Literature Report IV

Total Synthesis of Vilmoraconitine

Reporter: Zheng Liu

Checker: Yu-Qing Bai

Ji, J.; Qin, Y.* *J. Am. Chem. Soc.* **2023**, *145,* 3903.

2023-05-15

CV of Prof. Qin Yong

Background:

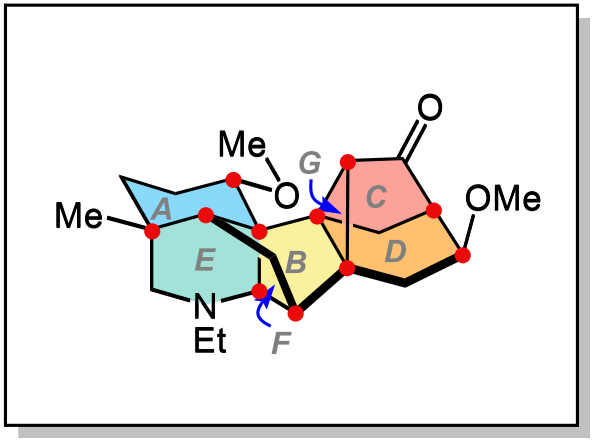
- **1985-1989** B.S., Yunnan University
- **1989-1992** M.S., Chengdu Institute of Organic Chemistry
- **1992-1995** Ph.D., Institute of Chemistry
- **1995-1996** Assistant to Associate Professor, CIOC
- **1996-2000** Postdoc., University of Vermont
- **2000-2003** Research Scientist, Triad Therapeutics Inc.
- **2003-now** Professor, Sichuan University

Research:

1. Total synthesis of natural products;
2. Medicinal chemistry.

Contents

Introduction



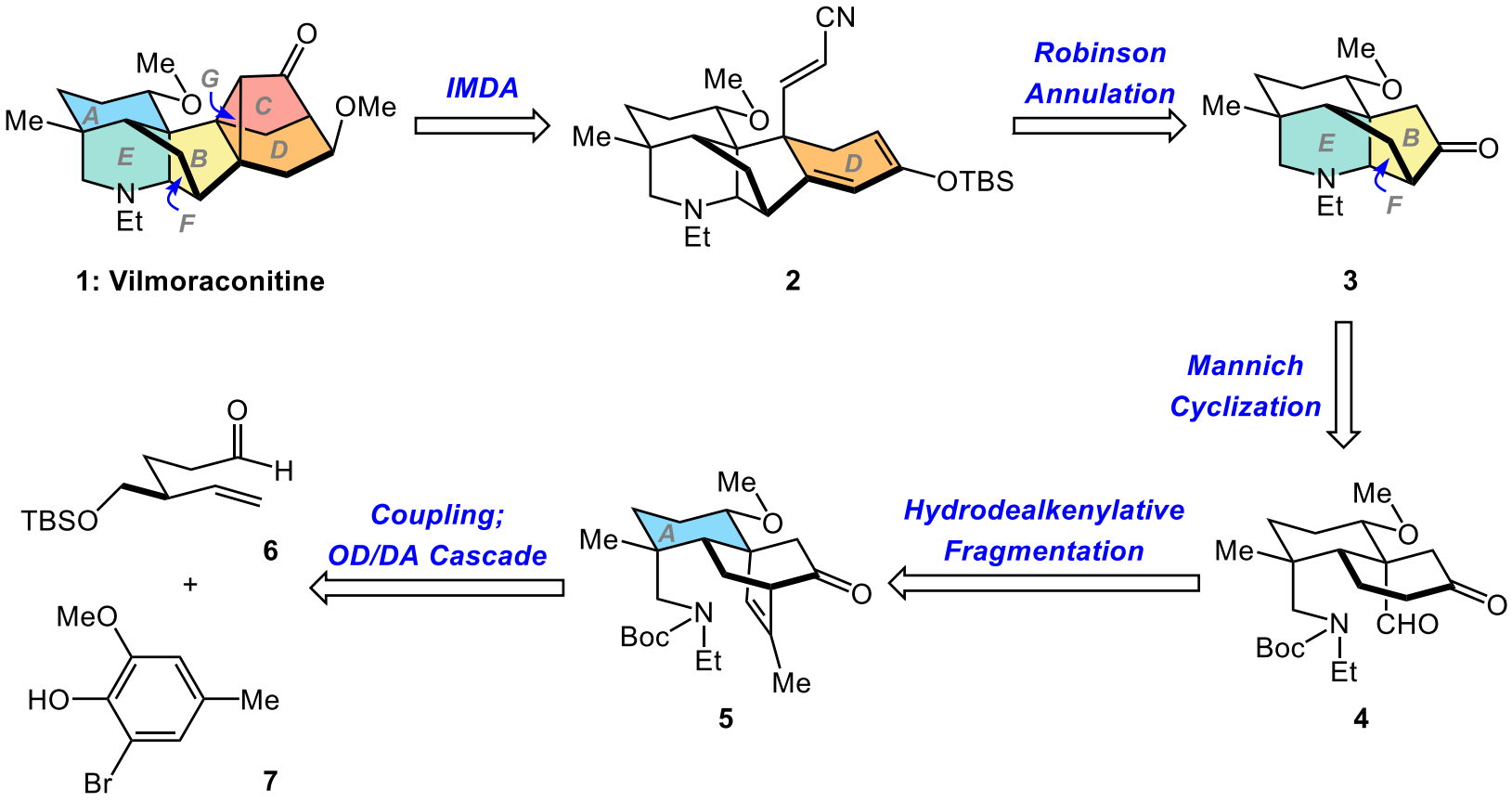
Vilmoraconitine

***Aconitum vilmorinianum* Kom.**

- Isolated from *Aconitum vilmorinianum Kom.* and characterized in 2008;
- A traditional Chinese medicine used to treat rheumatism and pains;
- Contain challenging 6/5/5/6/6/5/3 heptacyclic core with 11 chiral centers.

Xiong, J.; Tan, N.-H.*; Ji, C.-J.; Lu, Y.; Gong, N.-B. *Tetrahedron Lett.* **2008**, *49*, 4851.

