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Chiral α,ω-diaminoethers derived from D-mannitol and L-treitol as building blocks for the synthesis of macrocyclic compounds possessing 1,3-benzenedicarboxamide or 2,6-pyridinedicarboxamide subunits

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Abstract—Three new chiral α,ω-diaminoethers, derivatives of D-mannitol and L-treitol, possessing C_2 symmetry are prepared. The α,ω-diaminoethers were applied to the macrocyclization reaction under non-high-dilution conditions, which afforded chiral macrocyclic diamides possessing either 2,6-pyridinedicarboxamide or 1,3-benzenedicarboxamide moieties.

1. Introduction

We have been interested for some time in using the double-amidation reaction of methyl α,ω-carboxylates with primary α,ω-diamines under non-high-dilution conditions to obtain various macrocyclic amides.[1] The amide group exhibits dual complexing character (C=O and N or NH) thus amide-based molecular receptors can bind metal[1e,2] and ammonium[2d,3] cations, neutral organic molecules[4] as well as anionic species.[5] In recent years increasing attention has been paid to the interaction of anions with both acyclic and cyclic synthetic ligands.[6] The hydrogen bond donor capacity of the amide group, has been used as an anion binding element in several molecular receptors.[4a,5c,7] The 1,3-benzene- or 2,6-pyridinedicarboxamide moiety is a common structural feature of these molecular receptors. Recently, we have found that achiral macrocyclic 2,6-pyridine–amide based compounds bind halide and acetate anions, as verified by ^{1}H NMR titrations and X-ray structural analyses.[8] To expand our studies on anion receptors, we decided to prepare chiral macrocyclic diamides based on 1,3-benzene- or 2,6-pyridinedicarboxamide subunits. In contrast to achiral macrocyclic compounds of this type, the synthesis of chiral analogs is more difficult due to use of chiral α,ω-diaminoethers as substrates. Only few examples of the preparative procedure for homochiral diaminoethers are reported in the literature.[3a,9] Herein, we report a useful method for synthesis of C_2-symmetric α,ω-diaminoethers, containing three or five ethylene units and their application in a non-high-dilution reaction with dimethyl 1,3-benzenedicarboxylate or dimethyl pyridine 2,6-dicarboxylate yielding chiral macrocyclic diamides.

2. Results and discussion

1,2;5,6-Di-*O*-isopropylidene-D-mannitol **1** and 1,4-di-*O*-benzyl-L-threitol **2** were selected as convenient sources of chirality. These readily available building blocks were used previously for the synthesis of numerous chiral coronands.[10] The synthesis of D-mannitol derived α,ω-diaminoether **5**, possessing five ethylene bridges, began with preparation of 1,2;5,6-di-*O*-isopropylidene-3,4-bis-*O*-[(2-chloroethoxy)ethyl]-D-mannitol **3** (Scheme 1). The dichloride **3** was produced in 61% yield under PTC conditions ($ClCH_2CH_2OCH_2CH_2Cl$, NaOH, n-Bu_4NHSO_4) as reported in the literature.[11] Compound **3** was then converted into the corresponding diphthalimido derivative **4** by treatment with potassium phthalimide in DMF. Hydrazinolysis of **4** afforded α,ω-diaminoether **5** as a colorless oil. The purity of diamine **5** (~95% based on ^{1}H NMR) was sufficient for further transformations.

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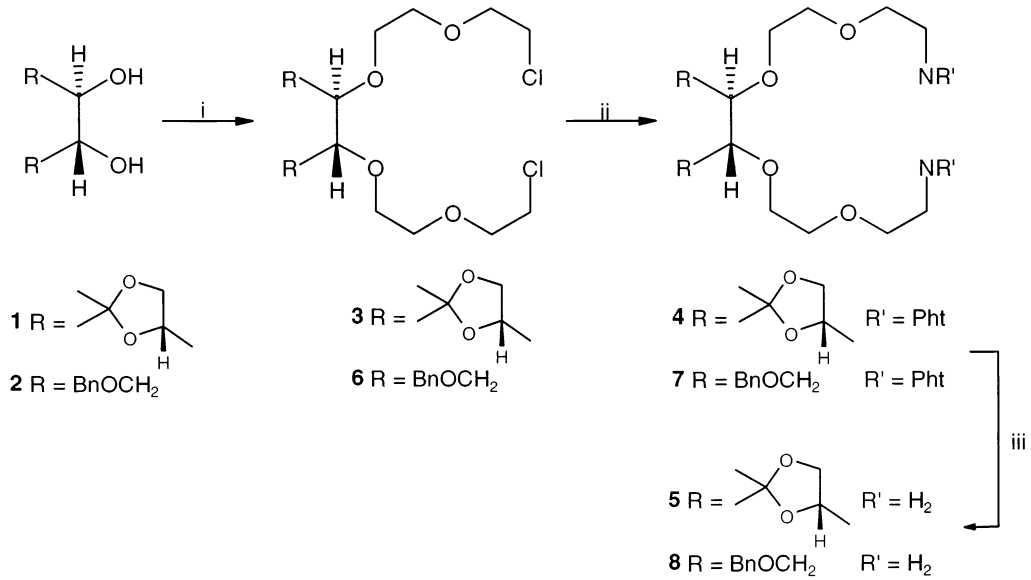


