Practical access to conformationally restricted β-prolines with 2,2-spiro-conjugation

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Background of the project

THE 15-YEAR-OLD EQUATION OF CLINICAL SUCCESS

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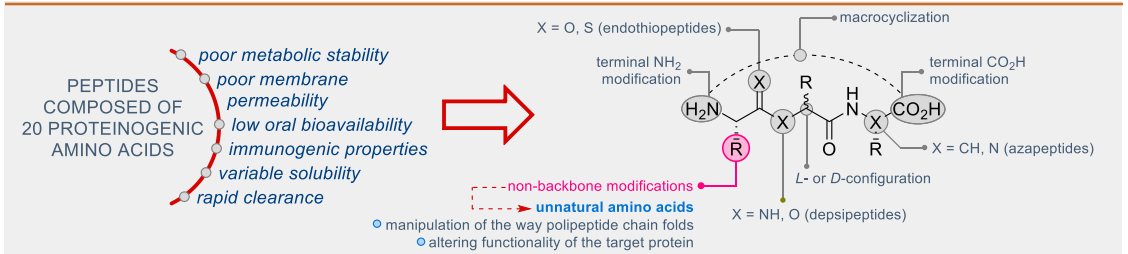
SATURATION + **THREE-DIMENSIONALITY** + **CONFORMATIONAL RESTRICTION**

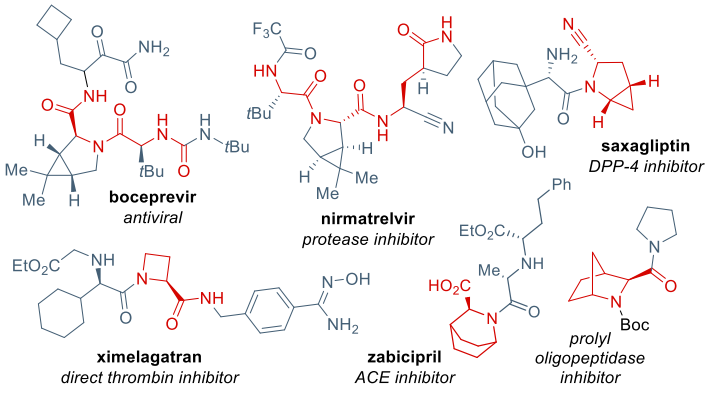
- solubility
- complexity

- receptor/ligand complementarity

- reducing entropy penalty
- well-defined vectorization

- reduction in entropy resulting from **conformational restriction** may enhance intermolecular interactions and contribute to biological activity
- **amino acids possessing rigid structures** are promising substrates for constructing peptidomimetics – small protein-like chains designed to mimic native counterparts and advantageously adjust pharmacological properties such as stability or biological activity





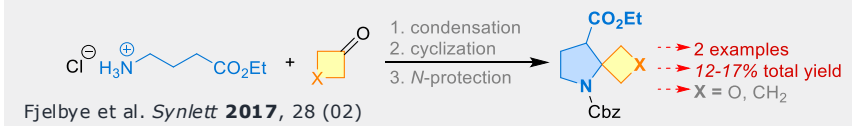
STRATEGIC GOAL

- chemical support of biomedical endeavors toward innovative peptidomimetics and amino acid-based agents

CURRENT STEP

- elaboration of robust synthetic avenues for **spirocyclic beta-proline frameworks**

TO DATE, THERE IS A SINGLE RELEVANT SYNTHETIC STRATEGY

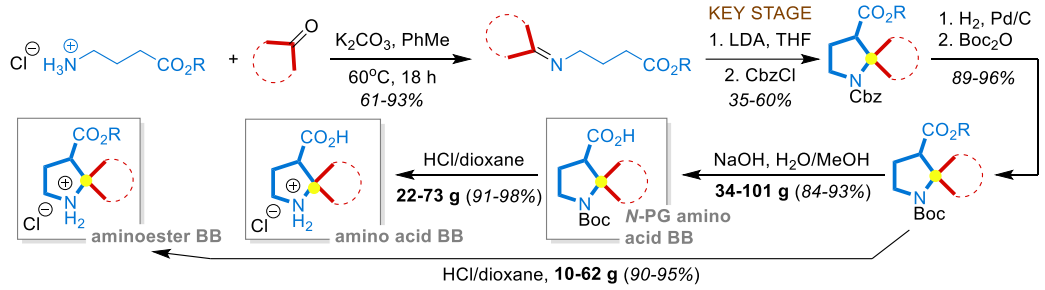


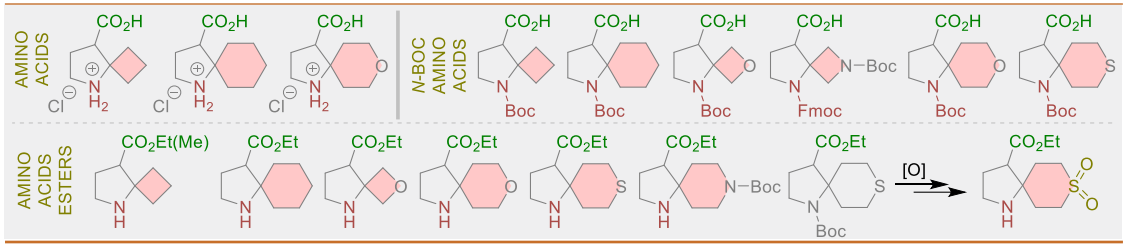
Fjelbye et al. *Synlett* **2017**, 28 (02)

Synthetic strategies toward α-spiro-β-prolines

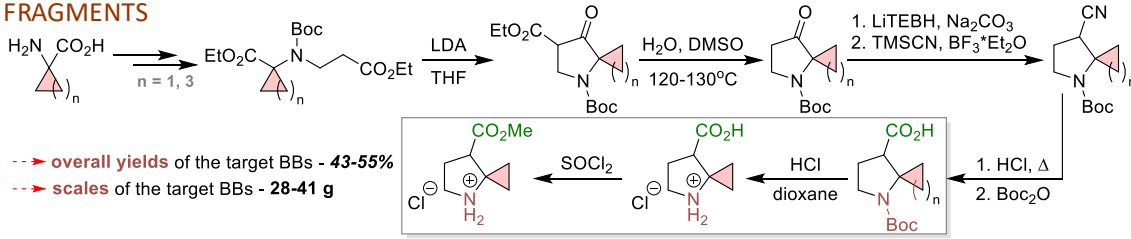
- our endeavors are reflected in three synthetic routes that are well-suited for synthesizing a wide range of the target spirocyclic prolines on a large scale and with moderate to high yields on each stage

STRATEGY #1 – THE OPTIMIZED, EXPANDED, AND SCALED-UP ROUTE BY *FJELBYE ET AL.*

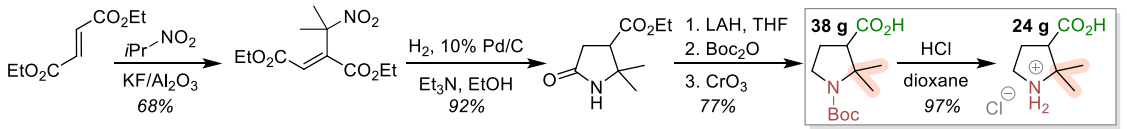




STRATEGY #2 – ROUT TOWARD PROLINES WITH **SPIROCYCLOPROPANE** AND – **CYCLOPENTANE** FRAGMENTS



STRATEGY #3 – ROUT TOWARD PROLINE WITH **2,2-DIMETHYL MOIETY** – OUT-OF-PLANE MIMIC OF SPIROCYCLIC COUNTERPARTS



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