

Literature Report V

Asymmetric Total Synthesis of Janthinoid A

Reporter: Yan-Xin Sun

Checker: Sai-Nan Yin

Date: 2025-03-31

Tang, F.; Zhang, Z.-C.*; Song, Z.-L.; Li, Y.-H.; Zhou, Z.-H.; Chen, J.-J.; Yang, Z.*
J. Am. Chem. Soc. **2025**, *147*, 4731

CV of Prof. Zhen Yang (杨震)



Background:

- **1978–1986** B.A., M.S., Shenyang College of Pharmacy
- **1989–1992** Ph.D., The Chinese University of Hong Kong
- **1992–1995** Postdoc., The Scripps Research Institute
- **1995–1998** Assistant Professor, The Scripps Research Institute
- **1998–2001** Institute Fellow, Harvard Medical School
- **2002–Curr.** Professor, Peking University

Research:

- Total Synthesis of Bioactive Natural Products
- Exploring the Thiourea Ligand
- Medicinal Chemistry of Natural Products

Contents

1

Introduction

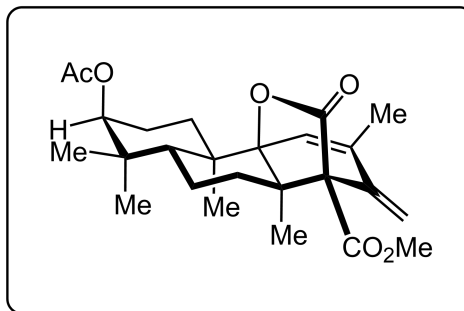
2

Asymmetric Total Synthesis of Janthinoid A

3

Summary

Introduction-Janthinoid A

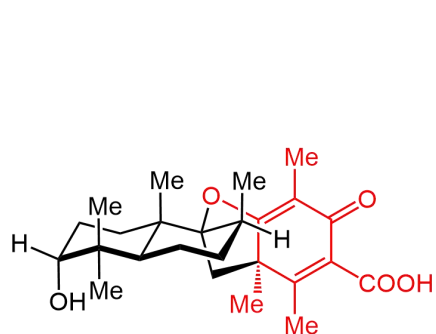


Janthinoid A

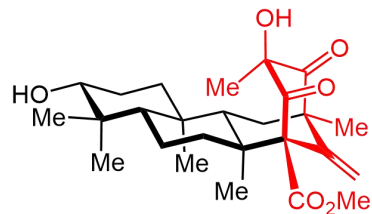
- In 2021, **Janthinoid A** was isolated from the tabacum-derived (烟草衍生的) endophytic fungus (内生真菌) *Penicillium janthinellum* TE-43 (微紫青霉菌) by Zhang and co-workers.
- **Janthinoid A**, characterized by a strained oxabicyclo[3.2.1]octane motif with **four continuous quaternary stereogenic centers** and hallmark embedded rigid lactone, exhibits *in vivo* antitumor activities against NSCLC cells A549.

Li, X.-D.; Su, J.-C.; Jiang, B.-Z.; Li, Y.-L.; Guo, Y.-Q.; Zhang, P. *Org. Chem. Front.* **2021**, 8, 6196

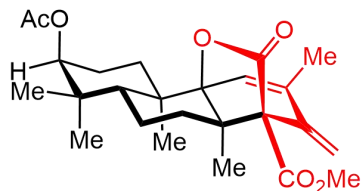
Introduction-Naturally occurring DMOA-derived meroterpenoids



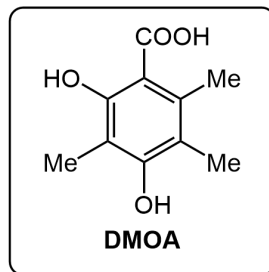
Simplicissin (2)



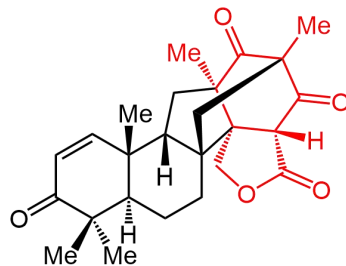
Berkeleyone A (4)



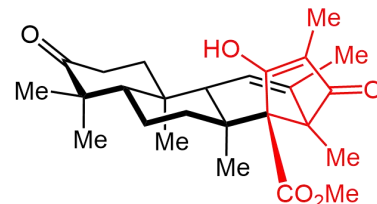
Janthinoid A (1)



