Literature Report 2

Total Synthesis of Herquline B and C

Reporter: Xiang Li
Checker: Zi-Biao Zhao
Date: 2019-04-08

Cox, J. B.; Kimishima, A.; Wood, J. L. *J. Am. Chem. Soc.* **2019**, *141*, 25.
He, C.; Stratton, T. P.; Baran, P. S. *J. Am. Chem. Soc.* **2019**, *141*, 29.
Zhu, X.; McAtee, C. C.; Schindler, C. S. *J. Am. Chem. Soc.* **2019**, *141*, 3409.

CV of John L. Wood

John L. Wood

Research:

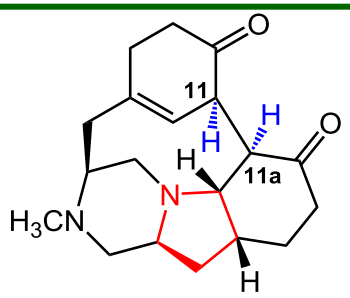
- Total synthesis of a number of complex, biologically active natural products, to develop innovative methods and strategies, which allow for rapid access to the target structure and the analogs.

Education:

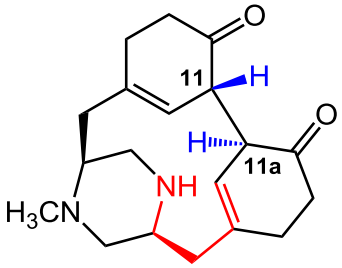
- **1980–1985** B.A., University of Colorado
- **1985–1991** Ph.D., University of Pennsylvania
- **1991–1993** American Cancer Society Postdoctoral Fellow, Harvard University
- **1993–1997** Assistant Professor of Chemistry, Yale University
- **1997–1998** Associate Professor of Chemistry (non tenured), Yale University
- **1998–2006** Professor of Chemistry, Yale University
- **2006–2013** A. I. Meyers Professor of Chemistry, Colorado State University
- **2013–Present** Robert A. Welch Distinguished Professor and Cancer Prevention Research Institute Scholar, Baylor University

Contents

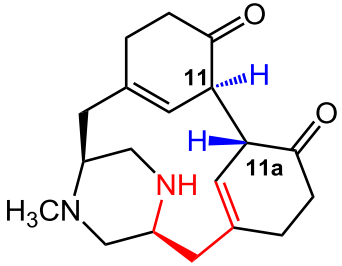
Introduction



Herquline A
(Ōmura, 1979)



Herquline B
(Ōmura, 1996)

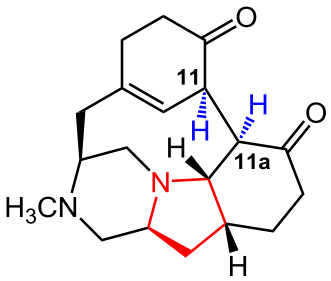


Herquline C
(Houk, Tang and Wood)

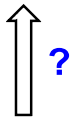
Penicillium herquei

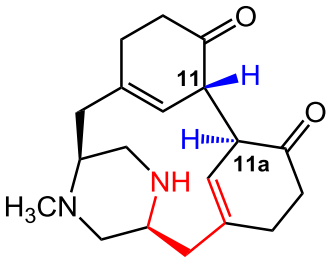
- Isolated from the *Penicillium herquei Fg-372* by Ōumra *et al*;
- Herquline A was shown to prevent platelet aggregation in addition to displaying antibiotic properties by inhibiting replication of the influenza virus;
- A sterically compact 6/9/6/5/6 pentacyclic skeleton.

