Synthesis of new enantiopure dimethyl-substituted pyridino-18-crown-6 ethers containing a hydroxymethyl, a formyl, or a carboxyl group at position 4 of the pyridine ring for enantiomeric recognition studies

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Dedicated to Professor Ferenc Fülöp on the occasion of his 60th birthday

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Abstract

An enantiomerically pure dimethyl-substituted pyridino-18-crown-6 ether containing a hydroxymethyl group at position 4 of the pyridine ring [(*S*,*S*)-**1**] has been prepared. This by Swern oxidation gave the formyl-substituted [(*S*,*S*)-**2**], then by further oxidation carboxy-substituted [(*S*,*S*)-**3**] pyridino-18-crown-6 ether derivatives. These enantiopure dimethyl-substituted pyridino-18-crown-6 ethers [(*S*,*S*)-**1**─(*S*,*S*)-**3**] are good candidates for enantiomeric recognition studies and also very useful precursors for enantioselective sensor and selector molecules with wide applications.

Keywords: Chiral crown ethers, pyridino-18-crown-6 ligands, macrocycles, enantiomeric recognition, chiral stationary phases, Fenton-type reaction

Introduction

The term molecular recognition refers to the specific interaction between two or more molecules through noncovalent bonding such as hydrogen bonding, hydrophobic forces, metal coordination, π-π interactions, van der Waals forces, electrostatic and/or electromagnetic[1] effects. The host and guest involved in molecular recognition exhibit molecular complementarity.[2,3] Molecular recognition plays an important role in biological systems and is observed in between receptor-ligand, antigen-antibody, RNA-ribosome, DNA-protein, sugar-lectin (a sugar-binding

protein), etc.. Imitating biochemical phenomena using synthetic compounds has demonstrated that biological behavior can be engineered into simple molecules like crown ethers.

Enantiomeric recognition as a special case of molecular recognition involves the discrimination of the enantiomers of a chiral guest molecule by a chiral host molecule. Since Cram and co-workers synthesized chiral crown ethers containing the twisted 1,1′-binaphthyl unit,[4] which were the first artificial enantioselective receptors for primary organoammonium salts, a great number of attempts have been made to distinguish the enantiomers of chiral ammonium ions by chiral crown ethers.[5-10]

Among other optically active synthetic macrocycles, enantiopure pyridino-18-crown-6 ethers have received great attention in the last few decades due to their ability to discriminate between the enantiomers of protonated primary organic amines, amino acids and their derivatives.[6,11-19] Selected enantiopure pyridino-18-crown-6 ethers have been immobilized by covalent bonds on solid supports such as silica gel[20-25] or Merrifield-type polymer resin.[26] In all these cases the linking units have been attached to the pyridine ring exclusively through an oxygen atom.

Our aim was to work out a suitable synthetic route to such new pyridino-18-crown-6 ether derivatives where the linking units at position 4 of the pyridine ring are attached to the pyridine ring through a carbon atom. We hoped that the chiral stationary phases (CSPs) prepared from the latter precursors would be more stable than their earlier analogues, and their discrimination power between the enantiomers of protonated primary amines and amino acid derivatives greater.

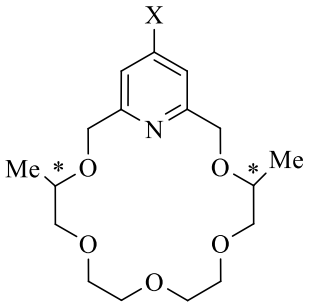
A carboxylic functional group at position 4 of the pyridine ring of pyridino-18-crown-6 ethers seems to be a good one, because its condensation reaction with 3-aminopropyl-triethoxysilane gives a crown ether derivative with the triethoxysilane end group, which can easily be attached to silica gel to produce a CSP.[24]

Our attempts to introduce directly a carboxyl group into the position 4 of the pyridine ring of the pyridino-crown ethers were unsuccessful. Direct lithiation of the pyridine ring or lithium-halogen exchange and treatment with carbon dioxide did not provide the corresponding carboxylic acid. The Minisci-type direct homolytic carboxylation of protonated pyridino-crown ethers using methoxycarbonyl radicals[27] resulted in a mixture of di- and trimethoxycarbonyl-substituted pyridino-crown ether derivatives. The hydrolysis of our earlier reported[28] pyridino-18-crown-6 ether containing a cyano group at position 4 of the pyridine ring would be a suitable precursor for the synthesis of the corresponding carboxylic acid, but the former can be obtained only in rather low yield.[28]

