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Synthesis and determination of alkali metal binding selectivities of chiral macrocyclic bisamides derived from D-mannitol and L-threitol possessing 2,6-pyridinedicarboxamide subunits

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Abstract—Five chiral macrocyclic bisamides derived from D-mannitol and L-threitol, possessing C_2 symmetry, were obtained by a macrocyclization reaction under two different conditions (MeOH, 12 kbar, rt or MeONa/MeOH, 1 bar, rt). Their applications for alkali metal binding processes are studied using ESI-MS technique.

1. Introduction

The chiral recognition and complexation properties of natural receptors have attracted considerable attention due to the design and synthesis of new chiral macrocyclic rings, for example, poliaza[1] and polyoxacoronands.[2] In the early 1990s, we found that α,ω-diaminoethers reacted under ambient conditions with dimethyl α,ω-dicarboxylates in methanol as a solvent, to afford the macrocyclic bisamides.[3] This method was also extensively investigated by using the high-pressure technique.[4] The amide group exhibits a dual complexing feature (C=O and N or NH), thus meaning amide-based molecular receptors can bind metal[5] and ammonium cations,[6] neutral organic molecules[7] as well as anionic species.[8] Moreover, macrocyclic bisamides can be synthesized in their optically active forms and applied to chiral recognition processes.[9] Recently, we published[10,11] an effective method for the synthesis of chiral bisamides using α,ω-diamines derived from D-mannitol and L-threitol. In contrast to achiral macrocyclic compounds, the synthesis of their chiral analogs is more difficult due to use of chiral α,ω-diaminoethers as substrates. Three diaminoethers **2**–**4** have been prepared by us previously.[10] Herein, we report a useful synthetic way of preparing their analog **1**. All four C_2-symmetric α,ω-diaminoethers containing three or five ethylene units were applied for macrocyclization reactions leading to eight chiral bisamides. Electrospray ionization mass spectrometry (ESI-MS) was used to evaluate the alkali metal binding selectivities of these chiral bisamide compounds possessing 2,6-pyridine subunits.

2. Results and discussion

2.1. Synthesis

1,2;5,6-Di-*O*-isopropylidene-D-mannitol and 1,4-di-*O*-benzyl-L-threitol were selected as inexpensive and convenient sources of chirality. These readily available building blocks were used for the synthesis of numerous chiral coronands.[12] The synthesis of D-mannitol-derived α,ω-diaminoethers **2** and **4** containing three and five ethylene units and L-threitol-derived α,ω-diaminoether **3** possessing five ethylene units have been already reported[10] (Fig. 1).

The synthesis of L-threitol-derived α,ω-diaminoether **1** possessing three ethylene units is presented at Scheme 1. 1,4-Di-*O*-benzyl-L-threitol **5** reacts with allyl bromide to give compound **6**, which was converted into diol **7** by ozonolysis and the following reduction with sodium borohydride. The conversion of diol **7** into intermediate diphthalimide derivative **9** was carried out in two ways: using either the Mitsunobu[13] or Gabriel reaction.[14] In

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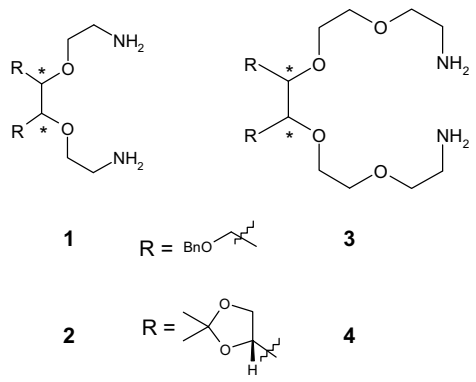
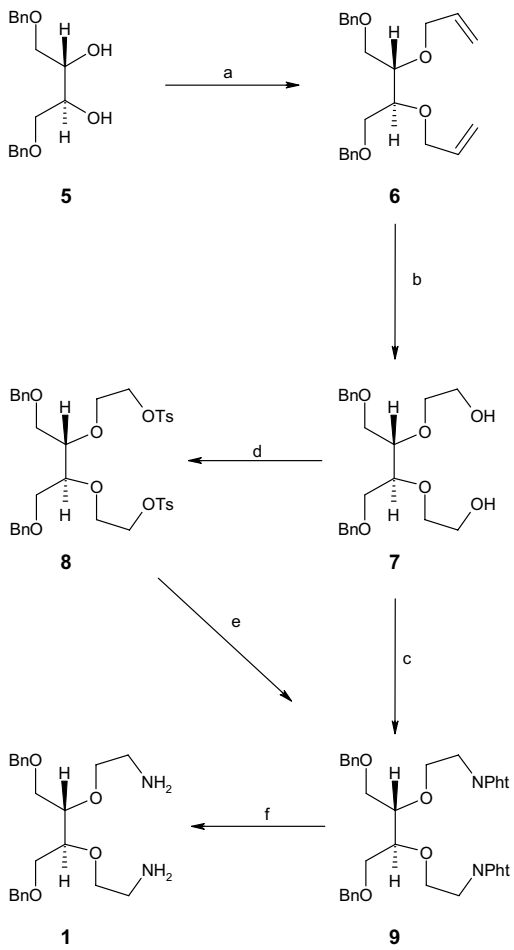


