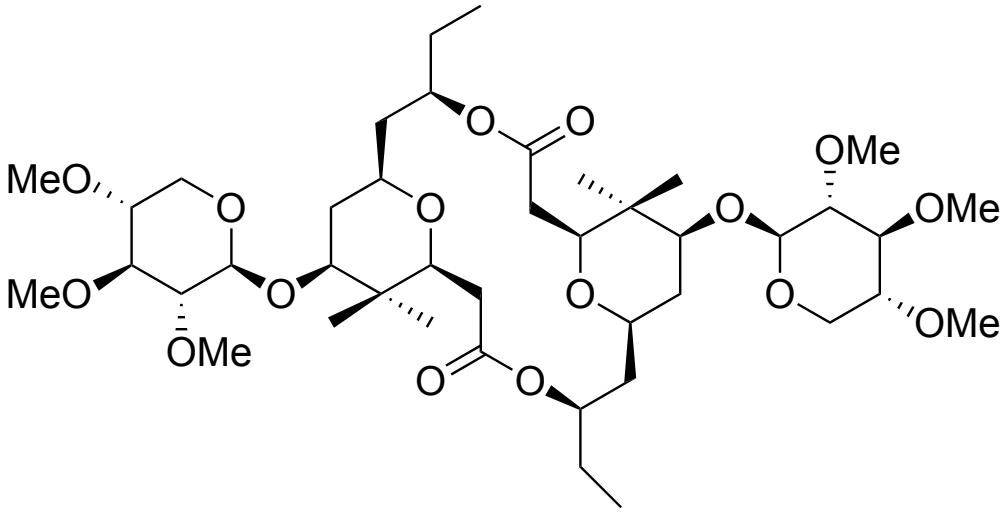
Total Synthesis of Cyanolide A in the Absence of Protecting Groups, Chiral Auxiliaries, or Premetalated Carbon Nucleophiles

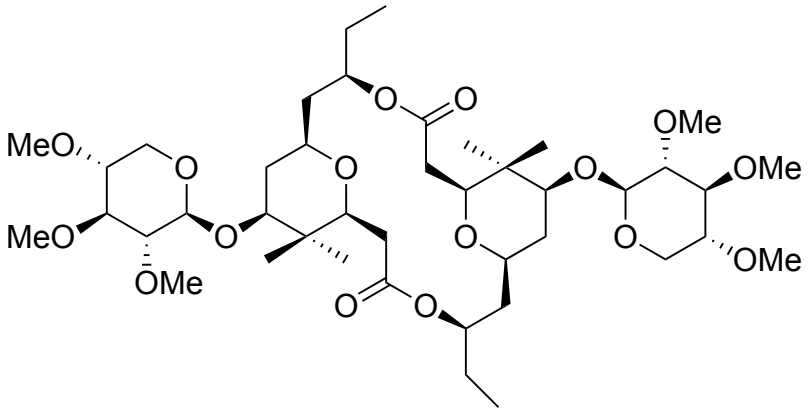
Waldeck, A.R.; Krische, M.J. *Angew. Chem. Soc.*, **2013**, *52*, 1.



Wipf Group Current Literature
Brandon Parks
March 23rd, 2013

Cyanolide A

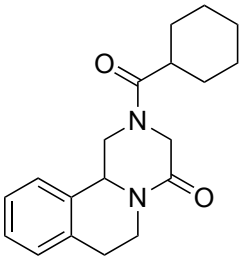
- Isolated cyanobacterium *Lyungbya bouillonii* in 2010
- Related to the clavoslide family of natural products
- Possesses significant molluscicidal activity (LC_{50} = 1.2 μM) against *Biophalaria glabrata* (water snail) involved in schistosomiasis



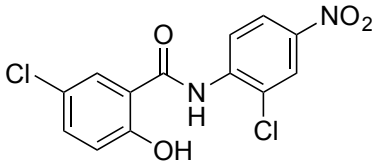
Pereira, A.R.; McCue, C.F.; Gerwick, W.H. *J. Nat. Prod.* **2010**, *73*, 217.

