

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/261330243>

# Tandem Deprotection–Dimerization–Macrocyclization Route to C<sub>2</sub> Symmetric Cyclo-Tetrapeptides

ARTICLE in CHEMISTRY - A EUROPEAN JOURNAL · APRIL 2014

Impact Factor: 5.73 · DOI: 10.1002/chem.201304262

---

CITATIONS

3

READS

63

---

## 11 AUTHORS, INCLUDING:



[Sadra Hamedzadeh](#)

University of Florida

2 PUBLICATIONS 3 CITATIONS

[SEE PROFILE](#)



[Girinath G. Pillai](#)

University of Florida

25 PUBLICATIONS 72 CITATIONS

[SEE PROFILE](#)



[Abdullah M. Asiri](#)

King Abdulaziz University

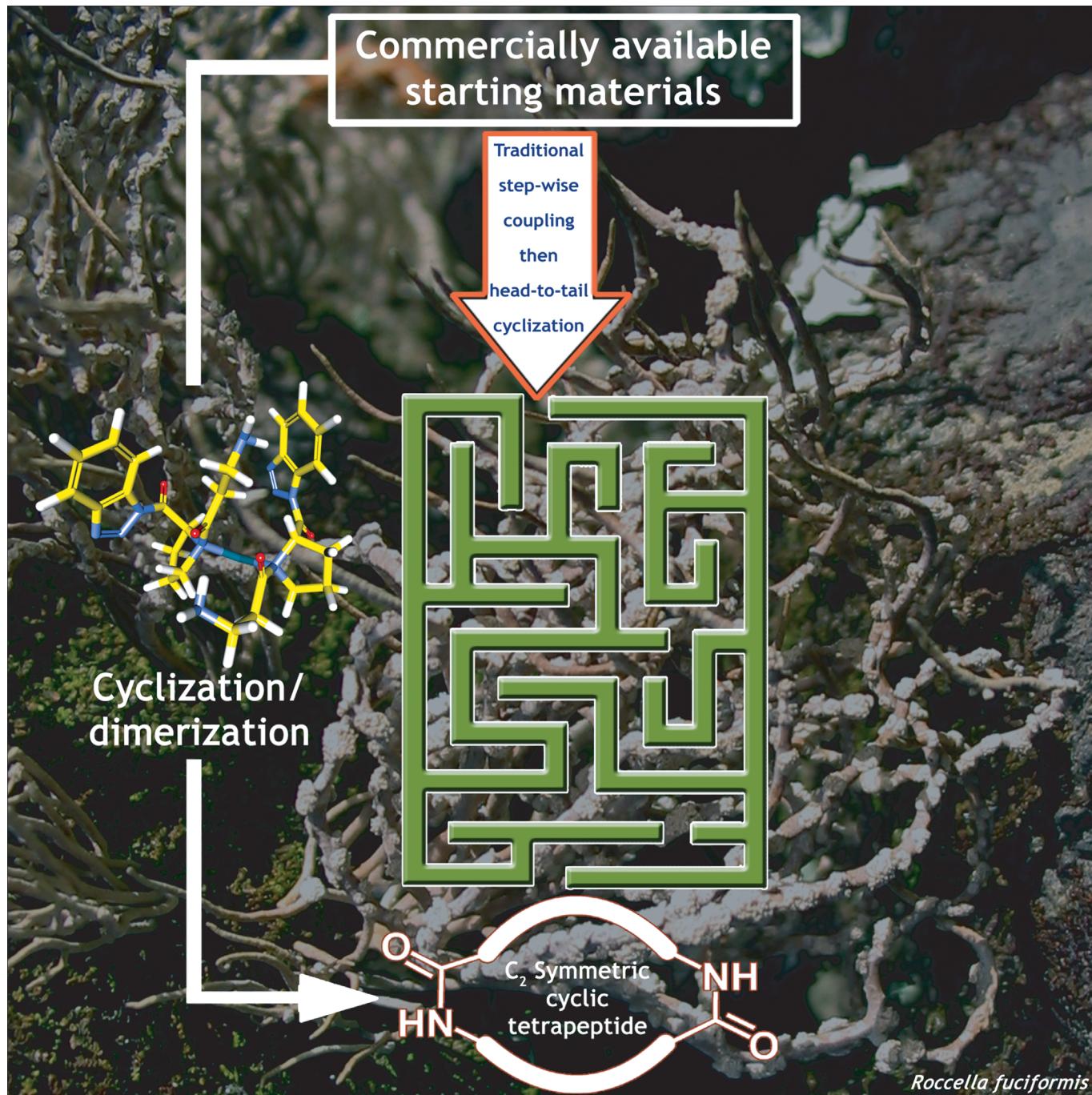
1,163 PUBLICATIONS 6,828 CITATIONS

[SEE PROFILE](#)

