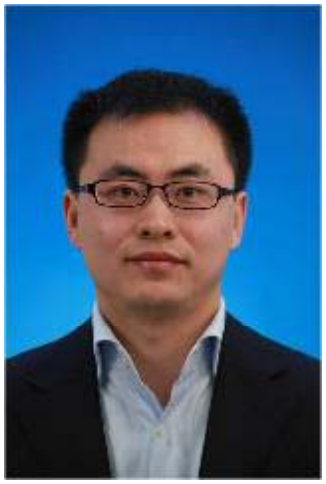
Total Synthesis of Gracilamine

Reporter: Ji Zhou
Checker: Bo Wu
Date: 2014/11/04



Shuanhu Gao
East China Normal University

Gao, S. *et al.*
Angew. Chem. Int. Ed. **2014**, *53*, 9539.

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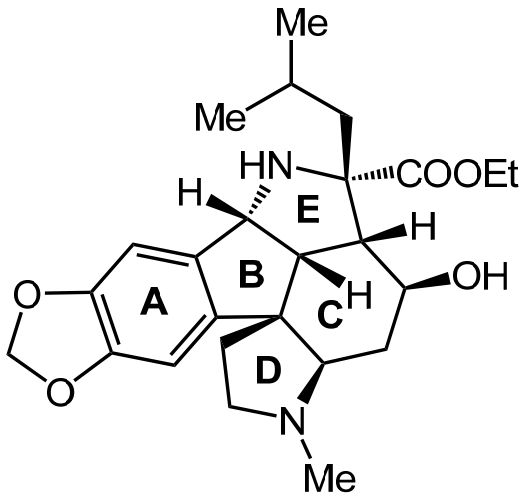
Introduction



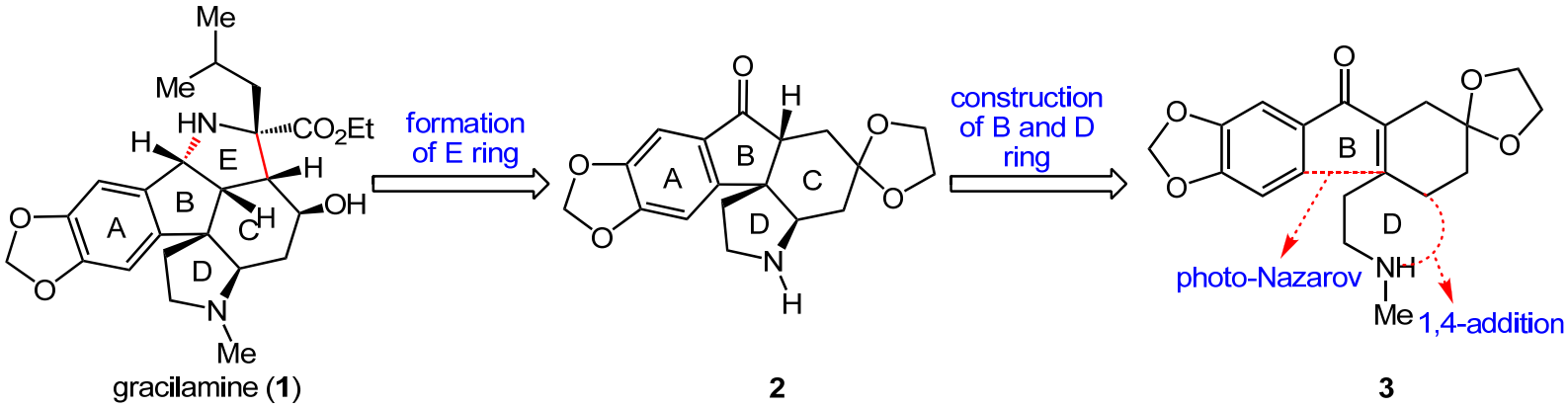
Gracilamine (**1**)

Galanthus gracilis

- Isolated from the *Galanthus gracilis* in 2005 by Unver and Kaya
- These alkaloids have shown significant biological effects, ranging from antitumor, antiviral, and antiinflammatory activities to immunosti-mulatory and acetylcholinesterase inhibitory activities

