Literature Report I

Divergent Total Synthesis of Biogenetically Related Tetracyclic Diterpenoids

Reporter: Xuan-Yu Gao
Checker: Yi-Xuan Ding
Date: 2021-01-11

Lou, H.-X. *et al. Angew. Chem. Int. Ed.* **2020**, *59,* 19919

CV of Prof. Hong-Xiang Lou

Education and Employment:

- **1981–1985** B.S., Shandong Medical University
- **1985–1988** M.S., Shandong Academy of Medical Sciences
- **1988–1991** Ph.D., Shenyang Pharmaceutical University
- **1991–1997** Lecture, Professor, Shandong Medical University
- **1997–1998** Visiting scholar, National Institute of Bioscience and Human Technology, Japan
- **1998–2000** Professor, Shandong Medical University
- **2000–now** Professor, Shandong University

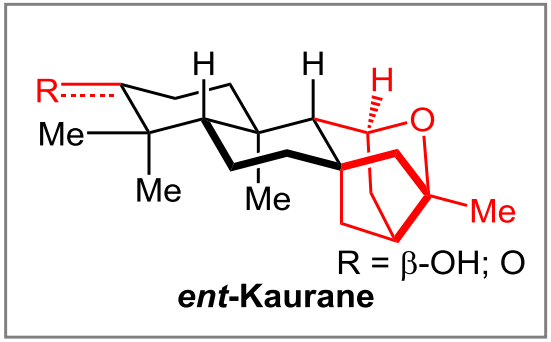
娄红祥

Research Interests:

- Bioactive Chemicals from Natural Products
- Biological Mechanisms of Natural Antifungal and Antitumor Constituents
- Syntheses of Important Natural Compounds

Contents

Introduction



Euphorbia micractina

- The most common type of tetracyclic diterpenoids;
- Isolated from ***Euphorbia micractina*** by Jia group in 1994;
- Many promising biological activities, including antitumor, antiviral, and antifungal activities.

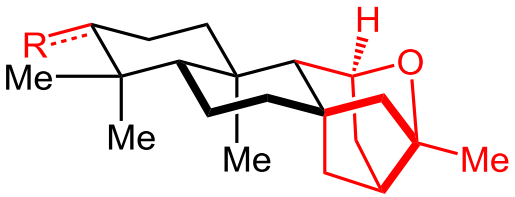
Jia, Z.-J.;Shi, J.-G.; Yang, L. *J. Nat. Prod.* **1994**, *57,* 811

Lou, H.-X.*;* Xu, Z.-J.; Zong, Y.; Qiao, Y.-N.; Zhang, J.-Z.; Liu, X.; Zhu, M.-Z.; Xu, Y.; Zheng, H.; Fang, l.; Wang, X.-N. *Angew. Chem. Int. Ed.* **2020**, *59*, 19919

Introduction

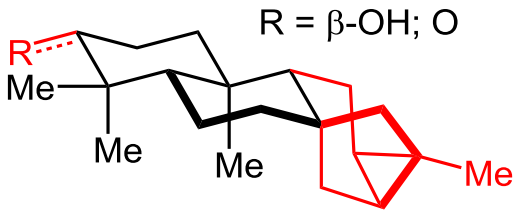
Representative Type of Tetracyclic Diterpenoids

***ent*-Kaurane**



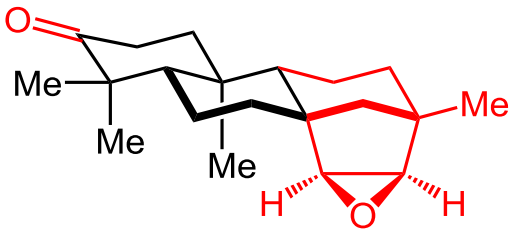
euphoranginol C (1)
euphoranginone D (2)

***ent*-Trachylobane**



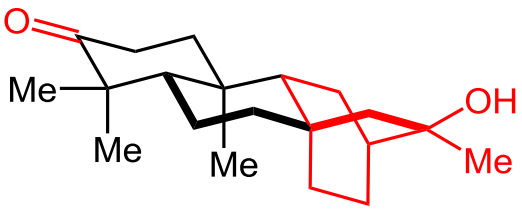
***ent*-trachyloban-3β-ol (3)**
***ent*-trachyloban-3-one (4)**

***ent*-Beyerane**



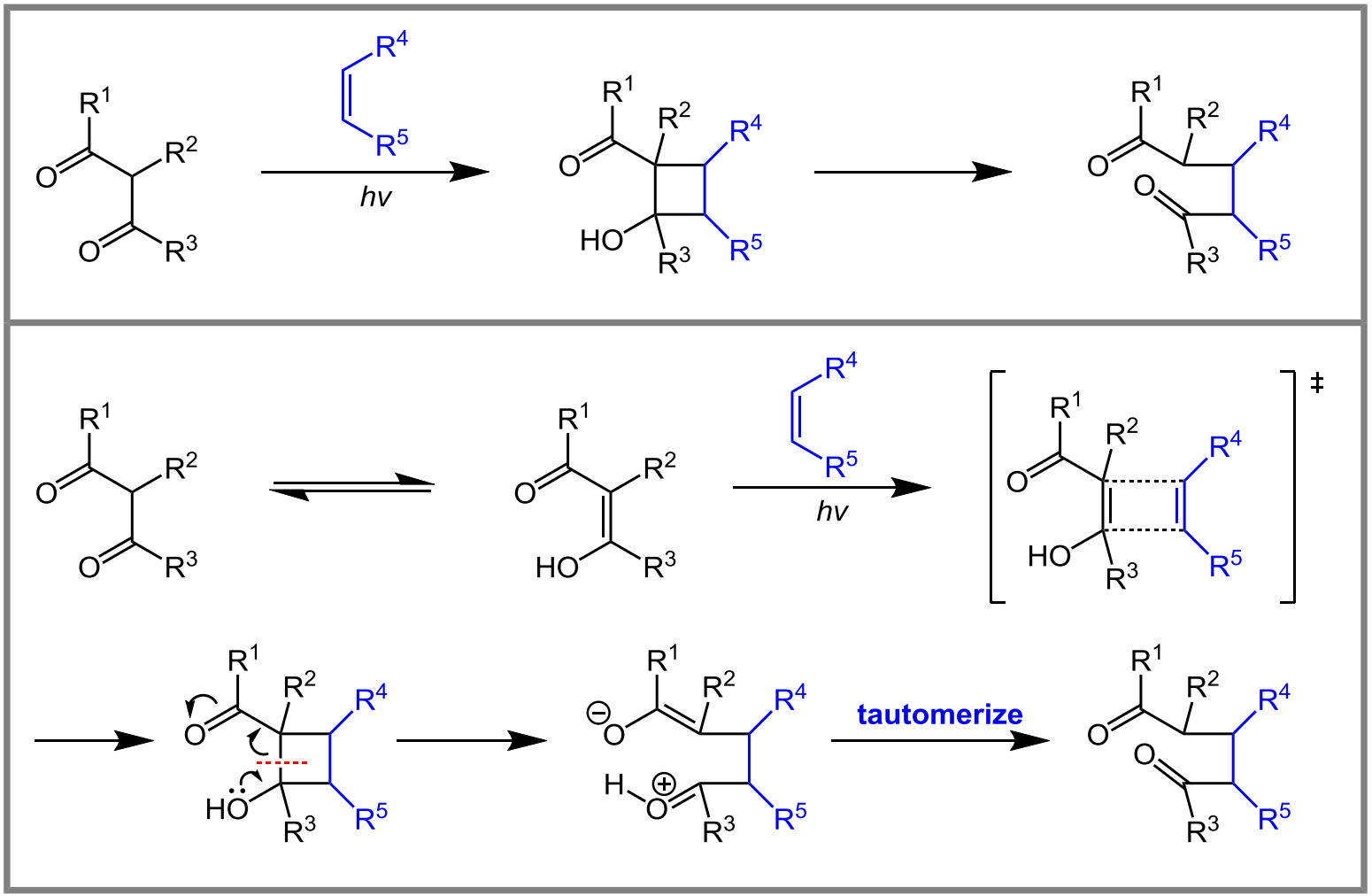
excoecarin E (5)

