Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4573–4583

TETRAHEDRON:
ASYMMETRY

Chromatographic enantioseparation of racemic α-(1-naphthyl)-ethylammonium perchlorate by a Merrifield resin-bound enantiomerically pure chiral dimethylpyridino-18-crown-6 ligand

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Received 27 October 1999; accepted 15 November 1999

Abstract

Three novel chiral pyridino-18-crown-6 ligands (*S*,*S*)-**1**, (*S*,*S*)-**2** and (*S*,*S*)-**3** were prepared and (*S*,*S*)-**1** was attached to a Merrifield resin. The resulting adsorbent (*S*,*S*)-**5** was used as a chiral stationary phase in the chromatographic enantioseparation of racemic α-(1-naphthyl)ethylammonium perchlorate. Also, a new chiral pyridono-18-crown-6 ligand (*S*,*S*)-**6**, used for the synthesis of (*S*,*S*)-**1** and (*S*,*S*)-**2**, was prepared in two different ways.

1. Introduction

Separation of enantiomers is a ubiquitous procedure in organic and analytical chemistry, in drug research and industry. The best method for enantiomeric separation, especially on analytical and semi-preparative scales, is chiral liquid chromatography (CLC), using chiral stationary phases (CSPs), which can be prepared by attaching suitable chiral molecules (chiral selectors) to achiral matrixes such as silica gel or polymeric resins. Among the chiral selectors, homochiral† crown ethers have been used successfully for enantioseparation of racemic organic ammonium salts.[1–13] Homochiral crown ethers have the ability of enantiomeric recognition, i.e. the homochiral crown ether host can differentiate between the enantiomers of the guest (a chiral ammonium salt, for example). Enantiomeric recognition of chiral organic ammonium salts by homochiral crown ethers was first studied by Cram and co-workers.[14]

We have reported the preparation of a number of homochiral pyridino-18-crown-6-type ligands,[15–20] and have thoroughly studied the factors governing their enantioselective complexation abilities with the enantiomers of selected chiral organic primary ammonium salts.[21,22] We have shown that three main

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† Homochiral means single pure enantiomer throughout.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00515-7

non-covalent intermolecular forces are responsible for the different stability of the complexes formed by homochiral pyridino-crown ethers and the selected chiral organic ammonium salts containing an aryl group: the tripod-like hydrogen bonding between the pyridine nitrogen and two alternate oxygens in the macro ring of the crown ether host and the three protons of the ammonium salt guest; the π–π stacking between the pyridine unit of the host and the aromatic ring of the ammonium salt guest; and the steric hindrance between certain hydrogens of the host and the guest.[21,22] When both partners are chiral these interactions, especially steric hindrance, are different in the two diastereomeric complexes. These differences result in enantioselectivity and if of sufficient magnitude, may provide the possibility that these homochiral crown ether hosts can be used for the separation of enantiomers of chiral organic ammonium salt guests by CLC.

In the late 1970s, Cram and co-workers reported their pioneering work on the attachment of substituted bis(dinaphthyl)-22-crown-6 ligands to both silica gel[1] and a polymer resin.[2] Using these CSPs they separated several racemic organic ammonium salts, mainly protonated amino acid esters.[1,2]

A few years ago, we attached dimethyl- and diphenyl-substituted chiral pyridino-18-crown-6 ligands to silica gel, and it was shown that these CSPs separated racemic α-(1-naphthyl)ethylammonium perchlorate (NEA).[15] Recently, we attached a homochiral di-*tert*-butylpyridino-18-crown-6 ligand to silica gel and enantiomers of selected racemic ammonium perchlorates were efficiently separated on this CSP.[23]

In continuation of our studies on developing novel CSPs capable of resolving racemic organic ammonium salts by CLC, we report here the preparation of a new homochiral pyridino-18-crown-6 ligand (*S,S*)-**1** and its attachment to Merrifield polymer resin by a covalent bond (see Fig. 1). The resulting adsorbent (*S,S*)-**5** was used as a CSP in the enantioseparation of racemic NEA. The advantage of this Merrifield-type resin based CSP is its high chemostability, which permits its application even under hard conditions (for example, using nucleophilic solvents and strong acidic or basic conditions).

