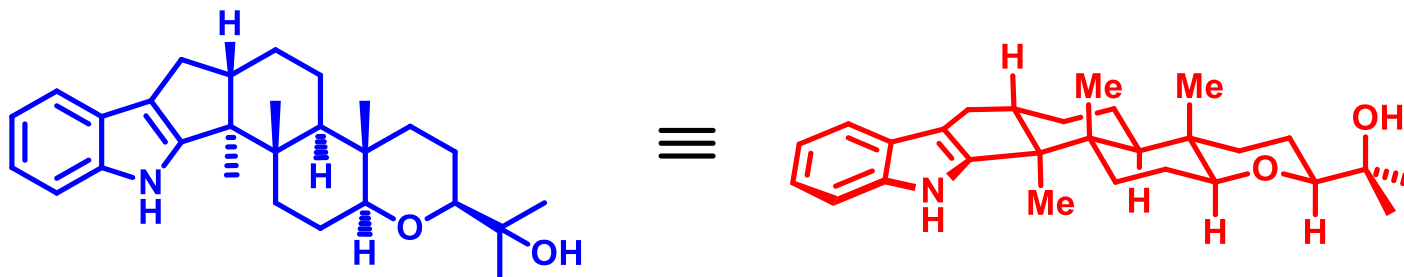


Total Synthesis of Paspaline



Group Seminar

Guang Li (Jieping Zhu's Lab)

Laboratory of Synthesis and Natural Products (LSPN)

Ecole Polytechnique Fédérale de Lausanne (EPFL)

Outline

❖ 1. Introduction

❖ 2. Total synthesis of Paspaline

- Smith's first-generation total synthesis
- Smith's second-generation total synthesis
- Johnson's total synthesis
- Newhouse's total synthesis

❖ 3. Summary and Outlook

Outline

❖ 1. Introduction

❖ 2. Total synthesis of Paspaline

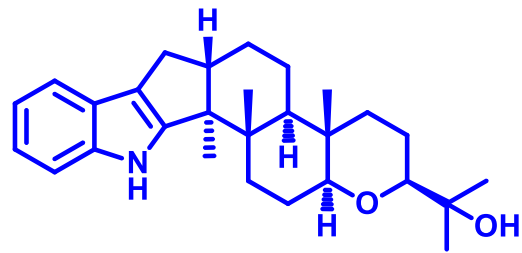
- Smith's first-generation total synthesis
- Smith's second-generation total synthesis
- Johnson's total synthesis
- Newhouse's total synthesis

❖ 3. Summary and Outlook

Introduction of Paspaline



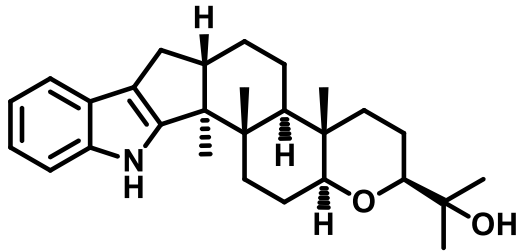
The structurally distinct indole diterpenoids paspaline were first discovered from *Claviceps paspali* in the 1966, related compounds including paspalicine, paspalinine, paxilline, aflatrem, paspalitrem.



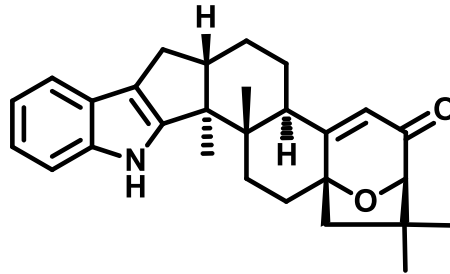
Paspaline

Derivatives of paspalinine have shown potent activity as potassium channel antagonists and may be useful in the treatment of glaucoma.

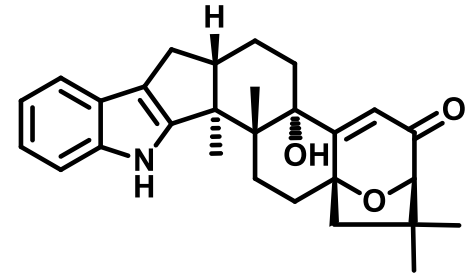
Introduction of Paspaline



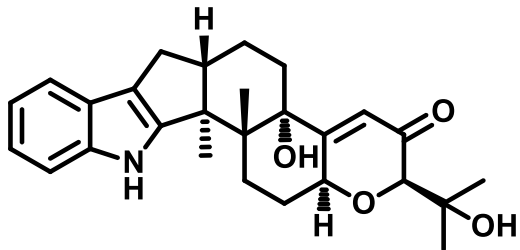
Paspaline



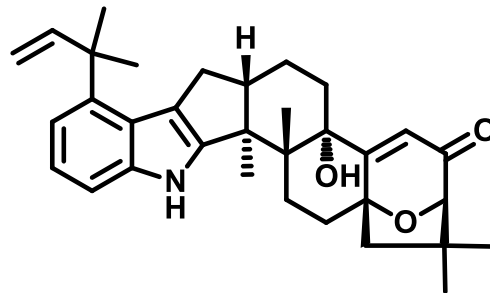
Paspalicine



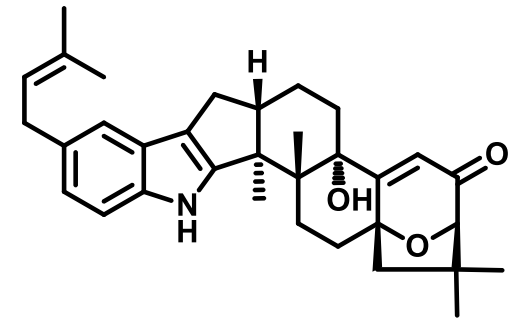
Paspalinine



Paxilline



Alflatrem



Paspalitrem

Total Synthesis of Paspaline



Amos B. Smith III



Timothy R. Newhouse



Jeffrey S. Johnson

Outline

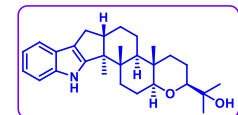
❖ 1. Introduction

❖ 2. Total synthesis of Paspaline

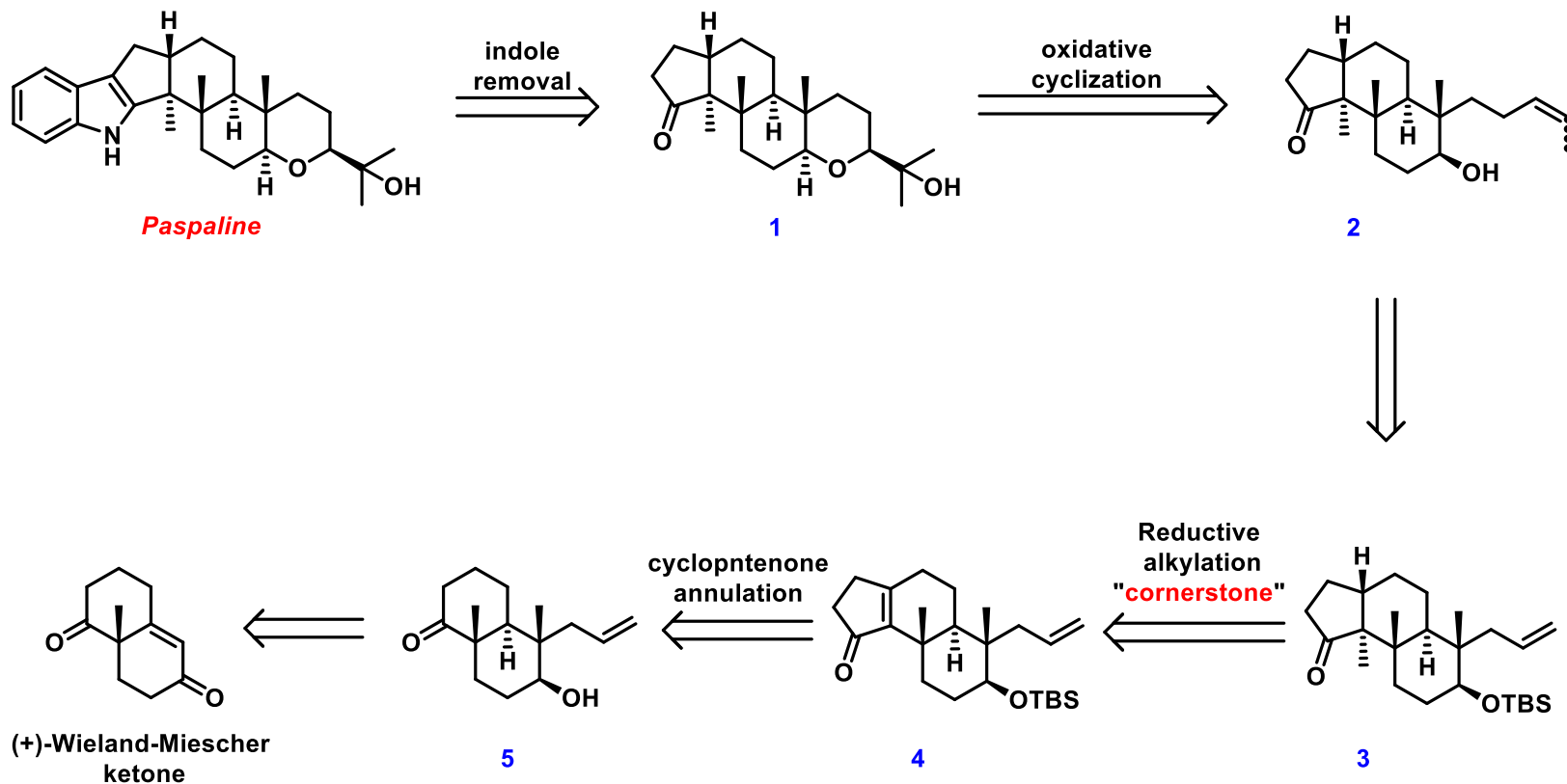
- Smith's first-generation total synthesis
- **Smith's second-generation total synthesis**
- Johnson's total synthesis
- Newhouse's total synthesis

