Literature Report 14

Concise Enantioselective Total Syntheses of Rearranged *ent*-Trachylobane Diterpenoids (-)-Wallichanols A and B

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Checker: Jian Chen
Date: 2025.06.03

Dethe, D. H.*; Sharma, N.; Juyal, S. *Angew. Chem. Int. Ed.* **2025**, e202505766.

CV of Dr. Dattatraya Dethe

Background:

1996-1999	M.S., Savitribai Phule Pune University
1999-2005	Ph.D., Indian Institute of Science, Bangalore
2011-2014	Assistant Prof., Indian Institute of Technology Kanpur
2014-2019	Associate Prof., Indian Institute of Technology Kanpur
2019-present	Full Prof., Indian Institute of Technology Kanpur

Research:

- ✓ **Total Synthesis of Natural Products**
- ✓ **Development of New Synthetic Methods and Strategies**
- ✓ **Design and Invention of New Annulation Strategies**

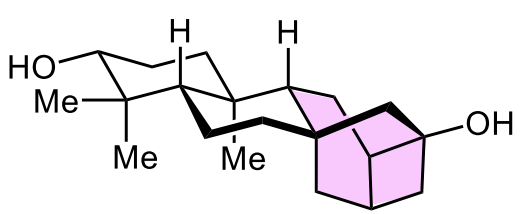
Contents

Introduction

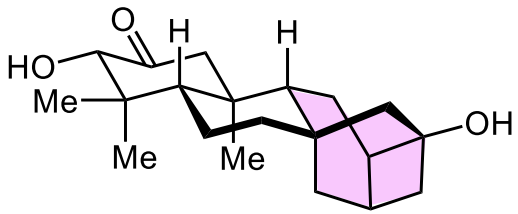
(-)-Wallichanol A and B

Euphorbia wallichii

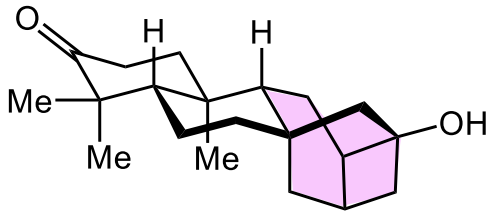
- ♣ First isolated from the *Euphorbia wallichii* in 2006
- ♣ Tibetan folk medicine to treat edema and various skin ailments
- ♣ 6/6/6/4/6-Fused pentacyclic scaffold
- ♣ Unprecedented tricyclo[3.3.1.$0^{2,7}$]nonane motif



Wallichanol A (1)



Wallichanol B (2)

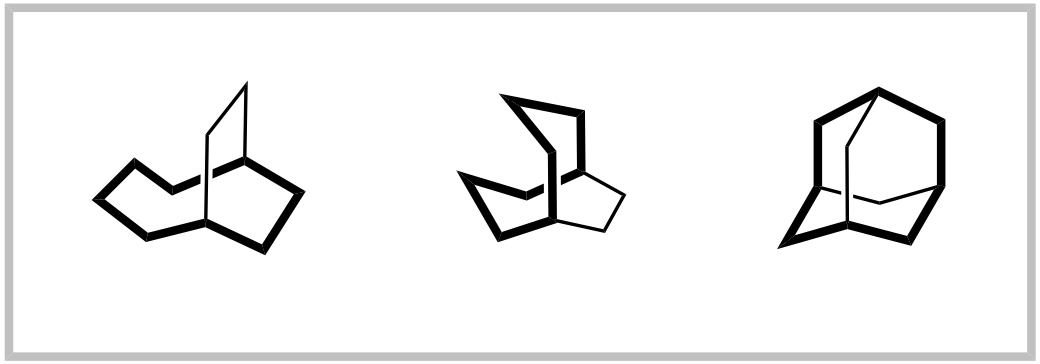


Sanguinolane (3)

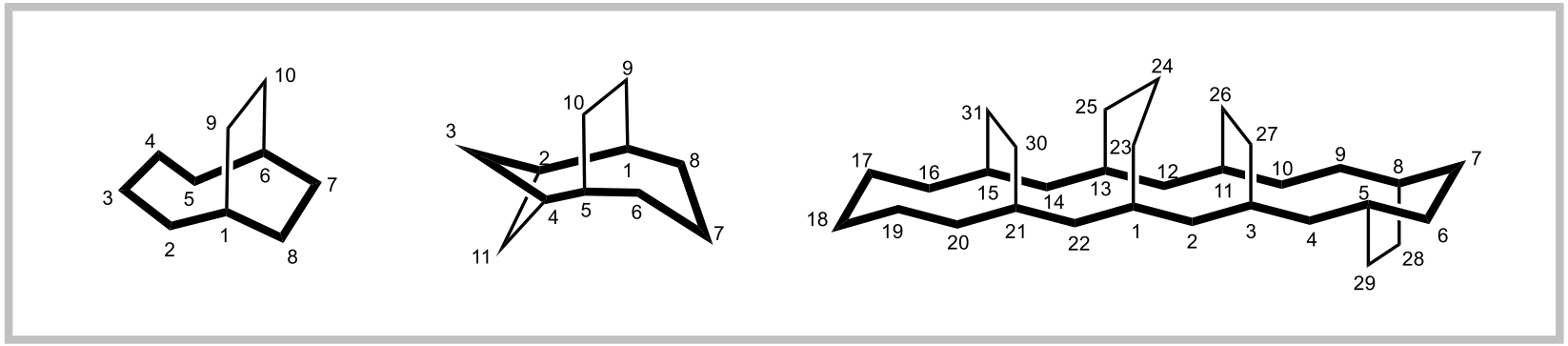
Pan, L.; Zhou, P.; Zhang, X.; Peng, S.; Ding, L.; Qiu, S. X. *Org. Lett.* **2006**, *8*, 2775.

