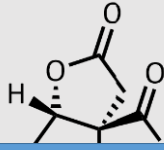


# Bilobalide

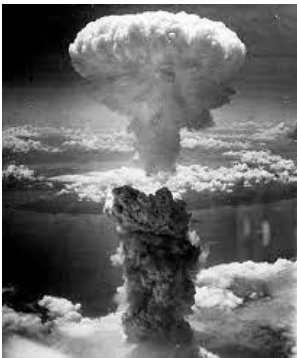
Brennan Rose

03/30/2021

# Ginkgo Biloba “Fossil Tree”

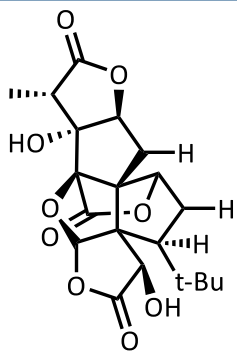
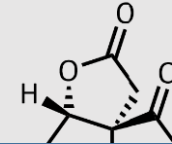


- Genus first appeared during the Jurassic period up to 300 million years ago
- Ginkgo Biloba is the only known living species of Ginkgophyta all other being extinct
- Renowned for its resistance to disease and insects
- Fossils that are over 200 million years old have been found
- 1000-year-old ginkgo at Tsurugaoka Hachimangū (blew down in 2010)
- Cultivated by early humans

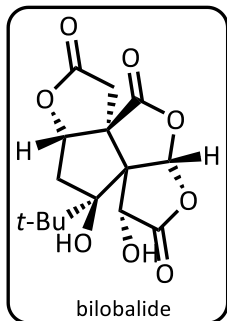


- 6 Ginkgo trees 0.5 to 1.5 miles outside Hiroshima, Japan were among the few living things in the area to survive the blast.
- The trees badly burned survived and were soon healthy again.

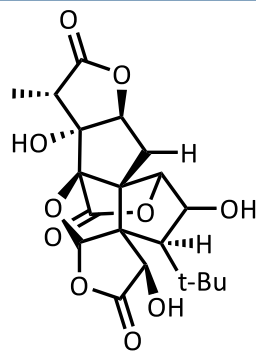
# Natural Products



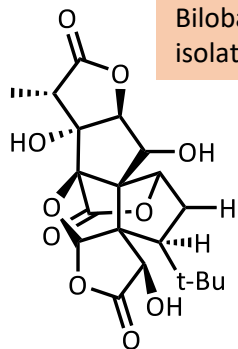
ginkgolide A



bilobalide

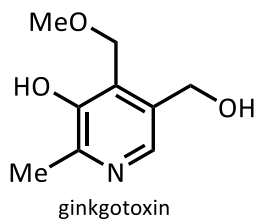


ginkgolide C



ginkgolide B

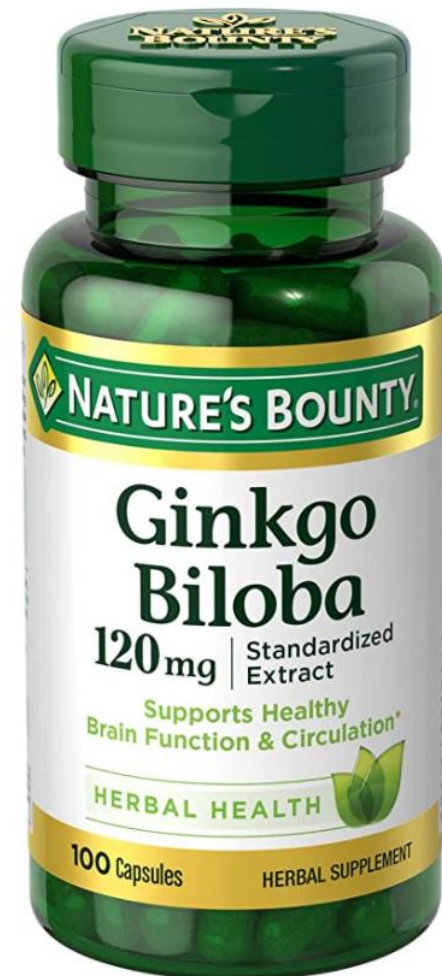
Bilobalide was isolated in 1969



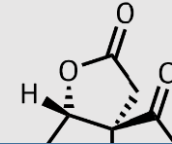
ginkgotoxin

Ginkgolides A-C were isolated in 1967 by two groups simultaneously

- Extracts from the ginkgo tree containing these compound have been used in Chinese medicine for >5000 years
- New medical fad marketing these extracts as anti-senility and improved brain function drugs
- Controversial bio activity towards improved mental function in mice with down syndrome
- Contain flavonoid glycosides and terpene lactones in a ratio of 24% to 6%, or 27% to 7% respectively.
- Notably Ginko Biloba produces ginkgotoxin a vitamin B6 antagonist that also inhibits production of 4-aminobutyric acid in the brain



- Extracts widely available (\$11.69 amazon **free shipping!!!**)

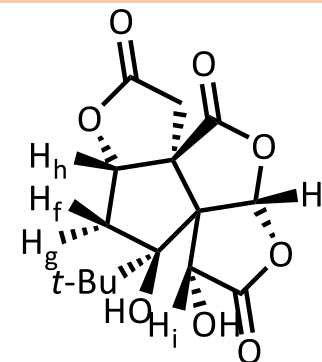
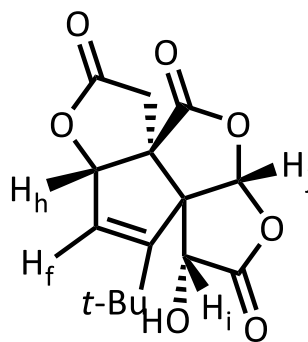


# Isolation and Characterization



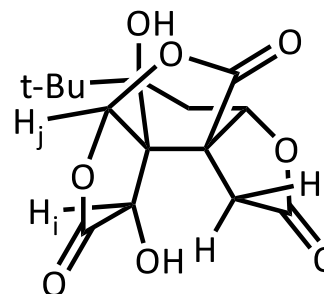
Isolated in 1969 by Bahr  
 Characterized by  $^1\text{H}$  NMR, MP, MS, optical rotation  
 Rough translation from German

50 kg of leaves extracted with ethanol was separated by polyamide column into 9 fractions. Fractions 1 and 2 contained ginkgolides and bilobalide were combined and concentrated. Residue digested in 4:1 benzene/acetone, filtered, and concentrated. The new residue was dissolved in 9:1 benzene acetone and separated by column chromatography to yield 4g of bilobalide as yellow crystals.

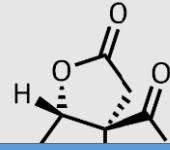


Structural assignment by Nakanishi  
 Derivatives and NOE help structural assignment

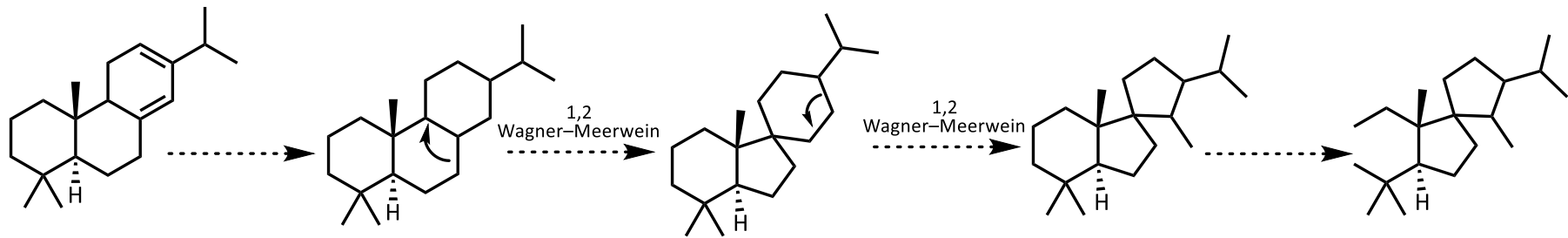
- Molecular formula ( $\text{C}_{15}\text{H}_{18}\text{O}_8$ ) requires either one carbocyclic ring or double bond in addition to the three lactones.
- The tert-Bu exhibit strong NOE with  $\text{H}_i$  and  $\text{H}_j$  in both bilobalide and in the anhydro derivative
- $\text{H}_i$  and  $\text{H}_j$  flank the tert-Bu assigning the stereochemistry at these positions
- From the strong NOEs 18-30% they concluded all lactones are cis fused making the molecule extremely rigid



# Speculative Biosynthesis

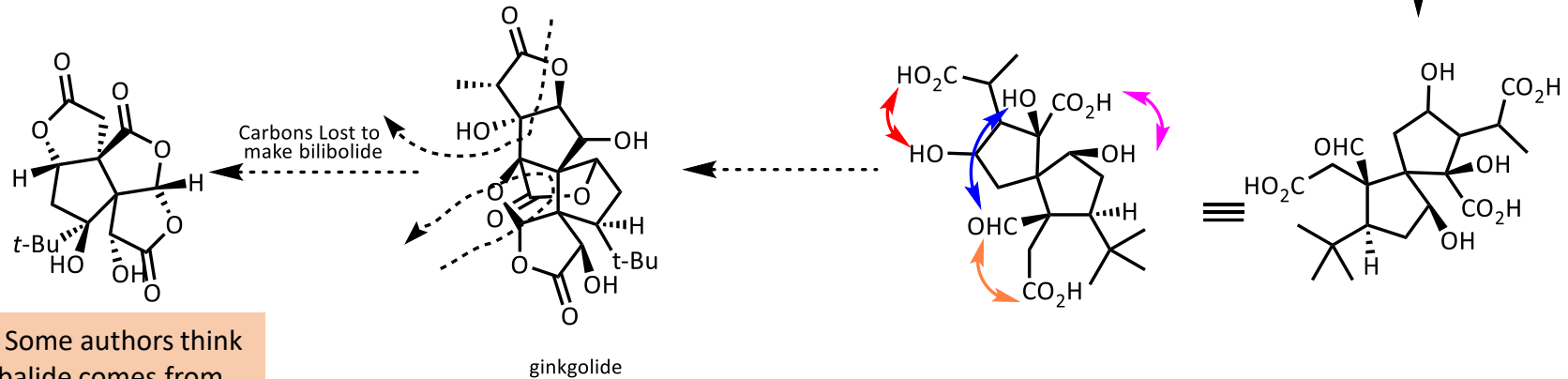


- 11 enzymes have been identified to catalyze the formation of ginkgolides
- The Final biosynthesis is still far from being understood



In 2001 levopimaradiene isolated from *G. biloba* Seedlings

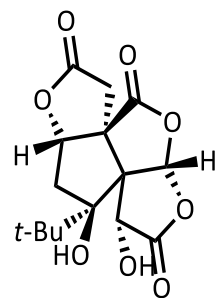
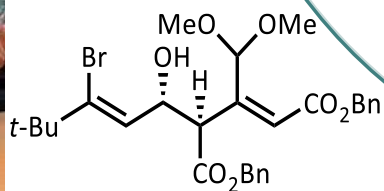
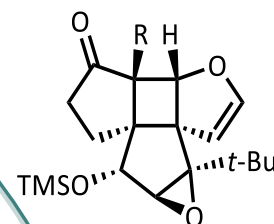
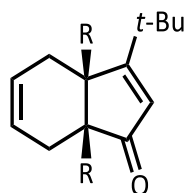
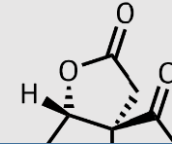
2017 paper suggesting CYP-450s involed in biosynthesis



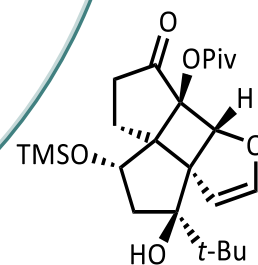
- Caution: Some authors think that bilobalide comes from farnesyl diphosphate due to it being a sesquiterpene

