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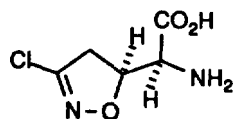
### Syntheses of Heterocyclic Amino Acid Derivatives via Nitrile Oxide Cycloadditions with $\beta,\gamma$ -Unsaturated- $\alpha$ -Amino Acid Compounds

Gyochang Keum, Yong Jun Chung, and  
Byeang Hyeon Kim\*

Department of Chemistry, Center for Biofunctional Molecules,  
Pohang Institute of Science and Technology,  
P.O.Box 125, Pohang 790-600

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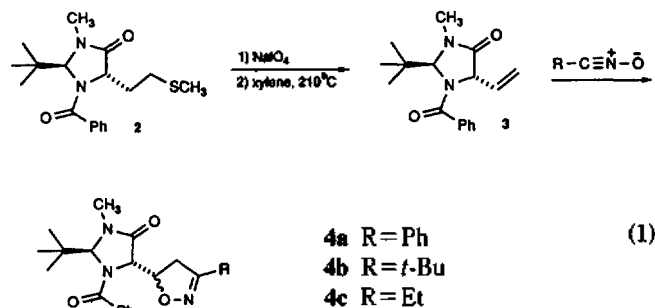
A novel antitumor antibiotic, ( $\alpha S$ ,  $5S$ )- $\alpha$ -amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (**1**, AT-125, Acivicin), isolated from fermentation broths of *Streptomyces sviveus*<sup>1</sup>, displayed significant activity against a number of tumors in experimental animals<sup>2</sup>. The biological activity of this unusual amino acid and its novel structure have elicited our interest in the synthesis of the related amino acid derivatives possessing 2-isoxazoline rings. We report here the preliminary results of our synthetic efforts.



**1**: AT-125(Acivicin)

To synthesize our desired products by cycloadditive approach, we needed to prepare the  $\beta,\gamma$ -unsaturated- $\alpha$ -amino acid derivatives as chiral dipolarophiles. The  $\beta,\gamma$ -unsaturated- $\alpha$ -amino acids are a class of compounds that possess antibiotic and enzyme inhibitory activity<sup>3</sup>. (2*S*, 5*S*)-Imidazolidinone **2**<sup>4</sup> was prepared from L-methionine in 5 steps (42% overall

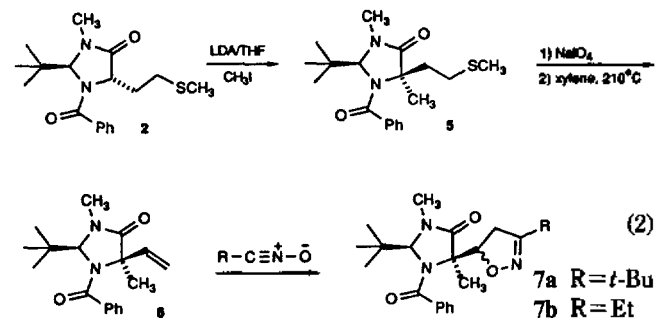
yield) by a modification of the Seebach's method<sup>5</sup>. Oxidation of **2** by  $\text{NaIO}_4$  (96%), followed by thermal elimination of the resulting sulfoxide (88%) provided the desired  $\beta,\gamma$ -unsaturated- $\alpha$ -amino acid derivative **3**. Dipolar cycloadditions of various nitrile oxides ( $\text{R}=\text{Ph}$ , *t*-Bu, Et) with **3** afforded the corresponding cycloadducts **4a-c** (Eq. 1).



In the case of benzonitrile oxide cycloaddition, a mixture of two diastereomers was obtained. The major diastereomer (**4am**) and minor one of the above cycloaddition were isolated in 56% and 2% yield, respectively. The major cycloadducts of 2,2-dimethylpropionitrile oxide and propionitrile oxide were isolated in 63% and 50% yield, respectively.

These amino acid derivatives possessing 2-isoxazoline rings underwent the pyramidal nitrogen inversion<sup>6</sup>. This dynamic equilibrium was detected by recording <sup>1</sup>H-NMR spectra of **4am** at room temperature and 70°C. The <sup>1</sup>H-NMR spectrum taken at 70°C showed the coalescence phenomenon due to the rapid equilibrium between two invertomers<sup>7</sup>. The absolute stereochemistry of the newly generated stereogenic center in the major products of **4a-c** was tentatively assigned as *R* by examining molecular models of **3** and **4a-c**.

L-Vinylalanine derivative **6** was prepared from **2** in 3 steps. Stereoselective methylation<sup>8</sup> of **2** provided **5** in 70% yield. Sequential  $\text{NaIO}_4$  oxidation (95%) and sulfoxide elimination (93%) afforded the chiral dipolarophile **6**. 2,2-Dimethylpropionitrile oxide and propionitrile oxide cycloadditions with **6** gave the diastereomeric mixtures (60:40 in both cases) of cycloadducts **7a-b** in 72% and 52% yield, respectively (Eq. 2).



The heterocyclic amino acid derivatives **4a-c** and **7a-b** have been easily prepared by nitrile oxide cycloadditions and these compounds have some antiviral activity<sup>9</sup>. Thus, the asymmetric cycloadditive approach<sup>10</sup> to  $\beta,\gamma$ -unsaturated  $\alpha$ -amino acids may provide a general entry for biofunctional heterocyclic amino acid derivatives.

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4. Major product, (2*S*, 5*S*)-Imidazolidinone **2**: Anal. Calculated for  $C_{18}H_{26}N_2O_2S$  (334.48): C, 64.64; H, 7.84; N, 8.38. Found: C, 64.49; H, 8.19; N, 8.48. Minor product, (2*R*, 5*S*)-Imidazolidinone **2n**: Anal. Calculated for  $C_{18}H_{26}N_2O_2S$  (334.48): C, 64.64; H, 7.84; N, 8.38. Found: C, 64.51; H, 8.01; N, 8.38. The X-ray crystal structures of both major and minor products were determined and full details of crystallographic results will be published elsewhere.
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