A Novel Synthesis of (-)-Huperzine A

J. D. White, Y. Li, J. Kim, M. Terinek *Org. Lett.* **2013**, *15*, 882-885.

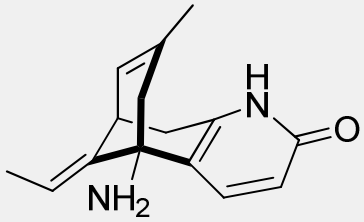
F. Giornal

14.11.2013

Introduction

(-)-Huperzine A

- Isolated from *Huperzia serrata*



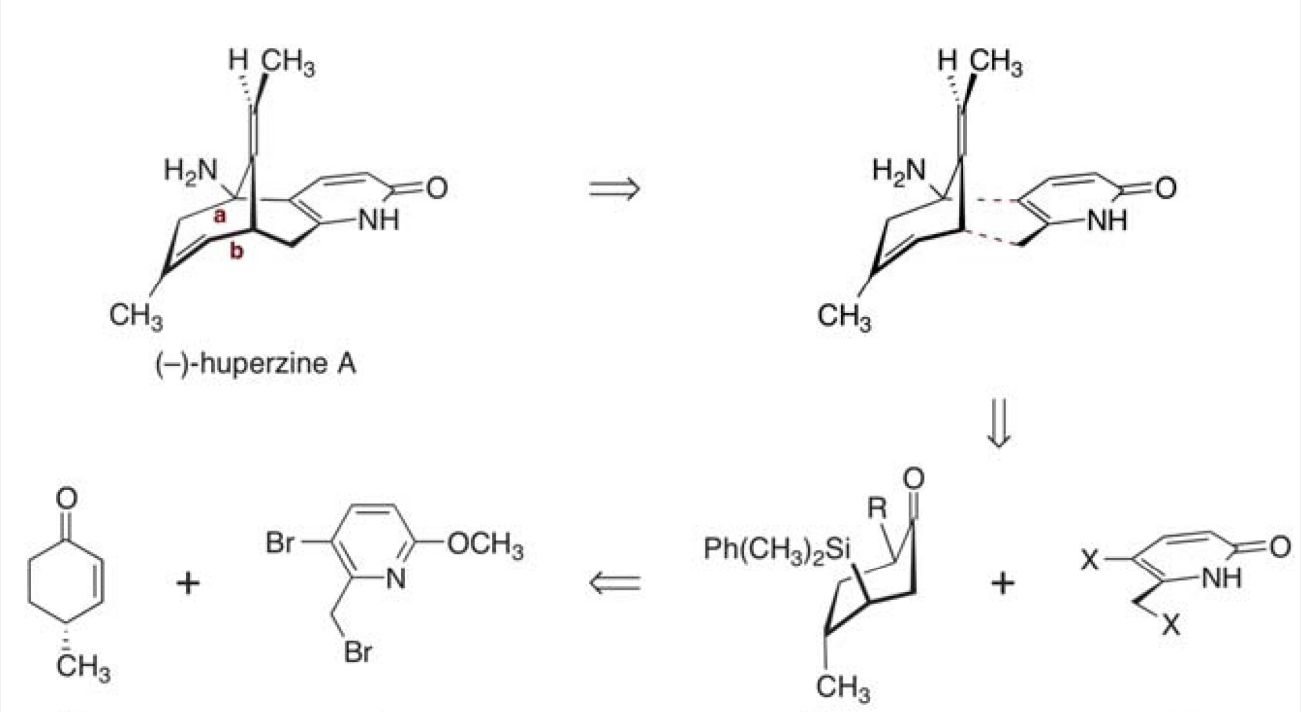
- Used in chinese medicine: schizophrenia, blood disorder, loss of memory
- Potent and reversible acetylcholinesteras inhibitor
- Clinical studies for the treatment of Alzheimer's disease
- High interest because of its biological activity
- Several previous total syntheses

(a) J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F.-W. Wu, B.-F. Qi *Can. J. Chem.* **1986**, *64*, 837. (b) X. C. Tang, X. C. He, D. L. Bai *Drugs Future* **1999**, *24*, 647. (c) R. Wang, H. Yan, X.-C. Tang *Acta Pharmacol. Sin.* **2006**, *27*, 1.

Introduction

(-)-Huperzine A

- First total syntheses of (±)-Huperzine by Kozikowski and Ji in 1989
- Most efficient enantioselective total synthesis: 16 steps, 35-45% overall yield

