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Optically active tetraazamacrocycles analogous to cyclam

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Abstract

The syntheses of enantiopure tetraazamacrocycles analogous to cyclam, (*S*,*S*)-**3**, (*R*,*R*)-**3** and (*S*,*S*,*S*,*S*)-**4**, have been carried out. NMR and semiempirical studies of **3** have revealed that this compound presents a rigid conformation with C_2 symmetry, which is stabilized by intramolecular bifurcated hydrogen bonds. Structural studies for macrocycle **4** have shown that the presence of two cyclohexane rings of (*S*,*S*) configuration leads to the loss of the D_2 symmetry in solution, which is in agreement with the AM1 calculated structure.

1. Introduction

Cyclam (1,4,8,11-tetraazacyclotetradecane) is a useful and versatile macrocyclic tetraamine. Its applications and those of its derivatives cover a variety of fields such as coordination chemistry, catalysis, biomimetic chemistry and medicine.[1] For instance, some cyclam derivatives bearing functionalized side chains at N and at C-6 have been used as bifunctional chelating agents for nuclear medicine applications.[2] In addition, some dimers of cyclam exhibit potent inhibition of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2).[3]

On the other hand, the design of ligands possessing C_2 symmetry has received much attention in recent years.[4] In particular, ligands bearing the (*R*,*R*)-cyclohexane-1,2-diamine unit have shown a high efficiency in many asymmetric reactions.[5] Moreover, this diamine has been used for the design of chiral molecular receptors with applications in a variety of fields.[6]

Based on the broad spectrum of applications of both cyclam and optically active cyclohexane-1,2-diamine, in this work we describe a simple approach to optically active cyclam analogues containing *trans*-cyclohexane-1,2-diamine moieties in their structures.

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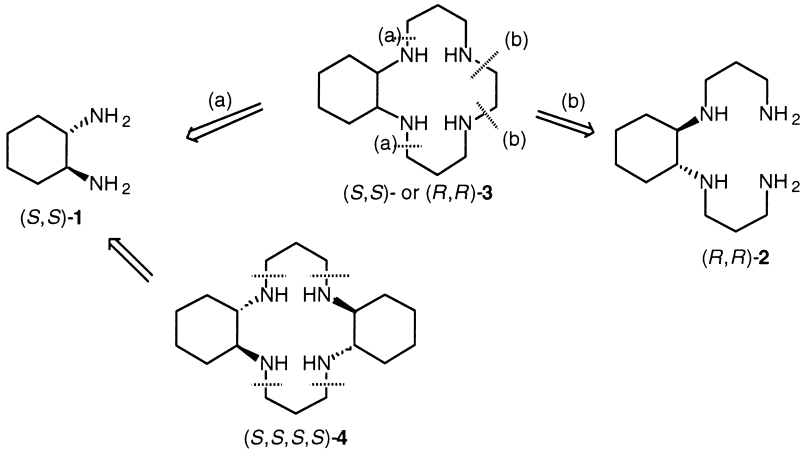
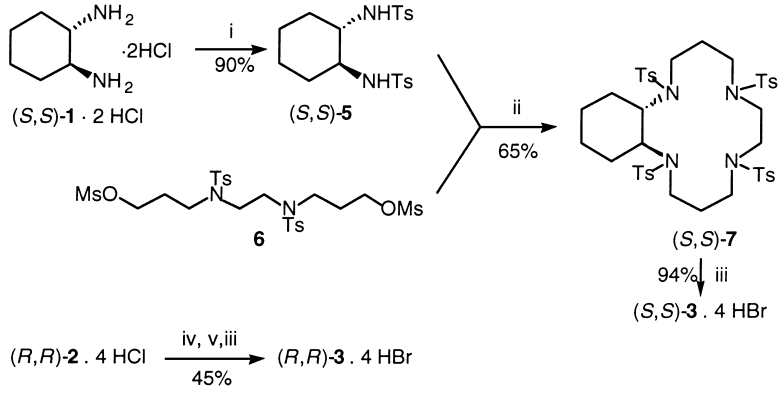
2. Results and discussion

We have recently developed an efficient and simple method for the preparation of enantiopure (*S*,*S*)-cyclohexane-1,2-diamine [(*S*,*S*)-**1**] and tetraamine (*R*,*R*)-**2** by chemoenzymatic methodology.[7] Following the Richman–Atkins cyclization procedure,[8,9] both of these compounds can be transformed into tetra-azamacrocycles **3** and **4**, analogous to cyclam (synthetic disconnections are outlined in Scheme 1). The main step of these strategies involves coupling of tosylated di or polyamine with the adequate doubly electrophilic reagent to complete the macrocyclic structure.