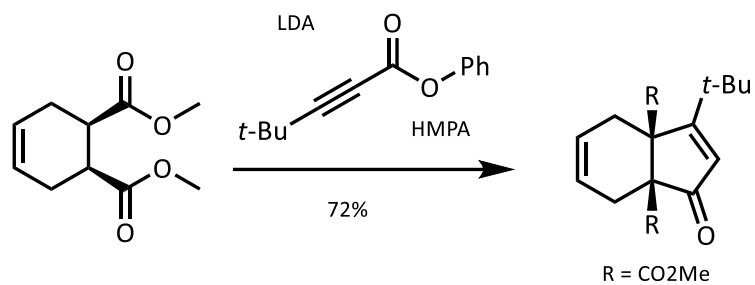
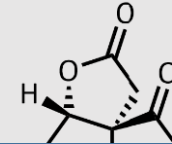
Dewick, P. M. Medicinal Natural Products: Products:A Biosynthetic Approach. 3rd.; Wiley&Sons: West Sussex, England, 2009

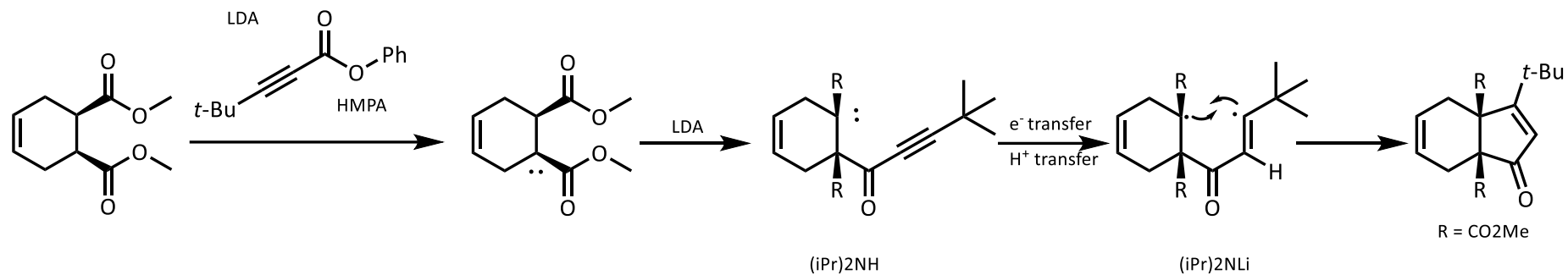
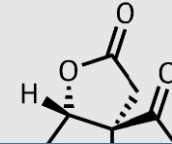
# Summary

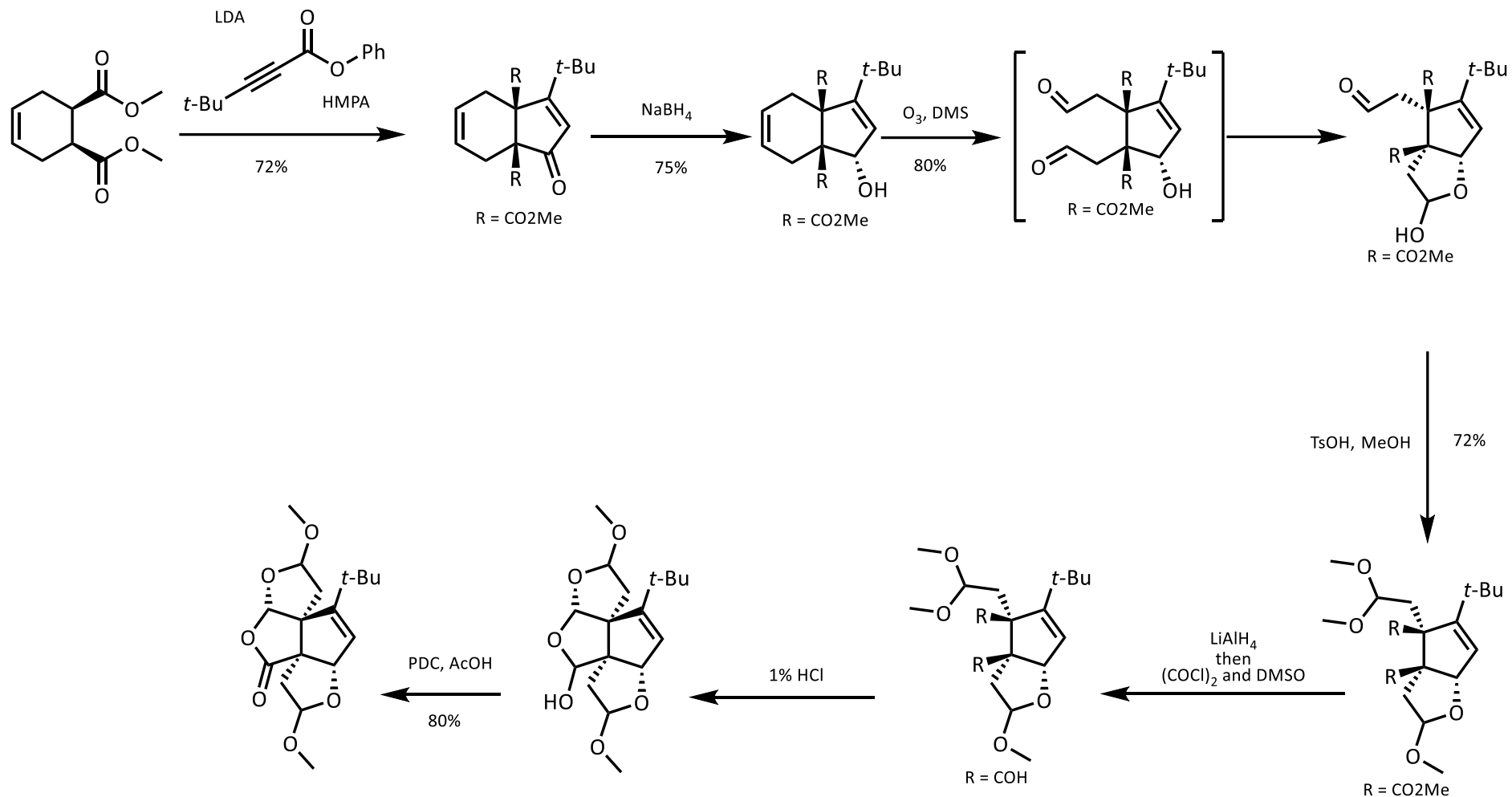
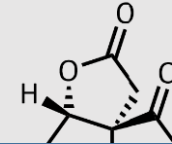


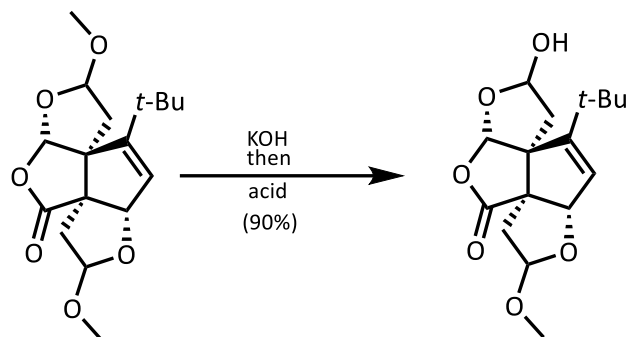
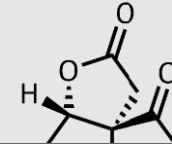
Bilobalide

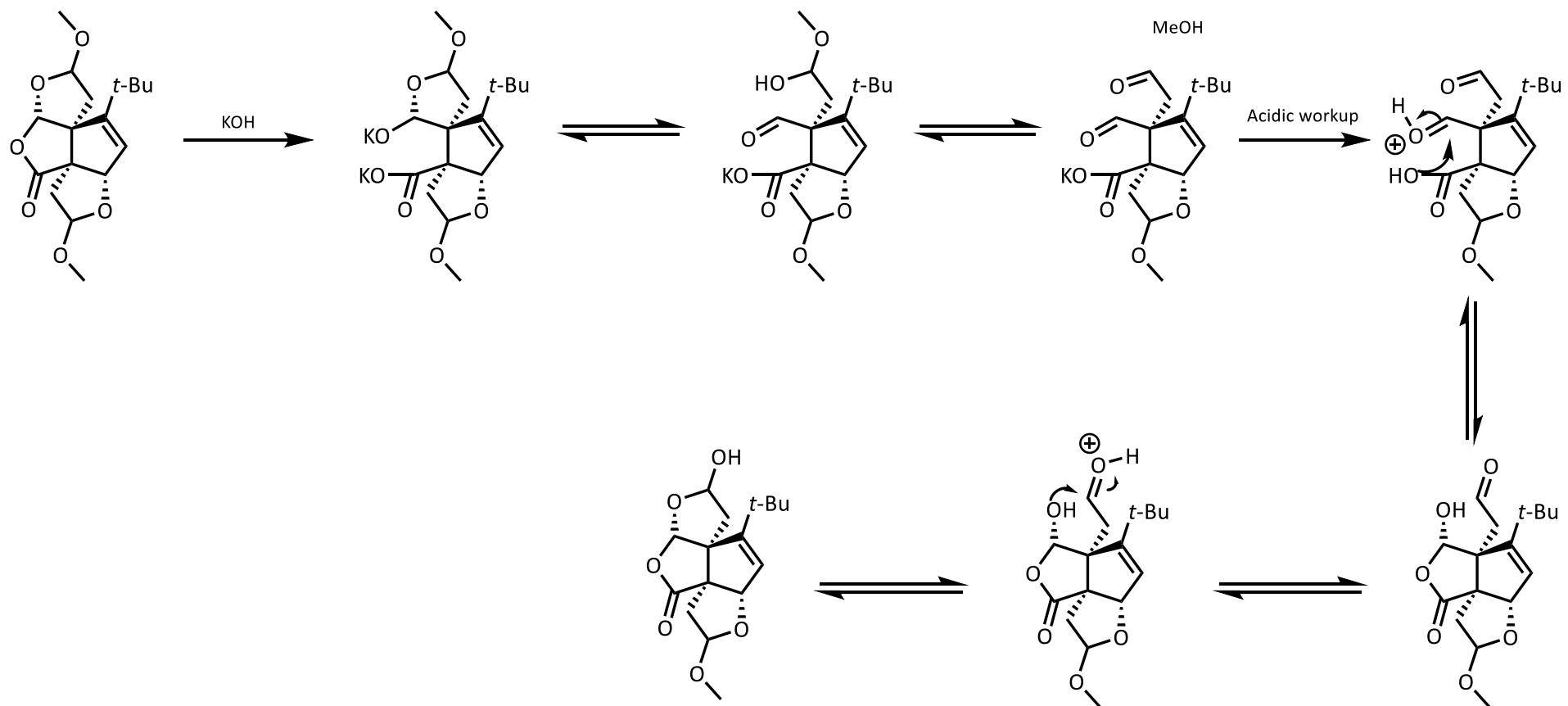
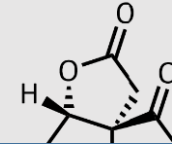


