Synthesis Researches Toward Ginkgolide B: Frustrations and Improvements

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Outline

- **Introduction**
  History and Biological Activity
  Biosynthesis Pathway
- **Total Synthesis**
  Corey (1988): A Feat of Organic Synthetic Chemistry
  Crimmins (1999): Failure and Improvement
- **Summary**
- **Acknowledgement**

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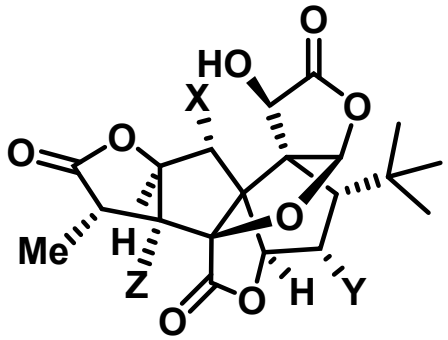
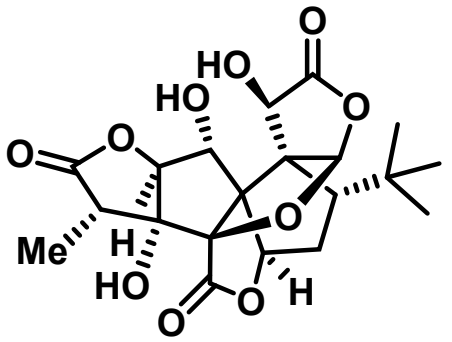
History and Biological Activity

- Ginkgolide family contains Ginkgolide A, B, C, M and J, which differ only in the number and location of hydroxyl groups. Ginkgolide B is the most potent platelet-activating factor (PAF) antagonist of the ginkgo extracts with an IC_{50} Value of 0.6 mM.

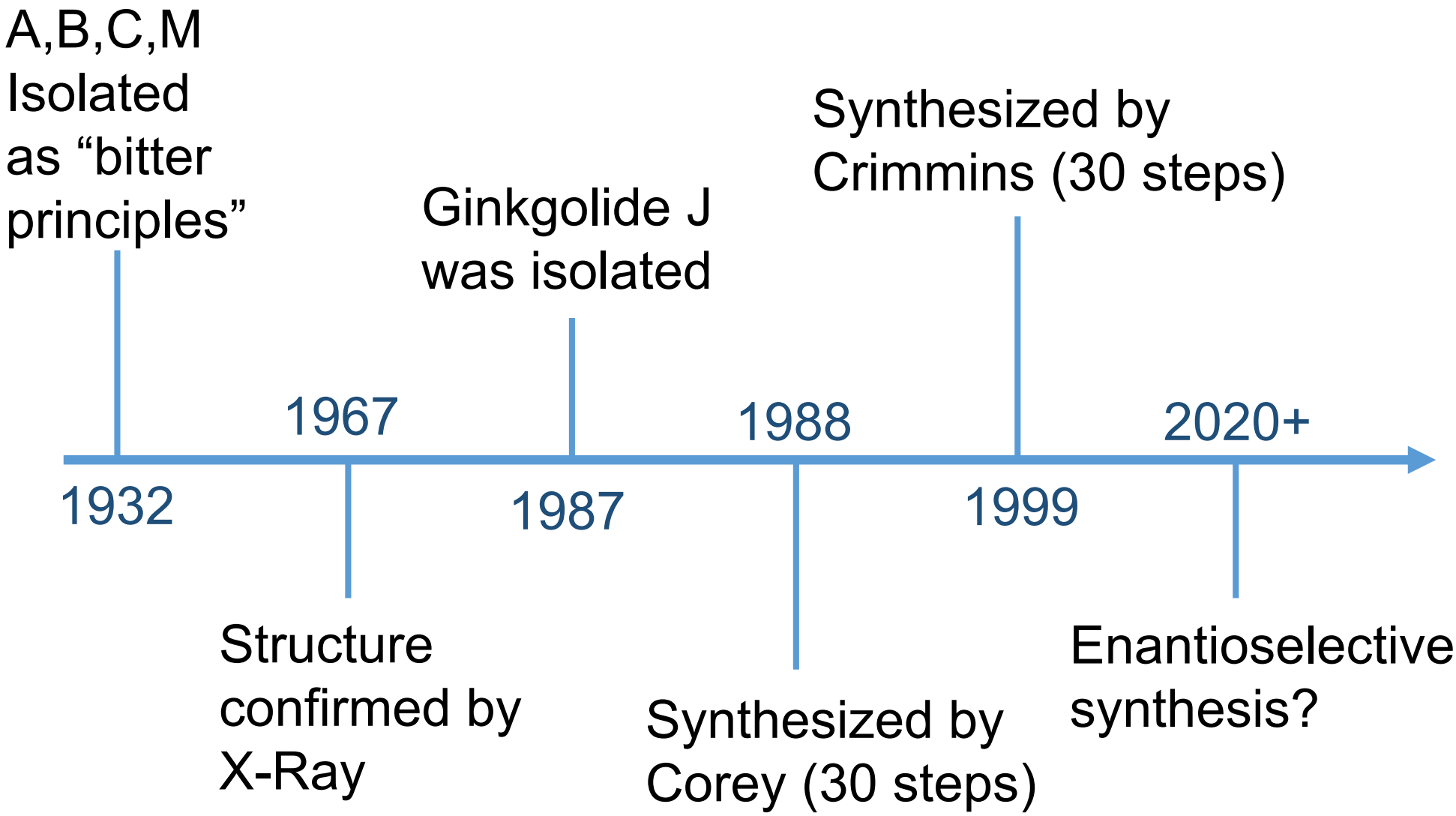


Ginkgolide B X=OH, Y=H, Z=OH
Ginkgolide A X=H, Y=H, Z=OH
Ginkgolide C X=OH, Y=OH, Z=OH
Ginkgolide M X=H, Y=OH, Z=OH
Ginkgolide J X=OH, Y=OH, Z=H

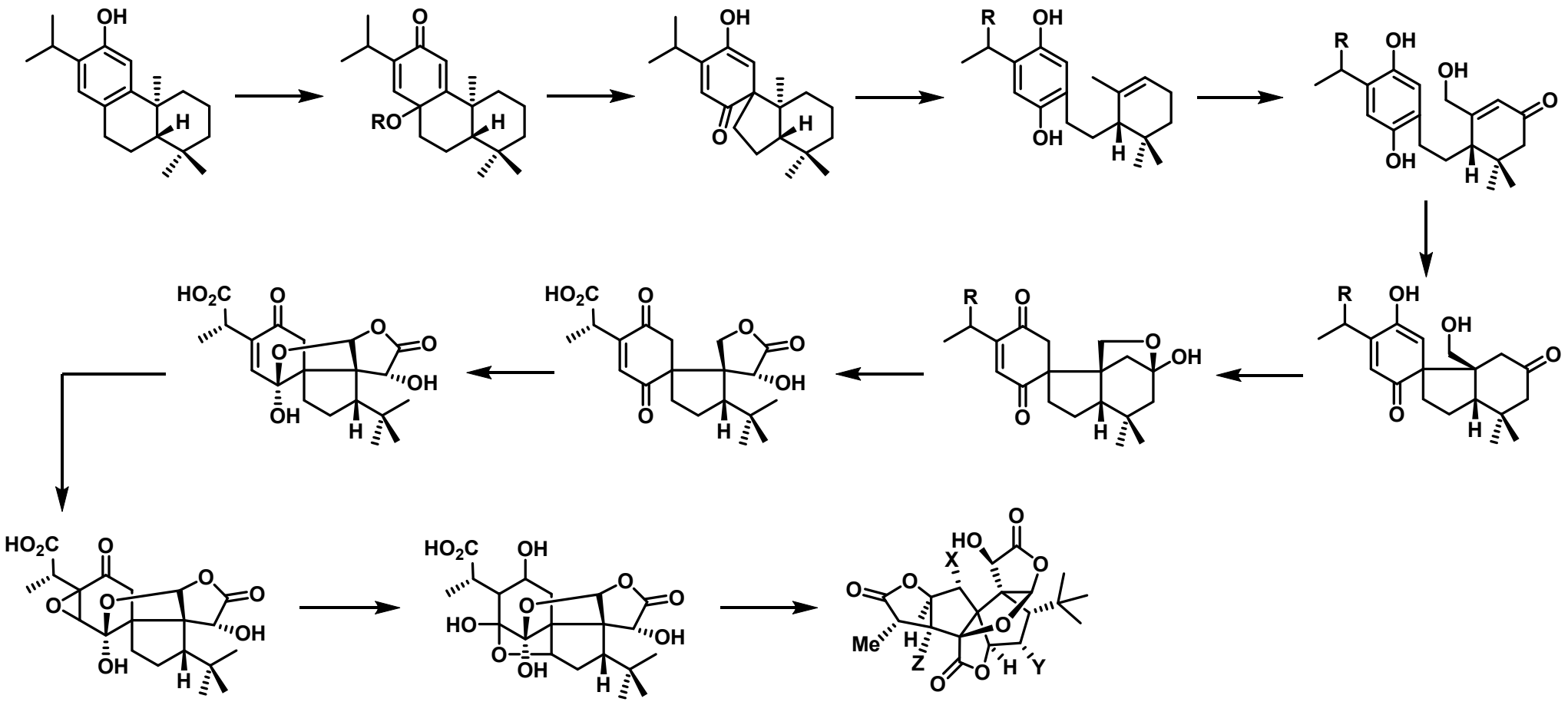


Ginkgolide B

History and Biological Activity



Biosynthesis Pathway



Nakanish, K et al. *J. Am. Chem. Soc*. **1971**, *93*, 3456. ; Schwarz, M et al. Ginkgolide Biosynthesis *In:* Barton DHR et al, eds. *Natural Product Chemistry.* 2. New York: Elservier, **1999**, 367-400.

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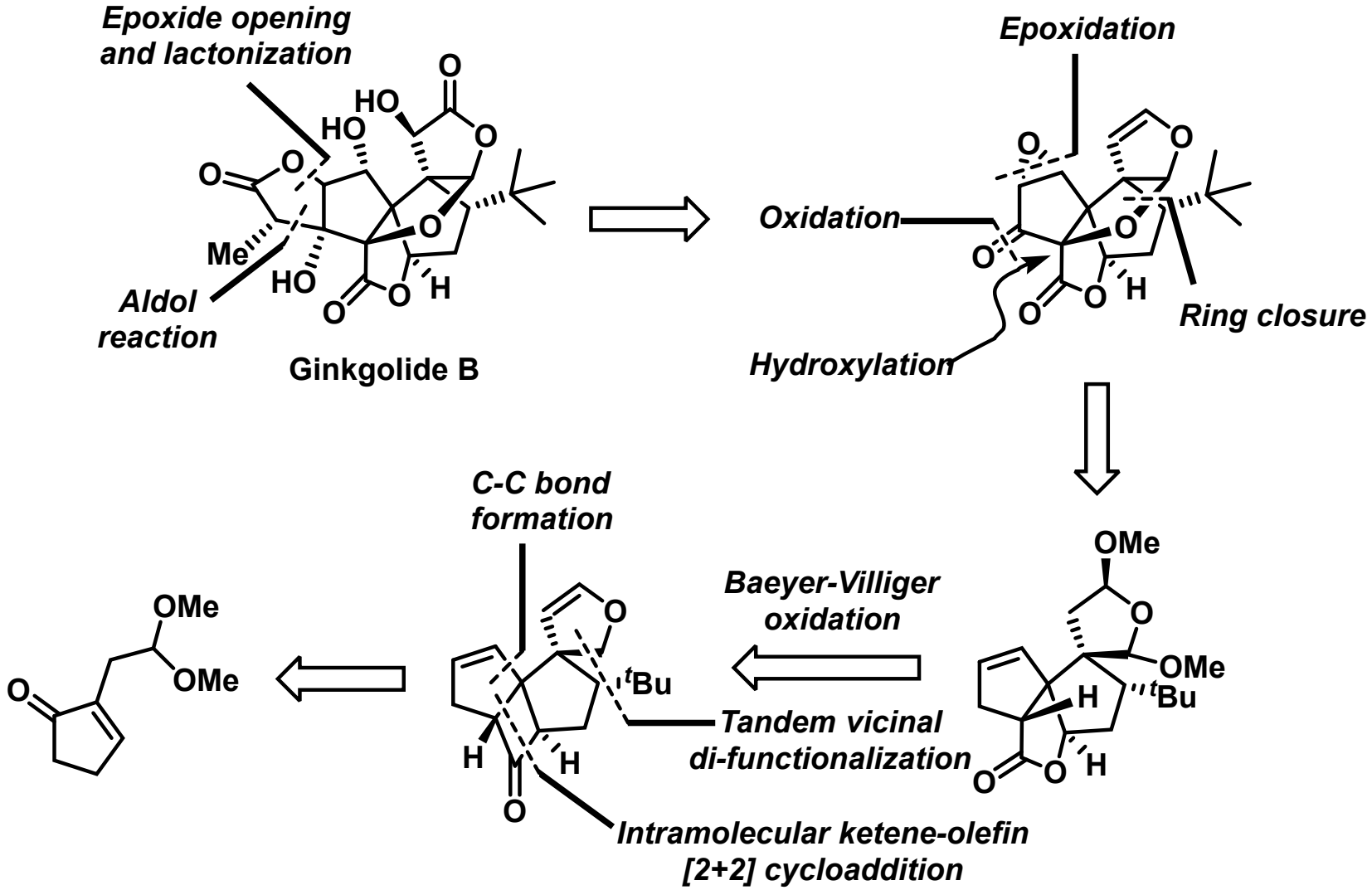
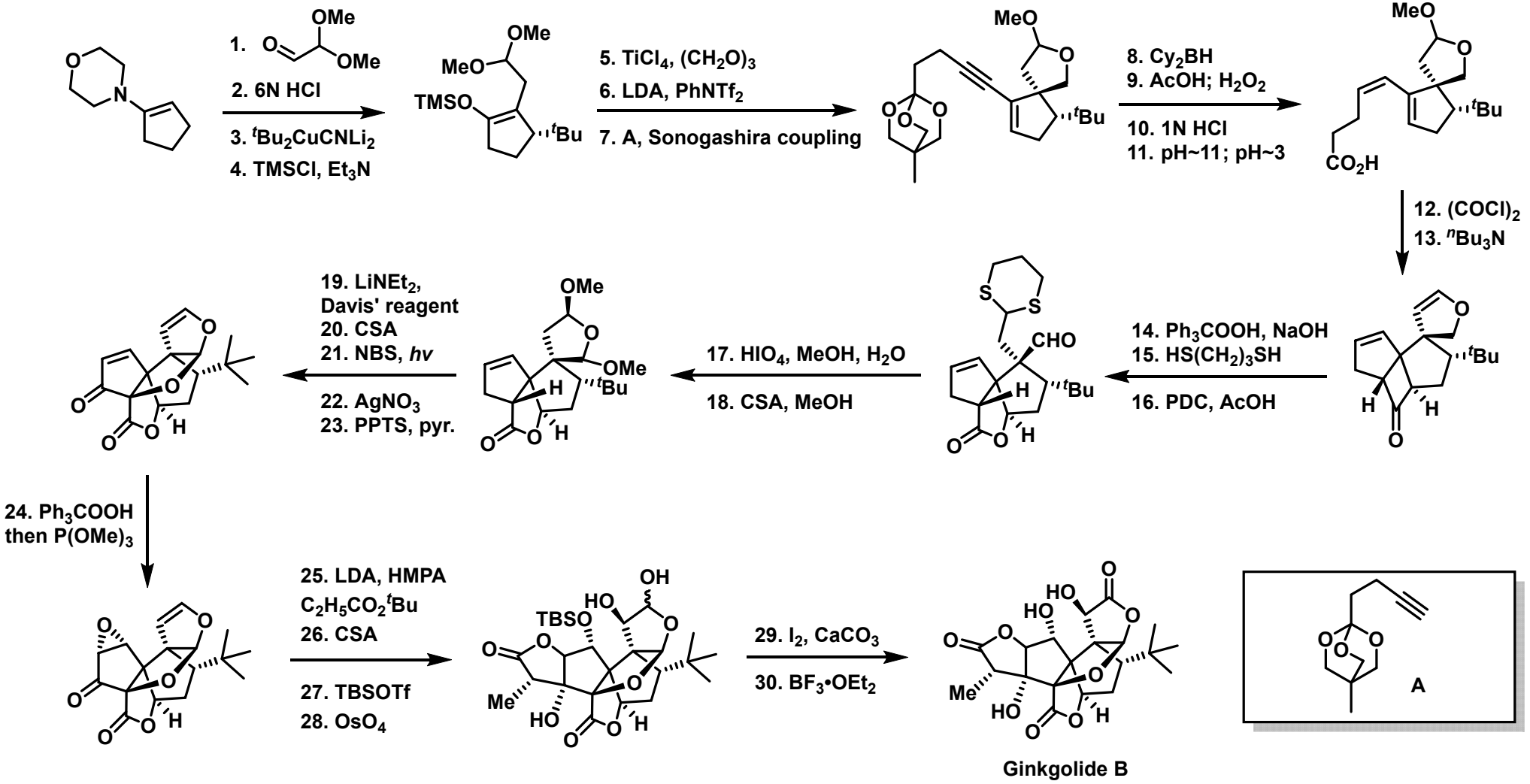
Corey (1988): Retrosynthesis

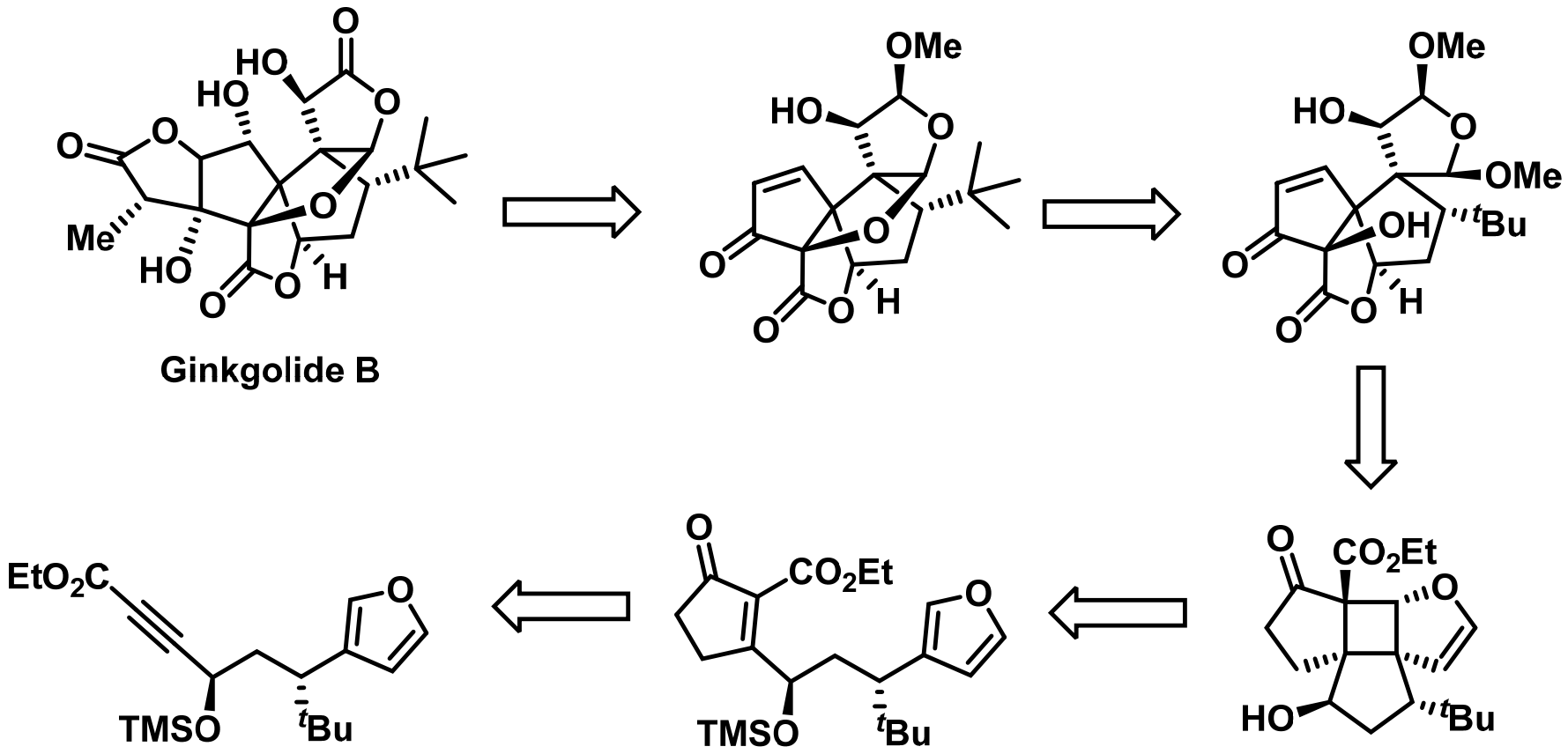


Nicolaou, K et al. *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122. ;Corey, E et al. *J. Am. Chem. Soc.* **1988**, *110*, 649-651.

Corey (1988): Total Synthesis

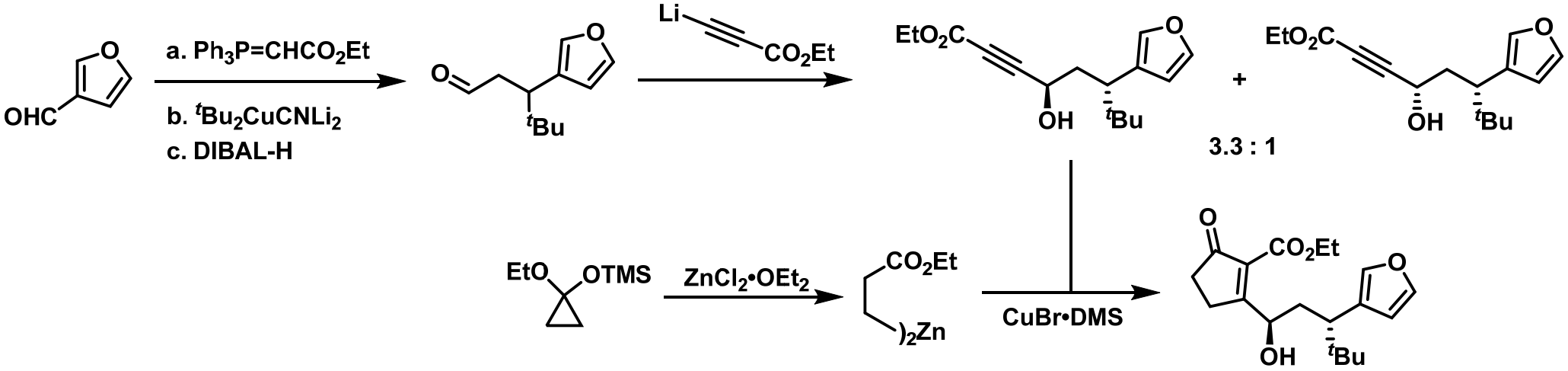


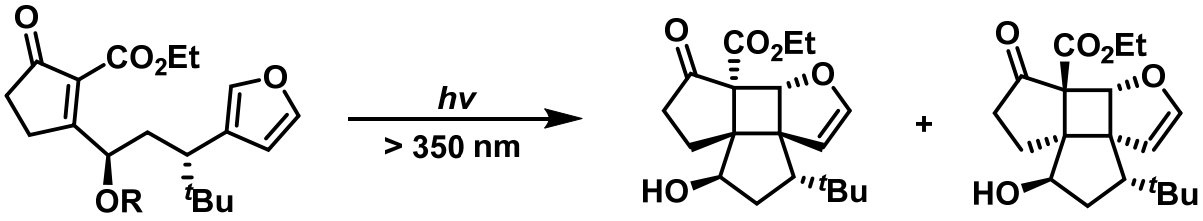
Crimmins (1999): Retrosynthesis



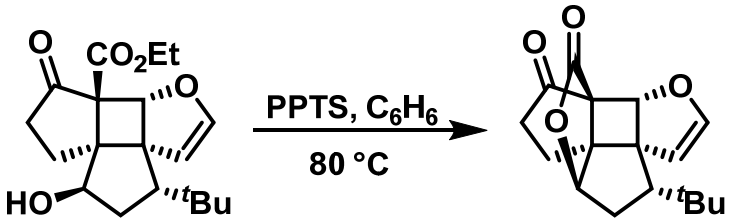
Crimmins, M et al. *J. Am. Chem. Soc.* **1999**, *121*, 10249-10250. ; Crimmins, M et al. *J. Am. Chem. Soc.* **2000**, *122*, 8453-8463.

[2+2] Cyclization: Selectivity Undesirable

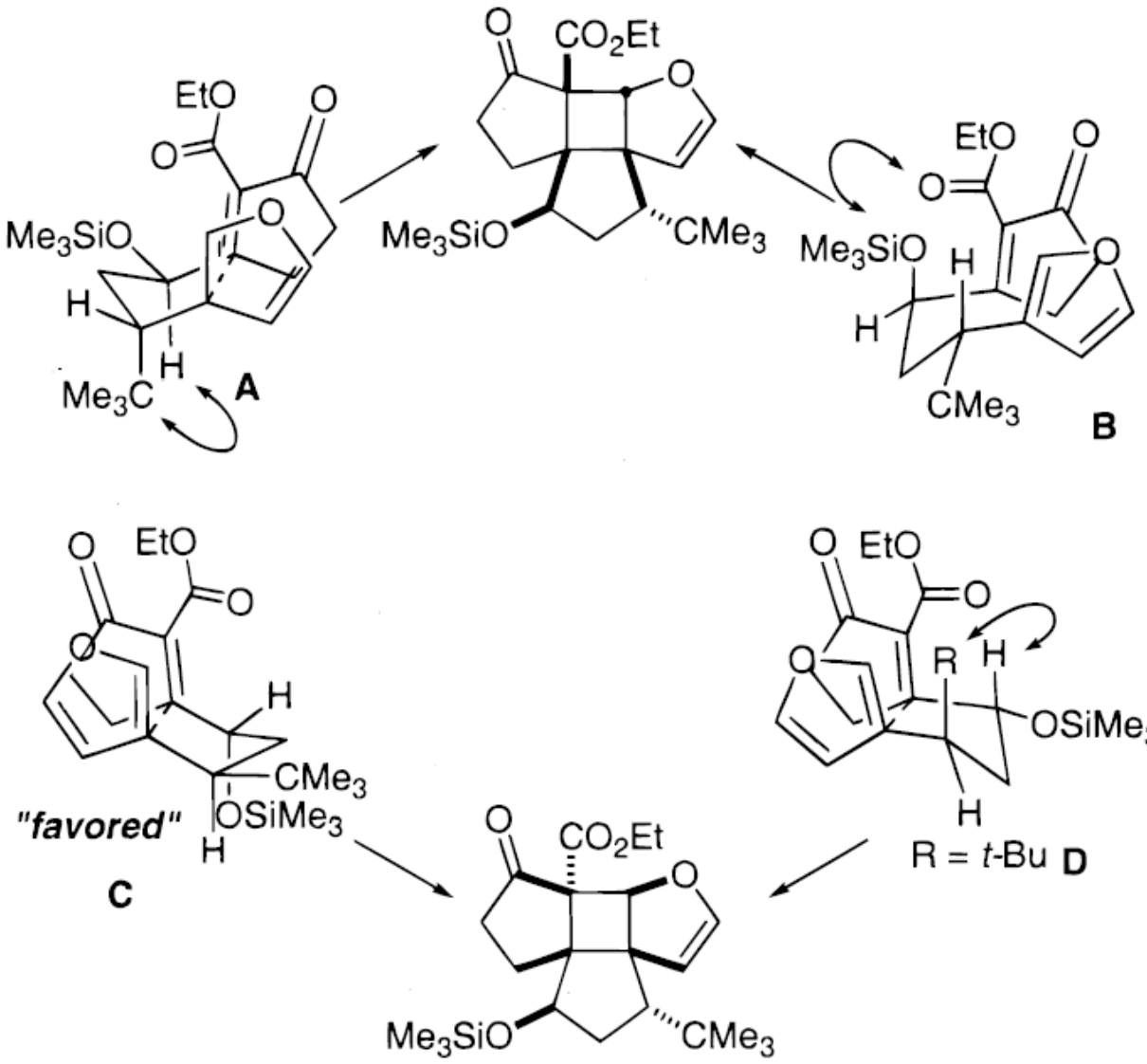




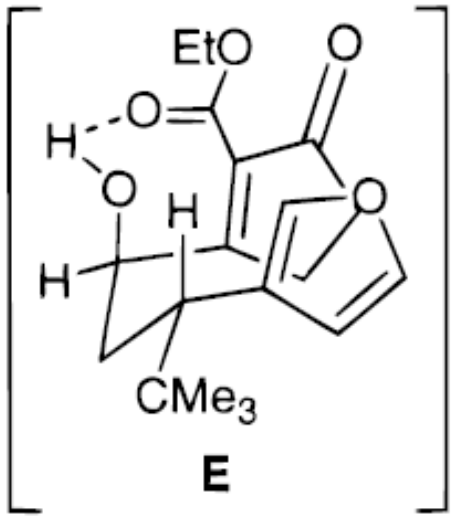
Substrate	Solvent	Product	
		Yield(%)	Ratio
R=TMS	hexane/C_6H_6	85	> 25 : 1
R=TMS	MeOH	80	> 25 : 1
R=H	hexane/C_6H_6	77	1.1 : 1
R=H	THF	79	7 : 1
R=H	MeOH	75	> 25 : 1



Stereoselectivity: Steric or H-B

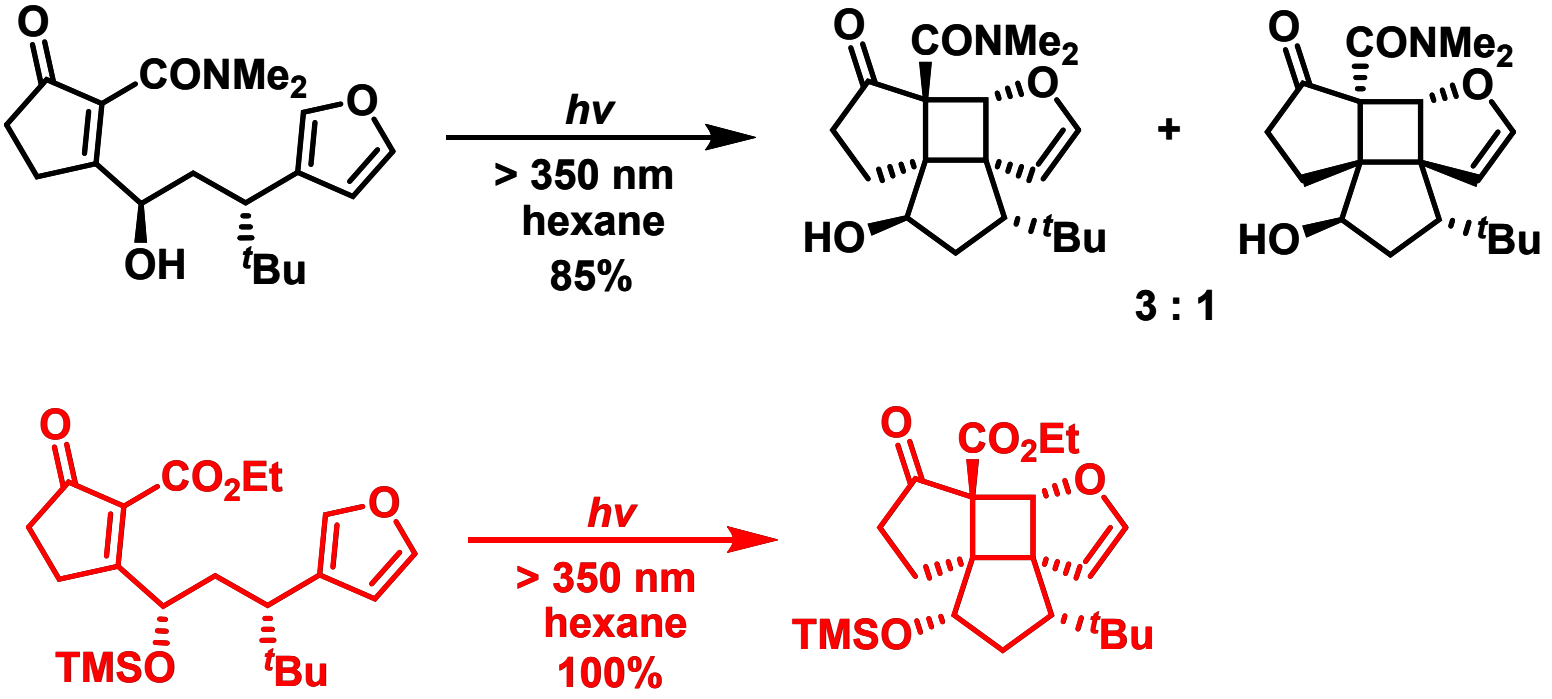


How to stabilize the desired conformation?

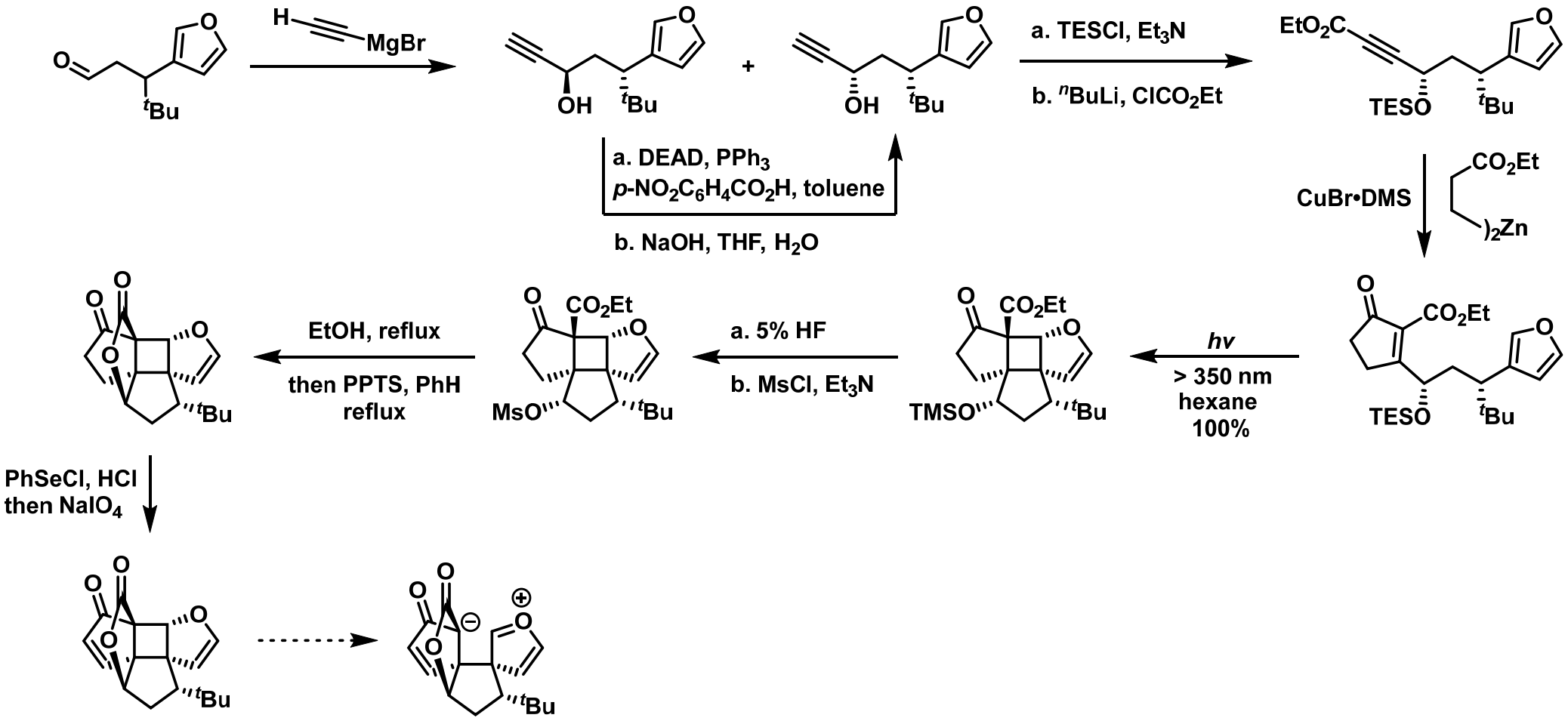


[2+2] Cyclization: Two Solutions

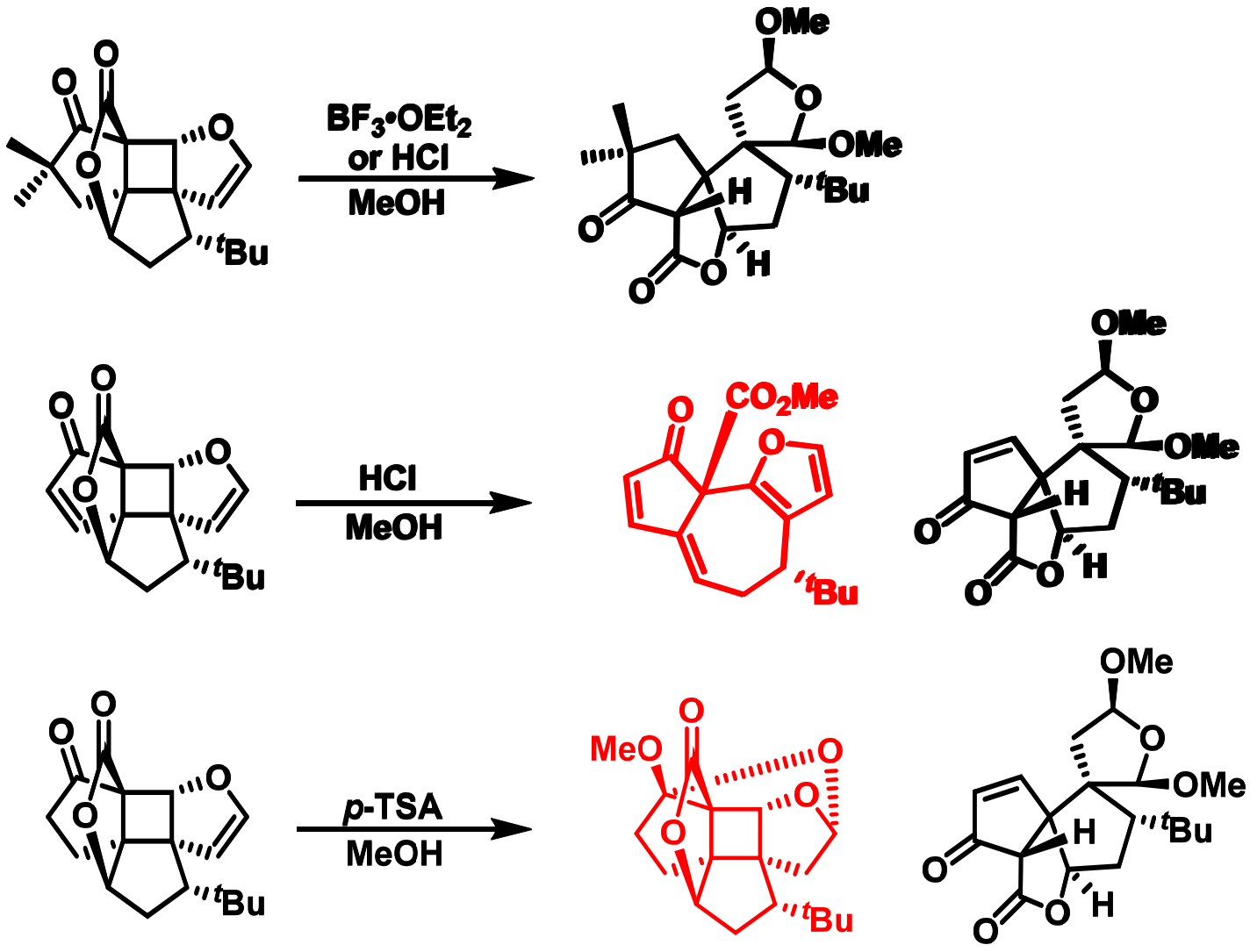
Two possible solutions: Increase the strength of hydrogen bond or create dual-equatorial substituent groups.



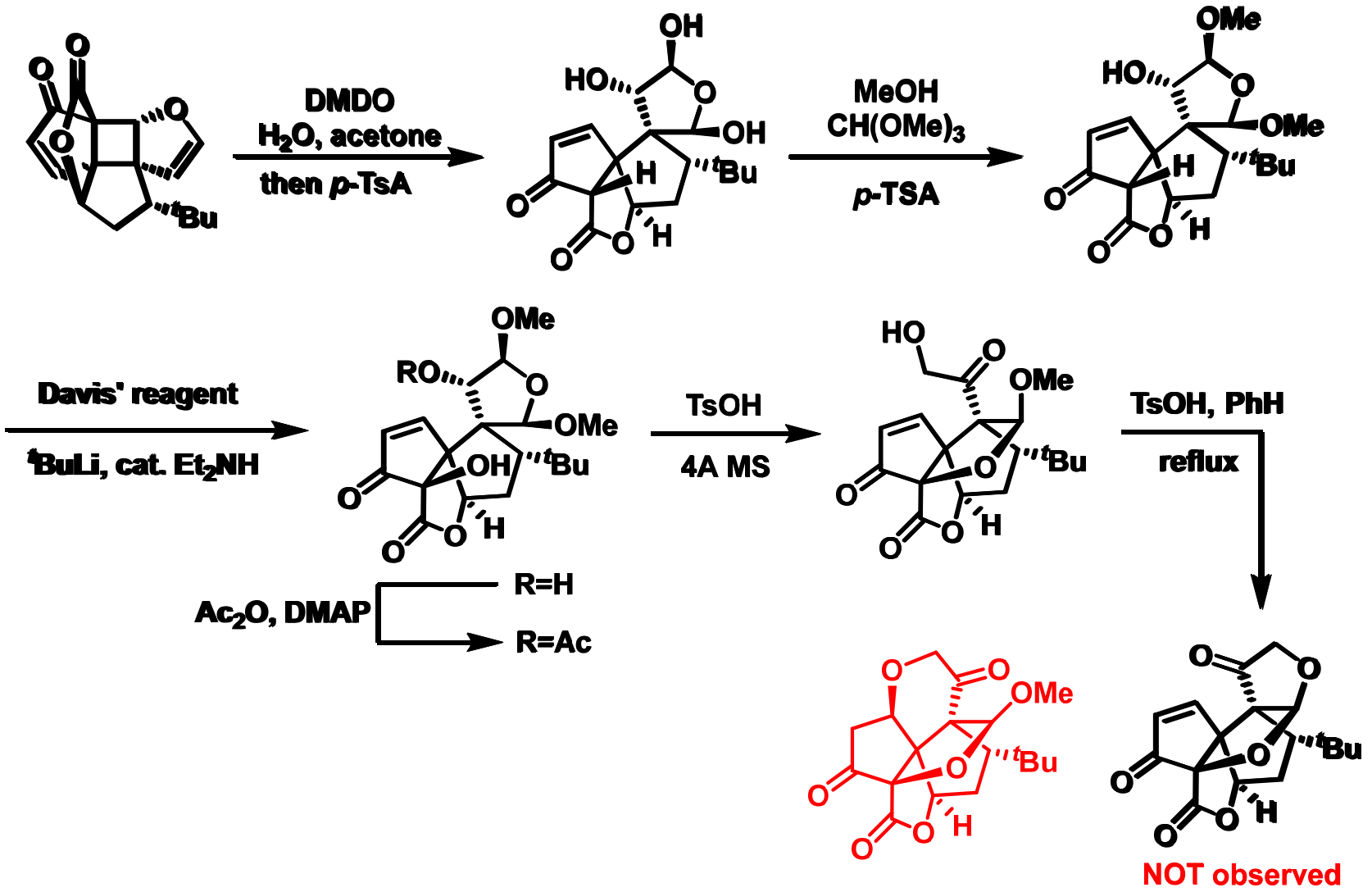
[2+2] Cyclization Path



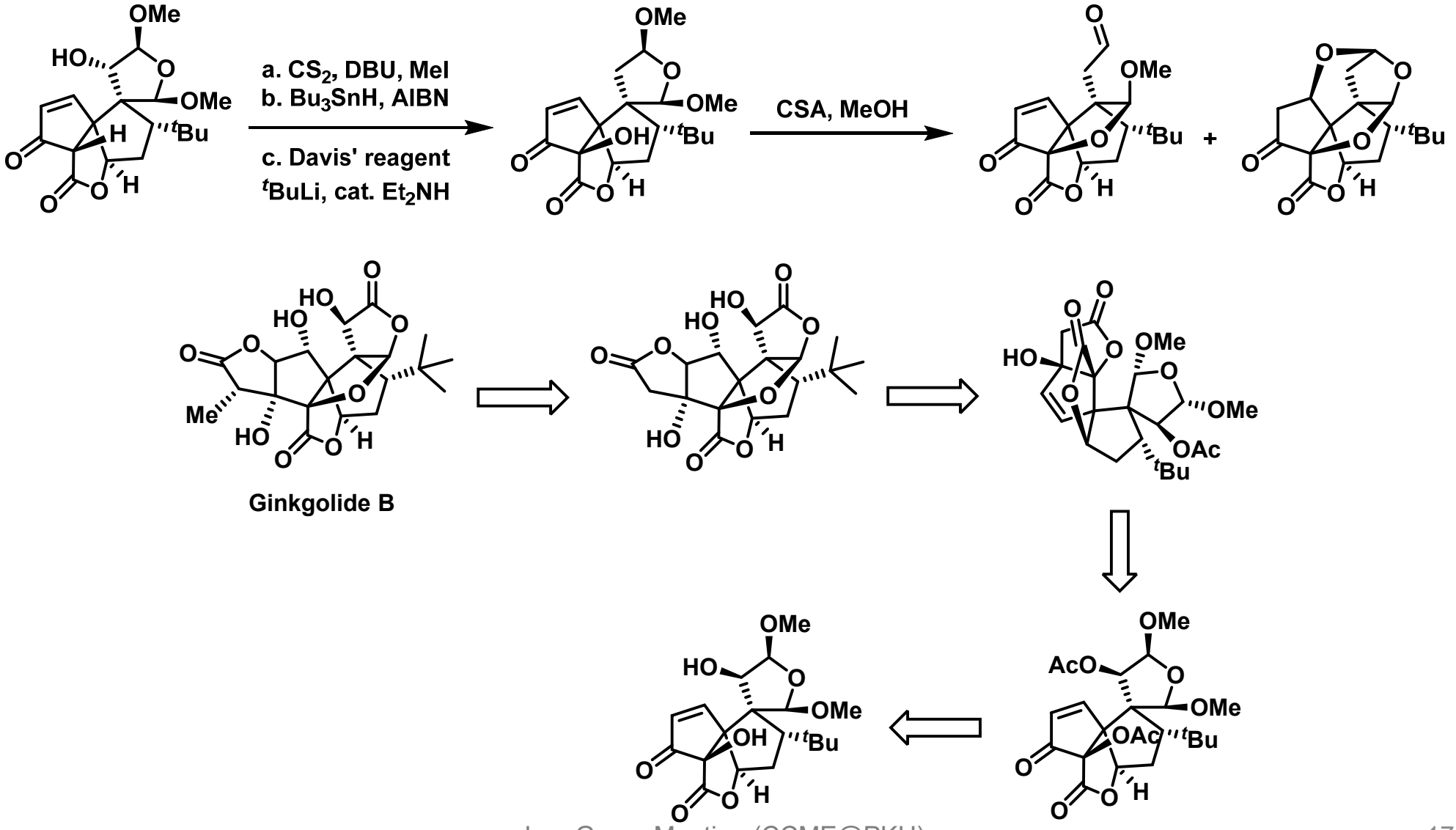
Ring Opening: Acidic Conditions Failed



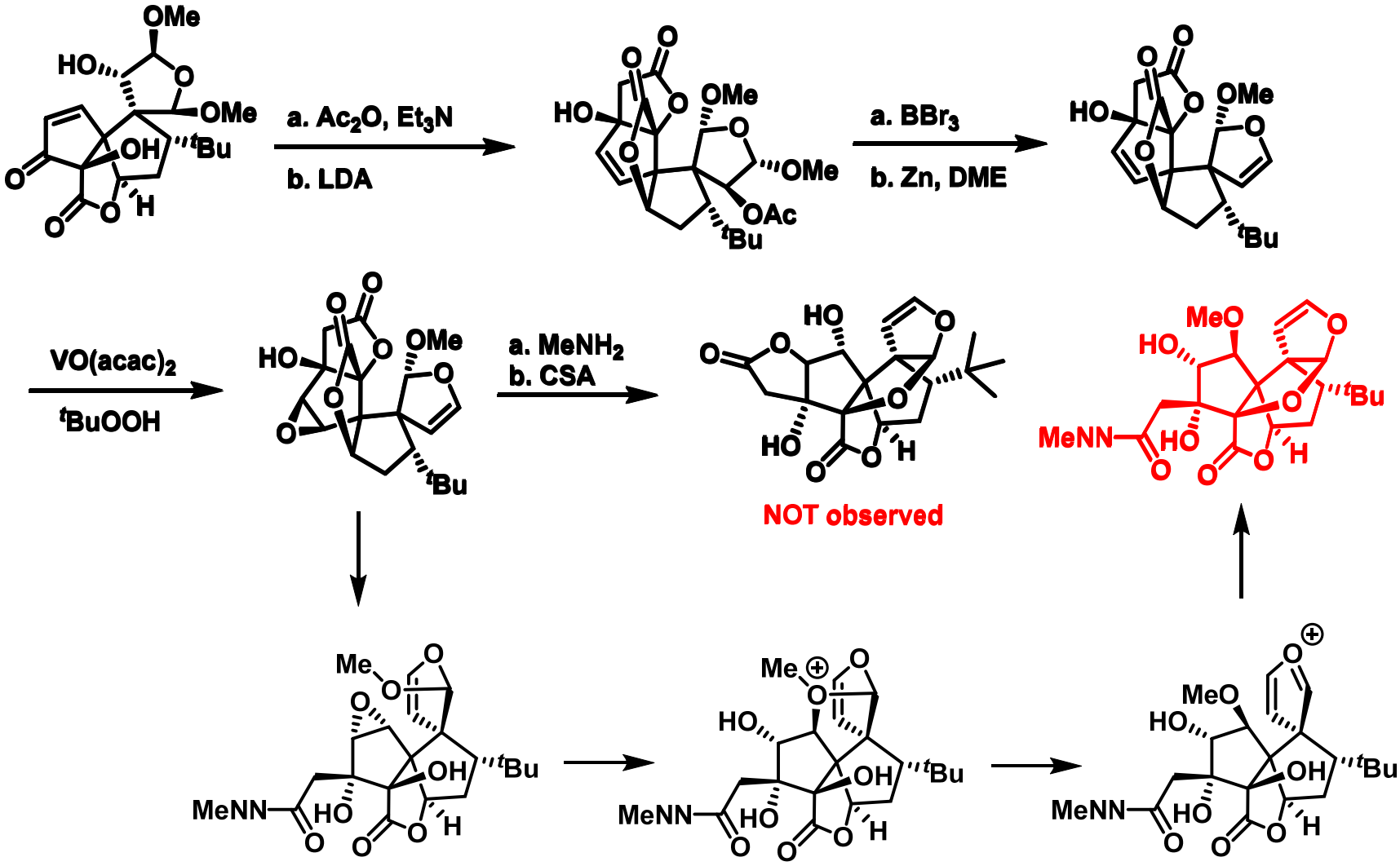
Solution: Block Enol Ether



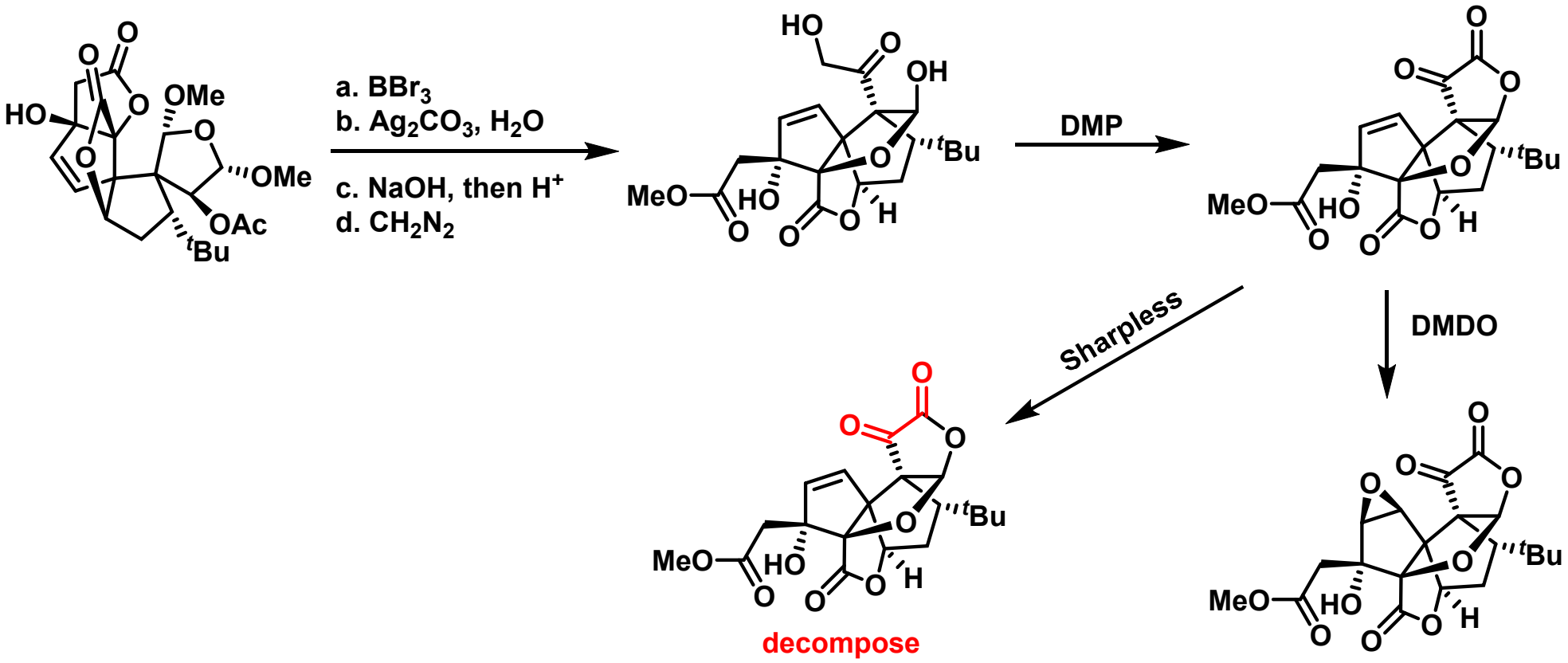
Retrosynthesis: Block Carbonyl Group



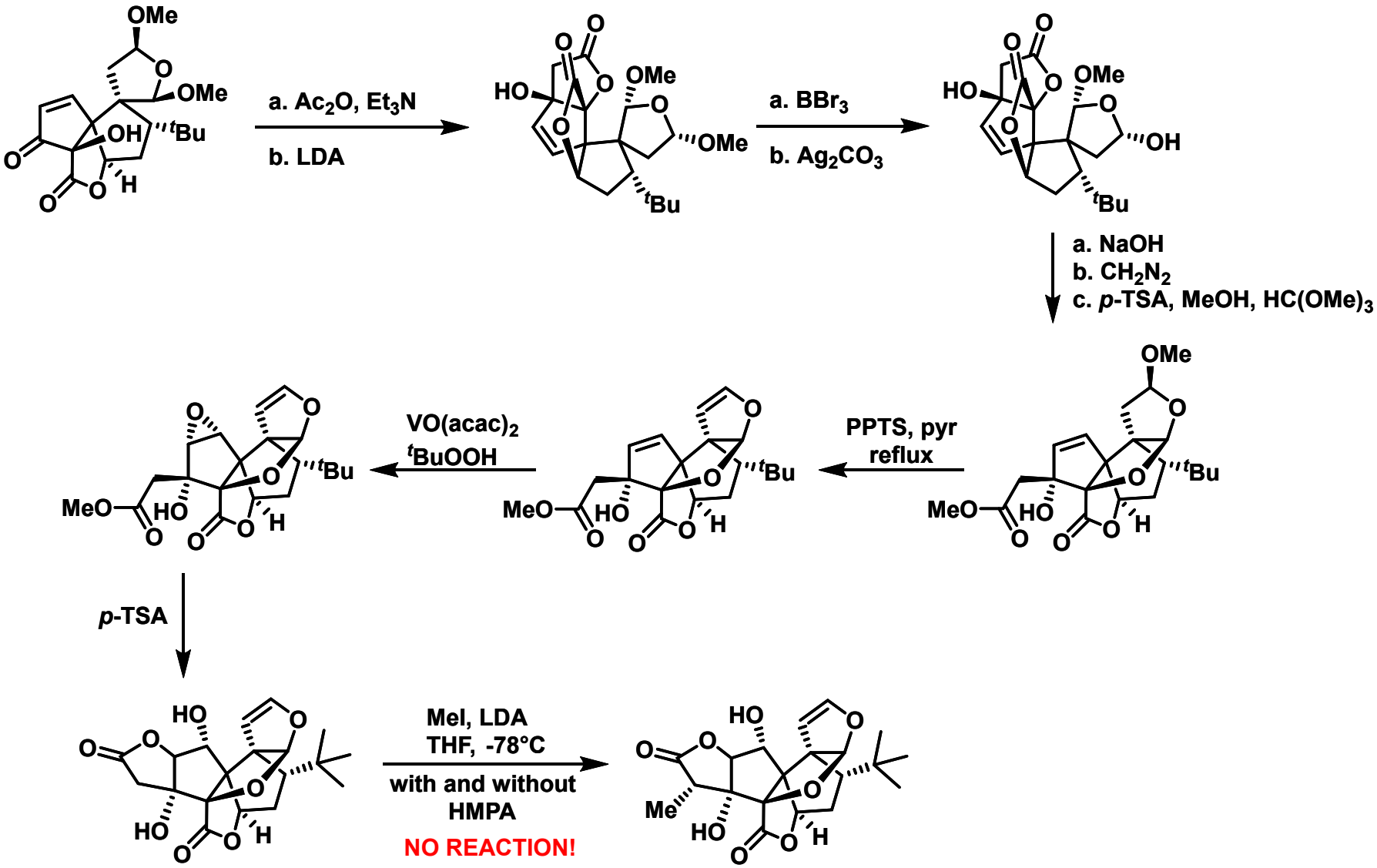
High Nucleophilic or Conformation Lock



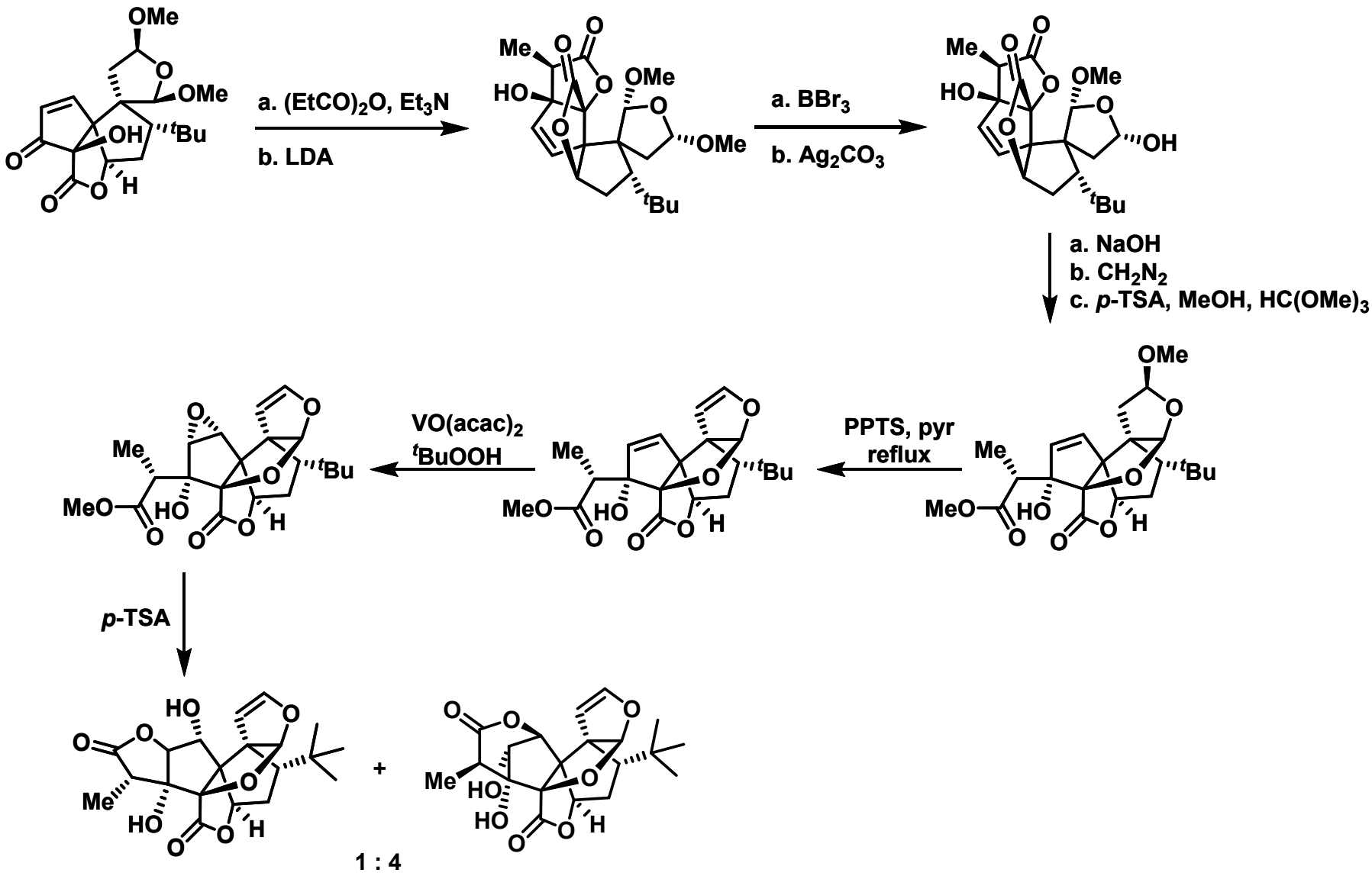
Step by Step Ring Formation: Failed



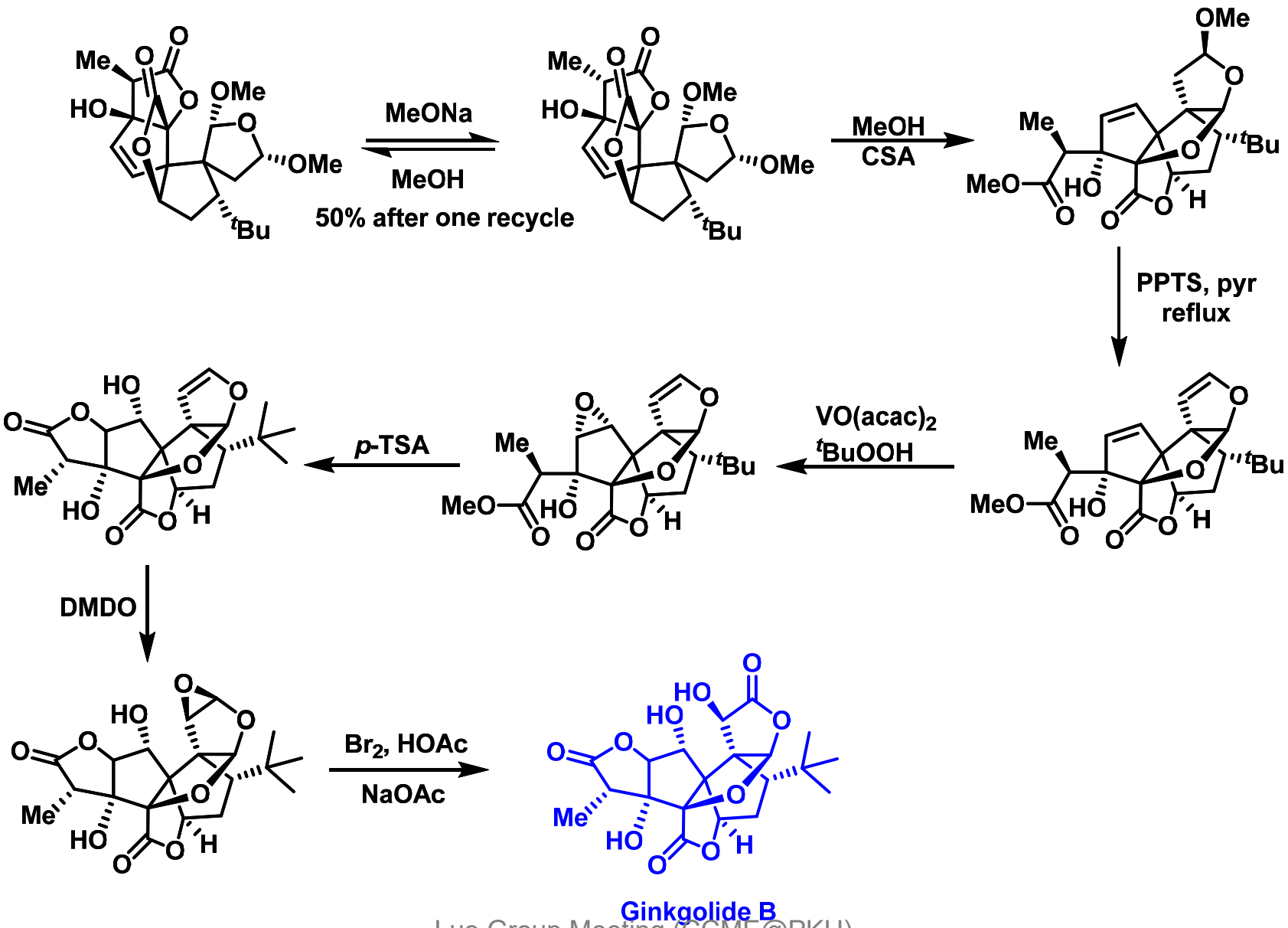
Methylation: Very Close to the Target



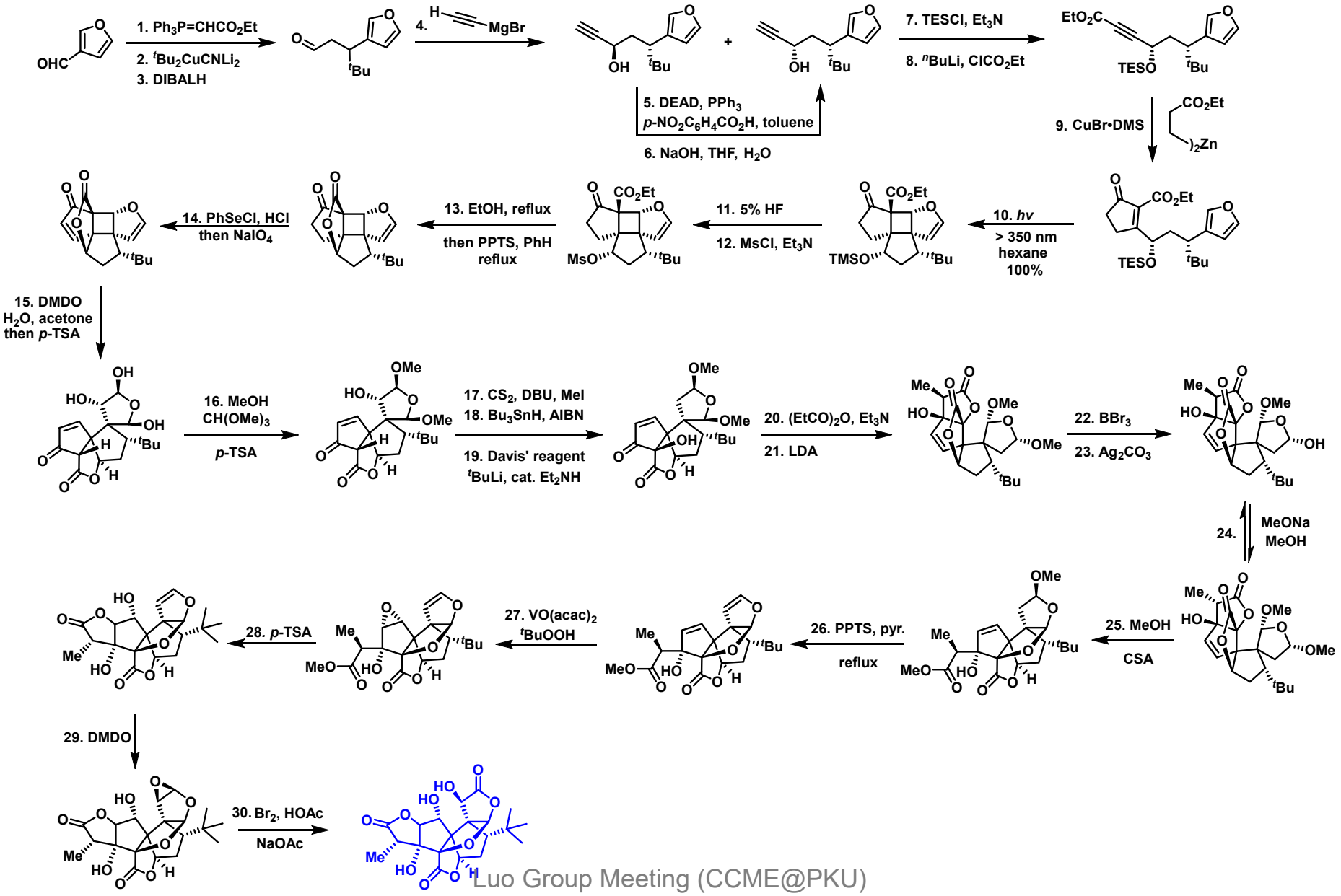
Propionate: Curtin-Hammett Principle?



Isomerization Before Epoxide Opening



Crimmins (1999): Total Synthesis



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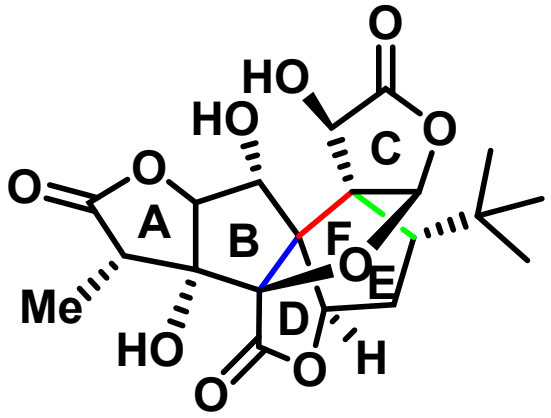
Summary

- Similar strategy for A and F ring
- Corey: Construct both B and D
- Crimmins: Construct E by [2+2]
- Involve *t*-Bu by 1,4-addition
- Construct both E and C?
- Radical reaction?



Corey
Crimmins

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