

Literature Report 1

Bioinspired Asymmetric Synthesis of Hispidanin A

Reporter: Zhou-Hao Zhu

Checker: Guang-Shou Feng

Date: 2017-12-04

Li, F.; Tu, Q.; Chen, S.; Zhu, L.; Lan, Y.*; Gong, J.*; **Yang, Z.***
Angew. Chem. Int. Ed. **2017**, *56*, 5844

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4 Summary

CV of Prof. Zhen Yang



Zhen Yang

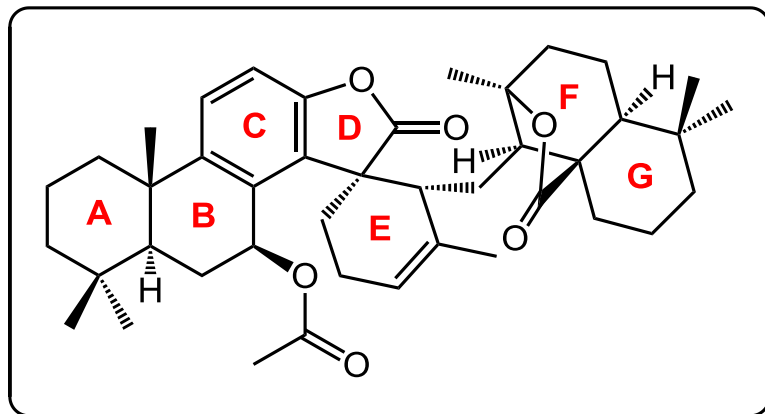
Background:

- 1978-1986 B.S. & M.S., Shenyang Pharmaceutical University
- 1989-1992 Ph.D., The Chinese University of Hong Kong
- 1992-1995 Postdoctoral, Scripps Research Institute
- 1995-1998 Assistant Professor, Scripps Research Institute
- 1998-2001 Institute Fellow, Harvard University

Research Interests:

Development of synthetic methods for synthesis of complex natural product molecules and application of synthetic chemistry for drug discovery.

Introduction



Hispidanin A



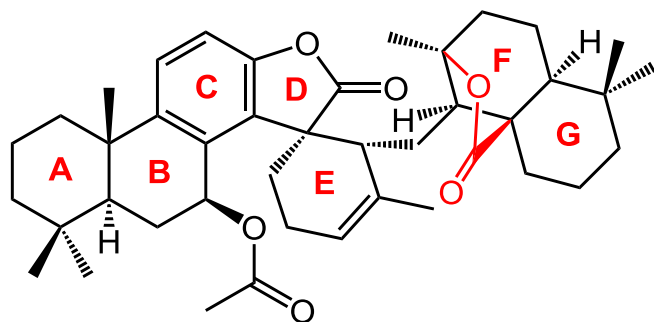
Rabdosia Hispida

- Isolated from the *Rabdosia Hispida* in 2014;
- 11 stereogenic centers and unique asymmetric structures formed by the bonding of totarane-type dienophile and labdane-type dienes;
- A folk medicine to treat cancers and inflammatory conditions in China.

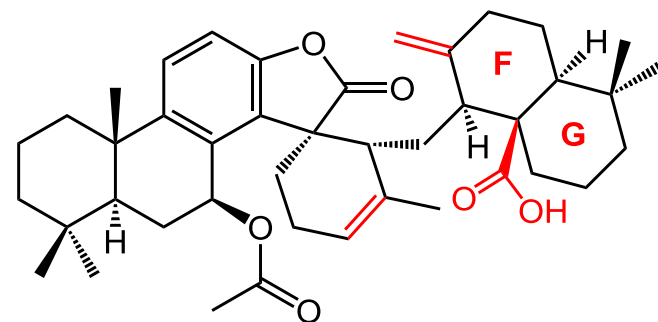
Huang, B.; Xiao, C.; Huang, Z.; Jiang, B.* *et al. Org. Lett.* **2014**, *16*, 3552

Introduction

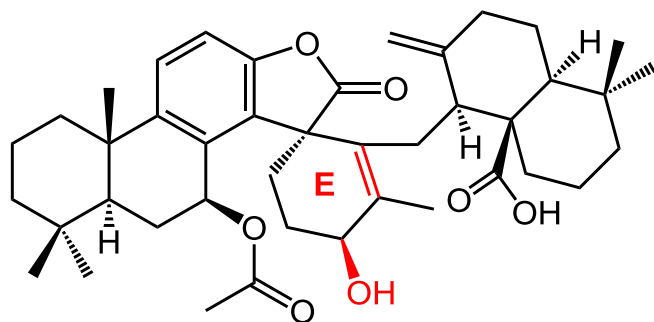
Natural Products Isolated from *Rabdosia Hispida*



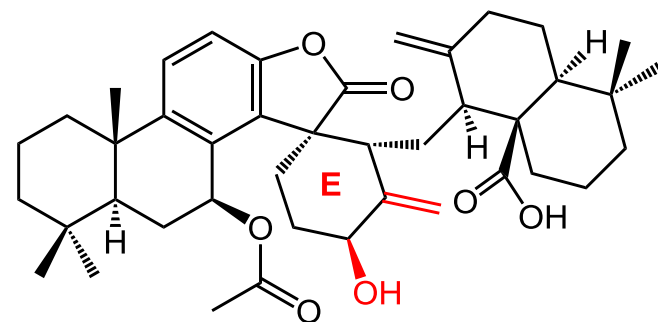
Hispidanin A



Hispidanin B



Hispidanin C

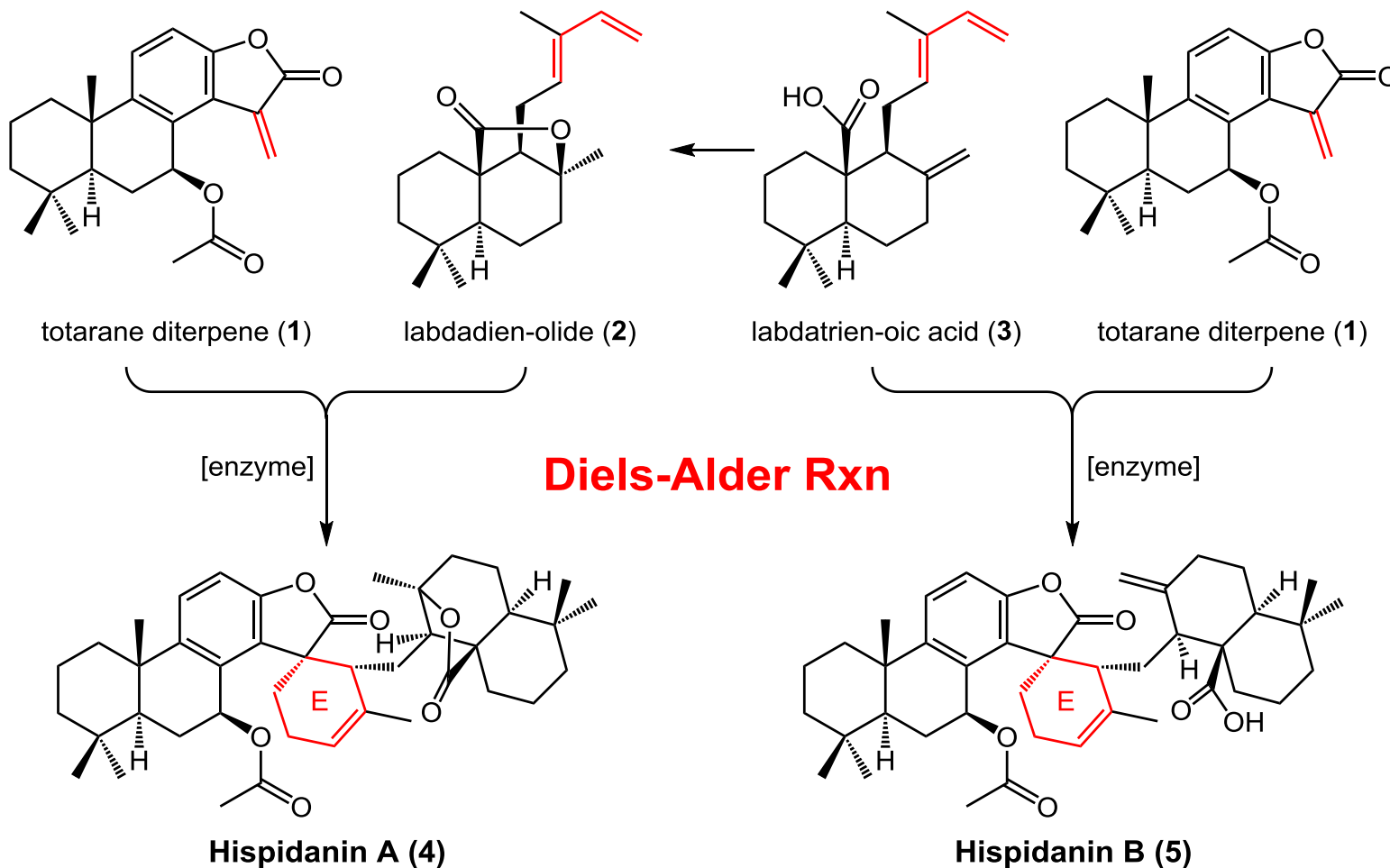


Hispidanin D

Huang, B.; Xiao, C.; Huang, Z.; Jiang, B.* *et al. Org. Lett.* **2014**, *16*, 3552

