Literature Report VII

Enantioselective Total Synthesis of (−)-Novofumigatonin

Reporter: Kai Xue
Checker: Xinyang Li
Date: 2025-10-20

Ruf, V. A. P.; Sprenger, L. J.; Volynskiy, K.; Kandler, V. M.; Nasiri, N.; Carreira, E. M.* *J. Am. Chem. Soc.* **2025**, *147*, 31456.

CV of Prof. Carreira, Erick M.

Background:

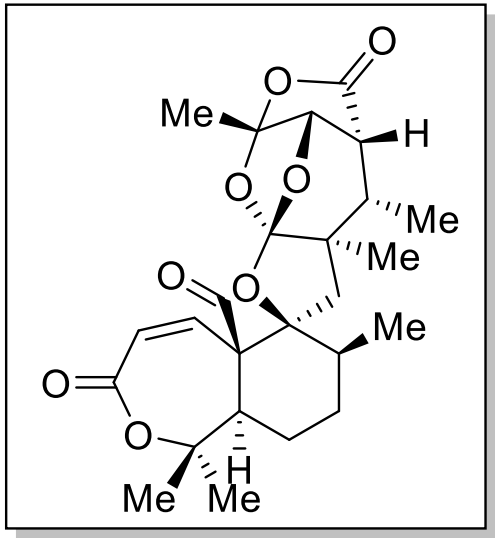
- **1984** B.S., University of Illinois at Urbana-Champaign
- **1984-1990** Ph.D., Harvard University (Prof. Evans, David A.)
- **1990-1992** Postdoc., California Institute of Technology
- **1996-1997** Professor, California Institute of Technology
- **1998-now** Professor, Swiss Federal Institute of Technology Zurich

Research:

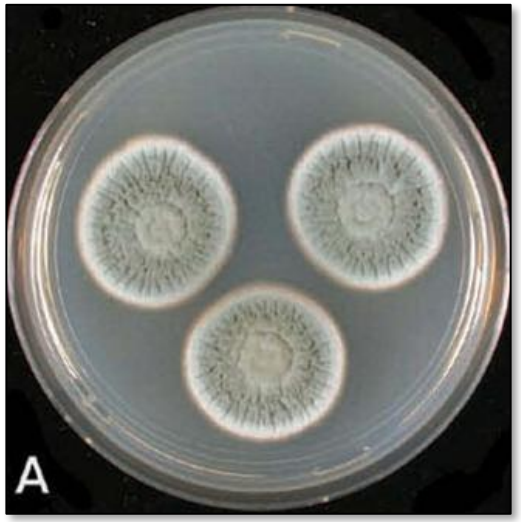
- **Natural Product Synthesis**
- **Chemical Biology**
- **Medicinal Chemistry**
- **Catalytic Methods**

Contents

Introduction



(-)-Novofumigatonin (1)



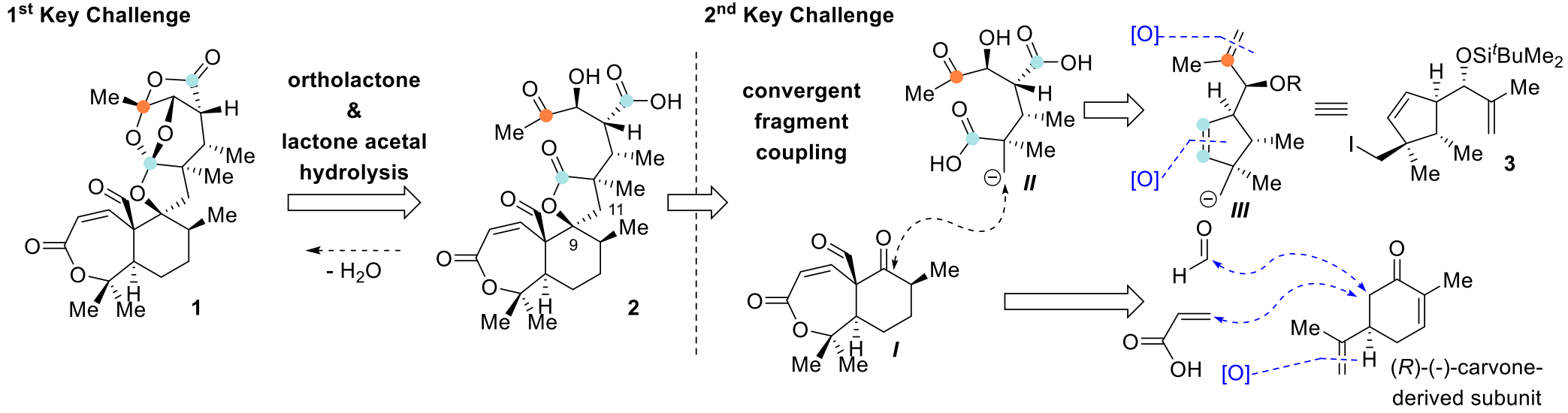
Aspergillus novofumigatus

- isolated from Aspergillus novofumigatus
- highly oxidized DMOA-meroterpenoid
- unique heterocyclic structure

