

Literature Report I

Total Synthesis of 1-Hydroxytaxinine

Reporter: Li-Xia Liu

Checker: Xiang Li

Date: 2019-12-23

Inoue, M. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 12159

CV of Professor Masayuki Inoue



Background:

- ❑ **1989-1998** B.S. and Ph.D., The University of Tokyo;
- ❑ **1998-2000** Postdoc., Sloan-Kettering Institute for Cancer Research;
- ❑ **2000-2003** Assistant Professor, Tohoku University;
- ❑ **2003-2004** Lecturer, Tohoku University;
- ❑ **2004-2007** Associate Professor, Tohoku University;
- ❑ **2007-Now** Professor, The University of Tokyo.

Research:

1. Total synthesis of highly oxygenated polycyclic natural products;
2. Total synthesis and functional analysis of ion channel-forming molecules and antimicrobial molecules;
3. Synthesis of new artificial molecules by modification of natural products templates.

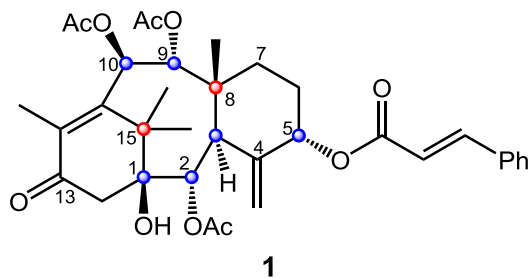
Contents

1 Introduction

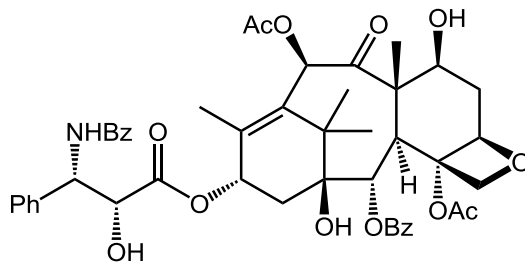
2 Total Synthesis of 1-Hydroxytaxinine

3 Summary

Introduction



1-Hydroxytaxinine



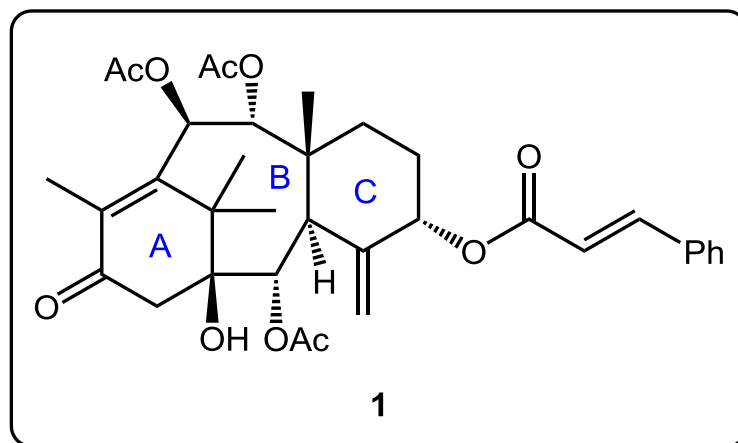
2
Taxol (紫杉醇)



- Isolated from the stems of the Japanese yew, *Taxus cuspidata*, 1-hydroxytaxinine is cytotoxic to murine leukemia L1210 cells and human epidermoid carcinoma KB cells;
- Whereas **2** has been chemically constructed by 10 research groups, the total synthesis of **1** was only reported in a dissertation from Kishi's group in 1998.

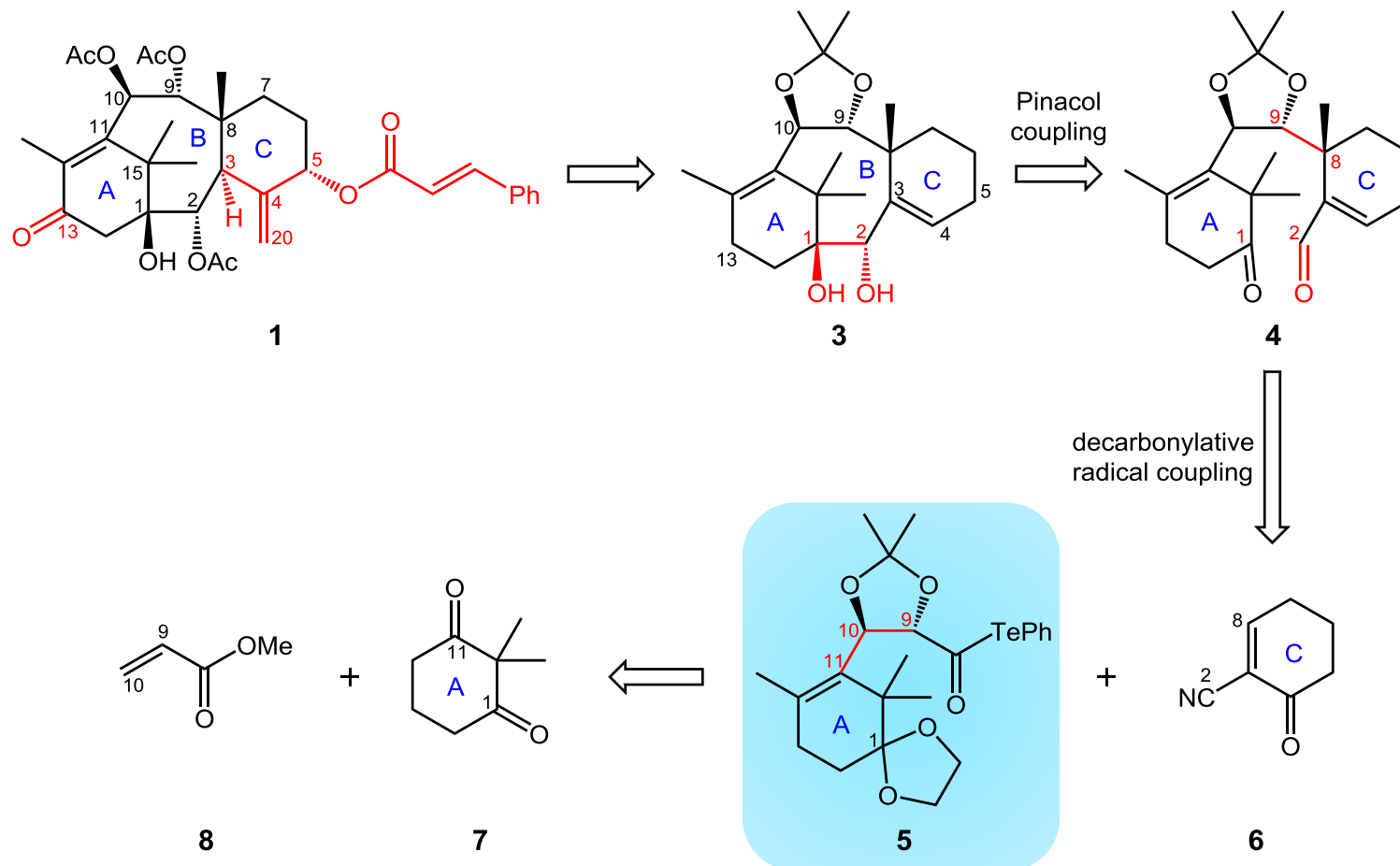
Kiyota, H. *et al. Chem. Rev.* **2011**, *111*, 7652
Inoue, M. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 12159

