

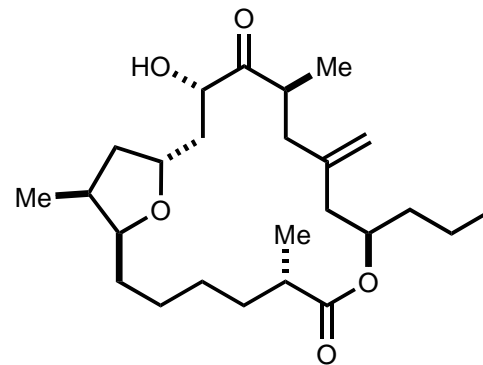
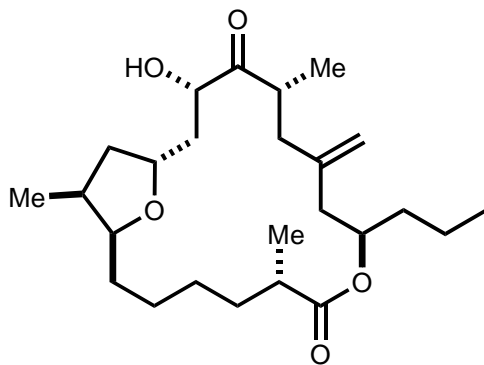
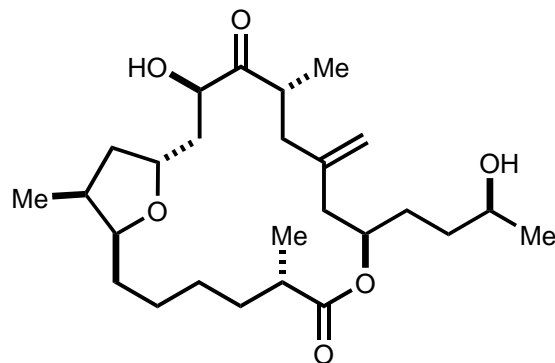
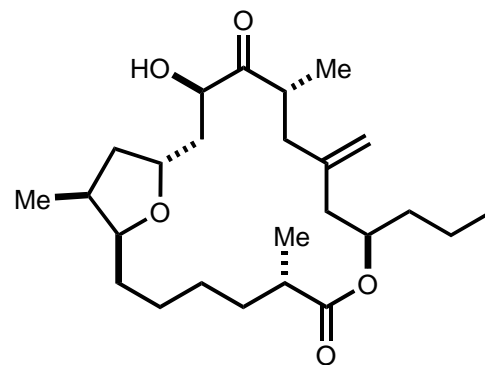
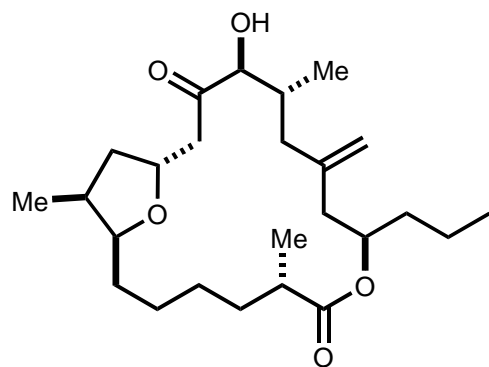
Amphidinolide Natural Products

- Isolated in 2000 from marine dinoflagellates of the genus *Amphidinium* living in symbiosis with Okinowan acoel flatworm *Amphiscolops*
- Have exhibited significant antitumor properties and cytotoxicity against a variety of NCI tumor cell lines as well as human carcinoma KB cells
- Consist of highly oxygenated, stereochemically rich macrolactones ranging from 12 to 29 atoms with various degrees of unsaturation.

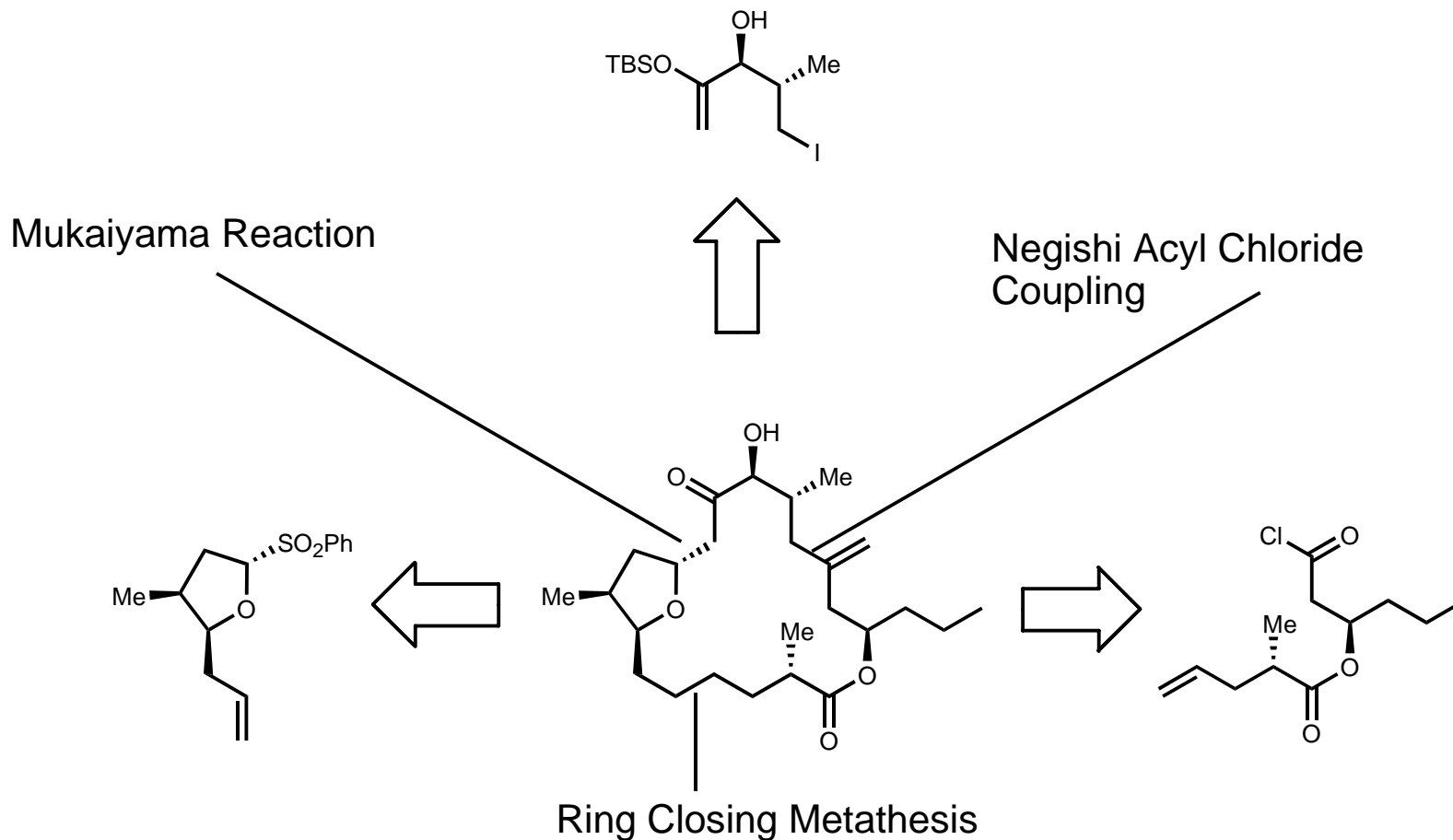
Total Synthesis of the T-Series

- Amphidinolides T1 and T3-5 have been synthesized to date
- The first total synthesis of T4 was reported by Fürstner in 2002 and T1, T3, T4, and T5 in 2003.
- The total synthesis of Amphidinolide T1 was first reported by Ghosh in 2003.
- The Jamison group reported the syntheses of Amphidinolide T1 and T4 in 2004 and 2005.
- In 2006 the Zhao group reported the total synthesis of Amphidinolide T3
- The library of the total synthesis of other Amphidinolides continues to grow steadily

A Glance at the T-Series

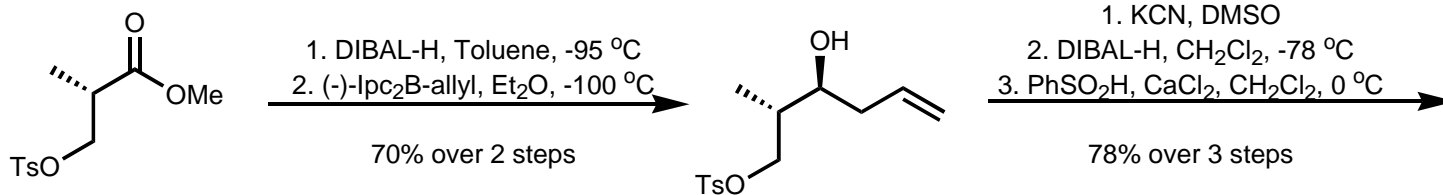


Fürstner's Retrosynthesis

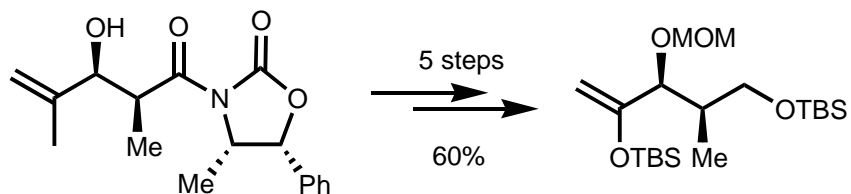
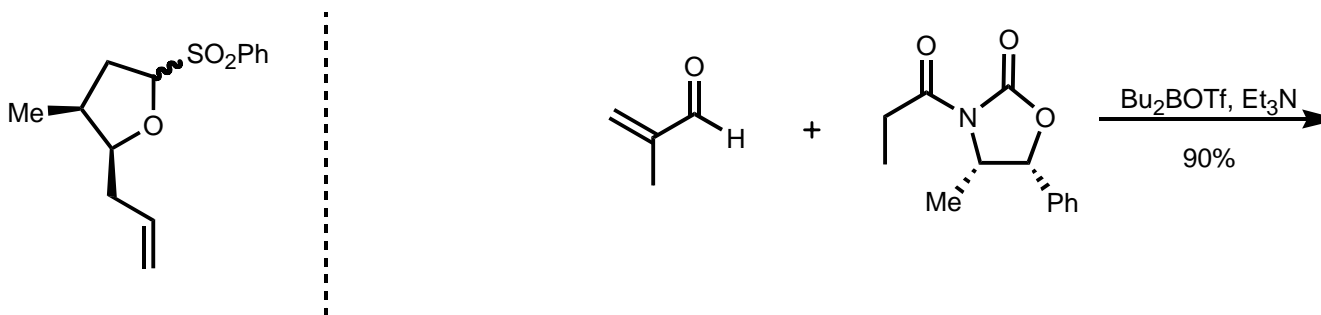


Fürstner, A.; Aïssa, C.; Ragot, J. *Angew. Chem.* **2002**, 114, 4958.
Fürstner, A.; Aïssa, C.; Ragot, J. *J. Am. Chem. Soc.* **2003**, 125, 15512.