❖ 3. Summary and Outlook

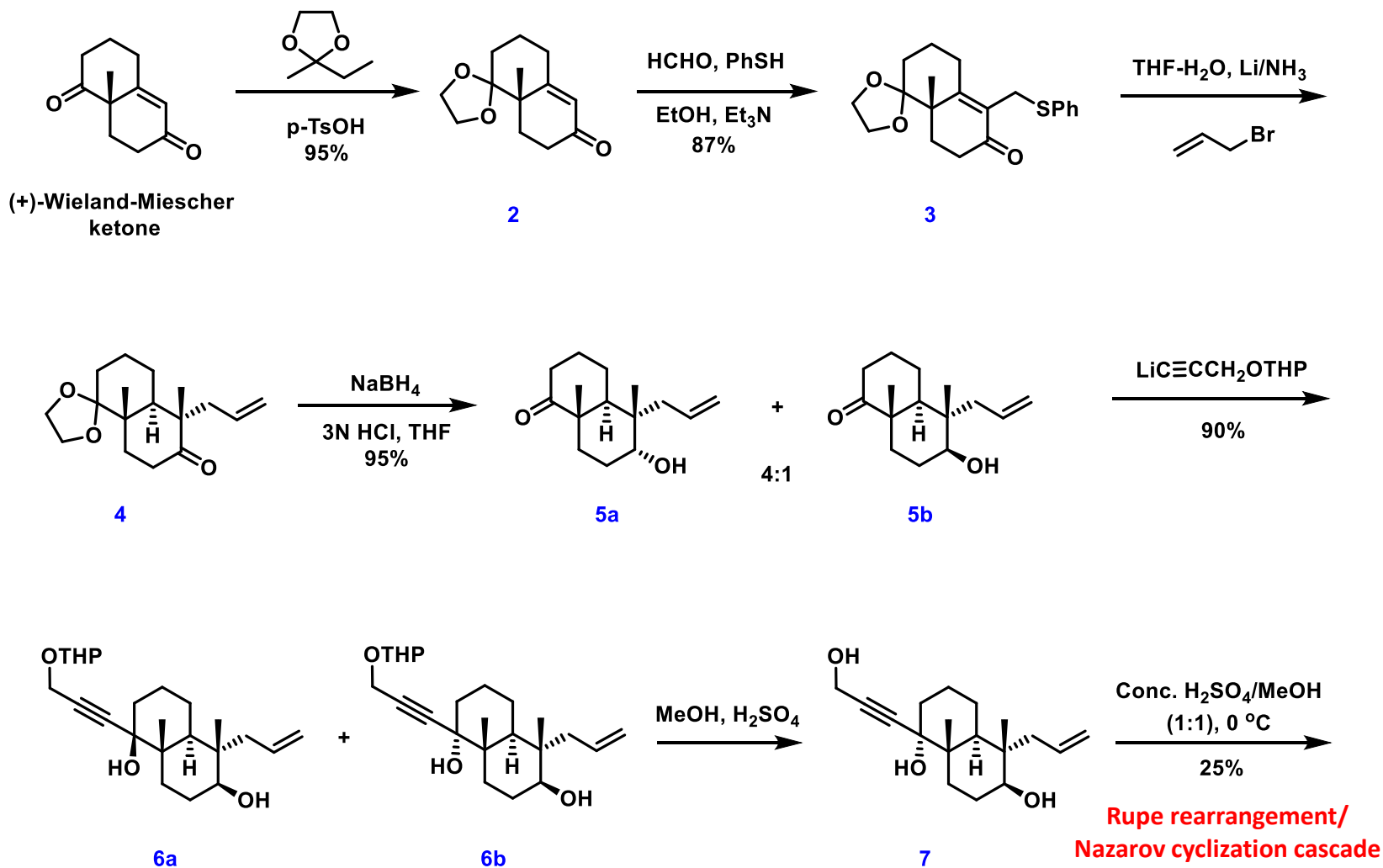
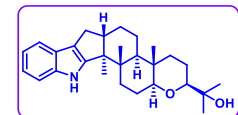
Smith's first generation total synthesis



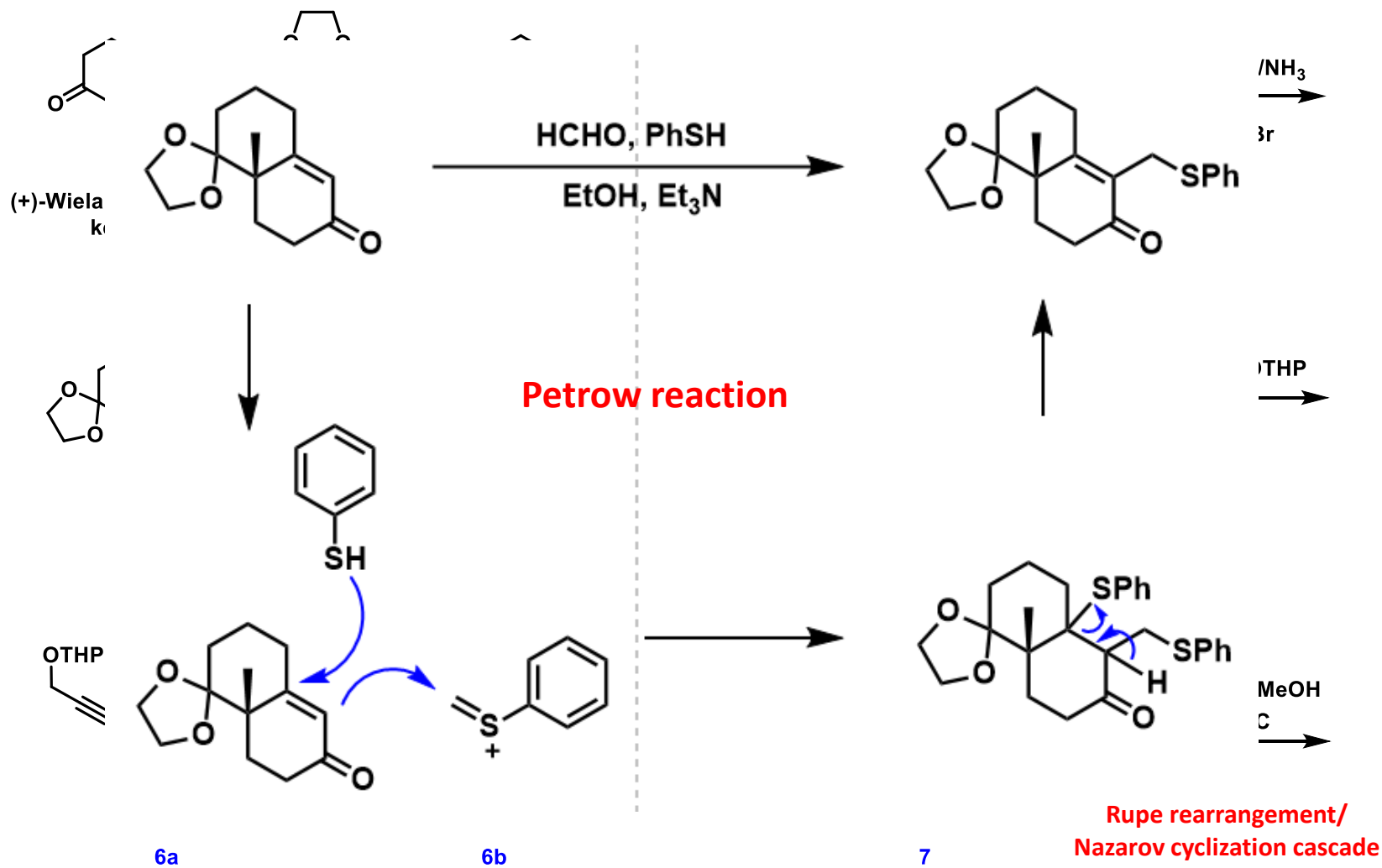
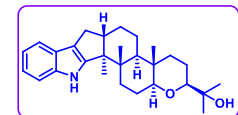
Retrosynthetic Analysis of Paspaline



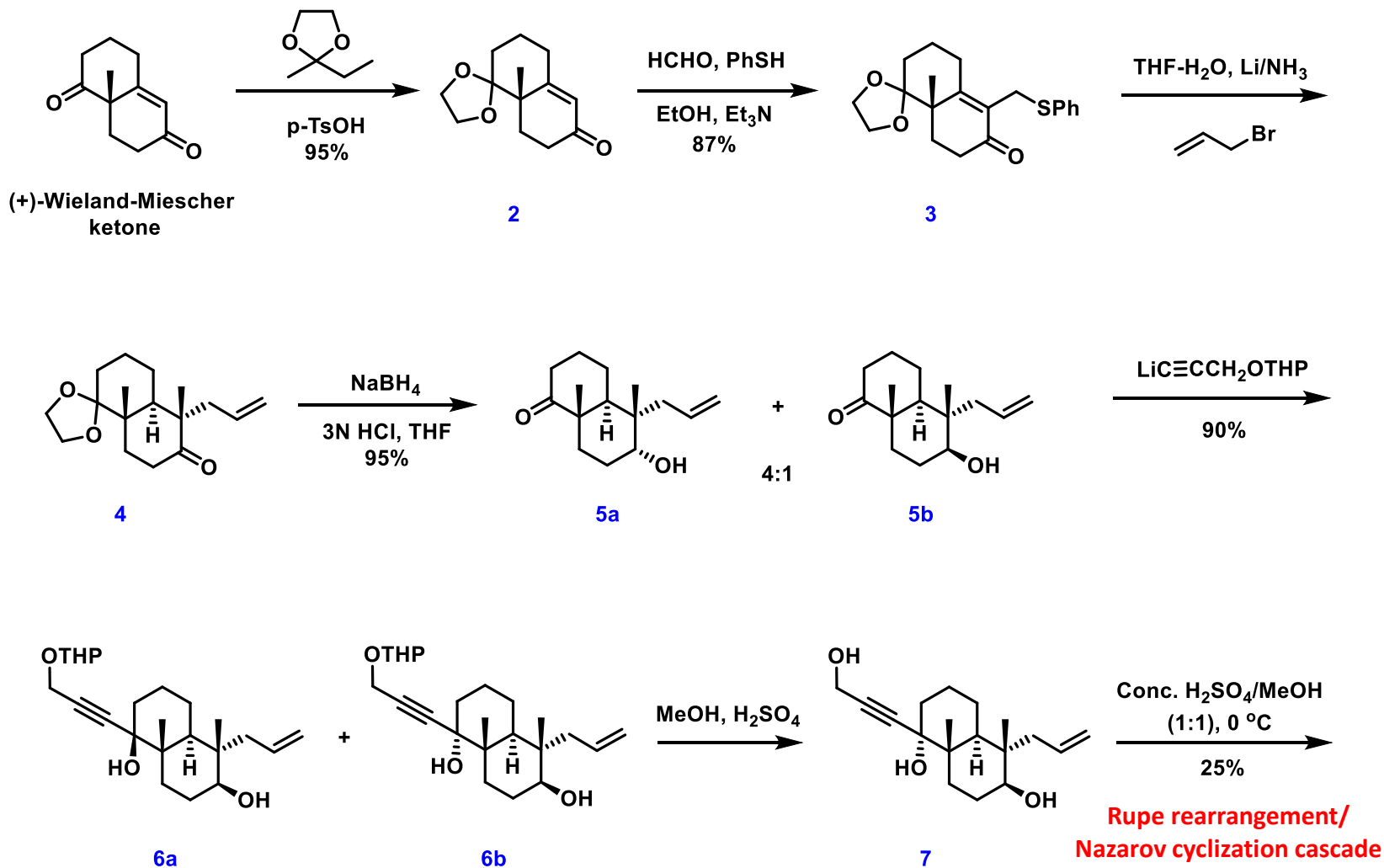
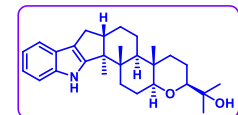
Smith's first generation total synthesis



