Literature Report III

Enantioselective Total Synthesis of (–)-Psiguadial A

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O’Grady L. P.; Achtenhagen M.; Wisthoff M. F.; Chain W. J. *Angew. Chem. Int. Ed.* **2025**, e202506537

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CV of Prof. William J. Chain

Background:

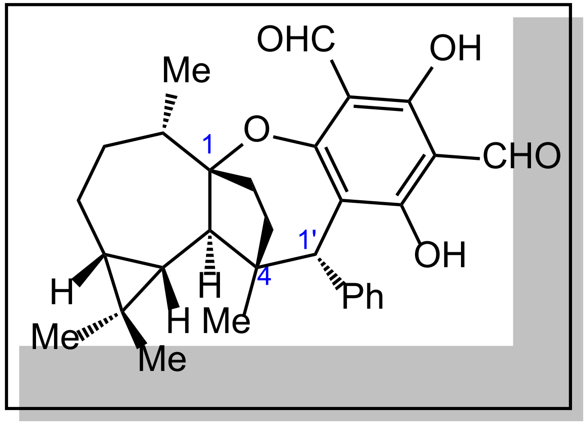
- ☐ **1997-2001** B.S., Pennsylvania State University
- ☐ **2001-2006** Ph.D., Harvard University
- ☐ **2006-2009** Postdoc., Princeton University
- ☐ **2009-2015** Assistant Professor, University of Hawaii at Manoa
- ☐ **2019-Now** Associate Professor, University of Delaware

Research Field:

- Total Syntheses of Natural Products
- Synthetic Methodology

Contents

Introduction



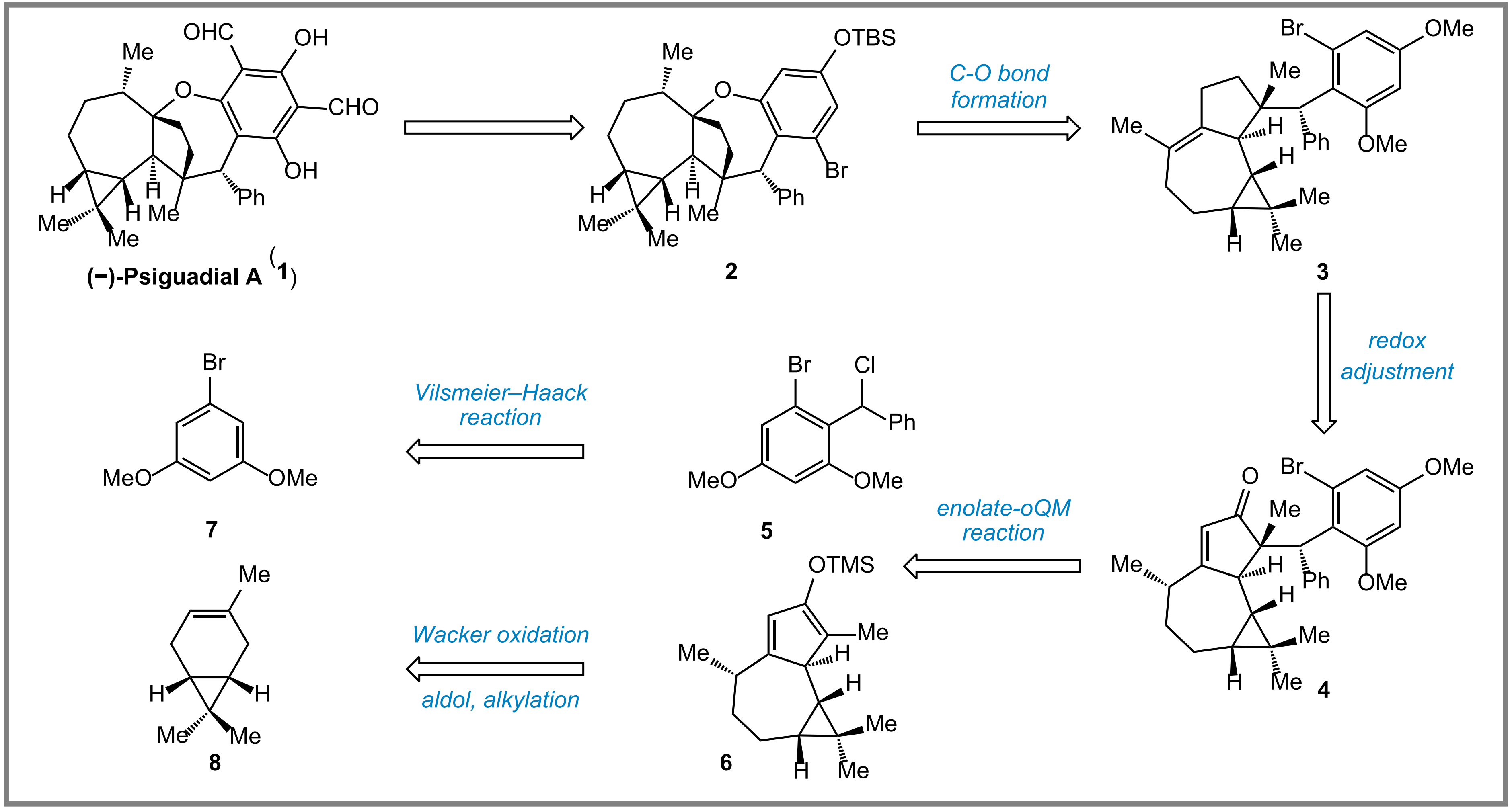
(–)-Psiguadial A

Psidium guajava

- It was Isolated from Leaves of *Psidium guajava* in 2010;
- It Contains a *cis* Fused Cyclopropane and Highly Functionalized Oxepane Ring;
- Potent Antiproliferative Compound (HepG2 IC50 = 61 nM).

Shao, M.; Wang, Y.; Liu, Z.; Ye, W.-C.*(叶文才) *Org. Lett.* **2010**, *12*, 5040–5043

Retrosynthetic Analysis



(−)-Psiguadial A (1)

