

Skeletal Rearrangements In Natural Product Synthesis

Matthew M. Kreilein
Wednesday, July 19th, 2006

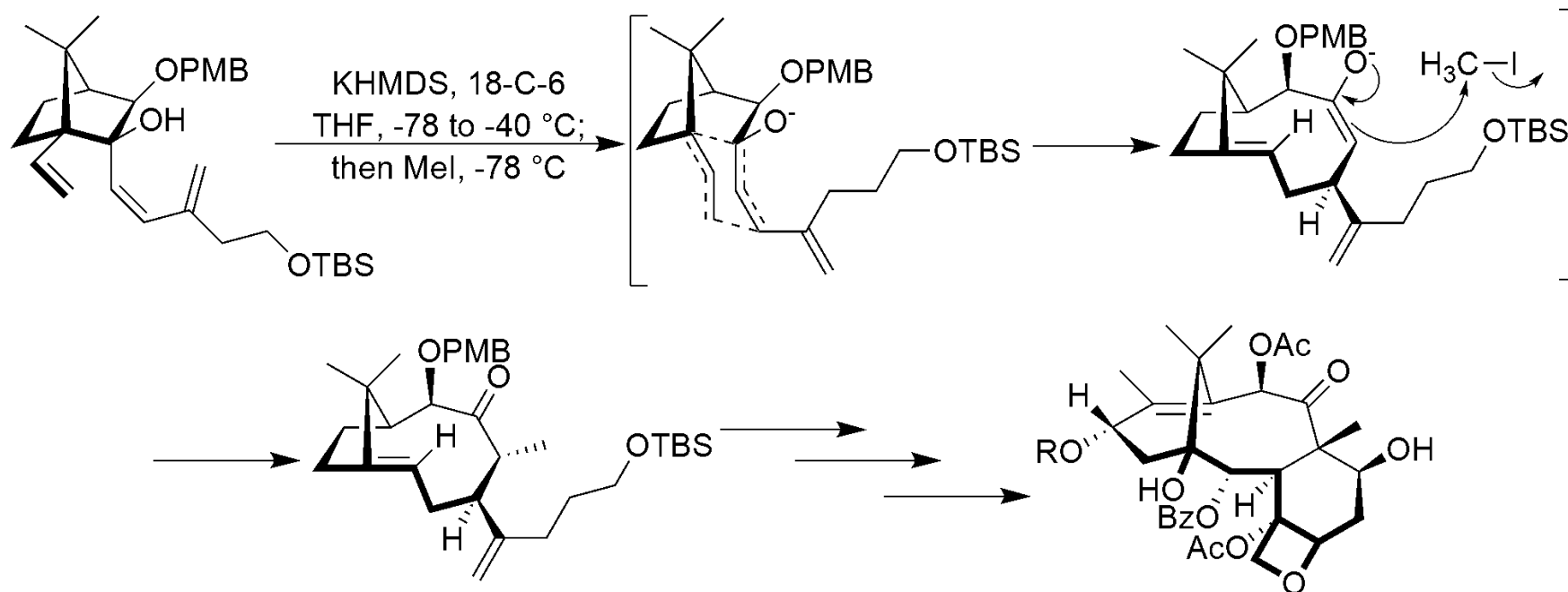
General Notes/Strategies:

Can be a very atom economical method for the synthesis of complex natural product structures.

Basically, set up a system, add a “trigger”, allow the system to do the rest of the work.

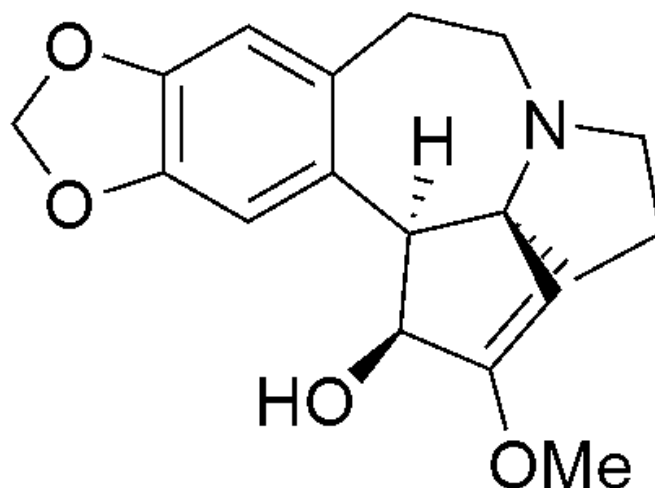
Ideally, the precursor is easy to synthesize in fewer steps than making the product in another method.

Editorial Statement: The hard part is “seeing it”.



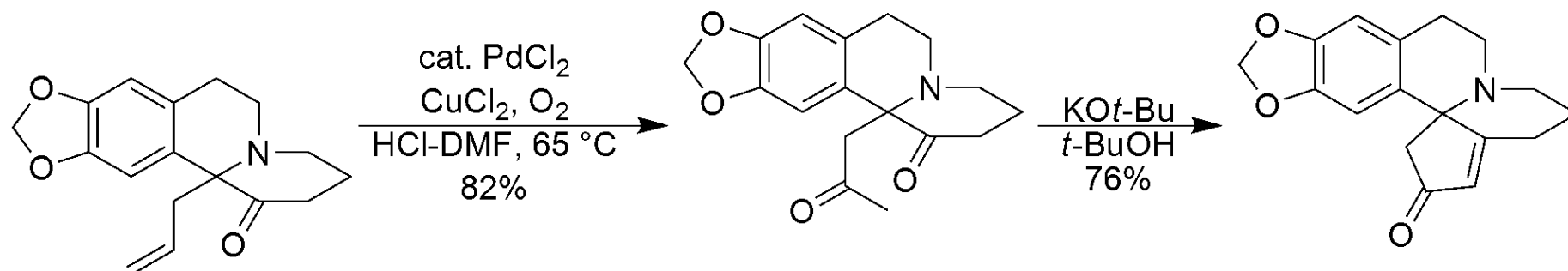
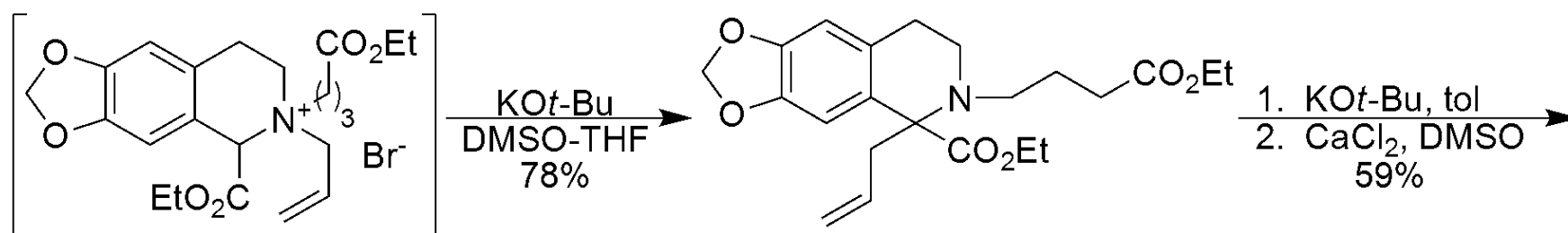
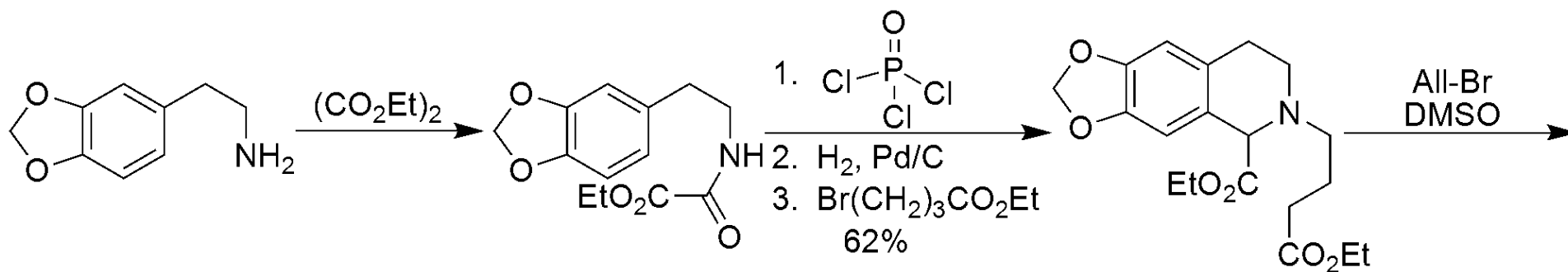
Synthesis of Cephalotaxine

