

Literature Report 1

Asymmetric Total Synthesis of the Highly Strained 4 β -Acetoxyprobotryane-9 β ,15 α -diol

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Checker : Yang Zhao
Date : 2021-04-12

Li, C.-C. *et al.* *J. Am. Chem. Soc.* **2020**, 142, 19868

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

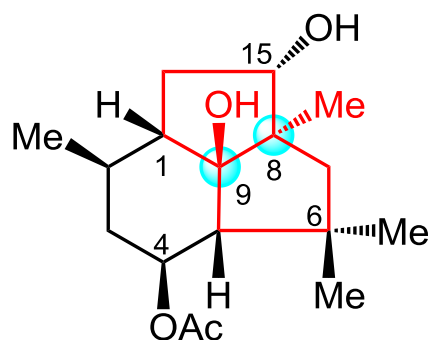
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Introduction



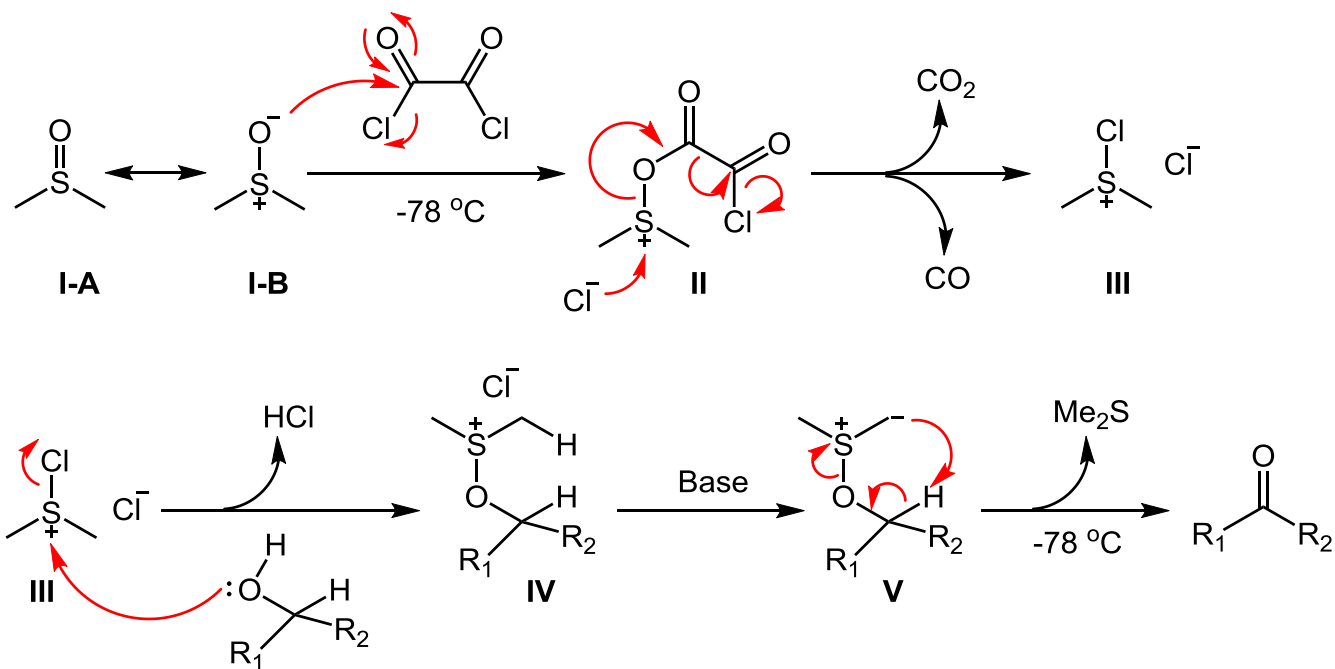
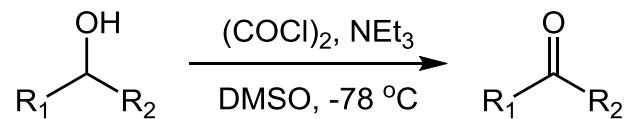
4 β -acetoxyprobotryane-9 β ,15 α -diol



Botrytis cinerea

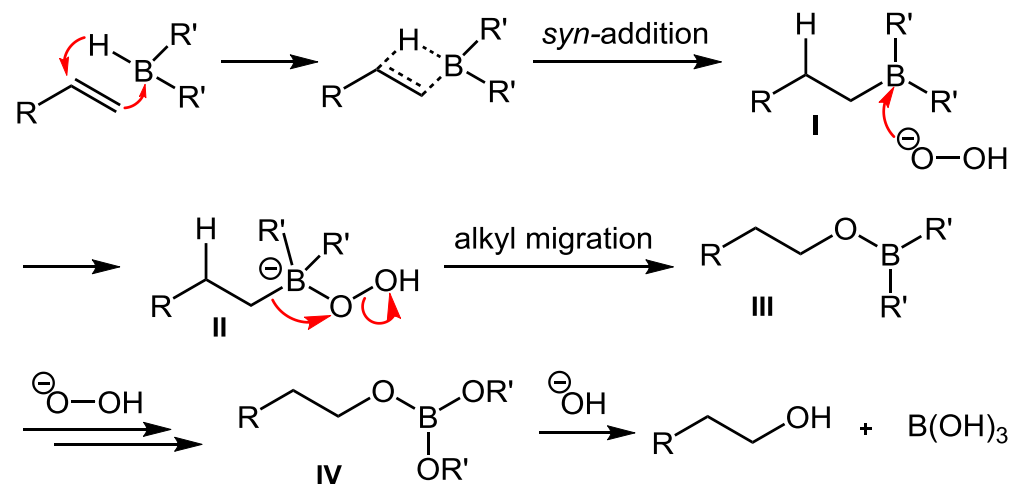
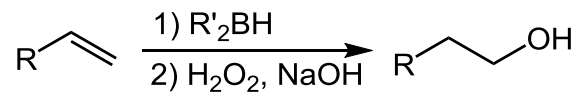
- Isolated from a culture of Botrytis cinerea;
- Sterically compact [6-5-5] tricyclic skeleton;
- Highly strained *trans*-fused bicyclo[3.3.0]octane ring system.

