Literature Report 1

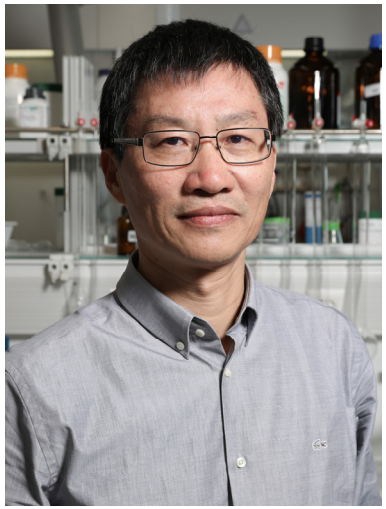
Total Synthesis of (+/−)-Crokonoid A

Reporter: Xin Zuo
Checker: Xin-Yu Zhan

Forster, D.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2025**, *147*, 36090–36096

2025-11-03

CV of Prof. Jieping Zhu (祝介平)



Background:

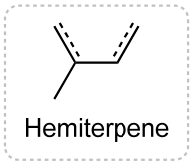
- **1980-1984** B.S., Hangzhou Normal University, P. R. China
- **1984-1987** M.S., Lanzhou University, P. R. China
- **1987-1991** Ph.D., Université Paris XI, France
- **1991-1992** Postdoctoral Researcher, Texas A & M University, USA
- **1992-2010** Director of Research, ICSN, CNRS, France
- **2010-present** Professor, ISIC, EPFL, Switzerland

Research:

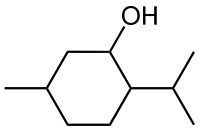
- Total Synthesis of Natural Products
- Metal-catalyzed Domino Process
- Multicomponent Reaction
- Catalytic Enantioselective Transformation

Contents

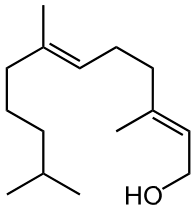
Introduction: Terpenoid (-terpene)



Hemiterpene

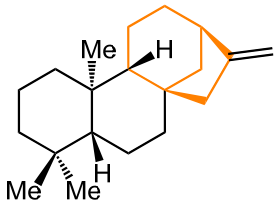


Menthol
(Monoterpene)



Farnesol
(Sesquiterpene)

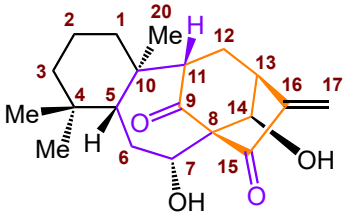
Diterpenes, Sesterterpenes, Triterpenes …



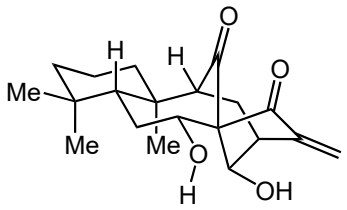
1 *ent*-Kaurene

- Constitute a large class of C_{20}-diterpenes
- Possess a bicyclo[3.2.1]octane core
- Exhibit striking structural diversity and potent biological activity

Introduction: Crokonoid A



2 Crokonoid A



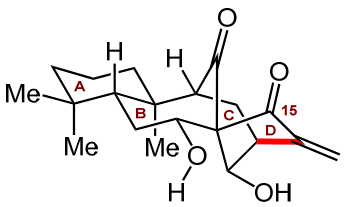
- Embeds a bicyclo[3.2.1]octane moiety
- Incorporates an unprecedented tricyclo[4.4.1.$1^{1,4}$]dodecane-2,11-dione core
- Features a novel 6/7/6/5 tetracyclic carbon framework
- Exhibits potent cytotoxicity against HL-60 and A549 cell lines

Only 6 mg isolated from 13 kg of *Croton kongensis* powder

Croton kongensis

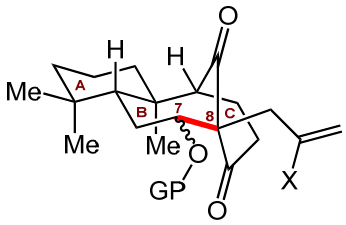
Fan, Y.-Y.; Shi, S.-Q.; Deng, G.-Z.; Liu, H.-C.; Xu, C.-H.; Ding, J.; Wang, G.-W.; Yue, J.-M. *Org. Lett.* **2020**, *22*, 929–933

Retrosynthetic Analysis



2 Crokonoid A

Pd-Catalyzed Cycloalkenylation



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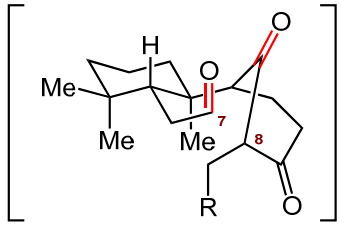
Aldol Reaction



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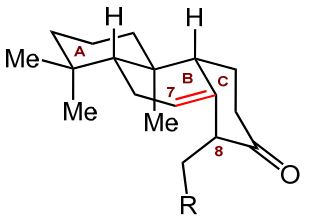
Ozonolysis



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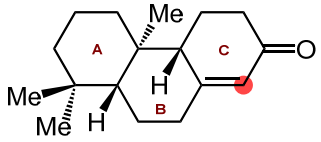
Deconjugative Allylation



