



中国科学院大连化学物理研究所

DALIAN INSTITUTE OF CHEMICAL PHYSICS, CHINESE ACADEMY OF SCIENCES

# Literature Report 1

## Total Synthesis of Rameswaralide Utilizing A Pharmacophore-Directed Retrosynthetic Strategy

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Reporter: Ying-Qi Wang

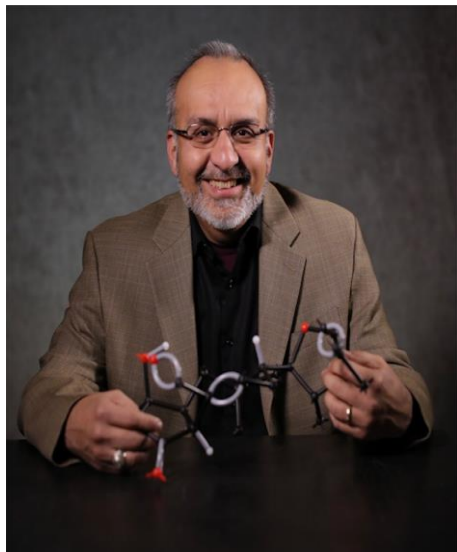
Checker: Yan-Jiang Yu

2023-01-11

Truax, N. J.; Ayinde, S.; Romo, D.\* *J. Am. Chem. Soc.* **2022**, *144*, 18575

# CV of Prof. Daniel Romo

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**Daniel Romo**

## Background:

- ❑ **1982-1986** B.A., Texas A&M University
- ❑ **1986-1991** Ph.D., Colorado State University
- ❑ **1991-1993** Postdoctoral, Harvard University
- ❑ **1993-1999** Assistant Professor, Texas A&M University
- ❑ **1999-2003** Associate Professor, Texas A&M University
- ❑ **2003-2016** Professor, Texas A&M University
- ❑ **2015-now** Professor, Baylor University

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## Research:

1. Total Synthesis of Natural Products by PDRs
2. Development of New Synthetic Methods

# Contents

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**1** Introduction

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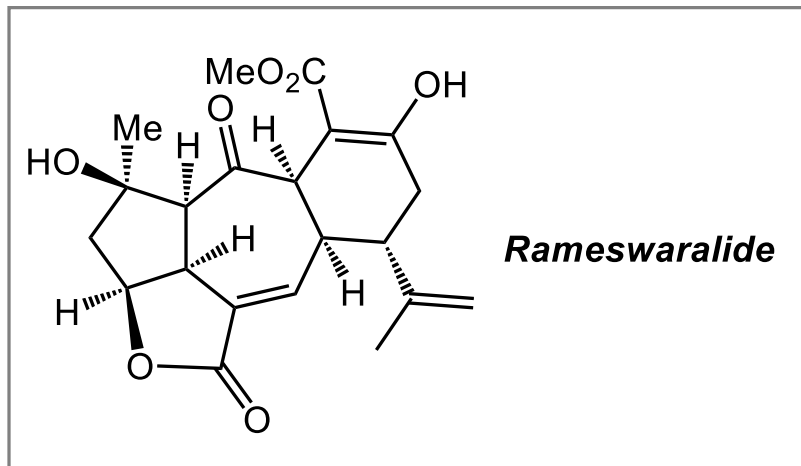
**2** Total Synthesis of Rameswaralide

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**3** Summary

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# Rameswaralide



*Rameswaralide*

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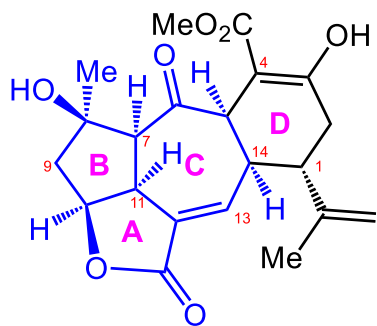


*Sinularia* (软珊瑚)

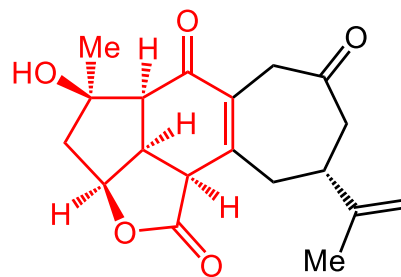
- Caged 5,5,7,6 All cis-Fused Ring System Containing 7 Chiral Centers
- Moderate Cytotoxicity and Possible anti-Inflammatory Activity
- First Isolated from the *Sinularia* in 1998 and Characterized in 2016

Ramesh, P.; Reddy, N. S.; Venkateswarlu, Y. *Tetrahedron Lett.* **1998**, 39, 8217  
Chitturi, B. R.; Tatipamula, V. B.; Venkateswarlu Y. *Tetrahedron* **2016**, 72, 1933

# Previous Work on Synthesis of Rameswaralide

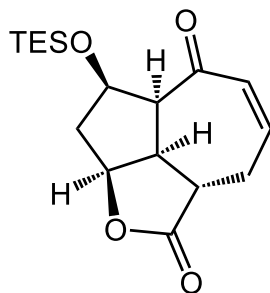


Rameswaralide

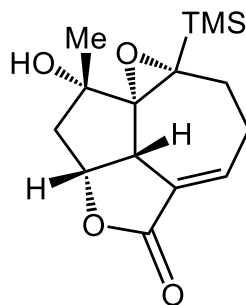


Scabrolide A

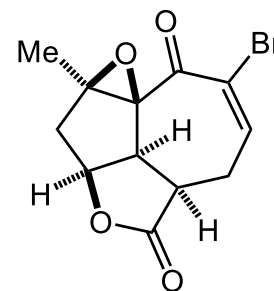
Stoltz **2020**  
Fürstner **2022**



Mehta **2006**

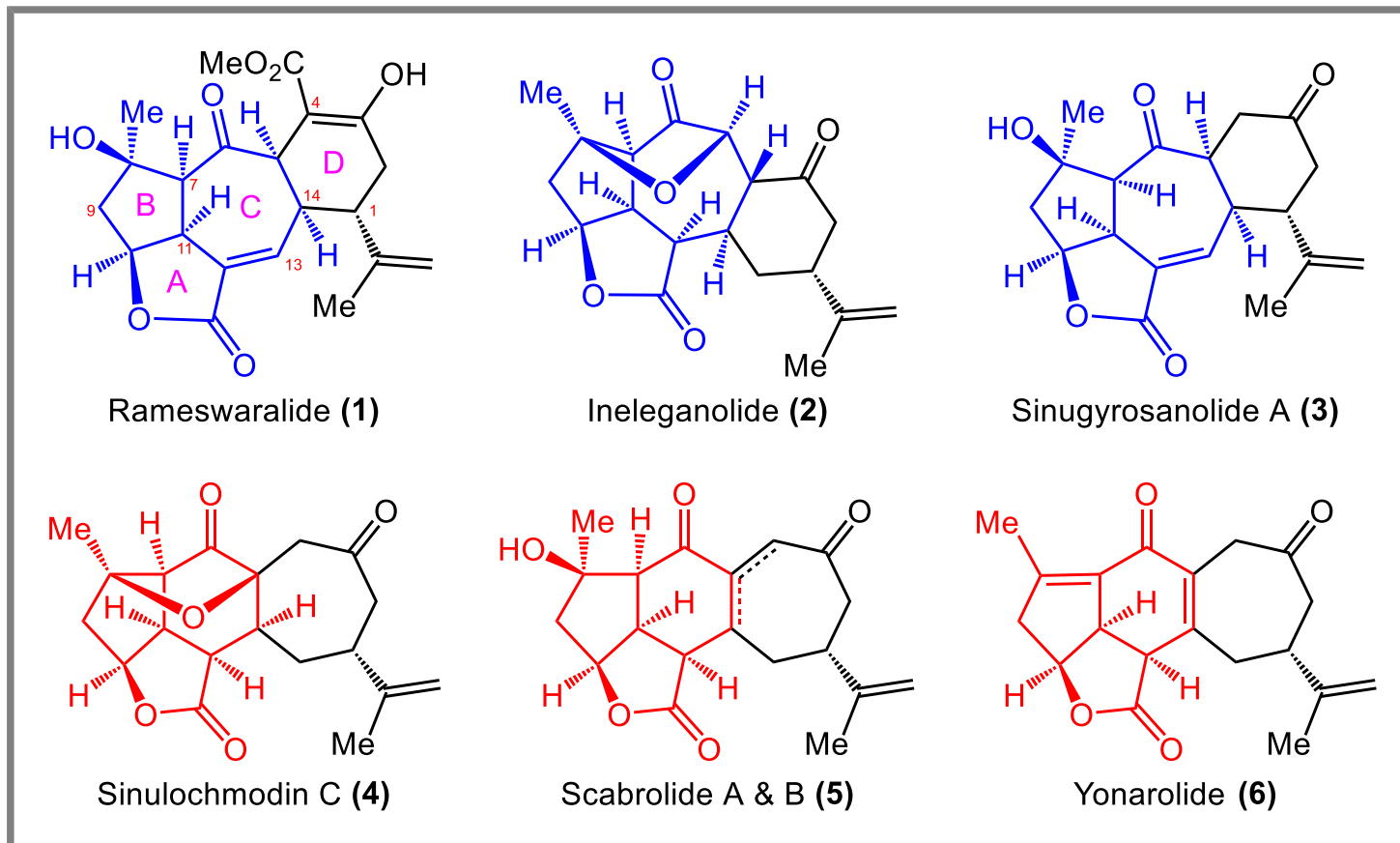


Trost **2010**



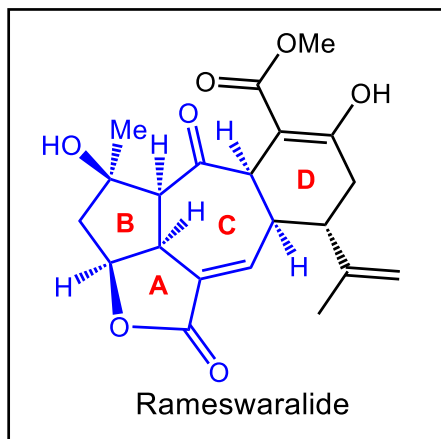
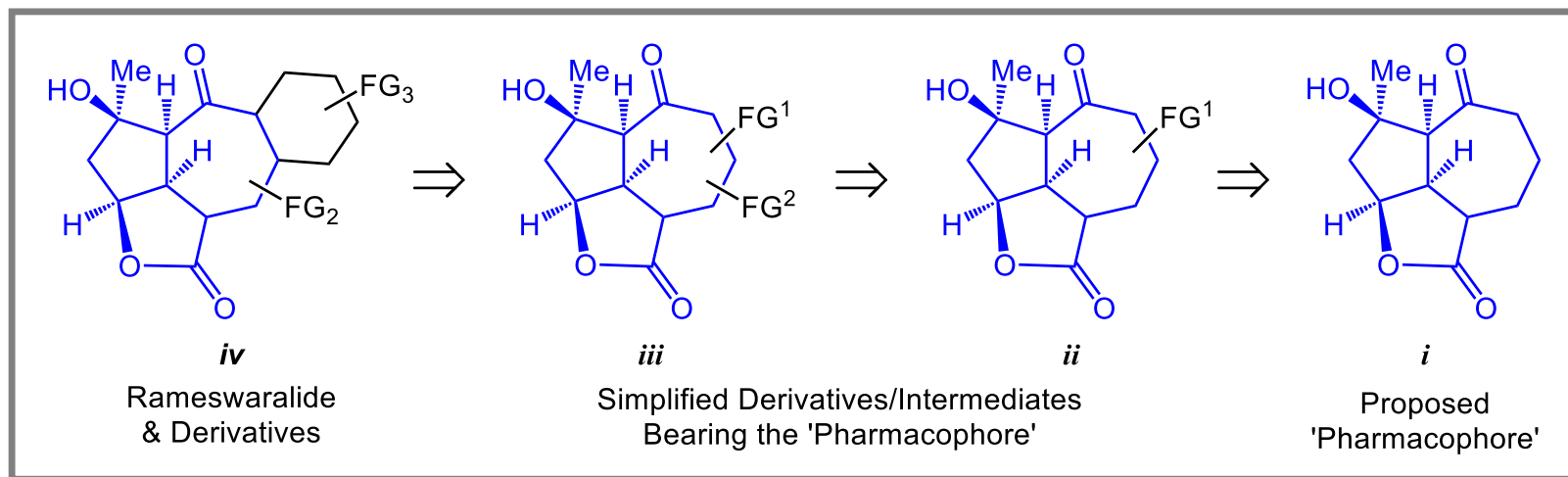
Romo **2019**

