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Synthesis of new optically active pyridino- and pyridono-18-crown-6 type ligands containing four lipophilic chains

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Abstract—Highly lipophilic enantiomerically pure pyridino- and pyridono-18-crown-6 type ligands containing four stereogenic centers to which butyl or butoxymethyl groups are attached have been synthesized. X-Ray analysis of the (*R*)-1-phenylethylammonium and benzylammonium perchlorate complexes of the unsubstituted pyridono ligand revealed, that, in contrast to the free ligand, in the complex the hydroxypyridine tautomer is present.

1. Introduction

Since the report of Bradshaw et al. on the first optically active pyridino-18-crown-6 type ligand (*S*,*S*)-**1** (Fig. 1) 20 years ago[1] several dozen similar macrocycles containing two stereogenic centers on the macroring have been prepared and studied for enantiomeric recognition of chiral protonated primary arylalkyl amines.[2–5] These studies have shown that the degree of enantiomeric recognition (enantioselectivity) is governed by the balance of intermolecular attractive and repulsive interactions. Probably the most important attractive interaction is the tripod-like H-bonding between the three ammonium hydrogens of the guest and the pyridine nitrogen and two alternate oxygen atoms of the host, respectively. Frequently,[6] but not necessarily, π–π stacking between the aromatic rings of the host and guest is added to this attractive interaction. The third and crucial interaction is the steric repulsion between the substituents at the stereogenic centers of the macrocycle and certain hydrogen atoms of the alkyl or arylalkyl ammonium salt.[5]

Although the enantiomerically pure pyridino macrocycles containing two substituents, such as (*S*,*S*)-**2**, (*R*,*R*)-**3** and (*S*,*S*)-**4** have been thoroughly studied,[5,6] to our knowledge only one enantiomerically pure analogue containing four alkyl substituents (*R*,*R*,*R*,*R*)-**4** (Fig. 1) has been reported.[7] The latter ligand showed high enantioselectivity towards the enantiomers of 1-(1-naphthyl)ethylammonium perchlorate (NEA) and especially to 1-phenylethylammonium perchlorate (PEA) expressed as the differences of the free energies of activation for the dissociation of diastereomeric complexes (*R*,*R*,*R*,*R*)-**4**–(*S*)-NEA and (*R*,*R*,*R*,*R*)-**4**–(*R*)-NEA ($\Delta\Delta G_c^{\#}$ 0.9 kcal/mol) and (*R*,*R*,*R*,*R*)-**4**–(*S*)-PEA and (*R*,*R*,*R*,*R*)-**4**–(*R*)-PEA ($\Delta\Delta G_c^{\#}$ 2.2 kcal/mol) respectively. $\Delta\Delta G_c^{\#}$ values were obtained using temperature dependent ^{1}H NMR experiments.[7] Ligand (*R*,*R*,*R*,*R*)-**4**, however, is not lipophilic enough for studying the enantioselective transport of chiral organic ammonium salts or the selective transport of metal ions in an aqueous source phase/organic membrane/aqueous receiving phase system[8] or for potentiometric sensing when incorporated into an electrode membrane.[3,9–11] For the above studies more lipophilic ligands than (*R*,*R*,*R*,*R*)-**4** are required. Lipophilic pyridino ligands containing substituents both at the pyridine ring in *p*-position, e.g. **5**,[12] or also at the macroring, e.g. (±)-**6**,[12] (*S*,*S*)-**7**[13] (*S*,*S*)-**8** and (*R*,*R*)-**9**[14] were also prepared. Unfortunately none of them was suitable for any of the intended applications, because they were very sensitive to acid and were immediately transformed into the stable pyridono ligands **10**,[12] (±)-**11**,[12] (*S*,*S*)-**12**[13], (*S*,*S*)-

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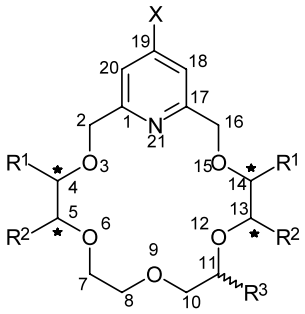
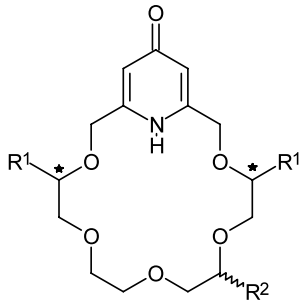


(*S,S*)-**1**: $R^1 = CH_3$, $R^2 = R^3 = X = H$
(*R,R*)-**2**: $R^1 = iBu$, $R^2 = R^3 = X = H$
(*S,S*)-**3**: $R^1 = tBu$, $R^2 = R^3 = X = H$
(*R,R,R,R*)-**4**: $R^1 = R^2 = Me$, $R^3 = X = H$
5: $R^1 = R^2 = R^3 = H$, X = OTHP
(±)-**6**: $R^1 = R^2 = H$, R^3 = octyl, X = OTHP
(*S,S*)-**7:** $R^1 = Me$, $R^2 = R^3 = H$, X = OTHP
(*S,S*)-**8:** $R^1 = iBu$, $R^2 = R^3 = H$, X = OTHP
(*R,R*)-**9:** $R^1 = tBu$, $R^2 = R^3 = H$, X = OTHP

OTHP = 2-tetrahydropyranyloxy



10: $R^1 = R^2 = H$
(±)-**11**: $R^1 = H$, R^2 = octyl
(*S,S*)-**12**: $R^1 = Me$, $R^2 = H$
(*S,S*)-**13**: $R^1 = iBu$, $R^2 = H$
(*R,R*)-**14**: $R^1 = tBu$, $R^2 = H$

Figure 1. Reported pyridino-, *p*-substituted-pyridino-, and pyridono-18-crown-6 type ligands relevant to the present work.

13[14] and (*R,R*)-**14**[14] by removal of the tetrahydropyranyl group.

Among the pyridono macrocycles the most lipophilic one i.e. (±)-**11** was studied thoroughly. It turned out to be a good carrier for Ag^+ and Pb^{2+} ions showing some selectivity for Pb^{2+} when applying a neutral source phase,[15] and in the case of a source phase pH higher than 12, the ligand transported K^+ very selectively over other alkali metal cations[15,16] in a water–CH_2Cl_2–water liquid membrane system.

Our recent results presented herein confirm that pyridono-18-crown-6 type macrocycles can also form stable complexes with primary alkyl or arylalkyl ammonium salts.

