Enantioselective Total Synthesis of Guanacastepene N Using an Uncommon 7-Endo Heck Cyclization as a Pivotal Step

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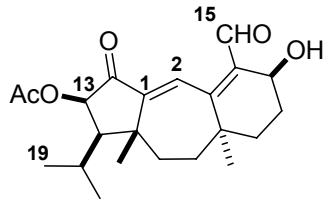
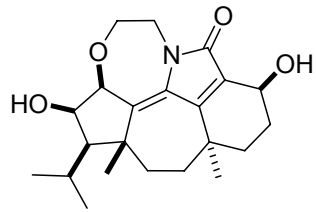
Stephan Elzner
September 30, 2006

Guanacastepenes - Structure

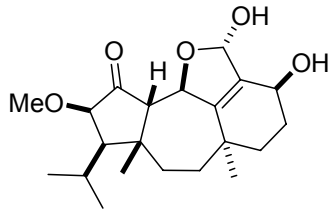
- Structures of the Guanacastepenes were reported by Clardy in 2000-2001
- Isolated from an endophytic fungus from a branch of *Daphnopsis americana* collected in Guatemala
- 15 compounds belonging to this family of natural products were isolated from the same fungus (guanacastepenes A-O)
- Structure: Diterpenes with a previously undescribed molecular architecture consisting of an 5-7-6 tricyclic carbon skeleton with a highly functionalized upper half



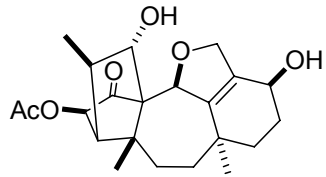
guanacastepene A



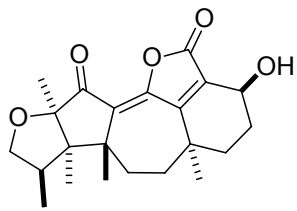
guanacastepene H



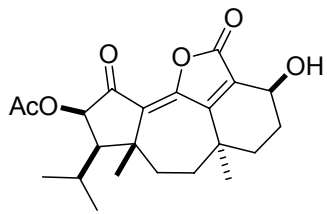
guanacastepene I



guanacastepene K



guanacastepene L

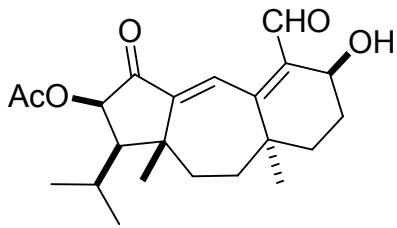


guanacastepene N

Clardy, *J. Am. Chem. Soc.* **2000**, *122*, 2116
Clardy, *J. Am. Chem. Soc.* **2001**, *123*, 9900

Guanacastepenes

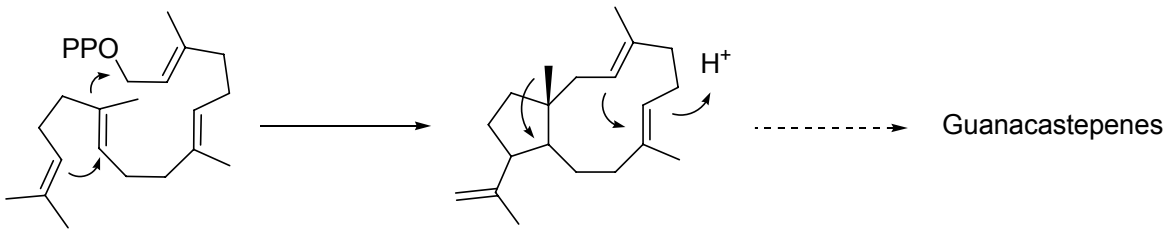
- Biological activity: Guanacastepenes A and I show antibacterial activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*. Further studies showed damage to human red blood cells, diminishing the therapeutic feasibility.



guanacastepene A

- More than 10 distinct approaches towards the synthesis of these molecules have been reported since 2001 and 4 total syntheses were completed.

