

# Stereoselective Bromination–Suzuki Cross-Coupling of Dehydroamino Acids To Form Novel Reverse-Turn Peptidomimetics: Substituted Unsaturated and Saturated Indolizidinone Amino Acids

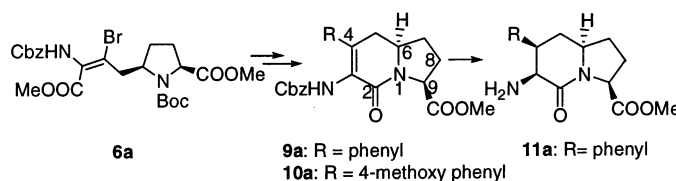
Junyi Zhang, Chiyi Xiong, Wei Wang,<sup>†</sup> Jinfa Ying, and Victor J. Hruby\*

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

hruby@u.arizona.edu

Received August 9, 2002

## ABSTRACT



A general and efficient methodology has been developed to prepare the C4-substituted dipeptide reverse-turn mimetics unsaturated (9a, 10a) and saturated (11a) azabicyclo[4.3.0] alkane amino acid derivatives. The side chain was introduced by bromination of dehydroamino acid intermediates followed by Suzuki coupling. Hydrogenation of the bicyclic dehydroamino acid 9a afforded saturated bicyclic lactam 11a. This approach can be further explored for the synthesis of a variety of such  $\beta$ -turn mimetics with aryl and alkyl side chain functionalities.

During the past years, we and other research groups have developed synthetic routes for the preparation of enantiopure indolizidinone type bicyclic lactam systems.<sup>1</sup> However, these approaches suffer from some limitations. For example, the introduction of side chain functionalities at the C4 position of azabicyclo[X.Y.0] alkane amino acids generally was not accessible, or required a long synthetic sequence;<sup>2</sup> most methodologies have no way to introduce a phenyl or a *p*-hydroxyl phenyl group, which corresponds to the side

chains in the amino acids Phe and Tyr, respectively. Moeller and co-workers chose a benzyl group to substitute for a phenyl group. However, their studies showed that the extra methylene group interfered badly in the binding to the TRH-R receptor.<sup>3</sup> In this paper, we report a novel methodology that can allow for the synthesis of 4-phenyl- or *p*-hydroxylphenyl-substituted saturated and unsaturated indolizidinone amino acids. Such reverse turn mimetics could be used to serve as surrogates of dipeptides Phe-Ala and Tyr-Ala. Their potential applications include our ongoing  $\alpha$ -MSH (melanocyte stimulating hormones) and opioid peptide programs, and the TRH-R peptide.<sup>3,4</sup>

Some groups have reported on the preparation of indolizidinone type compounds through dehydroamino acid intermediates.<sup>5</sup> Further applications to these methodologies have been successfully developed in our group to introduce side

\* Author to whom correspondence should be addressed at the University of Arizona. Phone: (520) 621-6332. Fax: (520) 621-8407.

<sup>†</sup> Current address: Genomics Institute of the Novartis Research Foundation, 9390 Towne Centre Dr., Suite 200, San Diego, CA 92121.

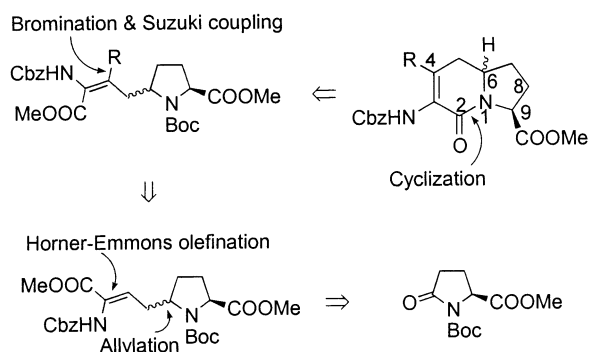
(1) (a) Mueller, R.; Revesz, L. *Tetrahedron Lett.* **1994**, 34, 4091–4092. (b) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1996**, 61, 9437–9446. (c) Kim, H.-O.; Kahn, M. *Tetrahedron Lett.* **1997**, 37, 6483–6484. (d) Wang, W.; Xiong, C.; Hruby, V. J. *Tetrahedron Lett.* **2001**, 42, 3159–3161.

