Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 4775–4783

TETRAHEDRON

Synthesis of macrocyclic tetraamides derived from α-amino acids and their investigations using ESI-MS technique

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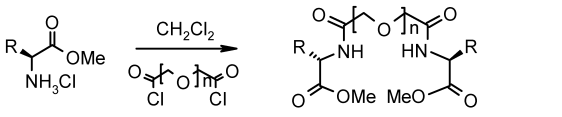
Received 29 January 2003; revised 7 April 2003; accepted 1 May 2003

Abstract—Chiral α,ω-diesters react under high-pressure conditions (10 kbar) with α,ω-diamines to give chiral cyclic tetraamides of C_2-symmetry. The complexation properties of tetraamides towards alkali metal cations (Li^+, Na^+, K^+, Rb^+ and Cs^+) were estimated on the basis of ESI-MS spectra. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Natural ionophores and synthetic receptors are capable of selective binding of charged hydrophilic species and shielding it from the lipophilic region of membrane.[1] The natural ion carriers valinomycin and nonactin are well known for their selectivity for potassium ions. Ionophores can discriminate between metal cations of different charge and different size. Thus they can work as ion carriers[2] as well as phase-transfer catalysts.[3] Crown ethers and analogous macrocyclic compounds are widely investigated for their complexation properties and used as host molecules for the simplest guests like alkali and alkaline earth cations.[4]

We have developed a method for the synthesis of diazacoronands. This method, introduced by Tabushi and co-workers,[5] is based on the condensation of α,ω-diamines with dimethyl esters of dicarboxylic acids.[6] Herein, we demonstrate the synthesis of chiral tetraamides using this synthetic approach and discuss the complexation of alkali metal cations employing electrospray ionization (ESI-MS) technique. Up to now there are only several reports using ESI-MS for determination the binding selectivities of crown ethers and related compounds for alkali metal cations.[7] Our studies are to evaluate the alkali metal binding selectivities and estimate relations between the structure and the observed binding strengths.

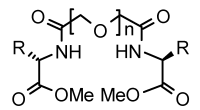


1a R=CH_3
1b R=CH_2OH

2a n=1
2b n=2
2c n=3

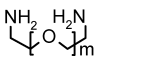
3a n=1, R=CH_3 3d n=1, R=CH_2OH
3b n=2, R=CH_3 3e n=2, R=CH_2OH
3c n=3, R=CH_3 3f n=3, R=CH_2OH

Scheme 1.



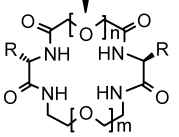
3a n=1, R=CH_3; 3d n=1, R=CH_2OH
3b n=2, R=CH_3; 3e n=2, R=CH_2OH
3c n=3, R=CH_3; 3f n=3, R=CH_2OH

+



4an=1
4bn=2
4cn=3

MeOH
10 kbar



5a n=1, m=1; **5b** n=1, m=2; **5c** n=1, m=3, R=CH_3
6a n=2, m=1; **6b** n=2, m=2; **6c** n=2, m=3, R=CH_3
7a n=3, m=1; **7b** n=3, m=2; **7c** n=3, m=3, R=CH_3
8a n=1, m=1; **8b** n=1, m=2; **8c** n=1, m=3, R=CH_2OH
9a n=2, m=1; **9b** n=2, m=2; **9c** n=2, m=3, R=CH2OH
10a n=3, m=1; **10b** n=3, m=2; **10c** n=3, m=3, R=CH_2OH

Scheme 2.

Keywords: tetraamide; amino acid; alkali metal ion receptor; electrospray; high pressure.

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0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00691-4

2. Results and discussion

2.1. Synthesis

In our syntheses we used L-alanine and L-serine as precursors of chiral diesters. To this end, we prepared the corresponding methyl ester hydrochlorides **1a**,**b**, which were reacted with 0.5 equiv. of dicarboxylic acids chlorides **2a**–**c** to afford diesters of the type **3** (Scheme 1).

They were subsequently subjected to cyclization reactions with achiral amines **4a**–**c** to afford chiral C_2-symmetric azacoronands of type **5**–**10** as shown in Scheme 2. The macrocyclization reactions were carried out in methanol under high-pressure conditions. The results are shown in Tables 1–4.

Since the macrocyclization reaction did not proceed at ambient conditions, we decided to check the influence of temperature and concentration on yields. We noticed that, in comparison to reactions carried out in 0.1 M solutions, decreasing the concentration of the substrates did not cause any improvement in forming the macrocyclic products. For instance, the reaction of diester **3b** with α,ω-diamine **4a** performed in 0.05 M solution at room temperature and under high-pressure conditions gave tetraamide **6a** in 30% yield. On the other hand, the reactions of diester **3b** with diamines **4a** and **4b** carried out under high-pressure conditions in 0.7 and 0.6 M solutions gave tetraamides **6a** and **6b** in very low yields of 5 and 6%, respectively. The increase of temperature to about 50°C and elongation of the reaction time also did not influence on yields what demonstrate results obtained in reaction of diester **3a** and diamine **4a**. Tetraamide **5a** was synthesized in 44% yield at room temperature and 42% yield at 50°C.

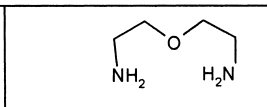
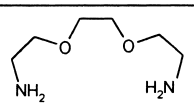
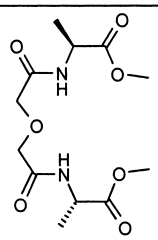
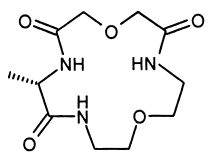
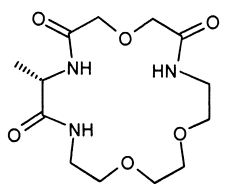
Except for typical (1:1) cyclization products, we also observed formation of macrocyclic triamides **11** and **12**. However, the yields of triamides were usually lower than the yields of tetraamides (Table 2). These results prompted us to undertake further investigation on synthesis of macrocyclic tetraamides. By the same route, we obtained several tetraamides **8**–**10** using methyl L-serinates **3d**–**f** that were reacted with achiral diamines **4a**–**c**. The yields

Table 1. Results of macrocyclization reaction of chiral diesters **3a**–**c** with diamines **4a**–**c**

	4a	**4b**	**4c**
3a	**5a** 44%[a] 42%[b]	**5b** 29%[a]	**5c** 27%[a]
3b	**6a** 37%[a] 24%[b]	**6b** 33%[a]	**6c** 21%[a]
3c	**7a** 26%[a]	**7b** 21%[a]	**7c** 12%[a]