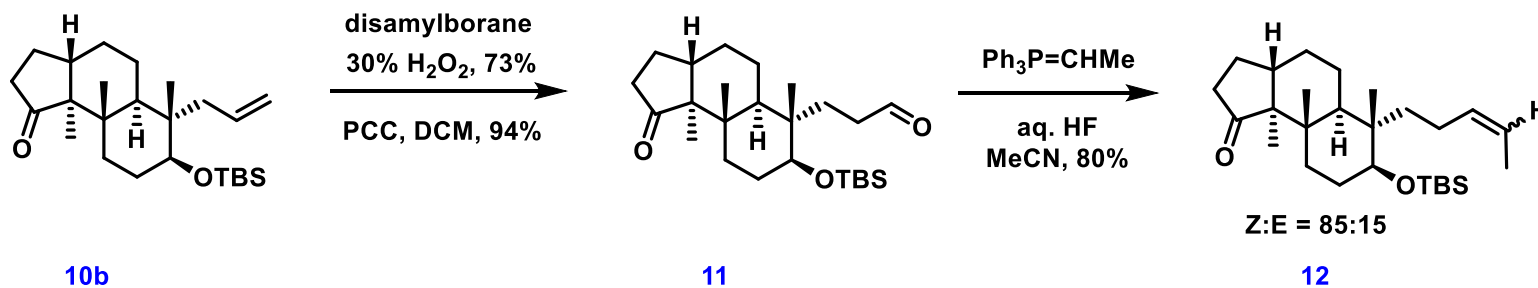
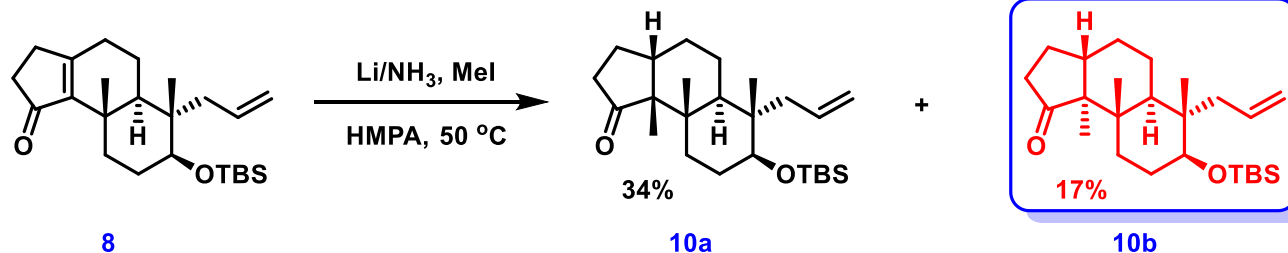
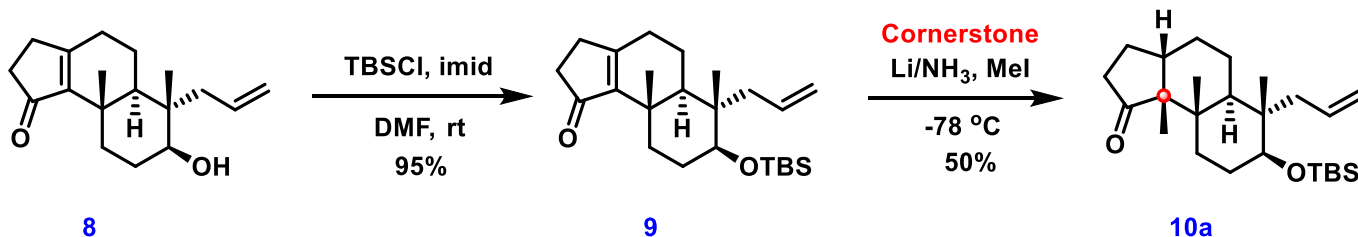
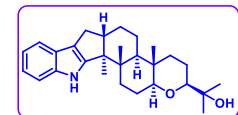
Smith's first generation total synthesis



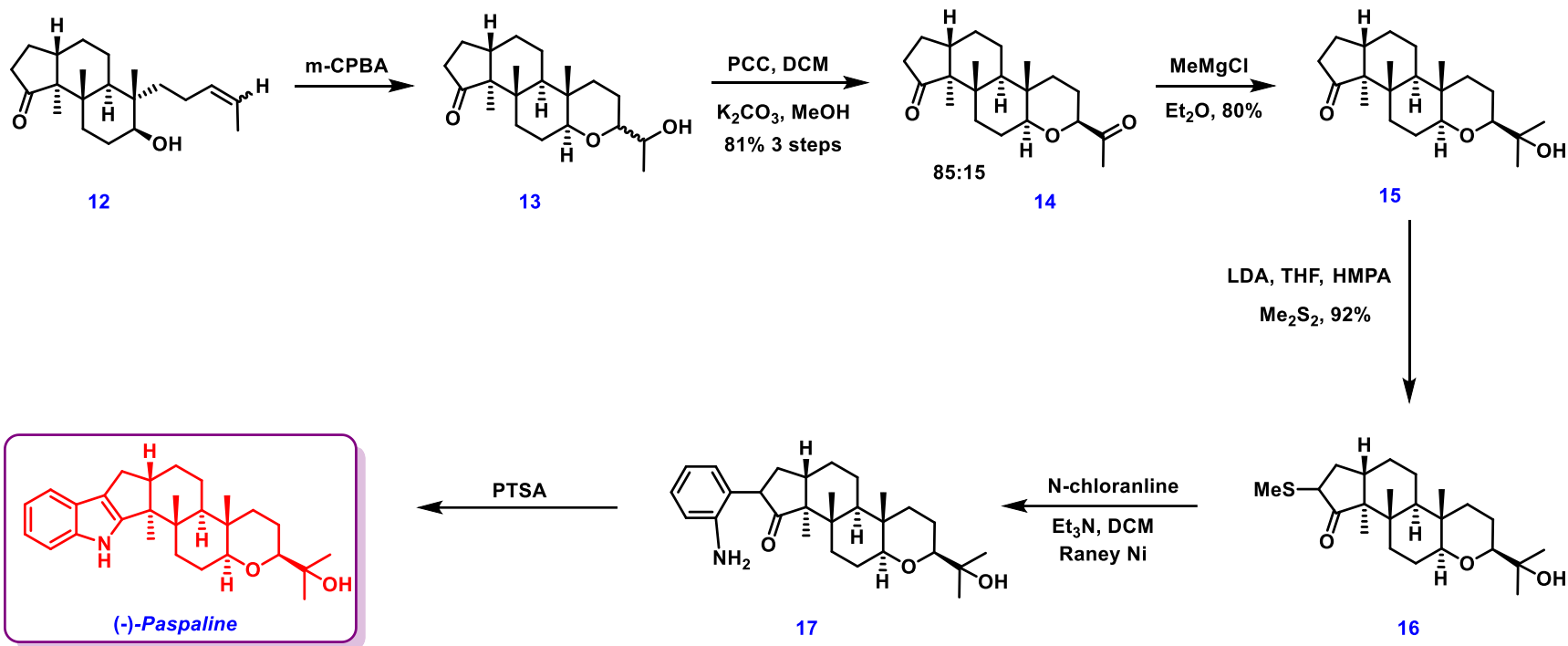
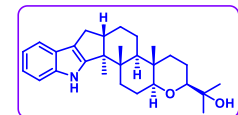
Smith's first generation total synthesis



Smith's first generation total synthesis

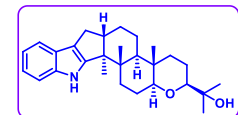


Smith's first generation total synthesis

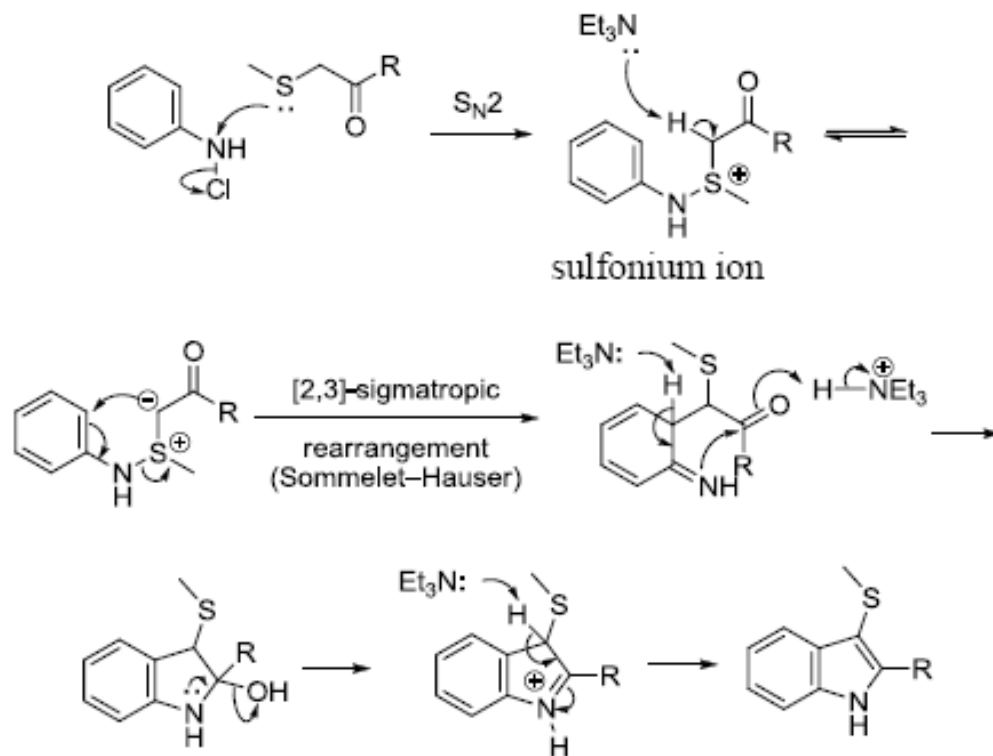
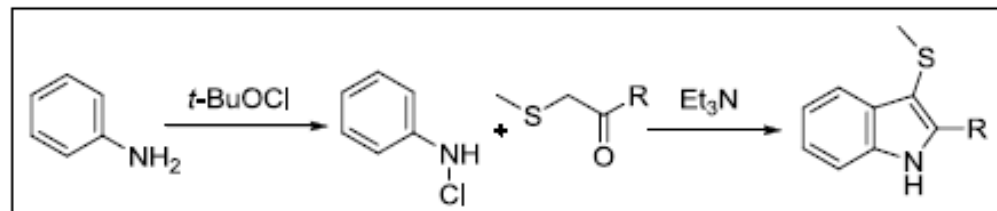