Schistosomiasis

- Caused by a parasitic worm often carried by *Biophalaria glabrata* (water snail)
  - ~200 million people are currently infected
- Leads to organ damage, impaired growth and cognitive development in children, associated with increased risks of bladder cancer
- Several treatments are known but have several side-effects



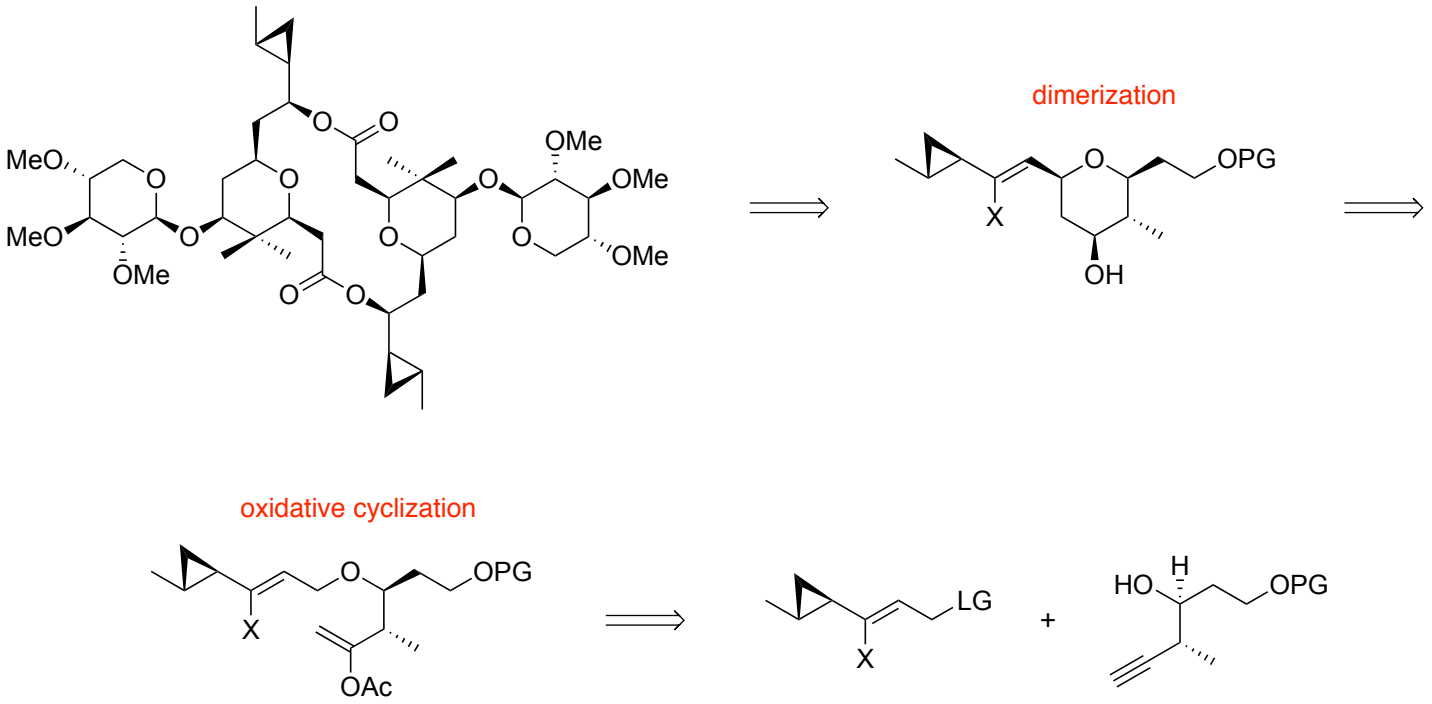
praziquantel



niclosamide

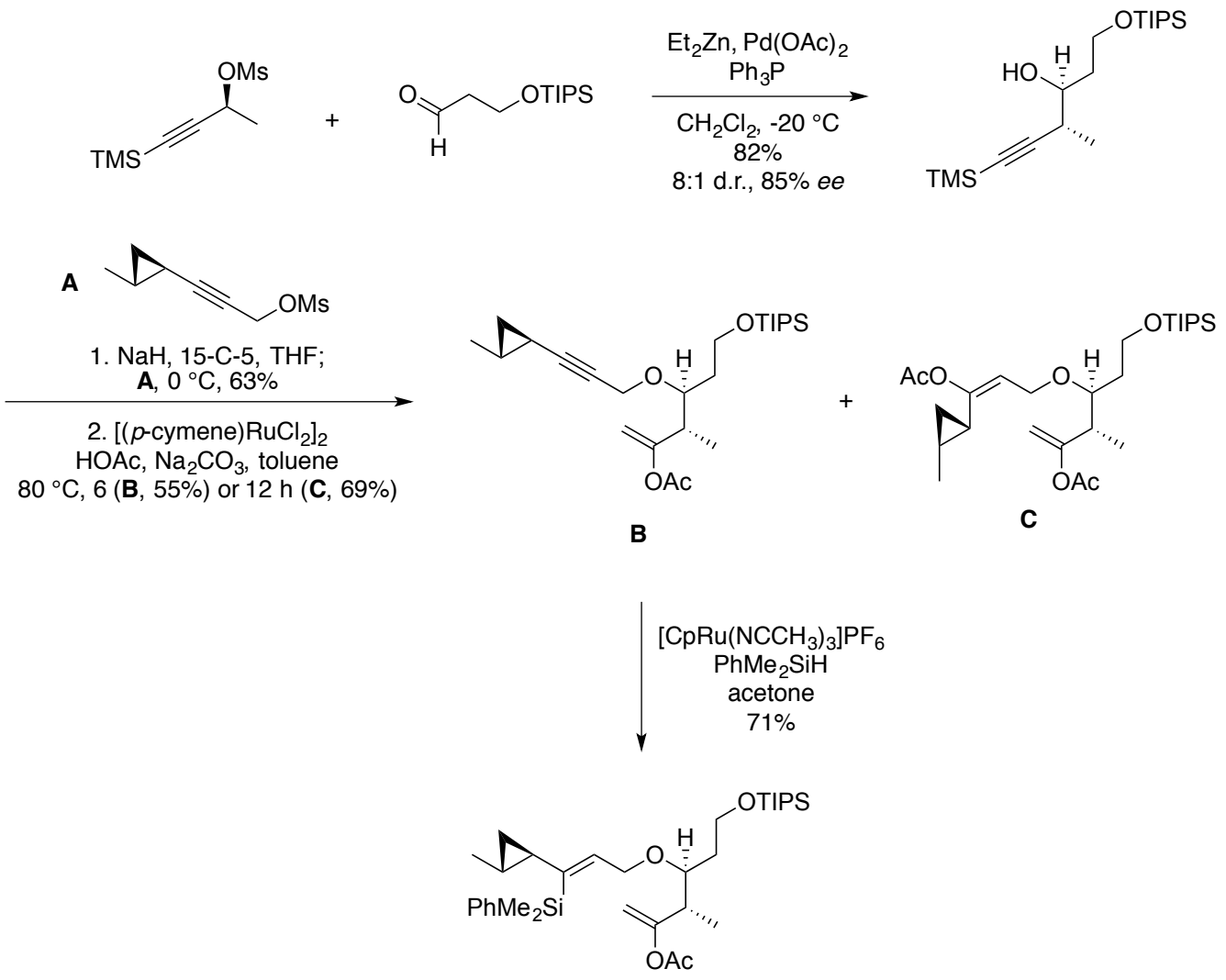
Chitsulo, L.; Engels, D.A.; Montresor, S.L. *Acta Trop*. **2000**, *77*, 41.

Floreancig Retrosynthesis of Clavsolide A

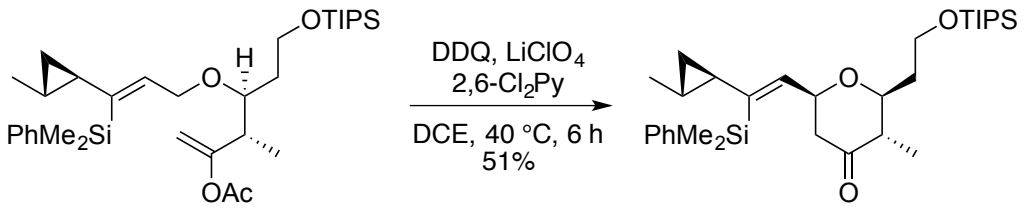


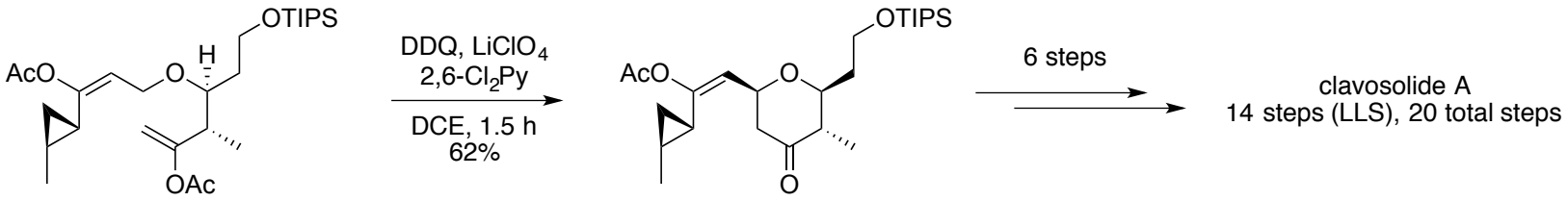
Peh, G.; Floreancig, P.E. *Org. Lett.* **2012**, *14*, 5614.

