

Literature Report 4

Biomimetic Total Synthesis of Homodimericin A

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Checker: Zhong Yan

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Ma, D.; Liu, Y.; Wang, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 7886.
Huang, J.; Gu, Y.; Guo, K.; Zhu, L.; Lan, Y.; Gong, J.; Yang, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 7890.

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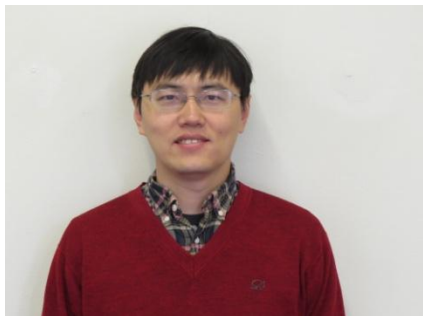
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- 2 Total Synthesis of Homodimericin A by Wang's Group**

- 3 Total Synthesis of Homodimericin A by Yang's Group**

- 4 Summary**

Biography



Zhang Wang

Areas of interest:

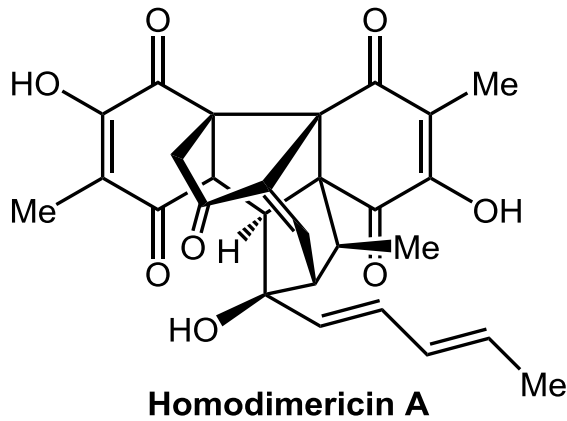
- Develop catalytic asymmetric organic reactions using environmentally benign reagents and catalysts for medicinally important agents.
- Total synthesis of natural products with intriguing structures and important biological activities.

Research experience:

- ❑ **2014-2017** Assistant Professor, Albany, State University of New York
- ❑ **2011-2014** Postdoctor, Princeton University (David W. C. MacMillan)
- ❑ **2006-2011** Ph.D., Columbia University (Samuel J. Danishefsky)
- ❑ **2005-2006** Research Assistant, Peking University (Xin Sheng Zhao)
- ❑ **2001-2005** B.S., Peking University (Jiaxi Xu)

Introduction

Structure of Homodimericin A

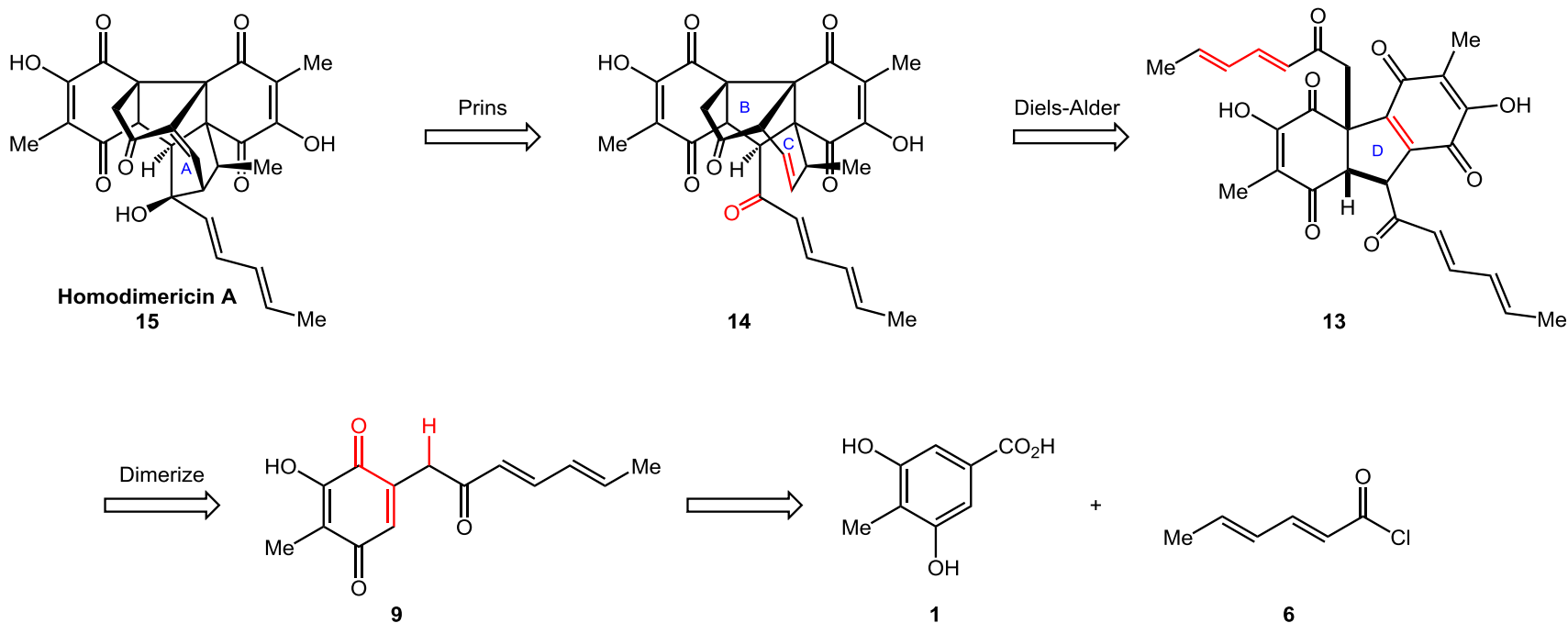


Trichoderma harzianum fungus
(哈茨木霉真菌)

