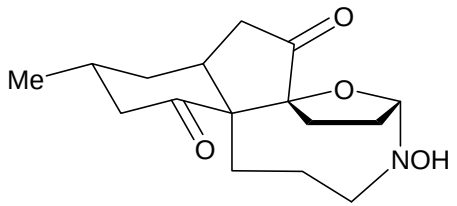
Total Synthesis of (+)-Sieboldine A

J. Am. Chem. Soc. **2010**, *132*, 7876–7877.

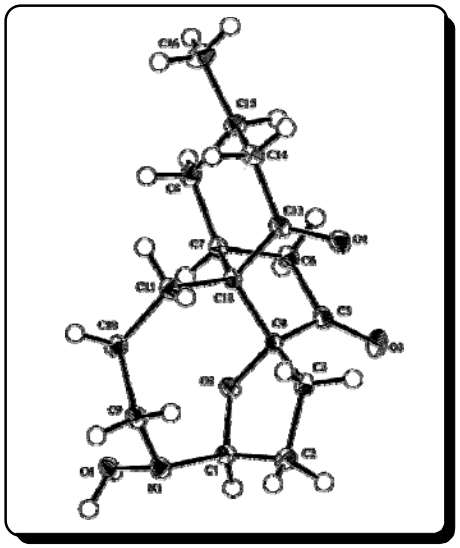


Current Literature Presentation

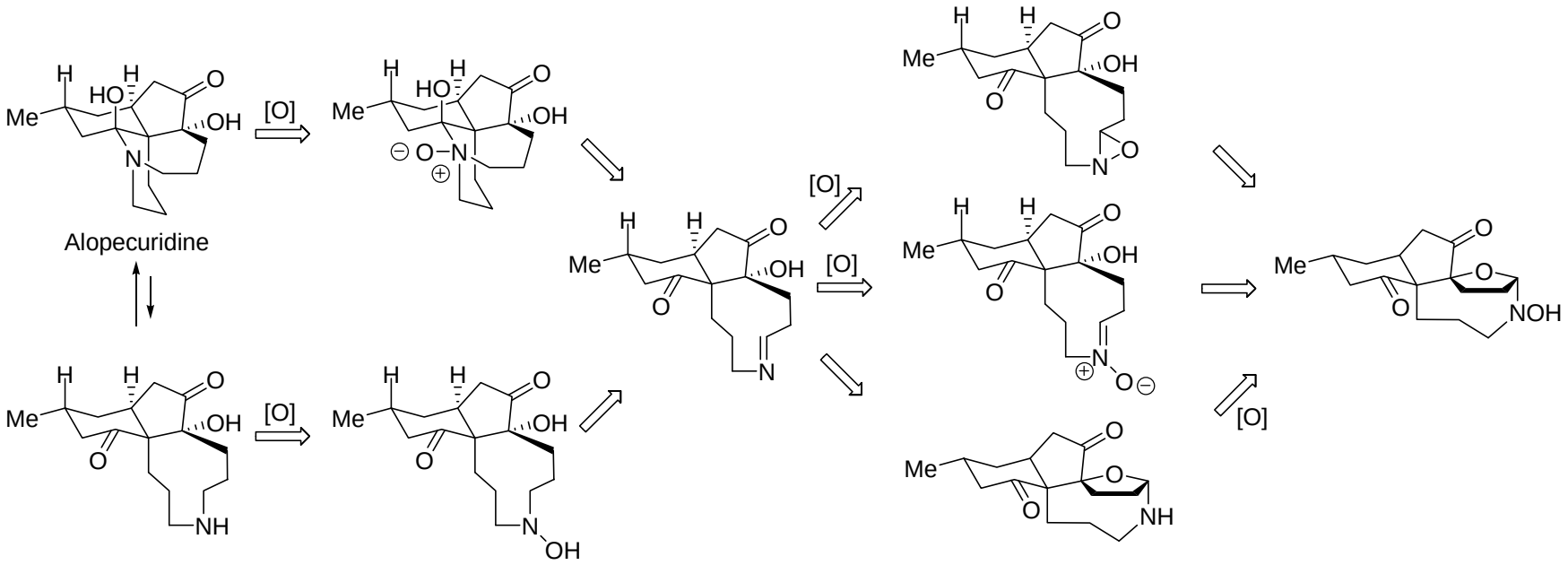
10JUL2010

Michael Yang

Sieboldine A Background

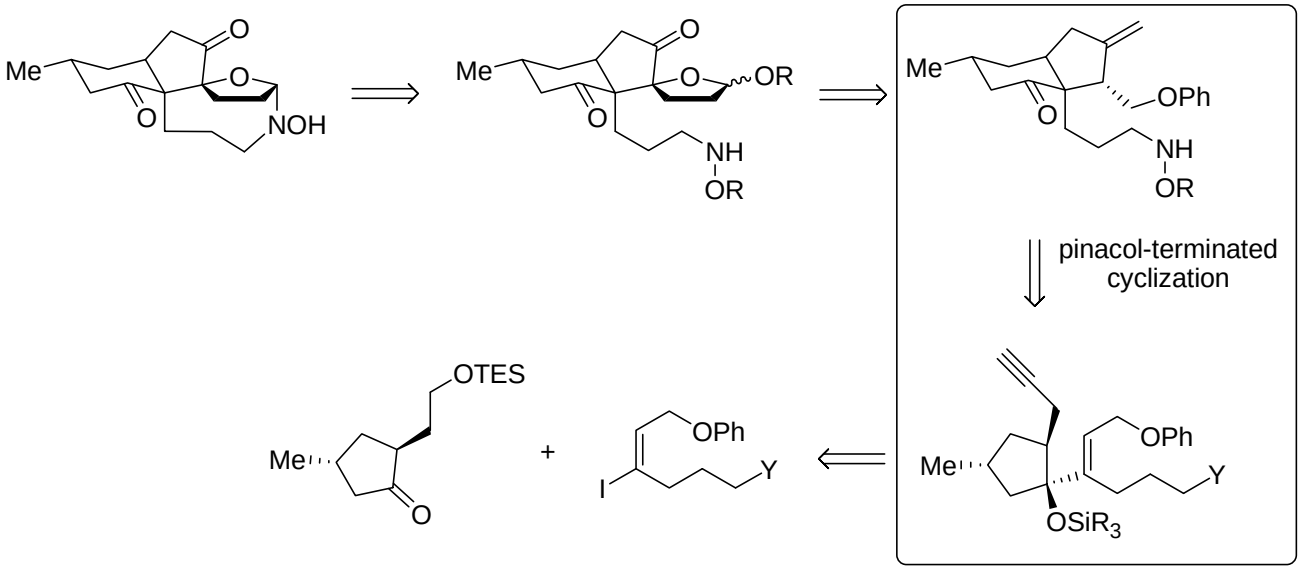


- Isolated from club Moss *Lycopodium sieboldii*
- Inhibition of acetylcholinesterase (IC_{50} 2.0 μg/mL)
- Cytotoxicity against murine lymphoma L1210 cells (IC_{50} 5.1 μg/mL)