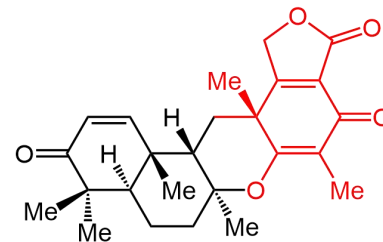
DMOA



Andiconin B (6)

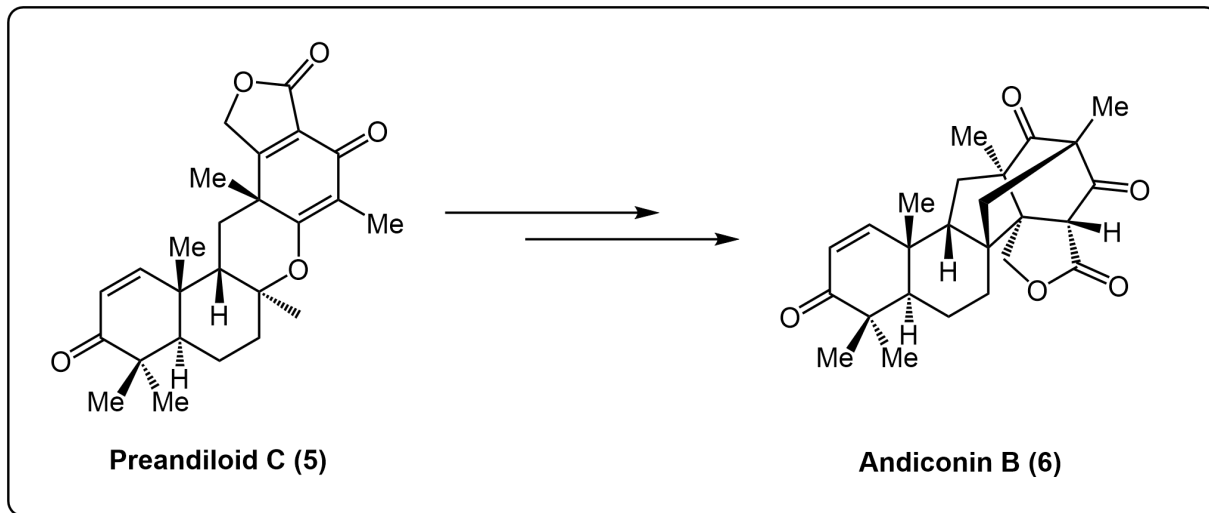


Andrastin D (3)



