

Literature Report I

Total Synthesis of Principinol B

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Checker: Jian Chen

Date: 2024-12-02

Du, Q.; Fan, Z.; [Yang, M.](#) *Angew. Chem. Int. Ed.* **2024**, 63, e202400956.

CV of Prof. Yang Ming



● Background:

- **2004-2008** B.S., Hubei University
- **2008-2013** Ph.D., Lanzhou University
- **2013-2015** Postdoctor Fellow, SIOC
- **2015-2019** Postdoctor Fellow, The University of Chicago
- **2019-now** Professor, Lanzhou University

Research Field:

- Total Synthesis of Natural Products
 - Medicinal Chemistry
-

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Introduction

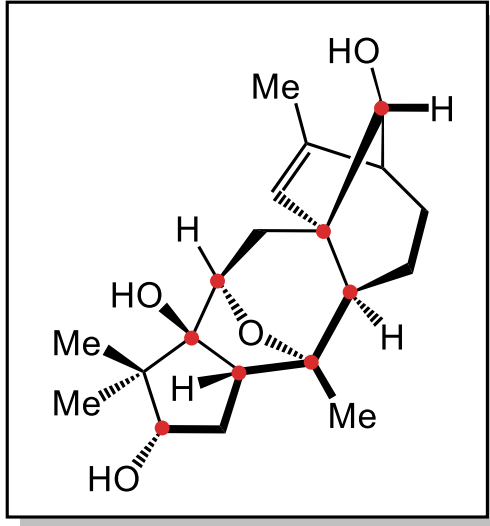
2

Total Synthesis of Principinol B

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Summary

Introduction



Principinol B



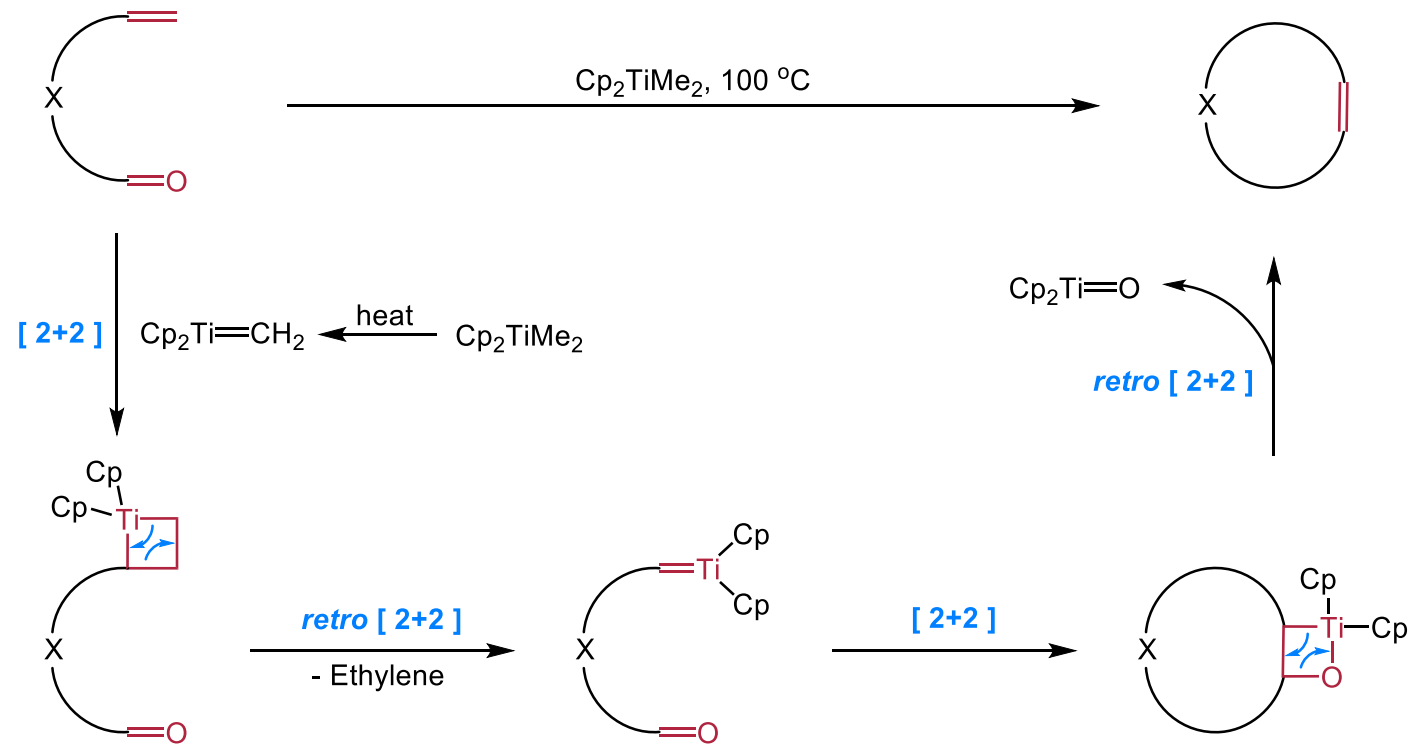
Ericaceae Juss

- It was isolated from the leaves of *Ericaceae Juss* in 2014
- It contains a 5/7/6/5-fused ring system and eight stereocenters (3 quaternary)
- Bioassays show that it exhibited potent analgesic activities and anticancer properties

Liu, C.; Lei, C.; Yu, M.; Li, J.; Hou, A. (侯爱军) *Tetrahedron* **2014**, 70, 4317-4322.