- Alopecuridine may be the biosynthetic precursor of Sieboldine A

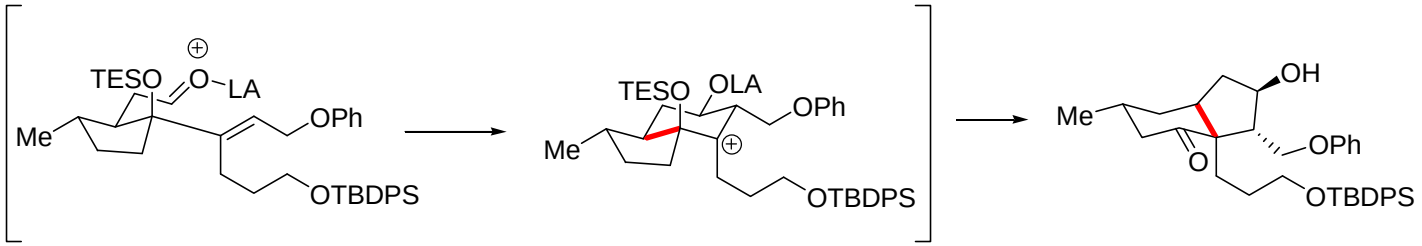


Hirasawa Y.; Morita, H.; Shiro, M.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 3991-3993.

Retrosynthetic Analysis



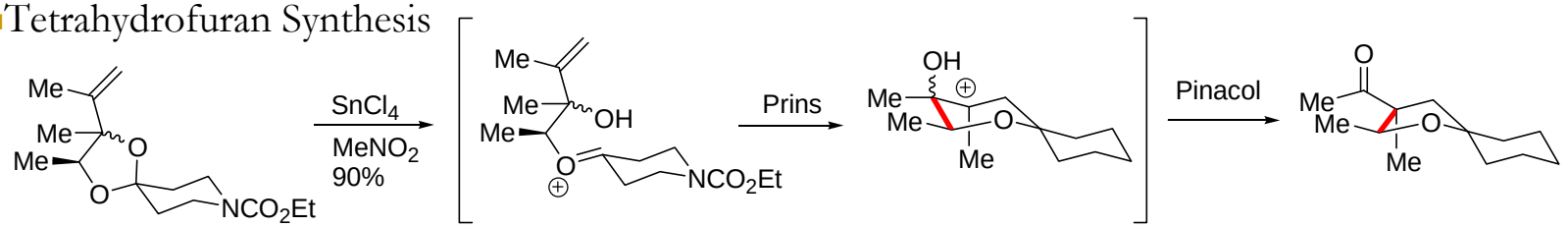
- Key Step: Pinacol-terminated Cyclization



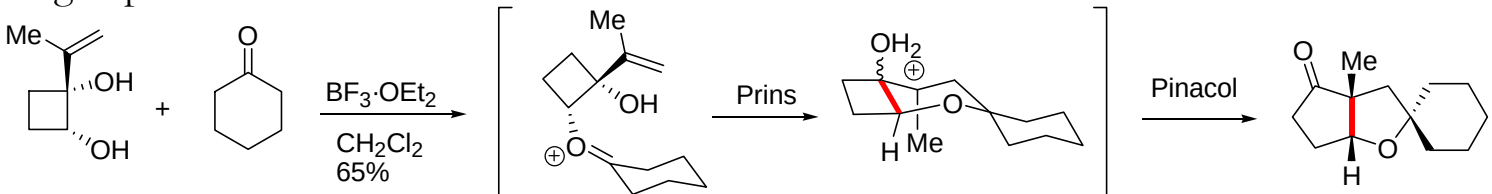
Canham, S. M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc*. **2010**, *132*, 7876–7877.

Pinacol-terminated Prins Cyclization (Oxacyclic Ring Systems)