## Macrocyclization

**Tandem Deprotection–Dimerization–Macrocyclization Route to C<sub>2</sub> Symmetric cyclo-Tetrapeptides**

Khanh Ha,<sup>[a]</sup> Iryna Lebedyeva,<sup>[a]</sup> Sadra Hamedzadeh,<sup>[a]</sup> Zhiliang Li,<sup>[a]</sup> Ryan Quiñones,<sup>[a]</sup> Girinath G. Pillai,<sup>[a, b]</sup> Byron Williams,<sup>[a]</sup> Amir Nasajpour,<sup>[a]</sup> Kristin Martin,<sup>[a]</sup> Abdullah M. Asiri,<sup>[c, d]</sup> and Alan R. Katritzky\*,<sup>[a, d]</sup>



**Abstract:** Dimerization–macrocyclization has been a long-standing problem in the cyclization of peptides since, together with the desired cyclic product, many cyclic oligomers and linear polymers may also be formed during the reaction. Therefore, the development of a process that affords the cyclic dimer predominantly is difficult. A novel and versatile strategy for the synthesis of symmetric cyclo-tetrapeptides by palladium-promoted tandem deprotection/cyclo-dimerization from readily available Cbz-dipeptidoyl benzotriazolides is reported (Cbz = carboxybenzyl).

Cyclic tetrapeptides represent a unique class with a wide diversity in both structural detail and biological activity.<sup>[1,2]</sup> Tetrapeptide macrocycles have shown potential applications ranging from nanomaterials to drug discovery. The first cyclic tetrapeptide nanotubes composed of  $\beta$ -amino acid residues were reported by Seebach.<sup>[3,4]</sup> Due to the additional carbon atom in the backbone of each residue, multiple conformers of the macrocycles permit hydrogen bonding and strong tubular arrays can be formed. Many naturally occurring cyclic tetrapeptides show biological activity,<sup>[5,3,6]</sup> and are highly selective in a wide range of therapeutic areas including: inhibition of histone deacetylase,<sup>[2,6]</sup> and tyrosinase,<sup>[7]</sup> cytotoxicity,<sup>[8,9]</sup> antimalaria,<sup>[7]</sup> and antibiotic activity.<sup>[10]</sup>

Cyclic tetrapeptides are a rich source of drug-like molecules due to their low molecular weight, favorable pharmacokinetic characteristics, and unique cyclic backbone, which provides a rigid framework able to support a wide range of functional groups.<sup>[6,11]</sup> Despite their interesting properties, the application of cyclic tetrapeptides is limited by synthetic difficulty.

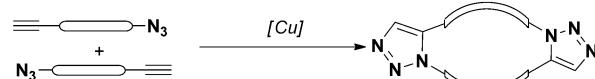
The cyclization event often poses a great challenge,<sup>[12,11]</sup> since direct macrolactamization to form *cyclo*-tetrapeptides by activation of a carboxylic acid is hampered by ring strain.<sup>[1]</sup> The primary reason for ineffective cyclization of a linear tetrapeptide originates from the difficulty of bringing the termini sufficiently close for cyclization.<sup>[11,12,13]</sup> Peptide bonds preferentially adopt trans conformations, and linear peptides prefer more extended conformations.<sup>[14,15]</sup>

Among contemporary strategies for peptide and peptidomimetic macrocyclization, a tandem dimerization–macrocyclization approach has proved to be a powerful tool to force dif-

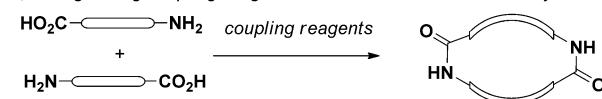
ficult lactamizations in the construction of peptide macrocycles.<sup>[16,17]</sup> Several tandem click reactions have facilitated difficult lactamization reactions in the construction of modified cyclic peptides.<sup>[18,17,19]</sup> For macrolactamization of a linear precursor, such an approach improved yields from 42 to 90%<sup>[20,17,21]</sup> (Figure 1).

