Synthesis of Cortistatins A, J, K and L

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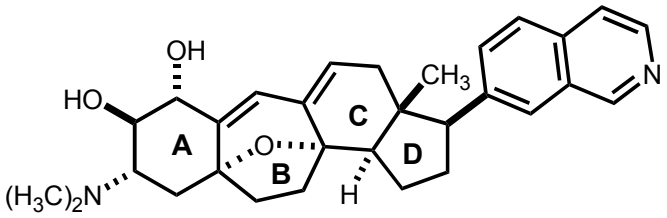
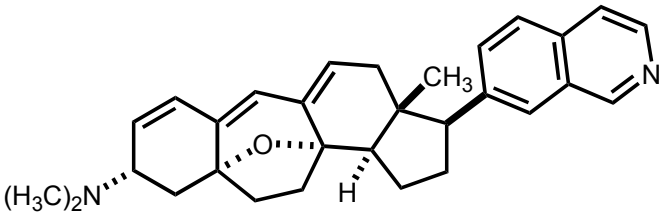
Nat. Chem., **2010**, *AOP.* DOI: 10.1038/nchem.794

Ki Bum Hong
Current Literature
Sept 25, 2010

Isolation, Background, and Cortistatin Synthesis



Cortistatin A

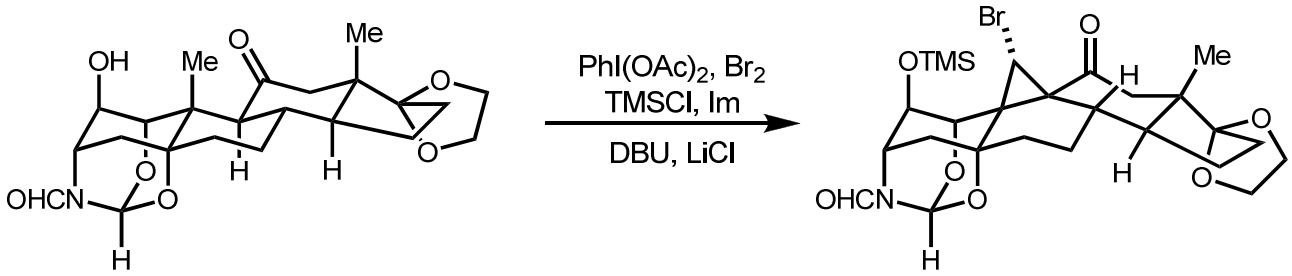


Cortistatin J

- Cortistatin A was elucidated by Kobayashi and colleagues in 2006
- Inhibitor of angiogenesis - potential antitumor agent
  Potent - IC_{50} of 1.8 nM for human umbilical vein endothelial (HUVEC) cells
- In 2008, Baran reported the first laboratory synthetic route to cortistatin A
- three independent routes to cortistatin A have been reported
  Baran, Nicolaou, Shair

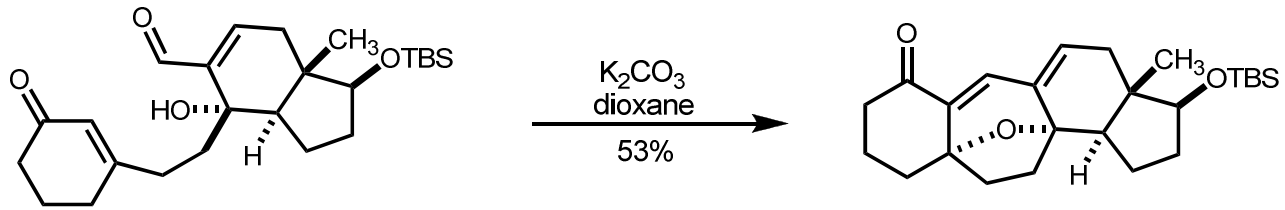
Previous Synthetic Approach

- Geminal dihalogenation of unactivated hydrocarbon



Baran, *J. Am. Chem. Soc.*, **2008**, *130*, 7241

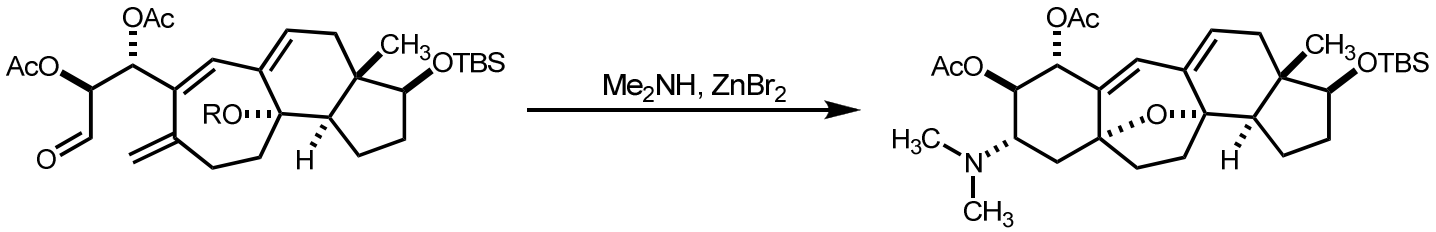
- 1,4-Addition / Aldol / dehydration Cascade