Introduction

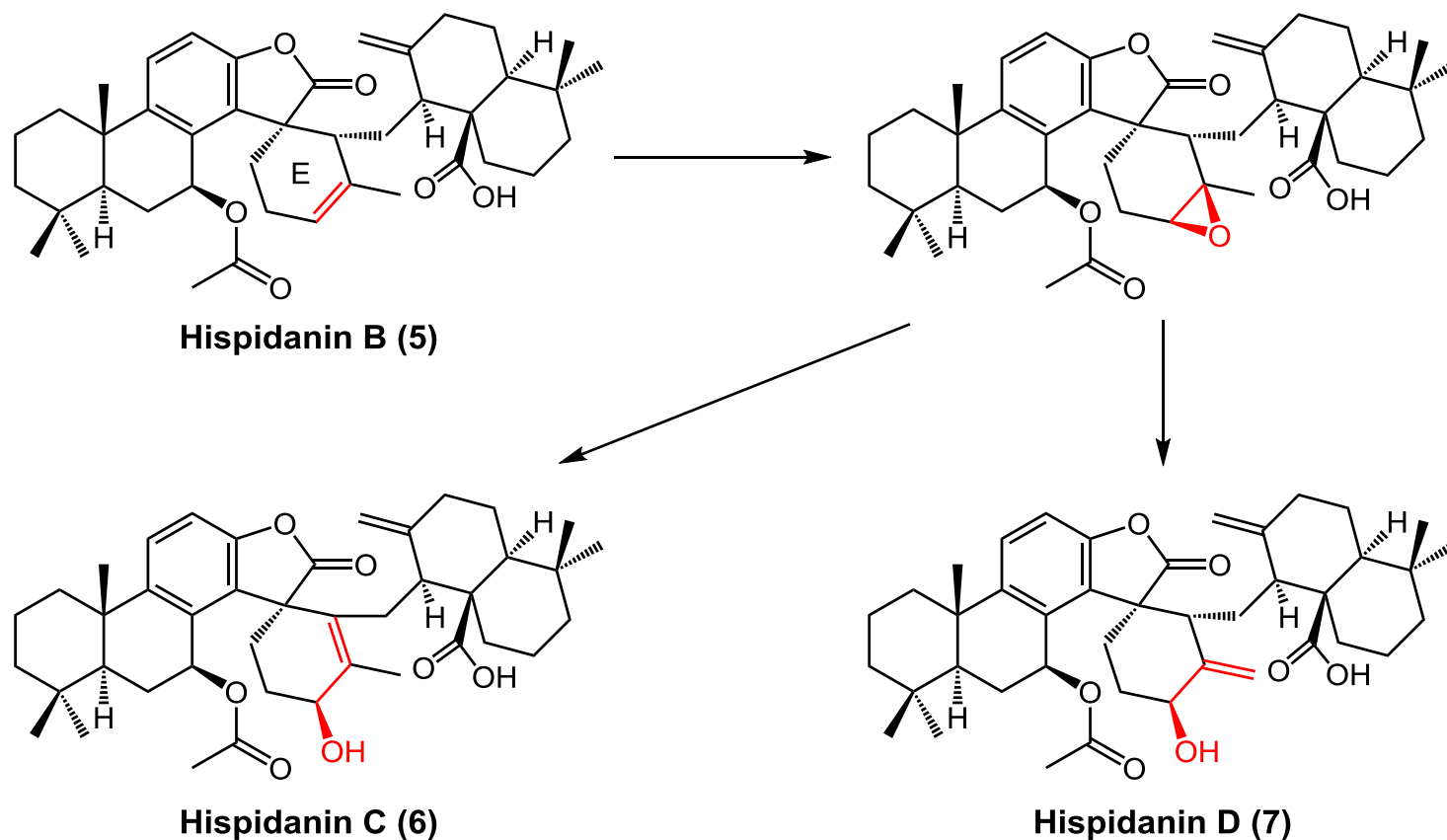
Hypothetical Biosynthetic Pathways for Hispidanins



Huang, B.; Xiao, C.; Huang, Z.; Jiang, B.* *et al. Org. Lett.* **2014**, *16*, 3552

Introduction

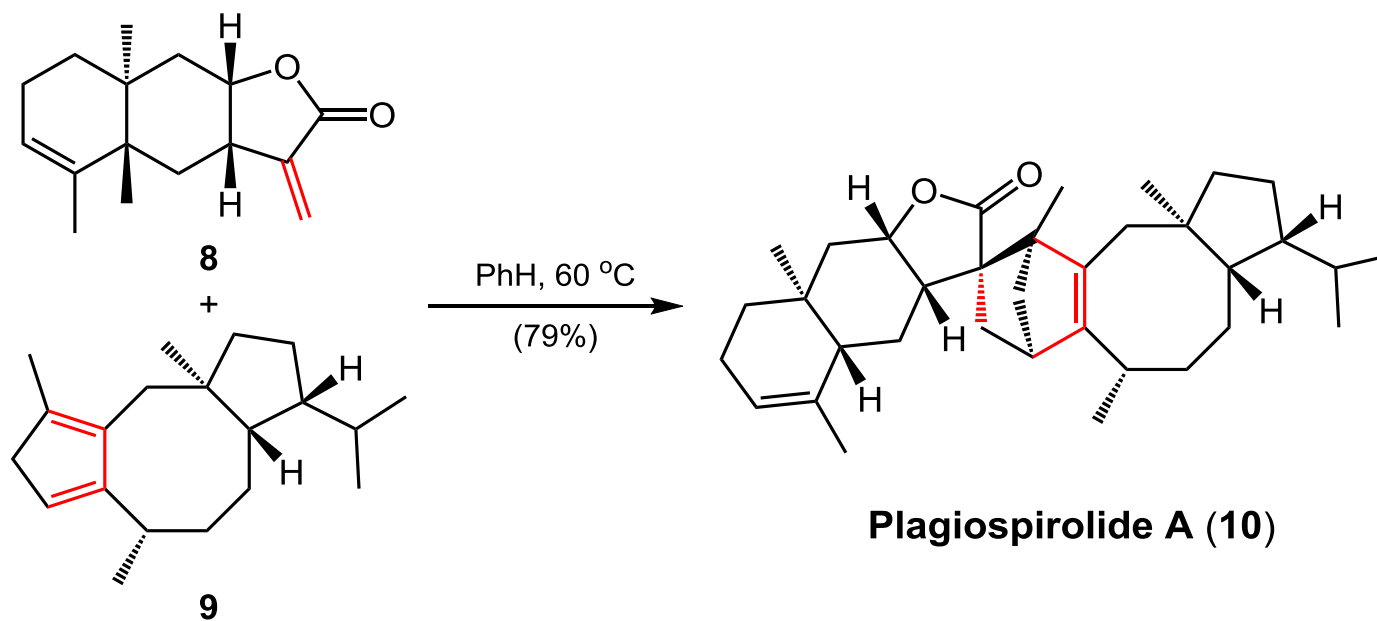
Hypothetical Biosynthetic Pathways for Hispidanins