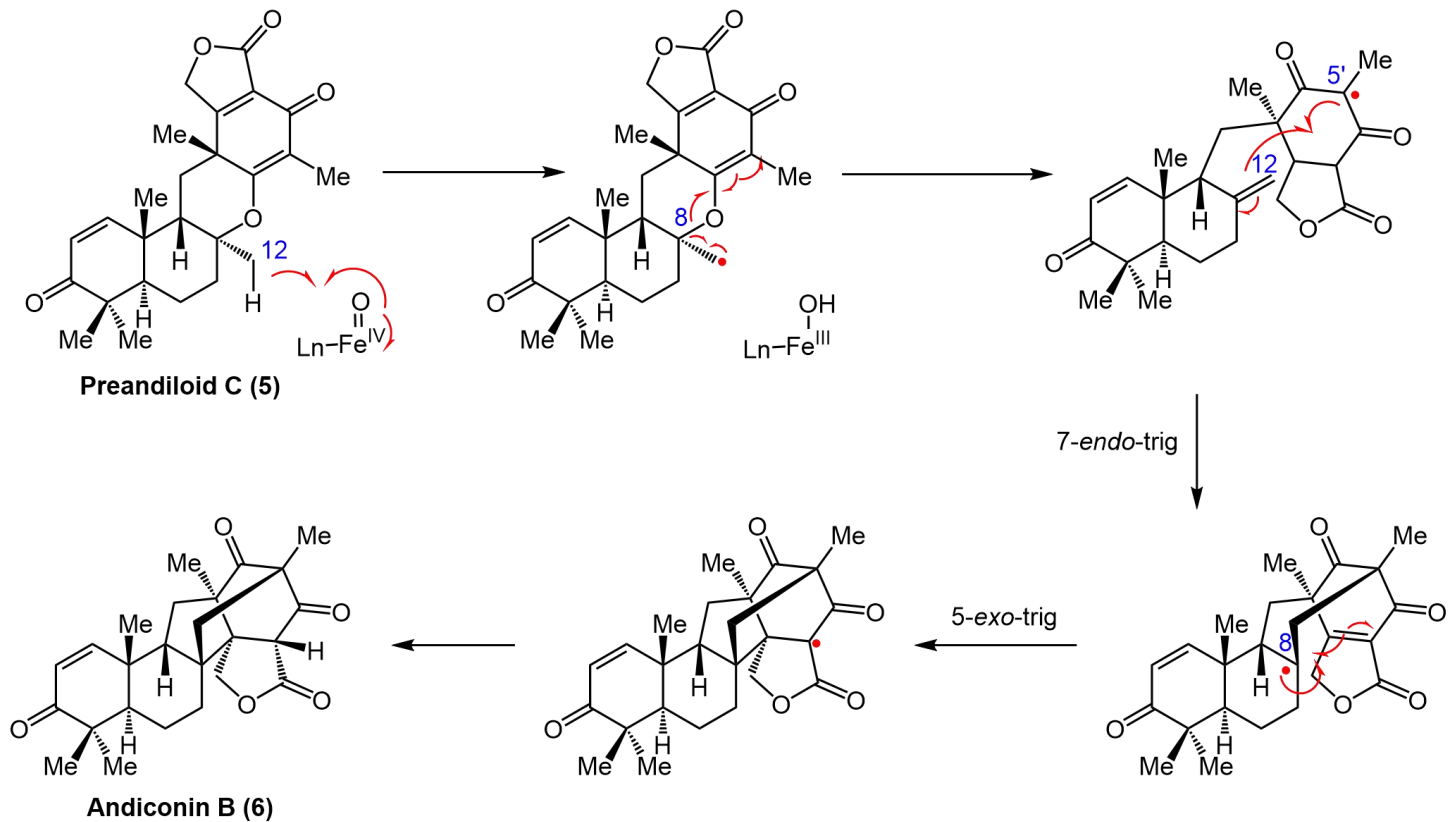
Preandiloid C (5)