Figure 1.



Scheme 1. Reagents: (a) $CH_2{=}CHCH_2Br$, KOH, toluene; (b) O_3, $NaBH_4$, MeOH; (c) DIAD, PPh_3, PhtNH, THF; (d) TsOH, NaOH, THF; (e) $PhtN^-K^+$, DMF; (f) $N_2H_4{\cdot}H_2O$, EtOH.

the first method, compound **7** reacted with phthalimide in the presence of triphenylphosphine and diisopropyl azodicarboxylate to give compound **9** in 82% yield. In the second reaction, which is based on the reaction of tosylate **8** with a phthalimide potassium salt, the yield was worse (55%). Finally, hydrazinolysis of **9** resulted in the formation of free chiral α,ω-diamine **1**, in high yield (91%).

The macrocyclization reactions (Scheme 2) were carried out in methanol as a solvent; however, two different reaction conditions were used. The first one (a) was carried out under high pressure (12 kbar) without any additives while the second (b) was performed at atmospheric pressure in the presence of 1 mol equiv of MeONa. Table 1 shows the results of the macrocyclization reactions.

According to the first method (a), the reaction time was always 48 h. In the latter method (b), the reaction time was variable, based on monitoring by TLC. In all macrocyclization reactions, bisamides were almost exclusive products; the traces of higher macrocyclic oligomers were observed only using the spectrometric technique and were not isolated.

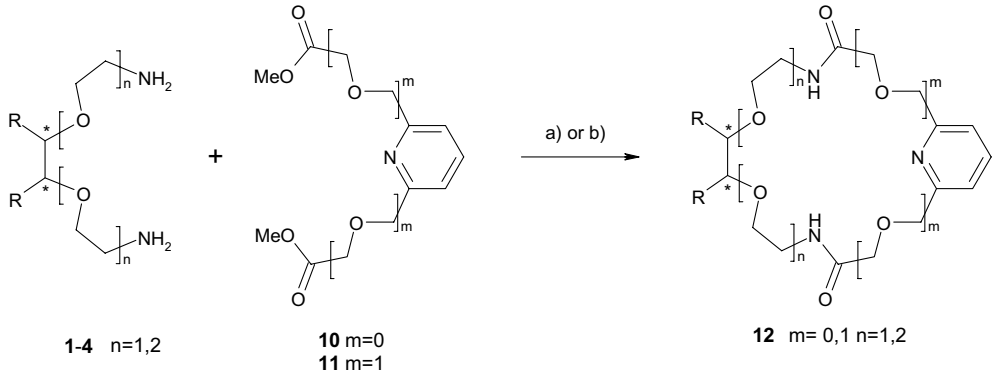
In most cases, the slightly better yields of macrocyclic diamides were obtained using method (b), performed under atmospheric pressure in the presence of MeONa. Moreover, method (b) is much more simple in comparison with (a), however, in the case on the macrocyclization of base-sensitive systems, method (a) is recommended.

2.2. ESI-MS experiments

Electrospray ionization mass spectrometry (ESI-MS) allows the analysis of a the broad range of non-covalent interactions of the host-molecules having various structure (crown ethers,[15–18] diazacoronands,[19] proteines,[20,21] cages,[22–24] and cyclodextrins[25,26]) with various types of guest-molecules (metal cations,[15–24] small neutral molecules,[25] and amino acids[26]). The ESI-MS analysis is quick, enables direct investigation of the solution of interest, and requires only a minute amount of sample. Therefore, this method is suitable for screening of the specifically selective receptors. Recently, we proposed an application of this method as an analytical tool for the determination of a general relationship between the simple diazacoronand structure and the complexation properties of these ligands with respect to the alkali metal cations.[19]

We decided to expand our studies with a series of eight ligands **12a**–**h**, keeping in mind that our approach is useful merely for estimating which of the comparison of two ligands is more selective toward one particular cation, as any quantitative determination of this selectivity is not possible.

