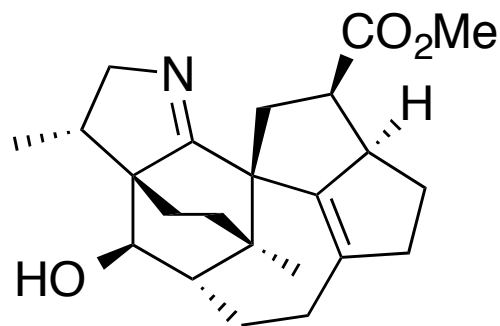


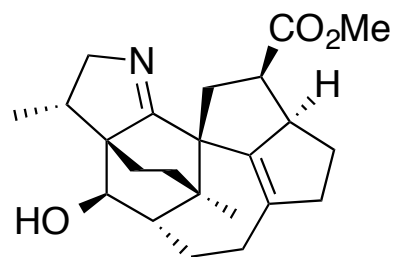
# The Daphniphyllum Alkaloids: Total Synthesis of (–)-Calyciphylline N

[Artem Shvartsbart and Amos B. Smith, III](#)

*J. Am. Chem. Soc.*, **2015**, *137* (10), pp 3510–3519



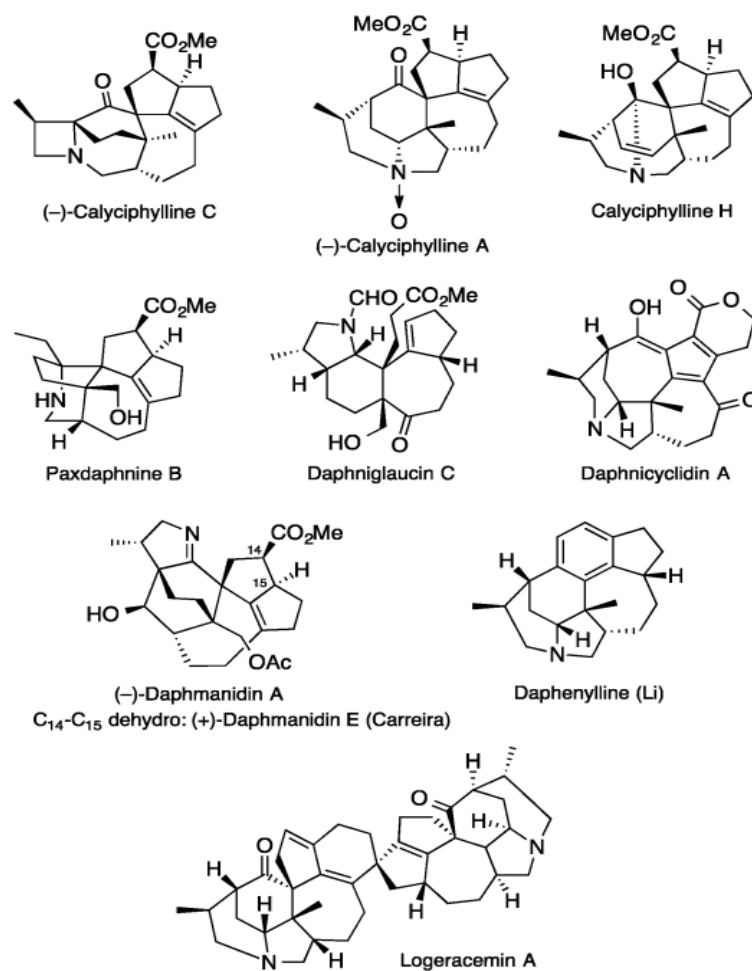
# (-)-Calyciphylline N



Isolated from the leaves and stems of *Daphniphyllum calycinum*

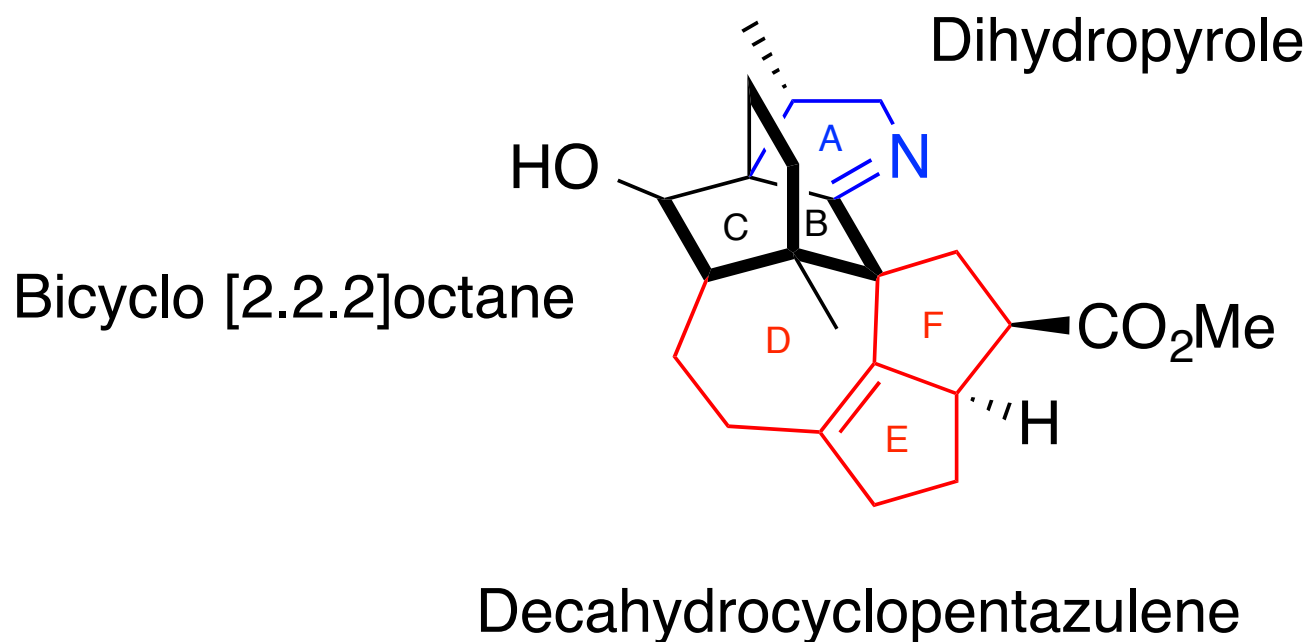


*J.Nat. Prod.* **2008**, 72, 148



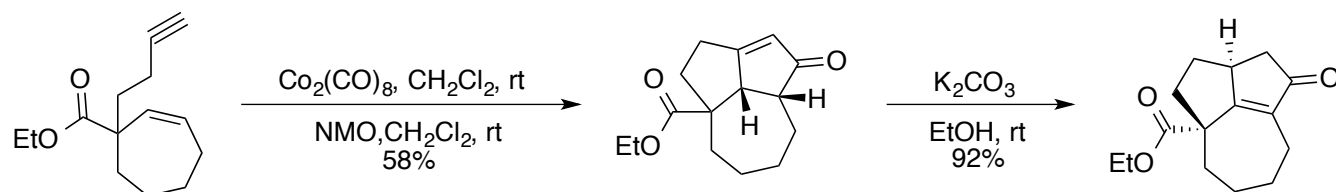
Representative daphniphyllum alkaloids

