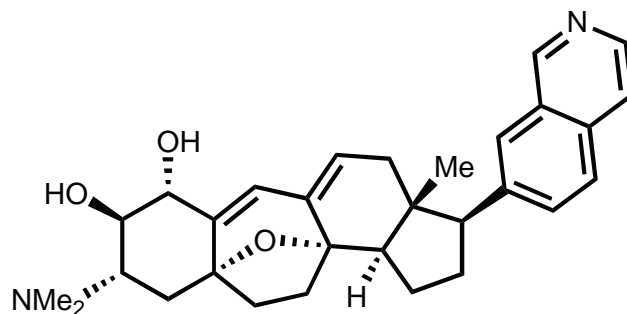


The Total Syntheses of Cortistatin A and Related Molecules



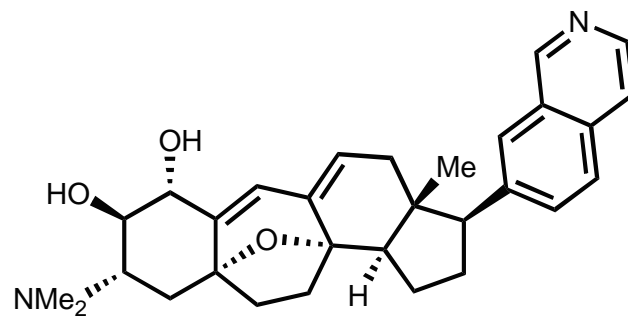
cortistatin A

Jason M. Stevens

09.24.2008

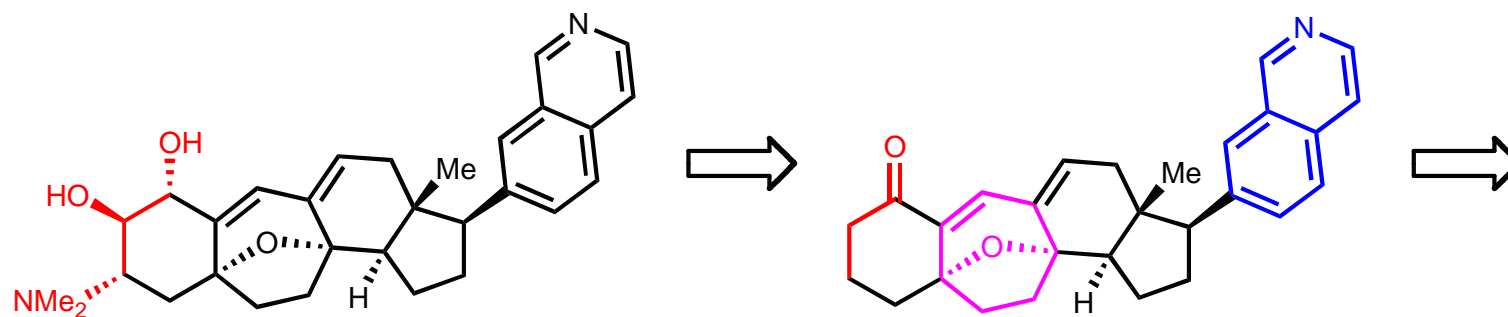
Cortistatin: Background

- Isolated from the Indonesian marine sponge *Corticum simplex* in 2006 by Kobayashi.
- Ref 4 from Barans synthesis “Notably, the natural products themselves are so scarce that no authentic sample of cortistatin A could be spared for comparison to synthetic material, without impeding the biological processes already underway.”
- Serves as an angiogenesis (formation of new blood capillaries) inhibitor.
- Cortistatin A has an IC_{50} value of 1.8 nM against human umbilical vein endothelial cells, which is the standard model for antiangiogenic activity.
- When administered alongside traditional chemotherapeutics, antiangiogenics suppress tumor growth. Thus, antiangiogenics provide an added bonus to existing treatments.
- Preliminary SAR's suggests the presence of the isoquinoline moiety is crucial for potent activity