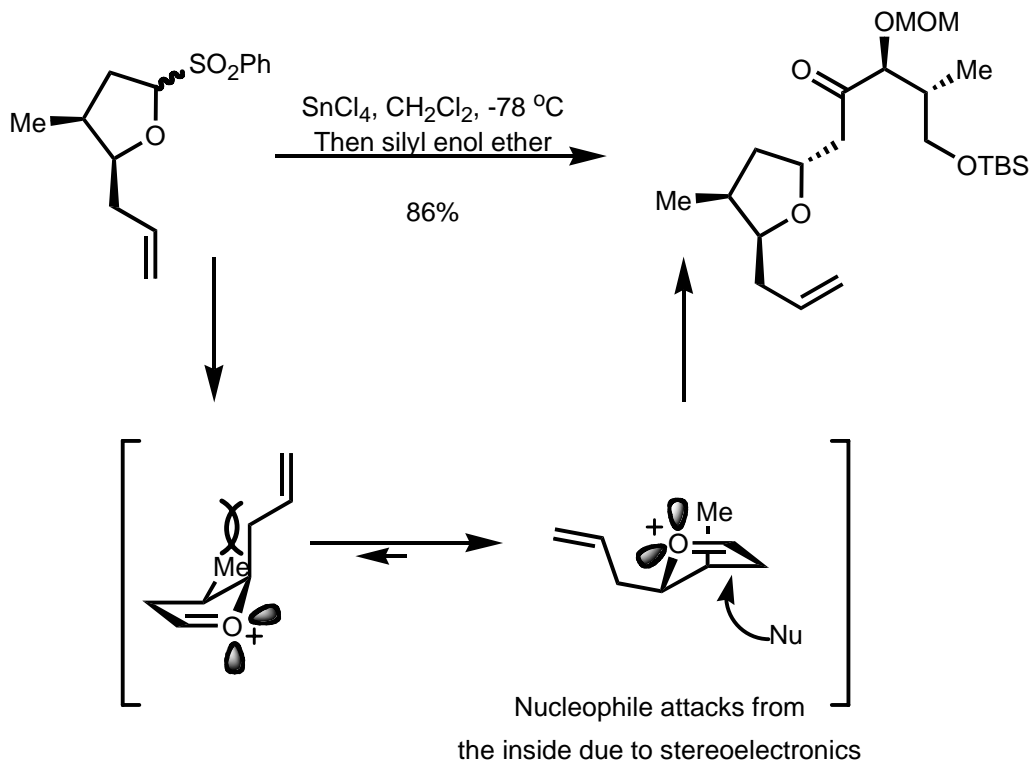
Assembly of the Mukaiyama Substrates



HO- is Commercially Available

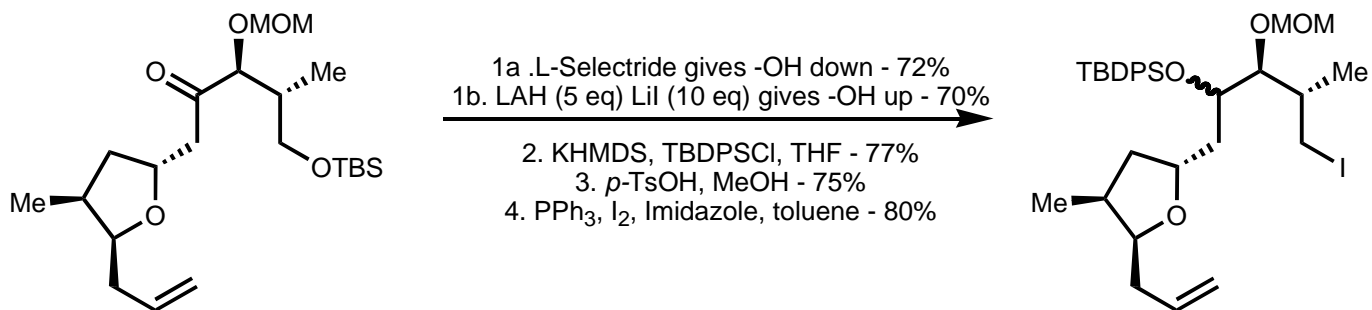
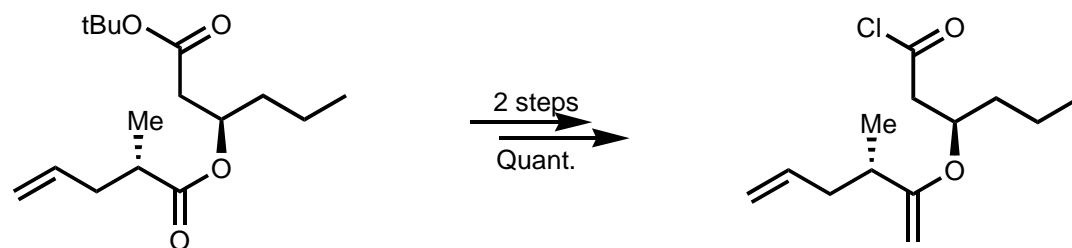
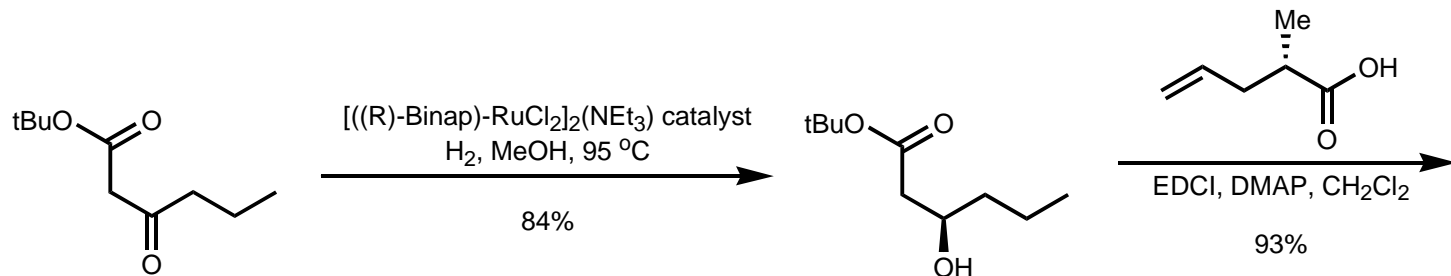