Introduction

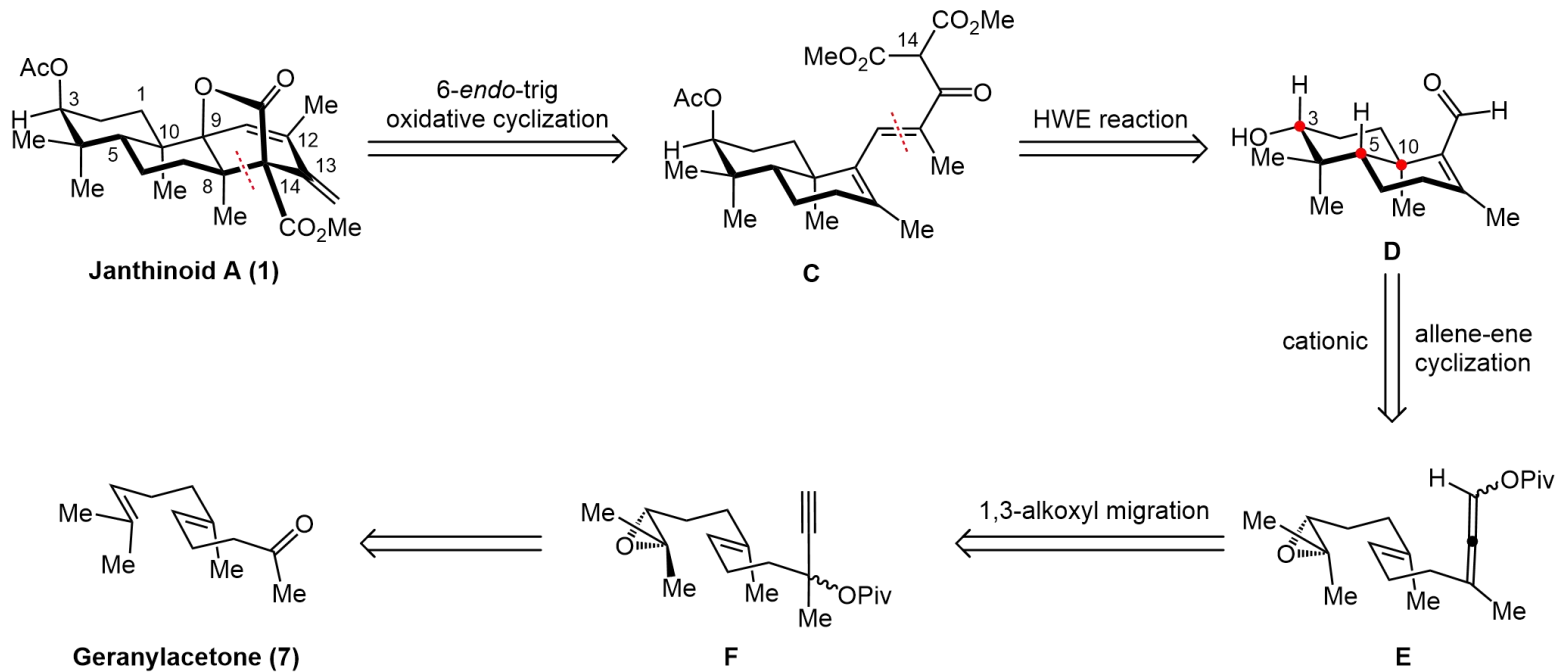


Matsuda, Y.; Wakimoto, T.; Mori, T.; Awakawa, T.; Abe, I. *J. Am. Chem. Soc.* **2014**, *136*, 15326

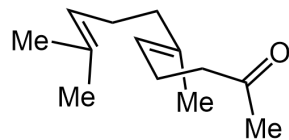
Introduction



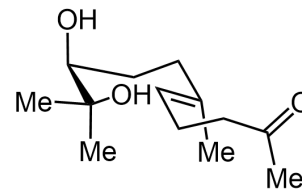
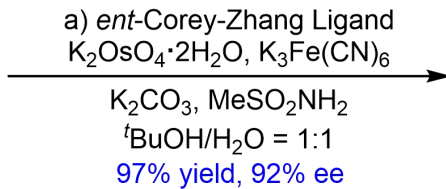
Retrosynthetic Analysis



