Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3615–3626

TETRAHEDRON: *ASYMMETRY*

Enantiomerically pure chiral pyridino-crown ethers: synthesis and enantioselectivity toward the enantiomers of α-(1-naphthyl)ethylammonium perchlorate †

Erika Samu,[a] Péter Huszthy,[b,*] György Horváth,[a] Áron Szöllősy [c] and András Neszmélyi [d]

[a]*Institute for Organic Chemistry, Technical University of Budapest, H-1521 Budapest, Hungary*
[b]*Research Group for Alkaloid Chemistry, Hungarian Academy of Sciences, H-1521 Budapest, Hungary*
[c]*Institute for General and Analytical Chemistry, Technical University of Budapest, H-1521 Budapest, Hungary*
[d]*Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, Hungary*

Received 8 August 1999; accepted 31 August 1999

Abstract

Seven new enantiomerically pure chiral pyridino-crown ethers (*S*,*S*)-**4**–(*R*,*R*)-**10** were prepared. Three of them [(*S*,*S*)-**4**, (*S*,*S*)-**7** and (*R*,*R*)-**10**] contain one, and two of them [(*S*,*S*)-**5** and (*S*,*S*)-**8**] contain two linker chains with a terminal double bond. These linker chains were connected to the carbon atom at position 9 (opposite the pyridine moiety) of the macrocycle. The terminal double bond of the linker makes it possible to attach these ligands to silica gel to obtain chiral stationary phases (CSPs). The enantioselectivity of the new ligands toward the enantiomers of α-(1-naphthyl)ethylammonium perchlorate (NEA) was also determined by a titration ^{1}H NMR method.

1. Introduction

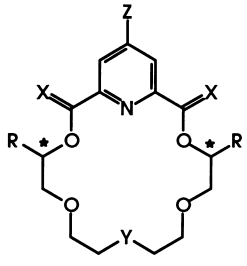
The important role of enantiodiscrimination with respect to biological regulation and activity phenomena, drug development, food and cosmetic industries, environmental and toxicity issues, stereoselective synthesis, sensing and separating of enantiomers, etc. has been increasingly recognized over the past years. In this context, a lot of attention has been devoted to the synthesis and evaluation of the enantioselectivity of artificial chiral receptors (hosts) with the aim of using them for the discrimination of enantiomers of chiral guest molecules.[1,2] Enantiomerically pure chiral macrocycles, for example, have proved to be very useful synthetic hosts for discriminating the enantiomers of chiral organic ammonium salt guest molecules.[3] Among these chiral macrocycles a number of chiral crown ethers containing

* Corresponding author. E-mail: huszthy.szk@chem.bme.hu
† Dedicated to Professor Károly Lempert on the occasion of his 75th birthday.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00381-X

pyridine subcyclic units have been prepared.[4–9] The enantioselectivity of chiral pyridino-18-crown-6 ligands toward the enantiomers of organic ammonium salts has been extensively studied.[3,5–12] These studies have established a tripod-like hydrogen bonding involving the pyridine nitrogen and two alternate oxygen atoms of the pyridino-crown ether and the three ammonium protons of the organic salt (attractive interaction), π–π stacking between the aromatic rings of the host and the guest (attractive interaction) as well as the steric repulsion caused by the substituent at the stereogenic center of the ligand and certain hydrogens of the ammonium salt (repulsive interaction), respectively.[3,5–12] Recently we turned our attention to the application of enantiopure chiral pyridino-18-crown-6 ligands in the separation of the enantiomers of selected chiral organic ammonium salts.[12–14] We have found that the enantioselectivity characterized in homogeneous solution by $\Delta\log K$ values, which were measured by a ^{1}H NMR titration method,[15] paralleled very well with the effectiveness of the enantioseparation on the chiral stationary phases (CSPs) prepared by attaching the chiral pyridino-host molecules covalently to silica gel[12–14] (K is the equilibrium constant for complex formation between one enantiomer of the chiral organic ammonium salt and the chiral pyridino-crown host, $\Delta\log K=\log K_{\text{heterochiral complex}}-\log K_{\text{homochiral complex}}$, heterochiral complex: (*R*,*R*)-host/(*S*)-guest complex or (*S*,*S*)-host/(*R*)-guest complex, homochiral complex: (*R*,*R*)-host/(*R*)-guest complex or (*S*,*S*)-host/(*S*)-guest complex).

In all cases, the tether which connected the chiral selector to the silica gel solid support was attached to position 4 of the pyridine ring, thus the starting material for the preparation of the CSP was either crown ether (*S*,*S*)-**3** (see Fig. 1) or its analog differing only in the length of the linker and/or the substituent at the stereogenic center.[12–14]



(*S*,*S*)-1: R = Me; X = O; Y = O; Z = H
(*S*,*S*)-2: R = Me; X = H_2; Y = O; Z = H
(*S*,*S*)-3: R = Me; X = H_2; Y = O; Z = $OCH_2CH=CH$
(*S*,*S*)-4: R = Me; X = H_2; Y = $CHCH_2CH=CH_2$; Z = H
(*S*,*S*)-5: R = Me; X = H_2; Y = $C(CH_2CH=CH_2)_2$; Z = H
(*S*,*S*)-6: R = *i*-Bu; X = H_2; Y = O; Z = H
(*S*,*S*)-7: R = *i*-Bu; X = H_2; Y = $CHCH_2CH=CH_2$; Z = H
(*S*,*S*)-8: R = *i*-Bu; X = H_2; Y = $C(CH_2CH=CH_2)_2$; Z = H
(*R*,*R*)-9: R = *t*-Bu; X = H_2; Y = O; Z = H
(*R*,*R*)-10: R = *t*-Bu; X = H_2; Y = $CHCH_2CH=CH_2$; Z = H

Figure 1. Chemical formulas of enantiomerically pure chiral pyridino-crown ethers

The immobilization of the chiral pyridino-crown ethers to the solid support by covalent Si–O–Si bonds was carried out by firstly reacting the terminal double bond with triethoxysilane in the presence of a Pt-catalyst, followed by heating the triethoxysilyl-derivative of the chiral ligand with silica gel in toluene.[12–14]