23 steps from
(+)-Wieland-Miescher ketone

Smith's first generation total synthesis



Gassman indolization



Outline

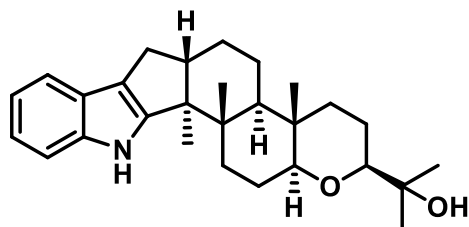
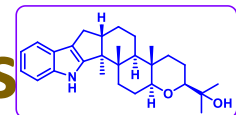
❖ 1. Introduction

❖ 2. Total synthesis of Paspaline

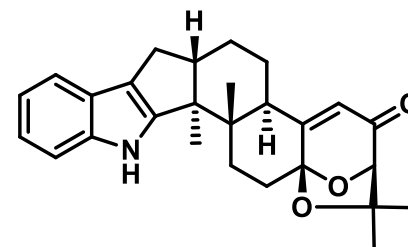
- **Smith's first-generation total synthesis**
- **Smith's second-generation total synthesis**
- **Johnson's total synthesis**
- **Newhouse's total synthesis**

❖ 3. Summary and Outlook

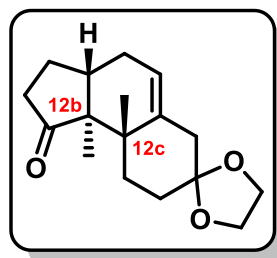
Smith's second generation total synthesis



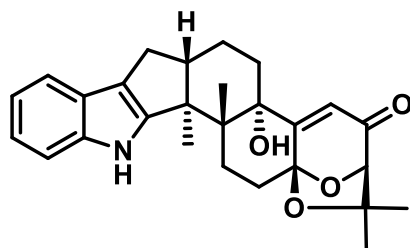
Paspaline



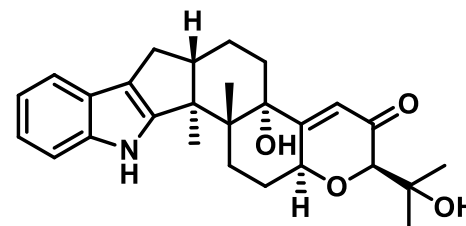
Paspalicine



Common Advanced intermediate
for Simple indole Deterperne
Tremorgens

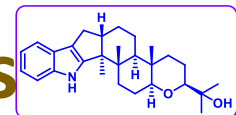


Paspalinine

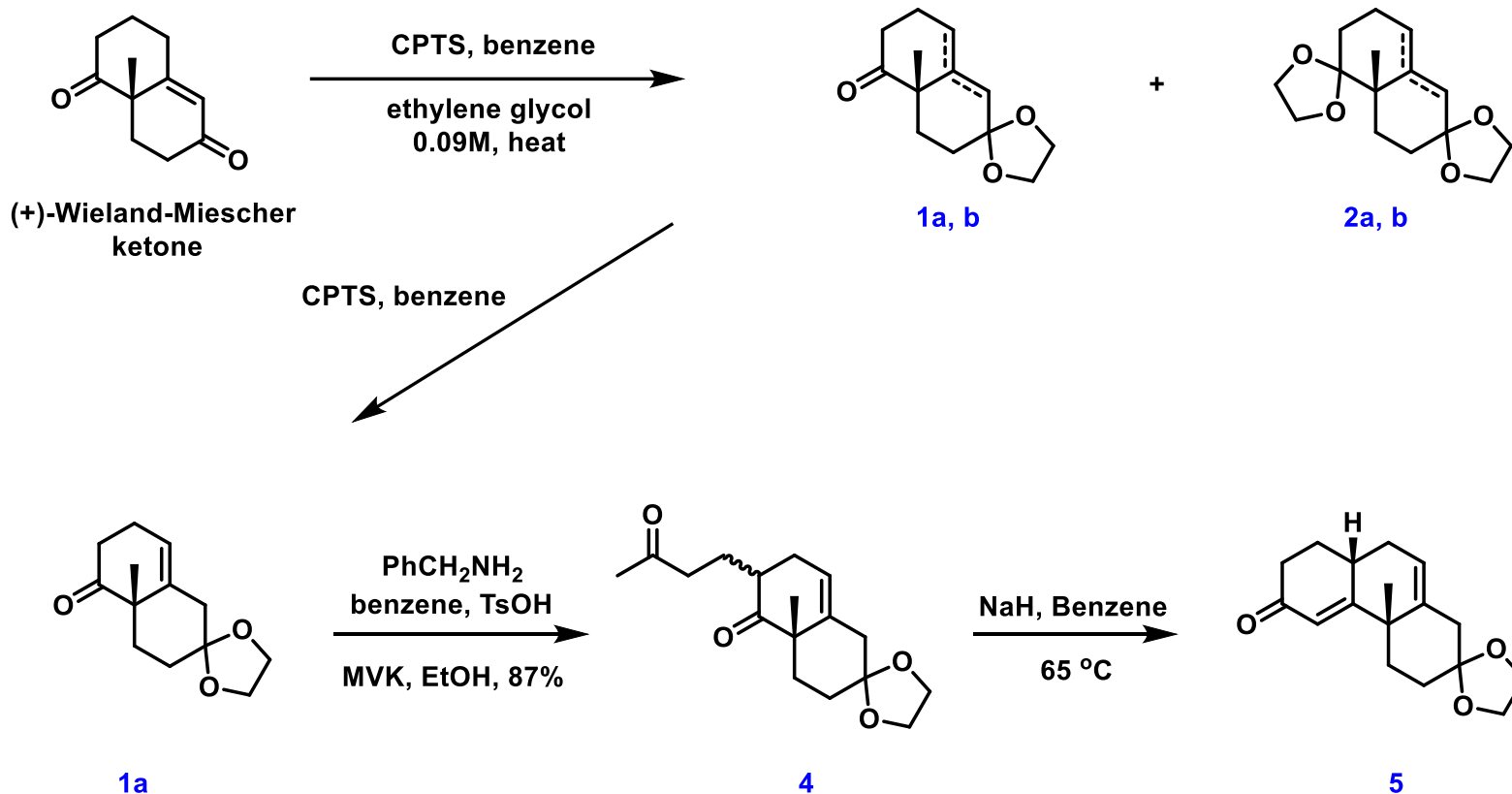


Paxilline

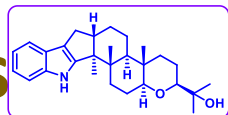
Smith's second generation total synthesis



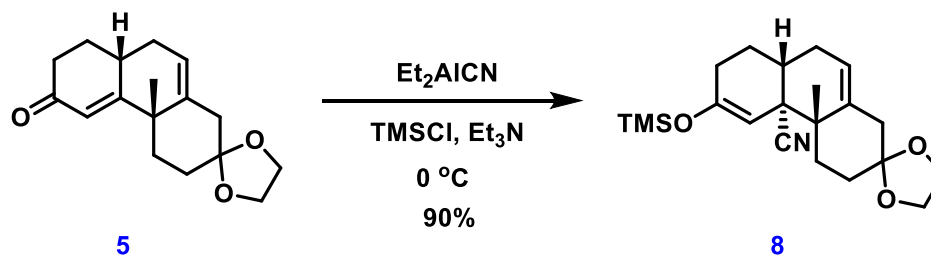
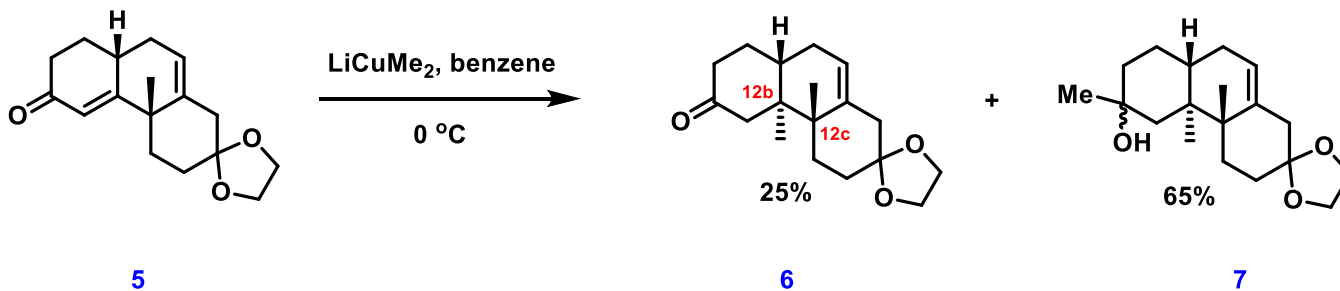
Construction of Tricyclic Enone



