Total Synthesis of Epicolactone

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Checker: Hong-Qiang Shen
Date: 2018/11/12

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Angew. Chem. Int. Ed. **2018**, *57*, 13159.

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CV of Prof. Erick M. Carreira

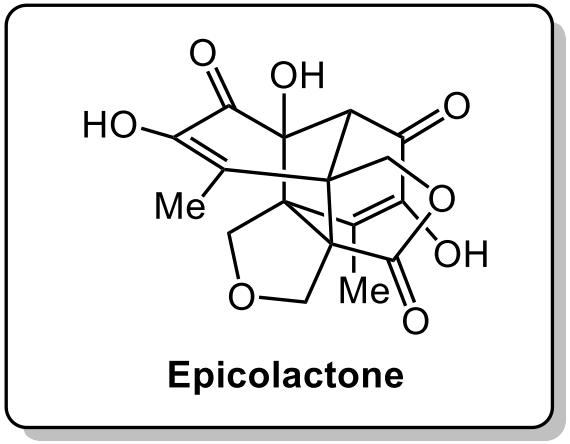
Background:

- **1980-1984** B.S., UIUC (Scott E. Denmark)
- **1984-1990** Ph.D., Harvard University (David A. Evans)
- **1990-1992** Postdoc, Caltech (Peter Dervan)
- **1992-1996** Assistant Professor, Caltech
- **1996-1997** Associate Professor, Caltech
- **1997-1998** Professor, Caltech
- **1998-Now** Professor, ETH Zurich

Research Interests:

- ✓ Asymmetric synthesis of biologically active and stereochemically complex natural products
- ✓ Organometallic chemistry, coordination chemistry and molecular recognition
- ✓ Catalytic and stoichiometric reagents for asymmetric stereocontrol, including chiral Lewis acids and transition-metal based reductants

Introduction



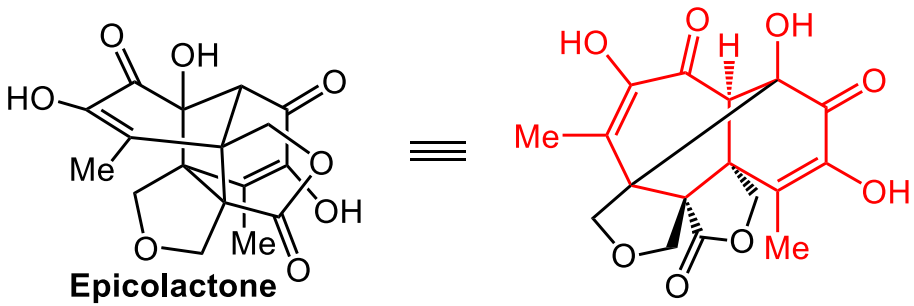
Epicolactone

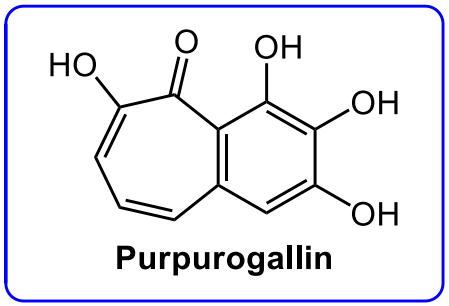
Epicoccum nigrum

- Isolated from the sugarcane endophytic fungus *Epicoccum nigrum* in 2012;
- Exhibiting both antimicrobial and antifungal activity;
- Highly oxygenated caged pentacyclic structure.

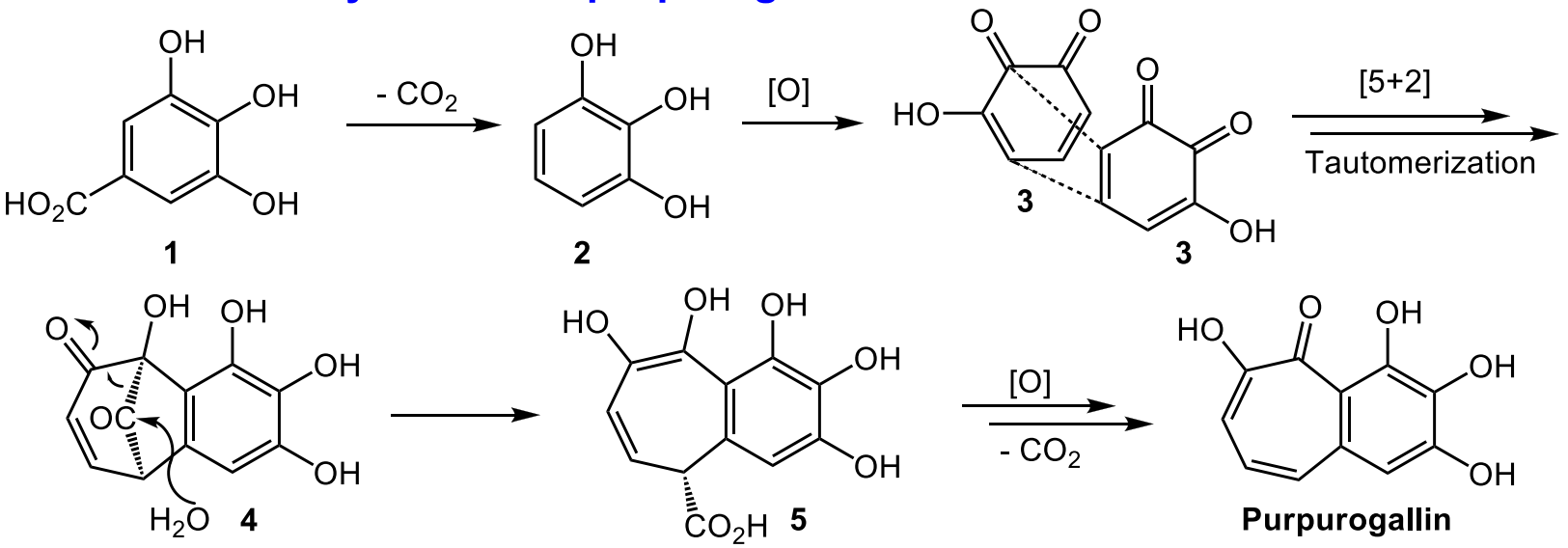
Marsaioli, A. J. et al. *Eur. J. Org. Chem.* **2012**, 5225.