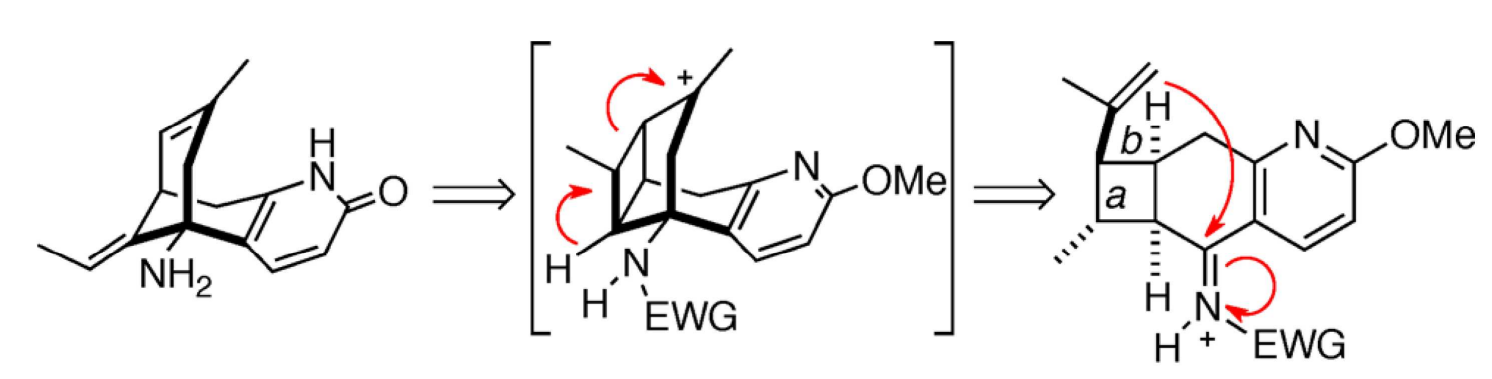


(a) Y. Xia, A. P. Kozikowski *JACS* **1989**, 4116. (b) L. Qian, R. Ji *Tetrahedron Lett.* **1989**, *30*, 2089. (c) P. Zhao, C. M. Beaudry *Org. Lett.* **2013**, *15*, 402-405.

Synthetic strategy

Tandem Aza-Prins cyclization / cyclobutane fragmentation

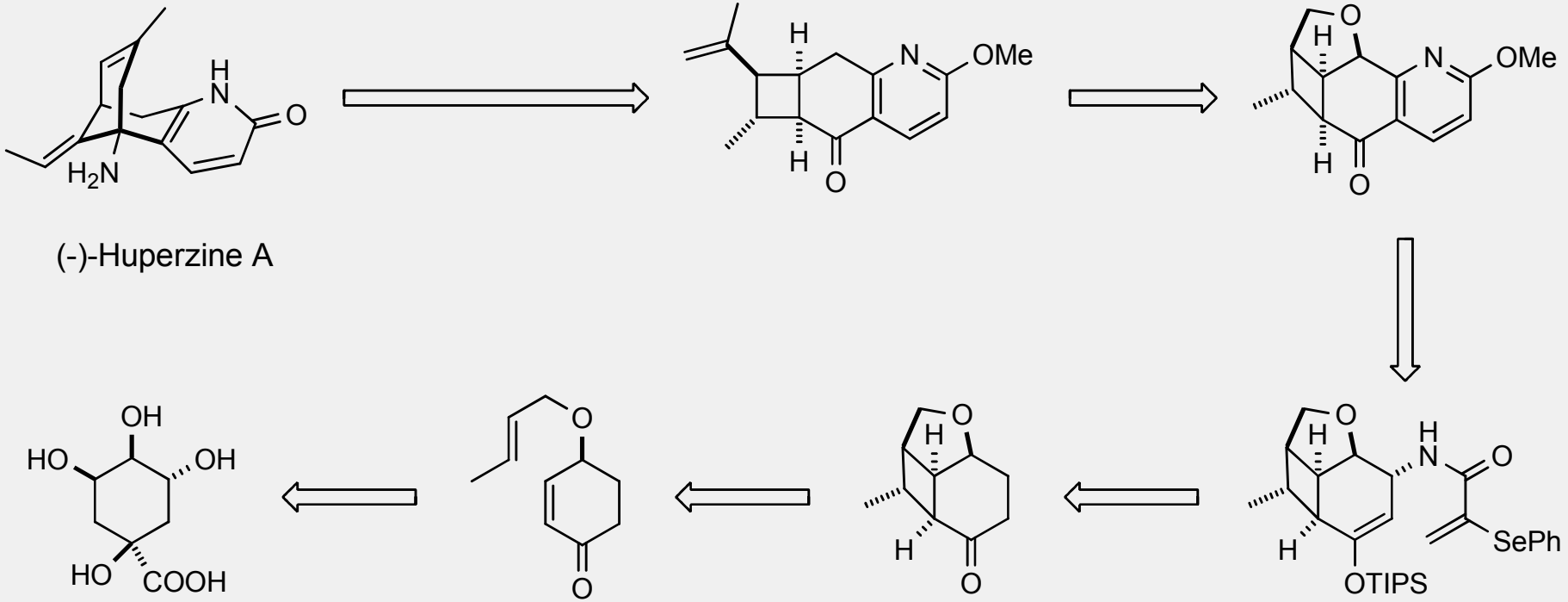
- 26-28 kcal/mol ring strain in cyclobutanes
- Use of the release of this ring strain



- Tandem of the fragmentation with Aza-Prins cyclisation, which will initiate the process