Nicolaou, *Angew. Chem., Int. Ed.*, **2008**, *47*, 7310

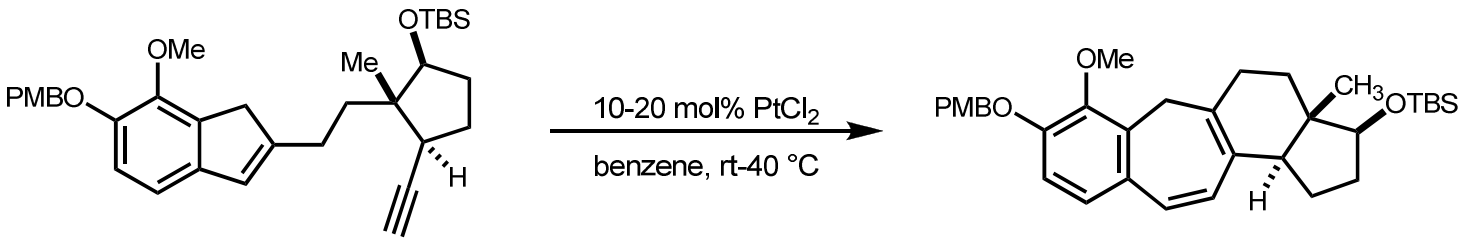
Previous Synthetic Approach

- aza-Prins Cyclization



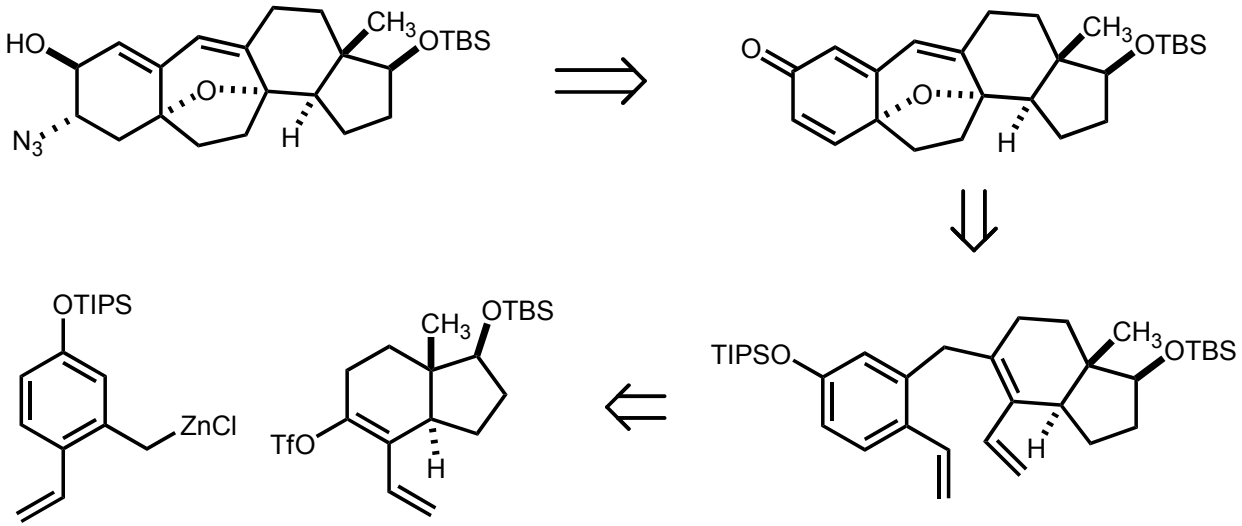
Shair, *J. Am. Chem. Soc.*, **2008**, *130*, 16864