# (-)-Calyciphylline N



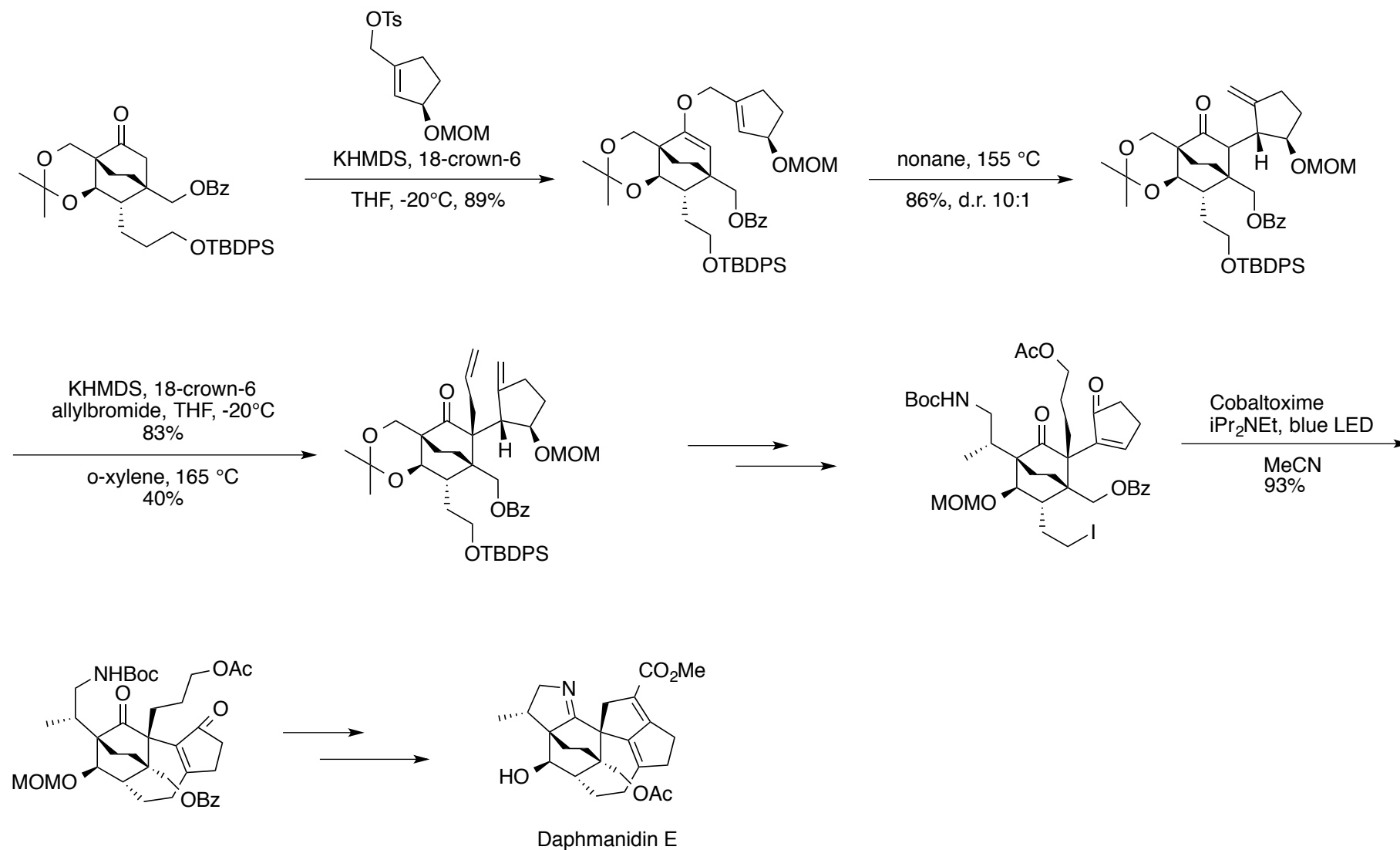
# Previous studies

- Dixon's synthesis of the DEF ring vis IPKR



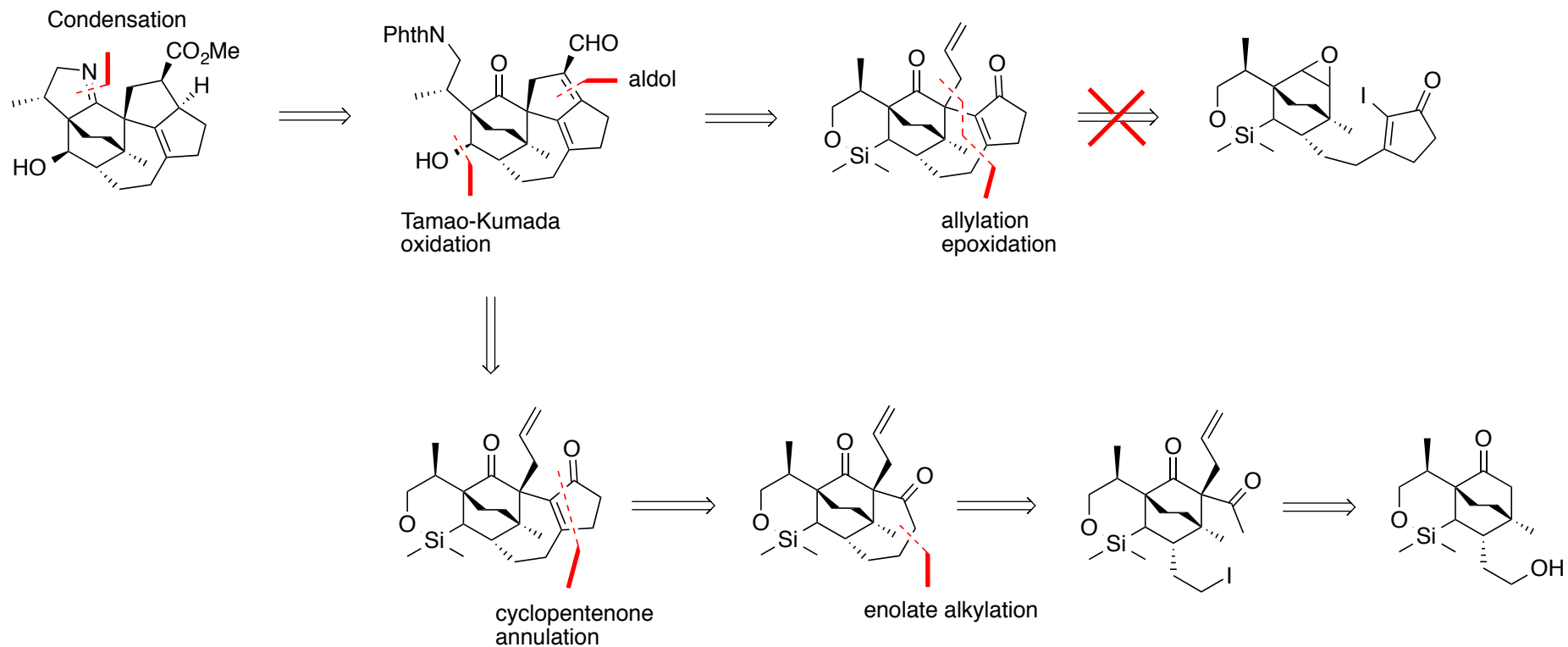
- Carreira's synthesis of Daphmanidin E via Claisen rearrangement and Heck reaction

