

# Literature Report III

## Concise Total Synthesis of (-)-Bipolarolide D

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**Reporter: Sai-Nan Yin**  
**Checker: Yan-Xin Sun**  
**Date: 2024-08-26**

Sun, S.; Wei, Q.; Liu, Y.; Lu, Z.\* *J. Am. Chem. Soc.* **2024**, *146*, 14427

# CV of Prof. Zhaohong Lu

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## Background:

- **2010** B.S., Sun Yat-Sen University
- **2010-2011** Research Assistant, Sun Yat-Sen University
- **2011-2016** Ph.D., Shanghai Institute of Organic Chemistry
- **2016-2017** Research Assistant, Shanghai Institute of Organic Chemistry
- **2017-2020** Postdoc., Massachusetts Institute of Technology
- **2020-2022** Associate Professor, Xiamen University
- **2022-now** Professor, Xiamen University

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## Research:

- Total Synthesis
- Organic Electrochemical Synthesis
- Fluid Chemistry

# Contents

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**1** Introduction

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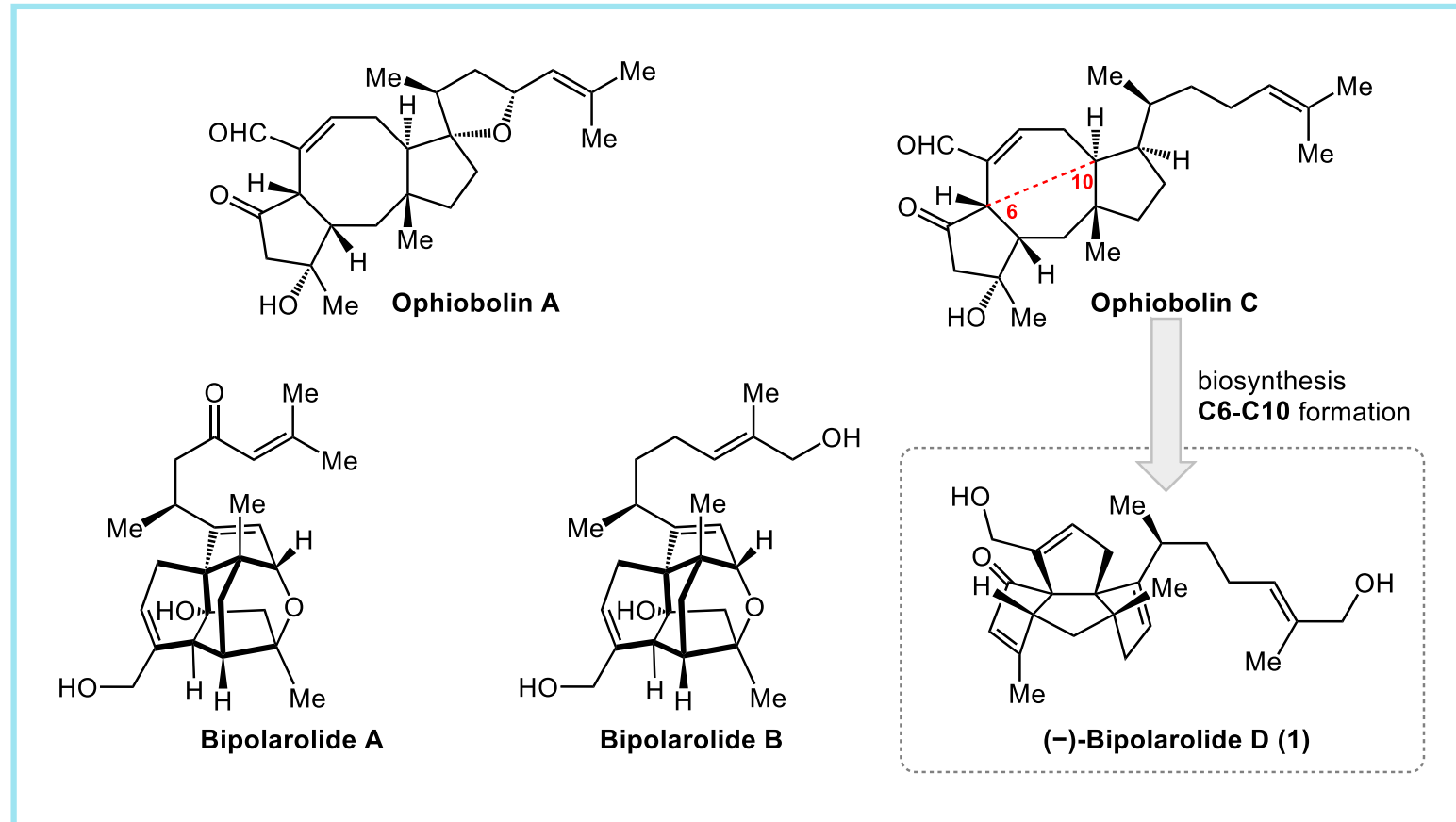
**2** Concise Total Synthesis of (-)-Bipolarolide D

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**3** Summary

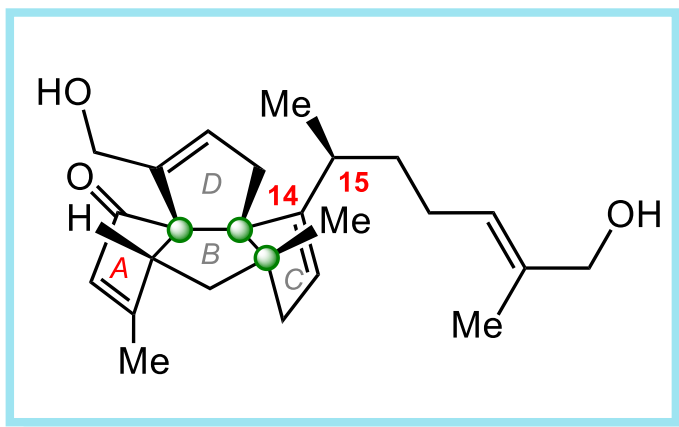
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# Introduction



