



中国科学院大连化学物理研究所

DALIAN INSTITUTE OF CHEMICAL PHYSICS, CHINESE ACADEMY OF SCIENCES

Literature Report 1

Total Synthesis of Yuzurine-type Alkaloid Daphgraciline

Reporter: Bao-Qian Zhao

Checker: Tong Niu

Date: 2023-01-04

Li, L.-X.; Min, L.; Li, C.-C. *J. Am. Chem. Soc.* **2022**, *144*, 18823

CV of Prof. Chuang-Chuang Li (李闯创)



Research:

- Development of novel synthetic methodology
- Total synthesis of biological activity natural products

Education & Professional Experience:

- **1997-2001** B.S., China Agricultural University
- **2001-2006** Ph.D., Peking University
- **2006-2008** Postdoctoral, The Scripps Research Institute (TSRI)
- **2008-2012** Associate Professor, Peking University
- **2013-now** Professor, Southern University of Science and Technology

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1 Introduction

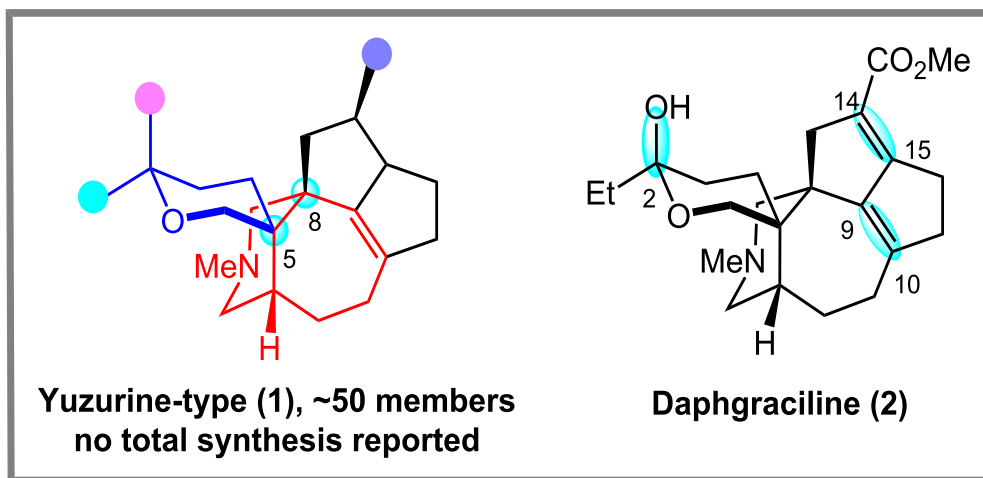
2 Total Synthesis of Daphgraciline (2)

3 Synthesis of Key Chiral Compound (+)-7

4 Summary

Introduction

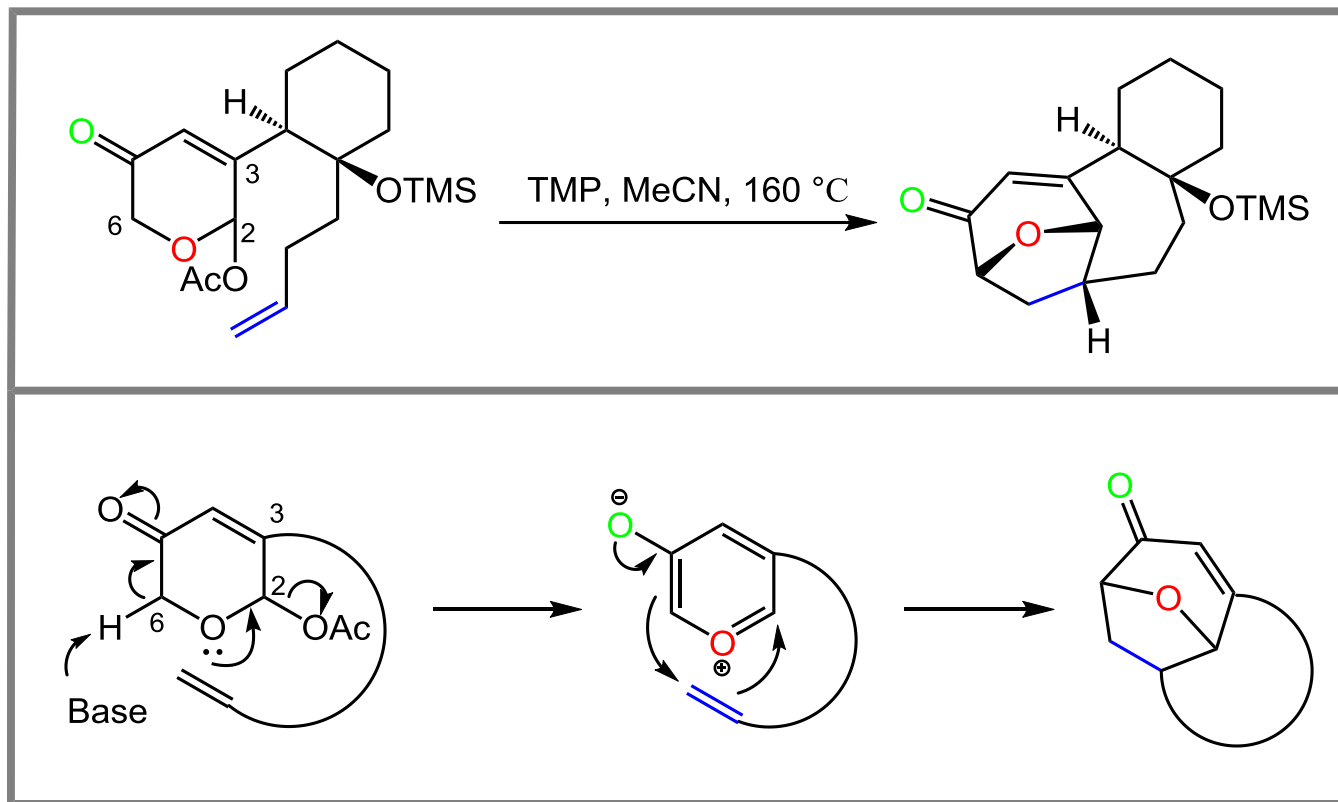
First Isolated by Yamamura (山村) in 1980



- ◆ Multiple Stereocenters
- ◆ Unusual Spiro Tetrahydropyran
- ◆ [6-7-5-5-6] Pentacyclic Core
- ◆ Unique Azabicyclo[4.3.1] Ring System

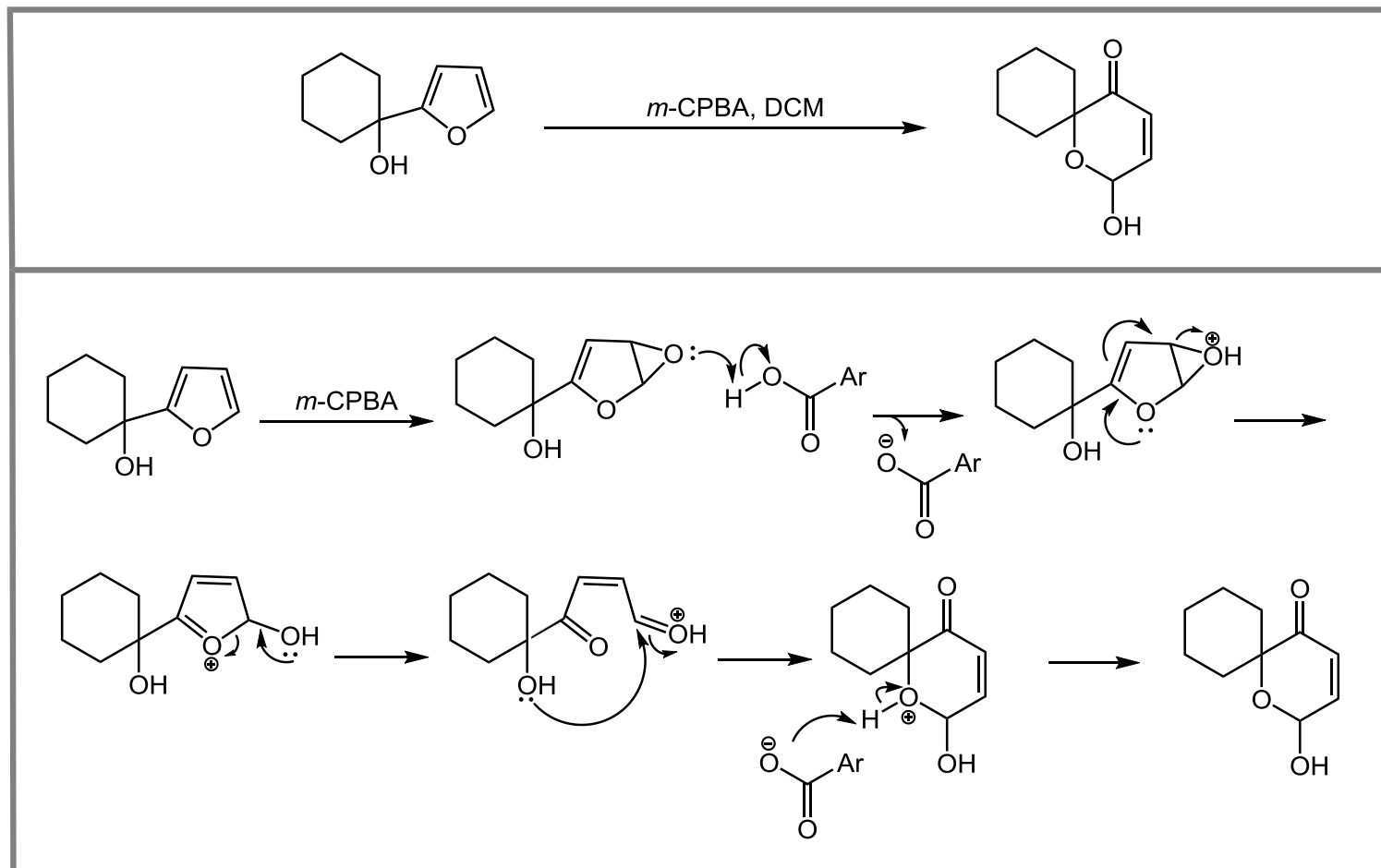
Yamamura, S.; Lambertson, J. A.; Niwa, M. *Chem. Lett.* 1980, 9, 393

