

# Literature Report 4

## Divergent Entry to Gelsedine-Type Alkaloids: Total Syntheses of (-)-Gelsedilam, (-)-Gelsenicine, (-)-Gelsedine, and (-)-Gelsemoxonine

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**Checker: Xiao-Yong Zhai**

**Date: 2018-10-8**

Wang, P.; Gao, Y.; Ma, D.  
*J. Am. Chem. Soc.* **2018**, *140*, 11608–11612.

# CV of Prof. Dawei Ma

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## *Research:*

- Total synthesis of complex natural product.
- New synthetic methodologies: Copper-catalyzed coupling reactions; Organocatalyzed asymmetric Michael addition, Henry reaction; Intramolecular dearomative oxidative coupling.
- Biochemistry.

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## *Background:*

- **1980–1984** B.S., Shandong University
- **1984–1989** Ph.D., Shanghai Institute of Organic Chemistry (Xiyun Lu)
- **1990–1994** Postdoc., University of Pittsburgh and Mayo Clinic, U.S.A.
- **1995–now** Prof., Shanghai Institute of Organic Chemistry

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# Introduction

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Gelsemium (钩吻属)



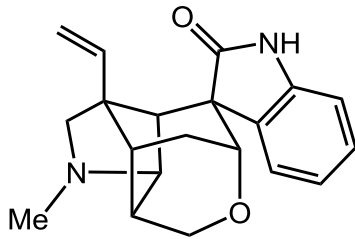
(断肠草)

- The genus *Gelsemium* plants are native to subtropical and tropical Asia and North America;
- Recognized as poisonous species and have been widely used in traditional Asian medicine to treat skin ulcers, dermatitis, and various ailments.

Kitajima, M.; Arai, Y.; Takayama, H.; Aimi, N. *Proc. Jpn. Acad., Ser. B* **1998**, 74, 159.

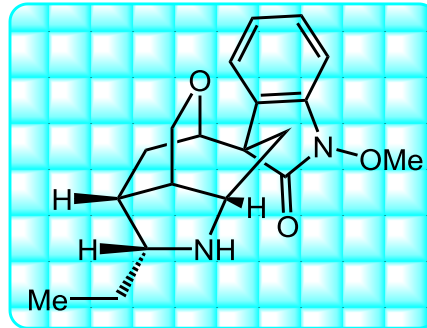
# Three Subclasses of Gelsemium Alkaloids

## Gelsemine-type

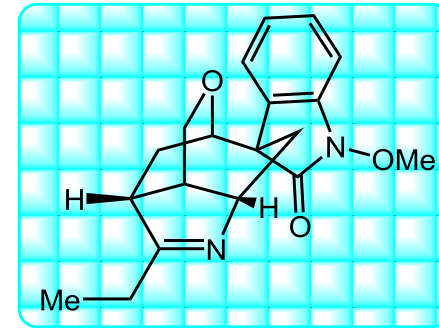


gelsemine (1)

## Gelsedine-type

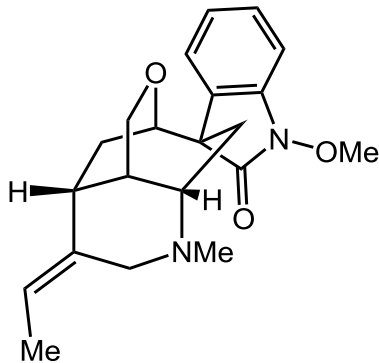


(-)-gelsedine (3)

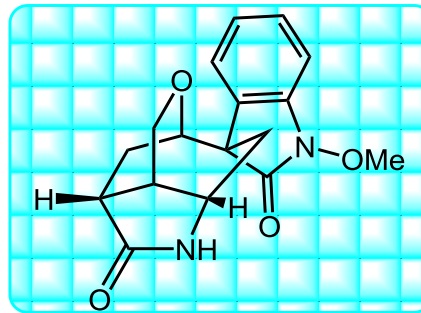


(-)-gelsenicine (4)

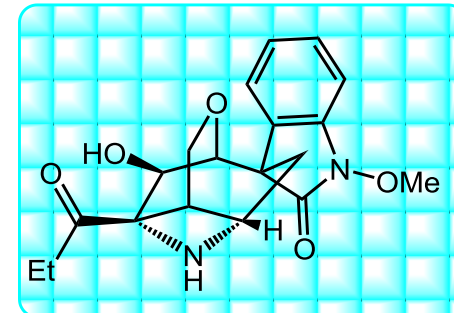
## Humantenine-type



humantenine (2)

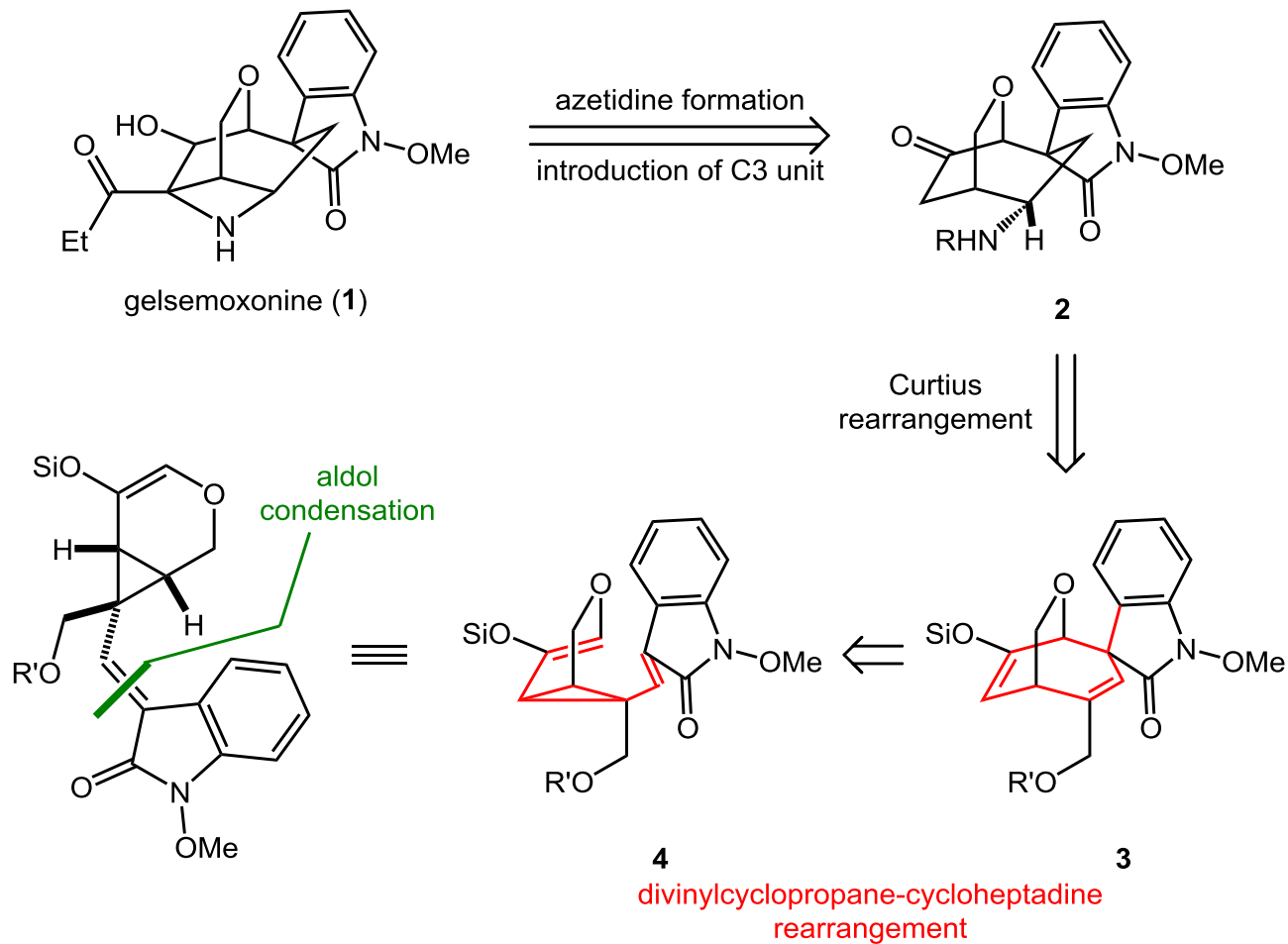


(-)-gelsedilam (5)