桥环化合物的系统命名法

1. 定主环：选择众多单环中**碳原子数最多**的环为主环



2. 编号：从**主环**一个**桥头碳**开始，在主环上沿最长路径到另一个桥头，再原路返回依次编号，最后再编桥上的碳原子。桥上**先编主桥**，**次桥再按碳原子数递减**依次编号



桥环化合物的系统命名法

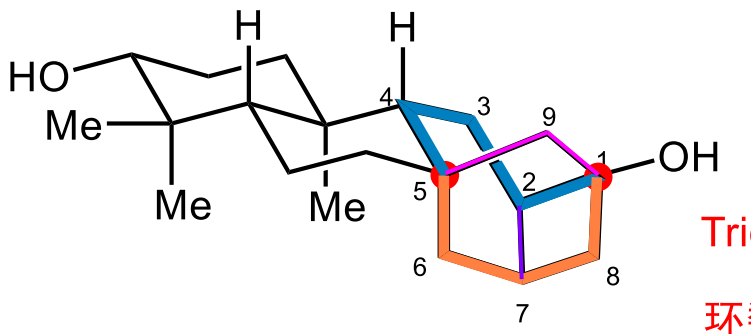
3. 命名：系统命名分为**环数**，**桥的位置**和**碳原子数**三部分

a. 桥环数等于不含不饱和键时该烃的不饱和度；

b. 桥的位置用方括号表示，其中前两个数表示主桥头碳分割主环两部分含碳原子数；

c. 第三个数表示桥上的碳原子数（可以为零）。如果有次桥，则在方括号中第三个数后加上次桥上的碳原子数，以此类推，多个次桥按碳原子数递减顺序排列。

d. 在每个次桥碳原子数的右上角标注次桥的两个桥头碳的编号，从小到大。

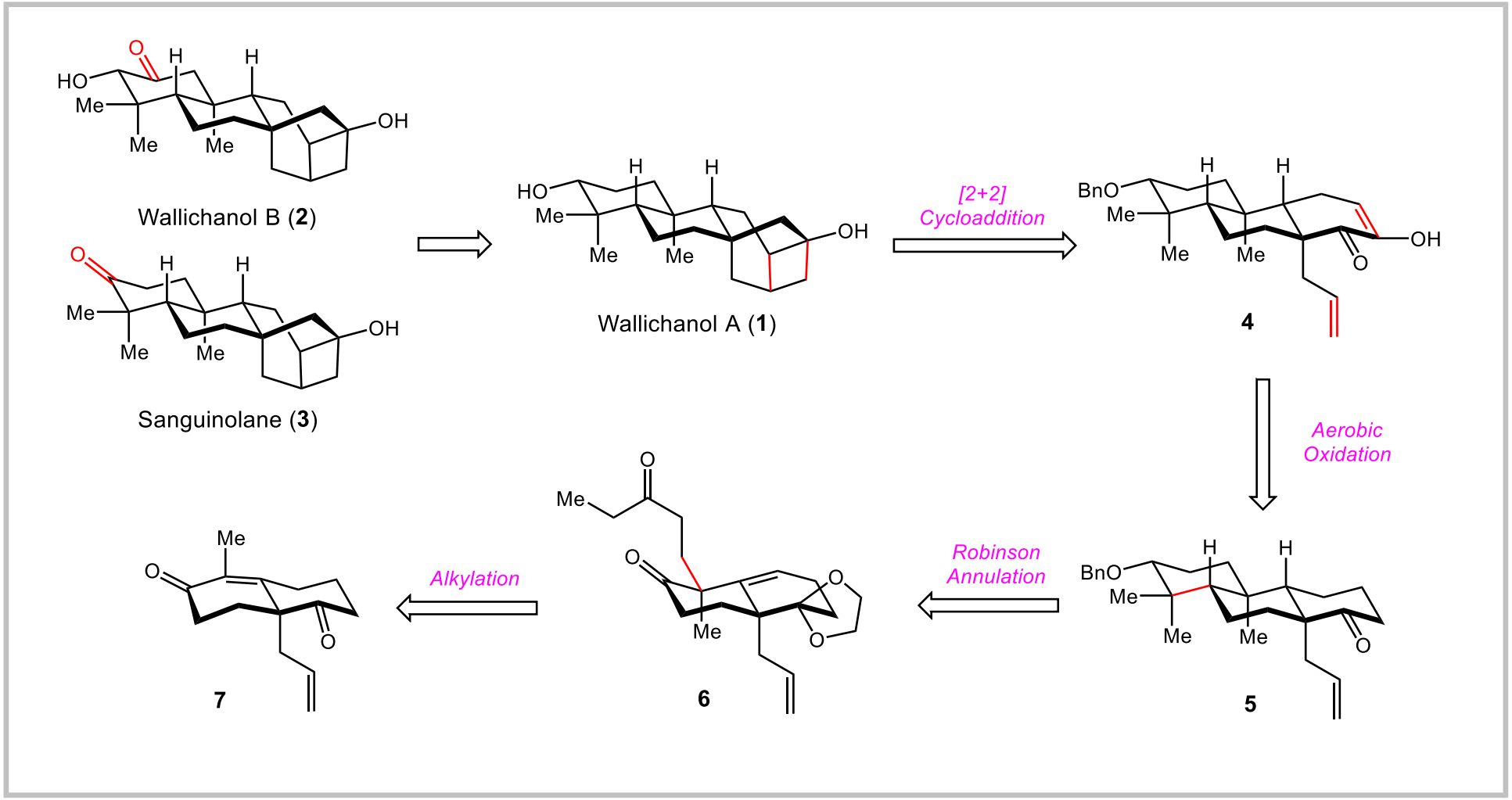


Wallichanol A (1)