Proposed biosynthesis:

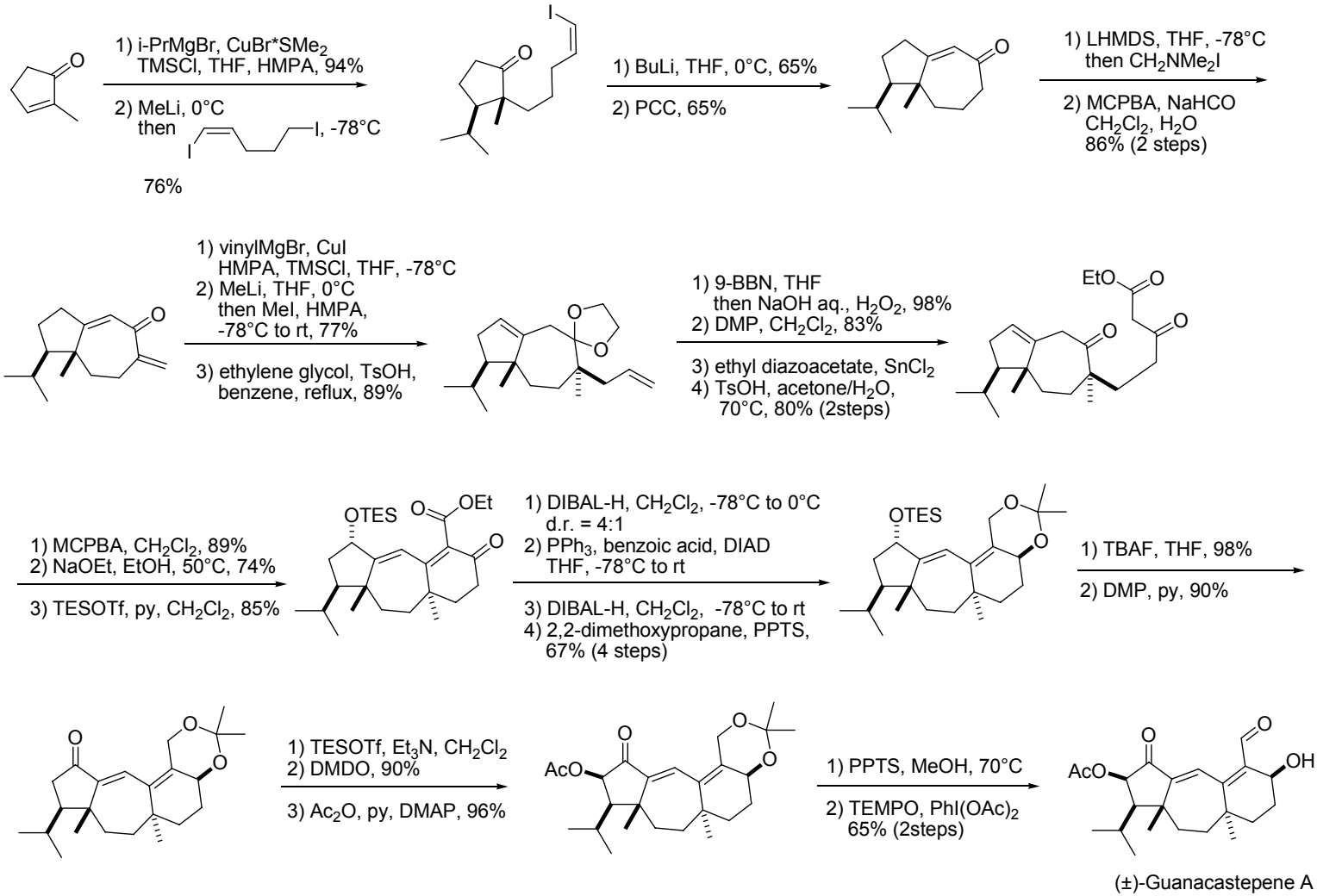


geranygeranyl pyrophosphate

dolastane

Clardy, *J. Am. Chem. Soc.* **2000**, *122*, 2116
Clardy, *J. Antibiot.* **2000**, *53*, 256
Clardy, *J. Am. Chem. Soc.* **2001**, *123*, 9900
Rodriguez, *Tetrahedron* **1998**, *54*, 11683