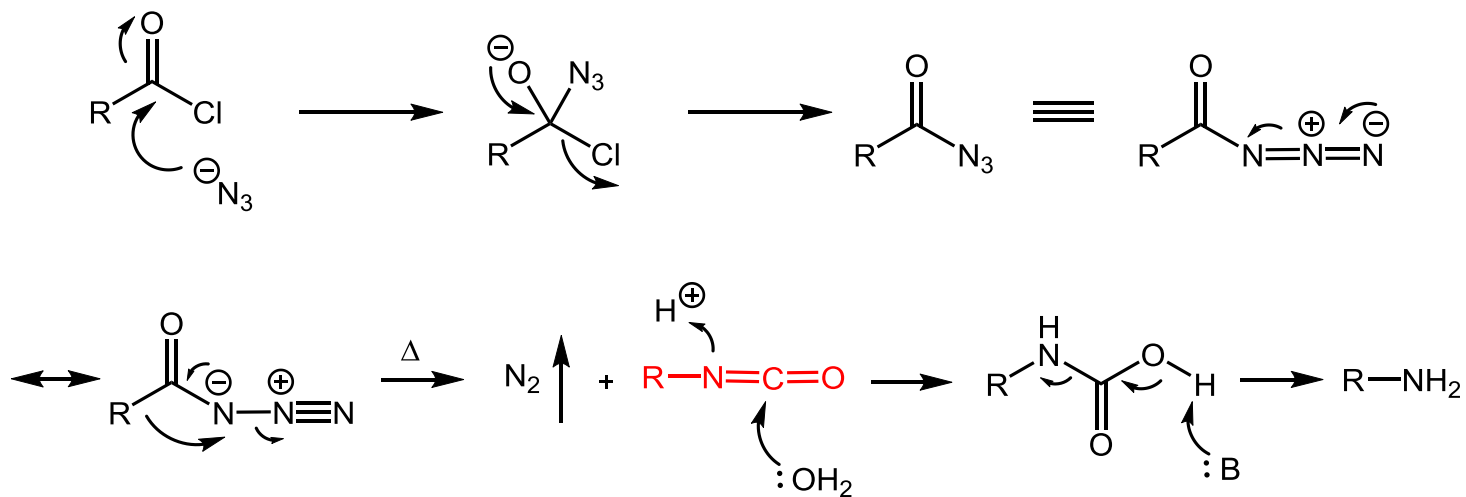
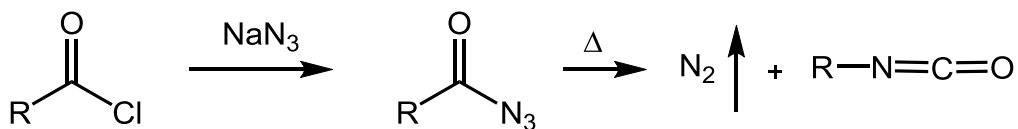
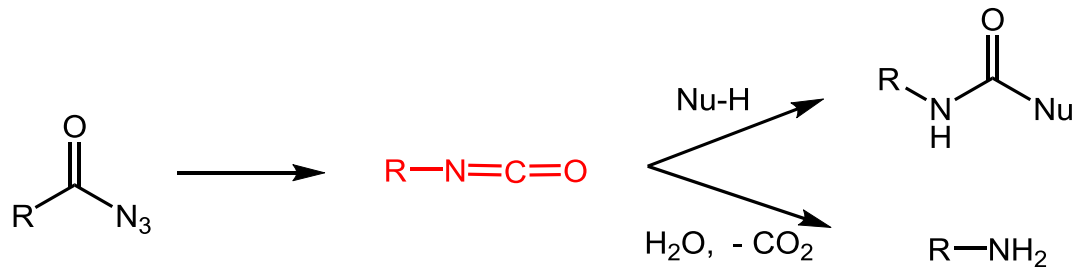
(-)-gelsemoxonine (6)

# Retrosynthetic Analysis of Gelsemoxonine

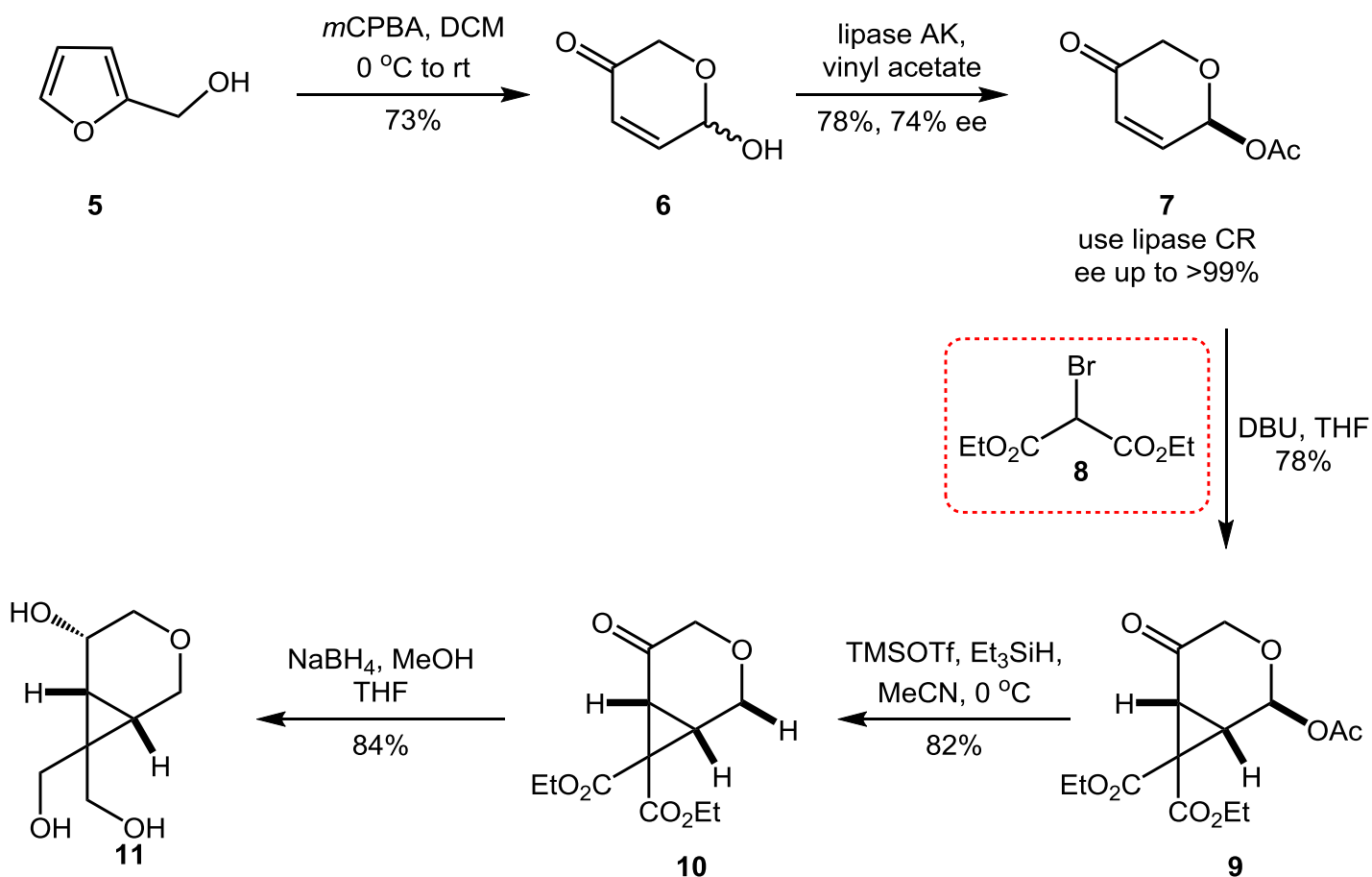


Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 17634.

