

# Literature Report 5

## Total Synthesis of Ileabethoxazole, Pseudopteroxazole, and seco-Pseudopteroxazole

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**Checker: Lei Shi**

**Date: 2016-04-12**

**Li, A. et al.**

*Angew. Chem. Int. Ed.* **2016**, *55*, 2851.



Shanghai Institute of  
Organic Chemistry

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# Introduction

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## Ang Li

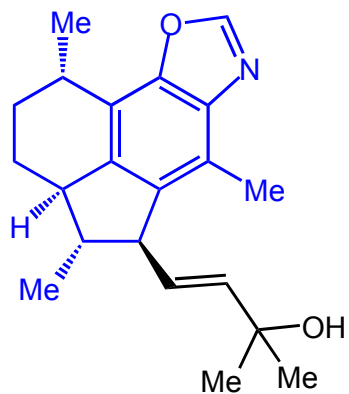
- 2000 – 2004      B.S., **Peking University**, Beijing, China  
Advisor: Prof. Zhen Yang
- 2004 – 2009      Ph.D., **The Scripps Research Institute**, California, USA  
Advisor: Prof. K. C. Nicolaou
- 2010              Research fellow, **Institute of Chemical and Engineering  
Sciences**, Singapore  
Advisor: Prof. K. C. Nicolaou
- 2010 – present    Professor, **Shanghai Institute of Organic Chemistry**, China

### Research Interests:

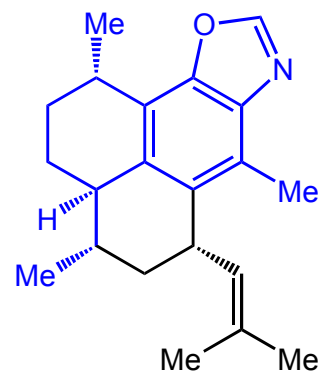
Total synthesis of structurally and biologically interesting natural products

# Introduction

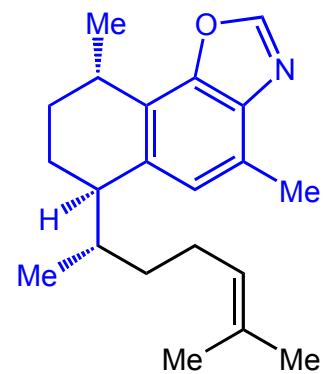
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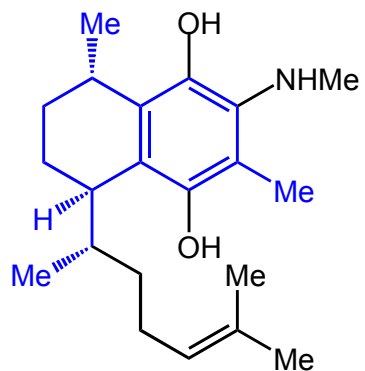
ileabethoxazole



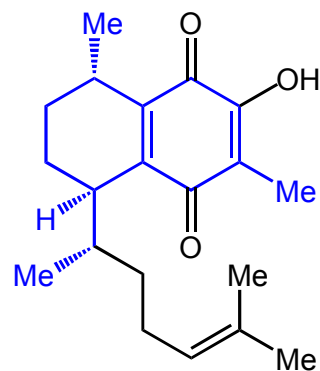
pseudopteroxazole



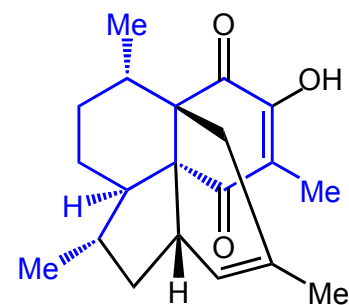
seco-pseudopteroxazole



elisabelthamine



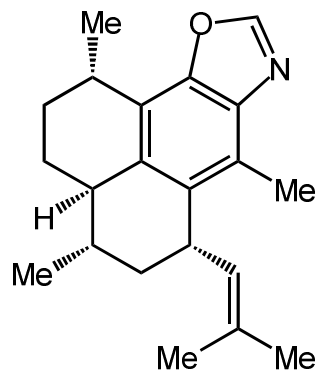
elisabelthadione



colombiasin A

## Introduction

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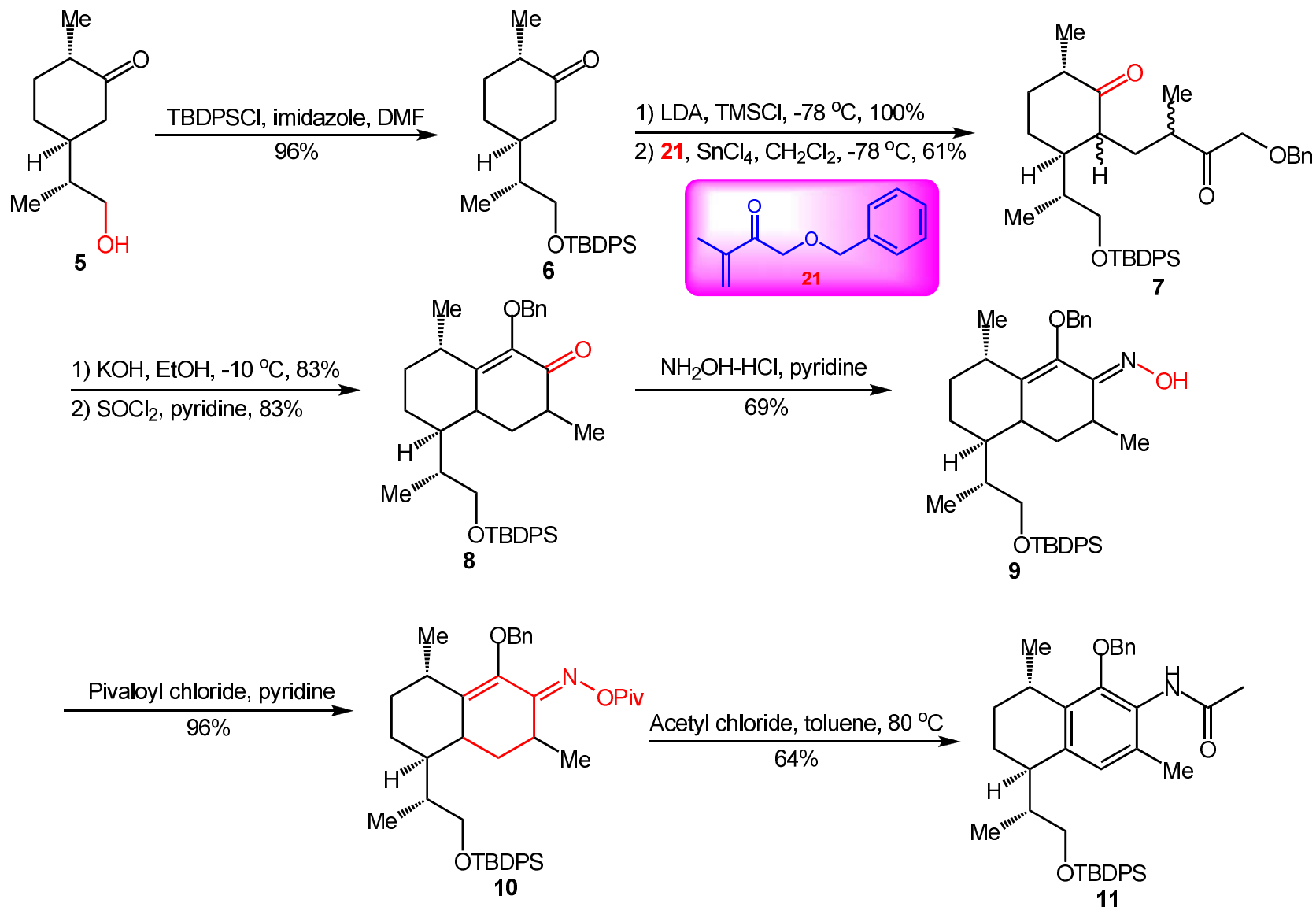
pseudopteroxazole