Synthetic strategy

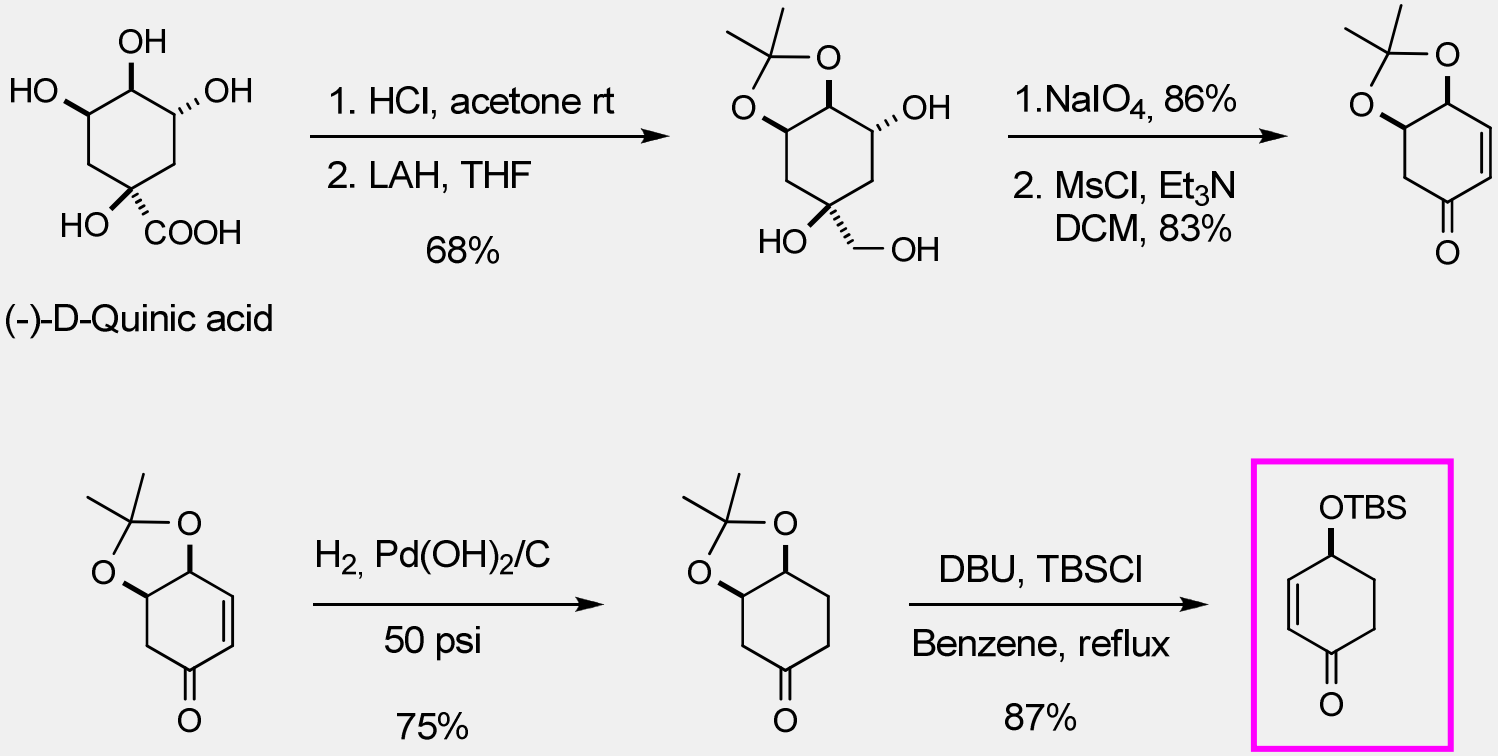
Retrosynthesis



(-)-Huperzine A

Synthesis of (-)-Huperzine A

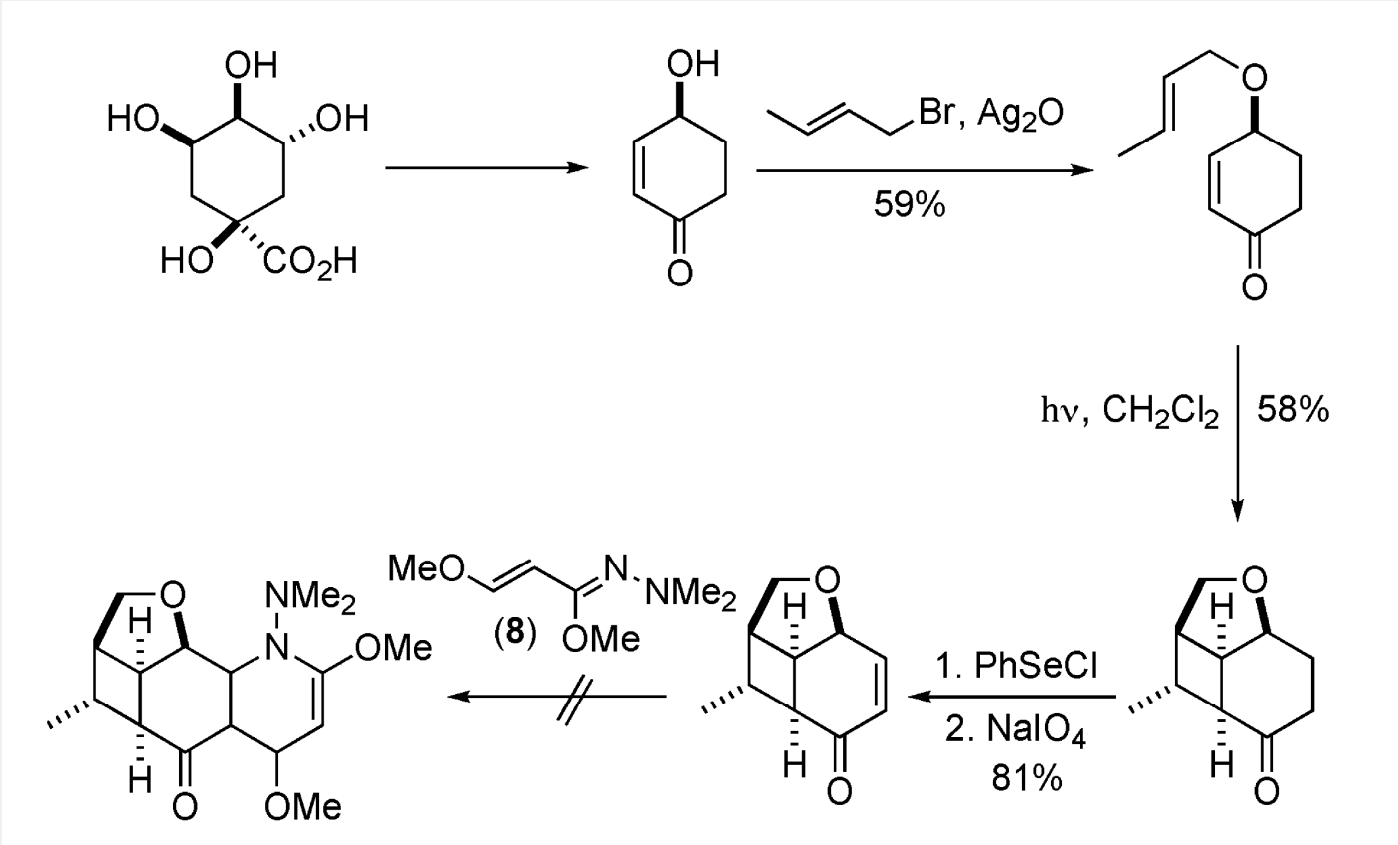
Preparation of the cyclohexenone



(a) Danishefsky et al. *JACS* **1989**, 3738. (b) B. M. Trost, A. G. Romero *JACS* **1986**, 2332.

