Accepted Manuscript

Microwave-mediated synthesis of a cyclic heptapeptoid through consecutive Ugi reactions

Angélica de Fátima S. Barreto, Carlos Kleber Z. Andrade

PII: S0040-4020(18)31212-2

DOI: 10.1016/j.tet.2018.10.018

Reference: TET 29851

To appear in: *Tetrahedron*

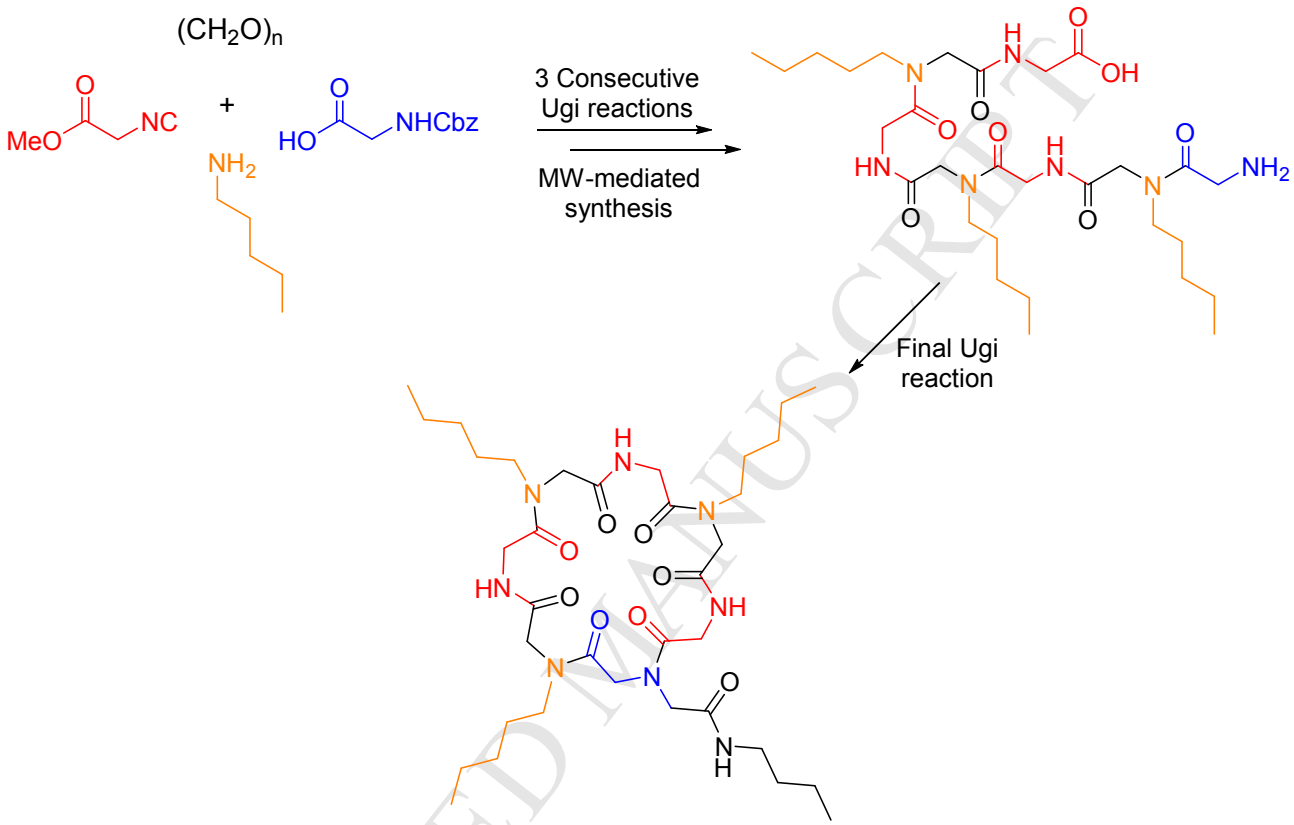
Received Date: 1 August 2018

Revised Date: 6 October 2018

Accepted Date: 10 October 2018

Please cite this article as: Barreto AngéFáS, Andrade CKZ, Microwave-mediated synthesis of a cyclic heptapeptoid through consecutive Ugi reactions, *Tetrahedron* (2018), doi: https://doi.org/10.1016/j.tet.2018.10.018.

Graphical Abstract



Microwave-mediated synthesis of a cyclic heptapeptoid through consecutive Ugi Reactions

Angélica de Fátima S. Barreto and Carlos Kleber Z. Andrade*

Laboratório de Química Metodológica e Orgânica Sintética, Instituto de Química, Universidade de Brasília, 70910-970, Brasília-DF, Brazil.

Email: angelfsb@gmail.com

ckleber@unb.br

*Corresponding author

Abstract

The combination of consecutive Isocyanide-based Multicomponent Reactions (IMCRs) allowed the synthesis of a cyclic heptapeptoid in a reduced number of steps. Herein, we describe this efficient approach using four consecutive Ugi reactions, being three Ugi four-center, four-component reactions, and one Ugi four-center, three-component reaction. Our strategy involved eight steps of which seven in a row were microwave-assisted with reaction times of 3-5 minutes and yields ranging from 88-98%.

Keywords

Cyclic peptoids, consecutive Ugi reactions, Isocyanide-based Multicomponent Reactions (IMCRs), microwave-mediated reactions, macroheterocycles.