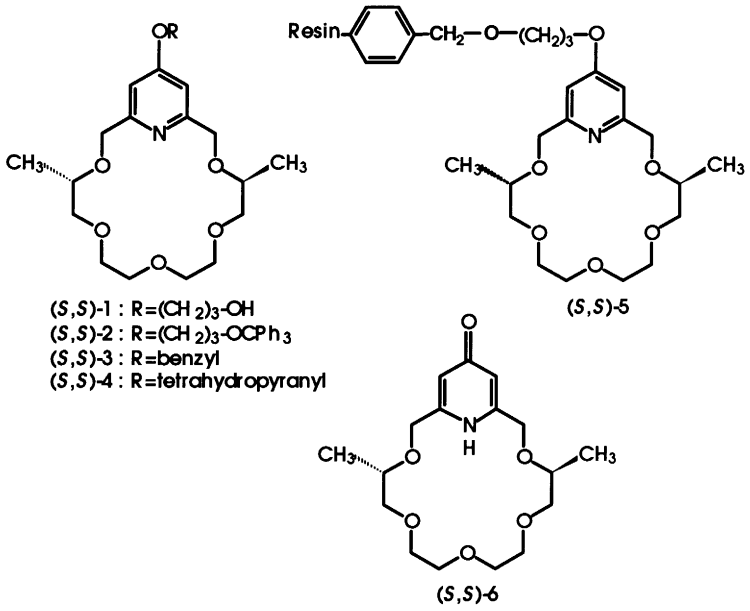
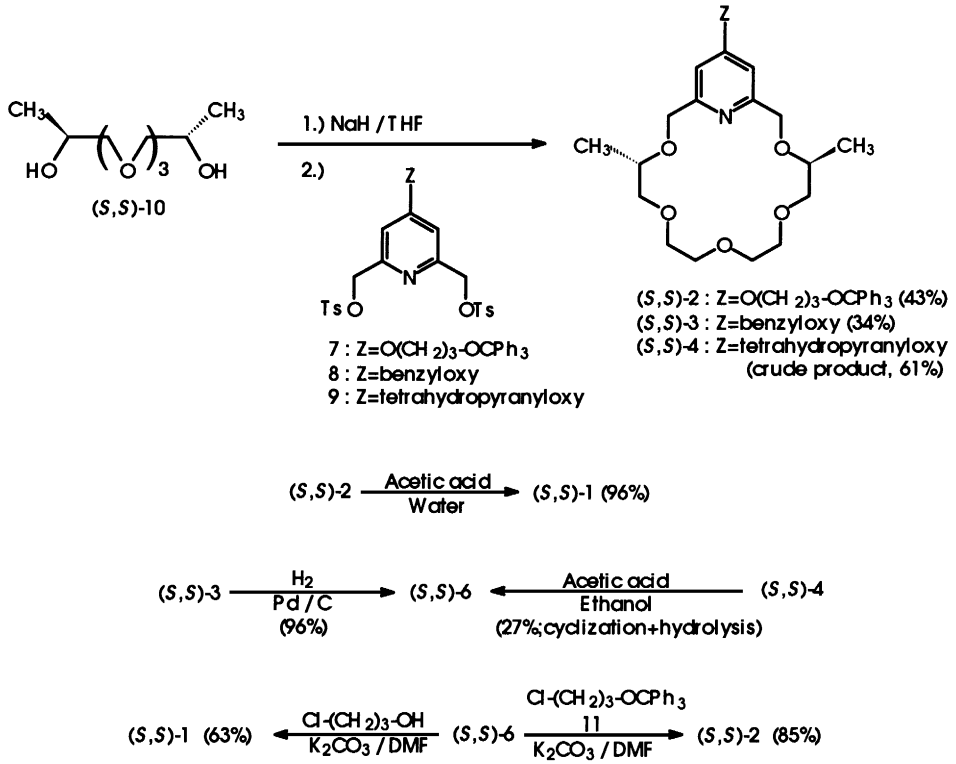


Fig. 1. Structures of the new chiral pyridino- and pyridono-18-crown-6 ligands and the modified Merrifield resin

In this paper we describe three ways for the preparation of ligand (*S,S*)-**1**, report the synthesis of a new proton-ionizable pyridono-crown compound (*S,S*)-**6** and also two other new pyridino-crown compounds,

with a benzyloxy (*S,S*)-**3** and a 3-trityloxypropyloxy group (*S,S*)-**2** at position 4 of the pyridine ring (see Fig. 1 and Scheme 1). Pyridono-crown (*S,S*)-**6** was transformed by regioselective alkylation with 3-chloropropan-1-ol and 1-chloro-3-trityloxypropane **11** into (*S,S*)-**1** and (*S,S*)-**2**, respectively, opening an alternative way for the preparation of 4-alkoxy-substituted pyridino-18-crown-6 ligands (see Scheme 1).



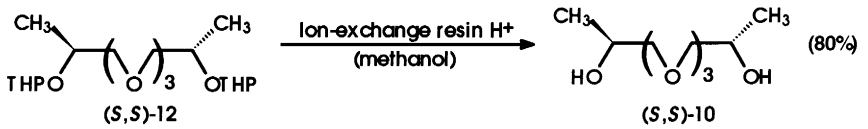
Scheme 1. Preparation of new chiral macrocycles

2. Results and discussion

All new crown compounds were prepared by the Williamson-type ether synthesis by reacting 4-substituted-2,6-pyridinedimethanol-bis(4-methyl-benzenesulphonate) **7**, **8**,[24] **9**[24] and the enantiomerically pure α,ω-dimethyl-substituted tetraethylene glycol (*S,S*)-**10**[25] to give ligands (*S,S*)-**2**, (*S,S*)-**3**, and (*S,S*)-**4**. Crude products were purified by Al_2O_3 column chromatography. Protecting groups were removed either by treatment with acetic acid in a water–ethanol mixture [in the case of (*S,S*)-**2** and (*S,S*)-**4**], which removes both trityl and tetrahydropyranyl moieties allowing the formation of (*S,S*)-**1** and (*S,S*)-**6**, respectively, or catalytic hydrogenation [in the case of (*S,S*)-**3**] to give (*S,S*)-**6** (Scheme 1).

