Total Synthesis of (±)-Gelsemoxonine

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Checker: Wen-Xue Huang
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Carreira, E. M. *et al.*
J. Am. Chem. Soc. **2013**, *135*, 8500.

Eidgenössische Technische Hochschule Zürich

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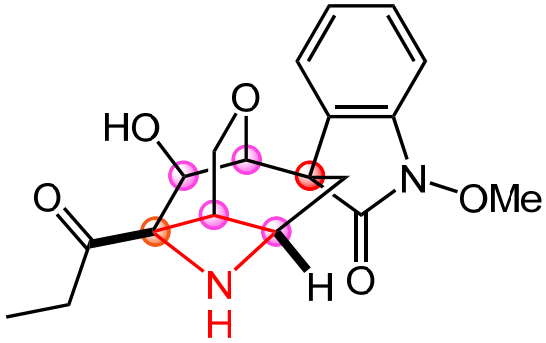
Introduction



Gelsemoxonine

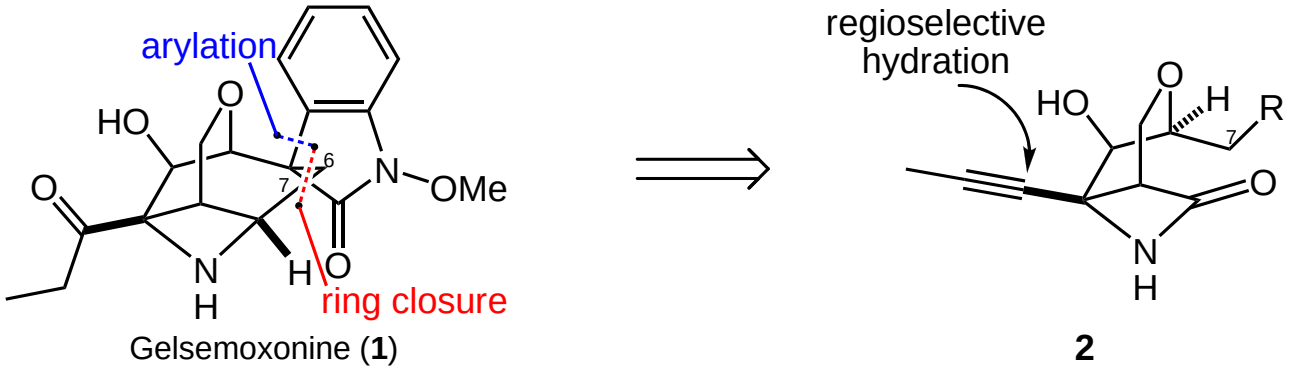
Gelsemium

Character:

- six contiguous, densely packed stereocenters including a quaternary carbon at the spirocyclic junction
- a fully substituted carbon within the azetidine

Carreira's Method

Retrosynthetic Analysis



Gelsemoxonine (**1**)

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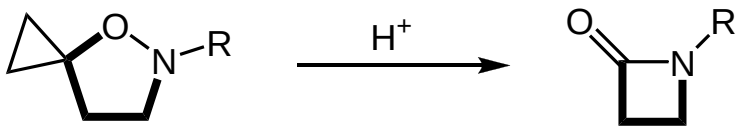
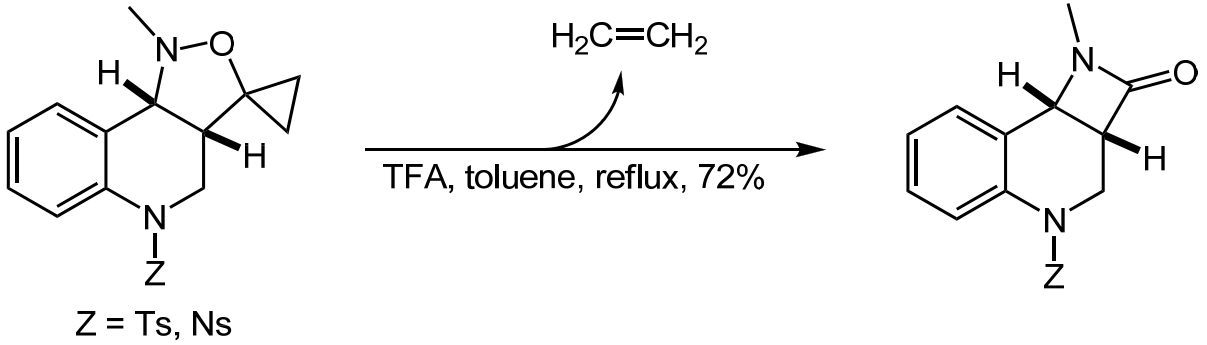
Ring Contraction

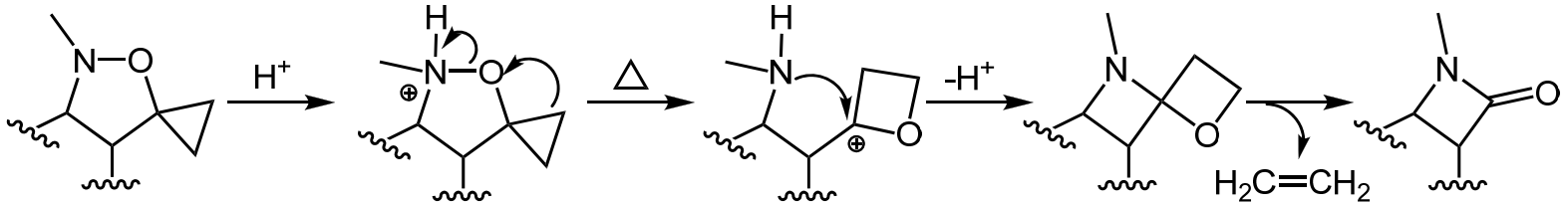


Carreira, E. M. *et al. J. Am. Chem. Soc.* **2013**, *135* , 8500.