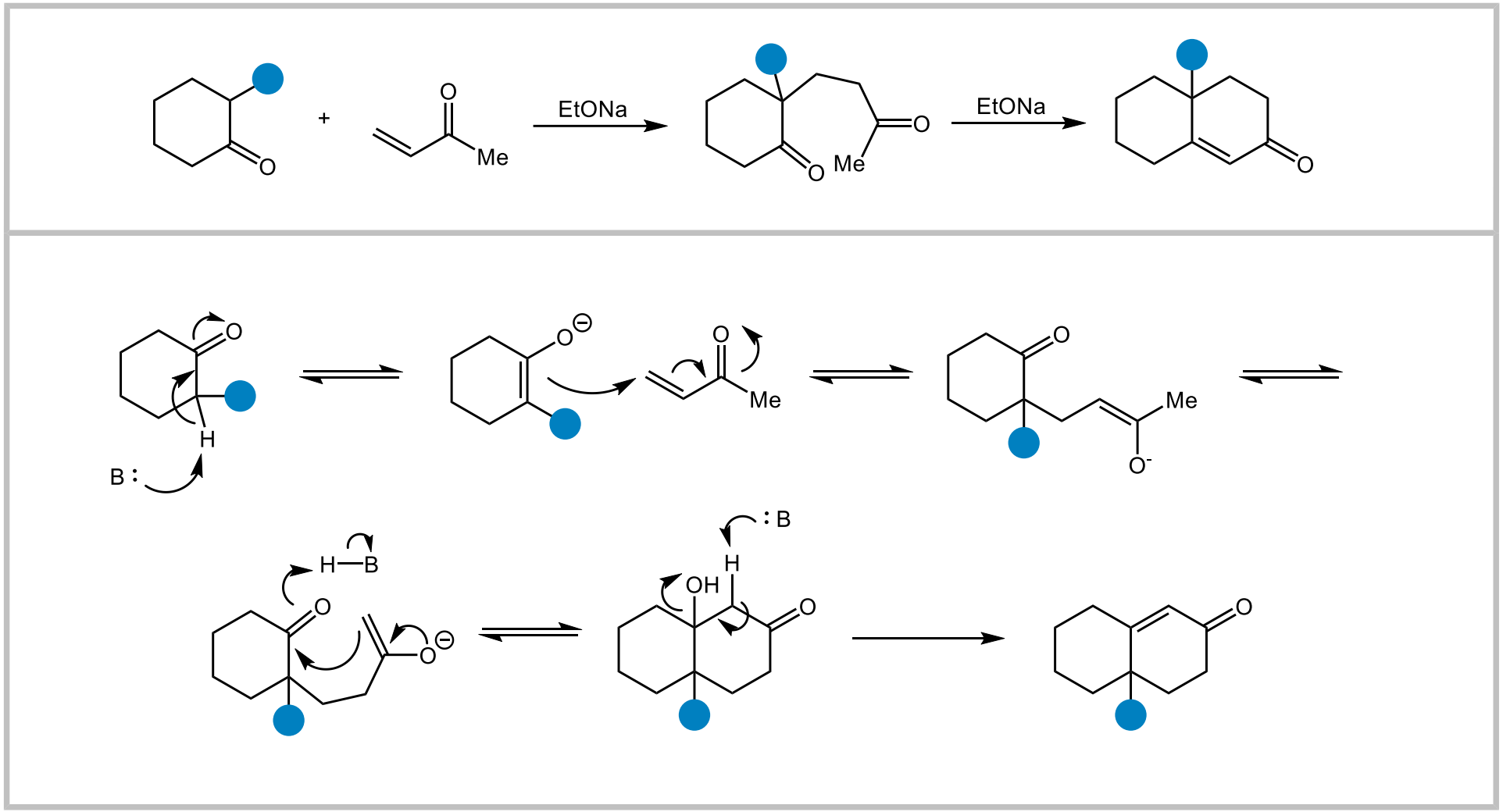
Tricyclo[3.3.1.$0^{2,7}$]nonane

环数　环的位置　碳原子数

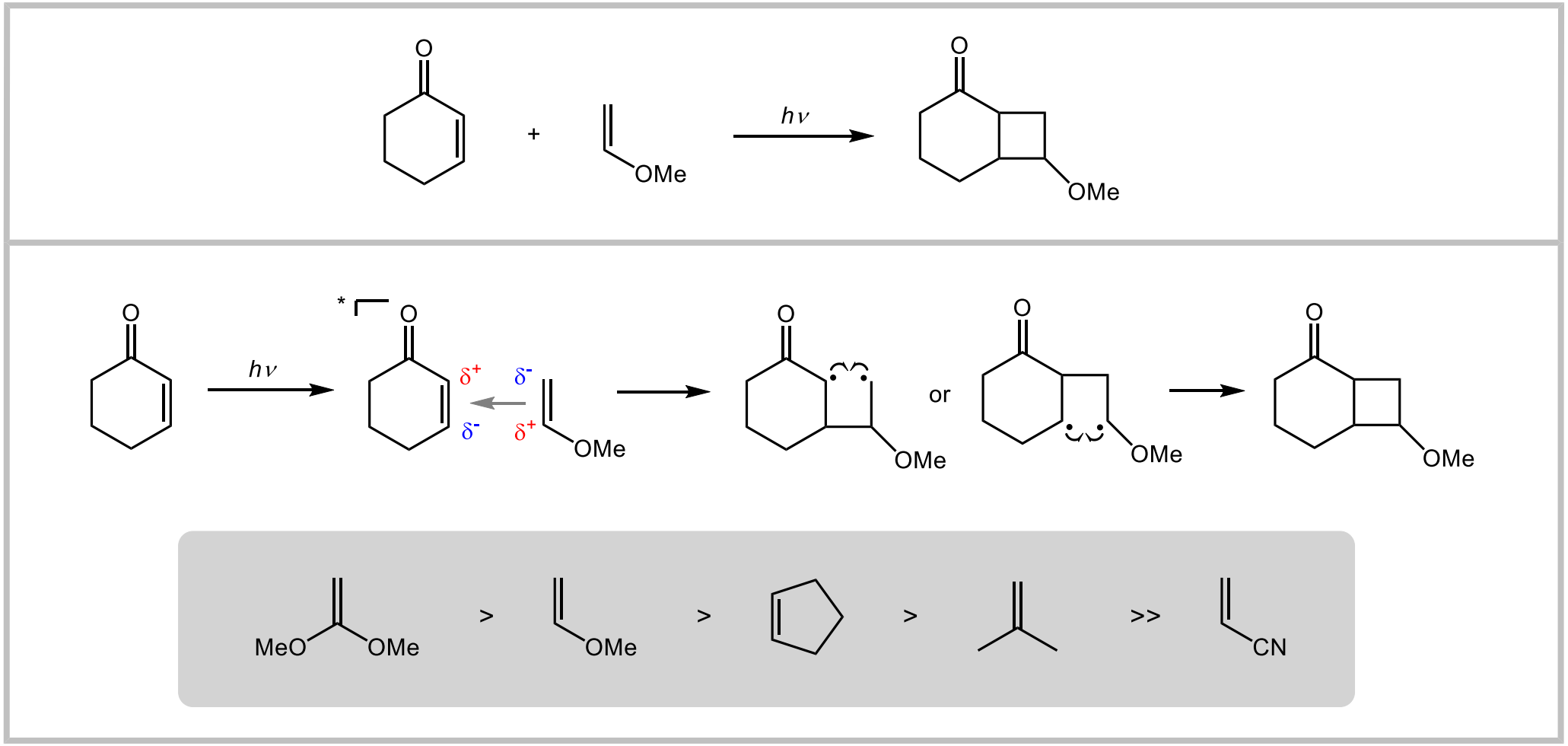
Retrosynthetic Analysis



