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Chemoenzymatic syntheses of two optically active hexa-azamacrocycles

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Abstract

Two optically active hexa-azamacrocycles with C_2 and D_2 symmetry, respectively, have been efficiently synthesized from the enzymatically prepared (*R*,*R*)-cyclohexane-1,2-diamine bis(amidoester) derivative (*R*,*R*)-**4**.

1. Introduction

The design and syntheses of organic receptor molecules capable of binding anionic species have wide interest in chemical and biological fields.[1] Several approaches are based on the use of protonated polyammonium macrocycles.[2] These compounds display positively charged binding sites at neutral pH, and their anion complexation properties have been extensively explored.[3,4] Besides charge–charge interactions, structural factors such as the cavity size of the macrocycle or the number of nitrogens play an important role in their anion-binding features.[3,5] Thus, protonated hexa- and hepta-azamacrocycles having from 18- to 24-membered rings are excellent receptors for organic phosphates[3a,4b,d] and polycarboxylates,[3b,c,4a,5] and some are involved in biological processes such as excitatory amino acids,[6] nucleotides or nucleic acids.[7] However, despite the importance of chirality in living organisms, examples of suitable ligands for the selective complexation of chiral anions are scarce.[8] As far as we know, there is only one example in which saphyrin-based receptors are used for molecular recognition of optically active dicarboxylates.[9]

Taking this into account, our purpose in this work has been the synthesis of two optically active 22-membered ring macrocyclic polyamines (**1a** and **2a**) bearing the chirality carrier (*R*,*R*)-cyclohexane-1,2-diamine fragment. The efficiency of optically active *trans*-cyclohexane-1,2-diamine derivatives in asymmetric syntheses,[10] and as molecular receptors,[11] is well documented.

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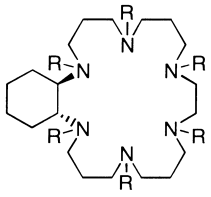
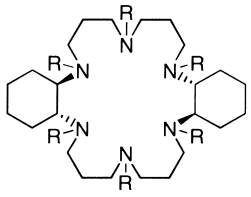


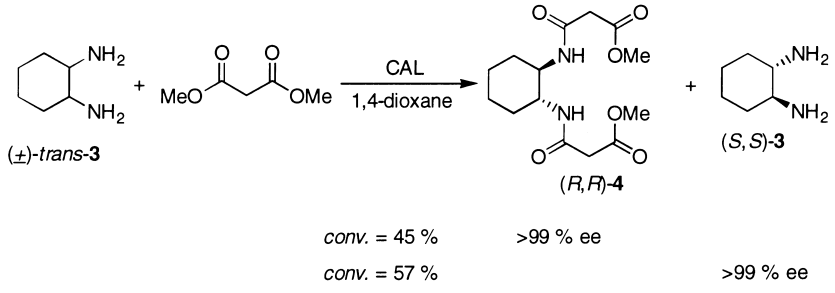
1a: R=H; **1b**: R=Ts



2a: R=H; **2b**: R=Ts

2. Results and discussion

Recently we have reported an easy and efficient method for the resolution of (±)-*trans*-cyclohexane-1,2-diamine by *Candida antarctica* lipase (CAL) catalyzed aminolysis of dimethyl malonate.[12] By controlling the conversion extent, this method allowed us to prepare the enantiopure bis(amidoester) (*R*,*R*)-**4** (Scheme 1), which was used in this work as a starting material for the synthesis of **1a** and **2a**.

