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The synthesis of L-proline derived tetraazamacrocyclic ligands of C_2 symmetry via intramolecular ester aminolysis

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Abstract—A convenient and efficient synthesis of enantiomerically pure 12-, 14-, and 16-membered tetraazamacrocyclic ligands, able to form complexes with transition metal cations, is discussed. Linear α,ω-aminoesters, prepared from L-proline, undergo intramolecular aminolysis to afford the corresponding macrocyclic amides in good yields.

1. Introduction

There is a growing interest in the application of polyazamacrocycles in transition metal coordination processes, such as ion sequestration,[1] biomimetic catalysis,[2] and biomedical uses,[3] since they are effective complexating agents.[4] Among the polyazamacrocycles, 14-membered cyclam ring system (1,4,8,11-tetraazacyclotetradecane) and the 12-membered cyclen ring system (1,4,7,10-tetraazacyclododecane) and their dioxo-derivatives are of importance due to their ability to form kinetically and thermodynamically stable complexes with Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}, and Pt^{II} ions, and their ability to stabilize high oxidation state metals.[1,5] Moreover, certain complexes of Ni^{II} and Fe^{II} with cyclam and its derivatives have been shown to catalyze organic reactions such as alkene epoxidation,[2,6,7] electrochemical epoxide carboxylation,[8] and intramolecular reductive cyclization.[9] As alkene oxidation processes such as epoxidation, are associated with the formation of new stereogenic centers, the use of optically active catalysts is of interest. Exploiting a concept that the incorporation of functionalized side chains into a cyclam framework may modify its coordination properties, Burrows et al. have synthesized an enantiomerically pure cyclam derivative using (*S*)-2,4-diaminobutyric acid,[10] and several 5,7-dioxocyclams, starting from L-phenylalanine,[7a] L-valine and L-leucine[7c] (enantiomerically pure cyclam derivatives could also be obtained by resolution of respective racemates,[11] or via the multicenter templated condensation of chiral amines with ketones[12]).

Our recent communication reported a straightforward route towards L-proline derived cyclams,[13] and detailed an attractive methodology for the preparation of substituted cyclam **5b** and its oxo- and dioxo-derivatives **6b** and **7b**. The present work extends these studies on the two other chiral tetraazamacrocycles: **5a** based on the 1,5-dioxocyclen 12-membered ring, and **5c**, its less common 16-membered analog (Scheme 1).

2. Results and discussion

N-Alkylation of L-proline ester with the appropriate *N*-Cbz-*O*-mesyl-aminoalcohols **1a–c** afforded, respectively, aminoesters **2a–c** in good yields of 72–75%. According to literature procedures compounds **1a**[14] and **1b**[15] are readily available from the corresponding aminoalcohols. The unreported **1c** was obtained from *N*-Cbz-4-aminobutan-1-ol[16] in analogous manner. In the next step, *N*-alkylated L-prolines **3a–c** were obtained via saponification of esters **2a–c**, and used in subsequent reactions without further purification. The amine protection was removed reductively from compounds **2a–c** (H_2, Pd/C in methanolic HCl). In the absence of hydrogen chloride upon hydrogenation of **2a**, we observed rapid intramolecular ester aminolysis leading to the bicyclic compound **8a** (Scheme 2, **2a**→**8a**). Since we assumed that such an undesired process could be expected for the other two Cbz-protected aminoesters **2b** and **2c**, they were also hydrogenated in the presence of hydrogen chloride.

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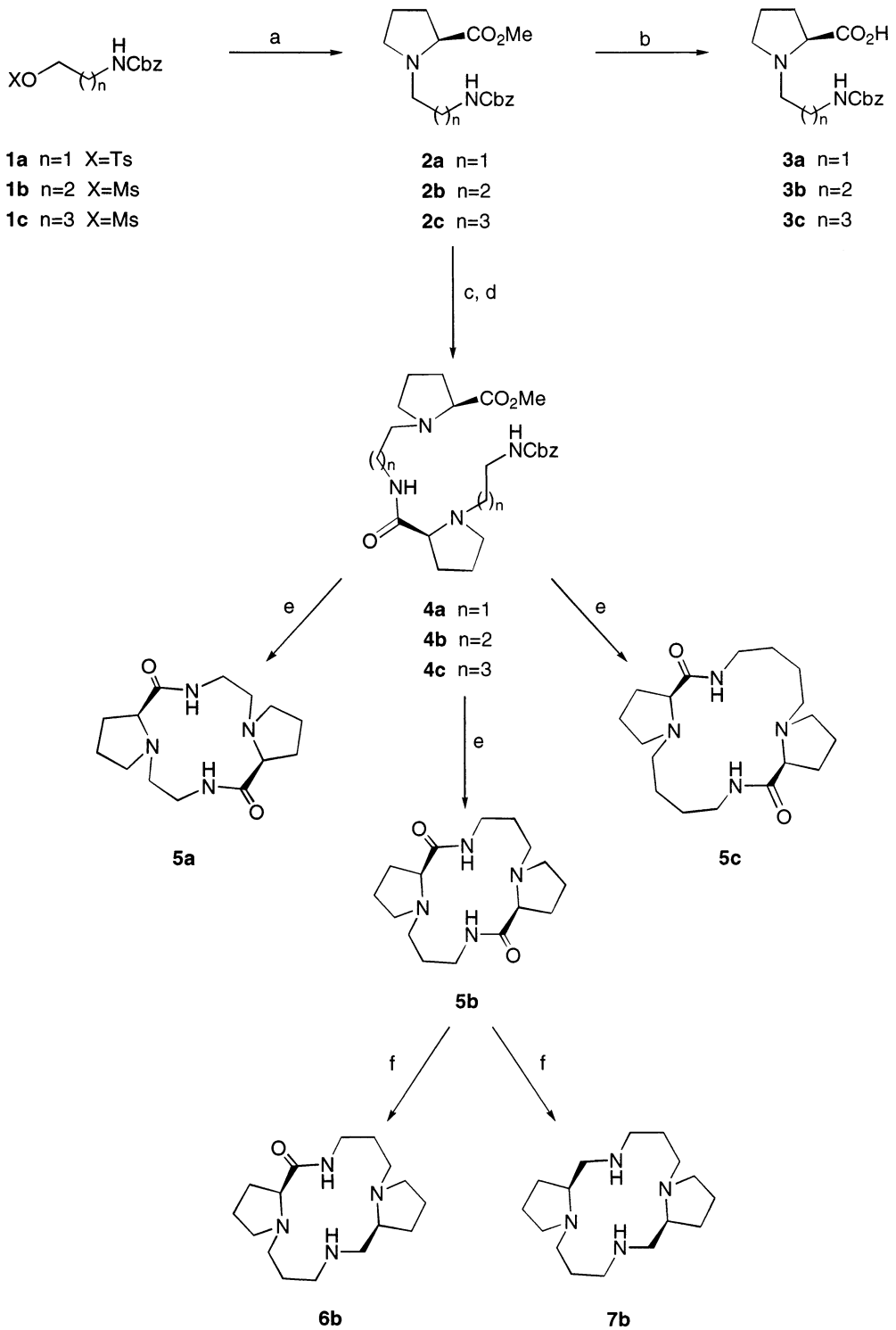
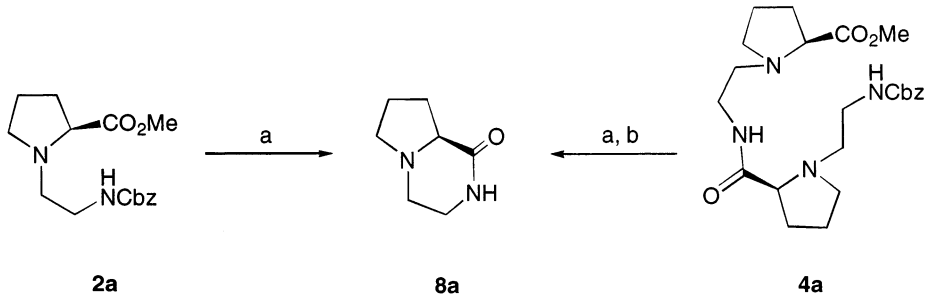


