Synthesis of a Cyclen-Functionalized α-Amino Acid and its Incorporation into Peptide Sequence

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Abstract: A cyclen-functionlized α-amino acid was obtained through embedding cyclen into the side chain of homoserine. The α-amino acid can be conveniently incorporated into peptide sequence to form new ligands, which have strong coordination ability for transition metal ions.

Key words: cyclen, unnatural amino acid, metallopeptides

In recent years, there has been an enormous interest in the synthesis of novel amino acids and peptides with unnatural side-chain functionalities due to their biological and toxicological properties.[1] Among the variety of unnatural amino acids, ligand-functionlized α-amino acid that can bind metal ions, are of special interest for their applications in the design of metalloproteins,[2,3] metallopeptides[4,5] and for the study of electron transfer in peptides.[6] Cyclen (1,4,7,10-tetraazacyclododecane) has strong coordination ability towards a wide range of cations, including transition metal ions and lanthanide ions,[7,8] and their complexes have been widely used as MRI contrast agents,[8,9] luminescent probes,[10,11] DNA recognition,[12,13] DNA cleavers,[14] enzyme mimics,[15,16] and medicines for radioimmunotherapy.[17,18] Yet, cyclen-functionalized amino acids and peptides with large affinity constants for transition metal ions are apparently rare. Suh and co-workers reported that cyclen can be located into the N-terminal of amino acids and demonstrated that their Cu(II) or Co(III) complexes can be used as catalytic drugs to promote the selective cleavage of protein.[19] Miltschitzky and Konig synthesized a glutamic derivative with protected cyclen side chain functionality.[20] The cyclen was anchored on the O-terminal of amino acids. Burger and Still found that the metal ion-binding properties of peptide-substituted cyclens do indeed vary with the nature of the peptide sequences and suggested that ionophore libraries having members capable of selectively binding many different ions are best constructed around cores that have relatively poor intrinsic ion-binding selectivities.[21] In all of the examples the cyclen core, attached through a linker, can be located at the terminus of a peptide, unlike the natural metalloenzymes where ligands for coordination with metal ions are always in the sequence of peptides. To develop a methodology applicable for designing a ligand-functionalized peptides in the side chains, we report here the synthesis of a cyclen-functionalized homoserine as a novel building block, which was conveniently incorporated into peptide sequence in high yield. The important building block is a particularly interesting target because: 1) the cyclen-functionalized peptides can be extended from N-terminal or C-terminal to synthesize multi-functionalized peptides; and 2) the cyclen-functionalized peptides can form stable complexes with different metal ions and that binding might be so dominated by the cyclen cores that the substituents would exert little effect.

Cyclen[22] and L-homoserine[23] were prepared as previously reported. Selective monoalkylation of cyclen can be run using two main strategies, i.e. direct alkylation of an excess of cyclen with the appropriate alkyl halide[24] or selective N-functionalization followed by alkylation-deprotection steps.[25] In this paper the selective monoalkylation of cyclen was first chosen to synthesize the aimed product **10** as described in Scheme 1. The amino group of L-homoserine (**3**) was protected with Boc (*tert*-butyloxycarbonyl) group and then the carboxyl group was converted to benzyl ester **4**. The hydroxyl group of *N*-Boc homoserine benzyl ester **4** was activated with *p*-toluenesulfonyl chloride to give active compound **5**, which was conveniently converted to bromo compound **6** in 73% yield by treatment with NaBr. Unfortunately, the coupling of **6** and tri-Boc-protected cyclen **7** did not give the desired product **10** due to the strong hindrance of **6**, which was facilely converted to the undesired product **8** in high yield (Scheme 2). The methyl ester of 4-bromo-2-*tert*-butyloxycarbonylaminobutanoic acid was also chosen as a starting material to synthesize 4-[tris(*N*-*tert*-butyloxycarbonyl)cylcen]-2-*N*-*tert*-butyloxycarbonylaminobutanoic acid methyl ester, an analogue of compound **10**, which similarly afforded the desired product in poor yield because of the direct formation of lactone **8**.