# The Analysis of Previous Work



5,5,7 Core Ring Displayed Greater Bioactivity than 5,5,6 Core Ring

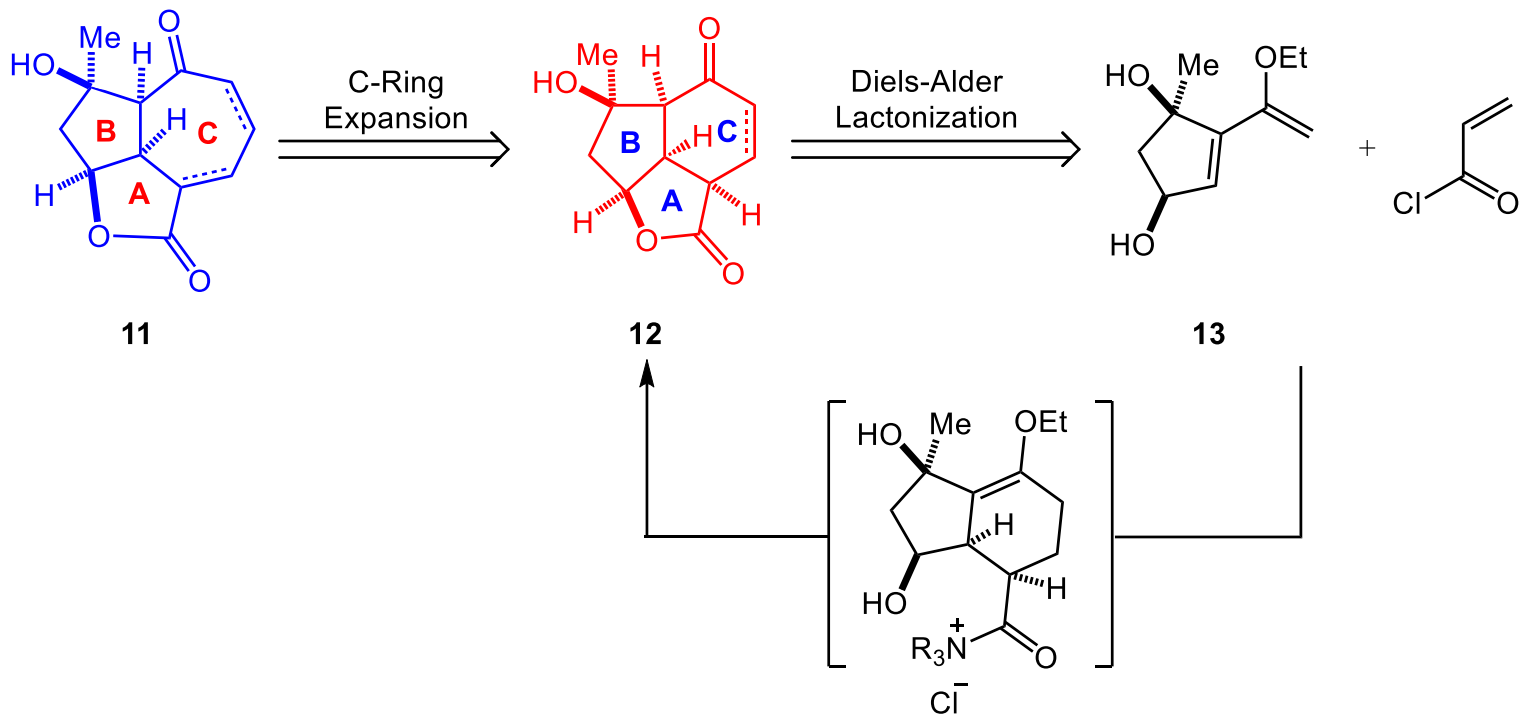
# Pharmacophore-Directed Retrosynthetic Strategy



----- Two Parts -----

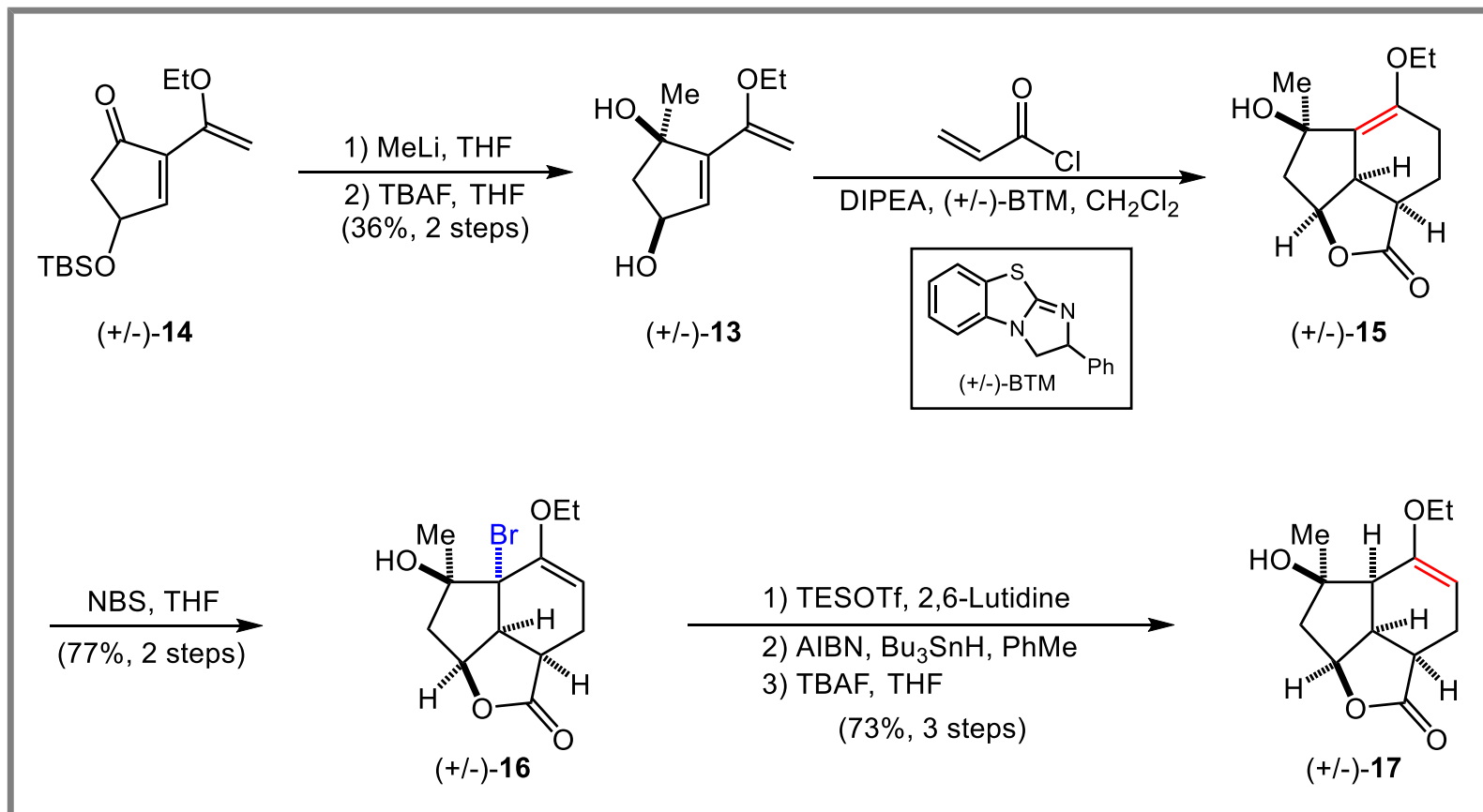
- I. The Construction of Pharmacophore
- II. D-Ring Annulations

