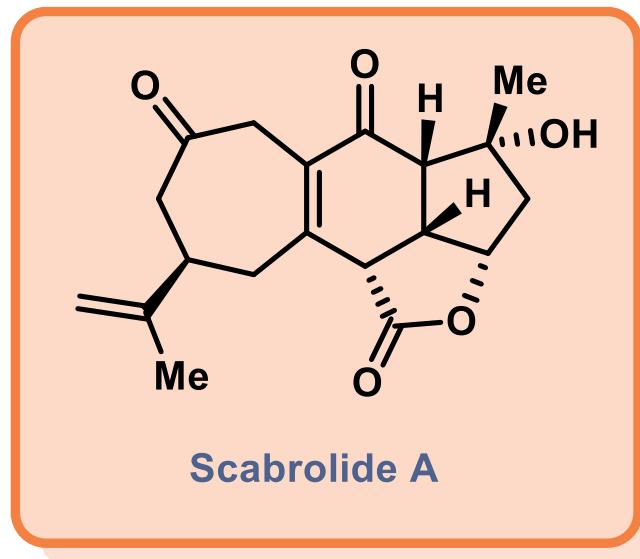


# *Syntheses of Scabrolide A*

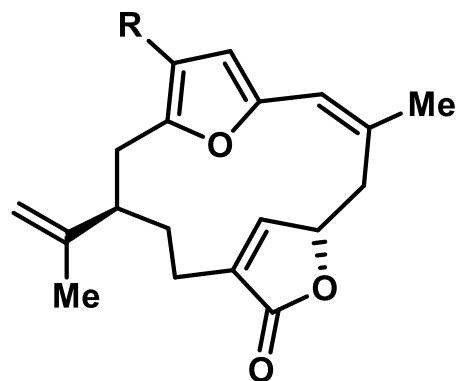


Hafeman, N. J.; Loskot, S. A.; Reimann, C. E.; Pritchett, B. P.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2020**, *142*, 13683-13688  
Meng, Z.; Fürstner, A. *J. Am. Chem. Soc.* **2022**, ASAPs

# The Scabrolides



*Sinularia scabra*



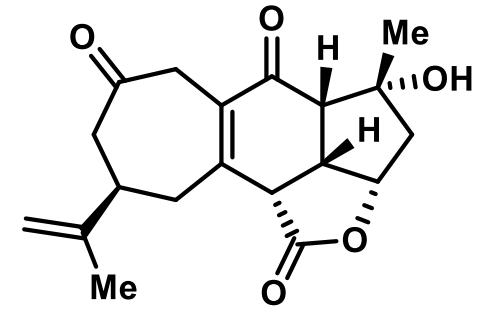
furanobutenolide macrocyclic core  
biosynthetic precursor

Scabrolides A-D isolated from the soft coral *Sinularia scabra* by Kuo et al. in 2002

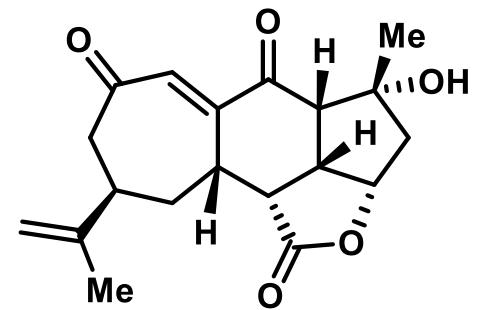
Furanobutenolide-derived C19 polycyclic norcembranoid diterpenoids

Scabrolide A inhibits IL-6 and IL-12 production in vitro, suggesting it may be of use as an anti-inflammatory

Characterized by a fused [5-6-7] framework featuring 6 stereocenters, 5 of which are contiguous



Scabrolide A



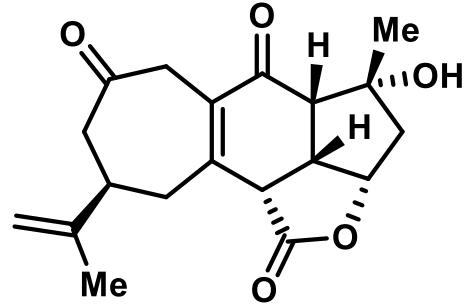
Scabrolide B

+ C and D

Isolation: Sheu, J.-H.; Ahmed, A. F.; Shiue, R.-T.; Dai, C.-F.; Kuo, Y.-H. *J. Nat. Prod.* **2002**, *65*, 1904.

Review of furanobutenolide cembranoids and norcembranoids: Craig II, R. A.; Stoltz, B. M.; *Chem. Rev.* **2017**, *117*, 7878.