Scheme 1. (a) L-Pro-OMe, Et_3N, MeCN, rt then reflux; (b) H_2O, reflux; (c) H_2, Pd/C, HCl/MeOH; (d) **3**, ^{t}BuOCOCl, Et_3N, CH_2Cl_2, −20 to 0°C; (e) H_2, Pd/C, MeOH; then NaOMe, MeOH, rt; or NaOH, MeOH, rt; or MeOH, 10 kbar, 50°C; (f) BMS, THF, reflux, 4 h (**6b**) or 20 h (**7b**).

Each of the aminoester hydrochlorides, obtained by hydrogenation under acidic conditions, was condensed with the appropriate, previously synthesized acid (**3a**–**c**), to furnish corresponding amides **4a**–**c** in a good (75–90%) overall yield. After deprotection of the amino group in amides **4a**–**c** (H_2, Pd/C in methanol), the resulting aminoesters were submitted to macrocyclization conditions. Originally,[13] for the synthesis of chiral cyclam **5b** we applied sodium methoxide in methanol (procedure A) as a cyclization reagent (82% yield). However, in the case of **4c**, the cyclization reaction led to a mixture of the desired product (*S*,*S*)-**5c** and its *meso*-diastereoisomer (*R*,*S*)-**5c** (ca. 2:1, 78% yield, see Table 1). In our opinion, the formation of the unde-



Scheme 2. (a) H_2, Pd/C, MeOH; (b) MeOH, 10 kbar, 50°C.

Table 1. Yields of bislactams under various macrocyclization conditions

Product	Procedure		
	A (NaOMe/MeOH, rt)	B (NaOH/MeOH, rt)	C (MeOH, 10 kbar/50°C)
5a	75%	81%	48%[a]
5b	82%	80%	66%
5c	78%[b]	37%	53%

[a] Accompanied by bicyclic side-product **8a**.
[b] 2:1 mixture of (*S*,*S*)-**5c**:(*S*,*R*)-**5c** diastereoisomers (based on ^{1}H NMR).

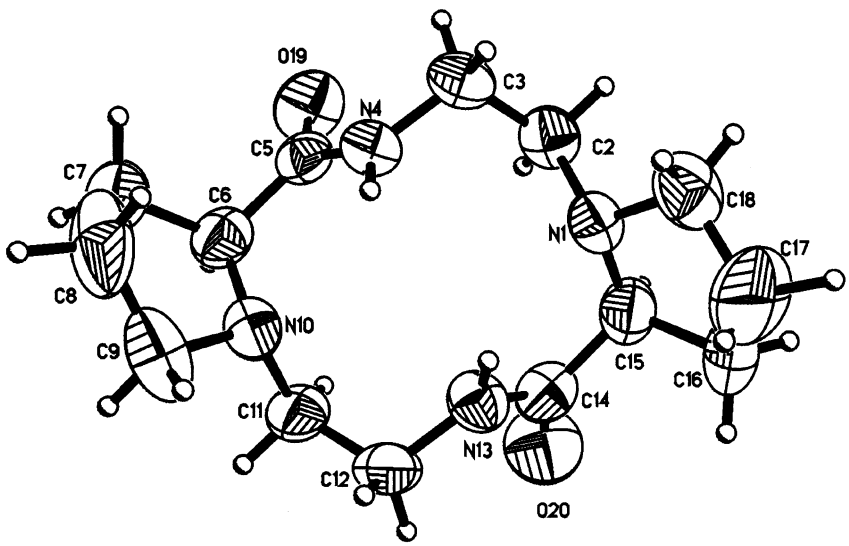


Figure 1. ORTEP view of compound **5a**.