- Unsaturated hexacyclic polyketide
- Highly sterically demanding cage-like core
- 8 Contiguous stereocenters (3 contiguous quaternary centers)

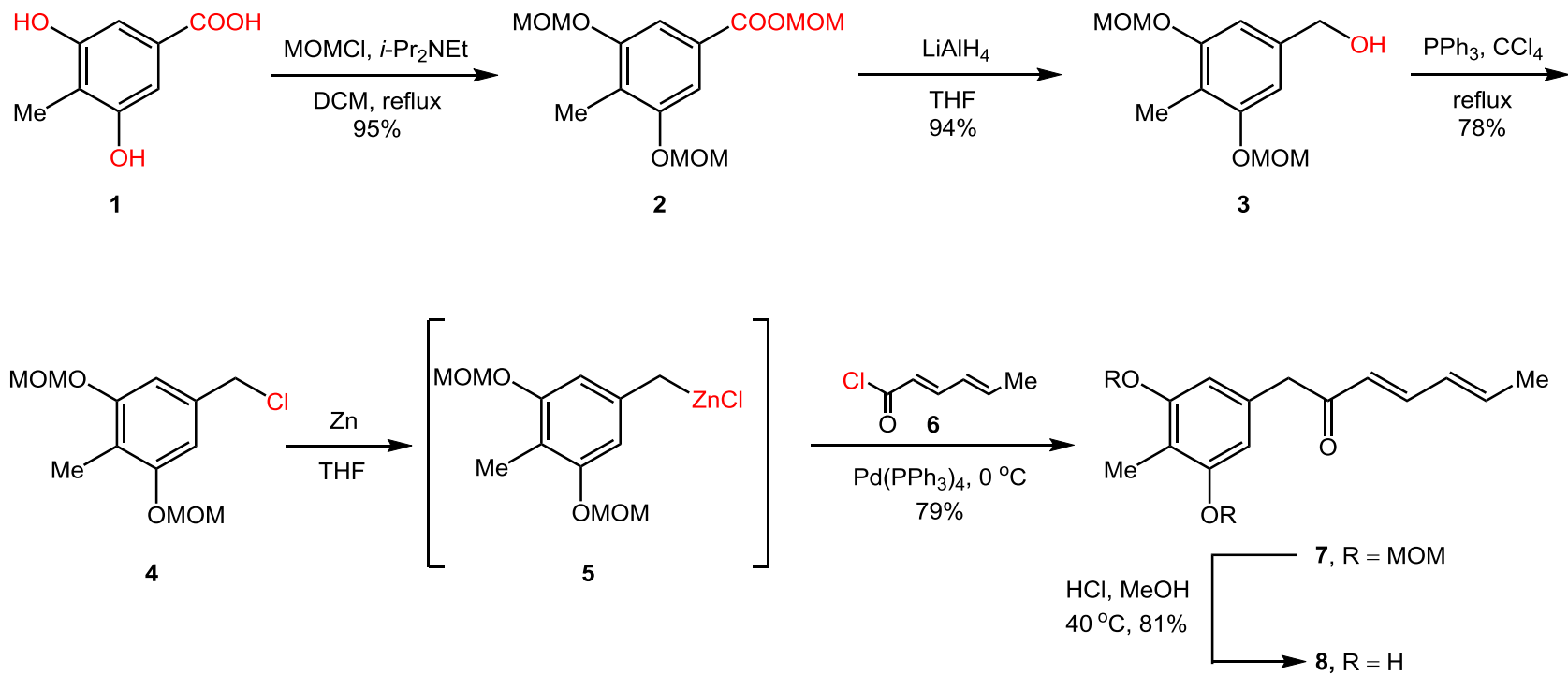
Total synthesis of Homodimericin A by Wang's group

Retrosynthetic analysis

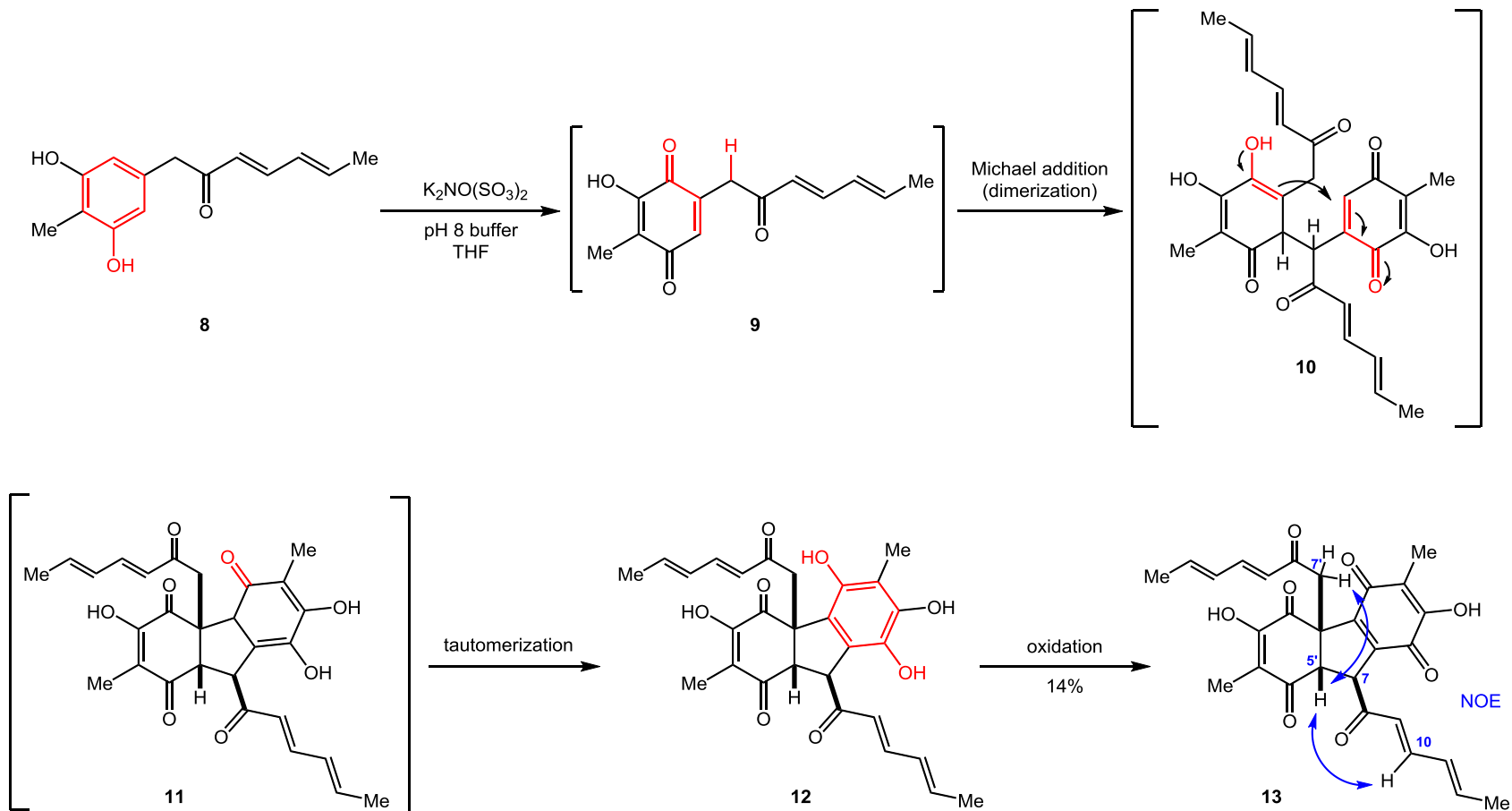


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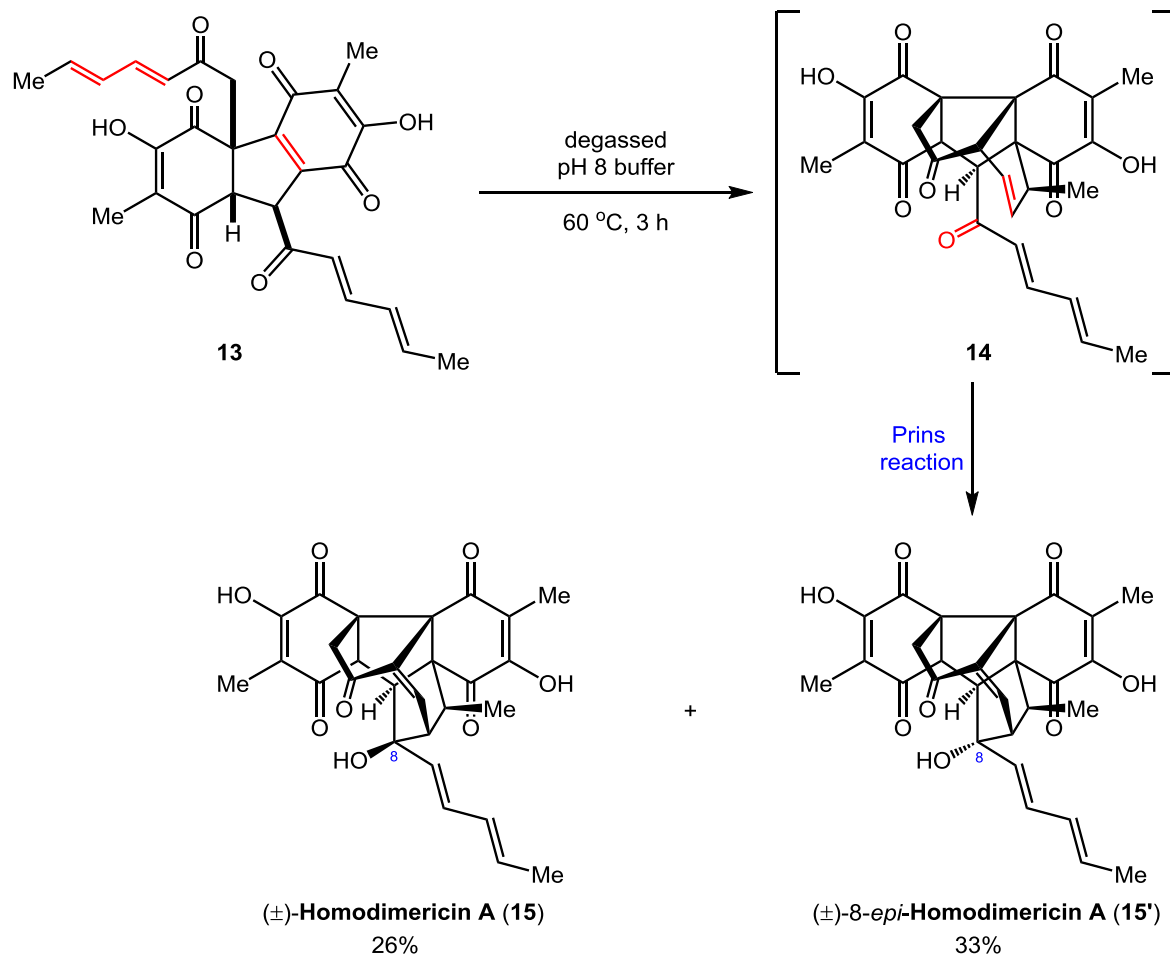
Synthesis of resorcinol 8