First Racemic Synthesis of Guanacastepene A (Danishefsky)

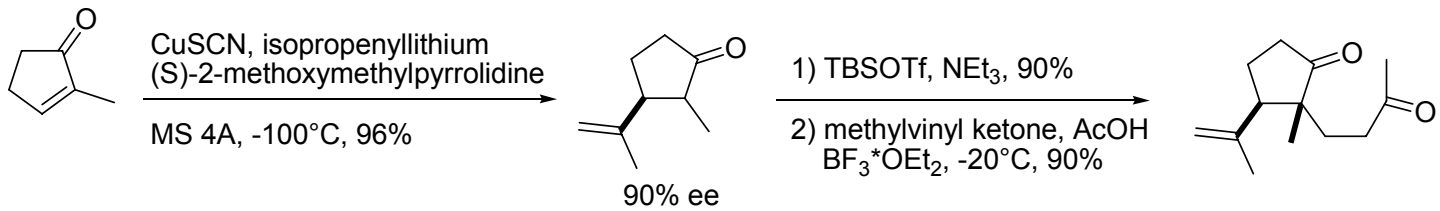


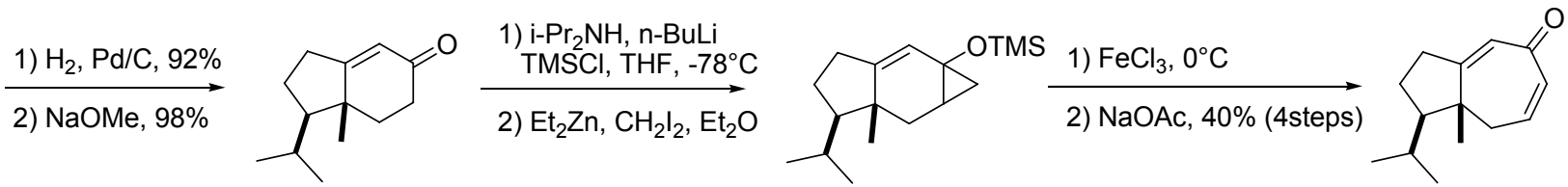
(±)-Guanacastepene A

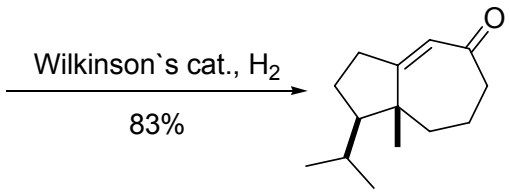
OL **2001**, *3*, 2399
Angew. Int. Ed. **2002**, *41*, 2185
Angew. Int. Ed. **2002**, *41*, 2188

Formal Enantioselective Total Synthesis (Danishefsky)

