Synthesis of new enantiopure dimethyl- and diisobutyl -substituted pyridino-18-crown-6 ethers containing a halogen atom or a methoxy group at position 4 of the pyridine ring for enantiomeric recognition studies

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Abstract

New enantiomerically pure dimethyl- and diisobutyl-substituted pyridino-18-crown-6 ethers containing a halogen atom or a methoxy group at position 4 of the pyridine ring [(*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3,** (*S*,*S*)-**4**] have been synthesized. A new synthetic route and the solid state structure of the reported enantiopure dimethyl-substituted pyridino-18-crown-6 ether [(*S*,*S*)-**5**] containing a chlorine atom at position 4 of the pyridine ring are also described. These ligands are good candidates for enantiomeric recognition studies of protonated primary amines, amino acids and their derivatives.

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

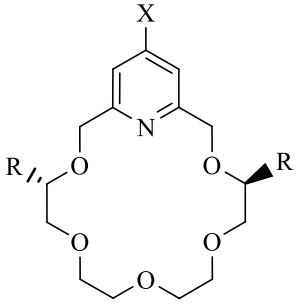
Introduction

There are numerous examples of molecular recognition in nature, such as the immunological response, storage and retrieval of genetic information by DNA, enzyme-substrate interactions, selective complexation and transport of metal ions across cell membranes by ionophore antibiotics and the metabolism of single enantiomeric forms of amino acids and sugars in biochemical pathways can be mentioned. The last example refers to enantiomeric recognition.

Enantiomeric recognition, as a special case of molecular recognition, involves the discrimination between the enantiomers of a chiral guest molecule by a chiral host molecule. Since Cram and his co-workers published their seminal work on the use of chiral macrocyclic ligands in enantiomeric recognition,[1] a great number of chiral macrocycles have been synthesized and studied.[2,3]

In the past quarter of the century, optically active pyridino-18-crown-6 ether type macrocycles have received a great deal of attention due to their ability of enantiomeric discrimination toward protonated chiral primary amines, amino acids and their derivates.[4-9]
Selected enantiopure pyridino-18-crown-6 ethers have been immobilized by covalent bonds on solid supports such as silica gel and Merrifield polymer resin and the chiral stationary phases (CSPs) so obtained have been used successfully for chromatographic enantioseparation of racemic protonated primary amines, amino acids and their derivates.[10-14]

In continuation of our studies in this area of research, our attention turned to the preparation of new enantiopure dimethyl- and diisobutyl-substituted pyridino-18-crown-6 ether type macrocycles containing a halogen atom or a methoxy group at position 4 of the pyridine ring [(*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3**, (*S*,*S*)-**4**, (*S*,*S*)-**5**, see Figure 1]. These macrocycles can be transformed to derivatives which are able to function as effective sensor and selector molecule.[9] Regarding the former derivatives up to now, only the dimethyl-substituted pyridino-18-crown-6 ether containing a chlorine atom at position 4 of the pyridine ring [(*S*,*S*)-**5**] has been synthesized from the appropriate enantiopure dimethyl-substituted pyridino-crown ether.[9] In this paper we describe a new route for the synthesis of the reported ligand (*S*,*S*)-**5** and also the preparation of new enantiopure dimethyl- and diisobutyl-substituted pyridino-18-crown-6 ethers containing a chlorine or a bromine atom or a methoxy group at position 4 of the pyridine ring [(*S*,*S*)-**1**–(*S*,*S*)-**4**, see Figure 1].



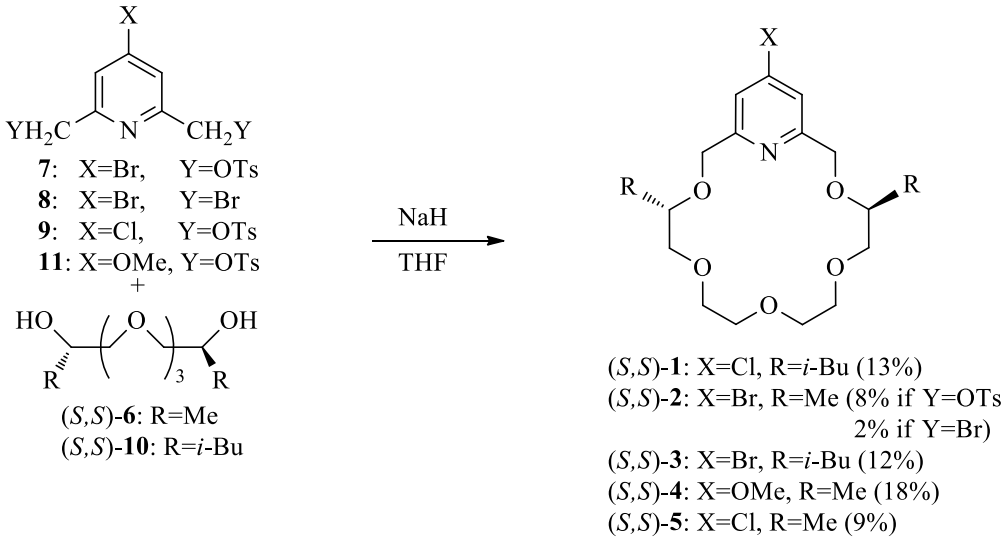
(*S*,*S*)-**1**: X=Cl, R=*i*-Bu
(*S*,*S*)-**2**: X=Br, R=Me
(*S*,*S*)-**3**: X=Br, R=*i*-Bu
(*S*,*S*)-**4**: X=OMe, R=Me
(*S*,*S*)-**5**: X=Cl, R=Me

Figure 1. Enantiopure pyridino-18-crown-6 ethers containing a halogen atom or a methoxy group at position 4 of the pyridine ring.

Results and discussion

Synthesis

For the synthesis of enantiopure dimethyl-substituted 4-bromo-pyridino-crown ether [(*S*,*S*)-**2**], two synthetic pathways were investigated. In both cases, a solution of the enantiopure dimethyl-substituted tetraethylene glycol [(*S*,*S*)-**6**][15] in THF was converted into the corresponding dialkoxide using NaH as a strong base and then this dialkoxide was reacted with the pyridine precursor **7** or **8** performing a Williamson-type macrocyclic ether formation reaction as shown in Scheme 1.