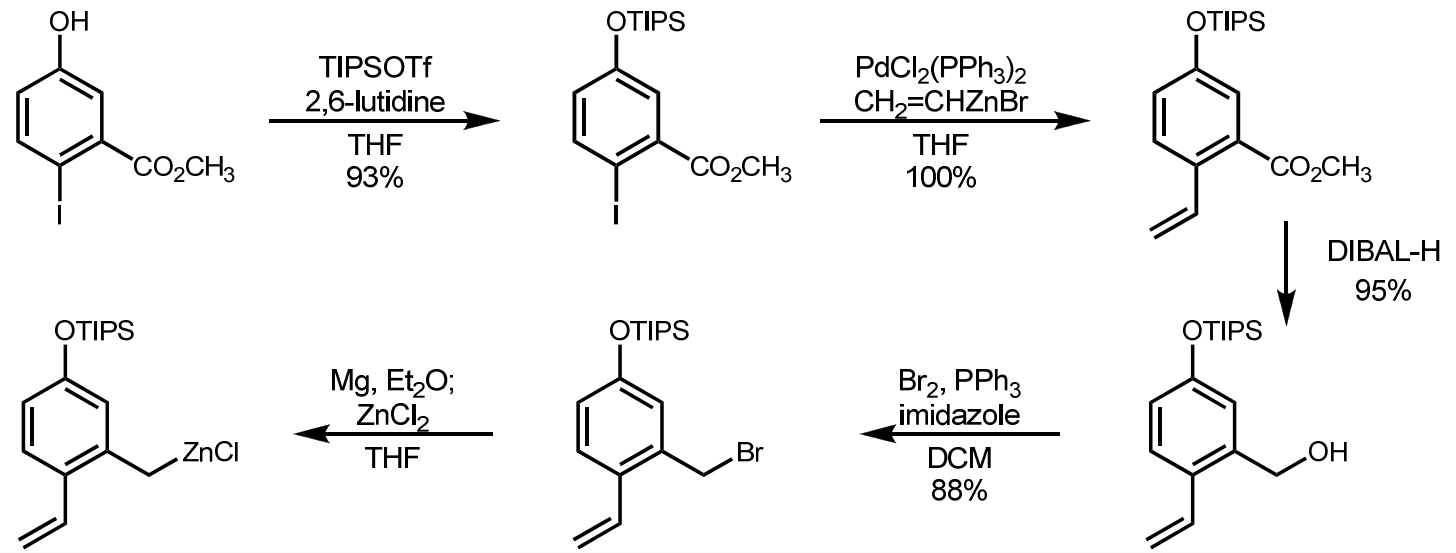
- $PtCl_2$ Catalyzed Cycloisomerization



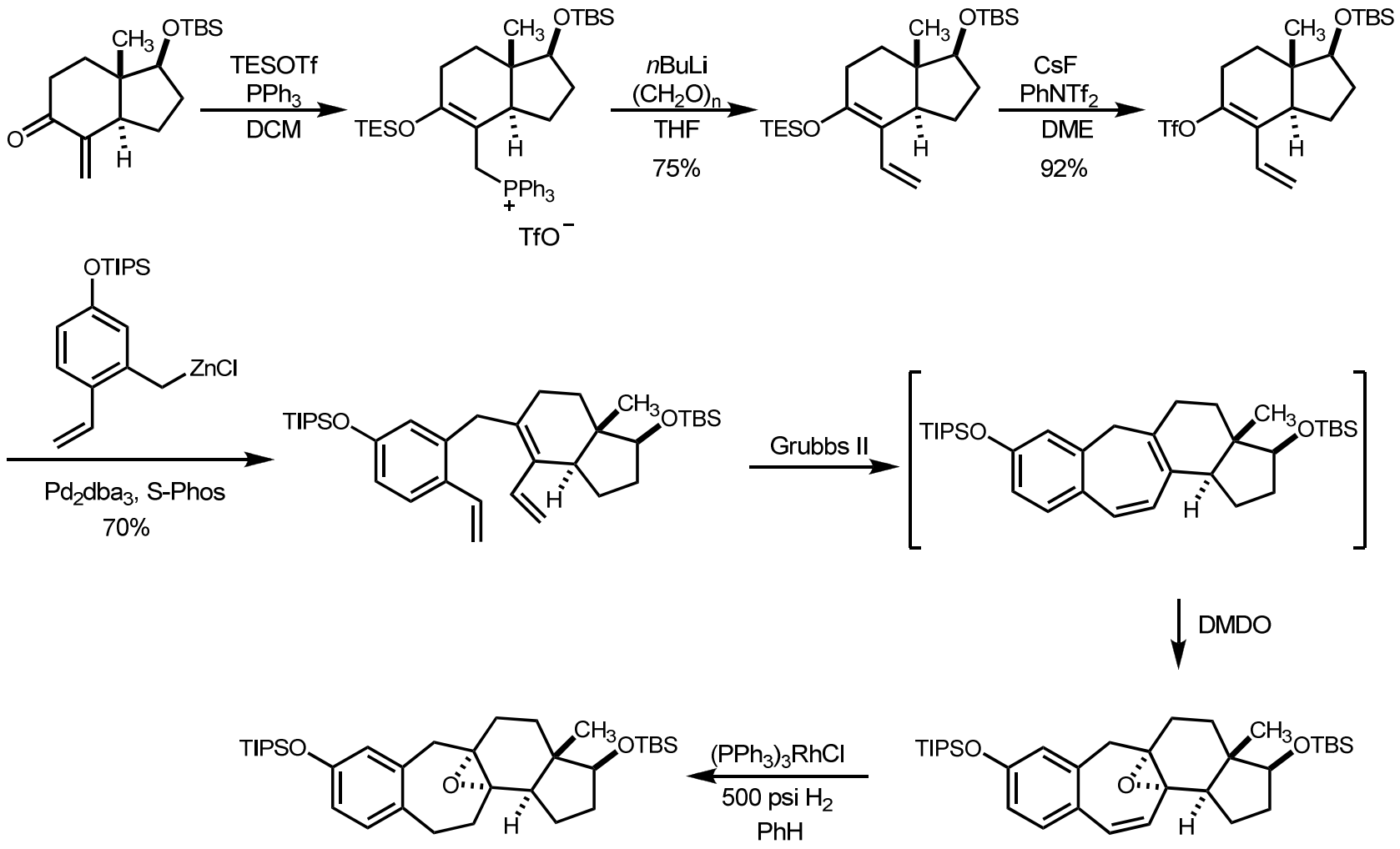
Sapong, *Angew. Chem., Int. Ed.*, **2008**, *47*, 6650