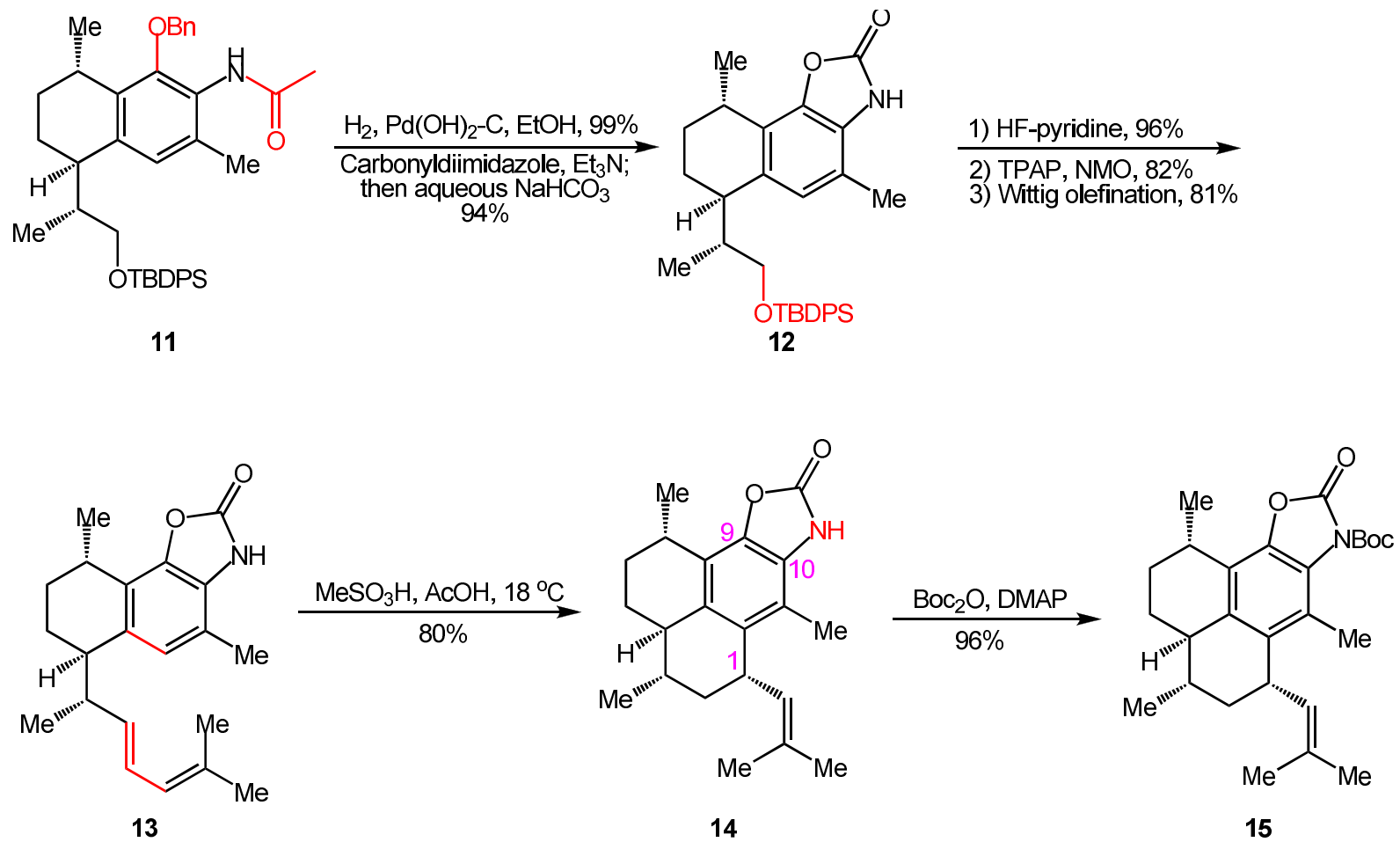
Pseudopterogorgia elisabethae  
(柳珊瑚)

- ◆ Isolated from *Pseudopterogorgia elisabethae* by Rodriguez's group in 1999
- ◆ Displaying promising inhibitory activity against *Mycobacterium tuberculosis*
- ◆ Belongs to a diverse diterpenoid family