Introduction

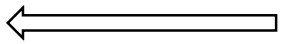


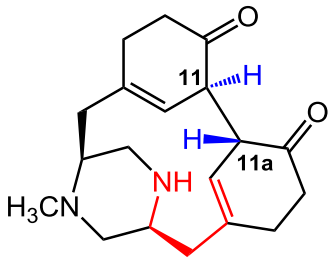
Herquline A





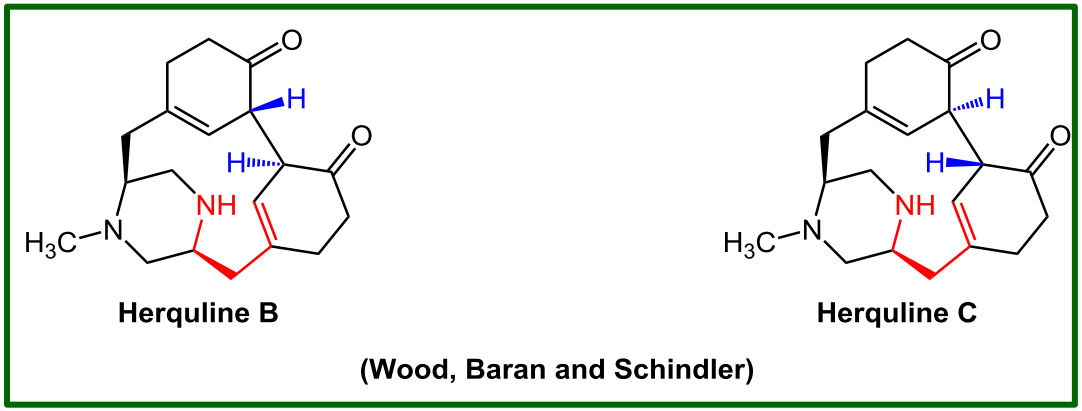
Herquline B

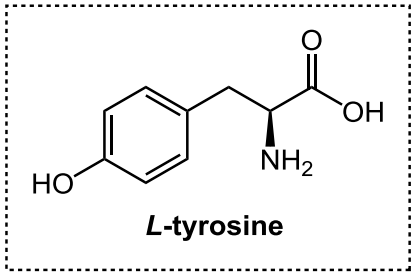




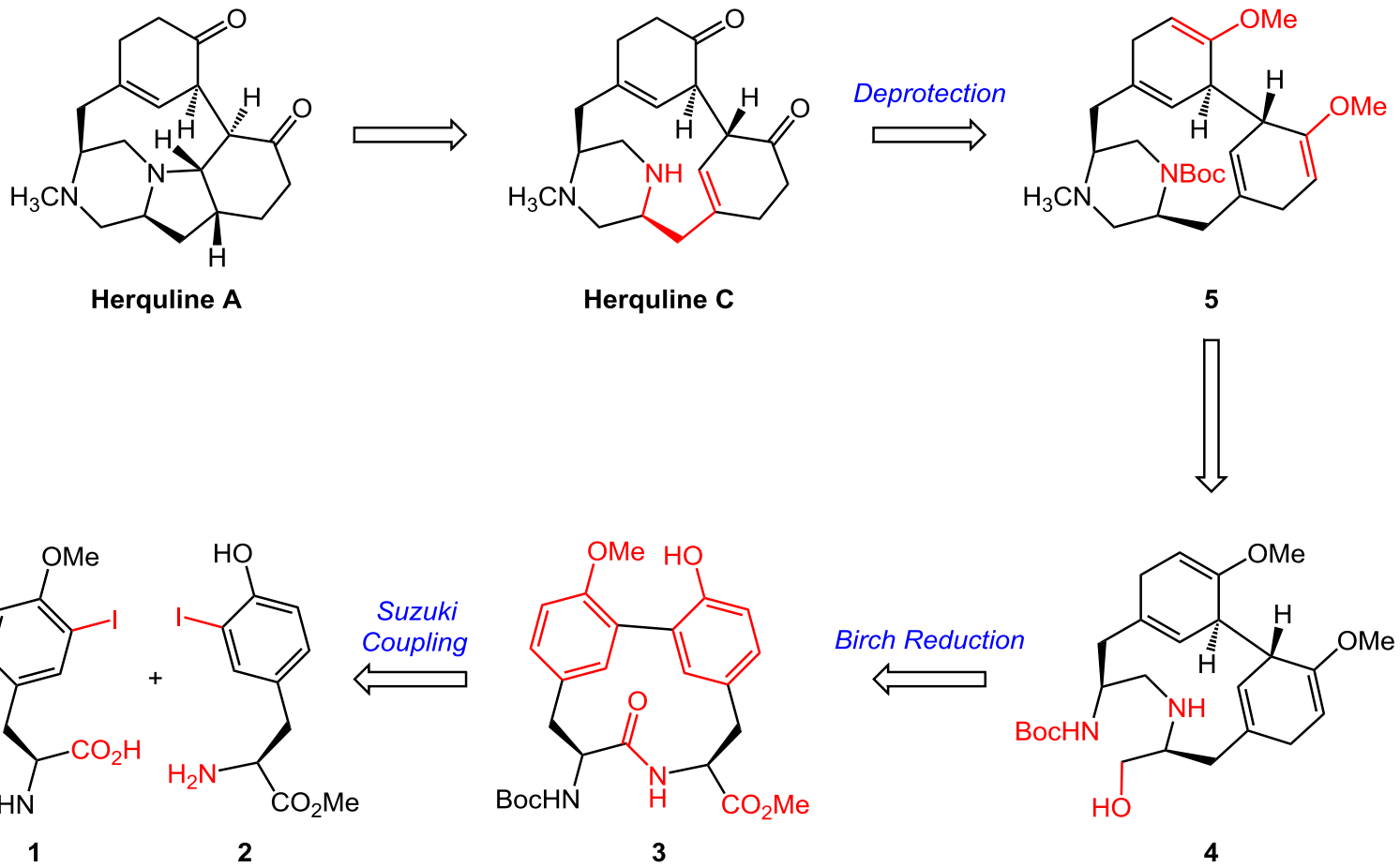
Herquline C

Total Synthesis of Herquline B and C



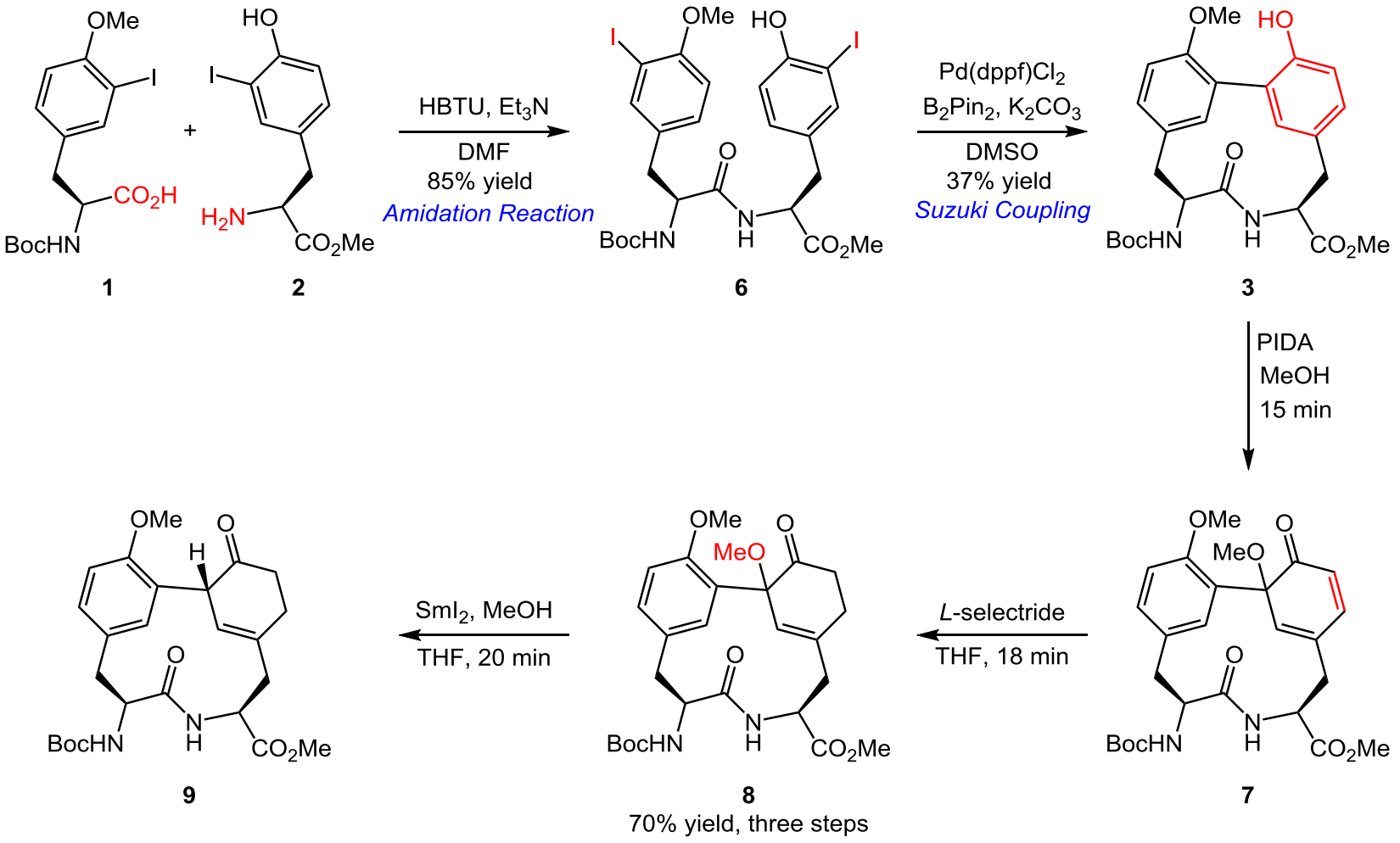


Retrosynthetic Analysis of Herquline B and C



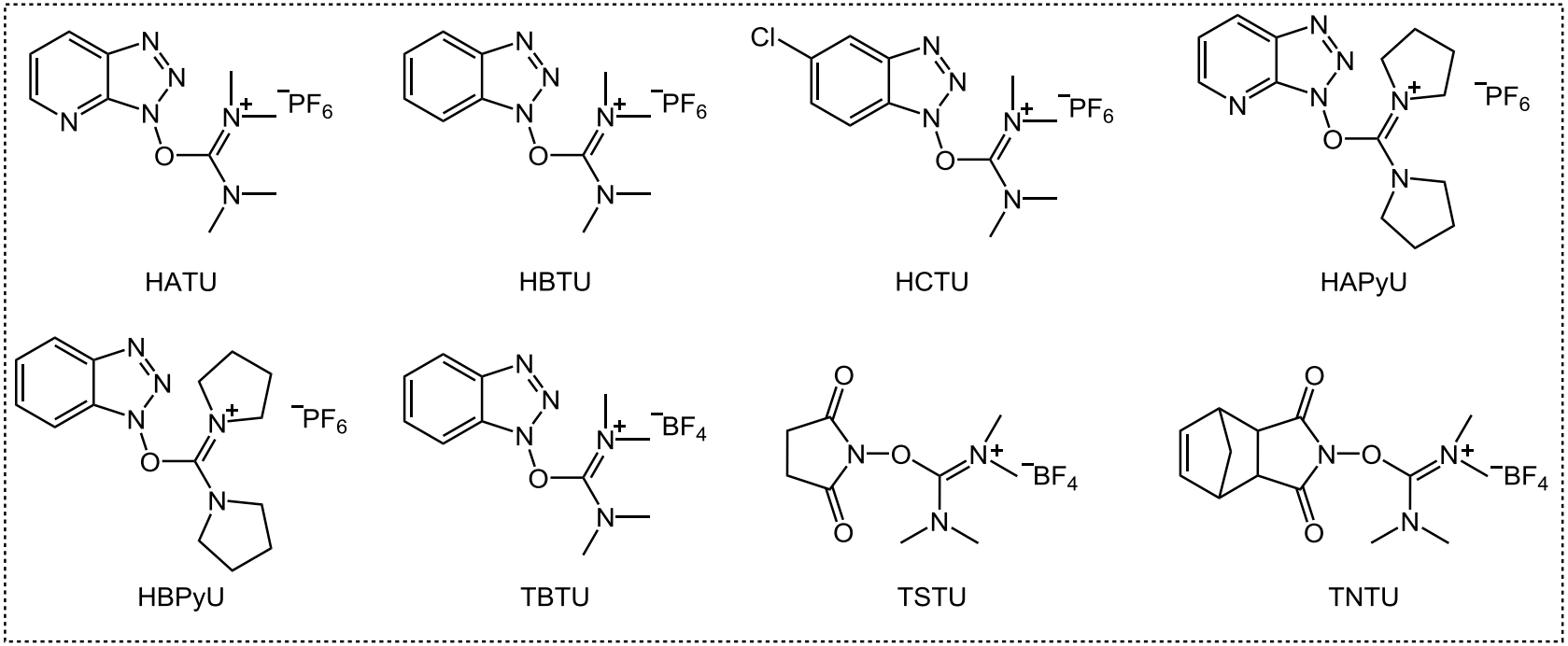
Wood, J. L. *et al*. *J*. *Am*. *Chem*. *Soc*. **2019**, *141*, 25.