Biomimetic Synthesis of Epicolactone



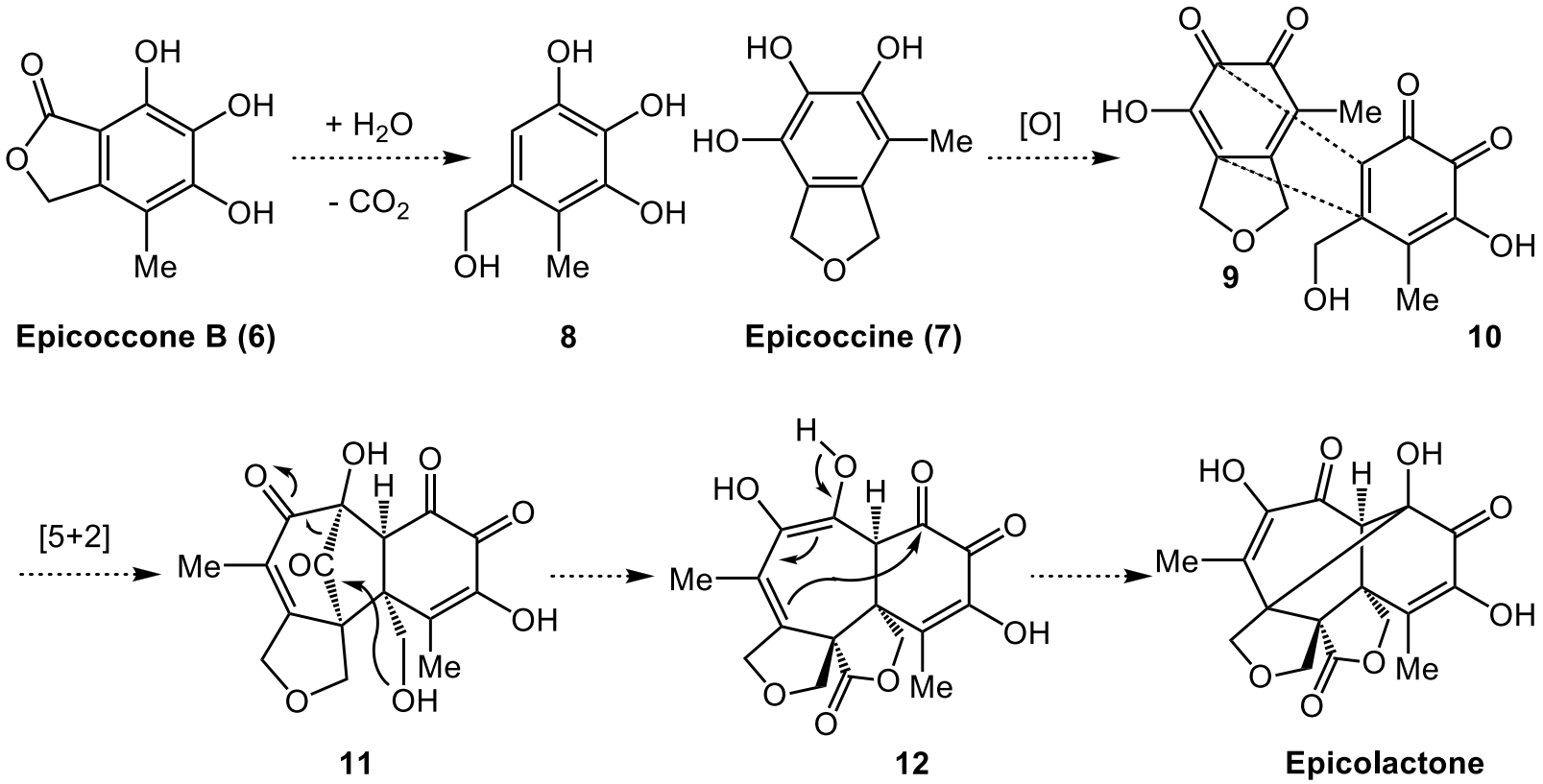


Established biosynthesis of purpurogallin

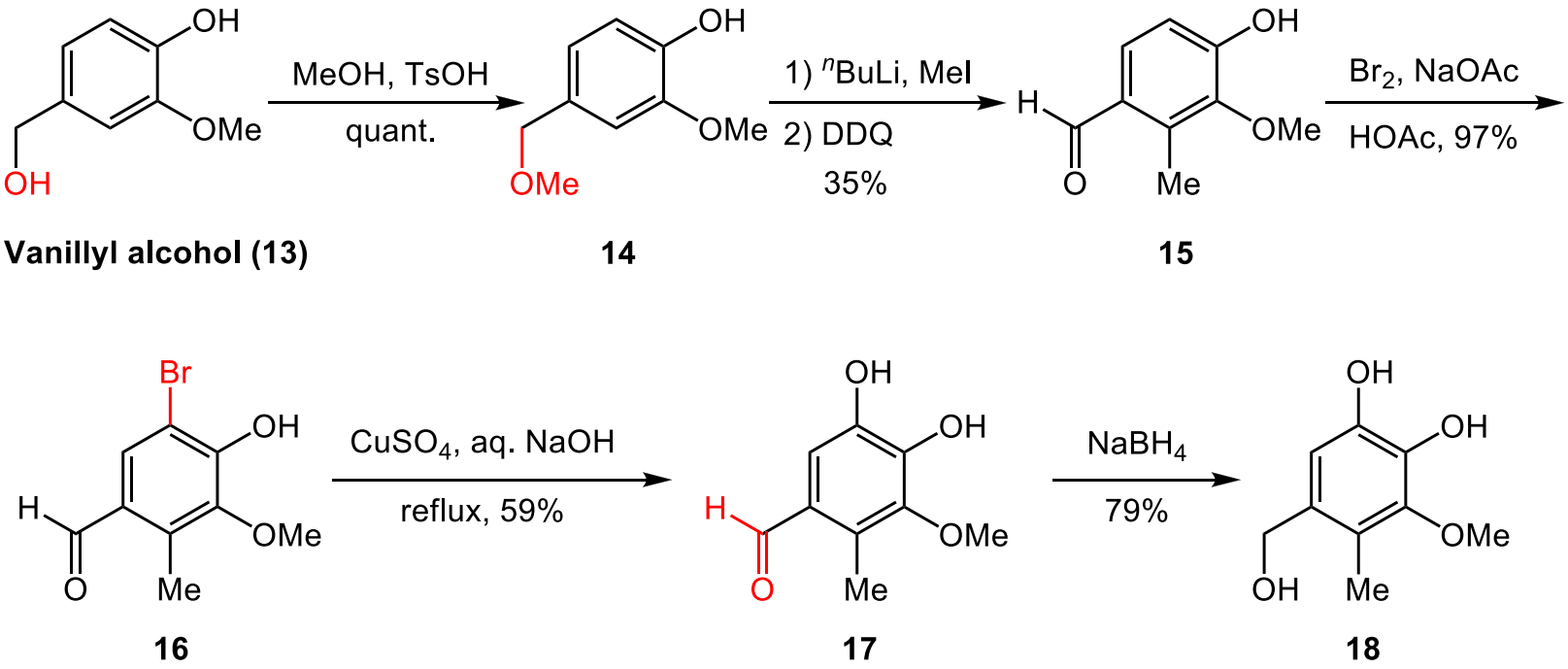


Trauner, D. et al. *Nat. Chem.* **2015**, *7*, 879.