Type II [5+2] Cycloaddition



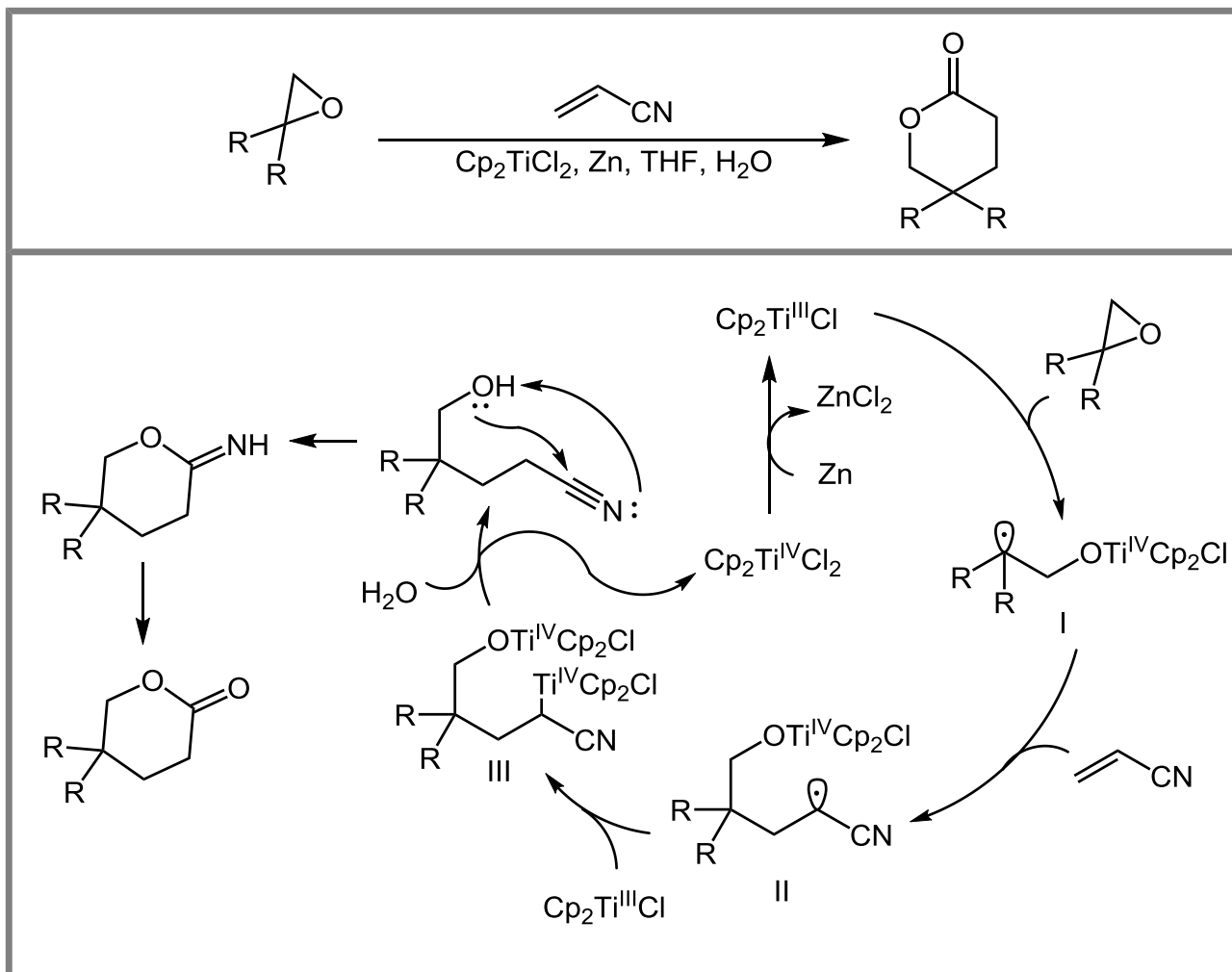
Mei, C.-J.; Liu, X.; Li, C.-C. *Angew. Chem. Int. Ed.* **2015**, *54*, 1754

Achmatowicz Rearrangement



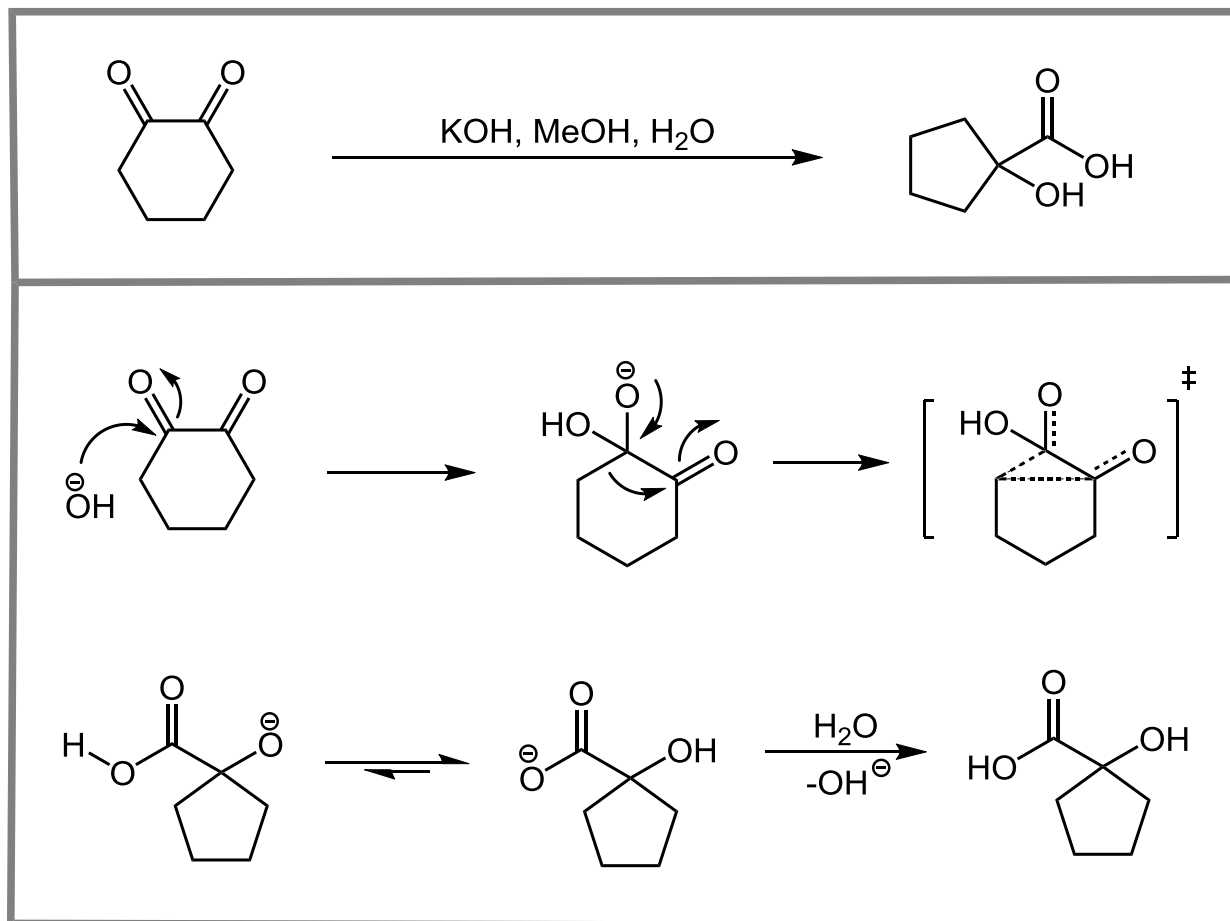
Plutschack, M. B.; Seeberger, P. H. *Org. Lett.* **2017**, *19*, 30