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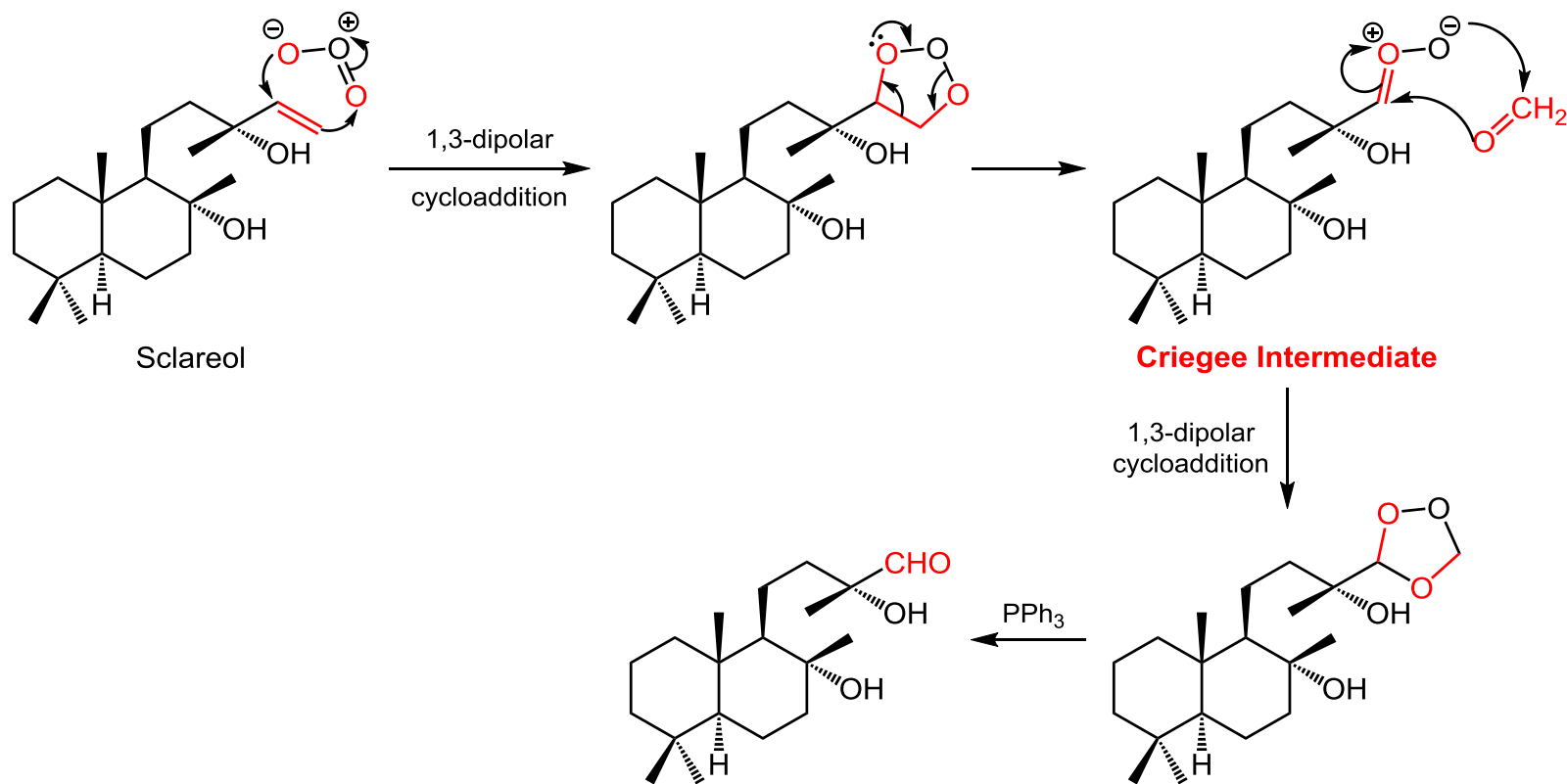
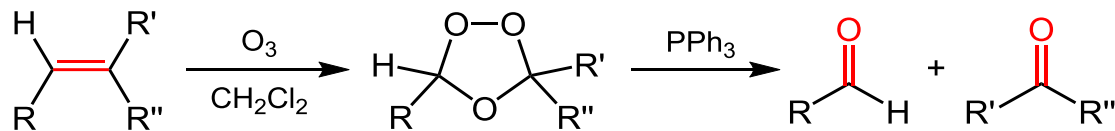
Introduction

Non-enzymatic Diels-Alder reaction For the synthesis of Plagiospirolide A

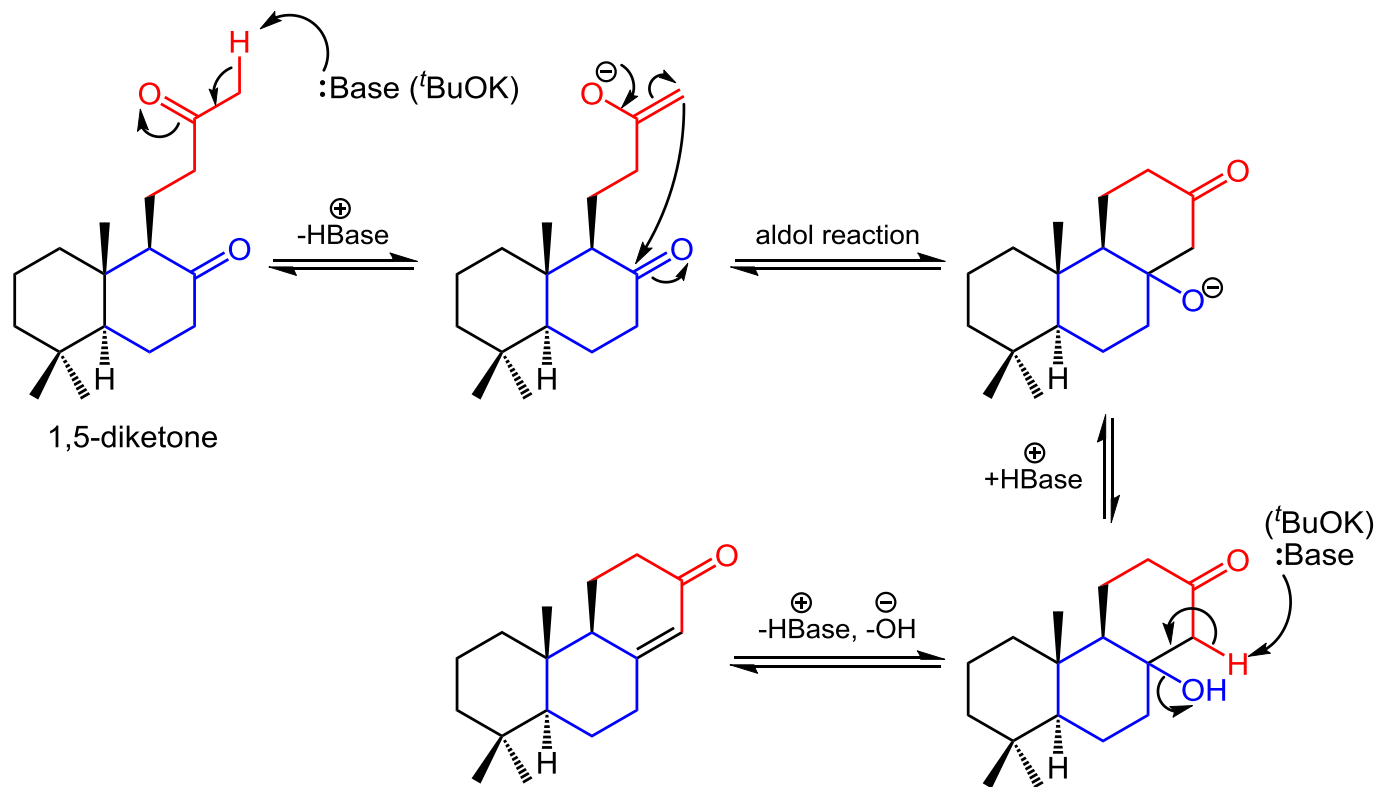
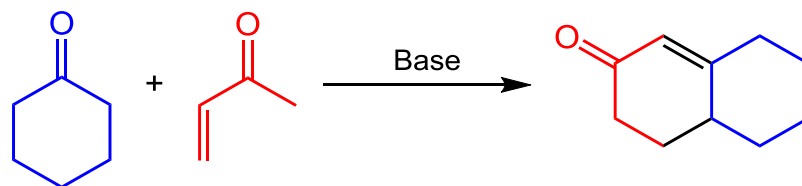


Kato, N.; Wu, X.; Takeshita, H.* *et al.* *J. Chem. Soc. Perkin Trans. 1.* **1994**, 1047