Retrosynthetic Disconnection and o-Vinyl Benzylzinc reagent Preparation

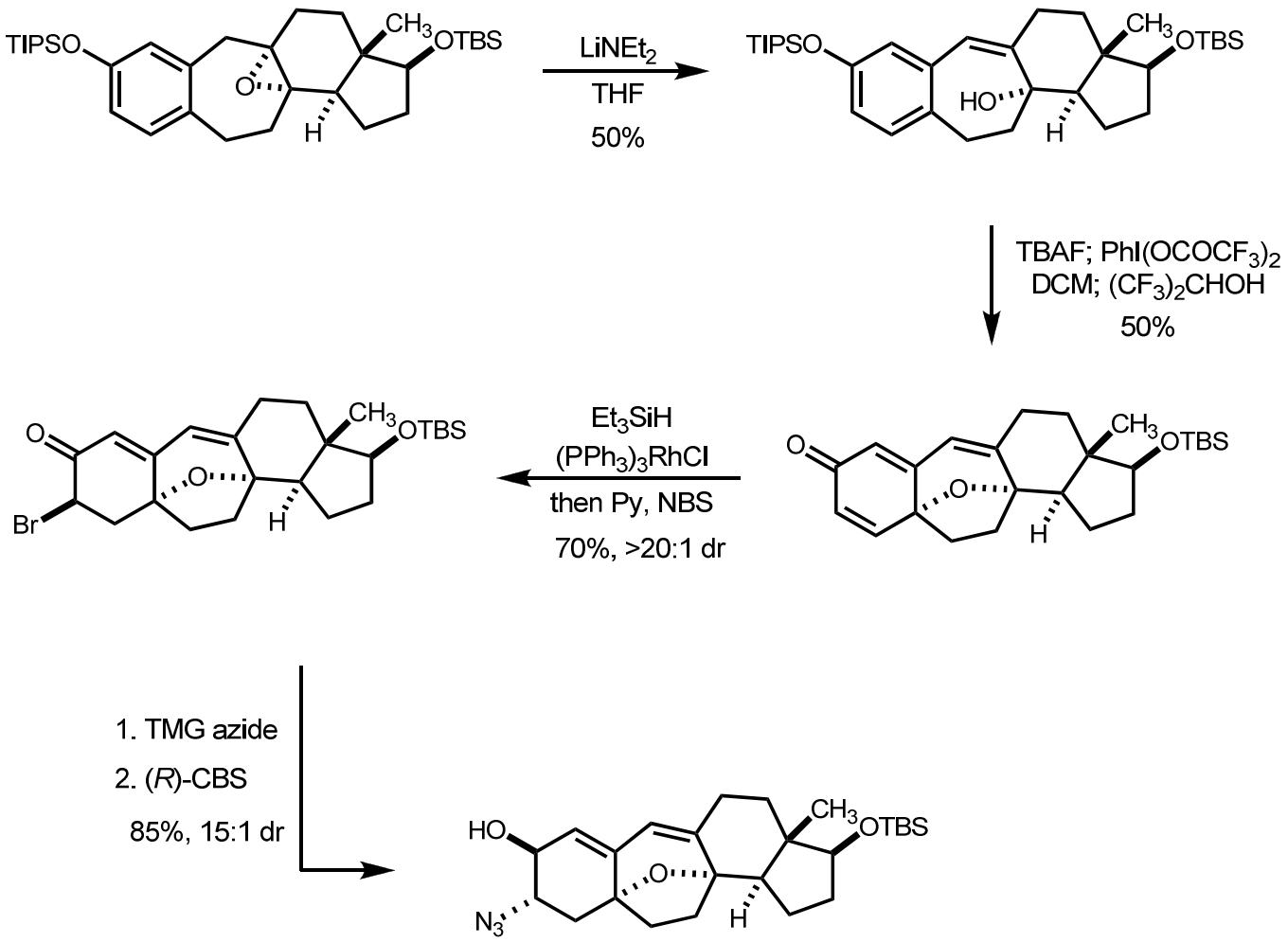




