

# Literature Report 6

## 11-Step Total Synthesis of Pallambins C and D

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**Baran, P. S. et al**  
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The Scripps Research Institute

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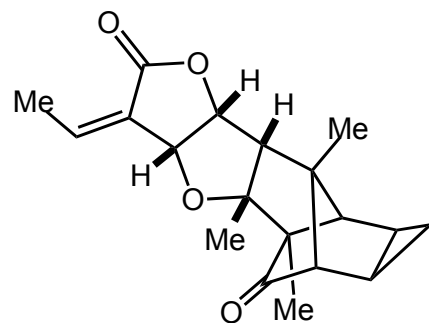
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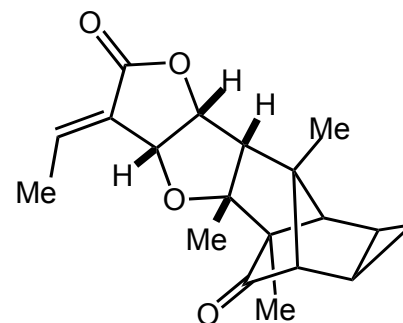
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# Introduction

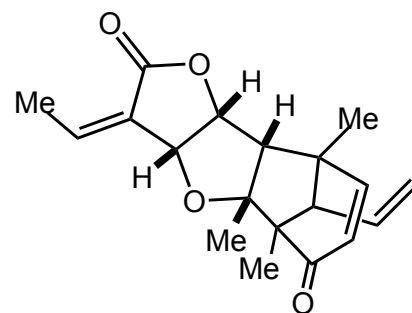
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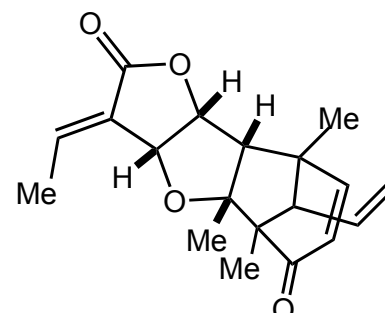
pallambin A



