

# Literature Report I

## Total Synthesis of Allenic Macrolide (+)-Archangiumide

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**Reporter: Shui-Long Lei**  
**Checker: Zheng Liu**

Sutro, J. L.; Fürstner, A.\* *J. Am. Chem. Soc.* **2024**, *146*, 2345-2350

# CV of Prof. Alois Fürstner

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## Background:

- **1987** Ph.D., Technical University Graz
- **1990-1991** Postdoctoral Fellow, University of Geneva
- **1992-1993** Habilitation, Technical University Graz
- **1993-1998** Group Leader, Max-Planck-Institut für Kohlenforschung
- **1998-2009** Director, Max-Planck-Institut für Kohlenforschung
- **2009-Now** Managing Director, Max-Planck-Institut für Kohlenforschung

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## Research Field:

- Alkene/Alkyne Metathesis
- $\pi$ -Acid Catalysis
- Iron Catalysis
- Total Synthesis of Natural Products

# Contents

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**1** Introduction

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**2** Total Synthesis of the Allenic Macrolide (+)-Archangiumide

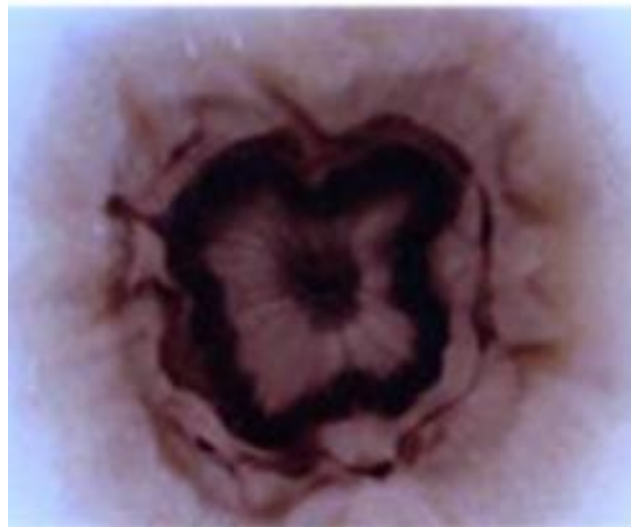
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**3** Summary

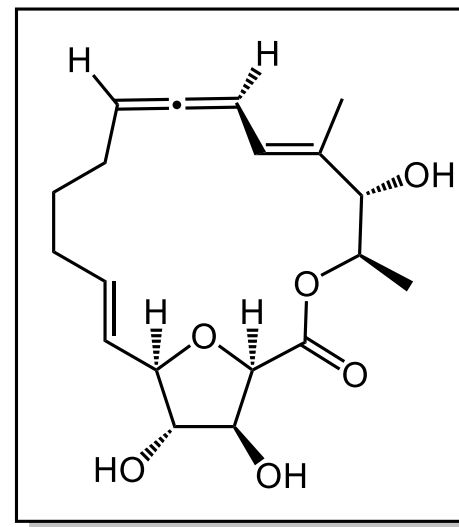
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# Introduction

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**Archangium violaceum SDU8**

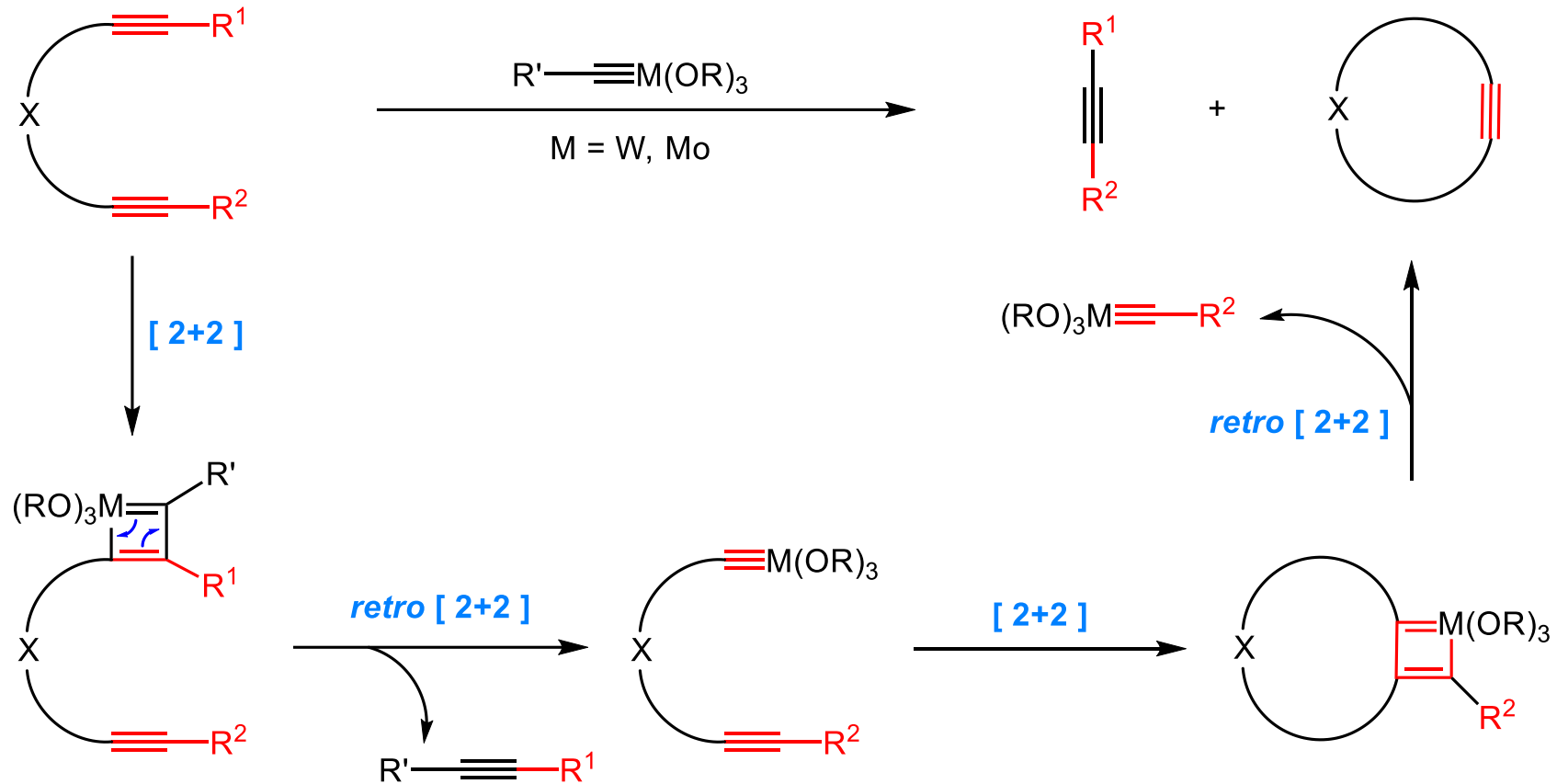


**(+)-Archangiumide**

- Discovered from the Myxobacterium *Archangium Violaceum* SDU8 in 2021;
- The First Known Macrolide Natural Product Comprising an Endocyclic Allene;
- A New Class of Secondary Metabolites of Microbial Origin.

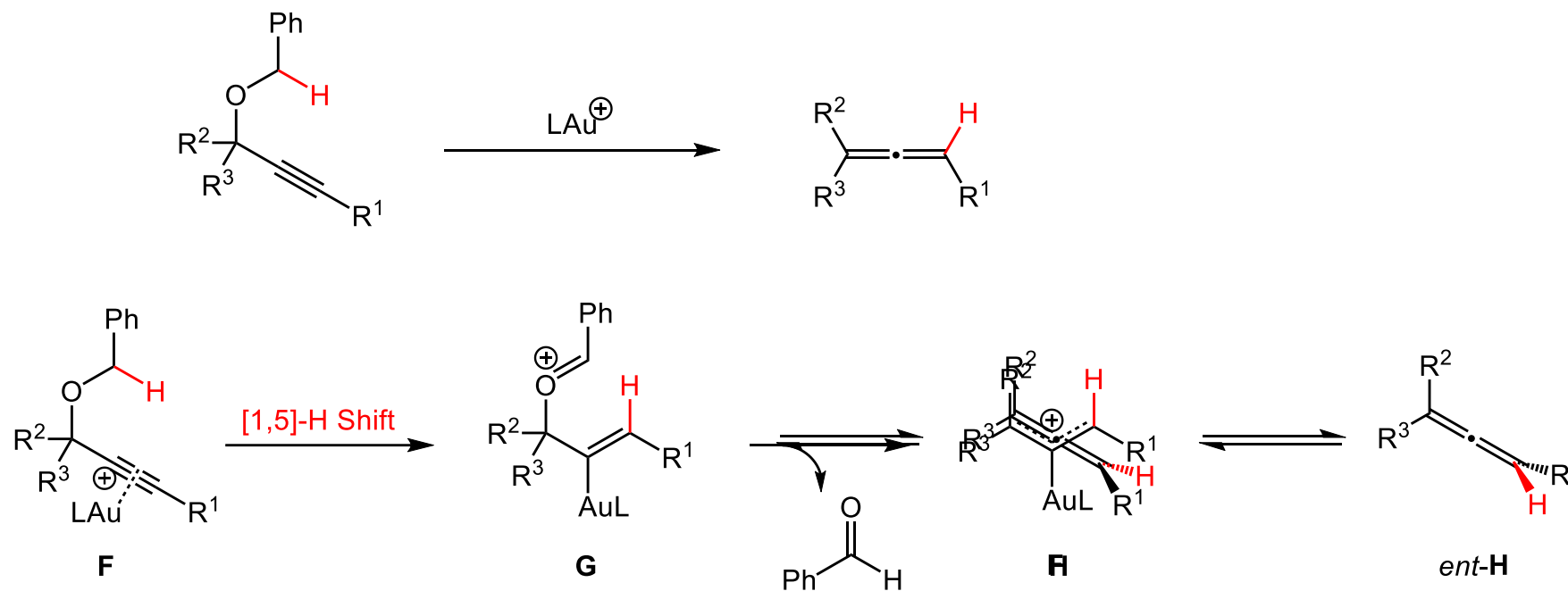
Hu, J.-Q.; W, J.-J.; Li, Y.-L.; Li, Y.-Z.\*; Wu, C.-S.\* *Org. Lett.* **2021**, 23, 2114