8 Podocarp-8(14)-en-13-one

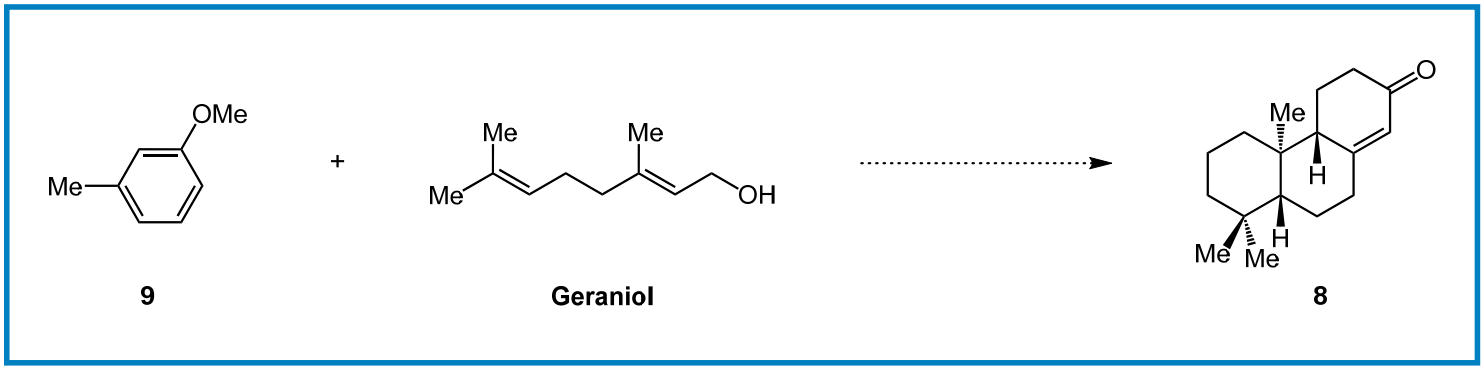
Stage 1: Synthesis of Known Compound **8**