It is well known that in the ESI-MS technique, the response factors depend on the solvation energy of the given ions. In order to perform a quantitative analysis of the results one should introduce the corresponding coefficients for correlation of the different ligand response factors. Such a procedure is possible but quite tedious and unnecessary from the viewpoint of this work. For our purposes it is rational to assume that the peak intensity ratios higher than 4:1 are indicative of the stronger complexing properties of one of the two complexing ligands.



Scheme 2. Reagents and conditions: (a) MeOH, 12 kbar, rt; (b) MeOH, NaOMe, 1 bar, rt.

2.2.1. Effect of the ring size. Table 2 shows four pairs of chiral macrocyclic bisamides **12a–h**, characterized by a different ring size (and very likely a different macrocyclic cavity). For two first pairs (**12a/c** and **12b/d**) a simple conclusion is that the bisamide possessing a larger ring size forms stronger complexes with alkali metal cations. However, if one compares the other two pairs of ligands (**12e/g** and **12f/h**) none of the above-mentioned selectivities are observed.

2.2.2. Effect of the substituents at the stereogenic centers. Comparison of complexation results for ligands having different substituents at the stereogenic centers shows no significant difference in selectivity between the L-threitol and D-mannitol derivatives (Table 3).

In such a situation we decided to investigate two other compounds **13** and **14** (Fig. 2), which were discussed by us previously.[27] Both of them are benzenedicarboxamide analogs of the examined pyridine bisamide macrocycles. An analysis of the complexation results for this pair of compounds confirms again that the difference between L-threitol and D-mannitol derivatives possessing the same ring size is negligible.

2.2.3. Effect of regioisomerism of the amido group. The data reported in Table 4 clearly show that both pairs of regioisomeric bisamides differ in their complexation ability. It seems to be very crucial that the positions, where the *–NHCO–* groups appear, play an important part in the association process. A comparison of two isomers (**12d/f**, and **12c/e**) shows the strongest binding property toward compounds which possess *–NHCO–* groups more distant from the 2,6-pyridine subunit. It is noteworthy that these experiments cannot be carried out directly because the ESI-MS technique excludes measurement of a pair of isomers. However, based on the similarity of the isomeric ligand response factors, the analysis of their behavior with respect to the same reference compound was performed.

2.3. Effect of presence of electron donating center in the macrocyclic ring

Table 5 shows the findings of the study of the system comprising of bisamide macrocycles **12c** and **d** possessing 2,6-pyridine subunits with their 1,3-benzenedicarboxamide analogs **13** and **14**. In this case, the presence of an additional electron donating center in the bisamide macrocyclic ring does not help macrocycles **12c** and **d** to bind alkali metal cations better than their analogs **13** and **14**, respectively.

3. Conclusions

As a result of our investigation, a new efficient method of macrocyclization leading to chiral macrocyclic bisamides has been developed. Moreover, we demonstrated that the ESI-MS technique can be successfully used for the preliminary determination of the selectivity of binding of the alkali metal cations by the prepared macrocyclic compounds.

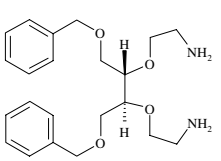
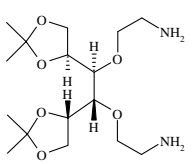
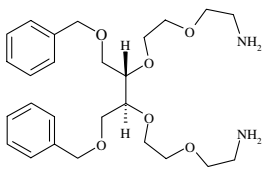
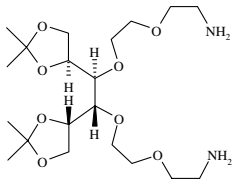
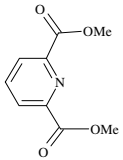
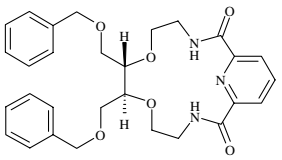
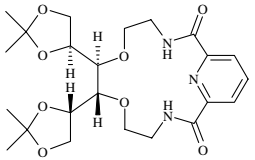
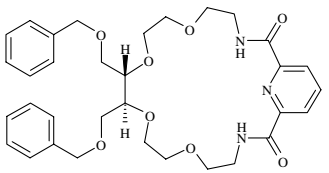
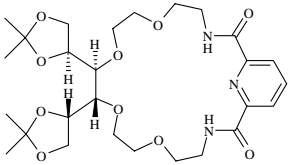
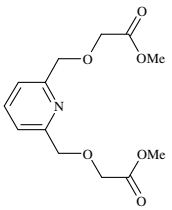
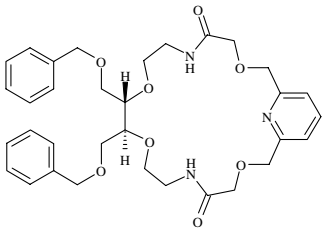
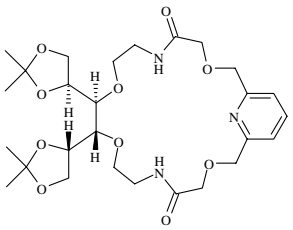
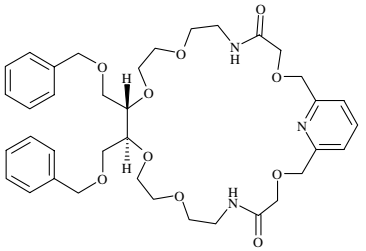
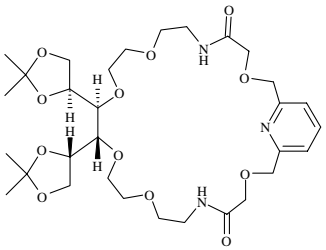
4. Experimental

