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TETRAHEDRON: *ASYMMETRY*

A simple synthesis of chiral macrocyclic tetraamides derived from α-amino acids

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Abstract—Bisamidation of oxalyl chloride using four L-α-amino acid esters afforded chiral diesters which were reacted with three α,ω-diamines under high-pressure conditions (10 kbar) to give macrocyclic tetramides of C_2-symmetry. © 2002 Published by Elsevier Science Ltd.

1. Introduction

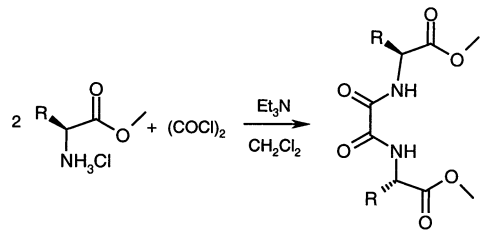
There is growing interest in the application of macrocyclic polyethers[1] and their polyaza analogues as ligands for transition metal catalysis,[2] and for their applications in molecular recognition[3] and biomedical techniques.[4] Among the latter class of molecules, special attention is given to polylactam systems, which are efficient neutral receptors for anions.[5] Although there are a great number of synthetic methods for the preparation of macrocyclic molecules, only a few chiral azamacrocyclic compounds have been reported.[6] Bearing in mind the great interest there is in asymmetric catalysis and chiral recognition, one important objective in this area is the improvement of existing procedures for the synthesis of chiral azaoxamacrocyclic compounds[7] in order to allow the efficient preparation of chiral azacoronands.

Our research team has investigated and developed the synthesis of diazacoronands based on the condensation of α,ω-diamines with dimethyl esters of dicarboxylic acids, which was introduced by Tabushi and co-workers,[8] and developed by us.[7b,c] Herein, we present the use of this method for the synthesis of a number of chiral tetraazacoronands using natural L-amino acids as the source of chirality; this is an extension of the synthetic approach reported by us previously.[9]

2. Results and discussion

We decided to use L-alanine, L-leucine, L-valine and L-phenylalanine as precursors of chiral diesters, which, after macrocyclisation with achiral diamines, should afford chiral C_2-symmetric azacoronands. To this end, we prepared the corresponding methyl ester hydrochlorides **1**, which were subsequently reacted with 0.5 equiv. of oxalyl chloride in the presence of triethylamine to afford diesters of the type **2** (Scheme 1).

Since the macrocyclisation reaction, carried out in neat methanol, did not proceed at room temperature or under reflux, the use of bis-amidation accelerators was necessary. The use of basic catalysts (DBU, NaCN) resulted in racemisation of the diesters **2**,[9] whereas the use of an acidic aminolysis catalyst (BBr_3)[10] gave no macrocyclic products. A solution to this problem was to carry out the reaction under high-pressure conditions, where the formation of macrocyclic products is preferred.



1a R=Me
1b R=Pr^i
1c R=Bu^i
1d R=Ph

2a R=Me
2b R=Pr^i
2c R=Bu^i
2d R=Ph

Scheme 1.

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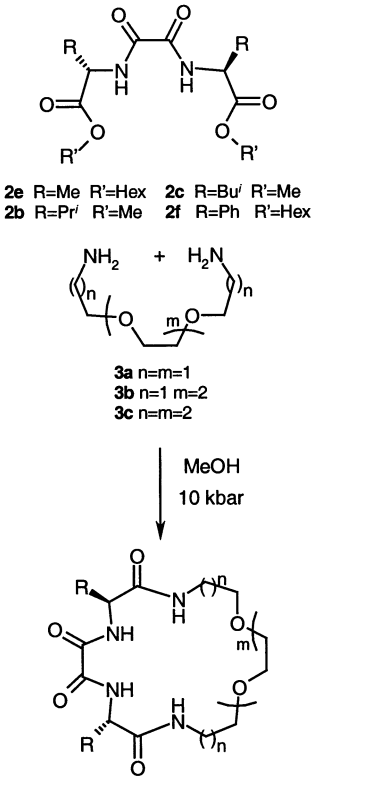
Since the methyl esters of L-alanine **2a** and L-phenylalanine **2d** are sparingly soluble in methanol, the use of other, more soluble, derivatives was necessary. In order to increase the solubility of the esters, we decided to replace the methyl group with the more lipophilic *n*-hexyl group. Two other esters, methyl L-leucinate **2c** and methyl L-valinate **2b** were sufficiently soluble in methanol. In this way we found the general conditions for the preparation of macrocyclic systems of the type **5–8**: diesters **2b**,**c**,**e** and **f** were dissolved, together with the appropriate amines **3**, in methanol (0.1 M concentration) and the reaction mixture was subjected to high-pressure treatment (Scheme 2). The results are shown in Table 1.