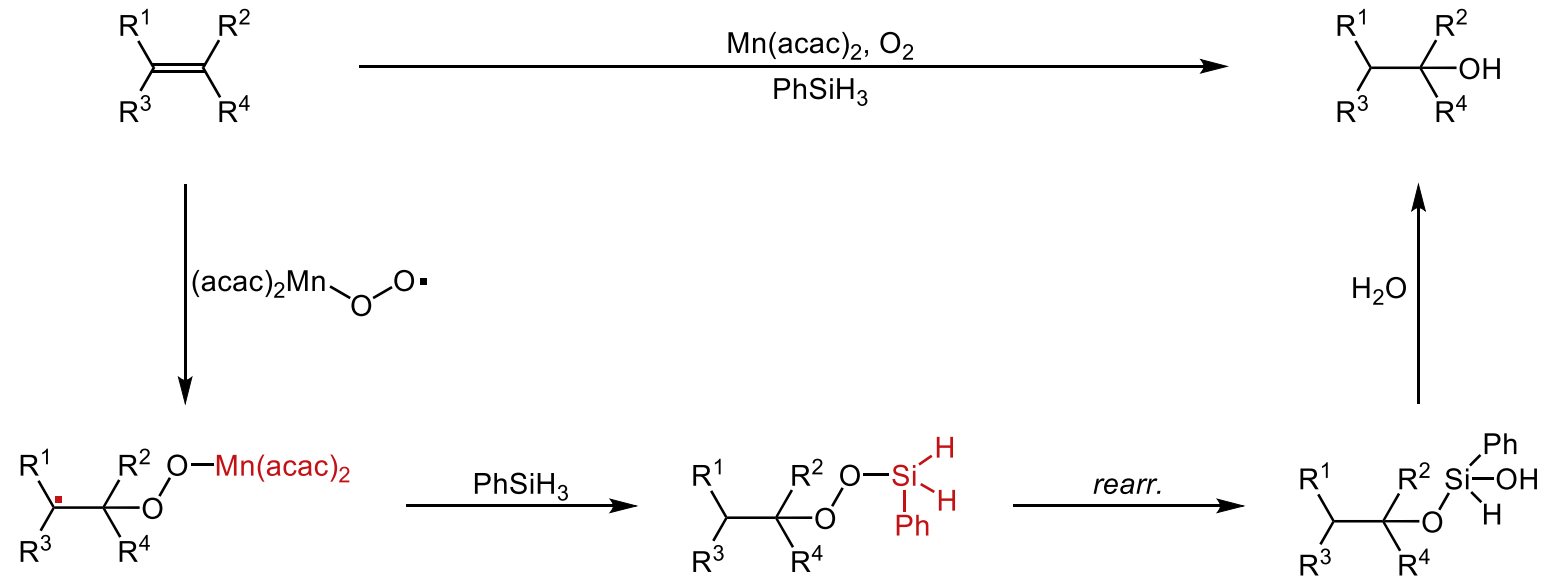
Carbonyl-Olefin Metathesis

Carbonyl-Olefin Metathesis

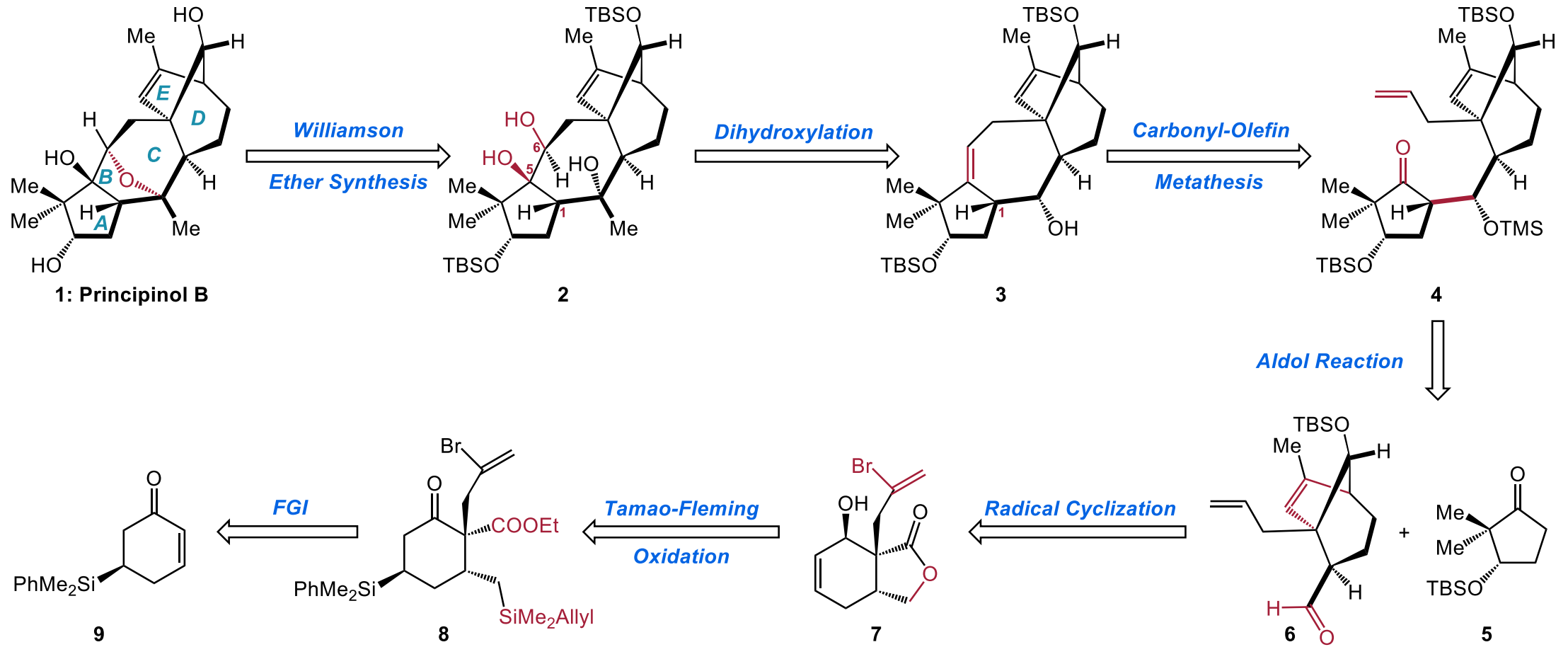


Mukaiyama Hydration

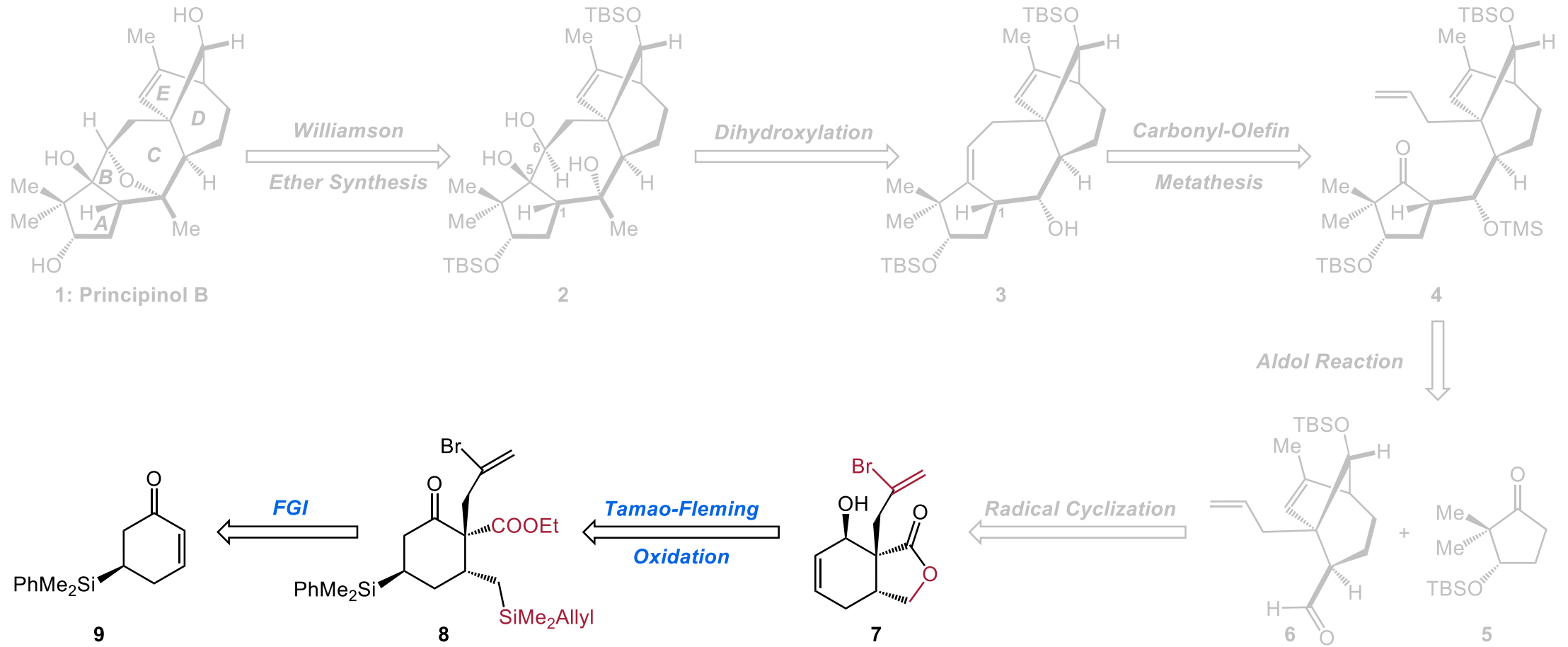
Mukaiyama Hydration



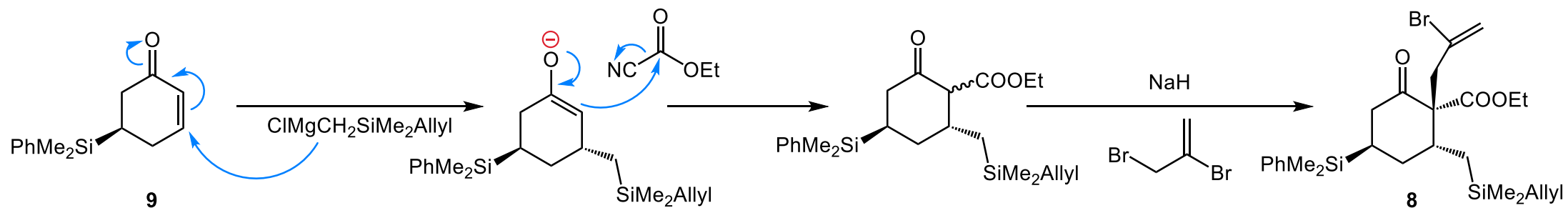
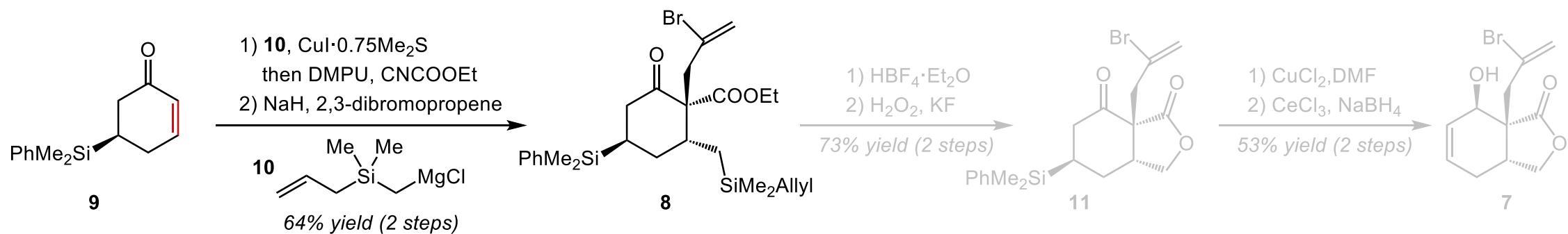
Retrosynthetic Analysis