# Stoltz's Retrosynthesis

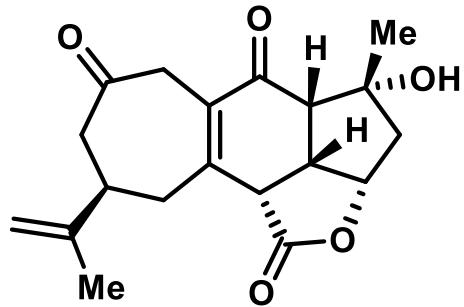


Scabrolide A



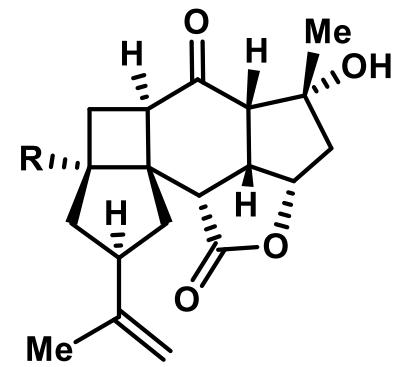
Brian Stoltz  
Caltech

## Stoltz's Retrosynthesis

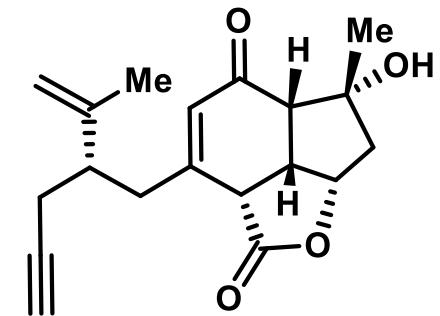


Scabrolide A

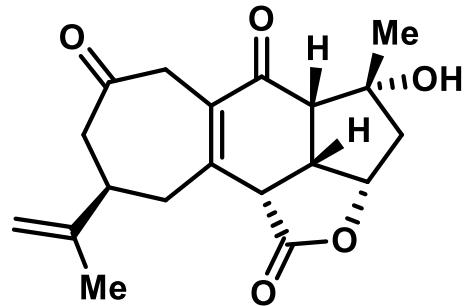
*oxidative  
fragmentation*



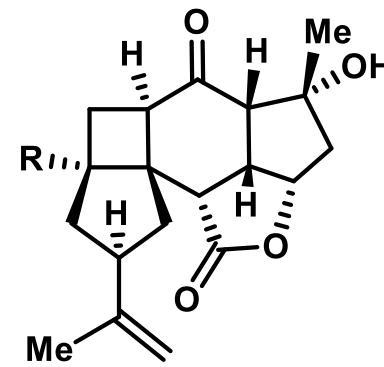
*intramol.  
[2+2]*



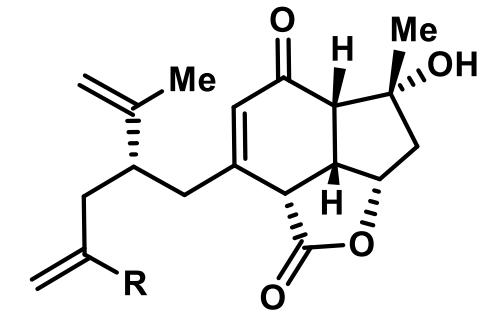
# Stoltz's Retrosynthesis



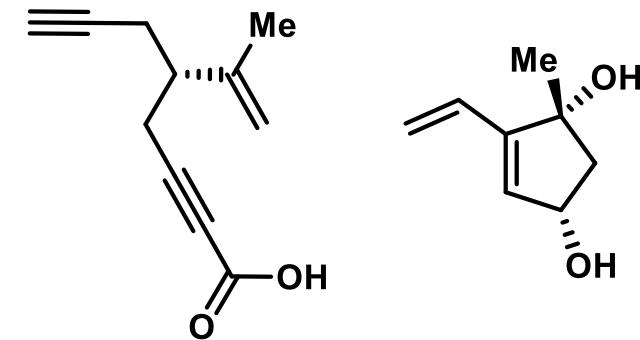
*oxidative  
fragmentation*



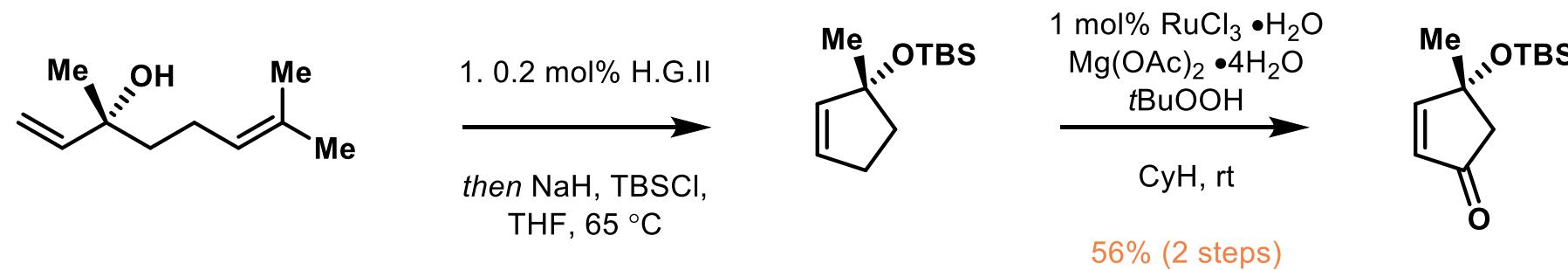
*intramol.  
[2+2]*



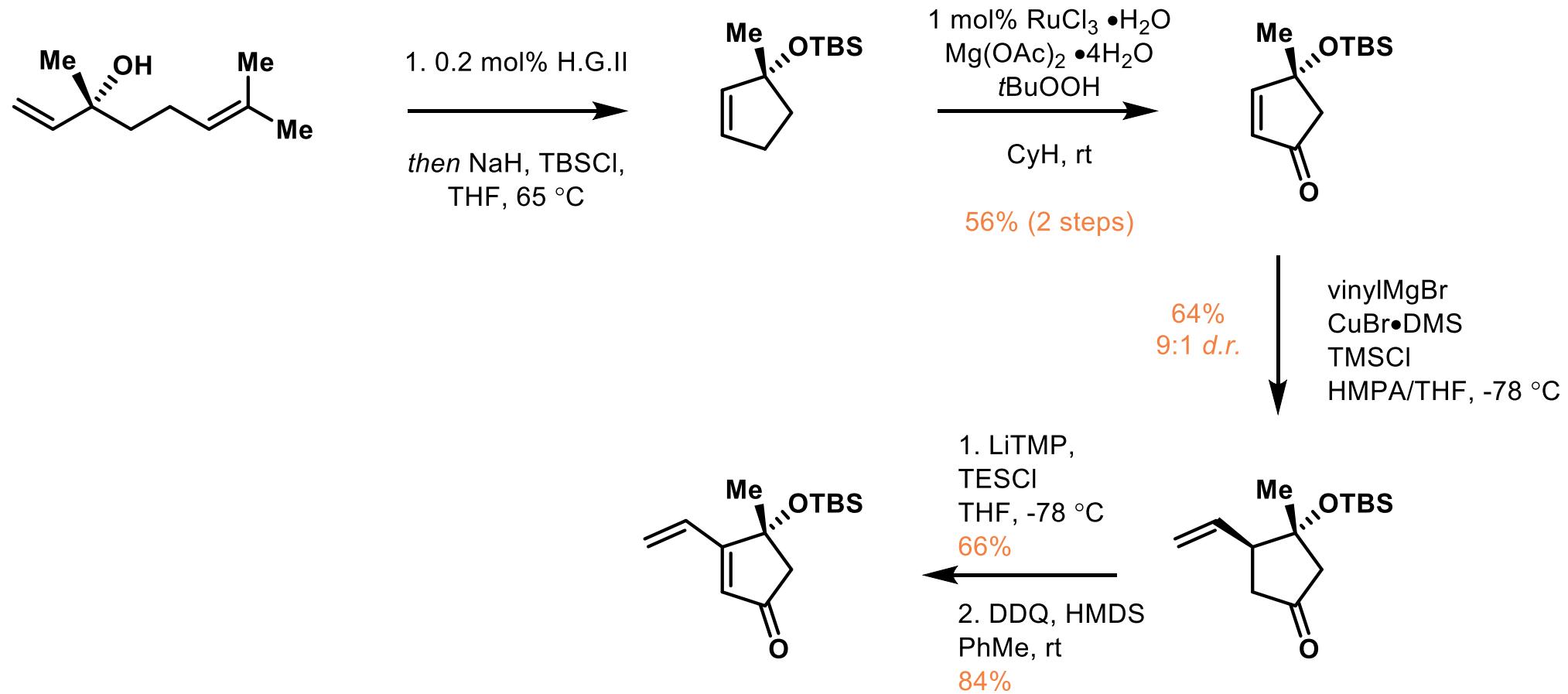
*esterification  
and Diels-Alder*



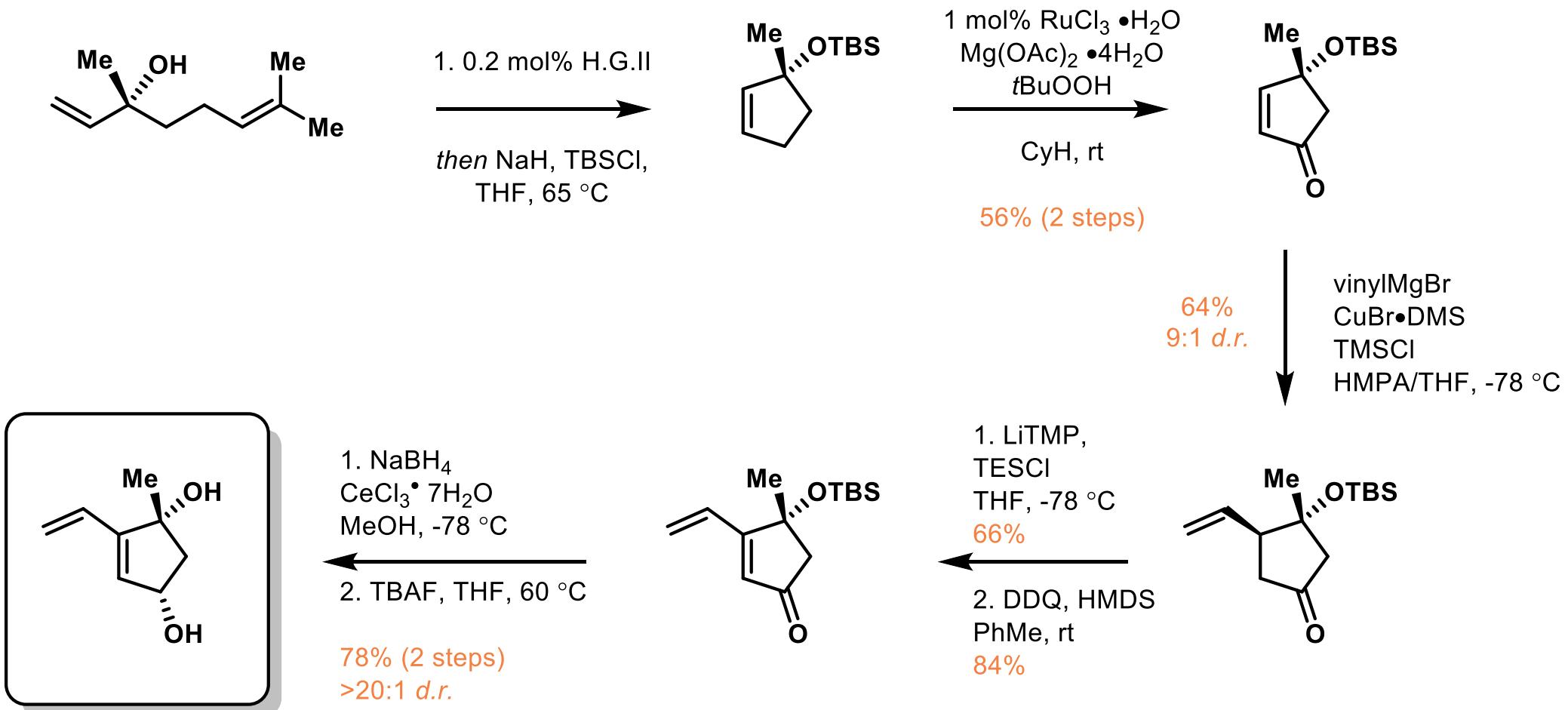
## Stoltz Synthesis: Fragment A



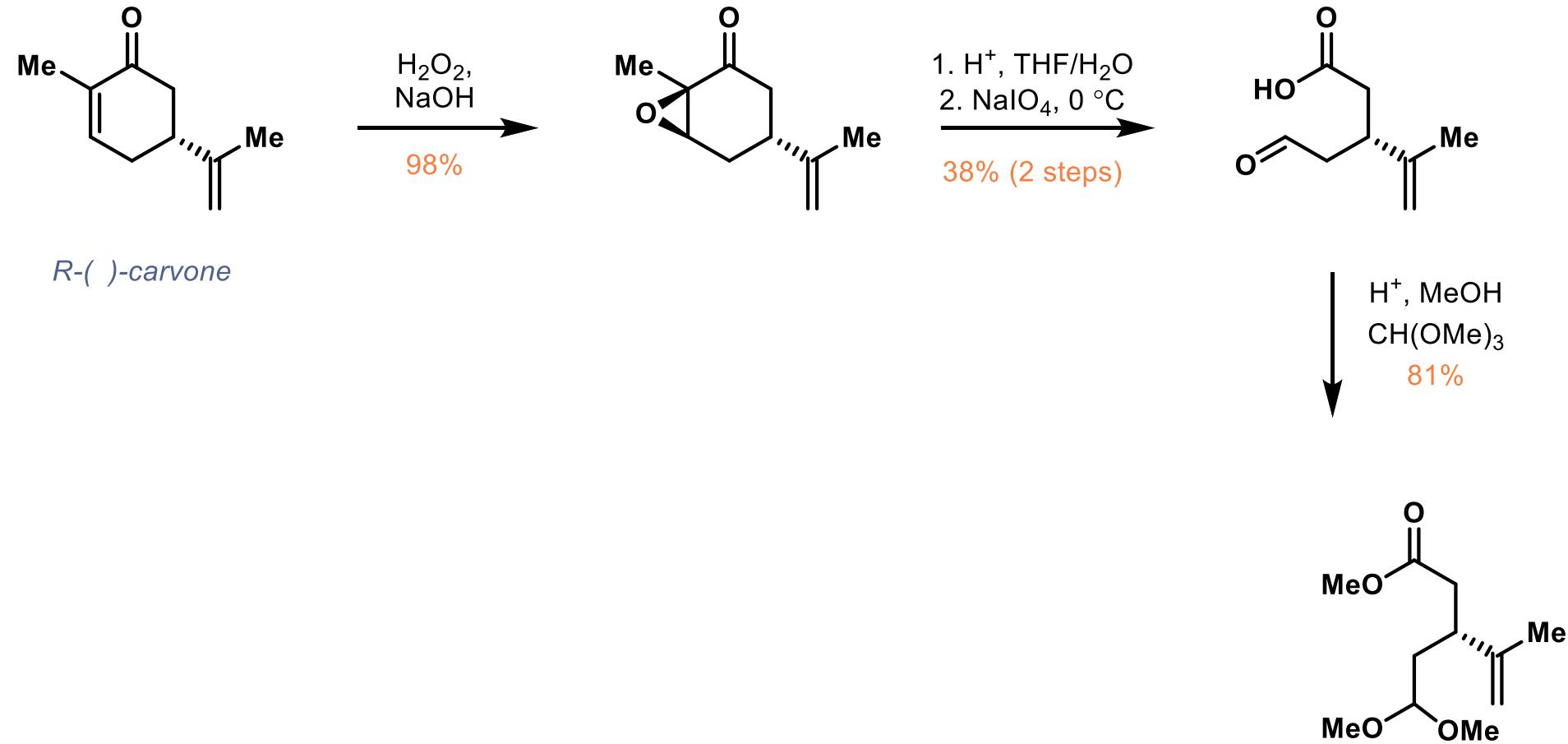
## Stoltz Synthesis: Fragment A



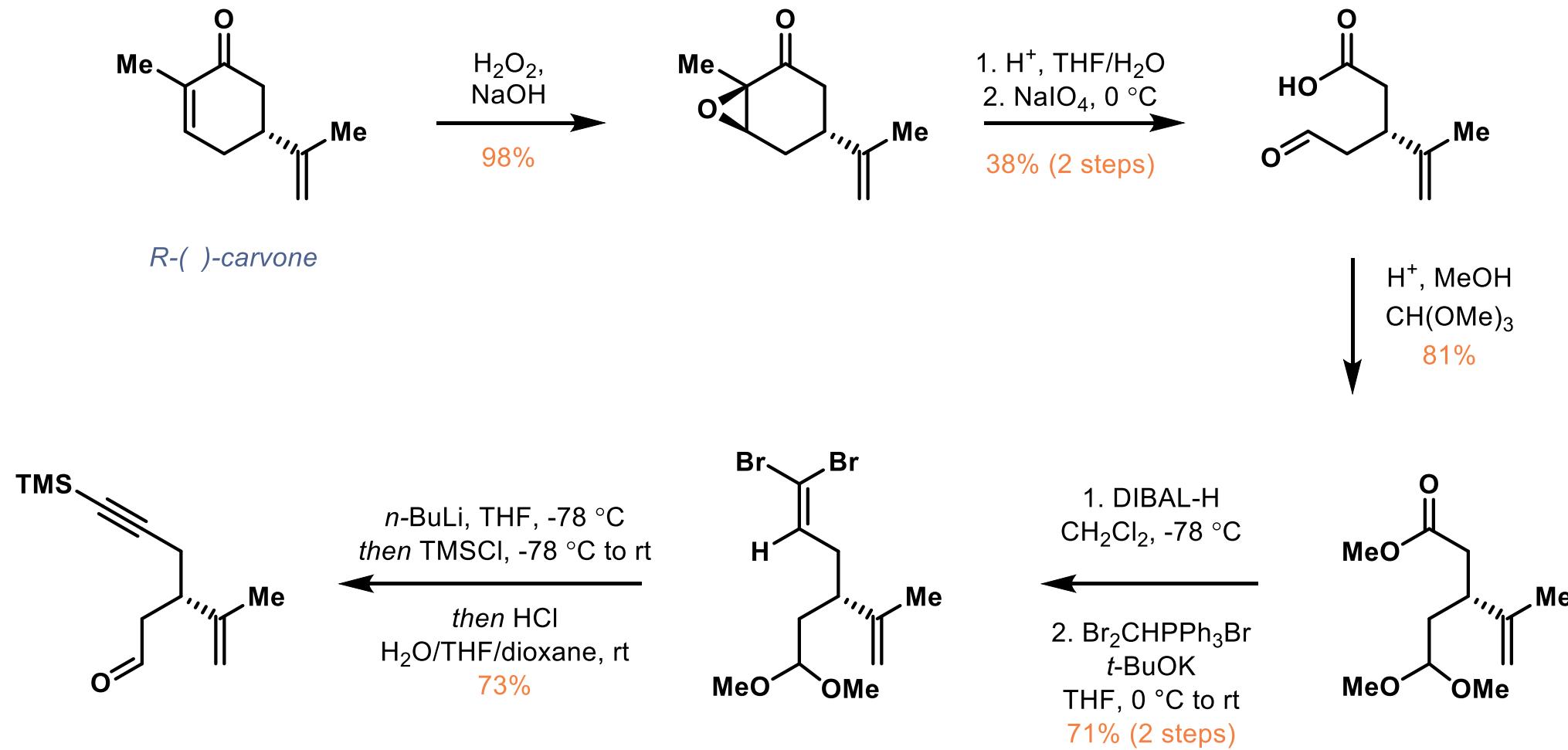
## Stoltz Synthesis: Fragment A



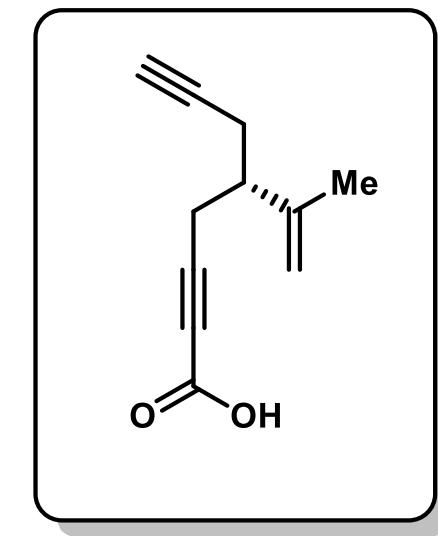
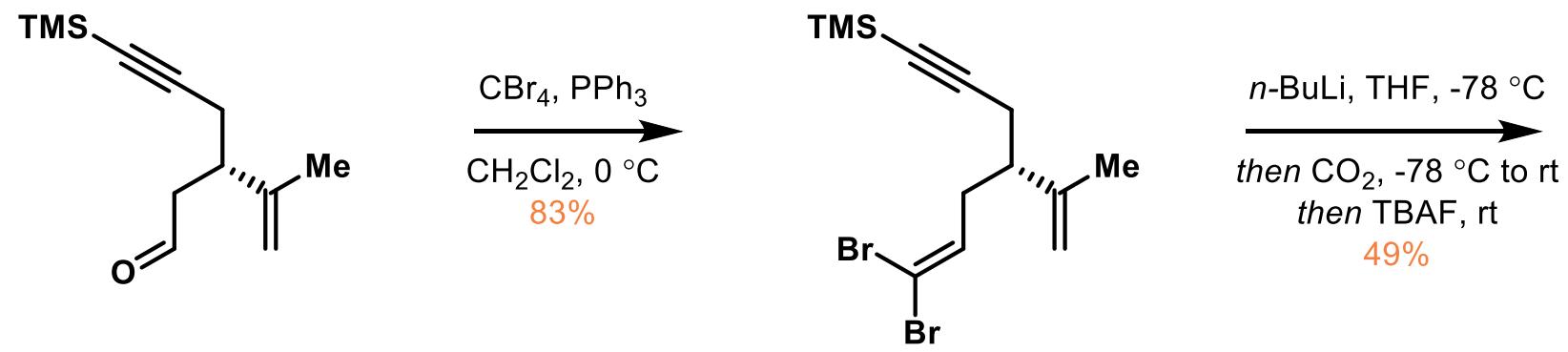
## Stoltz Synthesis: Fragment B