Synthesis of Compound 9



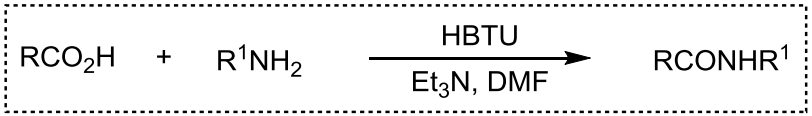
Amidation Reaction

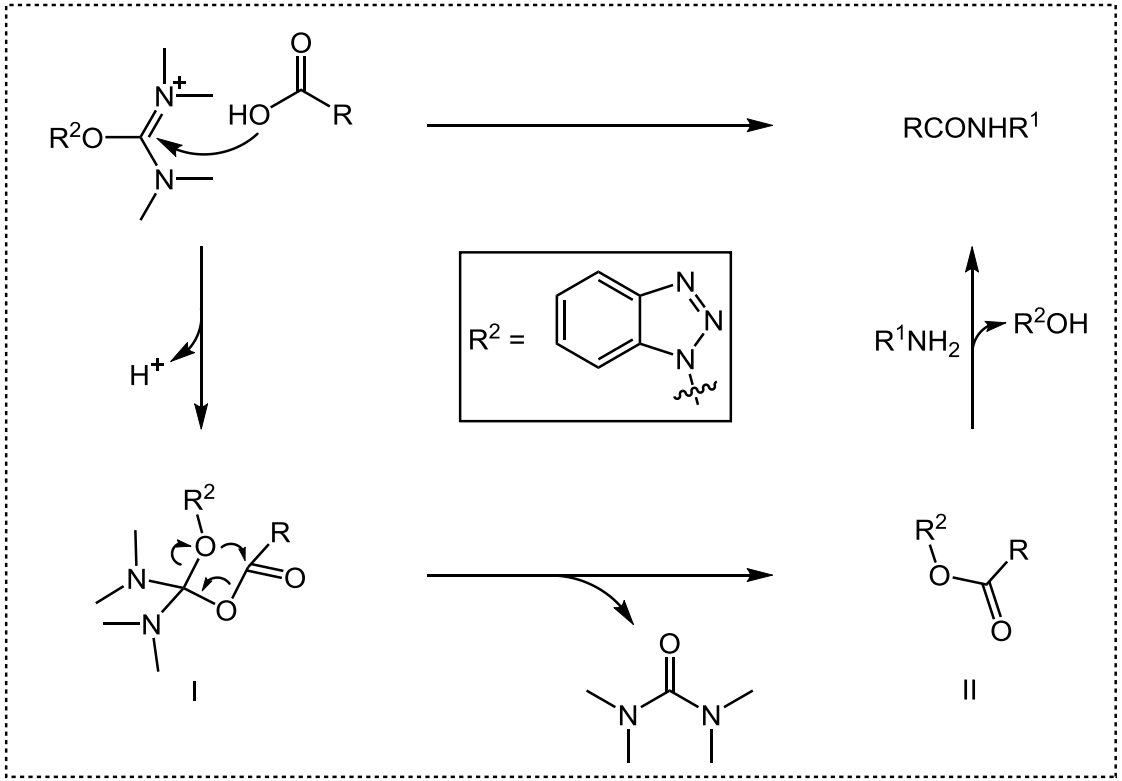
1. Condensating agent



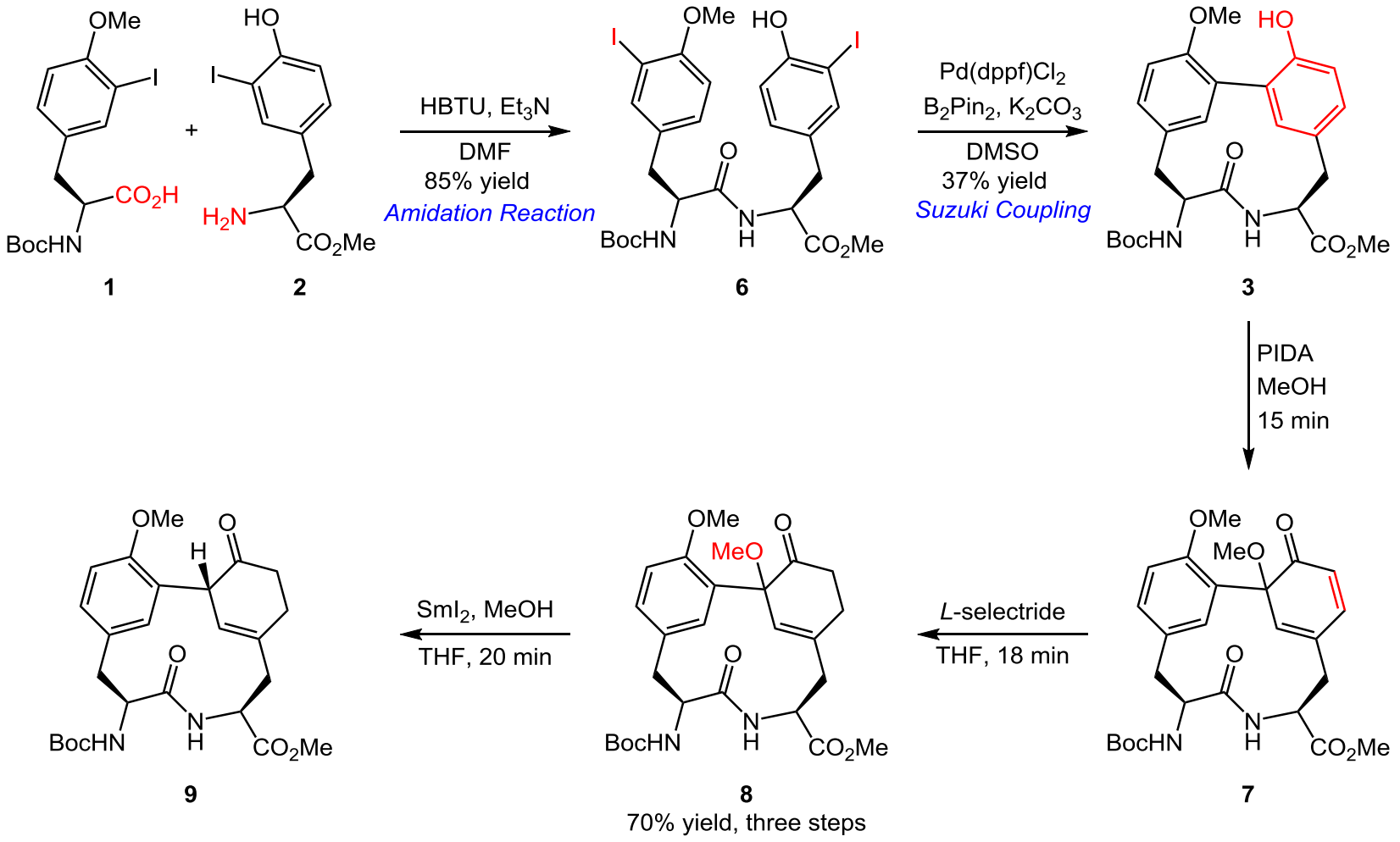
Amidation Reaction

2. Mechanism

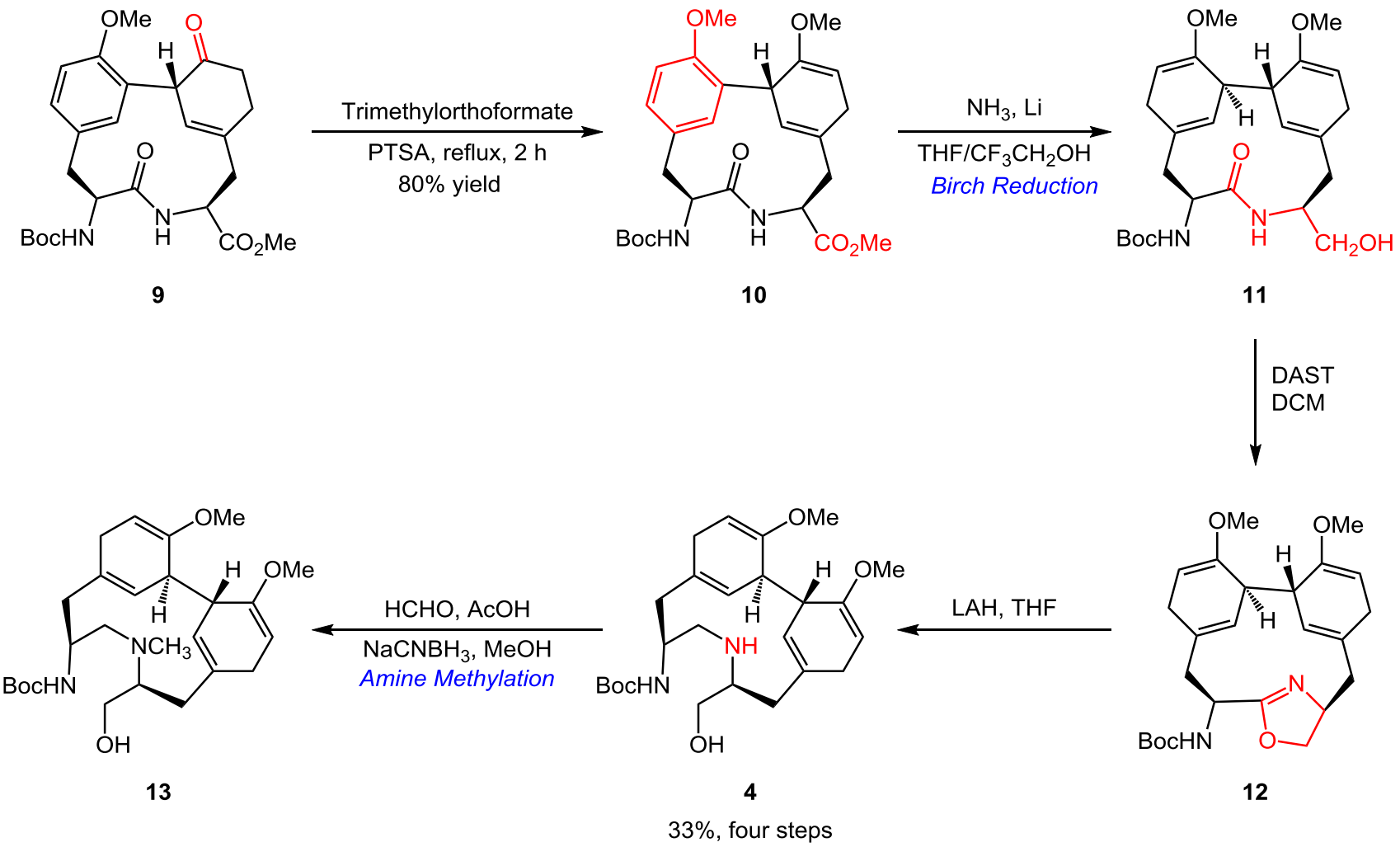




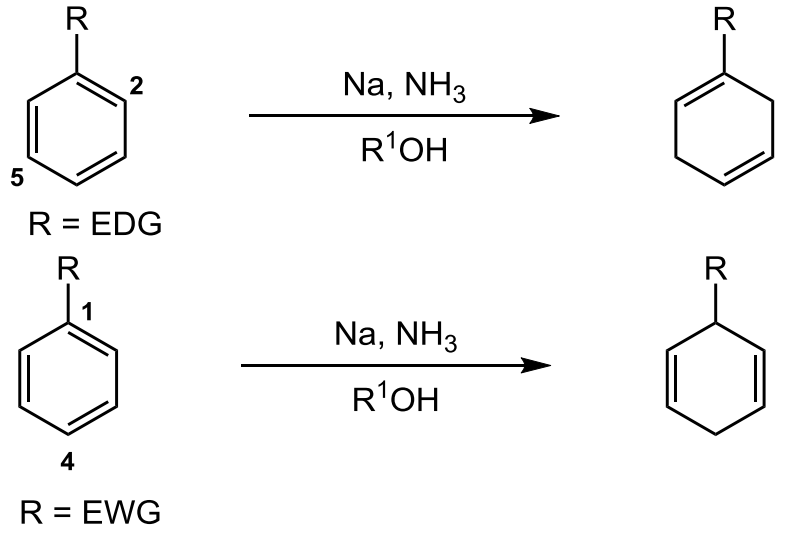
