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# A Pericyclic Approach to Eucalrobosone D

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## Dysfunctional Group

Jude Arokianathar, Nassilia Attaba, Calum McLaughlin,  
Elizabeth Munday, Stéphanie Spoehrle

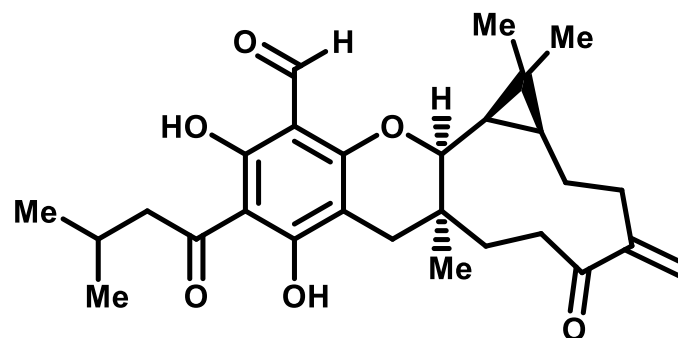


University of  
St Andrews



**4<sup>th</sup> National Retrosynthesis Competition**  
RSC SCI London | 10<sup>th</sup> March 2017

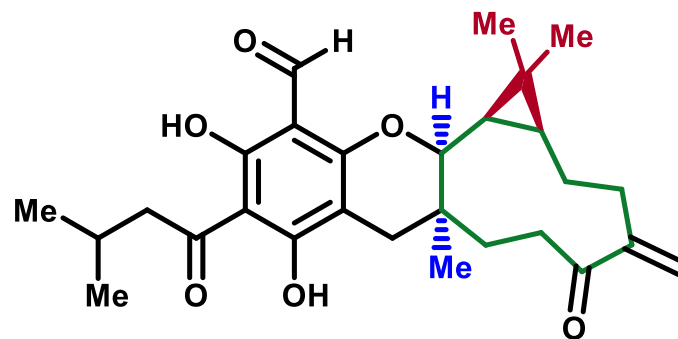
# Eucalrobosone D - Strategy



Eucalrobosone D

- Minimise protecting groups and oxidations/reductions
- Exploit pericyclic reactions to generate molecular complexity
- Early stage induction of enantioselectivity
- Concise synthesis

# Eucalrobusone D – Key Challenges

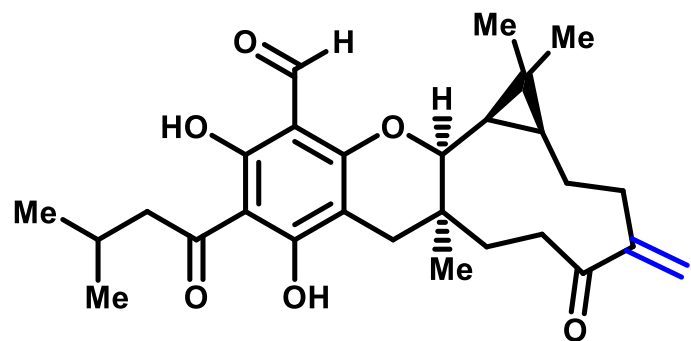


Eucalrobusone D

- *cis*-Fused ring junction
- Macrocyclic formation
- Stereoselective cyclopropanation

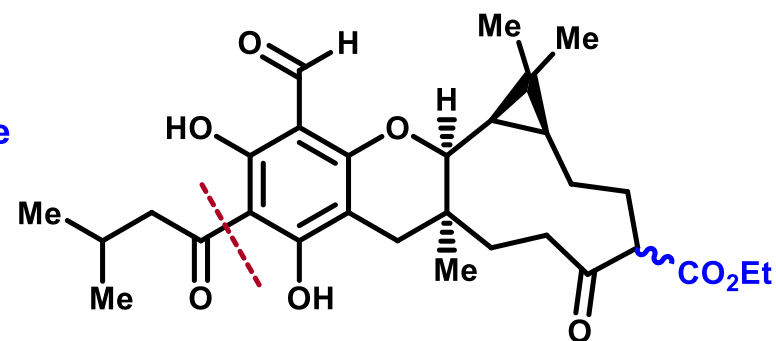
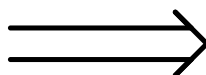


# Eucalrobosone D - Retrosynthesis

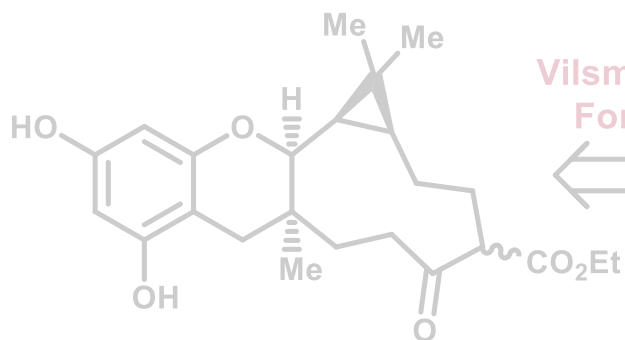


Eucalrobosone D

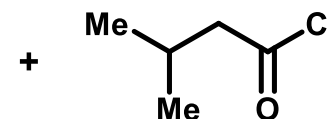
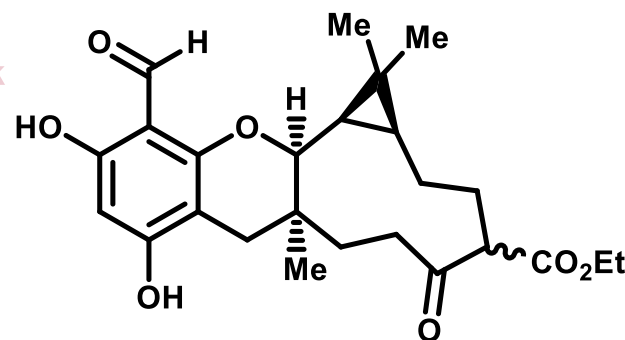
FGI: Vinyl ketone  
formation



Friedel-Crafts  
Acylation



Vilsmeier-Haack  
Formylation

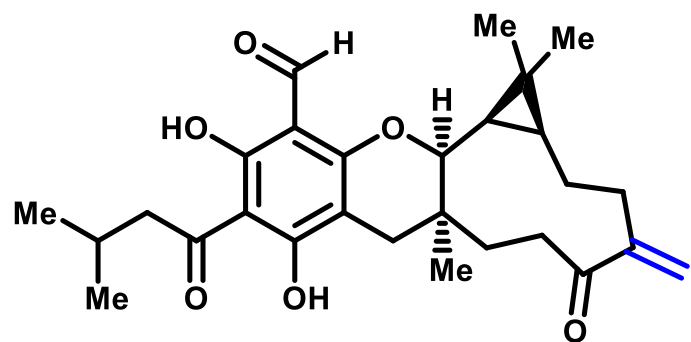


Isovaleryl chloride

CAS: 108-12-3

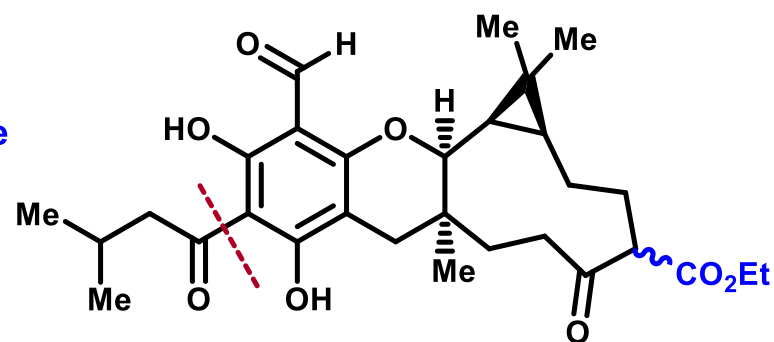
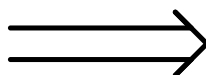
£ 0.24/g (Acros)

# Eucalrobosone D - Retrosynthesis

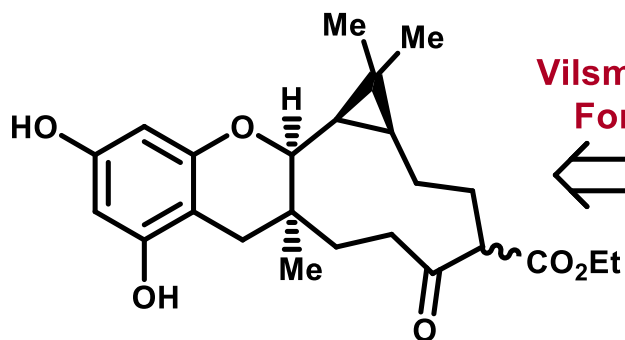


Eucalrobosone D

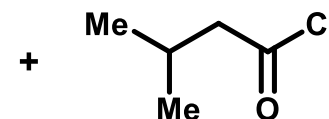
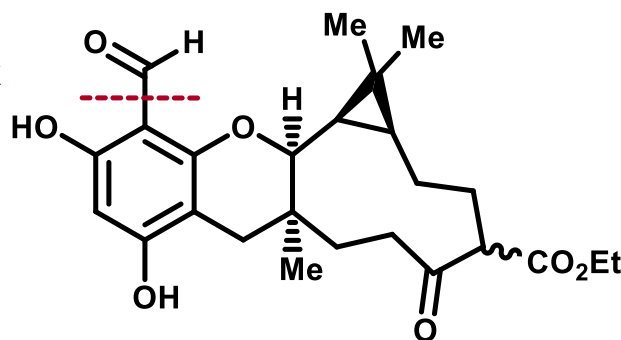
FGI: Vinyl ketone formation



Friedel-Crafts Acylation

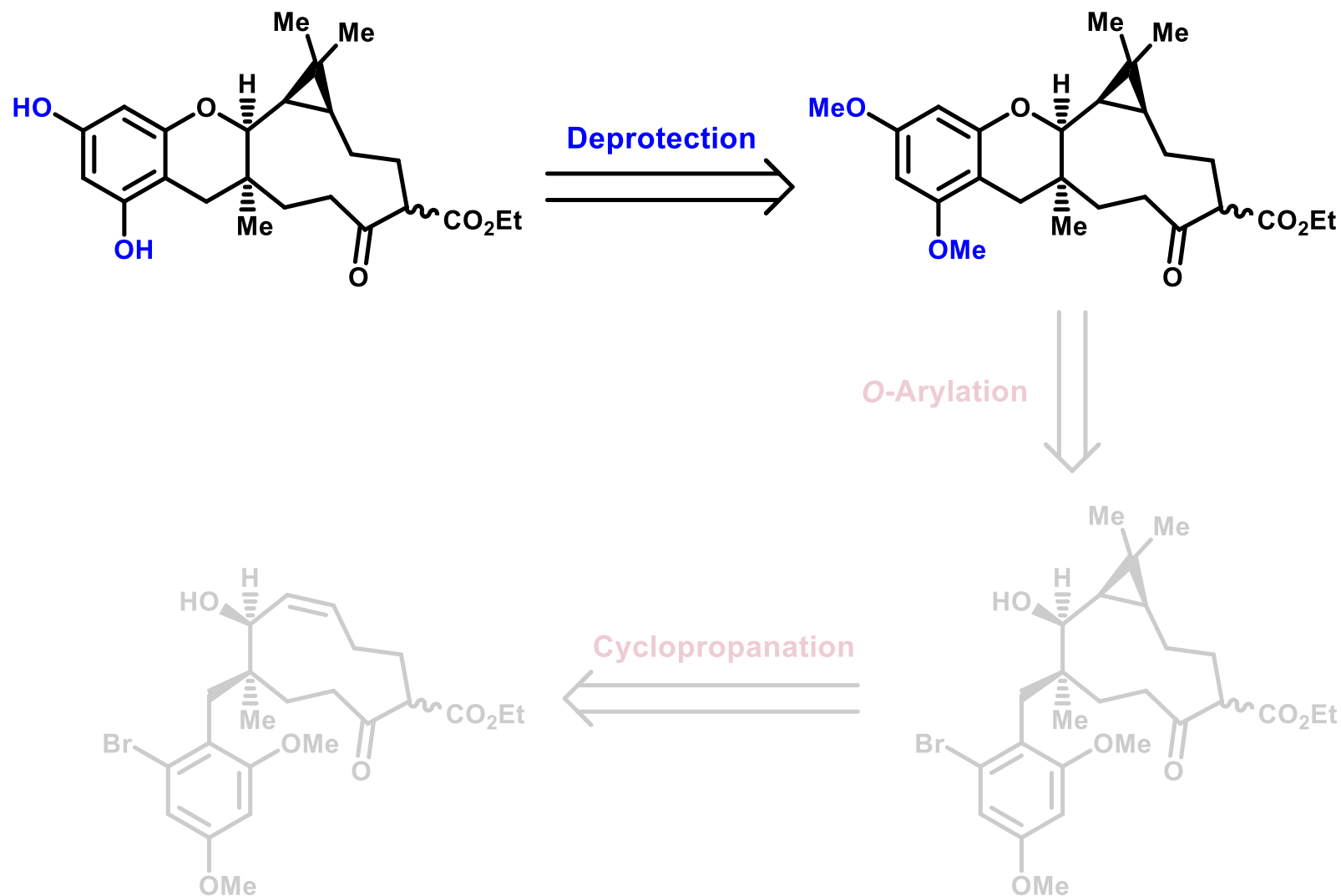


Vilsmeier-Haack Formylation

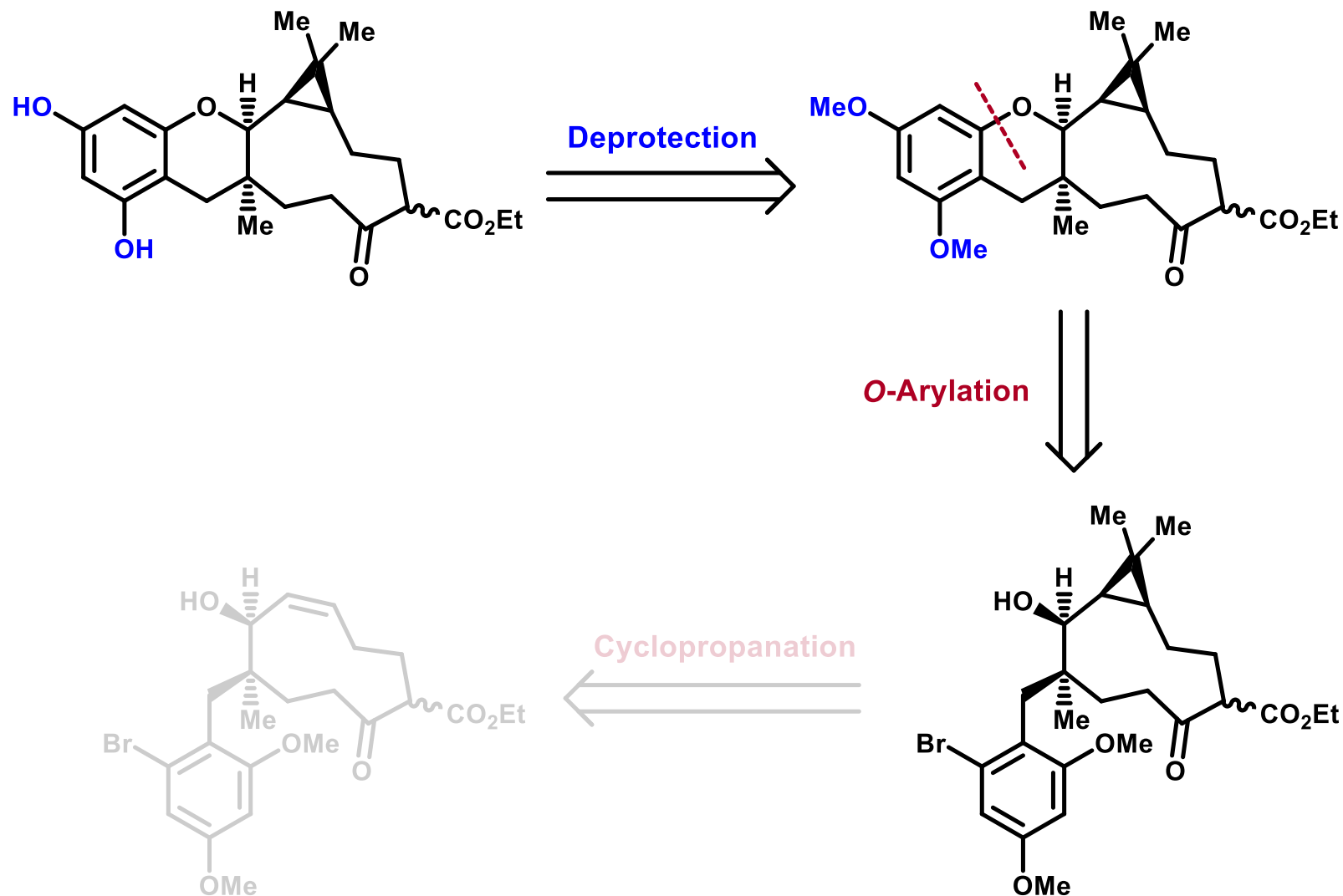


Isovaleryl chloride  
CAS: 108-12-3  
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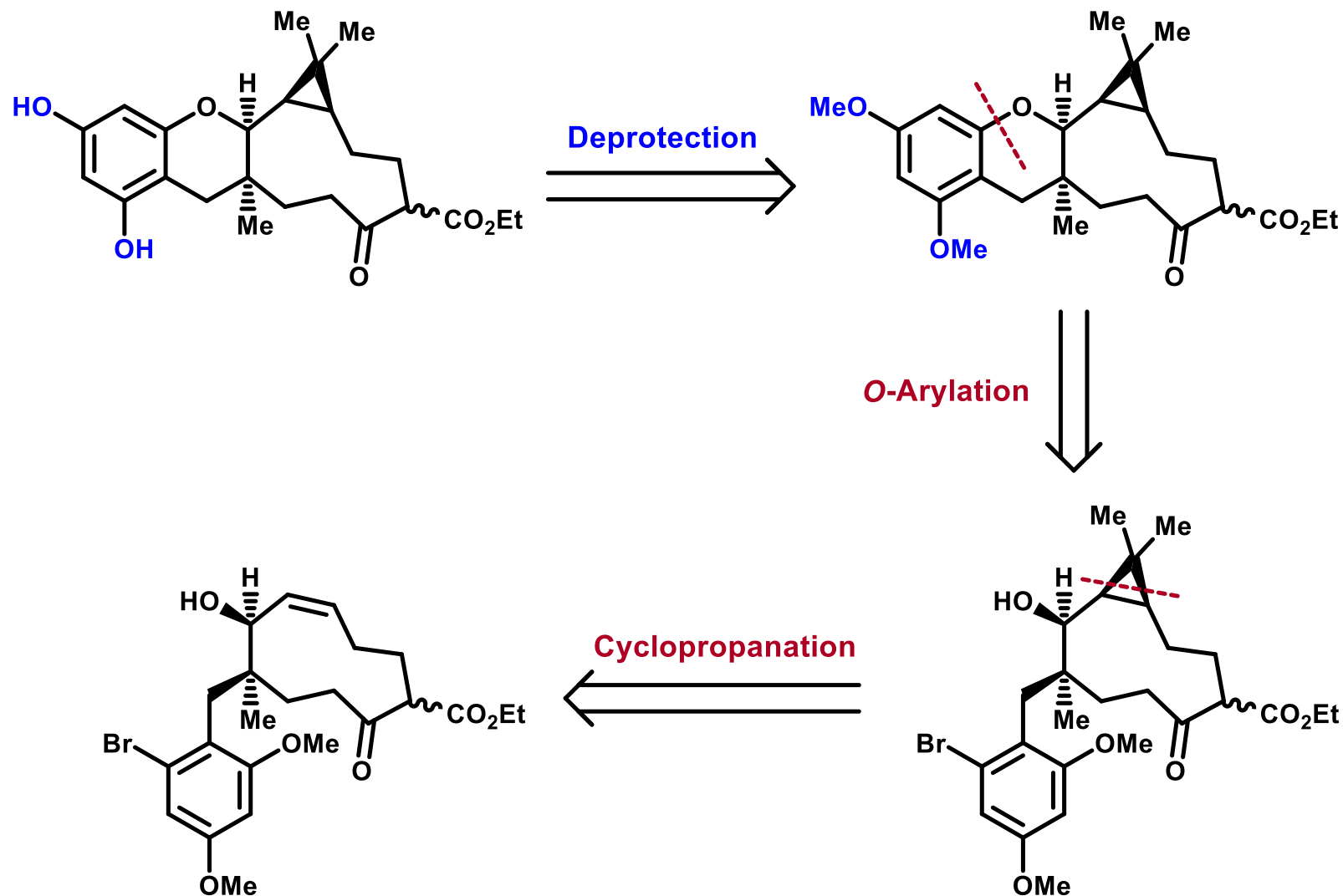