Proposed Biosynthesis of Epicolactone



Synthesis of Compound 18

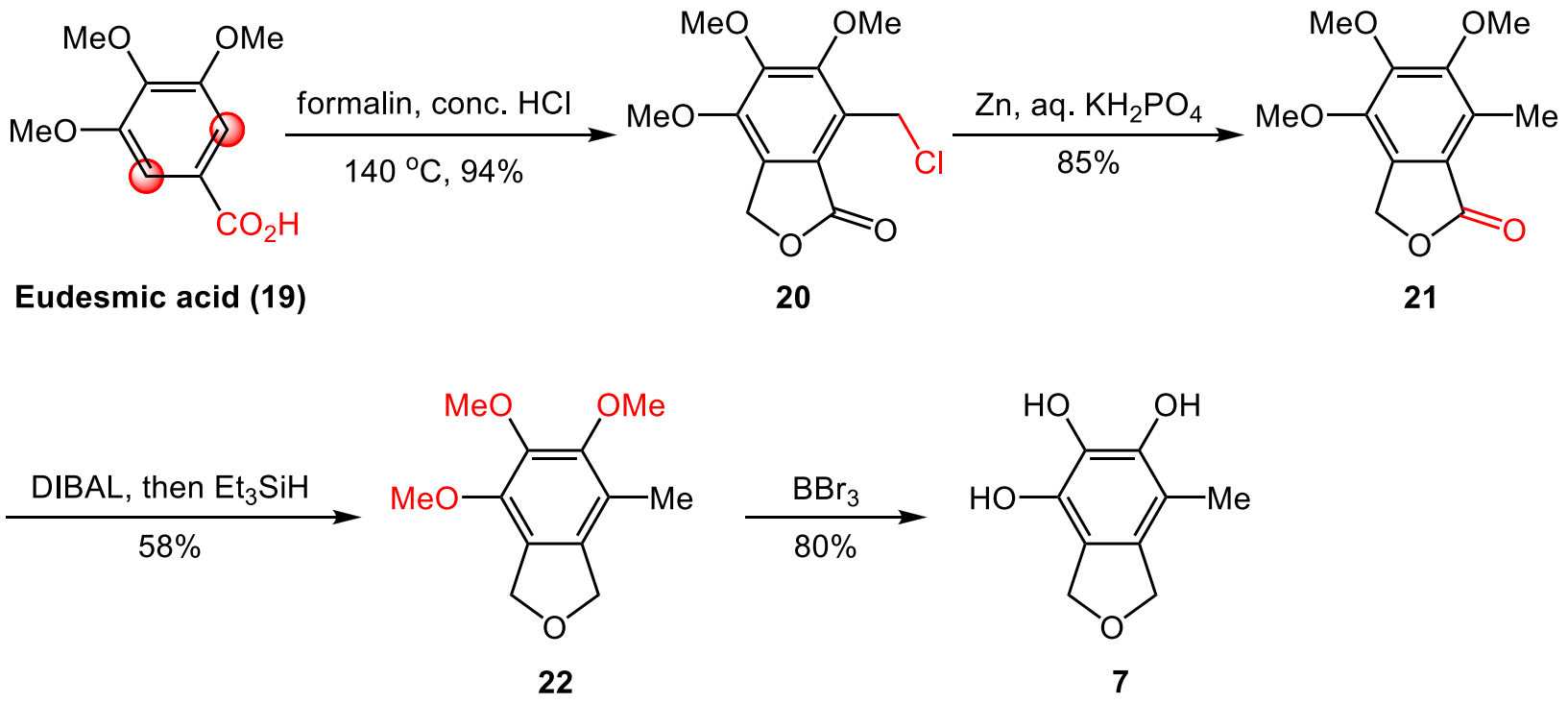


Vanillyl alcohol (13) **14** **15**

16 **17** **18**

Danishefsky, S. J. et al. *Org. Lett.* **2006**, *8*, 5693.

Synthesis of Compound 7

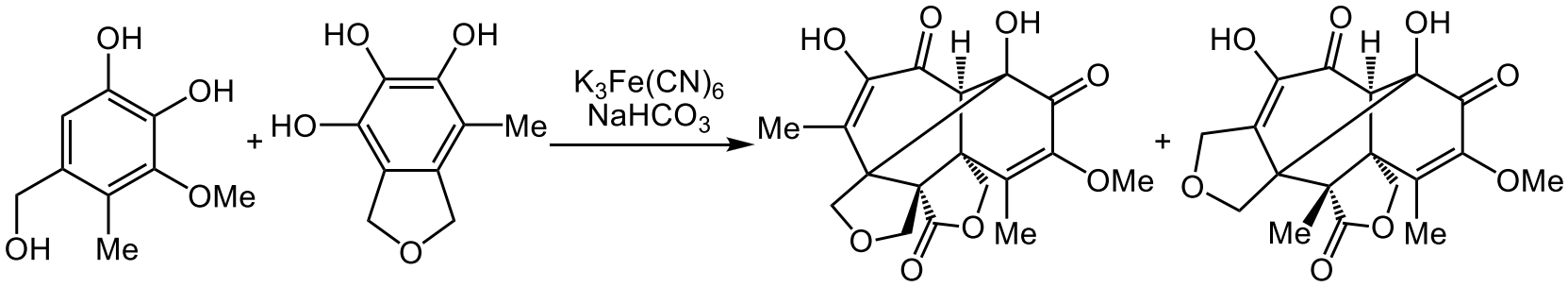


Eudesmic acid (19) **20** **21**

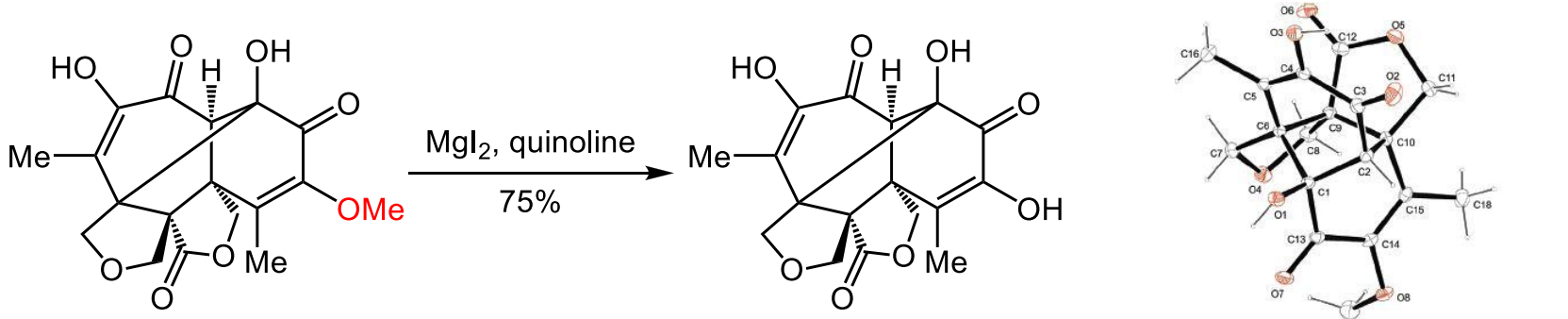
22 **7**

Trauner, D. et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 13414.

Synthesis of Epicolactone



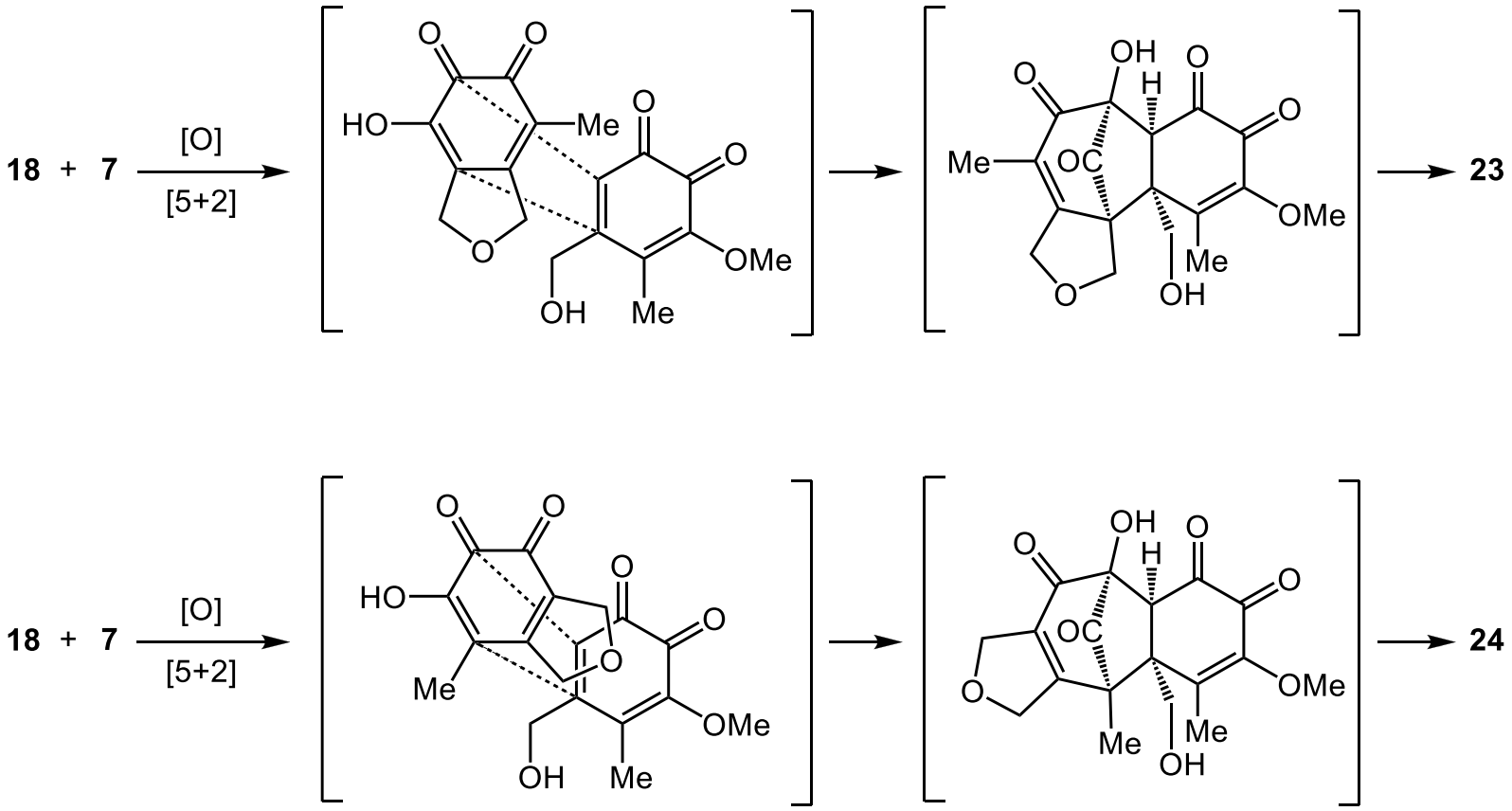
18 **7** **23** (42%) **24** (16%)