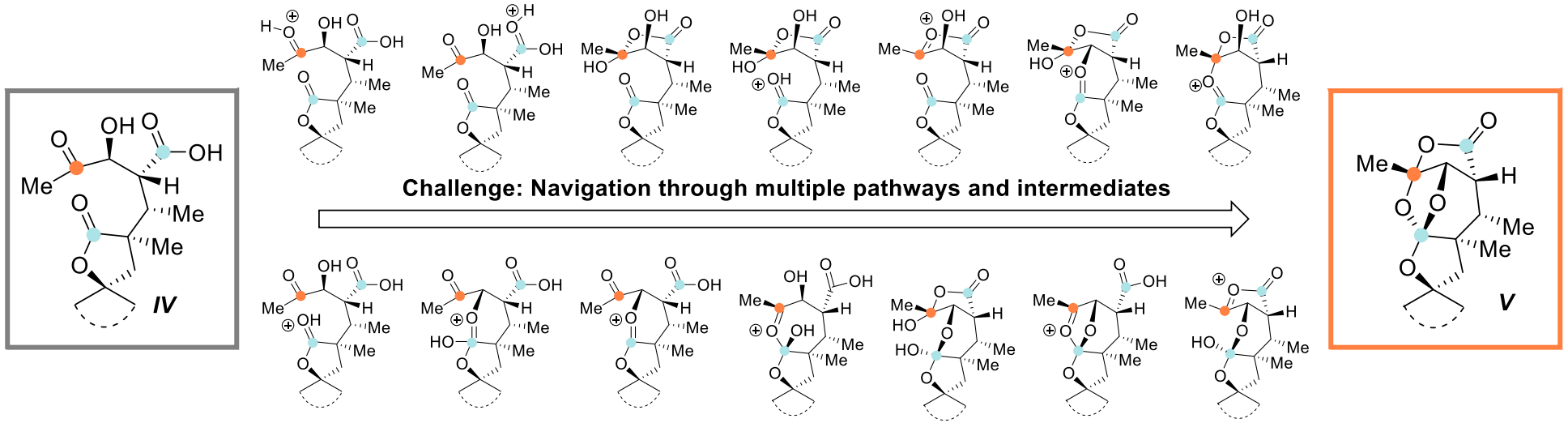
- 7/6/5/6/5/5 hexacyclic skeleton
- embedded ortholactone
- 10 stereogenic centers

Rank, C.; Phipps, R. K.; Harris, P.; Fristrup, P.; Larsen, T. O.; Gotfredsen, C. H. *Org. Lett.* **2008**, *10*, 401.