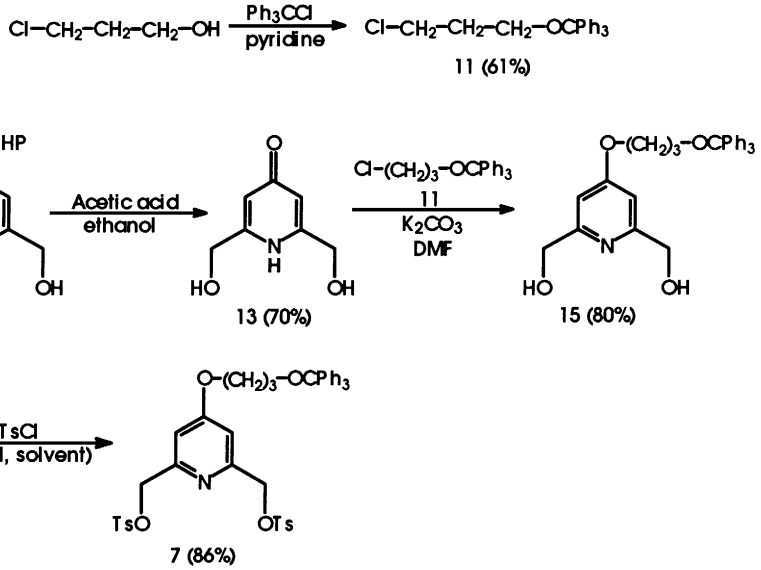
Enantiomerically pure (*S,S*)-**10** was prepared as reported[25] except that (*S,S*)-**12**[25] was deblocked by an acidic ion-exchange resin which increased the yield and purity of (*S,S*)-**10** (Scheme 2).

There is a method reported in the literature[26] for the synthesis of pyridonedimethanol **13** (the starting material for ditosylate **7**), but it has only been characterized by its ^{1}H NMR spectrum. Now we describe a different method for deprotection of 4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,6-pyridinedimethanol **14**[27] and fully characterize the product (Scheme 3). A band at 1640 cm^{-1} in the IR spectrum for compound **13**



Scheme 2. Preparation of chiral tetraethylene glycol (*S*,*S*)-**10**

is indicative of the pyridone carbonyl function[27–29] and compound **13** also has a singlet at δ=6.32 ppm in its ^{1}H NMR spectrum indicative of the two olefinic protons in a pyridone ring.[27–29]



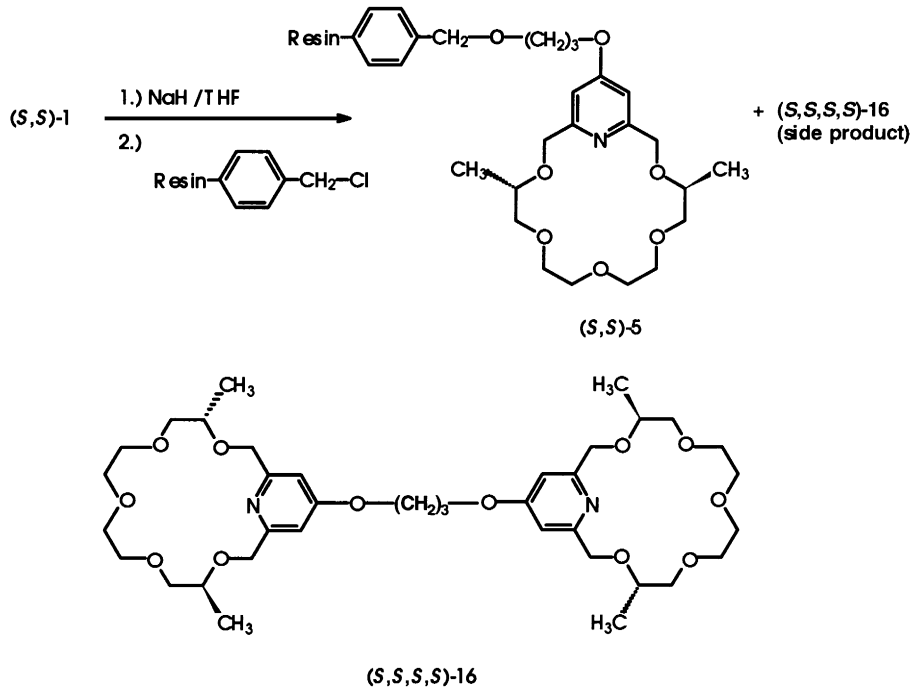
Scheme 3. Preparation of ditosylate **7**

Reaction of trityl chloride with 3-chloropropan-1-ol in pyridine gave ether **11**, which is a useful reagent for the formation of a suitable linker for macrocycle (*S*,*S*)-**1**. With the sixth atom provided by the chloromethyl group of the resin, the tether is a six-membered chain. Treatment of **13** with **11** in DMF, in the presence of potassium carbonate gave diol **15** in a good yield (Scheme 3). The disappearance of the band at 1640 cm^{-1} in the IR spectrum and the singlet at δ=6.32 ppm in the ^{1}H NMR (both for **13**), together with the appearance of the band at 1605 cm^{-1} in the IR spectrum of **15**, and a singlet at δ=6.72 ppm in the ^{1}H NMR spectrum are confirmative of the 4-alkoxypyridine system of **15**.[15,16,23,27] Diol **15** was reacted with tosyl chloride in tetrahydrofuran using finely powdered potassium hydroxide as a base to produce ditosylate **7** by the method well established in our laboratories[15–19,29] (Scheme 3).