Synthesis of chiral intermediate



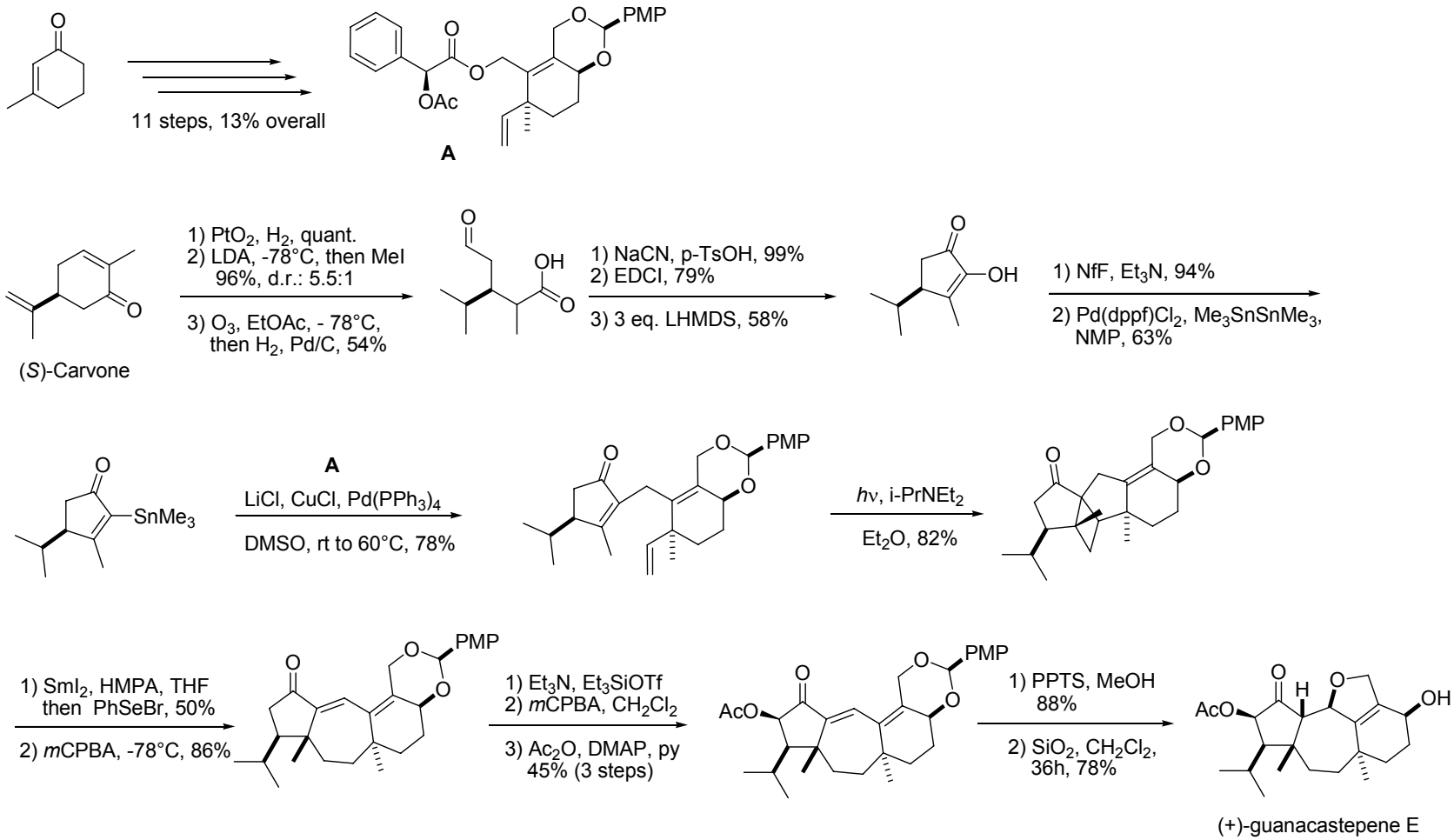




J. Org. Chem. **2005**, *70*, 10620

(+)-Guanacastepene E

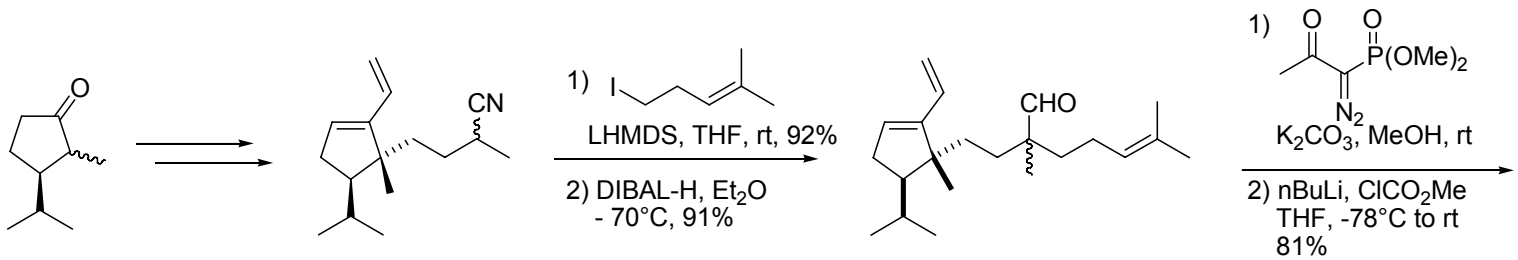
Sorensen: 2+2-Cycloaddition and Reductive Fragmentation