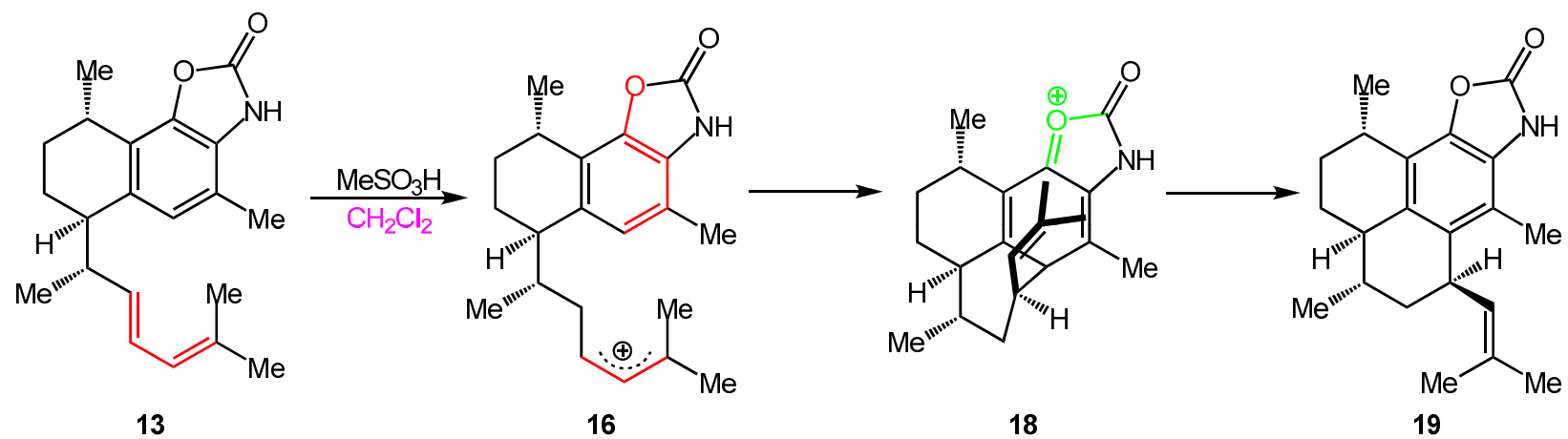
# Enantiospecific Total Synthesis of Pseudopteroxazole



# Enantiospecific Total Synthesis of Pseudopteroxazole

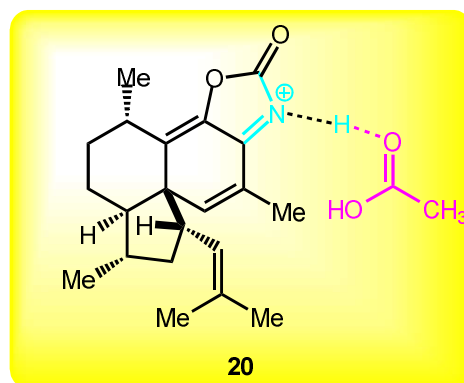
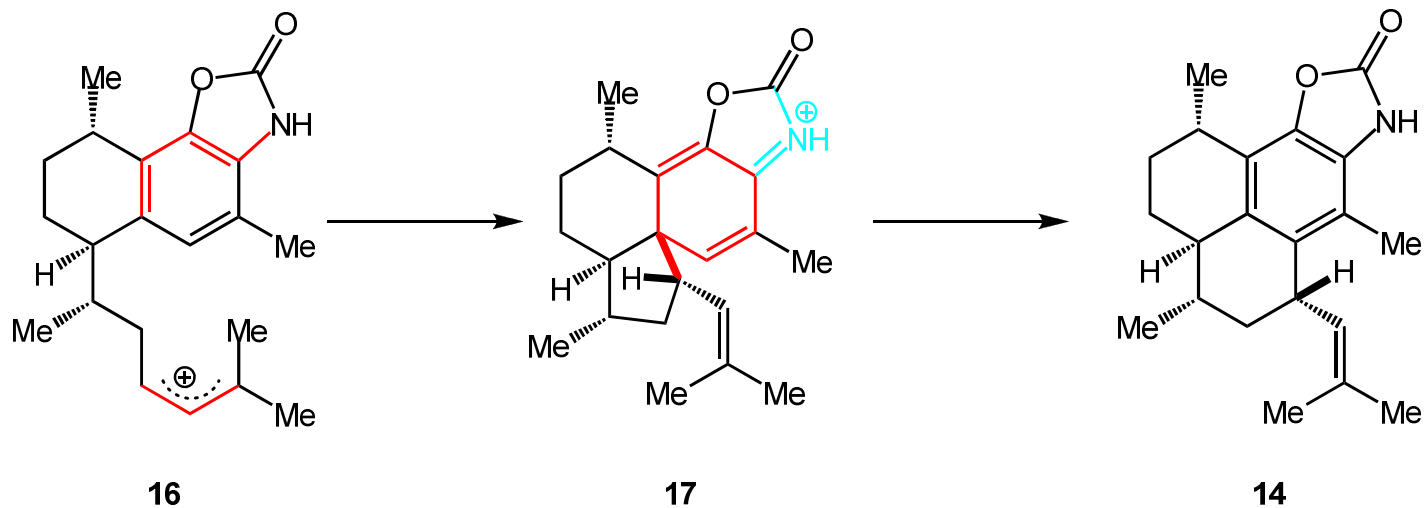