Mukaiyama Selectivity

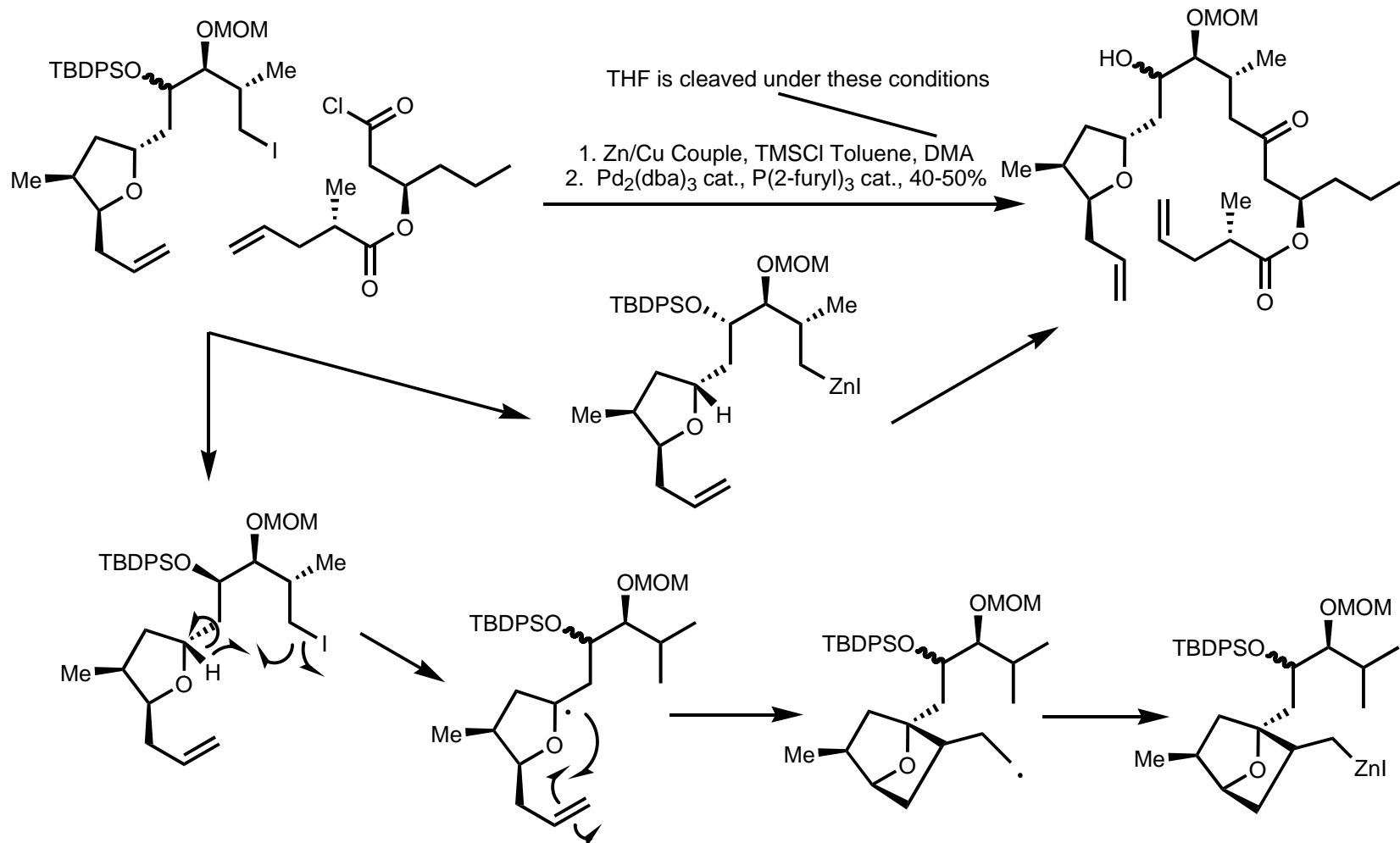


JACS 1999, 121, 12208

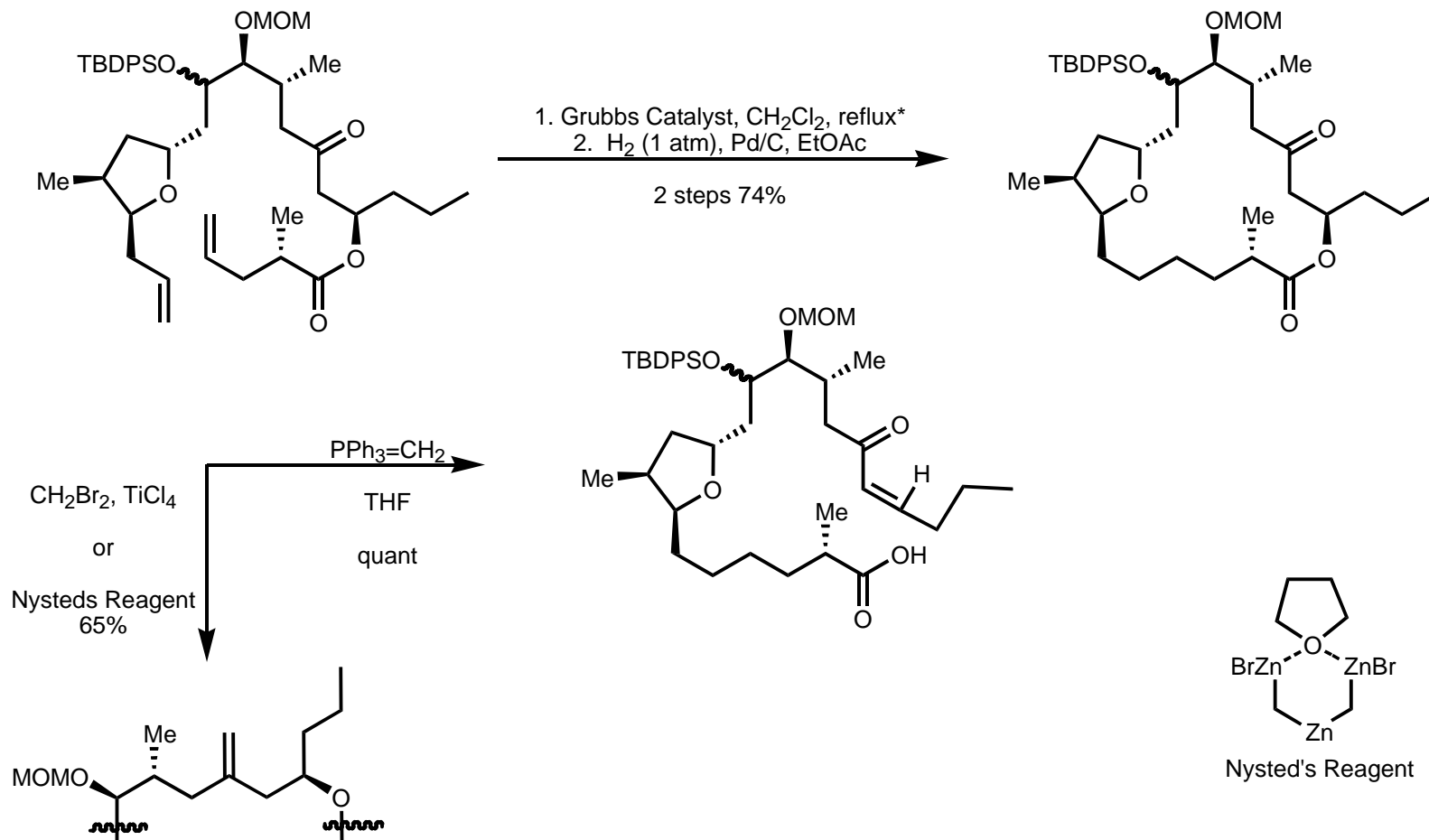
Negishi Coupling Partners



Negishi Acyl Chloride Coupling

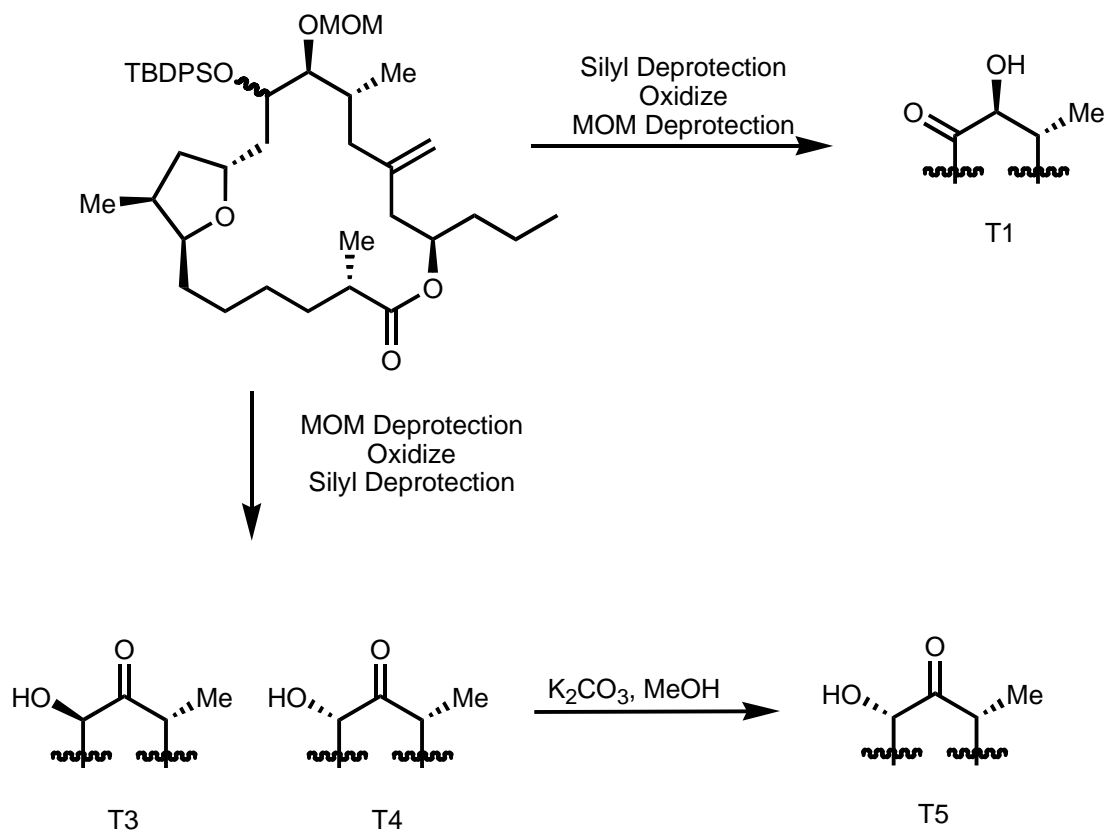


Olefin Issues



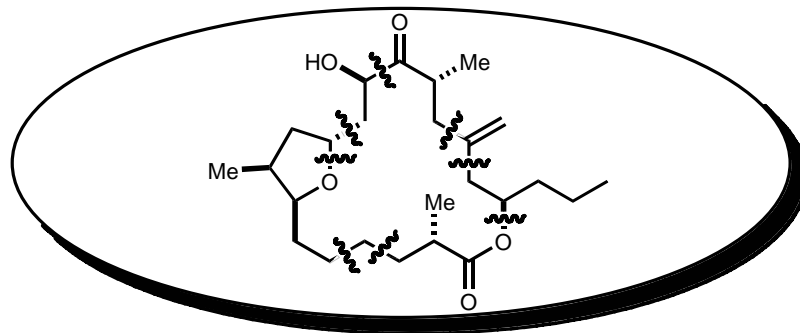
Peterson Olefination - complete failure

Endgame

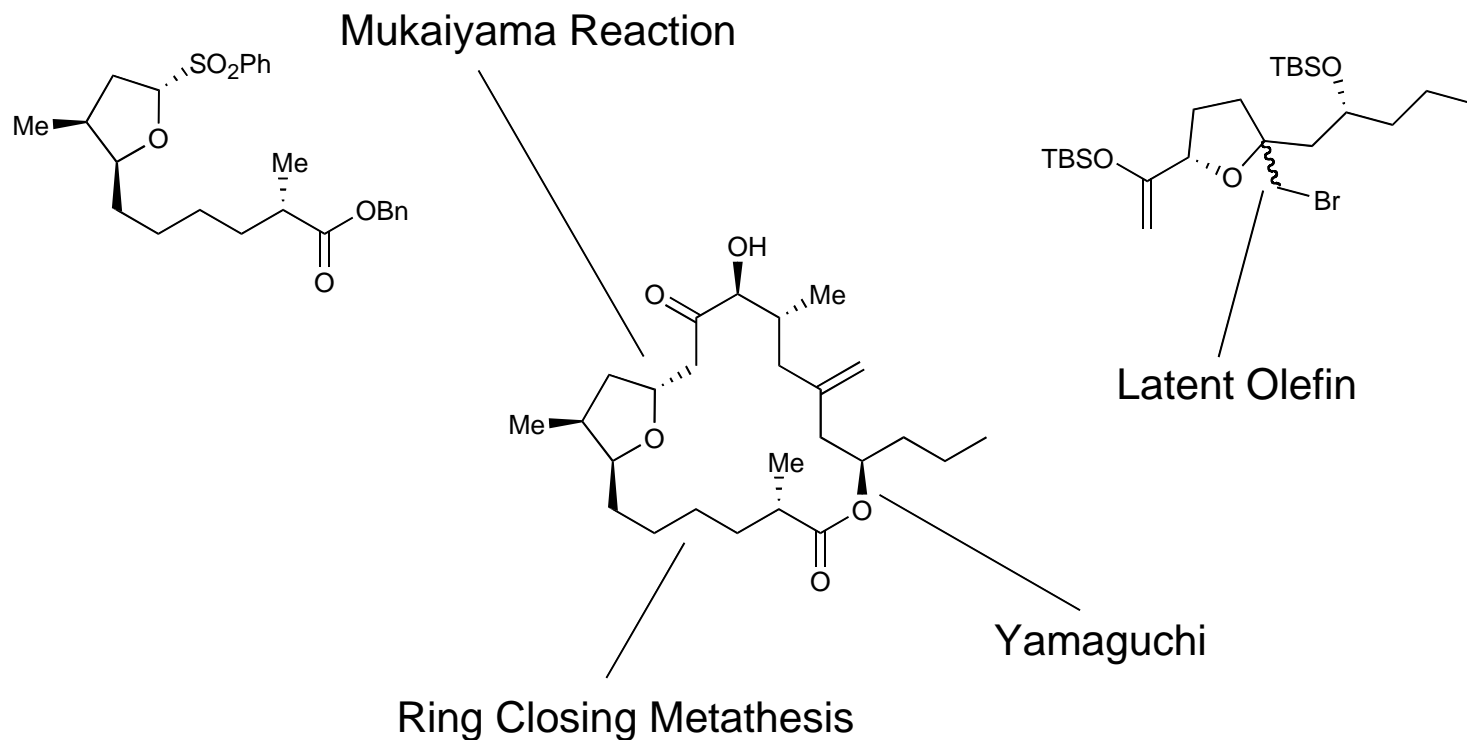


What we learned...