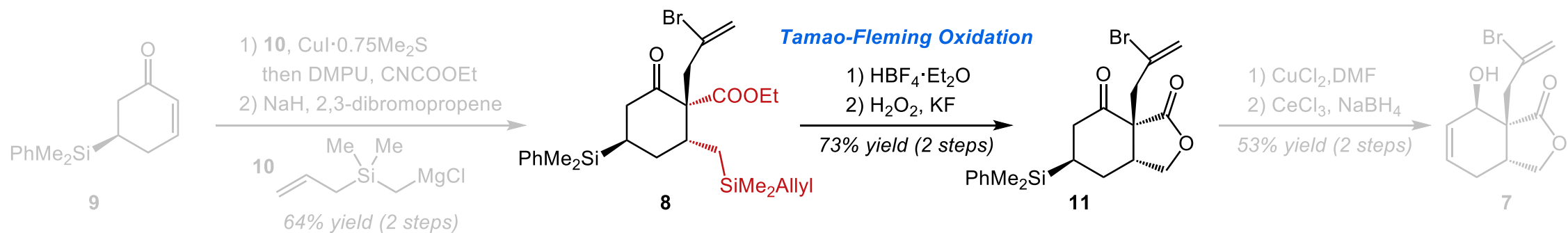
Retrosynthetic Analysis



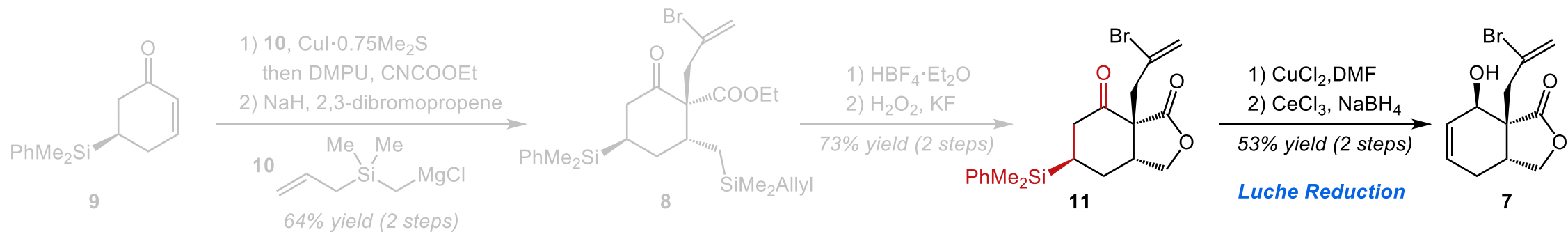
Stage 1: Synthesis of Compound 7



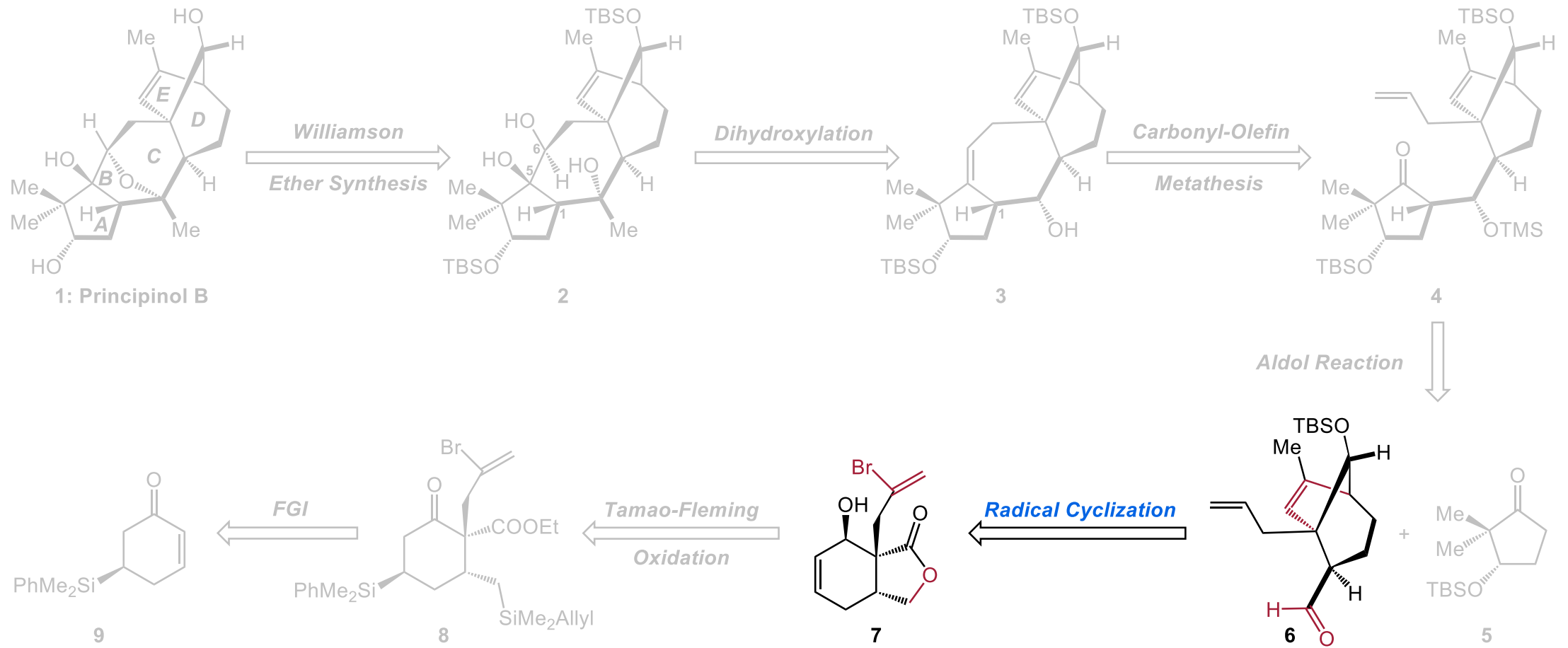
Stage 1: Synthesis of Compound 7



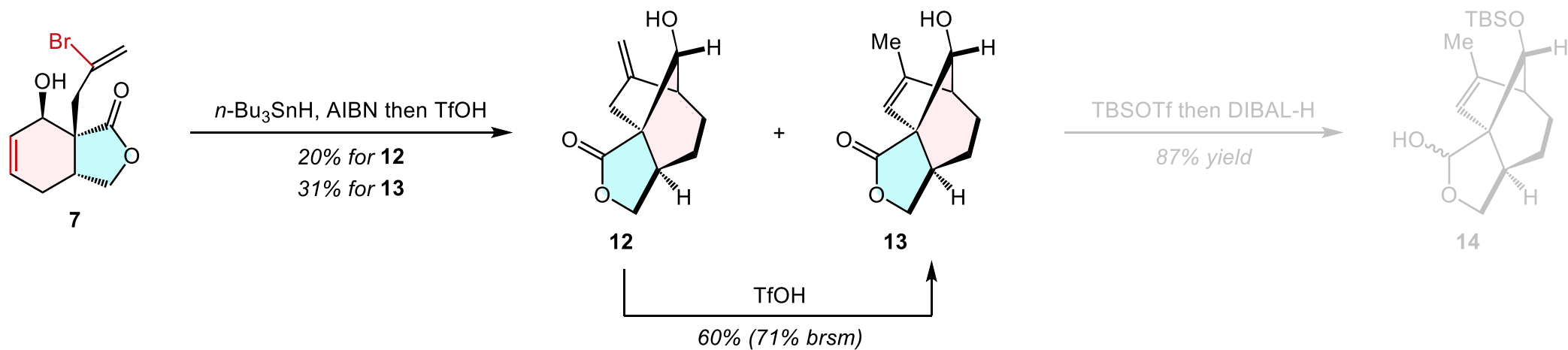
Stage 1: Synthesis of Compound 7



