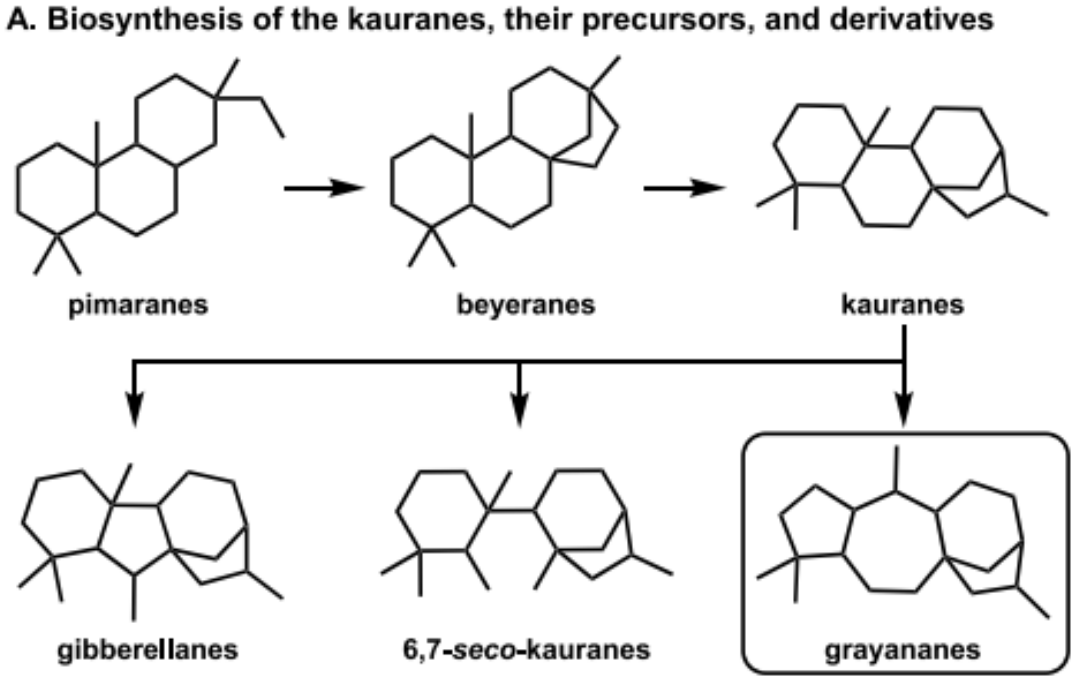
Convergent Total Synthesis of Principinol D, a Rearranged Kaurane Diterpenoid

Turlik, A. ; Chen Y.; Scruse A. C.; Newhouse T.R. Yale University ***J. Am. Chem. Soc. 2019, 141, 8088−8092***



Grayananes diterpenoids are among a broader class of rearranged kauranes . They are formed by rearrangement of the kaurane 6,6- ring system to a 5,7-ring system.

The kauranes are derived from rearrangement and cyclization of pimaranes via the beyeranes

Grayananes diterpenoids have recently been identified as structurally novel allosteric inhibitors of carbonic anhydrases and phosphatase

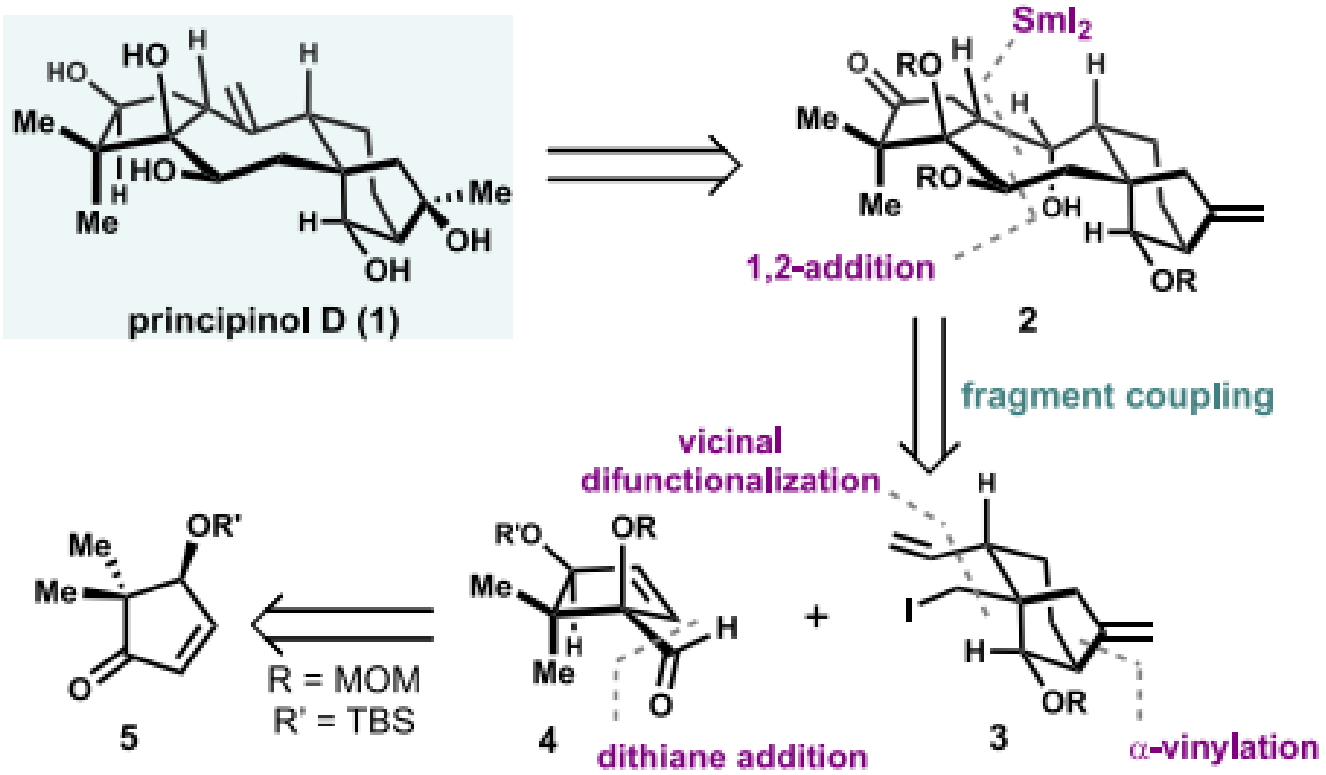
Potential therapeutic development could span numerous differentdisease areas from neurological dysfunction to cancer.