Synthesis of Compound 9

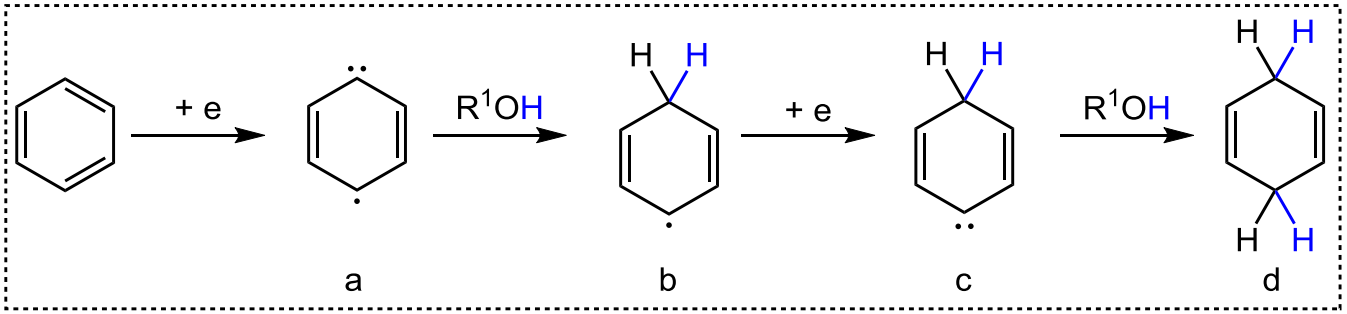


Synthesis of Compound 13

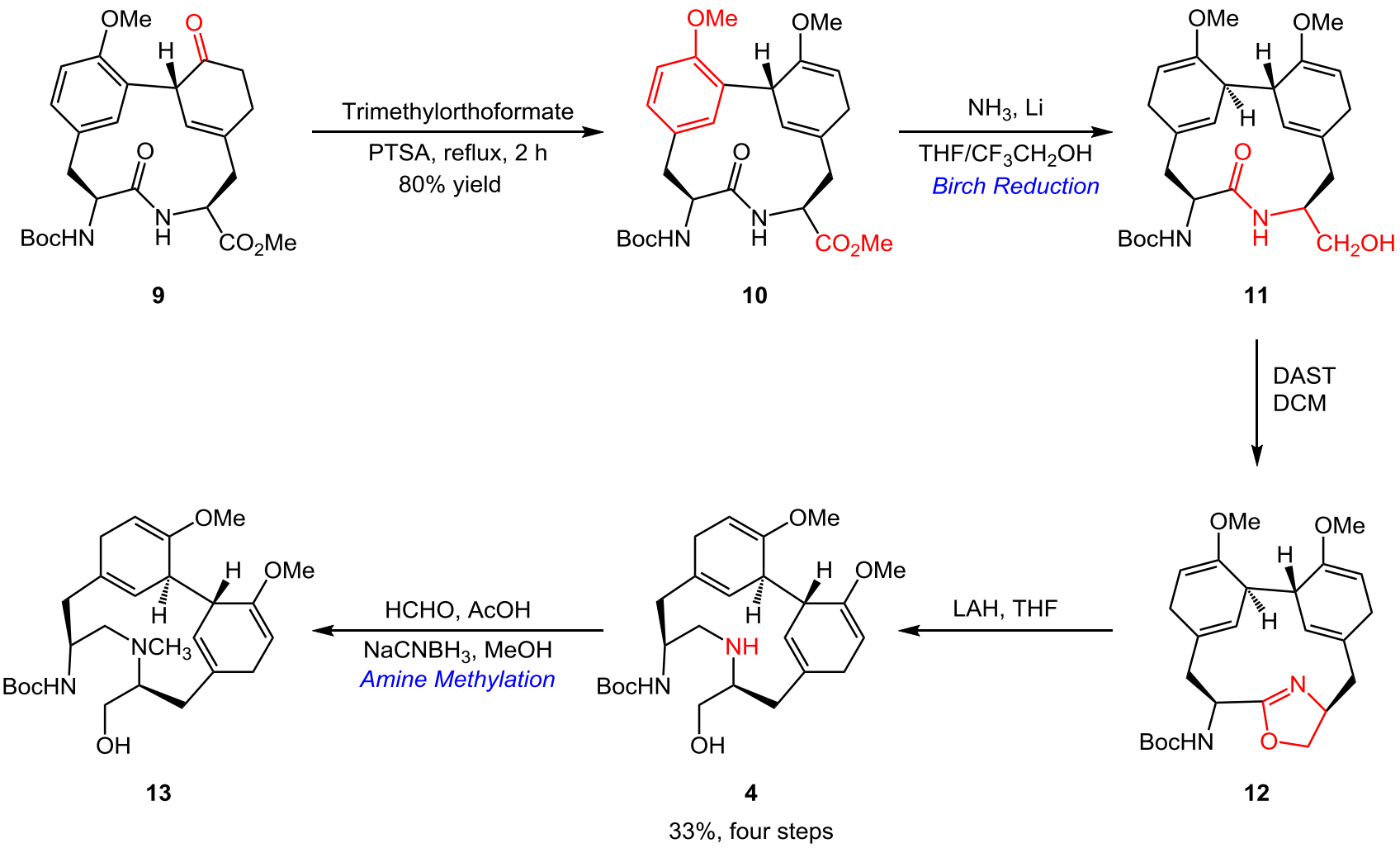


Birch Reduction

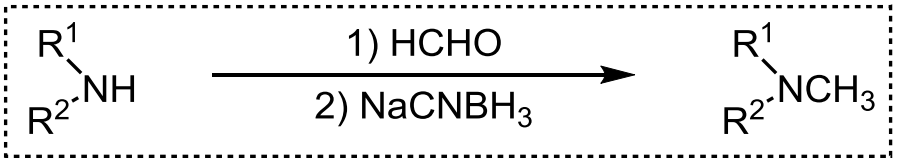


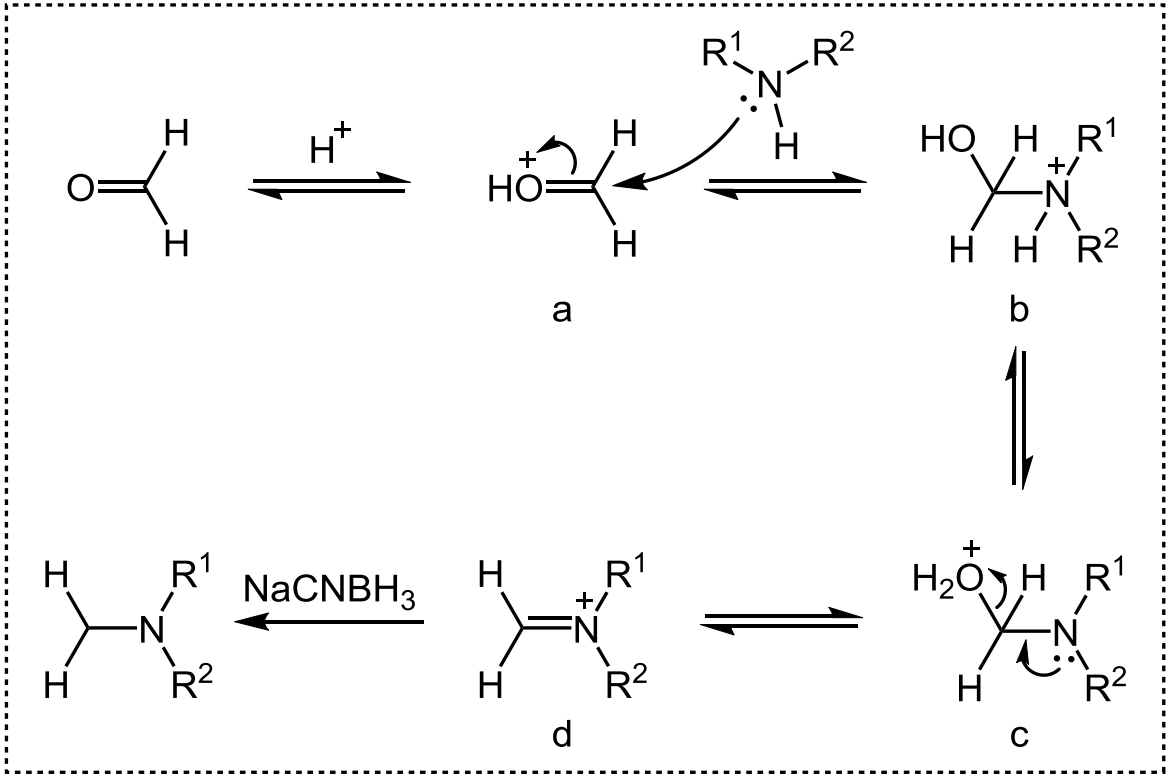


Synthesis of Compound 13