Dimerization cascade to compound 13



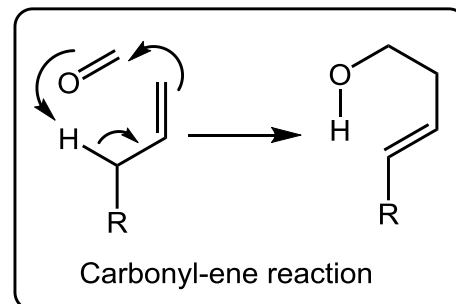
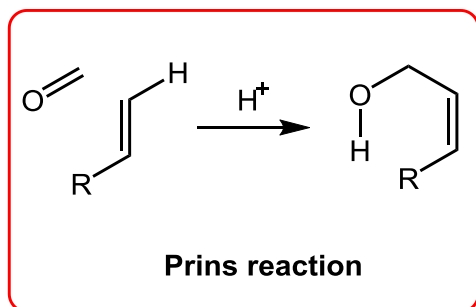
Synthesis of Homodimericin A and its C8 epimer



7 steps, 1.6% overall yield

Prins reaction

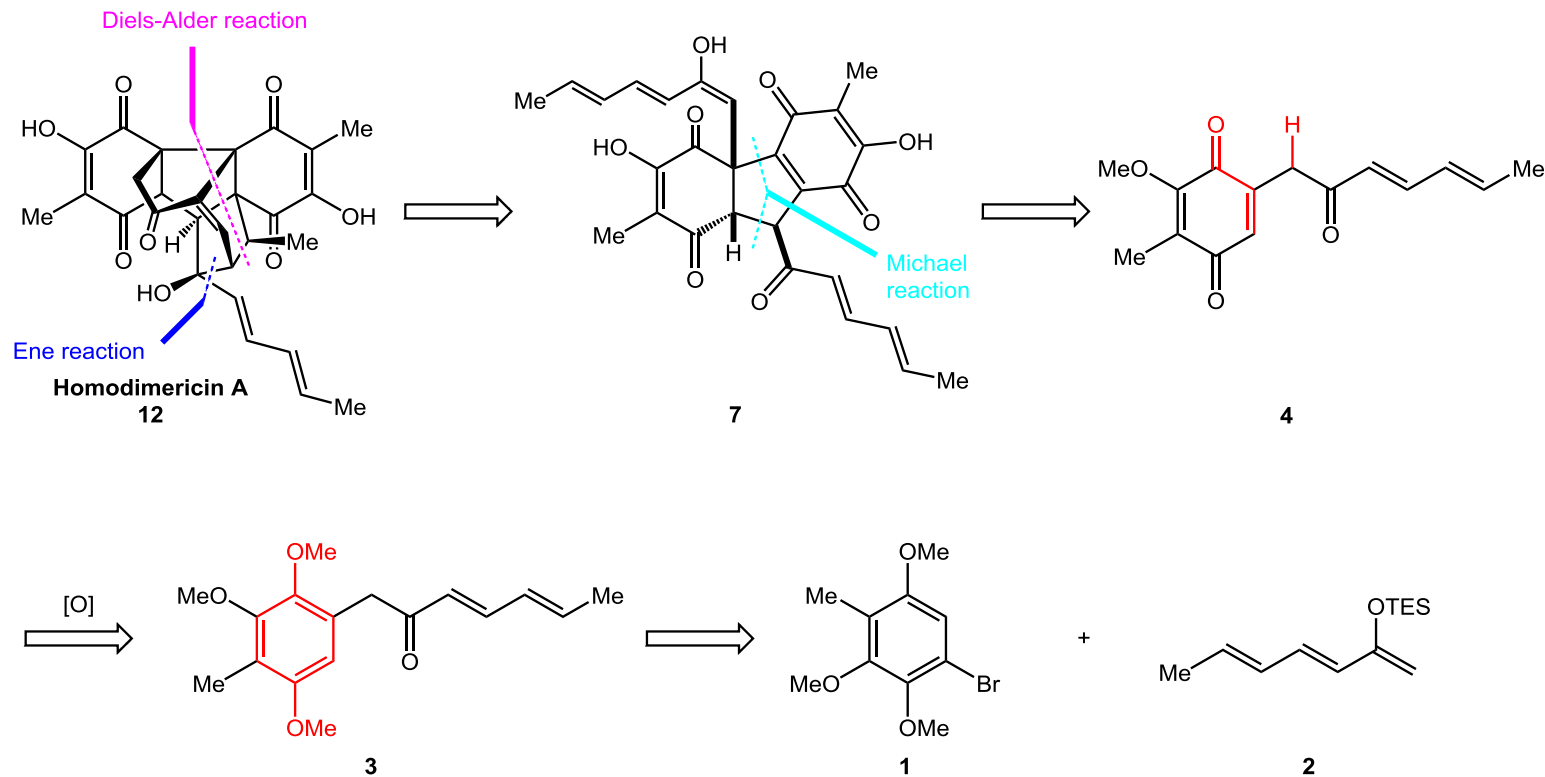
Prins反应最初是指由烯烃在酸催化下对甲醛的缩合反应，后来泛指一系列历经氧噻离子中间态的烯烃与羰基的加成反应。反应一般在酸性条件和较低温度下就可以实现。



