

Total Synthesis of Norhalichondrin B

Hong Ren

The Wulff Group

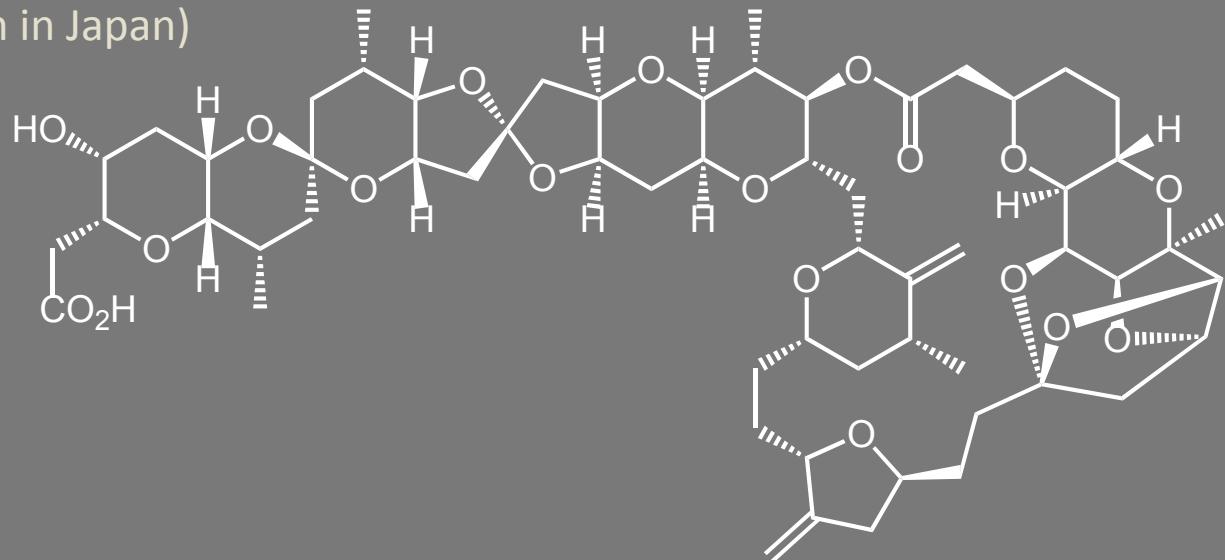
04-19-09

What is Norhalichondrin B?



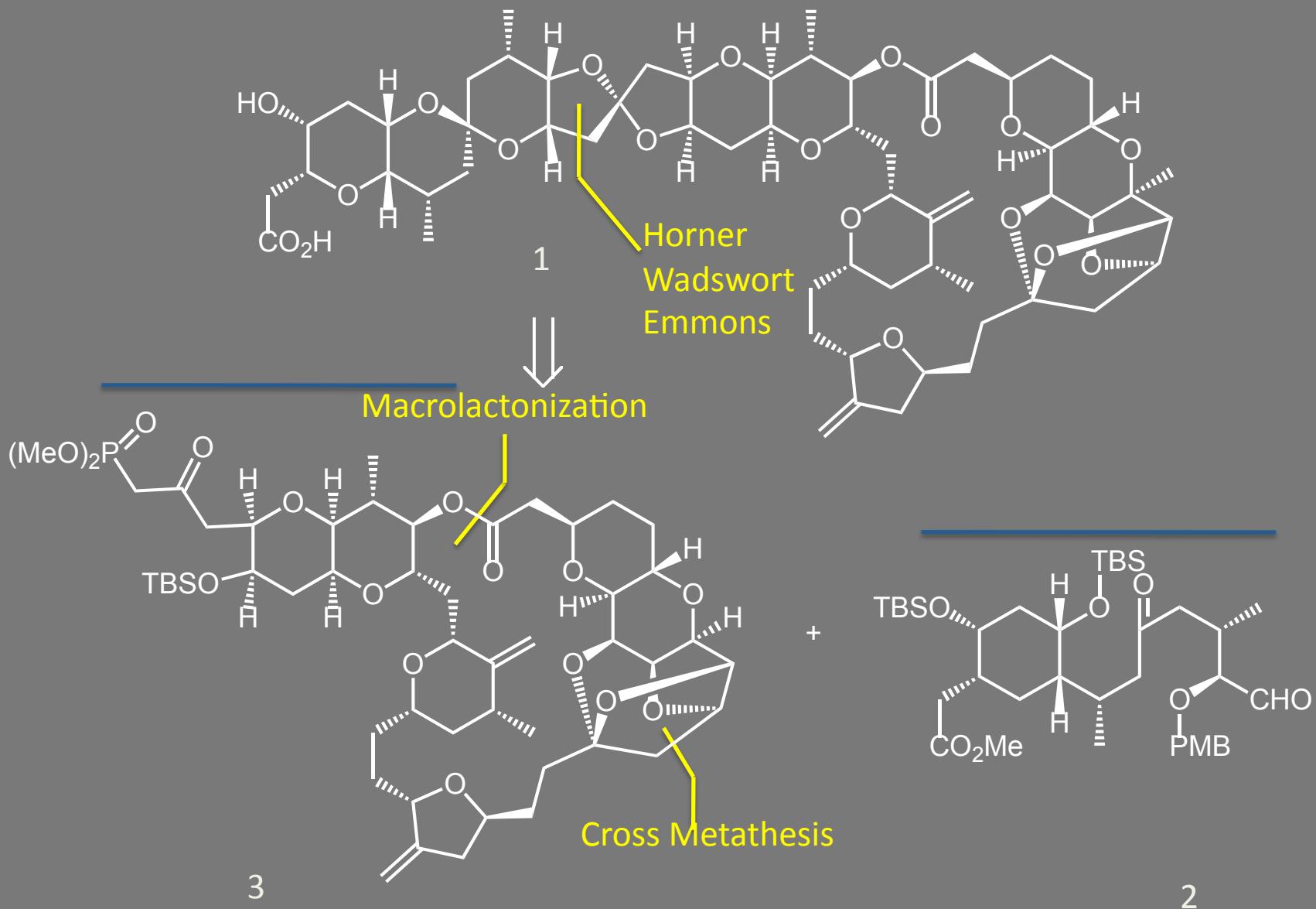
Halichondrin (Pacific Ocean in Japan)