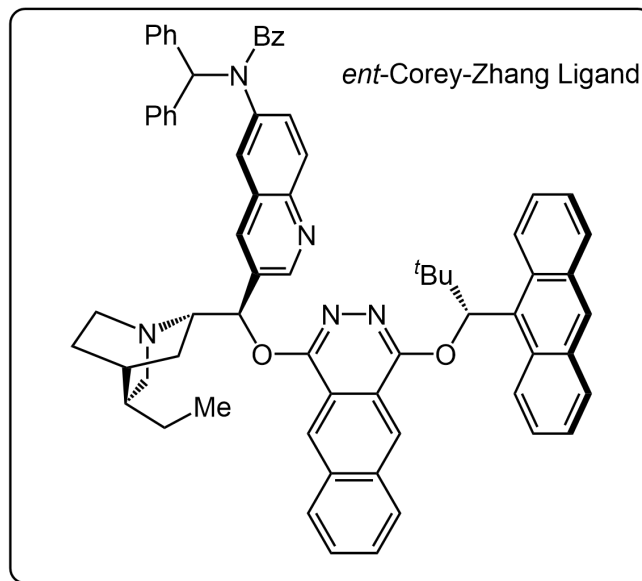
Synthesis of Aldehyde 11



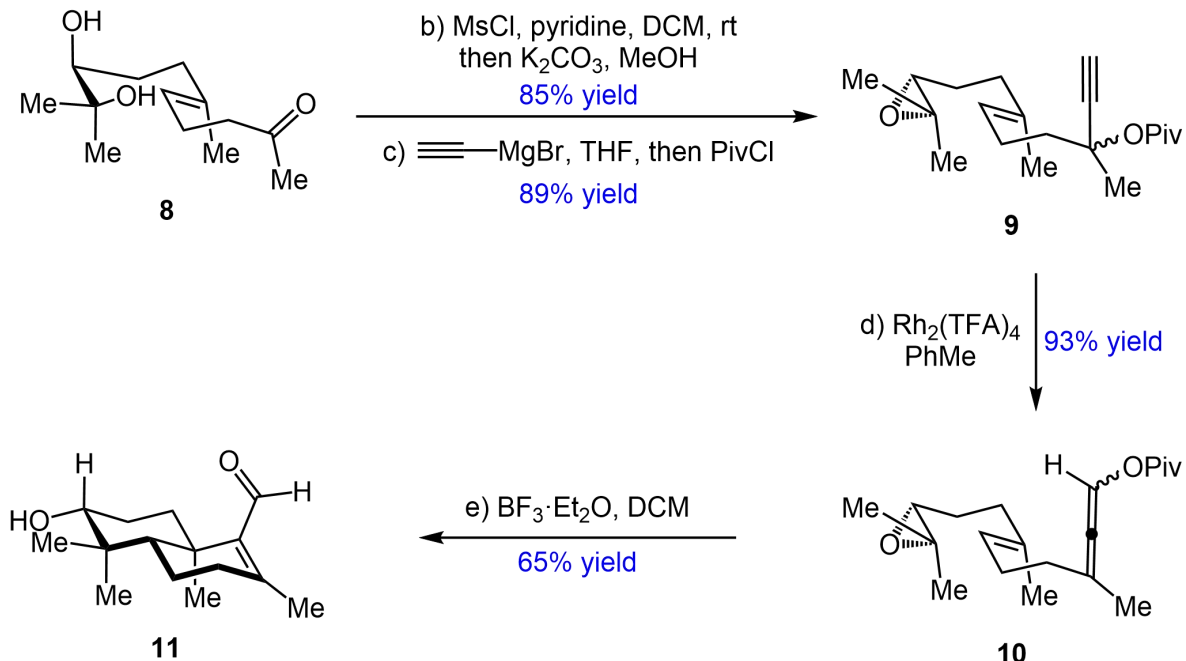
Geranylacetone (7)



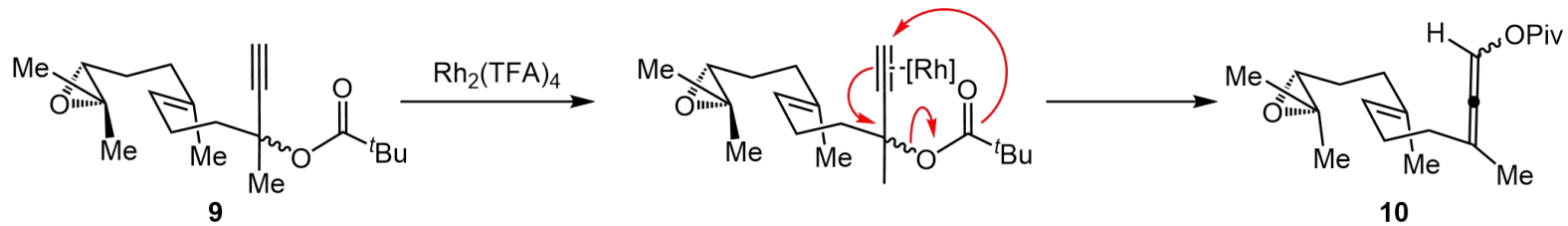
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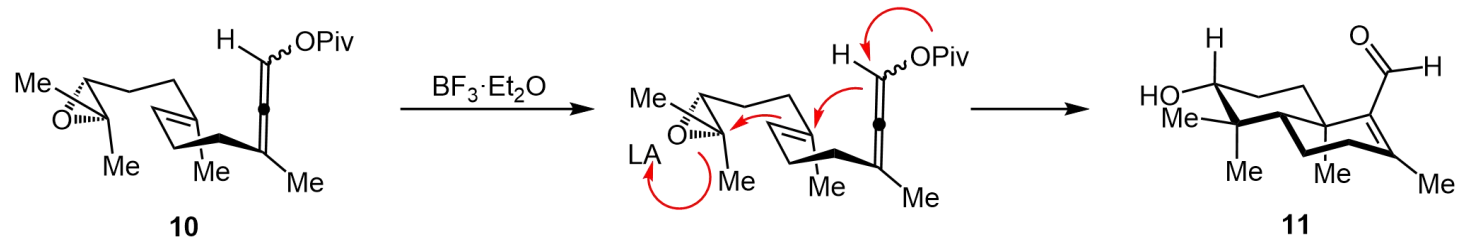
Synthesis of Aldehyde 11