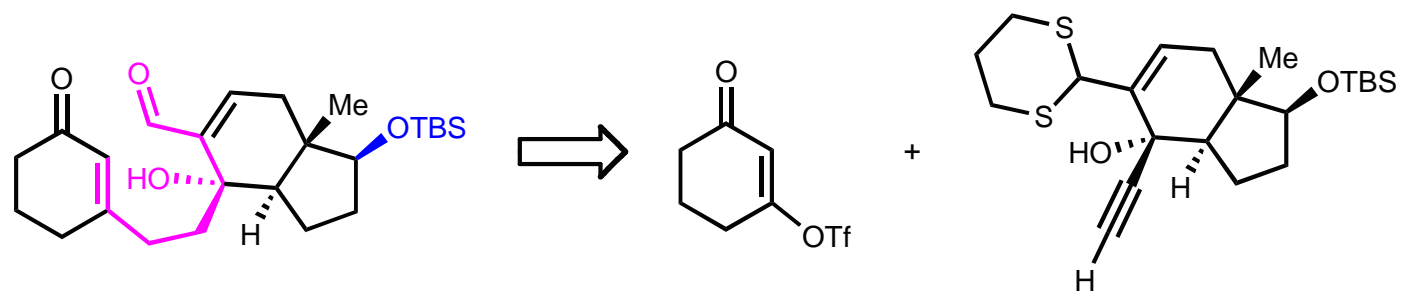


cortistatin A

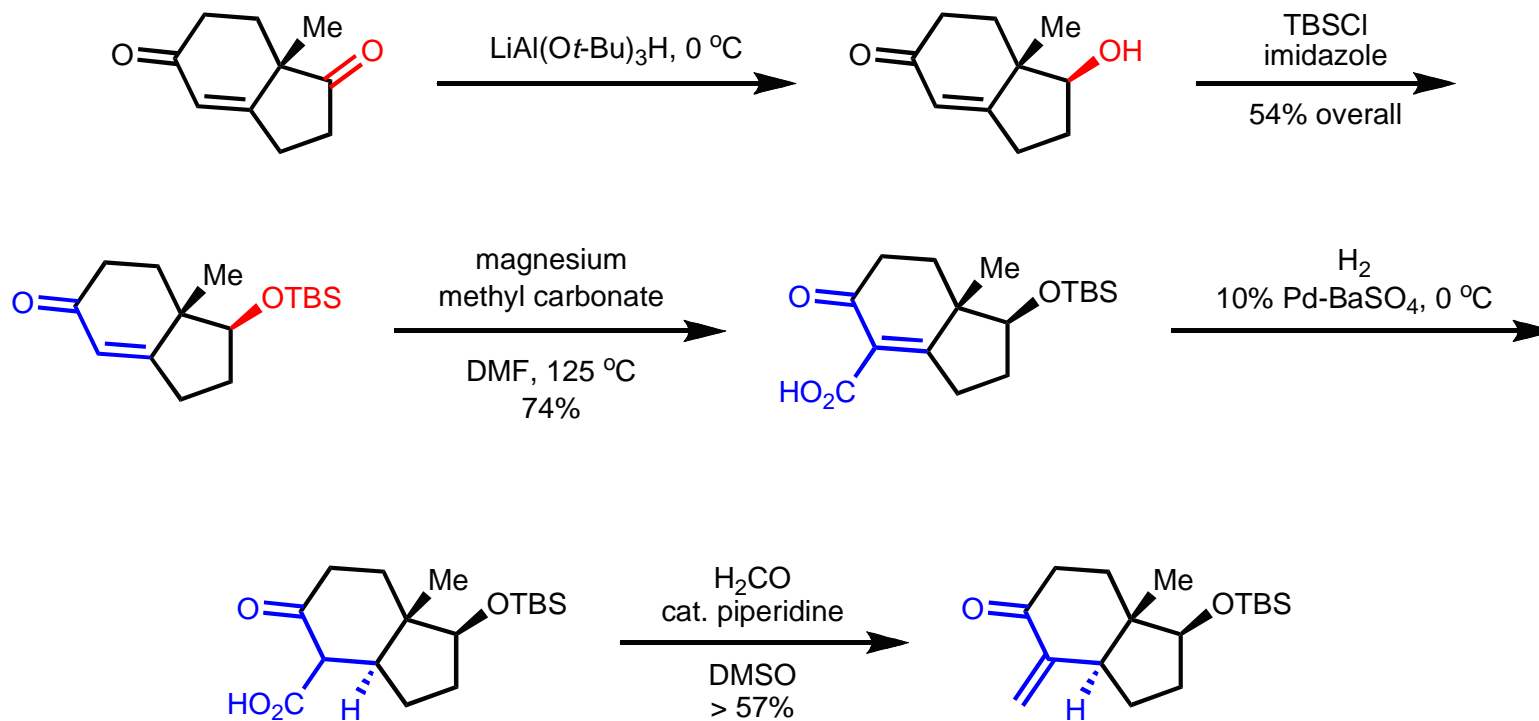
Nicolau Retrosynthesis



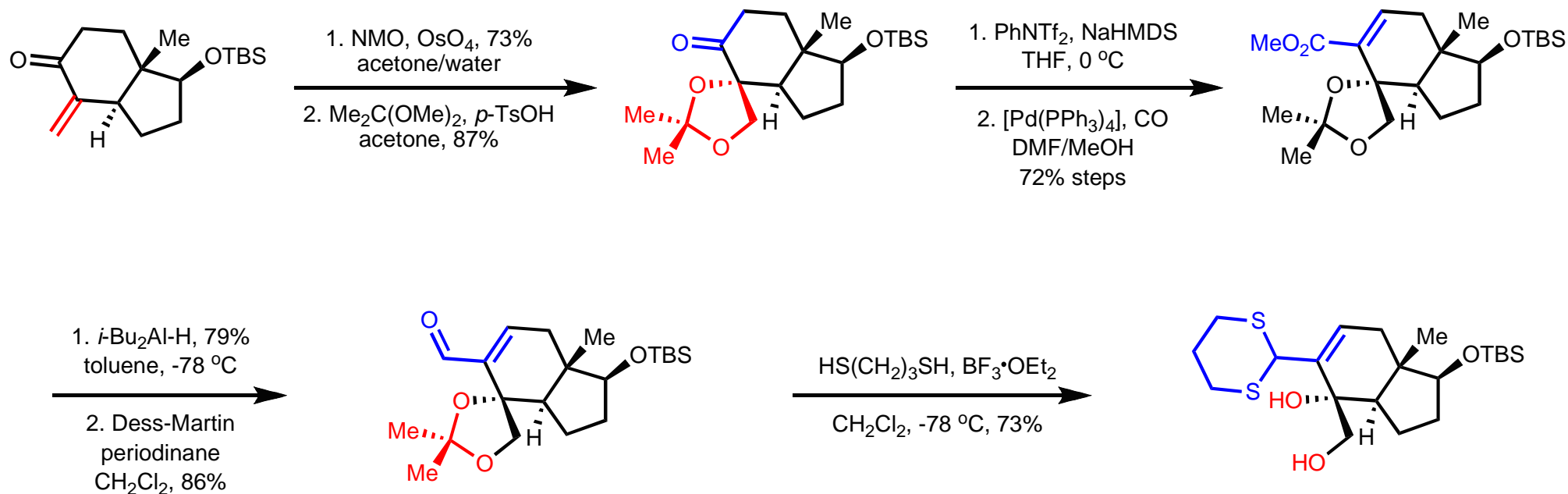
cortistatin A



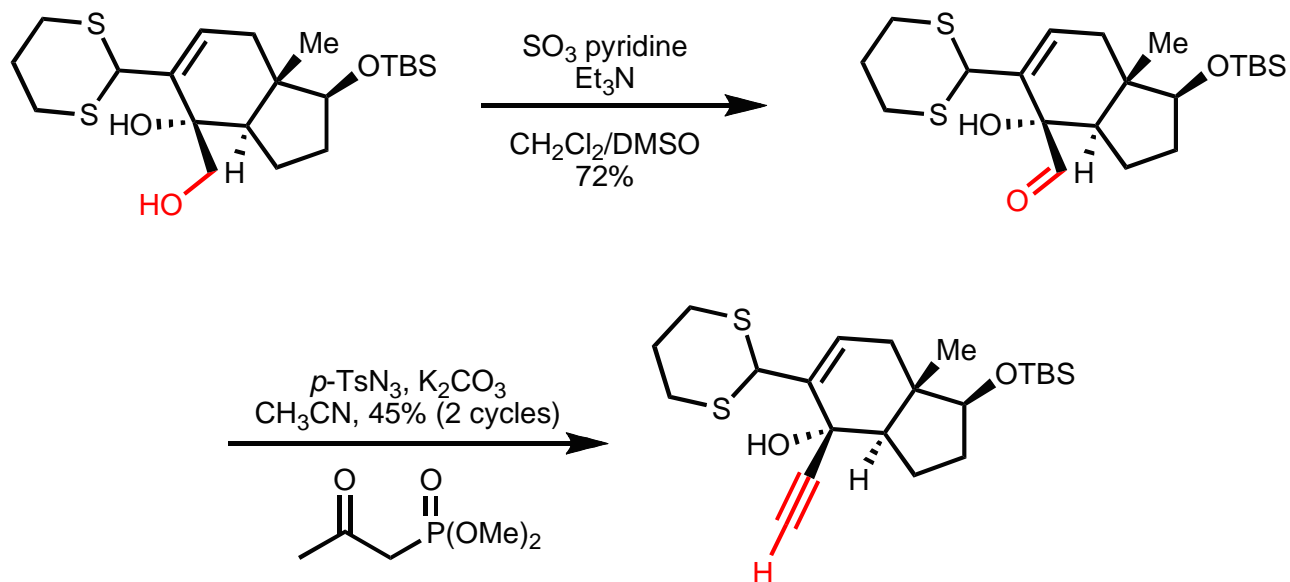
Use of Danishefsky's Taxol Intermediate



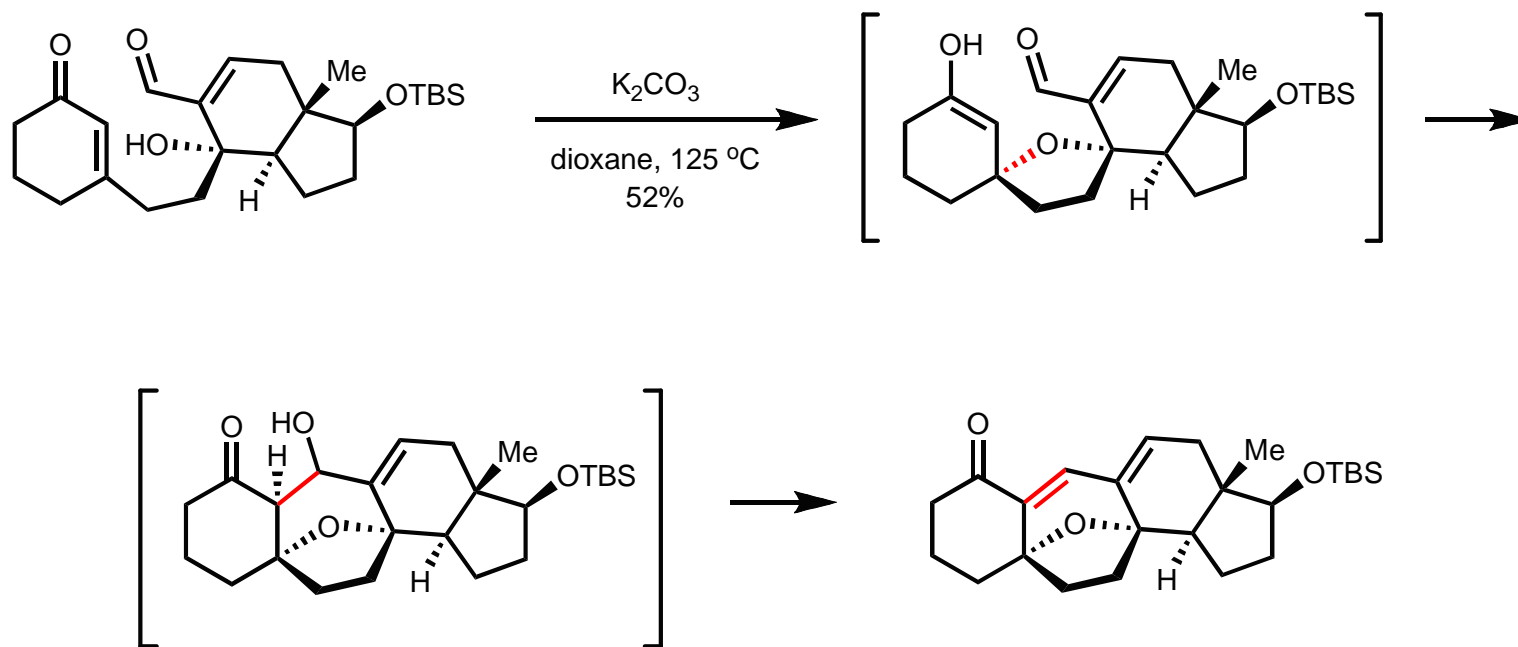
Synthesis of the Dithiane Fragment



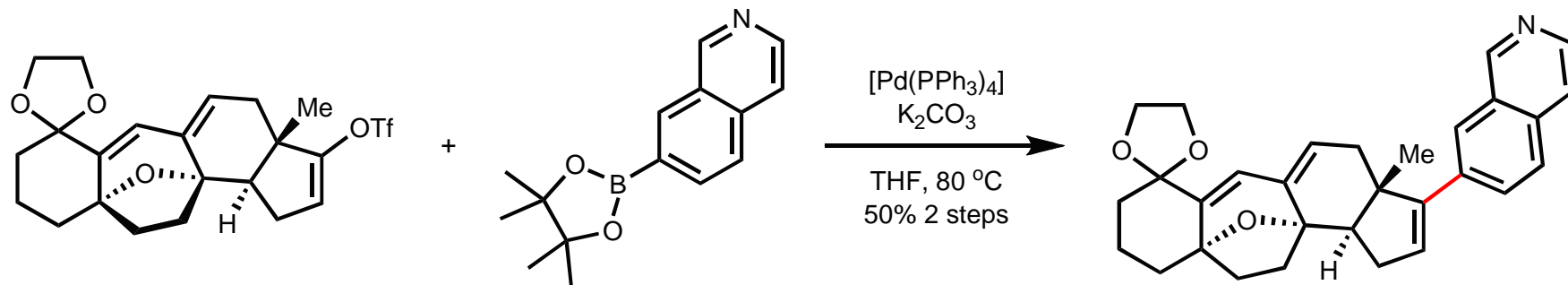