# Introduction

(-)-Bipolarolide D



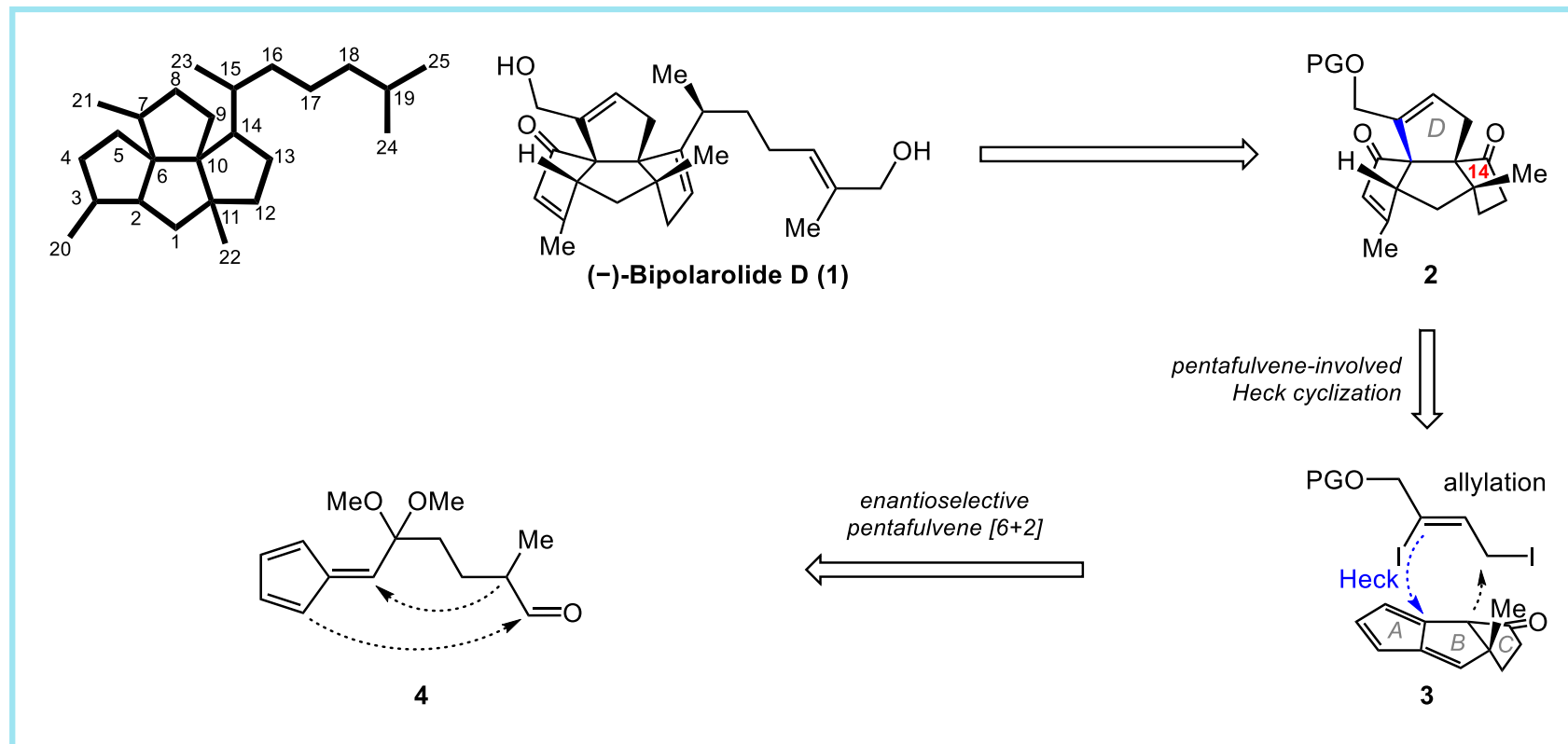
Fungus *Bipolaris* Sp. TJ403-B1



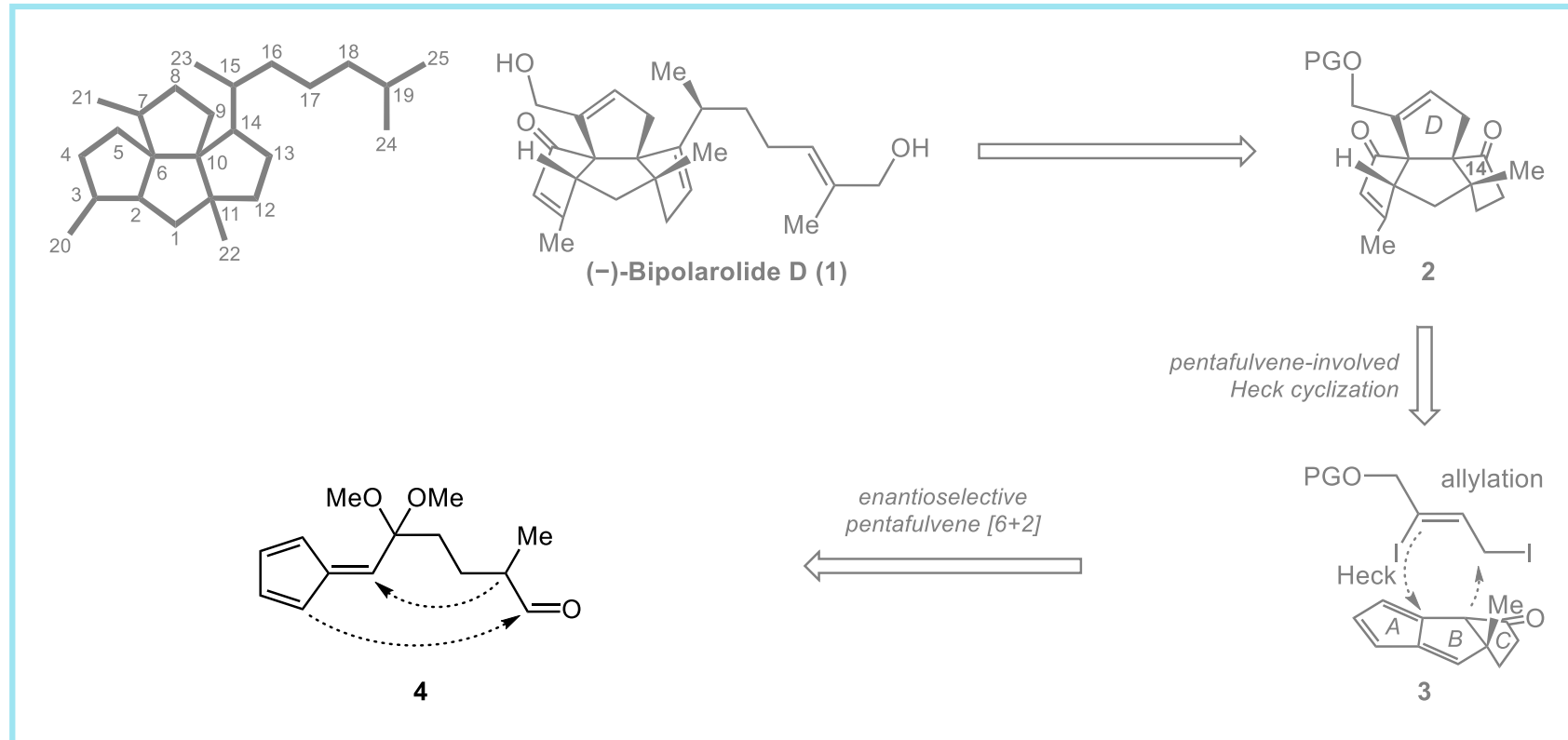
- It isolated from the fungus *Bipolaris* sp. TJ403-B1;
- It contains 5/5/5/5 nonlinear fused ring on convex surface, fully functionalized A-ring, 3 contiguous quaternary centers and a chiral side chain.