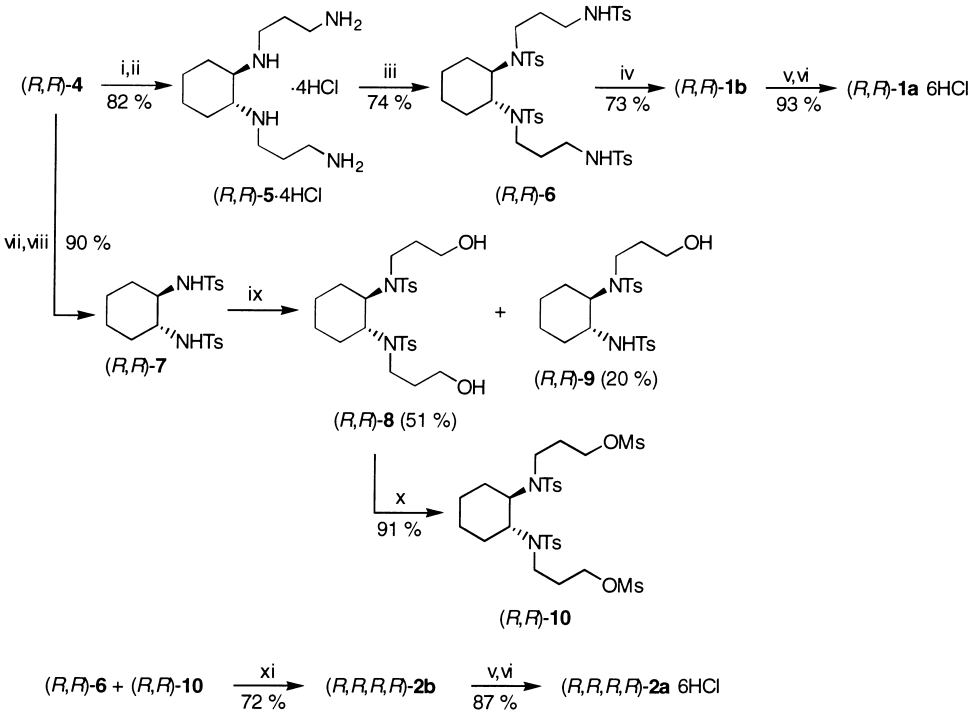


Scheme 1.

Transformation of (*R*,*R*)-**4** into the azamacrocycles **1a** and **2a** was carried out following the procedure outlined in Scheme 2, which mainly involves coupling the tosylated polyamine (*R*,*R*)-**6** with a doubly electrophilic reagent in the presence of a base. Compound (*R*,*R*)-**6** was easily obtained from the enantiopure bis(amidoester) (*R*,*R*)-**4** as follows. Activated ester functions of (*R*,*R*)-**4** were quantitatively converted into amides by conventional ammonolysis (ammonia in methanol). Subsequent BH_3/THF reduction of the tetra-amide led to the tetra-amine (*R*,*R*)-**5**, which was isolated and used in the next step as its tetrahydrochloride. Tosylation of (*R*,*R*)-**5**·4HCl with tosyl chloride (Scheme 2) was efficiently carried out in a biphasic system formed by tetrahydrofuran and aqueous potassium carbonate. Other attempts of tosylation of the free amine (*R*,*R*)-**5** using pyridine or triethylamine in tetrahydrofuran or dichloromethane afforded lower yields of (*R*,*R*)-**6** (20–27% yield) and mixtures of partially tosylated polyamines.

Coupling of (*R*,*R*)-**6** with the doubly electrophilic system, *N*,*N*′-ethylenebis-[3-(*p*-toluenesulphonylamino)propyl methanesulphonate][†] [13] bearing another fragment of the ring **1a**, was carried out with an excess of cesium carbonate in refluxing acetonitrile (a modification of the Richmann–Atkins[14] procedure). In these conditions the hexatosylated azamacrocycle (*R*,*R*)-**1b** was obtained with a 73% yield after the purification by flash chromatography. Hydrolysis of the sulphonamide functions of (*R*,*R*)-**1b** with 48% HBr and an excess of phenol yielded the desired hexa-azamacrocycle

[†] *N*,*N*′-Ethylenebis[3-(*p*-toluenesulphonylamino)propyl methanesulphonate] was prepared from ethylenebis(sulphonamide) following the same procedure as shown for (*R*,*R*)-**10**. Overall yield, 81%; mp 148–149°C, lit.[13] mp 148–149°C. MS (EI) *m/z* (rel. intensity): 485 (M^+–Ts, 6), 320 (100). The spectral data are in accordance with literature values.[13]



Scheme 2. Reagents and conditions: (i) NH_3/MeOH; (ii) BH_3/THF, reflux; (iii) TsCl, K_2CO_3, THF/H_2O; (iv) Cs_2CO_3/CH_3CN, 82°C then $MsO(CH_2)_3TsN(CH_2)_2NTs(CH_2)_3OMs$; (v) HBr(48%)/PhOH; (vi) Dowex, basic form, then 12 N HCl; (vii) 6 N HCl, reflux; (viii) TsCl, K_2CO_3, Et_2O/H_2O; (ix) K_2CO_3/CH_3CN, 3-bromopropan-1-ol; (x) MsCl/py, 0°C; (xi) Cs_2CO_3/CH_3CN, 82°C

(*R*,*R*)-**1a** as its hexahydrobromic salt. In order to facilitate the purification of the macrocyclic salt, bromide was changed to chloride by passing (*R*,*R*)-**1a**·6HBr through an anion exchanger and the subsequent addition of concentrated HCl. The resulting (*R*,*R*)-**1a**·6HCl was easily recrystallized in an ethanol–methanol mixture.