Some of the results obtained cannot be interpreted unequivocally. The yields of the tetraazacoronands decrease with increasing ring size. This relationship is typical for macrocyclization reactions. However, it is hard to explain the differences in yields for the reactions of various amino acid derivatives.

The lower yields from the macrocyclization reactions of diamines **3** with the L-alanine derivative **2e** can be explained by the presence of the hexyl diester. The hexyl esters are not very reactive in the aminolysis reaction, which must be preceded by transesterification with methanol (which is the reaction medium). The hypothesis regarding the unfavourable effect of the hexyl ester may be supported by the fact that the high-pressure reaction of the butyl diester occurs in 55% yield. The concentration of the reaction mixture is three times lower, so the results have to be compared carefully.

The side-chain methyl groups of L-valine are in the neighbourhood of the diester carbonyl groups, therefore they cause a high degree of steric overcrowding which may be responsible for the low yield in the macrocyclization reaction using the diester **2c**.



Scheme 2.

3. Conclusion

The results presented here demonstrate that chiral diesters of the type **2** can be obtained in good yields from the amino acid methyl or *n*-butyl ester hydrochlorides, or alternatively from the corresponding *n*-hexyl esters and oxalyl chloride. The chiral esters **2** can be successfully used for synthesis of tetraazacorronands **5–8** of C_2-symmetry through their high-pressure reaction with α,ω-diamines of the type **3**. The obtained chiral tetraamides, after reduction can then be used for the synthesis of more elaborate polyazamacrocyclic compounds.