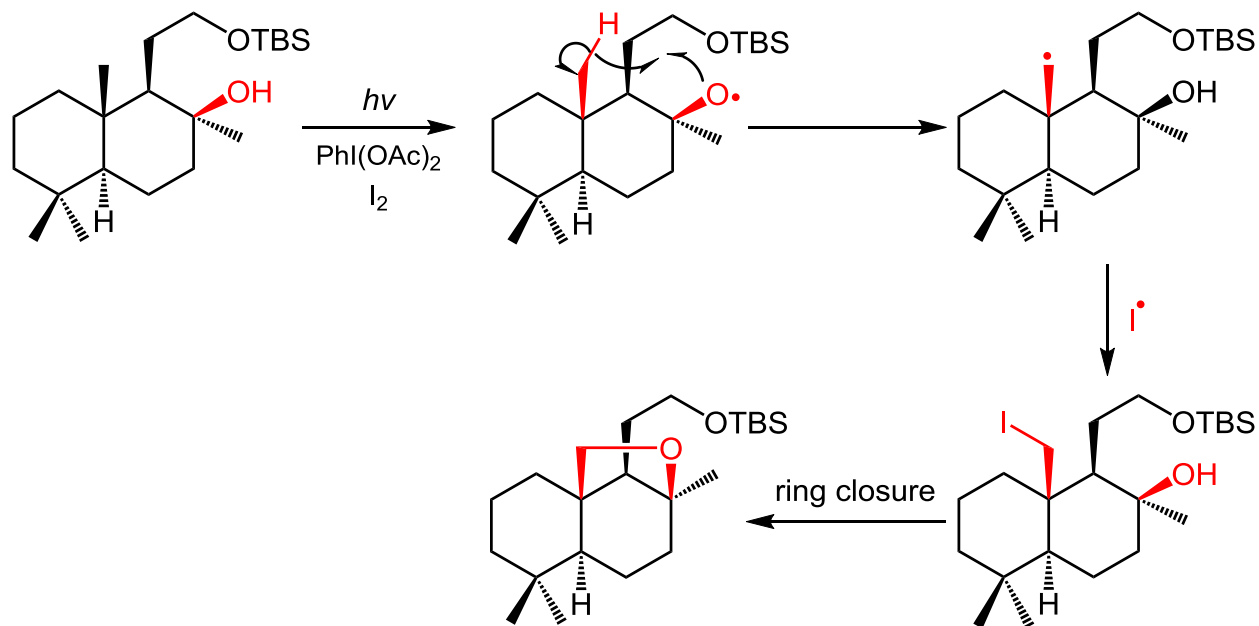
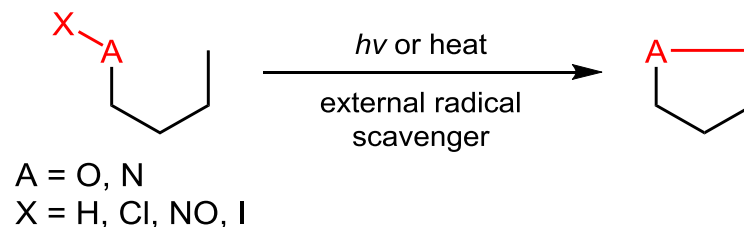
Criegee Mechanism of Ozonolysis



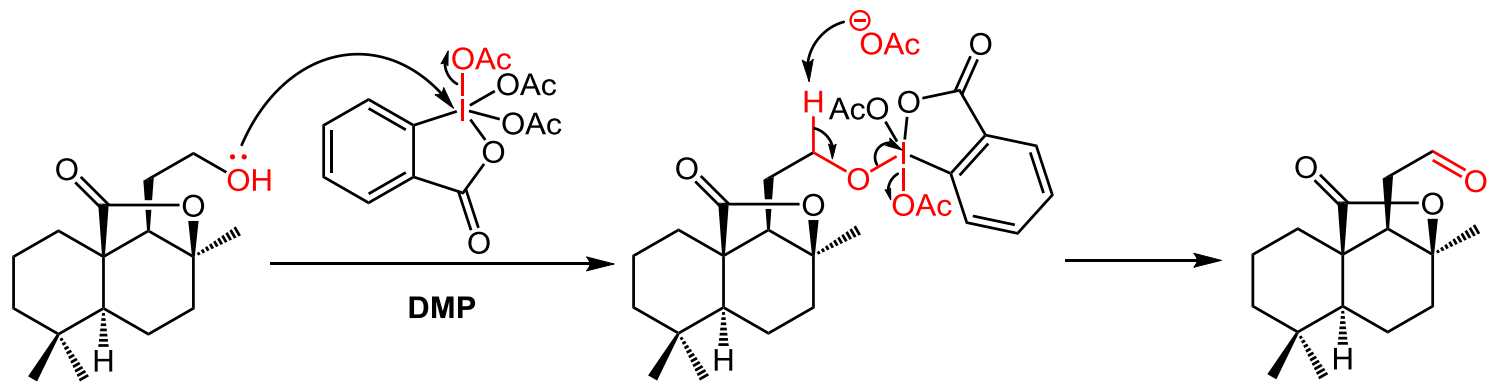
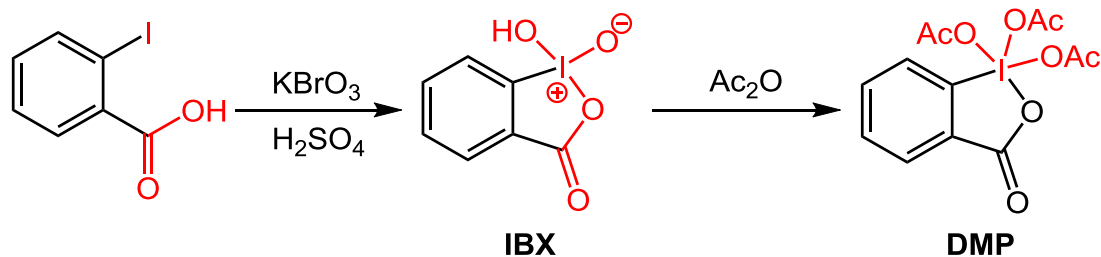
Robinson Annulation



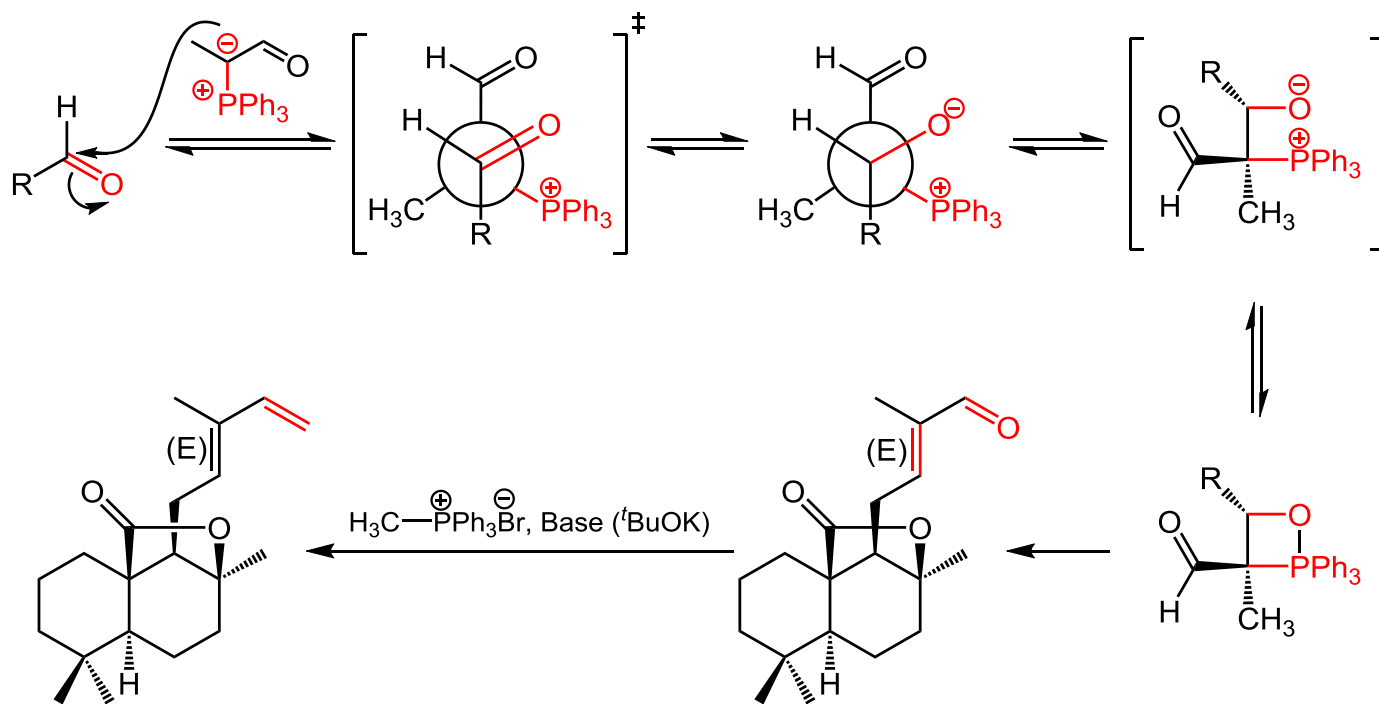
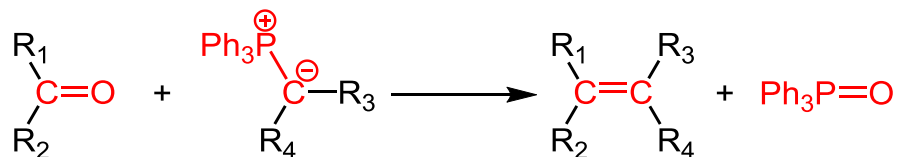
Remote Intramolecular Radical Cyclization



