# Literature Report VIII

## Total Synthesis of Acoapetaludine A Enabled by a Rhodium-Catalyzed Domino Cyclization

**Reporter:** Yan-Xin Sun
**Checker:** Xin-Yu Zhan
**Date:** 2026-01-19

Zhang, Y.; Wang, L.; Lei, X,; Jia, Y.* *J. Am. Chem. Soc.* **2025**, *147*, 47904–47910

# CV of Prof. Yan-Xing Jia

***Research:***

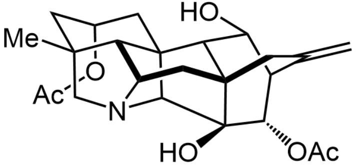
- Total Synthesis and Biomimetic Synthesis of Natural Products
- Drug Synthesis and Structure-Activity Relationship Studies
- New Methods for Organic Synthesis
- Discovery of Small Molecule Probes

***Background:***

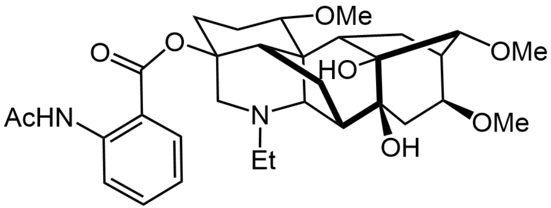
- **1997-2002** Ph.D., Lanzhou University (Prof. Yong-Qiang Tu)
- **2002-2007** Postdoc., Centre National de la Recherche Scientifique (Prof. Jie-Ping Zhu)
- **2007-2011** Associate Professor, Peking University, School of Pharmaceutical Sciences
- **2011- now** Professor, Peking University, School of Pharmaceutical Sciences

# Contents

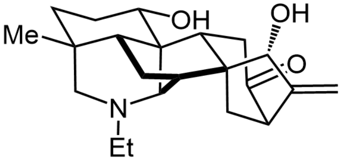
# Introduction-Bioactive Diterpenoid Alkaloids



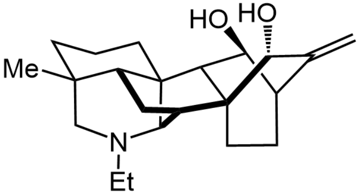
Guan-fu Base A
(anti-arrhythmia drug)



Lappaconitine
(non-narcotic analgesic drug)



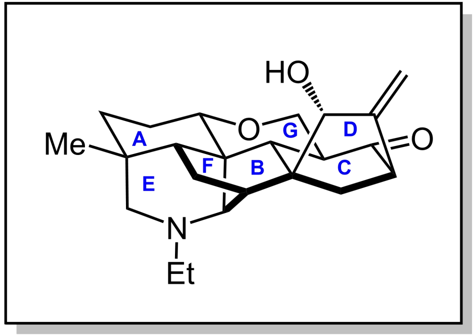
Songorine
(anti-cancer)



Bullatine A
(anti-inflammatory)

Wang, F.-P.; Chen, Q.-H.; Liu, X.-Y. *Nat. Prod. Rep.* **2010**, *27*, 529.

# Introduction-Acoapetaludine A



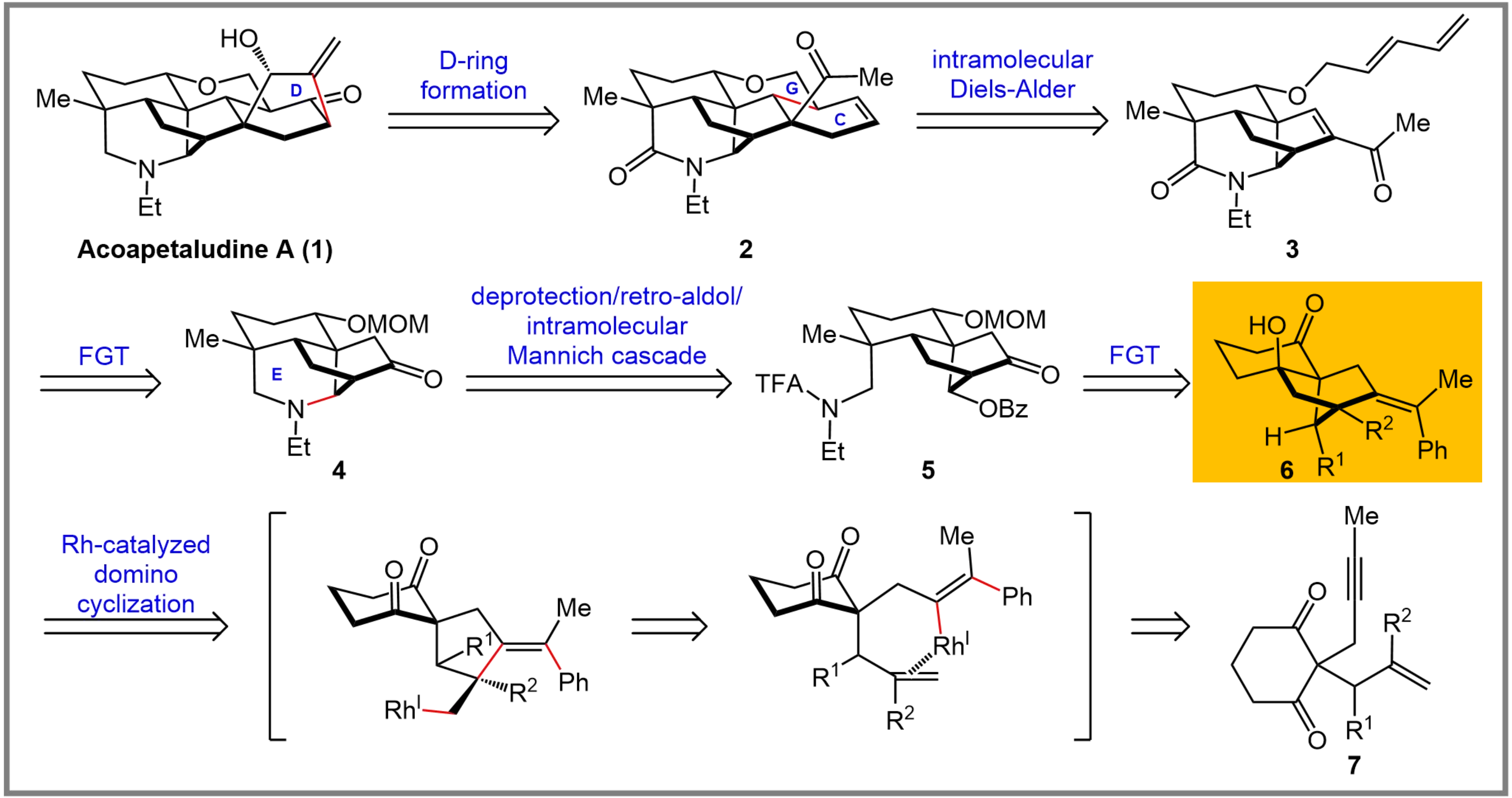
**Acoapetaludine A**

***Aconitum apetalum***

- **Acoapetaludine A** was isolated from *Aconitum apetalum* in 2019.
- **Acoapetaludine A** bears a caged-like 6/6/6/5/6/5/6 heptacyclic system with 11 stereocenters including three quaternary carbon centers.
- **Acoapetaludine A** features an additional ether ring (G-ring) integrated within the entire polycyclic bridged skeleton.

