Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1413–1415

TETRAHEDRON LETTERS

Efficient and stereoselective synthesis of novel *cis*-4-substituted proline analogues

Junyi Zhang,[a] Wei Wang,[b,*] Chiyi Xiong[a] and Victor J. Hruby[a,*]

[a]*Department of Chemistry, University of Arizona, 1306 E. University Boulevard, Tucson, AZ 85721, USA*
[b]*Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121, USA*

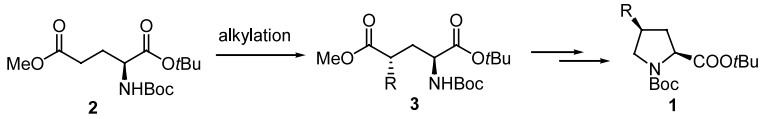
Received 29 October 2002; revised 18 December 2002; accepted 19 December 2002

Abstract—A series of novel *cis*-4-substituted proline analogues were designed and synthesized. Highly stereoselective alkylations at the γ-position of glutamic ester **2** were achieved, followed by reduction, mesylation, and cyclization to afford the title compounds **1** in good yields and high diastereoselectivity.

Proline is a unique amino acid with its rigid cyclic system. It exerts great influence on both the structure and function of peptides and proteins.[1] Peptides and proteins with a proline residue can influence important secondary structures such as a β-turn and an α-helix.[2] In addition, proline has been used as a rigid template to design conformationally constrained amino acids for the study of the interactions of peptide and protein ligands with their receptors/acceptors.[3–5] Such effects on peptide conformations have created a great deal of interests for the design of various substituted proline analogues. In these proline compounds, 4-substitued derivatives are particularly attractive since the C4 substituents can influence not only the conformation of the pyrrolidine ring, but the rate of *cis–trans* isomerization about the amide bond as well.[4,6,7] In our ongoing melanocyte stimulating hormones (MSH) project, the substitution of histidine with proline in MT-II has generated a potent and selective analogue with agonist activity at the human MC5R.[8] To further explore the structure–activity relationship (SAR) of this ligand and its receptors, we have designed novel 4-substituted prolines.

Several methods for the synthesis of 4-substitued prolines have appeared in the literature.[3–5] Recently, our and Goodman's group have reported the synthesis of *cis*- and *trans*-4-substituted proline analogues through hydrogenation reactions from 4-*trans*-hydroxy proline.[3,4] Meanwhile we have developed asymmetric hydrogenations/Suzuki-couplings for the preparation of a number of novel χ^2 constrained amino acids.[9] As an alterative to these methods, herein we would like to disclose an efficient and stereoselective approach to the synthesis of *cis*-4-subsititued prolines. The synthetic strategy for the preparation of the title compounds **1** employs stereoselective alkylation at the γ-position of glutamic ester **2**, followed by selective reduction, mesylation, and cyclization to obtain *cis*-4-substituted prolines **1** (Scheme 1).

The synthesis of *cis*-4-substituted proline analogues **1** started with commercially available (4*S*)-5-(*tert*-butoxy)-4-[(*tert*-butoxycarbonyl)amino]-5-oxopentanoic acid (Scheme 2). The carboxylic acid was protected as a *t*-butyl ester, which was orthogonal to the later ω-methyl ester **2**. Thus, the methyl ester could be selectively reduced without affecting the *t*-butyl ester. The free ω carboxyl functional group was converted into a methyl ester **2** using dicyclohexylcarbodiimide (DCC) as an activating agent with methanol in the presence of



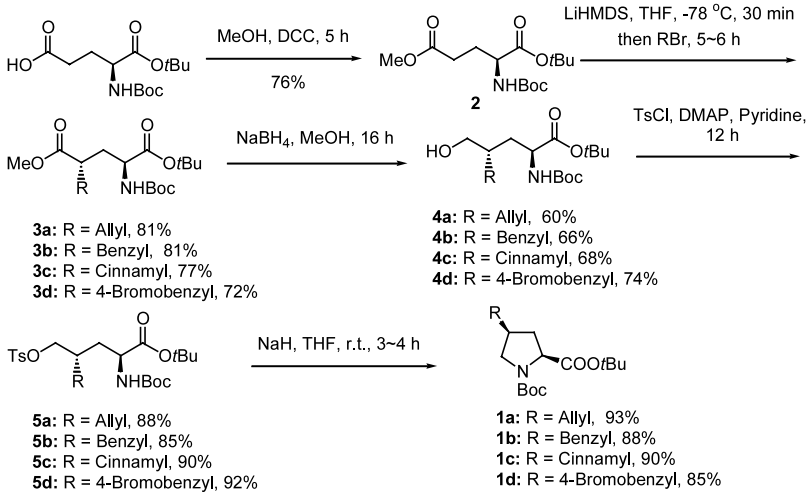
2 **3** **1**

Scheme 1. Strategy for the preparation of *cis*-4-substituted proline derivatives **1**.