Total Synthesis of 1-Hydroxytaxinine

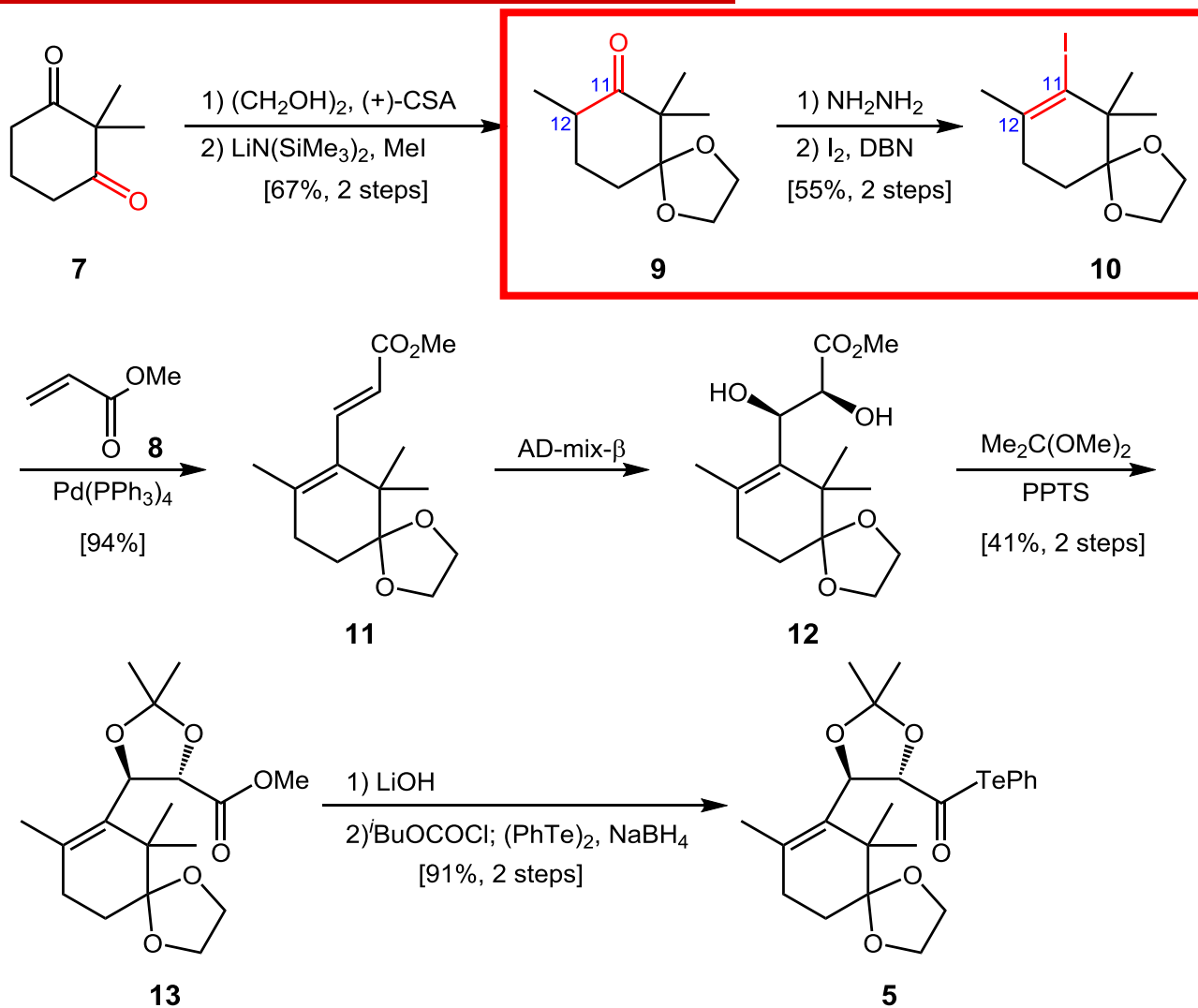


Inoue, M. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 12159

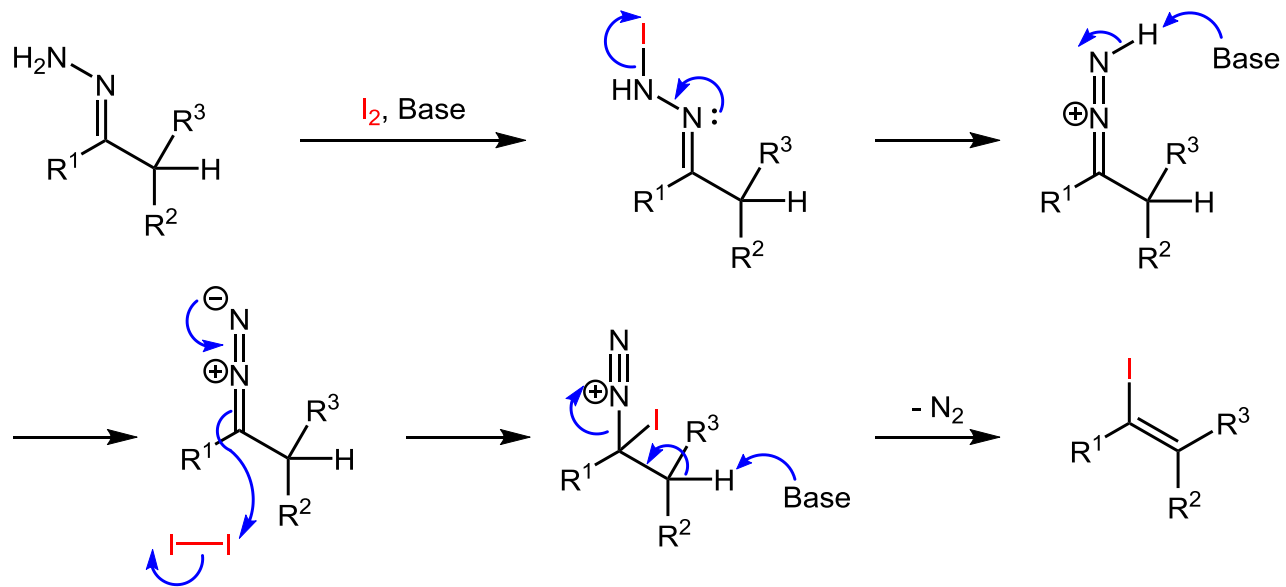
Retrosynthetic Analysis of 1-Hydroxytaxinine