Stage 2: B-Ring Expansion

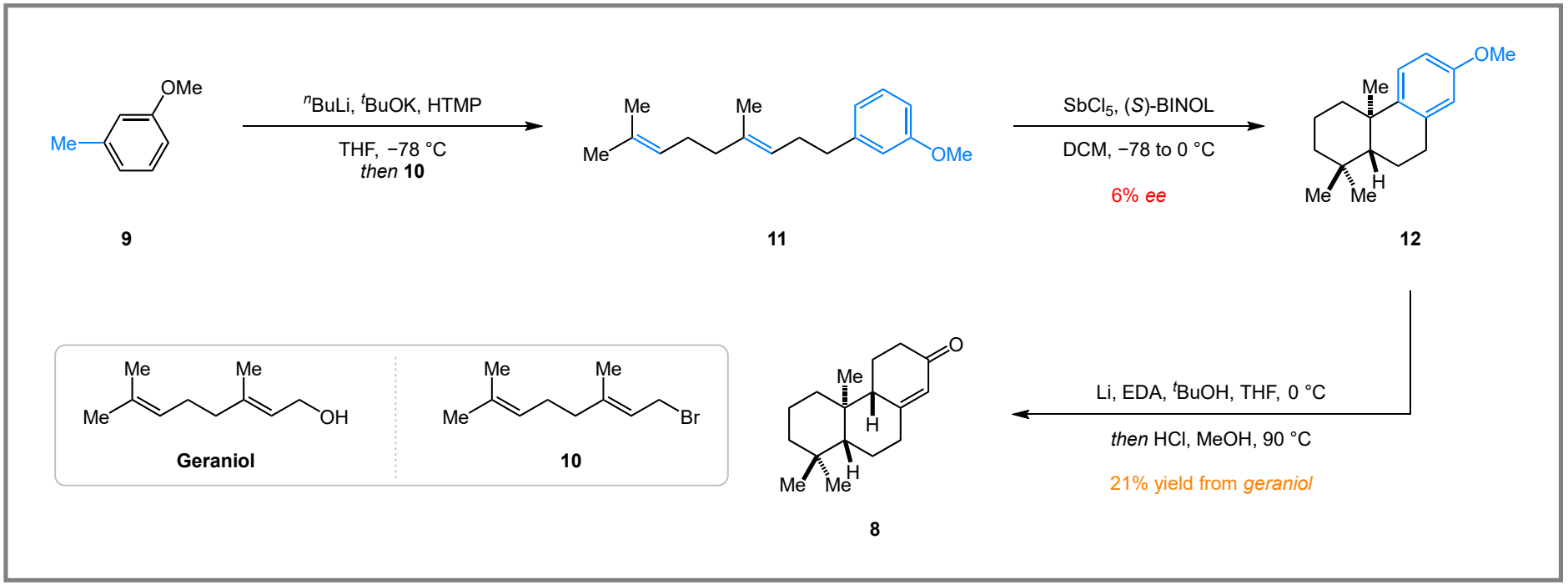
Stage 3: D-Ring Closure

Stage 4: Subsequent modifications

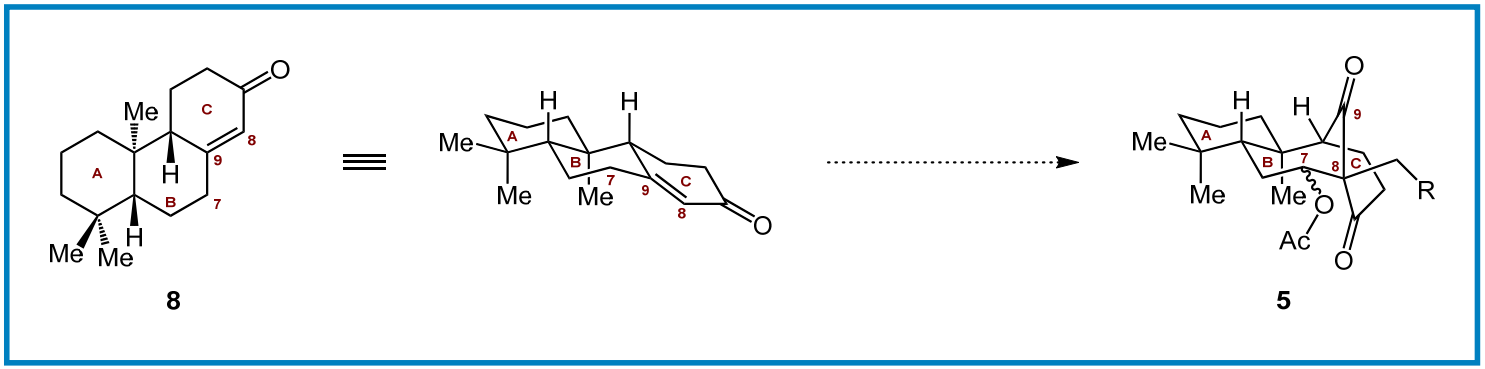
Stage 1: Synthesis of Known Compound 8