Swern Oxidation



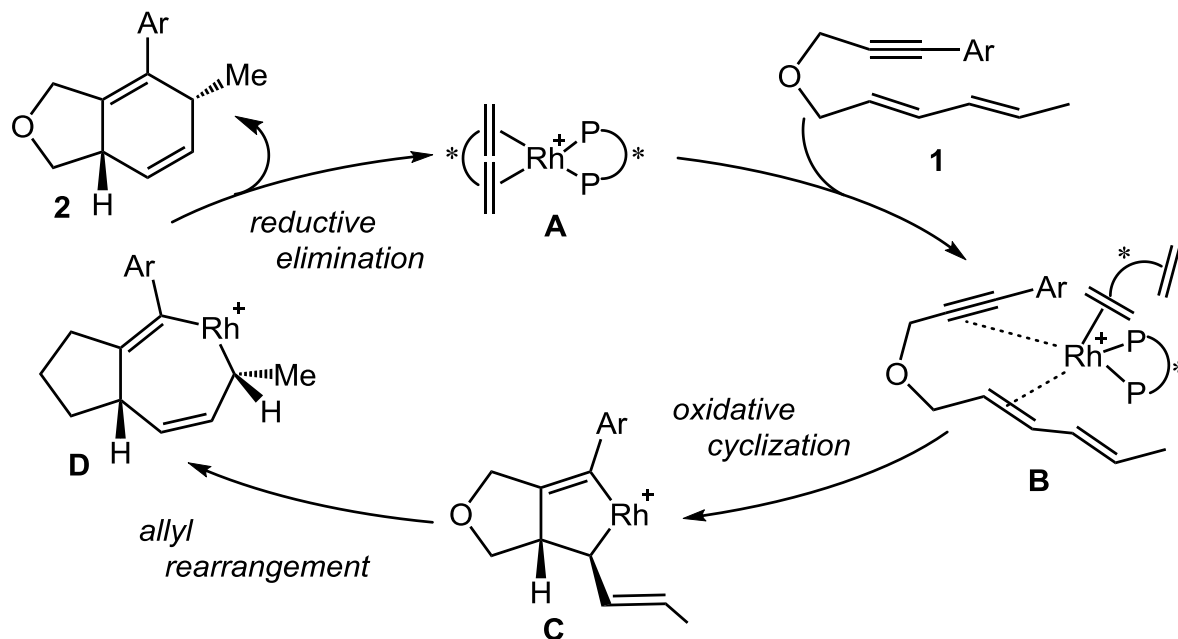
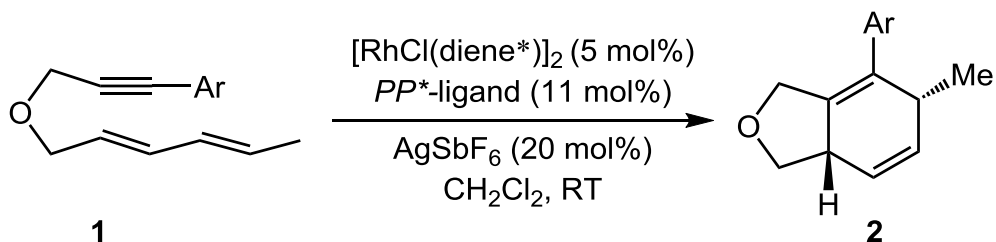
From name reaction