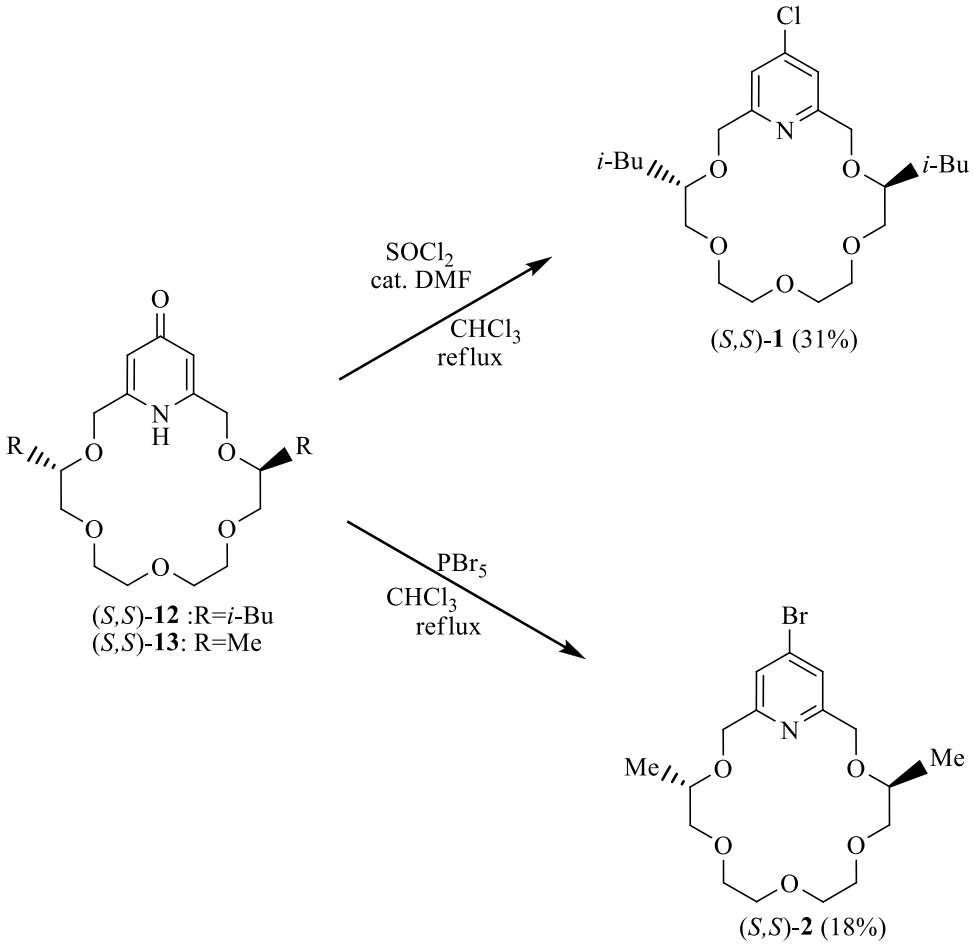
Scheme 1. Synthesis of pyridino-crown-ether derivatives (*S*,*S*)-**1**—(*S*,*S*)-**5**.

In contrast with the preparation of the achiral parent compound,[16] when 4-bromo-2,6-bis(tosyloxymethyl)pyridine **7** was used, much better yields were obtained than with 4-bromo-2,6-bis(bromomethyl)pyridine **8**. After the successful synthesis of enantiopure bromo-pyridino-crown ether derivatives, we tried to prepare the chloro- and methoxy-substituted ligands, too.

The chloro-pyridino-crown ethers [(*S*,*S*)-**1**, (*S*,*S*)-**5**] were synthesized from 4-chloro-2,6-bis(tosyloxymethyl)pyridine **9** and the corresponding enantiopure chiral tetraethylene glycol [(*S*,*S*)-**6**, (*S*,*S*)-**10**] dialkoxides in THF, analogously as mentioned above for the preparation of the bromo-crown ethers [(*S*,*S*)-**2**, (*S*,*S*)-**3**] (see Scheme1).

It was published earlier[17] that 4-methoxy-2,6-bis(tosyloxymethyl)pyridine **11** can be used for the preparation of an optically active crown ether containing a monosaccharide unit by macrocyclization with a dialkoxide. When the dialkoxide of enantiopure dimethyl-substituted tetraethylene glycol (*S*,*S*)-**6** was treated with the methoxy-substituted 2,6-bis(tosyloxymethyl)pyridine **11** in THF the methoxy-substituted pyridino-18-crown-6 ether (*S*,*S*)-**4** was obtained as shown in Scheme 1.

Pyridino-crown ether (*S*,*S*)-**1** substituted with a chlorine atom at position 4 of the pyridine ring was also synthesized from pyridono-crown ether (*S*,*S*)-**12** reacting the latter with thionyl chloride in $CHCl_3$ in the presence of a catalytic amount of *N*,*N*-dimethylformamide (DMF) (see Scheme 2). Pyridino-crown ether (*S*,*S*)-**2** substituted with a bromine atom at position 4 of the pyridine ring was also prepared from pyridono-crown ether (*S*,*S*)-**13**. We used phosphorus pentabromide and $CHCl_3$ as a solvent in this case.