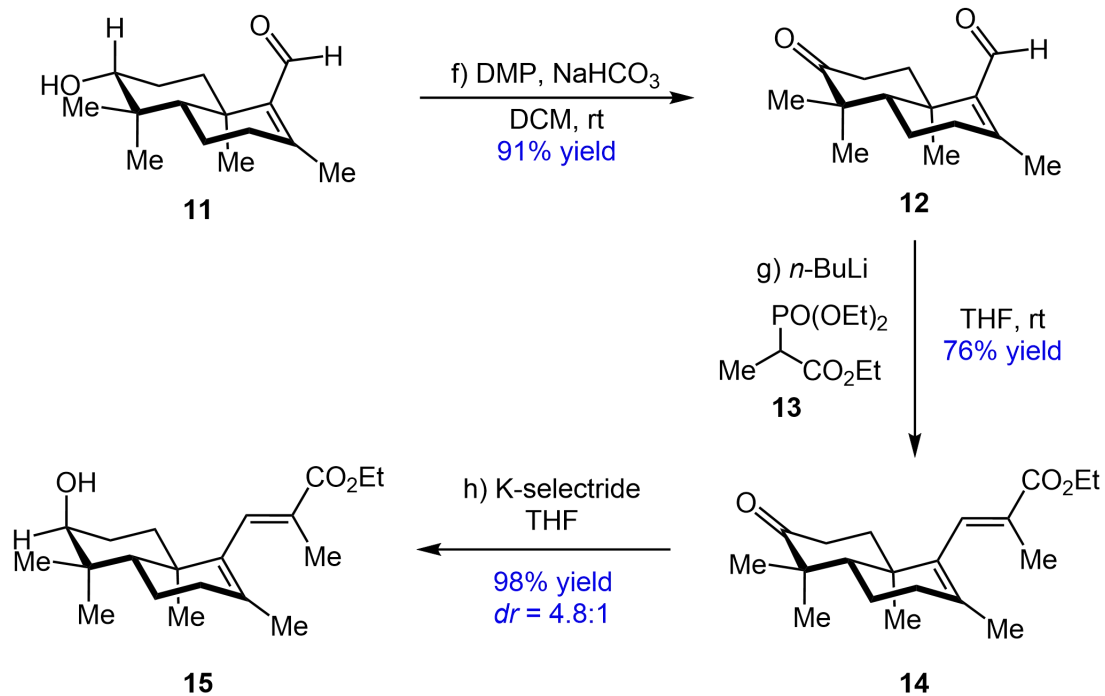
Synthesis of Aldehyde 11



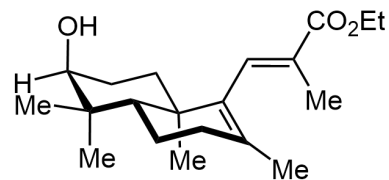
Synthesis of Aldehyde 11



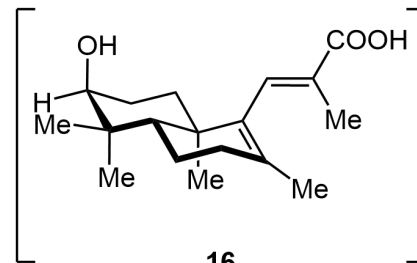
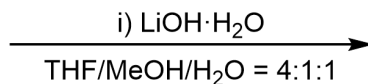
Synthesis of Enol 18



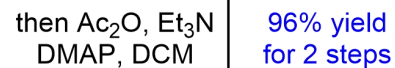
Synthesis of Enol 18



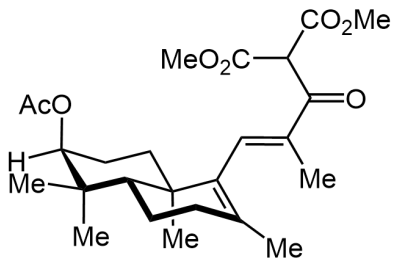
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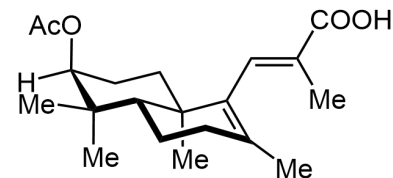
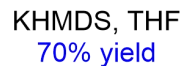
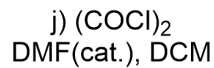
16