We tried to prepare the hydroxymethyl-functionalized pyridino-crown ether (*S*,*S*)-**1** starting from the parent pyridino-crown ether by Fenton-type hydroxymethylation reaction[29], because the former can be converted into carboxylic acid by two mild oxidation steps through an aldehyde intermediate. Unfortunately the highly acidic medium of the Fenton-type hydroxymethylation reaction led to the ring opening of the macrocycle.

Considering the above, we had to introduce the hydroxymethyl group into the position 4 of the pyridine ring before the macrocyclization reaction. The reported synthetic routes for the

preparation of achiral[30] and dimethyl-substituted enantiopure[26] pyridono-crown ethers afforded a good analogue for the preparation of enantiopure dimethyl-substituted hydroxymethyl-pyridino-crown ether derivative (*S*,*S*)-**1** (see Figure 1). Tetrahydropyranyl (THP) protecting group for the hydroxymethyl moiety seemed to be advantageous, because of its resistance to the highly basic conditions needed during the Williamson-type ether-forming macrocyclization.



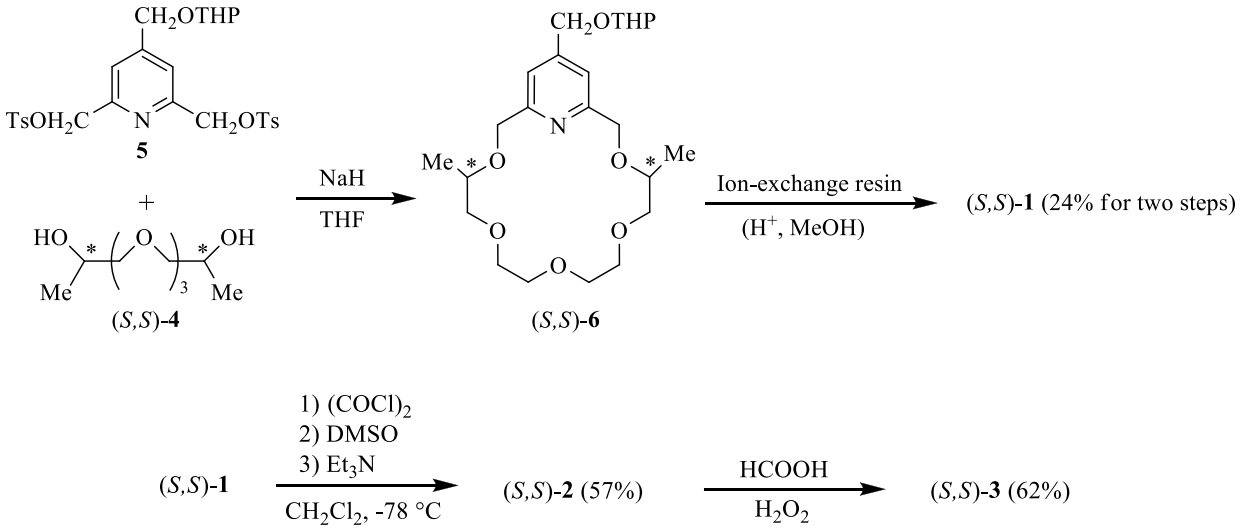
(*S*,*S*)-**1**: X=CH_2OH
(*S*,*S*)-**2**: X=CHO
(*S*,*S*)-**3**: X=COOH

Figure 1. Schematics of new enantiopure pyridino-18-crown-6 ethers containing a hydroxymethyl [(*S*,*S*)-**1**], a formyl [(*S*,*S*)-**2**] or a carboxyl group [(*S*,*S*)-**3**] at position 4 of the pyridine ring.