Synthetic efforts toward the grayananes have been especially limited to linear cyclization strategies.

Newhouse group speculated that a convergent retrosynthetic strategy, which isolates the two main constellations of stereocenters, would yield a laboratory route that could enable synthesis of grayanane analogs.

Herein, they report the first total synthesis of the grayanane analog principinol D

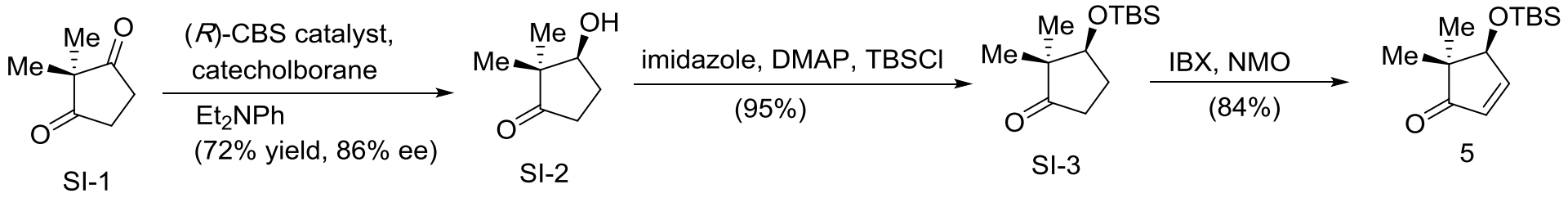
Retrosynthetic analysis: convergent approach



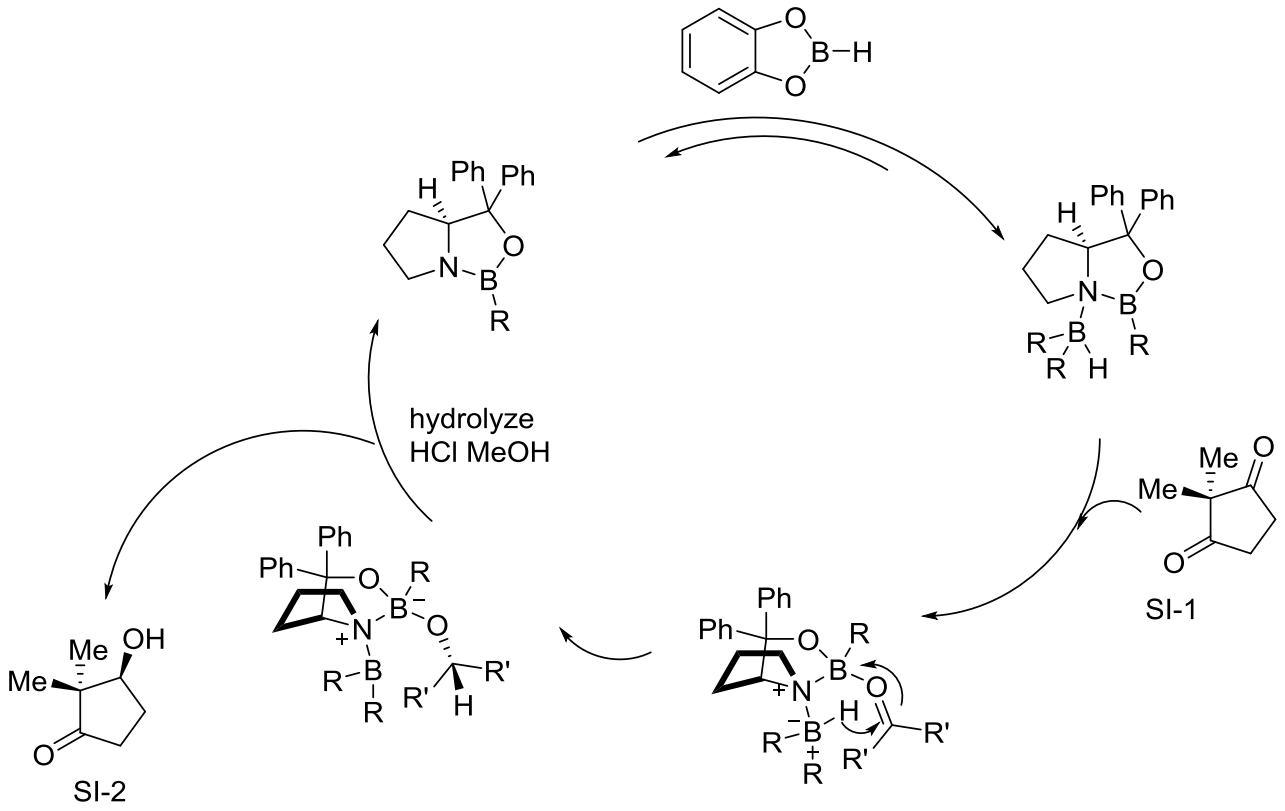
The principipinol D possess a highly oxidized tetracyclic framework, including a bicyclo[3.2.1]octane ring system.

Four stereocenters proximal to the left-most five-membered ring .
Additional five stereocenters that decorate the bicyclo[3.2.1]octane ring system.