Scheme 1. (i) $ClCH_2CH_2OCH_2CH_2Cl$, 50% $NaOH_{aq}$, n-Bu_4NHSO_4; (ii) potassiophthalimide (PhtNK), DMF, 90°C; (iii) H_2N–$NH_2{\cdot}H_2O$, EtOH, reflux.

The diaminoether **8**, derived from 1,4-di-*O*-benzyl-L-treitol, was prepared in a similar manner. Alkylation of diol **2** by 1,2-bis-(2-chloroethoxy)ethane resulted in dichloride **6**, accompanied by substantial amounts (~ 27%) of monoalkylated diol which was separated and converted separately into dichloride **6**. The overall yield of compound **6** was 81%. Next, the reaction of dichloride **6** with potassium phthalimide afforded compound **7**, which was readily recycled into diaminoether **8**.

A less direct pathway had to be followed for the synthesis of three ethylene units possessing α,ω-diaminoether derived from D-mannitol. Straightforward alkylation of diol **1** with 1,2-dichloroethane gave only the 1,4-dioxane ring containing compound. Therefore, we chose the C_2-elongated diol **12** as a convenient precursor of α,ω-diaminoether.

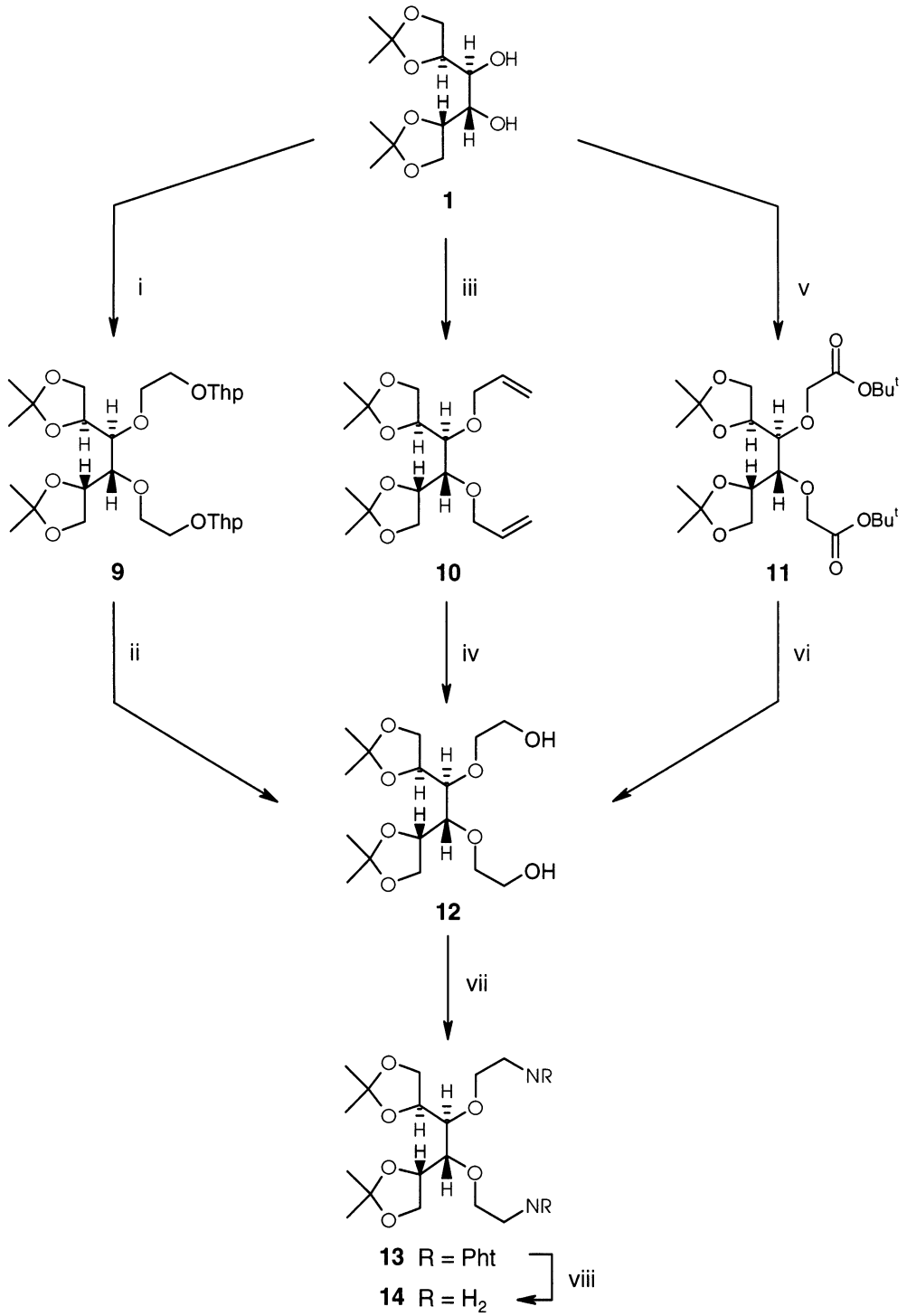
Three independent synthetic routes were developed for preparation of diol **12** (Scheme 2). The first one was based on alkylation of **1** with *O*-(2′-tetrahydropyranyl)-2-chloroethanol. The reaction carried out under PTC conditions led to 1,2;5,6-Di-*O*-isopropylidene-3,4-bis-*O*-[(2′-tetrahydropyranyloxyethyl]-D-mannitol **9** in 21% yield. Although both the isopropylidene and tetrahydropyranyl (THP) ether protective groups are acid sensitive, the reactivity of the THP ether is slightly higher.[12] Thus, di-THP-ether **9** was treated with catalytic *p*-toluenesulfonic acid in methanol affording diol **12** (39%) accompanied by products resulting from isopropylidene cleavage. This route is clearly impractical due to the low yield of both the alkylation and deprotection steps.