Liu, M.; Sun, W.; Shen, L.; He, Y.; Liu, J.; Wang, J.; Hu, Z.; Zhang, Y.\* *Angew. Chem., Int. Ed.* **2019**, *58*, 12091

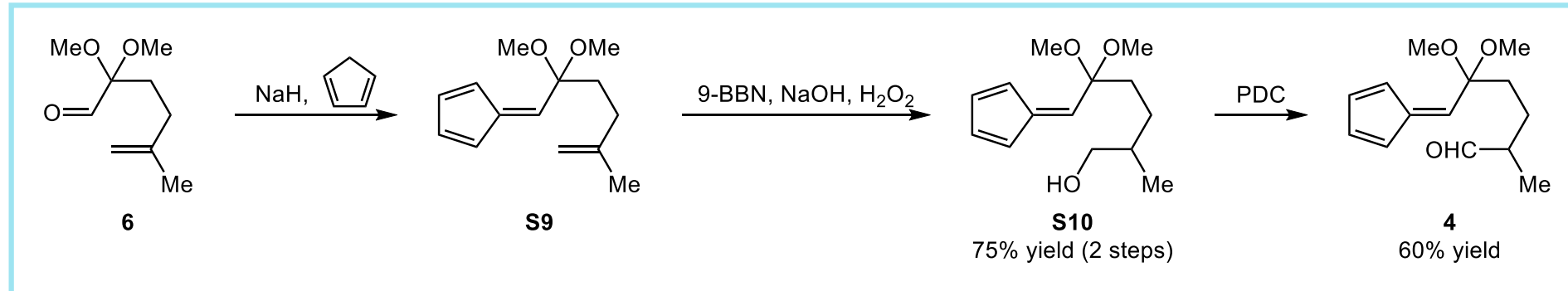
# Retrosynthetic Analysis



# Synthesis of Compound 4

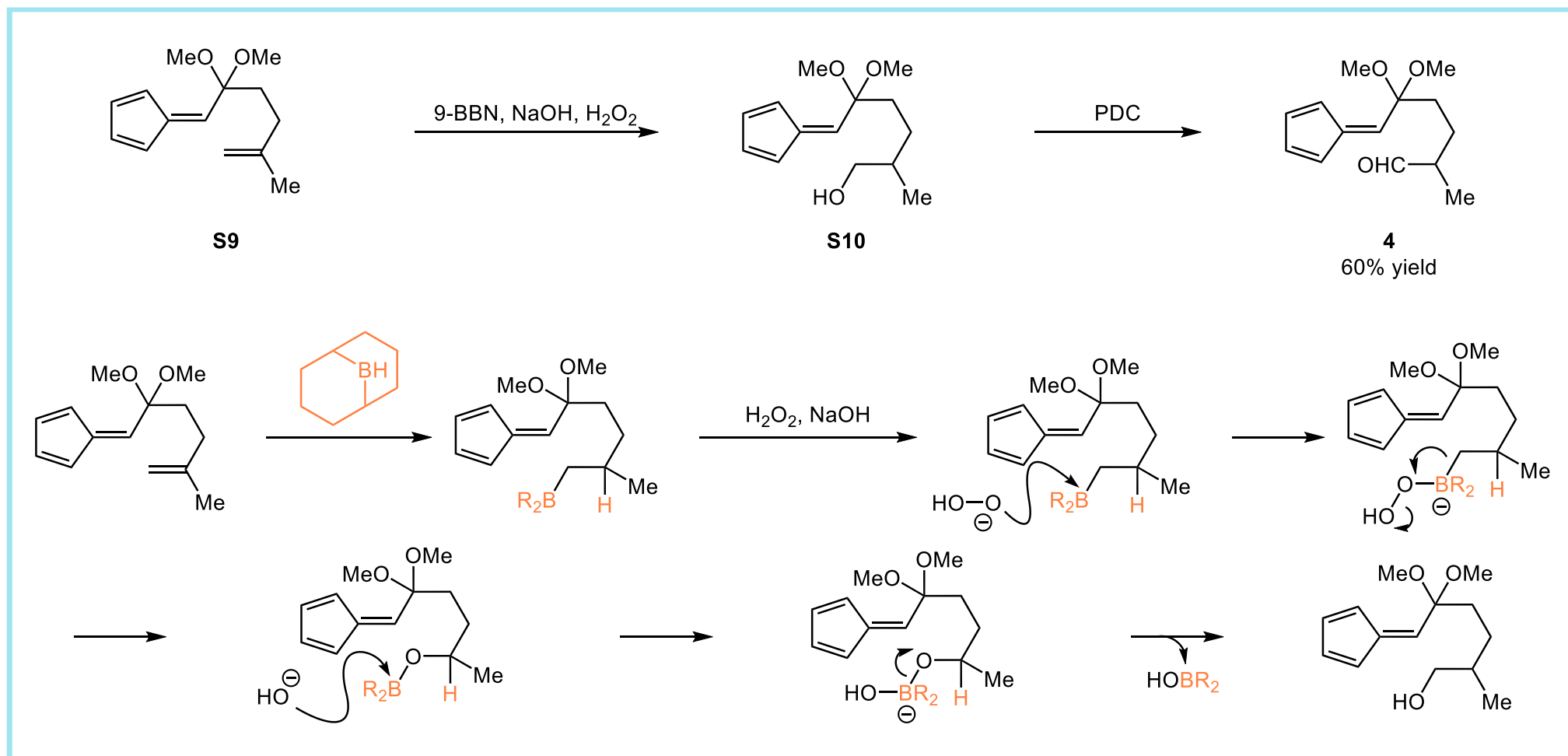


# Synthesis of Compound 4

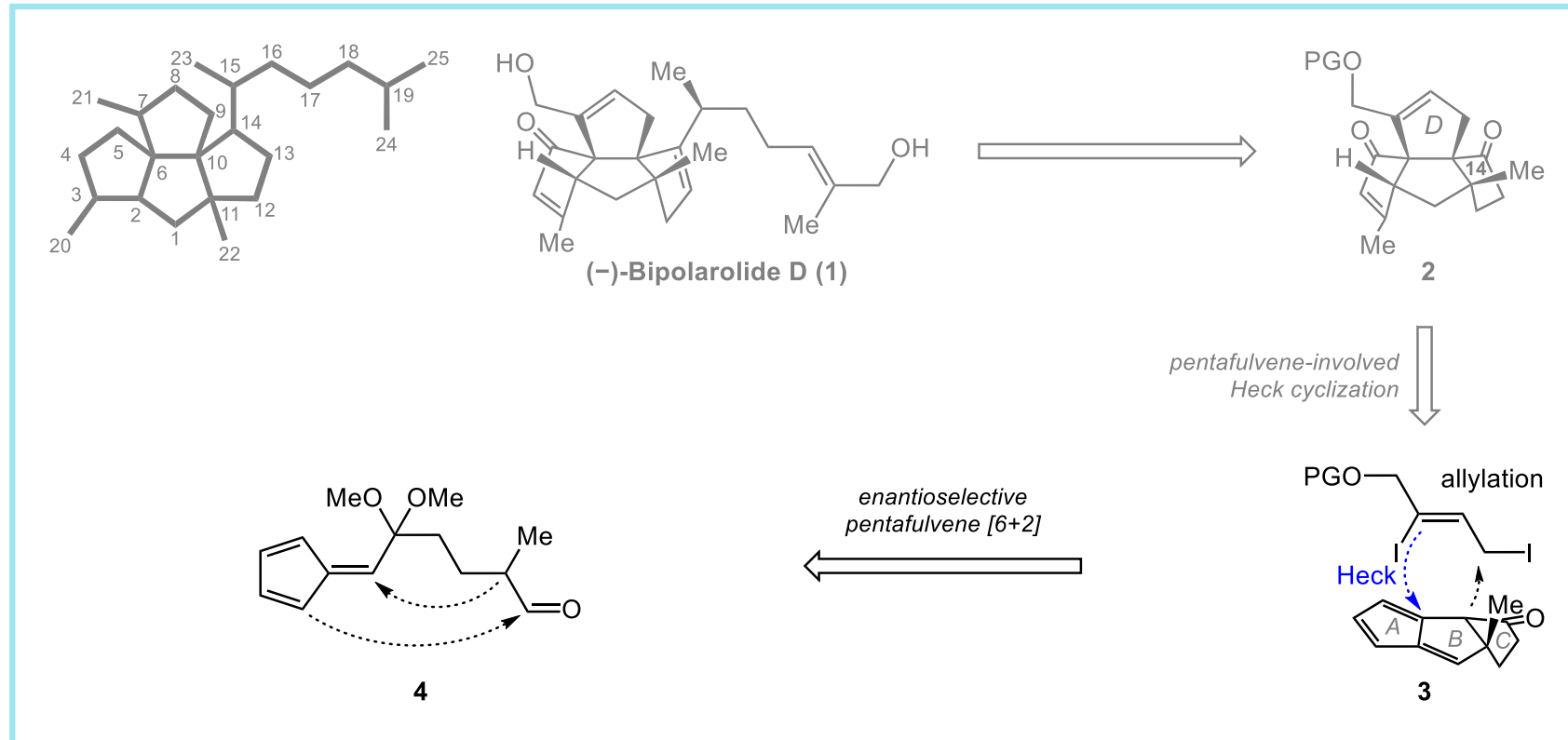




