Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 487–495

TETRAHEDRON: *ASYMMETRY*

The synthesis of L-proline derived hexaazamacrocyclic ligands of C_3 symmetry via intramolecular methyl ester aminolysis†

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Received 12 January 2001; accepted 9 February 2001

Abstract—A convenient synthesis of enantiomerically pure 18-, 21-, and 24-membered hexaaza-crown ligands is presented. Linear α,ω-aminoesters, prepared from L-proline, undergo intramolecular aminolysis to afford the corresponding 18-, 21-, and 24-membered macrocyclic amides in satisfactory yields (42, 65, and 22%, respectively). These were subsequently transformed into the title macrocyclic hexamines via exhaustive reduction with a borane–dimethylsulfide complex. X-Ray structures of two larger macrocyclic amides are also presented.

1. Introduction

Tetraazamacrocyclic compounds, such as cyclam (1,4,8,11-tetraazacyclotetradecane) and its derivatives, have been the subject of much interest mainly due to their ability to bind transition metal ions.[1] Their chiral derivatives have also been synthesised and investigated.[2] Peraza-crown macrocycles with larger cavities and higher numbers of donor nitrogen atoms are capable of accommodating more than one metal centre, giving rise to the possibility of polynuclear macrocyclic complex formation.[3] Although larger macrocycles, possessing more than four in-ring nitrogen atoms, seem to be equally interesting as ligands for transition metal cations, they have attracted much less attention than their smaller homologues.[3–7] Among several reports on unsubstituted hexadentate perazamacrocyclic ligands and their metal complexes, i.e. [18]aneN_6 (1,4,7,10,13,16-hexaazacyclooctadecane),[3b–d,4] [20]aneN_6 (1,4,7,11,14,17-hexaazacycloicosane),[3d,4a] [21]aneN_6 (1,4,8,11,15,18-hexaazacyclohenicosane)[5] and [24]aneN_6 (1,5,9,13,17,21-hexaazacyclotetracosane),[3a] there are only few chiral systems. To our best knowledge, the only chiral hexaazamacrocycles reported to date are [18]aneN_6,[5] and two [22]aneN_6 based compounds[6]—all are synthesised from enantiomerically pure (*R*,*R*)-cyclohexane-1,2-diamine, as well as functionalised [18]aneN_6 obtained from L-serine derived cyclic sulfamidate.[7]

We recently presented a convenient methodology for the synthesis of L-proline derived C_2-symmetric tetraazamacrocyclic compounds via intramolecular methyl ester aminolysis reactions.[2g] Prompted by these encouraging findings, we have investigated the possibility of extending this approach to their C_3-symmetric hexaaza analogues. Herein, we present the results of these studies that led to the synthesis of chiral [18]aneN_6, [21]aneN_6, as well as [24]aneN_6, perazamacrocycles.

2. Results and discussion

Starting materials (**1a–c** and **2a–c**) were synthesised according to procedures given in our previous paper.[2g] *N*-Cbz-Protected aminoesters **3a–c** were obtained in good yields (83–90%) by means of condensation of an appropriate carboxylic acid derivative (**1a–c**) with an amino compound (**2a–c**) using *iso*-butylchloroformate as a dehydrating agent (Scheme 1). In the next step, compounds **3a–c** were quantitatively *N*-deprotected under standard conditions (H_2/Pd–C, methanol) to afford the corresponding aminoesters **4a–c**, which were used as substrates for the subsequent macrocyclisation reaction step. According to our previous investigations,[2g] we anticipated that methyl ester aminolysis with **4a–c** in the absence of a catalyst would not be possible. Several experiments proved this to be the case. Indeed,

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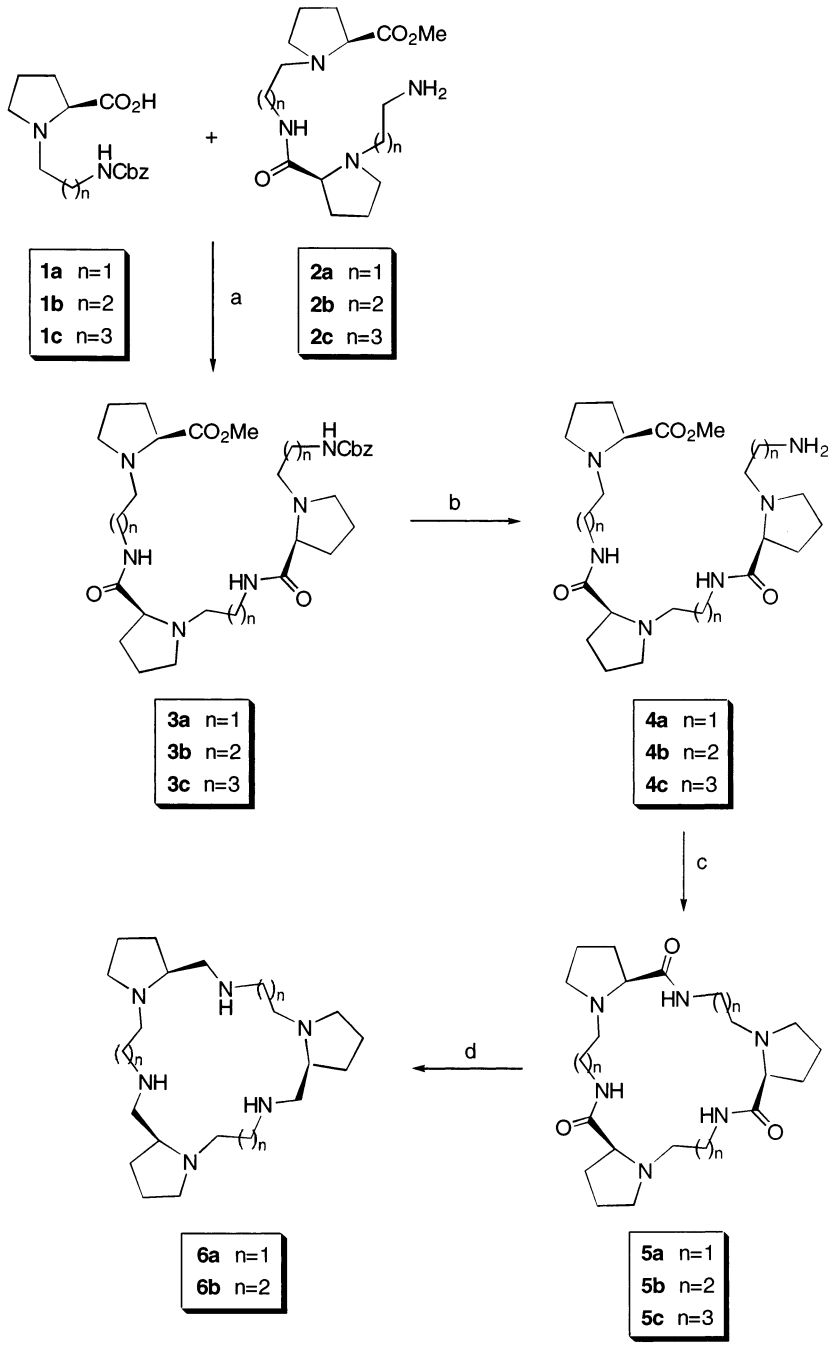
† Part III of the series 'Chiral perazamacrocycles'; Part I, see: Ref. 2f; Part II, see: Ref. 2g.

