α-Spiro-β-prolines – practical access to a rigid molecular platform

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Background of the project

THE 15-YEAR-OLD EQUATION OF CLINICAL SUCCESS

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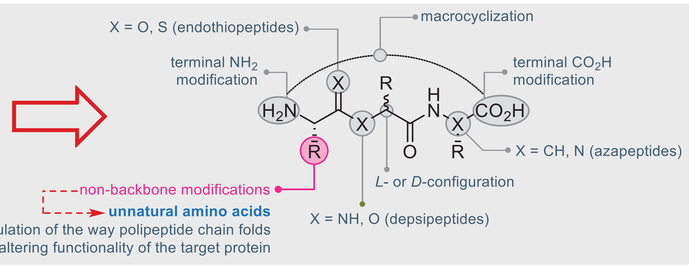
SATURATION + THREE-DIMENSIONALITY + CONFORMATIONAL RESTRICTION

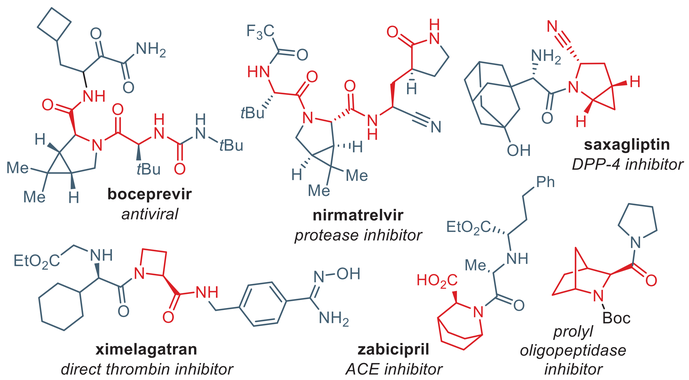
- **solubility**
- **complexity**
- **receptor/ligand complementarity**
- **reducing entropy penalty**
- **well-defined vectorization**

- 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

PEPTIDES COMPOSED OF 20 PROTEINOGENIC AMINO ACIDS

- *poor metabolic stability*
- *poor membrane permeability*
- *low oral bioavailability*
- *immunogenic properties*
- *variable solubility*
- *rapid clearance*





STRATEGIC GOAL

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

CURRENT STEP

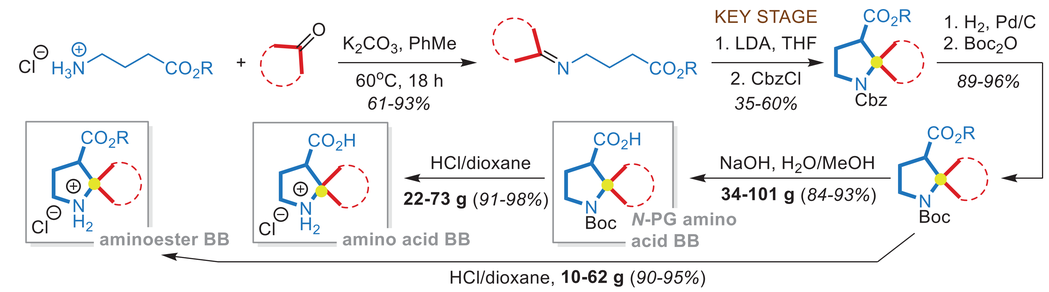
elaboration of robust synthetic avenues for spirocyclic beta-proline frameworks

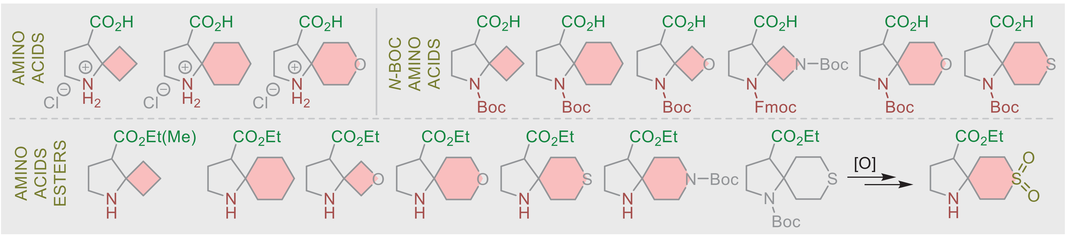
TO DATE, THERE IS A SINGLE RELEVANT SYNTHETIC STRATEGY

Synthetic strategies toward α-spiro-β-prolines

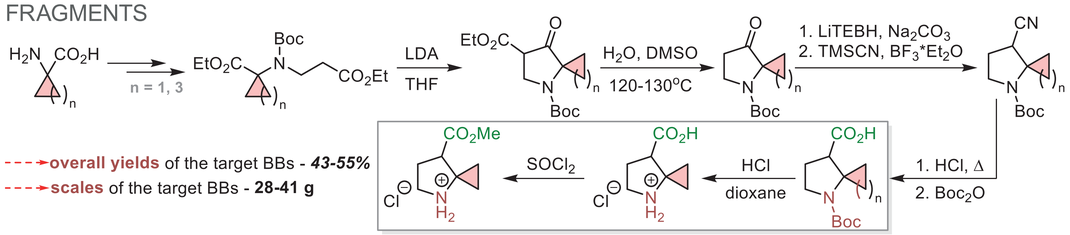
- our endeavors are reflected in three synthetic routes that are well-suited for synthesizing a wide range of the target spirocyclic prolines on a large scale and with moderate to high yields on each stage

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



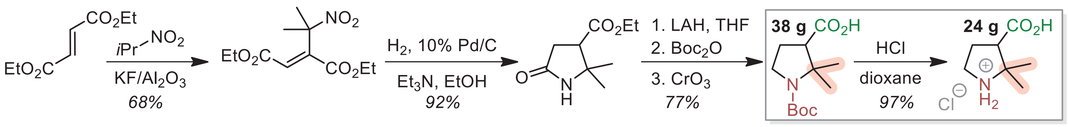


STRATEGY #2 – ROUT TOWARD PROLINES WITH **SPIROCYCLOPROPANE** AND – **CYCLOPENTANE** FRAGMENTS



- **overall yields** of the target BBs - ***43-55%***
- **scales** of the target BBs - **28-41 g**

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



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