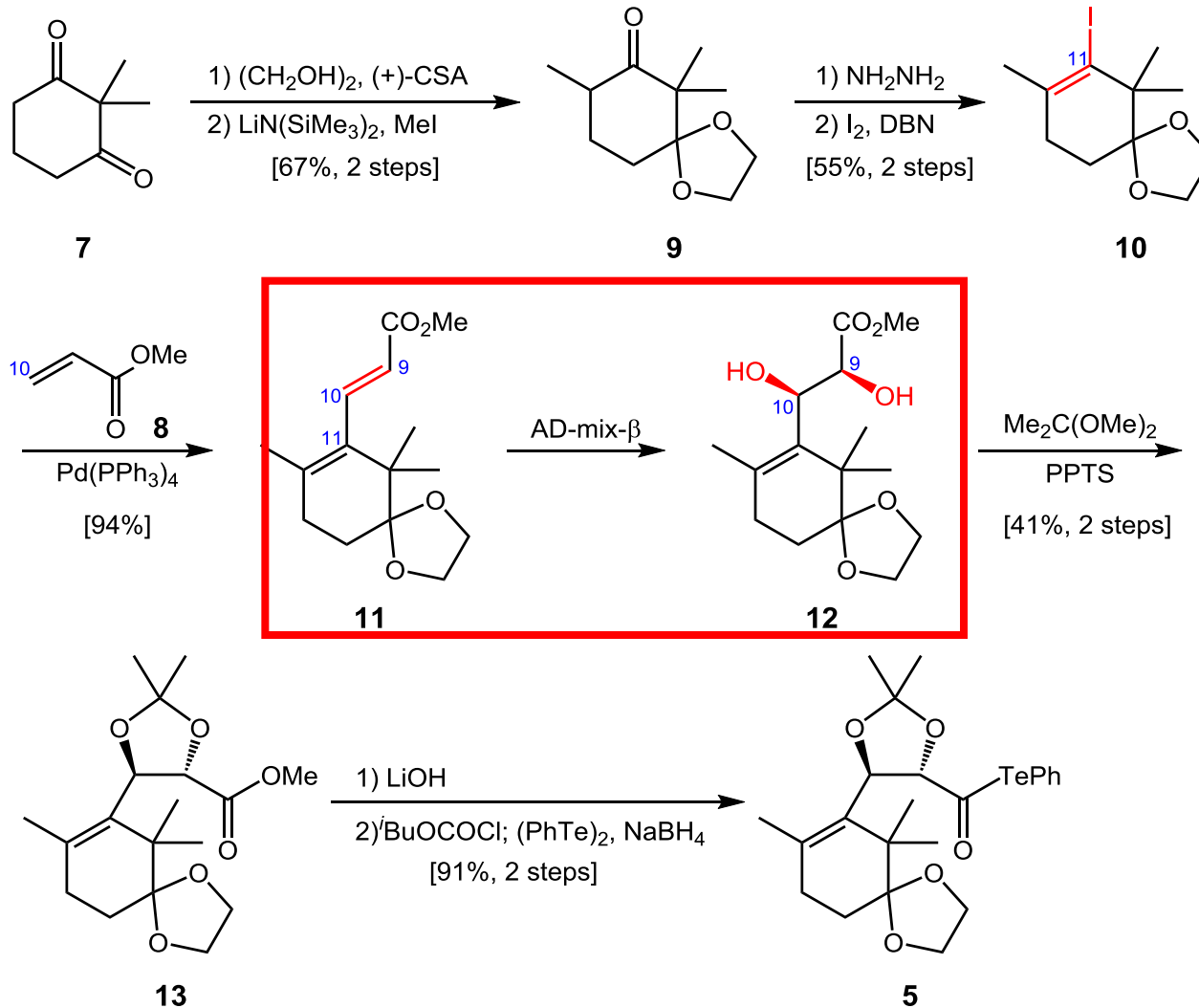
Synthesis of Key Radical Precursor 5



Proposed Mechanism



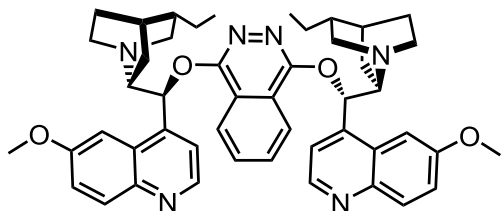
Synthesis of Key Radical Precursor 5



Sharpless Dihydroxylation

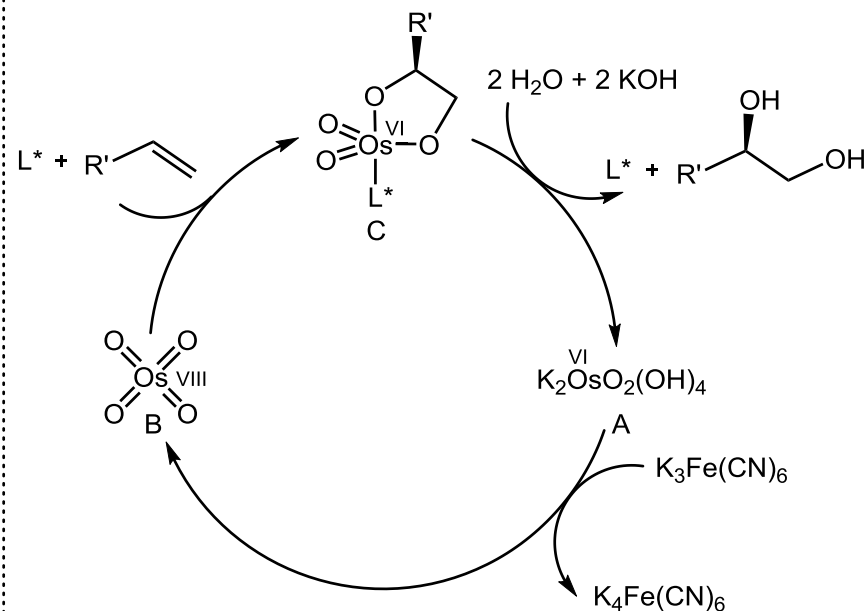
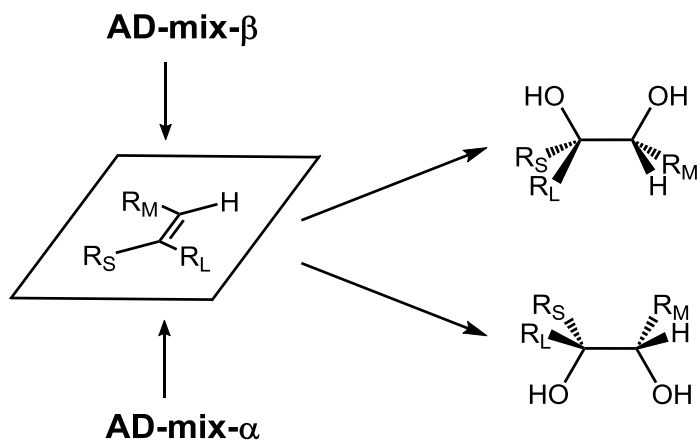
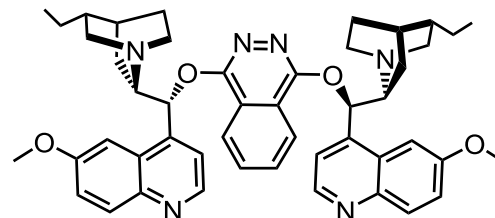
AD-mix- β :

$K_2OsO_2(OH)_4$ (cat.), K_2CO_3 , $K_3Fe(CN)_6$, $(DHQD)_2PHAL$ (cat.):



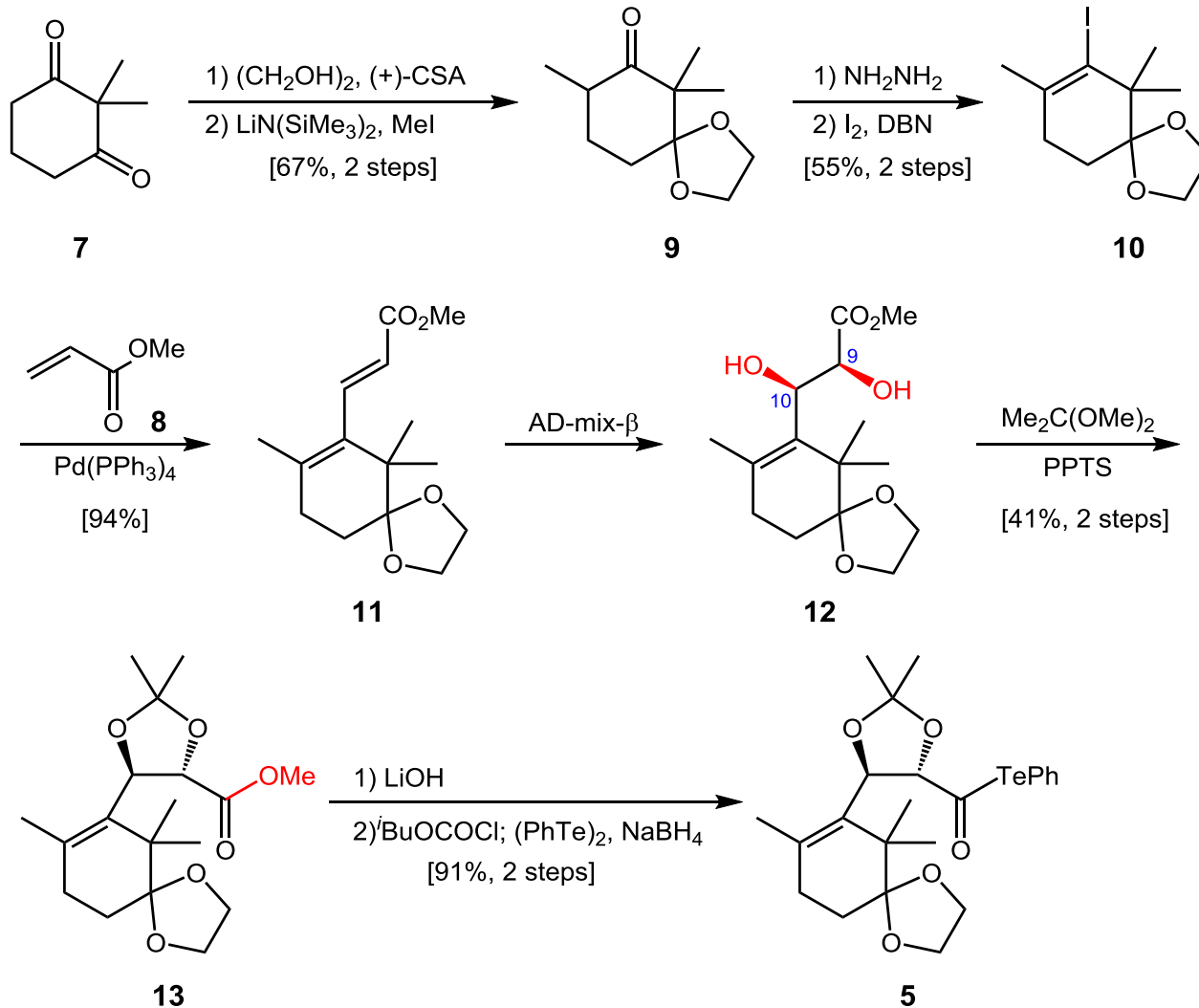
AD-mix- α :