Hu, Z.-X.; An, Q.; Tang, H.-Y.; Zhang, Y.; Hao, X.-J. *Phytochemistry* **2019**, *167*, 112111.

# Retrosynthetic Analysis



Acoapetaludine A (1)

D-ring formation

2

intramolecular Diels-Alder

3

FGT

4

deprotection/retro-aldol/ intramolecular Mannich cascade

5

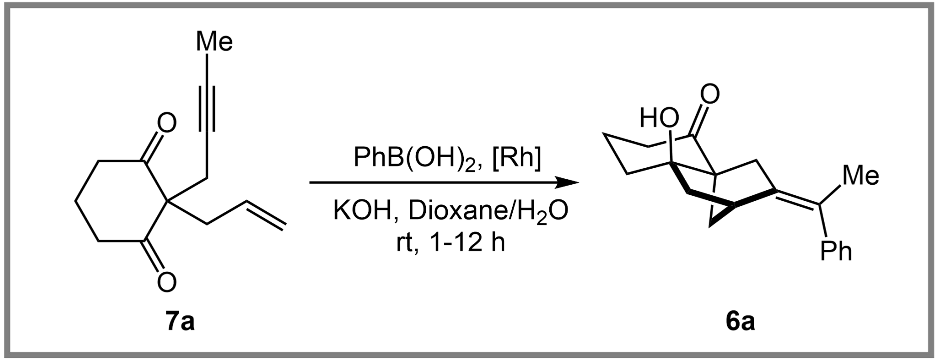
FGT

6

Rh-catalyzed domino cyclization

7

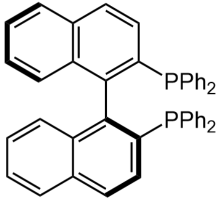
# Optimization of Reaction Conditions



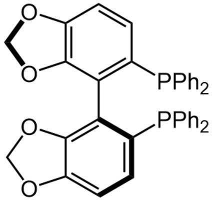
| Entry | Conditions | Yield (%)$^b$ | Ee (%)$^c$ |
|---|---|---|---|
| 1 | [Rh(cod)OH]$_2$, rt, 4 h | 64 | -- |
| 2 | [Rh(cod)Cl]$_2$, rt, 4 h | 61 | -- |
| 3 | [Rh($C_2H_4$)Cl]$_2$, rt, 4 h | -- | -- |

[a] Reaction conditions: **7a** (0.25 mmol), ligand (0.15 equiv), metal (0.05 equiv), phenylboronic acid (3.0 equiv), KOH (0.5 equiv), dioxane (5 mL) and $H_2O$ (0.5 mL). [b] Isolated yield. [c] The *ee* values determined by chiral HPLC analysis.

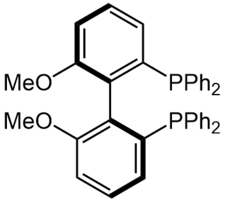
# Optimization of Reaction Conditions



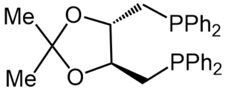
**(*S*)-L1**



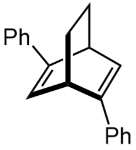
**(*S*)-L2**



**(*S*)-L3**



**(*S*)-L4**

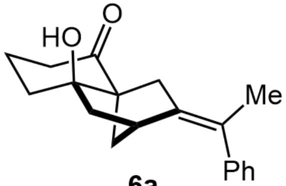


**(*S*)-L5**

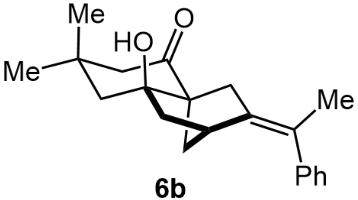
| Entry | Conditions | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|
| 1 | [Rh(cod)OH]$_2$, **L1**, rt, 4 h | -- | -- |
| 2 | [Rh(cod)OH]$_2$, **L1**, 100 °C, 1 h | 42 | 95 |
| 3 | [Rh($C_2H_4$)Cl]$_2$, **L1**, 100 °C, 1 h | 46 | 96 |
| 4 | [Rh($C_2H_4$)Cl]$_2$, **L1**, 50 °C, 8 h | 61 | 98 |
| 5 | [Rh($C_2H_4$)Cl]$_2$, **L2**, 50 °C, 8 h | 38 | 99 |
| 6 | [Rh($C_2H_4$)Cl]$_2$, **L3**, 50 °C, 8 h | 24 | 99 |
| 7 | [Rh($C_2H_4$)Cl]$_2$, **L4**, 50 °C, 8 h | -- | -- |
| 8 | [Rh($C_2H_4$)Cl]$_2$, **L5**, rt, 1 h | 80 | 99 |

[a] Reaction conditions: **7a** (0.25 mmol), ligand (0.15 equiv), metal (0.05 equiv), phenylboronic acid (3.0 equiv), KOH (0.5 equiv), dioxane (5 mL) and $H_2O$ (0.5 mL). [b] Isolated yield. [c] The *ee* values determined by chiral HPLC analysis.