We found another route for the production of 4-alkoxy-substituted-pyridino-18-crown-6 compounds by the alkylation of the pyridono ligands. Reaction of (*S*,*S*)-**6** with 3-chloropropan-1-ol and **11**, respectively, resulted in the formation of two macrocycles identical with (*S*,*S*)-**1** and (*S*,*S*)-**2** (Scheme 1). Similar to the alkylation of **13**, no *N*-alkyl product was detectable in the ^{1}H NMR spectrum of the crude products.

Attachment of the homochiral dimethylpyridino-18-crown-6 ligand (*S*,*S*)-**1** to the Merrifield resin is shown in Scheme 4. Ligand (*S*,*S*)-**1** was treated with sodium hydride and the resulting alkoxide was reacted with the chloromethyl groups of the resin. Because of the heterogenous phase conditions, the reaction was quite slow and reasonable conversion required a long time. According to elemental analysis the resin contained 0.56 mmol ligand/g. From the liquid phase, a new bis-crown compound, (*S*,*S*,*S*,*S*)-**16**, was isolated and its structure was determined by NMR, IR and MS spectroscopy and elemental analysis. This compound could be formed by nucleophilic attack of the alkoxide of (*S*,*S*)-**1** at position 4 of the

pyridine ring of another (*S*,*S*)-**1** molecule, followed by the release of 1,3-propanediol. The rate of the latter reaction is comparable to that with the chloromethyl groups of the resin, since the amount of dimer (*S*,*S*,*S*,*S*)-**16** was relatively large, and no monomer [(*S*,*S*)-**1**] was present in the recovered product.



Scheme 4. Attachment of the homochiral dimethylpyridino-18-crown-6 ligand (*S*,*S*)-**1** to Merrifield resin

The chromatographic resolution of NEA on CSP (*S*,*S*)-**5** is shown in Fig. 2. The separation experiments were carried out in a manner similar to that reported.[15,23] A concentrated solution of racemic NEA was placed on the column and eluted with different solvent mixtures. A mixture of methanol:acetonitrile (1:5) provided proper concentration of fractions and reduced tailing. The amount of (*R*)- and (*S*)-salts in each fraction was determined by polarimetry using calibration curves.[23] As shown in Fig. 2, (*S*)-NEA passes through the column faster because of the lower stability of the homochiral complex formed by (*S*,*S*)-**1** and (*S*)-NEA[21] (see Fig. 2).

3. Conclusions

The results obtained here show that the new chiral pyridino-18-crown-6 ligands (*S*,*S*)-**2**, (*S*,*S*)-**3** and (*S*,*S*)-**4** containing 3-trityloxypropyloxy, benzyloxy and tetrahydropyranyloxy groups at position 4 of the pyridine ring can be prepared with reasonable yields from the appropriate 4-substituted 2,6-pyridinedimethanol ditosylates and the chiral dimethyl-substituted tetraethylene glycol using NaH as a base in THF. Removal of the protecting groups from (*S*,*S*)-**3** and (*S*,*S*)-**4** resulted in the novel pyridono-crown (*S*,*S*)-**6** which was transformed by regioselective *O*-alkylation with 3-chloropropan-1-ol into the new pyridino-ligand (*S*,*S*)-**1** containing the 3-hydroxypropyloxy chain at position 4 of the pyridine ring. Deblocking the trityl group of (*S*,*S*)-**2** also resulted in the formation of (*S*,*S*)-**1** which was attached covalently to the Merrifield resin by an ether bond, and this novel CSP almost completely separated the enantiomers of racemic NEA by column chromatography.

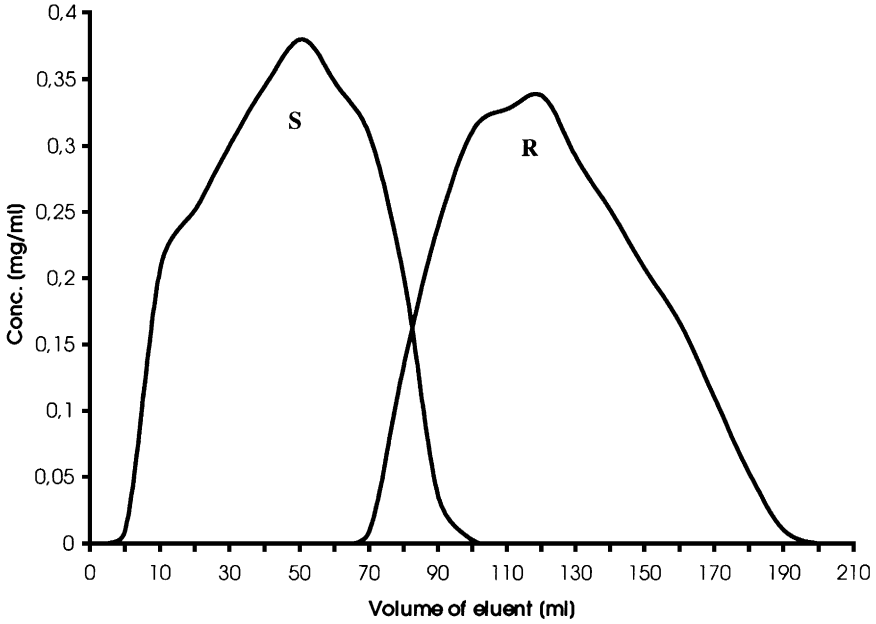


Fig. 2. A smoothed curve showing the separation of (*R*)- and (*S*)-NEA on (*S,S*)-**5** using 5:1 methanol:acetonitrile as an eluent (for details, see the Experimental section)