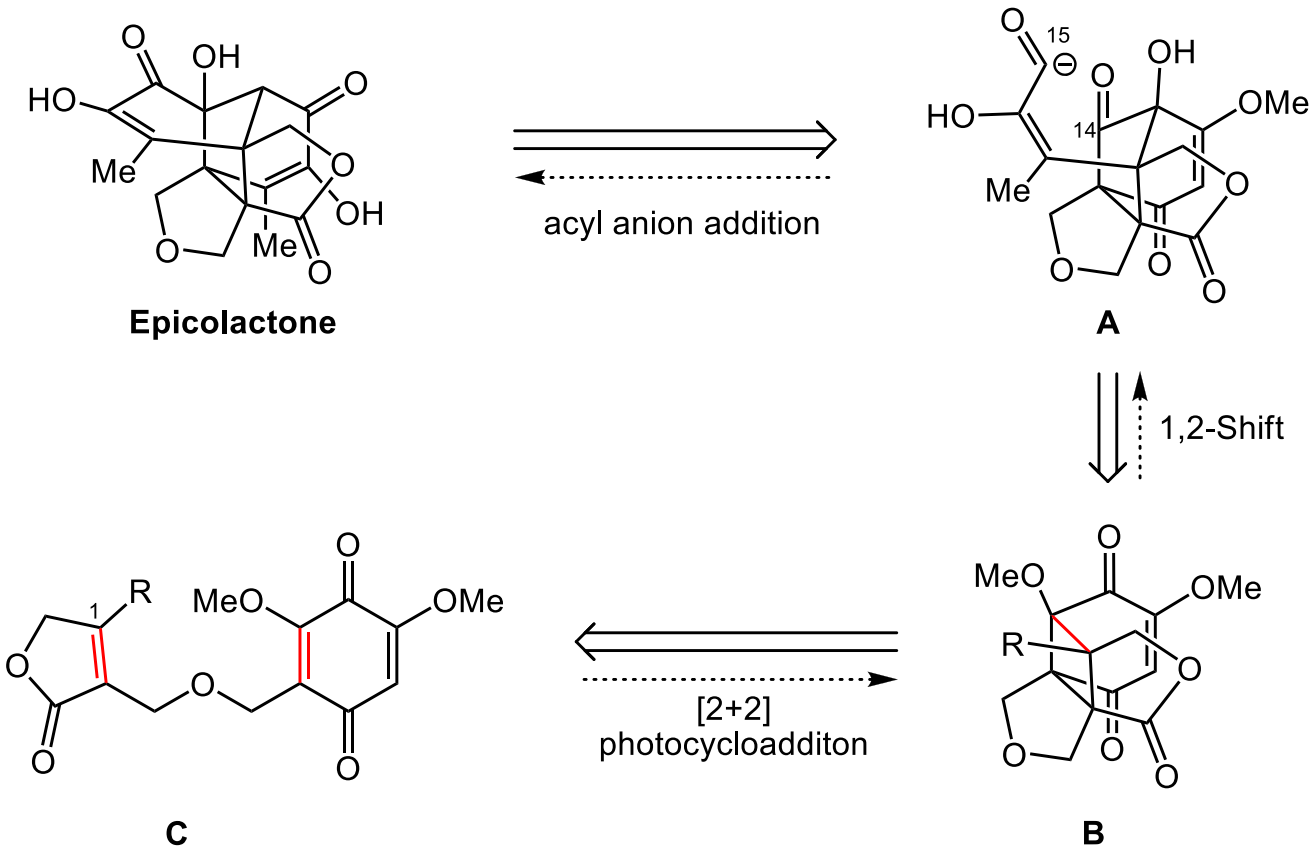
23 **Epicolactone**

23

Synthesis of Compounds 23 and 24

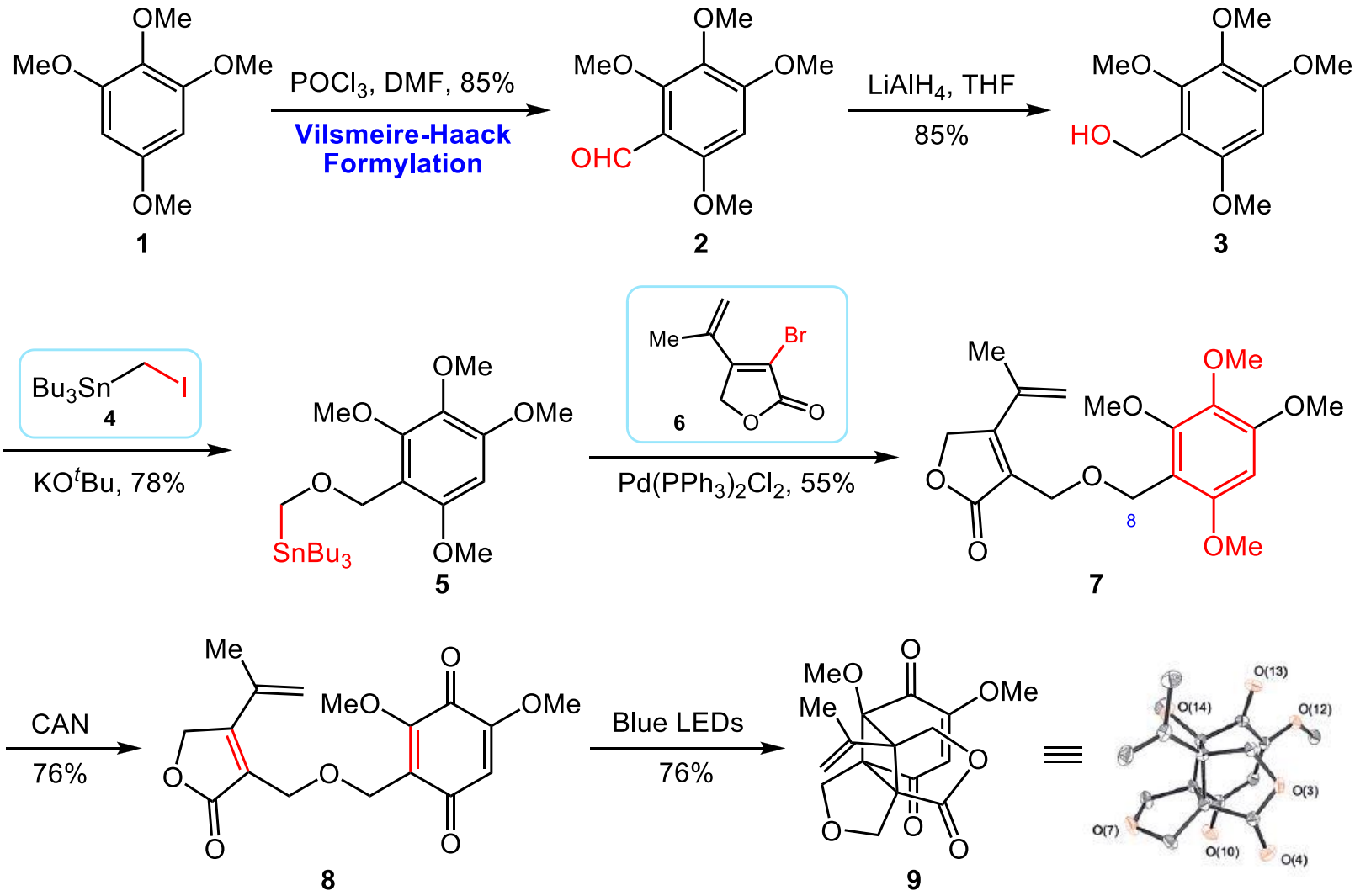


Retrosynthetic Analysis

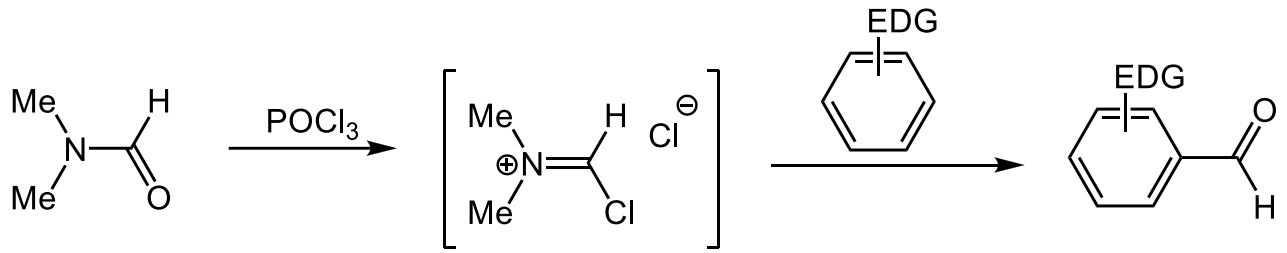


Carreira, E. M. et al. *Angew. Chem. Int. Ed.* **2018**, *57*, 13159.