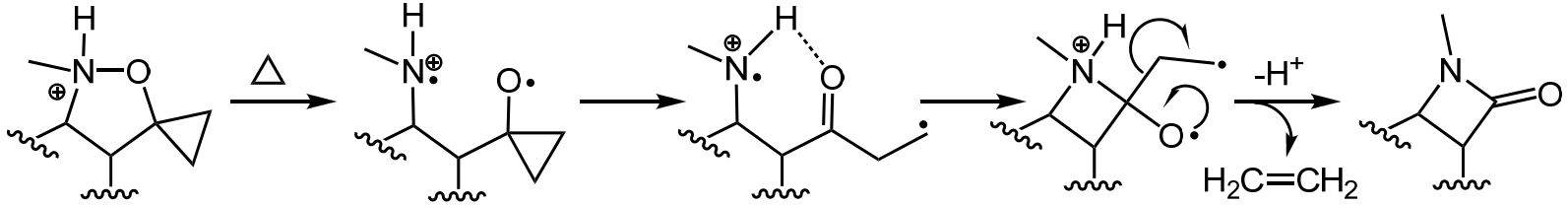
Ring Contraction



Mechanism I

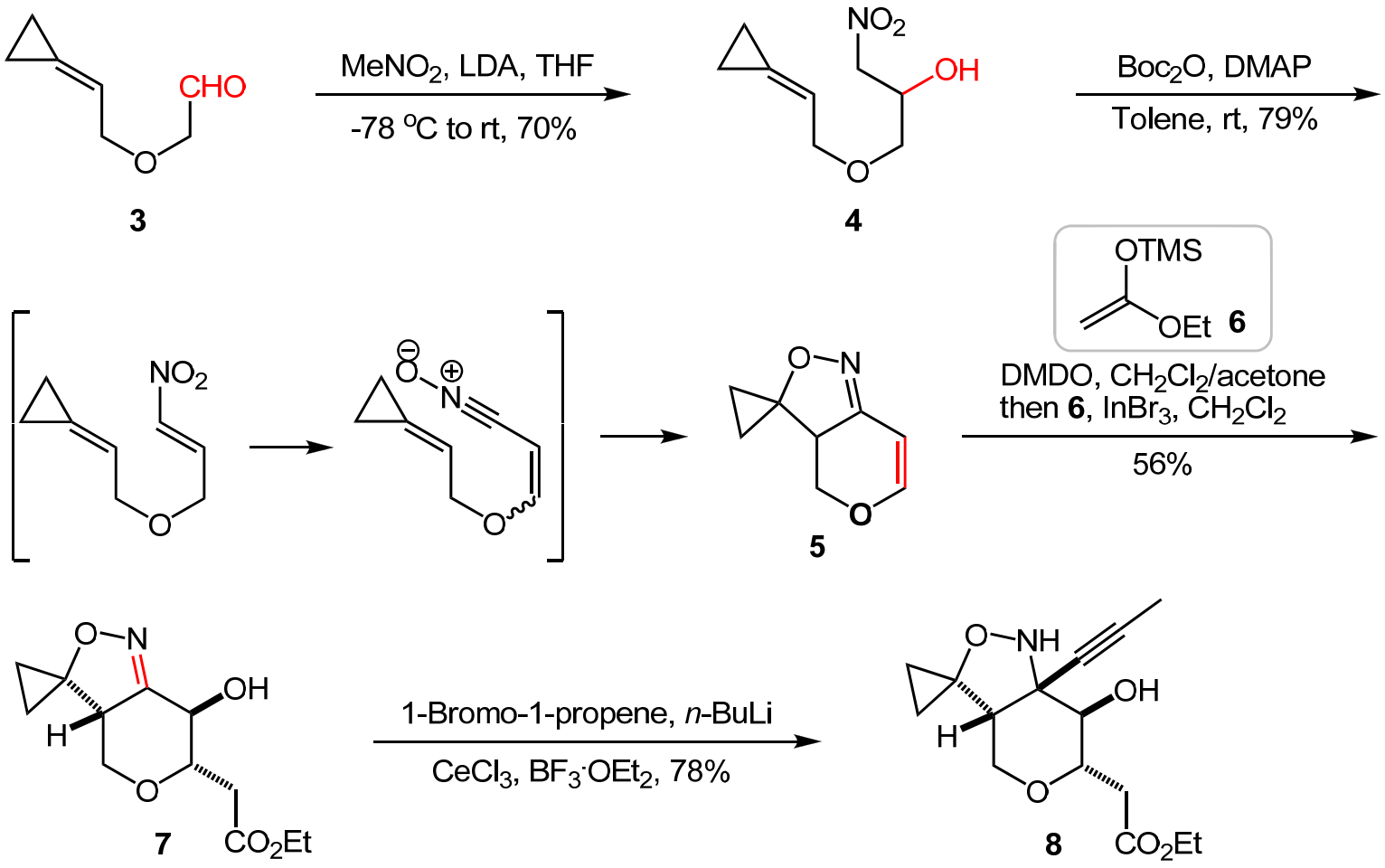


Mechanism II

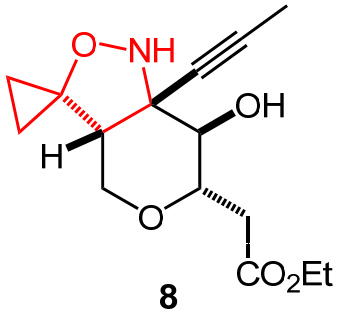


Brandi, A. *et al. J. Am. Chem. Soc.* **2000**, *122*, 8075.