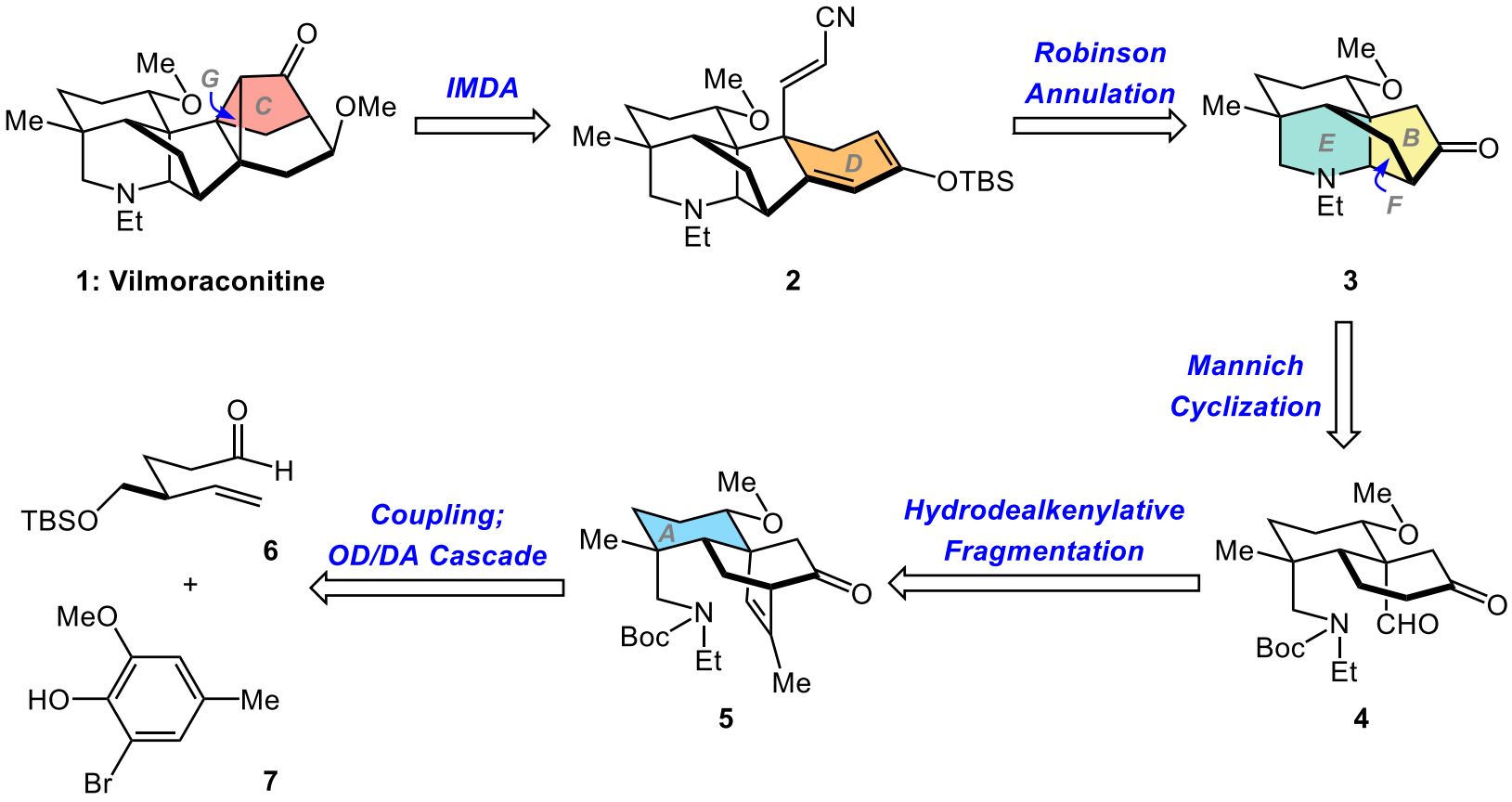
Retrosynthetic Analysis



1: Vilmoraconitine **2** **3**

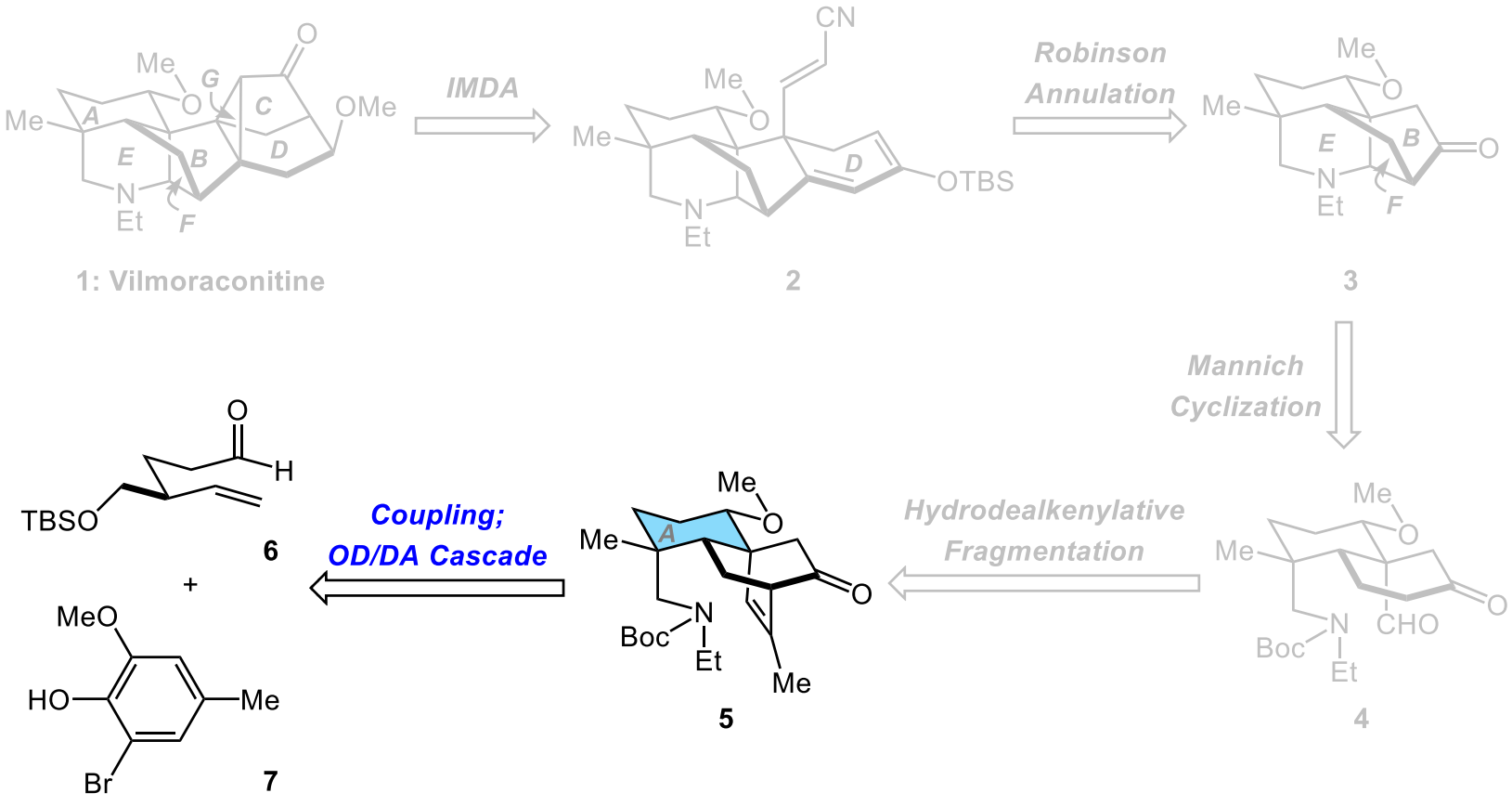
4 **5** **6** + **7**

Retrosynthetic Analysis