Alternatively, we turned our attention to the direct use of cyclen to synthesize cyclen-functionalized amino acid. As a general synthetic method, cyclen should be able to react with different activated or non-activated alkyl bromides due to its excellent nucleophilicity. In the traditional statistical method, a large excess amount of costly cyclen is needed. Previously Li and Wong found that 2 equivalents of tetraazamacrocycles versus alkylating agents is necessary to maintain the high yield of mono N-alkylated prod-

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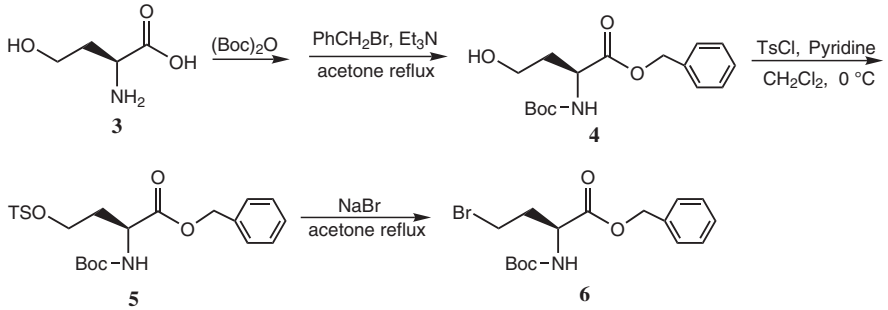
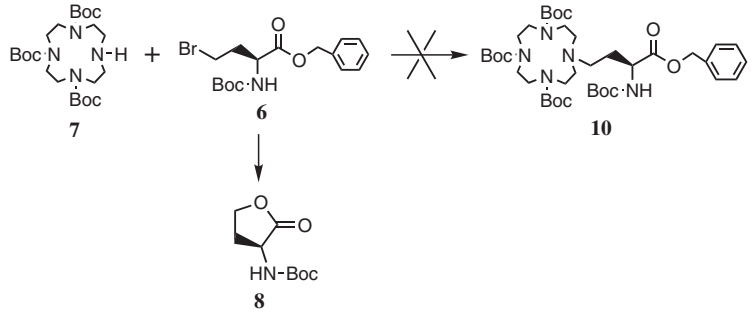
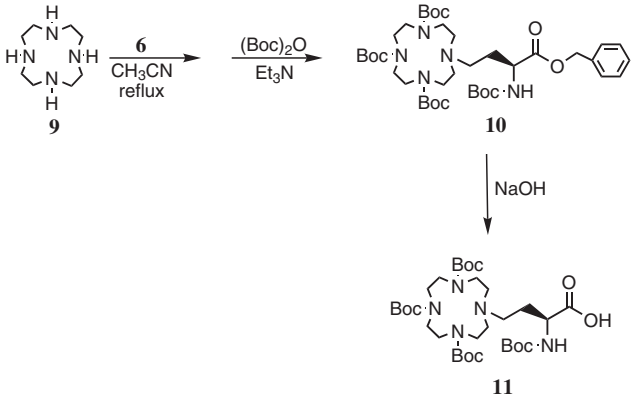


Scheme 1



Scheme 2

ucts.[26] We have now found that 1.8 equivalents of cyclen (**9**) can be used for coupling with **6**. Because the direct coupling product was very difficult to purify, the alkylation of cyclen (**9**) with compound **6** followed by protection with Boc group were employed and provided the desired compound **10** in 79% yield (Scheme 3). As a key intermediate, fully *N*-Boc protected product **11** could be obtained in 92% yield through the alkaline hydrolysis of **10**.



