

Literature Report 9

Total Synthesis of (-)-Retigeranic Acid A: A Reductive Skeletal Rearrangement Strategy

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Checker: Gao-Wei Wang

Date: 2023.07.31

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J. Am. Chem. Soc. **2023**, *145*, 11927-11932.

CV of Dr. Han-Feng Ding



Background:

- ❑ 1999-2003 B.S., Zhejiang University
- ❑ 2003-2008 Ph.D., Zhejiang University
- ❑ 2008-2011 Research Fellow, A*-STAR, Singapore (K. C. Nicolaou)
- ❑ 2011-2016 Distinguished Researcher, Zhejiang University
- ❑ 2016-now Professor, Zhejiang University

Research:

- ✓ Organic Synthetic Chemistry
- ✓ Novel Synthetic Methods of Natural Products (Drugs)
- ✓ Synthesis of Natural Products and Medicinal Chemistry

Contents

1 Introduction

2 Total Synthesis of (-)-Retigeranic Acid A

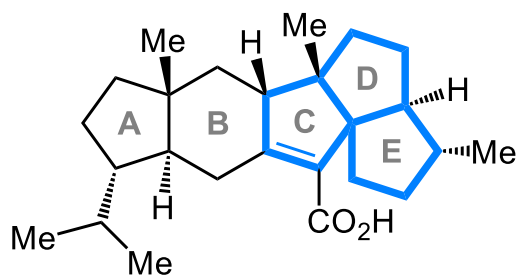
3 Summary

Introduction

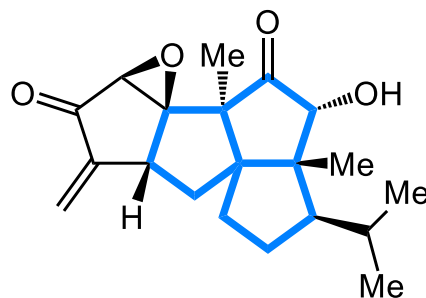
(-)-Retigeranic Acid A



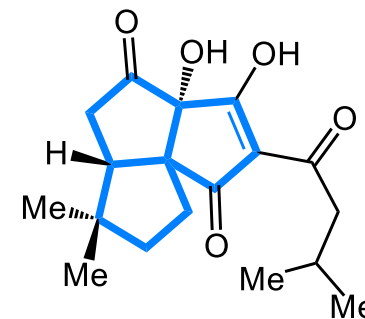
- ♣ First isolated from the *Lobaria retigera* group in 1965
- ♣ Utility in treating eczema and lung disorders
- ♣ Angular triquinane subunit and eight stereogenic centers



(-)-Retigeranic acid A



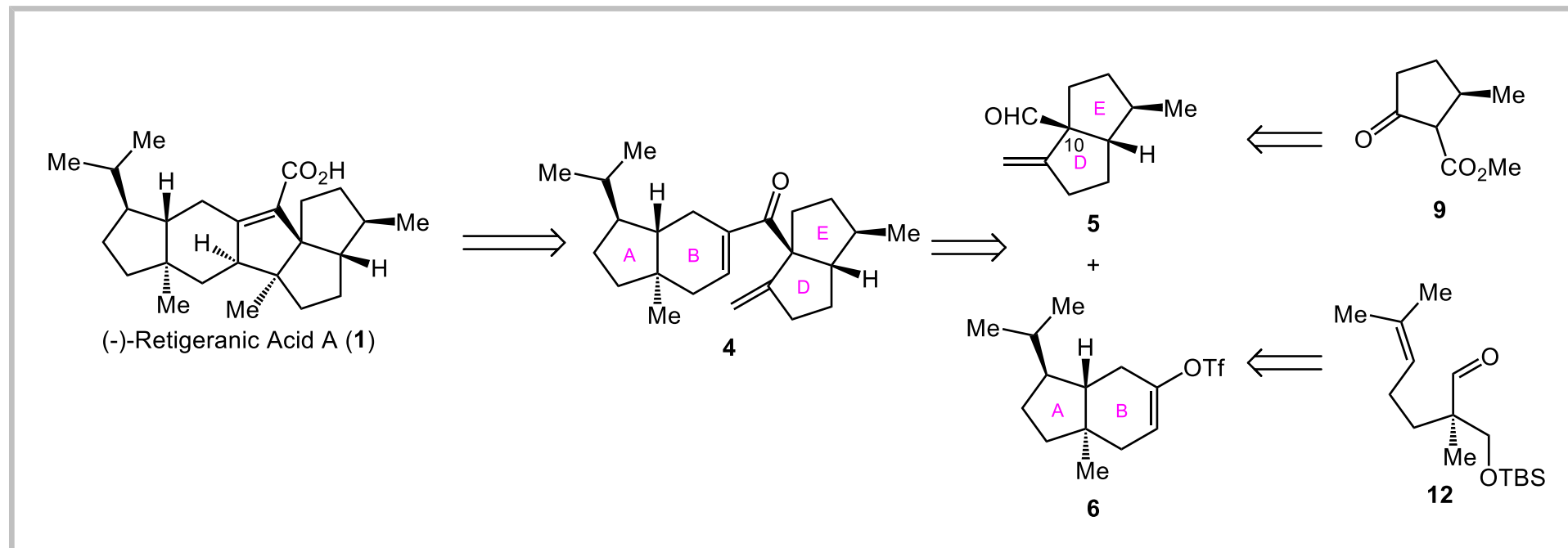
(-)-Crinipellin A



(+)-Deisopropyl-tricycloisohumulone

Seshadri, T. R. *et al. Curr. Sci.* **1965**, 34, 9.

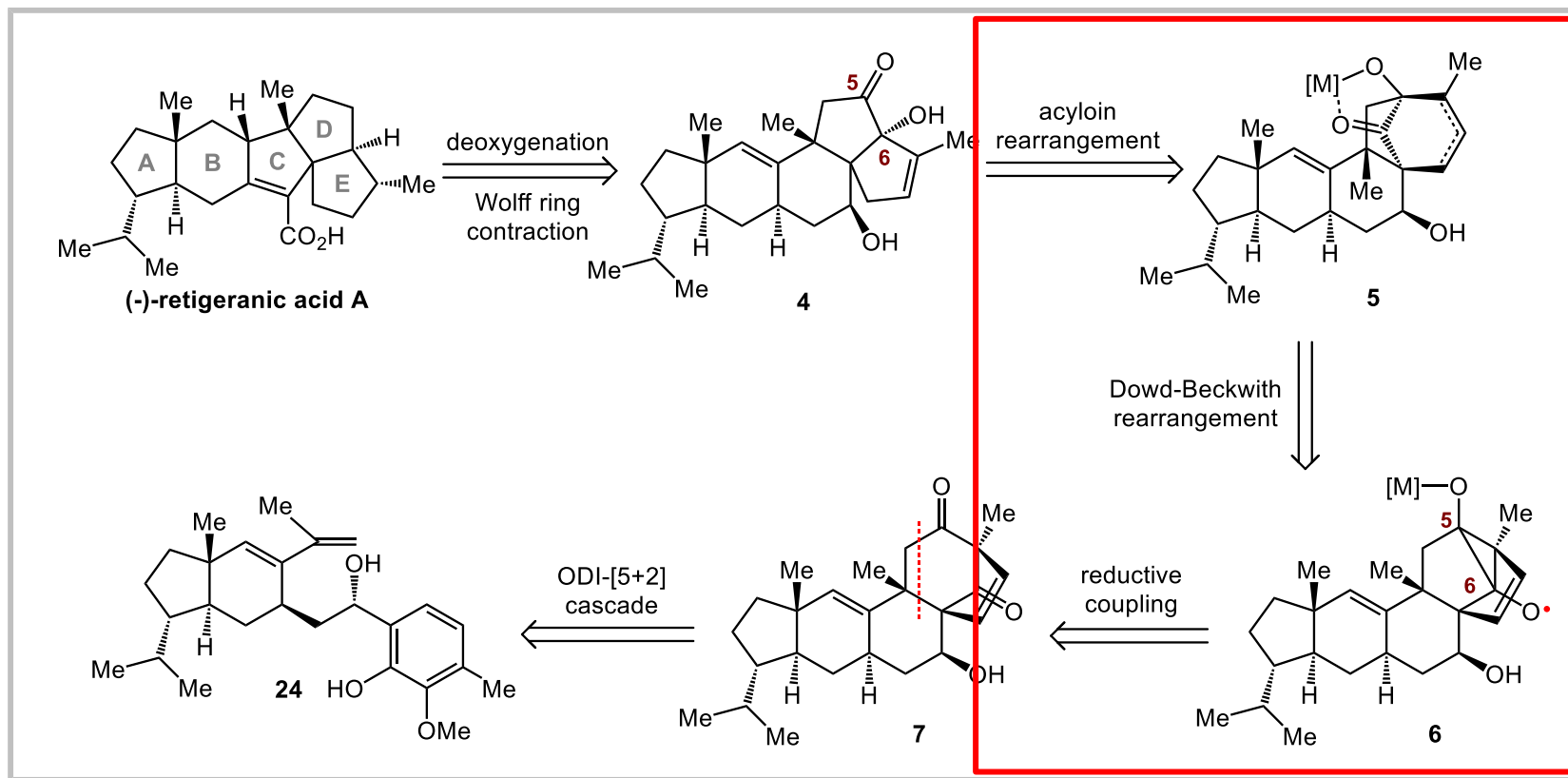
Retrosynthetic Analysis (Wang's Work)