$K_2OsO_2(OH)_4$ (cat.), K_2CO_3 , $K_3Fe(CN)_6$, $(DHQ)_2PHAL$ (cat.):

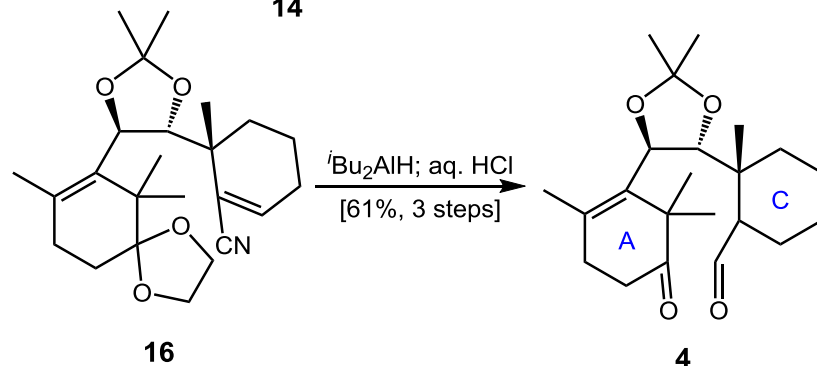
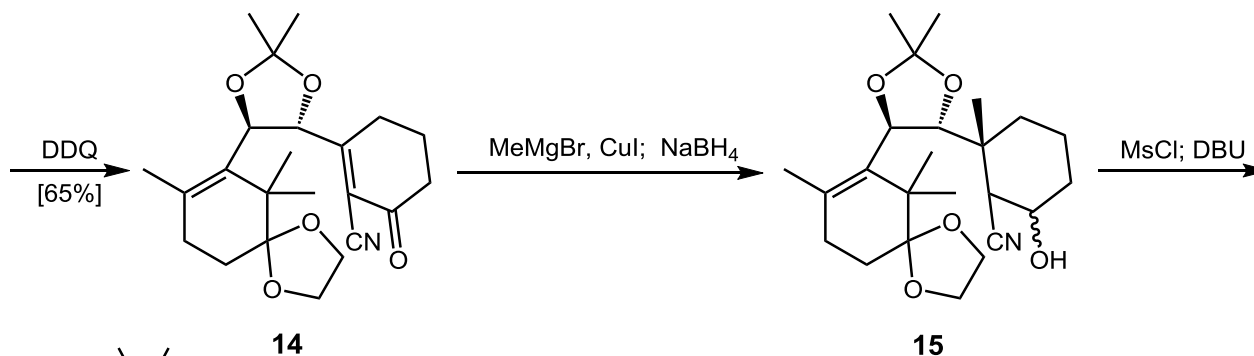
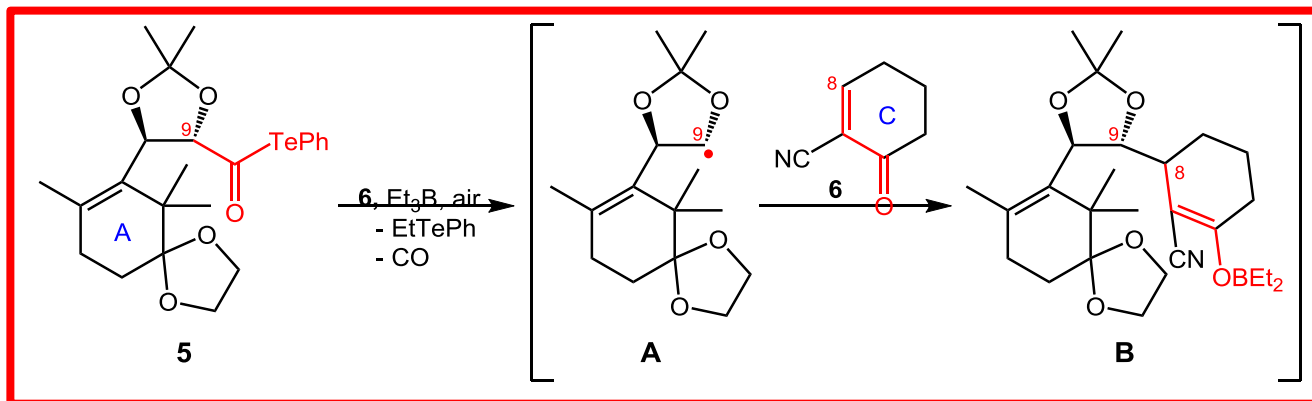