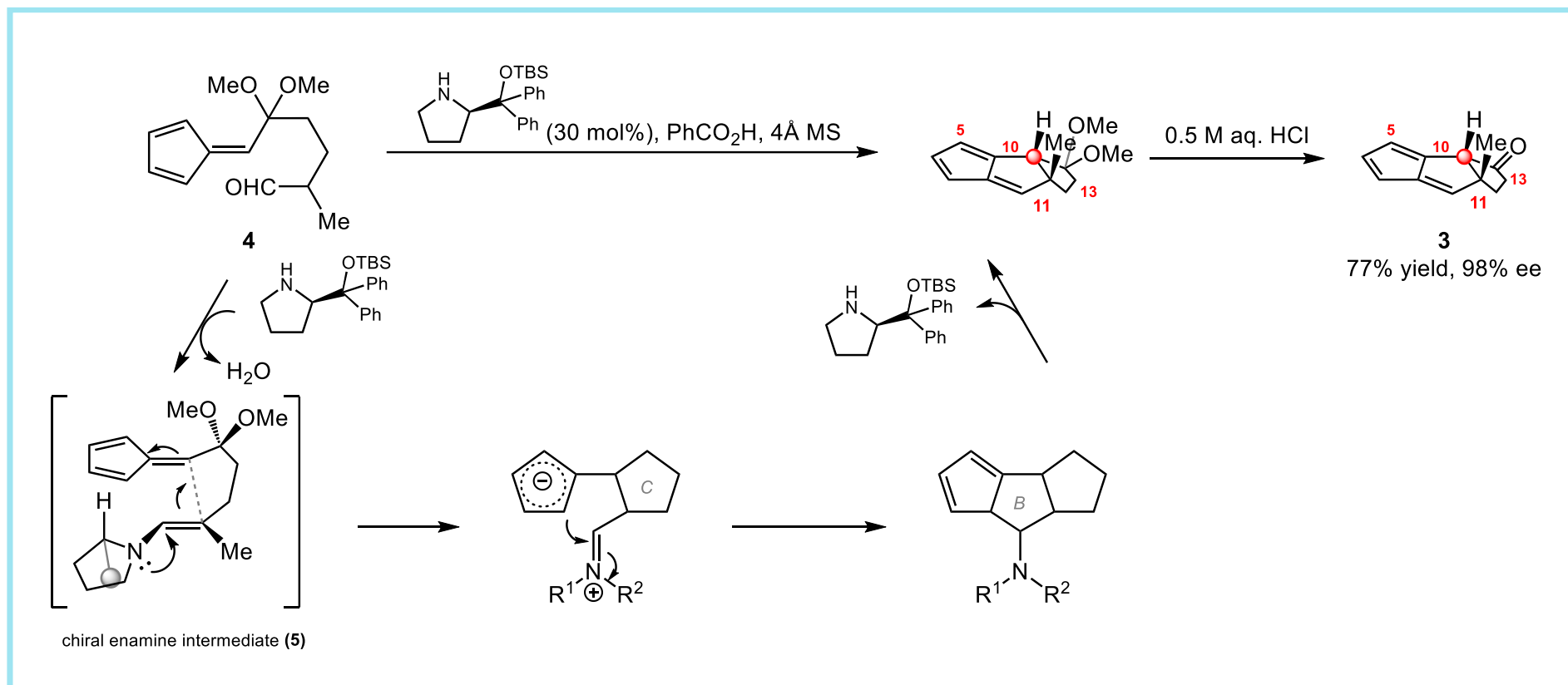
# Synthesis of Compound 4



# Synthesis of Compound 3

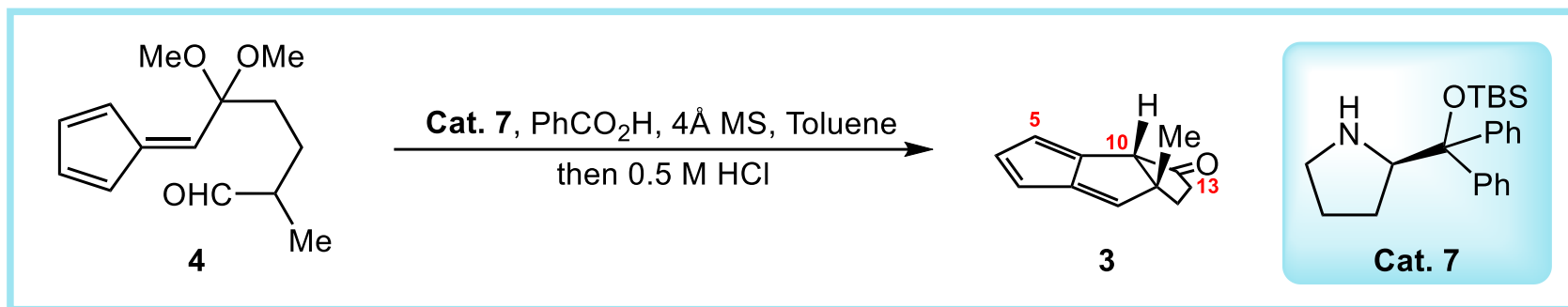


# Synthesis of Compound 3



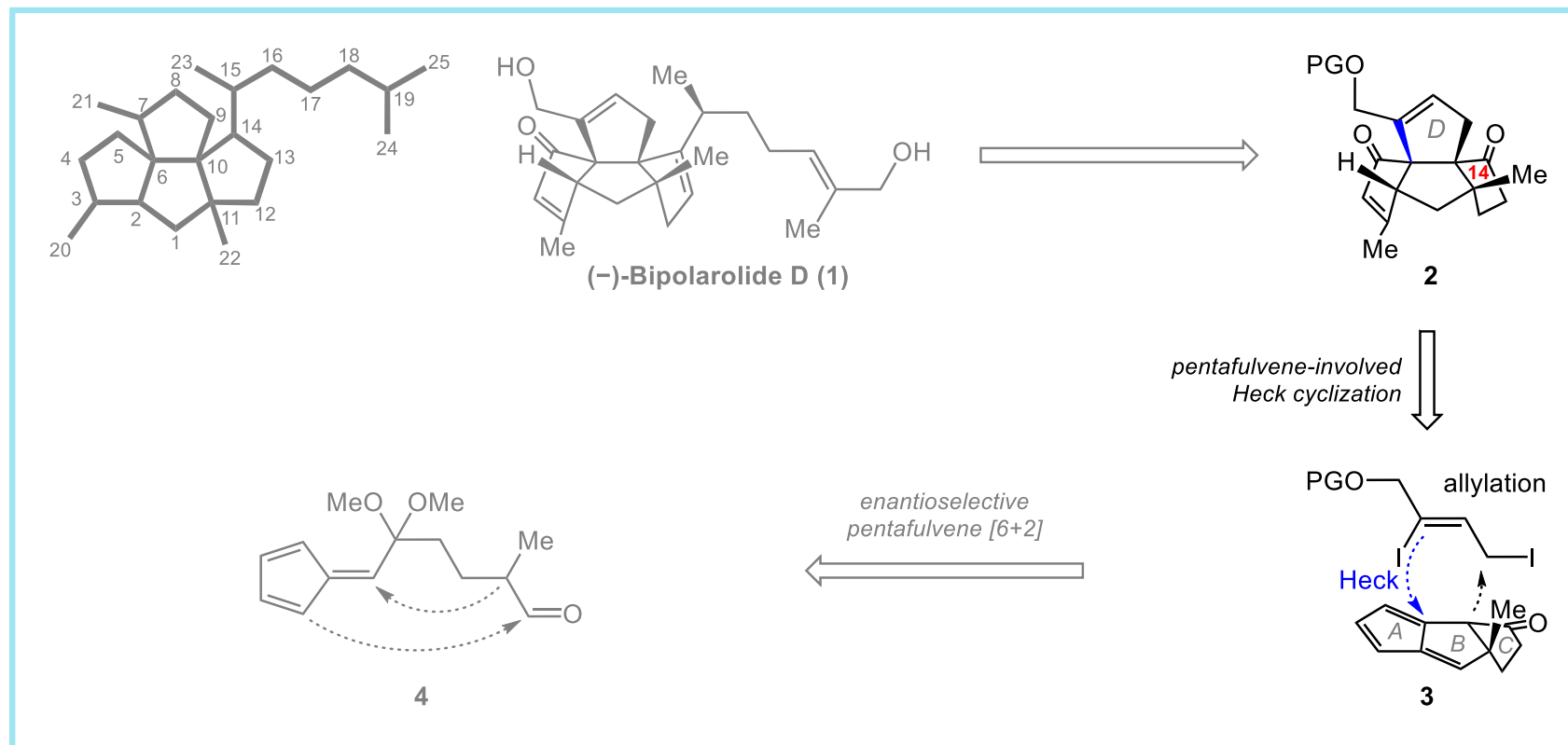
Hayashi, Y.; Gotoh, H.; Honma, M.; Sankar, K.; Kumar, I.; Uchimaru, T. *J. Am. Chem. Soc.* **2011**, *133*, 20175