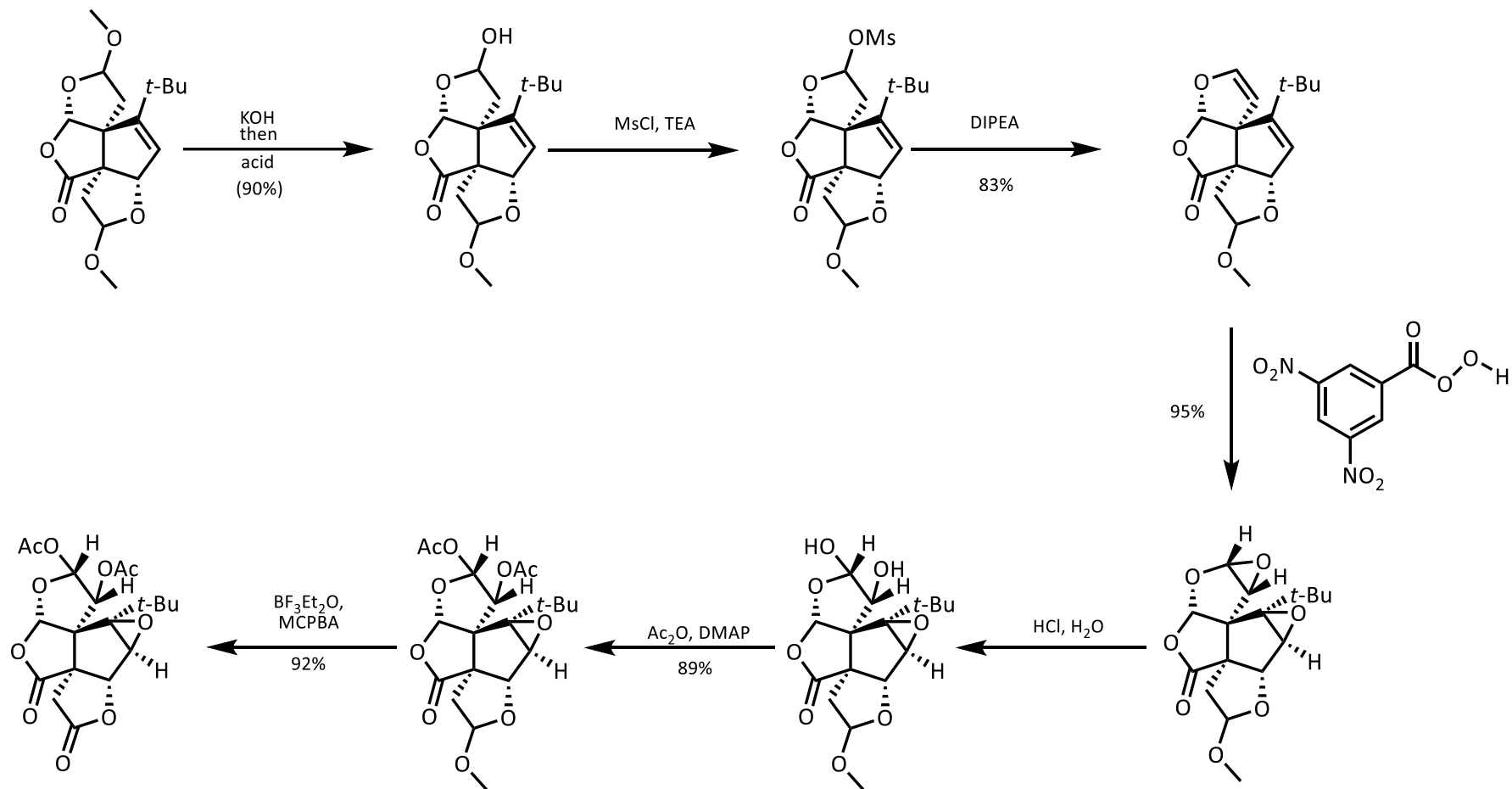
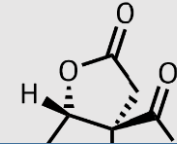


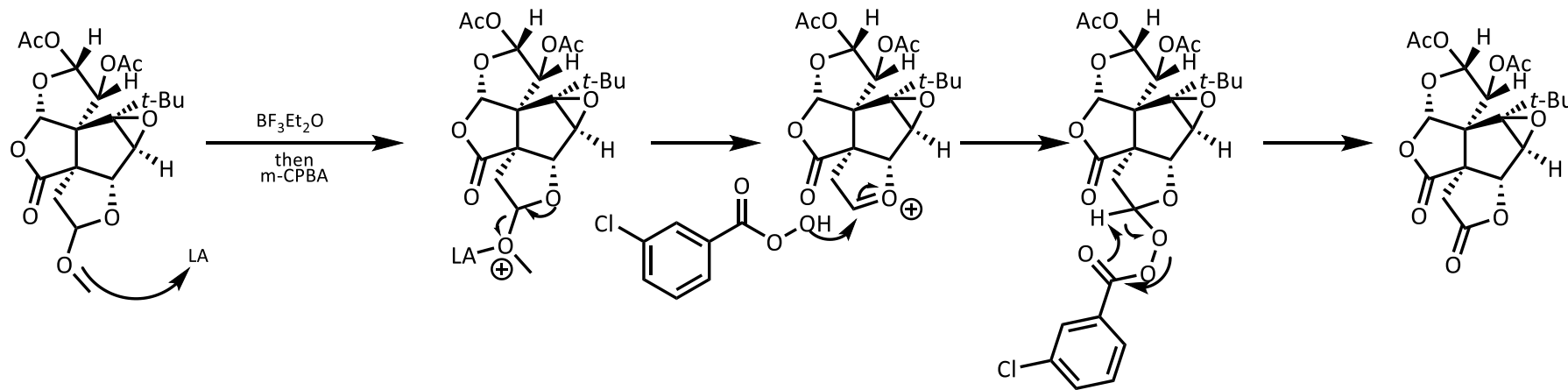
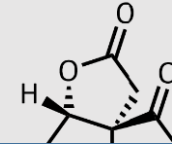


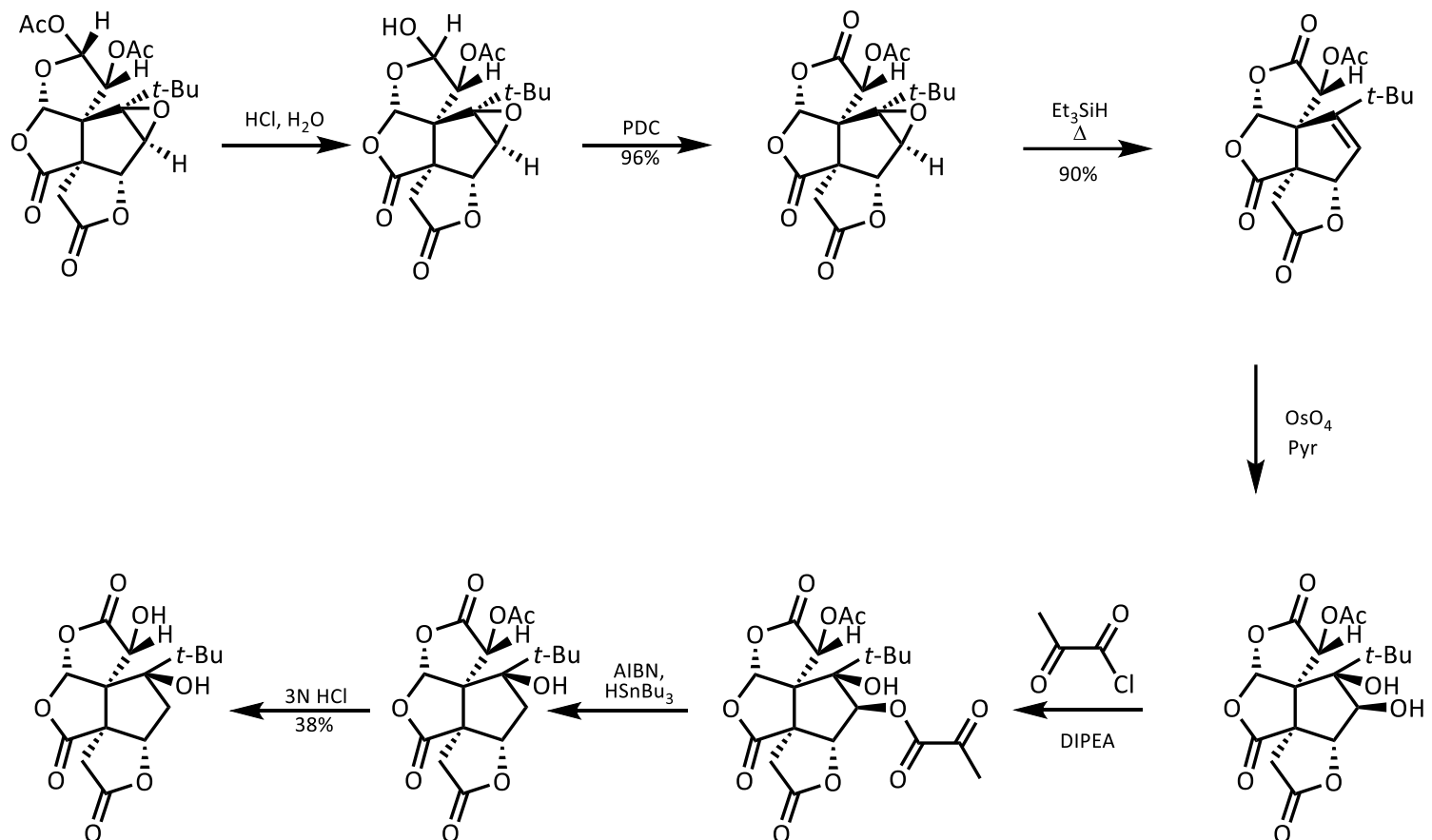
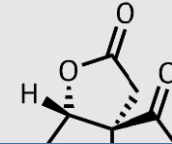




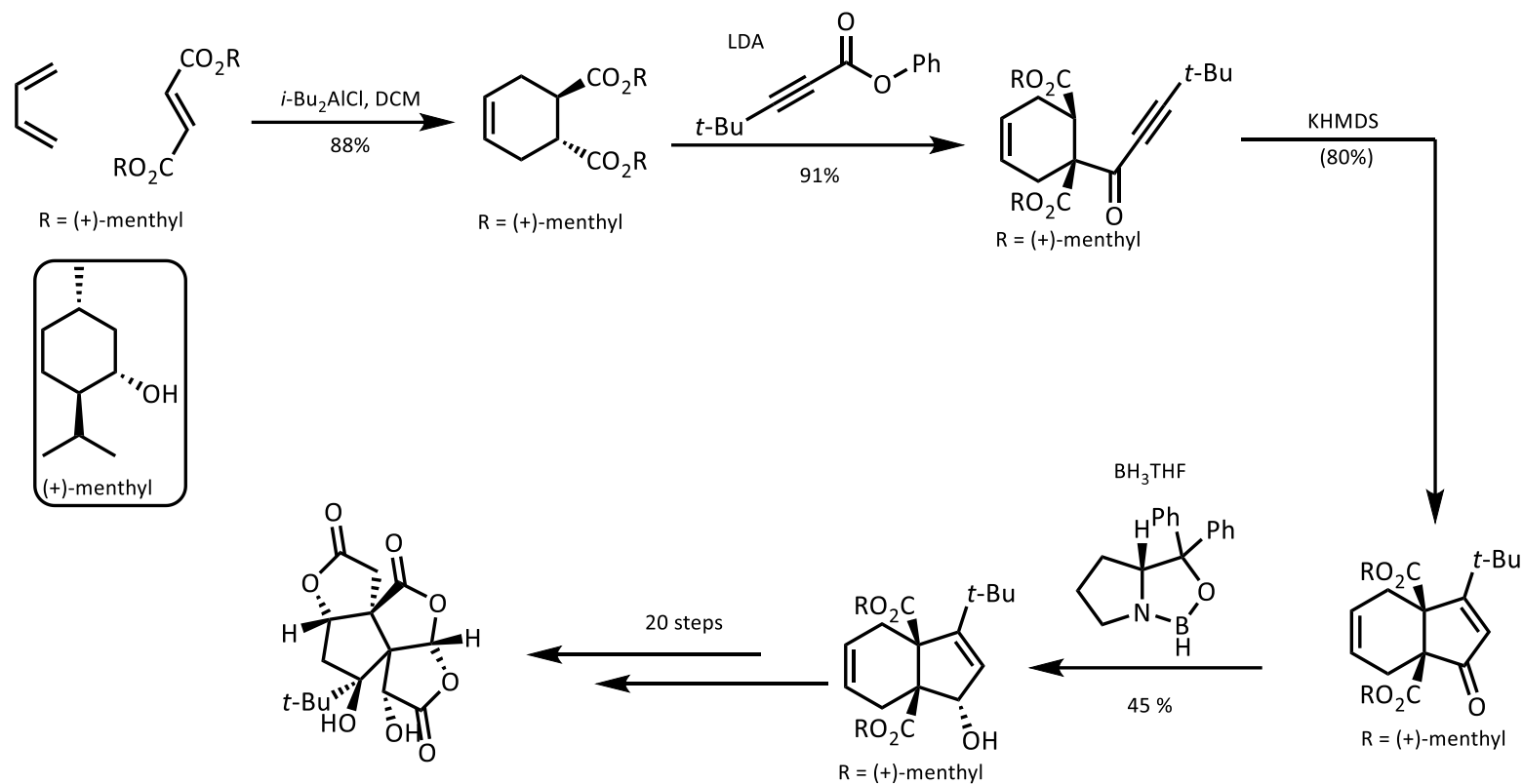
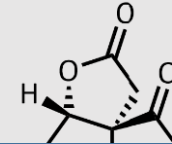