4.1. General methods

Melting points were taken on a Köfler-type (Boetius) hot-stage apparatus and are uncorrected. Optical rotations were measured using a Perkin–Elmer 241 polarimeter equipped with a thermally-jacketed 10 cm cell. ^{1}H NMR spectra were recorded with a Varian Gemini 200 (200 MHz) or a Varian Gemini 500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. ^{13}C NMR spectra were also recorded using a Varian Gemini 200 (50 MHz) or a Varian Gemini 500 (125 MHz) spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm), and coupling constants (J) are measured in hertz. The high-resolution mass spectrometry (HRMS) experiments were performed on a LCT Micromass instrument using the ESI technique. The column chromatography was carried out on silica gel (Kieselgel-60, 200–400 mesh). Methanol was freshly distilled from Mg/I_2 under Ar. THF was freshly distilled from Na/benzophenone under Ar. The high-pressure reactions were conducted under 12 kbar pressure using a custom-made cylinder-piston type apparatus. The elemental analyses (C, H, and N) were performed by the 'in-house' analytical service.

Diester **10** was purchased commercially. Diester **11** was synthesized according to the literature procedures, by

Table 1. Results of macrocyclization reaction

	 **1**	 **2**	 **3**	 **4**
 **10**	 **12a** 38.7[a] 42.0[b]	 **12b** 39.0[a] 50.3[b]	 **12c** 41.9[a] 40.2[b]	 **12d** 59.7[a] 50.7[b]
 **11**	 **12e** 14.1[a] 30.0[b]	 **12f** 17.6[a] 26.3[b]	 **12g** 22.6[b]	 **12h** 19.3[b]

[a]MeOH, rt, 12 kbar, 48h.

[b]MeOH, rt, NaOMe.

Table 2. Effect of the ring size on a competition between two ligands toward one cation

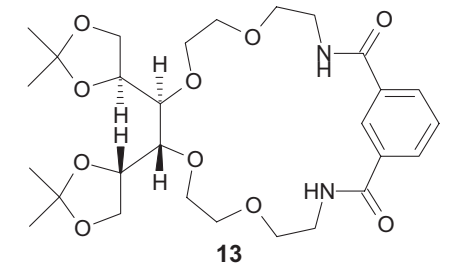
Ligands		Ratios of signal intensities in the ESI-MS spectra ($[L1 + M]^+/[L2 + M]^+$)[a]				
L1	L2	$[L1 + Li^+/L2 + Li^+]$	$[L1 + Na^+/L2 + Na^+]$	$[L1 + K^+/L2 + K^+]$	$[L1 + Rb^+/L2 + Rb^+]$	$[L1 + Cs^+/L2 + Cs^+]$
12c	**12a**	7.2	6.3	9.3	4.3	4.2
12d	**12b**	7.8	12.5	5.6	5.8	3.3
12g	**12e**	1.3	1.6	1.3	1.7	1.3
12h	**12f**	0.7	1.2	1.0	1.1	1.3

[a] The standard deviation is ±10% of the listed number.