# Eucalrobosone D - Retrosynthesis

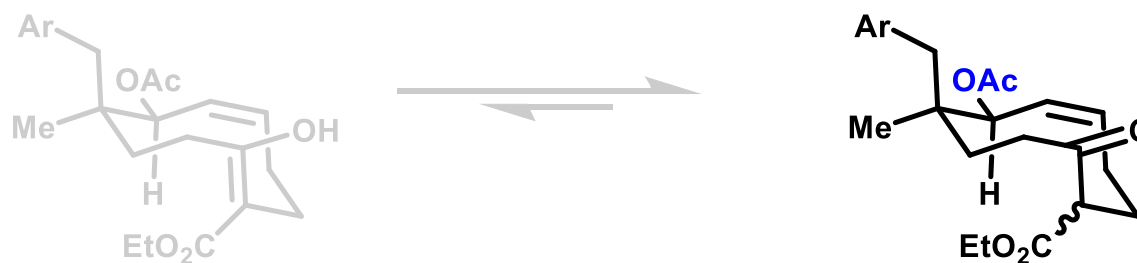
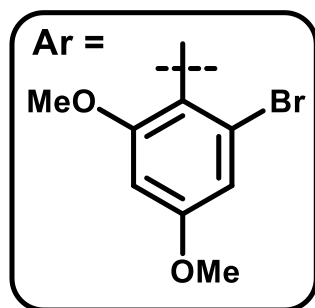
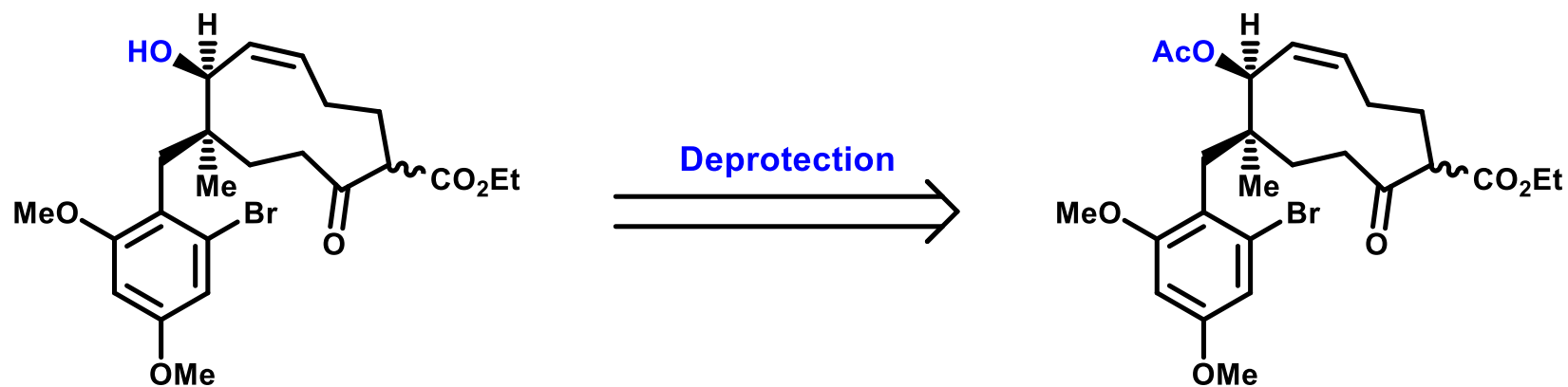




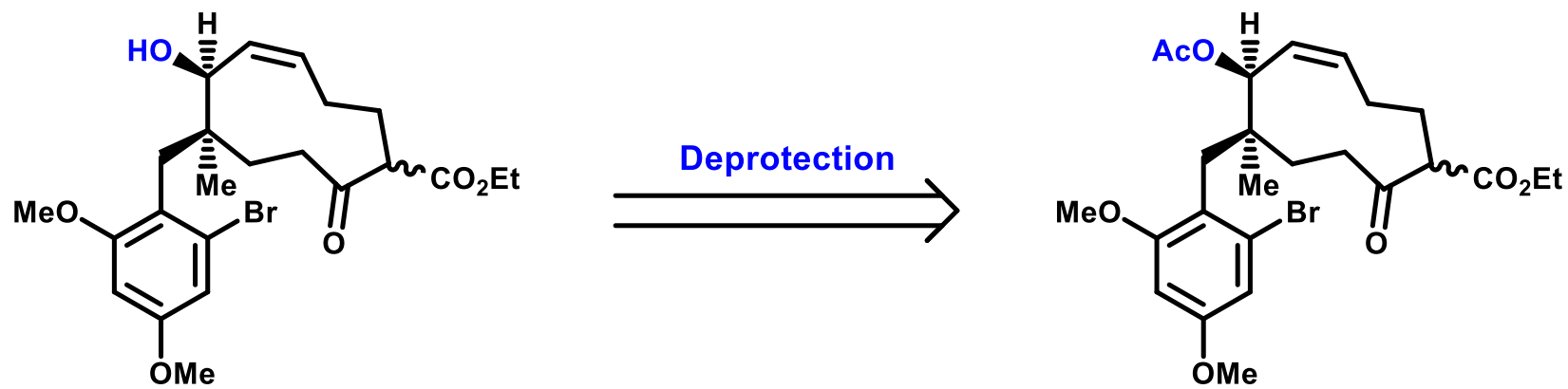
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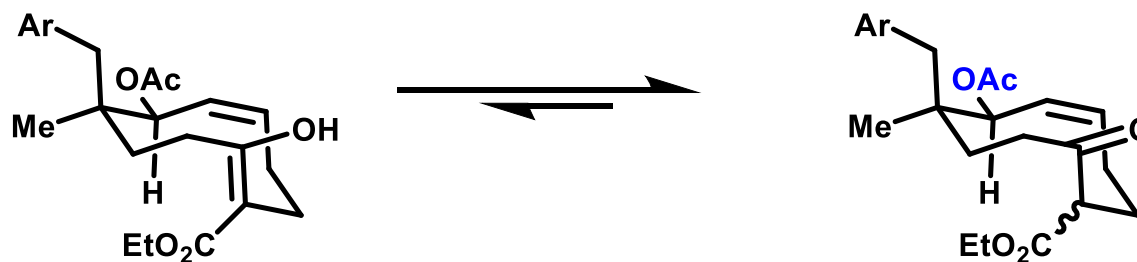
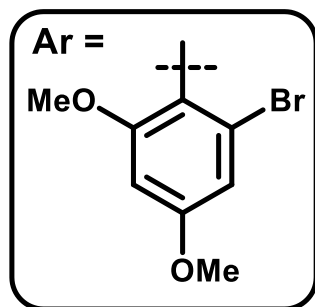
# Eucalrobosone D - Retrosynthesis



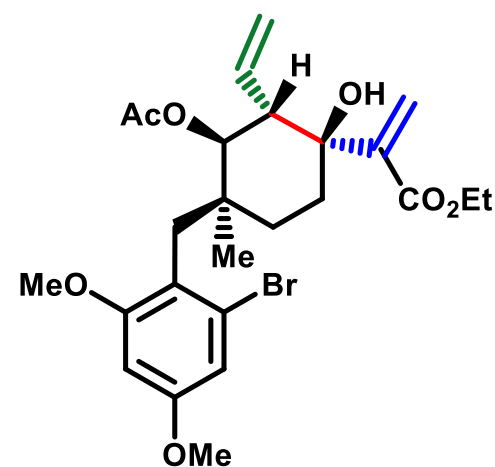
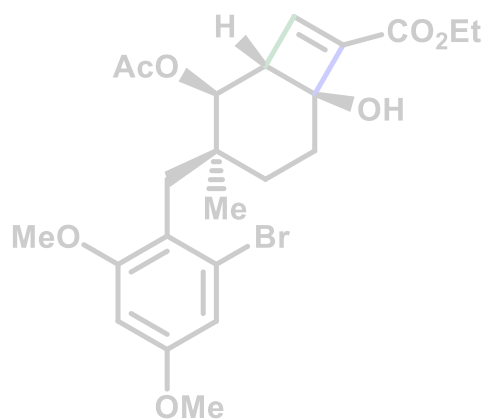
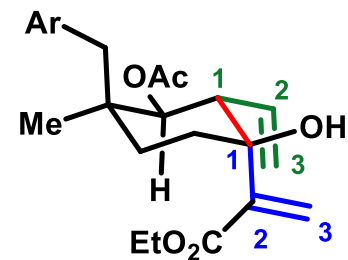
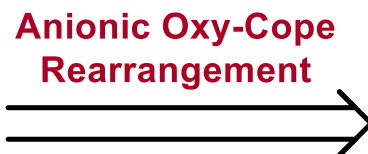
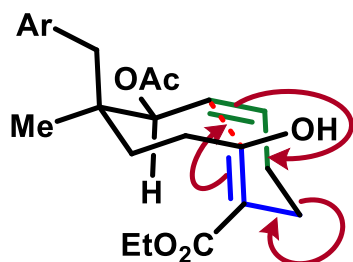
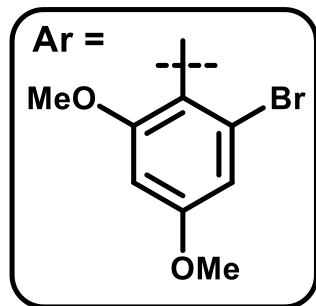
# Eucalrobosone D - Retrosynthesis



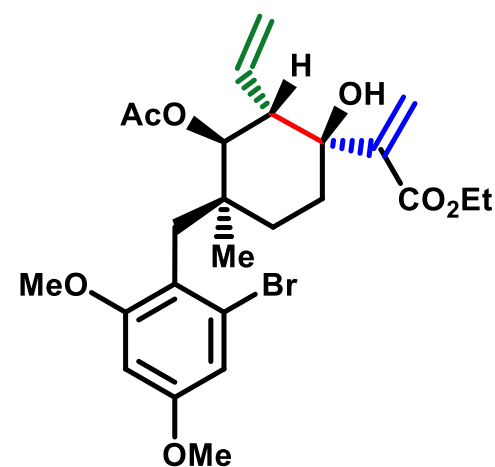
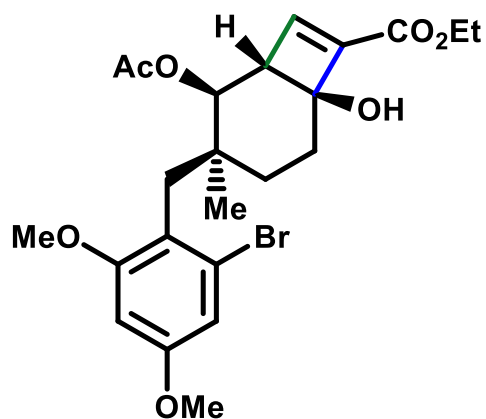
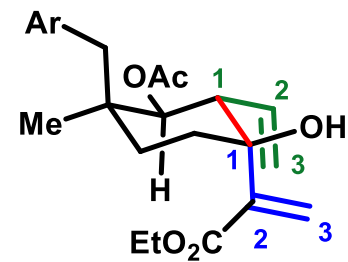
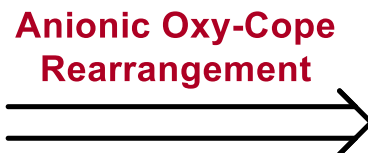
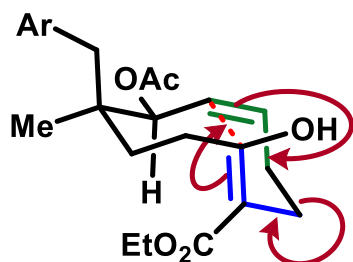
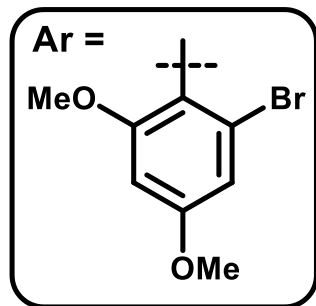
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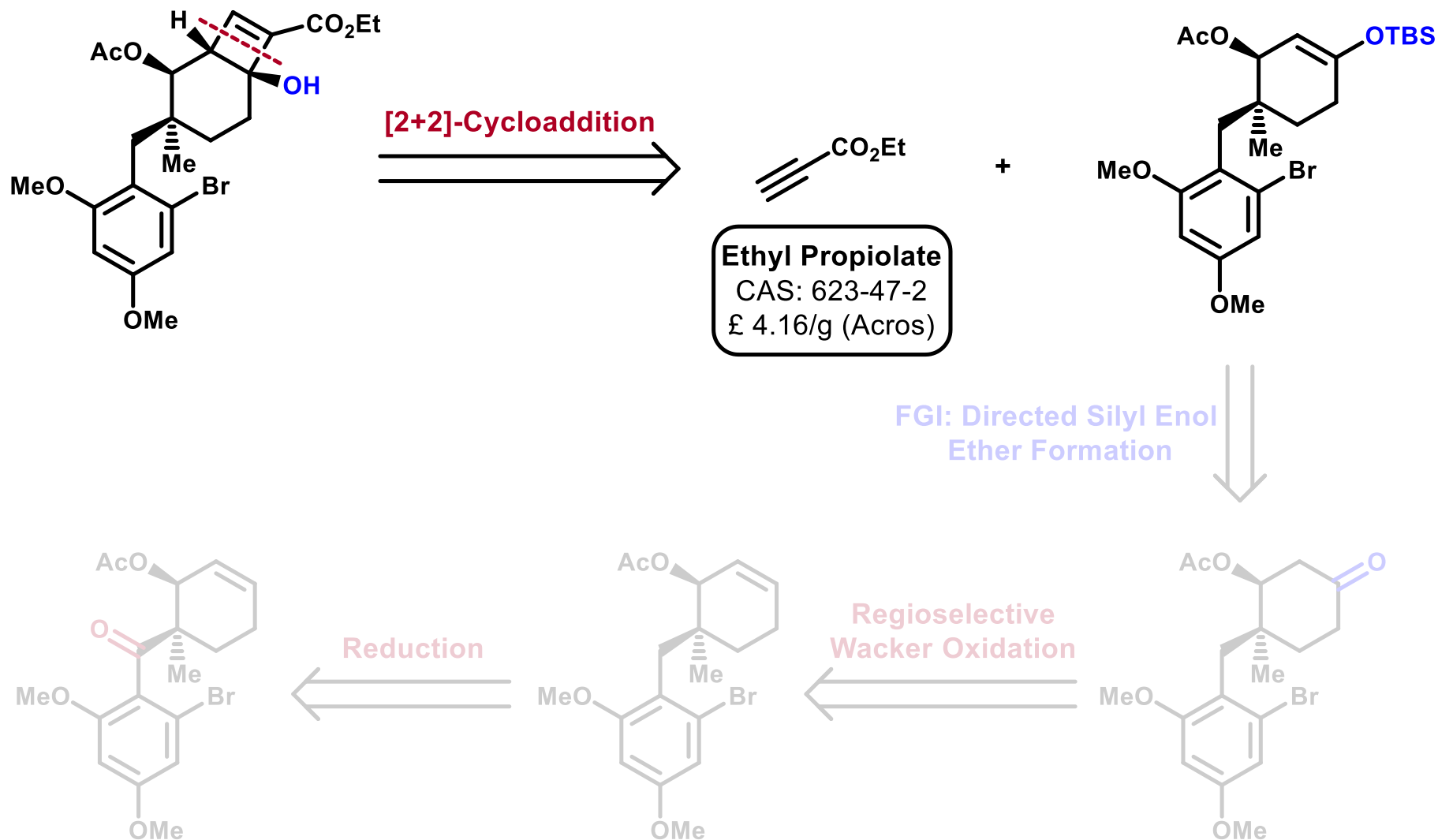
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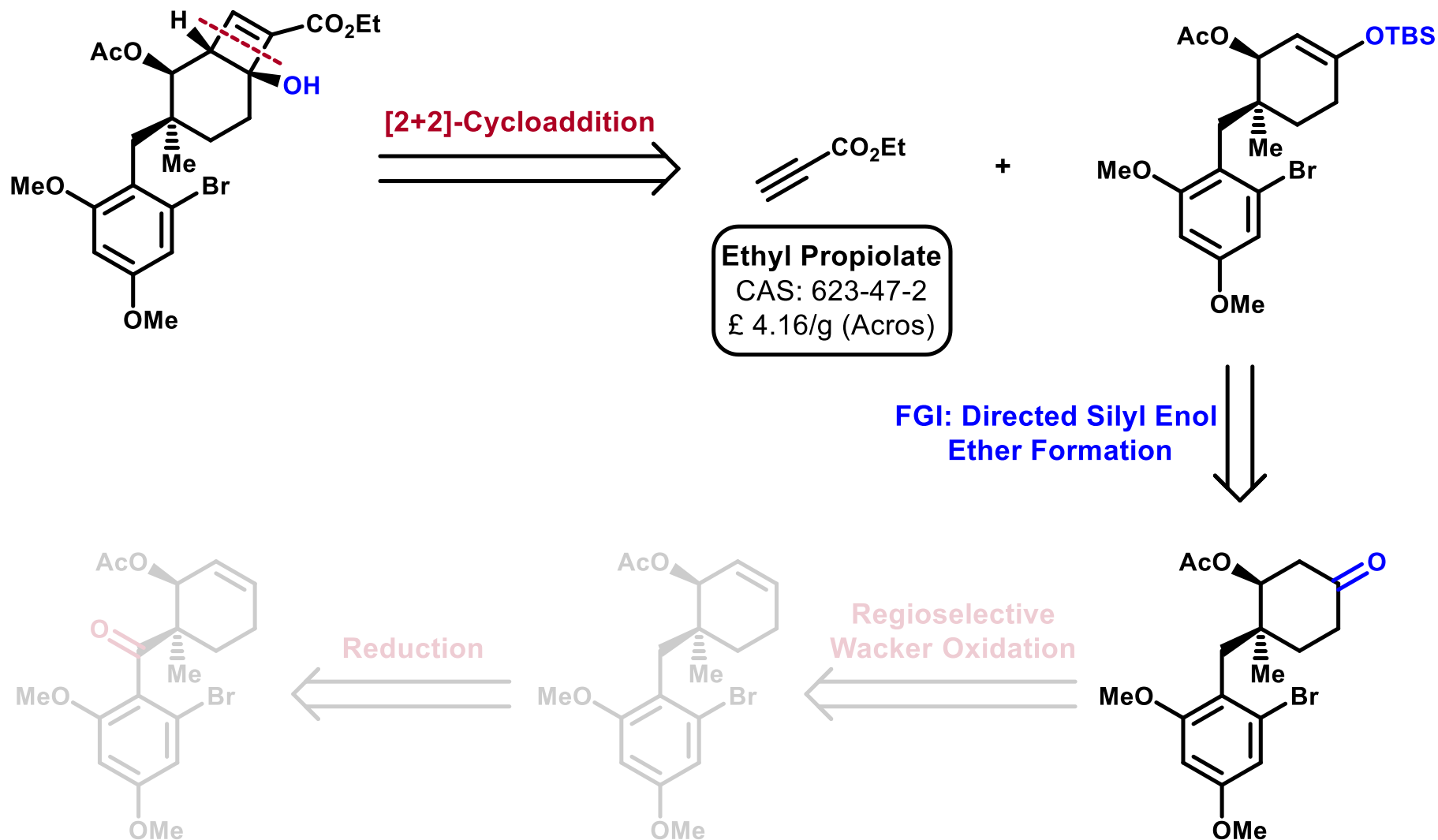
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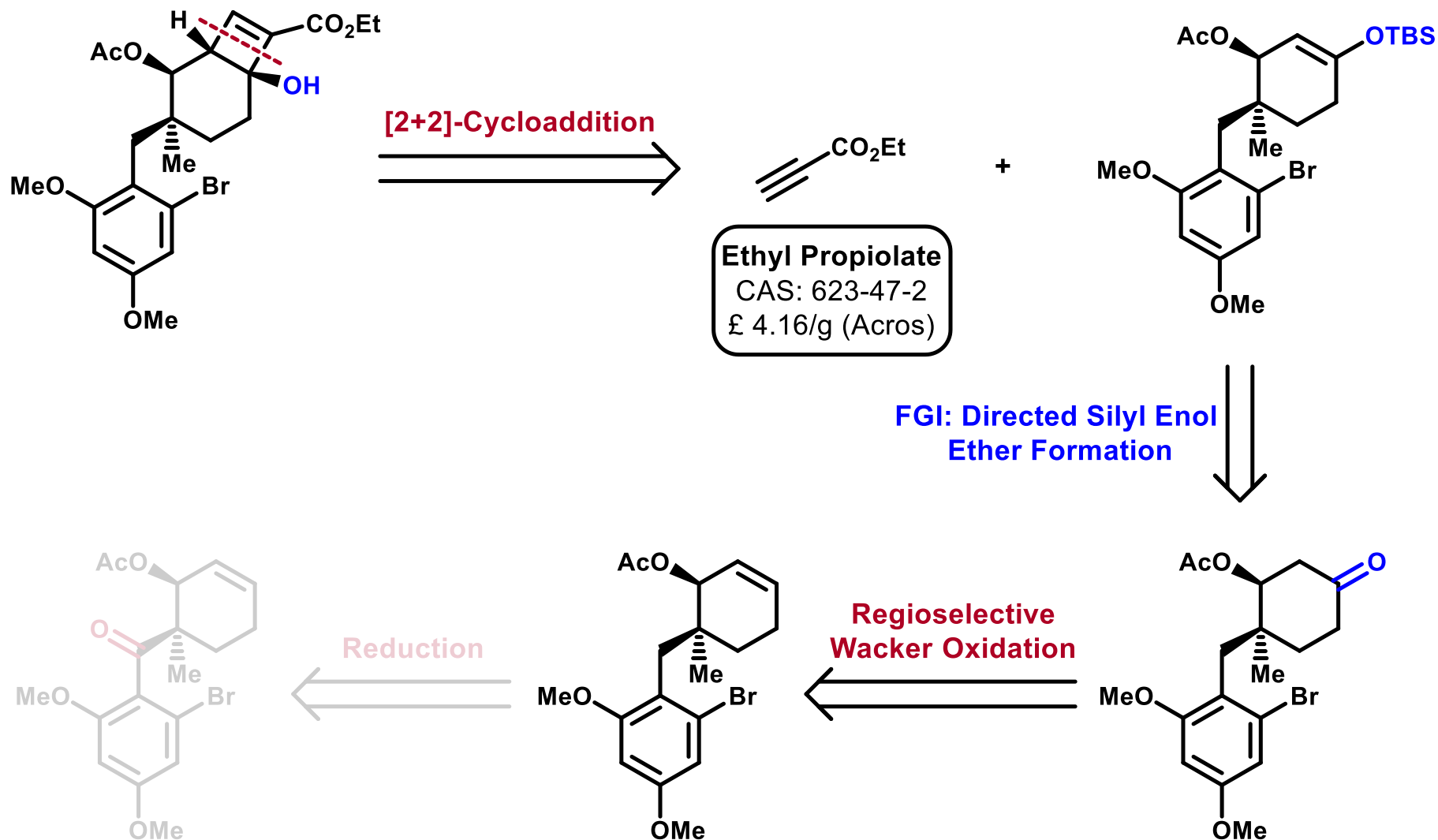
# Eucalrobosone D - Retrosynthesis