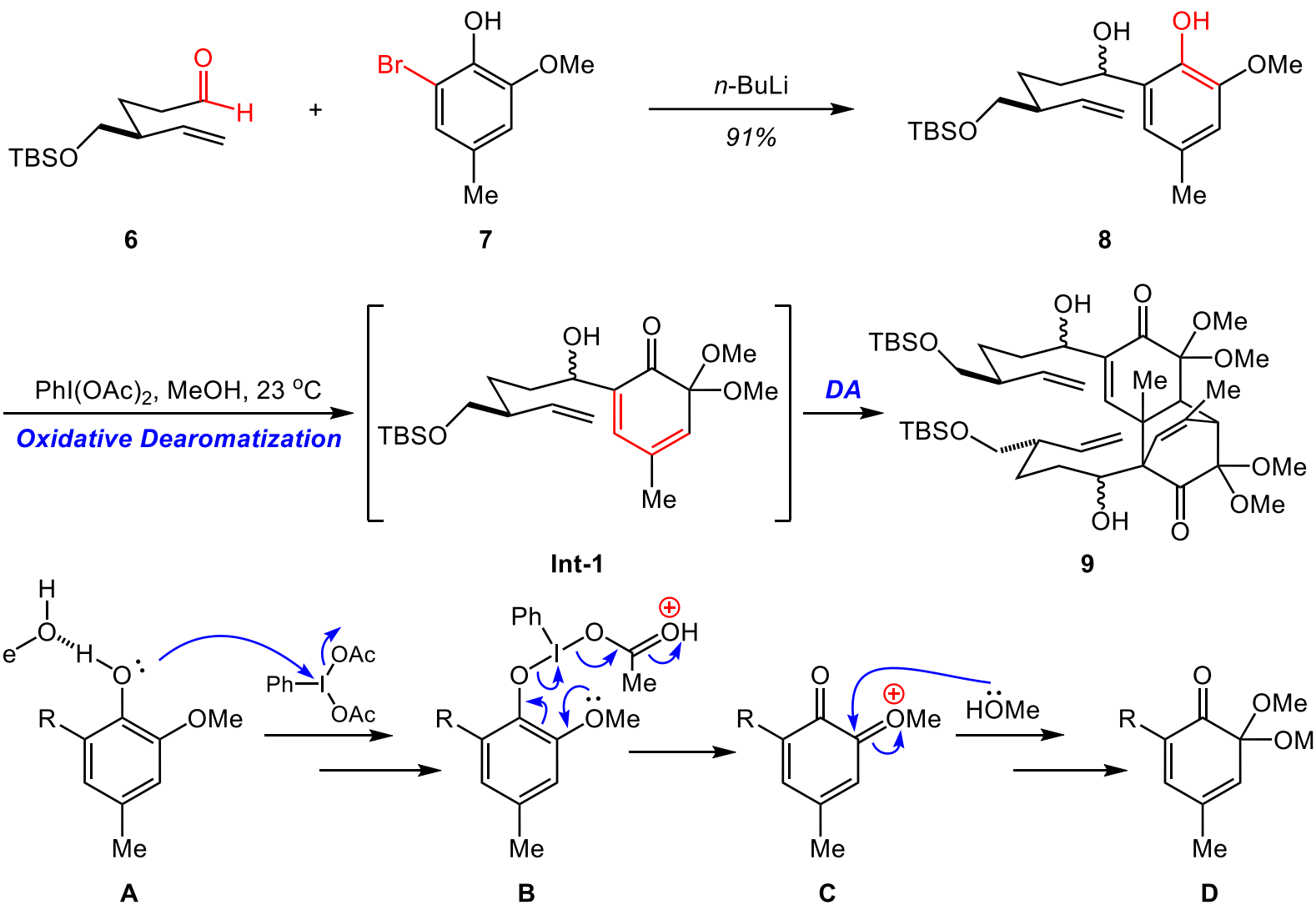


1: Vilmoraconitine **2** **3**

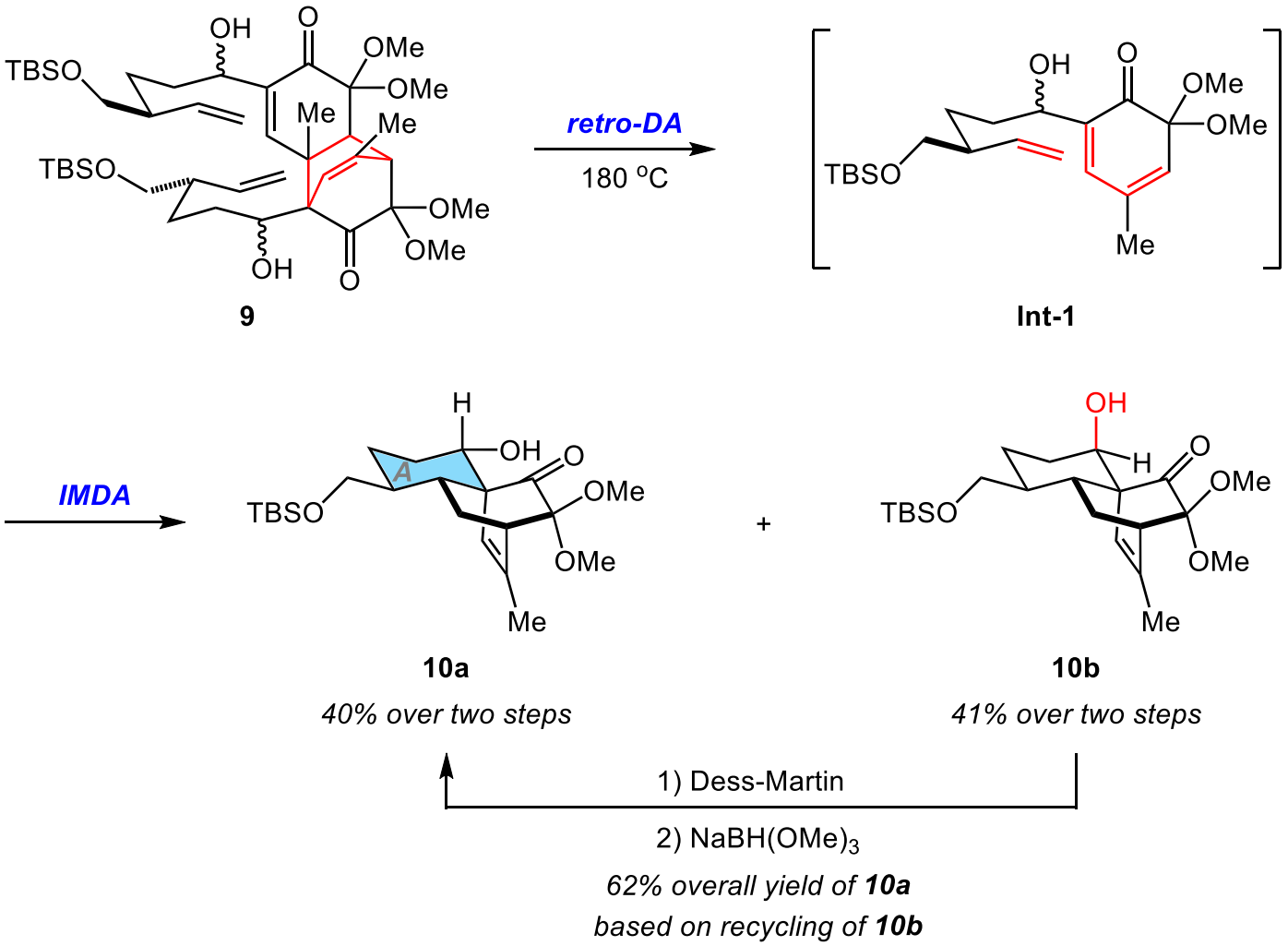
Retrosynthetic Analysis



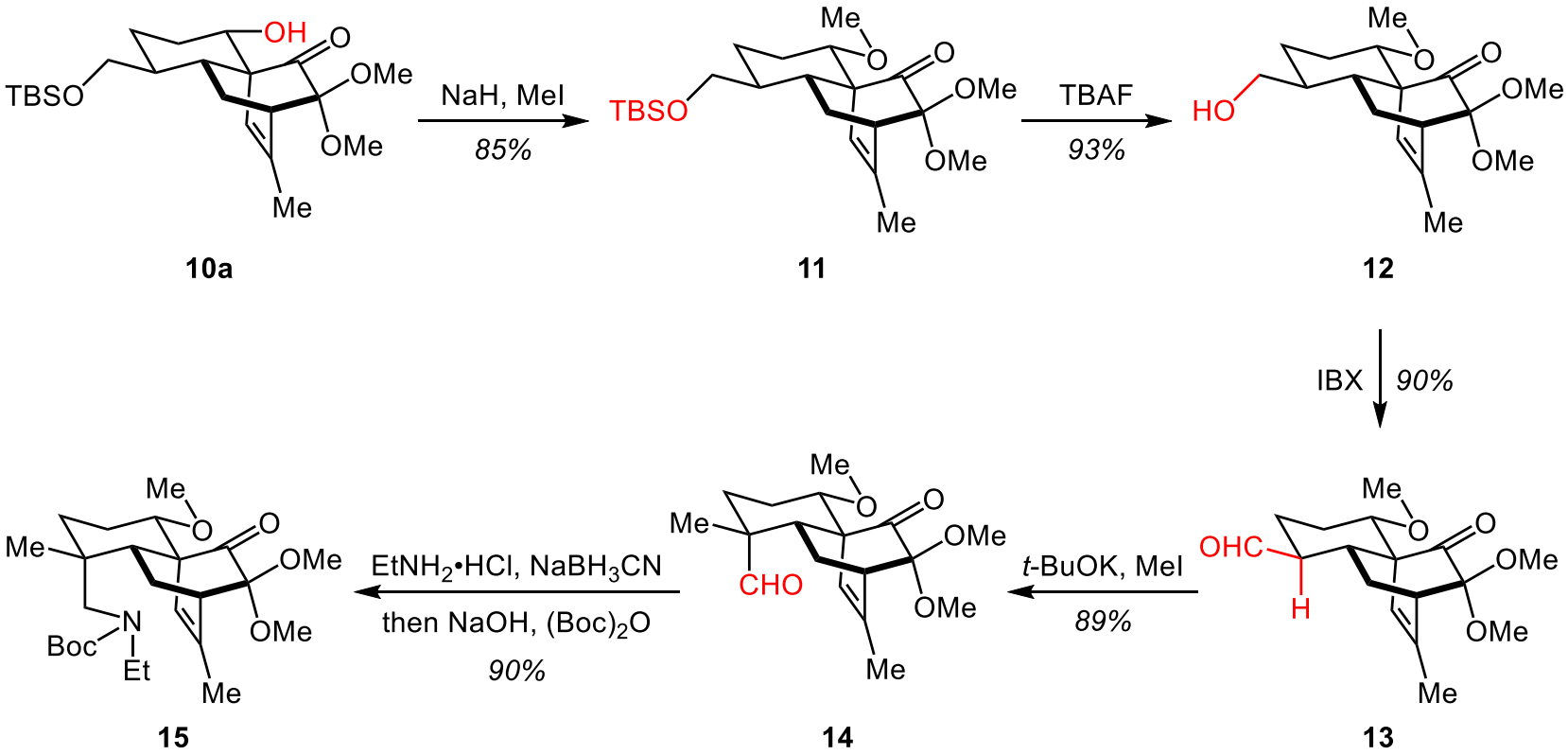