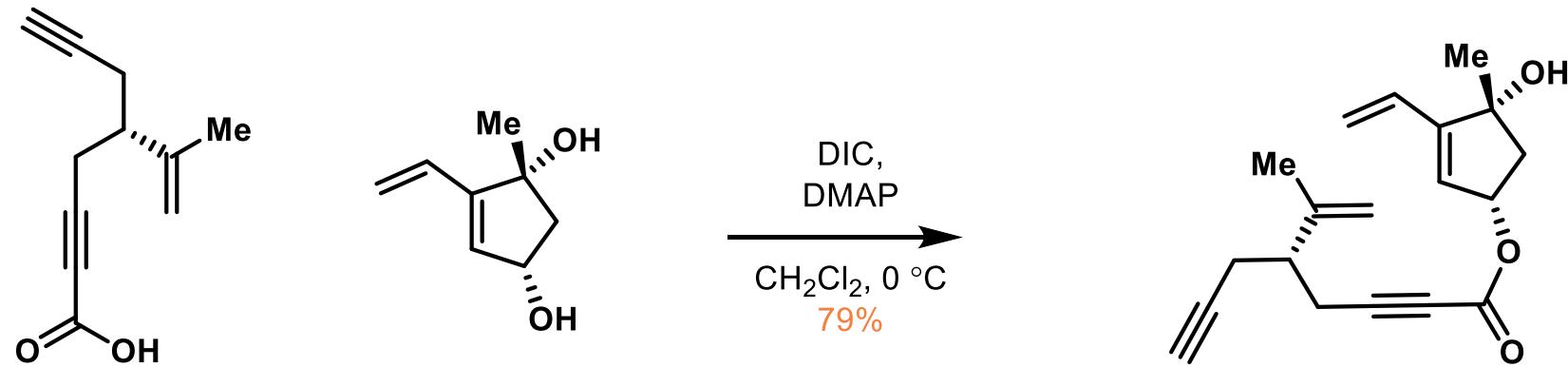
## Stoltz Synthesis: Fragment B



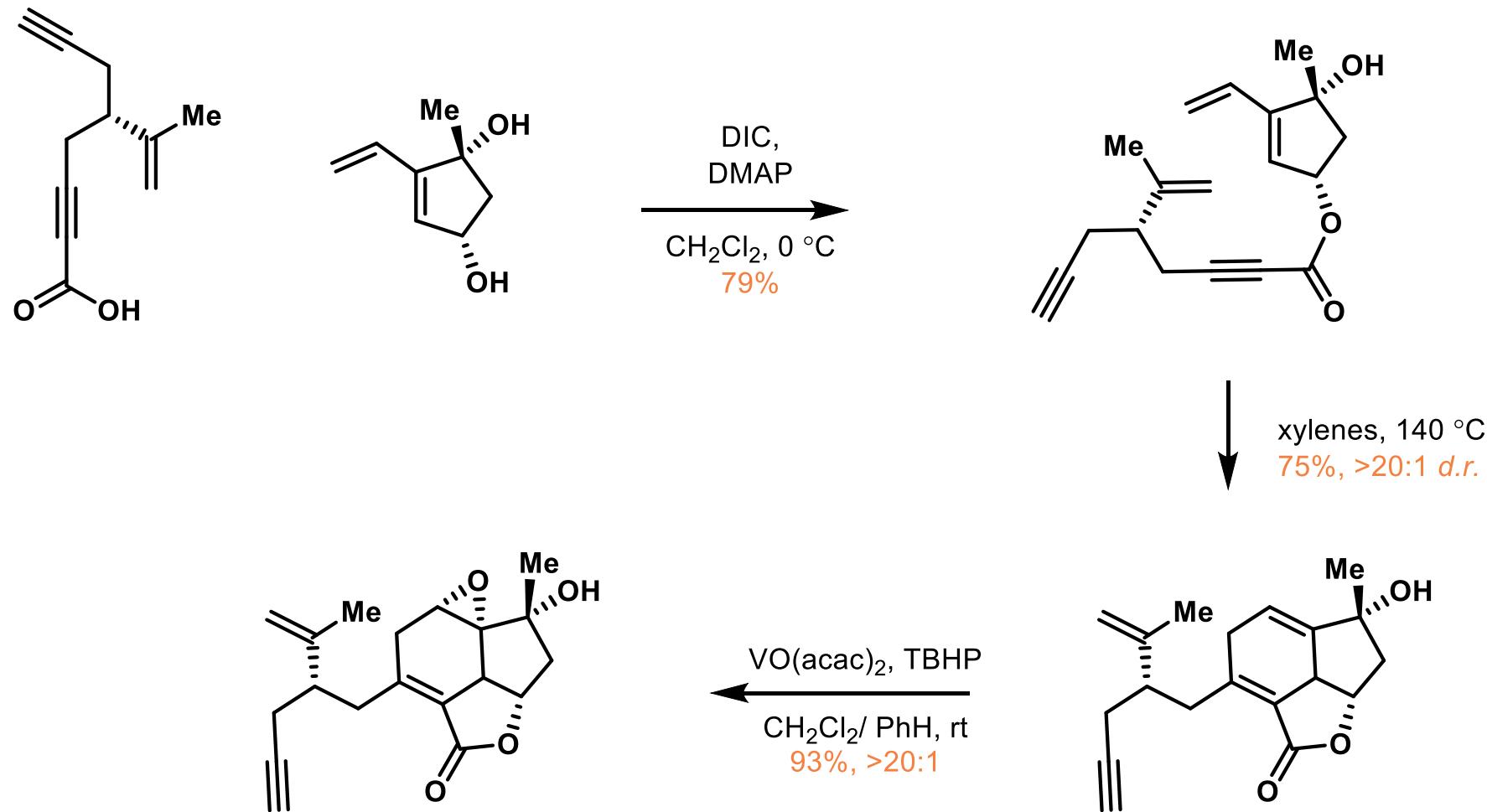
## Stoltz Synthesis: Fragment B



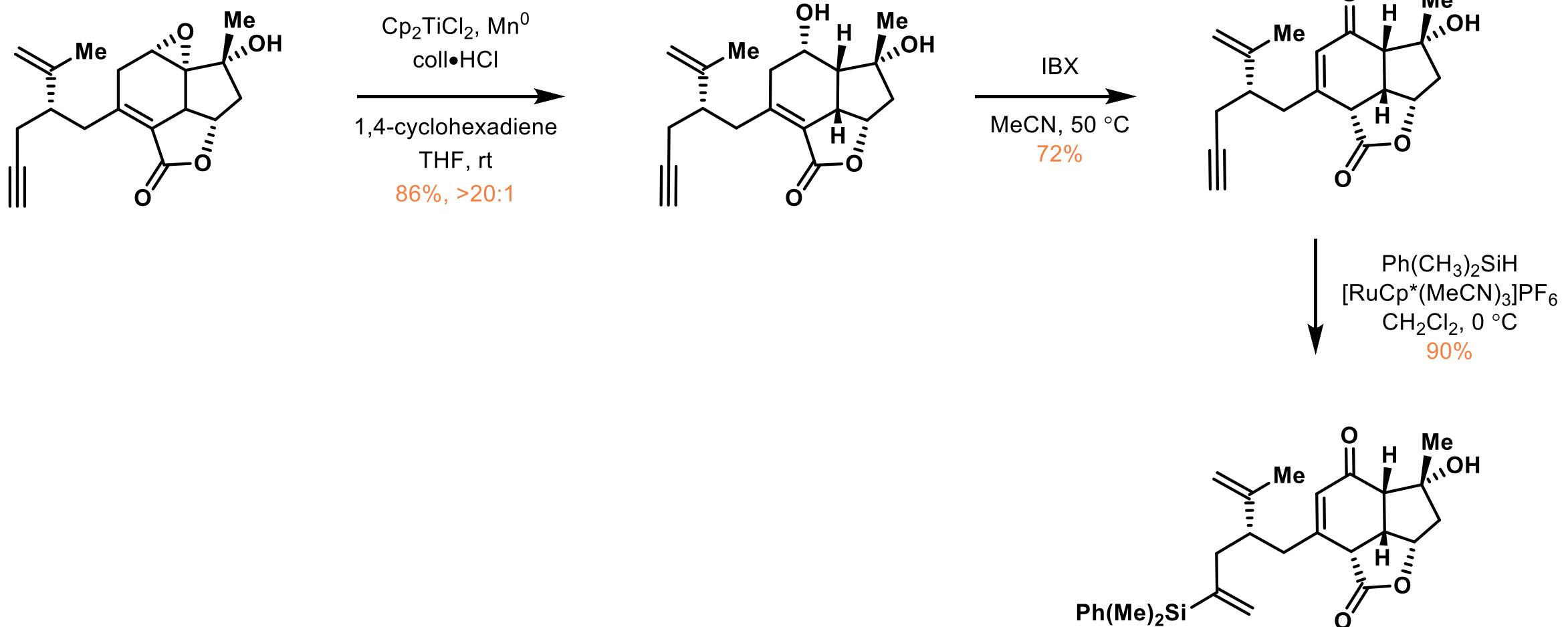
## Stoltz Synthesis: Union of the Fragments



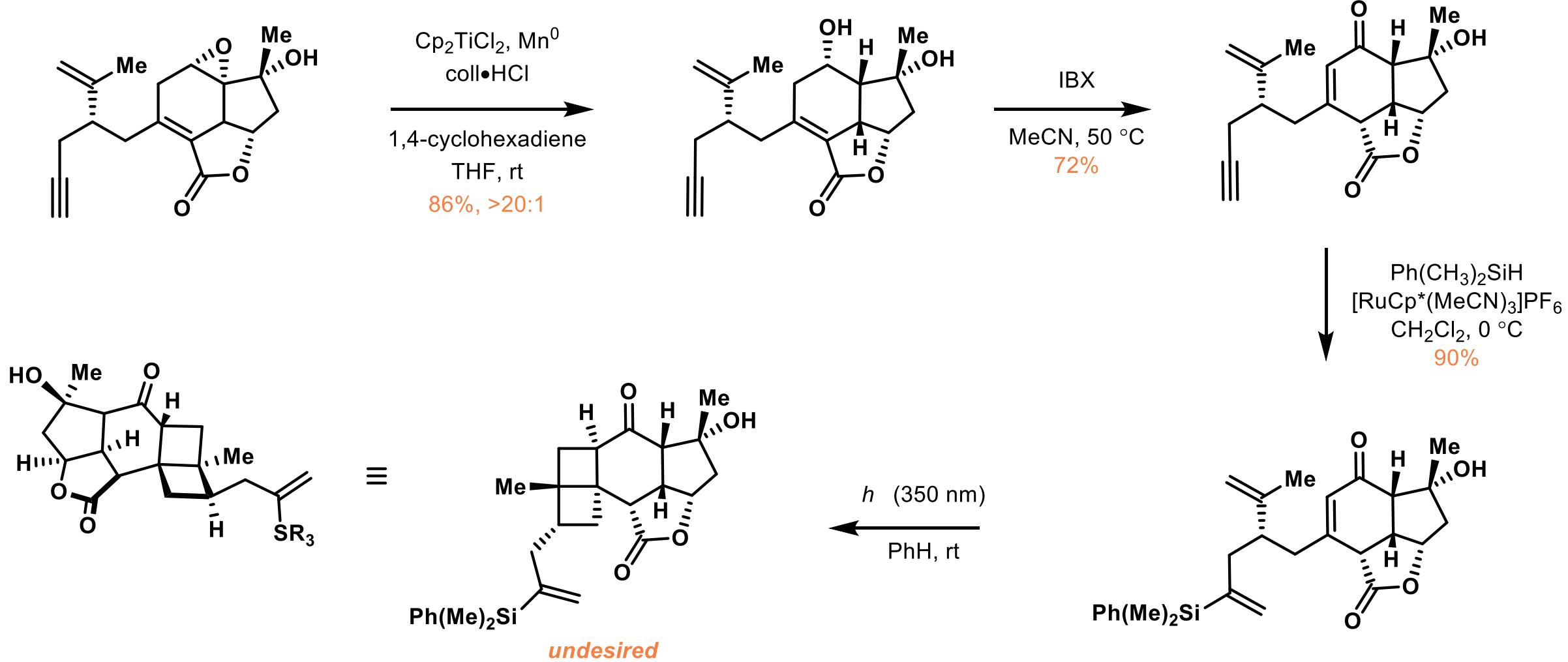
## Stoltz Synthesis: Union of the Fragments