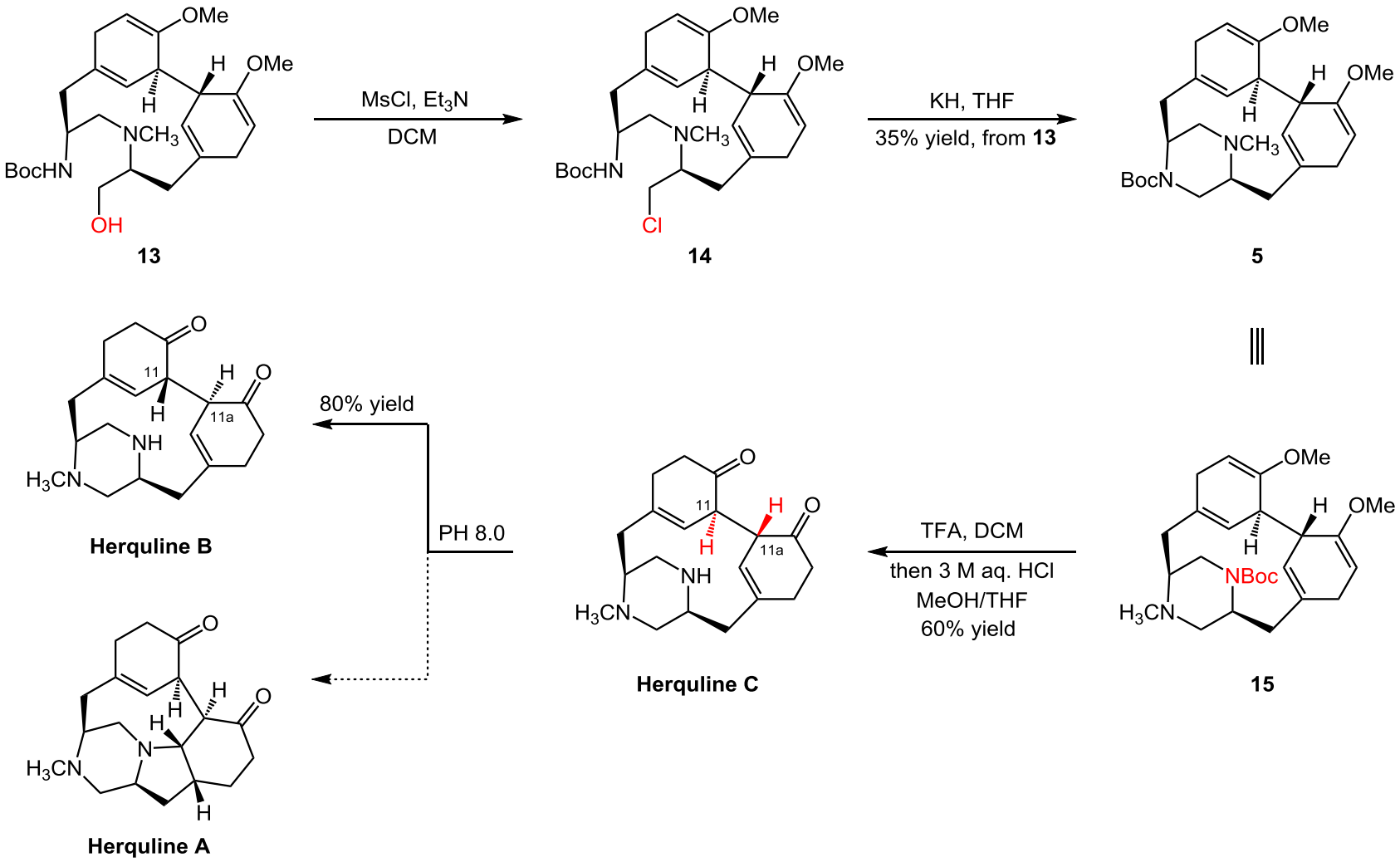


Amine Methylation

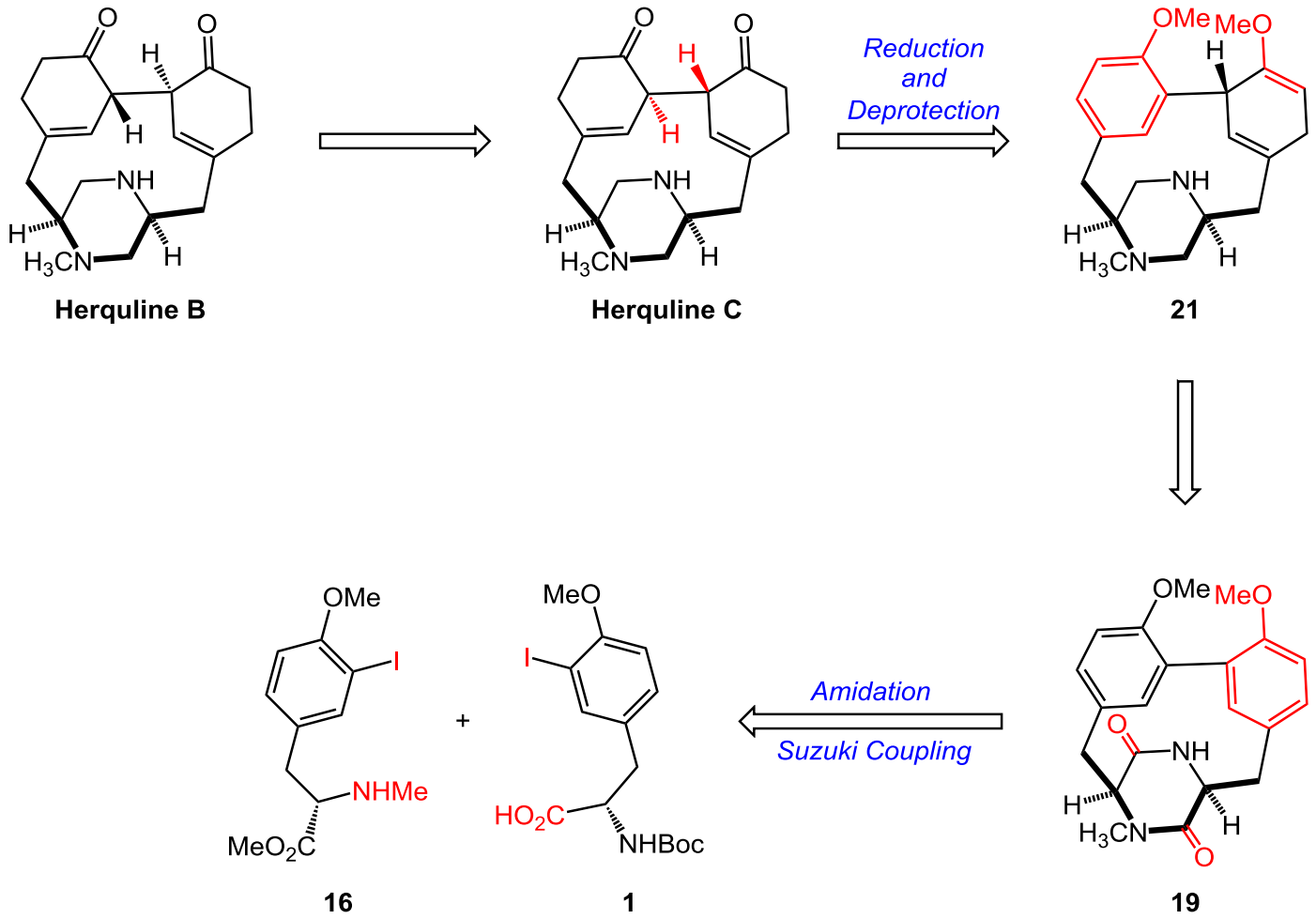




Synthesis of Herquline B and C

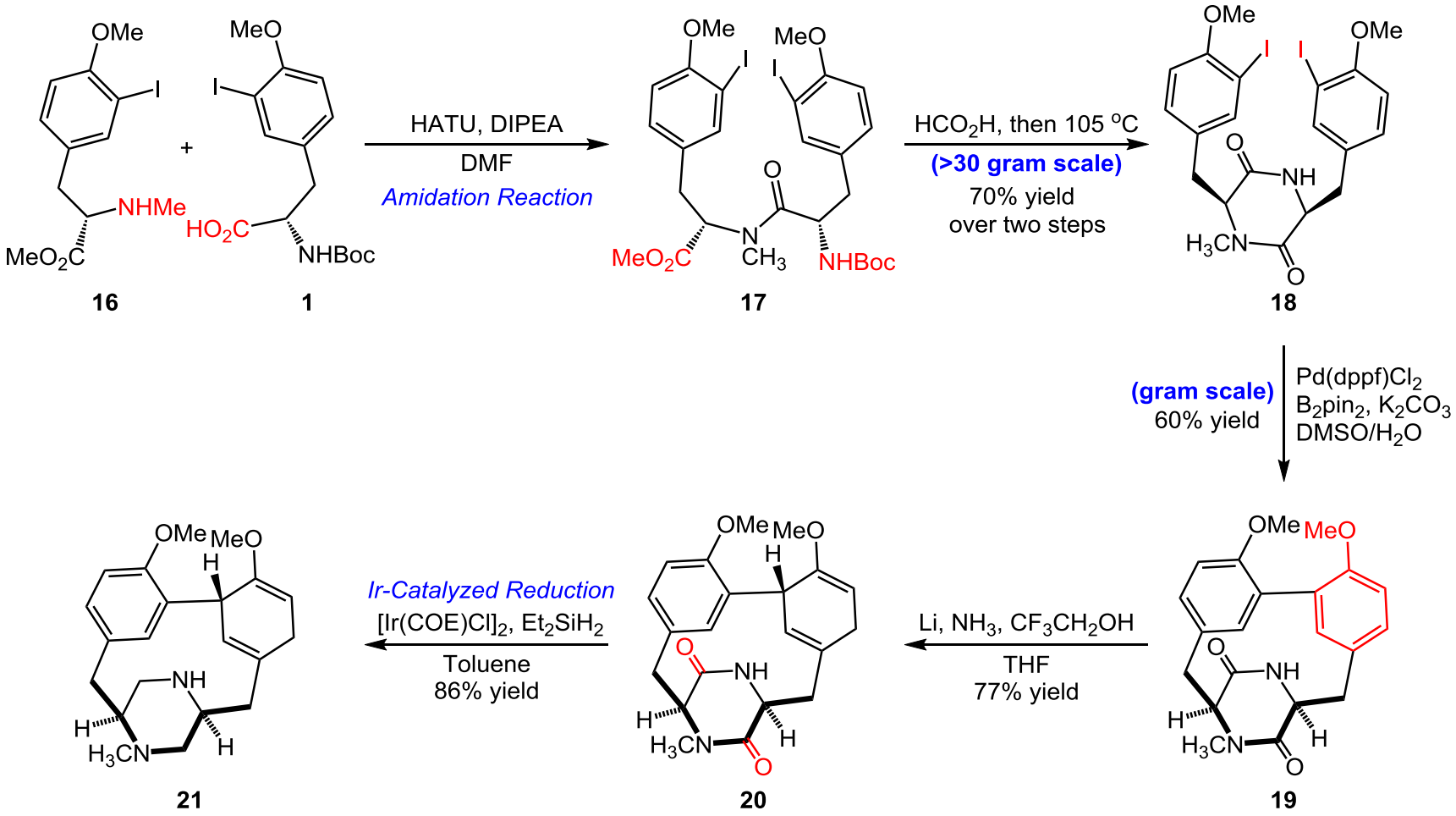


Retrosynthetic Analysis of Herquline B and C

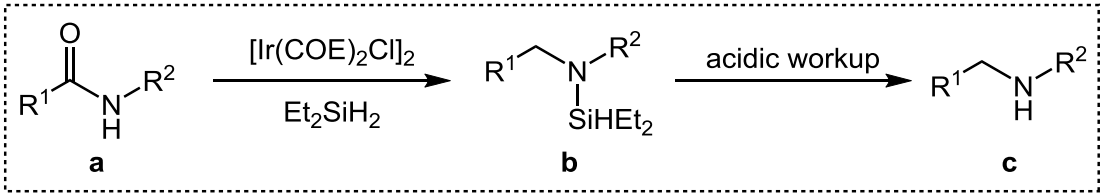


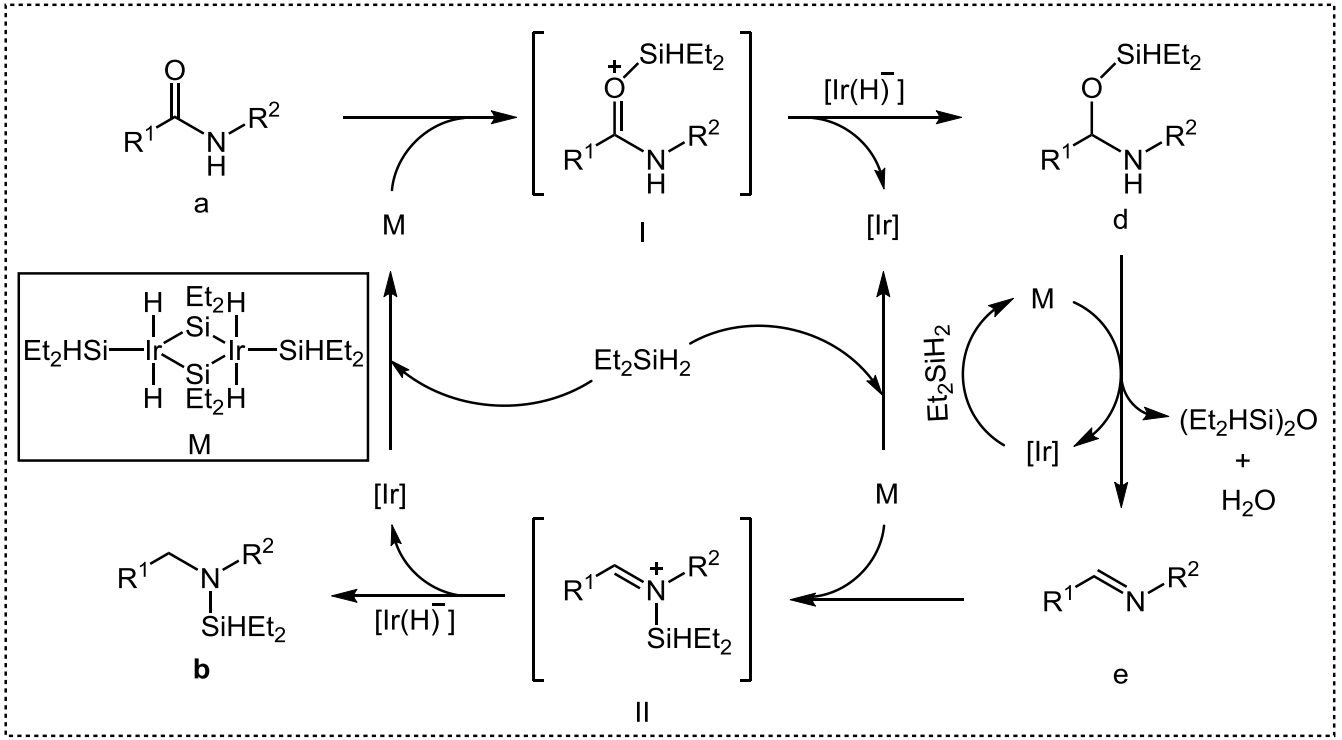