Carbonyl-ene 反应是指由羰基化合物与有 α -H的烯烃经协同反应机理发生反应。反应一般在加热或Lewis酸催化条件下实现。

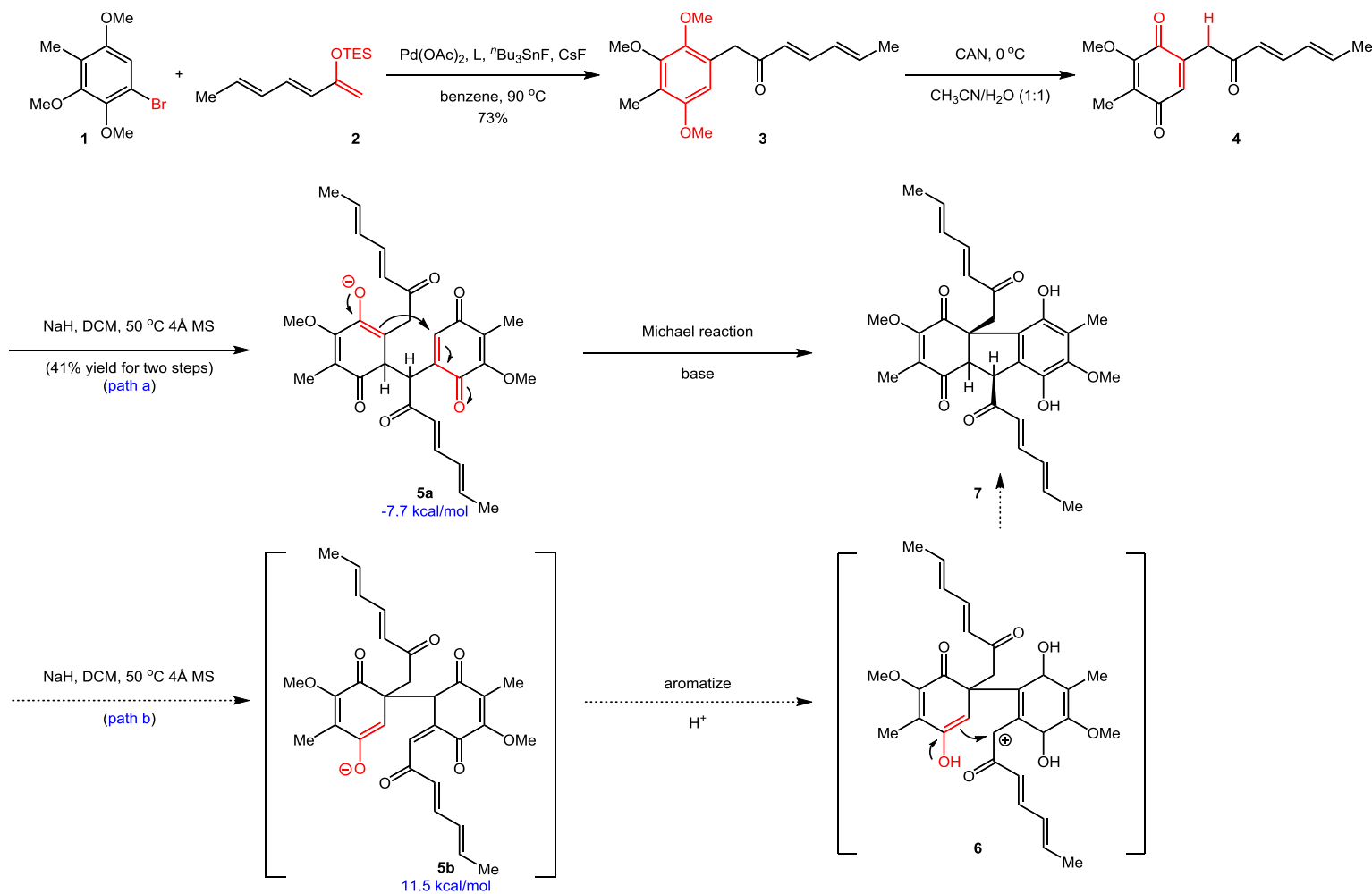
Total synthesis of Homodimericin A by Yang's Group