Synthesis of (-)-Huperzine A

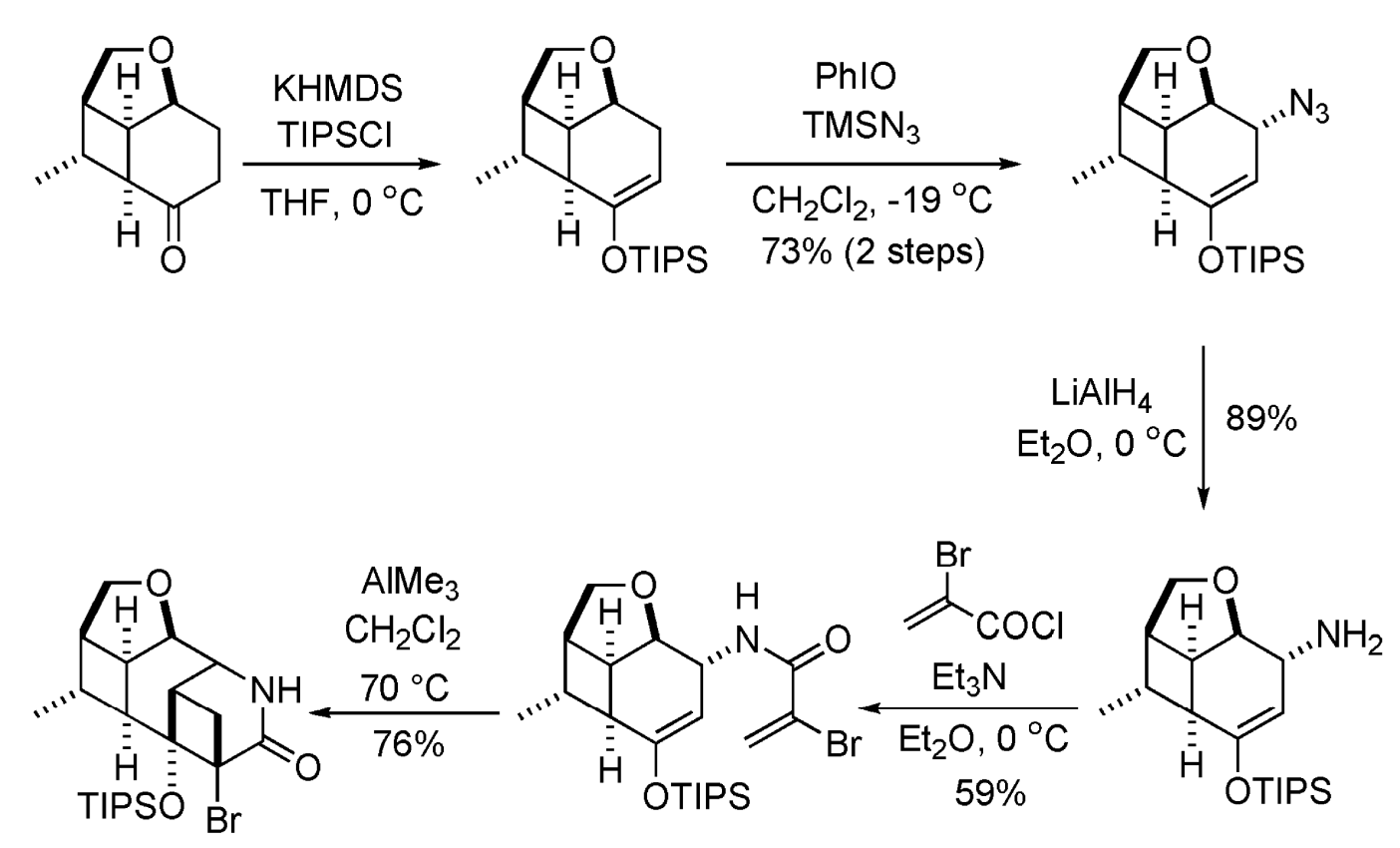
Preparation of the tricyclic core



- Change the strategy

Synthesis of (-)-Huperzine A

Construction of the Fused Pyridone *via* [2+2] cycloaddition