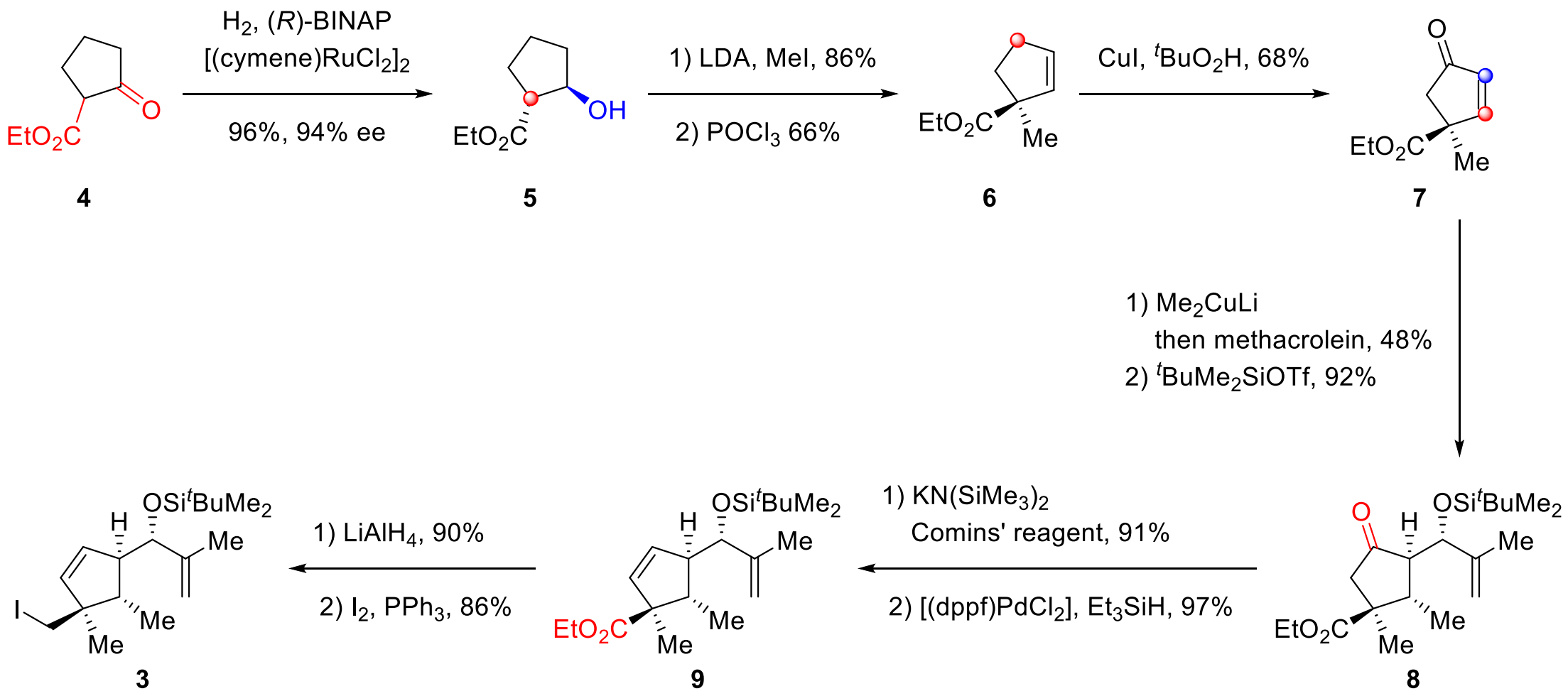
Retrosynthetic Analysis



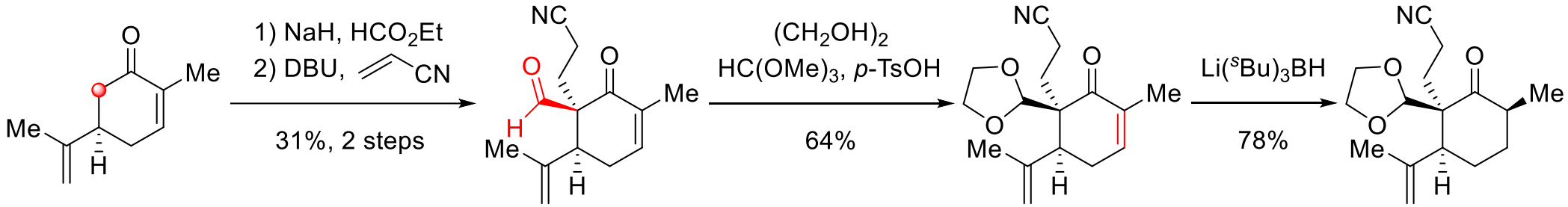
selected plausible intermediates in the dioxabicyclo[3.2.1]octane ortholactone-acetal formation



