

Literature Report V

Total Synthesis of Cerorubenic Acid-III

Reporter : Yang Zhao

Checker : Han Wang

Date : 2019-3-18

Paquette, L. A.; Dyck, B. P. *et al. J. Am. Chem. Soc.* **1998**, *120*, 5953

Li, C.-C.; Liu, X.; Liu, J. *et al. J. Am. Chem. Soc.* **2019**, *141*, 2872

CV of Prof. Chuang-Chuang Li



Research:

- ◆ Total synthesis of a number of complex, biologically active natural products, to develop innovative methods and strategies, which allow for rapid access to the target structure and the analogs

Education:

- **1997–2001** B.S., China Agricultural University
- **2001–2006** Ph.D., Peking University (Zhen Yang)
- **2006–2008** Postdoc., The Scripps Research Institute, CA, USA (P. Baran)
- **2008–2013** Associate Prof., Shenzhen Graduate School, Peking University
- **2013–2017** Associate Prof., Southern University of Science and Technology
- **2017–now** Research Prof., Southern University of Science and Technology

Contents

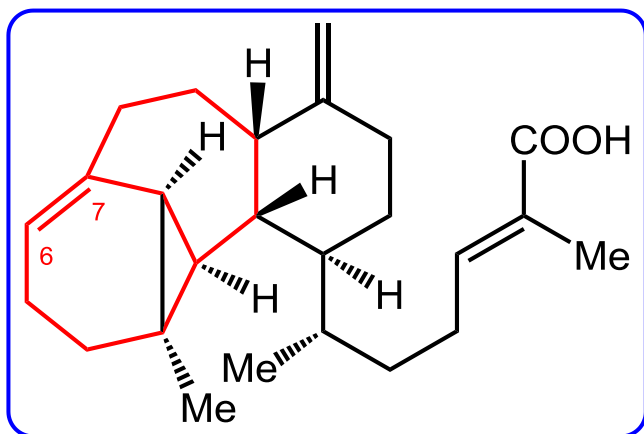
1 Introduction

2 Synthesis by Paquette

3 Synthesis by Li

4 Summary

Introduction



Cerorubenic Acid-III

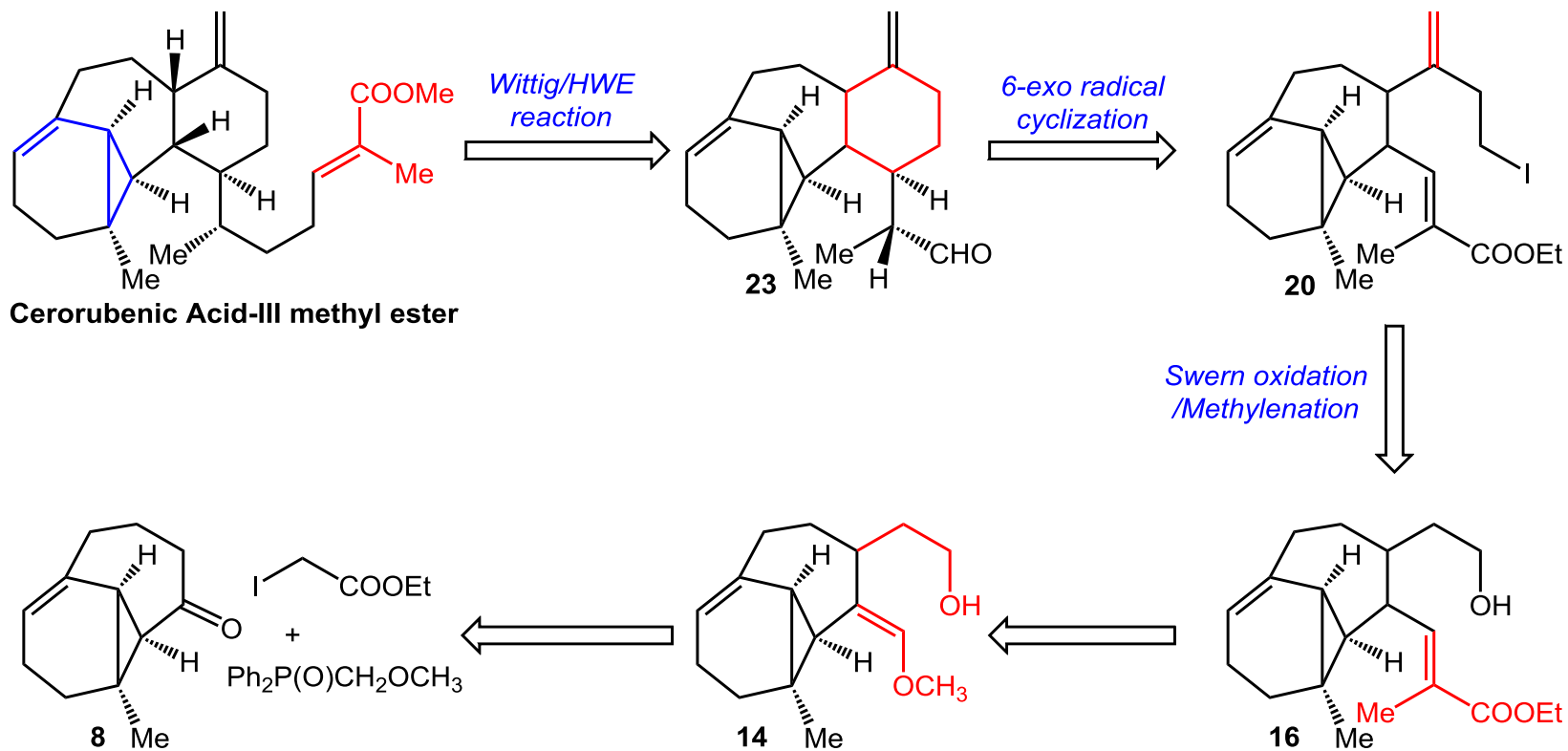


***Ceroplastes rubens* Maskell**

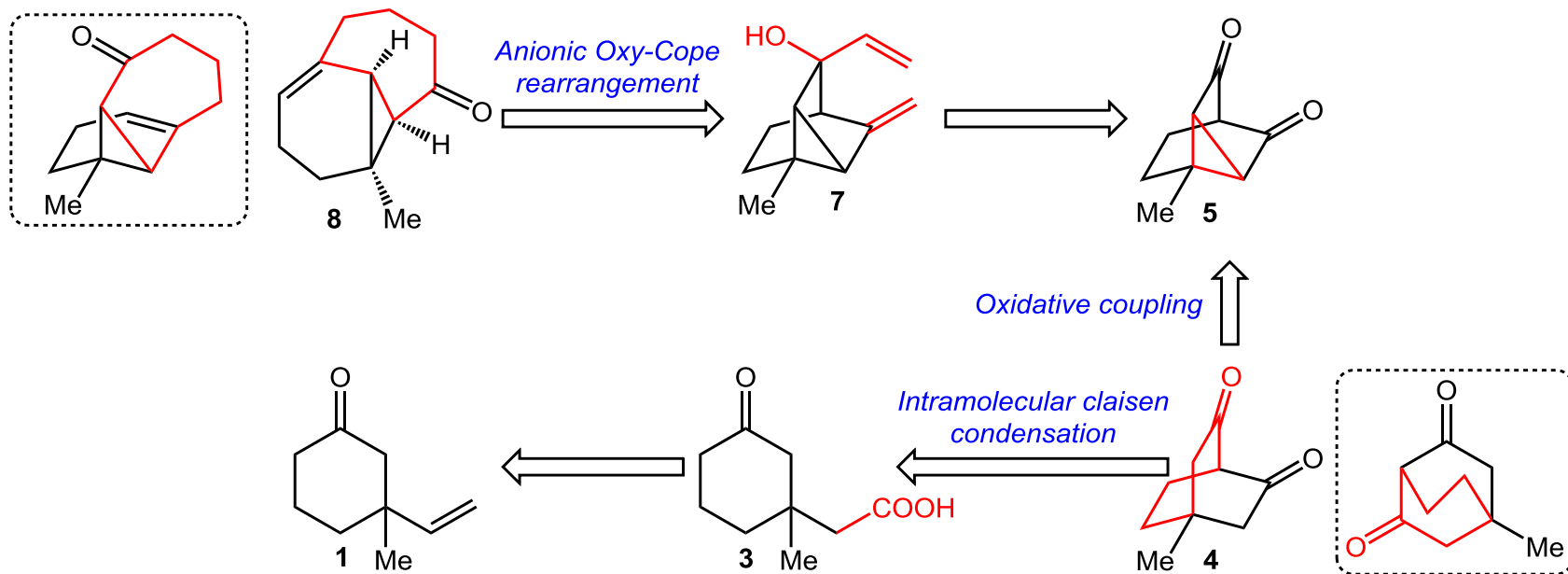
- Isolated by Naya in 1983 from secretions of *Ceroplastes rubens* Maskell
- Seven contiguous stereocenters including an quaternary stereocenter
- A sterically compact 6/3/7/6 tetracyclic skeleton
- A strained bridgehead (anti-Bredt) double bond at C6–C7

Naya, Y. *et al. J. Chem. Soc., Chem. Commun.* **1983**, 1182

Retrosynthetic Analysis (Paquette)