Retrosynthetic analysis



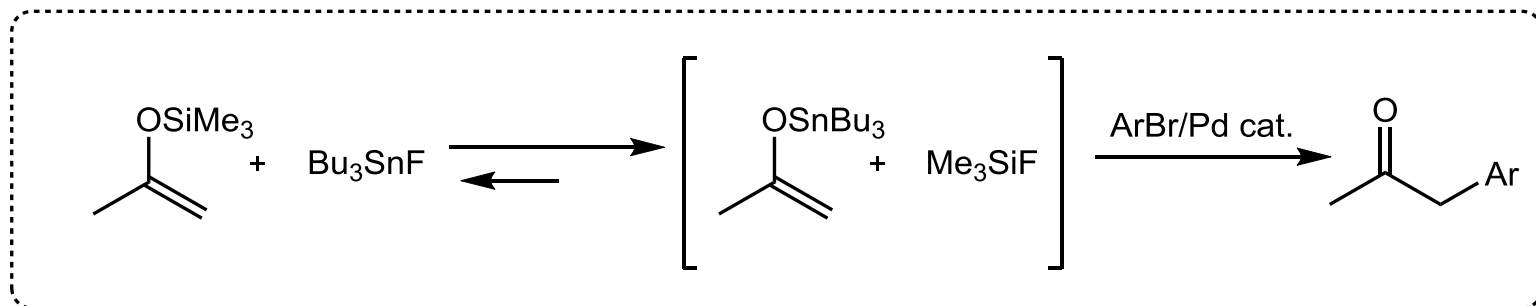
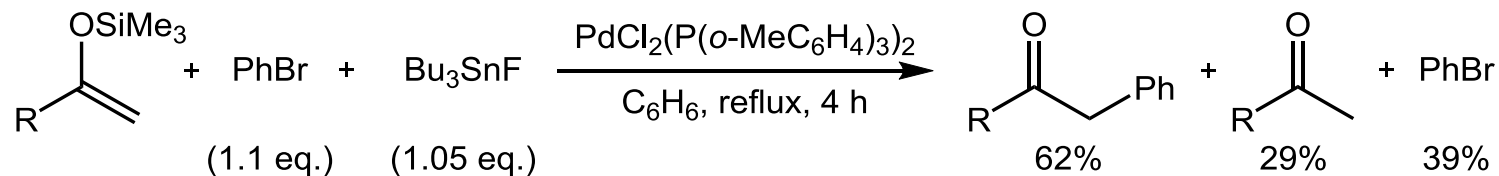
Huang, J.; Gu, Y.; Guo, K.; Zhu, L.; Lan, Y.; Gong, J.; Yang, Z. *Angew. Chem. Int. Ed.* **2017**, 56, 7890.

Synthesis of quinol 7 through a double Michael reaction



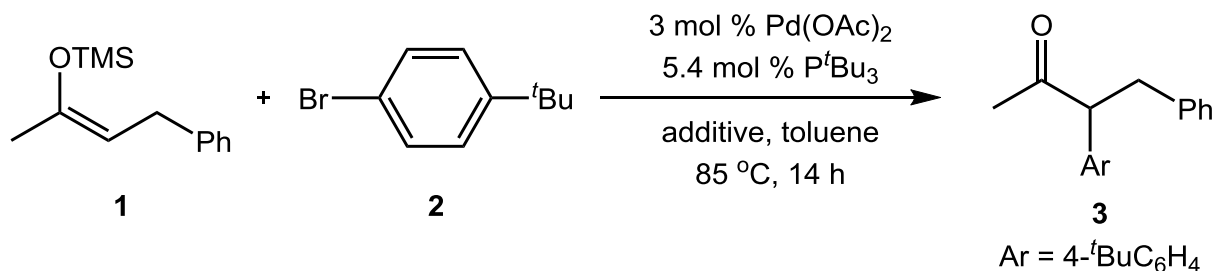
Kuwajima–Urabe arylation

Cross-coupling of enolate nucleophiles



Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831.
Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2006**, *45*, 5852.