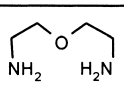
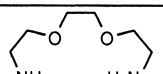
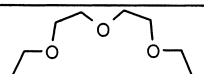
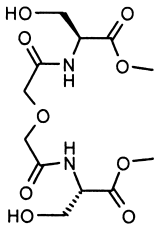
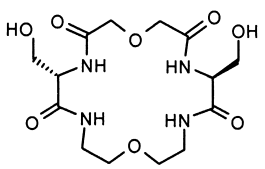
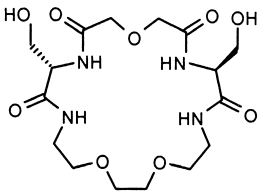
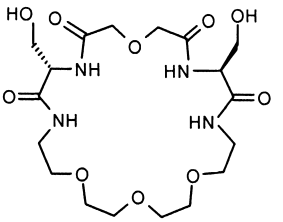
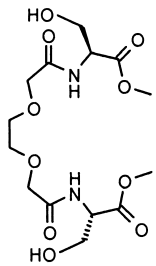
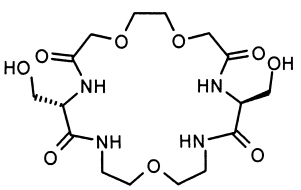
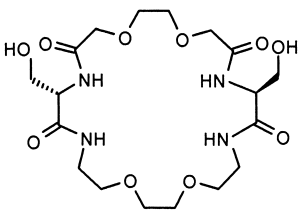
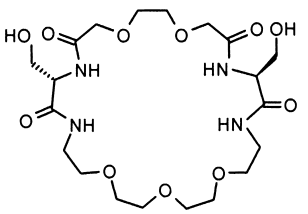
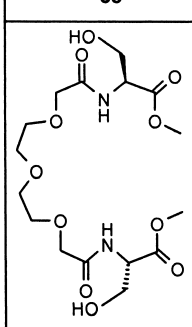
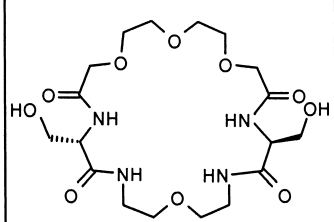
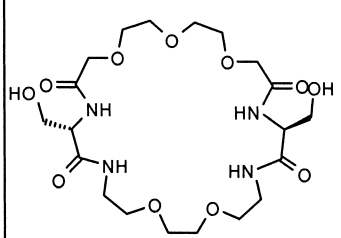
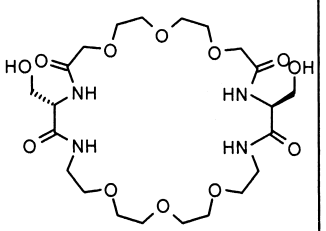
[a] MeOH, rt, 10 kbar, 20 h.
[b] MeOH, 60°C, 10 kbar, 20 h.

Table 2. Results of macrocyclization reaction of chiral diester **3a** with diamines **4a**,**b** giving unexpected macrocycles

	 **4a**	 **4b**
 **3a**	 **11** 13%	 **12** 15%

MeOH, rt, 10 kbar, 20 h.

Table 3. Results of macrocyclization reaction of chiral diesters **3d**–**f** with diamines **4a**–**c**

	 **4a**	 **4b**	 **4c**
 **3d**	 **8a** 20%[a]	 **8b** 16%[a]	 **8c** 10%[a]
 **3e**	 **9a** 26%[a] 25%[b]	 **9b** 27%[a]	 **9c** 20%[a]
 **3f**	 **10a** 22%[a]	 **10b** 22%[a]	 **10c** 12%[a]

[a] MeOH, rt, 10 kbar, 20 h.
[b] MeOH, 60°C, 10 kbar, 20 h.

Table 4. Results of macrocyclization reaction of chiral diesters **3d–f** with diamines **4a**,**b** giving unexpected macrocycles

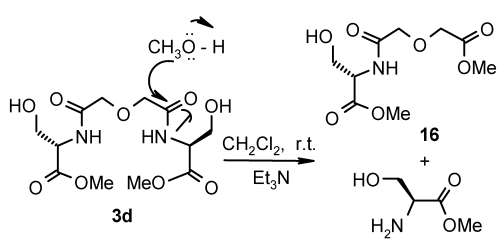
	4a	**4b**
3d	**13** [a]9%	**14** [a]16%
3e	**15** [a]10%, [b]7%	—

[a] MeOH, rt, 10 kbar, 20 h.
[b] MeOH, 60°C, 10 kbar, 20 h.

ranging from 10–27% were lower than the yield obtained for methyl L-alaninates. This can be explained by the higher steric hindrance of the hydroxymethyl substituent (Table 3). We also found that high temperature did not cause any increase of macrocyclization yields. Diester **3e** reacted with diamine **4a** under high-pressure conditions at 60°C to give tetraamide **9a** in 25% yield, very similar to the yield obtained at room temperature. As a rule, the yields decrease with the increasing ring size. This relationship is typical for macrocyclization reactions. In some cases we also isolated macrocyclic triamides (Table 4).

We found an explanation for the formation of this kind of compound. In the reaction of carboxylic acid dichloride **2a** with methyl L-serinate conducted under ambient conditions at room temperature in the presence of triethylamine, we obtained 0.2% of diester **16** in addition to the main product **3d**. We assume that amines catalyze the reaction where the nucleophilic attack of the methanol molecule on the carbonyl group results in elimination of the amino acid molecule. The formed diester can react with α,ω-diamines to give the triamide (Scheme 3).

Under the high-pressure conditions it is perhaps possible that the amine can also act as a nucleophile on the amide C=O group hence providing a direct mechanism for transamidation.



Scheme 3.

2.2. ESI-MS results

We used ESI-MS technique to determine the binding selectivities. Our experiments included both checking the competition of several alkali metal cations towards one ligand and two different macrocyclic compounds towards one metal cation. We assumed that the resulting ion signal intensities in ESI spectra are proportional to the distribution of the complexes in solution. We prepared equimolar methanolic solutions containing the ligand and five alkali metal chlorides (1.0×10^{-4} M each). The obtained results are shown in Table 5. We find that tetraamides **8a** and **9a** are selective towards cesium ions. This surprising result can be explained by a special influence of the hydroxymethyl substituents probably involved in complexation of cesium cation. Ligands **8a** and **9a** have similar complexation

Table 5. Signal intensities for ESI-MS spectra of one ligand and five alkali metal cations

Entry	Ligand	Type of complex	Signal intensities of complexes with alkali metal cations M^+				
			Li^+ (%)	Na^+ (%)	K^+ (%)	Rb^+ (%)	Cs^+ (%)
1	**8a**	$[L+M]^+$	61.7	78.5	56.1	58.5	100.0
		$[2L+M]^+$	0.8	0.4	0.3	–	0.2
		Total percentage	17.5	22.1	15.8	16.4	28.1
2	**8b**	$[L+M]^+$	60.9	100.0	59.2	49.5	34.4
		$[2L+M]^+$	–	0.1	0.1	0.1	–
		Total percentage	20.0	32.9	19.5	16.3	11.3
3	**9a**	$[L+M]^+$	89.1	86.5	69.6	79.2	100.0
		$[2L+M]^+$	1.7	0.4	0.2	0.1	–
		Total percentage	21.3	20.4	16.3	18.6	23.4
4	**9b**	$[L+M]^+$	54.0	100.0	64.8	56.7	34.3
		$[2L+M]^+$	0.1	–	0.1	–	–
		Total percentage	17.4	32.2	20.9	18.3	11.1
5	**10a**	$[L+M]^+$	68.1	95.7	94.7	100.0	68.0
		$[2L+M]^+$	0.1	0.1	0.1	–	–
		Total percentage	16.0	22.5	22.2	23.4	15.9

Table 6. Signal intensities for ESI-MS spectra for two ligands and one alkali metal cation

