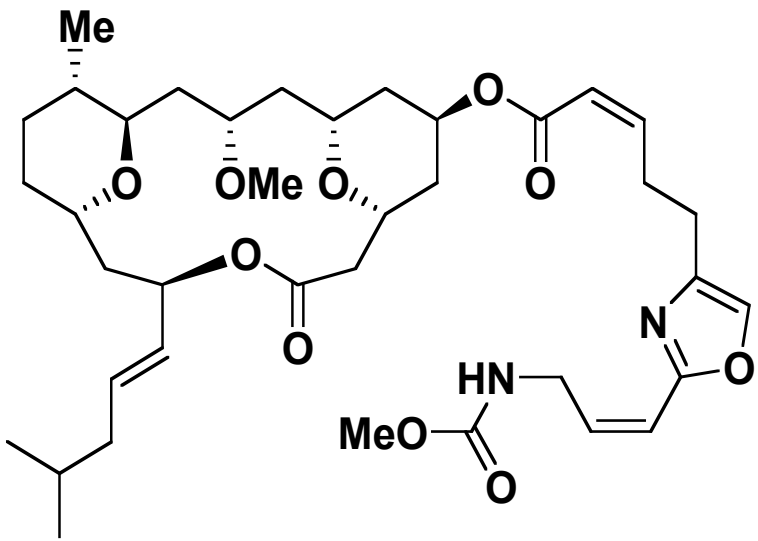
Syntheses of Leucascandrolide A



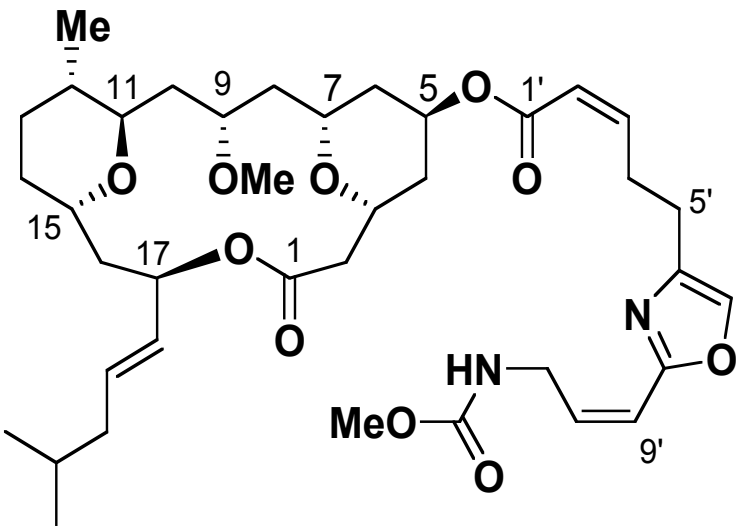
Introduction

- Discovered in the slope eastern coast of New Caledonia in 1996 by Pietra and coworkers from a new genus of calcareous sponge, *Leudcascandra caveolata*.
- Highly potent cytotoxic against KB oral epidermoid carcinoma (IC_{50} = 0.05 μgmL^{-1}) and P388 leukemia (IC_{50} = 0.25 μgmL^{-1}) cell lines as well as a powerful inhibitor of *Candida albicans*, a pathological yeast that attacks AIDS patient.
- Biogenesis origin unknown.
- Suspected to be of microbial origin.
- Later expedition failed to collect any more material.

Helv. Chim. Acta **1996**, *79*, 51.
Helv. Chim. Acta **1999**, *82*, 347.

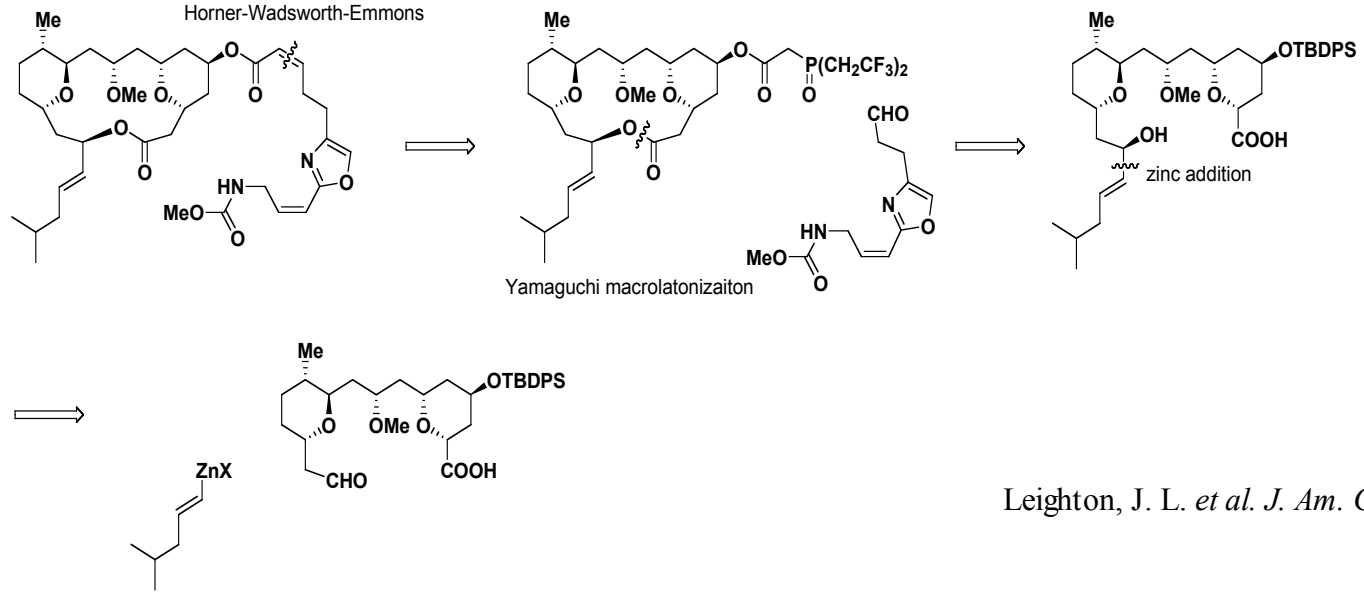
Introduction

- Structural features
  - Doubly O-bridged 18-membered macrolactone ring structure
  - Extensive 1,3-dioxygenation
  - Unusual oxazole bearing side chain

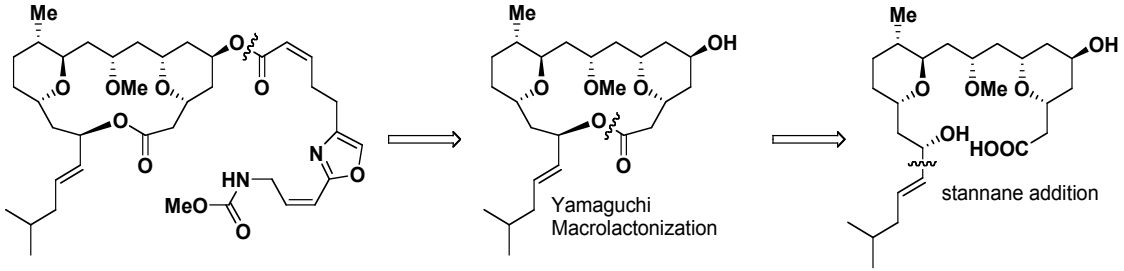


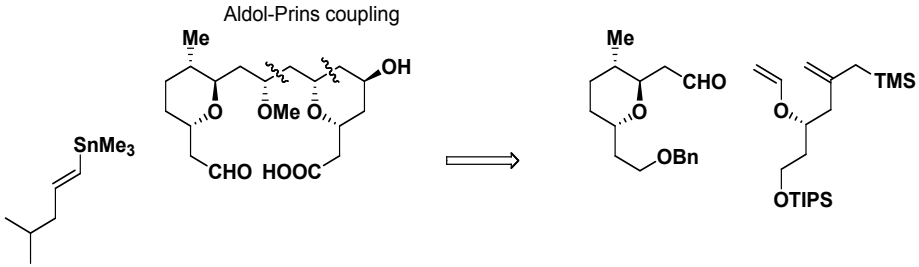
- Synthetic interest stirred by its unavailability, high bioactivity and unique structure
- Up-to-date, there are 2 formal syntheses and 4 total syntheses reported

Retrosynthetic Analyses



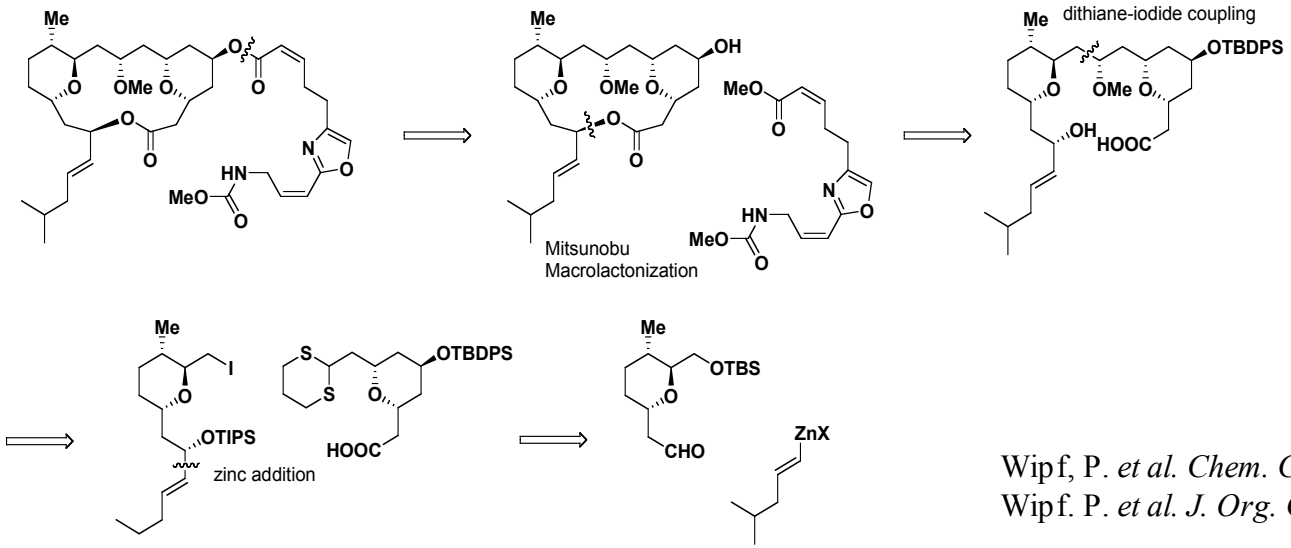
Leighton, J. L. *et al. J. Am. Chem. Soc.* **2000**, *122*, 12894.