Kuwajima–Urabe arylation

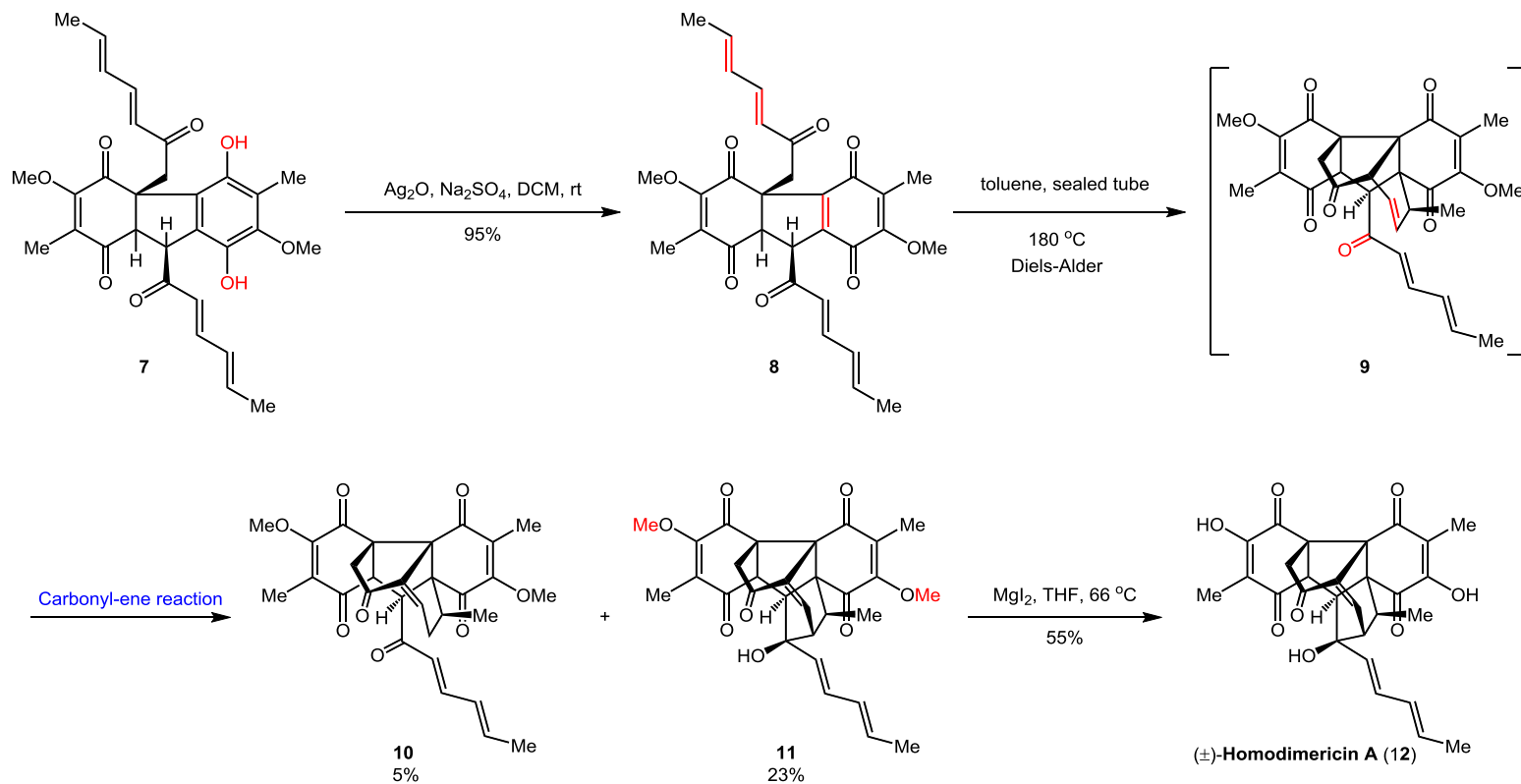


Entry ^a	Additive (equiv)	1:2	Yield (%) ^b
1	--	1.2:1	0
2	BuSnF (1.2)	1.2:1	34
3	CsF (1.2)	1.2:1	18
4	BuSnF (1.2), CsF (1.2)	1.2:1	81
5	Me ₄ NF (1.2)	1.2:1	0
6	BuSnF (1.2), CsF (1.2)	1:1.2	65
7	BuSnF (1.4), CsF (1.4)	1.4:1	98
8	BuSnF (0.14), CsF (1.4)	1.4:1	67

^a Reactions were run at 85 °C with 0.5 mmol **2** (0.25 M), ^b Yield of the isolated product.

Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2006**, *45*, 5852.

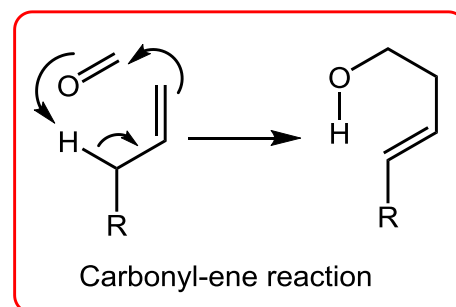
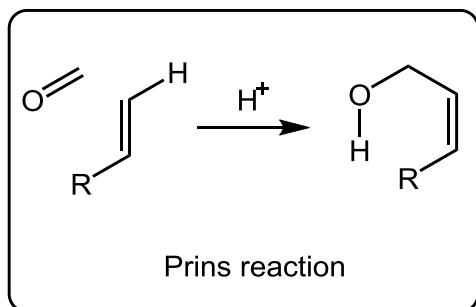
Synthesis of Homodimericin A