In order to get a deeper insight into the nature of selective complexation, crystals amenable to X-ray analysis were prepared from the complexes of (*R*)-1-phenylethylammonium and benzylammonium perchlorates [(*R*)-PEA and BA] of the unsubstituted achiral pyridono ligand **10**. An interesting result of this study was that in the complexes the ligand was in the hydroxypyridine form, in contrast to the free ligand which was shown to be in the tautomeric pyridone form.[12] Thus, similar to pyridino type ligands host and guest were held together by strong multipod-like hydrogen bonding.[5–7] Tautomerization during complexation was also confirmed by IR and NMR spectroscopy.

Thus, chiral lipophilic pyridono-18-crown-6 type ligands can also be good candidates as carriers for enantioselective transport in a water–CH_2Cl_2–water system, for enantioselective solvent extraction and for enantioselective potentiometric sensors of chiral primary ammonium salts. Ligands (*S,S*)-**12**, (*S,S*)-**13** and (*R,R*)-**14**, however, are not lipophilic enough for the above applications. The latter pyridono macrocycles were used in the preparation of such substituted pyridino hosts which were attached to different solid supports for enantioseparation of racemic primary organic ammonium salts.[13,14] To our knowledge no optically active pyridono-18-crown-6 type ligand containing four stereogenic centers has been reported to date. Note that natural ionophores, such as valinomycin, lasalocid, monensin, etc. also contain several stereogenic centers and use their chirality for the selective transport of metal ions through biological membranes.[17,18] Several studies have shown that the stereostructure of chiral synthetic ligands has also a great influence on binding, solvent extraction and transport of metal ions.[18–21]

In our search for enantiopure highly lipophilic chiral hosts with enhanced selectivity both for metal ions and the enantiomers of chiral guests in binding, solvent extraction, membrane transport and potentiometric studies, we prepared ligands (*R,R,R,R*)-**15**–(*S,S,S,S*)-**20** (see Fig. 2). In ligands (*R,R,R,R*)-**16** and (*S,S,S,S*)-**18** the benzyloxy group proved to be quite stable under mildly acidic and basic conditions. The benzyloxy group also increases lipophilicity, so these ligands not only serve as precursors for the pyridono analogues (*R,R,R,R*)-**19** and (*S,S,S,S*)-**20**, but are also excellent candidates for the above mentioned applications.

2. Results and discussion

Novel chiral pyridino-18-crown-6 type ligands (*R,R,R,R*)-**15**, (*R,R,R,R*)-**16**, (*S,S,S,S*)-**17** and (*S,S,S,S*)-**18** (Fig. 2) were prepared by the treatment of the new chiral tetraethylene glycols (*R,R,R,R*)-**21** and (*S,S,S,S*)-**22** with the corresponding pyridine-2,6-dimethanol ditosylates **23**[22] and **24**[22] in the presence of sodium hydride as a base (Scheme 1).

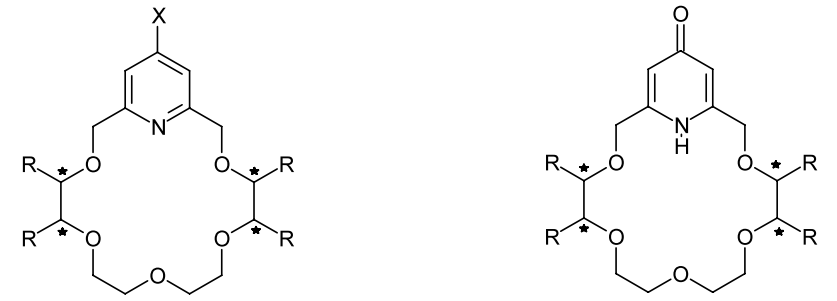
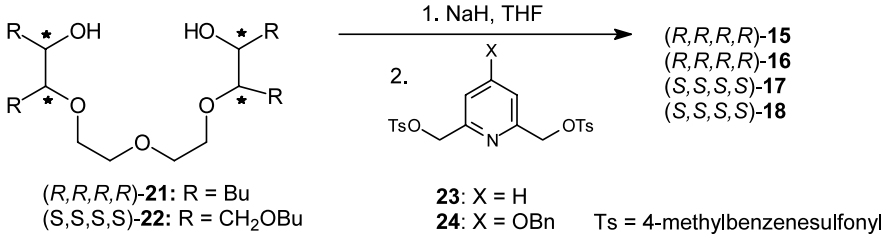
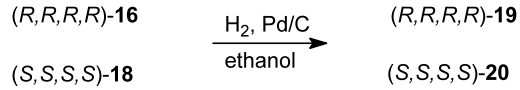


Figure 2. Novel optically active pyridino- and pyridono-18-crown-6 type ligands containing four lipophilic chains.



Scheme 1. Preparation of novel chiral pyridino-18-crown-6 type macrocycles.

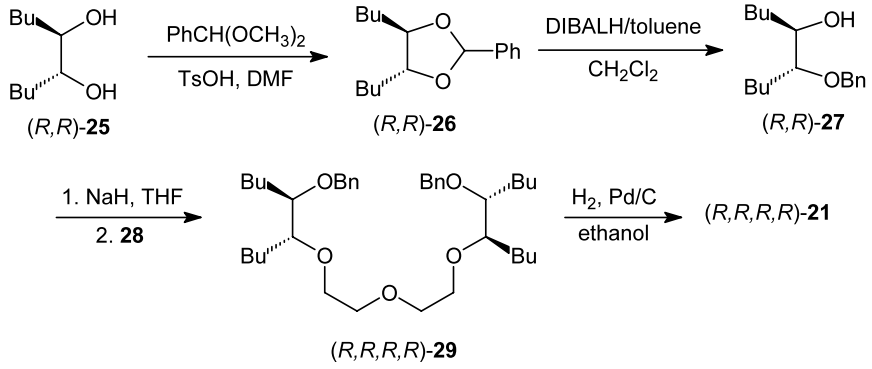
New chiral pyridono-18-crown-6 type macrocycles (*R*,*R*,*R*,*R*)-**19** and (*S*,*S*,*S*,*S*)-**20** were obtained by removal of the benzyl group from benzyloxypyridino-18-crown-6 ligands (*R*,*R*,*R*,*R*)-**16** and (*S*,*S*,*S*,*S*)-**18** by catalytic hydrogenation (Scheme 2).