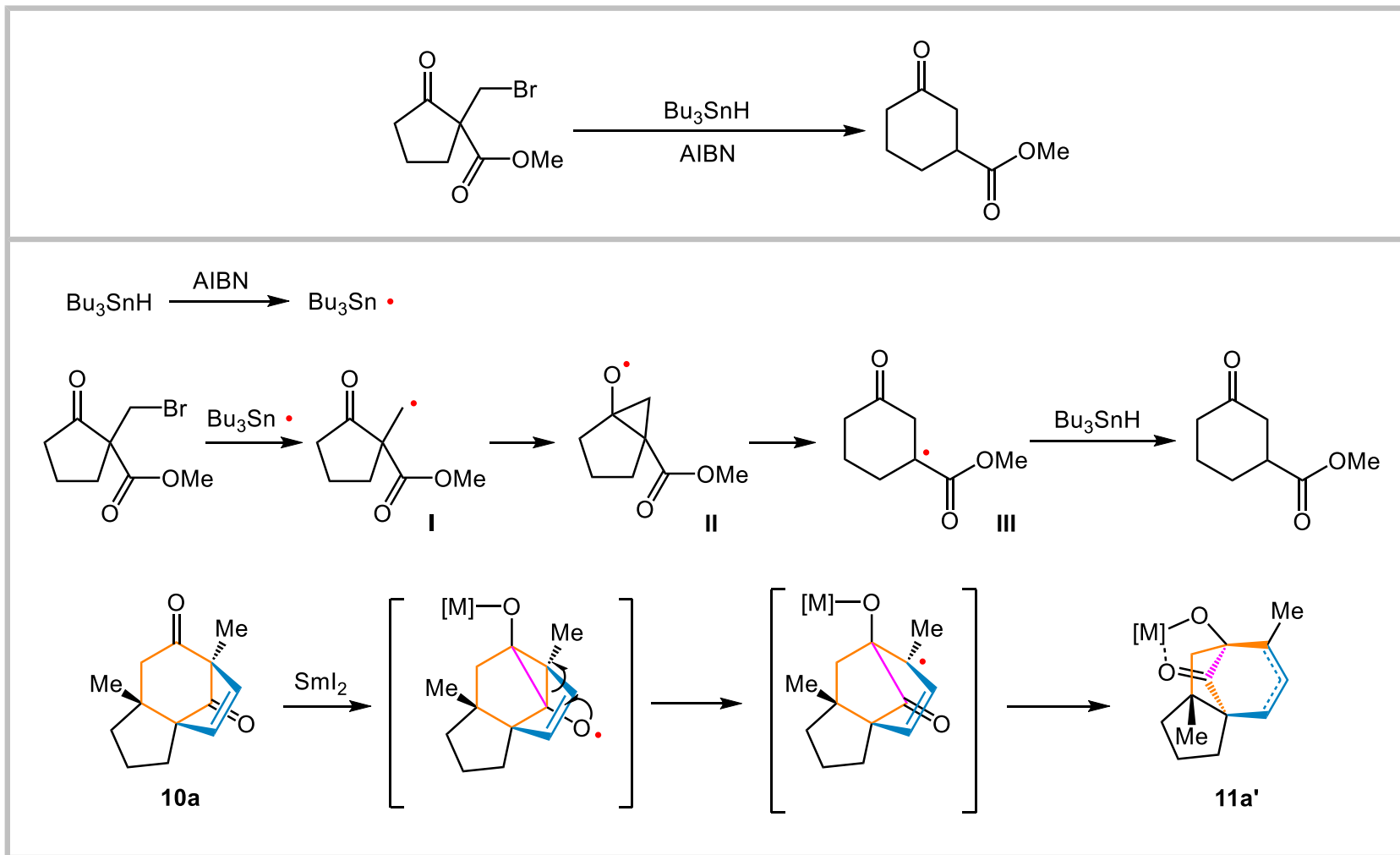
Chen, X.; Wang, S.-H. *et al. J. Am. Chem. Soc.* **2023**, *145*, 13549

From Yu-Qing Bai

Retrosynthetic Analysis (Ding's Work)