Ti(III)-Mediated Reductive Epoxide Coupling



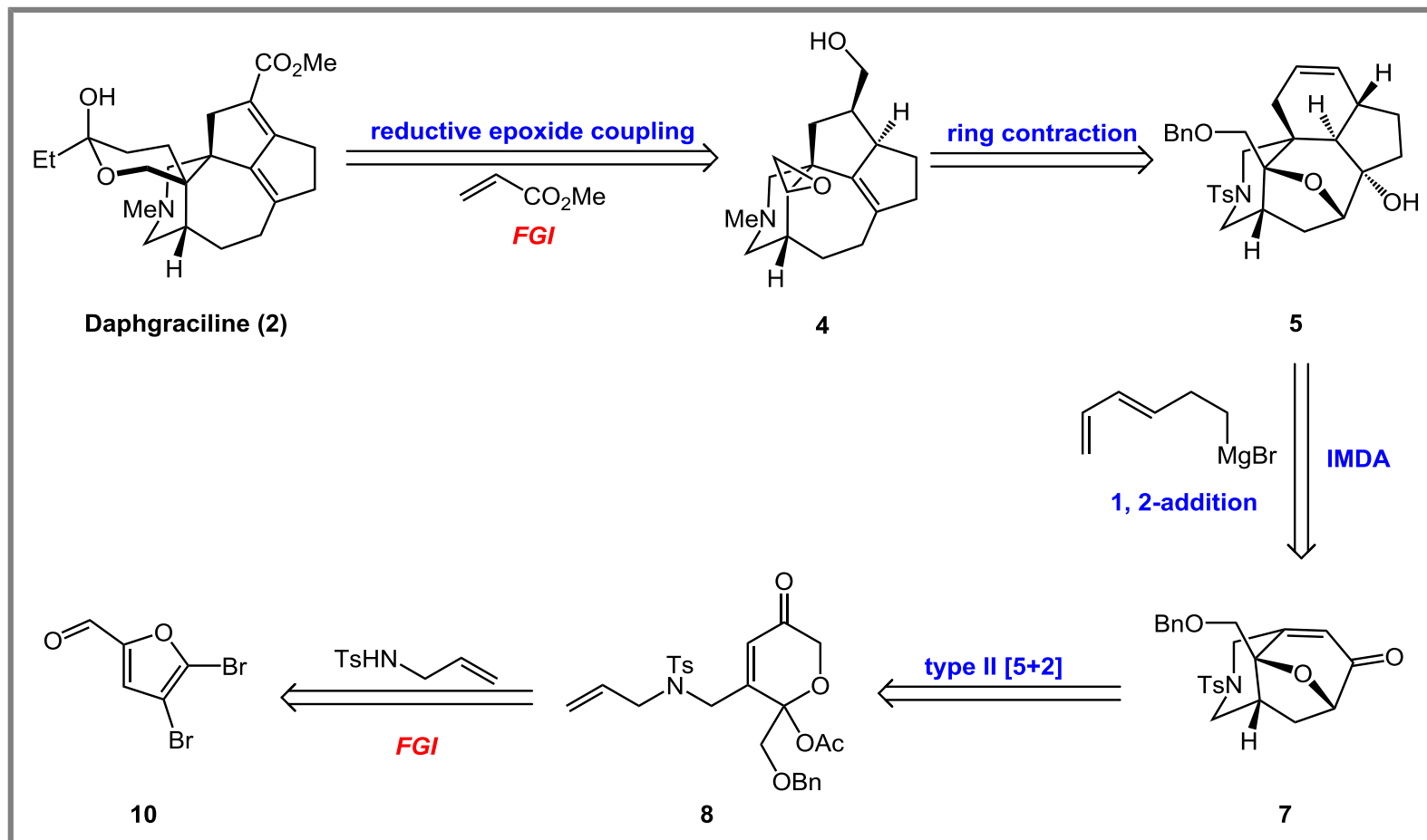
RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, 116, 986