4. Experimental

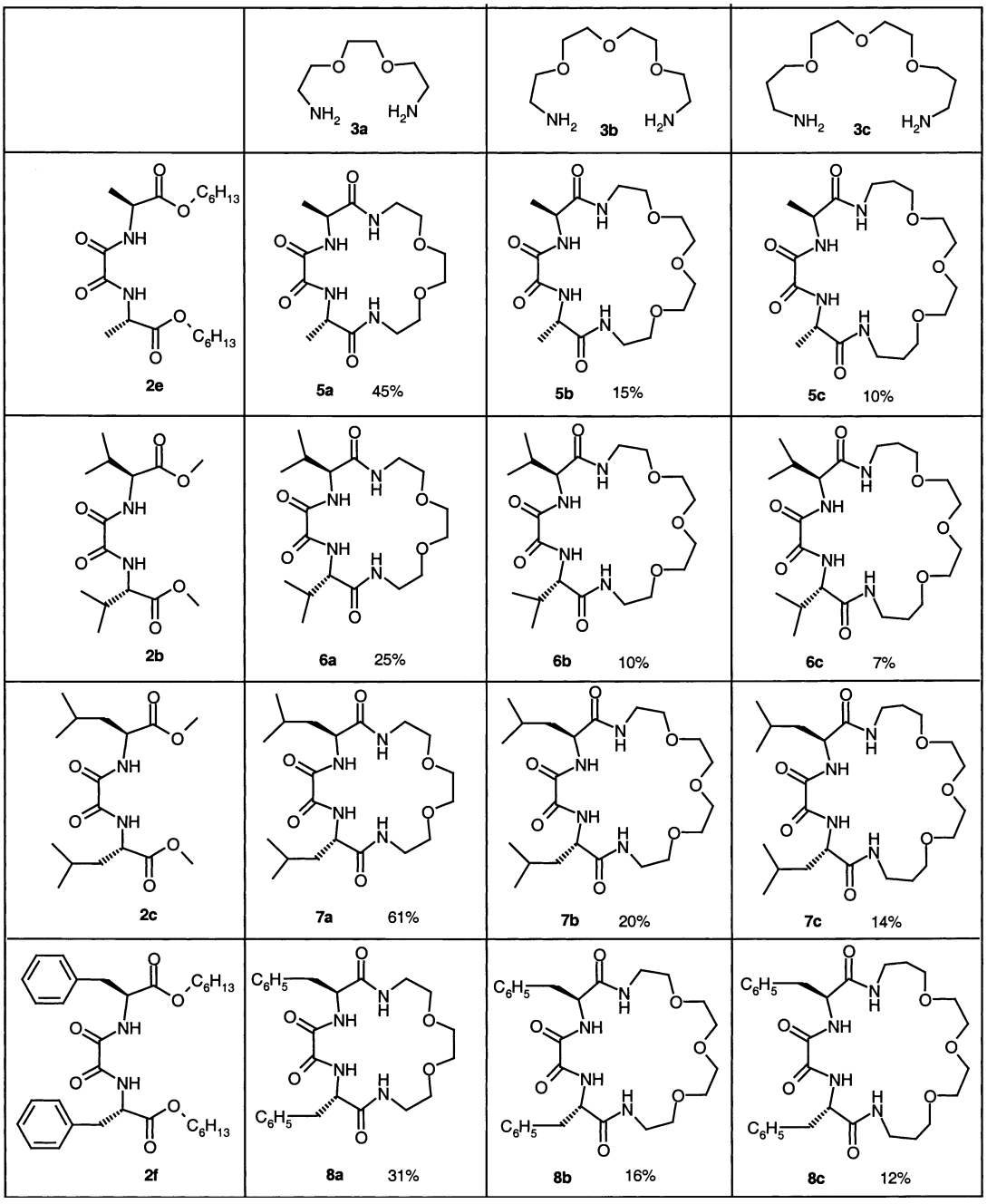
4.1. General methods

The optical rotation was measured using a JASCO DIP 360 apparatus, at sodium D line. The concentration and solvent used are given in parentheses. The ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 200BB (^{1}H at 200 MHz and ^{13}C at 50 MHz); or a Bruker AM 500 (^{1}H at 500 MHz and ^{13}C at 125 MHz). The actual apparatus used is indicated below by the measurement frequency. The mass spectral analysis was performed by the ESI-TOF technique on a Mariner mass spectrometer from Perseptive Biosystem or using LSIMS, EI technique on an AMD-604 Intectra instrument. The column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh), the thin-layer chromatography was carried out using Merck Kieselgel F_{254} plates. The high-pressure reactions were conducted under 10 kbar pressure using a custom-made cylinder–piston type apparatus.

4.2. General procedure for the preparation of the amino acid methyl ester hydrochlorides

A suspension of the amino acid (50 mmol) in methanol (100 ml) was cooled to 0°C. Thionyl chloride (55 mmol; 4 ml) was added dropwise, then the cooling bath was removed. The clear mixture was left at room temperature for 1 day. The solvent was then removed by rotary evaporation and the crude product was crystallised from methanol–diethyl ether (isopropanol–hexane, in the case of alanine methyl ester hydrochloride).

Table 1. Results of macrocyclization reaction of diamines **3a–c** with chiral diesters **2b**, **2c**, **2e** and **2f**



4.3. General procedure for the preparation of the amino acid butyl ester hydrochlorides

A suspension of the amino acid (50 mmol) in butanol (70 ml) was cooled to 0°C. Thionyl chloride (4 ml, 1.1 equiv.) was added dropwise, then the cooling bath was removed. The reaction mixture was left at room temperature for 24 h. The resulting product was purified by crystallisation from methanol–diethyl ether.

4.4. General procedure for the preparation of the amino acid hexyl esters

An amino acid (50 mmol), *p*-toluenesulphonic acid monohydrate (10.5 g, 1.1 equiv.) and hexanol (6.3 ml, 50 mmol) were placed into the reaction flask which was then equipped with the Dean–Stark trap containing 250 ml of toluene. The reaction mixture was heated until water ceased to collect in the trap. The reaction mixture

was washed with saturated aqueous Na_2CO_3 (2×25 ml), and water (25 ml). The toluene was then removed by rotary evaporation.

4.5. General procedure for preparation of diesters derived from amino acids and oxalyl chloride

Procedure 1 (preparation of the diesters from the corresponding amino acid ester hydrochlorides):

Triethylamine (7 ml, 50 mmol) was added dropwise to a suspension of the amino acid ester hydrochloride (25 mmol) in dry methylene chloride (200 ml). The mixture was cooled to −78°C. Oxalyl chloride (1.1 ml, 12.5 mmol) was added slowly drop by drop. Stirring was continued for 24 h at room temperature. The precipitate of triethylamine hydrochloride was filtered off, and the volume of the filtrate reduced to 100 ml by evaporation. This mixture was washed subsequently with water (2×20 ml), saturated aqueous ammonium chloride (3×20 ml), and water again (2×20 ml). The organic layer was dried over magnesium sulphate, then the volatiles were removed by rotary evaporation. Finally, the product was purified by crystallisation from boiling methanol.

Procedure 2 (preparation of the diesters from the corresponding amino acid hexyl esters):

The amino acid hexyl ester (25 mmol) was dissolved in methylene chloride (200 ml). Subsequently, triethylamine (3.5 ml, 1 equiv.) was added and the mixture was cooled to −78°C. Then oxalyl chloride (1.1 ml, 12.5 mmol) was added slowly drop by drop, followed by stirring for 24 h. The work-up was identical as in **Procedure 1** above.

4.5.1. Dimethyl (2*S*,7*S*)-3,6-diaza-4,5-dioxo-2,7-dimethyloctano-1,8-dicarboxylate, 2a. Prepared using **Procedure 1**. Recrystallisation from methanol yielded **2a** as white crystals (yield 72%). Mp 157.8–158.2°C; $[\alpha]_D^{20}=-82$ (*c* 2.9, DMSO); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=7.87$ (d, 1H, N*H*), 4.59 (dq, 1H, C*H*CO_2), 3.77 (s, 3H, OCH_3), 1.48 (d, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta=$ 171.9, 158.7, 52.6, 48.3, 17.9; HR LSIMS calcd for $C_{10}H_{17}N_2O_6$ $[M+H]^+$: 261,1086, found: 261,1079.