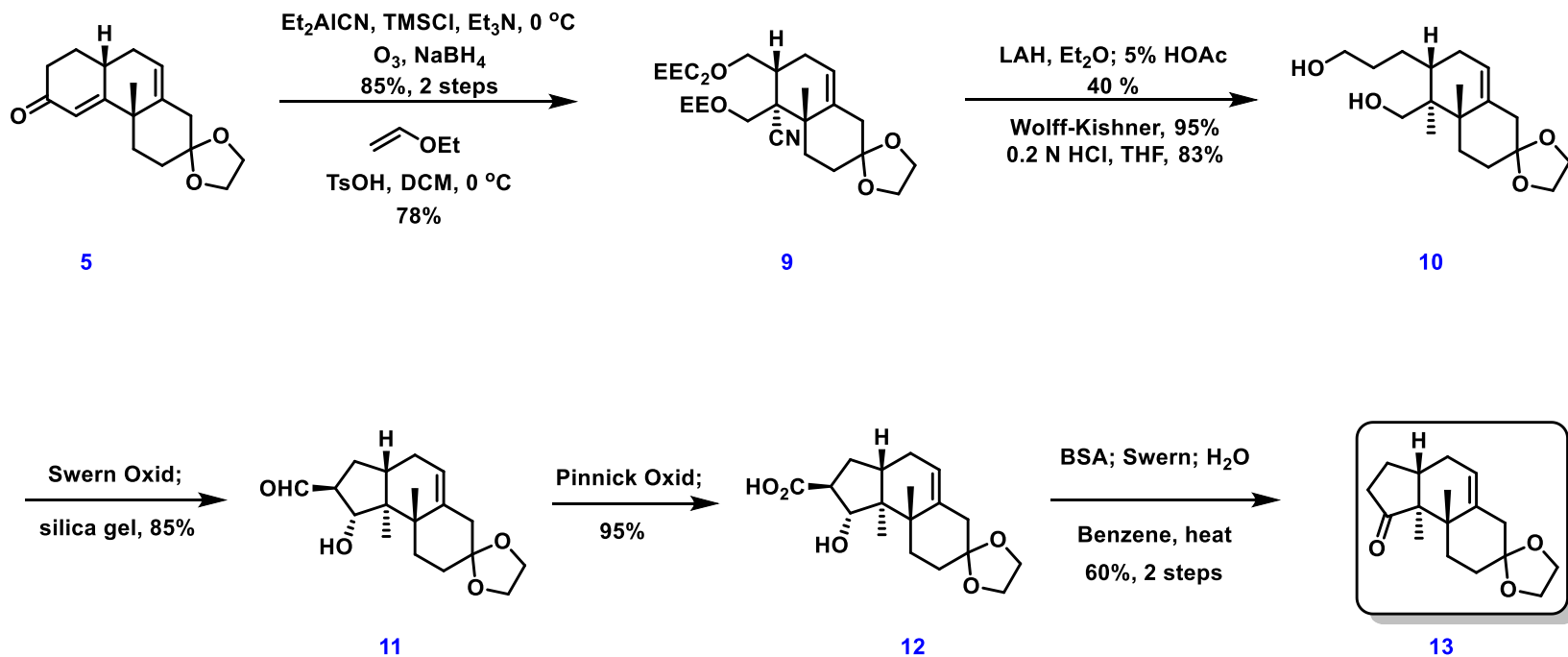
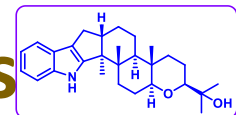
Smith's second generation total synthesis



Orchestration of the Vicinal Quaternary Centers: A Challenging Synthetic Problem

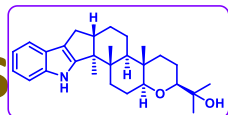


Smith's second generation total synthesis

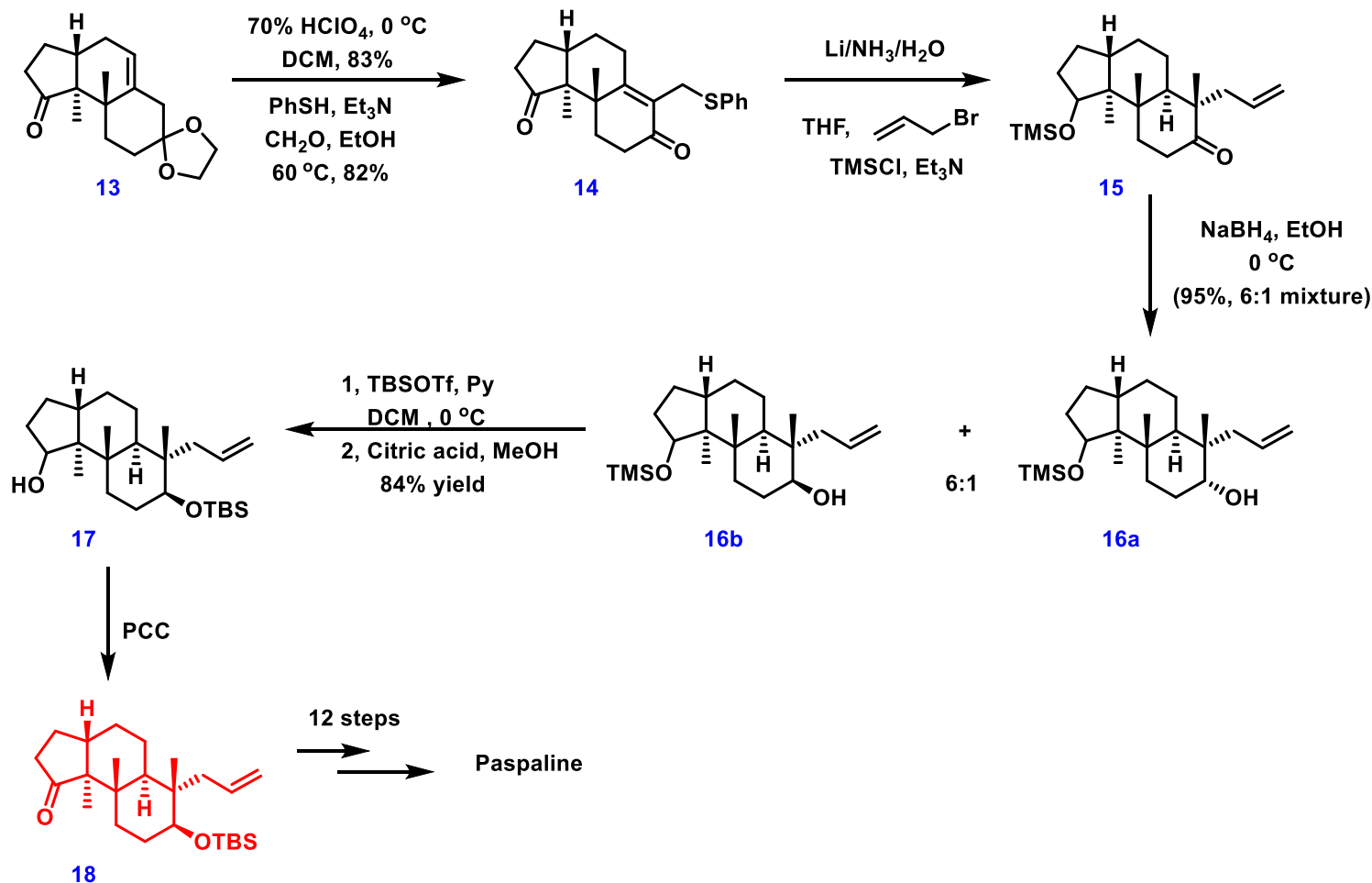


13 steps, 6.1% overall yield
from (+)-Wieland-Miescher ketone

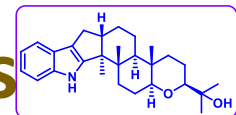
Smith's second generation total synthesis



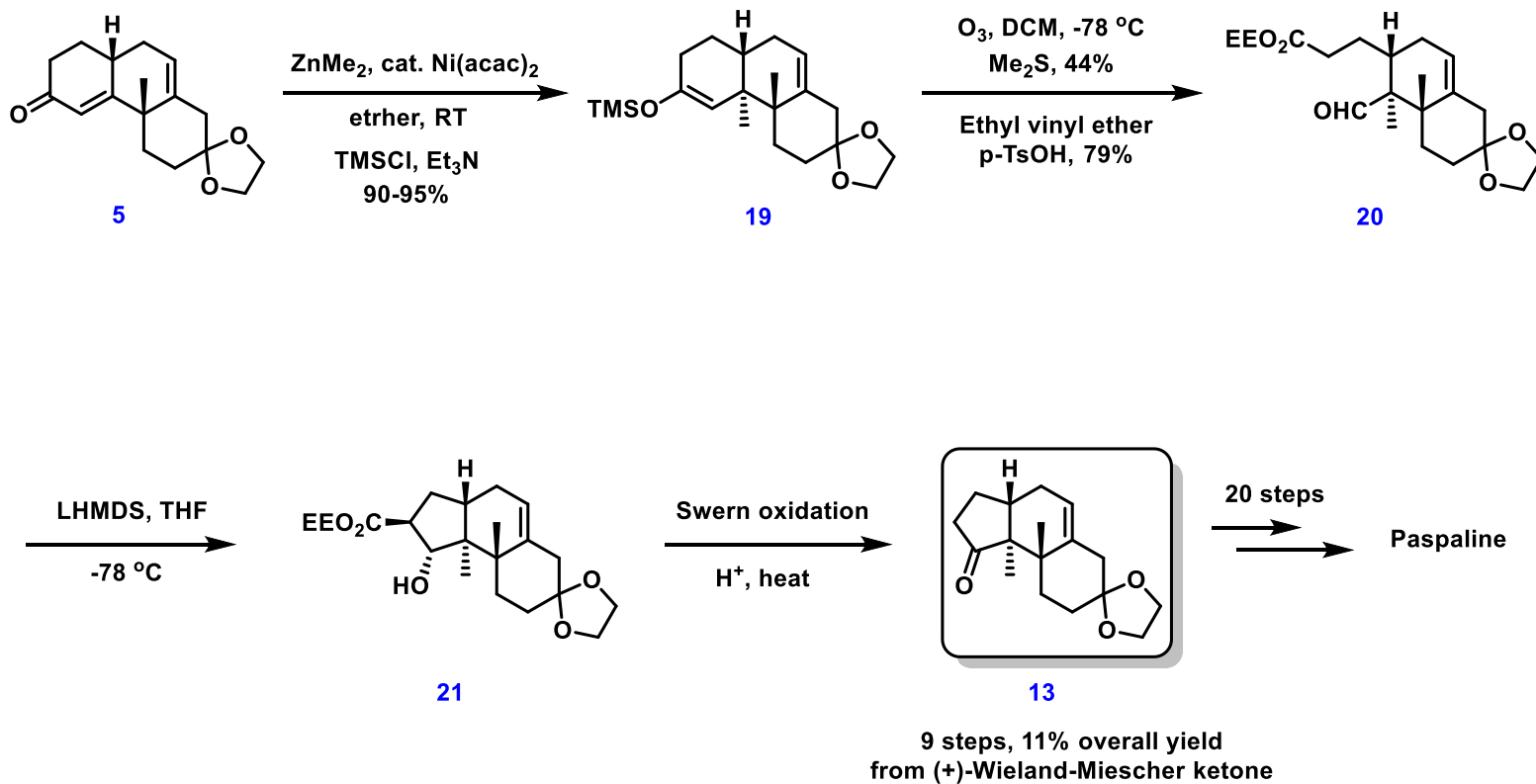
Completion of a Highly Stereocontrolled Total Synthesis of (-)-Paspaline.



