

Literature Report VI

Total Synthesis of Shearinines D and G: A Convergent Approach to Indole Diterpenoids

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Checker: Wen-Jun Huang

Date: 2022-05-23

Carreira, E. M. *et al. Angew. Chem. Int. Ed.* **2022**, 61, e202112838

Kuwahara, S. *et al. Angew. Chem. Int. Ed.* **2012**, 51, 12833

CV of Professor Erick M. Carreira



Research:

- ◆ The asymmetric synthesis of biologically active, stereochemically complex, natural products;
- ◆ The development of synthetic methods based on catalytic and stoichiometric reagents for asymmetric stereocontrol.

Background:

- **1980-1984** B.S., University of Illinois at Urbana-Champaign;
- **1984-1990** Ph.D., Harvard University;
- **1990-1992** Postdoc., California Institute of Technology;
- **1992-1997** Professor, California Institute of Technology;
- **1998-Now** Professor, ETH Zürich, Switzerland.

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1 Introduction

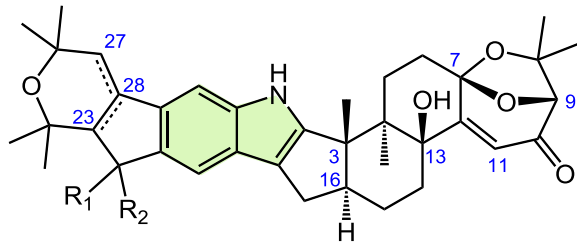
2 Total Synthesis of Paspalinine

3 Total Synthesis of Shearinines D and G

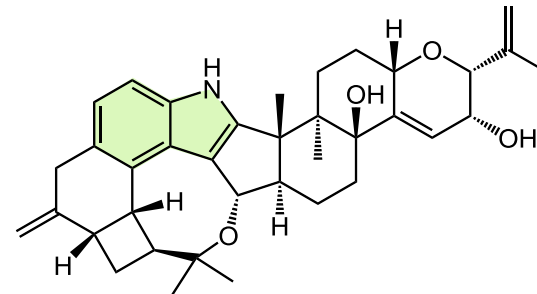
4 Summary

Introduction

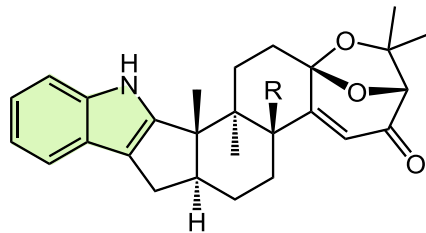
Related Indole Diterpenes



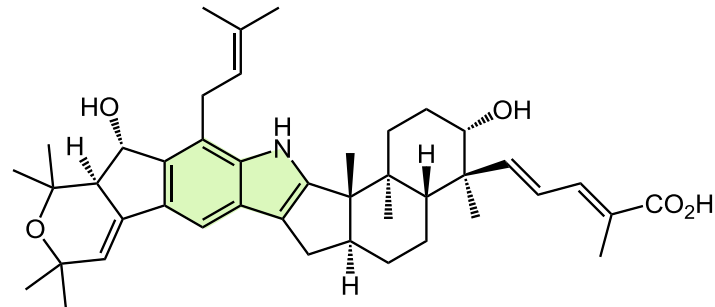
Shearinine G (1): R₁, R₂ = O, $\Delta_{23,28}$
Shearinine D (2): R₁ = OH, R₂ = H, $\Delta_{27,28}$



Penitrem D
Smith, A. B. *et al.* 2000

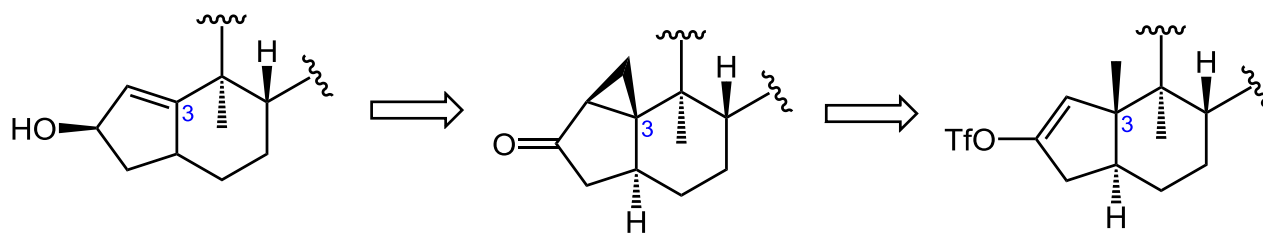
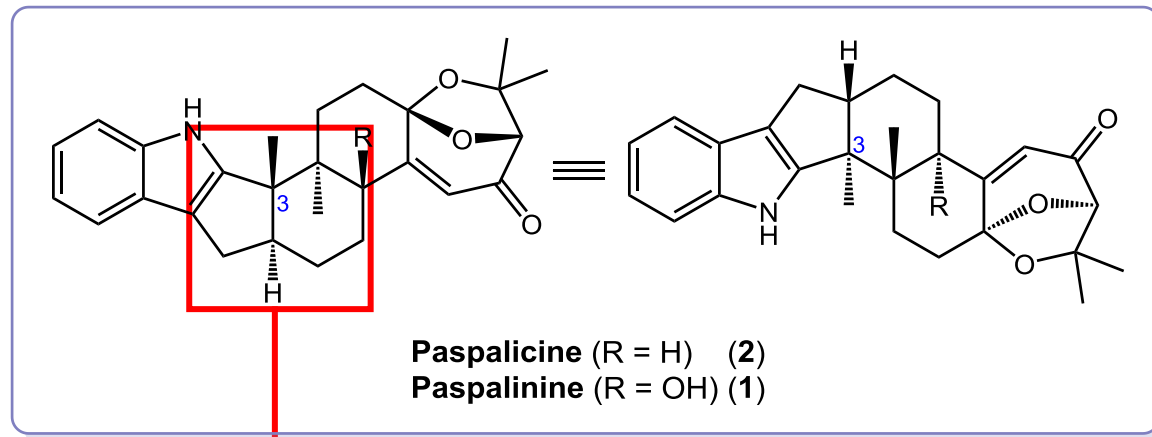


