

Literature Report I

Total Synthesis of Quebrachamine

Reporter: Fan-Jie Meng

Checker: Bo Song

Date: 2016-12-05

Tan, P. W.; Seayade, J.; Dixon, D. J.
Angew. Chem. Int. Ed. **2016**, *55*, 13436.

CV of Darren Dixon

Education:

- ❑ 1989–1993 M.S., University of Oxford
- ❑ 1993–1997 Ph.D., University of Oxford
- ❑ 1997–2000 Postdoc., University of Cambridge

Academic Positions:

- ❑ Since 2008 Professor, University of Oxford



Research Interests:

- His research program is centered on new, highly enantioselective methods development, total synthesis of complex natural products, new cooperative catalyst designs, and new cascade reactions.

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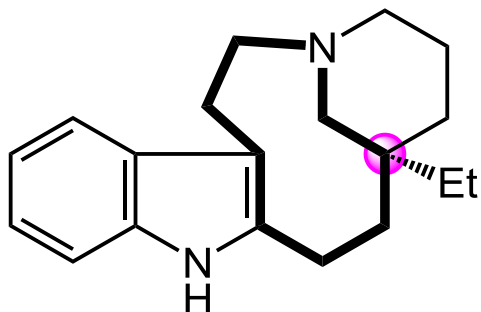
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Introduction

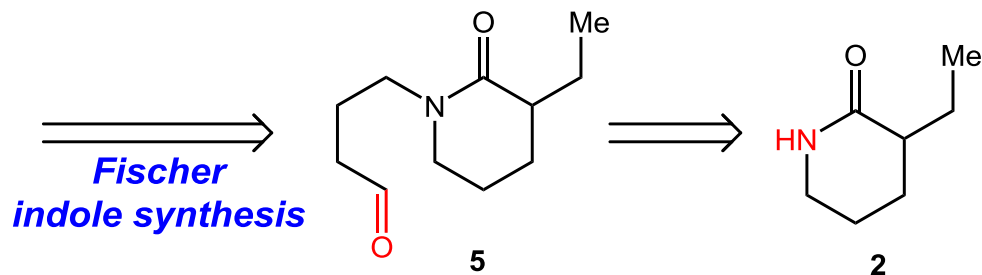
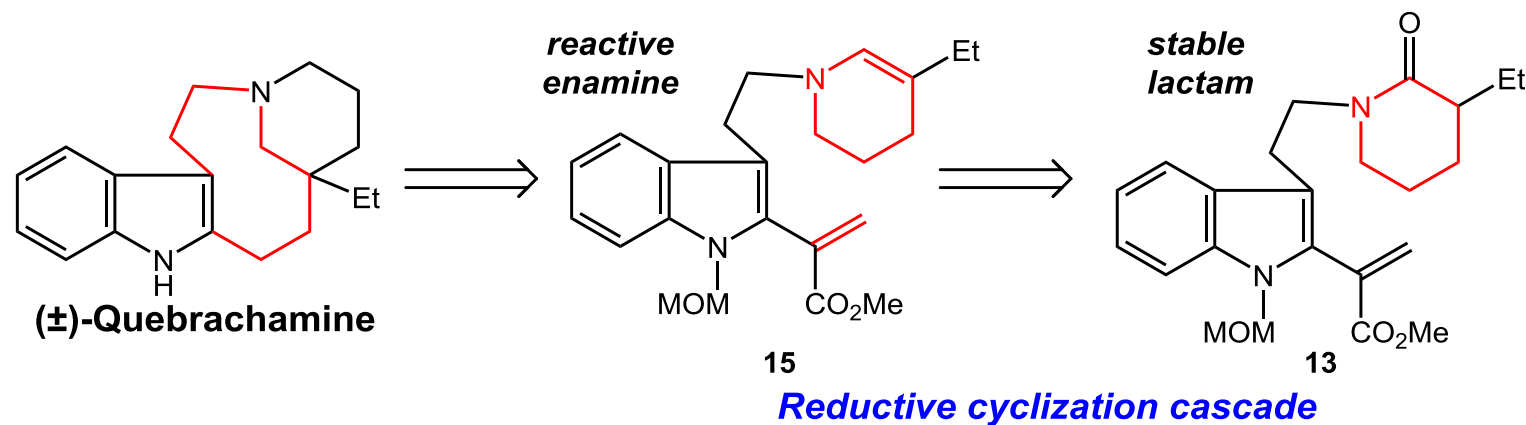