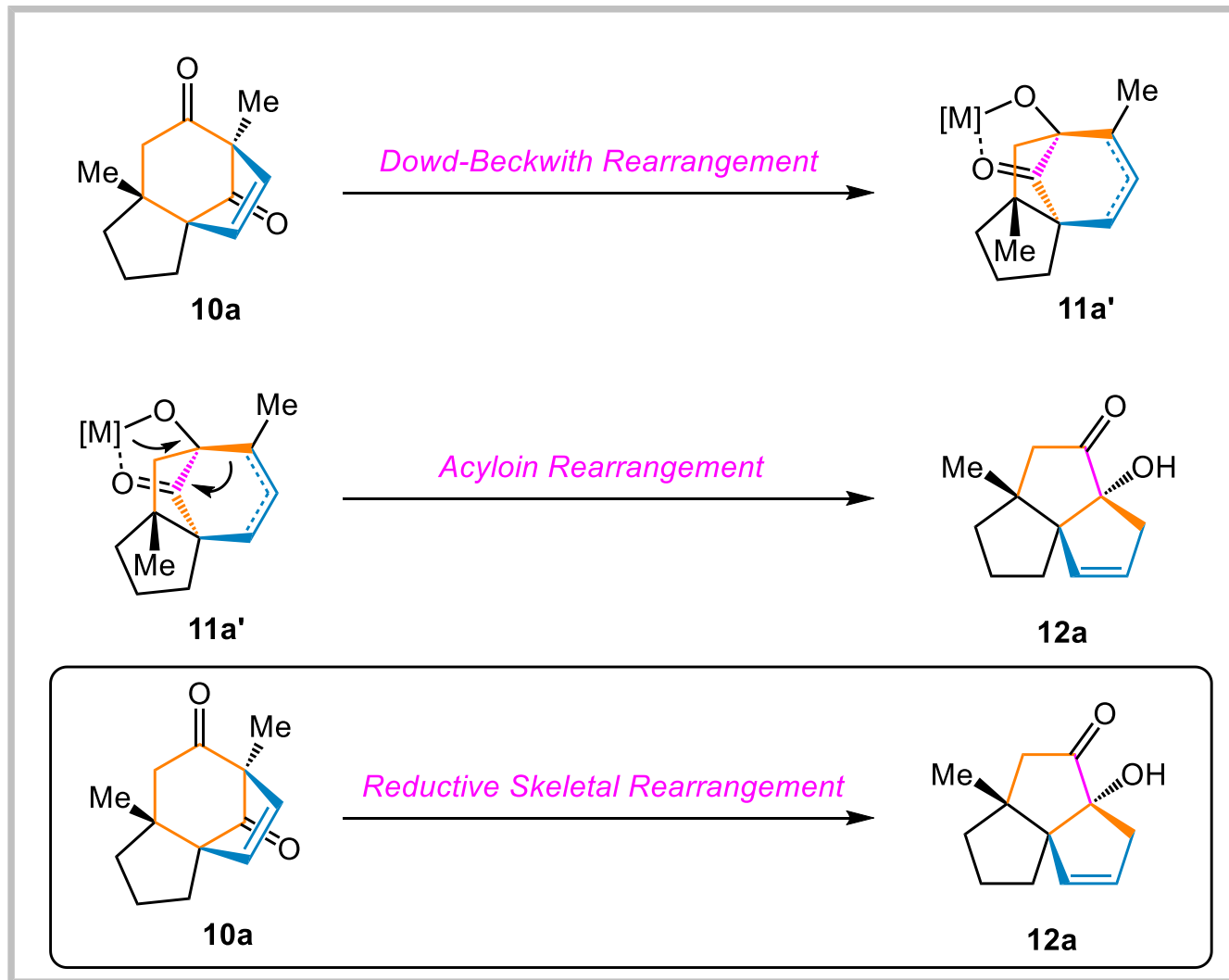


Dowd-Beckwith Rearrangement

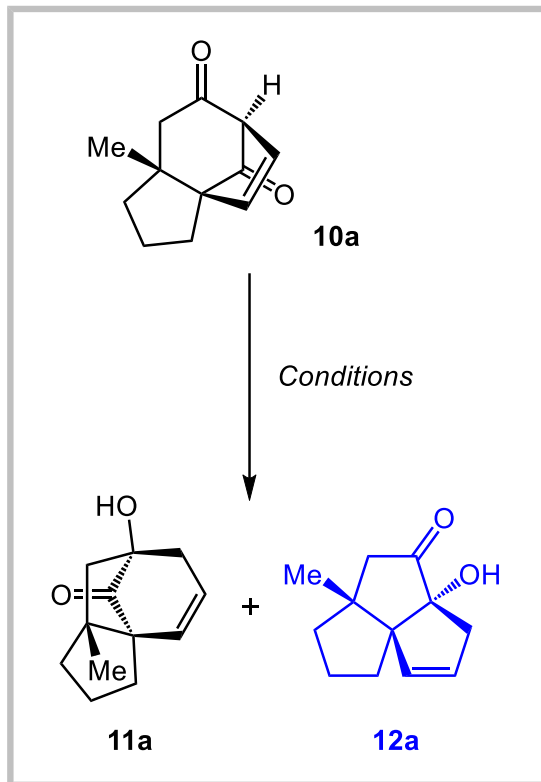


From Name Reaction

Dowd-Beckwith/Acyloin Rearrangement



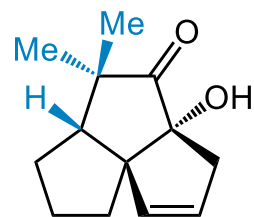
Reductive Skeletal Rearrangement



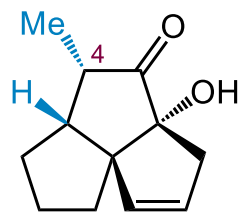
entry	conditions	yield [%]	
		11a	12a
1	$n\text{Bu}_3\text{SnH}$, AIBN, toluene, 90 °C	0	0
2	TiCl_4 , Zn, THF, 0 °C	0	0
3	$\text{VCl}_3(\text{THF})_3$, Zn, DCM, 25 °C	0	0
4	SmI_2 , THF, 0 to 25 °C	<5	0
5	SmI_2 , THF/MeOH, 0 °C	<5	0
6	SmI_2 , THF/ $t\text{BuOH}$, 0 °C	73	0
7	SmI_2 , THF/ $t\text{AmOH}$, 0 °C	70	0
8	SmI_2 , THF/ $t\text{BuOH}$, 0 °C; then KOH	<5	65

^a Reaction condition: **10a** (0.2 mmol), low-valent metal (2.2 equiv.) in solvent (9:1), T °C. ^b Isolated yield. ^c $n\text{Bu}_3\text{SnH}$ (2.0 equiv.), AIBN (0.5 equiv.). ^d No reaction. ^e **13a** (80% yield). ^f KOH (2.0 equiv.).

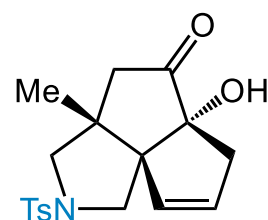
Substrate Scopes



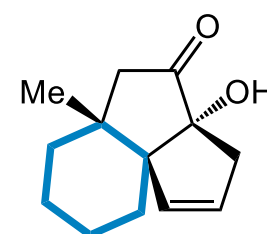
12b, 62%



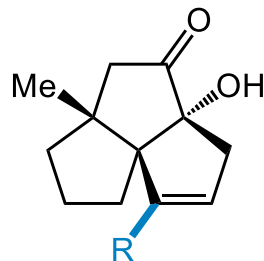
12c, 56%
1.8:1 dr



12d, 45%

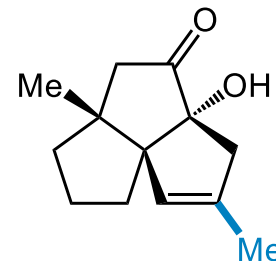


12e, 60%

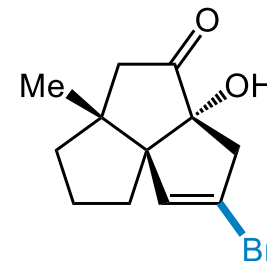


12d, 45%

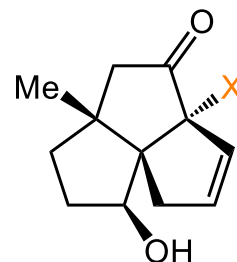
R = Me, **12f**, 62%
R = Br, **12g**, 60%
R = Ph, **12h**, 65%



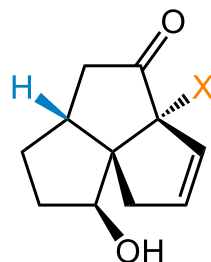
12i, 55%



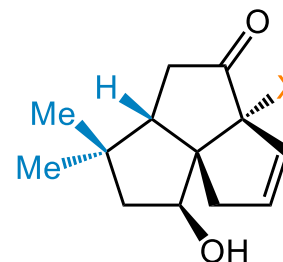
12j, 57%



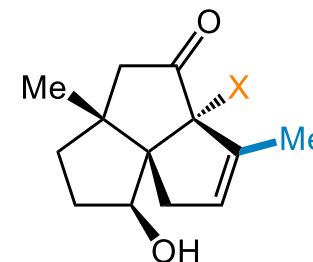
X = OH, **12k**, 65%
X = H, **12k'**, 60%