## CH<sub>2</sub>Cl<sub>2</sub> as Solvent

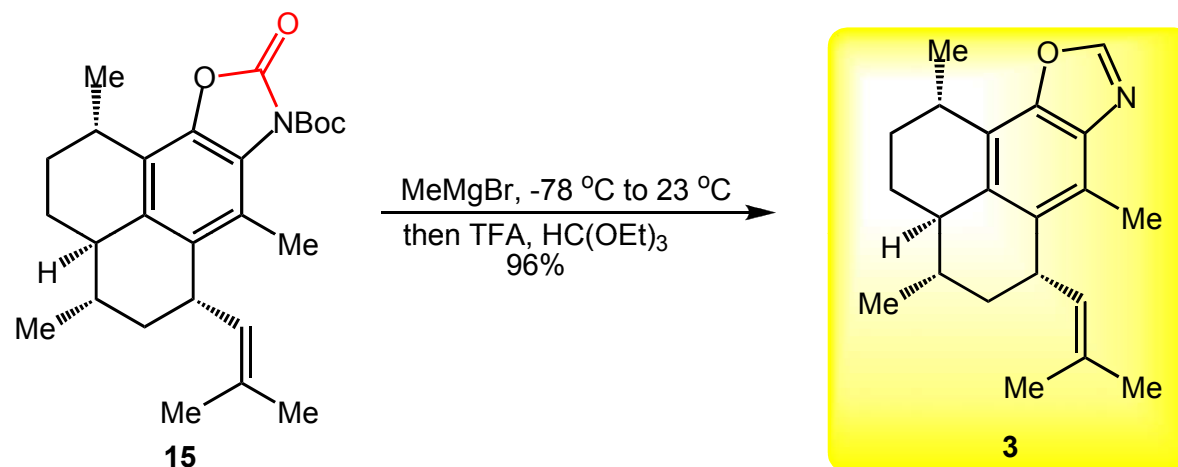




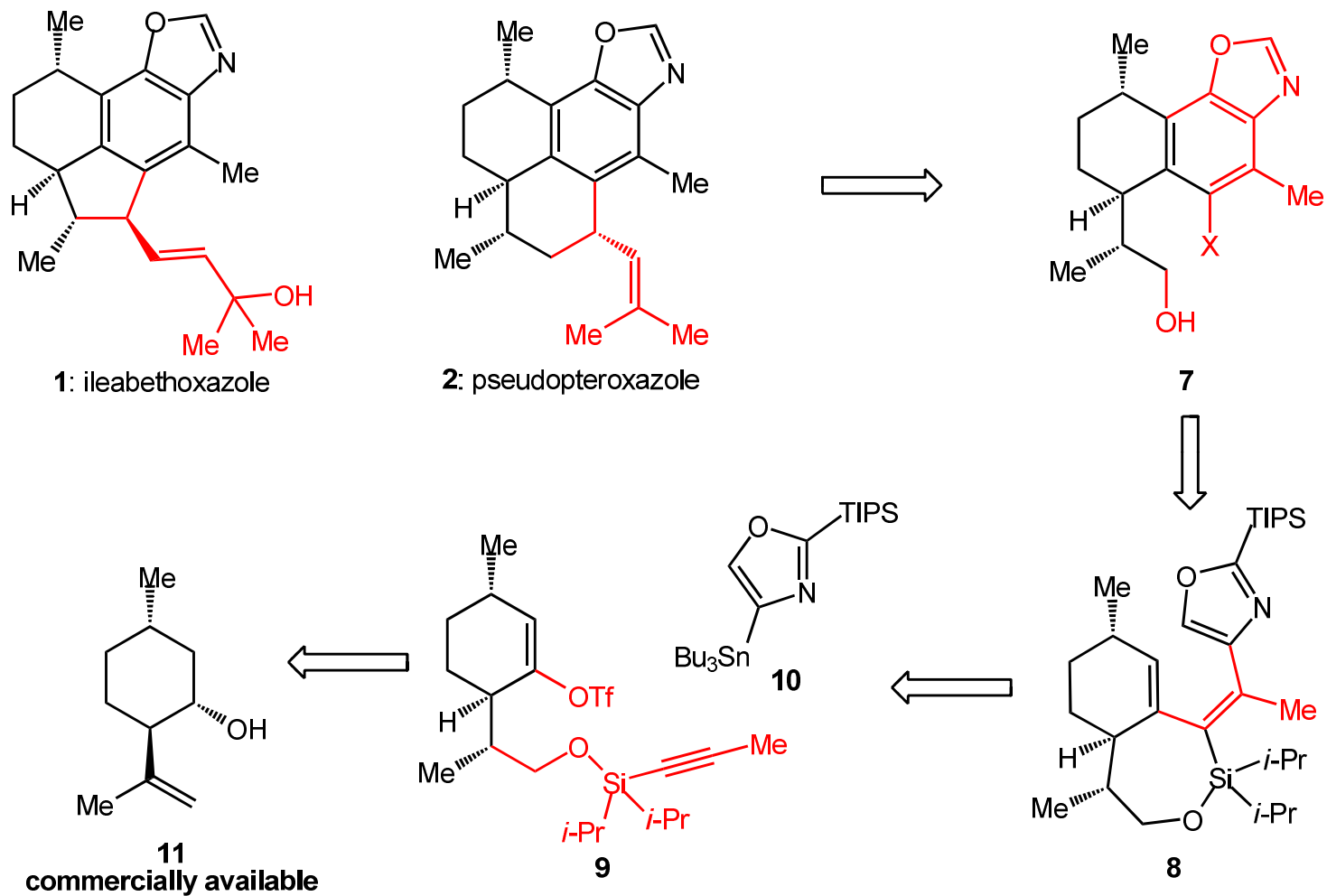
## Acetic Acid as Solvent



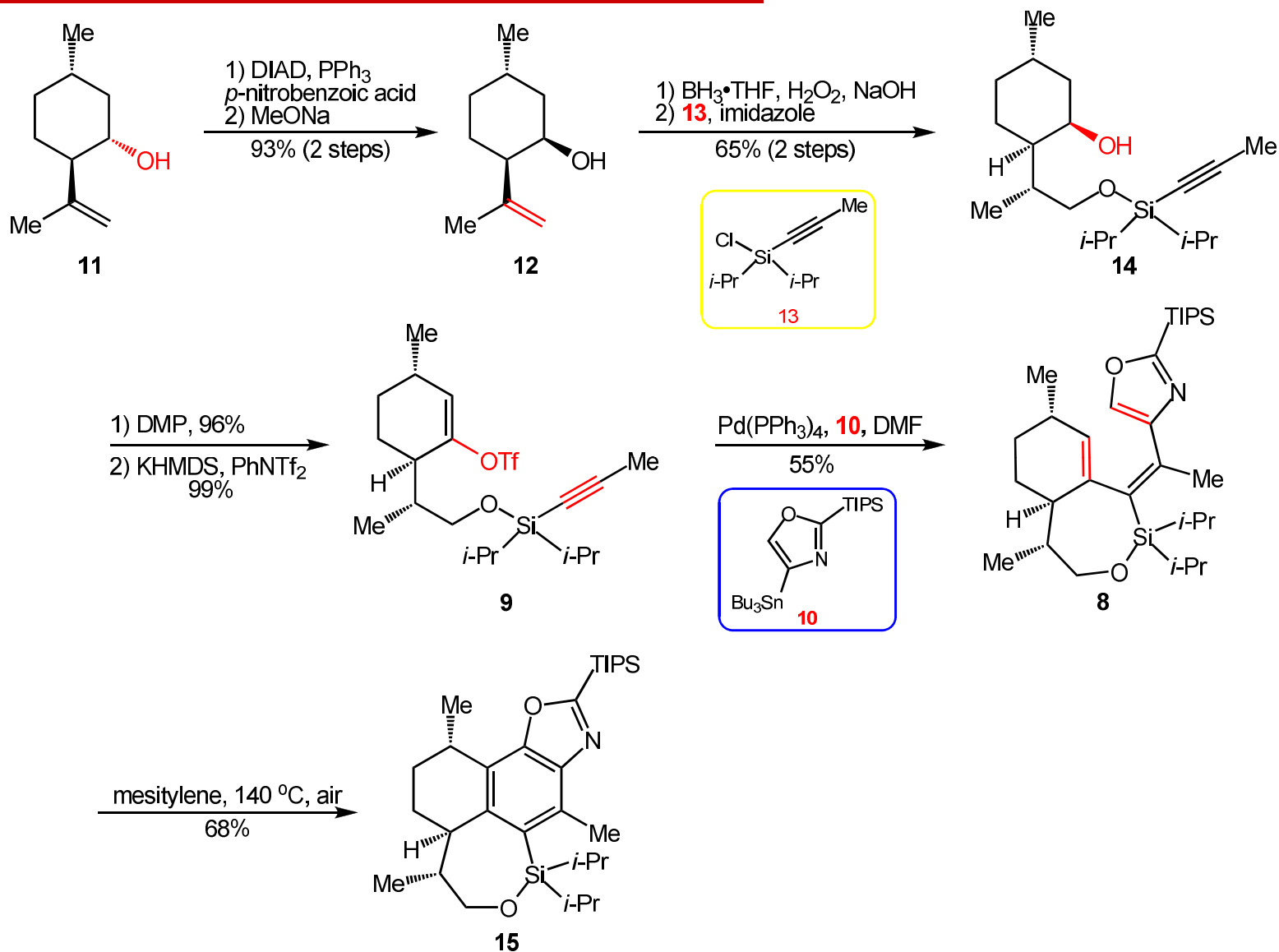