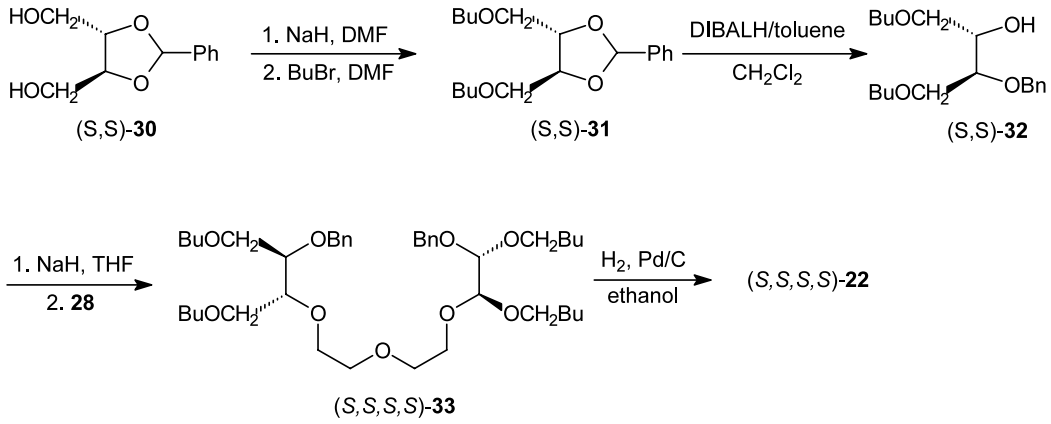
Scheme 2. Preparation of novel chiral pyridono-18-crown-6 type macrocycles.

Chiral tetraethylene glycol derivative (*R*,*R*,*R*,*R*)-**21** was prepared starting from (*R*,*R*)-decane-5,6-diol (*R*,*R*)-**25**,[23] which was transformed to its benzylidene acetal (*R*,*R*)-**26** followed by selective cleavage with diisobutylaluminum hydride (DIBALH)[24] to give the monobenzyl ether (*R*,*R*)-**27**. Reaction of (*R*,*R*)-**27** with diethylene glycol di-*p*-tosylate **28** in a 2:1 molar ratio followed by debenzylation of the resulting oligoether (*R*,*R*,*R*,*R*)-**29** gave the tetraethylene glycol (*R*,*R*,*R*,*R*)-**21** (Scheme 3). The tetrabutoxymethyl-substituted tetraethylene glycol (*S*,*S*,*S*,*S*)-**22**, our key intermediate needed for obtaining chiral ligands (*S*,*S*,*S*,*S*)-**17** and (*S*,*S*,*S*,*S*)-**18**, was prepared from the reported (*S*,*S*)-2,3-benzylidene-threitol (*S*,*S*)-**30**.[25] The disodium salt of diol (*S*,*S*)-**30** was reacted with butyl bromide and then the benzylidene acetal (*S*,*S*)-**31** was cleaved with DIBALH.[24] The sodium salt of monobenzyl ether (*S*,*S*)-**32** was reacted with 0.5 equiv. of diethylene glycol di-*p*-tosylate **28** followed by the removal of the benzyl groups from (*S*,*S*,*S*,*S*)-**33** by catalytic hydrogenation to give (*S*,*S*,*S*.*S*)-**22** (Scheme 4).

In order to obtain more information about the forces operating in the complexation, crystals amenable for



Scheme 3. Preparation of new chiral tetrabutyl-substituted tetraethylene glycol.



Scheme 4. Preparation of new chiral tetrabutoxymethyl-substituted tetraethylene glycol.

X-ray analysis were prepared from the (*R*)-1-phenylethylammonium [(*R*)-PEA] and benzylammonium (BA) perchlorate complexes of the achiral pyridono crown ether **10**. As the asymmetric unit contains two formula units of this complex salt, a principal observation for the (*R*)-1-phenylethylammonium perchlorate 1:1:1 complex of **10** (**10**-(*R*)-PEA) is that geometric properties of both complexes are identical within experimental error (Fig. 3). This applies regarding both their respective shape, (dimensions, conformation) and also other characteristics (e.g. H-bridge pattern, disorder appearance etc.). Since these structure models agree well and may be considered reliable, some interesting questions such as tautomerization of the pyridone rings and H-bonding pattern (Table 1) can be answered. (i) All experimentally localized relevant H-atoms show that all hydrogens of the ammonium group engage in H-bridges in a uniform manner. As mentioned earlier, even the appearance of bifurcated H-bonds is identical in both independent complexes (Fig. 3). (ii) A hydrogen atom involved in H-bonds to one of the oxygen atoms of a perchlorate anion was found at the oxygen atom of the pyridine moiety, indicating that it is in the hydroxypyridine tautomeric form. This is also reflected in the respective bond lengths (Fig. 4).

Table 1. Hydrogen bonding dimensions in the **10**-(*R*)-PEA complex

D–H···A	D–H1(L′)	H···A(L′)	D···A(L′)	D–H···A(°)
N1–H1···N21	0.97	1.94	2.882(0)	165
N1–H3···O3	1.03	2.45	3.021(9)	114
N1–H3···O6	1.03	1.92	2.922(4)	167
N1–H2···O9	0.85	2.40	3.01(0)	131
N1–H2···O12	0.85	2.25	2.987(0)	145

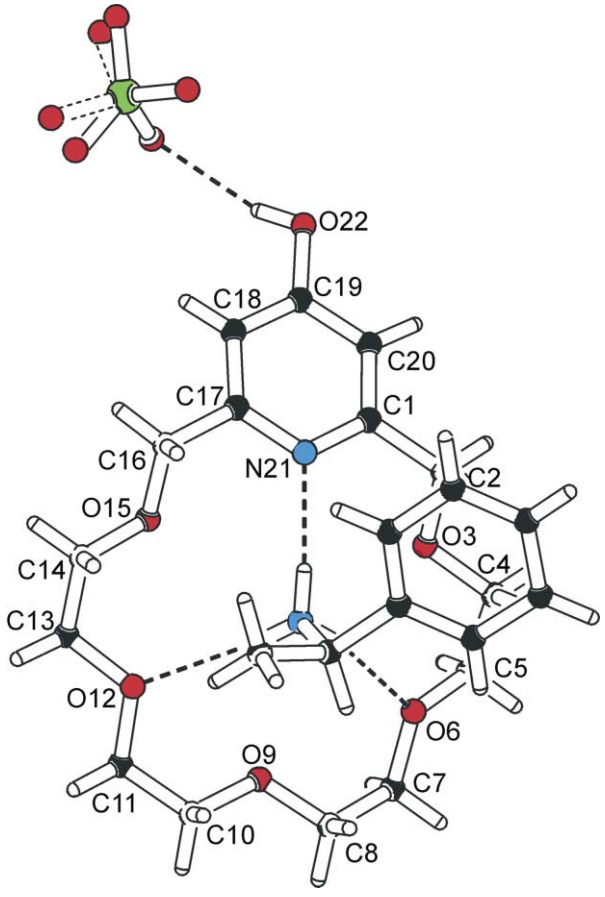


Figure 3. One of the **10**-(*R*)-PEA complexes in its asymmetric unit, with atomic numbering, H-bridges are in broken lines, extensive disorder of the perchlorate anion is visible.