Dess-Martin Oxidation



Wittig Olefination

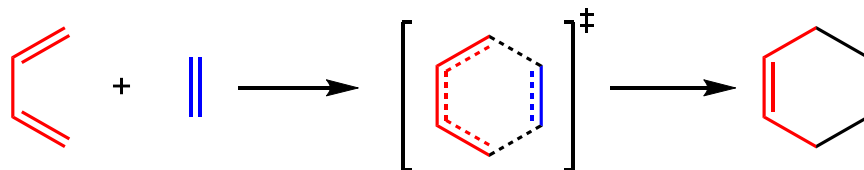


Unstabilized ylides give predominantly (*Z*)-Olefins

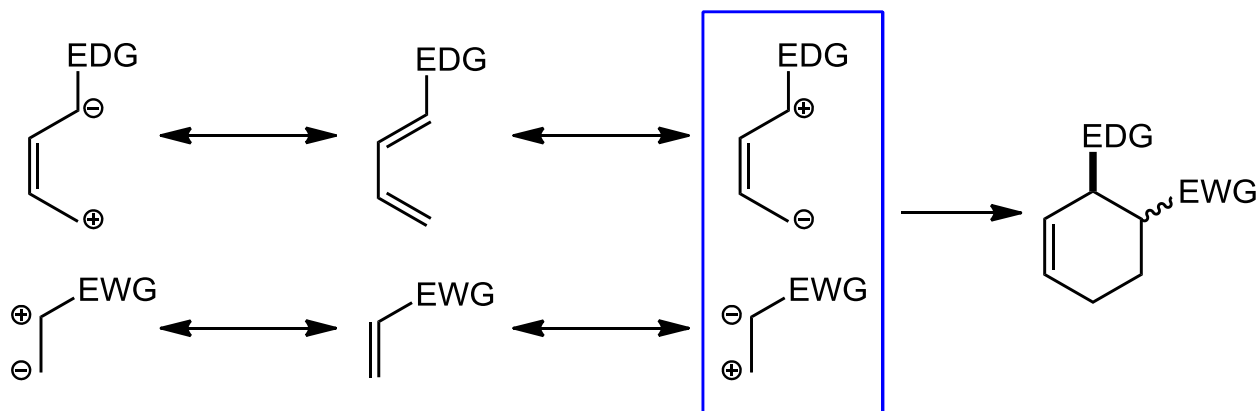
Stabilized ylides give predominantly (*E*)-Olefins

Semi-stabilized ylides give alkenes with poorer stereoselectivity

Diels-Alder Reaction

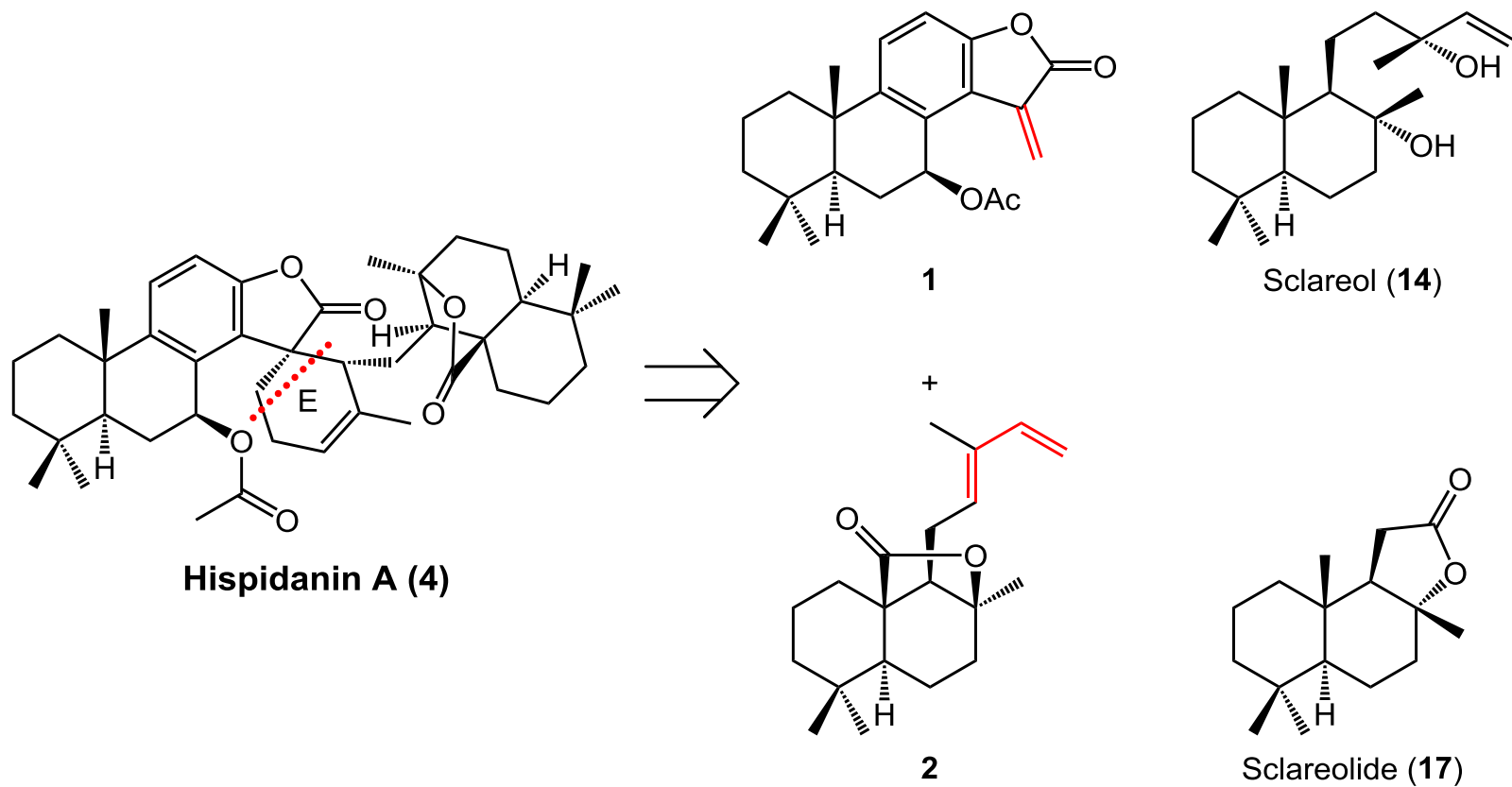


Device for predicting the regioselectivity: draw out “zwitterionic” representations (resonance structures) for the reactants.