# Curtius rearrangement

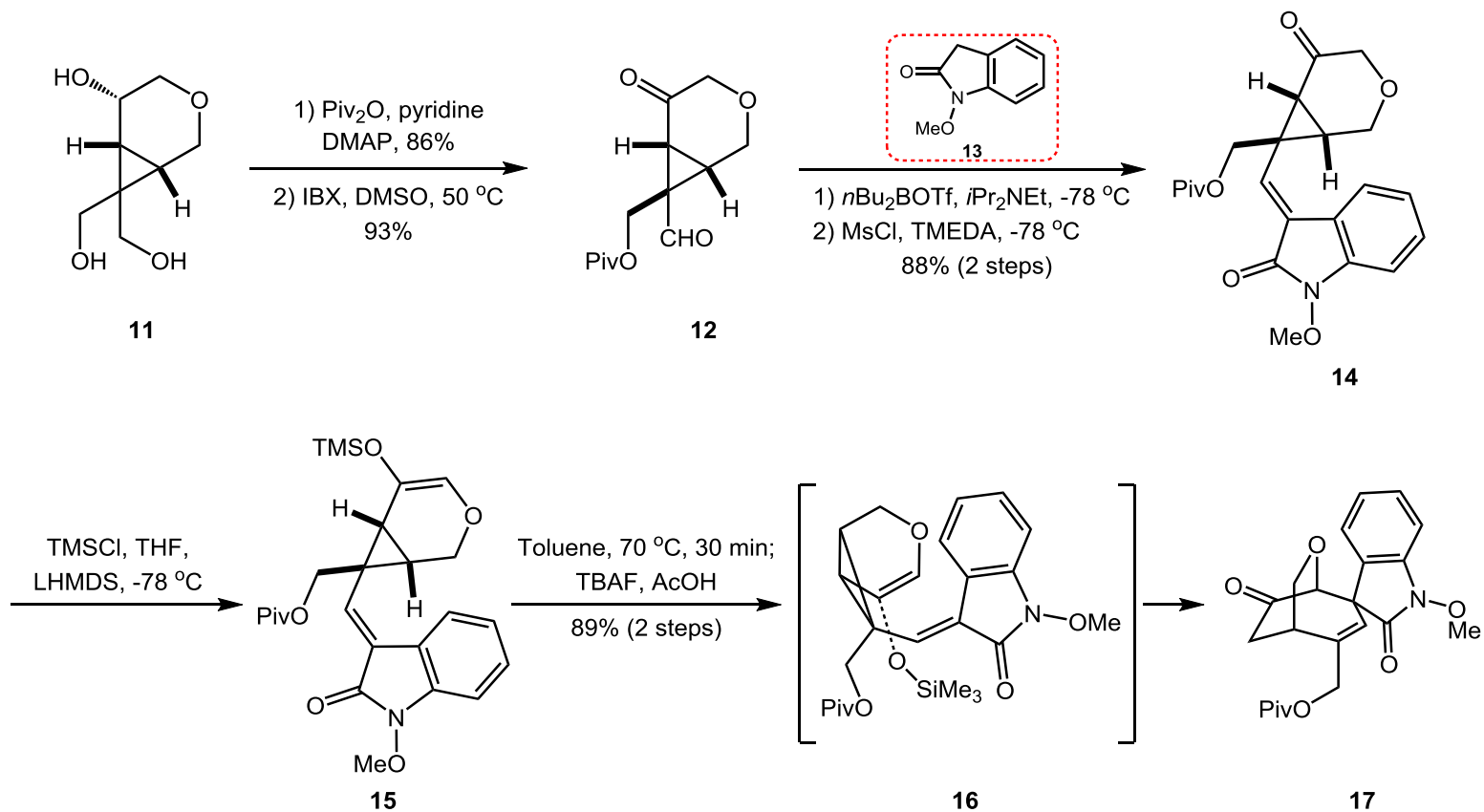


# Synthesis of Compound 11

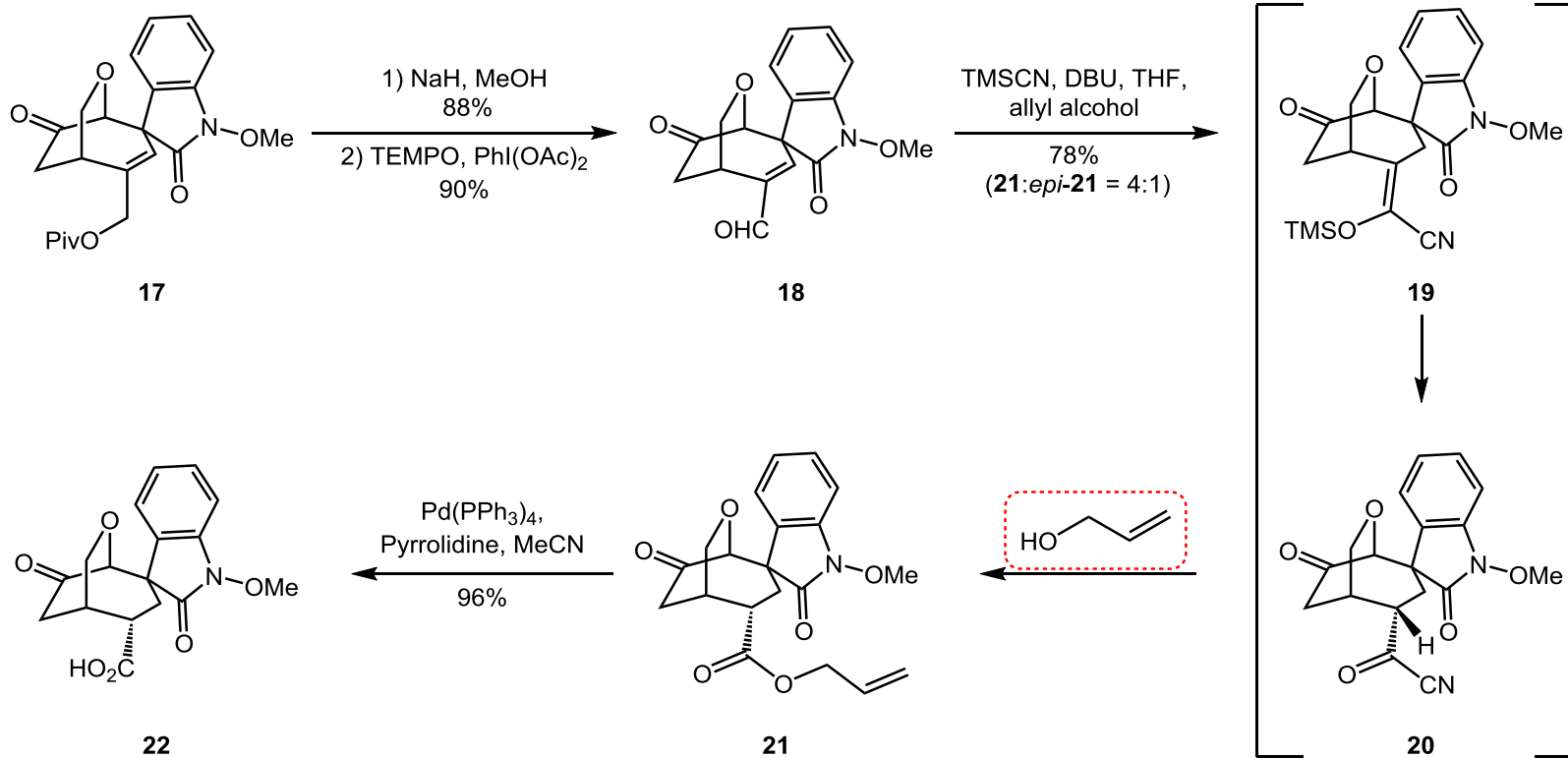




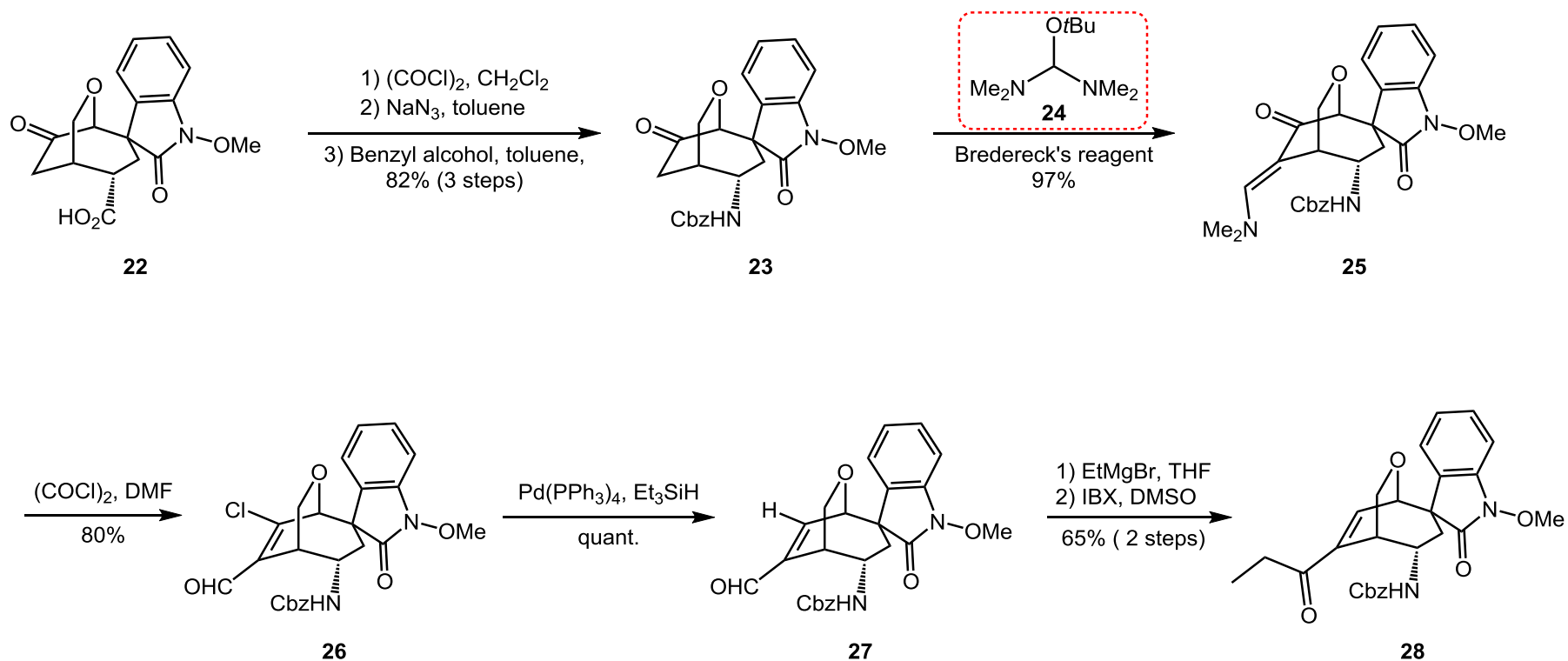