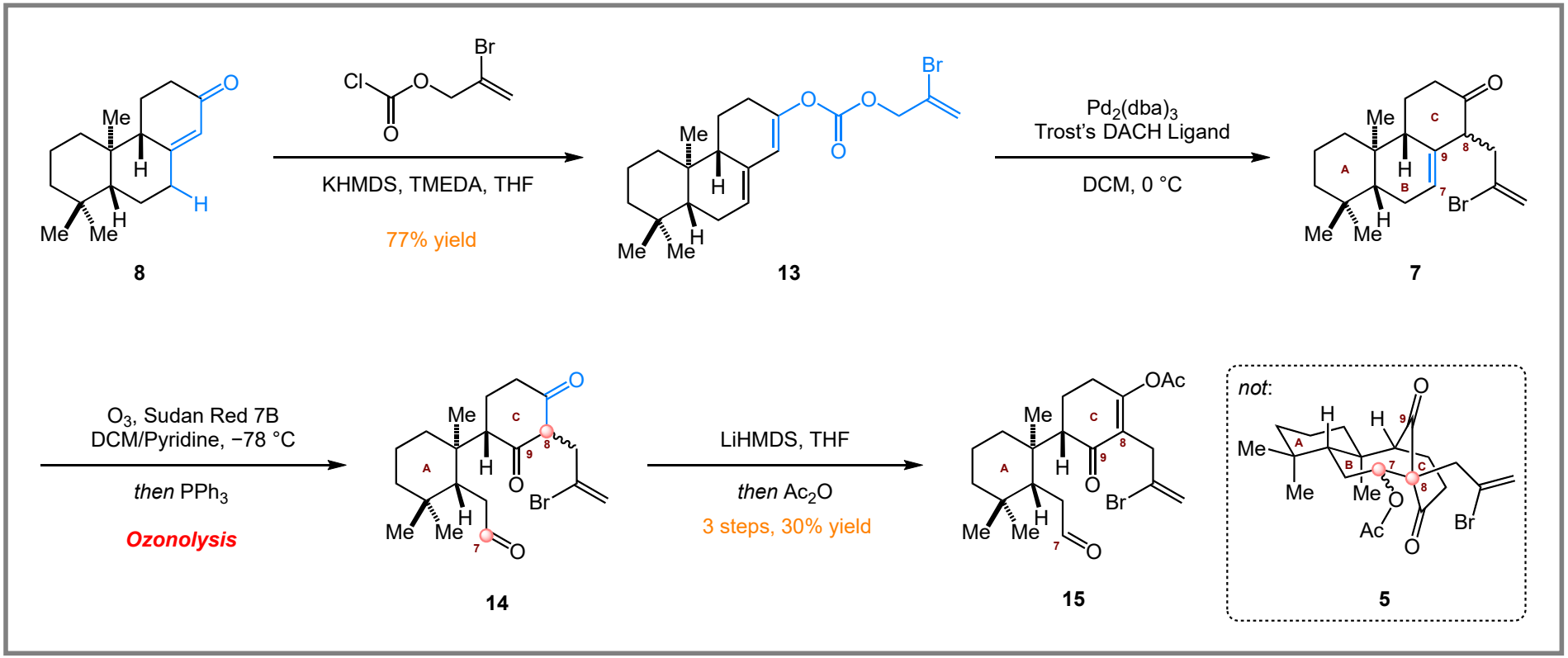
Stage 1: Synthesis of Known Compound 8



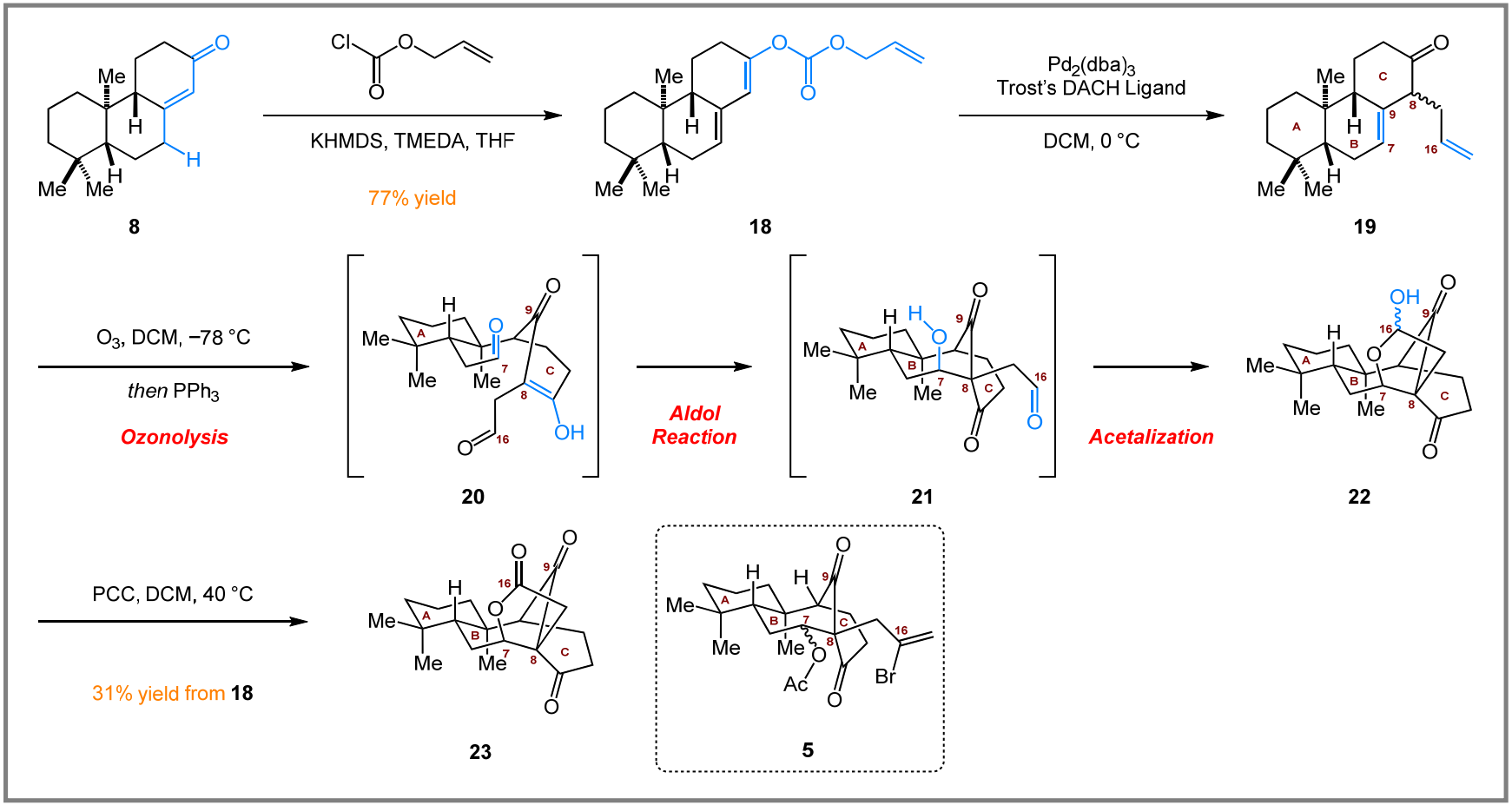
Stage 2: B-ring Expansion



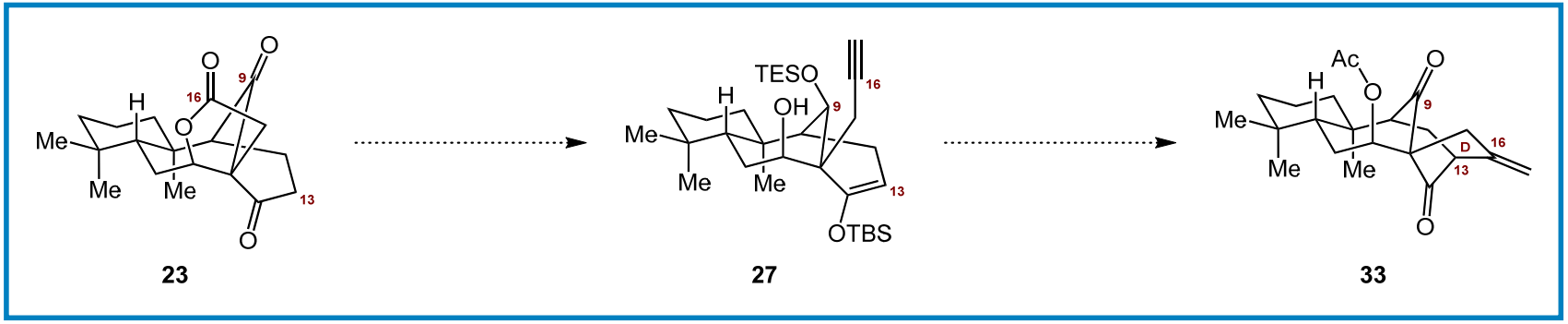
Stage 2: Synthetic Efforts Toward Compound 5