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00068-4



Scheme 1. (a) ^{i}BuOCOCl, Et_3N, CH_2Cl_2, −20→0°C; (b) H_2, Pd–C, MeOH; (c) 10 *or* 16 kbar, MeOH, 50°C; *or* NaOMe, MeOH, rt; *or* NaOH, MeOH, rt; (d) $BH_3{\cdot}Me_2S$, THF, reflux.

aminoesters **4a**–**c** did not react either intra- or intermolecularly when dissolved in a number of common solvents, even at elevated temperatures. The only exception was DMF, which upon heating reacted with the primary amine groups, affording *N*-formyl derivatives. Polar protic solvents, such as methanol, have been suggested to play a crucial role in the formation of a hydrogen-bonded, pre-organised structure, which, in turn, promotes *intra*molecular ring closure over *inter*molecular reaction between a methyl ester and a primary amino group.[8] Since both these functional groups were present in substrates **4a**–**c**, we anticipated similar behaviour in methanol. The only drawback was the low reactivity of the amino group towards the methyl ester carbonyl function, which had to be improved.

As previously demonstrated,[2g] this low reactivity can be circumvented either by means of basic catalysis or by use of high pressure reaction conditions. Investigations into the use of sodium methoxide in methanol as a basic catalyst in the macrocyclisation of **4a**–**c** led to the formation of the corresponding triamides **5a**–**c** in good yields of 42–65% (Table 1, entries 1–3). Unfortunately, under such conditions, the desired (*S*,*S*,*S*)-**5b** (65% yield; Table 1, entry 2) was accompanied by its (*R*,*S*,*S*)-epimer formed in 5% yield and, in the case of

Table 1. Intramolecular ester aminolysis (**4**→**5**): yields of the triamides **5a**–**c** under various macrocyclisation conditions

Entry	Triamide	Yield (%)	Reaction conditions	Reaction time (days)
1	**5a**	42[a]	$NaOCH_3$, CH_3OH, rt	30
2	**5b**	65[b]	$NaOCH_3$, CH_3OH, rt	30
3	**5c**	60[c]	$NaOCH_3$, CH_3OH, rt	30
4	**5a**	15	NaOH, CH_3OH, rt	7
5	**5b**	15	NaOH, CH_3OH, rt	7
6	**5c**	13	NaOH, CH_3OH, rt	7
7	**5a**	25[d]	10 kbar, CH_3OH, 50°C	7
8	**5a**	23[e]	10 kbar, CH_3OH, 50°C[f]	7
9	**5b**	22	10 kbar, CH_3OH, 50°C	7
10	**5b**	29	10 kbar, CH_3OH, 50°C	14
11	**5c**	22	10 kbar, CH_3OH, 50°C	7
12	**5a**	22[g]	16 kbar, CH_3OH, 50°C	7
13	**5b**	25[h]	16 kbar, CH_3OH, 50°C	7
14	**5c**	13[i]	16 kbar, CH_3OH, 50°C	7
15	**5b**	39	Bu_4NOH, CH_3OH, rt	30
16	**5b**	36[j]	DBU, CH_3OH, rt	90