Hydroboration-Oxidation Reaction



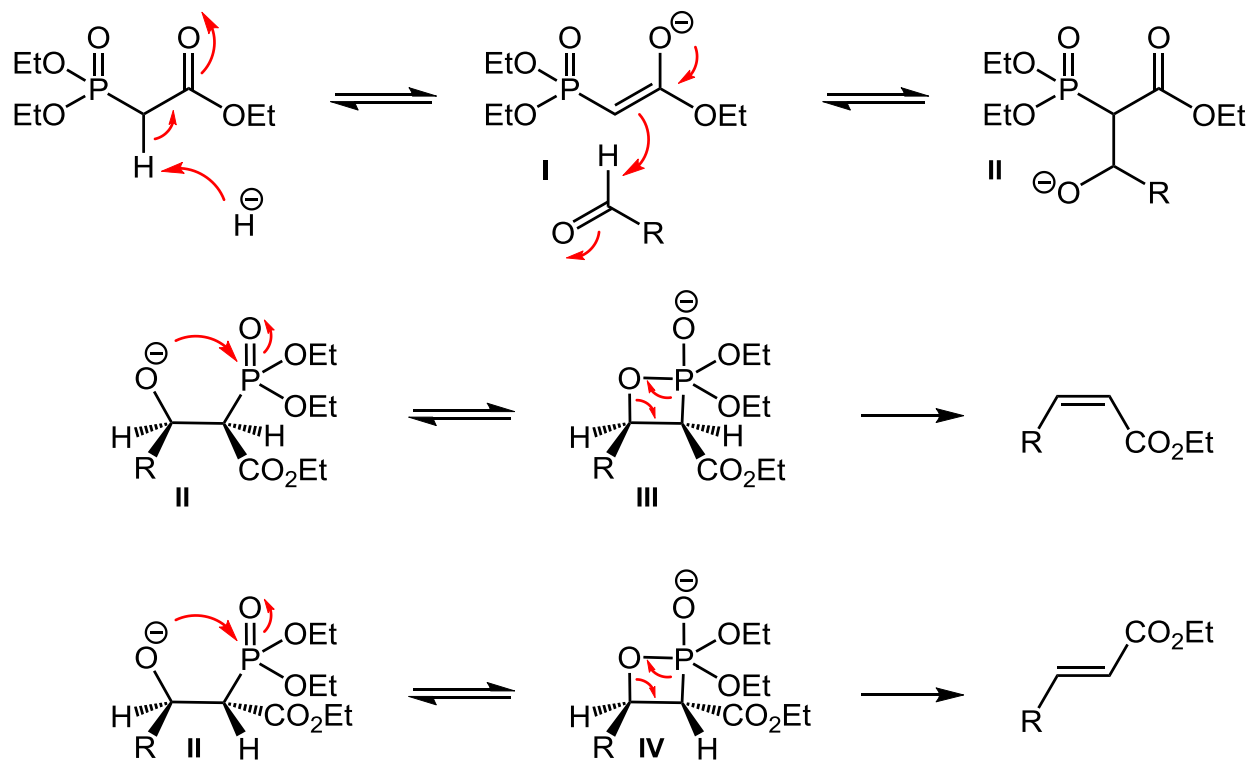
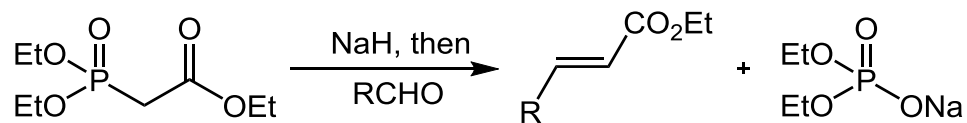
From name reaction

Rh-Catalyzed [4+2] Cycloaddition



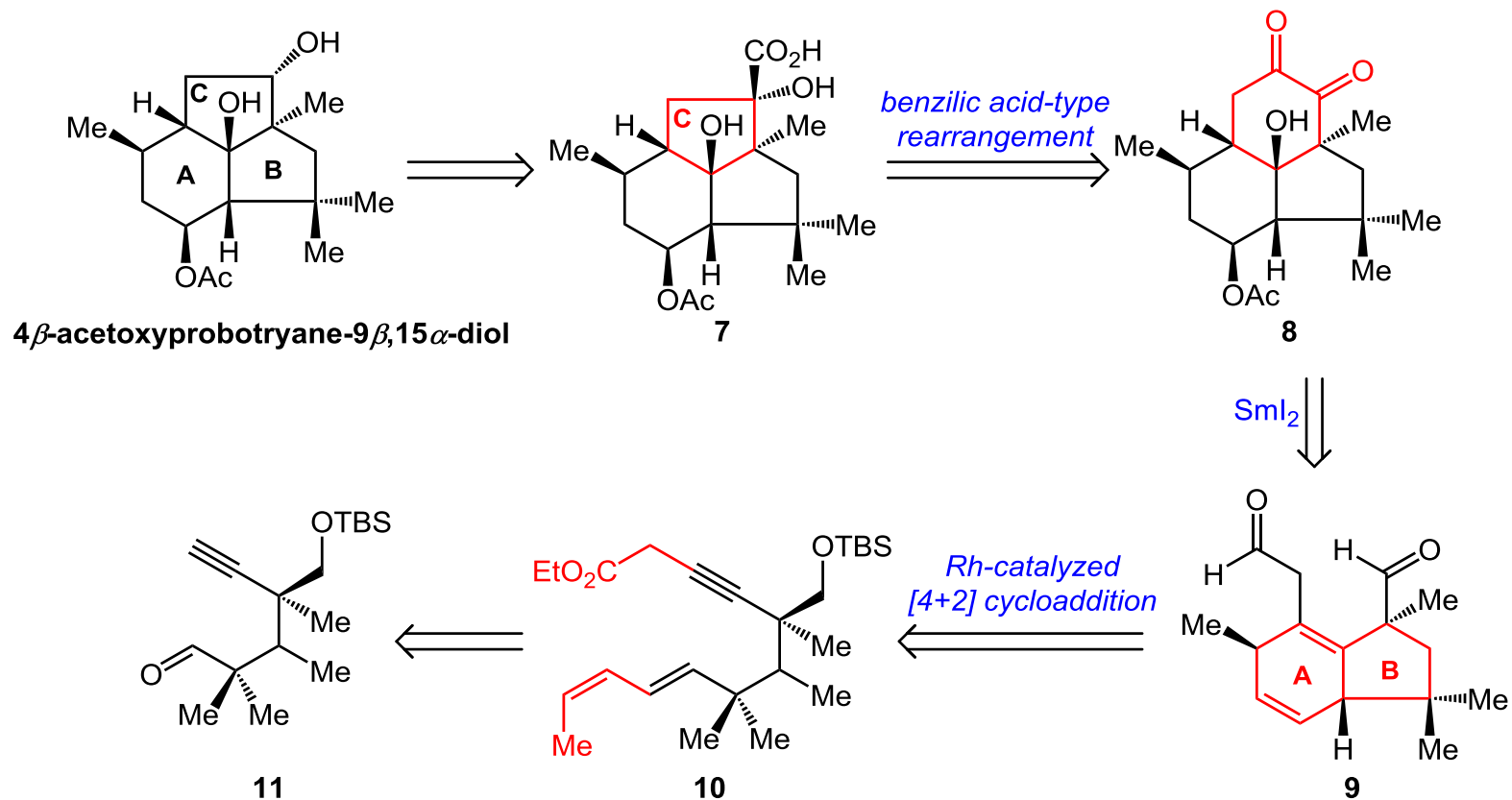
Kohsuke, A.; Susumu A.; Koichi, M. *J. Am. Chem. Soc.* **2006**, 128, 12648.