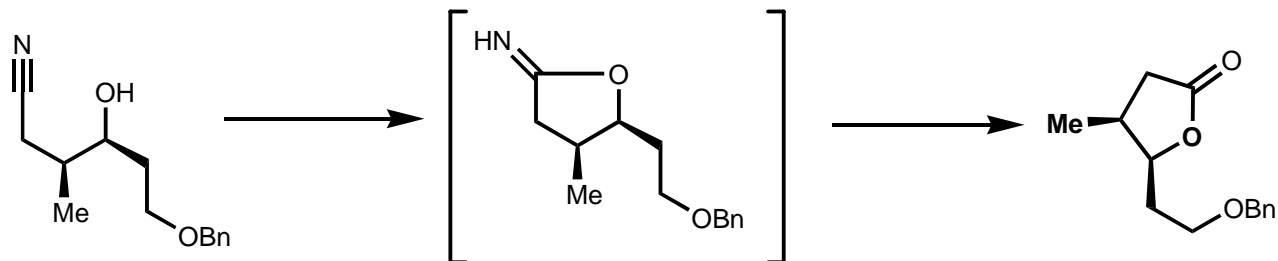
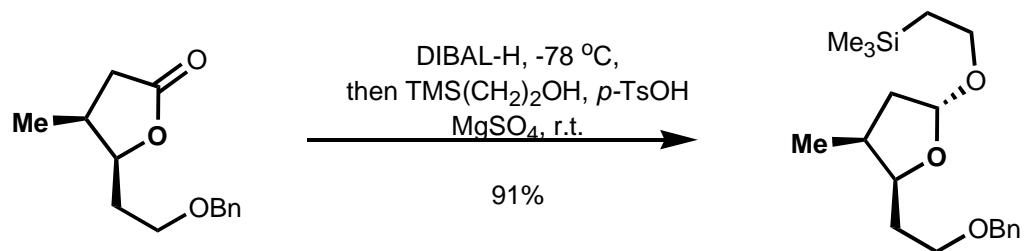
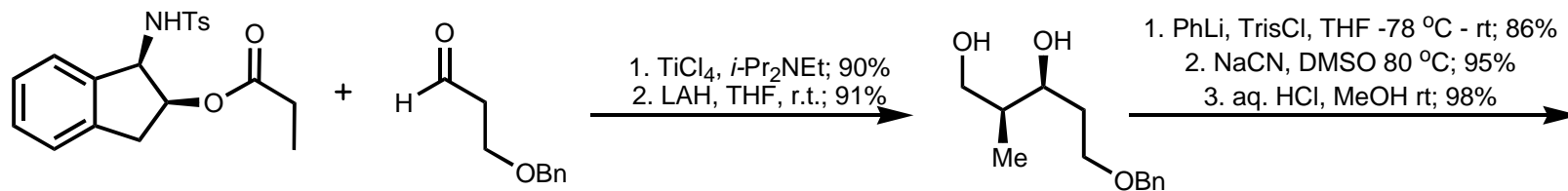
- The Mukaiyama reaction is an efficient method of building the molecule up from the furan
- Protecting groups, if not chosen carefully, may alter the desired conformations of advanced intermediates and produce unfavorable reactivity
- The Negishi coupling is probably not the best coupling reaction
- Olefination is problematic after generation of the macrolactone
- Synthesizing the Northern Hemisphere of the molecule with differentiable protecting groups provides a template for synthesis of 4 of 5 T-Amphidinolides



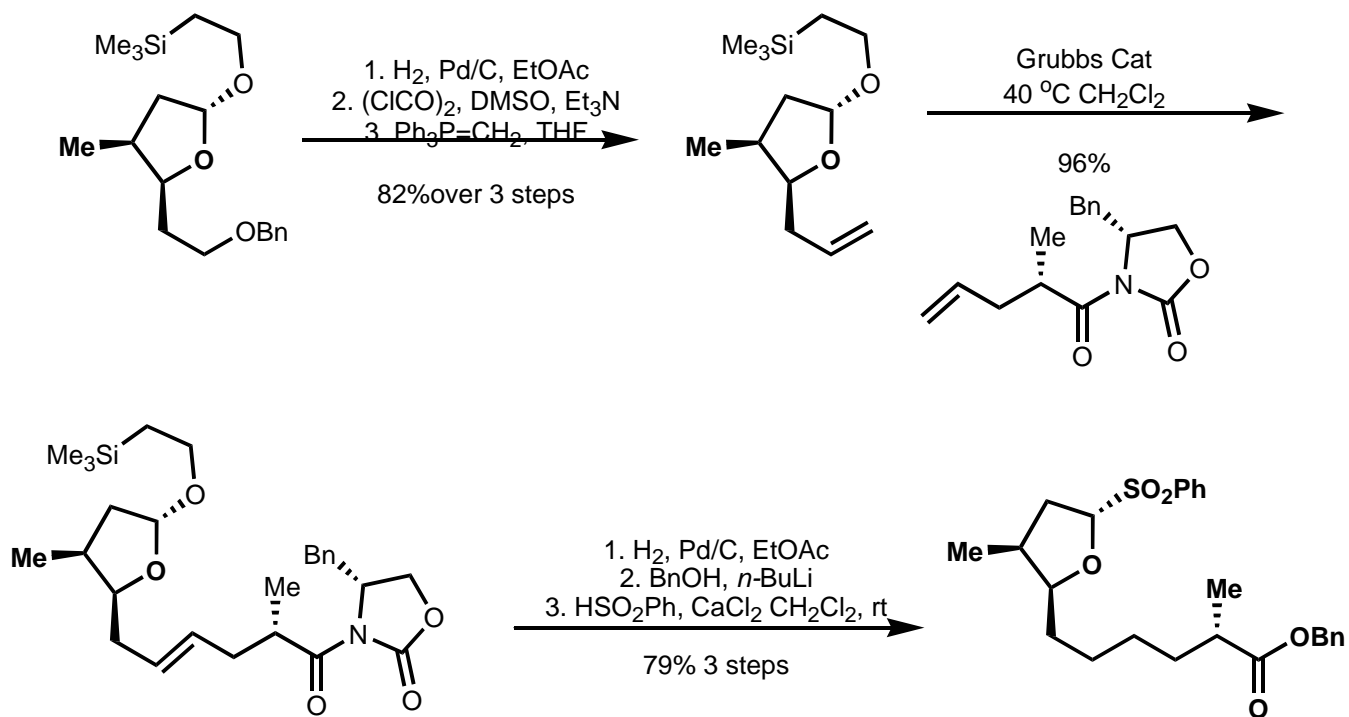
Ghosh's Retrosynthesis



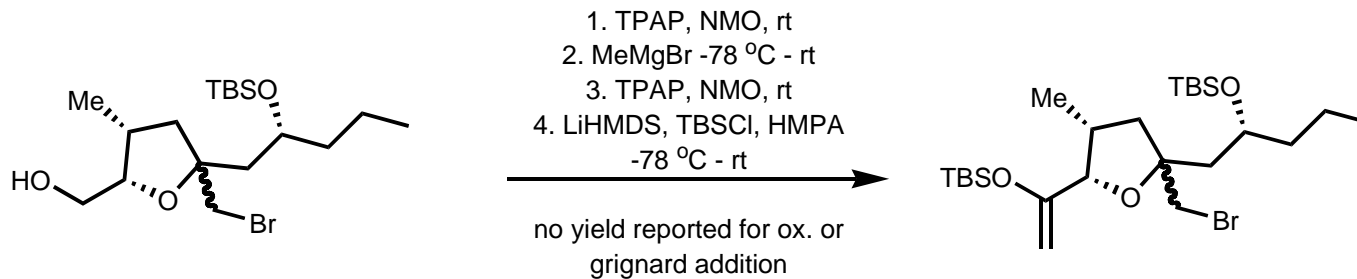
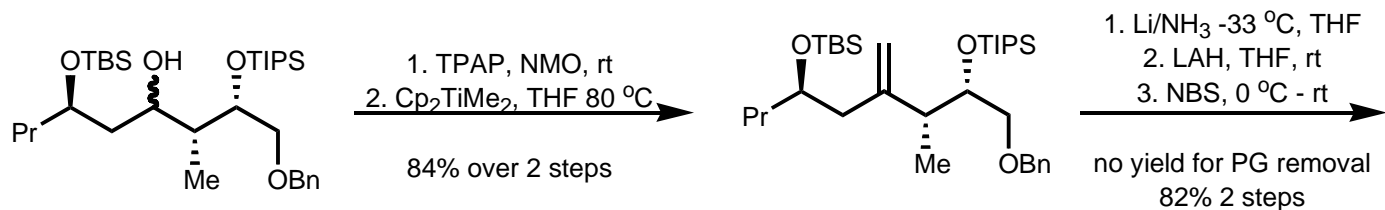
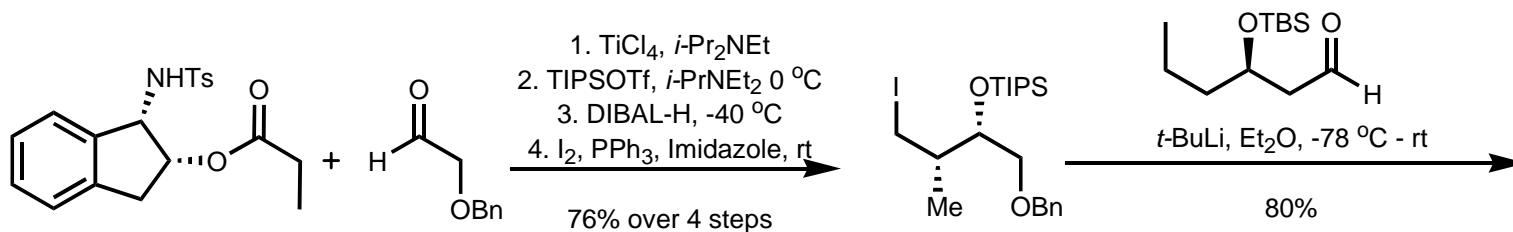
Building the Furan