- 😊 Isolated from Halichondrin Okadai Kadota in 1986
- 😊 Structure Elucidated in 1986
- 😊 Exhibits Extraordinary *in vitro* and *in vivo* Antitumor Activity

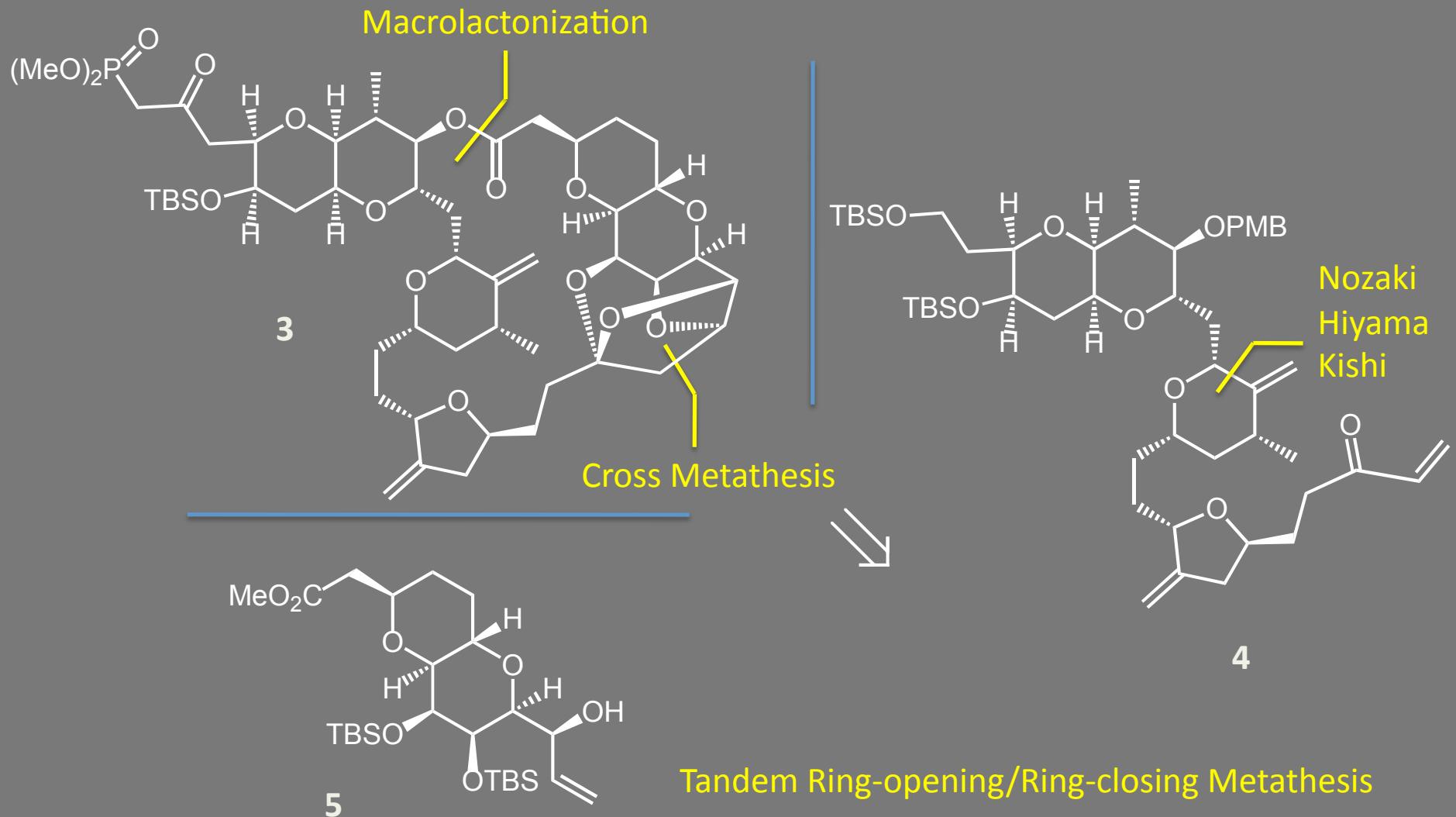


Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796-4798.
Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701-710.