Results and discussion

Synthesis

The synthesis of pyridino-18-crown-6 ether (*S*,*S*)-**1** containing a hydroxymethyl moiety started from the known enantiopure dimethyl-substituted tetraethylene glycol (*S*,*S*)-**4**[17,31] (Scheme 1) and the hitherto unreported pyridine derivative **5**. The former was converted into the corresponding dialkoxide using NaH as a strong base in THF and then this dialkoxide was reacted with the pyridine ditosylate **5** performing a Williamson-type ether formation macrocyclization as outlined in Scheme 1. The crude product was used in the next step without further purification. THP protected pyridino-crown ether (*S*,*S*)-**6** resulted in hydroxymethyl-substituted pyridino-18-crown-6 ether (*S*,*S*)-**1** by deblocking the THP protecting group with the help of an ion-exchange resin (H^+ form) in MeOH as reported[26] for a similar compound. We needed a metal ion-free oxidation reaction, because pyridino-crown ether (*S*,*S*)-**1** can complex metal ions. Therefore the hydroxymethyl-functionalized macrocycle (*S*,*S*)-**1** was oxidized by Swern oxidation to pyridino-crown ether containing a formyl group at position 4 of the pyridine ring [(*S*,*S*)-**2**]. In the last step, aldehyde (*S*,*S*)-**2** was converted into carboxylic acid (*S*,*S*)-**3**, also by a metal ion-free oxidation using H_2O_2 in HCOOH.

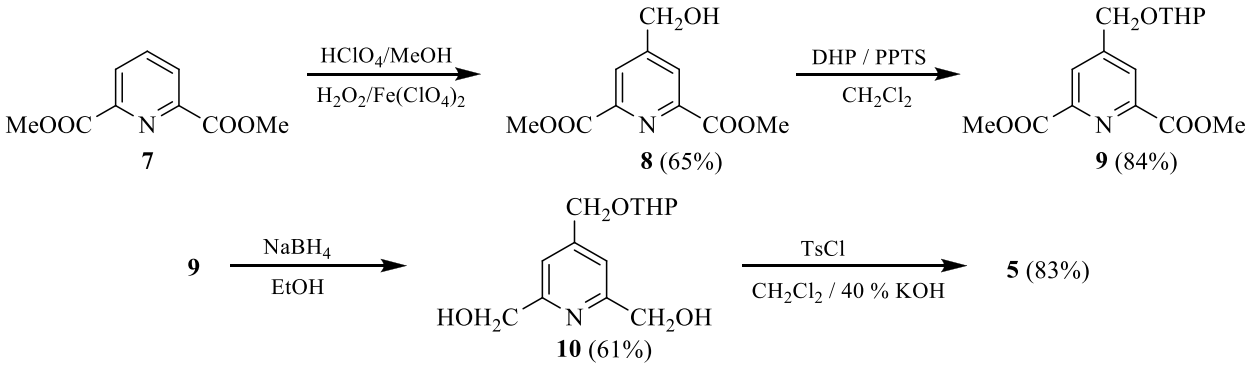


Scheme 1. Preparation of enantiopure hydroxymethyl-pyridino-18-crown-6 ether (*S*,*S*)-**1** and its transformation into formyl-[(*S*,*S*)-**2**] and carboxyl- [(*S*,*S*)-**3**] substituted pyridino-crown ethers.

For the preparation of 2,6-pyridinedimethanol ditosylate (**5**) we started from the commercially available and relatively cheap 2,6-lutidine. Pyridine-2,6-dicarboxylic acid (dipicolic acid, DPA) dimethyl ester (**7**, see Scheme 2) was prepared from 2,6-lutidine using aqueous $KMnO_4$,[32] followed by the esterification of DPA with $SOCl_2$/MeOH.[33]

DPA dimethyl ester **7** was subjected to a regioselective hydroxymethylation applying a modified Fenton-type reaction to give 4-hydroxymethyl-DPA dimethyl ester **8** (see Scheme 2). The free-radical derivatization at position 4 of the protonated DPA derivatives by Fenton-type reaction was reported first by Shelkov and Melman.[29] Their initial attempts to introduce a hydroxymethyl group into the position 4 of DPA dimethyl ester were carried out in aqueous solution acidified with 1-5 equiv. of H_2SO_4, which resulted in complete recovery of the starting material. To enforce protonation of DPA dimethyl ester **7** they performed the reaction in 30% aqueous H_2SO_4. This medium provided the necessary highly acidic conditions and the desired free-radical substitution then indeed took place. However, their synthesis of 4-hydroxymethyl-DPA dimethyl ester **8** gave only a moderate yield (30%). Instead of H_2SO_4 (pK_a value[34] in water: -3.0) we used one of the strongest Brønsted-Lowry acids, the concentrated (70% in water) $HClO_4$ (pK_a value[34] in water: -10.0).