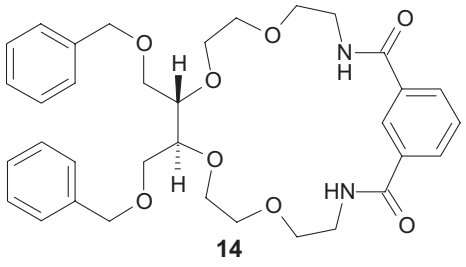
Table 3. Effect of substituents on a complexation ability between the L-threitol and D-mannitol derivatives

Ligands		Ratios of signal intensities in the ESI-MS spectra ($[L1 + M]^+/[L2 + M]^+$)[a]				
L1	L2	$[L1 + Li^+/L2 + Li^+]$	$[L1 + Na^+/L2 + Na^+]$	$[L1 + K^+/L2 + K^+]$	$[L1 + Rb^+/L2 + Rb^+]$	$[L1 + Cs^+/L2 + Cs^+]$
12a	**12b**	1.3	1.7	3.8	2.8	2.5
12c	**12d**	1.0	0.9	1.2	1.5	2.1
12f	**12e**	1.7	0.9	1.2	1.6	1.4
12g	**12h**	1.0	1.1	1.5	1.4	1.2
14	**13**	0.9	1.1	1.0	1.2	1.6

[a] The standard deviation is ±10% of the listed number.



13



14

Figure 2.

reduction of diester **10** with $NaBH_4$ to appropriate diol and following di-*O*-alkylation with bromoacetic acid methyl ester. Macrocyclic bisamides **12b–d**[10] and **13**, **14**[27] were synthesized previously.

4.2. ESI-MS experiments

Mass spectrometric measurements were made on a Quattro LC triple quadrupole mass spectrometer equipped with an ESI source. The Harvard syringe pump system ranged from 5.0 μL/min to 10.0 μL/min. The needle potential for the methanol solution was set to 3.0 kV for all experiments. Each spectrum taken had an average of 25–30 scans and was acquired three times for at least 180 s. All experimental conditions were held constant throughout each series of experiments to minimize the differences arising from inconsistencies in ion formation or transmission.

All solutions were prepared in 100% methanol. The chloride salts were mixed in solution with the host of interest to form the complexes studied. Host–guest solutions containing a single host–multiple guest had a

Table 4. Effect of regioisomerism on a complexation ability between two ligands toward one cation

Ligands		Ratios of signal intensities in the ESI-MS spectra ($[L1 + M]^+/[L2 + M]^+$)[a]				
L1	L2	$[L1 + Li^+/L2 + Li^+]$	$[L1 + Na^+/L2 + Na^+]$	$[L1 + K^+/L2 + K^+]$	$[L1 + Rb^+/L2 + Rb^+]$	$[L1 + Cs^+/L2 + Cs^+]$
12f	**12d**	5.0	4.4	1.5	1.8	1.7
12e	**12c**	2.6	2.3	1.4	2.2	1.5

[a] The standard deviation is ±10% of the listed number.

Table 5. Effect of presence of pyridine or benzene subunit on a complexation ability between two ligands toward one cation

Ligands		Ratios of signal intensities in the ESI-MS spectra ($[L1 + M]^+/[L2 + M]^+$)[a]				
L1	L2	$[L1 + Li^+/L2 + Li^+]$	$[L1 + Na^+/L2 + Na^+]$	$[L1 + K^+/L2 + K^+]$	$[L1 + Rb^+/L2 + Rb^+]$	$[L1 + Cs^+/L2 + Cs^+]$
12d	**13**	0.9	1.1	1.5	1.3	1.5
12c	**14**	0.7	1.2	1.5	1.7	1.9

[a] The standard deviation is ±10% of the listed number.

concentration 1×10^{-5} M of each component. The solutions containing two hosts and a single guest had a concentration ratio of 10:10:1, where the hosts concentrations were 1×10^{-4} M for each host.

4.3. 2,3-Di-*O*-allyl-1,4-di-*O*-benzyl-L-threitol 5

1,4-Di-*O*-benzyl-L-threitol (75 mmol), KOH (20 g), and allyl bromide (33.3 mL, 0.4 mol, freshly distilled) were added to anhydrous toluene (250 mL). The mixture was stirred at 90 °C for 24 h, then cooled, washed with water, dried over Na_2SO_4 and concentrated. The resulting oil was purified by column chromatography, using hexane–AcOEt (8:2 → 7:3) as an eluent to obtain **5** as colorless oil. Yield 88%, $[\alpha]_D^{20} = +8.4$ (*c* 2.12; $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.36–7.26 (m, 10H, –Ph); 6.00–5.80 (m, 2H, –CH=CH2); 5.29–5.08 (m, 4H, –CH=CH2); 4.51 (s, 4H); 4.24–3.94 (m, 4H); 3.77–3.50 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$), δ: 138.3; 135.3; 128.3; 127.6; 127.5; 116.9; 77.8; 73.4; 72.3; 69.8; MS (HR ESI) *m*/*z* calcd for $C_{24}H_{31}O_4$ $[M+H]^+$: 383.2222. Found: 383.2204.