Synthesis of Isoxazolidine 8

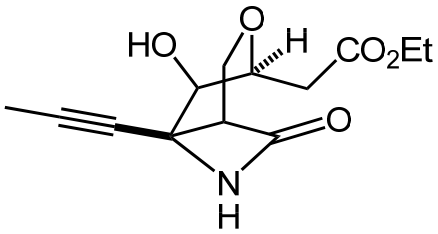


Ring Contraction of Isoxazolidine 8



8

TFA, MeCN, 80 °C, 40-45%



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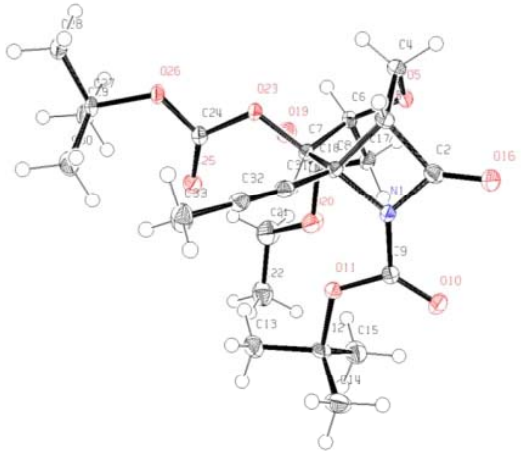

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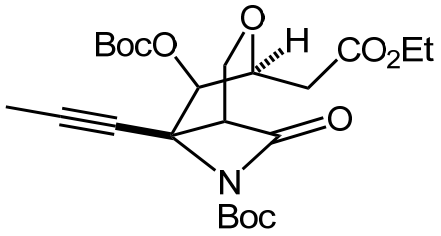