From *Name Reactions*

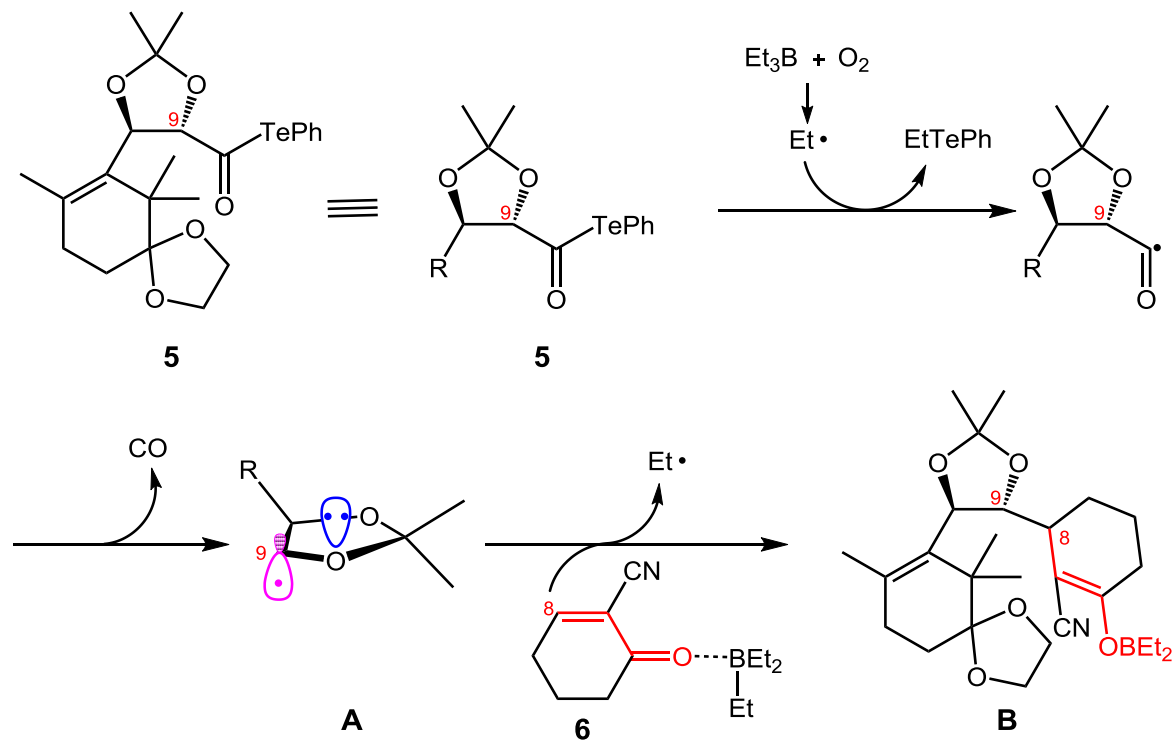
Synthesis of Key Radical Precursor 5



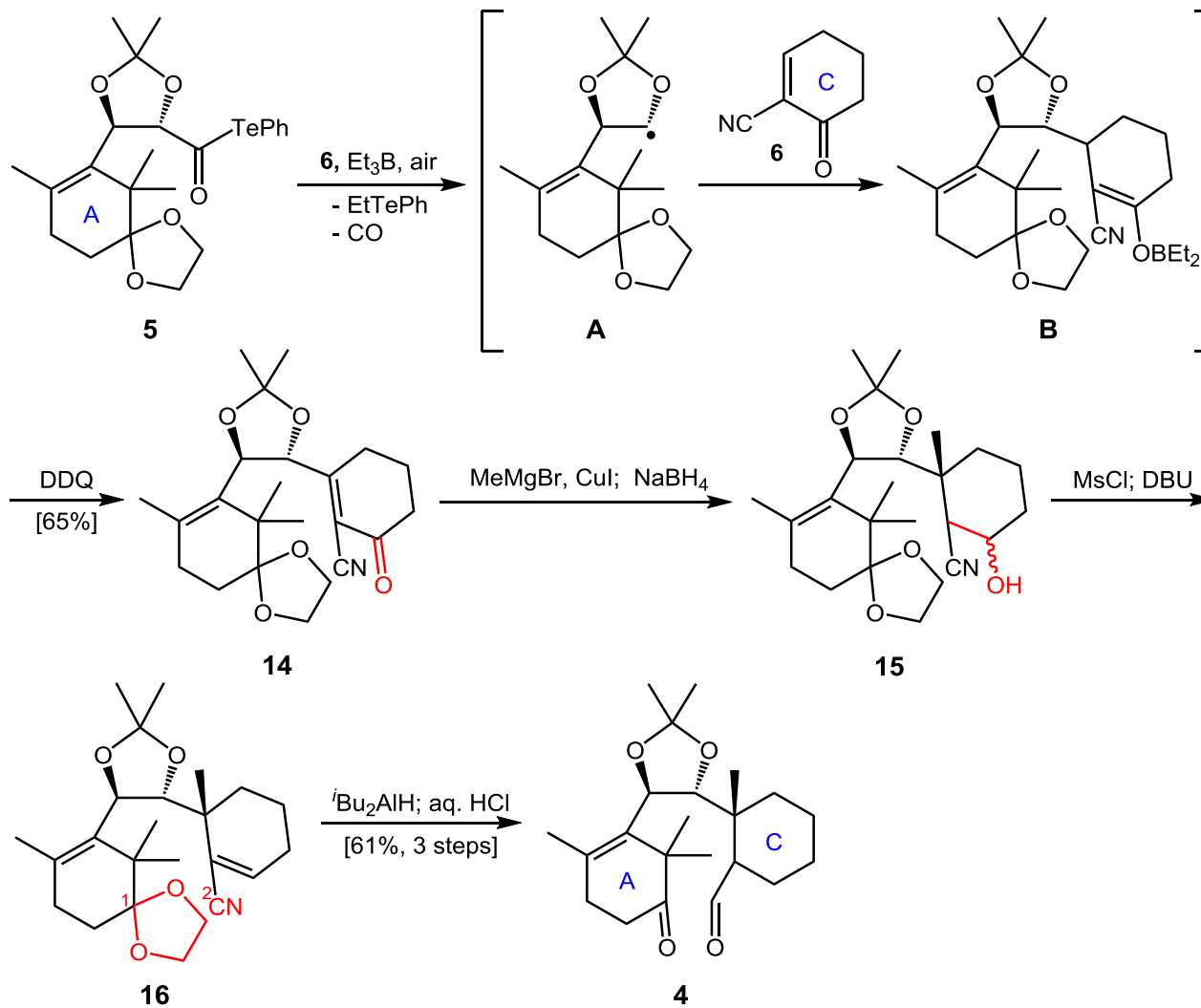
Synthesis of Compound 4



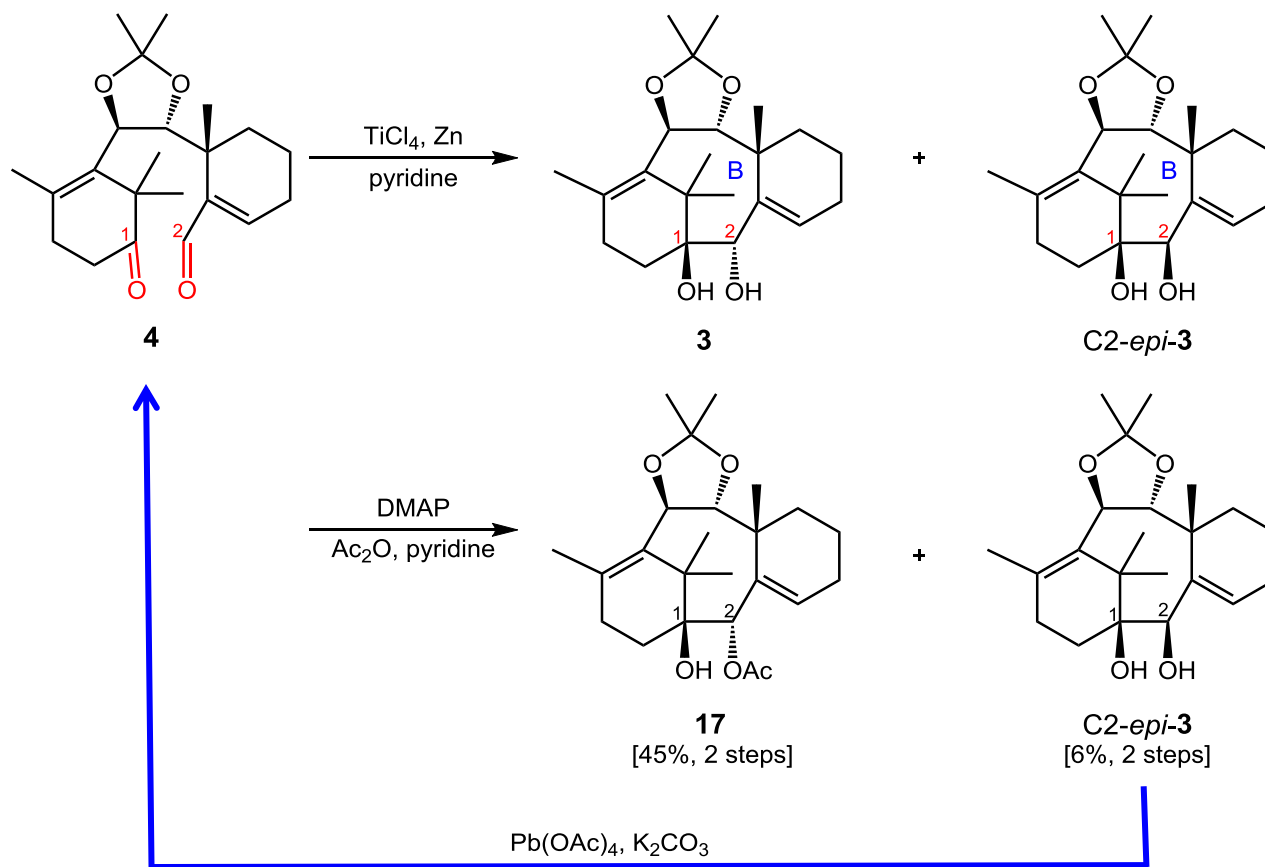
Proposed Mechanism