*Org. Lett.*, **2012**, 14 (7), pp 1684–1687

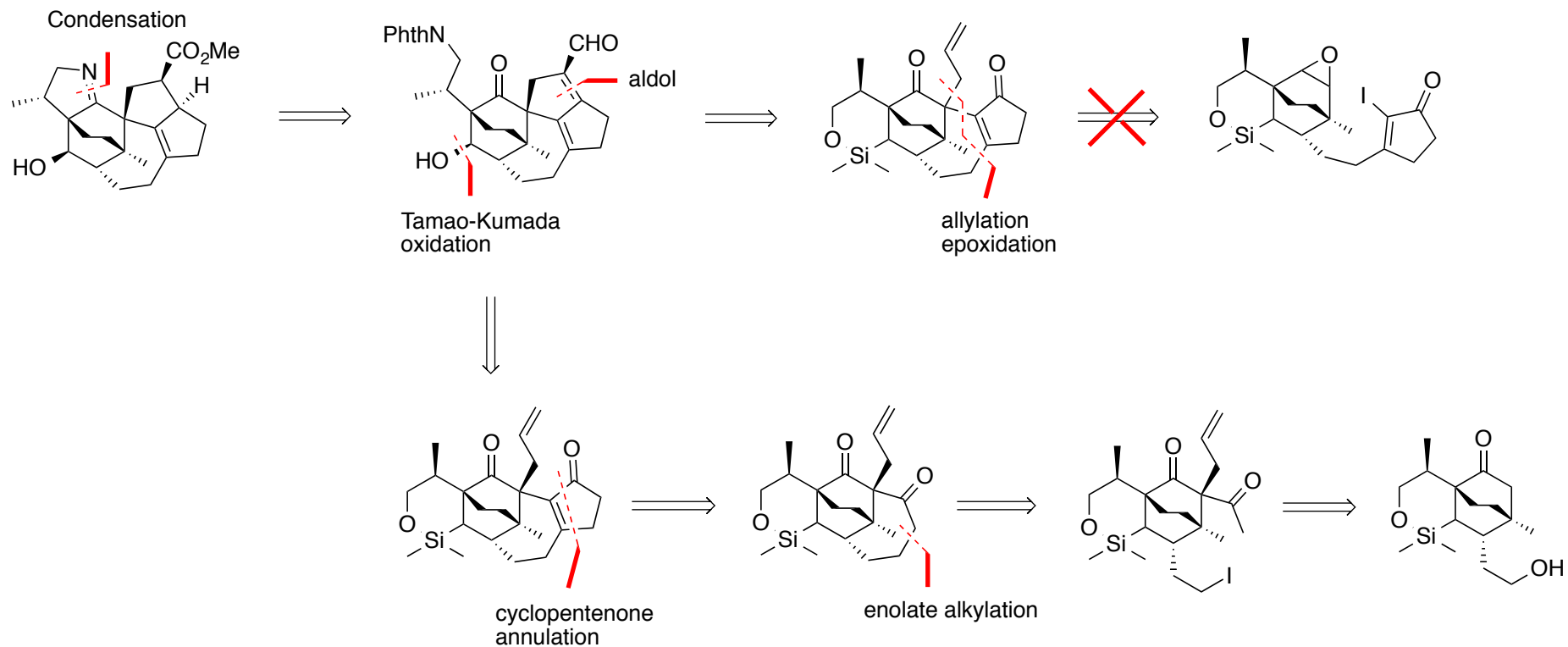


*Angew. Chem. Int. Ed.* **2011**, 50, 11501–11505

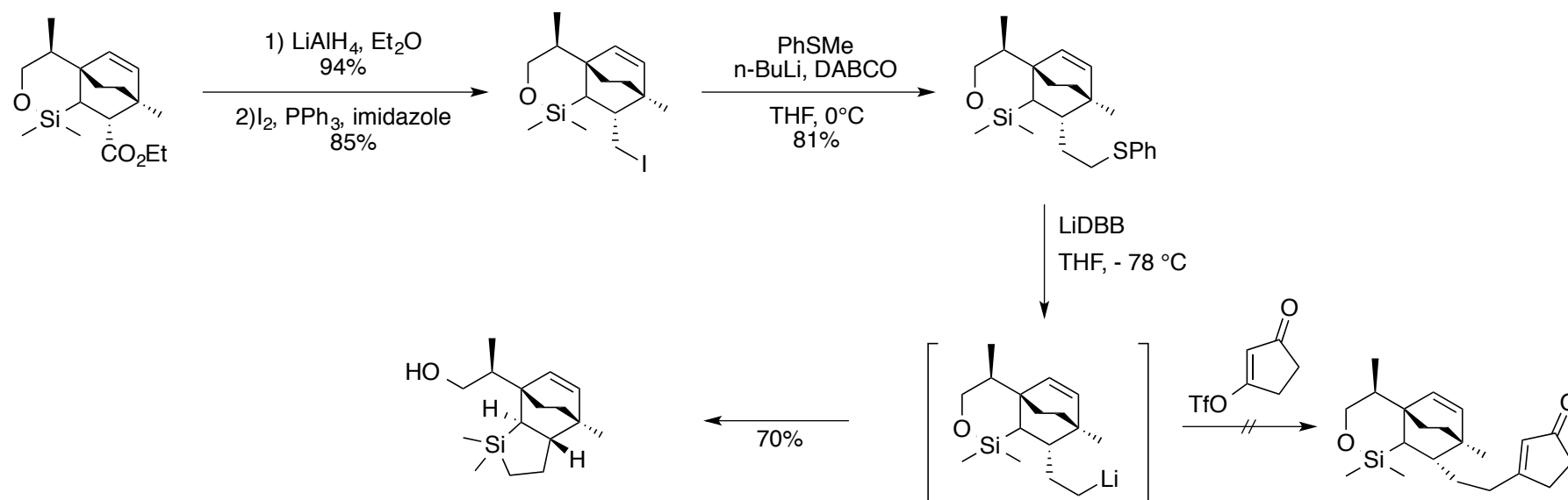