# Retrosynthetic Analysis of Pharmacophore

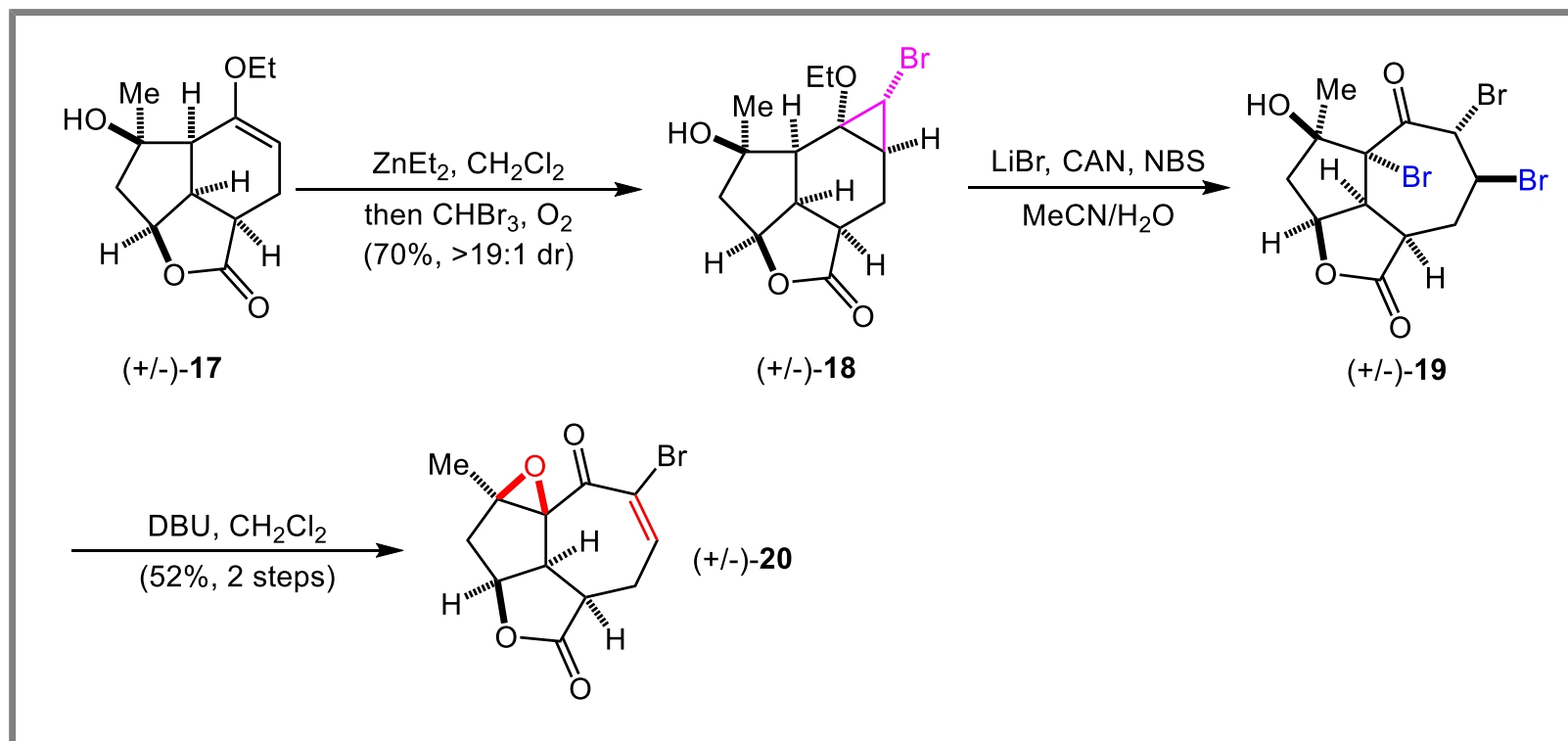




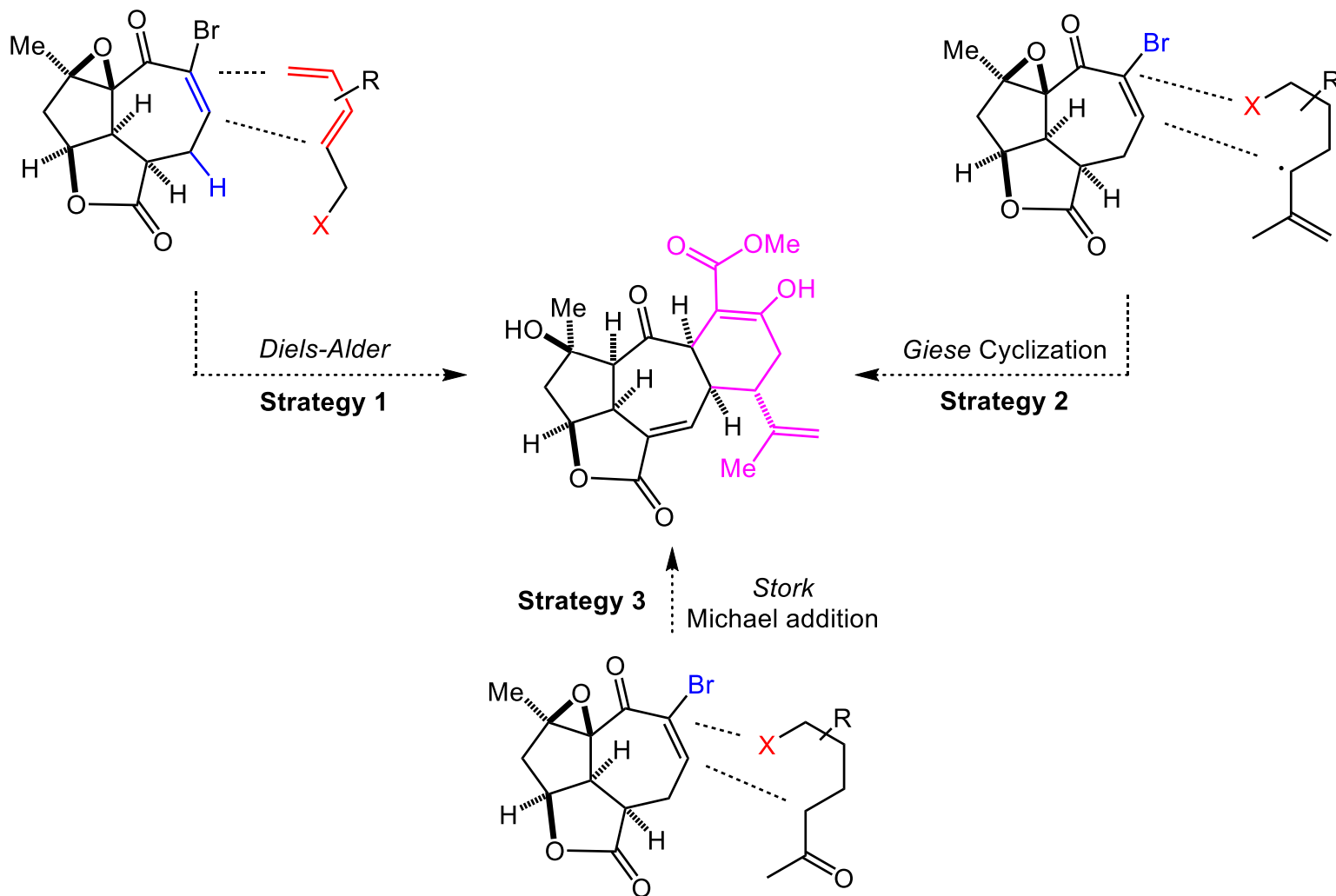
# Synthesis of Intermediate (+/-)-17



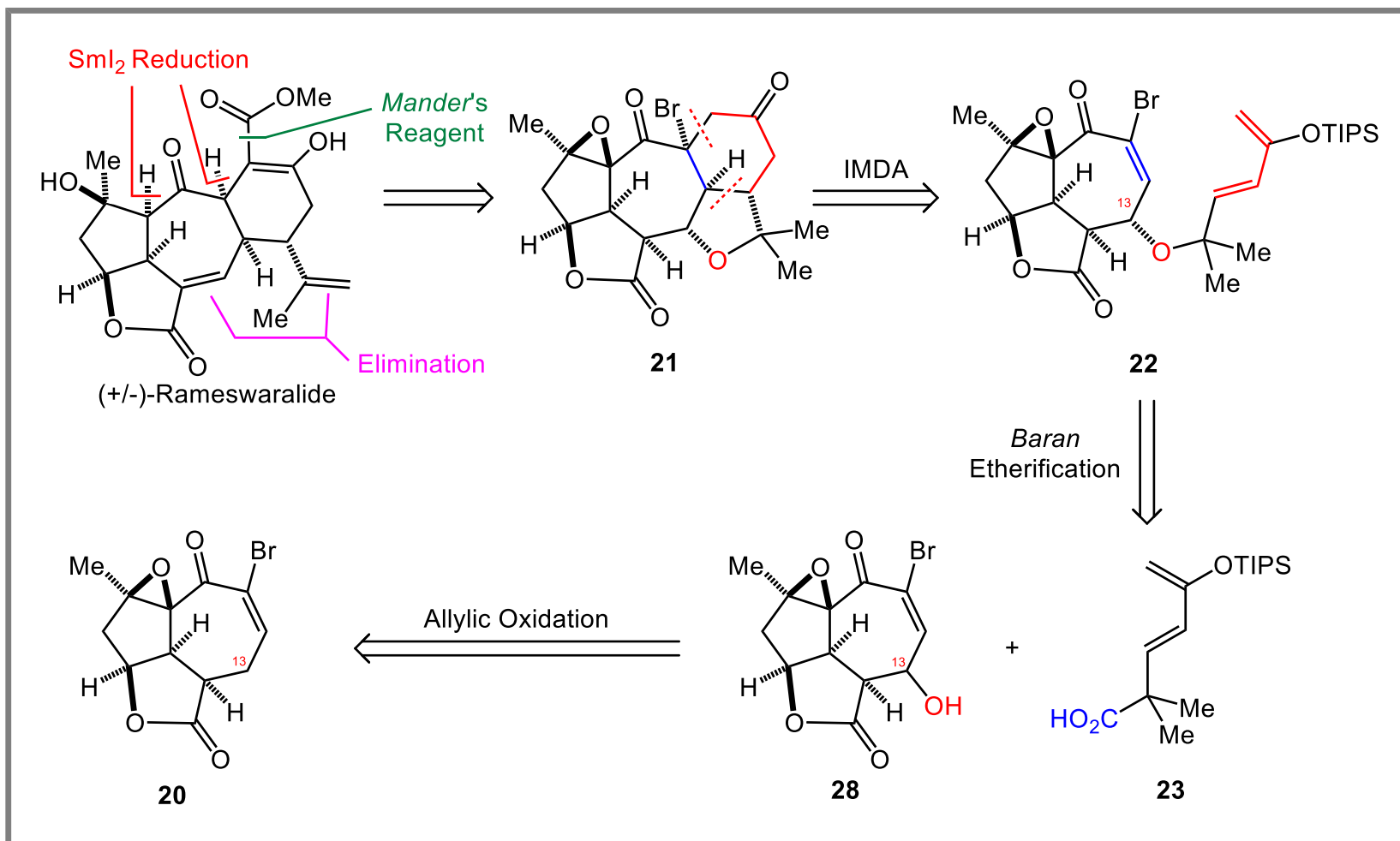
# Synthesis of Intermediate (+/-)-20



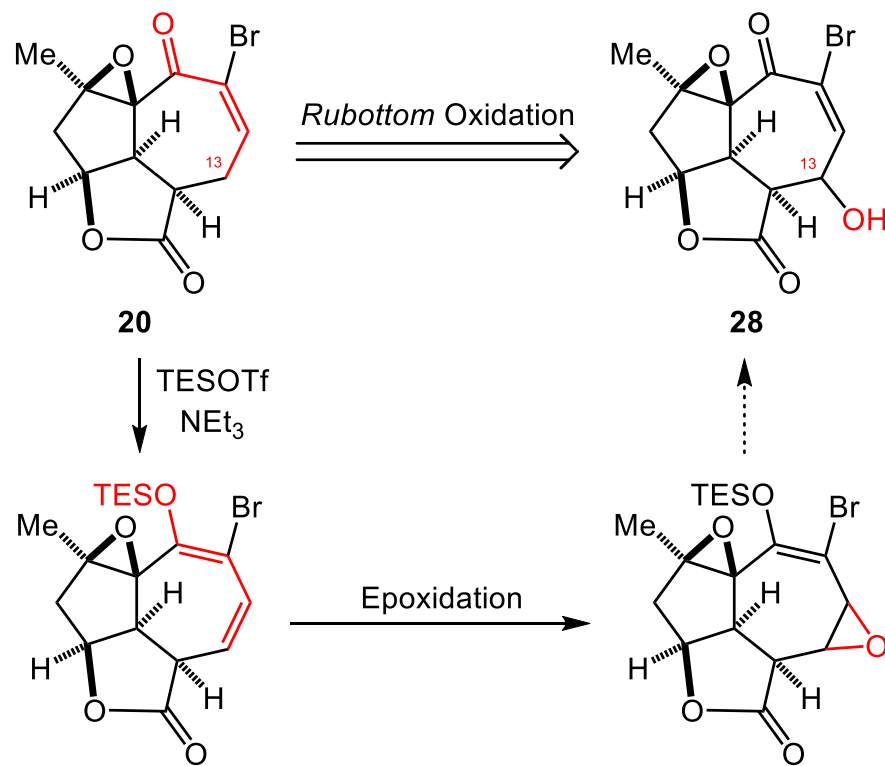
# Three Strategies of D-Ring Annulation



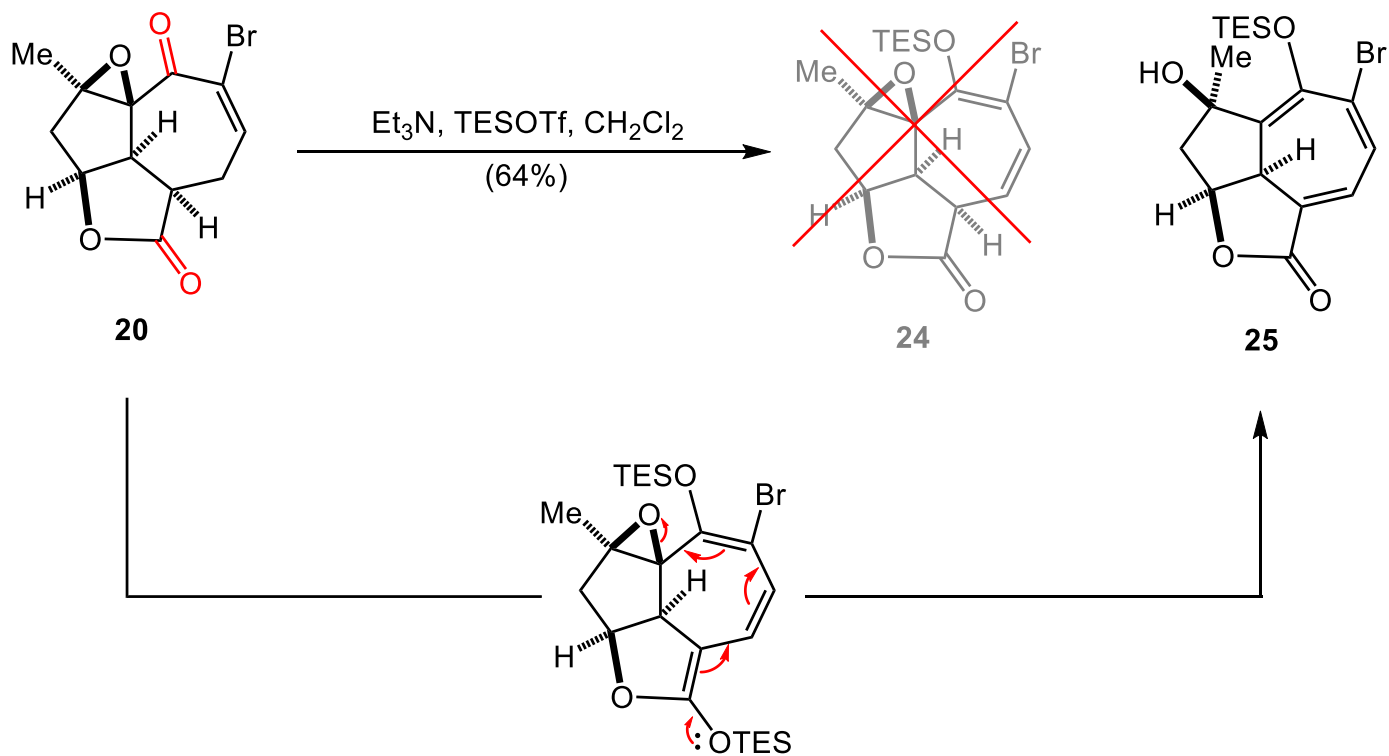
# D-Ring Annulation Strategy 1



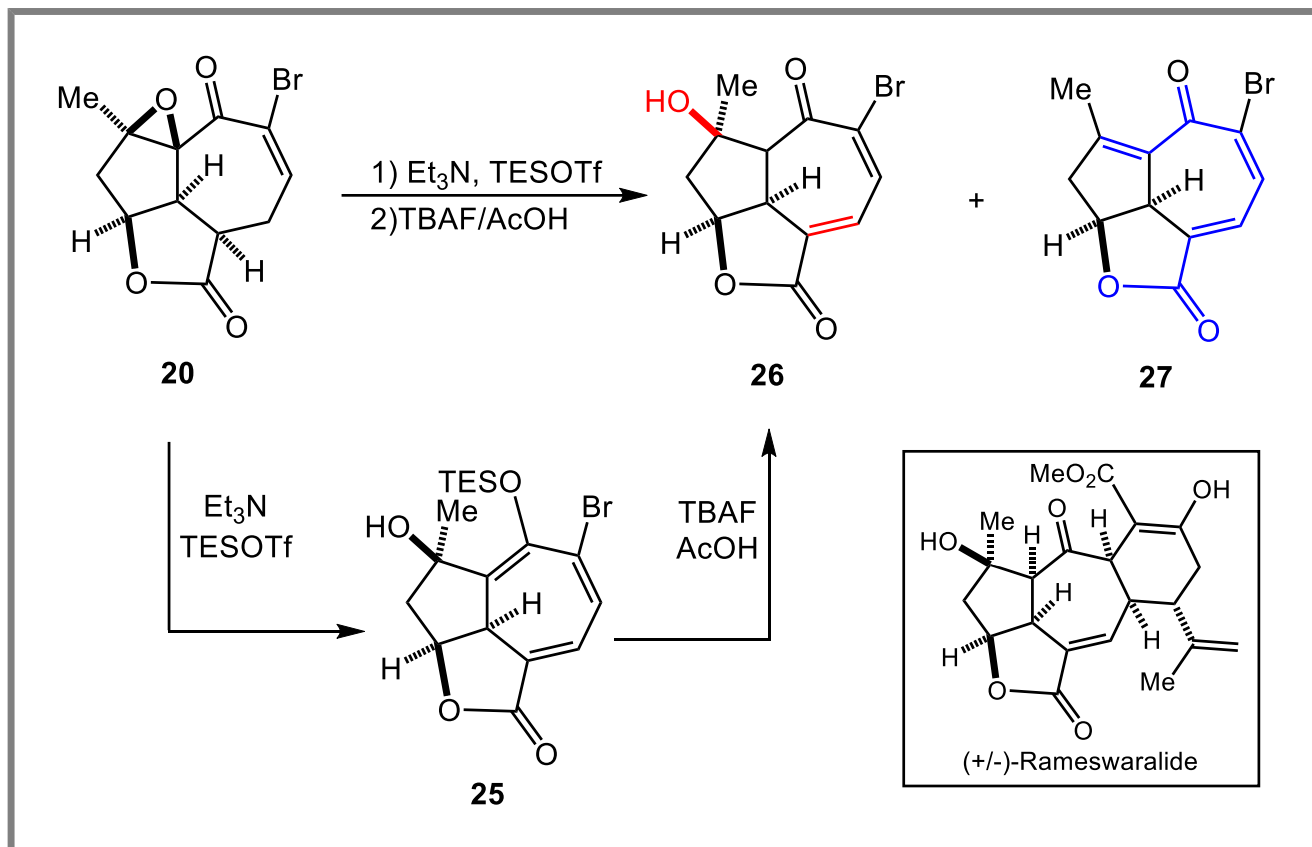
# Synthesis of Allyl Alcohol 28



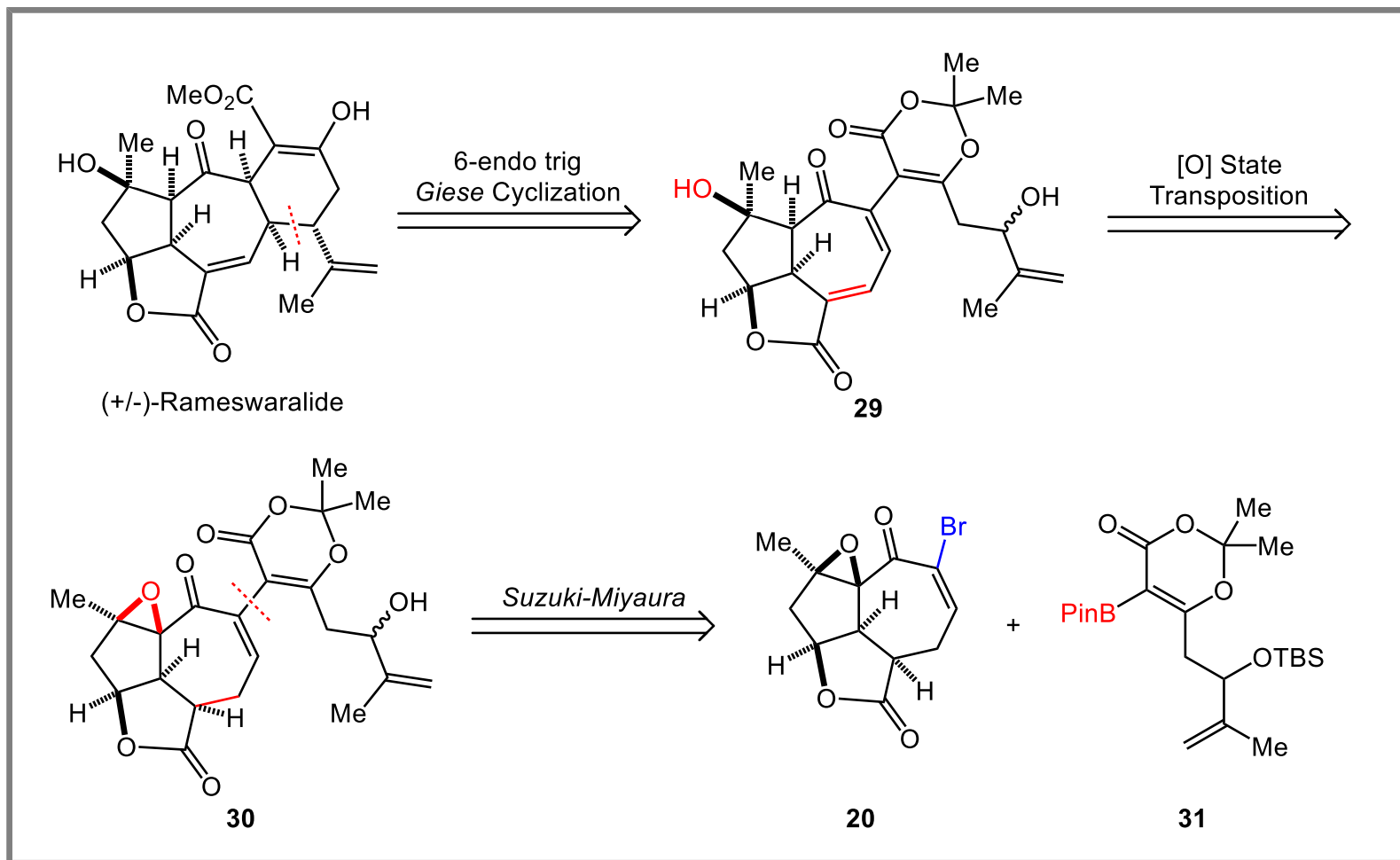
# Serendipitous Finding



# Serendipitous Finding

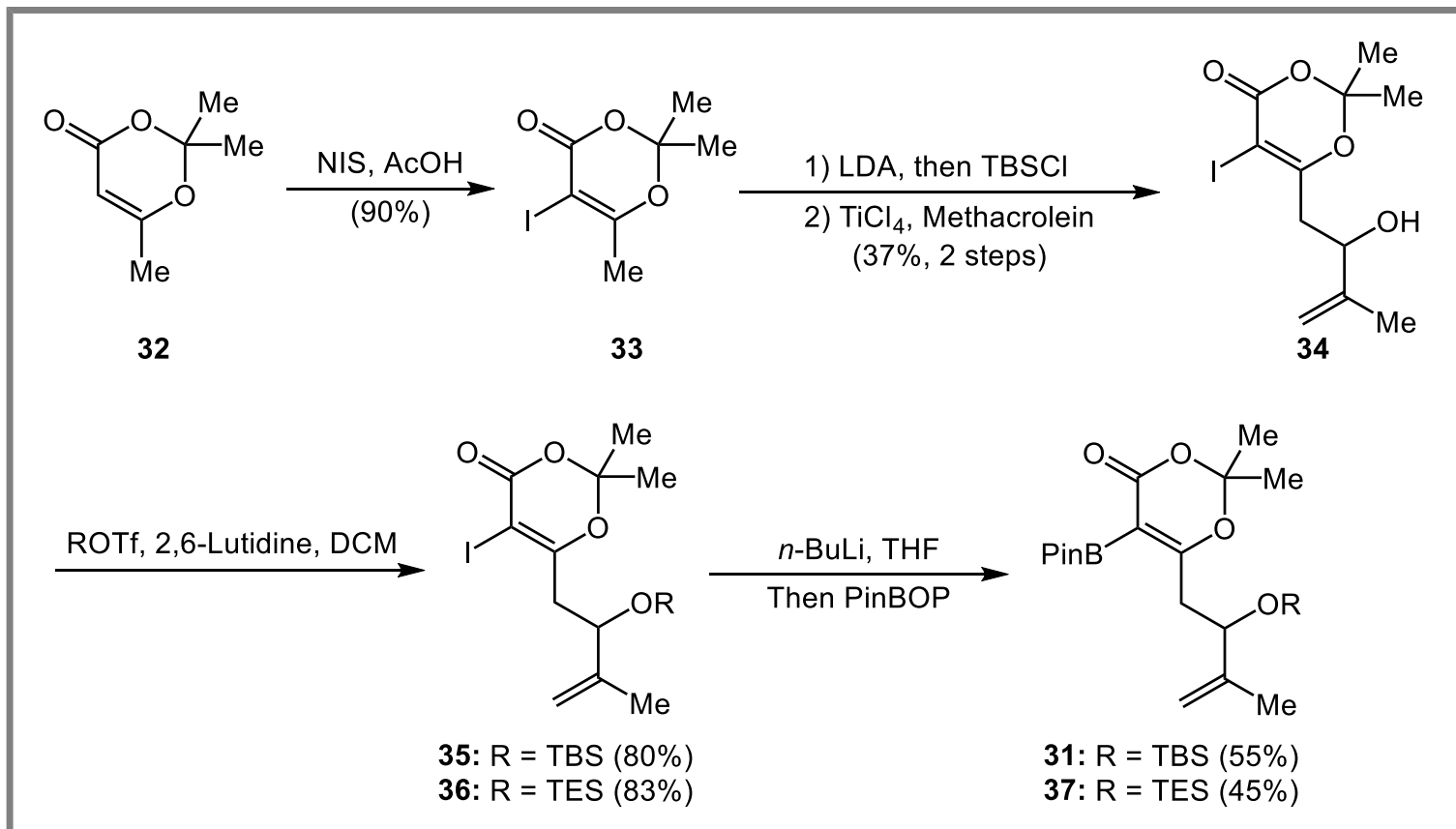


# D-Ring Annulation Strategy 2

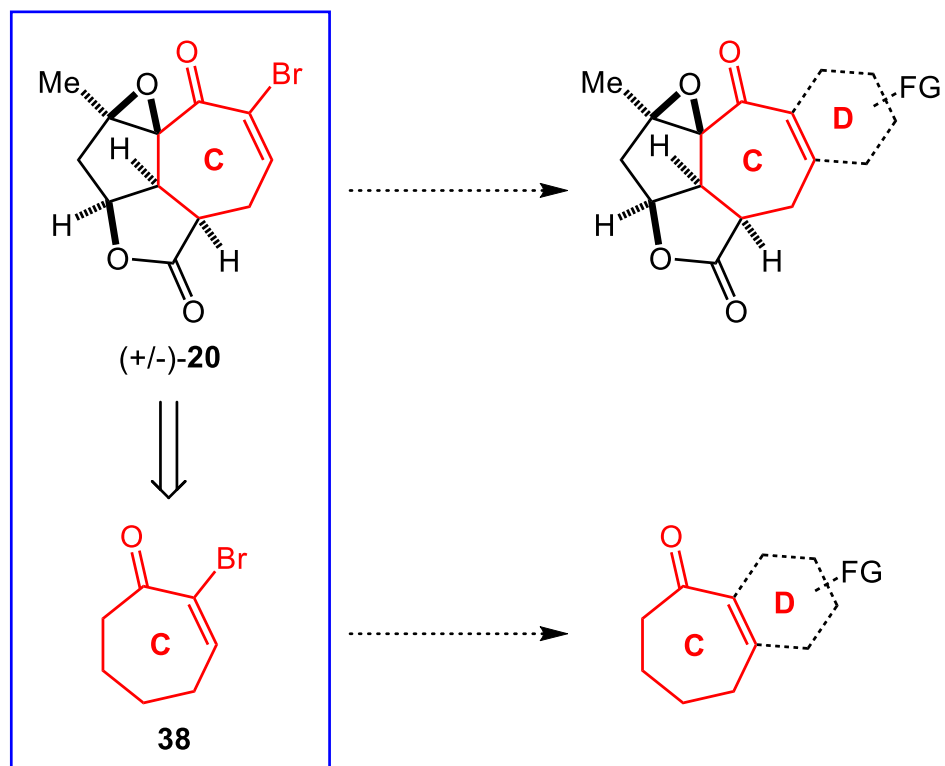




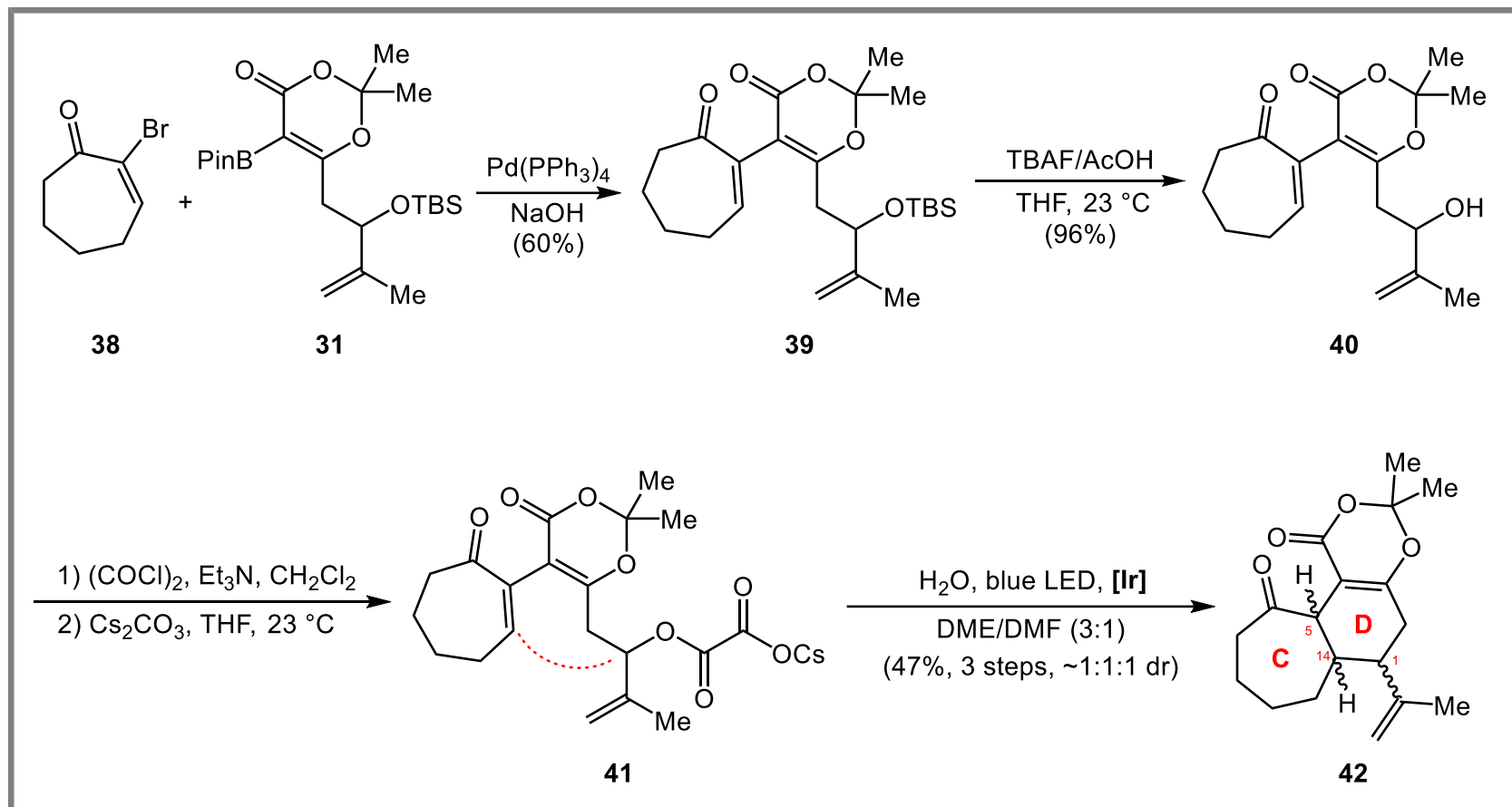
# Synthesis of Borate Esters 31 and 37



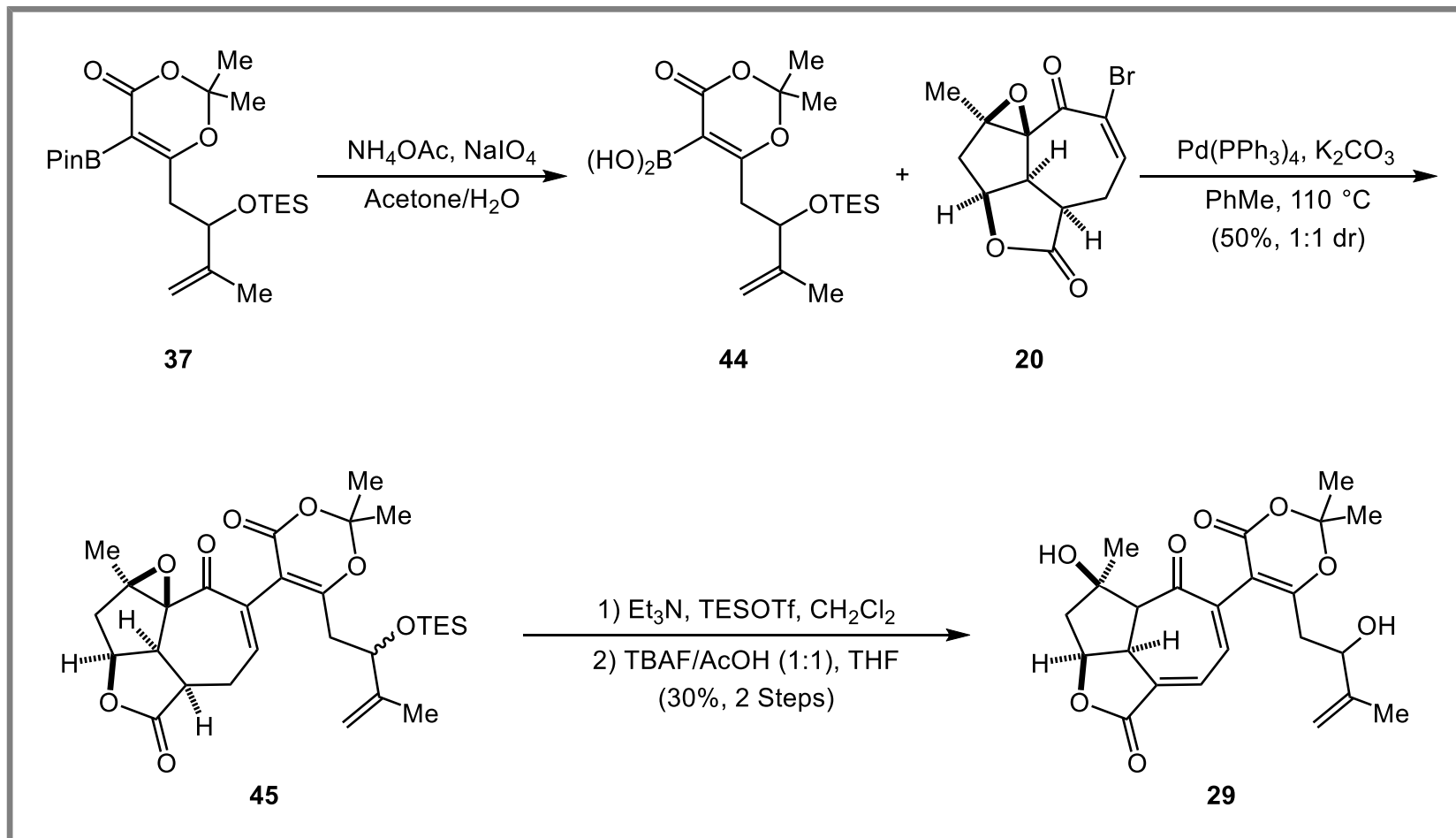