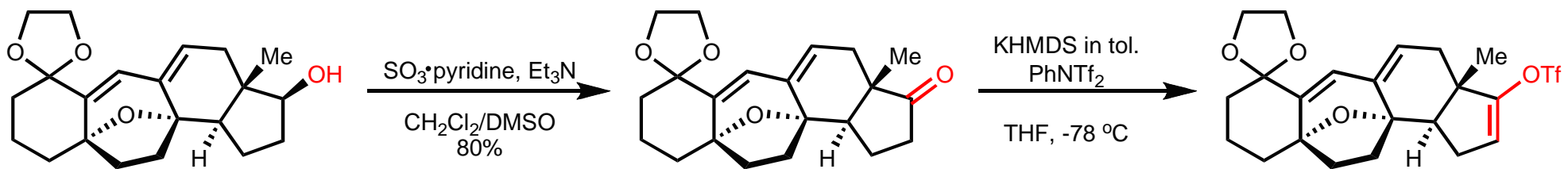
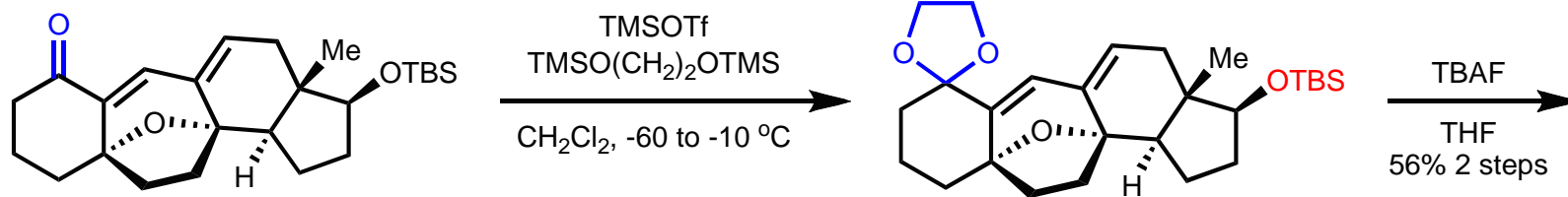
Synthesis of the Dithiane Fragment



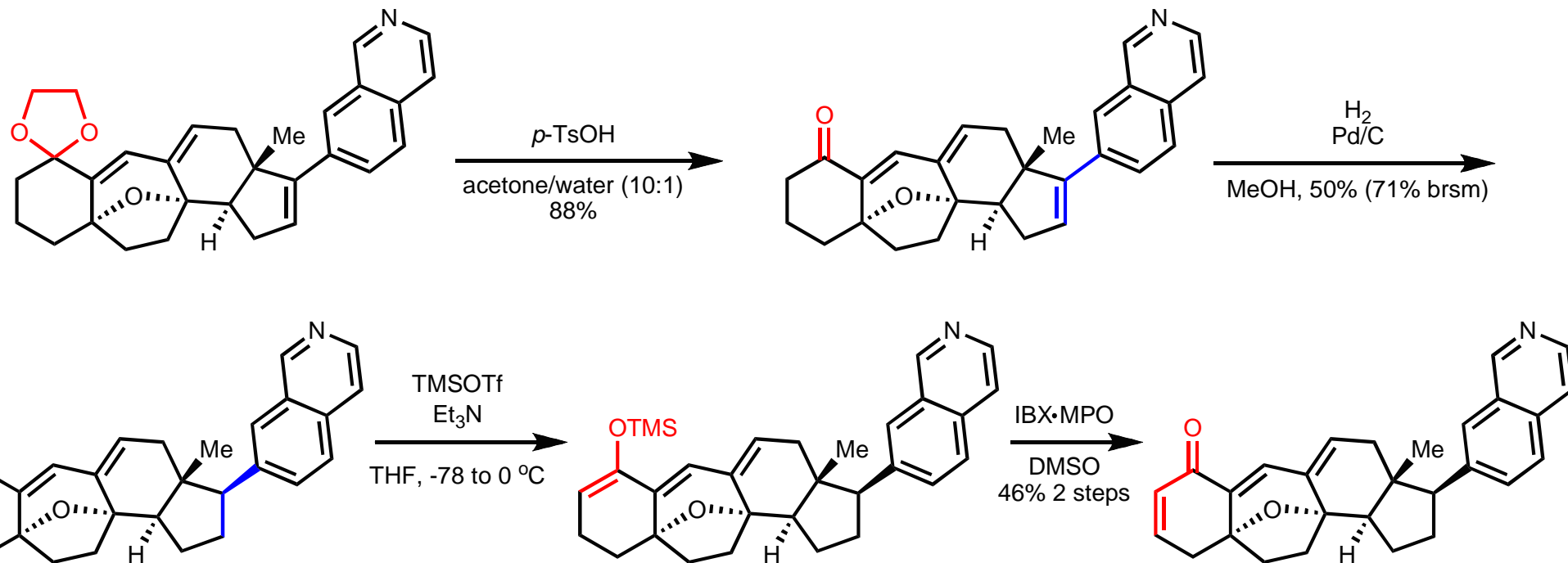
Micheal-Aldol-Elimination Cascade



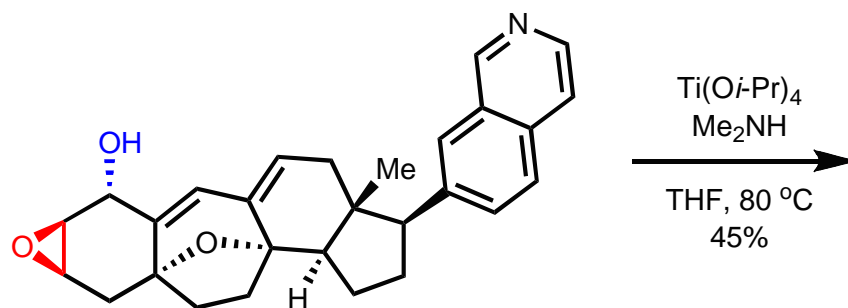
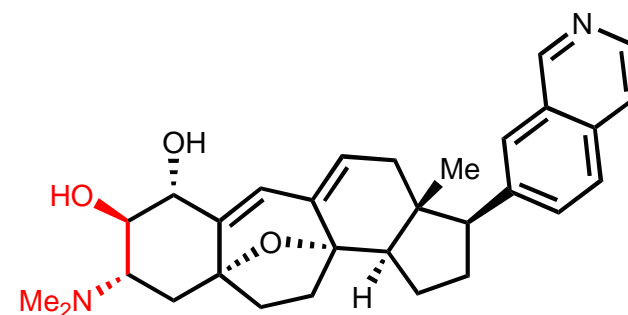
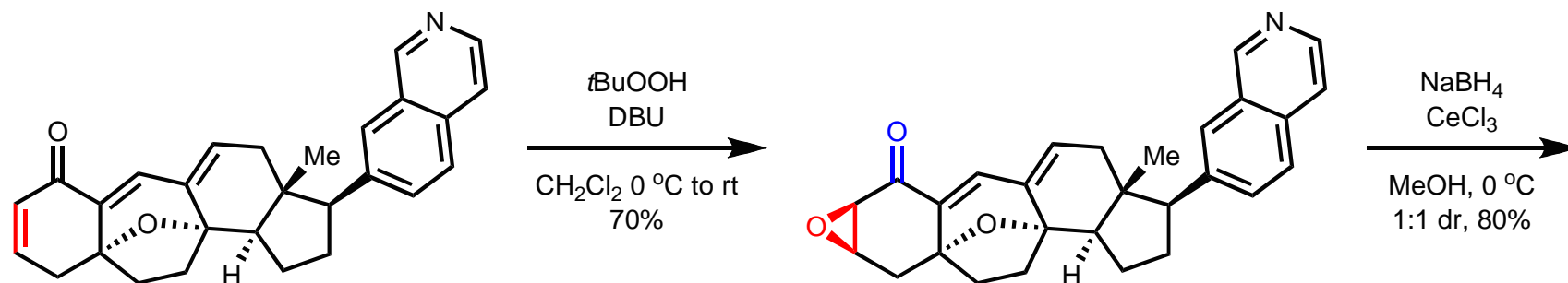
Coupling the Isoquinoline