Synthesis of Compound 9



Synthesis of Compound 10a



Synthesis of Compound 15



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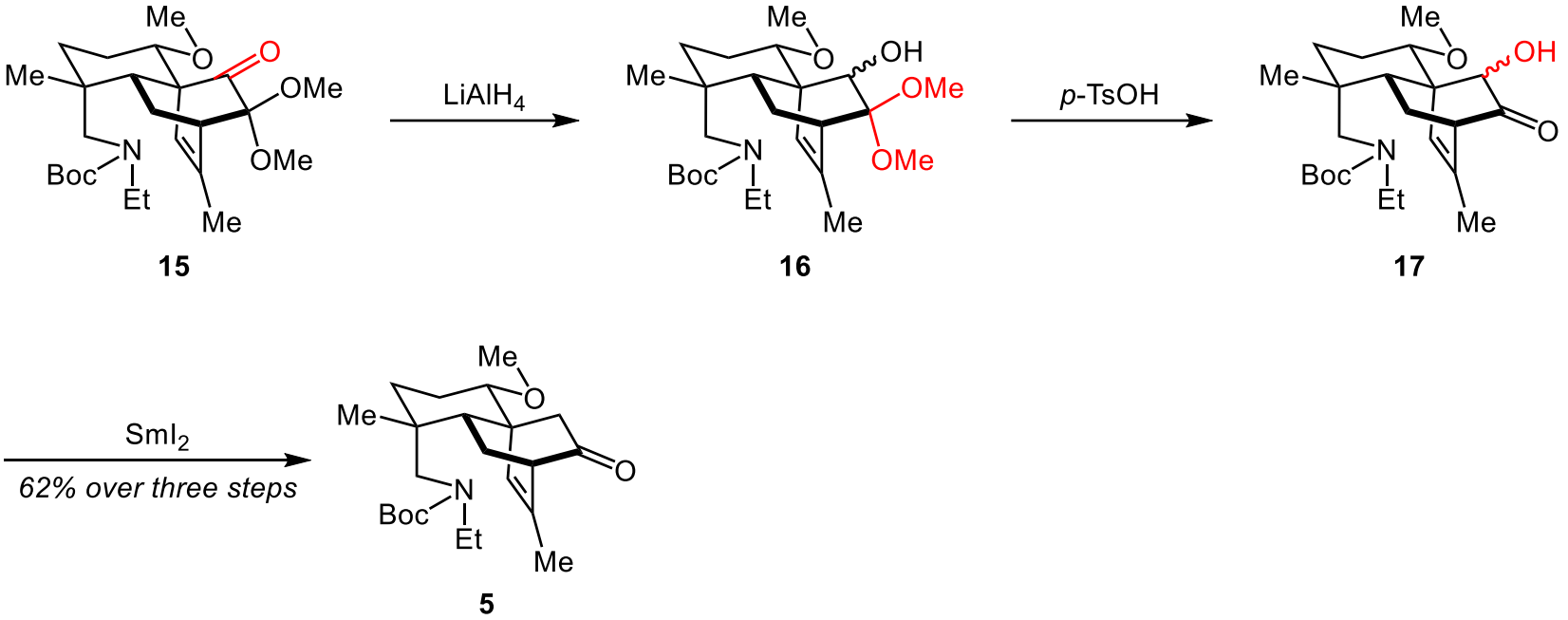