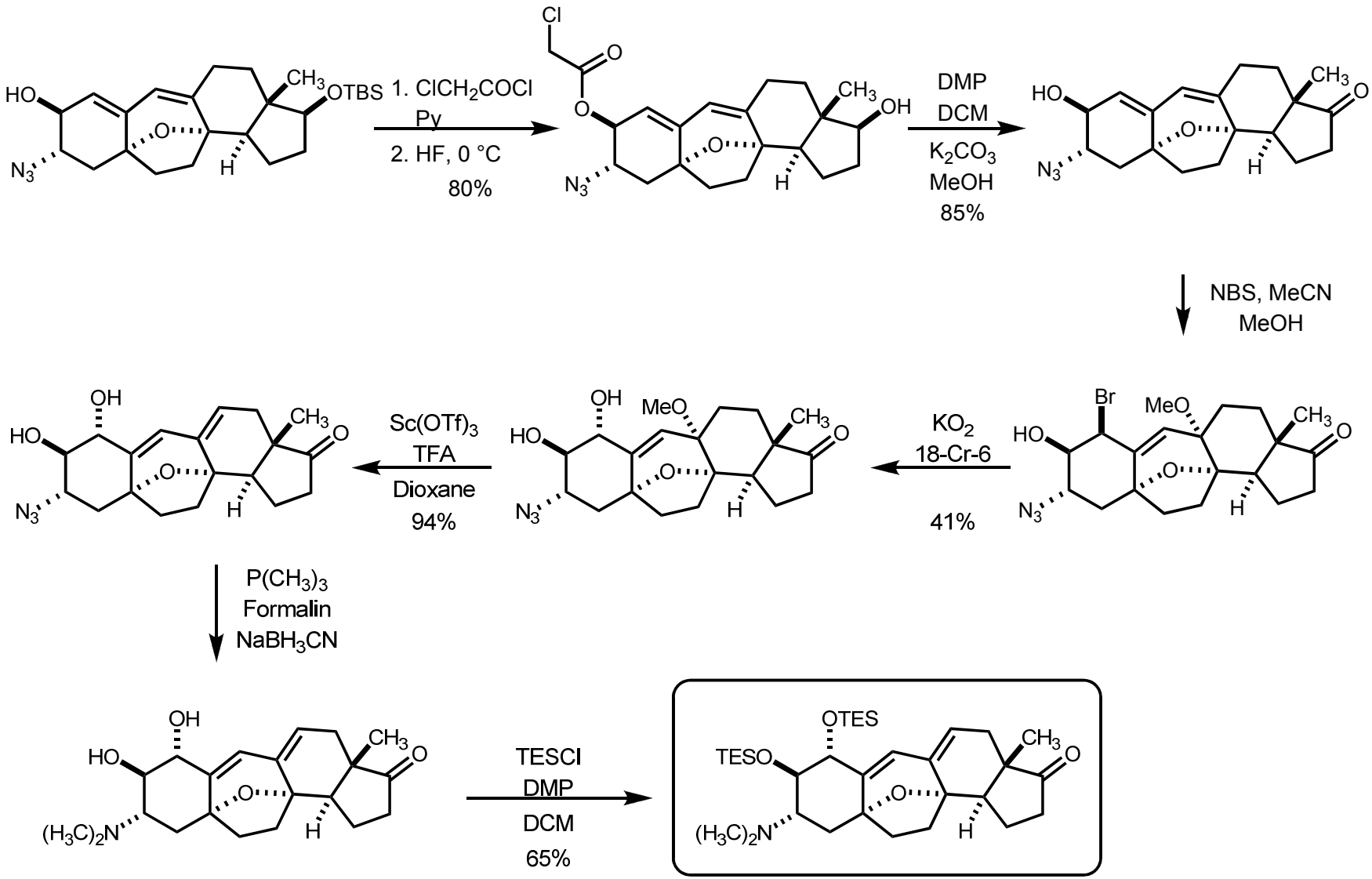
Synthesis of Azido Alcohol from α-Methylene Ketone - 1