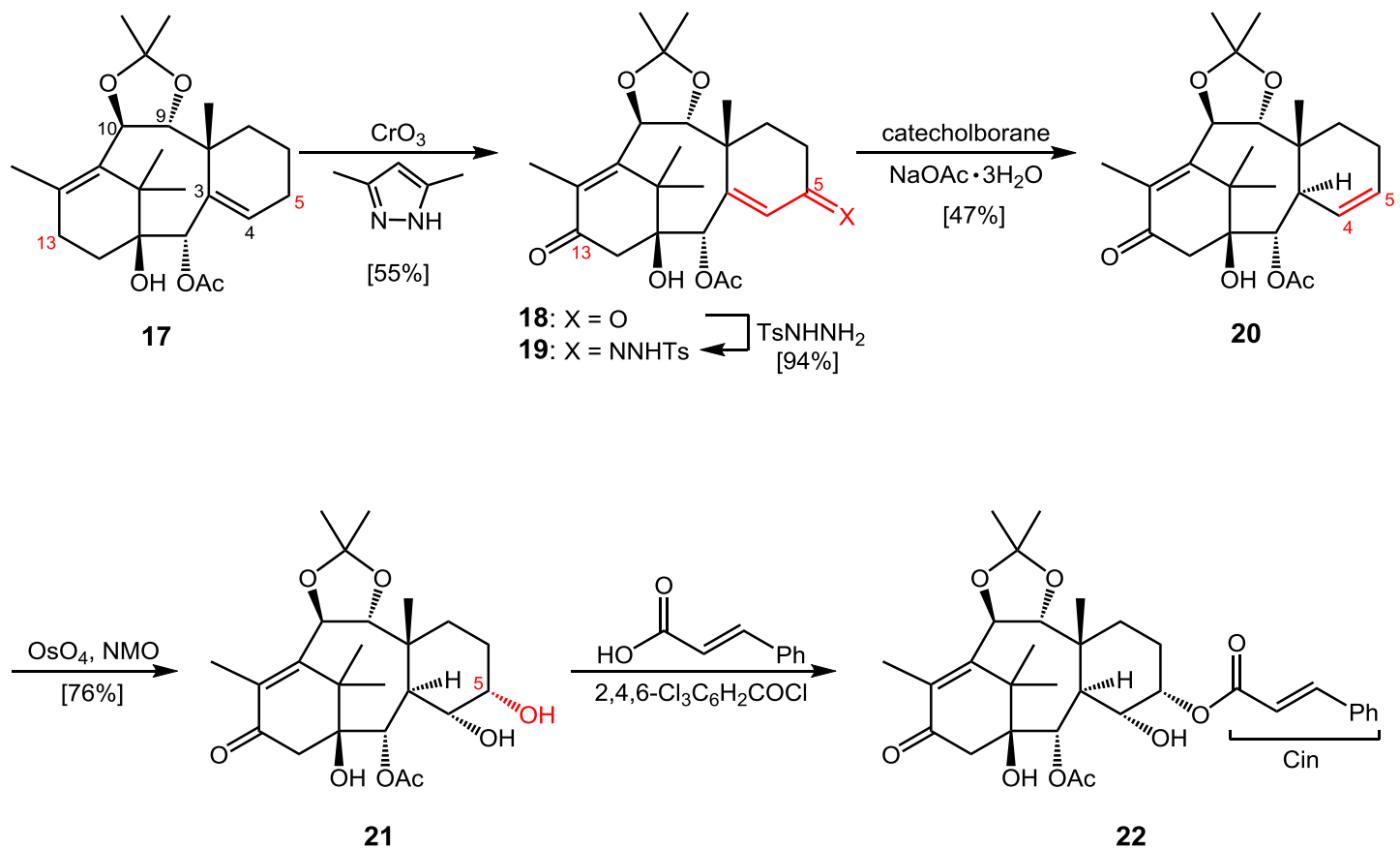
Synthesis of Compound 4



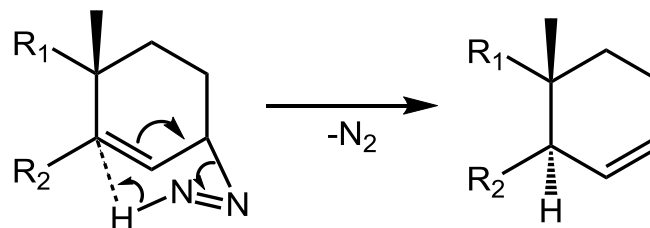
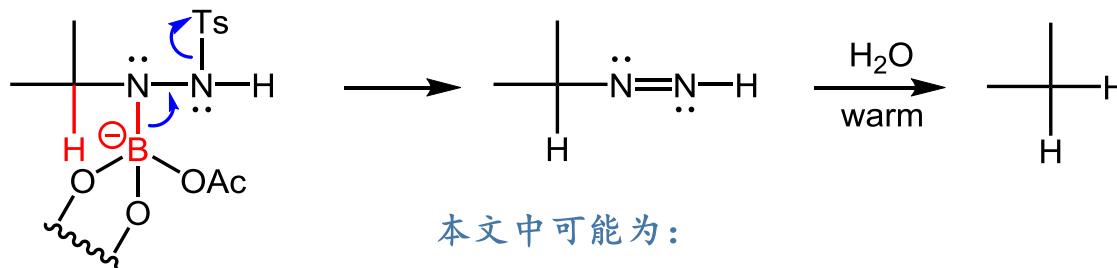
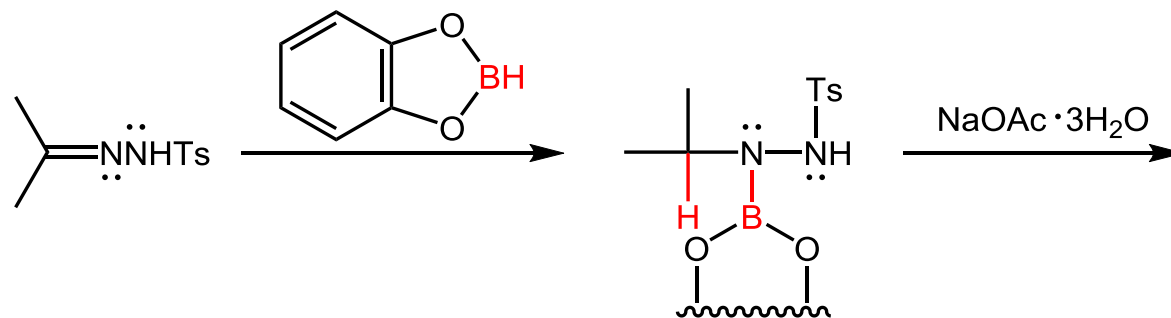
Synthesis of Compound 17