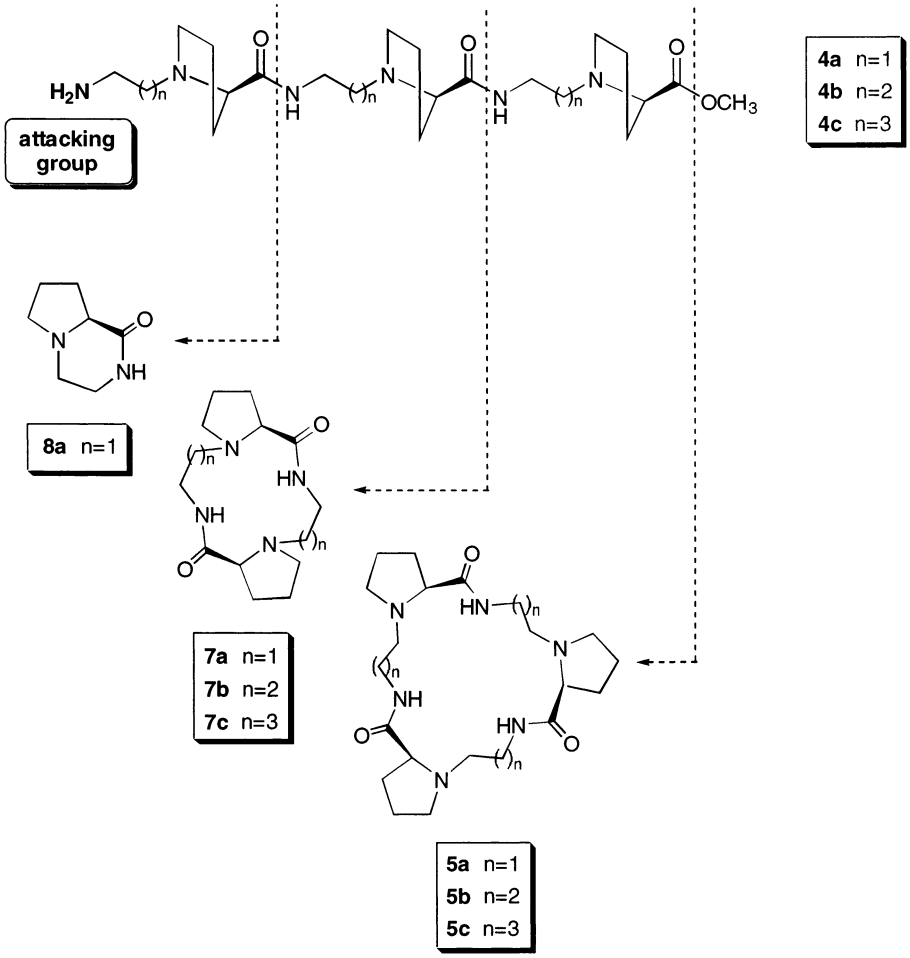
[a] Separated from the mixture of **5a**:**8a** (1:1.2).
[b] (*R*,*S*,*S*)-**5b** (5% yield) was separated from the main (*S*,*S*,*S*)-**5b** diastereoisomer.
[c] Inseparable mixture of diastereoisomers.
[d] Separated from the mixture of **5a**:**8a** (1:3.8).
[e] Separated from the mixture of **5a**:**7a**:**8a** (1.1:1:5.6).
[f] *iso*-Propyl ester was used instead of the methyl ester **4a**.
[g] Separated from the mixture of **5a**:**7a**:**8a** (1.8:1:8).
[h] Separated from the mixture of **5b**:**7b** (3.1:1).
[i] Separated from the mixture of **5c**:**7c** (1:1).
[j] (*R*,*S*,*S*)-**5b** (6% yield) was separated from the main (*S*,*S*,*S*)-**5b** isomer.

aminoester **5c**, the reaction led to a complex mixture of chromatographically inseparable diastereoisomers (60% overall yield; Table 1, entry 3). In the case of the macrocyclic triamide **5a** (42% yield; Table 1, entry 1), no epimerisation product was detected, but the yield of the macrocycle **5a** was lower compared to the larger trilactams **5b** and **5c**. The lowered yield of **5a** was associated with the formation of the bicyclic lactam **8a** (Table 1, footnote a)—a product of a competitive transamidation process involving attack by the amino group on the amide carbonyl rather than on the ester carbonyl group (Scheme 2).

In typical circumstances, the *N*-alkyl amide carbonyl group is a weak competitor when compared with the methyl ester carbonyl group, both in terms of electrophilicity and steric hindrance. However, in the case of the aminoester **4a**, there is a strong preference for nucleophilic attack, which leads to a six-membered ring and elimination of an **8a** molecule (Scheme 2). A similar observation was made in connection with smaller macrocycles having the same chiral subunit.[2g] The possibility of epimerisation, combined with the long reaction time of 30 days, rendered catalysis by sodium methoxide in methanol impractical for the synthesis of trilactam **5c**. Other basic additives, promoting methyl ester aminolysis, were tested, including sodium and tetrabutylammonium hydroxides, as well as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Sodium hydroxide promoted macrocyclisation reactions, after stirring for 1 week at room temperature, afforded trilactams **5a**–**c** in poor yields (13–15%; Table 1, entries 4–6). The sodium hydroxide/methanol system has already been shown to be the system of choice in the preparation of smaller 12- to 16-membered macrocycles (with yields of up to 82%).[2g] However, its usefulness is limited to the smaller ring compounds of up to about 16 in-ring atoms, for which the rate of intramolecular aminolysis is relatively fast when compared with competitive methyl ester hydrolysis. The DBU promoted reaction was carried out for 3 months affording (*S*,*S*,*S*)-**5b** (36% yield; Table 1, entry 16) accompanied by its (*R*,*S*,*S*)-epimer (6% yield; Table 1, footnote j). An analogous reaction, using tetrabutylammonium hydroxide, produced non-epimerised (*S*,*S*,*S*)-**5b** in comparable yield of 39% (Table 1, entry 15) after 1 month.

In order to improve both the yield and diastereoisomeric purity of products, we examined high pressure conditions, which previously allowed transformation of the similar α,ω-aminoesters into macrocyclic amides without basic additives and under neutral conditions.[2g] Again, intramolecular methyl ester aminolysis was slow and after 1 week at 50°C under 10 kbar pressure, the desired products **5a**–**c** were separated from starting materials in only moderate yields (22–25%; Table 1, entries 7–9 and 11). When the aminoester **4b** was allowed to react for 2 weeks, macrocycle **5b** was obtained in a better yield of 29% (Table 1, entry 10).

Although increasing the pressure from 10 to 16 kbar had a negligible effect on the yield of **5a** and **5b** (see Table 1, entries 12 and 13), the chemoselectivity of attack by the amino group towards the ester and amide functions was lowered substantially (Scheme 2). In all cases (Table 1, entries 12–14) the macrocyclic triamides



Scheme 2. Possible intramolecular aminolysis of compounds **5a**–**c**.