Smith's second generation total synthesis



A More Efficient Route to Tricyclic Ketone



Outline

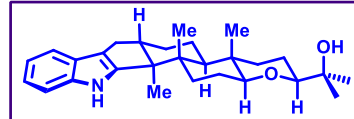
❖ 1. Introduction

❖ 2. Total synthesis of Paspaline

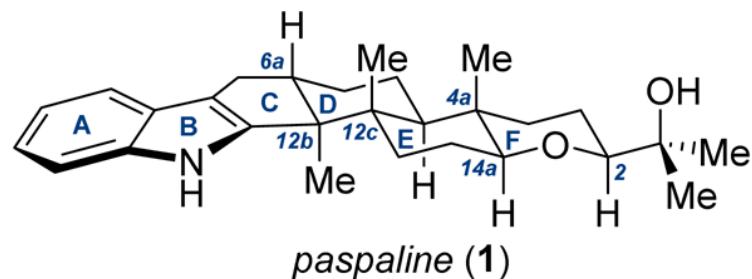
- **Smith's first-generation total synthesis**
- **Smith's second-generation total synthesis**
- **Johnson's total synthesis**
- **Newhouse's total synthesis**

❖ 3. Summary and Outlook

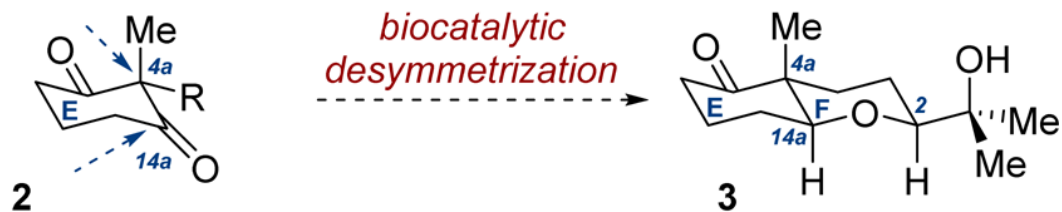
Johnson's total synthesis



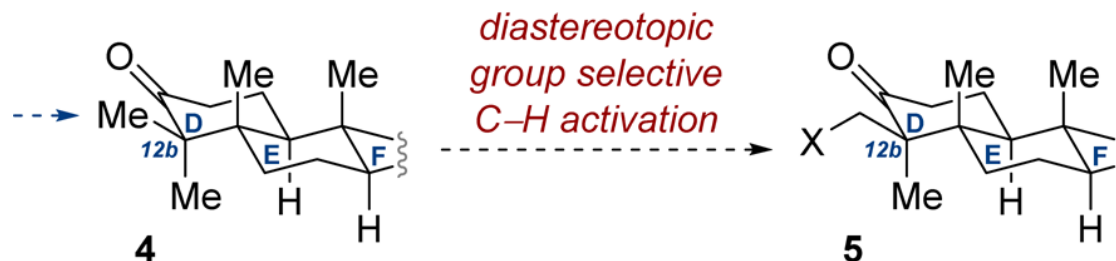
Synthesis Plan for Paspaline



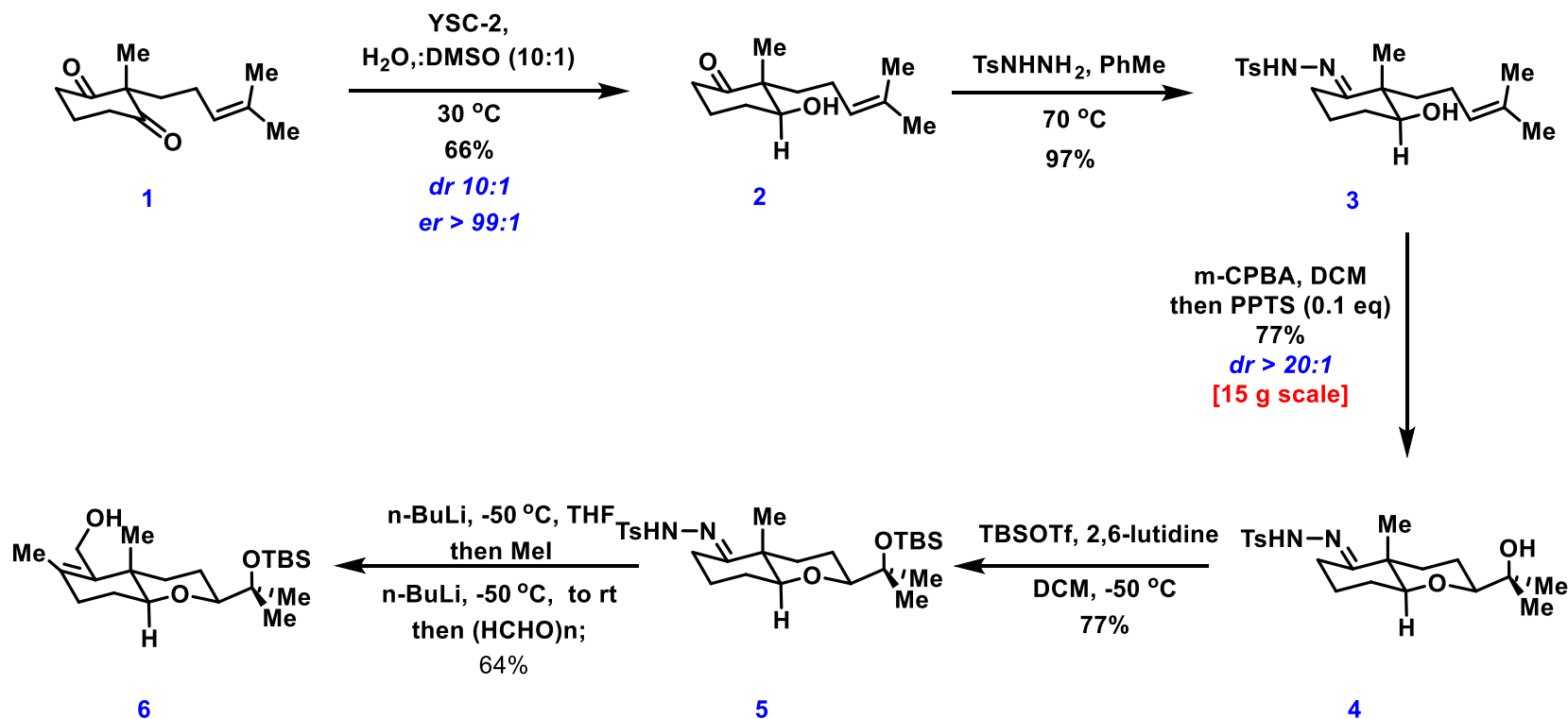
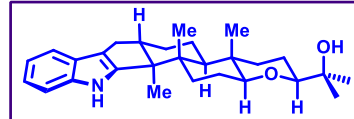
■ C4a-C14a stereocenters



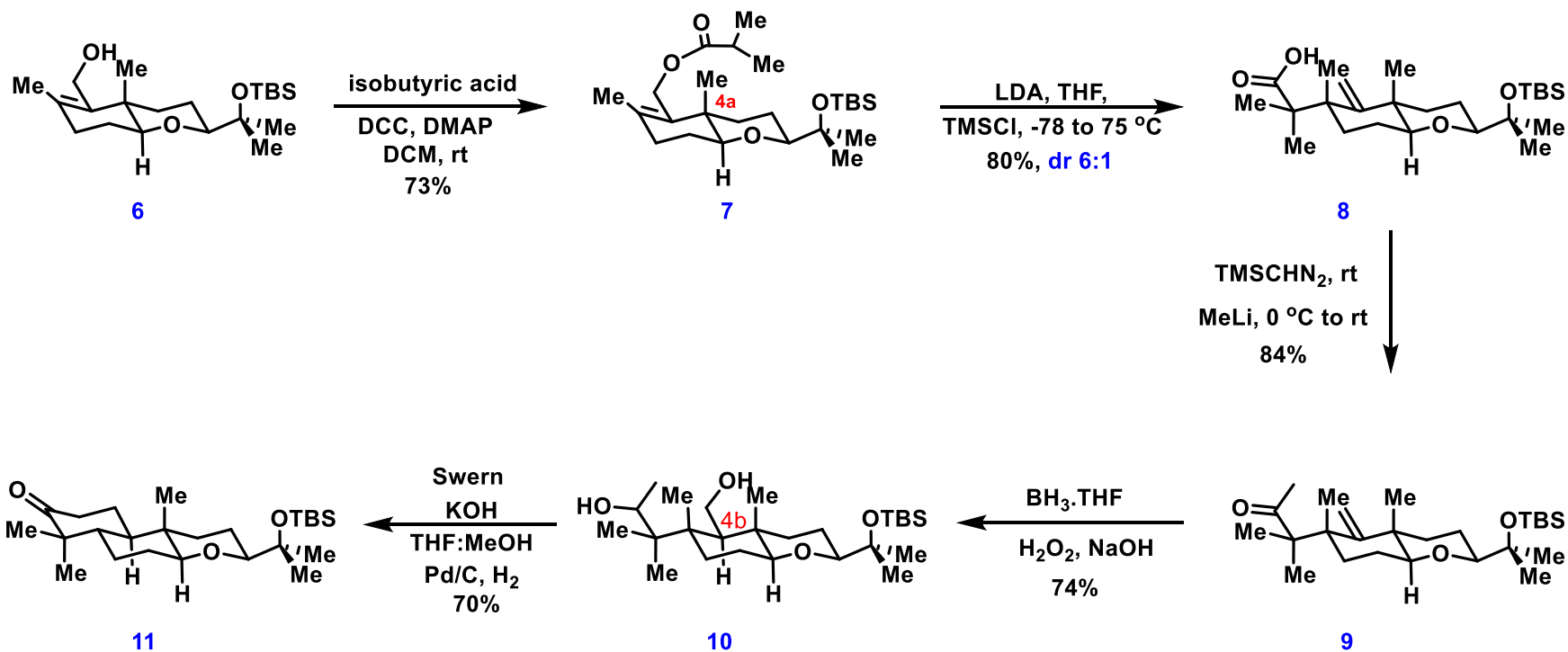
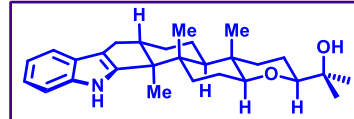
■ C12b quaternary center