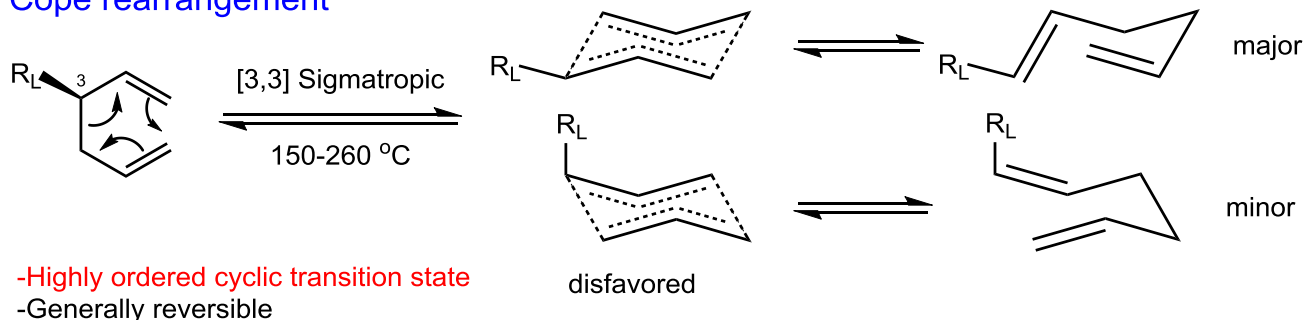


Retrosynthetic Analysis (Paquette)

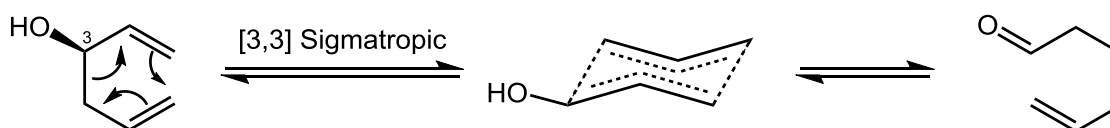


Anionic Oxy-Cope rearrangement

Cope rearrangement

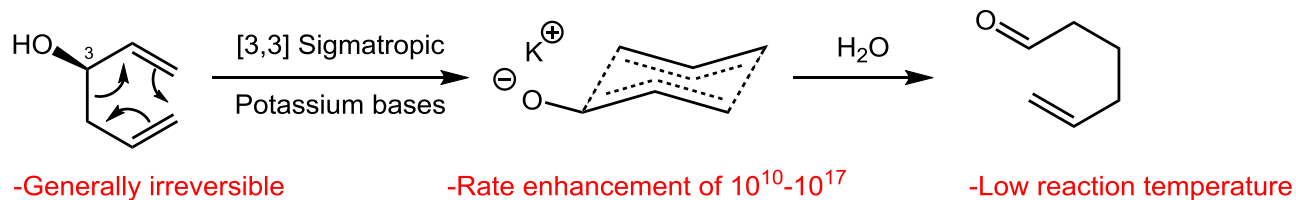


Oxy-Cope rearrangement

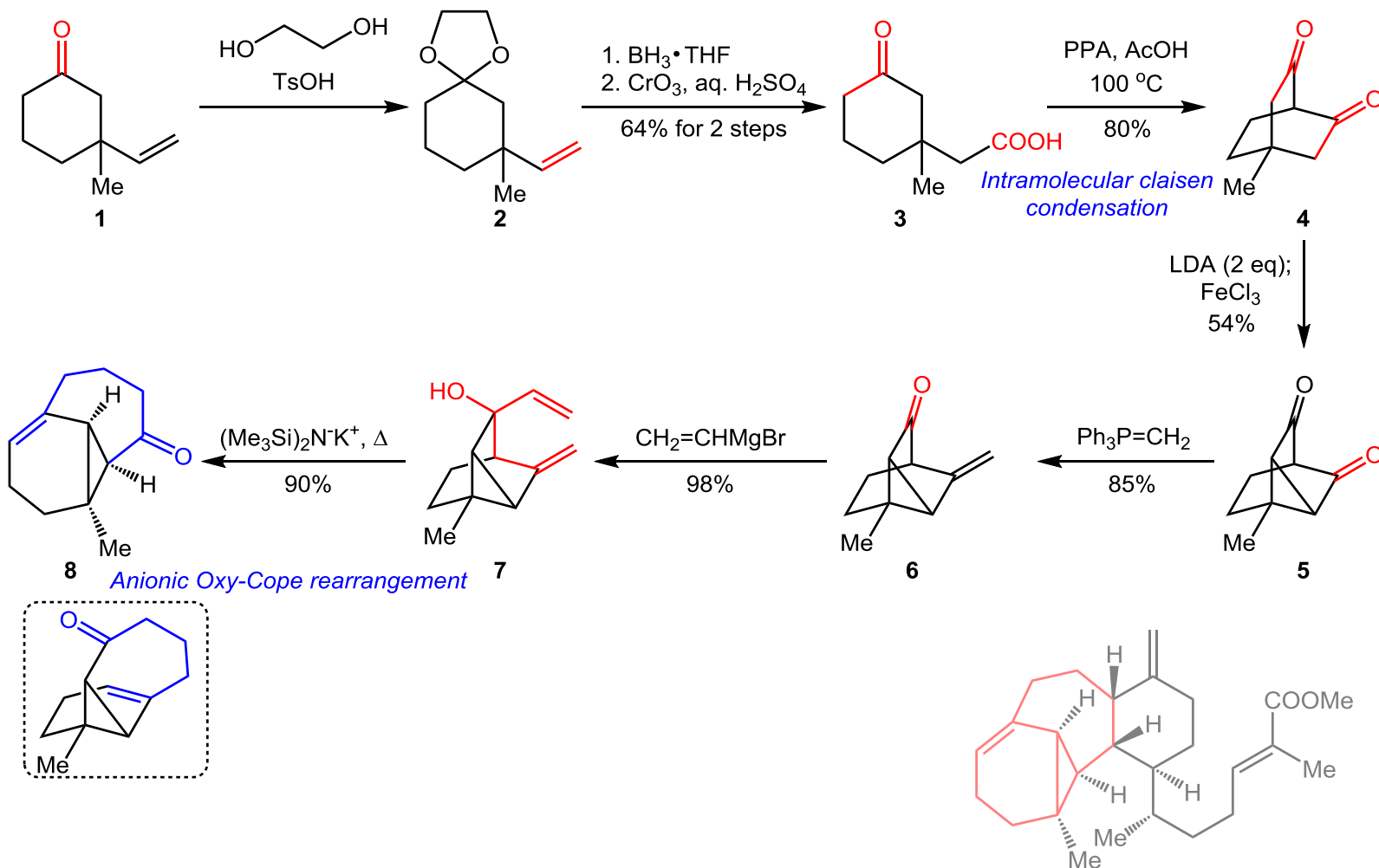


-The formation of the carbonyl compound is the **driving force** for the reaction