# Synthesis of Compound 17



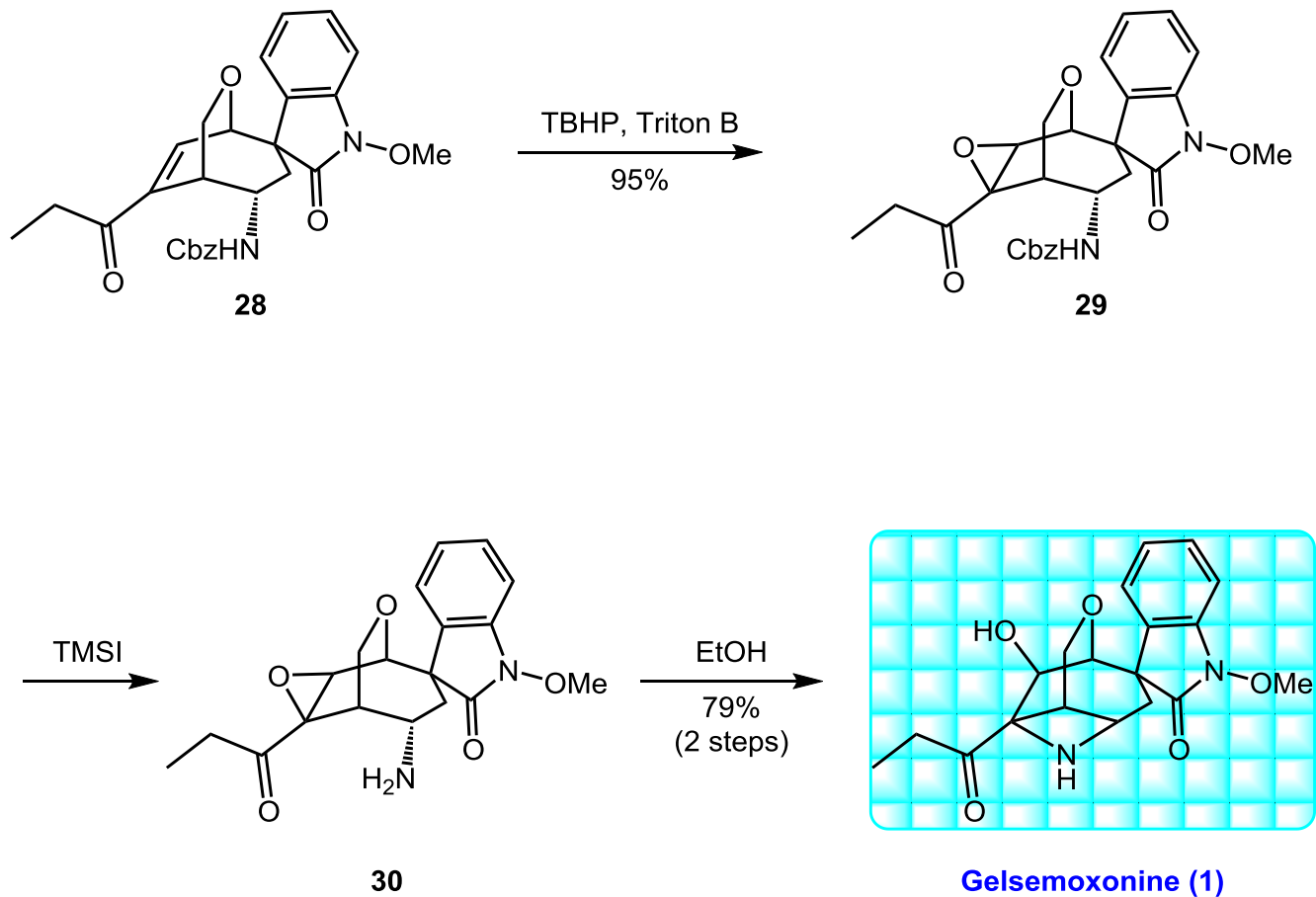
# Synthesis of Compound 22



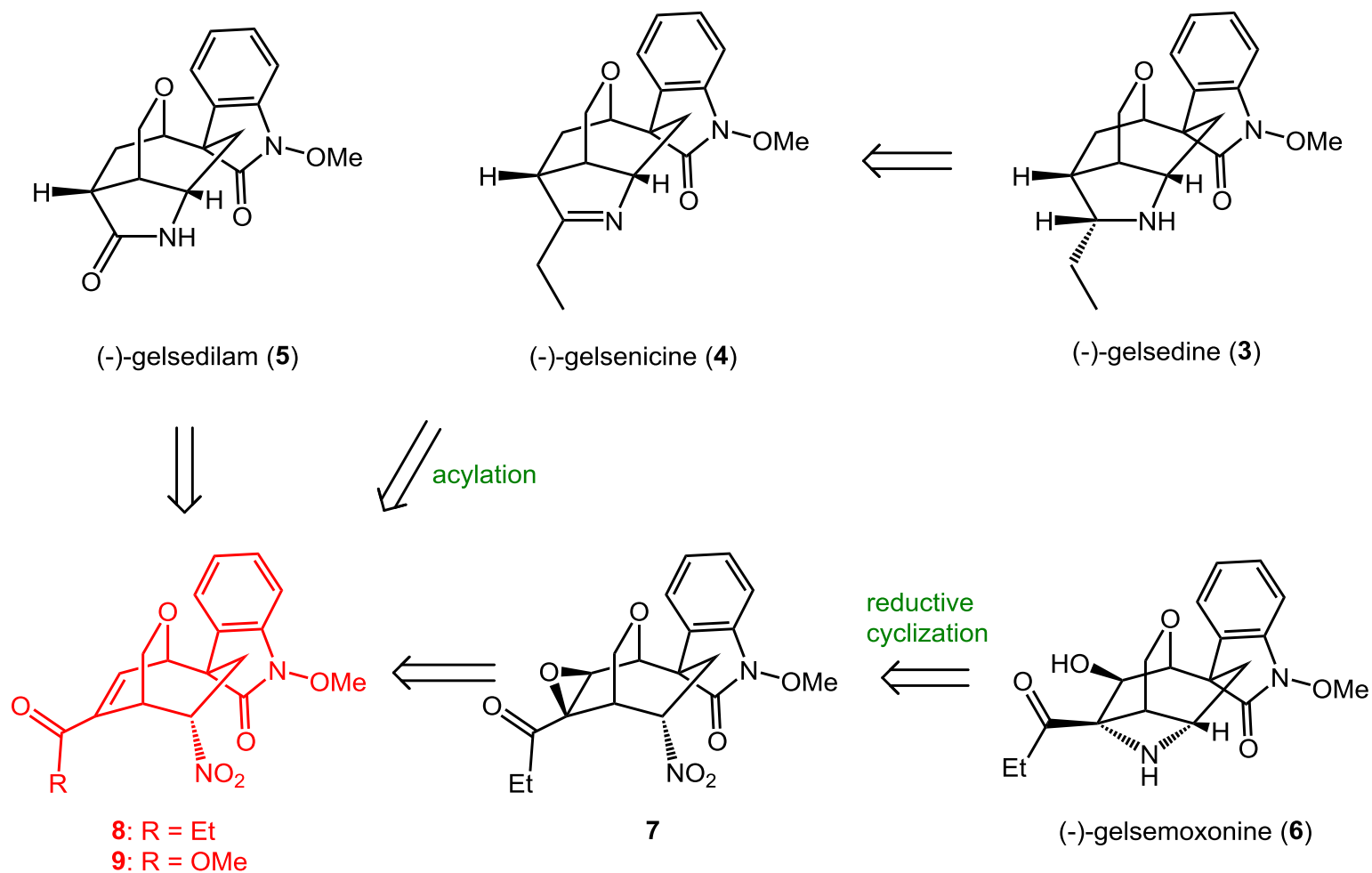