X = OH, **12l**, 56%
X = H, **12l'**, 52%

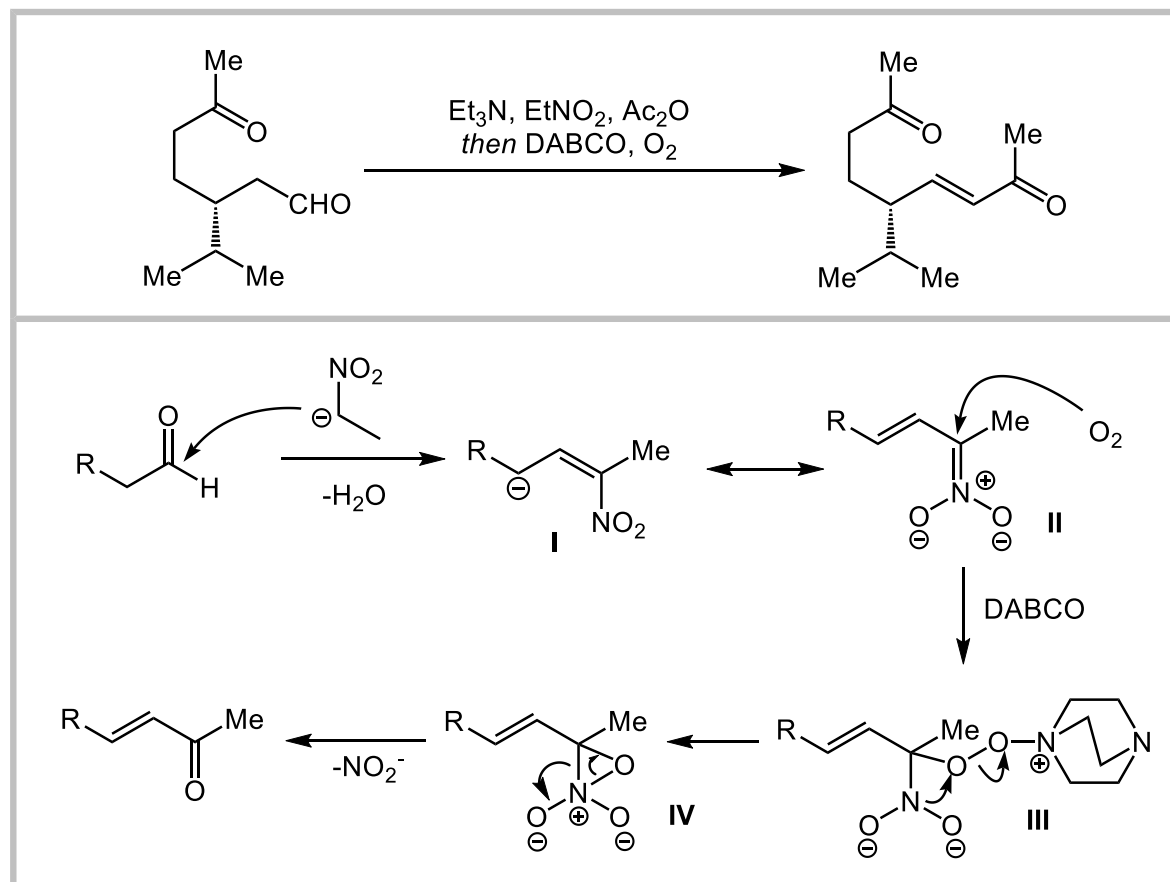


X = OH, **12m**, 55%
X = H, **12m'**, 50%



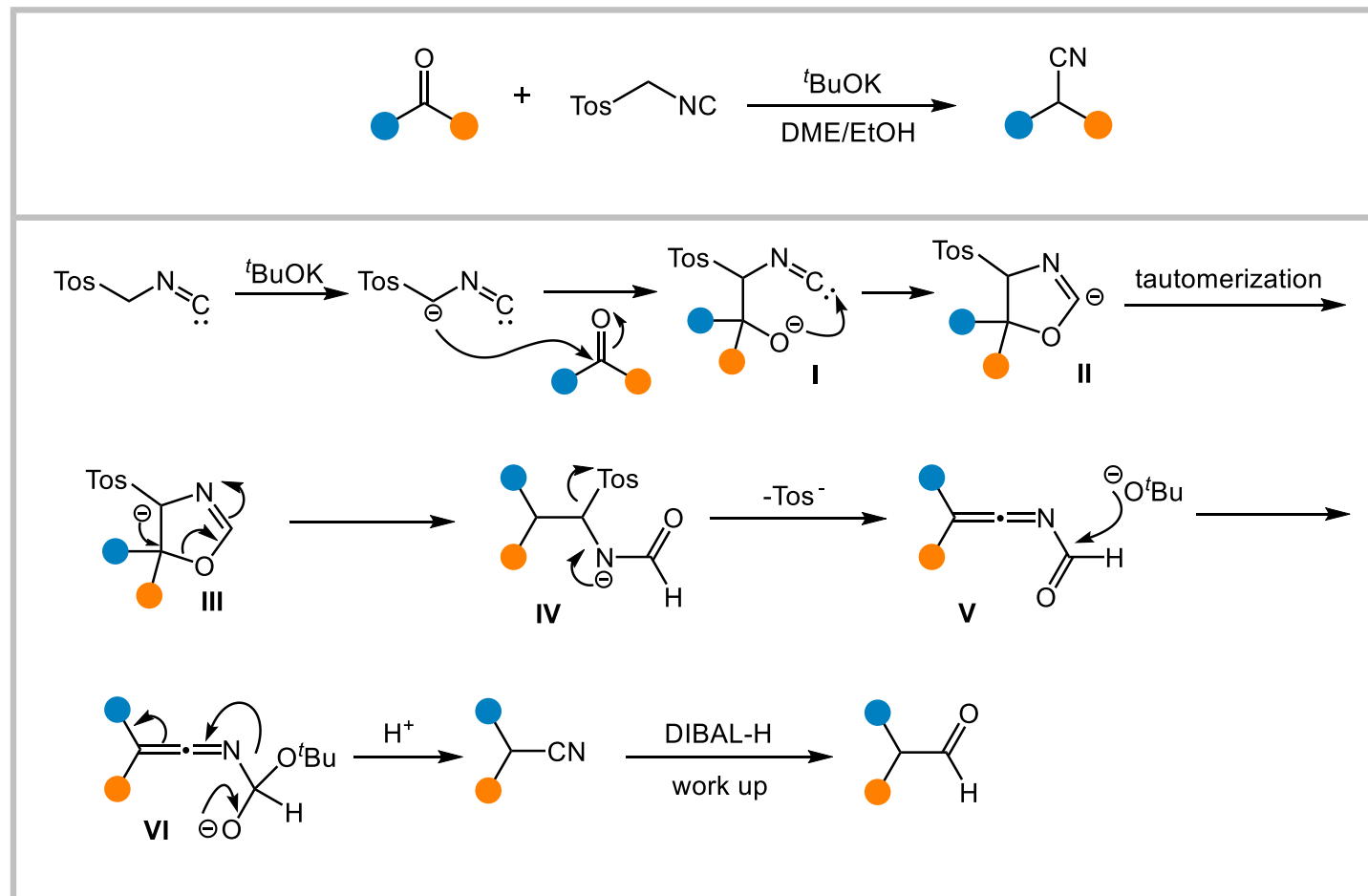
X = OH, **12n**, 70%
X = H, **12n'**, 64%