Baran, P. S. *et al*. *J*. *Am*. *Chem*. *Soc*. **2019**, *141*, 29.

Synthesis of Compound 21



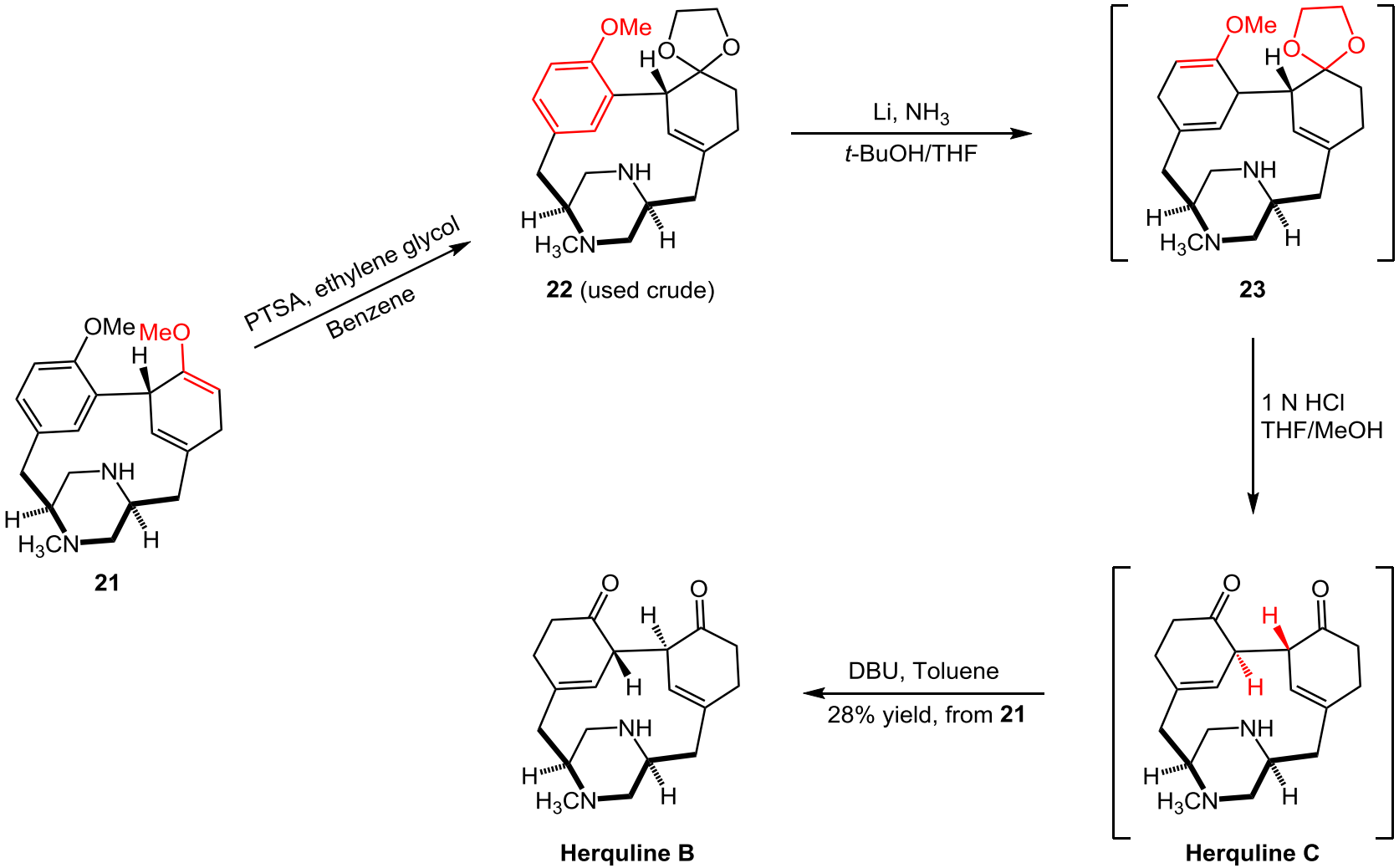
Ir-Catalyzed Reduction Reaction



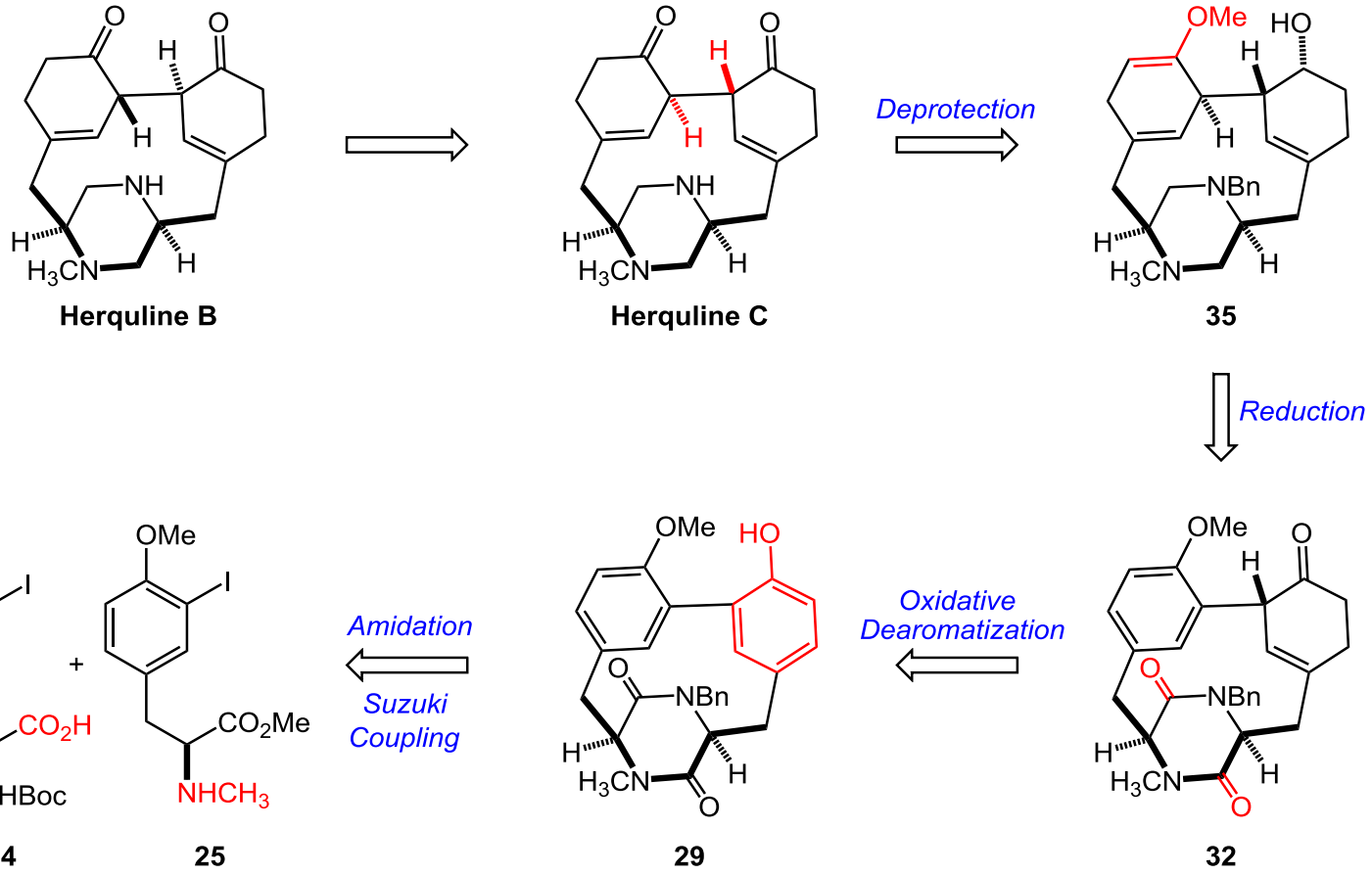


Brookhart, M. *et al*. *J*. *Am*. *Chem*. *Soc*. **2012**, *134*, 11304.