Horner-Wadsworth-Emmons Olefination

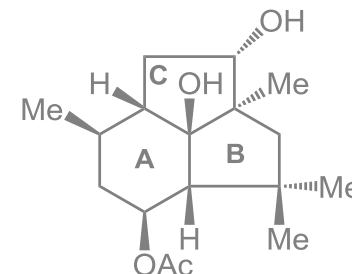
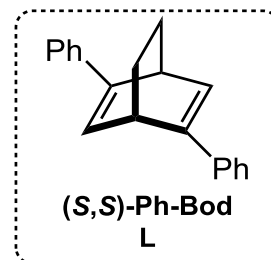
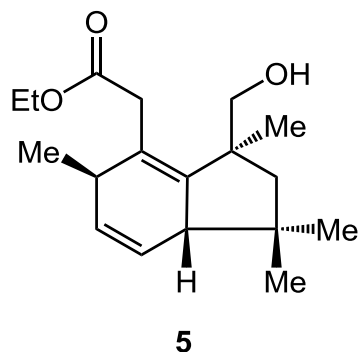
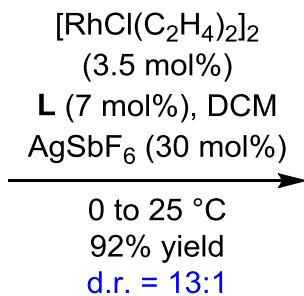
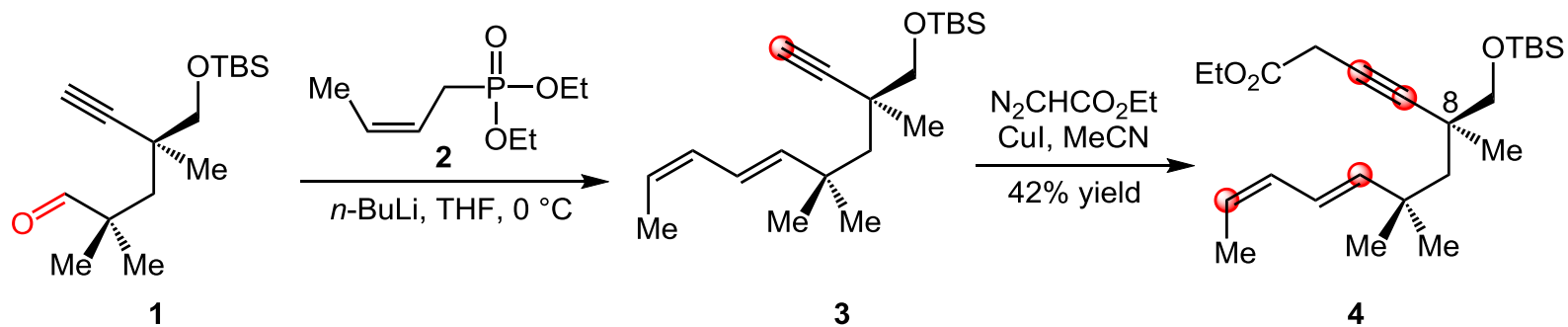