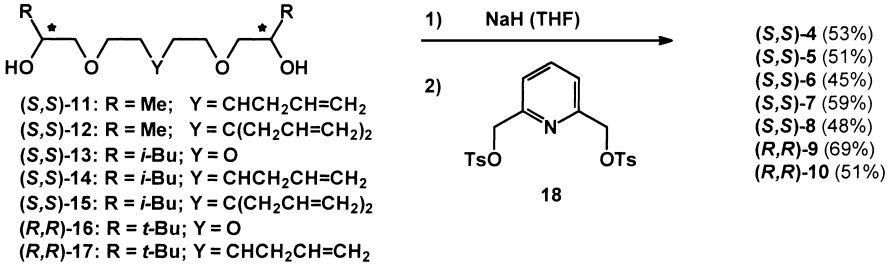
With the aim of improving enantioseparation using enantiopure pyridino-crown ethers as chiral selectors for silica gel-bound CSPs, we attached the linker(s) containing the terminal double bond to position 9 of the carba-analogs of crown ethers (*S*,*S*)-**2**, (*S*,*S*)-**6** and (*R*,*R*)-**9** to obtain ligands (*S*,*S*)-**4**, (*S*,*S*)-**5**, (*S*,*S*)-**7**, (*S*,*S*)-**8** and (*R*,*R*)-**10** (see Fig. 1).

The use of the latter chiral pyridino-crown ether ligands as chiral selectors instead of (*S*,*S*)-**3** and its analogs seems to be advantageous, because these macrocycles can be attached to the solid support further from the pyridine ring and the stereogenic centers, so the interference of the Si-OH groups of the silica gel becomes less pronounced with this portion of the macrocycle which is responsible mainly for the enantioselectivity. It is worth mentioning here that the X-ray structures of the solid diastereomeric complexes (*R*)-NEA–(*S*,*S*)-**1** and (*S*)-NEA–(*S*,*S*)-**1** clearly show that in the tripod-like hydrogen bonding the macrocycle oxygen atom at position 9 is not involved,[16] so crown ethers such as (*S*,*S*)-**4**, (*S*,*S*)-**5**, (*S*,*S*)-**7**, (*S*,*S*)-**8** and (*R*,*R*)-**10** with no heteroatom in that position could form the above mentioned hydrogen bonding.

In this paper, we report the synthesis of novel chiral macrocycles (*S*,*S*)-**4**, (*S*,*S*)-**5**, (*S*,*S*)-**6**, (*S*,*S*)-**7**, (*S*,*S*)-**8**, (*R*,*R*)-**9** and (*R*,*R*)-**10** and also their enantiomeric recognition data ($\Delta\log K$) for the enantiomers of α-(1-naphthyl)ethylammonium perchlorate (NEA) determined by a ^{1}H NMR titration method[15] in homogeneous solution (CD_3OD:$CDCl_3$ 1:1). The cheapest and easiest obtainable ligand (*S*,*S*)-**4** is planned to attach covalently to silica gel by the usual method,[12–14] and the CSP so prepared will be tested for the enantioseparation of racemic organic ammonium salts by chromatography. These studies will be reported in a future publication.

2. Results and discussion

Enantiomerically pure (*S*,*S*)-dimethyldiketopyridino-18-crown-6 ligand (*S*,*S*)-**1**[17] and (*S*,*S*)-dimethylpyridino-18-crown-6 ligand (*S*,*S*)-**2**[11] were prepared as reported. New enantiomerically pure chiral pyridino-crown ethers (*S*,*S*)-**4**–(*R*,*R*)-**10** were prepared as shown in Scheme 1.

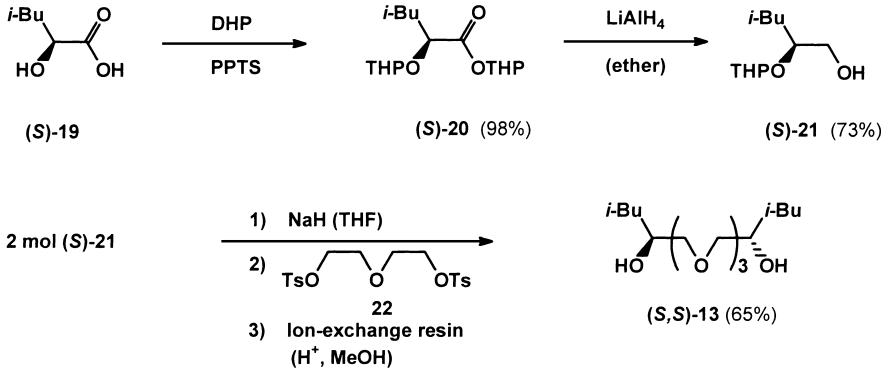


Scheme 1. Preparation of new enantiopure chiral ligands

The structures proposed for these new macrocycles are consistent with data obtained from ^{1}H and ^{13}C NMR, mass and IR spectra and elemental analyses. The yields for the Williamson-type macrocyclic ether formation reaction using the strong base NaH and THF as a solvent were in the 45–69% range. We should mention here that the syntheses of (*R*,*R*)-**6**[6] and (*S*,*S*)-**9**,[7] the antipodes of (*S*,*S*)-**6** and (*R*,*R*)-**9**, have been reported.

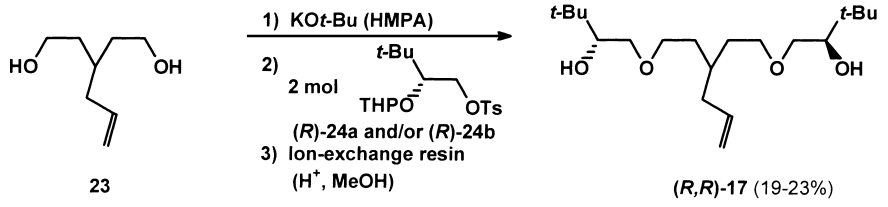
Diols (*S*,*S*)-**11**,[18] (*S*,*S*)-**12**,[18] (*S*,*S*)-**14**,[18] (*S*,*S*)-**15**[18] and tetraethylene glycol (*R*,*R*)-**16**[14] were obtained as described in the literature. The chiral diisobutyl-substituted tetraethylene glycol (*S*,*S*)-**13** needed for the preparation of macrocycle (*S*,*S*)-**6** was obtained as shown in Scheme 2.

