Literature Report VII

Total Synthesis of (−)-Psathyrin A Enabled by Radical Cyclization

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Checker: Hao-Dong Chen
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Zhao, W.; Al-Ahmad, R.; Dai, M.* *J. Am. Chem. Soc.* **2025**, *147*, 32365

CV of Prof. Mingji Dai (代明骥)

Background:

- **1998-2002:** B.S., Peking University
- **2002-2004**: Research Assistant, Peking University
- **2004-2009**: Ph.D., Columbia University
- **2009-2012**: Postdoc., Harvard University and The Broad Institute
- **2012-2022**: Assistant Professor, Associate Professor, Professor, Department of Chemistry and Center for Cancer Research, Purdue University
- **2022-present**: Asa Griggs Candler Professor of Chemistry, Emory University

Research:

- Total Synthesis
- Ring-Opening Chemistry
- Amphoteric Diamination to *N*-Heterocylces
- Medicinal Chemistry and Chemical Biology

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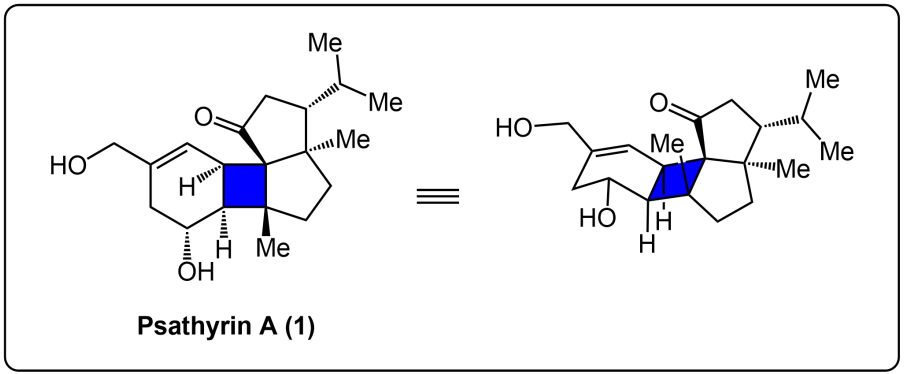
Introduction-Psathyrins A



Psathyrin A (1)