# Synthesis of Compound 28



# Total Synthesis of Gelsemoxonine

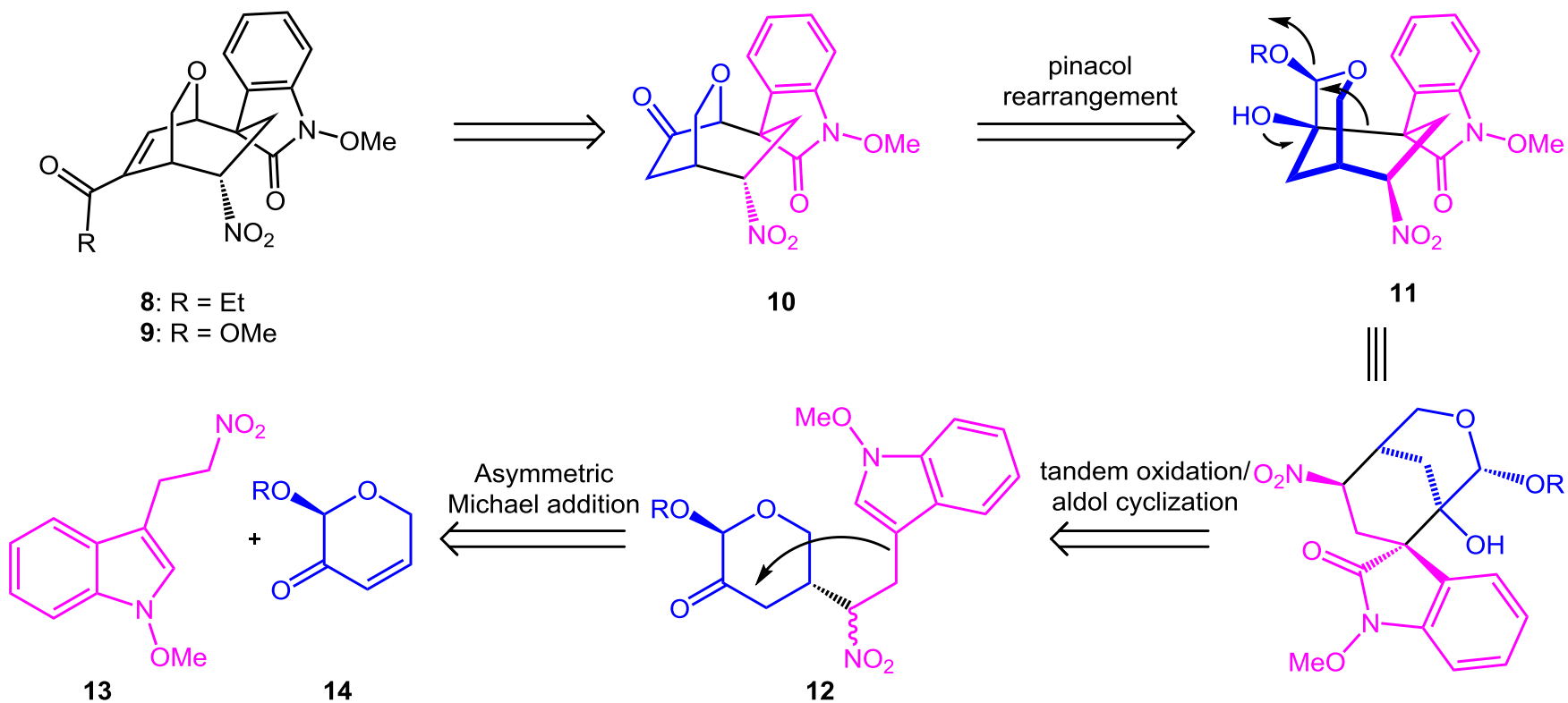


# Retrosynthetic Analysis of Gelsedine-Type Alkaloids

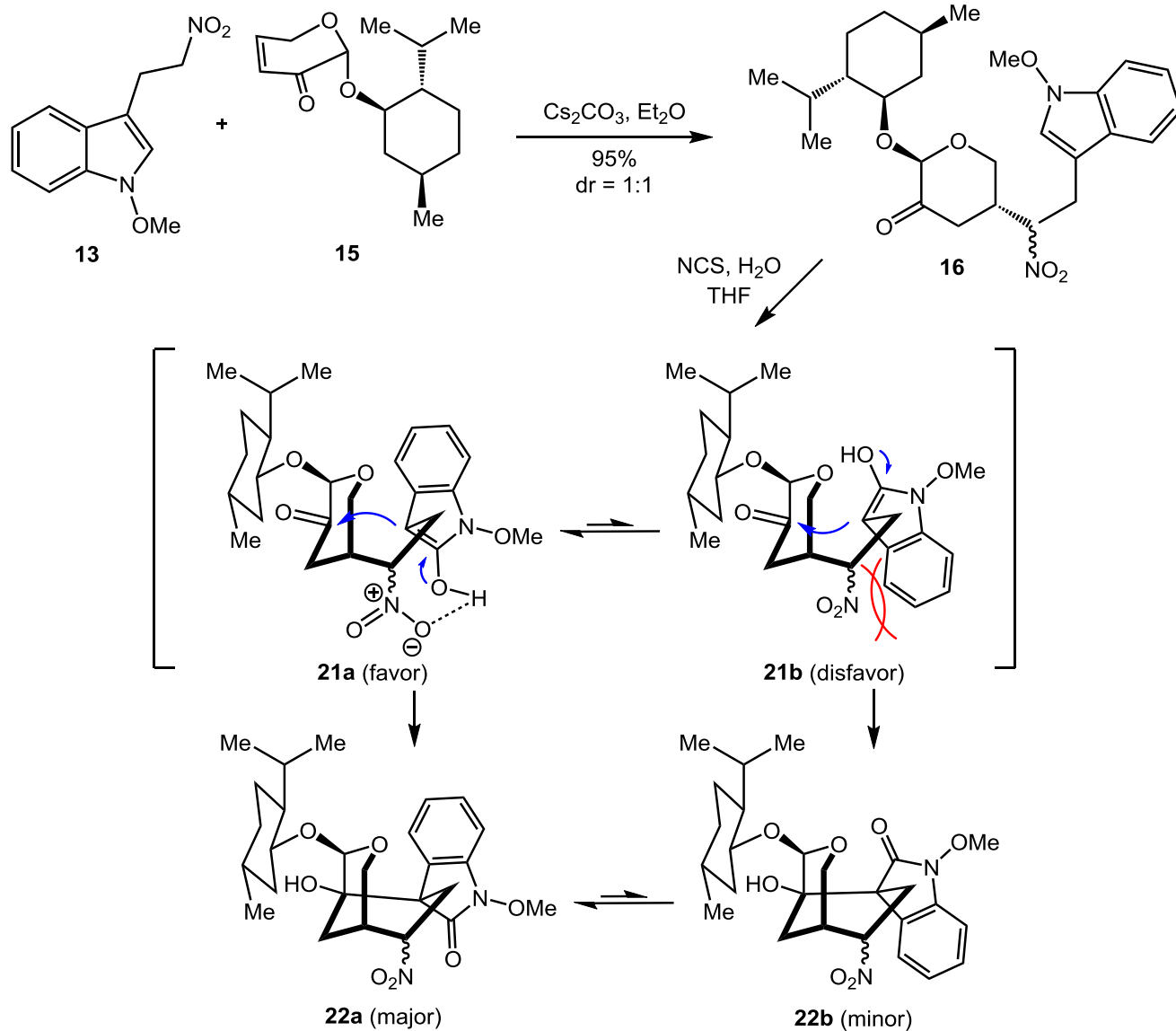