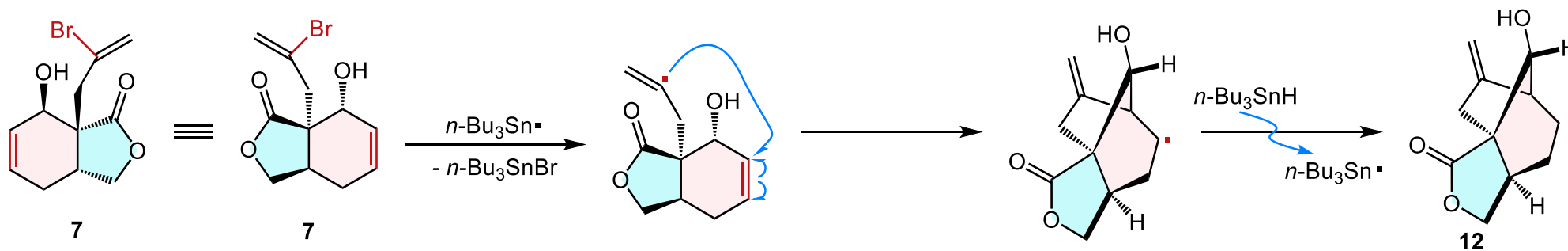
Retrosynthetic Analysis



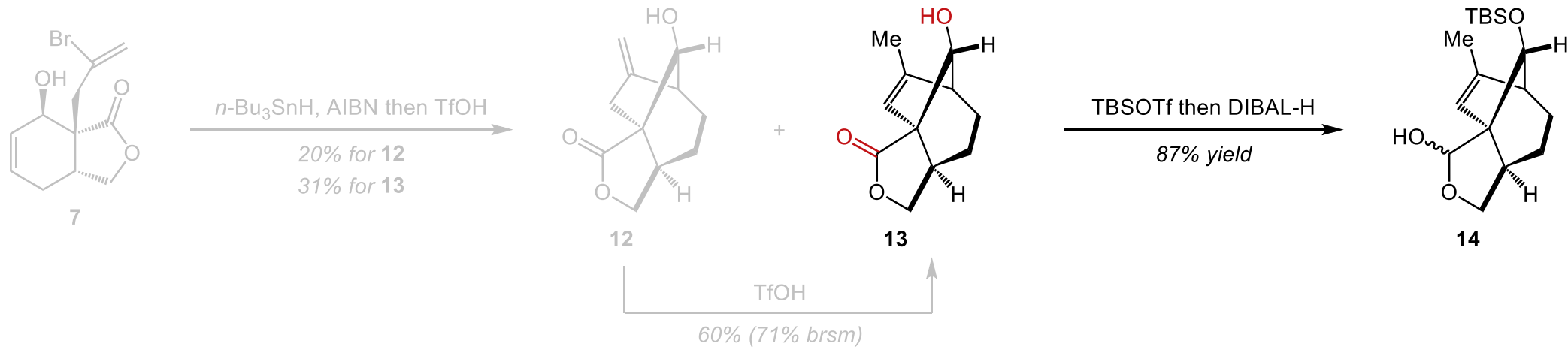
Stage 2: Synthesis of Compound 6



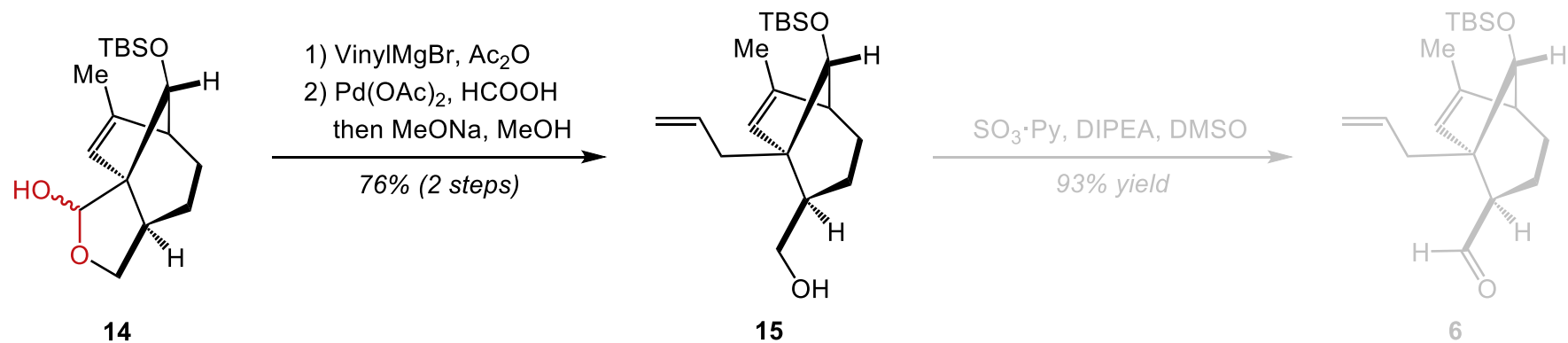
Radical Cyclization



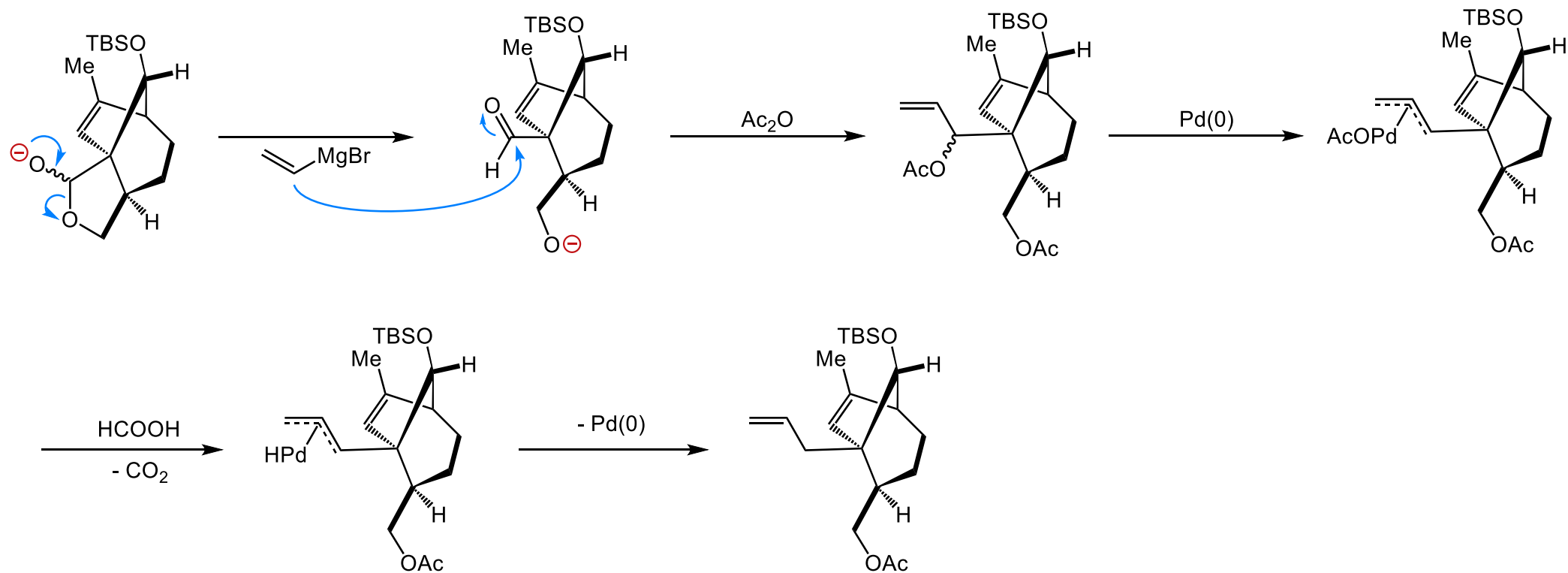
Stage 2: Synthesis of Compound 6



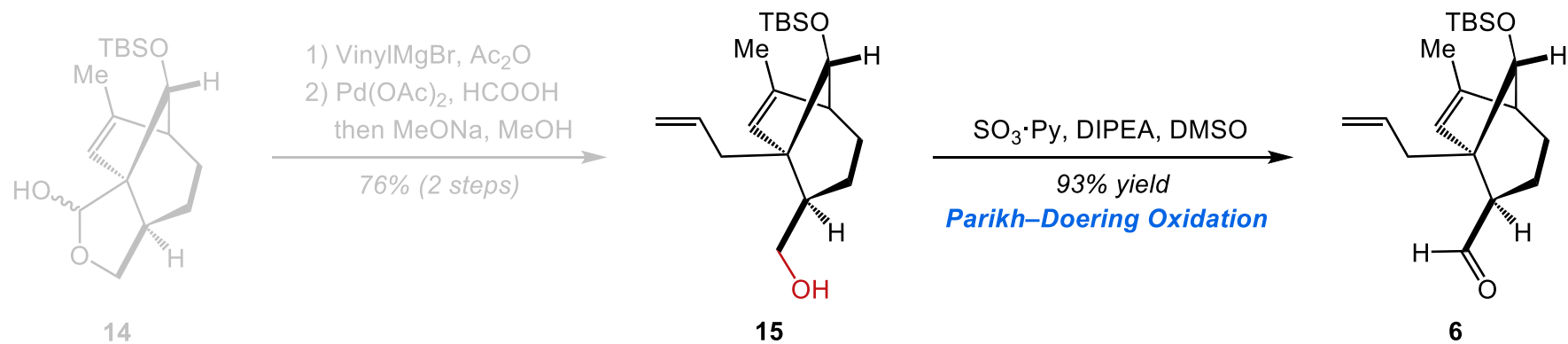