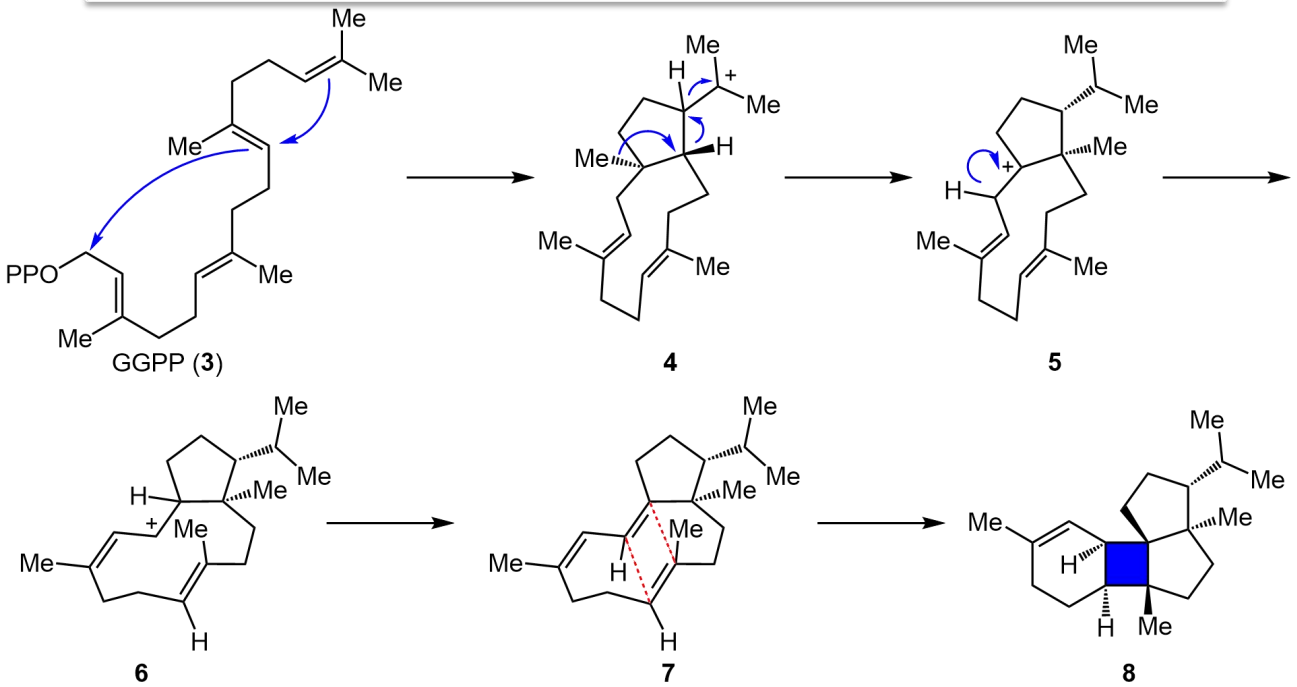
Psathyrella candolleana

- Psathyrin A was isolated from the fermentation broth (发酵液) of *Psathyrella candolleana* by Liu, Feng, and co-workers in 2020.
- Structurally, the psathyrin has a unprecedented 6/4/5/5 tetracyclic carbon skeleton. It contains seven contiguous stereocenters, including three adjacent all-carbon quaternary centers, two of which reside on the strained cyclobutane ring.
- Biologically, psathyrin A was found to exhibit weak activities against *Staphylococcus aureus* and *Salmonella enterica.*

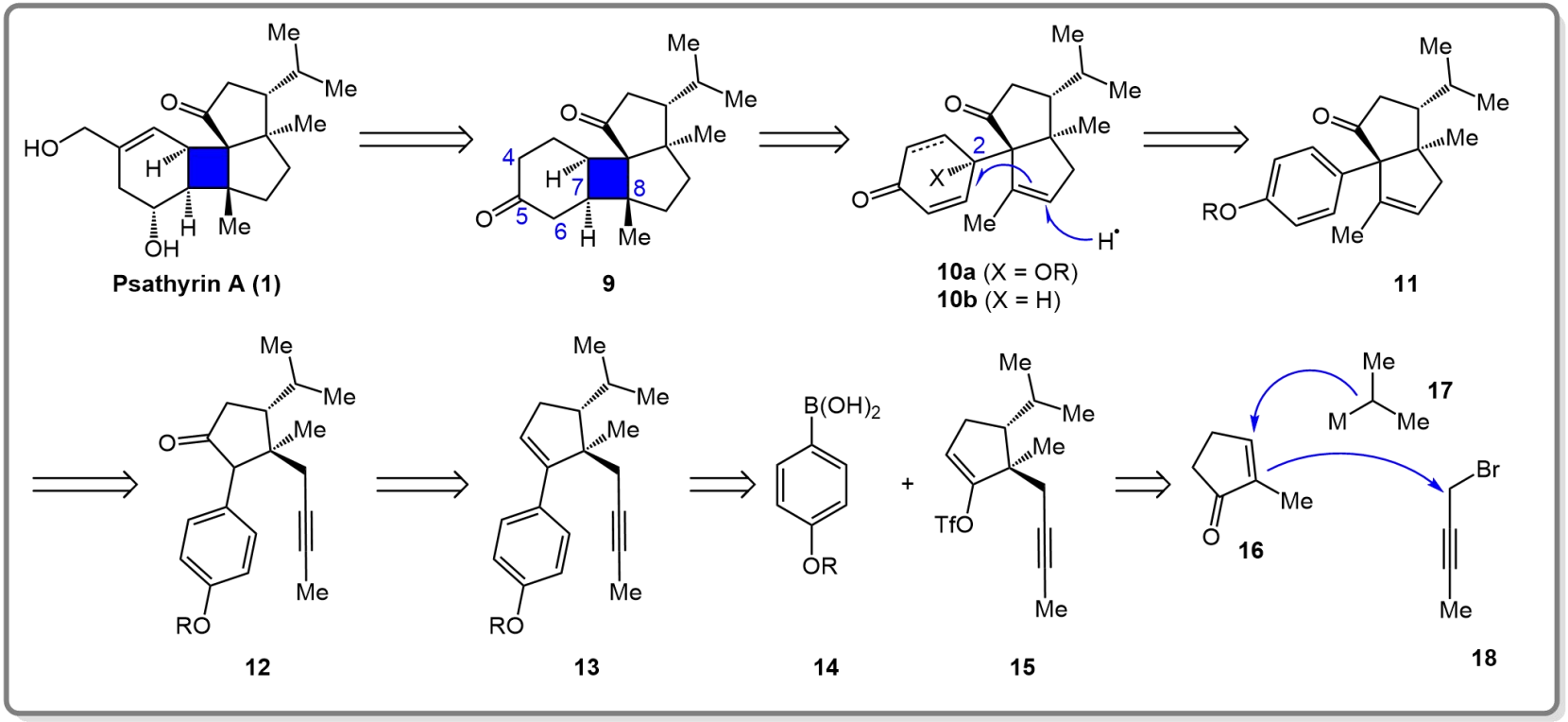
Liu, Y.-P.; Dai, Q.; Wang, W.-X.; He, J.; Li, Z.-H.; Feng, T.; Liu, J.-K. *J. Nat. Prod.* **2020**, *83*, 1725