1. Introduction

Natural products are an excellent source of new bioactive molecules [1,2,3]. Cyclic peptides occur naturally and exhibit diverse biological activities, such as antitumor, antibacterial and immunosuppressive, among others, and usually show better biological activities than linear peptides due to conformational rigidity. Examples of cyclic peptide drugs are the natural antibiotic Vancomycin and the neuropeptide Vasopressin. Figure 1 shows some structures of cyclic peptides, including the heptapeptides Cupolamide A that is active against P388 murine leukemia cells (IC_{50} = 7.5 μg/mL) [4], Axinellin A, which shows antitumor activity against a human bronchopulmonary carcinoma (IC_{50} = 3.0 μg/mL) [5], and Argyrin B that is a potent inhibitor of T-cell independent antibody formation [6], along with the octadepsipeptoid Verticilide, a potential insecticide with a different mode of action since it acts by inhibiting the binding of ryanodine to ryanodine receptors (RyR) [7,8]. Other important cyclic heptapeptides from natural origin include Cateritins A and B [9], poly-proline Euryjanicins E−G [10], Reniochalistatins A−E [11] and Stylissatins B–D [12], all of them isolated from marine sponges.

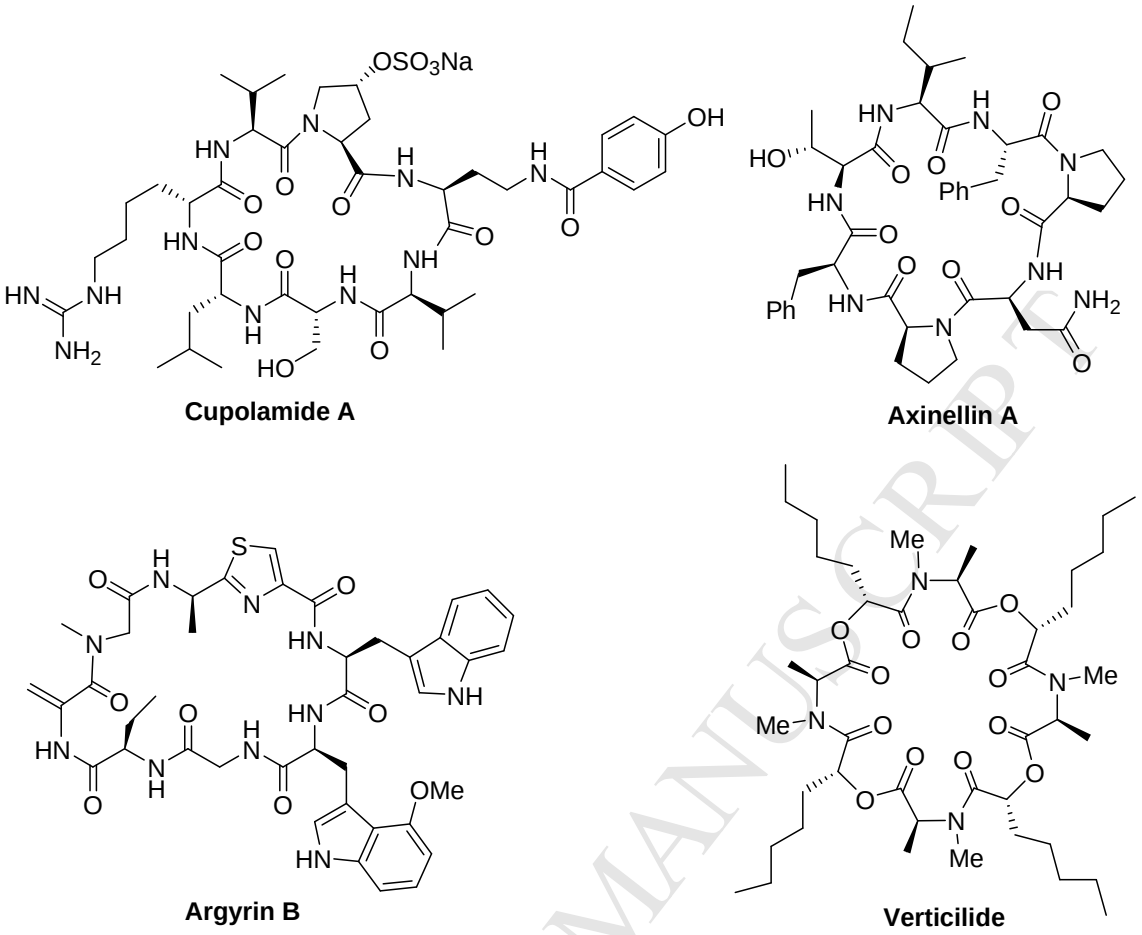


Figure 1. Examples of some bioactive cyclic peptides.