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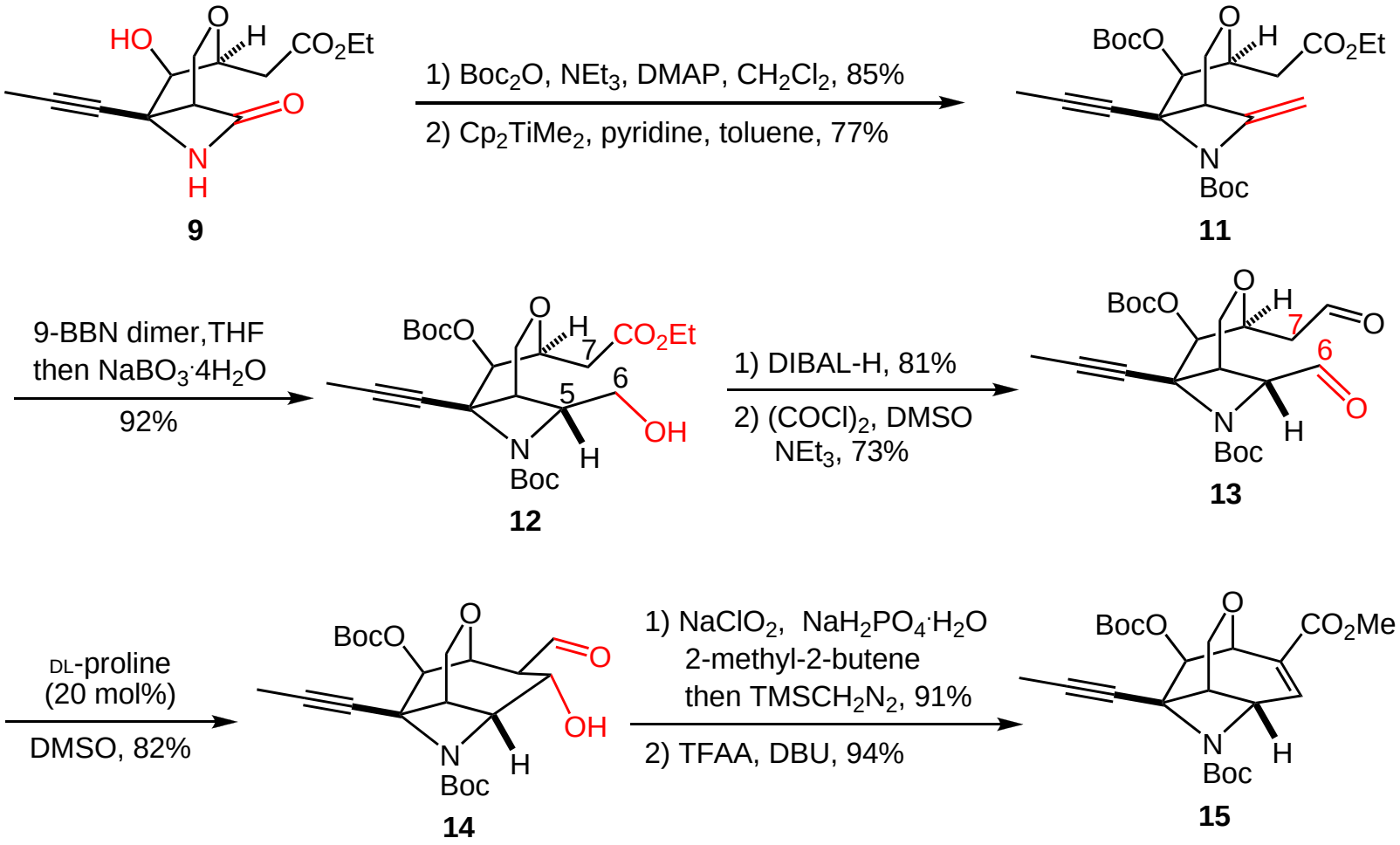
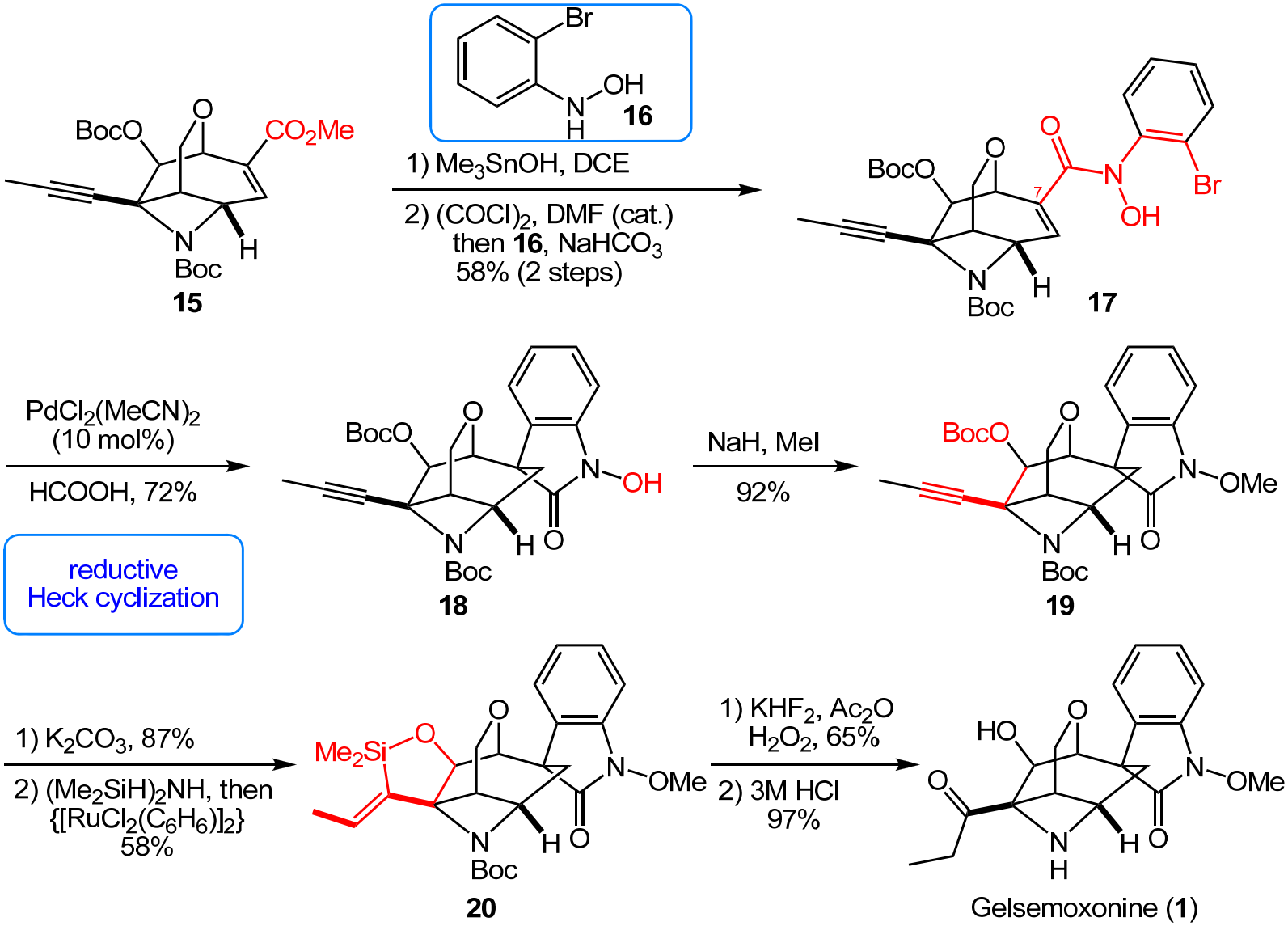
C(6)-C(7) Ring Closure