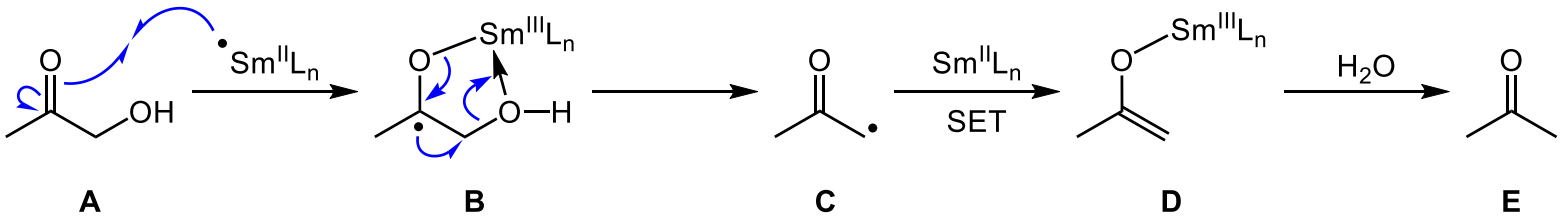

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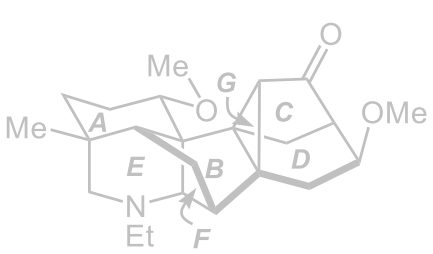
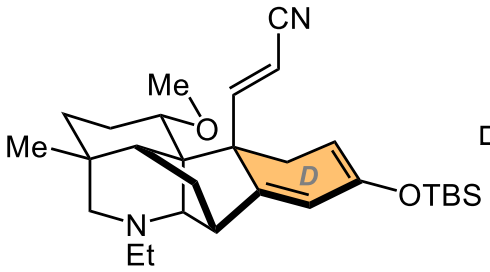