Li, W-D.Z.;Wang, Y.-Q. *Org. Lett.* **2003**, 5, 2931-2934

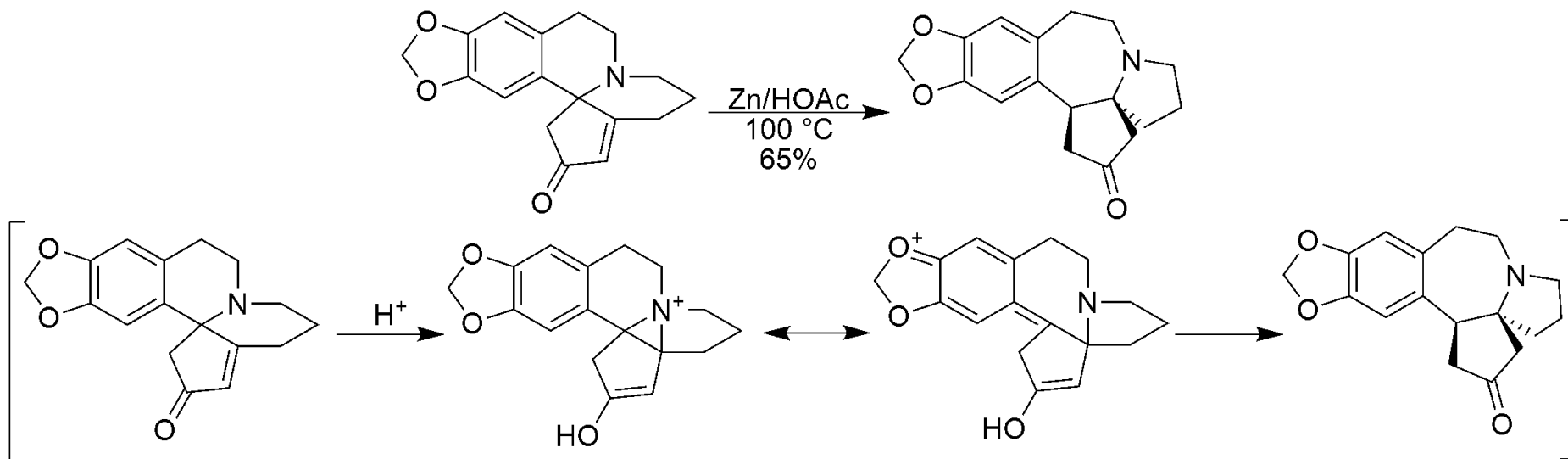


- + Parent member of the *Cephalotaxus* alkaloids
- + Ester derivatives (harringtonine and homoharringtonine) found to be effective at treating leukemia and are in clinical trials.
- + Harringtonine also potent against strains of malaria parasite.

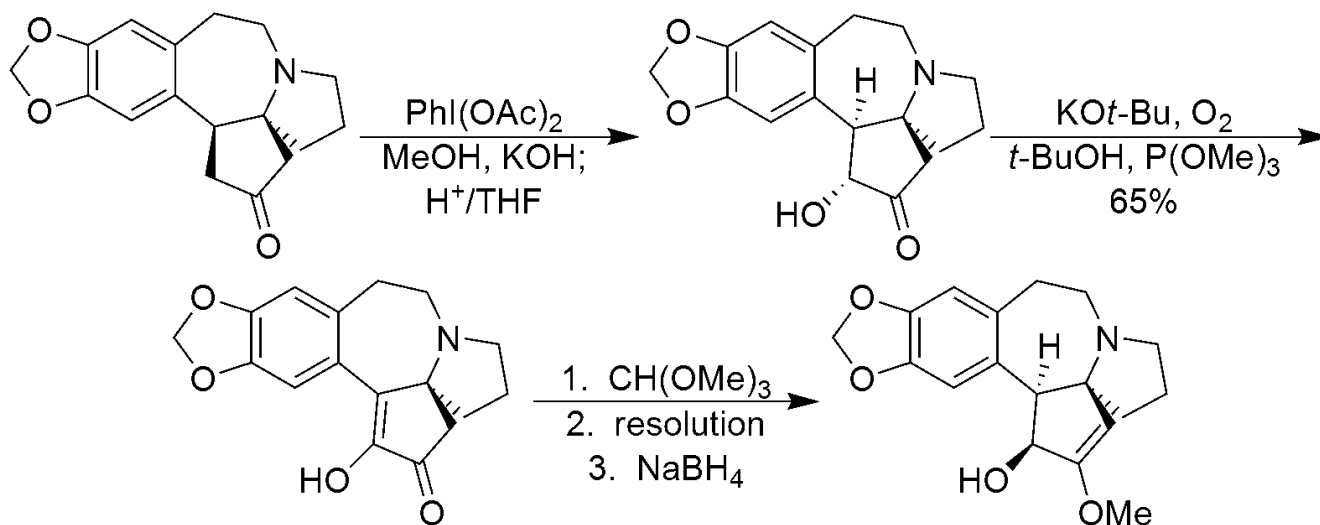
Synthesis of Rearrangement Precursor:



Rearrangement and Completion of the Target:



Clemmensen-Clemo-Prelog-Leonard Reductive Rearrangement

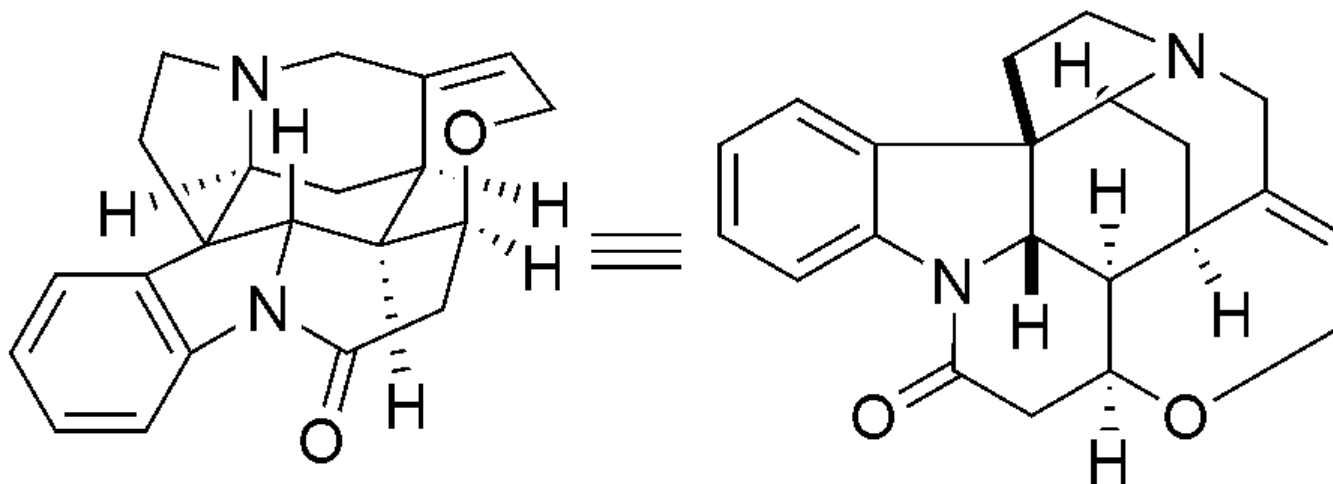


Synthesis of Strychnine

Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455-3482.

Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293-9294.

Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776-5788.

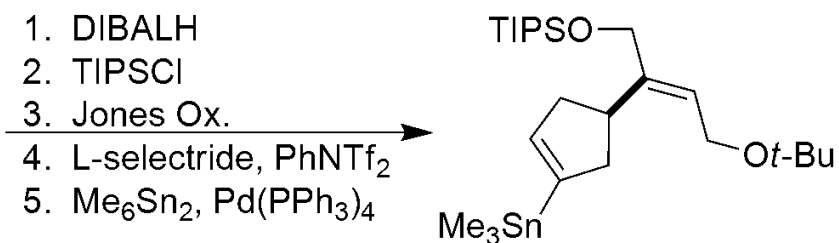
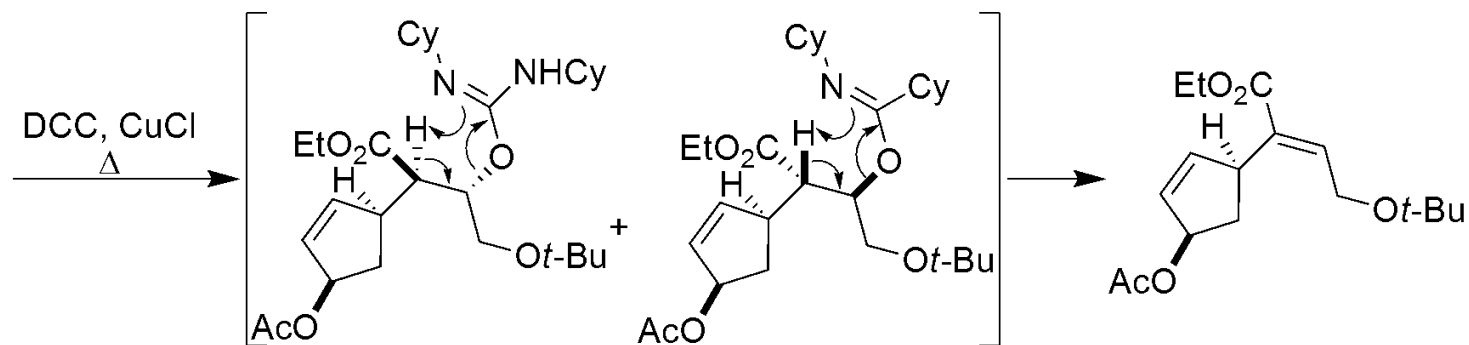
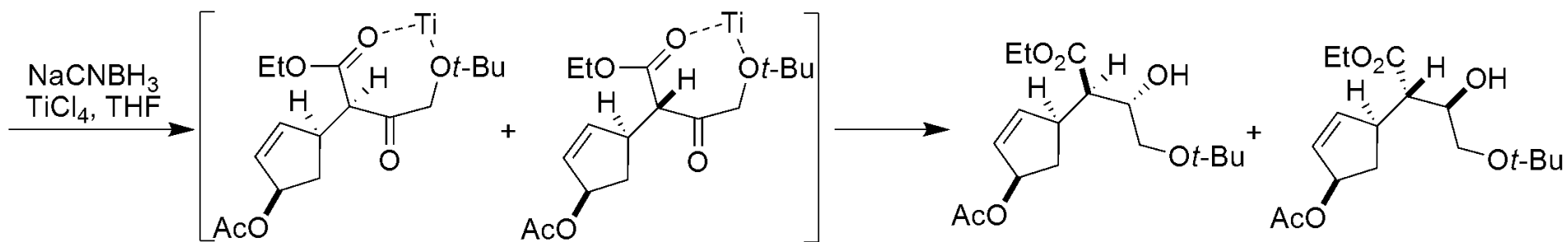
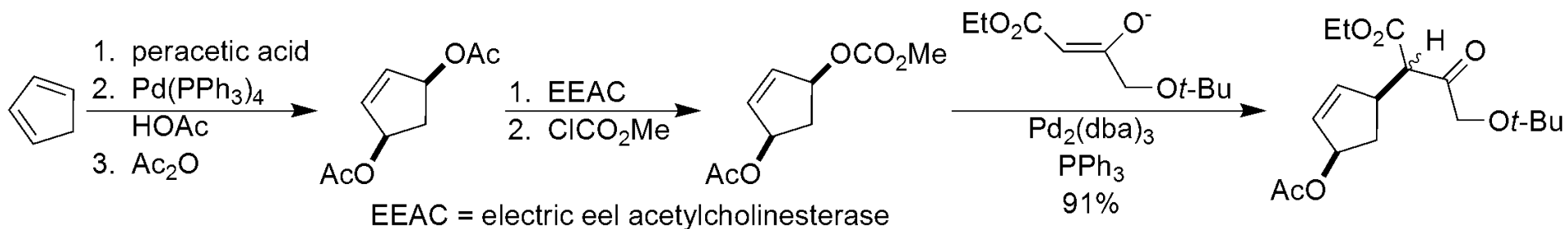