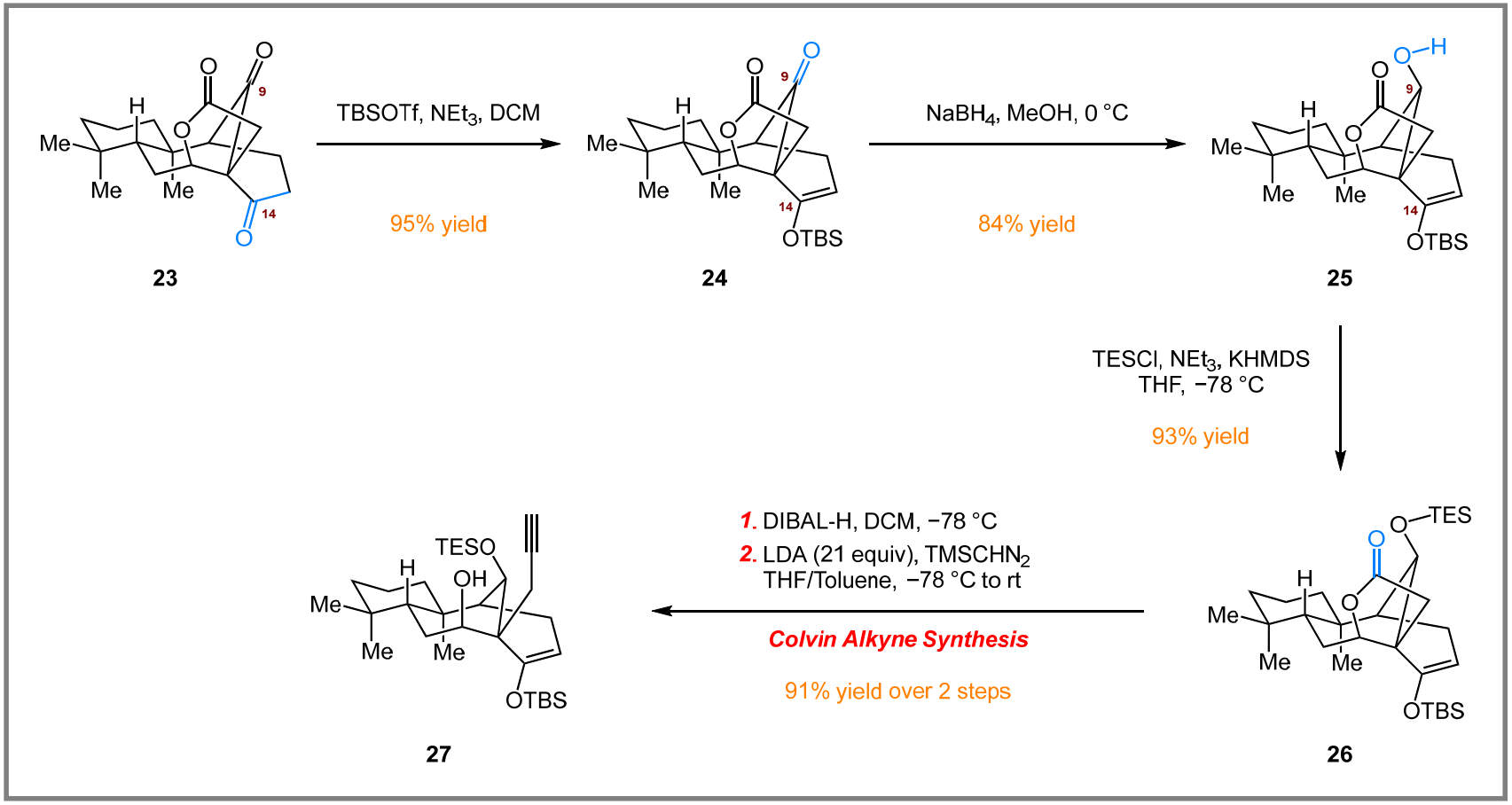
Stage 2: B-ring Expansion



Stage 3: D-ring Closure

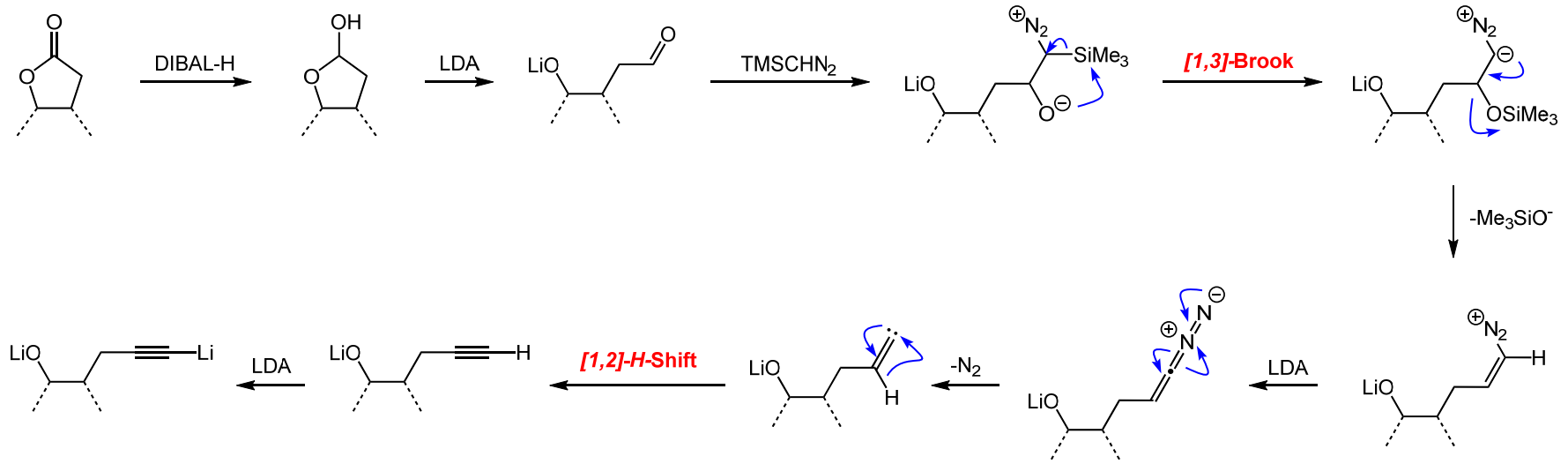


Stage 3: Synthesis of Compound 27

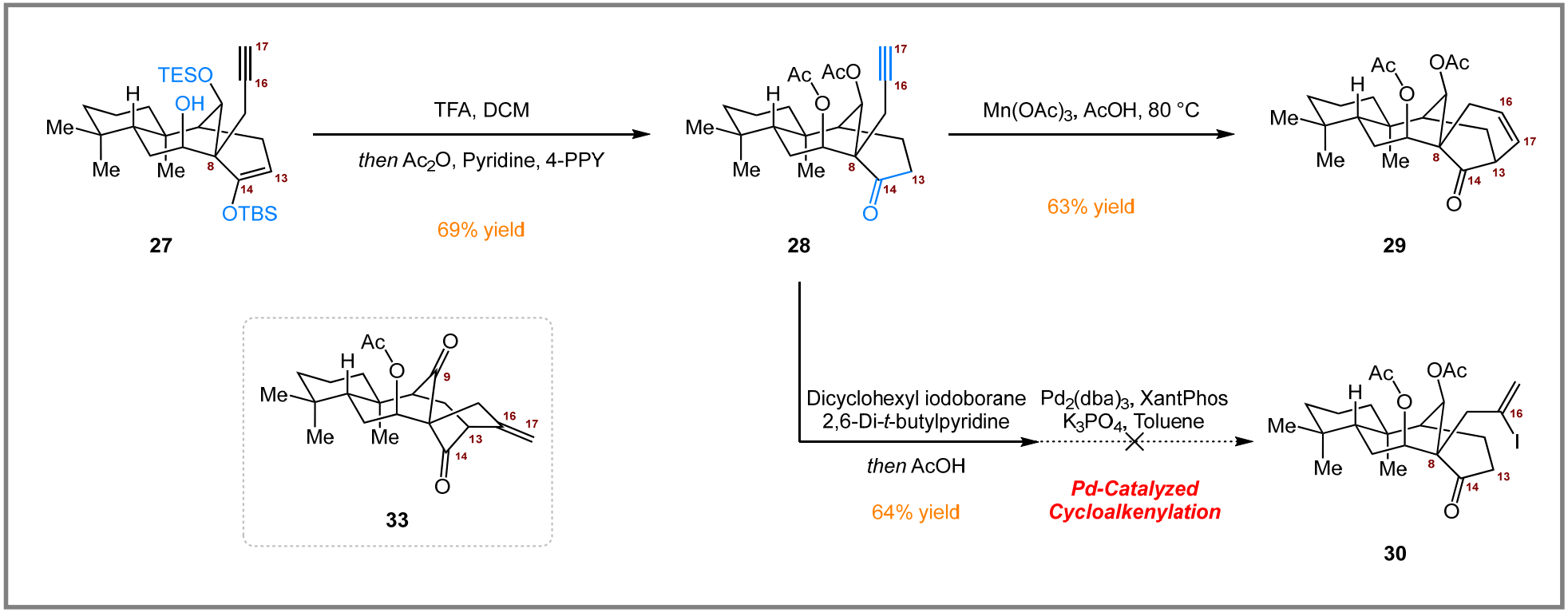


Colvin Rearrangement (Alkyne Synthesis)