Paspalcine (R = H)
Paspalinine (R = OH)
Kuwahara, S. *et al.* 2012

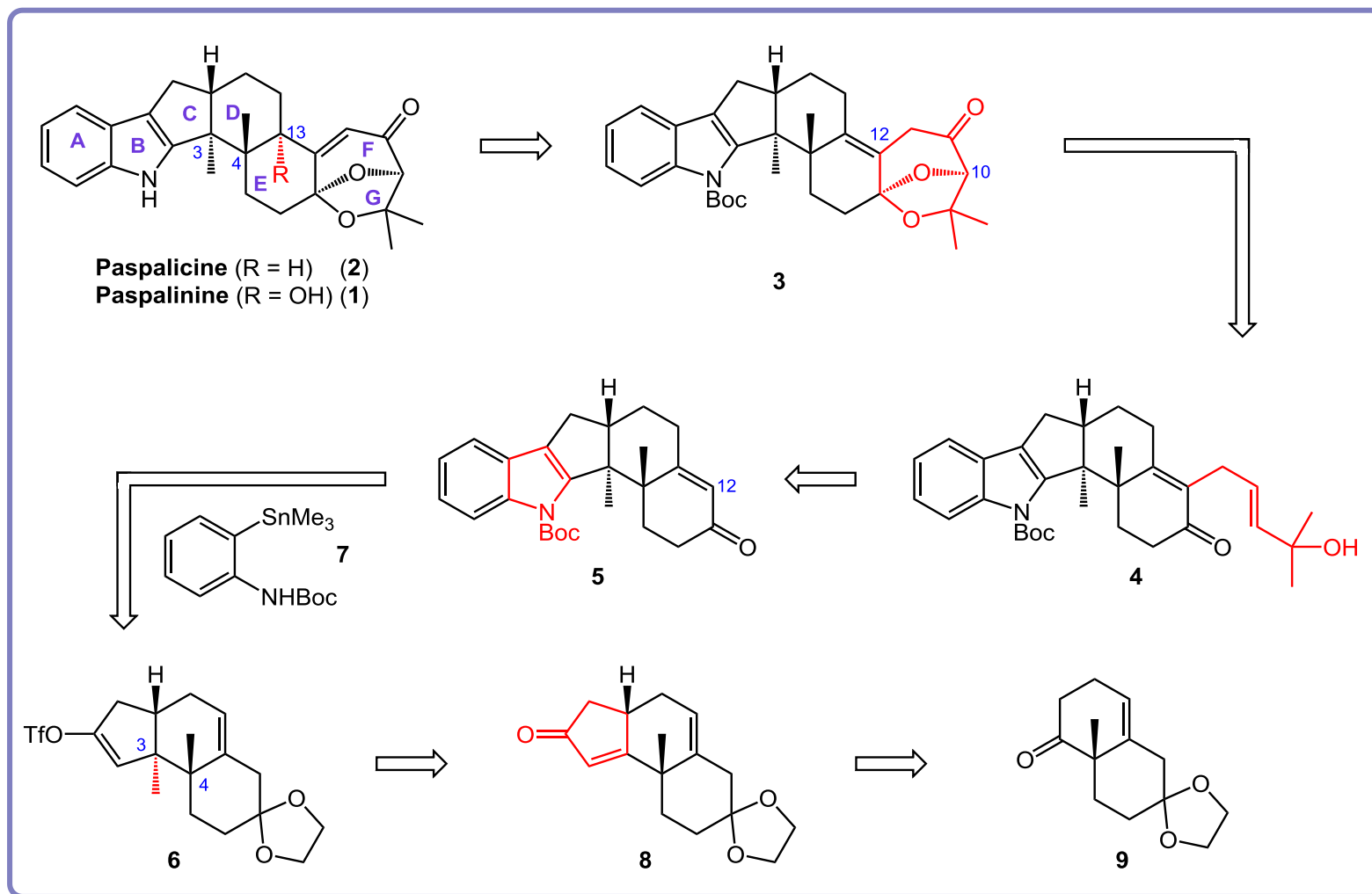


Nodulisporic acid C
Pronin, S. V. *et al.* 2018

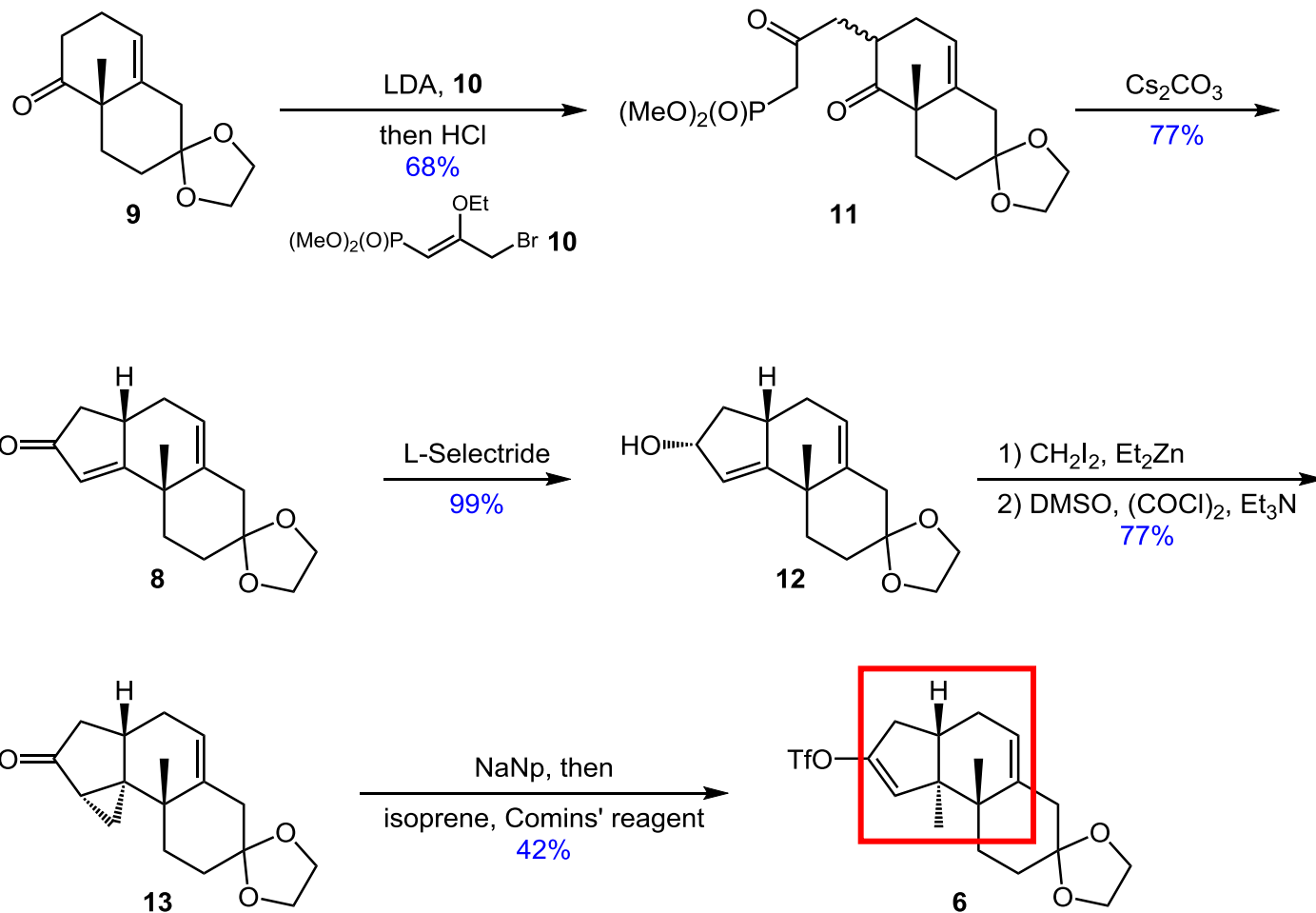
Total Synthesis of Paspalidine



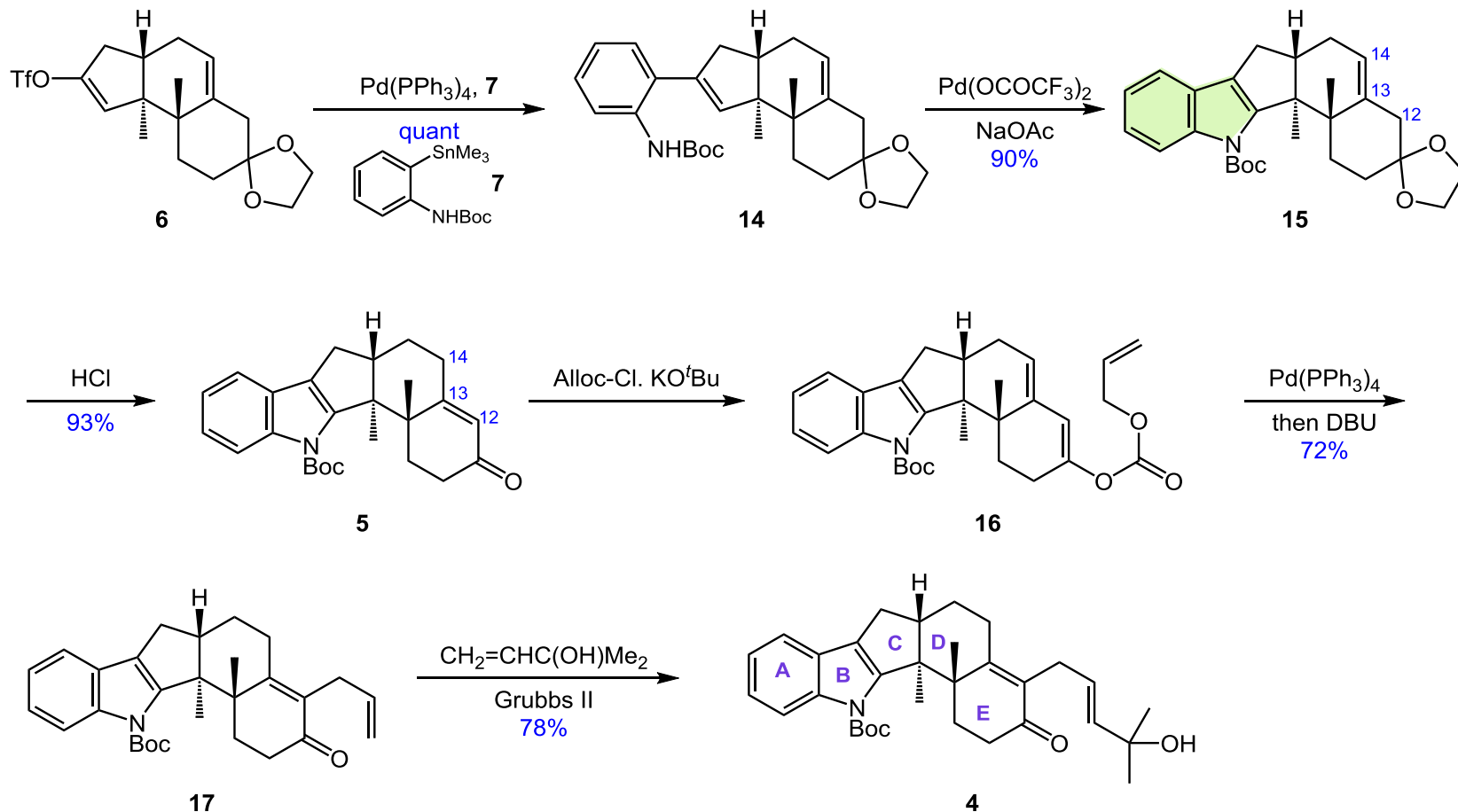
