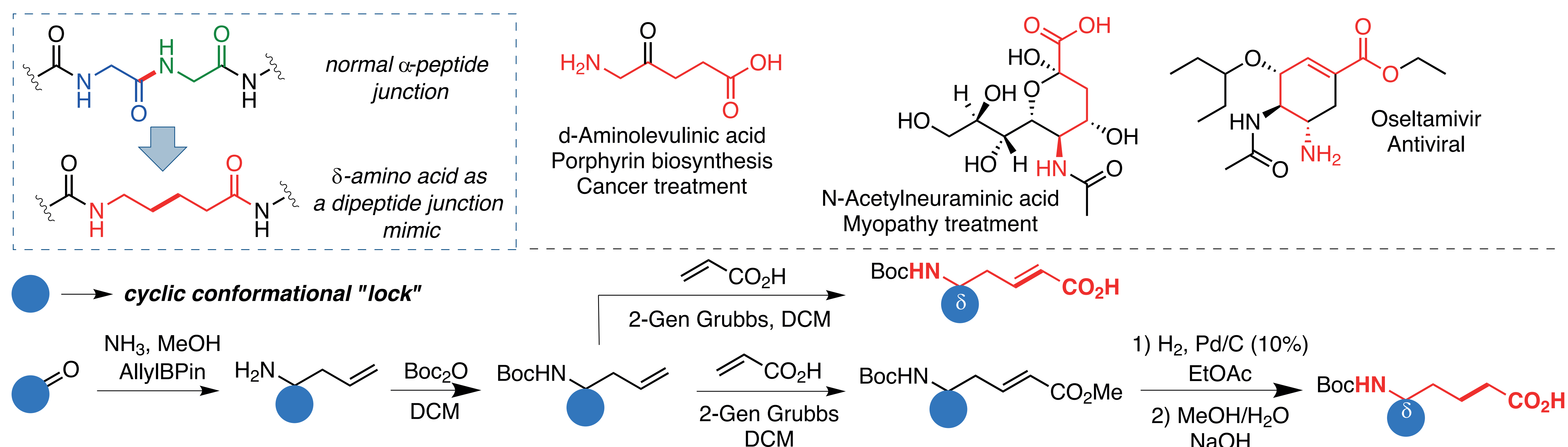


Diversity-oriented access to conformationally restricted δ -amino acids – a tool for the design of peptide-like foldamers

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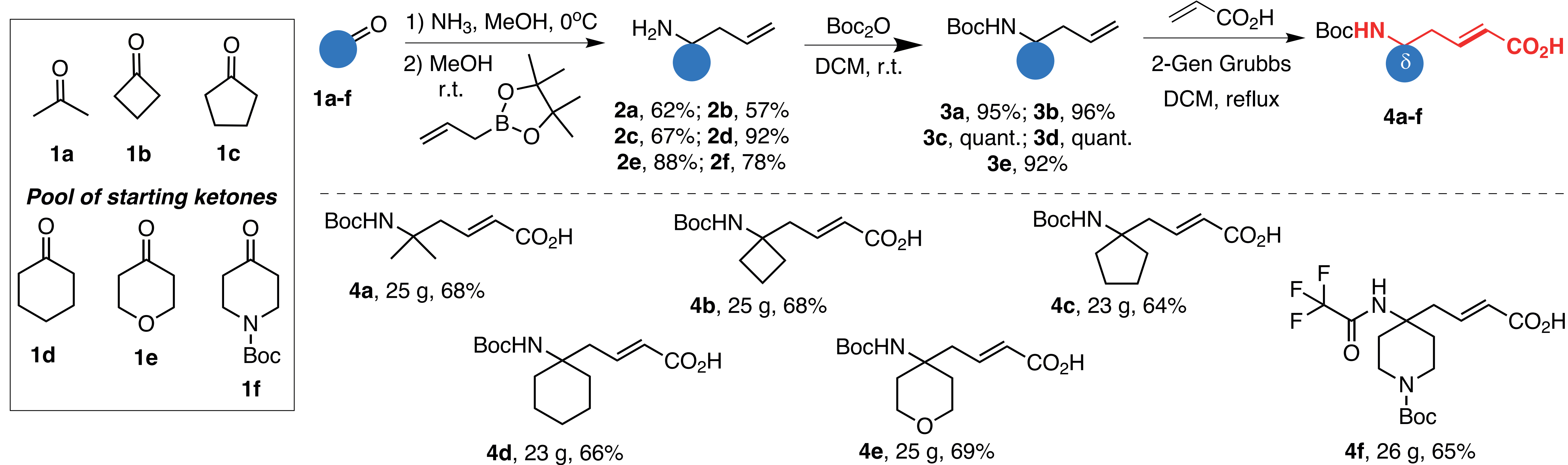
Background and synthetic strategy