From name reaction

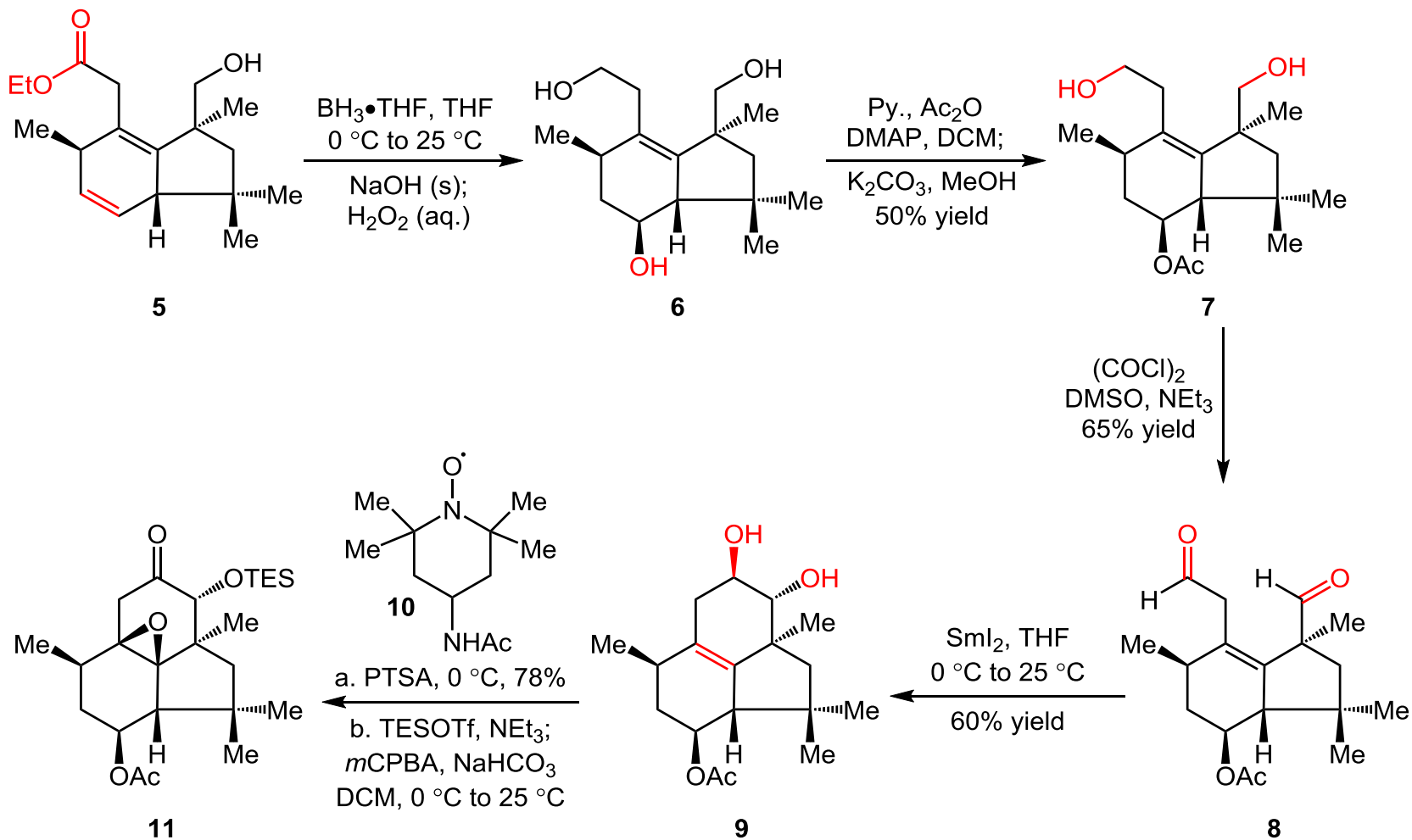
Retrosynthetic Analysis



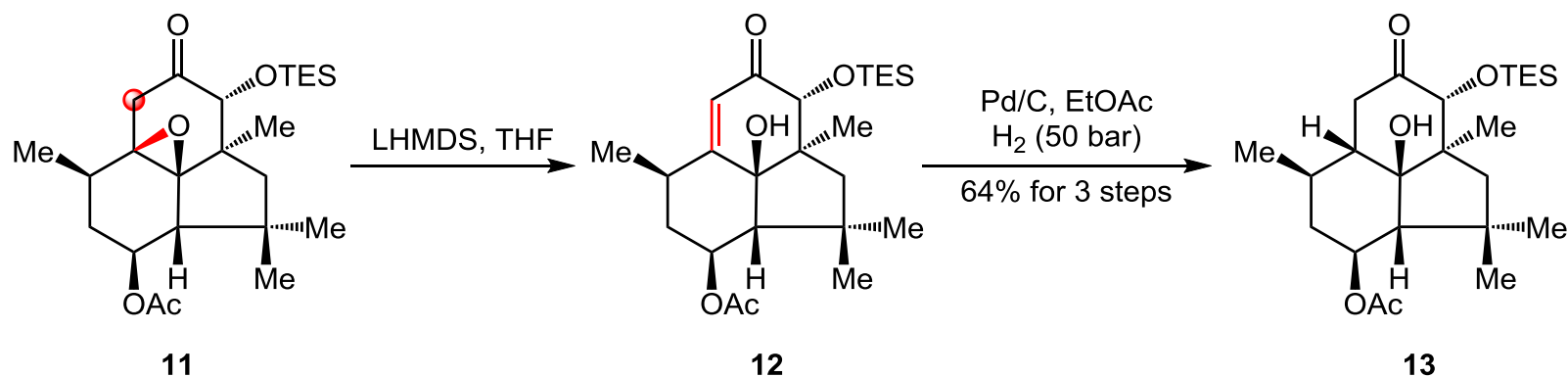