sired diastereoisomeric side-product (*R*,*S*)-**5c** should not be attributed to epimerization of the rigid macrocyclic product **5c**, but is presumably a result of a partial epimerization of the substrate prior to its cyclization caused by the strongly basic reaction conditions. The absence of side products in the case of **5b** could be attributable to faster cyclization of its precursor, which has only 12 atoms between reacting groups as compared to 14 atoms in the case of the precursor to **5c**. Faster cyclization would shorten the exposure of the precursor to epimerization conditions. To overcome this problem other conditions which would promote cyclization reaction were investigated. Several basic catalysts including organic bases (DBU, triethylamine) and basic salts (TBAF, NaCN) were tried and sodium hydroxide in methanol (procedure B) was found to be the most effective base. Although for the precursors **4b** and **4c** lower yields were observed compared to the sodium methoxide promoted reactions, no epimerization products were observed. Finally, as a third cyclization procedure, high pressure conditions were chosen. These reactions were carried out in methanol at 50°C under 10 kbar pressure in a piston–cylinder type apparatus[17] (procedure C). Intramolecular aminolysis discussed earlier was also detected under high pressure conditions (Scheme 2, **4a**→**8a**). Although the amide carbonyl group in **4a** is definitely less electrophilic than the ester carbonyl groups in both **2a** and **4a**, there is a strong preference for nucleophilic attack leading to a six-membered ring. Yields of lactams **5a–c** for all three macrocyclization protocols are summarized in Table 1.

The identity of ligands **5a–c** was confirmed by X-ray crystal structure analysis (Figs. 1–3).

Reduction of **5b** with $BH_3 \cdot Me_2S$ complex[7c] over 4 hours afforded the 2-oxocyclam **6b** as a major product, whereas exhaustive reduction of **5b** with the same reagent furnished the chiral cyclam **7b**. In much the same way this approach could be applied to compounds **5a** and **5c** offering a convenient route to corresponding analogs of **6b** and **7b**.

3. Conclusion

A synthetic pathway has been developed in which enantiomerically pure dioxo- (**5b**), monooxo- (**6b**), and saturated cyclams derived from L-proline were effectively prepared. The method has been extended for smaller (**5a**) and larger (**5c**) chiral macrocycles—**5c** being to our knowledge the first 1,4,7,10-tetraazacyclohexadecandione derivative reported to date. Three distinct protocols for the macrocyclization reaction (**4**→**5**), procedures A–C, have been developed. Employing sodium hydroxide in methanol is the most general procedure, both in terms of yield and enantiomeric purity. Nonetheless the other two procedures offer better performance in some particular cases. For example, procedure A is most suited to the synthesis of **5b**, whilst procedure C gave the most efficient route to **5c**. Thus the procedures are complementary to one another. The

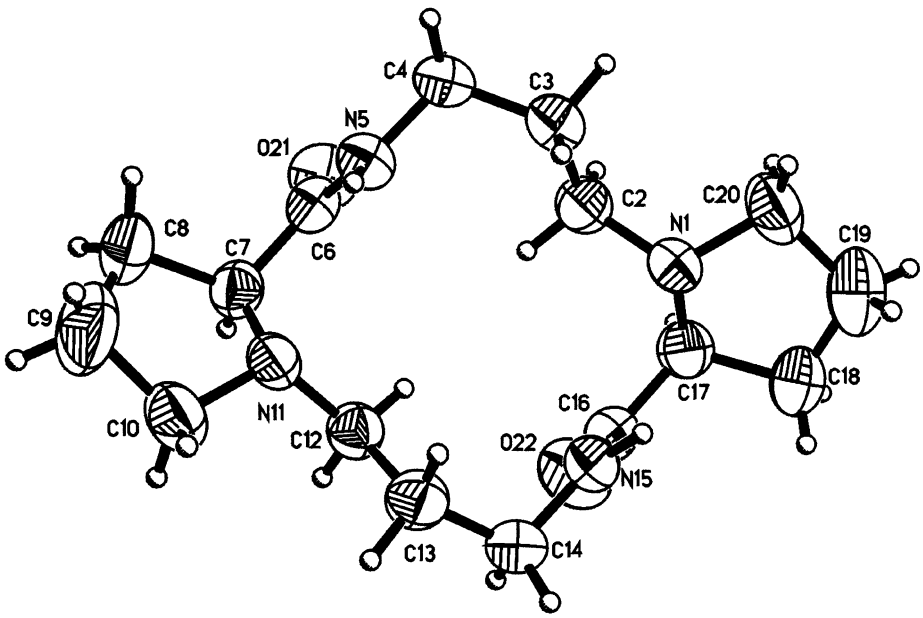


Figure 2. ORTEP view of compound **5b**.

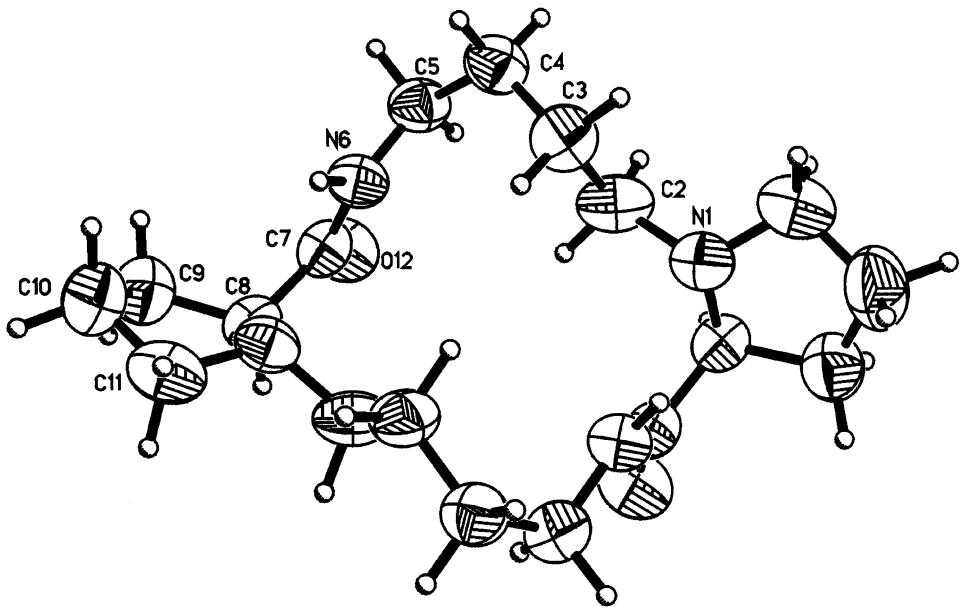


Figure 3. ORTEP view of compound **5c**.

methodology presented herein also offers an easy access to 13- and 15-membered tetraazamacrocycles, which can be synthesized via 'mixed' amides of type **4**.