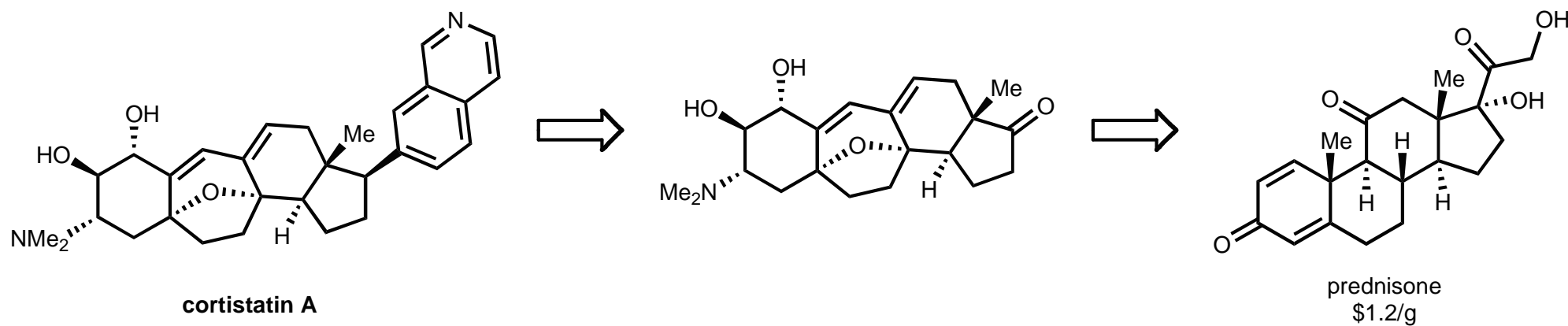
Functionalizing the A Ring



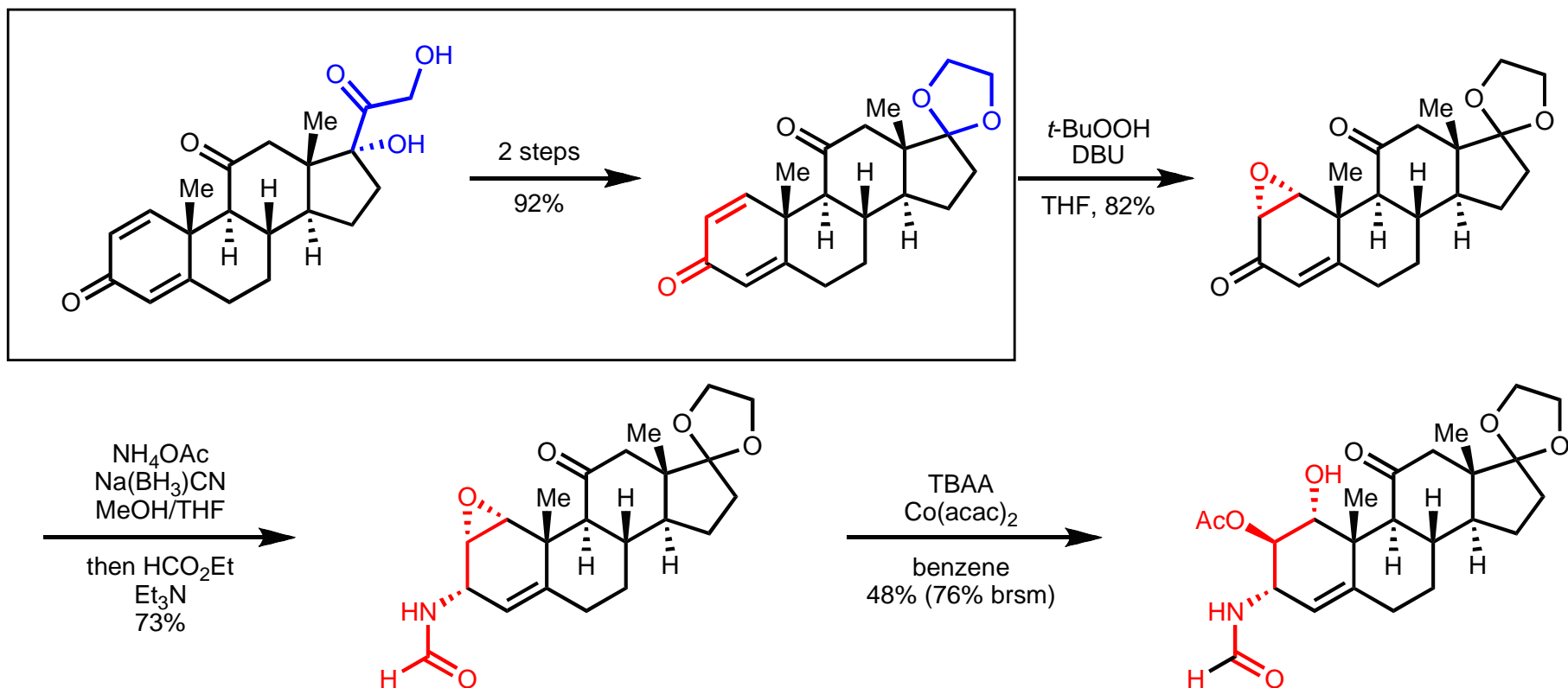
Completing the Synthesis



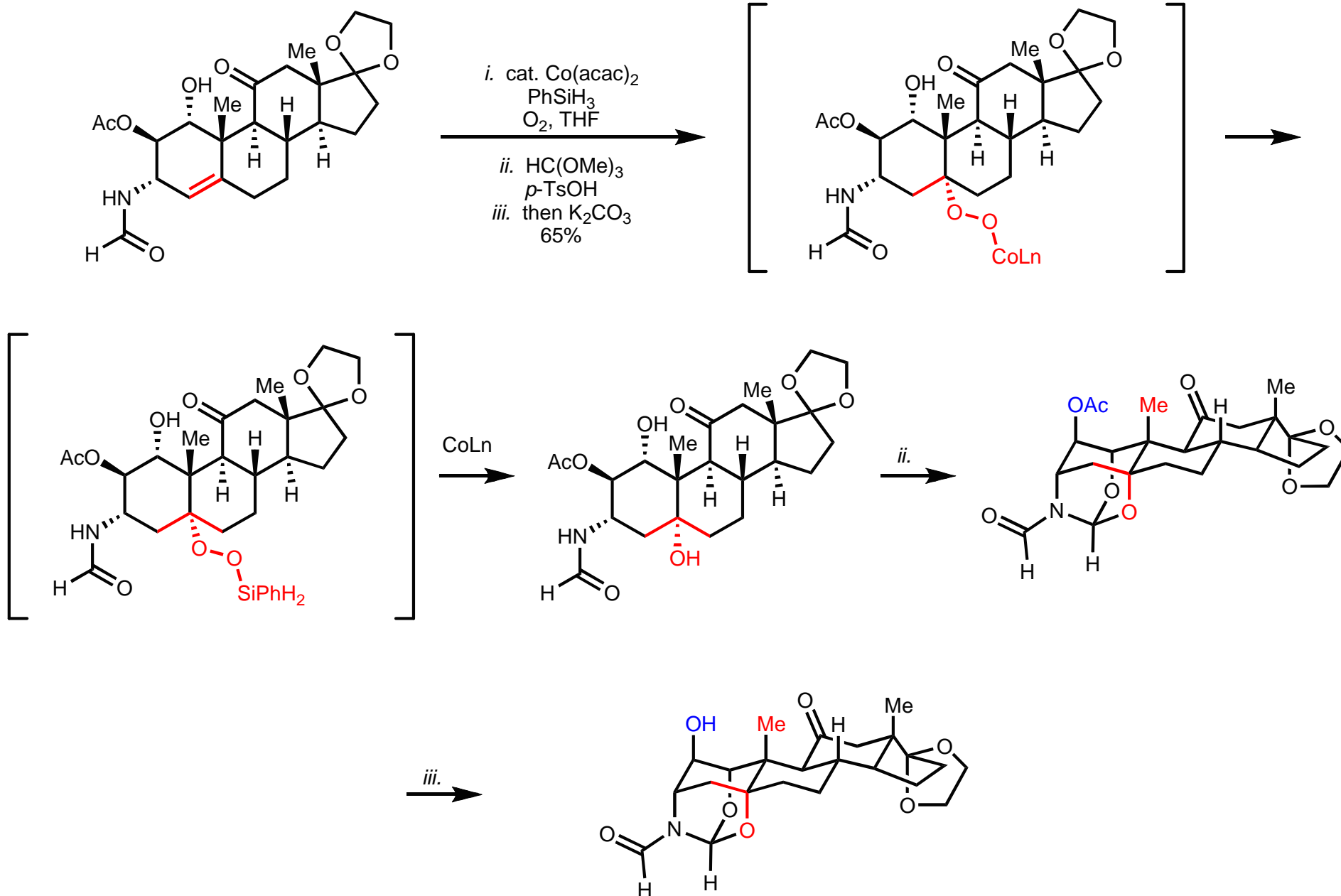
Barans Retrosynthesis



Functionalizing the A Ring

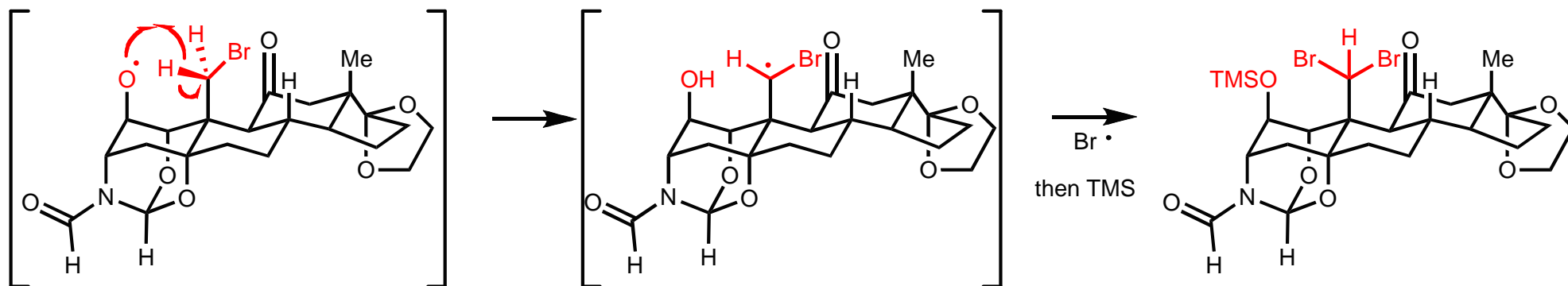
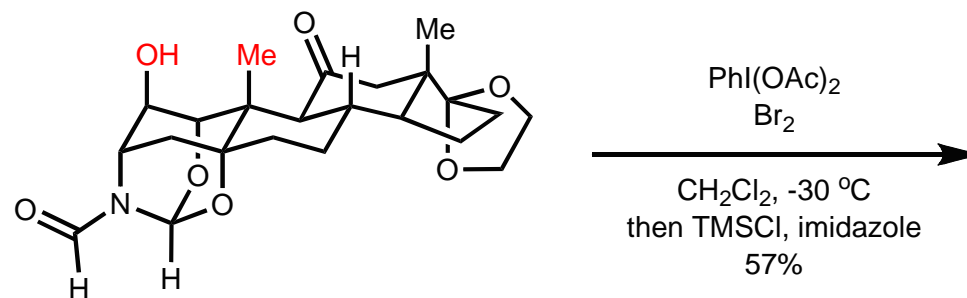