(2) Li, W.; Hanau, C. E.; d'Avignon, A.; Moeller, K. D. *J. Org. Chem.* **1995**, 60, 8155–8170.

(3) Li, W.; Moeller, K. D. *J. Am. Chem. Soc.* **1996**, 118, 10106–10112.

chain functionalities at the C7 and C8 positions.<sup>6</sup> Presently, we have extended these methodologies to introduce *aryl* groups at position 4 through Suzuki cross-couplings. The general retrosynthetic strategy is given in Scheme 1. The

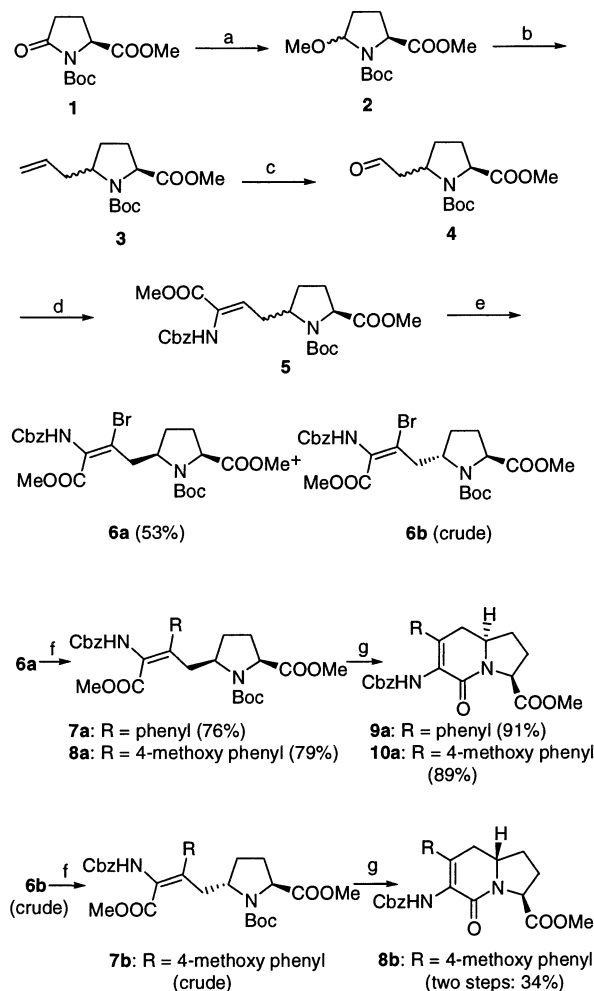
**Scheme 1.** Retrosynthetic Analysis



unsaturated bicyclic lactam system could be approached from a dehydroamino acid intermediate, which can be prepared by Horner–Emmons olefination of a proline aldehyde derivative. Two challenges must be faced in our synthetic approach to the novel targets. The first is the introduction of the side chain functionality at the C4 position from the precursor dehydroamino acid derivative. Second, the major *Z* dehydroamino acid products formed from the Horner–Emmons reaction may restrict the cyclization in the following step. We postulated that bromination of the dehydroamino acid could be a solution to these two problems. Bromination can generate a reactive site for Suzuki cross-coupling and also can provide the geometry required for cyclization. With this methodology, we also can introduce side chain functionalities at both C4 and C7 or C8 positions using the corresponding chiral pyroglutamic ester derivatives prepared by chemistries previously developed in our laboratory.<sup>7</sup> In this paper, we have demonstrated the synthetic method with side chain functionalities at the C4 position.