Precursor Synthesis

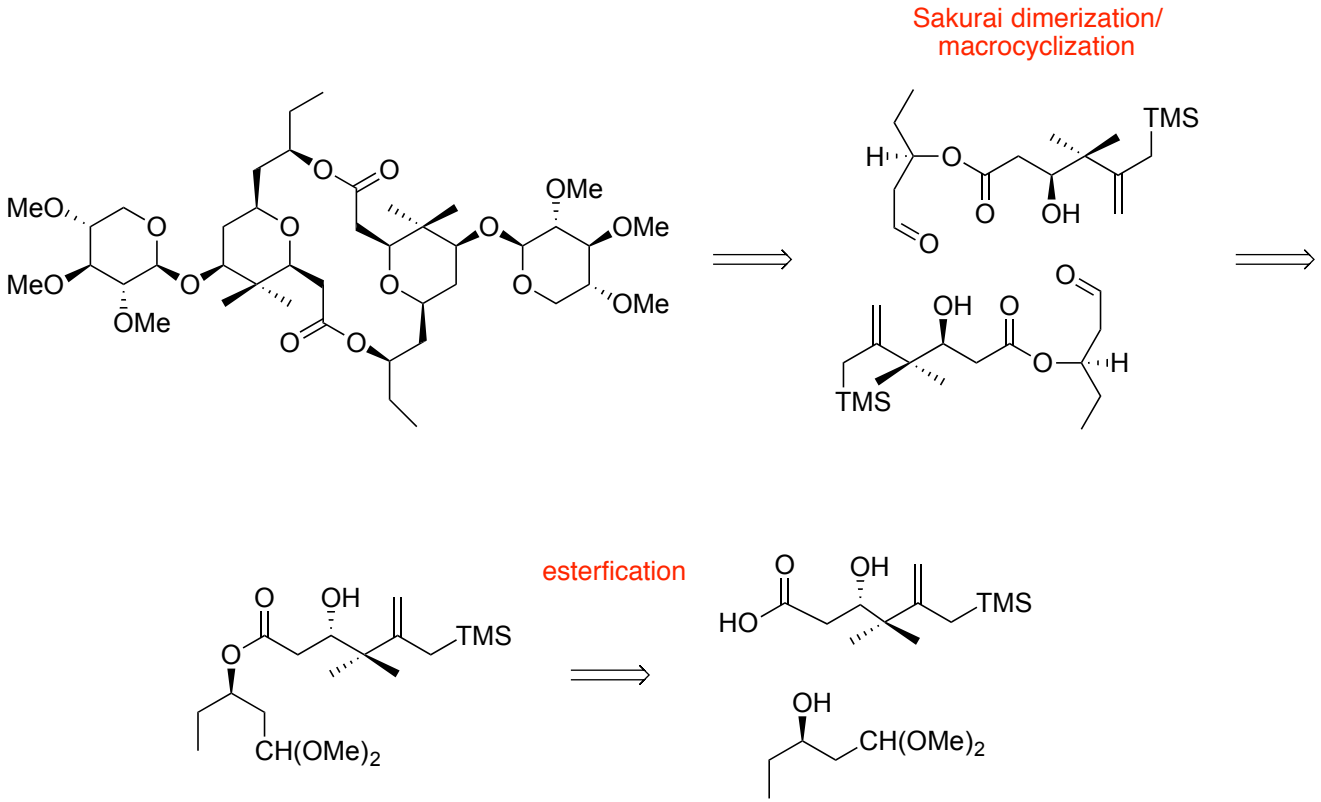


Key Oxidative Cyclization



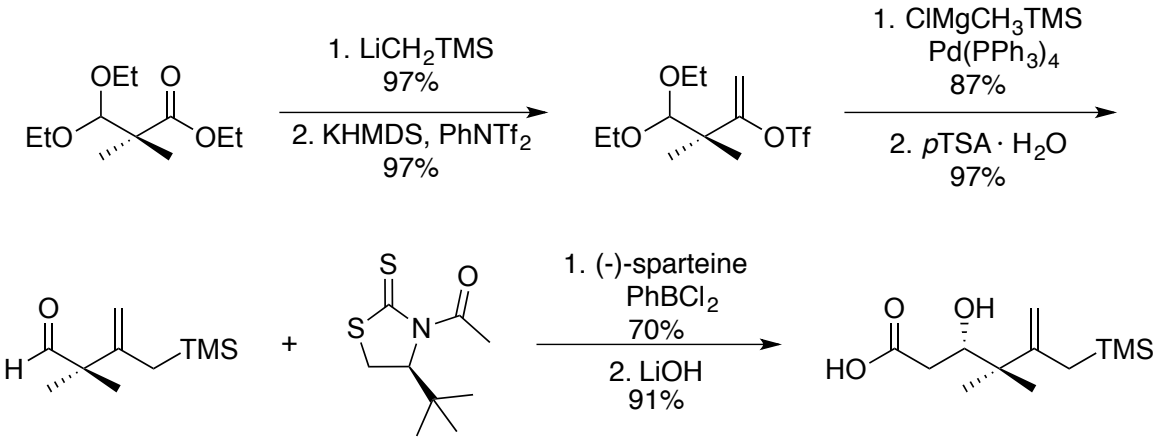


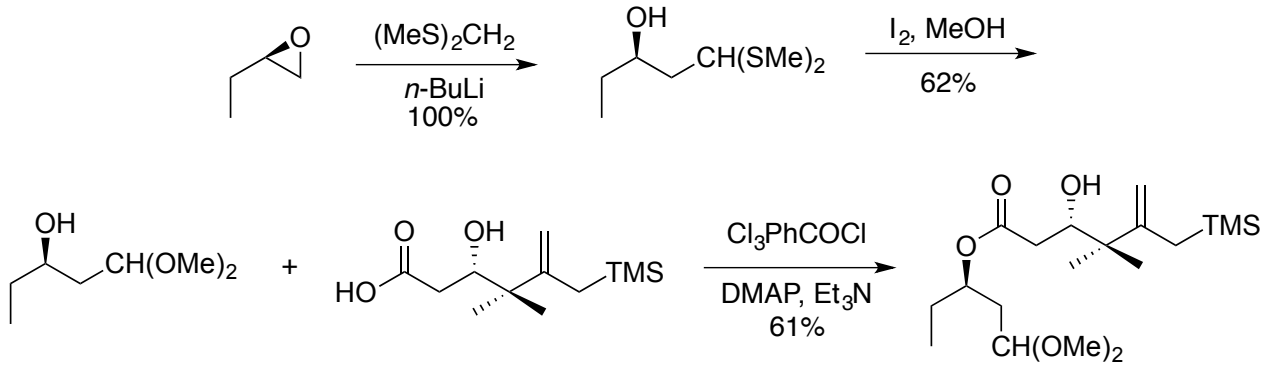