Retrosynthetic Analysis



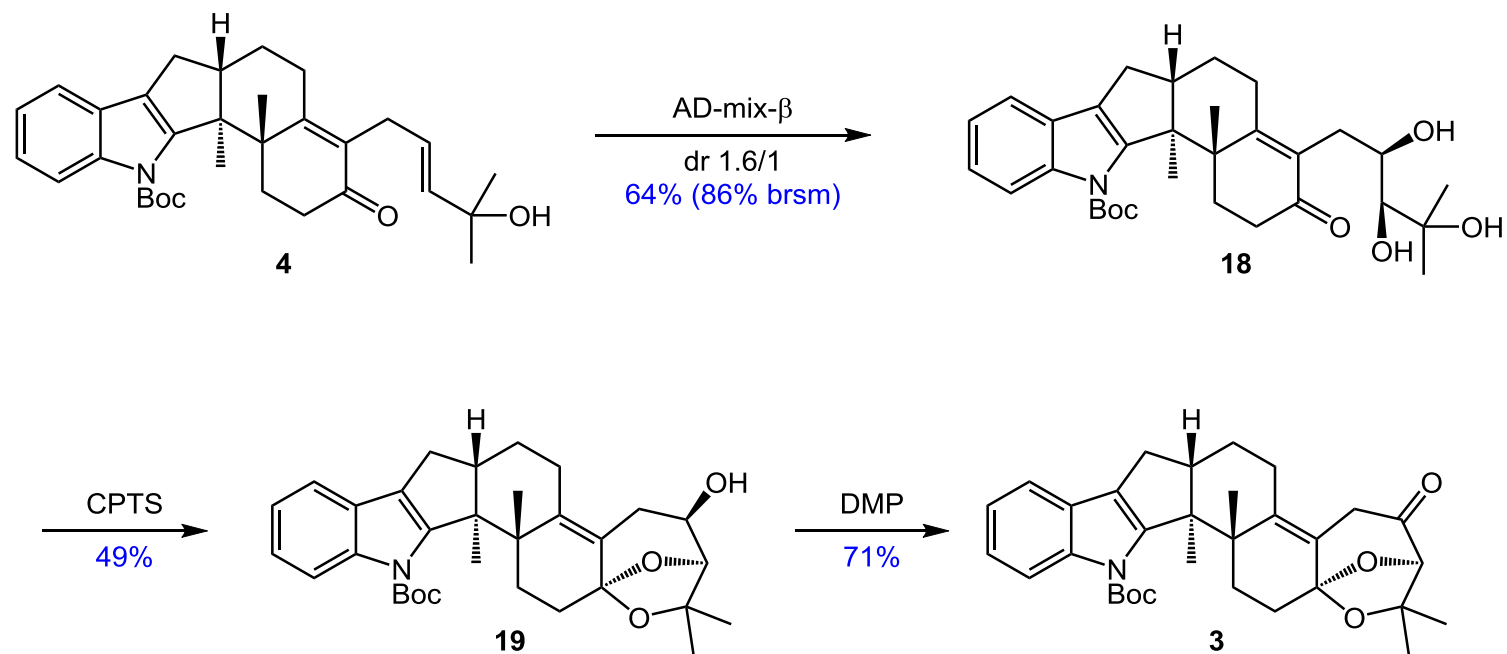
Synthesis of Compound 6



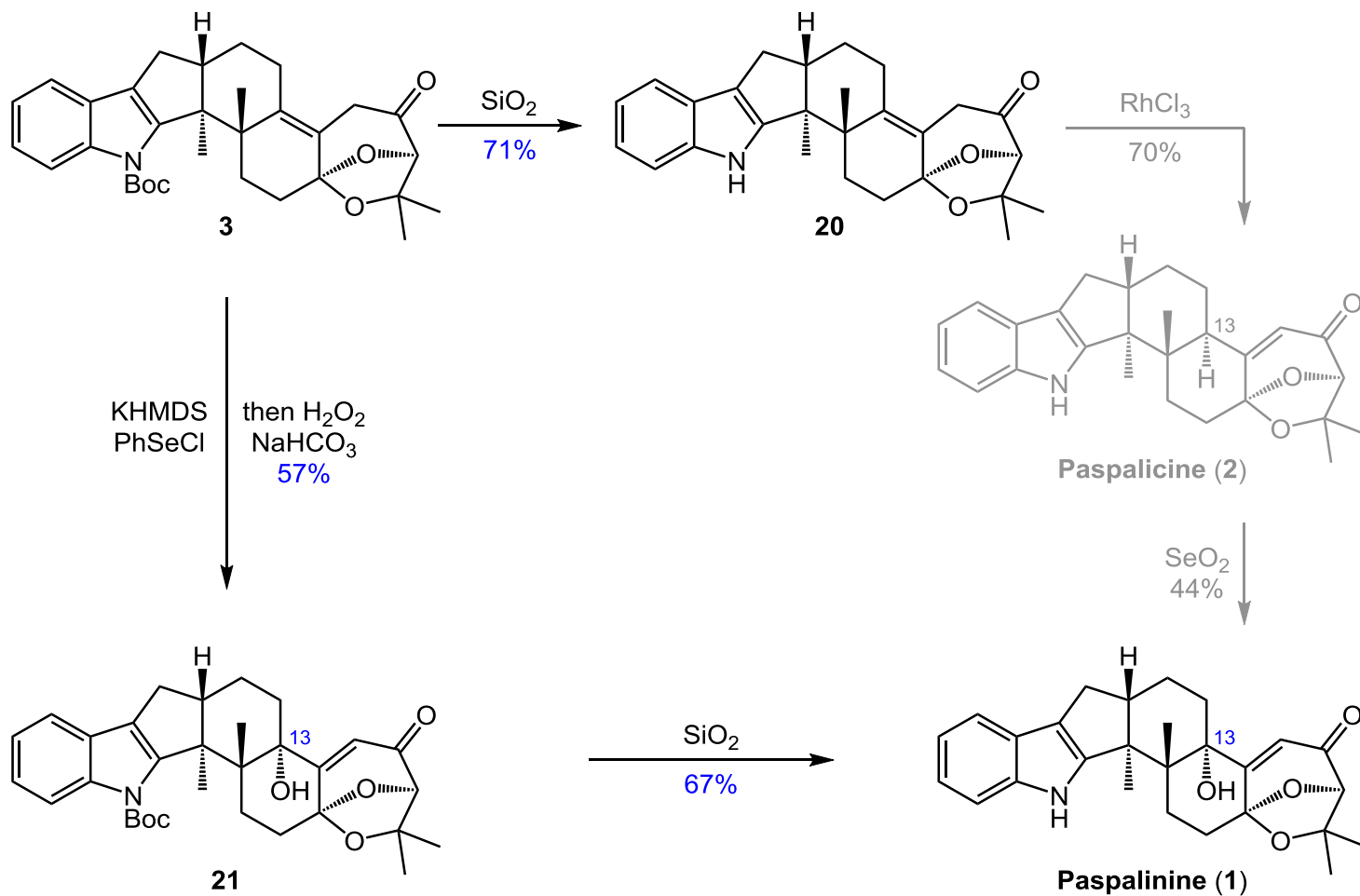
Synthesis of Compound 4



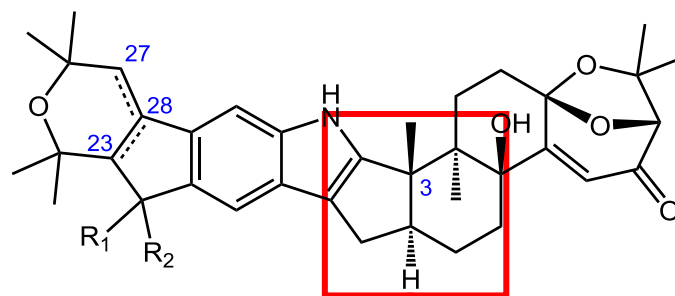
Synthesis of Compound 3



Synthesis of Paspaline