# Enantiospecific Total Synthesis of Pseudopteroxazole



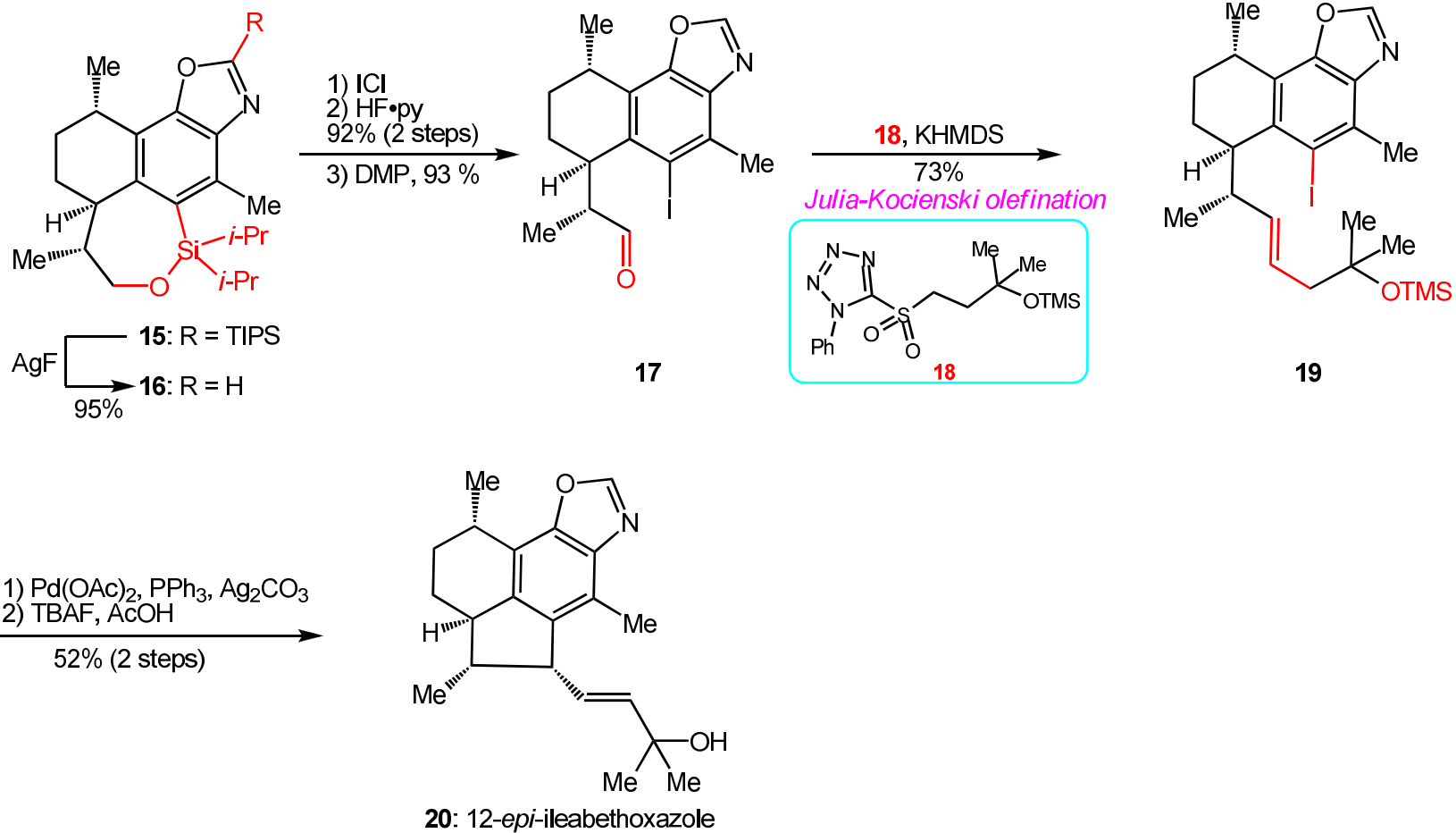
# Retrosynthesis of Ileabethoxazole, Pseudopteroxazole