# Retrosynthesis



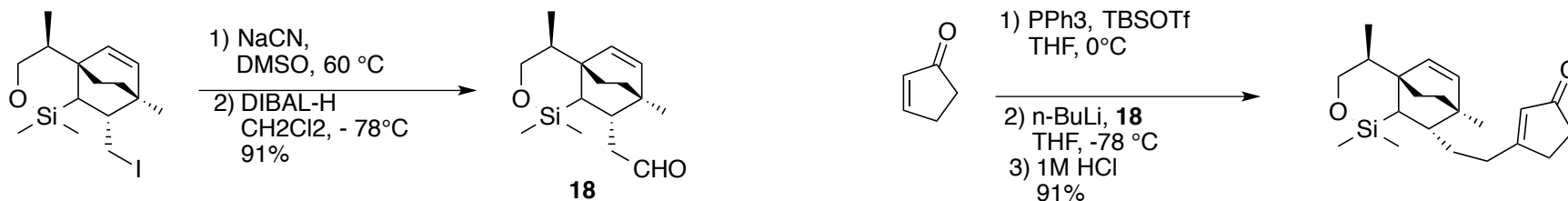
# Retrosynthesis



# Problem with the initial plan

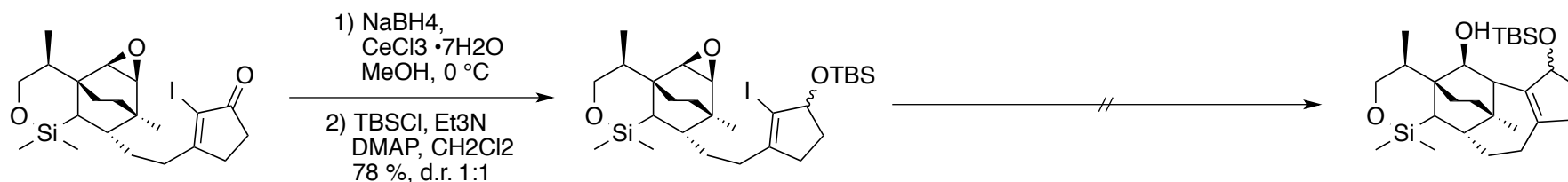
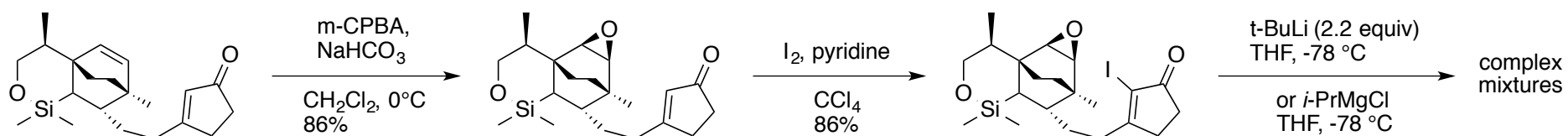