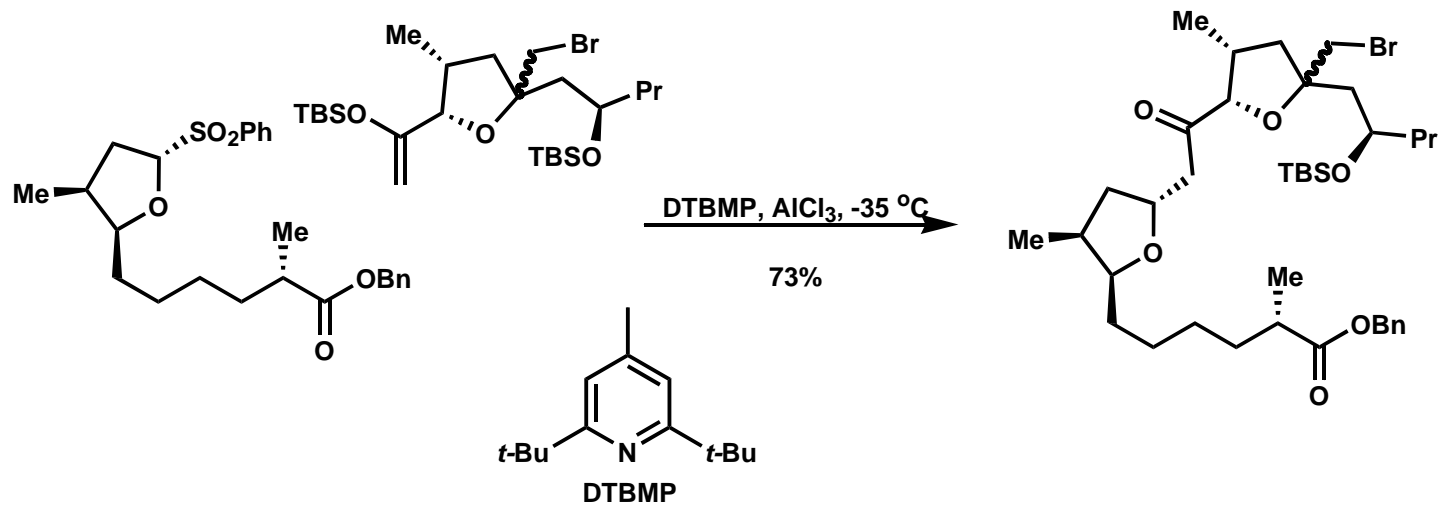
Mukaiyama Precursor



Silyl Enol Ether Construction

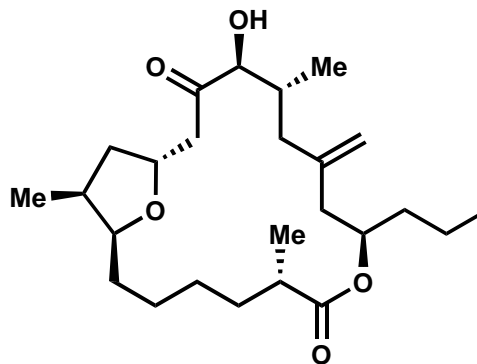


Endgame



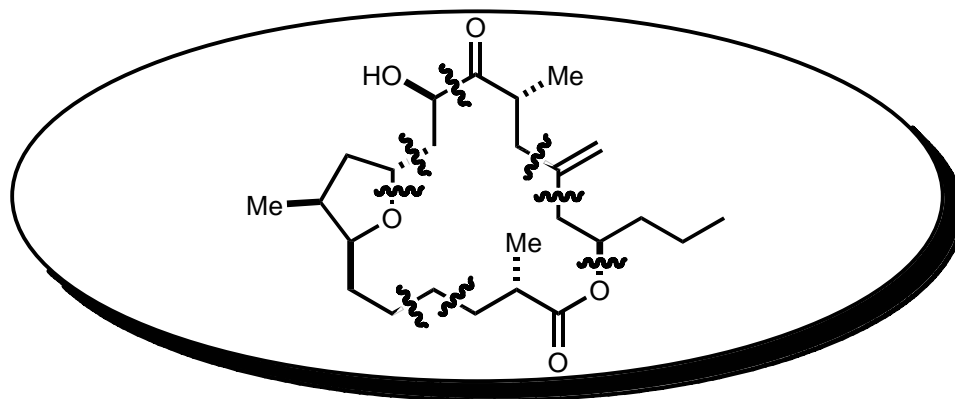
1. HF-pyr, pyr
2. H₂, Pd/C
3. 2,4,6-(Cl₃)PhCOCl
i-Pr₂NEt, then DMAP toluene
4. Zn, NH₄Cl, EtOH, 80 °C

38% over 4 steps
no yield reported for hydrog.



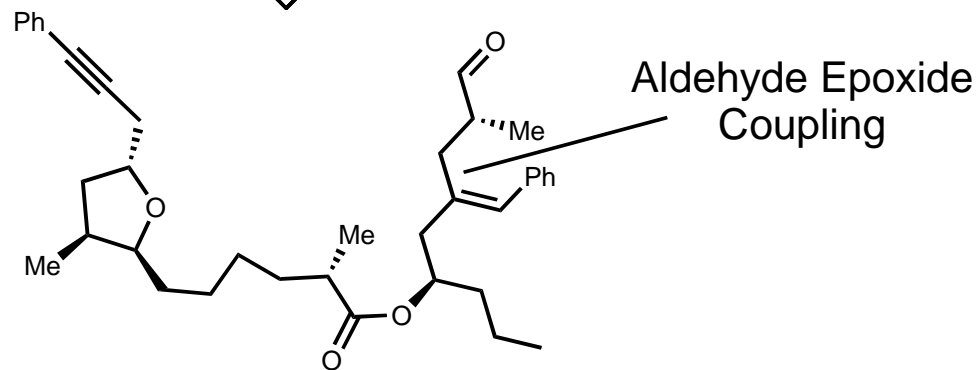
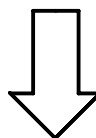
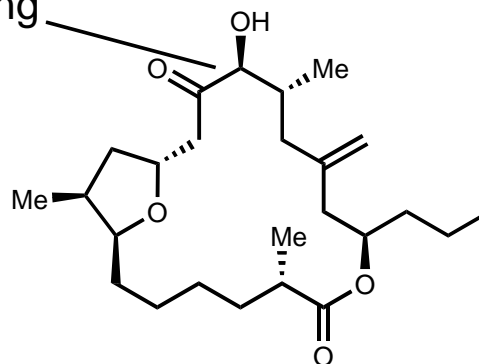
Improvements?

- The olefin was protected in this synthesis although it seems the protection wasn't very effective
- The furan was used as the foundation for building up the molecule and its construction was more concise
- RCM was an effective means of coupling for generation of the side chain prior to the macrocyclization
- Yamaguchi conditions provided to be an effective means of completing the synthesis