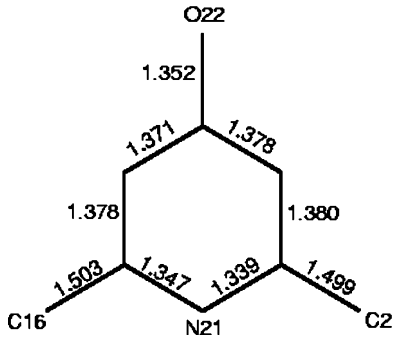


Figure 4. Averaged bond length schematics of the pyridine moiety in the **10**-(*R*)-PEA complex.

The interplanar angle of 56.7° in the **10**-(*R*)-PEA complex of the aromatic rings (shown in the side view in Fig. 5) suggests that there is no π–π-stacking interaction between the two aromatic rings. The evidence of a clear and uniform H-bonding pattern are consistent with that fixation of the ammonium ion in the crown ether cavity being mainly due to H-bonding. Although one of the hydrogens of one of the methylene groups points towards the center of the arene ring, the distance being the sum of the corresponding van der Waals radii (2.93 Å), this interaction should be rather weak and probably illustrates only an electrostatically favorable disposition (Fig. 5).

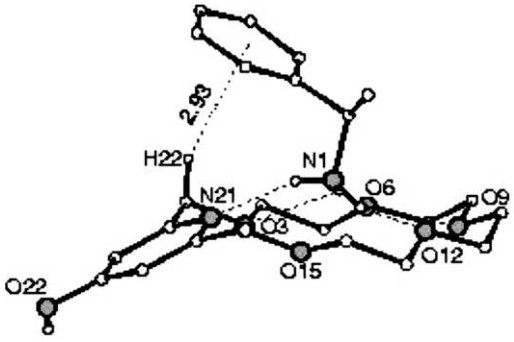


Figure 5. Side view of the **10**-(*R*)-PEA complex with relevant H-bridges in broken lines, also showing one of the methylene hydrogens juxtaposed against the aromatic ring of the cation.

The 1:1:1 complex of **10** with benzylammonium perchlorate **10**-BA crystallizes in a centrosymmetric space group with only one molecule in the asymmetric unit. Its overall appearance is rather similar to that of the **10**-(*R*)–PEA complex. In the solid state the pyridine ring is also in the hydroxy tautomer, the principal H-bonding scheme is identical and anion binding to the -OH group basic functions behave alike. Hydrogen bridges are short for the ammonium moiety (typical H···A distances range from 1.82–2.25 Å, D–H···A angles 160–178°) and are normal for -OH···anion contacts (mean distance is 2.00 Å, D–H···A angle 166°) for both complexes of **10**. The benzene ring of the ammonium salt is even more remote to the hydroxypyridine ring and to the closest methylene group (H···ring center distance 3.2–3.3 Å). Presence of the pyridol tautomer in the complexes [**10**-(*R*)-PEA and **10**-BA]has also been substantiated by NMR and IR evidence, notably the absence of a low field ^{13}C signal at around 180 ppm and the band at around 1635 cm^{-1}, both characteristic for the carbonyl group (Fig. 6).

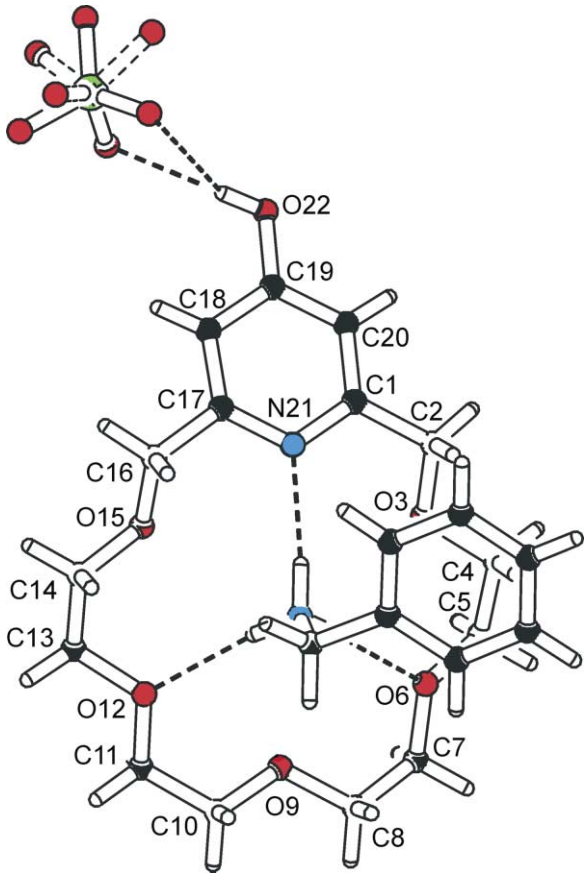


Figure 6. Anisotropic displacement representation of one of the **10**-BA complexes in the asymmetric unit. H-bridges in broken lines.

3. Experimental

3.1. 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. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were taken on a Bruker DRX-500 Avance spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, L. Eötvös University, Budapest, Hungary. MASS Spectra: VG-2AB-2 SEQ reverse geometry mass spectrometer. Melting points were taken on a Boetius micro melting point apparatus and were uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminum oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminum oxide (neutral, activated, Brockman I) and silica gel 60 (70–230 mesh, Merck) were used for column chromatography. Romil Ltd. (Cambridge UK) SuperPurity Solvent grade THF stored under argon was used in all reactions. Solvents were dried and purified according to the well established methods.[26] Evaporations were carried out under reduced pressure.

3.2. (4*R*,5*R*,13*R*,14*R*)-4,5,13,14-Tetrabutyl-3,6,9,12,15-pentaoxa-21-azabicyclo-[15.3.1]heneicosa-1(21),17,19-triene, (*R*,*R*,*R*,*R*)-15

To a suspension of sodium hydride (0.30 g; 7.5 mmol, 60% dispersion in mineral oil) in THF (5 mL) (*R*,*R*,*R*,*R*)-**21** (736 mg, 1.76 mM) in THF (12 mL) was added dropwise at 0°C under argon. The mixture was stirred for 15 min at rt and for 1 h at 50°C. Ditosylate **23** (787 mg, 1,76 mM) in THF (15 mL) was added at −78°C. The mixture was let to warm up to rt and stirring was continued for 24 h. After evaporation the residue was taken up in CH_2Cl_2 and extracted with water. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography first on Al_2O_3, (toluene/EtOH, 100:1) then on silica gel (toluene/EtOH, 9:1) to give (*R*,*R*,*R*,*R*)-**15** (482 mg, 53%). $[\alpha]_D^{23}=+8.9$ (*c* 0.62, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta=$ 0.89 (mc, 12H), 1.31 (mc, 16 H),1.45 (mc, 8H), 3.35 (mc, 2H), 3.43 (mc, 2H), 3.47 (mc, 4H), 3.59 (mc, 2H), 3.71 (mc, 2H), 4.70 (d, $J=12$ Hz, 2H), 4.88 (d, $J=12$ Hz, 2H), 7.37 (m, 2H), 7.72 (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=14.1$, 22.8, 22.9, 2 8.0, 28.1, 30.1, 30.2, 70.4, 70.9, 73.5, 80.1, 82.1, 121.0, 137.1, 158.3; MS (FAB): calcd for $C_{31}H_{56}NO_5$ 522.4146. Found: 522.4159 (M+H);. IR (film): $\nu=2928$, 2888, 2864, 1592, 1460, 1376, 1352, 1268, 1244, 1108, 992, 816, 760 cm^{-1}.