Adding Structural Rigidity

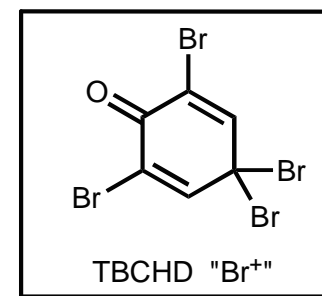
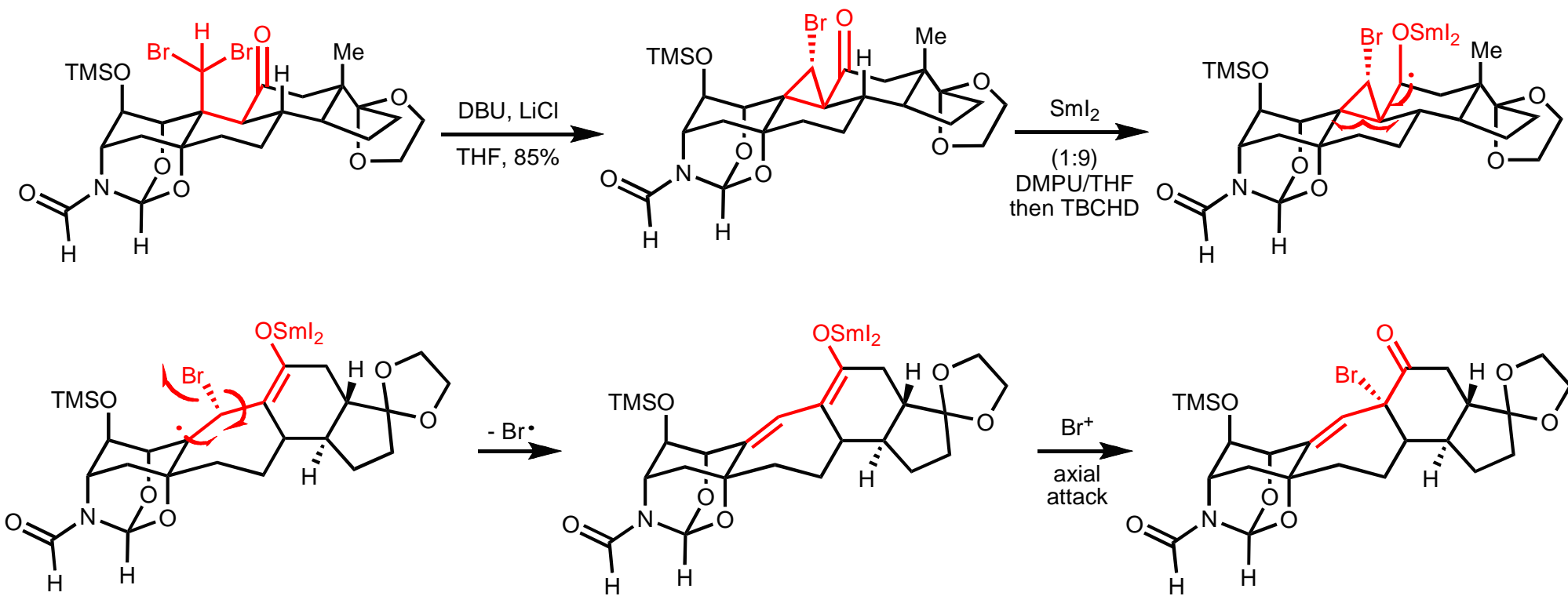


Mukaiyama Hydration: *Chem Lett* **1989**, 1071-1074.

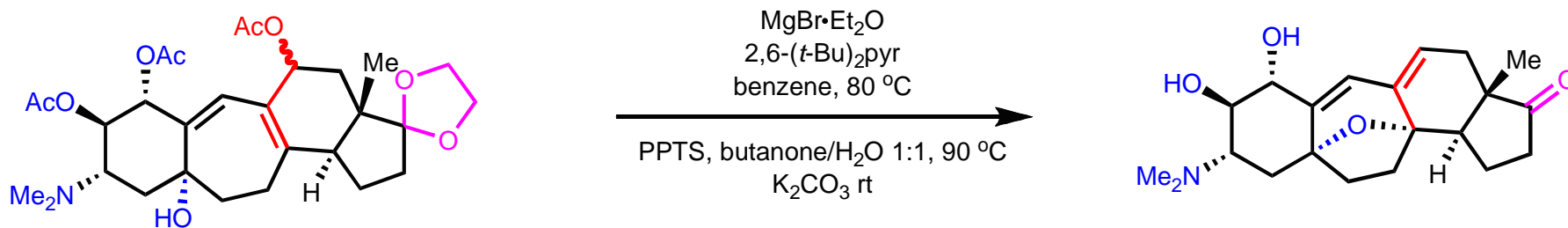
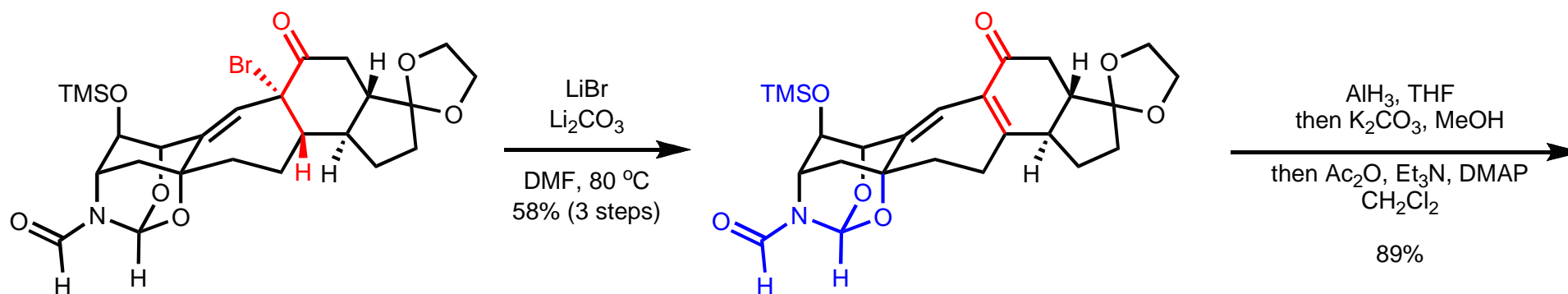
Selective Angular Methyl Oxidation