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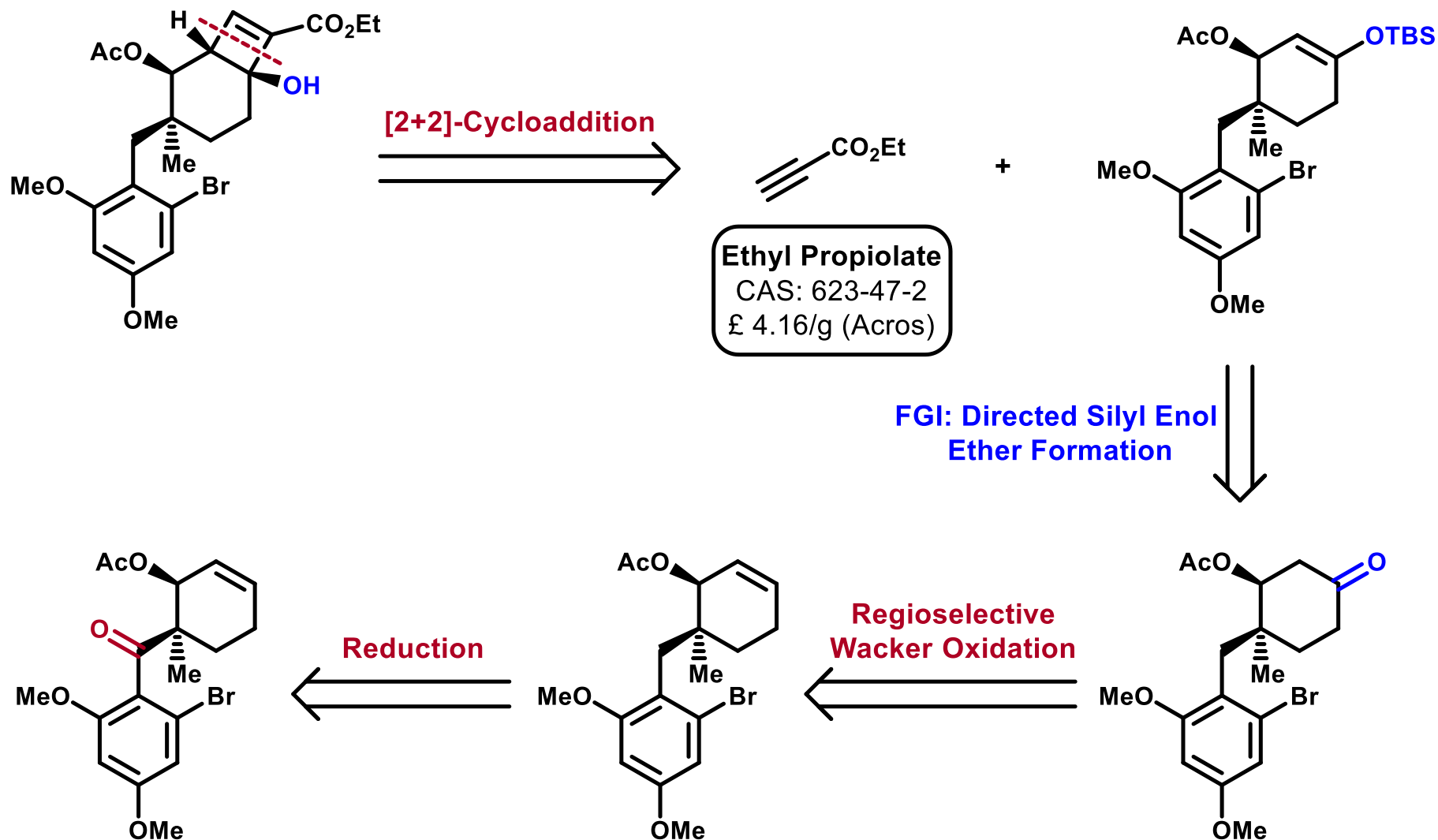


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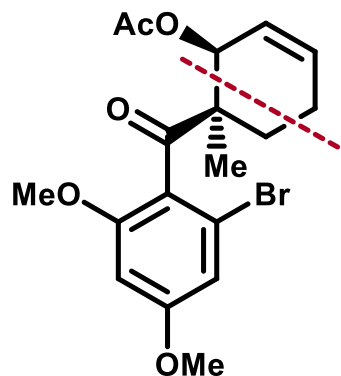




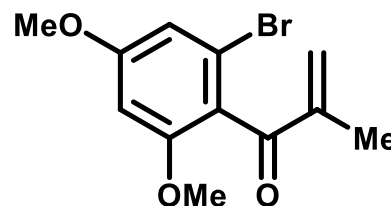
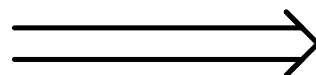
# Eucalrobosone D - Retrosynthesis



# Eucalrobosone D - Retrosynthesis



**Stereoselective  
Diels-Alder  
Reaction**



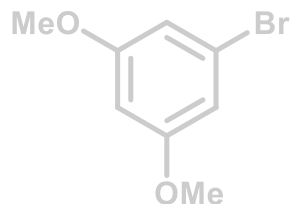
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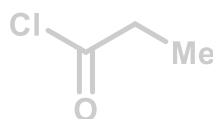
$\alpha$ -Methylenation



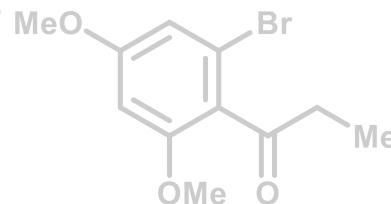
FGI:  
Enol Formation  
Acetylation



+



**Friedel-Crafts  
Acylation**

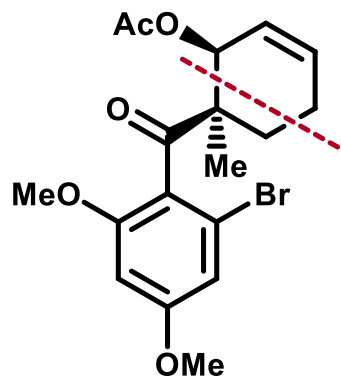


1-Bromo-3,5-dimethoxybenzene  
CAS: 20469-65-2  
£ 1.78/g (Acros)

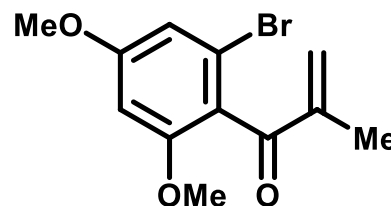
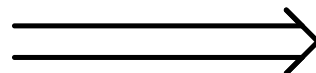
Propionyl chloride  
CAS: 79-03-8  
£ 0.07/g (Acros)

Crotonaldehyde  
CAS: 4170-30-3  
£ 1.78/g (Alfa)

# Eucalrobosone D - Retrosynthesis



**Stereoselective  
Diels-Alder  
Reaction**



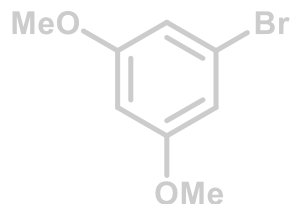
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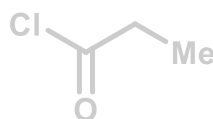
$\alpha$ -Methylenation



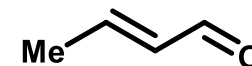
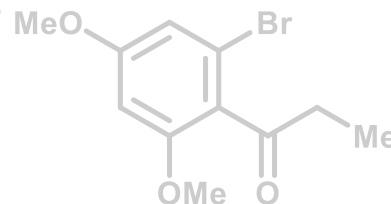
**FGI:  
Enol Formation  
Acetylation**



+



**Friedel-Crafts  
Acylation**



**1-Bromo-3,5-  
dimethoxybenzene**

CAS: 20469-65-2

£ 1.78/g (Acros)

**Propionyl  
chloride**

CAS: 79-03-8

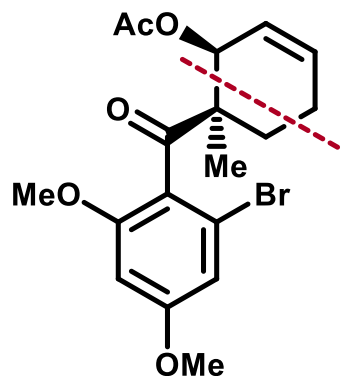
£ 0.07/g (Acros)

**Crotonaldehyde**

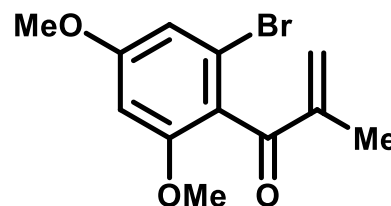
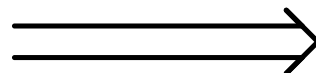
CAS: 4170-30-3

£ 1.78/g (Alfa)

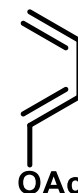
# Eucalrobosone D - Retrosynthesis



**Stereoselective  
Diels-Alder  
Reaction**



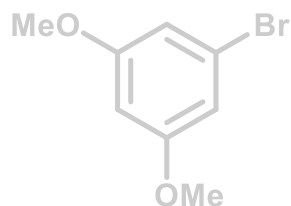
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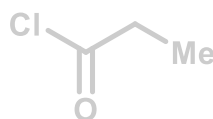
**$\alpha$ -Methylenation**



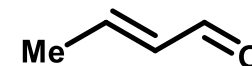
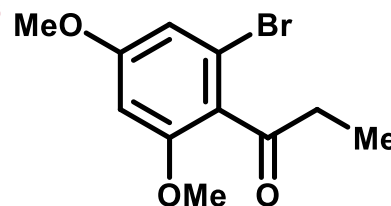
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**Friedel-Crafts  
Acylation**

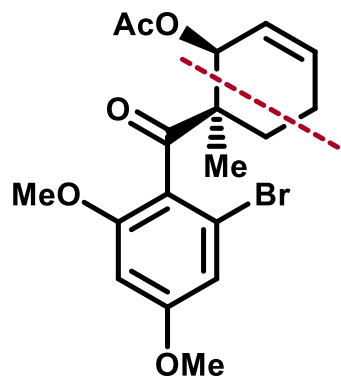


**1-Bromo-3,5-dimethoxybenzene**  
CAS: 20469-65-2  
£ 1.78/g (Acros)

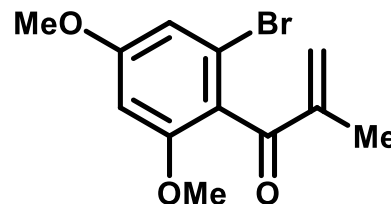
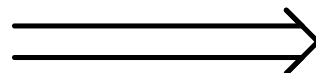
**Propionyl chloride**  
CAS: 79-03-8  
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**Crotonaldehyde**  
CAS: 4170-30-3  
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# Eucalrobosone D - Retrosynthesis



**Stereoselective  
Diels-Alder  
Reaction**



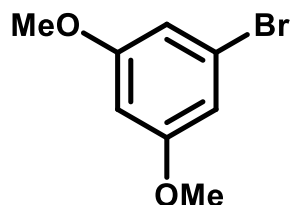
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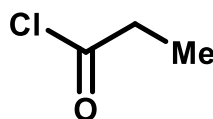
**$\alpha$ -Methylenation**



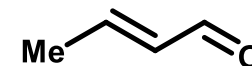
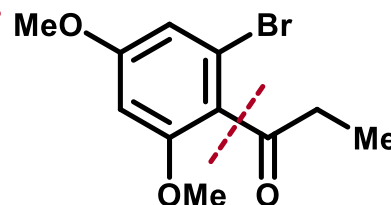
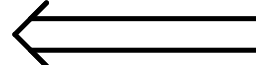
**FGI:  
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+



**Friedel-Crafts  
Acylation**

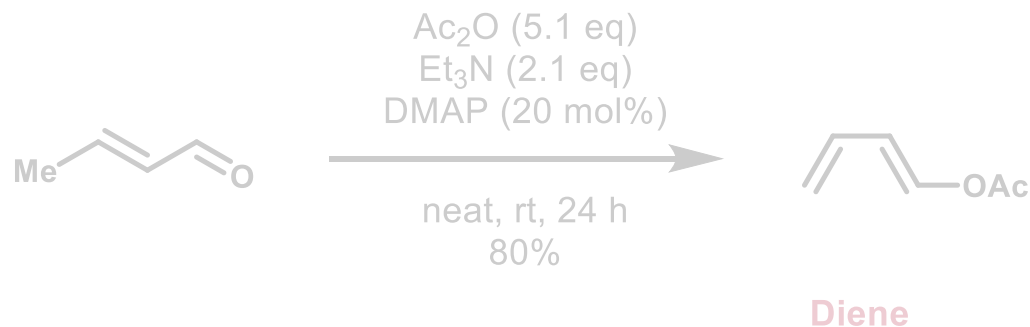
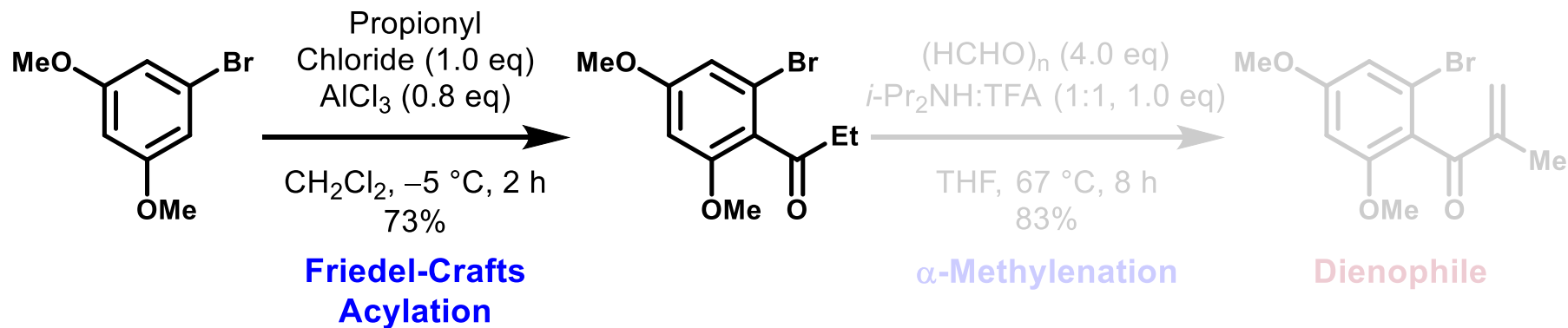


**1-Bromo-3,5-dimethoxybenzene**  
CAS: 20469-65-2  
£ 1.78/g (Acros)

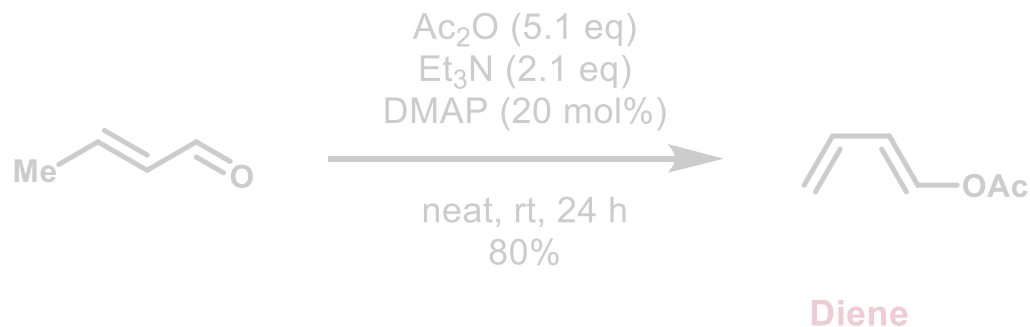
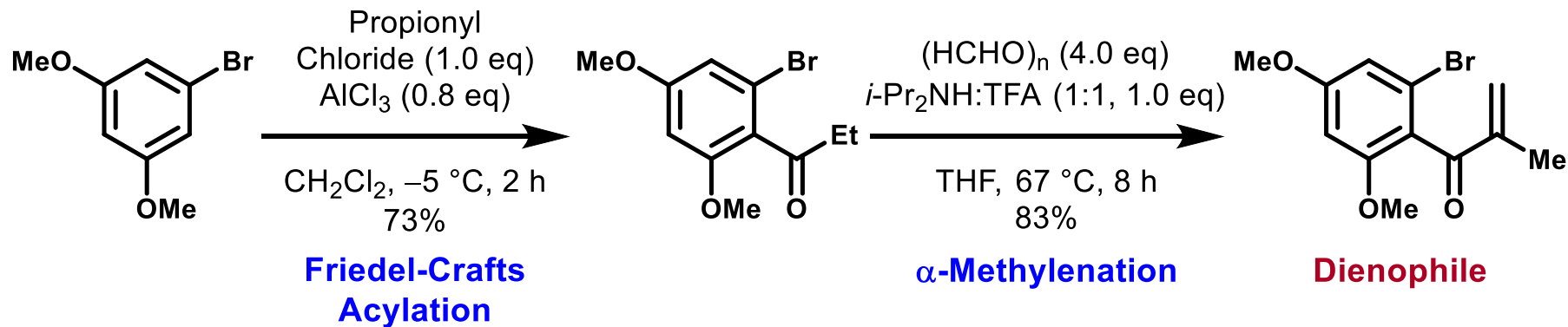
**Propionyl chloride**  
CAS: 79-03-8  
£ 0.07/g (Acros)

**Crotonaldehyde**  
CAS: 4170-30-3  
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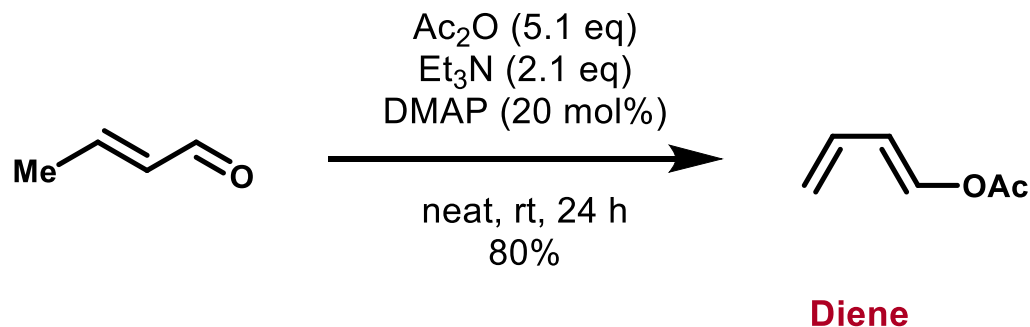
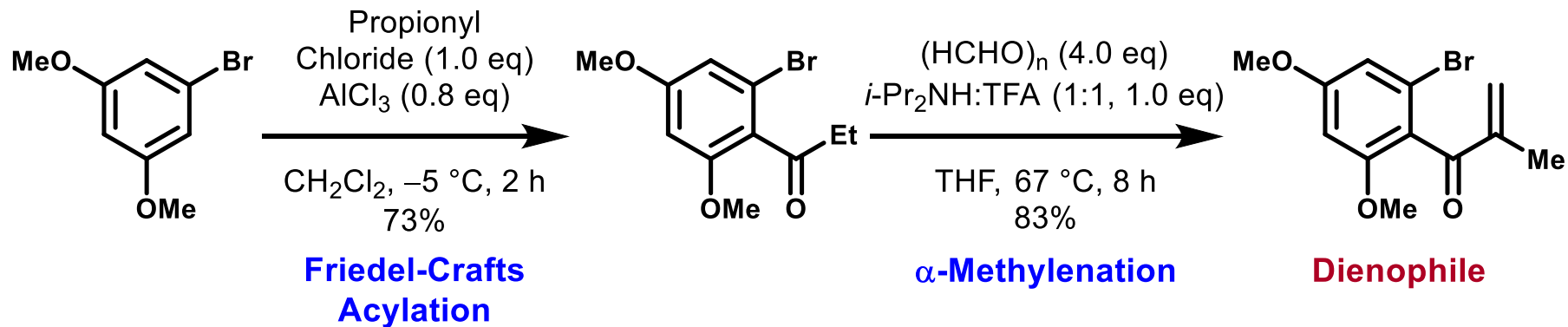
# Diels-Alder