# RCAM (Ring-Closing Alkyne Metathesis)



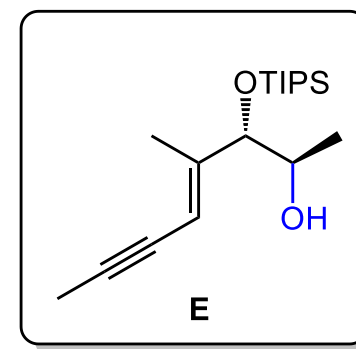
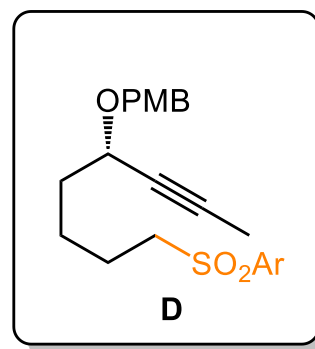
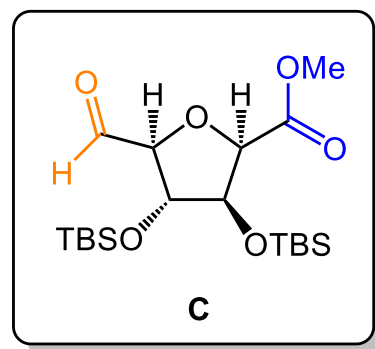
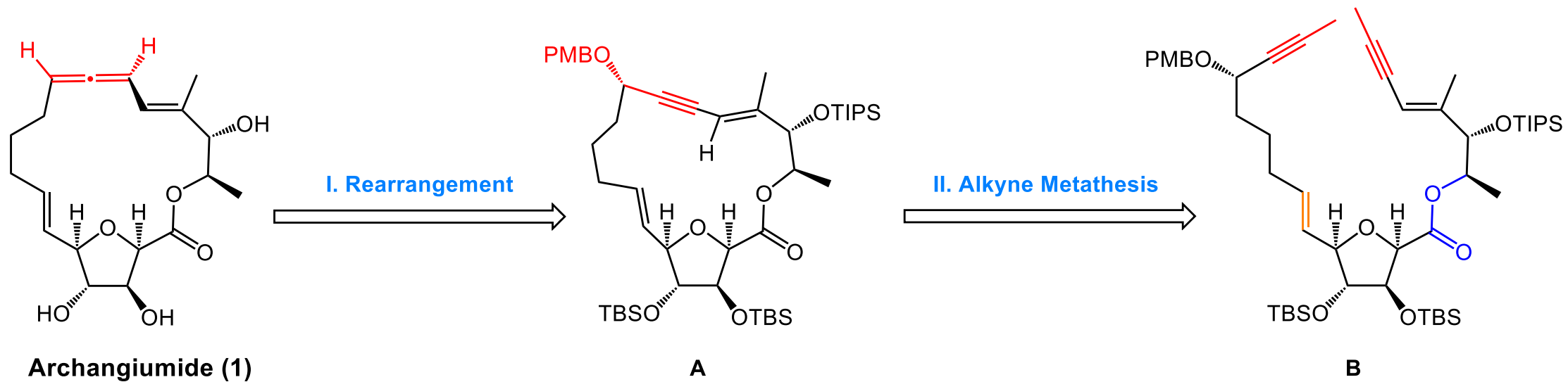
Fürstner, A.; Seidel, G. *Angew. Chem. Int. Ed.* **1998**, 37, 1734

# Gold(I)-Catalyzed Rearrangement

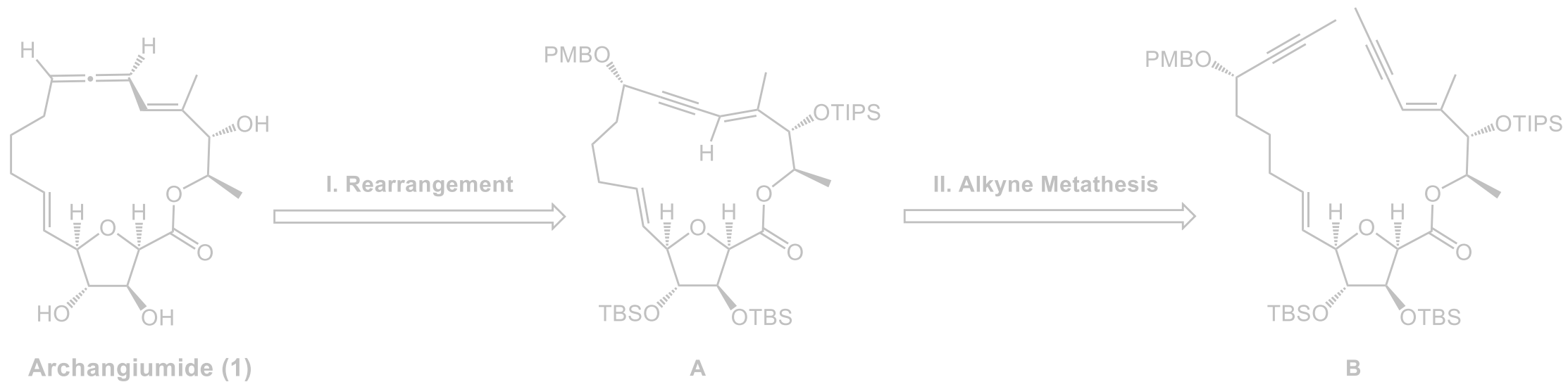


Bolte, B.; Odabachian, Y.; Gagosz, F.\* *J. Am. Chem. Soc.* **2010**, *132*, 7294

# Retrosynthetic Analysis

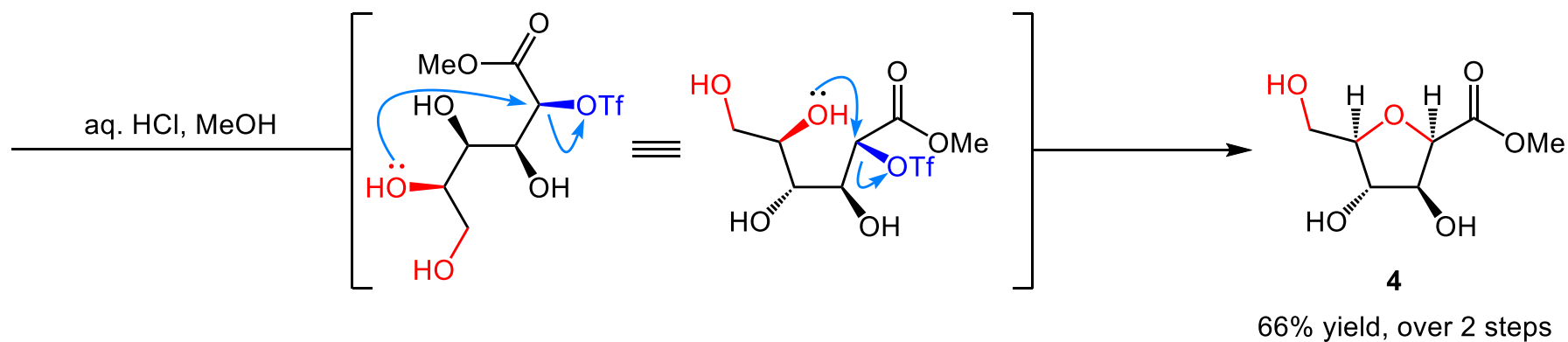
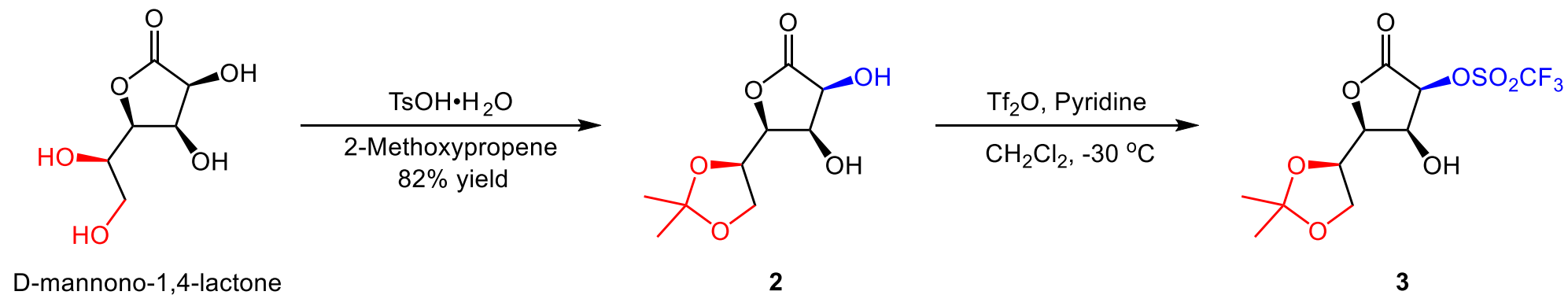