pallambin B

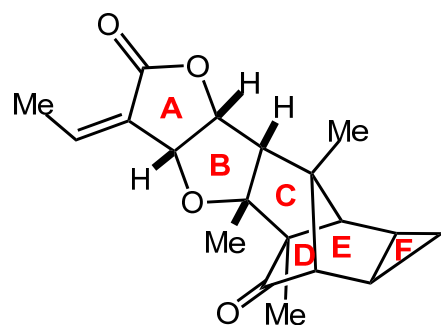


pallambin C

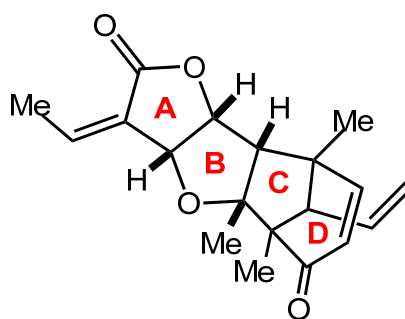


pallambin D

## Introduction



pallambin A



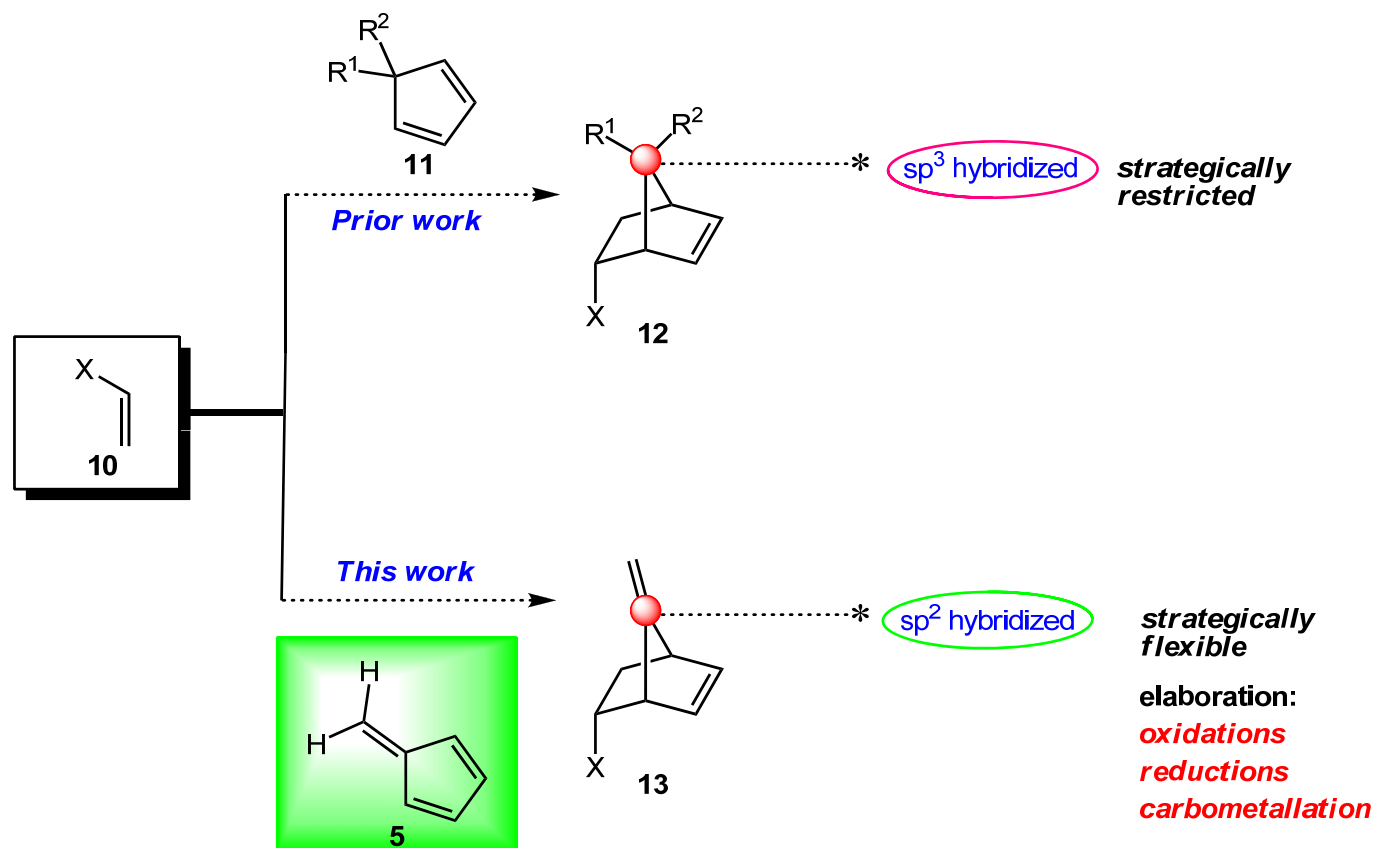
pallambin C



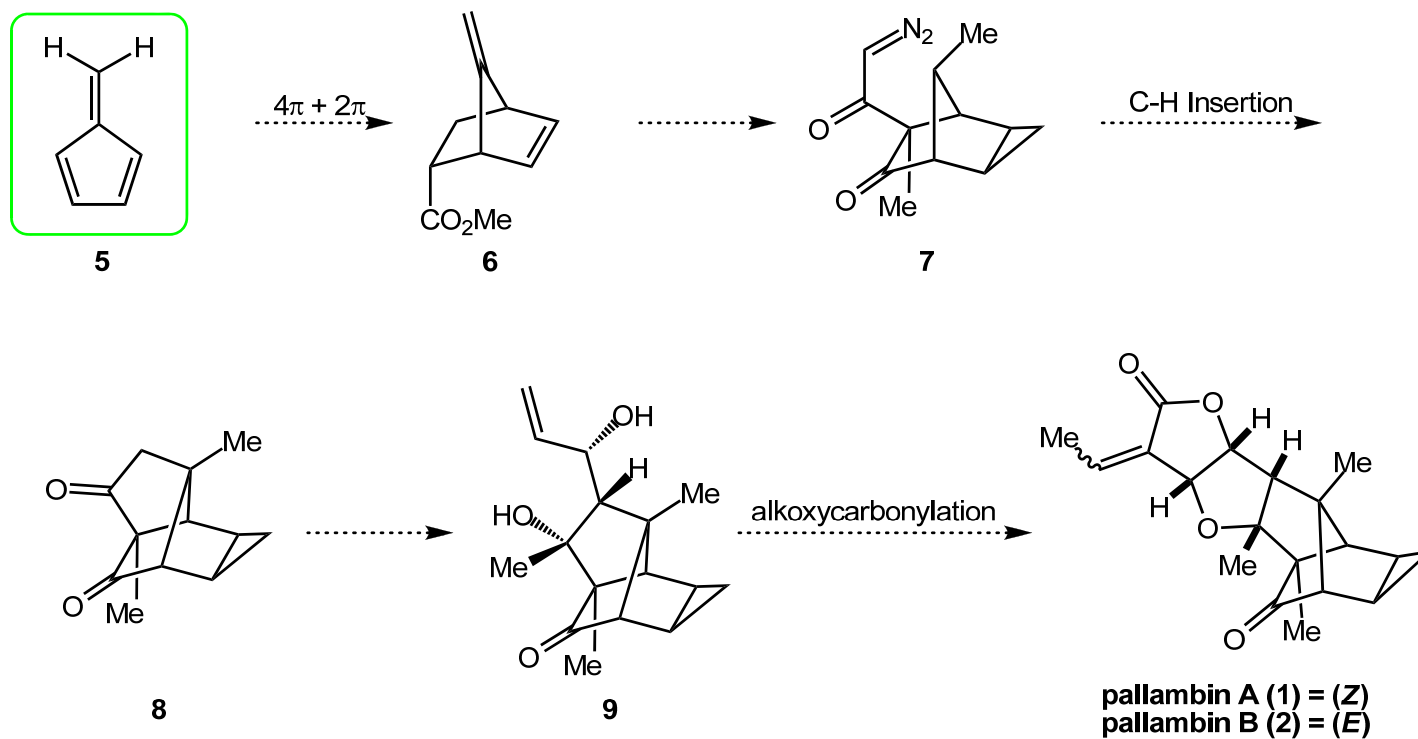
*Pallavicinia ambigua*  
(多形带叶苔)

- ◆ Pallambin A and pallambin B were isolated from extracts of the liverwort *Pallavicinia ambigua* by Lou group in 2012 .
- ◆ 4–6 rings, 7–10 contiguous stereocenters, and 2 quaternary stereocenters .

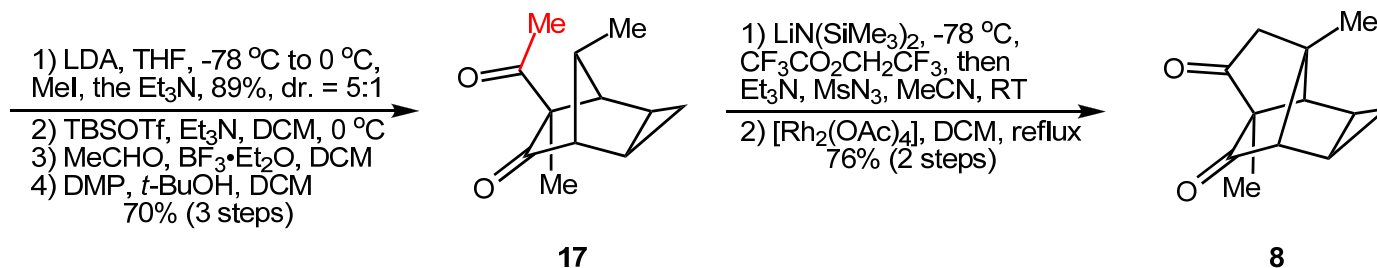
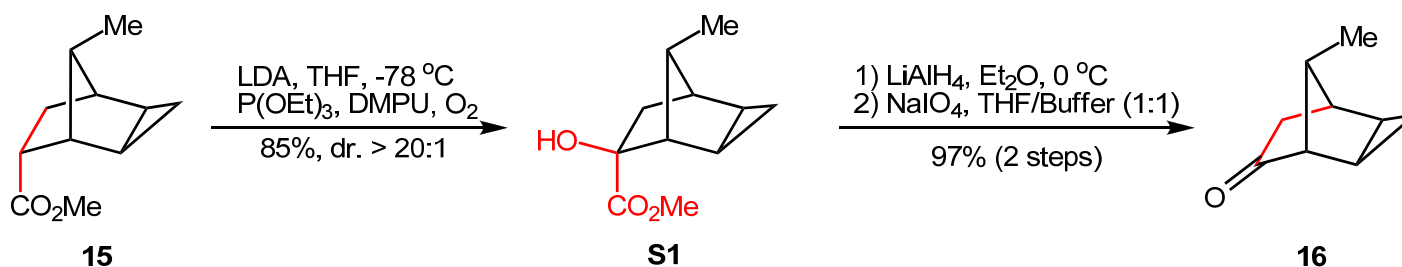
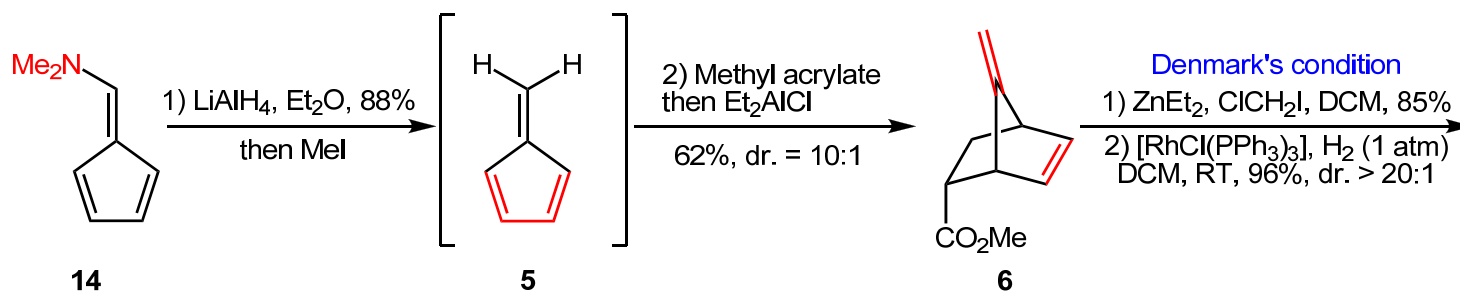
# Introduction