# Diels-Alder

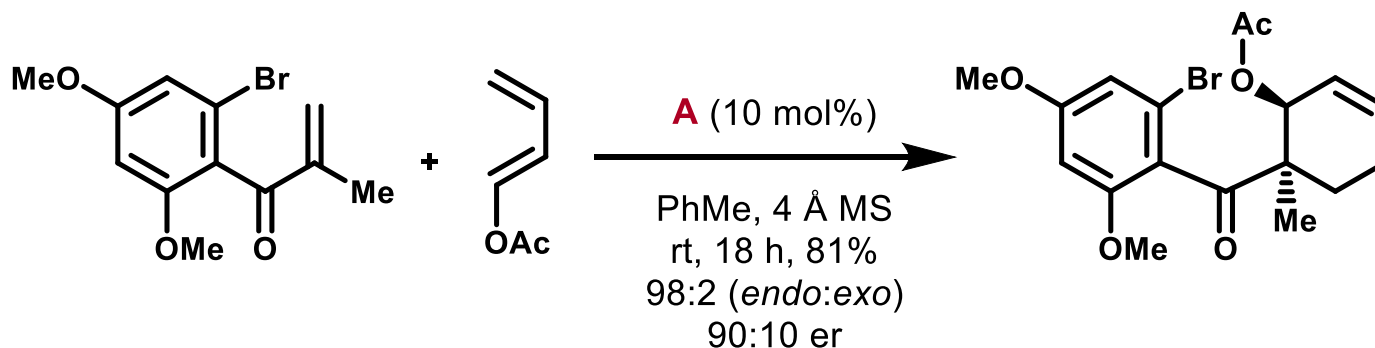


# Diels-Alder

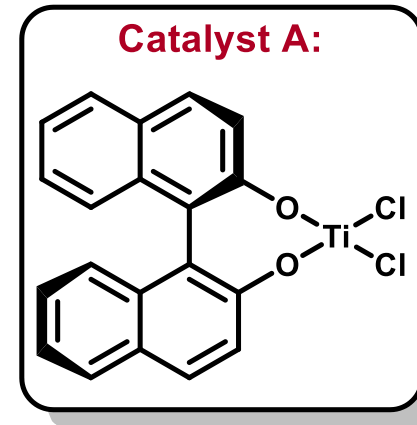




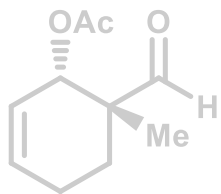
# Diels-Alder



**Catalytic Enantioselective  
Endo-selective Diels-Alder**

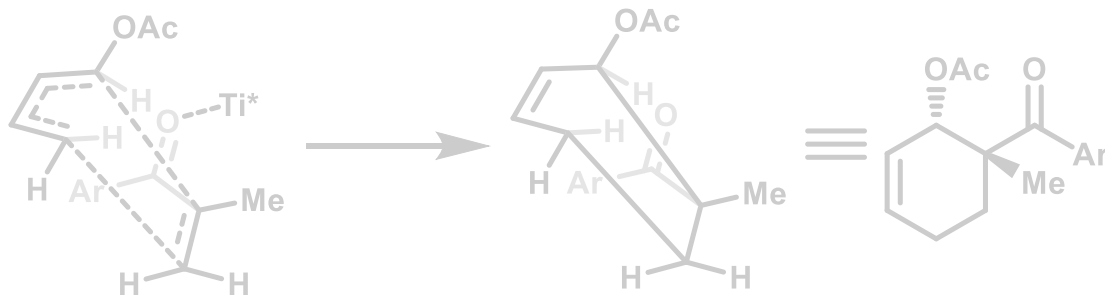


## Literature Precedent



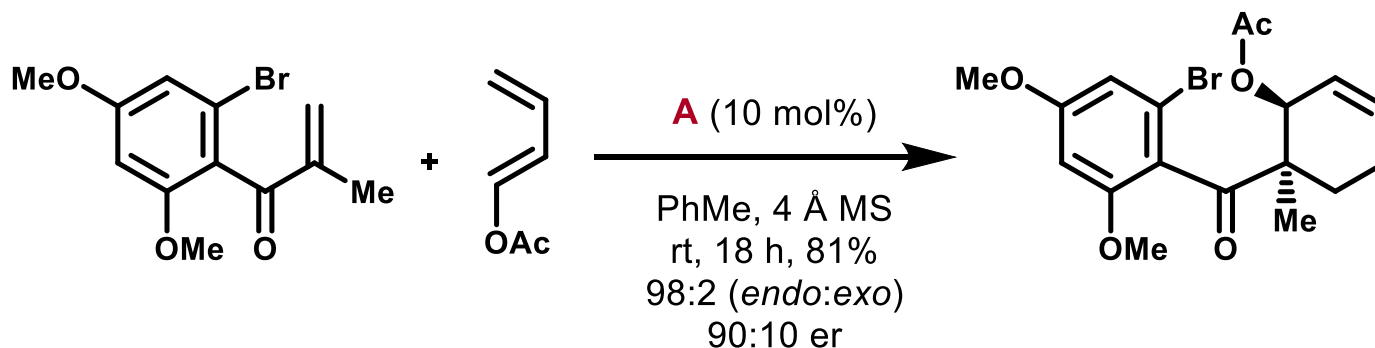
**Mikami and Nakai 1991**  
81%, 98:2 (*endo:exo*)  
90:10 er

## Enantioselective Diels-Alder: Proposed Transition State

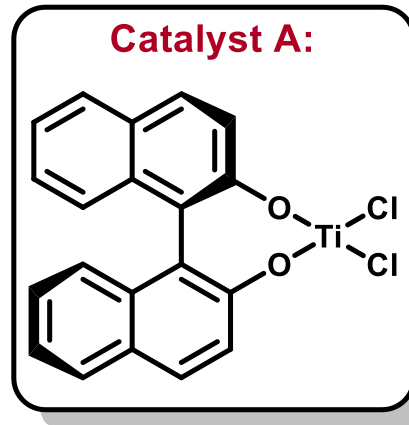


- *Endo* approach of diene
- (*R*)-Binol Ti catalyst governs  $\pi$ -facial selectivity
- Two defined stereogenic centres formed

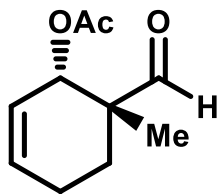
# Diels-Alder



**Catalytic Enantioselective  
Endo-selective Diels-Alder**

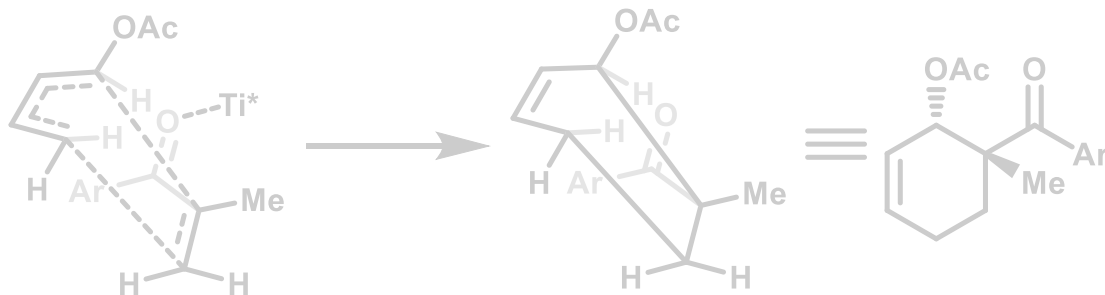


## Literature Precedent



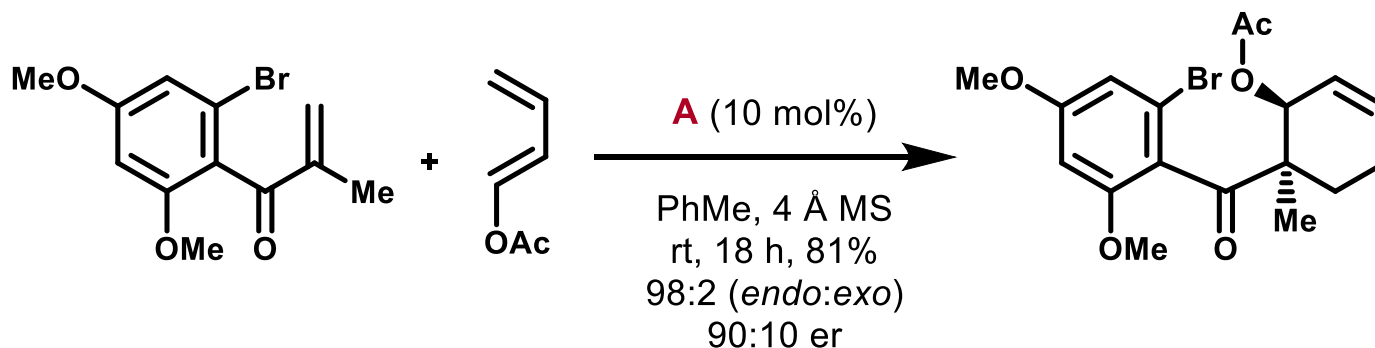
**Mikami and Nakai 1991**  
81%, 98:2 (*endo:exo*)  
90:10 er

## Enantioselective Diels-Alder: Proposed Transition State

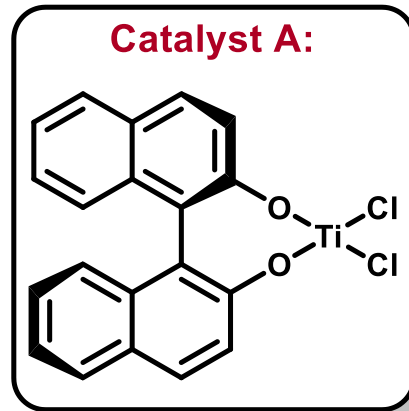


- *Endo* approach of diene
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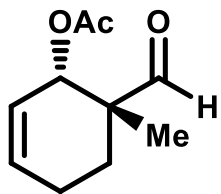
# Diels-Alder



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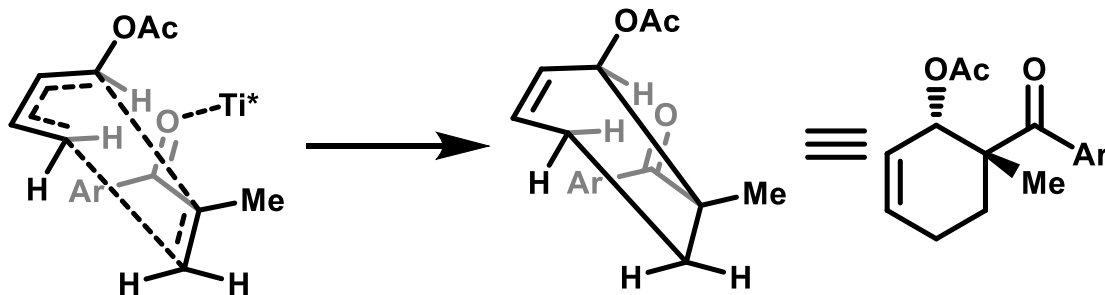


## Literature Precedent



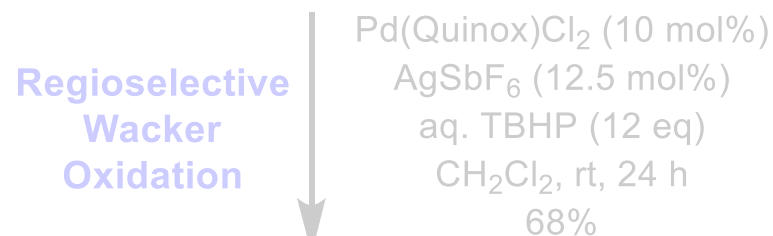
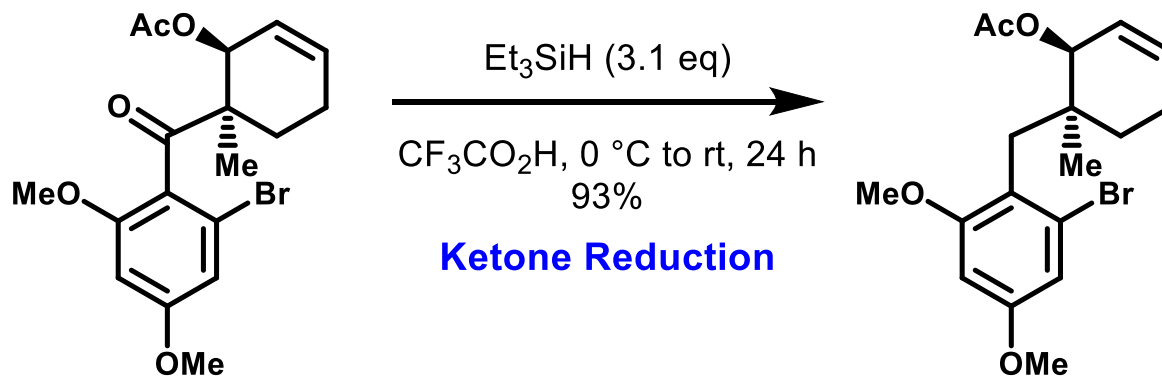
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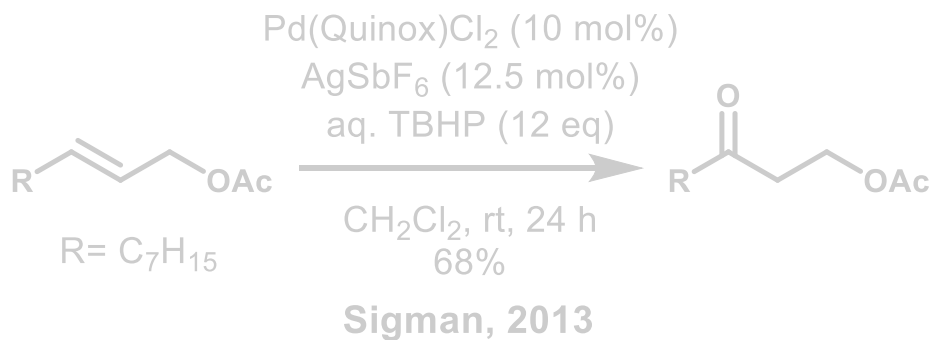


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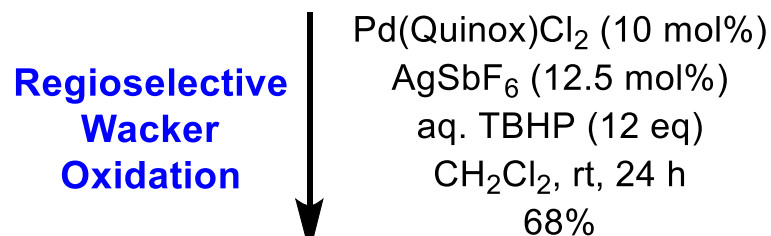
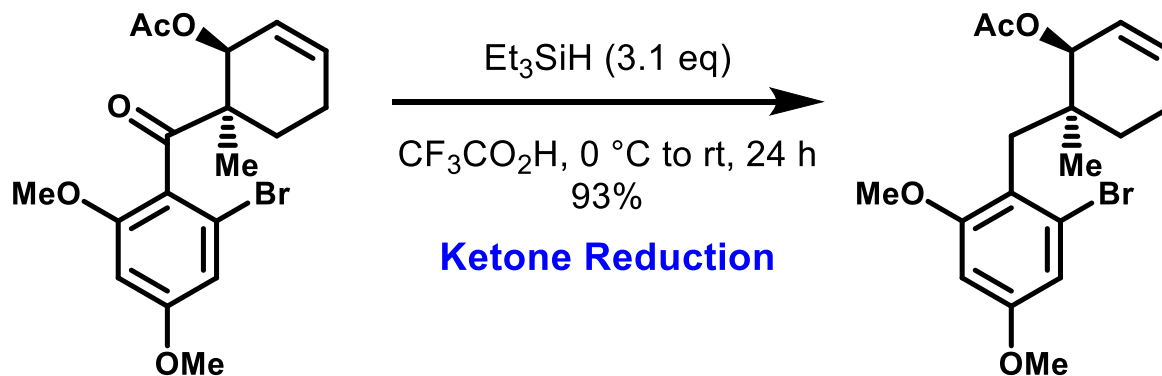
# Anionic Oxy-Cope Precursor



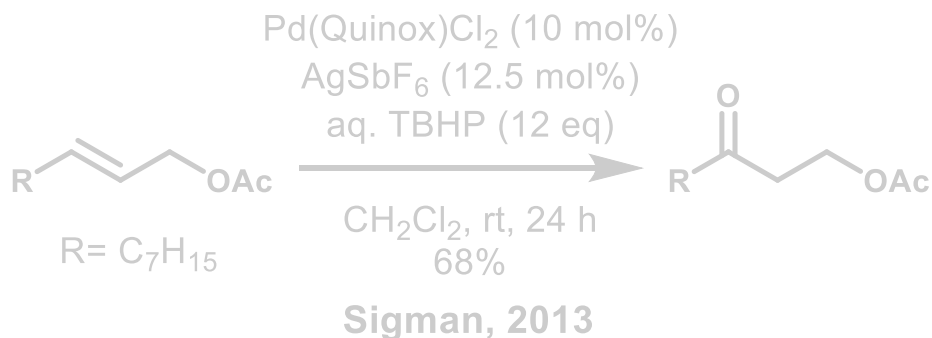
## Literature Precedent



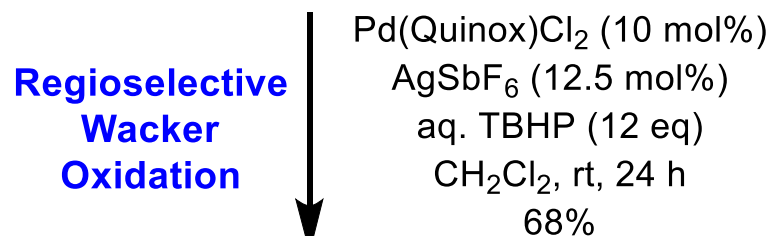
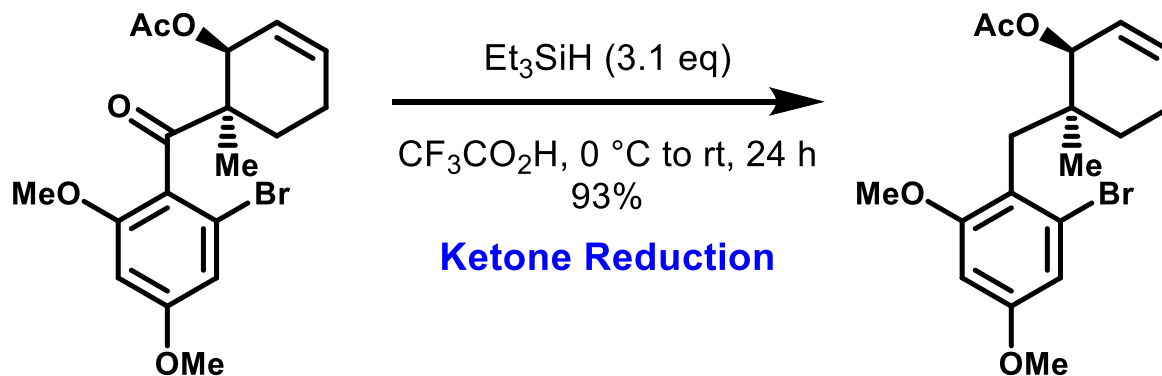
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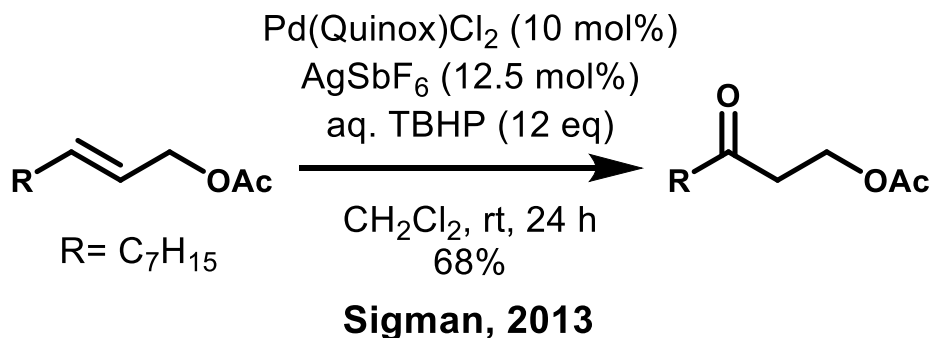
## Literature Precedent