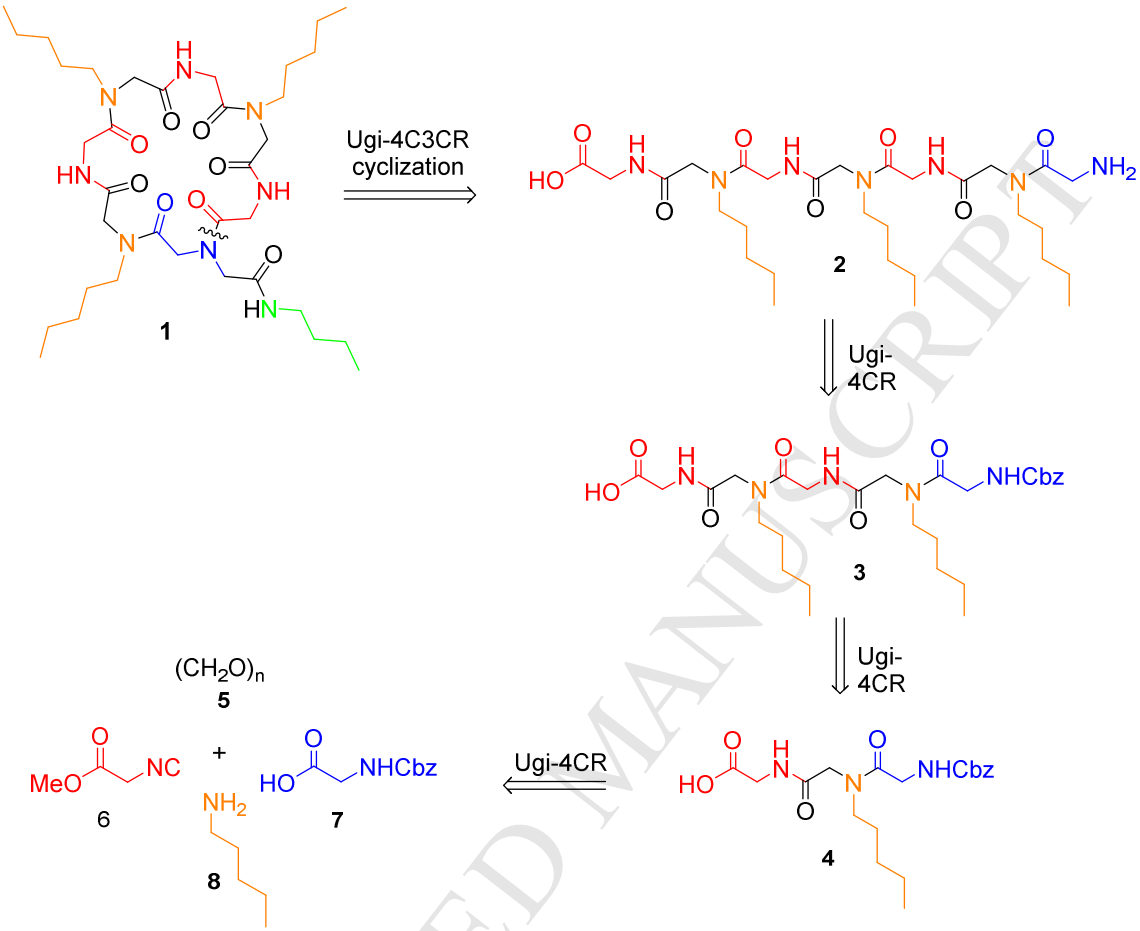
Oligomers of *N*-substituted glycine (peptoids) are versatile mimics of peptides with several advantages such as proteolytic stability and increased cell permeability [13,14]. These mimetics have the ability to link their natural targets in the same way as the natural sequence of peptides [14,15,16]. Cyclic peptoides [17,18,19] show several advantages over their acyclic counterparts such as high conformational stability and resistance to degradation by the action of proteases [20,21]. Furthermore, chirality is removed from the α-carbon atom, so as their H-bonding donor ability [22]. Currently, the Ugi four-component reaction (U-4CR) has proved to be a powerful synthetic strategy for the preparation of a peptoid backbone [23,24,25]. The advantages of this

versatile reaction include the use of commercial or readily available reagents, the avoidance of usually expensive coupling agents for the amide bond formation and the incredible variety of products that can be obtained by simply modifying the structures of the starting materials. Indeed, several works in the literature have shown that the combination of multicomponent reactions produces a plethora of macroheterocycles in a reduced number of steps [26,27,28,29].

In continuing our efforts in using consecutive multicomponent reactions to efficiently obtain novel heterocycles [28,29,30,31,32], herein we describe a concise and efficient strategy for the synthesis of a cyclic heptapeptoid that possesses the core of the molecules represented in Figure 1 with the *N*-pentyl side chains of Verticilide attached to three of its nitrogen atoms. Whereas heptapeptoids have already been described [19,33], to the best of our knowledge, there is only one previous example of a cyclic heptapeptoid in the literature [34]. Furthermore, this is the first example in which four consecutive Ugi reactions were employed in the synthesis of a particular molecule.

The retrosynthetic analysis (Scheme 1) shows that the target cyclic heptapeptoid **1** can be synthesized by three consecutive Ugi four-center, four-component reactions (Ugi-4CR), followed by the respective deprotections/hydrolysis, forming an acyclic intermediate (amino acid **2**) which is then cyclized by an intramolecular Ugi four-center, three-component reaction (Ugi-4C3CR). The use of methyl isocyanoacetate **6** as the isocyanide component is a widely used strategy and allows the obtention of the carboxylic acid component for the subsequent Ugi reactions [35]. Based on previous experience within our research group [26,27,36,37,38], microwave heating was

used in all steps of the synthesis except for the final cyclization step, which greatly speeded up the methodology as will be further discussed.