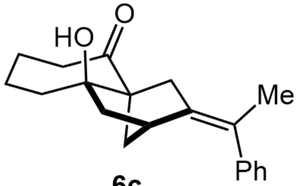
# Substrate Scope



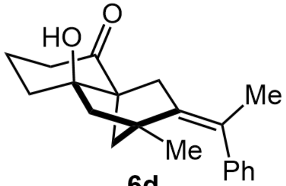
**6a**
80%, 99% ee



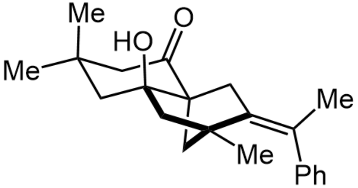
**6b**
75%, 99% ee



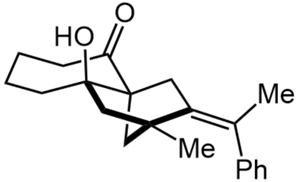
**6c**
77%, 99% ee



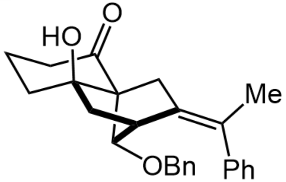
**6d**
83%, 45% ee



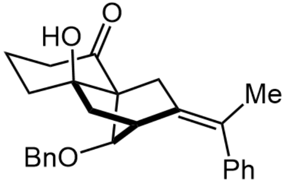
**6e**
91%, 61% ee



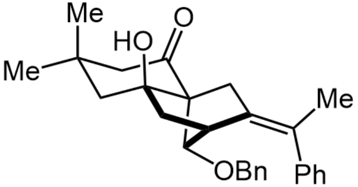
**6f**
81%, 99% ee



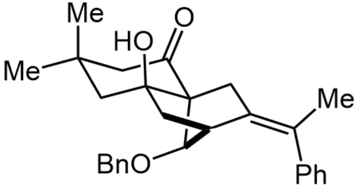
**6g**
46%, 62% ee



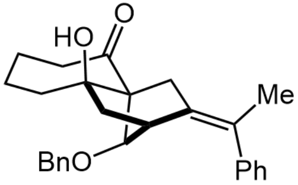
**6h**
20%, 99% ee