(a) P. Magnus, P. Rigollier, J. Lacour, H. Tobler *JACS* **1993**, 12629 (b) P. Magnus, J. Lacour *JACS* **1992**, 767.

Synthesis of (-)-Huperzine A

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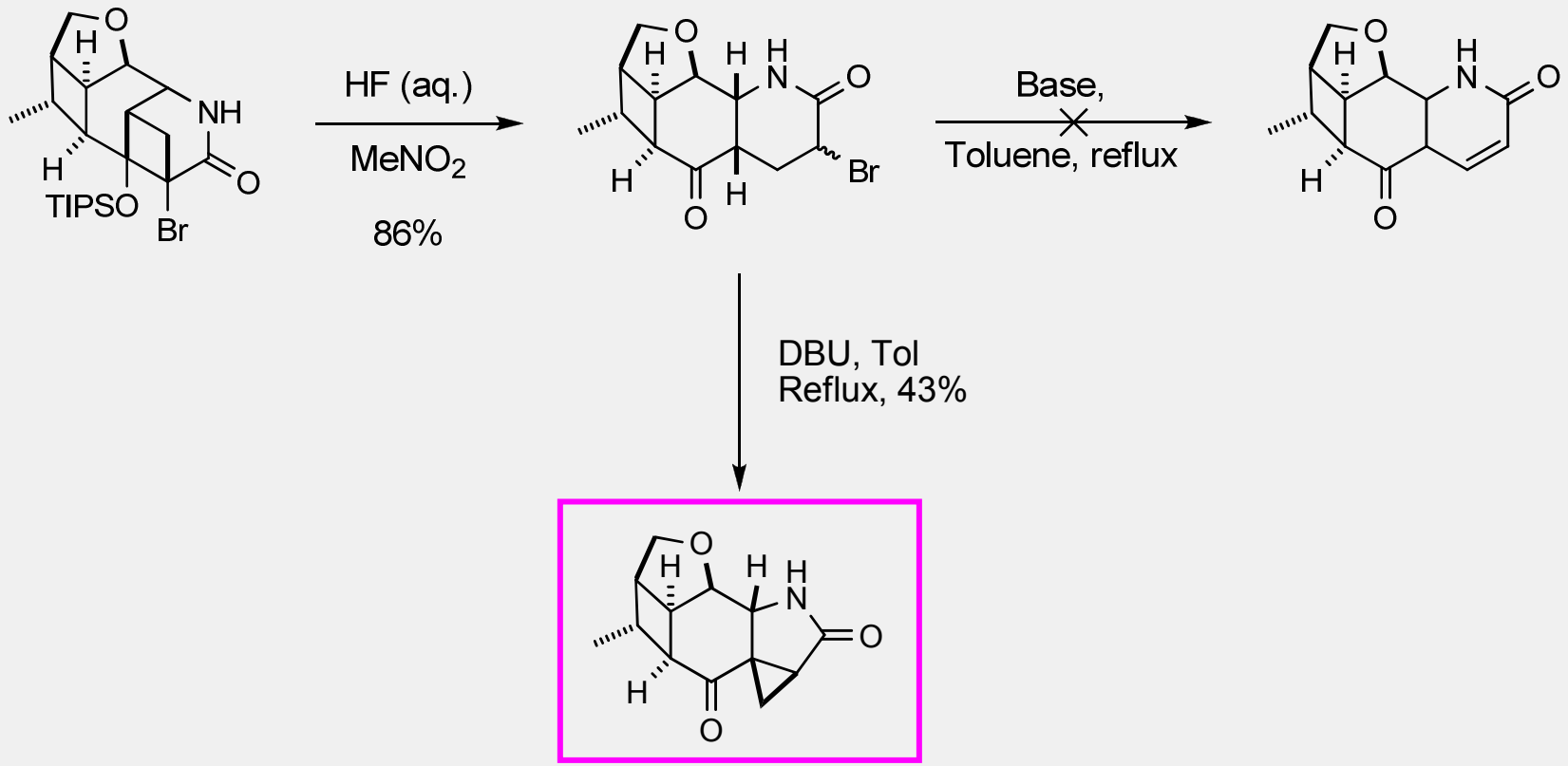

Synthesis of (-)-Huperzine A

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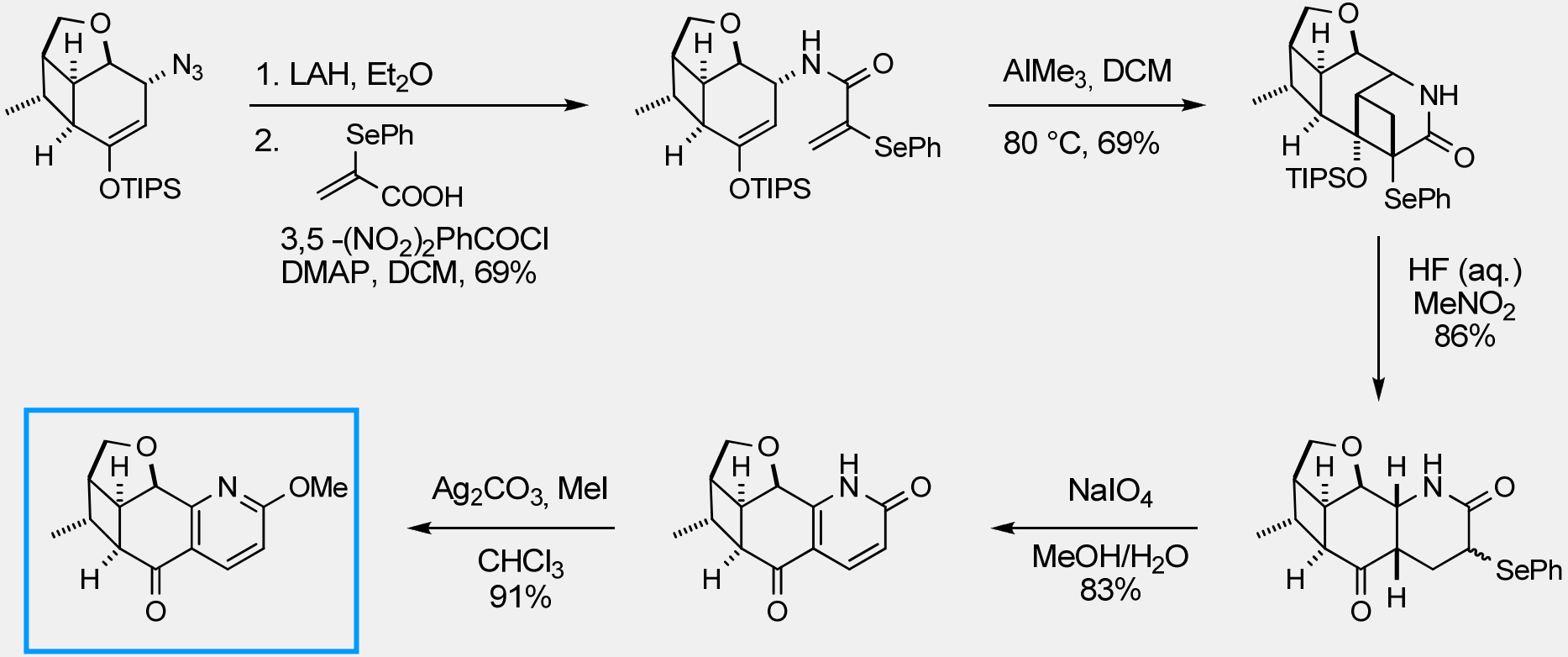
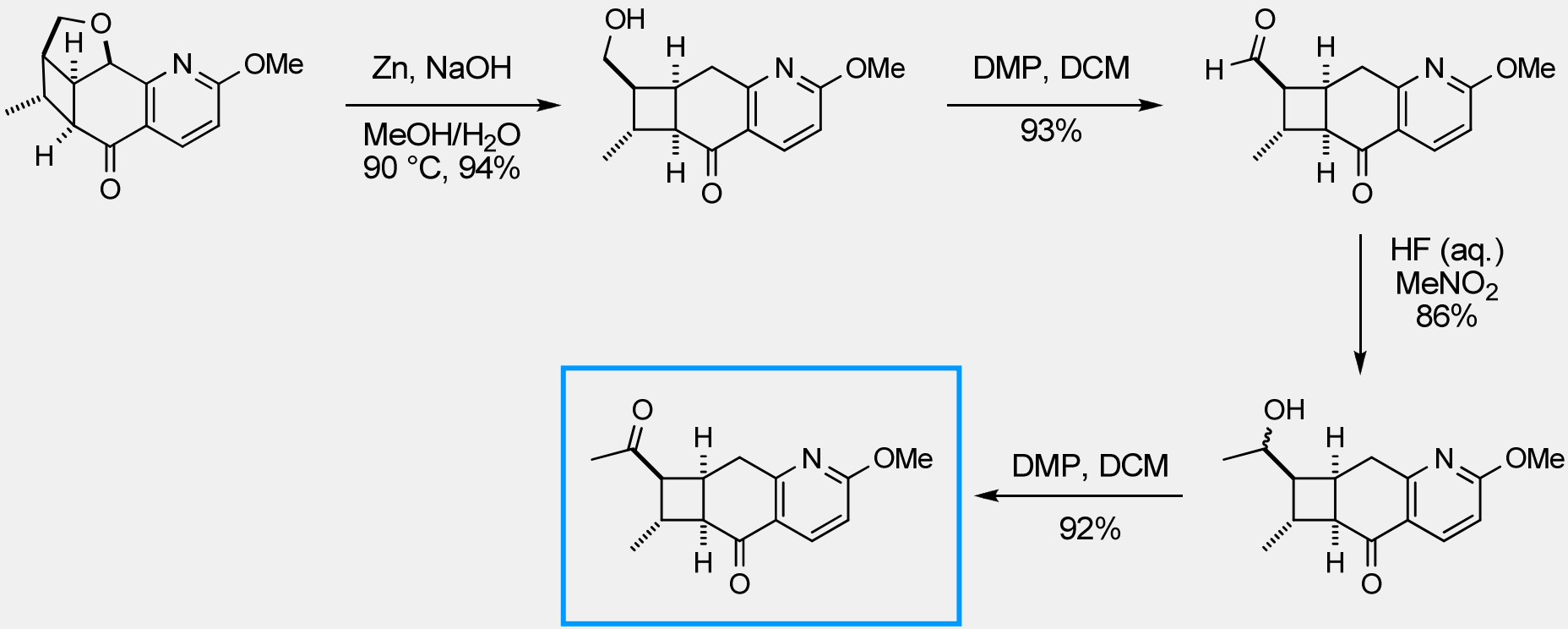