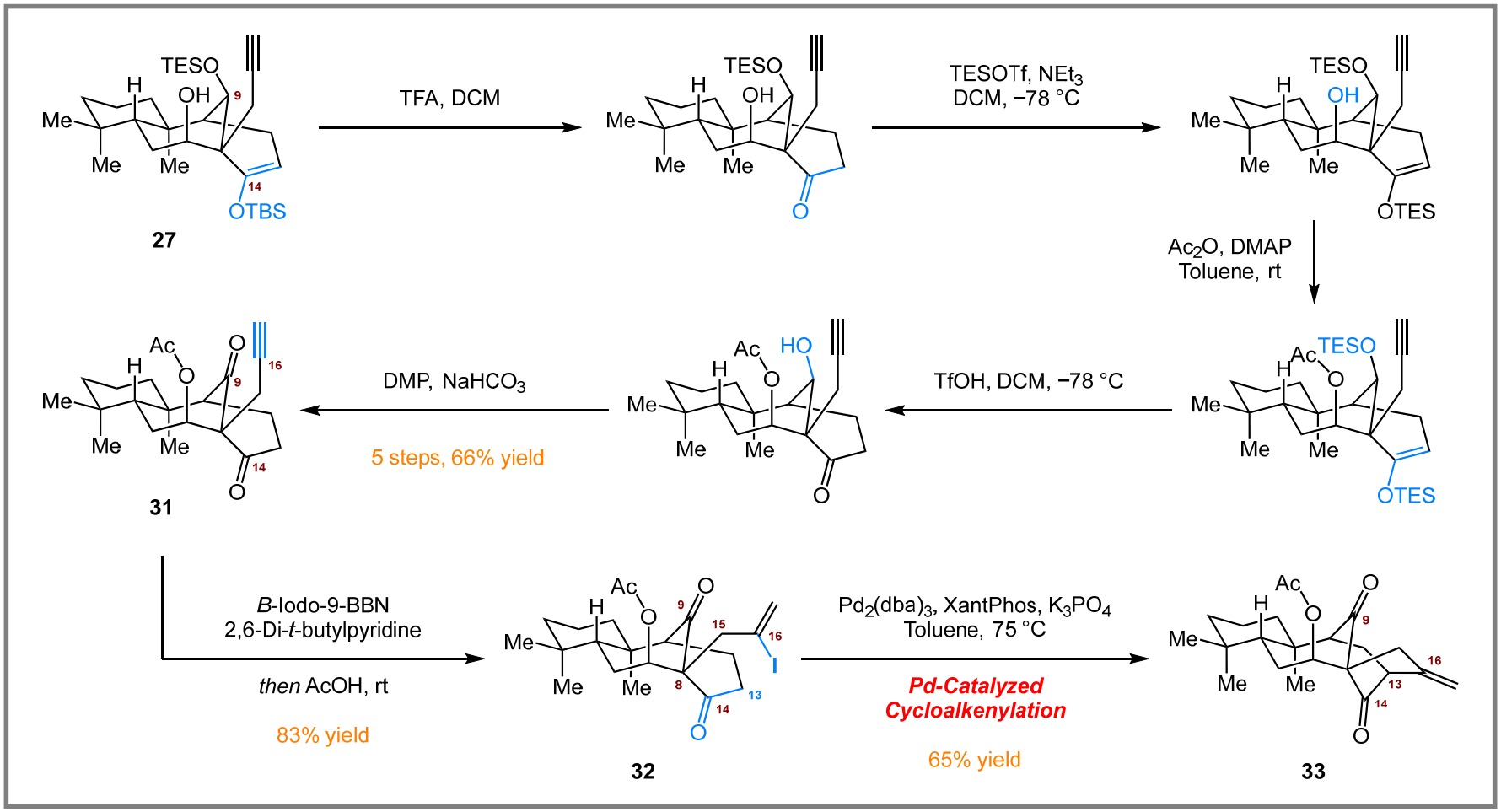
26 **27**



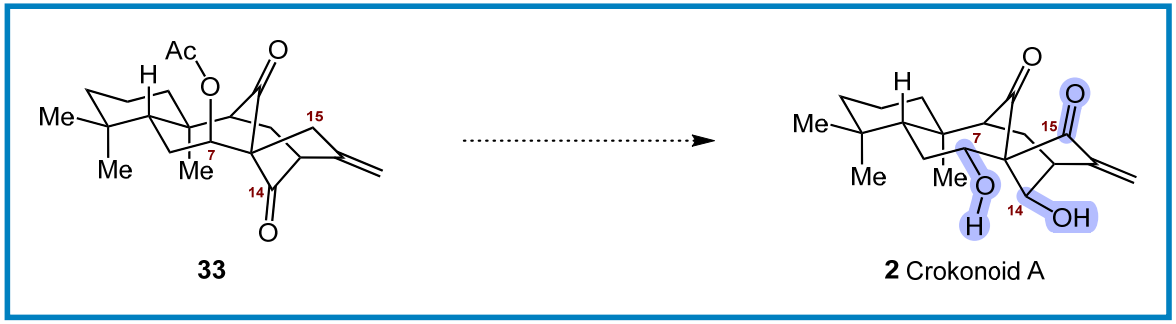
Stage 3: Synthetic Efforts Toward Compound 33