5a–**c** were isolated from the mixture of products from intramolecular aminolysis (Table 1, footnotes g–j; Scheme 2). In the case of the largest macrocycle, **5c**, completing the reaction under a pressure of 16 kbar led to a loss in selectivity and thence a substantial decrease in yield to 13% in comparison to the reaction performed under 10 kbar pressure, which afforded **5c** in 22% yield (Table 1, entries 11 and 13).

Reduction of **5a** and **5b** with a large excess of borane–dimethylsulfide complex in THF (Scheme 1) afforded the title homochiral hexaaza-crown macrocycles [18]aneN_6 **6a** and [21]aneN_6 **6b** in good yields of 85 and 70%, respectively. We were able to obtain compounds **5b** and **5c** as monocrystals suitable for X-ray analysis. Although several attempts were made, no X-ray quality crystals could be grown from the triamide **5a**. The relative flexibility of the macrocyclic rings of both **5b** and **5c** allows the formation of intramolecular hydrogen bonds (Fig. 1, Table 2; Fig. 2, Table 3, respectively), which induce a β-turn-like conformation in some parts of the macro-rings. Such intramolecular bonding interactions keep the molecules of triamides **5b** and **5c** in 'collapsed' rather than C_3-symmetrical conformations. ^{1}H and ^{13}C NMR spectra of **5a** and **5c** recorded at room temperature in $CDCl_3$ solution showed averaged signals from all the homotopic nuclei (see Section 4), indicating either a C_3-symmetrical conformation in solution, or a rapid interchange between their non-symmetrical conformations. On the other hand, in the case of the triamide **5b**, NMR spectra recorded in $CDCl_3$ at room temperature showed separate signals from chemically equivalent nuclei, suggesting that some of the hydrogen bonds present in solids also exist in solutions.

3. Conclusion

The present work was aimed at the synthesis of large, enantiomerically pure hexaazamacrocycles using the methodology previously shown[2g] to be effective for the synthesis of their smaller tetraaza analogues. Although the yields of the macrocyclisation reactions were not as high as those of tetraazamacrocycles, which formed in yields of up to 82%, the hexaaza-crown precursors **5a**–**c** were obtained in reasonable yields (22–65%). For the efficient intramolecular aminolysis of such long, linear α,ω-aminoesters as **3a**–**c** high pressure conditions (10 kbar) turned out to be the most general. An important feature of the methodology presented (compared with other large ring formation methods) is its facility. The macrocyclisation reactions are performed with relatively high concentrations of substrates (0.01–0.1 M) in methanol with normal water content.

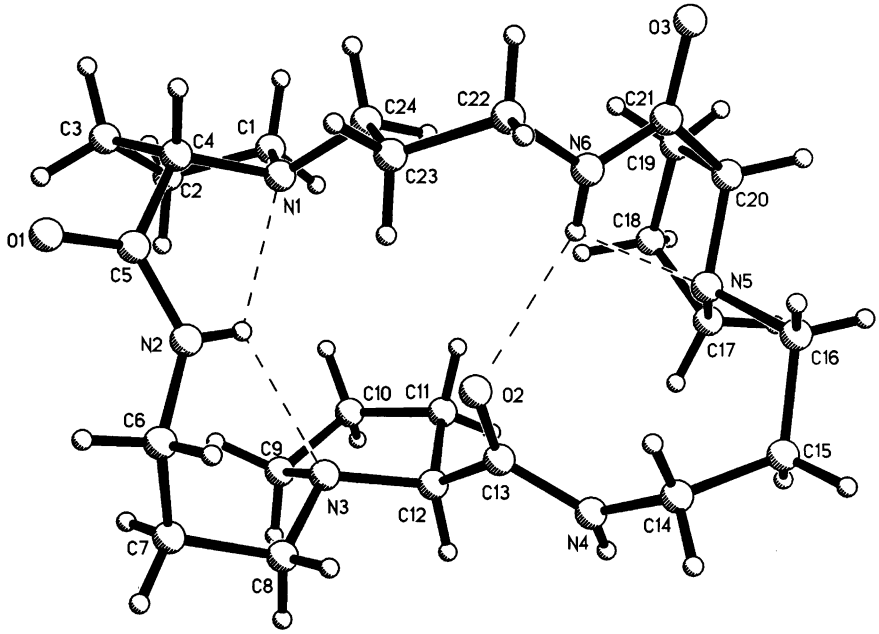


Figure 1. ORTEP view of compound **5b**.

Table 2. Geometry of hydrogen bonds in compound **5b**

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	DHA (°)
N2–H2···N1	0.82	2.23	2.738	120
N2–H2···N3	0.82	2.46	2.957	120
N4–H4···O1 $(x, y-1, z)$	0.90	2.13	2.942	150
N6–H6···N5	0.94	2.17	2.707	116
N6–H6···O2	0.94	2.37	3.094	134

Trilactams **5a**–**c**, which were precursors for the title hexaazamacrocycles, are very promising neutral hosts for anions, since macrocyclic polyamides are known to be able to bind such species.[9] Further studies, concerning the interaction of anions with triamides **5a**–**c** and the formation of transition metal complexes with ligands of the type **6**, are currently in progress.