The cyclams (**5b**–**7b**) served as chiral ligands for the formation of Ni^{II} complexes,[13] potentially useful as chiral catalysts. Further investigations, including synthesis of other more elaborated ligands of this type, their complexes with transition metals and their use in asymmetric catalysis are soon to be published.

4. Experimental

4.1. General methods

Melting points were determined on a Kofler hot-stage apparatus with 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 Bruker Avance 500 (500 MHz) and Varian Gemini AC-200 (200 MHz) spectrometers. 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 Perkin–Elmer FT-IR Spectrum 2000 spectrophotometer. High resolution mass spectra (LSIMS and EI) were recorded on 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} and were developed using ninhydrine solution in butanol/acetic acid mixture, in addition to visualization 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. *N*-(Benzyloxycarbonyl)-*O*-(methanesulphonyl)-aminobutanol 1c

Cbz-Protected 4-aminobutanol (19.1 mmol, 4.26 g) and triethylamine (3.0 mL, 1.1 equiv.) were dissolved in dry CH_2Cl_2 (100 mL), placed in a cooling bath, and methanesulphonyl anhydride (1.1 equiv., 3.76 g) was added in a few portions with vigorous stirring. The reaction was completed after the last portion of the anhydride had been added (TLC). The reaction mixture was transferred into a separatory funnel, washed with 0.5 M aq. HCl (50 mL), and satd aq. $NaHCO_3$ (50 mL). The organic layer was dried ($MgSO_4$), solvents were evaporated and the solid residue was recrystallized from CH_2Cl_2/hexanes, furnishing mesylate **1c** (5.63 g, 98% yield) as colorless crystals; mp 34–36°C; ^{1}H NMR (500 MHz, $CDCl_3$, 52°C, TMS): $\delta = 7.36$–7.28 (m, 5H; Ph), 5.10 (s, 2H; CH_2Ph), 4.76 (bs, 1H; NH), 4.23 (t, 2H, $J = 6.3$ Hz; OCH_2), 3.24 (q, 2H, $J = 6.6$ Hz; CH_2N), 2.97 (s, 3H; CH_3), 1.82–1.75 (m, 2H; CH_2), 1.67–1.61 (m, 2H; CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 52°C, TMS): $\delta = 156.5$, 136.7, 128.5, 128.1, 128.0, 69.3, 66.8, 40.5, 37.5, 26.5, 26.3; IR (KBr): $\nu = 3367$, 3035, 2940, 1693, 1533, 1349, 1263, 1176 cm^{-1}; MS (LSIMS HR) calcd for $[C_{13}H_{20}NO_5S]^+$: 302.10622, found: 302.10542. Anal. calcd for $C_{13}H_{19}NO_5S$: C, 51.83; H, 6.31; N, 4.65. Found: C, 51.69; H, 6.52; N, 4.69%.

4.3. General procedure for *N*-alkylation of L-proline methyl ester

A solution of L-proline methyl ester (19.3 mmol, 2.50 g), freshly liberated from its hydrochloride, mesylate **1b** (19.3 mmol, 5.54 g), and triethylamine (1.0 equiv., 2.7 mL) in acetonitrile (10 mL) was kept overnight at room temperature and then stirred at 50°C until the mesylate **1b** was consumed (TLC). Solvents were evaporated and the semi-solid residue was partitioned between ethyl acetate (0.2 L) and water (25 mL). Organic layer was then washed with water (25 mL), brine, and dried (Na_2SO_4). Chromatographic purification of the crude mixture (ethyl acetate/hexanes = 7/3) afforded pure Cbz-protected aminoester **2b** in 72% yield (4.46 g) as an oil. In the same manner, **2a** (73% yield) and **2c** (74% yield) were prepared.

4.3.1. (2*S*)-*N*-(*N*′-(Benzyloxycarbonyl)-2′-aminoethyl))-proline methyl ester 2a. A yellow oil; $[\alpha]_D^{20} = -34.1$ (c 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 30°C, TMS): $\delta = 7.45$–7.27 (m, 5H; Ph), 5.70 (bs, 1H; NH), 5.12 (bs, 2H; CH_2Ph), 3.70 (s, 3H; OCH_3), 3.34–3.10 (m, 3H; CH_2, CHCO$_2$), 2.86–2.58 (m, 2H; CH_2), 2.48–2.34 (m, 1H; CHH), 2.26–1.74 (m, 5H; CHH, 2×CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 30°C, TMS): $\delta = 174.8$, 156.4, 136.7, 128.3, 128.1, 127.8, 66.3, 65.5, 53.6, 53.2, 51.8, 39.6, 29.4, 23.4; IR ($CHCl_3$): $\nu = 3418$, 2955, 2823, 1715, 1512, 1456 cm^{-1}; MS (EI HR, 70 eV) calcd for $[C_{16}H_{22}N_2O_4]^+$: 306.15796, found: 306.15780. Anal. calcd for $C_{16}H_{22}N_2O_4$: C, 62.74; H, 7.19; N, 9.15. Found: C, 62.57; H, 7.37; N, 9.03%.