Rychnovsky Retrosynthesis of Cyanolide A



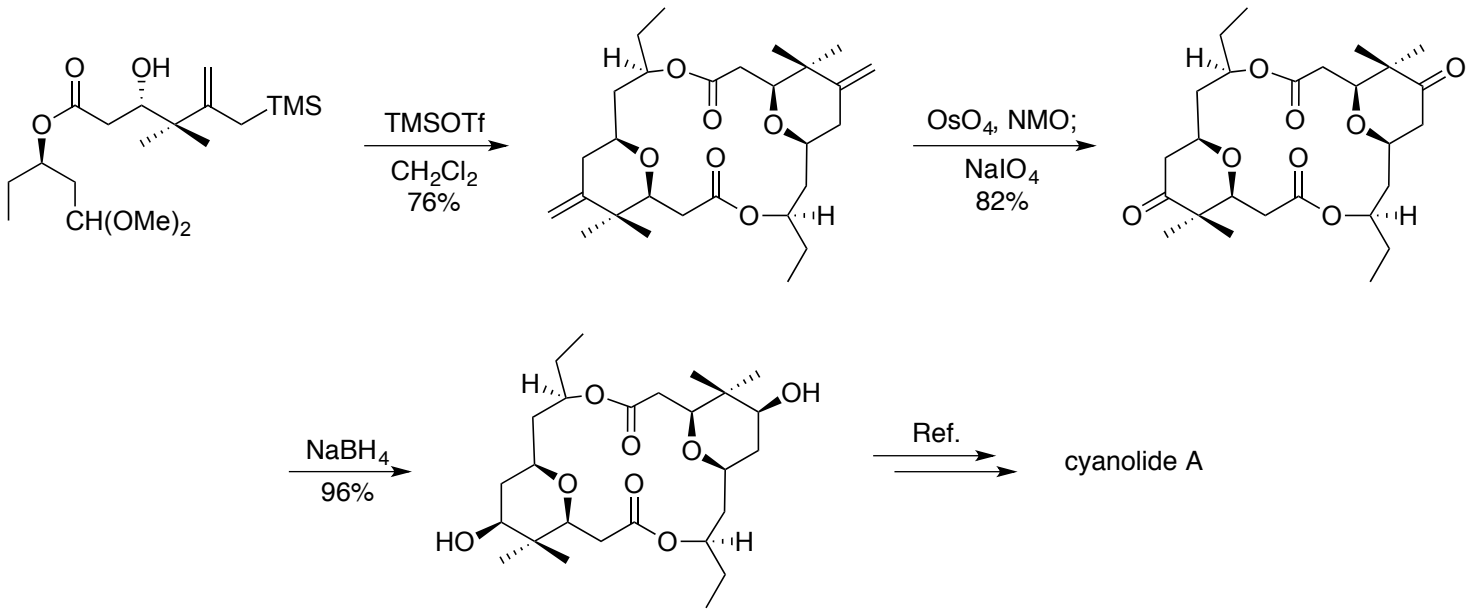
Gesinki, M.R.; Rychonovsky, S.D. *J. Am. Chem. Soc.* **2011**, *133*, 9727.