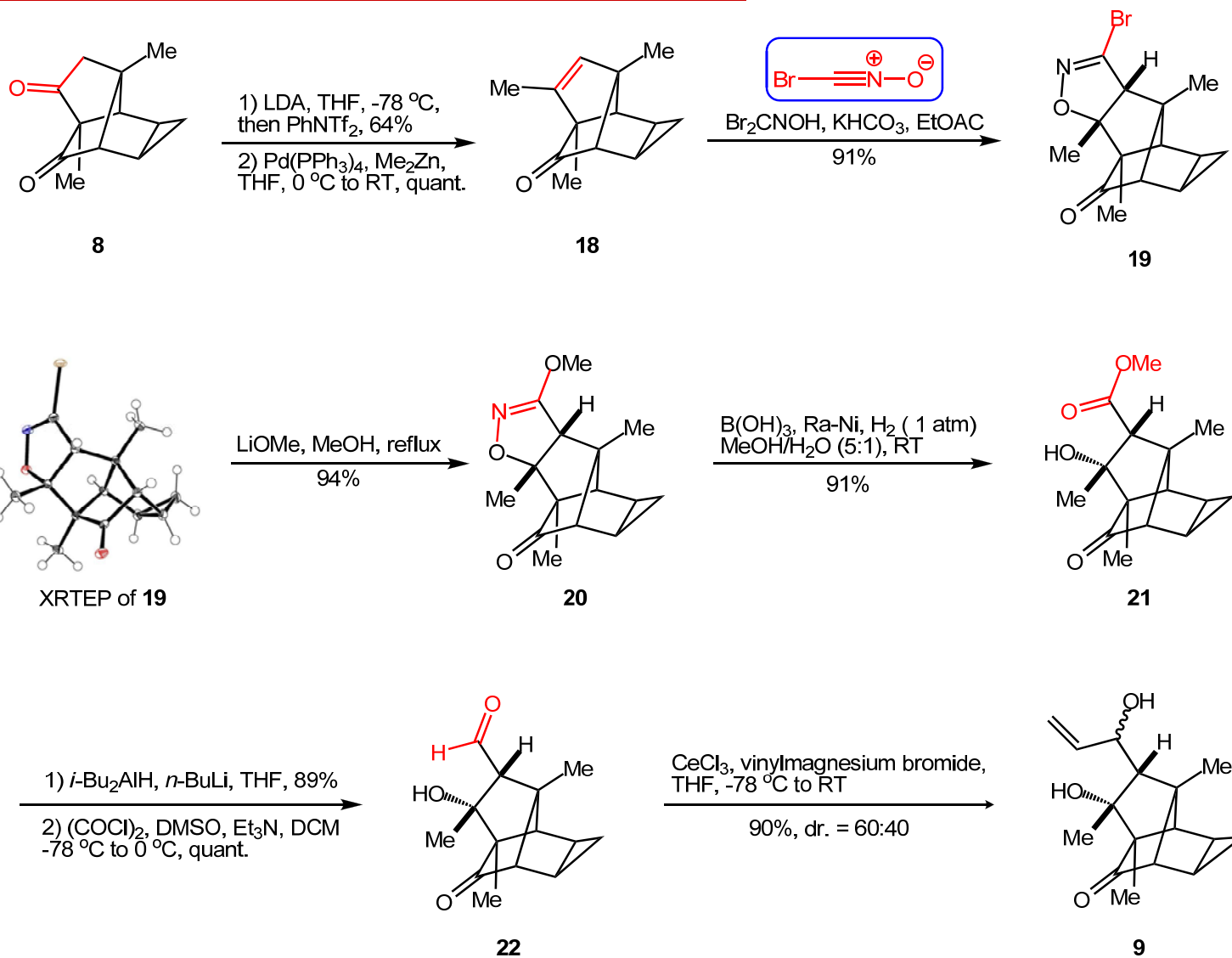
# Total synthesis of pallambins A and B by Carreira