Our approach to the synthesis of 4-substituted azabicyclo-[4.3.0] alkane amino acid derivatives **9a** and **10a** is illustrated

**Scheme 2<sup>a</sup>**



<sup>a</sup> Conditions: (a) (i) Super-Hydride, THF,  $-78^{\circ}\text{C}$ ; (ii) *p*-TsOH (cat.), MeOH; (b)  $\text{BF}_3\cdot\text{Et}_2\text{O}$ ,  $\text{Me}_3\text{SiCH}_2\text{CH}=\text{CH}_2$ , three steps: 77%; (c)  $\text{OsO}_4$ ,  $\text{NaIO}_4$ , THF/ $\text{H}_2\text{O}$ , 4 h; (d)  $(\text{MeO})_2\text{P}(\text{O})\text{CH}(\text{NHCBz})\text{COOCH}_3$ , DBU, DCM, rt, 8 h, two steps: 63%; (e) (i) NBS,  $\text{CHCl}_3$ , rt, 80 min; (ii) Dabco,  $\text{CHCl}_3$ , rt, 24 h; (f)  $\text{RB}(\text{OH})_2$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{P}(\text{o-tolyl})_3$ ,  $\text{Na}_2\text{CO}_3$ , DME,  $80^{\circ}\text{C}$ ; (g) (i) 20% TFA, DCM, rt, 30 min; (ii)  $\text{NaHCO}_3$ ; (iii)  $\text{CHCl}_3$ , rt, 24 h.

in Scheme 2. The readily available (*S*)-pyroglutamate **1** was reduced to the methoxy aminal **2** by treatment with Super-Hydride ( $\text{LiEtEt}_3\text{H}$ ) in THF at  $-78^{\circ}\text{C}$ , and then with methanol in the presence of a catalytic amount of *p*-TsOH. The crude product **2** was directly subjected to allyltrimethylsilane in the presence of boron trifluoride without further purification. The allylsilane addition to the *N*-acyliminium compound derived from **2** afforded a 3:1 *cis/trans* mixture of proline ester **3**. The intermediate **3** underwent osmylation and subsequent oxidation with  $\text{NaIO}_4$  to give aldehyde **4**. A *cis/trans* dehydroamino acid mixture **5** was obtained in a 3:1 ratio via Horner–Emmons olefination of **4**.<sup>8</sup>

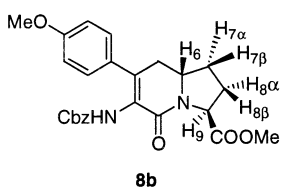
(8) The ratio was determined based on  $^1\text{H}$  NMR spectra. The assignment of the major product to a *cis* isomer was achieved according to the literature: Mulzer, J.; Schülzer, F.; Bats, J.-W. *Tetrahedron* **2000**, *56*, 4289–4298. It was further confirmed by the stereochemistry of the final product.

- (4) (a) Hruby, V. J.; Wikes, B. C.; Hadley, M. E.; Al-Obeidi, F.; Sawyer, T. K.; Staples, D. J.; deVaux, A. E.; Dym, O.; Castrucci, A. M. F.; Hintz, M. E.; Riehem, J. P.; Rao, R. *J. Med. Chem.* **1987**, *30*, 2126–2130. (b) Sawyer, T. K.; Hruby, V. J.; Darman, P. S.; Hadley, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 1751–1755. (c) Hruby, V. J.; Gehrig, C. A. *Med. Res. Rev.* **1989**, *9*, 343–401. (d) Mosberg, H. I.; Hurst, R.; Hruby, V. J.; Gee, K.; Yamamura, H. I.; Galligan, J. J.; Burks, T. F. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 5871–5874. (5) (a) Mulzer, J.; Schülzchen, F.; Bats, J.-W. *Tetrahedron* **2000**, *56*, 4289–4298. (b) Angiolini, M.; Araneo, S.; Belvisi, L.; Cesarotti, E.; Checchia, A.; Crippa, L.; Manzoni, L.; Scolastico, C. *Eur. J. Org. Chem.* **2002**, 2571–2581. (6) Wang, W.; Yang, J.; Ying, J.; Xiong, C.; Zhang, J.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2002**, *67*, 6353–6370. (7) (a) Ezquerro, J.; Pedregal, C.; Rubio, A.; Yrretagoyena, B.; Escribano, A.; Sanchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665–8678. (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *41*, 135–139. (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2172–2175. (d) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747–750. (e) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688–6696. (f) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L. *Tetrahedron* **1999**, *55*, 12045–12058.