3.3. (4*R*,5*R*,13*R*,14*R*)-19-Benzyloxy-4,5,13,14-tetrabutyl-3,6,9,12,15-pentaoxa-21-azabicyclo-[15.3.1]heneicosa-1(21),17,19-triene, (*R*,*R*,*R*,*R*)-16

Diol (*R*,*R*,*R*,*R*)-21 (500 mg, 0.84 mM) and ditosylate **24** (462 mg, 0.84 mM) was converted to (*R*,*R*,*R*,*R*)-**16** (272 mg, 52%) as described above for compound (*R*,*R*,*R*,*R*)-**15**. $[\alpha]_D^{25}=+35.1$ (*c* 0.52, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta=0.99$ (mc, 12H), 1.32 (mc, 12H), 1.49 (mc, 12H), 3.36 (mc, 2H), 3.47 (mc, 6H), 3.58 (mc, 2H), 4.66 (d, $J=13$ Hz, 2H) 4.81 (d, $J=13$ Hz, 2H) 5.14 (s, 2H), 6.99 (s, 2H), 7.39 (mc, 5H); ^{13}C NMR ($CDCl_3$): $\delta=14.3$, 22.9, 23.1, 28.2, 28.4, 30.2, 30.3, 70.0, 70.6, 71.1, 73.4, 80.1, 82.2, 107.7, 127.8, 128.5, 128.9, 136.1, 160.4, 166.4; MS (FAB): calcd for $C_{38}H_{62}NO_6$ 628.4577. Found: 628.4563 (M+H); IR (film): $\nu=2936$, 2872,1600, 1576, 1456, 1324, 1108, 864, 736, 696 cm^{-1}.

3.4. (4*S*,5*S*,13*S*,14*S*)-4,5,13,14-Tetrabutoxymethyl-3,6,9,12,15-pentaoxa-21-azabicyclo-[15.3.1]heneicosa-1(21),17,19-triene, (*S*,*S*,*S*,*S*)-17

Diol (*S*,*S*,*S*,*S*)-**22** (515 mg, 0.96 mM) and ditosylate **23** (428 mg, 0.96 mM) were converted to (*S*,*S*,*S*,*S*)-**17** (101 mg, 16%) as described above for compound (*R*,*R*,*R*,*R*)-**15**. $[\alpha]_D^{25}=+7.3$ (*c* 0.45, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta=0.92$ (mc, 12H), 1.38 (mc, 8H), 1.55 (mc, 8H), 3.39–3.95 (m, 28H), 4.83 (d, $J=13$ Hz, 2H) 4.89 (d, $J=13.0$ Hz, 2H), 7.39 (d, $J=8.0$ Hz, 2H), 7.67 (t, 1H, $J=8$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=14.1$, 14.2, 19.5, 19.6, 32.0, 70.6, 70.8, 71.0, 71.4, 71.5, 73.8, 78.6, 80.2, 121.3, 137.2, 158.4; MS (FAB): calcd for $C_{35}H_{64}NO_9$ 642.4586. Found: 642.4581 (M+H); IR (film): $\nu=2960$, 2928, 2838, 2856, 1592, 1460, 1376, 1264, 1112, 872, 812, 760 cm^{-1}.

3.5. (4*S*,5*S*,13*S*,14*S*)-19-Benzyloxy-4,5,13,14-tetrabutoxymethyl-3,6,9,12,15-pentaoxa-21-azabicyclo-[15.3.1]heneicosa-1(21),17,19-triene, (*S*,*S*,*S*,*S*)-18

Diol (*S*,*S*,*S*,*S*)-**22** (1,17 g, 2.18 mM) and ditosylate **24** (1,20 g, 2,18 mM) were converted to (*S*,*S*,*S*,*S*)-**18** (1.04 g, 64%) as described above for compound (*R*,*R*,*R*,*R*)-**15**. $[\alpha]_D^{23}=+20.5$ (*c* 1.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta=0.91$ (mc, 12H), 1.37 (mc, 8H), 1.56 (mc, 8H), 3.40–3.67 (m, 24H), 3.79 (mc, 4H), 4.65–4.81 (m, 4H), 5.12 (s, 2H), 6.96–7.05 (m, 2H), 7.35–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=14.2$, 19.6, 32.0, 70.0, 70.5, 70.8, 71.5, 71.5, 71.6, 73.5 78.5, 79.4, 107.9, 127.9, 128.5, 128.9, 136.1, 160.2, 166.3; MS (FAB): calcd for $C_{42}H_{70}NO_{10}$ 748.5000. Found: 748.5011 (M+H); IR (film): $\nu=2960$, 2928, 2888, 1600, 1456, 1372, 1112, 736, 696 cm^{-1}.

3.6. (4*R*,5*R*,13*R*,14*R*)-4,5,13,14-Tetrabutyl-3,6,9,12,15-pentaoxa-21-azabicyclo-[15.3.1]heneicosa-17,20-diene-19(21*H*)-one, (*R*,*R*,*R*,*R*)-19

Hydrogenation of (*R*,*R*,*R*,*R*)-**16** (410 mg, 0.6 mmol) in EtOH (20 mL) over 10% palladium-on-charcoal gave after the usual work-up and chromatography on silica gel (benzene/EtOH/25% aq. NH_4OH, 9:2:0.2) (*R*,*R*,*R*,*R*)-**19** (278 mg, 80%) as an amorphous solid. $[\alpha]_D^{25}=+1.61$ (*c* 5.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=$ 0.92 (t, $J=7.0$ Hz, 12H), 1.32–1.50 (m, 24H), 3.28 (mc, 4H), 3.63 (mc, 4H), 3.78 (mc, 2H), 3.90 (mc, 2H), 4.47 (d, $J=12.1$ Hz, 2H), 4.58 (d, $J=12.1$ Hz, 2H), 6.44 (s, 2H), 10.41 (br s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=14.3$, 23.2, 27.4, 31.0, 31.3, 69.3, 71.0, 81.8, 82.5, 104.2, 148.0, 180.6. MS (FAB): calcd for $C_{31}H_{56}NO_6$ 538.4108. Found: 538.4129 (M+H); IR (film): $\nu=3302$, 2928, 2838, 2856, 1636, 1536, 1450, 1376, 1130, 868 cm^{-1}.