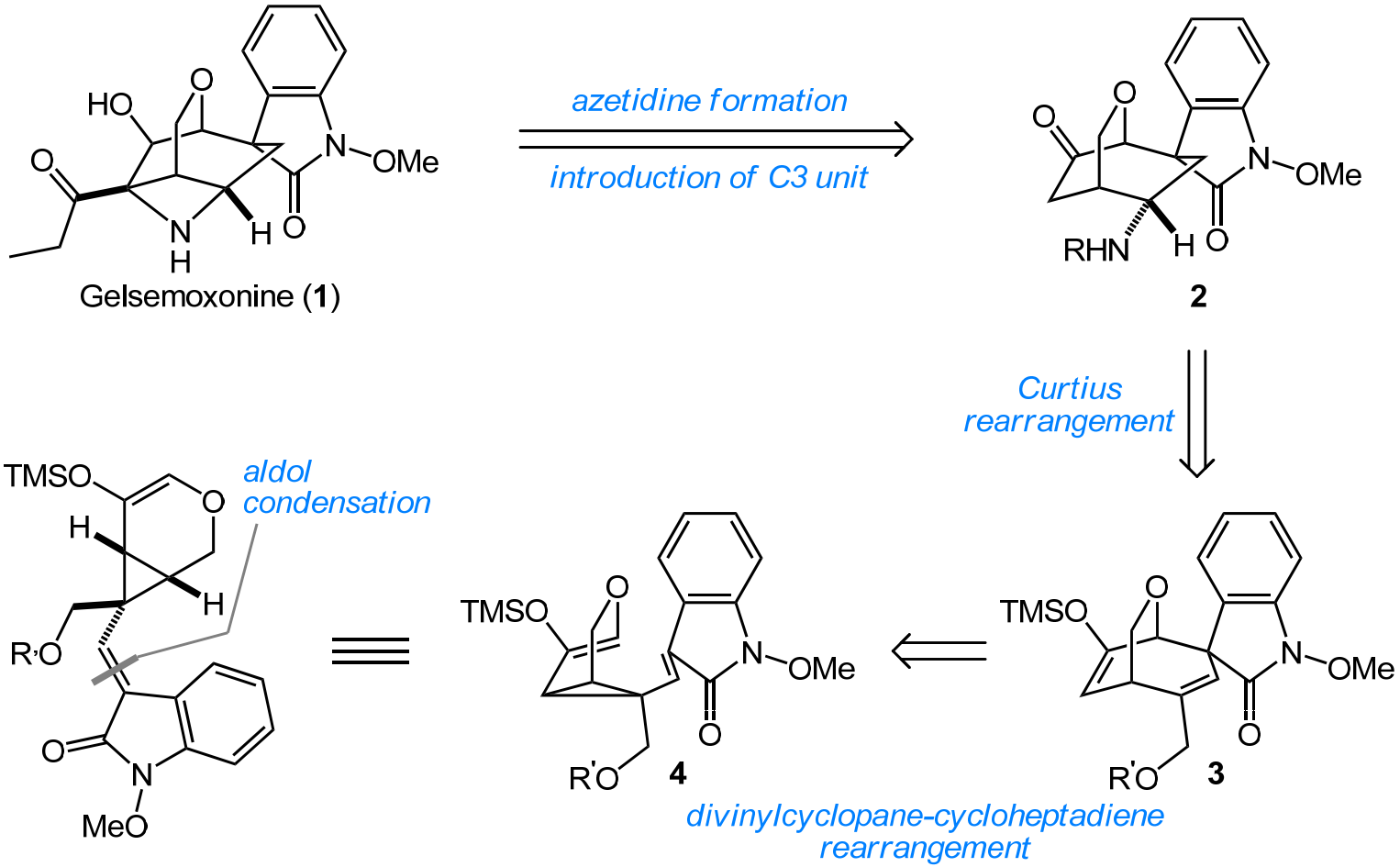


Completion of the Synthesis



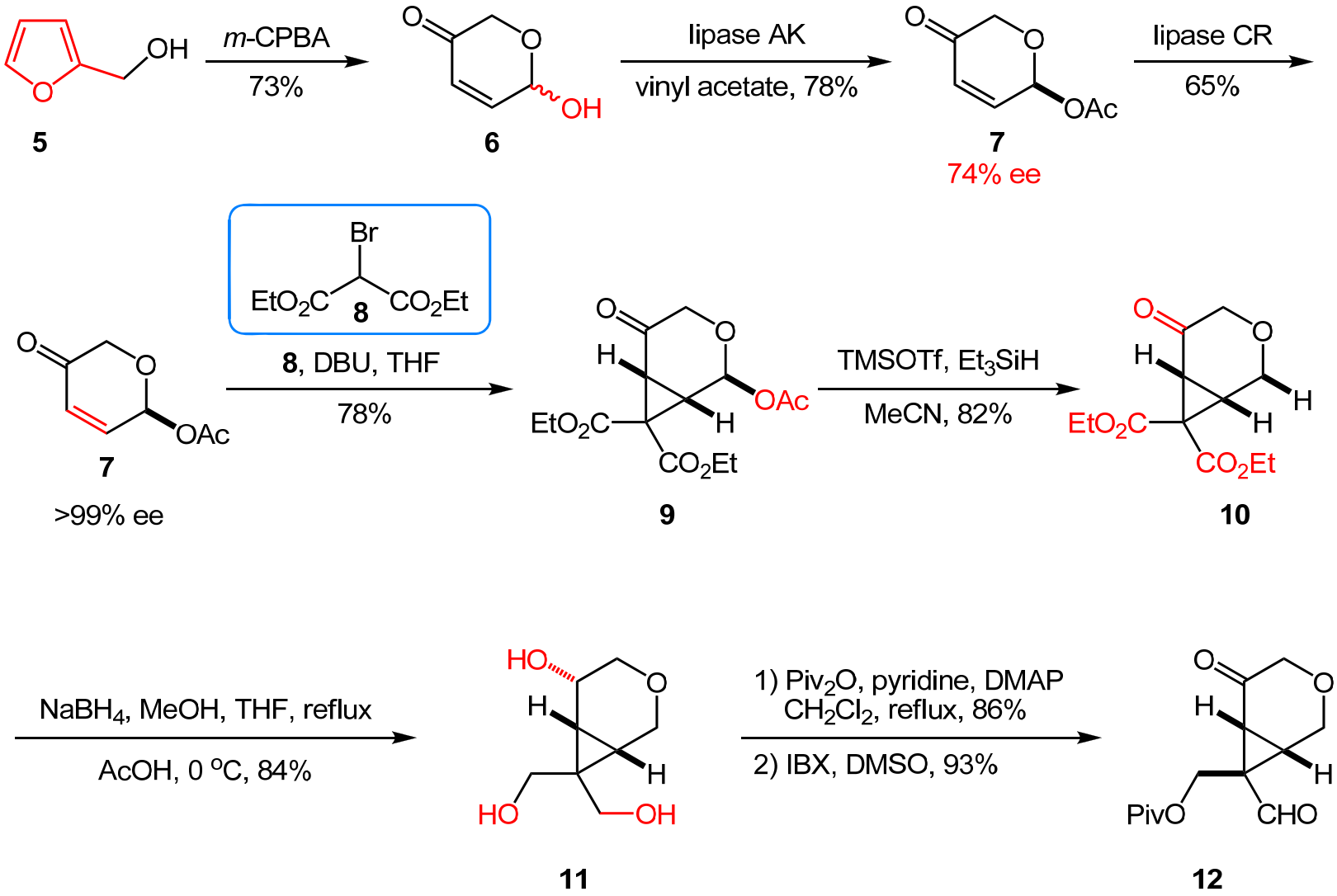
Fukuyama's Method