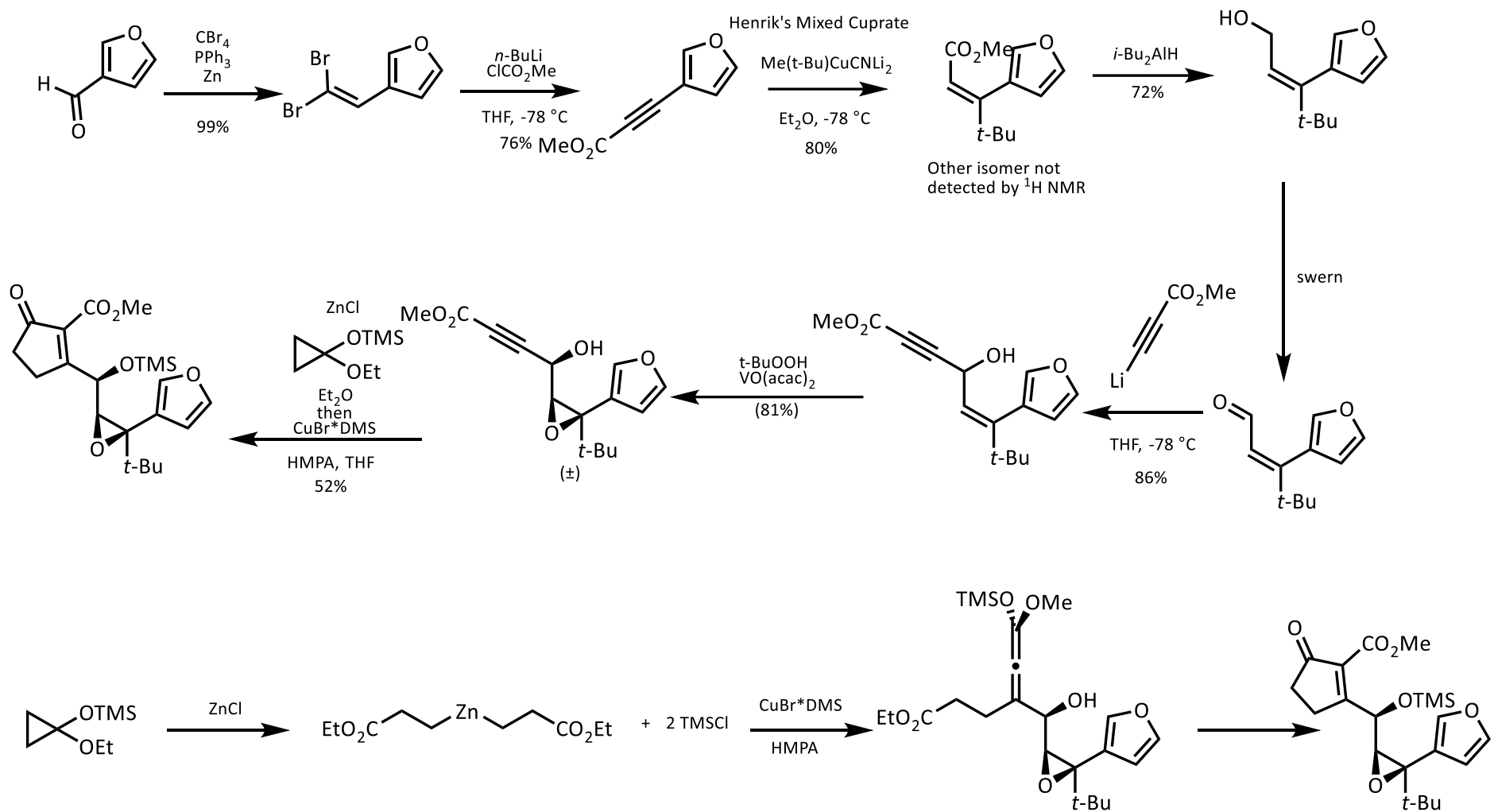
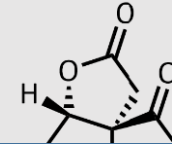




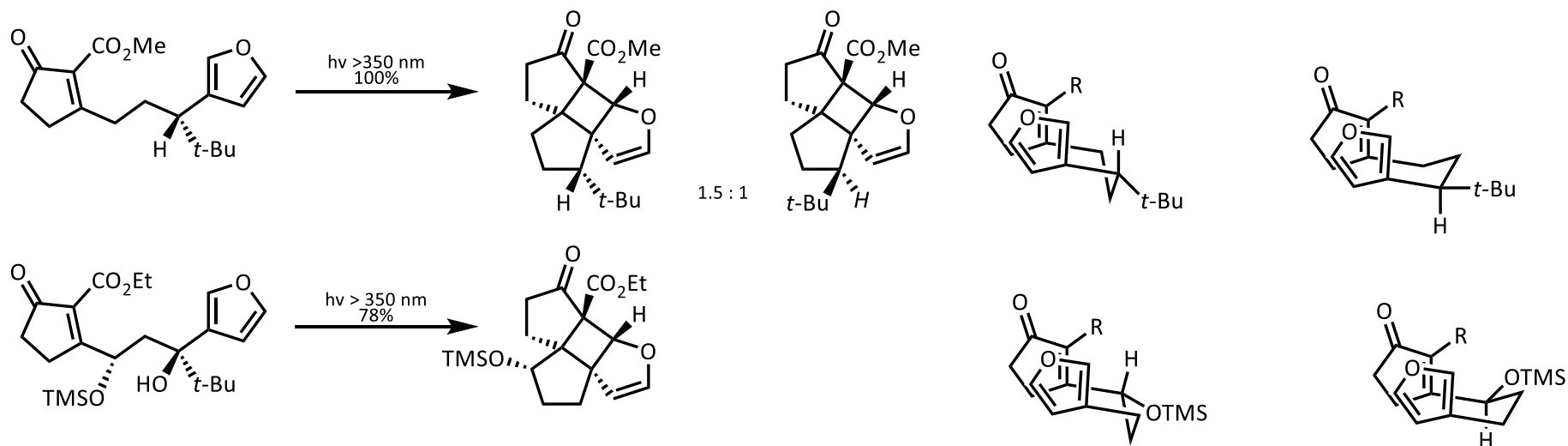
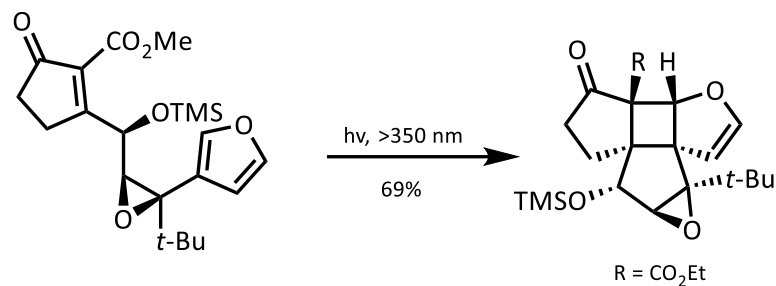
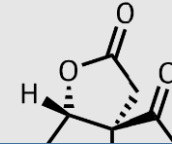
# Corey Asymmetric Synthesis



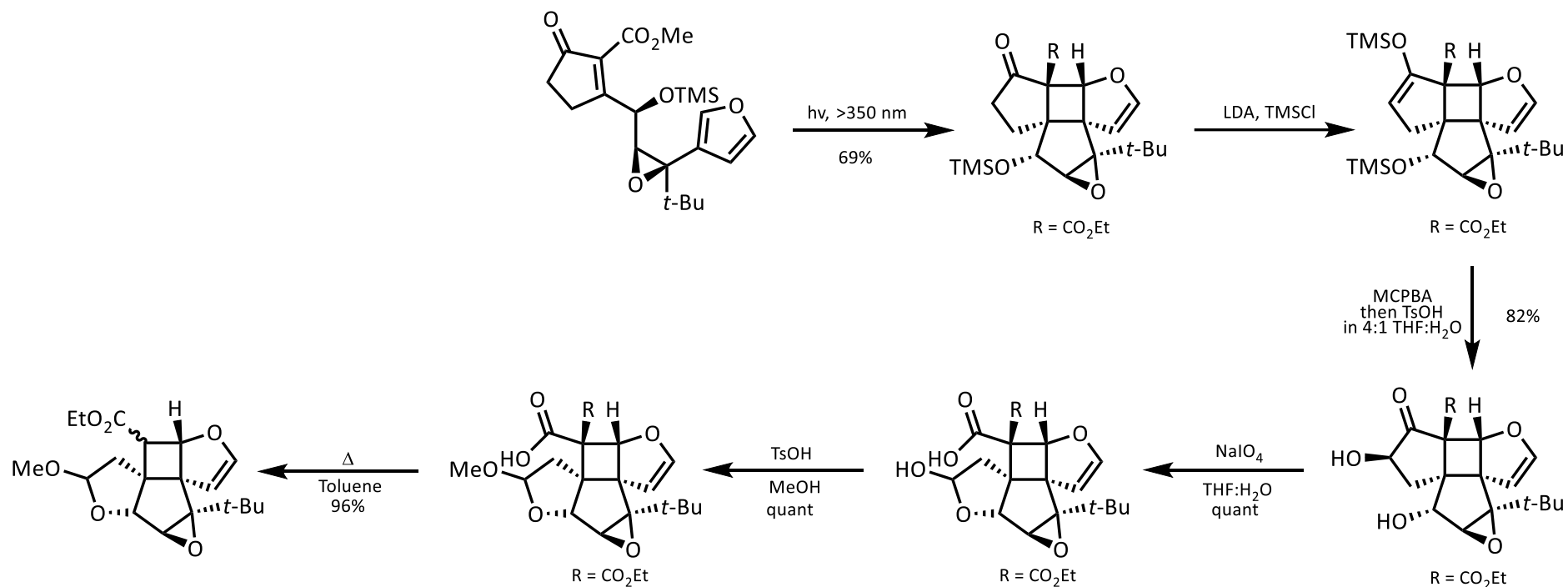
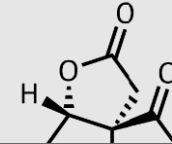
# Crimmins First Generation