(+)-Quebrachamine



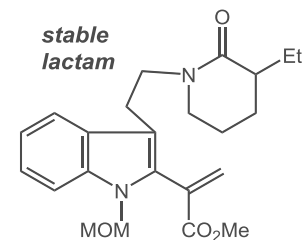
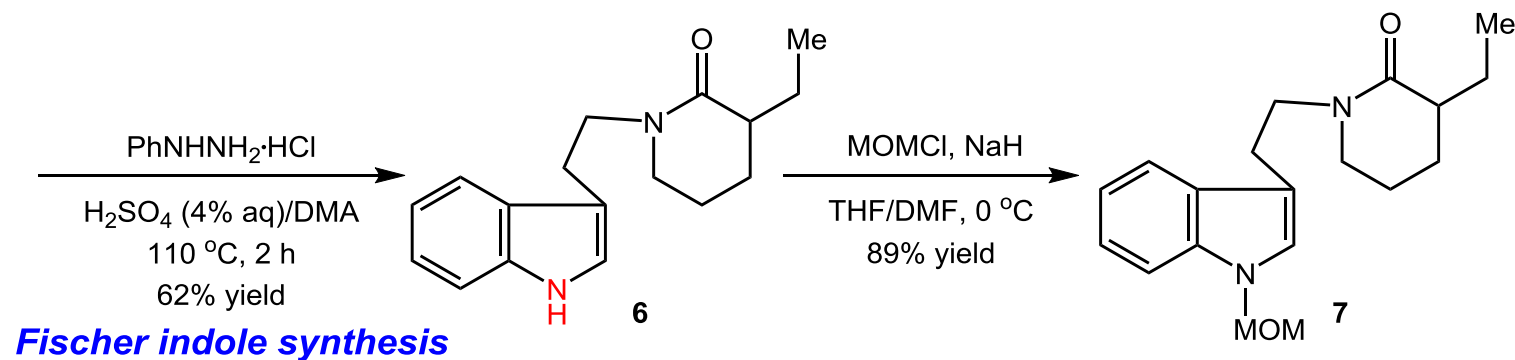
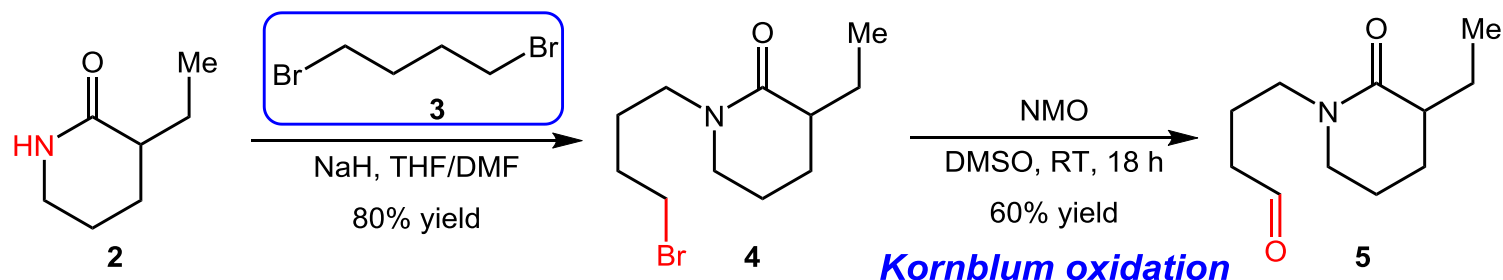
- Aspidosperma group of alkaloids (白坚木属)
- Adrenergic blocking agent (肾上腺素阻断剂)
- A bridged-ring compound bearing **one all carbon quaternary stereogenic center at the bridged-ring junction** and a **nine-membered ring**

Retrosynthetic analysis



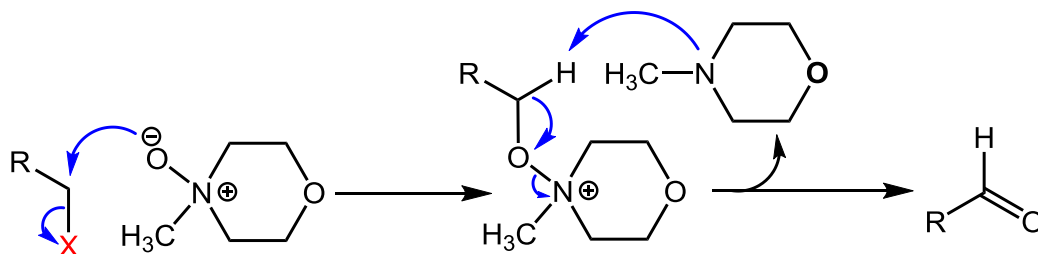
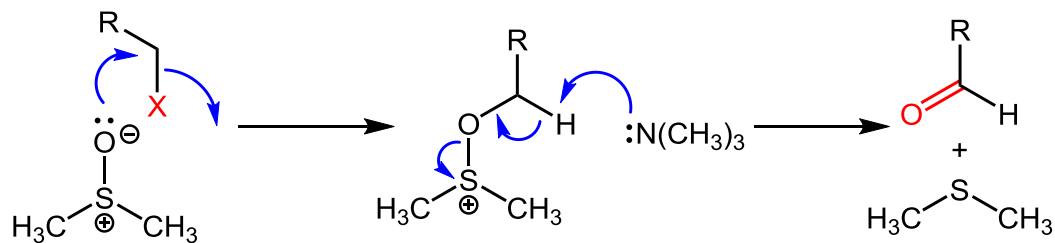
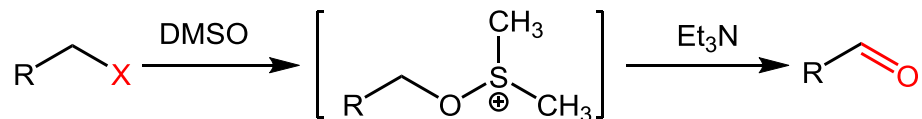
Tan, P. W.; Seayade, J.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 13436.

The synthesis of (+/-)-Quebrachamine



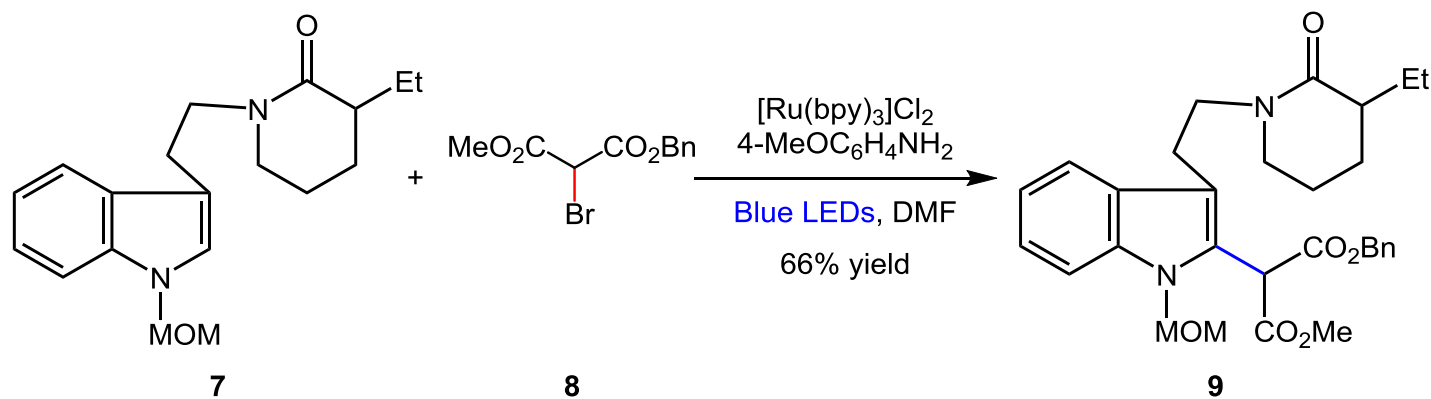
Kornblum Oxidation

The **Kornblum oxidation** is a chemical reaction of a primary halide with DMSO to form an aldehyde.