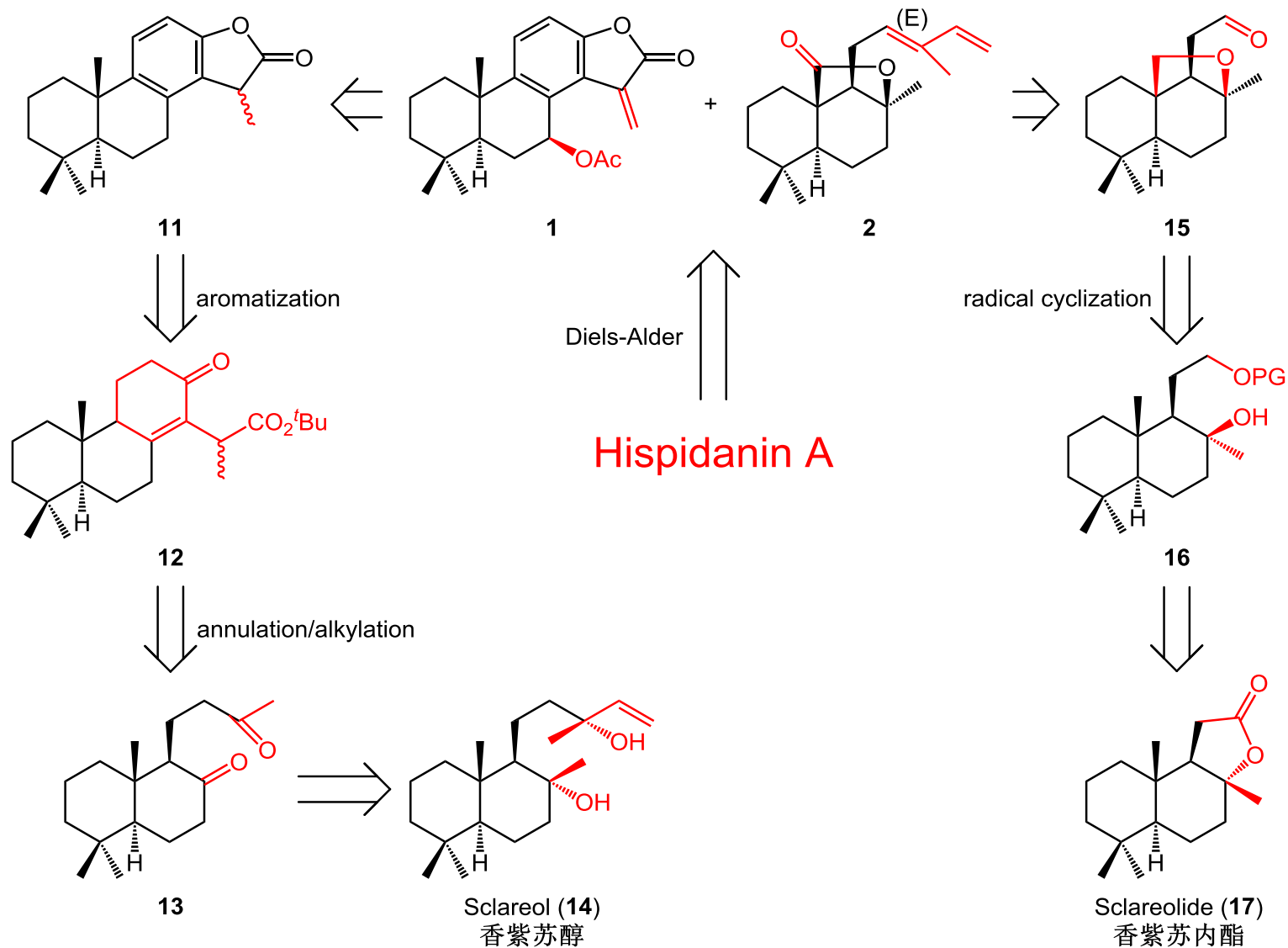


More stable resonance forms

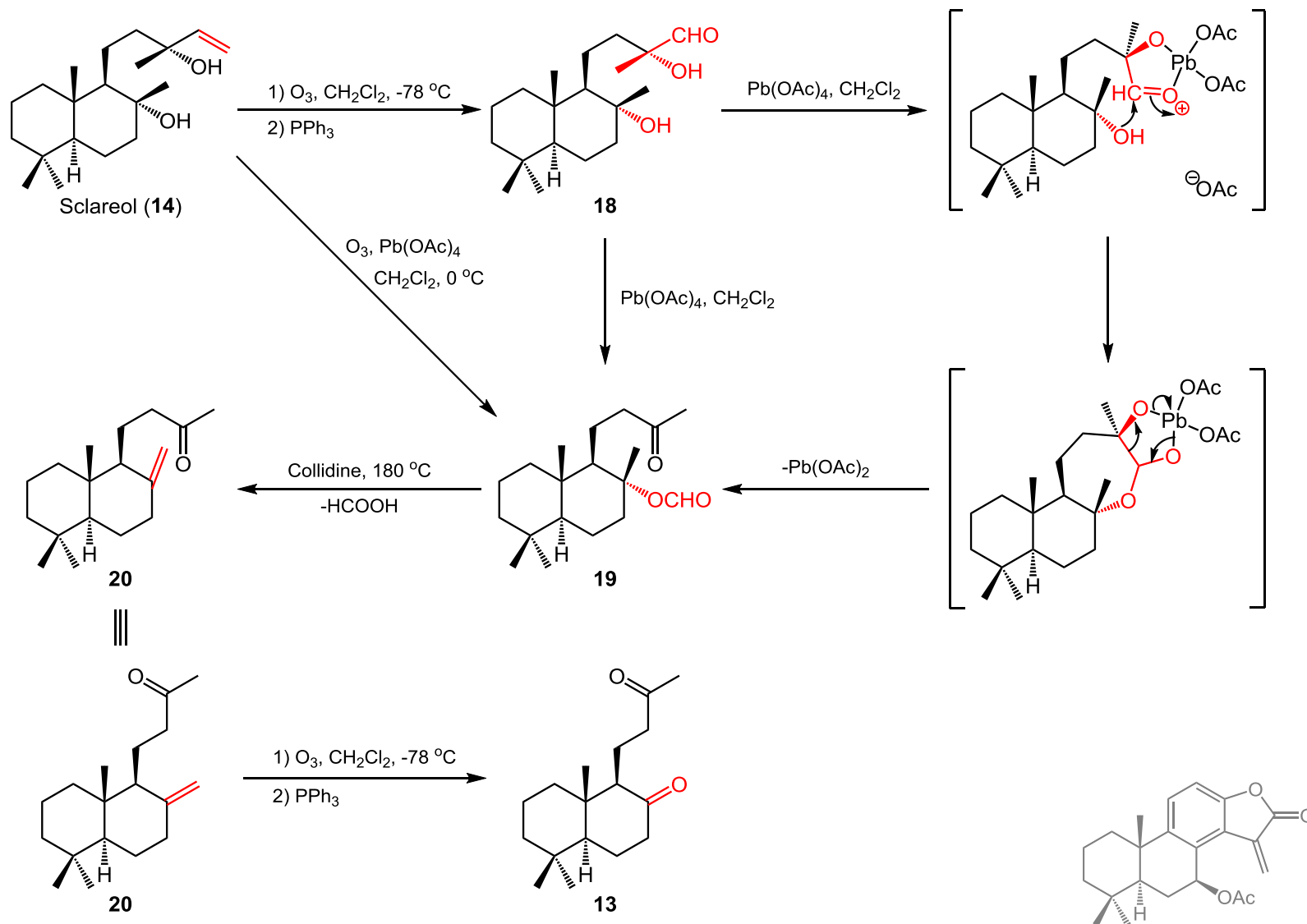
Retrosynthetic Analysis of Hispidanin A



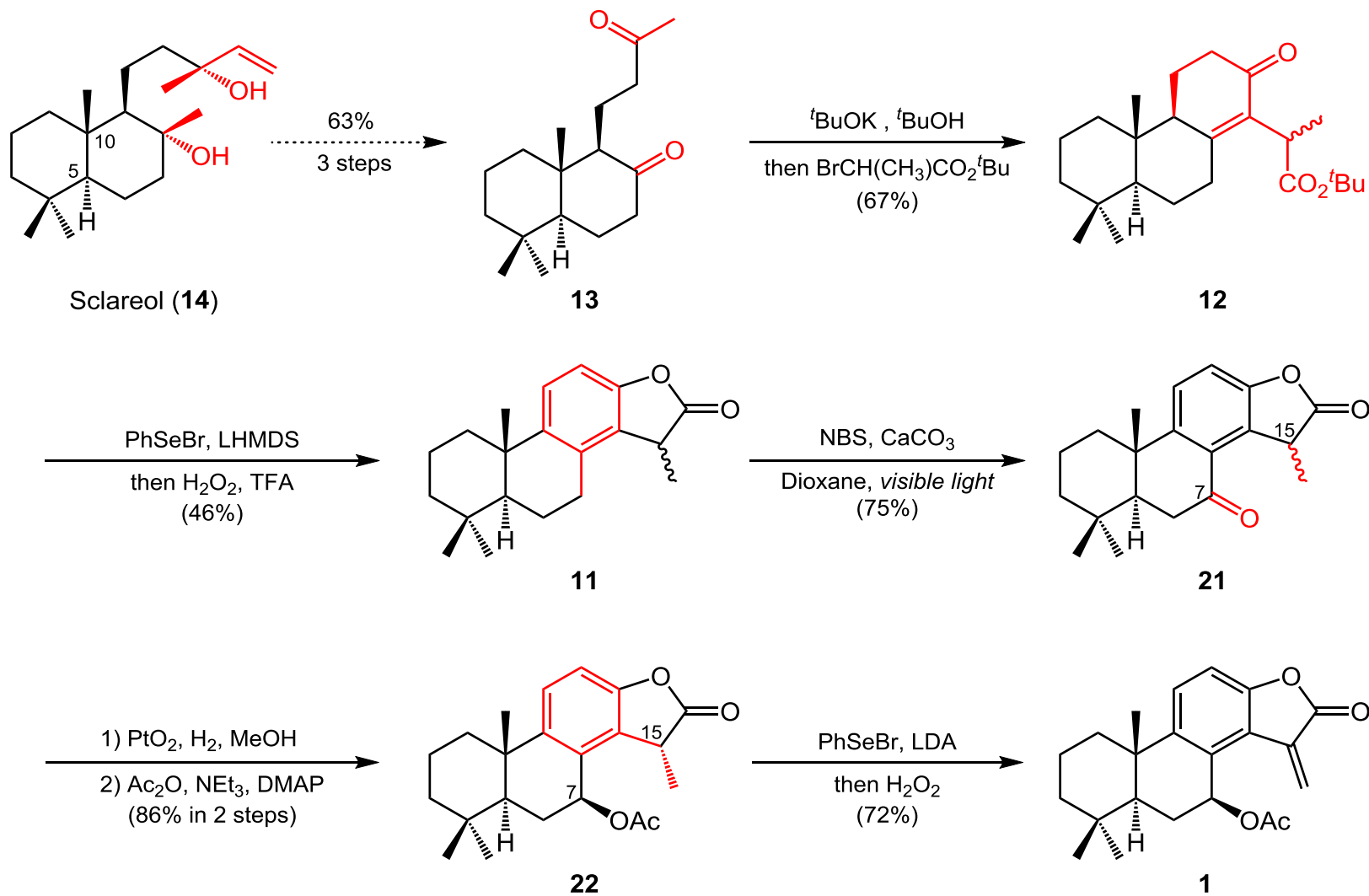
Retrosynthetic Analysis of Hispidanin A



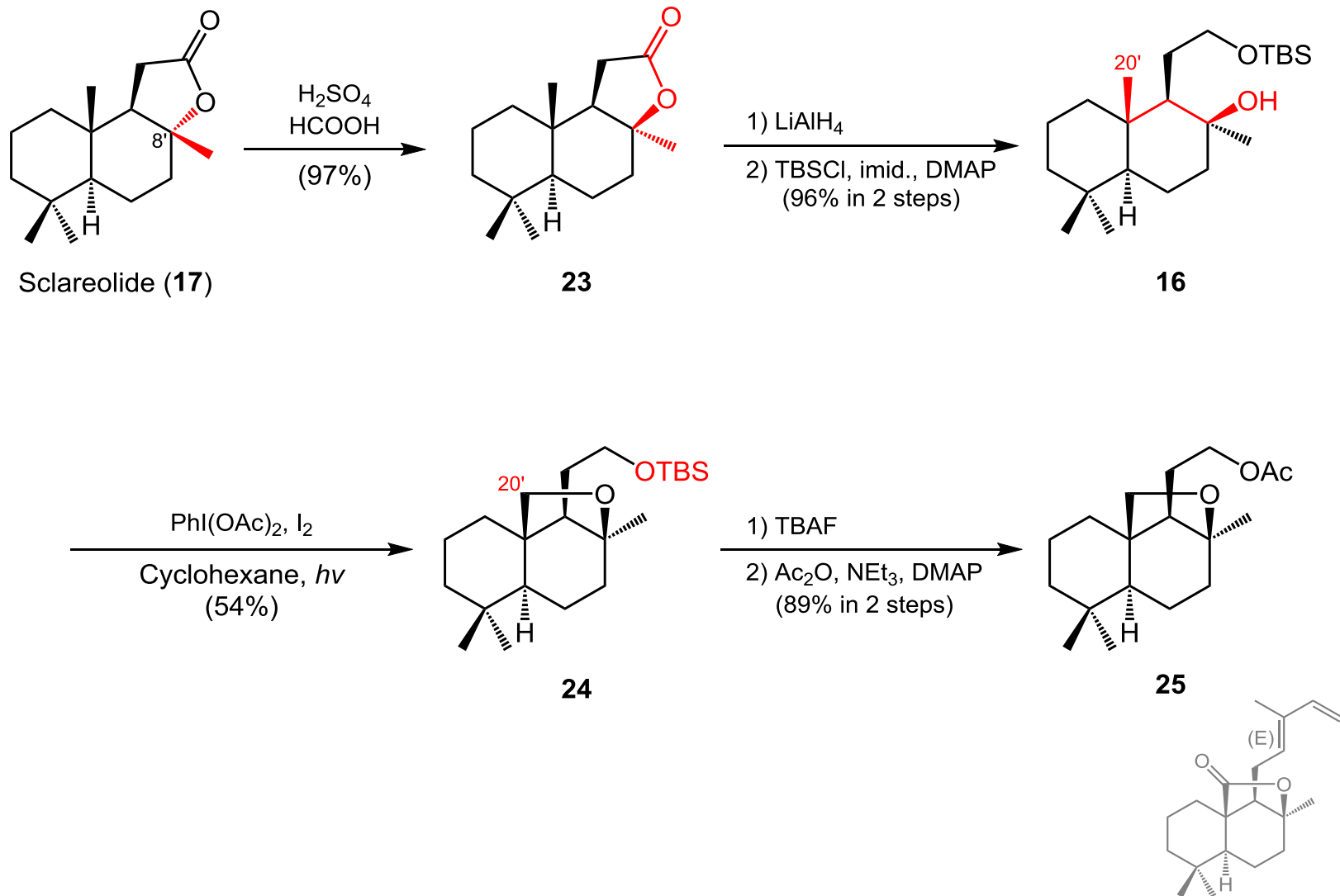