For the synthesis of the macrocycle (*R*,*R*,*R*,*R*)-**2a**, compound (*R*,*R*)-**6** was coupled with (*R*,*R*)-**10** in a similar way as for (*R*,*R*)-**1a**. The electrophilic partner (*R*,*R*)-**10** was also obtained from the bis(amidoester) (*R*,*R*)-**4** as shown in Scheme 2. Acidic hydrolysis of (*R*,*R*)-**4**, followed by tosylation of the resulting (*R*,*R*)-cyclohexane-1,2-diamine dihydrochloride (TsCl, diethyl ether/aqueous K_2CO_3) led to the bis(sulphonamide) (*R*,*R*)-**7**. Alkylation of (*R*,*R*)-**7** with 3-bromopropan-1-ol gave the diol (*R*,*R*)-**8** with a moderate yield only (51%) even after a long reaction time (5 days). In this reaction, besides (*R*,*R*)-**8**, the monoalkylated compound (*R*,*R*)-**9** was isolated with a 20% yield. We have unsuccessfully tried to improve the yield by changing the solvent and the base. Mesylation of (*R*,*R*)-**8** was readily achieved with mesyl chloride in pyridine at 0°C. Both the coupling of (*R*,*R*)-**6** with (*R*,*R*)-**10** and the subsequent hydrolysis of the resulting sulphonamide (*R*,*R*,*R*,*R*)-**2b** were carried out in the same conditions as shown previously for (*R*,*R*)-**1a**, obtaining compound (*R*,*R*,*R*,*R*)-**2a**·6HBr, which was also converted into the corresponding hexahydrochloride to facilitate its purification.

Taking into account that the asymmetric centers do not participate in any reaction step, no racemization is expected in these syntheses. Although ^{1}H NMR spectra of (*R*,*R*)-**1a** and (*R*,*R*,*R*,*R*)-**2a** consist of broad signals due to dynamic effects, ^{13}C NMR spectra show ten and six signals, respectively, thus revealing an effective C_2 and D_2 symmetry for each compound (see Experimental). These facts demonstrate that in the above synthetic routes, epimerization of the chiral centers has not taken place, since epimerization

would lead to the formation of *cis*/*trans* diastereomeric mixtures and so to an increase of the number of signals in the ^{13}C NMR spectra.

In conclusion, we have developed efficient syntheses of two optically active hexa-azamacrocycles bearing one and two (*R*,*R*)-cyclohexane-1,2-diamine moieties in their structure, respectively. These compounds, (*R*,*R*)-**1a** and (*R*,*R*,*R*,*R*)-**2a**, can be, in principle, good candidates for the chiral anion complexation due to their structural characteristics: (i) they are both 22-membered rings, a convenient size for the complexation of phosphates and polycarboxylates;[3–5] (ii) they have six nitrogens forming four propylene-1,3-diamine moieties. Azamacrocycles consisting of these groupings have increased their protonation abilities at neutral or weakly acidic pH with respect to those azamacrocycles with ethylene-1,2-diamine units;[15] (iii) compound **1a** presents C_2 symmetry, whereas **2a** possesses three C_2 axes to give it D_2 overall symmetry. Studies of the protonation features of (*R*,*R*)-**1a** and (*R*,*R*,*R*,*R*)-**2a**, as well as their chiral anion complexation properties, are currently in progress and will be reported elsewhere.

3. Experimental

All reagents were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. Precoated TLC plates silica gel 60 F_{254} from Merck were used, and for column chromatography, Merck silica gel 60/230–400 mesh was used. Mps were taken using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer 1720-X FT IR spectrometer. Mass spectra were recorded on a Hewlett–Packard 5987 A spectrometer. Microanalyses were performed on a Perkin–Elmer 240B elemental analyser. ^1H and ^{13}C NMR were obtained using a Bruker AC-300 (^1H, 400 MHz and ^{13}C, 75.5 MHz), a Bruker AC-200 (^1H, 200 MHz and ^{13}C, 50.3 MHz) or a Bruker AMX-400 (^1H, 300 MHz and ^{13}C, 100.7 MHz) spectrometer. For NMR spectra of (*R*,*R*)-**1a**·6HCl and (*R*,*R*,*R*,*R*)-**2a**·6HCl, samples were dissolved in D_2O and concentrated DCl was added until pD <2 to ensure the major existence of the hexaprotonated species in solution.