Scheme 1.

Synthesis of (*S*,*S*)-**3** from (*S*,*S*)-**1** (Scheme 1, route a) was accomplished in three steps, as shown in Scheme 2. Tosylation of the dihydrochloride of (*S*,*S*)-**1** with TsCl/K_2CO_3 in a diethyl ether–H_2O mixture gave (*S*,*S*)-**5**. The remaining portion of the macrocycle was constructed by *N*-alkylation of ethylendiamine ditosylate with 3-bromopropan-1-ol, and subsequent transformation of the resulting diol into the dimesylate **6**.[9,10] Coupling of (*S*,*S*)-**5** with **6** in the presence of cesium carbonate in acetonitrile afforded the macrocycle tetratosylate (*S*,*S*)-**7**, which was treated with 48% aqueous HBr and phenol to give the tetrahydrobromide of the cyclam (*S*,*S*)-**3**.



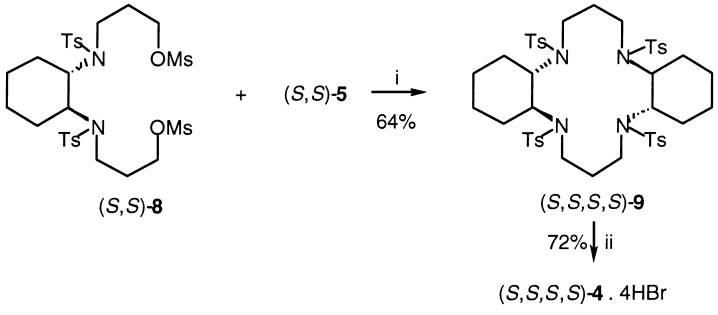
Scheme 2. Reagents and conditions: (i) TsCl, K_2CO_3, Et_2O/H_2O (see lit.[9]); (ii) Cs_2CO_3, CH_3CN; (iii) HBr (48%)/PhOH; (iv) TsCl, K_2CO_3, THF/H_2O (see lit.[9]); (v) Cs_2CO_3, CH_3CN, then $MsOCH_2CH_2OMs$

Starting from tetraamine (*R*,*R*)-**2** (Scheme 1, route b) as its tetrachlorhydrate salt,[7] and applying the same methodology, cyclam (*R*,*R*)-**3**·4HBr was obtained in 45% overall yield in three steps involving

the tetratosylation of (*R*,*R*)-**2**, the coupling of the resulting tetraamine tetratosylate with ethylenglycol dimesylate to give (*R*,*R*)-**7**, and the removal of the tosyl groups (Scheme 2).

It is notable that no differences (reaction time and yield) were observed in the above cyclization steps. Thus, starting from bis-sulphonamide (*S*,*S*)-**5** or from the less hindered (*R*,*R*)-**2** derived tetrasulphonamide, 65% of compound **7** was obtained after two days of reaction in both cases. This means that this reaction is not influenced by the proximity of the cyclohexane ring to the reactive centres.

Synthesis of (*S*,*S*,*S*,*S*)-**4** (Scheme 3) was carried out by coupling of tosylated diamine (*S*,*S*)-**5** with the electrophilic system (*S*,*S*)-**8**, this last being also obtained from (*S*,*S*)-**5** as described for its enantiomer[9] [alkylation of (*S*,*S*)-**5** with 3-bromopropan-1-ol and mesylation of the resulting diol]. Cesium carbonate promoted cyclization afforded the macrocycle tetratosylate (*S*,*S*,*S*,*S*)-**9** in 64% yield after five days of reaction. This longer reaction time compared with that found for the synthesis of both enantiomers of **7** might be due to the difficulty in coupling two (*S*,*S*)-*trans*-cyclohexane derivative fragments through a favoured conformation. Removal of the tosyl groups of **9** with HBr/phenol yielded (*S*,*S*,*S*,*S*)-**4**, which was isolated as its tetrahydrobromide.