+ Isolated (along with brucine) from the seeds of *Strychnos nux vomica*

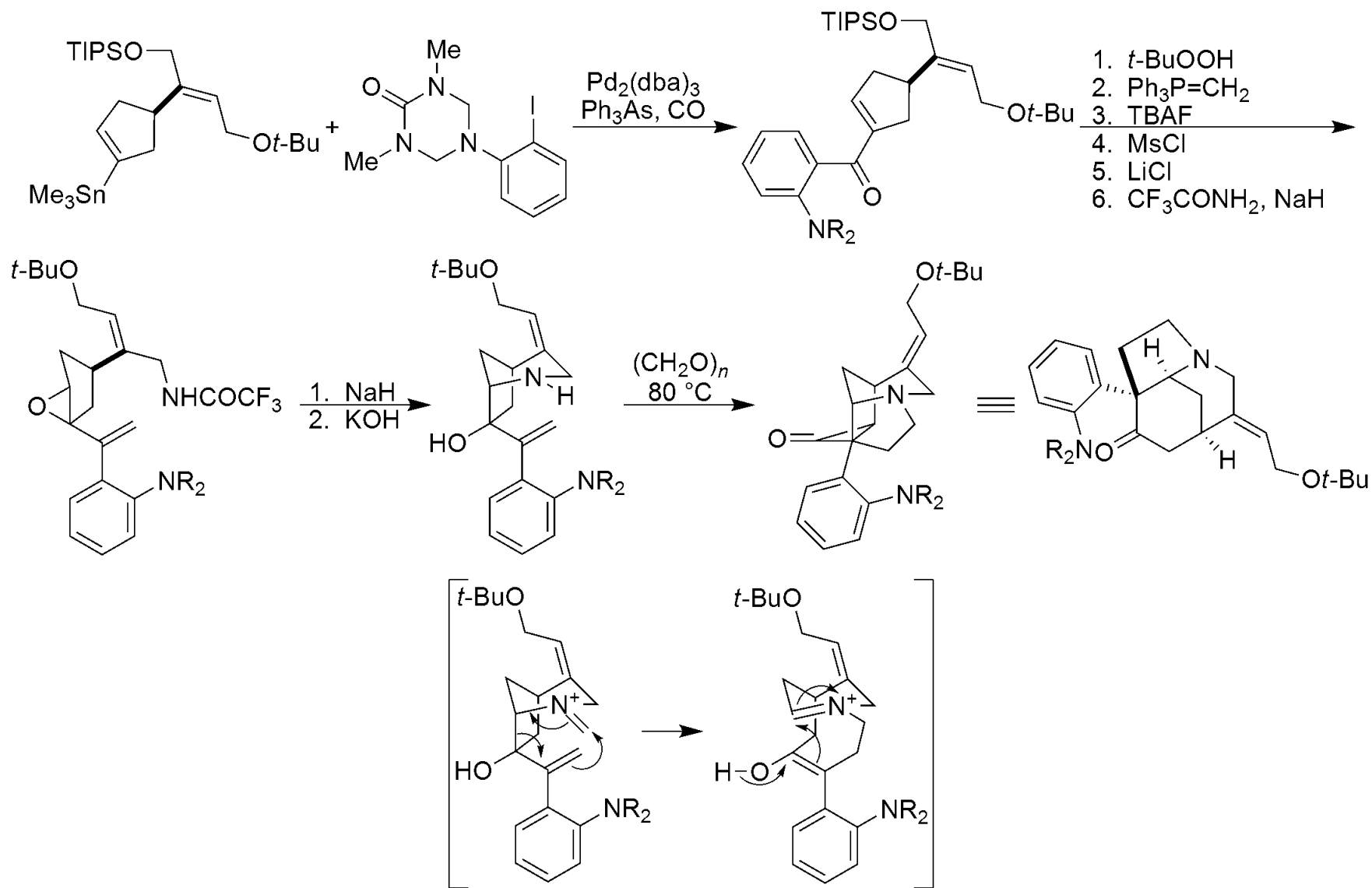
Strychnos = “death or deadly”, *nux* = “nut”, *vomica* = “vomit”

+ CAUTION - Very commonly called “Nux vomica” when sold online as an “herbal remedy”

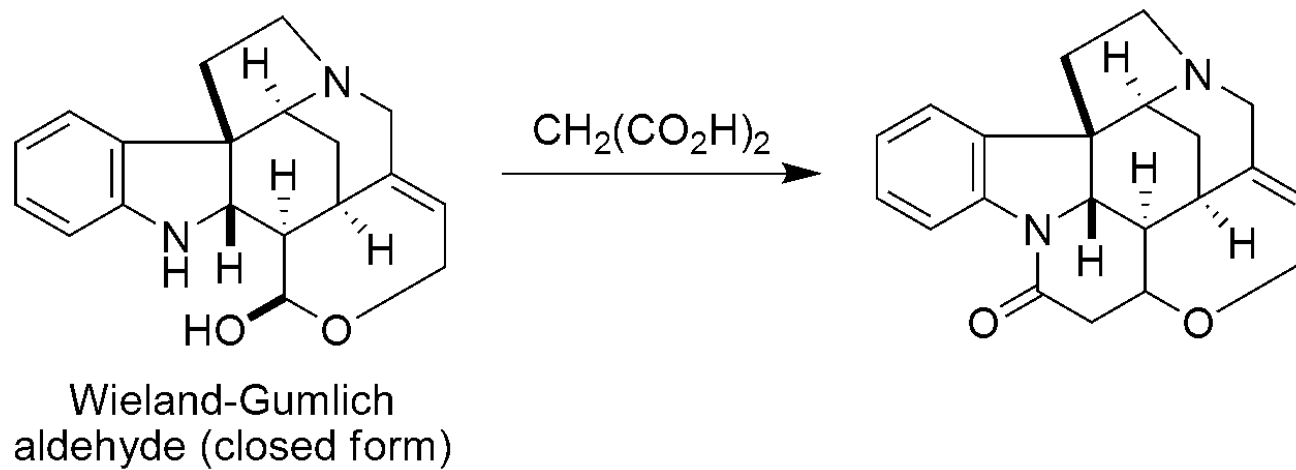
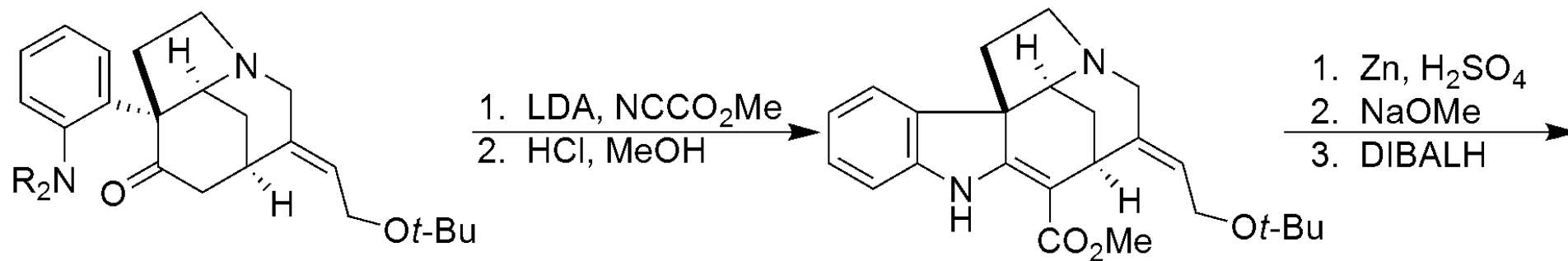
Synthesis of Alkenyl Stannane