Entry	Ligands		Signal intensities ratio in ESI-MS spectra				
	L1	L2	$[L1+Li]^+/[L2+Li]^+$	$[L1+Na]^+/[L2+Na]^+$	$[L1+K]^+/[L2+K]^+$	$[L1+Rb]^+/[L2+Rb]^+$	$[L1+Cs]^+/[L2+Cs]^{+n}$
1	**5a**	**8a**	5.1	7.1	7.0	5.5	5.9
2	**5b**	**8b**	4.1	5.0	5.4	4.3	4.6
3	**6a**	**9a**	3.2	4.7	4.2	3.9	3.7
4	**6b**	**9b**	3.0	3.0	3.6	4.0	4.4
5	**7a**	**10a**	3.2	3.3	4.1	4.3	4.1
6	**8b**	**8a**	2.1	3.6	4.7	6.8	5.9
7	**9a**	**8a**	2.3	2.5	3.6	4.4	4.9
8	**9b**	**9a**	3.5	4.0	3.7	3.2	2.6
9	**10a**	**9a**	1.5	2.0	2.5	2.2	2.6

properties when forming stable complexes in the following sequences: $Cs^+>Na^+>Li^+>Rb^+>K^+$ and $Cs^+>Li^+>Na^+>Rb^+>K^+$, respectively. Also 21-membered tetraamide **8b** and 24-membered tetraamide **9b** show very similar selectivities. We also observe small amounts of the sandwich complexes having the 2:1 stoichiometry where a cation is bound by two ligand molecules. The highest percentage of sandwich complexes is noticed for tetraamides **8a** and **9a**. Sandwich complexes are formed mainly with lithium cations and their percentage decreases with an increase of the radius of the complexed ion. Similar complexing features are shown by tetraamides having the same heteroatom system between nitrogen atoms situated at a β position with respect to alkyl substituents.

We also compared two different tetraamides interacting with one alkali metal cation. Isomeric ligands having the same *m*/*z* ratio are not distinguishable on the basis of mass spectra. Information concerning the complexing properties of this kind of ligands were concluded indirectly from a comparison of selectivities towards another macrocyclic tetraamide as a reference compound. In these experiments, the equimolar methanolic solutions containing two ligands and one alkali metal chloride (1.0×10^{-4}M each) were prepared. The results are shown in Table 6. The strength of interactions in host-guest complexes increases with an increase of the macrocyclic opening. Tetraamide **8b** demonstrates stronger interactions with alkali metal cations in comparison to tetraamide **9a** as determined from a comparison to ligand **8a**. The 24-membered ligand **9b** binds cations better than its isomer **10a** as concluded from comparison to tetraamide **9a**. Only the cesium cation is complexed by both tetraamides at a similar level. The analysis of the obtained results allows the conclusion that better complexing properties towards alkali metal cations are shown by these ligands, whose nitrogen atoms situated at β position with respect to methyl substituents are linked to the 3,6-dioxaoctane bridge. Moreover, the tetraamides having the methyl substituents bind alkali metal cations better than these having the hydroxymethyl substituents.

3. Conclusion

The results presented here demonstrate the considerable influence of high pressure on both the rate and equilibrium of macrocyclization reactions. The chiral diesters of the type **3a**–**f** can be prepared in good yields from L-amino acids and α,ω-carboxylic acid dichlorides. High-pressure reactions with α,ω-diamines lead to tetraazacoronands of C_2 symmetry. Electrospray ionization mass spectrometry was used to estimate the alkali metal binding selectivities of a group of macrocyclic amides of type **5**–**10**.

4. Experimental

4.1. General methods

Melting points were taken on a Boetius hot stage apparatus and were not corrected. The optical rotation was measured on a JASCO DIP-360 polarimeter using the sodium D line at 589 nm. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini AC-200 (^{1}H at 200 MHz and ^{13}C at 50 MHz), Mercury-400 BB (^{1}H at 400 MHz and ^{13}C at 100 MHz) and/or Bruker Avance 500 (^{1}H at 500 MHz and ^{13}C at 125 MHz) in $CDCl_3$, DMSO-d_6, D_2O or CD_3OD. Chemical shifts are given in ppm, using tetramethylsilane (TMS) as an internal standard. Infrared spectra were run on a Perkin–Elmer FT-IR Spectrum 2000 spectrophotometer. High-resolution mass spectra (LSIMS) were recorded on an AMD-604 Intectra instrument. Elemental analyses (C, H, and N) were taken by the 'in-house' analytical service. The high-pressure reactions were conducted under 10 kbar pressure using a custom-made cylinder-piston type apparatus. Analytical TLC was carried out on commercially prepared Plate coated with 0.25 mm of self-indicating gel (Merck Kieselgel 60 F_{254}) that were developed using ninhydrin solution in a butanol/acetic acid mixture, or visualized with iodine. The column chromatography was carried out on silica gel (Merck Kieselgel 60, 230–400 mesh). All reagents and solvents were purified and dried as necessary according to the standard procedures. L-Alanine and L-serine methyl ester hydrochlorides **1a**,**b**,[8] α,ω-dicarboxylic acids chlorides **2a**–**c**,[9] as well as diamines **4a** and **4c**[10] were prepared according to the literature procedures. α,ω-Diamine **4b** was purchased from Fluka.

4.2. ESI-MS measurements

All electrospray ionization mass spectra were recorded on a Quattro LC (3Q) Micromass instrument equipped with an ESI source. Electrospray ionization was achieved by application of a potential of 3.5 kV to a stainless needle. A Harvard Apparatus syringe pump system was set at

15.0 μL/min. Nitrogen as a nebulizer gas was delivered to the spectrometer by a nitrogen line.

All solutions were made with methanol of HPLC purity and consisted of either one host and multiple guests or two hosts and one guest. The concentration ratios were either 1:1:1:1:1:1 for the one host-five guests mixture or 1:1:1 for two hosts-one guest mixture, and the concentration of each component was 1.0×10^{-4}M. The alkali metal guests (Li, Na, K, Rb, and Cs) were added to the solution as their chloride salts. Solutions were filled up to 1 mL and after 30 min a spectrum scanned the quadrupole Q1 in the range of 100–1500 Da was recorded. The time of a single scan was 2 s. Average intensities from 2 min acquisition were taken to calculations. Corrections for natural abundance of isotopes were considered. The resulting intensities were multiplied by 1.08 for lithium, 1.0722 for potassium, and by 1.3856 for rubidium. The signal intensities in a modified spectrum were normalized against the strongest signal having 100% intensity.

4.3. General procedure for the preparation of diesters derived from amino acids and α,ω-dicarboxylic acids chlorides

Triethylamine (3 mL, 20 mmol) was added dropwise to a suspension of the amino acid ester hydrochloride (10 mmol) in dry methylene chloride (150 mL), cooled to 0°C. Dicarboxylic acid chloride (5 mmol) was added dropwise. Stirring was continued for 20 h at room temperature and the mixture was concentrated in vacuo. The residue was dissolved in water and extracted with chloroform (3×100 mL). The organic layer was dried over magnesium sulphate, and the volatiles were removed by rotary evaporation. Finally, the resulting oil was purified by silica gel column chromatography using CH_2Cl_2/MeOH 95:5 as an eluent.