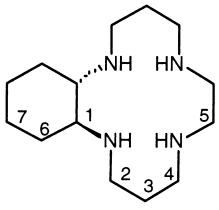
Scheme 3. Reagents and conditions: (i) Cs_2CO_3, CH_3CN; (ii) HBr (48%)/PhOH

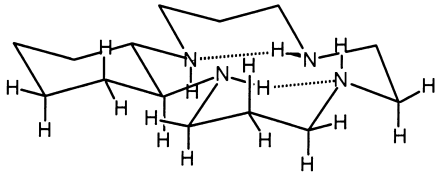
The unprotonated species [(*S*,*S*)-**3**, (*R*,*R*)-**3** and (*S*,*S*,*S*,*S*)-**4**] may be obtained by the addition of sodium hydroxide to the aqueous solution of the corresponding tetrahydrobromide until pH=13, followed by extraction with dichloromethane.

^{1}H and ^{13}C NMR spectra of (*S*,*S*)-**3** and (*R*,*R*)-**3** reveal an effective C_2 symmetry for this compound on the NMR time scale (Table 1).[11] This fact demonstrates that in the above synthetic procedures, racemization processes have not taken place since these would lead to *cis*/*trans* mixtures. Moreover, the ^{1}H NMR spectrum is in accordance with the *trans* configuration, as explained below. Chemical inequivalence is shown for all the CH_2 protons of both (6- and 14-membered) rings. As a general rule, for each CH_2 group the most deshielded proton shows a large coupling constant (assignable to $^2J_{HH}$) and at least two small ones (assignable to two *gauche* couplings), whereas the most shielded proton shows at least two large *J* values, which are assignable to $^2J_{HH}$ and to one *anti*-periplanar coupling. This indicates the presence in solution of one conformer with axial and equatorial positions for all the protons of the molecule, the most deshielded proton being the equatorial one.[12] Of all the hydrogens attached to carbons bearing amino groups, the highest field signal corresponds to H1, which is in agreement with an axial position for H1 protons and, therefore, with a *trans*-diequatorial positioning of the amino groups. Values of the coupling constants for the propylene unit (Table 1) are in accordance with the existence of a pseudo-chair conformation for the 6-membered ring, built up at the expense of a strong intramolecular hydrogen bond between nitrogen atoms. In addition, the ROESY spectrum of **3** shows a cross peak between H2e and H6e, supporting the co-planarity between the 6- and 14-membered rings. With this data, we propose a conformation as shown in Table 1.

The conformation obtained from the NMR analysis of **3** was optimized by the semiempirical molecular

Table 1
^{1}H NMR chemical shifts (ppm) and selected coupling constants (Hz) for **3**[a]





(*S*,*S*)-**3**

H1	H2e	H2a	H3e	H3a	H4e	H4a
2.12 (m)	3.12 (ddd)	2.40 (ddd)	1.82 (m)	1.67 (m)	2.97 (ddd)	2.55 (ddd)
	$^2J_{2e,2a}$ = −10.9		$^2J_{3e,3a}$ = −14.6		$^2J_{4e,4a}$ = −11.4	
	$^3J_{2e,3e}$ = 4.1	$^3J_{2a,3e}$ = 2.1	$^3J_{3e,4e}$ = 4.7	$^3J_{3a,4e}$ = 4.7		
	$^3J_{2e,3a}$ = 4.1	$^3J_{2a,3a}$ = 11.5	$^3J_{3e,4a}$ = 2.6	$^3J_{3a,4a}$ = 10.3		

H5e	H5a	H6e	H6a	H7e	H7a
2.78 (d)	2.62 (d)	2.22 (bd)[b]	0.90 (bdd)	1.73 (m)	1.23 (m)

[a] Recorded at 300 MHz in $CDCl_3$. [b] Overlapped with NH signals, bd when D_2O was added.

orbital method AM1 (Fig. 1).[13] Distances measured between adjacent nitrogen atoms (2.93–3.23 Å) are close to the sum of the van der Waals radii of the nitrogens (3.1 Å) thus indicating the presence of bifurcated hydrogen bonds,[14] which stabilize the conformation. It must be pointed out that the inversion of all the nitrogen atoms leads to an identical geometry by symmetry. In solution, this inversion is fast on the NMR time scale and makes H-bonded and non-H-bonded amine protons indistinguishable. Moreover, trace amounts of acid present in the $CDCl_3$ could accelerate this process by protonation/deprotonation sequences.