*3.1. (*R,R*)-N,N′-(Cyclohexane-1,2-diyl)bis(propane-1,3-diamine) tetrahydrochloride (*R,R*)-**5**·4HCl*[12]

Bis(amidoester) (*R*,*R*)-**4** (785 mg, 2.5 mmol) was added to a solution of NH_3 in methanol (10%, 75 mL). After stirring at 7°C during 12 h, the solvent was removed and (*R*,*R*)-*N*,*N*′-(cyclohexane-1,2-diyl)bis(2-carbamoylethanamide) was obtained quantitatively as a white solid; mp 252–253°C; $[\alpha]_D^{20}$ +70.1 (*c* 0.65, H_2O); IR (KBr) 3410, 3344, 3236, 3202, 1658, 1631 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 1.31 (bd, *J*=4.9 Hz, 4H), 1.73 (bs, 2H), 1.90 (bs, 2H), 3.04 (bs, 4H), 3.61 (bs, 2H), 7,13 (bs, 2H, NH), 7.47 (bs, 2H, NH), 7.92 (bd, *J*=7.8 Hz, 4H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ (ppm) 24.2 (CH_2), 31.7 (CH_2), 43.3 (CH_2), 51.8 (CH), 166.8 (C), 168.9 (C). MS (EI) *m/z* (rel. intensity): 284 (M^+, 5), 182 (100). A solution of BH_3·THF (50 mL, 1 M) was added dropwise to a suspension of this tetra-amide in tetrahydrofuran (100 mL) under nitrogen atmosphere. The obtained mixture was heated to reflux for 7 h. After this time, the reaction was treated at 0°C with 10 mL of water and evaporated to dryness. The solid thus obtained was refluxed in 6 N HCl (100 mL) for 4 h, and then the water removed in vacuo. The residue was dissolved in H_2O, passed over Dowex 1 (basic form) and eluted with deionized water. The solution containing (*R*,*R*)-**5** was acidified until pH=2 with conc. HCl. Evaporation of the solvent yielded (*R*,*R*)-**5**·4HCl (767 mg, 82%), which was recrystallized from EtOH. ^1H NMR (D_2O, 300 MHz) δ (ppm) 1.05 (bt, *J*=9.6 Hz, 2H), 1.53 (bs, 2H), 1.73 (bs, 2H), 2.09 (m, 4H), 2.22 (bd, *J*=12.7 Hz, 2H), 3.05 (t, *J*=12.7 Hz, 4H), 3.10 (m, 2H), 3.35 (m, 2H), 3.49 (m, 2H). ^{13}C NMR (D_2O, 75.5 MHz) δ (ppm)

22.2 (CH_2), 24.5 (CH_2), 26.1 (CH_2), 37.1 (CH_2), 43.3 (CH_2), 58.2 (CH). MS (FAB^+, nitrobenzyl alcohol matrix) *m/z* (rel. intensity): 229 [$(M+1)^+$, 2]. Anal. calcd for $C_{12}H_{32}Cl_4N_4$: C, 38.51; H, 8.62; N, 14.97. Found: C, 38.25; H, 8.97; N, 14.81.

*3.2. (*R,R*)-N,N′-(Cyclohexane-1,2-diyl)-N,N′,N″,N‴-tetrakis(*p*-toluenesulphonyl)bis(propane-1,3-diamine) (*R,R*)-**6***

To a suspension of K_2CO_3 (19.6 g) in water (16 mL), THF (16 mL), (*R,R*)-**5**·4HCl (748 mg, 2.0 mmol) and *p*-toluenesulphonyl chloride (2.28 g, 12.0 mmol) were added. The resulting biphasic system was vigorously stirred for 12 h. Water and ethyl acetate were then added to the mixture. The organic layer was washed with 3 N HCl, dried with sodium sulphate, and evaporated to give (*R,R*)-**5** in a 74% yield after the flash chromatography (ethyl acetate:hexane, 1:1); mp 72–73°C; $[\alpha]_D^{20}$ −8.8 (*c* 0.51, $CHCl_3$); IR (Nujol) 3279 cm^{-1}; ^1H NMR (CD_3CN, 300 MHz) δ (ppm) 1.09–1.40 (several m, 6H), 1.45–1.90 (several m, 4H), 2.27 (s, 12H), 2.40–3.15 (several m, 12H), 5.40–5.70 (several m, 2H), 7.41 (m, 8H), 7.73 (m, 8H). MS (FAB^+, glycerol matrix) *m/z* (rel. intensity): 845 [$(M+1)^+$, 29], 844 (M^+, 15), 689 [$(M-Ts)^+$, 39]. Anal. calcd for $C_{40}H_{52}N_4O_8S_4$: C, 56.87; H, 6.16; N, 6.63. Found: C, 56.78; H, 6.11; N, 6.34.