4.3.1. Dimethyl (2*S*,10*S*)-3,9-diaza-4,8-dioxo-2,10-dimethyl-6-oxaundecane-1,11-dicarboxylate, 3a. According to the above procedure, the product **3a** was obtained as a yellow oil in 58% yield. $[\alpha]_D^{20}=-25.6$ (*c* 1.0, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (d, 6H, *J*=7.2 Hz; 2×C*H*$_3$), 3.67 (s, 6H; 2×CO_2CH_3), 4.02 (s, 4H; 2×C*H*$_2$O), 4.45–4.65 (m, 2H; 2×CH_3C*H*), 7.10 (bd, 2H, *J*=7.2 Hz; 2×N*H*CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.8, 48.1, 53.1, 71.4, 168.7, 173.6; IR ($CHCl_3$): ν=3417, 2957, 2854, 1742, 1680, 1530, 1454, 1438, 1379, 1350 cm^{-1}; HRMS (LSIMS) calcd for $C_{12}H_{21}N_2O_7$ $[M+H]^+$: 305.1349. Found 305.1354. Anal. calcd for **3a** ($C_{12}H_{20}N_2O_7$): C, 47.37; H, 6.62; N, 9.21. Found: C, 47.27; H, 6.85; N, 9.18.

4.3.2. Dimethyl (2*S*,13*S*)-3,12-diaza-4,11-dioxo-2,13-dimethyl-6,9-dioxatetradecane-1,14-dicarboxylate, 3b. According to the above procedure, the product **3b** was obtained as a yellow oil in 54% yield. $[\alpha]_D^{20}=-28.3$ (*c* 1.0, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (dd, 6H, J_1=7.2 Hz, J_2=7.2 Hz; 2×C*H*$_3$), 3.64–3.72 (m, 10H; 2×CO_2CH_3, 2×OC*H*$_2$), 3.98 (s, 4H; 2×COC*H*$_2$), 4.50–4.70 (m, 2H; 2×CH_3C*H*), 7.20 (bs, 2H; 2×N*H*CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.7, 47.9, 52.9, 71.0, 71.2, 169.7, 173.6; IR ($CHCl_3$): ν=3409, 2956, 2919, 1742, 1674, 1528, 1455, 1438, 1378 cm^{-1}; HRMS (LSIMS) calcd for $C_{14}H_{25}N_2O_8$ $[M+H]^+$: 349.1611. Found 349.1601. Anal. calcd for **3b** ($C_{14}H_{24}N_2O_8$): C, 48.27; H, 6.94; N, 8.04. Found: C, 48.25; H, 6.81; N, 8.02.

4.3.3. Dimethyl (2*S*,16*S*)-3,15-diaza-4,14-dioxo-2,16-dimethyl-6,9,12-trioxaheptadecane-1,17-dicarboxylate, 3c. According the above procedure, the product **3c** was obtained as a yellow oil in 75% yield. $[\alpha]_D^{20}=-23.5$ (*c* 1.0, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (d, 6H, *J*=7.3 Hz; 2×C*H*$_3$), 3.65–3.75 (m, 14H; 2×CO_2CH_3, 2×OC*H*$_2$C*H*$_2$O), 3.99 (s, 4H; 2×COC*H*$_2$), 4.50–4.70 (m, 2H; 2×CH_3C*H*), 7.28 (bd, 2H, *J*=7.4 Hz; 2×N*H*CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.7, 47.9, 52.9, 70.8, 70.9, 71.4, 169.9, 173.5; IR ($CHCl_3$): ν=3411, 2956, 1743, 1673, 1527, 1454, 1438, 1378 cm^{-1}; HRMS (LSIMS) calcd for $C_{16}H_{29}N_2O_9$ $[M+H]^+$: 393.1873. Found 393.1870.

4.3.4. Dimethyl (2*S*,10*S*)-3,9-diaza-4,8-dioxo-2,10-dihydroxymethyl-6-oxaundecane-1,11-dicarboxylate, 3d. According the above procedure, the product **3d** was obtained as a yellow oil in 39% yield. $[\alpha]_D^{20}=-3.2$ (*c* 1.0, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.75 (s, 6H; 2×CO_2CH_3), 3.78–4.04 (m, 4H; 2×CHC*H*$_2$), 4.14 (s, 4H; 2×COC*H*$_2$), 4.40–4.53 (bs, 2H; 2×O*H*), 4.60–4.72 (m, 2H; 2×C*H*CH$_2$), 7.77 (d, 2H, *J*=8.2 Hz; 2×CON*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.3, 54.8, 62.7, 71.0, 170.3, 171.4; IR ($CHCl_3$): ν=3415, 2957, 2855, 1746, 1681, 1533, 1458, 1440, 1378 cm^{-1}; HRMS (LSIMS) calcd for $C_{12}H_{21}N_2O_9$ $[M+H]^+$: 337.1247. Found 337.1247.

4.3.5. Dimethyl (2*S*,13*S*)-3,12-diaza-4,11-dioxo-2,13-dihydroxymethyl-6,9-dioxatetradecane-1,14-dicarboxylate, 3e. According the above procedure, the product **3e** was obtained as a yellow oil in 70% yield. $[\alpha]_D^{20}=+8.1$ (*c* 1.0, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76–3.84 (m, 10H; 2×CO_2CH_3, 2×OC*H*$_2$), 3.86–4.18 (m, 10H; 2×COC*H*$_2$, 2×CHC*H*$_2$, 2×O*H*), 4.69–4.79 (m, 2H; 2×C*H*CH$_2$), 7.73 (d, 2H, *J*=8.1 Hz; 2×CON*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.3, 54.6, 63.2, 71.0, 71.4, 170.8, 171.7; IR ($CHCl_3$): ν=3405, 2957, 1744, 1673, 1529, 1440 cm^{-1}; HRMS (LSIMS) calcd for $C_{14}H_{25}N_2O_{10}$ $[M+H]^+$: 381.1509. Found 381.1483. Anal. calcd for **3e** ($C_{14}H_{24}N_2O_{10}$): C, 44.21; H, 6.36; N, 7.37. Found: C, 43.99; H, 6.55; N, 7.24.

4.3.6. Dimethyl (2*S*,16*S*)-3,15-diaza-4,14-dioxo-2,16-dihydroxymethyl-6,9,12-trioxaheptadecane-1,17-dicarboxylate, 3f. According the above procedure, the product **3f** was obtained as a yellow oil in 63% yield. $[\alpha]_D^{20}=+12.0$ (*c* 1.0, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.68–3.85 (m, 14H; 2×CO_2CH_3, 2×C*H*$_2$C*H*$_2$O), 3.86–4.05 (m, 6H; 2×C*H*$_2$O*H*), 4.06–4.15 (m, 4H; 2×COC*H*$_2$), 4.75–4.80 (m, 2H; 2×C*H*CH$_2$), 7.73 (d, 2H, *J*=8.1 Hz; 2×CON*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.2, 54.7, 63.3, 71.0, 71.3, 171.0, 171.2; IR ($CHCl_3$): ν=3409, 2956, 2917, 1746, 1672, 1531, 1461, 1439, 1378 cm^{-1}; HRMS (LSIMS) calcd for $C_{16}H_{29}N_2O_{11}$ $[M+H]^+$: 425.1771. Found 425.1776.