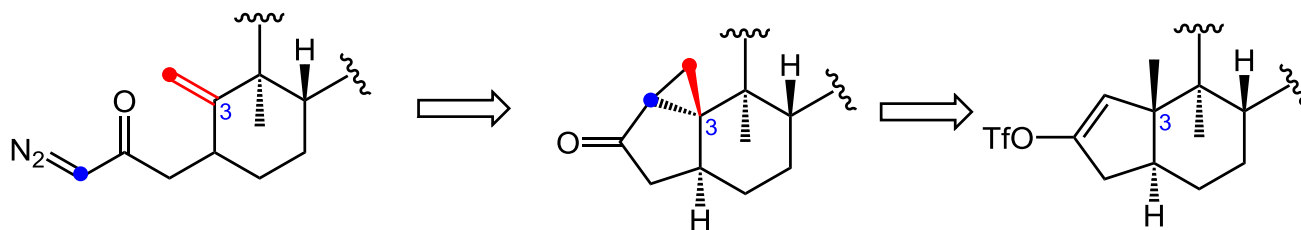


Total Synthesis of Shearinines D and G

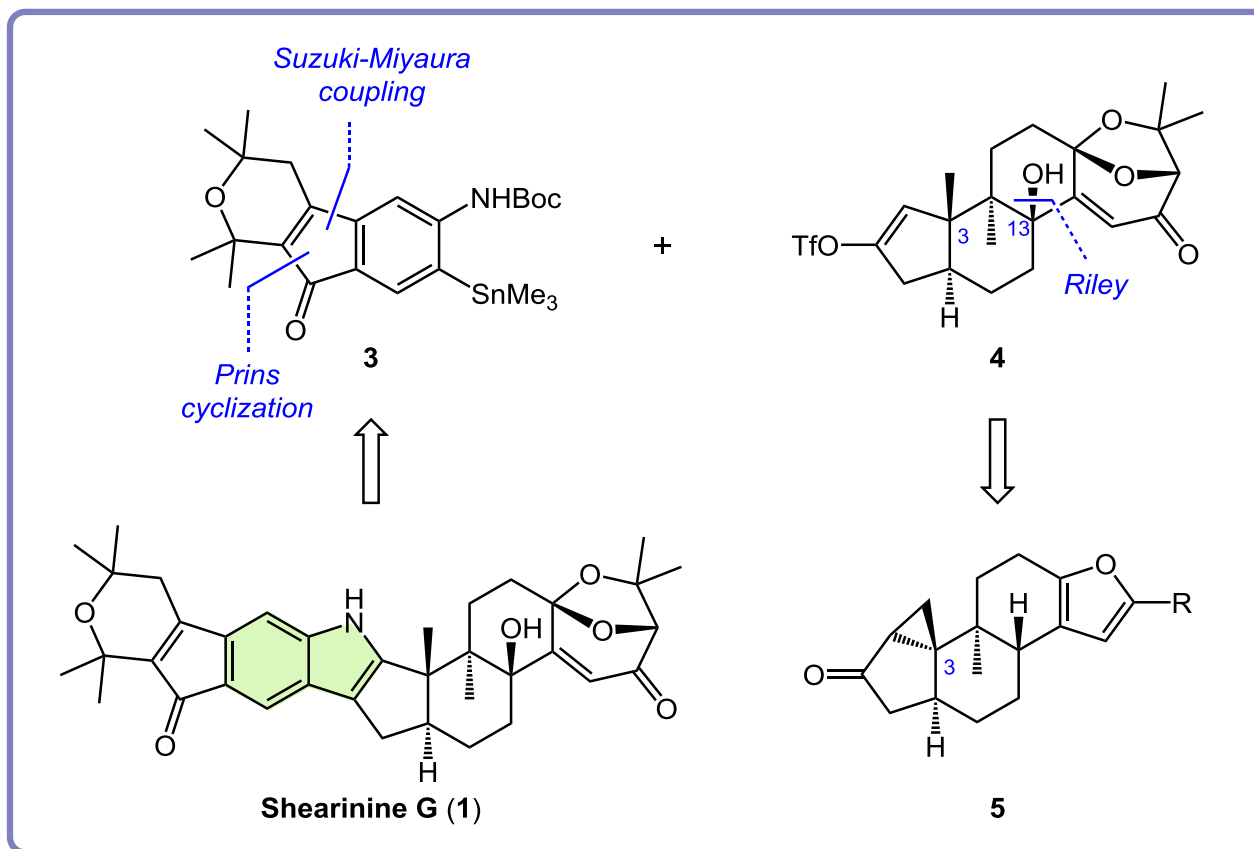


Shearinine G (1): $R_1, R_2 = O, \Delta_{23,28}$

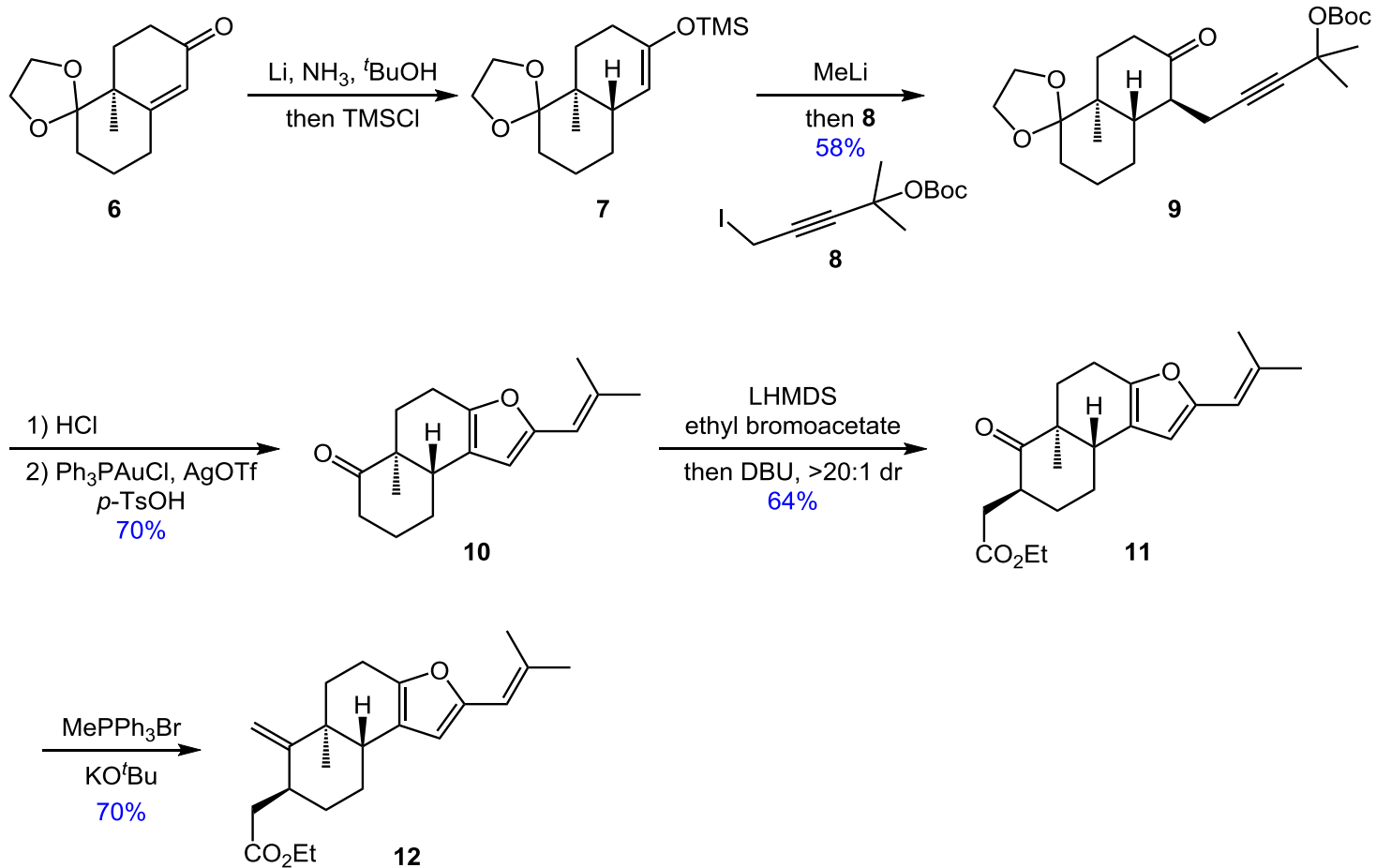
Shearinine D (2): $R_1 = OH, R_2 = H, \Delta_{27,28}$