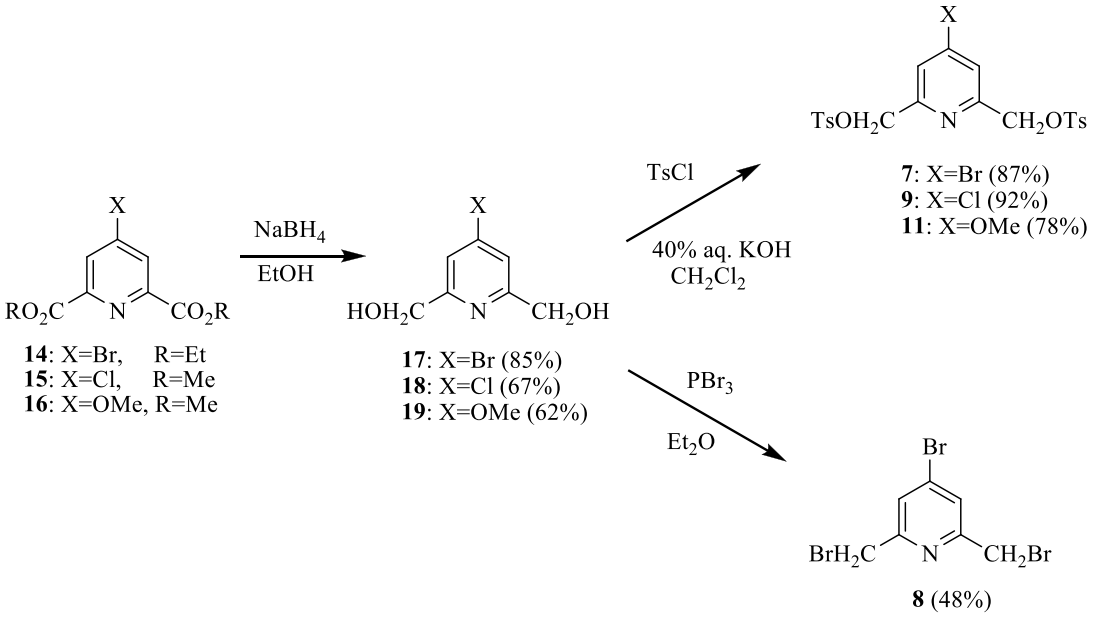


Scheme 2. Synthesis of pyridino-crown ether derivatives (*S*,*S*)-**1** and (*S*,*S*)-**2** from enantiopure pyridono-crown ethers (*S*,*S*)-**12** and (*S*,*S*)-**13**.

Tetraethylene glycols (*S*,*S*)-**6** and (*S*,*S*)-**10** (see Scheme1) were obtained as described in the literature.[8,15]

Upon reduction of diesters **14**, **15** and **16** with $NaBH_4$, 4-substituted pyridine-2,6-dimethanols **17, 18** and **19** were obtained (see Scheme3) in a similar manner as described in the literature for analogous compounds.[18] In the latter literature, this type of diols were not isolated. A modified procedure of Lüning *et al*[19] was used to synthesize chloro-diol **18**. Instead of the long time (2 days) continuous extracting, we isolated **18** by recrystallization from water. All of these diols **17**,

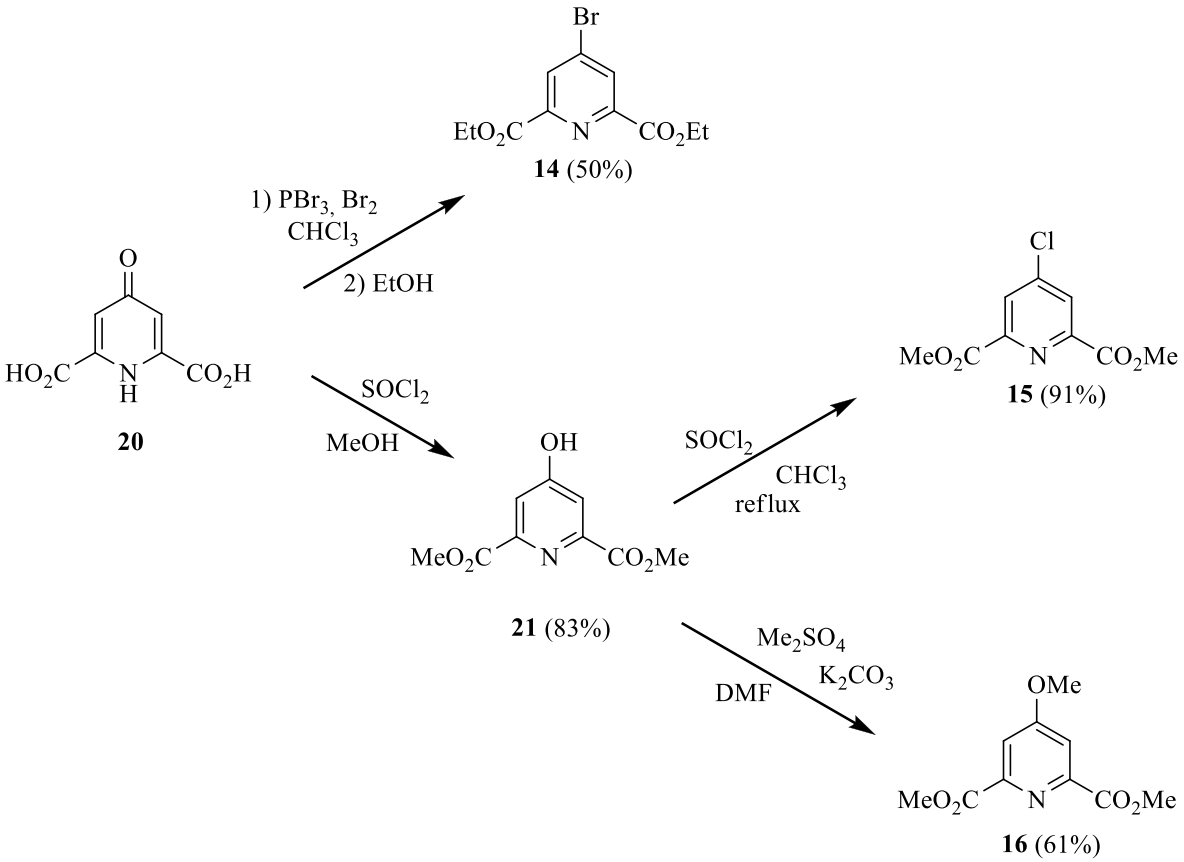
18 and **19** were converted to ditosylates **7, 9** and **11** with tosyl chloride in a mixture of CH_2Cl_2 and 40 % aqueous KOH. Bis-bromomethyl derivative **8** was prepared from bromo-diol **17** using phosphorus tribromide in ether[20] (Scheme3).



Scheme 3. Synthesis of precursors **7, 8, 9** and **11** for pyridino-crown ether derivatives.