Retrosynthetic Analysis

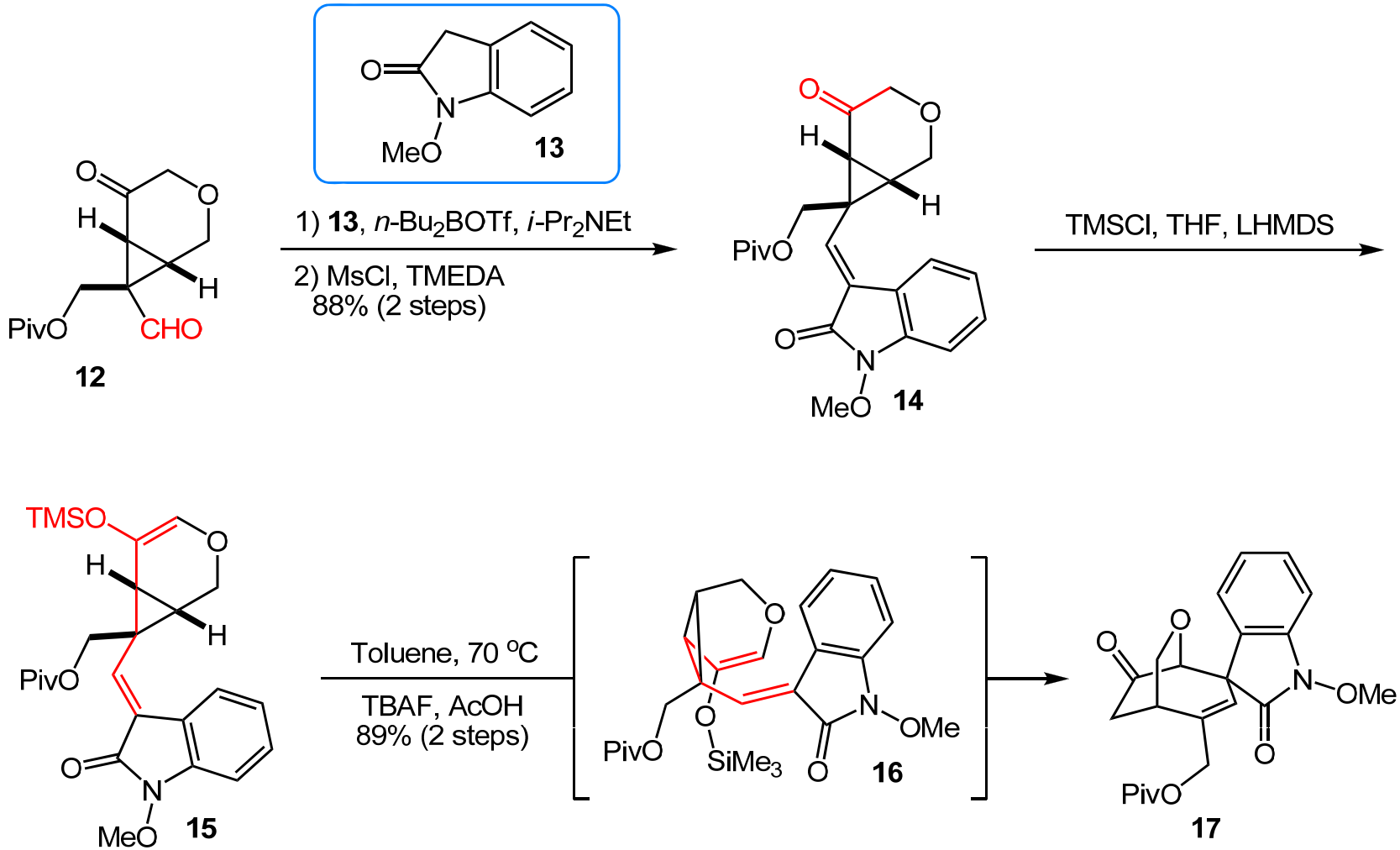


Fukuyama, T. *et al. J. Am. Chem. Soc.* **2011**, *133*, 17634.

