horwood: Chichester, 1989.
3. *Recent Advances in Chiral Separations*; Stevenson, D.; Wilson, I. D., Eds.; Plenum: New York, 1991.
4. Francotte, E.; Junker-Buchheit, A. *J. Chromatogr. Biomed. Appl*. **1992**, *576*, 1.
5. Allenmark, S. G. *Chromatographic Enantioseparations: Methods and Applications*, 2nd ed.; Ellis Horwood: New York, 1993.
6. *A Practical Approach to Chiral Separations by Liquid Chromatography*; Subramanian, G., Ed.; VCH: Weinheim, 1994.
7. Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev*. **1989**, *89*, 347.
8. Berthod, A.; Chang, S.-C.; Armstrong, D. W. *Anal. Chem*. **1992**, *64*, 395.
9. Sousa, L. R.; Sogah, G. D. Y.; Hoffman, D. H.; Cram, D. J. *J. Am. Chem. Soc*. **1978**, *100*, 4569.
10. Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc*. **1979**, *101*, 3035.
11. Udvarhelyi, P. M.; Sunter, D. C.; Watkins, J. C. *J. Chromatogr*. **1990**, *519*, 69.
12. Hilton, M.; Armstrong, D. W. *J. Liq. Chromatogr*. **1991**, *14*, 9.
13. Esquivel, B.; Nicholson, L.; Peerey, L.; Fazio, M. *J. High Resolut. Chromatogr*. **1991**, *14*, 816.
14. Aboul-Enien, H. Y.; Bakr, S. A.; Islam, M. R.; Rothchild, R. *J. Liq. Chromatogr*. **1991**, *14*, 3475.
15. Hilton, M.; Armstrong, D. W. *J. Liq. Chromatogr*. **1991**, *14*, 3673.
16. Kersten, B. S. *J. Liq. Chromatogr*. **1994**, *17*, 33.
17. Walbroehl, Y.; Wagner, J. *J. Chromatogr. A* **1994**, *680*, 253.
18. Walbroehl, Y.; Wagner, J. *J. Chromatogr. A* **1994**, *685*, 321.
19. Vaccher, C.; Berthelot, P.; Debaert, M. *J. Chromatogr*. **1995**, *715*, 361.
20. Lin, S.; Maddox, N. J. *J. Liq. Chromatogr*. **1995**, *18*, 1947.
21. Gimenez, F.; Soursac, M.; Farinotti, R. *Chirality* **1997**, *9*, 150.
22. Huszthy, P.; Bradshaw, J. S.; Bordunov, A. V.; Izatt, R. M. *ACH-Models in Chemistry* **1994**, *131*, 445.
23. Izatt, R. M.; Wang, T.-M.; Hathaway, J. K.; Zhang, X.-X.; Curtis, J. C.; Bradshaw, J. S.; Zhu, C.-Y.; Huszthy, P. *J. Inclusion Phenom. Mol. Recognit. Chem*. **1994**, *17*, 157.
24. Zhang, X.-X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev*. **1997**, *97*, 3133.
25. Huszthy, P.; Bradshaw, J. S.; Zhu, C.-Y.; Izatt, R. M.; Lifson, S. *J. Org. Chem*. **1991**, *56*, 3330.
26. Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C.-Y.; Dalley, N. K.; Izatt, R. M.; Lifson, S. *J. Org. Chem*. **1990**, *55*, 3129.
27. Bradshaw, J. S.; Huszthy, P.; Wang, T.-M.; Zhu, C.-Y.; Nazarenko, A. Y.; Izatt, R. M. *Supramolecular Chemistry* **1993**, *1*, 267.
28. Horváth, G.; Rusa, C.; Köntös, Z.; Gerencsér, J.; Huszthy, P. *Synth. Commun*., in press.
29. Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem*. **1991**, *56*, 2499.
30. Masamune, S.; Reed, L. A.; Davis, J. T.; Choy, W. *J. Org. Chem*. **1983**, *48*, 4441.
31. Riddick, J. A.; Burger, W. B. *Organic Solvents in Techniques of Organic Chemistry*, 3rd ed.; Weissberger, A., Ed.; Wiley-Interscience: New York, 1970; Vol. II.
32. Theilacker, W.; Winkler, H.-G. *Chem. Ber*. **1954**, *87*, 690.