***ent*-Atiserane**



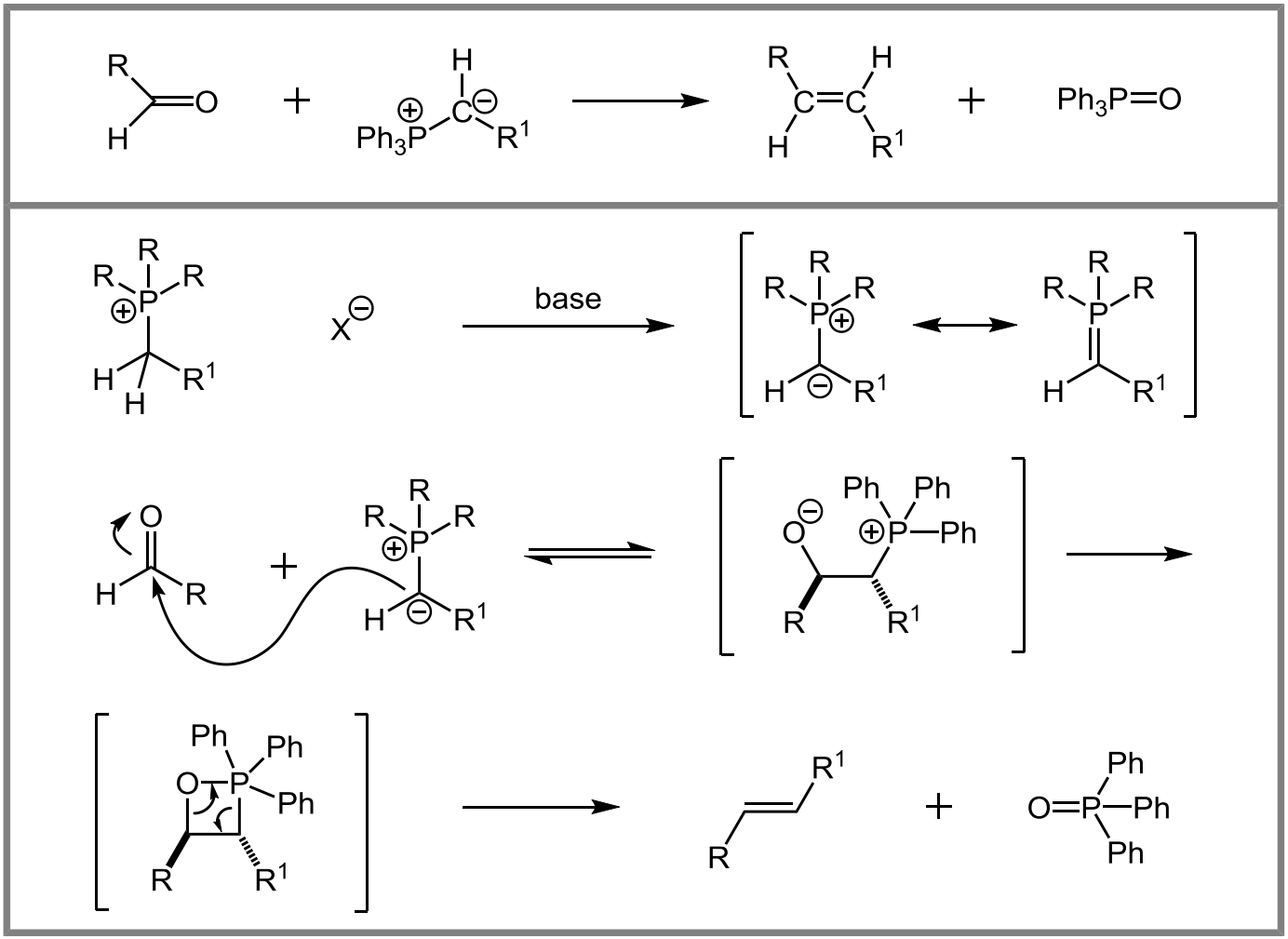
***ent*-16α-hydroxy-atisane-3-one (6)**

De Mayo Reaction



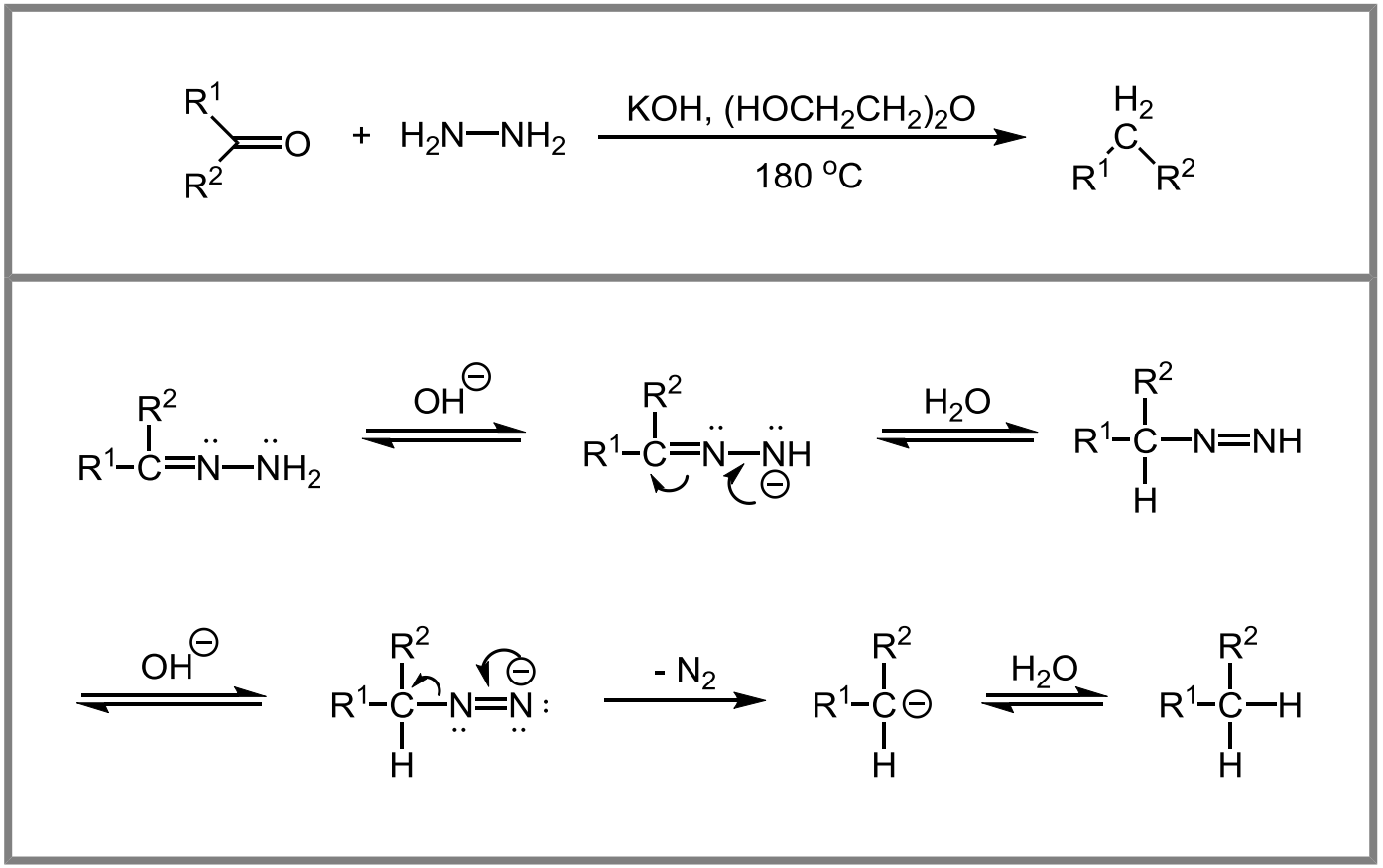
De Mayo, P.; Takeshita, H.; Satta, A. B. M. A. *Proc. Chem. Soc.* **1962**, 119

Wittig Reaction



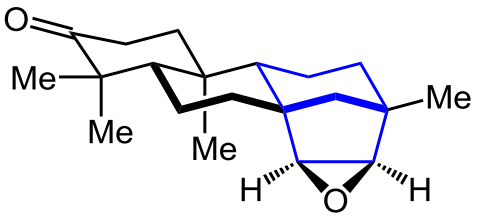
Wittig, G.; Geissler, G. *J. Am. Chem. Soc.* **1953**, *580*, 44

Wolff-Kishner-Reduction

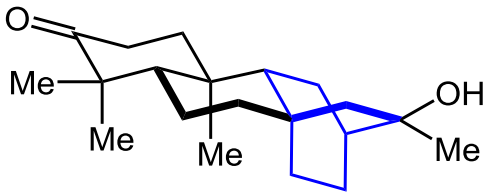


Kishner, N. *J. Russ. Phys. Chem. Soc*. **1911**, *43*, 582
Wolff, L. *Justus Liebigs Ann. Chem*. **1912**, *394*, 86