# Retrosynthetic Analysis



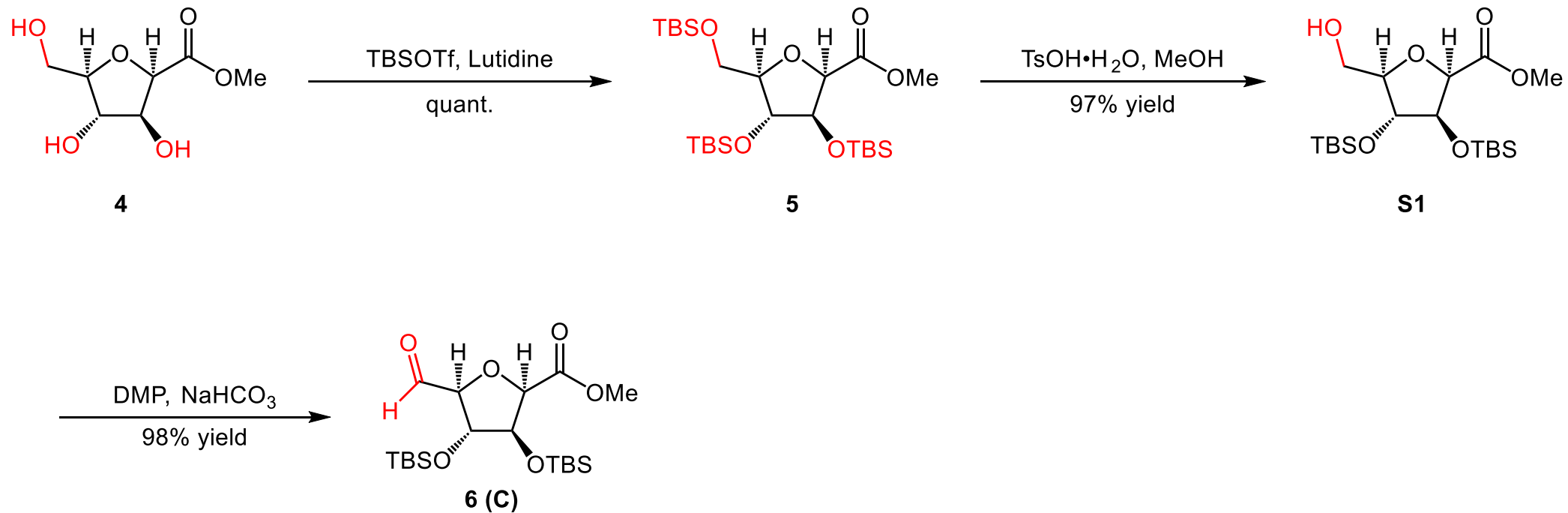


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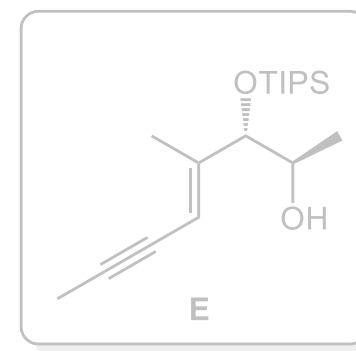
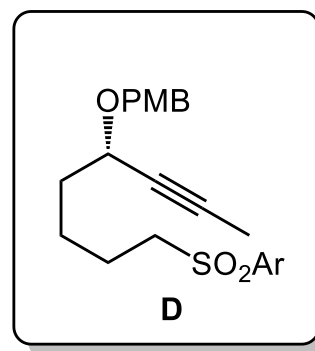
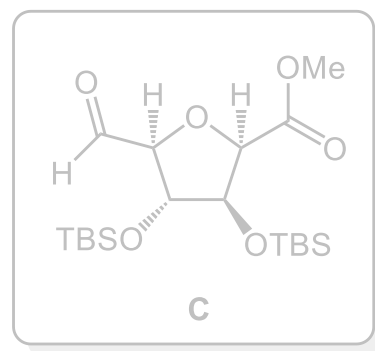
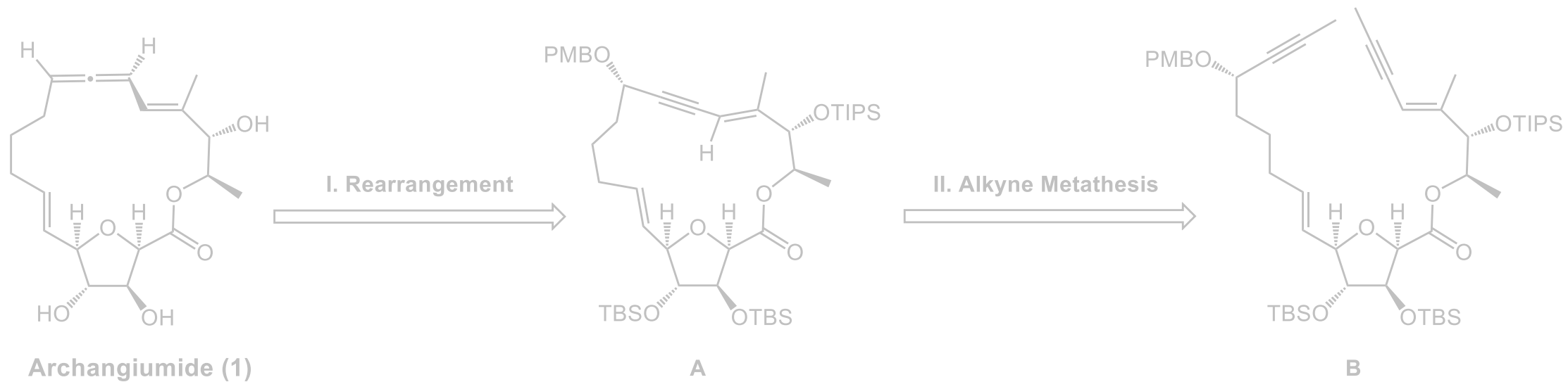


Long, D.-D.; Smith, M.-D.; Fleet, G. W. J.\* *J. Chem. Soc., Perkin Trans.* **2002**, 1, 1982