Anionic oxy-Cope rearrangement

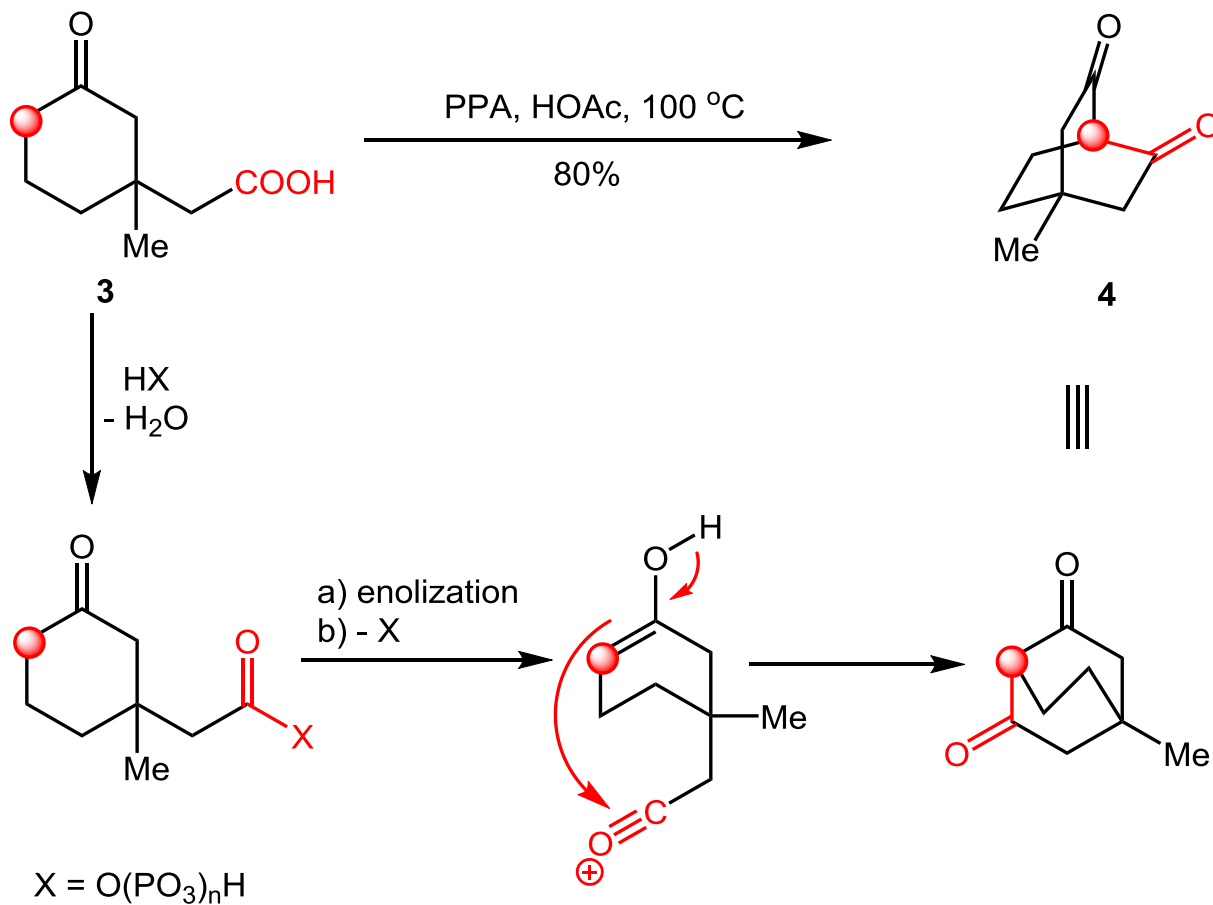


Synthesis by Paquette



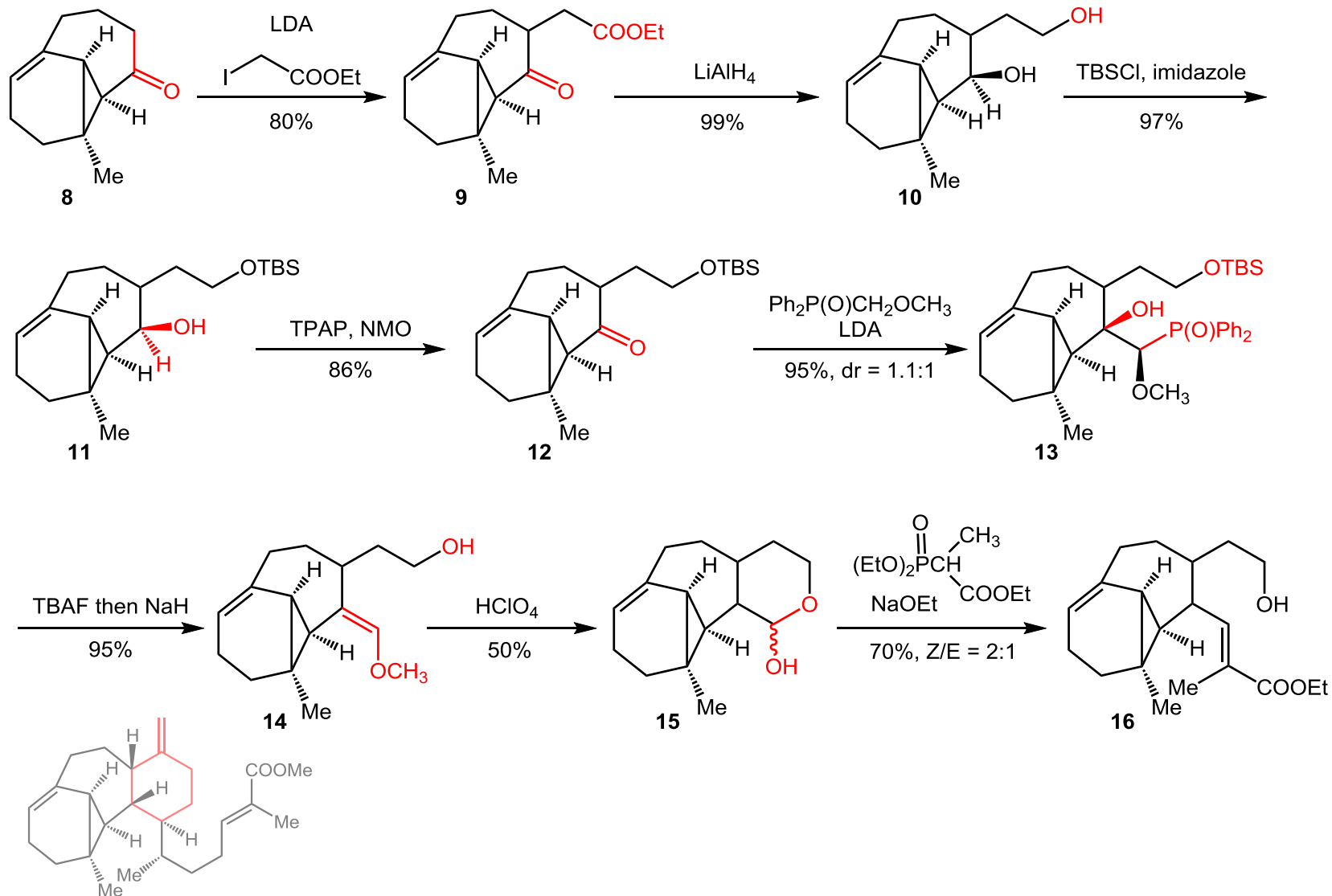
Synthesis by Paquette

Intramolecular claisen condensation

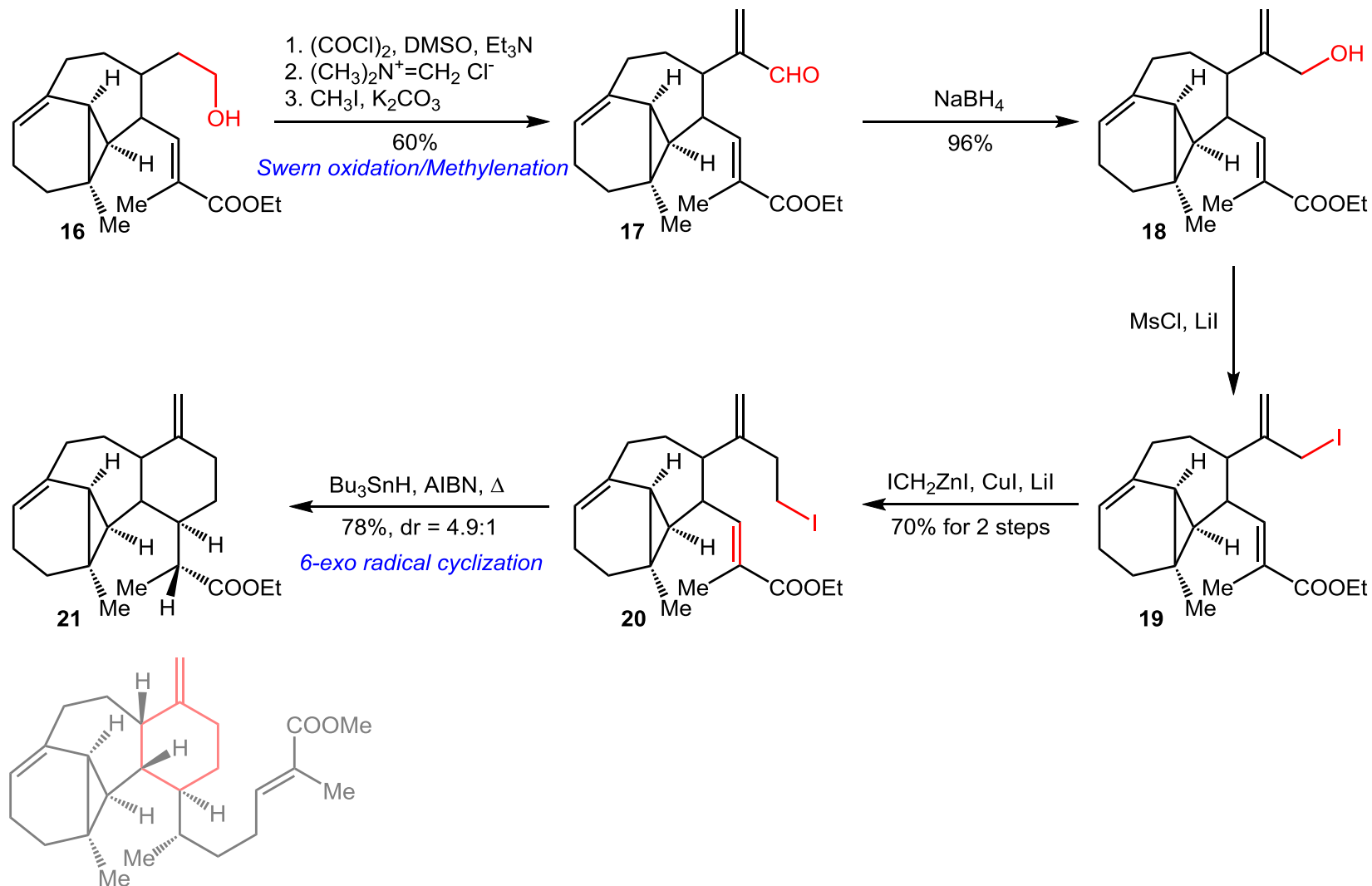


Gerlach, H. *et al. Angew. Chem. Int. Ed.* **1972**, *11*, 1030