Stage 1: Synthesis of Compound 3

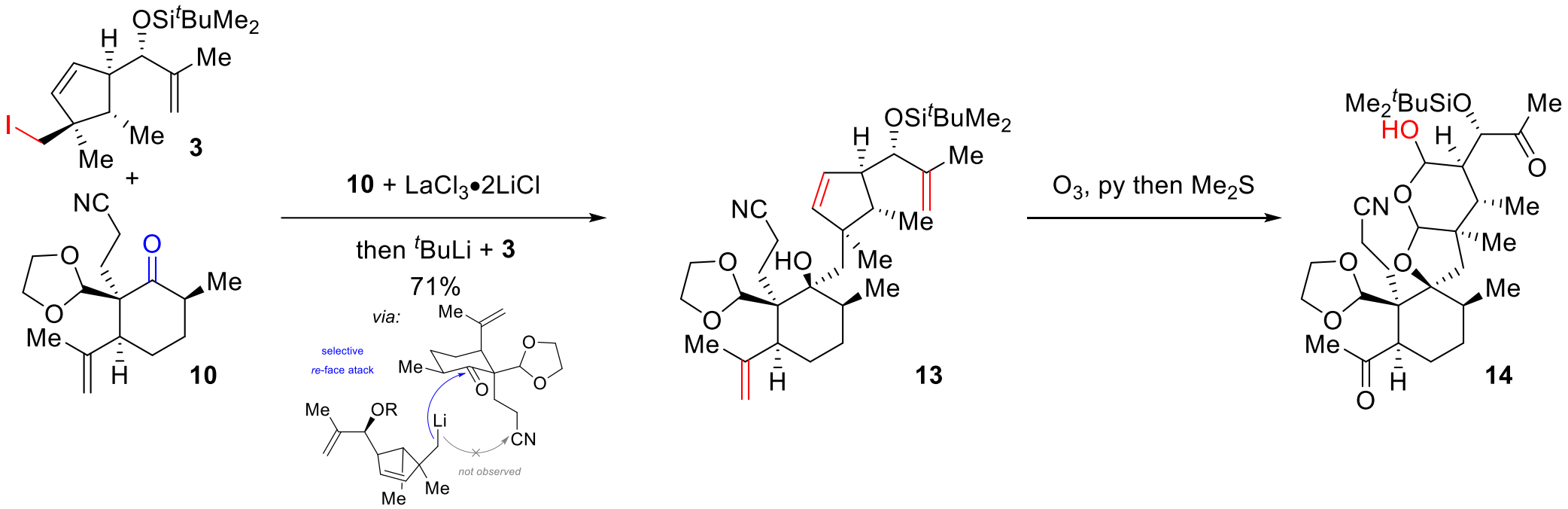


Stage 2: Synthesis of Compound 10

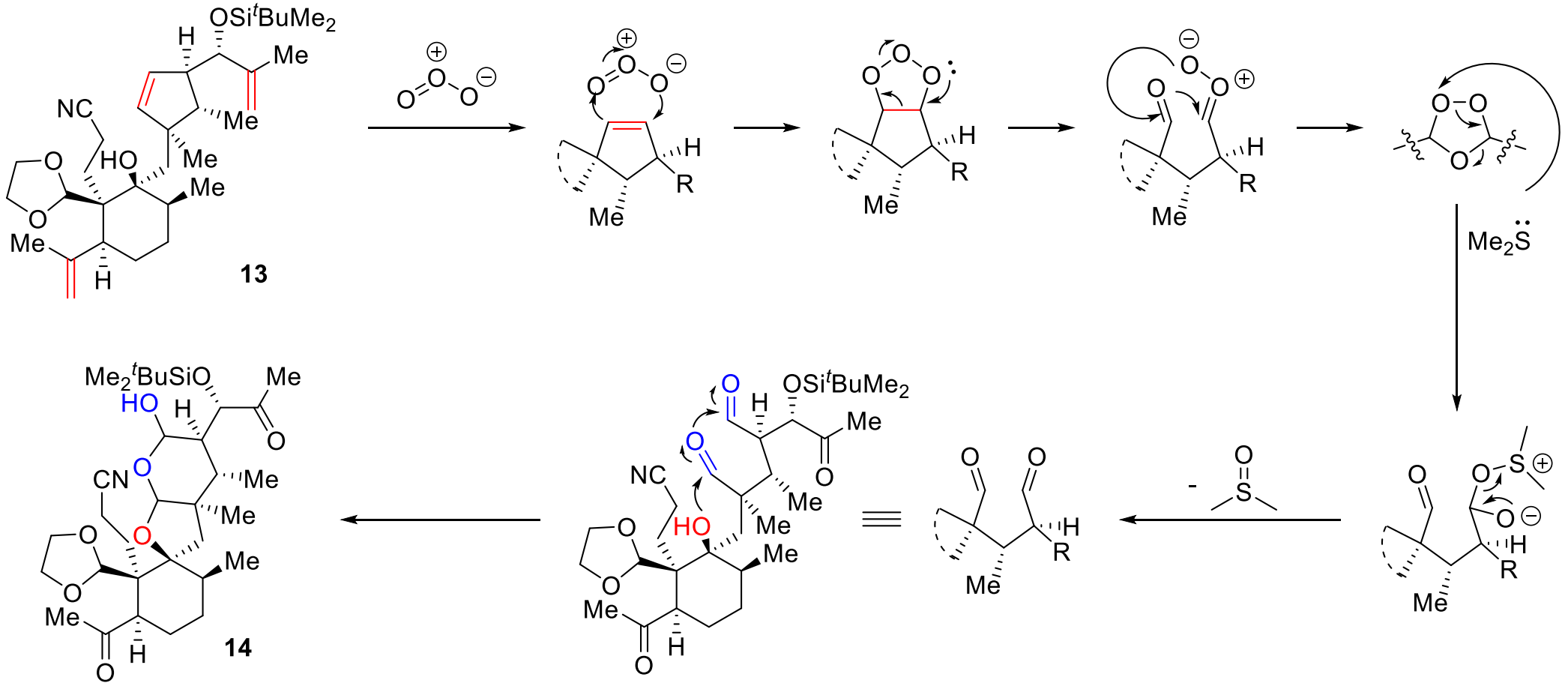


(*R*)-(-)-carvone **11** **12** **10**

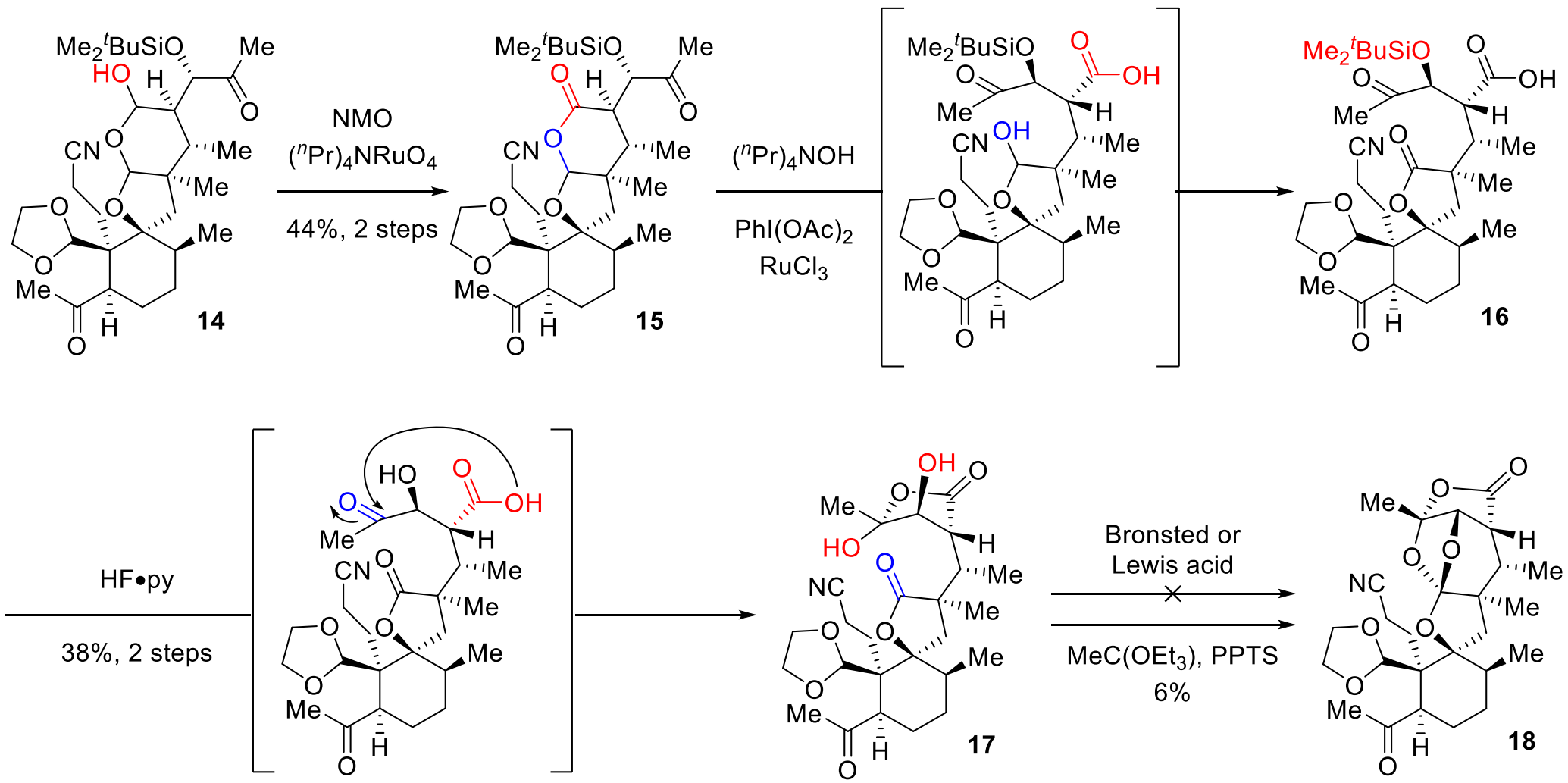
Stage 3: Fragment Coupling and Ortholactone Formation