Stage 2: Synthesis of Compound 6



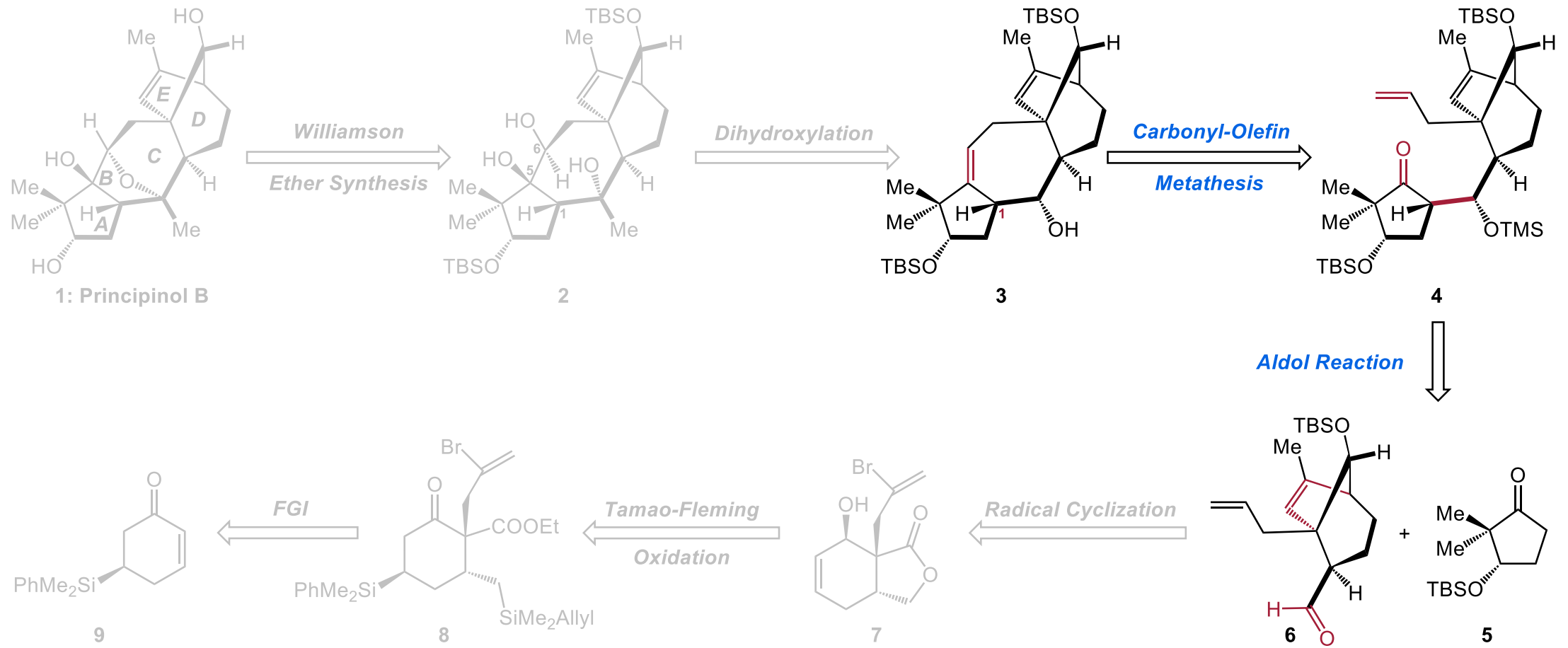
Mechanism of Compound 14 to 15



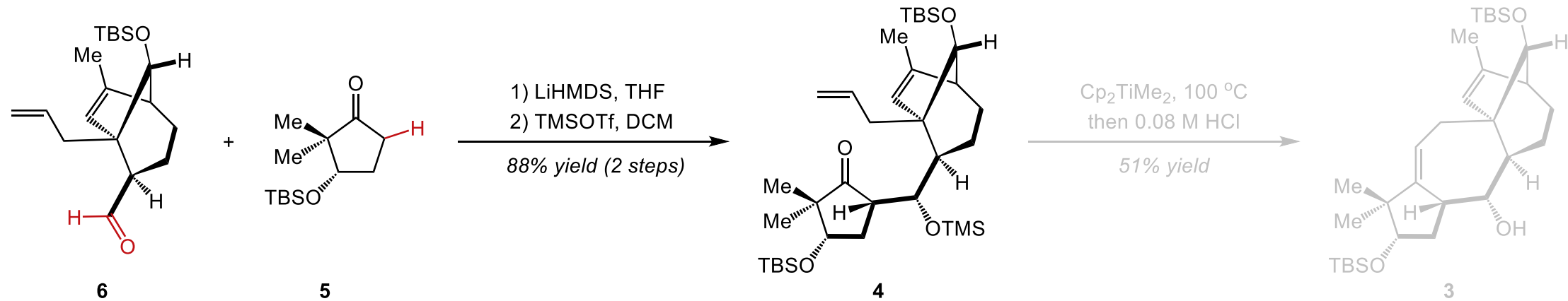
Stage 2: Synthesis of Compound 6



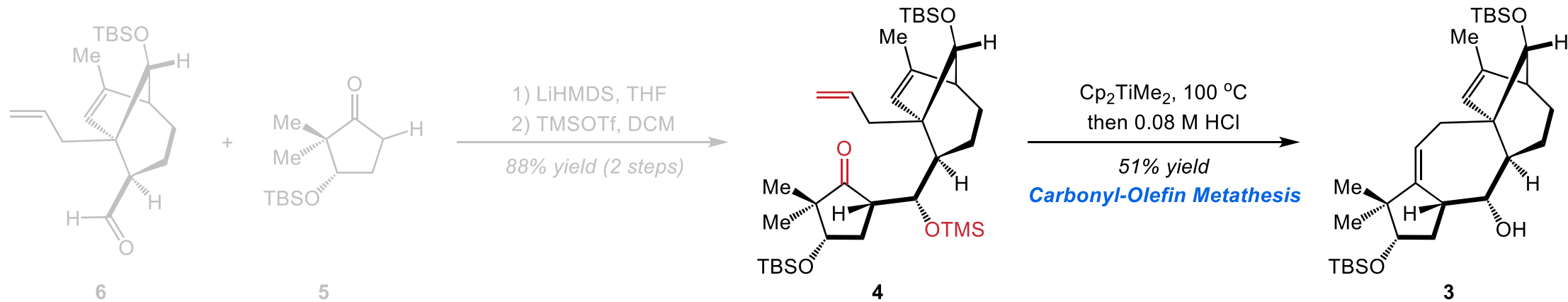
Retrosynthetic Analysis



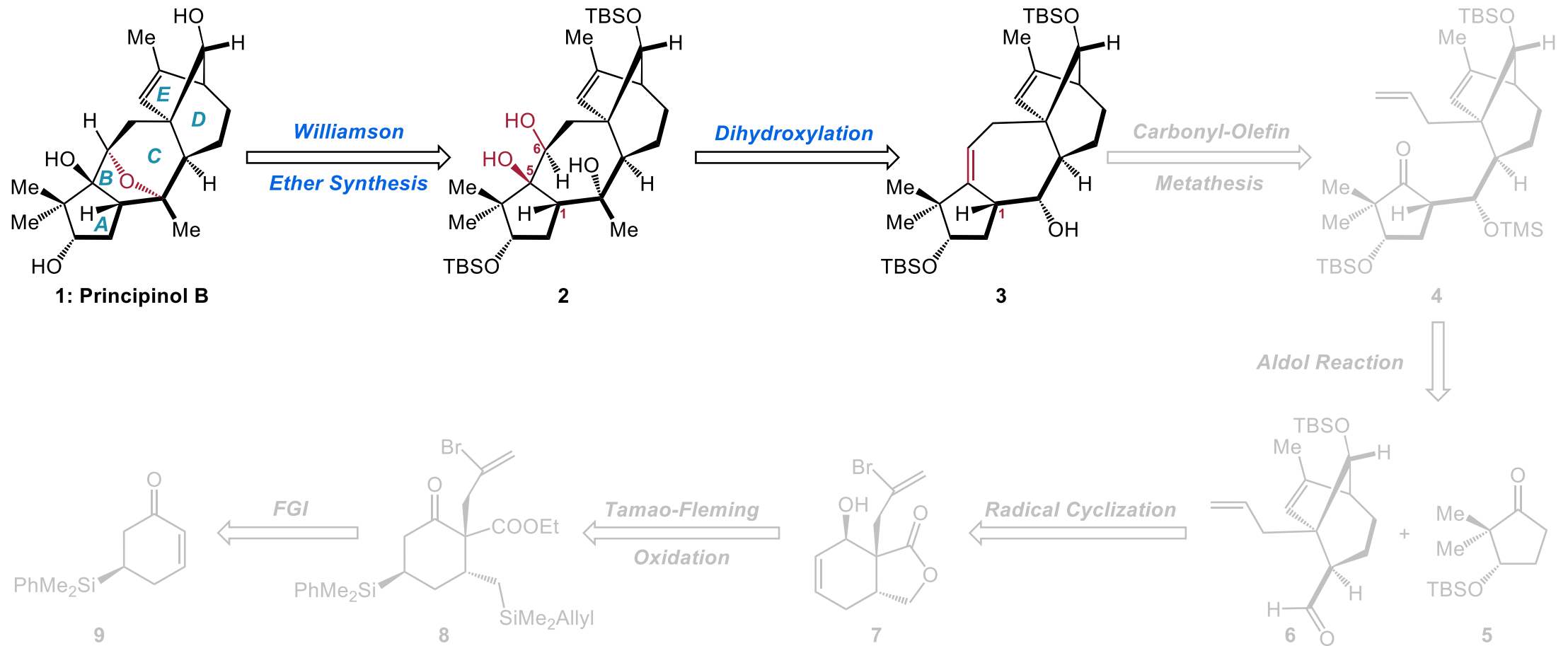
Stage 3: Synthesis of Compound 3