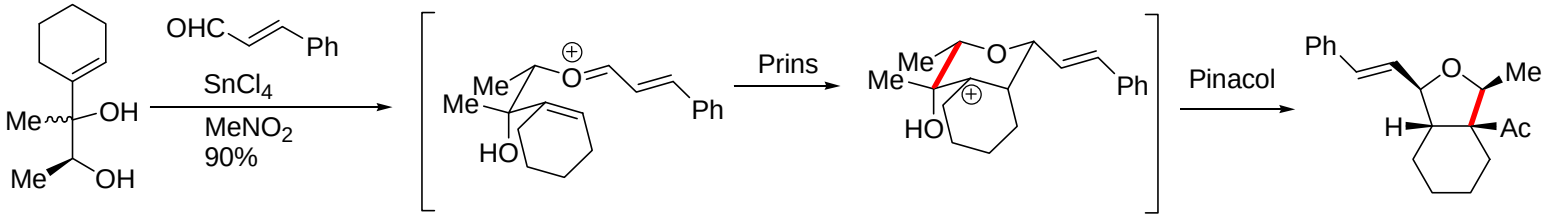
- Tetrahydrofuran Synthesis



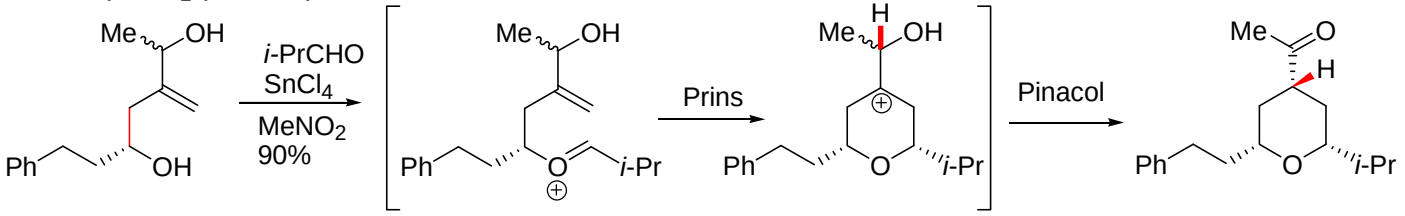
- Ring-expansion



- Hexahydroisobenzofuran



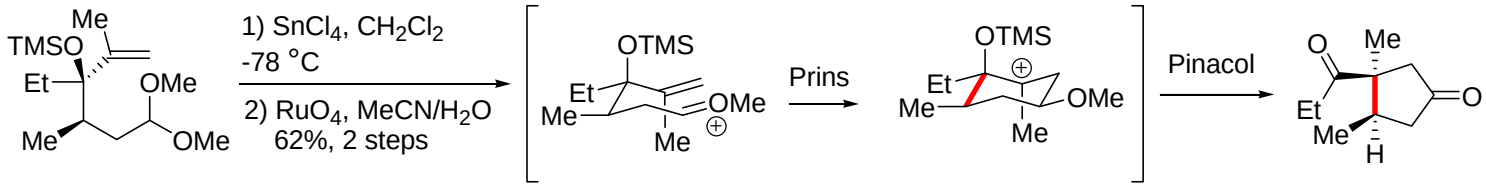
- Tetrahydropyran Synthesis



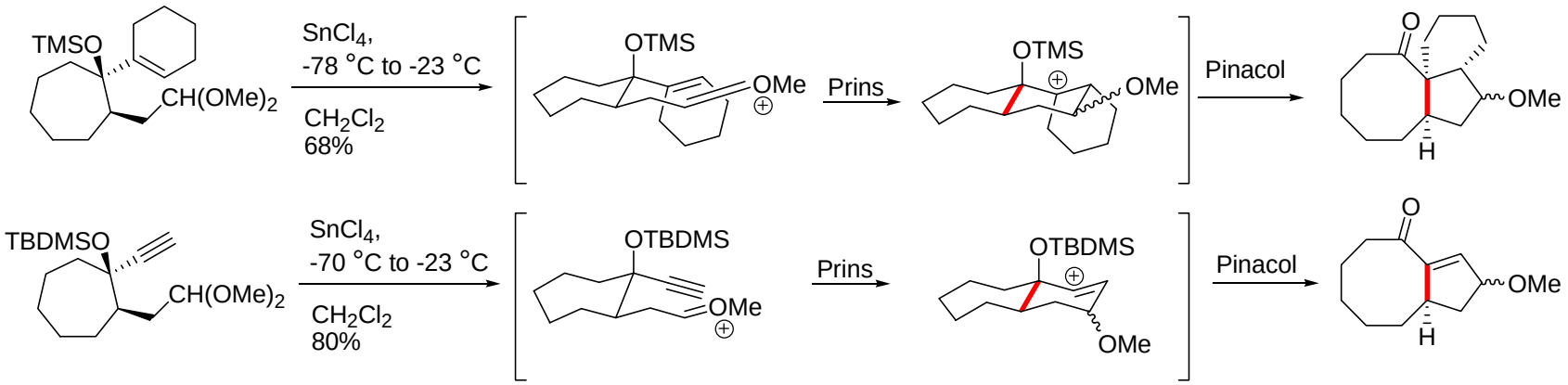
Overman, L. E.; Pennington, L. D. *J. Org. Chem*. **2003**, *68*, 7143–7157.

Pinacol-terminated Prins Cyclization (Carbocyclic Ring Systems)