#### Previous works

##### 1, Cu-catalysed "click" tandem dimerization-macrocyclization



##### 2, Using strong coupling reagents to force dimerization-macrocyclization



#### This work

##### Pd assisted tandem deprotection dimerization-cyclization

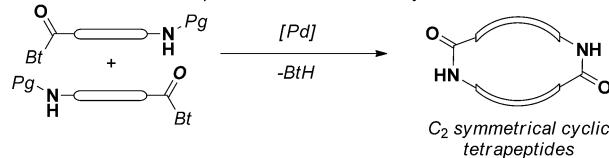


Figure 1. Contemporary ring construction strategies to form symmetrical cyclic peptides and peptide-mimetic.

A dimerization–macrocyclization approach using pentafluorophenyl diphenylphosphinate (FDPP) as a coupling reagent was successfully applied to the synthesis of sugar amino acid based 24-membered macrocyclic  $C_2$ -symmetric cationic peptides.<sup>[16]</sup> In addition, the utility of the dimerization–macrocyclization method was demonstrated in the synthesis of  $C_2$ -symmetrical decapeptide derivatives of the natural product pentapeptide Sansalvamide A and *cyclo*-(Lys-Lys-Pro-Tyr-Ile-Leu)<sub>2</sub> using HBTU.<sup>[22,23]</sup>

On the other hand, designing a dimerization–macrocyclization process to form  $C_2$ -symmetrical cyclic peptides can be a serious challenge: cyclization is a concentration-dependent reaction and many *cyclo*-oligomers or linear polymers can be formed (Figure 2).<sup>[24,25]</sup> A cyclic dimer is normally the predominant product at low concentration ( $10^{-2}$ – $10^{-4}$  M) and the percentage of linear polymers rises as concentration of the substrate increases.

Using a Pd-promoted tandem deprotection/cyclization dimerization method, we were able to control the cyclization reaction and selectively convert open chain *N*-Cbz-dipeptidoyl benzotriazole sequences into the corresponding  $C_2$  symmetrical 14- and 16-membered cyclic tetrapeptides (Scheme 1).

As outlined in Scheme 1,  $C_2$  symmetrical cyclic tetrapeptide [ $\beta$ -Ala-L-Pro]<sub>2</sub> **5a** was selected as our first target. Compound **5a** was synthesized in a four-step procedure starting from **1a**.<sup>[26,27]</sup> Cbz-*N*-protected  $\beta$ -amino acid **1a** was first converted into the benzotriazolide **2a** (Cbz = Carboxybenzyl); reaction of **2a** with proline gave **3a**, which was converted into Cbz-dipep-

[a] K. Ha, Dr. I. Lebedeva, S. Hamedzadeh, Z. Li, R. Quiñones, G. G. Pillai, B. Williams, A. Nasajpour, K. Martin, Prof. Dr. A. R. Katritzky  
Center for Heterocyclic Compounds, Department of Chemistry  
University of Florida, Gainesville, FL 32611-7200 (USA)  
E-mail: katritzky@chem.ufl.edu

[b] G. G. Pillai  
Department of Chemistry, University of Tartu, Tartu, 50411 (Estonia)

[c] Prof. Dr. A. M. Asiri  
Center of Excellence for Advanced Material Research  
King Abdulaziz University, Jeddah, 21589 (Saudi Arabia)

[d] Prof. Dr. A. M. Asiri, Prof. Dr. A. R. Katritzky  
Chemistry Department, King Abdulaziz University  
Jeddah, 21589 (Saudi Arabia)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201304262>.

Dimerization-macrocyclization often accompanied with many possible side products

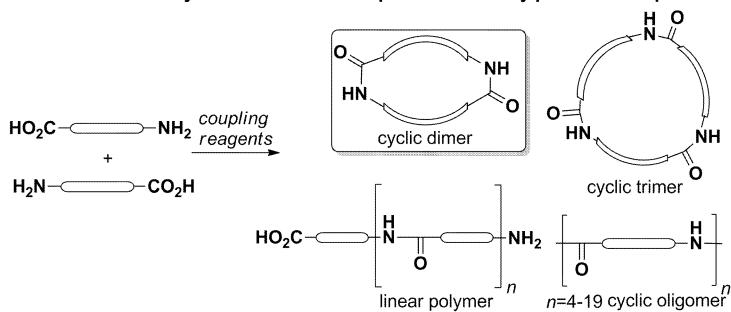


Figure 2. Challenges in dimerization-macrocyclization reaction to form cyclic peptides.