Benzilic Acid Rearrangement

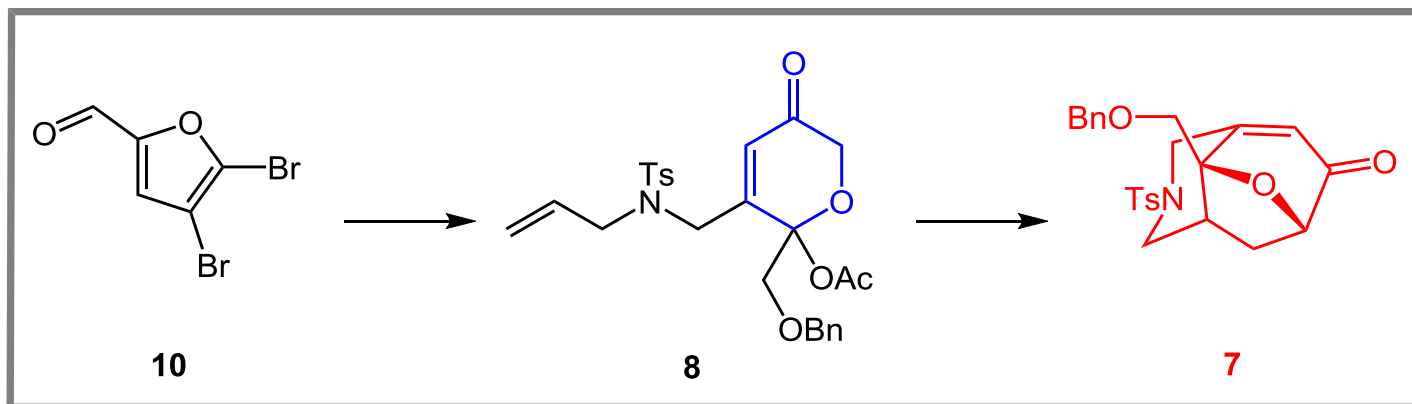


Form Name Reactions

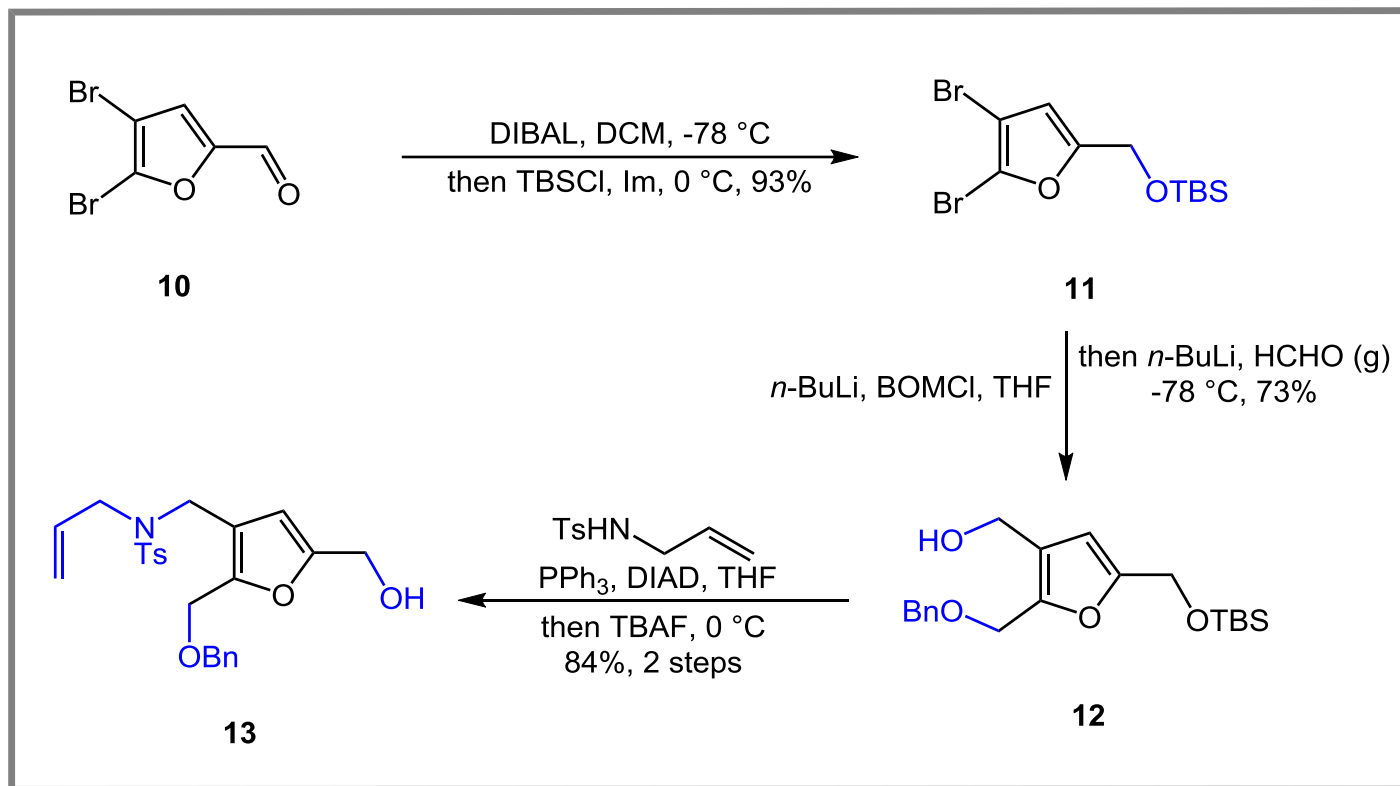
Retrosynthetic Analysis



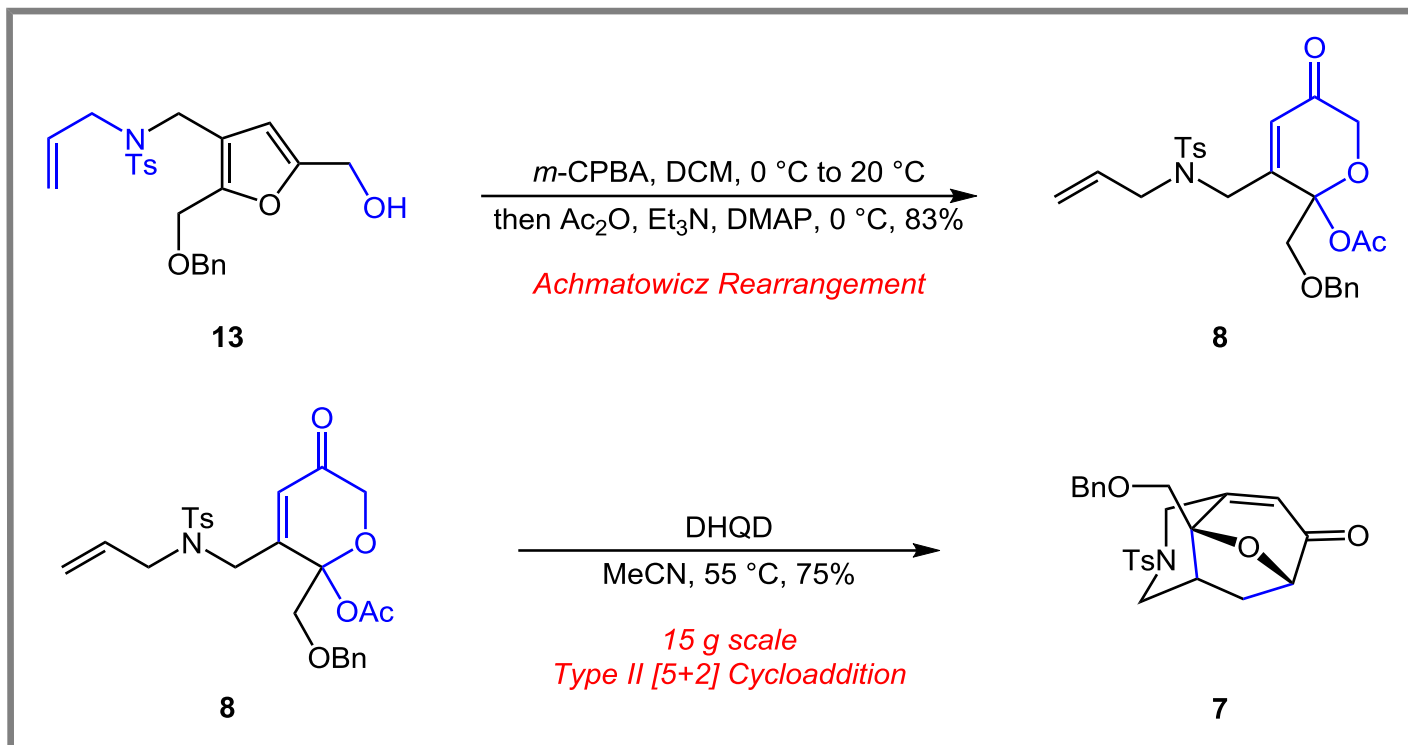
Stage 1--Synthesis of 7