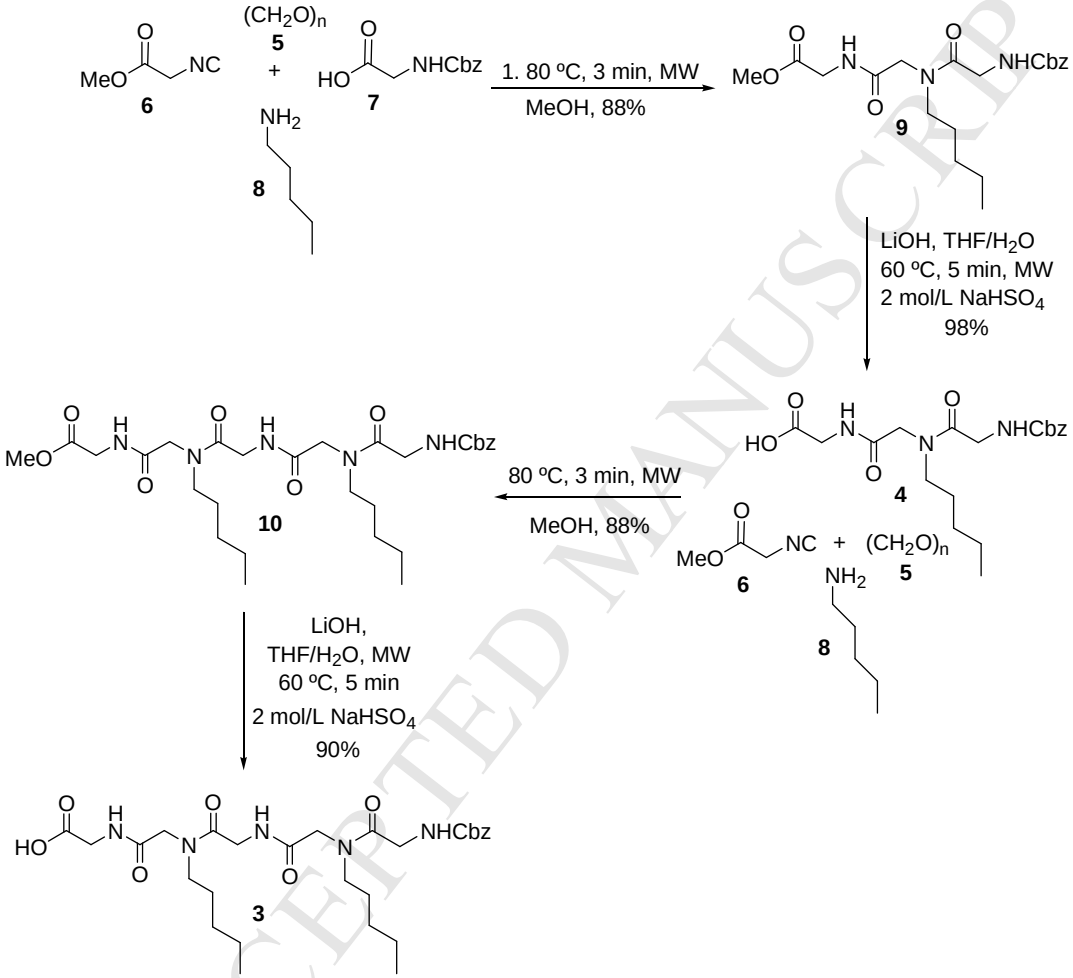


Scheme 1. Retrosynthetic analysis for the synthesis of cyclic heptapeptoid **1**.

2. Results and Discussions

The synthesis of compound **1** was initiated by an Ugi 4-component reaction (U-4CR) between methyl isocyanoacetate **6**, paraformaldehyde **5**, pentylamine **8** and N-*Cbz*-glycine **7** in methanol (80 ºC, 3 min, MW) to obtain peptoid **9** in 88% yield that was subjected to hydrolysis reaction with LiOH (60 ºC, 5 min, THF/H_2O, MW) followed by treatment with 2 mol/L $NaHSO_4$ providing the corresponding acid **4** in 98% yield (Scheme 2). Acid **4** was then employed in another Ugi reaction using paraformaldehyde **5**, pentylamine **8** and methyl

isocyanoacetate **6** in methanol under the same conditions as the first Ugi reaction affording the acyclic tetrapeptoid **10** in 88% yield. Basic hydrolysis as described for compound **9** led to acid **3** in 90% yield.