# Total synthesis of pallambins A and B by Carreira

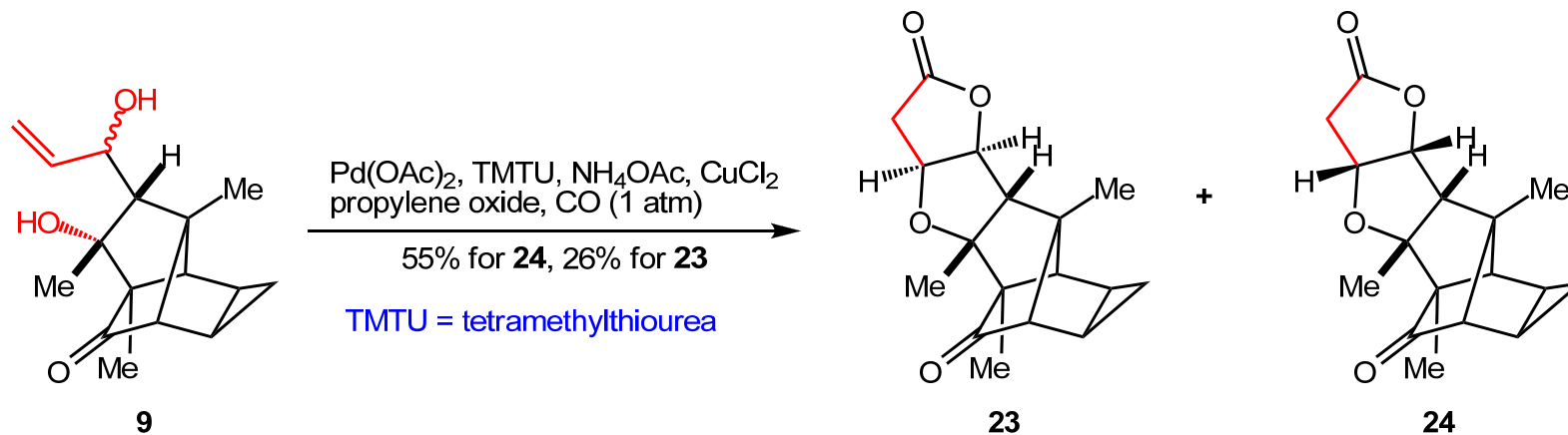


# Total synthesis of pallambins A and B by Carreira



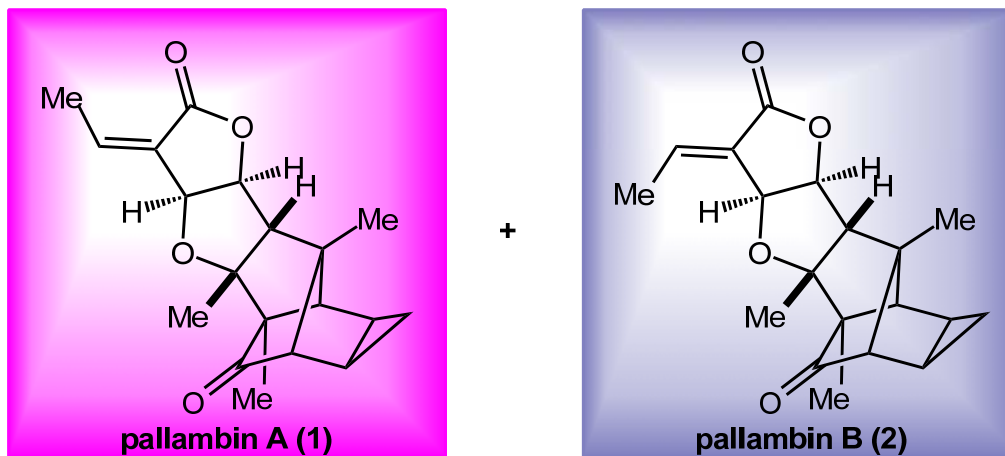


# Total synthesis of pallambins A and B by Carreira

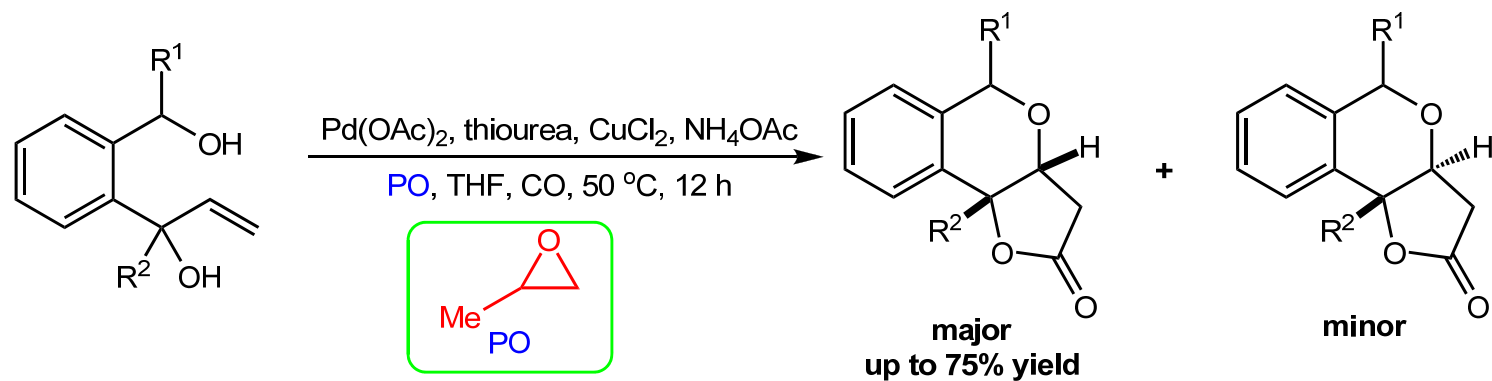


1). LDA, THF, -78 °C, then MeCHO, -78 °C to -40 °C  
2). Et<sub>3</sub>N, DMAP, MsCl

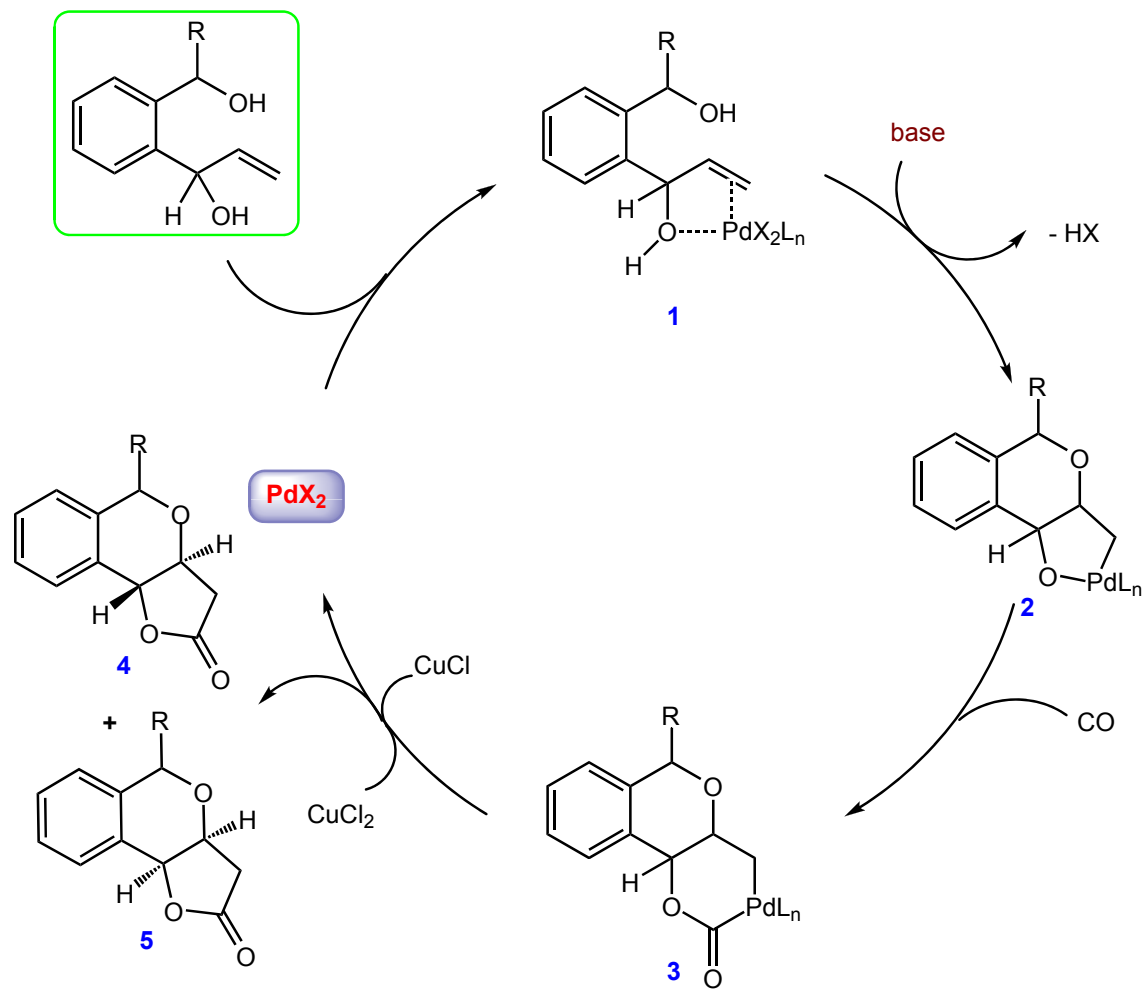
87% (pallambin B)  
11% (pallambin A)



# Pd/TMTU-catalyzed alkoxy carbonylative annulation

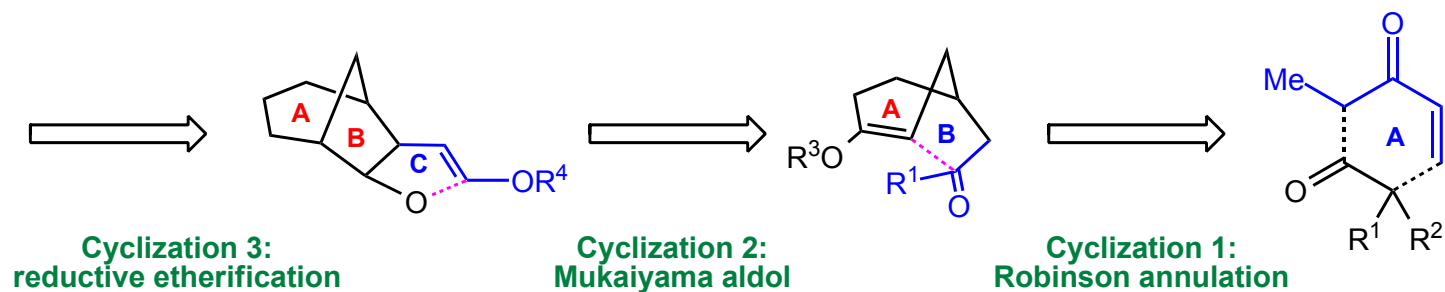
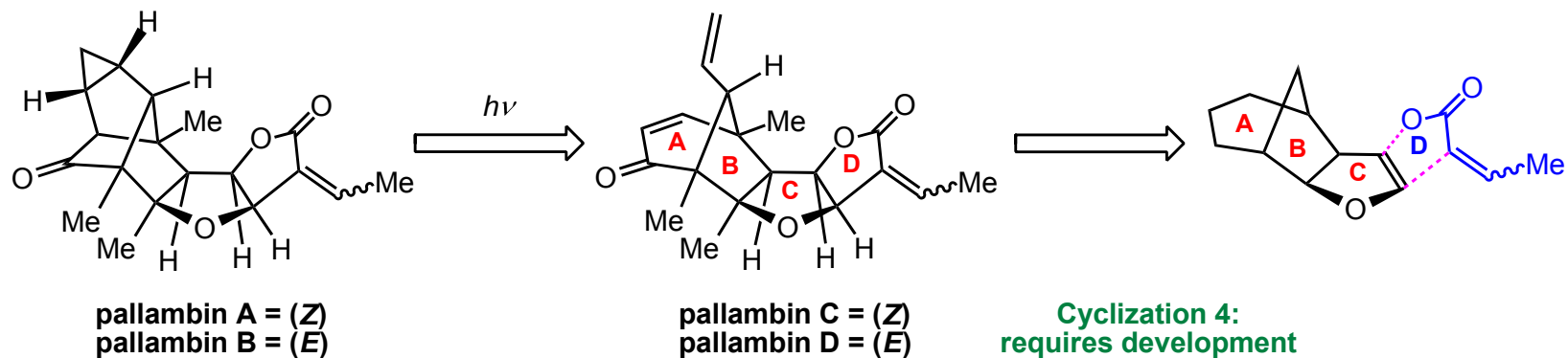