Dihydro-4-oxo-2,6-pyridinedicarboxylic acid **20** was prepared as reported[18] from commercially available and cheap starting materials like acetone, sodium, EtOH, diethyl oxalate and ammonia. Pyridone derivative **20** was treated with bromine and phosphorus tribromide and then with EtOH to yield diethyl 4-bromopyridine-2,6-dicarboxylate **14**, applying a modified procedure of the one reported by Takalo and Kankare[21] (Scheme 4). Dimethyl chelidamate **21** was prepared from chelidamic acid as reported.[6]

Diester **21** was treated with thionyl chloride and a catalytic amount of DMF for 2 days at reflux temperature in $CHCl_3$ to obtain dimethyl 4-chloro-pyridine-2,6-dicarboxylate **15** (see Scheme 4). This method gave **15** with a higher yield (91%) than applying the reported[22] one (69%), where Markees and Kidder used the more expensive and more dangerous PCl_5 for this transformation. Dimethyl 4-methoxypyridine-2,6-dicarboxylate **16** was synthesized according to the literature[18].



Scheme 4. Synthesis of pyridine diester derivatives **14**, **15** and **16** containing a bromine or a chlorine atom or a methoxy group at position 4 of the pyridine ring

X-ray analysis

In order to obtain more information about the structure of (*S*,*S*)-**5** in the solid state, a single crystal was grown using a mixture of heptane and CH_2Cl_2. Several dimethyl-substituted pyridino-crown ethers prepared from (*S*,*S*)-**5** form complexes with one molecule of water.[9] X-ray analysis proved that the water molecule is not complexed by the crystalline form of macrocycle (*S*,*S*)-**5**. Figure 2 shows the molecular diagram of crystalline (*S*,*S*)-**5** (where only the major disorder component is displayed).

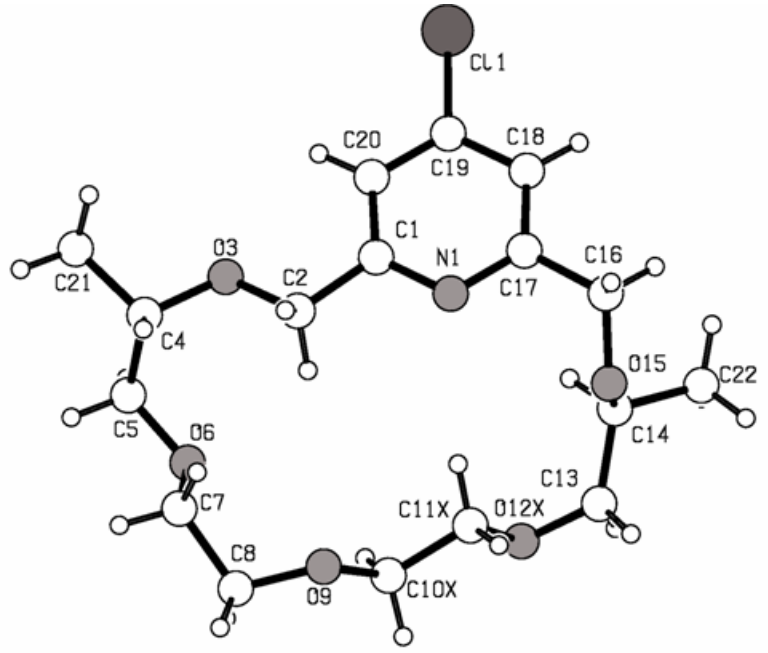


Figure 2. Molecular diagram of (*S*,*S*)-**5** with the numbering of atoms.

This paper reports only the synthesis of the new ligands, their precursors and the solid state structure of ligand (*S*,*S*)-**5**. Their transformation to enantioselective sensor and selector molecules and the applications of the latter compounds will be published in due course.

Conclusions

We can conclude that the enantiopure pyridino-18-crown-6 ethers (*S*,*S*)-**1**─(*S*,*S*)-**5** can be prepared from the enantiopure chiral tetraethylene glycol [(*S*,*S*)-**6** and (*S*,*S*)-**10**] dialkoxides in THF and pyridine derivatives **7**, **8**, **9** and **11** in THF by a Williamson-type macrocyclic ether formation reaction. Pyridino-crown ether derivatives (*S*,*S*)-**1** and (*S*,*S*)-**2** can also be synthesized from the corresponding pyridono-crown ethers (*S*,*S*)-**12** and (*S*,*S*)-**13** treating them with thionyl chloride or phosphorus pentabromide. These enantiopure dialkyl-substituted pyridino-18-crown-6 ethers [(*S*,*S*)-**1**─(*S*,*S*)-**5**] are useful precursors for enantioselective sensor and selector molecules with wide applications.

Experimental Section

General. Infrared spectra were recorded on a Zeiss Specord IR 75 spectrometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. NMR spectra were recorded in $CDCl_3$ either on

a Bruker DRX-500 Avance spectrometer (at 500 MHz for ^{1}H and at 125 MHz for ^{13}C spectra) or on a Bruker 300 Avance spectrometer (at 300 MHz for ^{1}H and at 75 MHz for ^{13}C spectra) and it is indicated in each individual case. Mass spectra were recorded on a ZQ 2000 MS instrument (Waters Corp.) using ESI method. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro-melting point apparatus and were uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminium oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminium oxide (neutral, activated, Brockman I) and silica gel 60 (70-230 mesh, Merck) were used for column chromatography. Ratios of solvents for the eluents are given in volumes (mL/mL). Solvents were dried and purified according to well established methods[23]. Evaporations were carried out under reduced pressure unless otherwise stated.

X-ray measurements. Intensity data were collected on an RAXIS-RAPID diffractometer (graphite monochromator Cu-*K*α radiation, λ = 1.54187 **Å**) at 293(2) *K* in the range 7.15 ≤θ≤ 70.05°. A multi-scan absorption correction was applied to the data (the minimum and maximum transmission factors were 0.666 and 1.000)[24].

The structure was solved by direct methods (SIR2004)[25]. Anisotropic full-matrix least-squares refinement[26] on F^2 for all non-hydrogen atoms yielded $R1$ = 0.0578 and $wR2$ = 0.1542 for 1332 [$I>2\sigma(I)$] and $R1$ = 0.0652 and $wR2$ = 0.1668 for all (3376) intensity data, (number of parameters = 248, S = 1.126, absolute structure parameter x = -0.03(3), the maximum and mean shift/esd is 0.003 and 0.000). The maximum and minimum residual electron density in the final difference map was 0.436 and -0.285 e.Å^{-3}. Hydrogen atomic positions were calculated from assumed geometries. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded to.