Wang, P.; Gao, Y.; Ma, D. *J. Am. Chem. Soc.* **2018**, *140*, 11608.

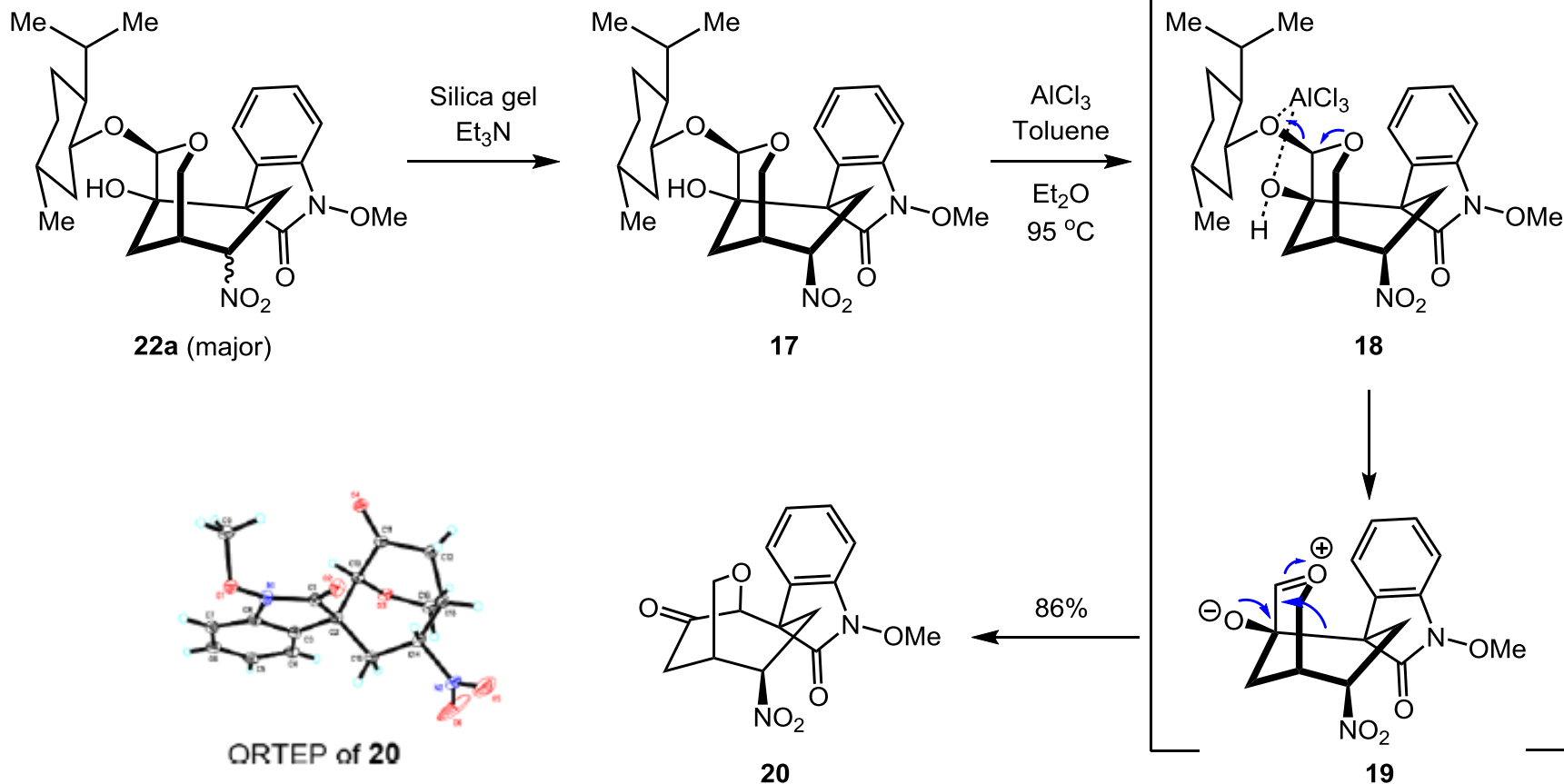
# Retrosynthetic Analysis of Gelsedine-Type Alkaloids