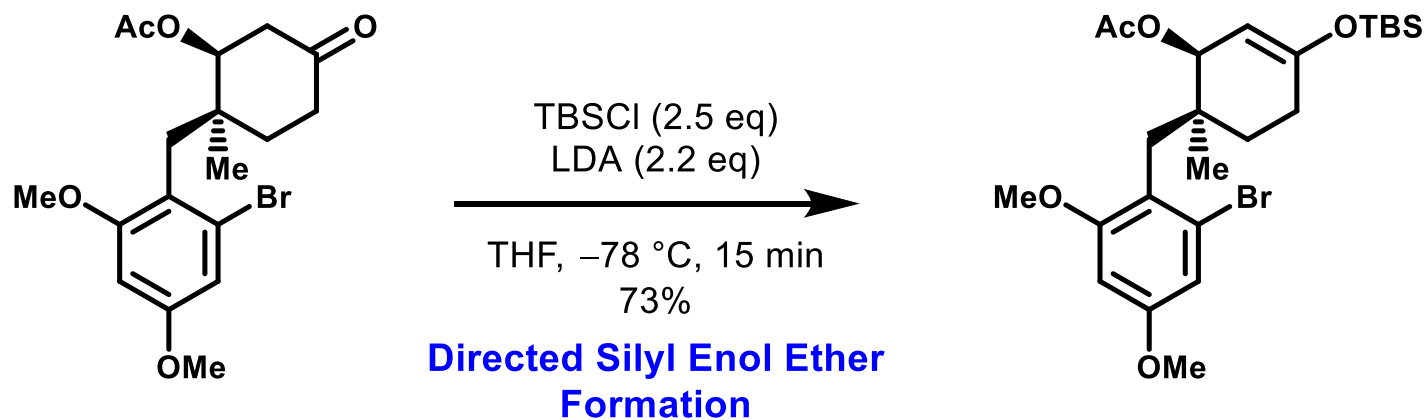
# Anionic Oxy-Cope Precursor



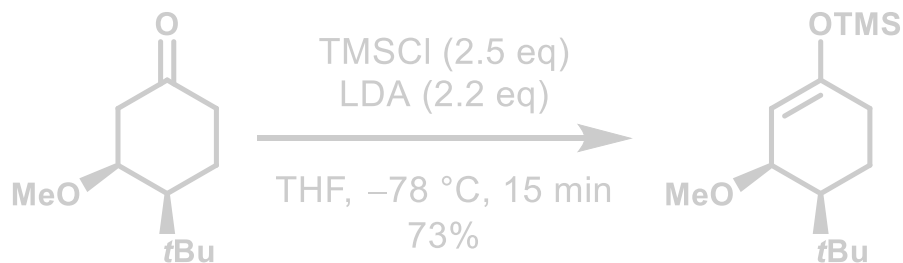
## Literature Precedent



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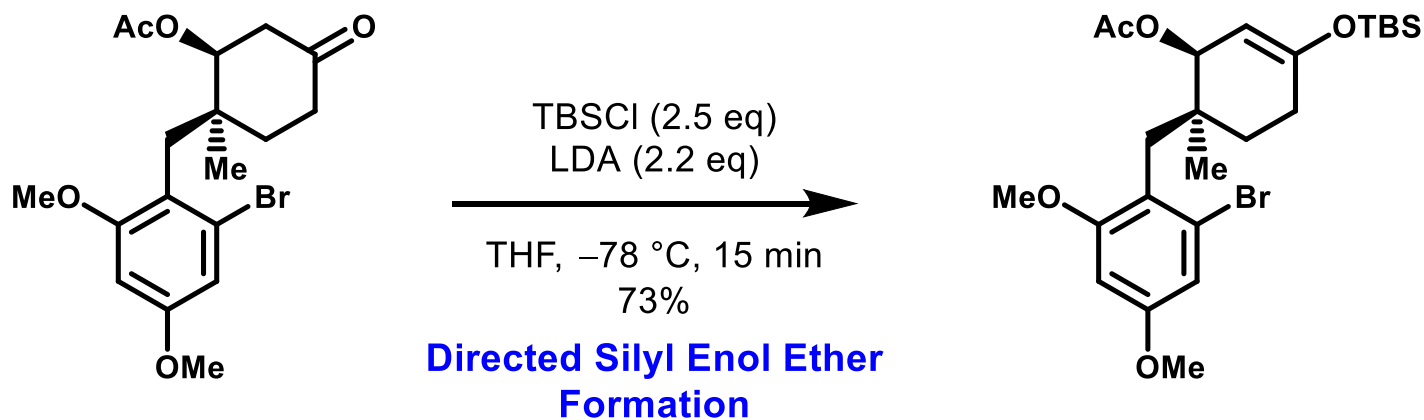
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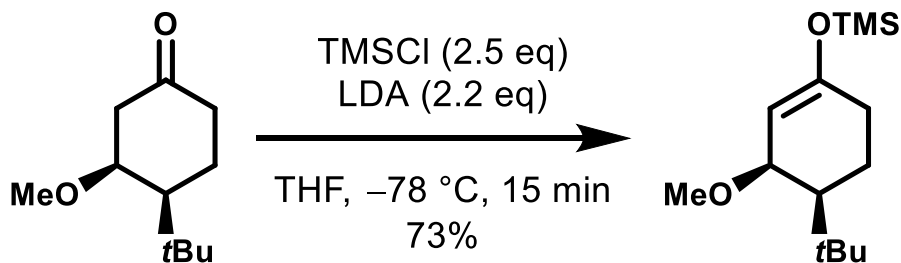
- Tuning the conditions can give either enolate
- Trapping with TMSCl at  $-78\text{ }^{\circ}\text{C}$  gave predominantly the proximal product

Martin, 1990

# Anionic Oxy-Cope Precursor



## Literature Precedent

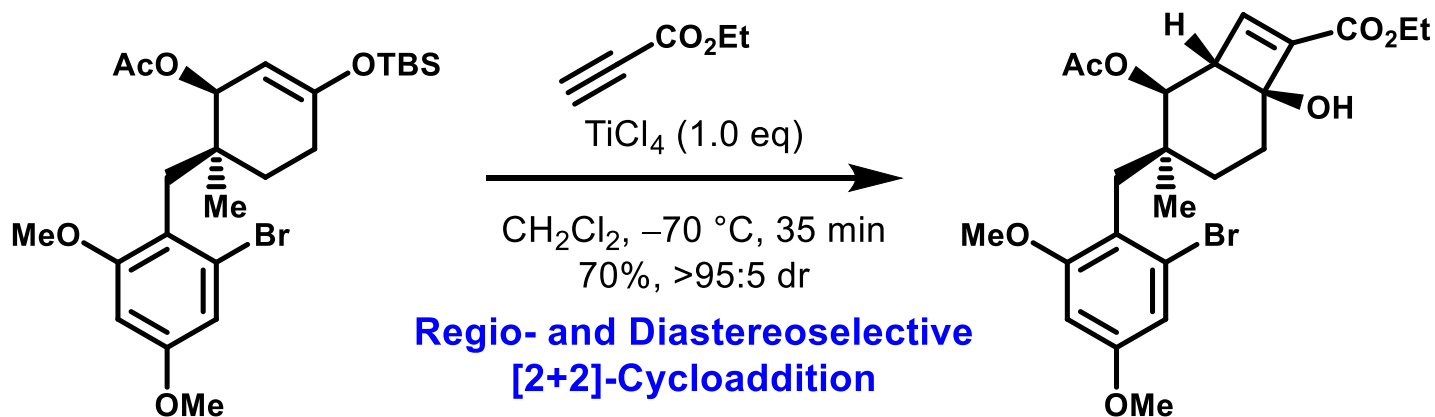


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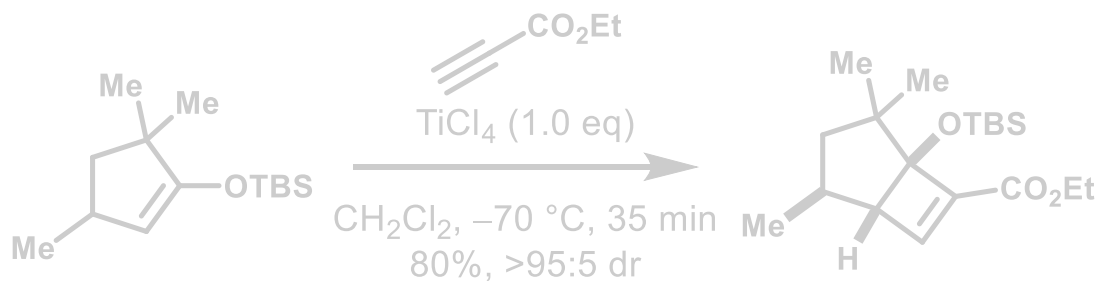
Martin, 1990



# Anionic Oxy-Cope Precursor

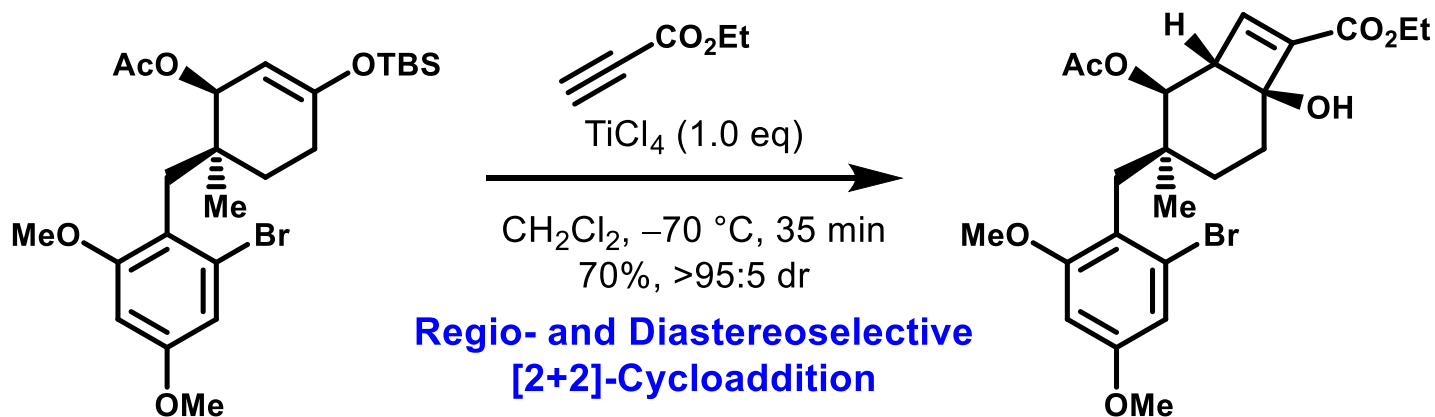


## Literature Precedent

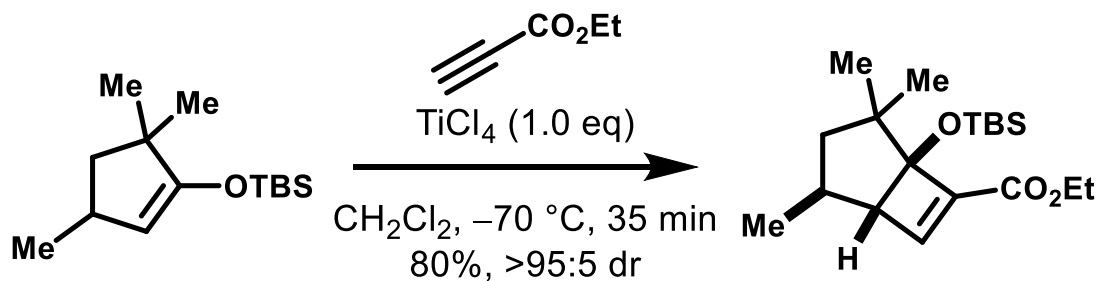


Clark and Untch, 1979

# Anionic Oxy-Cope Precursor

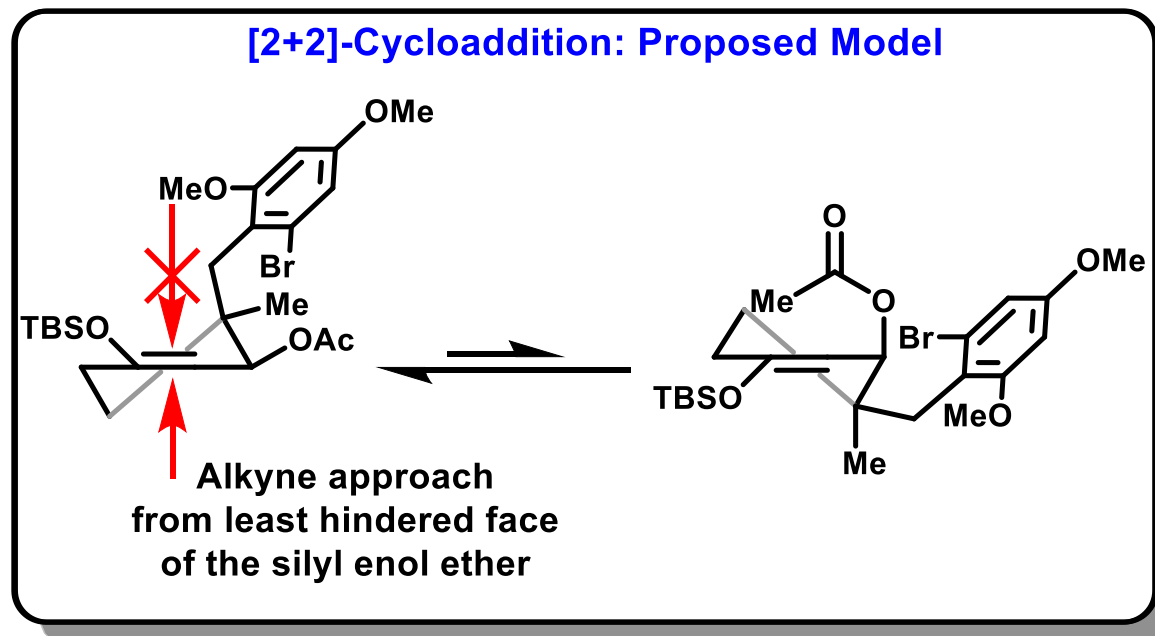
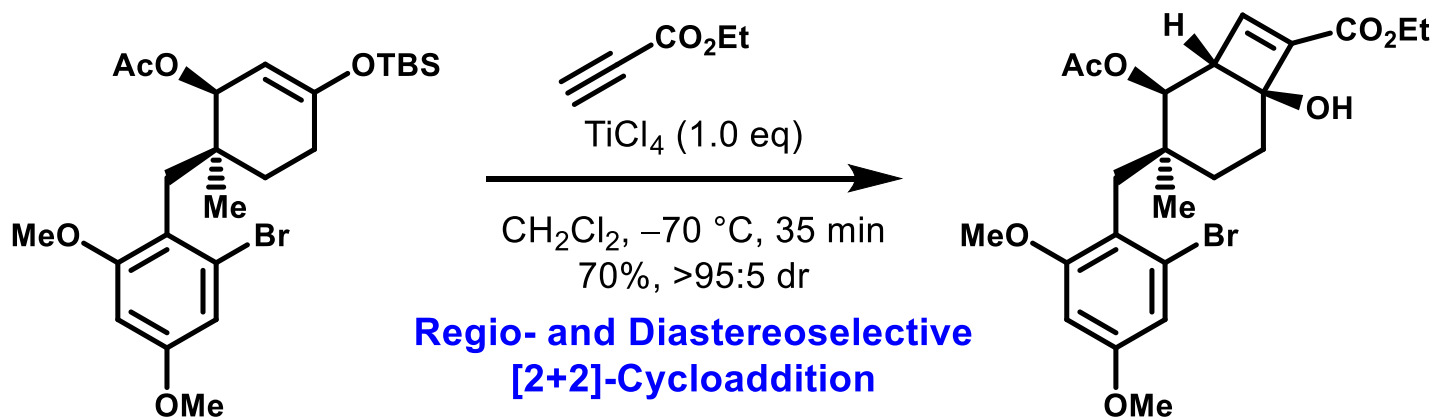


## Literature Precedent

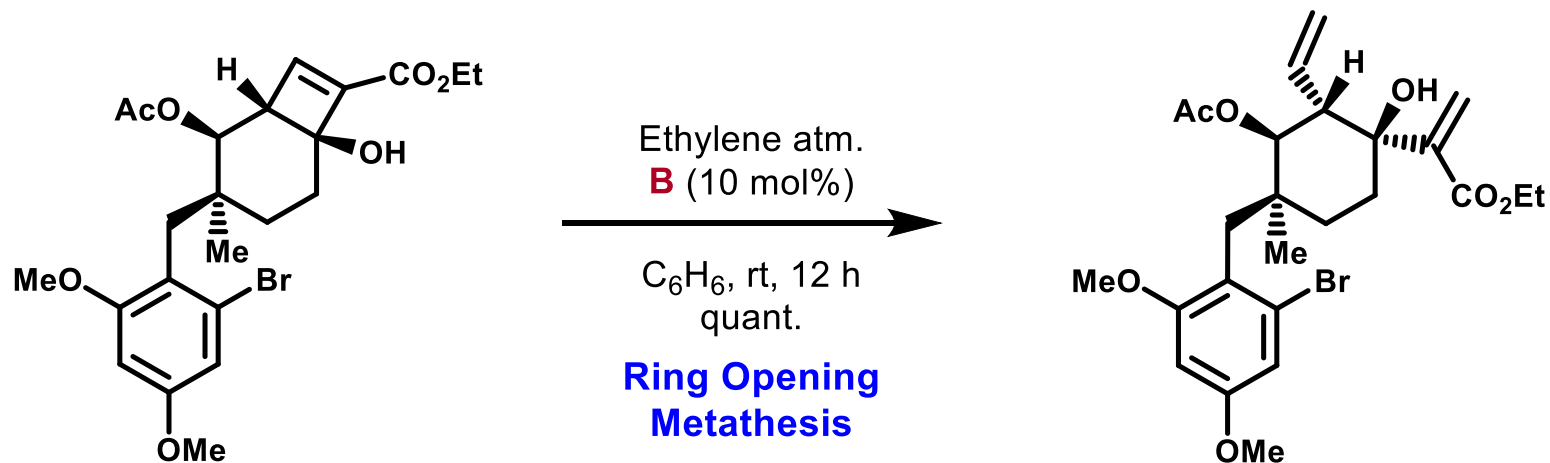


Clark and Untch, 1979

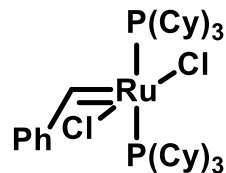
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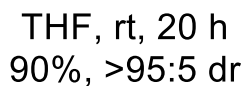
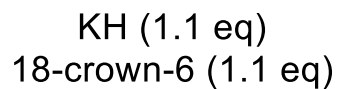
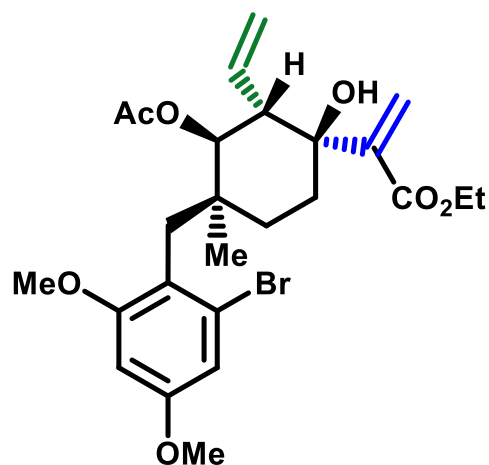


## Catalyst B:

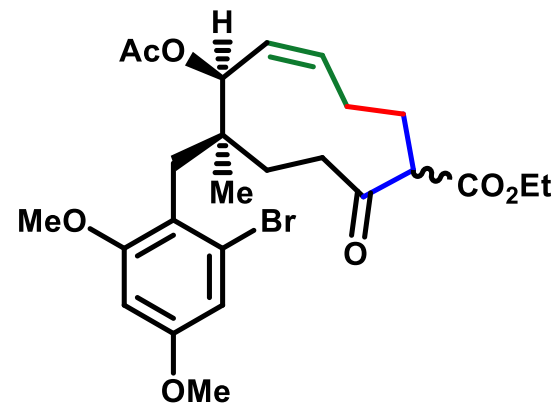
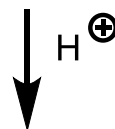
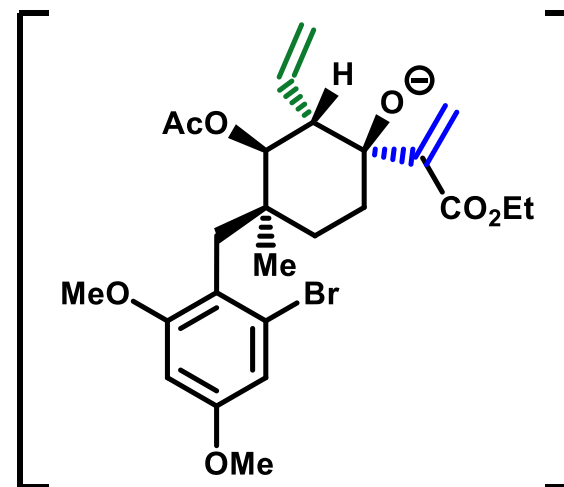