Robinson Annulation

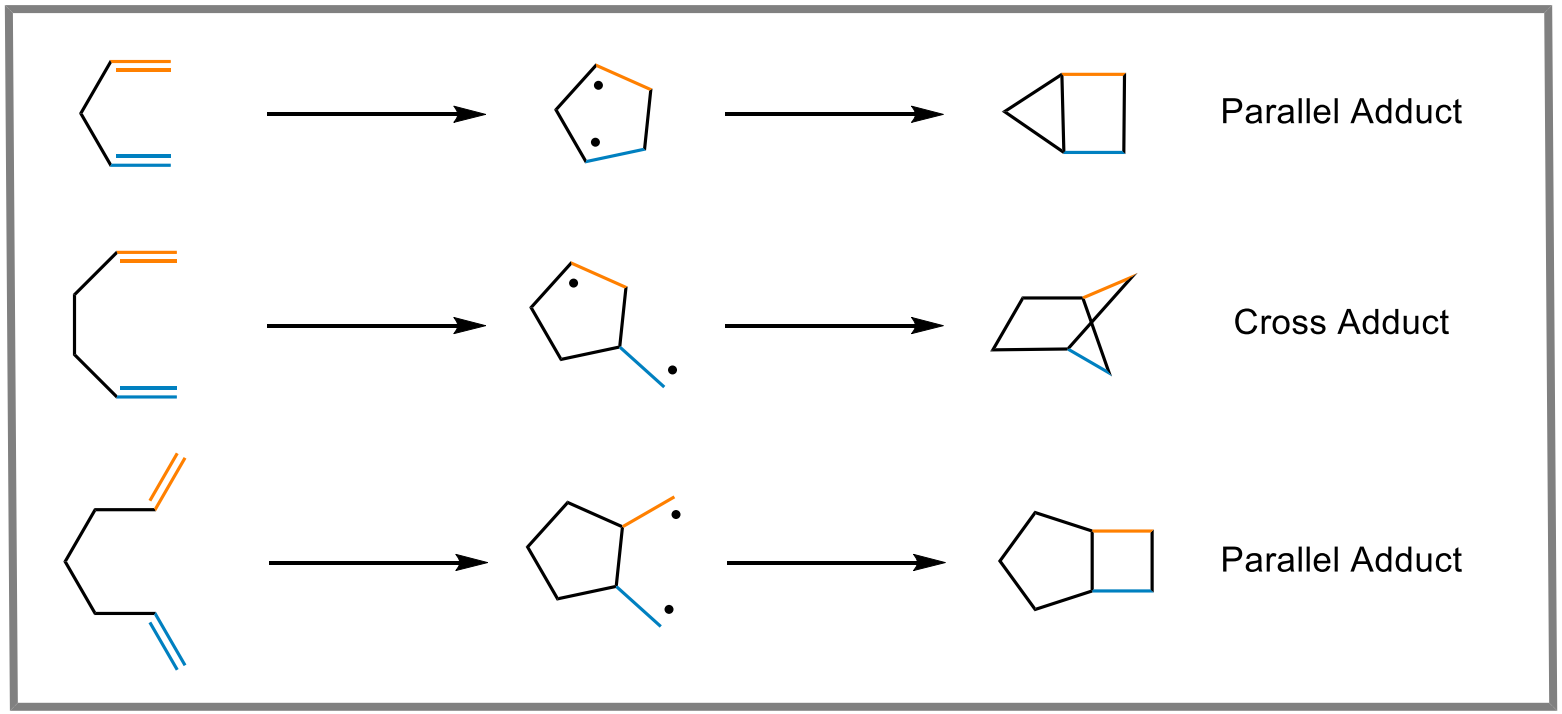


Eaton-de Mayo Reaction



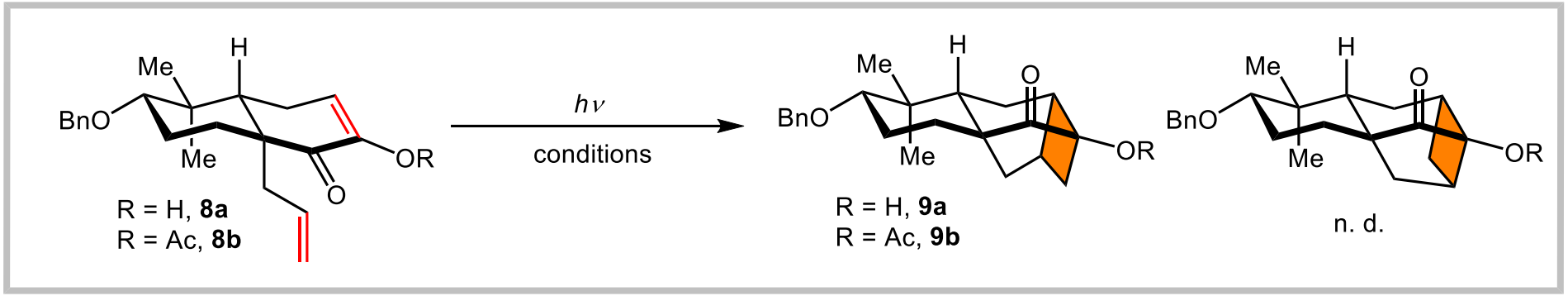
Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

