

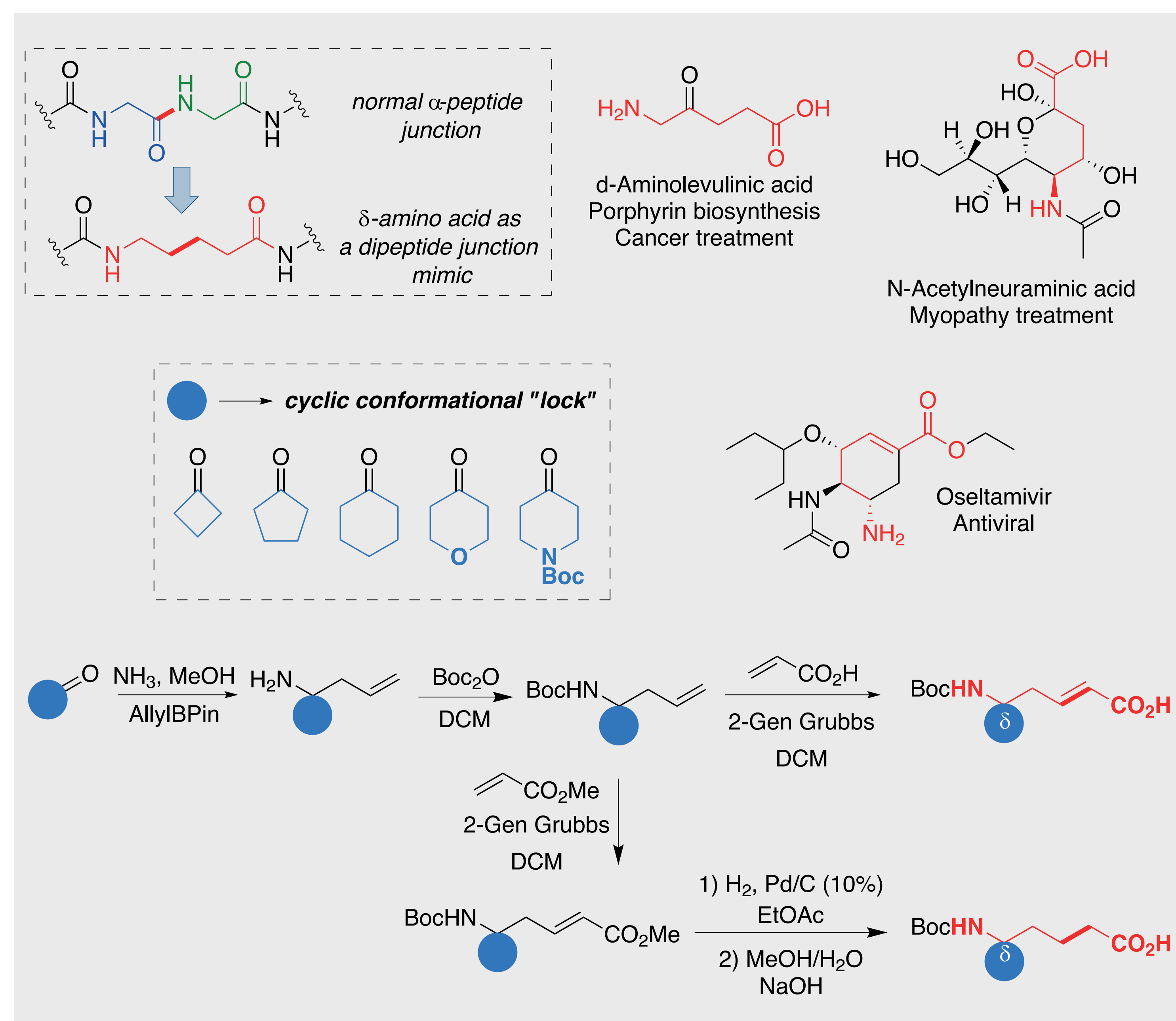
# Synthesis of conformationally limited $\delta$ -amino acids as a tool for the design of peptide-like foldamers



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## Background and synopsis of the project

- Conformationally limited amino acids are valuable for drug discovery. Their rigid 3D-shaped structure illustrates "Escape from Flatland" concept, while presence of carboxylic and amino groups opens the door to peptide synthesis.
- New concepts like DOS (Diversity Oriented Synthesis), LOS (Lead Oriented Synthesis), DTS (DNA-Templated Synthesis) appeared to satisfy MedChem needs in faster and more efficient ways in comparison to classical organic synthesis<sup>1</sup>.
- Earlier, we successfully tried Petasis reaction for construction of quaternary center in spirocyclic pyrrolidines synthesis<sup>2</sup>. Recently, we applied DOS strategy to synthesis of acyclic and monocyclic  $\delta$ -amino acids via Petasis-Grubbs sequence.