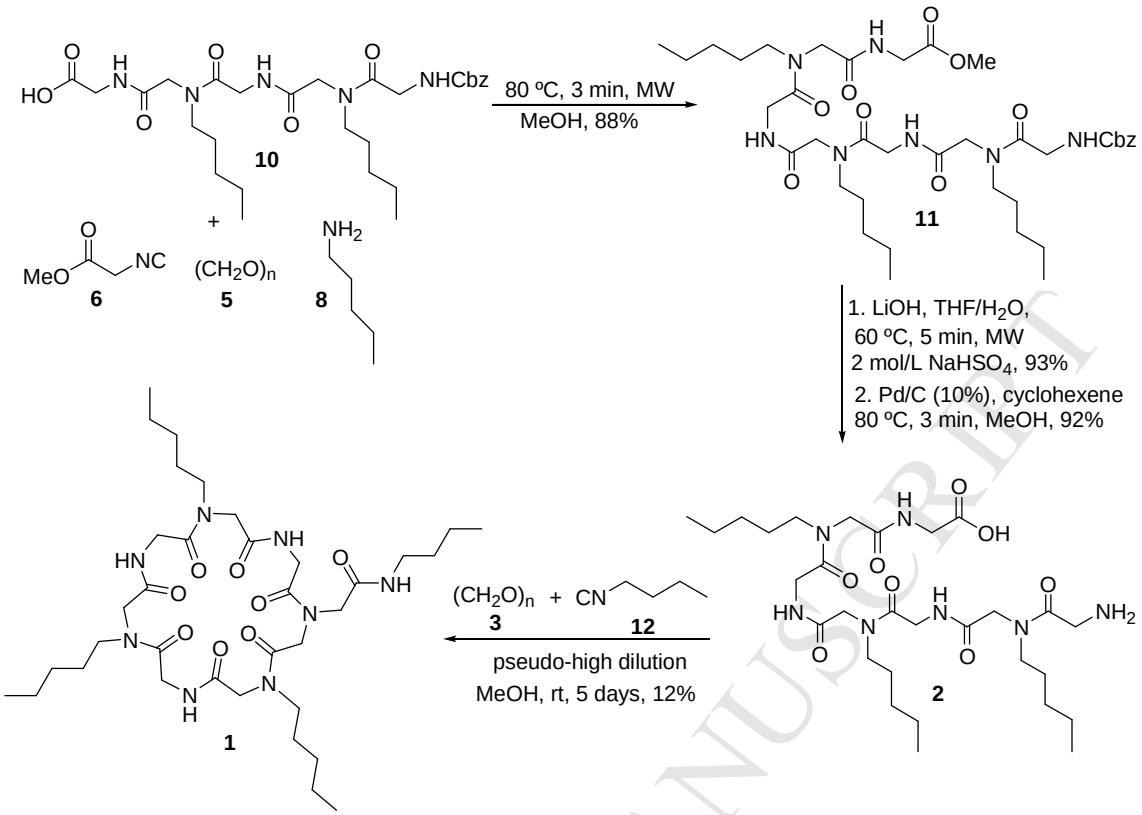


Scheme 2. Synthesis of acid **3**.

Subsequent use of acid **3** in the Ugi reaction with the same components as before (**5**, **6** and **8**) provided the acyclic hexapeptoid **11** in 88% yield (Scheme 3). Ester hydrolysis using lithium hydroxide under microwave irradiation (60 ºC, 5 min, 93%) and removal of the *Cbz* protecting group with Pd/C (10%) and

cyclohexene (80 ºC, 3 min, MeOH, MW) furnished the corresponding amino acid **12** in 92% yield. Up to this point, the acyclic hexapeptoid **2** was remarkably prepared in seven consecutive MW-mediated steps in a total reaction time of only 27 minutes (purification times not included).

In the last step, **2** was subjected to cyclization via an Ugi four-center, three-component reaction (head-to-tail macrocyclization of **2** using normal coupling agents was not the goal of this work, although the yields are usually better) [39,40,41]. Amino acid **2** was added under pseudo-high dilution conditions (in an attempt to avoid oligomerization) to a suspension of paraformaldehyde **5** and butyl isocyanide **12** in methanol to furnish cyclic heptapeptoid **1** in a non-optimized yield of 12%. The observed low yield in this last step may appear frustrating considering that all other steps were high-yielding but it cannot be considered a surprise. Despite the difficulties we encountered in the purification process, it is known that small linear peptides, especially from three to eight amino acids are tough to cyclize due to oligomerization [42,43]. As usual, the presence of rotamers complicated the spectroscopic analysis of the peptoids. Nevertheless, all compounds were fully and unequivocally characterized by ^{1}H- and ^{13}C-NMR spectra and HRMS.



Scheme 3. Final steps in the synthesis of the target cyclic heptapeptoid **1**.

3. Conclusion

In conclusion, the strategy of consecutive isocyanide-based multicomponent reactions employed herein allowed the fast and efficient obtention of a cyclic heptapeptoid and may be used to access other compounds of this type. It offers several advantages, such as easy access to macroheterocycles, simple synthetic procedures, and high atom-economy, which coupled with microwave irradiation is even more powerful allowing a fast synthesis of more complex molecules. Furthermore, it may also allow the obtention of larger cyclic peptoids by increasing the number of consecutive Ugi reactions.

4. Experimental Section

4.1. General remarks

NMR spectra were recorded on a Varian Mercury Plus 300 spectrometer at 300 MHz for ^{1}H and 75.46 MHz for ^{13}C in the presence of TMS as an internal standard. High-resolution ESI mass spectra were obtained on a Micro TOF-Bruker Daltonics instrument. Reactions were performed on a CEM Co., Discover microwave reactor using sealed vessels, dynamic program, temperature detection by internal fiber optic probe, simultaneous cooling, and media stirring. TLC plates were revealed by treatment with a 10% solution of phosphomolybdic acid in ethanol, followed by heating. Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use.

4.2. Methyl N-(((benzyloxy)carbonyl)glycyl)-N-pentylglycylglycinate (9)

A sealed 10 mL glass tube containing a mixture of pentylamine (**8**, 0.044 g, 0.50 mmol), methanol (0.25 mL), anhydrous sodium sulfate (0.150 g), paraformaldehyde (**5**, 0.015 g, 0.50 mmol), *Cbz*-glycine (**7**, 0.052 g, 0.25 mmol) and methyl isocyanoacetate (**6**, 0.023 mL, 0.25 mmol) was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated at 80 ºC for 3 min (ramp time: 98 s) under magnetic stirring. The residue was filtered, concentrated in vacuum and purified by column chromatography (CH_2Cl_2→ 1% MeOH/CH_2Cl_2) to yield peptoid **7** (0.090 g, 0.22 mmol, 88%) as a viscous yellow oil.

R_f (4% MeOH/CH_2Cl_2)= 0.30

^{1}H NMR (300 MHz, $CDCl_3$, presence of rotamers): δ 7.37-7.29 (m, 5H, Ar), 6.89 (br t, *J* = 5.2 Hz, 1H), 5.82 (br t, *J* = 4.7 Hz, 1H), 5.12 and 5.09 (2s, 2H), 4.10 (d,

J = 4.7 Hz, 2H), 4.05 (s, 2H), 3.98 (d, *J* = 5.3 Hz, 2H), 3.72 (s, 3H), 3.41 and 3.31 (2t, *J* = 7.6 and 7.9 Hz, 2H), 1.66-1.48 (m, 2H), 1.37-1.22 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75.46 MHz, $CDCl_3$, presence of rotamers): δ 170.1, 169.2, 168.9, 156.3, 136.2, 128.4, 128.1, 127.9, 66.9, 52.3, 50.1, 48.7, 42.3, 40.9, 28.7, 27.9, 22.3, 13.9.