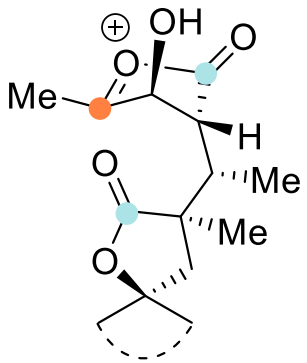
Stage 3: Fragment Coupling and Ortholactone Formation



Stage 3: Fragment Coupling and Ortholactone Formation



Revised Ortholactone Formation

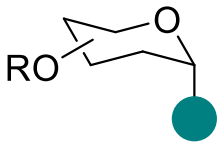


19

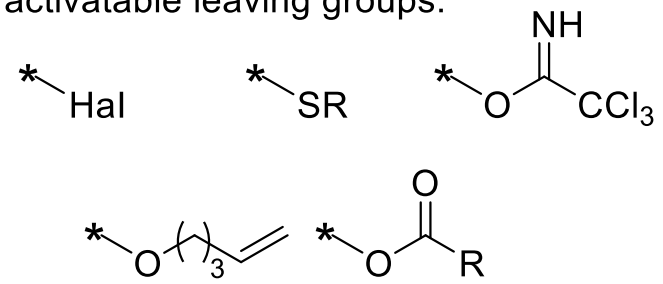
≡

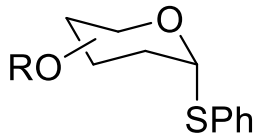
RO

Inspired by
glycosylation methods

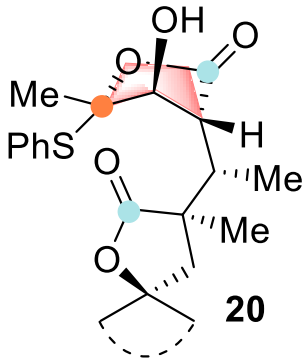


possible activatable leaving groups:





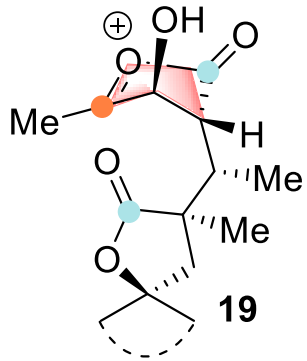
site-selective installation
stability through synthetic steps
chemoselective activation