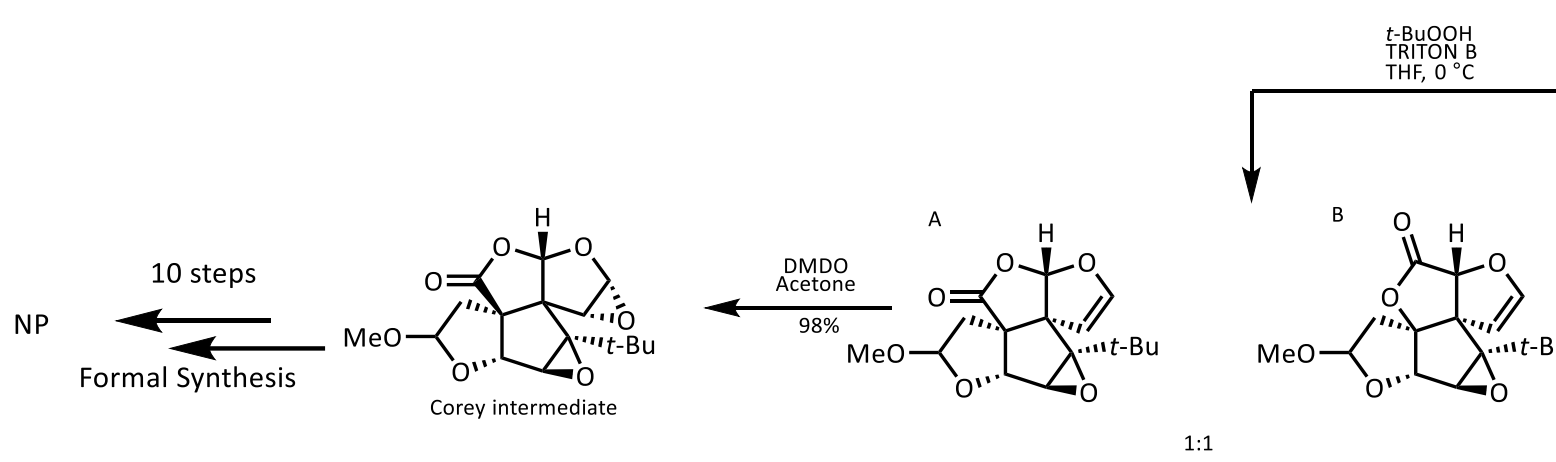
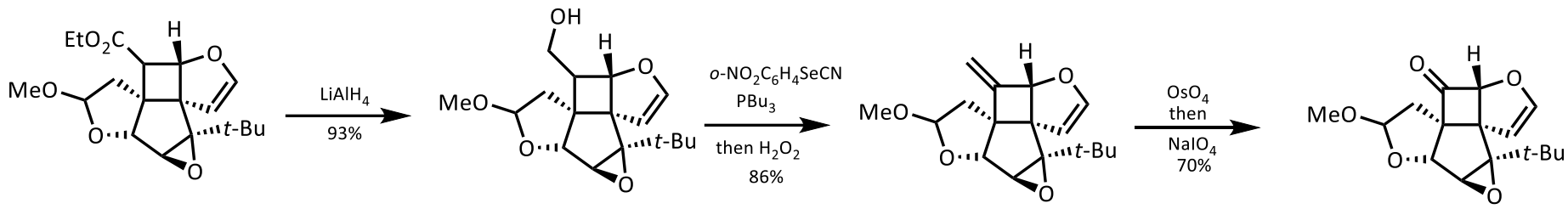
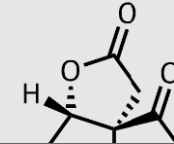
# Crimmins First Generation



# Crimmins First Generation



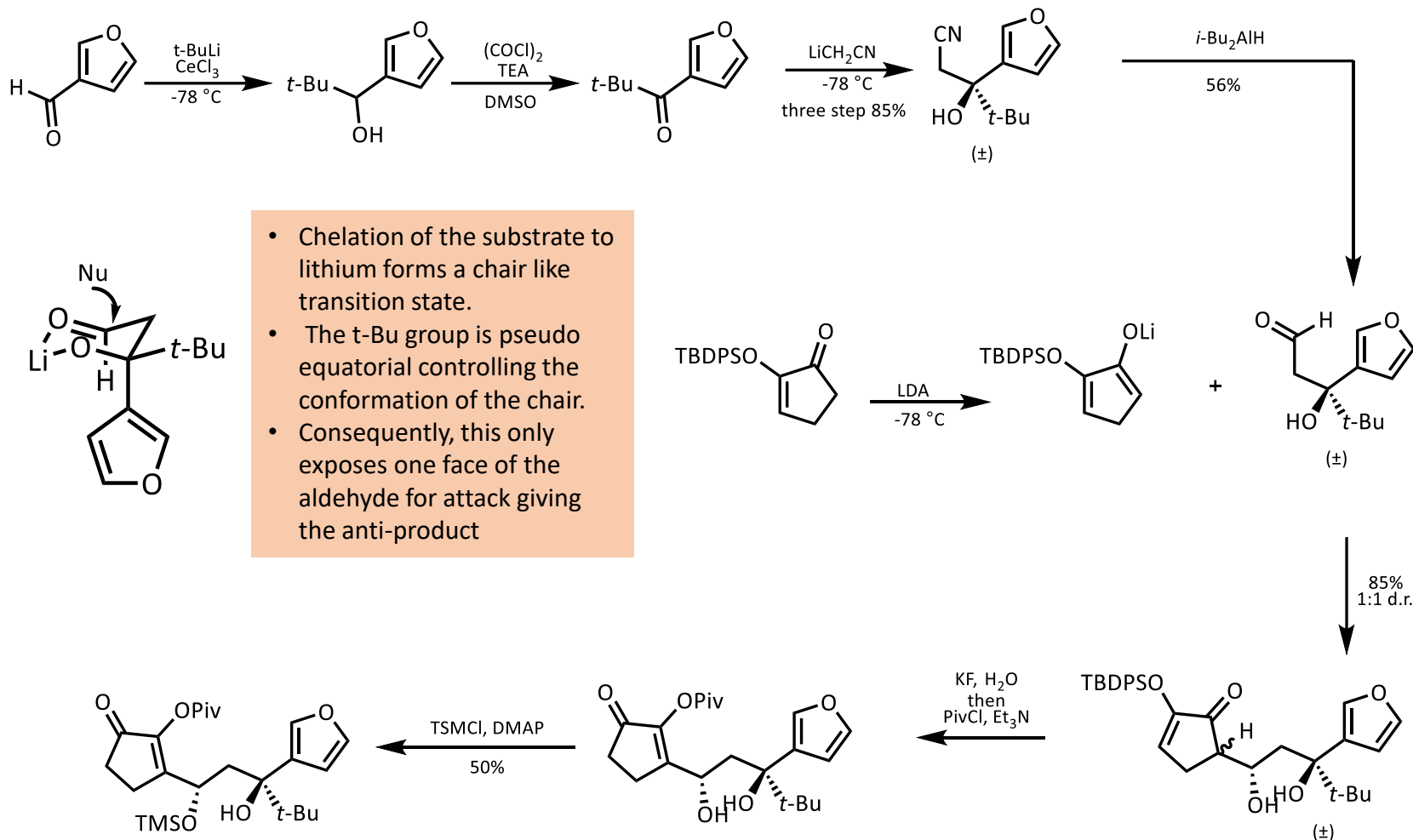
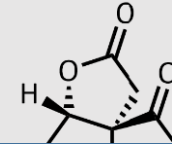
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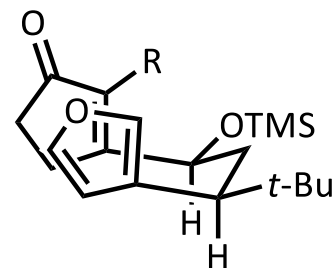
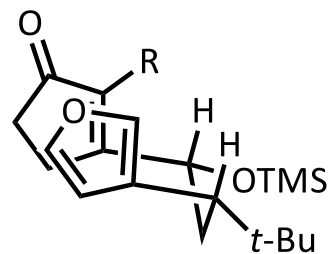
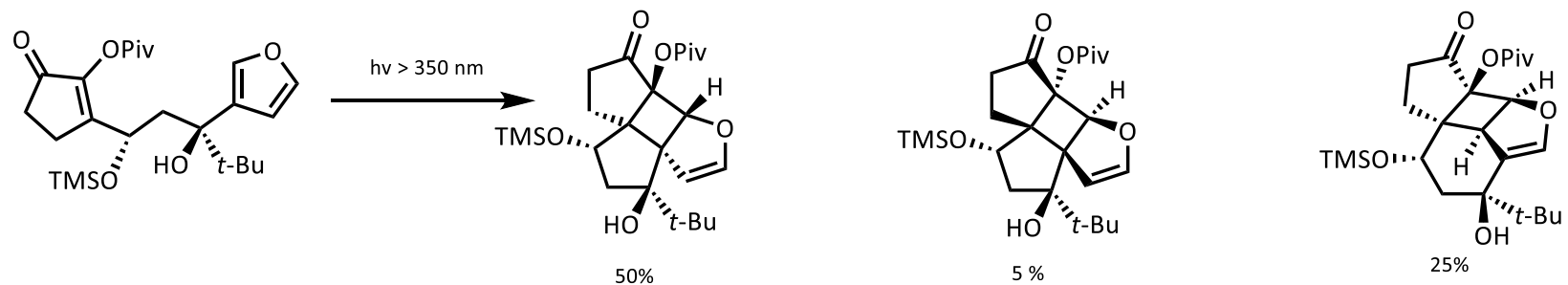
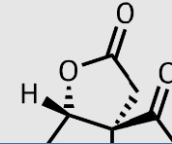
Conditions	A:B
<i>t</i> -BuOOH TRITON B THF, 0 °C	1:1
<i>t</i> -BuOOH TRITON B THF, -78 °C	1:4
Ph <sub>3</sub> COOH TRITON B THF, 0 °C	1:5
H <sub>2</sub> O <sub>2</sub> TRITON B THF, -78 °C	>97:3

NP  
Formal Synthesis  
10 steps

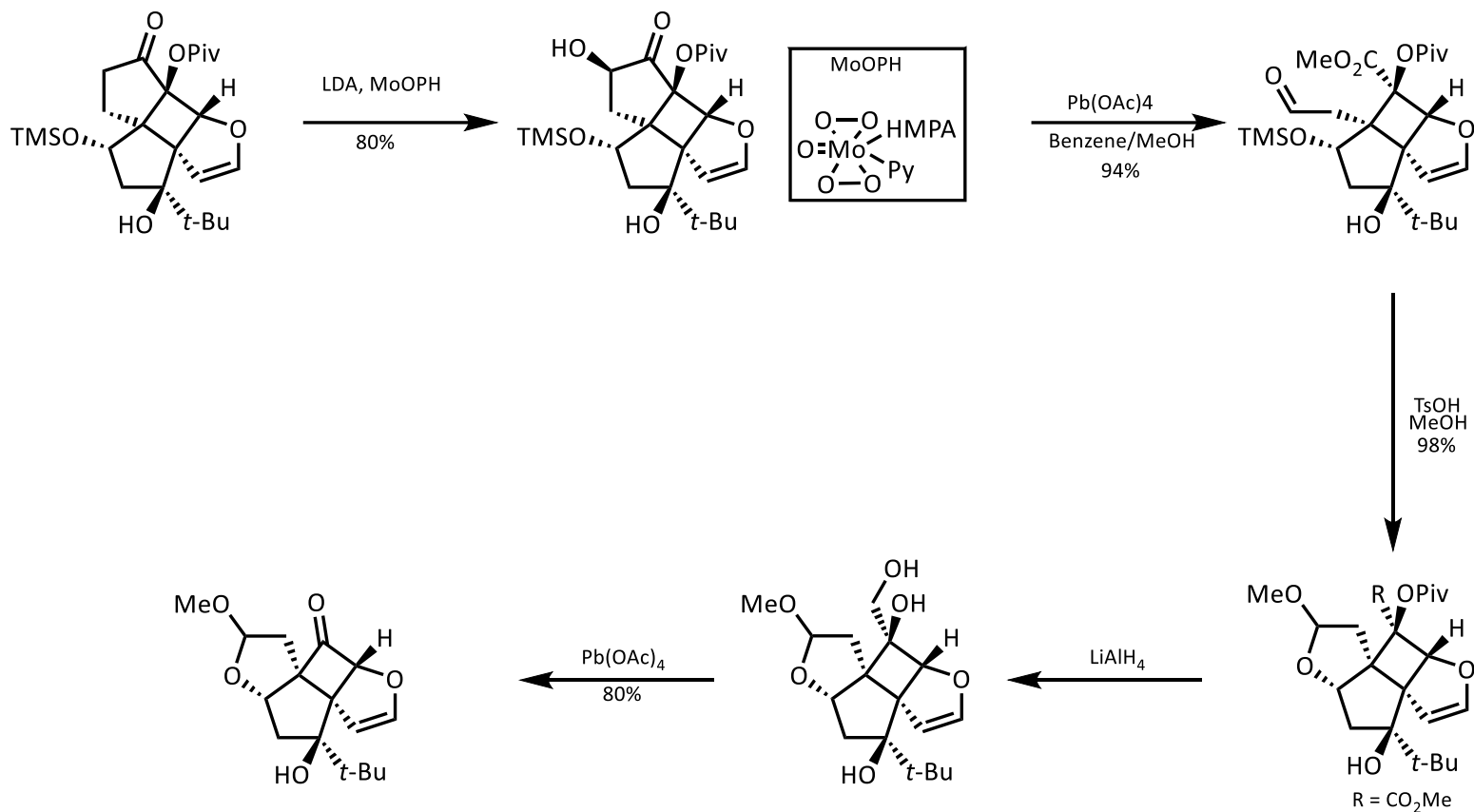
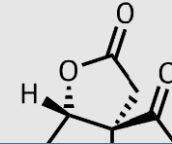
# Crimmins Second Generation