Synthesis of Azatricyclic Ketone



Completion of the (-)-strychnine



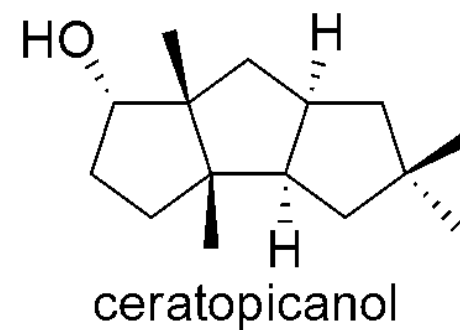
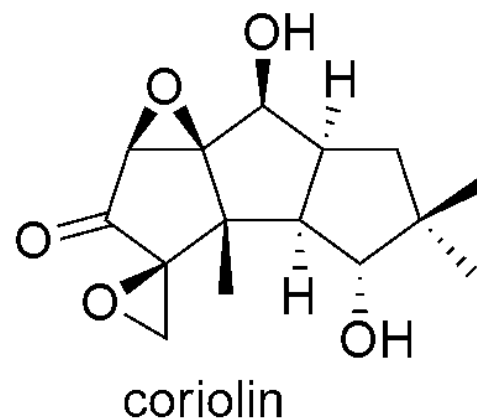
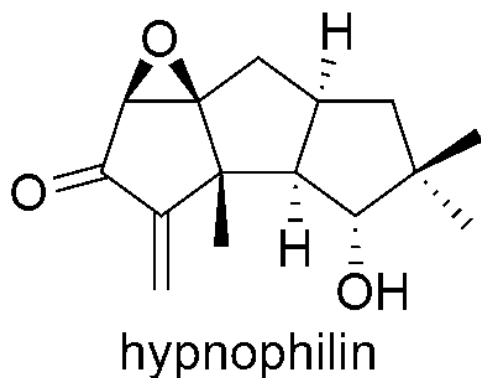
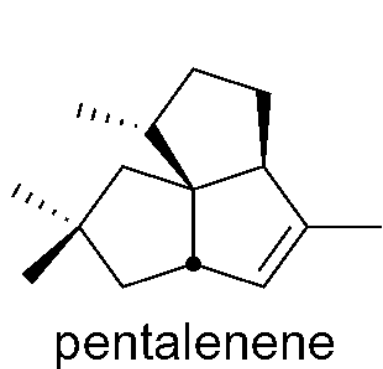
Polyquinanes via Squarate Ester Cascade

Geng, F.; Liu, J.; Paquette, L.A. *Org. Lett.* **2002**, *4*, 71-73.

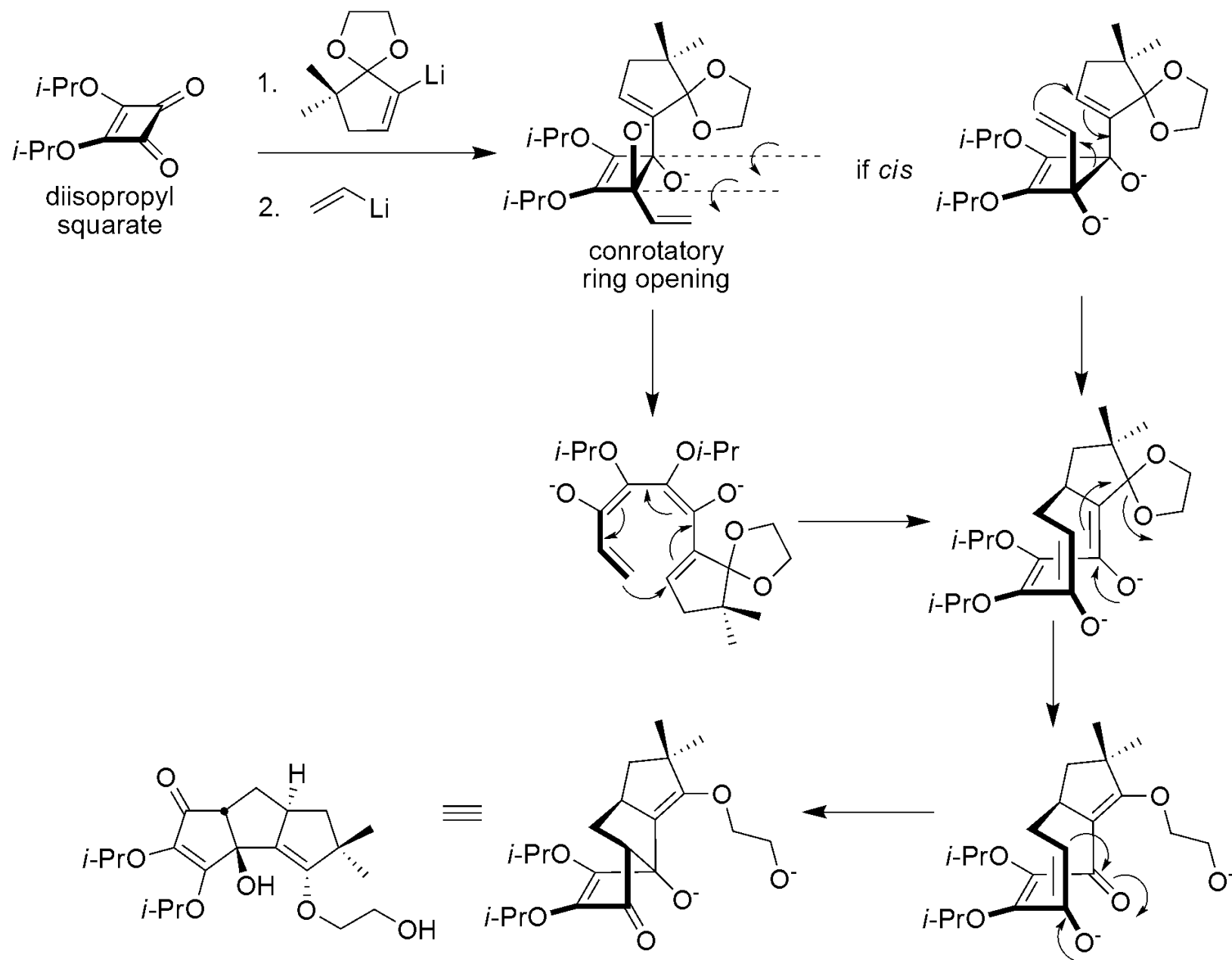
Paquette, L.A.; Geng, F. *Org. Lett.* **2002**, *4*, 4547-4549.

Paquette, L.A.; Geng, F. *J. Am. Chem. Soc.* **2002**, *124*, 9193-9203.