2

C-O bond formation

3

redox adjustment

4

enolate-oQM reaction

5

Vilsmeier–Haack reaction

7

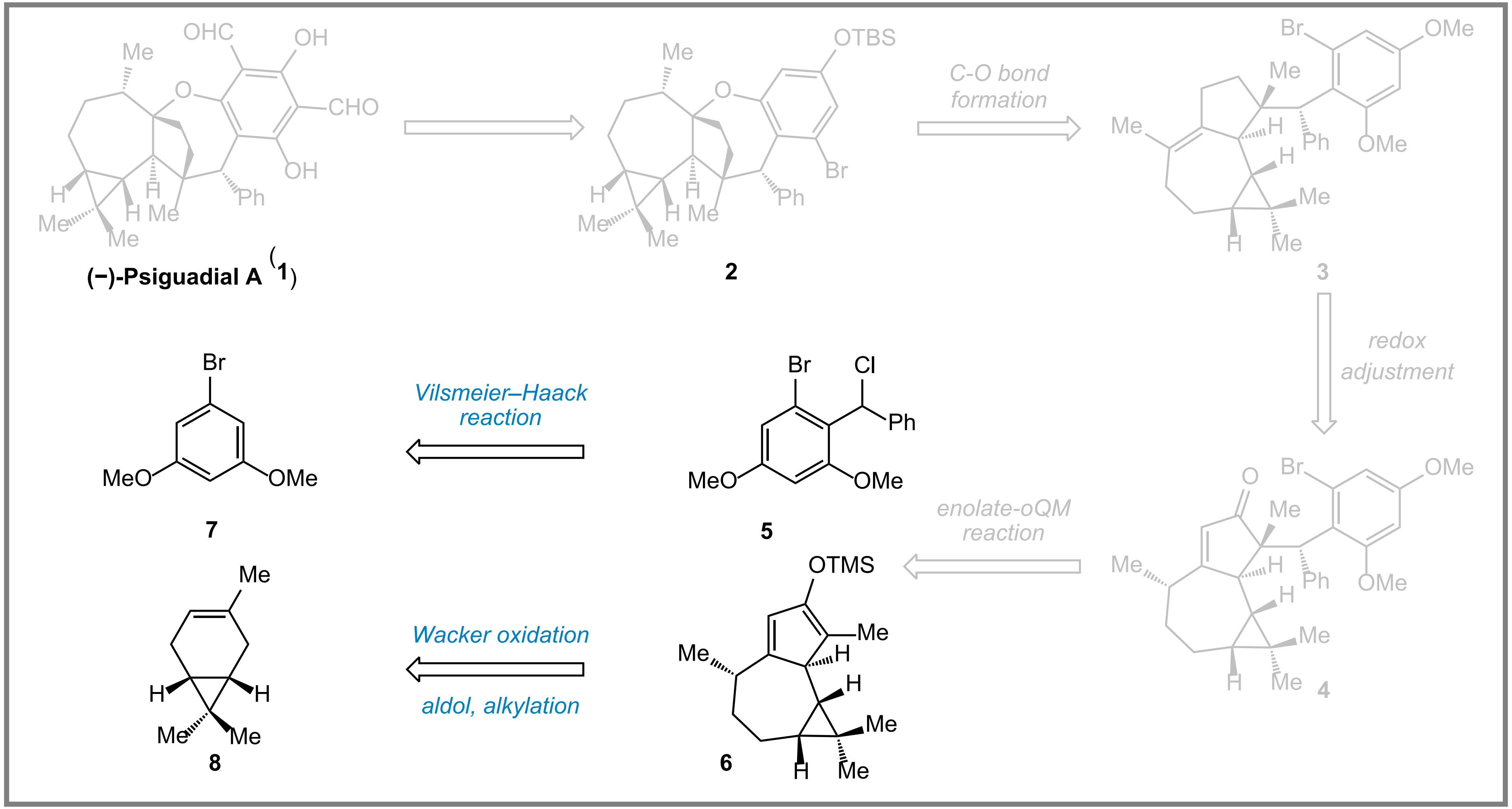
6

Wacker oxidation

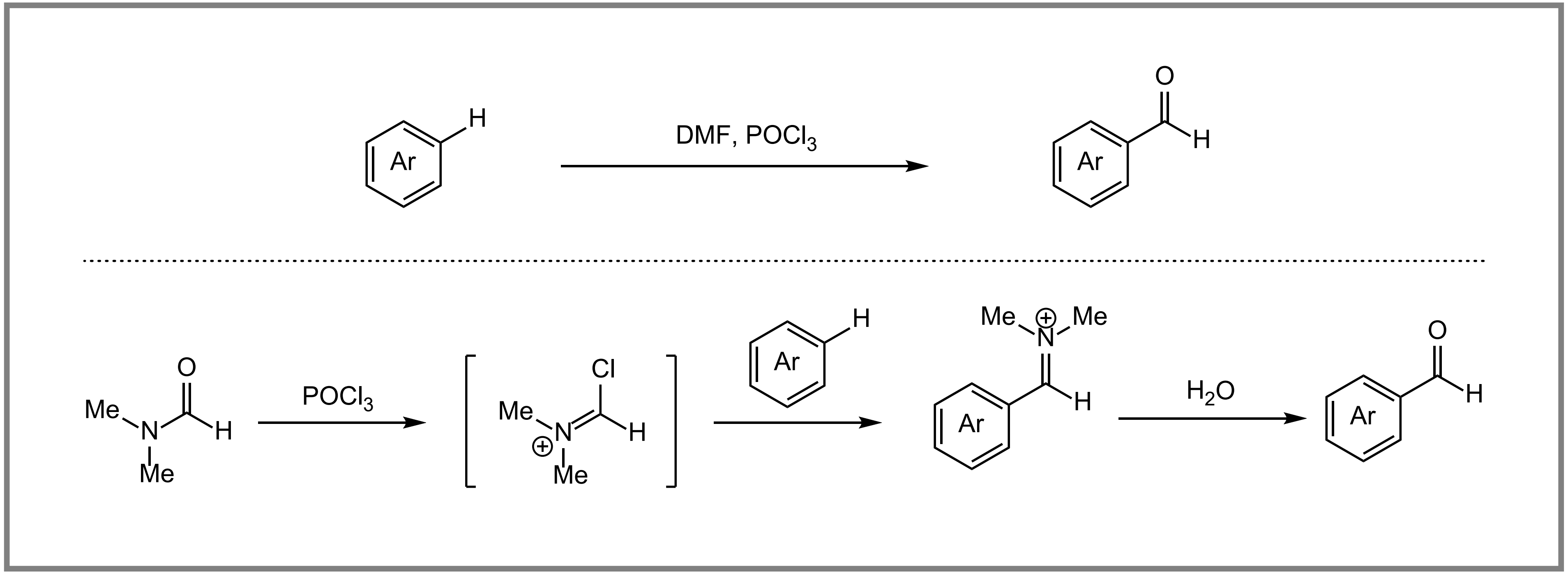
aldol, alkylation

8

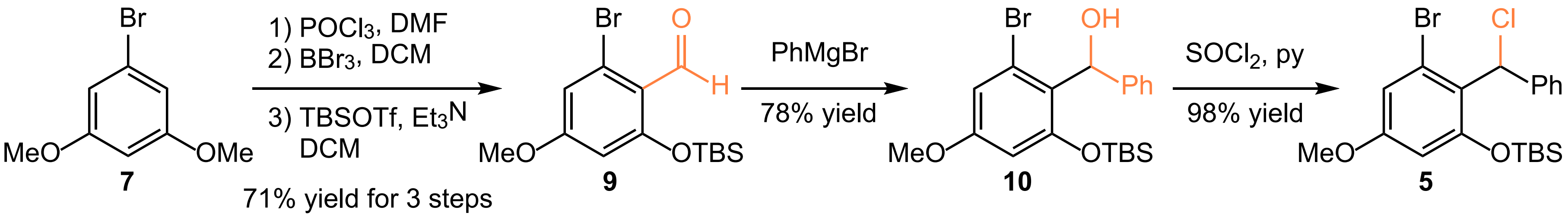
Retrosynthetic Analysis



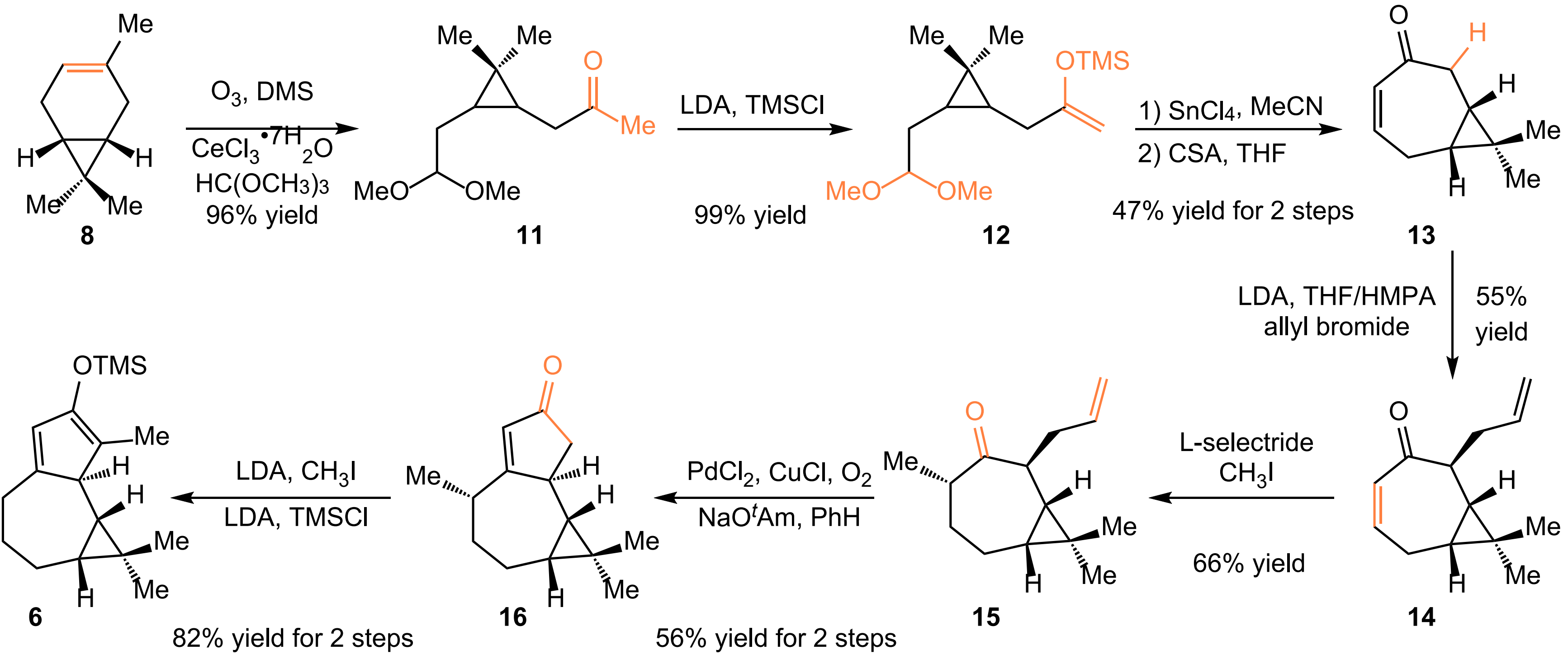
Vilsmeier–Haack Reaction



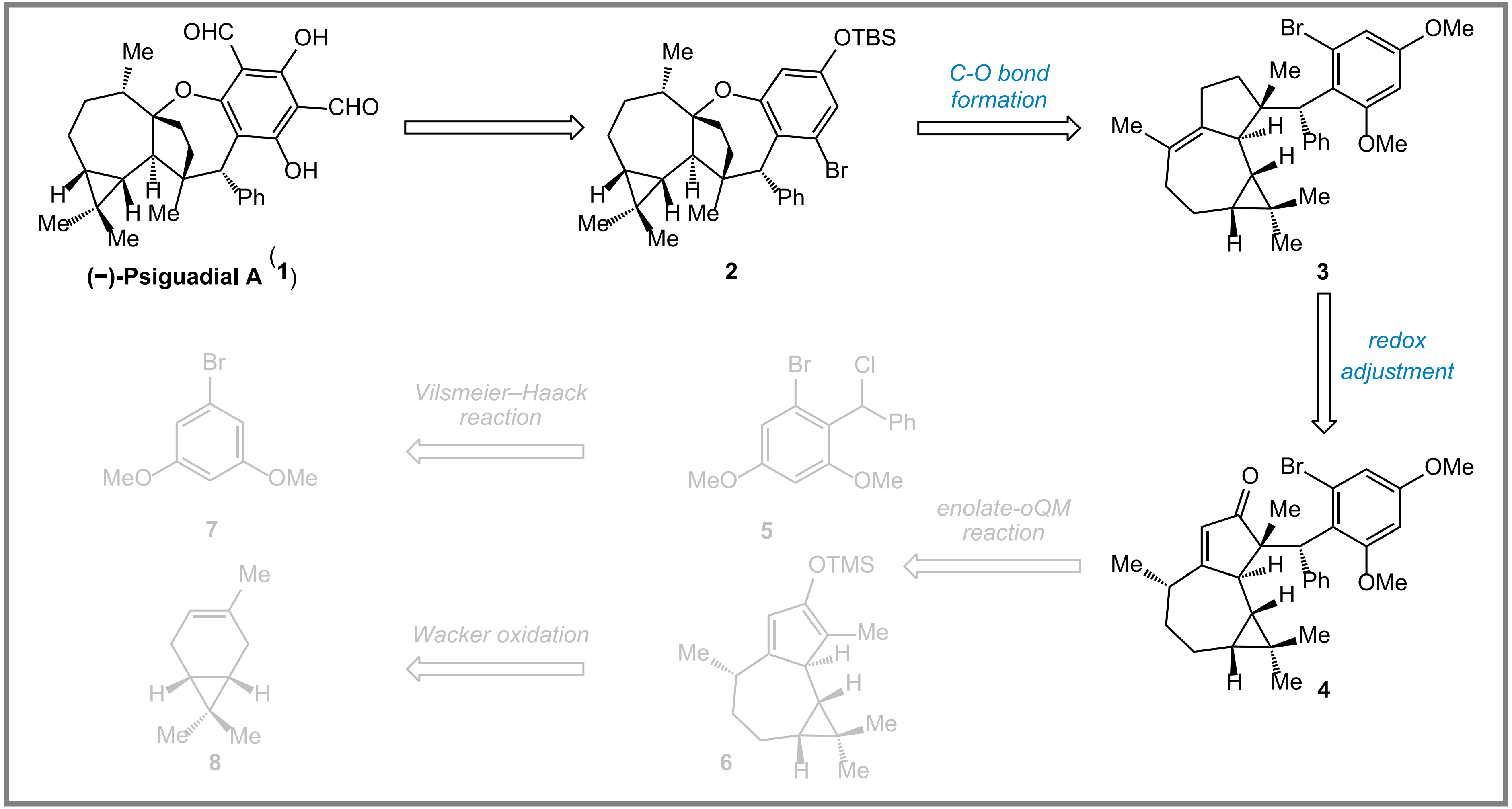
Synthesis of Compound 5



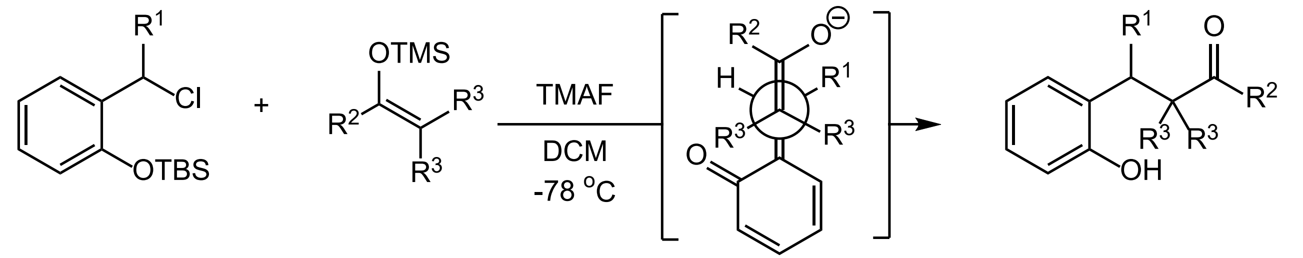
Synthesis of Compound 6

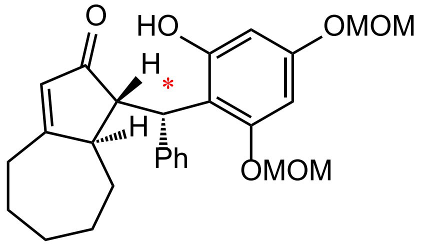


Retrosynthetic Analysis

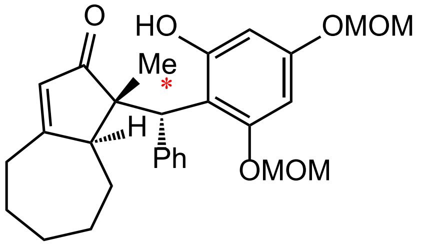


Enolate-*ortho*-quinone Methide Coupling Reaction