4. Experimental

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 rotation of both enantiomers of menthol. ^{1}H (500 MHz) and ^{13}C (125 MHz) spectra were taken on a Bruker DRX-500 Avance 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 are 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 (70–200 mesh, Merck) were used for column chromatography. Solvents were dried and purified according to well established methods.[30] Evaporations were carried out under reduced pressure unless otherwise stated.

*4.1. (4*S*,14*S*)-(+)-19-(3-Hydroxypropyloxy)-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo-[15.3.1]heneicosa-1(21),17,19-triene (*S,S*)-**1**

A mixture of (*S,S*)-**2** (9.4 g, 14.6 mmol, see below), glacial acetic acid (175 mL) and water (60 mL) was stirred at 80°C for 90 min. After the reaction was completed the solvents were evaporated and traces of acetic acid were removed by repeated distillation of toluene from the residue. The remaining oil was triturated with water (60 mL) and crystals of triphenylmethanol were filtered off, and washed with water (3×20 mL). Filtrate and washings were evaporated and the residual oil was dried by repeated distillation of benzene to give (*S,S*)-**1** (5.6 g, 96%) as a colourless oil; $[\alpha]_D^{25}$=+17.9 (*c* 0.695, CH_2Cl_2); IR (film) ν_{max} 3650, 3000, 2980, 2970, 2950, 2930, 2860, 1640, 1620, 1600, 1570, 1470, 1380, 1350, 1250, 1100,

1050, 800 cm^{-1}; ^1H NMR δ 1.15 (d, 6H, *J*=6 Hz), 2.03 (quin, 2H, *J*=6 Hz), 2.58 (s, 1H, disappears by addition of D_2O), 3.45–3.90 (m, 16H), 4.17 (t, 2H, *J*=6 Hz), the benzylic -CH_2- gives a diastereotopic AB spin system: δ_A=4.65, δ_B=4.78, J_{AB}=13 Hz, 4H, 6.74 (s, 2H); ^{13}C NMR δ 17.08, 31.76, 59.39, 65.15, 70.60, 70.78, 71.57, 73.70, 75.90, 106.93, 160.04, 166.15; MS: (FAB, glycerol matrix) 400 ($M+H^+$); anal. calcd for $C_{20}H_{33}NO_7$: C, 60.13; H, 8.33; N, 3.51. Found: C, 60.38; H, 8.17; N, 3.55.

*4.1.1. Preparation of (*S,S*)-**1** from (*S,S*)-**6***

A mixture of (*S,S*)-**6** (280 mg, 0.82 mmol), 3-chloro-1-propanol (130 mg, 1.38 mmol) and K_2CO_3 (340 mg, 242 mmol) was stirred in pure and dry DMF (5 mL), under argon, at 80°C for 2 days. The solvent was evaporated and the residue was dissolved in a mixture of ethyl acetate (50 mL) and water (25 mL). The aqueous phase was extracted with ethyl acetate (1×25 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed. The residue was purified by chromatography on alumina to give (*S,S*)-**1** (205 mg, 62.6%); $[\alpha]_D^{25}$=+16.6 (*c* 0.410, CH_2Cl_2). All spectral data of (*S,S*)-**1** were identical to those of (*S,S*)-**1** prepared from (*S,S*)-**2**.

*4.2. General procedure for preparation of chiral pyridino-18-crown-6 ligands (*S,S*)-**2**, (*S,S*)-**3** and (*S,S*)-**4***

A suspension of NaH (2.0 g, 50 mmol, 60% mineral oil dispersion) in pure and dry THF (30 mL) was stirred under argon at 0°C. A solution of (*S,S*)-**10** (3.5 g, 15.8 mmol) in THF (70 mL) was added to the suspension dropwise. The mixture was stirred at 0°C for 10 min, at rt for 30 min and refluxed for 4 h. The mixture was cooled to −60°C and a solution of 4-alkoxy-2,6-pyridinedimethanol-bis(4-methylbenzenesulphonate) (15.8 mmol) in THF (55 mL) was added, and the mixture was stirred at −60°C for 30 min than at rt for 1 week. The solvent was removed and the residue dissolved in a mixture of ether (300 mL) and ice cold water (100 mL). The aqueous phase was extracted with ether (4×100 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed. The residue was purified by column chromatography on alumina to give the pyridino-18-crown-6 compounds as colourless oils [(*S,S*)-**2**: 2.9 g (43.2%); (*S,S*)-**3**: 2.33 g (34.2%)]. [For crude (*S,S*)-**4** only the ^1H NMR spectrum was taken before it was transformed into (*S,S*)-**6** (see below).]