4.5.2. Dimethyl (2*S*,7*S*)-3,6-diaza-4,5-dioxo-2,7-diisopropyloctano-1,8-dicarboxylate, 2b. Prepared using **Procedure 1**. Recrystallisation from methanol yielded **2b** as white crystals (yield 70%). Mp 98.2–99.1°C; $[\alpha]_D^{20}=-53$ (*c* 2, DMSO); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=7.78$ (d, 1H, $J=9.4$ Hz; N*H*), 4.49 (dd, 1H, $J_1=9.4$ Hz, $J_2=5.2$ Hz; C*H*CO_2), 3.77 (s, 3H, OCH_3), 2.25 (m, 1H, C*H*$(CH_3)_2$), 0.98 (d, 3H, $J=6.9$ Hz; C$H_3$$(CH_3)$CH), 0.95 (d, 3H, $J=6.9$ Hz; C$H_3$$(CH_3)$CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 171.0, 159.2, 57.8, 52.36, 31.3, 18.9, 17.7; HR ESI (CH_3OH) calcd for $C_{14}H_{24}N_2NaO_6$ $[M+Na]^+$: 339,1527 found: 339,1543.

4.5.3. Dimethyl (2*S*,7*S*)-3,6-diaza-4,5-dioxo-2,7-diisobutyloctano-1,8-dicarboxylate, 2c. Prepared using **Procedure 1**. Recrystallisation from methanol yielded **2c** as white crystals (yield 75%). Mp 115.2–116.4°C; $[\alpha]_D^{20}=$ −61 (*c* 3.7, DMSO); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=$ 7.92 (d, 1H, $J=9.0$ Hz; N*H*), 4.57 (m, 1H, C*H*CO_2), 3.7 (s, 3H, OCH_3), 1.55–1.70 (m, 3H, CH_2CHCO_2, C*H*$(CH_3)_2$), 0.9 (d, 6H, $J=6.0$ Hz; $(CH_3)_2$CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 171.7, 158.9, 52.2, 50.9, 40.9, 24.5, 22.6, 21.5; HR EI calcd for $C_{16}H_{28}N_2O_6$: 344,1947 found: 344,1975.

4.5.4. Dimethyl (2*S*,7*S*)-3,6-diaza-4,5-dioxo-2,7-dibenzyloctano-1,8-dicarboxylate, 2d. Prepared using **Procedure 1**. Recrystallisation from methanol yielded **2d** as white crystals (yield 61%). Mp 191.5–192.3°C; $[\alpha]_D^{20}=-43$ (*c* 3, DMSO); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=7.7$ (d, 1H, $J=8.5$ Hz; N*H*), 7.28 (m, 3H, Ph), 7.1 (m, 2H, Ph), 4.8 (dt, 1H, $J_1=8.5$ Hz, $J_2=6.3$ Hz; C*H*CO_2), 3.7 (s, 3H, OCH_3), 3.15 (m, 2H, C*H*Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 170.5, 158.5, 135.2, 129.1, 128.7, 127.3, 53.5, 52.5, 37.9; HR LSIMS calcd for $C_{22}H_{25}N_2O_6$ $[M+H]^+$: 413,1712 found: 413,1726.

4.5.5. Dibutyl (2*S*,7*S*)-3,6-diaza-4,5-dioxo-2,7-dimethyloctano-1,8-dicarboxylate, 2g. Prepared using **Procedure 1**. Recrystallisation from methanol yielded **2g** as white crystals (yield 58%). Mp 105.3–106.2°C; $[\alpha]_D^{20}=-58$ (*c* 2, DMSO); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=7.89$ (d, 1H, $J=7.9$ Hz; N*H*), 4.56 (dq, 1H, $J_1=7.9$ Hz, $J_2=7.2$ Hz; C*H*CO_2), 4.16 (t, 2H, $J=6.5$ Hz; OCH_2), 1.647 (m, 2H, CH_2CH_2O), 1.47 (d, 3H, $J=7.2$ Hz; CH_3CH), 1.36 (m, 2H, CH_3CH_2), 0.97 (t, 3H, $J=7.2$ Hz; CH_3CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 171.5, 158.7, 65.53, 48.4, 30.4, 18.9, 18.0, 13.6; HR ESI (CH_3OH) calcd for $C_{16}H_{28}N_2NaO_6$ $[M+Na]^+$: 367.1840 found: 367.1861.