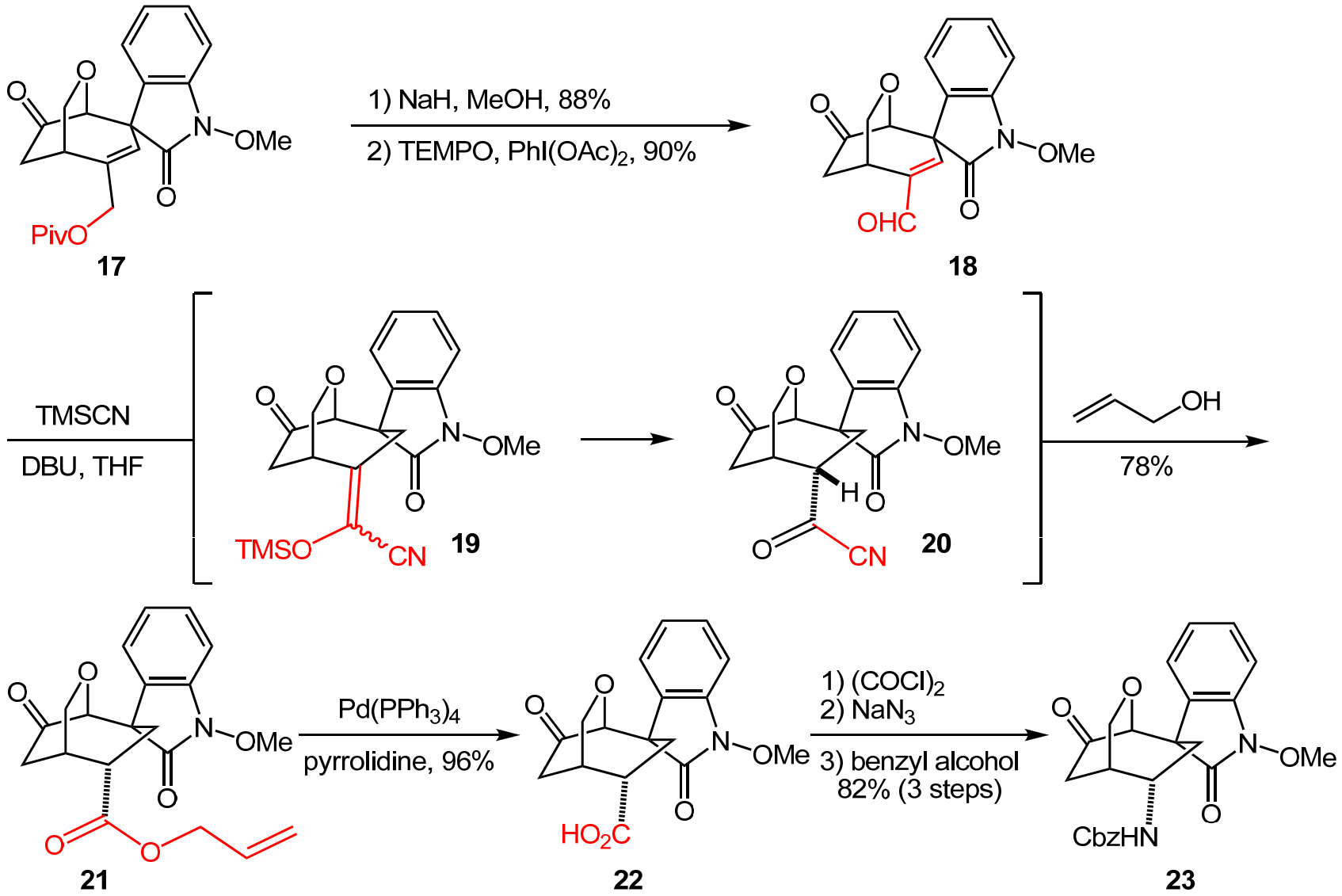
Divinylcyclopropane-Cycloheptadiene Rearrangement



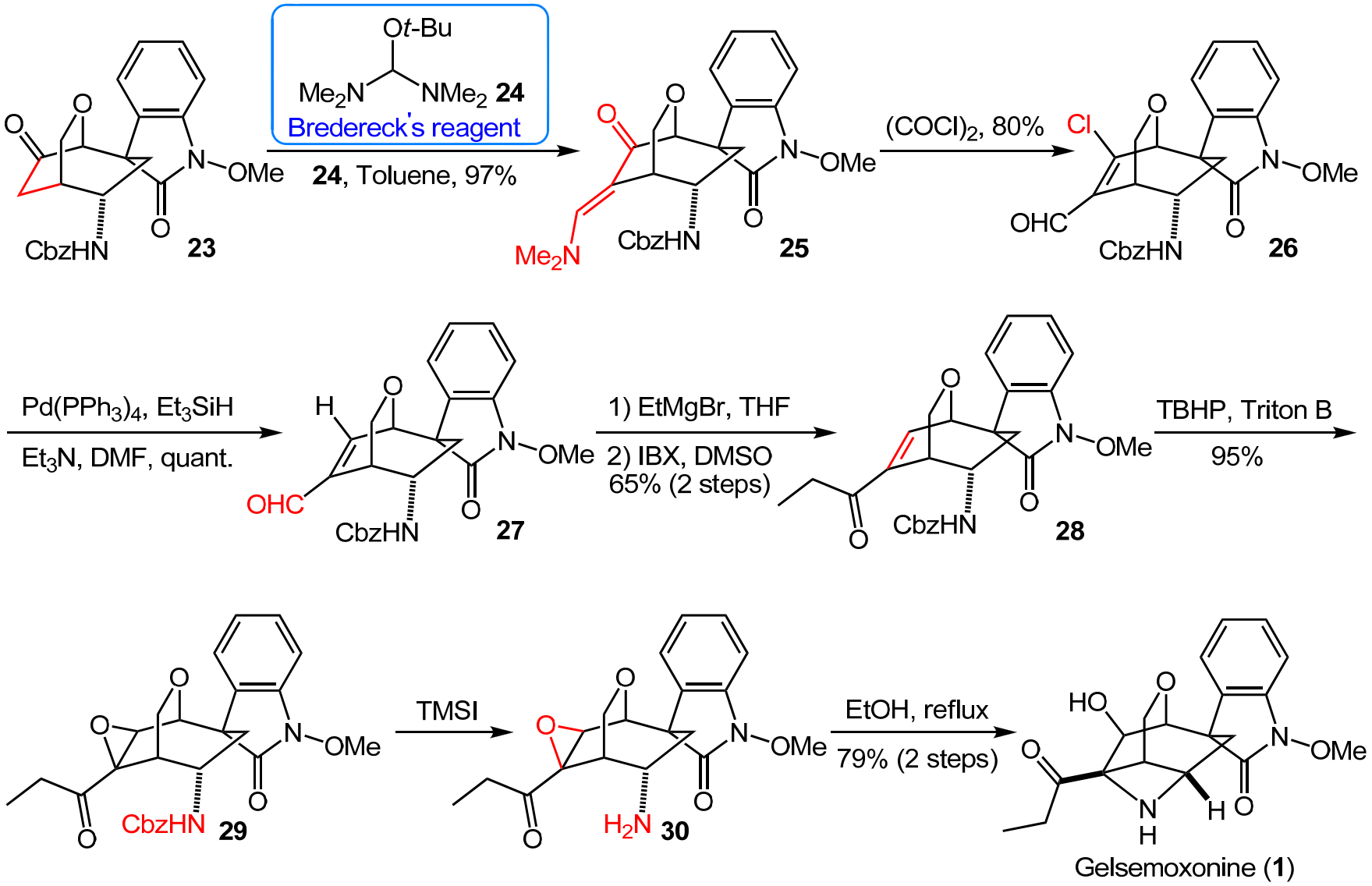
Divinylcyclopropane-Cycloheptadiene Rearrangement