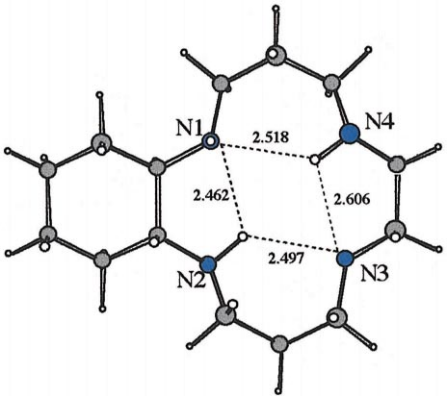


Figure 1. AM1 minimized structure of **3**. Distances N–H···N (Å) are indicated. Distances (Å) between nitrogen atoms: N1···N2, 2.931; N2···N3, 3.181; N3···N4, 3.018; N4···N1, 3.234

Because reactions involved in the syntheses of compounds **3** and **4** are similar, and taking into account that the asymmetric centres do not participate in any reaction step, we assume that compound **4** does

not suffer epimerization of its stereogenic centres and (*S*,*S*,*S*,*S*)-**4** is the only stereoisomer obtained. The ^{1}H NMR spectrum of (*S*,*S*,*S*,*S*)-**4** recorded in $CDCl_3$ at rt, consists of broad signals and its ^{13}C NMR spectrum shows 12 signals, suggesting dynamic effects and a loss of the symmetry in solution. In order to demonstrate the existence of these effects, a temperature-dependent ^{13}C NMR analysis was carried out using DMSO-d_6 as solvent. At rt the spectrum was similar to that obtained in $CDCl_3$. When the temperature was raised to 333 K, the range between 24 and 25 ppm was simplified, passing from three broad signals to two sharper signals. At 373 K the spectrum consisted of five signals but some of them were broad, meaning that a mixture of conformations was present. We have also carried out a theoretical conformational analysis obtaining two minima with very similar energy (Fig. 2). Both geometries present only one binary axis of symmetry and they differ in the conformation of the 14-membered ring as a consequence of the different configuration of the nitrogen atoms. Results obtained in the NMR experiments are in agreement with the presence of these conformations in solution.

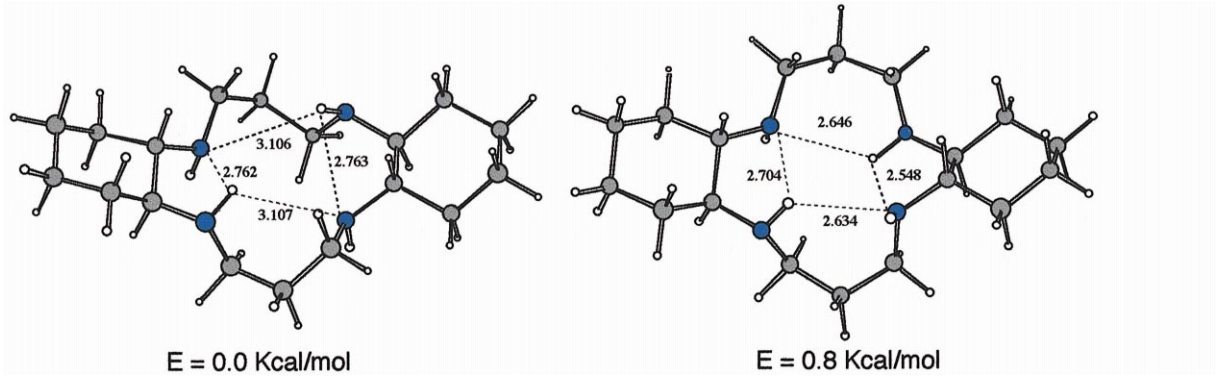


Figure 2. AM1 minimized structures of (*S*,*S*,*S*,*S*)-**4**. Relative energies are indicated

In conclusion, efficient syntheses of both enantiomers of a C_2-symmetrical cyclam derivative, (*S*,*S*)-**3** and (*R*,*R*)-**3**, and the macrocycle (*S*,*S*,*S*,*S*)-**4**, bearing (*S*,*S*)-cyclohexane-1,2-diamine moieties in their structures, have been carried out. Results obtained from the structural analysis of this kind of macrocycle should be of great interest for further applications of these compounds as chiral tools.

3. Experimental

All reagents were of commercial quality and were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. For column chromatography, Merck silica gel 60/230–400 mesh was used. Melting points 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 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AMX-400 (^{1}H 400 MHz and ^{13}C 100 MHz), Bruker AC-300 (^{1}H 300 MHz and ^{13}C 75.5 MHz) and Bruker AC-200 (^{1}H 200 MHz and ^{13}C 50.3 MHz) spectrometers, using TMS as internal standard. Mass spectra were recorded on a Hewlett–Packard 5987 A spectrometer. Microanalyses were performed on a Perkin–Elmer 240B elemental analyser.