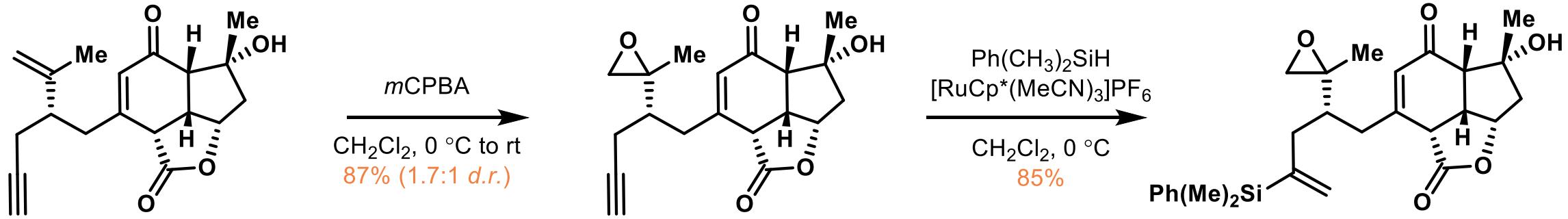
## Stoltz Synthesis: Advancing the Tricycle



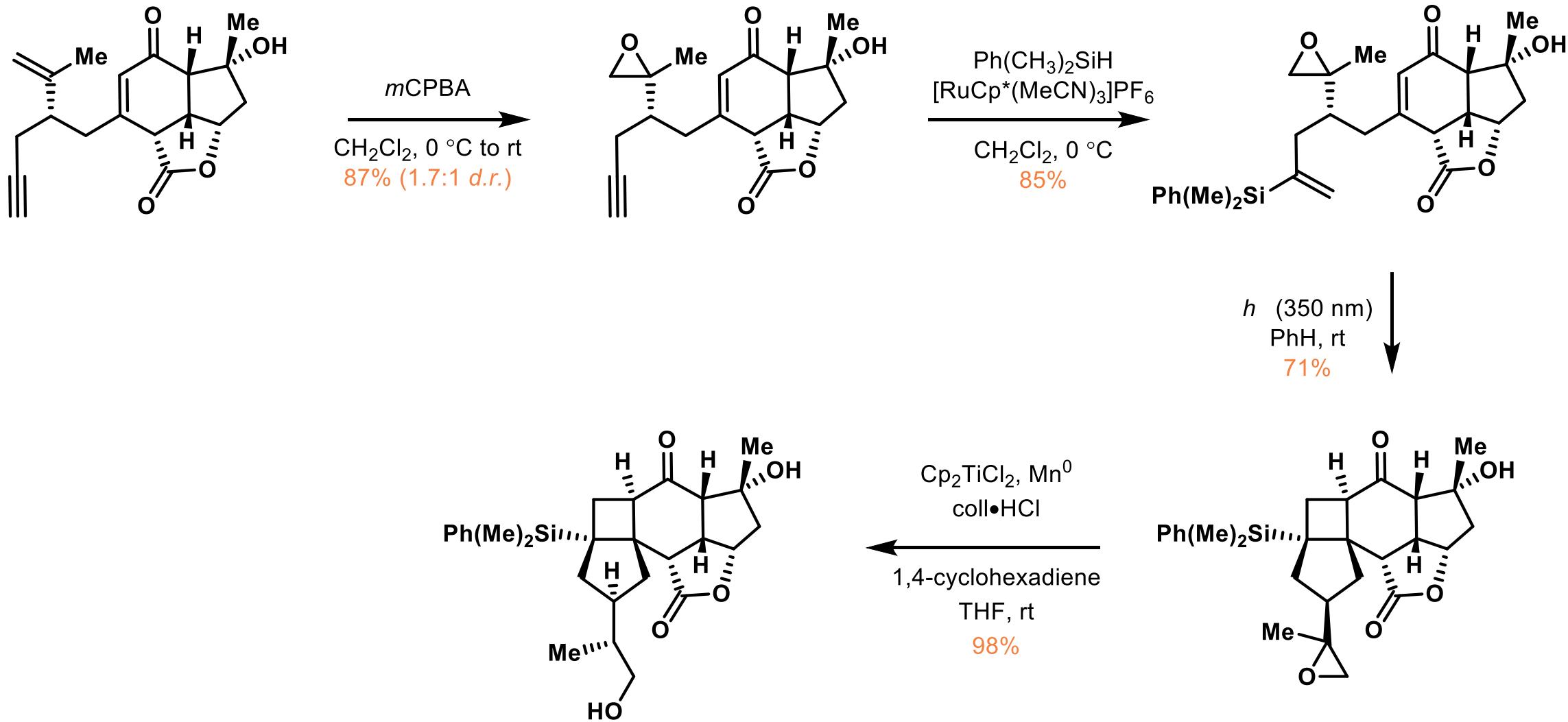
# Stoltz Synthesis: Advancing the Tricycle



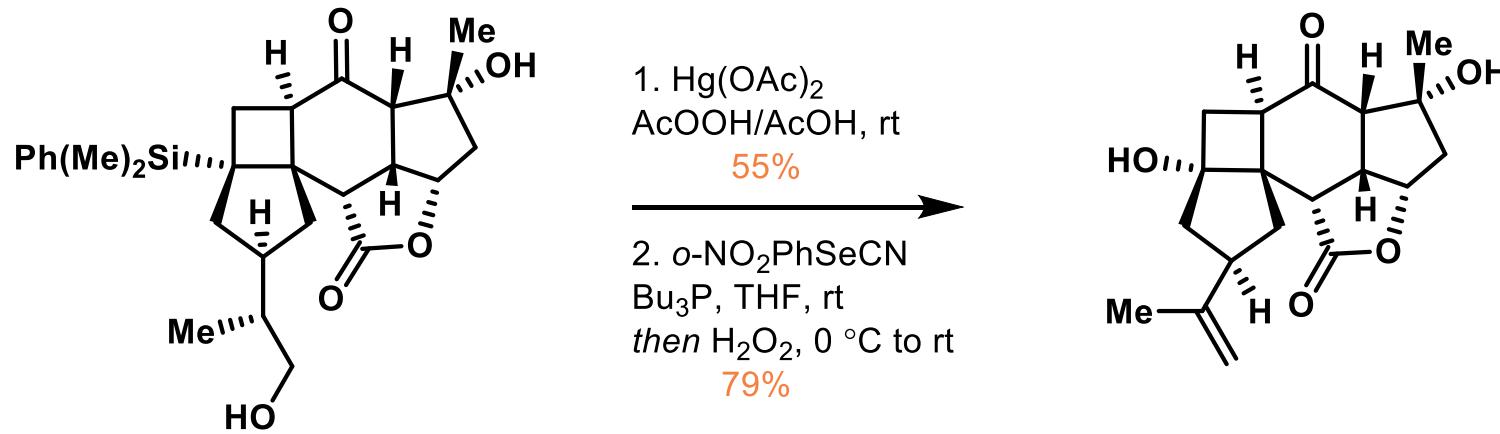
## Stoltz Synthesis: Necessary to Block the Alkene



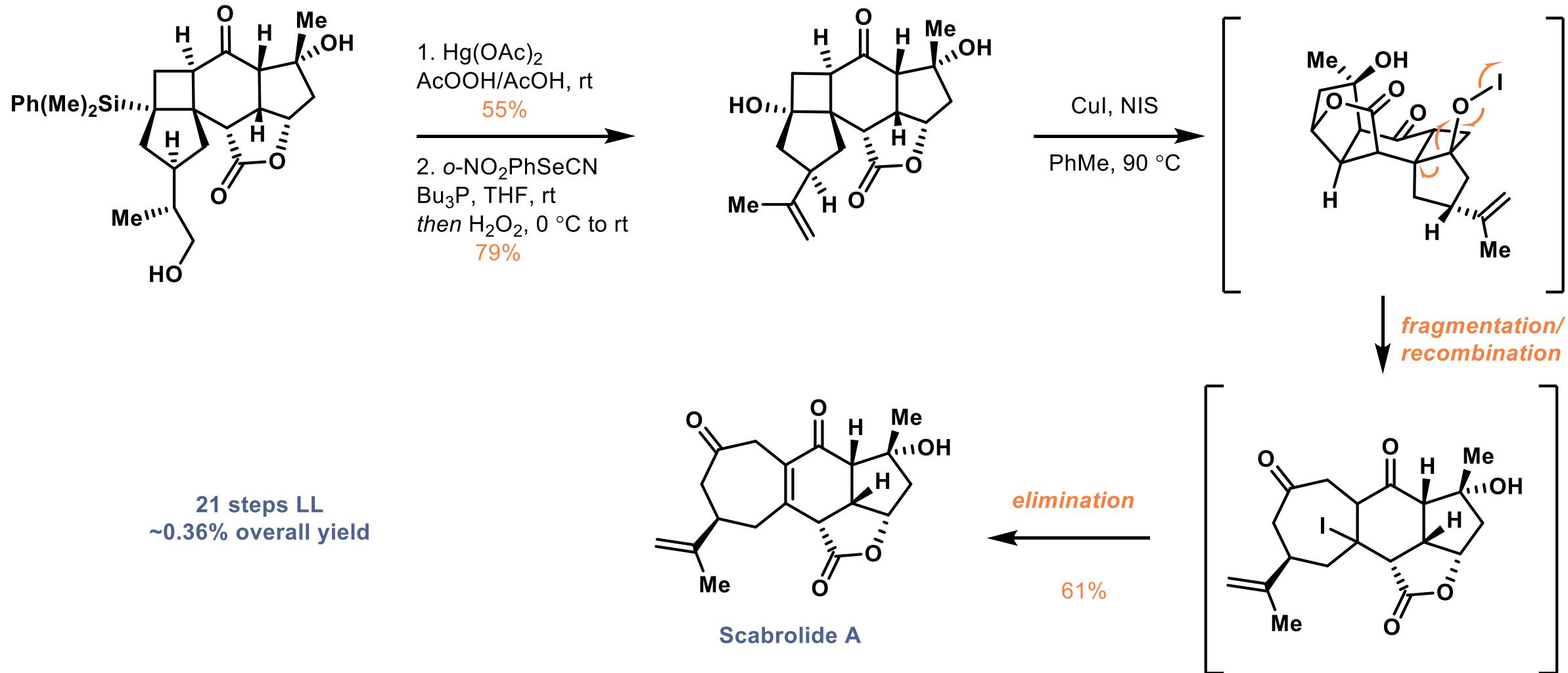
## Stoltz Synthesis: Necessary to Block the Alkene