4.4. 2,3-Bis-*O*-(2-hydroxyethyl)-1,4-di-*O*-benzyl-L-threitol 6

Diallyl ether **5** (60 mmol) was dissolved in methanol (400 mL), cooled to −78 °C and ozone was passed through the solution. When the solution turned blue, ozone was passed for additional 30 min, followed by oxygen for 30 min to remove the excess of ozone. To the stirred solution, maintained below −21 °C, a solution of sodium borohydride (10 g) in a mixture of methanol–water (1:1, 150 mL) was added dropwise. The mixture was stirred overnight at rt, then methanol was distilled off, and water (100 mL) was added. The solution was extracted with chloroform several times and the combined extracts was dried ($MgSO_4$), filtered, and concentrated, giving a colorless oil. The oil was chromatographed using chloroform–methanol as an eluent. Yield 62%, $[\alpha]_D^{20} = +2.4$ (*c* 2.0; $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.40–7.24 (m, 10H, –Ph); 4.52–4.51 (2 × s, 4H); 3.90–3.45 (m, 14H); 3.21 (br s 2H,–OH), ^{13}C NMR (125 MHz, $CDCl_3$), δ: 137.6; 129.6; 128.5; 127.8; 79.7; 73.5; 73.0; 69.4; 62.2; MS (HR ESI) *m*/*z* calcd for $C_{22}H_{30}O_6Na$ $[M+Na]^+$: 413.1935. Found: 413.1933.

4.5. 2,3-Bis-*O*-(2-*p*-toluenesulfonyloxyethyl)-1,4-di-*O*-benzyl-L-threitol 7

Diol **6** (3 mmol) and tosyl chloride (12 mmol) were dissolved in anhydrous THF (30 mL), cooled to 0 °C, and KOH (0.7 g, 12 mmol) then added. The mixture was stirred below 5 °C for 2 h, and then at rt for 20 h. The mixture was poured onto ice and the aqueous phase extracted (CH_2Cl_2, 3 × 30 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The obtained oil was purified by chromatography using hexane–AcOEt (3:2) as an eluent. Yield 92%. $[\alpha]_D^{23} = +1.1$ (*c* 2.3; $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.78–7.74 (AA′BB′, 4H, $J = 8.2$); 7.23–7.38 (m, 10H, –Ph); 4.54–4.36 (m, 4H); 4.09 (t, 4H, $J = 5.0$); 3.9–3.4 (m, 10H); 2.45 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$), δ: 144.8; 138.0; 132.9; 129.8; 129.6; 128.4; 127.9; 127.7; 79.6; 73.4; 69.7; 69.4; 69.1; 21.6; MS (HR ESI) *m*/*z* calcd for $C_{36}H_{42}O_{10}S_2Na$ $[M+Na]^+$: 721.2117. Found: 721.2149.

4.6. 2,3-Bis-*O*-(2-phthalimidoethyl)-1,4-di-*O*-benzyl-L-threitol 8

From diol **6**: to a solution of diol **3** (3 mmol), phthalimide (1.06 g, 7.2 mmol) and triphenylphosphine (1.89, 7.2 mmol) in dry THF (30 mL), di-*iso*-propyl azadicarboxylate (DIAD, 1.42 mL, 7.2 mmol) was added dropwise. The mixture was stirred at rt under argon for 3 days and the solvent evaporated. The crude oil was chromatographed using hexane–AcOEt (3:2) as an eluent to afford **8** as a colorless oil. Yield 82%.

From ditosylate **7**: The compound was prepared according to the literature procedure (procedure for compounds **4** and **7**) using ditosylate **4** instead of dichlorides. Purification as described above. Yield 55%. $[\alpha]_D^{20} = -1.0$ (*c* 4.5; $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.86–7.77 (AA′BB′/2, 4H, –NPht); 7.69–7.62 (AA′BB′/2, 4H, –NPht); 7.30–7.16 (m, 10H, –Ph); 4.31 and 4.30 (2 × s, 4H); 3.95–3.81 (m, 6H); 3.81–3.74 (m, 6H); 3.65–3.60 (m, 6H); 3.57–3.51 (m, 2H); 3.46–3.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 168.2; 138.2; 133.8; 132.1; 129.5; 128.3; 127.5; 127.4; 123.2; 79.3; 73.2; 69.8; 67.8; 38.0; MS (HR ESI) *m*/*z* calcd for $C_{38}H_{36}N_2O_8Na$ $[M+Na]^+$: 671.2369. Found: 671.2396.