*4.2.1. (4*S,14*S)-(+)-19-[(3-Trityloxypropyloxy]-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo-[15.3.1]heneicosa-1(21),17,19-triene (*S,S*)-**2***

$[\alpha]_D^{25}$=+1.8 (*c* 2.114, benzene); IR (film) ν_{max} 3100, 3080, 3040, 3010, 2990, 2950, 2920, 2890, 1605, 1590, 1500, 1460, 1380, 1360, 1340, 1100, 760, 750, 710, 640, cm^{-1}; ^1H NMR δ 1.16 (d, 6H, *J*=6 Hz), 2.06 (quin, 2H, *J*=6 Hz), 3.28 (t, 2H, *J*=6 Hz), 3.42–3.65 (m, 12H), 3.78–3.88 (m, 2H), 4.19 (t, 2H, *J*=6 Hz), the benzylic -CH_2- gives a diastereotopic AB spin system: δ_A=4.73, δ_B=4.78, J_{AB}=13 Hz, 4H, 6.78 (s, 2H), 7.17–7.47 (m, 15H); ^{13}C NMR δ 17.14, 29.58, 59.68, 64.82, 70.60, 71.80, 73.54, 86.53, 106.85, 126.93, 127.74, 128.17, 128.59, 128.97, 144.10, 160.02, 161.04; MS: (FAB, glycerol matrix) 642 ($M+H^+$).

*4.2.2. (4*S,14*S)-(+)-19-Benzyloxy-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (*S,S*)-**3***

$[\alpha]_D^{25}$=+5.2 (*c* 1.322, benzene); IR (film) ν_{max} 3090, 3070, 2960, 2910, 2880, 1600, 1580, 1490, 1450, 1370, 1340, 1250, 1130, 1110, 1050, 980, 850, 740, 690 cm^{-1}; ^1H NMR δ 1.15 (d, 6H, *J*=6 Hz), 3.42–3.61 (m, 12H), 3.81 (t, 2H, *J*=6 Hz), the benzylic -CH_2- gives a diastereotopic AB spin system: δ_A=4.73, δ_B=4.77, J_{AB}=13 Hz, 4H, 5.12 (s, 2H), 6.87 (s, 2H), 7.35–7.43 (m, 5H); ^{13}C NMR δ 17.29,

69.97, 70.79, 70.96, 71.95, 73.84, 76.13, 107.32, 127.76, 128.47, 128.88, 136.11, 160.39, 166.06; HRMS calcd for $C_{24}H_{33}NO_6$: 431.2308. Found: 431.2290.

*4.2.3. (4*S*,14*S*)-19-Tetrahydropyranyloxy-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]-heneicosa-1(21),17,19-triene (*S,S*)-**4***

^{1}H NMR δ 1.15 (d, 6H, J=6 Hz), 1.53–1.86 (m, 6H), 3.43–3.66 (m, 14H), 3.92 (t, 2H, J=6 Hz), the benzylic -CH_2- gives a diastereotopic AB spin system: δ_A=4.74, δ_B=4.78, J_{AB}=13 Hz, 4H, 5.42 (quin, 1H), 6.81 (s, 2H).

*4.2.4. Preparation of (*S,S*)-**2** starting from (*S,S*)-**6***

A mixture of (*S,S*)-**6** (62 mg, 0.18 mmol), **11** (64 mg, 0.183 mmol) and K_2CO_3 (80 mg, 0.55 mmol) was stirred in pure and dry DMF (5 mL) under argon at 100°C for 24 h. The solvent was evaporated and the residue was dissolved in a mixture of CH_2Cl_2 (50 mL) and water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (4×30 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed. The residue was purified by column chromatography on alumina to give (*S,S*)-**2** (100 mg, 85%) as a colourless oil. Spectral data and physical properties of (*S,S*)-**2** prepared in this way were identical to those of (*S,S*)-**2** obtained as described above.

*4.3. Modified Merrifield resin (*S,S*)-**5** and side product (*S,S,S,S*)-**16***

To a stirred suspension of NaH (830 mg, 20.7 mmol, 80% dispersion in mineral oil) in dry THF (10 mL) was added a solution of (*S,S*)-**1** (5.6 g, 14 mmol) in THF (90 mL) under argon at 0°C. The mixture was stirred at 0°C for 10 min, at rt for 40 min, and then at reflux temperature for 4 h. The reaction mixture was cooled to 0°C, and Merrifield resin (11.6 g, Aldrich, 2% cross-linked, 200–400 mesh, 1 meq Cl/g; anal: Cl, 3.51%) was added. The mixture was refluxed for 7 days without stirring in order to avoid milling of the resin. The modified resin was filtered and washed with solvents in the following order: THF (4×20 mL), *i*PrOH (1×20 mL), MeOH (3×20 mL), water (3×20 mL), MeOH (1×40 mL), CH_2Cl_2 (2×40 mL), ether (2×20 mL). The filtrate and washings were combined and evaporated, and the residue was purified by column chromatography on alumina to give 2.1 g (41%) of dimer (*S,S,S,S*)-**16** as a pale yellow oil. Analysis of the modified resin [(*S,S*)-**5**]: C, 84.10; H, 7.69; N, 0.79; Cl, 0.00%. This means that it contained 0.56 mmol of crown-compound for each gram of (*S,S*)-**5** (yield: 14.7 g).