96% yield
for 2 steps

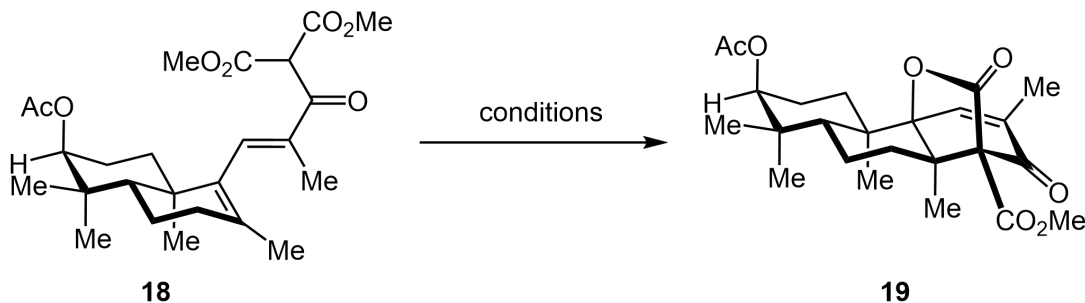


18



17

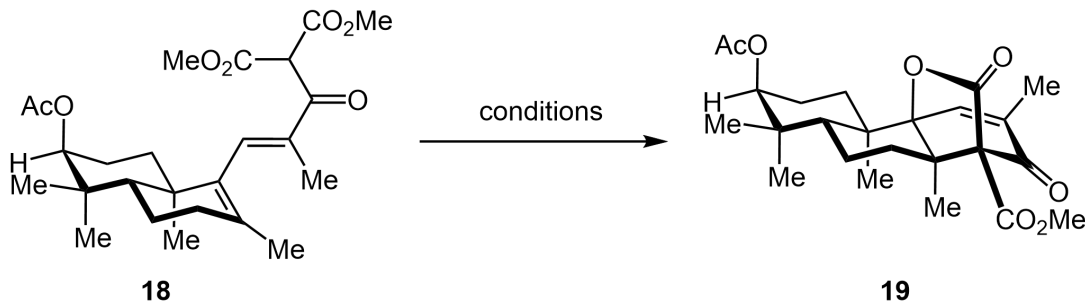
Oxidative Cascade Cyclization of Ketoester **18**



Entry	Conditions	Outcome/Yield
1	Mn(OAc) ₃ ·2H ₂ O (2.2 eq.), Cu(OAc) ₂ (1.0 eq.), AcOH, 25 °C, 1 h	decomposed
2	Mn(OAc) ₃ ·2H ₂ O (2.2 eq.), Cu(OAc) ₂ (1.0 eq.), MeCN, 25 °C to reflux, 18 h	no reaction
3	Mn(OAc) ₃ ·2H ₂ O (2.2 eq.), DCM, 25 °C to reflux, 18 h	no reaction
4	Mn(OAc) ₃ ·2H ₂ O (2.2 eq.), TFA (1.0 eq.), 25 °C, 18 h	20%

Reaction were carried out at 100 mg scale of **18** at a concentration of 0.01 M.

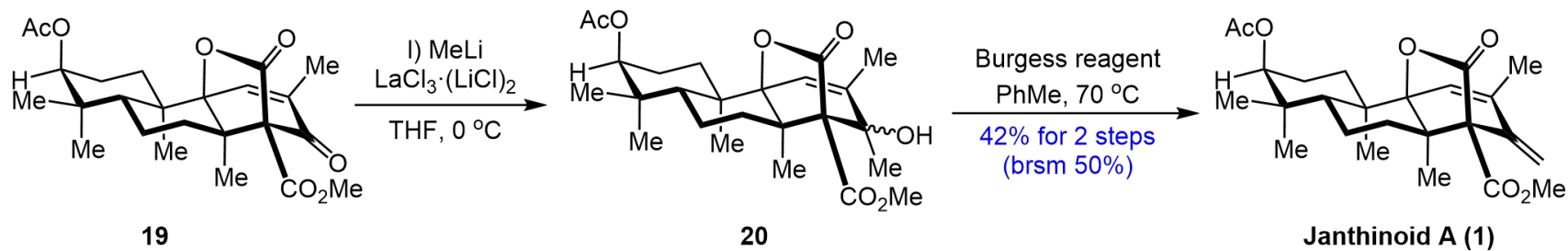
Oxidative Cascade Cyclization of Ketoester 19