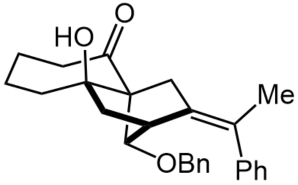
**6i**
53%, 71% ee



**6i**
21%, 97% ee

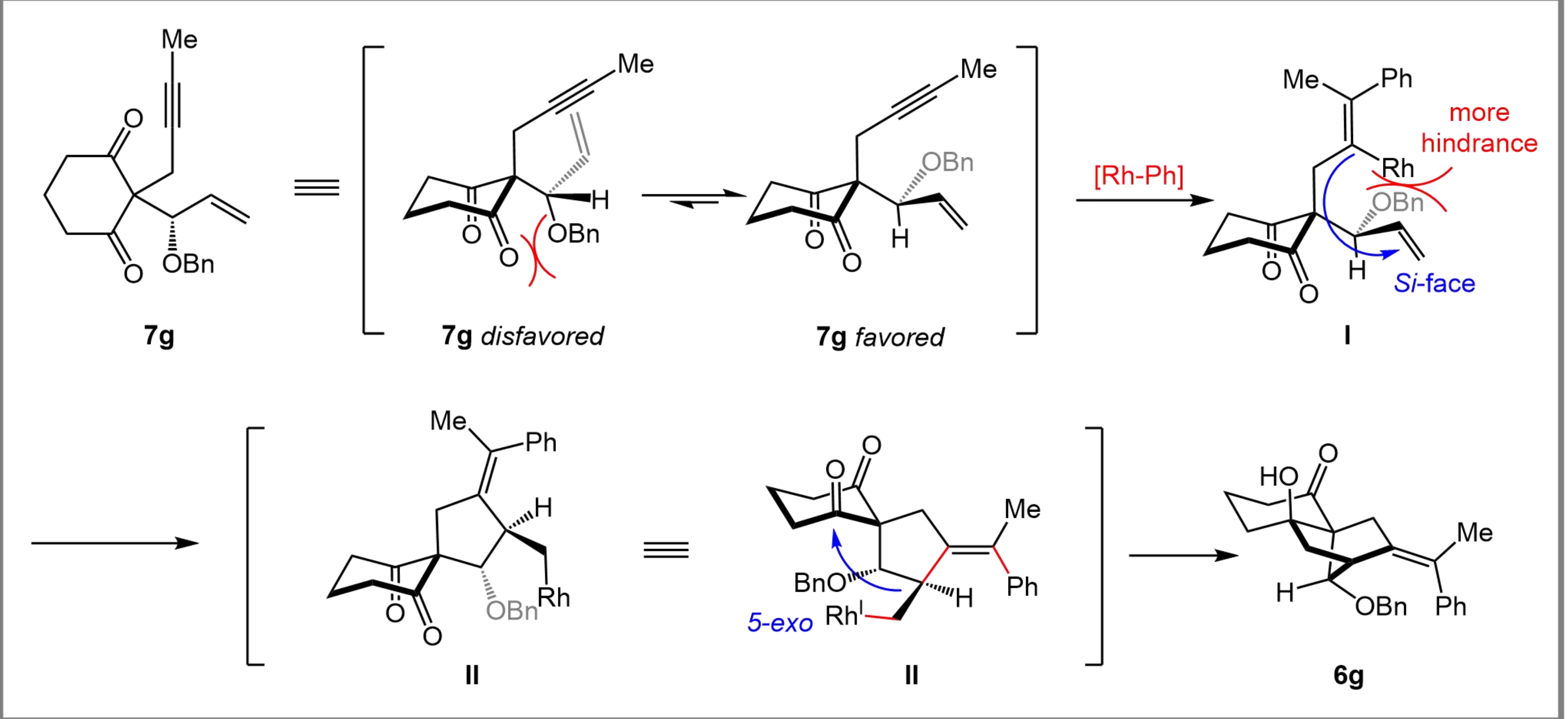


**6k**
43%, 88% ee

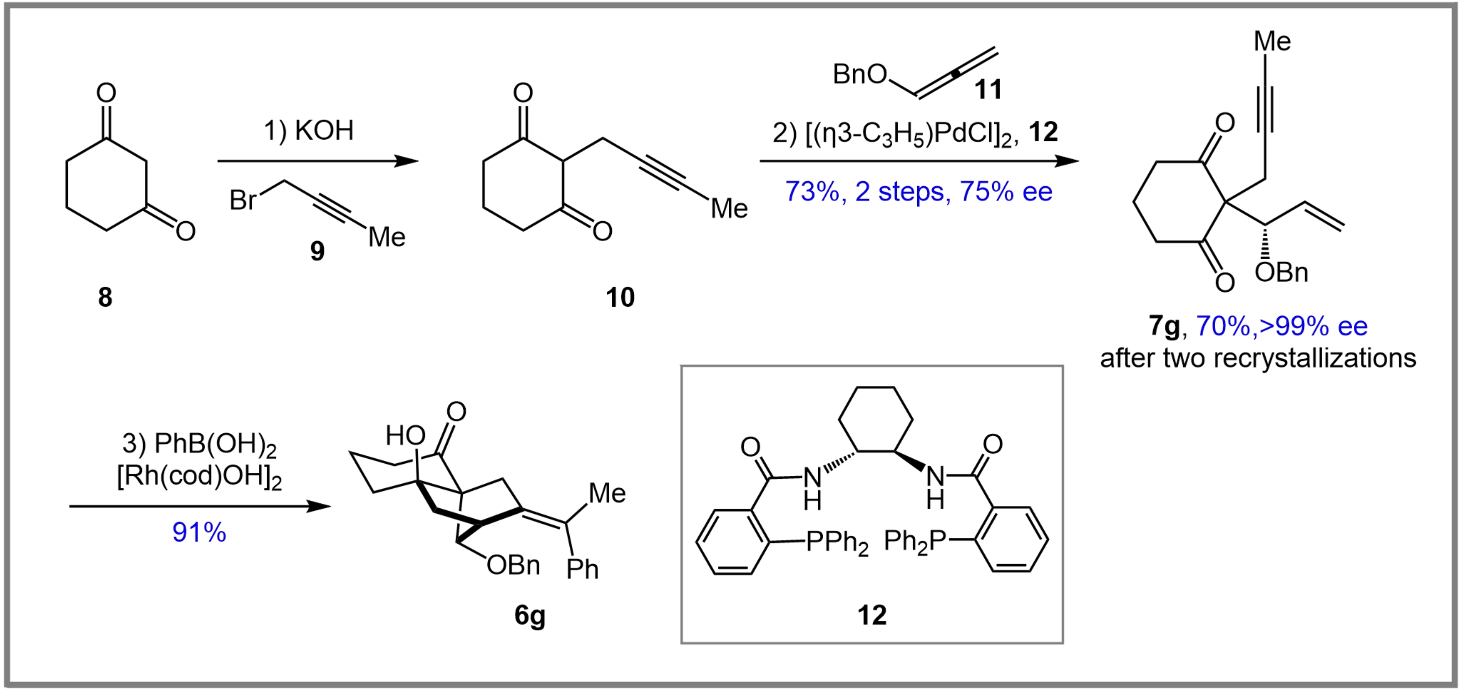


**6l**
35%, 98% ee

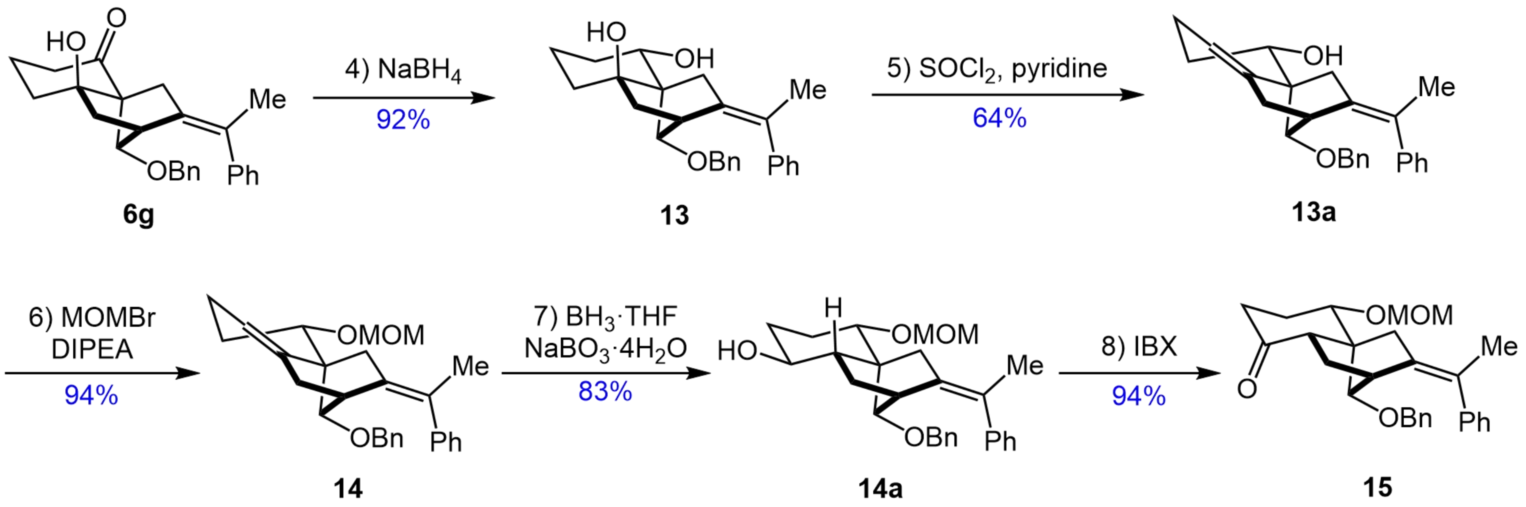
# Proposed Mechanistic Pathway



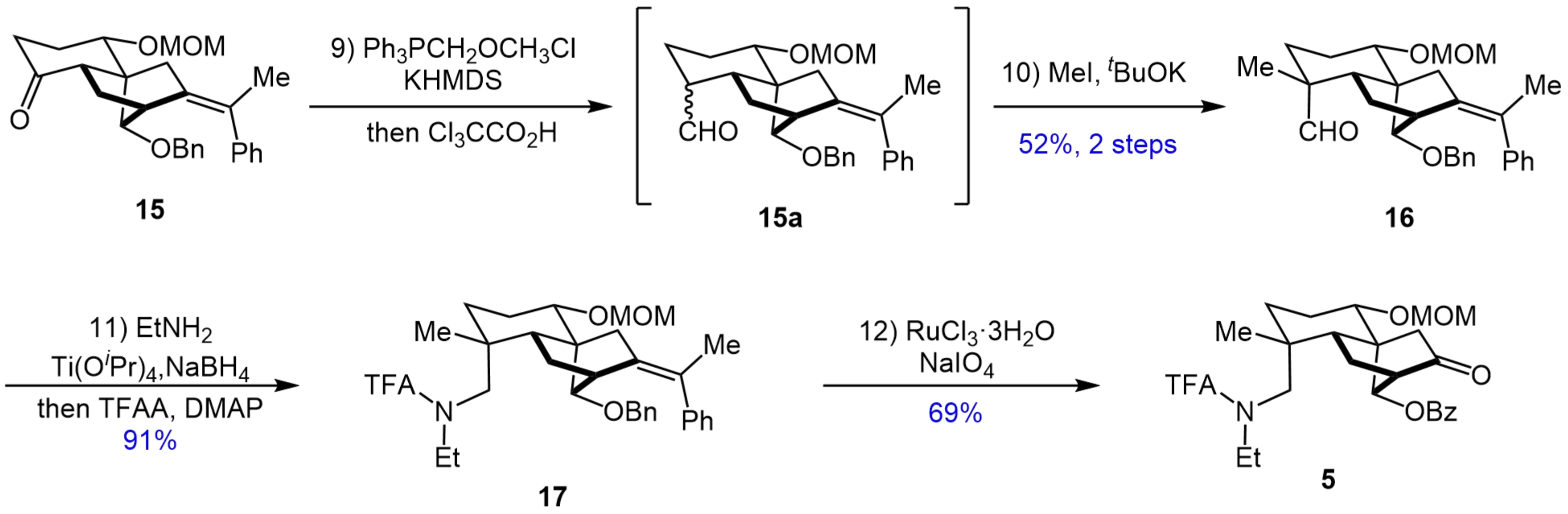