*4.3.1. 1,3-Bis[19-(4*S*,14*S*)-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-trienyloxy]-propane (*S,S,S,S*)-**16***

$[\alpha]_D^{25}$=+12.0 (*c* 0.300, CH_2Cl_2); IR (film) ν_{max} 3100, 3040, 2950, 2880, 2850, 1600, 1580, 1500, 1450, 1440, 1370, 1330, 1170, 1080, 1020, 900, 850, 760, 690, 540 cm^{-1}; ^{1}H NMR δ 1.17 (d, 12H, J=7 Hz), 2.29 (quin, 2H, J=6 Hz), 3.45–3.61 (m, 24H), 3.78–3.85 (m, 4H), 4.23 (t, 4H, J=6 Hz), the benzylic -CH_2- gives a diastereotopic AB spin system: δ_A=4.72, δ_B=4.76, J_{AB}=13 Hz, 8H, 6.82 (s, 4H); ^{13}C NMR δ 17.27, 28.90, 64.27, 70.77, 70.92, 71.82, 73.84, 76.98, 107.16, 160.20, 166.19; MS: (FAB glycerol matrix) 723 (M+H$^+$); anal. calcd for $C_{37}H_{58}N_2O_{12}$: C, 61.52; H, 8.09; N, 3.88. Found: C, 61.71; H, 8.17; N, 3.65%.

4.4. (4S,14S)-(+)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19-(21H)-one (S,S)-6

A mixture of crude (*S,S*)-**4** (5.5 g), ethanol (100 mL), water (2 mL) and glacial acetic acid (3 mL) was stirred for one night at rt (TLC monitoring in 1:20 MeOH:CH_2Cl_2 on silica). The solvent was evaporated and the traces of acetic acid were removed by repeated distillation of toluene from the mixture. The residue was purified by column chromatography on alumina to give a slightly yellow oil (overall yield of cyclization and hydrolysis: 1.48 g, 27.4%.); $[\alpha]_D^{25}$=+24.2 (*c* 0.808, CH_2Cl_2); IR (film) ν_{max} 3100, 2990, 2950, 2900, 2870, 2850, 1640, 1580, 1550, 1530, 1460, 1380, 1250, 1110, 1090, 1040, 1000, 920, 880 cm^{-1}; ^1H NMR δ 1.18 (d, 6H, *J*=6 Hz), 3.4–3.7 (m, 12H), 3.78 (t, 2H, *J*=6 Hz), the benzylic -CH_2- gives a diastereotopic AB spin system: δ_A=4.59, δ_B=4.61, J_{AB}=13 Hz, 4H, 6.42 (s, 2H), 11.01 (s, 1H, NH); ^{13}C NMR δ 16.22, 67.28, 70.28, 70.91, 74.75, 75.48, 114.60, 147.51, 181.20; HRMS calcd for $C_{17}H_{27}NO_6$: 341.1838. Found 341.1823; anal. calcd for $C_{17}H_{27}NO_6 \cdot 0.5\ H_2O$: C, 58,31; H, 8.06; N, 4.00. Found: C, 58.39; H, 8.24; N, 3.84.

4.4.1. Preparation of (S,S)-6 starting from (S,S)-3

A solution of (*S,S*)-**3** (2.33 g) in methanol (50 mL) was hydrogenated in the presence of Pd/C catalyst (380 mg, Merck palladium/charcoal; activated, 10% Pd). After 5 min the reaction was complete. The catalyst was filtered off and washed with methanol (2×10 mL). The filtrate and washings were evaporated to give pure (*S,S*)-**6** as a pale yellow oil (1.77 g, 96%). Physical properties and spectral data of (*S,S*)-**6** prepared this way were identical to those of (*S,S*)-**6** obtained as described above.

4.5. 4-(3-Trityloxypropyloxy)-2,6-pyridinedimethanol-bis(4-methyl-benzenesulphonate) 7

A suspension of finely powdered KOH (12.6 g, 268 mmol) in dry THF (45 mL) was vigorously stirred under argon at 0°C. First a solution of **15** (20.5 g, 45 mmol) in THF (120 mL), and then a solution of tosyl chloride (22.9 g, 120 mmol) in THF (120 mL) were added to the suspension. The mixture was stirred at 0°C for 2 h and at rt for 4 h. The solvent was removed and the residue was dissolved in a mixture of CH_2Cl_2 (400 mL) and ice-water (200 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed. The residue was recrystallized from a mixture of CH_2Cl_2 and ether to give pale yellow crystals of **7** (29.5 g, 86%); mp: 126–128°C; IR (KBr) ν_{max} 3160, 3120, 3090, 3030, 2990, 2490, 1650, 1600, 1598, 1570, 1490, 1440, 1350, 1330, 1170, 1150, 1000, 900, 790, 780, 700, 670, 620, 500 cm^{-1}; ^1H NMR δ 2.04 (quin, 2H, *J*=6 Hz), 2.39 (s, 6H), 3.29 (t, 2H, *J*=6 Hz), 4.09 (t, 2H, *J*=6 Hz), 4.97 (s, 4H), 6.75 (s, 2H), 7.21–7.28 (m, 13H), 7.42 (d, 6H, *J*=8 Hz), 7.79 (d, 4H, *J*=8 Hz); ^{13}C NMR δ 21.63, 29.48, 59.43, 65.38, 71.24, 86.64, 107.76, 127.05, 127.82, 128.06, 128.63, 129.92, 132.75, 144.07, 145.12, 155.06, 166.67.