# Synthesis of Compound 22

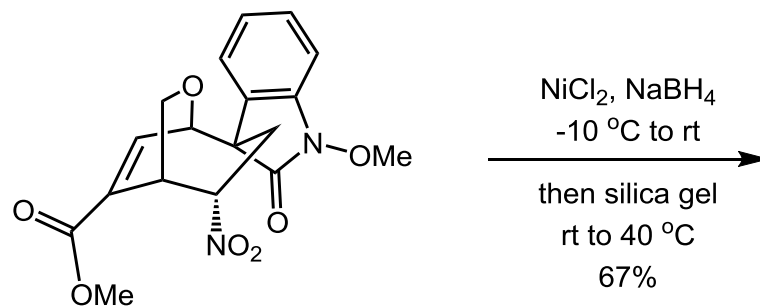
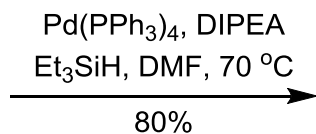
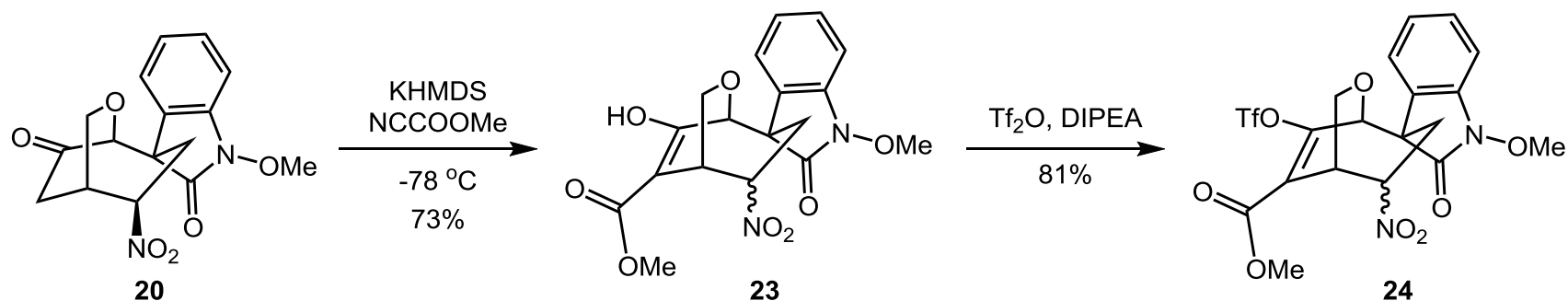


# Synthesis of Compound 20

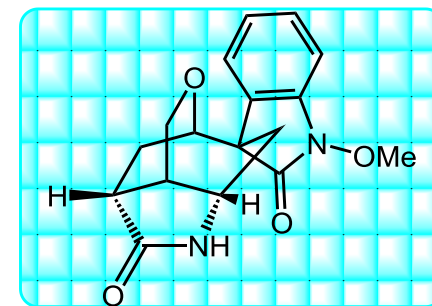




# Total Synthesis of (-)-Gelsedilam (5)

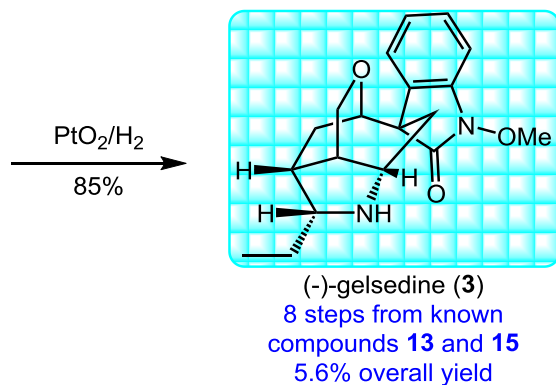
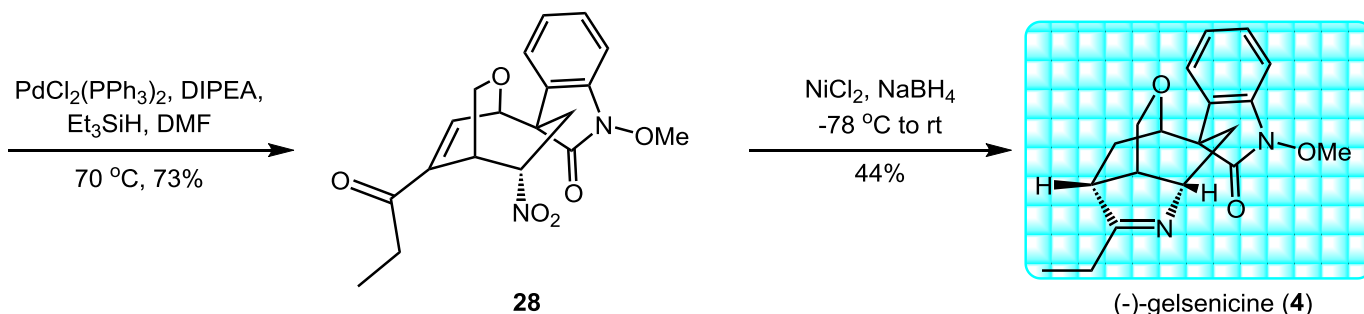
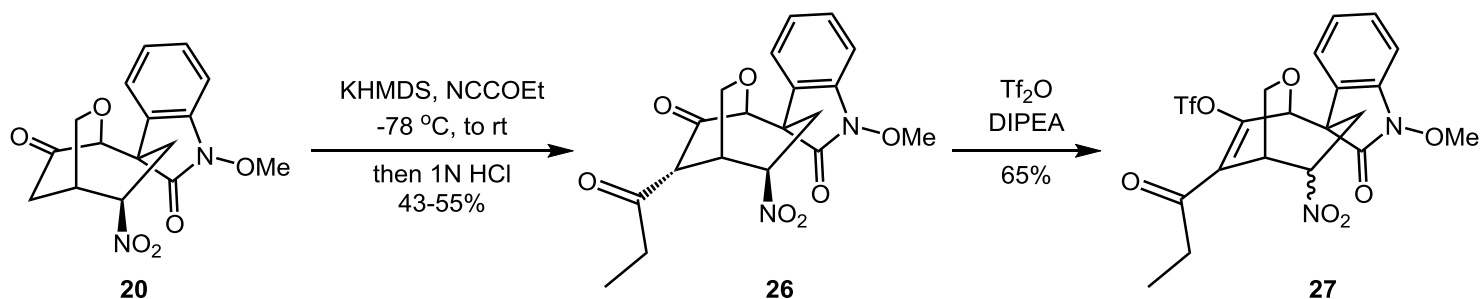