# Possible mechanistic pathways

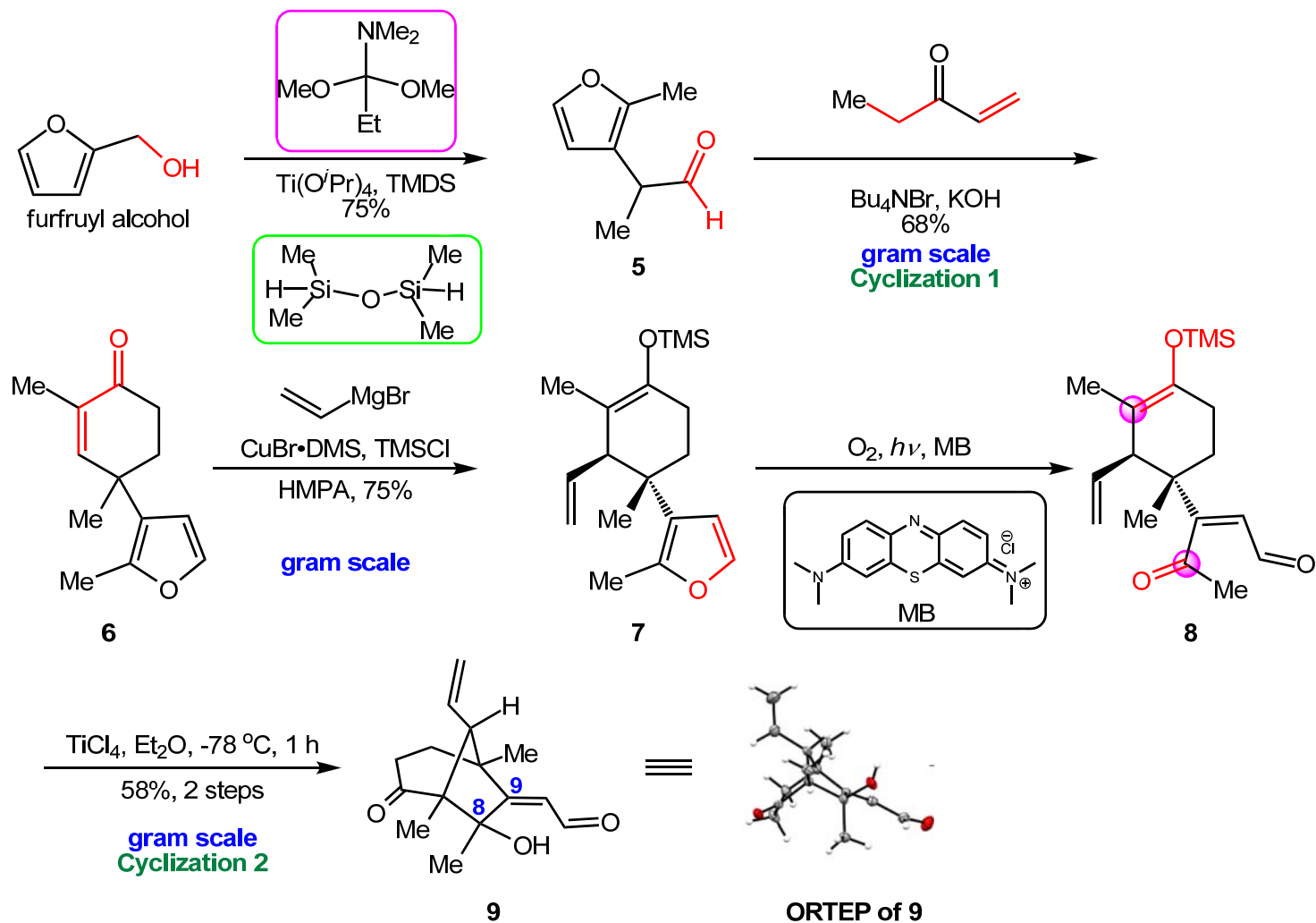


# Total synthesis of pallambins C and D by Baran

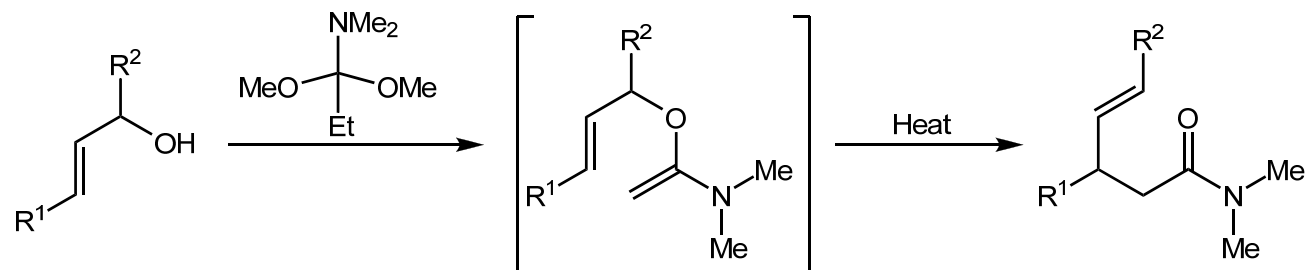
## Retrosynthetic analysis



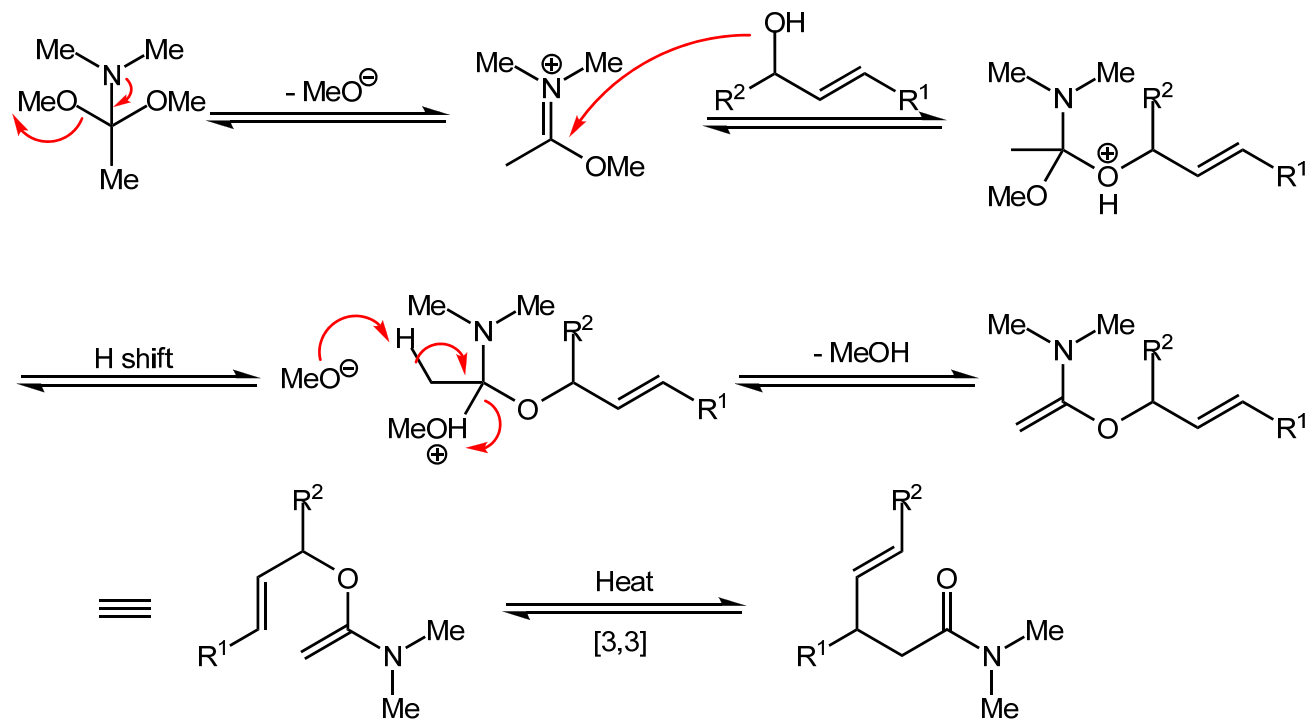
# Total synthesis of pallambins C and D by Baran