For the theoretical calculations, a preliminary conformational searching was performed with the MMX force field as implemented in PCMODEL program.[15] The structures thus obtained were used as starting geometries for the semiempirical AM1 level of theory in the Gaussian 94 program.[13] They were fully

minimized without symmetry constraints and the frequencies analysis showed they were minima of energy.

3.1. (S,S)-N,N′-(Cyclohexane-1,2-diyl)bis(p-toluenesulphonamide) (S,S)-5

The title compound was obtained from (*S*,*S*)-**1** as described for its enantiomer (*R*,*R*)-**5**.[9] 90% Yield: mp 180–181°C; $[\alpha]_D^{20}$ −7.7 (*c* 0.56, $CHCl_3$). The spectral data are in accordance with literature values.[9]

3.2. (1S,14S)-2,6,9,13-Tetrakis(p-toluenesulphonyl)-2,6,9,13-tetraazabicyclo[12.4.0]octadecane (S,S)-7

Dry acetonitrile (30 mL) was added to a flask containing (*S*,*S*)-**5** (423 mg, 1.0 mmol) and cesium carbonate (3.23 g, 10.0 mmol) under a nitrogen atmosphere. The mixture was refluxed for 30 min and then a solution of **6** (640 mg, 1.0 mmol) in dry acetonitrile (20 mL) was added dropwise. The reaction mixture was kept at reflux for 2 days; after this time the solvent was removed and the residue was subjected to column chromatography (ethyl acetate:hexane 1:1) to yield (*S*,*S*)-**7** (565 mg, 65%) as a white solid, mp 126–128°C; $[\alpha]_D^{20}$ +18.3 (*c* 0.54, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70–1.10 (several m, 6H), 1.10–1.70 (several m, 4H), 2.27 (m, 12H), 2.75–3.90 (several m, 14H), 7.41 (m, 8H), 7.73 (m, 8H). HRMS (EI) *m/z* calcd for $C_{35}H_{47}N_4O_6S_3$ ($C_{42}H_{54}N_4O_8S_4$−Ts) 715.2658; found, 715.2661.

3.3. (1S,14S)-2,6,9,13-Tetraazabicyclo[12.4.0]octadecane tetrahydrobromide (S,S)-3·4HBr

Compound (*S*,*S*)-**7** (422 mg, 0.5 mmol) and phenol (0.55 mL, 6.2 mmol) were dissolved in aqueous 48% HBr (6.6 mL), and the solution was heated at reflux for 4 days. Water and dichloromethane were then added and the aqueous phase was repeatedly washed with dichloromethane. The organic layer was discarded and the aqueous one was evaporated under reduced pressure. Recrystallization of the residue from EtOH–48% aq. HBr yielded (*S*,*S*)-**3**·4HBr (272 mg, 94%) as a white solid, which was dried under vacuum. Decomposition of the compound was observed when heated at 250°C. $[\alpha]_D^{20}$ −20.7 (*c* 0.56, H_2O). ^{1}H NMR (D_2O, 200 MHz) δ 1.25–1.60 (bm, 6H), 1.75–1.60 (bm, 6H), 2.85–3.35 (bm, 14H). ^{13}C NMR (D_2O, 200 MHz) δ 21.7 (CH_2), 22.3 (CH_2), 26.5 (CH_2), 41.1 (CH_2), 43.0 (CH_2), 44.3 (CH_2), 54.9 (CH). MS (FAB$^+$, NBA matrix) *m/z* (rel. intensity): 255 [$(M+1)^+$, 100], 335 [$(M+1+H^{79}Br)^+$, 8], 337 [$(M+1+H^{81}Br)^+$, 8]. Anal. calcd for $C_{14}H_{34}N_4Br_4$: C, 29.09; H, 5.93; N, 9.69. Found: C, 28.71; H, 5.76; N, 9.48. For the free amine ^{1}H NMR data are collected in Table 1. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0 (C7), 29.3 (C3), 31.2 (C6), 47.9 (C2), 49.3 (C5), 50.7 (C4), 62.2 (C1).