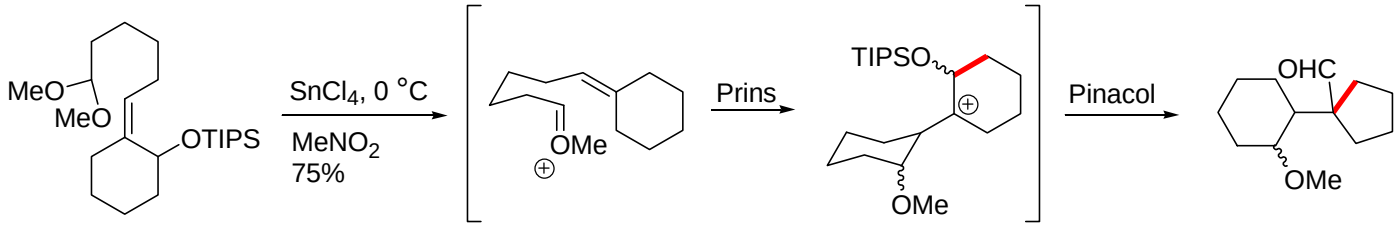
- Cyclopentane Synthesis



- Ring Expansions



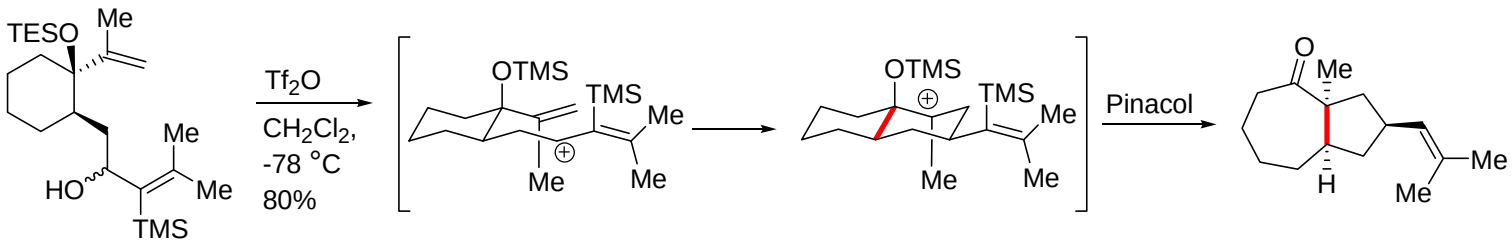
- Ring Contraction



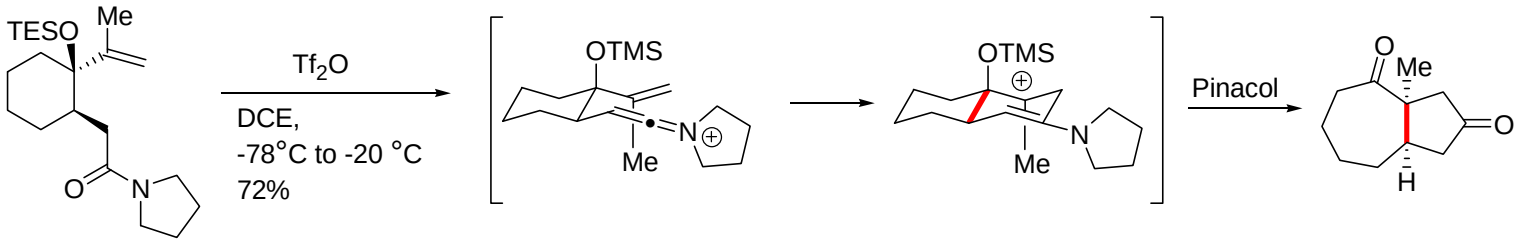
Overman, L. E.; Pennington, L. D. *J. Org. Chem*. **2003**, *68*, 7143–7157.