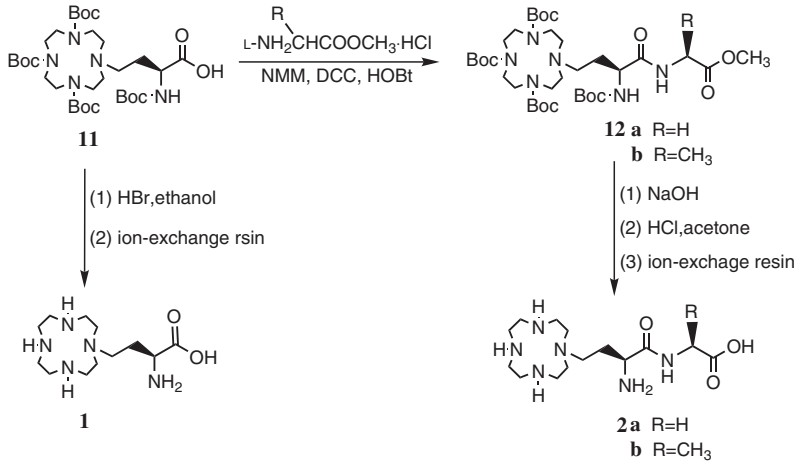
Scheme 3

As outlined in Scheme 4, compound **11** can be conveniently converted to cyclen-functionalized amino acid **1** in 91% yield by deprotection of Boc group with 47% HBr, which can be used as an important building block for the synthesis of multi-functionalized organic compounds or complexes.

By using DCC as coupling agent, in the presence of NMM, the protective cyclen-functionalized amino acid **11** was facilely coupled with L-amino acid methyl ester hydrochloride to afford the desired product **12** in over 60% yield. The saponification of **12** with aqueous 2 N sodium hydroxide solution was monitored by TLC and followed to remove the Boc group by HCl in acetone. The hydrochloride of compound **2** was eluted over a basic anion exchange column to give the cyclen-functionalized dipeptide **2** in high yield (Scheme 4). Preliminary results indicate that the affinity of cyclen-functionalized dipeptide (as free base) towards transition metal ions such as Zn^{2+} is not affected by its incorporation into peptide. The synthesis of complexes of cyclen-functionalized dipeptide and their catalytic feature for hydrolytic reaction is currently pursued in our laboratory.

In conclusion, a cyclen-functionalized amino acid as a new ligand with strong binding ability for metal ions has been synthesized. Our results indicate that the functionalized α-amino acid as a novel building block can be incorporated into peptide sequence conveniently.

ESI-MS and HRMS spectral data were recorded on Finnigan LCQ^{DECA} and Bruker Daltonics Bio TOF mass spectrometer respectively. IR spectra were recorded on FT-IR 16PC spectrometer. ^{1}H NMR spectra were measured on a Varian INOVA-400 spectrometer and chemical shifts in ppm are reported relative to internal Me_4Si ($CDCl_3$) or 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt (D_2O). ^{13}C NMR spectra were measured on a Bruker Avance 600 spectrometer. Polarimetric analyses were determined on a WZZ-2B automatic polarimeter. Melting points were determined by using a micro-melting point apparatus without any corrections. All chemi-



Scheme 4

cals and reagents were obtained commercially and used without further purification. Petroleum ether used had bp 60–90 °C.

N-tert-Butyloxycarbonyl-L-homoserine Benzyl Ester (4)

To a stirred solution of L-homoserine (**3**; 11.9 g, 100 mmol) in H_2O (100 mL) was added dioxane (50 mL), solid $NaHCO_3$ (8.4 g, 200 mmol) and di-*tert*-butyl dicarbonate (26 g, 120 mmol). After stirring for 20 h at r.t., the solution was neutralized with aq sat. citric acid, and concentrated to 60 mL in vacuo. The mixture was acidified with aq 10% citric acid, and extracted with EtOAc (4 × 20 mL). The EtOAc extracts were combined and dried (Na_2SO_4). Then the solvent was evaporated in vacuo. To the residue in acetone (100 mL) was added Et_3N (12.3 mL, 100 mmol) and benzyl bromide (20.5 g, 120 mmol). After refluxing for 5 h, the solvents were evaporated and the residue was dissolved in EtOAc (100 mL). The EtOAc layer was washed with 0.5 N HCl, and dried (Na_2SO_4). After evaporating the solvent, petroleum ether was added and shaken well. The mixture was stored overnight in a refrigerator, filtered and washed with petroleum ether to give a white solid; yield: 21.6 g (70%, based on the amount of homoserine); mp 58–59 °C.

ESI-MS: *m*/*z* = 344.2 (M + Cl).