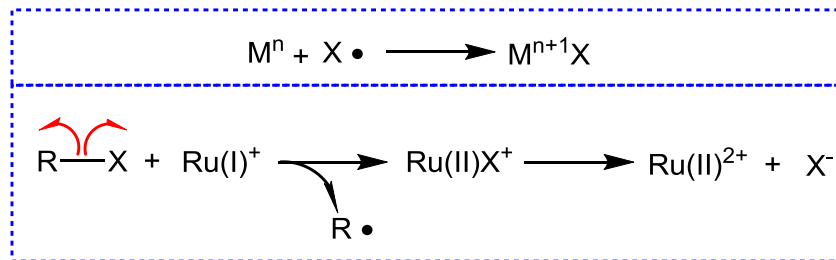
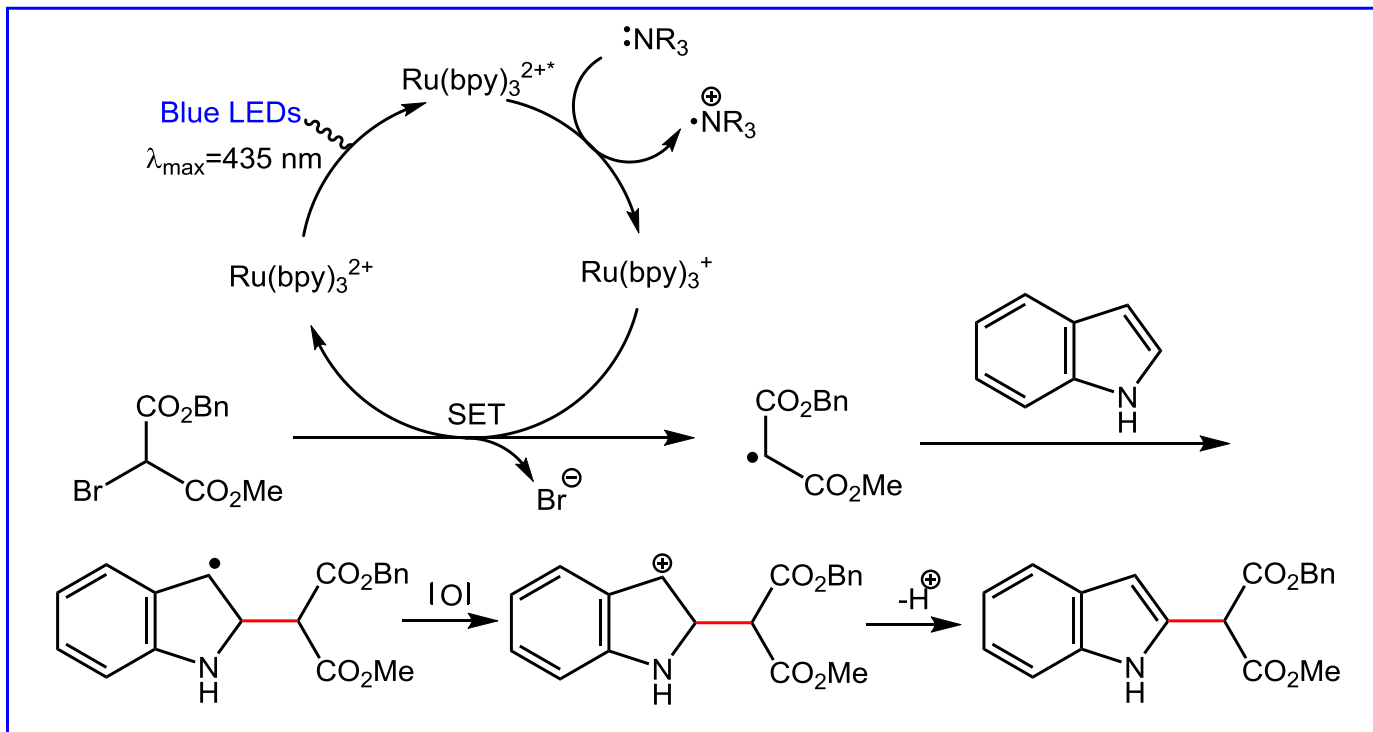
Kornblum, N.; Powers, J. W.; Anderson, G. J. *J. Am. Chem. Soc.* **1957**, 79, 6562.