The stereoselective  $\beta$ -bromination of dehydroamino acid esters has been well documented.<sup>9</sup> Nunami and co-workers described that the *Z*-selectivity of the bromination was improved by increasing the bulkiness of  $\beta$ -substituents.<sup>10</sup> Carpenter and co-workers proposed that the *Z*-vinyl bromide was the thermodynamically more stable product and the kinetically formed *E*-vinyl bromide could be interconverted to the *Z*-isomer through DABCO-induced isomerization.<sup>11</sup> In our case, we treated the dehydroamino acid ester **5** with *N*-bromosuccinimide (NBS) to produce  $\alpha$ -bromo-imines, which underwent tautomerization to afford (*Z*)- $\beta$ -bromo- $\alpha$ ,  $\beta$ -dehydroamino acids **6a,b** upon treatment with an amine base. We examined various amine bases which could be used in the tautomerization step. The results showed that the use of DABCO instead of Et<sub>3</sub>N and DBU as a base improved *Z*-selectivity and gave the *Z*-isomer exclusively. This result was consistent with the observations of Carpenter and co-workers.<sup>11</sup> The *cis/trans* isomers **6a,b** were able to be separated at this point by column chromatography eluting with hexanes/ethyl acetate (4/1). However, the attempts to purify compound **6b** were not successful due to a contamination of the  $\alpha$ -bromo-imine intermediate in this reaction.

We then investigated the Suzuki cross-coupling of **6a** with aryl boronic acids. We chose phenyl boronic acid and 4-methoxyphenyl boronic acid to use in the couplings because Phe and Tyr are two important amino acid moieties in our  $\alpha$ -MSH and  $\delta$ -opioid studies. Suzuki coupling went smoothly to afford **7a** and **8a**, in 76% and 79% yields, respectively. Deprotection of the *N* $^{\alpha}$ -Boc group was performed in 20% TFA in dichloromethane (DCM) at room temperature (rt). The TFA was neutralized with NaHCO<sub>3</sub>, and the reaction was stirred in chloroform at room temperature for 48 h. Deprotected **7a**, **8a** underwent slow cyclization to afford **9a**, **10a** in good yields.

**Table 1.** NOE Data for **8b**



protons		NOE (%)
H <sub>9</sub>	H <sub>8α</sub>	1.93
H <sub>9</sub>	H <sub>8β</sub>	0.39
H <sub>6</sub>	H <sub>8α</sub>	n.o. <sup>a</sup>
H <sub>6</sub>	H <sub>8β</sub>	0.68
H <sub>8β</sub>	H <sub>7α</sub>	0.47
H <sub>8β</sub>	H <sub>7β</sub>	1.30
H <sub>6</sub>	H <sub>7α</sub>	0.26
H <sub>6</sub>	H <sub>7β</sub>	2.01

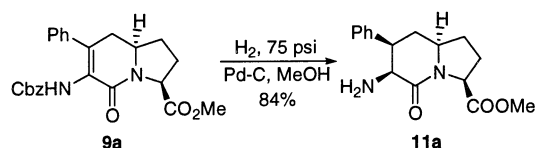
<sup>a</sup> NOE not observed.

The configuration of the bridgehead proton in **9a**, **10a** has been described in the literature.<sup>5a</sup> Our efforts to further confirm the stereochemistry by NMR led to difficulty

because the NOE spectrum was complicated due to the overlap of proton peaks. Thus, we evaluated the other bridgehead stereoisomer. We used the crude compound **6b** in Suzuki coupling and the crude product was cyclized to give **8b** in 34% overall yield from **6b**. The stereochemistry of **8b** was assigned with the use of a 1D-NOE experiment (Table 1).