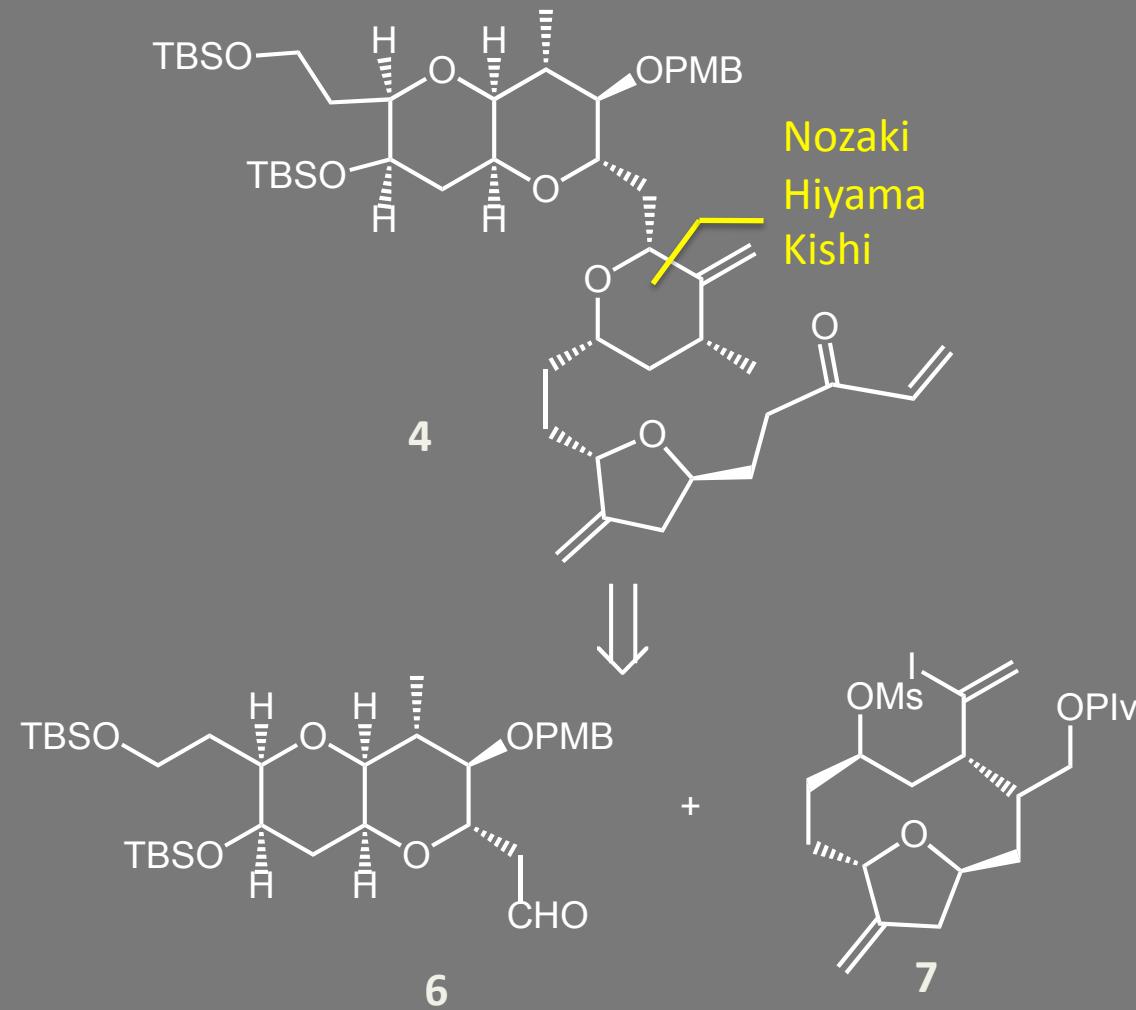
Strategy-Level Analysis Showing Key Disconnections



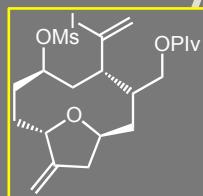
Strategy-Level Analysis Showing Key Disconnections



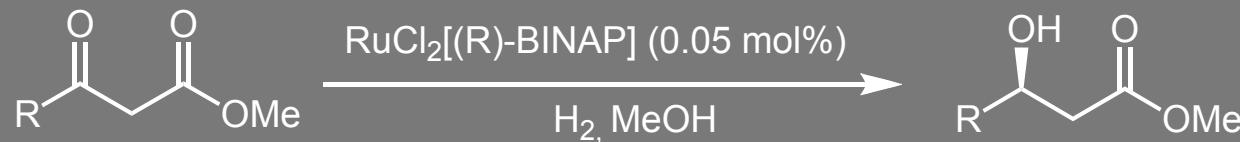
Strategy-Level Analysis Showing Key Disconnections



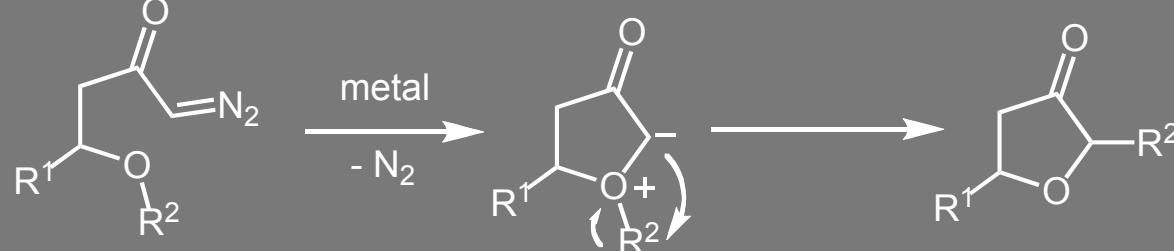
Key Reactions for the Synthesis of Compound 7