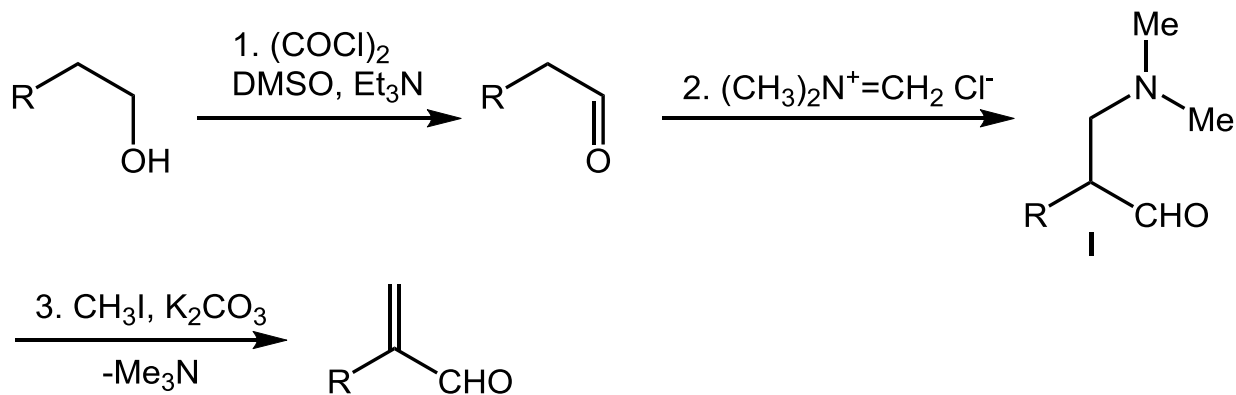
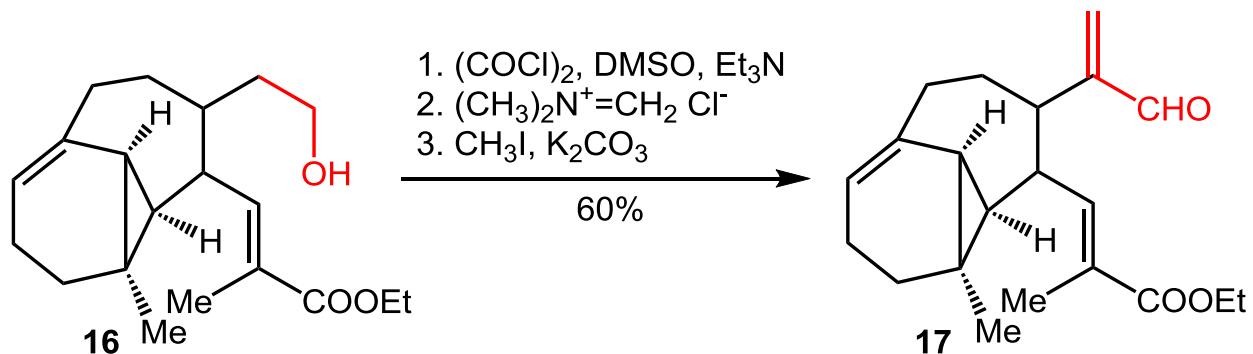
Synthesis by Paquette



Synthesis by Paquette

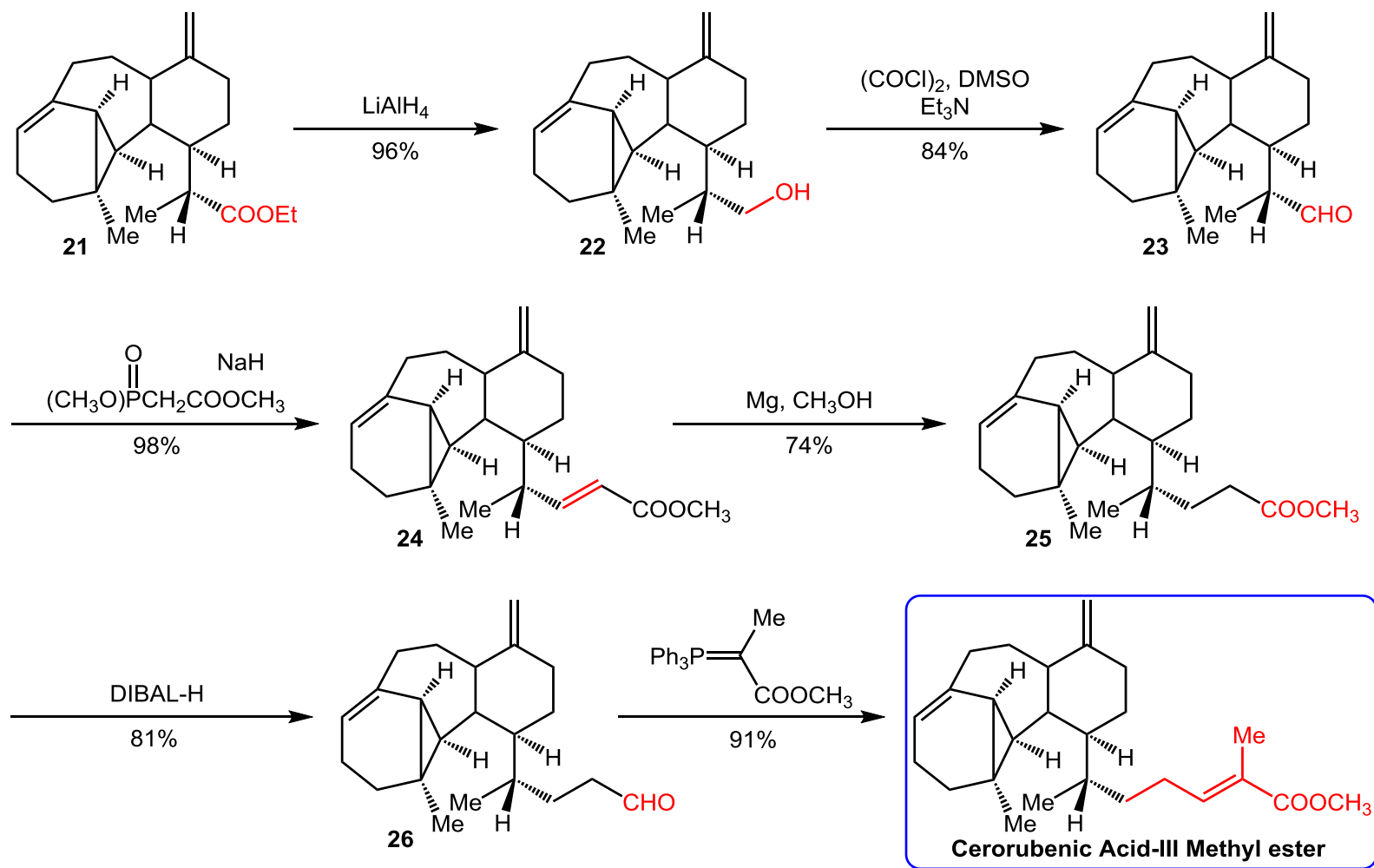


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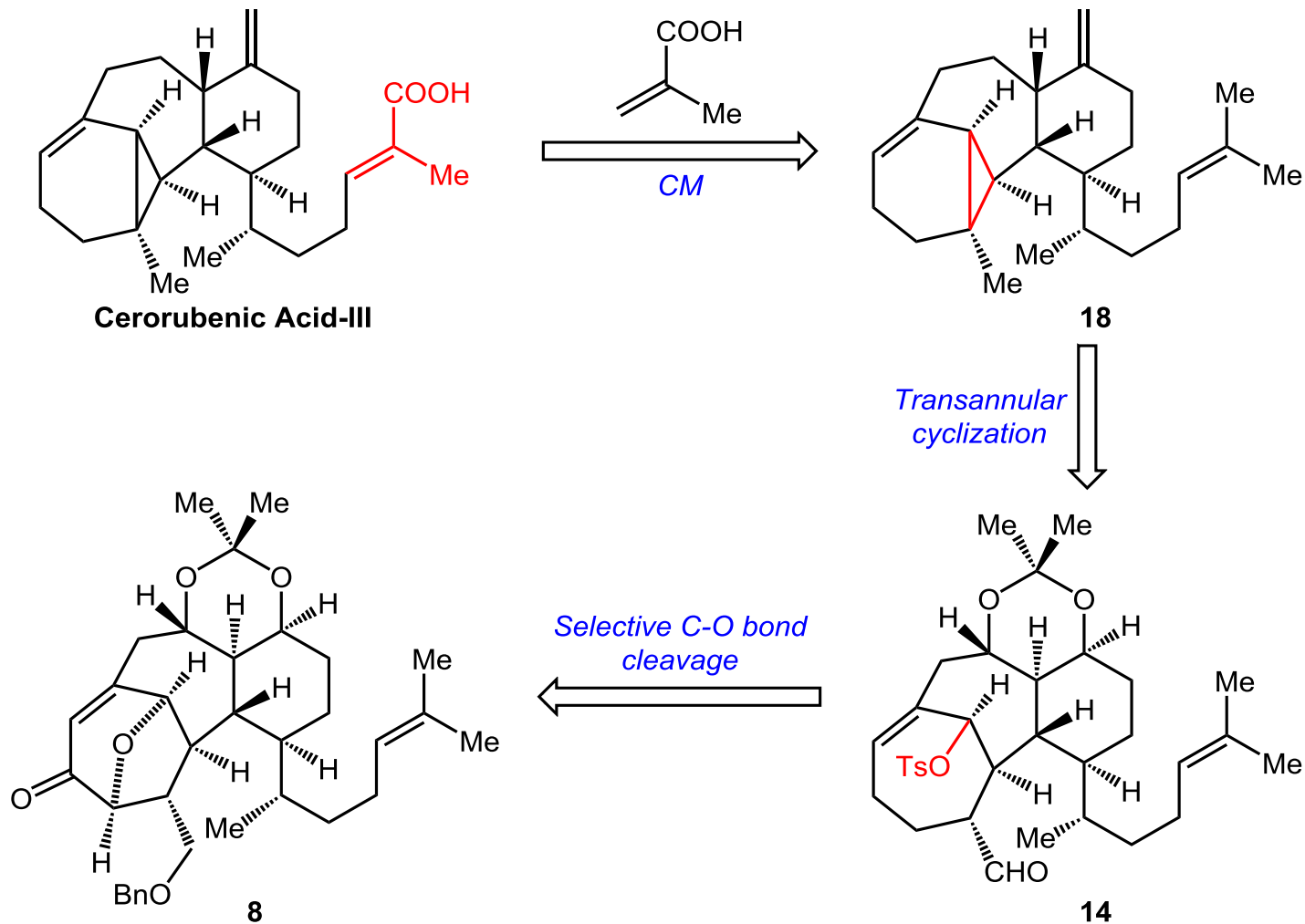