General procedure for the preparation of the chiral pyridino-crown ethers

(*S*,*S*)-1—(*S*,*S*)-5 (see Scheme 1). In a dry three-necked round-bottom flask equipped with a reflux condenser, argon inlet and a dropping funnel, a suspension of NaH (1.53 g, 38.4 mmol, 60% dispersion in mineral oil) in pure and dry THF (30 mL) was stirred vigorously at 0 °C for 2 min.

To this suspension was added slowly the appropriate optically active tetraethylene glycol (*S*,*S*)-**6** or (*S*,*S*)-**10** (13.7 mmol) dissolved in pure and dry THF (170 mL) under Ar 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 to -10°C and 2,6-bis(tosyloxymethyl)pyridine derivative **7** or **8** or **9** or **11** (14.5 mmol) dissolved in pure and dry THF (200 mL) was added in 0.5 h. After addition of the appropriate ditosylate the reaction mixture was allowed to warm up slowly to room

temperature and it was stirred under these conditions until the TLC analysis (Al_2O_3 TLC; EtOH - toluene 1:30) showed the total consumption of the starting materials (2 days).
The solvent was evaporated, and the residue was dissolved in a mixture of CH_2Cl_2 (100 mL) and ice-water (100 mL). The phases were shaken thoroughly and separated. The aqueous phase was extracted with CH_2Cl_2 (3×200 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified as described below for each compound to result in the optically active pyridino-crown ethers [(*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3**, (*S*,*S*)-**4**, (*S*,*S*)-**5**].

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

A. From (*S*,*S*)-10 and 9 (see Scheme 1). Crown ether (*S*,*S*)-**1** was prepared as described above in the General procedure starting from diisobutyl-substituted tetraethylene glycol (*S*,*S*)-**10** (3.78 g, 12.3 mmol) and ditosylate **9** (5.50 g, 13.1 mmol). The crude product was purified by column chromatography first on neutral aluminium oxide using EtOH-toluene (1:140) mixture as an eluent followed by aluminium oxide preparative thin layer chromatography using isopropyl-alcohol-toluene (1:40) mixture to yield (*S*,*S*)-**1** (710 mg, 13%) as a pale yellow oil. Rf: 0.87 (aluminium oxide TLC, EtOH-toluene 1:20). $[\alpha]^{25}_D$= -14,9 (c 1.36, CH_2Cl_2); IR (neat) ν_{max} 2954, 2923, 2867, 1574, 1466, 1413, 1385, 1366, 1349, 1277, 1115, 1042, 943, 921, 856, 837, 754, 662, 542, 408 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 0.89 (d, 6H, *J*=6.3 Hz, diastereotopic methyl group), 0.91 (d, 6H, *J*=6.6 Hz, diastereotopic methyl group), 1.15-1.21 (m, 2H), 1.46-1.53 (m, 2H), 1.72-1.81 (m, 2H), 3.43-3.59 (m,12H), 3.66-3.71 (m, 2H), the diastereotopic benzylic protons give AB quartet δ_A: 4.77 and δ_B: 4.82 (J_{AB} = 13.0 Hz, 4H), 7.27 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.5, 23.6, 24.8, 41.2, 70.8, 71.2, 72.0, 75.6, 76.6, 120.6, 145.2, 160.6.; MS: 443.2 $(M+1)^+$. Anal. Calcd. for $C_{23}H_{38}ClNO_5$: C, 62.22; H, 8.63; Cl, 7.98; N, 3.15. Found C, 62.02; H, 8.66; Cl, 7.89; N, 3.18.

B. From (*S*,*S*)-12 and thionyl chloride (see Scheme 2). To a solution of diisobutyl-substituted pyridono-crown ether (*S*,*S*)-**12** (937 mg, 2.16 mmol) in pure and dry $CHCl_3$ (20 mL) was added firstly a catalytic amount of pure and dry DMF (three drops) followed by thionyl chloride (3.9 mL, 6.26 g, 53.5 mmol), and the resulting mixture was stirred at reflux temperature under Ar for 1.5 h. The volatile components were removed and the residue was dissolved in a mixture of CH_2Cl_2 (100 mL) and 12.5% aqueous tetramethylammonium hydroxide (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3X30 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by column chromatography on neutral aluminium oxide using EtOH-toluene (1:160) mixture as an eluent to gain (*S*,*S*)-**1** (297 mg, 31 %) as a pale yellow oil. Macrocycle (*S*,*S*)-**1** obtained this way was identical in every aspect to that prepared by the previous procedure (A).

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

A. From (*S*,*S*)-6 and 7 (see Scheme 1). Crown ether (*S*,*S*)-**2** was prepared as described above in the General procedure starting from dimethyl-substituted tetraethylene glycol (*S*,*S*)-**6** (3.05 g, 13.7 mmol) and ditosylate derivative **7** (7.66 g, 14.5 mmol). The crude product was purified by column chromatography first on neutral aluminium oxide using EtOH-toluene (1:100) mixture as an eluent followed by column chromatography on silica gel using MeOH-$CHCl_3$-triethylamine (1:10:0.01) to give (*S*,*S*)-**2** (443 mg, 8%) as a pale yellow oil. Rf: 0.58 (aluminium oxide TLC, EtOH-toluene 1:30). $[\alpha]^{25}_D$=+17.7 (c 1.516, CH_2Cl_2); IR (neat) ν_{max} 2968, 2865, 1565, 1452, 1409, 1372, 1350, 1332, 1268, 1108, 925, 858, 815, 749, 661, 528, 490, 413 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.13 (d, *J*=6.4 Hz, 6H), 3.42-3.61 (m, 12H), 3.72-3.81 (m, 2H), 4.74-4.76 (m, 4H), 7.38 (s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.2, 70.8, 71.0, 71.4, 74.2, 75.0, 76.3, 123.6, 133.7, 160.3; MS: 403,1 $(M+1)^+$. Anal. Calcd. for $C_{17}H_{26}BrNO_5$: C, 50.50; H, 6.48; Br, 19.76; N, 3.46. Found: C, 50.62; H, 6.60; Br, 19.84; N, 3.44.