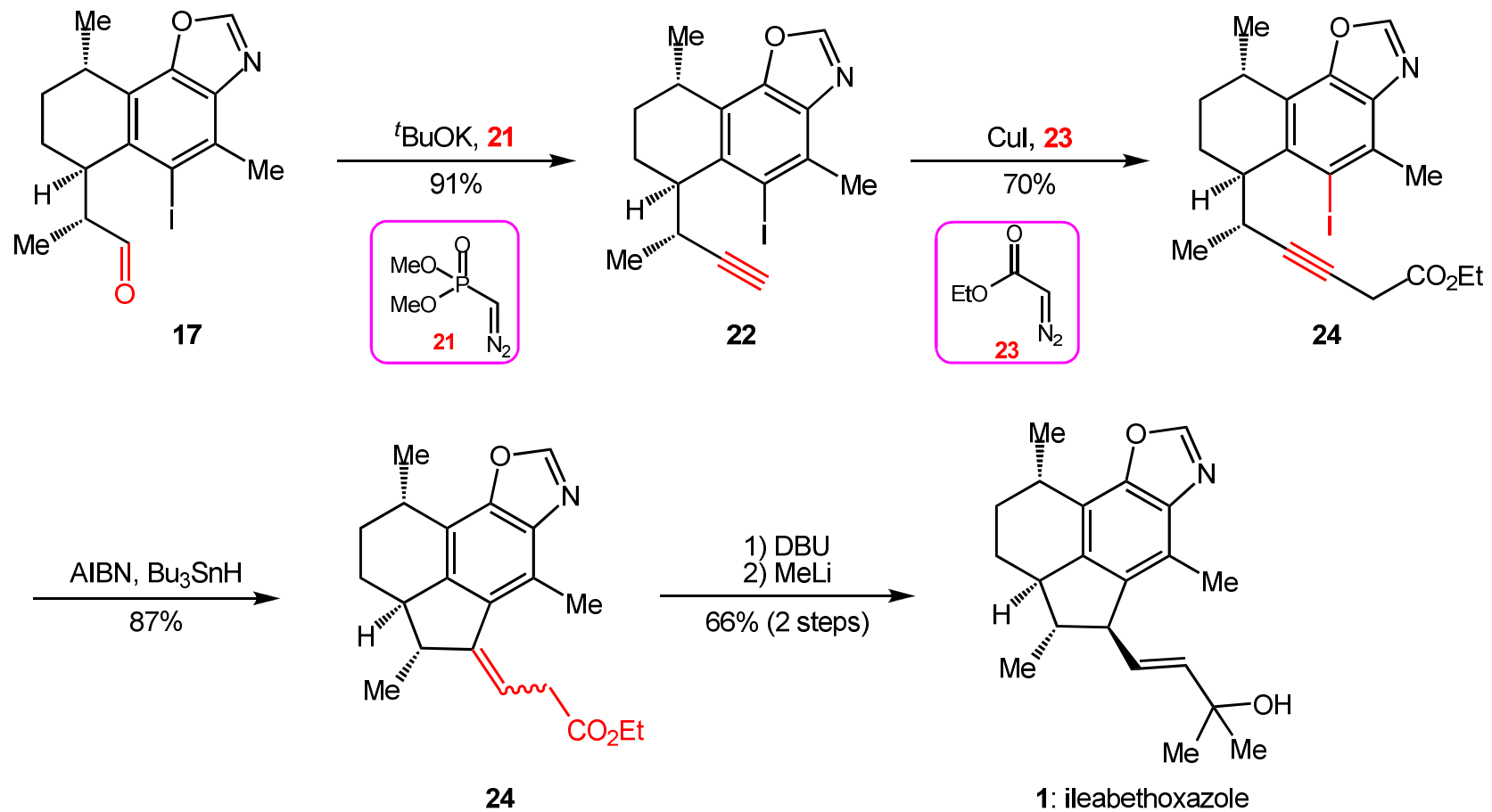
# Total Synthesis of Ileabethoxazole



# Total Synthesis of Ileabethoxazole

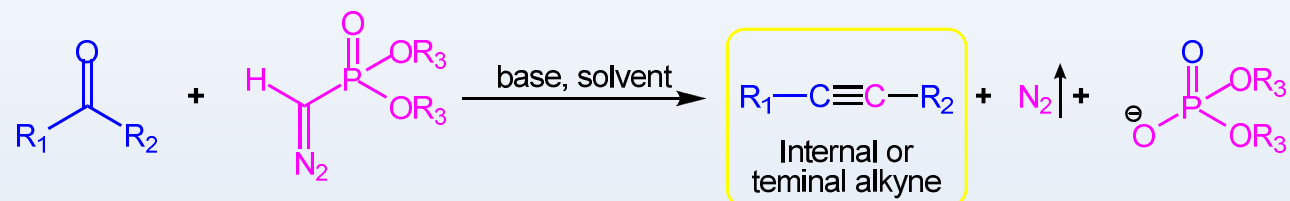


# Total Synthesis of Ileabethoxazole

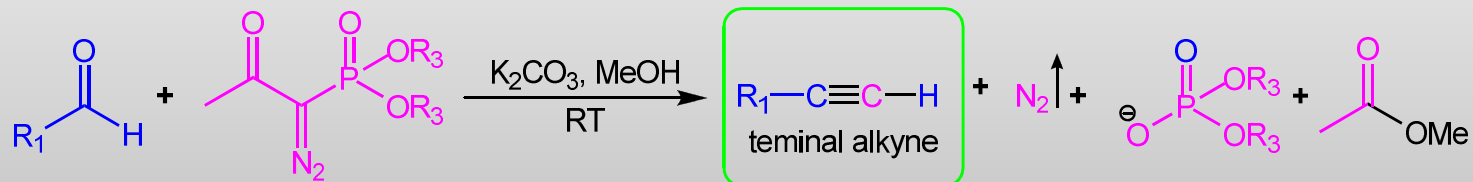


# Seyferth–Gilbert Homologation Reaction

## Seyferth-Gilbert homologation

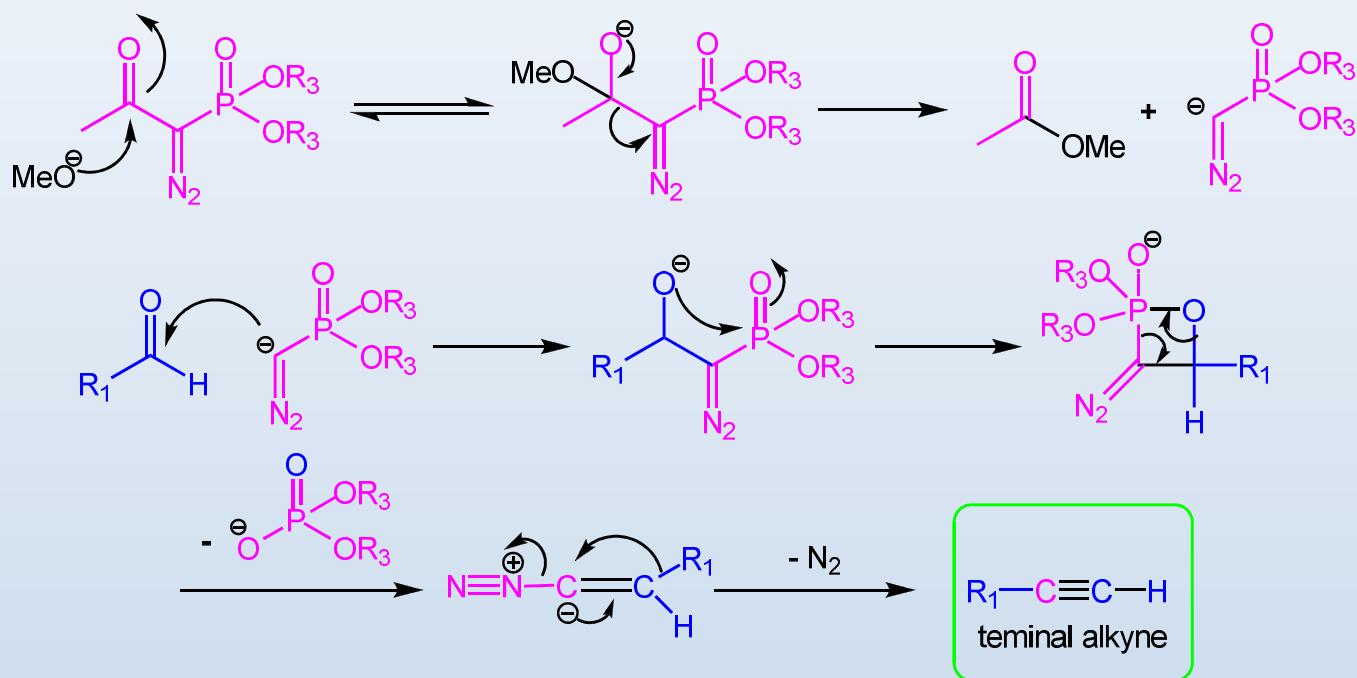