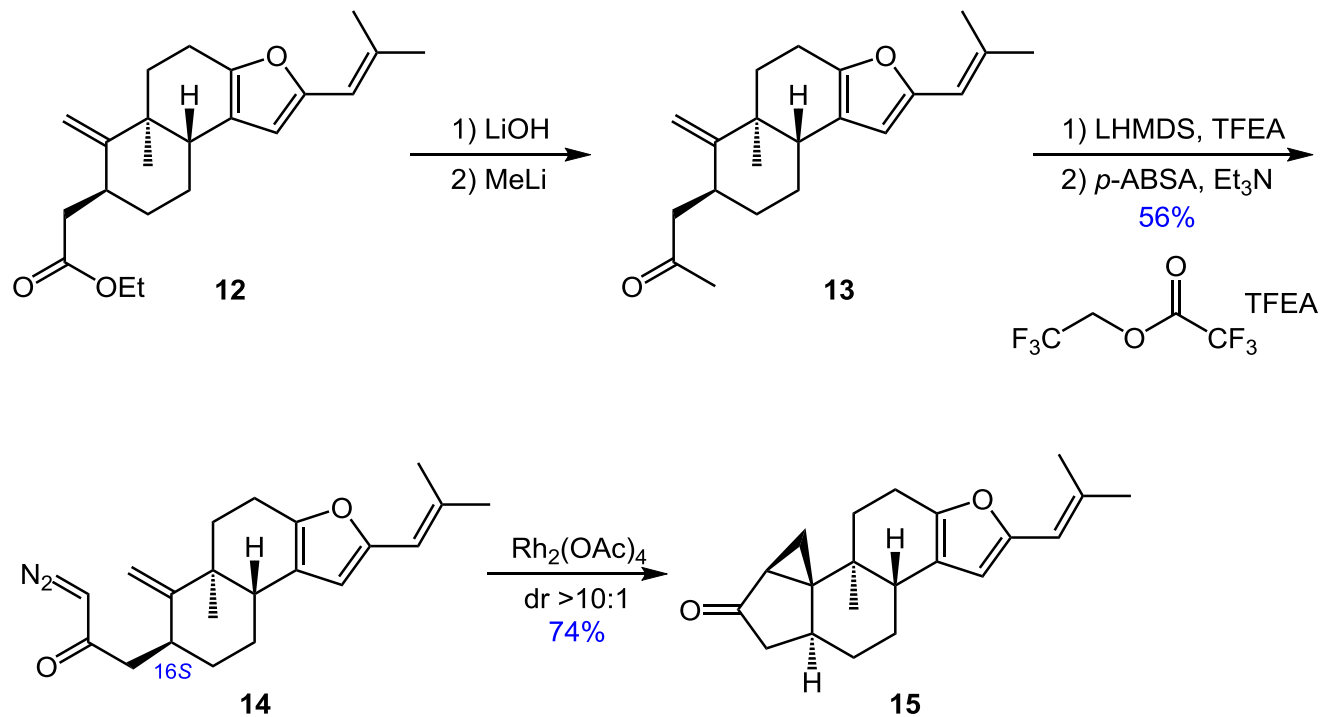
Retrosynthetic Analysis



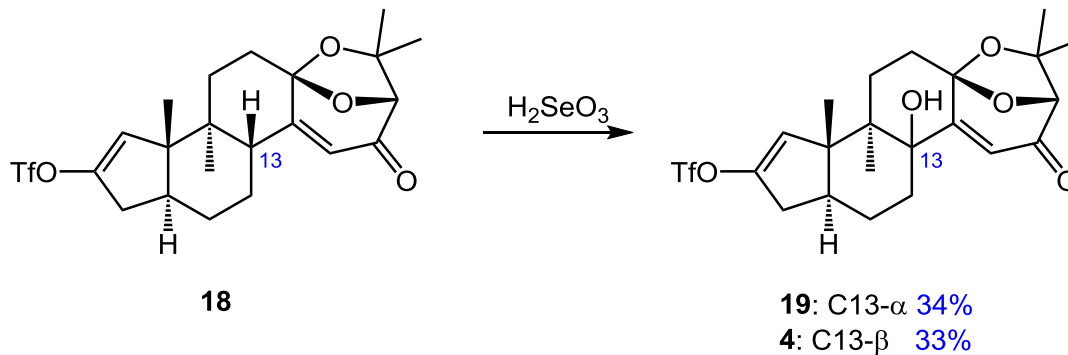
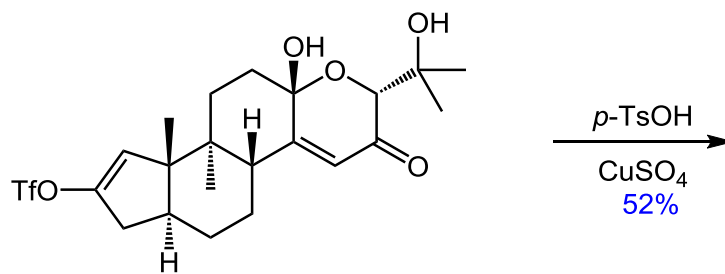
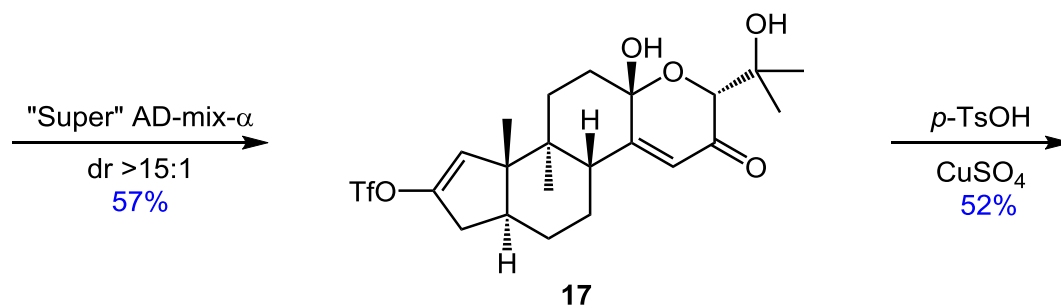
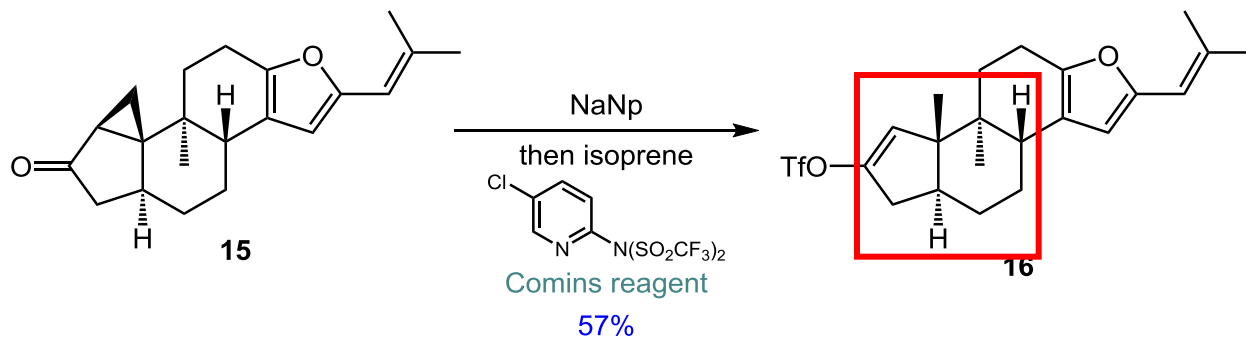
Synthesis of Compound 12