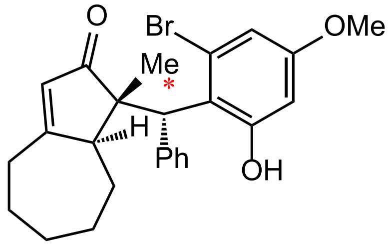




46% yield, 1.5:1 *dr*

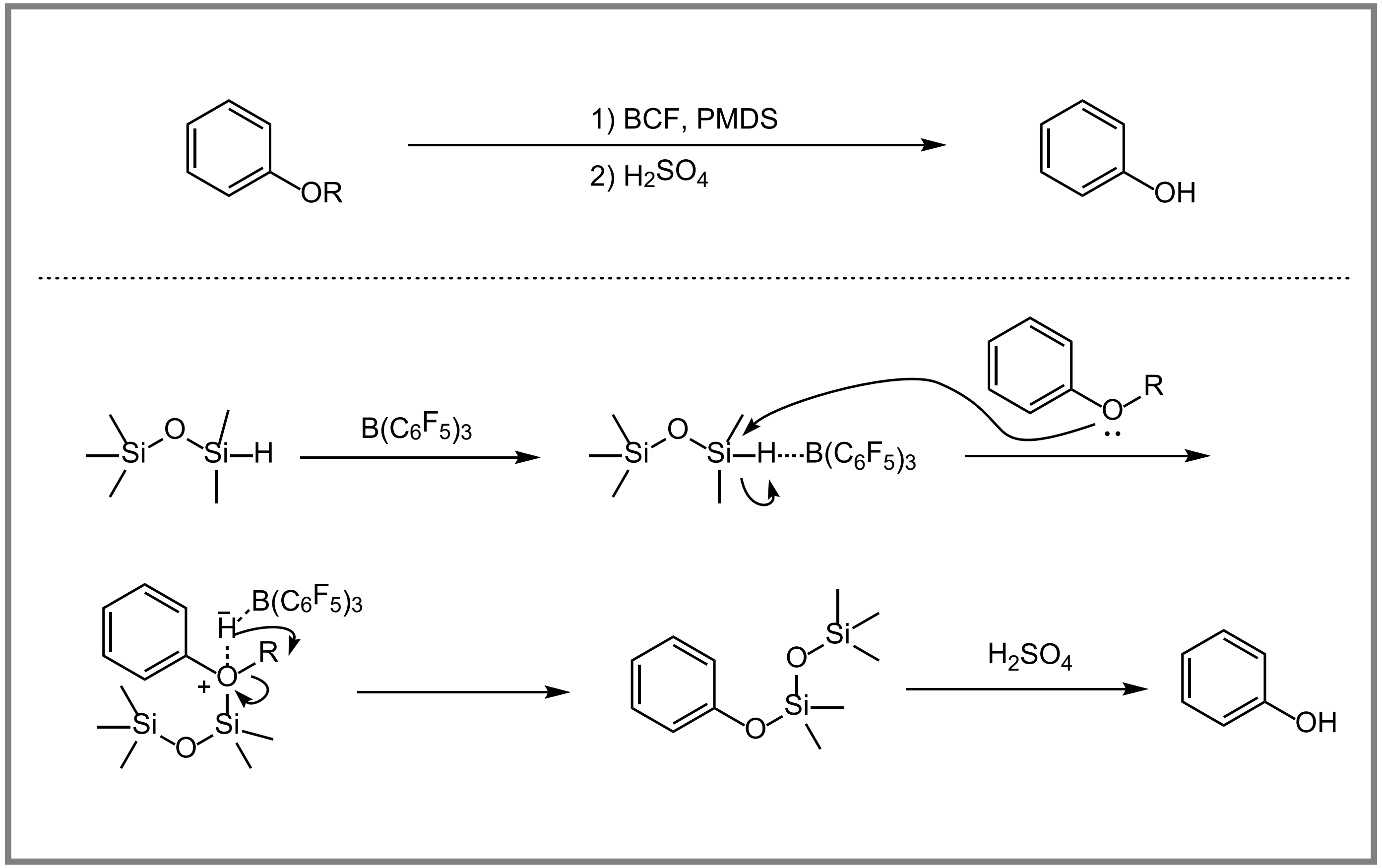


34% yield, 1:1 *dr*

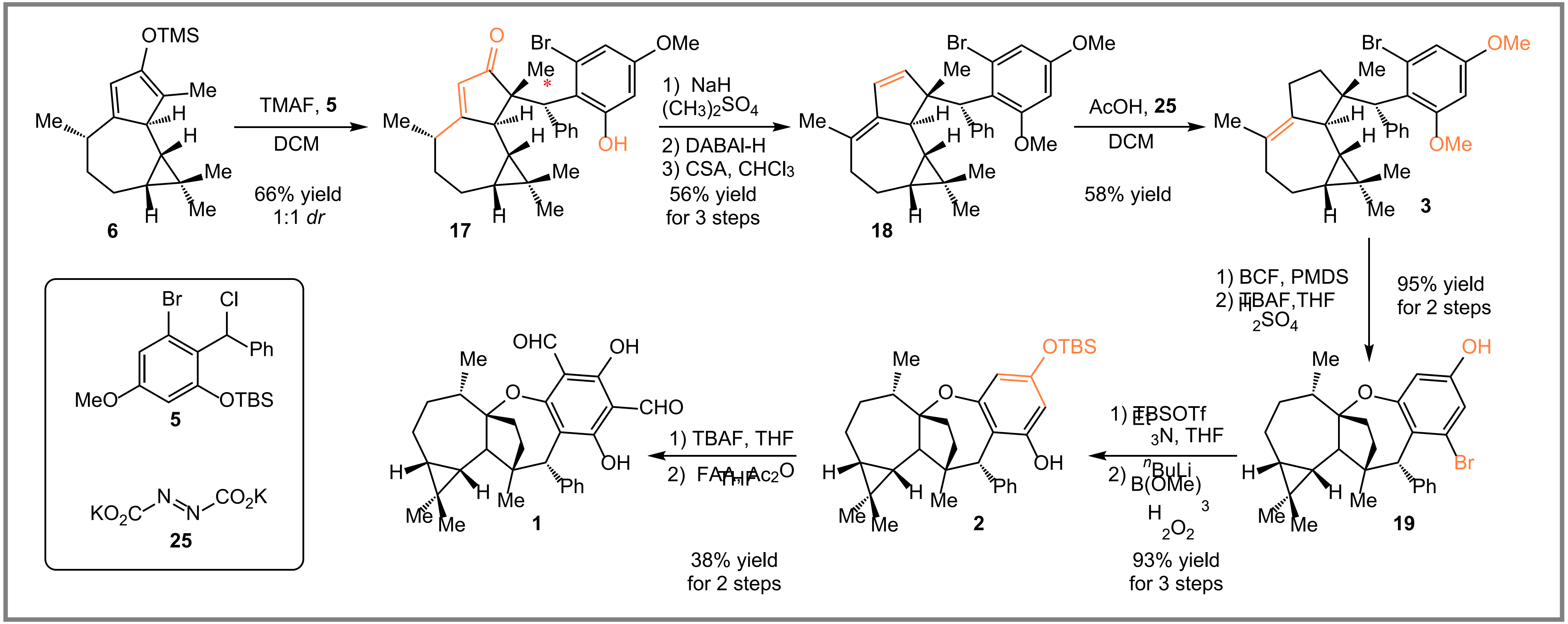


62% yield, 1:1 *dr*

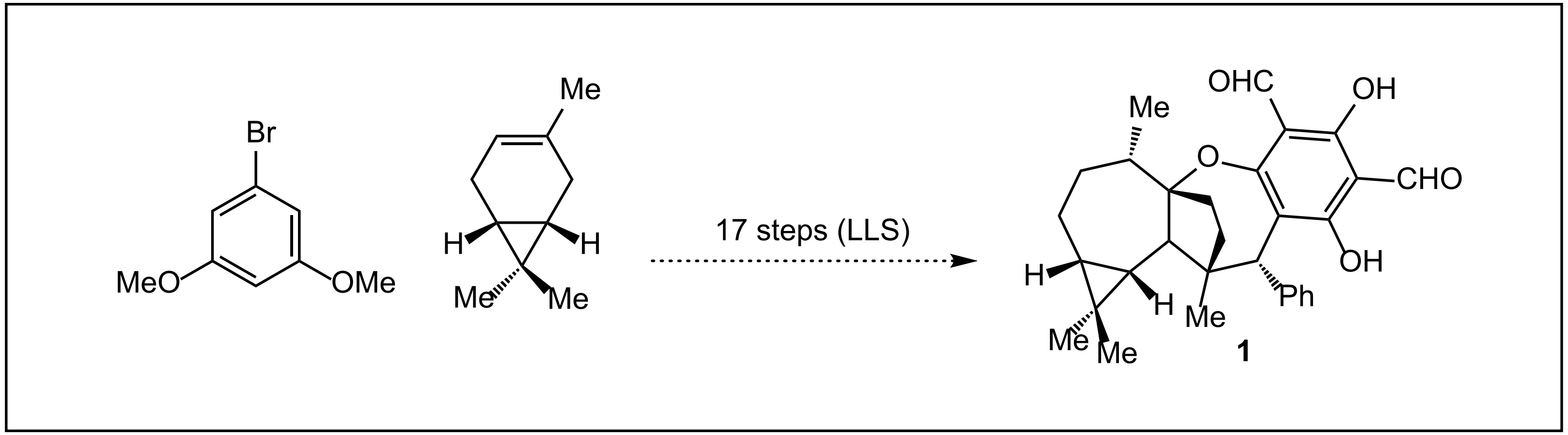
Mechanism of Piers-Rubinsztajn Demethylation Reaction



Synthesis of Compound 1



Summary



1

- An Efficient Enolate-*ortho*-quinone Methide Coupling Reaction Forges the Key C1’—C4 Bond;
- An Acid-mediated Intramolecular Hydration Ring-closure Leveraging Fully Substituted Alkene to Generate the Unique Oxepane Core Structure