3.7. (4*S*,5*S*,13*S*,14*S*)-4,5,13,14-Tetrabutoxymethyl-3,6,9,12,15-pentoxa-21-azabicyclo-[15.3.1]heneicosa-17,20-diene-19(21*H*)-one, (*S*,*S*,*S*,*S*)-20

(*S*,*S*,*S*,*S*)-**18** (934 mg, 1.25 mM) was hydrogenated on 10% palladium-on-charcoal catalyst (0.2 g) in EtOH using the standard methodology to give (*S*,*S*,*S*,*S*)-20 (800 mg, 98%) as an oil. $[\alpha]_D^{25}=+18.3$ (*c* 1.58, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta=0.90$ (t, $J=7.0$ Hz, 12H), 1.33 (q, $J=7.0$ Hz, 8H), 1.51 (quint, $J=7.0$ Hz, 8H), 3.41 (quint, $J=7.0$ Hz, 8H), 3.52–3.65 (m, 16H), 3.88 (mc, 4H), 4.53 (d, $J=13$ Hz, 2H) 4.63 (d, $J=13$ Hz, 2H) 6.16 (s, 2H), 10.88 (bs, 1H); ^{13}C NMR ($CDCl_3$): $\delta=14.1$, 19.5, 31.9, 69.5, 70.2, 70.5, 70.5, 70.7, 71.6, 71.6, 78.8, 78.9, 114.4, 147.7, 180.3; MS (FAB): calcd for $C_{35}H_{64}NO_{10}$ 658.4530. Found: 658.4564 (M+H); IR (film): $\nu=3304$, 2936, 2888, 2872, 1960, 1632, 1464, 1376, 1116 cm^{-1}.

3.8. (5*R*,6*R*,14*R*,15*R*)-6,14-Dibutyl-7,10,13-trioxanonadecane-5,15-diol, (*R*,*R*,*R*,*R*)-21

Dibenzylether (*R*,*R*,*R*,*R*)-**29** (600 mg, 1.0 mM) was debenzylated as described above for compound (*R*,*R*,*R*,*R*)-**19** to give (*R*,*R*,*R*,*R*)-**21** (402 mg, 97%) as an oil after chromatography on silica gel (hexane/acetone, 10:1). $[\alpha]_D^{25}=+11.0$ (*c* 0.36, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta=0.91$ (t, $J=7.0$ Hz, 12H), 1.31–1.53 (m, 24H), 3.10 (mc, 2H), 3.42 (bs, 2H), 3.47 (mc, 2H), 3.60 (mc, 2H), 3.68 (quint, $J=7$ Hz, 4H), 3.80 (mc, 2H); ^{13}C NMR ($CDCl_3$): $\delta=14.3$, 23.0, 23.2, 27.9, 28.0, 31.2, 33.1, 70.4, 70.9, 73.7, 84.9. IR (film): $\nu=3456$, 2928, 2872, 1464, 1424, 1348, 1328, 1272, 1100, 732 cm^{-1}.

3.9. (7*S*,8*S*,16*S*,17*S*)-8,16-Bis(butoxymethyl)-5,9,12,15,19-pentaoxatricosan-7,17-diol, (*S*,*S*,*S*,*S*)-22

To a stirred suspension of sodium hydride (2.7 g, 90 mmol, as 80% dispersion in mineral oil) in THF (20 mL) (*S*,*S*)-**32** (10.7 g, 33.0 mM) in THF (20 mL) was added dropwise at 0°C under an argon atmosphere. The mixture was stirred for 15 min at 0°C and for 1 h at 50°C. Diethylene glycol di-*p*-tosylate **28** (4.3 g, 10 mM) in THF (15 mL) was added at 0°C. The reaction mixture was maintained at 60°C for 2 h, and then for 24 h at rt. The solvent was evaporated and water was added. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated. The crude (*S*,*S*,*S*,*S*)-**33** was subjected to catalytic hydrogenation in EtOH (50 mL) over 10% palladium on charcoal as described above for compound (*R*,*R*,*R*,*R*)-**19** to yield (*S*,*S*,*S*,*S*)-**22** (2.5 g, 45%) and (*S*,*S*)-1,4-*O*,*O*′-dibutylthreitol (1.8 g) after purification by chromatography on silica gel (CH_2Cl_2/acetone 9:1). $[\alpha]_D^{23}=+22.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): $\delta=0.92$ (t, $J=7.3$ Hz, 12H), 1.36 (mc, 8H), 1.55 (mc, 8H), 3.17 (bs, 2H), 3.43–3.67 (m, 24H), 3.79 (mc, 2H), 3.92 (mc, 2H); ^{13}C NMR ($CDCl_3$): $\delta=14.1$, 19.5, 32.0, 70.6, 70.8, 71.1, 71.3, 71.5, 71.6, 80.2; IR (film): $\nu=3448$, 2928, 2896, 2872, 1728, 1464, 1376, 1268, 1120, 768 cm^{-1}.

3.10. (*R*,*R*)-2-Phenyl-4,5-dibutyl-1,3-dioxolane, (*R*,*R*)-26

Benzaldehyde dimethylacetal (4.9 g, 32 mM) and *p*-toluenesulfonic acid (260 mg, 1.4 mM) was added to (*R*,*R*)-**25**[23] (4.7 g, 27 mM) in DMF (20 mL). The reaction mixture was maintained at 60°C until the reaction was completed. The mixture was then poured into an ice-cold solution of $NaHCO_3$ (3%, 150 mL). The resulting suspension was extracted with ether (3× 100 mL), then the combined organic layers was washed with water (70 mL). The organic phase was dried over $MgSO_4$ and evaporated to give (*R*,*R*)-**26** (6.6 g, 100%) as an oil. $[\alpha]_D^{23}=+16.7$ ($CHCl_3$, *c* 1.14). ^{1}H NMR ($CDCl_3$): $\delta=0.94$ (2t, $J=7.0$, 6H), 1.41 (mc, 6H), 1.55 (mc, 3H), 1.67 (mc, 3H), 3.79 (mc, 2H), 5.89 (s, 1H), 7.36–7.40 (m, 3H), 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=14.2$, 22.9, 23.0, 28.4, 28.5, 32.9, 33.0, 81.8, 83.1, 102.8, 126.9, 128.5, 129.3, 138.7; IR (film): $\nu=2960$, 2936, 2864, 1460, 1408, 1380, 1220, 1092, 1076, 1004, 760, 696 cm^{-1}.