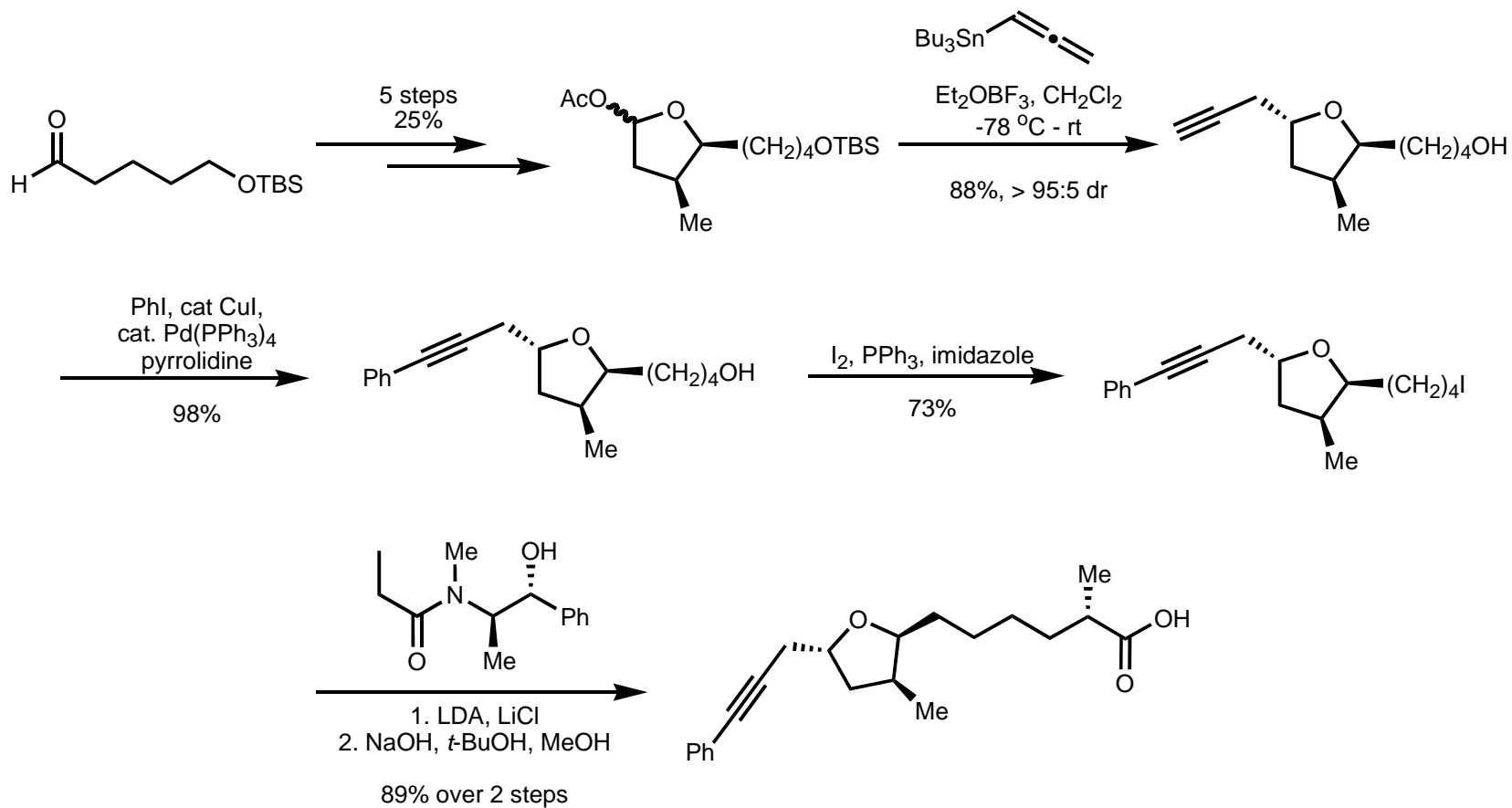


Jamison Retrosynthesis

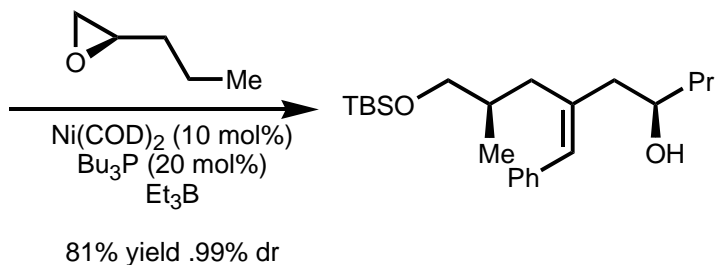
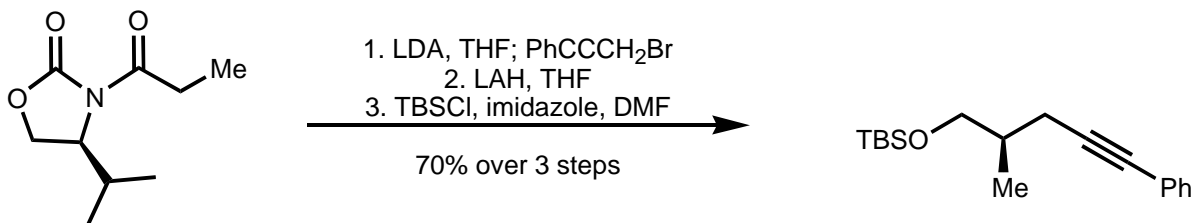
Aldehyde Alkyne Coupling



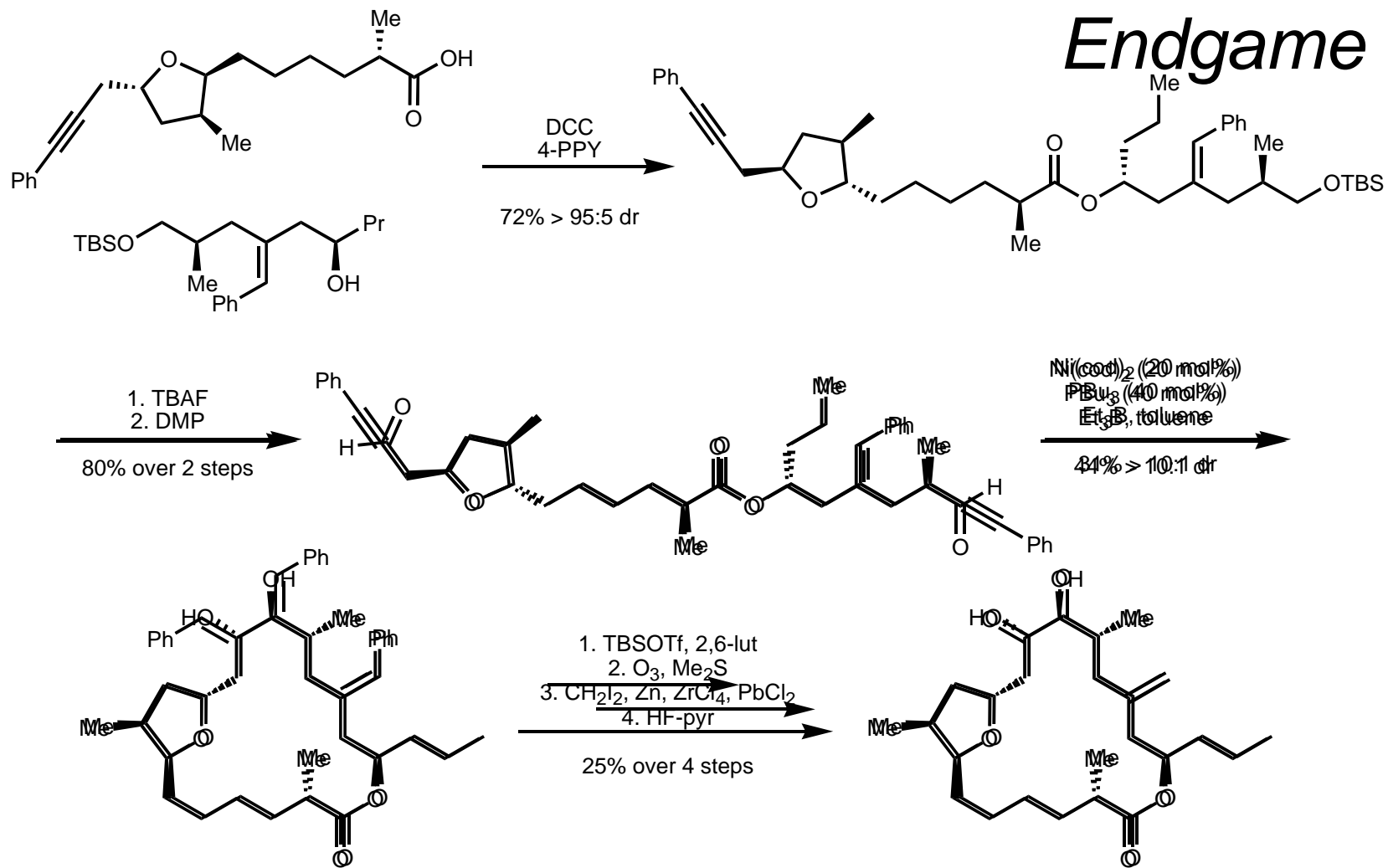
Lactone Precursor



Epoxide-Alkyne Coupling



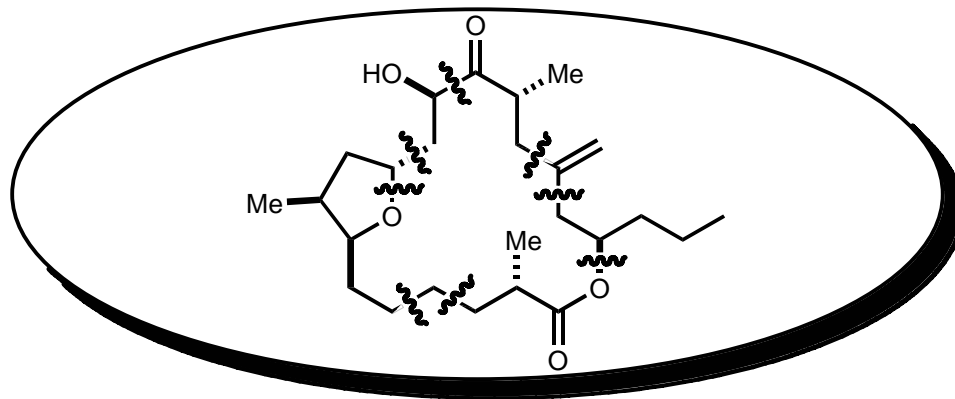
Jamison, T.F.; Molinaro, C. *J. Am. Chem. Soc.* **2003**, 125, 8076



Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, 68, 156

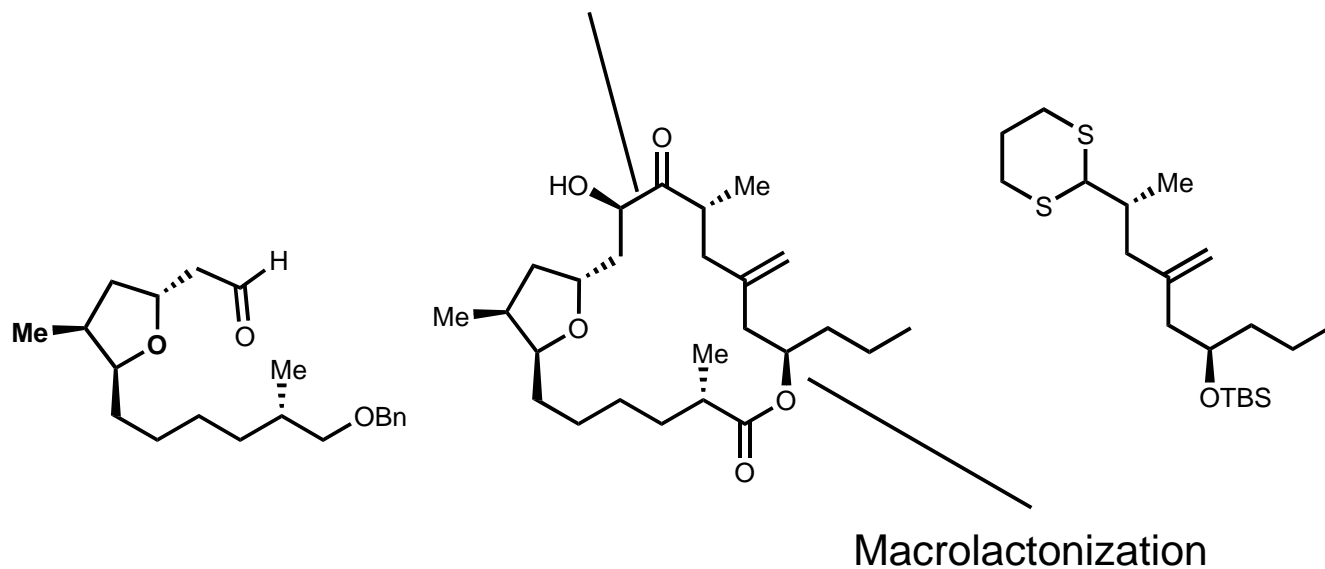
Improvements?