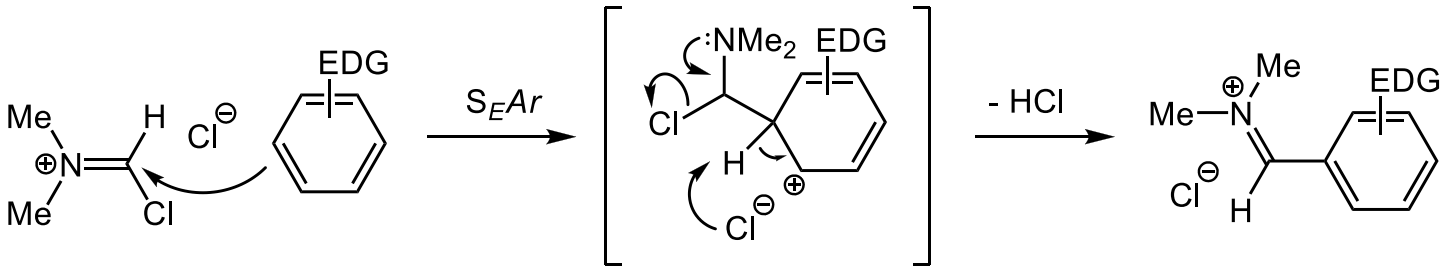
Synthesis of Compound 8

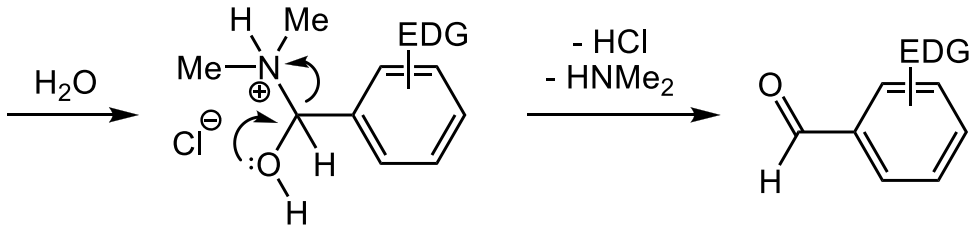


Vilsmeire-Haack Formylation

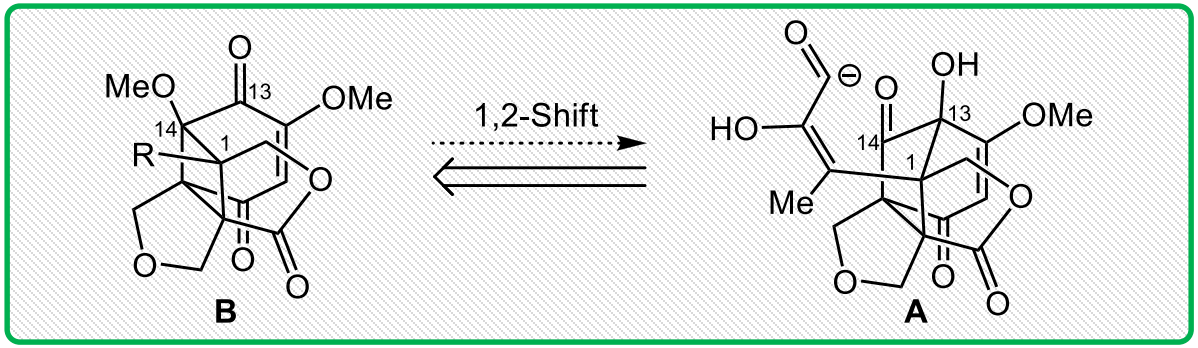


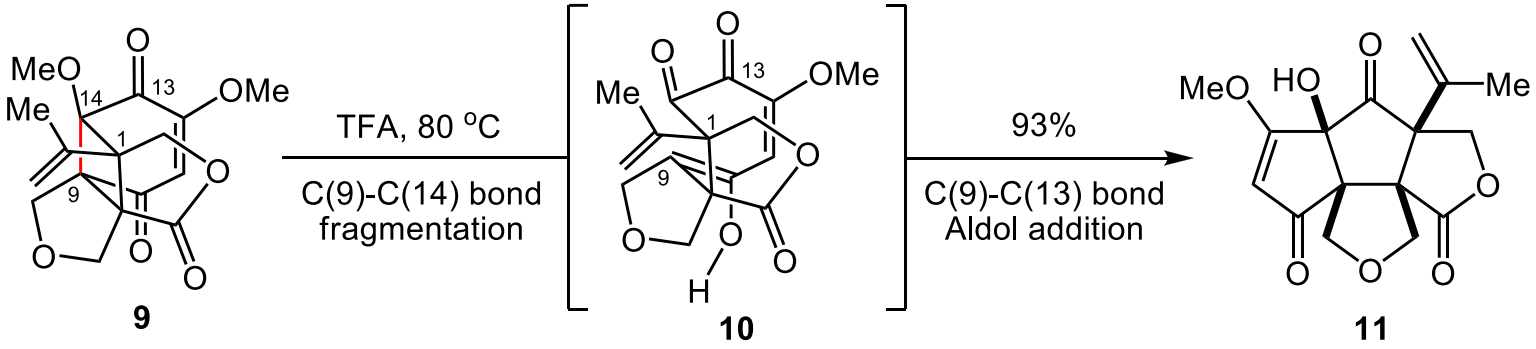
Vilsmeier reagent

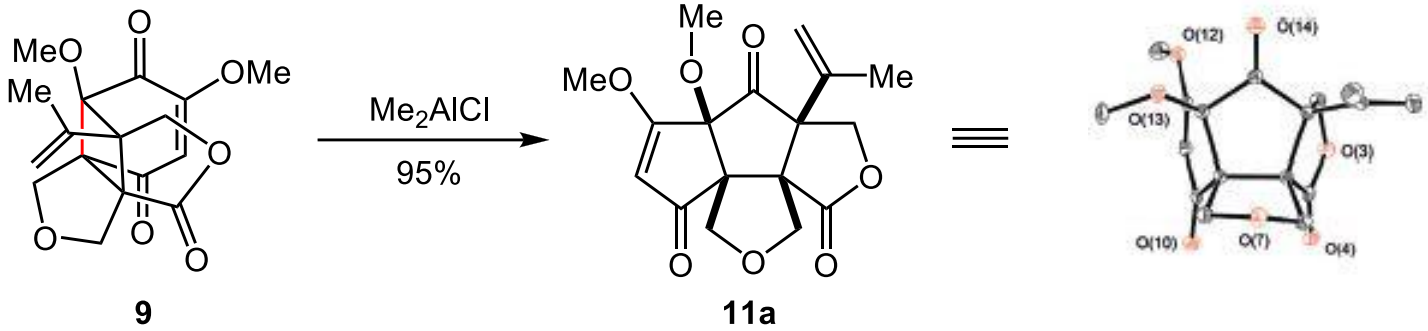




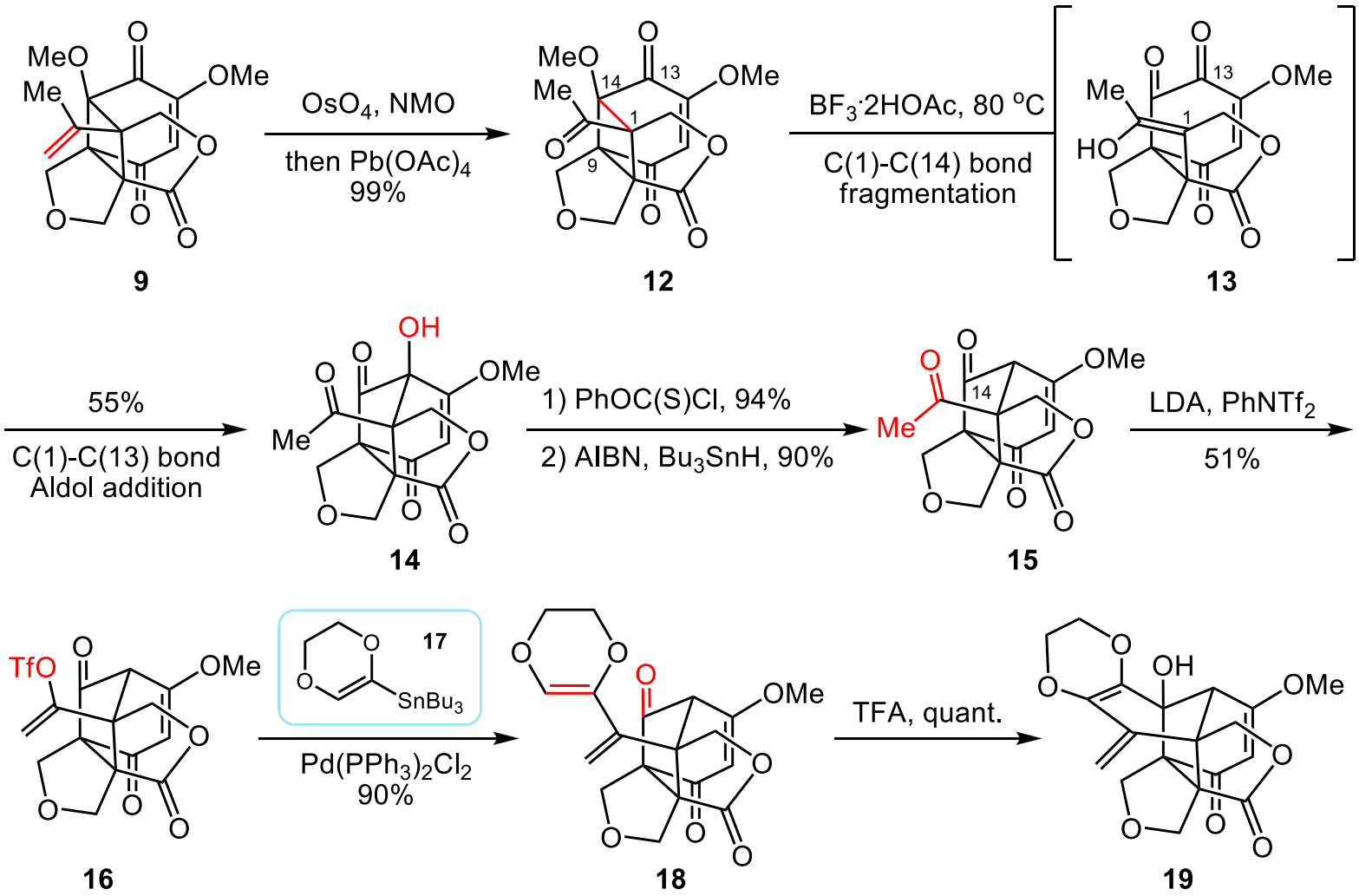
Synthesis of Compound 11



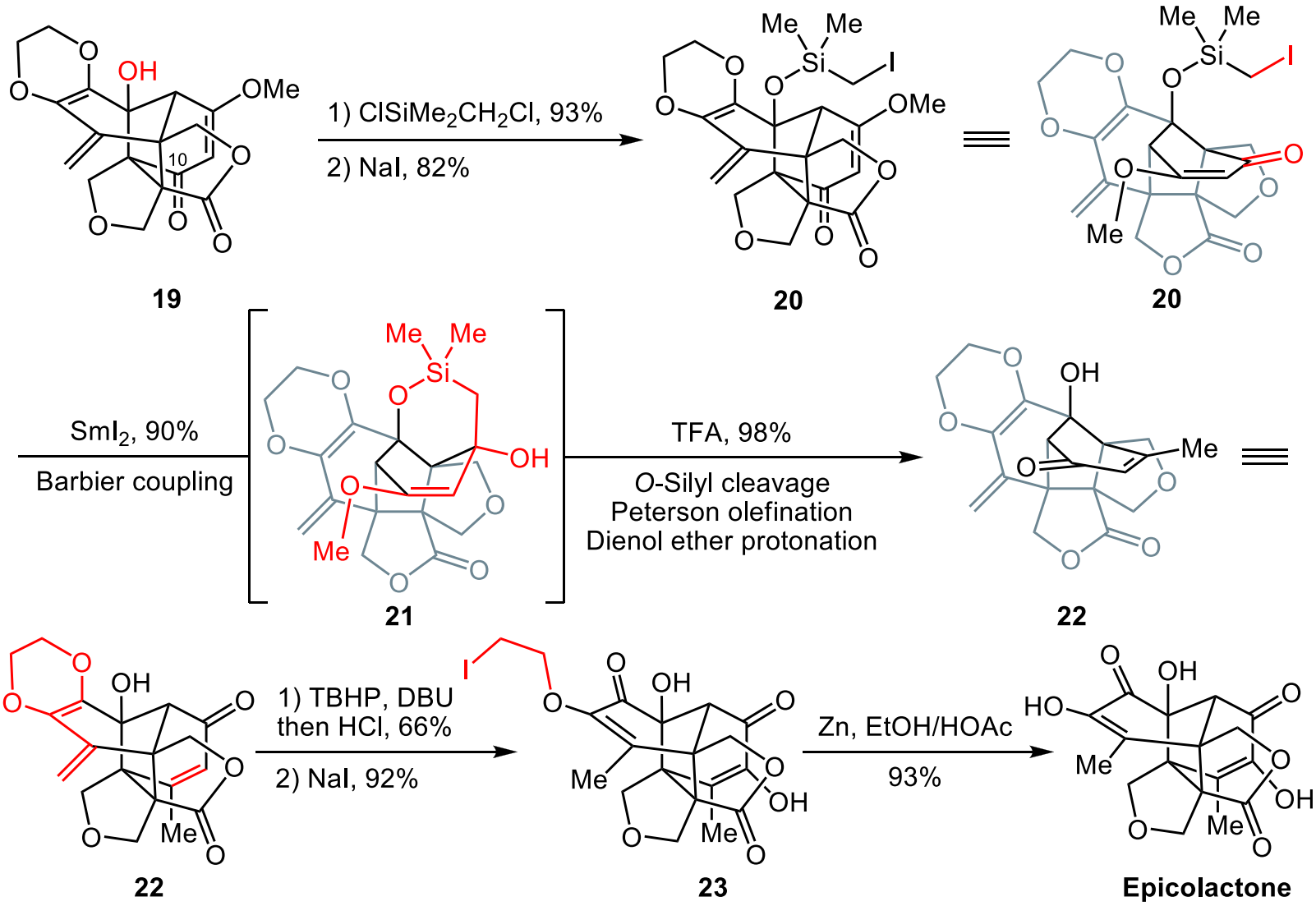




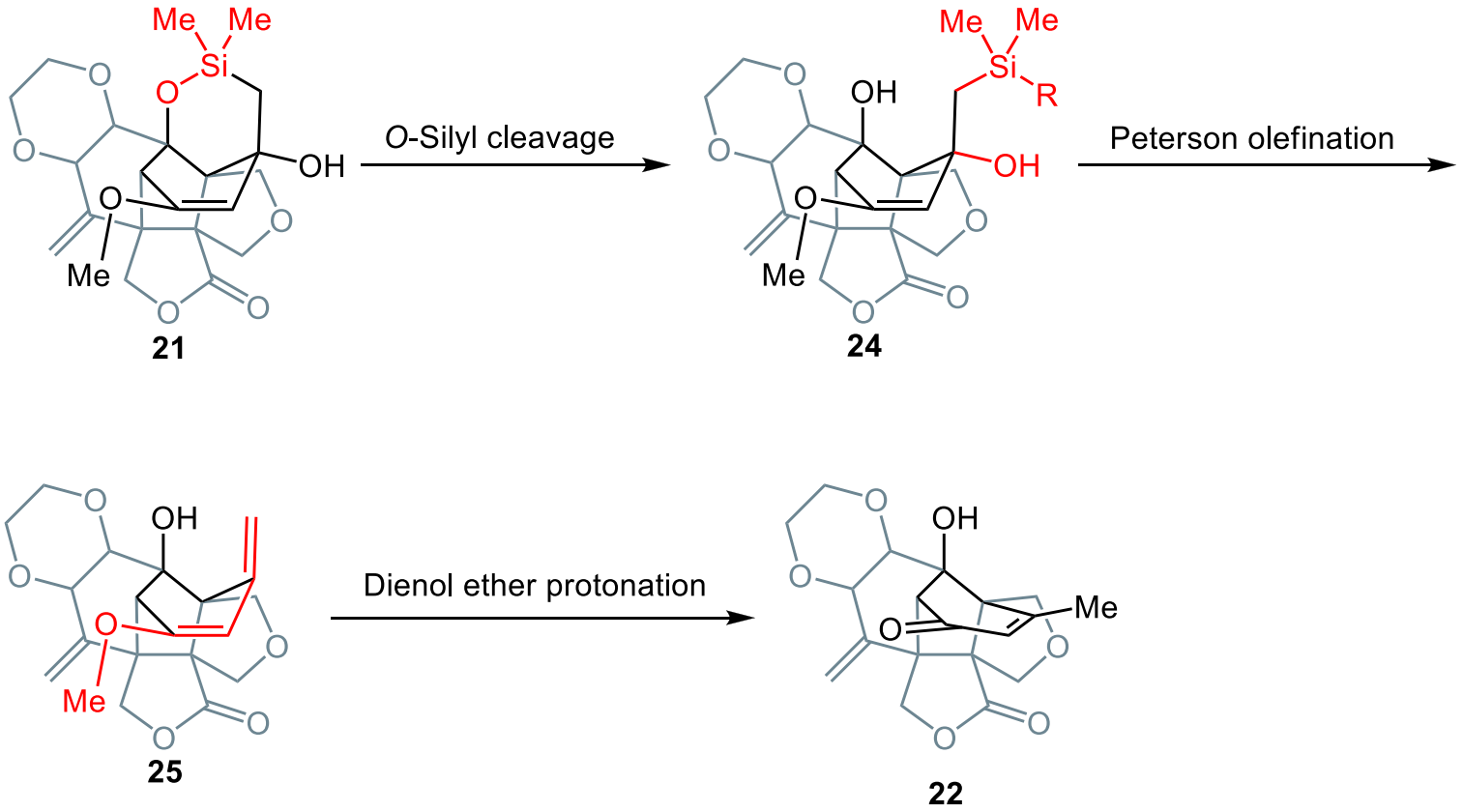
Synthesis of Compound 19



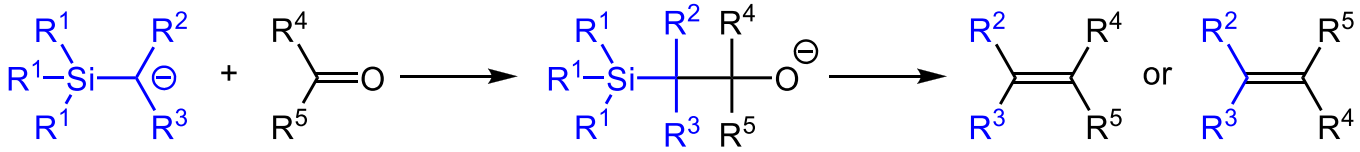
Synthesis of Epicolactone



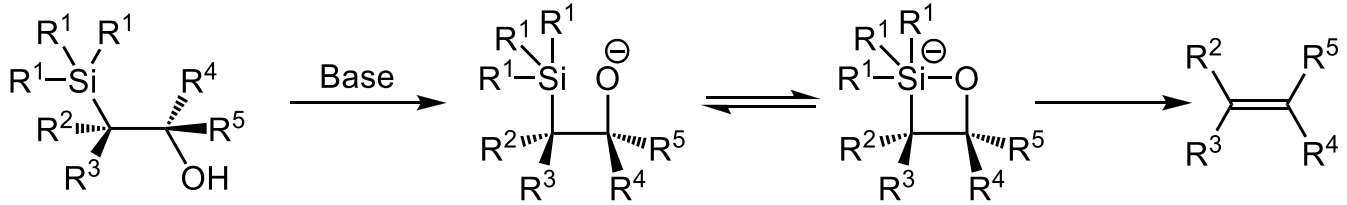
Synthesis of Compound 22



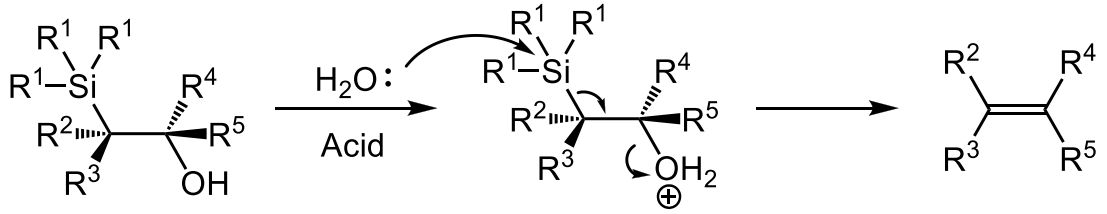
Peterson Olefination



Basic elimination

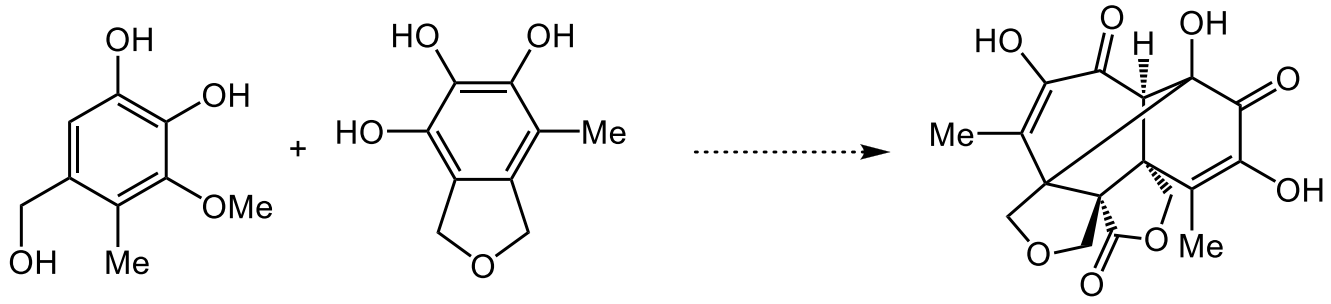


Acidic elimination



Summary

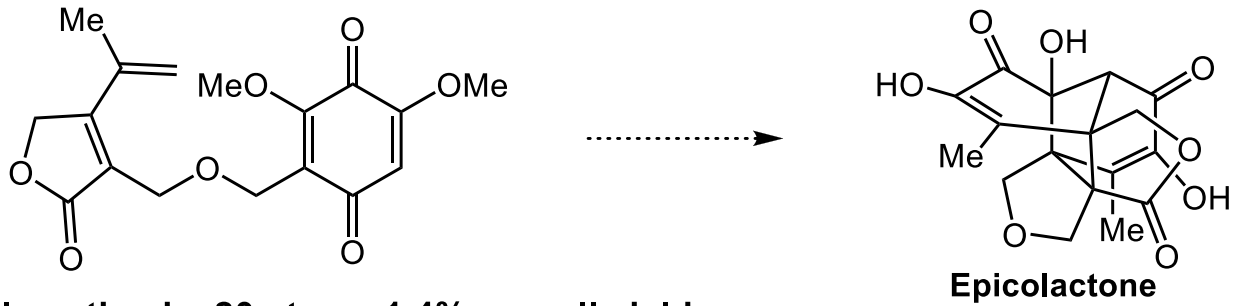
Trauner's Group in 2015