Total Synthesis by Gao's Group

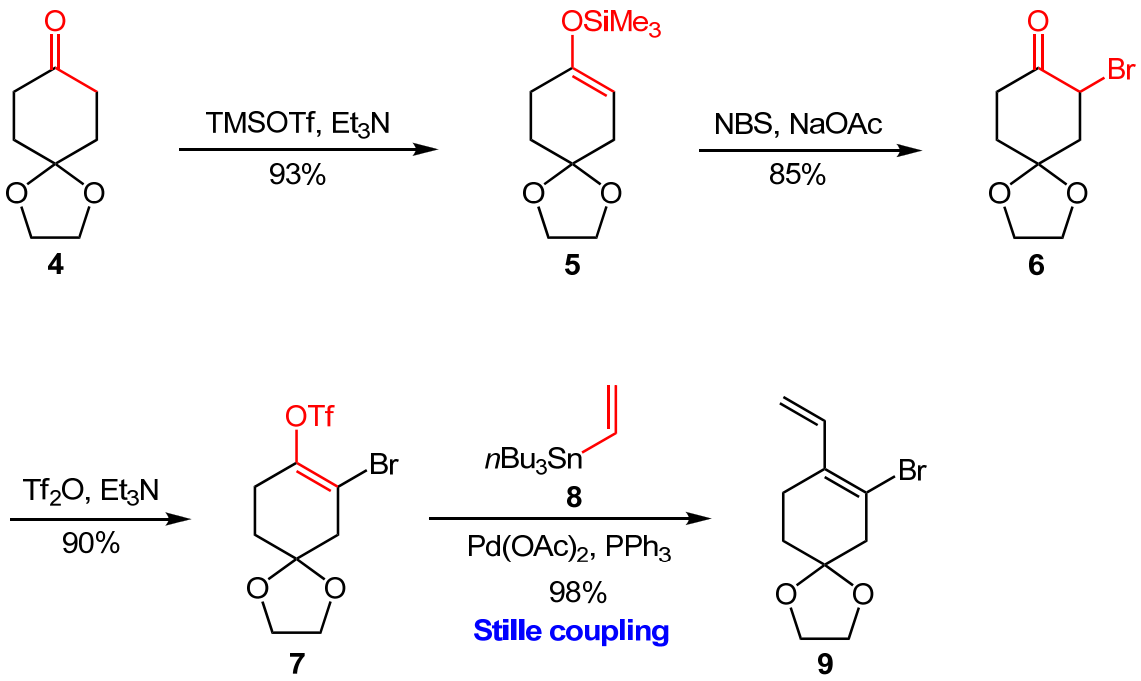
Retrosynthetic Analysis



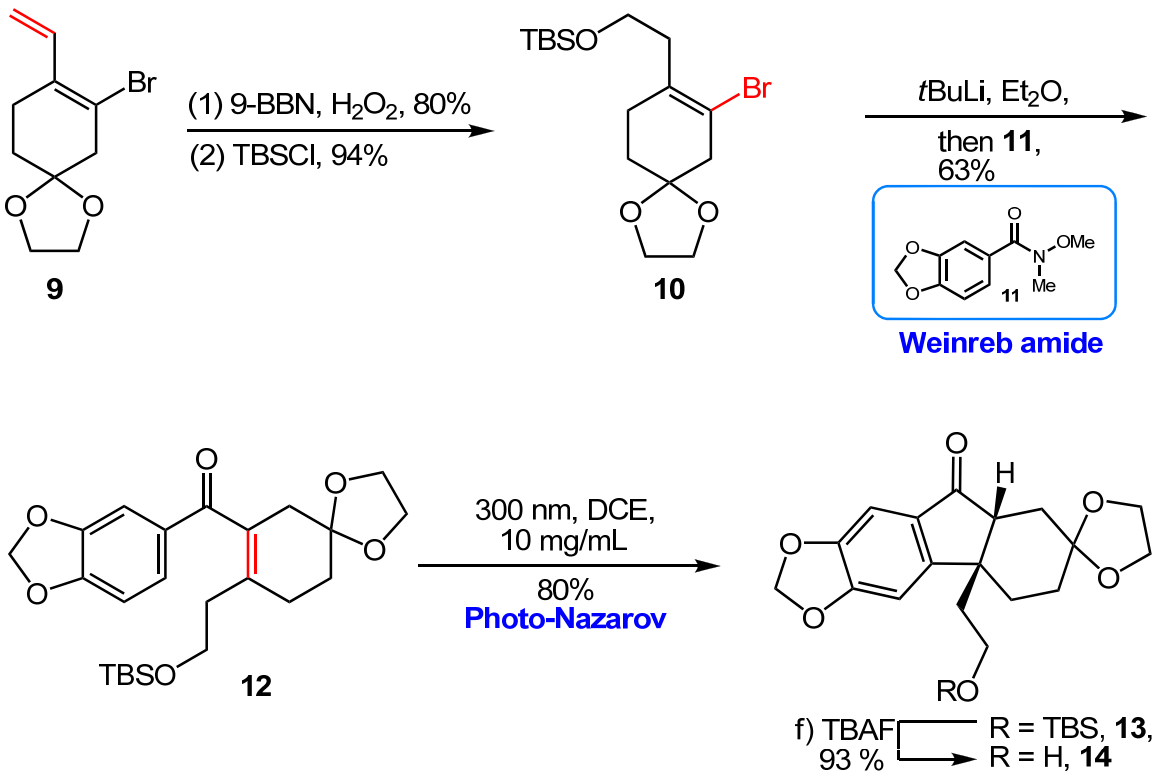
- Mild photo-Nazarov reaction to form the B ring
- 1, 4-Addition to form the D ring
- Intramolecular Mannich reaction to form the E ring

Gao, S. *et al*. *Angew. Chem. Int. Ed.* **2014**, *53*, 9539.