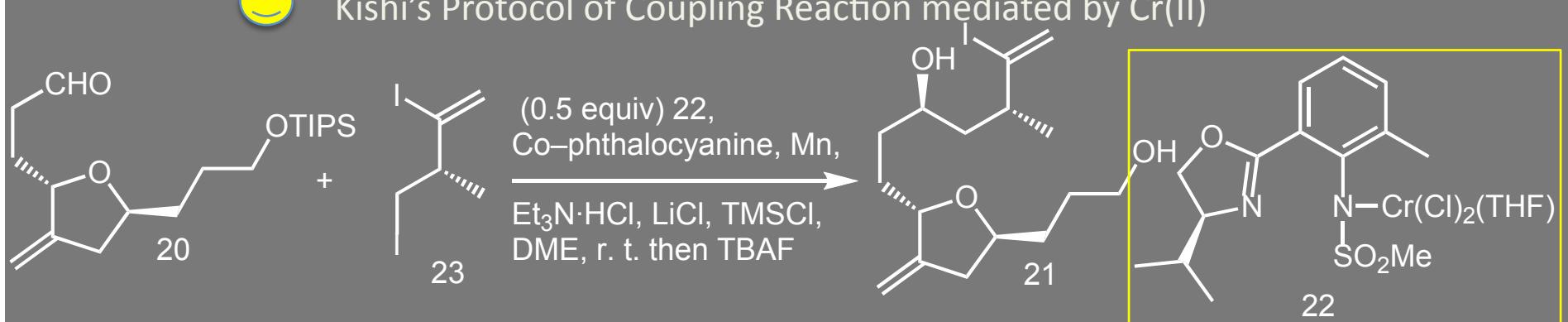
Noyori Asymmetric Hydrogenation of β - ketoester

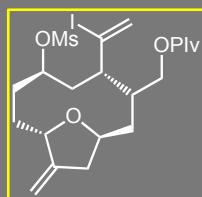


Formation of THF Ring by Copper Catalyzed [2, 3] Sigmatropic Rearr.

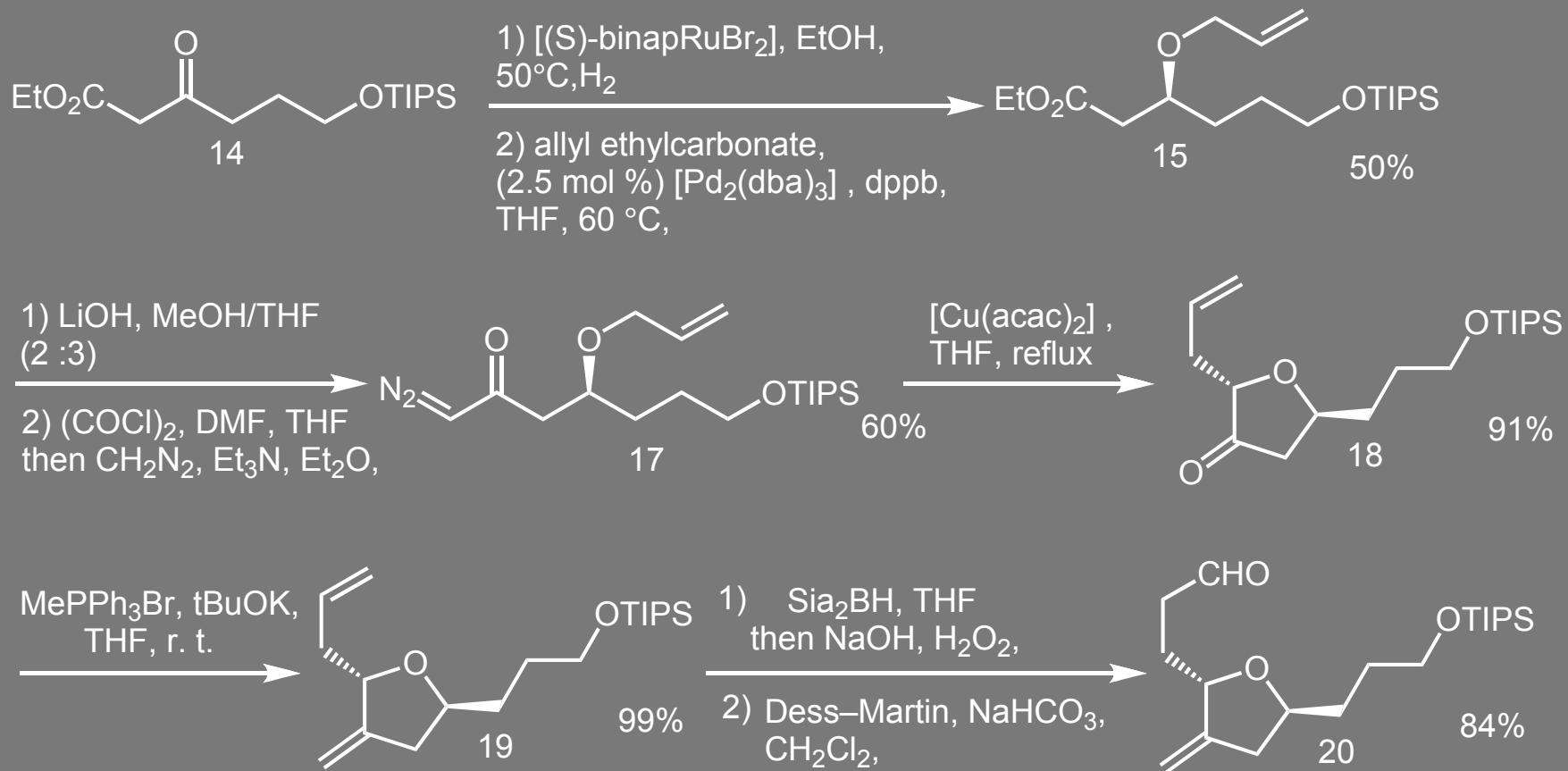


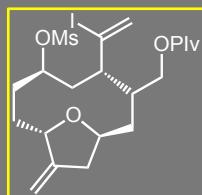
Kishi's Protocol of Coupling Reaction mediated by Cr(II)