4.3.2. (2*S*)-*N*-(*N*′-(Benzyloxycarbonyl)-3′-aminopropyl))-proline methyl ester 2b. A yellow oil; $[\alpha]_D^{20} = -62.3$ (c 1.43 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta = 7.37$–7.26 (m, 5H; Ph), 5.89 (bs, 1H; NH), 5.11 (bs, 2H; CH_2Ph), 3.69 (s, 3H; OCH_3), 3.36–3.25 (m, 2H; CH_2NH), 3.18–3.12 (m, 2H; NCHH, CHCO$_2$), 2.80–2.78 (m, 1H; NCHH), 2.46–2.39 (m, 1H; NCHH), 2.24 (d_{AB}, 1H, $J_{AB} = 8.5$ Hz, $\delta_{AB} = 16.9$ Hz; NCHH), 2.15–2.06 (m, 1H; CHH), 1.94–1.75 (m, 3H; CHH,

CH_2), 1.71–1.61 (m, 2H; CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): δ = 174.8, 156.6, 137.0, 128.5, 127.8, 66.3, 66.1, 52.9, 52.6, 51.8, 39.5, 29.3, 27.8, 23.2; IR ($CHCl_3$): ν = 3451, 3349, 2954, 2813, 1714, 1517, 1438 cm^{-1}; MS (EI HR, 70 eV) calcd for $[C_{17}H_{24}N_2O_4]^+$: 320.17361, found: 320.17479.

4.3.3. (2*S*)-*N*-(*N*′-(Benzyloxycarbonyl)-4′-aminobutyl))-proline methyl ester 2c. A yellow oil; $[\alpha]_D^{20} = -44.3$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 46°C, TMS): δ = 7.35–7.26 (m, 5H; Ph), 5.18 (bs, 1H; N*H*), 5.09 (bs, 2H; CH_2Ph), 3.68 (s, 3H; OCH_3), 3.24–3.08 (m, 4H; CH_2NH, NC*H*H, C*H*CO_2), 2.70–2.63 (m, 1H; NC*H*H), 2.44–2.37 (m, 1H; NCH*H*), 2.36–2.29 (m, 1H; NCH*H*), 2.12–2.02 (m, 1H; C*H*H), 1.94–1.73 (m, 3H; CH*H*, CH_2), 1.60–1.48 (m, 4H; 2×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 46°C, TMS): δ = 174.6, 156.5, 136.9, 128.4, 128.0, 127.9, 66.6, 66.0, 54.5, 53.3, 51.5, 41.0, 29.3, 27.8, 26.0, 23.2; IR ($CHCl_3$): ν = 3453, 2953, 2813, 1720, 1516, 1455, 1438 cm^{-1}; MS (LSIMS HR) calcd for $[C_{18}H_{27}N_2O_4]^+$: 335.19708, found: 335.19565.

4.4. General procedure for amide bond formation

A mixture of *N*-(benzyloxycarbonyl) aminoester **2a** (2.17 g, 7.10 mmol) and water (0.10 L) was vigorously stirred while refluxed until saponification was complete (TLC). Water was evaporated, followed by azeotropic water removal with dichloromethane (three times) affording crude *N*-(benzyloxycarbonyl) amino acid **3a** (2.1 g) which was used for condensation reaction without further purification. The amino acid **3a** (2.1 g, 7.1 mmol) and triethylamine (4 equiv., 4.0 mL) were dissolved in dry CH_2Cl_2 (70 mL). The solution was cooled to −20°C under argon and *iso*-butylchloroformate (0.93 mL, 7.15 mmol) was added dropwise. The reaction mixture was stirred at −20°C for 1 hour, and then at 0°C for an additional 1 hour. A solution of aminoester hydrochloride (7.20 mmol, 1.50 g) [prepared in parallel by hydrogenolysis of *N*-(benzyloxycarbonyl) aminoester **2a** (7.20 mmol, 2.20 g) in methanolic hydrogen chloride (ca. 0.1 M, 8 mmol) over 5% Pd/C] was added in dry CH_2Cl_2 (25 mL) at 0°C. The reaction mixture was allowed to warm up and was kept at room temperature overnight. Solvents were evaporated, and the residue was taken up in ethyl acetate (0.20 L), washed with water (2×50 mL), brine (50 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 **4a** (2.56 g, 85% yield) as an oil. Amides **4b** (90% yield) and **4c** (75% yield) were obtained analogously.

4.4.1. (2*S*,11*S*)-2,6-Cyclo-11,15-cyclo-17-(benzyloxycarbonylamino)-6,9,15-triaza-10-oxoheptadecanoic acid methyl ester 4a. A yellow wax; $[\alpha]_D^{20} = -70.6$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): δ = 7.78 (bs, 1H; CON*H*), 7.37–7.28 (m, 5H; Ph), 6.50 (bs, 1H; CO_2N*H*), 5.18 (d, 1H, *J* = 12.1 Hz; C*H*HPh), 5.03 (d, 1H, *J* = 12.1 Hz; CH*H*Ph), 3.62 (s, 3H; OCH_3), 3.58–3.47 (m, 2H; 2×NHC*H*H), 3.37–3.31 (m, 1H; NC*H*H), 3.22–3.11 (m, 2H; NHCH*H*, NCH*H*), 3.08–2.97 (m, 2H; 2×C*H*CO), 2.94–2.81 (m, 2H; NHCH*H*, NC*H*H), 2.72 (dt, 1H, J_1 = 3.0 Hz, J_2 = 12.6 Hz; NC*H*H), 2.54 (dt, 1H, J_1 = 3.7 Hz, J_2 = 12.4 Hz; NCH*H*), 2.35–2.26 (m, 2H; NC*H*H, NCH*H*), 2.22–2.11 (m, 1H; C*H*H), 2.10–2.00 (m, 2H; NCH*H*, C*H*H), 1.85–1.60 (m, 6H; 2×CH*H*, 2×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): δ = 174.9, 174.7, 157.1, 136.9, 128.4, 128.3, 128.1, 67.8, 66.5, 66.2, 55.2, 54.8, 53.4, 53.1, 51.8, 40.1, 37.2, 30.4, 29.5, 24.1, 22.9; IR ($CHCl_3$): ν = 3360, 2884, 2816, 1714, 1655, 1526, 1439 cm^{-1}; MS (EI HR, 70 eV) calcd for $[C_{23}H_{34}N_4O_5]^+$: 446.25292, found: 446.25212. Anal. calcd for $C_{23}H_{34}N_4O_5 \cdot 0.5H_2O$: C, 60.66; H, 7.69; N, 12.31. Found: C, 60.86; H, 7.64; N, 12.27%.