Introduction

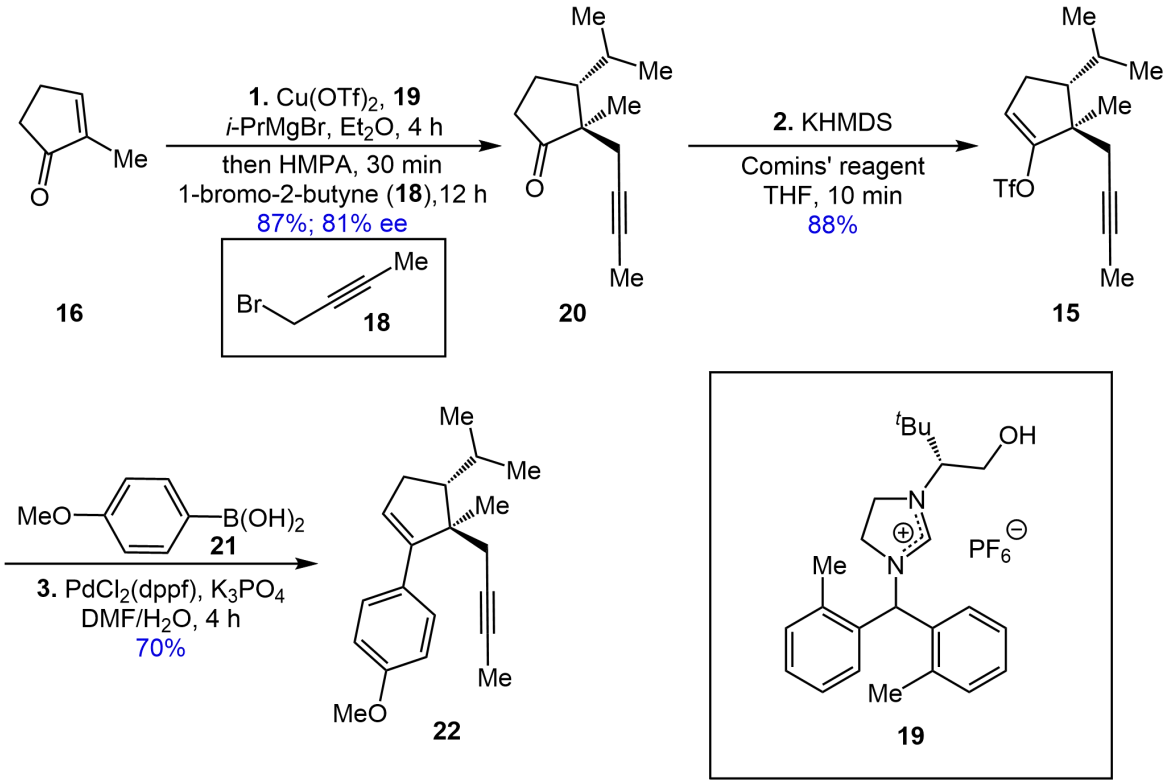
A plausible biosynthetic construction of the carbon skeleton *via* transannular [2+2] cycloaddition