4.5.6. Dibutyl (2*S*,7S)-3,6-diaza-4,5-dioxo-2,7-dibenzyloctano-1,8-dicarboxylate, 2h. Prepared using **Procedure 1**. Recrystallisation from methanol yielded **2h** as white crystals (yield 55%). Mp 132.7–133.6°C; $[\alpha]_D^{20}=59$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=7.65$ (d, 1H, $J=8.6$ Hz; N*H*), 7.2 (m, 3H, Ph), 7.05 (m, 2H, Ph), 4.71 (dt 1H, $J_1=8.6$ Hz, $J_2=6.4$ Hz; C*H*CO_2), 4.02 (t, 2H, $J=6.6$ Hz; OCH_2), 3.05 (m, 2H, CH_2Ph), 1.5 (m, 2H, CH_2CH_2O), 1.25 (m, 2H, CH_2CH_3), 0.85 (t, 3H, $J=7.2$ Hz; CH_3CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 170.1, 158.5, 135.5, 129.5, 128.6, 127.2, 65.5, 53.6, 38.0, 19.0, 13.6; HR ESI (CH_3OH) calcd for $C_{28}H_{36}N_2NaO_6$ $[M+Na]^+$: 519.2466 found: 519.2492.

4.5.7. Dihexyl (2*S*,7*S*)-3,6-diaza-4,5-dioxo-2,7-dimethyloctano-1,8-dicarboxylate, 2e. Prepared using **Procedure 2**. Recrystallisation from methanol yielded **2e** as white crystals (yield 56%). Mp 97–99°C; $[\alpha]_D^{20}=-51$ (*c* 2, DMSO); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=7.94$ (d, 1H, $J=7.8$ Hz; N*H*), 4.55 (dq, 1H, $J_1=7.8$ Hz, $J_2=7.2$ Hz; C*H*CO_2), 4.14 (t, 2H, $J=6.7$ Hz; OCH_2), 1.65 (m, 2H, CH_2CH_2O), 1.47 (d, 3H, $J=7.2$ Hz; CH_3CH), 1.30 (m, 6H, CH_2), 0.9 (t, 3H, $J=6.3$ Hz; CH_3CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 171.5, 158.6, 65.7, 48.4, 31.2, 28.3, 25.3, 22.3, 17.9, 13.8; HR ESI (CH_3OH) calcd for $C_{20}H_{36}N_2NaO_6$ $[M+Na]^+$: 423.2466 found: 423.2482.

4.5.8. Dihexyl (2*S*,7*S*)-3,6-diaza-4,5-dioxo-2,7-dibenzyl-octano-1,8-dicarboxylate, 2f. Prepared using **Procedure 2**. Recrystallisation from methanol yielded **2f** as white crystals (yield 54%). Mp 90.5–92°C; $[\alpha]_D^{20}=45$ (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) $\delta=7.73$ (d, 1H, $J=8.6$ Hz; N*H*), 7.26 (m, 3H, Ph), 7.13 (m, 2H, Ph), 4.8 (dt, 1H, $J_1=8.6$ Hz, $J_2=6.2$ Hz; C*H*CO_2), 4.08 (t, 2H, $J=6.8$ Hz; OCH_2), 3.13 (m, 2H, CH_2Ph), 1.56 (m, 2H, CH_2CH_2O), 1.25 (m, 6H, CH_2), 0.88 (t, 3H, $J=6.2$ Hz; CH_3CH2); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 170.2, 158.6, 135.3, 129.2, 128.6, 127.2, 65.9, 53.7, 38.1, 31.3, 28.3, 25.4, 22.4, 13.9; HR ESI (CH_3OH) calcd for $C_{32}H_{44}N_2NaO_6$ $[M+Na]^+$: 575.3092 found: 575.3105.

4.6. The synthesis of tetraazacoronands

The appropriate diester (0.5 mmol) was placed in a thin-walled Teflon vessel, followed by the diamine (0.5 mmol) and methanol (up to 5 ml). The vessel was placed in a high-pressure chamber under a pressure of 10 kbar. The reaction was allowed to run for 24 h. Then the solvent was evaporated from the reaction mixture and the residue was purified by column chromatography using silica gel in a gel:mixture ratio of 60:1, and using CH_2Cl_2:MeOH 100:4 as an eluent.

4.6.1. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-dimethyl-13,16-dioxa-2,5,6,9-cyclooctadekatetraone, 5a. Compound **5a** was prepared using the hexyl diester **2e** and the diamine **3a** at 50°C. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **5a** as a white solid in 45% yield. Mp decomposition at 293°C; $[\alpha]_D^{20}=-121$ (*c* 0.75, H_2O); ^1H NMR (200 MHz, DMSO) $\delta=9.03$ (d, 1H, $J=8.1$ Hz; NHCH), 7.36 (bs, 1H, N*H*CH_2), 4.24 (dq, 1H, $J_1=8.1$ Hz, $J_2=7.2$ Hz; C*H*CO), 2.90–3.5 (m, 6H, OCH_2CH_2O, NCH_2CH_2O, NCH_2CH_2O), 1.30 (d, 3H, $J=7.3$ Hz CH_3CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 171.3, 159.3, 70.1, 69.1, 49.7, 17.1; HR ESI (CH_3OH) calcd for $C_{14}H_{24}N_4NaO_6$ $[M+Na]^+$: 367.1588, found: 367.1568.