Hydroxy acid (*S*)-**19** was treated with an excess of dihydropyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS) catalyst to obtain bis(THP)-derivative (*S*)-**20** which was reduced to THP-protected glycol (*S*)-**21**. Two moles of the monosodium salt of alcohol (*S*)-**21** were reacted with one mole of diethylene glycol ditosylate **22** followed by deblocking the THP protecting groups to give tetraethylene



Scheme 2. Preparation of new enantiomerically pure diisobutyl-substituted tetraethylene glycol (*S*,*S*)-**13**

glycol (*S*,*S*)-**13**. Enantiomerically pure di-*tert*-butyl-substituted diol (*R*,*R*)-**17** needed for the preparation of chiral ligand (*R*,*R*)-**10** was obtained as shown in Scheme 3.

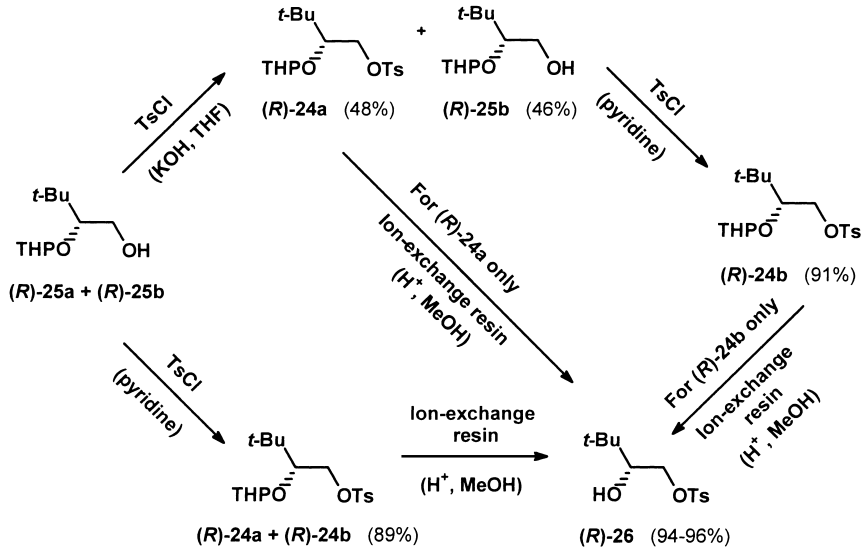


Scheme 3. Preparation of new enantiopure di-*tert*-butyl-substituted diol (*R*,*R*)-**17** containing a side chain with a terminal double bond

One mole of allyl-substituted-pentan-1,5-diol **23**[18] was treated first with an excess of strong base KO*t*-Bu, then the resulting dialkoxide was reacted with two moles of (*R*)-**24a** and/or (*R*)-**24b** (see Scheme 3) followed by deblocking the THP protecting groups to give chiral diol (*R*,*R*)-**17**. It is interesting that the two diastereomeric diols (*R*)-**25a** and (*R*)-**25b** behave very differently in certain tosylation reactions as shown in Scheme 4.

When the mixture of (*R*)-**25a** and (*R*)-**25b** was treated with tosyl chloride using powdered KOH as a base in THF, only one of the diastereomers [(*R*)-**25a**] reacted and the other [(*R*)-**25b**] remained intact. Using pyridine as a base and a solvent both diastereomeric alcohols (*R*)-**25a** and (*R*)-**25b** were transformed to tosylates (*R*)-**24a** and (*R*)-**24b**. Tosylate(s) (*R*)-**24a** and/or (*R*)-**24b** resulted in the same *tert*-butyl-substituted glycol monotosylate (*R*)-**26** by deblocking the THP protecting group with the help of ion-exchange resin (H^+ form) in methanol.

Pyridino-18-crown 6 ligands are appropriate hosts for primary ammonium salts like NEA.[3] The chiral hosts form complexes of different equilibrium constants with the two enantiomers of NEA so that the difference in log*K* values could serve as a parameter referring to the enantioselectivity of a ligand. The equilibrium constants were determined by the ^{1}H NMR titration method originally described by Zhu et al.[15] Adding small quantities of NEA (guest) to the solution of a ligand (host) and taking ^{1}H NMR spectra after each charge induce shifts of selected signals. The induced shift (δ_i) is a function of the molar ratio (ρ=guest/host), the actual equilibrium constant (*K*) as well as the shift which could be measured in the case of complex (δ_c) (the complex is formed by one host and one guest molecule).[15] With a known starting concentration the molar ratios were determined by the integration of the NMR spectra. The equilibrium constant and the chemical shift of the complex were determined by a two-parameter nonlinear regression fit. Although complexation induces shifts at several signals of the host, and these



Scheme 4. Tosylation of diastereomeric diols (*R*)-**25a** and (*R*)-**25b** and deblocking the THP protecting group of the tosylates (*R*)-**24a** and (*R*)-**24b**

shifts can be used for calculation, the best results could be achieved by monitoring those signals where the induced shifts are quite large (δ_i>0.1 ppm).

Reliability of our measurements and calculations were checked by comparison of our data for (*S*,*S*)-**1** and (*S*,*S*)-**2** with those reported for (*S*,*S*)-**1**[11] and (*S*,*S*)-**2**[19] earlier in the literature.

The log*K* and Δlog*K* values shown in Table 1 are in accord with the generally observed heterochiral preference for the interactions between the pyridino-crown ethers and the enantiomers of NEA.[3,10,11]

Table 1
Enantiomeric recognition data (Δlog*K*) determined by the ^{1}H NMR titration method in homogeneous solution (CD_3OD:$CDCl_3$ 1:1) for the enantiomer pairs of NEA with chiral pyridine-containing macrocycles at 298 K

Ligand	log*K*		Δlog*K*
	(*S*)-NEA	(*R*)-NEA	
(*S*,*S*)-**4**	2.06	1.31	0.75
(*S*,*S*)-**5**	2.04	2.23	0.19
(*S*,*S*)-**6**	2.20	3.07	0.87
(*S*,*S*)-**7**	1.54	0.76	0.78
(*S*,*S*)-**8**	1.04	1.60	0.56
(*R*,*R*)-**9**	1.59	0.40	1.19
(*R*,*R*)-**10**	2.28	1.43	0.85

The two exceptions to this general observation are the homochiral preference of ligands (*S*,*S*)-**4** and (*S*,*S*)-**7** containing one linker chain. It can also be seen from the data in Table 1, that the presence of one linker chain decreases the enantioselectivity only to a very small extent, while the incorporation of two linker chains results in a more significant decrease in Δlog*K* values. This tendency in enantioselectivity was also observed in the case of analogous phenazino-crown ethers when one and two

of the same linker chains were incorporated in similar positions of the macrocycle as shown by circular dichroism spectroscopy.[18] Thus (*S*,*S*)-**4**, (*S*,*S*)-**7** and (*R*,*R*)-**9** are all suitable selectors for chromatographic enantioseparation of racemic NEA and probably other racemic organic ammonium salts as well.