Nef Reaction



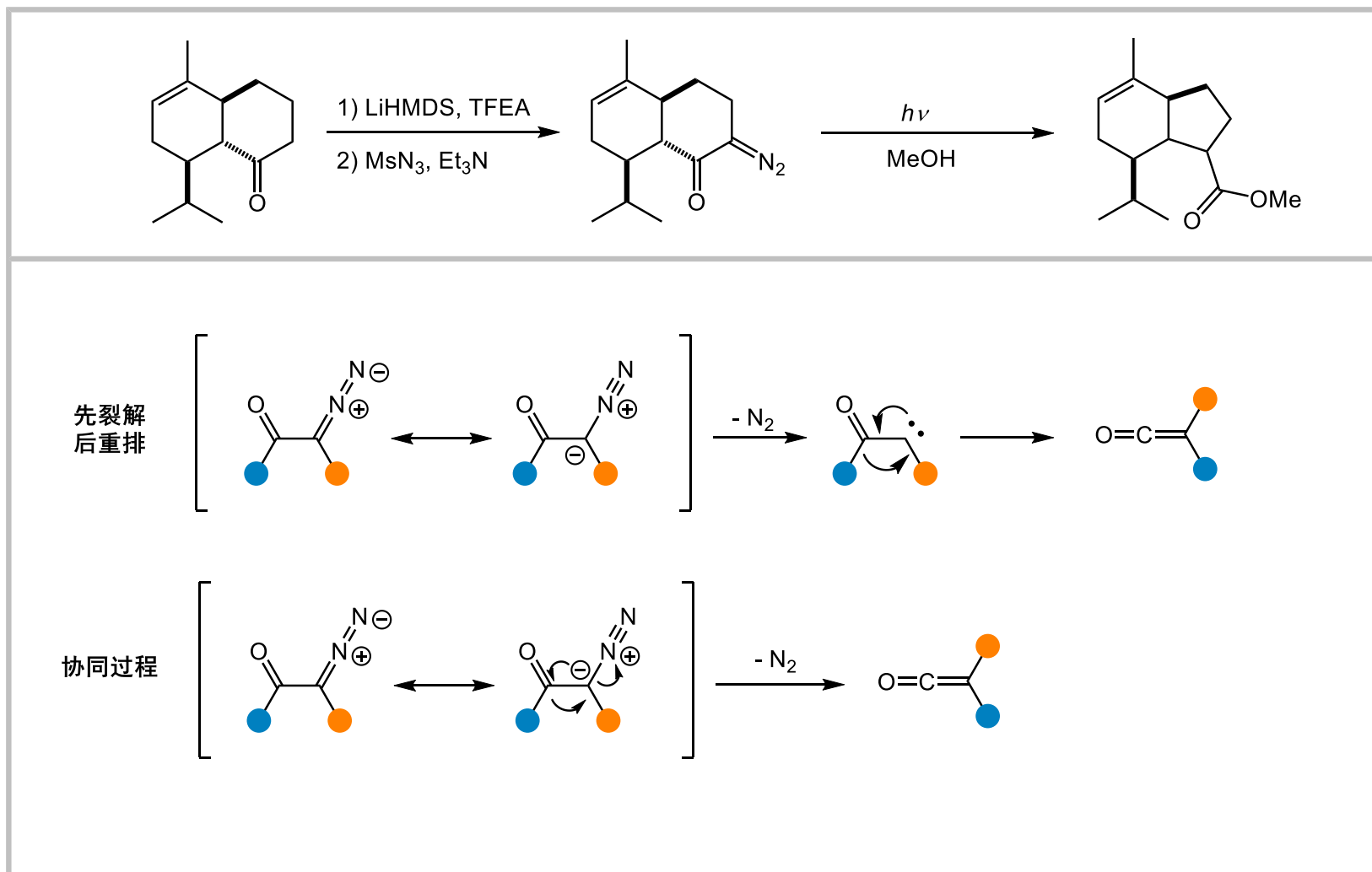
From Name Reaction

Van Leusen Reaction



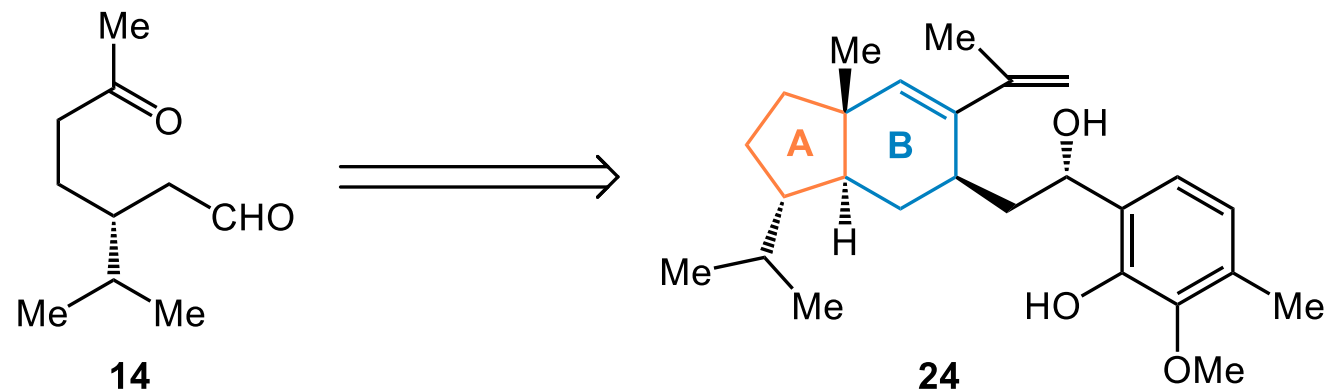
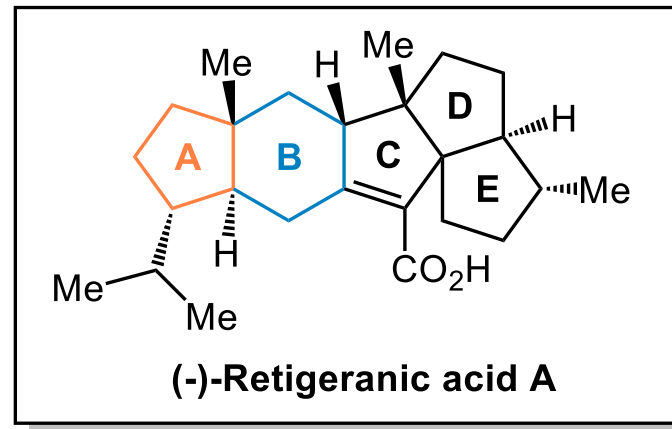
From Name Reaction