## Problem solving:



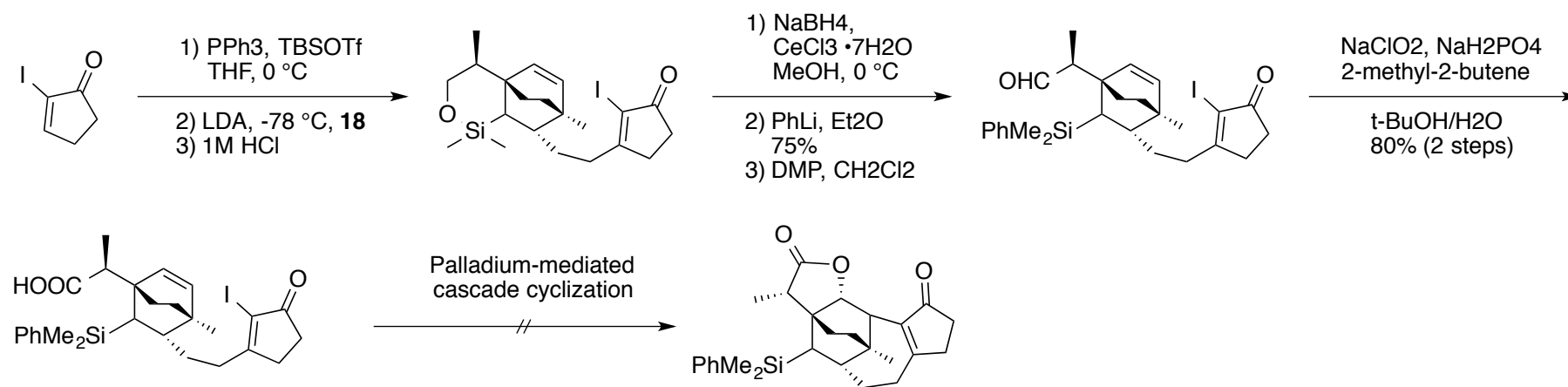


# Problem with the initial plan

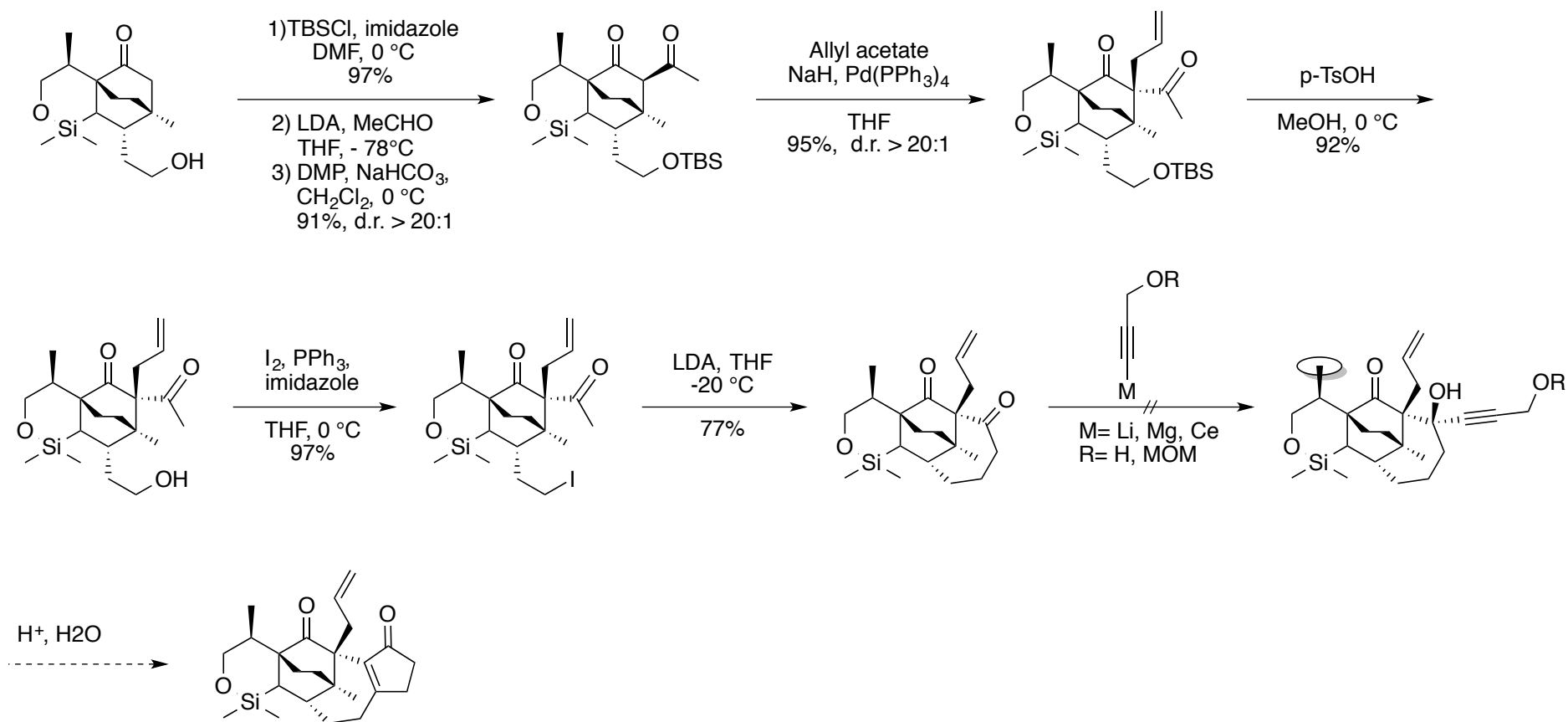


entry	conditions	result
1	<i>t</i> -BuLi; THF; $-78^\circ\text{C} \rightarrow \text{rt}$	metal-halogen exchange exclusively
2	<i>i</i> -PrMgCl; THF; $-78^\circ\text{C} \rightarrow \text{rt}$	metal-halogen exchange exclusively
3	<i>t</i> -BuLi, $\text{ZnCl}_2$ , $\text{Ti}(\text{OiPr})_4$ , etc.; THF; $-78^\circ\text{C} \rightarrow \text{rt}$	metal-halogen exchange exclusively
4	<i>t</i> -BuLi, $\text{BF}_3 \cdot \text{OEt}_2$ , $\text{TiCl}_4$ , $\text{Et}_2\text{AlCl}$ , etc.; THF; $-78^\circ\text{C}$	skeletal rearrangement
5	<i>t</i> -BuLi, CuI or CuBr or CuCN, etc.; THF; $-78^\circ\text{C} \rightarrow \text{rt}$	metal-halogen exchange exclusively