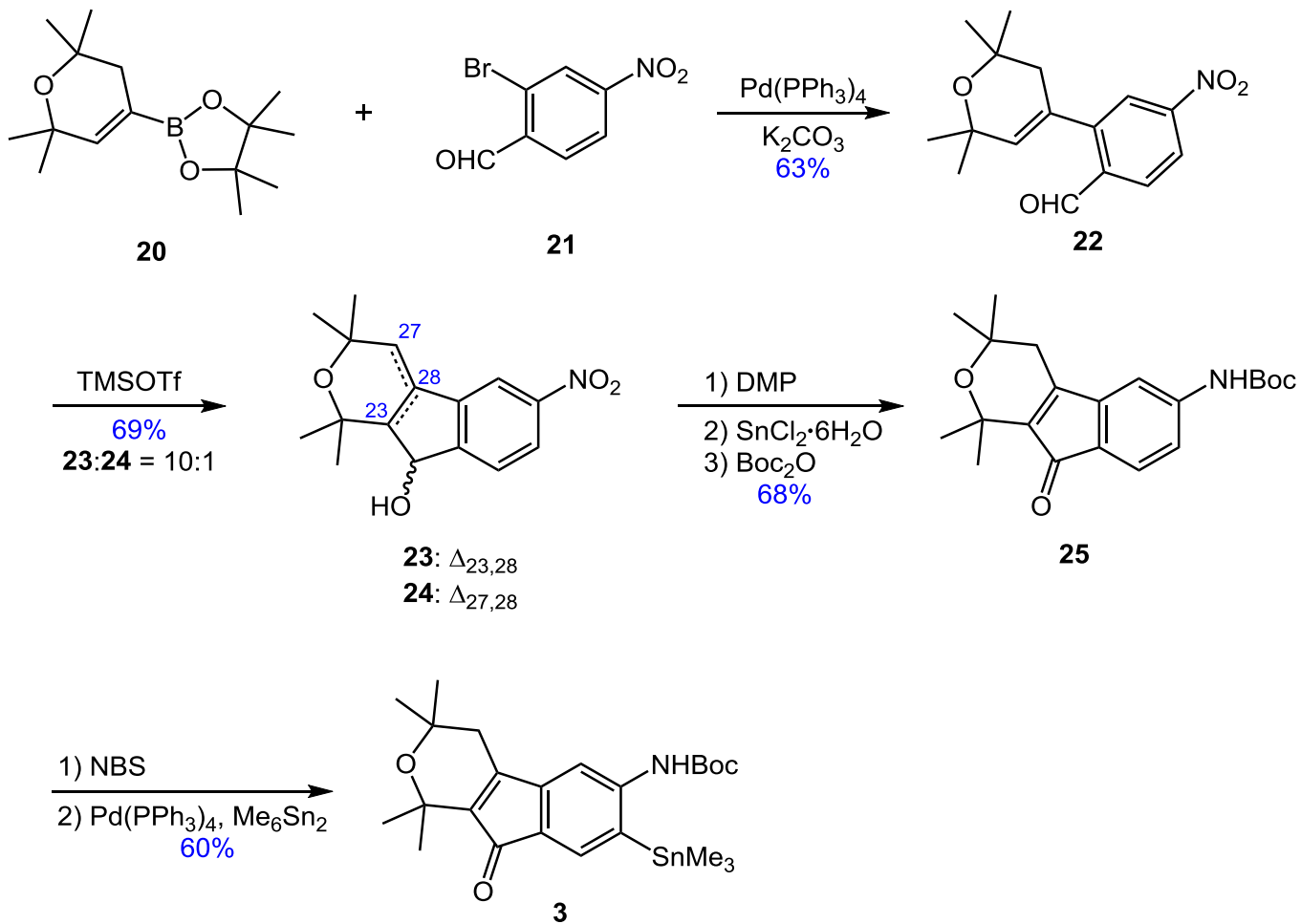
Synthesis of Compound 15



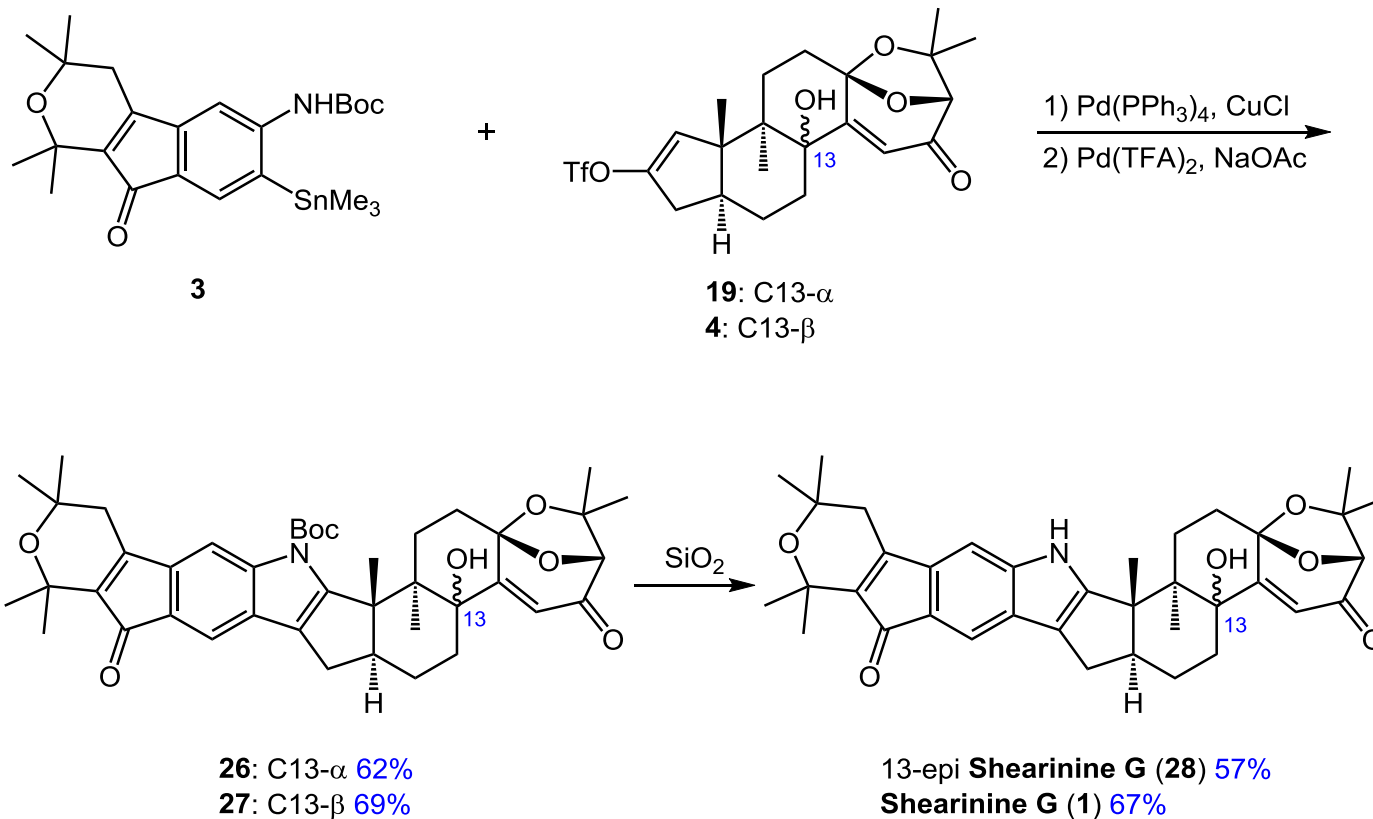
Synthesis of Compound 4



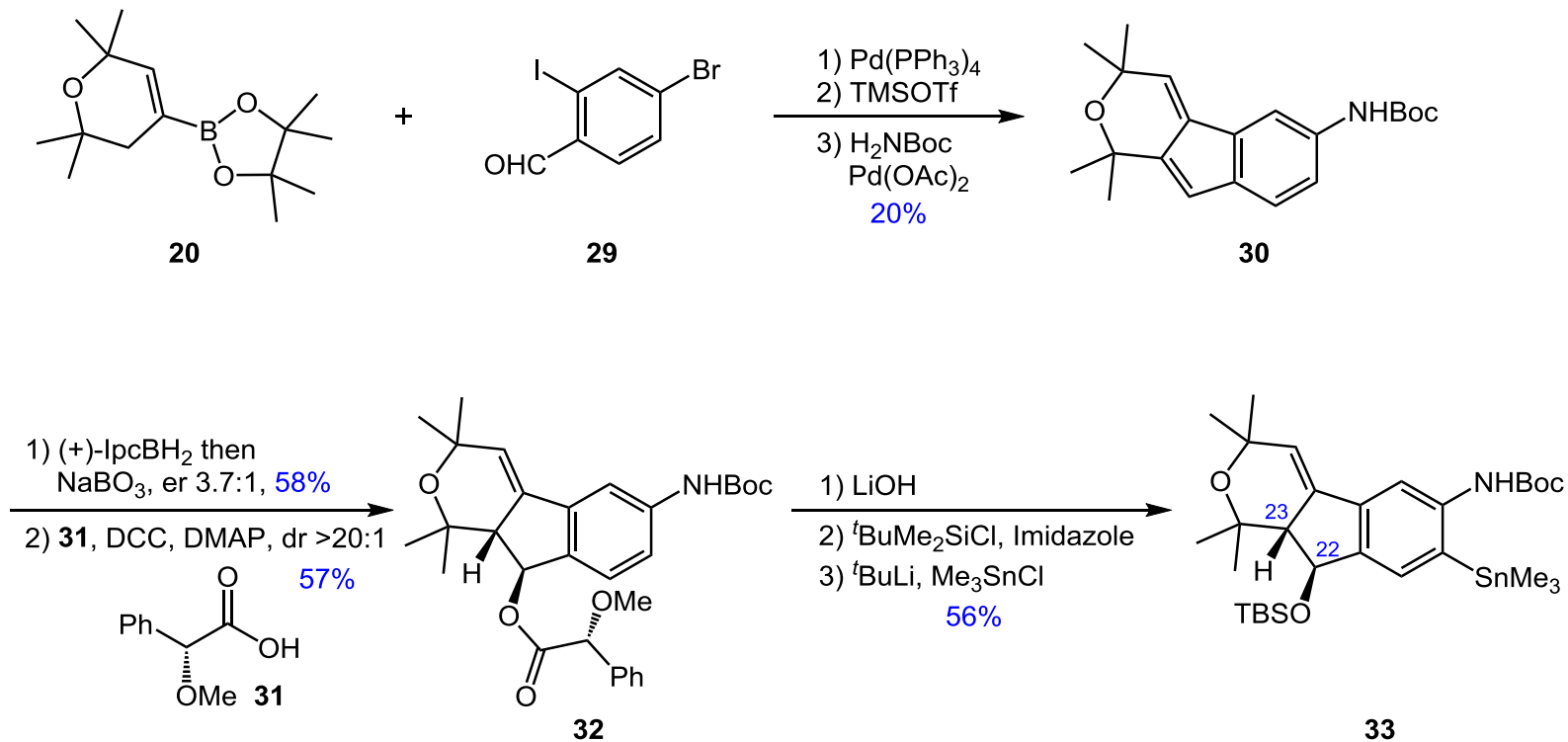
Synthesis of Compound 3



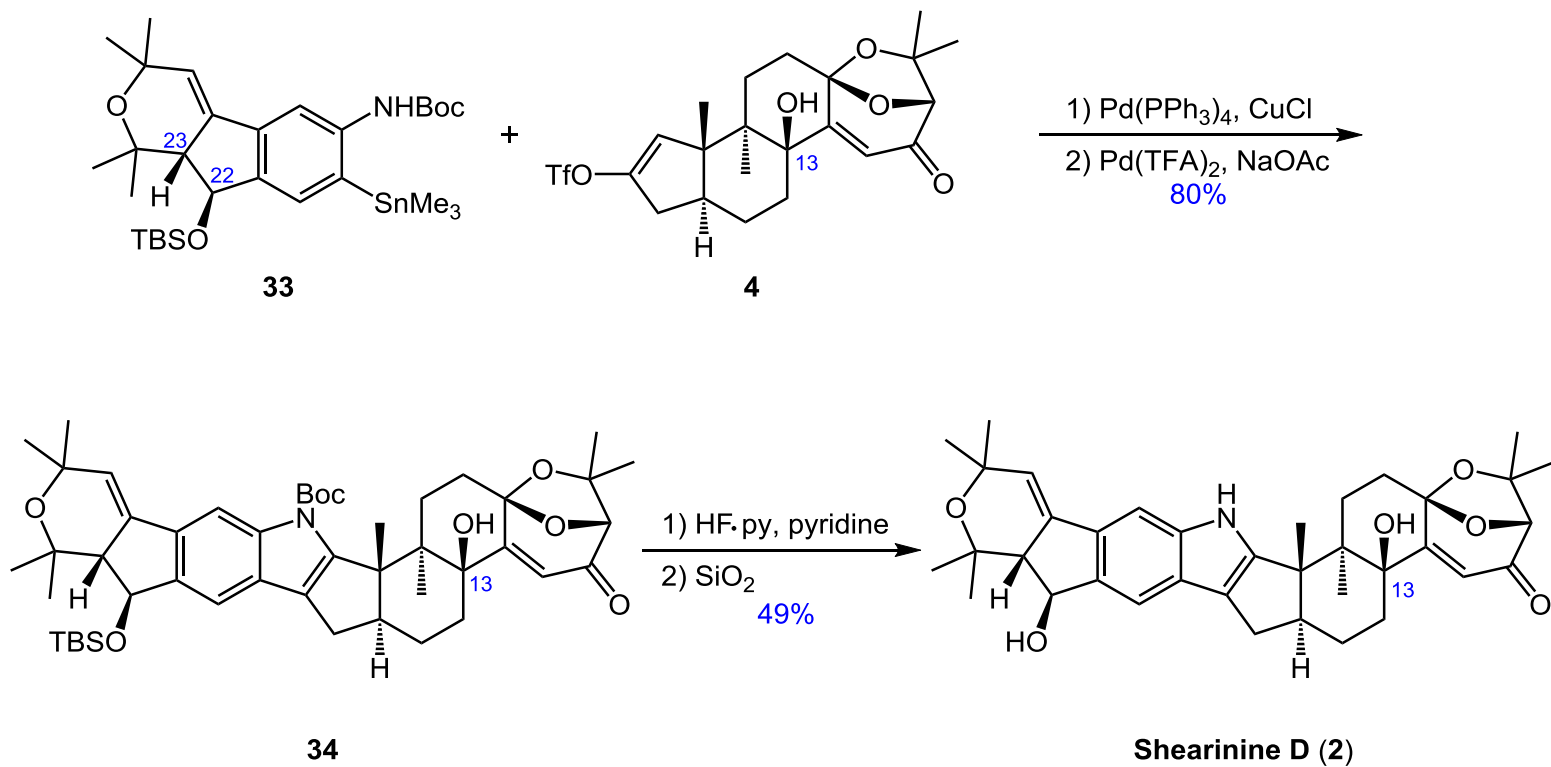
Synthesis of Shearinines G



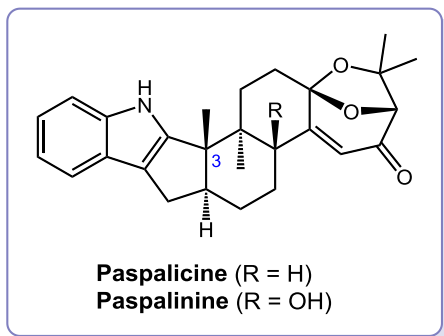
Synthesis of compound 33



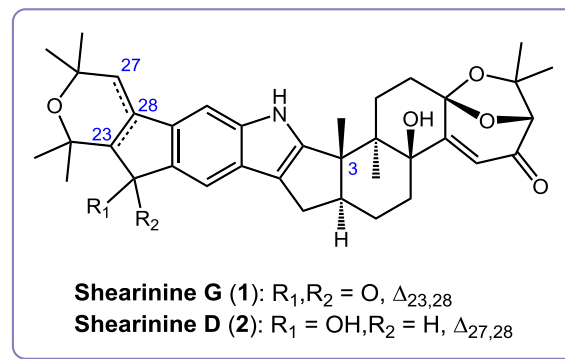
Synthesis of Shearinines D



Summary



- Paspalinine: 17 steps, 0.67% overall yield
- Hydroxy-directed cyclopropanation
- Palladium-mediated two-step indole ring formation
- Allylic selenoxide [2,3]-sigmatropic rearrangement