Takano, S. *et al. Chem. Lett.* **1989**, 1283

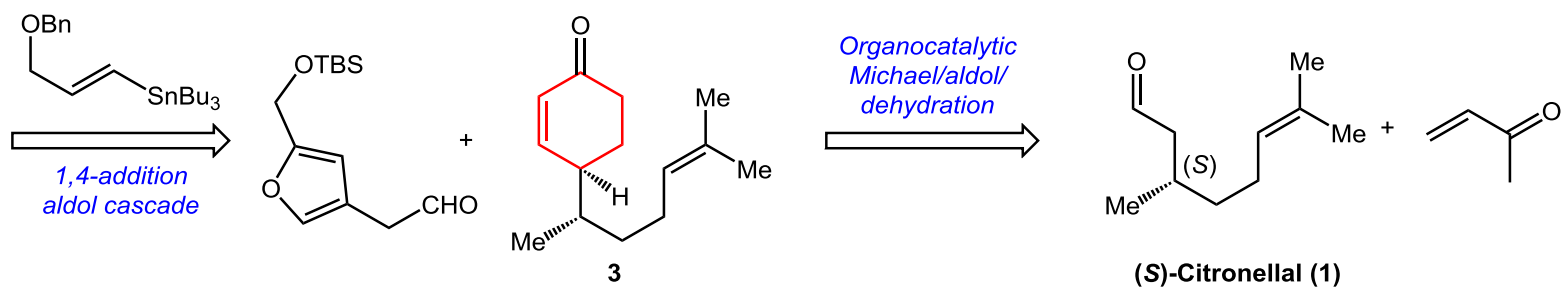
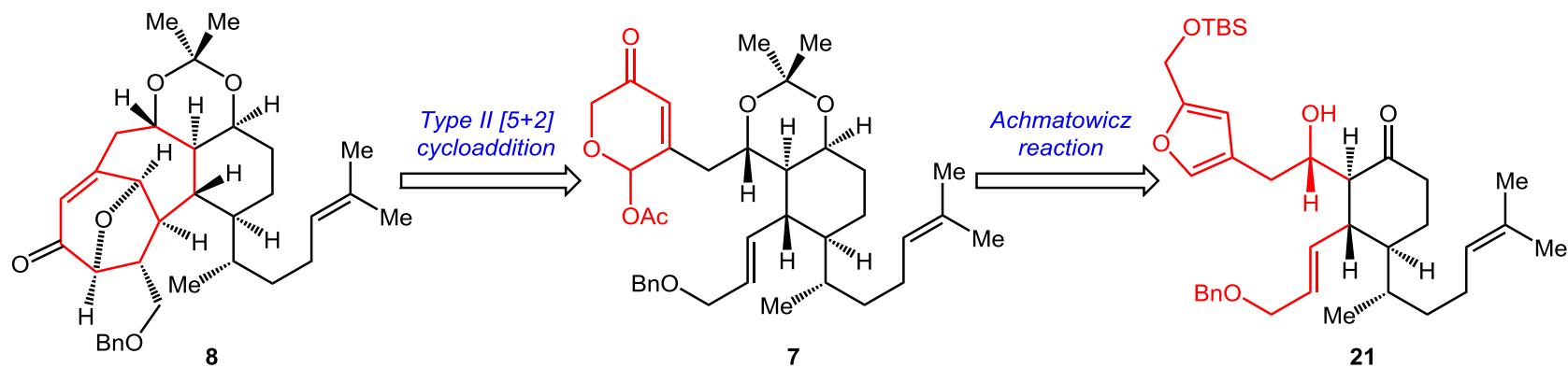
Synthesis by Paquette



Retrosynthetic Analysis (Li)

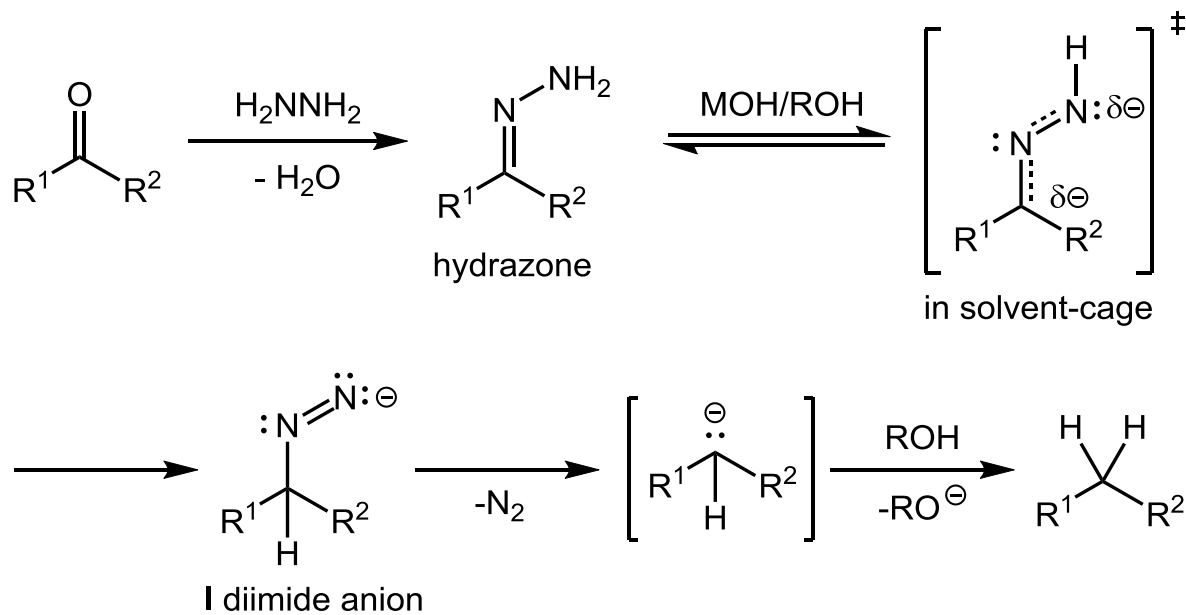
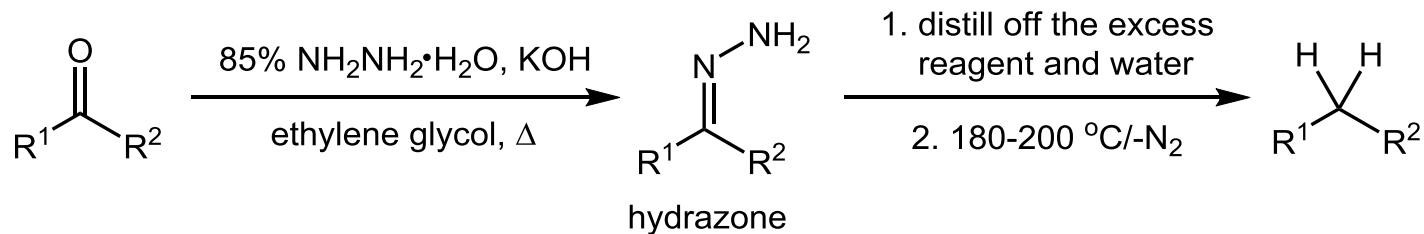


Retrosynthetic Analysis (Li)