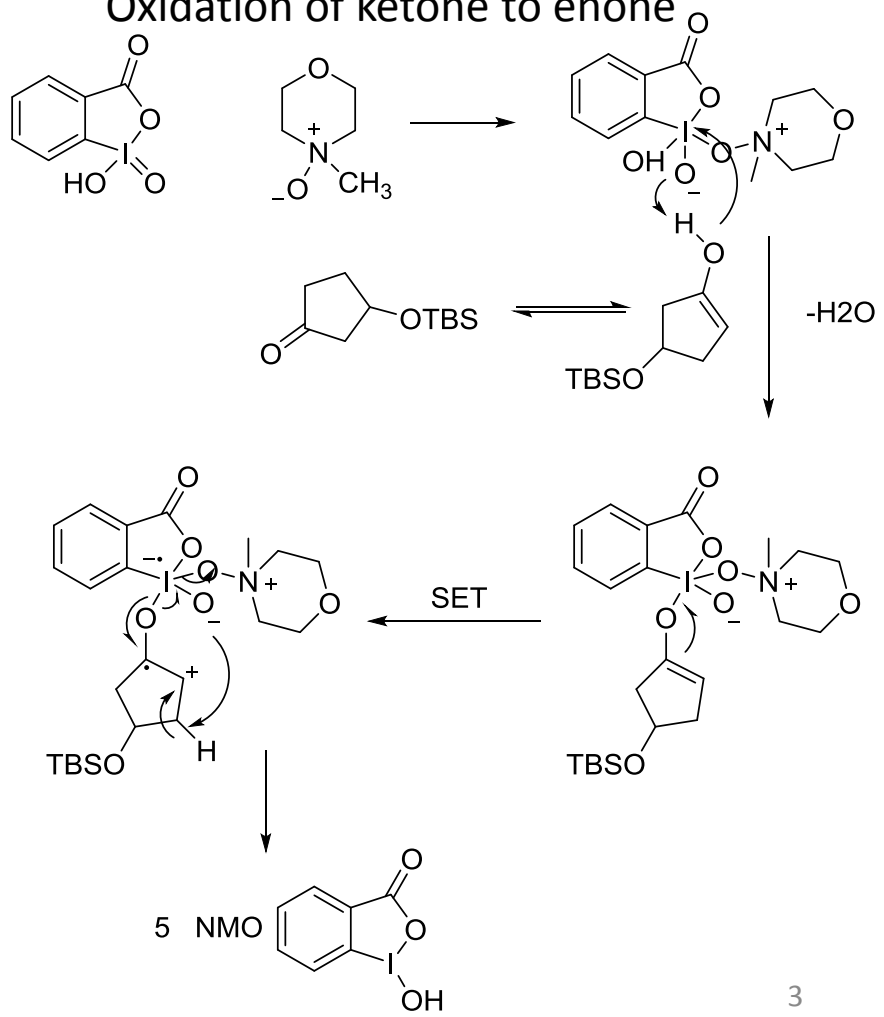
Synthesis of Cyclopentyl fragment **4** (SI)

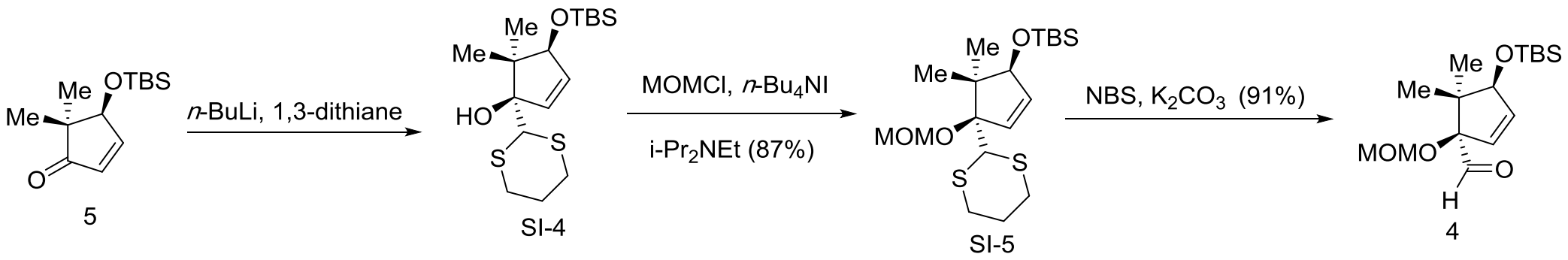


Corey-Bakshi-Shibata Reduction (Borane as reductant and oxazaborioidine as catalyst)