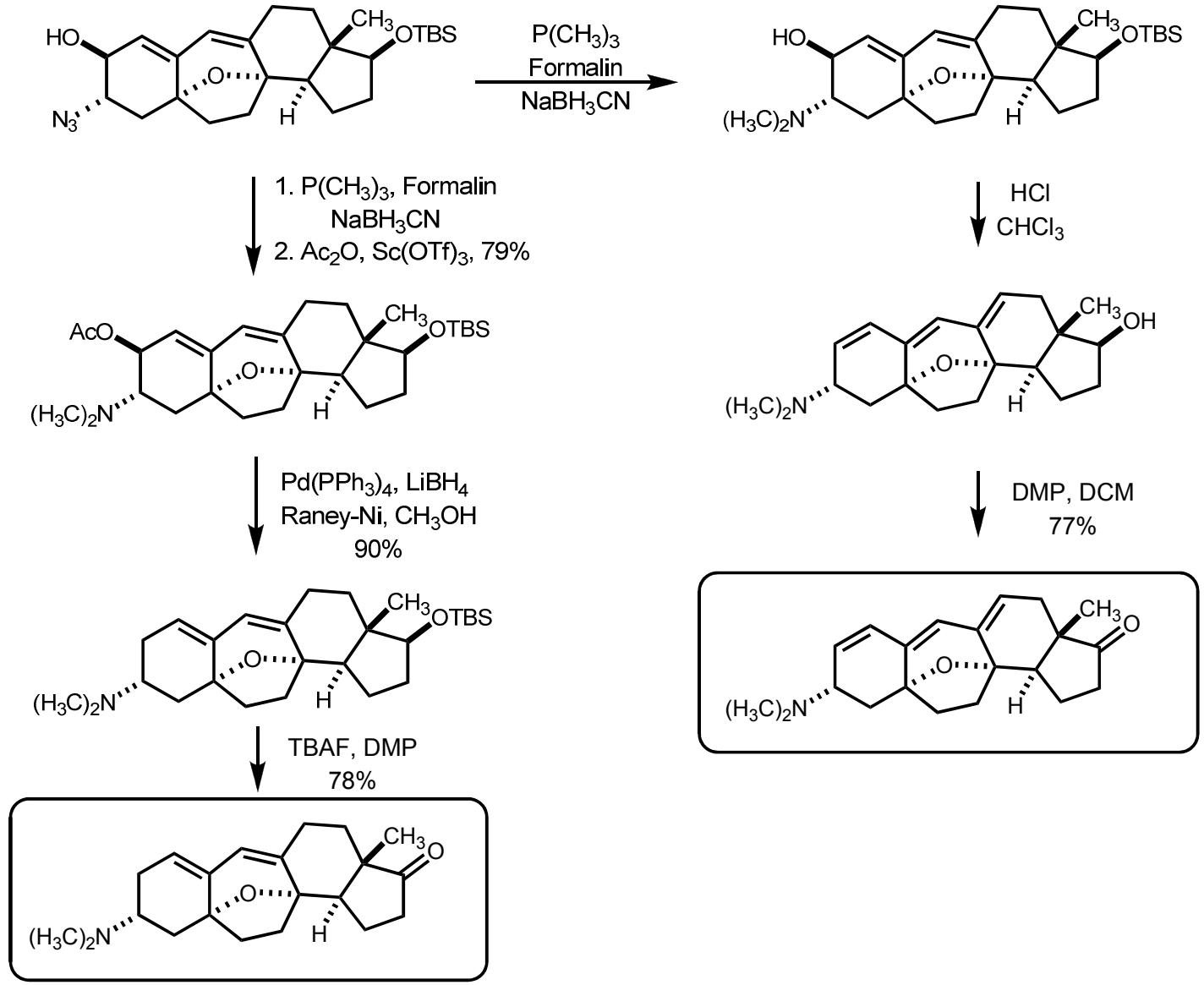
Synthesis of Azido Alcohol from α-Methylene Ketone - 2