HRMS (ESI): *m/z*: calc. for $[M+H]^+$ $C_{20}H_{30}N_3O_6$: 408.2135; found: 408.2127.

*4.3. N-(((Benzyloxy)carbonyl)glycyl)-N-pentylglycylglycine (**9**)*

A sealed 10 mL glass tube containing a solution of peptoid **7** (0.442 mmol, 0.180 g) in THF/H_2O (2:1, 6.6 mL) and LiOH (1.1 mmol, 0.026 g) at room temperature was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated at 60 ºC for 5 min under magnetic stirring. The reaction mixture was then acidified with a 2 M solution of $NaHSO_4$ to pH 2 and extracted twice with ethyl acetate (2 x 30 mL). The organic phase was dried over sodium sulfate, filtered and concentrated to yield acid **9** (0.432 mmol, 0.170 g, 98%), which was used without further purification.

^{1}H NMR (300 MHz, CD_3OD, presence of rotamers): δ 7.47-7.26 (m, 5H), 5.09 (s, 2H), 4.12-3.90 (m, 6H), 3.39-3.34 (m, 2H), 1.67-1.46 (m, 2H), 1.37-1.19 (m, 4H), 0.95-0.87 (m, 3H).

^{13}C NMR (75.46 MHz, CD_3OD, presence of rotamers): δ 173.0, 171.7, 171.2, 159.0, 138.0, 129.5, 129.0, 128.8, 67.8, 50.8, 49.5, 43.3, 41.8, 30.1, 28.9, 23.4, 14.4.

HRMS (ESI): *m/z*: calc. for $[M+Na]^+$ $C_{19}H_{27}N_3O_6Na$: 416.1798; found: 416.1810.

*4.4. Methyl N-N-(((benzyloxy)carbonyl)glycyl)-N-pentylglycylglycyl-N-pentylglycylglycinate (**10**)*

A sealed 10 mL glass tube containing a mixture of pentylamine (**8**, 0.052 g, 0.60 mmol), methanol (0.30 mL), anhydrous sodium sulfate (0.180 g), paraformaldehyde (**5**, 0.018 g, 0.60 mmol), acid (**9**, 0.118 g, 0.30 mmol) and methyl isocyanoacetate (**6**, 0.027 mL, 0.30 mmol) was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated at 80 ºC for 3 min (ramp time: 103 s) under magnetic stirring. The residue was filtered, concentrated in vacuum and purified by column chromatography (CH_2Cl_2→ 3% MeOH/CH_2Cl_2) to yield peptoid **10** (0.157 g, 0.266 mmol, 88%) as a viscous yellow oil.

R_f (8% MeOH/CH_2Cl_2)= 0.25

^{1}H NMR (300 MHz, $CDCl_3$, presence of rotamers): δ 7.36-7.24 (m, 5H), 7.13 (br t, *J* = 5.3 Hz, 1H), 5.93 (br t, *J* = 4.5 Hz, 1H), 5.11 and 5.08 (2s, 2H), 4.14-3.96 (m, 10H), 3.70 (s, 3H), 3.42-3.24 (m, 4H), 1.64-1.45 (m, 4H), 1.37-1.19 (m, 8H), 0.92-0.85 (m, 6H).

^{13}C NMR (75.46 MHz, $CDCl_3$, presence of rotamers): δ 170.2, 169.1, 168.9, 168.7, 168.3, 156.3, 136.3, 128.4, 128.0, 127.9, 66.8, 52.2, 49.9, 49.7, 49.6, 48.6, 47.8, 42.4, 40.9, 28.9, 28.7, 27.9, 27.9 (2C), 26.9, 26.8, 22.3, 13.9.

HRMS (ESI): *m/z*: calc. for $[M+Na]^+$ $C_{29}H_{45}N_5O_8Na$: 614.3166; found: 614.3166.

4.5. *N-N-(((Benzyloxy)carbonyl)glycyl)-N-pentylglycylglycyl-N-pentylglycylglycine (**3**)*

A sealed 10 mL glass tube containing a solution of peptoid **10** (0.282 mmol, 0.167 g) in THF/H_2O (2:1, 4.2 mL) and LiOH (0.71 mmol, 0.017 g) at room temperature was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated at 60 ºC for 5 min under magnetic stirring. The reaction mixture was then acidified with a 2 M solution of $NaHSO_4$ to pH 2 and extracted twice with ethyl acetate (4 x 30 mL). The organic phase was dried over sodium sulfate, filtered and concentrated to yield acid **3** (0.255 mmol, 0.147 g, 90%), which was used without further purification.

HRMS (ESI): *m/z*: calc. for $[M+Na]^+$ $C_{28}H_{43}N_5O_8Na$: 600.3009; found: 600.3010.

4.6. *Methyl N-N-N-(((benzyloxy)carbonyl)glycyl)-N-pentylglycylglycyl-N-pentylglycylglycyl-N-pentylglycylglycinate (**12**)*

A sealed 10 mL glass tube containing a mixture of pentylamine (**8**, 0.044 g, 0.50 mmol), methanol (1.50 mL), anhydrous sodium sulfate (0.151 g), paraformaldehyde (**5**, 0.015 g, 0.50 mmol), acid (**3**, 0.145 g, 0.25 mmol) and methyl isocyanoacetate (**6**, 0.023 mL, 0.25 mmol) was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated at 80 ºC for 3 min (ramp time: 59 s) under magnetic stirring. The residue was filtered, concentrated in vacuum and purified by column chromatography (CH_2Cl_2→ 4% MeOH/CH_2Cl_2) to yield peptoid **12** (0.172 g, 0.222 mmol, 88%) as a viscous brown oil.