4.4. General procedure for the synthesis of macrocyclic tetraamides 5–10

A Teflon ampoule was filled with an equimolar solution of the dimethyl α,ω-diester (0.5 mmol) and the appropriate diamine (0.5 mmol) in 10 mL of methanol and was placed in a high-pressure vessel filled with ligroin as a transmission

medium and compressed (10 kbar) at room temperature for 20 h. After decompression, the reaction mixture was transferred quantitatively to a round-bottomed flask and the solvent was evaporated. The residue was purified by column chromatography using silica gel and CH_2Cl_2/MeOH 95:5 as an eluent.

4.4.1. (2*S*,18*S*)-1,4,16,19-Tetraaza-2,18-dimethyl-7,10,13,22-tetraoxa-3,17,20,24-cyclotetraeicosatetraone, 5c. Compound **5c** was prepared using the diamine **4c** and dimethyl ester **3a**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **5c** as a white solid in 27% yield. Mp 64°C; $[\alpha]_D^{20}=-30.6$ (*c* 0.5, EtOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.38 (d, 6H, J=7.3 Hz; 2×CH_3), 3.29–3.46 (m, 4H; 2×NHCH_2), 3.50–3.58 (m, 4H; 2×NHCH$_2$CH_2O), 3.58–3.66 (m, 8H; 2×OCH_2CH_2O), 4.14 (s, 4H; 2×COCH_2), 4.43 (q, 2H, J=7.3 Hz; 2×CH$_3$CH); ^{13}C NMR (100 MHz, CD_3OD) δ 17.9, 40.6, 50.3, 70.4, 71.3, 71.4, 71.6, 172.1, 174.9; IR ($CHCl_3$): ν=3363, 2937, 2875, 1672, 1522, 1454, 1374, 1349 cm^{-1}; HRMS (LSIMS) calcd for $C_{18}H_{32}N_4O_8Na$ [M+Na]$^+$: 455.2118. Found 455.2122.

4.4.2. (2*S*,18*S*)-1,4,16,19-Tetraaza-2,18-dimethyl-7,10,13,22,25-pentaoxa-3,17,20,27-cycloheptaeicosa-tetraone, 6c. Compound **6c** was prepared using the diamine **4c** and dimethyl ester **3b**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **6c** as a white solid in 21% yield. Mp 142–143°C; $[\alpha]_D^{20}=-24.5$ (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, 6H, J=7.1 Hz; 2×CH_3), 3.33–3.57 (m, 4H; 2×NHCH_2), 3.57–3.69 (m, 12H; 2×CH_2OCH_2CH_2O), 3.70–3.81 (m, 4H; 2×OCH_2), 3.99 (d$_{AB}$, 4H, J_{AB}=15.4 Hz; 2×COCH_2), 4.52–4.61 (m, 2H; 2×CH$_3$CH), 7.19 (bt, 2H, J=5.1 Hz; 2×CONHCH$_2$), 7.35 (d, 2H, J=8.2 Hz; 2×CHNHCO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 39.4, 48.7, 69.4, 69.9, 70.4, 71.4, 71.8, 169.7, 172.6; IR ($CHCl_3$): ν=3357, 2920, 2875, 1739, 1659, 1525, 1454, 1376, 1349 cm^{-1}; HRMS (LSIMS) calcd for $C_{20}H_{36}N_4O_9Na$ [M+Na]$^+$: 499.2380. Found 499.2392.

4.4.3. (2*S*,18*S*)-1,4,16,19-Tetraaza-2,18-dimethyl-7,10,13,22,25,28-hexaoxa-3,17,20,30-cyclotriaconta-tetraone, 7c. Compound **7c** was prepared using the diamine **4c** and dimethyl ester **3c**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **7c** as a white solid in 12% yield. Mp 82–83°C; $[\alpha]_D^{20}=-12.6$ (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, 6H, J=7.1 Hz; 2×CH_3), 3.39–3.47 (q, 4H, J=5.3 Hz; 2×NHCH_2), 3.52–3.85 (m, 20H; 10×CH_2O), 4.06 (d$_{AB}$, 4H, J_{AB}=15.4 Hz; 2×COCH_2), 4.54–4.63 (m, 2H; 2×CH$_3$CH), 7.22 (bt, 2H, J=5.3 Hz; 2×CONHCH$_2$), 7.54 (d, 2H, J=8.0 Hz; 2×CHNHCO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 39.3, 48.5, 69.6, 70.0, 70.4, 70.5, 70.7, 70.8, 169.9, 172.4; IR ($CHCl_3$): ν=3404, 2879, 1744, 1663, 1603, 1526, 1453, 1348 cm^{-1}; HRMS (LSIMS) calcd for $C_{22}H_{41}N_4O_{10}$ [M+H]$^+$: 521.2823. Found 521.2829.

4.4.4. (2*S*,12*S*)-1,4,10,13-Tetraaza-2,12-dihydroxy-methyl-7,16-dioxa-3,11,14,18-cyclooctadecatetraone, 8a. Compound **8a** was prepared using the diamine **4a** and dimethyl ester **3d**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **8a** as a white solid in 20% yield. Mp 173–175°C; $[\alpha]_D^{20}=-31.6$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 3.34–3.47 (m, 4H; 2×NHCH_2), 3.54 (dd, 4H, J_1=8.9 Hz, J_2=4.5 Hz; 2×CHCH_2), 3.87 (ddt, 4H, J_1=11.1 Hz, J_2=5.3 Hz, J_3=4.3 Hz; 2×CH_2O), 4.28 (s, 4H; 2×COCH_2), 4.43 (dd, 2H, J_1=4.5 Hz, J_2=5.1 Hz; 2×CHCH$_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 40.7, 57.2, 62.7, 70.5, 72.7, 172.5, 173.4; IR (KBr): ν=3467, 3406, 3309, 3094, 2938, 2875, 1665, 1541, 1457, 1374, 1347 cm^{-1}; HRMS (LSIMS) calcd for $C_{14}H_{25}N_4O_8$ [M+H]$^+$: 377.1672. Found 377.1695. Anal. calcd for **8a** ($C_{14}H_{24}N_4O_8$): C, 44.68; H, 6.43; N, 14.89. Found: C, 44.42; H, 6.67; N, 14.58.

4.4.5. (2*S*,15*S*)-1,4,13,16-Tetraaza-2,15-dihydroxy-methyl-7,10,19-trioxa-3,14,17,21-cyclouneicosatetraone, 8b. Compound **8b** was prepared using the diamine **4b** and dimethyl ester **3d**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **8b** as a white solid in 16% yield. Mp 184–186°C; $[\alpha]_D^{20}=-39.5$ (*c* 0.25, MeOH); ^{1}H NMR (200 MHz, DMSO-d$_6$) δ 3.10–3.85 (m, 16H; 2×NHCH_2CH_2OCH_2, 2×CHCH_2), 4.16 (d$_{AB}$, 4H, J_{AB}=10.6 Hz; 2×COCH_2), 4.24–4.32 (m, 2H; 2×CHCH$_2$), 5.02 (bs, 2H; 2×OH), 7.87 (dt, 2H, J_1=5.5 Hz, J_2=5.4 Hz; 2×CONHCH$_2$), 8.29 (dd, 2H, J_1=8.5 Hz, J_2=8.6 Hz; 2×CHNHCO); ^{13}C NMR (50 MHz, DMSO-d$_6$) δ 55.4, 61.6, 69.1, 70.1, 71.0, 169.8, 170.0, 170.1; IR (KBr): ν=3418, 3365, 3103, 2928, 2874, 1653, 1520, 1452, 1429, 1350 cm^{-1}; HRMS (LSIMS) calcd for $C_{16}H_{28}N_4O_9Na$ [M+Na]$^+$: 443.1754. Found 443.1757.