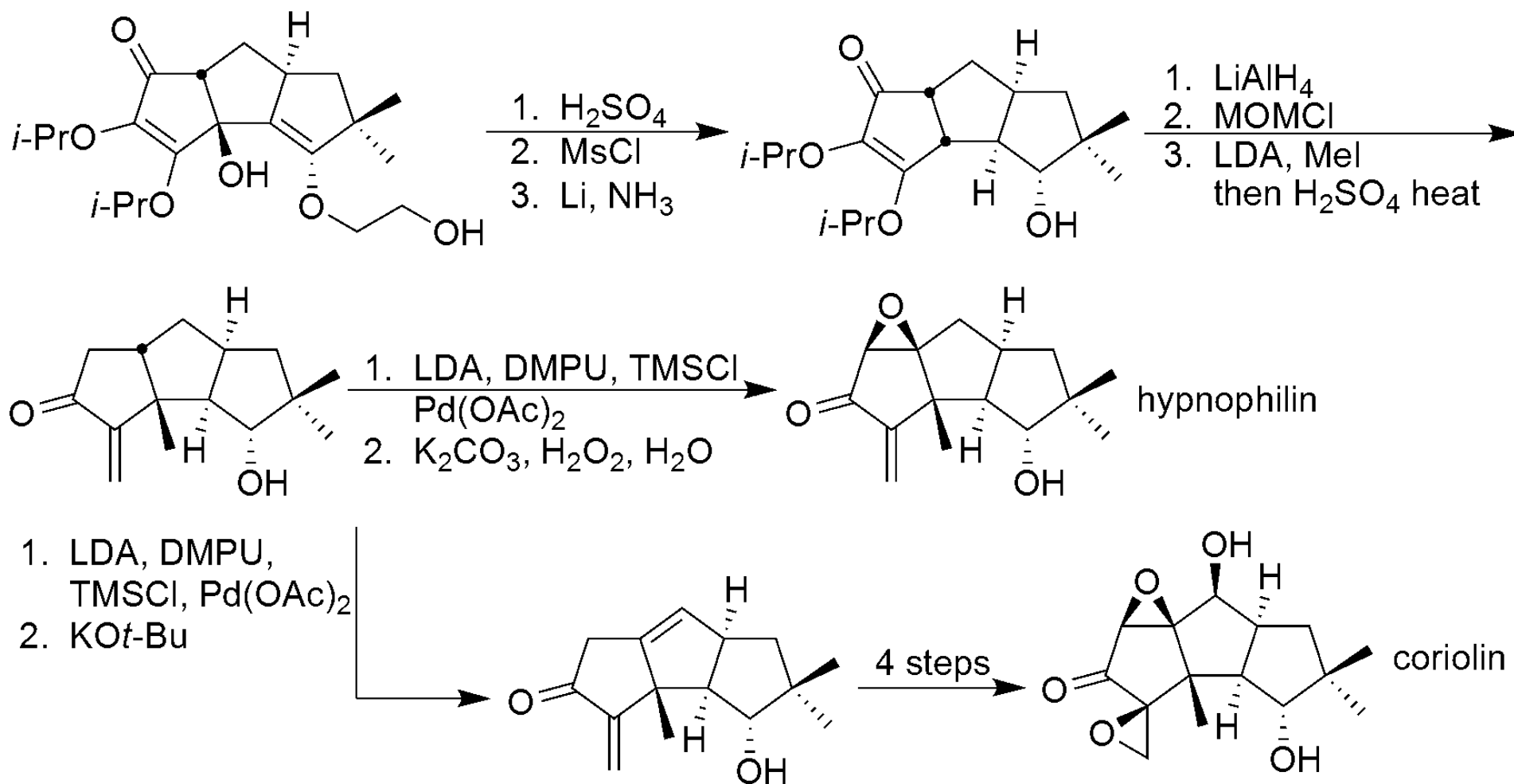
Review: Paquette, L.A. *Eur. J. Org. Chem.* **1998**, 1709-1728.



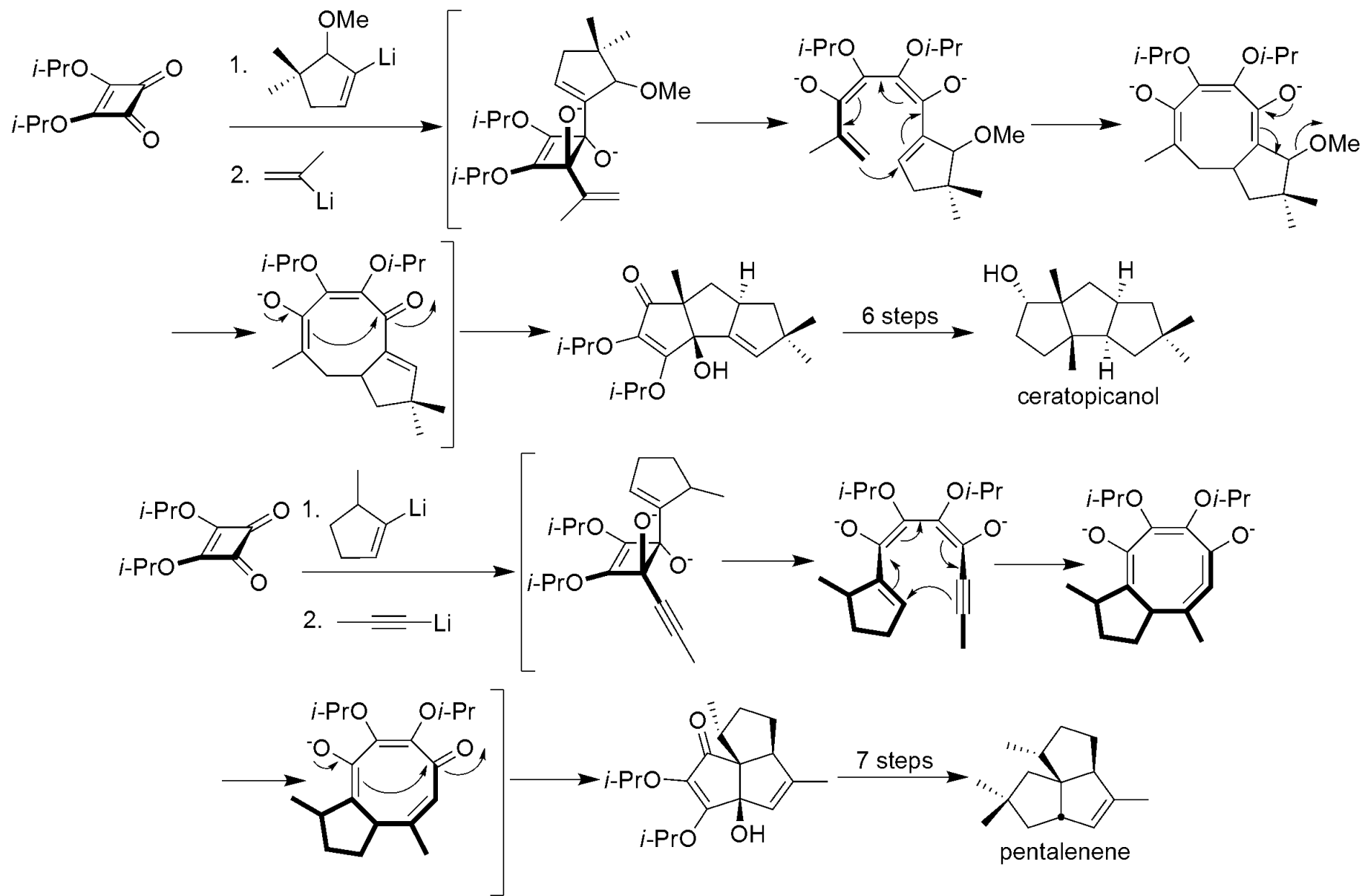
Squarate Ester Cascade to Hypnophilin and Coriolin:



Arrival at Hypnophilin and Coriolin:



Similar Strategy for Ceratopicanol and Pentalenene:



Total Synthesis of Jatrophatrione And Citlaltione

Paquette, L.A.; Colapret, J.A.; Andrews, D.R. *J. Org. Chem.* **1985**, *50*, 201-205.