The introduction of a hydroxymethyl group into the position 4 of the DPA dimethyl ester **7** involves the generation of hydroxyl radicals through Fenton-type reaction with use of H_2O_2/$FeSO_4$ system,[29] followed by abstraction of a hydrogen atom from MeOH. We used saturated aqueous $Fe(ClO_4)_2$ solution instead of saturated aqueous $FeSO_4$. In this case 4-hydroxymethyl-DPA dimethyl ester **8** was obtained in better yield (65%) due to the applied highly acidic reaction media and the change of $FeSO_4$ to $Fe(ClO_4)_2$. Furthermore, we did not observe any detectable amount of polymeric byproducts or isomeric products, and we could also recover the unreacted ester **7**.



Scheme 2. Synthesis of precursor **5** needed for the preparation of the pyridino-crown ether derivative (*S*,*S*)-**1**.

4-Hydroxymethyl-substituted DPA dimethyl ester **8** was treated with an excess of dihydropyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS) catalyst to obtain the THP derivative **9**, which was reduced to THP-protected diol **10** with $NaBH_4$ in a similar manner as described for substituted pyridine diesters in our previous publication.[35] Finally, the diol **10** was converted into ditosylate **5** with tosyl chloride in a mixture of CH_2Cl_2 and 40% aqueous KOH according to the procedure previously described[36-38] for similar transformations.
This paper reports only the synthesis of the new ligands and their precursors. Their transformation to enantioselective sensor and selector molecules and the applications of the latter compounds will be published when the work connected with them is finished.

Conclusions

We can conclude that new enantiopure dimethyl-substituted hydroxymethyl-pyridino-18-crown-6 ether (*S*,*S*)-**1** can be prepared from the disodium derivative of enantiopure chiral tetraethylene glycol (*S*,*S*)-**4** and the pyridinedimethanol ditosylate **5** in THF by a Williamson-type ether formation macrocyclization. Hydroxymethyl-substituted crown ether (*S*,*S*)-**1** can be converted into carboxy-substituted pyridino-crown ether (*S*,*S*)-**3** by two mild oxidation steps through (*S*,*S*)-**2** aldehyde. The carboxylic functional group at position 4 of the pyridine ring of crown ether (*S*,*S*)-**3** is suitable for a condensation reaction with 3-aminopropyltriethoxysilane which gives the crown ether derivative with the triethoxysilane end group. The latter can easily be attached to silica gel with covalent bonds to produce a CSP.

Experimental Section

General. Infrared spectra were recorded on a Bruker Alpha-T FT-IR spectrometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. NMR spectra were recorded in $CDCl_3$ either on a Bruker DRX-500 Avance spectrometer (at 500 MHz for ^1H and at 125 MHz for ^{13}C spectra) or on a Bruker 300 Avance spectrometer (at 300 MHz for ^1H and at 75 MHz for ^{13}C spectra) and it is indicated in each individual case. Mass spectra were recorded on an Agilent-1200 Quadrupole LC/MS instrument using ESI method. Elemental analyses were performed on a Vario EL III instrument (Elementanalyze Corp., Germany) 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 F254 (Merck) and aluminium oxide 60 F254 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 methods.[39] Evaporations were carried out under reduced pressure unless otherwise stated.