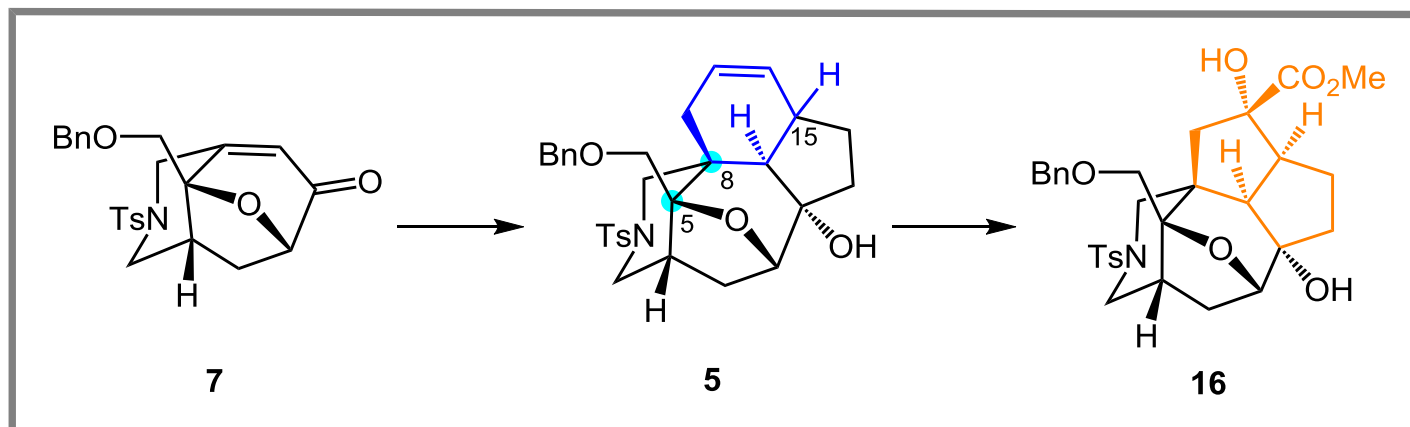
Stage 1--Synthesis of 7



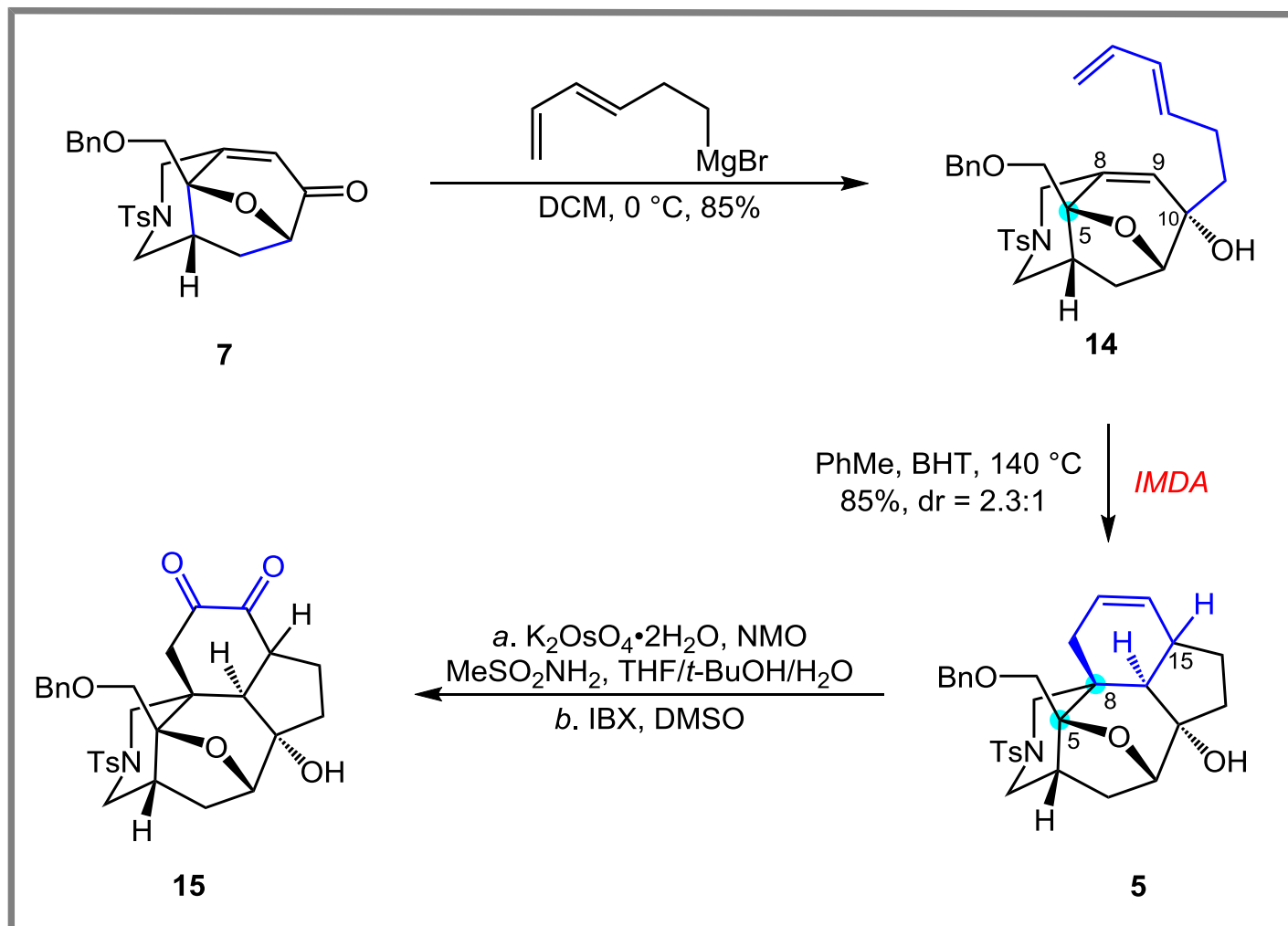
Stage 1--Synthesis of 7



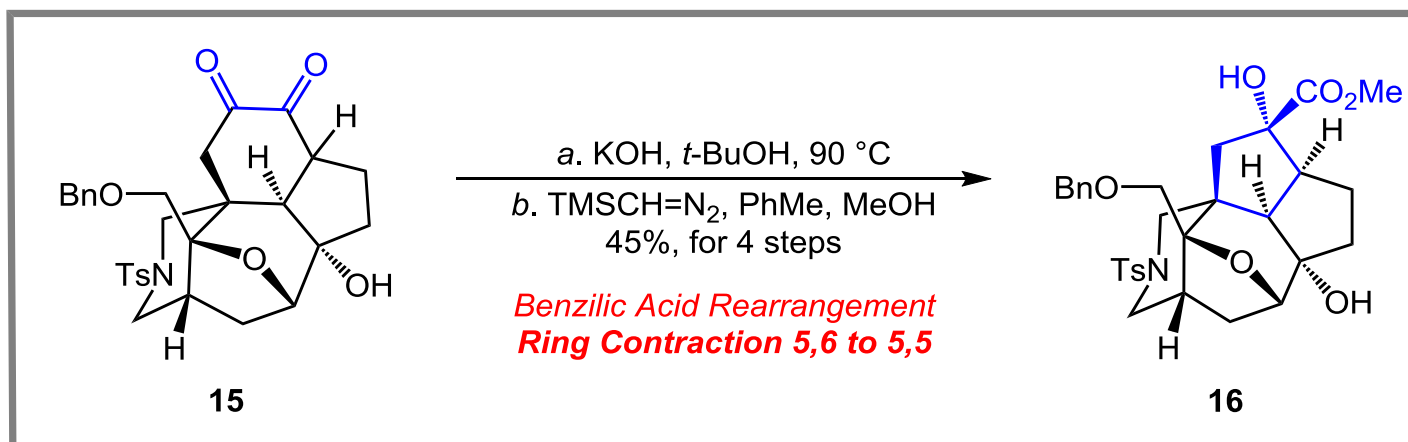
Stage 2--Synthesis of Tetracyclic Core 16



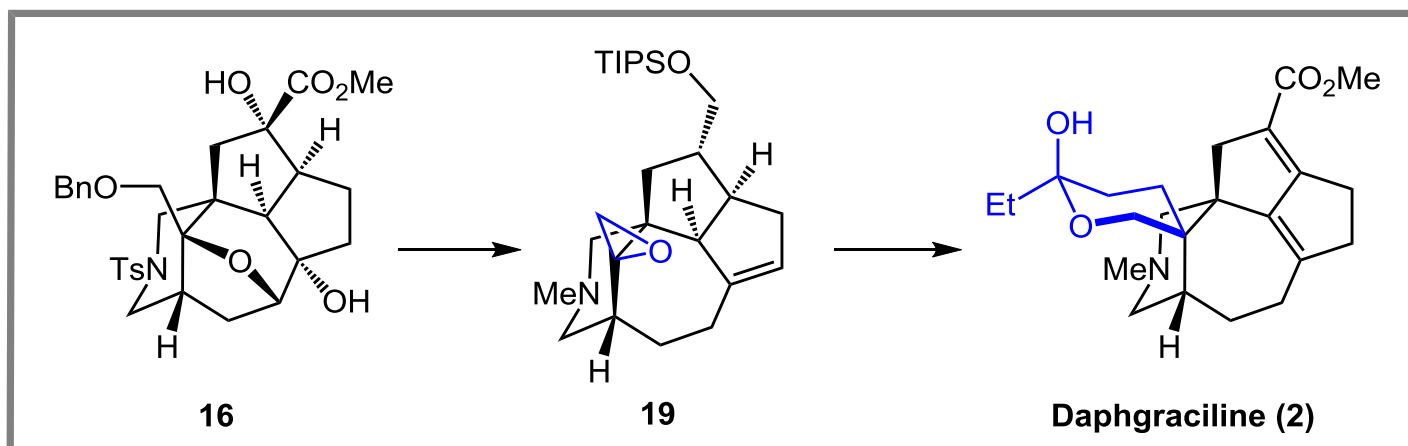