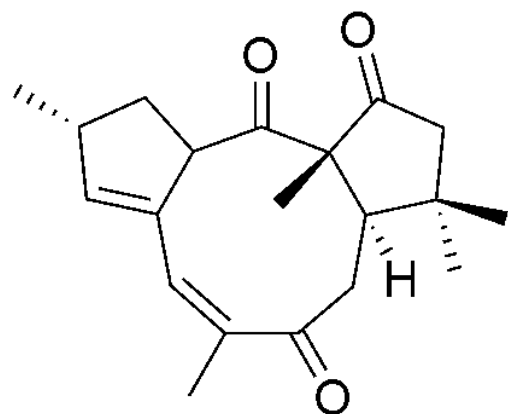
Paquette, L.A.; Nakatani, S.; Zydowsky, T.M.; Edmonson, S.D.; Sun, L.-Q.; Skerlj, R.
J. Org. Chem. **1999**, *64*, 3244-3254.

Paquette, L.A.; Edmonson, S.D.; Monck, N.; Rogers, R.D.
J. Org. Chem. **1999**, *64*, 3255-3265.

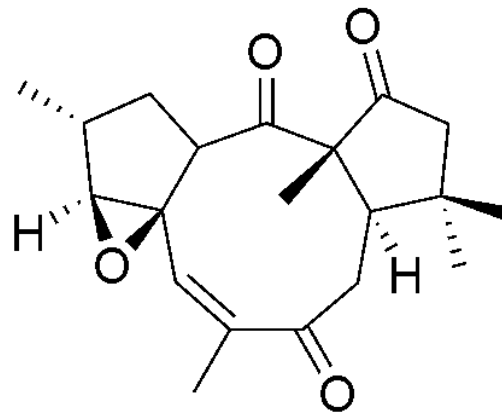
Paquette, L.A.; Yang, J.; Long, Y.O. *J. Am. Chem. Soc.* **2002**, *124*, 6542-6543.

Yang, J.; Long, Y.O.; Paquette, L.A. *J. Am. Chem. Soc.* **2003**, *125*, 1567-1574.

Paquette, L.A. in "Strategies and Tactics in Organic Synthesis", Vol. 4, p 97-133

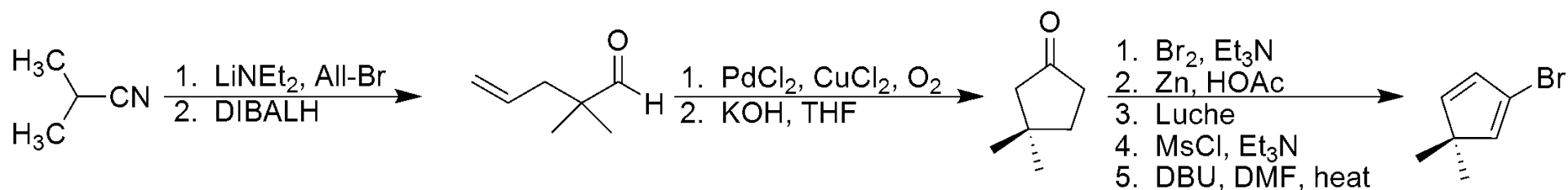
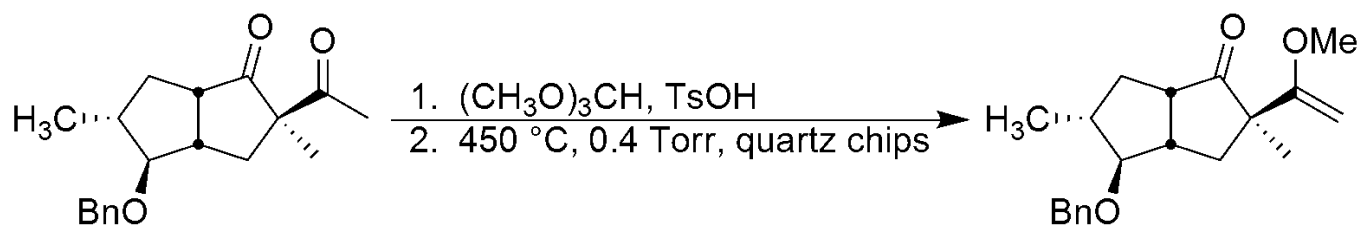
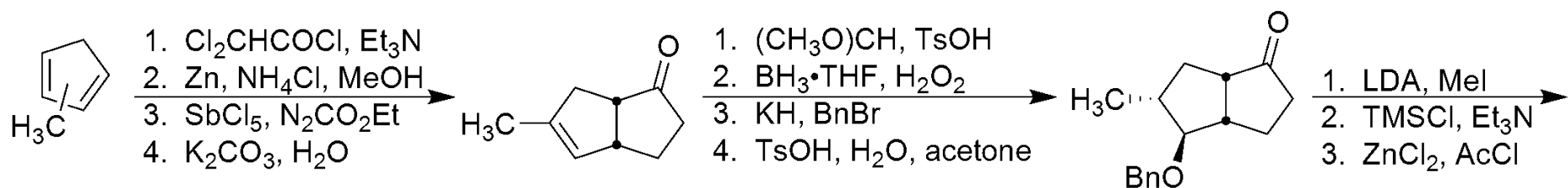