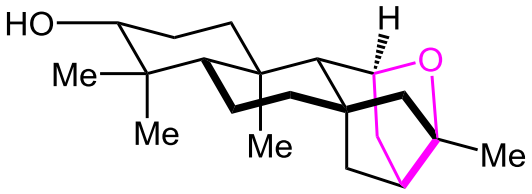
Retrosynthetic Analysis



(5)
ent-Beyerane

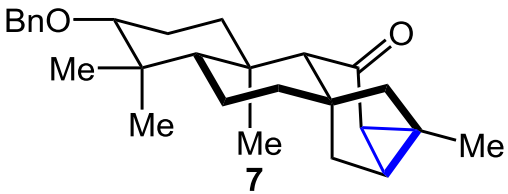


(6)
ent-Atiserane



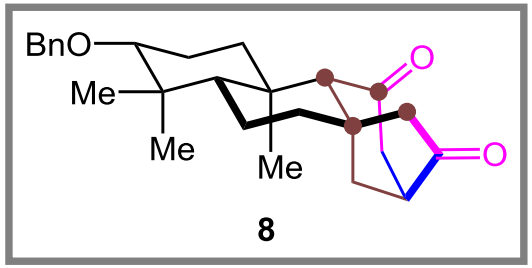
(1)
ent-Kaurane

regioselective
cyclopropane
fragmenlation



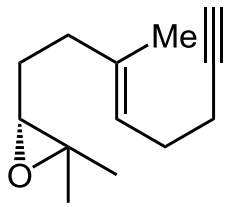
7
ent-Trachylobane

nucleophilic
cyclopropanation



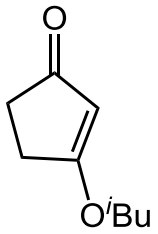
8

De Mayo reaction



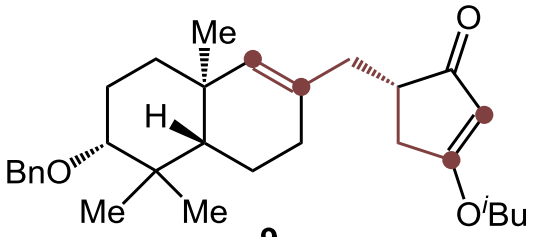
11

+



10

fragment coupling

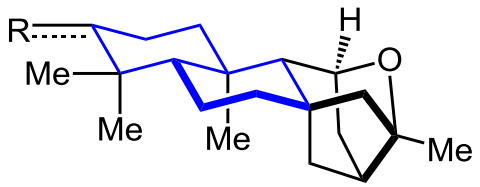


9

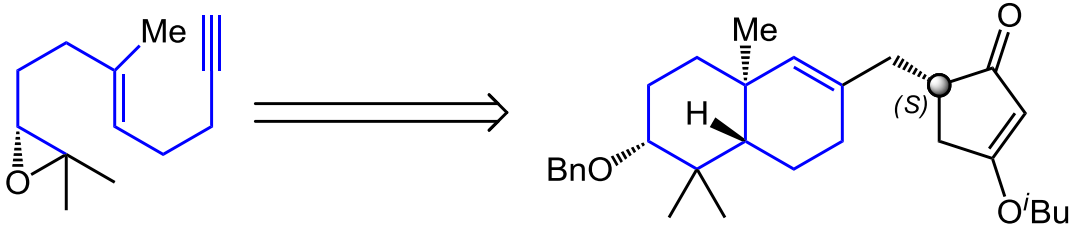
The Synthesis of *ent*-Kaurane

***ent*-Kaurane**

R = β-OH; O