4.4.6. (2*S*,18*S*)-1,4,16,19-Tetraaza-2,18-dihydroxy-methyl-7,10,13,22-tetraoxa-3,17,20,24-cyclotetraeicosa-tetraone, 8c. Compound **8c** was prepared using the diamine **4c** and dimethyl ester **3d**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **8c** as a white solid in 10% yield. Mp 179°C; $[\alpha]_D^{20}=-9.4$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 3.33–3.47 (m, 4H; 2×NHCH_2), 3.51–3.70 (m, 14H; 6×CH_2O, 2×OH), 3.80 (dd, 4H, J_1=10.5 Hz, J_2=16.2 Hz; 2×CH_2OH), 4.19 (d$_{AB}$, 4H, J_{AB}=15.4 Hz; 2×COCH_2), 4.44–4.55 (m, 2H; 2×CHCH$_2$); ^{13}C NMR (50 MHz, CD_3OD) δ 40.7, 56.7, 62.9, 70.4, 71.3, 71.4, 71.6, 172.3, 172.4; IR ($CHCl_3$): ν=3404, 3358, 2930, 2877, 1669, 1524, 1457, 1350 cm^{-1}; HRMS (LSIMS) calcd for $C_{18}H_{32}N_4O_{10}Na$ [M+Na]$^+$: 487.2016. Found 487.2009.

4.4.7. (2*S*,12*S*)-1,4,10,13-Tetraaza-2,12-dihydroxy-methyl-7,16,19-trioxa-3,11,14,21-cyclouneicosatetraone, 9a. Compound **9a** was prepared using the diamine **4a** and dimethyl ester **3e**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **9a** as a white solid in 26% yield. Mp 181–183°C; $[\alpha]_D^{20}=+23.6$ (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 3.20–3.29 (m, 2H; 2×NHCHH), 3.33–3.49 (m, 2H; 2×NHCHH), 3.54–3.69 (m, 6H; 2×CH_2O, 2×OH), 3.79–4.01 (m, 8H; 2×CH_2O, 2×CHCH_2), 4.23 (dd$_{AB}$, 4H, J_{AB1}=16.3 Hz, J_{AB2}=15.8 Hz; 2×COCH_2), 4.47–4.53 (m, 2H; 2×CHCH$_2$); ^{13}C NMR (100 MHz, D_2O) δ 38.6, 54.3, 54.4, 60.1, 60.3, 68.0, 68.1, 68.2, 68.3, 69.3, 69.4, 170.6, 170.7, 171.9, 172.7; IR (KBr): ν=3436, 3298, 3102, 2944, 2877, 1649, 1556, 1441, 1359 cm^{-1}; HRMS (LSIMS) calcd for $C_{16}H_{28}N_4O_9Na$ [M+Na]$^+$: 443.1754. Found 443.1741.

Anal. calcd for **9a** ($C_{16}H_{28}N_4O_9$): C, 45.71; H, 6.71; N, 13.33. Found: C, 45.61; H, 6.81; N, 13.24.

4.4.8. (2*S*,15*S*)-1,4,13,16-Tetraaza-2,15-dihydroxymethyl-7,10,19,22-tetraoxa-3,14,17,24-cyclotetraeicosatetraone, 9b. Compound **9b** was prepared using the diamine **4b** and dimethyl ester **3e**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **9b** as a white solid in 27% yield. Mp 123–124°C; $[\alpha]_D^{20}=-11.7$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.10–3.85 (bm, 22H; 2×OCH_2, 2×NHCH_2CH_2OCH_2, 2×CH_2OH), 4.08 (d_{AB}, 4H, J_{AB}=16.0 Hz; 2×COCH_2), 4.40–4.65 (m, 2H; 2×CHCH$_2$), 7.21 (bs, 2H; 2×CONHCH$_2$), 7.90 (d, 2H, *J*=7.9 Hz; 2×CHNHCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.4, 55.3, 63.2, 69.7, 70.4, 71.2, 71.4, 171.1, 171.4; IR (KBr): ν=3378, 3299, 3101, 2932, 2891, 1652, 1531, 1470, 1437, 1338 cm^{-1}; HRMS (LSIMS) calcd for $C_{18}H_{32}N_4O_{10}Na$ $[M+Na]^+$: 487.2016. Found 487.2008. Anal. calcd for **9b** ($C_{18}H_{32}N_4O_{10}$): C, 46.55; H, 6.94; N, 12.06. Found: C, 46.36; H, 7.00; N, 11.80.

4.4.9. (2*S*,18*S*)-1,4,16,19-Tetraaza-2,18-dihydroxymethyl-7,10,13,22,25-pentaoxa-3,17,20,27-cycloheptaeicosatetraone, 9c. Compound **9c** was prepared using the diamine **4c** and dimethyl ester **3e**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **9c** as a white solid in 20% yield. Mp 127–129°C; $[\alpha]_D^{20}=-2.6$ (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33–3.52 (m, 4H; 2×NHCH_2), 3.54–3.80 (m, 18H; 8×CH_2O, 2×OH), 3.82–4.02 (m, 4H; 2×CHCH_2), 4.10 (dd, 4H, J_1=15.8 Hz, J_2=15.0 Hz; 2×COCH_2), 4.49–4.58 (m, 2H; 2×CHCH$_2$), 7.11 (bt, 1H, *J*=5.4 Hz; CH$_2$NHCO), 7.30 (bt, 1H, *J*=5.2 Hz; CH$_2$NHCO), 7.72 (d, 1H, *J*=7.9 Hz; CHNHCO), 7.80 (d, 1H, *J*=8.1 Hz; CHNHCO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0, 39.3, 54.5, 54.8, 62.7, 62.8, 69.1, 69.2, 69.7, 69.9, 70.4, 70.6, 70.7, 70.8, 70.9, 71.2, 170.3, 170.4, 170.6, 170.7; IR ($CHCl_3$): ν=3693, 3396, 2931, 2878, 1743, 1674, 1603, 1520, 1456, 1436, 1348 cm^{-1}; HRMS (LSIMS) calcd for $C_{20}H_{36}N_4O_{11}Na$ $[M+Na]^+$: 531.2278. Found 531.2263.

