

## Introduction

Vinylglycine is the simplest natural  $\beta,\gamma$ -unsaturated amino acid and it is widely studied for its various biological properties [1]. D-Vinylglycine is produced by the mushroom *Rhodophyllus nidorosus* (Figure 1) and L-Vinylglycine is generated in a variety of PLP-dependent enzymes as a mechanistic intermediate. Thanks to its inhibition properties, L-Vinylglycine proved to be a useful tool to study these enzymes.

L-Vinylglycine is also an interesting building block in organic chemistry, notably for the synthesis of meso-diaminopimelic acid derivatives [2].

In this work, we present a new protocol for the enantioselective synthesis of a library of *N,C*-protected vinylglycine derivatives using continuous-flow thermolysis of oxidized methionine derivatives.

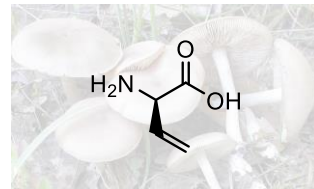


Figure 1 | d-Vinylglycine and *Rhodophyllus nidorosus*.

## Results

First, L- or D-methionine was fully protected and then oxidized using  $\text{NaIO}_4$ . Finally, the corresponding sulfoxides were exposed to heat to effect thermolysis towards the desired vinylglycine derivatives (Figure 2).

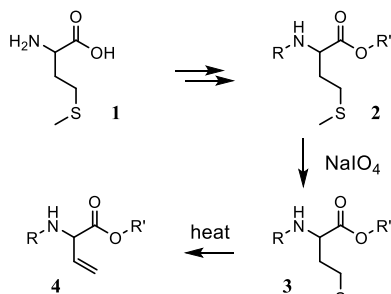


Figure 2 | General strategy.

This last step is crucial in terms of enantioselectivity and global yield. Two previously reported methods [3,4] were tested but failed to achieve satisfying results concerning one or both aspects. In batch mode, at least two hours of reflux were required to complete the thermolysis of oxidized methionine derivatives but this long process also yields to the formation of large amounts of dehydrobutyrine analogues (*E/Z*)-5 (up to 50%) and partial racemization of the desired protected vinylglycine.

Based on these observations, we designed a new continuous mesofluidic device for high temperature applications. This mesofluidic device allows us to have a very accurate control over residence time, temperature and pressure (Figure 3). We chose toluene as solvent and a concentration of  $10 \text{ g}\cdot\text{L}^{-1}$  of *N,C*-protected oxidized methionine.

Theoretical studies were performed at the B3LYP/6-31+G\* level of theory to rationalize the formation of dehydrobutyrine, and the corresponding results are presented in Figure 4. We found from these results that methylsulfenic acid is implicated in the formation of dehydrobutyrine. Methylsulfenic acid was quenched *in situ* with dimethyl acetylenedicarboxylate (Figure 5). This strategy significantly reduced the amount of contaminating dehydrobutyrine (Chart 1).

Best conditions ( $1 \text{ mL}\cdot\text{min}^{-1}$ ,  $270^\circ\text{C}$ , 1 eq. of dimethyl acetylenedicarboxylate) afforded high conversion (99%) and very good enantiomeric excess (over 97%).

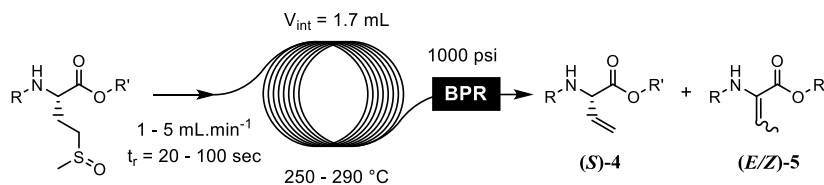


Figure 3 | Flow chart of the mesofluidic device and thermolysis reaction.

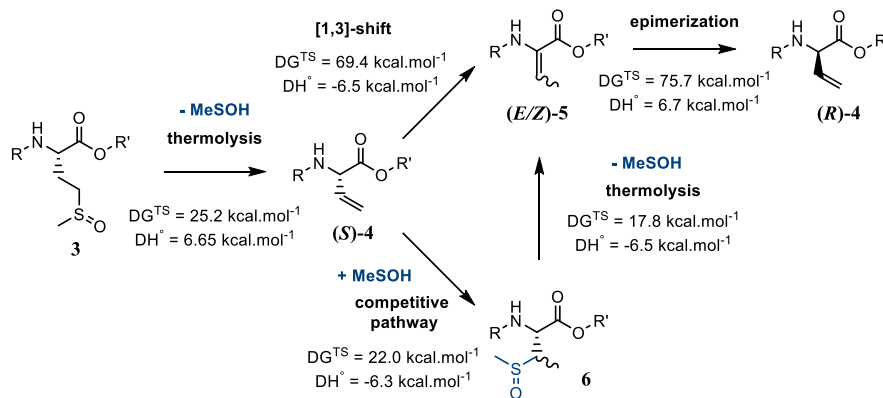


Figure 4 | Theoretical studies (B3LYP/6-31+G\*) of the different competitive reactions.

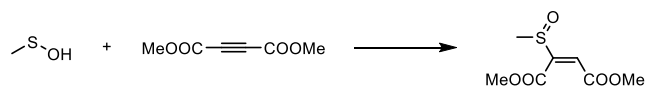


Figure 5 | *In situ* quench of methylsulfenic acid by dimethyl acetylenedicarboxylate.

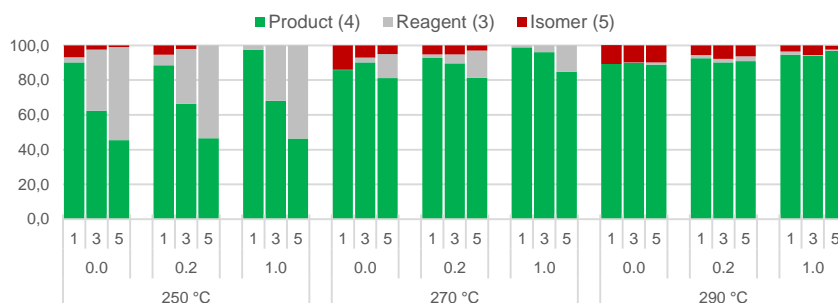


Chart 1 | Composition of the crude obtained after continuous flow thermolysis of CbzHN-Vgl-Ome (determined by HPLC) in function of flow-rate (1, 3, 5  $\text{mL}\cdot\text{min}^{-1}$ ), quantity of dimethyl acetylenedicarboxylate (0, 0.2, 1.0 eq.) and temperature (250, 270, 290  $^\circ\text{C}$ ).

## Conclusion

In this work, we present a new protocol for the enantioselective synthesis of a library of *N,C*-protected vinylglycine derivatives using continuous-flow thermolysis of oxidized methionine derivatives. This method allows us to produce large quantities of *N,C*-protected vinylglycine derivatives with excellent yields, enantiomeric excess and good reproducibility.

## References

[1] D.B. Berkowitz et al., *Tetrahedron: Asymmetry*, 17, 869-882, 2006.

[2] A. R. Chowdhury et al., *Tet. Lett.* 2005, 46, 1675-1678.

[3] S.K. Patel et al., *Tetrahedron Lett.*, 50, 5067-5070, 2009.

[4] C-H. Küchanthal et al, *Amino Acids*, 39, 443-448, 2010.

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