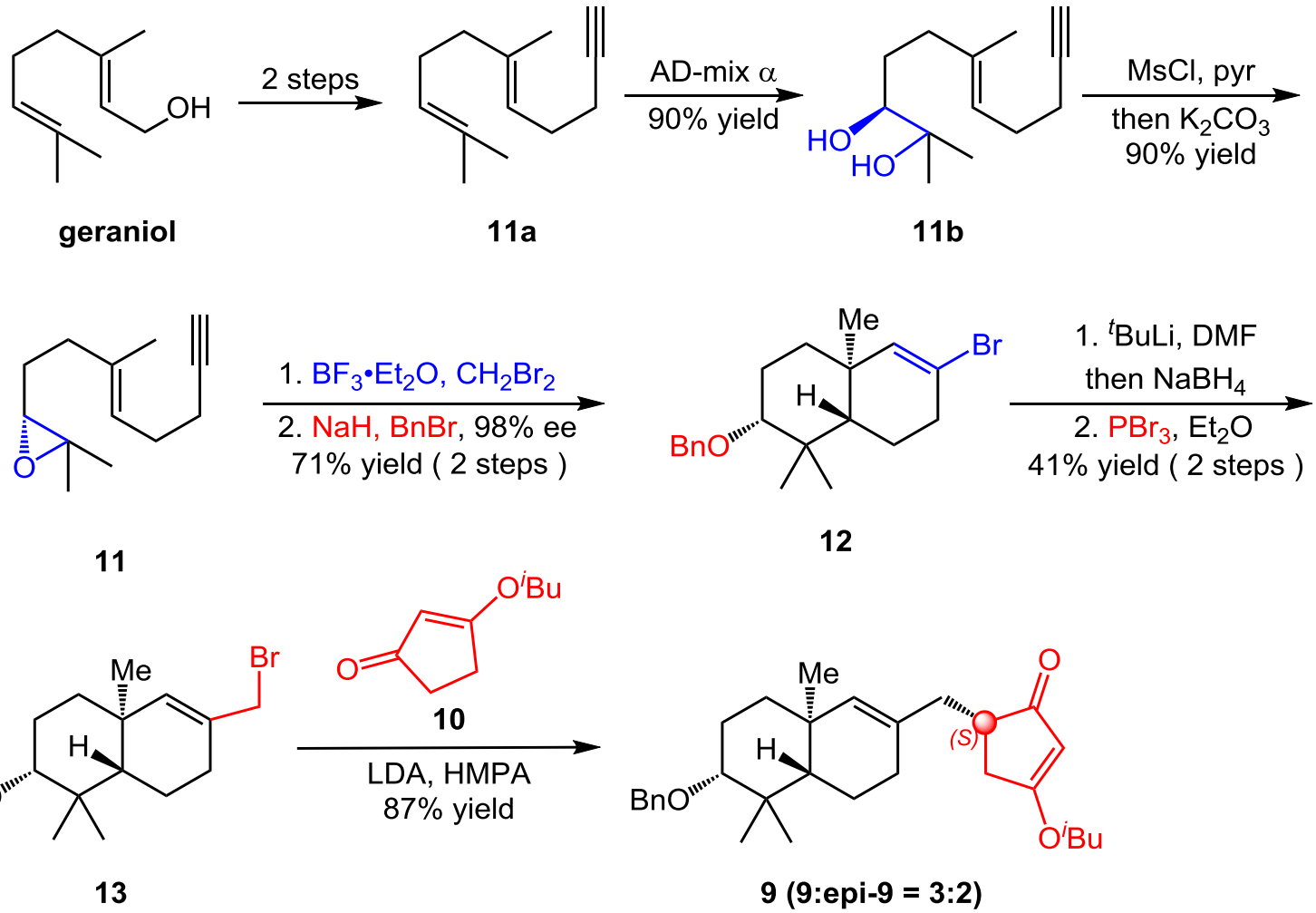


euphoranginol C (1)
euphoranginone D (2)



11 **9**

The Synthesis of 9



The Synthesis of *ent*-Kaurane

***ent*-Kaurane**

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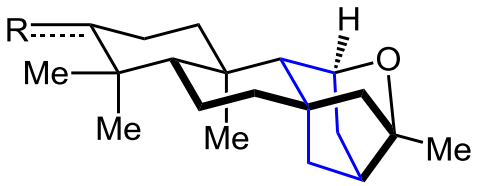
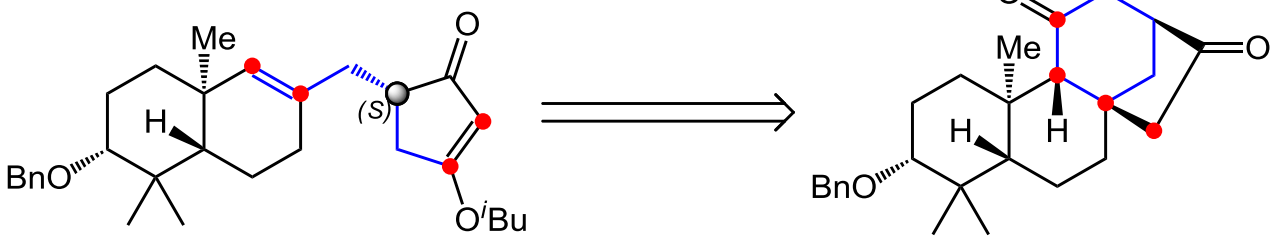
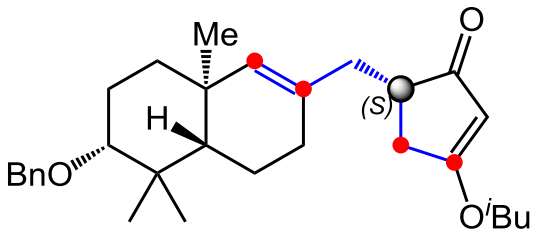


euphoranginol C (1)
euphoranginone D (2)



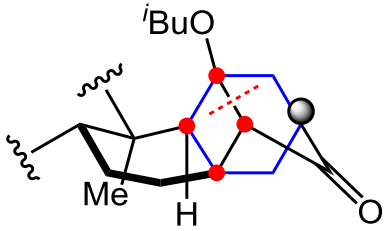
9 **8**

The Synthesis of 8



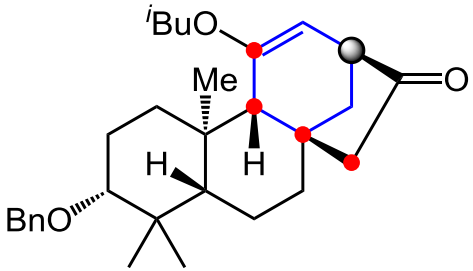
9

hv (254 nm)



14'

BF_3•2AcOH

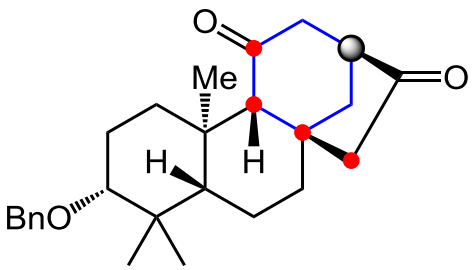


14
kaurene-type

3N HCl (10 eq.)