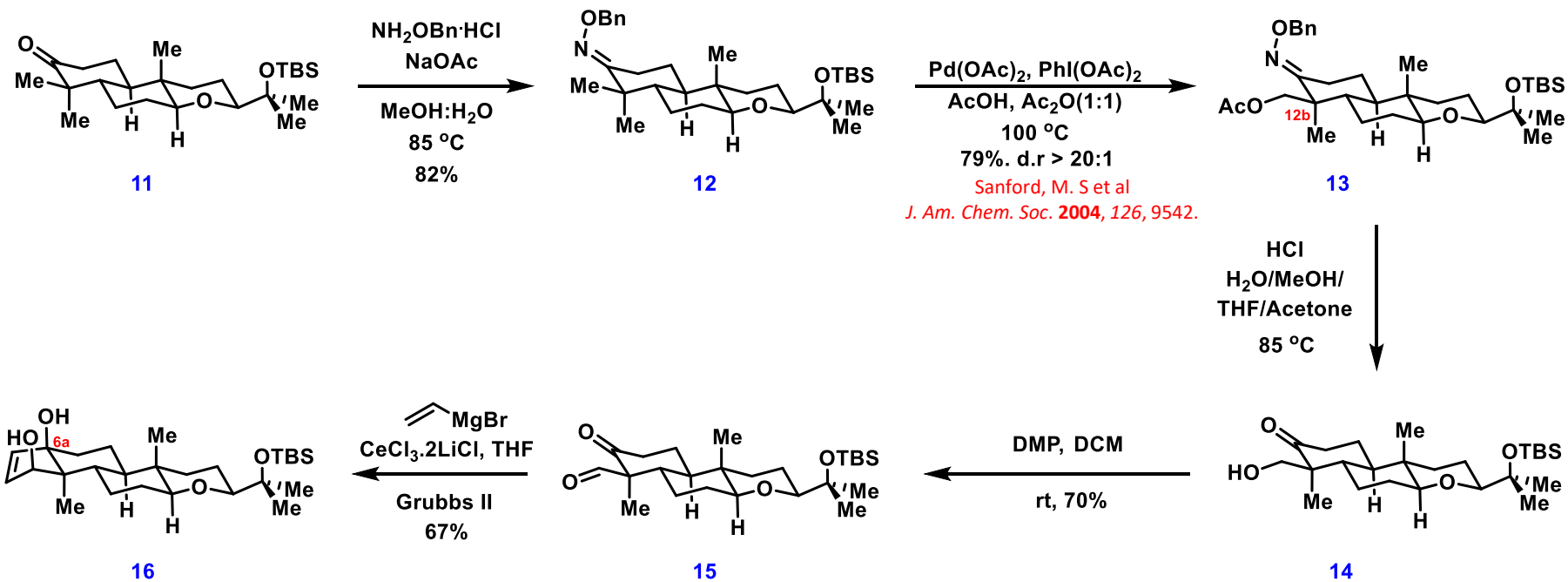
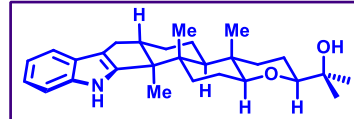
Johnson's total synthesis



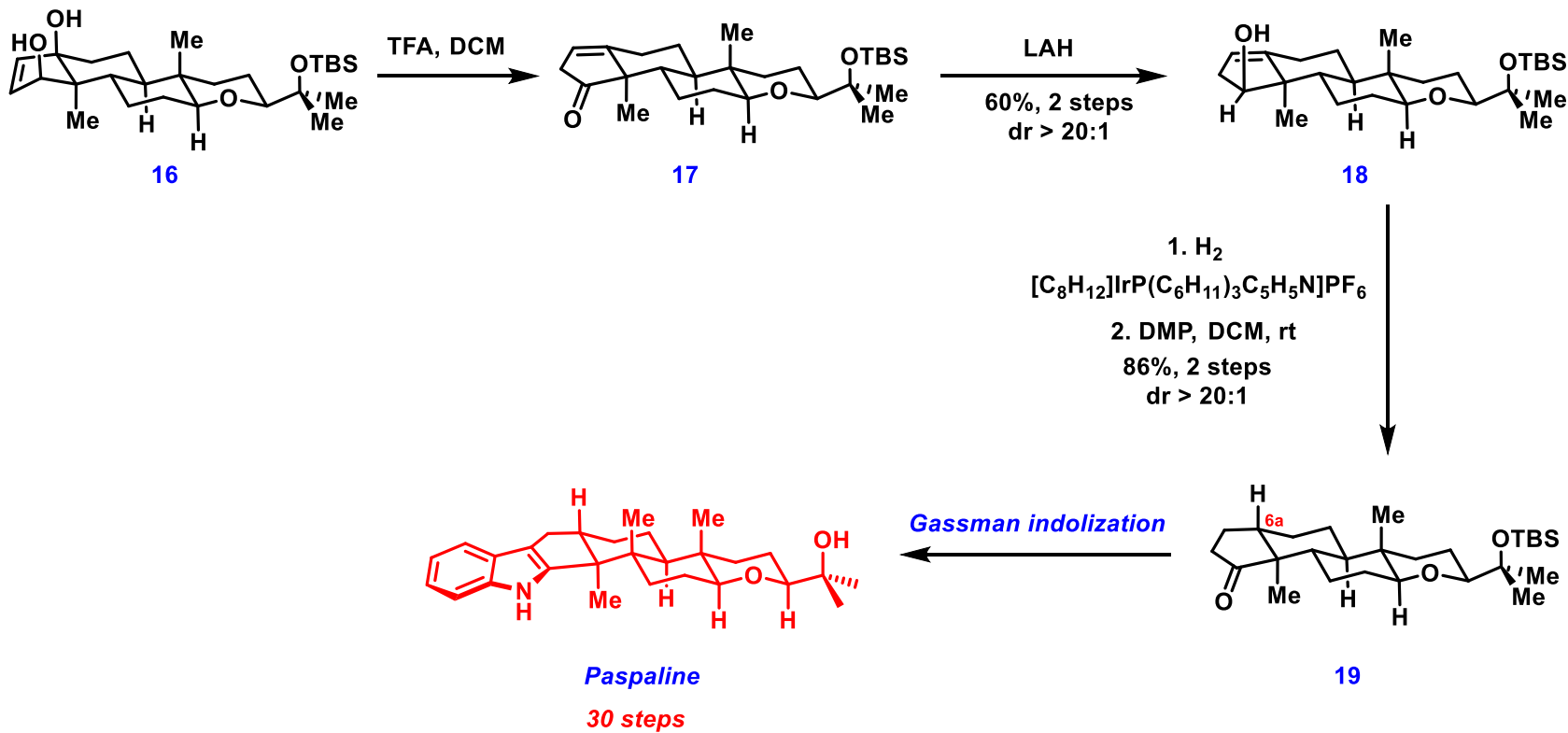
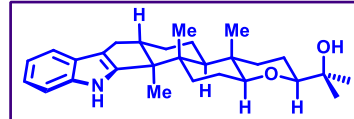
Johnson's total synthesis



Johnson's total synthesis



Johnson's total synthesis



Outline

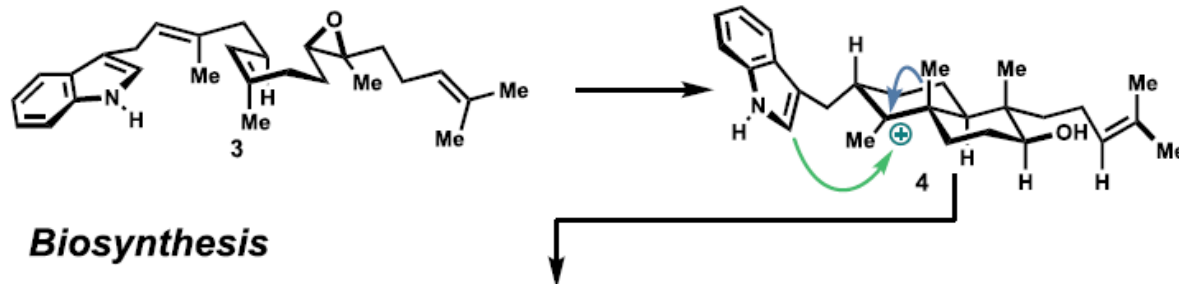
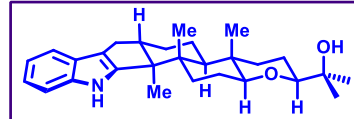
❖ 1. Introduction

❖ 2. Total synthesis of Paspaline

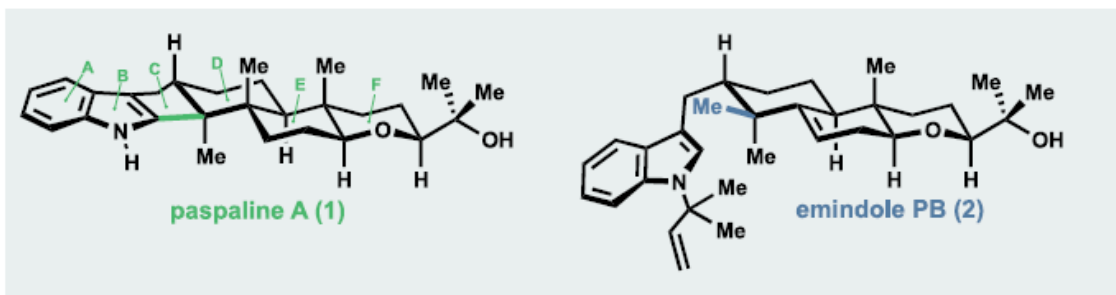
- Smith's first-generation total synthesis
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❖ 3. Summary and Outlook