# Synthesis of Acoapetaludine A



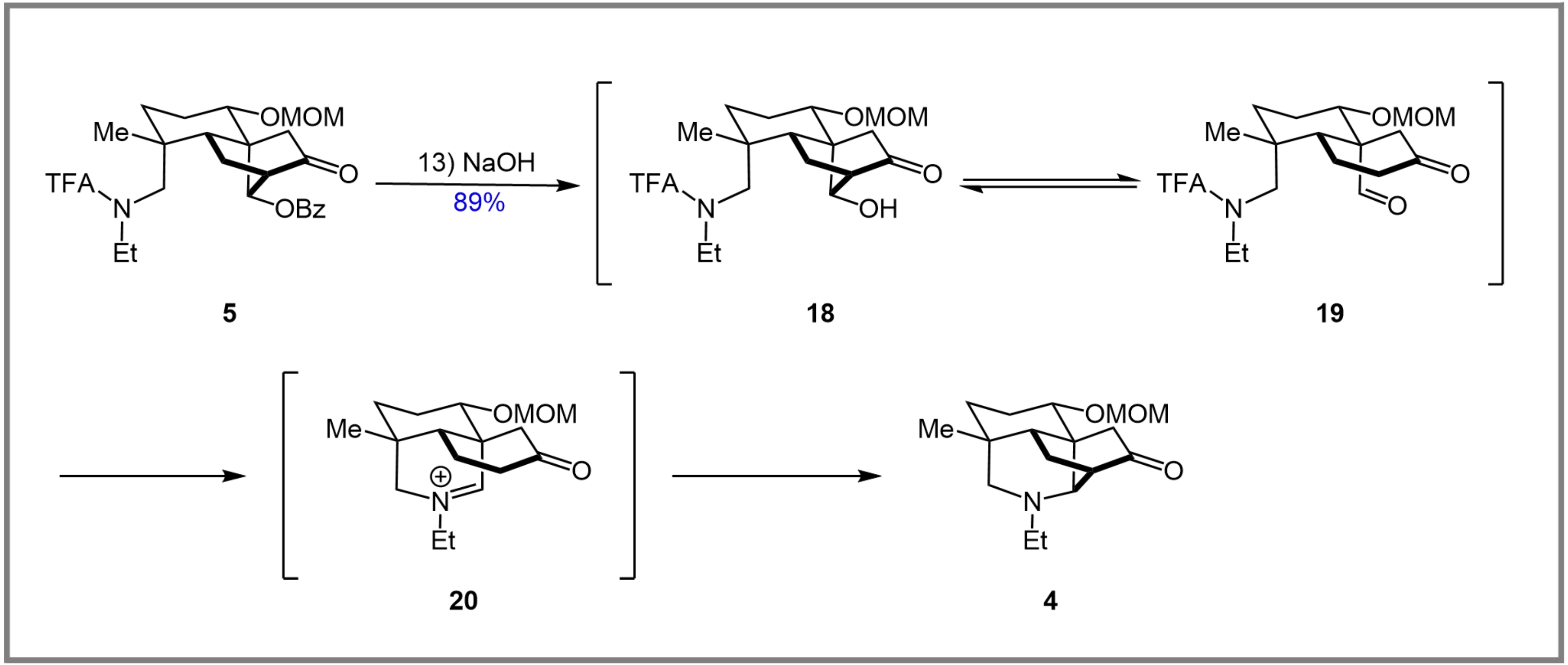
# Synthesis of Acoapetaludine A



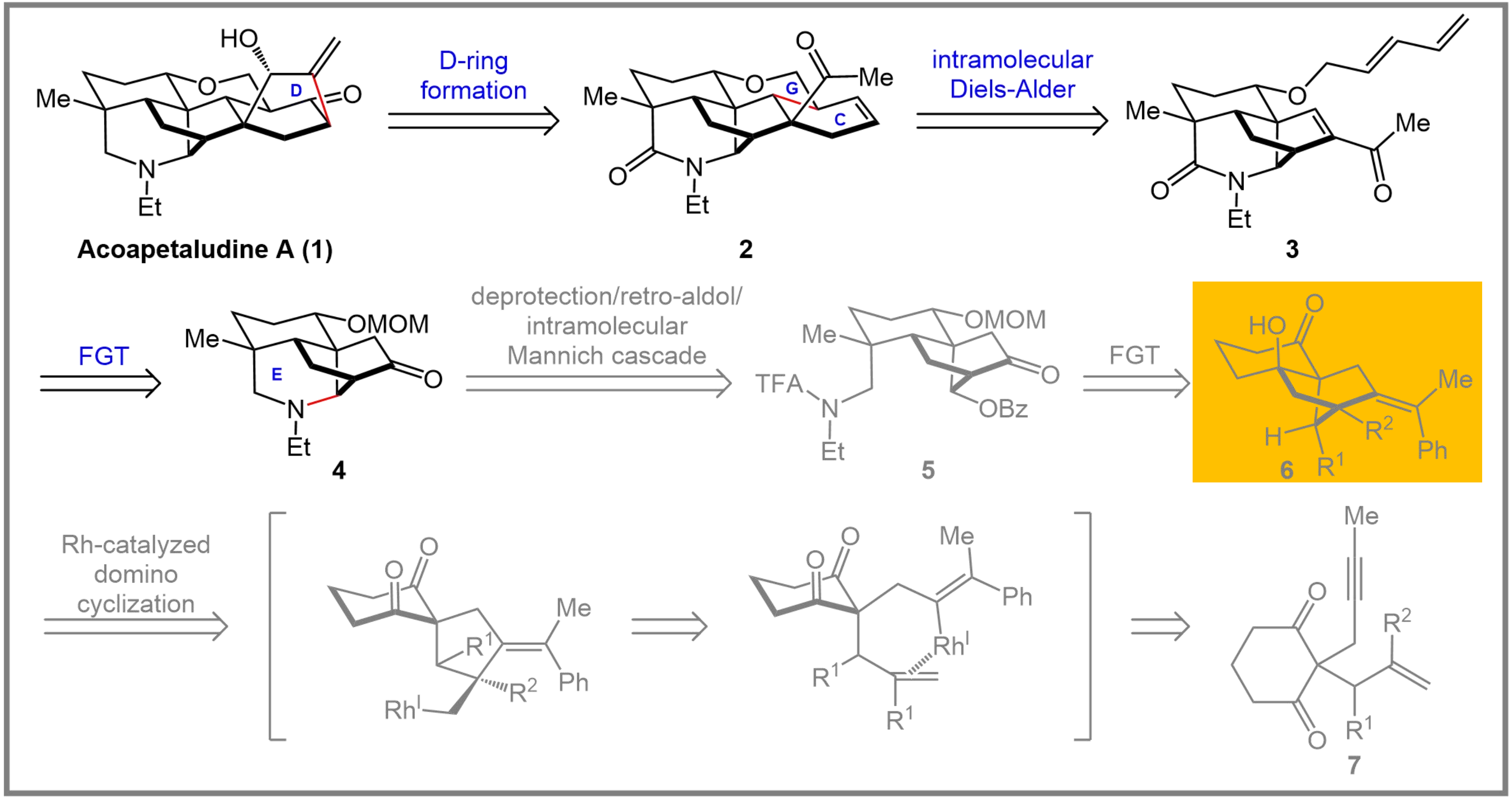
# Synthesis of Acoapetaludine A



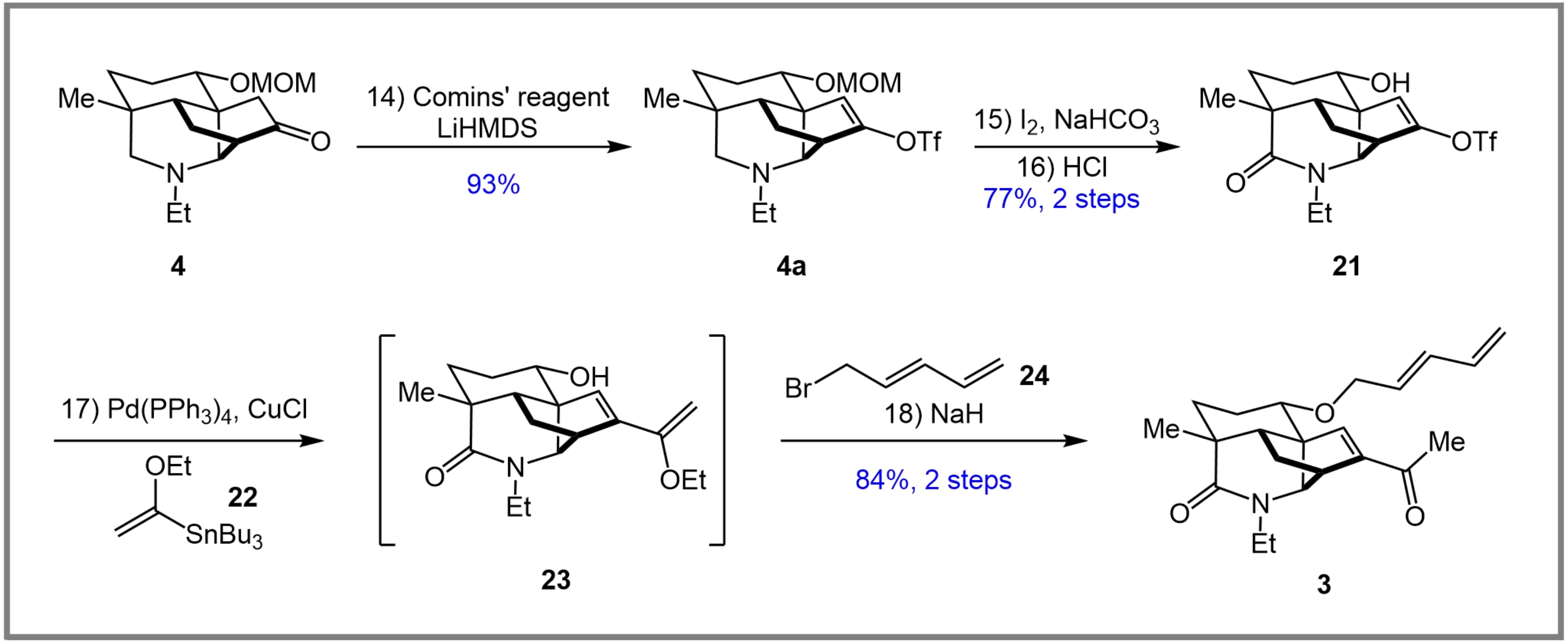
# Synthesis of Acoapetaludine A



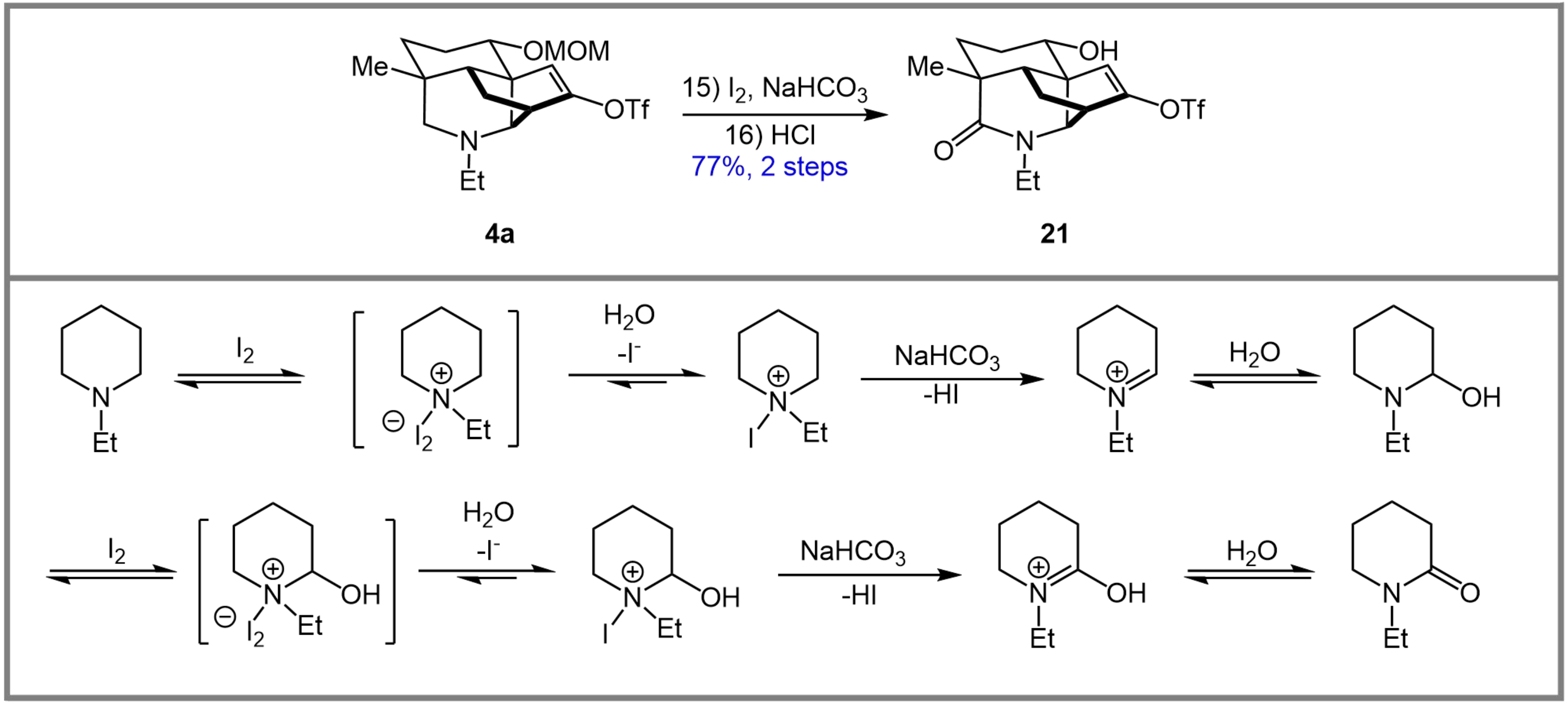