Total Synthesis by Gao's Group

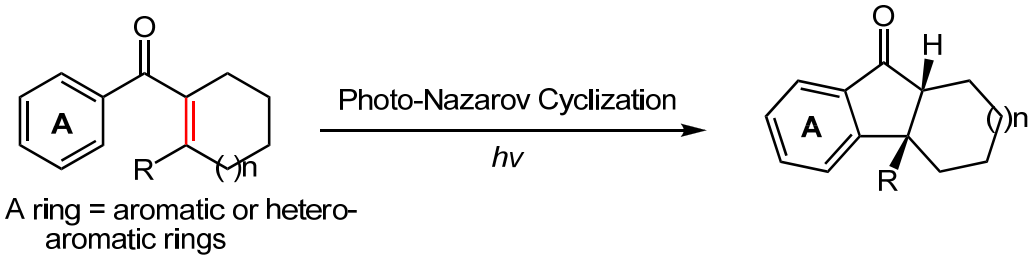


Total Synthesis by Gao's Group

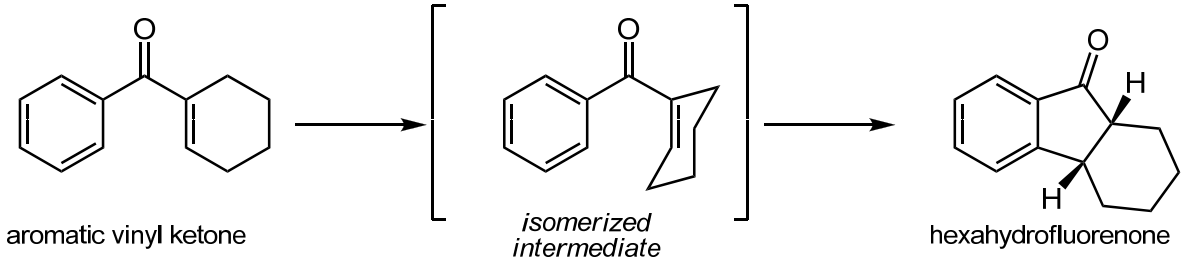


Total Synthesis by Gao's Group

Photo-Nazarov Reaction



A ring = aromatic or hetero-aromatic rings



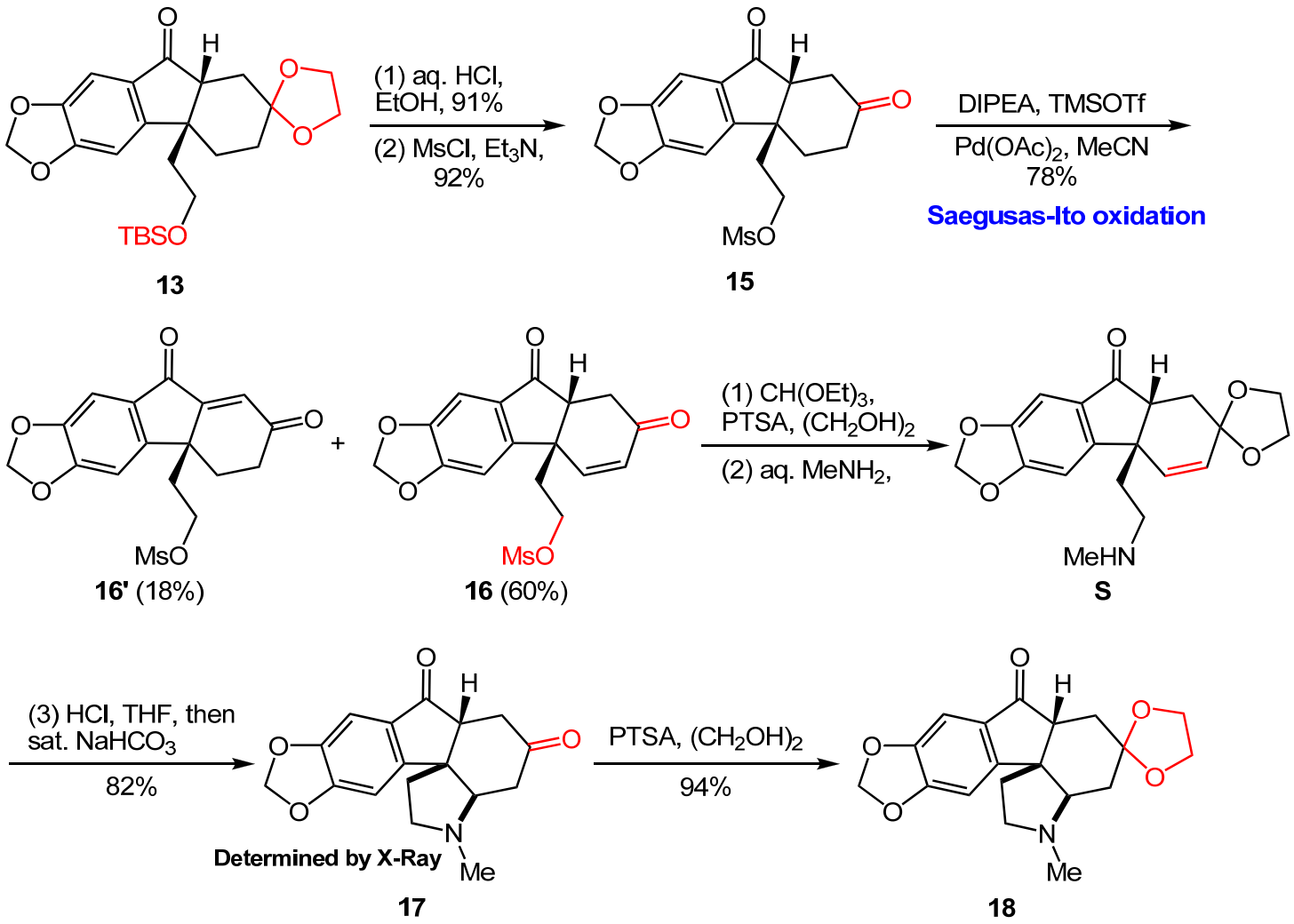
aromatic vinyl ketone

isomerized intermediate

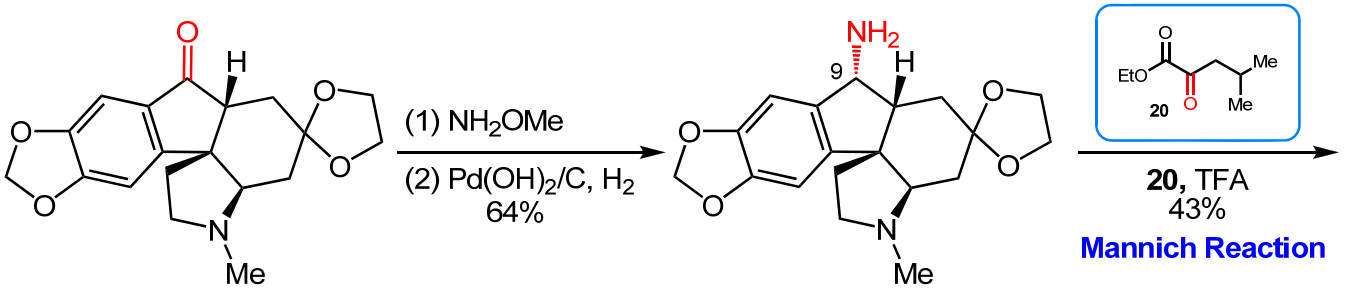
hexahydrofluorenone

A. B. Smith III. *et al. J. Am. Chem. Soc.* **1973**, *95*, 1961.
J. Leitich, I. *et al . J. Photochem. Photobiol. A .* **1991**, *57*, 127.