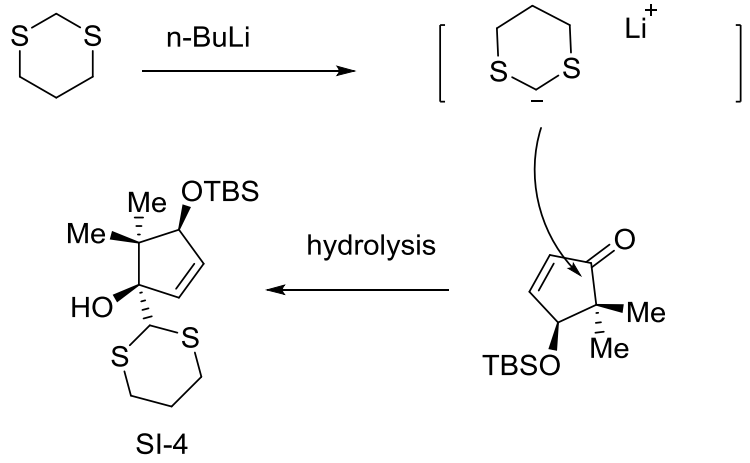


Oxidation of ketone to enone

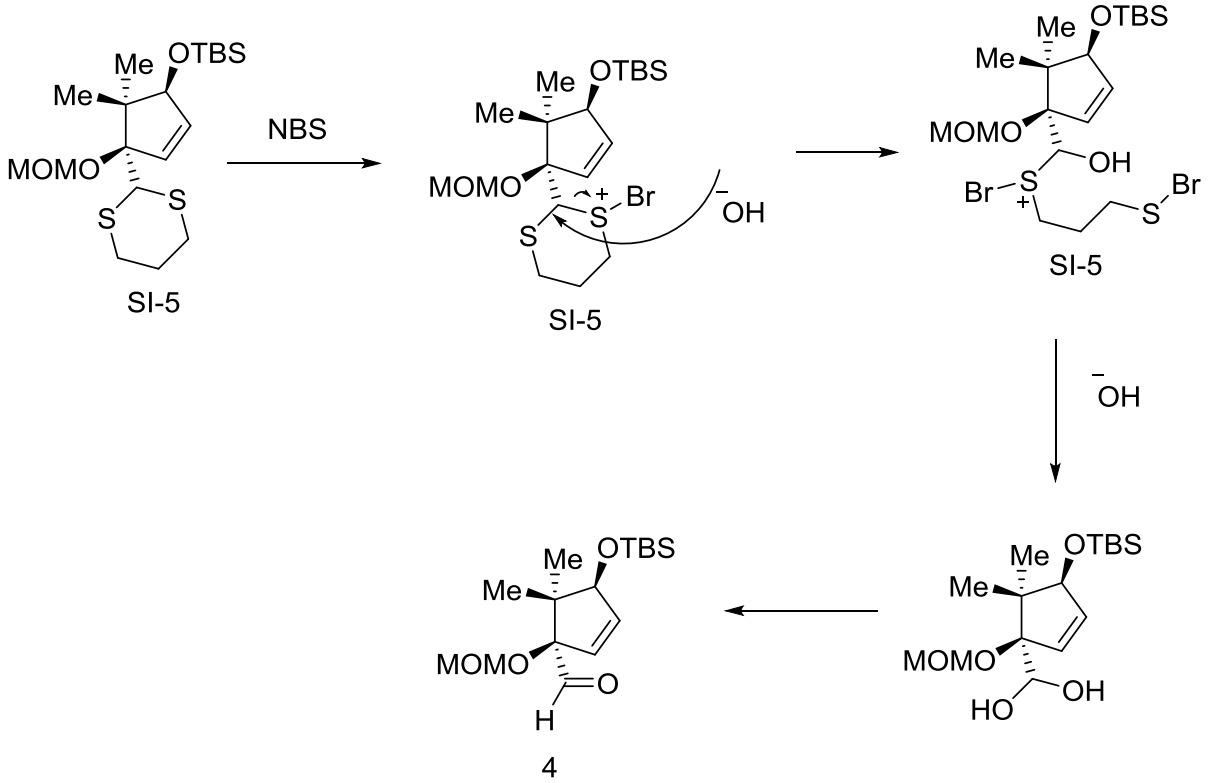




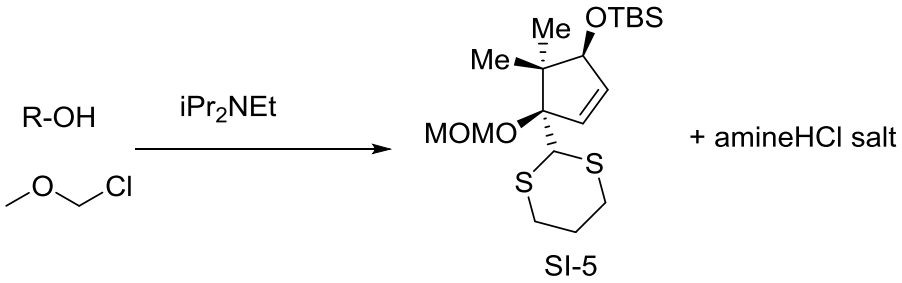
Dithiane addition



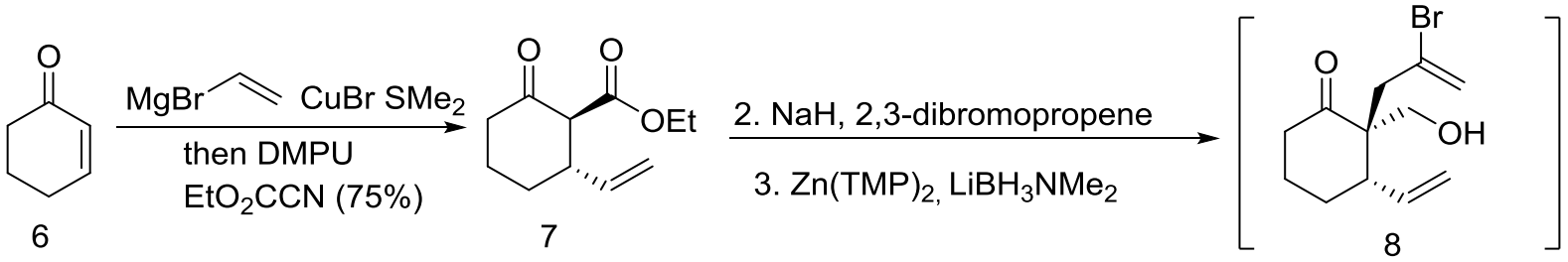
Dithiane deprotection



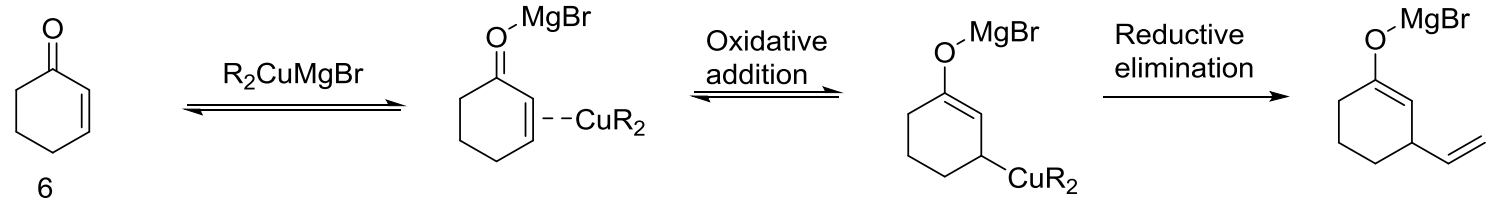
MOM protection