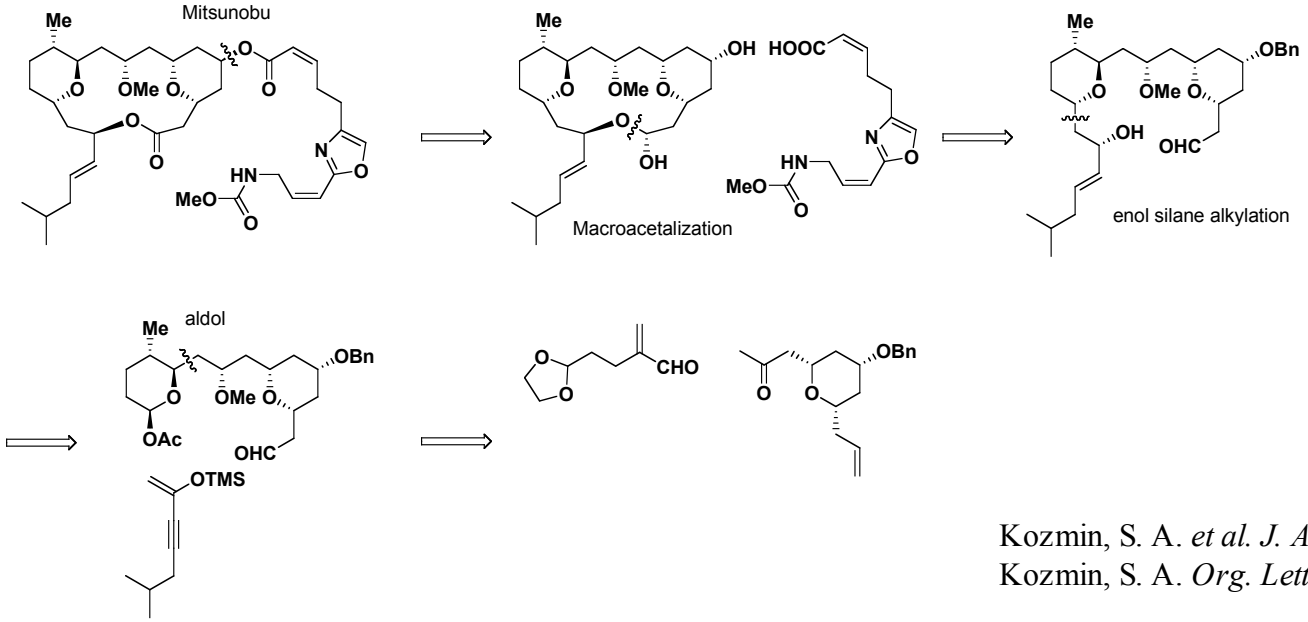


Rychnovsky, S. D. *et al. J. Am. Chem. Soc.* **2001**, *123*, 8420.

Retrosynthetic Analyses

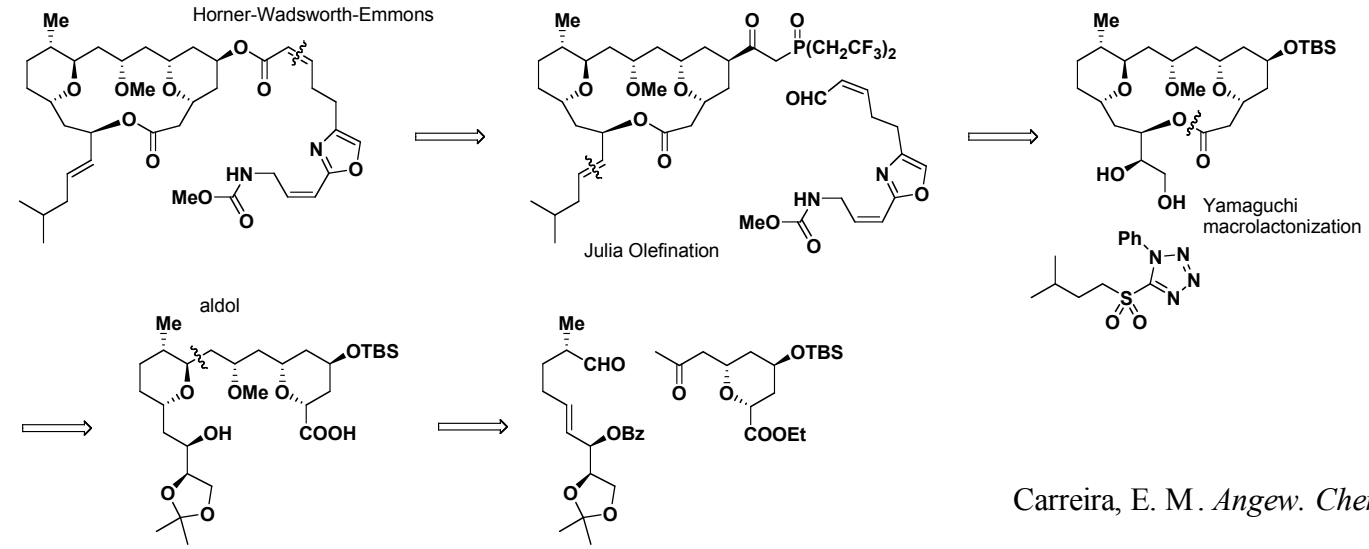


Wipf, P. *et al. Chem. Commun.* **2002**, 2006.
Wipf. P. *et al. J. Org. Chem.* **2001**, *66*, 3242.

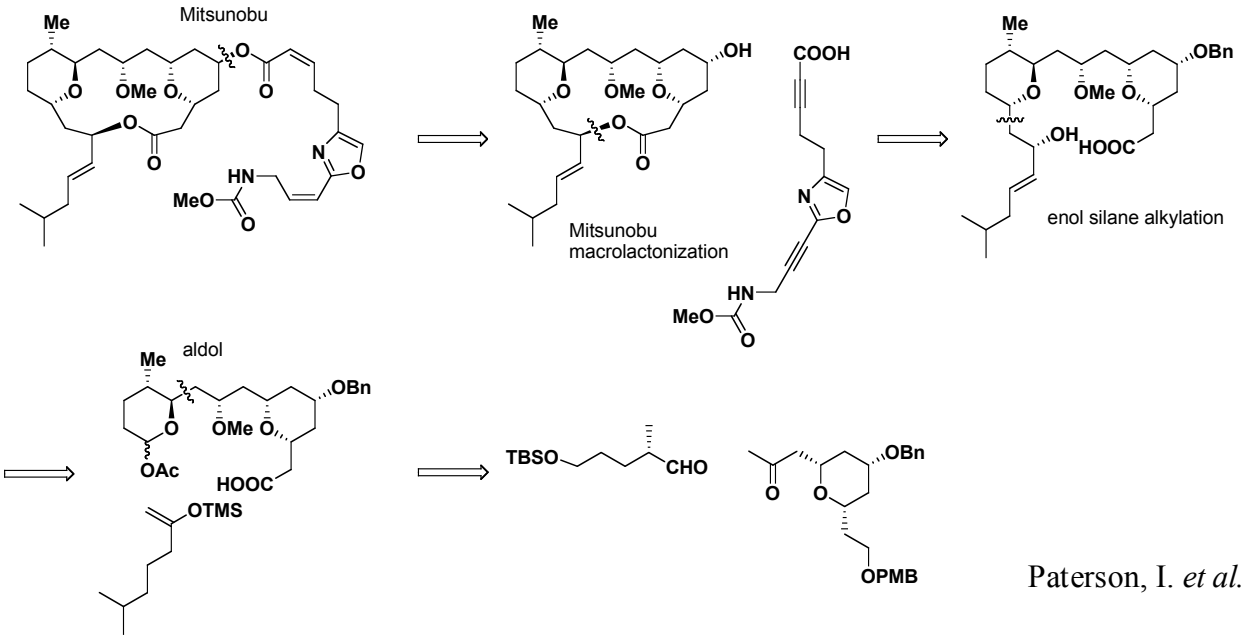


Kozmin, S. A. *et al. J. Am. Chem. Soc.* **2002**, *124*, 13670.
Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755.

Retrosynthetic Analyses

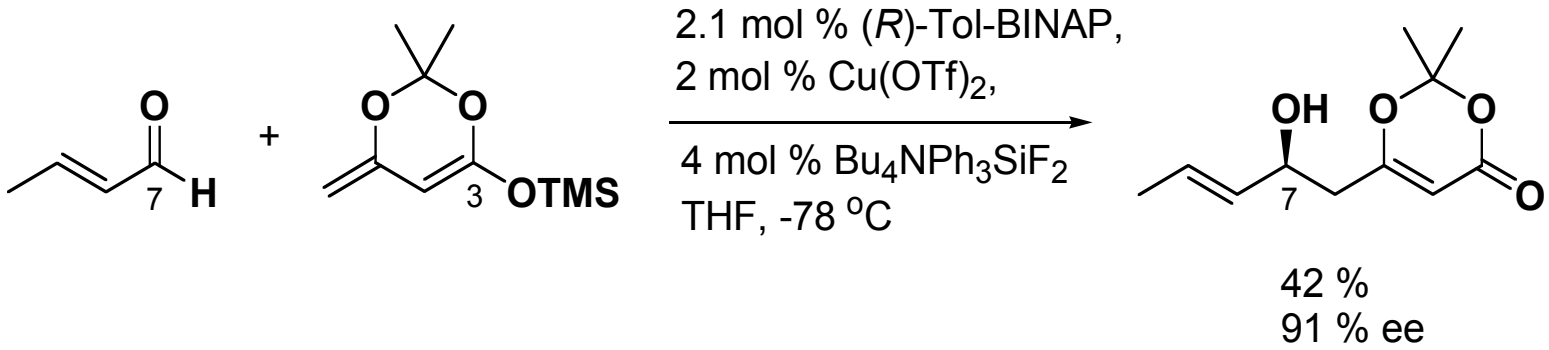


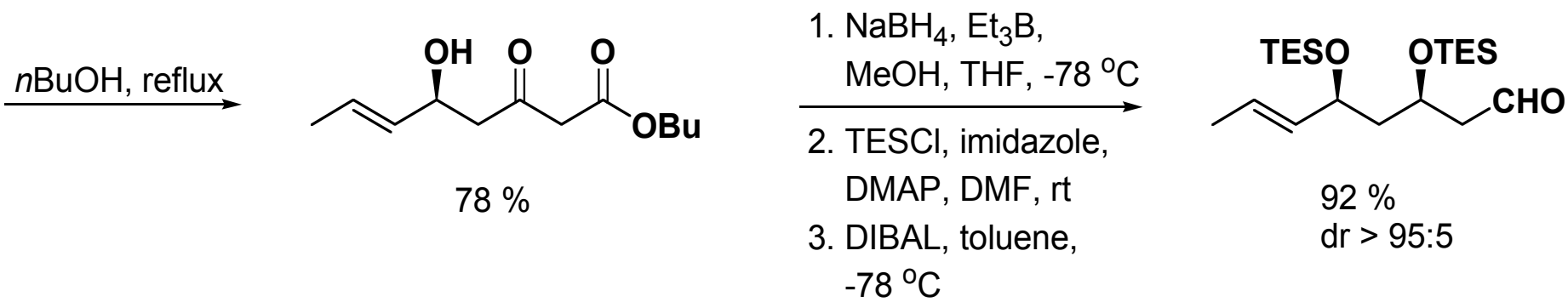
Carreira, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2908.

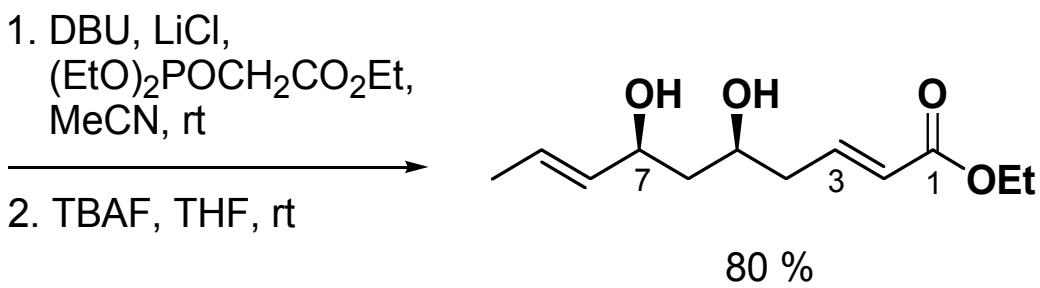


Paterson, I. *et al. Angew. Chem. Int. Ed.* **2003**, *42*, 343.