R_f (5% MeOH/CH_2Cl_2)= 0.20

^{1}H NMR (300 MHz, $CDCl_3$, presence of rotamers): δ 7.49 (br s, 1H), 7.43-7.28 (m, 6H), 6.04 and 5.96 (br 2s, 1H), 5.11 and 5.09 (2s, 2H), 4.18-3.95 (m, 14H), 3.70 (s, 3H), 3.43-3.24 (m, 6H), 1.66-1.39 (m, 6H), 1.37-1.21 (m, 12H), 0.92-0.85 (m, 9H).

^{13}C NMR (75.46 MHz, $CDCl_3$, presence of rotamers): δ 169.2, 169.1 (2C), 169.0 (2C), 168.7 (2C), 156.4, 136.3, 128.4, 128.0, 127.9, 66.8, 52.2, 49.8, 49.6 (2C), 48.6, 48.5, 42.4, 41.1, 40.9, 28.9, 28.7, 27.9, 22.3 (2C), 13.9.

HRMS (ESI): *m/z*: calc. for $[M+Na]^+$ $C_{38}H_{61}N_7O_{10}Na$: 798.4378; found: 798.4369.

*4.7. N-N-N-Glycyl-N-pentylglycylglycyl-N-pentylglycylglycyl-N-pentylglycylglycine (**2**)*

A sealed 10 mL glass tube containing a solution of peptoid **12** (0.222 mmol, 0.172 g) in THF/H_2O (2:1, 3.3 mL) and LiOH (0.55 mmol, 0.013 g) at room temperature was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated at 60 ºC for 5 min under magnetic stirring. The reaction mixture was then acidified with a 2 M solution of $NaHSO_4$ to pH 2 and extracted twice with ethyl acetate (4 x 30 mL). The organic phase was dried over sodium sulfate, filtered and concentrated to yield acid **13** (0.206 mmol, 0.157 g, 93%), which was used without further purification. A sealed 10 mL glass tube containing a solution of acid **13** (0.126 mmol, 0.096 g) in methanol, cyclohexene (1:1. 3.2 mL) and 10% Pd-C (0.0096 g) was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated at 80 ºC for 3 min (ramp time: 125 s, 150 W) under magnetic stirring. After filtration under Celite®, the solvent was concentrated, and amino acid **2** (0.116 mmol, 0.073 g) was

obtained in 92% yield and was used in the subsequent reaction without prior purification.

HRMS (ESI): *m/z*: calc. for $[M+Na]^+$ $C_{29}H_{53}N_7O_8Na$: 650.3853; found: 650.3872.

*4.8. N-Butyl-2-(2,5,8,11,14,17,20-heptaoxo-7,13,19-tripentyl-1,4,7,10,13,16,19-heptaazacyclohenicosan-1-yl)acetamide (**1**)*

A solution of the amino acid **2** (0.143 mmol, 0.090 g) in 60 mL of methanol at room temperature was added via a syringe pump to a solution of paraformaldehyde (**5**, 0.143 mmol, 0.004 g), anhydrous sodium sulfate (2.25 g), butyl isocyanide (**14**, 0.572 mmol, 0.060 mL) in methanol (200 mL) at a rate of 0.6 mL/h (addition time: 100 h). After the addition was complete (~ 4 days), the reaction mixture was stirred for further 24 h, filtered and concentrated under vacuum. The cyclic heptapeptoid **1** (0.071 mmol, 0.051 g) was purified by preparative TLC plate (CH_2Cl_2/MeOH 5% [2x]) to furnish the pure product (0.008 mmol, 0.006 g) in 12% yield.

^{1}H NMR (300 MHz, $CDCl_3$, presence of rotamers): δ 7.94 (br s, 2H), 4.23-3.63 (m, 16H), 3.41-3.15 (m, 8H), 1.73-1.41 (m, 8H), 1.39-1.18 (m, 14H), 0.96-0.77 (m, 12H).

HRMS (ESI): *m/z*: calc. for $[M+Na]^+$ $C_{35}H_{62}N_8O_8Na$: 745.4588; found: 745.4593.

Acknowledgments

The authors thank the Instituto de Química, Universidade de Brasília and CNPq for financial support.

Appendix A. Supplementary data

Detailed experimental procedures, NMR and mass spectra of all compounds.

References

[1] M.S. Butler, J. Nat. Prod. 67 (2004) 2141-2153.

[2] F.E. Koehn, G.T. Carter, Nature Rev. Drug Discov. 4 (2005) 206-220.

[3] D.D. Baker, M. Chu, U. Oza, V. Rajgarhia, Nat. Prod. Rep. 24 (2007) 1225-1244.

[4] L.S. Bonnington, J. Tanaka, T. Higa, J. Org. Chem. 62 (1997) 7765-7767.

[5] K.A. Fairweather, N. Sayyadi, C. Roussakis, K.A. Jolliffe, Tetrahedron 66 (2010) 935-939.

[6] S.V. Ley, A. Priour, C. Heusser, Org. Lett. 4 (2002) 711-714.

[7] S. Monma, T. Sunazuka, K. Nagai, T. Arai, K. Shiomi, R. Matsui, S. Omura, Org. Lett. 24 (2006) 5601-5604.

[8] R. Zucchi, S.R. Testoni, Pharmacol. Rev. 49 (1997) 1-51.