4.7. 2,3-Bis-*O*-(2-aminoethyl)-1,4-di-*O*-benzyl-L-threitol 9

Diphthalimide **5** (1.5 mmol) was dissolved in warm ethanol (96%, 50 mL), to which hydrazine monohydrate (1 mL) was added and the solution refluxed for 8 h. Ethanol was evaporated, the white residue dissolved in aqueous sodium hydroxide (20%, 30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with water (30 mL) and dried over Na_2SO_4. The filtrate was evaporated to afford diamine **9** as a yellowish oil, which was stored in a frigde. Yield >91%, $[\alpha]_D^{21} = +8.9$ (*c* 2.05; $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.37–7.26 (m, 10H, –Ph); 4.50 (s, 4H); 3.72–3.63 (m, 6H); 3.57–3.50 (m, 4H); 2.87–2.77 (m, 4H); 1.66 (br s, 4H, $-NH_2$); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 138.0; 128.4; 127.7; 127.68; 78.9; 73.7; 73.4; 69.3; 42.1; MS (HR ESI) *m*/*z* calcd for $C_{22}H_{33}N_2O_4$ $[M+H]^+$: 389.2440. Found: 389.2451.

4.8. General procedures for the syntheses of macrocycles 12

4.8.1. Method A (under high pressure). An equimolar solution of dimethyl α,ω-dicarboxylate (0.5 mmol) and the appropriate α,ω-diamine (0.5 mmol) in methanol (5 mL) was charged into a Teflon ampoule, sealed, placed in a high-pressure vessel filled with ligroin as a transmission medium, and compressed (12 kbar) at room temperature for 48 h. After decompression, the reaction mixture was transferred quantitatively to a round-bottomed flask and the solvent evaporated. The

residue was chromatographed on a silica gel column using 0.5–3% mixtures of methanol in chloroform.

4.8.2. Method B (in the presence of MeO^-). Sodium (1 equiv) was added to a cooled (5 °C) solution (0.1 mol/L) of diester in dry methanol. Then an equal volume of a solution (0.1 mol/L) of diamine in dry methanol was added. The mixture was left at rt over a period of several days (monitored by TLC). Then the solvent was evaporated and the residue was purified by column chromatography using a gradient of toluene/chloroform, chloroform and chloroform/methanol mixtures as eluent.

4.9. (7*S*,8*S*)-7,8-Bis(benzyloxymethyl)-6,9-dioxa-3,12,18-triaza-bicyclo[12.3.1]octadeca-1(17),14(18),15-triene-2,13-dione 12a

4.9.1. Method A: 38.7%; method B. 7 days, 42.0%. Thick, yellowish oil; $[\alpha]_D^{24} = -28.8$ (*c* 2.1; $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$), δ: 8.89 (br m, 2H, –NHCO–); 8.24 (d, $J = 7.8$, 2H); 8.03 (t, $J = 7.8$, 1H); 7.34–7.25 (m, 10H, –Ph); 4.47 (AB/2, $J = 12.2$, 2H); 4.42 (AB/2, $J = 12.2$, 2H); 3.90–3.84 (m, 2H); 3.84–3.80 (m, 2H); 3.76–3.64 (m, 4H); 3.59–3.51 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$), δ: 162.5; 148.1; 139.4; 137.5; 128.4; 128.0; 127.9; 123.7; 78.7; 73.4; 67.3; 67.0; 38.7; MS (HR ESI) *m*/*z* calcd for $C_{29}H_{33}N_3O_6Na$ $[M+Na]^+$: 542.2267. Found: 542.2262.

4.10. (10*S*,11*S*)-10,11-Bis(benzyloxymethyl)-3,9,12,18-tetraoxa-6,15,24-triaza-bicyclo[18.3.1]tetracosa-1(23),20(24),21-triene-5,16-dione 12e

4.10.1. Method A 14.1%; method B. 8 days, 30.0%. Thick, yellowish oil. $[\alpha]_D^{24} = +2.2$ (*c* 2.2; $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$), δ: 7.71 (t, $J = 7.8$, 1H); 7.63 (br t, $J = \sim 5.5$, 2H, –NHCO–); 7.35–7.23 (m, 12H); 4.64 (AB/2, $J = 11.2$, 2H); 4.61 (AB/2, $J = 11.2$, 2H); 4.40 (AB/2, $J = 12.2$, 2H); 4.36 (AB/2, $J = 12.1$, 2H); 4.13 (AB/2, $J = 15.6$, 2H); 4.08 (AB/2, $J = 15.6$, 2H); 3.73–3.68 (m, 2H); 3.62–3.48 (m, 10H); 3.44–3.36 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$), δ: 169.4; 156.3; 137.8; 137.5; 128.4; 127.7; 127.6; 122.2; 78.3; 74.5; 73.3; 70.8; 70.3; 69.1; 39.7; MS (ESI LR) *m*/*z* calcd for $C_{33}H_{41}N_3O_8Na$ $[M+Na]^+$: 630.69. Found: 630.3.