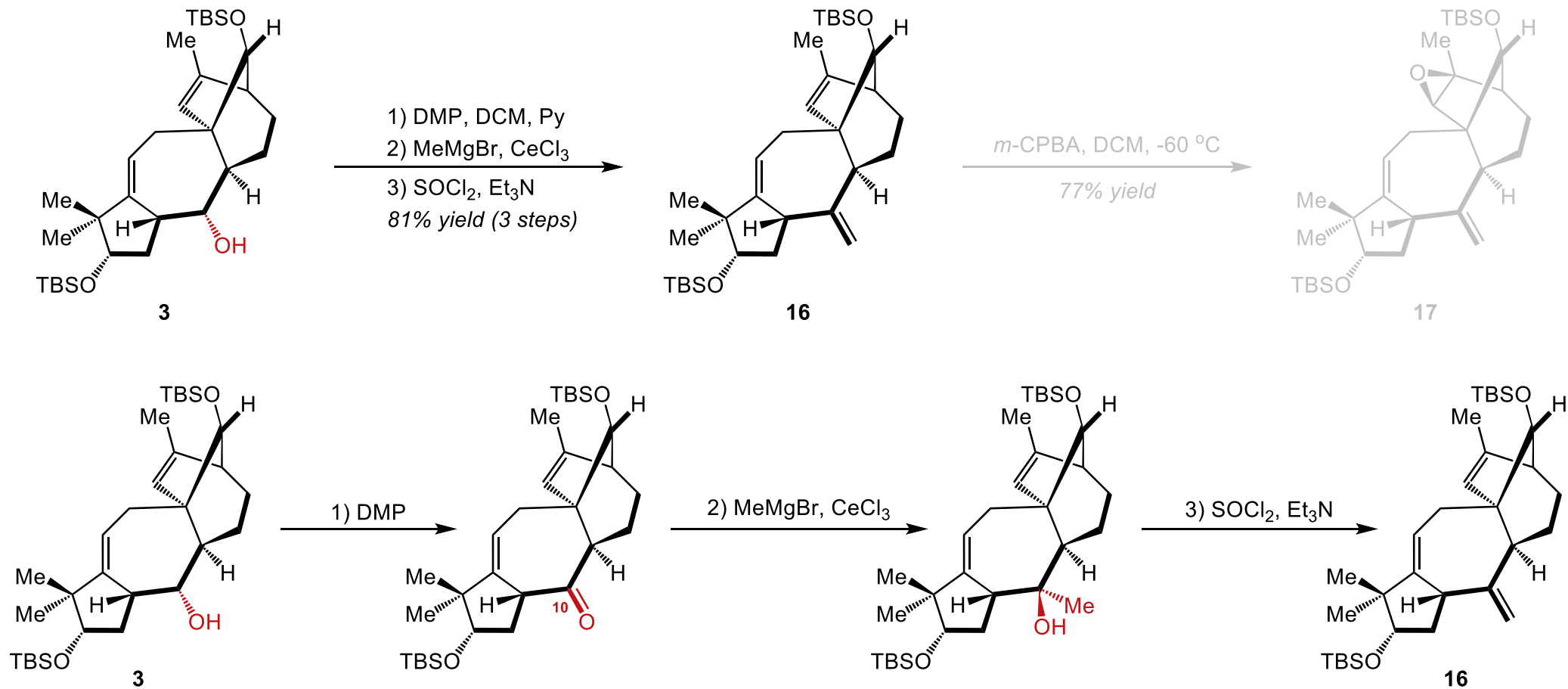
Stage 3: Synthesis of Compound 3



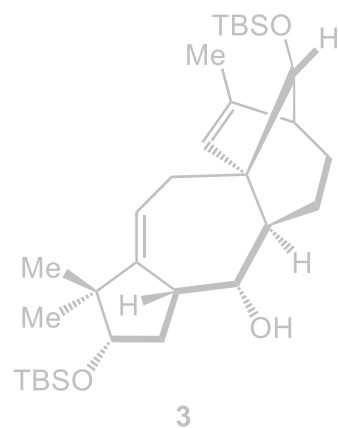
Retrosynthetic Analysis



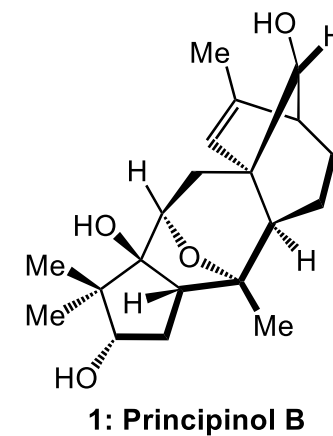
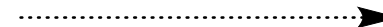
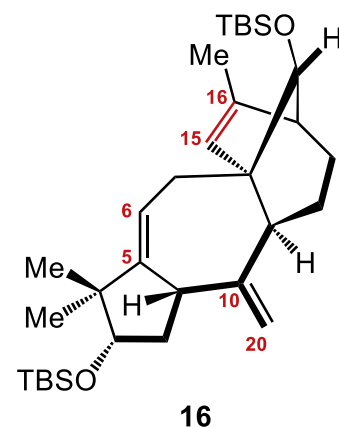
Stage 4: Synthesis of Principinol B