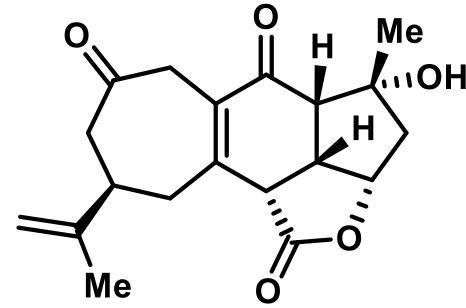
## Stoltz Synthesis: Key Fragmentation



# Stoltz Synthesis: Key Fragmentation



# Fürstner's Retrosynthetic Analysis

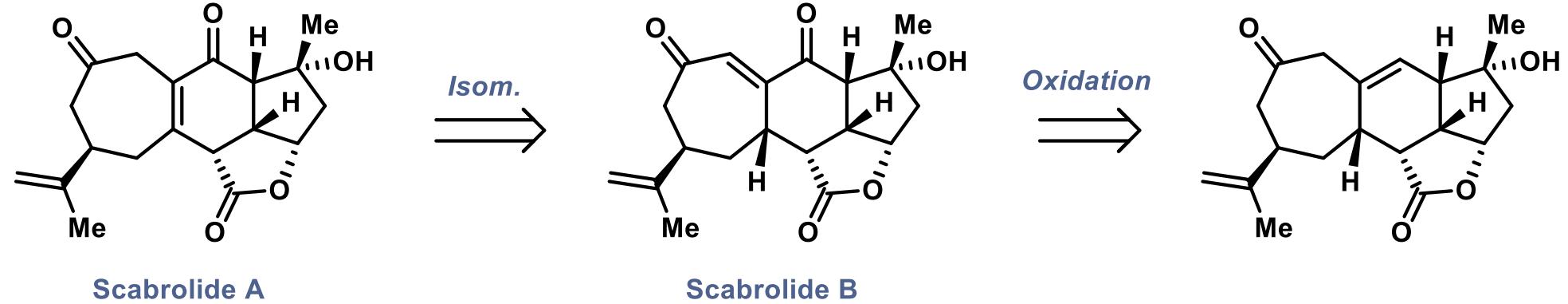


Scabrolide A

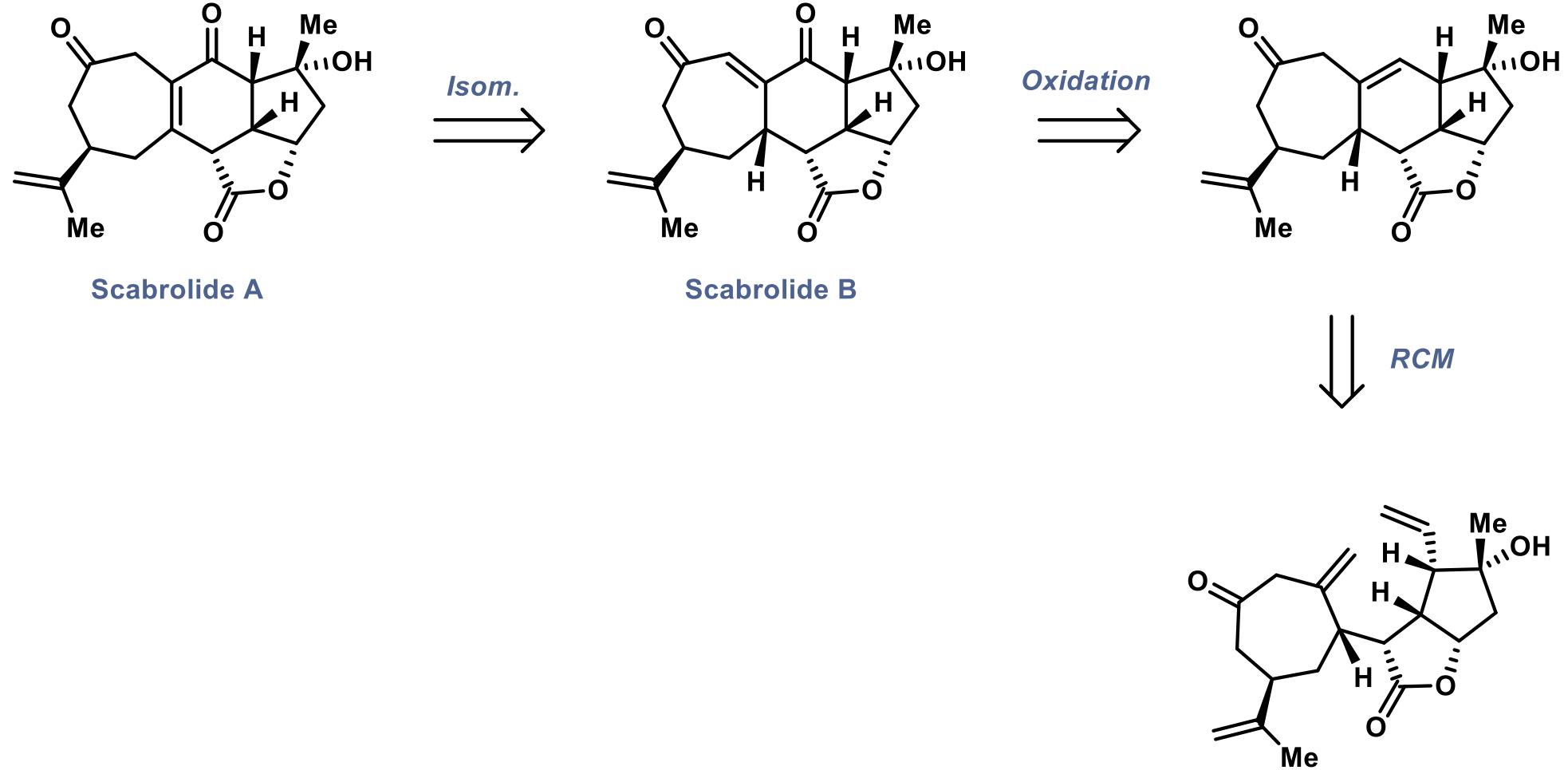


Alois Fürstner  
Max Planck Institute

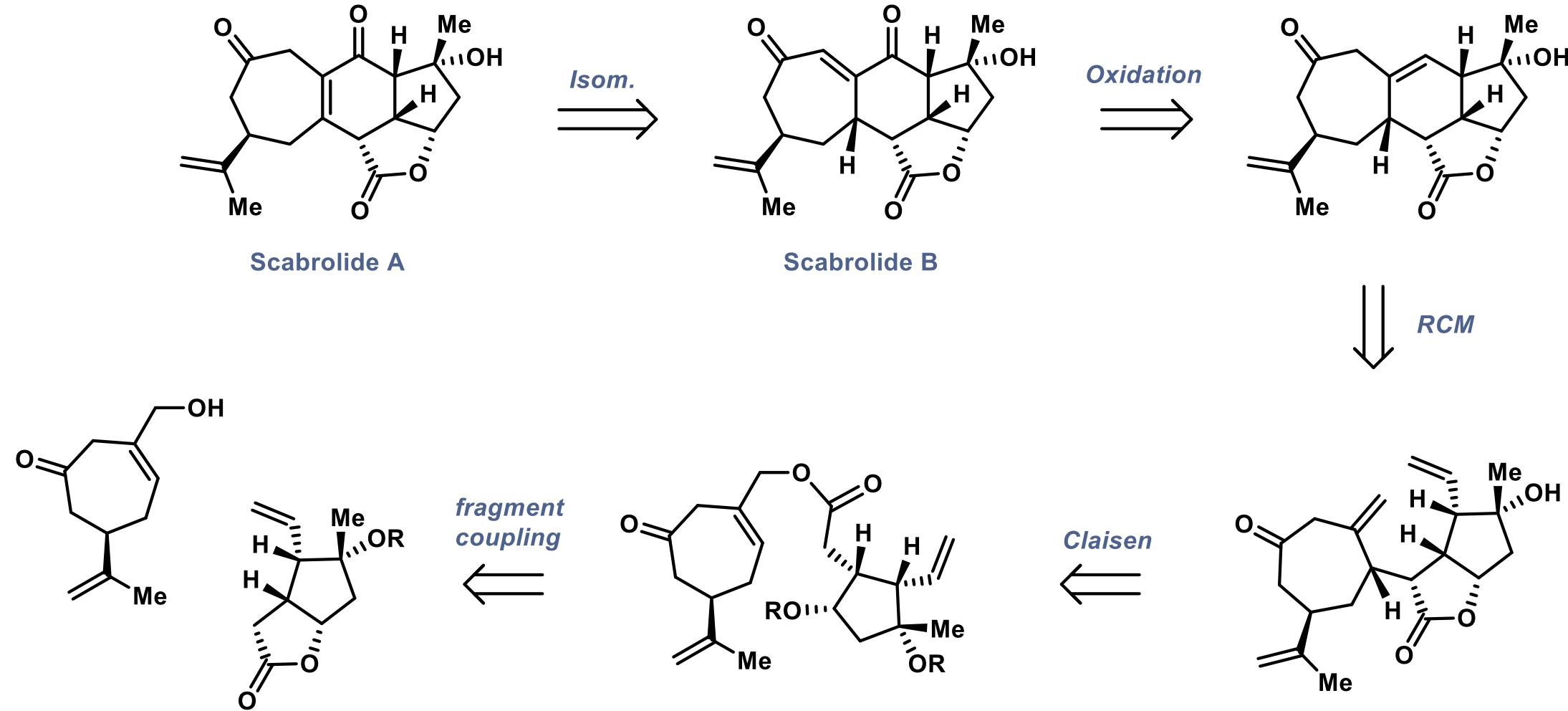
# Fürstner's Retrosynthetic Analysis



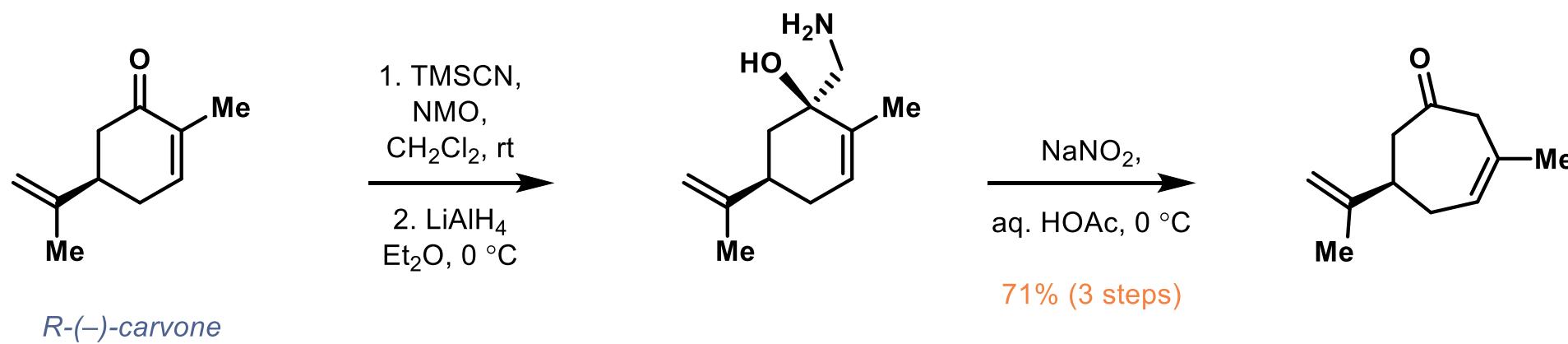
