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Liu Research Group

10/5/2022

Total Synthesis of Resiniferatoxin

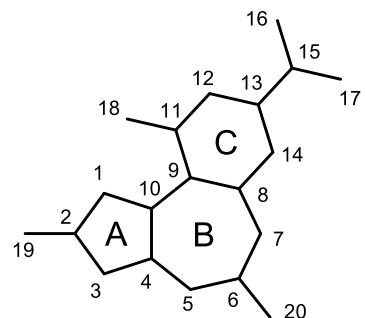
Vasil H. Vasilev, Lukas Spessert, Kuan Yu, and Thomas J. Maimone*



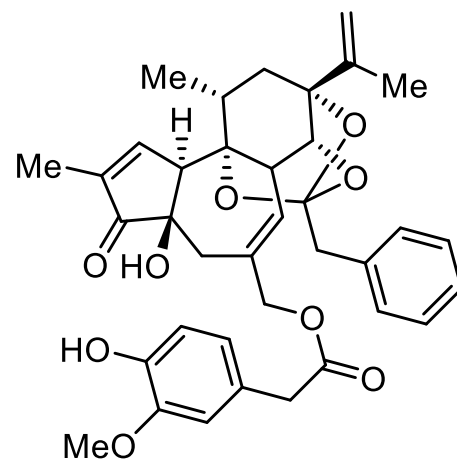
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daphnane diterpene
 carbocyclic core