Stage 2--Synthesis of Tetracyclic Core 16



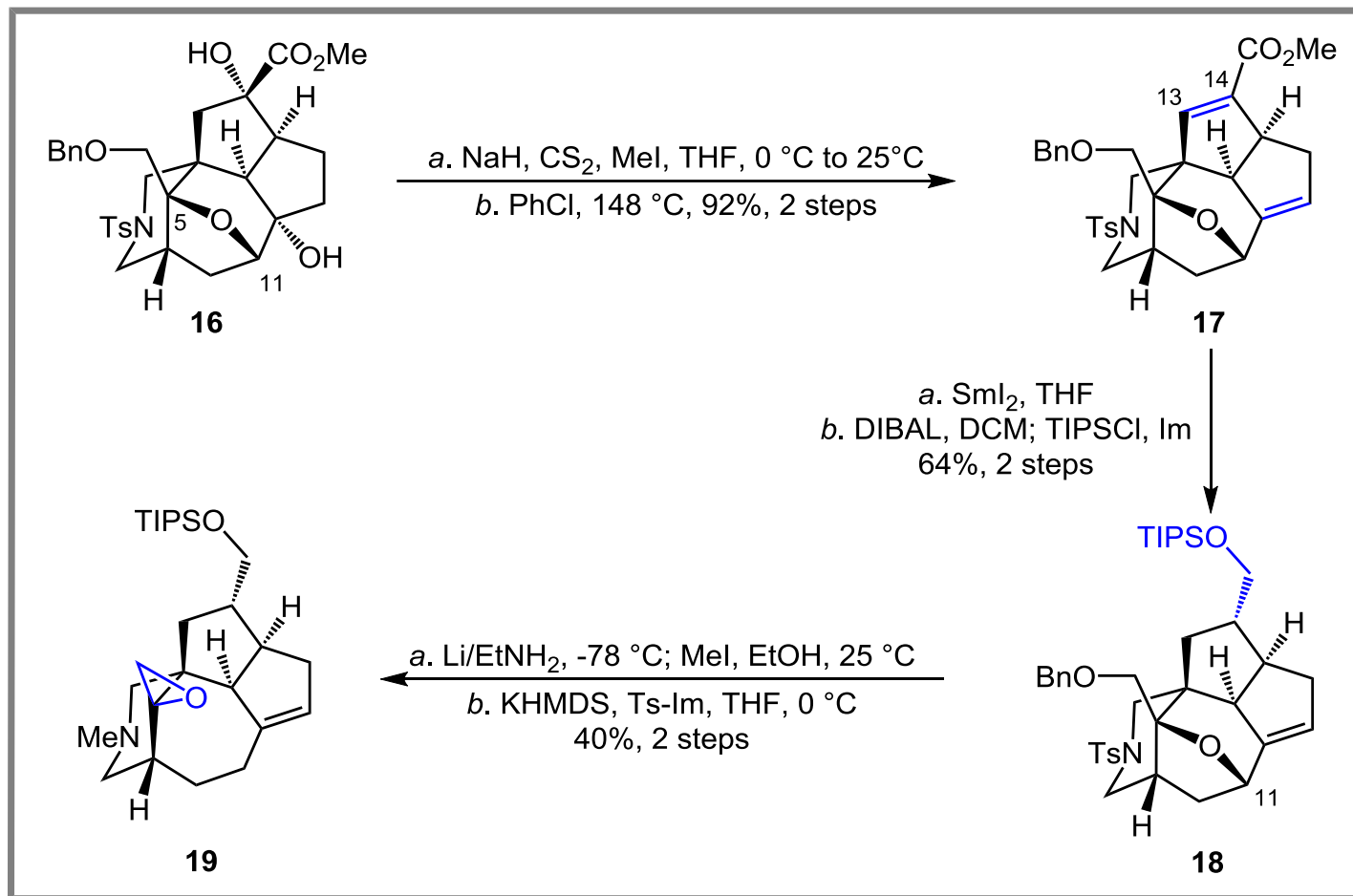
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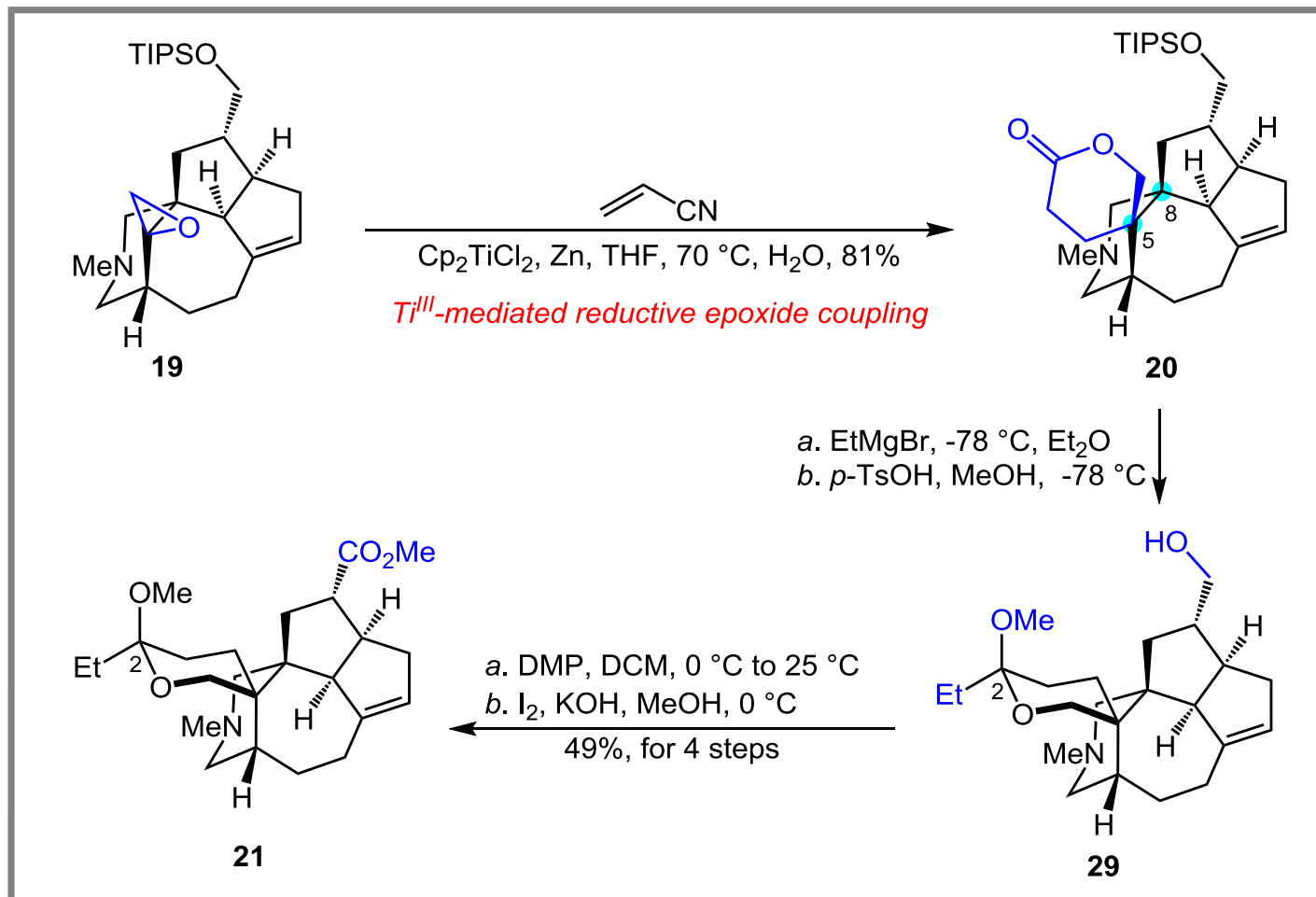
Stage 3--Total Synthesis of Daphgraciline (2)