Total Synthesis of Hispidanin A



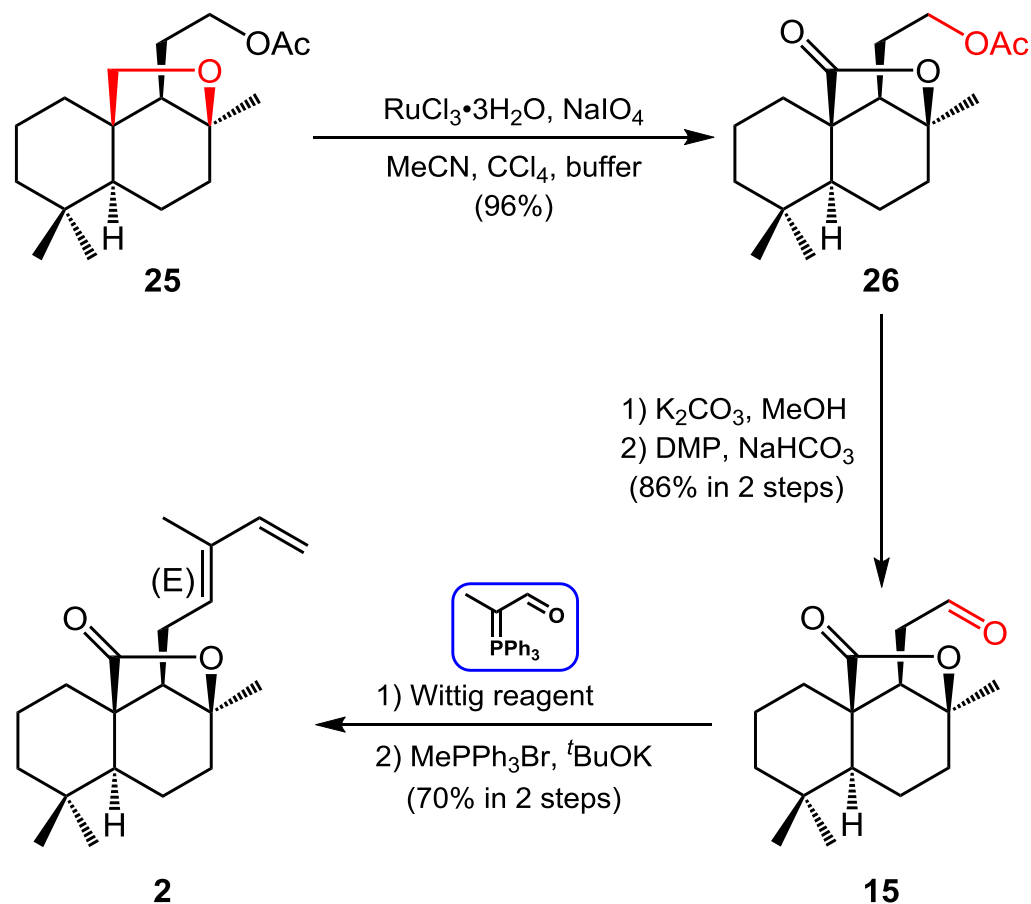
Total Synthesis of Hispidanin A



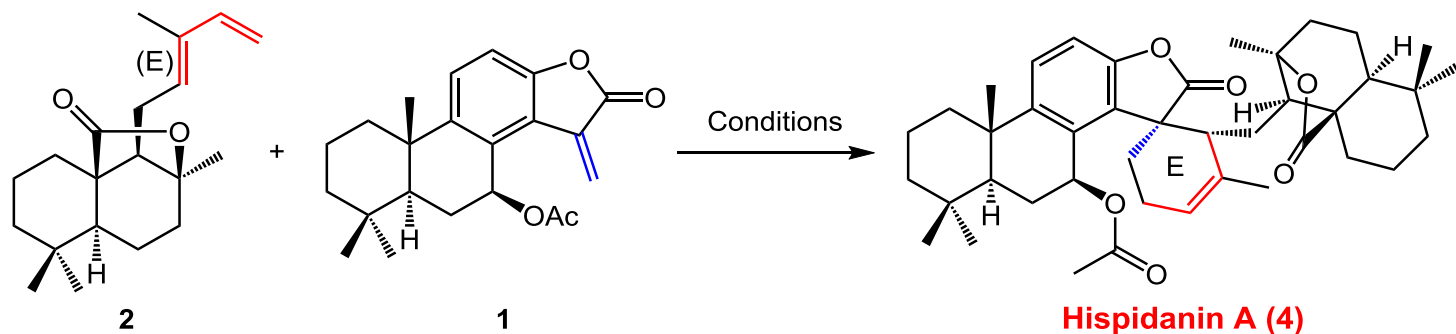
Total Synthesis of Hispidanin A



Total Synthesis of Hispidanin A

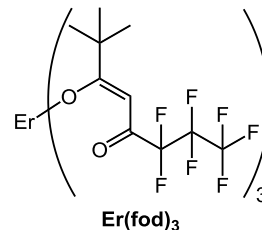
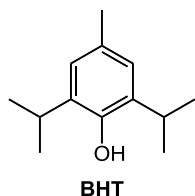