4.11. (10*R*,11*R*)-10,11-Di-[(4*R*)-2,2-dimethyl-1,3-dioxalane-4-yl]-3,9,12,18-tetraoxa-6,15,24-triaza-bicyclo[18.3.1]tetracosa-1(23),20(24),21-triene-5,16-dione 12f

4.11.1. Method A: 17.6%; method B. 8 days, 26.3%. Colorless solid (foam), mp 51–54 °C; $[\alpha]_D^{20} = +15.8$ (*c* 2.1; $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$), δ: 7.77 (t, $J = 7.8$, 1H); 7.58 (br t, $J = \sim 5.5$, 2H, –NHCO–); 7.33 (d, $J = 7.8$, 2H); 4.67 (AB/2, $J = 11.3$, 2H); 4.65 (AB/2, $J = 11.3$, 2H); 4.17 (AB/2, $J = 15.1$, 2H); 4.13 (AB/2, $J = 15.1$, 2H); 4.11–4.06 (m, 2H); 3.94 (dd, $J = 5.9$, $J = 8.3$, 2H); 3.83 (dd, $J = 5.4$, $J = 8.3$, 2H); 3.80–3.75 (m, 2H); 3.71–3.65 (m, 2H); 3.56–3.52 (m, 2H); 3.52–3.41 (m, 4H); 1.36 (s, 6H); 1.29 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 169.4; 156.31; 137.7; 122.5; 108.9; 80.1; 75.0; 74.6; 71.9; 70.8; 66.9; 39.0; 26.7; 25.3; MS (HR EI) *m*/*z* calcd for $C_{27}H_{42}O_{10}N_3$ $[M+H]^+$: 568.2870. Found: 568.2845; EA (%) calcd: C, 57.1; H, 7.3; N, 7.4. Found: C, 56.9; H, 7.0; N, 7.3.

4.12. (13*S*, 14*S*)-13,14-Bis-benzyl-oxymethyl-3,9,12,15,18,24-hexaoxa-6,12,30-triaza-bicyclo[24.3.1]triaconta-1(29),26(30),27-triene-5,22-dione 12g

4.12.1. Method B. 8 days, 39%. Yellowish oil. $[\alpha]_D^{20} = +14.6$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 8.08 (2H, br s –N*H*CO–), 7.67 (1H, t, $J = 10.0$), 7.32–7.21 (12H, m), 4.69 (4H, s), 4.47 (4H, s), 4.09 (4H, s), 3.68–3.51 (22H, m). ^{13}C NMR ($CDCl_3$), δ: 169.9, 157.1, 138.3, 137.9 (–Ph), 128.5 (–Ph), 127.8 (–Ph), 121.0, 79.1, 74.3, 73.5, 73.3, 70.8, 70.7, 69.9, 69.6, 38.9. HR ESIMS *m*/*z* calcd for $C_{37}H_{49}N_3O_{10}$ $[M+Na]^+$: 718.3316. Found: 718.3329.

4.13. (13*R*, 14*R*)-13,14-Bis(2,2-dimethyl-[1,3]dioxalan-4-yl)-3,9,12,15,18,24-hexaoxa-6,21,30-triaza-bicyclo-[24.3.1]triaconta-1(29),26(30),27-triene-5,22-dione 12h

4.13.1. Method B. 7 days, 43%. Yellowish oil. $[\alpha]_D^{20} = +10.6$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 8.19 (2H, br s –N*H*CO–), 7.76 (1H, t, $J = 9.25$), 7.27 (2H, m), 4.74 (4H, s), 4.23–3.91 (10H, m), 3.77–3.72 (4H, m), 3.55 (12H, m), 1.38 (6H, s), 1.31 (6H, s). ^{13}C NMR ($CDCl_3$), δ: 170.1, 157.2, 138.1, 121.1, 108.8, 80.6, 75.7, 74.4, 72.2, 70.9, 70.8, 70.0, 66.7, 38.9, 26.9, 25.5. HR ESIMS *m*/*z* calcd for $C_{31}H_{49}N_3O_{12}$ $[M+Na]^+$: 678.3214. Found: 678.3220.

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