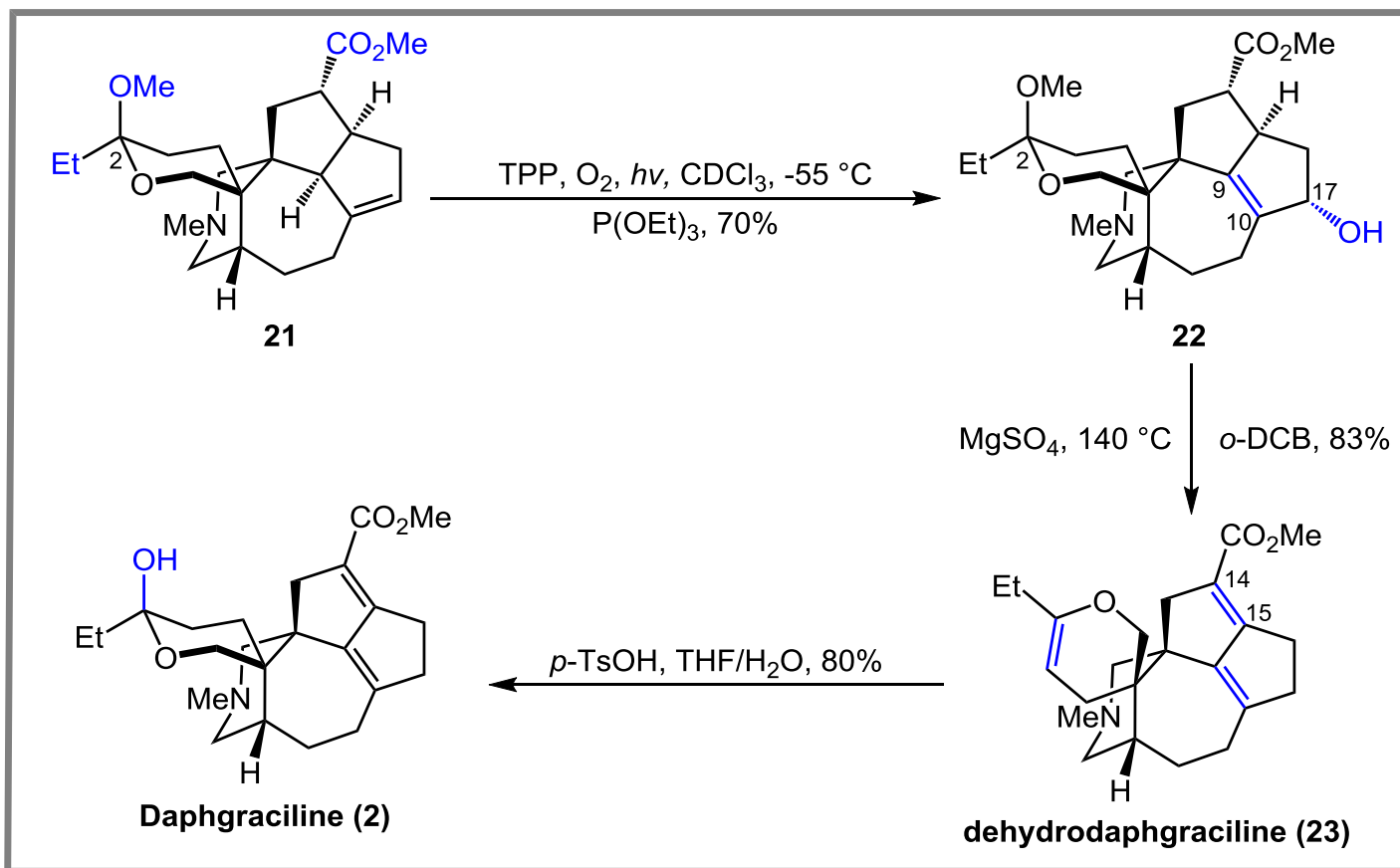
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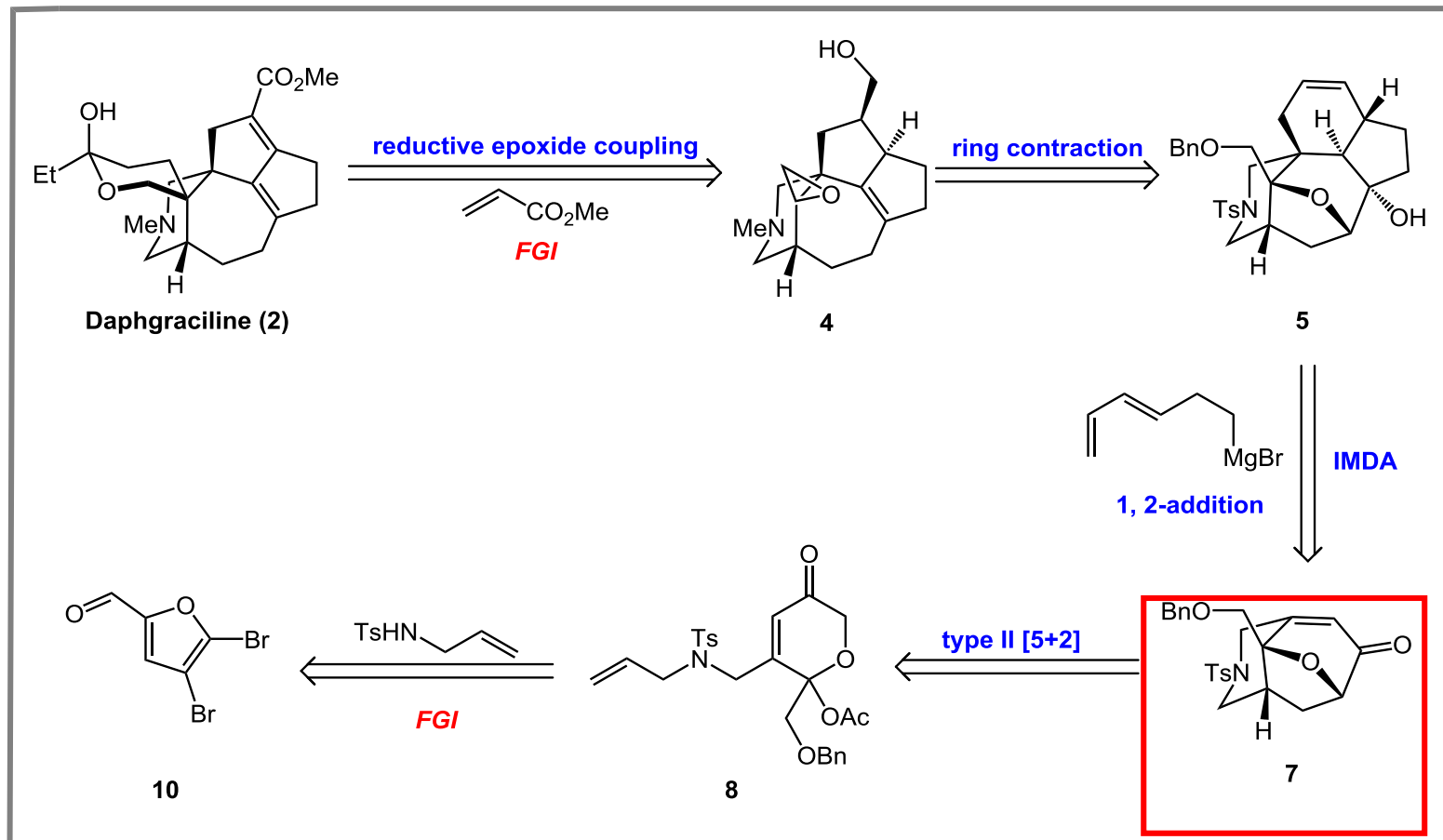
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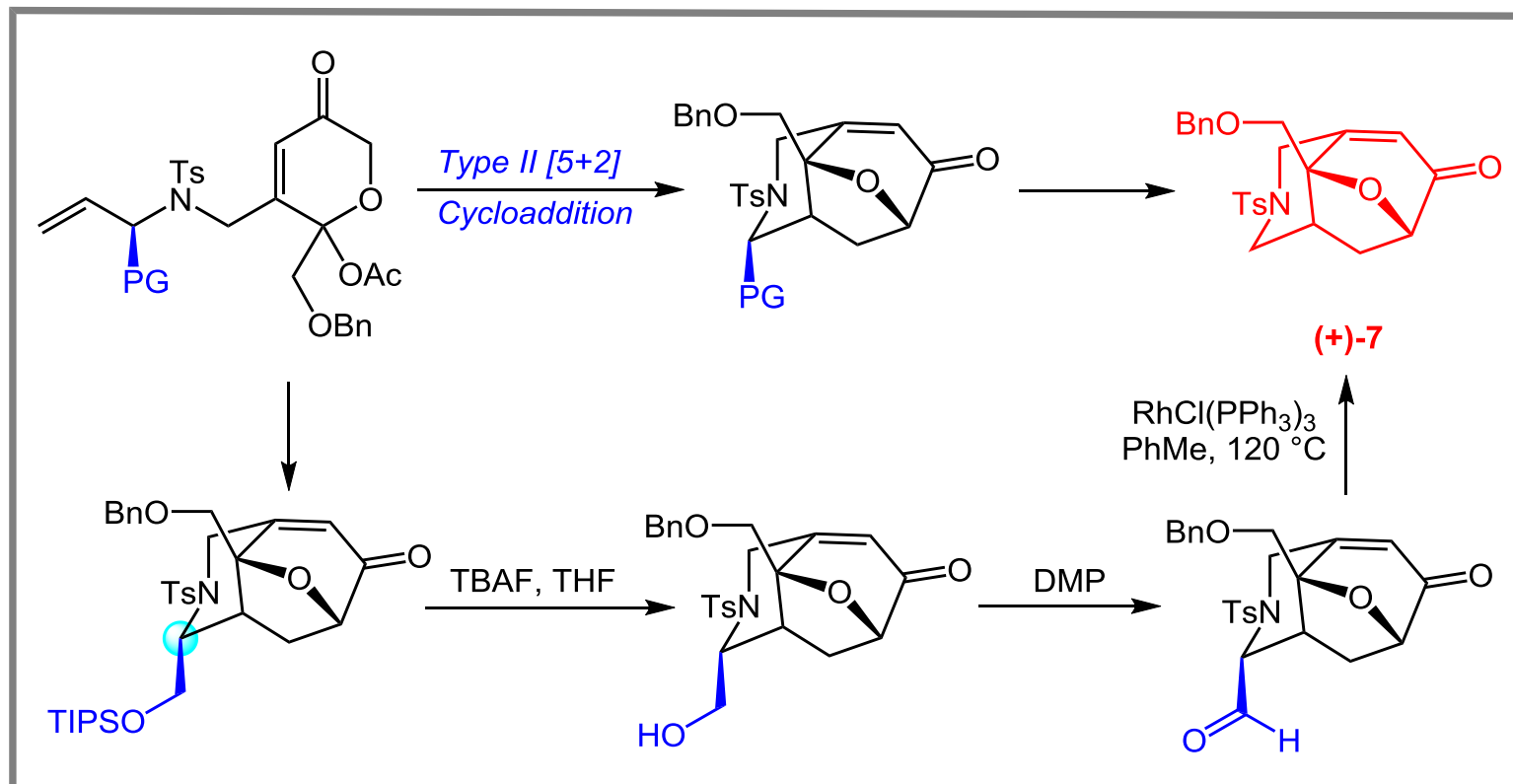
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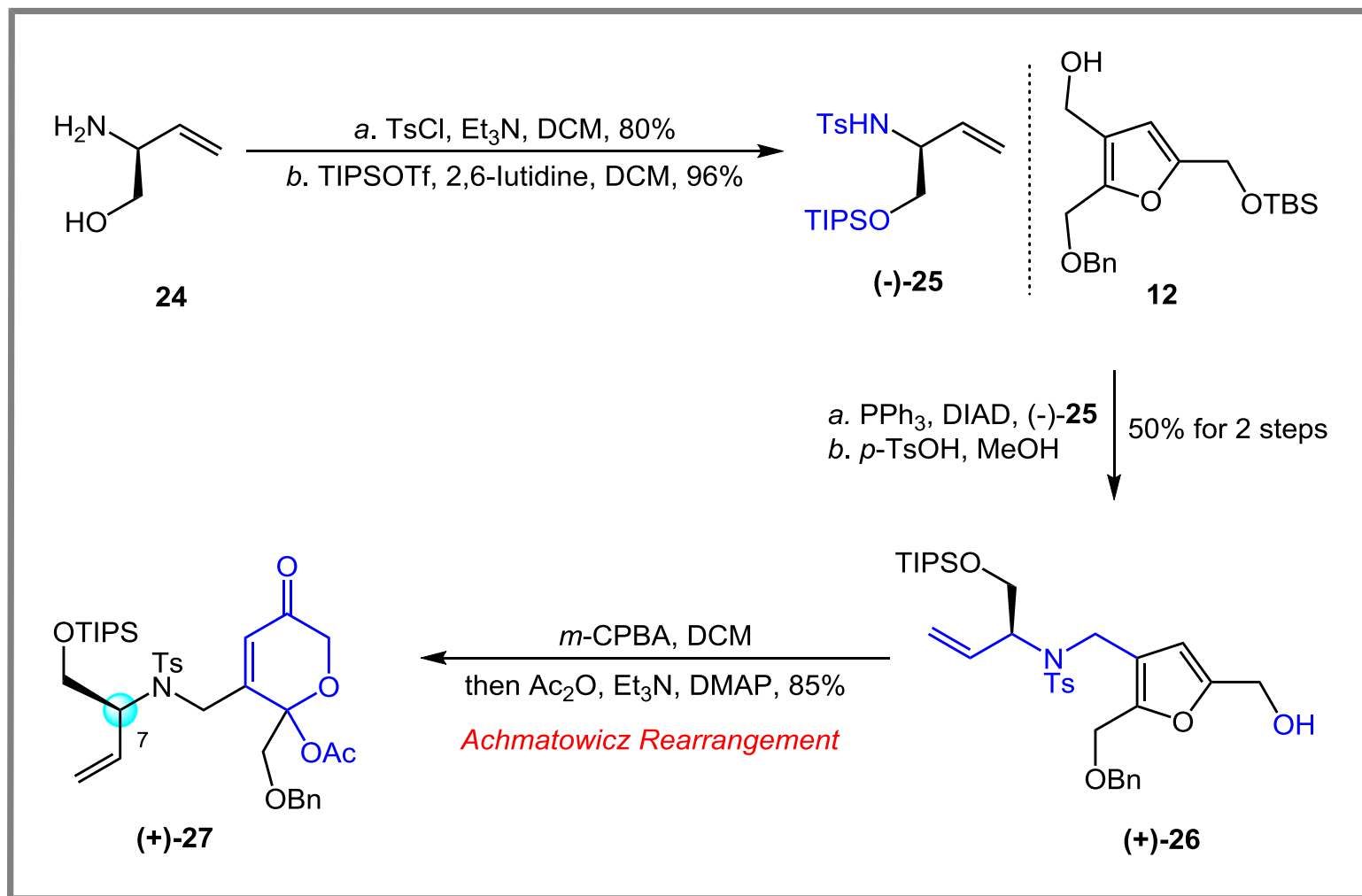
Retrosynthetic Analysis