Rule of Five



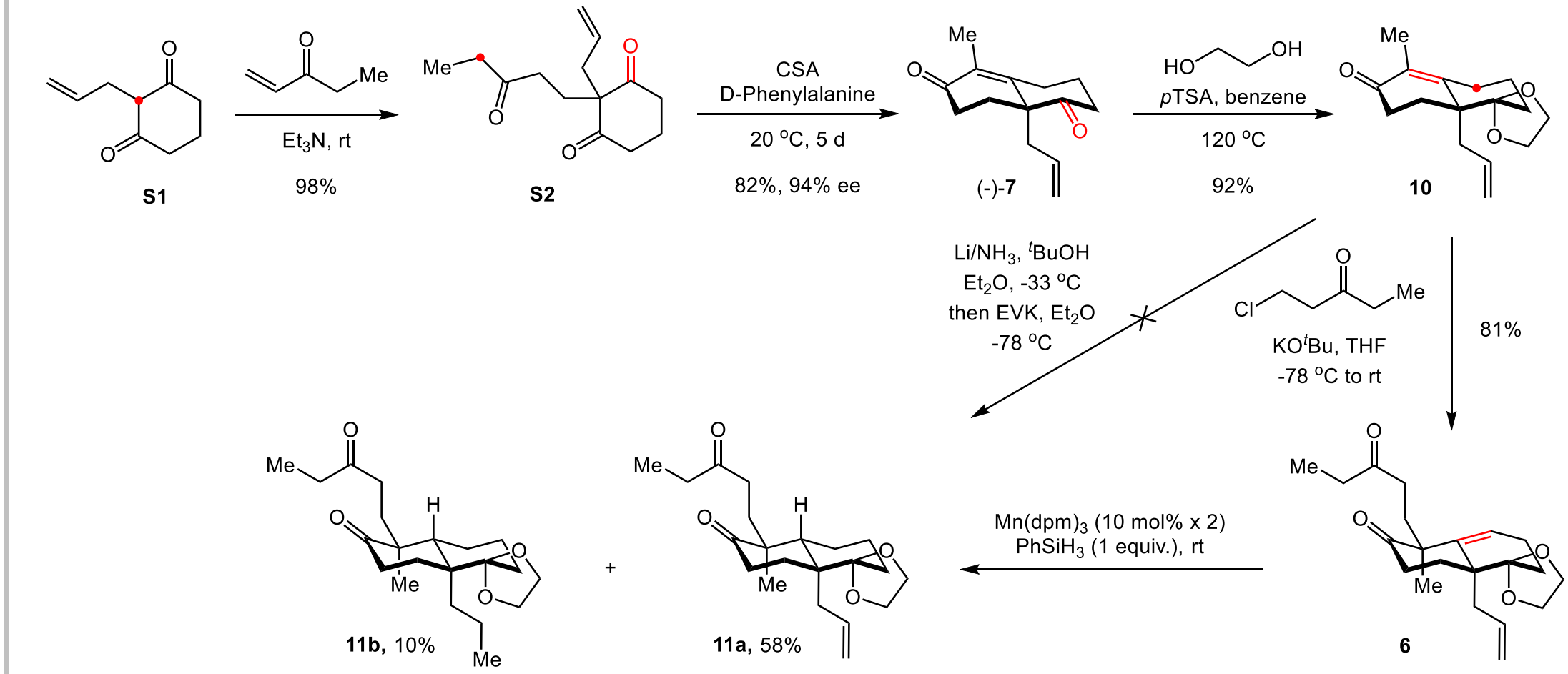
Srinivasan, R.; Carlough, K. H. *J. Am. Chem. Soc.* **1967**, *89*, 4932.