B. From (*S*,*S*)-6 and 8 (see Scheme 1). Crown ether (*S*,*S*)-**2** was prepared as described above starting from dimethyl-substituted tetraethylene glycol (*S*,*S*)-**6** (590 mg, 2.66 mmol) and tribromo derivative **8** (914 mg, 2.66 mmol) instead of the ditosylate derivate **7**. The crude product was purified as above (A) to yield (*S*,*S*)-**2** (21.5 mg, 2%). Macrocycle (*S*,*S*)-**2** obtained this way was identical in every aspect to that prepared by the previous (A) procedure.

C. From (*S*,*S*)-13 and phosphorus pentabromide (see Scheme 2). To a solution of dimethyl-substituted pyridono-crown ether (*S*,*S*)-**13** semihydrate (602.2 mg, 1.72 mmol) in pure and dry $CHCl_3$ (6 mL) was added phosphorus pentabromide (3.43 g, 6.88 mmol) dissolved in $CHCl_3$ (4 mL), and the resulting mixture was stirred at reflux temperature under Ar until the TLC analysis (Al_2O_3 TLC; EtOH-toluene 1:30) showed the total consumption of the starting dimethyl-substituted pyridono-crown ether (*S*,*S*)-**13** and also the formation of the new compound (*S*,*S*)-**2** (2 days). The reaction mixture was poured into ice-water (20 mL) and the pH of the mixture was adjusted to 9 with aqueous Me_3N solution. The mixture was shaken with $CHCl_3$ (3X20 mL), the combined organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by preparative thin layer chromatography on silica gel using EtOH-acetone-hexane (2:1:1) mixture as an eluent to furnish (*S*,*S*)-**2** (125.2 mg, 18%). The product obtained this way had the same physical and spectral data as the one prepared above from the reaction of (*S*,*S*)-**6** and **7**.

(4*S*,14*S*)-(-)-4,14-Diisobutyl-19-bromo-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene [(*S*,*S*)-**3**] (see Scheme 1). Crown ether (*S*,*S*)-**3** was prepared as described above in the General procedure starting from diisobutyl-substituted tetraethylene glycol (*S*,*S*)-**10** (2.71 g, 8.84 mmol) and ditosylate **7** (4.93 g, 9.35 mmol). The crude product was purified by column chromatography first on neutral aluminium oxide using EtOH-toluene (1:100) mixture as an eluent followed by column chromatography on silica gel using EtOH-acetone-hexane (1:1:20) mixture as an eluent to give (*S*,*S*)-**3** (518 mg, 12%) as a pale yellow oil. Rf: 0.69 (aluminium oxide TLC, EtOH-toluene 1:30).

$[\alpha]^{25}_D$= -14.6 (c 0.807, CH_2Cl_2); IR (neat) ν_{max} 2954, 2920, 2868, 1567, 1467, 1411, 1386, 1367, 1350, 1261, 1116, 1043, 942, 907, 865, 803, 731, 662, 646, 529, 440 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.92 (d, 6H, *J*=7.3 Hz, diastereotopic methyl group), 0.95 (d, 6H, *J*=7.0 Hz, diastereotopic methyl group), 1.10-1.23 (m, 2H), 1.46-1.59 (m, 2H), 1.73-1.84 (m, 2H), 3.40-3.57 (m, 12H), 4.80-4.93 (m, 4H), 7.52 (s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.6, 23.6, 24.8, 41.2, 70.8, 71.0, 72.2, 74.7, 76.5, 123.0, 134.4, 160.4; MS: 487.2 $(M+1)^+$. Anal. Calcd. for $C_{23}H_{38}BrNO_5$: C, 56.56; H, 7.84; Br, 16.36; N, 2.87. Found C, 56.80; H, 7.79; Br, 16.07; N, 2.57.

(4*S*,14*S*)-(+)-4,14-Dimethyl-19-methoxy-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]-heneicosa-1(21),17,19-triene [(*S*,*S*)-**4**] (see Scheme 1). Crown ether (*S*,*S*)-**4** was prepared as described above in the General procedure starting from dimethyl-substituted tetraethylene glycol (*S*,*S*)-**6** (2.31 g, 10.0 mmol) and ditosylate **11** (5.32 g, 11.0 mmol). The crude product was purified by column chromatography first on neutral aluminium oxide using EtOH-toluene (1:80) mixture as an eluent followed by column chromatography on silica gel using EtOH-acetone-hexane (2:1:1) eluent to furnish (*S*,*S*)-**4** (603.7 mg, 16%) as a pale yellow oil. Rf: 0.81 (aluminium oxide TLC, EtOH-toluene 1:10). $[\alpha]^{25}_D$= +14.3 (c 0.81, CH_2Cl_2); IR (neat) ν_{max} 2967, 2863, 1597, 1575, 1460, 1392, 1370, 1341, 1323, 1252, 1193, 1106, 1050, 989, 920, 852, 763, 688 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 1.16 (d, *J*=6.4 Hz, 6H); 2.67 (br. s half mol of complexed water, 1H); 3.43-3.63 (m, 12H); 3.78-3.83 (m, 2H), 3.85 (s, 3H), the diastereotopic benzylic protons give an AB quartet δ_A: 4.73 and δ_B: 4.76 (J_{AB} = 13 Hz, 4H), 6.79 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.3, 55.3, 70.8, 70.9, 72.0, 73.8, 76.1, 106.6, 160.3, 166.9; MS: 356.2 $(M+1)^+$; Anal. Calcd. for $C_{18}H_{29}NO_6 \cdot 0.5H_2O$: C, 59.32; H, 8.30; N, 3.84. Found C, 59.35; H, 8.15; N, 3.73.

(4*S*,14*S*)-(+)-4,14-Dimethyl-19-chloro-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene [(*S*,*S*)-**5**] (see Scheme 1). Crown ether (*S*,*S*)-**5** was prepared as described above in the General procedure starting from dimethyl-substituted tetraethylene glycol (*S*,*S*)-**6** (380 mg, 1.7 mmol) and ditosylate **9** (760 mg, 1.8 mmol). The crude product was purified by column chromatography first on neutral aluminium oxide using EtOH-toluene (1:100) mixture as an eluent followed by column chromatography on silica gel using MeOH-CH_2Cl_2-triethylamine (1:10:0.01) mixture as an eluent to give (*S*,*S*)-**5** (55 mg, 9%) as a pale yellow oil. The latter was kept in a freezer for 2 days until that time it solidified. We obtained single crystals using a mixture of heptane and CH_2Cl_2. Rf: 0.60 (aluminium oxide TLC, EtOH-toluene 1:20). Mp: 45 °C (heptane-CH_2Cl_2)

The product had the same spectral data as reported in the literature[9].