Keywords: proline; constrained amino acids; alkylation.

* Corresponding authors. Tel.:+1-(858)-332-4710; fax: +1-(858)-812-1942 (W.W.); Tel.: +1-(520)-621-6332; fax: +1-(520)-621-8407 (V.J.H.); e-mail: wwang@gnf.org; hruby@u.arizona.edu

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02865-4



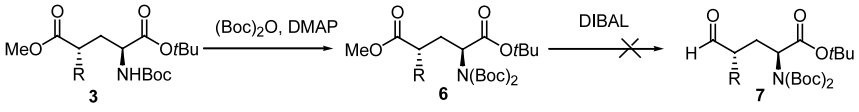
Scheme 2.

a catalytic amount of dimethylaminopyridine (DMAP) and triethylamine (TEA) in 76% yield (Scheme 2).[10] The resulting compound **2** was used for the alkylations. Alkylation at the C4 position of glutamates has been reported in the literature.[11,12] The studies indicated that the stereoselectivity depended on the nature of the *N*-substitutents[13] and the esters.[14,15] Recently, Hanessian and co-workers achieved highly stereoselective alkylations with N^{α}-Boc or Cbz and the methyl ester.[11,12] The stereoselectivity was attributed to a highly coordinated dianionic chair-like transition state. However substrates with the bigger *t*-butyl ester, as in our case, have not been studied. We believed that the size of the ester groups would play an important role in controlling the stereoselectivity of the alkylations based on the proposed transition state. The large *t*-butyl ester would further enhance the diastereoselectivity of the alkylations by stabilization of the chair-like transition state. As expected, only one single diastereomer (*anti* product) was obtained based upon ^{1}H NMR analysis (Scheme 2).

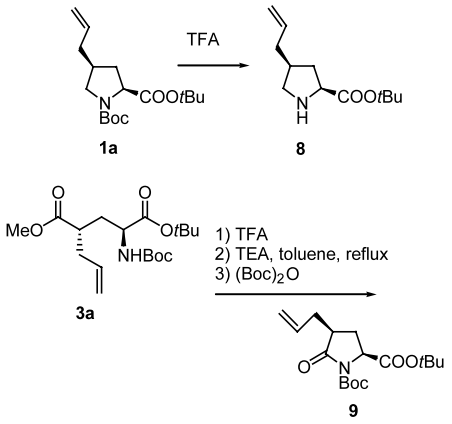
With the optically pure γ-substituted alkyl glutamic acid ester **3** in hand, initially we planed to selectively reduce the methyl ester by diisobutylaluminumhydride (DIBAL) at −78°C to an aldehyde, which subsequently could undergo reductive amination to give the final products **1**. Based on our earlier study, the mono Boc protected nitrogen interfered with the reduction.[10] Therefore, a second Boc protecting group was introduced by reaction of **3** with di-*t*-butyldicarbonate [$(Boc)_2O$] in the presence of a catalytic amount of DMAP in acetonitrile after chromatography to give the bis-Boc protected methyl ester **6** in over 80% yield (Scheme 3).[10] However, the reduction of the methyl ester in **6** using DIBAL at −78°C did not give the desired aldehyde **7**. Even higher reaction temperatures (room temperature to 70°C) did not work either. In all cases, only starting materials were recovered. In contrast, our previous study with reduction of a similar substrate without γ-substituents under the same reaction condition gave an aldehyde in excellent yield.[10] The presumed reason was steric hindrance in the γ-substituted substrates **6**.