acetone

95% yield

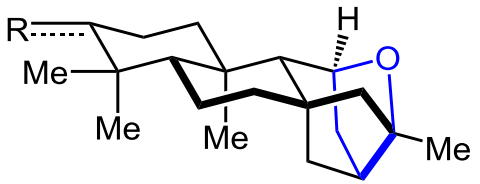


8

The Synthesis of *ent*-Kaurane

***ent*-Kaurane**

R = β-OH; O



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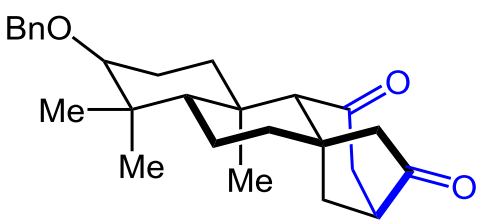
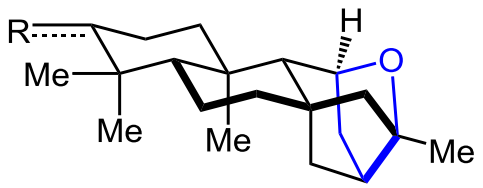
euphoranginone D (2)



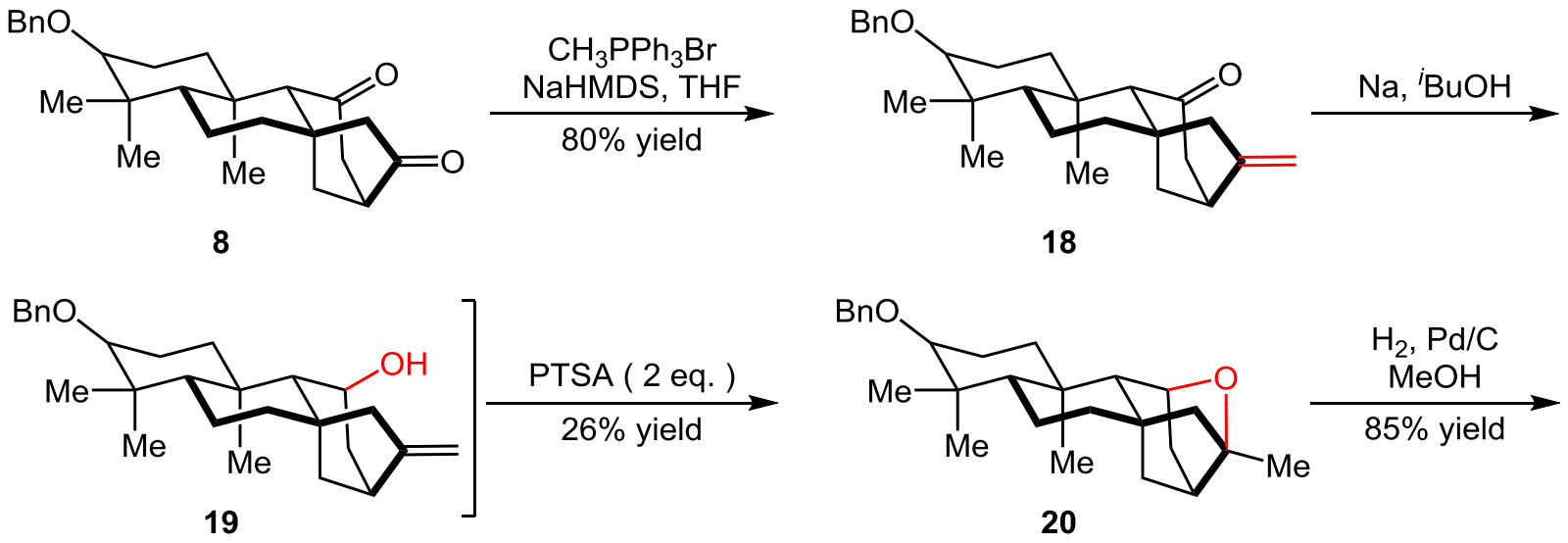
8

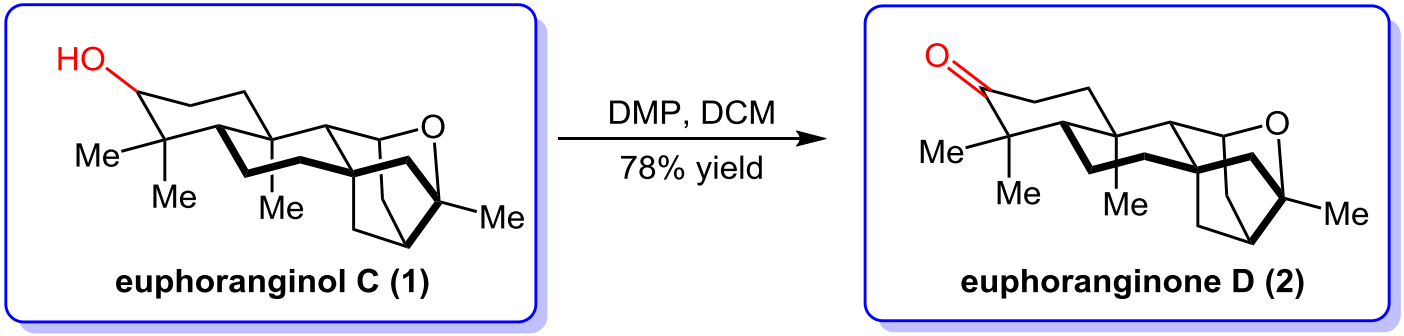
R = β-OH; O



euphoranginol C (1)
euphoranginone D (2)