4.4.10. (2*S*,12*S*)-1,4,10,13-Tetraaza-2,12-dihydroxymethyl-7,16,19,22-tetraoxa-3,11,14,24-cyclotetraeicosatetraone, 10a. Compound **10a** was prepared using the diamine **4a** and dimethyl ester **3f**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **10a** as a white solid in 22% yield. Mp 157°C; $[\alpha]_D^{20}=-8.9$ (*c* 0.5, MeOH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.10–3.33 (m, 4H; 2×NHCH_2), 3.43 (bs, 4H; 2×CH_2O), 3.67 (bs, 12H; 4×CH_2O, 2×CHCH_2), 4.01 (s, 4H; 2×COCH_2), 4.33 (dt, 2H, J_1=5.3 Hz, J_2=7.9 Hz; 2×CHCH$_2$), 5.04 (bt, 2H, *J*=5.3 Hz; 2×OH), 7.71 (d, 2H, *J*=7.9 Hz; CHNHCO), 7.89 (bt, 2H, *J*=5.2 Hz; 2×CONHCH$_2$); ^{13}C NMR (50 MHz, DMSO-d_6) δ 55.1, 61.7, 69.0, 69.9, 70.2, 70.6, 169.8, 170.1; IR (KBr): ν=3436, 3100, 2934, 2874, 1655, 1550, 1445, 1349 cm^{-1}; HRMS (LSIMS) calcd for $C_{18}H_{32}N_4O_{10}Na$ $[M+Na]^+$: 487.2016. Found 487.2040.

4.4.11. (2*S*,15*S*)-1,4,13,16-Tetraaza-2,15-dihydroxymethyl-7,10,19,22,25-pentaoxa-3,14,17,27-cycloheptaeicosatetraone, 10b. Compound **10b** was prepared using the diamine **4b** and dimethyl ester **3f**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **10b** as a white solid in 22% yield. Mp 138–140°C; $[\alpha]_D^{20}=-8.0$ (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25–3.52 (m, 4H; 2×NHCH_2), 3.52–3.65 (m, 8H; 4×CH_2O), 3.65–3.74 (dt, 4H, J_1=4.6 Hz, J_2=3.8 Hz; 2×NHCH$_2$CH_2O), 3.74–3.87 (m, 4H; 2×CH_2O), 3.87–4.04 (m, 4H; 2×CHCH_2), 4.08 (dd_{AB}, 4H, J_{AB1}=15.6 Hz, J_{AB2}=15.7 Hz; 2×COCH_2), 4.20–4.36 (m, 2H; 2×OH), 4.55–4.67 (m, 2H; 2×CHCH$_2$), 7.43 (t, 2H, *J*=5.5 Hz; 2×CONHCH$_2$), 7.81 (dd, 2H, J_1=8.1 Hz, J_2=7.9 Hz; 2×CHNHCO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2, 39.3, 54.4, 62.6, 62.7, 69.3, 69.4, 70.1, 70.2, 70.4, 70.5, 70.6, 70.6, 70.7, 70.8, 170.5, 170.6, 170.7, 170.8; IR (KBr): ν=3423, 3095, 2928, 1657, 1541, 1466, 1350 cm^{-1}; HRMS (LSIMS) calcd for $C_{20}H_{36}N_4O_{11}Na$ $[M+Na]^+$: 531.2278. Found 531.2280.

4.4.12. (2*S*,18*S*)-1,4,16,19-Tetraaza-2,18-dihydroxymethyl-7,10,13,22,25,28-hexaoxa-3,17,20,30-cyclotriacontatetraone, 10c. Compound **10c** was prepared using the diamine **4c** and dimethyl ester **3f**. Purification by silica gel column chromatography using CH_2Cl_2 and MeOH (95:5) gave **10c** as a colorless oil in 12% yield. $[\alpha]_D^{20}=-1.1$ (*c* 1.0, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.25–3.85 (m, 26H; 10×CH_2O, 2×NHCH_2, 2×OH), 4.07 (d_{AB}, 4H, J_{AB}=15.6 Hz; 2×COCH_2), 3.93–4.10 (m, 4H; 2×CHCH_2), 4.50–4.61 (m, 2H; 2×CHCH$_2$), 7.26 (bs, 2H; 2×CH$_2$NHCO), 7.80 (d, 2H, *J*=7.8 Hz; 2×CHNHCO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.2, 54.6, 62.9, 69.5, 70.0, 70.6, 70.9, 71.0, 71.1, 170.5, 170.7; IR ($CHCl_3$): ν=3676, 3397, 2918, 2880, 1745, 1667, 1526, 1456, 1439, 1348 cm^{-1}; HRMS (LSIMS) calcd for $C_{22}H_{40}N_4O_{12}Na$ $[M+Na]^+$: 575.2540. Found 575.2548.

4.4.13. (2*S*)-1,4,10-Triaza-2-methyl-7,13-dioxa-3,11,15-cyclopentadecatrione,11. Compound **11** was obtained as a white solid in 13% yield. Mp 135–140°C; $[\alpha]_D^{20}=-26.1$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (d, 3H, *J*=7.1 Hz; CH_3), 3.10–3.29 (m, 1H; NHCHH), 3.40–3.62 (m, 6H; CH_2CH_2OCH_2), 3.63–3.82 (m, 1H; NHCHH), 4.10 (dd_{AB}, 4H, J_{AB1}=15.7 Hz, J_{AB2}=14.8 Hz; 2×COCH_2), 4.64 (m, 1H; CHCH$_3$), 6.81 (bs, 1H; CH$_2$NHCO), 7.01 (d, 1H, *J*=7.9 Hz; CHNHCO), 7.17 (bs, 1H; CH$_2$NHCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0, 39.0, 39.6, 48.9, 69.6, 70.0, 71.3, 71.4, 169.2, 169.4, 172.0; IR ($CHCl_3$): ν=3689, 3607, 3441, 3413, 3013, 2932, 2873, 2806, 1681, 1603, 1532, 1456, 1436, 1382, 1346 cm^{-1}; HRMS (LSIMS) calcd for $C_{11}H_{20}N_3O_5$ $[M+H]^+$: 274.1403. Found 274.1417.

4.4.14. (2*S*)-1,4,13-Triaza-2-methyl-7,10,16-trioxa-3,14,18-cyclooctadecatrione, 12. Compound **12** was obtained as a white solid in 15% yield. Mp 68–69°C; $[\alpha]_D^{20}=+63.7$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (d, 3H, *J*=7.2 Hz; CH_3), 3.10–3.82 (m, 12H; 6×CH_2), 4.07 (dd_{AB}, 4H; J_{AB1}=15.2 Hz, J_{AB2}=14.5 Hz; 2×COCH_2), 4.70 (m, 1H; CHCH$_3$), 6.82 (bm, 1H; CONHCH$_2$), 7.27 (d, 1H, *J*=7.9 Hz; CHNHCO), 7.48 (bm, 1H; CONHCH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.4, 39.0, 39.8, 48.9, 70.3, 70.6, 70.8, 70.9, 71.0, 71.1, 168.6, 168.8, 172.0; IR ($CHCl_3$): ν=3433, 2922, 1676, 1532, 1455, 1348 cm^{-1}; HRMS (LSIMS) calcd for $C_{13}H_{23}N_3O_6Na$ $[M+Na]^+$: 340.1485. Found 340.1494.