The second synthetic pathway used by us gave better results. The reaction of **1** with allyl bromide provided diallyl ether **10** in excellent yield, which was subsequently converted into diol **12** via ozonolysis followed by reduction with sodium borohydride.[10b] Chromatographic purification afforded diol **12** in a 55% overall yield. According to Stodart et al.[10b] the yield of **12** could be increased to 82% if the chromatographic step is omitted. However, in our case the purity of **12** was insufficient for further application without chromatographic purification.

Finally, diol **12** was produced in a yield of 74% by lithium aluminum hydride reduction of di-*tert*-butyl ester **11**. Ester **11** was prepared by reaction of 1,2;5,6-di-*O*-isopropylidene-D-mannitol **1** with *tert*-butylbromoacetate, according to our own procedure described previously for the synthesis of several other *tert*-butyl esters derived from chiral diols.[1c] The overall yield of the last two procedures is nearly the same but the method based on reduction of di-*tert*-butyl ester **11** is more practical due to the simplicity of the purification processes.

Conversion of diol **12** into the appropriate diamide **14** was performed according to the Mitsunobu protocol.[13] Treatment of diol **12** with phthalimide, in the presence of triphenyl phosphine and di-*iso*-propyl azodicarboxylate (DIAD),[14] led to diphthalimide **13** in a yield of 69%. Finally hydrazinolysis of **13** afforded chiral α,ω-diaminoether **14** in 91% yield.

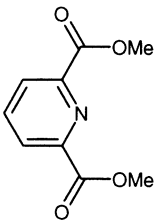
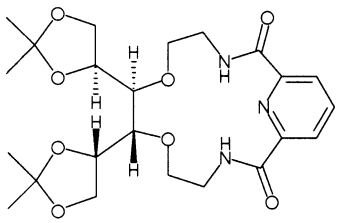
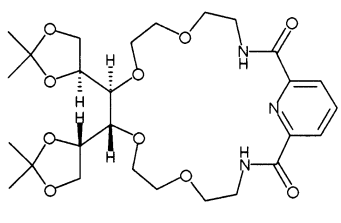
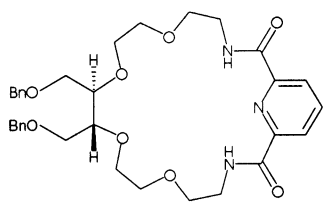
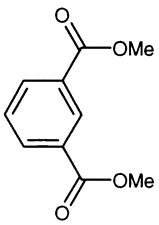
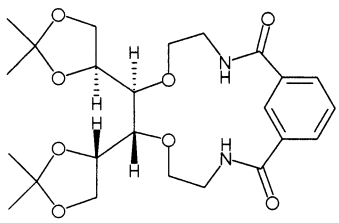
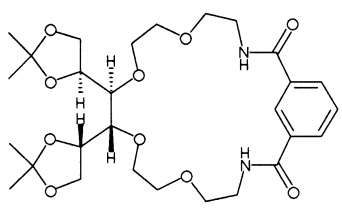
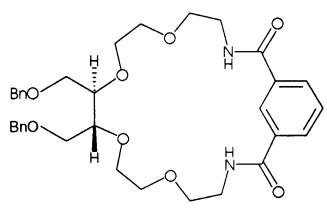
With the necessary α,ω-diaminoethers **5**, **8** and **14** at hand we investigated the macrocyclization reactions. Initially, however, some difficulties occurred: when we treated diamines **5**, **8** and **14** with dimethyl pyridine 2,6-dicarboxylate **15** or dimethyl 1,3-benzodicarboxylate **16** in methanol no reaction was observed. These results indicated that dimethyl esters **15** and **16** were inactive under such conditions. To overcome this problem we used two previously reported efficient methods for activation of the double-amidation reaction, namely: application of sodium methoxide as basic mediator[15] and high pressure[1c–d,16] as a non-thermal