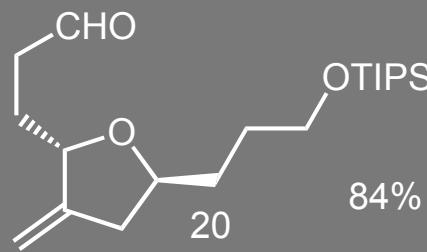


Synthesis of Compound 7

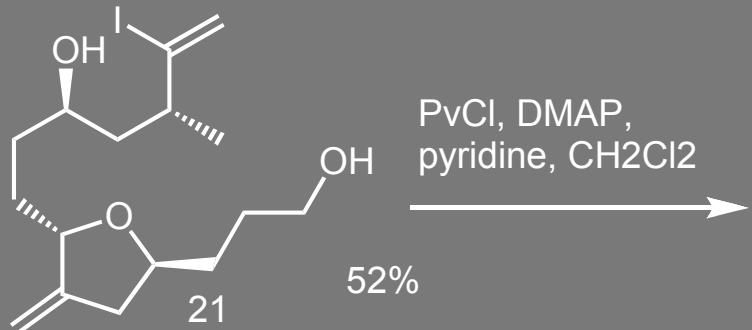




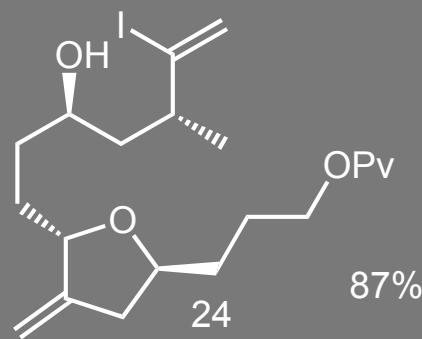
Synthesis of Compound 7



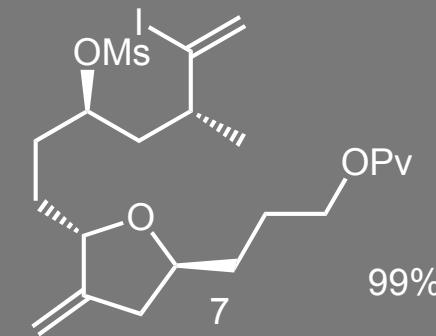
23 (2 equiv), 22 (0.5 equiv),
Co-phthalocyanine, Mn,
Et₃N·HCl, LiCl, TMSCl,
DME, r. t. then TBAF



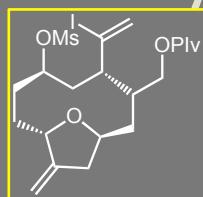
PvCl, DMAP,
pyridine, CH₂Cl₂



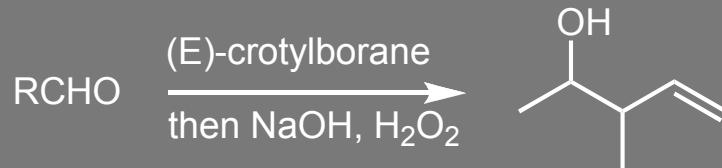
Ms₂O, Et₃N, DMAP, CH₂Cl₂



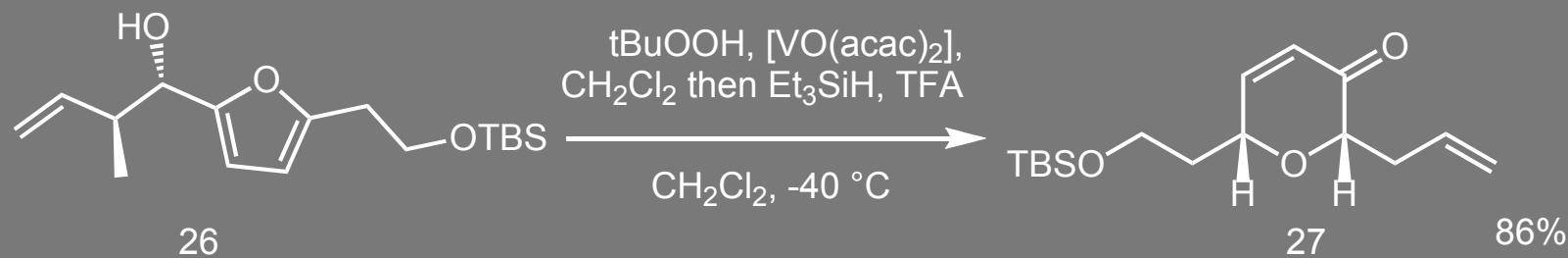
Key Reactions for the Synthesis of Compound 6