# Investigations of Asymmetric [6+2] Cycloaddition

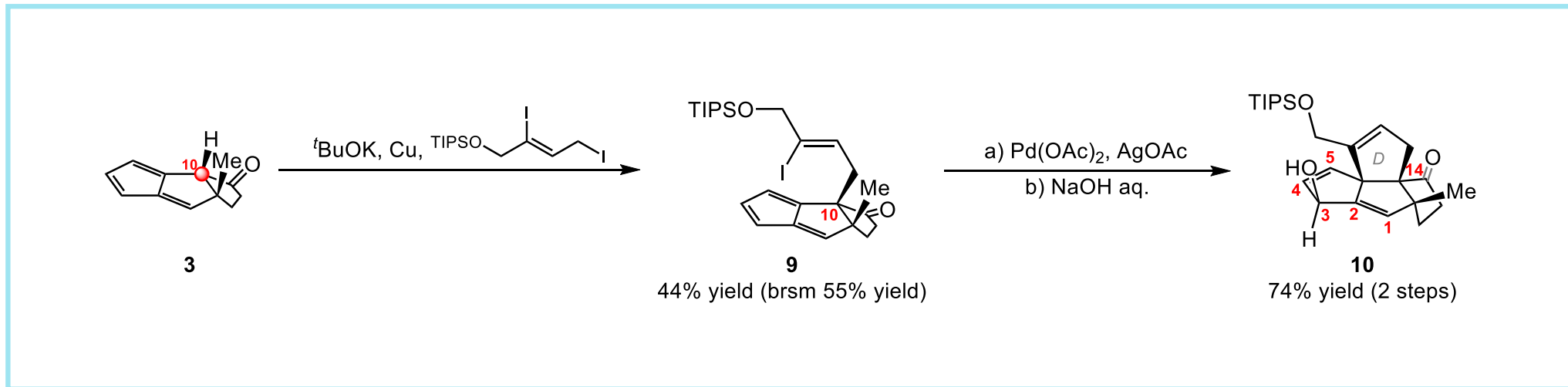


Entry	4Å MS (mg)	T (°C)	Cat. 7	$\text{PhCO}_2\text{H}$	Yield (%)	ee (%)
1	none	rt	10 mol%	20 mol%	trace	-
2	200	rt	10 mol%	20 mol%	75	86
3	200	-30	10 mol%	20 mol%	17	93
4	200	-30	20 mol%	20 mol%	30	98
5	200	-30	30 mol%	15 mol%	77	98
6	200	-30	30 mol%	20 mol%	75	98
7	200	-30	30 mol%	30 mol%	47	98