Pinacol-terminated Cyclizations – Alternative Cationic Initiators

- Allyl cation as cyclization initiator

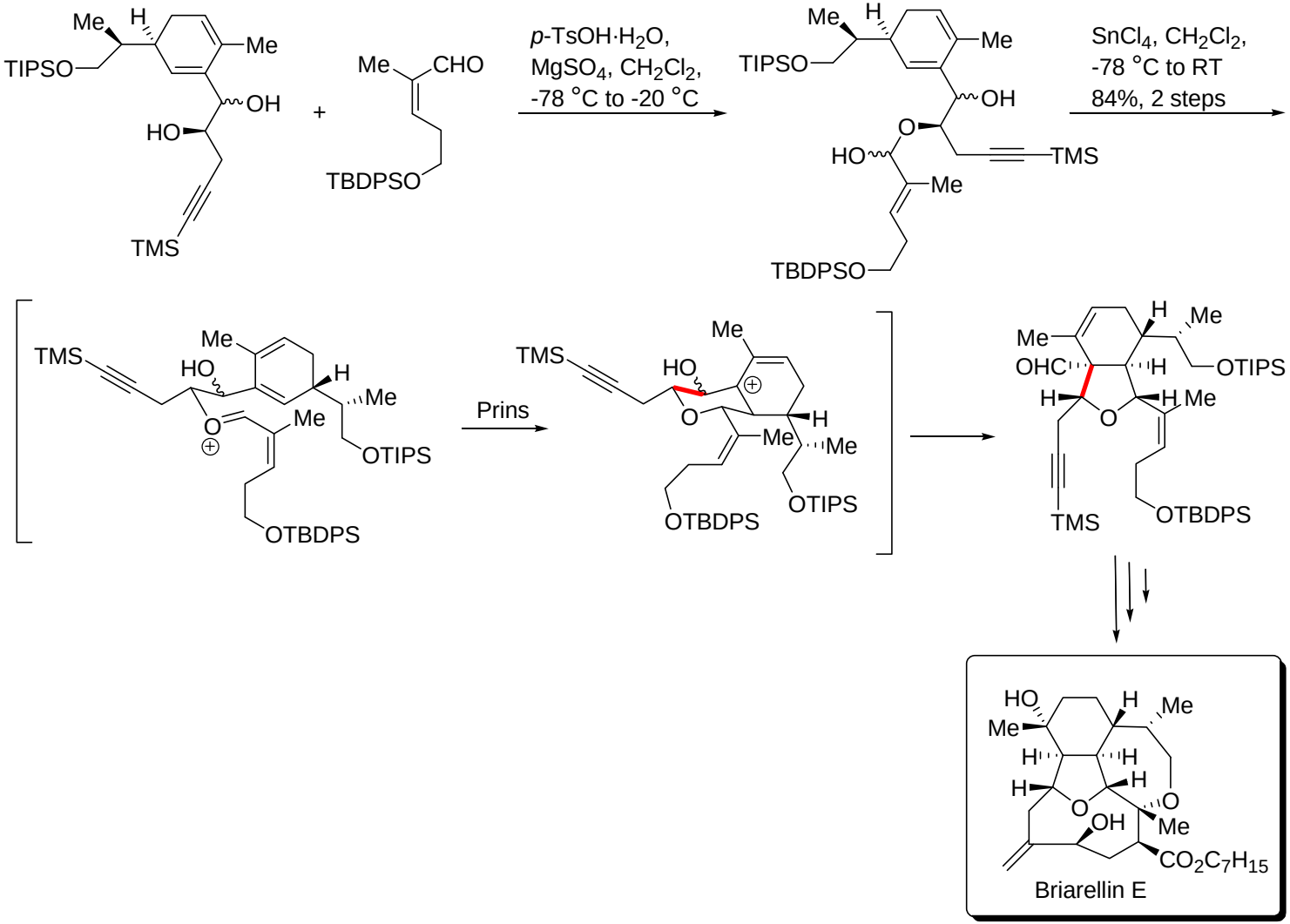


- Keteniminium ion as cyclization initiator



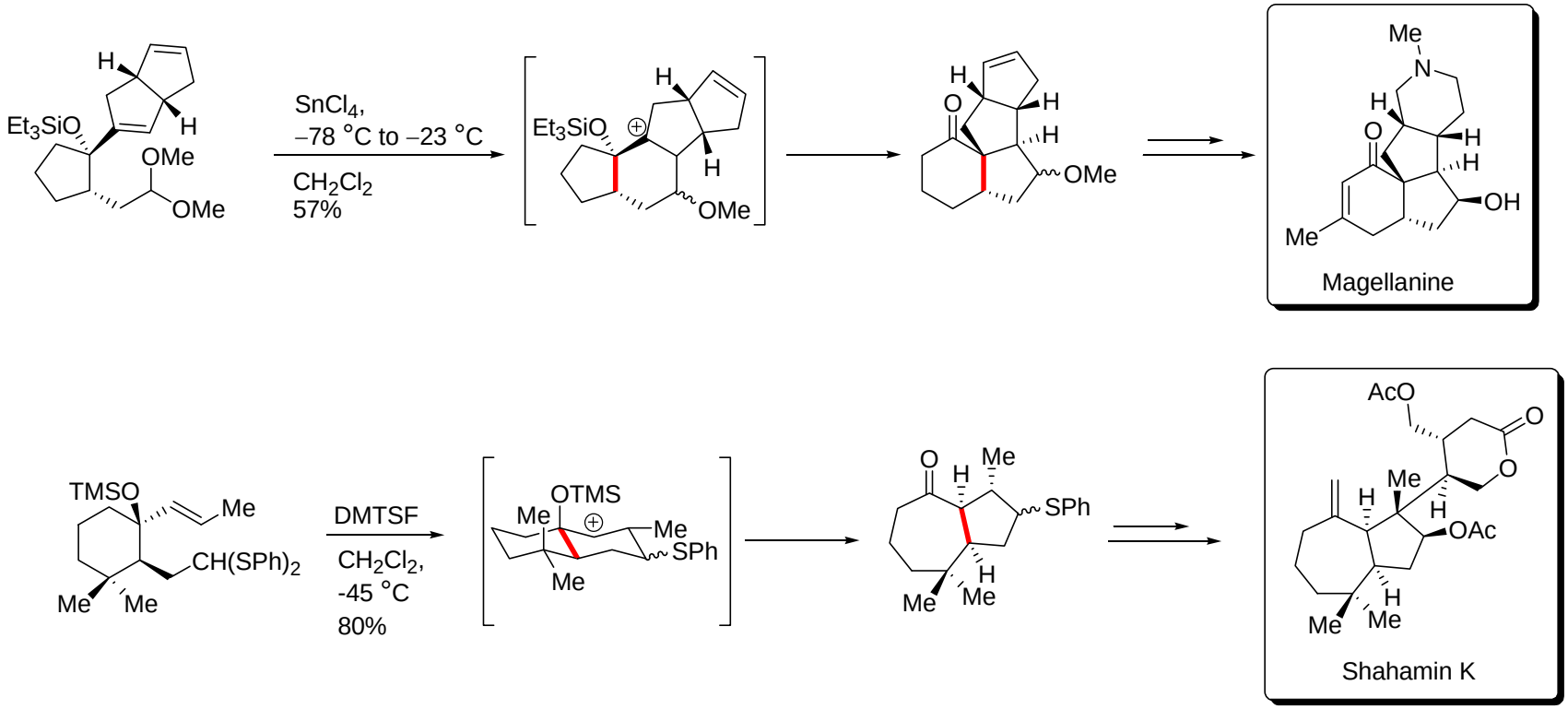
Overman, L. E.; Wolfe, J. P. *J. Org. Chem.* **2002**, *67*, 6421–6429.

Prins-Pinacol to Form Oxacyclic Core of Briarellin E



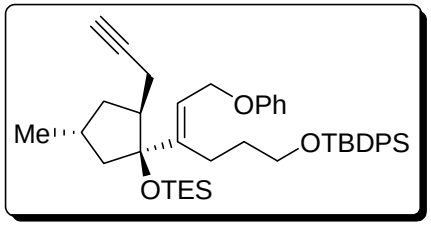
Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650–6652.

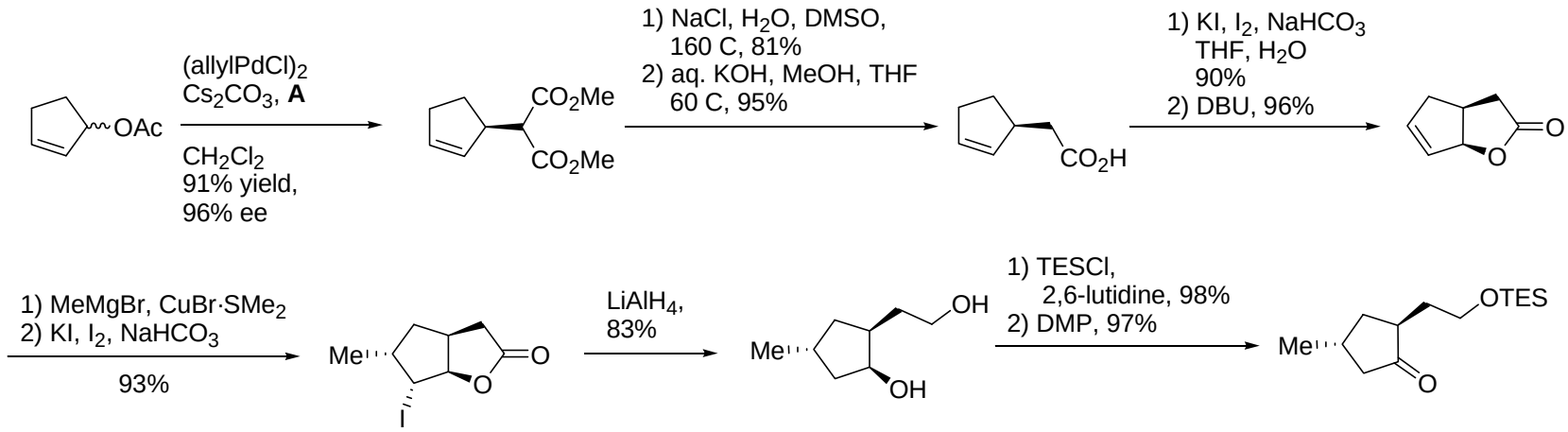
Prins-Pinacol to Form Carbocyclic Core of Magellanine and Shahamin K