2.9% overall yield

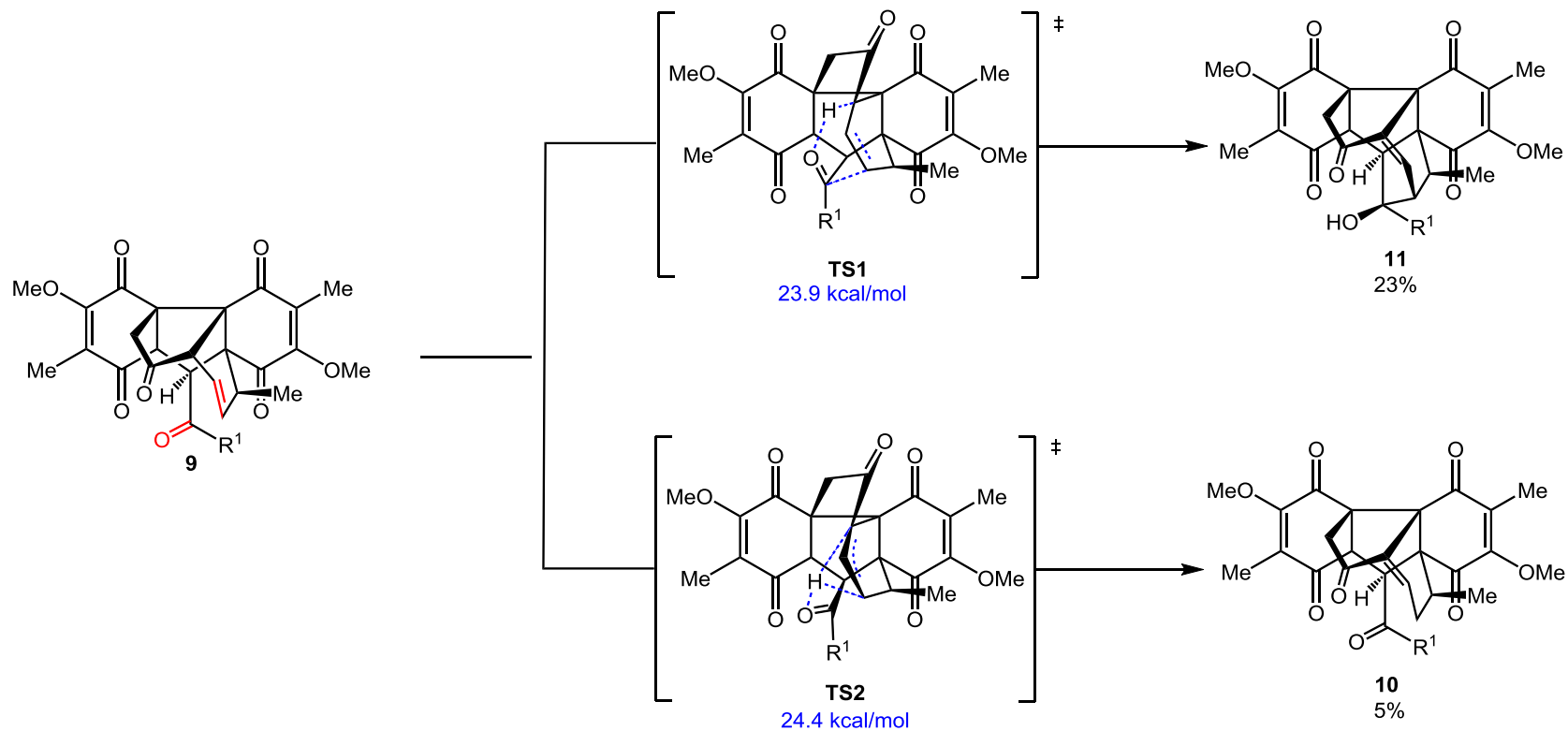
Carbonyl-ene reaction

Prins反应最初是指由烯烃在酸催化下对甲醛的缩合反应，后来泛指一系列历经氧鎓离子中间态的烯烃与羰基的加成反应。反应一般在酸性条件和较低温度下就可以实现。

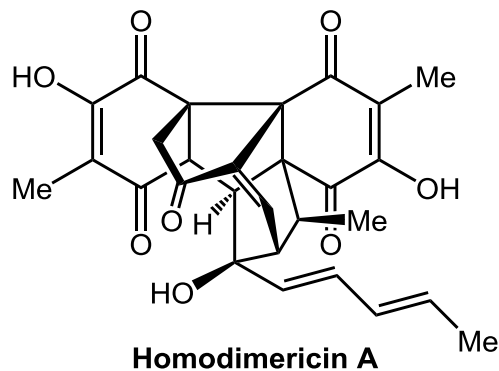


Carbonyl-ene 反应是指由羰基化合物与有 α -H的烯烃经协同反应机理发生反应。反应一般在加热或Lewis酸催化条件下实现。

Free-energy profiles for the formation of 11 and 10



Summary



Wang's work

- 7 Steps, 1.6% overall yield
- Double Michael reaction
- Diels-Alder reaction
- Prins reaction

Yang's work

- 8 Steps, 2.9% overall yield
- Double Michael reaction
- Diels-Alder reaction
- Carbonyl-ene reaction

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The First Paragraph

Nature usually creates secondary metabolites in a sophisticated way involving a number of enzymes, leading to enantiopure natural products. However, some natural products exist as a racemate, indicating that post-enzymatic reactions of achiral starting materials should be present in the biogenetic process. A well-known example is the endiandric acid family of natural products, where a series of pericyclic reactions occur on an achiral linear polyolefinic substrate to generate different endiandric acids, as proposed by Black et al. Nicolaou et al. successfully utilized a biomimetic approach to synthesize the endiandric acids and validated Black's biosynthetic proposal.

The First Paragraph

Recently, in the study of molecular exchange between bacteria and fungi, Clardy and co-workers isolated a complex hexacyclic natural product, homodimericin A, as a fungal metabolite. The structure of homodimericin A was proposed based on comprehensive NMR experiments with support from computational chemistry. Inspired by the fact that homodimericin A exists as a racemate, Clardy and co-workers proposed that a 1,3,4-benzenetriol derivative undergoes a series of reactions involving oxidation, dimerization, oxidation, intramolecular Diels-Alder and Prins cyclization, and eventually generates homodimericin A. The novel structure of homodimericin A and the proposed biosynthetic pathway from a simple precursor attracted our attention. Herein we report the first biomimetic total synthesis of homodimericin A with evidence to support its biosynthetic proposal.

The Last Paragraph

In summary, the first biomimetic total synthesis of hexacyclic natural product (+/-)-homodimericin A was achieved in seven steps involving two cascade transformations. Key steps in the biosynthetic proposal of homodimericin A by Mevers et al. were validated with experimental support. Homodimericin A and other intermediates in this study may serve as markers for investigation of fungal response to oxidative stresses.

***Thanks for
your attention!***