The synthesis of (+/-)-Quebrachamine



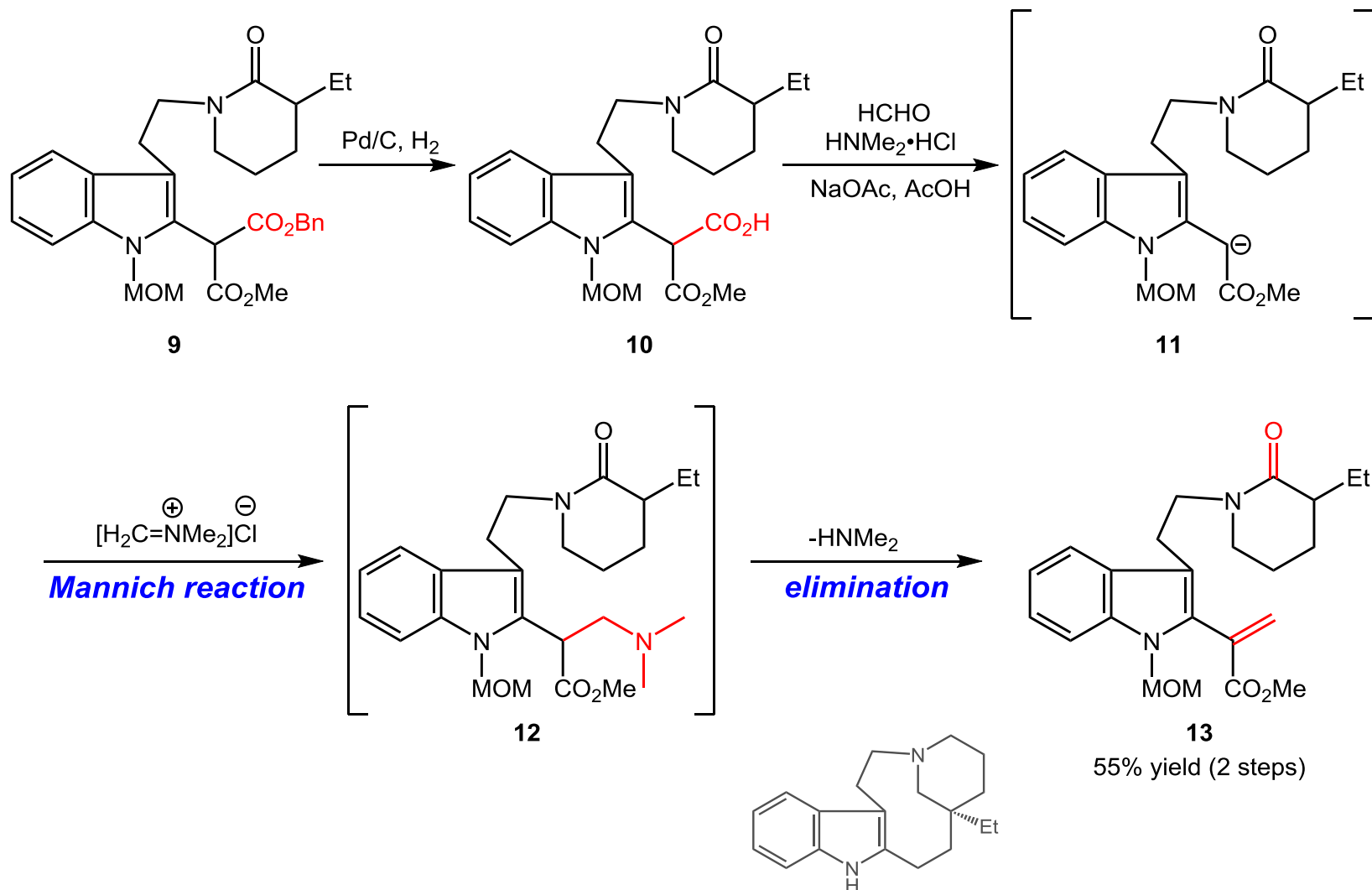
Furst, L.; Matsuura, B. S.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3104.