(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-methanol [(*S*,*S*)-**1**] (see Scheme 1). A solution of crude (*S*,*S*)-**6** (0.70 g) in MeOH (9 mL) was stirred with acidic ion-exchange resin (0.41 g, Fluka Amberlite® IR-120), at rt for 18 h. The resin was filtered off, washed and the filtrate and washings were evaporated. The residue was purified by column chromatography on neutral Al_2O_3 using EtOH-toluene (1:20) mixture as an eluent to furnish (*S*,*S*)-**1** (197.8 mg, 24% overall yield for the macrocyclization and THP-deblocking steps) as a pale yellow oil. R_f =0.50 (Al_2O_3 TLC, EtOH-toluene 1:10); $[\alpha]^{25}_D$= +12.3 (*c* 1.76, acetone); IR (neat) ν_{max} 3390, 2868, 1638, 1610, 1570, 1452, 1375, 1350, 1226, 1201, 1090, 1033, 1011, 923, 857, 816, 682, 568 cm^{-1}; ^1H-NMR (500 MHz, $CDCl_3$) δ (ppm) 1.17 (d, *J*=6 Hz, 6H); 3.47-3.64 (m, 13H, 1H disappears after shaking with D_2O); 3.80-3.83 (m, 2H), 4.71 (s, 2H), the diastereotopic benzylic protons of the macroring give an AB quartett δ_A: 4.76 and δ_B: 4.80 (J_{AB} = 13 Hz, 4H), 7.29 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.0, 63.5, 70.7, 70.9, 71.4, 74.1, 75.9, 118.6, 150.7, 157.9; MS: 356.1 $(M+1)^+$; Anal. Calcd. for $C_{18}H_{29}NO_6$: C, 60.83; H, 8.22; N, 3.94. Found: C, 60.54; H, 8.29; N, 3.87.

(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-carboxaldehyde [(*S*,*S*)-**2**] (see Scheme 1). In a dry two-necked round-bottom flask equipped with an argon inlet and a dropping funnel was stirred oxalyl chloride (138.6 mg, 92 μL, 1.09 mmol) in pure and dry CH_2Cl_2 (0.5 mL). The solution was cooled to -78 °C and DMSO (133.8 mg, 122 μL, 1.72 mmol) was added dropwise in 10 min. To this reaction

mixture was added slowly, a solution of hydroxymethyl-pyridino-crown ether derivative (*S*,*S*)-**1** (46.1 mg, 0.13 mmol) in dry CH_2Cl_2 (0.13 mL) in 10 min. Et_3N (256.8 mg, 353 μL, 3.9 mmol) was added dropwise and the reaction mixture stirred for an additional 45 min. The cooling bath was removed and the reaction mixture was allowed to reach 0 °C and it was stirred at this temperature until the TLC analysis (Al_2O_3 TLC; EtOH-toluene 1:10) showed the total consumption of the starting materials and only one main spot (R_f =0.69; positive 2,4-dinitrophenylhydrazine test) for the product (1.5 h). The solution was poured onto crushed ice (10 g), and the mixture was washed into a separatory funnel with water and CH_2Cl_2 (10 mL of each). The resulting mixture was shaken well and separated. The aqueous phase was shaken with CH_2Cl_2 (3X10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by Al_2O_3 preparative thin layer chromatography using EtOH-toluene (1:10) mixture as an eluent to yield (*S*,*S*)-**2** (25.9 mg, 57%) as a pale yellow oil. $[\alpha]^{25}_D$= +14.0 (*c* 1.64, acetone); IR (neat) ν_{max} 3398, 2959, 2922, 2853, 1708, 1607, 1571, 1561, 1459, 1376, 1351, 1258, 1088, 1013, 870, 796, 721, 703, 684, 669, 622, 601, 583, 569, 552, 517, 503, 487, 472, 453 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 1.12 (d, *J*=6 Hz, 6H); 3.40-3.57 (m, 12H); 3.75-3.78 (m, 2H), 4.71 (s, 2H), the diastereotopic benzylic protons of the macroring give an AB quartett δ_A: 4.83 and δ_B: 4.89 (J_{AB} = 14 Hz, 4H), 7.60 (s, 2H), 10.03 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 17.0, 70.6, 70.9, 71.4, 74.1, 76.2, 118.8, 142.5, 160.7, 192.1 ; MS: 354.4 $(M+1)^+$; Anal. Calcd. for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 60.88; H, 7.82; N, 3.83.