4.4.2. (2*S*,12*S*)-2,6-Cyclo-12,16-cyclo-19-(benzyloxycarbonylamino)-6,10,16-triaza-11-oxononadecanoic acid methyl ester 4b. A yellow oil; $[\alpha]_D^{20} = -71.8$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): δ = 7.61 (bs, 1H; CON*H*), 7.37–7.28 (m, 5H; Ph), 5.23 (bs, 1H; CO_2N*H*), 5.09 (bs, 2H; CH_2Ph), 3.67 (s, 3H; OCH_3), 3.43–3.36 (m, 1H; NHC*H*H), 3.32–3.19 (m, 3H; NHCH_2, NHCH*H*), 3.18–3.11 (m, 3H; C*H*CO_2, NCH_2), 2.99 (dd, 1H, J_1 = 5.0 Hz, J_2 = 9.9 Hz; C*H*CO), 2.74 (dt, 1H, J_1 = 7.9 Hz, J_2 = 12.0 Hz; NC*H*H), 2.69–2.60 (m, 1H; NCH*H*), 2.45–2.37 (m, 2H; NCH_2), 2.31–2.23 (m, 2H; NCH_2), 2.18–2.06 (m, 2H; CH_2), 1.98–1.62 (m, 10H; 5×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): δ = 174.7, 174.6, 156.5, 136.7, 128.4, 128.0, 68.1, 66.5, 66.1, 53.9, 53.2, 53.0, 51.7, 39.1, 37.3, 30.5, 29.2, 28.6, 24.0, 23.1; IR ($CHCl_3$): ν = 3451, 3348, 2953, 2815, 1719, 1658, 1520, 1455 cm^{-1}; MS (LSIMS HR) calcd for $[C_{25}H_{39}N_4O_5]^+$: 475.29205, found: 475.29123.

4.4.3. (2*S*,13*S*)-2,6-Cyclo-13,17-cyclo-21-(benzyloxycarbonylamino)-6,11,17-triaza-12-oxoheneicosanoic acid methyl ester 4c. A yellow oil; $[\alpha]_D^{20} = -70.5$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): δ = 7.39–7.29 (m, 5H; Ph), 5.22 (bs, 1H; CO_2N*H*), 5.09 (bs, 2H; CH_2Ph), 3.69 (s, 3H; OCH_3), 3.32–3.08 (m, 6H), 3.00 (dd, 1H, J_1 = 4.7 Hz, J_2 = 10.1 Hz; C*H*CO), 2.70–2.63 (m, 1H), 2.61–2.53 (m, 1H), 2.47–2.23 (m, 4H), 2.18–2.02 (m, 2H), 1.99–1.43 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): δ = 174.9, 174.8, 156.5, 136.6, 128.5, 128.1, 128.0, 67.9, 66.5, 66.2, 55.7, 54.8, 53.8, 53.5, 51.7, 40.9, 38.6, 30.6, 29.3, 28.0, 27.6, 26.3, 26.1, 24.2, 23.1; IR ($CHCl_3$): ν = 3453, 3348, 2948, 2867, 2814, 1719, 1658, 1520, 1456, 1438 cm^{-1}; MS (LSIMS HR) calcd for $[C_{27}H_{43}N_4O_5]^+$: 503.32335, found: 503.32445. Anal. calcd for $C_{27}H_{42}N_4O_5 \cdot 0.5H_2O$: C, 63.41; H, 8.41; N, 10.96. Found: C, 63.40; H, 8.69; N, 10.78%.

4.5. Macrocyclization procedures

N-Cbz-Protected aminoesters **4a**–**c** were subjected to catalytic hydrogenation (H_2 over Pd/C in methanol) prior to cyclization reactions. Each of the following procedures (A–C) are exemplified by the preparation of one of the macrocyclic bisamides (**5b**, **5a**, and **5c**, respectively).

4.5.1. Procedure A. The aminoester (1.53 g, 4.5 mmol), obtained from **4b**, was dissolved in 0.4 M sodium methoxide methanolic solution (0.45 L) and allowed to stand at room temperature for 28 days. After neutralization with hydrogen chloride in methanol, the solvent was evaporated, and the solid residue was extracted with CH_2Cl_2. The combined extracts were passed through a short Celite plug and the solvent was evaporated. The crude product was purified by column chromatography (CH_2Cl_2/methanol = 19/1), and finally recrystallized from CH_2Cl_2/Et_2O to afford the macrocyclic bislactam **5b** (1.14 g, 82% yield).

4.5.2. Procedure B. The aminoester (593 mg, 1.90 mmol), obtained from **4a**, was dissolved in 0.5 M NaOH solution in methanol (0.20 L), and allowed to stand at room temperature for 6 days. The reaction mixture was neutralized 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 = 19/1), followed by recrystallization from CH_2Cl_2/hexanes, afforded the macrocyclic bislactam **5a** (430 mg, 81% yield).

4.5.3. Procedure C. A solution of the aminoester (144 mg, 0.391 mmol), obtained from **4c**, in methanol (2.5 mL) was filled into a Teflon® ampule, placed in a high-pressure vessel filled with ligroin as a transmission medium and compressed at 10 kbar and 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 = 19/1), followed by recrystallization from CH_2Cl_2/hexanes, to afford the macrocyclic bislactam **5c** (70 mg, 53% yield).