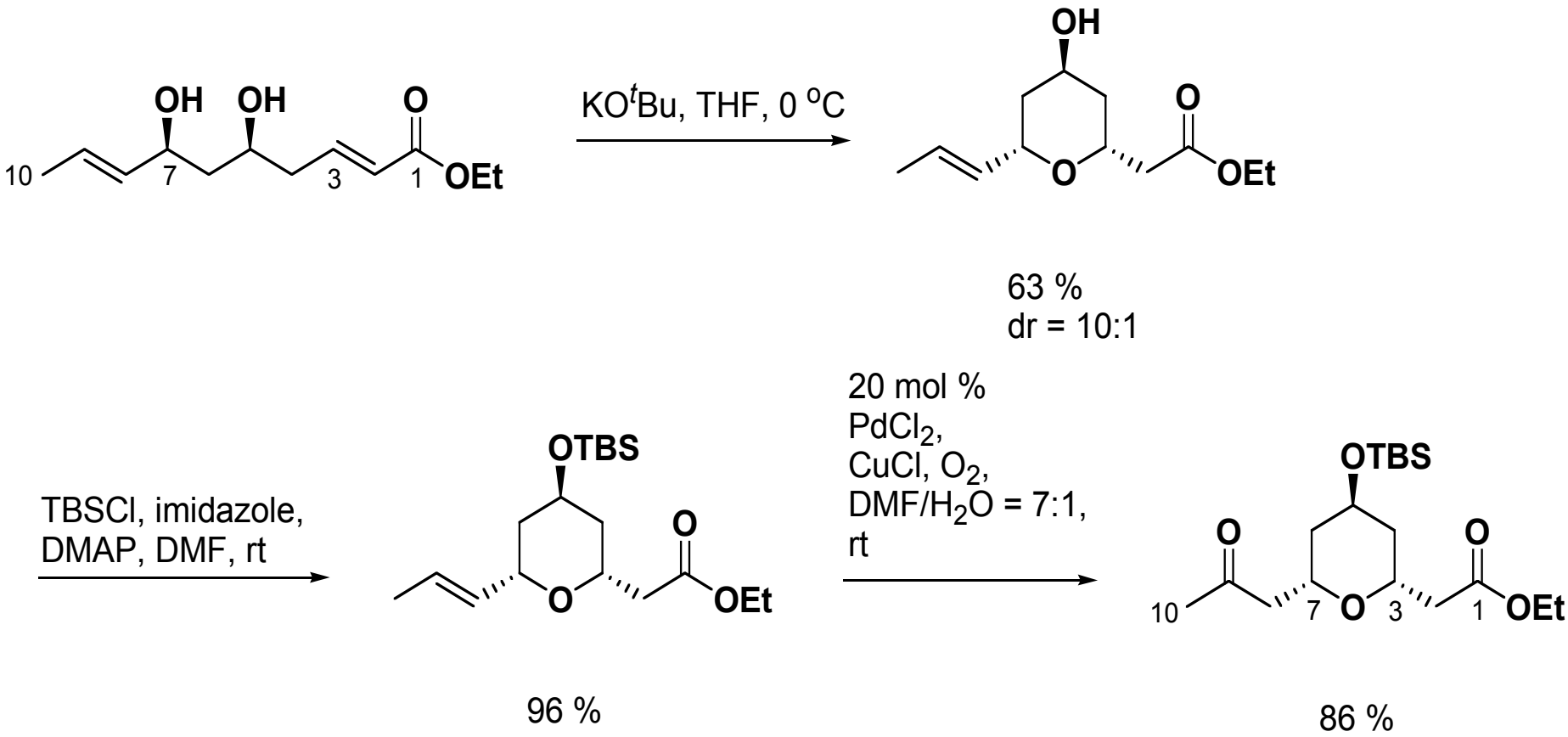
Carreira Synthesis: Construction of C1-C9 Fragment



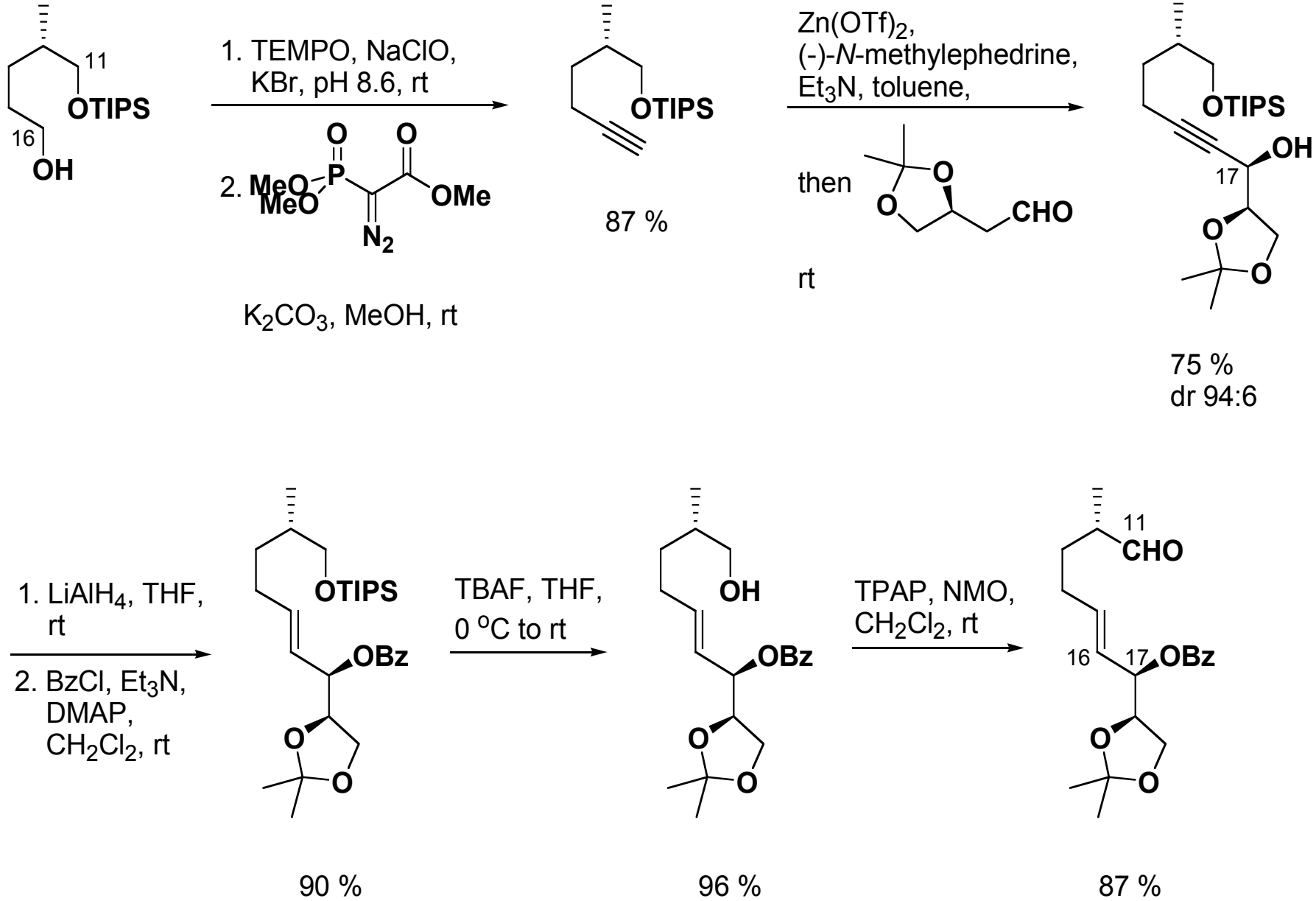




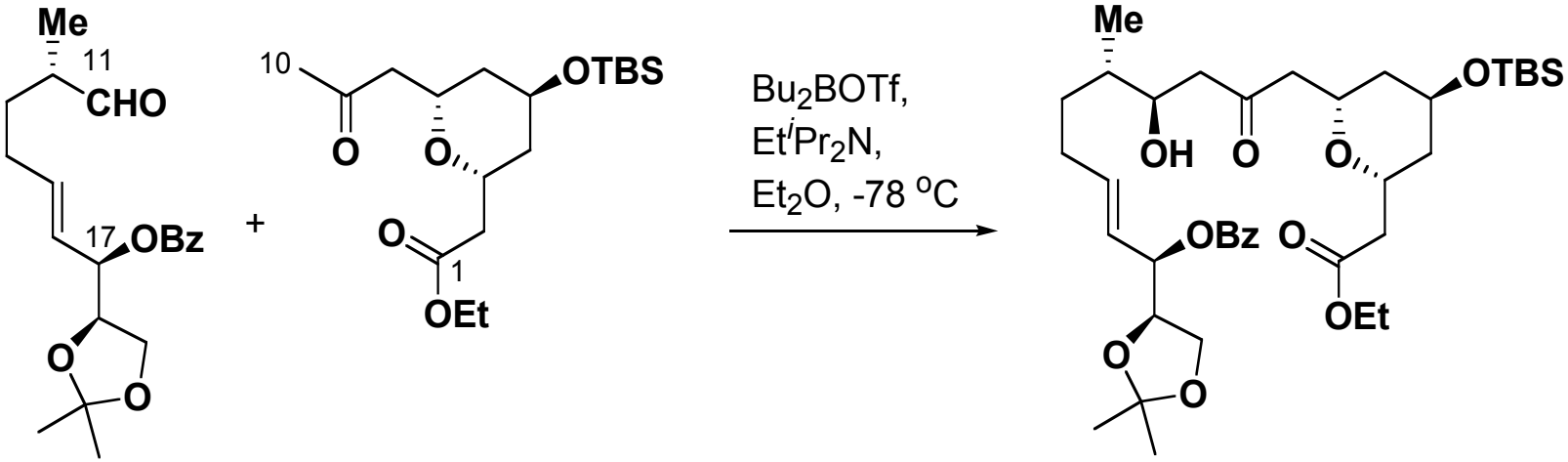
Carreira Synthesis: Construction of C1-C10 Fragment



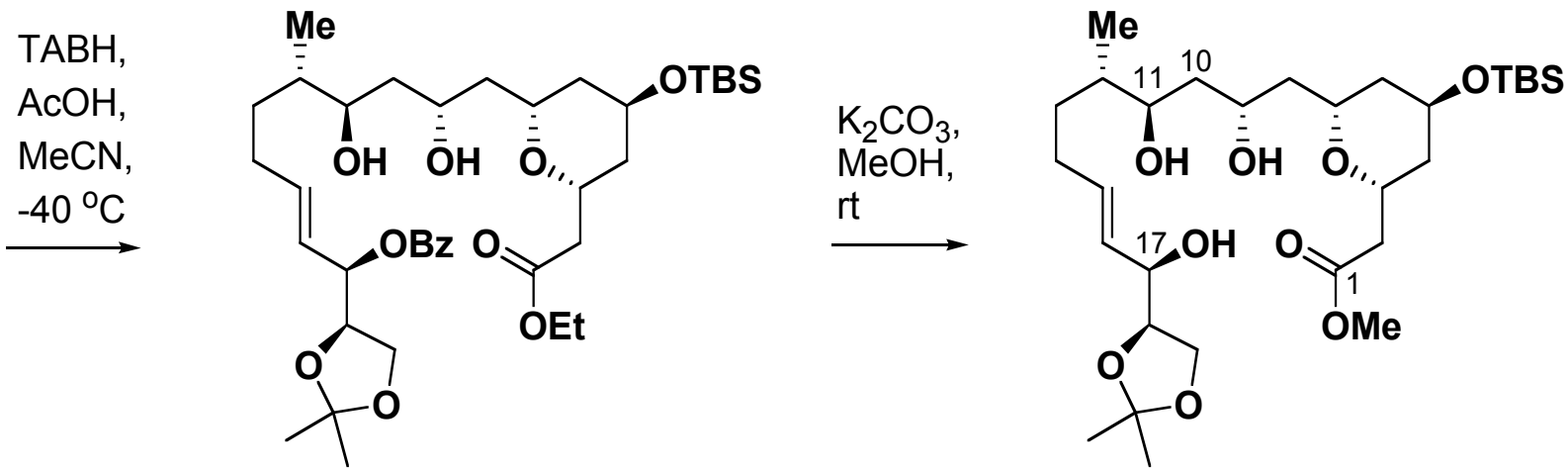
Carreira Synthesis: Construction of C11–C18 fragment