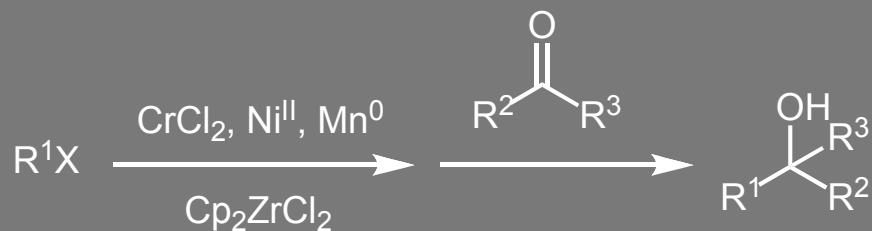
Brown Crotylation



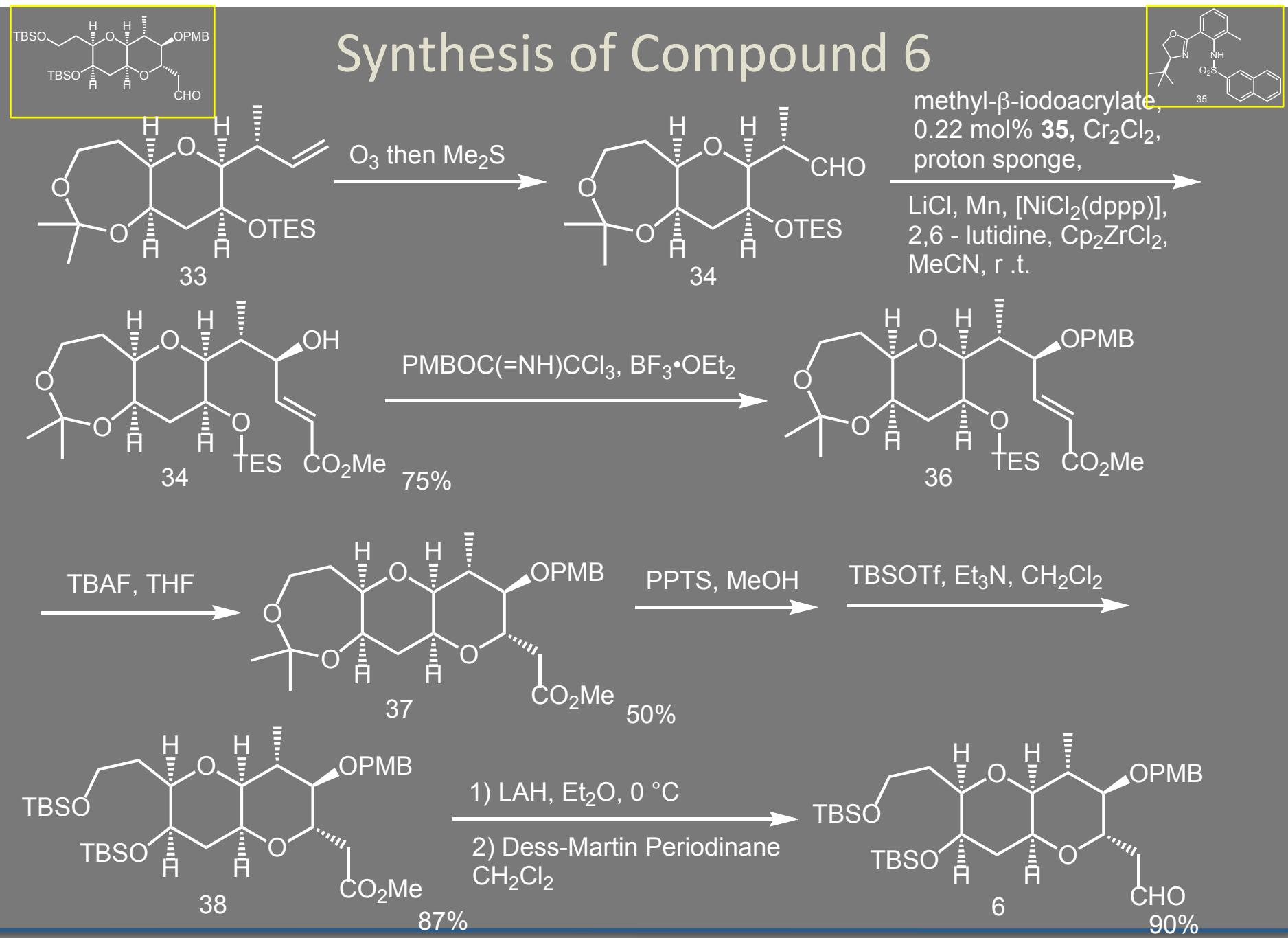
Achmatowicz Oxidation and Kishi Reduction