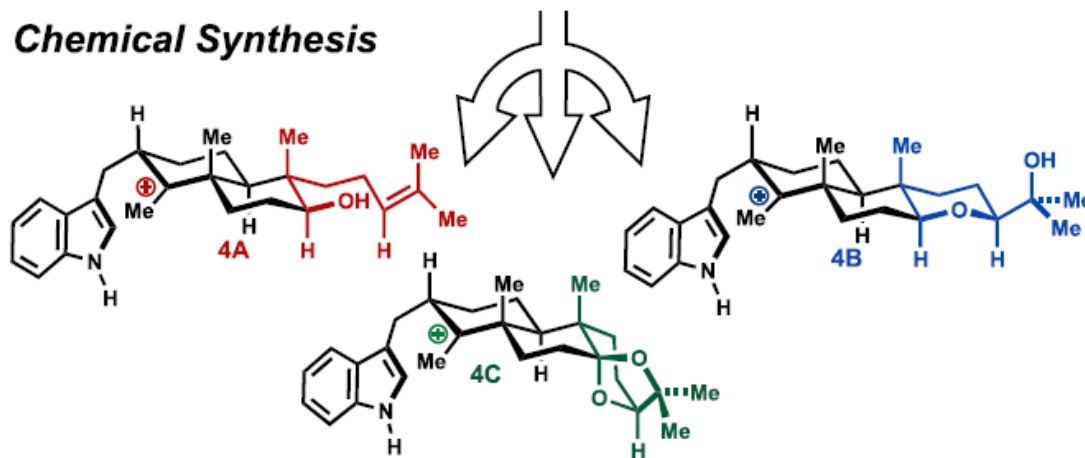
Newhouse's total synthesis



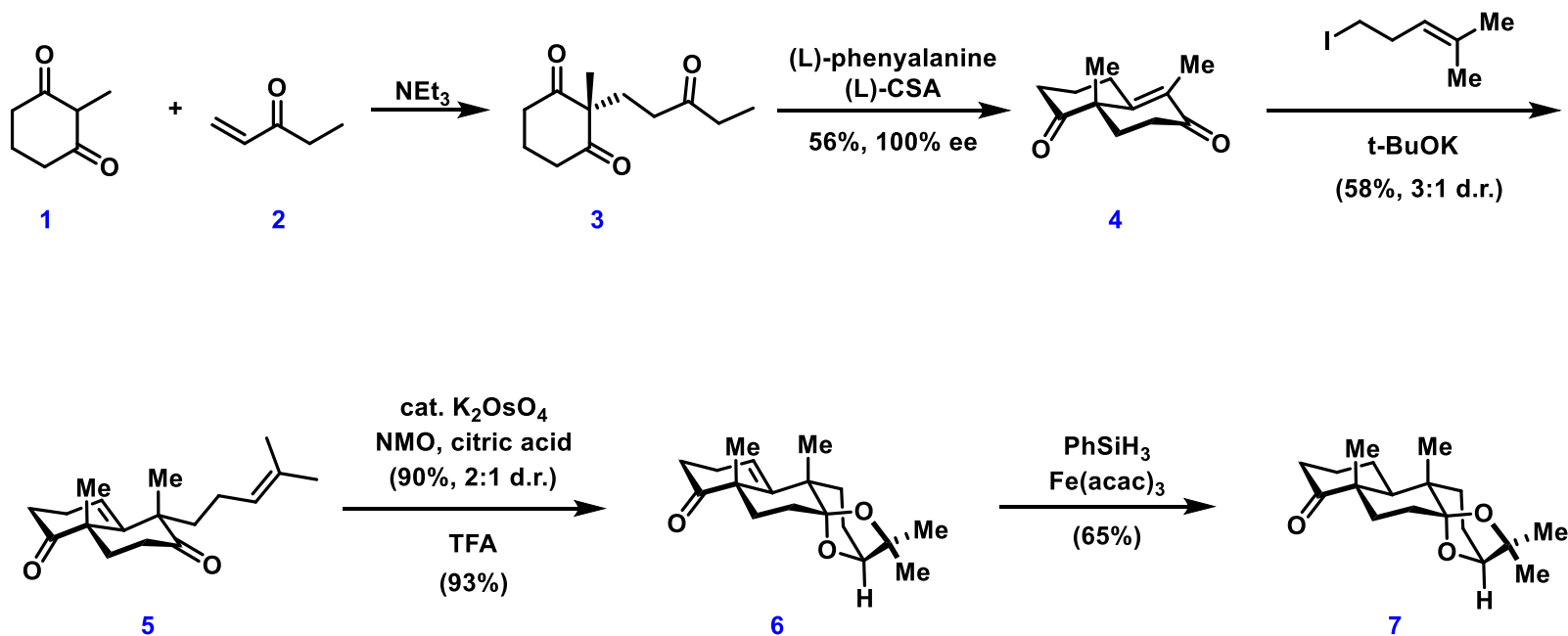
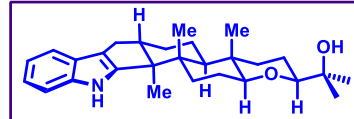
Biosynthesis



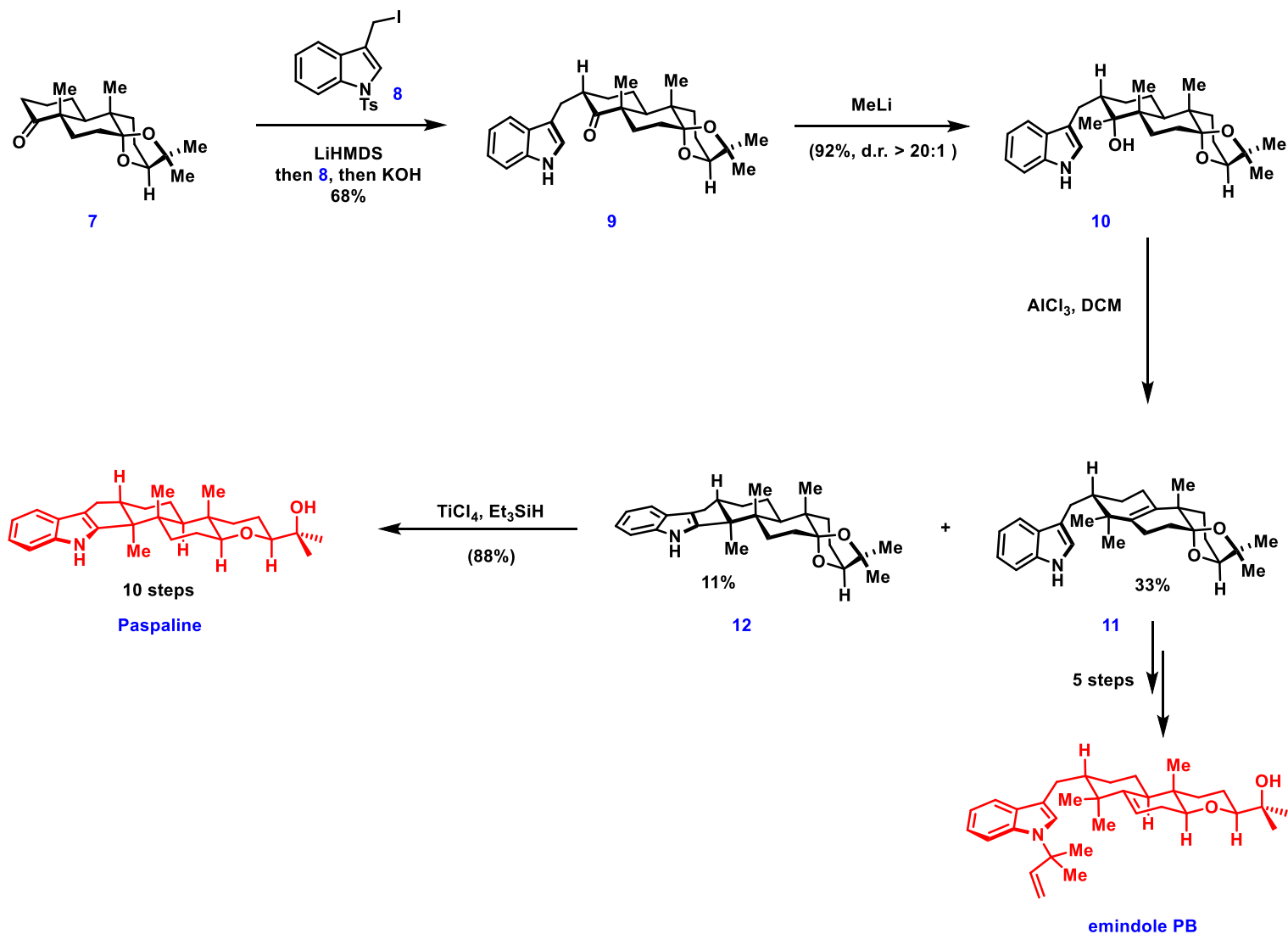
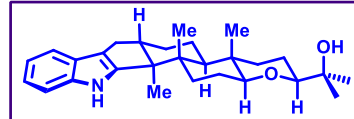
Chemical Synthesis



Newhouse's total synthesis



Newhouse's total synthesis



Summary

Smith's first generation

23 steps.

Key steps:

Reductive alkylation

Rupe rearrangement/Nazarov

Cyclization

Smith's second generation

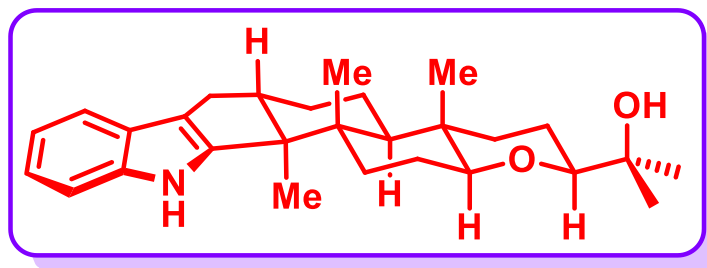
29 steps.

Key steps:

Common advanced intermediate

1, 4-addition for vicinal quaternary

center



Johnson's

30 steps.

Key steps:

highly diastereoselective enzymatic desymmetrization.

Ireland-Claisen rearrangement.

Diastereotopic group selective C-H.

Newhouse's

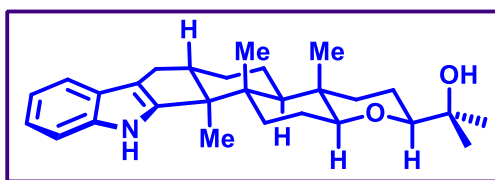
10 steps.

Key steps:

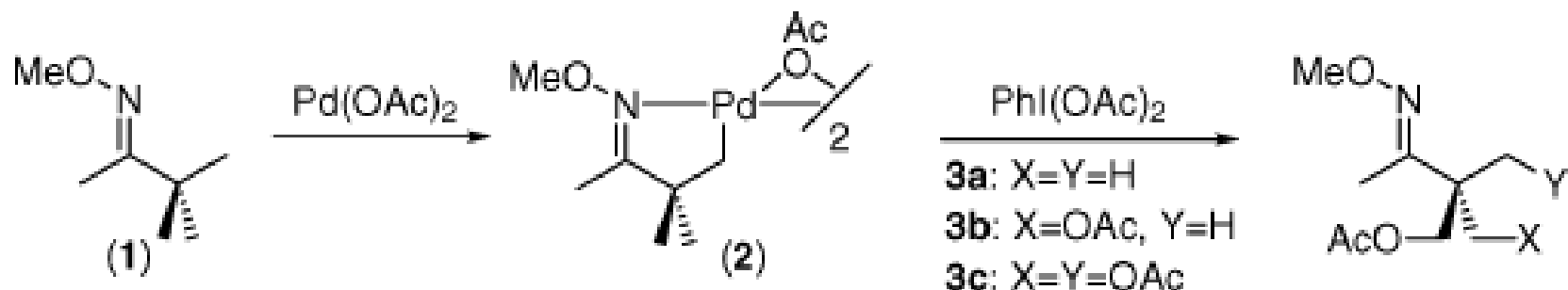
Biomimetic F-C cyclization

Thanks for your attention !

Total synthesis of Paspaline



Scheme 1. Chelate-Directed Oxidation of Pinacalone *O*-Methyl Oxime



Lopa V. Desai, Kami L. Hull, Melanie S. Sanford. *J. Am. Chem. Soc.* **2015**, 137, 4968.