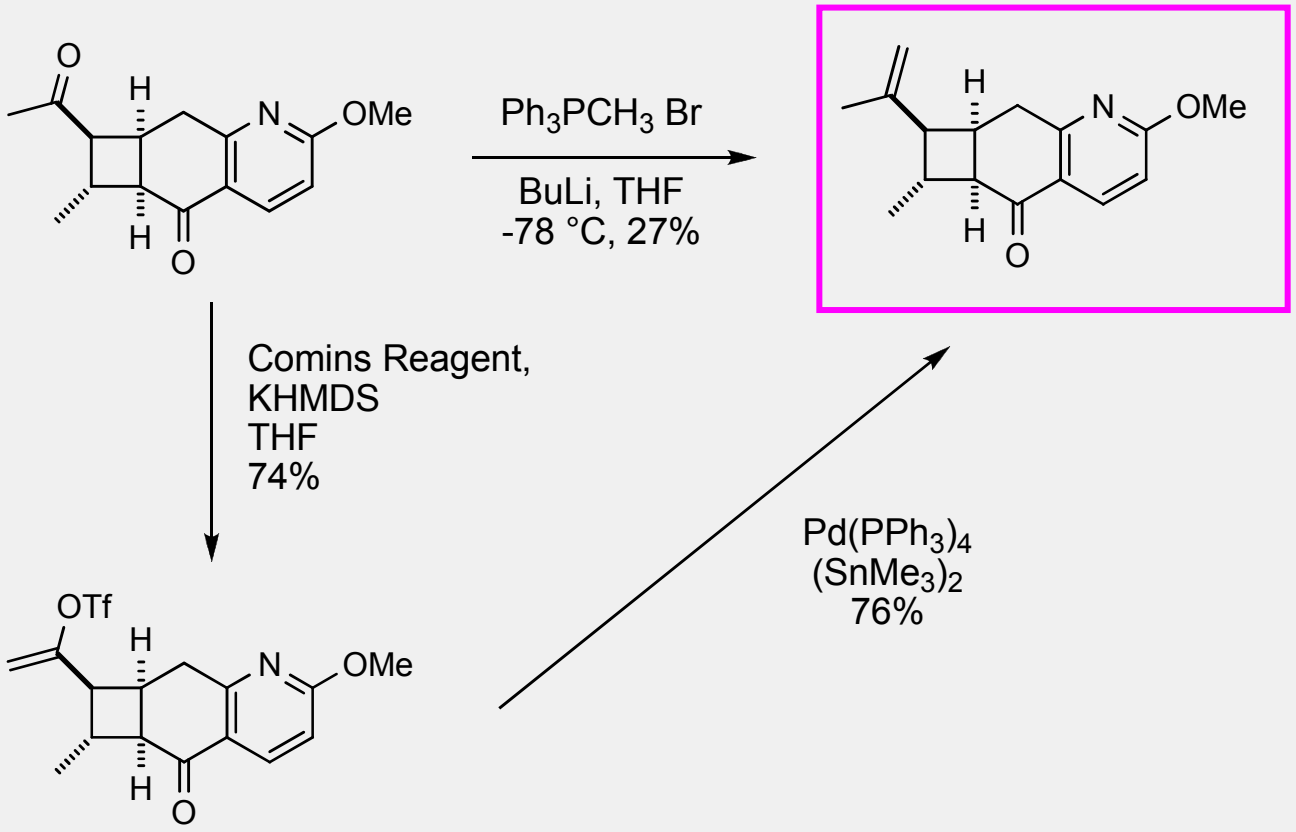
Synthesis of (-)-Huperzine A

Opening of the ether and preparation of the last intermediate



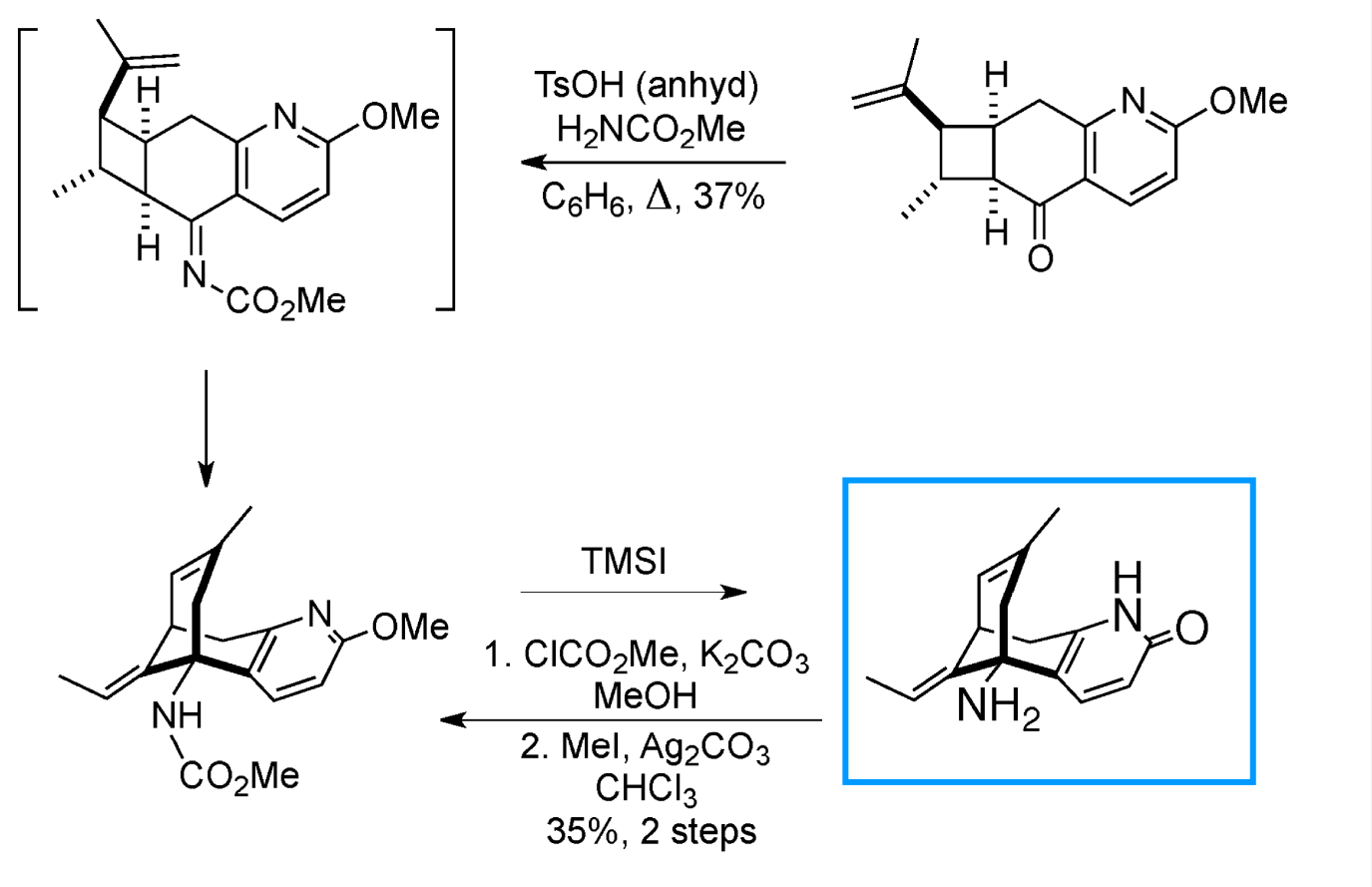
Synthesis of (-)-Huperzine A

Construction of the Fused Pyridone *via* [2+2] cycloaddition



Synthesis of (-)-Huperzine A

Tandem Aza-Prins / Cyclobutane fragmentation



Conclusion

- Novel strategy implying cyclobutane-strain release
- Use of [2+2] cycloadditions
- Low conversion for the key step
- Several changes of strategy: versatility of the synthetic path

Thanks for your attention