- Demonstrated that the molecule can tolerate a fair amount of manipulation during the late stages
- The conformation of the molecule in the late stages can terminate both internal and external means of stereocontrol
- Selective oxidative cleavage can be a useful means of protection



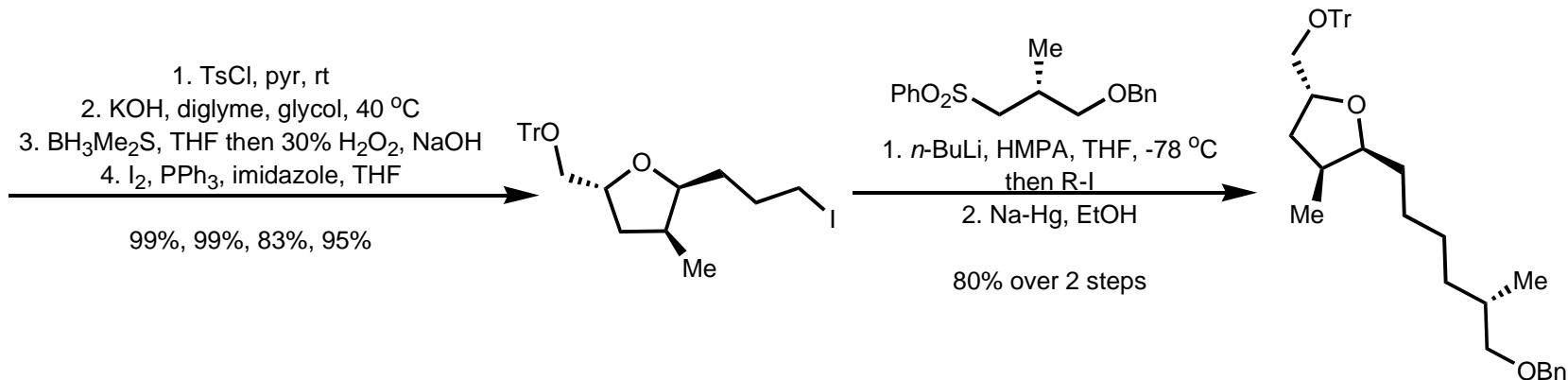
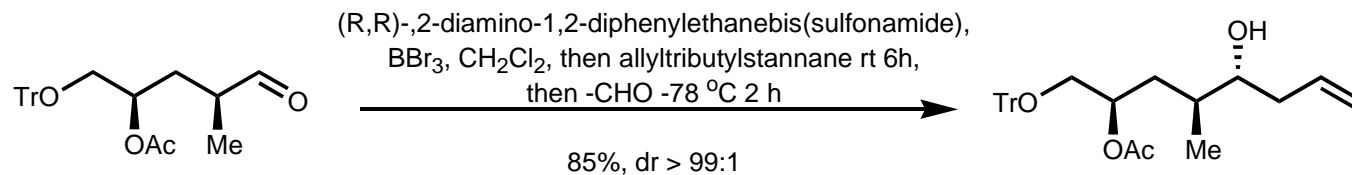
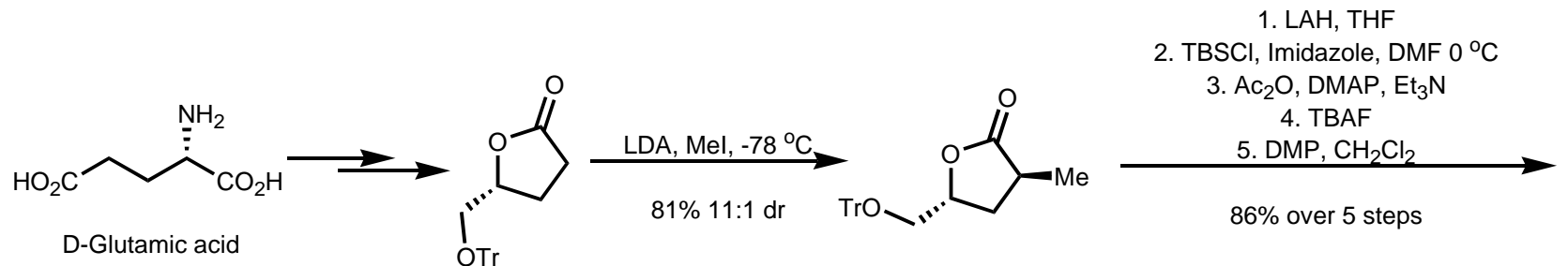
Zhao's Retrosynthesis

1,3-Dithiane Addition

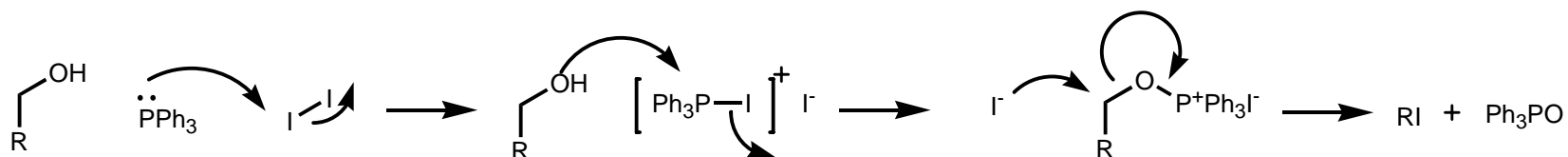
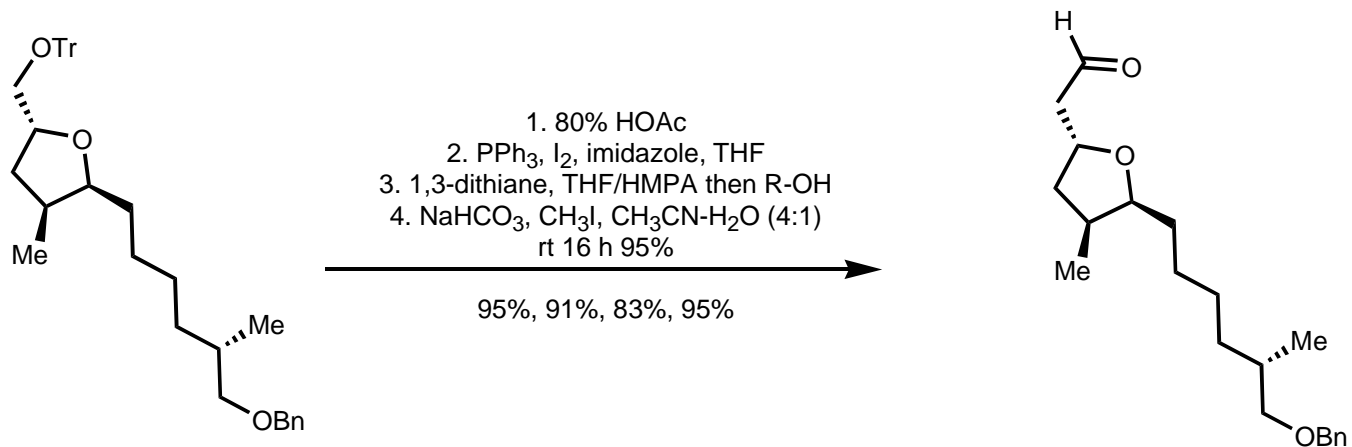


Deng, L.; Huang, X.; Zhao, G. *J. Org. Chem.* **2006**, 71, 4625.