Synthesis of Herquline B and C

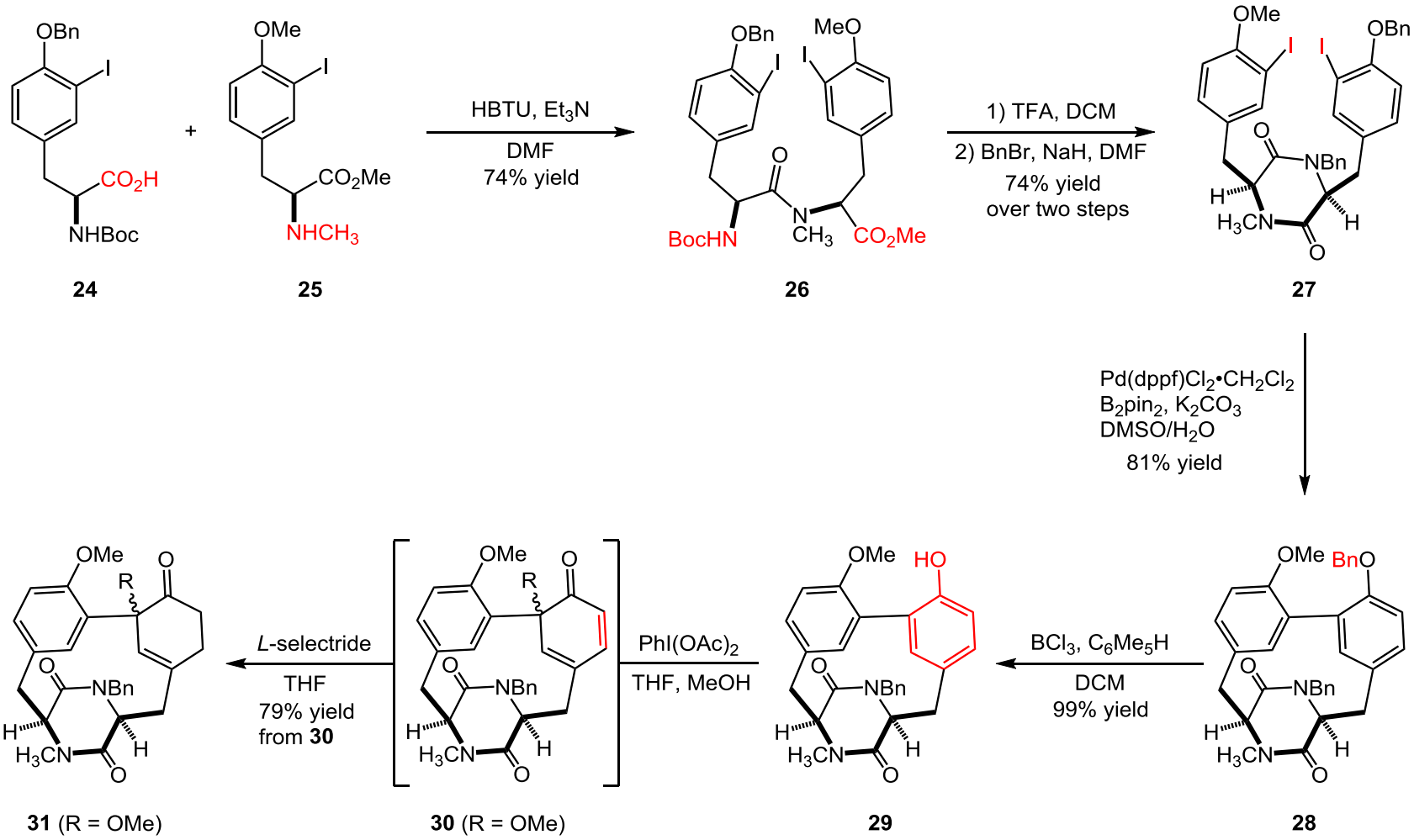


Retrosynthetic Analysis of Herquline B and C

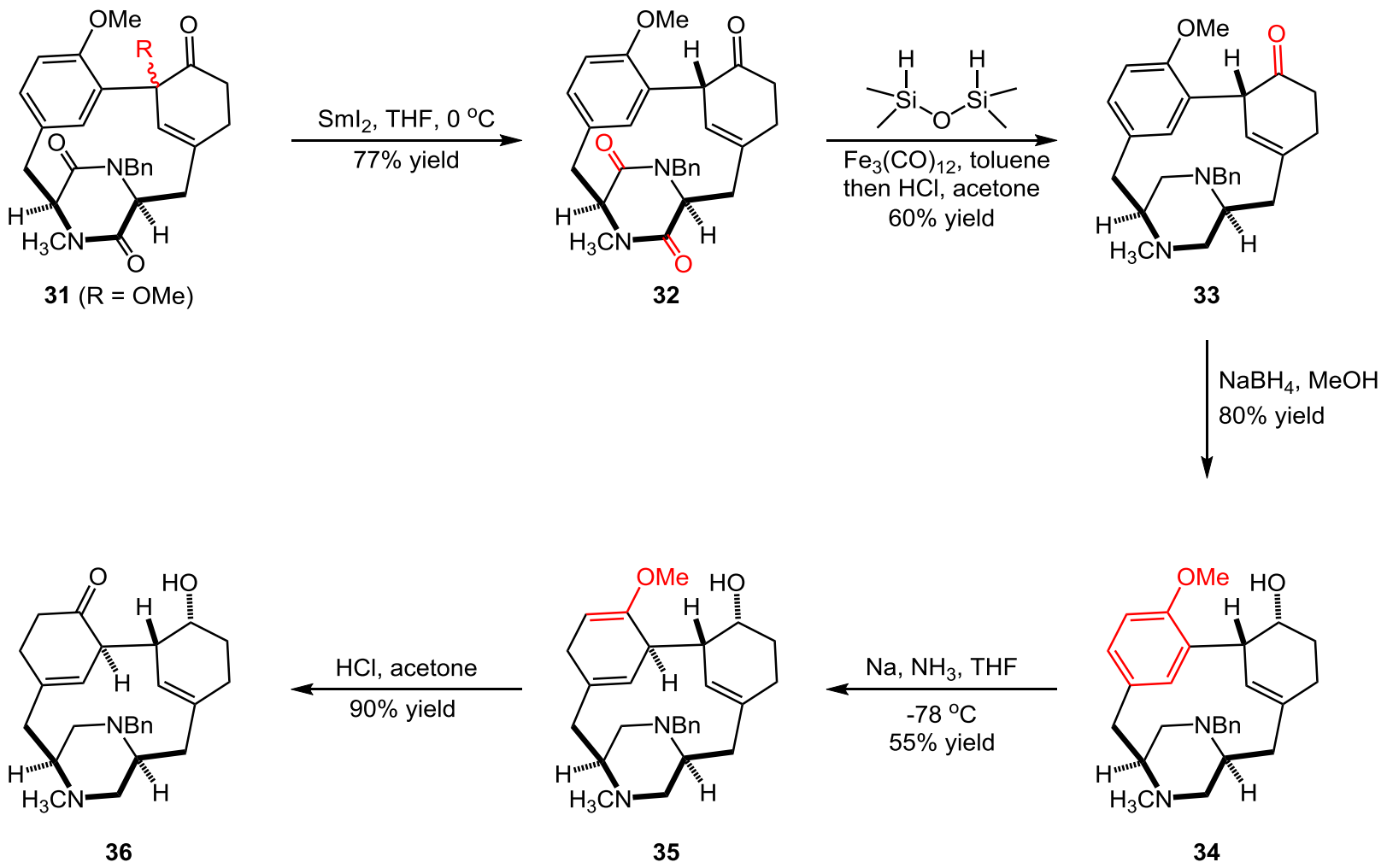


Schindler, C. S. *et al*. *J*. *Am*. *Chem*. *Soc*. **2019**, *141*, 3409.