3. Experimental

Infrared spectra were obtained on a Zeiss Specord IR 75 spectrometer. Optical rotations were taken on a Perkin–Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer and ^{1}H (80 MHz) NMR spectra were obtained on a Bruker AW-80 spectrometer in $CDCl_3$ unless otherwise indicated. Molecular weights were determined by a VG-ZAB-2 SEQ reverse geometry mass spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminum oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminum oxide (neutral, activated, Brockman I) and silica gel 60 (70–230 mesh, Merck) were used for column chromatography. Solvents were dried and purified according to well established methods.[20] Evaporations were carried out under reduced pressure unless otherwise stated.

For determination of log*K* values ligands (*S*,*S*)-**4** -(*R*,*R*)-**10** were dissolved in $CDCl_3$:CD_3OD (1:1; v/v). The NMR spectra were recorded at 298 K on a Bruker DRX-500 Avance spectrometer. To enhance the integral accuracy, 5 s delay time and 64 K zero filling were applied for recording the ^{1}H NMR spectra.

*3.1. (4*S*,14*S*)-(+)-4,14-Dimethyl-9-(2-propenyl)-3,6,12,15-tetraoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (*S,S*)-**4**

To a well stirred suspension of NaH (224 mg, 5.6 mmol, 60% dispersion in mineral oil) in THF (10 mL) was added dropwise under Ar at rt (2*S*,12*S*)-(+)-7-(2-propenyl)-4,10-dioxatridecane-2,12-diol (*S*,*S*)-**11**[18] (520 mg, 2 mmol) dissolved in THF (20 mL). The mixture was stirred at rt for 10 min and at reflux temperature for 3 h. The reaction mixture was cooled to −60°C and ditosylate **18**[6,21] (984 mg, 2.2 mmol) dissolved in THF (20 mL) was added dropwise. The resulting mixture was stirred at −60°C for 20 min and then at rt for 5 days. After the reaction was completed, the solvent was removed. The residue was taken up in the mixture of ice-water (15 mL) and ether (50 mL). The resulting mixture was mixed well and separated. The aqueous phase was shaken with ether (2×50 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by chromatography on neutral alumina using 1% EtOH in toluene as an eluent to give pure (*S*,*S*)-**4** (385 mg, 53%) as a clear oil; R_f=0.33 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$ +23.8 (c 0.567, CH_2Cl_2); IR (neat) ν 3072, 3040, 2960, 2940, 2870, 2860, 1640, 1592, 1576, 1460, 1368, 1336, 1110, 1000, 912, 816, 760 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.15 (d, *J*=7 Hz, 3H), 1.16 (d, *J*=7 Hz, 3H), 1.40–1.46 (m, 4H), 1.65–1.70 (m, 1H), 1.97–2.01 (m, 2H), 3.33–3.42 (m, 6H), 3.47–3.51 (m, 2H), 3.77–3.82 (m, 2H), 4.69–4.82 (m, 4H), 4.93–4.98 (m, 2H), 5.64–5.72 (m, 1H), 7.24 (d, *J*=8 Hz, 1H), 7.28 (d, *J*=8 Hz, 1H), (t, *J*=8 Hz, 1H); ^{13}C NMR: (125 MHz) δ 17.60, 17.76, 31.37, 33.95, 34.05, 38.36, 69.35, 69.94, 72.16, 72.68, 73.86, 74.55, 75.98, 76.00, 116.62, 120.93, 120.97, 137.01, 137.20, 158.62, 158.89; HRMS (EI) calcd for $C_{21}H_{33}NO_4$: 363.2410, found: 363.2397. Anal. calcd for $C_{21}H_{33}NO_4$: C, 69.38; H, 9.16; N, 3.86; found: C, 69.20; H, 9.36; N, 3.95.

3.2. (4S,14S)-(+)-4,14-Dimethyl-9,9-bis(2-propenyl)-3,6,12,15-tetraoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (S,S)-5

Macrocycle (*S*,*S*)-**5** was prepared as described above for macrocycle (*S*,*S*)-**4** starting from (2*S*,12*S*)-(+)-7,7-bis(2-propenyl)-4,10-dioxatridecane-2,12-diol (*S*,*S*)-**12**[18] (600 mg, 2 mmol) and ditosylate **18** (984 mg, 2.2 mmol). The reaction was completed at rt in 6 days. The crude product was purified by chromatography on neutral alumina using 1% EtOH in toluene as an eluent to give pure (*S*,*S*)-**5** (412 mg, 51%) as a clear oil; R_f=0.39 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$ +20.6 (c 2.08, CH_2Cl_2); IR (neat) ν 3072, 3040, 2976, 2960, 2928, 2860, 1640, 1592, 1576, 1560, 1456, 1376, 1336, 1264, 1116, 1000, 912, 816, 760 cm^{-1}; ^1H NMR (500 MHz) δ 1.18 (d, *J*=7 Hz, 6H), 1.42–1.48 (m, 4H), 1.94 (d, *J*=7 Hz, 4H), 3.35–3.45 (m, 8H), 3.77–3.83 (m, 2H), the benzylic -CH_2- gives an AB spin system: δ_A 4.69, δ_B 4.81, (J_{AB}=13 Hz, 4H), 4.98–5.04 (m, 4H), 5.72–5.80 (m, 2H), 7.30 (d, *J*=8 Hz, 2H), 7.67 (t, *J*=8 Hz, 1H); ^{13}C NMR (125 MHz) δ 17.60, 36.47, 37.24, 42.11, 67.60, 72.27, 74.22, 75.38, 117.74, 121.12, 134.69, 137.11, 158.49; HRMS (EI) calcd for $C_{24}H_{37}NO_4$: 403.2723, found: 403.2730. Anal. calcd for $C_{24}H_{37}NO_4$: C, 71.42; H, 9.25; N, 3.47; found: C, 71.31; H, 9.04; N, 3.71.

