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Rapid Syntheses of 3-Amino-5-Hydroxymethyl-γ-Lactones from *L*-Allylglycine.

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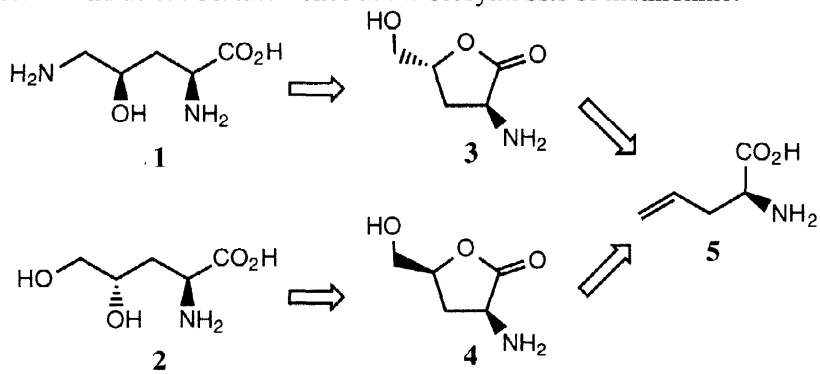
***Abstract** : (3R, 5R) and (3R, 5S) N-protected 3-amino-5-hydroxymethyl-γ-lactones were obtained by one dihydroxylation step from methyl N-protected L-allylglycinate.*

The 1,3-amino alcohol fragment is found in many natural products in particular as a central moiety of non proteinogenic amino acids. Important examples are (2*S*, 4*R*)-4-hydroxyornithine **1** and (2*S*, 4*S*)-4,5-dihydroxynorvaline **2**. **1** is a component of the biphenomycins A and B, cyclopeptides which exhibit high antibiotic activities against Gram positive β-lactam resistant bacteria.[1] **2** is involved, as a key intermediate, in the synthesis of clavalanine, a clavam antibiotic which is an antimetabolite of O-succinic homoserine and as such it intervenes in the biosynthesis of methionine.[2]



The lactones **3** and **4** are known to be the key intermediates in the synthesis of of (2*S*, 4*R*)-4-hydroxyornithine **1** and (2*S*, 4*S*)-4,5-dihydroxynorvaline **2** respectively. The obtention of the N-Boc protected **3** was proposed in four steps starting from *D*-glyceraldehyde.[3] Two multistep preparations of the lactone **4** have been reported starting from *D*-xylose[4] and from *D*-ribonolactone.[5] In continuation of our studies on the synthesis of non proteinogenic hydroxy amino acids of pharmaceutical interest,[6] we investigated an alternative more efficient synthesis of **1** and **2** starting from *L*-allylglycine **5**.

The dihydroxylation of γ,δ-unsaturated esters is known to produce hydroxy-γ-lactones in one step.[7] We thought that *L*-allylglycine **5** would be an efficient precursor of the lactones **3** and **4** involving the dihydroxylation of the terminal double bond. The influence on the stereoselectivity of the chiral center at the β position was examinated. Methyl-N-Boc-*L*-allylglycinate **6** was prepared quantitatively in two steps from *L*-allylglycine **5** by protection of the amine as *t*-butylcarbamate and esterification of the acid with diazomethane. Achiral and chiral oxidative systems have been used for the dihydroxylation step. The results are reported in table 1.

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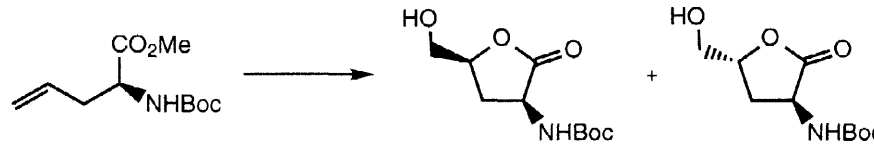

6 7 8

Oxidant	Solvent	Temp.(°C)	Time (h)	Yield (%)	7/8
OsO_4-TMNO 5%	CH_3COCH_3/H_2O	20	2	96	70/30
OsO_4-TMNO 5%	CH_3COCH_3/H_2O	0	24	64	70/30
AD-mix-α 1%	*t*-BuOH/H_2O	0	48	90	70/30
AD-mix-β 1%	*t*-BuOH/H_2O	0	48	41	70/30

Table 1

First, we carried out the dihydroxylation at room temperature using osmium tetroxide in presence of trimethylamine N-oxide, the reaction proceeded smothly in good yield 96% and 70/30 diastereomeric ratio. In order to improve the diastereoselectivity, the temperature was decreased to 0°C : the diastereomeric ratio was not affected but a lower chemical yield was obtained (64%). The lactones **7** and **8** could be separated by recristallisation in methanol. To confirm the relative stereochemistry, the *t*-butylcarbamate was removed and the amine was protected by a benzylcarbamate under classical conditions. The cis and trans N-Boc-3-amino-5-hydroxymethyl-γ-lactones were separable by flash chromatography and correlated with the physical and spectrometric data of the literature.[8] The cis relative stereochemistry was confirmed for the major stereomer **7**.

Double diastereoselection was reported in asymmetric dihydroxylation of chiral allylic alcohol.[9] However for the methyl-N-Boc-*L*-allylglycinate **6**, any matched or mismatched effect was found using dihydroxylating chiral reagents (AD-mix-α or AD-mix-β) : the diastereoselectivity was identical to that observed with achiral osmium tetroxide but a decrease of the chemical yield was noticed using AD-mix-β. 1,3 Asymmetric induction of the *S* aminoacid center control the diastereoselection.

In conclusion, we proposed here a practical method for the syntheses of both N-protected 3-amino-5-hydroxymethyl-γ-lactones from N-protected methyl *L*-allylglycinate via a single dihydroxylation step. These lactones can be transformed into the corresponding optically pure γ-hydroxy-α-amino acids.

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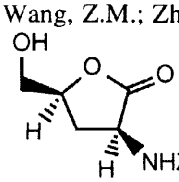
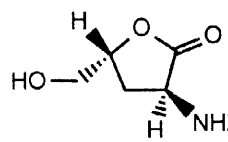
8 - 

$[\alpha]_D$=-1 (c:0.48, MeOH)
Lit.[10] : -1



$[\alpha]_D$=-53 (c:0.48, MeOH)
Lit.[11] : -50.9

NOE experiments confirmed the relative stereochemistry.

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