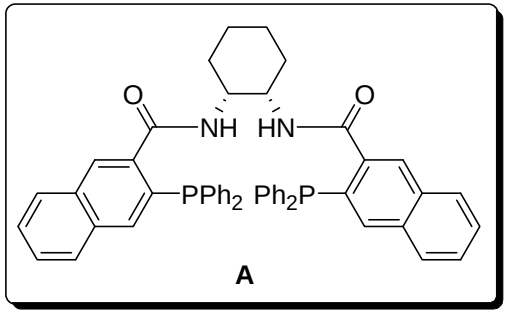


Hirst, G. C.; Johnson, T. O.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992–2993.
Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc*. **2001**, *123*, 4851–4852.

Preparation of Chiral Cyclopentanone

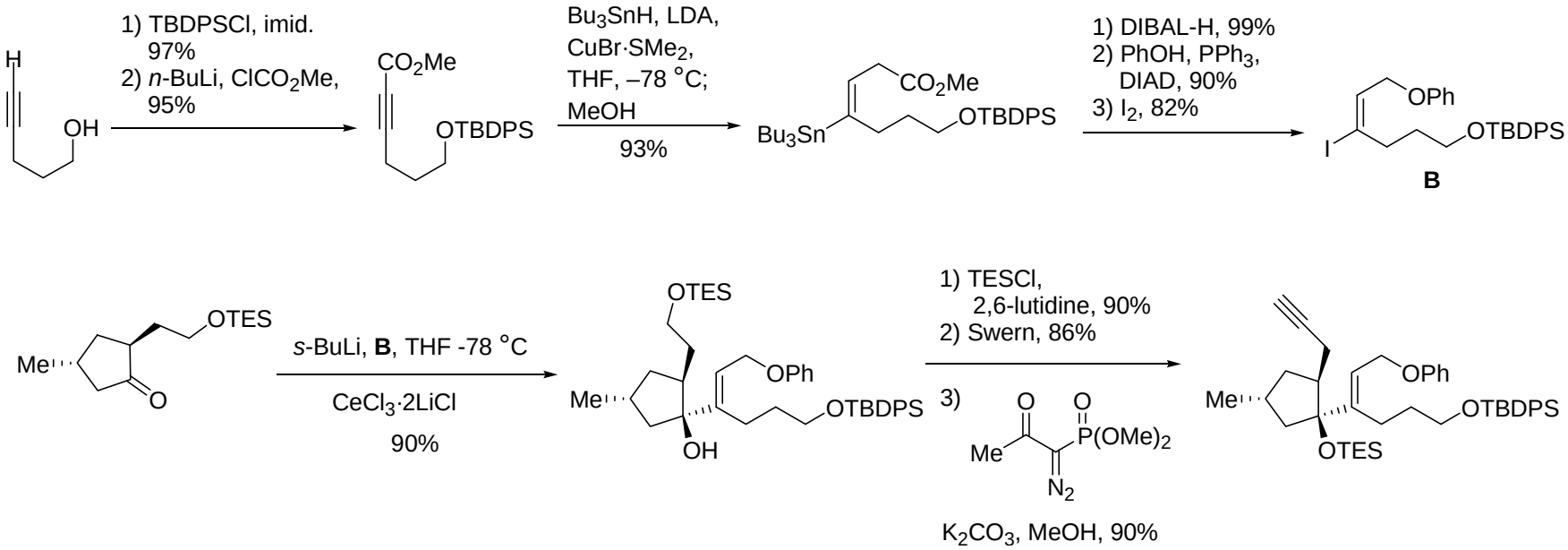






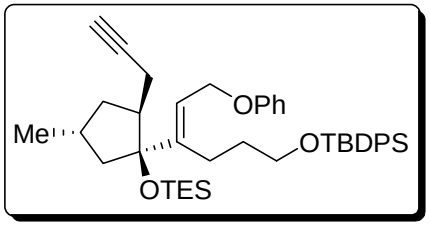
Trost, B. M.; Bunt, R. C. *Angew. Chem. Int. Ed*. **1996**, *35*, 99–102.
Miyazaki, T.; Yokoshima, S.; Simizu, S.; Osada, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett*. **2007**, *9*, 4737–4740.
Canham, S. M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc*. **2010**, *132*, 7876–7877.

Preparation of Precursor

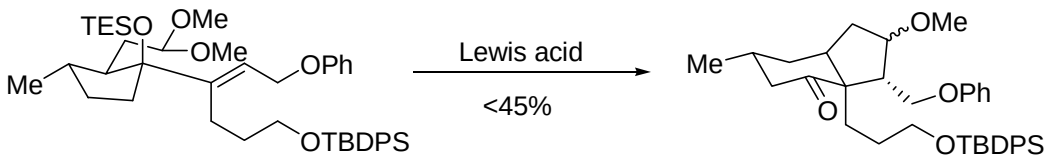


Delongchamps, P.; Hall, D. G. *J. Org. Chem*. **1995**, *60*, 7796–7814.
Canham, S. M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc*. **2010**, *132*, 7876–7877.