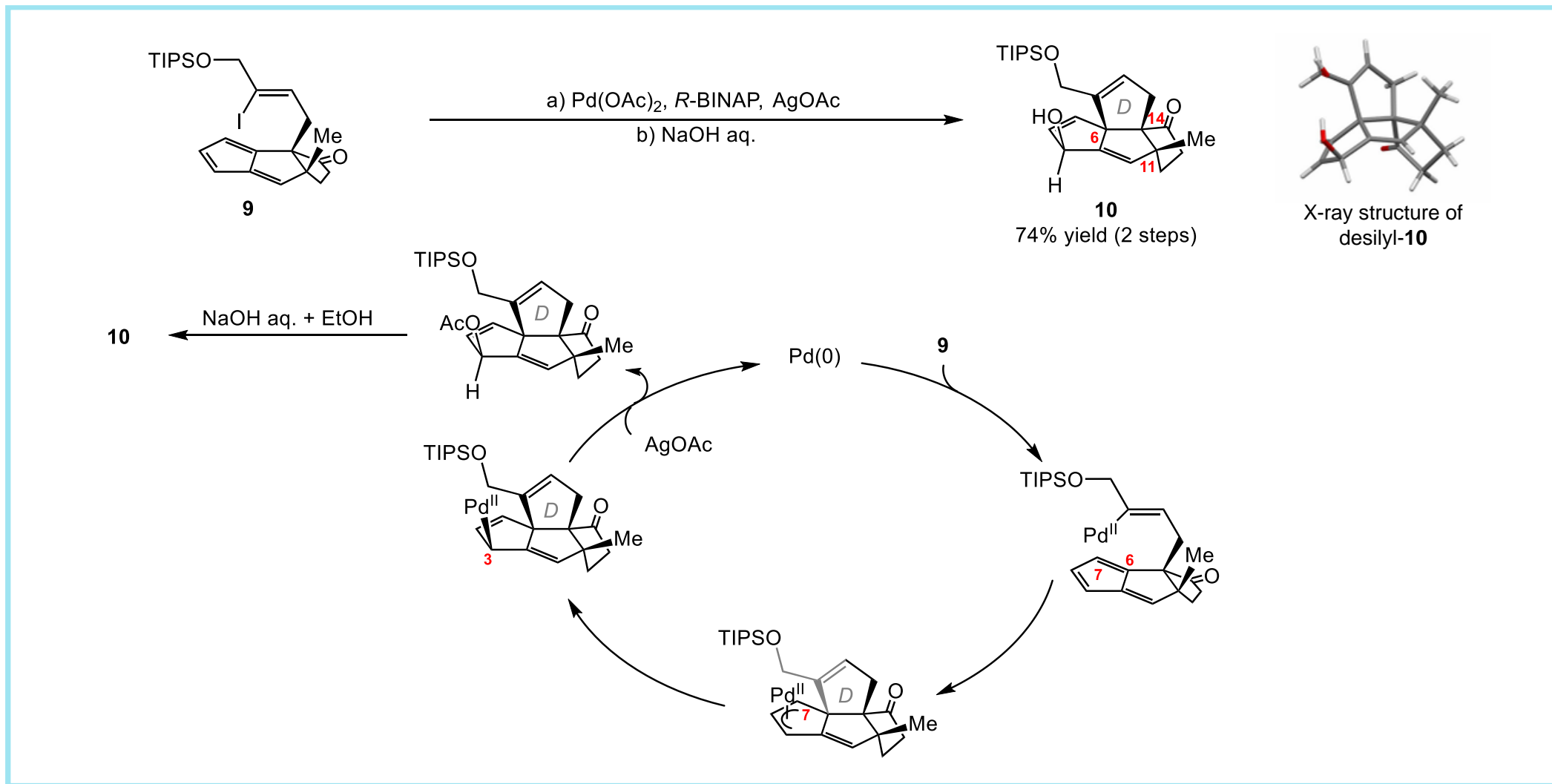
# Synthesis of Compound 2



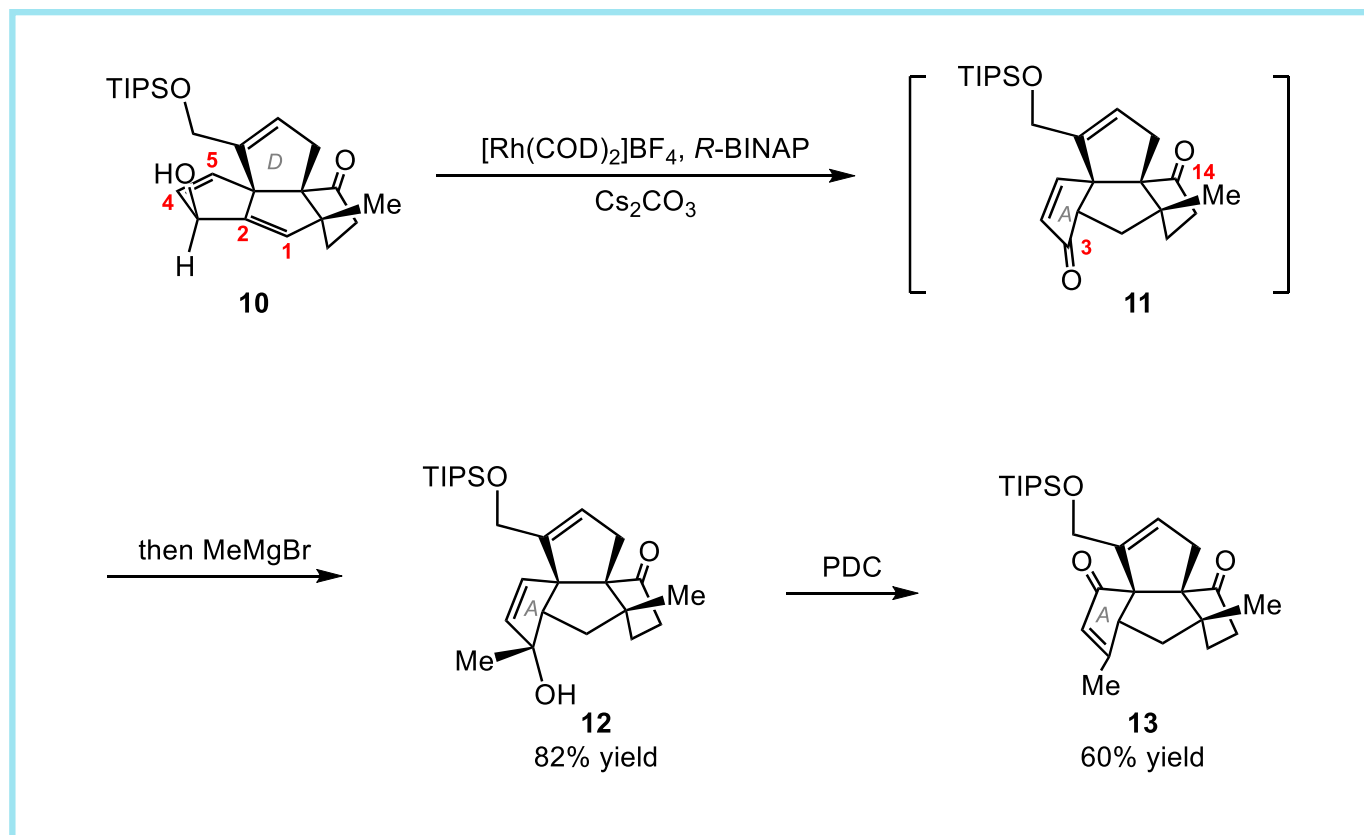
# Synthesis of Compound 10



# Synthesis of Compound 10

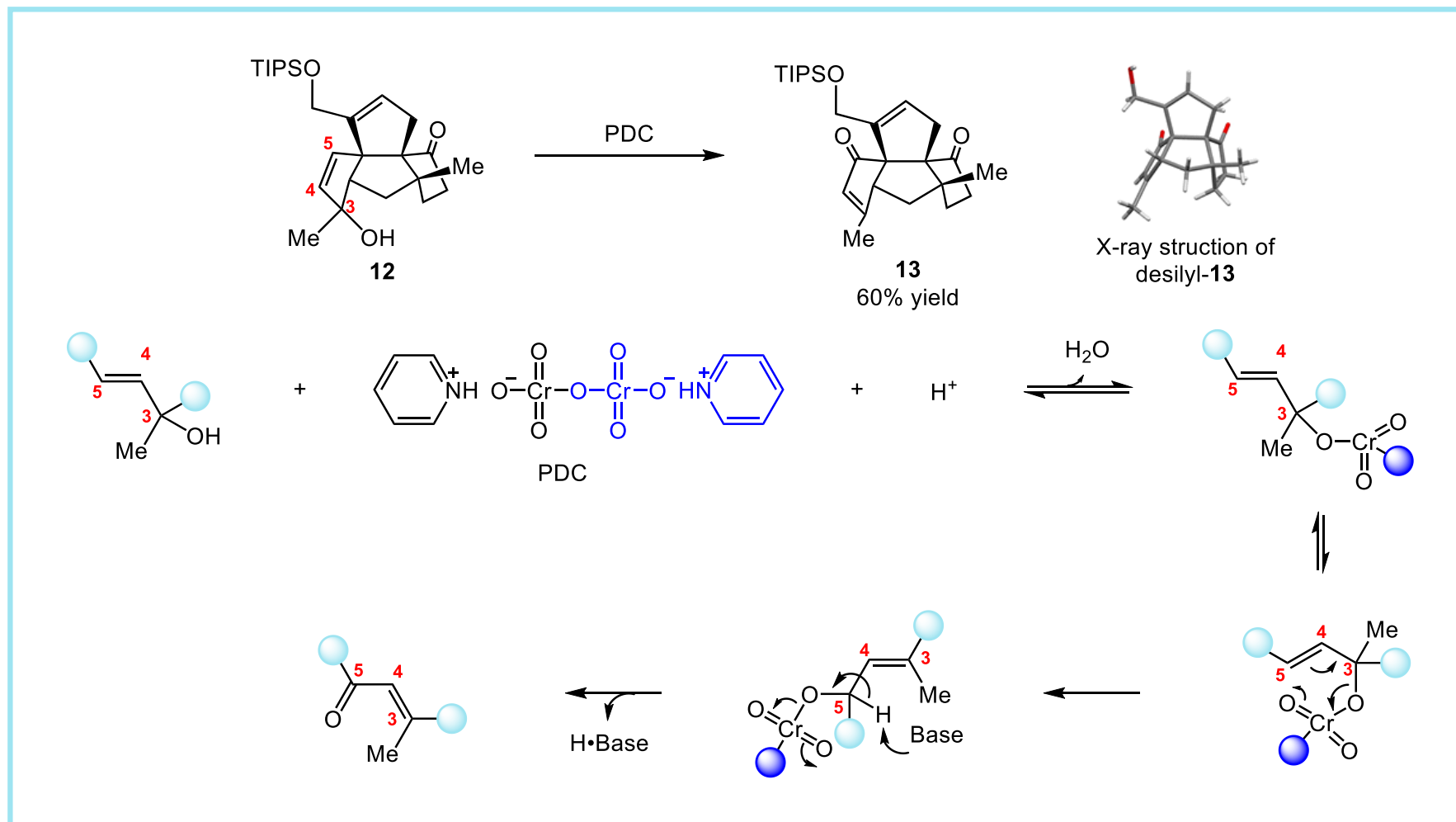


# Synthesis of Compound 13

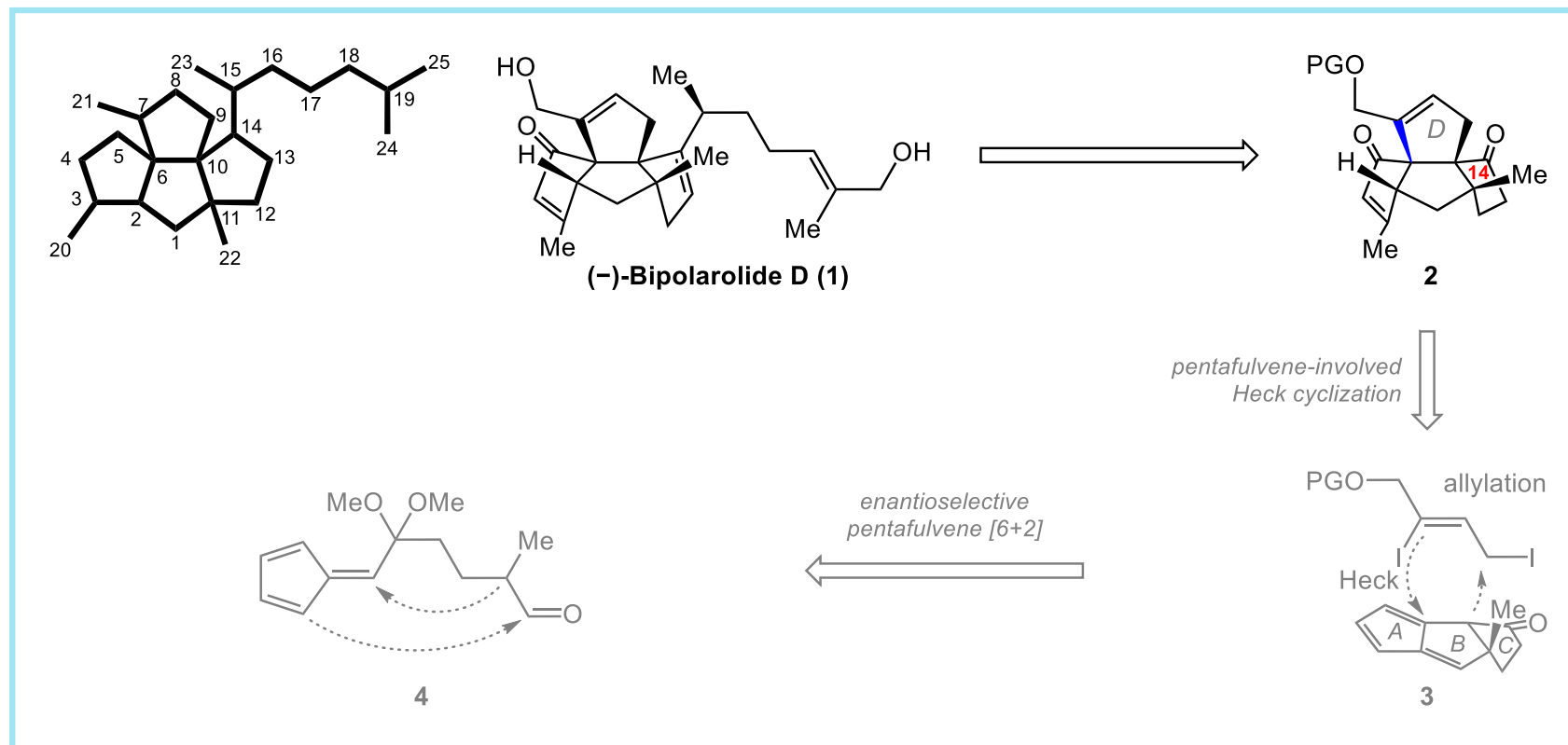




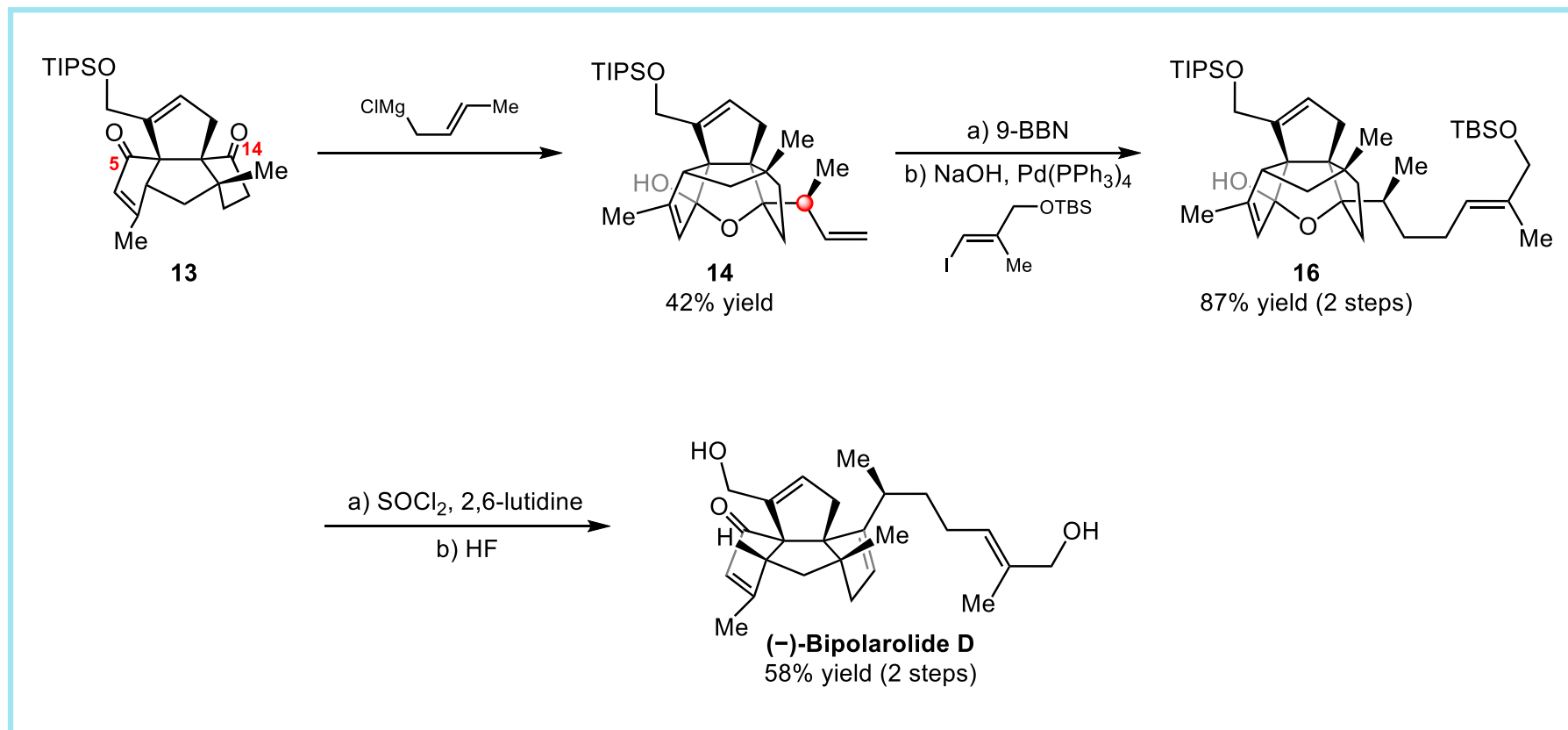
# Synthesis of Compound 13



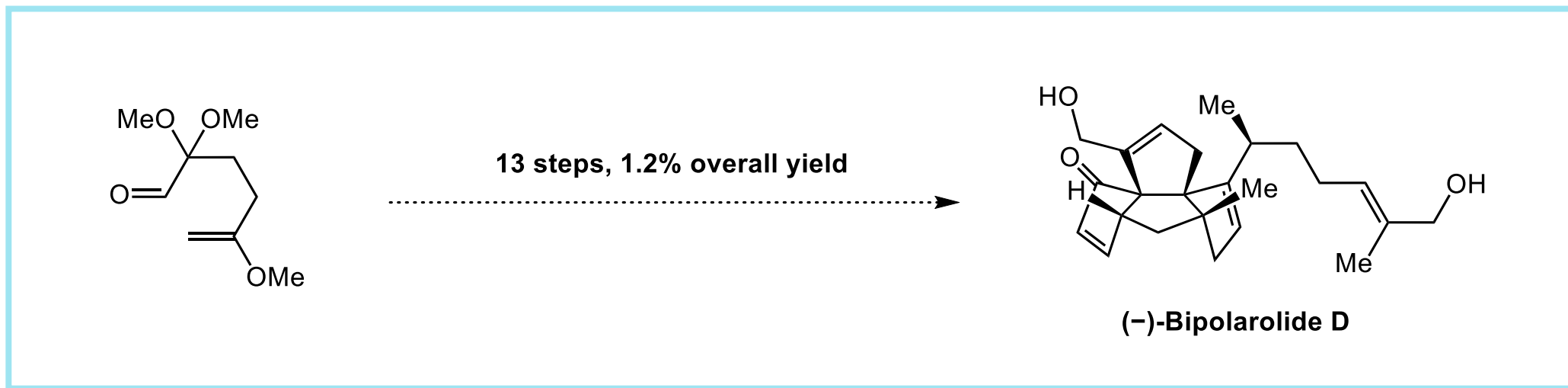
# Synthesis of (-)-Bipolarolide D



# Synthesis of (-)-Bipolarolide D



# Summary



- ✓ Asymmetric pentafulvene [6+2] cyclo addition to construct a 5/5/5 fused ring;
- ✓ A Heck cyclization to complete the 5/5/5/5 fused ring.

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# Strategy for Writing The First Paragraph

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**Bipolarolide的结构和种类**



**引出本文工作**

Terpenes, as vital components of natural products, play a significant role in pharmaceutical chemistry research. Ophiobolin comprises a class of