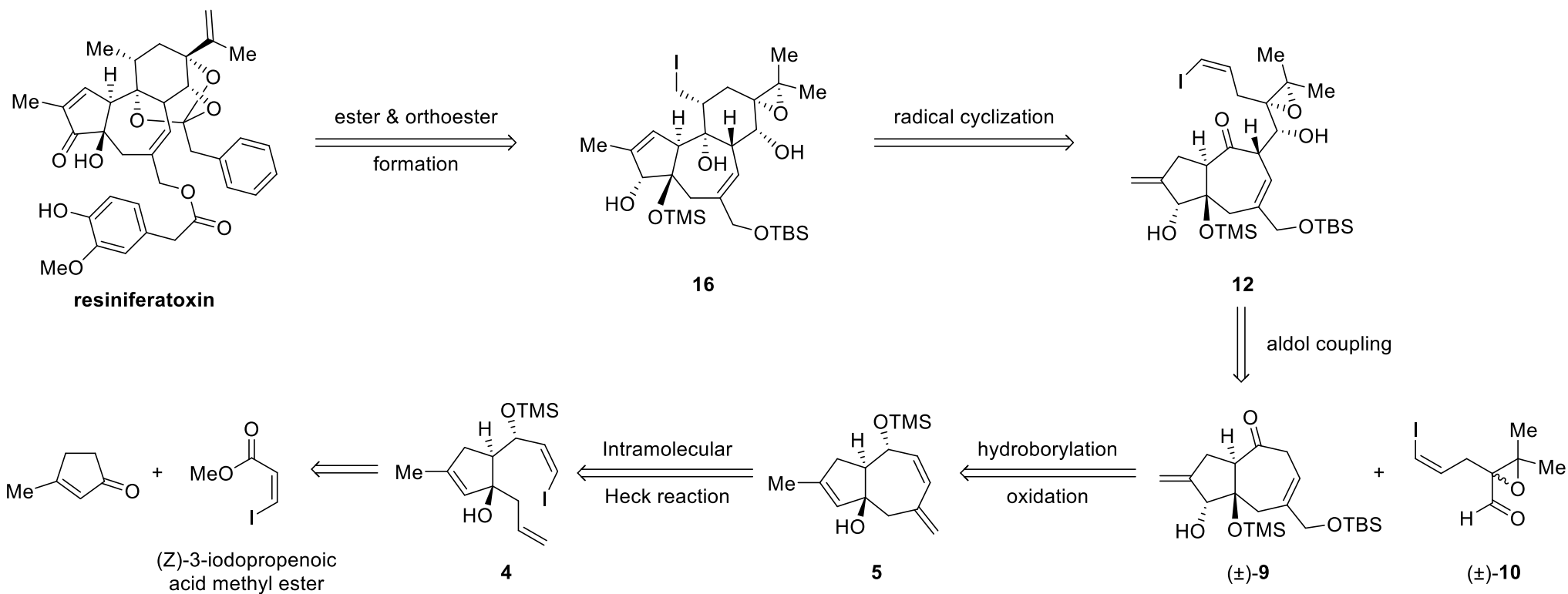


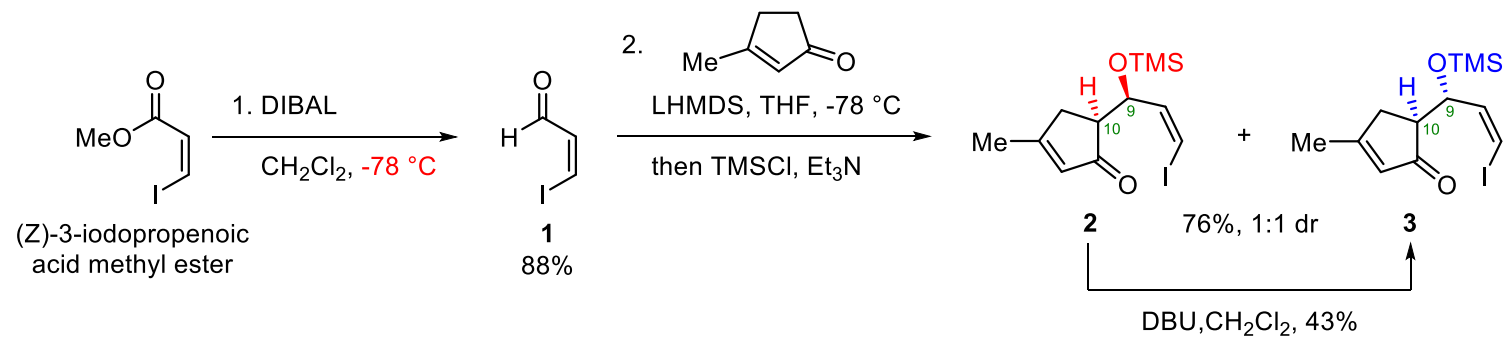
resiniferatoxin

Introduction:

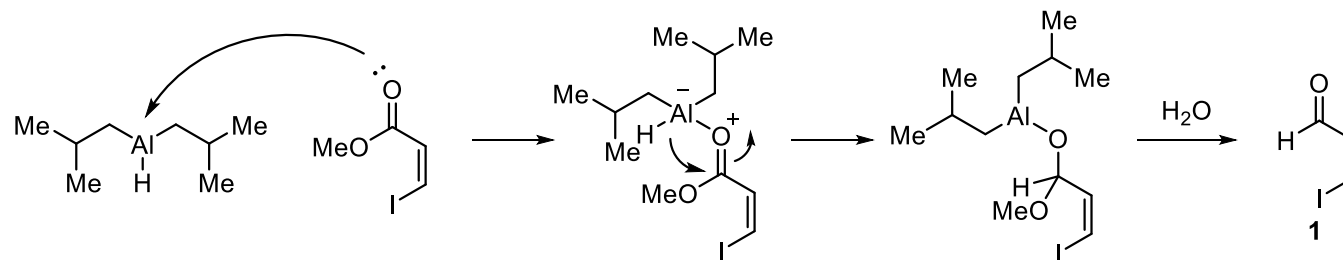
- Resiniferatoxin, a potent TRPV1 activator and potential analgesic, was discovered by Hecker in 1975.
- It features a complex 5,7,6-fused tricyclic ring system (daphnane core) and hallmark embedded orthoester
- 15-step total synthesis of resiniferatoxin was accomplished with a high degree of convergence and notable diastereocontrol.