Optimization of Eaton-de Mayo Reaction

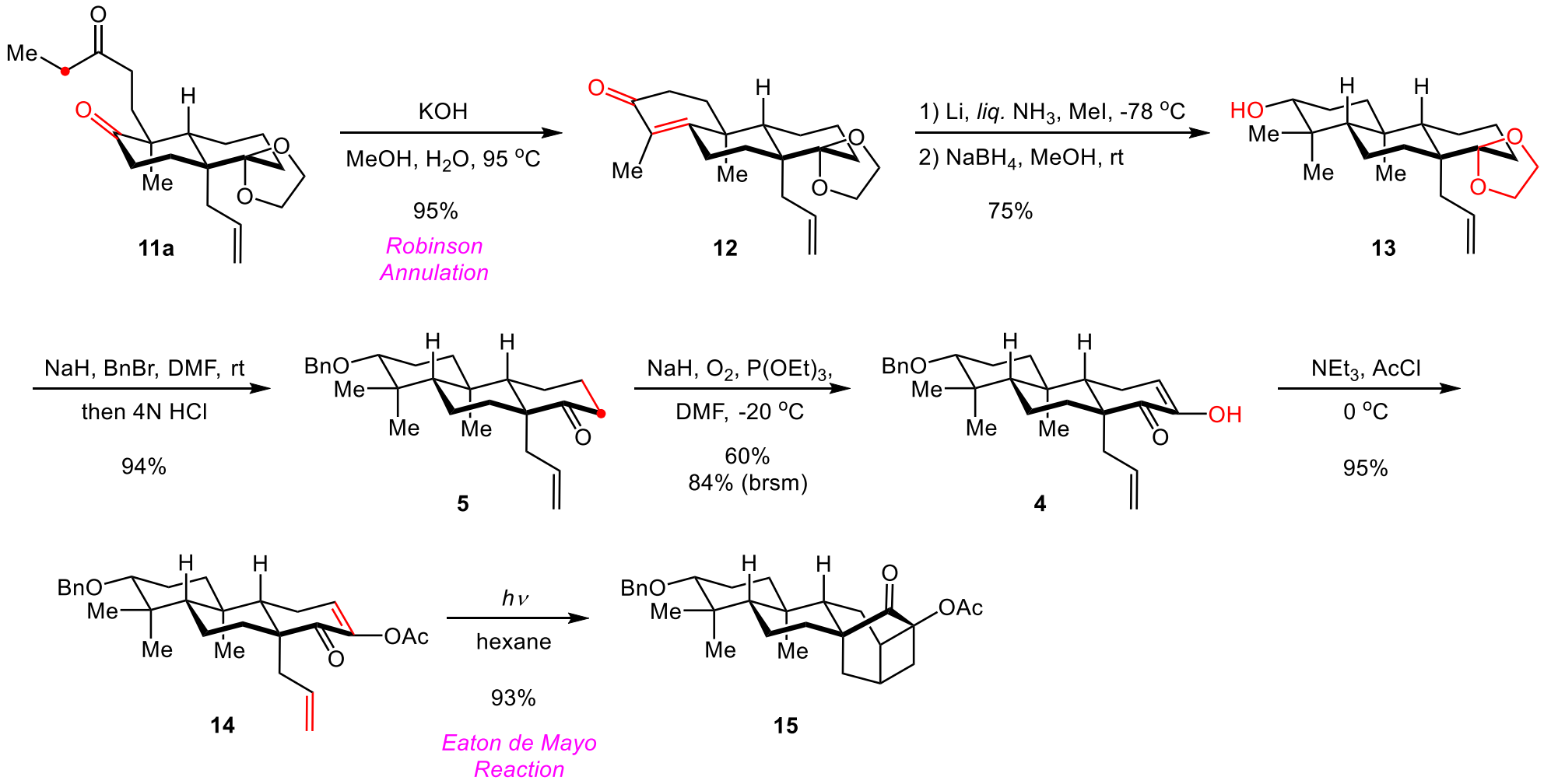


Substrate	Light Source	Solvent	Time	Product (yield)
8a	Blue LED	Acetone	10 min	decomposed
8a	Hg lamp	Acetone	10 min	decomposed
8a	Hg lamp	Hexane	30 min	**9a** (0)
8b	Hg lamp	Acetone	1 h	**9b** (85)
8b	Hg lamp	MeCN	1 h	**9b** (90)
8b	Hg lamp	Hexane	35 min	**9b** (97)