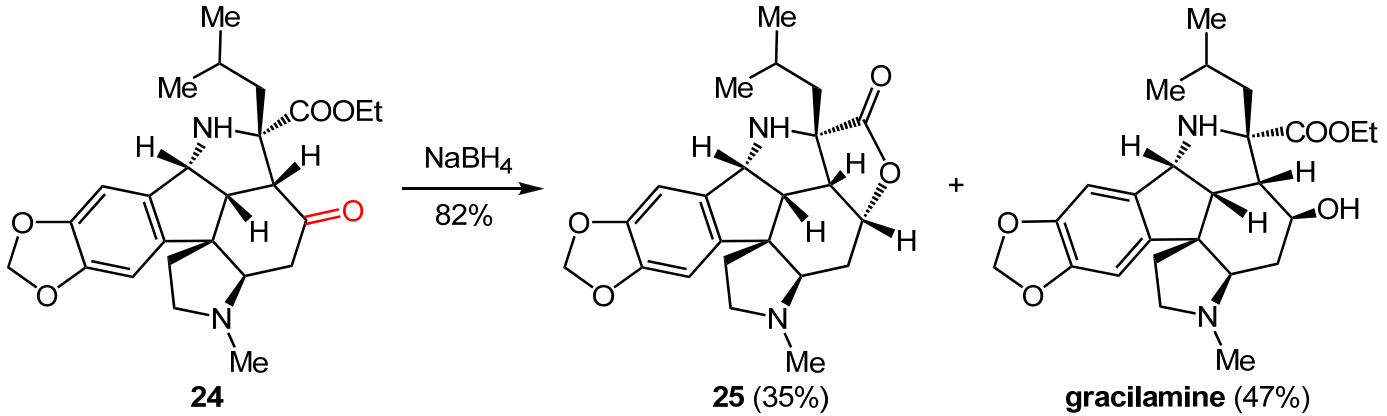
Total Synthesis by Gao's Group



Total Synthesis by Gao's Group



18 **19** d. r. (at C_9) = 5:1

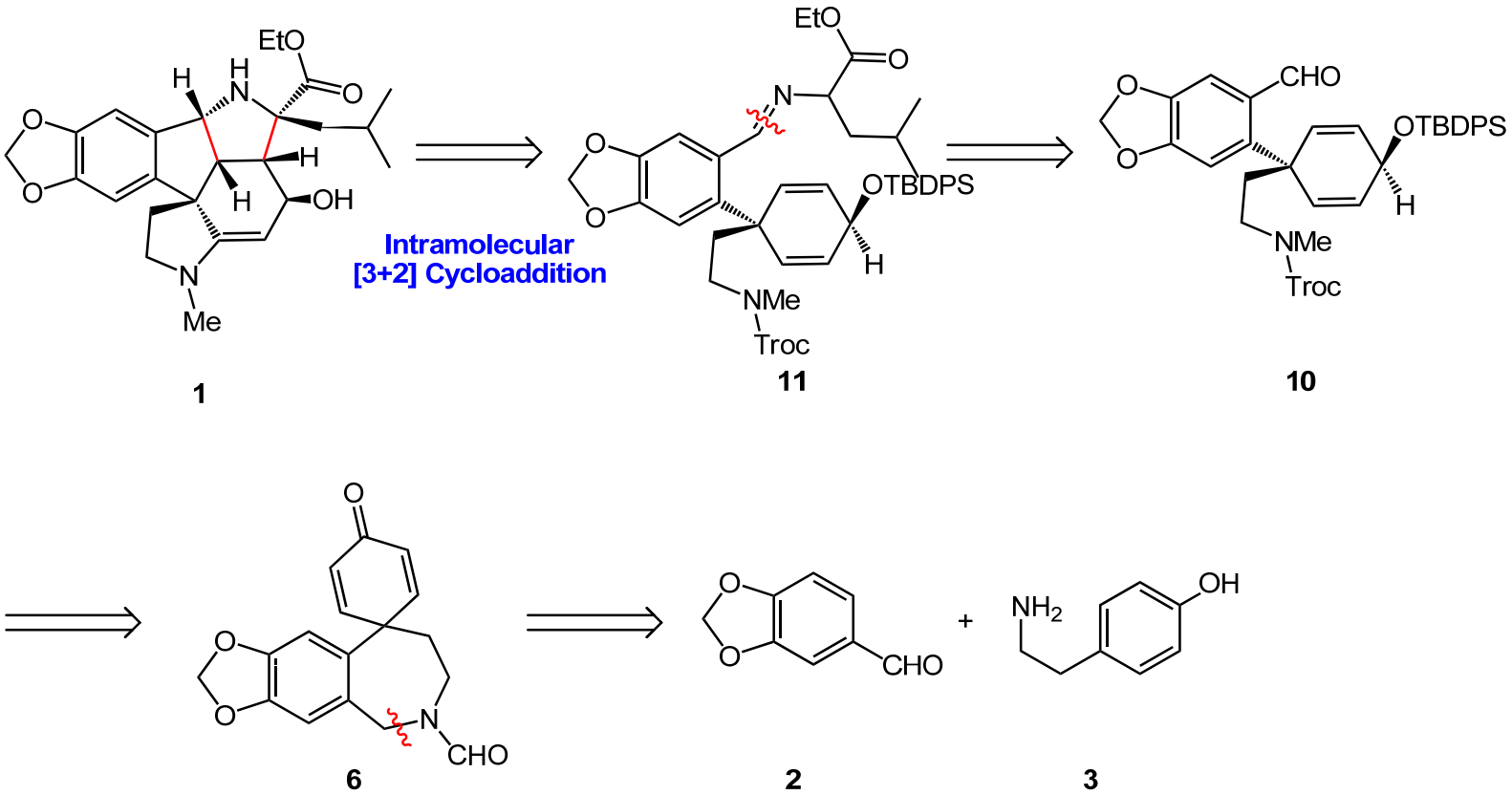


24 **25** (35%) + **gracilamine** (47%)