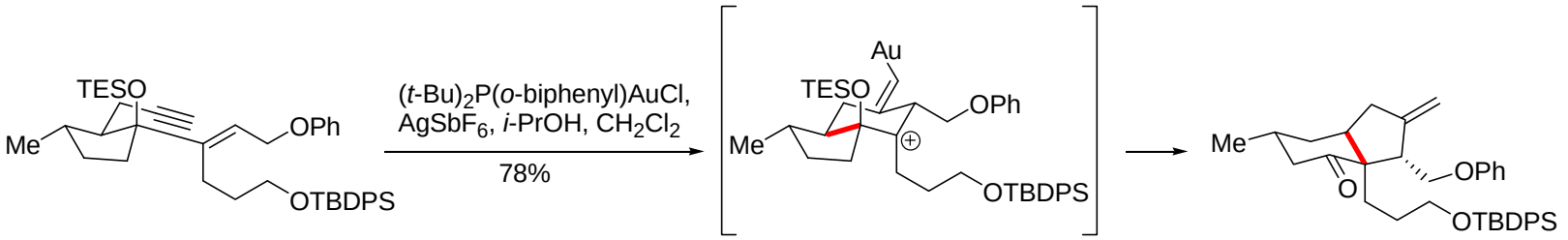
Pinacol-terminated Cyclizations



- Pinacol-terminated Prins cyclization



- Pinacol-terminated enyne cyclization



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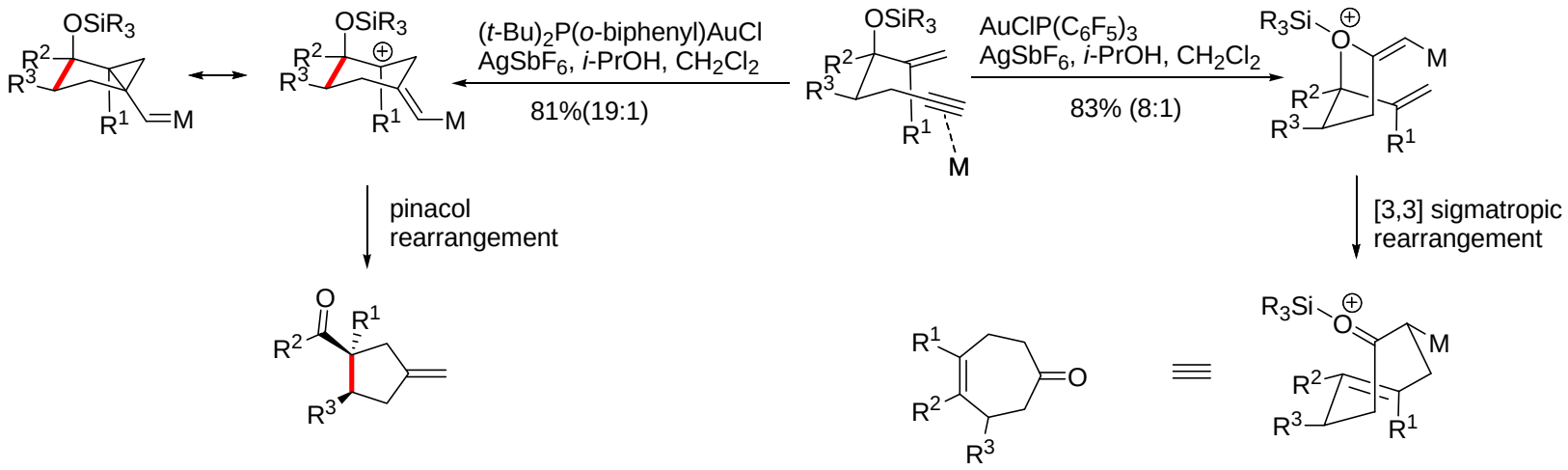
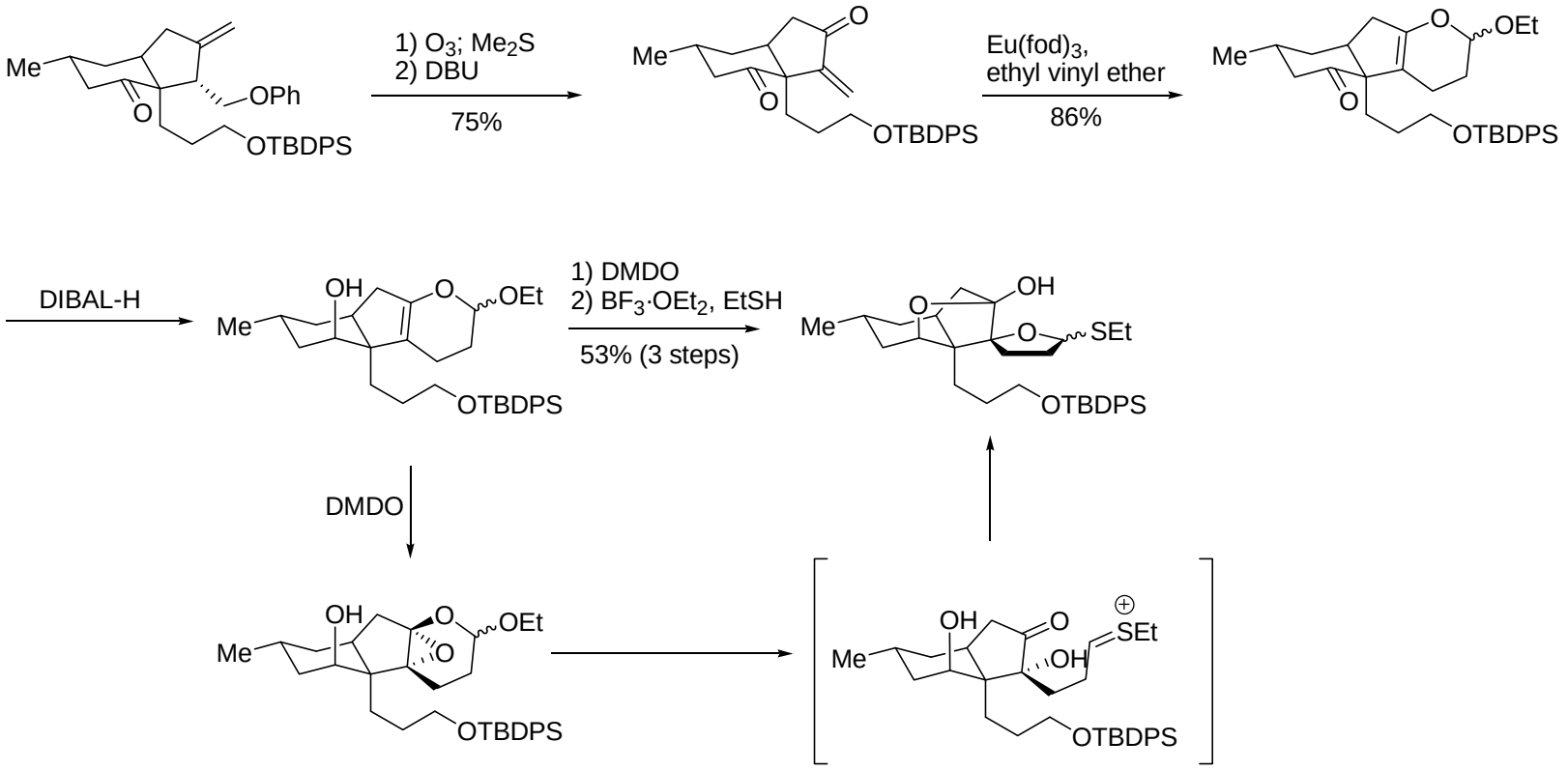
Divergent reactivity of 3-Siloxy 1,6 Enynes