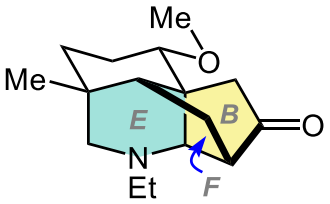
1: Vilmoraconitine

IMDA



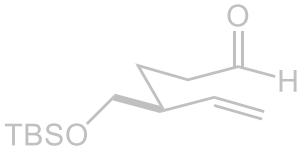
2

Robinson Annulation



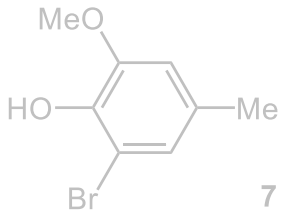
3

Mannich Cyclization



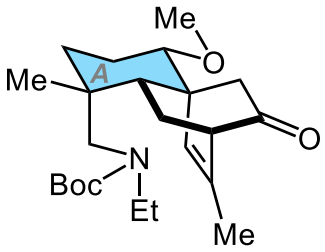
6

+



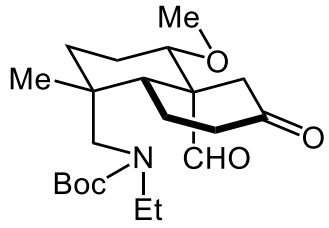
7

Coupling; OD/DA Cascade



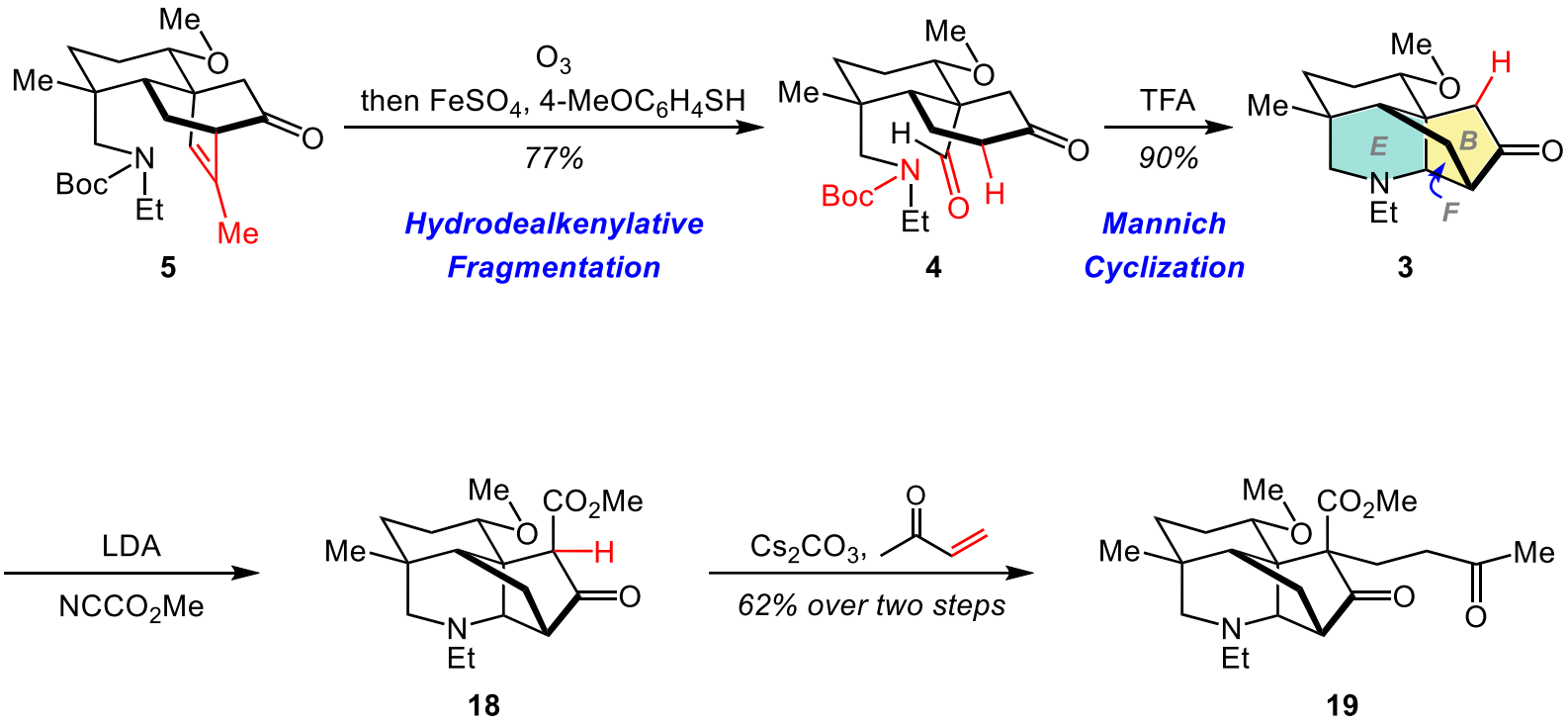
5

Hydrodealkenylative Fragmentation

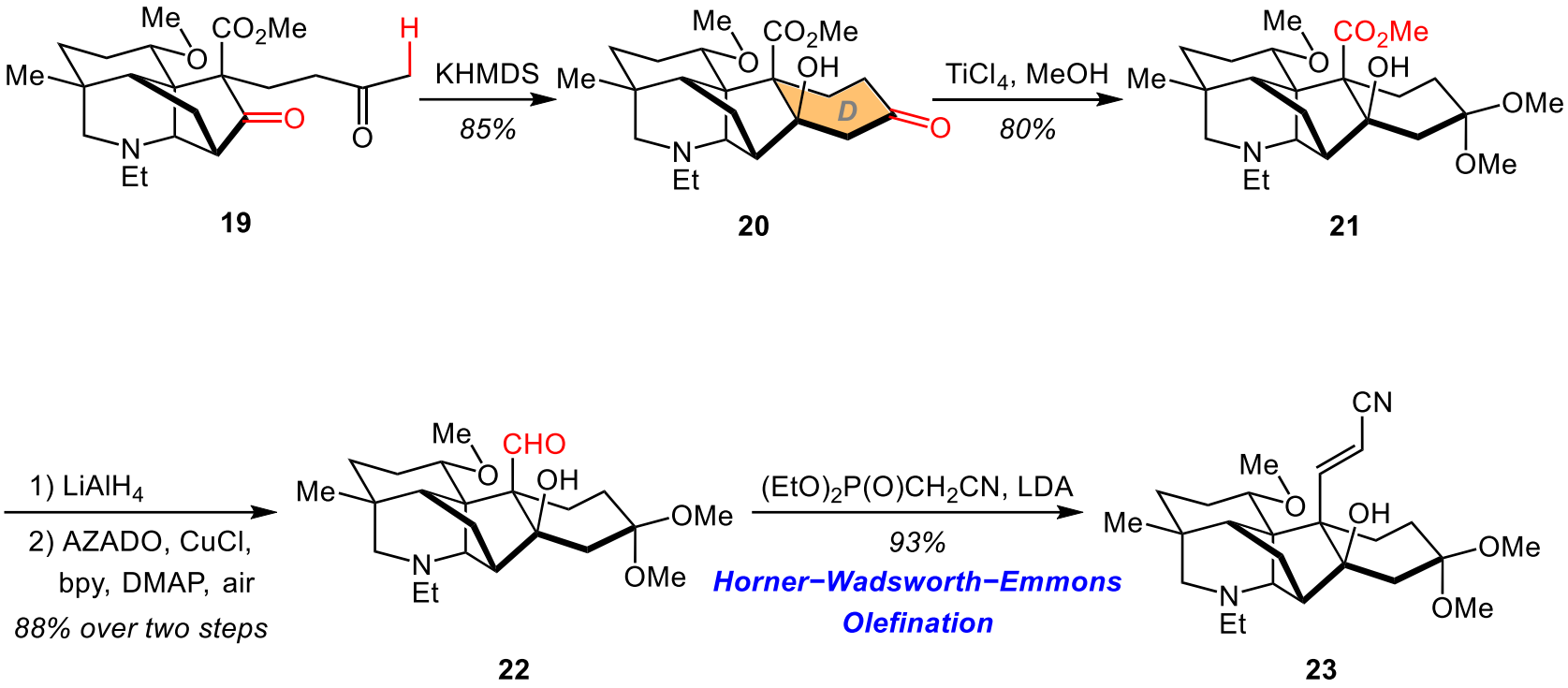


4

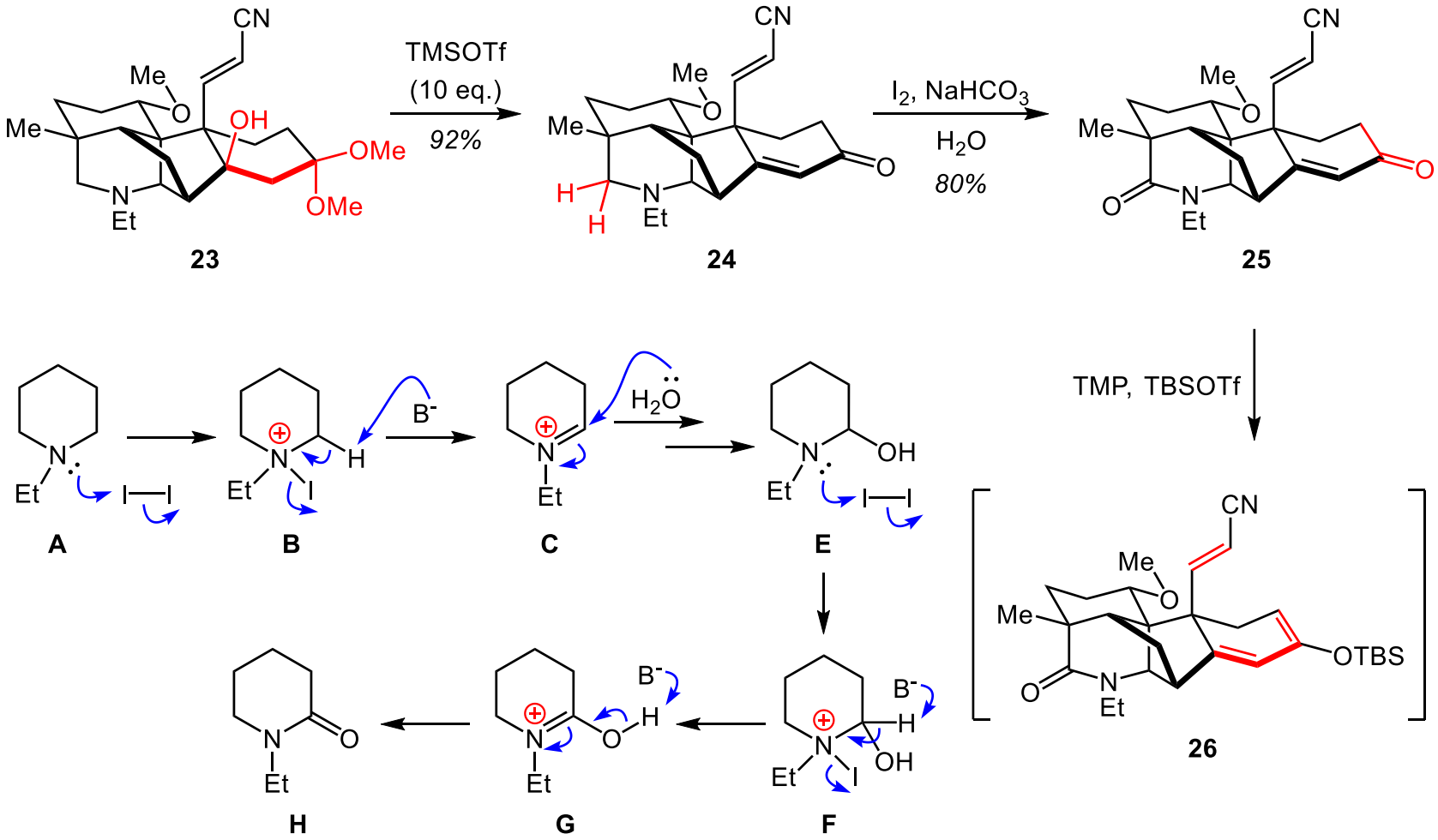
Synthesis of Compound 19



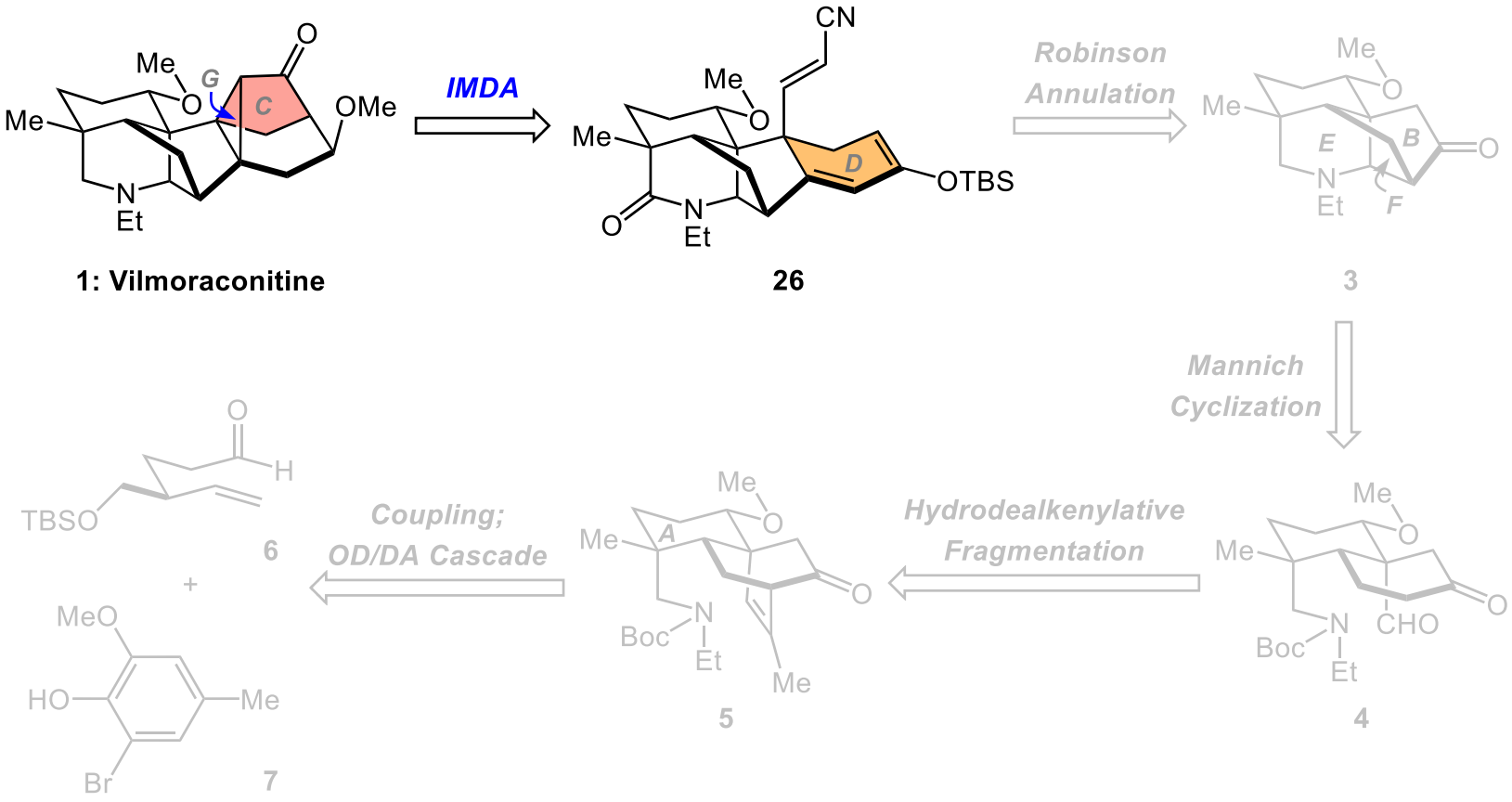
Synthesis of Compound 23



Synthesis of Compound 26

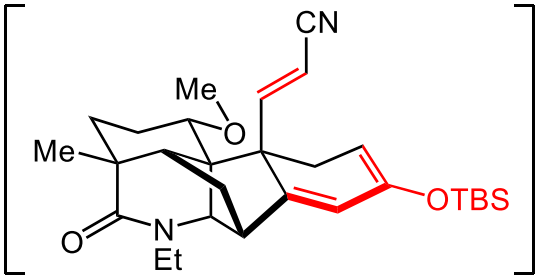


Retrosynthetic Analysis



1: Vilmoraconitine **26** 3

Synthesis of Compound 29

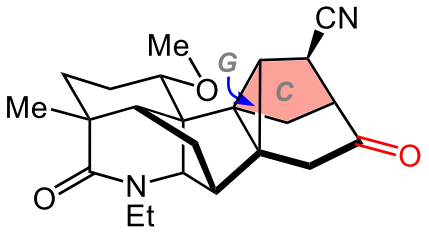


26

150 °C then aq. *p*-TsOH

75%

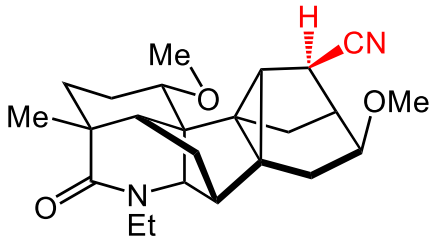
IMDA



27

67% over two steps

1) $NaBH_4$
2) *t*-BuOK, MeI

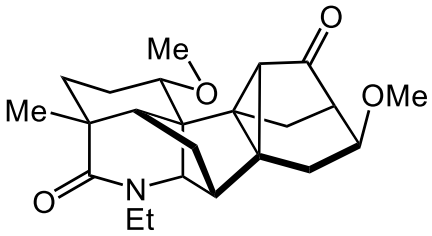


28

LDA, O_2

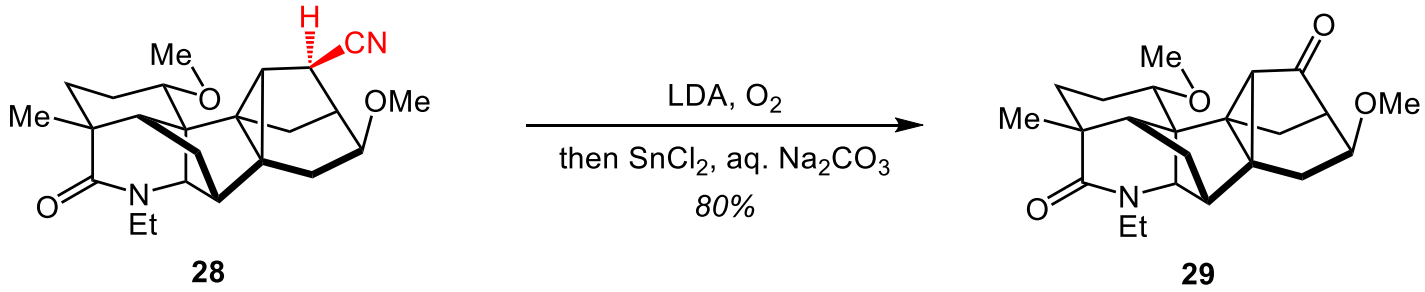
then $SnCl_2$, aq. Na_2CO_3

80%

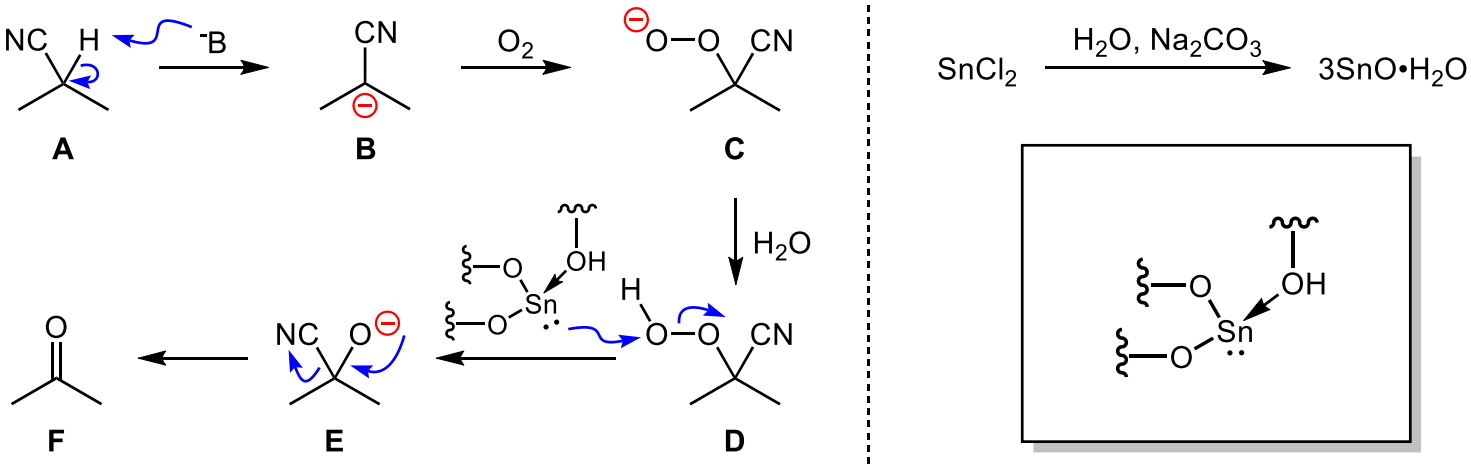


29

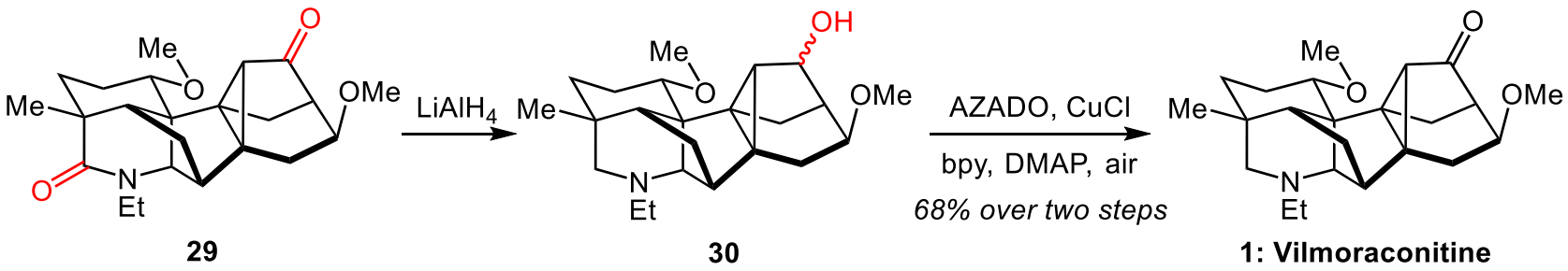
Synthesis of Compound 29



28 29

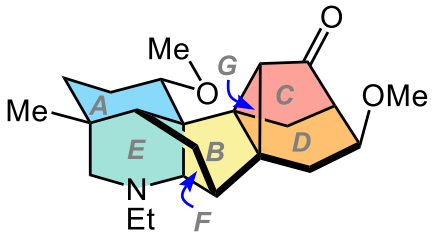