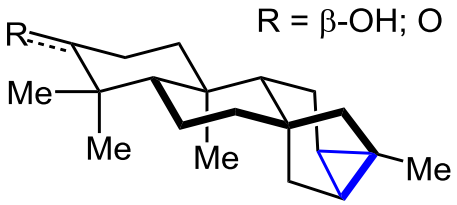
The Synthesis of *ent*-Kaurane



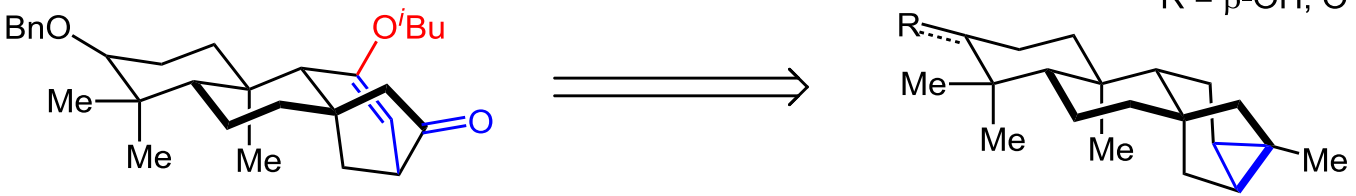


The Synthesis of *ent*-Trachylobane

***ent*-Trachylobane**



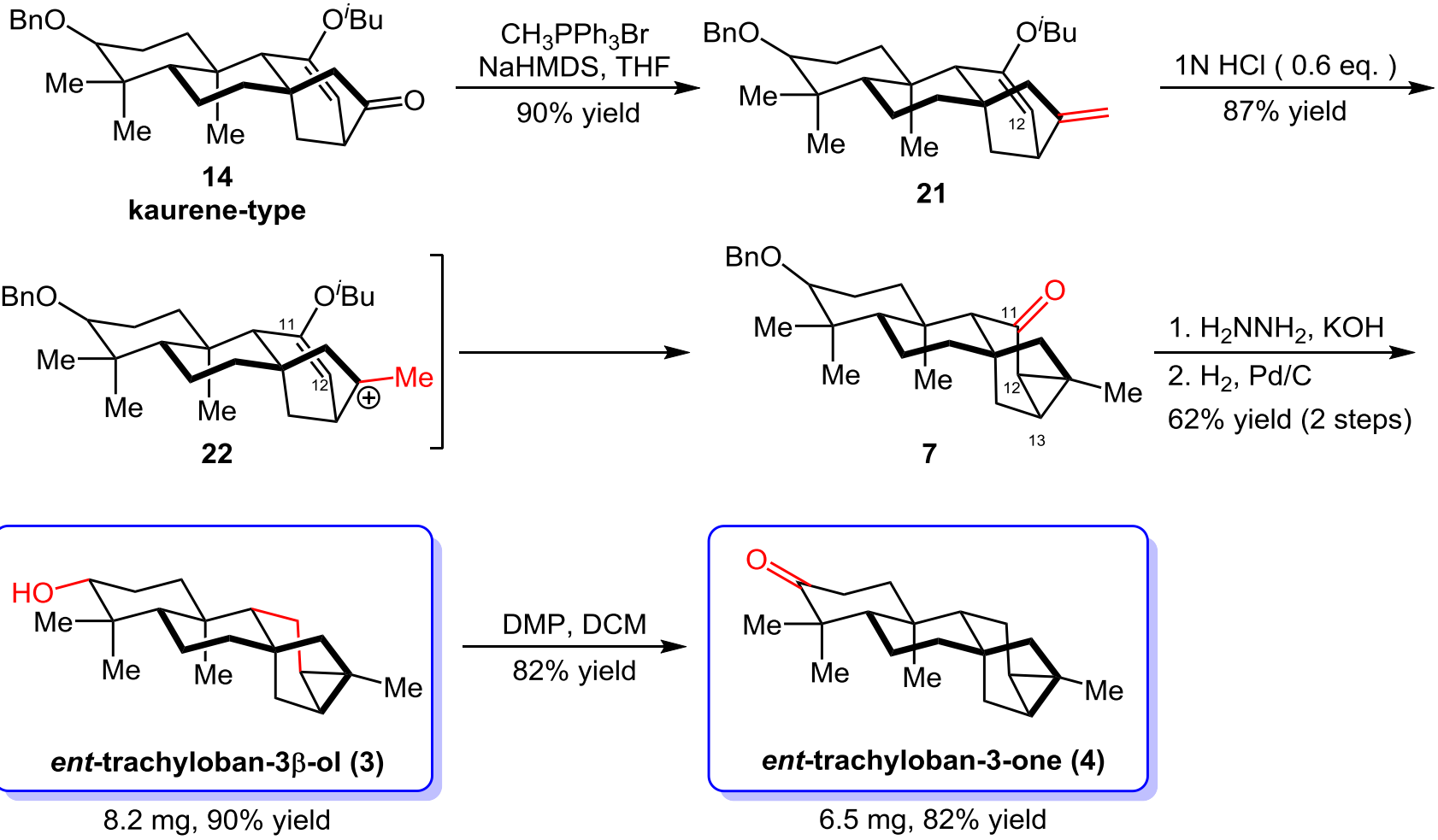
***ent*-trachyloban-3β-ol (3)**
***ent*-trachyloban-3-one (4)**



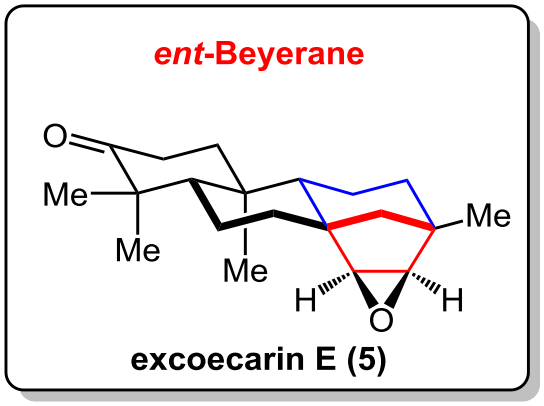
14
kaurene-type

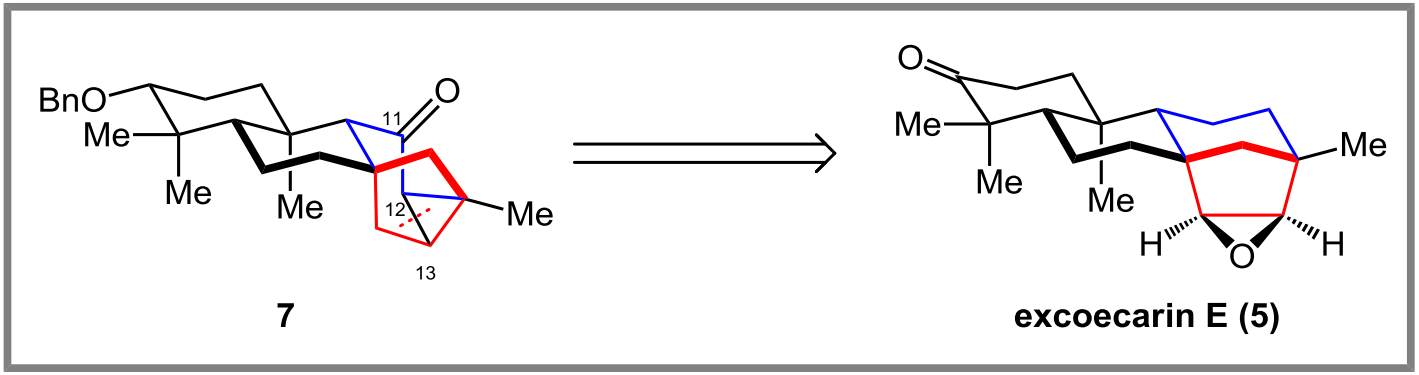
***ent*-trachyloban-3β-ol (3)**
***ent*-trachyloban-3-one (4)**

The Synthesis of *ent*-Trachylobane

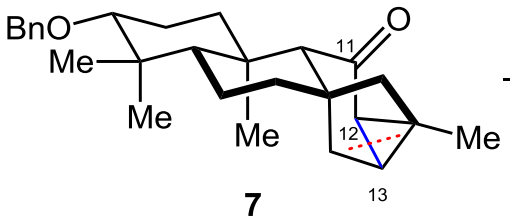


The Synthesis of *ent*-Beyerane





The Synthesis of 5

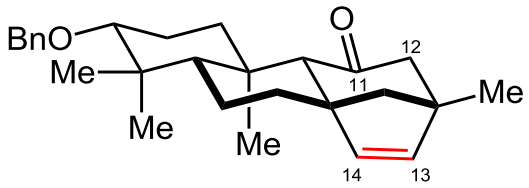


7

PhSeSePh, $AlCl_3$, Zn

then H_2O_2

76% yield

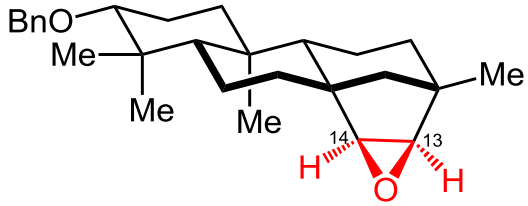


23

1. H_2NNH_2
KOH

2. ^{m}CPBA

48% yield (2 steps)