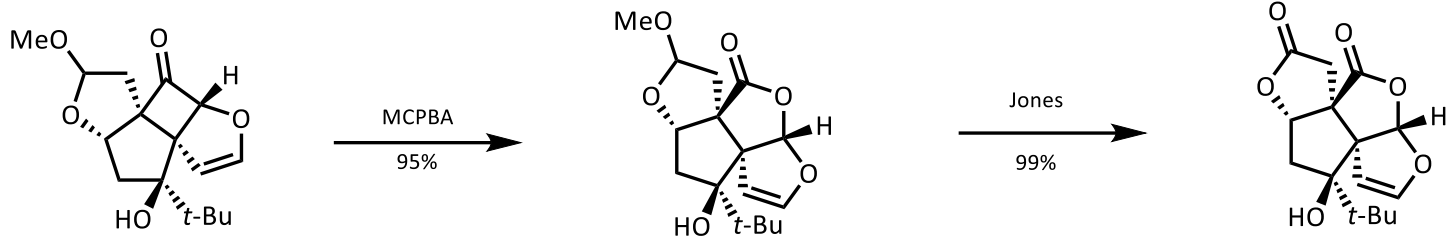
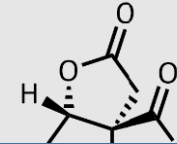
# Crimmins Second Generation



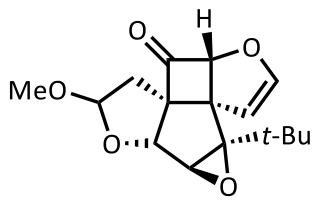
# Crimmins Second Generation



# Crimmins Second Generation

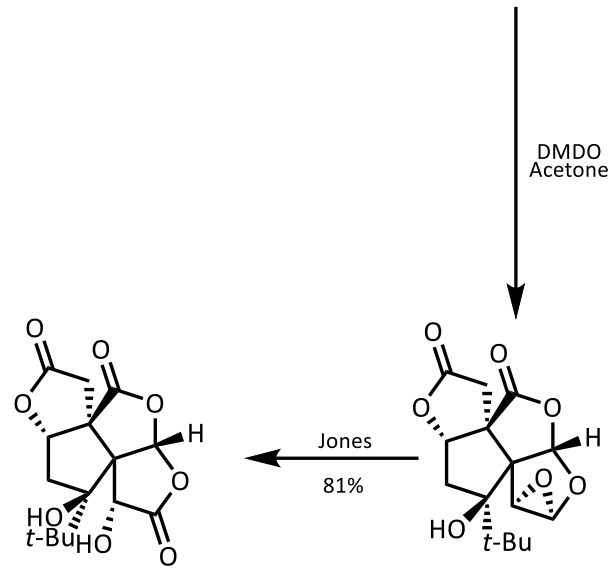
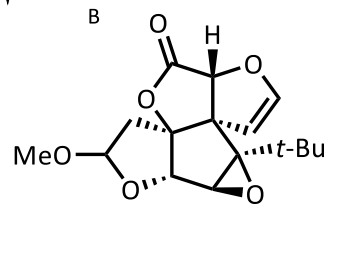
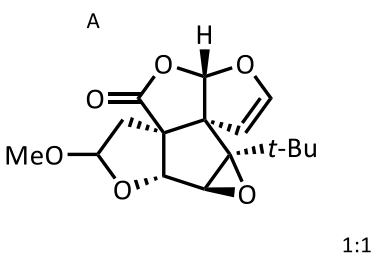


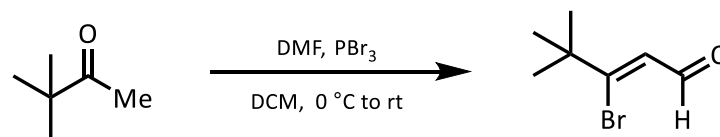
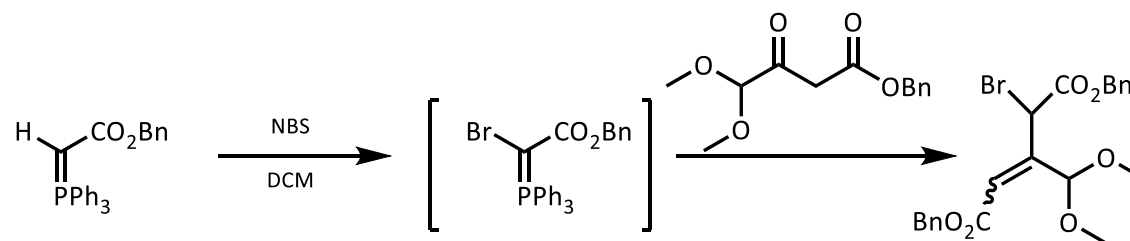
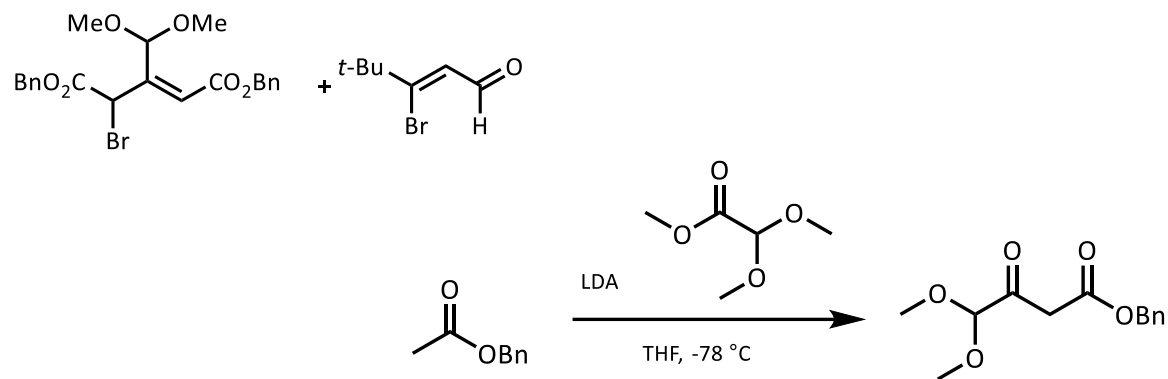
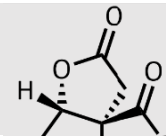
• When first gen conditions were used only migration from the wrong substituent was observed

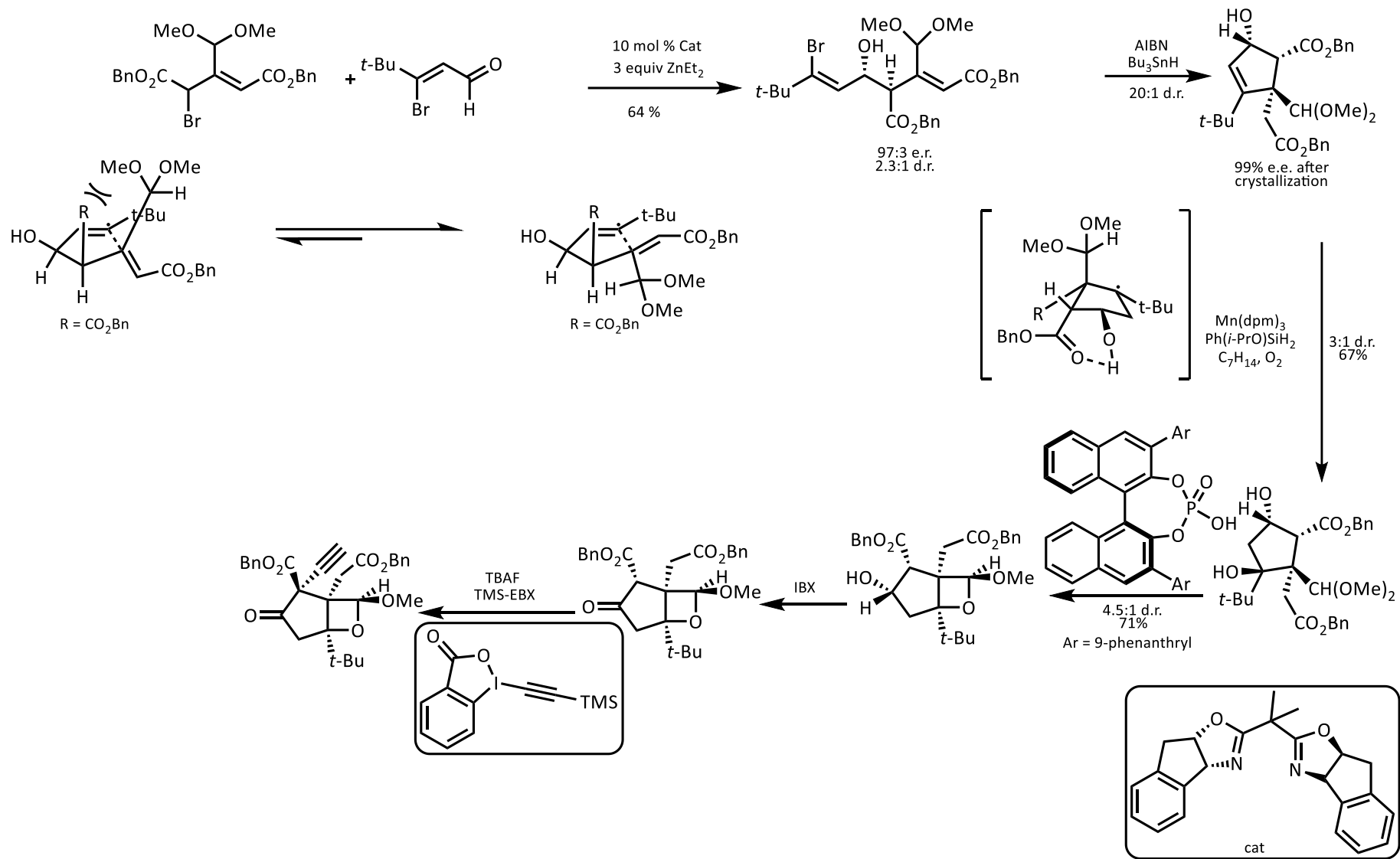
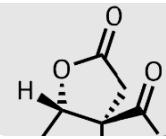