4.6. (2S,12S)-2,12-Dimethyl-4,7,10-trioxatridecane-2,12-diol (S,S)-10

A solution of (2*S*,12*S*)-2,12-bis[tetrahydropyranyloxy]-2,12-dimethyl-4,7,10-trioxatridecane-2,12-diol [(*S,S*)-**12**[25]] (22.3 g, mmol) in MeOH (300 mL) was stirred with acidic ion-exchange resin (8 g, Fluka Amberlite® IR-120), at rt for 18 h. The resin was filtered off, washed and the filtrate and washings were evaporated. The slightly coloured crude product was purified by fractional distillation under reduced pressure to give (*S,S*)-**10** as a colourless liquid (11.2 g, 80%, bp: 109–111°C/0.1 mmHg). Spectral data and physical properties of (*S,S*)-**10** were identical to those reported for (*S,S*)-**10** in the literature.[25]

4.7. 3-Chloro-1-trityloxypropane **11**

To a stirred solution of 3-chloro-1-propanol (10.7 g, 111 mmol) in dry pyridine (30 mL) was added a solution of trityl chloride (31.6 g, 113 mmol) in pyridine (90 mL) at rt dropwise. The mixture was stirred for 1 week (TLC monitoring in 1:2 EtOH:toluene on silica). The solvent was removed and the residue was dissolved in a mixture of water (400 mL) and ether (800 mL). The organic phase was shaken with saturated brine (1×150 mL), dried ($MgSO_4$), filtered and the solvent was evaporated to give a slightly coloured oil, which crystallized from EtOH in a refrigerator overnight. Recrystallization from a mixture of CH_2Cl_2–MeOH gave pure **11** (22.7 g, 61%), mp: 73–75°C; IR (KBr) ν_{max} 3080, 3030, 3020, 2970, 2930, 2880, 1520, 1480, 1360, 1110, 1080, 910, 900 cm^{-1}; ^1H NMR δ 1.96 (quin, 2H, *J*=6 Hz), 3.20 (t, 2H, *J*=6 Hz), 3.68 (t, 2H, *J*=6 Hz), 7.06–7.53 (m, 15H).

4.8. Bis[2,6-hydroxymethyl]pyridine-4(1H)-one **13**

A solution of 4-tetrahydropyranyloxy-2,6-pyridinedimethanol (**14**) (10 g, 41.8 mmol) in a mixture of EtOH (250 mL), water (5 mL) and glacial acetic acid (5 mL) was stirred at 120°C for 2 h. After the reaction was completed the mixture was stored at 0°C overnight. The crystals were filtered off, and recrystallized from ethanol to give white needles of **13** (4.5 g, 70%), mp: 187–189°C; IR (KBr) ν_{max} 3340, 3120, 2940, 2920, 2900, 2840, 1640, 1600, 1550, 1520, 1500, 1470, 1320, 1190, 1090, 1020, 1010, 880, 810, 530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.40 (s, 4H), 5.38 (s, 3H, disappears by addition of D_2O), 6.32 (s, 2H); MS: (FAB, glycerol matrix) 155 (M^+); anal. calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85. Found: C, 54.33; H, 6.00.

4.9. 4-(3-Trityloxypropyloxy)-2,6-pyridinedimethanol **15**

A mixture of **13** (7.75 g, 50.0 mmol), **11** (16.85 g, 50.0 mmol) and anhydrous K_2CO_3 (23.5 g, 150.0 mmol) was stirred in dry DMF (150 mL) under argon at 110°C for 72 h. After the reaction was completed the solvent was removed and the residue was dissolved in a mixture of $CHCl_3$ (500 mL) and ice-water (150 mL). The aqueous phase was shaken with $CHCl_3$ (3×200 mL). The combined organic phase was shaken with 10% NaOH solution (200 mL) and water (200 mL), dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was triturated with ether, stored in a refrigerator for one night to give **15** as white crystals (20.0 g, 80%), mp: 168–170°C; IR (KBr) ν_{max} 3430, 3130, 3080, 3060, 3030, 2990, 2950, 2930, 2920, 1605, 1580, 1490, 1470, 1440, 1360, 1130, 1060, 970, 710, 660, 590 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.00 (quin, 2H, *J*=6 Hz), 3.22 (t, 2H, *J*=6 Hz), 4.12 (t, 2H, *J*=6 Hz), 4.21 (s, 4H), 6.72 (s, 2H), 6.98–7.52 (m, 15H).

4.10. Enantiomeric separation of racemic NEA on CSP (S,S)-**5** by chromatography

Racemic NEA was prepared as reported earlier.[16] The racemic salt (50 mg) was dissolved in 0.5 mL of the eluent and was placed onto the column containing (*S,S*)-**5** (14 g) and eluted with a mixture of methanol:acetonitrile (1:5). The flow rate was 0.4 mL/min. Each fraction (10 mL) was evaporated, the salt was dissolved in methanol and the optical rotation was measured. Amounts of enantiomers were calculated relying upon a calibration curve in the same manner as reported earlier.[23]

Acknowledgements

Financial support by the Hungarian Scientific Research Found (OTKA T-14942 and T-25071) is gratefully acknowledged.

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