- 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 synthesis¹.
- Earlier, we successfully tried Petasis reaction for construction of quaternary center in spirocyclic pyrrolidines synthesis². Recently, we applied DOS strategy to synthesis of acyclic and monocyclic δ -amino acids via Petasis-Grubbs sequence.

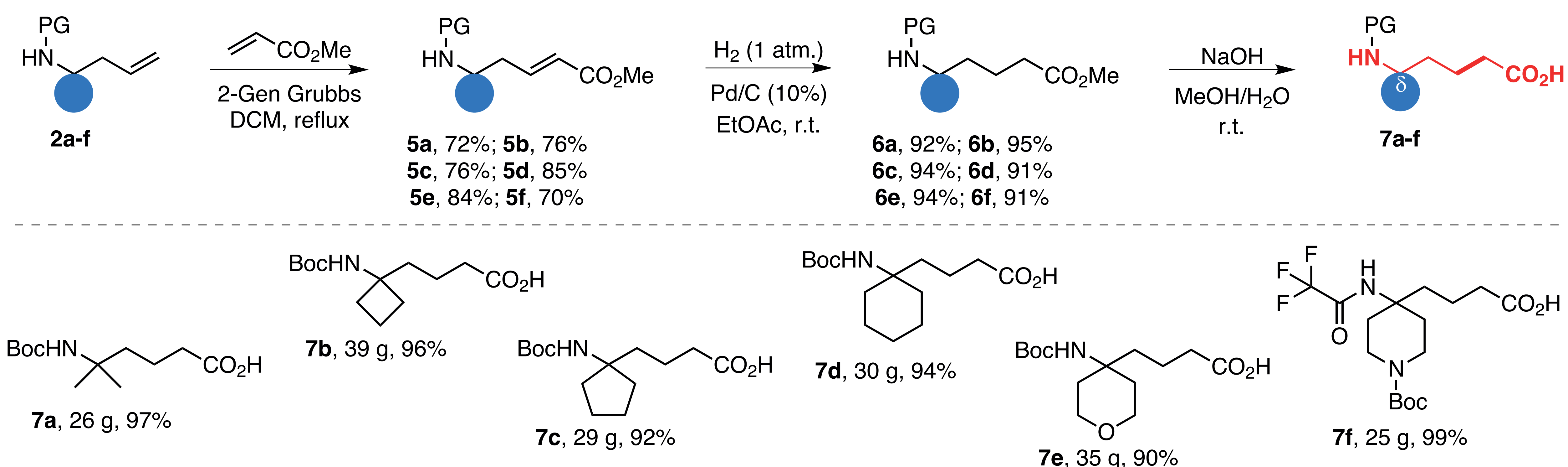


Synthesis Optimization and Products Diversity

- 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 α,β -unsaturated acids **4a-f**.



- After Grubbs metathesis with methyl acrylate, α,β -unsaturated esters **5a-f** were isolated as valuable intermediates for synthesis of branched and functionalized derivatives.
- Hydrogenation with subsequent hydrolysis gave the desired saturated δ -amino acids **7a-f**.



- In summary, the three-step route for synthesis of α,β -unsaturated δ -amino acids with 37-61% overall yields was proposed.
- The approach to saturated δ -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.

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