(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-carboxylic acid [(*S*,*S*)-**3**] (see Scheme 1). To a well stirred solution of 4-formyl-substituted pyridino-crown ether (*S*,*S*)-**2** (18.4 mg, 0.052 mmol) in HCOOH (10 μl, 12.0 mg, 0.26 mmol) was added dropwise hydrogen peroxide (39 μl, 43.1 mg, 0.38 mmol, 30% solution in water). The mixture was stirred at 0 °C until the TLC analysis (Al_2O_3 TLC; EtOH-toluene 1:2) showed the total consumption of the starting material and only one main spot (R_f =0.31) for the product (7 h). The volatile components were evaporated under reduced pressure and the traces of HCOOH were removed by repeated distillation of toluene from the mixture to give (*S*,*S*)-**3** (12.0 mg, 62%) as a colorless oil.

$[\alpha]^{25}_D$= +9.3 (*c* 0.86, acetone); IR (neat) ν_{max} 3419, 2967, 2915, 2875, 2513, 1715, 1679, 1655, 1649, 1638, 1631, 1612, 1571, 1451, 1375, 1350, 1340, 1306, 1222, 1162, 1089, 919, 890, 858, 801, 776, 710, 670, 666, 640 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 1.23 (d, *J*=6 Hz, 6H); 3.46-3.63 (m, 12H); 3.86-3.95 (m, 2H), 4.71 (s, 2H), the diastereotopic benzylic protons of the macroring give an AB quartett δ_A: 4.86 and δ_B: 4.96 (J_{AB} = 13 Hz, 4H), 8.11 (s, 2H), 8.70 (br. s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.4, 69.2, 70.4, 71.0, 75.0, 75.4, 123.1, 149.5, 156.3, 166.2; MS: 370.8 $(M+1)^+$; Anal. Calcd. for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37; N, 3.79. Found: C, 58.40; H, 7.49; N, 3.51.

4-{[(Tetrahydro-2*H*-pyran-2-yloxy)methyl]pyridine-2,6-diyl}bis(methylene) bis(4-methylbenzenesulfonate) (**5**) (see Scheme 2)

Diol **10** (0.54 g, 2.14 mmol) was vigorously stirred in a mixture of CH_2Cl_2 (9 mL) and 40% aqueous KOH solution (12 mL) at 0 °C and a solution of tosyl chloride (0.92 g, 4.80 mmol) in CH_2Cl_2 (3mL) was added dropwise to it. The mixture was stirred at 0 °C for one hour then at room temperature until the TLC analysis (SiO_2 TLC; MeOH-toluene 1:3) showed the total consumption of the starting material and only one main spot (R_f =0.70) for the product (24 h). The mixture was washed into a separatory funnel with water and CH_2Cl_2 (20 mL of each). The resulting mixture was shaken well and separated. The aqueous phase was shaken with CH_2Cl_2 (3X30 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated to yield **5** (1.00 g, 83%) as a pale yellow oil. IR (neat) ν_{max} 2946, 2870, 1613, 1598, 1572, 1453, 1358, 1307, 1292, 1201, 1189, 1173, 1122, 1095, 1076, 1034, 995, 937, 904, 869, 834, 812, 776, 746, 705, 662, 608, 552, 543, 431 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 1.56-1.68 (m, 3H), 1.68-1.76 (m, 1H), 1.76-1.84 (m, 1H), 1.84-1.95 (m, 1H), 2.45 (s, 6H), 3.53-3.61 (m, 1H), 3.84-3.90 (m, 1H), the diastereotopic benzylic protons at position 4 of the pyridine ring give an AB quartett δ_A: 4.34 and δ_B: 4.90 (J_{AB} =14 Hz, 2H), 4.68-4.72 (m, 1H), 5.07 (s, 4H), 7.33 (s, 2H), 7.34 (d, *J*=7 Hz, 4H), 7.81 (d, *J*=7 Hz, 4H); ^{13}C-NMR (75MHz, $CDCl_3$) δ 19.42, 21.83, 25.49, 30.54, 62.47, 67.03, 71.42, 98.62, 119.79, 128.25, 130.01, 130.10, 132.90, 145.33, 150.63, 153.65; MS: 563.0 $(M+1)^+$; Anal. Calcd. for $C_{27}H_{31}NO_8S_2$: C, 57.74; H, 5.56; N, 2.49; S: 11.42. Found: C, 57.50; H, 5.63; N, 2.58; S: 11.38.