# Retrosynthetic Analysis



# Synthesis of Acoapetaludine A

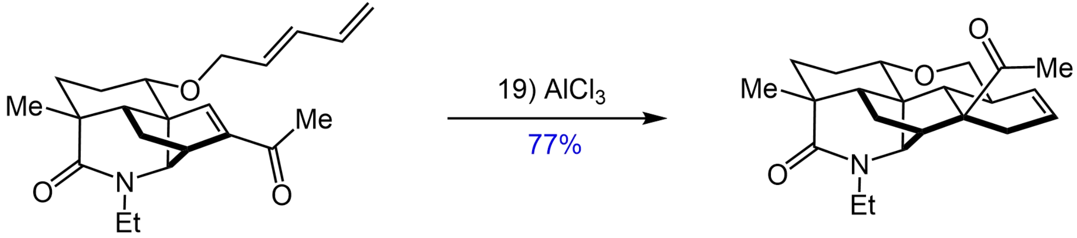


# Amine Oxidation



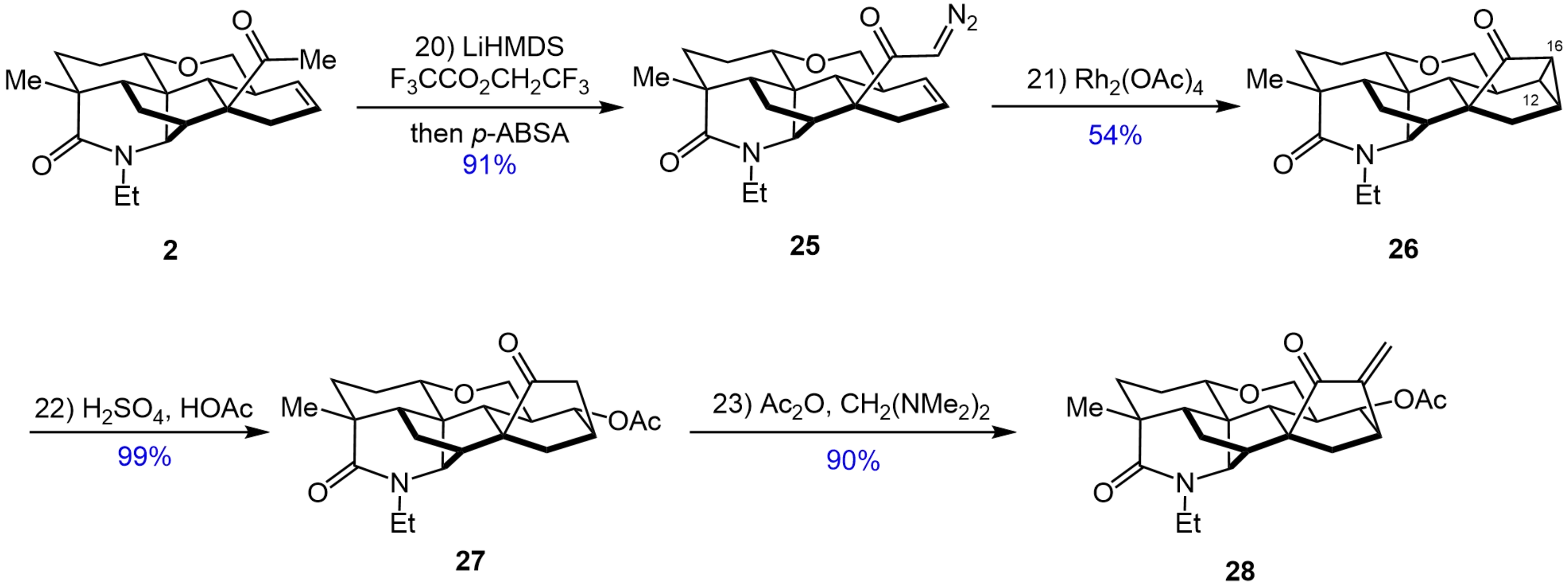
Griffiths, R. J.; Burley, G. A.; Talbot, E. P. A. *Org. Lett.* **2017**, *19*, 870.