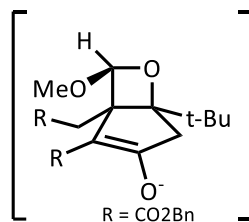
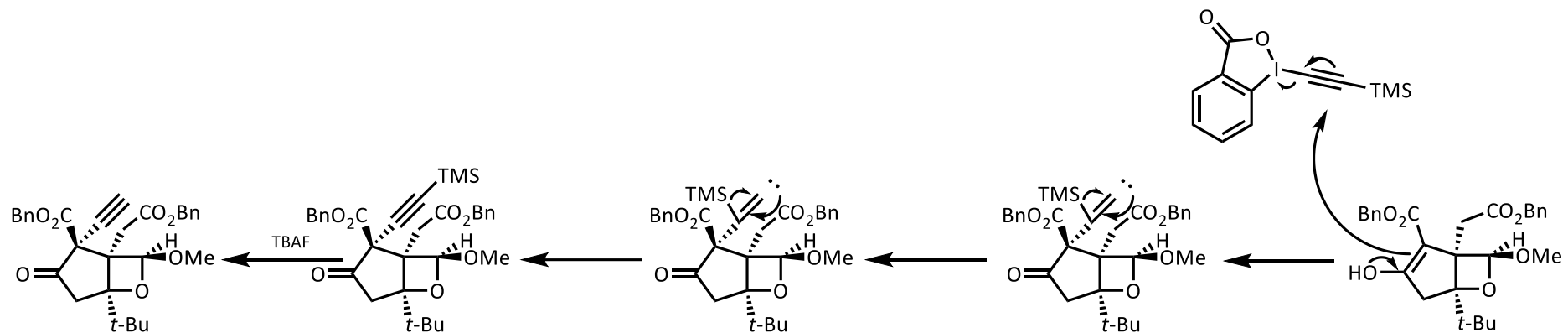
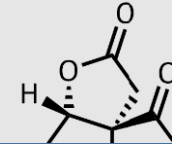
*t*-BuOOH  
TRITON B  
THF, 0 °C

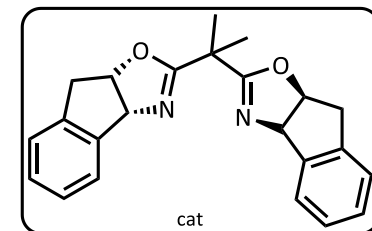
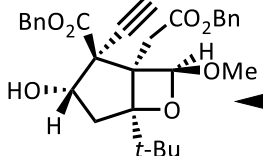
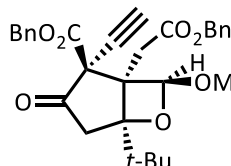
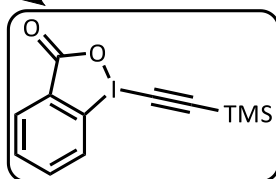
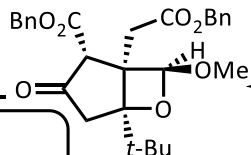
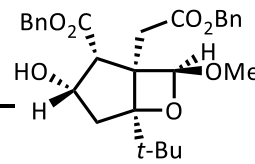
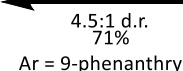
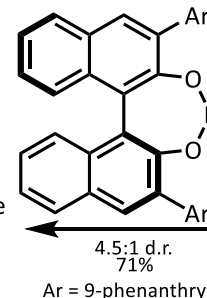
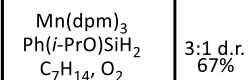
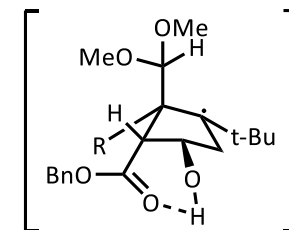
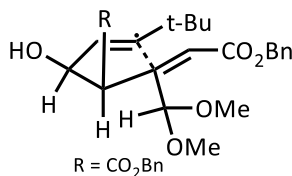
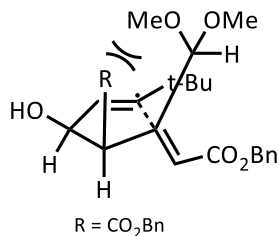
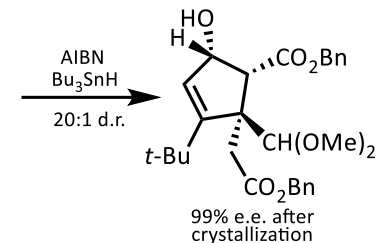
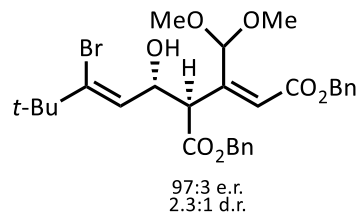
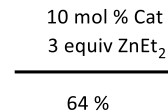
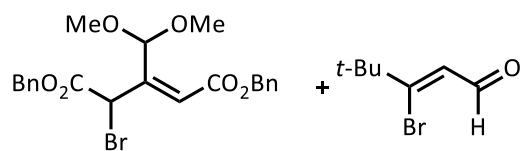
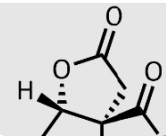
Conditions	A:B
<i>t</i> -BuOOH TRITON B THF, 0 °C	1:1
<i>t</i> -BuOOH TRITON B THF, -78 °C	1:4
Ph <sub>3</sub> COOH TRITON B THF, 0 °C	1:5
H <sub>2</sub> O <sub>2</sub> TRITON B THF, -78 °C	>97:3

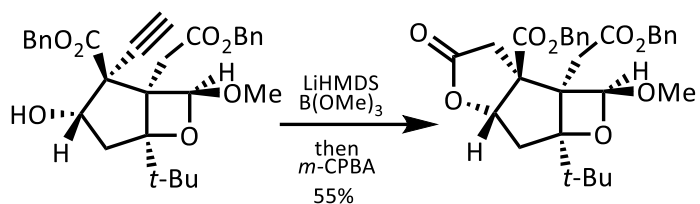
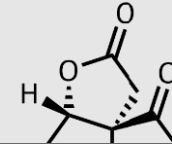




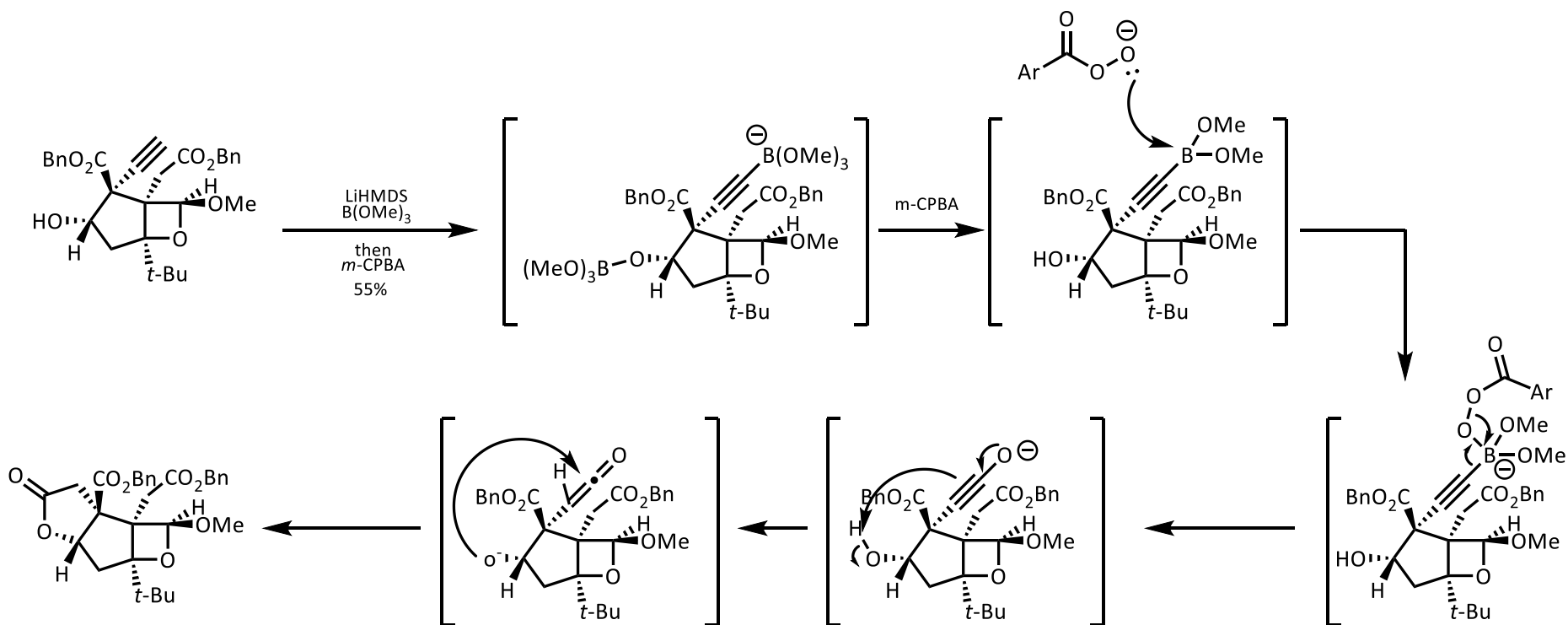


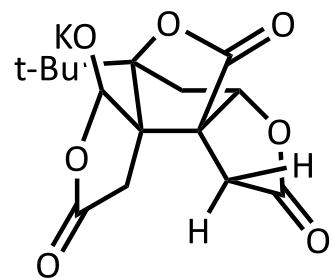
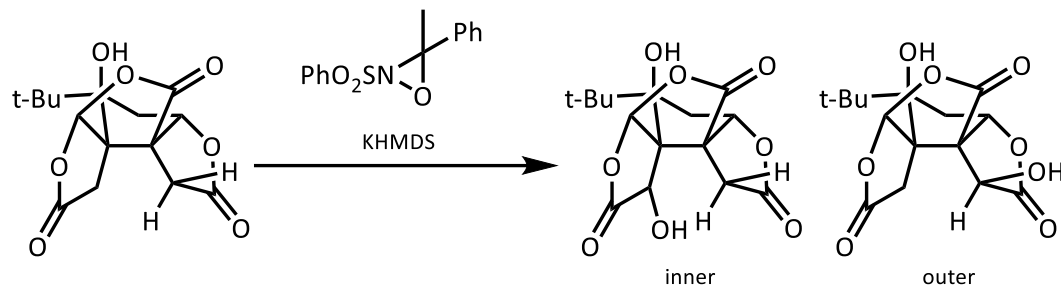
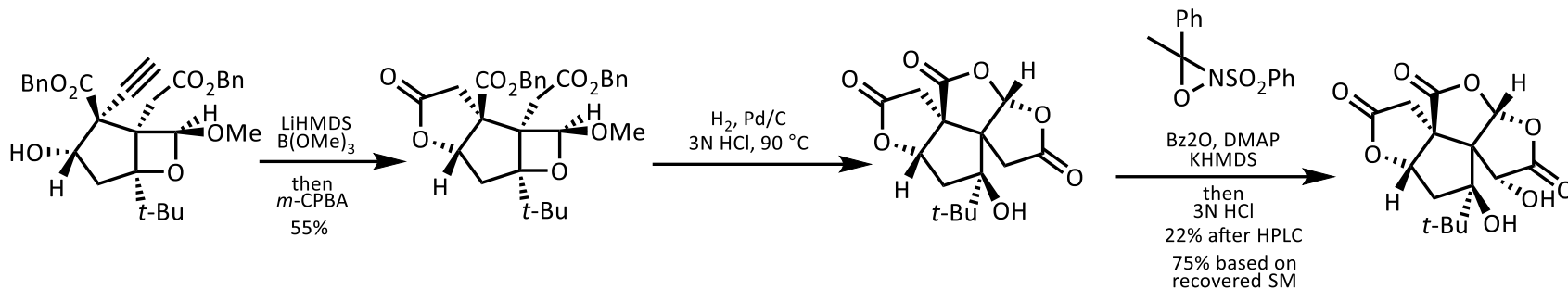
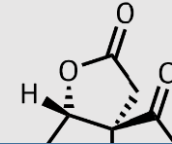






“This reaction was conceived and executed in October 2017 by Dr. Masaki Ohtawa, presented in November 2017 at ISONIS-11, posted to ChemRxiv (May 30, 2019) and published in ref 31. (October 16, 2019). A variation on this same reaction was published recently (March 27, 2020): Li, C.; Zhao, P.; Li, R.; Zhang, B.; Zhao, W. Oxidation of Alkynyl Boronates to Carboxylic Acids, Esters, and Amides. *Angew. Chem., Int. Ed.* 2020, 59, 10913. A revised manuscript now cites our work.”