Completion of Compound 22

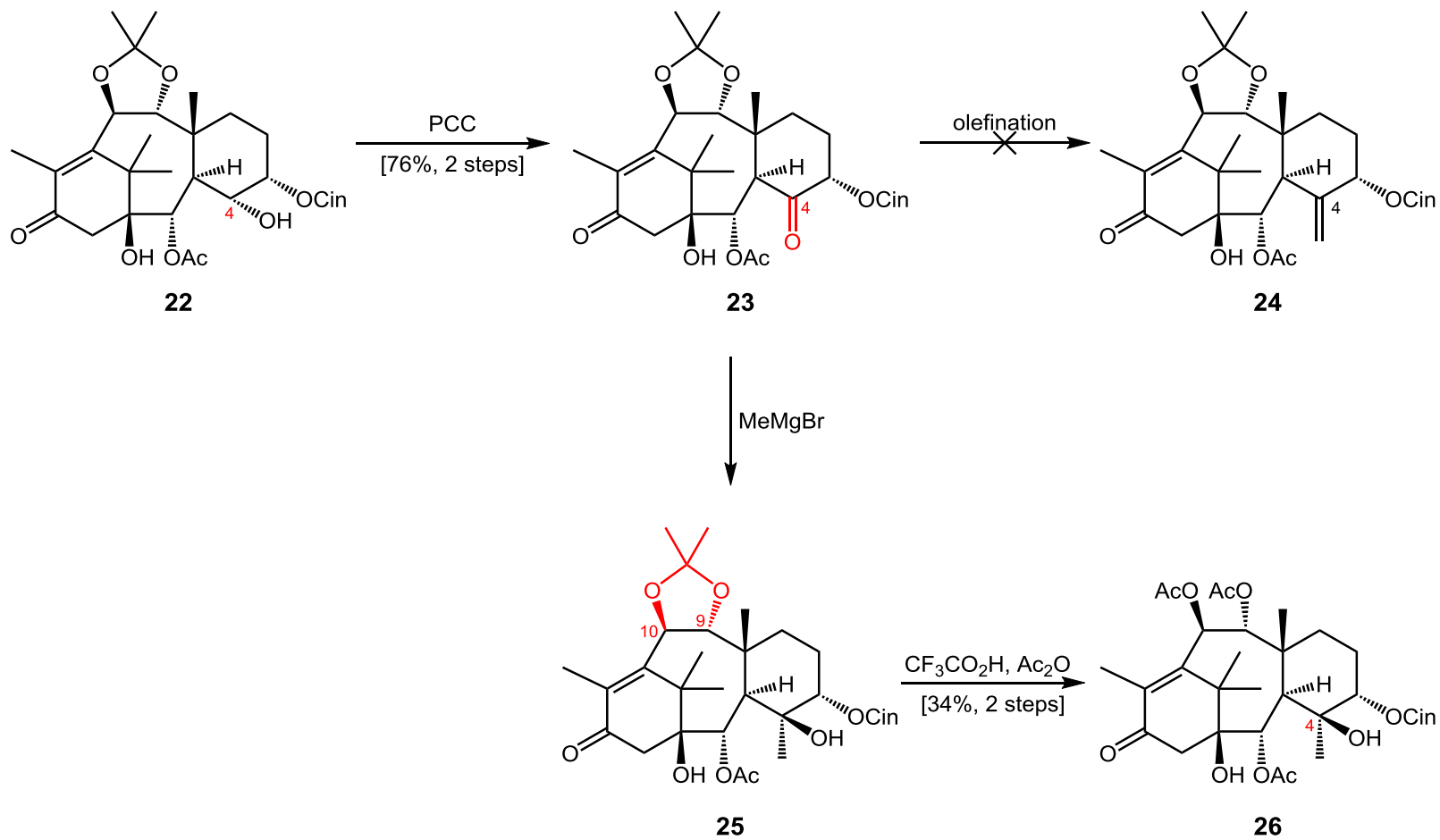


Proposed Mechanism

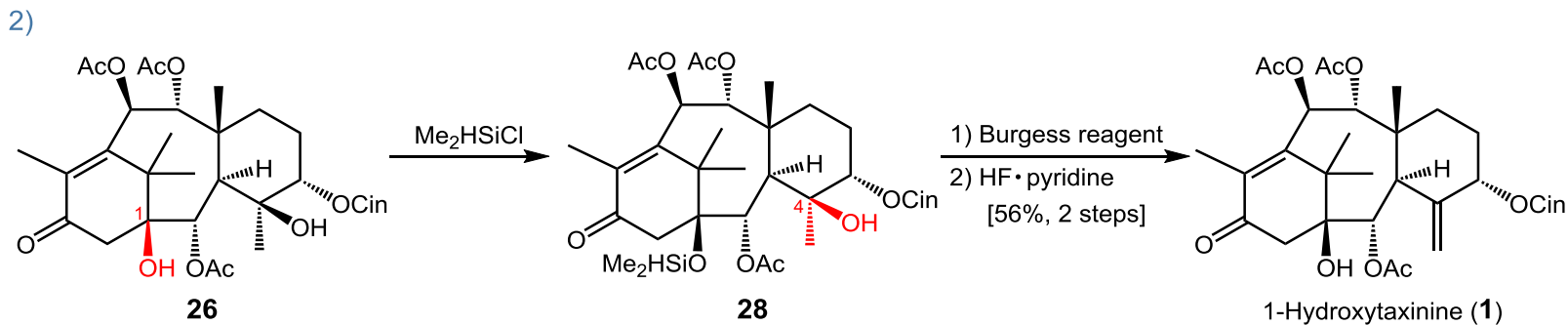
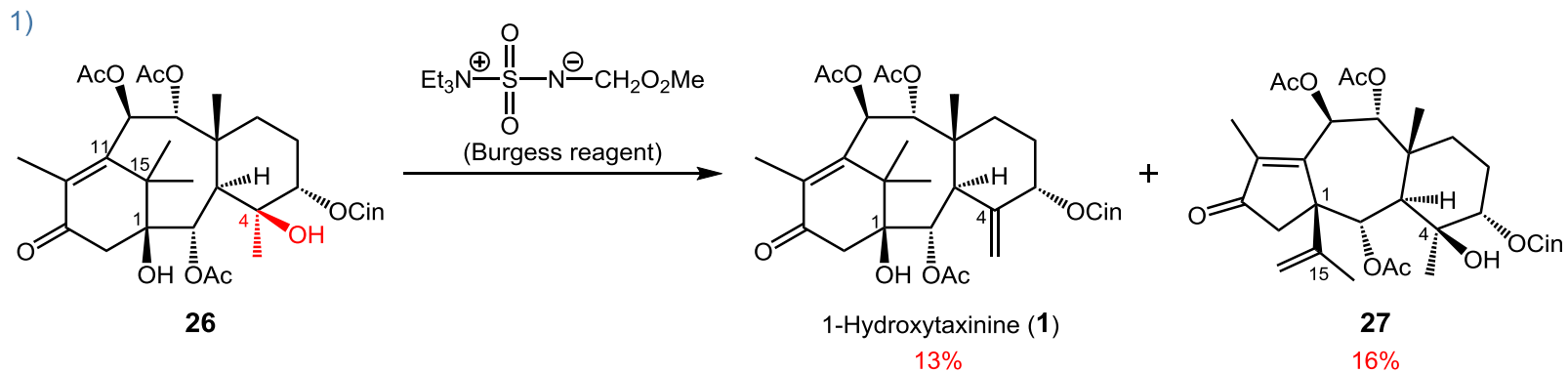


Baker, J. D. *et al.* *J. Org. Chem.* **1976**, *41*, 574

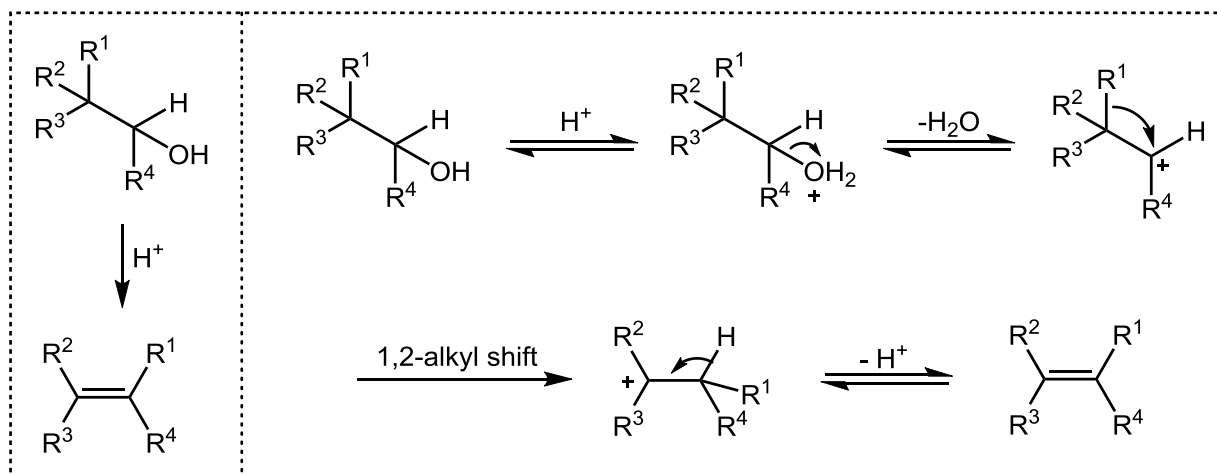
Completion of Compound 26



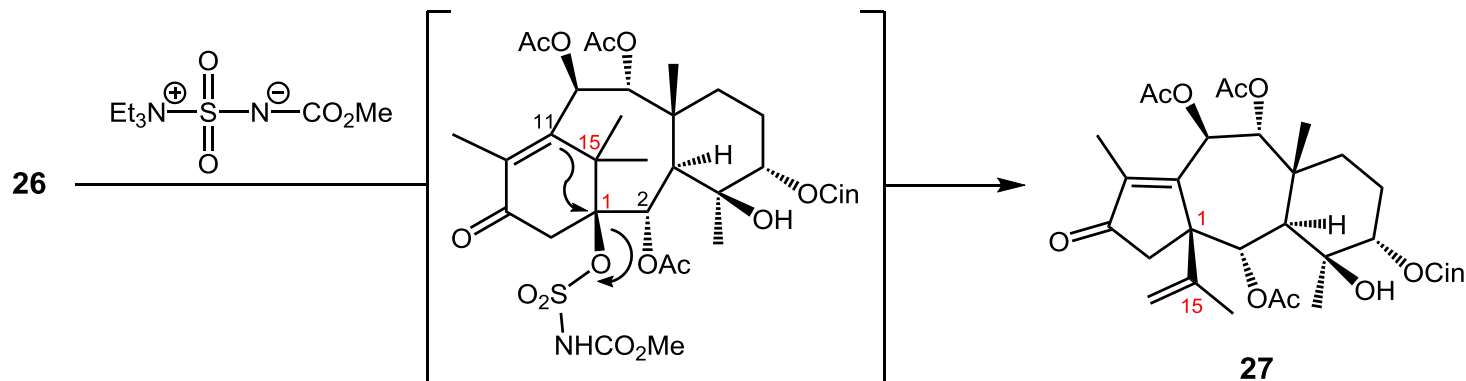
Completion of 1-Hydroxytaxinine (1)