Rychnovsky “Monomer” Synthesis

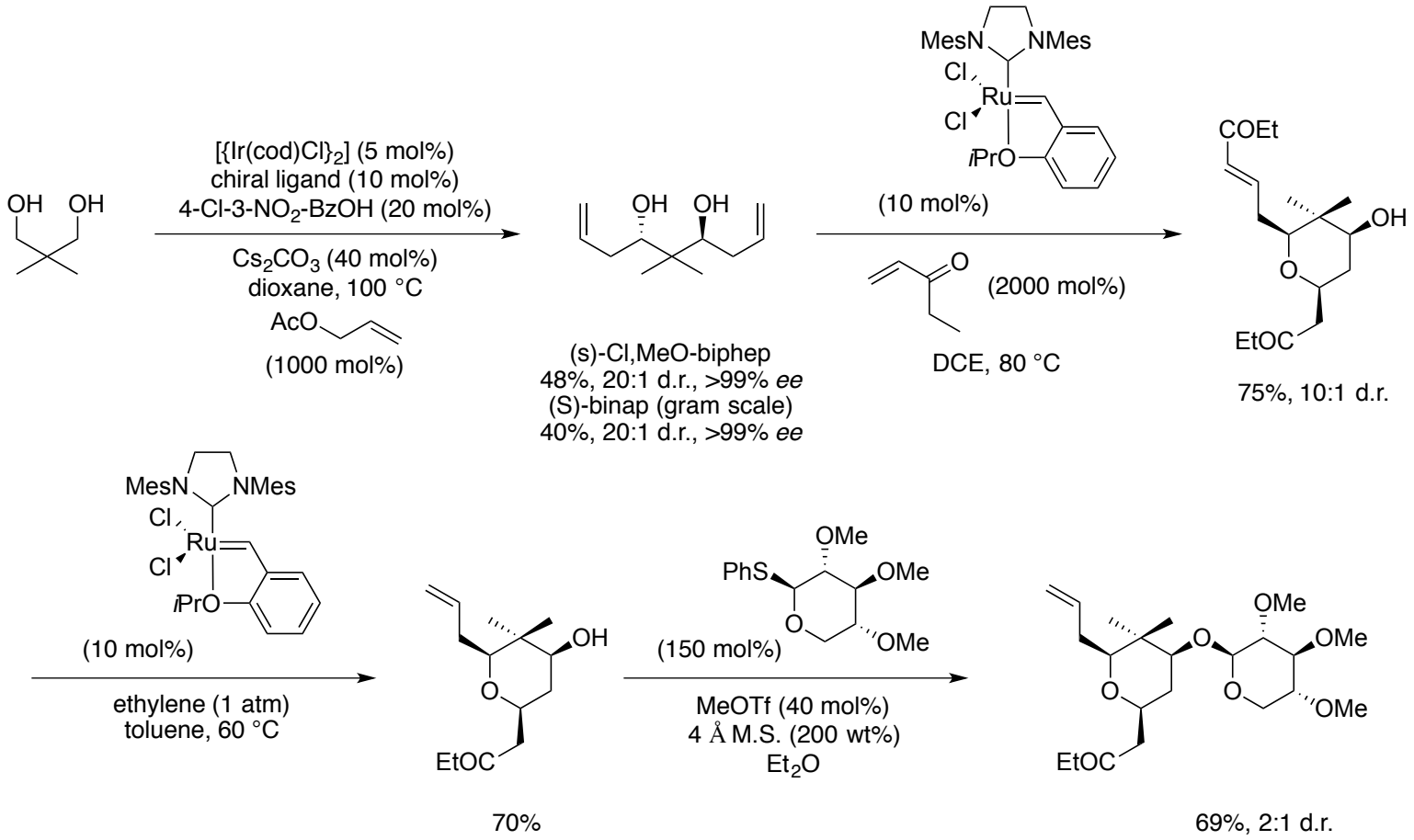




Rychnovsky Formal Total Synthesis



Krische First Generation Synthesis



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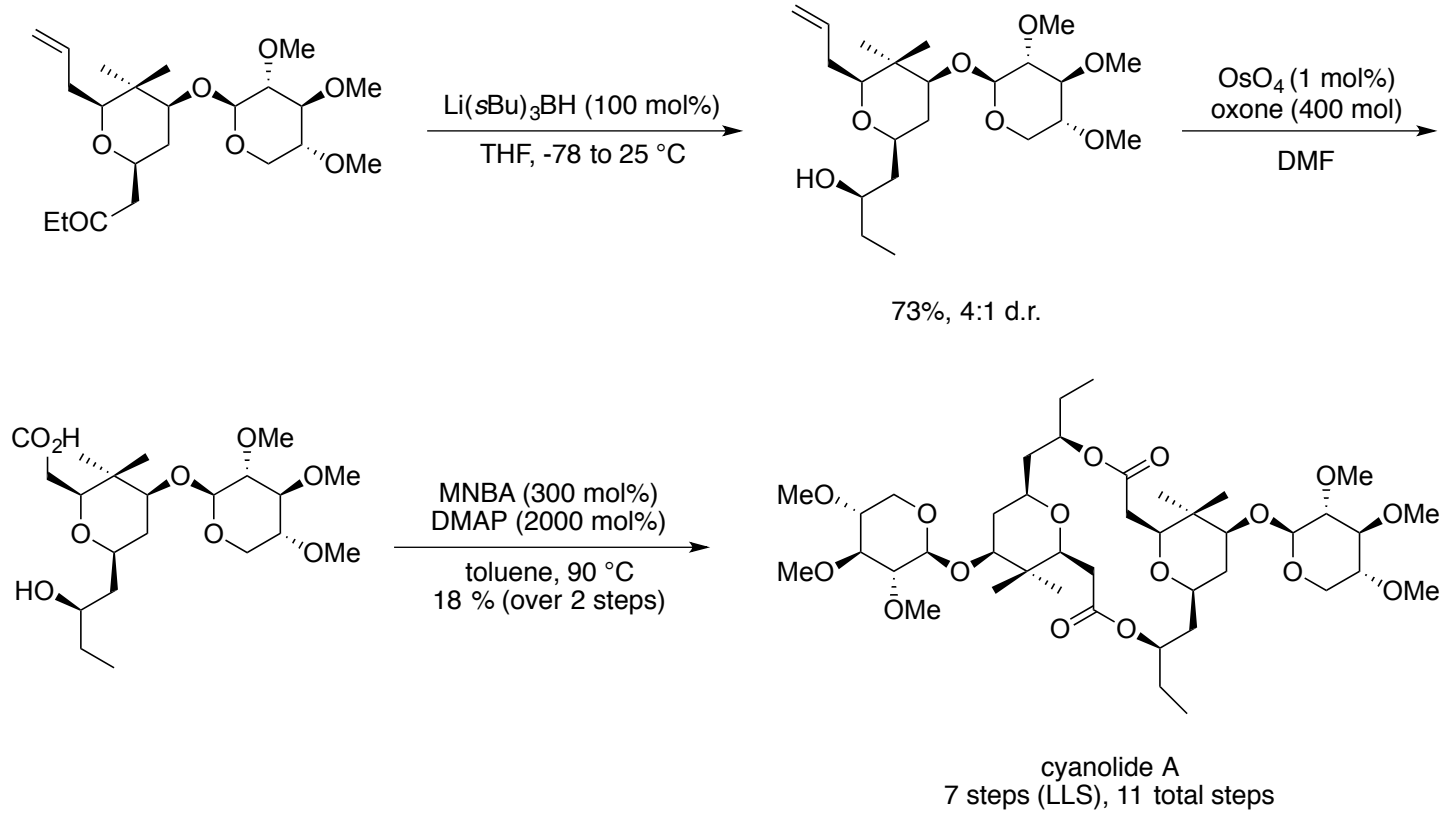