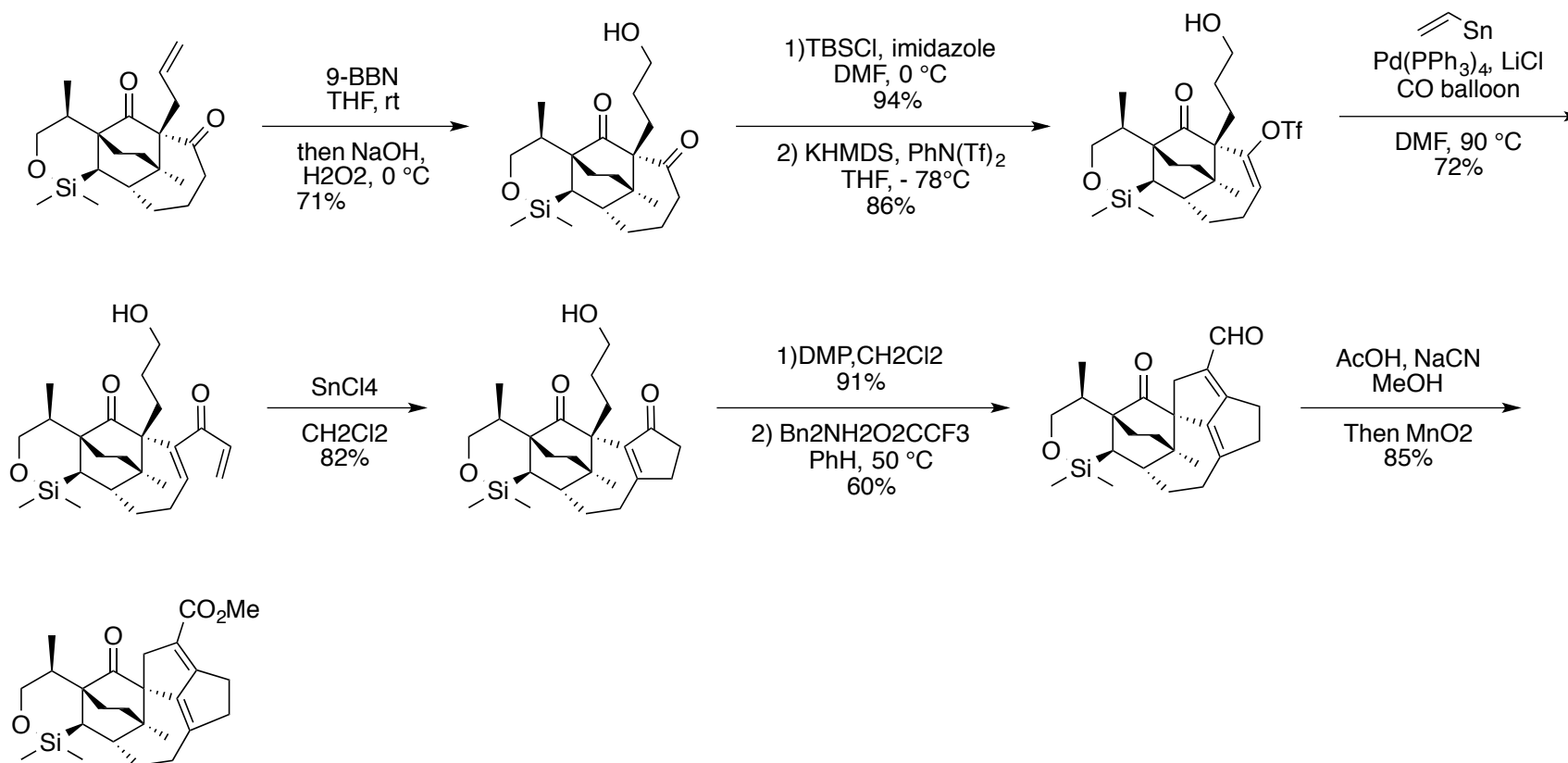
# Problem with the initial plan



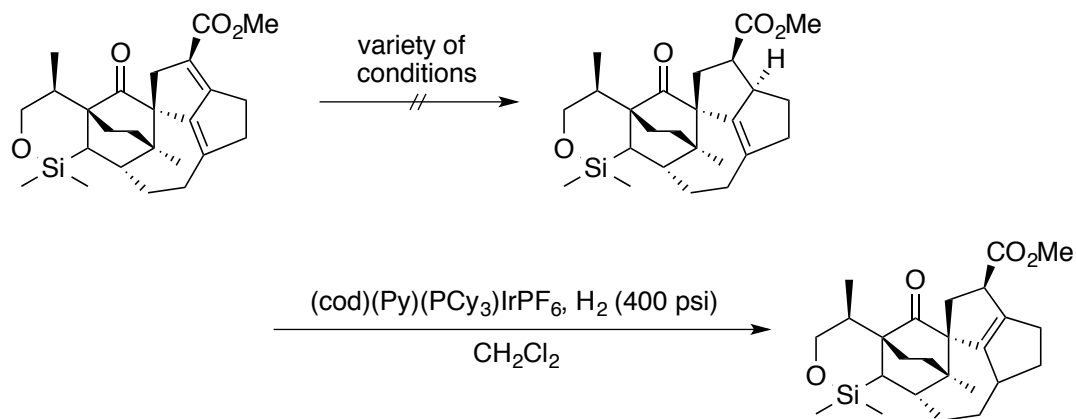
# Modified plan-D ring first



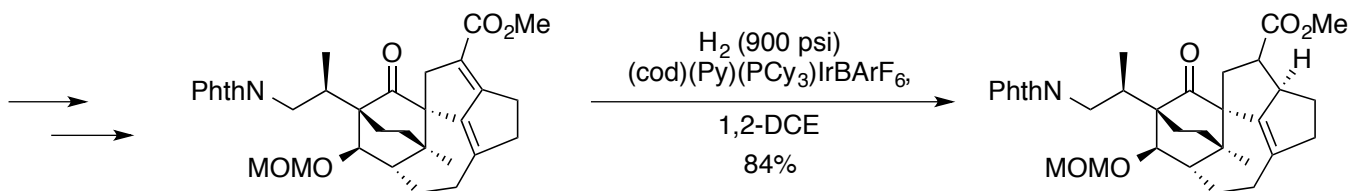
# Formation of E F rings



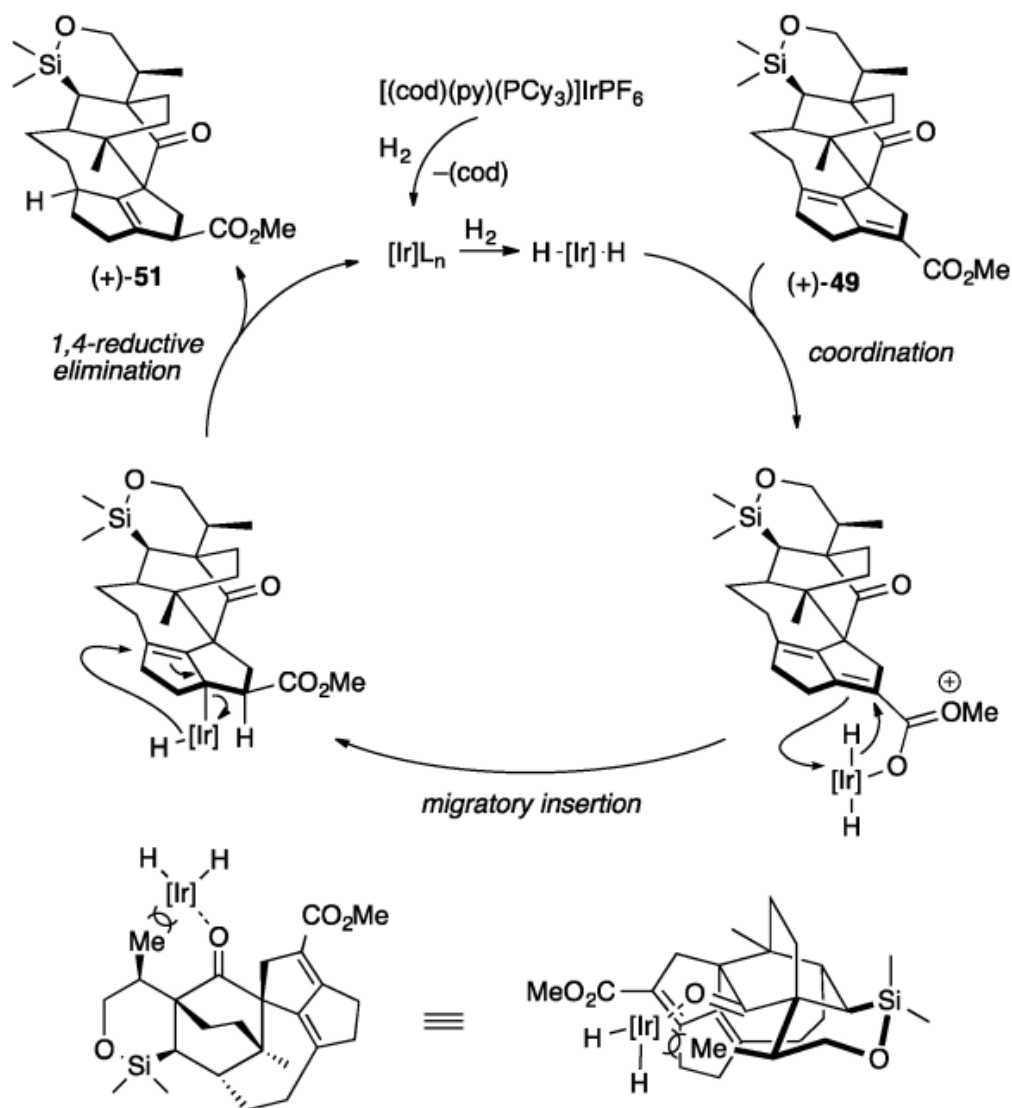
# Selective reduction of the diene ester



## Alternative:



### Scheme 18. Proposed Mechanism for the Formation of (+)-51



# Conclusion

- First total synthesis of (–)-calyciphylline N
- Transannular enolate alkylation to form the D ring
- One-pot Nazarov cyclization/proton-desilylation sequence to form the E ring
- Chemoselective hydrogenation of a fully substituted diene ester