Diastereoselective Synthesis of 5



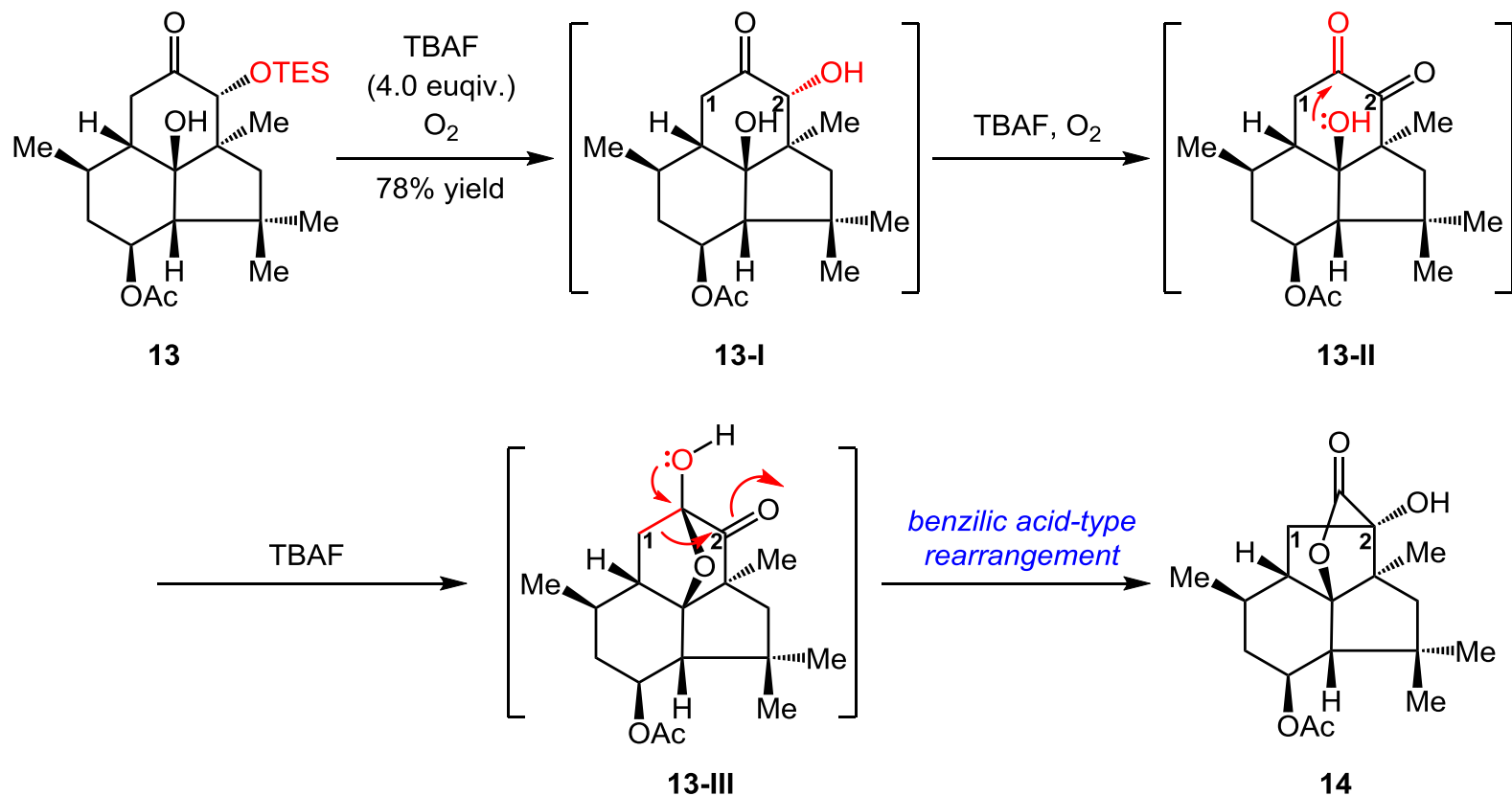
Total Synthesis of 4 β -acetoxyprobotryane-9 β ,15 α -diol