N-tert-Butyloxycarbonyl-*O*-tosyl-L-homoserine Benzyl Ester (5)

To a solution of *N*-Boc-L-homoserine benzyl ester (**4**; 9.27 g, 30 mmol) in anhyd CH_2Cl_2 (60 mL) was added *p*-toluenesulfonyl chloride (8.6 g, 45 mmol), followed by anhyd pyridine (10 mL) and the mixture was stirred overnight at 0 °C. The CH_2Cl_2 layer was washed with aq citric acid, dried (Na_2SO_4) and evaporated to give a yellow oil which was chromatographed (EtOAc–petroleum ether, 1: 3) to give a white solid; yield: 11.1 g (80%); mp 86–88 °C.

ESI-MS: *m*/*z* = 498.4 (M + Cl).

4-Bromo-2-butyloxycarbonylaminobutanoic Acid 6

To **5** (9.3 g, 20 mmol) in acetone (100 mL) was added NaBr (10.3 g, 100 mmol) and refluxed for 10 h under N_2. After filtration, the solvent was evaporated in vacuo to give a yellow oil. The crude product was chromatographed (EtOAc–petroleum ether, 1: 3) to give a colorless oil, which solidified overnight in a refrigerator; yield: 5.4 g (73%); mp 50–52 °C (Lit.[27] mp 53 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 5 H, C_6H_5), 5.19 (m, 2 H, CH_2Ph), 5.11 (s, 1 H, NH), 4.47 (s, 1 H, C_αH), 3.41 (t, 2 H, *J* = 8.3 Hz, CH_2Br), 2.43 (m, 1 H, $C_\beta H_2$), 2.23 (m, 1 H, $C_\beta H_2$), 1.44 (s, 9 H, CH_3-Boc).

ESI-MS: *m*/*z* = 371.3 (M).

4-[Tris(*N-tert*-butyloxycarbonyl)cyclen]-2-*N-tert*-butyloxycarbonylaminobutanoic Acid Benzyl Ester (10)

To a solution of cyclen (**9**; 3.1 g, 18 mmol) in anhyd MeCN (40 mL) was added **6** (3.73 g, 10 mmol) in anhy MeCN (50 mL) dropwise during 4 h at 85 °C under N_2. The mixture was then refluxed for 3 h. Et_3N (10 mL) was added at r.t., followed by di-*tert*-butyl dicarbonate (14.9 g, 68 mmol). The solution was stirred for another 10 h at r.t. The solvents were removed in vacuo to give a yellow oil which was chromatographed on silica gel (EtOAc–petroleum ether, 1:5) to give an amorphous solid; yield: 5.3 g (79%, based on the amount of **6**); $[\alpha]_D^{20}$ –4.8 (*c* = 0.5, MeOH).

IR (KBr): 3434, 3076, 2976, 1694, 1464, 1416, 1366, 1166 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 5 H, C_6H_5), 5.61 (s, 1 H, NH), 5.23-5.08 (dd, 2 H, *J* = 12.0, 12.4 Hz, CH_2Ph), 4.23 (s, 1 H, C_αH), 3.47–3.25 (m, 12 H, CH_2-cyclen), 2.58–2.49 [m, 6 H, CH_2N(CH_2)CH_2], 1.95–1.89 (m, 2 H, $C_\beta H_2$), 1.44–1.41 (m, 36 H, CH_3-Boc).

^{13}C NMR (600 MHz, $CDCl_3$): δ = 172.2, 156.0, 155.6, 155.2, 135.4, 128.6, 128.4, 79.8, 79.7, 79.5, 79.3, 67.0, 54.8, 53.8, 52.3, 50.1, 48.4, 48.0, 47.7, 47.3, 28.6, 28.4, 28.3, 27.5.

HRMS-ESI: *m*/*z* calcd for $C_{39}H_{66}N_5O_{10}$ $[MH]^+$: 764.4804; found: 764.4763.

4-[Tris(*N-tert*-butyloxycarbonyl)cyclen]-2-*N-tert*-butyloxycarbonylaminobutanoic Acid (11)

To **10** (3.36 g, 5.0 mmol) in MeOH (20 mL), was added NaOH (2 N, 10 mL). The solution was stirred for 1 h at r.t., acidified with citric acid, and extracted with EtOAc (3 × 20 mL). The EtOAc layer was dried (Na_2SO_4) and the solvent was removed in vacuo to give an amorphous solid; yield: 3.09 g (92%); $[\alpha]_D^{20}$ +4.6 (*c* = 0.5, MeOH).