Synthesis of Vilmoraconitine



29 **30** **1: Vilmoraconitine**

Summary



Vilmoraconitine

28 steps

1.0% overall yield

- OD/DA cascade *(A ring);*
- Hydrodealkenylative fragmentation/Mannich sequence *(B/E/F rings);*
- Robinson annulation *(D ring);*
- IMDA reaction *(C/G rings).*

Writing Strategy

Introduction

Source and physiological activity

- The C19-diterpenoid alkaloids (C19-DTAs) are the primary chemical components isolated from the medicinal plants of the genus Aconitum. This family of natural compounds and their synthetic analogues display significant anti-inflammatory, analgesic, and cardioactive effects.

Structural features

- Structurally, the C19-DTAs feature complex cage-like frameworks and denselyoxygenated sub-stituents, which have attracted considerable attention from the synthetic community over decades.

Examples of synthesis

- Inparticular, elegant total syntheses of the hexacyclic aconitinetype C19-DTAs) have been independently achieved by the groups of Wiesner, Sarpong, Fukuyama, Inoue, and Reisman.

Writing Strategy

Last paragraph

Summary

- In summary, we have accomplished the first total synthesis of vilmoraconitine, a rare heptacyclic rearranged-type C19-DTA.

Committed steps

- Strategically, an efficient hydrodealkenylative fragmentation/Mannich sequence was utilized to assemble the B/E/Frings. Of note, it represents the first application of thehydrodealkenylative fragmentation of an endocyclic alkene innatural product synthesis, which, in combination with a Mannich reaction, rapidly set up the molecular complexity. Additionally, an IMDA reaction allowed for construction of the C/G rings bearing a highly substituted cyclopropane moiety in a one-pot manner.

Prospect

- Further efforts to develop efficient synthetic strategies to access intriguing diterpenoid alkaloids are underway in our laboratory.

Representative Examples

- Given the challenging heptacyclic core present in the target vilmoraconitine, we envisaged that an efficient synthetic route would require strategies to simultaneously assemble its multiring units through single-step transformations. （阐述难点）

- Accordingly, we devised our retrosynthetic analysis of **3** as outlined in **Scheme 1**.（adv. 相应地，照着；因此，所以）

- Strategically, an efficient hydrodealkenylative fragmentation/Mannich sequence was utilized to assemble the B/E/F rings.（adv. 战略性地；策略上）

Acknowledgement

Thanks for your attention