4. Experimental

4.1. General methods

Melting points were determined on a Kofler hot-stage apparatus with a microscope and are uncorrected. Optical rotations were measured on a JASCO P 3010 polarimeter using the sodium D line at 589 nm. ^{1}H NMR spectra were recorded on a Bruker Avance 500 (500

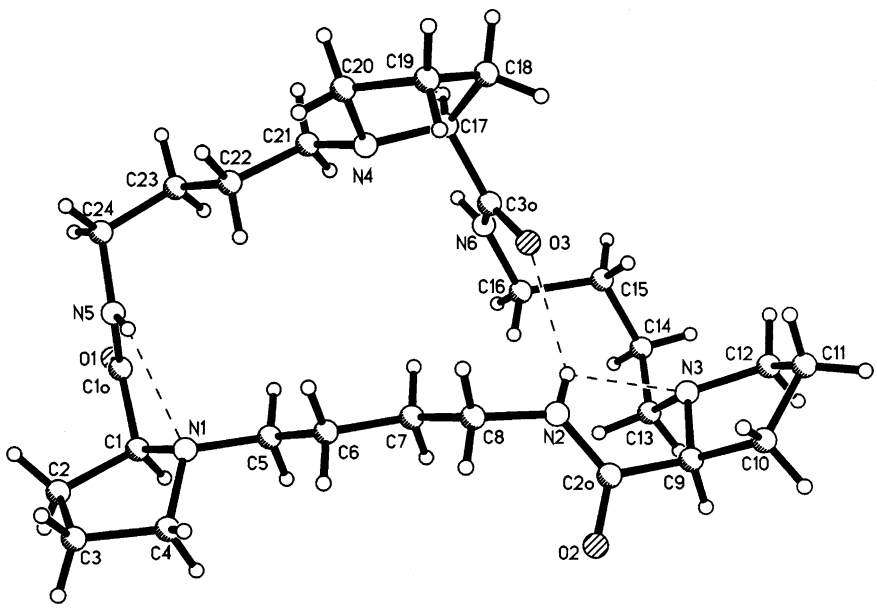


Figure 2. ORTEP view of compound **5c**.

Table 3. Geometry of hydrogen bonds in compound **5c**

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	DHA (°)
N2–H2N···N3	0.74	2.45	2.745	107
N6–H6N···O2 ($x-1$, y, z)	0.86	2.00	2.843	167
N2–H2N···O3	0.73	2.27	2.891	144
N5–H5N···N1	0.90	2.24	2.757	116

MHz) spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane at $\delta=0$, with tetramethylsilane or the residual non-deuterated solvent signal as internal standard. In addition to the conventional abbreviations for multiplicity, the following have been used for first-order spectra: m = multiplet, b = broad. ^{13}C NMR spectra were recorded on Bruker Avance 500 (125 MHz) and Varian Gemini AC-200 (50 MHz) spectrometers and were proton decoupled. ^{1}H,^{1}H-COSY and ^{1}H,^{13}C-HETCOR experiments were carried out on some samples to aid in the assignment of spectra. Infrared spectra were run on a Perkin–Elmer FT-IR Spectrum 2000 spectrophotometer. High-resolution mass spectra (LSIMS and EI) were recorded on an Intectra AMD 604 spectrometer. Electrospray (ESI) high-resolution spectra were recorded on Perseptive Biosystems Mariner (TOF) or Sciex API 365 (triple quadrupole) spectrometers. Elemental analyses (C, H, and N) were performed by the 'in-house' analytical service.

Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} that were developed using ninhydrin solution in a butanol/acetic acid mixture, in addition to visualisation by UV and I_2. Preparative flash silica chromatography was performed using Merck Kieselgel 60 (230–400 mesh). All reagents and solvents were purified and dried as necessary according to standard procedures.

4.2. General procedure for the amide bond formation (1+2→3)

The *N*-Cbz-protected amino acid **1**[2g] (2.05 mmol) and triethylamine (2.5 equiv., 0.70 mL) were dissolved in dry CH_2Cl_2 (20 mL). The solution was cooled to −20°C under argon and *iso*-butylchloroformate (0.27 mL, 2.1 mmol) was added dropwise. The reaction mixture was stirred at −20°C for 1 h, and then at 0°C for 1 h. To this solution was added a solution of aminoester **2** (see Ref. 2g, 2.03 mmol) in dry CH_2Cl_2 (15 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight, and was then evaporated. The residue was dissolved in ethyl acetate (0.10 L), washed with water (2×25 mL), brine (25 mL) and dried (Na_2SO_4). After solvent evaporation, the residue was purified by column chromatography (CH_2Cl_2/methanol = 19/1) to afford pure amide **3**.

4.2.1. (2*S*,11*S*,20*S*)-2,6-*cyclo*-11,15-*cyclo*-20,24-*cyclo*-26 - (Benzyloxycarbonylamino) - 6,9,15,18,24 - pentaaza-10,19-dioxohexacosanoic acid methyl ester 3a. Yield 83%; mp 77–78°C; $[\alpha]_D^{20}=-99.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta=7.64$ (bs, 1H; CON*H*), 7.36–7.28 (m, 6H; CON*H*, Ph), 6.17 (bs, 1H; CO_2NH), 5.15 (d, 1H, $J=12.2$ Hz; C*H*HPh), 5.05 (d, 1H, $J=12.2$ Hz; CH*H*Ph), 3.67 (s, 3H; OCH_3), 3.58–3.50 (m, 1H; NHC*H*H), 3.41–3.03 (m, 10H; 2× C*H*CO, NHCH*H*, 2×NHCH_2, NCH_2, NC*H*H), 2.99–2.90 (bs, 1H; C*H*CO), 2.84–2.69 (m, 3H; 3×NC*H*H), 2.58–2.41 (m, 3H; 3×NCH*H*), 2.38–2.20 (m, 3H; NCH_2, NCH*H*), 2.19–2.01 (m, 3H; CH_2, C*H*H), 1.92–1.65 (m, 15H; 7×CH_2, CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta=175.2$, 174.6, 136.0, 128.4, 128.2, 128.0, 68.2, 68.1, 66.5, 65.7, 55.4, 54.9, 53.9, 53.7, 53.6, 53.2, 51.8, 40.2, 38.0, 37.7, 30.5, 30.3, 29.5, 24.2, 23.7, 23.5; IR ($CHCl_3$): $\nu=3355$, 2981, 2955, 2883, 2817, 1715, 1659, 1523, 1455 cm^{-1}; MS (EI HR): calcd for $[C_{30}H_{46}N_6O_6]^+$ 586.34788, found 586.34907.