Scheme 2. (i) $ClCH_2CH_2OTHP$, 50% $NaOH_{aq}$, *n*-Bu_4NHSO_4; (ii) TsOH, MeOH; (iii) $CH_2{=}CHCH_2Br$, KOH, toluene; (iv) O_3, $NaBH_4$, MeOH; (v) $BrCH_2CO_2Bu^t$, *n*-Bu_4NCl, 35% $NaOH_{aq}$, toluene; (vi) LAH, dioxane; (vii) DIAD, PPh_3, PhtNH, THF; (viii) $H_2N{-}NH_2{\cdot}H_2O$, EtOH.

means to drive the reaction forward. The reactions of α,ω-diaminoethers **5**, **8** and **14** with diester **15** were carried out in methanol in the presence of methoxide ion. This method furnished macrocyclic diamides **17**, **18** and **19** with yields of 18, 48 and 40%, respectively (Table 1). Using high pressure conditions (MeOH, 10 kbar, rt) compounds **17**–**18** were procured with similar yields 39, 59 and 41%, respectively. Reactions of dimethyl 1,3-benzodicarboxylate **16** with diamines **8** or **14** in the presence of MeO^- or under high pressure conditions gave compounds **21** and **22** with satisfactory yields, albeit lower than in the reactions with component **15**. Unfortunately, we failed to form macrocyclic diamide **20** both in the presence of MeO^- ions and under high pressure conditions.

Table 1. Yields of diamides under various macrocyclization conditions

	Amine 5		Amine 8		Amine 14	
	With MeO⁻	*high pressure*	*with MeO⁻*	*high pressure*	*with MeO⁻*	*high pressure*
 **15**	 **17**		 **18**		 **19**	
	18.8	39.0	48.8	59.7	40.2	41.9
 **16**	 **20**		 **21**		 **22**	
	–	–	24.0	25.1	11.0	28.2

As a result of our investigations, two new and efficient synthetic routes for the transformation of 1,2;5,6-di-*O*-isopropylidene-D-mannitol **1** and 1,4-di-*O*-benzyl-L-threitol **2** to chiral α,ω-diaminoethers **5**, **8** and **14** have been developed. Both strategies include elongation of the diol, introduction of *N*-phthaloyl groups using Gabriel or Mitsunobu protocols and liberation of amine groups. The α,ω-diaminoethers **5**, **8** and **14** were successfully applied to the macrocyclization reaction under non-high-dilution conditions under which chiral macrocyclic diamides **17**–**19**, **21** and **22**, possessing 2,6-pyridine- or 1,3-benzenedicarboxamide moiety, were obtained in good to acceptable yields.

3. Experimental

3.1. General methods

Melting points were taken on a Köfler type (Boetius) hot-stage apparatus and are not corrected. Optical rotations were measured using a Perkin–Elmer 241 polarimeter with a thermally jacketed 10 cm cell. ^{1}H NMR spectra were recorded with a Varian Gemini (200 or 500 MHz) spectrometers in $CDCl_3$ using TMS as an internal standard. ^{13}C NMR spectra were also recorded using a Varian Gemini (50 or 125 MHz) spectrometers. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ, 0.00 ppm), and coupling constants (J) are measured in Hertz. High-resolution mass spectrometry (HRMS) experiments were performed on an AMD-604 Intectra instrument using LSIMS or EI technique. Column chromatography was carried out on silica gel (Kieselgel-60, 200–400 mesh). Methanol was freshly distilled from Mg/I_2 under Ar. THF and dioxane were also freshly distilled from Na/benzophenone under Ar. Diesters **15** and **16** were purchased commercially. Compounds **3**, **10**, **11** were prepared according to the literature procedures.