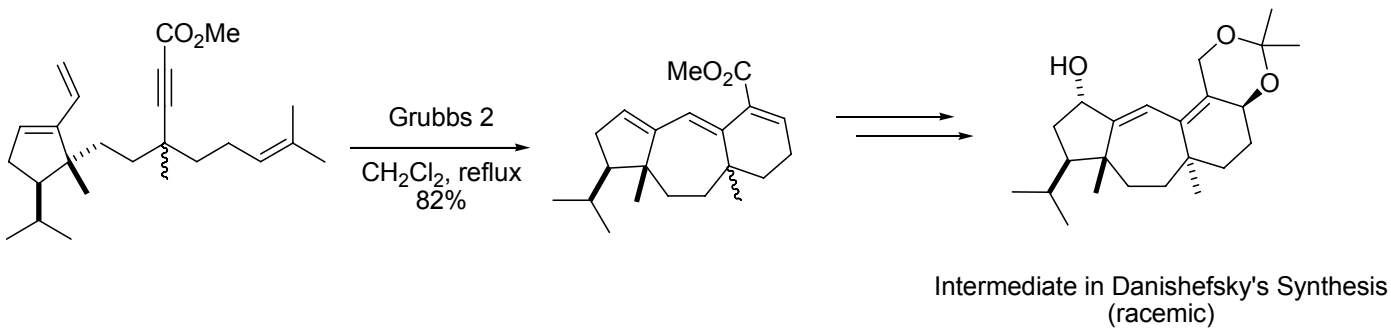


Org. Lett. **2002**, *4*, 2063
J. Am. Chem. Soc. **2006**, *128*, 7025

Core Synthesis of Guanacastepene A

Hanna : Tandem Ring Closing Metathesis



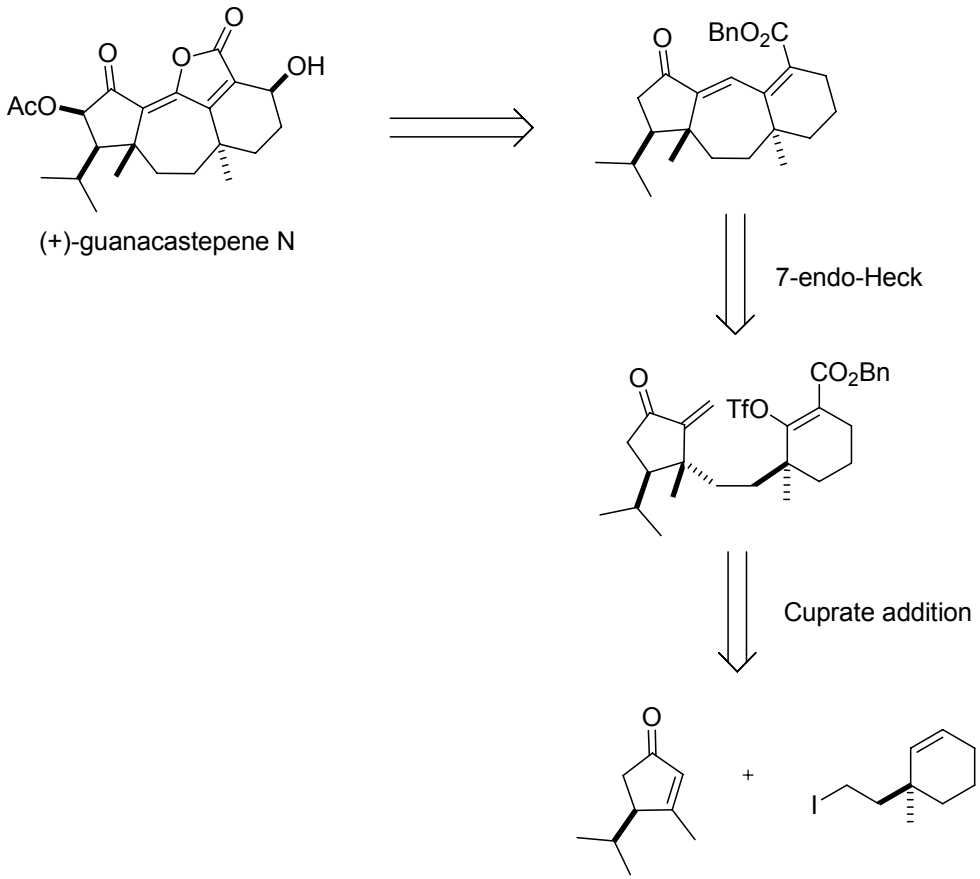


Intermediate in Danishefsky's Synthesis
(racemic)