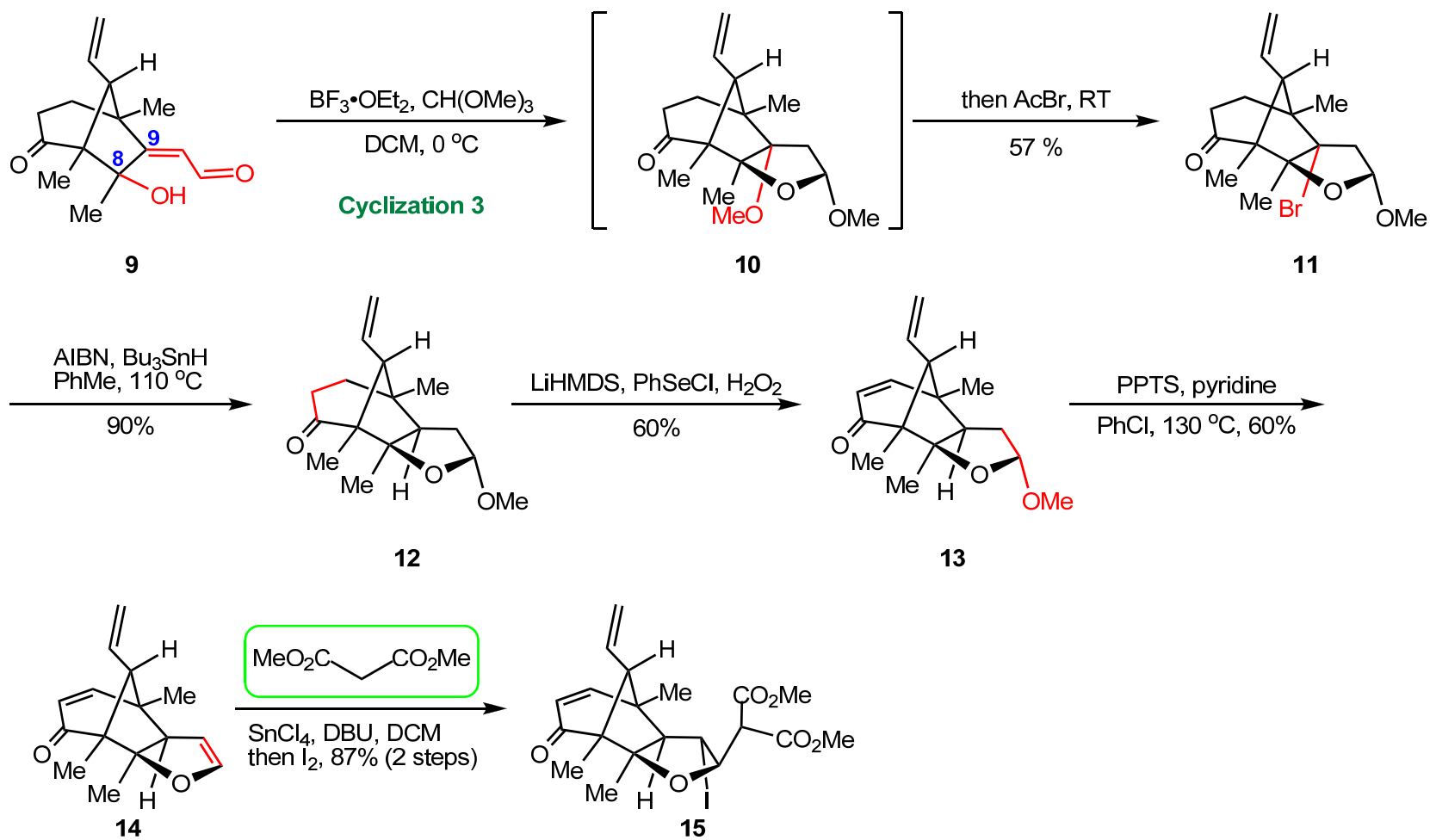
# Eschenmoser-Claisen rearrangement



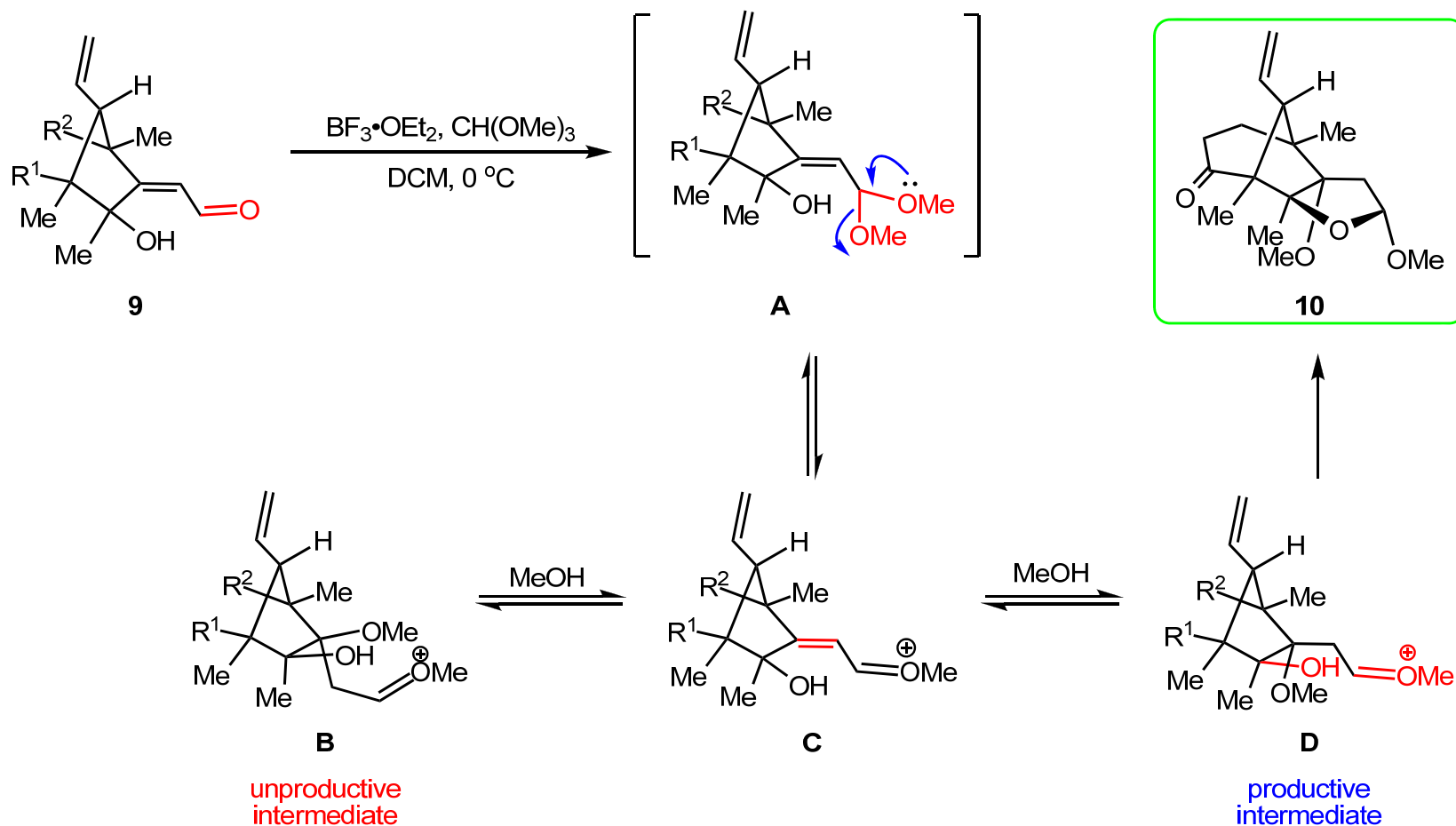
## Mechanism:



# Total synthesis of pallambins C and D by Baran

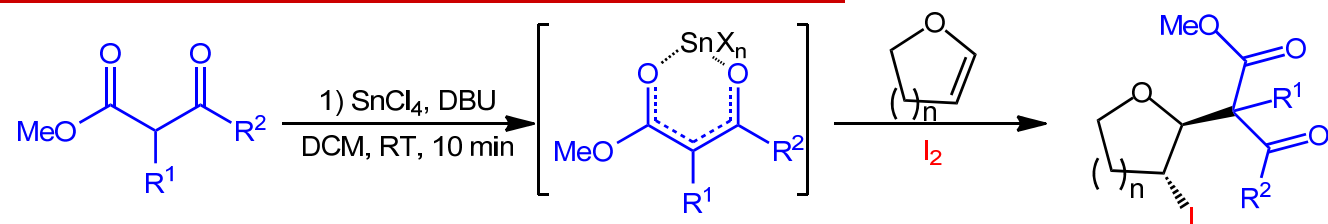


# A mechanistic model for C-ring formation

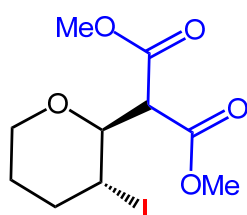




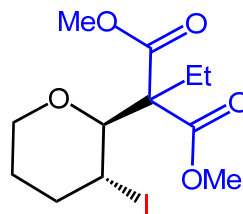
# Scope of the enol-ether difunctionalization reaction



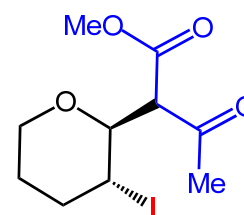