# Substitution of Model Substrates



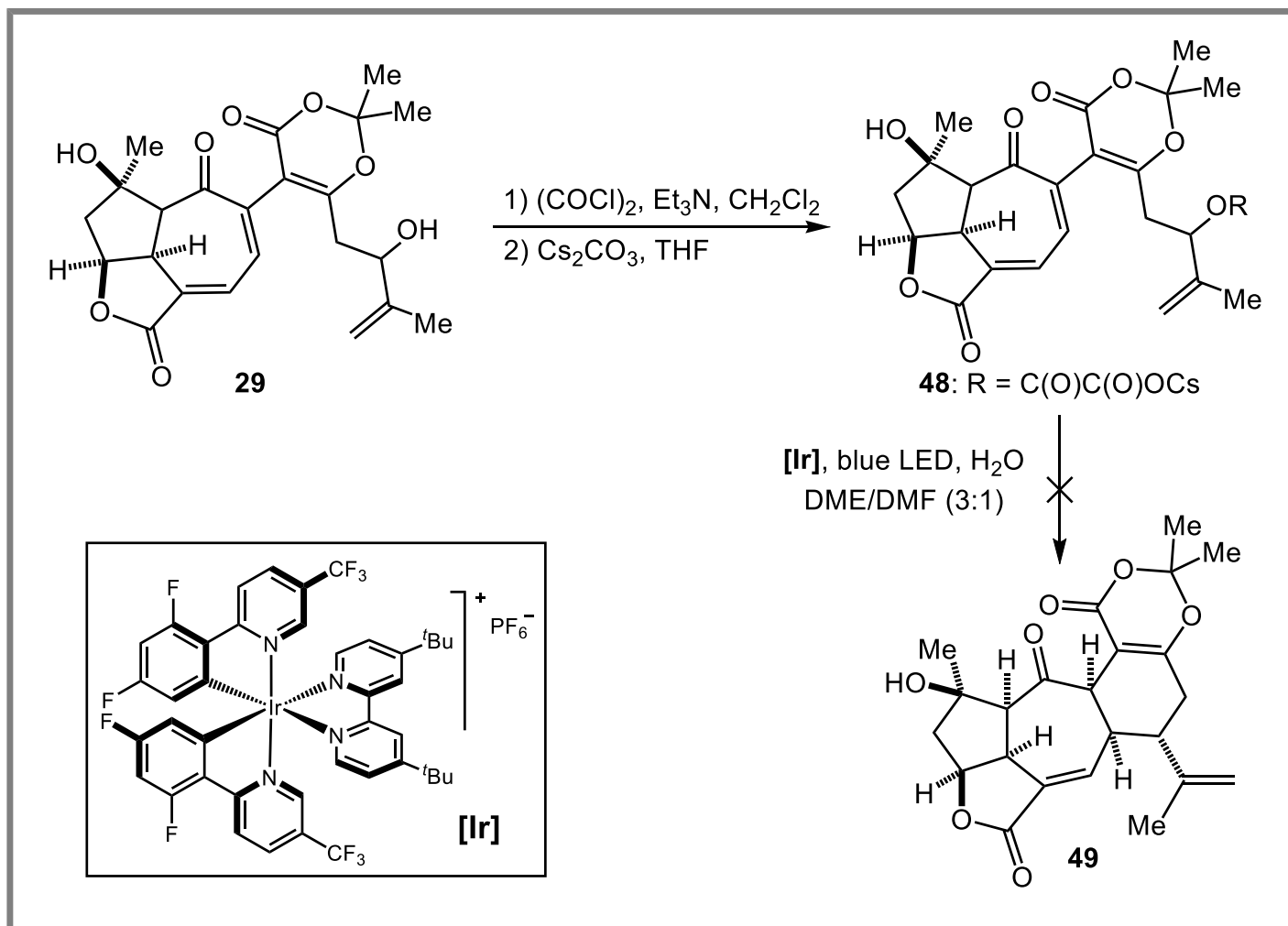
# D-Ring Annulation Strategy 2



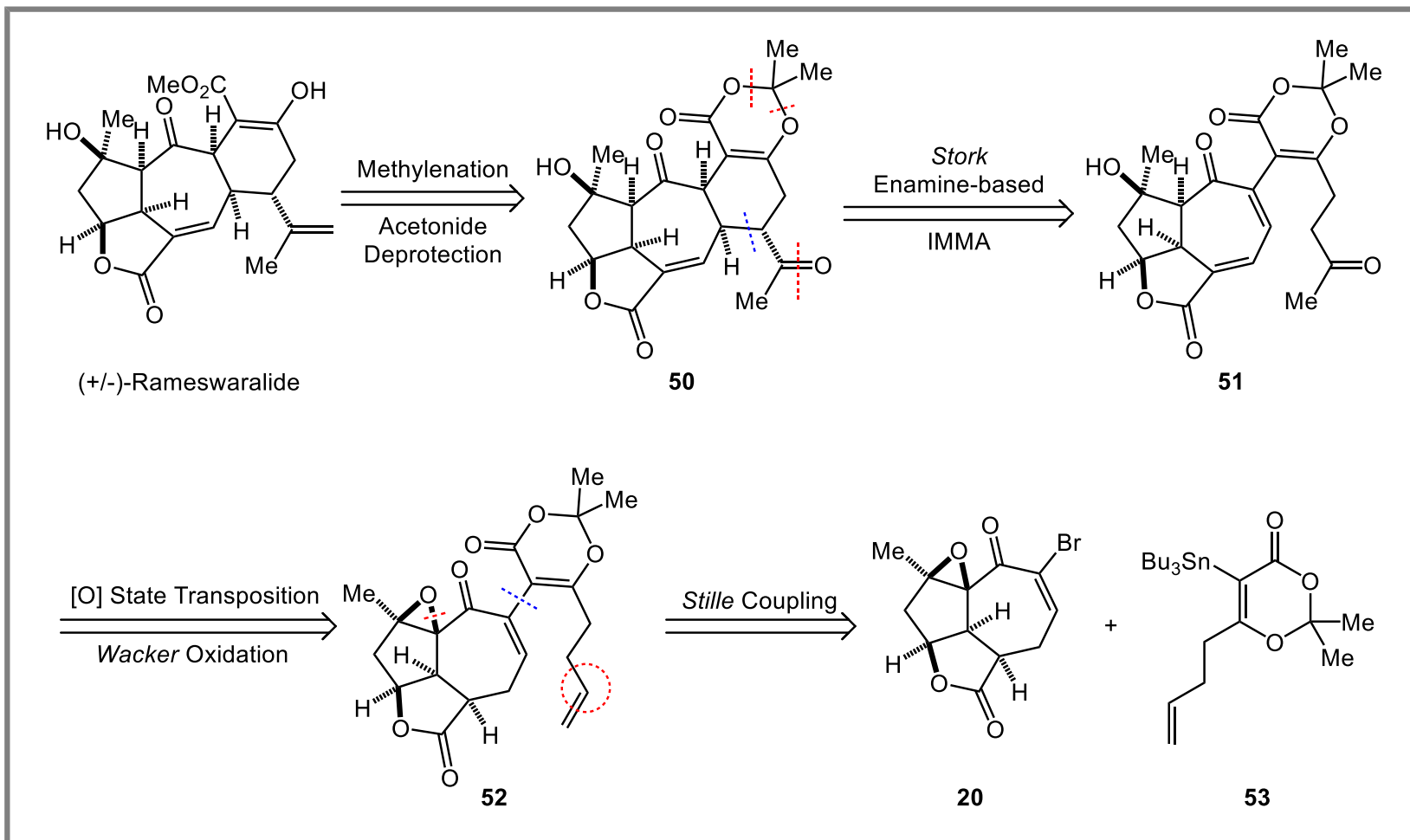
# Synthesis of Intermediate 29



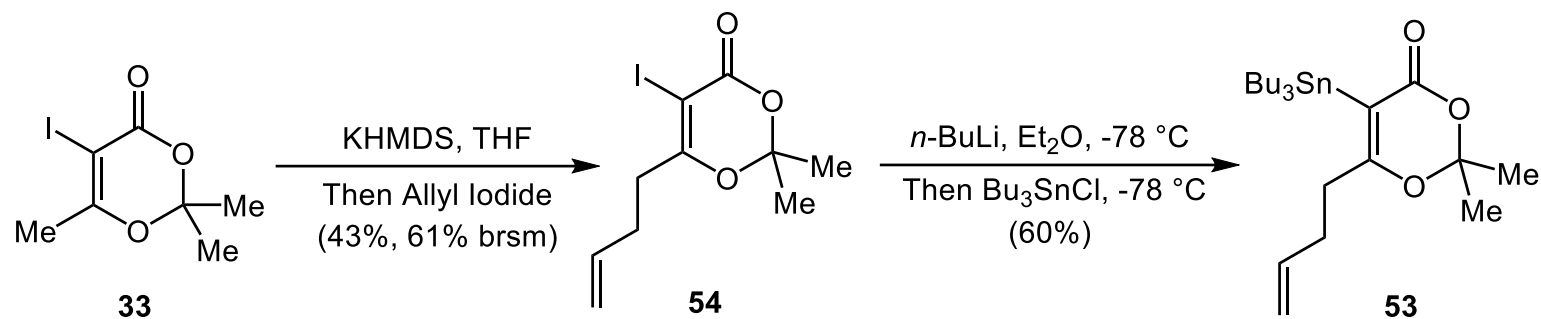
# Synthesis of Compound 49



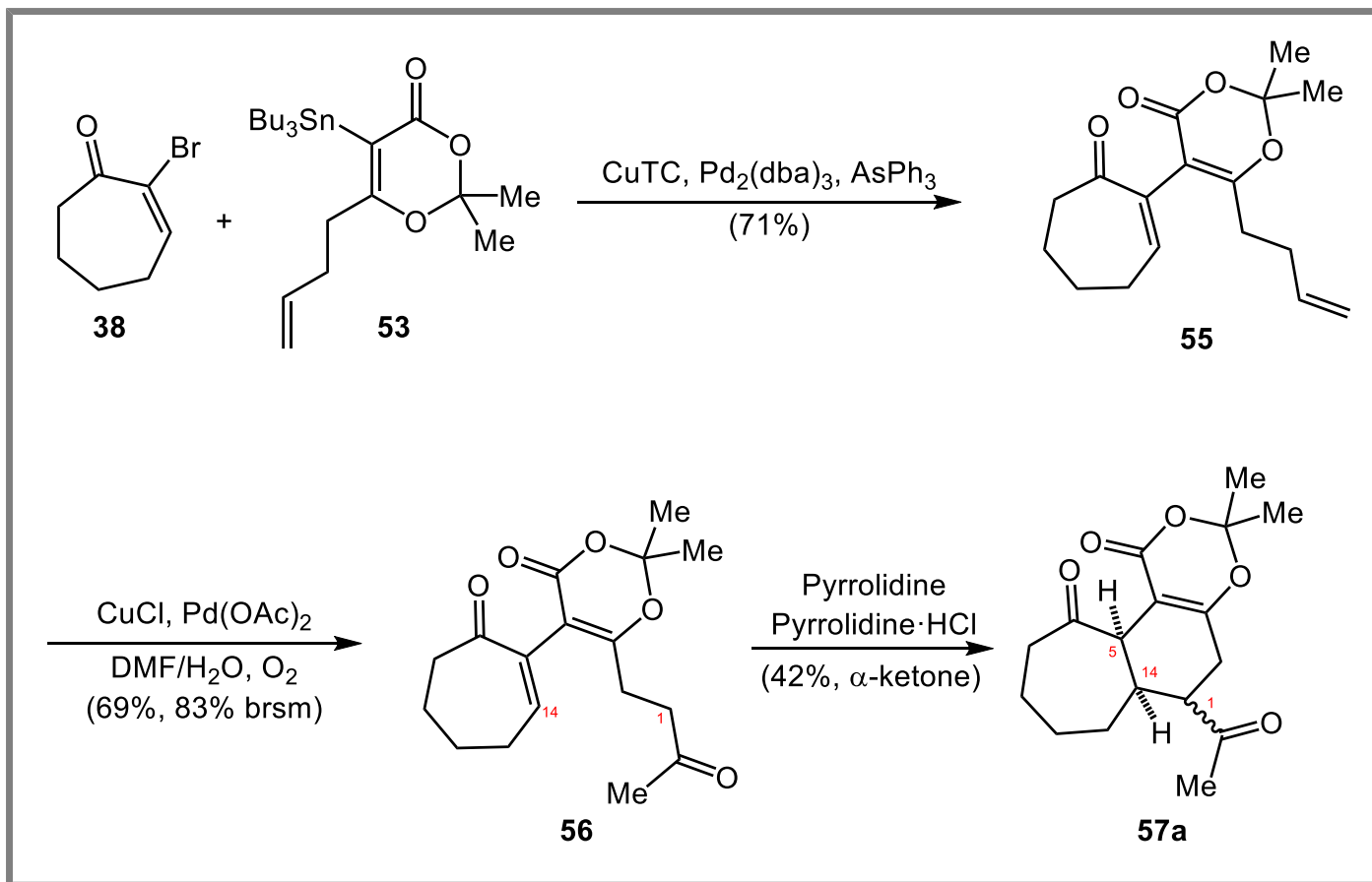
# D-Ring Annulation Strategy 3



# Synthesis of Organotin 53

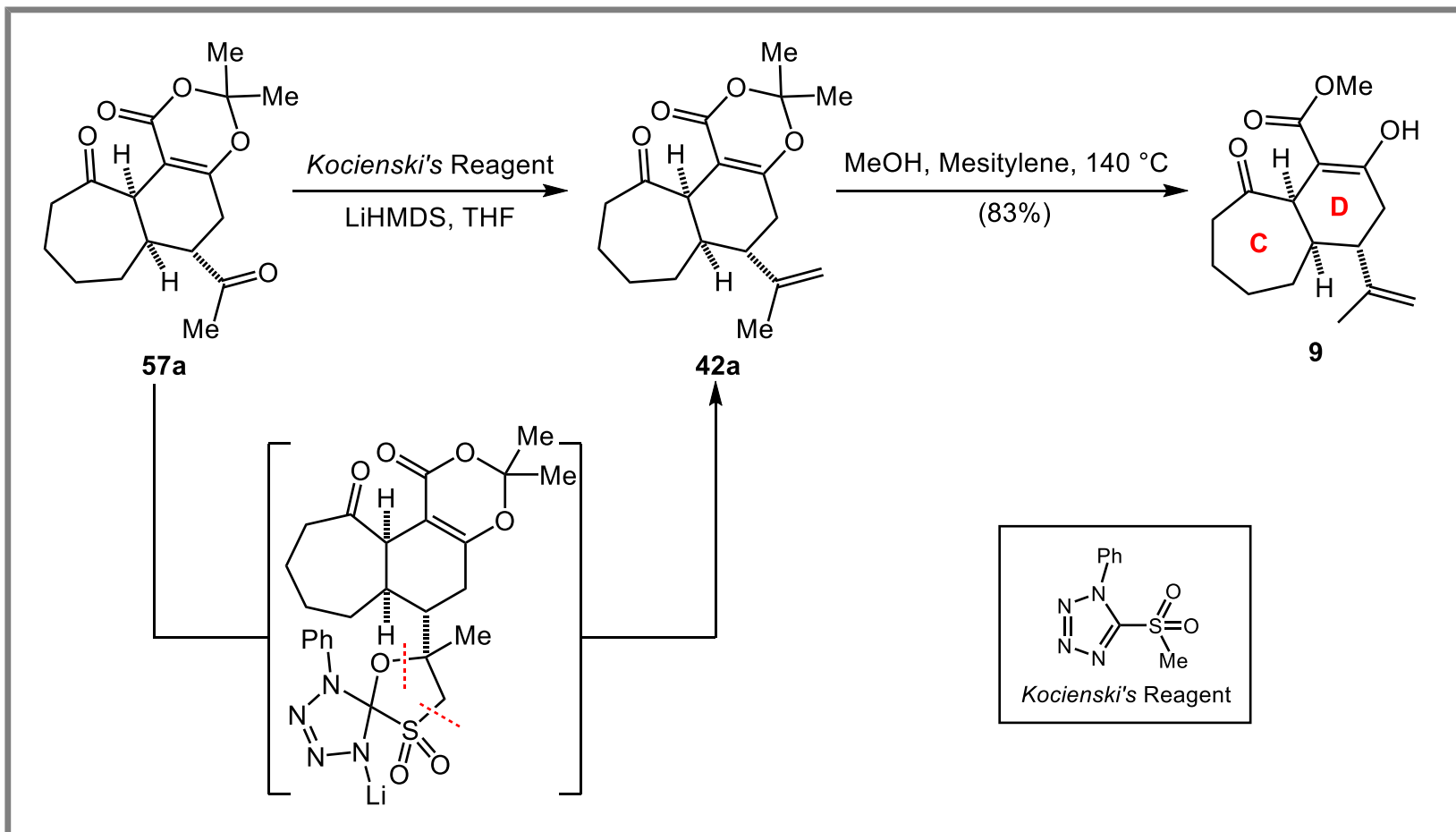


# D-Ring Annulation Strategy 3

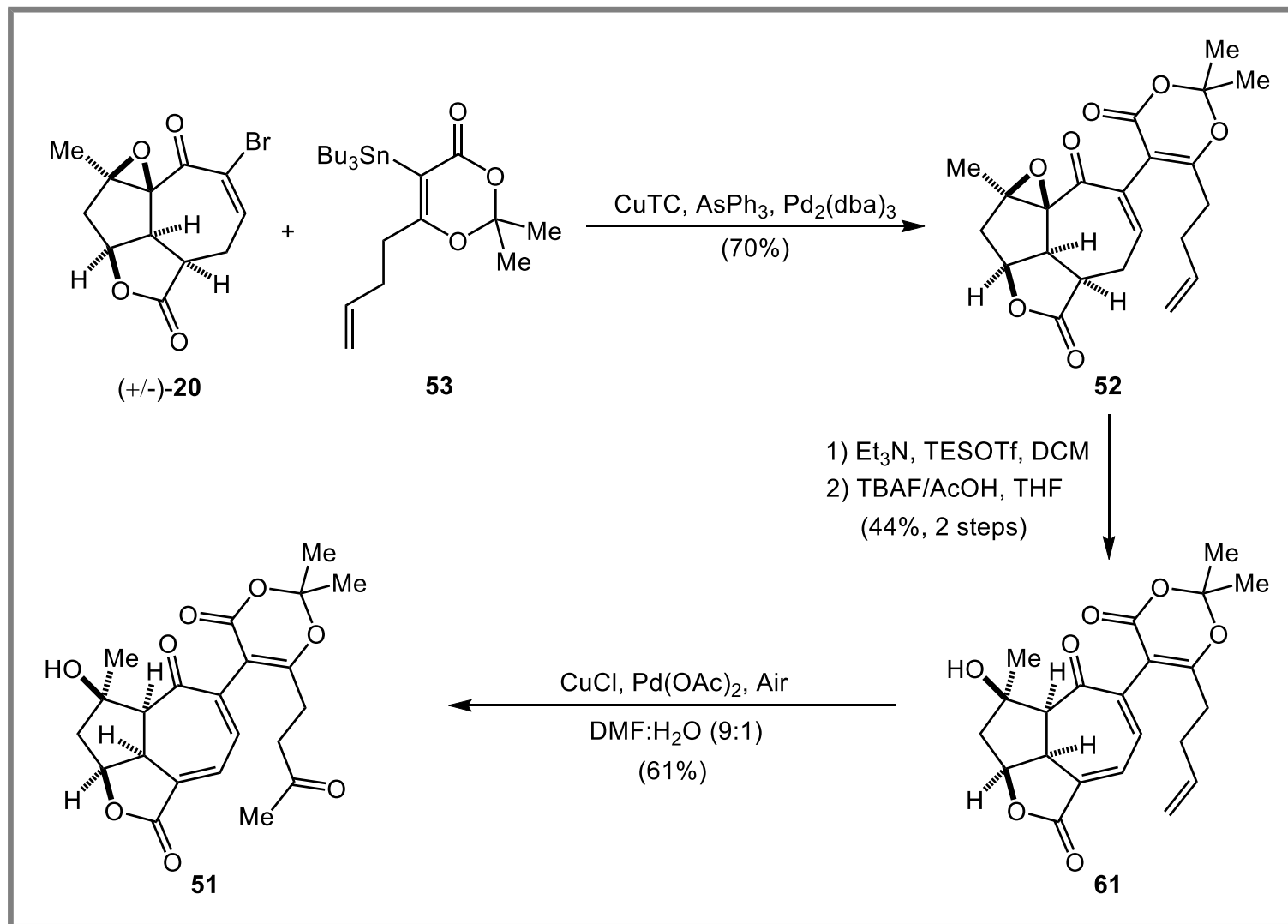




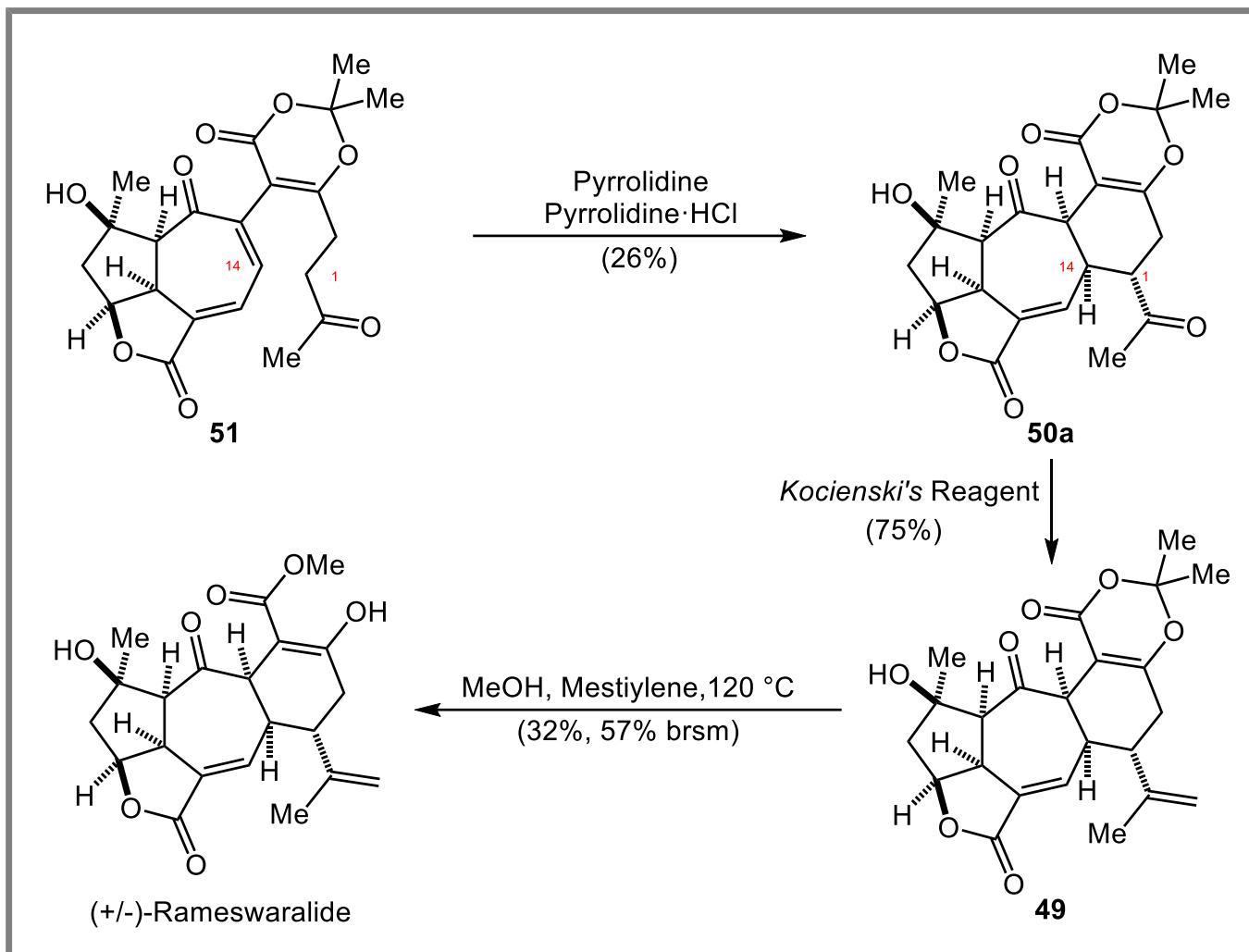
# D-Ring Annulation Strategy 3



# Synthesis of Intermediate 51

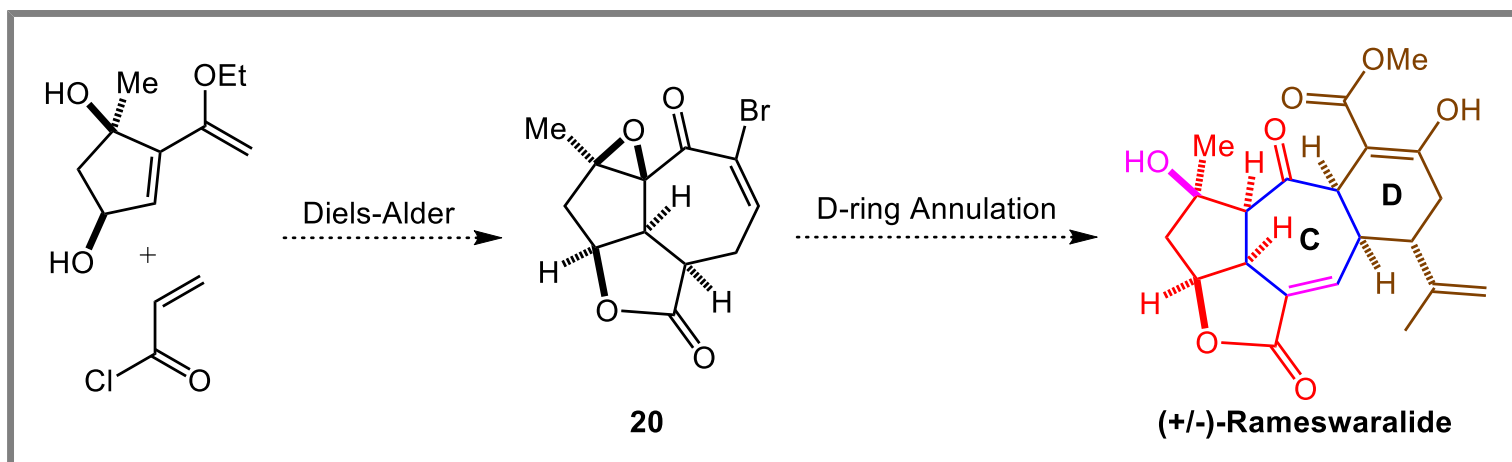


# Synthesis of (+/-)-Rameswaralide



# Summary

- ◆ The First Total Synthesis of (+/-)-Rameswaralide by PDRs Strategy