3.2. 2,3-Bis-*O*-(5-chloro-3-oxapentyl]-1,4-di-*O*-benzyl-L-threitol 6

Diol **2** (3 g, 10 mmol) and tetrabutylammonium hydrogensulfate (6.8 g, 20 mmol) were dissolved in bis(2-chloroethyl) ether (50 mL), cooled to 5°C and added to cooled 50% aqueous sodium hydroxide (50 mL). The resulting mixture was stirred at 5°C for 4 h, and at rt for 2 days. The mixture was diluted with water (50 mL) and dichloromethane (50 mL), separated and the aqueous phase was extracted with dichloromethane. The combined extracts were washed with water, dried ($MgSO_4$) and concentrated. Excess chloroethyl ether was evaporated and the resulting material was purified

by column chromatography, using hexane/ethyl acetate (3:1) as eluent. The dichloride **6** (3.15 g, R_f=0.65, hexane/AcOEt 1:1) and monochloride (1.1 g, R_f=0.45, hexane/AcOEt 1:1) were obtained as colorless oils. The monoalkylated compound was converted into dichloride **6** by the same procedure. The total yield of dichloride **6** was 4.14 g (81%). $[\alpha]_D^{20}$=+5.2 (c=1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.4–7.2 (10H, m, -Ph); 4.51 (4H, s, -$\underline{CH_2}$Ph); 3.8–3.5 (22H, m); ^{13}C NMR (50 MHz, $CDCl_3$), δ 138.5; 128.5; 127.8; 127.7; 79.5; 73.5; 71.4; 71.0; 70.9; 69.9; 43.0 (-CH_2NH_2); HR LSIMS m/z calcd for $C_{26}H_{36}O_6Na^{35}Cl_2$ [M+Na]$^+$: 537.1787; found 537.1794.

3.3. General procedure for the synthesis of diphthalimide ethers 4 and 7

A solution of dichloride **3** or **6** (3 mmol) and potassium phthalimide (1.3 g, 7.2 mmol) in dry DMF (50 mL) was stirred for 24 h at 90°C under argon. The solvent was evaporated under reduced pressure. The resulting material was dissolved in water (50 mL) and dichloromethane (50 mL), phases were separated and the aqueous one was extracted with dichloromethane (3×30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated to afford crude diphthalimide ether, which was purified by column chromatography using hexane/ethyl acetate (1:1) as eluent.

3.3.1. 3,4-Bis-*O*-(5-phthalimido-3-oxapentyl)-1,2;3,4-di-*O*-isopropylideno-D-mannitol 4. White crystals, yield 81%, mp 109–111°C, $[\alpha]_D^{24}$=+11.4 (c=1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.86–7.82 (4H, AB/2, -NPht); 7.73–7.69 (4H, AB/2, -NPht); 4.14 (2H, m); 4.08 (2H, dd, J=6, J=8.5); 3.92 (2H, dd, J=6, J=8.5); 3.88 (4H, m); 3.73 (4H, t, J=5); 3.69 (4H, t, J=6); 3.56 (4H, t, J=5); 3.52 (2H, m); 1.36 (6H, s, -CH_3); 1.29 (6H, s, -CH_3); ^{13}C NMR (250 MHz, $CDCl_3$), δ 168.2; 133.9; 132.2; 123.2; 108.6; 80.6; 75.6; 72.1; 70.2; 67.8; 66.6; 37.4; 26.7; 25.3; HR LSIMS m/z, calcd for $C_{36}H_{44}O_{12}N_2Na$ [M+Na]$^+$: 719.2792; found 719.2805.

3.3.2. 2,3-Bis-*O*-(5-phthalimido-3-oxapentyl)-1,4-di-*O*-benzyl-L-threitol 7. Colorless oil, yield 75%, $[\alpha]_D^{20}$=+4.0 (c=1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.85–7.62 (8H, AB, -NPht); 7.32–7.20 (10H, m); 4.46 (4H, s, -$\underline{CH_2}$Ph); 3.90–3.78 (4H, m); 3.78–3.42 (18H, m); ^{13}C NMR (50 MHz, $CDCl_3$), δ 168.2; 138.4; 133.9; 132.1; 128.3; 127.6; 127.5; 123.2; 79.2; 73.2; 70.7; 70.3; 69.8; 67.8; 37.4; HR LSIMS m/z, calcd for $C_{42}H_{44}O_8N_2Na$ [M+Na]$^+$: 759.2893; found 759.2867.

3.4. General procedure for the synthesis of diamines 5, 8 and 14

To a solution of the diphthalimide **4**, **7** or **13** (1.5 mmol) in 96% ethanol (50 mL) was added hydrazine monohydrate (1 mL), and the solution was stirred under reflux for 24 h. Ethanol was evaporated, the white residue was dissolve in aqueous sodium hydroxide (20%, 30 mL), and extracted with dichloromethane (3×30 mL). The combined extracts were washed with water (30 mL) and dried (Na_2SO_4). The filtrate was evaporated to give diamine **5**, **8** or **14** as an oil. (The diaminoethers were stored under argon.)