Both determined by X-ray

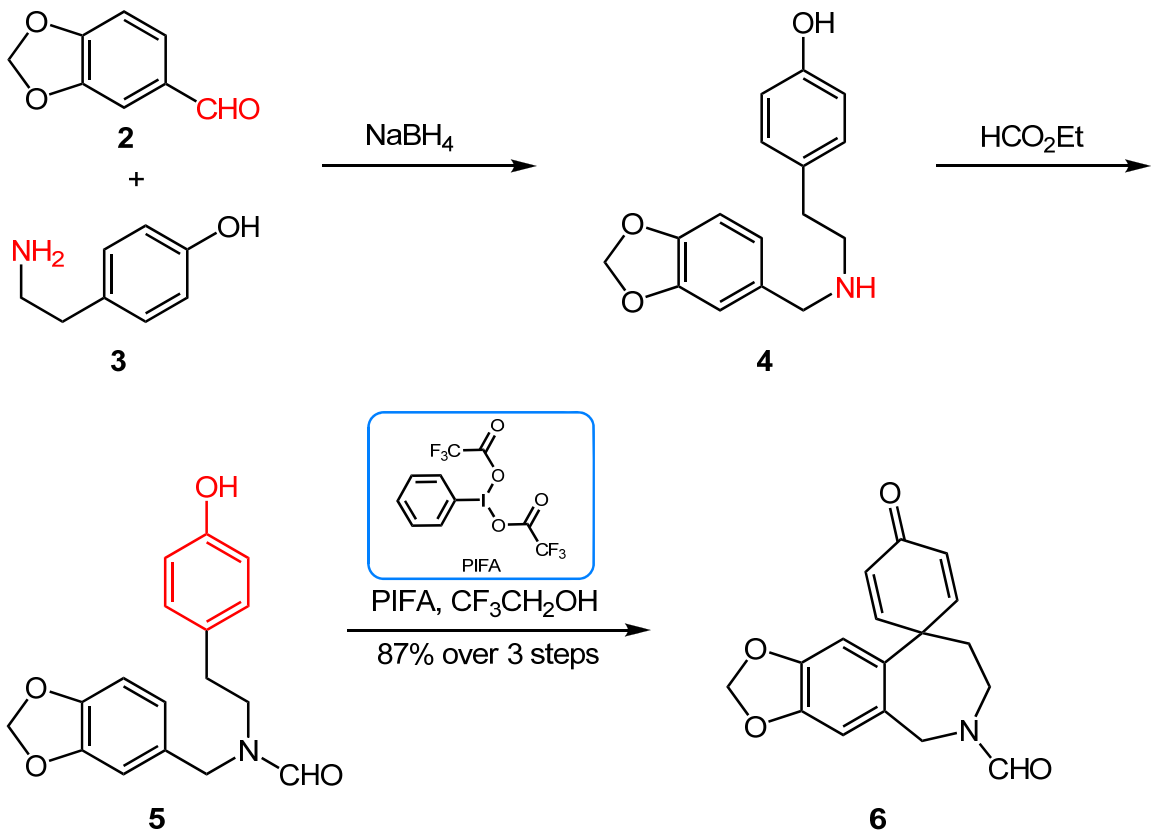
Total Synthesis by Ma's Group

Retrosynthetic Analysis

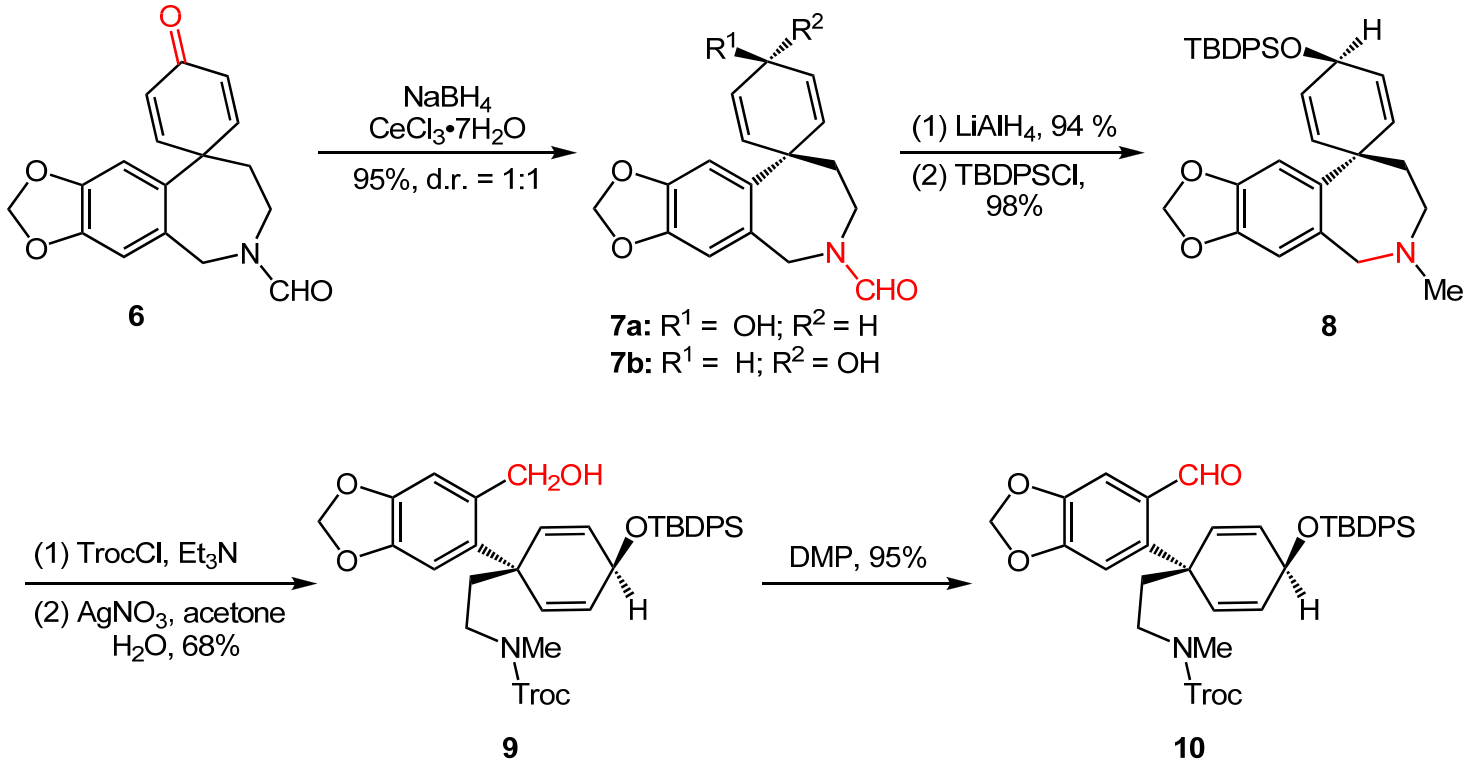


Ma, D. *et al*. *Angew. Chem. Int. Ed.* **2012**, *51*, 10141.