# Synthesis of Acoapetaludine A

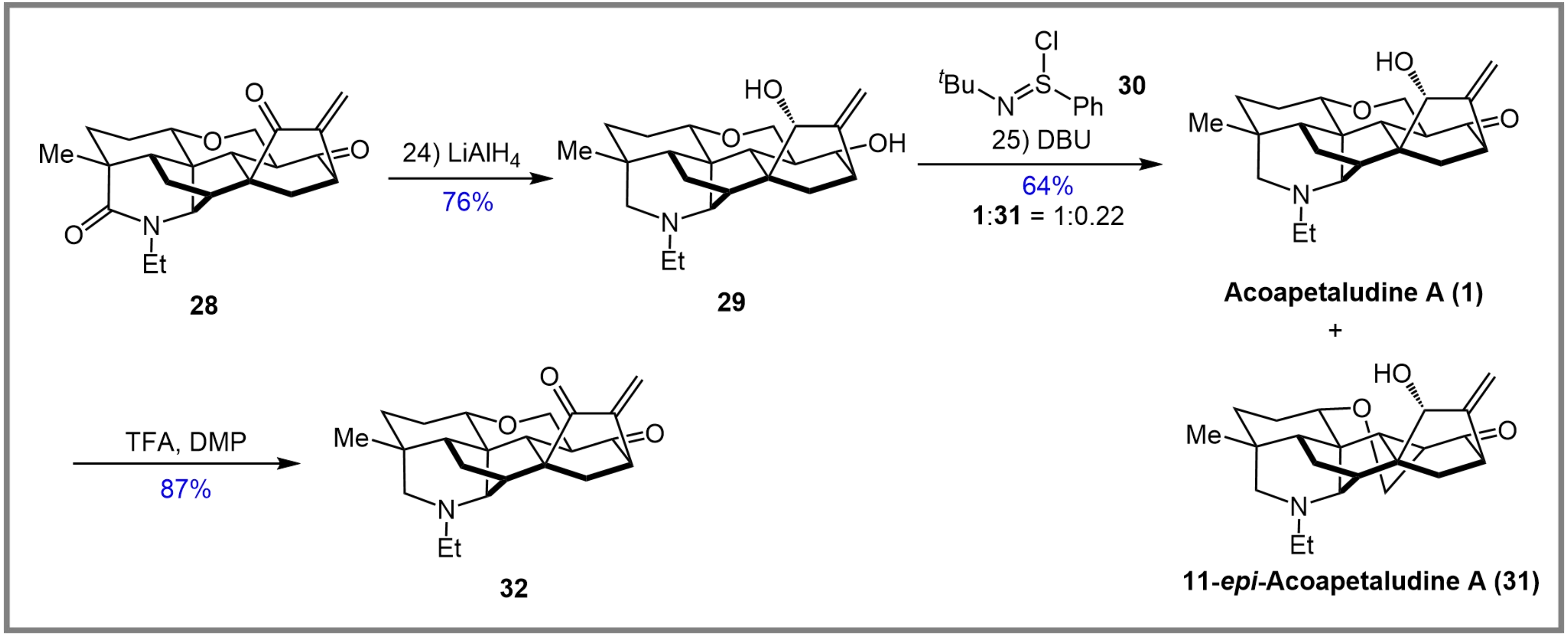


**3** **2**

# Synthesis of Acoapetaludine A



# Synthesis of Acoapetaludine A



**28**

24) $LiAlH_4$
76%

**29**

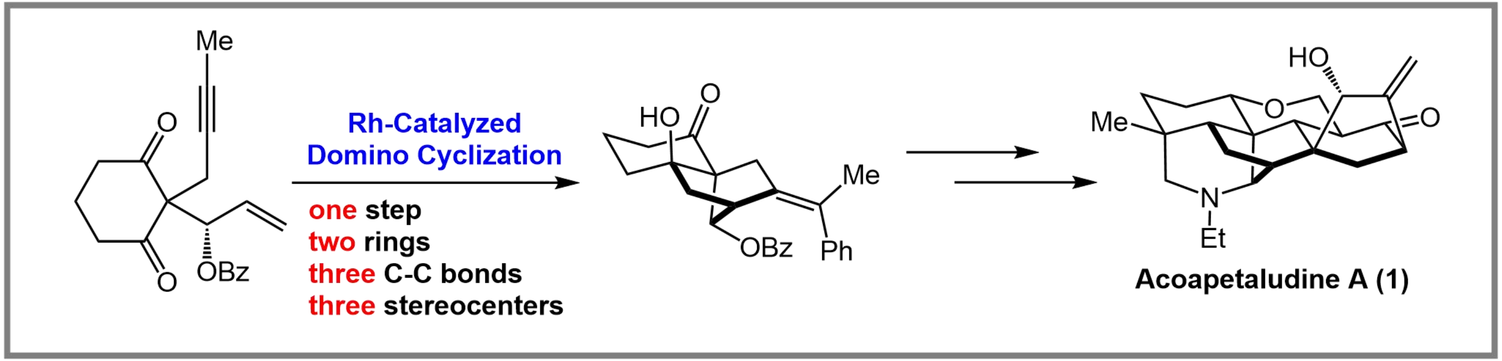
**30**
25) DBU
64%
**1**:**31** = 1:0.22

**Acoapetaludine A (1)**
+
**11-*epi*-Acoapetaludine A (31)**

TFA, DMP
87%

**32**

# Summary



**Acoapetaludine A (1)**

- Total synthesis of **Acoapetaludine A** in 25 linear steps, 0.73% overall yield.
- The key steps were an unprecedented deprotection/retro-aldol/intramolecular Mannich reaction cascade and a crucial intramolecular Diels−Alder cycloaddition
- We have developed a unique strategy to enable rapid construction of highly strained and functionalized bridged tricyclic skeletons *via* a Rh-catalyzed asymmetric domino cyclization.

# Strategy for Writing The First Paragraph

**Introduction of the diterpenoid alkaloids**

- The diterpenoid alkaloids are a large class of structurally complex natural products mainly isolated from the *Aconitum, Consolidum, Delphinium,* and *Spiraea genera* of plants, many of which are widely used in traditional Chinese medicine for the treatment of pain and cardiovascular diseases.

**Structural feature of Acoapetaludine A**

- Among them, acoapetaludine A (1) is a unique member of the homonapelline-type C20-diterpenoid alkaloids, featuring a caged-like 6/6/6/5/6/5/6 heptacyclic system with 11 stereocenters including three quaternary carbon centers. Beyond the napelline scaffold, acoapetaludine A features an additional ether ring (G-ring) integrated within the entire polycyclic bridged skeleton, posing formidable synthetic challenges

# Strategy for Writing The Last Paragraph

**Summary**

- In summary, we have developed a unique strategy to enable rapid construction of highly strained and functionalized bridged tricyclic skeletons from 2,2-disubstituted 1,3-cyclodiketones *via* a Rh-catalyzed asymmetric domino cyclization. Substrates with different ring sizes and substituents underwent this transformation assembling a diverse array of tricyclo[6.2.1.0$^{1,6}$]undecanes and tricyclo[7.2.1.0$^{1,7}$]dodecanes.

**Highlights**

- These bridged tricyclic molecules can serve as core scaffolds, followed by an unprecedented deprotection/retro-aldol/intramolecular Mannich reaction cascade and a crucial intramolecular Diels−Alder cycloaddition, leading to a concise total synthesis of C20 diterpenoid alkaloid acoapetaludine A (1).

# Representative Examples

- The distinct biological activity and intricate molecular architectures of diterpenoid alkaloids render them highly sought-after targets for synthetic chemists. (intricate adj. 错综复杂的；难理解的，难学会的；highly sought-after 备受追捧的)
- Leveraging this insight, we plan to devise a cascade strategy for the rapid synthesis of this common core skeleton and, building upon it, achieve the concise synthesis of this class of natural products. (leverage n.影响力，手段；杠杆作用；v. 充分利用（资源、观点等））
- To test our hypothesis, cyclohexanedione 7a was used as the model substrate. (hypothesis n. 假说，假设，猜想，猜测，前提)

# Acknowledgement

***Thanks for Your Attention***