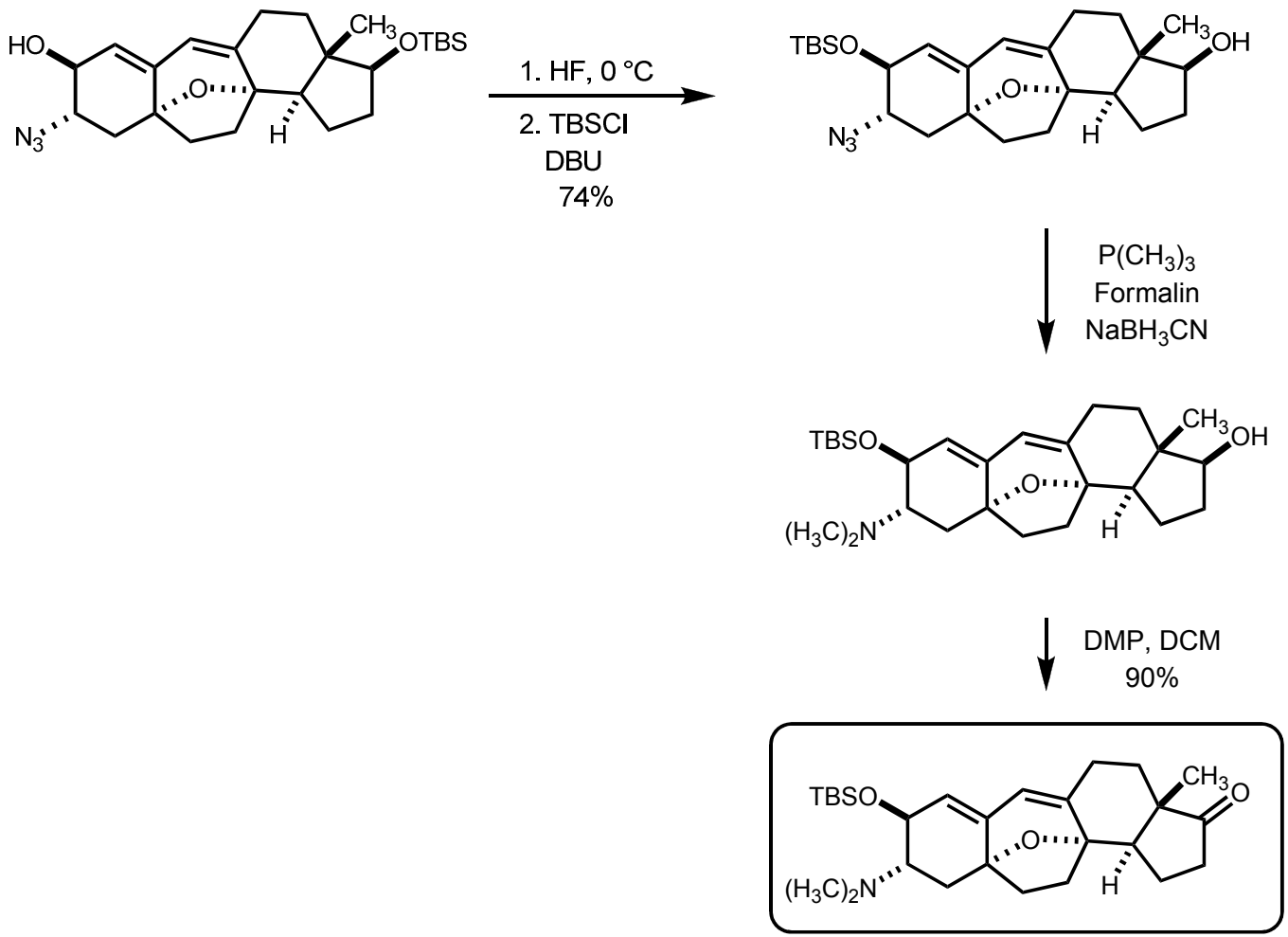
Cortistatin A Series



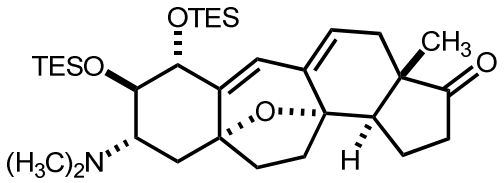
Cortistatin J, K Series



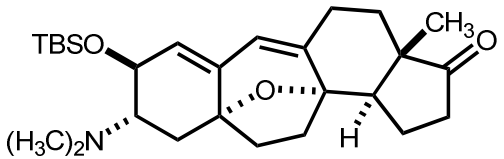
Cortistatin L Series



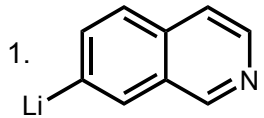
Synthesis of Cortistatins A, L, J and K



A precusor

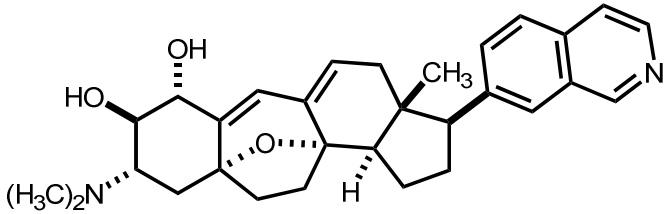


L precusor

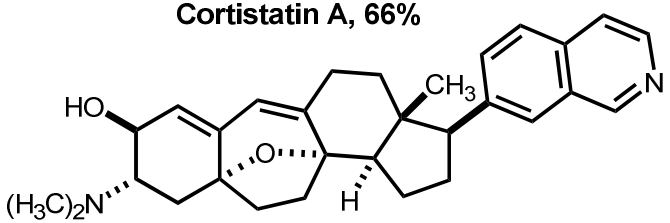


TMEDA, THF, -78 °C

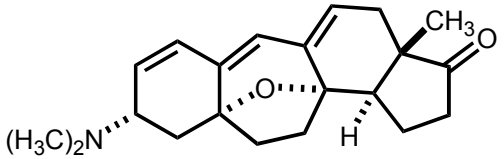
2. TFAA, Py, DMAP
3. Bu_3SnH, AIBN
4. TBAF



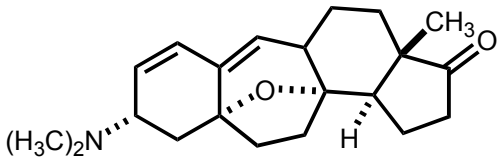
Cortistatin A, 66%