*3.3. (*R,R*)-N,N′-(Cyclohexane-1,2-diyl)bis(*p*-toluenesulphonamide) (*R,R*)-**7***

6 N HCl (45 mL) was added to the bis(amidoester) (*R,R*)-**4** (1.3 g, 4 mmol) and the mixture was heated at 110°C for 3 h. The reaction mixture was then evaporated to dryness and the residue was recrystallized from ethanol. The resulting (*R,R*)-cyclohexane-1,2-diamine dihydrochloride, obtained quantitatively, was dissolved in a biphasic system formed by diethyl ether (16 mL) and a concentrated K_2CO_3 aqueous solution (8.8 g of K_2CO_3 dissolved in 16 mL of water). An excess of *p*-toluenesulphonyl chloride (1.82 g, 9.6 mmol) was then added at room temperature and the mixture vigorously stirred for 12 h. The white solid formed during this time was filtered, successively washed with water and hot hexane and dried to give pure (*R,R*)-**7** (1.52 g, 90% yield); mp 180–181°C; $[\alpha]_D^{20}$ +7.7 (*c* 0.56, $CHCl_3$); IR (KBr) 3367 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.10 (bs, 4H), 1.55 (bs, 2H), 1.83 (bs, 2H), 2.40 (bs, 6H), 2.73 (bs, 2H), 4.95 (bs, 2H, NH), 7.45 (d, *J*=8.0 Hz, 4H), 7.72 (d, *J*=8.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 21.5 (CH_3), 24.1 (CH_2), 33.2 (CH_2), 56.5 (CH), 127.1 (CH), 129.7 (CH), 136.9 (C), 143.5 (C). MS (FAB^+, glycerol matrix) *m/z* (rel. intensity): 423 [$(M+1)^+$, 100]. Anal. calcd for $C_{20}H_{26}N_2O_4S_2$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.66; H, 6.05; N, 6.45.

*3.4. (*R,R*)-N,N′-(Cyclohexane-1,2-diyl)bis-[3-(*p*-toluenesulphonylamino)propan-1-ol] (*R,R*)-**8***

(*R,R*)-Cyclohexane-1,2-diamine ditosylate [(*R,R*)-**7**] (844 mg, 2.0 mmol) and K_2CO_3 (2.76 g, 20 mmol) were suspended in dry acetonitrile (12 mL) and the mixture heated at 70°C for 30 min. 3-bromopropan-1-ol (0.72 mL, 8.0 mmol) was then added dropwise. The reaction mixture was stirred at 70°C until starting (*R,R*)-**7** was not detected (TLC, ethyl acetate:hexane, 3:2). After 3 days aqueous 3 N HCl (15 mL) was added and the resulting mixture extracted with dichloromethane (3×15 mL). The combined organic layers were dried and concentrated in vacuo to give a mixture of (*R,R*)-**8** and (*R,R*)-**9**, which was separated by flash chromatography using ethyl acetate:hexane (3:2) as eluent. (*R,R*)-**8** was isolated with 51% yield; mp 141–143°C; $[\alpha]_D^{20}$ +7.2 (*c* 0.58, $CHCl_3$); IR (Nujol) 3138–3547 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.05–1.35 (m, 6H), 1.55 (bd, *J*=7.3 Hz, 2H), 2.25 (m, 4H), 2.45 (s, 6H), 2.99–3.09 (m, 2H), 3.28–3.38 (m, 2H), 3.55 (m, 2H), 3.75–3.90 (m, 4H), 7.31 (m, 4H), 7.72 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 22.1 (CH_3), 25.7 (CH_2), 30.5 (CH_2), 34.2 (CH_2), 41.8 (CH_2),

60.5 (CH), 61.1 (CH_2), 128.0 (CH), 130.4 (CH), 137.8 (C), 144.2 (C). MS (CI) *m/z* (rel. intensity): 539 [$(M+1)^+$, 15], 383 [$(M-Ts)^+$, 100]. Anal. calcd for $C_{26}H_{38}N_2O_6S_2$: C, 57.96; H, 7.11; N, 5.20. Found: C, 57.92; H, 7.43; N, 4.88.