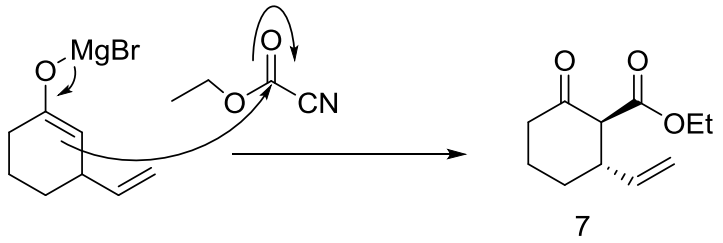


Synthesis of Bicyclo[3.2.1]octane Fragment Coupling Partner **3**

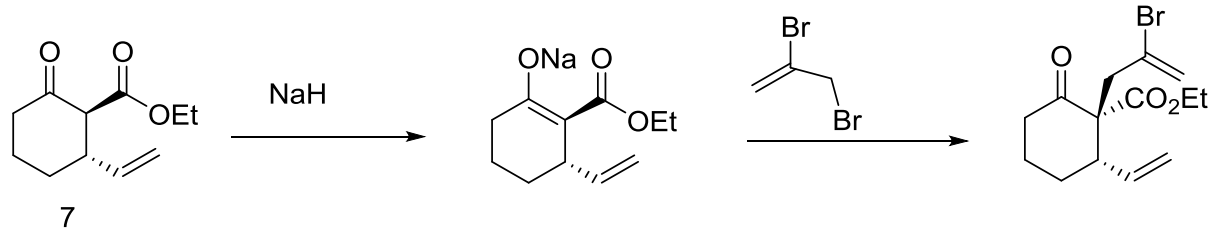


Vicinal difunctionalization

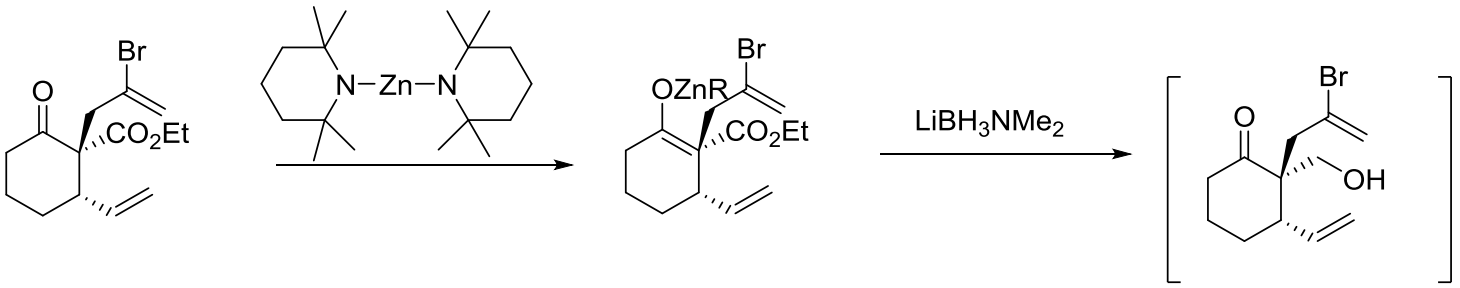


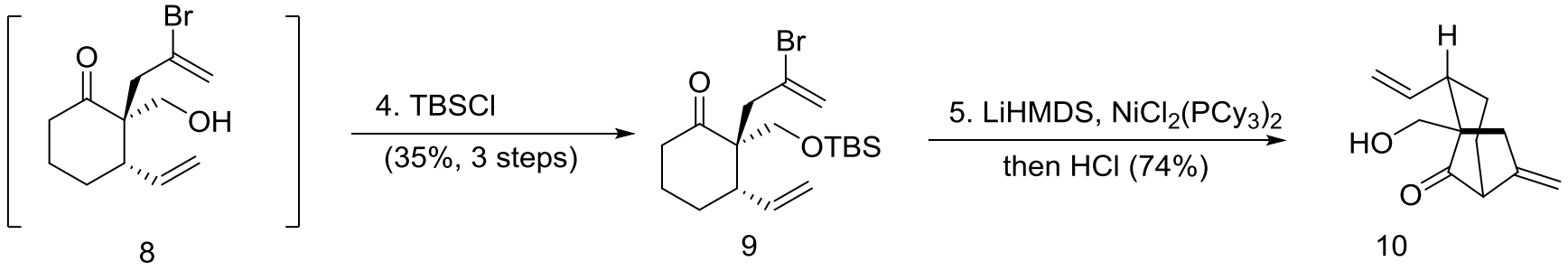


Allylation

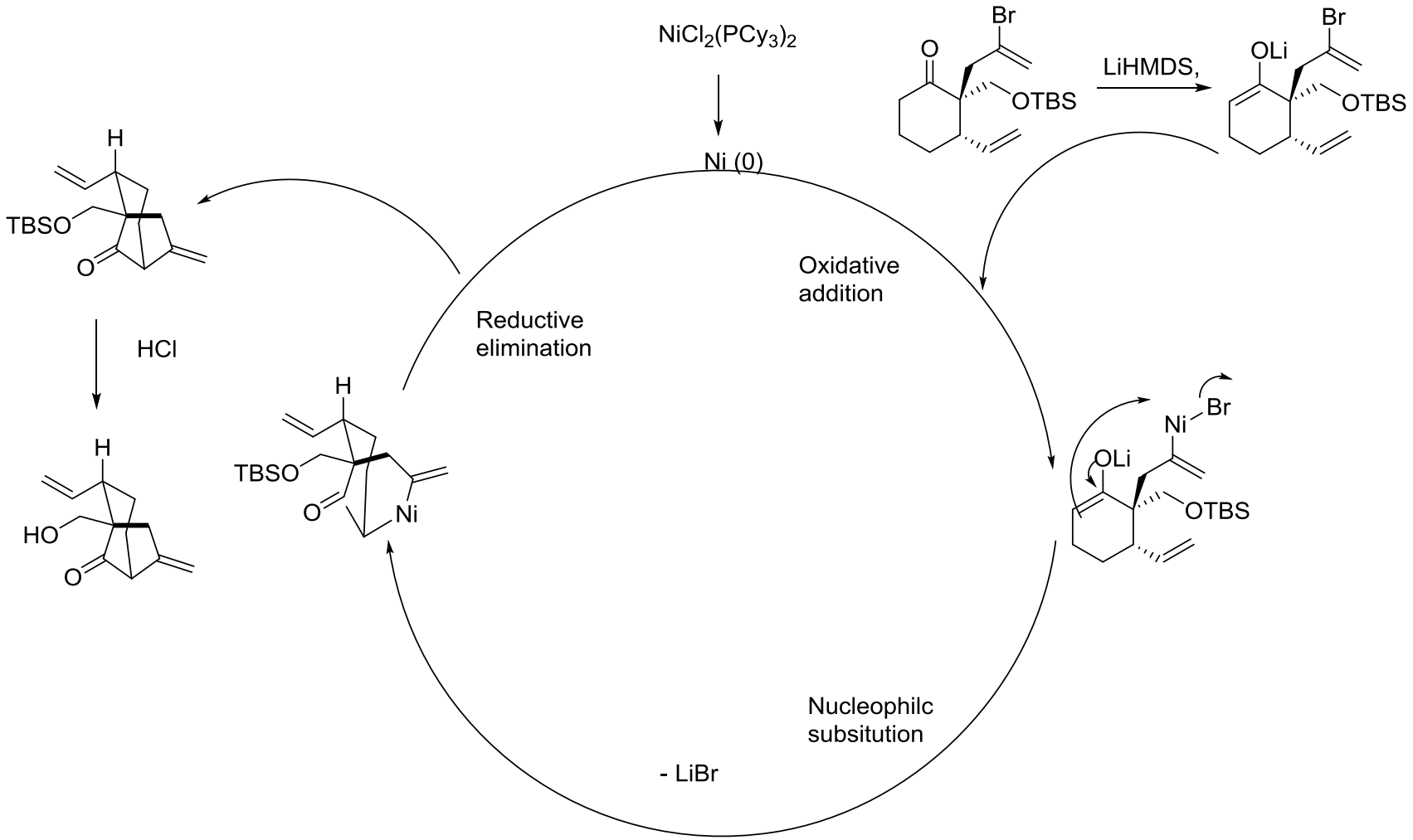