## Modification for the synthesis of terminal alkynes (Ohira and Bestmann)



# Seyferth–Gilbert Homologation Reaction

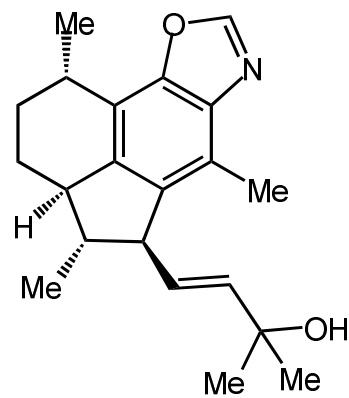
Mechanism: <sup>a</sup>



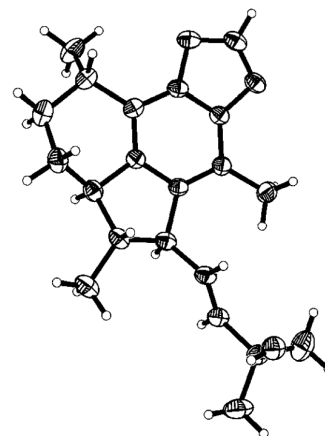


# Total Synthesis of Ileabethoxazole

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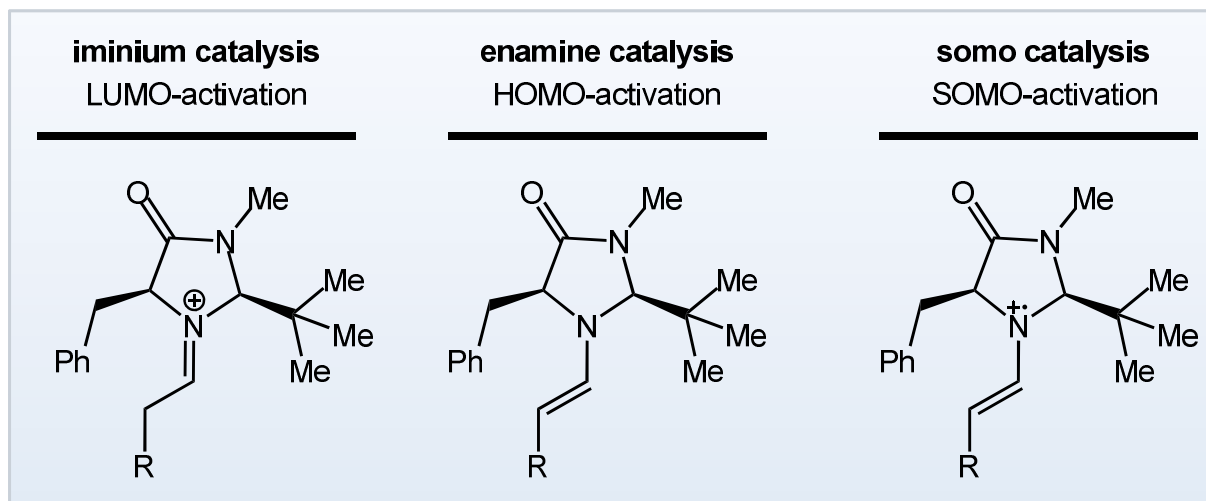
1: ileabethoxazole