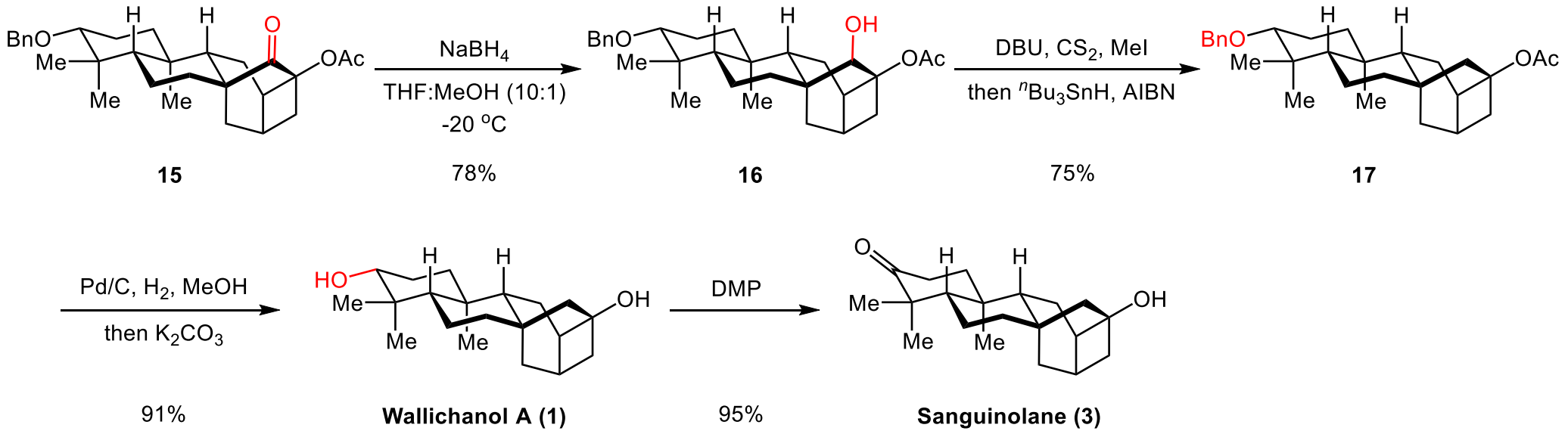
Synthesis of 11a



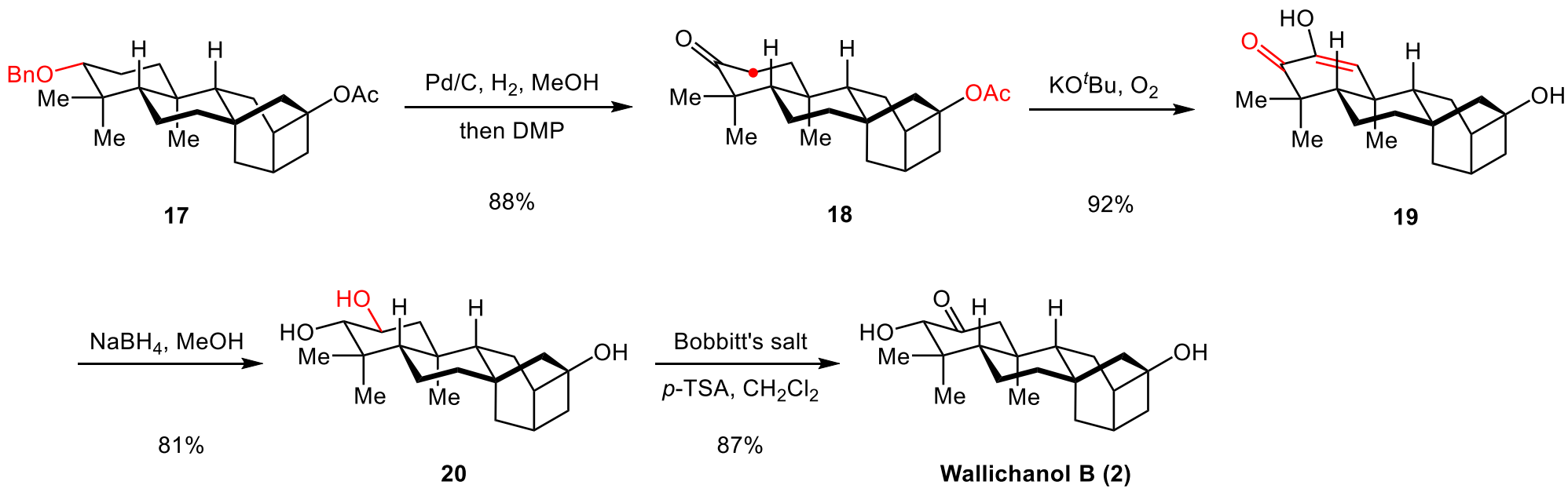
Synthesis of 13



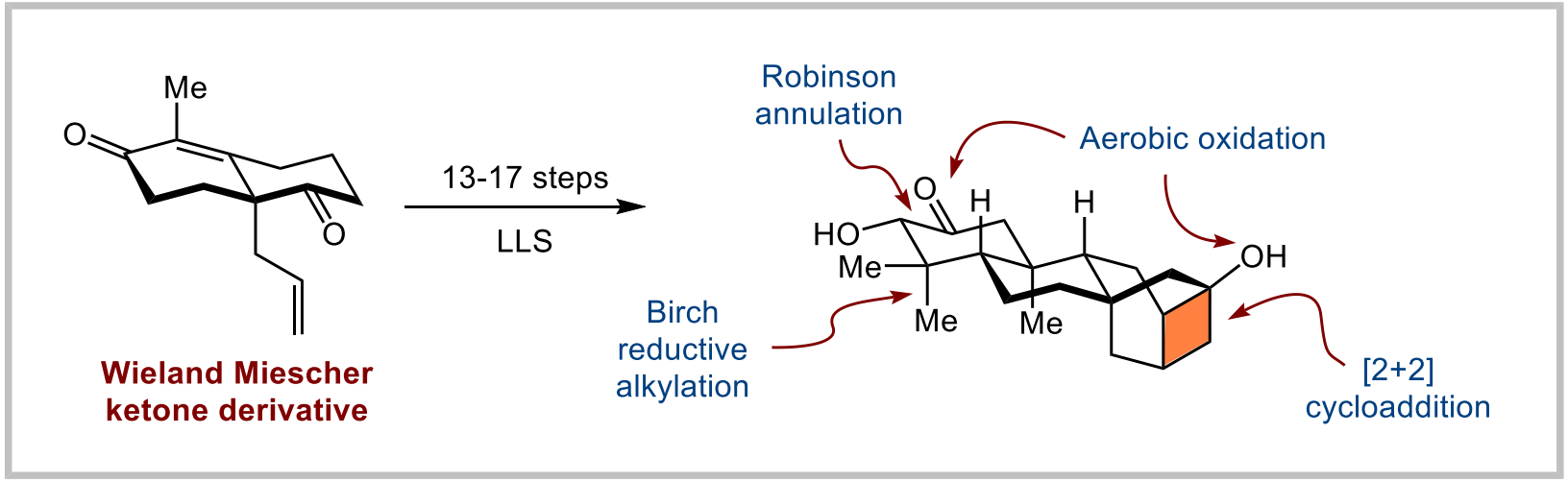
Synthesis of Wallichanol A and Sanguinolane



Synthesis of Wallichanol B



Summary



- First total synthesis of *ent*-trachylobane diterpenoids;
- 6/6/6/4/6-Fused pentacyclic scaffold;
- Unprecedented tricyclo[3.3.1.$0^{2,7}$]nonane motif;
- 13-17 LLS, Wallichanol A (6.6%); Wallichanol B (4.1%); Sanguinolane (6.2%).

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Writing Strategy

➢**The First Paragraph**

Wallichanol A and B的来源

分离工作及生物活性

- Euphorbia wallichii has long been used in Tibetan folk medicine to treat edema and various skin ailments, including abscesses, eruptions, and anthrax infections.
- In 2006, Qiu and co-workers isolated two novel rearranged trachylobane diterpenoids from the roots of this medicinal herb, named wallichanol A and wallichanol B, both of which feature a unique pentacyclic structure containing an integrated cyclo-butane ring. The isolation group reported that both **1** and **2** effectively inhibit osteoclastogenesis through in vitro studies, demonstrating their potential as therapeutic agents

Writing Strategy

➢The Last Paragraph

对全合成进行总结

↓

介绍合成的关键步骤

↓

对核心方法学的展望