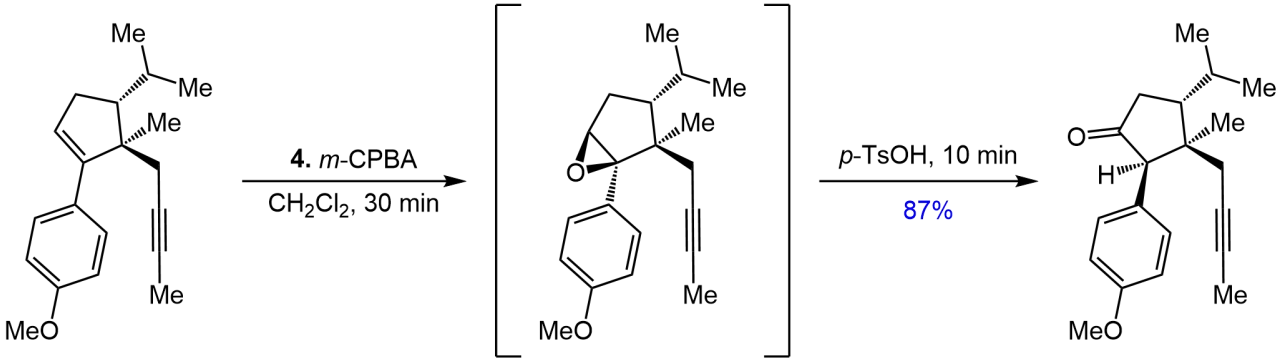
Retrosynthetic Analysis



Synthesis of 22

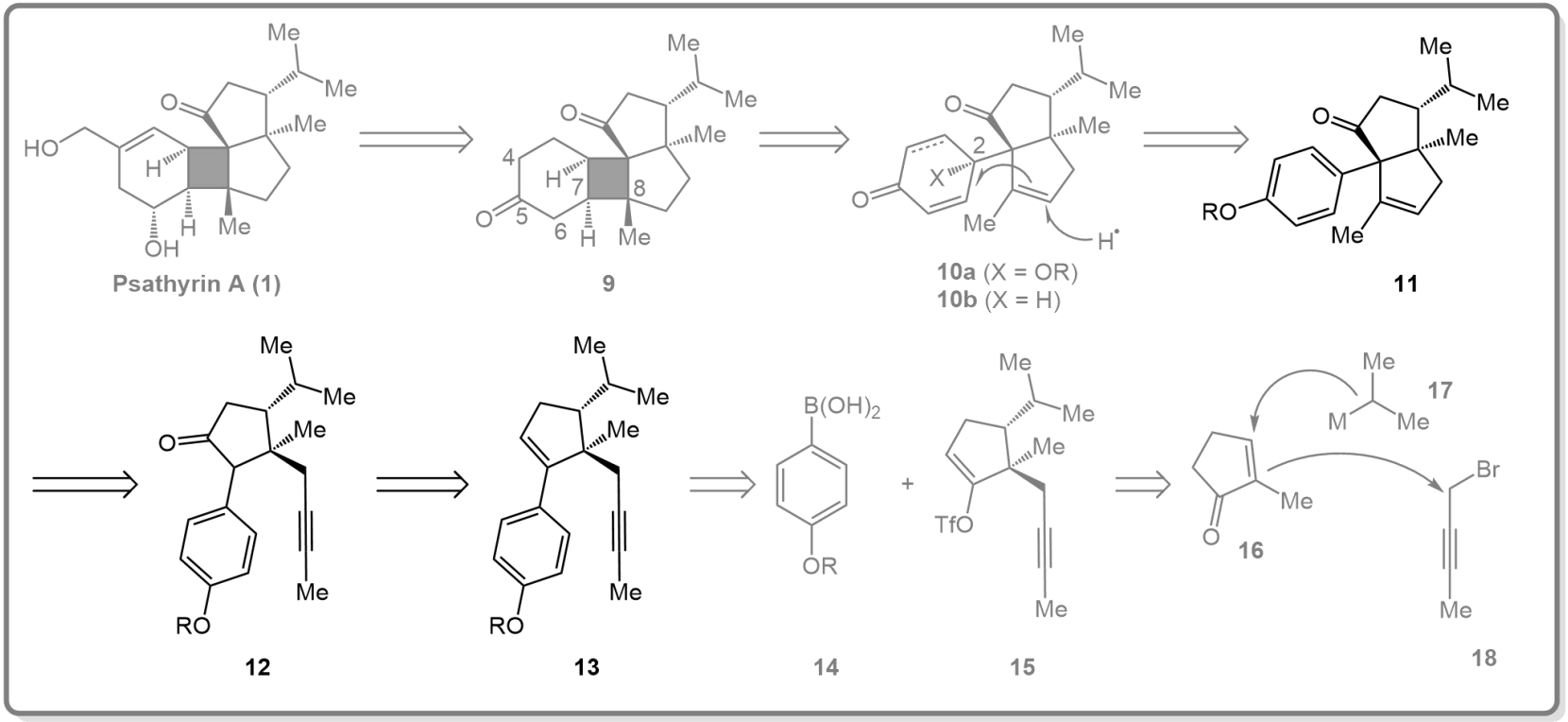


Synthesis of 24

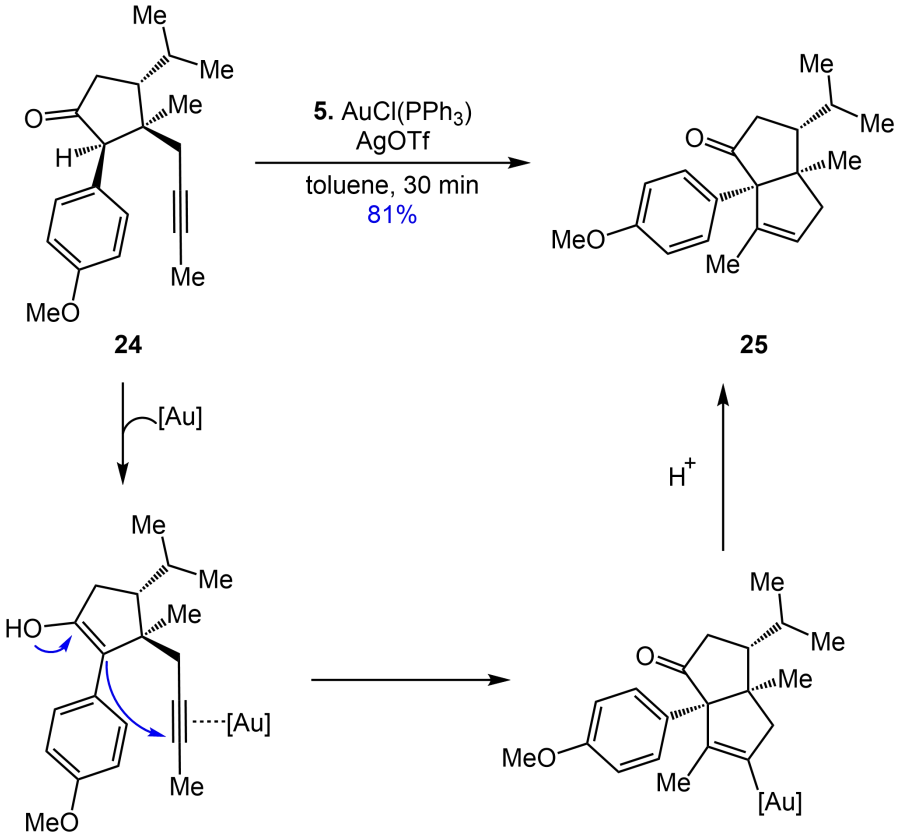


22 **23** **24**

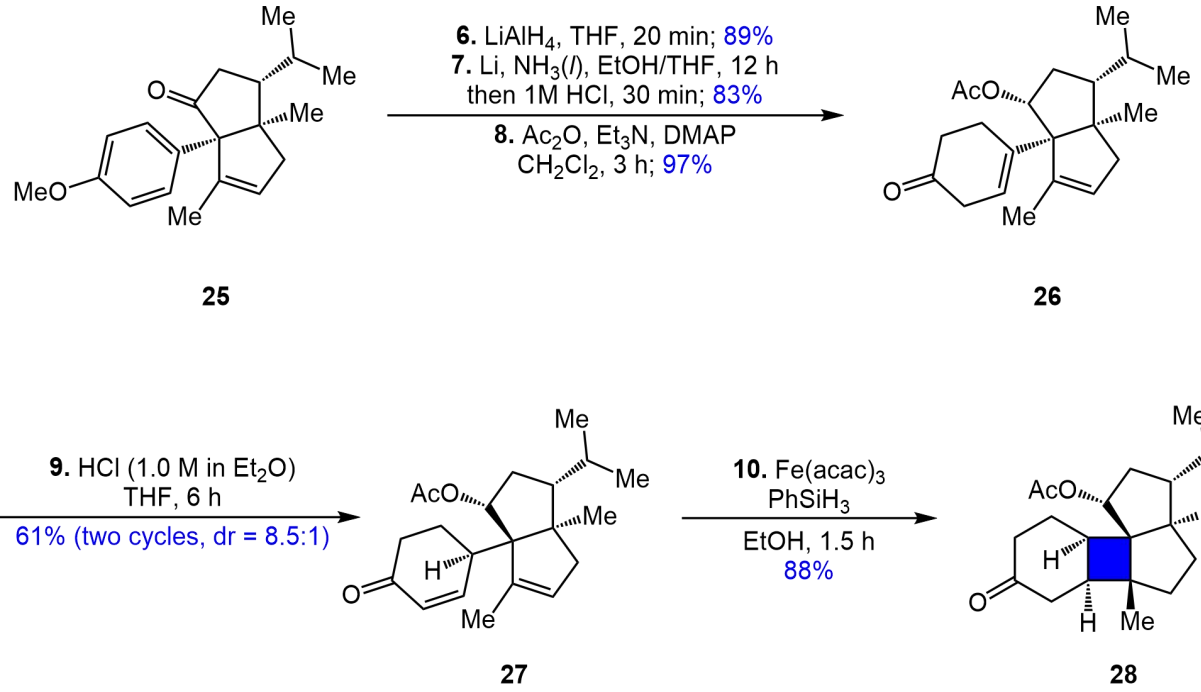
Synthesis of 28



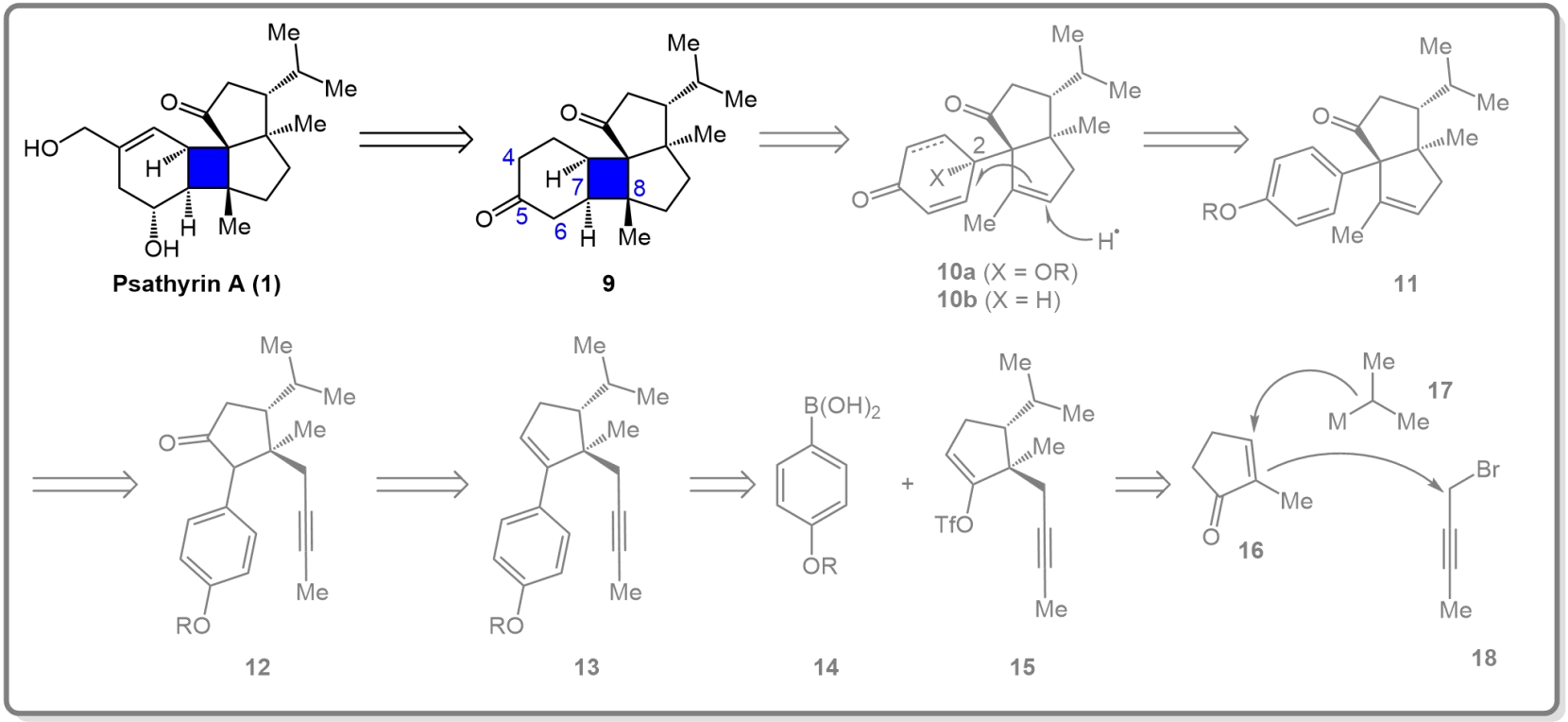
Synthesis of 28



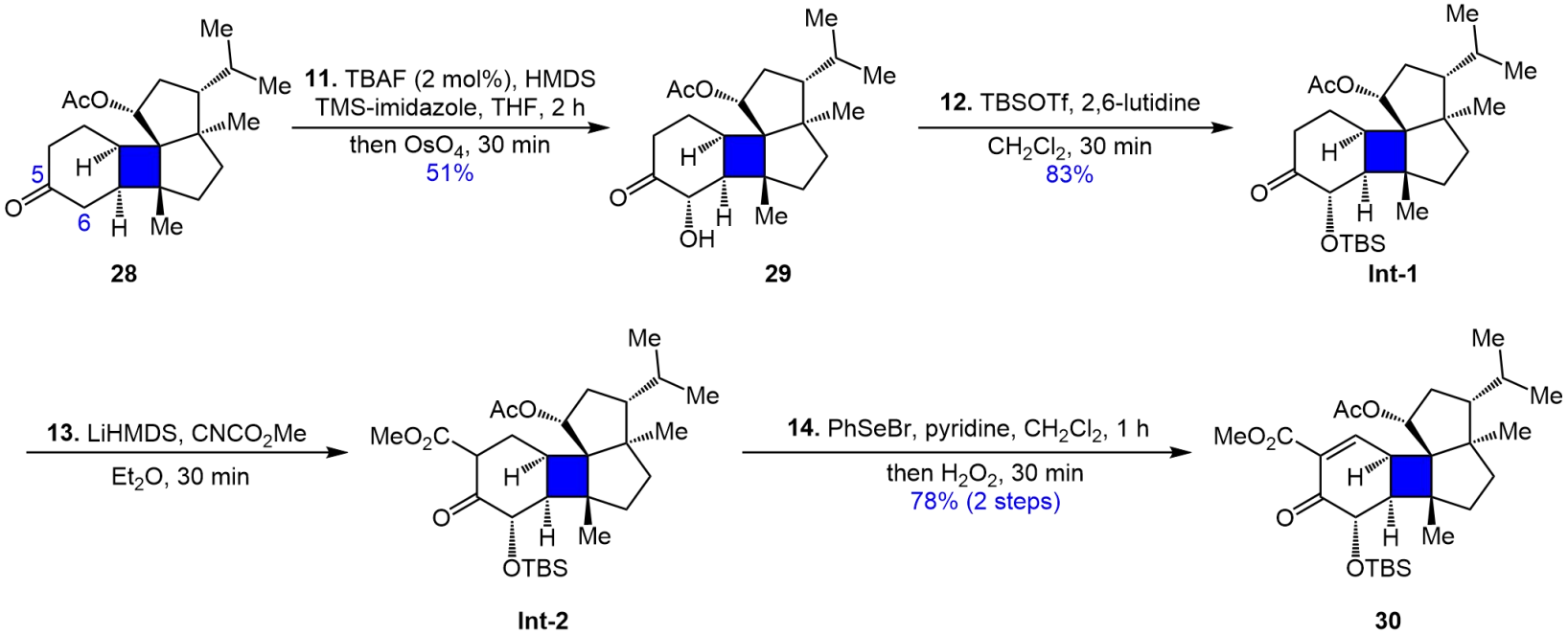
Synthesis of 28



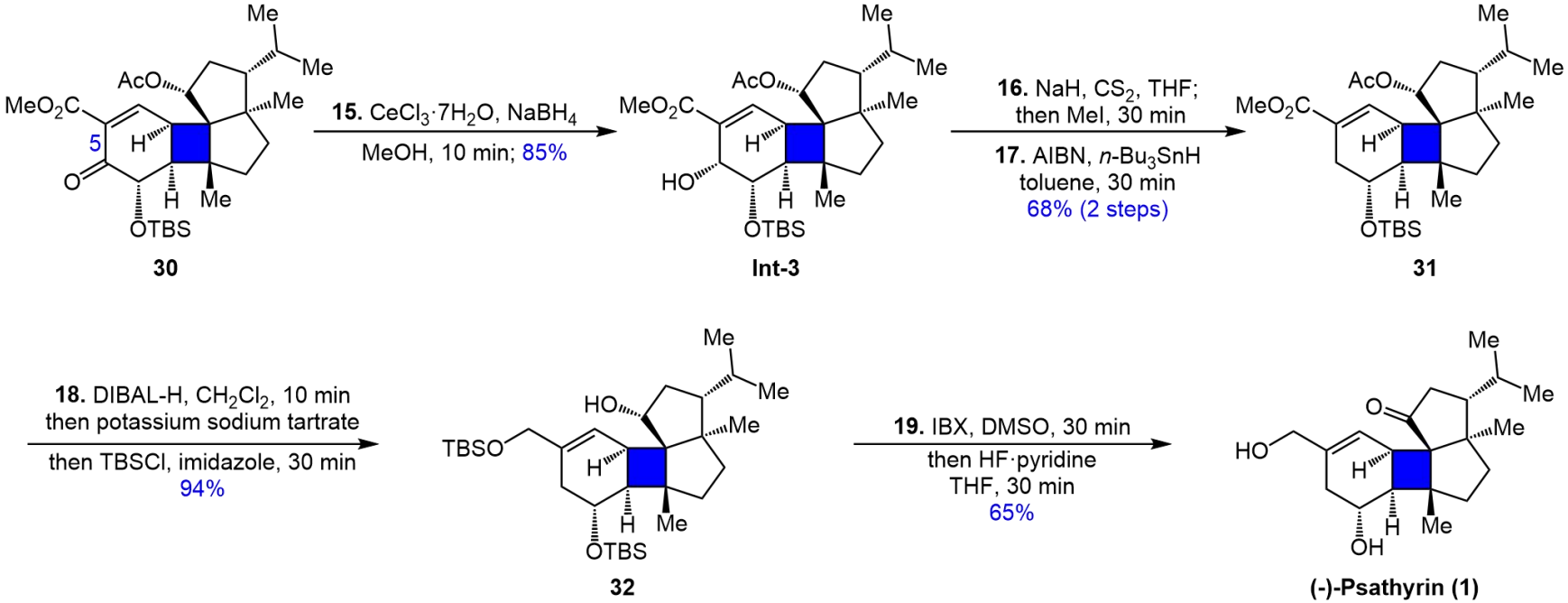
Synthesis of (−)-Psathyrin A



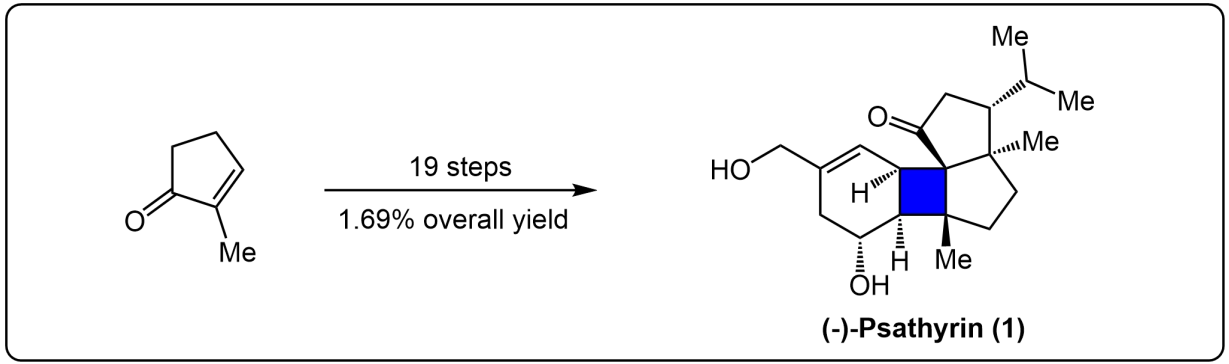
Synthesis of (−)-Psathyrin A



Synthesis of (−)-Psathyrin A



Summary



- The total synthesis of (−)-psathyrin A was completed in 19 steps.