- ◆ enol ether difunctionalization
- ◆ quaternary centers
- ◆ cyclic or acyclic substrates



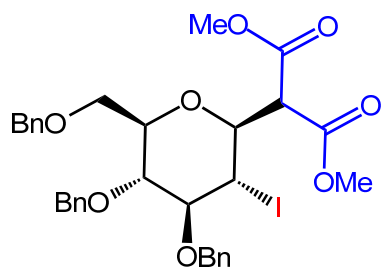
**16** (92%)



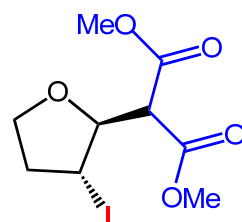
**17** (76%)



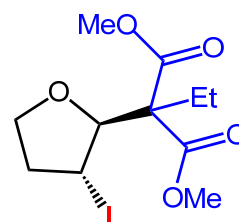
**18** (52%, dr. = 1:1)



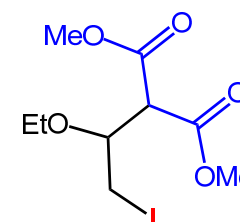
**19** (73%)



**20** (89%)

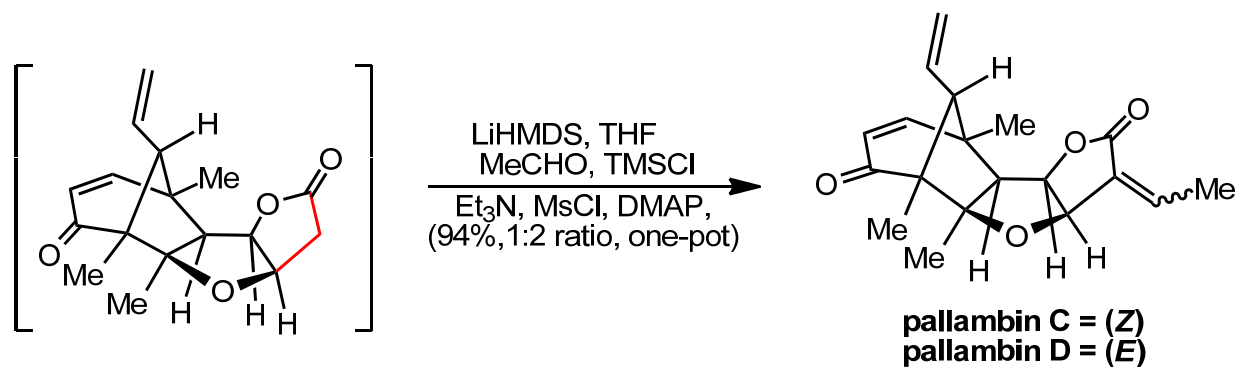
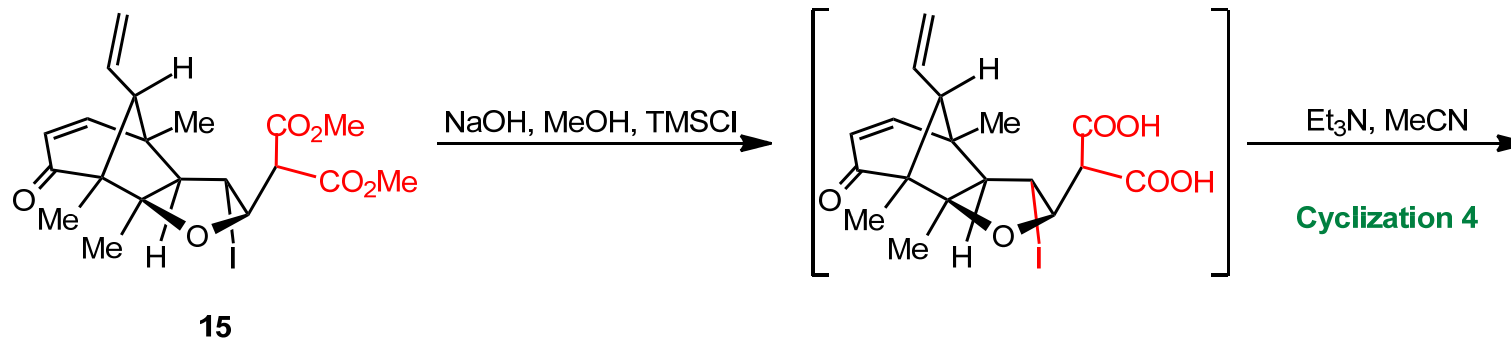