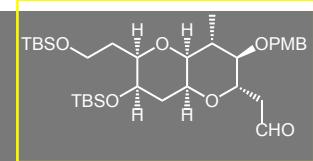


Nozaki-Hiyama-Kishi Reaction

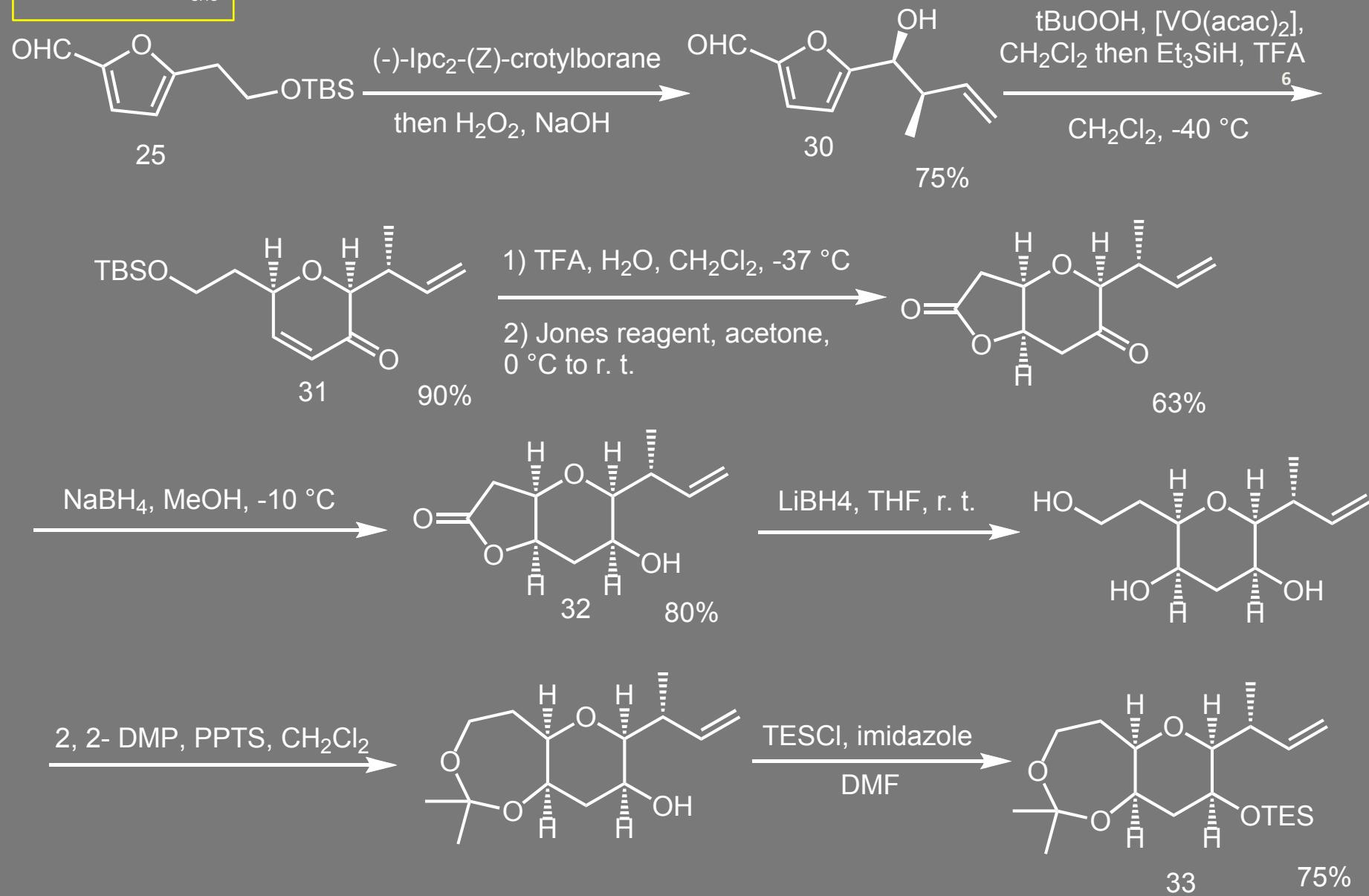


Synthesis of Compound 6

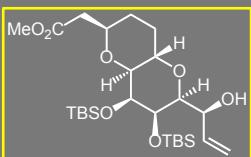




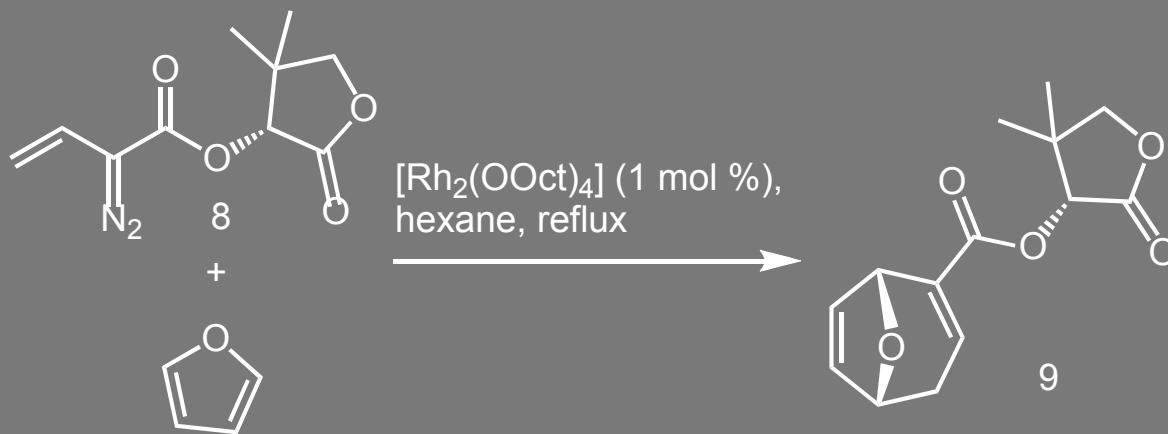
Synthesis of Compound 6

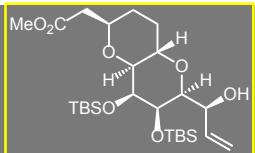