4.6.2. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-dimethyl-13,16,19-trioxa-2,5,6,9-cyclohenicosatetraone, 5b. Compound **5b** was prepared using the hexyl diester **2e** and the diamine **3b** at 50°C. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH gave **5b** as a white solid in 15% yield. Mp decomposition at 260°C; $[\alpha]_D^{20}=-72$ (*c* 0.5, H_2O); ^1H NMR (200 MHz, DMSO) $\delta=8.77$ (d, 1H, $J=8.6$ Hz; N*H*CH), 7.77 (t, 1H, $J=5.6$ Hz; NHCH_2), 4.32 (dq 1H, $J_1=8.6$ Hz, $J_2=7.2$ Hz; C*H*CO), 3.15–3.60 (m, 8H, NCH_2CH_2O, OCH_2CH_2O), 1.28 (d, 3H, $J=7.2$ Hz; CH_3CH); ^{13}C NMR (50 MHz, DMSO) δ (ppm): 171.3, 158.9, 70, 69.7, 69.0, 49.2, 17.8; HR ESI (CH_3OH) calcd for $C_{16}H_{28}N_4NaO_7$ $[M+Na]^+$: 411.1850, found: 411.1915.

4.6.3. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-dimethyl-14,17,20-trioxa-2,5,6,9-cyclotricosatetraone, 5c. Compound **5c** was prepared using the hexyl diester **2e** and the diamine **3c** at 50°C. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **5c** as a white solid in 10% yield. Mp 212–214°C; $[\alpha]_D^{20}=-30$ (*c* 0.5, H_2O); ^1H NMR (200 MHz, DMSO) $\delta=8.7$ (d, 1H, $J=8.1$ Hz; N*H*CH), 7.73 (t, 1H, $J=5.3$ Hz; N*H*CH_2), 4.25 (dq 1H, $J_1=8.1$ Hz, $J_2=7.0$ Hz; C*H*CO), 3.10–3.50 (m, 8H, NCH_2CH_2CH_2O, OCH_2CH_2O), 1.62 (m, 2H, CH_2CH_2CH$_2$), 1.27 (d, 3H, $J=7.0$ Hz; CH_3CH); ^{13}C NMR (200 MHz, DMSO) δ (ppm): 171.1, 159.2, 69.6, 69.4, 67.8, 49.1, 35.9, 28.8, 17.6; HR ESI (CH_3OH) calcd for $C_{18}H_{32}N_4NaO_7$ $[M+Na]^+$: 439.2163, found: 439.2145.

4.6.4. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-diisopropyl-13,16-dioxa-2,5,6,9-cyclooctadekatetraone, 6a. Compound **6a** was prepared using the methyl diester **2b** and the diamine **3a**. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **6a** as a white solid in 25% yield. Mp decomposition at 309°C; $[\alpha]_D^{20}=-93$ (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) $\delta=7.64$ (d, 1H, $J=9.0$ Hz; N*H*CH), 6.76 (bs, 1H, N*H*CH_2), 4.33 (dd, 1H, $J_1=9.1$ Hz, $J_2=4.4$ Hz; C*H*CO), 3.4–3.57 (m, 6H, NCH_2CH_2O, OCH_2CH_2O), 2.6 (m, 1H, C*H*$(CH_3)_2$), 1.01 (d, 3H, $J=6.9$ Hz; C$H_3$$(CH_3)$CH), 0.95 (d, 3H, $J=6.9$ Hz; C$H_3$$(CH_3)$CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.4, 159.9, 70.6, 69.9, 59.2, 39.3, 28.8, 19.6, 16.7; HR ESI (CH_3OH) calcd for $C_{18}H_{32}N_4NaO_6$ $[M+Na]^+$: 423.2214, found: 423.2200.

4.6.5. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-diisopropyl-13,16,19-trioxa-2,5,6,9-cyclohenicosatetraone, 6b. Compound **6b** was prepared using the methyl diester **2b** and the diamine **3b**. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **6b** as a white solid in 10% yield. $[\alpha]_D^{20}=-108$ (*c* 0.25, $CHCl_3$); ^1H NMR (500 MHz, DMSO) $\delta=8.42$ (d, 1H, $J=9.8$ Hz; N*H*CH), 8.10 (t, 1H, $J=5.4$ Hz; N*H*CH_2), 4.05 (dd, 1H, $J_1=9.7$ Hz, $J_2=8.2$ Hz; C*H*CO), 3.20–3.50 (m, 8H, NCH_2CH_2O, OCH_2CH_2O), 2.05 (m, 1H, C*H*$(CH_3)_2$), 0.86 (d, 3H, $J=6.8$ Hz; C$H_3$$(CH_3)$CH), 0.84 (d, 3H, $J=6.8$ Hz; C$H_3$$(CH_3)$CH); ^{13}C NMR (125 MHz DMSO) δ (ppm): 170.0, 159.0, 69.8, 69.8, 68.7, 59.4, 39.5, 30.2, 19.0, 18.5; HR ESI (CH_3OH) calcd for $C_{20}H_{36}N_4NaO_7$ $[M+Na]^+$: 467.2476, found: 467.2496.