Wolff Ring Contraction

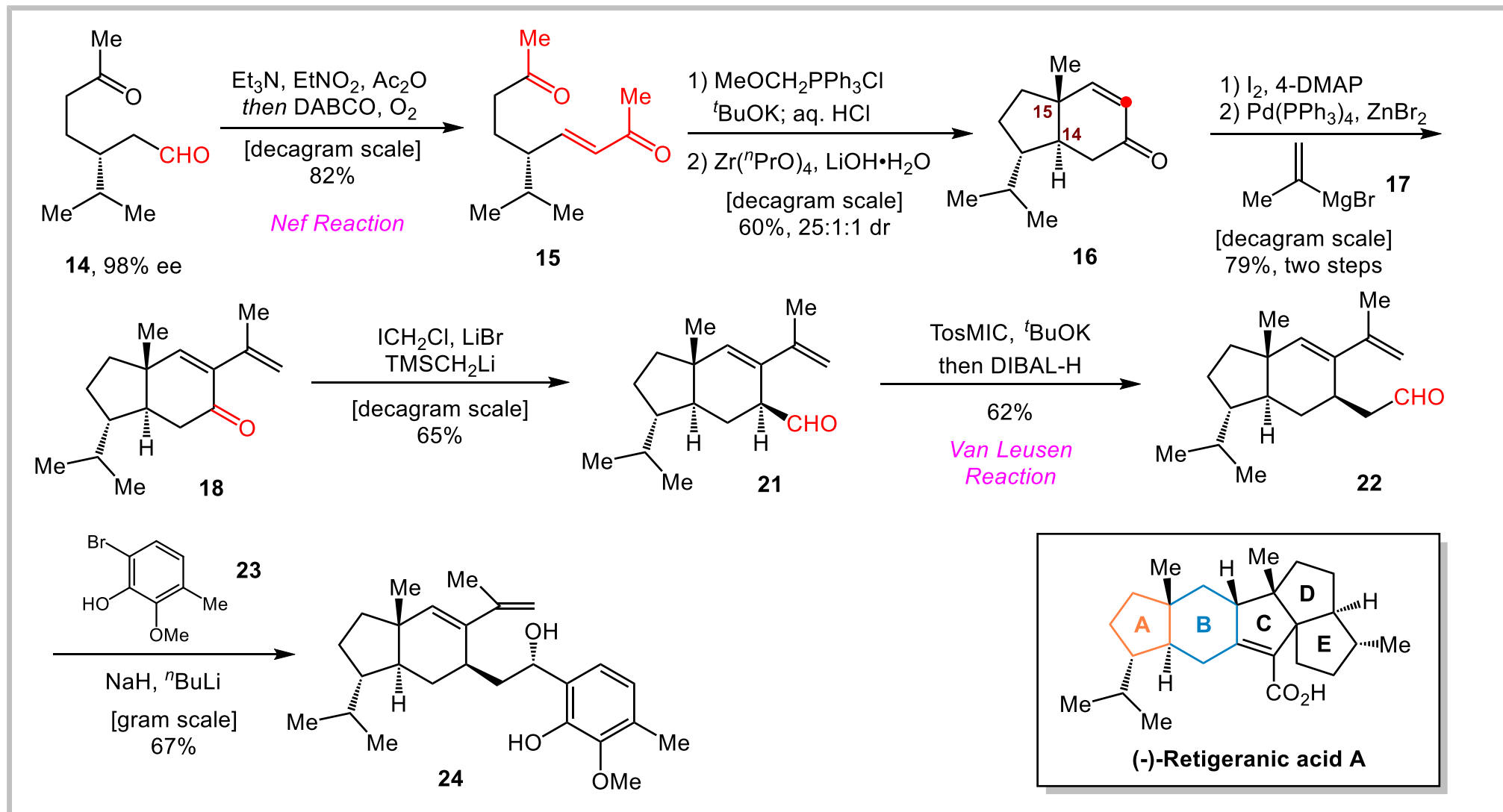


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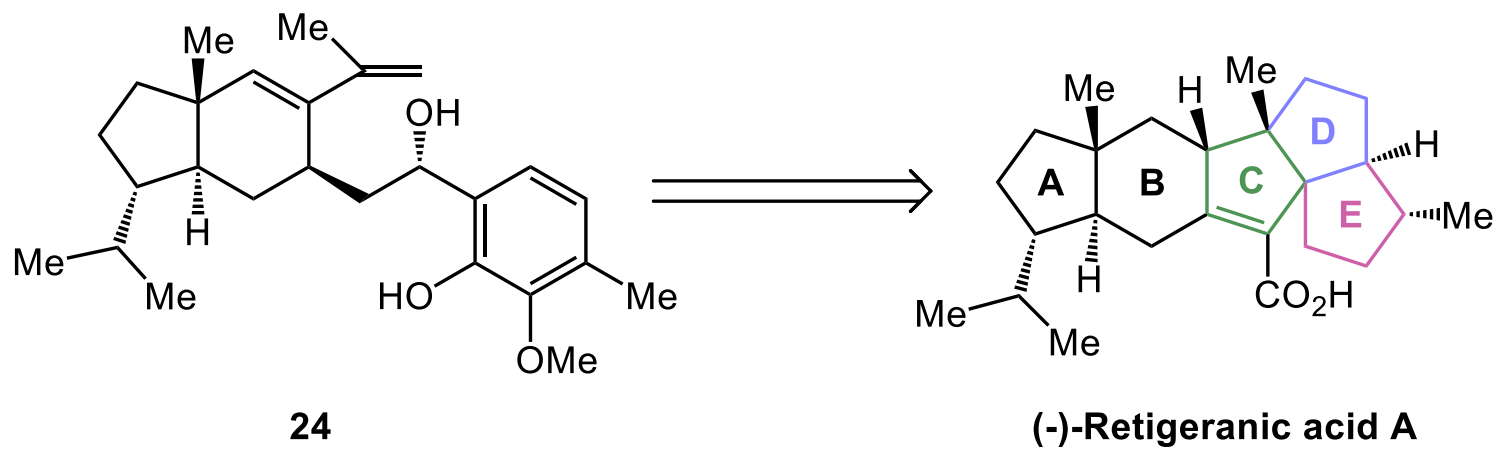
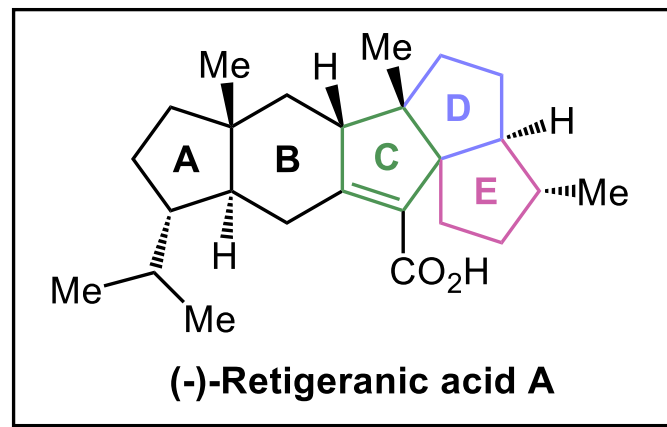
Stage 1