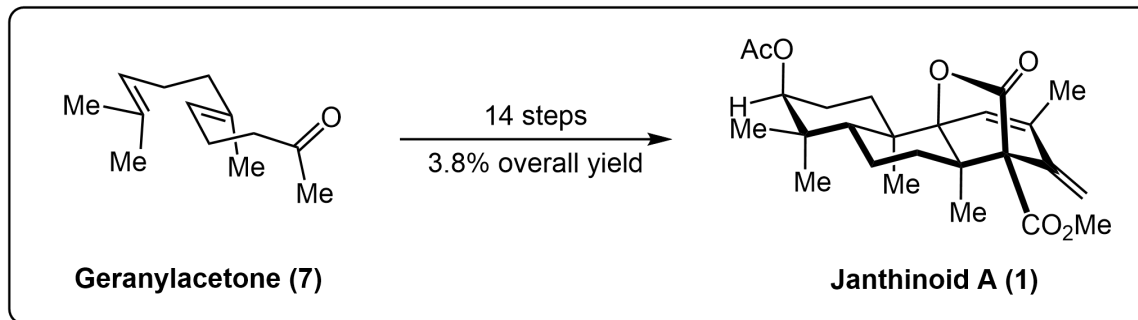
Entry	Conditions	Outcome/Yield
5	Fe(ClO ₄) ₃ ·9H ₂ O (2.2 eq.), MeCN, 25 °C, 18 h	55%
6	Fe(ClO ₄) ₃ ·9H ₂ O (2.2 eq.), MeCN, 0 °C, 18 h	46%
7	Fe(ClO ₄) ₃ ·9H ₂ O (2.2 eq.), MeCN, 50 °C, 18 h	40%
8	Fe(ClO ₄) ₃ ·9H ₂ O (2.2 eq.), DCM, 25 °C, 18 h	no reaction
9	FeCl ₃ ·6H ₂ O (2.2 eq.), MeCN, 25 °C, 18 h	trace
10	Fe(acac) ₃ (2.2 eq.), MeCN, 25 °C, 18 h	no reaction

Reaction were carried out at 100 mg scale of **18** at a concentration of 0.01 M.

Synthesis of Janthinoid A



Summary



- In summary, the asymmetric, protecting-group-free synthesis of **Janthinoid A (1)** is accomplished in 14 steps starting from the commercially available geranylacetone.
- The enabling tandem reactions of **Lewis-acid-mediated cationic-allene-ene cyclization** and **Fe(ClO₄)₃-mediated oxidative annulation** provide novel ways for the synthesis of the *trans*-decalin-based aldehyde **11** and the oxabicyclo[3.2.1]octane core **19** in a regio- and stereoselective manner.

Strategy for Writing The First Paragraph

介绍DMOA衍生化合物



介绍Janthinoid A

- 3,5-Dimethylorsellinic acid (DMOA)-derived meroterpenoids, encompassing over 200 known compounds, have attracted attention due to their structural diversity and intriguing biological activities.....
- In 2021, a novel DMOA-derived tri-*nor*-meroterpenoid Janthinoid A was isolated from the tabacum-derived endophytic fungus *Penicillium janthinellum* TE-43 by Zhang and co-workers. Janthinoid A, characterized by a strained oxabicyclo[3.2.1]octane motif with four continuous quaternary stereogenic centers and hallmark embedded rigid lactone, exhibits *in vivo* antitumor activities against NSCLC cells A549.....

Strategy for Writing The Last Paragraph

总结工作



强调亮点



提出展望

- In summary, the asymmetric, protecting-group-free synthesis of janthinoid A is accomplished for the first time in 14 steps starting from the commercially available geranylacetone.
- The enabling tandem reactions of Lewis-acid-mediated cationic-allene-ene cyclization and $\text{Fe}(\text{ClO}_4)_3$ -mediated oxidative annulation provide novel ways for the synthesis of the *trans*-decalin-based aldehyde 11 and the oxabicyclo[3.2.1]-octane core 19 in a regio- and stereoselective manner.
- Application of the developed chemistry for the synthesis of other types of complex natural products is currently underway in our laboratories and will be reported in due course.

Representative Examples

- 3,5-Dimethylorsellinic acid-derived meroterpenoids, **encompassing** over 200 known compounds, have attracted attention due to their structural diversity and intriguing biological activities. (**encompass**, v. 包含, 包括; 围绕, 包围; 促成, 实现)
- Retrosynthetically, we **envisaged** that the oxabicyclo[3.2.1]octane core of compound **1** could be constructed from ketoester C *via* a sequence of oxidation, double bond isomerization, 6-endo-trig radical cyclization, and intramolecular oxidative lactonization. (**envisage**, v. 设想, 面对, 正视)
- **With an efficient and scalable route** to aldehyde **11**, we started to explore the preparation of ketoester **18**. (**with an efficient and scalable route** 通过有效且可放大的路线)

Acknowledgement

Thanks for Your Attention