X-ray measurements

Crystal data: $C_{17}H_{26}ClNO_5$, Fwt.: 359.84, colorless chunk, size: 0.68 x 0.63 x 0.55 mm, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 8.9604(2) Å, *b* = 9.2765(2) Å, *c* = 22.4807(6) Å, *V* = 1868.62(8) $Å^3$, *T* = 293(2) *K*, *Z*= 4, *F*(000) = 768, *Dx* = 1.279 Mg/m^3, m = 2.029 mm^{-1}.

A summary of crystal data, data collection and least-squares is given in Table1.

Table 1. Crystal data and details of the structure determination for (*S*,*S*)-**5**

Crystal Data	
Formula	$C_{17}H_{26}ClNO_5$
Formula weight	359.84
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (No. 19)
Unit cell *a*, *b*, *c* (Å)	8.9604(2), 9.2765(2), 22.4807(6)
V (Å^3)	1868.62(8)
Z	4
D(calc) (g/cm^3)	1.28
m(Cu*K*α) (mm^{-1})	2.03
F(000)	768
Crystal size (mm)	0.55 x 0.63 x 0.68
Data Collection	
Temperature (*K*)	293
Radiation (Å)	l = 1.54187 (Cu*K*α)
Q_{min}, Q_{max} (°)	7.2, 70.1
Total, unique data, *R*(int)	36160, 3376, 0.066
Observed data [*I* > 2.0 s(*I*)]	2980
Refinement	
N_{ref}, N_{par}	3376, 248
R, *wR*2, *S*	0.0578, 0.1668, 1.14
Max. and average shift/error	0.02, 0.00
Flack *x*	-0.03(3)
Min. and max. residual density (e/Å^3)	-0.285, 0.436

Cell parameters were determined by least-squares using 28844 (6.87≤ θ ≤ 70.05°) reflections.

Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary material (CCDC-800246).

Note on disorder: Atoms O12, C11, C10 split into two positions marked with x and y in 0.53: 0.47 ratio.

4-Bromo-2,6-bis[(*p*-tolylsulfonyl)oxymethyl]pyridine (7) (see Scheme 3). Bromo ditosylate **7** was prepared in the same way as described above for its chloro analogue **9** starting from bromo diol **17** (1.0 g, 4.57 mmol), tosyl chloride (1.83 g, 9.59 mmol), CH_2Cl_2 and 40 % aqueous KOH solution (50 mL of each). We gained the desired **7** (2.1 g, 87 %) as white crystals. Rf: 0.28 (silica gel TLC, acetone-hexane 1:2). Mp: 110-111 °C (CH_2Cl_2-MeOH) (lit. mp: 110-111 °C[16] (CH_2Cl_2-hexane)). Bromo ditosylate **7** obtained this way had the same spectroscopic data than those of reported[16].

4-Bromo-2,6-bis(bromomethyl)pyridine (8) (see Scheme 3). Tribromo derivative **8** was synthesized with a modification of a reported procedure.[20] To a suspension of bromo diol **17** (1.0 g, 4.57 mmol) in ether (50 mL) at 0 °C, phosphorus tribromide (0.65 mL, 6.86 mmol) was added dropwise, after which the mixture was stirred at room temperature for 30 min and then refluxed for 4 h, until TLC analysis (SiO_2 TLC, acetone-hexane 1:2) showed the total consumption of the starting material and only one main spot for the product. After cooling down the mixture to room temperature, the pH of it was adjusted to 7 with 5 % aqueous $NaHCO_3$ solution (95 mL). The aqueous solution was extracted with ether (3X30 mL) and the combined organic phase was evaporated. The residue was recrystallyzed from CH_2Cl_2-MeOH mixture to give **8** (0.75 g, 48 %) as white crystals. Rf: 0.48 (silica gel TLC, acetone-hexane 1:2). Mp: 125-126 °C (CH_2Cl_2-MeOH) (lit. mp: 128-129 °C[20] (CH_2Cl_2-hexane)). Tribromo derivative **8** obtained this way had the same spectroscopic data than those reported[20].

4-Chloro-2,6-bis[(*p*-tolylsulfonyl)oxymethyl]pyridine (9) (see Scheme 3). Chloro diol **18** (1.0 g, 5.76 mmol) was vigorously stirred in a mixture of CH_2Cl_2 and 40 % aqueous KOH solution (60 mL of each) at 0 °C and tosyl chloride (2.31 g, 12.1 mmol) was added to it in one portion. The mixture was stirred at 0 °C for one hour then at room temperature until the TLC analysis (SiO_2 TLC; MeOH-toluene 1:4) showed the total consumption of the starting material and only one main spot for the product. The mixture was washed into a separatory funnel with water and CH_2Cl_2 (30 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. The residue was recrystallyzed from a mixture of CH_2Cl_2-MeOH to give **9** (2.22 g, 92%) as white needles. Rf: 0.47 (silica gel TLC, acetone-hexane 1:2). Mp: 101 °C (CH_2Cl_2-MeOH). IR (KBr) ν_{max} 3024, 2923, 2853, 1600, 1592, 1582, 1450, 1371, 1361, 1188, 1175, 1027, 939, 851, 812, 670, 607, 558, 549, 543, 535 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 6H), 5.03 (s, 4H), 7.29 (s, 2H), 7.35 (d, *J*=8.0 Hz, 4H), 7.81 (d, *J*=8.0 Hz, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.8, 70.7, 121.7, 128.2, 130.2, 132.8, 145.6,

146.3, 155.4; MS: 481.0 $(M+1)^+$; Anal. Calcd. for $C_{21}H_{20}ClNO_6S_2$: C, 52.33; H, 4.18; Cl, 7.36; N, 2.91; S, 13.31; Found C, 52.05; H, 3.93; Cl, 7.38; N, 2.84; S, 12.40.