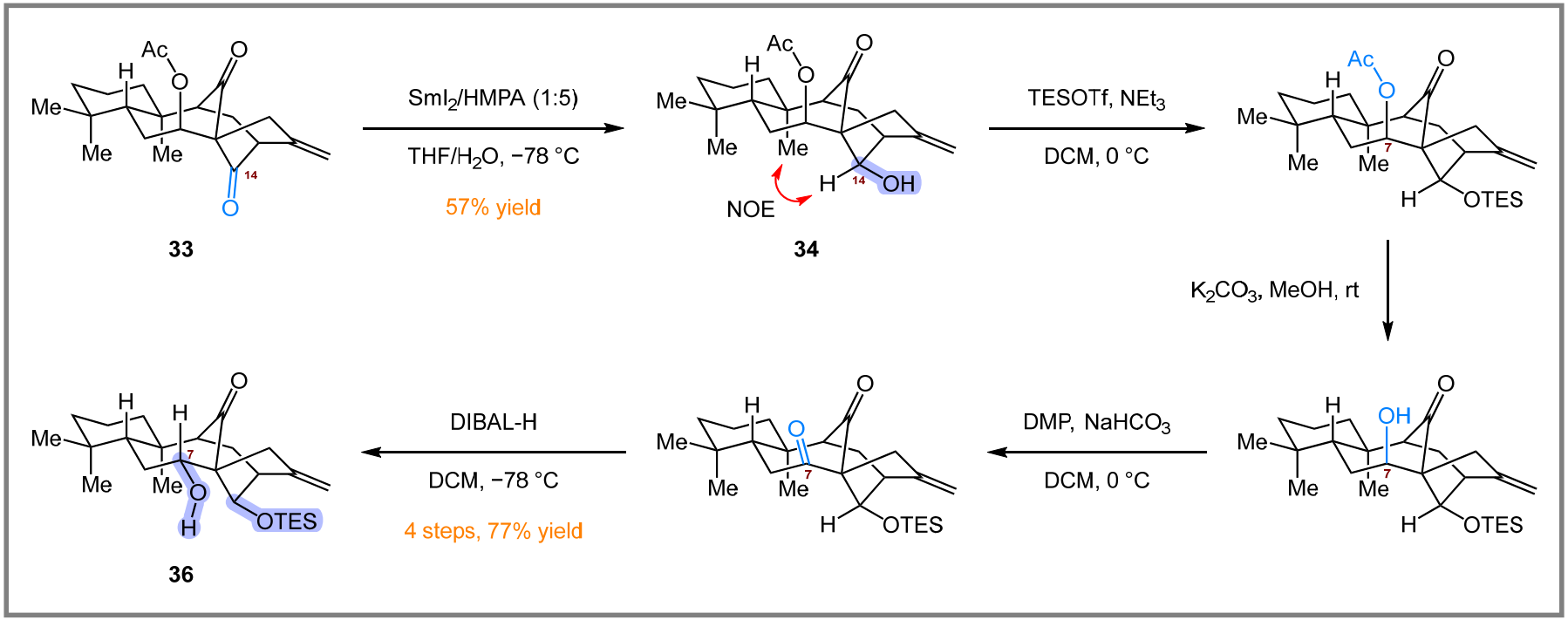
Stage 3: Synthesis of Compound 33



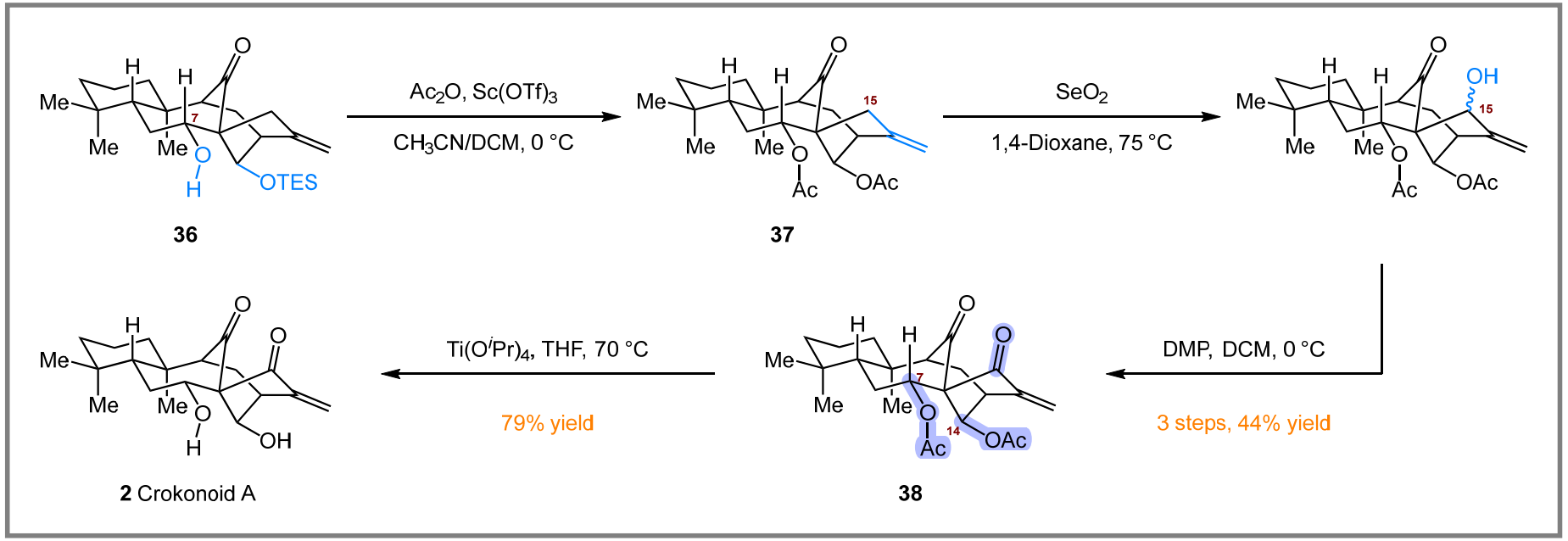
Stage 4: Subsequent Modifications



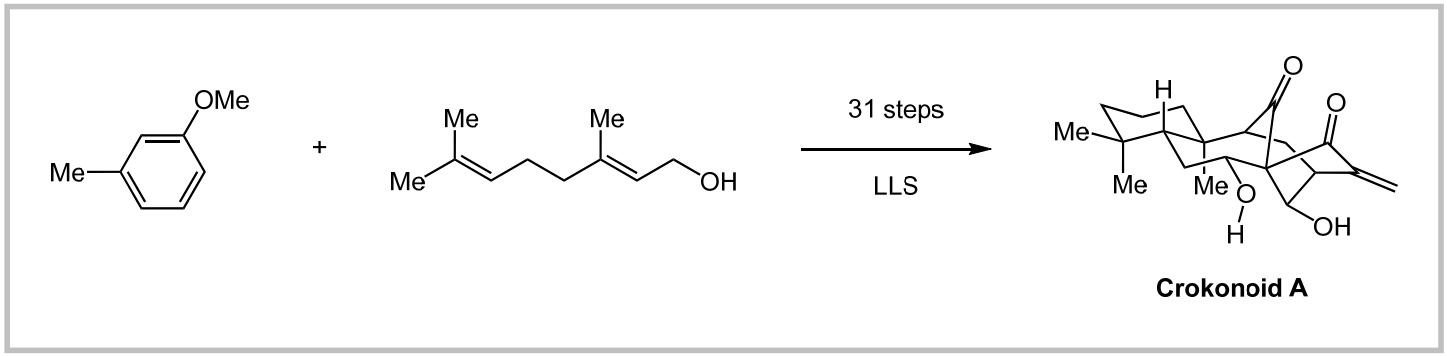
Stage 4: Synthesis of Compound 36



Stage 4: Synthesis of Crokonoid A



Summary



- Regioselective decarboxylative allylation of a 1,3-dienyl carbonate;
- Domino sequence involving ozonolysis, intramolecular aldol reaction, and acetalization;
- Palladium-catalyzed intramolecular cycloalkenylation of a ketone;
- SmI_2−HMPA-mediated regio- and stereoselective reduction.

Forster, D.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2025**, *147*, 36090–36096

Writing Strategy

➢ **First paragraph**

Species and Structure

Biological Activities

- The *ent*-kauranoids, characterized by a bicyclo[3.2.1]octane core, constitute a large class of C_{20}-diterpenes with striking structural diversity and potent biological activity. Since the structural elucidation of *ent*-kaurene (**1**) in 1961, over a thousand congeners have been identified, including highly oxidized, rearranged, and C−C-bond-cleaved derivatives of the core tetracyclic scaffold. Following Ireland's pioneering total synthesis of **1**, the structural complexity and dense functionalization of these molecules have continued to inspire the development of increasingly sophisticated strategies.