- Our synthesis centers on a MHAT-initiated radical cyclization.
- Other notable steps include a tandem enantioselective conjugate addition and alkylation, a Suzuki−Miyaura reaction to introduce an aromatic ring as the six-membered ring precursor, and a gold(I)-catalyzed Conia-ene reaction to form the 5/5-fused bicyclic ring system and an all-carbon quaternary center.

Strategy for Writing The First Paragraph

Psathyrin A 来源

Psathyrin A 结构特征

Psathyrin A 生物活性

- Psathyrins A and B were isolated from the fermentation broth of Psathyrella candolleana by Liu, Feng, and co-workers in 2020.
- Structurally, the psathyrins represent two unique diterpene natural products featuring a complex and unprecedented 6/4/5/5 tetracyclic carbon skeleton. Each of them contains seven contiguous stereocenters, including three adjacent all-carbon quaternary centers, two of which reside on the strained cyclobutane ring.
- Biologically, psathyrins A and B were evaluated against Gram-positive Staphylococcus aureus and Gram-negative Salmonella enterica and Pseudomonas aeruginosa. Both compounds were found to exhibit weak activities against Staphylococcus aureu and Salmonella enterica, but not Pseudomonas aeruginosa.

Strategy for Writing The Last Paragraph

总结工作

- In summary, the first enantioselective total synthesis of (−)-psathyrin A was completed in 19 steps.

强调亮点

- Our synthesis centers on a MHAT-initiated radical cyclization to construct the highly congested and connected cyclobutane ring encoded by psathyrin A..... Other notable steps include a tandem enantioselective conjugate addition and alkylation to form the first two guiding stereocenters in the entire total synthesis, and a gold(I)-catalyzed Conia-ene reaction to form the 5/5-fused bicyclic ring system and an all-carbon quaternary center.

提出展望

- The application of radical cyclization strategies to synthesize strained molecules, particularly complex natural products, is currently ongoing in our laboratory and will be reported in due course.

Representative Examples

- Our longstanding interest in leveraging metal-catalyzed hydrogen atom transfer (MHAT) initiated radical cyclization for constructing strained ring systems prompted our pursuit of the psathyrins. (leverage v. 举债经营；充分利用(资源、观点等))
- Alternatively, we proposed another biosynthetic pathway from 5 to 8 involving a transannular [2 + 2] cycloaddition. (alternatively adv. (引出第二种选择或可能的建议)要不，或者)
- We utilized a counterintuitive MHAT-initiated radical cyclization to build its highly congested cyclopropane ring. (counterintuitive adj. 违反直觉的)

Acknowledgement

Thanks for Your Attention