Org. Lett. **2004**, *6*, 1817

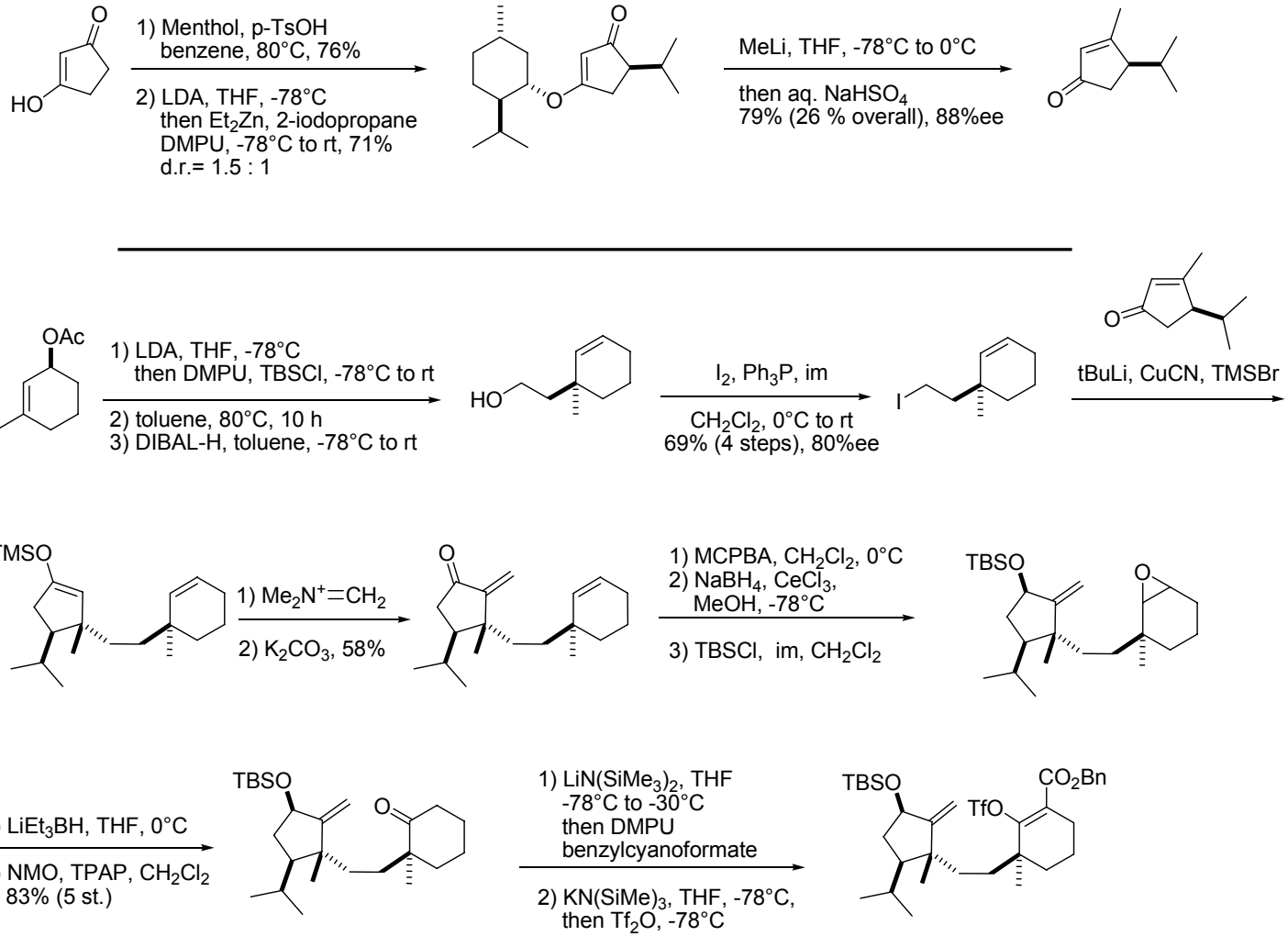
Overman – Total Synthesis of (+)-Guanacastepene N