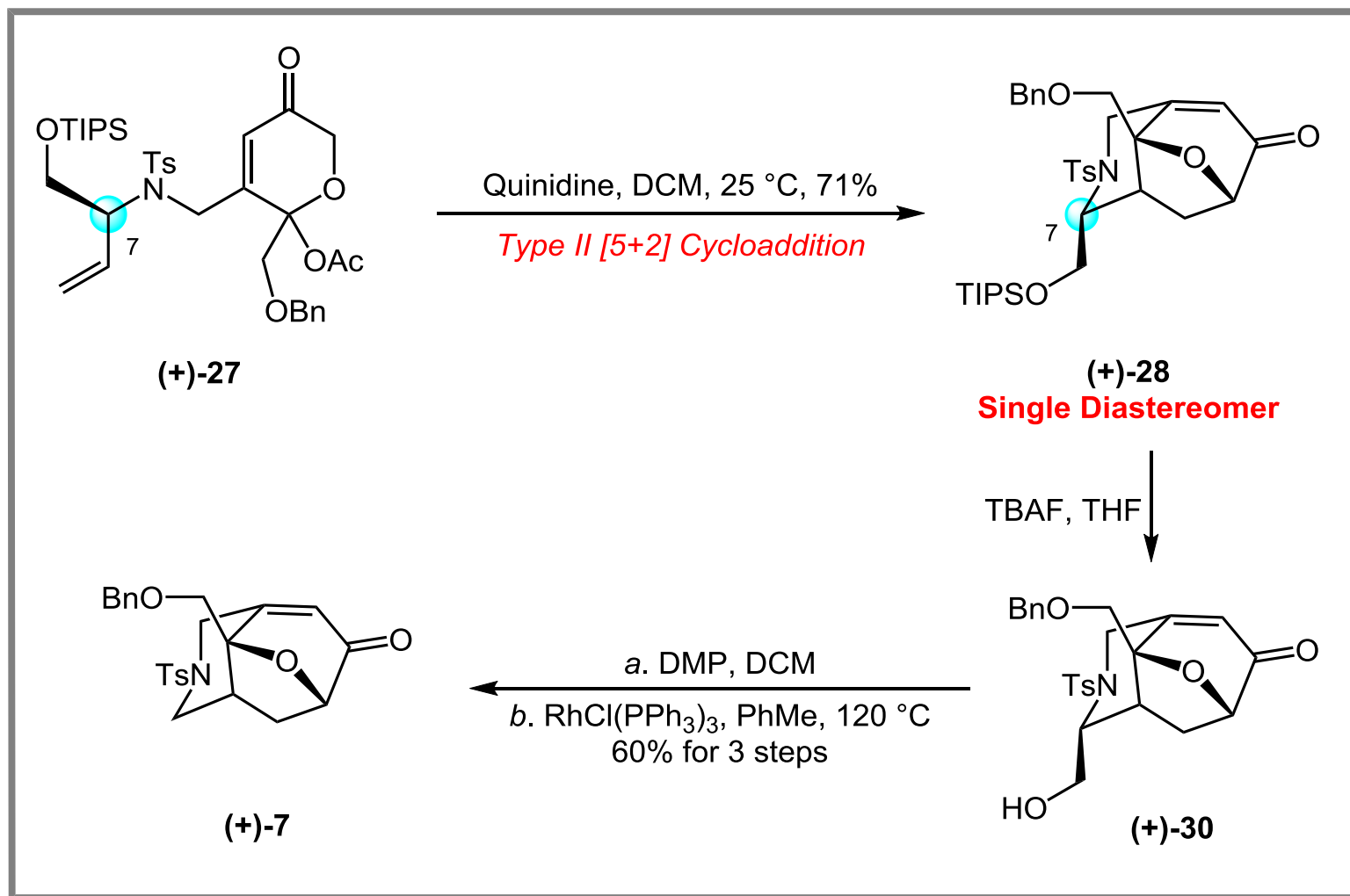
Retrosynthetic Analysis



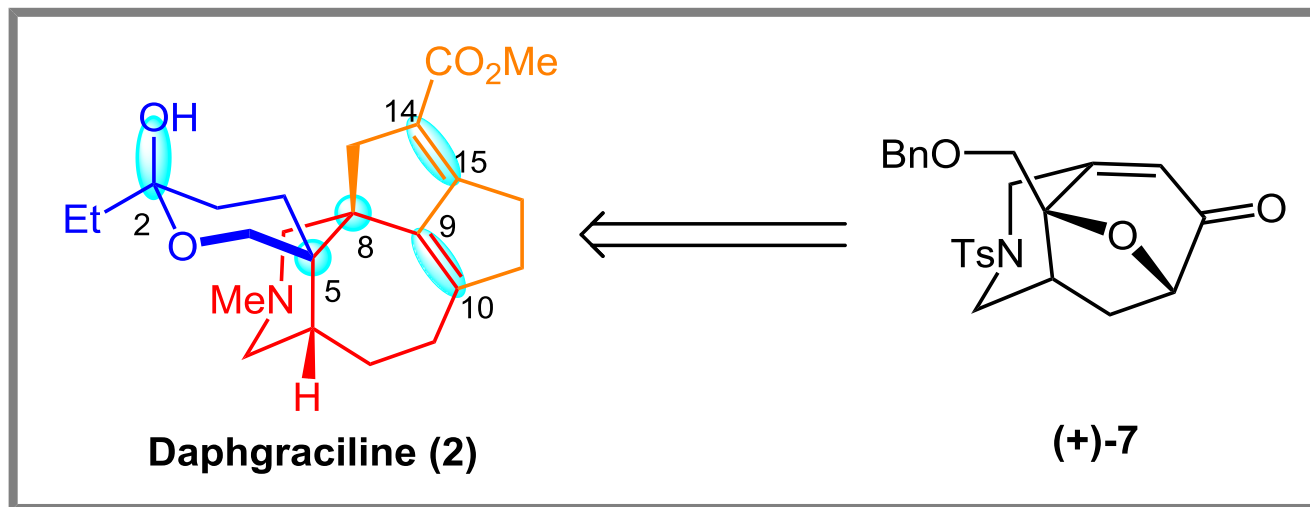
Synthesis of Chiral Intermediate (+)-7



Synthesis of Chiral Intermediate (+)-7



Summary



- ✓ A Mild Type II [5+2] Cycloaddition
- ✓ Low Valent Ti-mediated Reductive Epoxide Coupling
- ✓ IMDA Reaction Followed by Benzilic Acid-type Rearrangement
- ✓ First Total Synthesis of (+/-)-2: 17 Steps, 0.5% Overall Yield

Writing Strategies

□ The First Paragraph

The **Importance** of Alkaloid



Some yuzurine-type alkaloids have shown interesting **cytotoxic activity** against the murine lymphoma L1210 cells **and pesticidal activity** against brine shrimp.

The Synthetic **Challenge** of Daphgraciline



Additionally, **2** contains **two sterically hindered tetra-substituted double bonds** (C9-10, C14-15) and a C2 hemiketal moiety. The synthesis of **2** therefore poses a formidable challenge.

Main Content of **This Work**

In our ongoing efforts to achieve total syntheses of bioactive natural products with bridged ring systems, we have completed **the first total synthesis of (+/-)-2**.

Writing Strategies

□ The Last Paragraph

Summary of This Work



We have **achieved the first total synthesis of (+/-)-(2)**, which also represents the first example of the synthesis of Daphniphyllum yuzurine-type alkaloids.

Elucidate The **Highlights**



This work is the **first demonstration** of using a type II [5+2] cycloaddition or Ti-mediated reductive epoxide coupling in alkaloid synthesis.

The **Prospects** of This Work

This methodology **could be used to synthesize other members** of yuzurine-type subfamily of alkaloids and their analogs.

Representative Examples

- **Sequential** (依次发生的) Li–Br exchanges of dibromofuran **11** with *n*-BuLi were achieved followed by sequential additions of BOMCl, and formaldehyde to afford **12** in 73% yield .
- **After extensive investigation** (经过广泛的调查), mild and optimized conditions for the desired cleavage of the C11–O bond were identified .
- **On the basis of** (基于.....) our previous work, a Schenck ene reaction of **21** using tetraphenylporphyrin (TPP) as the photosensitizer afforded the alcohol **22** with the desired synthetically challenging C9=C10 tetrasubstituted double bond.

Acknowledgement

Dr. Bo Wu, Tong Niu

Thank for Your Attentions!