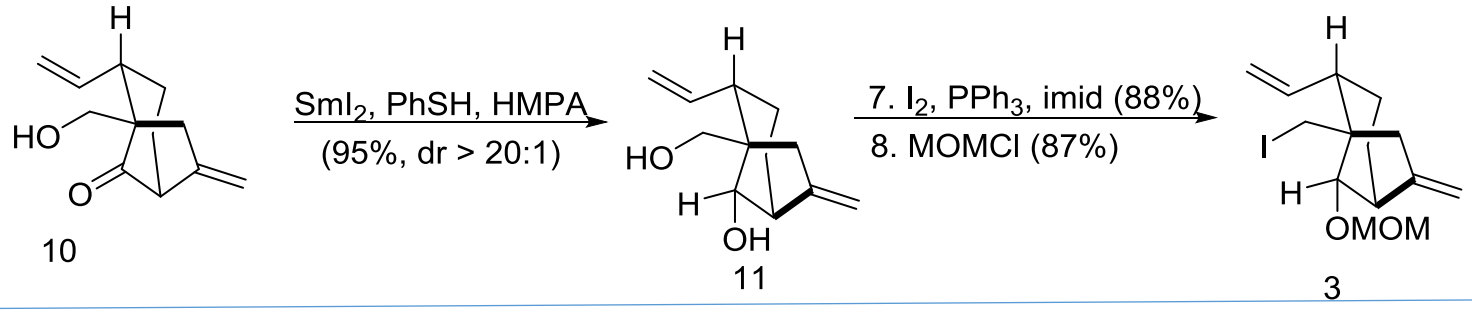
Selective reduction of esters in the presence of ketone



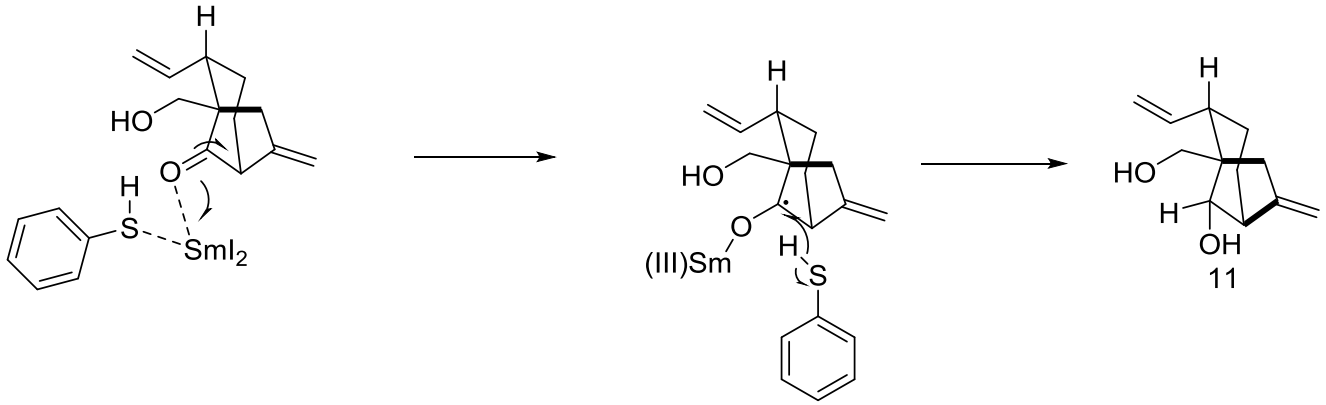


Ni catalyzed C-vinylation

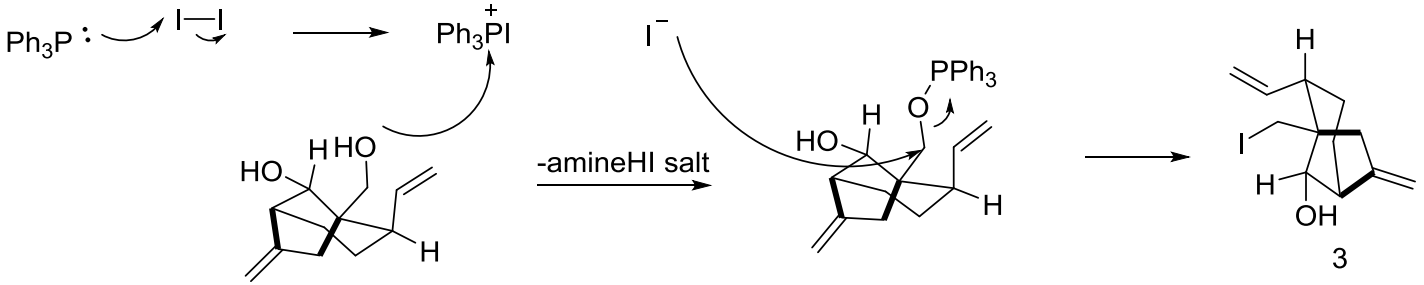




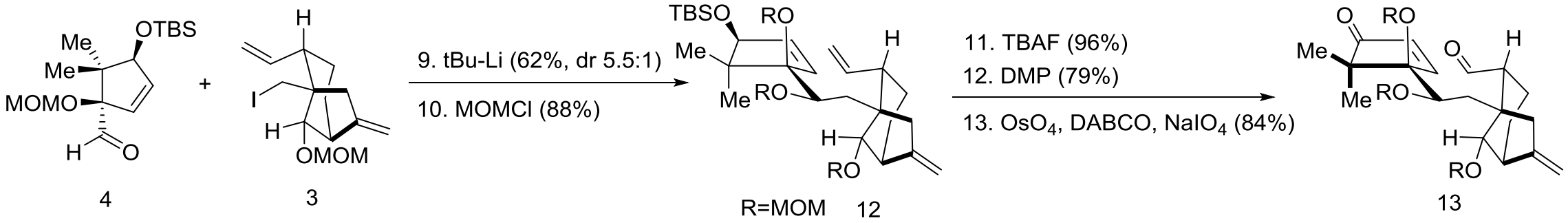
SmI2-mediated diastereoselective ketone reduction