4.6.6. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-diisopropyl-14,17,20-trioxa-2,5,6,9-cyclotricosatetraone, 6c. Compound **6c** was prepared using the methyl diester **2b** and the diamine **3c**. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **6c** as white solid in 7% yield. $[\alpha]_D^{20}=-27$ (*c* 0.45, $CHCl_3$); ^1H NMR (200 MHz DMSO) $\delta=8.37$ (d, 1H, $J=9.3$ Hz; N*H*CH), 8.05 (t, 1H, $J=4.8$ Hz; N*H*CH_2), 4.00 (dd, 1H, $J_1=9.1$ Hz, $J_2=8.1$ Hz; C*H*CO), 3.20–3.50 (m, 8H, NCH_2CH$_2$CH_2O, OCH_2CH_2O), 2.10 (m, 1H, C*H*$(CH_3)_2$), 1.61 (m, 2H, NCH$_2$CH_2CH$_2$), 0.87 (d, 3H, $J=6.8$ Hz; C$H_3$$(CH_3)$CH), 0.83(d, 3H, $J=6.8$ Hz; C$H_3$$(CH_3)$CH); ^{13}C NMR (125 MHz DMSO) δ (ppm): 169.9, 159.2, 69.6, 69.4, 67.5, 59.4, 35.4, 30.0, 28.8, 19.1, 18.6; HR ESI (CH_3OH) calcd for $C_{22}H_{40}N_4NaO_7$ $[M+Na]^+$: 495.2789, found: 495.2828.

4.6.7. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-diisobutyl-13,16-dioxa-2,5,6,9-cyclooctadekatetraone, 7a. Compound **7a** was prepared using the methyl diester **2c** and the diamine **3a**. Purification by silica gel column chro-

matography with CH_2Cl_2 and MeOH (100:4) gave **7a** as a white solid in 65% yield. Mp decomposition at 290°C; $[\alpha]_D^{20}=-91$ (*c* 1.3, MeOH); ^{1}H NMR (200 MHz $CDCl_3$) $\delta=7.75$ (d, 1H, $J=8.6$ Hz; N*H*CH), 6.84 (bs, 1H, N*H*CH_2), 4.5 (m, 1H, C*H*CO), 3.56 (s, 2H, OCH_2CH_2O), 3.40–3.60 (m, 4H, NCH_2CH_2O), 1.99 (m, 1H, C*H*$(CH_3)_2$) 1.68 (m, 2H, CH_2CHCO), 0.98 (d, 3H, $J=6.2$ Hz; CH_3), 0.95 (d, 3H, $J=6.2$ Hz; CH_3); ^{13}C NMR (50 MHz $CDCl_3$) δ (ppm): 170.5, 159.6, 70.4, 69.5, 52.3, 39.7, 39.5, 24.75, 23.0, 22.0; HR LSIMS calcd for $C_{20}H_{37}N_4O_6$ [M+H]$^+$: 429.2713, found: 429.2727.

4.6.8. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-diisobutyl-13,16,19-trioxa-2,5,6,9-cyclohenicosatetraone, 7b. Compound **7b** was prepared using the methyl diester **2c** and the diamine **3b**. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **7b** as white solid in 20% yield. Mp 225–227°C; $[\alpha]_D^{20}=-79$ (*c* 0.66, DMSO); ^{1}H NMR (200 MHz $CDCl_3$) $\delta=7.85$ (d, 1H, $J=8.9$ Hz; N*H*CH), 6.95 (bs, 1H, N*H*CH_2), 4.5 (m, 1H, C*H*CO), 3.30–3.70 (m, 8H, NCH_2CH_2O, OCH_2CH_2O), 1.8–2.0 (m, 1H, C*H*$(CH_3)_2$) 1.5–1.80 (m, 2H, C*H*$(CH_3)_2$) 0.98 (d, 3H, $J=6.0$ Hz; CH_3), 0.94 (d, 3H, $J=6.0$ Hz; CH_3); ^{13}C NMR (50 MHz $CDCl_3$) δ (ppm): 170.7, 159.5, 70.5, 70.1, 69.6, 52.3, 40.2, 39.4, 24.7, 22.9, 21.7; HR EI calcd for $C_{22}H_{40}N_4O_7$: 472.2897, found: 472.2886.