20

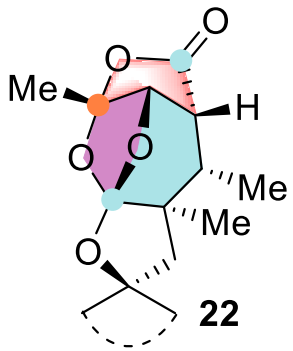
+ Promoter

sulfur activation



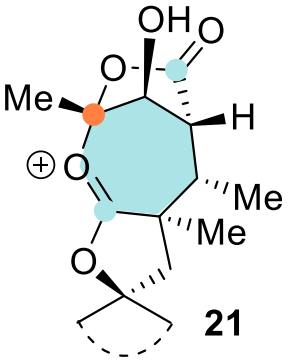
19

lactone activation



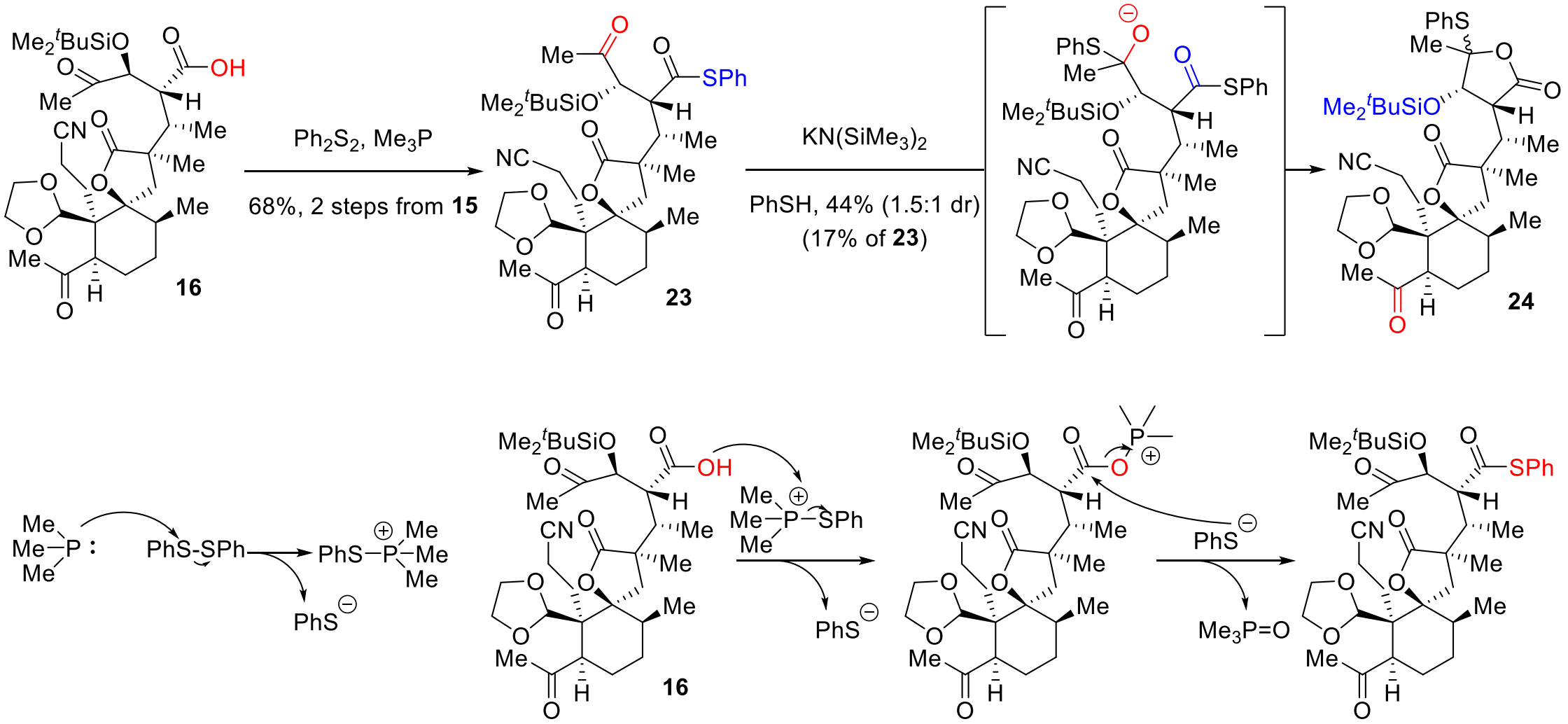
22

ortho-lactone formation

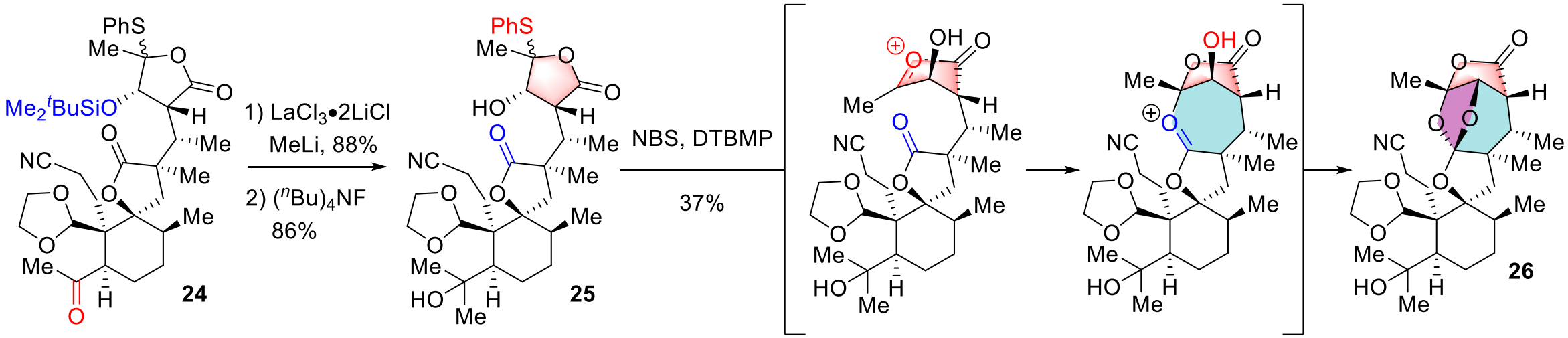


21

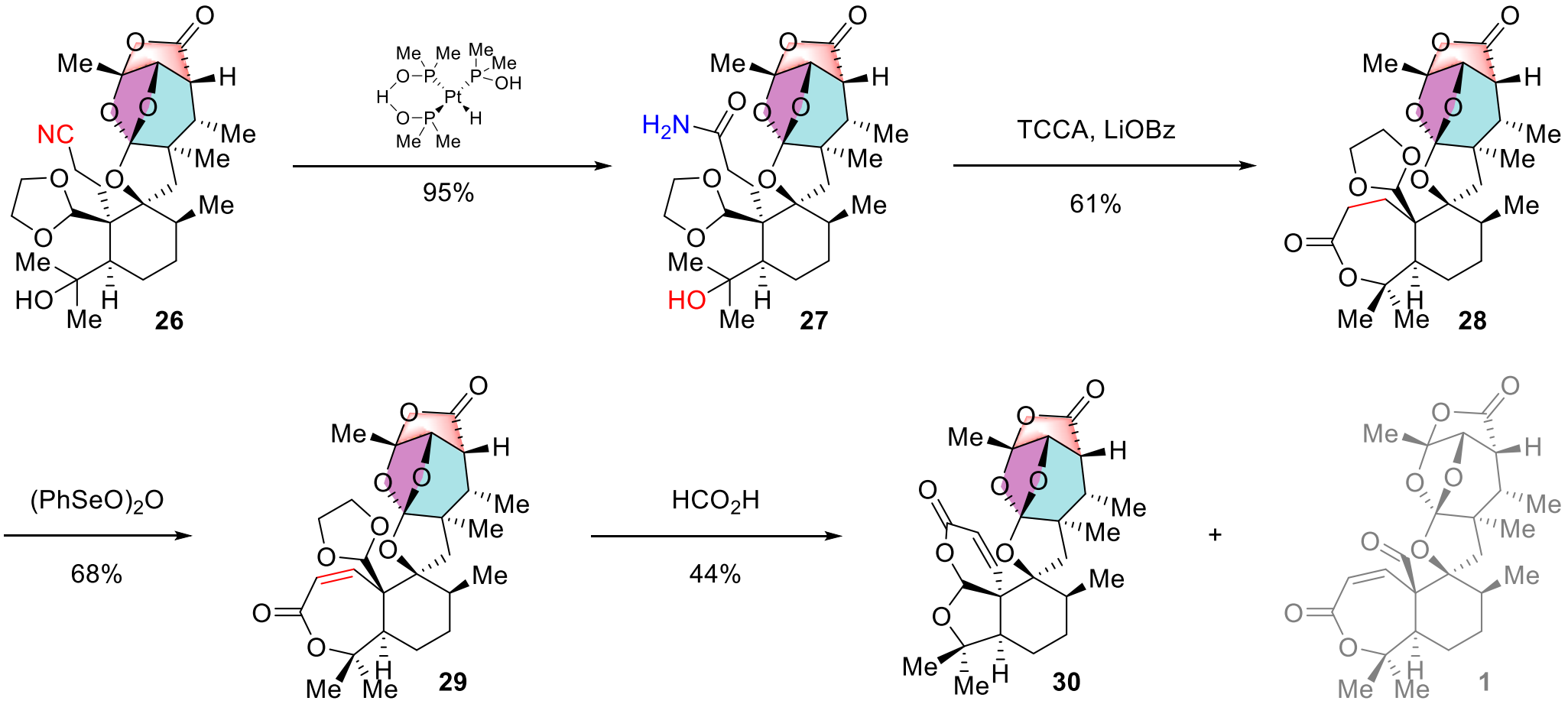
Stage 4: Completion of the Synthesis



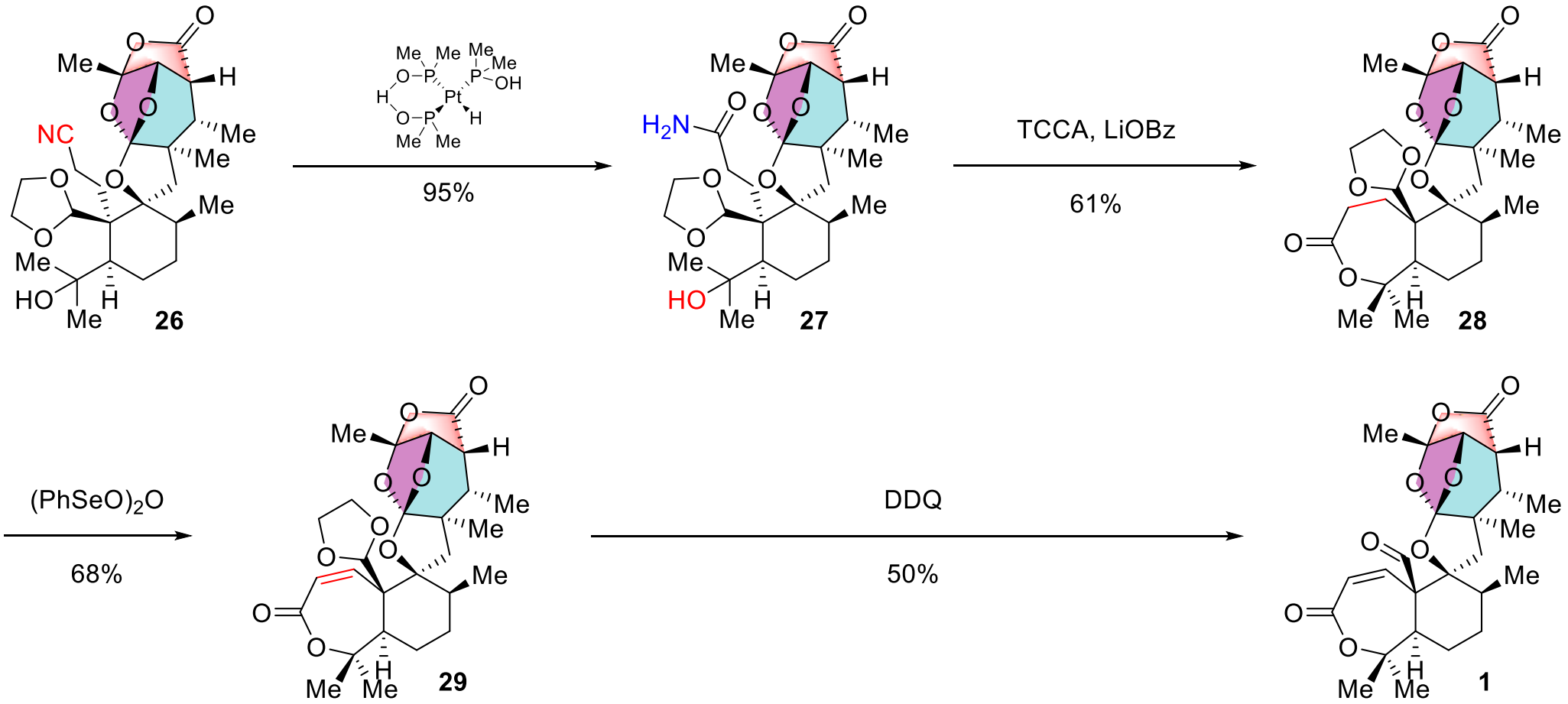
Stage 4: Completion of the Synthesis



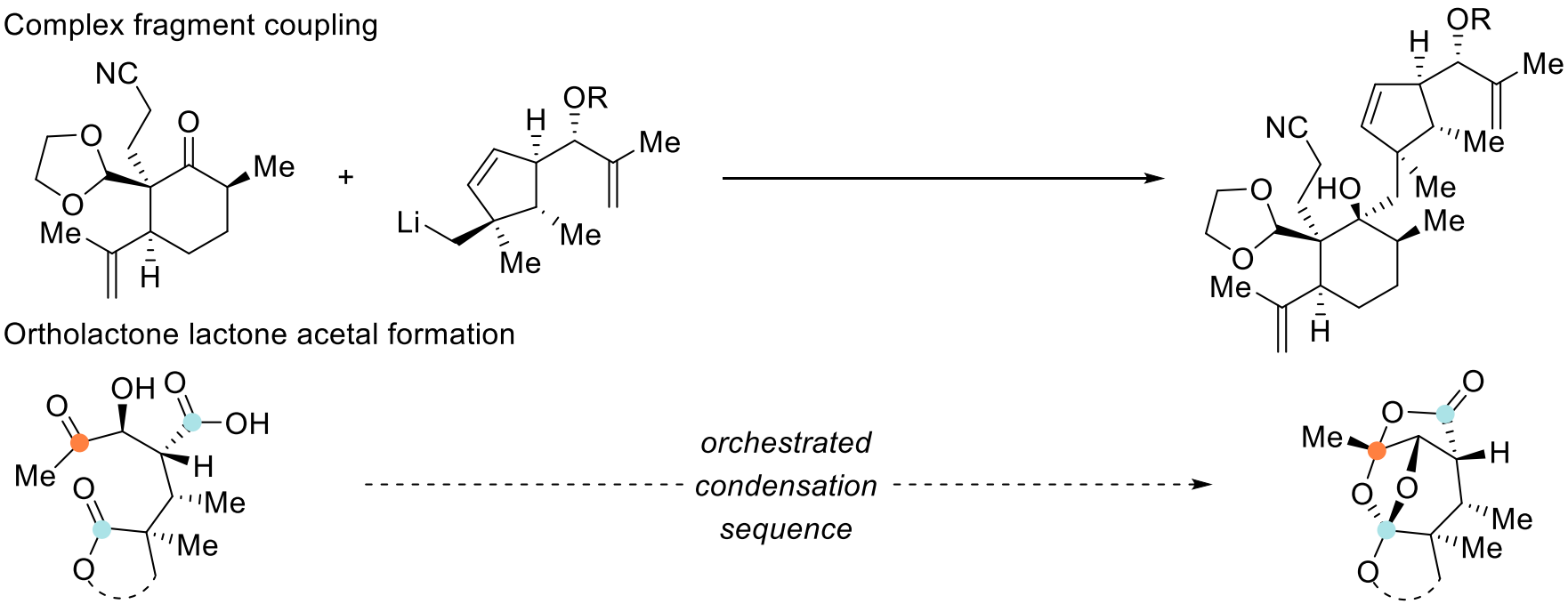
Stage 4: Completion of the Synthesis



Stage 4: Completion of the Synthesis



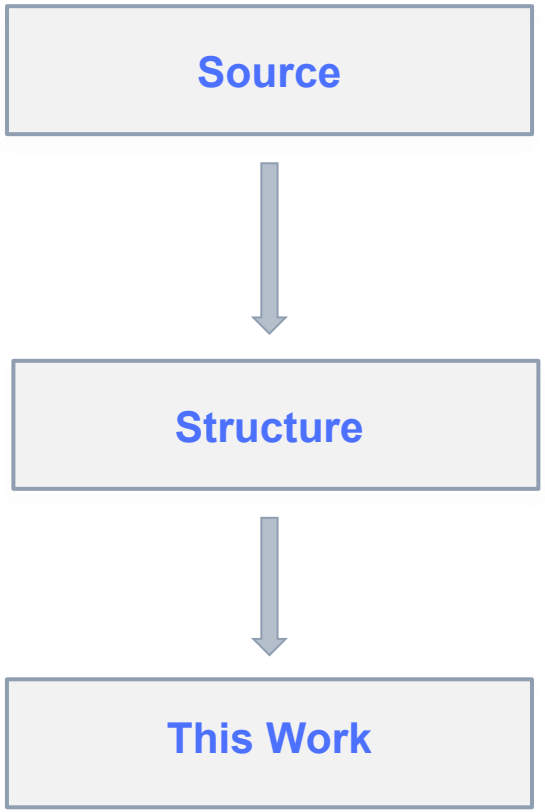
Summary



- Achieved the first and enantioselective total synthesis of **novofumigatonin (1)**
- A powerful anionic fragment coupling followed by oxidative transformations led to the construction of the highly oxygenated backbone

Strategy for Writing The First Paragraph

First paragraph



- In 2008, novofumigatonin (**1**) was isolated by Rank from cultures of *Aspergillus novofumigatus*, a found in the Galápagos Islands. Novofumigatonin is one of the most structurally complex and heavily oxygenated members of the 3,5-dimethyl-orsenillic acid (DMOA) meroterpenoid class of secondary metabolites.