First Generation  
Grubb's Catalyst

# Anionic Oxy-Cope

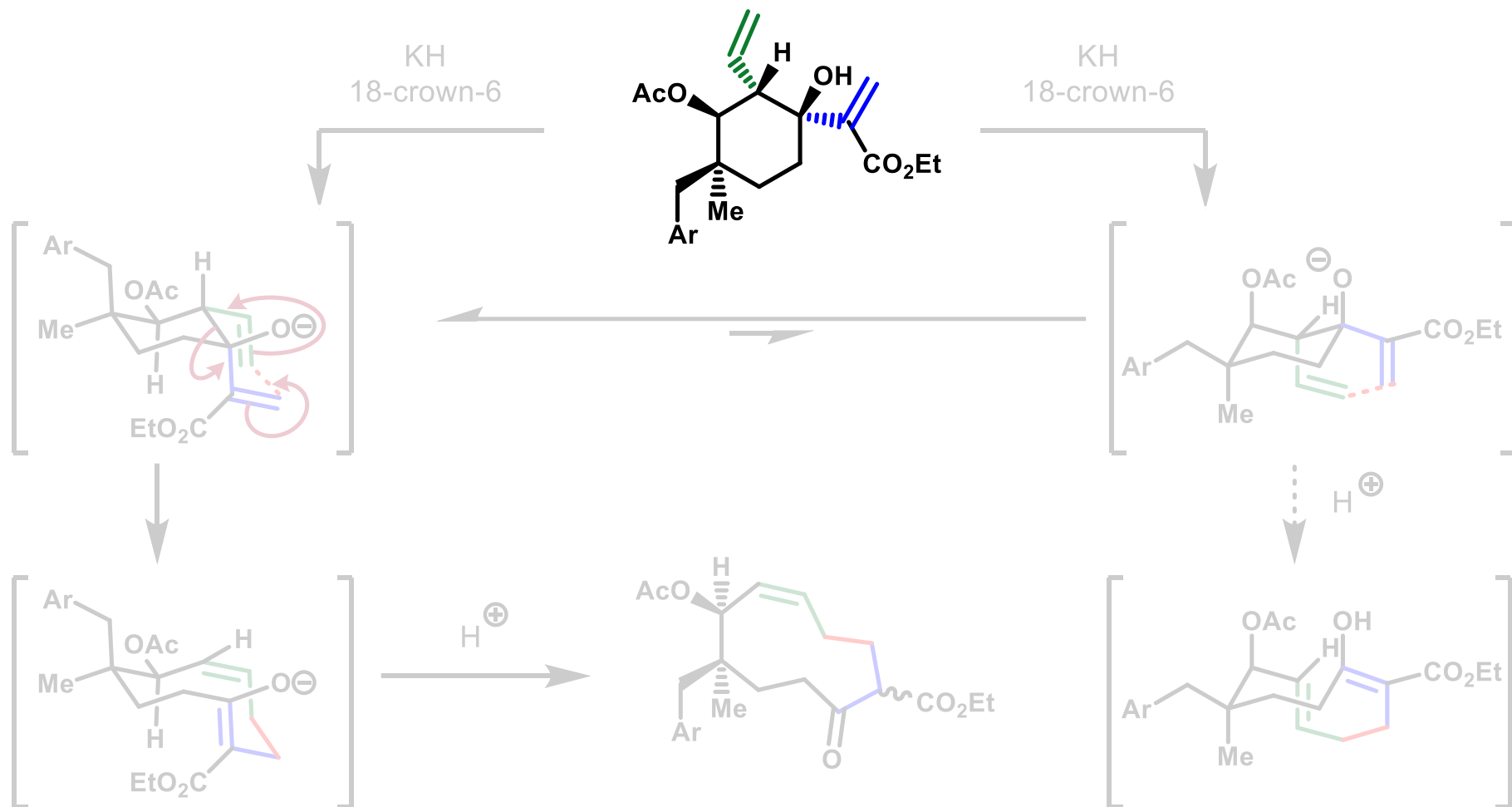


**Anionic Oxy-Cope**

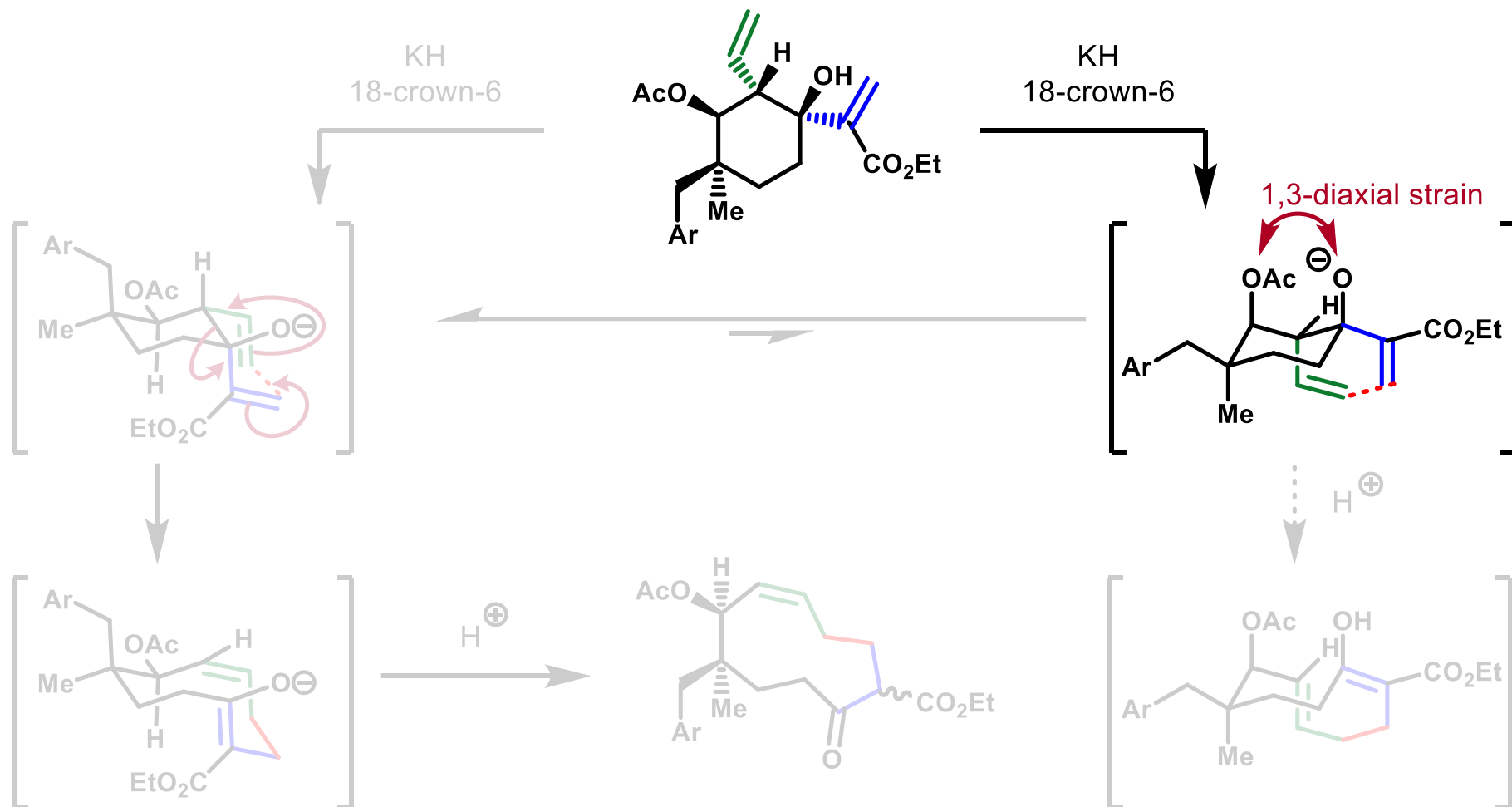


- Anionic Oxy-Cope vs Oxy-Cope: rate enhancement  $10^{10}$ - $10^{17}$  with lower T
- Substrate control

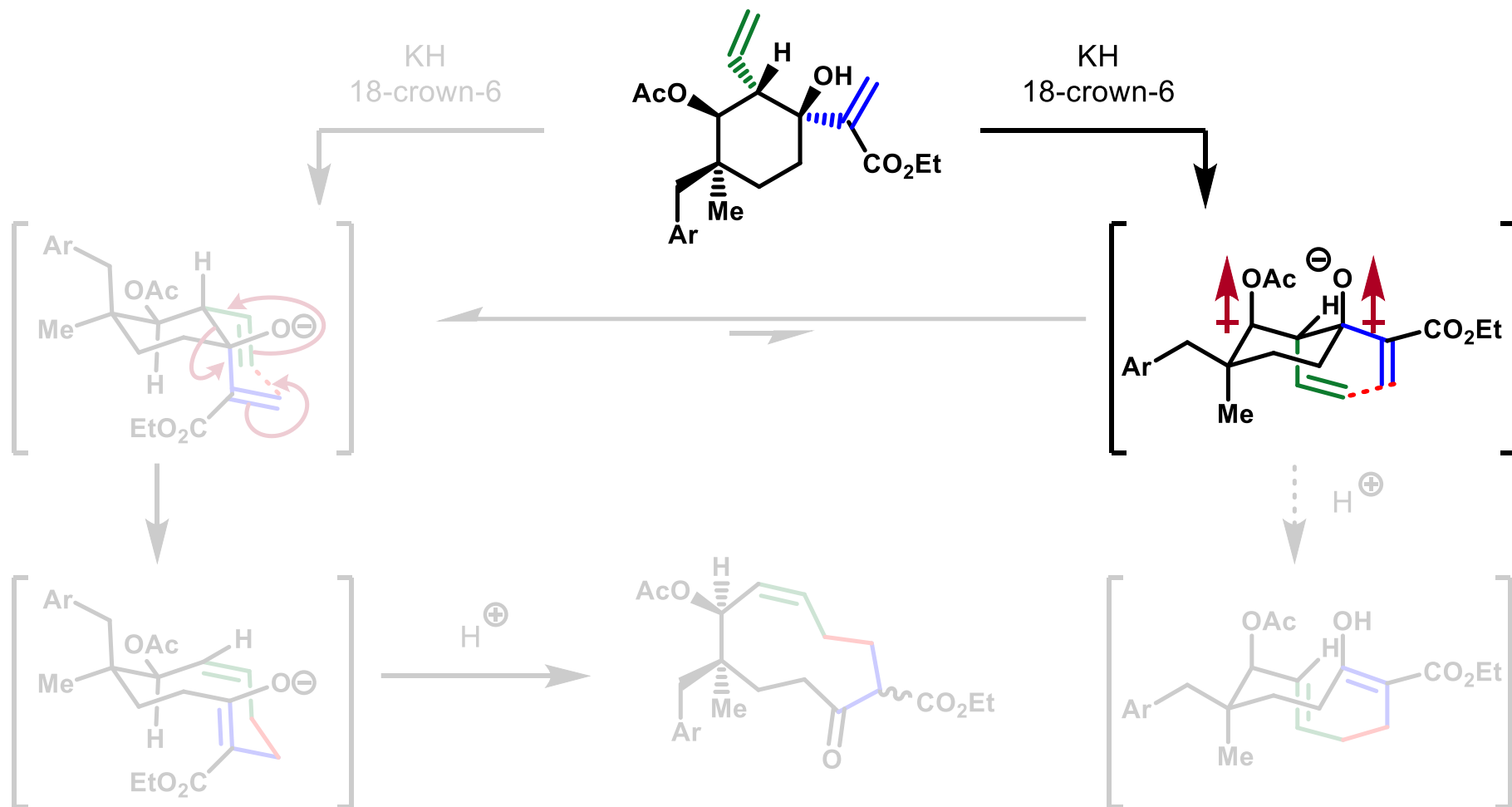
# Anionic Oxy-Cope



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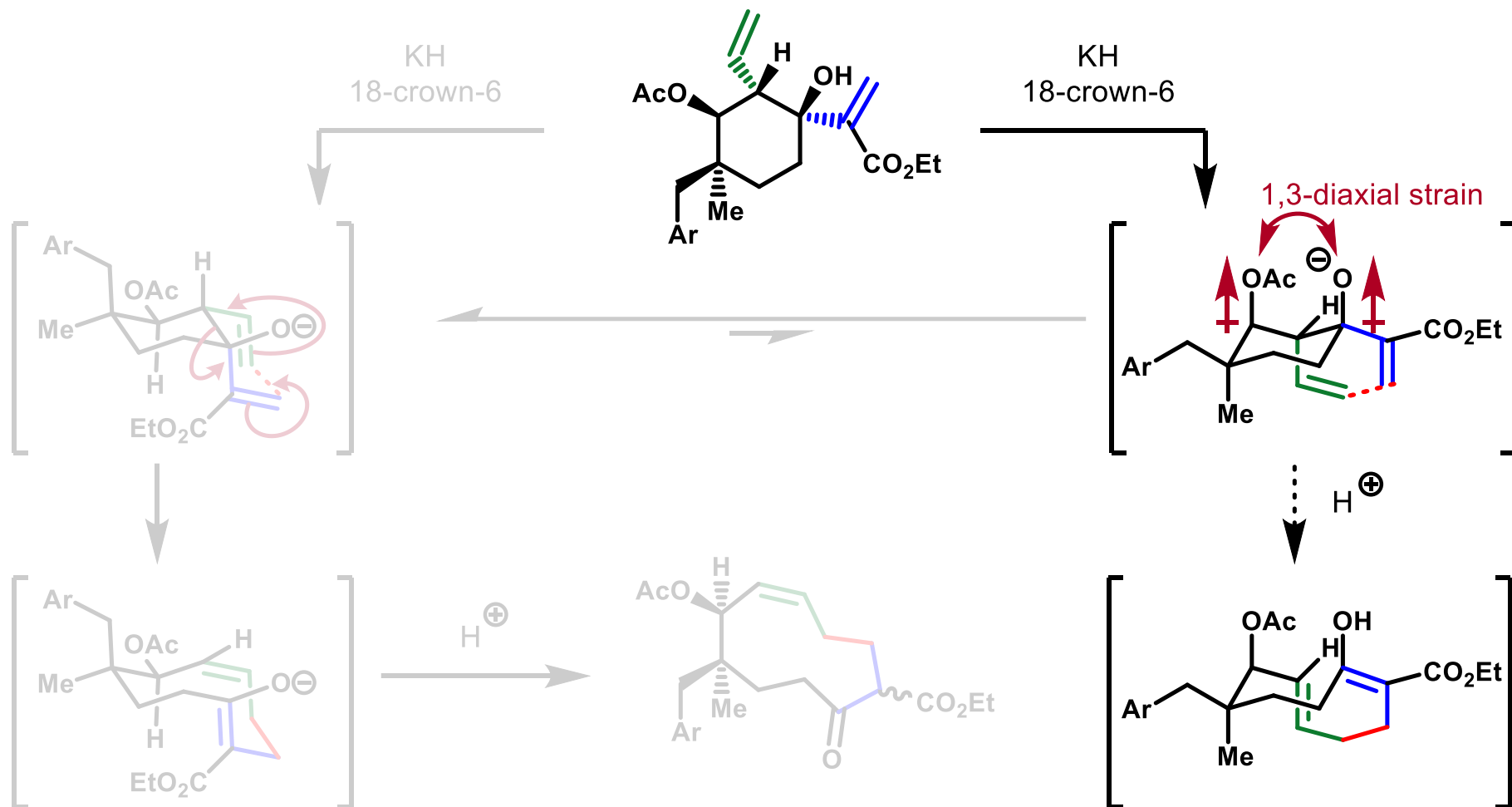


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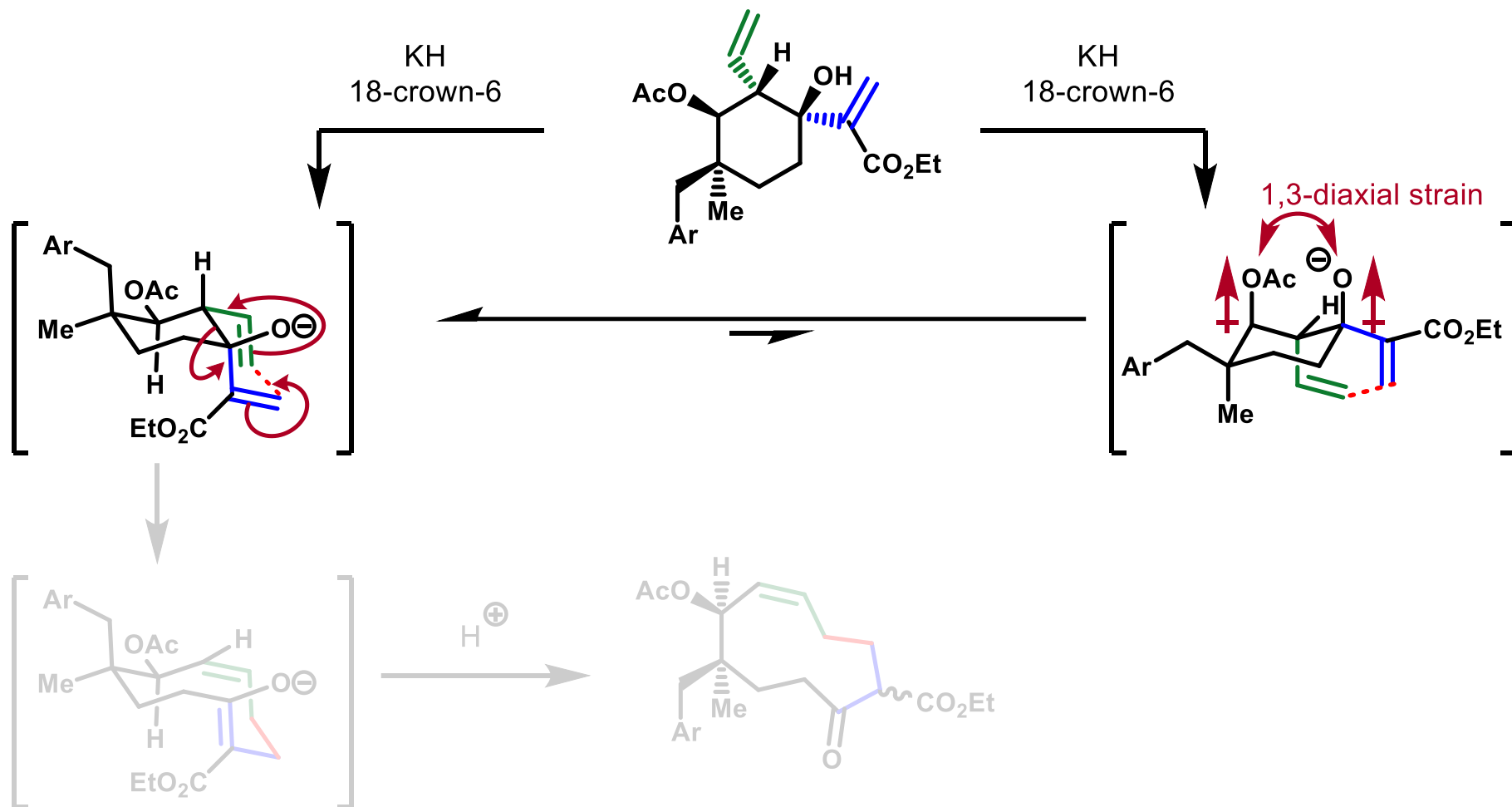