4.2.2. (2*S*,12*S*,22*S*)-2,6-*cyclo*-12,16-*cyclo*-22,26-*cyclo*-29 - (Benzyloxycarbonylamino) - 6,10,16,20,26 - pentaaza-11,21-dioxononanoic acid methyl ester 3b. Yield 90%; a yellow oil; $[\alpha]_D^{20}=-89.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta=7.63$ (bs, 1H; CON*H*), 7.43–7.28 (m, 6H; CON*H*, Ph), 5.31 (bs, 1H; CO_2NH), 5.09 (bs, 2H; CH_2Ph), 3.69 (s, 3H; OCH_3), 3.47–3.39 (m, 1H; NHC*H*H), 3.36–3.29 (m, 1H; NHC*H*H), 3.27–3.12 (m, 8H; C*H*CO$_2$, 2×NHCH*H*, NHCH_2, NCH_2, NC*H*H), 3.03–2.95 (m, 2H; 2×C*H*CO), 2.73 (dt, 1H, $J_1=7.9$ Hz, $J_2=12.0$ Hz; NC*H*H), 2.67–2.56 (m, 2H; NCH_2), 2.46–2.35 (m, 3H; NCH_2, NH*H*), 2.32–2.22 (m, 3H; NCH_2, NH*H*), 2.19–2.06 (m, 3H; CH_2, C*H*H), 1.94–1.61 (m, 15H; 7×CH_2, CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta=174.9$, 174.7, 174.6, 156.5, 136.7, 128.5, 128.1, 68.1, 68.0, 66.5, 66.6, 66.1, 53.9, 53.8, 53.4, 53.3, 52.9, 51.7, 39.1, 37.4, 36.8, 30.7, 30.6, 29.6, 29.3, 29.1, 28.6, 24.2, 23.2; IR ($CHCl_3$): $\nu=3671$, 3450, 3346, 2952, 2816, 1719, 1658, 1522, 1455 cm^{-1}; MS (LSIMS HR): calcd for $[C_{33}H_{53}N_6O_6]^+$ 629.40265, found 629.40138.

4.2.3. (2*S*,13*S*,24*S*)-2,6-*cyclo*-13,17-*cyclo*-24,28-*cyclo*-32 - (Benzyloxycarbonylamino) - 6,11,17,22,28 - pentaaza-12,23-dioxodotriacontanoic acid methyl ester 3c. Yield 86%; a yellow oil; $[\alpha]_D^{20}=-73.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta=7.40$–7.29 (m, 6H; CON*H*, Ph), 5.09 (bs, 3H; CON*H*, CH_2Ph), 3.71 (s, 3H; OCH_3), 3.30–3.10 (m, 10H; 3×NHCH_2, NCH_2, NC*H*H, C*H*CO), 3.02–2.96 (m, 2H; 2× C*H*CO), 2.71 (m, 1H; NC*H*H), 2.62–2.54 (m, 2H; NCH_2), 2.47–2.36 (m, 3H; NCH_2, NH*H*), 2.34–2.24 (m, 3H; NCH_2, NH*H*), 2.19–2.04 (m, 3H; CH_2, C*H*H), 1.95–1.42 (m, 21H; 10×CH_2, CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta=174.9$, 174.7, 156.4, 136.6, 128.5, 128.1, 67.9, 67.8, 66.6, 66.1, 55.7,

55.6, 54.6, 53.9, 53.8, 53.4, 51.7, 40.9, 38.7, 38.6, 30.7, 30.6, 29.3, 28.0, 27.8, 27.7, 26.3, 26.2, 26.0, 24.2, 23.2; IR ($CHCl_3$): ν = 3453, 3344, 3007, 2947, 2868, 2814, 1721, 1659, 1521, 1455 cm^{-1}; MS (EI HR): calcd for $[C_{36}H_{58}N_6O_6]^+$ 670.44178, found 670.44270.

4.3. Macrocyclisation procedures (3→4→5)

N-Cbz-Protected aminoesters **3a–c** were subjected to catalytic hydrogenation (H_2 over 5% Pd–C in methanol) affording aminoesters **4a–c**, which were used without further purification for subsequent macrocyclisation reactions.

4.3.1. Macrocyclisation reactions (4→5) promoted by basic additives (NaOMe, NaOH, DBU, or TBAOH). The following procedure for the macrocyclisation employing sodium methoxide is representative for all reactions promoted by basic additives. Aminoester **4** (1.87 mmol) was dissolved in NaONa solution in methanol (0.4 M, 0.19 L), and allowed to stand at room temperature for 30 days (for DBU and TBAOH promoted reactions 10 equiv. of base were used). The reaction mixture was neutralised with aq. HCl and evaporated to dryness. The solid residue was dissolved in water (20 mL) and extracted with $CHCl_3$ (4×20 mL). The combined chloroform extracts were dried (Na_2SO_4) and the solvent was evaporated. Chromatographic purification (CH_2Cl_2/methanol = 9/1) followed by recrystallisation from CH_2Cl_2/Et_2O afforded the macrocyclic triamide **5** as colourless crystals.

4.3.2. Macrocyclisation reactions (4→5) carried out under high pressure conditions. A solution of the aminoester **4** (0.409 mmol) in methanol (2.5 mL) was added to a Teflon® ampoule, placed in a high-pressure vessel filled with ligroin as a transmission medium and compressed (10 kbar or 16 kbar) at 50°C for 7 days. After decompression, the mixture was transferred quantitatively to a round-bottomed flask and the solvent was evaporated. The crude product was purified by column chromatography on silica (CH_2Cl_2/methanol = 9/1), followed by recrystallisation from CH_2Cl_2/Et_2O, to afford the macrocyclic triamide **5** as colourless crystals.