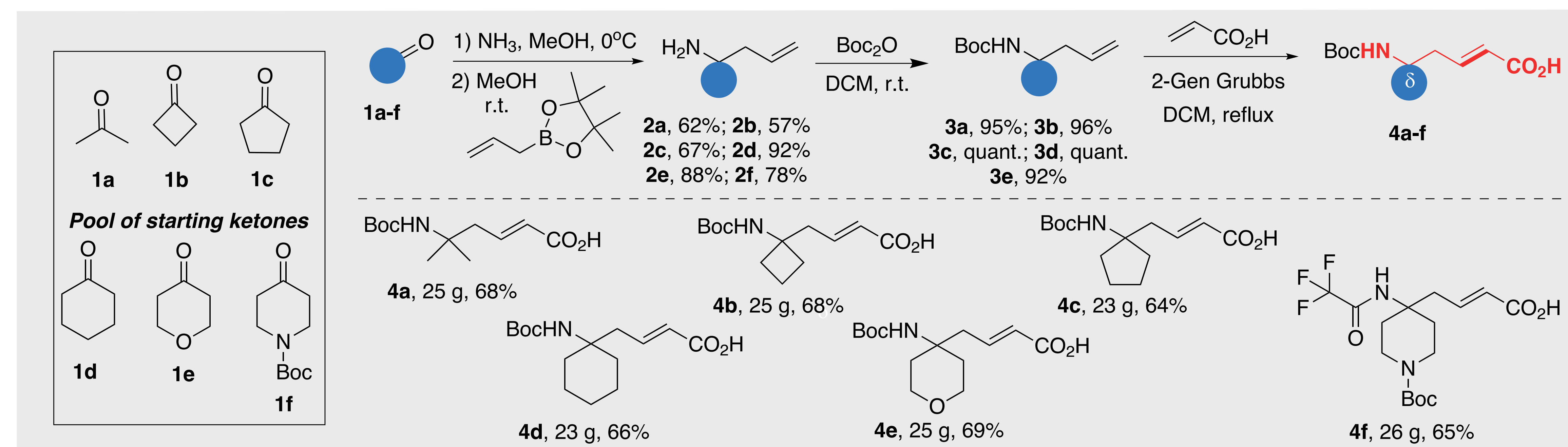
- The obtained  $\delta$ -amino acids can be regarded as dipeptide mimetics with stable C-C bond instead of cleavable amide junction.
- Cyclic conformational "lock" presented by 4- to 6-membered rings rigidifies the carbon skeleton without substantial increase in molecular weight and lipophilicity.

## Contact

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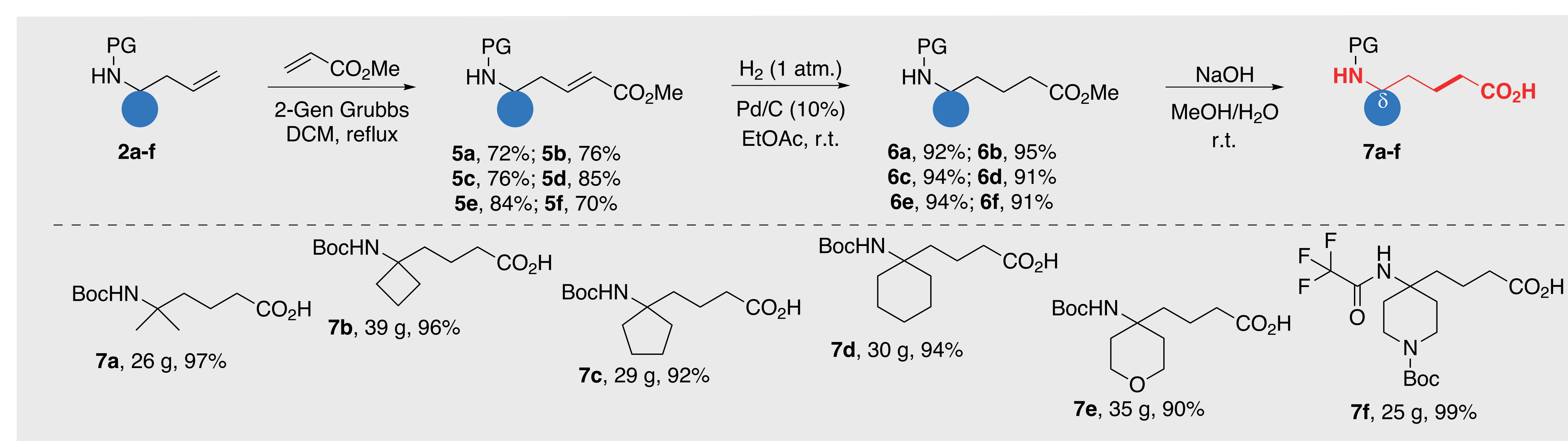
## Synthesis optimization and products diversity

- Homoallylamines **2a-f** were obtained from corresponding ketones *via* Petasis reaction. The yields were moderate on substrates with smaller rings and high with 6-membered one. The reaction was scaled up to 100 g per run.
- The obtained products were turned to Boc-protected amines **3a-e**. In case of the amine **2f** already bearing Boc-group, orthogonal TFA-protection was applied.
- Grubbs metathesis with acrylic acid provided the desired  $\alpha,\beta$ -unsaturated acids **4a-f**.



- After Grubbs metathesis with methyl acrylate,  $\alpha,\beta$ -unsaturated esters **5a-f** were isolated as valuable intermediates for synthesis of branched and functionalized derivatives.

- Hydrogenation with subsequent hydrolysis gave the desired saturated acids **7a-f**.



- In summary, the three-step route for synthesis of  $\alpha,\beta$ -unsaturated  $\delta$ -amino acids with 37-61% overall yields was proposed.
- The approach to saturated  $\delta$ -amino acids was slightly longer (5 steps), however, without any decrease in overall yield (38-67%).
- All reactions were conducted in mild conditions, therefore the scope of the method can likely be widened.

## References

- Grygorenko O. O. *et al. Chem. Eur. J.* **2020**, *26*, 6, 1196.
- Melnykov K. P. *et al. ACS Omega* **2019**, *4*, 4, 7498.