Retro-synthetic route

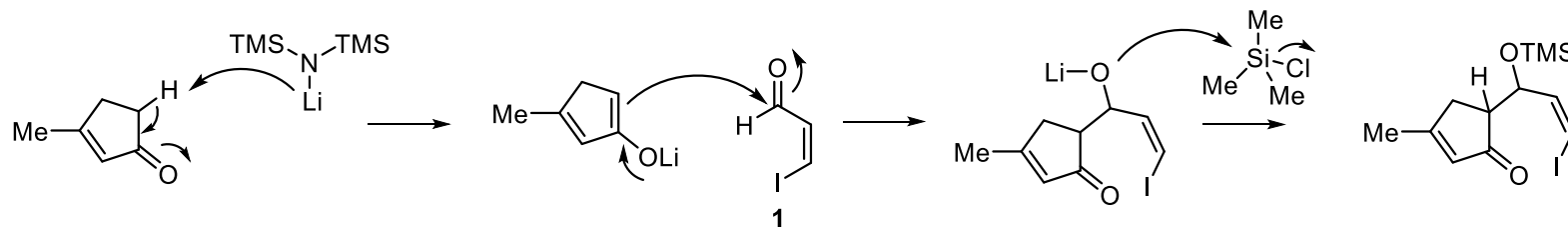




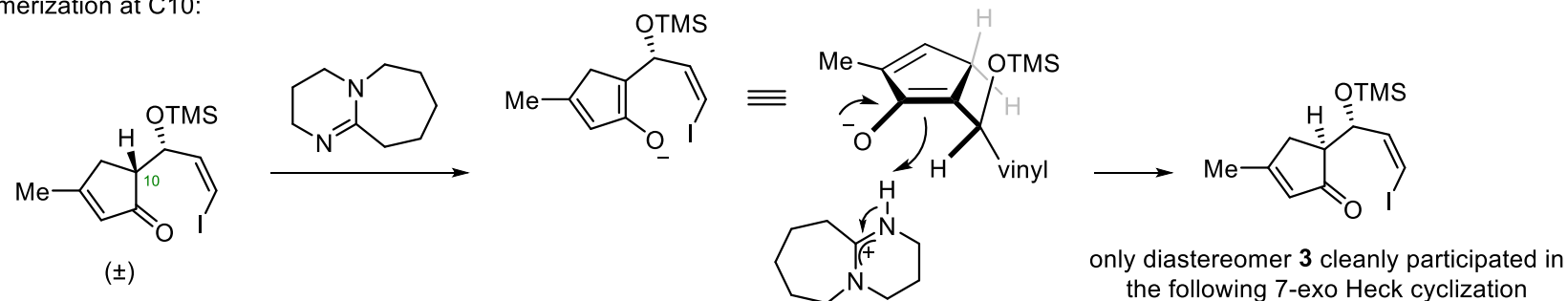
Reduction of ester to aldehyde:

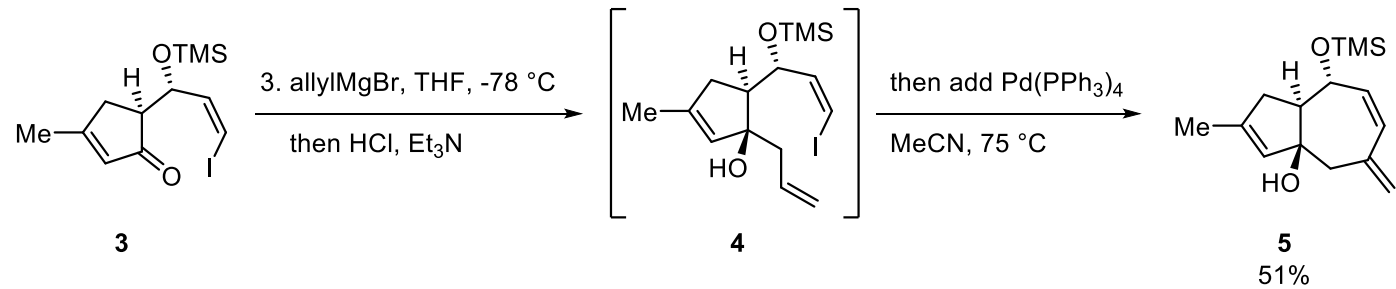


Aldol reaction:

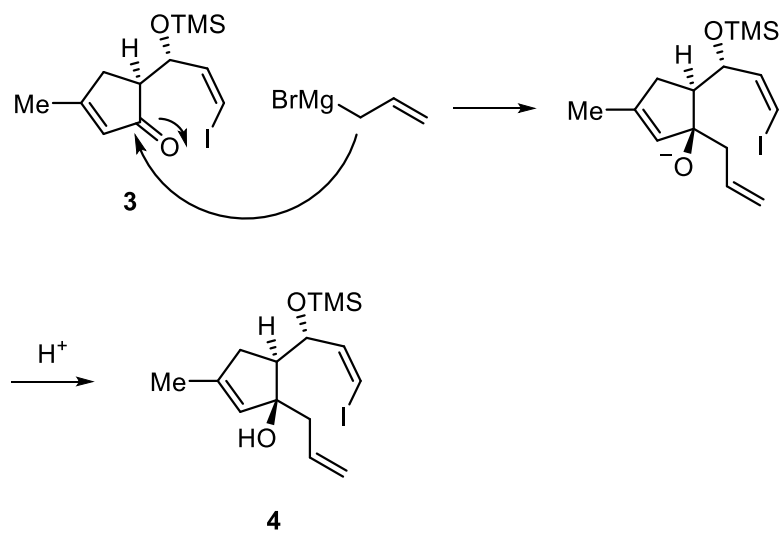


Epimerization at C10:

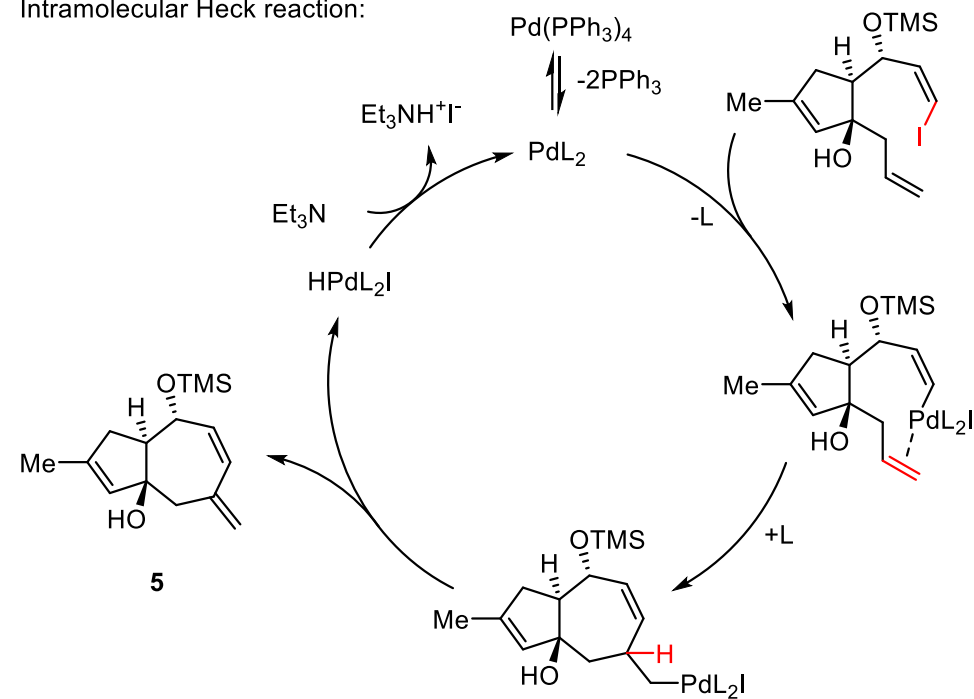


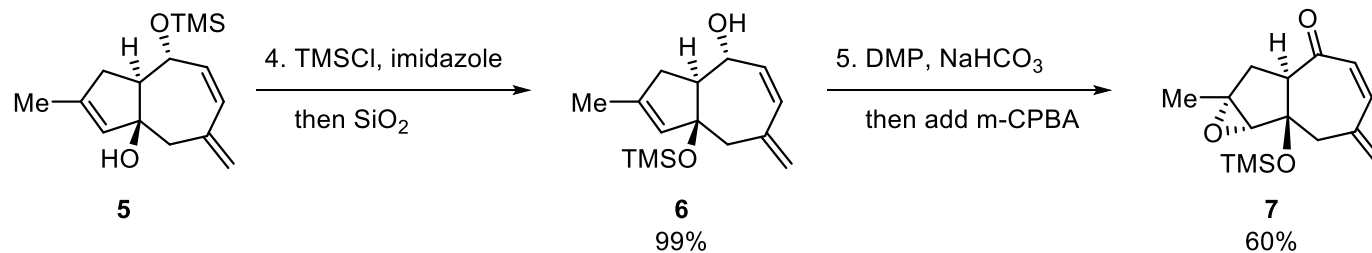


Grignard addition:

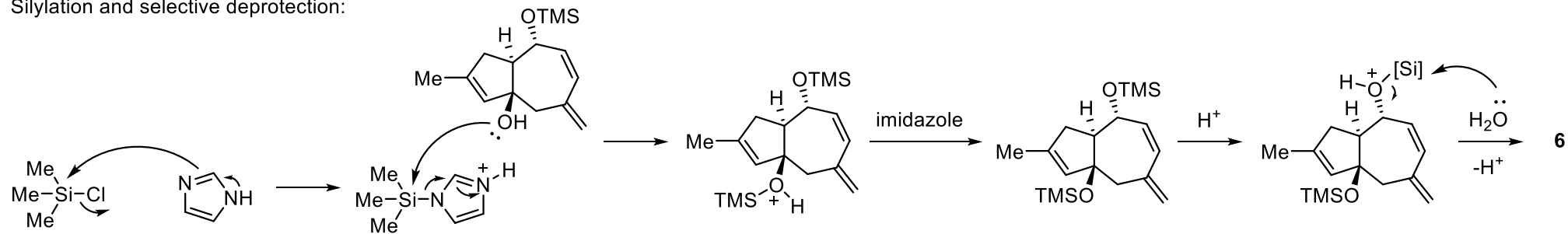


Intramolecular Heck reaction:

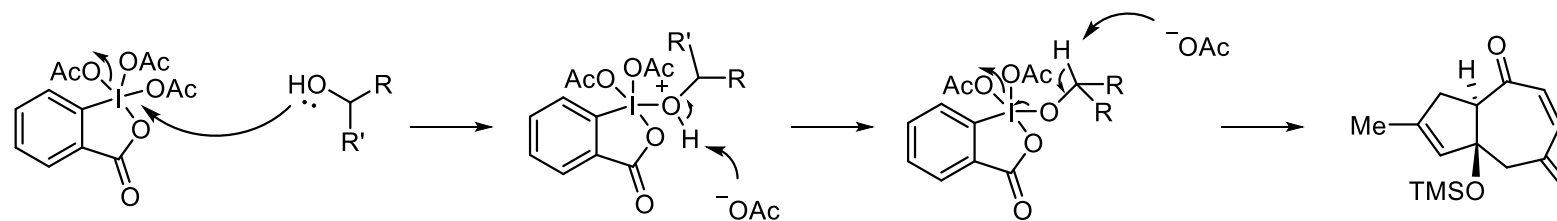




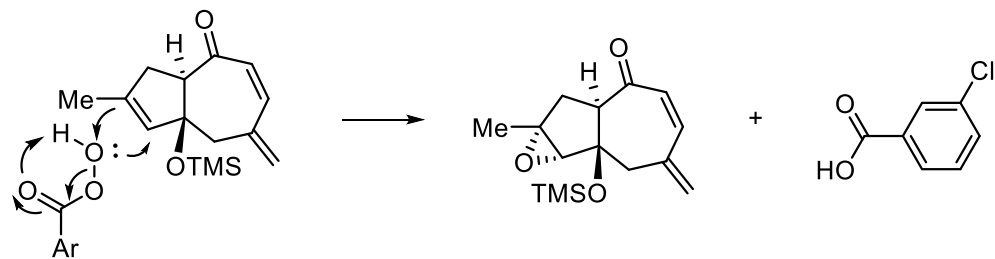
Silylation and selective deprotection:

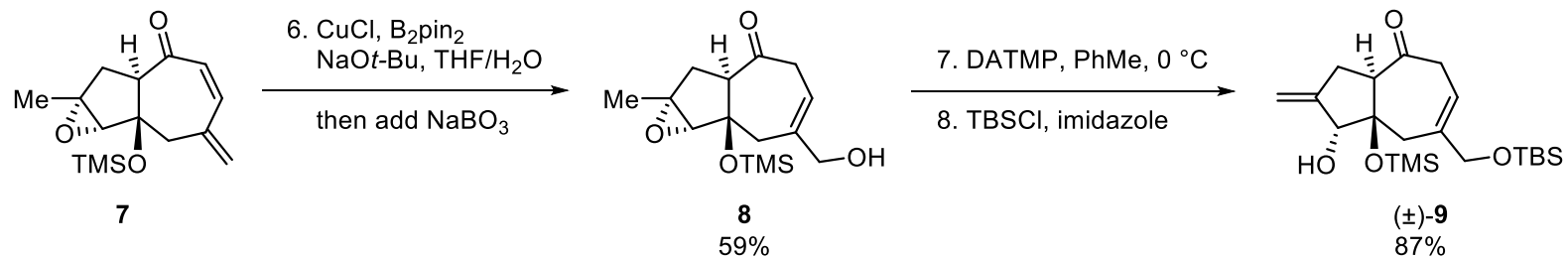


Dess-Martin oxidation:

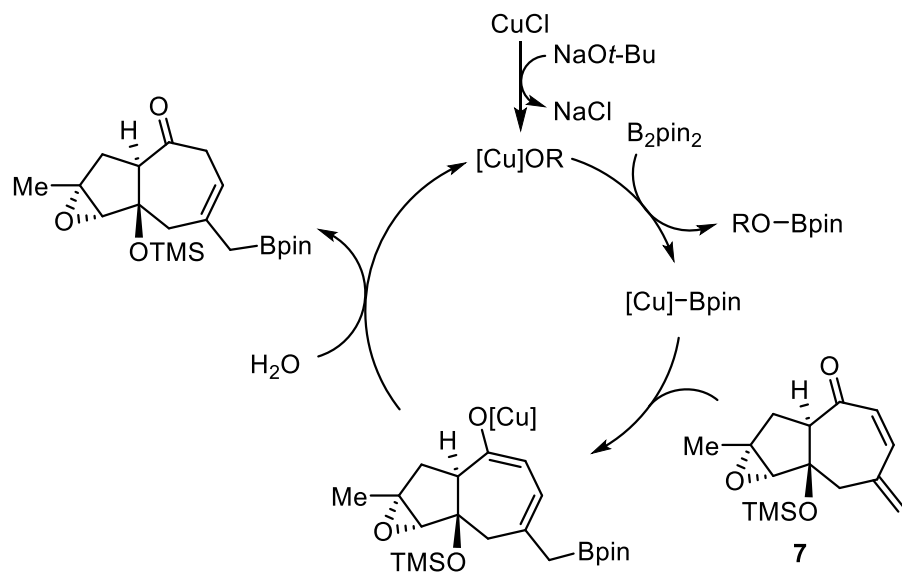


Prilezhaev epoxidation:

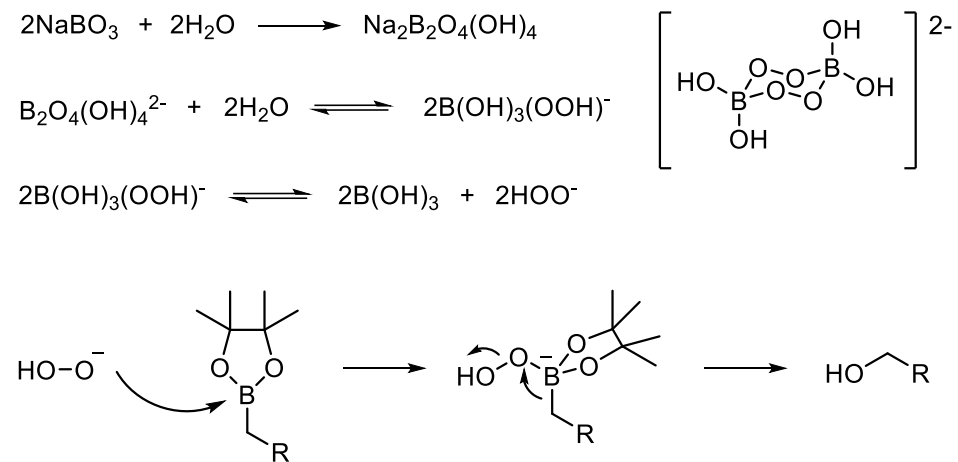




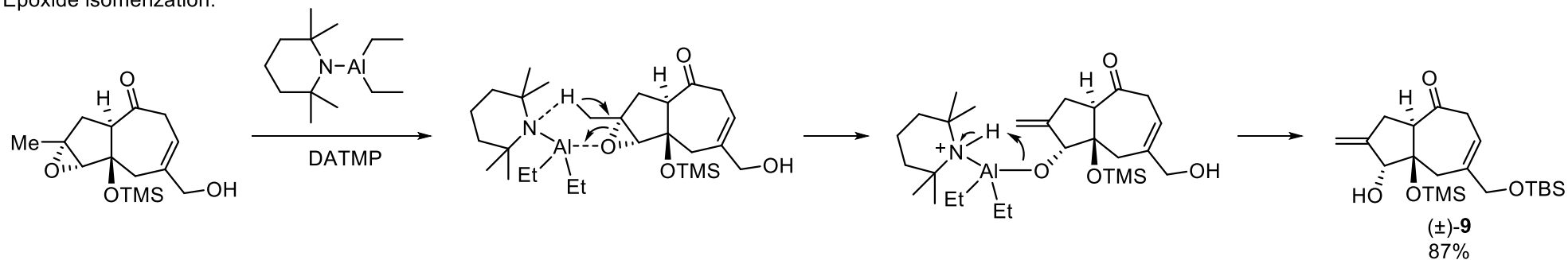
Cu-mediated hydroborylation:

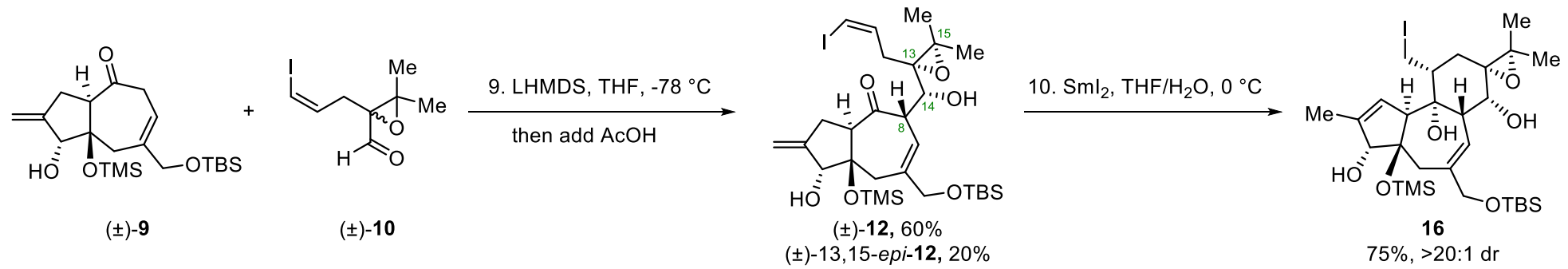


Bpin oxidation:

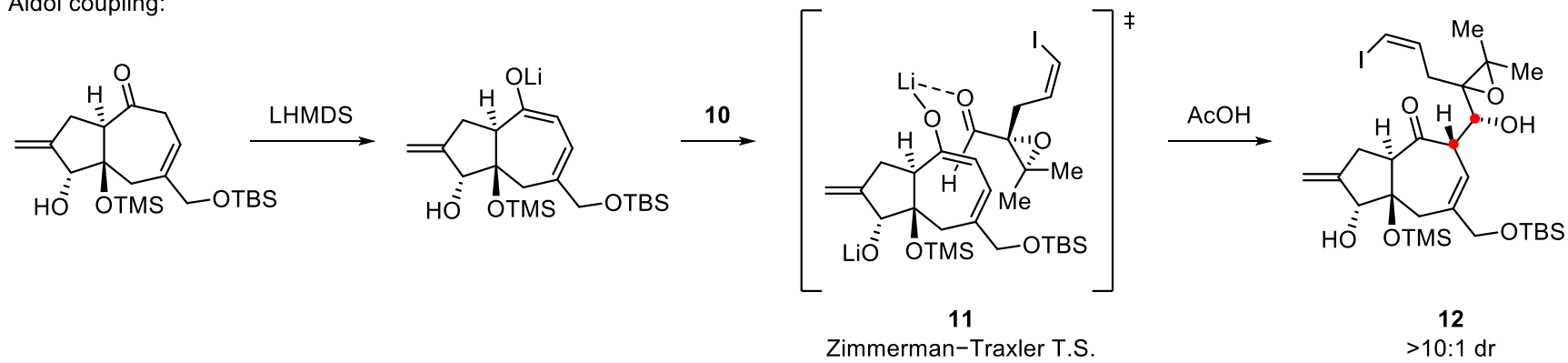


Epoxide isomerization:

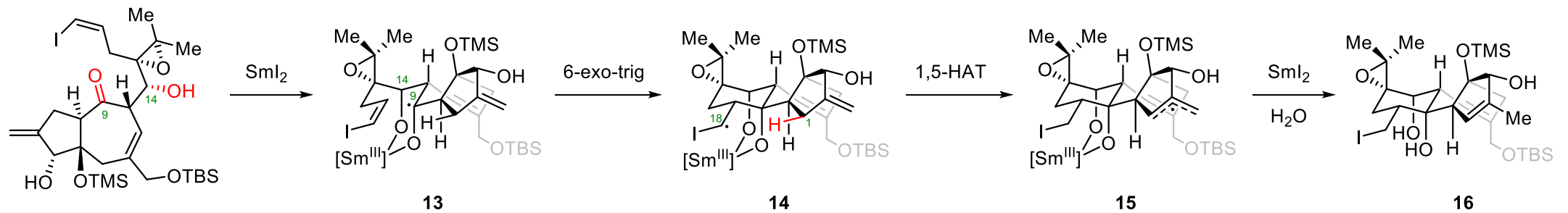


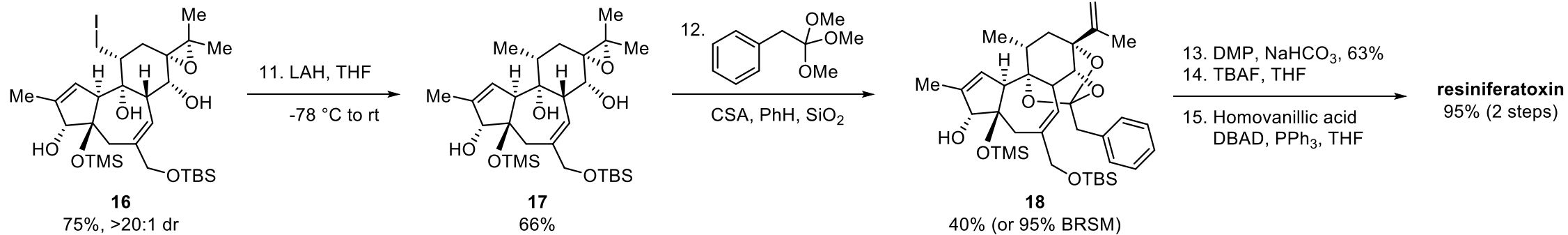


Aldol coupling:

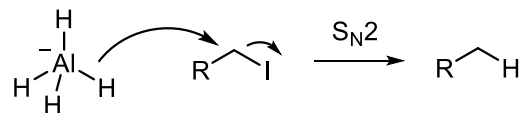


Samarium-mediated radical cyclization/HAT cascade:

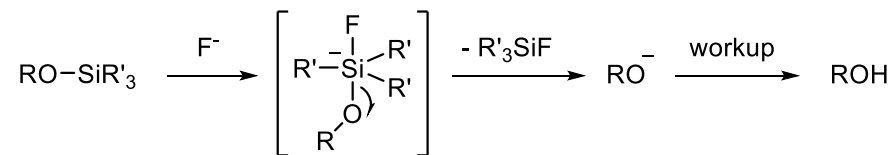




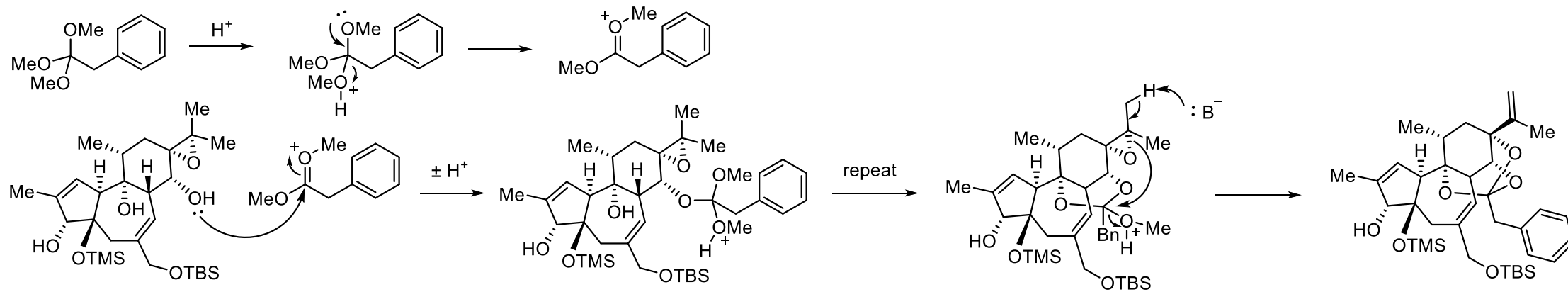
Reduction of iodide with LAH:



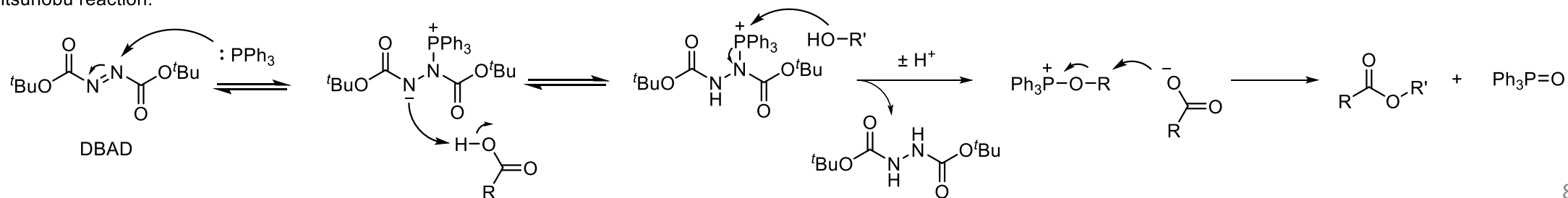
Desilylation with TBAF:



Orthoester formation:



Mitsunobu reaction:



Thanks for your attention