4.3.3. (6*S*,15*S*,24*S*)-1,4,10,13,19,22-Hexaazatetracyclo-[22.3.0.0^{6,10}.0^{15,19}]heptacosane-5,14,23-trione 5a. Mp 224–225°C; $[\alpha]_D^{20} = -149$ (*c* 1.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): δ = 7.43 (bs, 3H; 3×N*H*), 3.57–3.49 (m, 3H; 3×NHC*H*H), 3.29–3.22 (m, 3H; 3×NHCH*H*), 3.16–3.08 (m, 6H; 3×NC*H*H, 3×C*H*CO), 2.89 (ddd, 3H, J_1 = 4.8 Hz, J_2 = 8.1 Hz, J_3 = 12.7 Hz; NC*H*H), 2.64 (dt, 3H, J_1 = 5.1 Hz, J_2 = 12.6 Hz; 3×NCH*H*), 2.42 (dt, 3H, J_1 = 9.5 Hz, J_2 = 6.8 Hz; 3×NCH*H*), 2.25–2.14 (m, 3H; 3×CH*H*), 1.94–1.87 (m, 3H; 3×CH*H*), 1.86–1.77 (m, 3H; 3×C*H*H), 1.74–1.63 (m, 3H; 3×CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): δ = 174.7, 67.9, 54.7, 54.1, 38.5, 30.1, 23.9; IR ($CHCl_3$): ν = 3347, 2822, 1663, 1524, 1450 cm^{-1}; MS (ESI HR): calcd for $[C_{21}H_{37}N_6O_3]^+$ 421.2922, found 421.2914. Anal. calcd for $C_{21}H_{36}N_6O_3$: C, 60.00; H, 8.57; N, 20.00. Found: C, 59.75; H, 8.42; N, 19.77%.

4.3.4. (7*S*,17*S*,27*S*)-1,5,11,15,21,25-Hexaazatetracyclo-[25.3.0.0^{7,11}.0^{17,21}]triacontane-6,16,26-trione 5b. Mp 151–153°C; $[\alpha]_D^{20} = -68.5$ (*c* 1.9, $CHCl_3$); ^{1}H NMR (500 MHz, d_8-toluene, 90°C, TMS): δ = 6.85 (bs, 3H; 3×N*H*), 3.28–3.17 (m, 6H; 3×NHCH_2), 2.91 (ddd, 3H, J_1 = 2.9 Hz, J_2 = 7.0 Hz, J_3 = 9.5 Hz; 3×NC*H*H), 2.86 (dd, 3H, J_1 = 5.6 Hz, J_2 = 9.3 Hz; 3×C*H*CO), 2.46 (dt, 3H, J_1 = 7.6 Hz, J_2 = 12.4 Hz; 3×NC*H*H), 2.21 (ddd, 3H, J_1 = 5.7 Hz, J_2 = 7.0 Hz, J_3 = 12.5 Hz; 3×NCH*H*), 1.99 (dt, 3H, J_1 = 7.0 Hz, J_2 = 9.3 Hz; 3×NCH*H*), 1.94–1.79 (m, 6H; 3×CH_2), 1.58–1.38 (m, 12H; 6×CH_2); ^{13}C NMR (125 MHz, d_8-toluene, 90°C, TMS): δ = 173.6, 69.1, 55.2, 54.8, 38.0, 30.8, 30.4, 24.5; IR ($CHCl_3$): ν = 3341, 2948, 2821, 1660, 1518 cm^{-1}; MS (EI HR): calcd for $[C_{24}H_{42}N_6O_3]^+$ 462.33184, found 462.33206. Anal. calcd for $C_{24}H_{42}N_6O_3$: C, 62.34; H, 9.09; N, 18.18. Found: C, 62.06; H, 8.94; N, 18.26%.

4.3.5. (8*S*,19*S*,30*S*)-1,6,12,17,23,28-Hexaazatetracyclo-[28.3.0.0^{8,12}.0^{19,23}]triacontane-7,18,29-trione 5c. Mp 151–153°C; $[\alpha]_D^{20} = -152$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): δ = 7.35 (bt, 3H, J = 5.6 Hz; 3×N*H*), 3.50–3.42 (m, 3H; 3×NHC*H*H), 3.15 (dt, 3H, J_1 = 1.4 Hz, J_2 = 7.8 Hz; 3×NC*H*H), 3.12–3.05 (m, 3H; 3×NHCH*H*), 3.01 (dd, 3H, J_1 = 4.8 Hz, J_2 = 10.1 Hz; 3×C*H*CO), 2.61 (dt, 3H, J_1 = 7.6 Hz, J_2 = 11.9 Hz; 3×NC*H*H), 2.49–2.43 (m, 3H; 3×NCH*H*), 2.32–2.25 (m, 3H; NCH*H*), 2.22–2.17 (m, 3H; 3×C*H*H), 1.88–1.77 (m, 6H; 3×CH*H*, 3×C*H*H), 1.75–1.61 (m, 6H; 3×CH*H*, 3×C*H*H), 1.54–1.41 (m, 9H; 3×CH_2, 3×CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): δ = 174.7, 68.0, 55.6, 53.7, 38.6, 30.4, 27.9, 26.4, 24.2; IR ($CHCl_3$): ν = 3345, 2942, 2864, 2817, 1660, 1523, 1460 cm^{-1}; MS (EI HR): calcd for $[C_{27}H_{48}N_6O_3]^+$ 504.37879, found 504.37919.