4-Methoxy-2,6-bis[(*p*-tolylsulfonyl)oxymethyl]pyridine (11) (see Scheme 3). Methoxy diol **19** (2.43 g, 14.4 mmol) was stirred in a mixture of CH_2Cl_2 and 40 % aqueous KOH solution (120 mL of each) at 0 °C and tosyl chloride (7.39 g, 38.99 mmol) was added to it in one portion. The mixture was stirred at 0 °C for one hour, then at room temperature until the TLC analysis (silica gel TLC, MeOH-toluene 1:4) showed the complete conversion of the starting materials and only one main spot for the product. The mixture was washed into a separatory funnel with water and CH_2Cl_2 (60 mL of each). The resulting mixture was shaken well and separated. The aqueous phase was shaken with CH_2Cl_2 (3X60 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed. The residue was recrystallyzed from CH_2Cl_2-MeOH to give ditosylate **11** (7.06 g, 78%) as white crystals. Mp 77-78 °C (CH_2Cl_2-MeOH) (lit. mp: 77-78 °C[18] ($ClCH_2CH_2Cl$-MeOH)). Rf: 0.37 (silica gel TLC, acetone-hexane 1:2). Ditosylate **11** obtained this way had the same spectroscopic data than those of reported[18].

Diethyl 4-bromo-2,6-pyridinedicarboxylate (14) (see Scheme 4). Bromo diester **14** was prepared with a modification of a reported procedure[21]. In a dry three-necked round-bottom flask equipped with a reflux condenser, argon inlet and a dropping funnel was stirred vigorously a solution of bromine (3.8 mL, 74.5 mmol) in pure and dry $CHCl_3$ (38 mL). To this solution was added phosphorus tribromide (8.4 mL, 89.5 mmol) drop by drop at 0 °C. Stirring was continued at 0 °C for 5 minutes to obtain phosphorus pentabromide. Dry dihydro-4-oxo-2,6-pyridinedicarboxylic acid **20** (5.0 g, 25 mmol) was added to the reaction mixture and after stirring it at room temperature for 5 minutes, the temperature was raised to 90 °C and maintained at this temperature overnight. After cooling down the mixture to 0 °C, EtOH (300 mL) was added slowly to it and after half an hour the solution was concentrated under reduced pressure. The residue was triturated with a mixture of ice and water (50 g of each), to obtain white crystals. The TLC analysis (SiO_2 TLC, acetone-hexane 1:2) showed the total consumption of the starting material and only one main spot for the product. This crude product was recrystallized from diisopropyl ether, to yield bromo diester **14** (11.4 g, 50 %) as white crystals. Mp:95-96 °C (diisopropyl ether) (lit. mp: 95-96 °C[21] (hexane)). Rf: 0.39 (silica gel TLC, acetone-hexane 1:2). Bromodiester **14** obtained this way had the same spectroscopic data than those of reported[21].

Dimethyl 4-chloro-2,6-pyridinedicarboxylate (15) (see Scheme 4). In a dry three-necked round-bottom flask equipped with a reflux condenser, argon inlet and a dropping funnel was stirred vigorously a solution of dimethyl 4-hydroxy-pyridine-2,6-dicarboxylate **21** (3.0 g, 14.2 mmol) in pure and dry $CHCl_3$ (30 mL). Thionyl chloride (10.4 ml, 142 mmol) was added slowly at 0 °C to the mixture followed a catalytic amount of DMF (2 drops) was added. The reaction mixture was stirred at 0 °C for 10 min, then at reflux temperature for 2 days. The volatile components were evaporated under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 and 10% aqueous $NaHCO_3$ solution (30 mL of each). The phases were shaken well and separated. The organic phase was shaken with water (2×30 mL), dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was recrystallized from MeOH to give chloro diester **15**

(2.97 g, 91%) as colorless needles. Mp: 139-141 °C (MeOH) (lit. mp: 139-140 °C[27] (MeOH)). Rf: 0.54 (silica gel TLC, MeOH-toluene 1:4). Chlorodiester **15** obtained this way had the same spectroscopic data than those of reported[27].

4-Bromo-2,6-pyridinedimethanol (17) (see Scheme 3). Bromo diol **17** was prepared applying the same reaction conditions as described for the synthesis of chloro diol **18** using bromo ester **14** (5.0 g, 16.5 mmol), dry EtOH (130 mL) and $NaBH_4$ (3.33 g, 88 mmol). We obtained bromo diol **17** (3.04 g, 85 %) as white crystals. Mp:158-160 °C (water) (lit. mp: 162-164 °C[20] (acetone)). Rf: 0.34 (silica gel TLC, acetone-hexane 1:1). Bromodiol **17** obtained this way had the same spectroscopic data than those of reported[20].

4-Chloro-2,6-pyridinedimethanol (18) (see Scheme 3). Chloro diol **18** was synthesized with a modification of the reported procedure[19].To a suspension of chloro ester **15** (12.88 g, 56.1 mmol) in dry EtOH (360 mL) at 0 °C, $NaBH_4$ (11.33 g, 300 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 for 24 h. Acetone (220mL) 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 Na_2CO_3 solution (140 mL). The mixture was refluxed for 1 h. Water was distilled off, then the residue was recrystallized from water. Chloro diol **18** (6.52 g, 67 %) was obtained as white crystals. Mp:134-136 °C (water) (lit. mp: 134-135 °C[19]). Rf: 0.16 (silica gel TLC, acetone-hexane 1:2). Chlorodiol **18** obtained this way had the same spectroscopic data than those of reported[19].

4-Methoxy-2,6-pyridinedimethanol (19) (see Scheme 3). Methoxy diol **19** was prepared in a similar manner as described above for chloro diol **18** using methoxy ester **16** (5.19 g, 23 mmol), dry EtOH (40 mL) and $NaBH_4$ (2.7 g, 71 mmol). The crude product was recrystallized from $CHCl_3$ to obtain **19** (2.43 g, 62 %). The white crystals melted at 125-127 °C ($CHCl_3$) (lit. mp: 121-122 °C[28] ($CHCl_3$)). Rf: 0.46 (silica gel TLC, MeOH-CH_2Cl_2 1:5). Methoxydiol **19** obtained this way had the same spectroscopic data than those of reported[28].

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