Consequently we modified our synthetic strategy (Scheme 2). We proposed the conversion of the methyl ester **3** to an alcohol, which then was transformed into a good leaving group for cyclization. The intramolecular nuclear substitution (cyclization) would provide the target molecules. Reduction of the mono-Boc protected methyl esters **3** with $NaBH_4$ to give alcohols **4** were achieved in good yields. Then the alcohols were converted into mesylates **5** in high yields. The mesylated intermediates were treated with NaH to give the cyclic proline derivatives **1** in good yields. To test for racemization during these conversions, we selectively deprotected the Boc group in **1a** (due to rotamers) to **8**, which gave a 'clean' NMR (Scheme 4). One isomer was observed by NMR indicating that no isomerization occurred. With compound **3a** as an example, an important synthetic intermediate, the pyroglutamate ester **9**, which can be used as starting material in our dipeptide β-turn mimetic synthesis,[16] was obtained in three steps (Scheme 4).

In conclusion, a series of novel *cis*-4-substituted proline derivatives **1** were efficiently synthesized from readily available starting materials. High stereoslective alkylations at the γ-position of the glutamic ester **2** were



Scheme 3.



Scheme 4.

achieved. The resulting alkylation compounds were transformed to the final products **1** through reduction/mesylation/cyclization in high yields. The incorporation of these unnatural amino acids into α-MSH peptides is under investigation.

Acknowledgements

This work was supported by US Public Health Service (DK 17420) and the National Institute of Drug Abuse (DA 13449). We thank Professor Dominic V. McGrath for the use of his group's polarimeter. The opinions expressed are those of the authors and not necessarily those of the US Public Health Service.

References

1. Saviano, M.; Isernia, C.; Rossi, F.; Blasio, B. D.; Iacovino, R.; Mazzeo, M.; Pedone, C.; Benedetti, E. *Biopolymers* **2000**, *53*, 189.
2. Lee, H.-S.; Syud, F. A.; Wang, X.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 7721.
3. Our group has synthesized 4-guanidino and 4-phenyl prolines. See: (a) Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1038; (b) Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 3593 and references cited therein.
4. Recently, Goodman's group reported the synthesis of *cis*- and *trans*-trifluoro prolines. See: Del Valle, J. R.; Goodman, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1600 and references cited therein.
5. Bunuel, E.; Gil, A. M.; Diaz-de-Villegas, M. D.; Cativiela, C. *Tetrahedron* **2001**, *57*, 6417.
6. Improta, R.; Benzi, C.; Barone, V. *J. Am. Chem. Soc.* **2001**, *123*, 12568.
7. Renner, C.; Alefelder, S.; Bae, J. H.; Budisa, N.; Huber, R.; Moroder, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 923.
8. Grieco, P.; Lavecchia, A.; Cai, M.; Trivedi, D.; Weinberg, D.; MacNeil, T.; Van der Ploeg, L. H. T.; Hruby, V. J. *J. Med. Chem.* **2002**, *45*, 5287.
9. We have synthesized χ^2 constrained amino acids using asymmetric hydrogenations/Suzuki couplings. See: (a) Wang, W.; Xiong, C. Y.; Yang, J. Q.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 7717; (b) Wang, W.; Zhang, J.; Xiong, C.; Hruby, V. J. *Tetrahedron Lett.* **2002**, *43*, 2137; (c) Wang, W.; Xiong, C.; Zhang, J.; Hruby, V. J. *Tetrahedron* **2002**, *58*, 3101; (d) Wang, W.; Cai, M.; Xiong, C.; Zhang, J.; Tevil, D.; Hruby, V. J. *Tetrahedron* **2002**, *58*, 7365.
10. Wang, W.; Xiong, C.; Yang, J.; Hruby, V. J. *Synthesis* **2002**, 94.
11. Hanessian, S.; Schaum, R. *Tetrahedron Lett.* **1997**, *38*, 163.
12. Hanessian, S.; Margarita, R. *Tetrahedron Lett.* **1998**, *39*, 5887.
13. Gu, Z.-Q.; Hesson, D. P.; Pelletier, J. C.; Maccecchini, M. L. *J. Med. Chem.* **1995**, *38*, 2518.
14. Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859.
15. Baldwin, J. E.; North, M.; Flinn, A.; Moloney, M. G. *J. Chem. Soc., Chem. Commun.* **1988**, 828.
16. We have used pyroglutamic acid derivatives as starting materials for the synthesis of dipeptide β-turn mimetics. See: (a) Wang, W.; Yang, J.; Ying, J.; Xiong, C.; Zhang, J.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2002**, *67*, 6353; (b) Zhang, J.; Xiong, C.; Wang, W.; Ying, J.; Hruby, V. J. *Org. Lett.* **2002**, *4*, 4029.