4.5.4. (6*S*,15*S*)-1,4,10,13-Tetraazatricyclo[13.3.0.0^{6,10}]-octadecane-5,14-dione 5a. Colorless needles; mp 153–155°C; $[\alpha]_D^{20} = -183$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta = 7.60$ (bd, 2H, $J = 8.2$ Hz; 2×N*H*), 3.79–3.73 (ddt, 2H, $J_1 = 3.3$ Hz, $J_1 = 9.5$ Hz, $J_1 = 17.1$ Hz; 2×NHC*H*H), 3.37–3.32 (m, 2H; 2×NC*H*H), 3.12 (dd, 2H, $J_1 = 5.4$ Hz, $J_2 = 10.4$ Hz; 2×C*H*CO), 2.91 (ddt, 2H, $J_1 = 2.8$ Hz, $J_1 = 10.5$ Hz, $J_1 = 13.5$ Hz; 2×NHCH*H*), 2.69–2.58 (m, 4H; 2×NCH_2), 2.35 (m, 2H; 2×NCH*H*), 2.27–2.17 (m, 2H; 2×C*H*H), 1.93–1.81 (m, 6H; 2×CH*H*, 2×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta = 174.4$, 68.4, 56.4, 53.7, 37.1, 30.2, 24.7; IR (KBr): $\nu = 3305$, 2947, 2800, 1658, 1534, 1440 cm^{-1}; MS (EI HR, 70 eV) calcd for $[C_{14}H_{24}N_4O_2]^+$: 280.18993, found: 280.19006. Anal. calcd for $C_{14}H_{24}N_4O_2$: C, 60.00; H, 8.57; N, 20.00. Found: C, 59.78; H, 8.52; N, 20.03%.

4.5.5. (7*S*,17*S*)-1,5,11,15-Tetraazatricyclo[15.3.0.0^{7,11}]-icosane-6,16-dione 5b. Colorless needles; mp 250°C (decomp.); $[\alpha]_D^{20} = -182$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta = 7.78$ (bs, 2H; 2×N*H*), 3.41–3.35 (m, 4H; 2×CH_2), 3.24–3.19 (m, 2H; 2×CH*H*), 2.98 (dd, 2H, $J_1 = 5.7$ Hz, $J_2 = 9.9$ Hz; 2×C*H*), 2.87–2.80 (m, 2H; CH*H*), 2.45–2.39 (m, 2H; CH*H*), 2.27–2.17 (m, 4H; 4×CH*H*), 1.95–1.60 (m, 10H; 2×CH*H*, 4×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta = 174.5$, 69.5, 54.0, 53.1, 38.2, 30.3, 26.3, 24.0; IR ($CHCl_3$): $\nu = 3334$, 2820, 1660, 1528 cm^{-1}; MS (EI HR, 70 eV) calcd for $[C_{16}H_{28}N_4O_2]^+$: 308.22123, found: 308.22126. Anal. calcd for $C_{16}H_{28}N_4O_2$: C, 62.3; H, 9.09; N, 18.1. Found: C, 62.2; H, 9.01; N, 18.1%.

4.5.6. (8*S*,19*S*)-1,6,12,18-Tetraazatricyclo[17.3.0.0^{8,12}]-docosane-7,18-dione 5c. Colorless needles; mp 163–165°C; $[\alpha]_D^{20} = -165$ (*c* 0.41 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta = 7.50$ (bs, 2H; 2×N*H*), 3.65–3.57 (m, 2H; 2×NHC*H*H), 3.25–3.19 (m, 2H; 2×NC*H*H), 3.03 (dd, 2H, $J_1 = 4.7$ Hz, $J_2 = 10.1$ Hz; 2×C*H*), 2.98–2.91 (m, 2H; 2×NHCH*H*), 2.55–2.45 (m, 4H; 2×NCH_2), 2.35–2.29 (m, 2H; 2×NHCH*H*), 2.21–2.13 (m, 2H; 2×C*H*H), 1.86–1.43 (m, 14H; 2×CH*H*, 6×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta = 175.0$, 68.0, 55.8, 54.5, 37.9, 30.4, 27.6, 27.2, 24.4; IR (KBr): $\nu = 3303$, 2944, 2867, 2780, 1652, 1520, 1457 cm^{-1}; MS (ESI HR, CH_3OH) calcd for $[C_{18}H_{33}N_4O_2]^+$: 337.2598, found: 337.2623. Anal. calcd for $C_{18}H_{32}N_4O_2$: C, 64.29; H, 9.52; N, 16.67. Found: C, 64.58; H, 9.51; N, 16.39%.

4.6. Reduction of dioxocyclam 5b

4.6.1. (7*S*,17*S*)-1,5,11,15-Tetraazatricyclo[15.3.0.0^{7,11}]-icosane-6-one 6b. To a vigorously stirred suspension of **5b** (102 mg, 0.331 mmol) in dry THF (10 mL), under argon, $BH_3{\cdot}Me_2S$ complex in THF (~10 M, 2.0 mmol, 0.20 mL) was added dropwise. The reaction mixture was then stirred at reflux for 4 h. The mixture was cooled to room temperature and a mixture of THF/water = 4/1 was carefully added (3 mL) and the solvents were evaporated to dryness. The resulting solid was taken up in 6 M aq. HCl (10 mL) and a suspension was stirred at reflux until the mixture turned clear (ca. 25 min.). The solvents were then evaporated to dryness, the solid residue was dissolved in 4 M aq. NaOH (5 mL) and extracted with $CHCl_3$ (5×10 mL). The combined extracts were dried (Na_2SO_4) and the solvents were evaporated. Chromatographic separation of the post-reaction mixture (CH_2Cl_2/methanol = 9/1) afforded the unreacted substrate **5b** (18 mg) and title compound (46 mg, 57% yield calculated on converted substrate) as a colorless oil; $[\alpha]_D^{20} = -66.5$ (*c* 0.66 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta = 8.50$ (br. s, 1H; CON*H*), 3.89–3.81 (m, 1H; CH*H*), 3.64–3.28 (m, 2H; N*H*, CH*H*), 3.22 (t, 1H; $J = 7.5$ Hz; CH*H*), 3.09–3.01 (m, 2H; 2×CH*H*), 2.98 (dt, 1H, $J_1 = 9.2$ Hz, $J_2 = 2.9$ Hz; CH*H*), 2.88 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 9.6$ Hz; C*H*), 2.84–2.76 (m, 2H; CH*H*, CH*H*), 2.70 (dd, 1H, $J_1 = 2.6$ Hz, $J_2 = 11.6$ Hz; CH*H*), 2.66–2.61 (m, 1H; C*H*), 2.60–2.51 (m, 2H; 2×CH*H*), 2.47–2.40 (m, 1H; CH*H*), 2.27–2.10 (m, 3H; 2×CH*H*, CH*H*), 2.06–1.96 (m, 2H; CH*H*, CH*H*), 1.95–1.59 (m, 9H; 2×CH*H*, 2×CH_2, CH*H*, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta =$ 174.3, 70.3, 63.9, 56.7, 56.1, 54.5, 53.1, 52.5, 51.9, 39.9, 30.5, 27.9, 26.5, 26.4, 24.4, 23.5; IR ($CHCl_3$): $\nu = 3289$, 2971, 2949, 2879, 2812, 1651, 1526, 1464, 1146,