3.4.1. 3,4-Bis-*O*-(5-amino-3-oxapentyl)-1,2;3,4-di-*O*-isopropylideno-D-mannitol 5. Yield 93%, colorless oil, $[\alpha]_D^{24}$=+6.2 (c=2.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.30–3.96 (6H, m); 3.85–3.75 (4H, m); 3.65–3.53 (6H, m); 3.48 (4H, t, J=5, -$\underline{CH_2}CH_2NH_2$); 2.85 (4H, t, J=5, -$\underline{CH_2}NH_2$); 1.60 (4H, bs, -NH_2); 1.41 (6H, s, -CH_3); 1.34 (6H, s, -CH_3); ^{13}C NMR (50 MHz, $CDCl_3$), δ 108.5; 80.6; 75.7; 73.4; 72.2; 70.4; 66.50; 41.9; 26.7; 25.3; HR LSIMS m/z, calcd for $C_{20}H_{40}O_8N_2Na$ [M+Na]$^+$: 459.2682; found 459.2706.

3.4.2. 2,3-Bis-*O*-(5-amino-3-oxapentyl)-1,4-di-*O*-benzyl-L-threitol 8. Yield 90%, yellowish oil, $[\alpha]_D^{20}$=+7.9 (c=2.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.31 (10H, s); 4.51 (4H, s); 3.88–3.50 (14H, m); 3.45 (4H, t, J=5.2, -$\underline{CH_2}CH_2NH_2$); 2.80 (4H, t, J=5.2, -$\underline{CH_2}NH_2$); 1.47 (4H, bs, -NH_2); ^{13}C NMR (50 MHz, $CDCl_3$), δ 138.4; 128.4; 127.7; 127.6; 79.3; 73.4; 73.3; 70.8; 70.6; 69.8; 41.9 (-CH_2NH_2); HR LSIMS m/z, calcd for $C_{26}H_{41}O_6N_2$ [M+H]$^+$: 477.2965; found 477.2978.

3.4.3. 3,4-Bis-*O*-(2-aminoethyl)-1,2;3,4-di-*O*-isopropylideno-D-mannitol 14. Yield 91%, yellowish oil, $[\alpha]_D^{24}$=+14.8 (c=2.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.3–3.9 (6H, m); 3.7–3.6 (6H, m); 2.84 (4H, t, J=5.2 Hz, -$\underline{CH_2}NH_2$); 1.41 (6H, s, -CH_3); 1.34 (6H, s, -CH_3); ^{13}C NMR (50 MHz, $CDCl_3$), δ 108.4; 80.3; 75.2; 75.1; 66.60; 42.2; 26.5; 25.1; HR LSIMS m/z, calcd for $C_{16}H_{33}O_6N_2$ [M+H]$^+$: 349.2329; found 349.2351.

3.5. 3,4-Bis-*O*-(2-*O*-tetrahydropyranyloxyethyl)-1,2;5,6-di-*O*-isopropylidene-D-mannitol 9

To a solution of **1** (2.0 g, 7.63 mmol) and tetrabutylammonium hydrogen sulfate (0.24 g, 0.69 mmol) in THPOCH_2CH_2Cl (6.8 mL, 7.51 g, 45.8 mmol) aqueous sodium hydroxide (50%, 17 mL) was added dropwise. The resulting two-phase system was vigorously stirred at 65°C for 2 days under argon. The mixture was then diluted with dichloromethane, washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was eluted through a silica column (hexane/ethyl acetate 4:2) to give the pure product as a colorless oil (0.83 g, 21%). $[\alpha]_D^{20}$=+5.9 (c=2.85, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.64 (2H, t, J=2.7); 4.21 (2H, m); 4.14–3.46 (18H, m); 1.94–1.42 (12H, m); 1.41 (3H, s, -CH_3); 1.38 (3H, s, -CH_3); 1.35 (3H, s, -CH_3); 1.34 (3H, s, -CH_3); ^{13}C NMR (50 MHz, $CDCl_3$), δ 109.05; 108.56; 98.71; 98.67; 79.18; 78.84; 75.72; 75.36; 72.28; 72.22; 67.50; 66.72; 65.91; 62.06; 61.94; 30.39; 30.30; 26.64; 26.41; 25.21; 19.23; 19.17; HR LSIMS m/z, calcd for $C_{26}H_{46}O_{10}Na$ [M+Na]$^+$: 541.2989; found 541.2979.

3.6. 3,4-Bis-*O*-(2-hydroxyethyl)-1,2;5,6-di-*O*-isopropylidene-D-mannitol 12

From **9**: To a solution of the bis(tetrahydropyranyl) compound **9** (0.49 g, 0.95 mmol) in MeOH–CH_2Cl_2 (1:1) mixture (100 mL) p-toluenesulfonic acid (10 mg)

was added. The solution was stirred overnight at 40°C and $NaHCO_3$ (2 g) was added, and the mixture stirred for 1 h. The mixture was filtered and the filtrate evaporated. The oil residue was purified by column chromatography using hexane/ethyl acetate (2:3) as eluent giving diol **12** as a colorless oil (0.13 g, 39%).

From **10**: The compound was prepared according to literature procedure.