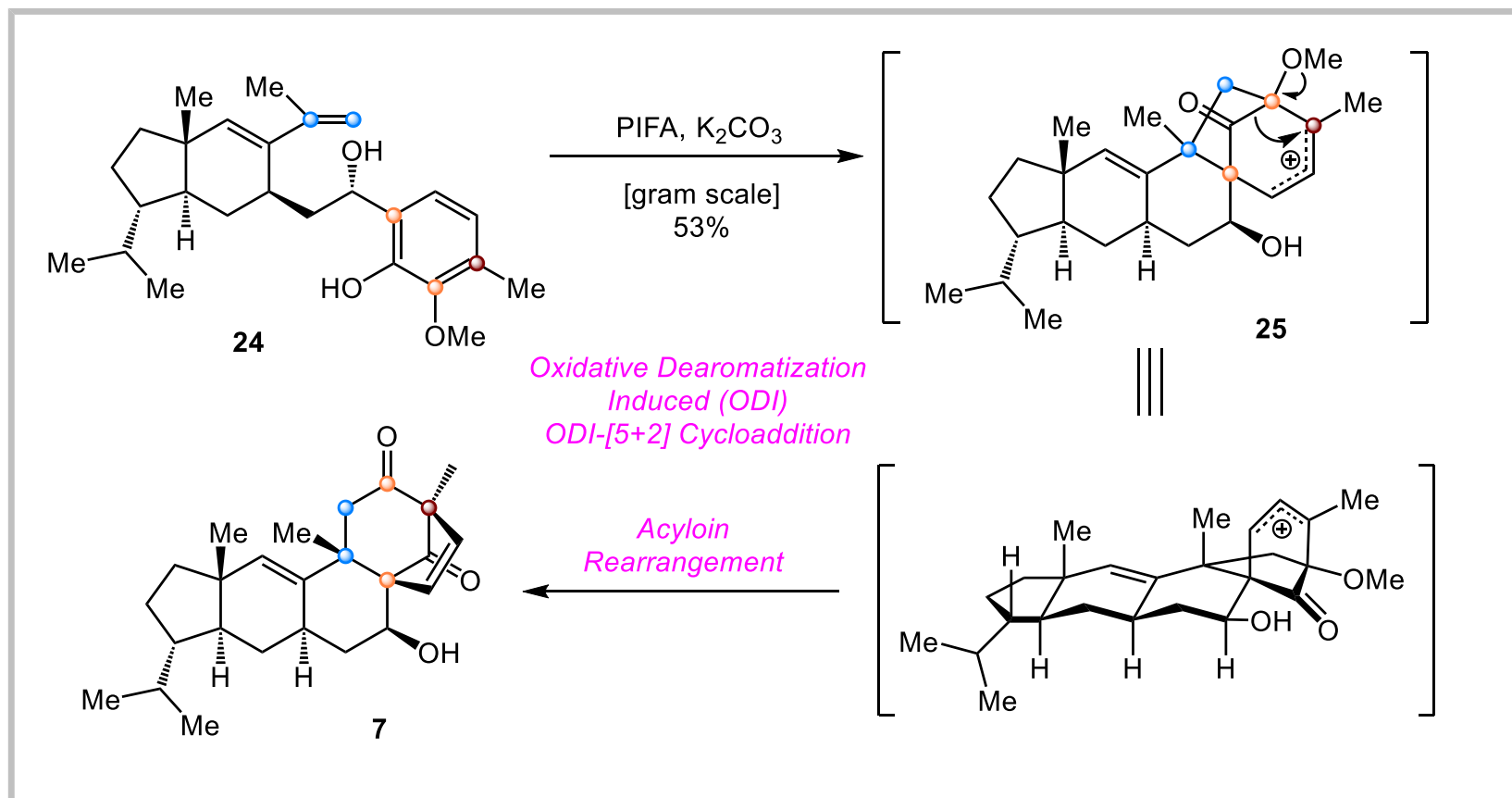
Construction of Ring A and B



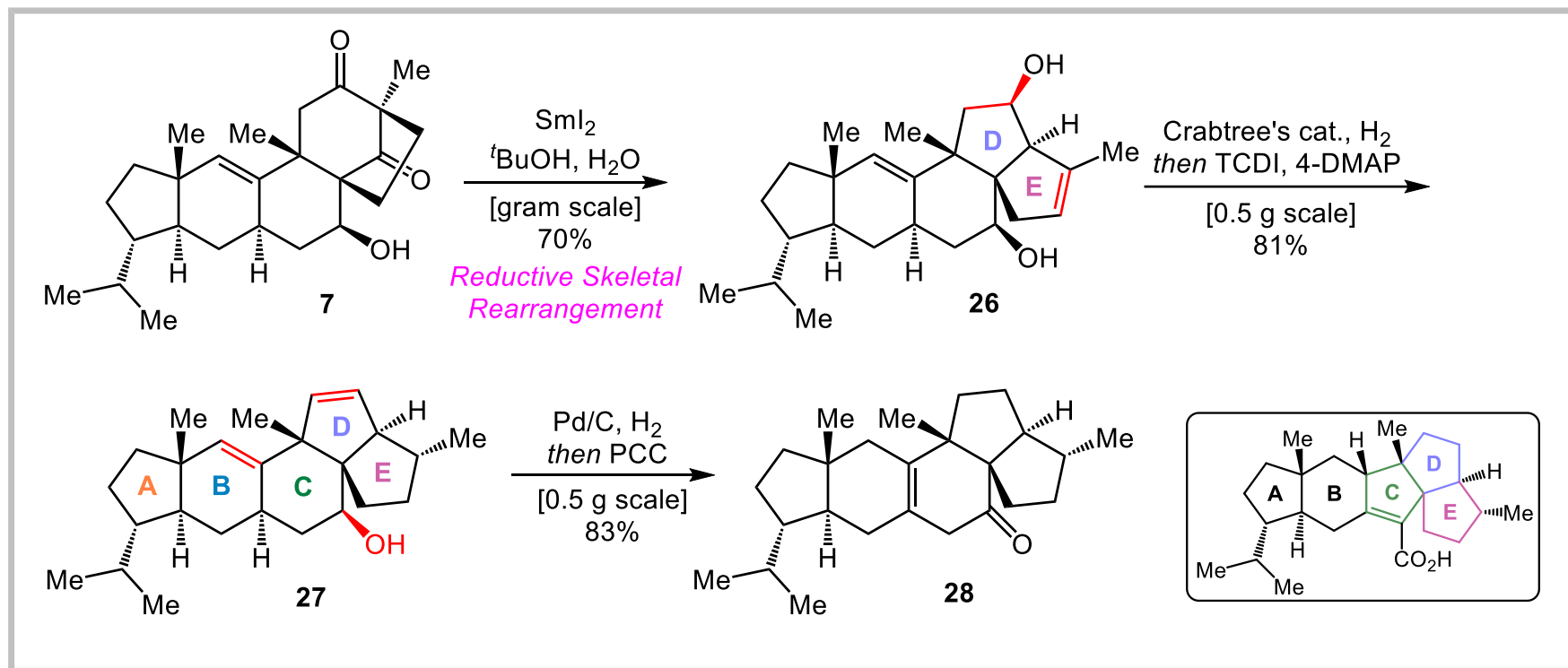
Stage 2



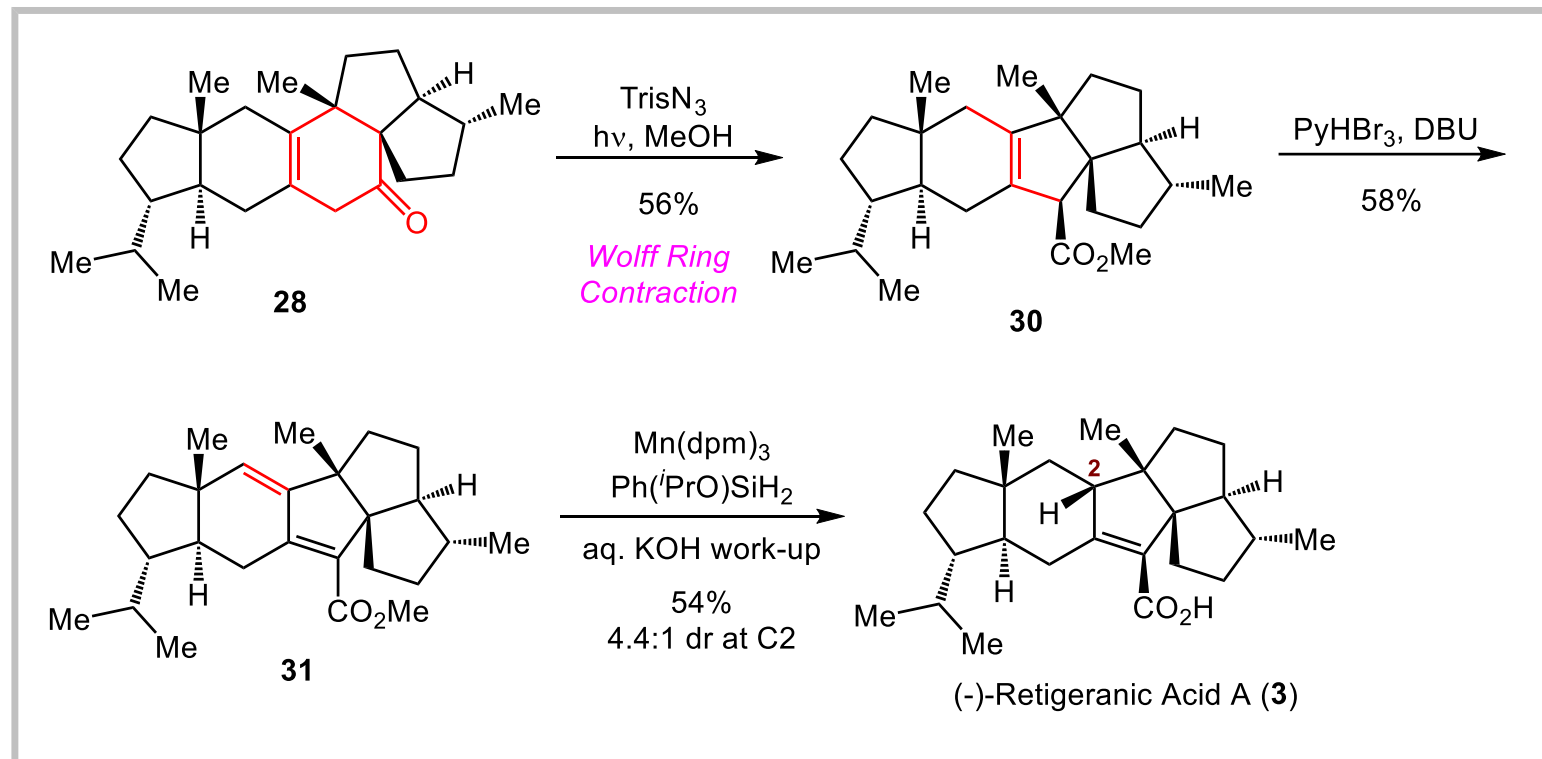
Construction of Angular Triquinane



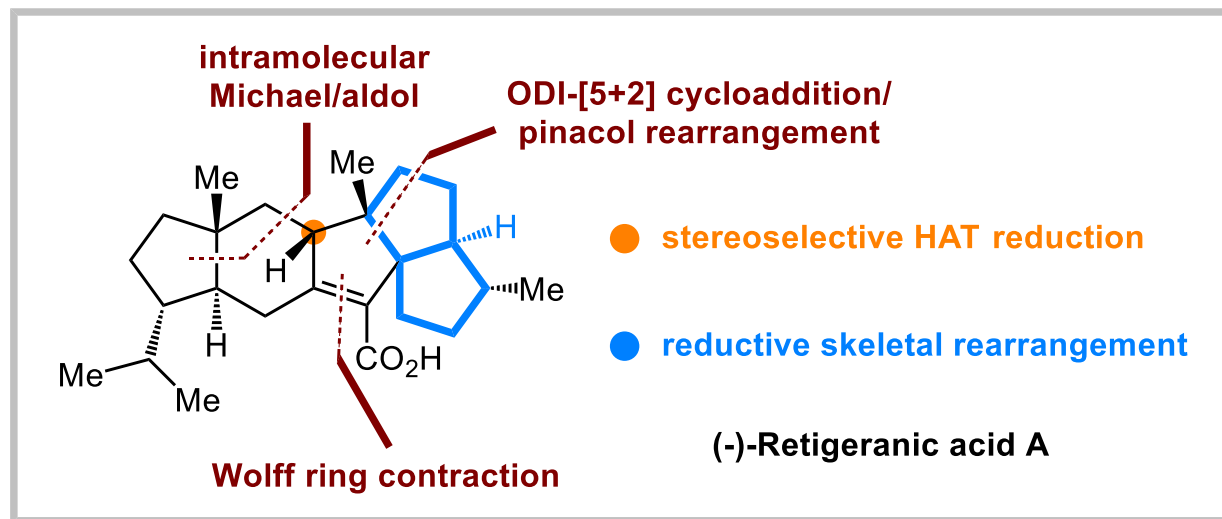
Construction of Angular Triquinane



Construction of Angular Triquinane



Summary



- A reductive skeletal rearrangement for construction of angular triquinane subunits;
- Utilizing cascade reaction to simplify synthetic design;
- A concise total synthesis of (-)-retigeranic acid A: 15 steps, 5.1% overall yield.

Writing Strategy

➤ Introduction

The importance
of Polyquinanes



Our group's efficient
approaches to
angular triquinane
and applications

- ♣ Polyquinanes, consisting of fused five-membered rings in diverse connection patterns, belong to an important class of carbocyclic skeletons prominent in terpenoids and steroids. Besides intriguing biological properties, these molecules continue to attract attention from the synthetic community due to their congested architectures and overall stereochemical complexity, which have stimulated a number of innovative tactics and methodologies toward the construction of the core structures.
- ♣ Over the past few years, we have engaged in a program aiming at developing efficient approaches to angular triquinane natural products. Recently, we accomplished the total syntheses of (-)-crinipellins, which comprise three consecutive all-carbon quaternary centers at the bridgehead positions of BCD rings. However, at least one of these bridgehead stereocenters, especially the one at C6, was found to be tertiary or oxa-quaternary in the vast majority of angular triquinanes, such as (+)-deisopropyltricycloisohumulone, (-)-retigeranic acid A, silphinenes, and bipolarolides.