Stereoselective Introduction of a Nitrogen Atom

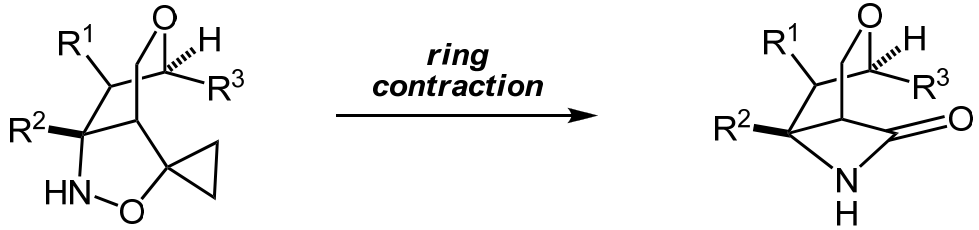


Completion of the Synthesis

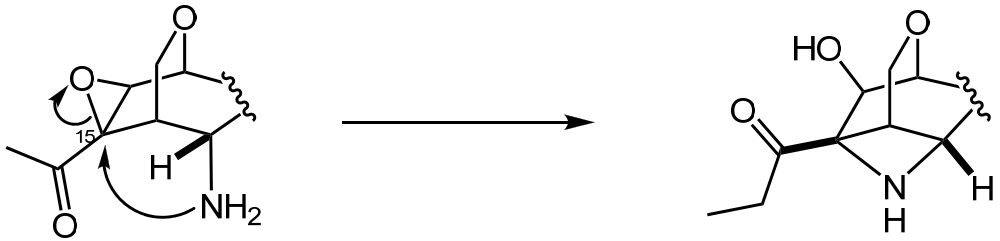


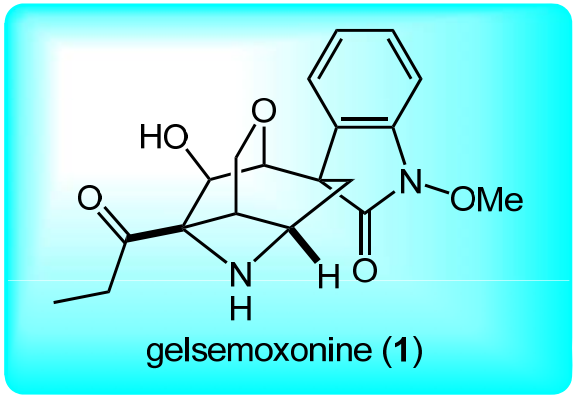
Summary

Carreira's Method



Fukuyama's Method





gelsemoxonine (**1**)

Plants from the genus *Gelsemium* have proven to be a rich source of structurally diverse monoterpenoid indole alkaloids. The compact structures of these natural products have inspired multiple generations of chemists to develop strategies for their synthesis. Of the three known *Gelsemium* species, extracts of *Gelsemium elegans benth* have found use in traditional Asian medicine for over a thousand years. It is from this source that in 1991 Clardy isolated the alkaloid Gelsemoxonine (**1**). Revision of the originally proposed structure based on X-ray crystallographic analysis revealed that it includes an azetidine embedded within a compact polycyclic scaffold. Furthermore, Gelsemoxonine harbors six contiguous, densely packed stereocenters, including a quaternary carbon at the spirocyclic junction and a fully substituted carbon within the azetidine. These features, along with its medical relevance, render it a veritable target for study. Herein, we report a total synthesis of Gelsemoxonine that utilizes a strategic ring contraction of a spirocyclopropane isoxazolidine to provide access to the azetidine. An additional salient feature of the synthesis is the introduction of the congested quaternary oxindole stereocenter at C(7) by a diastereoselective reductive Heck cyclization.

In summary, we have achieved the total synthesis of Gelsemoxonine (**1**) in a sequence of 21 linear steps starting from aldehyde **3**. The synthesis relies on the ring contraction of a spirocyclopropane isoxazolidine to deliver a *β*-lactam intermediate, which was further used to build up the azetidine ring of Gelsemoxonine. Additional salient features of the synthesis include a diastereoselective reductive Heck cyclization for the construction of the oxindole ring and directed hydrosilylation of a triple bond to generate the ethyl ketone. Over the course of the synthesis, we have established the use of the ring contraction reaction of spirocyclopropane isoxazolidine to give a *β*-lactam in a complex setting. This little-studied, mechanistically intriguing reaction is sure to find additional tactical applications in the synthesis of complex structures incorporating azetidines.