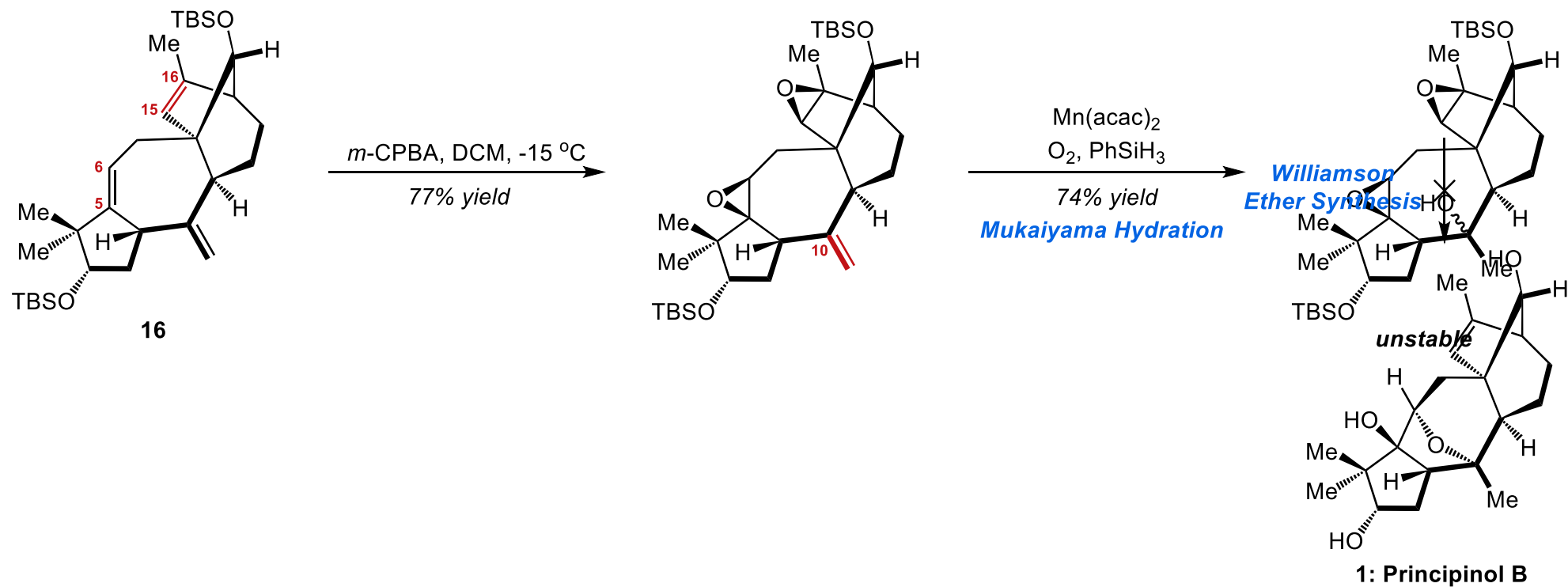
Stage 4: Synthesis of Principinol B



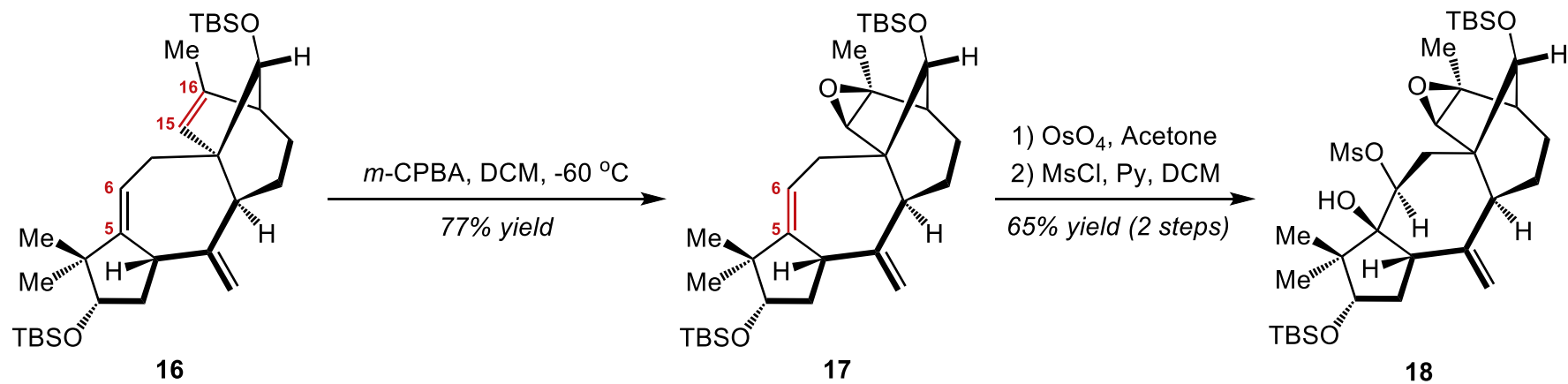
1) DMP, DCM, Py
2) MeMgBr, CeCl₃
3) SOCl₂, Et₃N
81% yield (3 steps)



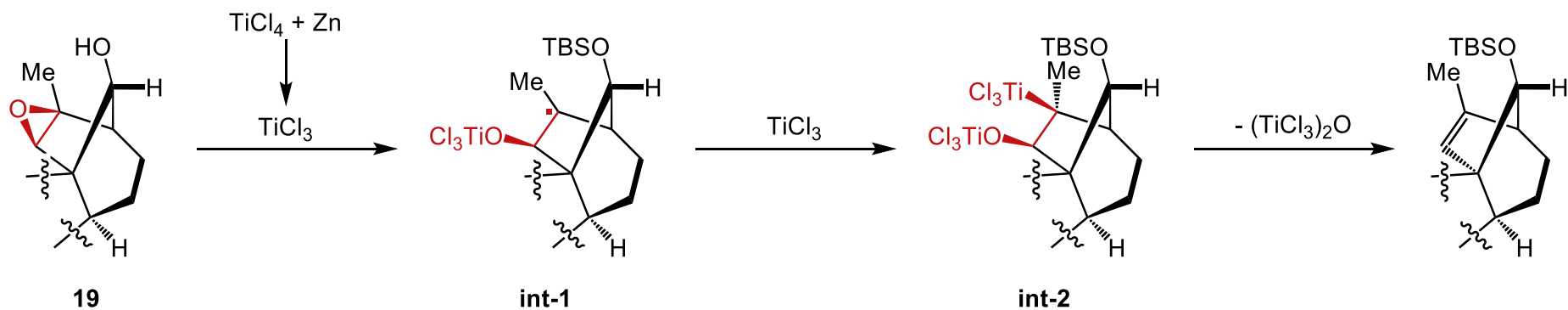
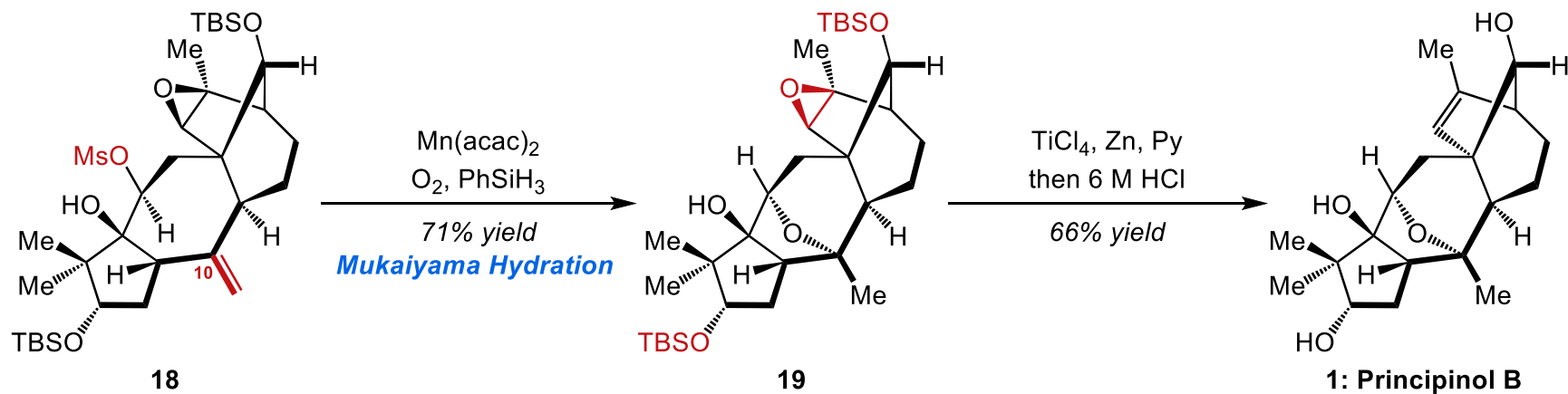
Stage 4: Synthesis of Principinol B