Carreira Synthesis: Coupling of Two Main Fragments



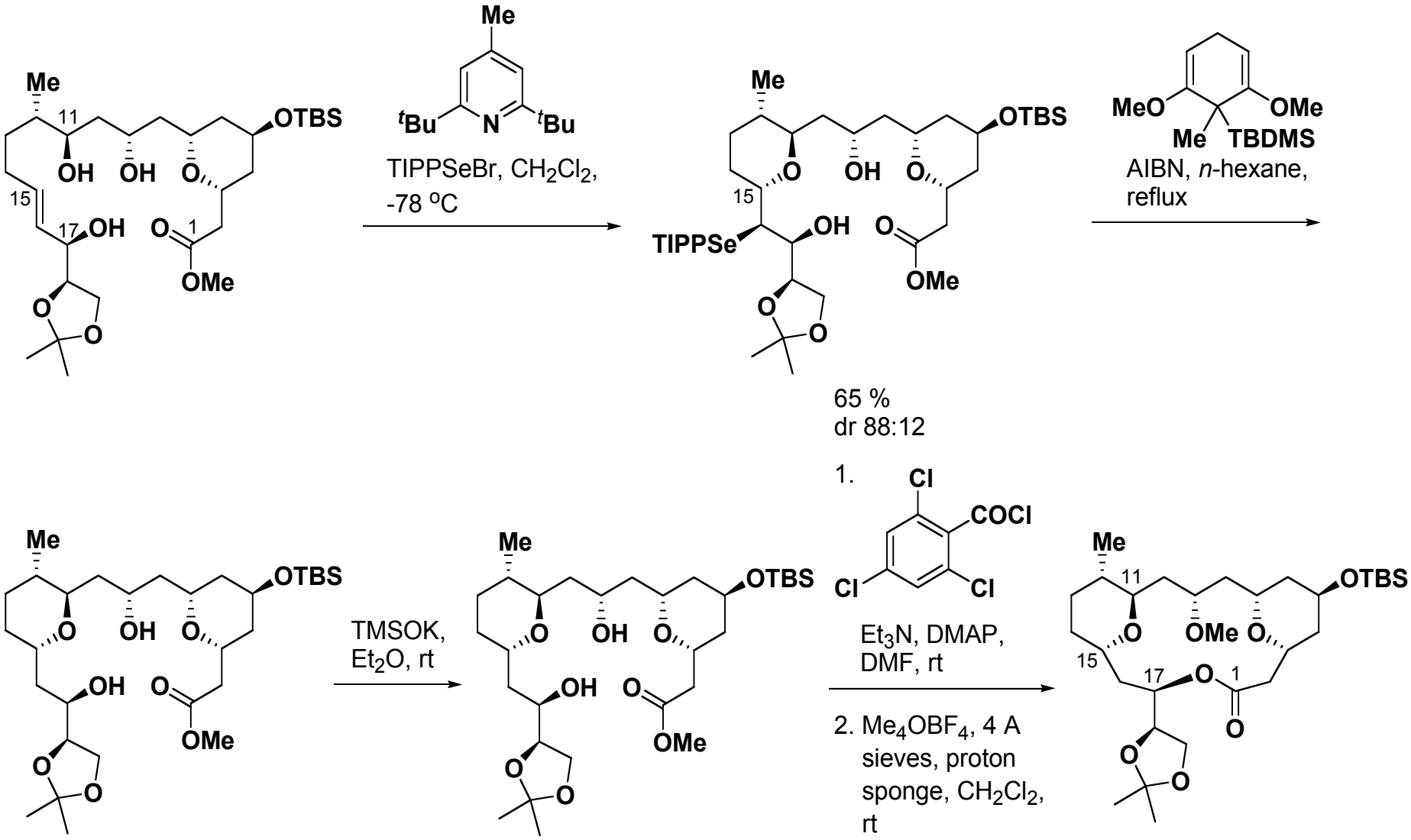
80%
dr > 95:5



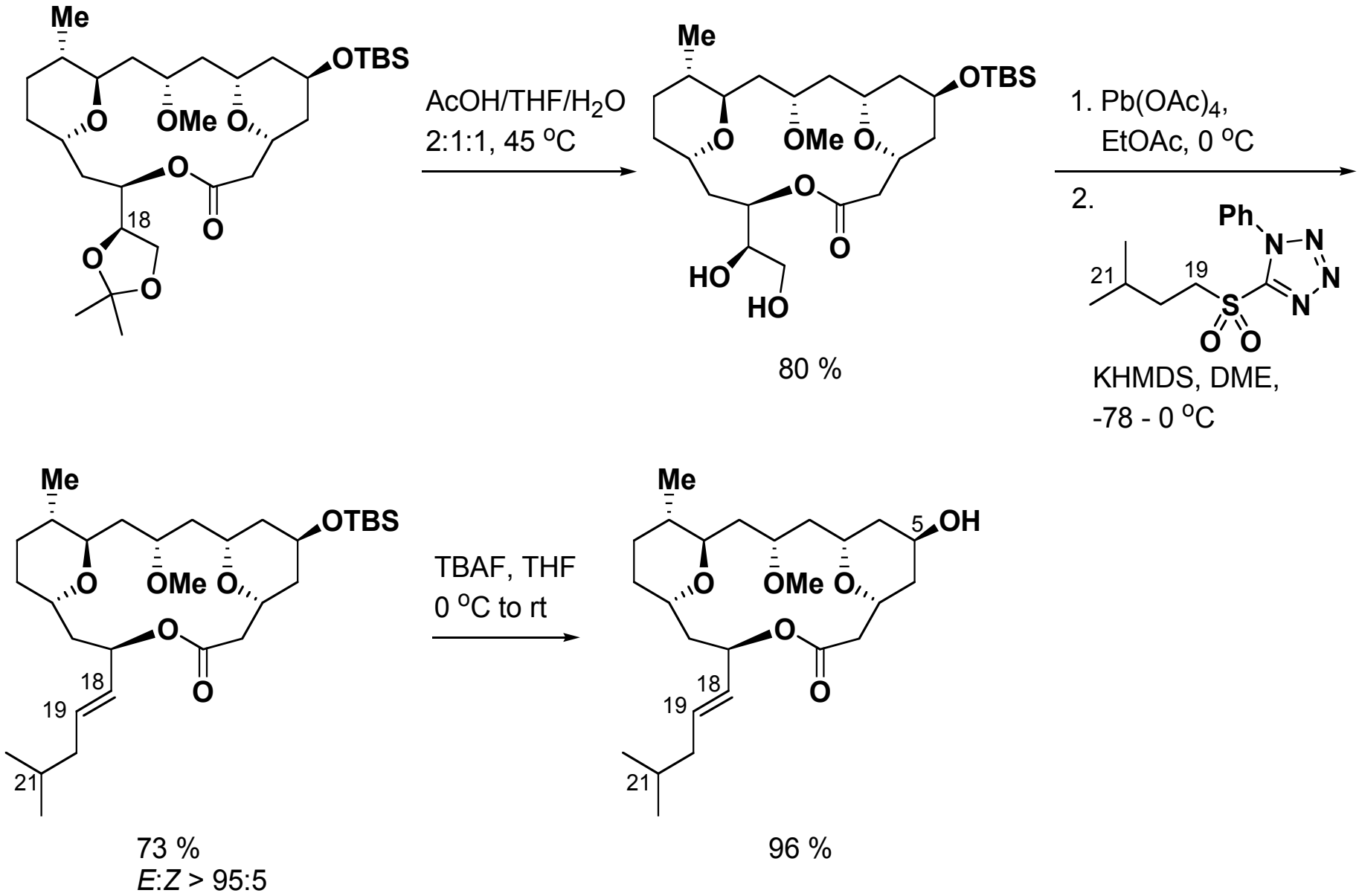
97%
dr > 95:5

92 %

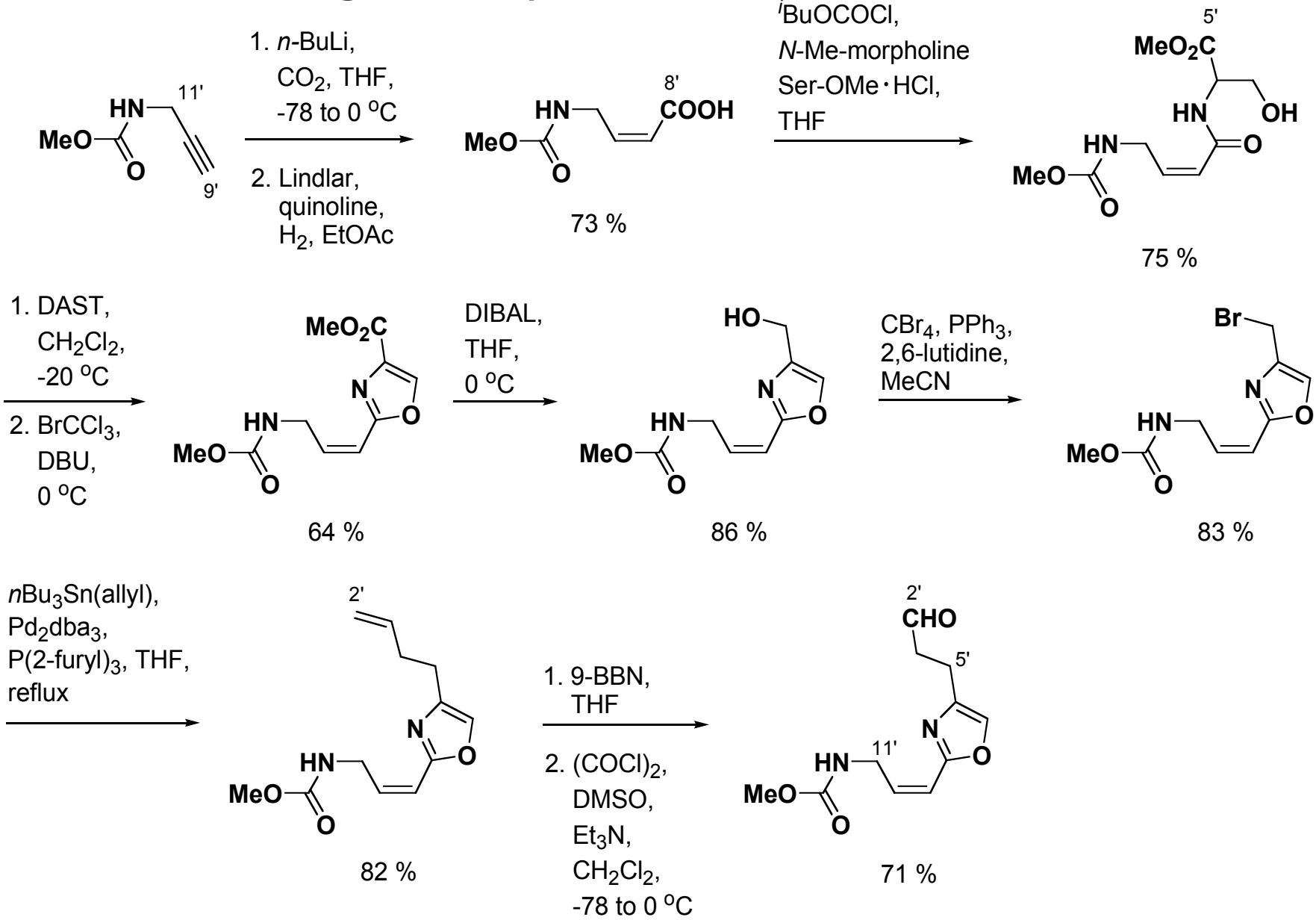
Carreira Synthesis: Macrolactonization



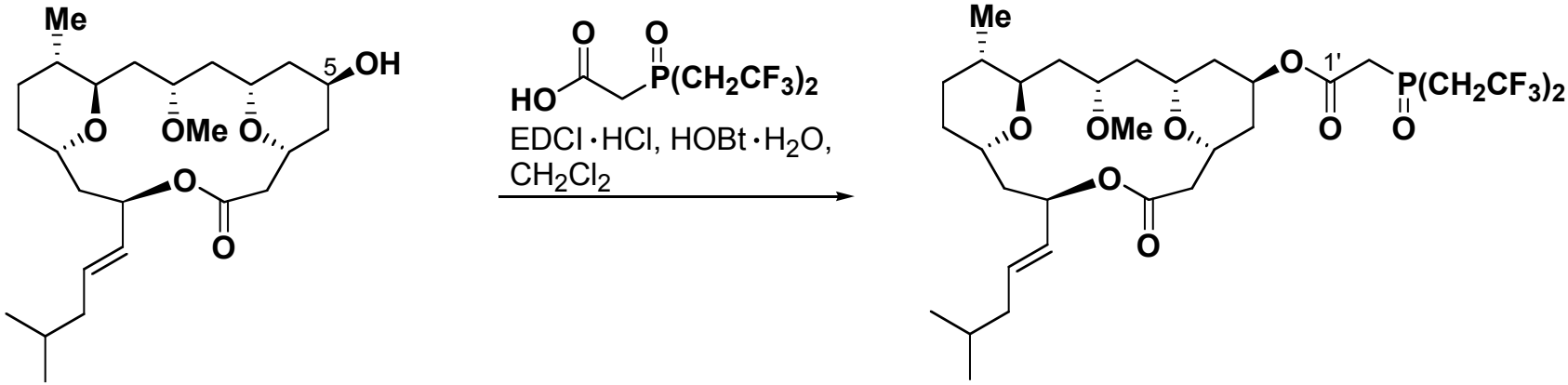
Carreira Synthesis: Installation of Side Chain C19-C22