4.4. Reduction of the macrocyclic triamides (5→6)

4.4.1. (7*S*,17*S*,27*S*)-1,5,11,15,21,25-Hexaazatetracyclo-[25.3.0.0^{7,11}.0^{17,21}]triacontane 6b. The following procedure for amide reduction is representative. To a vigorously stirred suspension of **5b** (102 mg, 0.220 mmol) in dry THF (10 mL) under argon, $BH_3{\cdot}Me_2S$ complex (10 M, 0.66 mL, 6.6 mmol) was added dropwise. For a short period of time the reaction mixture turned into a clear solution. The reaction mixture was then stirred at reflux overnight (19 h), cooled to room temperature, and a mixture of THF/water = 4/1 (5 mL) was carefully added. The mixture was evaporated to dryness. The residue was taken up in aq. HCl (6 M, 10 mL) and the suspension stirred under reflux until a clear solution was seen (ca. 1 h). The mixture was evaporated to dryness and the solid residue was dissolved in aq. NaOH (4 M, 5 mL) and extracted with $CHCl_3$ (5×10 mL). The combined extracts were dried (Na_2SO_4) and evaporated. Chromatographic purification of the crude product (methanol/aq. NH_3 = 9/1) afforded the title compound (65 mg, 70% yield) as a colourless oil; $[\alpha]_D^{20} = -88.1$ (*c* 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): δ = 3.18–3.15 (m, 3H; 3×NC*H*H), 2.81 (dt, 3H, J_1 = 8.1 Hz, J_2 = 12.0 Hz; 3×NHC*H*H), 2.71–2.61 (m, 9H; 3×CHCH_2NH, 3×NC*H*H), 2.58–2.47 (m, 6H; 3×NCH*H*, 3×C*H*), 2.25

Table 4. Crystal data and structure refinement for compounds **5b** and **5c**

	5b	**5c**
Empirical formula	$C_{24}H_{42}N_6O_3$	$C_{27}H_{48}N_6O_3$
Formula weight	462.64	504.71
Temperature (K)	293(2)	293(2)
Wavelength (Å)	1.54178	0.71073
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a (Å)	7.3420(10)	9.0210(18)
b (Å)	10.099(2)	9.6610(19)
c (Å)	17.338(3)	32.156(6)
β (°)	91.69(3)	90
Volume (Å^3)	1285.0(4)	2802.5(10)
Z	2	4
Calculated density (Mg m^{-3})	1.196	1.196
μ (mm^{-1})	0.644	0.079
$F(000)$	504	1104
θ range (°)	2.55–74.28	3.39–20.00
Index ranges	$0\le h\le 9$, $-12\le k\le 0$, $-21\le l\le 21$	$-4\le h\le 8$, $-9\le k\le 9$, $-30\le l\le 30$
Reflections collected/unique	1470/1366 [R(int) = 0.0262]	9752/2605 [R(int) = 0.0762]
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	1366/1/350	2605/0/334
GooF	1.085	1.120
R indices [$I>2\sigma(I)$]	$R_1 = 0.0681$, $wR_2 = 0.1522$	$R_1 = 0.0688$, $wR_2 = 0.1308$
Absolute structure parameter	−0.1(12)	−5(4)
Extinction coefficient	0.015(2)	0.0024(5)
Largest difference peak and hole (e Å^{-3})	0.247 and −0.219	0.211 and −0.183

(dt, 3H, $J_1 = 5.7$ Hz, $J_2 = 11.7$ Hz; 3×NHCH*H*), 2.17–2.09 (m, 3H; 3×NCH*H*), 1.90–1.88 (m, 3H; 3×C*H*H), 1.75–1.55 (m, 18H; 6×CH_2, 3×CH*H*, 3×N*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta = 64.1$, 54.4, 53.7, 53.6, 49.5, 29.3, 29.0, 23.3; IR ($CHCl_3$): $\nu = 3278$, 2949, 2879, 2811, 1603, 1462 cm^{-1}; MS (ESI HR): calcd for $[C_{24}H_{49}N_6]^+$ 421.40187, found 421.39984.

4.4.2. (6*S*,15*S*,24*S*)-1,4,10,13,19,22-Hexaazatetracyclo[22.3.0.0^{6,10}.0^{15,19}]heptacosane 6a. Yield 85%; a colourless oil; $[\alpha]_D^{20} = -69.9$ (c 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta = 3.17$–3.08 (m, 6H; 3×NC*H*H), 2.77 (dd, 3H, $J_1 = 4.4$ Hz, $J_2 = 11.4$ Hz; 3×CHC*H*HNH), 2.74–2.67 (m, 6H; 3×NHCH_2), 2.64–2.58 (m, 3H; 3×C*H*), 2.52 (dd, 3H, $J_1 = 6.1$ Hz, $J_2 = 11.4$ Hz; 3×CHCH*H*NH), 2.29 (dt, 3H, $J_1 = 4.5$ Hz, $J_2 = 12.1$ Hz; 3×NCH*H*), 2.26–2.10 (m, 6H; 3×NCH*H*, 3×N*H*), 1.90–1.83 (m, 3H; 3×CHC*H*H), 1.74–1.68 (m, 6H; 3×CH_2), 1.57–1.49 (m, 3H; 3×CHCH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta = 63.7$, 54.5, 54.2, 53.6, 48.6, 28.9, 23.2; IR ($CHCl_3$): $\nu = 3689$, 3295, 2954, 2814, 1603, 1448 cm^{-1}; MS (ESI HR): calcd for $[C_{21}H_{43}N_6]^+$ 379.3544, found 379.3572.

4.5. X-Ray structure analysis of compounds 5b and 5c

X-Ray data for **5b** were collected on a Nonius MACH3, and on a KumaCCD diffractometer for **5c**. Data reduction was performed with the use of an OpenMoleN system.[10a] Structures were solved with direct methods SHELXS-86[10b] and refined with SHELXL-97.[10c] Crystal data and details of structure solution and refinement are summarised in Table 4.

Acknowledgements

This work was supported by the State Committee for Scientific Research (Project 3T09A 127 15). The authors wish to thank the Polish Science Foundation for additional financial support. They are also indebted to Dr. Agnieszka Szumna and Dr. Krzysztof Wozniak for the X-ray structural analyses.

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