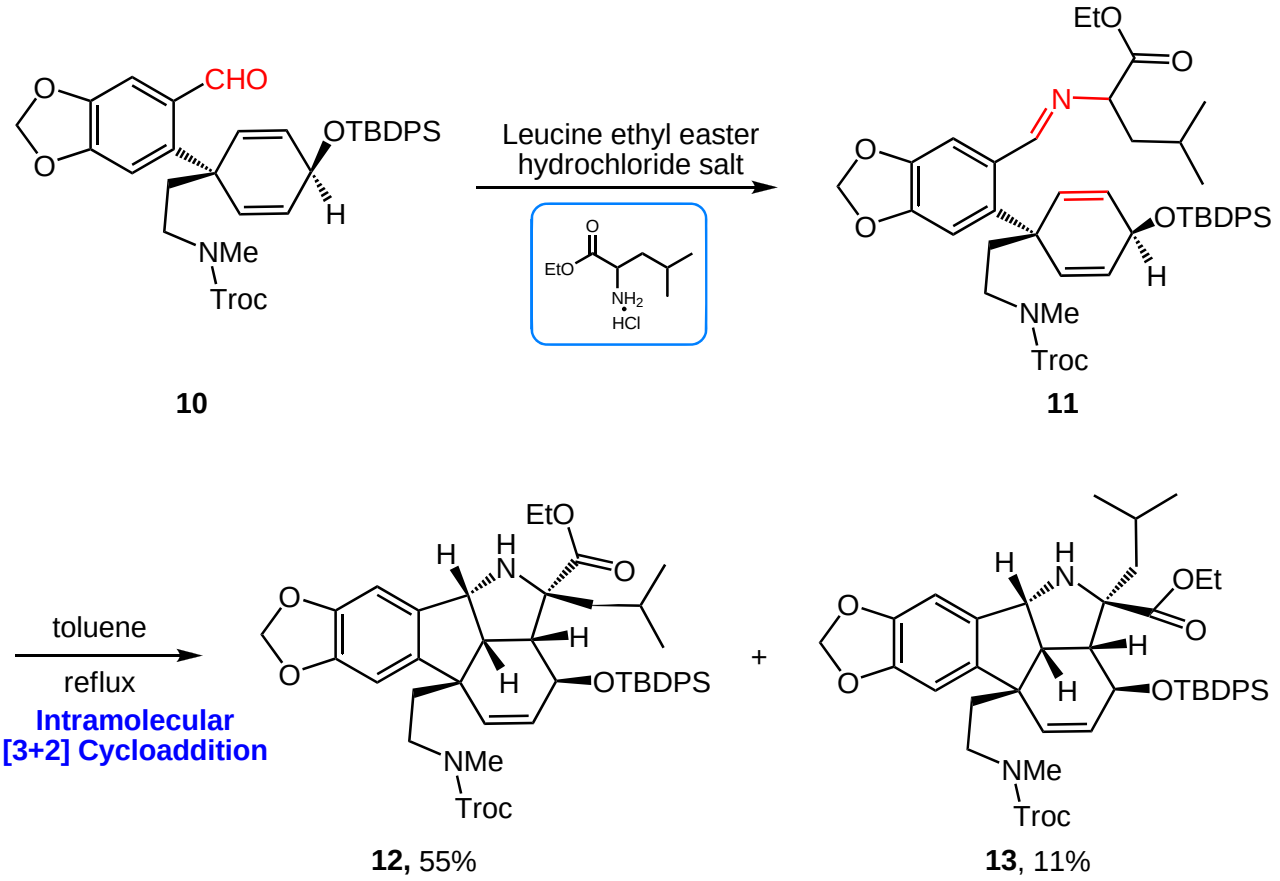
Total Synthesis by Ma's Group



Total Synthesis by Ma's Group



Total Synthesis by Ma's Group



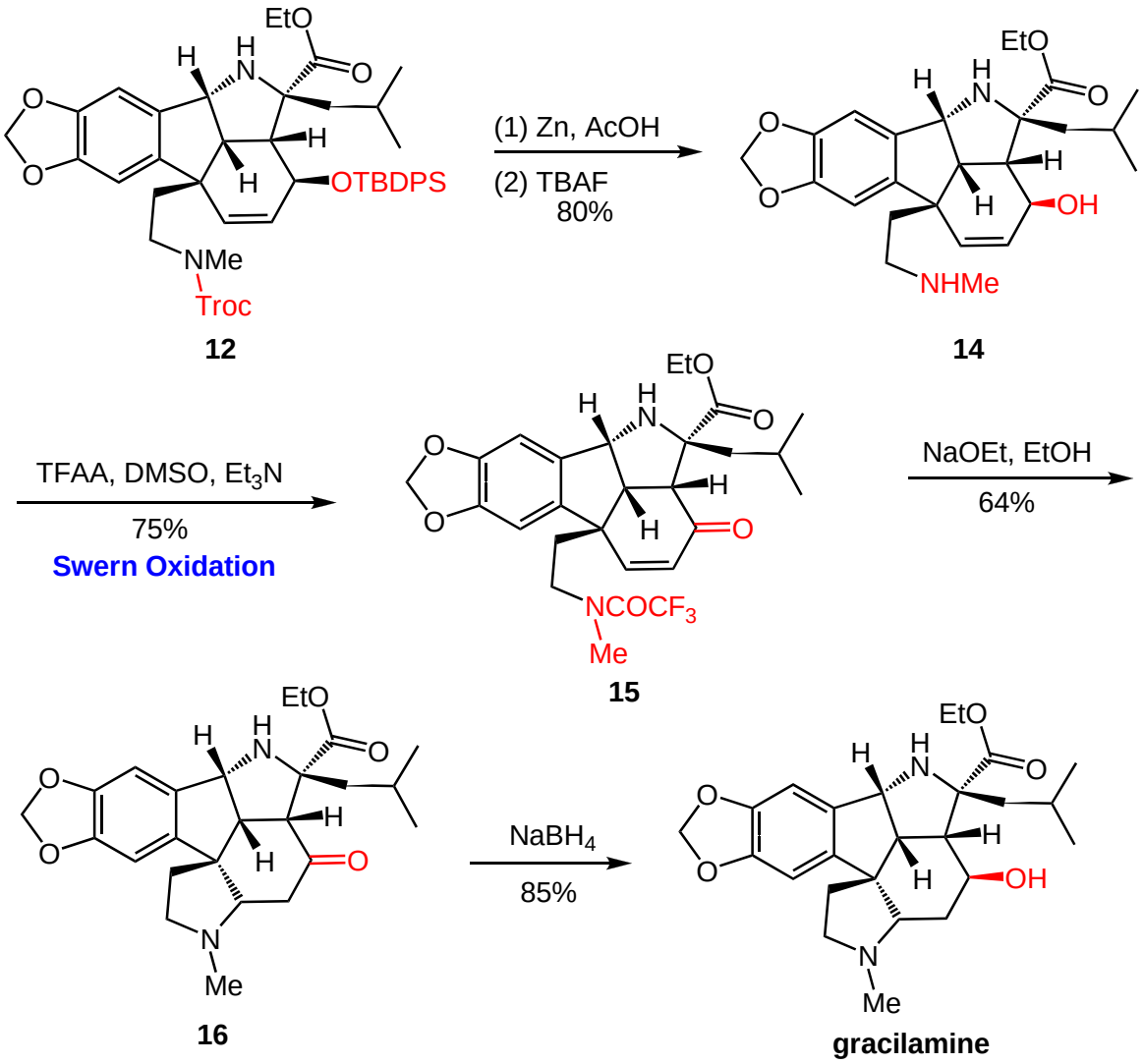
10

11

12, 55%

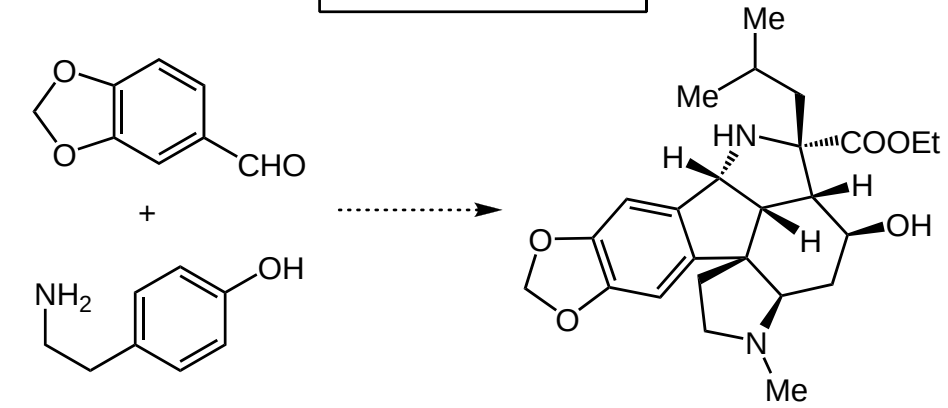
13, 11%

Total Synthesis by Ma's Group



Summary

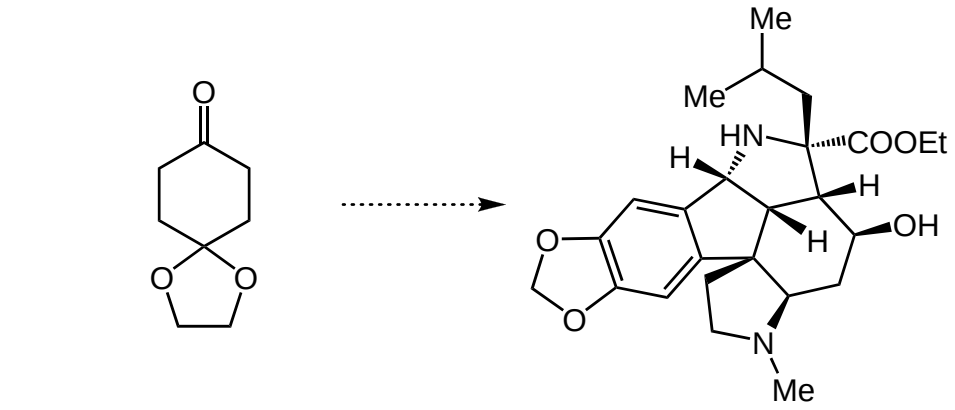
Ma's Method



gracilamine

- **First total synthesis**
- **17 linear steps, 4.5% overall yield**
- **Intramolecular [3+2] Cycloaddition**

Gao's Method



gracilamine

- **Photo-Nazarov Reaction, Michael Addition, Intramolecular Mannich Reaction**
- **18 linear steps, 1.4% overall yield**

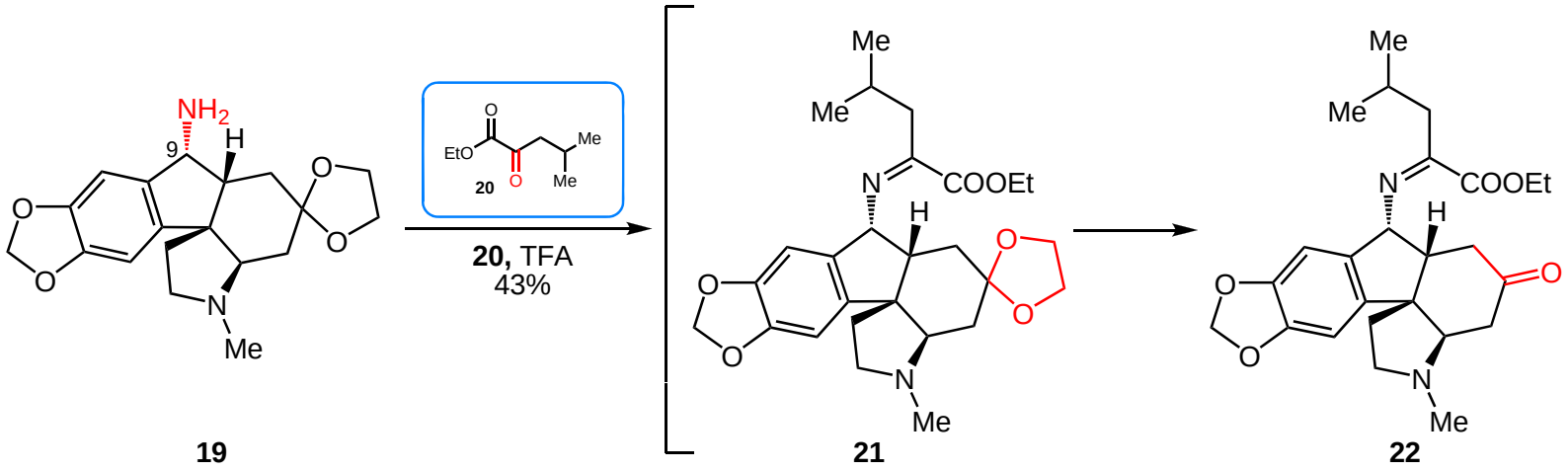
Amaryllidaceae plants have proven to be an important source of natural products with appealing structures and promising biological activities. Gracilamine (**1**), a member of the Amaryllidaceae alkaloid family, was isolated from Galanthus gracilis collected from a