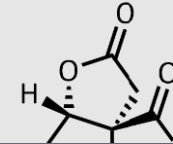




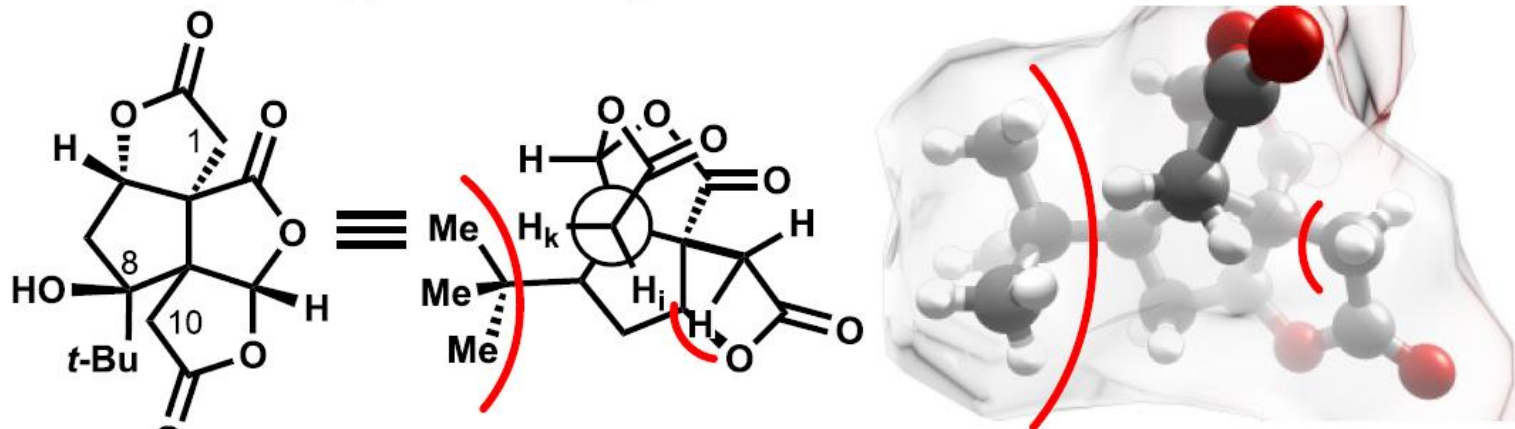
Conditions	Yield bilobalide	Yield unwanted
NaHMDS, P(OEt) <sub>3</sub> O <sub>2</sub> on crude material	Major* Product	
KHMDS, Davis(±) THF, -78 °C then 2 M HCl, 60 °C	0 %	100%
1. TBSOTf, 2,6 lut 2. KHMDS Davis(±) THF, -78 °C then 2 M HCl, 60 °C	6 %	94%
1. EDCI, BzOH, DMAP, 2. KHMDS, Davis(±) THF, -78 °C then 2 M HCl, 60 °C	91%	9%

\* = "This result was extraordinary given the apparent inaccessibility of the C10 protons. Out delight was fleeting: the reaction has never been reproduced to this day"

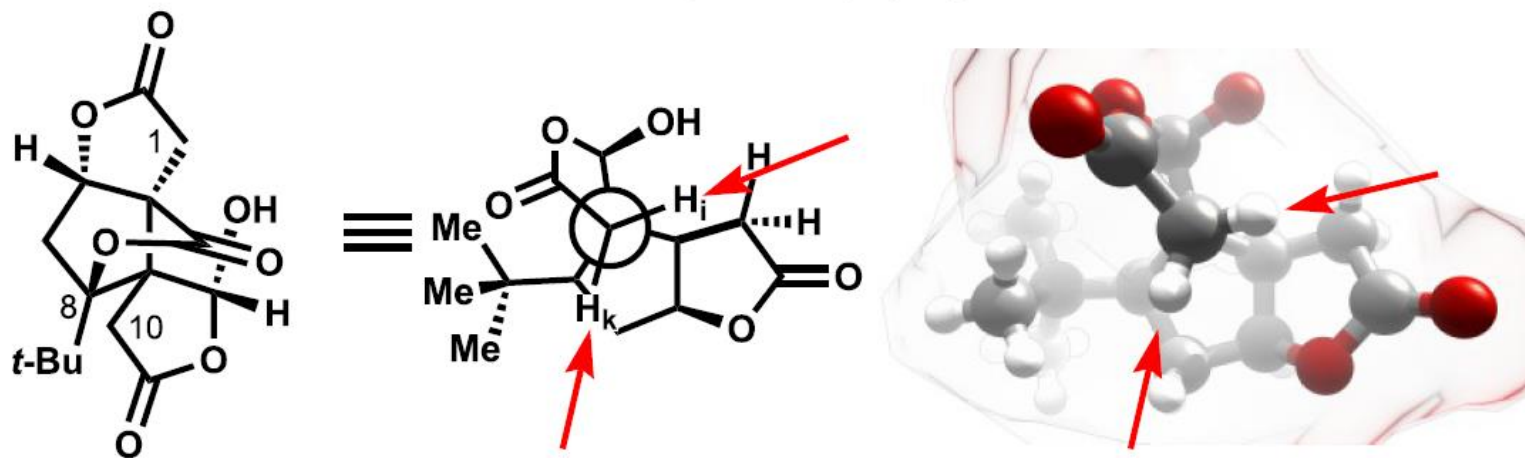
# Proton Accessibility



b. isomerization appears to change inner lactone accessibility



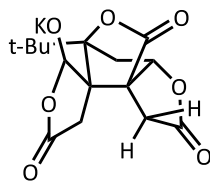
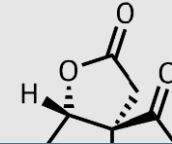
*inner lactone protons ( $H_i$ ,  $H_k$ ) inaccessible*



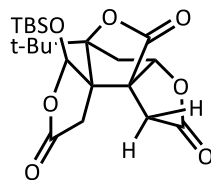
**iso-2**

*inner lactone protons ( $H_i$ ,  $H_k$ ) more accessible*

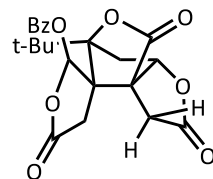
# $\pi$ - $\sigma^*$ Hyperconjugation



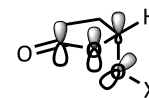
Failed to give product



Failed to give product



Gave mostly Bilobalide



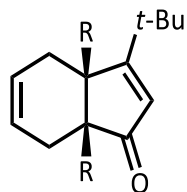
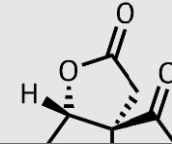
- hypothesize that for  $\alpha$ -hydroxylactones the oxygen lone pair can delocalize into the antibonding orbital of the hydroxide.
- Results in a reduction of donation into the carbonyl and there for increasing the acidity of the the protons.
- The selectivity they observed loosely correlates with length of bond a and b and pKa
- They attribute this effect to the vastly improved selectivity observed

**d**

R	a	b	$\Delta G_{\text{depr}}$	pKa	$\Delta$ pKa
H	1.35	1.44	27.5	22	0
OTBS	1.36	1.44	27.2	21.8	0.2
OB(OH) <sub>2</sub>	1.36	1.43	23.2	18.6	3.4
OCOMe	1.36	1.41	21.6	17.3	4.7
OCOPh	1.37	1.41	22.2	17.8	4.2

- The Shenvi synthesis can be carried out by one person in a week to give 0.35g of bilobalide

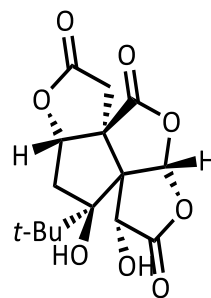
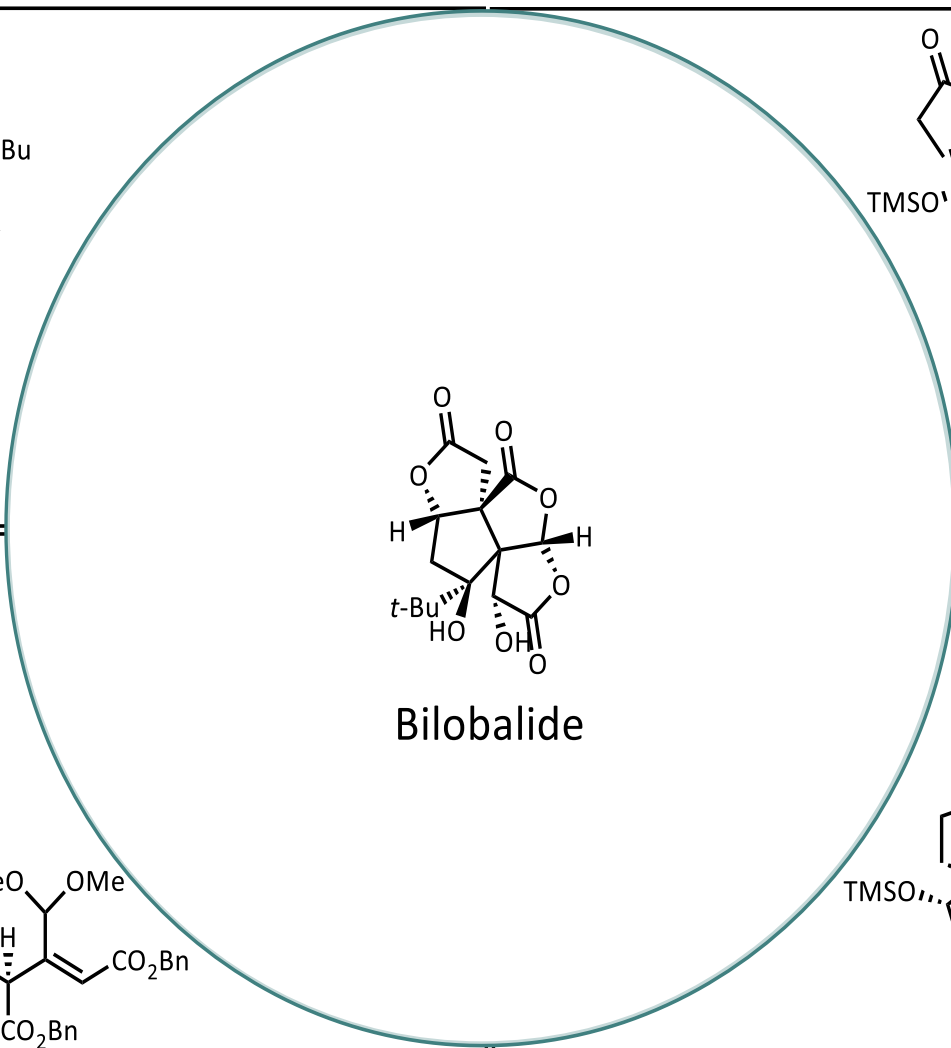
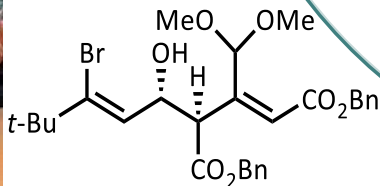
# Summary



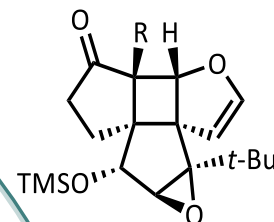
- 24 steps
- 11 redox steps



- 10 step synthesis
- 3 redox steps



Bilobalide



- 29 step formal synthesis
- 9 redox steps

- 18 step synthesis
- 8 redox steps