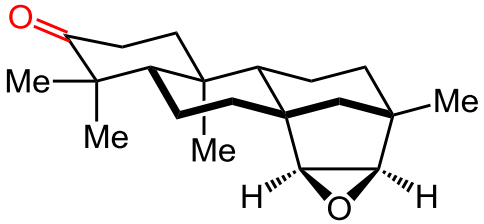
24

1. H_2, Pd/C, MeOH

2. DMP, DCM

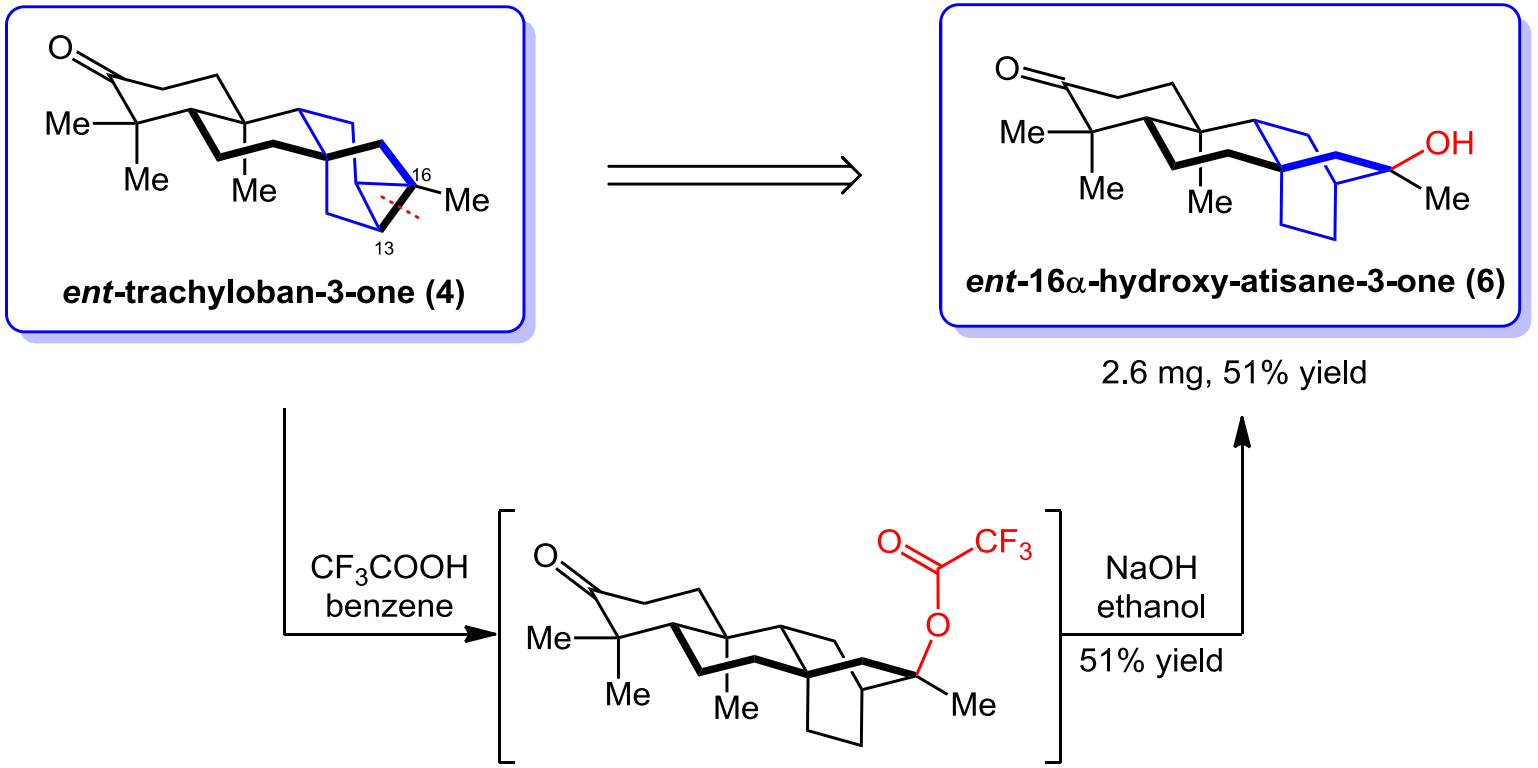
77% yield (2 steps)