3.11. (*R*,*R*)-6-Benzyloxy-decan-5-ol, (*R*,*R*)-27

To dioxolane (*R*,*R*)-**26** (6.6 g, 26.8 mM) in 200 mL of CH_2Cl_2 DIBALH (90 mL, 1.5 M in toluene) was added dropwise at 0°C. The mixture was stirred for 24 h at rt. The reaction mixture was then cooled to 0°C and methanol (12 mL) followed by sat. aq. NH_4Cl solution (30 mL) was added carefully. 5% aqueous HCl was added and the organic phase was washed with water, dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by chromatography on silica gel (hexane/acetone, 9:1) to give (*R*,*R*)-**27** (5.6 g, 84%) as an oil. $[\alpha]_D^{25}=+22.3$ (*c* 0.87, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta=0.93$ (mc, 6H), 1.33–1.67 (m, 12H), 2.21 (bs, 1H), 3.29 (q, $J=5.5$ Hz, 1H), 3.56 (m, 1H), 4.51 (d, $J=11.3$ Hz, 1H), 4.68 (d, $J=11.3$ Hz, 1H), 7.31–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=14.5$, 23.2, 23.5, 27.8, 28.4, 30.5, 33.7, 72.9, 73.1, 82.9, 128.2, 128.3, 128.9, 139.0; IR (film): $\nu=3550$, 3510, 3440, 3405, 3030, 3000, 2935, 2910, 1495, 1466, 1450, 1380, 1215, 1100, 1075, 1020, 745, 705 cm^{-1}.

3.12. (5*R*,6*R*,14*R*,15*R*)-5,15-Dibenzyloxy-6,14-dibutyl-7,10,13-trioxanonadecane, (*R*,*R*)-29

To a stirred suspension of sodium hydride (260 mg, 6.5 mmol, as a 60% dispersion in mineral oil) in THF (10 mL) (*R*,*R*)-**27** (1.2 g, 4.55 mM) in THF (10 mL) was added at 0°C under an argon atmosphere. The mixture was stirred for 15 min at 0°C and for 1 h at 50°C. Diethylene glycol di-*p*-tosylate **28** (0.624 g, 1.51 mM) in THF (5 mL) was added at 0°C. The reaction mixture was maintained at 60°C for 2 h, and then for 24 h at rt. The solvent was evaporated and water was added. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on silica gel (hexane:EtOAc, 30:1) to yield (*R*,*R*)-**29** (0.658 g, 73%). $[\alpha]_D^{23}=+27.4$ (*c* 0.54, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta=0.89$ (t, $J=7$ Hz, 6H), 0.90 (t, $J=7$ Hz, 6H), 1.30 (mc, 12H), 1.44 (mc, 8H), 1.56 (mc, 4H), 3.33 (mc, 2H), 3.41 (mc, 2H), 3.59 (mc, 4H), 3.63 (mc, 2H), 3.70 (mc, 2H), 4.55 (d, $J=11.5$ Hz, 2H) 4.63 (d, $J=11.5$ Hz, 2H) 7.26–7.36 (m, 10H). ^{13}C NMR ($CDCl_3$): $\delta=14.5$, 14.6, 23.3, 28.6, 30.1, 30.3, 70.5, 71.3, 73.1, 80.8, 82.1, 127.9, 128.4, 128.7, 139.5; IR (film): $\nu=3088$, 3064, 3048, 3032, 2952, 1496, 1456, 1376, 1248, 1208, 1096, 736, 696 cm^{-1}.

3.13. (*S*,*S*)-2-Phenyl-4,5-bis(butoxymethyl)-1,3-dioxolane, (*S*,*S*)-31

To a suspension of sodium hydride (2.12 g, 80% dispersion in mineral oil) in DMF (10 mL) diol (*S*,*S*)-**30**[25] (5.3 g, 25.2 mM) in DMF (10 mL) was added at 0°C under an argon atmosphere. The mixture was stirred for 15 min at rt and for 1 h at 50°C. The reaction mixture was cooled to 0°C and butyl bromide (9.8 g, 70 mM; 7.6 mL) in DMF (10 mL) was added. The mixture was stirred for 4 h at rt, then the solvent was evaporated, water added and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ then the solvent

was evaporated. The residue was purified by chromatography on silica gel (hexane/acetone, 30:1) to give (*S*,*S*)-**31** (7.0 g, 86%) as an oil. $[\alpha]_D^{25}=+0.7$ (*c* 2.40, CH_2Cl_2), $[\alpha]_{Hg\ 365}^{25}=+21.0$ (*c* 2.40, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta=0.92$ (t, $J=7.0$ Hz, 3H), 0.93 (t, $J=7.0$ Hz, 3H), 1.38 (mc, 4H), 1.58 (mc, 4H), 3.51 (mc, 4H), 3.64 (mc, 4H), 4.12 (mc, 1H), 4.21 (mc, 1H), 5.95 (s, 1H), 7.35 (m, 3H), 7.49 (m, 2H). ^{13}C NMR ($CDCl_3$): $\delta=$ 14.1, 19.5, 31.9, 71.3, 71.5, 71.8, 78.2, 78.6, 104.3, 127.0, 128.4, 129.5, 137.9;. IR (film): $\nu=2944$, 2928, 2896, 1460, 1376, 1280, 1220, 1112, 984, 744, 672 cm^{-1}.

3.14. (*S*,*S*)-1,4-*O*,*O*′-Dibutyl-2-*O*-benzylthreitol (*S*,*S*)-32

To dioxolane (*S*,*S*)-**31** (4.8 g, 14.9 mM) in CH_2Cl_2 (150 mL) DIBALH (65 mL, 1.2 M in toluene) was added dropwise at 0°C. The mixture was stirred for 24 h at rt. The reaction mixture was then cooled to 0°C and methanol (10 mL) followed by the careful addition of sat. aq. NH_4Cl (20 mL) and then 5% aqueous HCl. The organic phase was washed with water, dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by chromatography on silica gel (hexane/acetone, 5:1) to give (*S*,*S*)-**32** (4.0 g, 83%) as an oil. $[\alpha]_D^{25}=+12.5$ (*c* 1.59, MeOH). ^{1}H NMR ($CDCl_3$): $\delta=$ 0.91 (mc, 6 H), 1.35 (mc, 4H), 1.56 (mc, 4H), 2.65 (bs, 1H), 3.41–3.49 (m, 6H), 3.61 (m, 1H), 3.66 (mc, 2H), 3.87 (mc, 1H), 4.60 (d, $J=11.7$ Hz, 1H), 4.76 (d, $J=11.7$ Hz, 1H), 7.35 (mc, 5H). ^{13}C NMR ($CDCl_3$): $\delta=14.4$, 19.8, 32.2, 32.2, 71.3, 71.4, 71.7, 71.9, 72.0, 73.4, 78.0, 128.2, 128.4, 128.8, 138.9; IR (film): $\nu=3464$, 3032, 3016, 2960, 2944, 2888, 1456, 1376, 1120, 736, 684 cm^{-1}.