Baskar, B.; Bae, H. J.; An, S. E.; Cheong, J. Y.; Rhee, Y. H.; Duscheck, A.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 2605–2607.

Formation of THF ring



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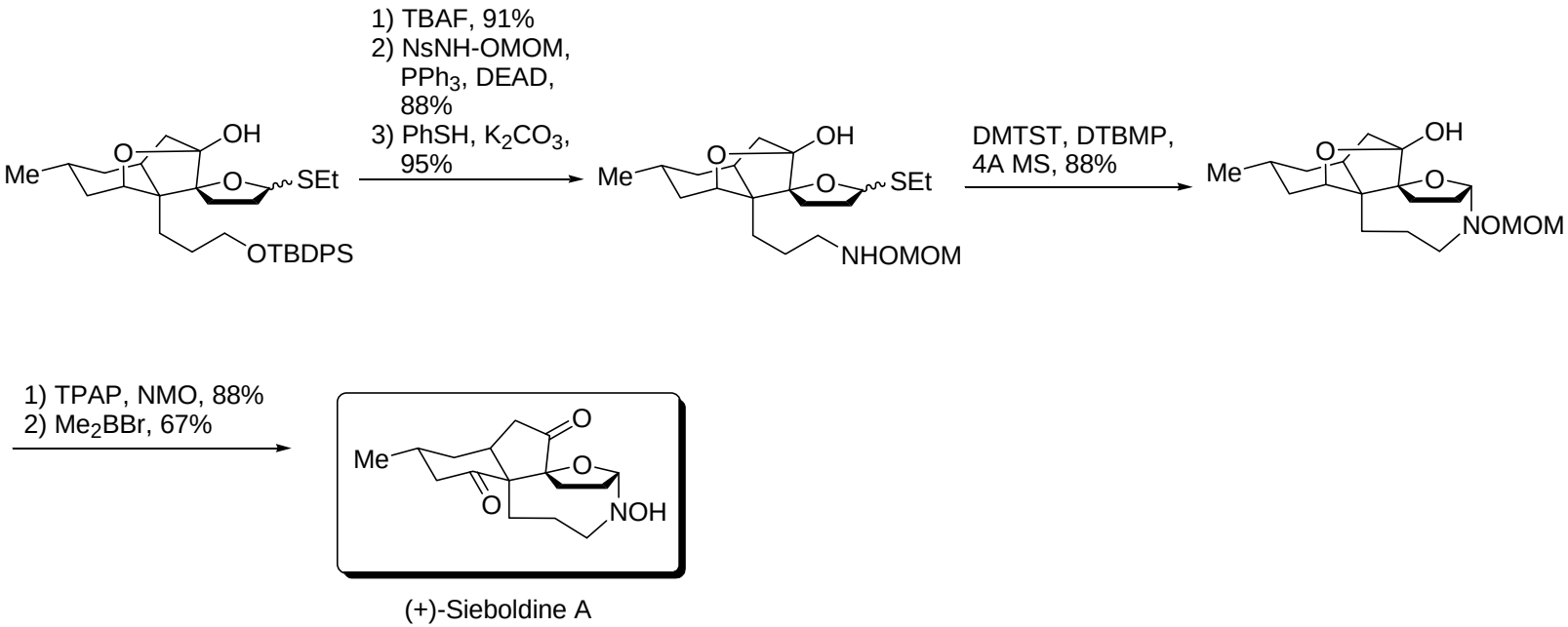
Endgame



(+)-Sieboldine A

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Summary

- Pinacol-terminated Prins cyclizaion have been used to form the oxacyclic and carbocyclic core of many alkaloid.

- Alternative cationic initiators can be used: Gold-catalyzed enyne cyclization used in Sieboldine A.

- Sieboldine A prepared in 27 linear steps from commercially available material (33 overall).