- In summary, we accomplished the first enantioselective total syntheses of the rearranged *ent*-trachylobane diterpenoids in 13-17 step longest-linear sequences, starting from the allyl Wieland-Miescher ketone derivative (–)-**7**.
- We utilized a [2+2]-cycloaddition as an efficient methodology to access the highly substituted cyclobutane ring and completed the penta-cyclic framework featuring a unique tricyclo[3.3.1.$0^{2,7}$]nonane motif. Additionally, the synthesis evoked a challenging selective olefin reduction *via* hydrogen atom transfer. A highly efficient Robinson-type annulation was employed to construct the A ring of the natural products. Furthermore, strategic aerobic oxidations at two distinct stages generated α-hydroxy ketones.
- This modular and concise synthetic strategy offers a streamlined and innovative approach to this family of diterpenoid natural products.

Representative Examples

- **A brief screening of** solvents and time **indicated that** **8b** on irradiation with 450 W Hg lamp for 35 minutes in degassed hexane gave the complete conversion to **9b** with 97% yield. (描述条件筛选句式)

- **Our findings align with** previous work on enone-olefin photochemistry, where excited-state dynamics and steric constraints ultimately dictate the product distribution. (将结果与前人文献对比)

- To **circumvent** this problem, we explored hydrogen atom transfer reaction, aiming to exploit the thermodynamic preference for forming a tertiary carbon-centered radical. (规避，绕行)