(4*S*,14*S*)-(+)-4,14-Dimethyl-19-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene [(*S,S*)-**6**] (see Scheme 1). In a dry three-necked round-bottom flask equipped with a reflux condenser, argon inlet and a dropping funnel was stirred vigorously a suspension of NaH (293 mg, 7.3 mmol, 60% dispersion in mineral oil) in pure and dry THF (5 mL) at 0 °C for 2 min. To this suspension was added slowly dimethyl-substituted tetraethylene glycol (*S,S*)-**4** (517 mg, 2.32 mmol) dissolved in pure and dry THF (12 mL) under argon at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, at room temperature for 30 min and at reflux temperature for 4 h.

The mixture was cooled down to -20 °C and pyridine-2,6-dimethanol ditosylate **5** (1.326 g, 2.36 mmol) dissolved in pure and dry THF (9 mL) was added in 0.5 h. After addition of the ditosylate **5** the reaction mixture was allowed to warm up slowly to room temperature and it was stirred at this temperature until the TLC analysis (Al_2O_3 TLC; EtOH-toluene 1:20) showed the total consumption of the starting materials and only one main spot (R_f =0.60) for the product (13 h). The solvent was evaporated, and the residue was dissolved in a mixture of Et_2O and ice-water (20 mL of each). The phases were shaken thoroughly and separated. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated. This crude product was used in the next step without further purifications. A small *aliquot* of it was taken and purified by column chromatography on neutral

Al_2O_3 using EtOH-toluene (1:50) mixture as an eluent to furnish an analytical sample. $[\alpha]^{25}_D$= +4.3 (*c* 0.73, acetone); IR (neat) ν_{max} 2931, 2868, 1609, 1571, 1453, 1371, 1341, 1260, 1201, 1114, 1077, 1035, 977, 948, 904, 869, 814, 537, 430 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 1.12 (3H, d, *J*=6 Hz), 1.18 (3H, d, *J*=6 Hz), 1.60-1.64 (m, 6H), 3.52-3.67 (m, 13H), 3.82-3.85 (m, 1H), 3.88-3.92 (m, 1H), 3.98-4.02 (m, 1H), 4.52-4.54 (m, 1H), 4.69-4.73 (m, 2H), the diastereotopic benzylic protons of the macroring give an AB quartett δ_A: 4.80 and δ_B: 4.84 (J_{AB} = 13 Hz, 4H), 7.26 (s, 2H); MS: 440.0 $(M+1)^+$.

Dimethyl 4-(hydroxymethyl)pyridine-2,6-dicarboxylate (8)[29] (see Scheme 2).
4-Hydroxymethyl DPA dimethyl ester **8** was synthetized with a modification of a reported[29] procedure. Solutions of $Fe(ClO_4)_2$•$6H_2O$ (4.64 g, 12.8 mmol) in H_2O (4.7 mL) and H_2O_2 (30% aqueous solution, 8 mL, 77.6 mmol) were added dropwise at 0 °C over 30 min to a mixture of DPA dimethyl ester (2.5 g, 12.8 mmol) **7**, MeOH (7.5 mL) and $HClO_4$ (70% aqueous solution, 5.6 mL, 9.32 g, 64.9 mmol). The reaction mixture was allowed to warm up slowly to room temperature and it was stirred at this temperature for 3 h. The volatile components were evaporated under reduced pressure, and the pH of the residue was adjusted to 9 with saturated Na_2CO_3 solution. The aqueous solution was extracted with EtOAc (3X30 mL) and the combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The residue was recrystallyzed from toluene to give **8** (1.87 g, 65%) as white crystals. Mp: 158-159 °C (toluene) (lit. mp: 154-158 °C[40]), R_f =0.11 (SiO_2 TLC; EtOAc-toluene 1:1). 4-Hydroxymethyl DPA dimethyl ester **8** obtained this way had the same spectroscopic data than those of reported.[29]