- The 7/6/5/6/5/5 hexacyclic skeleton of **1**, with its unique embedded ortholactone and lactone−acetal cage, sparked our interest. Orthoesters and ortholactones are un-common structural motifs in natural products and, other than ortho-formates and -acetates, rare in small-molecules. They are typically not considered robust, and they are rather acid labile.

- A second salient feature of the strategy is the orchestration of steps that proceed from a highly functional-group-dense hydroxy-keto-lactone-acid precursor to the di-oxabicyclo[3.2.1]octane ortholactone-acetal tetracyclic core of the target.

Strategy for Writing The Last Paragraph

Last paragraph

Summary

Committed Steps

Prospect

- In conclusion, we have achieved the first and enantioselective total synthesis of novofumigatonin (**1**).
- A powerful anionic fragment coupling followed by a series of oxidative transformations led to the rapid construction of the highly oxygenated backbone of **1**. Access to the uniquely complex heterocyclic cage of the natural product was enabled by a cascade of reactions hinging on a novel, sulfur-mediated ortholactone formation.
- We present a synthetic strategy to this class of oxygenated DMOA-meroterpenoids, exemplified by the synthesis of one of its most highly oxidized members isolated to date. This study serves as an entry point for the synthesis of other complex natural products bearing embedded ortholactones.

Representative Examples

- The 7/6/5/6/5/5 hexacyclic skeleton of 1, with its unique embedded ortholactone and lactone−acetal cage, sparked our interest. (激发了我们的兴趣)
- A second salient feature of the strategy is the orchestration of steps that proceed from a highly functional-group-dense hydroxy-keto-lactone-acid… (显著特征)
- We present a synthetic strategy to this class of oxygenated DMOA-meroterpenoids, exemplified by the synthesis of one of its most highly oxidized members isolated to date.(是……的典范/迄今)

Acknowledgement

Thanks for your attention