3.4. (1R,14R)-2,6,9,13-Tetraazabicyclo[12.4.0]octadecane tetrahydrobromide (R,R)-3·4HBr

Dry acetonitrile (12 mL) was added to a flask containing the tetrasulphonamide derivative of (*R*,*R*)-**2**[9] (338 mg, 0.4 mmol) and cesium carbonate (1.30 g, 4.0 mmol) under a nitrogen atmosphere. The mixture was refluxed for 30 min and then a solution of ethylenglycol dimesylate (87.2 mg, 0.4 mmol) in dry acetonitrile (8.0 mL) was added dropwise. The reaction mixture was kept at reflux for 2 days, and the corresponding macrocycle tetratosylate (*R*,*R*)-**7** (226 mg, 65%) was isolated using the same procedure described for (*S*,*S*)-**7**. Hydrolysis of (*R*,*R*)-**7** to (*R*,*R*)-**3**·4HBr was carried out following the same procedure as for (*S*,*S*)-**3**·4HBr.

3.5. (S,S)-N,N′-(Cyclohexane-1,2-diyl)bis-[3-(p-toluenesulphonylamino)propyl methanesulphonate] (S,S)-8

The title compound was obtained from (*S*,*S*)-**1** as described for its enantiomer (*R*,*R*)-**8**.[9] 42% Yield: mp 138–140°C; $[\alpha]_D^{20}$ +20.4 (*c* 0.25, $CHCl_3$). The spectral data are in accordance with literature values.[9]

3.6. (1S,7S,12S,18S)-2,6,13,17-Tetrakis(p-toluenesulphonyl)-2,6,13,17-tetraazatricyclo[16.4.0.0^{7,12}]-docosane (S,S,S,S)-9

Dry acetonitrile (45 mL) was added to a flask containing (*S*,*S*)-**5** (633 mg, 1.5 mmol) and cesium carbonate (4.89 g, 15.0 mmol) under a nitrogen atmosphere. The mixture was refluxed for 30 min and then a solution of (*S*,*S*)-**8** (1044 mg, 1.5 mmol) in dry acetonitrile (30 mL) was added dropwise. The reaction mixture was kept at reflux for 5 days; after this time the solvent was removed and the residue was subjected to column chromatography (ethyl acetate:hexane 2:3) to yield (*S*,*S*,*S*,*S*)-**9** (875 mg, 64%) as a foamy solid which was precipitated in hexane, mp 152–154°C; $[\alpha]_D^{20}$ +28.5 (*c* 0.52, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70–1.70 (several m, 14H), 1.80–2.20 (several m, 6H), 2.40 (m, 12H), 2.75–3.90 (several m, 12H), 7.41 (m, 8H), 7.73 (m, 8H). MS (FAB$^+$, NBA matrix) *m/z* (rel. intensity): 947 [(M+Na)$^+$, 25], 925 [(M+1)$^+$, 13], 769 [(M−Ts)$^+$, 18].

3.7. (1S,7S,12S,18S)-2,6,13,17-Tetraazatricyclo[16.4.0.0^{7,12}]docosane tetrahydrobromide (S,S,S,S)-4·4HBr

Compound (*S*,*S*,*S*,*S*)-**9** (750 mg, 0.81 mmol) and phenol (0.90 mL, 10.1 mmol) were dissolved in aqueous 48% HBr (11 mL), and the solution was heated at reflux for 4 days. Water and dichloromethane were then added and the aqueous phase was repeatedly washed with dichloromethane. The organic layer was discarded and the aqueous one was evaporated under reduced pressure. Recrystallization of the residue from EtOH–48% aq. HBr yielded (*S*,*S*,*S*,*S*)-**4**·4HBr (272 mg, 72%) as a white solid, which was dried under vacuum. Decomposition of the compound was observed when heated at 160°C. $[\alpha]_D^{20}$ +18.1 (*c* 0.53, H_2O). ^{1}H NMR (D_2O, 300 MHz) δ 1.00 (bm, 4H), 1.22 (bm, 4H), 1.40 (bm, 4H), 1.70–2.10 (bm, 8H), 2.60–3.50 (bm, 12H). MS (FAB$^+$, NBA matrix) *m/z* (rel. intensity): 309 [(M+1)$^+$, 55], 389 [(M+1+H^{79}Br)$^+$, 12], 391 [(M+1+H^{81}Br)$^+$, 12]. ^{13}C NMR of the free amine (*S*,*S*,*S*,*S*)-**4** (DMSO-d_6, 75 MHz, 373 K) δ 24.2 (CH_2), 24.4 (CH_2), 30.7 (CH_2), 44.3 (CH_2), 60.6 (CH).

Acknowledgements

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