**25**

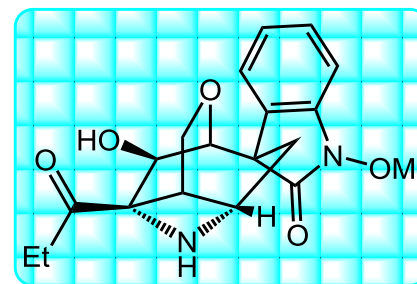
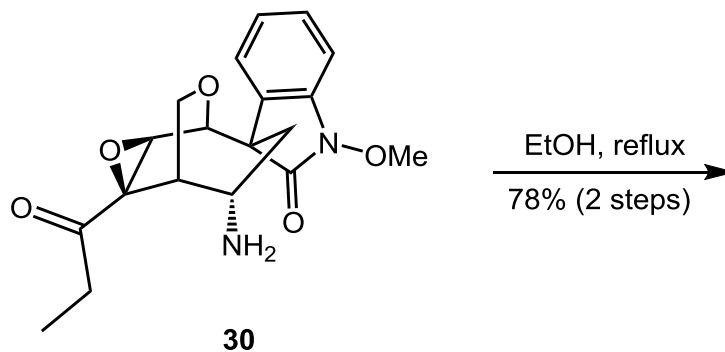
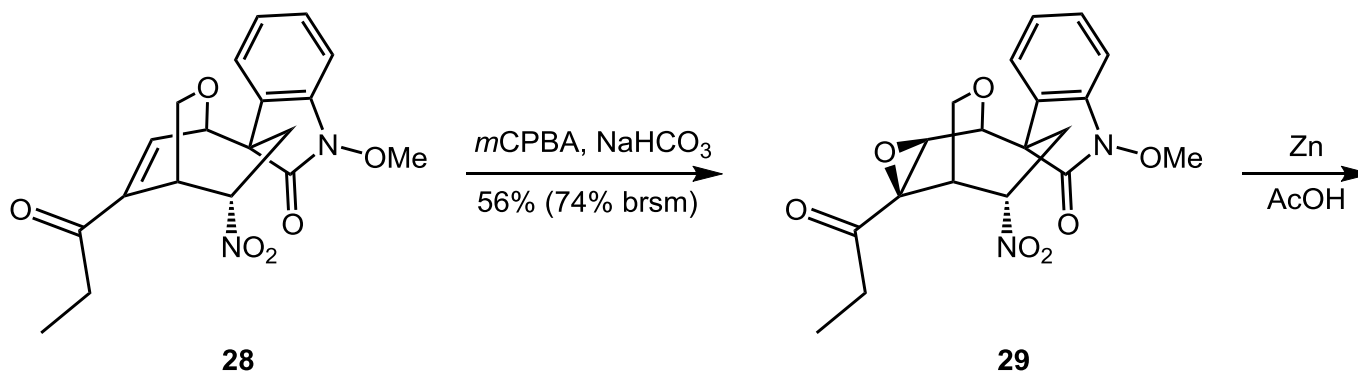


(-)-gelsedilam (**5**)  
7 steps from known  
compounds **13** and **15**  
24% overall yield

# Total Synthesis of Gelsedine-Type Alkaloids



# Total Synthesis of (-)-Gelsemoxonine (6)

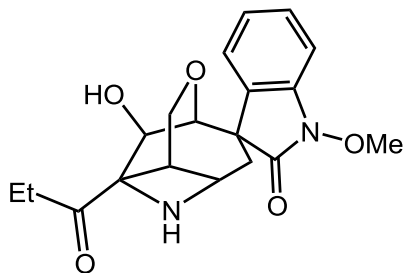


(-)-gelsemoxonine (**6**)

9 steps from known compounds **13** and **15**  
6.6% overall yield

# Summary

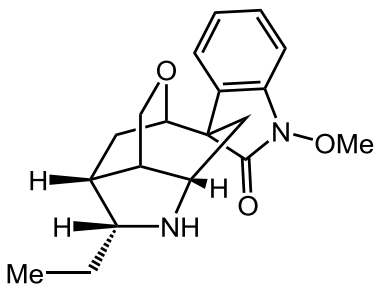
## Fukuyama's work:



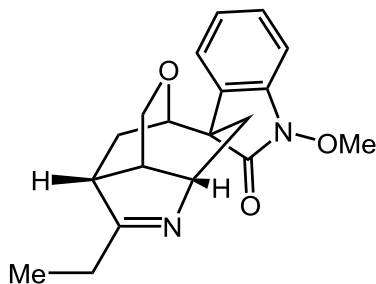
Gelsemoxonine (1)

- The first total synthesis of gelsemoxonine; 2.29% overall yield;
- Divinylcyclopropane-cycloheptadiene rearrangement;
- Redox isomerization via the TMSCN-DBU combination.

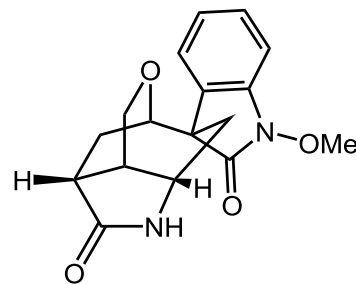
## Ma's work:



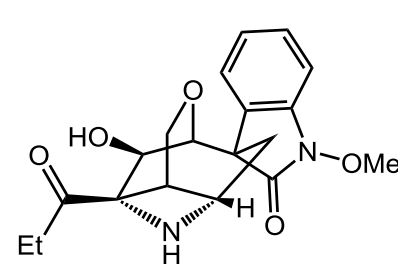
(-)-Gelsedine (3)



(-)-Gelsenicine (4)



(-)-Gelsedilam (5)



(-)-Gelsemoxonine (6)

- Total synthesis of gelsedine-type alkaloids in seven to nine steps; 5.6%-24% yield;
- Asymmetric Michael addition; tandem oxidation/aldol cyclization; pinacol rearrangement.

# The First Paragraph

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Treating human diseases by means of plant extracts has a rich history in traditional medicine all around the world. Plants from the genus Gelsemium, native to subtropical and tropical Asia and North America, are recognized as poisonous species and have been widely used in traditional Asian medicine to treat skin ulcers, dermatitis, and various ailments for over a thousand years. Extensive phytochemical studies on Gelsemium plants have led to the isolation of a series of structurally diverse alkaloids, some of which exhibit a variety of promising therapeutic properties, including analgesic, anti-inflammatory, and immunomodulating characteristics in addition to potent antitumor activity.

# The First Paragraph

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Nevertheless, the narrow therapeutic window of these alkaloids limits their clinical use because of the lack of comprehensive biological profiling, which is largely hampered by synthetic accessibility. Among the five known classes of Gelsemium alkaloids, three subfamilies possess a common spiro-indolinone motif, namely, the gelsemine, humantenine, and gelsedine types.

# The Last Paragraph

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In brief, we developed and implemented a divergent route to gelsedine-type alkaloids that culminated in the total syntheses of (-)-gelsedilam, (-)-gelsedine, (-)-gelsenicine, and (-)-gelsemoxonine in seven to nine steps from known fragments **13** and **15** without using any protecting groups. These synthetic routes feature a number of key elements, including an asymmetric Michael addition and a tandem oxidation/aldol cyclization for the introduction of the quaternary center in the spiro-*N*-methoxyindolinone moiety, an unprecedented oxonium ion-induced pinacol rearrangement to construct the common oxabicyclo[3.2.2]nonane core, and a late-stage heterocyclization process for structural diversity.

# The Last Paragraph

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The above endeavor represents the shortest synthetic routes of gelsedine-type alkaloids to date. The versatility of advanced intermediate **20** would facilitate the total synthesis of a diverse set of structurally related alkaloids as well as unnatural analogues, which should accelerate further investigations of pharmacological action and structure-activity relationships.



# Acknowledgement

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***Thanks  
for your attention***