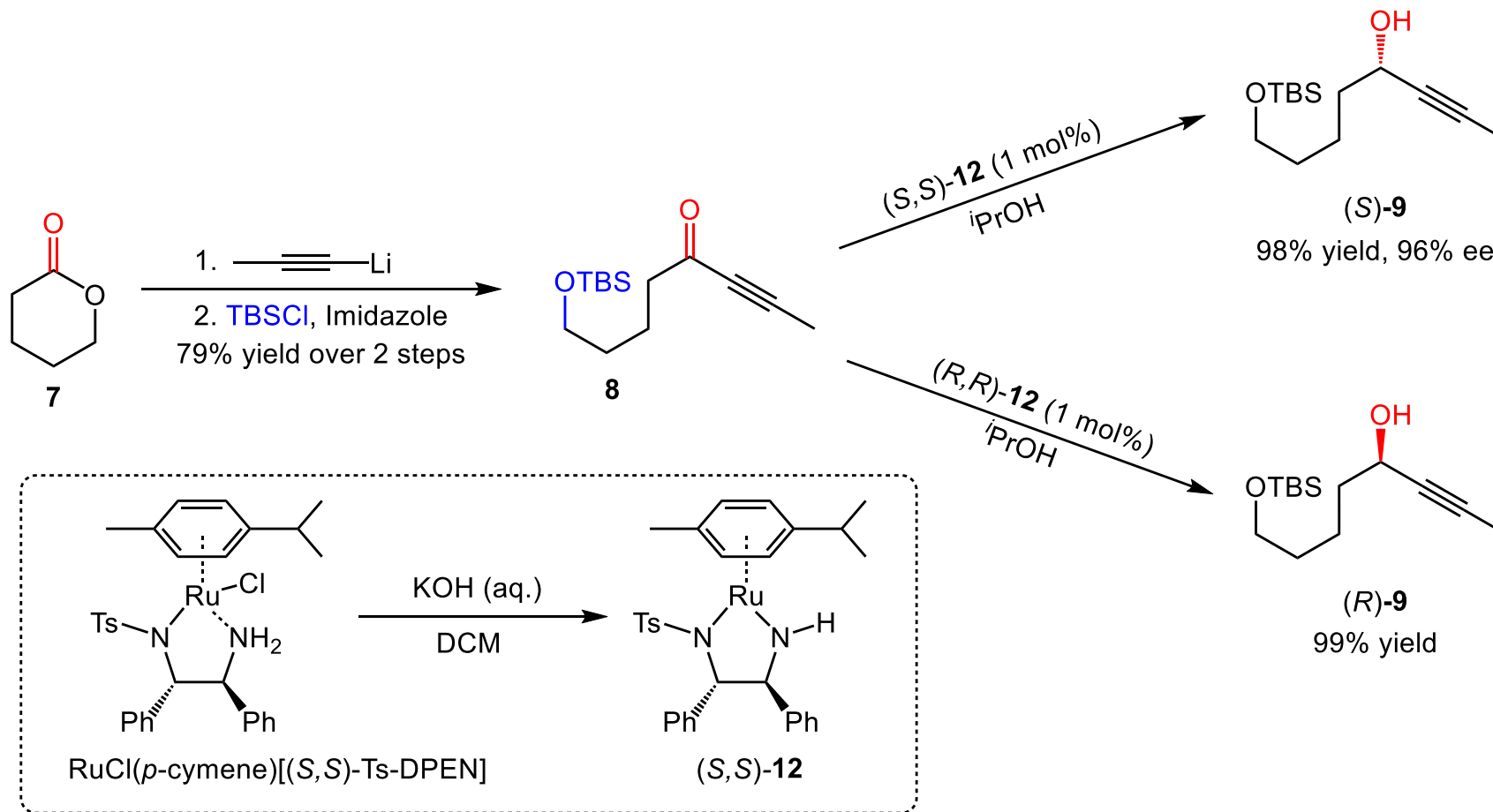
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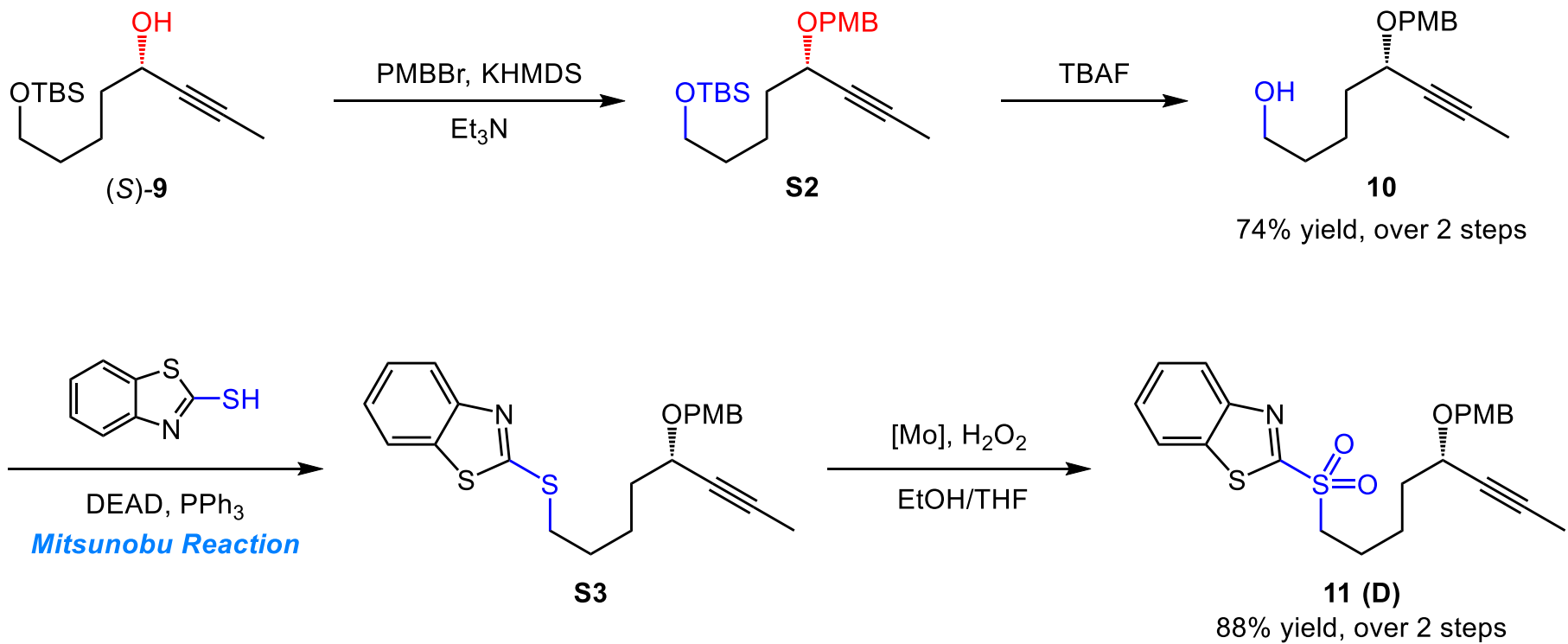
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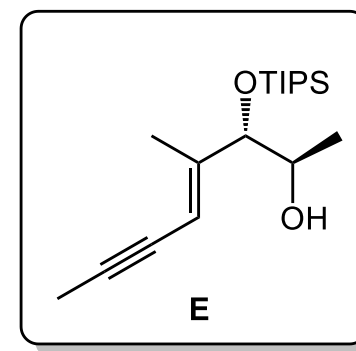
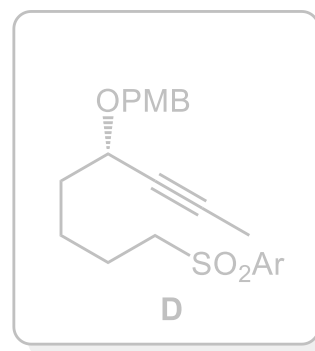
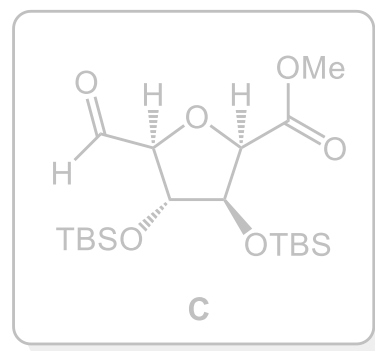
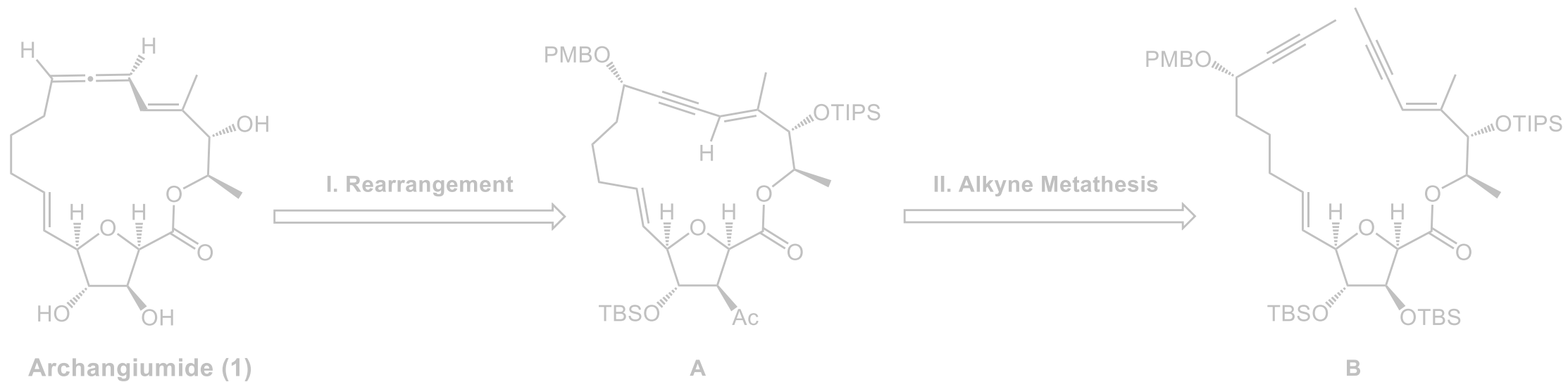
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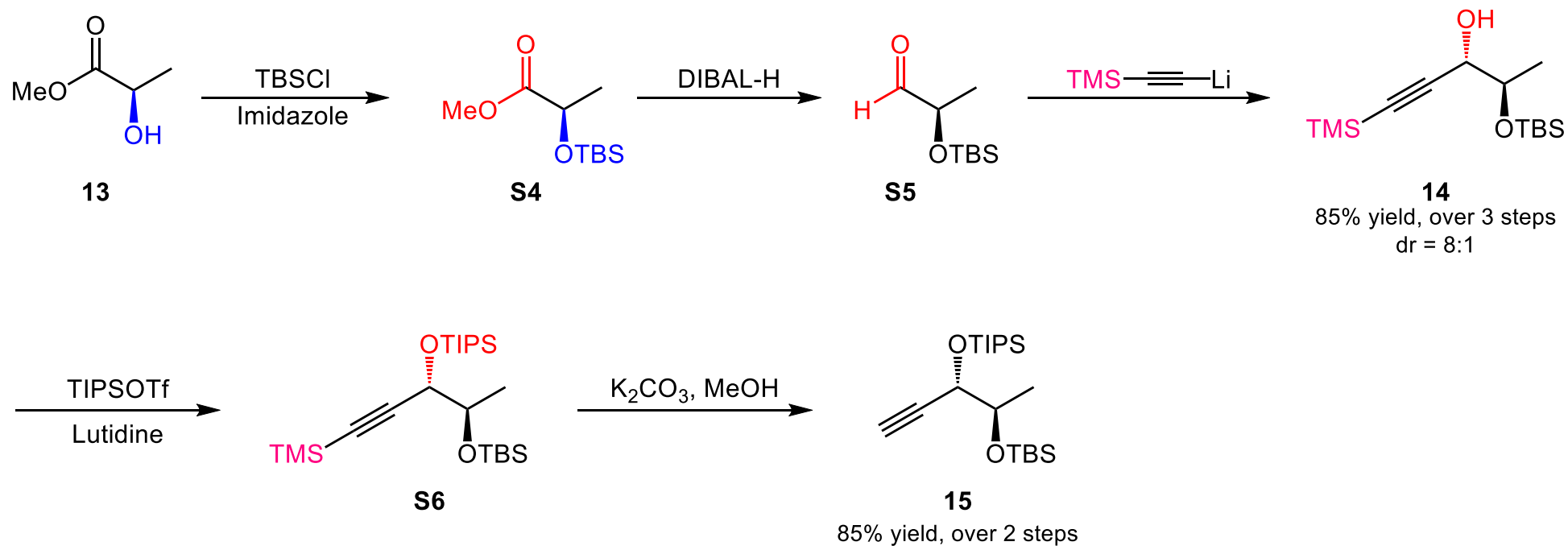
# Synthesis of Fragment D



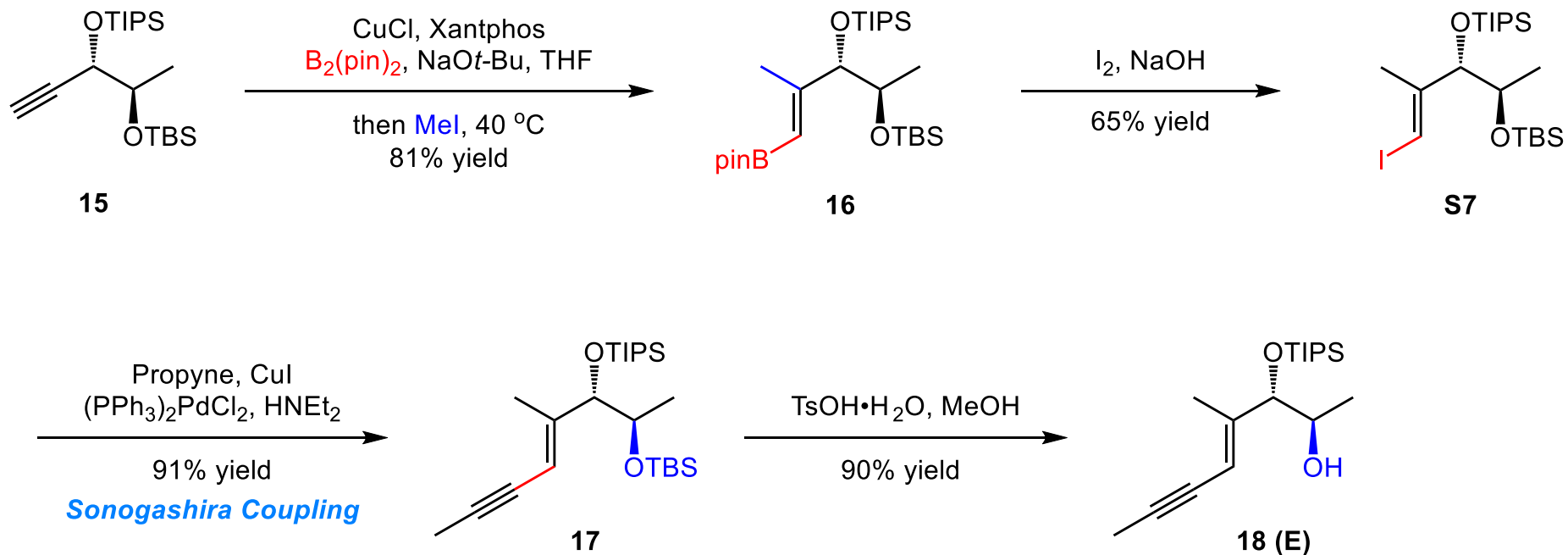
# Retrosynthetic Analysis



# Synthesis of Fragment E

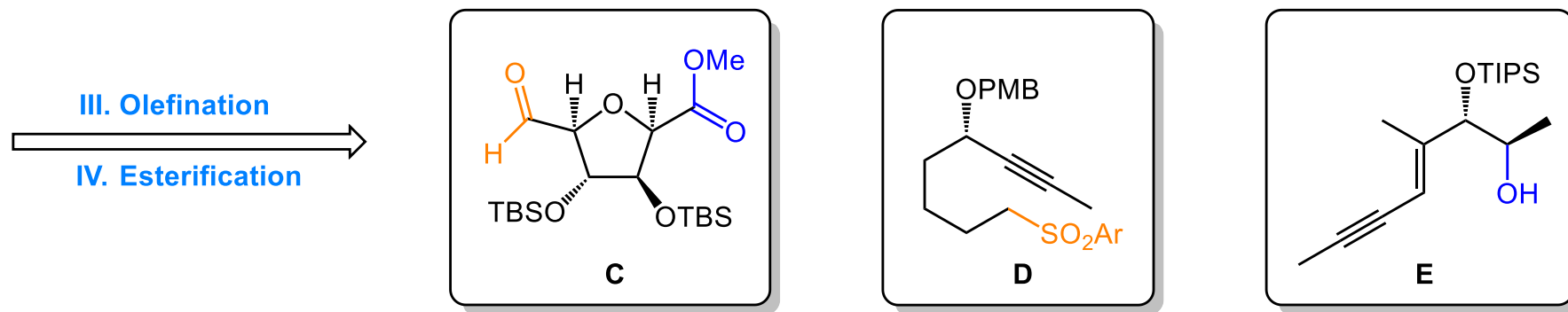
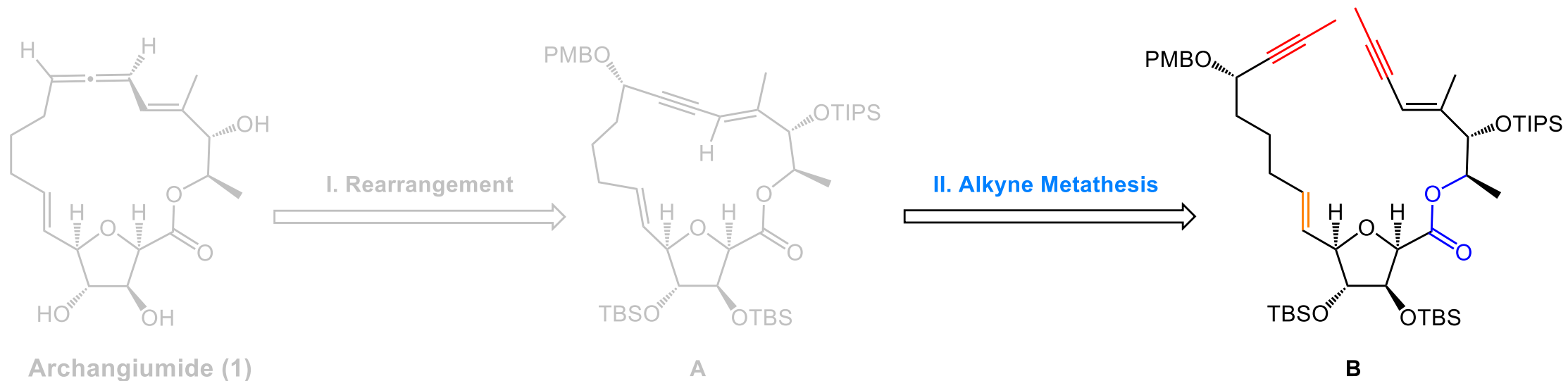


# Synthesis of Fragment E

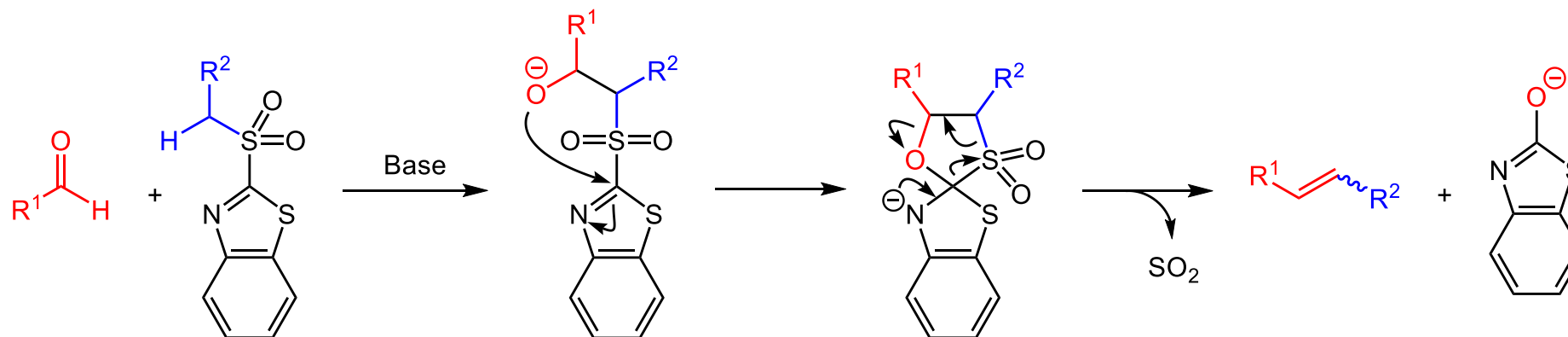
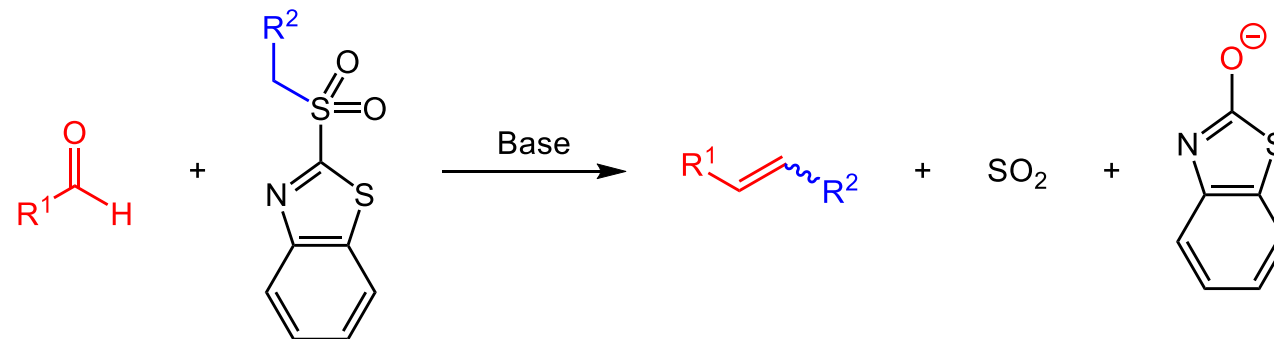




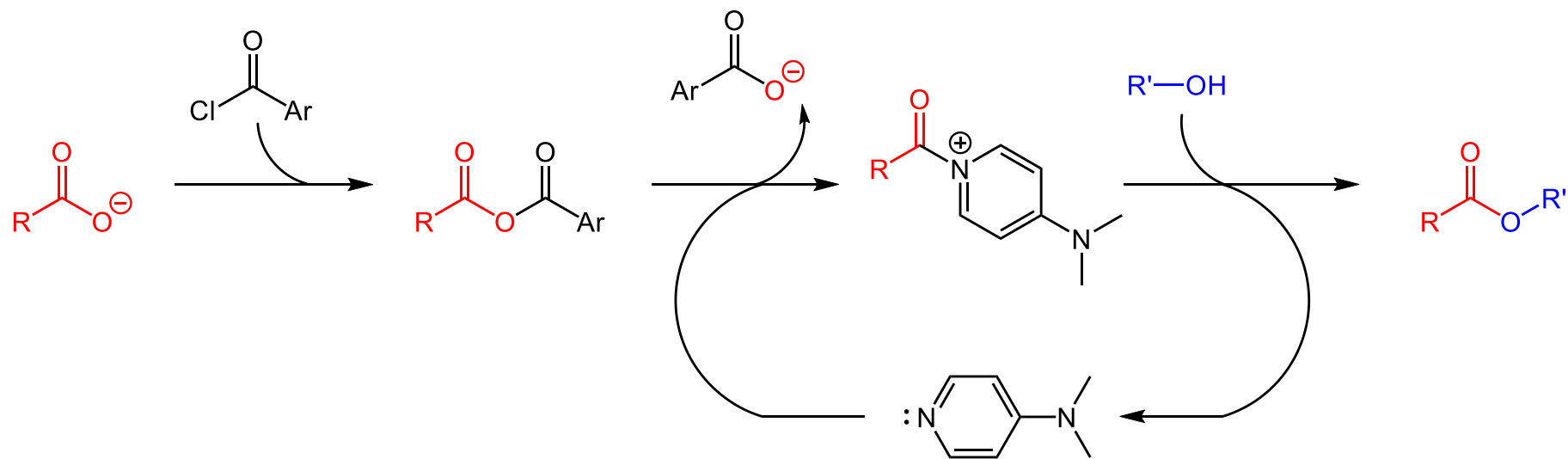
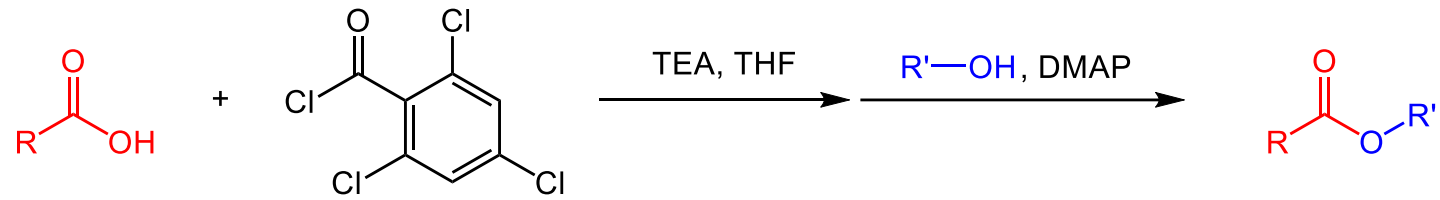
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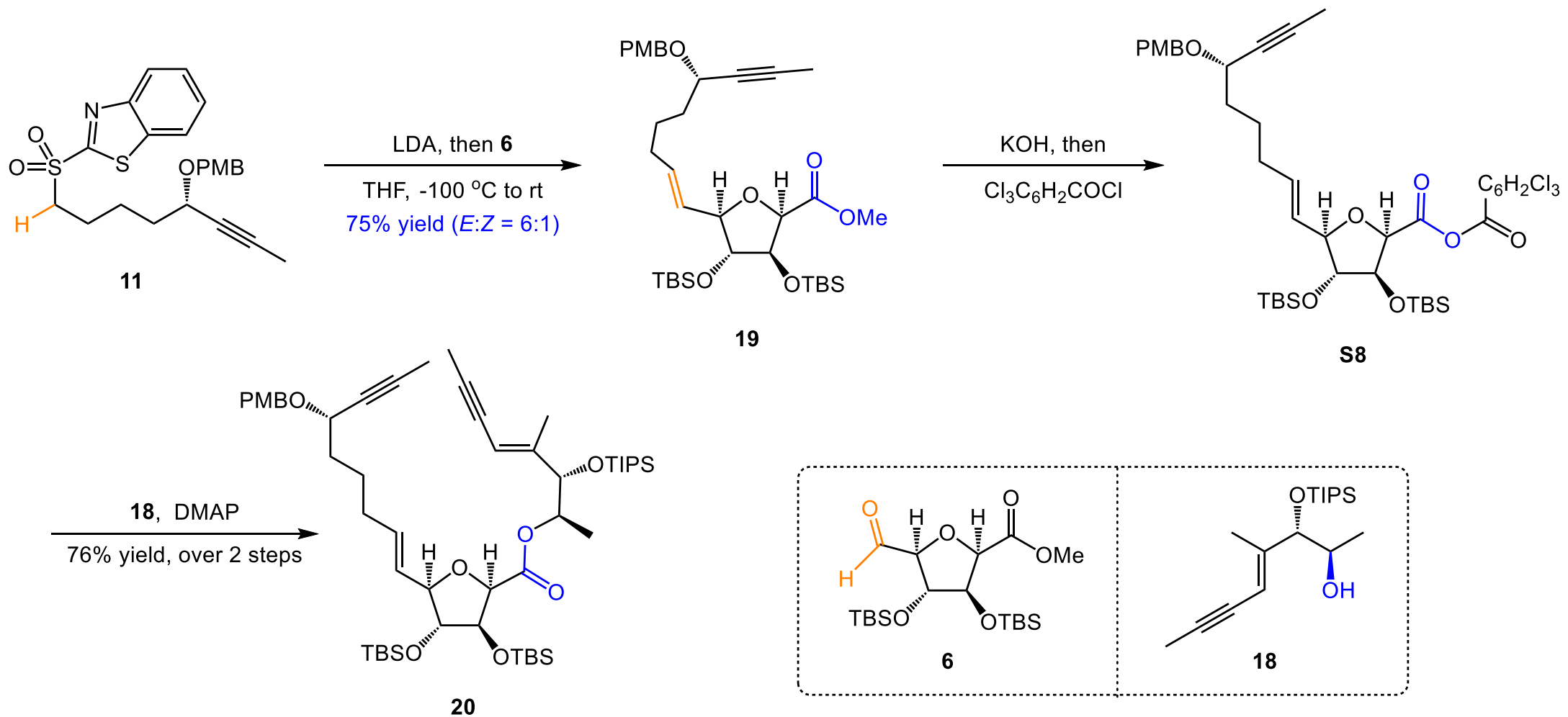
# Modified Julia Olefination



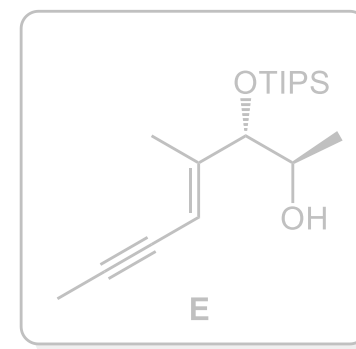
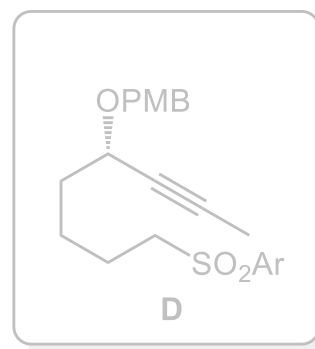
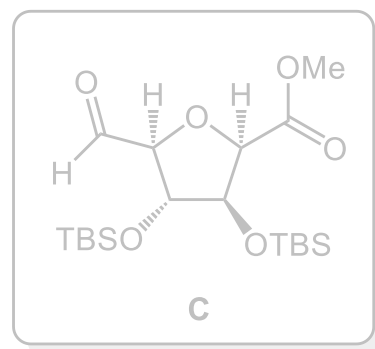
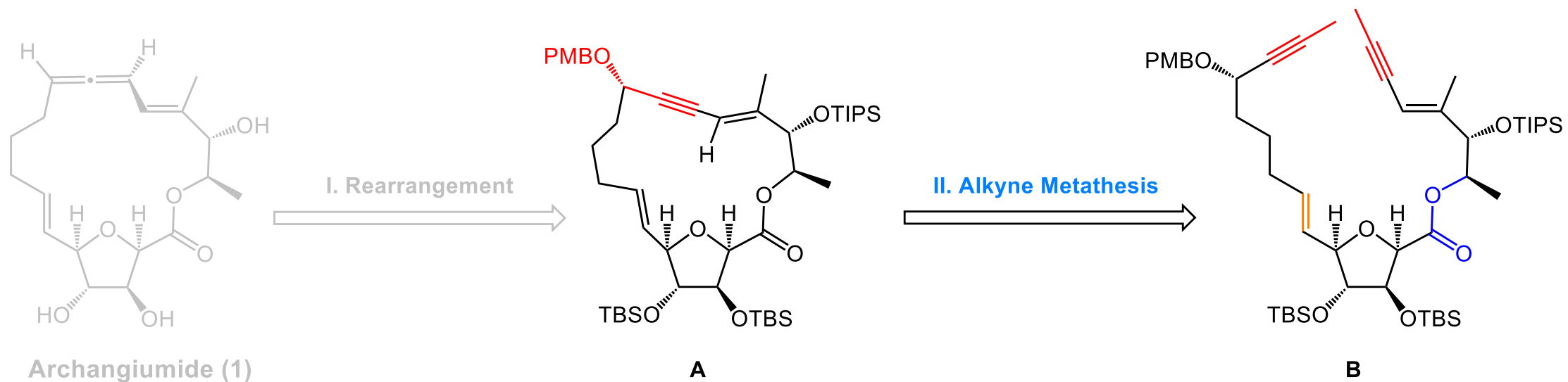
# Yamaguchi Esterification



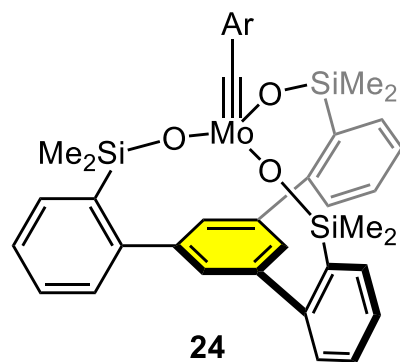
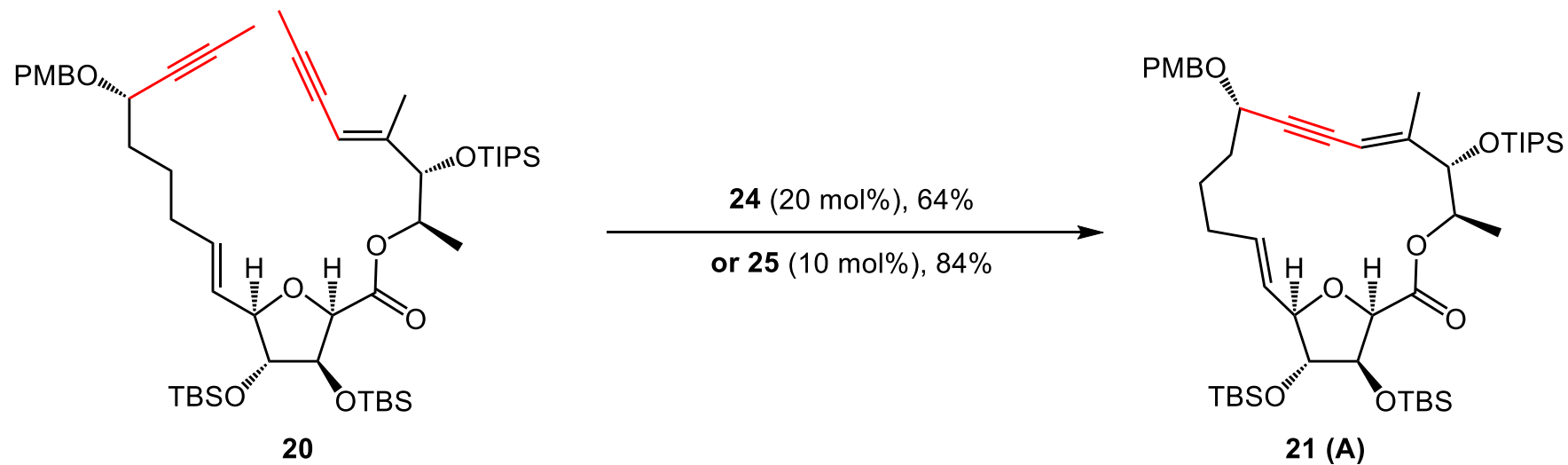
# Synthesis of Fragment B



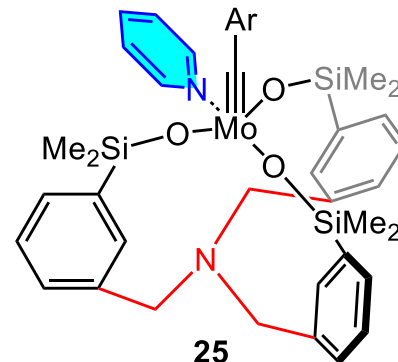
# Retrosynthetic Analysis



# Synthesis of Fragment A

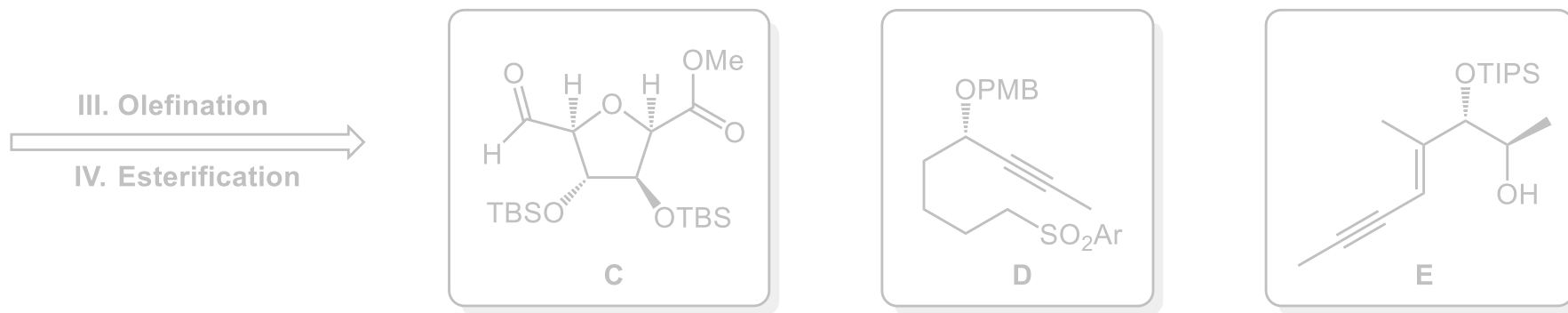
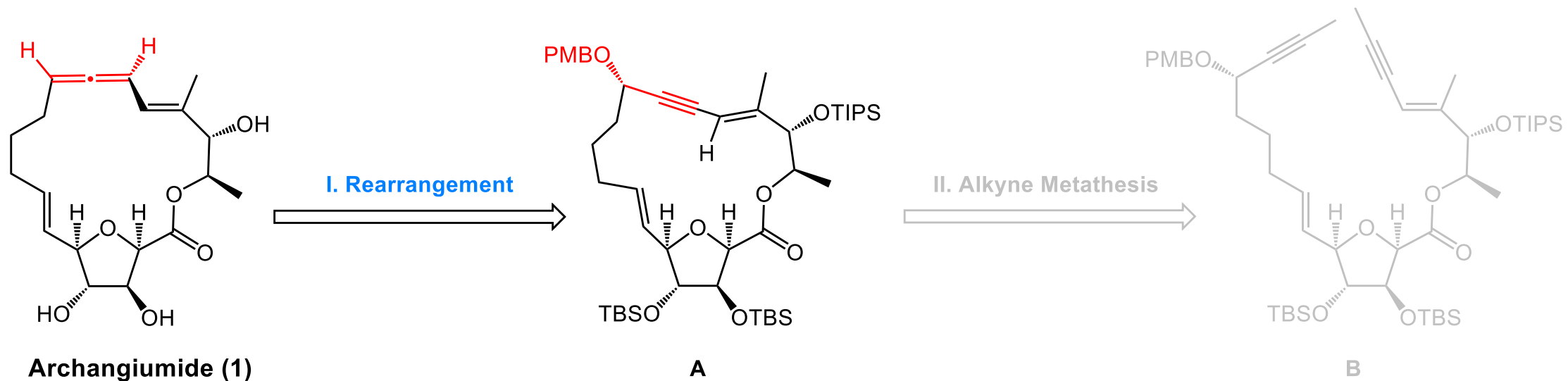


Ar = 2,6-Dimethylphenyl

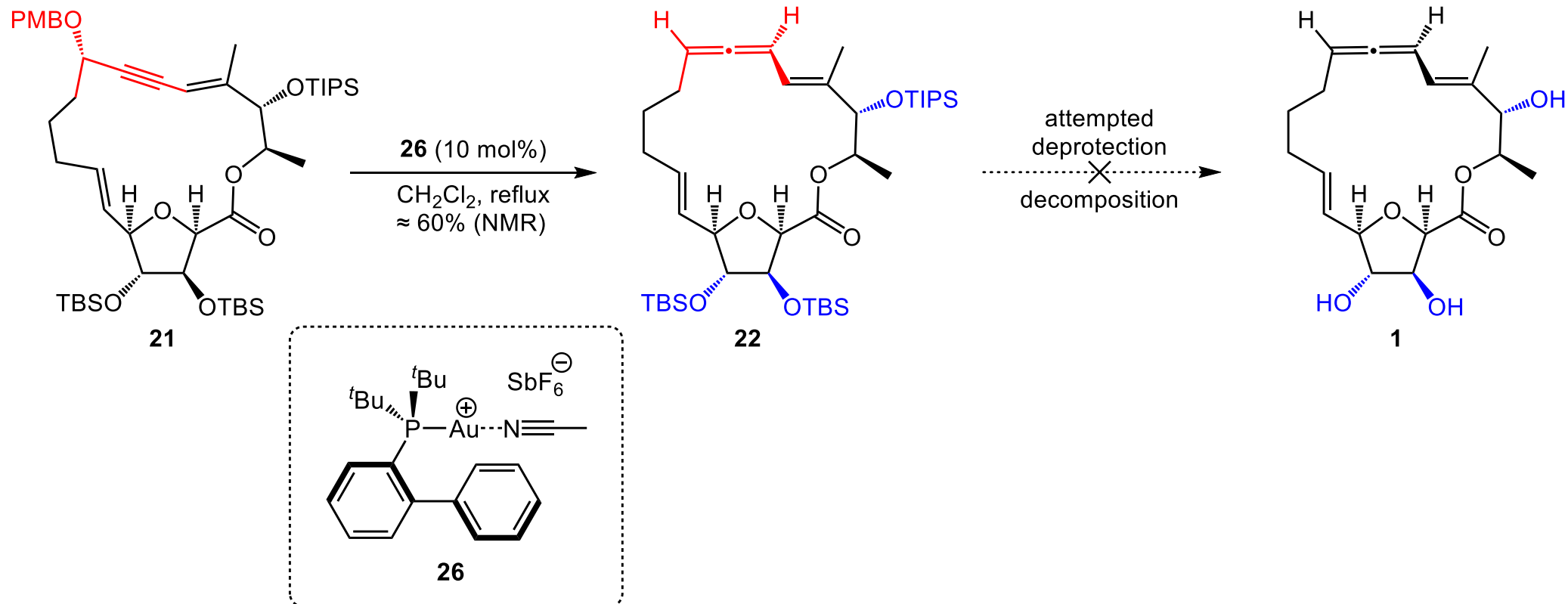


Ar = 2,6-Dimethylphenyl

# Retrosynthetic Analysis

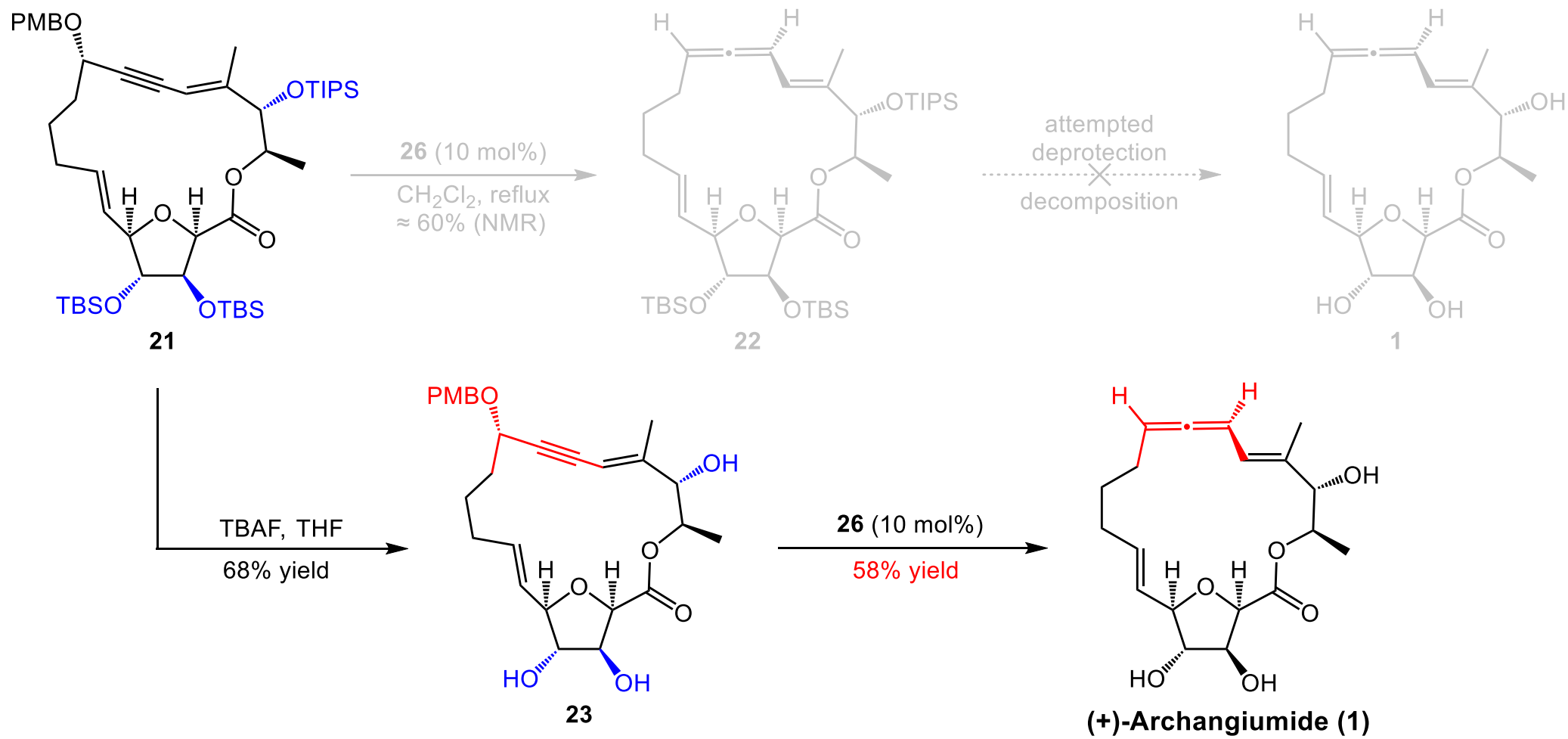


# Attempted Synthesis of (+)-Archangiumide

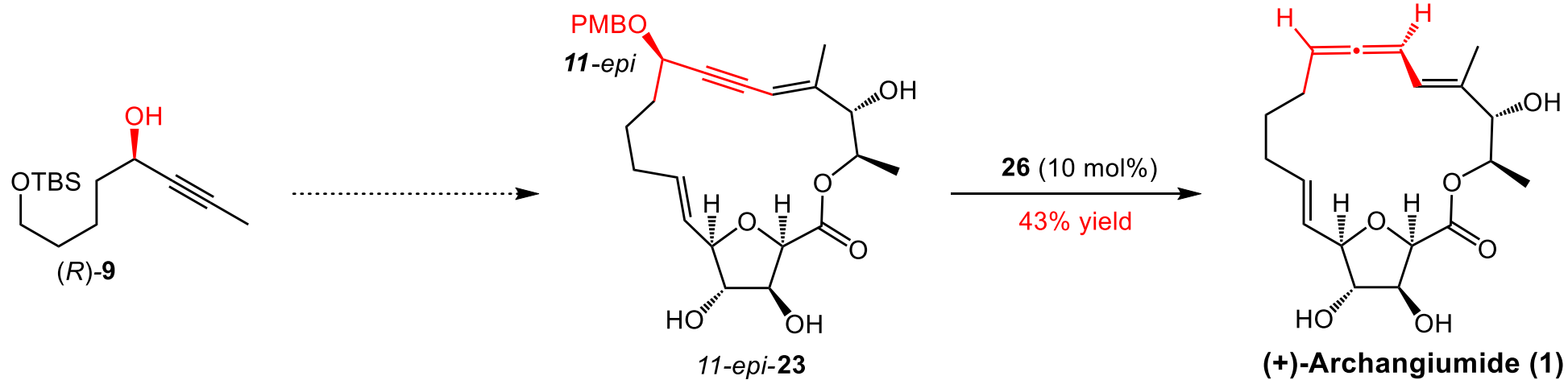




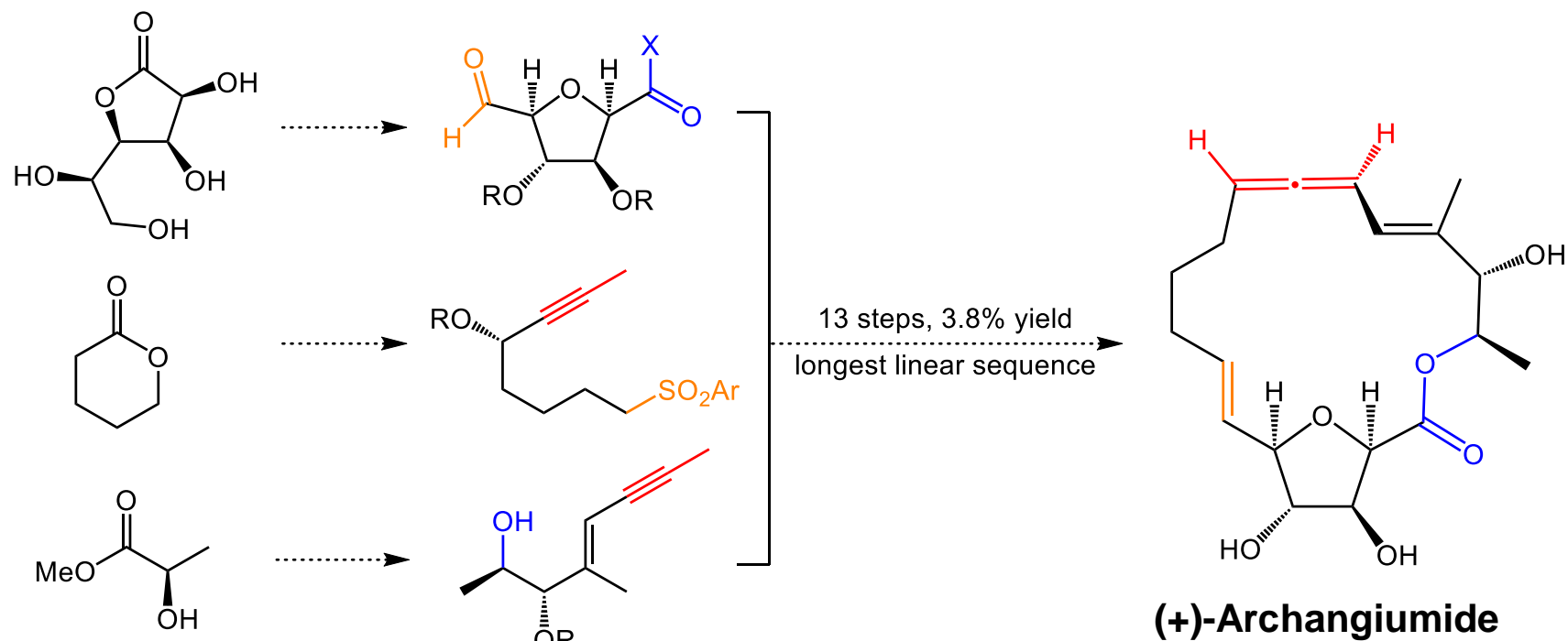
# Attempted Synthesis of (+)-Archangiumide



# Attempted Synthesis of 11-*epi*-1



# Summary



- The Modified Julia Olefination was Applied to Construct *trans* Olefin;
- A New Air-Stable Molybdenum Alkylidyne Catalyst for RCAM;
- The Construction of a Key Stereogenic Allene Using a Gold Catalyst.

# Writing Strategy

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## ➤ First Paragraph

Allenic Natural Products



Structure and Origin

- Allenic natural products are scarce overall, but examples comprising an allene as part of a macrocycle are exceedingly rare. **Only a single type of plant-derived germacranolide had been assigned such a substructure before the macrolide Archangiumide was disclosed in 2021.**
- **This unique polyketide incorporates a stereogenic allene in a 17-membered lactone, as rigorously proven by X-ray diffraction.** The myxobacterium *Archangium violaceum* SDU8 found to produce **1** was collected in Shandong province, China, and **had been singled out by combined genome mining and NMR-based metabolomic profiling as a potential source of secondary metabolites with little structural redundancy.**

# Writing Strategy

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## ➤ Last Paragraph

Synthesis Strategies



Summary

- This perplexing stereoconvergence compelled us to subject the acyclic substrate **27** (96% ee), derived from one of intermediates passed through during the preparation of the sulfone building block, to the same reaction conditions. In this case, the resulting allene **28** was racemic, **which shows that the gold catalyzed reaction per se is stereoablative and does not transmit stereochemical information from the propargyl benzyl ether center to the incipient chiral axis of the resulting allene.**
- **The fact that Archangiumide was obtained as a single diastereomer, independent of whether **23** or 11-epi-**23** was used as the substrate, is therefore attributed to thermodynamic control;** it is the macrobicyclic framework decorated with six stereogenic centers and two E-alkenes that determines the stereochemical course. This conclusion may even bear implications for the biosynthesis of the natural product

# Representative Examples

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- Sulfone **11** **was secured by** (由...获得) addition of propynyllithium to  $\delta$ -valerolactone in THF at low temperature to give the corresponding alkynylketone, which was isolated only after silylation of the primary -OH group. (**secure v.** 使安全; 经过努力获得; 做担保, **adj.** 安全的, 可靠的)
- This **unorthodox** orchestration arguably marks an underappreciated opportunity provided by  $\pi$ -acid catalysis. (**adj.** 非正统的, 非传统的)
- If so, and **under the proviso that** (在...条件下) the epimeric allene is not an as yet undiscovered discrete natural product, three scenarios can be envisaged. (**proviso n.** 附加条款)

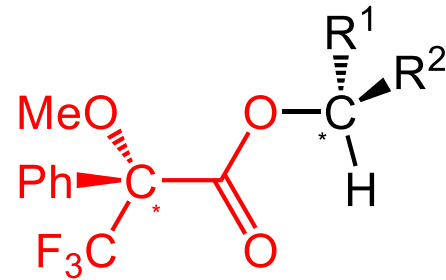
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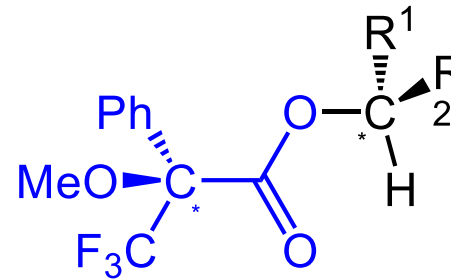
***Thank You for Your Attention!***

# Mosher

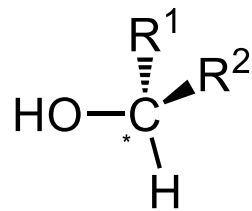
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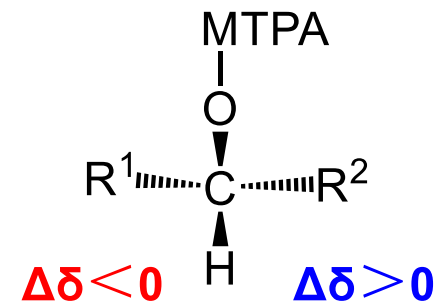
(*R*)-MPTA derivative



(*S*)-MPTA derivative



Chiral secondary alcohol





# Julia olefination

