Synthetic studies towards (+)-rauvomine B and other macroline/sarpagine alkaloids

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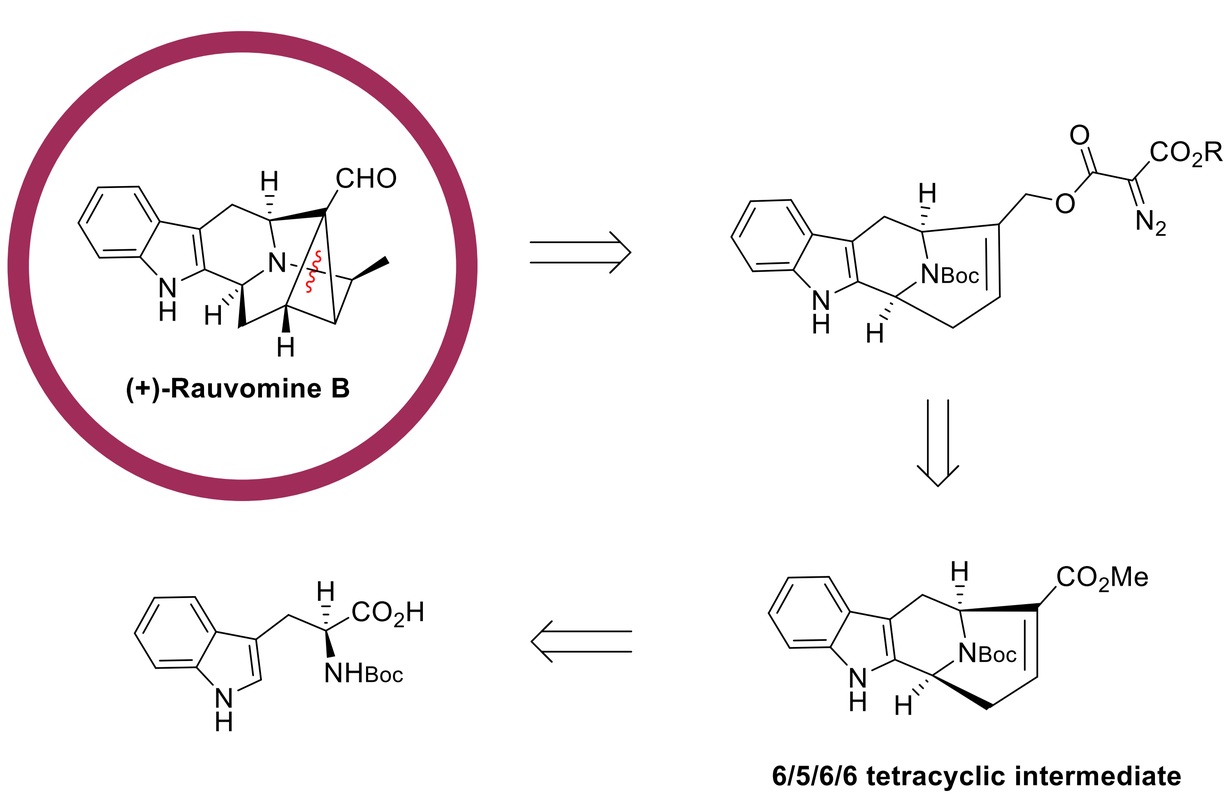
Introduction