Mechanism

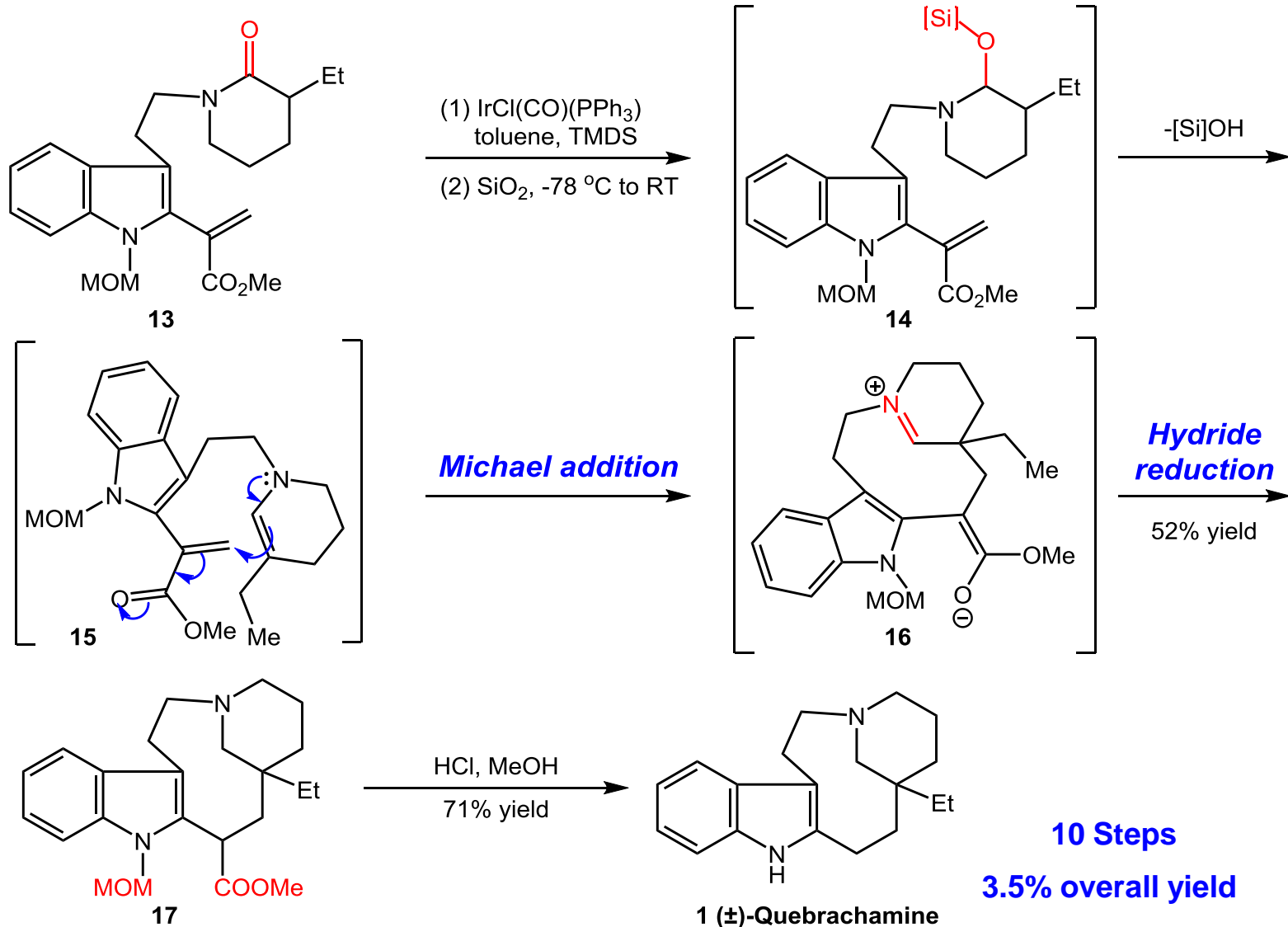


Furst, L.; Matsuura, B. S.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3104.