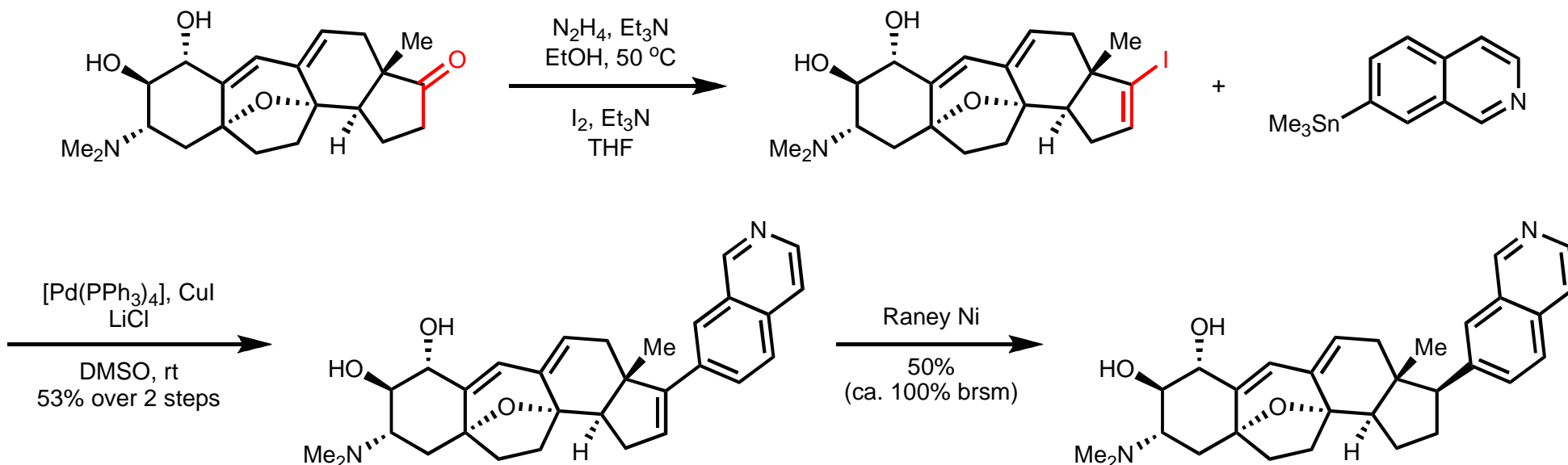
Ring Expansion



Forming the Bicyclic Ether

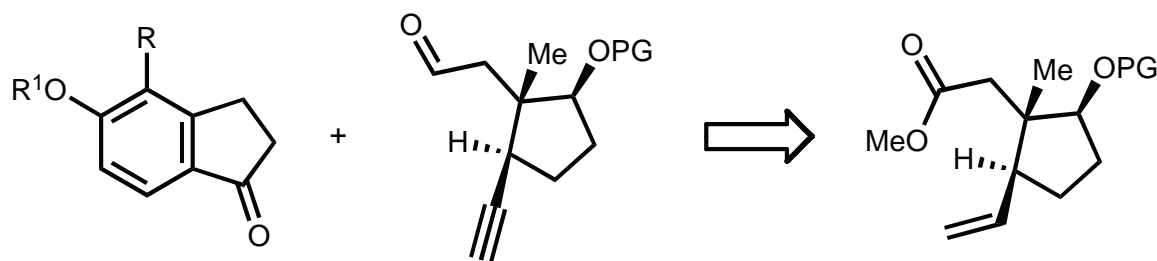
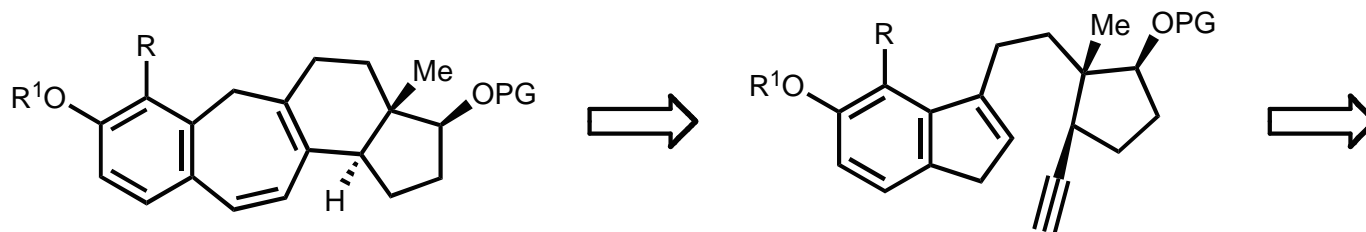
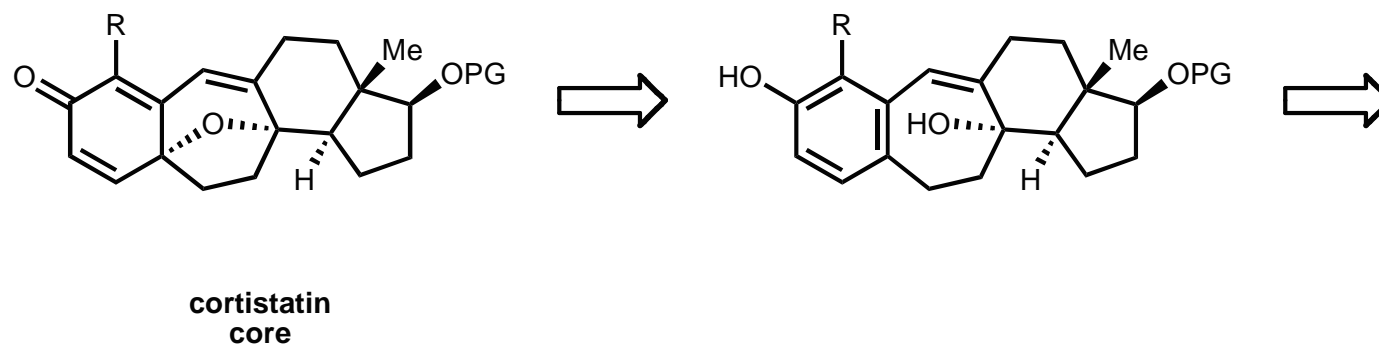


Completing the Synthesis

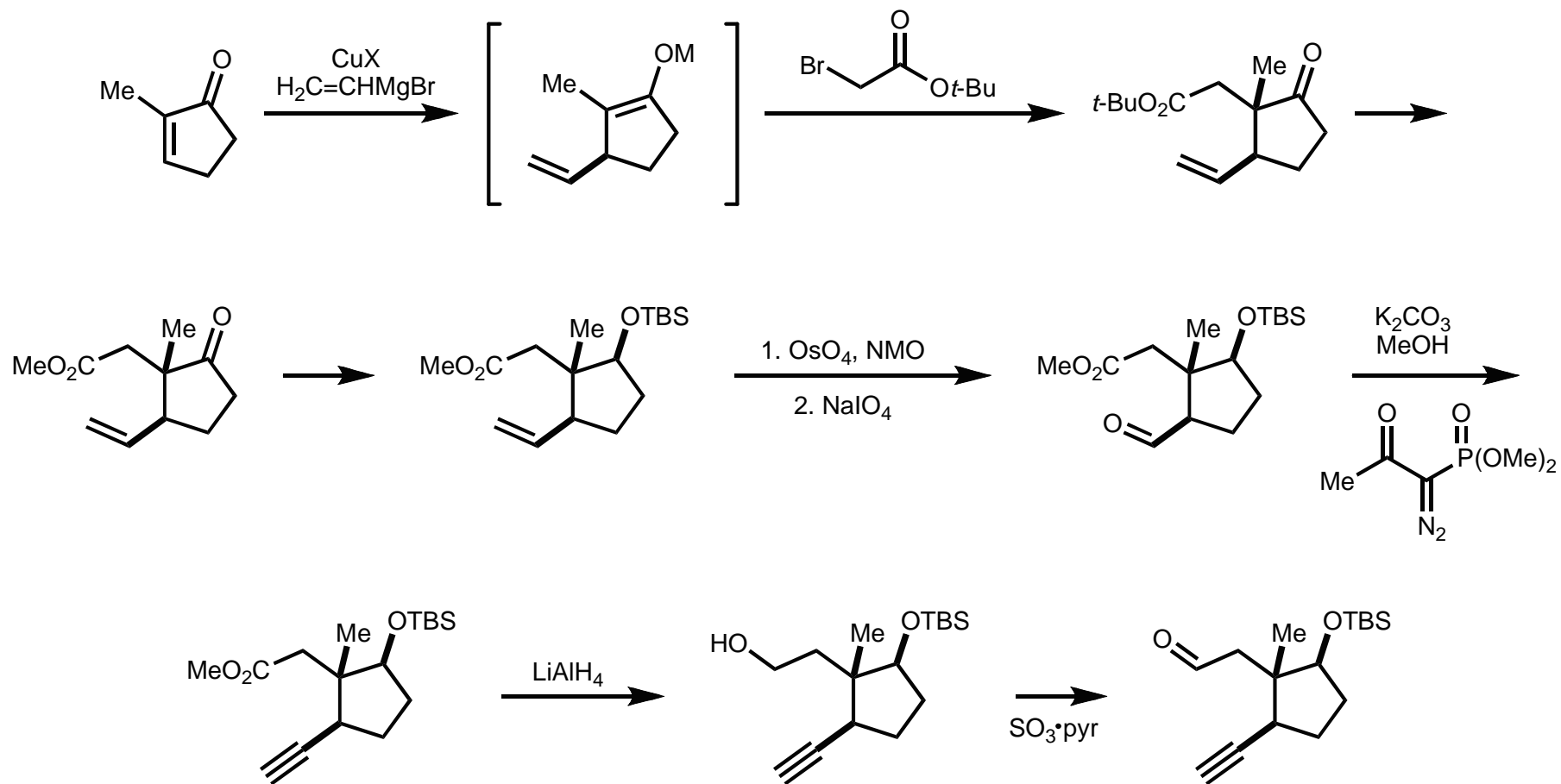


Vinyl Iodide: *J Chem Soc* **1962**, 470-476. Stille: *JACS* **1999**, 121, 7600-7605