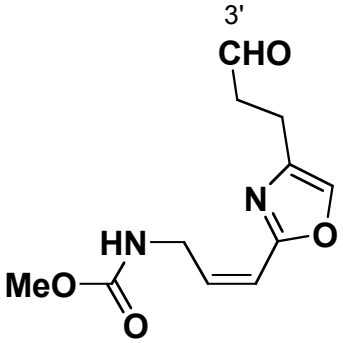


Carreira/Leighton Synthesis: Side Chain C2'-C11'

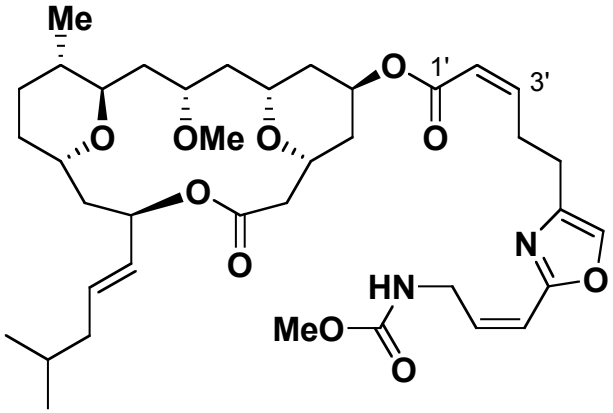


Carreira/Leighton: Completion of the Total Synthesis





KHMDS, 18-crown-6,
THF, -100 ^{o}C

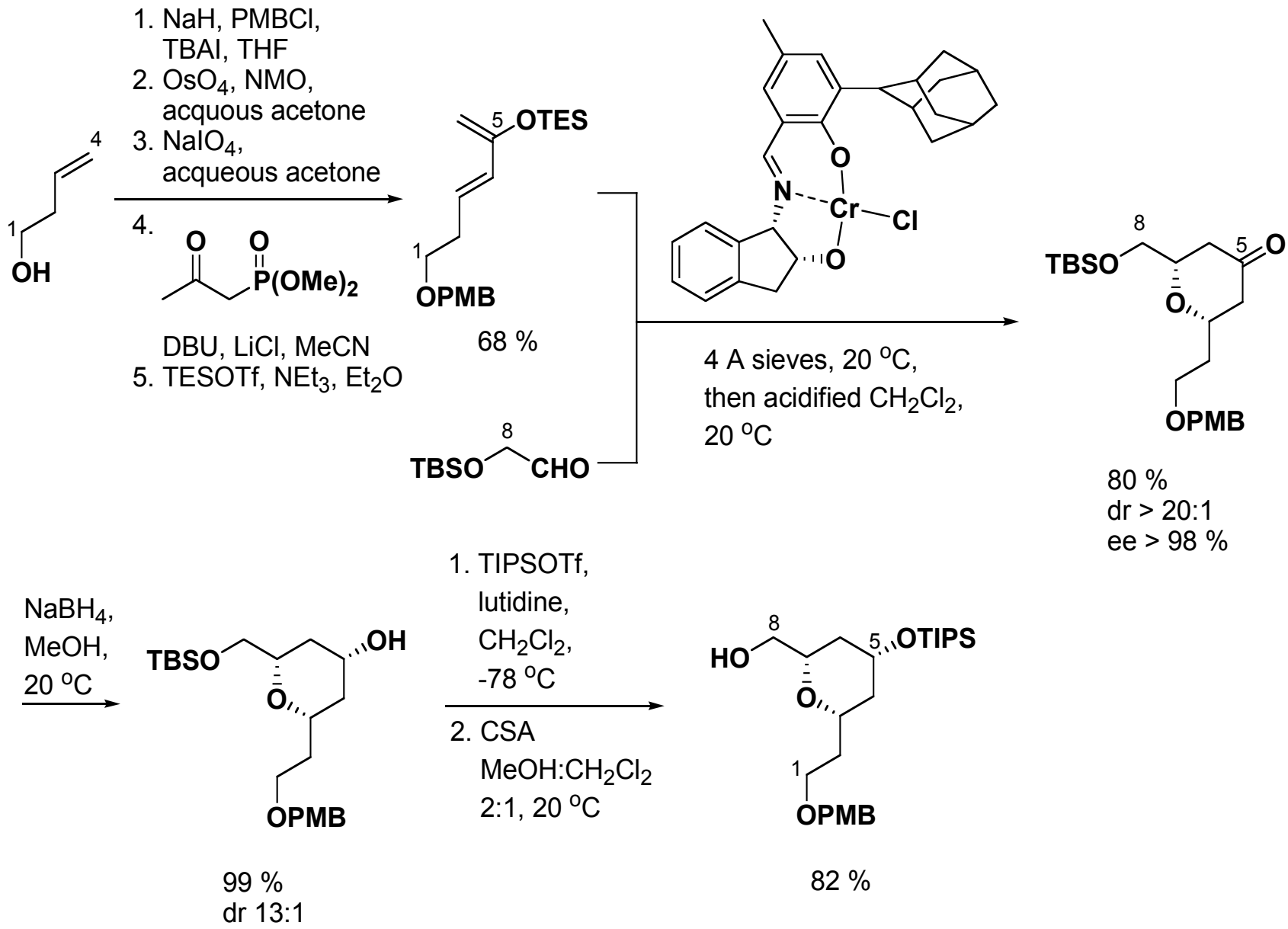


55 %

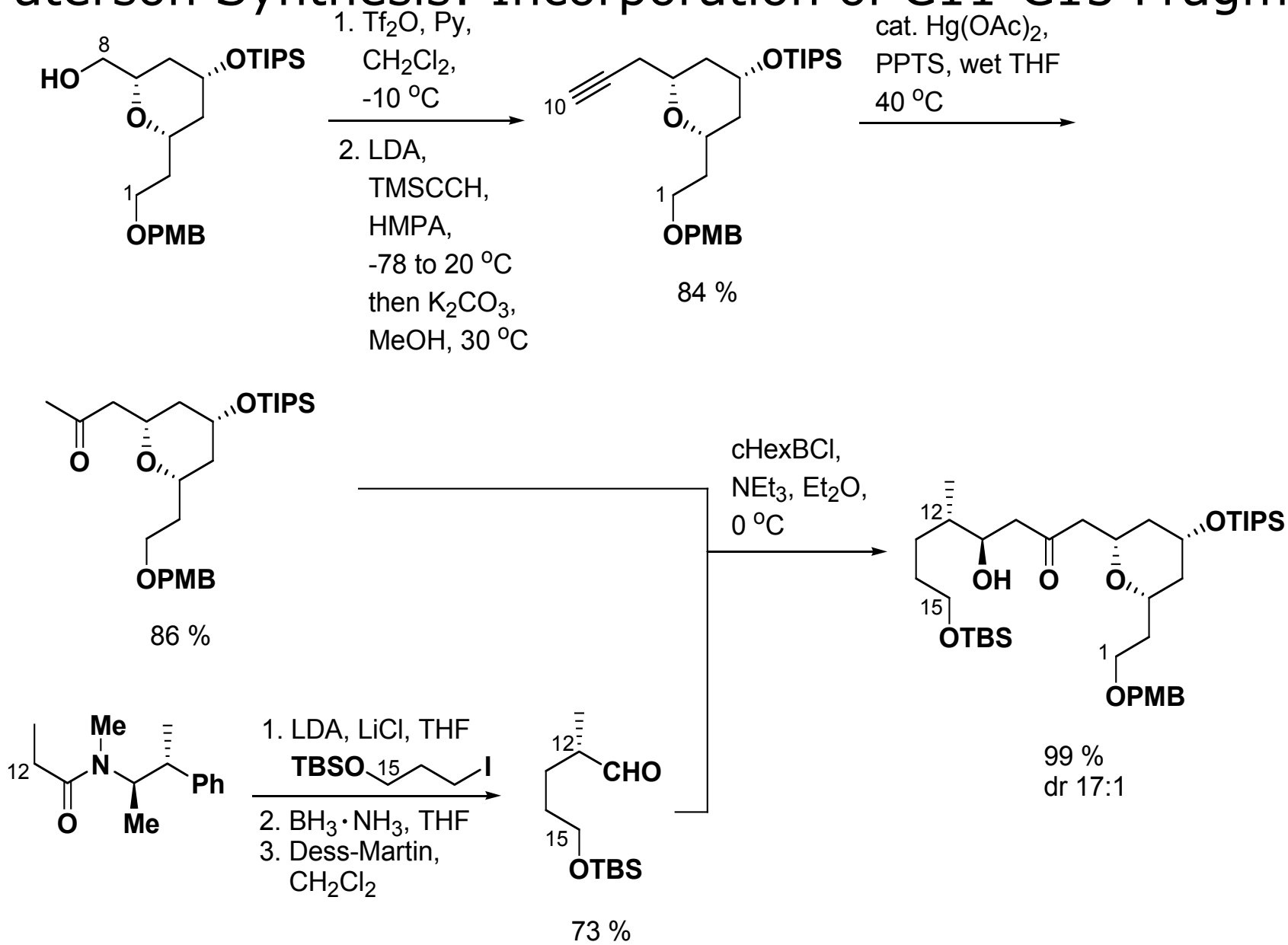
Z:*E* = 7:1

Leucascandrolide A