3.3. (4S,14S)-(−)-4,14-Diisobutyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (S,S)-6

Macrocycle (*S*,*S*)-**6** was prepared as described above for macrocycle (*S*,*S*)-**4** starting from (4*S*,14*S*)-(−)-2,16-dimethyl-6,9,12-trioxaheptadecane-4,14-diol (*S*,*S*)-**13** (613 mg, 2 mmol) and ditosylate **18** (984 mg, 2.2 mmol). The reaction was completed at rt in 4 days. The crude product was purified by chromatography on neutral alumina using 1% EtOH in toluene as an eluent to give pure (*S*,*S*)-**6** (369 mg, 45%) as a clear oil; $[\alpha]_D^{25}$ −2.1 (c 1.04, CH_2Cl_2); $[\alpha]_D^{25}$ −3.9 (c 0.204, $CHCl_3$), lit.[6] $[\alpha]_D^{25}$ +2.97 (c 0.204, $CHCl_3$) for the other enantiomer (*R*,*R*)-**6**. All other physical properties and spectral data were identical to those reported[6] for (*R*,*R*)-**6**.

3.4. (4S,14S)-(−)-4,14-Diisobutyl-9-(2-propenyl)-3,6,12,15-tetraoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (S,S)-7

Macrocycle (*S*,*S*)-**7** was prepared as described above for macrocycle (*S*,*S*)-**4** starting from (4*S*,14*S*)-(+)-2,16-dimethyl-9-(2-propenyl)-6,12-dioxaheptadecane-4,14-diol (*S*,*S*)-**14**[18] (689 mg, 2 mmol) and ditosylate **18** (984 mg, 2.2 mmol). The reaction was completed at rt in 5 days. The crude product was purified by chromatography on neutral alumina using 0.7% EtOH in toluene as an eluent to give pure (*S*,*S*)-**7** (528 mg, 59%) as a clear oil; R_f=0.61 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$ −10.6 (c 0.404, CH_2Cl_2); IR (neat) ν 3072, 3040, 2960, 2928, 2860, 1640, 1592, 1576, 1460, 1368, 1320, 1120, 992, 912, 816, 760 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (d, *J*=7 Hz, 6H), 0.91 (d, *J*=7 Hz, 3H), 0.93 (d, *J*=7 Hz, 3H), 1.17–1.22 (m, 2H), 1.44–1.54 (m, 6H), 1.65–1.72 (m, 1H), 1.75–1.81 (m, 2H), 2.00–2.04 (m, 2H), 3.39–3.53 (m, 8H), 3.67–3.72 (m, 2H), 4.79–4.85 (m, 4H), 4.96–5.00 (m, 2H), 5.67–5.76 (m, 1H), 7.31 (d, *J*=8 Hz, 1H), 7.33 (d, *J*=8 Hz, 1H), 7.68 (t, *J*=8 Hz, 1H); ^{13}C NMR (125 MHz) δ 22.26, 23.38, 24.59, 31.02, 33.44, 33.71, 37.95, 41.10, 41.24, 69.00, 69.68, 72.14, 72.51, 74.76, 74.91, 75.75, 76.27, 116.25, 120.59, 136.55, 136.99, 158.20, 158.31; HRMS (EI) calcd for $C_{27}H_{45}NO_4$: 447.3349, found: 447.3357. Anal. calcd for $C_{27}H_{45}NO_4$: C, 72.43; H, 10.14; N, 3.13; found: C, 72.24; H, 10.08; N, 3.15.

3.5. (4S,14S)-(−)-4,14-Diisobutyl-9,9-bis(2-propenyl)-3,6,12,15-tetraoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (S,S)-**8**

Macrocycle (*S*,*S*)-**8** was prepared as described above for macrocycle (*S*,*S*)-**4** starting from (4*S*,14*S*)-(+)-2,16-dimethyl-9,9-bis(2-propenyl)-6,12-dioxaheptadecane-4,14-diol (*S*,*S*)-**15**[18] (769 mg, 2 mmol) and ditosylate **18** (984 mg, 2.2 mmol). The reaction was completed at rt in 6 days. The crude product was purified by chromatography on neutral alumina using 0.5% EtOH in toluene as an eluent to give pure (*S*,*S*)-**8** (468 mg, 48%) as a clear oil; R_f=0.70 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$ −10.6 (c 1.04, CH_2Cl_2); IR (neat) ν 3072, 3040, 2952, 2928, 2888, 2872, 1640, 1592, 1576, 1460, 1368, 1336, 1260, 1116, 996, 912, 816, 760 cm^{-1}; ^1H NMR (500 MHz) δ 0.85 (d, *J*=7 Hz, 6H), 0.91 (d, *J*=7 Hz, 6H), 1.17–1.22 (m, 2H), 1.42–1.52 (m, 6H), 1.74–1.79 (m, 2H), 1.94 (d, *J*=7 Hz, 4H), 3.36–3.46 (m, 8H), 3.67–3.71 (m, 2H), the benzylic -CH_2- gives an AB spin system: δ_A 4.74, δ_B 4.79, (J_{AB}=13 Hz, 4H), 4.97–5.03 (m, 4H), 5.72–5.80 (m, 2H), 7.31 (d, *J*=8 Hz, 2H), 7.67 (t, *J*=8 Hz, 1H); ^{13}C NMR (125 MHz) δ 22.61, 23.84, 24.94, 36.67, 37.42, 41.72, 42.34, 67.88, 72.97, 74.92, 76.59, 118.01, 121.30, 134.87, 137.34, 158.72; HRMS (EI) calcd for $C_{30}H_{49}NO_4$: 487.3662, found: 487.3667. Anal. calcd for $C_{30}H_{49}NO_4$: C, 73.87; H, 10.13; N, 2.87; found: C, 74.02; H, 9.88; N, 3.09.

3.6. (4R,14R)-(+)-4,14-Di-tert-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (R,R)-**9**

Macrocycle (*R*,*R*)-**9** was prepared as described above for macrocycle (*S*,*S*)-**4** starting from (3*R*,13*R*)-(−)-2,2,14,14-tetramethyl-5,8,11-trioxapentadecane-3,13-diol (*R*,*R*)-**16**[14] (613 mg, 2 mmol) and ditosylate **18** (984 mg, 2.2 mmol). The reaction was completed at rt in 4 days. The crude product was purified by chromatography on neutral alumina using 0.5% EtOH in toluene as an eluent to give pure (*R*,*R*)-**9** (565 mg, 69%) as a clear oil; $[\alpha]_D^{25}$ +11.3 (c 1.01, CH_2Cl_2), $[\alpha]_D^{25}$ +15.1 (c 0.425, benzene), lit.[7] $[\alpha]_D^{25}$ −15.09 (c 0.424, benzene) for the other enantiomer (*S*,*S*)-**9**. All other physical properties and spectral data were identical to those reported[7] for (*S*,*S*)-**9**.