3.5. *(1′*R,*2′*R)-N-*(3-Hydroxypropyl)*-N-*[2-(*p-*toluenesulphonylamino)cyclohexyl]*-p-*toluenesulphonamide (*R,R*)-**9***

Yield, 20%; mp 178–180°C; $[\alpha]_D^{20}$ −11.7 (*c* 0.62, $CHCl_3$); IR (Nujol) 3231, 3551 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.09–1.28 (m, 4H), 1.57–1.79 (m, 5H), 1.99 (m, 1H), 2.14 (m, 1H), 2.43 (s, 6H), 2.92 (m, 2H), 3.19 (m, 1H), 3.36 (m, 1H), 3.56 (m, 2H), 5.40 (d, *J*=4.4 Hz, 1H), 7.30 (m, 4H), 7.67 (m, 2H), 7.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 21.4 (CH_3), 23.8 (CH_2), 25.1 (CH_2), 29.7 (CH_2), 32.9 (CH_2), 34.6 (CH_2), 40.1 (CH_2), 54.2 (CH), 59.5 (CH_2), 60.1 (CH), 126.6 (CH), 126.9 (CH), 129.5 (CH), 129.8 (CH), 137.2 (C), 138.4 (C), 143.1 (C), 143.6 (C). MS (EI) *m/z* (rel. intensity): 325 [$(M-Ts)^+$, 80], 96 (100), 91 (84). Anal. calcd for $C_{23}H_{32}N_2O_5S_2$: C, 57.47; H, 6.71; N, 5.83. Found: C, 57.26; H, 7.05; N, 5.69.

3.6. *(*R,R*)*-N,N′-*(Cyclohexane-1,2-diyl)bis-[3-(*p-*toluenesulphonylamino)propyl methanesulphonate] (*R,R*)-**10***

Methanesulphonyl chloride (0.40 mL, 5.2 mmol) was added dropwise under nitrogen to a solution of (*R,R*)-**8** (700 mg, 1.3 mmol) in dry freshly distilled pyridine (3.9 mL). After stirring at 0°C for 1.5 h, the mixture was treated with 3 N HCl (10 mL) and extracted with dichloromethane (3×20 mL). The combined organic layers were dried and concentrated in vacuo yielding the product (*R,R*)-**9** as a white solid (822 mg, 91%), mp 137–139°C; $[\alpha]_D^{20}$ −17.3 (*c* 0.51, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.05–1.40 (m, 6H), 1.55 (bs, 2H), 2.38 (m, 4H), 2.45 (s, 6H), 3.06 (s, 6H), 3.15 (m, 4H), 3.88 (m, 2H), 4.32 (m, 4H), 7.34 (m, 4H), 7.72 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 21.4 (CH_3), 25.0 (CH_2), 29.9 (CH_2), 30.1 (CH_2), 37.1 (CH_3), 40.9 (CH_2), 59.6 (CH_3), 69.2 (CH_2), 127.2 (CH), 129.8 (CH), 137.0 (C), 143.6 (C). MS (FAB^+, nitrobenzyl alcohol matrix) *m/z* (rel. intensity): 797 [$(M+23)^+$, 67], 695 [$(M+1)^+$, 56]. Anal. calcd for $C_{28}H_{42}N_2O_{10}S_4$: C, 48.39; H, 6.09; N, 4.03. Found: C, 48.76; H, 5.94; N, 3.82.

3.7. *General procedure for the cyclization reactions of (*R,R*)-**6***

Dry acetonitrile (30 mL) was added to a flask containing (*R,R*)-**6** (844 mg, 1.0 mmol) and Cs_2CO_3 (3.26 g, 10.0 mmol) under a nitrogen atmosphere. The mixture was refluxed for 30 min, and then a solution of the adequate electrophilic reagent (1.0 mmol) in dry acetonitrile (20 mL) was added dropwise. The reaction mixture was kept to reflux for 2 days. After this time, the solvent was removed and the residue was subjected to flash chromatography (ethyl acetate:hexane, 1:1) to yield the corresponding tosylated azamacrocycle.

3.7.1. *(*R,R*)-2,6,10,13,17,21-Hexakis(*p-*toluenesulphonyl)-2,6,10,13,17,21-hexaazabicyclo-[20.4.0]hexaicosane (*R,R*)-**1b***

Yield, 73%, white solid; mp 110–112°C; $[\alpha]_D^{20}$ −20.9 (*c* 0.58, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.95–1.60 (several m, 8H), 1.70–2.25 (several m, 8H), 2.43 (m, 18H), 2.65–3.90 (several m, 22H), 7.31 (m, 12H), 7.73 (m, 12H). MS (FAB^+, nitrobenzyl alcohol matrix) *m/z* (rel. intensity): 1293 [$(M+1)^+$,

2], 1137 [(M−Ts)$^+$, 5]. Anal. calcd for $C_{62}H_{80}N_6O_{12}S_6$: C, 57.56; H, 6.23; N, 6.49. Found: C, 57.48; H, 6.47; N, 6.11.