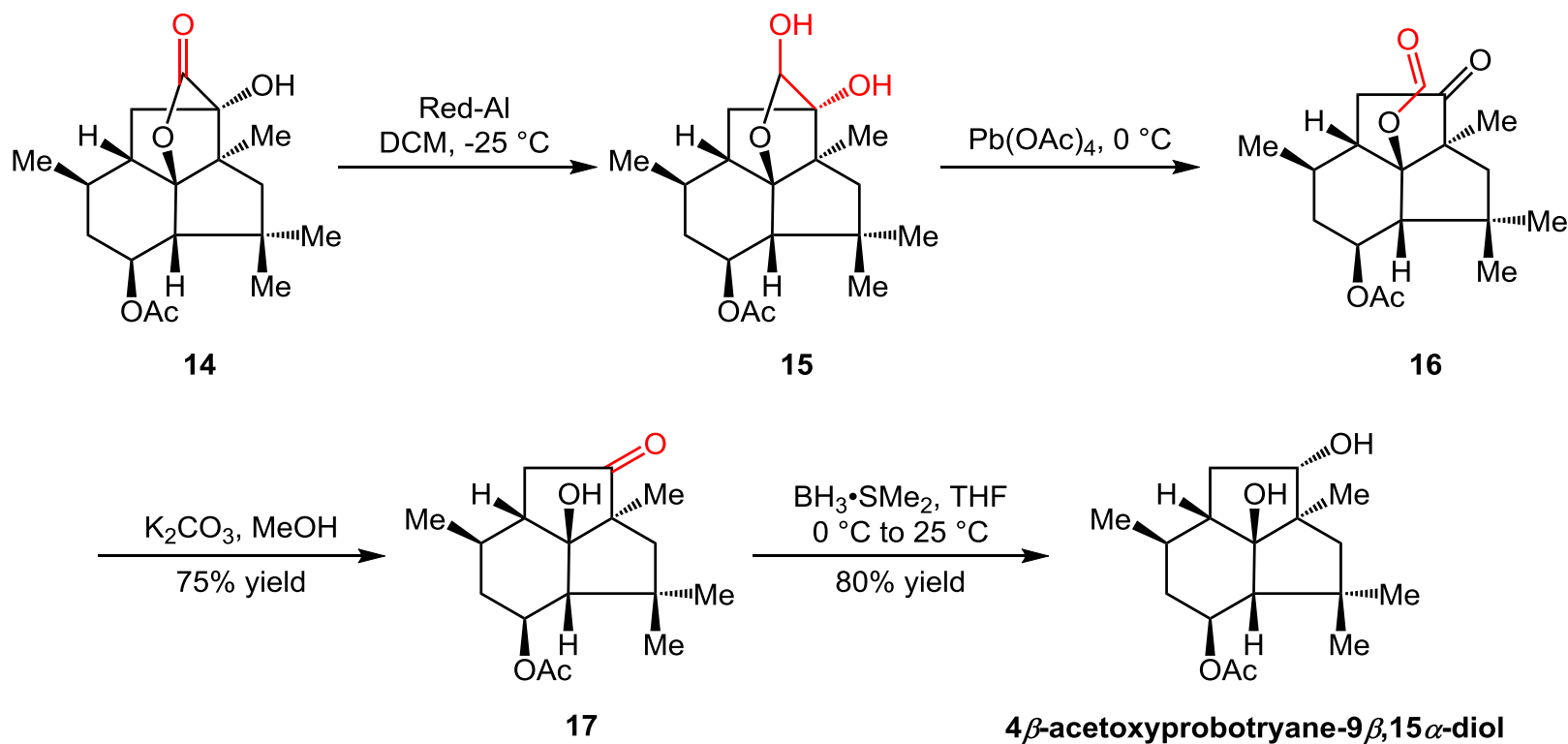
Total Synthesis of 4 β -acetoxyprobotryane-9 β ,15 α -diol



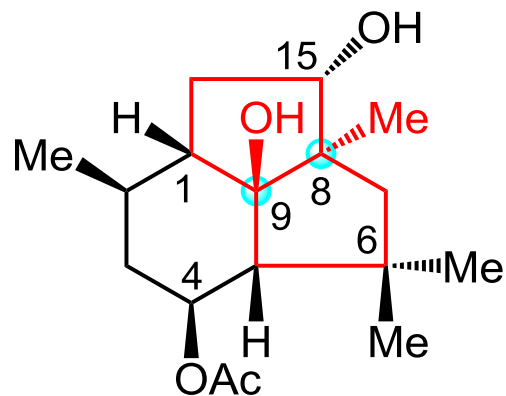
Total Synthesis of 4 β -acetoxyprobotryane-9 β ,15 α -diol