- ◆ Provide a Variety of Schemes for the D-ring Annulations



## Key Reactions

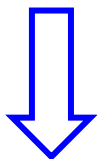
- Diels-Alder Lactonization Offer 5,5,6-Tricyclic Skeleton;
- Smith Cyclopropanation and Radical Bromination;
- Serendipity Led to the Rearrangement of Epoxy Moiety;
- Stork Enamine-based Intramolecular Michael Addition.

# The First Paragraph

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## 雷美沃内脂

### 来源与结构



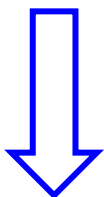
### 合成进展

- ✓ First isolated from the soft coral *Sinularia dissecta* in 1998, rameswaralide is a tetracyclic diterpene belonging to the broader class of marine cembranoid secondary metabolites. Its structure, was later verified in 2016 by X-ray crystallography, revealing a complex, highly oxygenated, caged 5,5,7,6 all cis-fused ring system containing seven stereogenic centers, has moderate cytotoxicity and possible anti-inflammatory activity, piquing the interest of various synthetic groups.
- ✓ Despite this broad interest, a total synthesis of rameswaralide has not been reported. Only two members possessing related tetracyclic frameworks have been reported, namely, scabrolide A by both Stoltz and Fürstner groups, with the latter report including the synthesis of nominal scabrolide B.

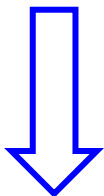
# The Last Paragraph

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## 成果总结



## 关键反应



## 成果展望

- ✓ In conclusion, we report the first total synthesis of the caged cembrenoid (+/-)-Rameswaralide employing a PDRs strategy.