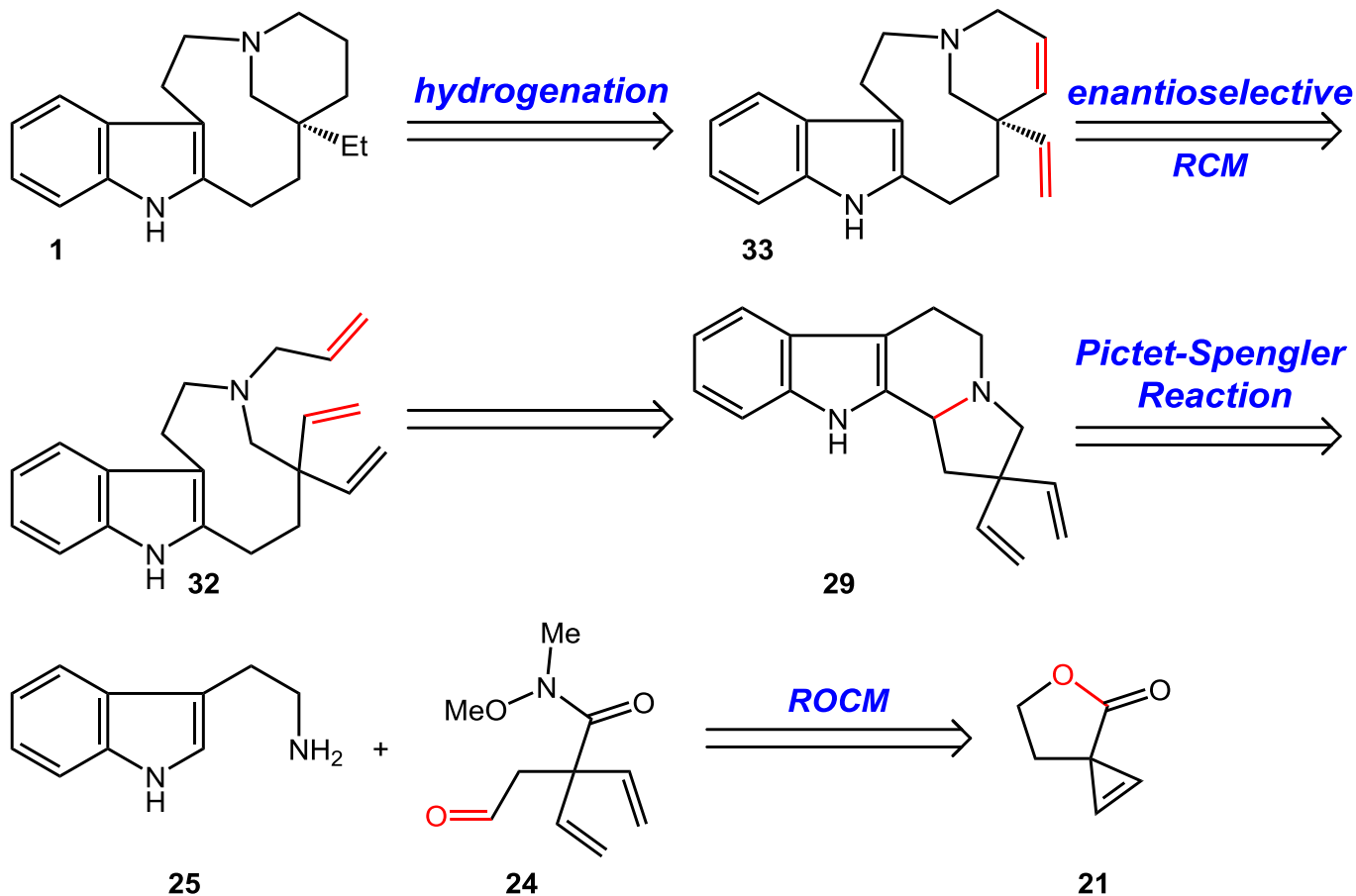
The synthesis of (+/-)-Quebrachamine



The synthesis of (+/-)-Quebrachamine

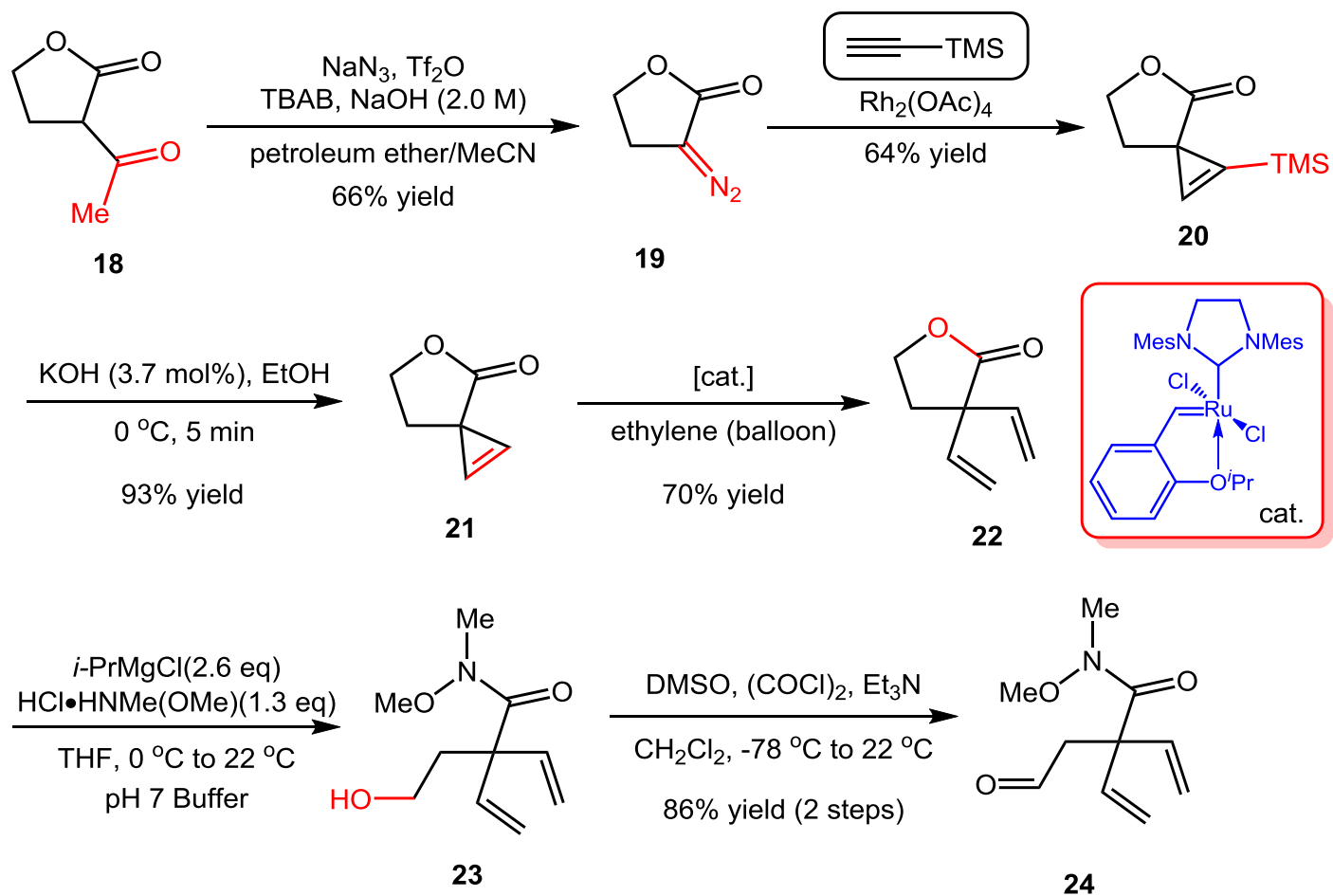


Retrosynthetic analysis

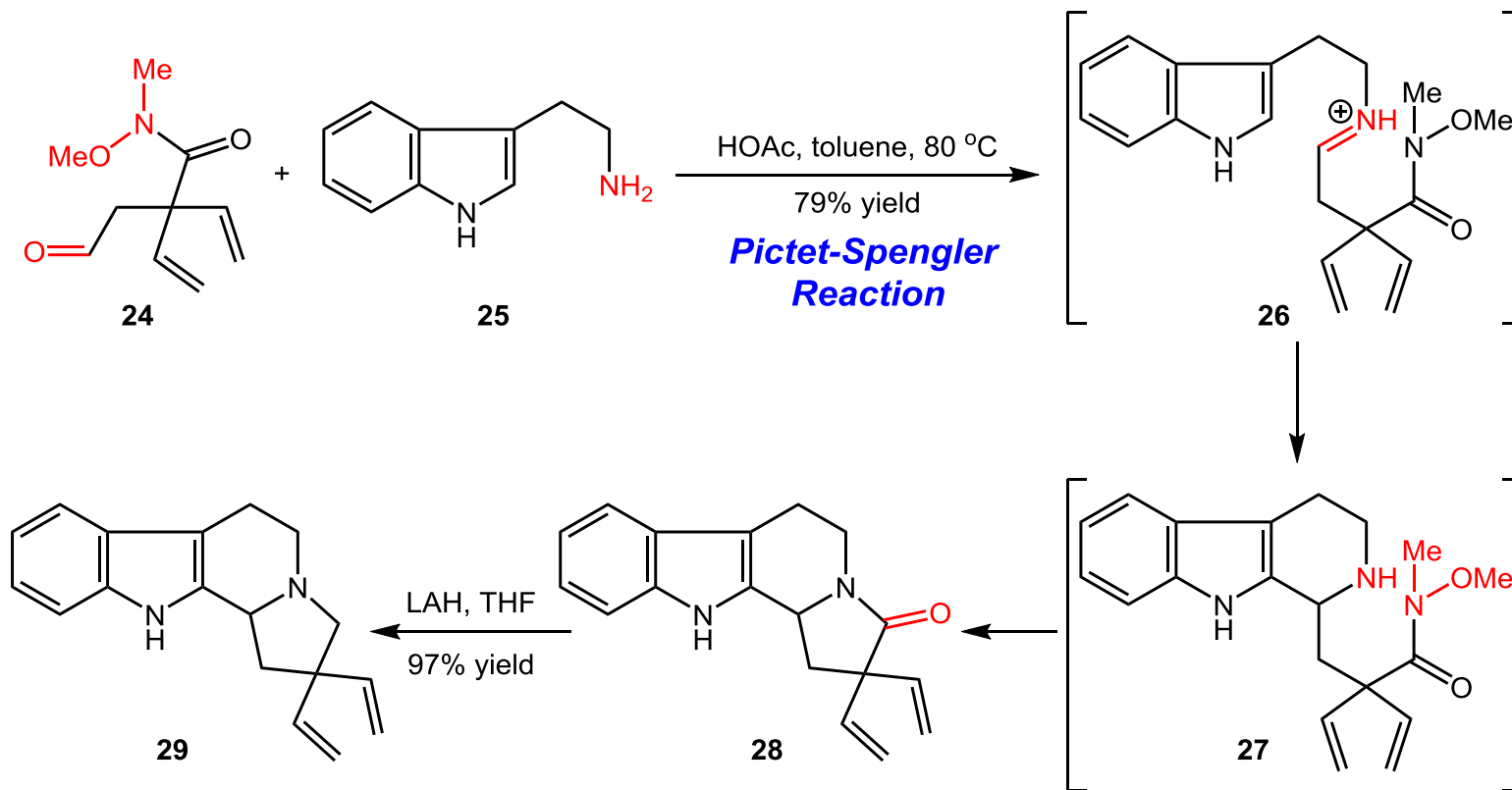


