Synthesis of an Advanced Intermediate of α-*Allo*enduracididine from α-Allylglycine.

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INTRODUCTION

α-Alloenduracididine 3-(2-amino-4,5-dihydro-1H-imidazole-4-yl)-2-aminopropionic acid) **1** and its diastereoisomer, enduracididine **2**, are two non-proteinogenic amino acids isolated in 1968 from *Streptomyces fungicidicus* as part of a cyclopeptide the enduracidine, which has antibiotic activity.[1,2]

α-Alloenduracididine, which can be viewed as a constrained analogue of arginine **3**, belongs to a family of natural amino acids having the terminal guanidine nitrogen atom linked to the methylene backbone.

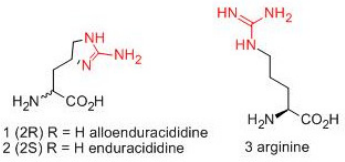
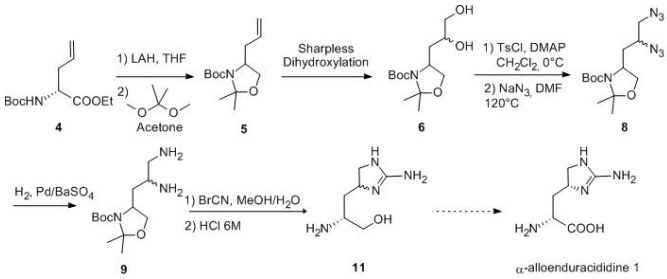


Figure 1 Alloenduracididine, enduracididine and arginine

Most of these amino acids are components of peptide antibiotics isolated from extracts of microorganisms and include: β-hydroxyenduracididine and β-hydroxy*allo*enduracididine (constituents of (α-ε)-mannopeptimycins)[3] tetrahydrolathyrin**e,** capreomycidine (constituent of capreomycins).Our laboratory has recently completed the first total synthesis and determination the absolute configuration of tetrahydrolathyrine[4]. Here, we report the synthesis of an advanced intermediate of α-*allo*enduracididine.

RESULTS AND DISCUSSION

1,3-oxazolidine **5** was prepared from ethyl (*R*)-*N*-Boc-allylglycinate **4**. First, the ester group of **4** was reduced with $LiAlH_4$ in THF to provide an amino alcohol. The latter was protected in the form of an *N,O*-isopropylidene acetal by treatment with 2,2-dimethoxypropane in acetone, leading to 1,3-oxazolidine **5** in 64% yield for 2 steps. The intermediate **5** was submitted to conditions of the Sharpless asymmetric dihydroxylation to give the diol **6** in 93% yield, as a 54:46 mixture of diastereoisomers as determined by GC/MS. At this stage the mixture of diastereoisomers **6** was separated, by successive column chromatographic purification, to provide the diols **6a** and **6b**. The diols were converted to the tosylates **7a** and **7b** (85% and 58%) using tosyl chloride, DMAP (5 equiv.) in dichloromethane at 0°C for 4 hours. The preparation of diazides **8a** and **8b** was performed by treatment of ditosylates **7a** and **7b** with 3 equivalents of sodium azide in DMF at 100°C for 12 h. The diazides **8a** and **8b** were obtained in 60% and 67% yield, respectively. The diazides **8a** and **8b** were then reduced by hydrogenation in the presence of $Pd/BaSO_4$ in ethanol to give the diamines **9a** and **9b**, which were purified by simple filtration. The cyclic guanidine nucleus was constructed by reaction of diamines **9a** and **9b** with cyanogen bromide (BrCN) in a mixture of methanol:water. The guanidines **10a** and **10b** were purified by reverse phase chromatography ($EtOH/H_2O$) and were obtained in 86% and 73% yield, respectively. The removal of the isopropylidene acetal was realized using a solution of 6M HCl for 4 hours.



Scheme 1: Synthetic route to the α-alloenduracididine intermediate.

CONCLUSION

In conclusion, we describe herein an efficient synthetic route to acess the α-alloenduracididine. After eight steps, the intermediates **11a** and **11b** were obtained in satisfactory yields from **4.** Studies concerning the oxidation of the amino alcohol to the amino acid and determination of the absolute configuration at C4 of each diastereoisomer are in progress.

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