IR (KBr): 3054, 2964, 1684, 1286 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (s, 1 H, NH), 4.05 (s, 1 H, C_αH), 3.50–3.37 (m, 12 H, CH_2-cyclen), 2.91–2.87 [m, 6 H, CH_2N(CH_2)CH_2], 2.03–1.96 (m, 2 H, $C_\beta H_2$), 1.51–1.43 (m, 36 H, CH_3-Boc).

^{13}C NMR (600 MHz, $CDCl_3$): δ = 174.3, 156.1, 155.8, 80.4, 80.0, 79.6, 49.8, 48.7, 48.4, 48.2, 28.5, 28.4, 28.3, 27.6.

HRMS: *m*/*z* calcd for $C_{32}H_{60}N_5O_{10}$ $[MH]^+$: 674.4335; found: 674.4334.

Dipeptides 12a,b; General Procedure

Aminoacid methyl ester hydrochloride (1.0 mmol), 1-hydroxybenzotriazole monohydrate (0.15 g, 1.0 mmol), **11** (0.67 g, 1 mmol) and *N*-methylmorpholine (0.13 mL, 1.2 mmol) were dissolved in anhyd THF (20 mL). The mixture was stirred and cooled in an ice-water bath while 1,3-dicyclohexylcarbodiimide (0.23 g, 1.1 mmol) was added. The mixture was stirred for 1 h at 0 °C and overnight at r.t. The *N*,*N*′-dicyclohexylurea was removed by filtration and the solvents were evaporated in vacuo. The crude product was dissolved in EtOAc (30 mL), and washed with aq 10% citric acid (3 × 10 mL), aq sat. $NaHCO_3$ (3 × 10 mL) and H_2O (2 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo to give an amorphous solid.

12a

Yield: 0.47 g (64%).

IR (KBr): 3326, 2930, 1684 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.04 (s, 1 H, NH), 5.78 (s, 1 H, NH-Boc), 4.10 (s, 1 H, $C_\alpha H$), 4.03 (d, 2 H, *J* = 4.8 Hz, $NHCH_2COOCH_3$), 3.74 (s, 3 H, $COOCH_3$), 3.55–3.36 (m, 12 H, CH_2-cyclen), 2.67 [s, 6 H, $CH_2N(CH_2)CH_2$], 2.01–1.98 (m, 1 H, $C_\beta H_2$), 1.83–1.80 (m, 1 H, $C_\beta H_2$), 1.46–1.44 (m, 36 H, CH_3-Boc).

^{13}C NMR (600 MHz, $CDCl_3$): δ = 172.1, 170.0, 156.1, 155.9, 155.2, 80.0, 79.7, 79.5, 79.3, 55.5, 54.7, 53.2, 50.2, 48.8, 47.5, 47.2, 41.1, 28.6, 28.5, 28.3, 27.0.

HRMS: *m*/*z* calcd for $C_{35}H_{65}N_6O_{11}$ $[MH]^+$: 745.4706; found: 745.4697.

12b

Yield: 0.57 g (75%).

IR (KBr): 3332, 2976, 1690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.08–6.90 (s, 1 H, NH), 5.80–5.70 (s, 1 H, NH-Boc), 4.60–4.52 (m, 1 H, $C_\alpha H$), 4.15–4.06 (m, 1 H, $C_\alpha H$), 3.73 (s, 3 H, $COOCH_3$), 3.53–3.34 (m, 12 H, CH_2-cyclen), 2.65 [s, 6 H, $CH_2N(CH_2)CH_2$], 1.99–1.97 (m, 1 H, $C_\beta H_2$), 1.77–1.71 (m, 1 H, $C_\beta H_2$), 1.46–1.44 (m, 36 H, CH_3-Boc), 1.26 (t, 3 H, *J* = 8.0 Hz, $CH_3C_\alpha H$).

^{13}C NMR (600 MHz, $CDCl_3$): δ = 173.0, 171.4, 156.1, 155.9, 155.2, 79.8, 79.7, 79.5, 79.2, 55.8, 54.9, 53.3, 52.9, 52.3, 50.2, 49.0, 48.5, 48.0, 47.7, 47.5, 28.6, 28.4, 28.3, 27.0, 18.0.