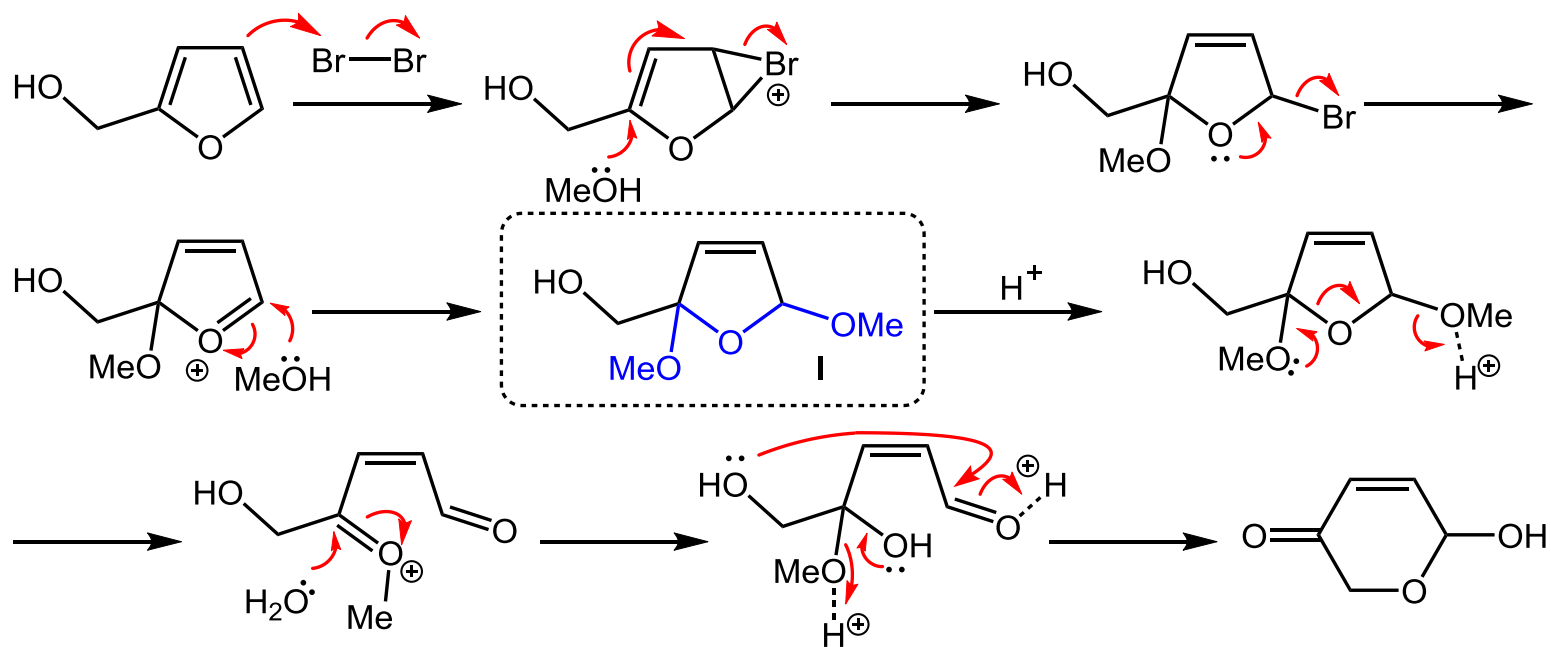
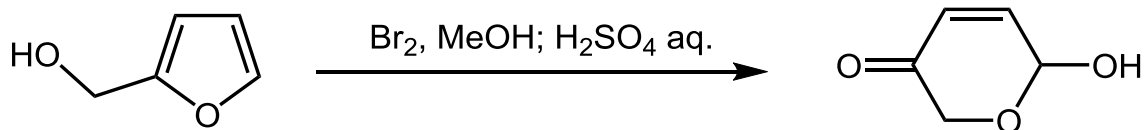


Wolff-Kishner reduction

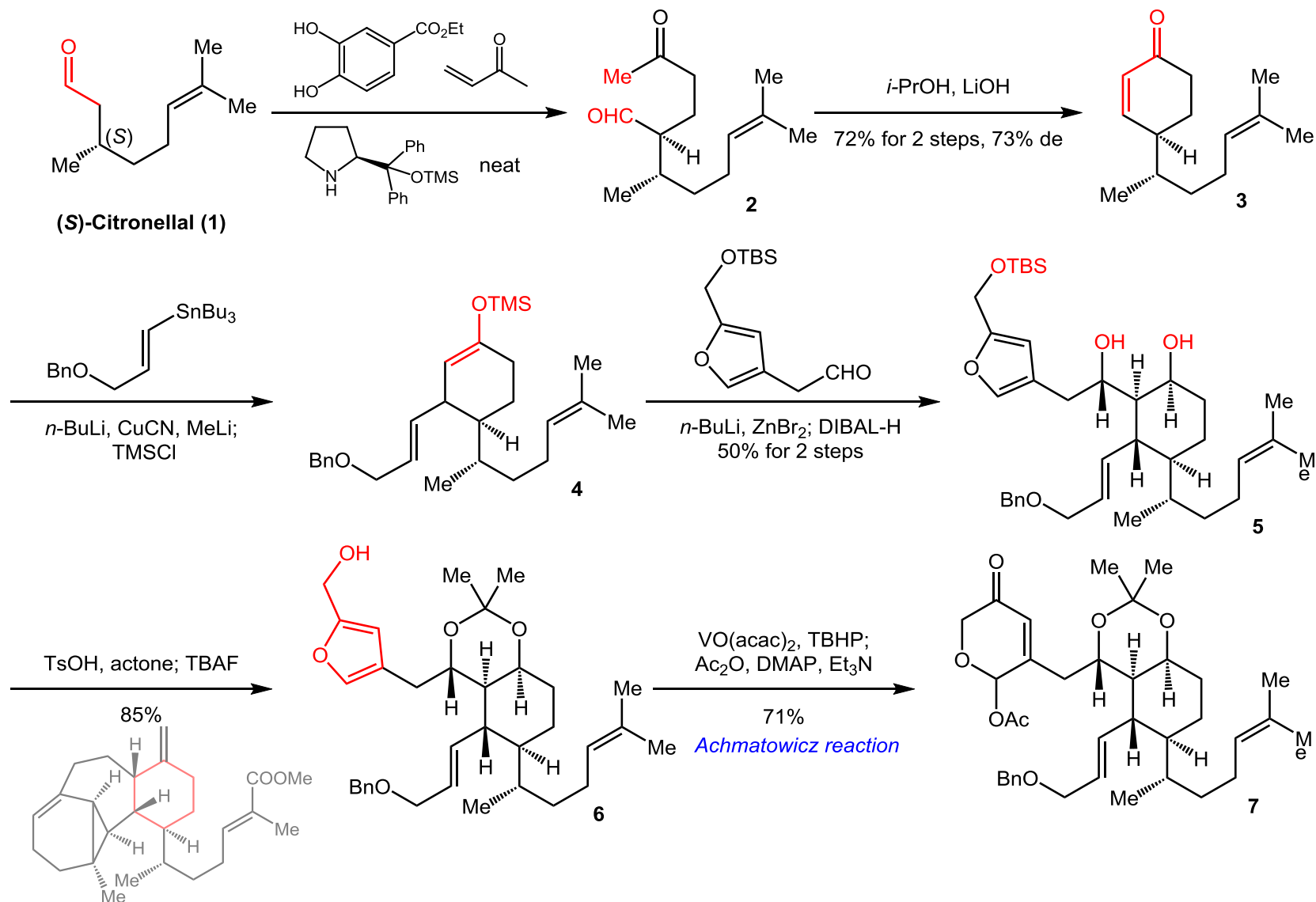
Huang's modification



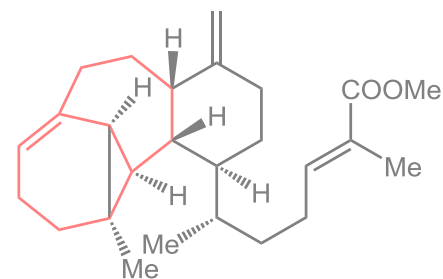
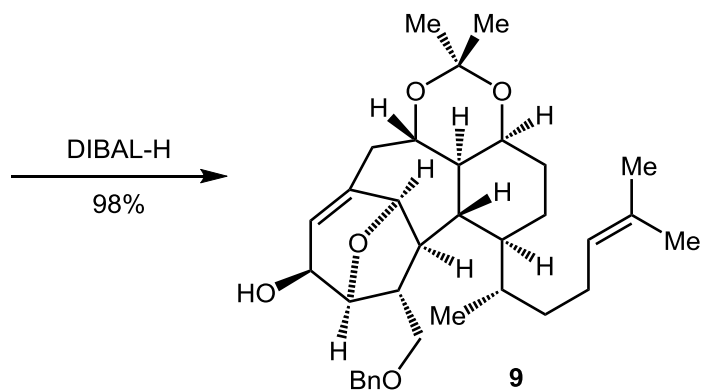
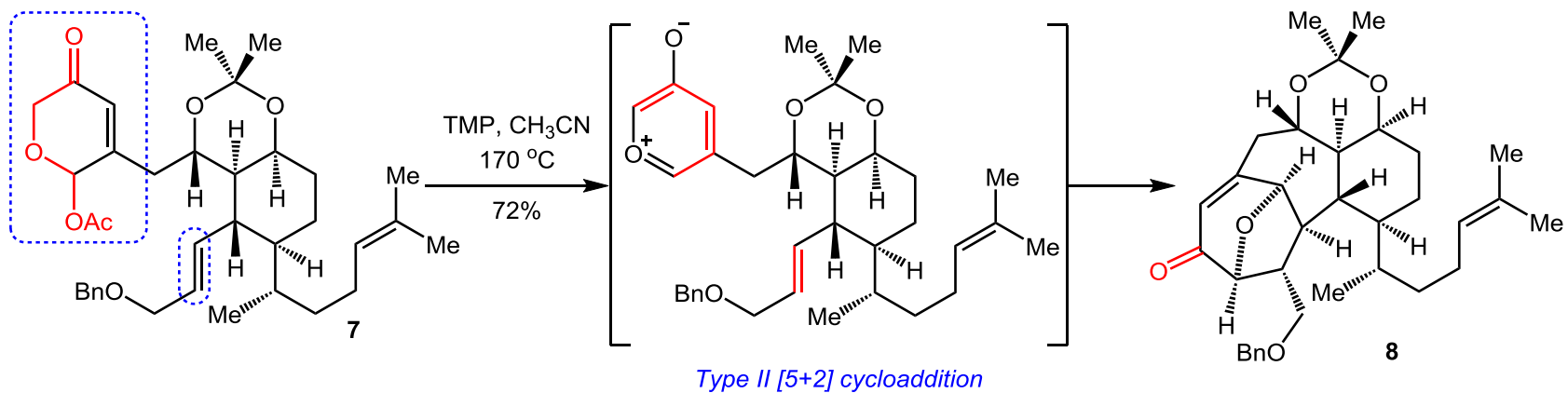
Achmatowicz reaction