mountain in Turkey by Unver and Kaya in 2005. The structure and relative stereochemistry of **1**, except for the configuration of the hydroxy group on C6, were determined by NMR spectroscopy. However, the biological activities of this potentially valuable natural product are unknown because of its scarcity in nature. In 2012, Ma and co-workers reported the first total synthesis of **1** using a biomimetic intramolecular [3+2] cycloaddition. This synthetic breakthrough not only suggested how the compound is produced in nature, but it also provided evidence of the relative stereochemistry of C6.

Since our research group is devoted to the synthesis of bioactive natural products, we set out to develop a new strategy to solve the efficiency of the chemical synthesis of **1** and facilitate the preparation of its analogues and derivatives for medicinal studies. We report herein the total synthesis of **1** using a photo-Nazarov reaction, Michael addition, and an intramolecular Mannich reaction as key steps. Our synthesis provides additional evidence to support the C6 stereochemistry of natural product reported by Ma and co-workers.

In summary, we have accomplished the total synthesis of gracilamine, a pentacyclic Amaryllidaceae alkaloid. Our synthetic approach relies on three key ring-forming steps: 1) a mild photo-Nazarov reaction to form the B ring, 2) 1,4-addition to form the D ring, and 3) intramolecular Mannich reaction to form the E ring. Our research findings further confirm the C6 configuration of natural gracilamine. The synthetic strategies developed here should facilitate production of a variety of gracilamine derivatives and structurally related natural products, thus leading to biological studies.

Total Synthesis by Gao's Group

Intramolecular Mannich Reaction



Total Synthesis by Gao's Group

Saegusas-Ito oxidation