3.7. (4R,14R)-(+)-4,14-Di-tert-butyl-9-(2-propenyl)-3,6,12,15-tetraoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (R,R)-**10**

Macrocycle (*R*,*R*)-**10** was prepared as described above for macrocycle (*S*,*S*)-**4** starting from (3*R*,13*R*)-(−)-2,2,14,14-tetramethyl-8-(2-propenyl)-5,11-dioxapentadecane-3,13-diol (*R*,*R*)-**17** (689 mg, 2 mmol) and ditosylate **18** (984 mg, 2.2 mmol). The reaction was completed at rt in 6 days. The crude product was purified by chromatography on neutral alumina using 0.4% EtOH in toluene as an eluent to give pure (*R*,*R*)-**10** (457 mg, 51%) as a clear oil; R_f=0.81 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$ +20.8 (c 2.48, CH_2Cl_2); IR (neat) ν 3072, 3040, 2952, 2920, 2888, 2864, 1640, 1592, 1576, 1480, 1460, 1360, 1336, 1112, 992, 912, 800, 760 cm^{-1}; ^1H NMR (500 MHz) δ 0.97 (s, 9H), 0.99 (s, 9H), 1.35–1.53 (m, 4H), 1.71–1.78 (m, 1H), 1.99–2.09 (m, 2H), 3.21–3.23 (m, 1H), 3.26–3.28 (m, 1H), 3.40–3.53 (m, 6H), 3.68–3.72 (m, 2H), 4.84–4.92 (m, 4H), 5.00–5.04 (m, 2H), 5.71–5.79 (m, 1H), 7.35 (d, *J*=8 Hz, 1H), 7.38 (d, *J*=8 Hz, 1H), 7.70 (t, *J*=8 Hz, 1H); ^{13}C NMR (125 MHz) δ 26.57, 26.61, 31.23, 33.67, 34.31, 34.73, 34.75, 37.93, 69.02, 69.99, 72.30, 72.82, 74.38, 74.70, 85.35, 85.80, 116.41, 120.53, 120.81, 136.82, 136.84, 158.37, 158.67; HRMS (EI) calcd for $C_{27}H_{45}NO_4$: 447.3349, found: 447.3344. Anal. calcd for $C_{27}H_{45}NO_4$: C, 72.43; H, 10.14; N, 3.13; found: C, 72.28; H, 10.03; N, 3.24.

3.8. (4S,14S)-(−)-2,16-Dimethyl-6,9,12-trioxaheptadecane-4,14-diol (S,S)-**13**

To a well stirred suspension of NaH (5.11 g, 153 mmol, 60% dispersion in mineral oil) in THF (30 mL) was added dropwise at 0°C and under Ar (*S*)-(−)-4-methyl-2[(tetrahydro-2*H*-pyran-2-yl)oxy]-pentan-1-ol [(*S*)-**21**, see Section 3.11] (21.7 g, 107 mmol) dissolved in THF (145 mL). The reaction mixture was stirred at 0°C for 10 min, at rt for 20 min and at reflux temperature for 3 h. The reaction mixture was cooled to 0°C and diethylene glycol di-*p*-tosylate **22** (20.9 g, 50 mmol) dissolved in THF (75 mL) was added dropwise. Stirring was continued at 0°C for 10 min then at rt for 4 days. The solvent was removed and the residue was taken up in a mixture of ice (50 g), water (100 mL) and ether (300 mL). The mixture was shaken well and separated. The aqueous phase was extracted with ether (2×100 mL). The combined organic phase was shaken with saturated brine (200 mL), dried over $MgSO_4$, filtered and the solvent was evaporated. The residue (28 g) was dissolved in MeOH (500 mL) and Amberlite® IR-120 strong acidic ion-exchange resin (H^+ form) (4 g) was added to this solution. After stirring the mixture at rt for 1 day, the resin was filtered off and washed with MeOH (3×30 mL). The filtrate and washings were combined and the solvent evaporated. The residue was taken up in a mixture of water (40 mL), methanol (200 mL) and hexane (60 mL). The mixture was shaken well and separated. The aqueous methanol phase was extracted with hexane (3×60 mL). The combined hexane phase was shaken with 20% water in methanol (120 mL). The combined aqueous methanol solution was evaporated. The residue was dissolved in toluene and the solvent was removed. The latter procedure was repeated twice to remove traces of water. The crude product was purified by distillation to give (*S*,*S*)-**13** (10.1 g, 65%) as a clear oil; bp: 125–136°C (0.1 mmHg); R_f=0.50 (silica TLC 9% EtOH in toluene); $[\alpha]_D^{25}$ +9.6 (c 0.101, $CHCl_3$), lit.[6] $[\alpha]_D^{25}$ −8.57 (c 0.103, $CHCl_3$) for the other enantiomer (*R*,*R*)-**13**. All other physical properties and spectral data were identical to those reported[6] for (*R*,*R*)-**13**.

3.9. (3R,13R)-(−)-2,2,14,14-Tetramethyl-8-(2-propenyl)-5,11-dioxapentadecane-3,13-diol (R,R)-**17**