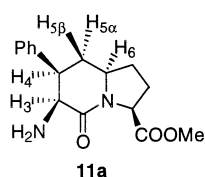
Once the unsaturated bicyclic lactams **9a**, **10a** were obtained, we investigated the possibility of converting the unsaturated bicyclic structures to the saturated structures by hydrogenation. The literature reported that the hydrogenation of dehydroamino acids in open chain substrates proceeded with poor stereoselectivity.<sup>5b</sup> However, the restricted conformation in the bicyclic compound provided an asymmetric environment in hydrogenation. As we expected, compound **9a** was hydrogenated (Pd-C, H<sub>2</sub>, 75 psi) to give **11a**

**Scheme 3**



exclusively (Scheme 3).<sup>12</sup> The stereochemistry of **11a** was determined based on the NOE data (Table 2), and the relative

**Table 2.** NOE Data for **11a**



protons		NOE (%)
H <sub>5β</sub>	H <sub>6</sub>	0.35
H <sub>5α</sub>	H <sub>6</sub>	1.15
H <sub>5β</sub>	H <sub>4</sub>	0.50
H <sub>5α</sub>	H <sub>4</sub>	1.25
H <sub>5β</sub>	H <sub>3</sub>	n.o. <sup>a</sup>
H <sub>5α</sub>	H <sub>3</sub>	0.05

<sup>a</sup> NOE not observed.

configuration between the C3 and C4 protons was further confirmed by the *J* coupling constants.<sup>13</sup> The backbone conformations of the compound best fit the criteria for type II' and V'  $\beta$ -turn structures.<sup>14</sup>

(9) (a) Olsen, R. K.; Hennen, W. J.; Wardke, R. B. *J. Org. Chem.* **1982**, 47, 7, 4605–5611. (b) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1992**, 57, 5813–5815. (c) Armstrong, R. W.; Moran, E. J. *J. Am. Chem. Soc.* **1992**, 114, 371–372.

(10) Yamada, M.; Nakao, K.; Fukui, T.; Nunami, K.-I. *Tetrahedron* **1996**, 52, 5751–5764.

(11) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1993**, 58, 4452–4461. Please see the reaction mechanism in the Supporting Information.

In conclusion, we have successfully developed an approach to the synthesis of unsaturated and saturated azabicyclo[4.3.0] alkane amino acids with an aryl side chain at the C4 position. This methodology potentially can be extended to the preparation of more complex molecules, such as 7/5 and 5/5 azabicyclo[X.Y.0] alkane amino acids. The synthesis of more complex bicyclic lactams with side chains at the C4, C7, and/or C8 positions is under investigation. Future efforts will aim at the incorporation of these  $\beta$ -turn mimetic molecules into biologically active peptides and the study of structure–activity relationships.

**Acknowledgment.** This work was supported by the U.S. Public Health Service (DK 17420) and the National Institute of Drug Abuse (DA 13449). We thank Professor Dominic

(12) We have performed some modeling studies in order to explain the stereoselectivity of hydrogenation. Please see details in the Supporting Information.

V. McGrath for the use of his group's polarimeter. The opinions expressed are those of the authors and not necessarily those of the U.S. Public Health Service.

**Supporting Information Available:** Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL020160A

(13) Our modeling study showed the dihedral angles between H<sub>3</sub> and H<sub>4</sub> are 40° and 57° (two conformations) in the *syn* isomer and –169° in the *anti* isomer. The calculation of the *J* coupling constant was on the basis of this conclusion: *J*<sub>*syn*</sub> = 4.1 Hz; *J*<sub>*anti*</sub> = 12.5 Hz. The observed *J* coupling constant was 6.9 Hz. Considering the additional fact that *syn* addition has been observed in most metal-catalyzed hydrogenations, we drew the conclusion that the relative configuration of H<sub>3</sub> and H<sub>4</sub> in compound **11a** is *syn*.

(14) Superposition of two lowest energy conformations of the compound **11a** onto a peptide with various types of  $\beta$ -turn structures using backbone heavy atoms gave an RMSD of 0.42 Å for the type II' structure for one conformation, and an RMSD of 0.56 Å for the type V' structure for the other conformation.