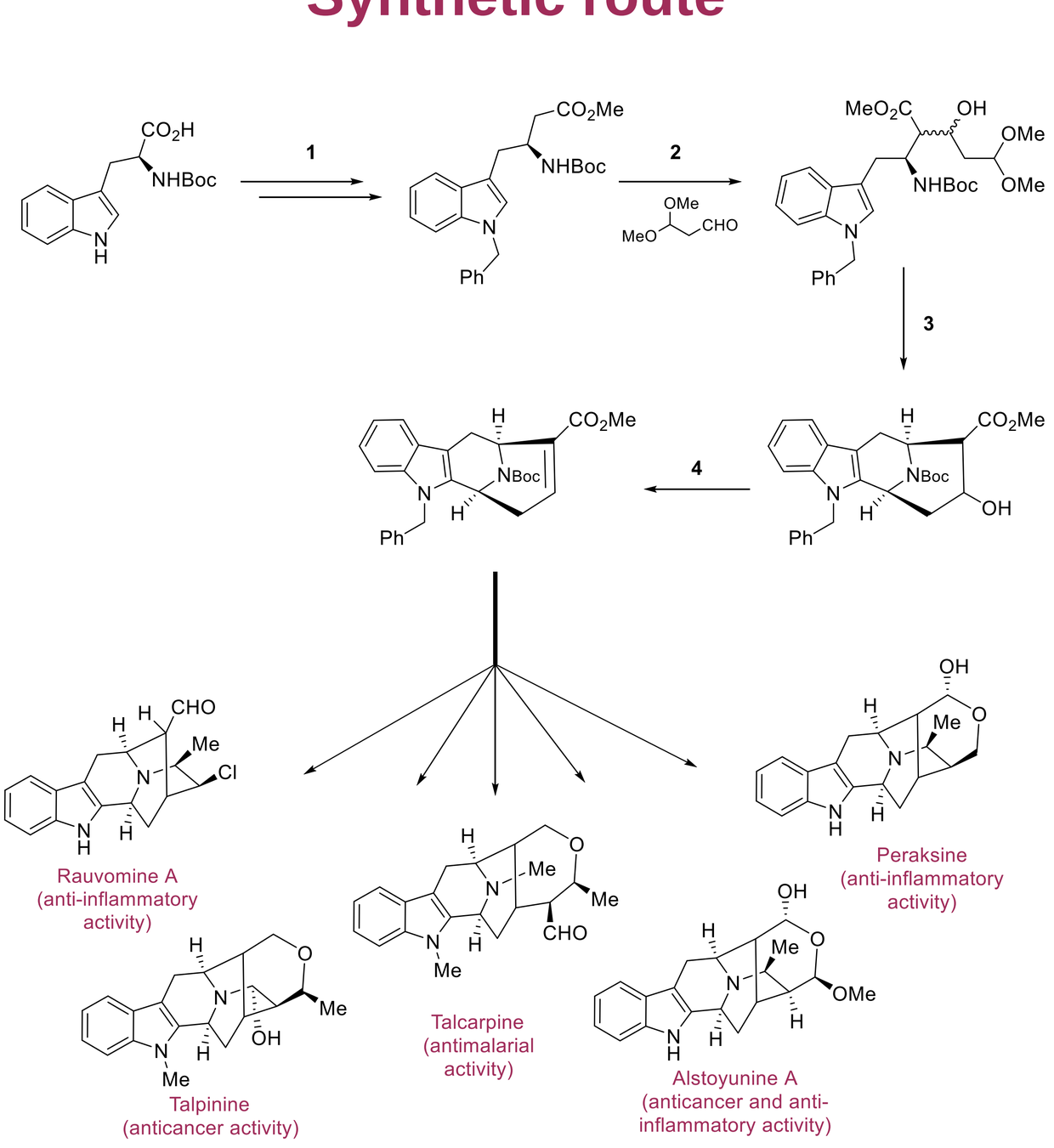
(+)-Rauvomine B[1] is an indole alkaloid with an unusual structure, containing a cyclopropane ring incorporated in the 6/5/6/6/3/5 hexacyclic system, ornate with six stereocenters, making this compound a challenging synthetic task.

(+)-Rauvomine B was isolated from the plant *Rauvolfia vomitoria* and exhibits anti-inflammatory activity.

Our strategy for (+)-Rauvomine B total synthesis proceeds via a key 6/5/6/6 tetracyclic intermediate, which could be efficiently prepared from commercially available *N*-Boc-(*S*)-tryptophan.



Synthetic route



Synthesis

The synthesis of tetracyclic intermediate was performed from *N*-Boc-(*S*)-tryptophan via 4 major transformations:

1. Homologation to homotryptophan through Wolff rearrangement in the presence of a Ag(I) salt,
2. Aldol reaction with 3,3-dimethoxypropanal,
3. Pictet-Spengler reaction as a key step that allows simultaneous closure of two six-membered rings,
4. Ph_3P/DEAD promoted water elimination.

The tetracyclic intermediate could be utilized as a starting material for the synthesis of many other members of macroline/sarpagine indole alkaloids with a broad bioactivity range, including Rauvomine A, Peraksine, Talcarpine, Talpinine, and Alstoyunine A.

Conclusion

The synthesis of a tetracyclic intermediate as a possible precursor for synthetic routes towards multiple macroline/sarpagine alkaloids was successfully achieved in 4 major steps.

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[1] J. Zeng, D.-B. Zhang, P.-P. Zhou, Q.-L. Zhang, L. Zhao, J.-J. Chen, K. Gao, *Org. Lett.* **2017**, *19*, 3998