[9] A.H. Afifi, A.H. El-Desoky, H. Kato, R.E.P. Mangindaan, N.J. de Voogd, N.M. Ammar, M.S. Hifnawy, S. Tsukamoto, Tetrahedron Lett. 57 (2016) 1285-1288.

[10] E. Avilez, A.D. Rodríguez, Tetrahedron 69 (2013) 10797-10804.

[11] K.-X. Zhan, W.-H. Jiao, F. Yang, J. Li, S.-P. Wang, Y.-S. Li, B.-N. Han, H.-W. Lin, J. Nat. Prod. 77 (2014) 2678-2684.

[12] J. Sun, W. Cheng, N.J. de Voogd, P. Proksch, W. Lin, Tetrahedron Lett. 57 (2016) 4288-4292.

[13] S.M. Miller, R.J. Simon, S. Ng, R.N. Zuckermann, J.M. Kerr, W.H. Moos, Bioorg. Med. Chem. Lett. 4 (1994) 2657-2662.

[14] R.J. Simon, R.S. Kania, R.N. Zuckermann, V.D. Huebner, D.A. Jewell, S. Banville, S. Ng, L. Wang, S. Rosenberg, C.K. Marlowe, Proc. Natl. Acad. Sci. USA 89 (1992) 9367-9371.

[15] S.A. Fowler, H.E. Blackwell, Org. Biomol. Chem. 7 (2009) 1508-1524.

[16] J. Seo, A.E. Barron, R.N. Zuckermann, Org. Lett 12 (2010) 492-495.

[17] L.A. Wessjohann, C.K.Z. Andrade, O.E. Vercillo, D.G. Rivera, Target Heterocycl. Systems 10 (2006), 24-53.

[18] T. Rezai, B. Yu, G.L. Milhauser, M.P. Jacobson, R.S. Lokey, J. Am. Chem. Soc. 128 (2006) 2510-2511.

[19] A. M. Webster, S. L. Cobb. Chem. Eur J. 24 (2018) 7560-7573.

[20] L.A. Wessjohann, C.K.Z. Andrade, O.E. Vercillo, D.G. Rivera, Target Heterocycl. Systems 10 (2006), 24-53.

[21] T. Rezai, B. Yu, G.L. Milhauser, M.P. Jacobson, R.S. Lokey, J. Am. Chem. Soc. 128 (2006) 2510-2511.

[22] M. Crisma, M. De Zotti, F. Formaggio, C. Peggion, A. Morettoa, C. Toniolo, J. Pept. Sci. 21 (2015) 148-177.

[23] A. Dömling, B. Beck, U. Eichelberger, S. Sakamuri, S. Menon, Q.-Z. Chen, Y. Lu, L.A. Wessjohann, Angew. Chem., Int. Ed. 45 (2006) 7235-7239.

[24] A. Dömling, Chem. Rev. 106 (2006) 17-89.

[25] A. Dömling, W. Wang, K. Wang, Chem. Rev. 112 (2012) 3083-3135.

[26] L.A. Wessjohann, E. Ruijter, Mol. Divers. 9 (2005) 159-169.

[27] D.G. Rivera, L.A. Wessjohann, J. Am. Chem. Soc. 128 (2006) 7122-7123.

[28] O.E. Vercillo, C.K.Z. Andrade, L.A. Wessjohann, Org. Lett. 10 (2008) 205-208.

[29] A.F.S. Barreto, O.E. Vercillo, L.A. Wessjohann, C.K.Z. Andrade, Beilstein J. Org. Chem. 10 (2014) 1017-1022.

[30] A.F.S. Barreto, O.E. Vercillo, M.A. Birkett, J.C. Caulfied, L.A. Wessjohann, C.K.Z. Andrade, Org. Biomol. Chem. 9 (2011) 5024-5027.

[31] A.F.S. Barreto, V.A. Santos, C.K.Z. Andrade, Beilstein J. Org. Chem. 12 (2016) 2865-2872.

[32] A.F.S. Barreto, V.A. Santos, C.K.Z. Andrade, Beilstein J. Org. Chem. 13 (2017) 2596-2602.

[33] G. Maayan, M.D. Ward, K. Kirshenbaum, Proceed. Natl. Acad. Sci. USA 106 (2009) 13679-13684.

[34] K.J. Lee, H.-S. Lim, Org. Lett 16 (2014) 5710-5713.

[35] A.V. Gulevich, A.G. Zhdanko, R.V.A. Orru, V.G. Nenajdenko, Chem. Rev. 110 (2010) 5235-5331.

[36] A.F.S. Barreto, C.E.M. Salvador, T.P.F. Rosalba, C.K.Z. Andrade, Curr. Microwave Chem. 4 (2017) 168-172.

[37] A.F.S. Barreto, O.E. Vercilo, C.K.Z. Andrade, J. Braz. Chem. Soc. 22 (2011) 462-467.

[38] C.K.Z. Andrade, A.F.S. Barreto, W.A. Silva, Arkivoc 2008 (2008) 226-232.

[39] Shin, S. B. Y.; Yoo, B.; Todaro, L. J.; Kirshenbaum, K. J. Am. Chem.Soc. 2007, 129, 3218

[40] Roy, O.; Faure, S.; Thery, V.; Didierjean, C.; Taillefumier, C. Org. Lett. 2008, 10, 921,

[41] Kaniraj, P. J.; Maayan, G. Org. Lett. 2015, 17, 2110

[42] K.D. Kopple, J. Pharm. Sci. 61 (1972) 1345–1356.

[43] A. Ehrlich, H.-U. Heyne, R. Winter, M. Beyermann, H. Haber, L. A. Carpino, M. Bienert, J. Org. Chem. 61 (1996) 8831–8838.