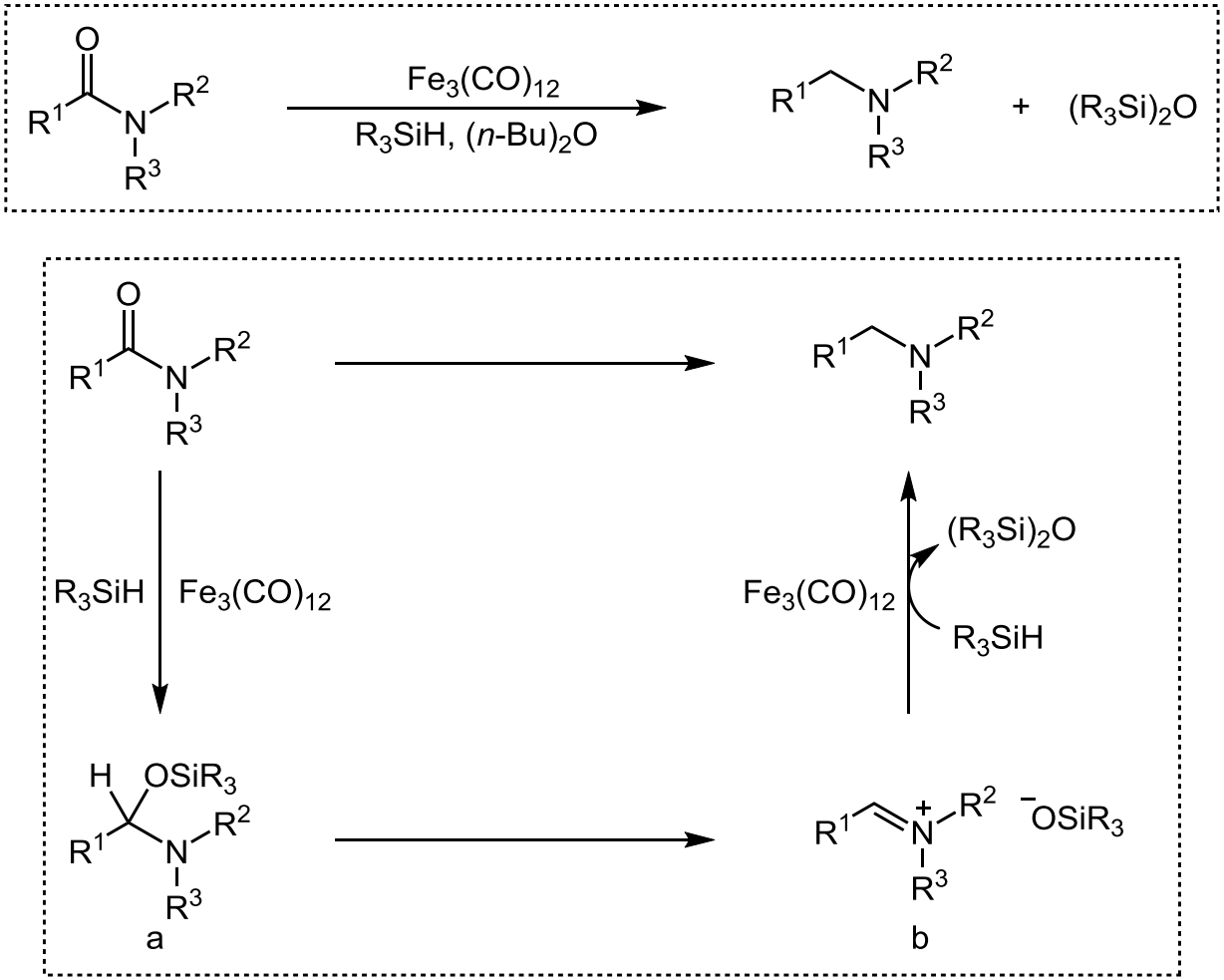
Synthesis of Compound 31



Synthesis of Compound 36

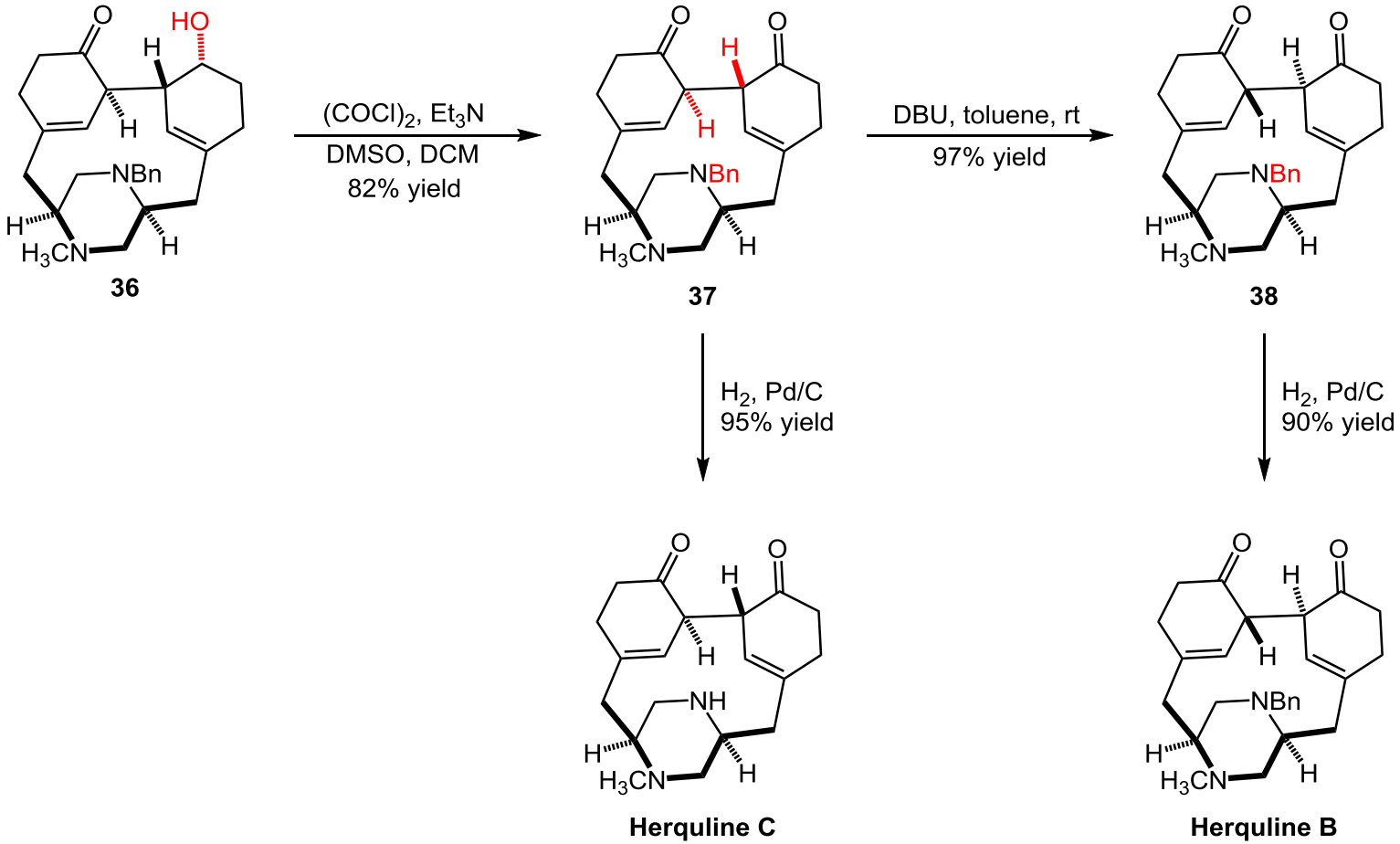


Fe-Catalyzed Reduction Reaction

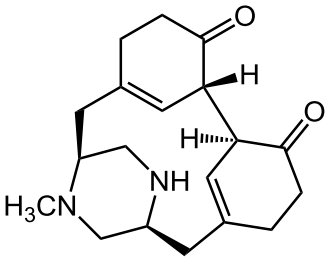


Beller, M. *et al*. *Angew. Chem. Int. Ed*. **2009**, *48*, 9507.

Synthesis of Herquline B and C

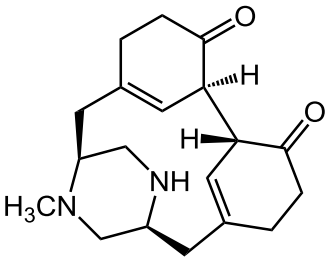


Summary



Herquline B

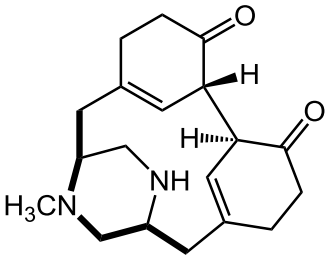
- 14 Steps, 0.98% overall yield;
- Amidation Reaction;
- Suzuki Coupling Reaction;
- Birch Reduction.



Herquline C

- 13 Steps, 1.22% overall yield;
- Amidation Reaction;
- Suzuki Coupling Reaction;
- Birch Reduction.

Wood, J. L. *et al*. *J*. *Am*. *Chem*. *Soc*. **2019**, *141*, 25.

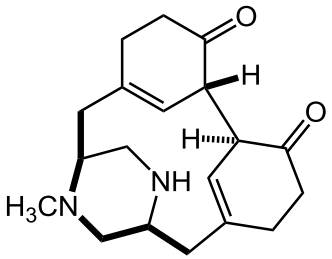


Herquline B

- 9 Steps, 7.79% overall yield;
- Amidation Reaction and Ir-Catalyzed Reduction;
- Suzuki Coupling Reaction;
- Birch Reduction.

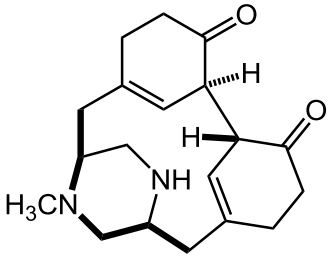
Baran, P. S. *et al*. *J*. *Am*. *Chem*. *Soc*. **2019**, *141*, 29.

Summary



Herquline B

- 13 Steps, 5.75% overall yield;
- Amidation Reaction and Fe-Catalyzed Reduction;
- Suzuki Coupling Reaction;
- Birch Reduction.



Herquline C

- 12 Steps, 6.07% overall yield;
- Amidation Reaction and Fe-Catalyzed Reduction;
- Suzuki Coupling Reaction;
- Birch Reduction .

Schindler, C. S. *et al*. *J*. *Am*. *Chem*. *Soc*. **2019**, *141*, 3409.

The First Paragraph

In 1979 and 1996, Ōmura and co-workers reported the isolation of herqulines A (**1**) and B (**2**), two secondary metabolites produced by a fungal strain originally isolated from a soil sample collected in the Saitama Prefecture of Japan, Penicillium herquei Fg-372. Preliminary evidence from these studies suggested tyrosine as a biosynthetic precursor to both congeners and screens for biological activity revealed **1** and **2** to be inhibitors of platelet aggregation. In a subsequent study, **1** was demonstrated to be an effective inhibitor of influenza virus replication. The structure of **1** was confirmed via single-crystal X-ray analysis, which allowed complete assignment of the illustrated relative stereochemistry. In contrast, the structure of **2** was deduced solely from spectral data and the stereochemistry at C(11) and C(11a) was left unassigned.

The Last Paragraph

In conclusion, efforts to develop a synthesis capable of delivering herqulines A and B have been successful in providing access to (−)-herquline B (**2**) and a heretofore unrecognized congener (+)-herquline C (**3**). These studies have also revealed that, in contrast to earlier reports, **3** does not undergo conversion to herquline A (**1**) upon exposure to pH 8.0 buffer; thus, the biosynthetic origins of **1** have yet to be fully delineated and it remains an intriguing target for synthesis.

Acknowledgement

Thanks
for your attention