# Fürstner's Retrosynthetic Analysis



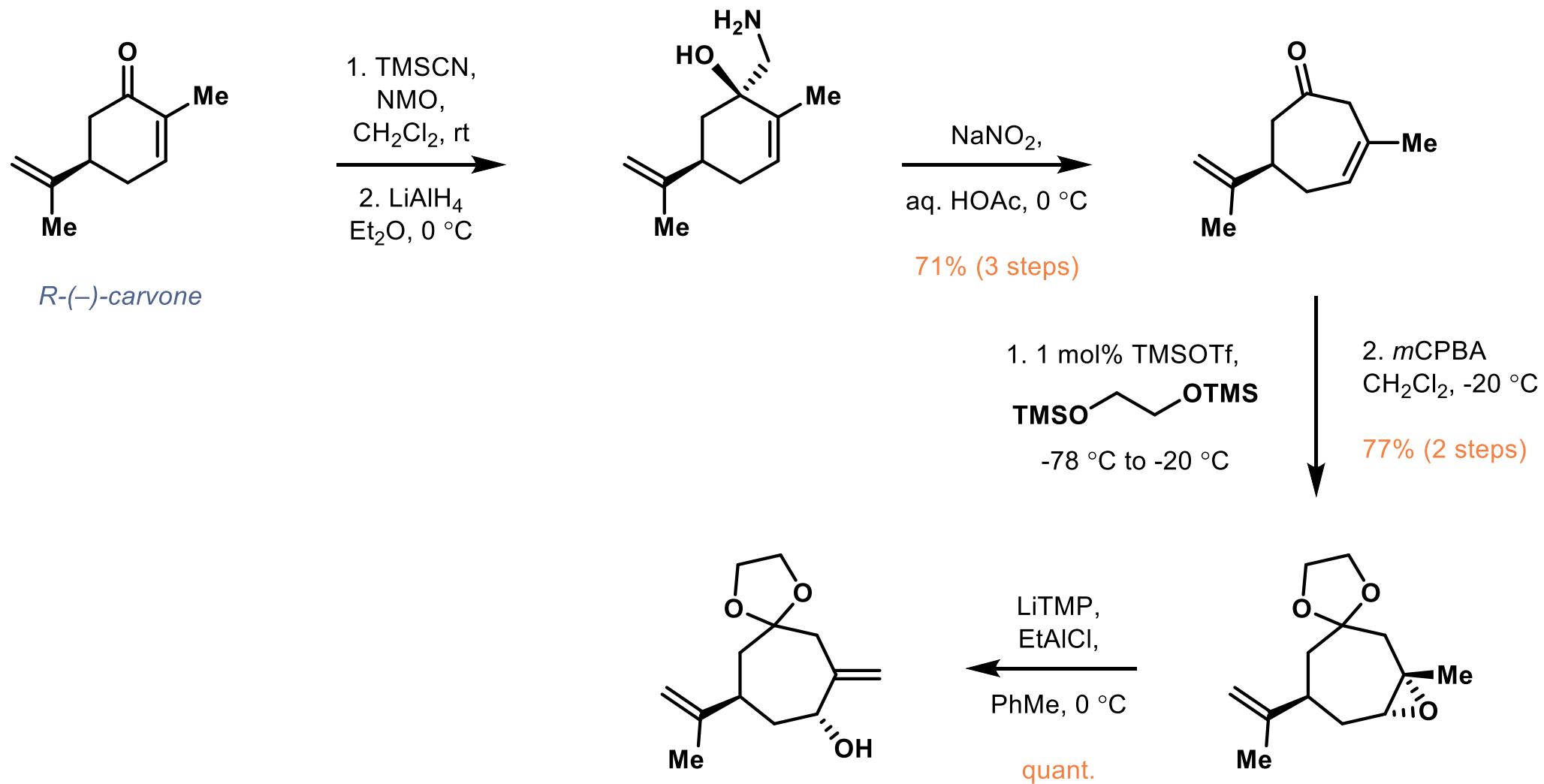
# Fürstner's Retrosynthetic Analysis



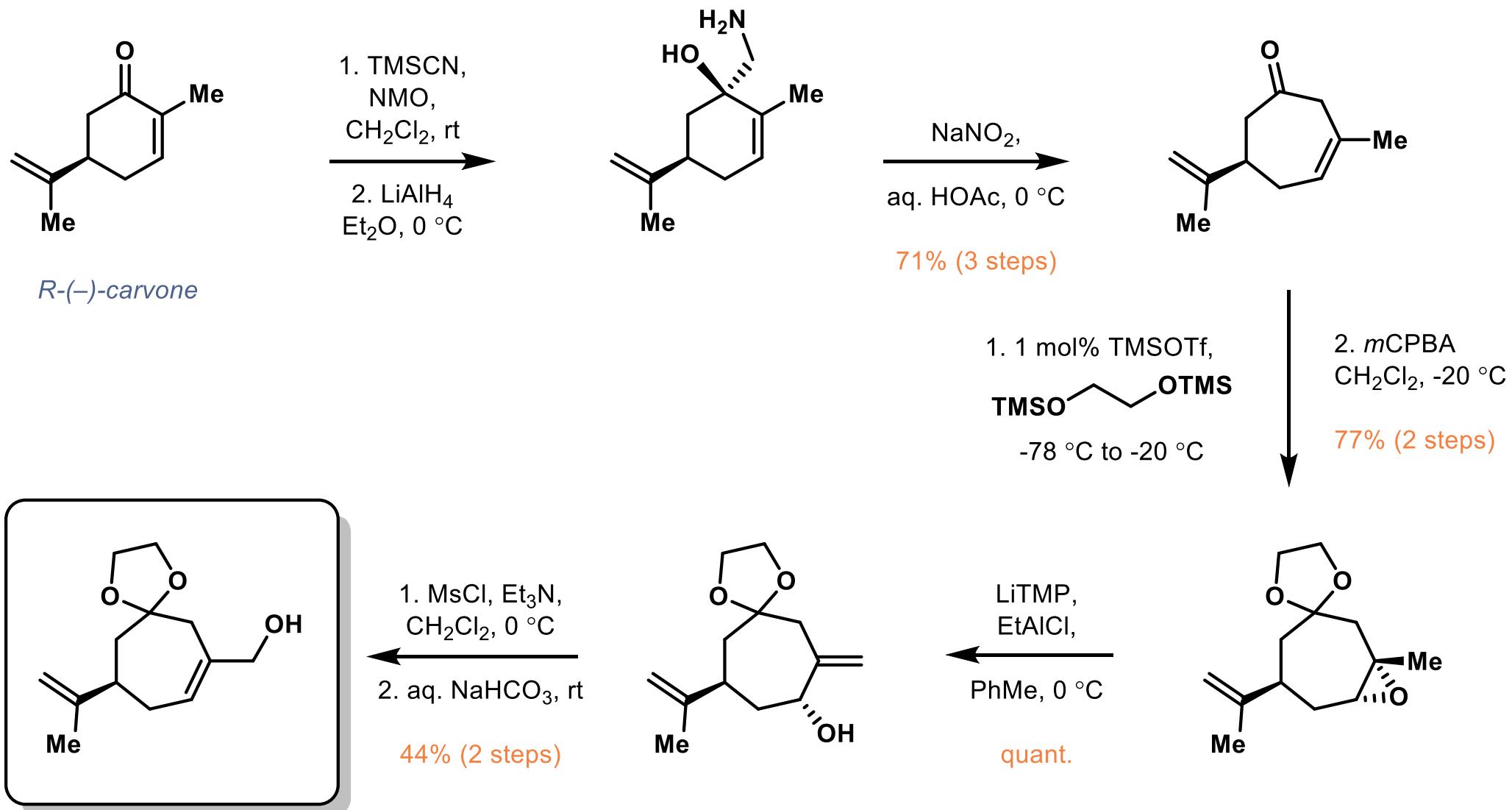
## Fürstner Synthesis: Fragment A



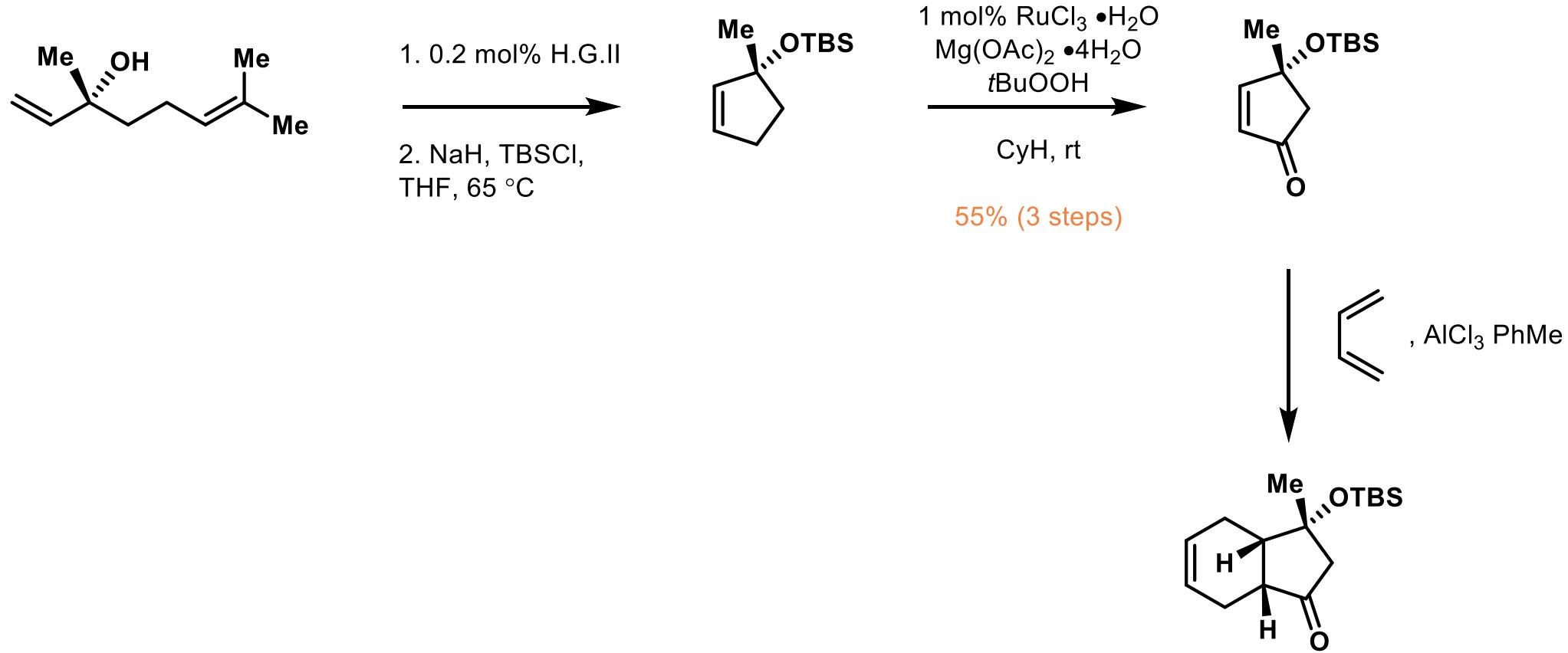
## Fürstner Synthesis: Fragment A



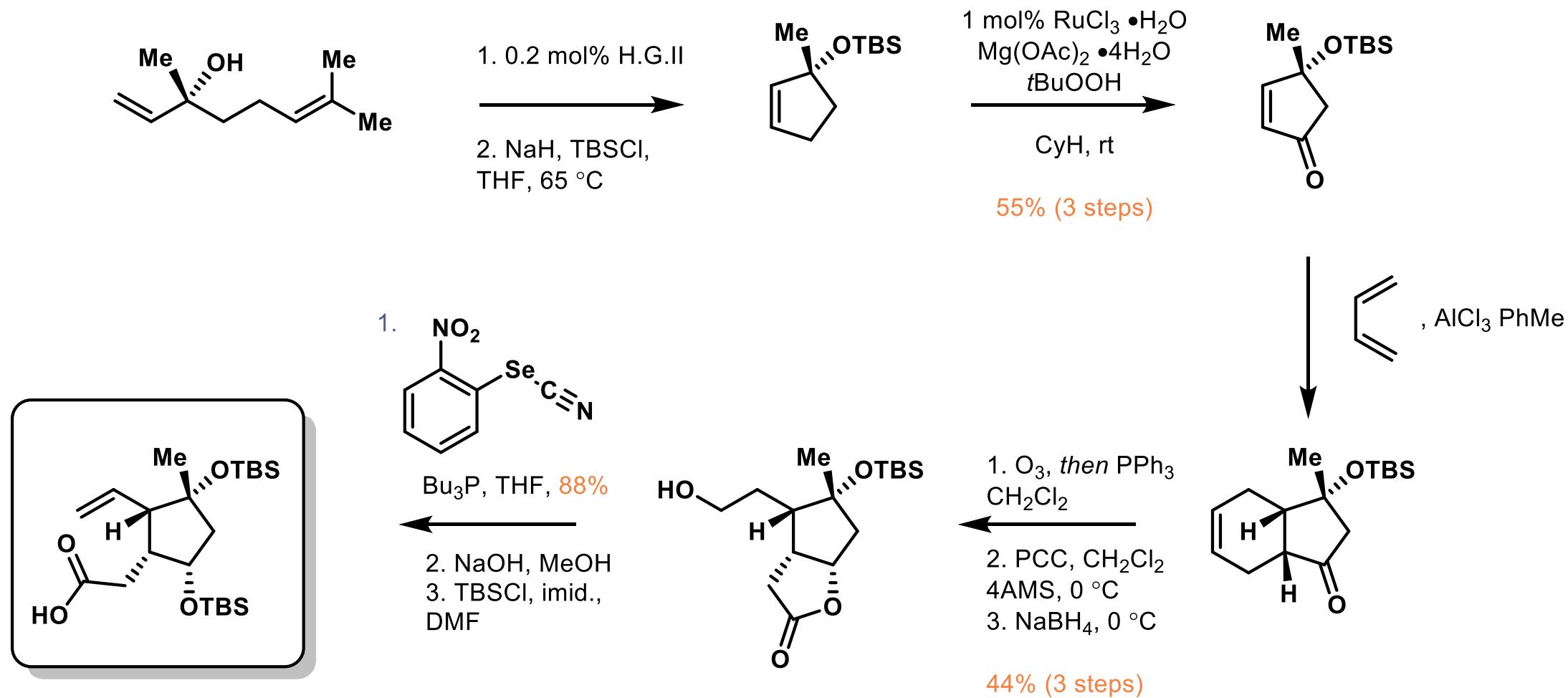
## Fürstner Synthesis: Fragment A



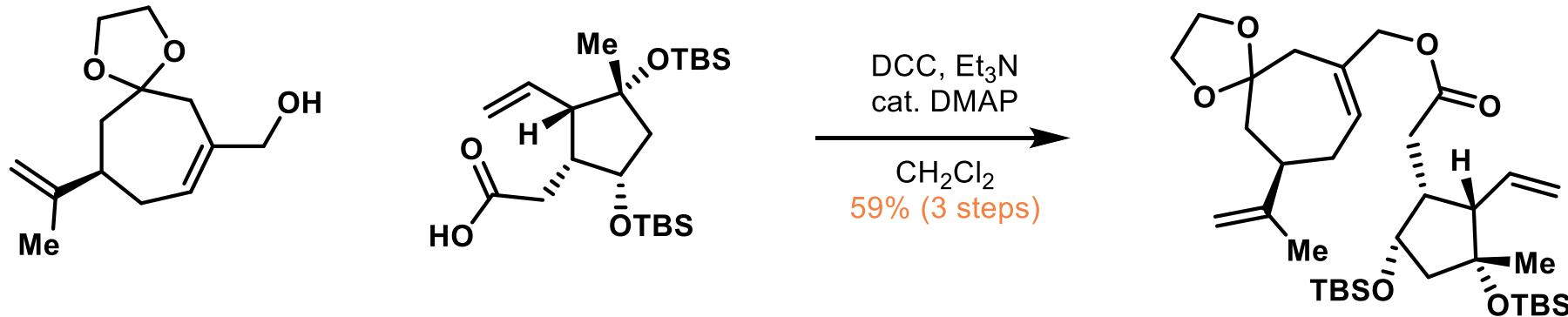
## Fürstner Synthesis: Fragment B



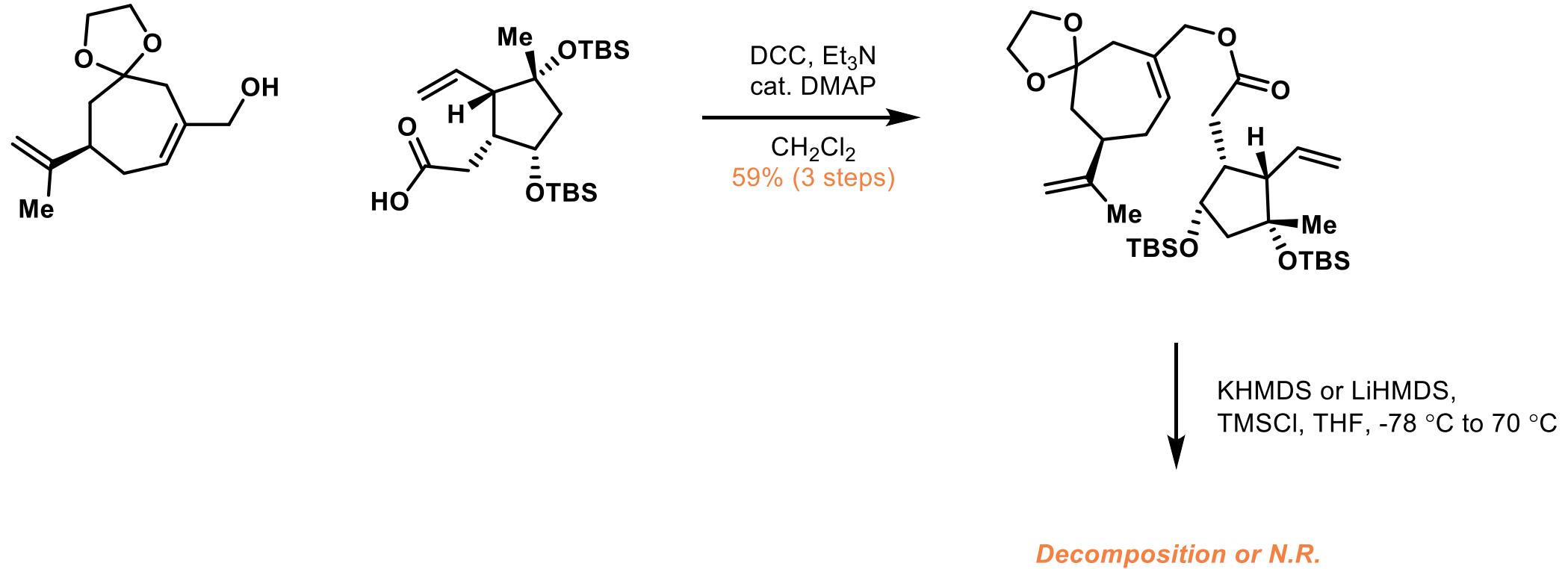