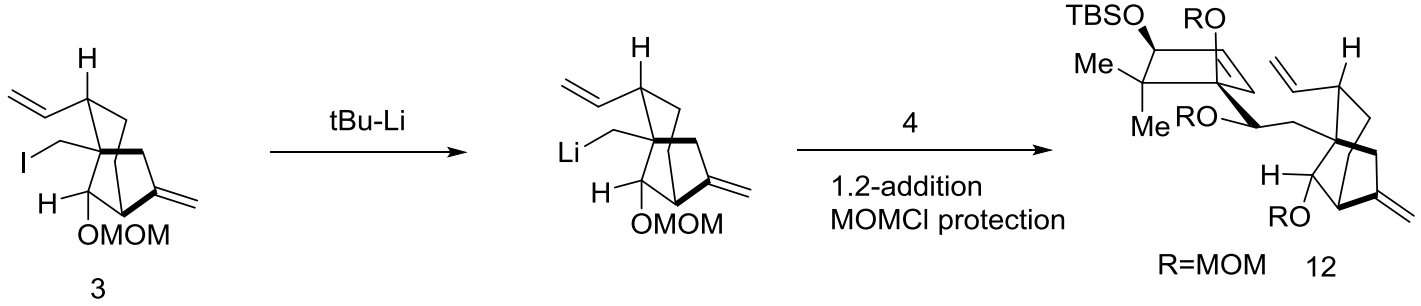
Appel reaction



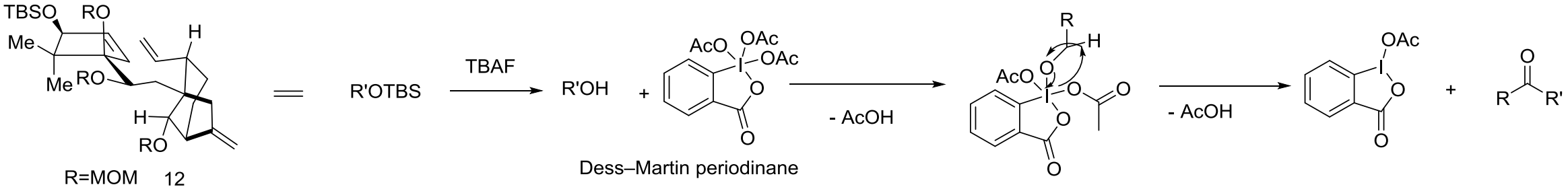
Total Synthesis of Principinol D (**1**) via Fragment Coupling and Reductive Cyclizationa



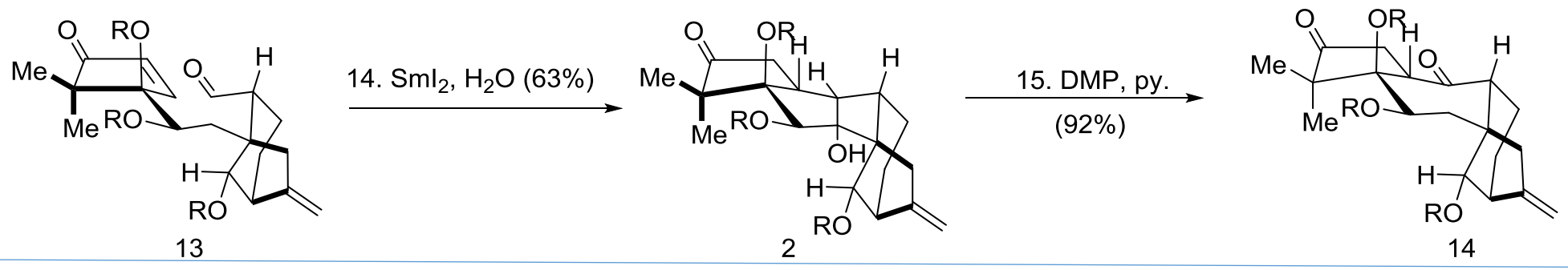
1,2-addition, MOM protection



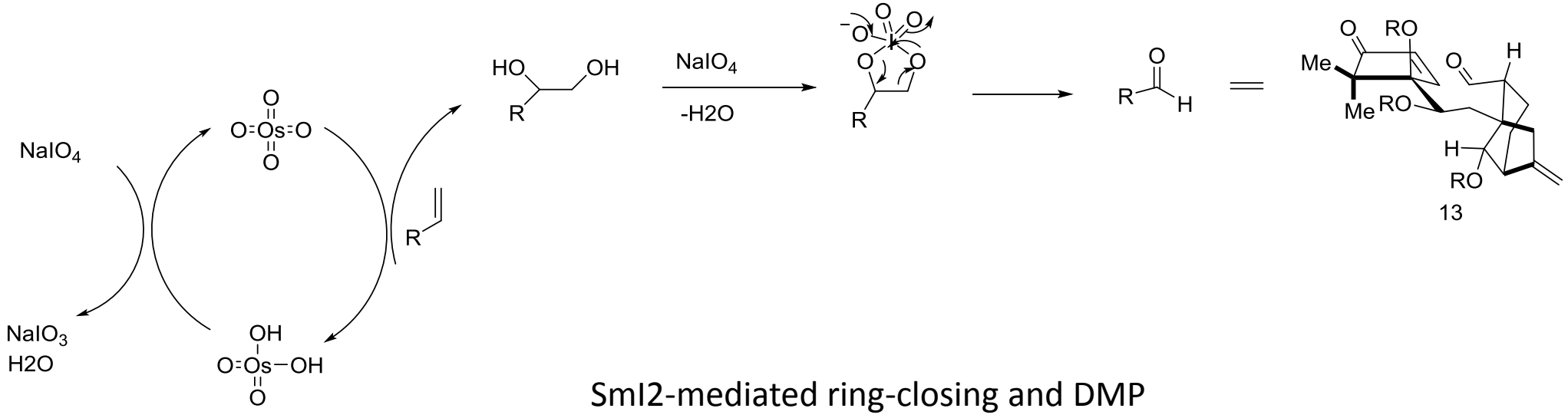
TBS deprotection and DMP



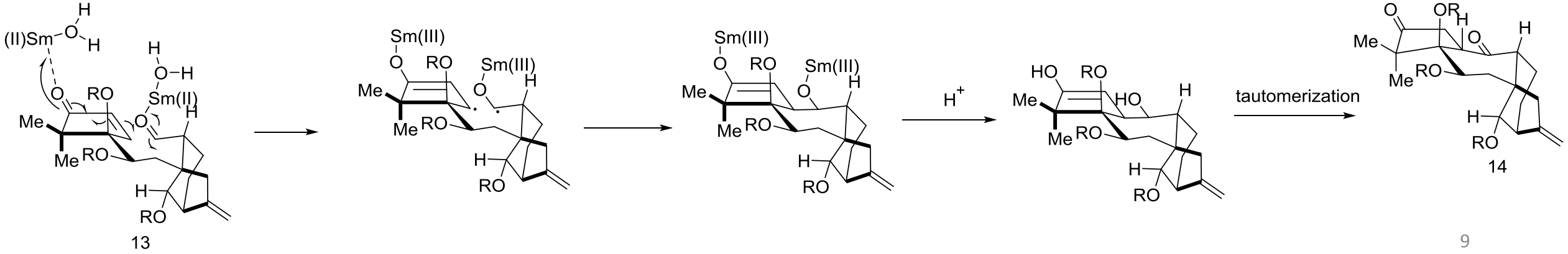
Selective oxidative cleavage of monosubstituted alkene (**<u>Mechanism see next page</u>**)