- In 2020, Yue, Wang, and co-workers reported the isolation of crokonoid A (**2**) from the aerial parts of *Croton kongensis*. This compound features a novel 6/7/6/5 tetracyclic carbon framework incorporating an unprecedented tricyclo[4.4.1.$1^{1,4}$]dodecane-2,11-dione core, which embeds a bicyclo[3.2.1]-octane moiety, characteristic of *ent*-kaurene diterpenoids …

Writing Strategy

➢ Last paragraph

Summary

■ We accomplished the total synthesis of crokonoid A, distinguished by its dually bridged 6/7/6/5 fused tetracyclic carbon framework featuring an unprecedented tricyclo[4.4.1.$1^{1,4}$]dodecane-2,11-dione core.

Pivotal Steps

■ Our synthetic approach leverages four pivotal steps: (a) a regioselective decarboxylative allylation of a 1,3-dienyl carbonate, furnishing an *α*-allyl-*β*,*γ*-unsaturated ketone; (b) a domino sequence involving ozonolysis, intramolecular aldol reaction, and acetalization which is instrumental in assembling the bicyclo[4.3.1]decanedione core from a fused ring system; (c) a palladium-catalyzed intramolecular cycloalkenylation of a ketone to construct the bicyclo[3.3.1]octane-dione system; and (d) SmI_2−HMPA-mediated regio- and stereoselective reduction of the C14 ketone.

Representative Examples

- … controlling the stereocenters at C7 and C14 was anticipated to be nontrivial. (*adj*. 重要的)
- The diastereoselective reduction of the C14 ketone warrants further discussion. (值得进一步讨论)
- … distinguished by its dually bridged 6/7/6/5 fused tetracyclic carbon framework featuring an unprecedented tricyclo[4.4.1.1^{1,4}]dodecane-2,11-dione core. (*adv*. 双重地；从两个方面)

Acknowledgement

Thank You for Your Attention!