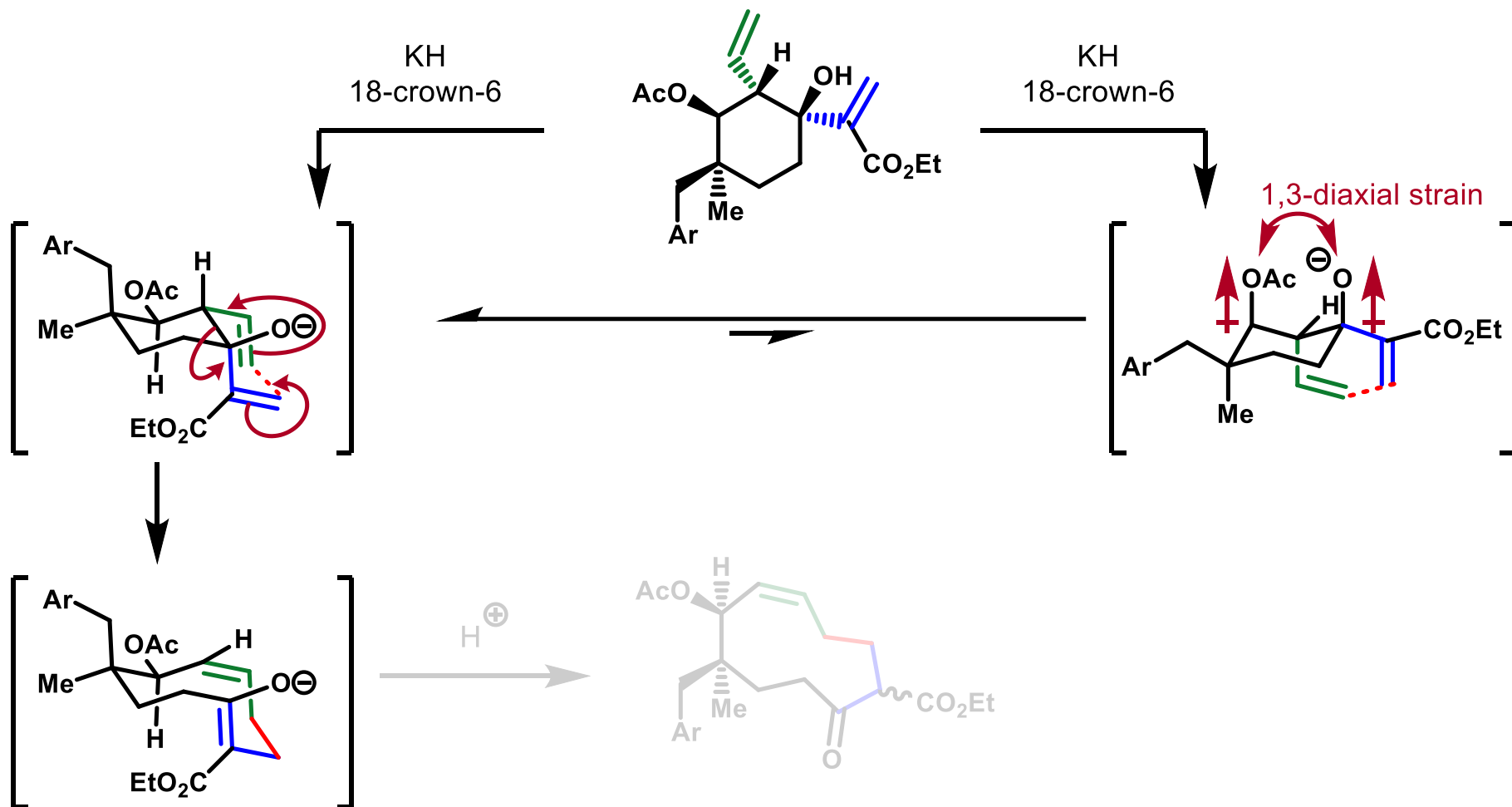
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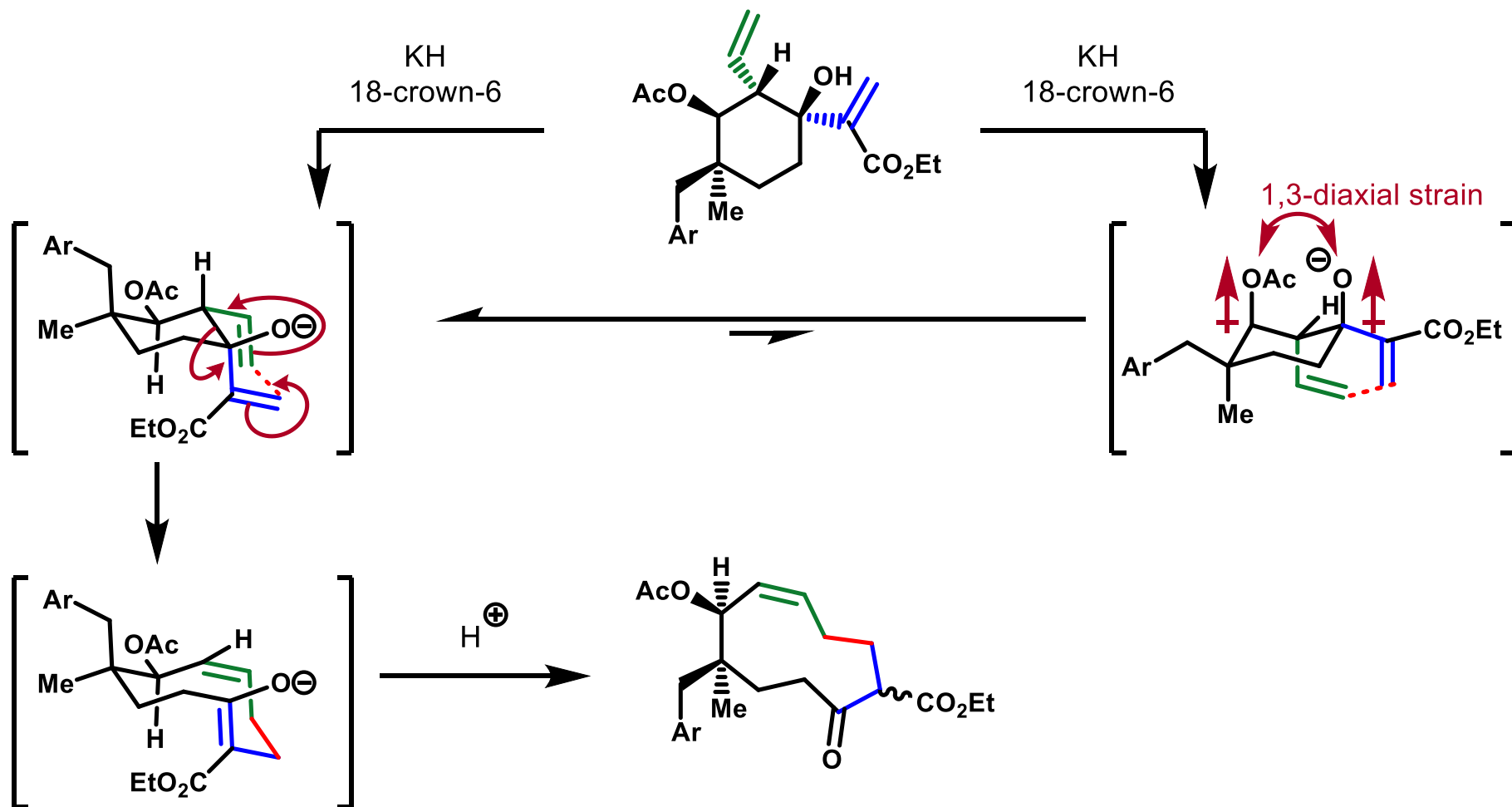
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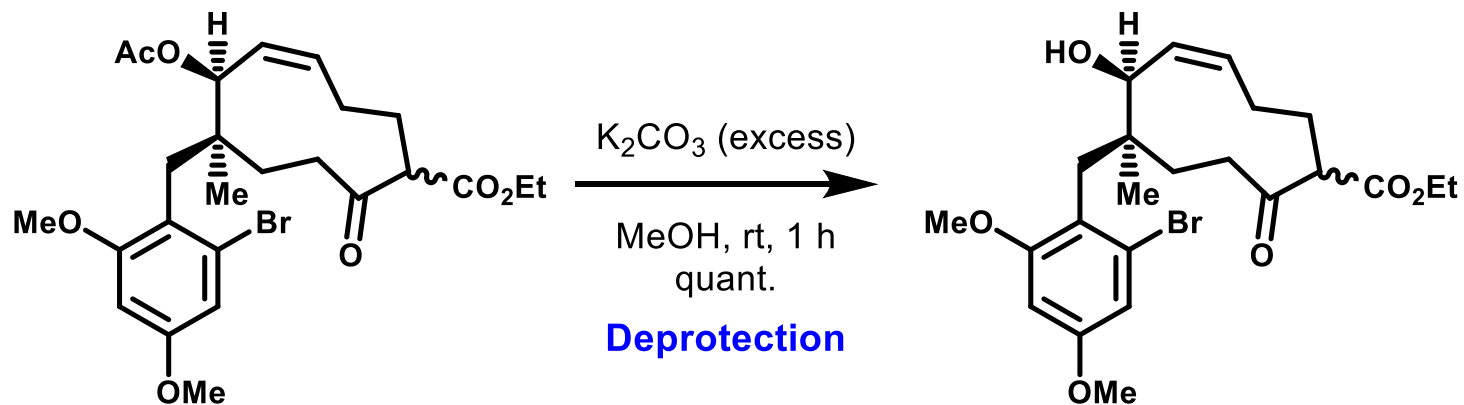
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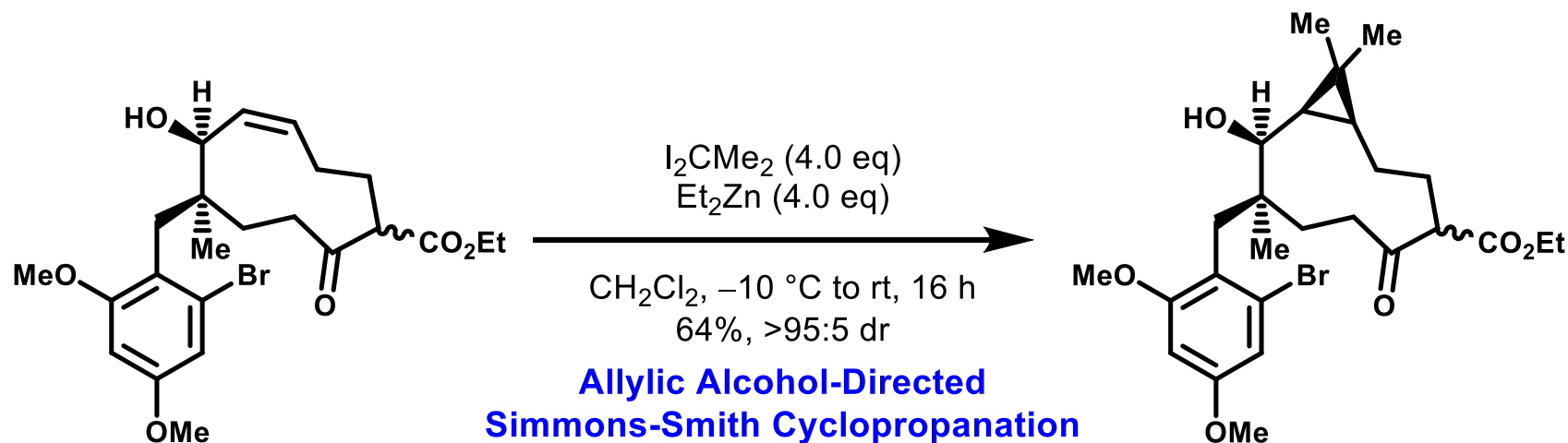
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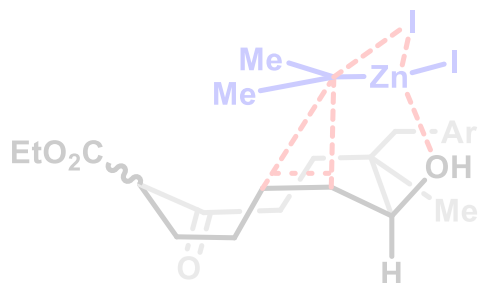
# Simmons-Smith Cyclopropanation



# Simmons-Smith Cyclopropanation

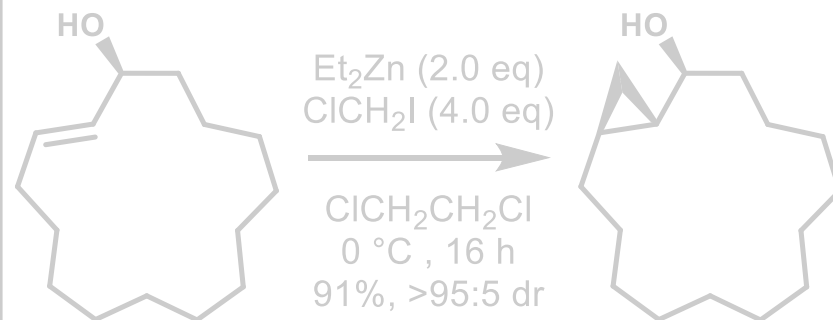


## Allylic Alcohol-Directed Simmons-Smith Cyclopropanation: Proposed Transition State



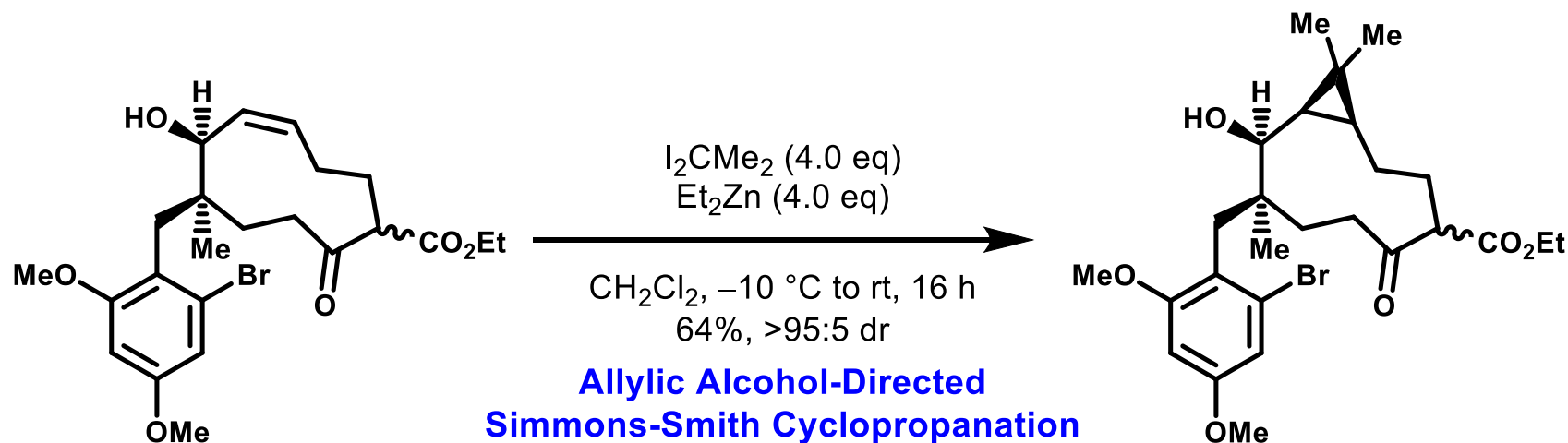
- Facial selectivity through Zn-O coordination and steric hindrance: cyclopropane *cis* to hydroxyl group

## Literature Precedent

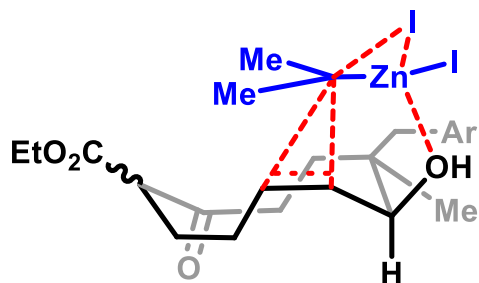


Oppolzer, 1993

# Simmons-Smith Cyclopropanation

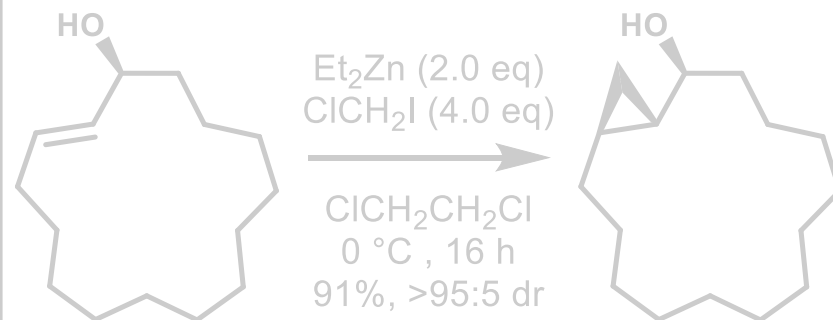


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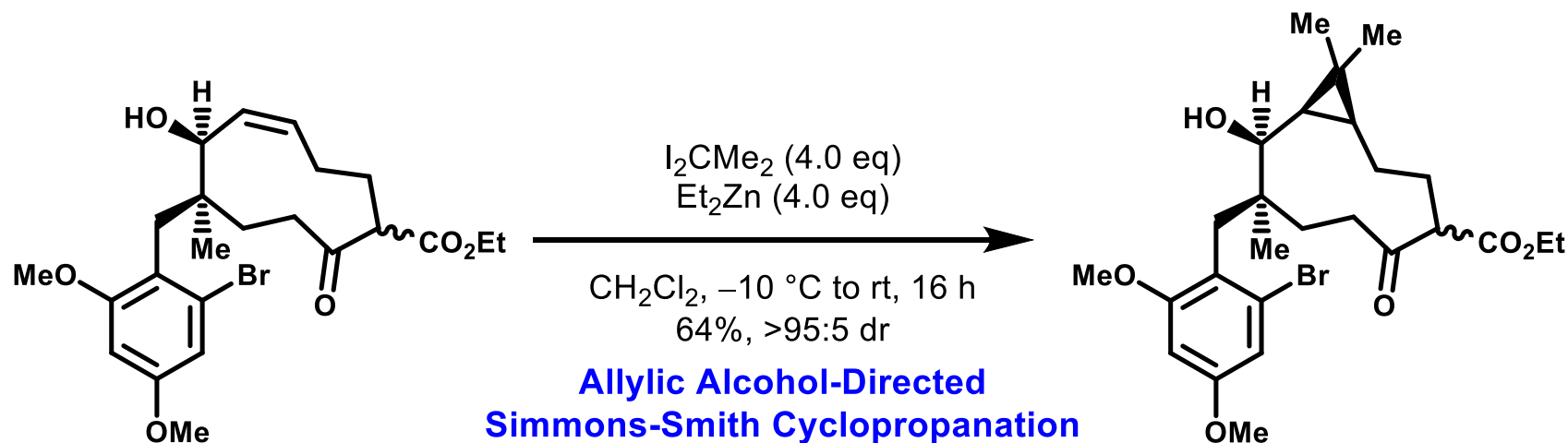
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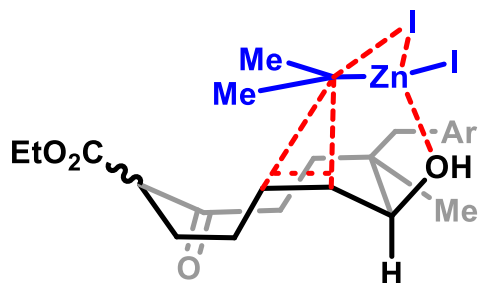


Oppolzer, 1993

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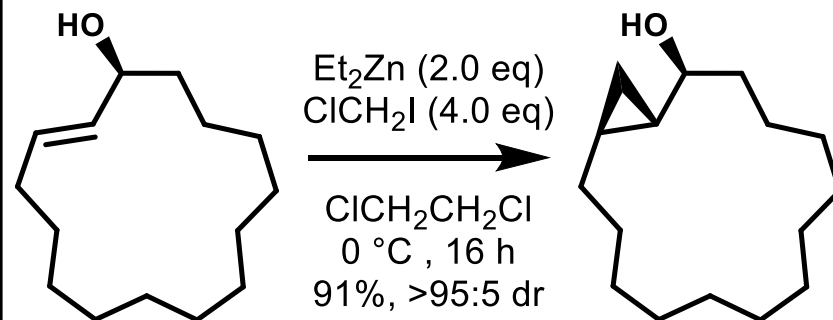


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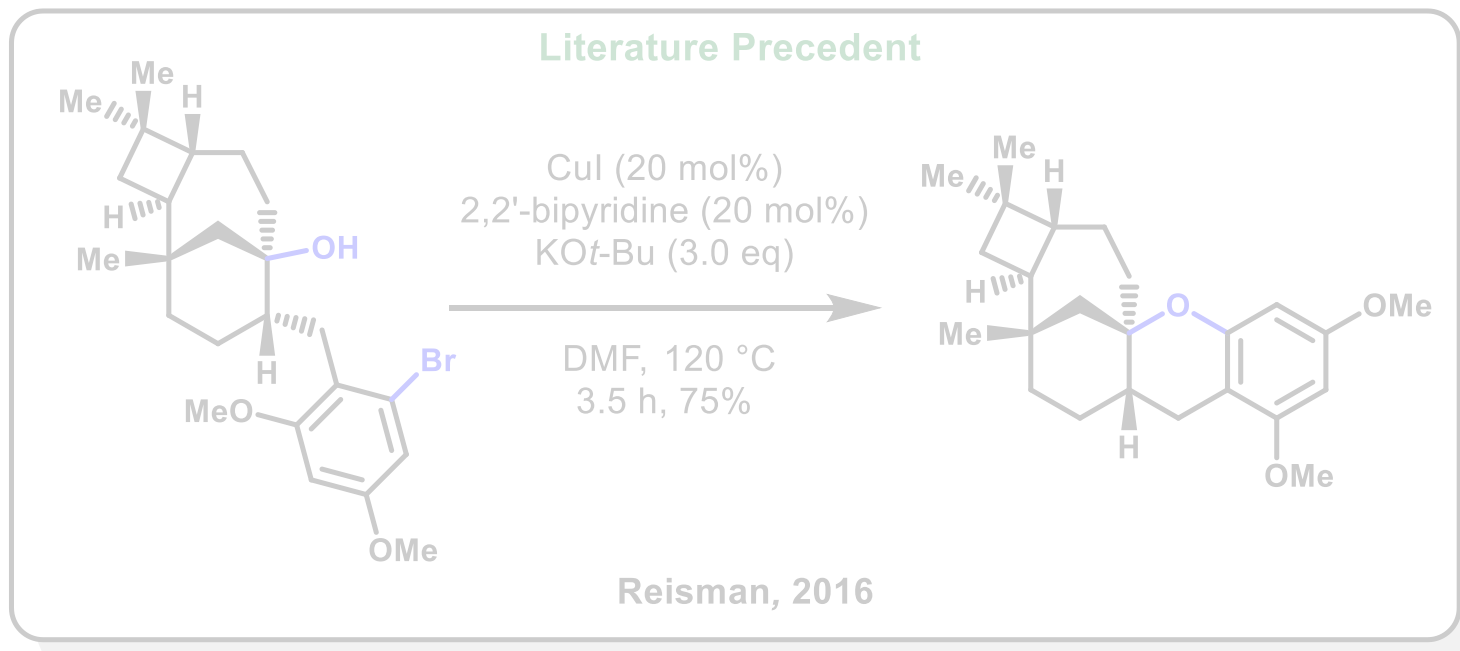
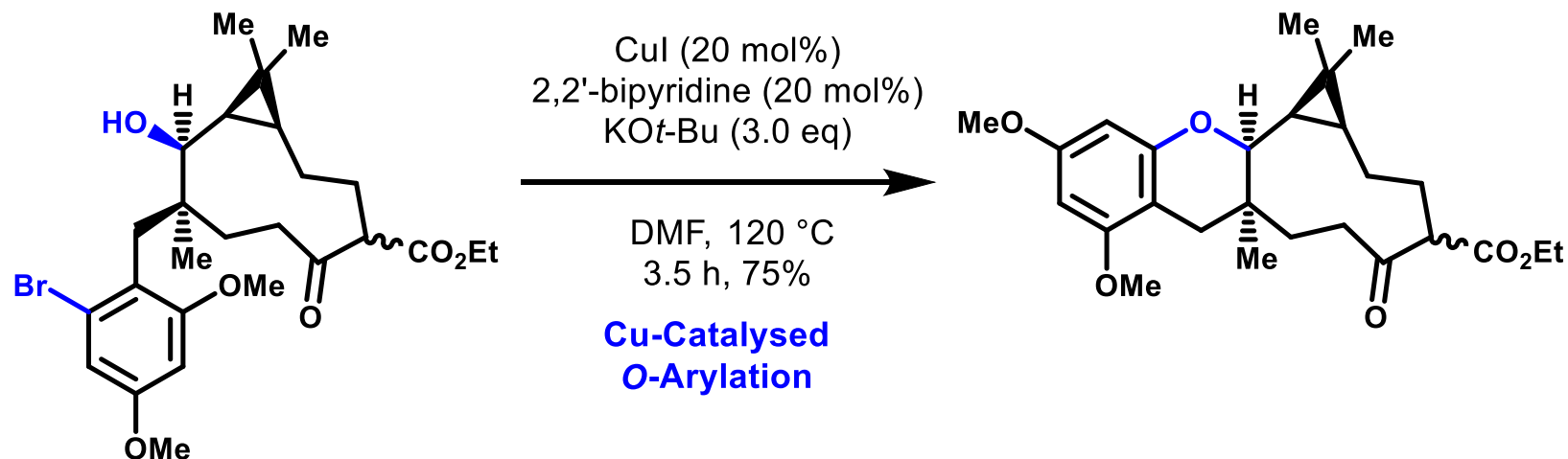
## Literature Precedent