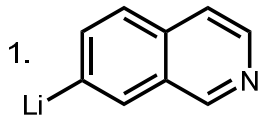
Cortistatin L, 72%



J precusor



K precusor



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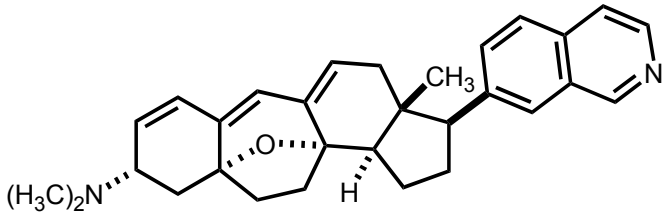
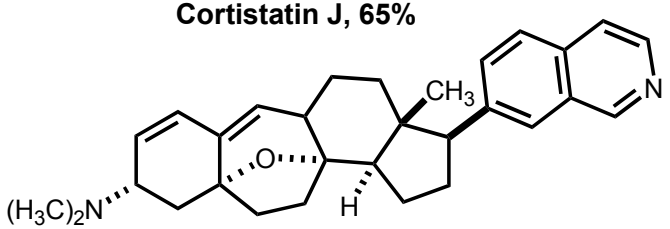
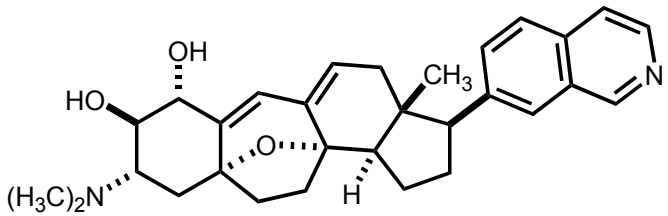


Cortistatin J, 65%

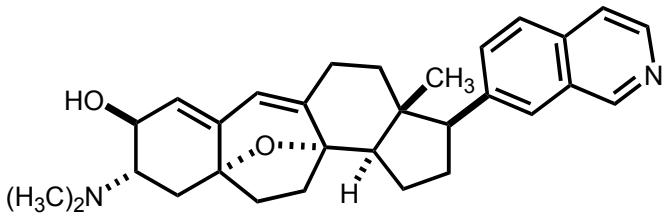


Cortistatin K, 65%

Conclusions



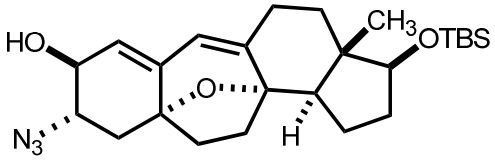
Cortistatin A



Cortistatin L

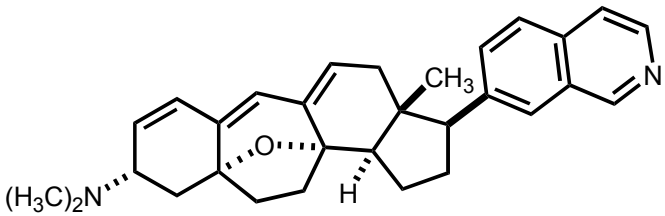
12 steps

8 steps

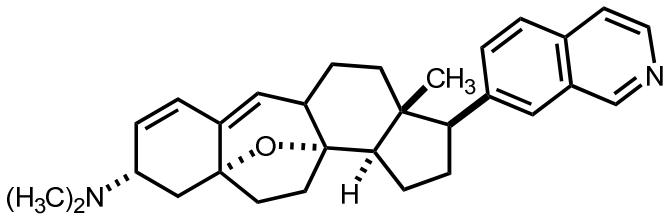


6 steps

8 steps



Cortistatin J



Cortistatin K