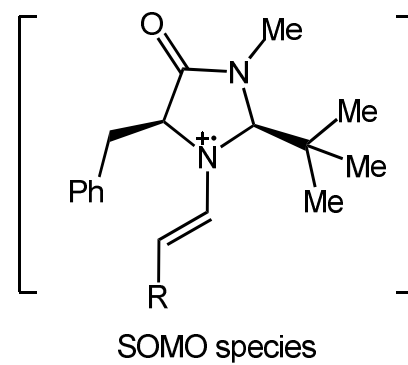
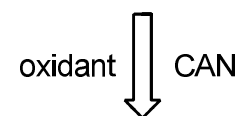
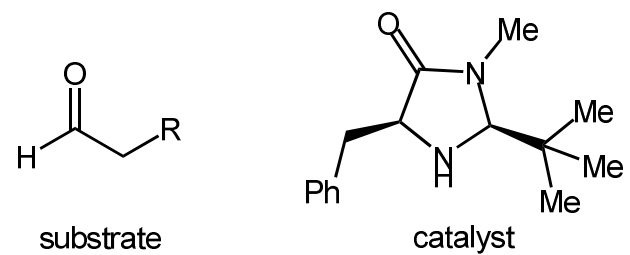


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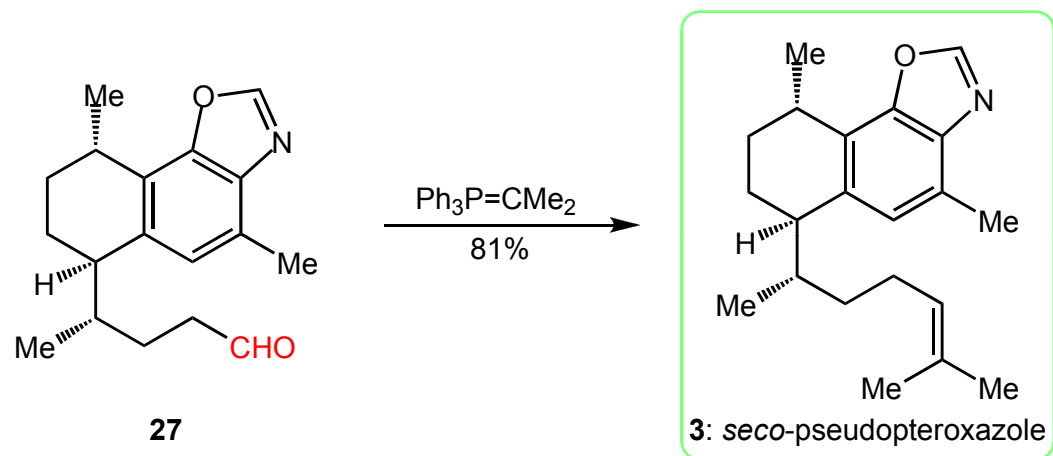
## Three modes of MacMillan catalyst



**SOMO** (Singly Occupied Molecular Orbital) **catalysis** was developed to allow for  $\pi$ -neutral or  $\pi$ -rich nucleophiles to add to the three- $\pi$  electron radical cation species at the now electrophilic  $\alpha$ -position of an aldehyde.

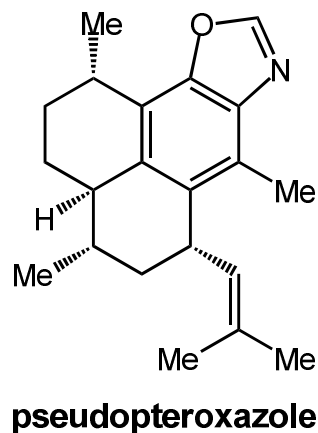


# Total Synthesis of *seco*-Pseudopteroxazole



## Summary

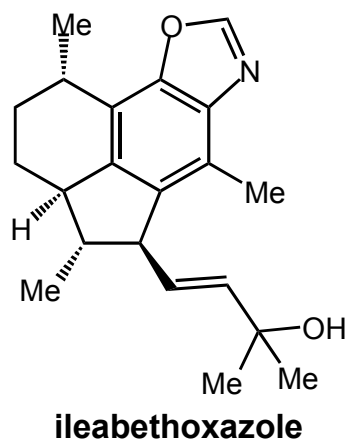
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- ◆ First enantiospecific total synthesis of Pseudopteroxazole.
- ◆ Stereocontrolled cyclization to form compound 14 diastereoselectively.

Corey, E. J. et al *J. Am. Chem. Soc.* **2003**, *125*, 13486.

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- ◆ A cascade alkyne carbopalladation/Stille reaction to construct a triene precursor.
- ◆ One-pot  $6\pi$  electrocyclization/aromatization.

Li, A. et al *Angew. Chem. Int. Ed.* **2016**, *55*, 2851.

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Tuberculosis (TB) has long been a severe threat to human health. In recent years, the rapid increase in multidrug-resistant and extensively drug-resistant TB infections and TB/ HIV co-infection raises the demand for more effective chemotherapeutics. Natural products provide an unparalleled source of lead compounds for *anti*-TB drug development. Ileabethoxazole, pseudopteroxazole, and seco-pseudopteroxazole are benzoxazole alkaloids that were isolated by Rodriguez and co-workers from the Caribbean sea whip *Pseudopterogorgia elisabethae* and display promising inhibitory activity against *Mycobacterium tuberculosis*. From structural and biosynthetic perspectives, these molecules belong to a large and diverse diterpenoid family isolated from the same species, and some of their congeners are shown in Figure 1. Notably, a significant number of the family members possess multisubstituted aromatic cores, which enhances the difficulty of their chemical synthesis.

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In summary, we have accomplished the total syntheses of ileabethoxazole, pseudopteroxazole, and *seco*-pseudopteroxazole (**1–3**) in a collective manner. The key step was a one-pot 6  $\pi$  electrocyclization/aromatization sequence, which efficiently constructed the multisubstituted arene scaffold from a geometry-defined hexasubstituted triene. This work provides a versatile synthetic approach to analogues of benzoxazole diterpenoids and may facilitate their biological studies.