*3.7.2. (*R,R,R,R*)-2,6,10,13,17,21-Hexakis(*p*-toluenesulphonyl)-2,6,10,13,17,21-hexaazatricyclo-[20.4.0.0^{11,16}] triacontane (*R,R,R,R*)-**2b***

Yield, 72%, white solid; mp 114–116°C; $[\alpha]_D^{20}$ −36.8 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.95–1.60 (several m, 16H), 1.70–2.25 (several m, 8H), 2.43 (m, 18H), 2.65–3.90 (several m, 20H), 7.31 (m, 12H), 7.73 (m, 12H). MS (FAB$^+$, nitrobenzyl alcohol matrix) *m/z* (rel. intensity): 1347 [(M+1)$^+$, 2], 1191 [(M−Ts)$^+$, 5]. Anal. calcd for $C_{66}H_{86}N_6O_{12}S_6$: C, 58.81; H, 6.43; N, 6.23. Found: C, 58.90; H, 6.57; N, 5.95.

3.8. General procedure for the hydrolysis of the hexatosylated azamacrocycles

Hexatosylated azamacrocycle (0.7 mmol) and an excess of phenol (1.14 mL, 13 mmol) were dissolved in 48% aqueous HBr (21 mL), and the solution was heated at reflux during 3 days. Water and dichloromethane were then added and the aqueous layer was repeatedly washed with dichloromethane. The organic layer was discarded and the aqueous layer was evaporated under reduced pressure. The residue was dissolved in the minimum amount of water, passed over an anion exchanger (Dowex 1, basic form) and eluted with deionized water until neutral pH. Concentrated HCl was added until pH ≤2 and the acid solution was evaporated to dryness. The residue was recrystallized in a mixture of EtOH–MeOH yielding the corresponding hexa-azamacrocycle hexahydrochloride as a white solid, which was dried in vacuo.

*3.8.1. (*R,R*)-2,6,10,13,17,21-Hexaazabicyclo[20.4.0]hexaicosane hexahydrochloric salt (*R,R*)-**1a**·6HCl*

Yield, 93%, decomposes at 250°C. $[\alpha]_D^{20}$ −16.1 (*c* 0.59, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ (ppm) 1.38 (m, 2H), 1.55–1.80 (bm, 4H), 2.05–2.45 (m, 10H), 3.10–3.52 (m, 16H), 3.55 (s, 4H), 3.64 (m, 4H). ^{13}C NMR (D_2O, 100 MHz) δ (ppm) 22.3 (CH_2), 23.3 (CH_2), 23.5 (CH_2), 26.2 (CH_2), 43.3 (CH_2), 43.8 (CH_2), 45.2 (CH_2), 45.3 (CH_2), 45.7 (CH_2), 58.3 (CH). MS (FAB$^+$, nitrobenzyl alcohol matrix) *m/z* (rel. intensity): 369 [(M+1)$^+$, 2]. Anal. calcd for $C_{20}H_{50}N_6Cl_6$: C, 40.89; H, 8.58; N, 14.31. Found: C, 40.72; H, 8.38; N, 14.61.

*3.8.2. (*R,R,R,R*)-2,6,10,13,17,21-Hexaazatricyclo[20.4.0.0^{11,16}]triacontane hexahydrochloric salt (*R,R,R,R*)-**2a**·6HCl*

Yield, 87%, decomposes at 245°C. $[\alpha]_D^{20}$ −55.6 (*c* 0.50, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ (ppm) 1.45 (m, 4H), 1.65 (bm, 4H), 1.85 (m, 4H), 2.25 (m, 8H), 2.33 (bd, *J*=11.0 Hz, 4H), 3.24 (m, 4H), 3.28 (t, *J*=8.0 Hz, 4H), 3.48 (m, 4H), 3.64 (m, 4H). ^{13}C NMR (D_2O, 100 MHz) δ (ppm) 22.1 (CH_2), 23.5 (CH_2), 26.1 (CH_2), 43.3 (CH_2), 45.3 (CH_2), 58.2 (CH). MS (FAB$^+$, nitrobenzyl alcohol matrix) *m/z* (rel. intensity): 423 [(M+1)$^+$, 2]. Anal. calcd for $C_{24}H_{56}N_6Cl_6$: C, 44.93; H, 8.80; N, 13.11. Found: C, 45.02; H, 9.13; N, 12.81.