Synthesis by Li

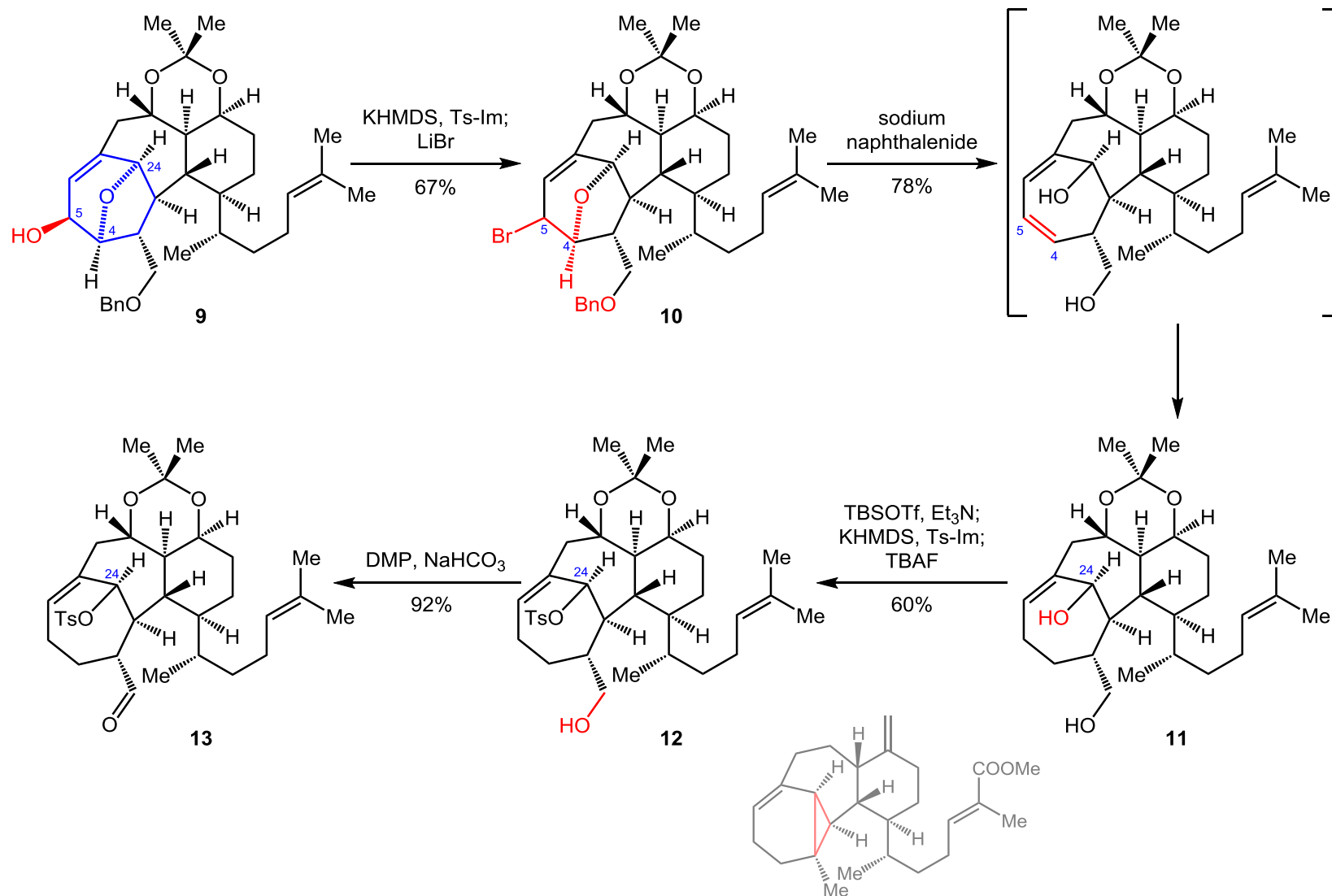


Synthesis by Li

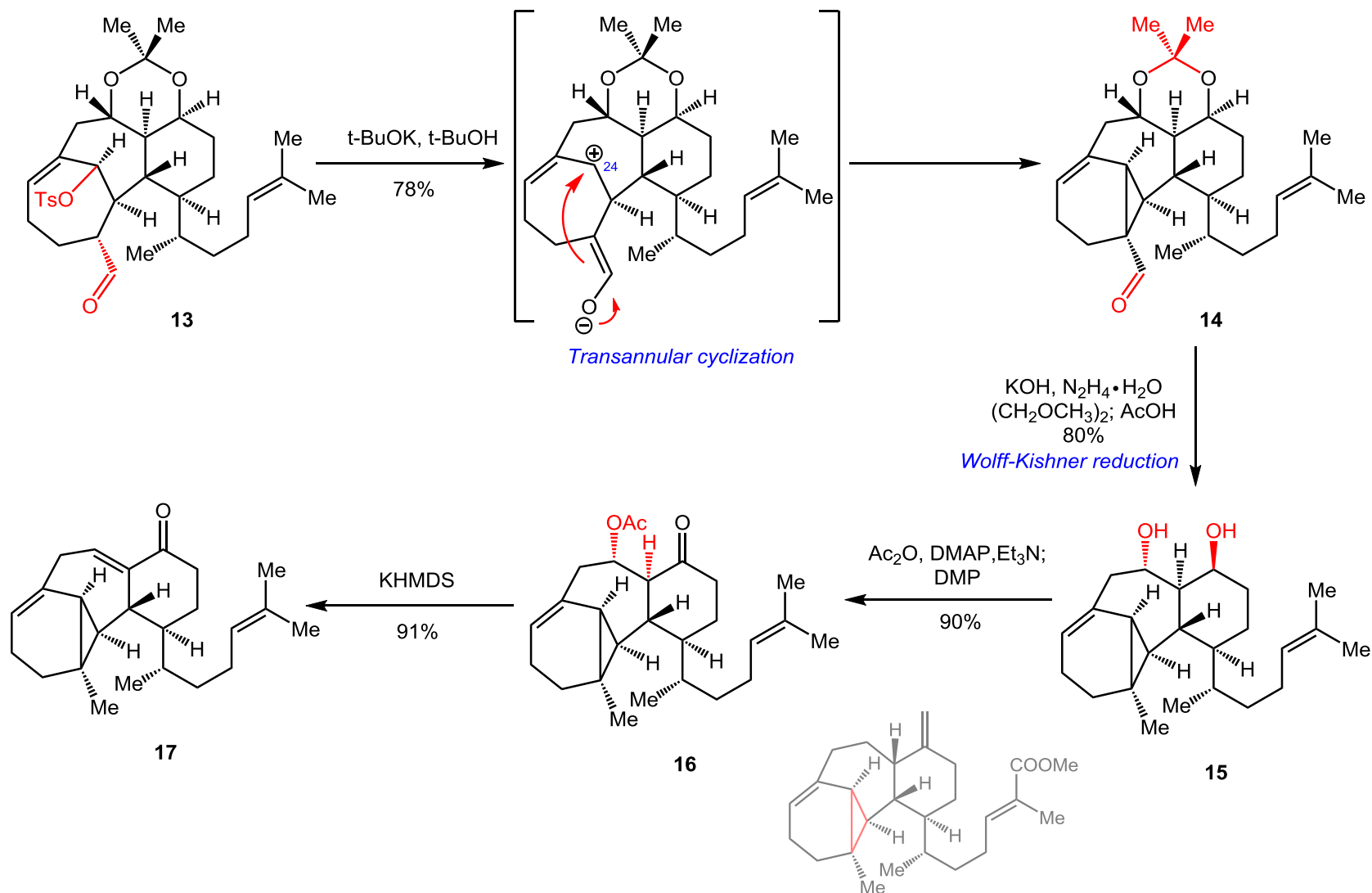


Li, C.-C. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 1754

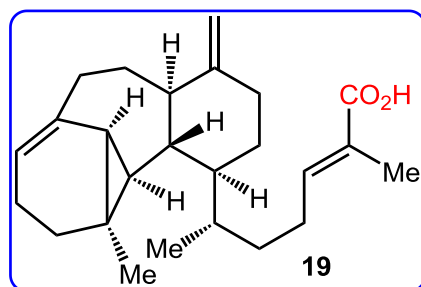
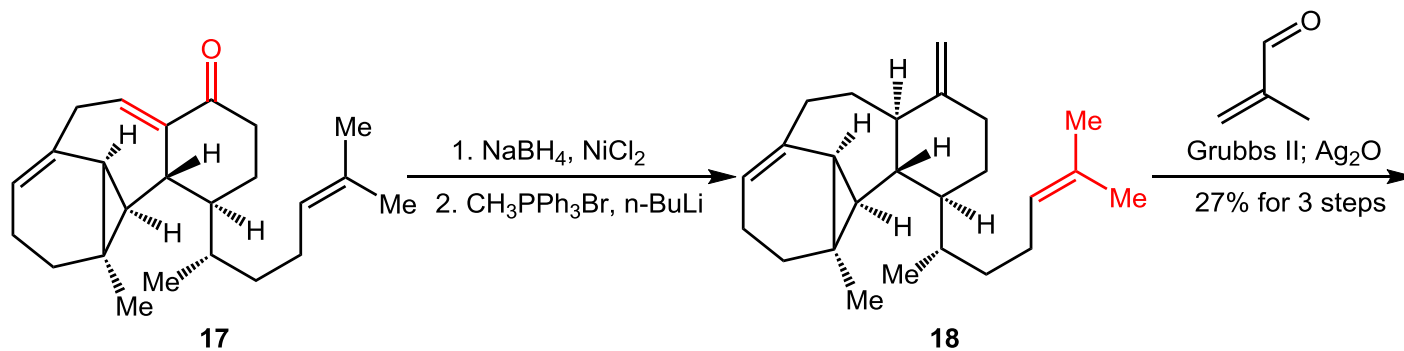
Synthesis by Li



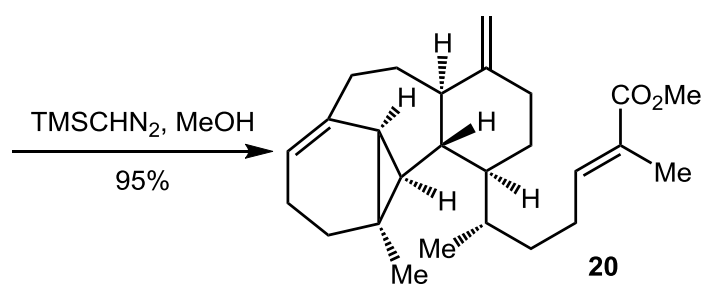
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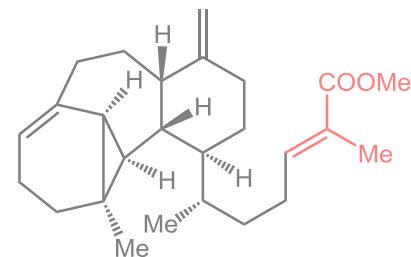
Synthesis by Li



Cerorubenic Acid-III



Cerorubenic Acid-III Methyl ester

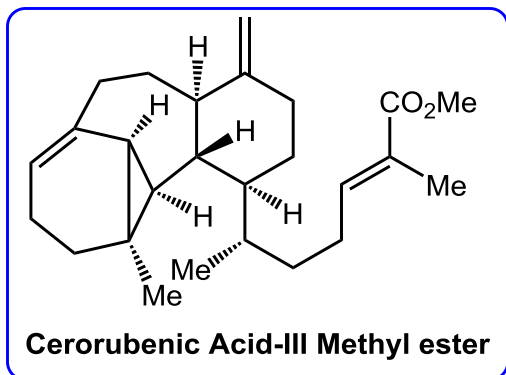


Summary

Synthesis by Paquette

- ◆ 30 steps, 0.3% overall yield
- ◆ Anionic Oxy-Cope rearrangement
- ◆ 6-exo radical cyclization

Paquette, L. A. *et al. J. Am. Chem. Soc.* **1998**, *120*, 5953



Synthesis by Li

- ◆ 20 steps, 0.6% overall yield
- ◆ A type II intramolecular [5 + 2] cycloaddition
- ◆ Transannular cyclization

Li, C.-C. *et al. J. Am. Chem. Soc.* **2019**, *141*, 2872

The First Paragraph

Sesterterpenoids continue to play a significant role in synthetic organic chemistry and drug discovery, owing to their intriguing and broad range of biological activities and complicated, diverse structures. **Cerorubenic acid-III**, a sesterterpenoid with a novel tetracyclo[8.4.1.0.0]-pentadecane skeleton, was first isolated by Naya and coworkers in 1983 from secretions of the scale insect *Ceroplastes rubens Maskell*. This compound plays an important role in insect communication, although the relative scarcity of **1** from natural sources has impeded a more systematic evaluation of its biological activity. **Therefore, the development of an efficient synthesis of 1 and its analogues is highly desirable.** Structurally, **1** comprises a sterically compact 6/3/7/6 tetracyclic skeleton, with a unique bridged bicyclo[4.4.1]undecene ring system and a vinylcyclopropane fragment.