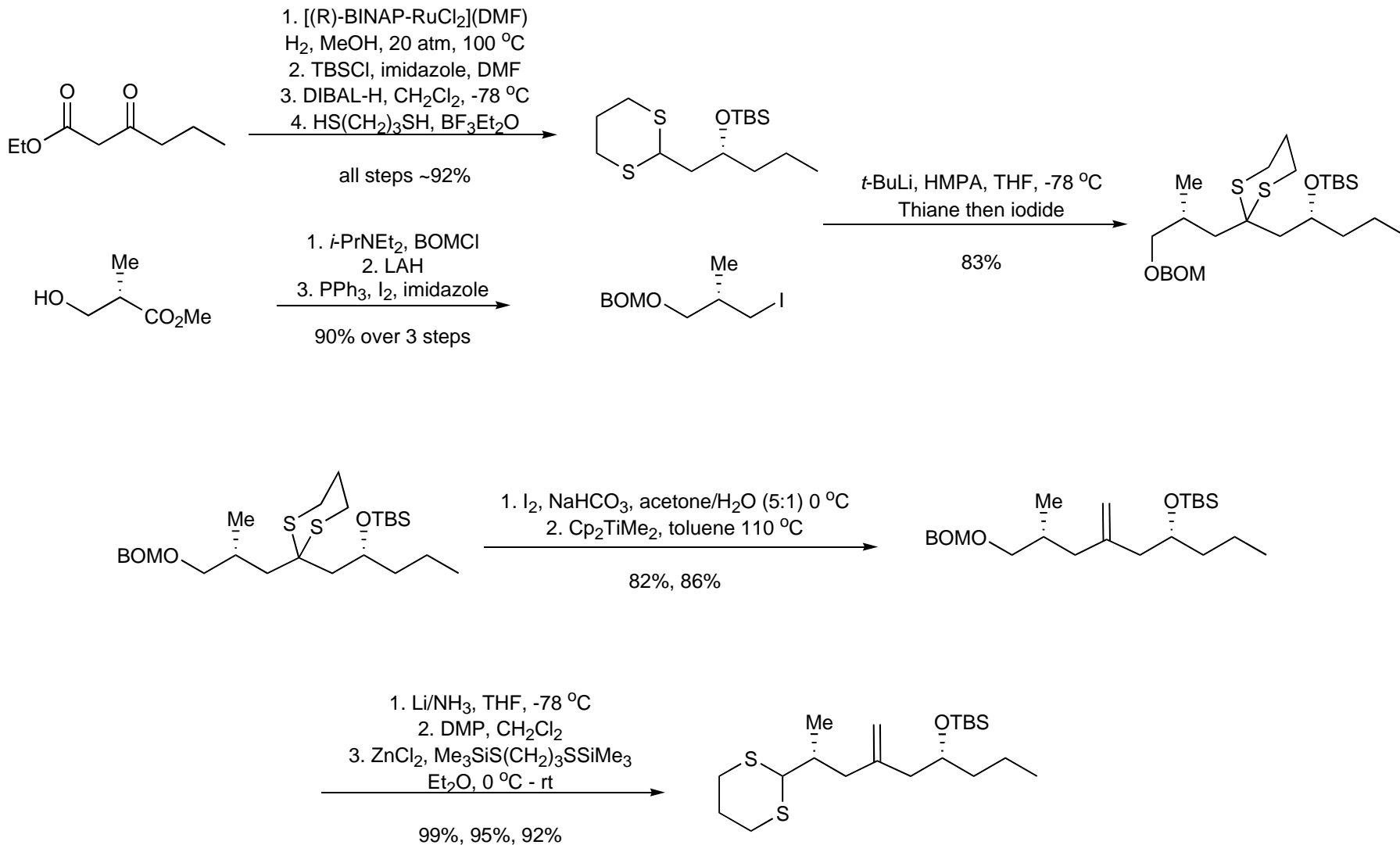
Building the Furan



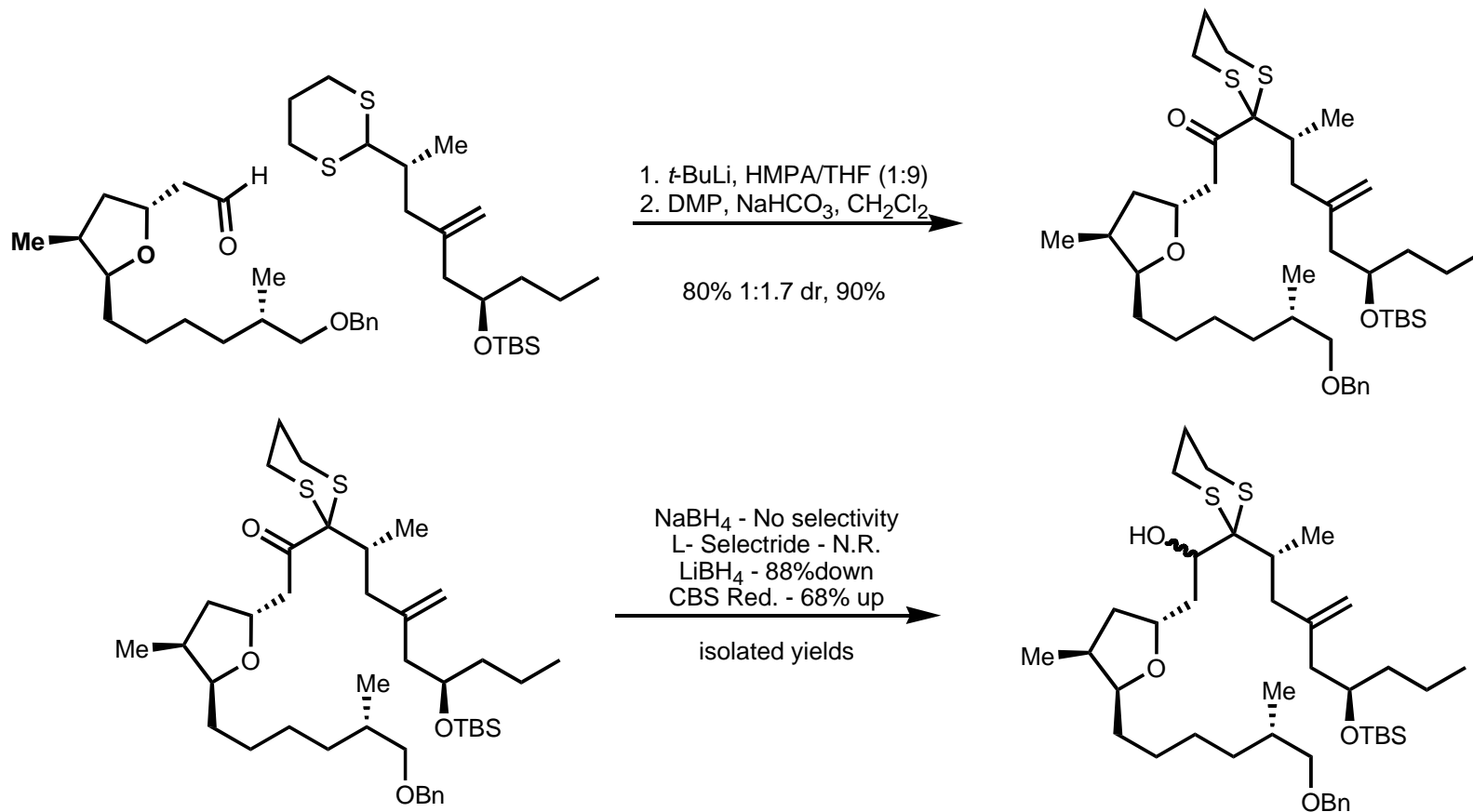
Generating the Aldehyde



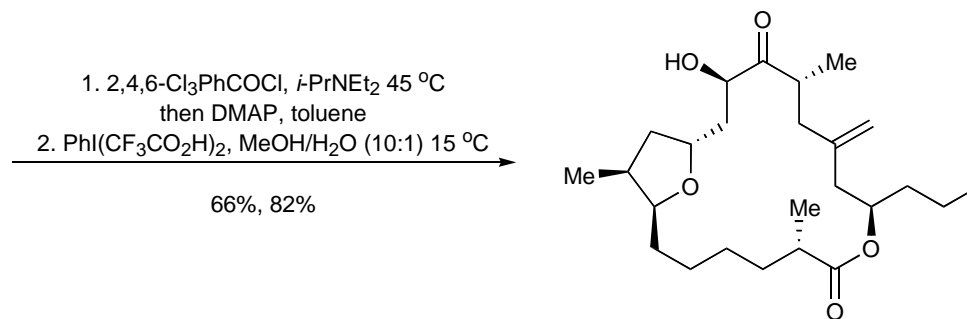
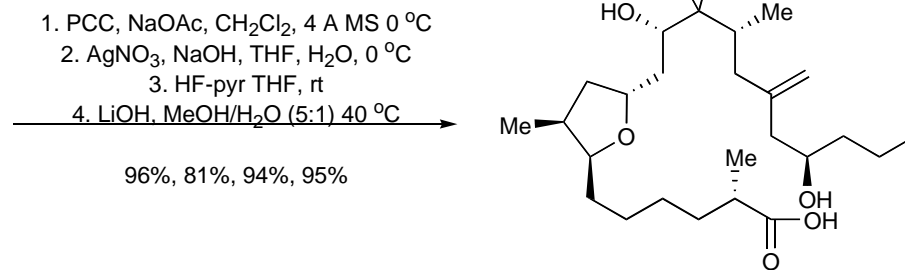
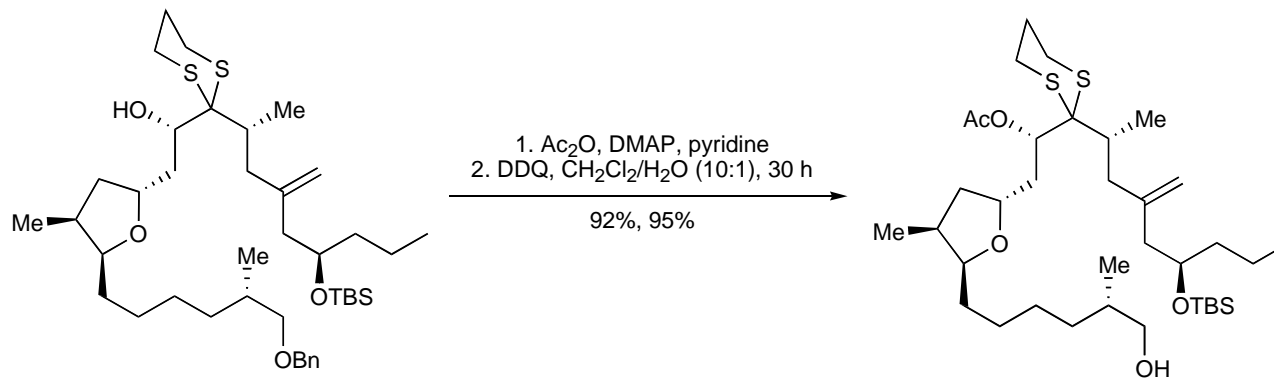
Umipoles Everywhere!



Back to Asymmetric Reductions

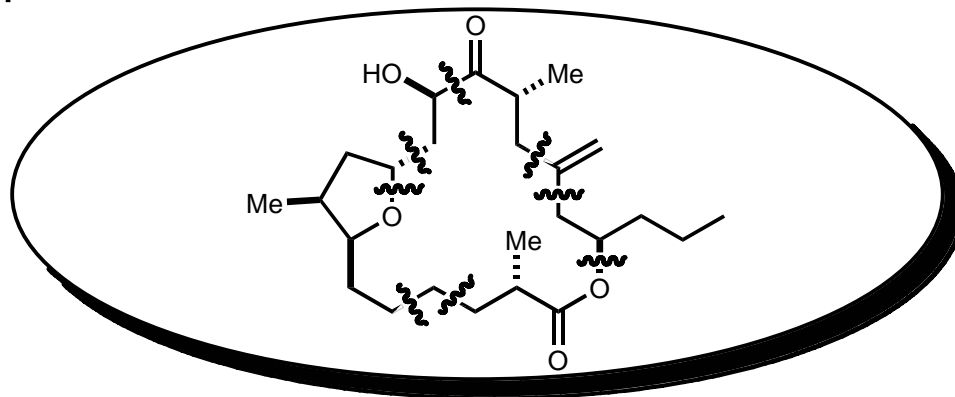


Endgame



Improvements?

- The olefin was installed early to prevent future problems and carried through successfully
- The furan was again used as a foundation for building the molecule although it was prepared in a different way
- The macrolactonization that was demonstrated by Ghosh was effectively used
- The current synthesis provides a template for preparation of future amphidinolides



Final Thoughts

- After several total syntheses the reactivity has been sufficiently investigated
- Of the four syntheses each has its own highlights and drawbacks with the “best” synthesis probably as a blend of each
- The broad scope and report by Fürstner provided future researchers a template to follow and improve upon
- The evolution is apparent in that each subsequent synthesis drew upon what was learned from previous efforts to continuously improve how the target molecule is prepared