HRMS: *m*/*z* calcd for $C_{36}H_{67}N_6O_{11}$ $[MH]^+$: 759.4862; found: 759.4862.

(2*S*)-2-Amino-4-(1,4,7,10-tetraazacyclododecan-1-yl)butanoic Acid (1)

To a solution of **11** (0.67 g, 1.0 mmol) in EtOH (2 mL) was added 47% HBr (3 mL). After stirring at 0 °C for 4 h, the white solid formed was filtered, and washed with absolute EtOH to give the hydrobromide of **1**. The above hydrobromide was dissolved in H_2O (1.5 mL) and eluted over a basic anion exchange column. The solution was evaporated to dryness under reduced pressure to give **1** as a white solid; yield: 0.23 g (84%); mp 165–170 °C; $[\alpha]_D^{20}$ +13.3 (*c* = 0.6, MeOH).

IR (KBr): 3424, 2960, 1624 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 3.76 (m, 1 H, $C_\alpha H$), 3.04–2.96 (m, 8 H, CH_2-cyclen), 2.95–2.87 (m, 4 H, CH_2-cyclen), 2.86–2.78 [m, 6 H, $CH_2N(CH_2)CH_2$], 1.88–1.83 (m, 2 H, $C_\beta H_2$).

^{13}C NMR (600 MHz, D_2O): δ = 181.1, 56.1, 54.3, 52.2, 51.6, 49.9, 44.5, 44.1, 42.6, 42.2, 29.7.

HRMS: *m*/*z* calcd for $C_{12}H_{27}N_5NaO_2$ $[M + Na]^+$: 296.2057; found: 296.2064.

Compounds 2a,b; General Procedure

To a solution of **12** (0.4 mmol) in MeOH (2 mL) was added aq 2 N NaOH (1 mL). After stirring for 1 h at r.t., the solution was acidified with aq 10% citric acid, and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with H_2O (10 mL) and brine (2 × 15 mL), and dried (Na_2SO_4). The solvent was removed in vacuo to give an amorphous solid. The solid was dissolved in acetone (10 mL) and HCl was bubbled through this solution. After stirring for 2 h at r.t., the white solid formed was filtered, and washed with acetone to give the hydrochloride of compound **2**. The above hydrochloride was dissolved in H_2O (1.5 mL) and eluted over a basic anion exchange column. The solution was evaporated to dryness under reduced pressure to give compound **2** as a white solid.

2a

Yield: 0.11 g (83%); mp 221–225 °C.

IR (KBr): 3422, 2930, 1679 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 3.99 (d, 1 H, *J* = 4.0 Hz, $C_\alpha H$), 3.81 (d, 2 H, *J* = 16.0 Hz, CH_2-Gly), 2.69–3.16 (m, 18 H, CH_2), 2.16–2.10 (m, 1 H, $C_\beta H_2$), 2.06–1.99 (m, 1 H, $C_\beta H_2$).

^{13}C NMR (600 MHz, D_2O): δ = 176.5, 173.1, 54.4, 51.6, 51.5, 51.2, 44.8, 44.4, 44.2, 43.7, 43.3, 42.5, 42.1, 28.3.

HRMS: *m*/*z* calcd for $C_{14}H_{31}N_6O_3$ $[MH]^+$: 331.2452; found: 331.2467.

2b

Yield: 0.10 g (73%); mp 203–208 °C.

IR (KBr): 3422, 2970, 1704 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 4.25–4.20 (m, 1 H, $C_\alpha H$), 4.06–4.03 (m, 1 H, $C_\alpha H$), 3.21 (s, 8 H, CH_2-cyclen), 3.10–2.76 (m, 10 H, CH_2), 2.18–2.12 (m, 2 H, $C_\beta H_2$), 1.41 (d, 3 H, *J* = 8.2 Hz, CH_3).

^{13}C NMR (600 MHz, D_2O): δ = 179.5, 168.2, 51.7, 51.4, 51.3, 47.5, 47.0, 44.3, 42.9, 42.0, 41.5, 25.2, 25.0.

HRMS: *m*/*z* calcd for $C_{15}H_{33}N_6O_3$ $[MH]^+$: 345.2609; found: 345.2626.

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