4.4.15. (2*S*)-1,4,10-Triaza-2-hydroxymethyl-7,13-dioxa-3,11,15-cyclopentadecatrione, 13. Compound **13** was

obtained as a white solid in 9% yield. Mp 185–187°C; $[\alpha]_D^{20}=-16.6$ (*c* 0.5, EtOH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.10–3.80 (m, 10H; 2×NHCH_2CH_2, CHCH_2), 4.08 (dd_{AB}, 4H; $J_{AB1}=15.4$ Hz, $J_{AB2}=15.2$ Hz; 2×COCH_2), 4.30–4.40 (m, 1H; C*H*CH$_2$), 5.03 (t, 1H, $J=5.8$ Hz; O*H*), 7.54 (bt, 1H, $J=4.4$ Hz; CH$_2$N*H*CO), 8.24 (bt, 1H, $J=5.0$ Hz; CH$_2$N*H*CO), 8.45 (d, 1H, $J=8.8$ Hz; CHN*H*CO); ^{13}C NMR (50 MHz, DMSO-d_6) δ 56.1, 61.3, 68.2, 69.5, 71.1, 71.2, 169.5, 169.8, 169.9; IR ($CHCl_3$): $\nu=3679$, 3532, 3441, 3408, 2929, 2857, 1678, 1593, 1533, 1459, 1347 cm^{-1}; HRMS (LSIMS) calcd for $C_{11}H_{20}N_3O_6$ $[M+H]^+$: 290.1352. Found 290.1328.

4.4.16. (2*S*)-1,4,13-Triaza-2-hydroxymethyl-7,10,16-trioxa-3,14,18-cyclooctadecatrione, 14. Compound **14** was obtained as a white solid in 16% yield. Mp 140–145°C; $[\alpha]_D^{20}=+30.0$ (*c* 0.5, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.15–3.60 (m, 6H; 2×CONHCH_2, CH_2O), 3.61–3.89 (m, 8H; 3×CH_2O, CHCH_2), 4.09 (dd_{AB}, 4H; $J_{AB1}=15.0$ Hz, $J_{AB2}=14.7$ Hz; 2×COCH_2), 4.24–4.31 (m, 1H; O*H*), 4.72–4.85 (m, 1H; C*H*CH$_2$), 7.05 (bm, 1H; CON*H*CH$_2$), 7.82 (bm, 1H; CON*H*CH2), 8.05 (bd, 1H, $J=8.0$ Hz; CHN*H*CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.7, 38.4, 39.3, 53.7, 62.8, 69.7, 70.2, 70.3, 70.5, 168.1, 168.9, 170.0; IR ($CHCl_3$): $\nu=3410$, 2926, 1675, 1602, 1534, 1476, 1457, 1435, 1348 cm^{-1}; HRMS (LSIMS) calcd for $C_{13}H_{23}N_3O_7Na$ $[M+Na]^+$: 356.1434. Found 356.1450.

4.4.17. (2*S*)-1,4,10-Triaza-2-hydroxymethyl-7,13,16-trioxa-3,11,18-cyclooctadecatrione, 15. Compound **15** was obtained as a white solid in 10% yield. Mp 149–155°C; $[\alpha]_D^{20}=+2.7$ (*c* 0.5, EtOH); ^{1}H NMR (200 MHz, CD_3OD) δ 3.18–3.45 (m, 4H; 2×NHCH_2), 3.45–3.59 (m, 4H; 2×CH_2O), 3.59–3.70 (m, 2H; CH_2O), 3.70–3.88 (m, 5H; CH_2O, CH_2O*H*), 3.96 (d_{AB}, 2H; $J_{AB}=10.9$ Hz; COCH_2), 4.06 (d_{AB}, 2H, $J_{AB}=15.4$ Hz; COCH_2), 4.53 (m, 1H, C*H*CH$_2$); ^{13}C NMR (50 MHz, CD_3OD) δ 40.0, 40.4, 56.0, 63.0, 70.2, 70.6, 70.8, 71.3, 71.4, 71.6, 172.2, 172.3, 172.9; IR ($CHCl_3$): $\nu=3423$, 3401, 2926, 2874, 1674, 1532, 1495, 1434, 1339 cm^{-1}; HRMS (LSIMS) calcd for $C_{13}H_{24}N_3O_7$ $[M+H]^+$: 334.1614. Found 334.1601.

Acknowledgements

This work was supported by the State Committee for Scientific Research (Project T09A 087 21). The authors wish to thank the Polish Science Foundation for additional financial support.

References

1. Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*. Wiley: New York, 2000.
2. (a) Gokel, G. *Chem. Commun.* **2000**, 1–9. (b) Shabany, H.; Gokel, G. *Chem. Commun.* **2000**, 2373–2374. (c) Shabany, H.; Murray, C. L.; Gloeckner, Ch. A.; Grayson, M. A.; Gross, M. L.; Gokel, G. *Chem. Commun.* **2000**, 2375–2376. (d) Gokel, G. W.; Ferdani, R.; Liu, J.; Pajewski, R.; Shabany, H.; Uetrecht, P. *Chem. Eur. J.* **2001**, *7*, 33–39.
3. Mąkosza, M. *Mod. Synth. Meth.* **1987**, 9–86.
4. (a) Inoue, Y.; Gokel, G. W. *Cation Binding by Macrocycles*; Marcel Dekker: New York, 1990. (b) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1995**, *95*, 2529–2586.
5. (a) Tabushi, I.; Okino, H.; Kuroda, Y. *Tetrahedron Lett.* **1976**, *48*, 4339–4342. (b) Tabushi, I.; Taniguchi, Y.; Kato, H. *Tetrahedron Lett.* **1977**, *12*, 1049–1052.
6. (a) Jurczak, J.; Stankiewicz, T.; Sałański, P.; Kasprzyk, S.; Lipkowski, P. *Tetrahedron* **1993**, *49*, 1478–1488. (b) Jurczak, J.; Gryko, D. T.; Lipkowski, P.; Sałański, P. *Rev. High Pressure Technol.* **1998**, *7*, 1236–1240. (c) Gryko, D. T.; Piątek, P.; Sałański, P.; Jurczak, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1771–1778. (d) Gryko, D. T.; Piątek, P.; Jurczak, J. *Synthesis* **1999**, 336–340. (e) Szczepańska, A.; Sałański, P.; Jurczak, J. *Heterocycles* **2000**, *52*, 537–540. (f) Achmatowicz, M.; Szczepańska, A.; Gryko, D. T.; Sałański, P.; Jurczak, J. *Supramol. Chem.* **2000**, *12*, 93–95.
7. (a) Reyzer, M. L.; Brodbelt, J. S.; Marchand, A. P.; Chen, Z.; Huang, Z.; Namboothiri, I. N. N. *Int. J. Mass Spectrom.* **2001**, *204*, 133–142. (b) Blair, S. M.; Brodbelt, J. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 884–891. (c) Blair, S. M.; Brodbelt, J.; Reddy, G. M.; Marchand, A. P. *J. Mass Spectrom.* **1998**, *33*, 721–728. (d) Wang, K.; Han, X.; Gross, R. W.; Gokel, G. W. *J. Am. Chem. Soc.* **1995**, *117*, 7680–7686.
8. Zieliński, T.; Achmatowicz, M.; Jurczak, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2053–2059.
9. Rosatzin, T.; Andersson, L. J.; Simon, W.; Mosbach, K. *J. Chem. Soc., Perkin Trans. 2* **1991**, *8*, 1261–1266.
10. Kulstad, S.; Malmsten, L. A. *Acta Chem. Scand.* **1979**, *B33*, 469–474.