To a well stirred mixture of KO*t*-Bu (2.69 g, 0.024 mol) and HMPA (30 mL) was added in an ice-water bath and under Ar 3-(2-propenyl)-pentan-1,5-diol **23**[18] (865 g, 6 mmol). The reaction mixture was stirred in an ice-water bath for 5 min then (*R*)-(−)-3,3-dimethyl-2[(tetrahydro-2*H*-pyran-2-yl)oxy]-butan-1-ol *p*-tosylate [(*R*)-**24a** and/or (*R*)-**24b**, see below] (8.56 g, 24 mmol) was added and stirring was continued in the ice-water bath for 4 h and at rt for 1 day. The resulting mixture was taken up in ice-water (100 mL) and ether (200 mL). The aqueous phase was extracted with ether (3×120 mL). The combined organic phase was shaken with ice cold water (500 mL), saturated brine (250 mL), dried over $MgSO_4$, filtered and evaporated. The residue (4 g) was dissolved in MeOH (50 mL) and Amberlite® IR-120 strong acidic ion-exchange resin (H^+ form) (0.5 g) was added to this solution. After stirring the mixture at rt for 1 day, the resin was filtered off and washed with MeOH (3×5 mL). The filtrate and washings were combined and the solvent evaporated. The residue was dissolved in toluene and the solvent was removed. The latter procedure was repeated twice to remove traces of water. The crude product was purified by chromatography on silica gel using 6% acetone in CH_2Cl_2 as an eluent to give (*R*,*R*)-**17** (393–475 mg, 19–23%) as a colorless oil. R_f=0.52 (silica gel TLC, 14% acetone in CH_2Cl_2); $[\alpha]_D^{25}$ −28.9 (c 1.44, CH_2Cl_2); IR (neat) ν 3580–3220 (broad), 3080, 3048, 2960, 2910, 2870, 1640, 1480, 1460, 1384, 1368, 1324, 1184, 1116, 1080, 1016, 916, 760 cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (s, 18H), 1.56–1.64 (m, 4H), 1.74–1.80 (m, 1H), 2.05–2.08 (m, 2H), 2.83 (broad s, 2H), 3.25–3.32 (m, 2H), 3.43–3.59 (m, 8H), 5.01–5.04 (m, 2H), 5.72–5.80 (m, 1H); ^{13}C NMR (125 MHz) δ 26.23, 31.89, 33.46, 33.50, 33.62, 38.85, 69.31, 69.63, 72.19, 72.36, 76.97, 77.36, 116.66, 136.86.

3.10. (S)-(−)-(Tetrahydro-2H-pyran-2-yl) 2-[(tetrahydro-2H-pyran-2-yl)oxy]-4-methylpentanoate (S)-**20**

To a well stirred mixture of hydroxy acid (*S*)-**19** (29.6 g, 0.224 mol), dihydropyran (DHP) (63.2 mL, 58 g, 0.69 mol) and pure and dry CH_2Cl_2 (60 mL) was added in an ice–salt bath and under Ar pyridinium *p*-toluenesulfonate (PPTS) catalyst (2.2 g) and one drop of pyridine. After stirring the reaction mixture in the ice–salt bath for 10 min and at rt for 1 day, CH_2Cl_2 (300 mL) was added. The resulting mixture was shaken with 5% $NaHCO_3$ (100 mL) and water (2×100 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed to give crude (*S*)-**20** (65.6 g, 98%) as a mixture of four diastereomers, which was used without further purification; R_f=0.7, 0.8, 0.9 (silica gel TLC 20% 2-butanone in toluene); $[\alpha]_D^{25}$ −5.1 (c 1.21, CH_2Cl_2); IR (neat) ν 3080, 3030, 2960, 2930, 2870, 1750, 1468, 1424, 1380, 1360, 1320, 1296, 1270, 1250, 1185, 1120, 1080, 1024, 984, 928, 904, 870, 812, 752 cm^{-1}; ^1H NMR (80 MHz) δ 0.90 (d, *J*=6 Hz, 6H), 1.2–2.1 (m, 15H), 3.3–4.1 (m, 5H), 4.5–4.7 (m, 1H), 5.9–6.1 (m, 1H).

3.11. (S)-(−)-4-Methyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]-pentan-1-ol (S)-**21**

To a well stirred suspension of $LiAlH_4$ (9.6 g, 0.25 mol) in ether (80 mL) was slowly added crude (*S*)-**20** (65.6 g, 0.22 mol) dissolved in ether (90 mL) under Ar at 0°C. The mixture was stirred at 0°C for 30 min, at rt for 1 day, and at reflux temperature for 48 h. When the reduction was completed, the mixture was cooled in an ice–salt bath and first saturated NH_4Cl (10 mL) then 5% NaOH solution (20 mL) were added very slowly. The resulting mixture was stirred at rt for 4 h, at reflux temperature for 14 h and at rt again for 6 h. The precipitate was filtered and washed with ether (3×30 mL). The combined ethereal solution was shaken with saturated brine, dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by distillation to give (*S*)-**21** (33 g, 73%) as a mixture of two diastereomers; bp: 72–76°C (0.1 mmHg); R_f=0.25, 0.35 (silica TLC 20% EtOAc in toluene); $[\alpha]_D^{25}$ −20.1 (c 1.91, CH_2Cl_2); IR (neat) ν 3620–3220 (broad), 3080, 3050, 3030, 2960, 2930, 2882, 2876, 1468, 1424, 1380, 1360, 1272, 1198, 1185, 1144, 1088, 1024, 984, 888, 816 cm^{-1}; ^1H NMR (80 MHz) δ 0.9 (d, *J*=6 Hz, 6H), 1.1–2.0 (m, 9H), 2.4 (broad s, disappeared with D_2O, 1H), 3.3–4.2 (m, 5H), 4.7–4.9 (m, 1H).

3.12. (R)-(+)-3,3-Dimethyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]-butan-1-ol p-tosylate (R)-**24a** (first diastereomer)

To a well stirred mixture of finely powdered KOH (8.71 g, 85%, 132 mmol) in THF (30 mL) was added dropwise at −20°C and under Ar first a mixture of alcohol (*R*)-**25a** and (*R*)-**25b**[14] (6.65 g, 33 mmol) dissolved in THF (40 mL), then tosyl chloride (8.8 g, 46 mmol) dissolved in THF (40 mL). The resulting mixture was stirred at −20°C for 2 h, then it was allowed to warm up to rt and stirring was continued at rt for 1 day. The solvent was evaporated at rt, and the residue was taken up in ice-water (75 mL) and CH_2Cl_2 (150 mL). The aqueous phase was extracted with CH_2Cl_2 (3×75 mL). The combined organic phase was shaken with distilled water (200 mL), dried over $MgSO_4$, filtered and evaporated. The crude material was purified first by chromatography on silica gel using 10% EtOAc in hexane as an eluent, then triturating the product with hexane to give (*R*)-**24a** (5.18 g, 48%, one of the two diastereomers) as white crystals. Mp: 52°C (hexane); R_f=0.50 (silica gel TLC, 20% EtOAc in hexane); $[\alpha]_D^{25}$ +34.1 (c 4.51, CH_2Cl_2); IR (KBr) ν 3080, 3030, 2960, 2930, 2870, 1600, 1492, 1475, 1456, 1395, 1364, 1185, 1176, 1144, 1088, 1028, 960, 904, 816, 752, 688, 664, 552 cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (s, 9H), 1.44–1.51 (m, 4H), 1.59–1.64 (m, 1H), 1.73–1.79 (m, 1H), 2.46 (s, 3H), 3.42–3.47 (m, 1H), 3.54–3.57 (m, 1H), 3.87–3.92

(m, 1H), 3.99–4.04 (m, 1H), 4.25–4.29 (m, 1H), 4.66–4.69 (m, 1H), 7.36 (d, *J*=8 Hz, 2H), 7.80 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz) δ 20.06, 21.55, 25.28, 26.41, 30.97, 34.01, 63.40, 71.17, 80.80, 98.77, 127.76, 129.78, 132.92, 144.77.