From **11**: To a solution of diester **11** (2.45 g, 5 mmol) in dry dioxane (40 mL) $LiAlH_4$ (0.4 g, 10.5 mmol) was added. The mixture was stirred under reflux under argon for 12 h. After cooling, water (5 mL), aqueous NaOH (20%, 10 mL) and water (50 mL) were sequentially added. The mixture was extracted with dichloromethane (3×50 mL), and the combined extracts were dried over $MgSO_4$. After filtration, the solvent was evaporated to yield diol **12** as a colorless oil or semi-solid. Crude product was purified by column chromatography using gradient eluation with toluene/chloroform–chloroform/methanol to yield diol **12** (1.42 g, 81%). White crystals, mp 76–77°C, $[\alpha]_D^{20}=+15.3$ ($c=1.1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.3–3.65 (16H, m); 3.53 (2H, bs, -OH); 1.44 (6H, s, -CH_3); 1.35 (6H, s, -CH_3); ^{13}C NMR (50 MHz, $CDCl_3$), δ 109.5; 108.6; 78.2; 76.6; 75.2; 74.1; 72.7; 67.5; 65.7; 62.7; 26.8; 26.4; 25.7; HR LSIMS m/z, calcd for $C_{16}H_{30}O_8Na$ $[M+Na]^+$: 373.1838; found 373.1841.

3.7. 3,4-Bis-*O*-(2-phthalimidoethyl)-1,2;5,6-di-*O*-isopropylidene-D-mannitol 13

To a solution of diol **12** (1 g, 2.86 mmol), phthalimide (1 g, 6.86 mmol) and triphenylphosphine (1.8 g, 6.86 mmol) in dry THF (50 mL) was added dropwise di-*iso*-propyl azadicarboxylate (DIAD) (1.35 mL, 6.86 mmol). The mixture was stirred at rt under argon for 3 days and the solvent was evaporated. The crude oil was purified by column chromatography using hexane/ethyl acetate (3:2) as an eluent to afford the diphthalimide as white crystals (1.27 g, 73%), mp 131–135°C. $[\alpha]_D^{24}=+12.8$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.90–7.65 (8H, AB, -NPht); 4.20–3.50 (16H, m); 1.32 (6H, s, -CH_3); 1.23 (6H, s, -CH_3); ^{13}C NMR (50 MHz, $CDCl_3$), δ 168.0; 133.9; 132.0; 123.2; 108.6; 80.7; 76.2; 75.2; 69.2; 66.4; 37.9; 26.5; 25.0; HR LSIMS m/z, calcd for $C_{32}H_{36}O_{10}N_2Na$ $[M+Na]^+$: 631.2267; found 631.2279.

3.8. General procedures for synthesis of bisamides 17–22

Method A (in the presence of MeO^-): The solution of ester (0.35 mmol) in dry methanol (5 mL) was cooled to 5°C and sodium (8 mg, 0.35 mmol) was added. A solution of diamine (0.35 mmol) in dry methanol (5 mL) was added. The mixture was left at rt for a period of 2–26 days (monitored by TLC). The solvent was evaporated and the residue was purified by column chromatography using gradient eluation with toluene/chloroform, chloroform and chloroform/methanol mixtures as eluent.

Method B (under high pressure): An equimolar solution of the dimethyl α,ω-dicarboxylate (0.5 mmol) and the appropriate α,ω-diamine (0.5 mmol) in methanol (5 mL) was filled into a Teflon ampoule, placed in a high-pressure vessel filled with ligroine 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 was evaporated. The residue was chromatographed on a silica gel column using 0.5–3% mixtures of methanol in chloroform.

3.8.1. (7*R*,8*R*)-7,8-Bis((4*R*)-2,2-dimethyl-1,3-dioxalan-4-yl)-6,9-dioxa-3,12,18-triazabicyclo[12.3.1]octadeka-1(17),14(18),15-triene-2,13-dione 17

Method A. Reaction time 6 days. Yield 18.8%. *Method B*. Yield 39.0%. White solid, $[\alpha]_D^{24}=-2.1$ ($c=1.2$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.93 (2H, bt, -NHCO-); 8.27 (2H, d, $J=7.5$); 8.06 (1H, t, $J=7.5$); 4.20 (2H, m); 4.12 (2H, dd, $J=6$, $J=8.5$); 3.92 (2H, dd, $J=6$, $J=8.5$); 3.89–3.83 (4H, m); 3.76–3.65 (4H, m); 3.65–3.58 (2H, m); 1.40 (6H, s, -CH_3); 1.32 (6H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$), δ 162.59; 148.34; 139.64; 123.93; 108.76; 78.91; 75.46; 68.13; 67.13; 38.62; 26.68; 25.30; HR EI m/z, calcd for $C_{23}H_{33}O_8N_3$ $[M]^+$: 479.2268; found 479.2243.