**21** (80%)



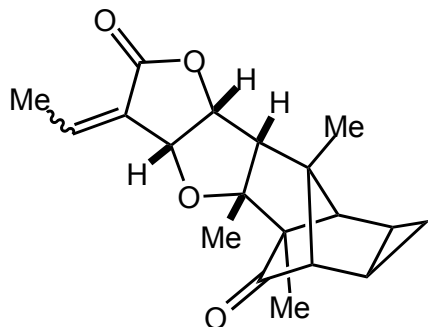
**22** (77%)

# Total synthesis of pallambins C and D by Baran



## Summary

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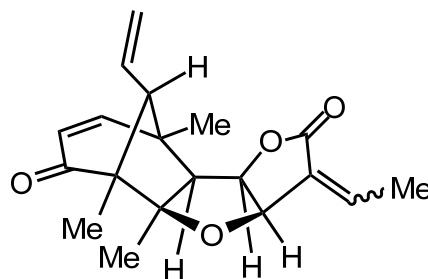


Pallambin A = (Z)  
Pallambin B = (E)

- ◆ The first total synthesis of pallambins A and B in 23 steps.
- ◆ Unprecedented Diels–Alder reaction by the use of pentafulvene.

Carreira, E. M. et al *Angew. Chem. Int. Ed.* **2015**, 54, 11227

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Pallambin C = (Z)  
Pallambin D = (E)

- ◆ Four sequential cyclizations.
- ◆ 11 steps route of synthesis pallambins C and D.

Baran, P. S. et al *J. Am. Chem. Soc.* **2016**, 138, 7536.

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Pallambins A-D isolated from the epilithic liverwort *Pallavicinia ambigua*, exhibit no significant bioactivity, and their sole justification for study in the laboratory rests on their extraordinary chemical architectures. Indeed, with 4–6 rings, 7–10 contiguous stereocenters, and 2 quaternary stereocenters, these challenging terpenoid isolates are an ideal proving ground for the development of unique strategies and methods. Two elegant approaches to the synthesis of pallambins have appeared, one from the Wong group and the other from the Carreira group. The former route furnished **3** and **4** in 38 steps from the Wieland-Miescher ketone, and the latter afforded **1** and **2** in 23 steps from a fulvene. Ongoing interest in simplifying the synthesis of complex natural products by eliminating concession steps inspired our route to the pallambins. Here, an 11-step route to **3** and **4** is documented, wherein 9 of the 11 steps are strategic and protecting group manipulations are absent.

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A concise synthesis of the pallambins has thus been achieved. The four key ring systems found in **3** and **4** were generated by employing four sequential cyclizations, two of which are precedented and two of which required development. This design originated from a desire to eliminate extraneous redox-manipulations, functional group interconversions, and protecting group manipulations. In fact, of the 11 discrete steps of this synthesis, only two are nonstrategic (steps 7 and 9), making it 81% ideal.

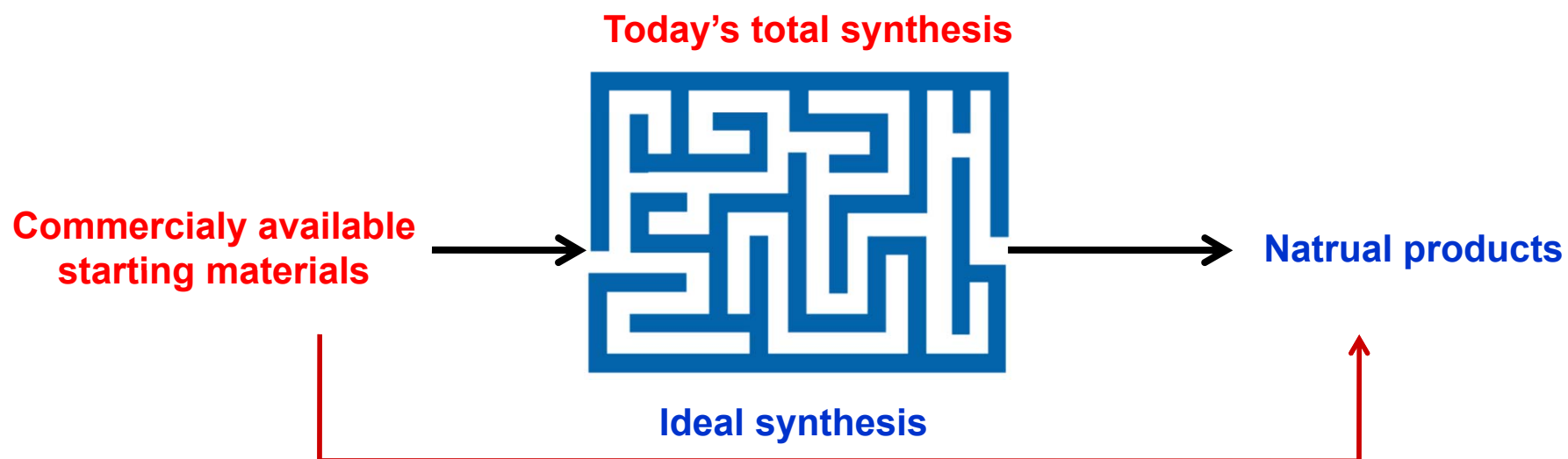
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## Evaluate three specific metrics

overall yield

step count

percent ideality



# Ideal Synthesis

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$$\% \text{ ideality} = \frac{(\text{No. of construction reactions}) + (\text{No. of strategic redox reactions})}{(\text{total No. of construction reactions})}$$

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**Construction reactions**, as defined by Hendrickson, are those which form skeletal bonds (C-C and C-heteroatom).

**Strategic redox reactions** have been previously defined as those that directly establish the correct functionality found in the final product, such as asymmetric oxidations and reductions or C-H oxidations.

## Ideal Synthesis

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$$\% \text{ ideality} = \frac{(\text{No. of construction reactions}) + (\text{No. of strategic redox reactions})}{(\text{total No. of construction reactions})} \times 100\%$$

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All other types of reactions fall into the category of a concession step:

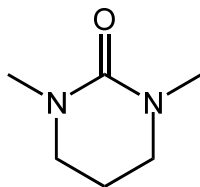
- (1) Nonstrategic redox manipulations (i.e., reduction of ester to alcohol);
- (2) Functional group interconversions (i.e., alcohol to mesylate to azide);
- (3) Protecting group manipulations.

$$\% \text{ ideality} = \frac{9}{11} \times 100\% = 81.8\%$$



# Abbreviations

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DMPU

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