4.6.9. (3*S*,8S)-1,4,7,10-Tetraaza-3,8-diisobutyl-14,17,20-trioxa-2,5,6,9-cyclotricosatetraone, 7c. Compound **7c** was prepared using the methyl diester **2c** and the diamine **3c**. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **7c** as white solid in 14% yield. Mp 208–210°C; $[\alpha]_D^{20}=-58$ (*c* 0.66, DMSO); ^{1}H NMR (200 MHz $CDCl_3$) $\delta=7.6$ (d, 1H, $J=9.3$ Hz; N*H*CH), 7.10 (bs, 1H, N*H*CH_2), 4.40 (m, 1H, C*H*CO), 3.20–3.70 (m, 8H, $CH_2CH_2CH_2$, OCH_2CH_2O), 1.50–1.90 (m, 5H, $CH_2CH_2CH_2$, CH_2CHCO, C*H*$(CH_3)_2$), 0.95 (d, 3H, $J=6.2$ Hz; CH_3), 0.92 (d, 3H, $J=6.2$ Hz; CH_3); ^{13}C NMR (50 MHz $CDCl_3$) δ (ppm): 170.2, 159.4, 70.4, 69.1, 52.5, 40.9, 38.6, 28.3, 24.8, 22.9, 21.7; HR EI calcd for $C_{24}H_{44}N_4O_7$: 500.3210, found: 500.3165.

4.6.10. (3*S*,8S)-1,4,7,10-Tetraaza-3,8-dibenzyl-13,16-dioxa-2,5,6,9-cyclooctadekatetraone, 8a. Compound **8a** was prepared using the hexyl diester **2f** and the diamine **3a** at 50°C. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **8a** as white solid in 31% yield. Mp decomposition at 300°C; $[\alpha]_D^{20}=-120$ (*c* 0.25, DMSO); ^{1}H NMR (200 MHz DMSO) $\delta=9.00$ (d, 1H, $J=9.3$ Hz; N*H*CH), 7.5 (bs, 1H, N*H*CH_2), 7.10–7.30 (m, 5H, Ph), 4.40 (dt, 1H, $J_1=9.3$ Hz, $J_2=4.7$ Hz; C*H*CO), 3.30–3.60 (m, 6H, NCH_2CH_2O, OCH_2CH_2O), 3.1 (m, 2H, CH_2Ph); ^{13}C NMR (125 MHz DMSO) δ (ppm): 170.6, 159.7, 138.1, 129.2, 128.8, 126.9, 70.5, 69.5, 56.0, 49.0, 36.8; HR ESI (CH_3OH) calcd for $C_{26}H_{32}N_4NaO_6$ [M+Na]$^+$: 519.2214, found: 519.2232.

4.6.11. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-dibenzyl-13,16,19-trioxa-2,5,6,9-cyclohenicosatetraone, 8b. Compound **8b** was prepared using the hexyl diester **2f** and the diamine **3b** at 50°C. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **8b** as a white solid in 16% yield. $[\alpha]_D^{20}=-60$ (*c* 0.45, $CHCl_3$); ^{1}H NMR (200 MHz DMSO) $\delta=8.77$ (d, 1H, $J=9.3$ Hz; N*H*CH), 7.90 (t, 1H, $J=5.3$ Hz; N*H*CH_2), 7.10–7.30 (m, 5H, Ph), 4.50 (m, 1H, C*H*CO), 3.20–3.70 (m, 8H, NCH_2CH_2O, OCH_2CH_2O), 3.02 (m, 2H, C*H*Ph); ^{13}C NMR (50 MHz DMSO) δ (ppm): 170.1, 159.2, 137.4, 128.8, 126.3 69.9, 69.8, 69.7, 54.9, 37.0; HR ESI (CH_3OH) calcd for $C_{28}H_{36}N_4NaO_7$ [M+Na]$^+$: 563.2476, found: 563.2492.

4.6.12. (3*S*,8*S*)-1,4,7,10-Tetraaza-3,8-dibenzyl-14,17,20-trioxa-2,5,6,9-cyclotricosatetraone, 8c. Compound **8c** was prepared using the hexyl diester **2f** and the diamine **3c** at 50°C. Purification by silica gel column chromatography with CH_2Cl_2 and MeOH (100:4) gave **8c** as white solid in 12% yield. $[\alpha]_D^{20}=-11$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (200 MHz DMSO) $\delta=8.77$ (d, 1H, $J=9.3$ Hz; N*H*CH), 7.90 (t, 1H, $J=5.4$ Hz; N*H*CH_2), 7.10–7.30 (m, 5H, Ph), 4.50 (m, 1H, C*H*CO), 3.20–3.50 (m, 8H, $CH_2CH_2CH_2$, OCH_2CH_2O), 3.05 (m, 2H, CH_2Ph), 1.62 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (50 MHz DMSO) δ (ppm): 169.8, 159.1, 128.9, 128.1, 126.3, 69.5, 69.4, 67.7, 54.8, 35.7, 35.8, 28.8; HR ESI (CH_3OH) calcd for $C_{30}H_{40}N_4NaO_7$ [M+Na]$^+$: 591.2789, found: 591.2793.

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