## Fürstner Synthesis: Fragment B



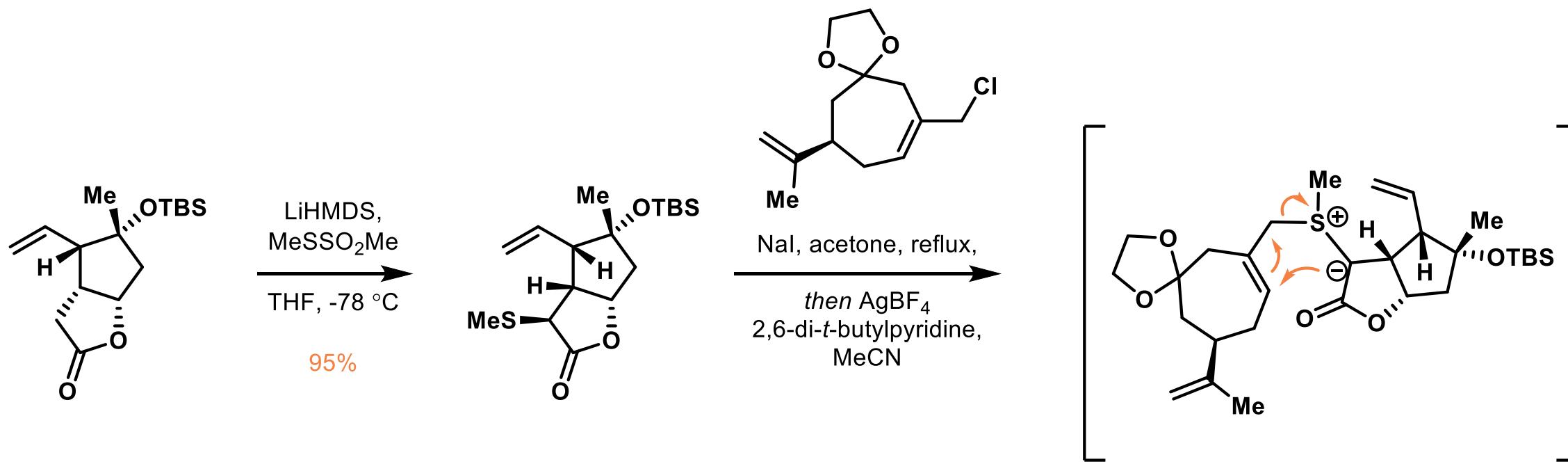
## Fürstner Synthesis: Fragment Coupling



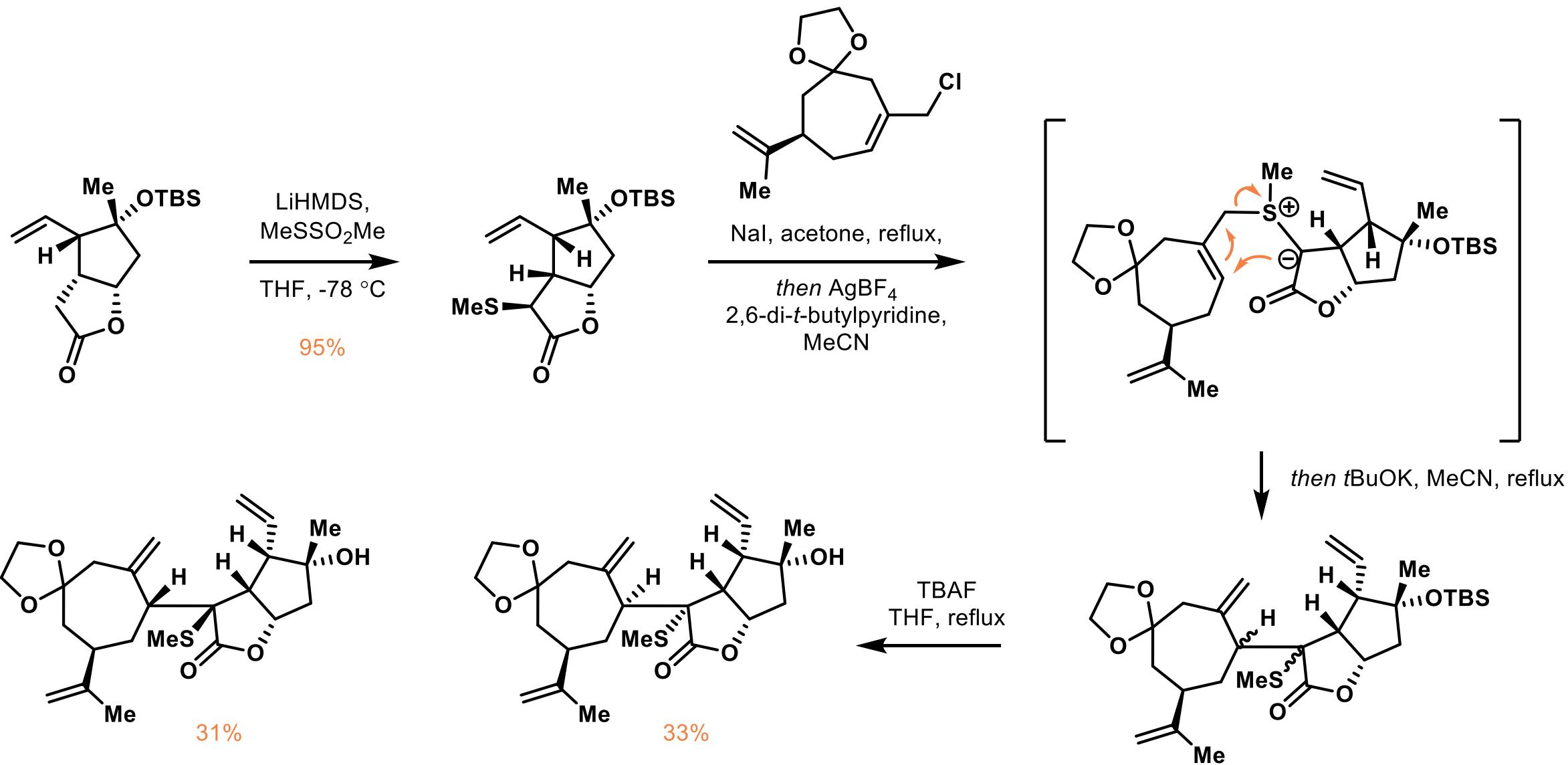
## Fürstner Synthesis: Fragment Coupling



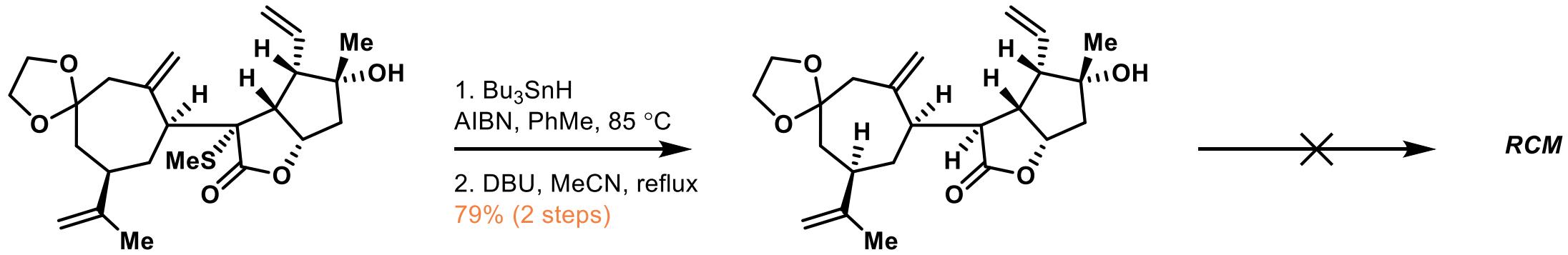
# Fürstner Synthesis: Backup Plan



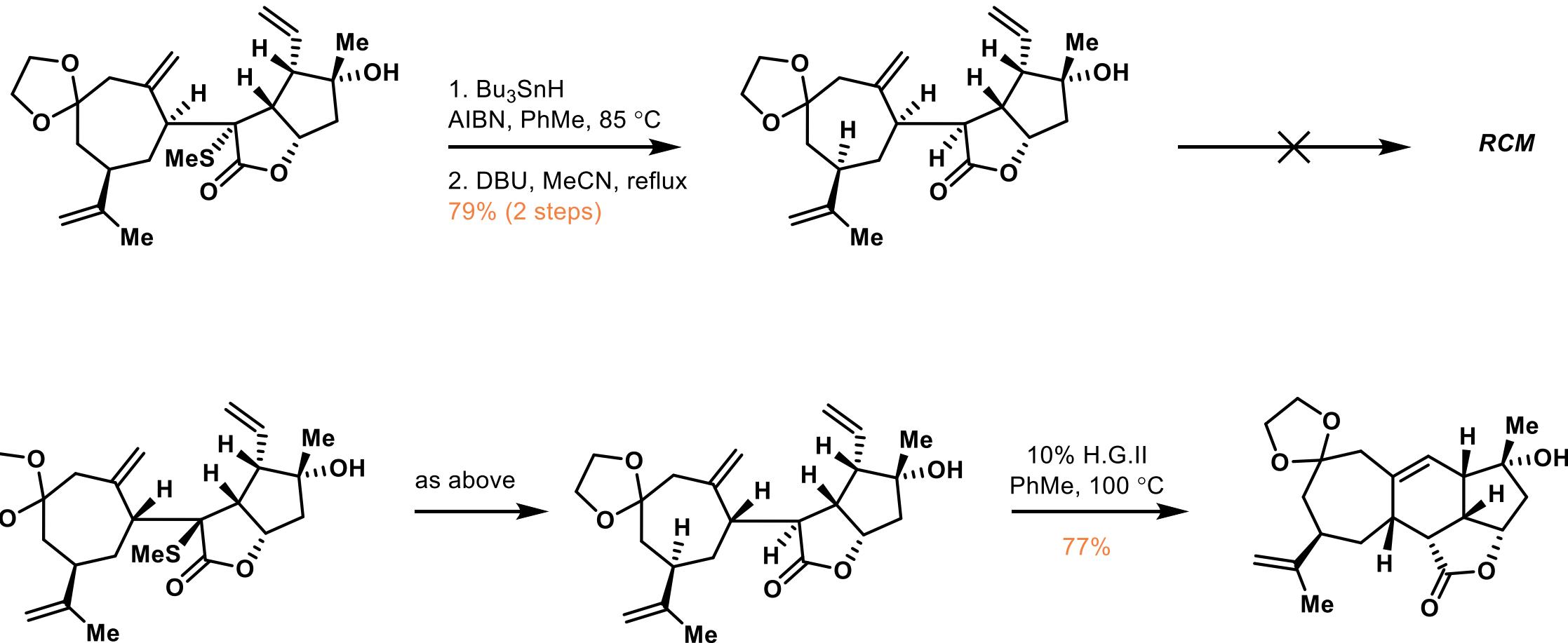
# Fürstner Synthesis: Backup Plan



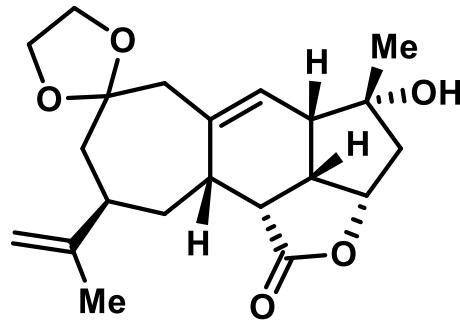
## Fürstner Synthesis: Completing the Core