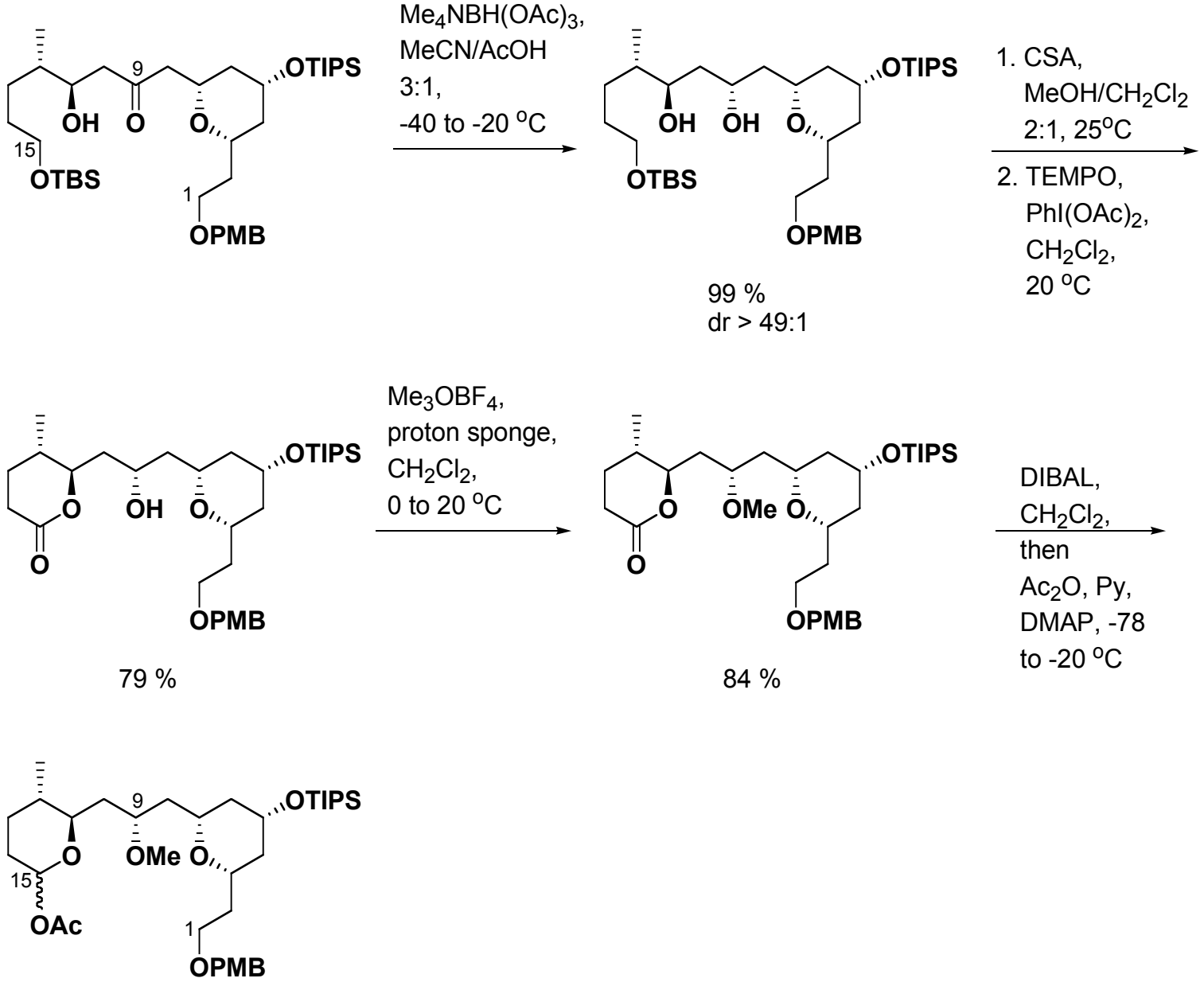
Paterson Synthesis: Construction of C1-C8 Fragment



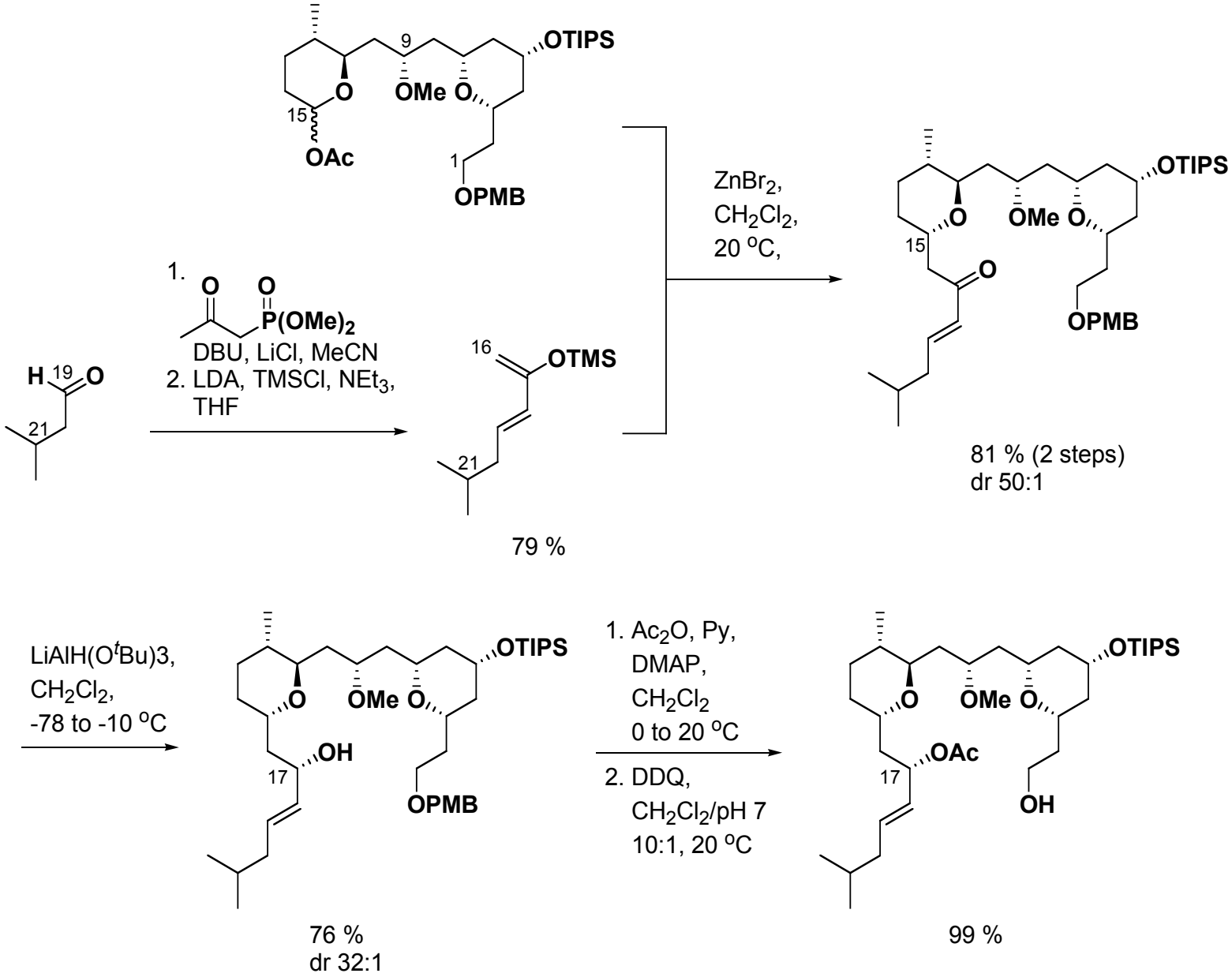
Paterson Synthesis: Incorporation of C11-C15 Fragment



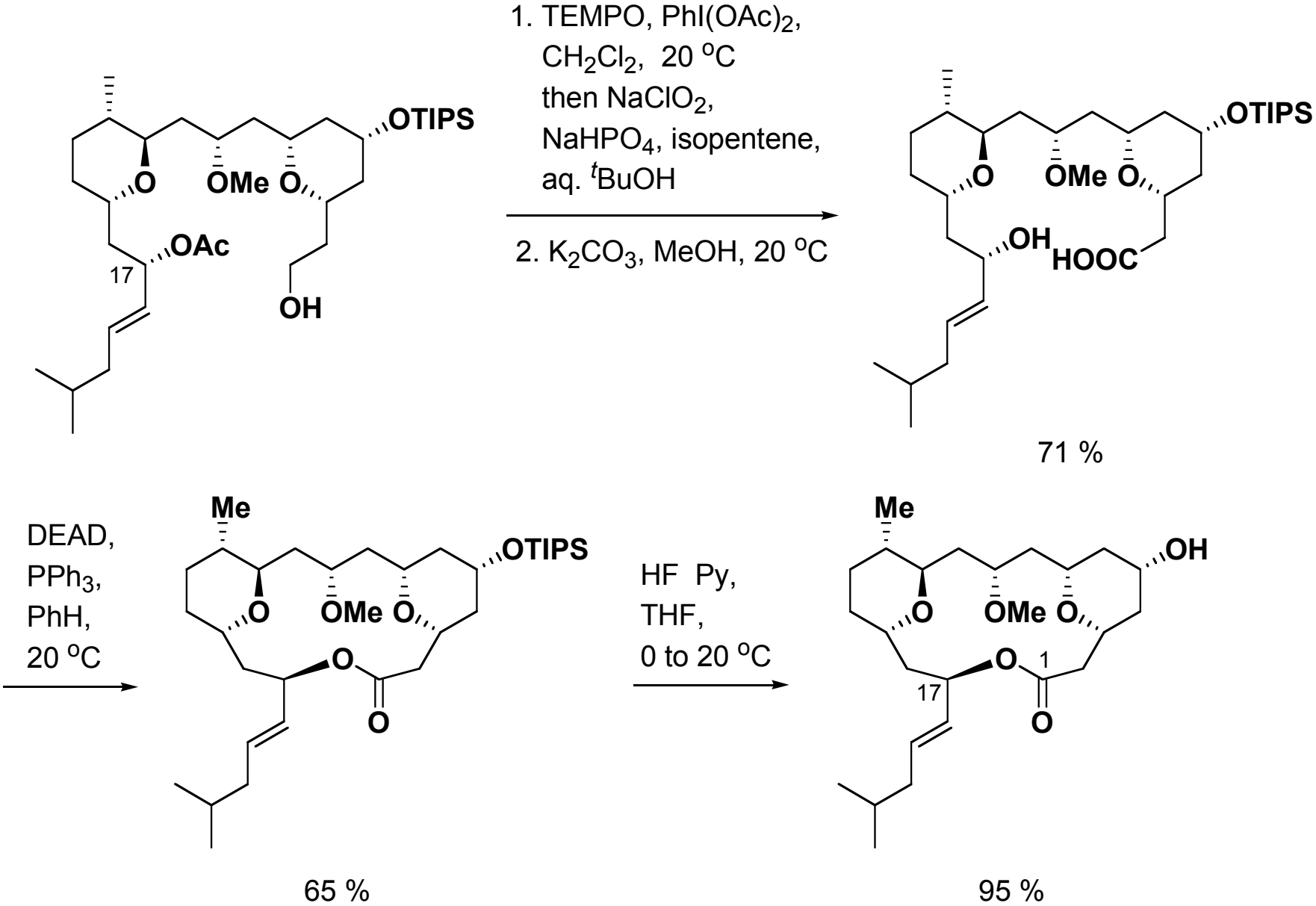
Paterson Synthesis: Further Modification of Skeleton



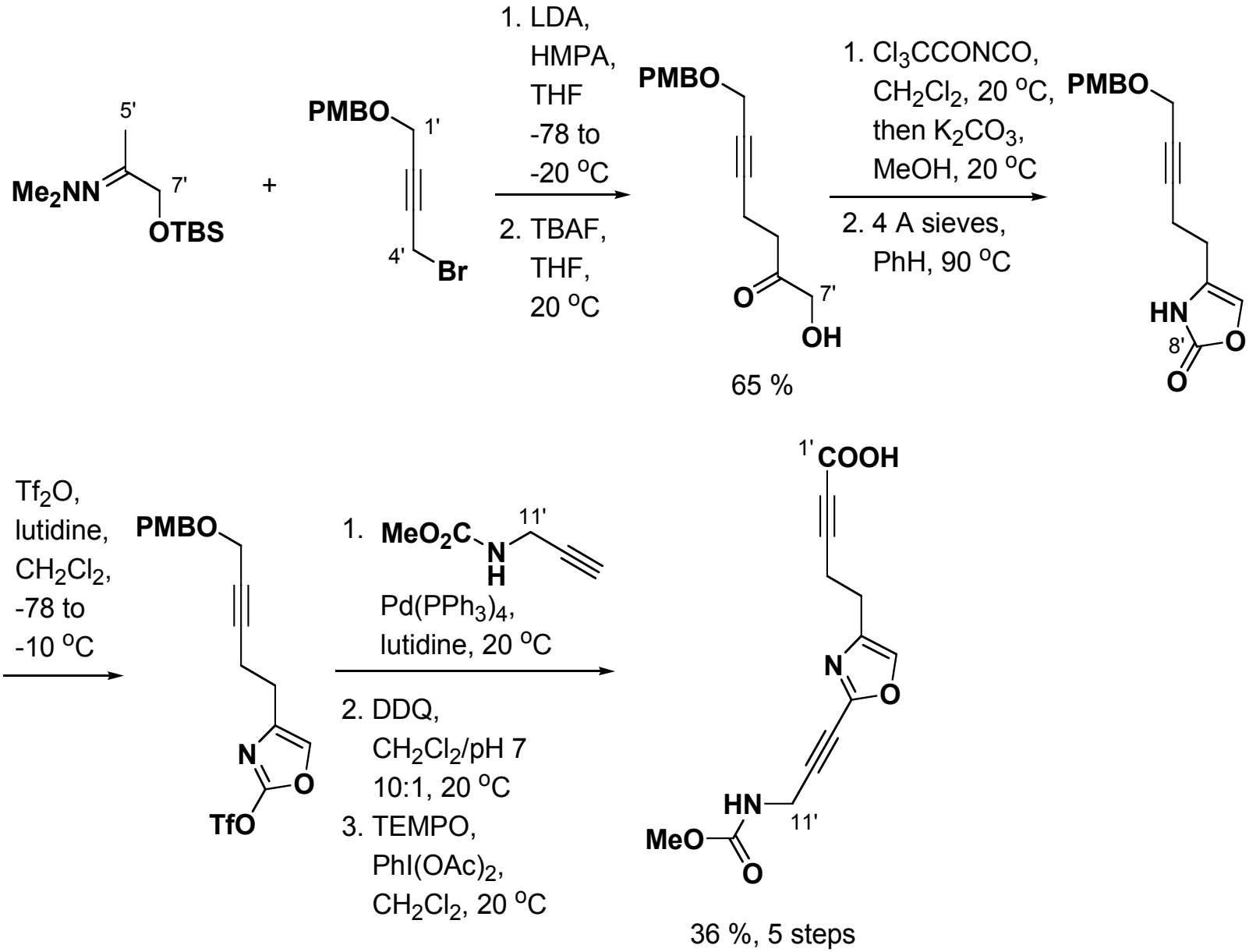
Paterson Synthesis: Installation of Side Chain C18-C22