sesterterpene natural products characterized by a unique 5–8–5 ring system structure, including antibiotic, immunosuppressant properties, cytotoxic, and These intricate molecular architectures, coupled with their significant biological potencies, have garnered considerable interest from synthetic chemists, leading to numerous synthetic endeavors.

However, the complexity of the ophiobolin structure has posed a significant synthetic challenge on their total synthesis, with only four total syntheses reported to date.

# Strategy for Writing The Last Paragraph

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总结工作



合成(-)-Bipolarolide D的意义

In summary, starting from the known aldehyde 6, the first modular and enantioselective total synthesis of (-)-bipolar olide D (1) was achieved in 13 steps in 1.2% overall yield. The key steps involved an asymmetric pentafulvene [6+2] cyclo addition to construct a 5/5/5 fused ring and establish the first chiral center, alkylation to generate the second quaternary carbon center, a Heck cyclization to complete the 5/5/5/5 fused ring, a hydrogen transfer reaction to modify the A ring, and allylic addition to complete the side chain.

This efficient synthesis facilitates the bioactivity investigation of 1 and highlights the powerful utility of pentafulvene in the construction of complex molecules.

# Representative Examples

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- We **hypothesized** that the reaction was hindered by the water produced during the enamination process of the catalyst and aldehyde. (v. 假定, 假设, 猜测)
- We **leveraged** these synthetic benefits of pentafulvene [6+2] cycloadduct **to** simultaneously accomplish the construction of the D ring and the functionalization on the A ring through Heck reaction. (n. 影响力, 手段, 杠杆作用 v. 充分利用)

# Acknowledgement

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*Thanks for your attention*