tidoyl benzotriazolide **4a**.<sup>[28,29]</sup> Stirring at a concentration of 12 mM under hydrogen in the presence of Pd/C (10 wt %) at 20 °C for 48 h, **4a** afforded **5a** (Scheme 1) by tandem dimerization-macrocyclization: HPLC-MS confirmed the major product is symmetrical cyclic tetrapeptide *cyclo*-(β-Ala-L-Pro)<sub>2</sub> **5a** which, after purification by gradient chromatography (MeOH/ether) was obtained in 70% isolated yield. Similarly, **5a** was synthesized in 72% yield by deprotection/cyclo-dimerization of Cbz-L-Pro-β-Ala-Bt **4aa**.

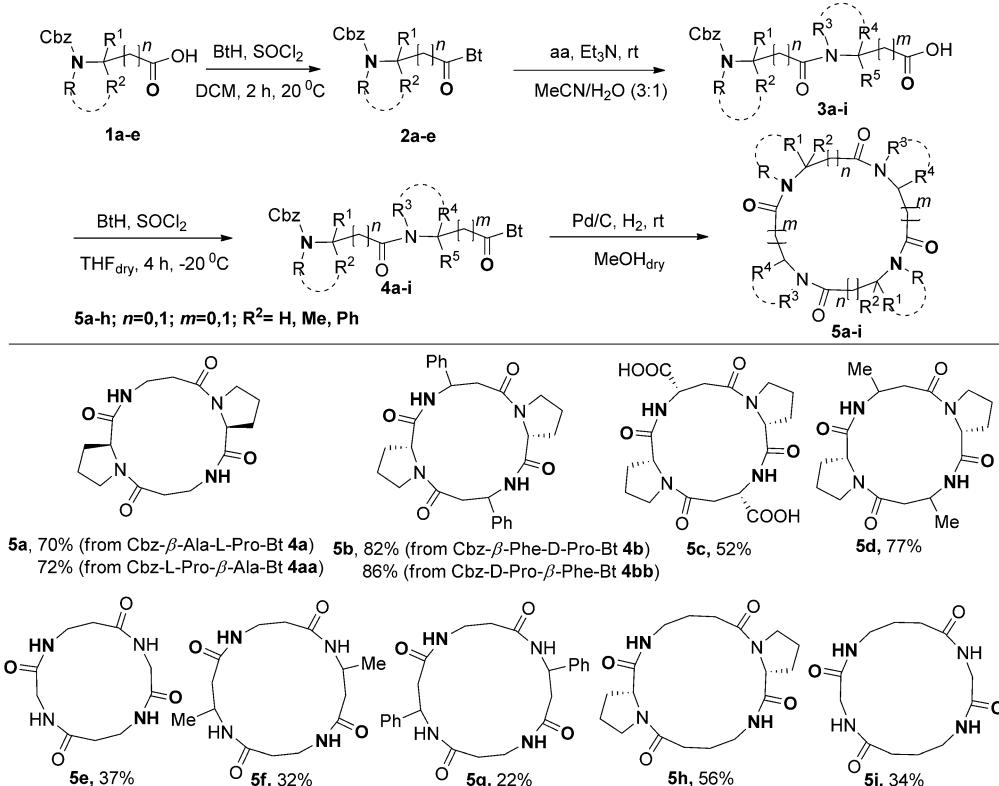
Next, we turned our attention to *cyclo*-(D,L-β-Phe-D-Pro)<sub>2</sub> **5b**, whose diastereomer was isolated from *Roccella canariensis*.<sup>[30]</sup> Peptide **5b** is inaccessible or can only be prepared with great difficulty by traditional step-wise coupling and head-to-

tail cyclization methods.<sup>[30]</sup> Using our tandem deprotection/cyclization dimerization method, compound **5b** was synthesized in 82% yield from **4b** or 86% from **4bb** with a product selectivity of 92%. To prove the generality of the method, 1-N-Cbz-benzotriazolyl dipeptides **4c** and **d** were cyclo-dimerized to give cyclic tetrapeptide products **5c** and **d** in 52 and 77% yield, respectively.

Cyclization of linear N-Cbz-dipeptidoyl benzotriazolide **4e** employing similar conditions as for **4a-d** (10 wt % Pd/C in MeOH<sub>dry</sub>) afforded cyclic peptide **5e** in 37% yield after HPLC purification.

The few literature examples of 16-membered cyclic tetrapeptides are endowed with promising biological activities. Cyclic peptides bearing aliphatic side chains attached to a 16-membered ring are more favorable with respect to the binding affinity.<sup>[31]</sup> To broaden the scope of our methodology, 16-membered cyclic tetrapeptides **5f-i** were considered as potential targets. The macrolactamizations of **4f-i** were each initiated by treatment with Pd/C (10 wt %) at 20 °C for 24–36 h in dry MeOH at room temperature. The unfunctionalized 16-membered symmetrical *cyclo*-tetrapeptides **5f-i** were isolated in high purities after separation by gradient chromatography (Scheme 1).

To rationalize the reaction pathways of Cbz-dipeptidoyl benzotriazolides and gain further insight into the Pd-assisted tandem deprotection/cyclization macrocyclization process, we employed theoretical calculations. Scheme 1 implies that Cbz-



Scheme 1. Tandem deprotection-dimerization-macrocyclization of Cbz-dipeptidoyl benzotriazoles.

deprotection of Cbz-1-N-benzotriazolyl dipeptide **4a** forms intermediate **I** (Figure 3) that cyclises intermolecularly in a “dimerization–macrocyclization” pathway to **5a**, with benzotriazole as leaving group. On the other hand, unprotected dipeptide intermediate **I** can also cyclise “head-to-tail” to form intramolecular lactamization product **5a'** (Figure 3), which was detected as a trace component in the reaction mixture by HPLC-MS analysis.

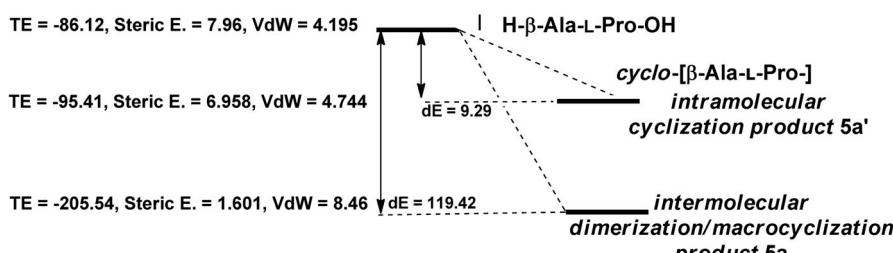


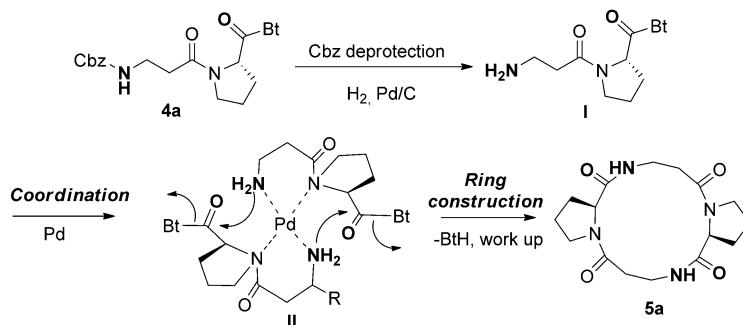
Figure 3. Energy diagram for the formation of **5a**.

These two products **5a** and **a'** differ mainly in ring sizes. Compound **5a'** is a 7-membered cyclic dipeptide and **5a** is a 14-membered symmetrical *cyclo*-tetrapeptide. Molecular structures of the unprotected dipeptide intermediate **I** and the structures of products **5a** and **a'** were drawn using Marvin Sketch,<sup>[32]</sup> and geometries were optimized using the semi-empirical program MOPAC2012<sup>[33,34]</sup> under PM6<sup>[35,36]</sup> parameterization. Further, the optimized geometry is considered for calculating the heat of formation and reaction energy using Turbomole<sup>[37,38]</sup> (A development of Universität Karlsruhe (TH) and Forschungszentrum Karlsruhe GmbH, 1989–2007, TURBOMOLE GmbH, since 2007. The Turbomole program package can be obtained from COSMOlogic GmbH&Co.) Later, calculations performed under DFT level of theory, B3LYP function<sup>[39]</sup> and def-TZVP<sup>[40]</sup> basis set. We considered large basis set, as this is the only one with more realistic predictions of energies for compounds with Pd (Palladium), even though def-TZVP basis set took more computation time and power. For the reaction of **4a** to form **5a** and **a'**, assuming compound **I** is the intermediate as shown in Figure 3, we calculated relative energies (taken as differences of total electronic energies) of the two reaction pathways: I) intermolecular dimerization/macrocyclization leading to the isolated 14-membered cyclic tetrapeptide **5a**; II) intramolecular cyclization leading to the macrocycle **5a'**. It is seen that the total energy of product **5a** lies 9.29 kcal mol<sup>-1</sup> lower than the intermediate **I**. As for the intramolecular pathway **I**–**5a'**, it can be considered as an isodesmic reaction involving two disjoint products: cyclic structure **5a'** and benzotriazole. The reaction energy of this isodesmic reaction was calculated to be –205.54 kcal mol<sup>-1</sup>, which means that reaction pathway **I**–**5a** is 110.13 kcal mol<sup>-1</sup> and they are more favorable than pathway **I**–**5a'**. The calculations were carried out in vacuum

and the solvation was not considered. Steric energy refers to energy associated with a bond being stretched or compressed. Since, there is no intermolecular interaction in the gas phase, bond lengths between *b*(C–N) and *b*(O–H) have to be significantly different from those between same atoms when the molecule is complexed. Steric energies are calculated using molecular mechanics with MMX<sup>[41]</sup> forcefield in PCModel<sup>[42]</sup> (Figure 3). Our calculation results suggest that **5a** has lower steric energy than **5a'**; therefore, formation of **5a** would be more favoured.

Another factor contributing to the more favourable formation of **5a** may be the relative energies of transition state (TS)-II. Coordination of the N-unprotected dipeptide **I** to the Pd could form **(I)**<sub>2</sub>Pd complex **II**, which in-turn could lower the activation energy in the formation of the intermolecular dimerization/cyclization product **5a** (Scheme 2).

To test this hypothesis, unprotected dipeptidoyl benzotriazide **I** was synthesized by boc-deprotection of compound **6** using previously reported method,<sup>[43]</sup> and dissolved in MeOH. The reaction mixture was treated with one equivalent of *N,N*-diisopropylethylamine (DIPEA) and stirred for 48 h at 20 °C (Scheme 3). Interestingly, the HPLC-MS analysis of the reaction mixture revealed that the major components were linear oligo-



Scheme 2. Ring-construction events in the formation of **5a**.

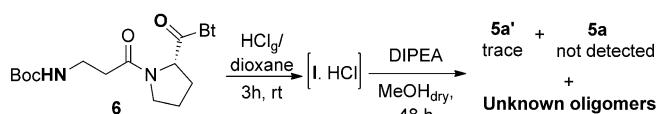
mers, which shows that Pd plays an important role in the ring-construction leading to formation of the intermolecular cyclodimerization product.

The approach of tandem dimerization–macrocyclization can also be applied to the synthesis of unsymmetrical cyclic peptide sequences by taking advantage of the statistical product distribution from the reaction of two different linear precursors. As an example, subjecting an equimolar mixture of peptides **4a** and **b** or **d** to the standard reaction conditions should give a mixture of homo- and heterodimeric products. This ap-

**Table 1.** Crosscyclo-dimerization route to cyclic tetrapeptides.

Peptide 1	Peptide 2	Heterodimer, ratio <sup>[a]</sup> (homo <sup>[b]</sup> /hetero)
Cbz- $\beta$ -Ala-d-Pro-Bt	Cbz-d,L- $\beta$ -Phe-d-Pro-Bt	cyclo-( $\beta$ -Ala-d-Pro-d,L- $\beta$ -Phe-d-Pro) (3:2.5)
Cbz- $\beta$ -Ala-d-Pro-Bt	Cbz-d,L- $\beta$ -H-Ala-d-Pro-Bt	cyclo-( $\beta$ -Ala-d-Pro-d,L-H-Ala-d-Pro) (3:4)

[a] The ratio was calculated from HPLC-MS of the crude mixture. [b] Only cyclic homo-dimer from peptide 1, 5a was detected.



**Scheme 3.** Control cyclization reaction of  $\beta$ -Ala-L-Pro-Bt.

proach could provide a rapid and convergent route for synthesis of non-symmetrical cyclo-tetrapeptides (Table 1).

In summary, we have developed new and powerful synthetic strategies to force the dimerization/cyclization of open chain *N*-Cbz-dipeptidoyl benzotriazoles to form both  $C_2$  symmetrical and unsymmetrical cyclic tetrapeptides utilizing a Pd-assisted tandem deprotection/cyclization reaction. The methodology was demonstrated by ring-closure of a series of dipeptidoyl benzotriazoles yielding a small library of cyclo-tetrapeptides, which cannot be prepared efficiently using previously reported methods. The approach described here should provide a convenient entry for the design and synthesis of a variety of cyclo-tetrapeptides with potential utility in medicinal chemistry and material science. Currently, work is in progress to apply our method to the macrocyclization forming other difficult medium-sized cyclic peptides, and peptide-mimetics.

## Acknowledgements

We thank the University of Florida and the Kenan Foundation for financial support. This paper was also funded in part by support from King Abdulaziz University under grant no. (D-006/431). The authors are grateful to Dr. C. D. Hall, Mrs. Galyna Vakulenko, and Mr. Z. Wang for helpful discussions, and to Dr. M. C. A. Dancel and Dr. Jodie Johnson for MS analysis. S. Hammedzadeh is grateful to UF-HHMI Science for Life program for Intramural Undergraduate Research Award. G.G. Pillai is grateful to the European Social Fund under project 1.2.0401.09-0079 supported by graduate school "Functional materials and technologies".

**Keywords:** benzotriazoles • cyclodimerization • lactamization • macrocycles • peptides

- [1] F. Cavelier-Frontin, G. Pèpe, J. Verducci, D. Siri, R. Jacquier, *J. Am. Chem. Soc.* **1992**, *114*, 8885–8890.
- [2] L. Gomez-Paloma, I. Bruno, E. Cini, S. Khochbin, M. Rodriguez, M. Taddei, S. Terracciano, K. Sadoul, *ChemMedChem* **2007**, *2*, 1511–1519.
- [3] K. Gademann, M. Ernst, D. Hoyer, D. Seebach, *Angew. Chem.* **1999**, *111*, 1302; *Angew. Chem. Int. Ed.* **1999**, *38*, 1223–1226.
- [4] R. Chapman, M. Danial, M. L. Koh, K. Jolliffe, S. Perrier, *Chem. Soc. Rev.* **2012**, *41*, 6023–6041.
- [5] E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug Discov.* **2008**, *7*, 608–624.
- [6] L. Rodriguez, Manuela; Aquino, Maurizio; Bruno, Ines; De Martino, Giovanni; Taddei, Maurizio; Gomez-Paloma, *Curr. Med. Chem.* **2006**, *13*, 1119–1139.
- [7] S. B. Singh, D. L. Zink, J. D. Polishook, A. W. Dombrowski, S. J. Darkin-rattray, D. M. Schmatz, M. A. Goetz, *Tetrahedron Lett.* **1996**, *37*, 8077–8080.
- [8] M. Kijima, M. Yoshida, K. Sugita, S. Horinouchi, T. Beppu, *J. Biol. Chem.* **1993**, *268*, 22429–22435.
- [9] W. D. Clark, T. Corbett, F. Valeriote, P. Crews, *J. Am. Chem. Soc.* **1997**, *119*, 9285–9286.
- [10] H. A. Lim, C. Kang, C. S. B. Chia, *Int. J. Pept. Res. Ther.* **2010**, *16*, 145–152.
- [11] W. D. F. Meutermans, G. T. Bourne, S. W. Golding, D. Horton, M. R. Campitelli, D. Craik, M. Scanlon, M. L. Smythe, *Org. Lett.* **2003**, *5*, 2711–2714.
- [12] J. Pastuszak, J. H. Gardner, J. Singh, D. H. Rich, *J. Org. Chem.* **1982**, *47*, 2982–2987.
- [13] D. A. Horton, G. T. Bourne, M. L. Smythe, *J. Comput. Mol. Des.* **2002**, *16*, 415–430.
- [14] U. Schmidt, J. Langner, *J. Pept. Res.* **2009**, *49*, 67–73.
- [15] K. Ha, J.-C. M. Monbaliu, B. C. Williams, G. G. Pillai, C. E. Ocampo, M. Zeller, C. V. Stevens, A. R. Katritzky, *Org. Biomol. Chem.* **2012**, *10*, 8055–8058.
- [16] T. K. Chakraborty, D. Koley, R. Ravi, V. Krishnakumari, R. Nagaraj, A. C. Kunwar, *J. Org. Chem.* **2008**, *73*, 8731–8744.
- [17] C. J. White, A. K. Yudin, *Nat. Chem.* **2011**, *3*, 509–524.
- [18] S. Punna, J. Kuzelka, Q. Wang, M. G. Finn, *Angew. Chem.* **2005**, *117*, 2255–2260; *Angew. Chem. Int. Ed.* **2005**, *44*, 2215–2220.
- [19] M. R. Krause, R. Goddard, S. Kubik, *Chem. Commun.* **2010**, *46*, 5307–5309.
- [20] J. H. van Maarseveen, W. S. Horne, M. R. Ghadiri, *Org. Lett.* **2005**, *7*, 4503–4506.
- [21] S. W. Horne, D. C. Stout, R. M. Ghadiri, *J. Am. Chem. Soc.* **2003**, *125*, 9372–9376.
- [22] M. R. Davis, T. J. Styers, R. Rodriguez, P.-S. Pan, R. C. Vasko, S. R. McAlpine, *Org. Lett.* **2008**, *10*, 177–180.
- [23] P. Bredeloux, F. Cavelier, I. Dubuc, B. Vivet, J. Costentin, J. Martinez, *J. Med. Chem.* **2008**, *51*, 1610–1616.
- [24] Y. Singh, N. Sokolenko, M. J. Kelso, L. R. Gahan, G. Abbenante, D. P. Fairlie, *J. Am. Chem. Soc.* **2001**, *123*, 333–334.
- [25] N. Sokolenko, G. Abbenante, M. J. Scanlon, A. Jones, L. R. Gahan, G. R. Hanson, D. P. Fairlie, *J. Am. Chem. Soc.* **1999**, *121*, 2603–2604.
- [26] S. S. Panda, D. Hall, E. Scriven, A. R. Katritzky, *Aldrichimica Acta* **2013**, *46*, 43–55.
- [27] S. S. Panda, M. A. Ibrahim, A. Oliferenko, A. M. Asiri, A. R. Katritzky, *Green Chem.* **2013**, *15*, 2709–2712.
- [28] S. S. Panda, C. El-Nache, K. Bajaj, A. R. Katritzky, *Eur. J. Org. Chem.* **2013**, 4156–4162.
- [29] K. Ha, I. Lebedeva, Z. Li, K. Martin, B. Williams, E. Faby, A. Nasajpour, G. G. Pillai, A. O. Al-youbi, A. R. Katritzky, *J. Org. Chem.* **2013**, *78*, 8510–8523.
- [30] G. Bohman-Lindgren, U. Ragnarsson, *Tetrahedron* **1972**, *28*, 4631–4634.
- [31] L. Sheh, H.-W. Chang, C.-W. Ong, S.-L. Chen, C. Bailly, R. E. Linssen, M. J. Waring, *Anticancer. Drug Des.* **1995**, *10*, 373–388.
- [32] Marvin Sketch version 5.11, 2012, ChemAxon Kft., Hungary.

- [33] MOPAC 2012, James J. P. Stewart, Stewart Computational Chemistry, Colorado Springs, CO: <http://www.openmopac.net>, 2012.
- [34] J. J. P. Stewart, *J. Mol. Model.* **2007**, *13*, 1173–1213.
- [35] P. Hohenberg, W. Kohn, *Phys. Rev.* **1964**, *136*, B864–B71.
- [36] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- [37] A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571–2577.
- [38] R. Ahlrichs, M. Bar, H. Marco, H. Horn, C. Kolmel, *Chem. Phys. Lett.* **1989**, *162*, 165–169.
- [39] L. H. Jensen, H. Liang, R. Shoemaker, M. Grauslund, M. Sehested, B. B. Hasinoff, *Mol. Pharmacol.* **2006**, *70*, 1503–1513.
- [40] R. A. Bachorz, F. A. Bischoff, S. Höfener, W. Klopper, P. Ottinger, R. Leist, J. A. Frey, S. Leutwyler, *Phys. Chem. Chem. Phys.* **2008**, *10*, 2758–2766.
- [41] MMX: An Enhanced Version of MM2, J. J. Gajewski, K. E. Gilbert, and J. McKelvey, in *Advances in Molecular Modeling* (Ed.: D. Liotta), Vol. 2, p.65, JAI, 1990.
- [42] PCModel V 9.0, 2011, Serena Software, USA.
- [43] K. Ha, M. Chahar, J.-C. M. Monbaliu, E. Todadze, F. K. Hansen, A. A. Olierenko, C. E. Ocampo, D. Leino, A. Lillicotch, C. V. Stevens, A. R. Katritzky, *J. Org. Chem.* **2012**, *77*, 2637–2648.

---

Received: October 31, 2013

Revised: December 24, 2013

Published online on April 2, 2014

---