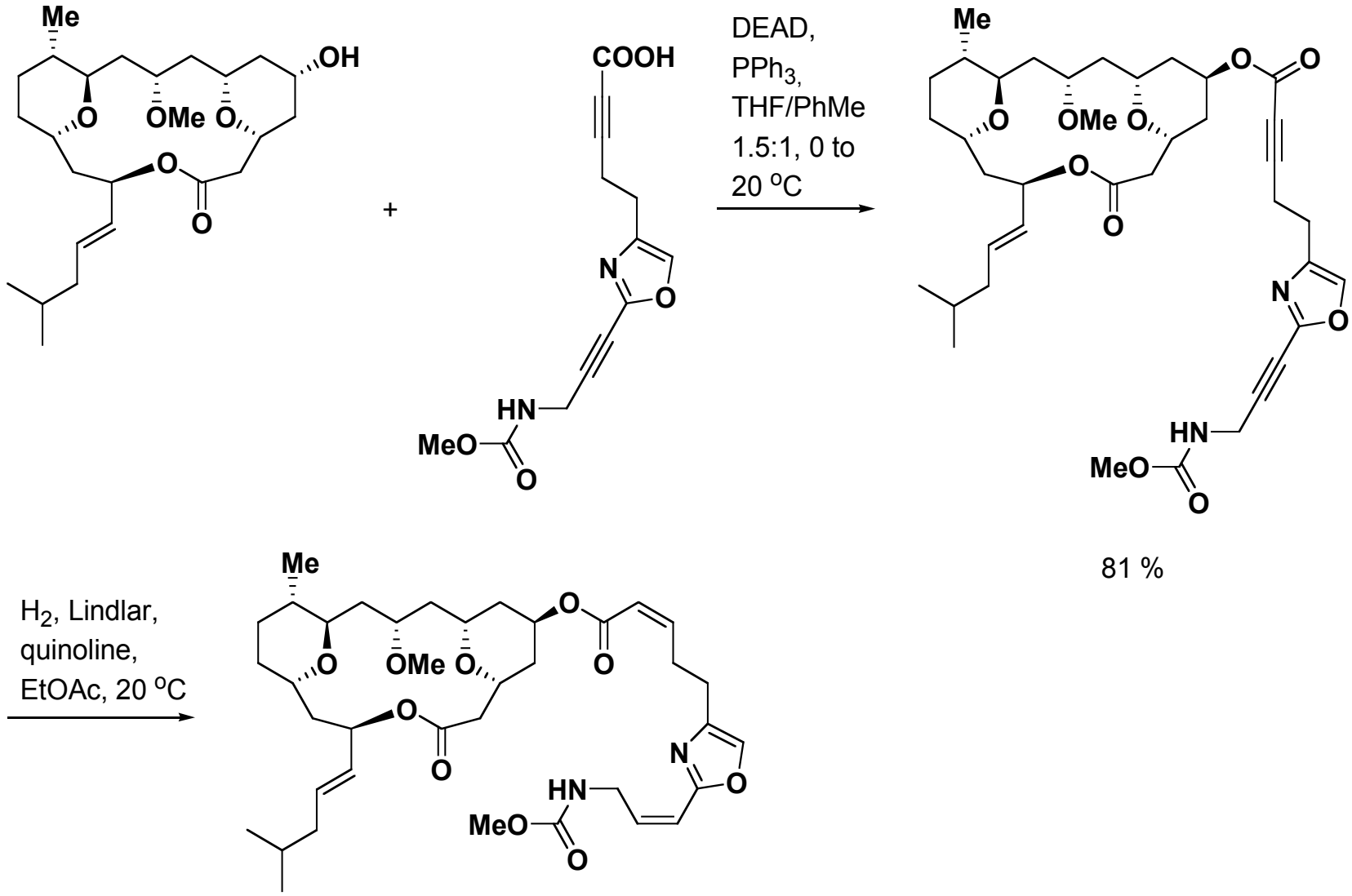
Peterson Synthesis: Macrolactonization



Paterson Synthesis: Construction of Side Chain C1'-C11'