3.5 mg, 77% yield

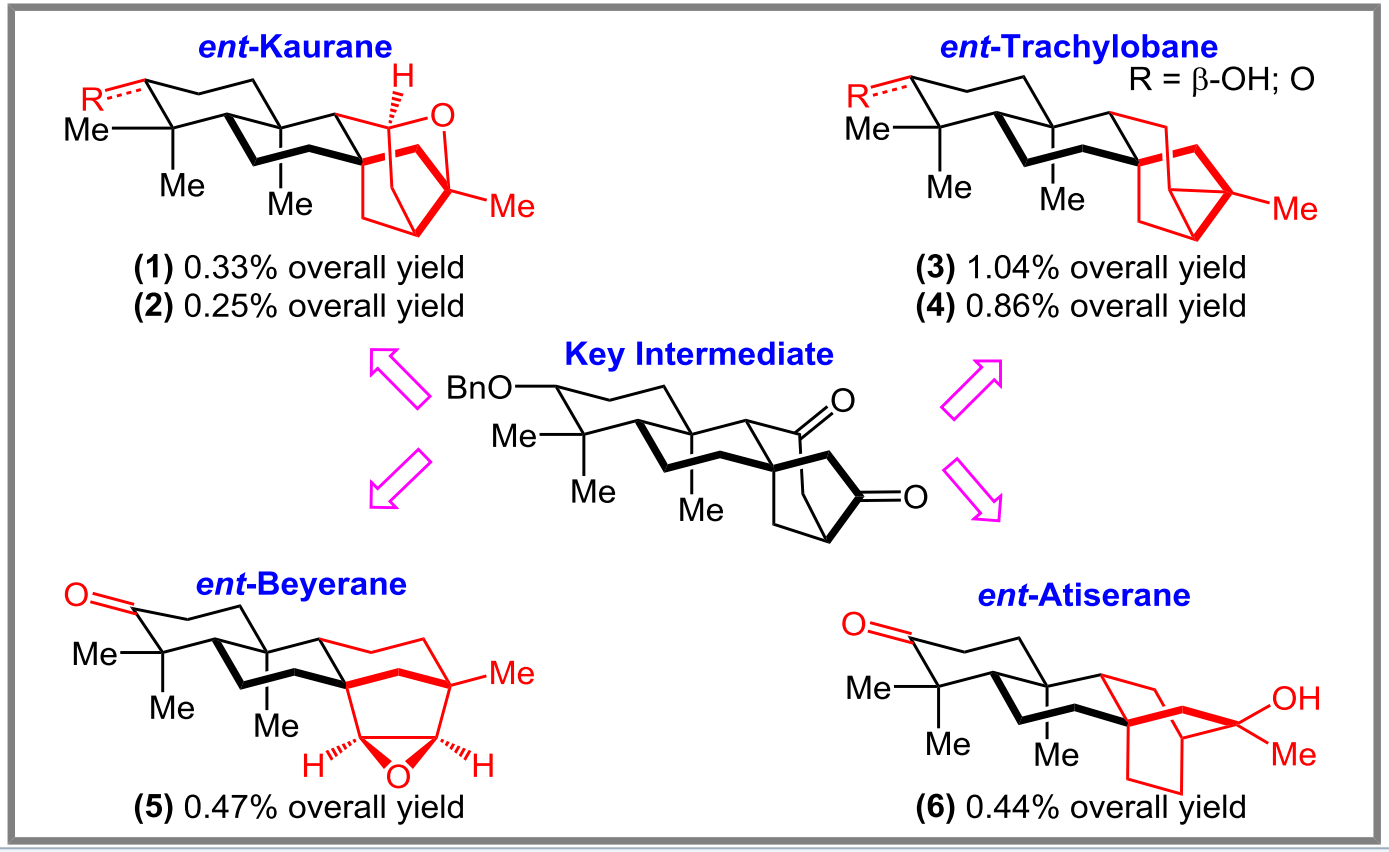


excoecarin E (5)

The Synthesis of *ent*-Atiserane



Summary



- Divergent total synthesis of six diterpenoids: 14-16 steps
- De Mayo reaction
- Wittig reaction
- Wolff-Kishner-reduction

Writing Strategy

The species of biogenetically related tetracyclic diterpenoids

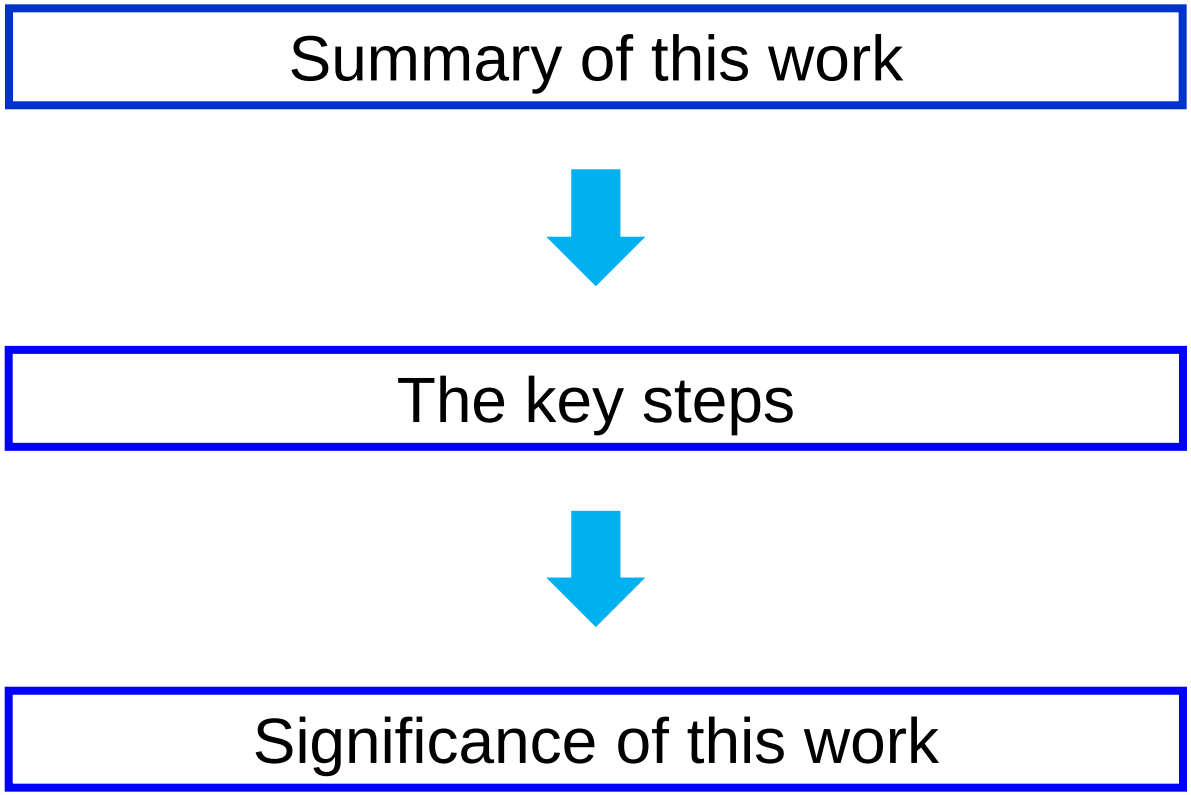
The structural features of biogenetically related tetracyclic diterpenoids

Importance of biogenetically related tetracyclic diterpenoids

The First Paragraph

Tetracyclic diterpenoids constitute a large family of plant terpenoids, and they mainly refer to the biogenetically related carbon skeletons derived from *ent*-copalyl diphosphate (*ent*-CPP). *ent*-Kauranes are the most common type of tetracyclic diterpenoids, which also include *ent*-beyerane, *ent*-atiserane, *ent*-trachylobane, and *ent*-grayanane. Structurally, each family has a characteristic bicyclo[3.2.1]-, bicyclo-[2.2.2]-, or tricyclo[3.2.1.0]-octane framework containing several consecutive stereocenters. These natural diterpenoids have been found to exhibit many promising biological activities, including antitumor, antiviral, and antifungal activities.

Writing Strategy



The Last Paragraph

In summary, we have developed a divergent route that enables the total synthesis of some biogenetically related polycyclic diterpenoids, namely, *ent*-kauranes, *ent*-trachylobanes, *ent*-beyerane, and *ent*-atisane. De Mayo reaction was employed to generate the pivotal bicyclo[3.2.1] moiety of *ent*-kaurane. Conversion to *ent*-trachylobane from *ent*-kaurane was achieved through bioinspired nucleophilic cyclopropanation. Regio-selective cyclopropane fragmentations of *ent*-trachylobane, furnishing *ent*-beyerane and *ent*-atisane, were achieved through the nucleophilic attack and protonation of the cyclopropane ring. Analog synthesis and evaluation of biological activities are being undertaken and will be repor-ted in due course.

Representative Examples

In the course of our ongoing investigations on the biological activities of these molecules, we sought to develop a divergent protocol for the synthesis of these biogenetically related diterpenoids.（在…的过程中；进行中的实验）

Since 14 played a key role in the latter nucleophilic cyclopropanation, we next screened different acids to improve yield of 14.（扮演重要角色）

Moving forward, reduction of the highly sterically hindered C11 ketone was achieved under drastic Wolff–Kishner conditions by stirring at 210 ^{o}C for 50 h.（表递进，陈述下一步反应）

Acknowledgement

Thanks
for your attention