Retrosynthesis



J. Am. Chem. Soc **2006**, ASAP

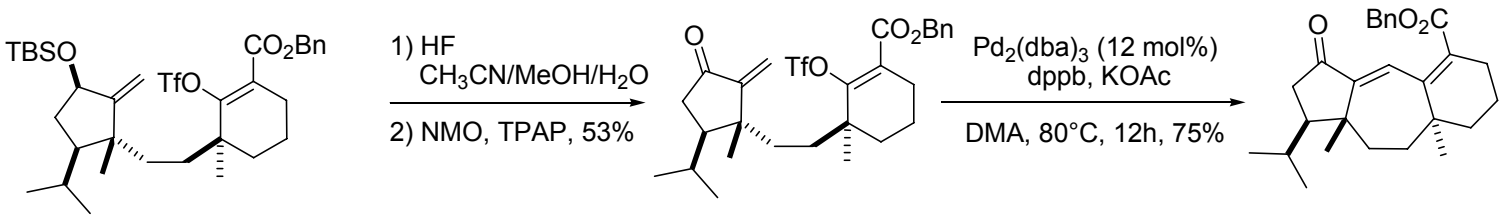
Total Synthesis of (+)-Guanacastepene N



J. Am. Chem. Soc **2006**, ASAP

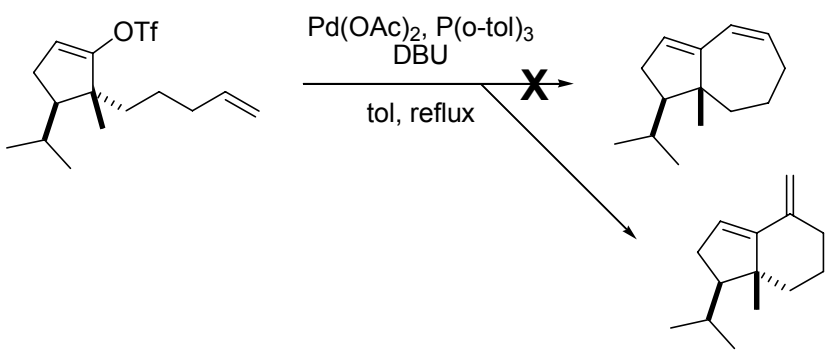
Total Synthesis of (+)-Guanacastepene N

7-Endo-Heck Cyclization

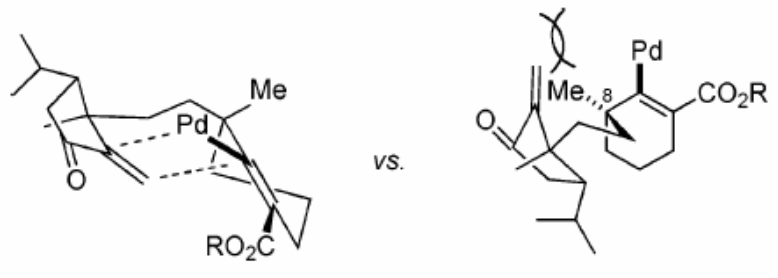


Mechanism

The 6-exo-cyclization is usually favored over the 7-endo, unless the 6-exo cyclization leads to an intermediate lacking β-hydrogen or a sterically disfavored eclipsed conformation in the transition state.