Sattely, E. S.; Meek, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943.

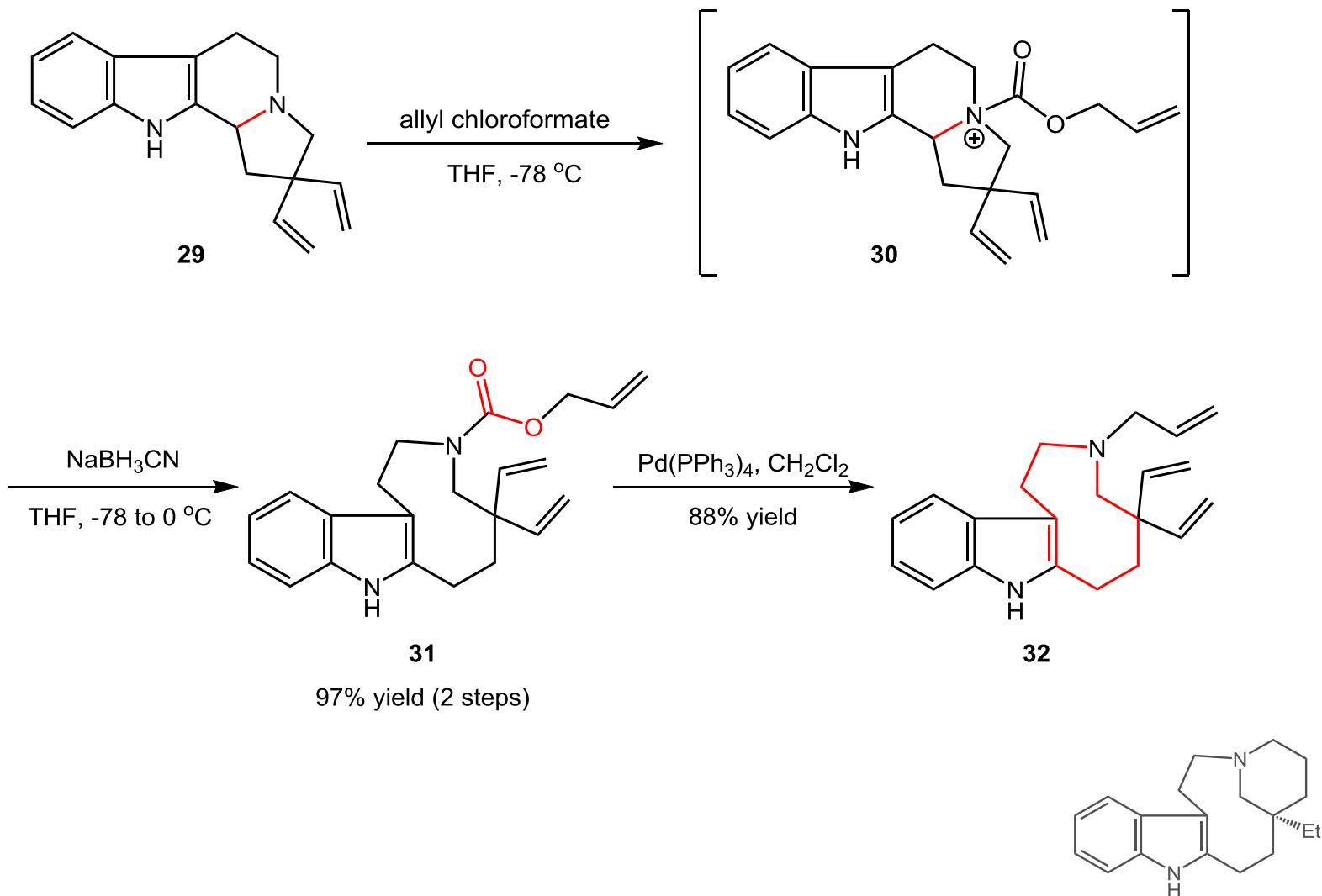
The synthesis of (+)-Quebrachamine



The synthesis of (+)-Quebrachamine

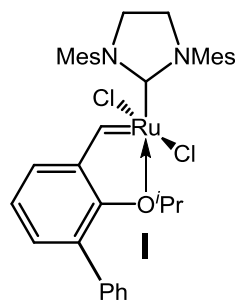
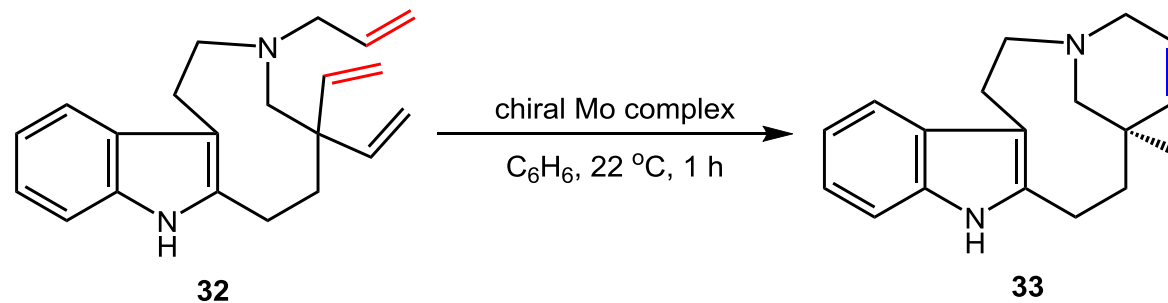