Dimethyl 4-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]pyridine-2,6-dicarboxylate (9) (see Scheme 2). To a well stirred mixture of 4-hydroxymethyl DPA dimethyl ester **8** (3.0 g, 13 mmol), dihydropyran (DHP) (5 mL, 4.62 g, 55 mmol) and pure and dry CH_2Cl_2 (8mL) was added dropwise in an ice-salt bath and under argon a solution of pyridinium *p*-toluenesulfonate (PPTS) catalyst (0.336 g, 1.3 mmol) in pure and dry CH_2Cl_2 (7 mL) and one drop of pyridine. The mixture was stirred at 0 °C for one hour then at reflux temperature until the TLC analysis (SiO_2 TLC; EtOAc-toluene 1:1) showed the total consumption of the starting material and only one main spot (R_f =0.88) for the product (24 h). The mixture was washed into a separatory funnel with CH_2Cl_2 (30 mL) and shaken with 5% aqueous $NaHCO_3$ solution (30 mL) and water (2×30 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The residue was recrystallyzed from toluene-hexane mixture to give **9** (3.38 g, 84%) as white crystals. Mp: 78-80 °C (toluene-hexane); IR (KBr) ν_{max} 2954, 2930, 1743, 1719, 1605, 1442, 1391, 1330, 1323, 1270, 1244, 1213, 1202, 1194, 1180, 1159, 1136, 1128, 1113, 1073, 1044, 1036, 1025, 1015, 996, 971, 916, 872, 785, 735 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 1.55-1.73 (m, 3H), 1.73-1.86 (m, 2H), 1.86-1.95 (m, 1H), 3.47-3.58 (m, 1H), 3.83-3.88 (m, 1H), 3.99 (s, 6H), 4.60-4.63 (s, 1H), 4.71-4.74 (m, 1H), 4.89-4.92 (m, 1H), 8.27 (s, 2H); ^{13}C-NMR (75MHz,$CDCl_3$) δ 19.26, 25.40, 30.43, 55.31, 62.37, 66.75, 98.73, 126.14, 148.43, 151.35,

165.30; MS: 310.6 $(M+1)^+$; Anal. Calcd. for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 57.98; H, 6.16; N, 4.34.

{4-[(Tetrahydro-2*H*-pyran-2-yloxy)methyl]pyridine-2,6-diyl}dimethanol (10) (see Scheme 2). To a suspension of 4-[(tetrahydropyranyloxy)methyl]pyridine diester **9** (1.50 g, 4.85 mmol) in dry EtOH (15 mL) at 0 °C $NaBH_4$ (0.887 g, 23.44 mmol) was added, then the mixture was stirred at 0 °C for 1 h, at room temperature for another 1 h, and at reflux temperature until the TLC analysis (SiO_2 TLC; 100% EtOAc) showed the total consumption of the starting material and only one main spot (R_f =0.14) for the product (24 h). Acetone (18 mL) was added, and the mixture was refluxed for 1 h. The volatile components were distilled off, and the waxy residue was triturated with saturated aqueous K_2CO_3 solution (15 mL). The mixture was refluxed for 1 h. Water was distilled off, then the residue was washed into a separatory funnel with brine (30 mL) and CH_2Cl_2 (40 mL). The phases were shaken well and separated. The aqueous phase was shaken with CH_2Cl_2 (3×30 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The residue was recrystallyzed from diisopropyl ether to give **10** (0.75 g, 61%) as white crystals. Mp: 69-70 °C (diisopropyl ether). IR (KBr) ν_{max} 3358, 2940, 2851, 1612, 1570, 1440, 1388, 1350, 1323, 1261, 1201, 1183, 1121, 1075, 1031, 978, 921, 904, 866, 810, 730, 668, 645, 570, 545, 447, 429 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 1.57-1.64 (m, 3H), 1.68-1.72 (m, 1H), 1.76-1.81 (m, 1H), 1.86-1.90 (m, 1H), 3.55-3.57 (m, 1H), 3.85-3.90 (m, 1H), 4.27 (s, 2H, disappears after shaking with D_2O), the diastereotopic benzylic protons at position 4 of the pyridine ring give an AB quartett δ_A: 4.37 and δ_B: 4.95 (J_{AB} =14 Hz, 2H), 4.71 (t, 1H), 4.75 (s, 4H), 7.22 (s, 2H); ^{13}C-NMR (125MHz, $CDCl_3$) δ 19.23, 25.28, 30.37, 62.29, 64.24, 67.13, 98.41, 117.50, 149.97, 158.75; MS: 253.9 $(M+1)^+$; Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.29; H, 7.75; N, 5.49.

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