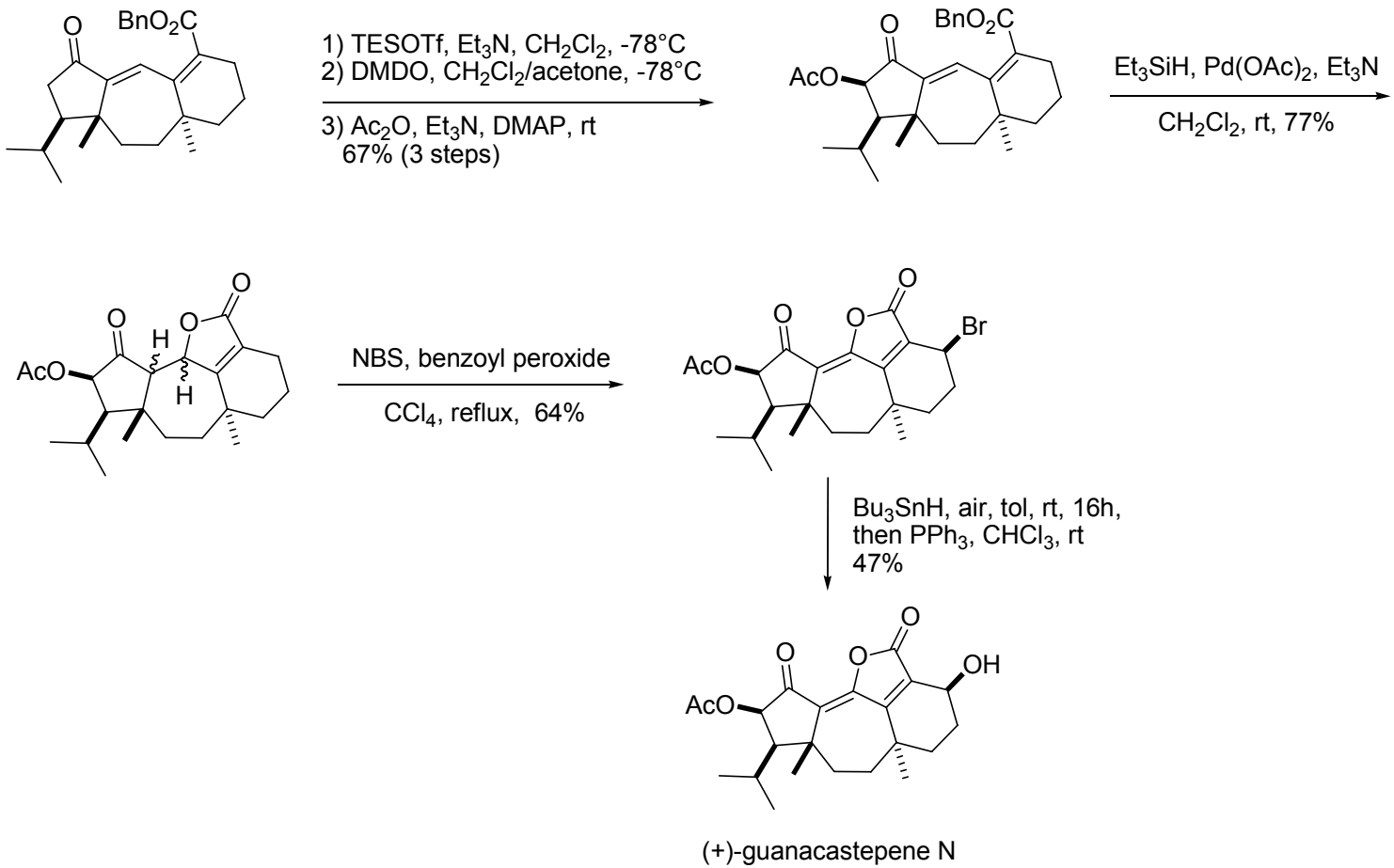


Snider, *OL* **2001**, *4*, 2063



J. Am. Chem. Soc **2006**, ASAP

Total Synthesis of (+)-Guanacastepene N



(+)-guanacastepene N

J. Am. Chem. Soc **2006**, ASAP

Conclusion

- An enantioselective total synthesis of guanacastepene N was accomplished in 25 steps (22 longest linear)
- Key steps in the synthesis included:
  - (1) Sterically challenging conjugate addition
  - (2) 7-endo Heck cyclization
- This synthetic strategy allows access to other members of the guanacastepene family as well as analogues of the natural product