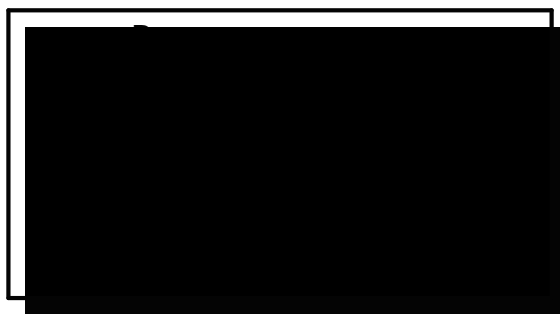
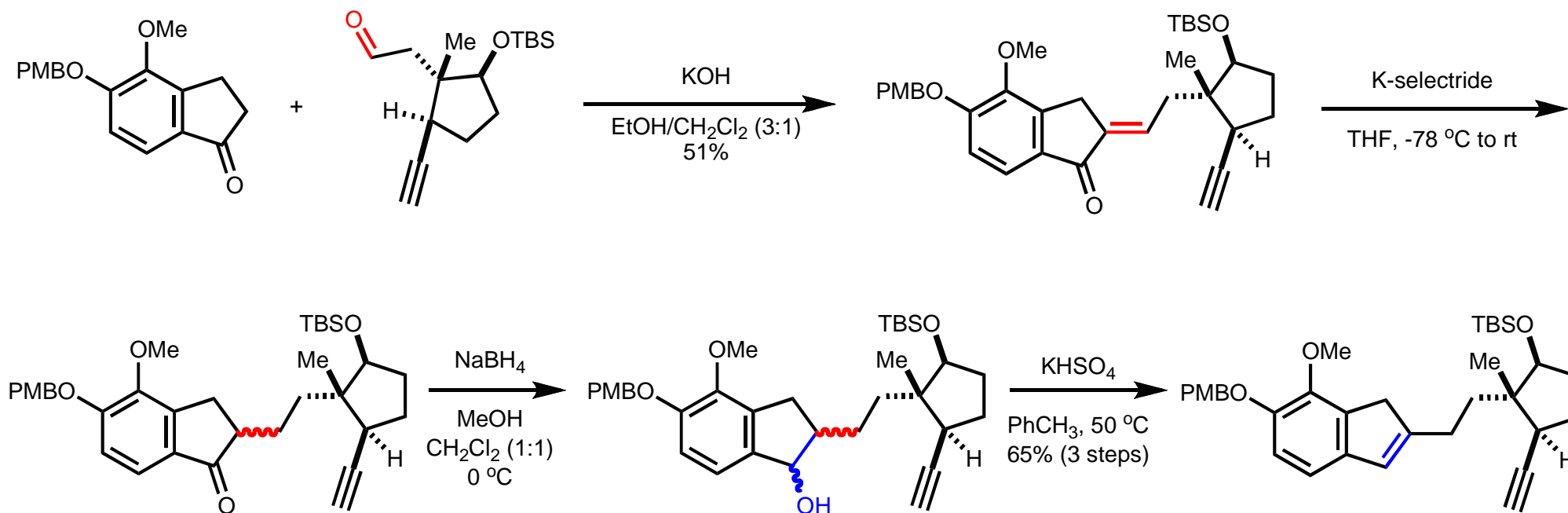
Sarpongs Retrosynthesis



Synthesis of the Starting Aldehyde



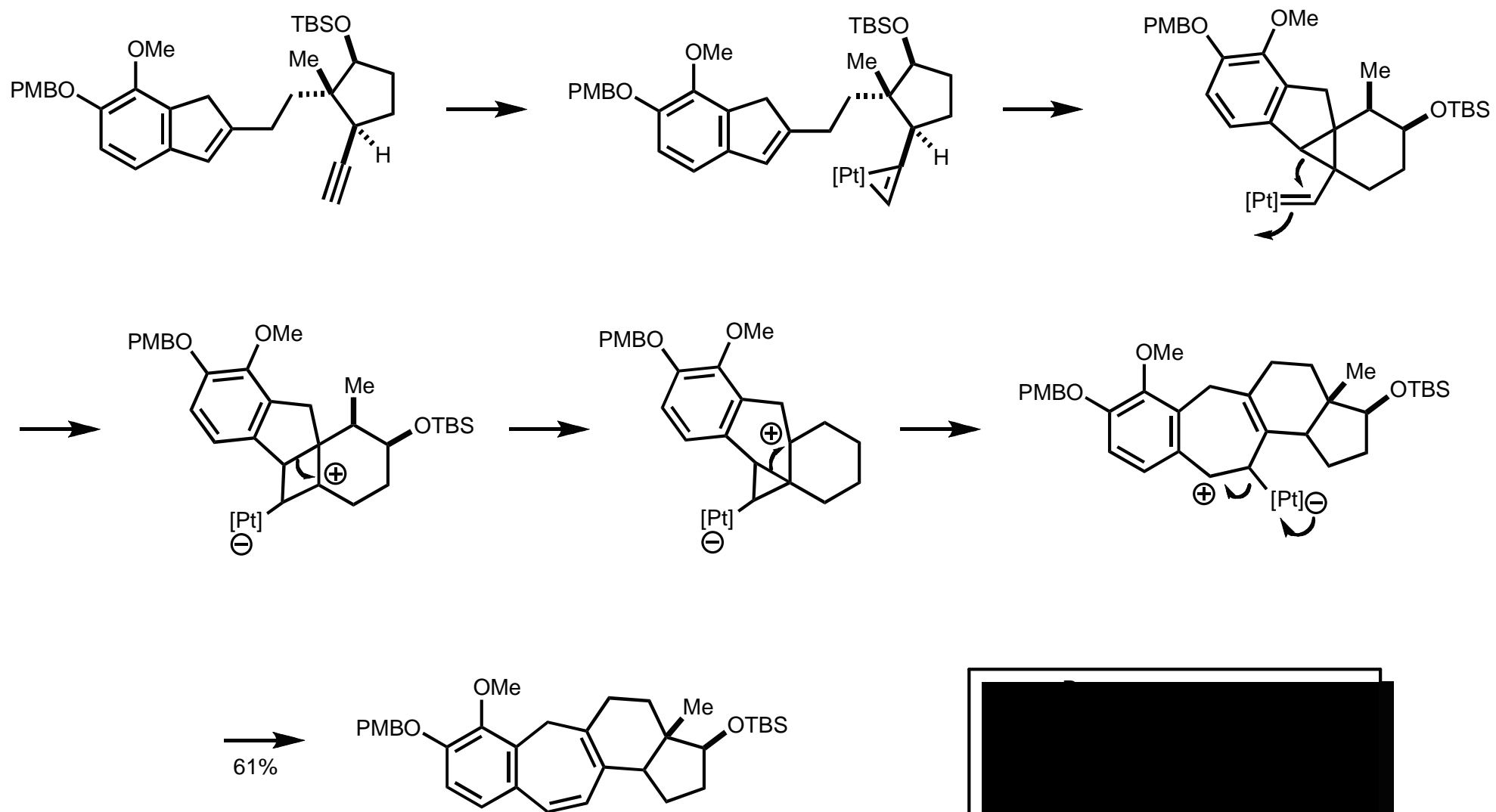
Preparing the Cycloisomerization Precursor



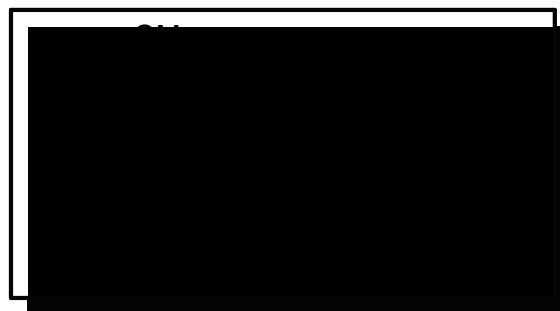
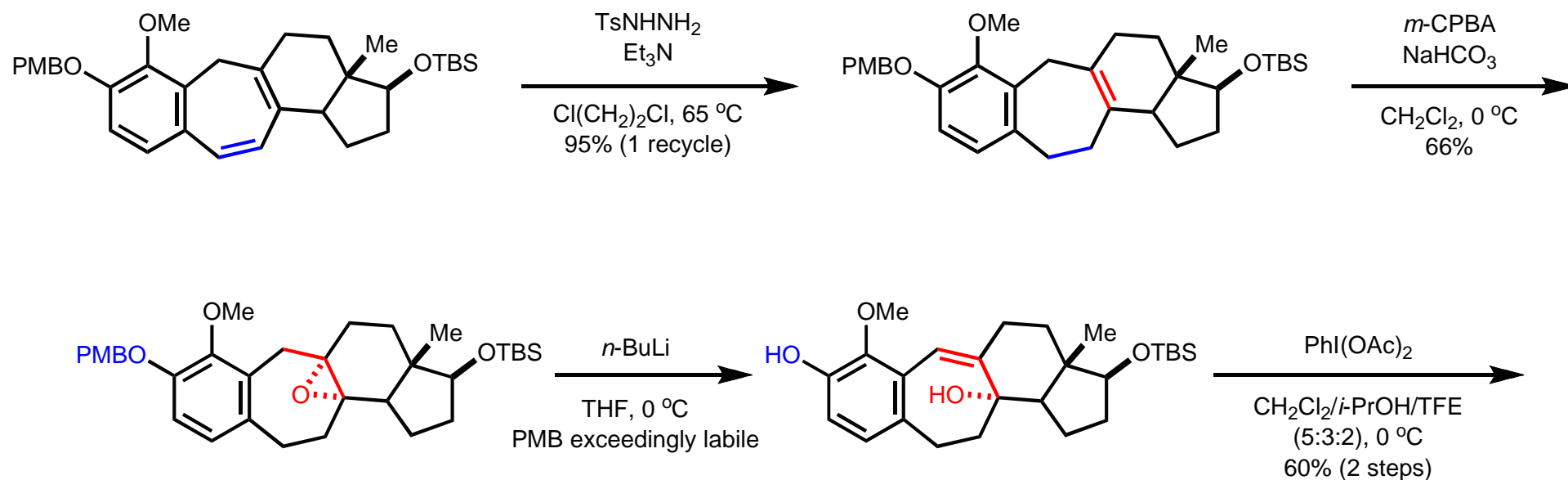
Disclaimer

What you are about to see may not be correct as no mechanism was provided for the reaction. Thus, based on the relevant information provided in the reviews I have put forth a mechanism consistent with intermediates proposed for similar transformations. If anyone feels as though they have any relevant or pertinent information that may assist in the understanding of this mechanism please feel free to speak up and keep me from embarrassing myself (further).

PtCl₂ Catalyzed Cycloisomerization

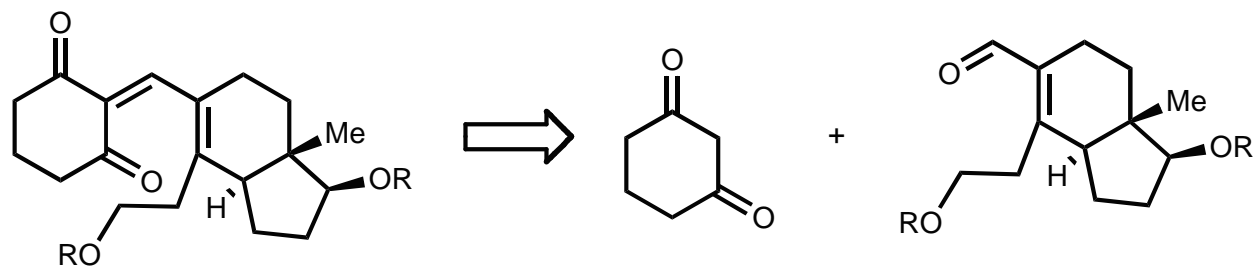
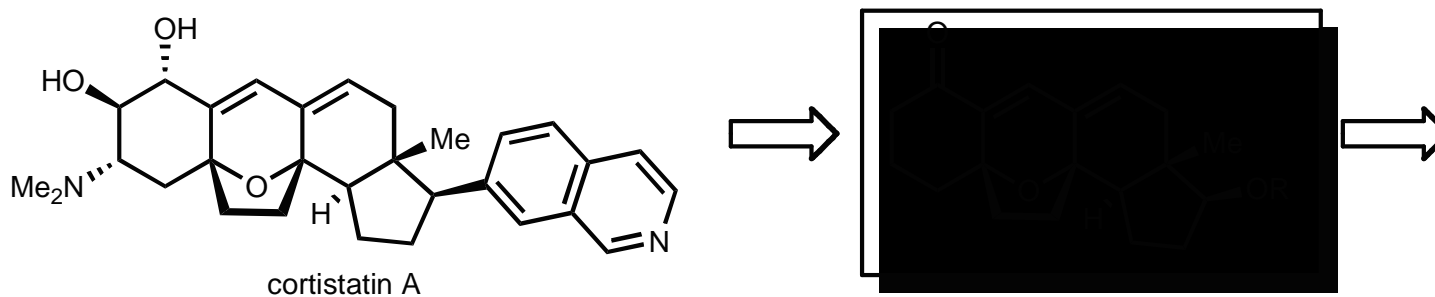


Completing the Synthesis of the Cortistatin Core

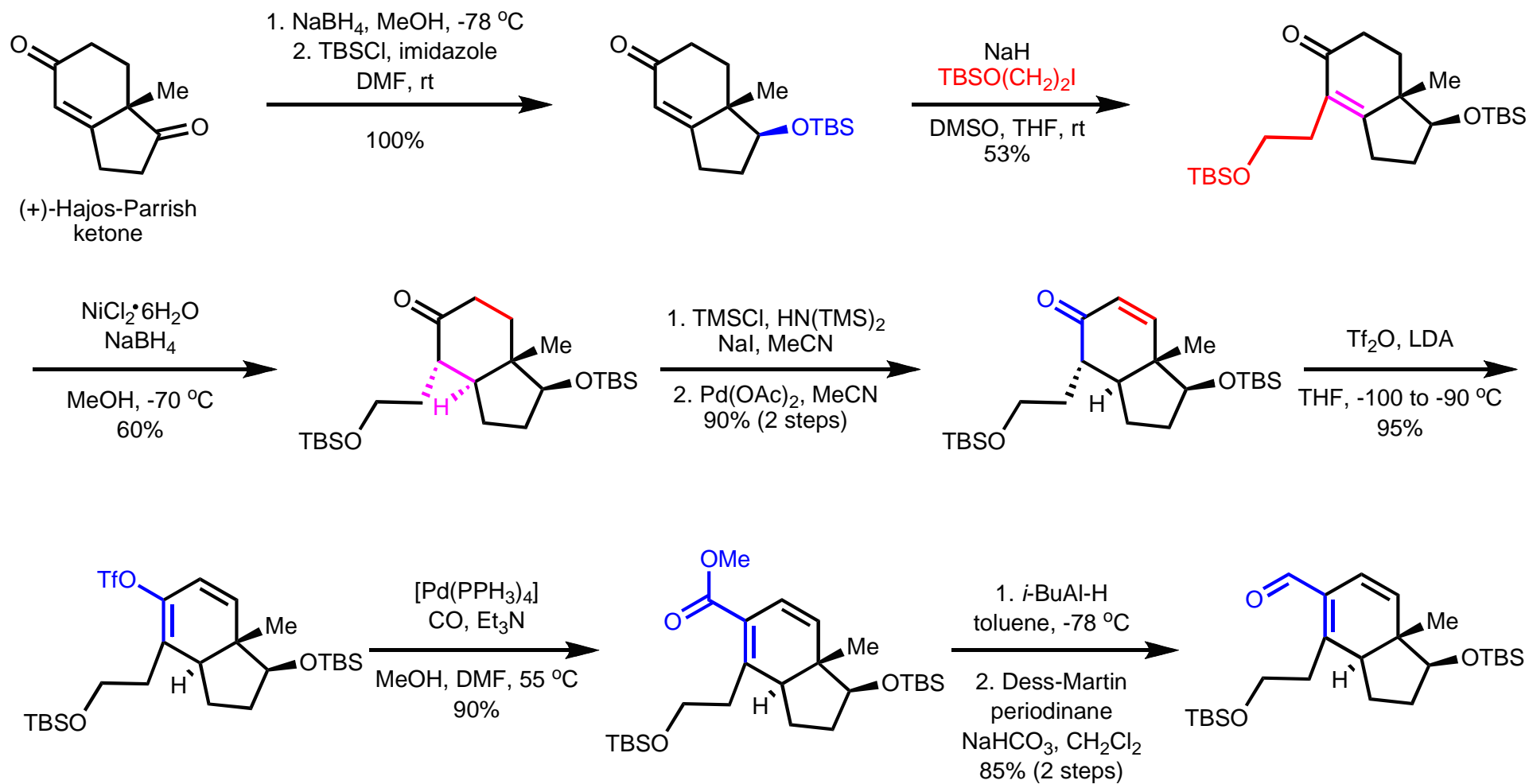


Danishefsky Cortistatin Oxidative Cyclization with PFIA: Heterocycles **ASAP**

Hirama's Retrosynthesis



Preparation of the Knoevenagel Substrate



Knoevenagel, Electrocyclization, Radical Cyclization