Total Synthesis of 4 β -acetoxyprobotryane-9 β ,15 α -diol



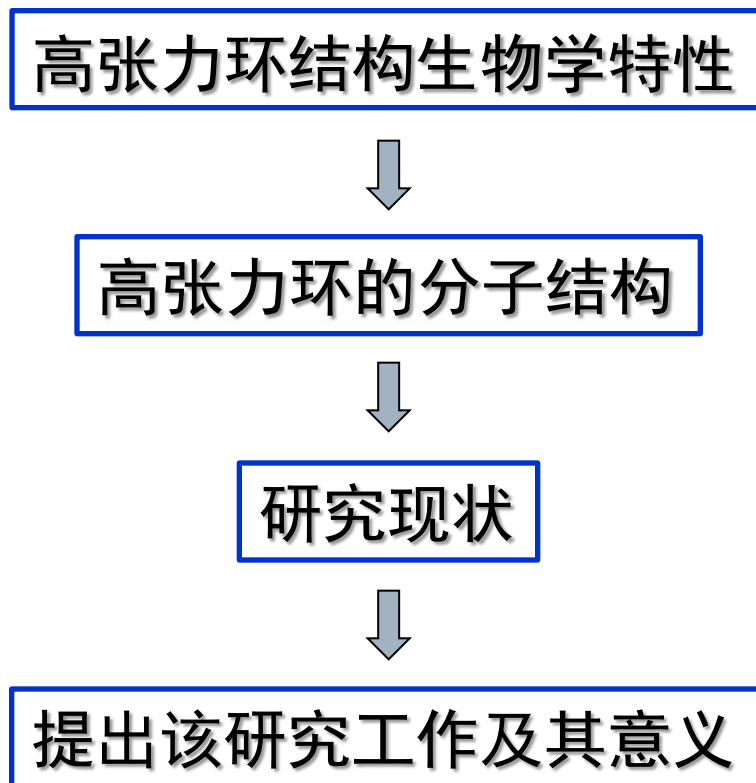
Summary



- ✓ 14 steps, 1.8% overall yield
- ✓ Rhodium-catalyzed [4+2] cycloaddition reaction
- ✓ Benzilic acid type rearrangement

The First Paragraph

写作思路



The First Paragraph

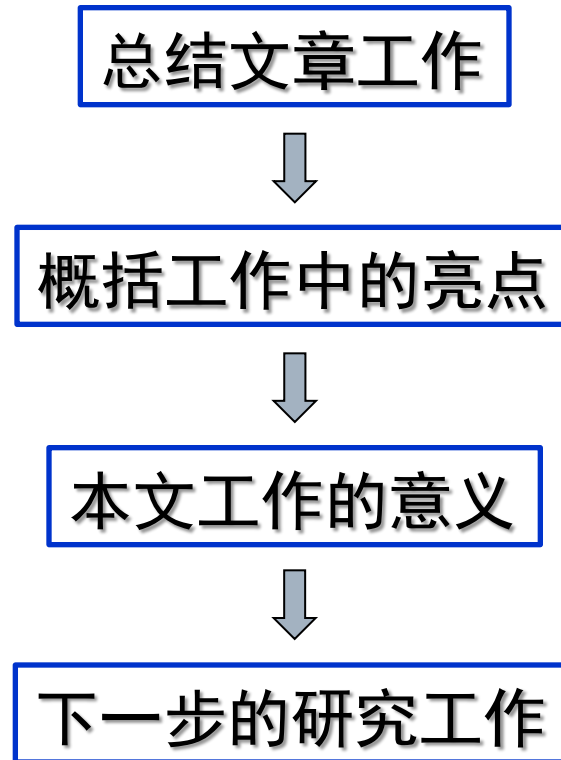
Strained natural products are beneficial for their pharmacological capabilities, and for binding to the desired biological targets tightly and selectively. There are several unique structures in natural products that are highly strained, including anti-Bredt double bonds, bent arene rings, medium-sized ring systems with several sites of unsaturation, and *trans*-fused bicyclo[3.3.0]octane ring systems. Notably, it was reported that *trans*-fused bicyclo[3.3.0]octane is more unfavorable than its *cis*-fused counterpart by calculation and experiment, respectively. Owing to the high strain energy, molecules with *trans*-fused bicyclo[3.3.0]octane ring systems are difficult to synthesize, and there are very few approaches to access them.

The First Paragraph

To date, only a limited number of natural products with such ring systems have been made by the synthetic community, including the groups of Schreiber, Paquette, Baran, Namba/Tanino, Shenvi, Snyder, and Rychnovsky. Therefore, developing new strategies for efficiently constructing these attractive *trans*-fused bicyclo[3.3.0]octane ring systems is still highly desirable.

The Last Paragraph

写作思路



The Last Paragraph

In summary, we have achieved the first and asymmetric total synthesis of the highly strained 4β -acetoxyprobotryane- $9\beta,15\alpha$ -diol via a linear sequence of 14 steps from the readily available compound 1. Notably, the synthetically challenging [6-5-5] tricyclic ring system of 4β -acetoxyprobotryane- $9\beta,15\alpha$ -diol was synthesized efficiently and diastereoselectively via an asymmetric rhodium-catalyzed [4+2] cycloaddition reaction, followed by a unique and very mild benzilic acid type rearrangement. To the best of our knowledge, this work represents the first example of a benzilic acid type rearrangement to construct the highly strained *trans*-fused bicyclo[3.3.0]octane ring system.

The Last Paragraph

This work also represents the first application of a chiral rhodium complex-catalyzed [4+2] reaction in natural product synthesis. Furthermore, the seven contiguous stereocenters were constructed efficiently and diastereoselectively. This approach could be extended to the synthesis of other bioactive molecules with strained *trans*-fused bicyclo[3.3.0]octane ring systems to enable further biological research. Such effort is ongoing in our laboratory and will be reported in due course.

Representative Examples

However, there have been no reports on the application of this method in the synthesis of *trans*-fused bicyclo[3.3.0]octane ring systems. (该方法的应用还没有过报道)

Moving forward, we continued toward the last stage of the synthesis via a chemo- and diastereoselective reduction. (进一步，接下来)

To the best of our knowledge, this work represents the first example of a benzilic acid type rearrangement to construct the highly strained *trans*-fused bicyclo[3.3.0]octane ring system. (这项工作是该方法的第一个例子)

Acknowledgement

***Thanks
for your attention***