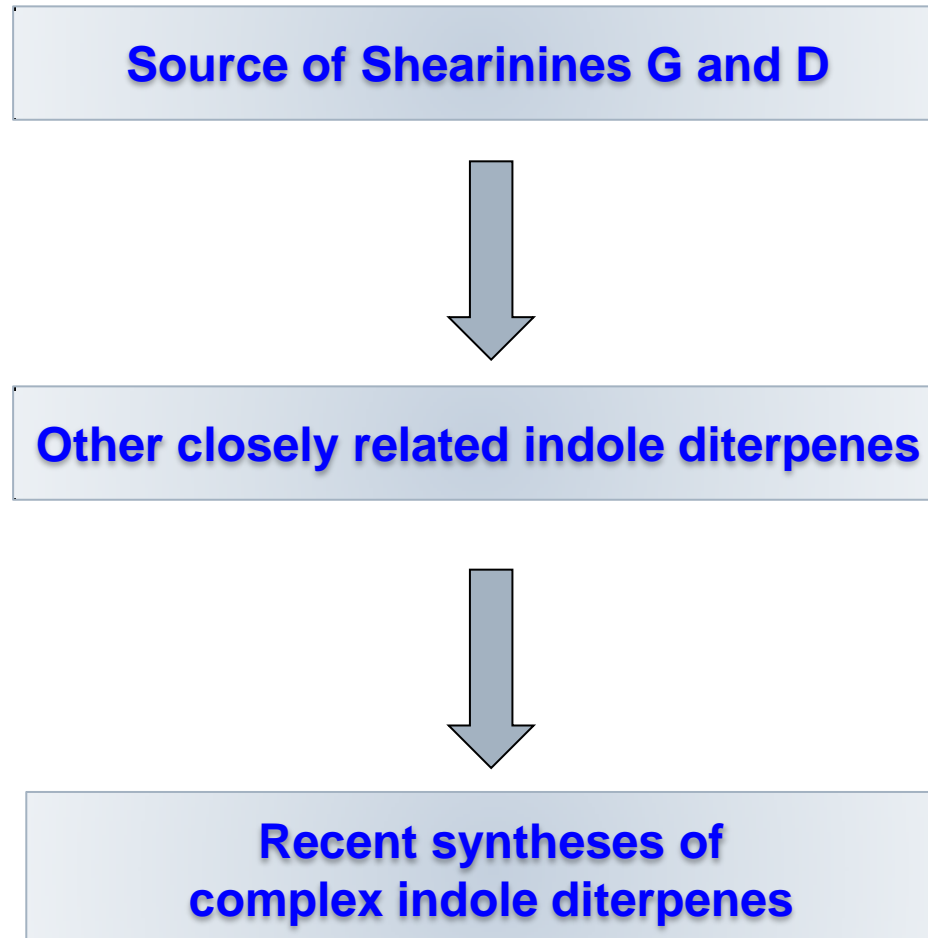


- Shearinines G: 18 steps, 0.19% overall yield
- Shearinines D: 19 steps, 0.16% overall yield
- Intramolecular rhodium(II)-catalyzed cyclopropanation
- One-pot Sharpless dihydroxylation/Achmatowicz reaction
- Riley oxidation

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The First Paragraph

Writing Strategy

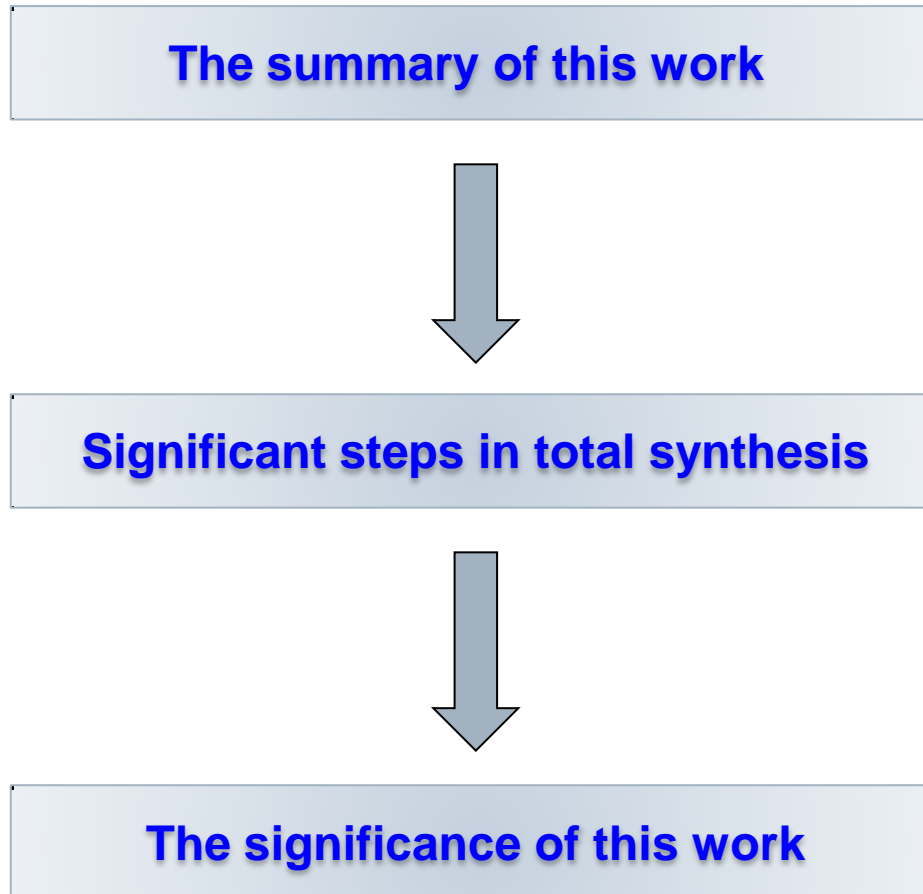


The First Paragraph

The Shearinines G and D are complex indole diterpenoids from the *Janthinem* class of natural products. They were initially isolated from the marine fungi *Eupenicillium* spp. and *Penicillium janthinellum* and later from *Escovopsis weberi*, a fungal pathogen interfering with the symbiosis of *Acromyrmex* leaf-cutter ants and the garden fungus *Leucoagaricus gongylophorus*. Other well-known, closely related indole diterpenes include paspalicine and tremorgenic paspalinine, which have been the subject of several synthetic studies. These have culminated in the first total syntheses by Smith of the bioactive indole terpenoids as well as penitrem and nodulisporic acids, resulting in a variety of creative approaches to the synthetically challenging motifs. Recent syntheses of paspalicine, paspaline, nodulisporic acid C, emindole SB and emindole PB highlight the continued interest of the synthetic community in complex indole diterpenes.

The Last Paragraph

Writing Strategy



The Last Paragraph

In summary, we have accomplished the first total syntheses of (+)-shearinines G (1) and D (2) through convergent and efficient routes. Highlights are a gold(I)-catalyzed cycloisomerization to access 2-isobutenyl furans, intramolecular rhodium(II)-catalyzed cyclopropanation to form the *trans*-hydrindane motif with two quaternary stereocenters, and onepot Sharpless dihydroxylation/Achmatowicz reaction en route to the dioxabicyclo[3.2.1]octane. Furthermore, the unexpected preference of the late-stage Riley oxidation for the *cis*-C13-hydroxydecalin from the *trans*-decalin precursor was investigated and rationalized. The modular route towards the indenopyran subunit and our convergent strategy allow access to related natural products and congeners.

Representative Examples

- The thermodynamic preferences for *trans*- versus *cis*-hydrindanes is complicated as it depends on the substitution pattern. (...很复杂, 因为...)
- More recently, cationic cyclization has provided entry to the *trans*-hydrindane, albeit as the minor product. (conj. 虽然, 尽管)
- As the diastereomers were inseparable, we proceeded to move forward with the diastereomeric mixture. (由于非对映异构体是不可分离的, 我们继续...)

Acknowledgement

Thanks for your attention !