- FAA/Ac_2O Fomylation Protocol Proved Uniquely Effective in the Synthesis and is a Powerful Method for the Preparation of Complex Formylated Phenols;

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Writing Strategy

First Paragraph

History

Biological Activity

Challenge

- The extracts of the leaves and bark of the common guava (Psidium guavajava [Myrtaceae]) have yielded over 50 distinct natural products to date with myriad biological properties including anti-inflammatory, anti-bacterial, and anticancer activities.
- Psiguadial A is a polycyclic meroterpenoid that was isolated along with its congener psiguadial B in 2010 by Ye and coworkers and is a potent antiproliferative compound (HepG2 IC50 = 61 nM)
- This unique core presents a dense array of contiguous stereogenic centers with high hydrocarbon character that lack convenient functional groups that might serve as synthetic handles. In addition, the C1'—C4 and C1—O bond connections feature fully substituted carbons that are particularly challenging to generate synthetically.

Writing Strategy

Last Paragraph

Summary

Key Steps

Prospect

- In summary, we completed a convergent, enantioselective total synthesis of psiguadial A that leverages an efficient enolate-ortho-quinone methide coupling reaction.
- This powerful methodology forges the key C1’—C4 bond, which could not be achieved by alkylative methods with conventional metal enolates and alkyl halide electrophiles. The unique oxepane core 26 of the natural product was completed in just 17 steps from (+)-3-carene (9), showcasing an elegant and biomimetic acid-mediated ring closure event in a highly complex setting ……
- Our current efforts are directed toward the application of enolate-*ortho*-quinone methide coupling strategies to the psidials and other related meroterpenoid natural products to support biological studies with these fascinating scaffolds

Representative Examples

- A biomimetic approach harnessing reactive species enabled the enantioselective synthesis of the complex meroterpenoid psiguadial A through an enolate-*ortho*-quinone methide (oQM) umpolung strategy and late-stage cationic ring closure. (*adj*. 极性反转)
- In principle, the C1—O bond could arise from a straightforward intramolecular oxa-Michael reaction joining the phenol with the proximal cyclopentenone . (*adj*.邻近的, 近端的)
- Exposure of the bisphenol to aqueous sulfuric acid and THF induced an acid-mediated hydration reaction of the alkene forging the C1—O bond and affording pure oxepane 26 in 95% yield over two steps. (*n*. 暴露, 揭露)

Acknowledgement

Thank You for Your Attention!