Epicolactone

- **Biomimetic synthesis, 8 steps, 5.0% overall yield**
- **Oxidation, [5+2] cycloaddition, vinylogous aldol addition**

Carreira's Group in 2018



Epicolactone

- **Total synthesis, 20 steps, 1.4% overall yield**
- **[2+2] Photocycloaddition, retroaldol-aldol sequence, acid-catalyzed aldol addition**

The First Paragraph

Epicoccum nigrum, a ubiquitous endophytic fungus known to colonize economically important cash crops such as sugarcane and cocoa tree, is a source of biologically active secondary metabolites. Among these, a complex and highly oxygenated caged pentacyclic structure, epicolactone (**1**), was first isolated in 2012. Inspired by the accompanied isolation of speculated biosynthetic precursors from Epicoccum caftbo, elegant biomimetic total syntheses of epicolactone and its related analog dibefurin were reported by Trauner and co-workers. Epicolactone's high density of electrophilic and nucleophilic functional groups make it a formidable task for total synthesis. Moreover, given its quasisymmetric nature, a synthesis of this molecule necessitates the development of chemo- and regioselective transformations on a highly hindered molecular scaffold. Herein, we report a total synthesis of epicolactone which addresses these challenges and provides a complementary entry into this structurally intriguing natural product.

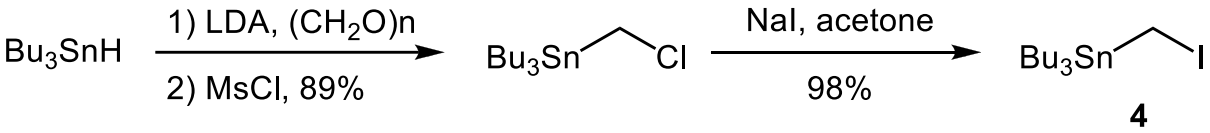
The Last Paragraph

In conclusion, we have developed a robust route for the synthesis of the structurally complex and highly oxygenated natural product epicolactone. An unusual [2+2] photocycloaddition between two electronically similar