**Oppolzer, 1993**

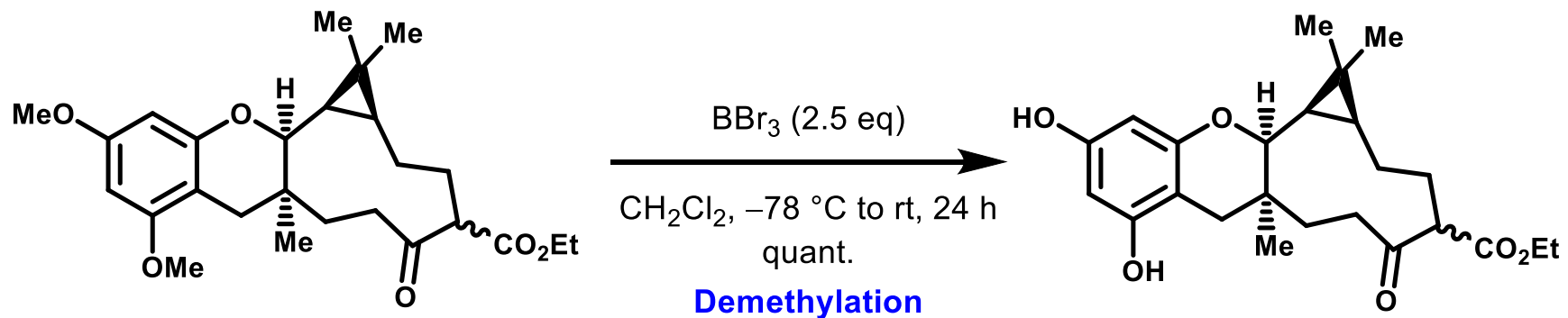


# O-Arylation

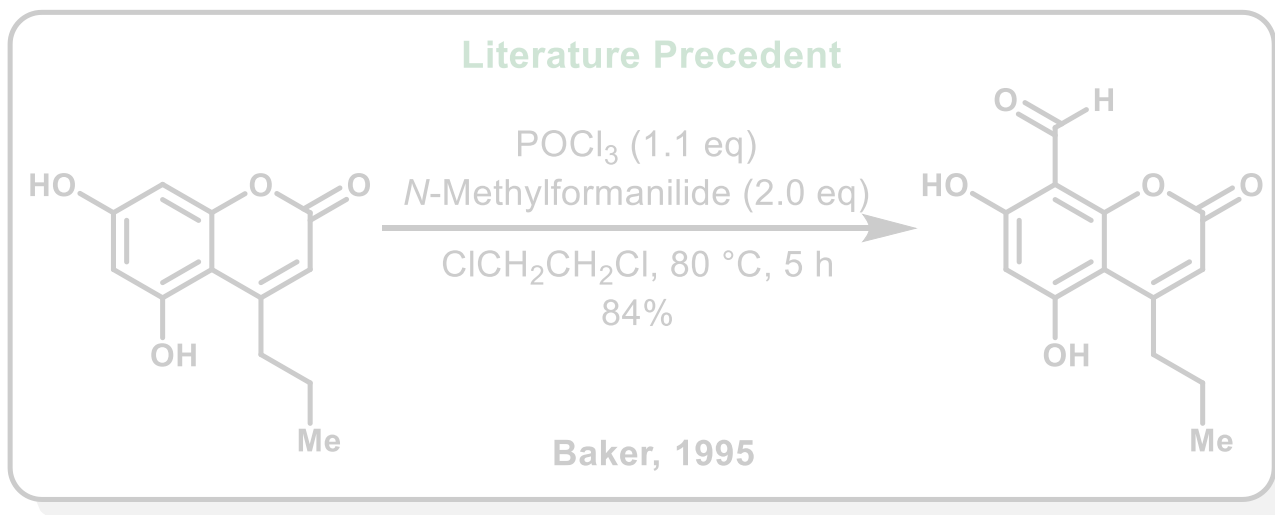
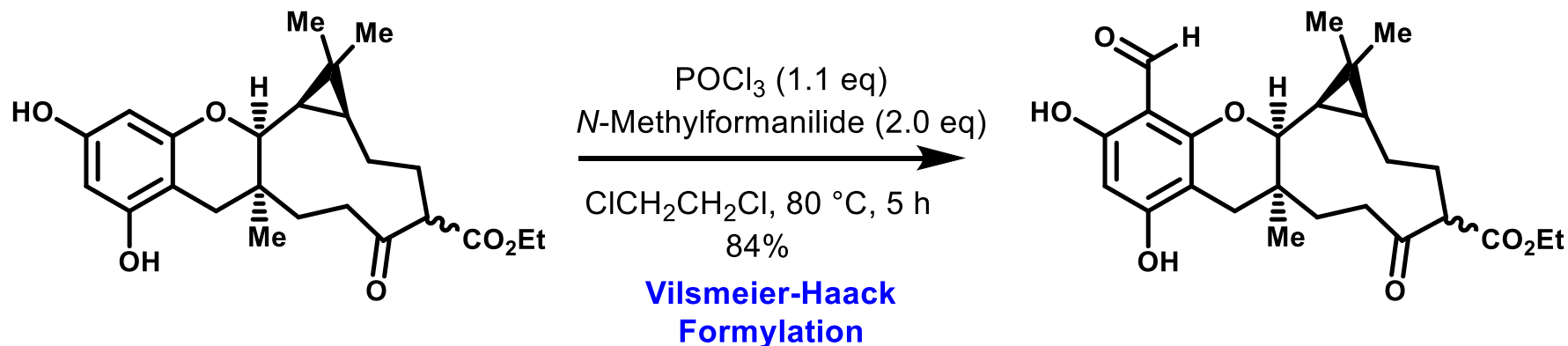




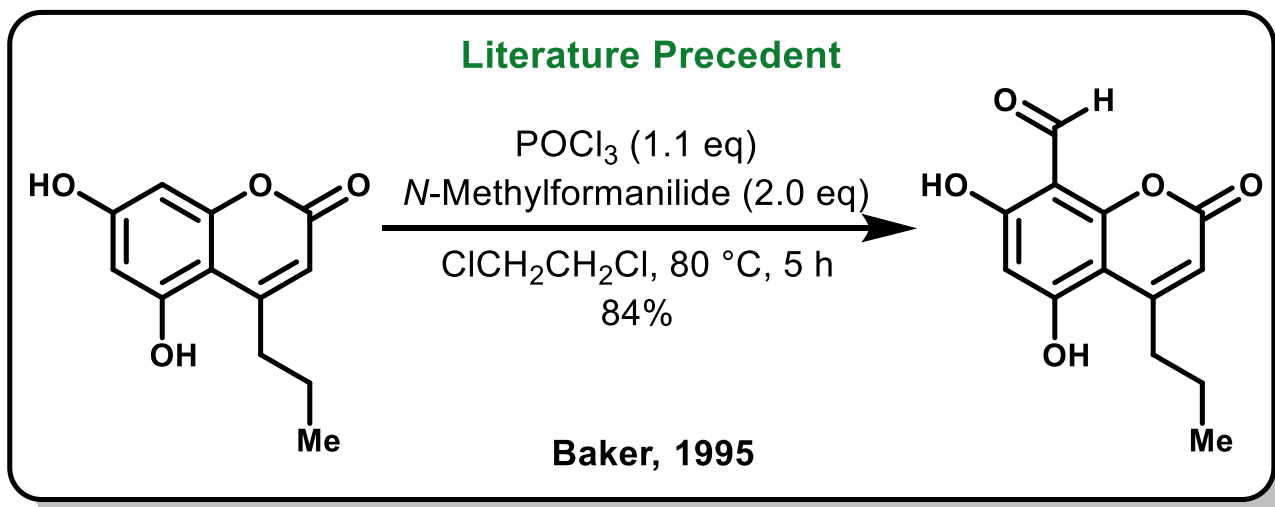
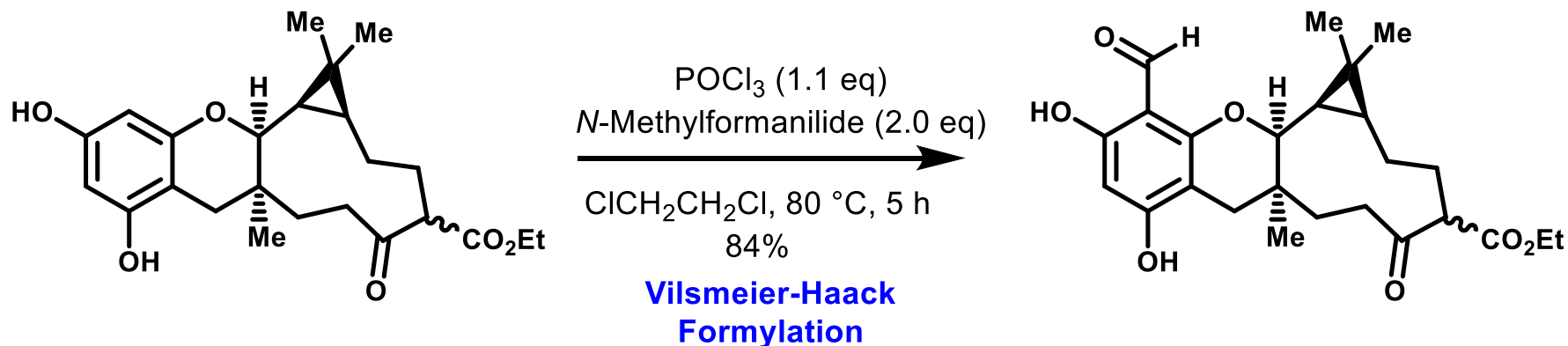
# Demethylation



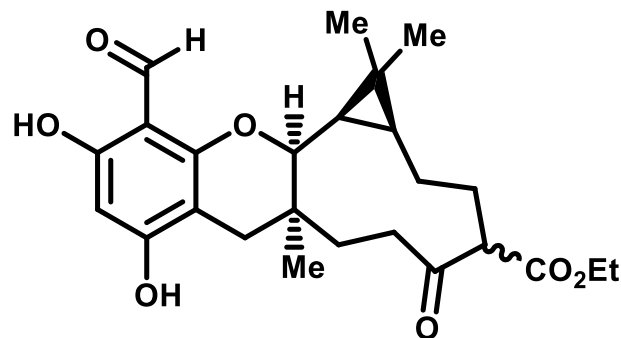
# Electrophilic Aromatic Substitution



# Electrophilic Aromatic Substitution



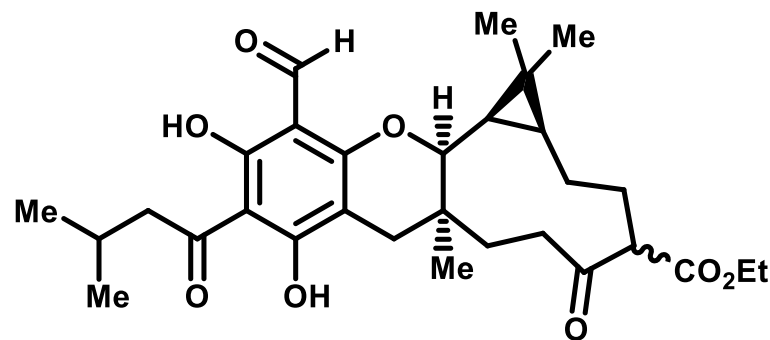
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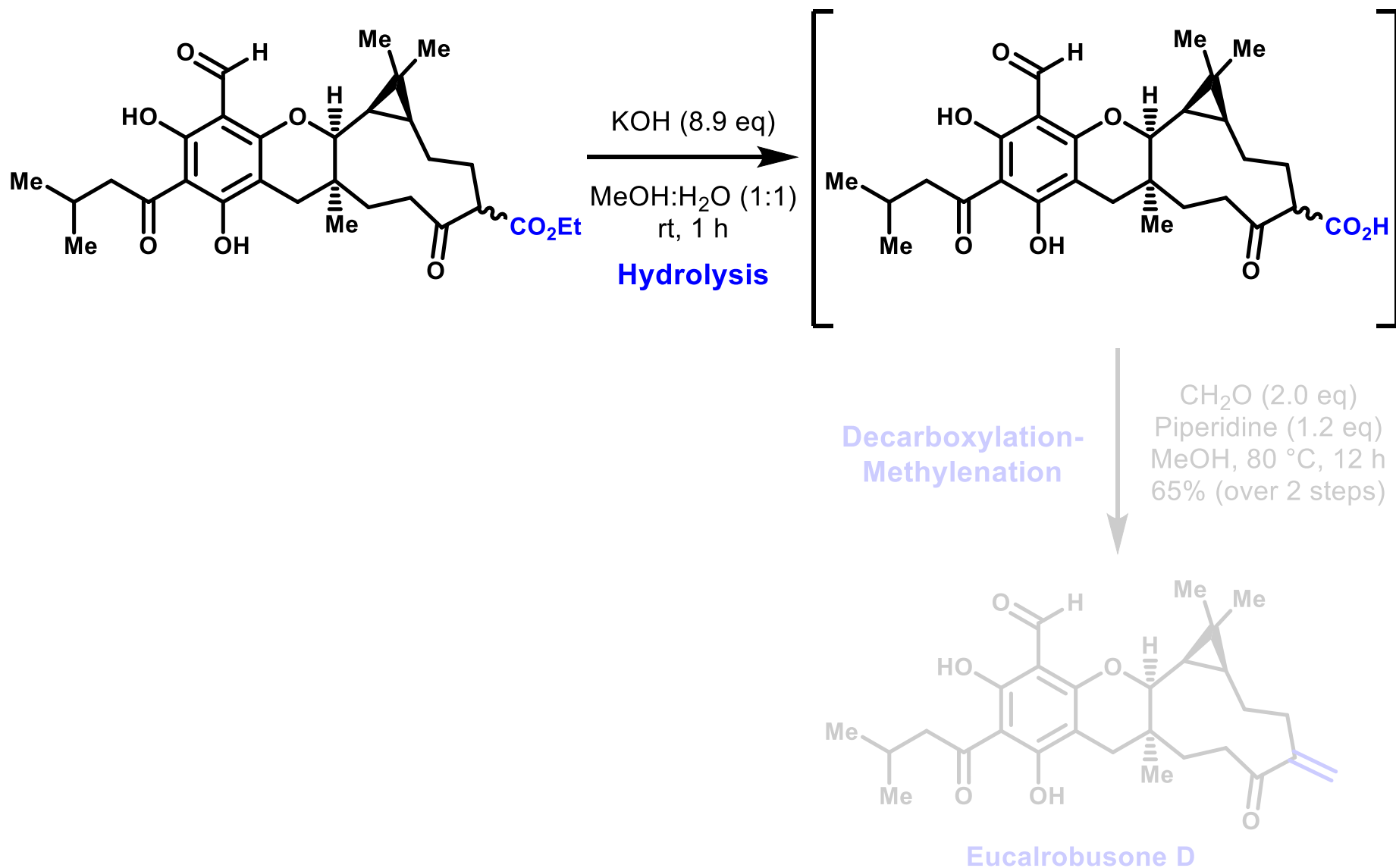
Isovaleryl chloride (1.1 eq)  
 $\text{TiCl}_4$  (0.9 eq)

$\text{CH}_2\text{Cl}_2$ , 0 °C, 30 min  
85%

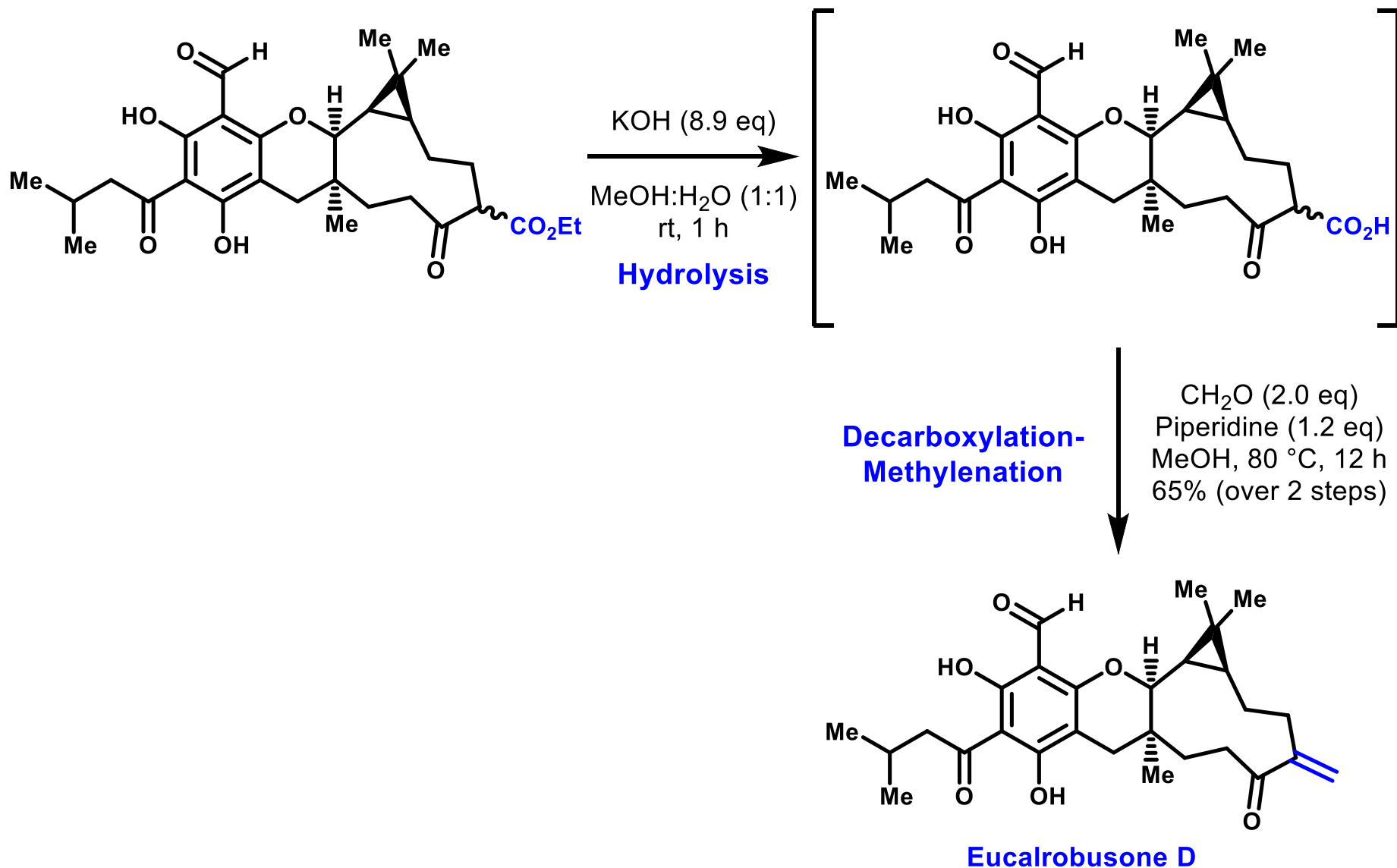
**Friedel-Crafts  
Acylation**



# Vinyl Ketone Formation

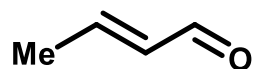
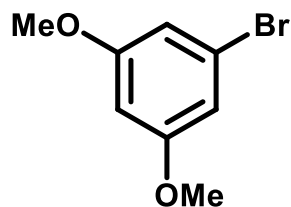


# Vinyl Ketone Formation



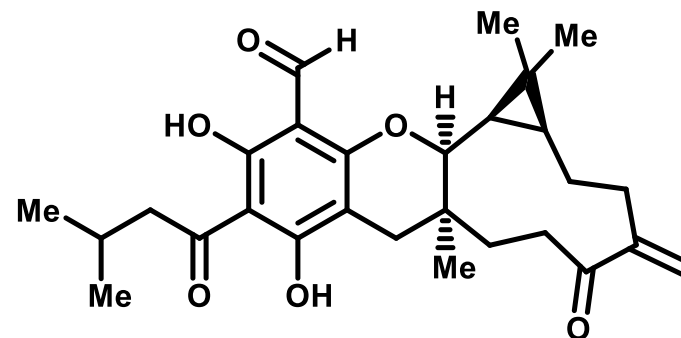


# Summary: Eucalrobosone D Synthesis



16 Steps

- Stereoselective Diels-Alder
  - [2+2]-Cycloaddition
  - Ring Opening Metathesis
  - Anionic Oxy-Cope Rearrangement
  - Diastereoselective Cyclopropanation
- 
- Minimal protecting group use
  - Minimal redox steps



Eucalrobosone D

- 15 linear steps
- Predicted  $\approx 3.5\%$  yield
- Single enantiomer
- Single diastereomer