The First Paragraph

In particular, **1** possesses a strained bridgehead (anti-Bredt) double bond at C6-C7, as is also found in the well-known natural drug Taxol. **This double bond is unstable in air, as it oxidizes to give the corresponding epoxide.** These unique structural features of **1** make it highly strained. **Moreover, 1 has seven contiguous stereocenters, including an all-carbon quaternary stereocenter on the cyclopropane moiety.** Therefore, **1** presents a formidable synthetic challenge.

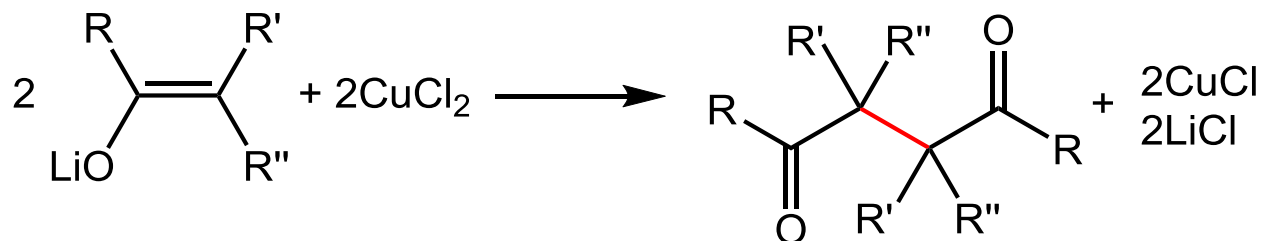
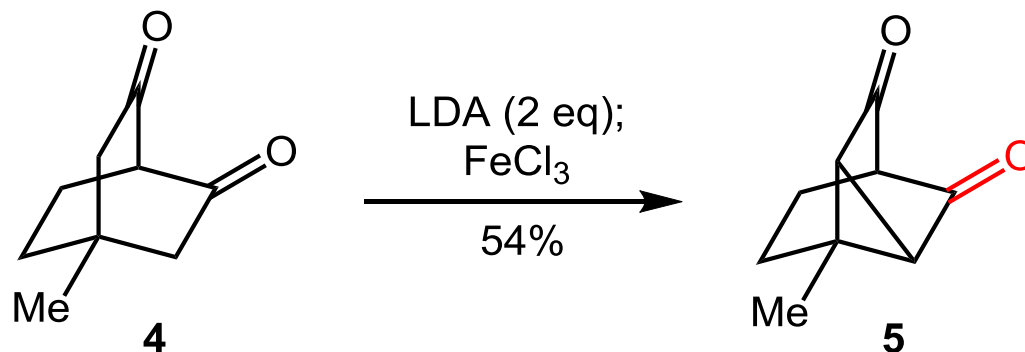
The Last Paragraph

In summary, this work demonstrated the first asymmetric total synthesis of the highly strained compound cerorubenic acid-III. Notably, a type II intramolecular [5 + 2] cycloaddition enabled efficient and diastereoselective construction of the synthetically challenging bicyclo[4.4.1] ring system having a strained bridgehead anti-Bredt double bond in **1**. A unique cascade reduction of 8-oxabicyclo[3.2.1]octene in **10** was achieved chemoselectively using sodium naphthalenide, and an unusual transannular cyclization installed the vinylcyclopropane moiety with retention of the desired stereochemistry. This approach could be extended to the asymmetric synthesis of other cerorubenic acids and their analogues to allow further biological studies. Such work is ongoing, and the results will be reported in due course.

Acknowledgement

***Thanks
for your kind attention !***

Synthesis by Paquette



Saegusa, T. *et al.* *J. Am. Chem. Soc.* **1977**, 99, 1487

Ley oxidation