olefins was employed for the formation of the quaternary centers of the sterically encumbered molecule. A retroaldol-aldol sequence dictated by functional group relationships was employed to synthesize the central cyclopentane embedded in the molecule. In the endphase, an unprecedented acid-catalyzed aldol addition of a dioxene and an intramolecular carbonyl methenylation were developed en route to epicolactone. The application of these reactions to the synthesis of other highly caged and oxygenated natural products is subject to further research in our laboratories and will be reported in due course.

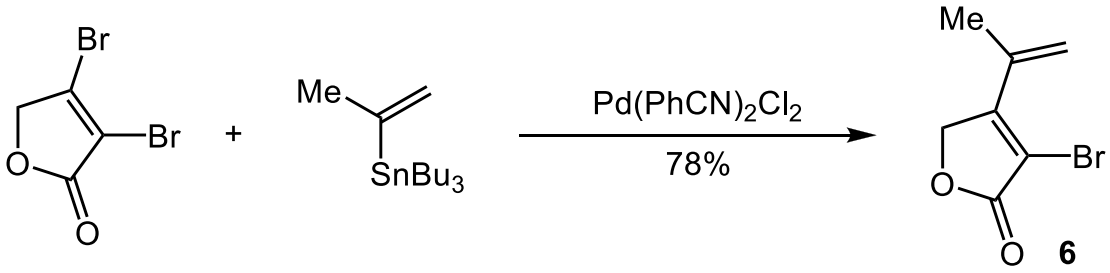
Acknowledgement

Thanks
for your attention

Synthesis of Compounds 4 and 6



Bode, J. W. et al. *Org. Lett.* **2014**, *16*, 1236.



Rossi, R. et al. *Synthesis* **2007**, 1887.