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References

1. (a) Lehn, J. M. *Supramolecular Chemistry*, VCH: Weinheim, 1995; (b) Bianchi, A.; Bowman-James, K.; García-España, E. *The Supramolecular Chemistry of Anions*, VCH: Weinheim, 1997; (c) Dietrich, B. *Pure Appl. Chem.* **1993**, *65*, 1457–1464; (d) Seel, C.; Galán, A.; de Mendoza, J. *Top. Curr. Chem.* **1995**, *175*, 102–132; (e) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1995**, *97*, 1609–1646.
2. Izatt, R. M.; Pawlak, K.; Bradshaw, S. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529–2586.
3. (a) Dietrich, B.; Hosseini, M. W.; Lehn, J. M.; Sessions, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 1282–1283; (b) Hosseini, M. W.; Lehn, J. M. *Helv. Chim. Acta.* **1986**, *69*, 587–603; (c) Hosseini, M. W.; Lehn, J. M. *Helv. Chim. Acta.* **1988**, *71*, 749–756.
4. (a) Kimura, E.; Sakonaka, A.; Yatsunami, T.; Kodama M. M. *J. Am. Chem. Soc.* **1981**, *103*, 3041–3045; (b) Kimura, E.; Kodama, M.; Yatsunami, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 3182–3187; (c) Kimura, E.; Sakonaka, A. *J. Am. Chem. Soc.* **1982**, *104*, 4984–4985; (d) Kimura, E.; Kuramoto, Y.; Koike, T.; Fujioka, H.; Kodama, M. *J. Org. Chem.* **1990**, *55*, 42–46.
5. (a) Bencini, A.; Bianchi, A.; Burguete, M. I.; García-España, E.; Luis, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1919–1920; (b) Bencini, A.; Bianchi, A.; Burguete, M. I.; Dapporto, P.; Doménech, A.; García-España, E.; Luis, S. V.; Paoli, P.; Ramírez, J. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, *114*, 569–577
6. (a) Siegel, G. J.; Agranoff, B. W.; Albers, R. W.; Molinoff, P. B. *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*, 5th Edn; Raven Press: New York, 1994; pp. 367–387; (b) Yeh, J. I.; Biemann, H. P.; Prive, G. G.; Pandit, J.; Koshland Jr., D. E.; Kim, S. H. *J. Mol. Biol.* **1996**, *262*, 186–201.
7. Stryer, L. *Biochemistry*, W. H. Freeman and Company: New York, 1988.
8. For chiral recognition of dicarboxylic acids, but not dicarboxylate anions, see: Lustenberger, P.; Martinborough, E.; Mordasini-Denti, T.; Diederich, F. *J. Chem. Soc., Perkin Trans. 2* **1998**, 747–761, and references cited therein.
9. Sessler, J. L.; Andrievsky, A.; Kral, V.; Lynch, V. *J. Am. Chem. Soc.* **1997**, *119*, 9385–9392.
10. For some recent applications see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815–816; (b) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948–954; (c) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104–1105; (d) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403–405.
11. (a) Farrell, N.; Kiley, D. M.; Schmidt, W.; Hacker, M. P. *Inorg. Chem.* **1990**, *29*, 397–403; (b) Skog, K.; Wennerström, O. *Tetrahedron Lett.* **1992**, *33*, 1751–1754; (c) Still, W. C. *Acc. Chem. Res.* **1996**, *29*, 155–163; (d) Reedijk, J. *J. Chem. Soc., Chem. Commun.* **1996**, 801–806; (e) Pan, Z.; Still, W. C. *Tetrahedron Lett.* **1996**, *37*, 8699–8702; (f) Gasparrini, F.; Misiti, D.; Still, W. C.; Villani, C.; Wennemers, H. *J. Org. Chem.* **1997**, *62*, 8221–8224.
12. Alfonso, I.; Astorga, C.; Rebolledo, F.; Gotor, V. *J. Chem. Soc., Chem. Commun.* **1996**, 2471–2472.
13. Bridger, G. J.; Skerlj, R. T.; Padmanabhan, S.; Thornton, D. *J. Org. Chem.* **1996**, *61*, 1519–1522.
14. (a) Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268–2270; (b) Vriesema, B. K.; Butler, J.; Kellog, R. M. *J. Org. Chem.* **1984**, *49*, 110–113.
15. Dietrich, B.; Hosseini, M. W.; Lehn, J. M.; Sessions, R. B. *Helv. Chim. Acta* **1983**, *66*, 1262–1278.