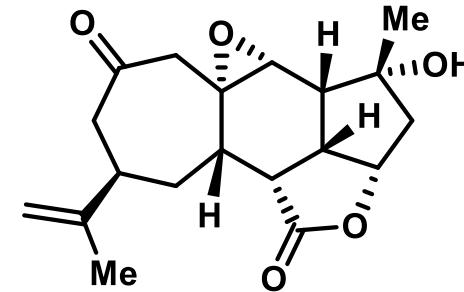
## Fürstner Synthesis: Completing the Core



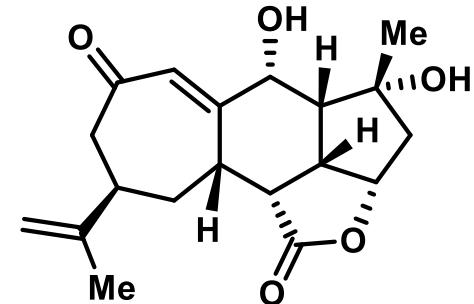
## Fürstner Synthesis: Completing the Synthesis



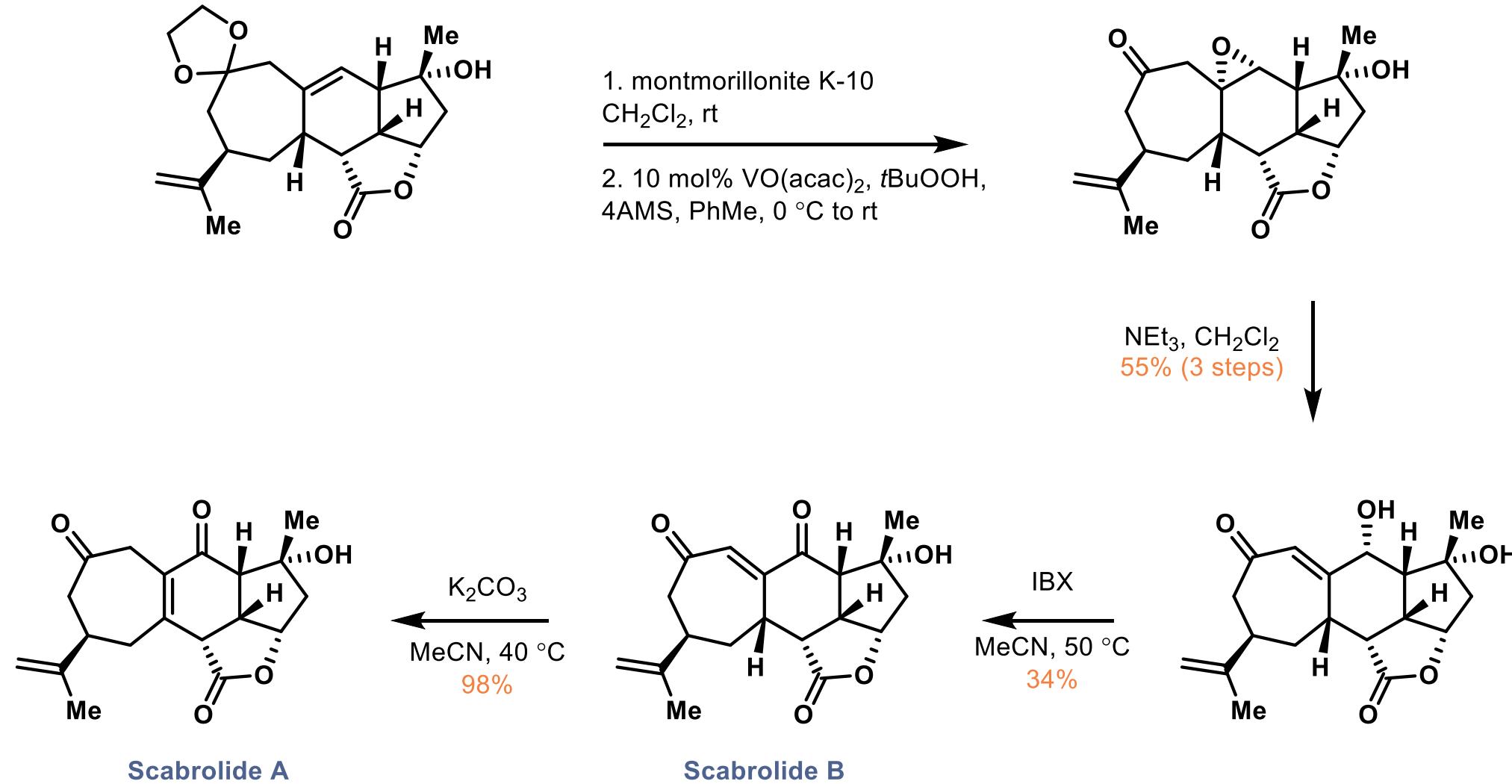
1. montmorillonite K-10  
 $\text{CH}_2\text{Cl}_2$ , rt  
→  
2. 10 mol%  $\text{VO}(\text{acac})_2$ ,  $t\text{BuOOH}$ ,  
4AMS, PhMe, 0 °C to rt



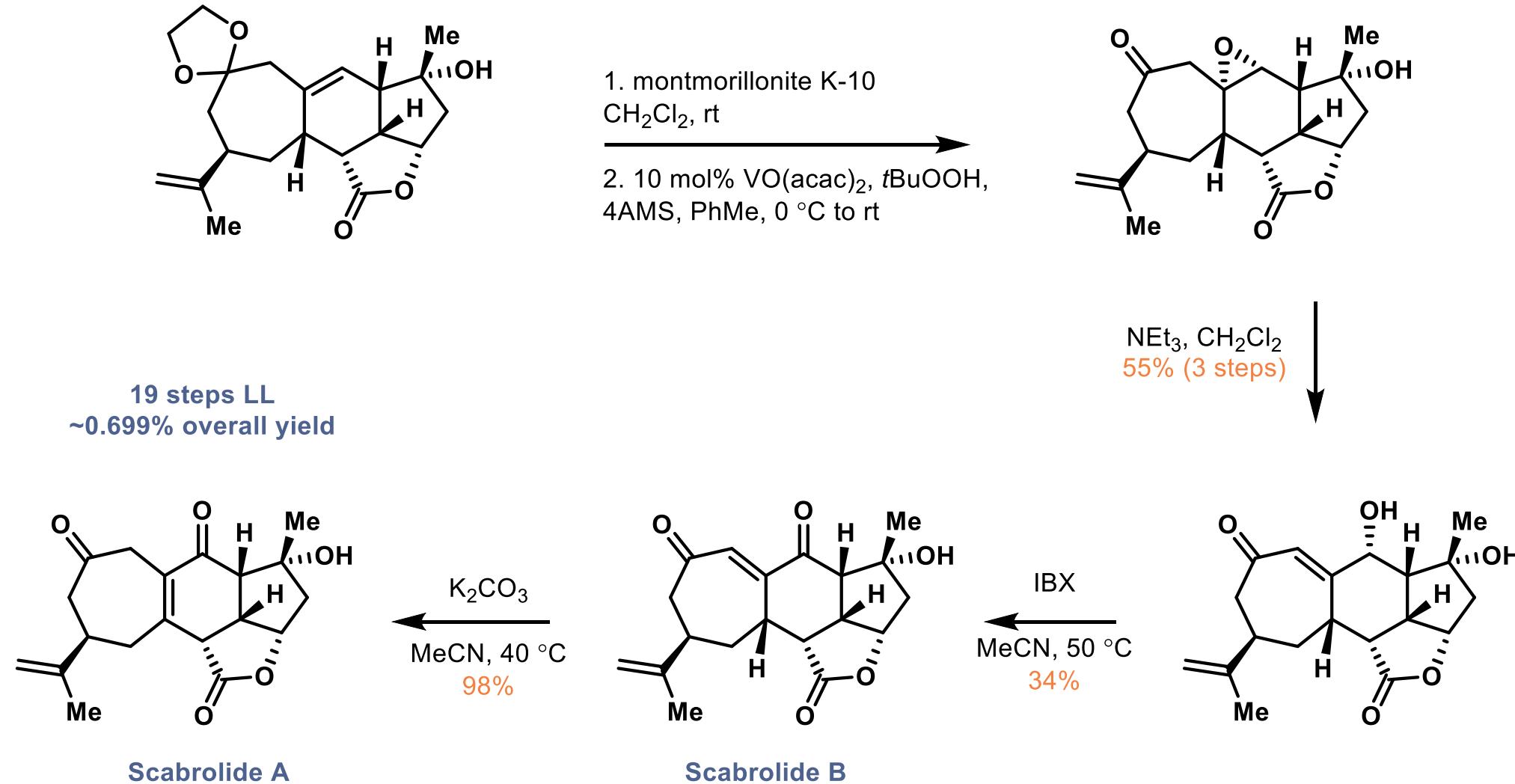
$\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$   
55% (3 steps)



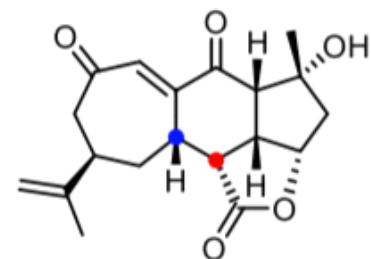
# Fürstner Synthesis: Completing the Synthesis



# Fürstner Synthesis: Completing the Synthesis

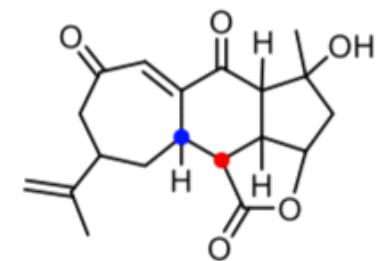


## But Wait! The NMRs don't match!



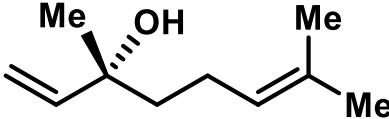
3.19 ppm    3.02 ppm  
36.4 ppm    43.4 ppm

synthetic 1

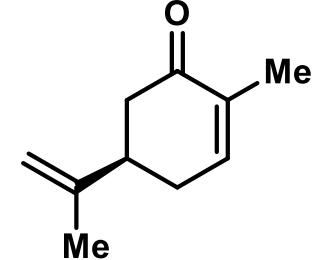


2.75 ppm    3.14 ppm  
41.6 ppm    45.3 ppm

authentic scabrolide B  
[proposed constitution]

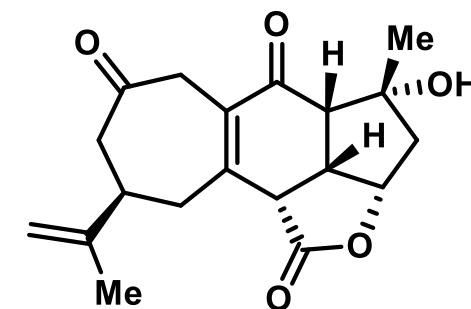


# Final Evaluation



**21 steps LL  
~0.36% overall yield**

## first synthesis



**19 steps LL  
~0.70% overall yield**

## structure disproved