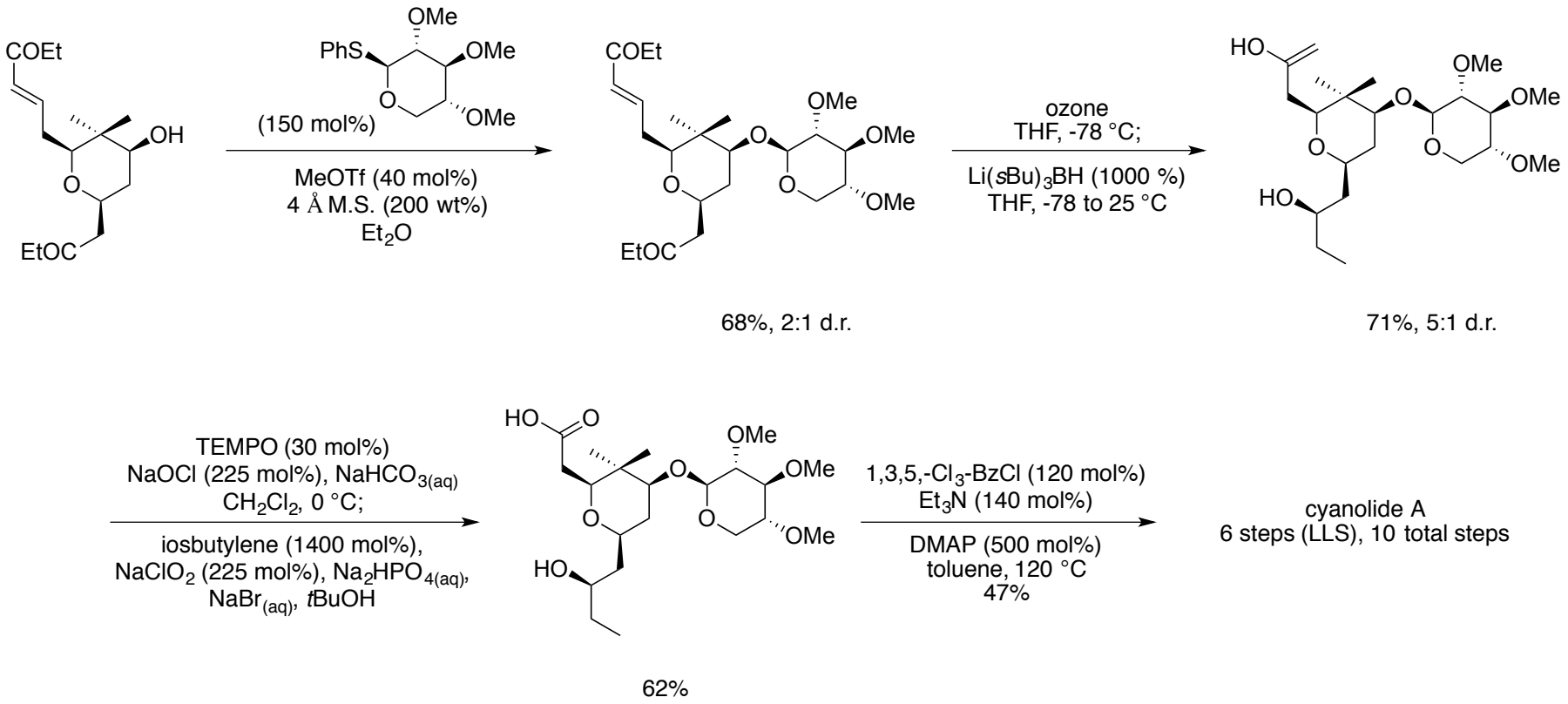
Iridium-Catalyzed Carbonyl Allylation: Kim. I.S.; Ngai, M.Y.; Krische, M.J. *J. Am. Chem. Soc.* **2008**, *130*, 14891.

Krische First Generation Synthesis



Krische Second Generation Synthesis



Conclusions

- Shortest route (6 steps LLS) to cyanolide A to date in 5.1% overall yield
- Showcases an enantioselective Ir-catalyzed carbonyl allylation methodology utilizing alcohols
- Demonstrates a Ru-catalyzed cross-metathesis/oxa-Michael cyclization