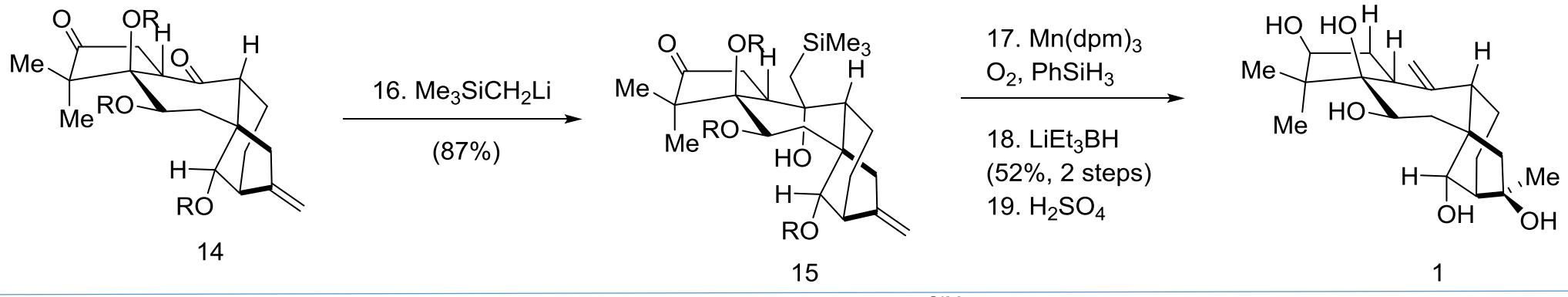


Selective oxidative cleavage of monosubstituted alkene (Lemieux-Johnson Oxidation)



SmI2-mediated ring-closing and DMP





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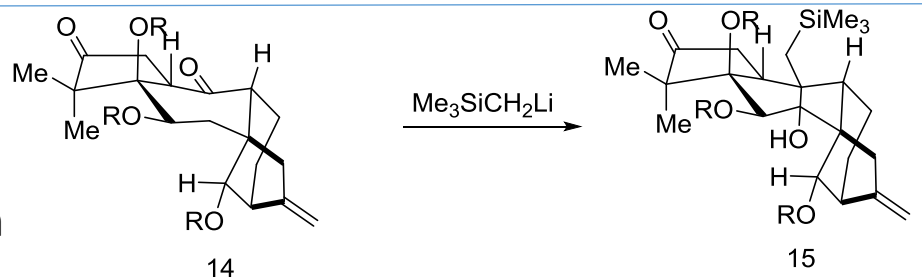
Peterson adduct



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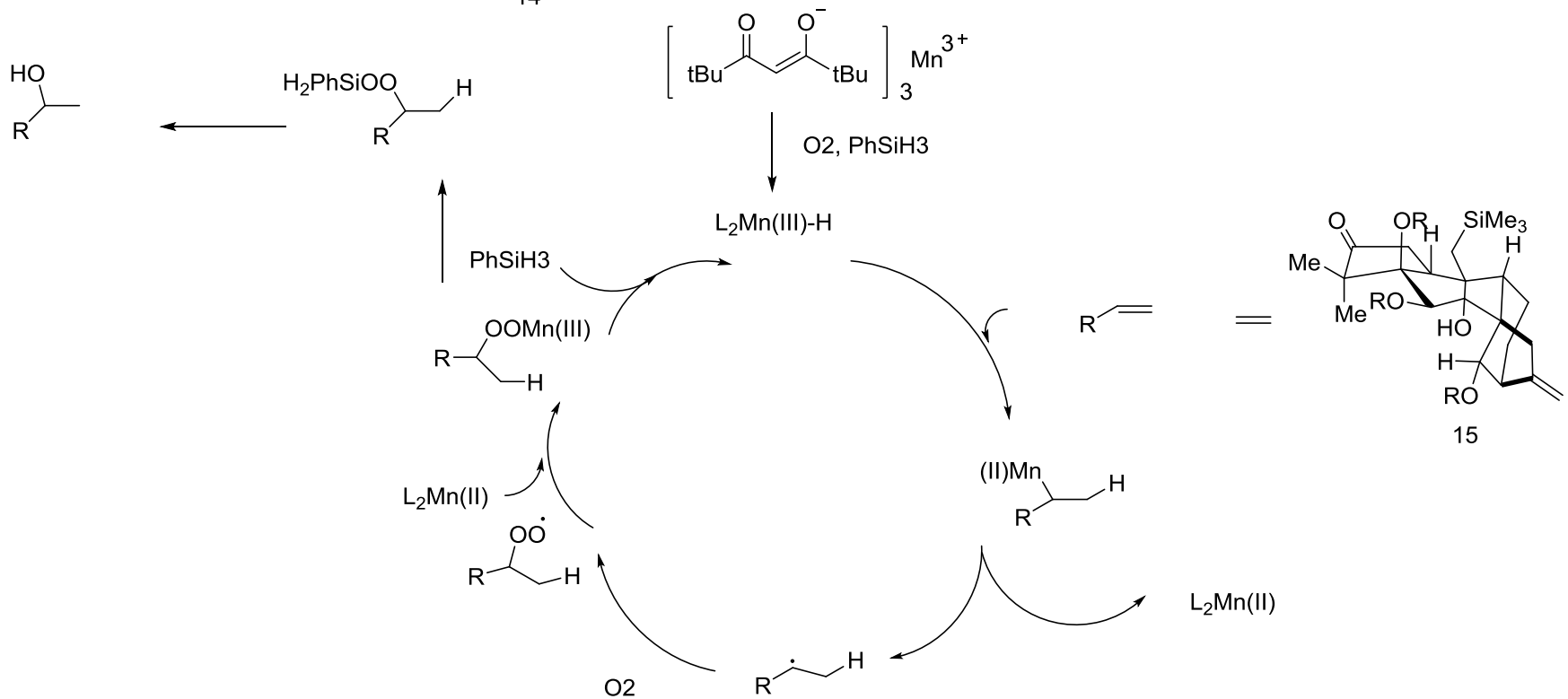
Global MOM deprotection

Mukaiyama Hydration



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