Wagner-Meerwein Rearrangement

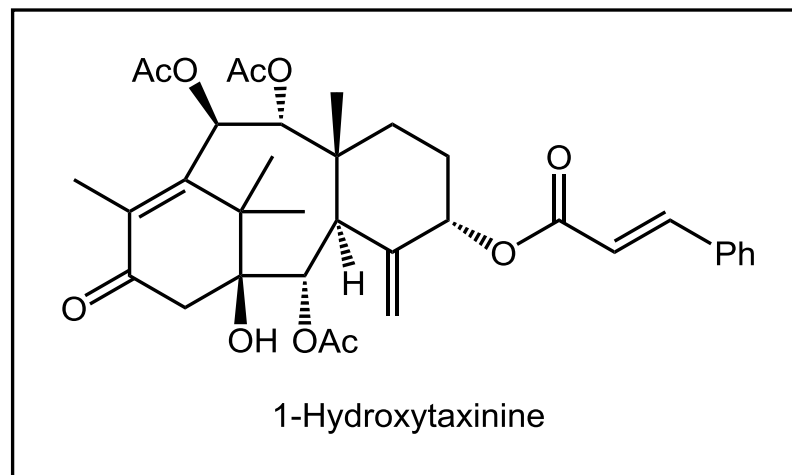


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From Name Reactions

Summary

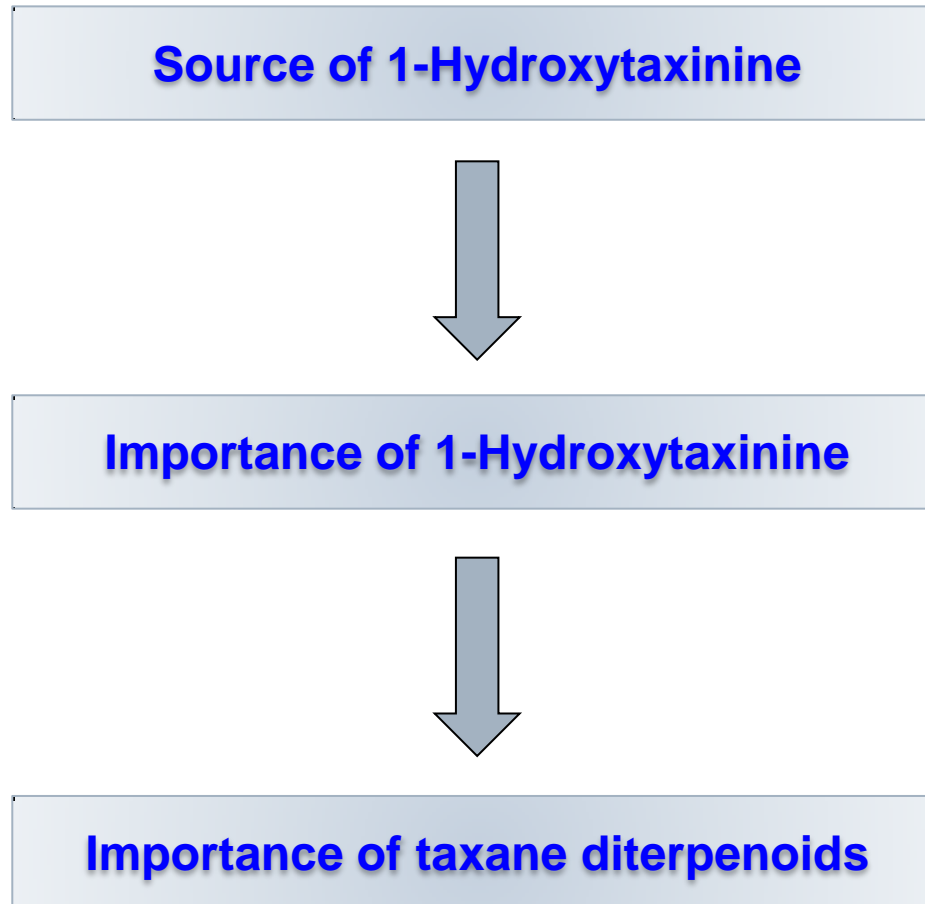


- 26 Total steps, 0.06% overall yield;
- $\text{Et}_3\text{B}/\text{O}_2$ -Promoted decarbonylative radical formation;
- Pinacol coupling reaction.

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The First Paragraph

Writing Strategy

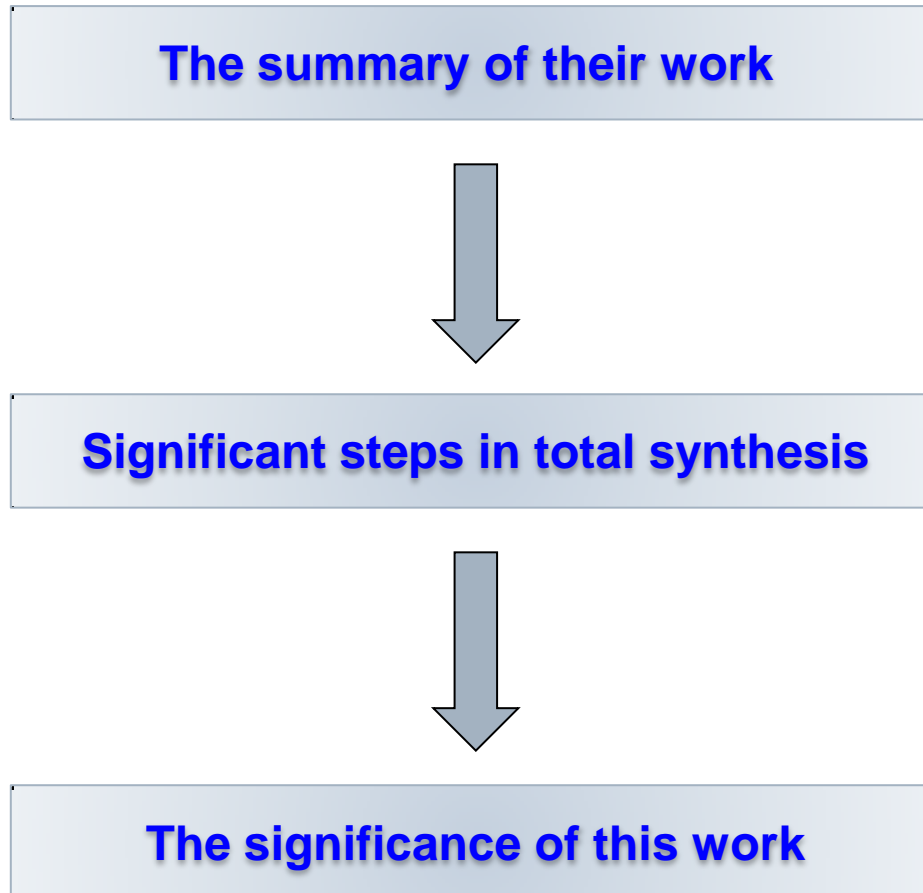


The First Paragraph

Isolated from the stems of the Japanese yew, *Taxus cuspidata*, 1-hydroxytaxinine (**1**) is cytotoxic to murine leukemia L1210 cells and human epidermoid carcinoma KB cells. This natural product belongs to a family of taxane diterpenoids containing more than 400 congeners. Many compounds in this family have biologically important properties, and taxol (**2**), one of the most bioactive congeners, is used clinically to treat various cancers.

The Last Paragraph

Writing Strategy



The Last Paragraph

In summary, we achieved an asymmetric total synthesis of 1-hydroxy-taxinine (**1**) in 26 total steps from 2,2-dimethylcyclohexane-1,3-dione (**7**). The two powerful radical reactions annulated the B-ring from the judiciously designed A- and C-ring substrates and streamlined the overall synthetic sequence. Because of their flexibility and robustness, the strategy and tactics developed here should be applicable to the synthesis of highly oxygenated taxane diterpenoids, including taxol (**2**).

Representative Examples

Hence, **1** was to be assembled from three commercially available components, **6**, **7**, and **8**. (因此, **1**是由三个商业可得的组分**6**, **7**和**8**组装而成。)

Namely, detailed NMR analysis of **4** at room temperature in [D8]THF revealed that it exists as a 2:1 mixture of conformers, **4a** and **4b**, because of the high rotational barrier around the C10-C11 bond. (换句话说, 在[D8]THF中, 对**4**在室温下的详细NMR分析表明, 由于C10-C11键的高转动势垒, 它以2: 1的构象**4a**和**4b**的形式存在。)

Because of their flexibility and robustness, the strategy and tactics developed here should be applicable to the synthesis of highly oxygenated taxane diterpenoids, including taxol (**2**). (由于它们的灵敏性和稳定性, 这里开发的策略方法应该也适用于合成高氧化的紫杉烷二萜类化合物, 包括紫杉醇(**2**)。)

Acknowledgement

Thanks for your attention !