- ✓ Key reactions in the total synthesis include an organocatalytic D–A lactonization organocascade, which provides rapid access to the common 5,5,6-tricycle core of several *Sinularia* natural product family members. Finally, a serendipitous, E1-type elimination of an epoxy enone led to a desired net oxidation state transposition and paved the way to study three distinct D-ring annulation strategies. These strategies included a photoredox-initiated 6-endo-trig Giese-type cyclization process and the successful Stork enamine-based intramolecular Michael addition.
- ✓ In addition, we surprisingly found that the simplified CD ring system of rameswaralide possessing a  $\beta$ -keto ester displayed increased the antiproliferative activity compared to (+/-)-rameswaralide.

# Representative Examples

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- I. Our interest in rameswaralide **stems from** (源于) its complex architecture coupled with an interest in applying the pharmacophore-directed retrosynthesis (PDR) to this and related cembranoids to gain a greater understanding of their SARs.
- II. This **serendipitous** (偶然的) finding demonstrated that the epoxide, through an oxidation state transposition, is an efficient strategy to introduce the  $\alpha$ -methylene butyrolactone present in rameswaralide.
- III. These preliminary studies led to the synthesis of epoxy  $\alpha$ -bromo enone, which became a **versatile** (多用途的) intermediate for the final D-ring annulation strategies described below.

# Acknowledgement

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**Thank You for Your Attention !**