Writing Strategy

➤ The Last Paragraph

Summary of the
work



Applications,
mechanism and
prospection

- ♣ In conclusion, we have developed an unprecedented reductive skeletal rearrangement cascade for controllable fabrication of diverse angular triquinane subunits. Combined with an intramolecular Michael/aldol cyclization, an ODI-[5+2] cycloaddition/pinacol rearrangement cascade, a Wolff ring contraction and a stereoselective HAT reduction, our approach has facilitated a concise total synthesis of (-)-retigeranic acid A.
- ♣ Given significant simplification in the synthetic design, further application of the described strategies and tactics would open a new avenue for the practical total syntheses of numerous angular triquinane natural products containing a tertiary or oxa-quaternary carbon center at C6. These followup studies are currently underway and will be reported in due course.

Representative Examples

- Herein, we describe our **endeavors** in this field culminating in the concise total synthesis of (-)-**3** based on a reductive skeletal rearrangement strategy that differs significantly from prior approaches. (努力; 奋力, 用于引出自己的工作)
- When **10a** was subjected to $n\text{-Bu}_3\text{SnH/AIBN}$ or low-valent titanium and vanadium reagents, no reaction occurred, implying their **inadequacy** for reduction. (不足; 缺陷; 不够; 不充分, 用于描述相对不好的条件)
- In view of the above outcomes, successive acyloin arrangement was attempted by **scrutinizing a plethora of** Lewis acids. (scrutinizing 仔细查看, 仔细筛选了各种Lewis酸)

Acknowledgement

***Thanks
for your attention***