The synthesis of (+)-Quebrachamine

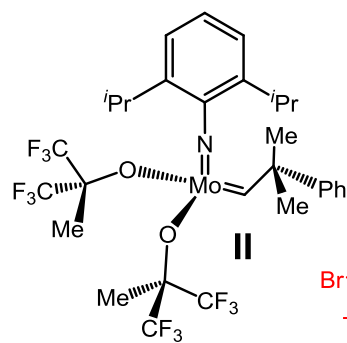


The synthesis of (+)-Quebrachamine

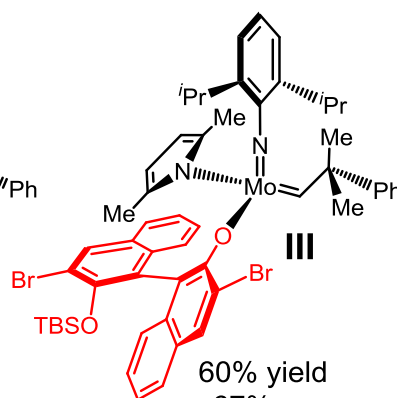
Enantioselective RCM of Triene



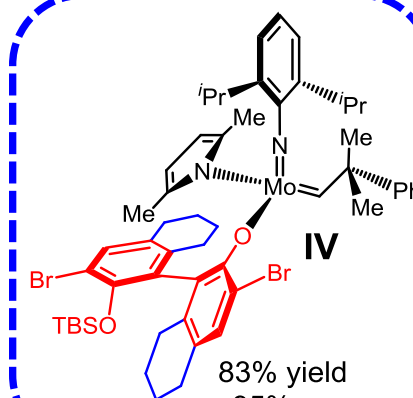
49% yield



59% yield

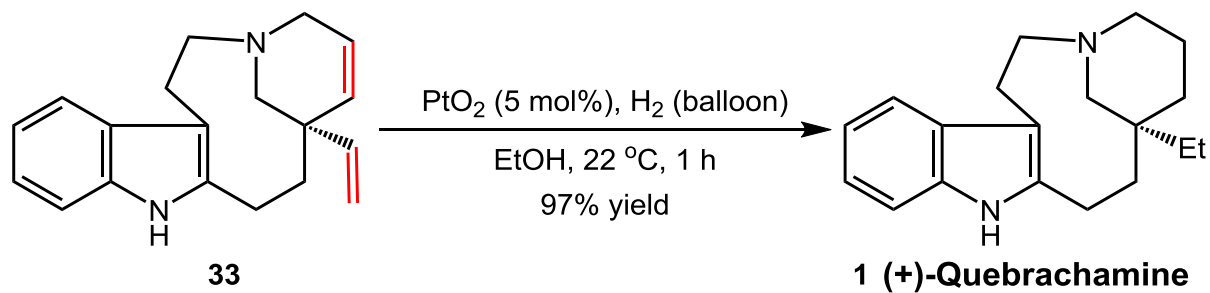


60% yield
67% ee



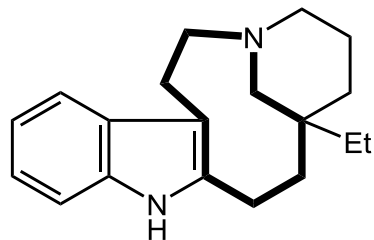
83% yield
95% ee

The synthesis of (+)-Quebrachamine



13 Steps, 1.2% overall yield

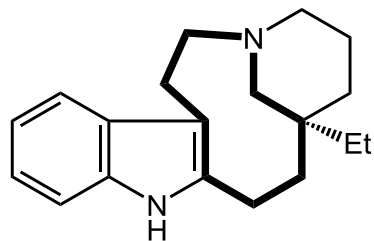
Summary



(±)-Quebrachamine

- 10 Steps, 3.5% overall yield
- C-H Functionalization *via* Photoredox Catalysis
- Reductive Cyclization Cascade

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(+)-Quebrachamine

- 13 Steps, 1.2% overall yield
- Ring Opening/Cross Metathesis (ROCM)
- Enantioselective Ring-Closing Metathesis

Sattely, E. S.; Meek, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943.

The first paragraph

Monoterpene indole alkaloids are a diverse class of natural products that is comprised of at least 2000 members. They possess inherent structural complexity and a range of important biological activities that qualifies a number of them to be ideal candidates for anti-cancer, anti-malarial and anti-arrhythmic agents. As a result, these natural products have inspired the synthetic community to devise innovative and elegant approaches that allow their efficient synthesis. Interestingly, and despite the many successful synthetic approaches already reported, recent efforts have shifted towards demonstrating unified, general and concise strategies that enable collective synthesis of a range of structurally related natural products.

The last paragraph

In conclusion, we have developed an expeditious and divergent reaction sequence to aspidosperma-type alkaloids quebrachamine in excellent diastereoselectivities. **Strategically, the route relied on the late-stage generation of reactive enamine functionality from stable indole-linked delta lactams via a highly chemoselective iridium(I)-catalyzed reduction.** This secodine intermediate could subsequently undergo either a formal Diels–Alder cycloaddition or Michael addition/reduction to provide the target products.

The last paragraph

This study demonstrated that subtle modifications of the indole lactam precursors could control the preference of the secodine intermediate to undergo either of the two reaction pathways. Furthermore, we have demonstrated the versatility of our synthetic approach by applying it to an asymmetric synthesis of iboga-type alkaloid 20-epiibophyllidine, starting from γ -lactam. Investigations into the development of an enantio-selective variant of this iridium(I)-catalyzed reductive cyclization sequence are currently ongoing and will be disclosed in due course.

Acknowledgement

***Thanks
for your attention***