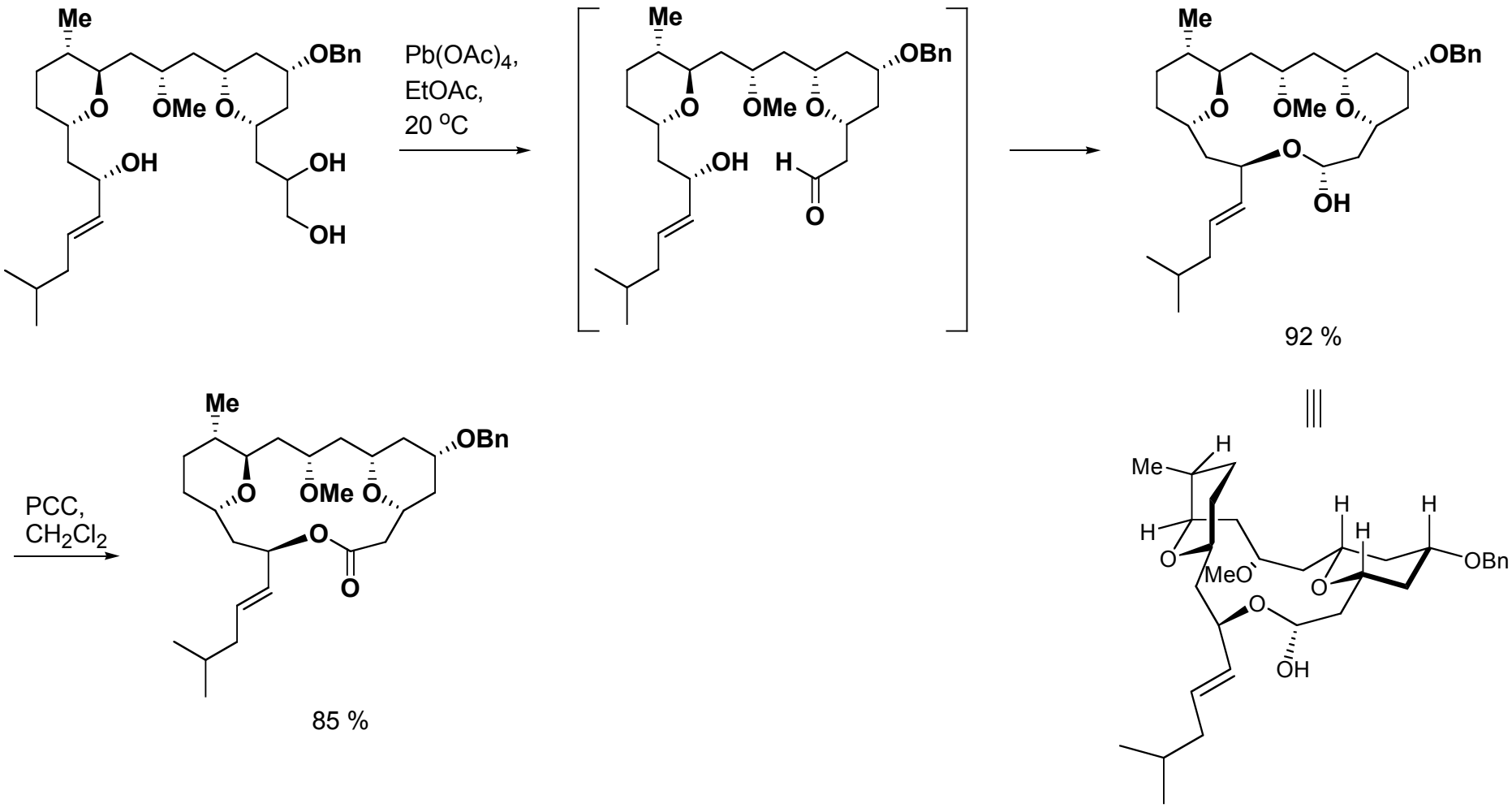


Paterson Synthesis: Completion of Total Synthesis

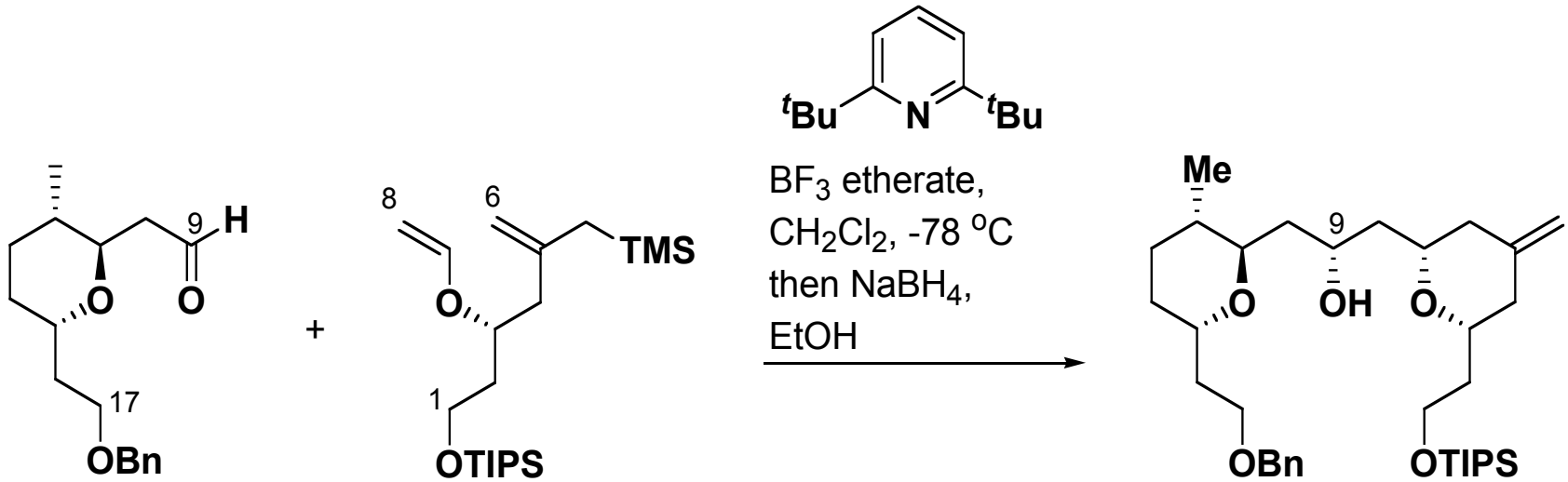


Leucascandrolide A

Highlight of Other Interesting Syntheses: Kozmin

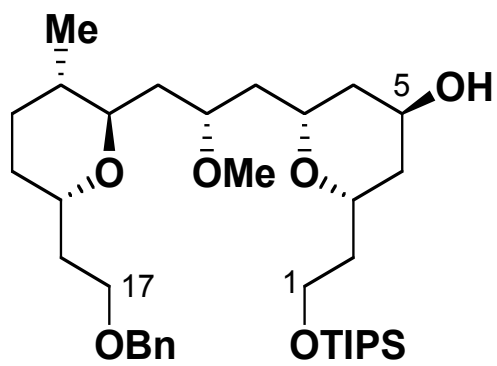


Highlight of Other Interesting Syntheses: Rychnovsky

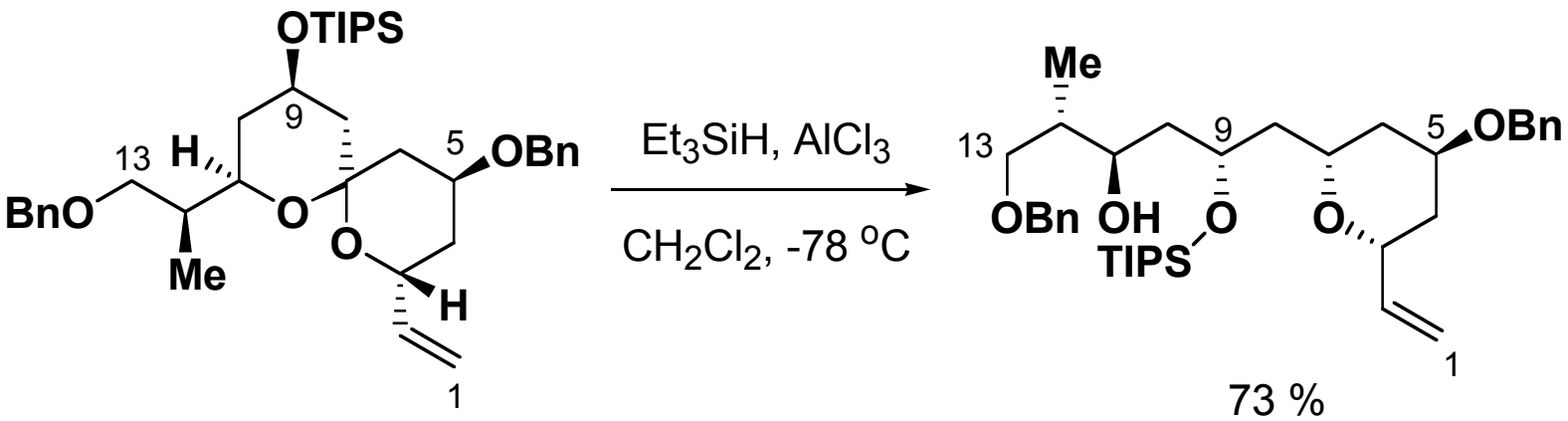


78 %
dr 5.5:1

1. Me_3OBF_4, proton sponge, 4 A sieves, CH_2Cl_2, 79 %
2. OsO_4, NMO, then $NaIO_4$, 80 %
3. L-Selectride, THF, -90 to -60 ^oC, 82 %



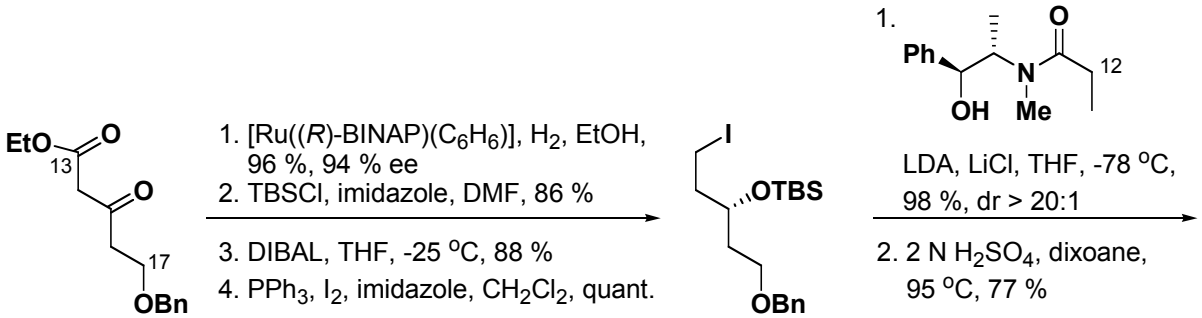
Highlight of Other Interesting Syntheses: Crimmins

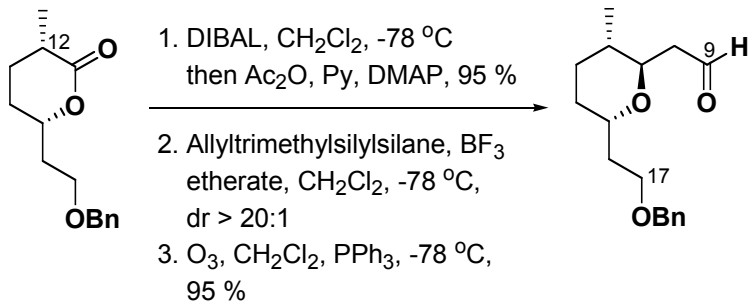


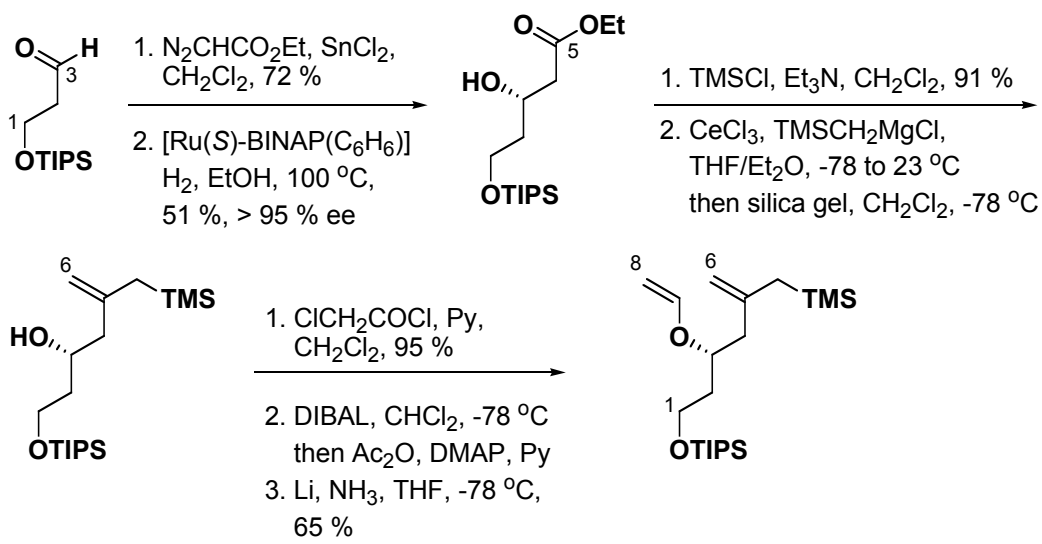
Summary

- Leighton: Most linear synthesis.
- Richnovsky: Featuring Aldol-Prins cylclization to construct the skeleton.
- Wipf: Dithiane-iodide coupling was used to construct the skeleton.
- Kozmin: Most distinct feature: Spontaneous Macroacetalization.
- Carreira: Most convergent of all syntheses. Both substrate control and reagent control were used to carry out a highly diastereoselective synthesis.
- Paterson: Only substrate control of stereochemistry after the first chiral induction.
- Crimmins: Featuring selective opening of functionalized siproketal to construct the skeleton.

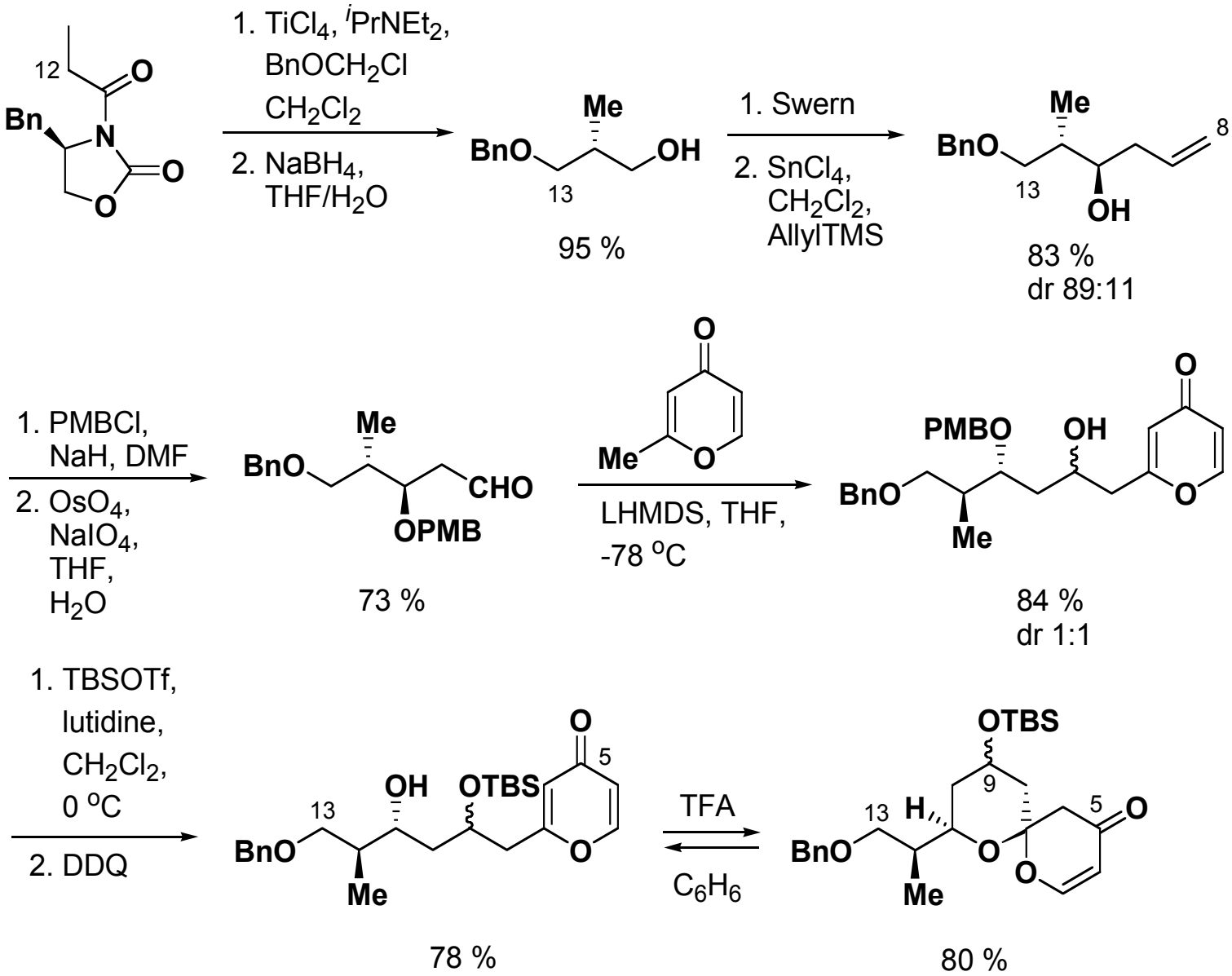
Rychnovsky Synthesis: Syntheses of Building Blocks







Crimmins Synthesis: Construction of Spiroketal



Crimmins Synthesis: Modification of Spiroketal