3.8.2. (9*R*,10*R*)-9,10-Bis((4R)-2,2-dimethyl-1,3-dioxalan-4-yl)-6,9,12,15-tetraoxa-3,18,24-triazabicyclo[18.3.1]-tetracoza-1(23),20(24),21-triene-2,19-dione 18

Method A. Reaction time 5 days. Yield 48.8%. *Method B*. Yield 59.7%. White solid, $[\alpha]_D^{24}=+7.6$ ($c=2.5$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$), δ 9.23 (2H, bt, -NHCO-); 8.33 (2H, d, $J=7.6$ Hz); 8.00 (1H, t, $J=7.6$); 4.3–3.5 (24H, m); 1.39 (6H, s, -CH_3); 1.32 (6H, s, -CH_3); ^{13}C NMR (50 MHz, $CDCl_3$), δ 164.0; 148.7; 138.4; 124.6; 108.8; 80.0; 74.4; 71.6; 71.4; 70.2; 67.1; 39.7; 26.8; 25.3; HR EI m/z, calcd for $C_{27}H_{41}O_{10}N_3$ $[M]^+$: 567.2792; found 567.2799.

3.8.3. (9*S*,10*S*)-9,10-Bis(benzyloxymethyl)-6,9,12,15-tetraoxa-3,18,24-triazabicyclo[18.3.1]tetracoza-1(23),20(24),21-triene-2,19-dione 19

Method A. Reaction time 2 days. Yield 40.2%. *Method B*. Yield 41.9%. White solid, $[\alpha]_D^{20}=+42.3$ ($c=1.97$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.95 (2H, bt, -NHCO-); 8.32 (2H, d, $J=7.5$); 7.97 (1H, t, $J=7.5$); 7.34–7.25 (10H, m); 4.49 (2H, d_{AB}, $J=12$); 4.44 (2H, d_{AB}, $J=12$); 3.85–3.79 (2H, m); 3.77–3.52 (20H, m); ^{13}C NMR (125 MHz, $CDCl_3$), δ 164.0; 148.9; 138.5; 138.0; 128.4; 127.7; 124.8; 78.5; 73.4; 70.8; 70.7; 70.6; 69.1; 39.8; HR LSIMS m/z, calcd for $C_{33}H_{41}O_8N_3Na$ $[M+Na]^+$: 630.2791; found 630.2795.

3.8.4. (9*R*,10*R*)-9,10-Bis((4R)-2,2-dimethyl-1,3-dioxalan-4-yl)-6,9,12,15-tetraoxa-3,18-diazabicyclo[18.3.1]tetracoza-1(23),20(24),21-triene-2,19-dione 21

Method A. Reaction time 26 days. Yield 24.0%. *Method B*. Yield 25.1%. Colorless crystals, mp 109–116°C, $[\alpha]_D^{20}=-28.5$ ($c=2.2$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.38 (1H, s); 8.21 (2H, dd, $J=7.5$, $J=1.5$); 7.62 (2H, bt, $J=5$, -NHCO-); 7.56 (1H, t, $J=7.5$); 4.25–4.20 (2H, m); 4.14 (2H, dd, $J=5.5$, $J=8.5$); 3.97–3.89 (6H, m); 3.80–3.74 (2H, m); 3.71–3.50 (14H, m); 1.41 (6H, s, -CH_3);

1.34 (6H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$), δ 166.3; 133.6; 131.8; 129.1; 123.2; 109.1; 80.46; 74.6; 72.4; 71.2; 70.5; 67.0; 39.8; 26.9; 25.4; HR LSIMS m/z, calcd for $C_{48}H_{42}O_{10}N_2Na$ $[M+Na]^+$: 589.2737; found 589.2744.

3.8.5. (9*S*,10*S*)-9,10-Bis(benzyloxymethyl)-6,9,12,15-tetraoxa-3,18-diazabicyclo[18.3.1]tetracoza-1(23),20(24),21-triene-2,19-dione 22. *Method A*. Reaction time 26 days. Yield 11.0%. *Method B*. Yield 28%. White solid, $[\alpha]_D^{20} = +33.4$ ($c=1.44$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.26 (1H, s); 8.18 (2H, dd, $J=1.5$, $J=7.5$); 7.54 (1H, t, $J=7.5$); 7.49 (2H, bt, -NHCO-); 7.33–7.25 (10H, m); 4.49 (2H, d_{AB}, $J=12$); 4.44 (2H, d_{AB}, $J=12$); 3.86–3.80 (2H, m); 3.79–3.70 (6H, m); 3.69–3.52 (14H, m); ^{13}C NMR (125 MHz, $CDCl_3$), δ 166.4; 137.8; 133.8; 131.8; 129.1; 128.4; 127.82; 127.78; 123.1; 78.3; 73.4; 70.8; 70.7; 70.6; 68.9; 39.9; HR LSIMS m/z, calcd for $C_{34}H_{42}O_8N_2Na$ $[M+Na]^+$: 629.2839; found 629.2835.

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