Total Synthesis of Hispidanin A

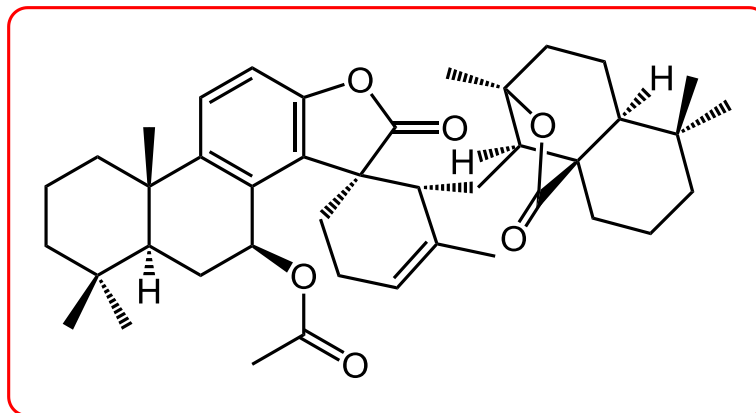


Entry	Conditions	Yield [%] ^[a]
1	BHT, neat, 120 °C, 24 h	59
2	Er(fod) ₃ , neat, 120 °C, 24 h	64
3	BF ₃ ·Et ₂ O, toluene, 100 °C, 24 h	Decomposed
4	ZnCl ₂ , toluene, 0 °C to RT, 24 h	35 ^[b]
5	Me ₂ AlCl, toluene, 0 °C to RT, 24 h	27

^[a] Yield of isolated product. ^[b] Overall yield of compound 4 and its diastereoisomer (2:1).



Summary



Hispidanin A

- 12 steps, 6.5% overall yield
- The first enantiospecific synthesis of Hispidanin A
- Use of abundant and naturally occurring diterpenoids (+)-*sclareolide* and (+)-*sclareol* as starting materials
- Construction of the tetrahydrofuran ring achieved through remote intramolecular free radical functionalization
- A highly enantioselective intermolecular Diels-Alder reaction

The First Paragraph

该天然产物的由来和作用



该天然产物可能的合成途径



论证该猜想的可靠性



合成该天然产物家族的方法

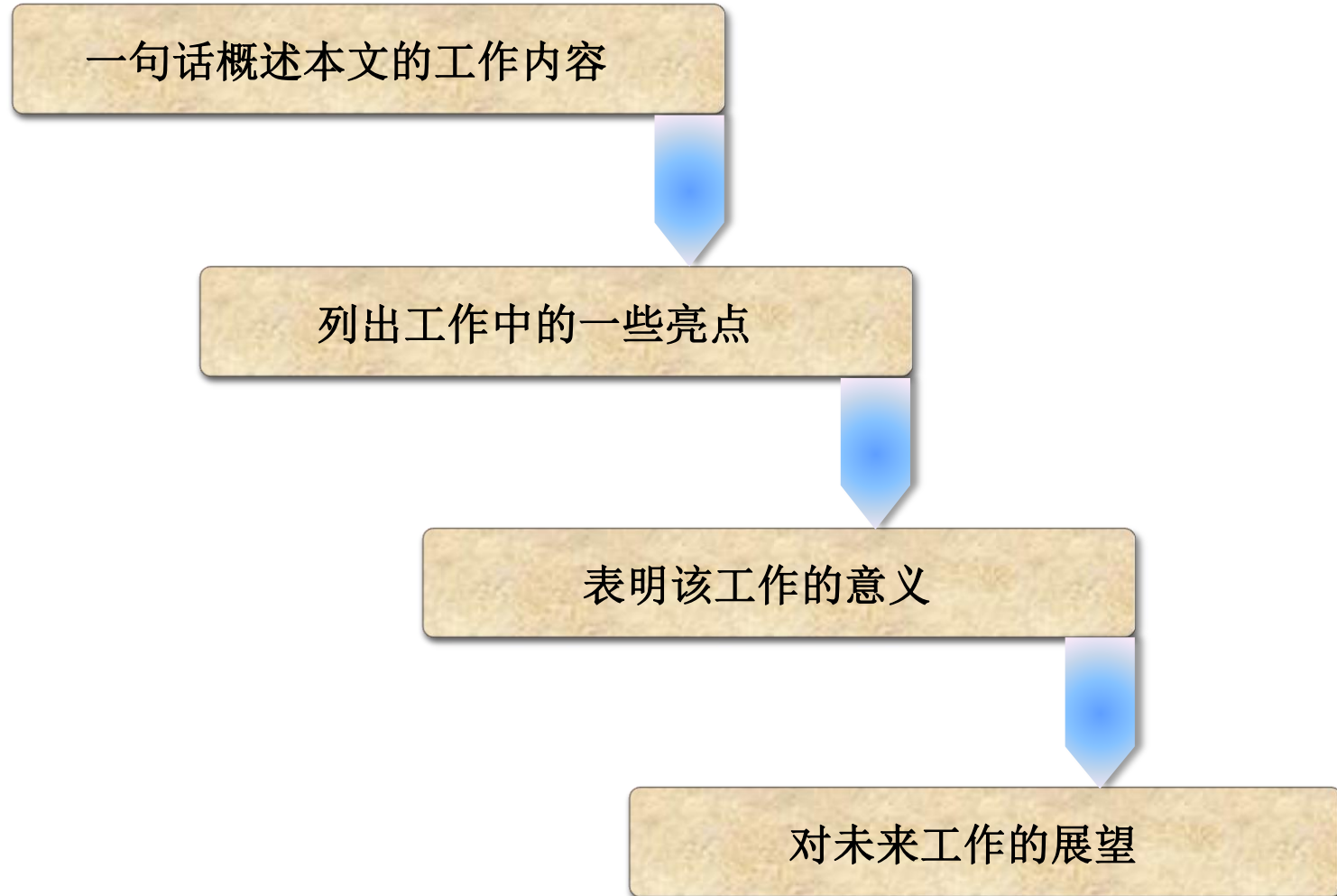
The First Paragraph

Hispidanins A–D comprise a class of unprecedented dimeric diterpenoids isolated from the rhizomes of *Isodon hispida*, which are widely used as a folk medicine to treat cancers, inflammatory conditions, and various other diseases in China. According to the report of its isolation, hispidanins A and B were proposed to be biosynthesized through enzyme-catalyzed intermolecular Diels–Alder reactions of the totarane-type dienophile **1** with the labdane-type dienes **2** and **3**, respectively. Such a proposal is reasonable based on earlier observations that support the endo-selective DA process and electronic factors that favor the addition of the terminal double bond (C15') in **2** to the β -position (C17) in **1** to form the sterically demanding central E ring.

The First Paragraph

Furthermore, hispidanins C and D were expected to be derived from hispidanin B through a sequential epoxidation and reductive epoxide-opening reactions.

The Last Paragraph



The Last Paragraph

In summary, we accomplished an enantioselective total synthesis of hispidanin A (**4**) with a longest linear sequence of 12 steps and an overall yield of 6.5%. The key features of our synthesis include: 1) oxidative alkoxylation of the C20' methyl group to construct the tetrahydrofuran ring in **21**, which was achieved through remote intramolecular free radical functionalization; 2) a highly enantioselective intermolecular DA reaction. Our results demonstrated that the naturally occurring **4** is the favored product of naturally occurring sclareol and sclareolide generated under nonenzymatic conditions using either thermal conditions or an Erbium-mediated asymmetric intermolecular DA reaction. This also provides evidence that the biosynthetic route for hispidanin B might be similar.

Acknowledgement

***Thanks
for your attention***