Table 2. Crystal data and structure refinement for compounds **5a–c**

Identification code	**5a**	**5b**	**5c**
Empirical formula	$C_{14}H_{24}N_4O_2$	$C_{16}H_{28}N_4O_2$	$C_{18}H_{32}N_4O_2$
Formula weight	280.37	308.42	336.48
Temperature (K)	293(2)	293(2)	293(2)
Wavelength (Å)	1.54178	1.54178	1.54178
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$C2$
a (Å)	11.842(1)	5.078(1)	20.403(5)
b (Å)	10.284(1)	19.230(4)	5.2552(5)
c (Å)	13.127(1)	9.107(2)	17.862(2)
β (°)	103.930(7)	105.16(3)	104.42(1)
Volume (Å^3)	1551.6(2)	858.3(3)	1854.9(5)
Z	4	2	4
Calculated density (Mg m^{-3})	1.200	1.193	1.205
μ (mm^{-1})	0.664	0.642	0.634
$F(000)$	608	336	736
θ Range (°)	3.85–64.62	4.60–73.80	4.48–66.21
Index ranges	$0\le h\le 13,\ -12\le k\le 0,$ $-15\le l\le 14$	$0\le h\le 6,\ -23\le k\le 0,$ $-11\le l\le 10$	$0\le h\le 23,\ -6\le k\le 0,$ $-20\le l\le 20$
Reflections collected/unique	1580/1505 [R(int) = 0.0243]	1663/1491 [R(int) = 0.0277]	1331/1291 [R(int) = 0.0354]
Refinement method	Full-matrix least-squares on F^2		
Data/restraints/parameters	1505/1/378	1491/1/232	1291/1/226
GooF	0.946	0.913	1.076
R indices [$I>2\sigma(I)$]	$R_1 = 0.0537,\ wR_2 = 0.1305$	$R_1 = 0.0846,\ wR_2 = 0.1664$	$R_1 = 0.0866,\ wR_2 = 0.2162$
Absolute structure parameter	0.1(8)	0.3(5)	0.4(1)
Extinction coefficient	0.0045(8)	0.93(6)	0.020(2)
Largest difference peak and hole (e Å^{-3})	0.159 and −0.176	0.360 and −0.505	0.237 and −0.266

1129 cm^{-1}; MS (EI HR, 70 eV) calcd for $[C_{16}H_{30}N_4O]^+$: 294.24196, found: 294.24148.

4.6.2. (7*S*,17*S*)-1,5,11,15-Tetraazatricyclo[15.3.0.0^{7,11}]-icosane 7b. To a vigorously stirred suspension of **5b** (101 mg, 0.328 mmol) in dry THF (10 mL), under argon atmosphere, $BH_3{\cdot}Me_2S$ complex in THF (~10 M, 6.4 mmol, 0.64 mL) was added dropwise. The reaction mixture was then stirred at reflux for 20 h. It was cooled to room temperature, a mixture of THF/water = 4/1 was carefully added (5 mL) and solvents were evaporated to dryness. The resulting solid was taken up in 6 M aq. HCl (10 mL) and a suspension was stirred at reflux until a mixture became a clear solution (ca. 1 h). Solvents were then evaporated to dryness, the solid residue was dissolved in 4 M aq. NaOH (6.5 mL) and extracted with $CHCl_3$ (5×10 mL). Combined extracts were dried (Na_2SO_4) and solvents were evaporated. Chromatographic purification of the crude product (methanol/aq. NH_3 = 19/1) afforded title compound (70 mg, 75% yield) as a colorless oil; $[\alpha]_D^{20} = -56.5$ (c 0.60 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): δ = 3.35–3.30 (m, 2H; 2×CH*H*), 2.94–2.88 (m, 2H; 2×CH*H*), 2.84 (dt, 2H, J_1 = 2.6 Hz, J_2 = 12.6 Hz; 2×CH*H*), 2.67–2.63 (m, 4H; 2×CH_2), 2.54 (dt, 2H; J_1 = 1.9 Hz, J_2 = 11.0 Hz; 2×CH*H*), 2.49–2.43 (m, 2H; 2×C*H*), 2.39–2.34 (m, 2H, 2×CH*H*), 2.06–1.91 (m, 6H; 2×CH_2, 2×CH*H*), 1.83–1.58 (m, 8H; 2×CH*H*, 2×CH_2, 2×CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): δ = 64.2, 56.4, 54.3, 52.3, 51.9, 27.6, 27.3, 24.1; IR ($CHCl_3$): ν = 3272, 2946, 2877, 2802, 1458, 1357, 1133 cm^{-1}; MS (EI HR, 70 eV) calcd for $[C_{16}H_{32}N_4]^+$: 280.26270, found: 280.26180.

4.7. X-Ray structure analysis of compounds 5a–c

X-Ray data were collected on a Nonius MACH3 four-circle diffractometer using the EXPRESS procedure.[18] The ω–2θ scanning mode was applied. Unit cell parameters were obtained by refinement of 25, 15, and 25 reflections in the θ-range 21.0–41.3, 18.7–23.3, and 20.9–43.2° for compounds **5a–c**, respectively. Data reduction was performed with the use of an OpenMoleN system.[19] Structures were solved with direct methods using the SHELXS-86[20] program and refined with SHELXL-97.[21] Crystal data and details of structure solution and refinement are shown in Table 2.

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