The other starting diastereomer alcohol (*R*)-**25b** was recovered in 46% yield (3.2 g). R_f=0.35 (silica gel TLC, 20% EtOAc in hexane); $[\alpha]_D^{25}$ −62.5 (c 0.510, CH_2Cl_2); IR (KBr) ν 3080, 3030, 2960, 2930, 2870, 1600, 1492, 1475, 1456, 1395, 1364, 1185, 1176, 1144, 1088, 1028, 960, 904, 816, 752, 688, 664, 552 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.90 (s, 9H), 1.48–1.56 (m, 4H), 1.82–1.86 (m, 2H), 3.20 (broad s, 1H), 3.47–3.54 (m, 2H), 3.66 (t, *J*=10 Hz, 1H), 4.02 (d, *J*=10 Hz, 1H), 4.10 (d, *J*=10 Hz, 1H), 4.35–4.37 (m, 1H); ^{13}C NMR (125 MHz) δ 21.48, 24.91, 26.21, 31.11, 34.19, 62.25, 65.46, 92.20, 103.20.

*3.13. (*R*)-(−)-3,3-Dimethyl-2-[(tetrahydro-2*H*-pyran-2-yl)oxy]-butan-1-ol* p-*tosylate (*R*)-**24b** (second diastereomer)*

To a stirred solution of alcohol (*R*)-**25b** (3.2 g, 16 mmol, one of the two diastereomers) in pyridine (10 mL) at rt and under Ar was added tosyl chloride (4.7 g, 24 mmol) dissolved in pyridine (5 mL). The reaction mixture was stirred at rt for 1 day then it was poured into ice-water (150 mL). The aqueous mixture was extracted with ether (2×150 mL). The combined organic phase was shaken with distilled water (300 mL), saturated brine (150 mL), dried over $MgSO_4$, filtered, and the solvent evaporated. The rest of the pyridine was removed under strongly reduced pressure (0.2 mmHg). The crude product was purified by chromatography on silica gel using 10% EtOAc in hexane as an eluent to give (*R*)-**24b** (5.1 g, 91%, one of the two diastereomers) which solidified after standing; mp: 38°C; R_f=0.45 (silica gel TLC, 20% EtOAc in hexane); $[\alpha]_D^{25}$ −44.5 (c 4.61, CH_2Cl_2); IR (KBr) ν 3080, 3030, 2960, 2930, 2870, 1600, 1468, 1424, 1380, 1360, 1296, 1185, 1176, 1120, 1080, 1024, 984, 960, 928, 888, 840, 812, 744, 672, 648, 552, 504 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.90 (s, 9H), 1.44–1.57 (m, 4H), 1.62–1.68 (m, 1H), 1.73–1.79 (m, 1H), 2.44 (s, 3H), 3.33–3.38 (m, 2H), 3.78–3.83 (m, 1H), 4.14–4.20 (m, 2H), 4.54–4.57 (m, 1H), 7.33 (d, *J*=8 Hz, 2H), 7.81 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz) δ 19.59, 21.54, 25.26, 25.72, 26.07, 30.58, 35.03, 62.57, 70.48, 84.12, 101.43, 127.99, 129.60, 132.97, 144.52.

*3.14. Mixture of the two diastereomeric tosylates (*R*)-**24a** and (*R*)-**24b***

A mixture of the tosylates (*R*)-**24a** and (*R*)-**24b** was prepared as described above for tosylate (*R*)-**24b** starting from a mixture of the alcohols (*R*)-**25a** and (*R*)-**25b** (10.1 g, 50 mmol). The crude product was purified by chromatography on silica gel using 10% EtOAc in hexane as an eluent to give (*R*)-**24a** and (*R*)-**24b** (15.8 g, 89%) which solidified after standing; mp: 34–36°C; R_f=0.45, 0.50 (silica gel TLC, 20% EtOAc in hexane); $[\alpha]_D^{25}$ −9.4 (c 4.45, CH_2Cl_2). The IR, ^{1}H NMR and ^{13}C NMR spectra contained all the spectral data of the two individual diastereomeric tosylates (*R*)-**24a** and (*R*)-**24b**. From the ^{1}H NMR spectrum of the mixture a ratio of 44:56 [(*R*)-**24a**]:[(*R*)-**24b**] for the two diastereomeric tosylates could be calculated.

*3.15. (*R*)-(−)-1-(Tosyloxy)-3,3-dimethyl-butan-2-ol (*R*)-**26***

Diastereomeric ditosylate (*R*)-**24a** or (*R*)-**24b**, or the mixture of the two (0.71 g, 2 mmol) was dissolved in MeOH (10 mL) and Amberlite® IR-120 strong acidic ion-exchange resin (H^+ form) (0.1 g) was added to this solution. After stirring the mixture at rt for 1 day, the resin was filtered off and washed with MeOH (3×5 mL). The filtrate and washings were combined and the solvent evaporated. The residue was dissolved in toluene and the solvent was removed. The latter procedure was repeated twice to remove

traces of water. The crude product was purified by chromatography on silica gel using 10% EtOAc in hexane as an eluent to give (*R*)-**26** (0.51–0.52 g, 94–96%) as white crystals. According to their physical and spectroscopical data in all three cases the same monotosylate (*R*)-**26** was obtained; $[\alpha]_D^{25}$ +27.7 (c 1.12, benzene), lit.[7] $[\alpha]_D^{25}$ −27.42 (c 1.098, benzene) for the other enantiomer (*S*)-**26**. All other physical properties and spectral data were identical to those reported[7] for (*S*)-**26**.

Acknowledgements

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

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