3.15. [(*R*)-PEA] complex of 3,6,9,12,15-pentoxa-21-azabicyclo-[15.3.1]heneicosa-17,20-diene-19(21*H*)-one 10

Compound **10** (66 mg, 0.2 mmol) and (*R*)-1-phenylethylammonium perchlorate (44 mg, 0.2 mmol) in EtOH (1 mL) was dissolved by heating, allowed to stand for 1 day and then in a refrigerator overnight. The crystals (67 mg, 64%,) were filtered off and air dried, yield 62 mg (58%), mp 159–161°C. Crystals for X-ray analysis were prepared by letting a nearly saturated solution of the salt to evaporate slowly at rt. ^{1}H NMR ($CDCl_3$+CD_3OD, 1:1): $\delta=1.34$ (d, 3H), 3.28, 3.36, 3.38 (3×s, 16H), 4.00–4.11 (m, 5H), 4.29 (br s, 3H), 6.17 (br s, 2H), 7.08 (s, 5H); ^{13}C NMR ($CDCl_3$+ CD_3OD, 1:1): $\delta=19.3$, 47.5, 47.7, 47.9, 50.8, 69.3, 69.5, 69.8, 70.0, 128.8, 128.7, 128.9, 137.5;. IR (KBr): $\nu=$ 3310, 3220, 3110, 2905, 1610, 1540, 1450, 1350, 110, 1080, 1040, 1020, 690, 610 cm^{-1}.

3.16. Benzylammonium perchlorate (BA) complex of 3,6,9,12,15-pentaoxa-21-azabicyclo-[15.3.1]heneicosa-17,20-diene-19(21*H*)-one 10

Compound **10** (66.2 mg, 0.2 mmol) and 1-benzylammonium perchlorate (41.5 mg, 0.2 mmol) in EtOH (10 mL) was dissolved by heating, allowed to stand for 1 day and then in a refrigerator overnight. The crystals (67 mg, 64%,) were filtered off and air dried, mp 197–198°C (EtOH). Crystals for X-ray analysis were prepared by letting a nearly saturated solution of the salt to evaporate slowly at rt. ^{1}H NMR ($CDCl_3$+CD_3OD, 1:1): $\delta=3.57$, 3.64, 3.66 (3×s, 16H), 3.96 (s, 2H), 4.35 (4H), 4.60 (br s, 3H), 6.55 (br s, 2H), 7.37 (s, 5H); ^{13}C NMR ($CDCl_3$+CD_3OD, 1:1): $\delta=69.3$, 69.5, 69.8, 70.0, 128.6, 128.9, 129.4, 132.4;. IR (KBr): $\nu=3320$, 3130, 3040, 2915, 1610, 1540, 1450, 1355, 110, 1080 cm^{-1}.

3.17. Crystal data for the 10–(*R*)-PEA complex

$C_{23}H_{35}ClN_2O_{10}$, Fwt.: 534.98, colorless prism, space group $P2_1$, $a=8.850(1)$Å, $b=25.848(3)$ Å, $c=11.820(1)$ Å, $\alpha=90°$, $\beta=96.11(2)°$, $\gamma=90°$, $V=2688.5(5)$ Å^3, $Z=4$, $D_X=1.322$ Mg/m^3. A crystal of **10**–(*R*)-PEA was mounted on a glass fiber on an Enraf–Nonius CAD4 diffractometer (graphite monochromator; Cu-*K*α radiation, $\lambda=1.54180$ Å) at 295(2) K in the range $3.42\leq\theta\leq$ 66.40° using $\omega/2\theta$ scans. A total of 10286 reflections were collected of which 9205 were unique [$R_{(int)}=$ 0.0124, $R(\sigma)=0.0575$]; intensities of 5170 reflections were greater than $2\sigma(I)$. Empirical absorption correction[27] was applied to the data (the minimum and maximum transmission factors were 0.5423 and 0.7219). Initial structure model was refined by direct methods[28] and completed in subsequent difference syntheses. Anisotropic full-matrix least-squares refinement[29] on F^2 for all non-hydrogen atoms yielded $R_1=0.0480$ and $wR^2=0.1109$ for 5170 [$I>2\sigma(I)$] and $R_1=0.0995$ and $wR^2=0.1258$ for all 9205 intensity data, (goodness-of-fit = 0.926, Flack $x=0.01(2)$.[30] Hydrogen atomic positions were calculated from assumed geometries except those of the ammonium group and that of the -OH which were located in difference electron density maps. 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.

3.18. Crystal data, for the 10–BA complex

$C_{22}H_{33}ClN_2O_{10}$, Fwt.: 520.95, space group $P2_1/a$, $a=$ 8.436(1) Å, $b=26.265(2)$ Å, $c=11.733(1)$ Å, $\alpha=90°$, $\beta=95.49(1)°$, $\gamma=90°$, $V=2587.8(4)$ Å^3, $Z=4$, F(000)= 1104, $Dx=1.337$ Mg/m^3. A crystal of **10**·BA was mounted on a glass fiber on a diffractometer (graphite monochromator; Cu-*K*α radiation, $\lambda=1.54180$ Å) at 293(2) K in the range $3.37\leq\theta\leq75.74°$ using $\omega/2\theta$ scans. A total of 5861 reflections were collected of which 5340 were unique [$R_{(int)}=0.0086$, $R(\sigma)=0.0268$]; intensities of 2997 reflections were greater than $2\sigma(I)$. An empirical absorption corrections[27] was applied to the data (the minimum and maximum transmission factors were 0.5334 and 0.7151). Initial structure model was refined by direct methods[28] and completed in subsequent difference syntheses. Anisotropic full-matrix least-squares refinement[29] on F^2 for all non-hydrogen atoms yielded $R_1=0.0624$ and $wR^2=0.1802$ for 2997 [$I>2\sigma(I)$] and $R_1=0.1004$ and $wR^2=0.2015$ for all 5340 intensity data, (goodness-of-fit = 0.995, extinction coefficient = 0.0005(3).[30] Hydrogen atomic positions

were calculated from assumed geometries except those of the ammonium group and that of the -OH which were located in difference electron density maps. 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.

CCDC 213627 [**10**–(*R*)-PEA] and CCDC 213628 [**10**–BA) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/prods/encifer/ (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK, (fax (+44)-1223-336-033 or deposit@ccdc.cam.ac.uk).

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