jatrophatrione

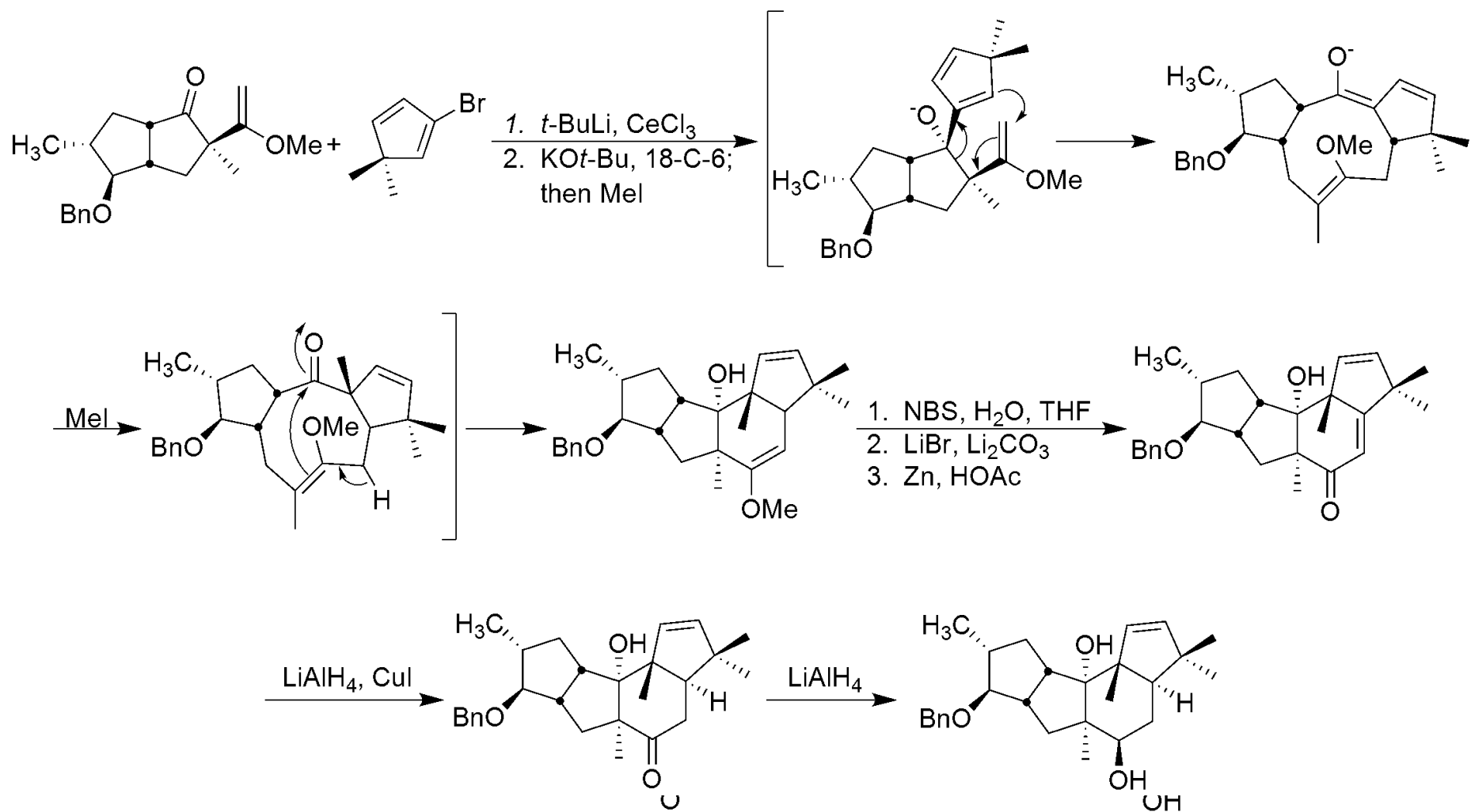


citlaltione

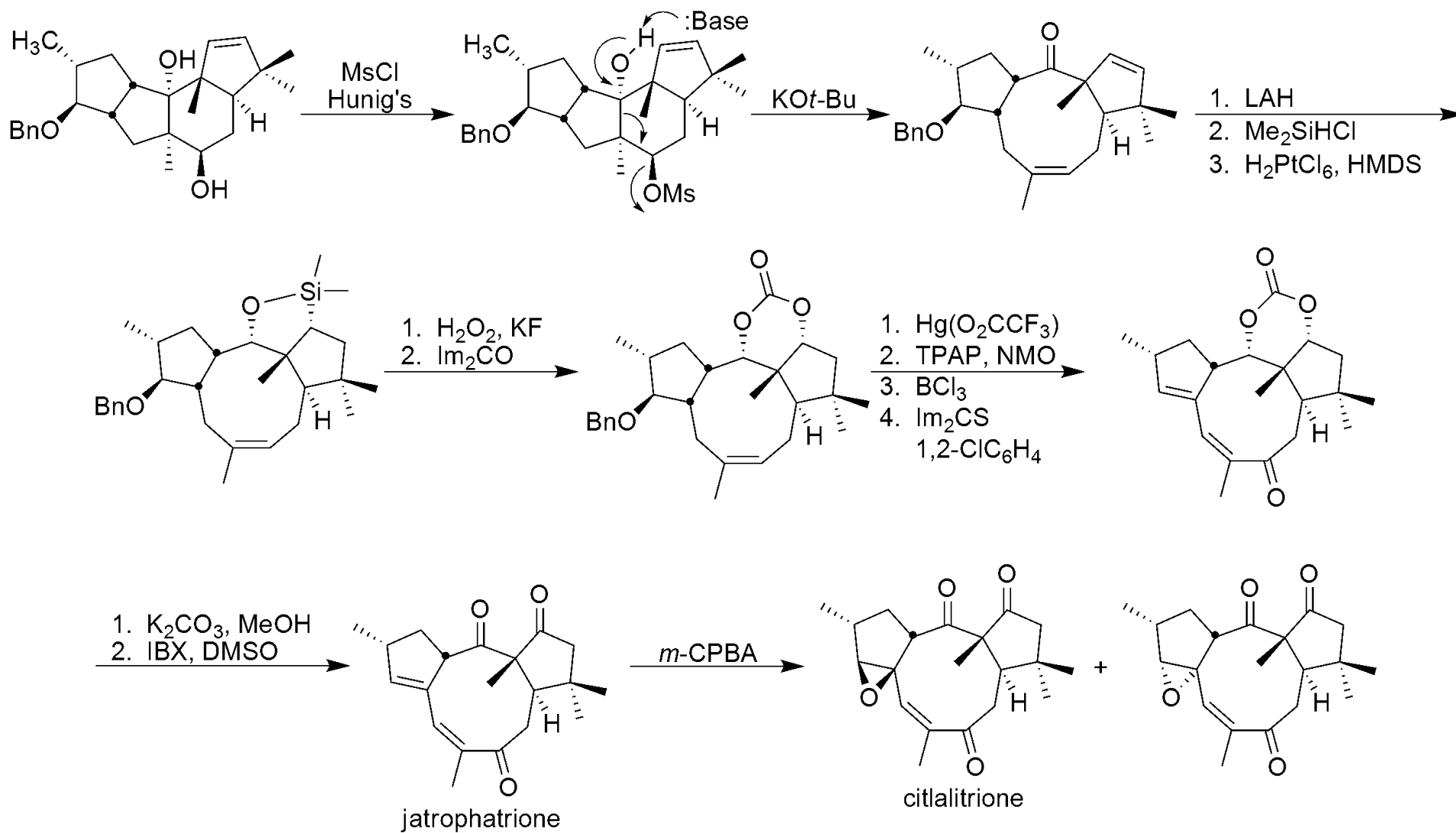
Synthesis of Coupling Fragments:



Coupling & Skeletal Rearrangement:



Completion of the Target:



A side note:

