Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 4769–4770

Design and synthesis of a 1,5-diazabicyclo[6,3,0] dodecane amino acid derivative as a novel dipeptide reverse-turn mimetic

Yuefeng Peng, Haiying Sun and Shaomeng Wang*

Departments of Internal Medicine, Medicinal Chemistry and Pharmacology and Comprehensive Cancer Center, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, United States

Received 20 January 2006; accepted 12 April 2006

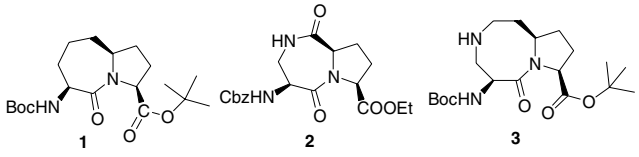
Abstract—*N*-Boc-1,5-diazabicyclo[6,3,0] dodecane amino acid *tert*-butyl ester (**3**), designed as a novel dipeptide reverse-turn mimetic, was synthesized in a concise method from the known compound **4** in an overall yield of 47%.

Design and synthesis of conformationally constrained non-peptidic mimetics of natural peptides, has attracted much attention among organic and medicinal chemists.[1] Such mimetics have the promising potential to overcome a number of major intrinsic limitations associated with natural peptides such as poor cell-permeability, poor in vivo stability and bioavailability, while maintaining the desired conformation of natural peptides and their biological activities.[1,2]

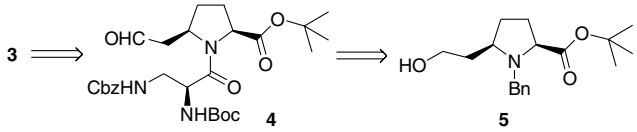
Reverse-turn is an important secondary structure frequently observed in proteins. It describes a site where the peptide backbone adopts a U-shaped conformation, reversing the geometrical direction of propagation. Azabicyclo[*x*,*y*,0] alkyl amino acid derivatives, such as **1** (Scheme 1), have been designed as dipeptide reverse-turn mimetics and several research groups have reported the synthesis of this type of compound.[3] Recently, we have employed compound **1** as a conformationally constrained reverse-turn dipeptide mimetic in the design and synthesis of a class of novel, high-affinity, Smac mimetics as modulators of cellular apoptosis.[4]

Since the side chain in reverse-turn peptides is often involved in interactions with its targeted protein, we are interested in introducing a substituent into the bicyclic structures of azabicyclo[*x*,*y*,0] alkyl amino acid derivatives in order to probe such interactions. One approach is to replace one of the carbon atoms in the bicyclic structure with a nitrogen atom, which can be used as the basic key intermediate to synthesize a series of side chain-containing reverse-turn mimetics by linking the side chains to the amino group with the formation of an amide or amine. To this end, 5-aza-pyrroloazepin-2,6-dione *N*-(Cbz)-amino acid ethyl esters, such as **2** (Scheme 1), were designed, but selective reduction of the secondary amide in these compounds has proved to be difficult to achieve.[5] Accordingly, we have designed *N*-Boc-1,5-diazabicyclo[6,3,0]dodecane amino acid *tert*-butyl ester (**3**, Scheme 1) as a novel, conformational constrained dipeptide reverse-turn mimetic. Herein, we report an efficient synthetic method for this compound.

A retrosynthetic analysis is shown in Scheme 2. The key step in this synthesis is **4** → **3**, the formation of the



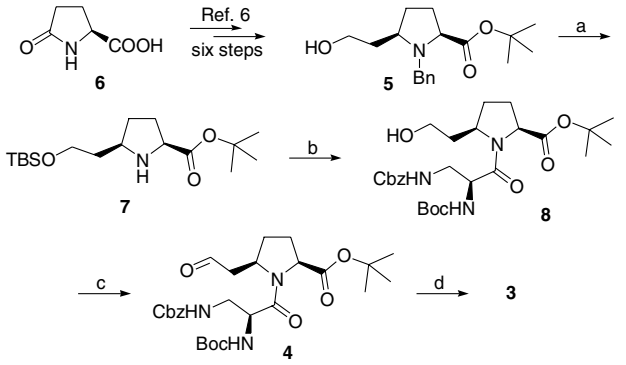
Scheme 1. Chemical structures of compound **1**, **2** and **3**.



Scheme 2. Retrosynthetic analysis of compound **3.**

* Corresponding author. Tel.: +1 734 615 0362; fax: +1 734 647 9647; e-mail: shaomeng@umich.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.053



Scheme 3. Reagents and conditions: a. (i) TBSCl, *N*,*N*-diisopropylethyl amine, CH_2Cl_2; (ii) H_2, 10% Pd–C, EtOAc, 88% over two steps, b. (i) Boc-Dap(Z)-OH, EDC, HOBt, *N*,*N*-diisopropylethyl amine, CH_2Cl_2, (ii) TBAF, THF, 87% over two steps; c. Dess–Martin periodinane, CH_2Cl_2, 96%; d. 10% Pd–C, H_2, MeOH, 64%.

eight-membered ring. This was approached by intramolecular condensation of the amino aldehyde formed by the removal of the carbobenzoxy group from **4**. Compound **4** can be obtained from the known compound **5**.

As outlined in Scheme 3, compound **5** was prepared in six steps from pyroglutamic acid (**6**) by previously reported methods.[6] Protection of the hydroxyl group in **5** as the *tert*-butyldimethylsilyl (TBS) ether, followed by the removal of the benzyl group by hydrogenation, gave the amine **7**. Condensation of **7** with *N*-α-(*tert*-butoxylcarbonyl)-*N*-β-benzoxylcarbonyl)-L-diamino-propionic acid (Boc-Dap(Z)-OH) followed by the removal of the TBS group, yielded amide **8** in high yield. Oxidation of the hydroxyl group in **8** by Dess–Martin periodinane furnished aldehyde **4** in nearly quantitative yield.

Finally, removal of the Cbz protecting group in compound **4** by hydrogenation, intramolecular condensation of the amine with the aldehyde and subsequent reduction of the resulted enamine were carried out in one pot to give the desired compound **3**.[7] Hence, starting from compound **5**, this synthetic route involved six steps and achieved an overall yield of 47%.

In summary, we have designed a 1,5-diazabicyclo[6,3,0] dodecane amino acid derivative (**3**) as a novel reverse-turn dipeptide mimetic and developed an efficient method for the synthesis of this compound. The application of this mimetic in the design and synthesis of novel Smac mimetics with different side chains on the eight-membered ring is in progress in our laboratory and will be reported in due course.

Acknowledgments

We are grateful for the financial support from the National Cancer Institute, National Institutes of Health (1R01CA109025 to S.W.).

References and notes

1. Recent reviews: (a) Souers, A. J.; Ellman, J. A. *Tetrahedron* **2001**, *57*, 7431–7448 (Review); (b) Loughlin, W. A.; Tyndall, J. D. A.; Glenn, M. P.; Fairlie, D. P. *Chem. Rev.* **2004**, *104*, 6085–6118 (Review); (c) Hanessian, S.; Mcnaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854; (d) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937 (Review); (e) Cluzeau, J.; Lubell, W. D. *Biopolymers* **2005**, *80*, 98–150 (Peptide Science); (f) Zhang, J.; Xiong, C.; Wang, W.; Ying, J.; Hruby, V. J. *Org. Lett.* **2002**, *4*, 4029–4032; (g) Polyak, F.; Lubell, W. D. *J. Org, Chem.* **1998**, *63*, 5937–5949.
2. (a) Etzkorn, F. A.; Guo, T.; Lipton, M. A.; Goldberg, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1994**, *116*, 10412; (b) Haubner, R.; Schmitt, W.; Holzemann, G.; Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7881; (c) Li, W.; Moeller, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 10106–10112; (d) Belvisi, L.; Riccioni, T.; Marcellini, M.; Vesci, L.; Chiarucci, I.; Efrati, D.; Potenza, D.; Scolastico, C.; Manzoni, L.; Lombardo, K.; Stasi, M. A.; Orlandi, A.; Ciucci, A.; Nico, B.; Ribatti, D.; Giannini, G.; Presta, M.; Carminati, P.; Pisano, C. *Mol. Cancer Ther.* **2005**, *4*, 1670.
3. (a) Angiolini, M.; Araneo, S.; Belvisi, L.; Cesarotti, E.; Checchia, A.; Crippa, L.; Manzoni, L.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 2571–2581; (b) Dietrich, E.; Lubell, W. D. *J. Org. Chem.* **2003**, *68*, 6988, and the paper cited therein; (c) Duggan, H. M. E.; Hitchcock, P. B.; Young, D. W. *Org. Biomol. Chem.* **2005**, *3*, 2287–2295.
4. (a) Sun, H.; Nikolovska-Coleska, Z.; Yang, C.-Y.; Xu, L.; Liu, M.; Tomita, Y.; Pan, H.; Yoshioka, Y.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Am. Chem. Soc.* **2004**, *126*, 16686–16687 (Communication); (b) Sun, H.; Nikolovska-Coleska, Z.; Yang, C.-Y.; Xu, L.; Tomita, Y.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2004**, *47*, 4147–4150 (Letter); (c) Sun, H.; Nikolovska-Coleska, Z.; Yang, C.-Y.; Wang, S. *Tetrahedron Lett.* **2005**, *46*, 7015–7018.
5. Curran, T. P.; Marcaurelle, L. A.; O'Sullivan, K. M. *Org. Lett.* **1999**, *1*, 1225–1228.
6. Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539–4547.
7. Chemical data for compound **3**: $[\alpha]_D^{20}$ −8.4 (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 5.49 (br d, $J = 8.1$ Hz, 1H), 4.70 (m, 1H), 4.41 (t, $J = 9.3$ Hz, 1H), 4.30 (m, 1H), 3.25–3.18 (m, 2H), 2.89 (m, 1H), 2.75 (dd, $J = 13.5$, 11.1 Hz, 1H), 2.34 (m, 1H), 2.18–1.60 (m, 6H), 1.49 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.4, 155.2, 81.7, 79.5, 60.6, 58.5, 54.9, 52.3, 46.9, 37.5, 32.1, 28.3, 28.0, 27.0; HRMS: calcd *m*/*z* 406.2318 for $[M+Na]^+$; found 406.2317.