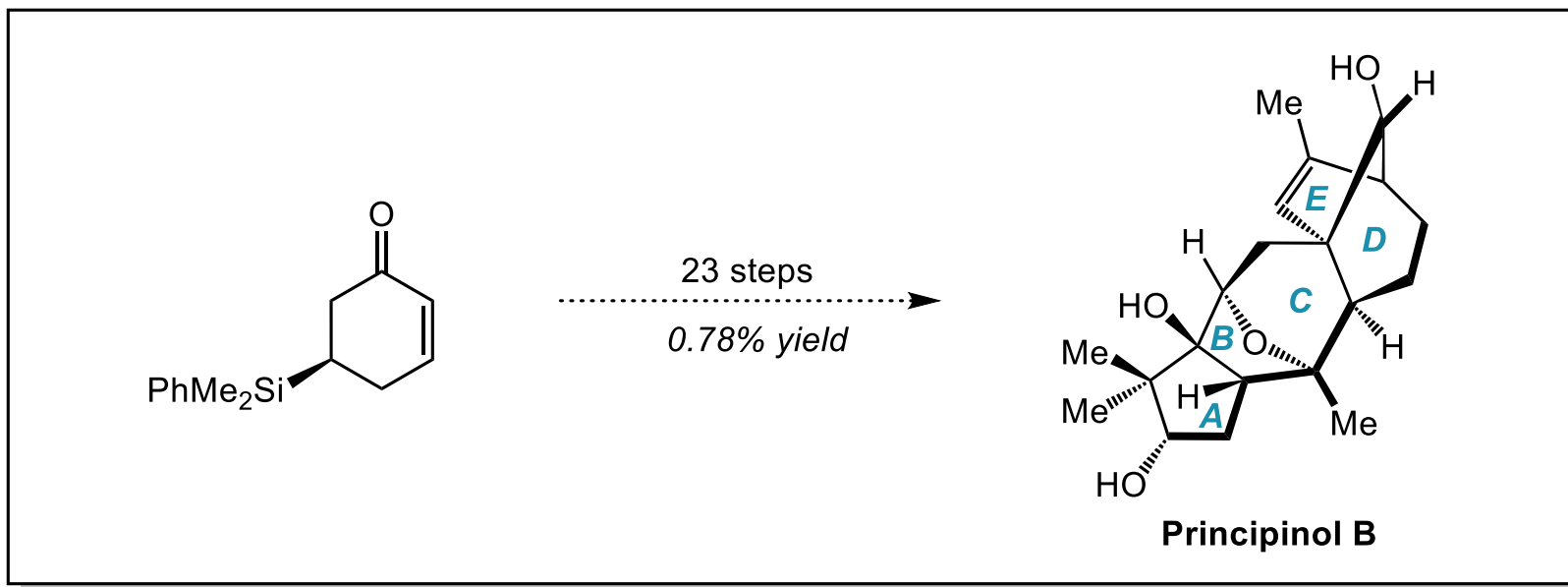
Stage 4: Synthesis of Principinol B



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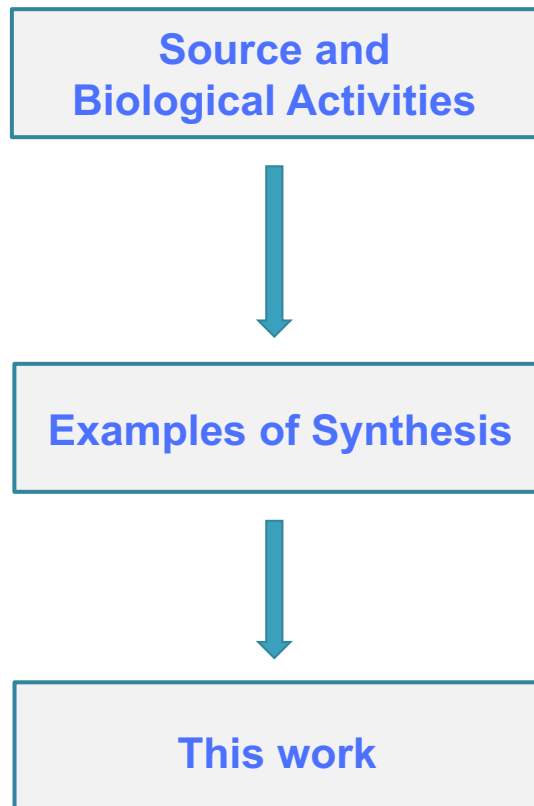
Summary



- Tamao-Fleming Oxidation, Radical Cyclization (Bicycle[3.2.1]Octane Framework)
- Aldol Reaction, Carbonyl-Olefin Metathesis (5/7/6/5 Pentacyclic Carbon Skeleton)
- Mukaiyama Hydration, Williamson Ether Synthesis (Oxa-Bicyclo[3.2.1]core)

Writing Strategy

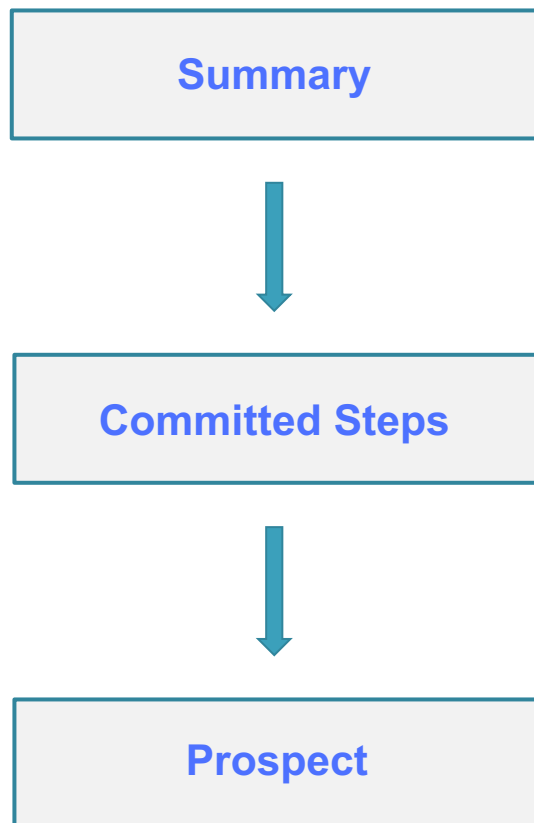
➤ First paragraph



- Grayanoids are a large family of polycyclic natural products (> 300 members) isolated from the flowering plants of the genus Ericaceae. They exhibit a wide range of biological activities, including anticancer, antiviral, antifeedant, insecticidal and bactericidal activities, and attract significant attention from synthetic chemists.
- Originating from the *ent*-kaurane skeleton through a A-nor-B-homo rearrangement, typical grayanoids possess a 5/7/6/5 tetracyclic carbon framework, and the central seven-membered carbon ring has become a signature feature of the family. To date, 18 total syntheses of grayanoids have been accomplished by seven research groups.....
- Herein, we report the first and asymmetric total synthesis of principinol B by direct introduction of the C1 and C5 stereogenic centers and construction of the central seven-membered ring by carbonyl–olefin metathesis.

Writing Strategy

➤ Last paragraph



- In conclusion, we have accomplished the first and asymmetric total synthesis of principinol B through convergent and modular synthetic strategies.
- An initially introduced removable silyl moiety carrying information of chirality effected stereocontrol in the synthesis. The bridged D/E ring fragment, which constitutes a bicycle[3.2.1]octane framework, was constructed through a radical cyclization. The 5/7/6/5 pentacyclic carbon skeleton was assembled by a diastereoselective intermolecular aldol reaction/carbonyl-olefin metathesis sequence. The ether ring of the oxabicyclo [3.2.1] core structure was closed by the Williamson ether synthesis.
- This synthesis expands the strategies for the construction of the tricky seven-membered carbon ring, and will provide further inspiration for similar events in other contexts.

Representative Examples

- **Pleasingly**, when we treated **7** with $n\text{-Bu}_3\text{SnH}$ and AIBN, the cyclization reaction proceeded smoothly to give the desired product. (*adv.* 高兴地)
- It seemed that the SN_2 substitution of the Williamson ether synthesis on this substrate was a **spontaneous** reaction, which was also different from our previous experience. (*adj.* 自发的, 本能的)
- The structure of **26** was **unambiguously** confirmed by X-ray crystallographic analysis. (*adv.* 明确地)

Acknowledgement

Thank You for Your Attention