Key Reactions for the Synthesis of Compound 5

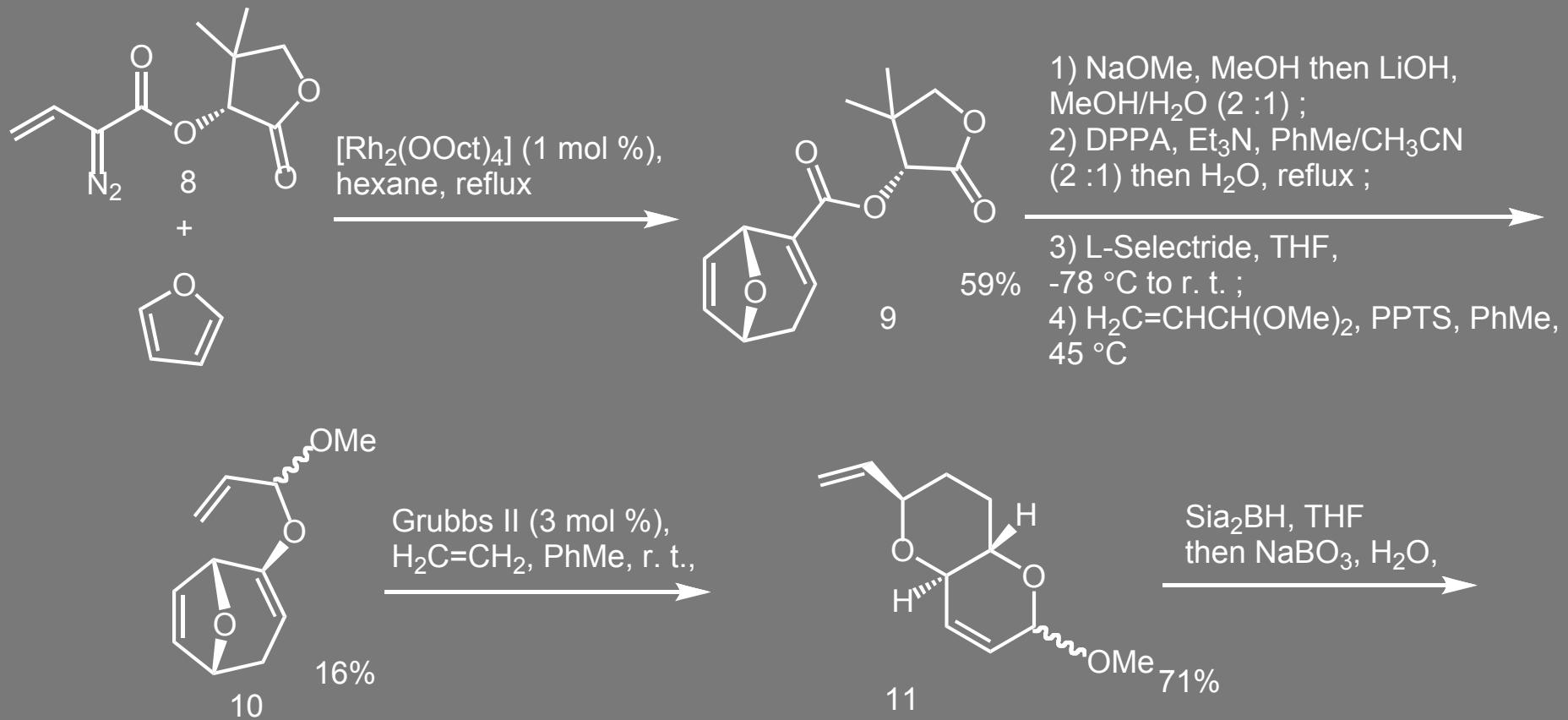


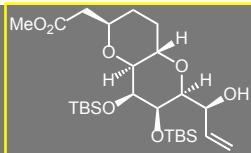
Davies Asymmetric Synthesis of 8-Oxabicyclo[3.2.1] octene



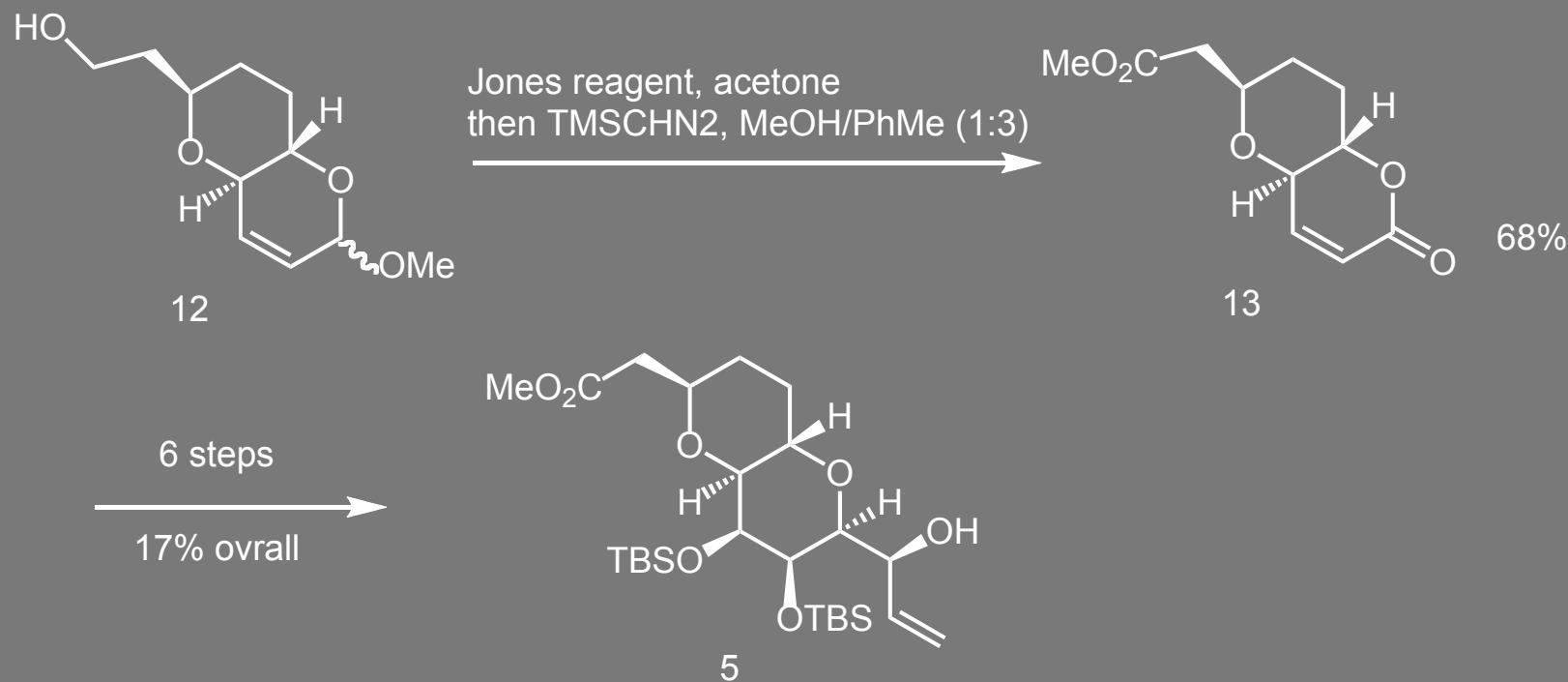


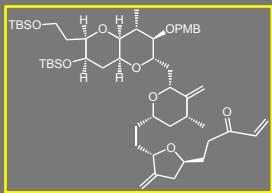
Synthesis of Compound 5



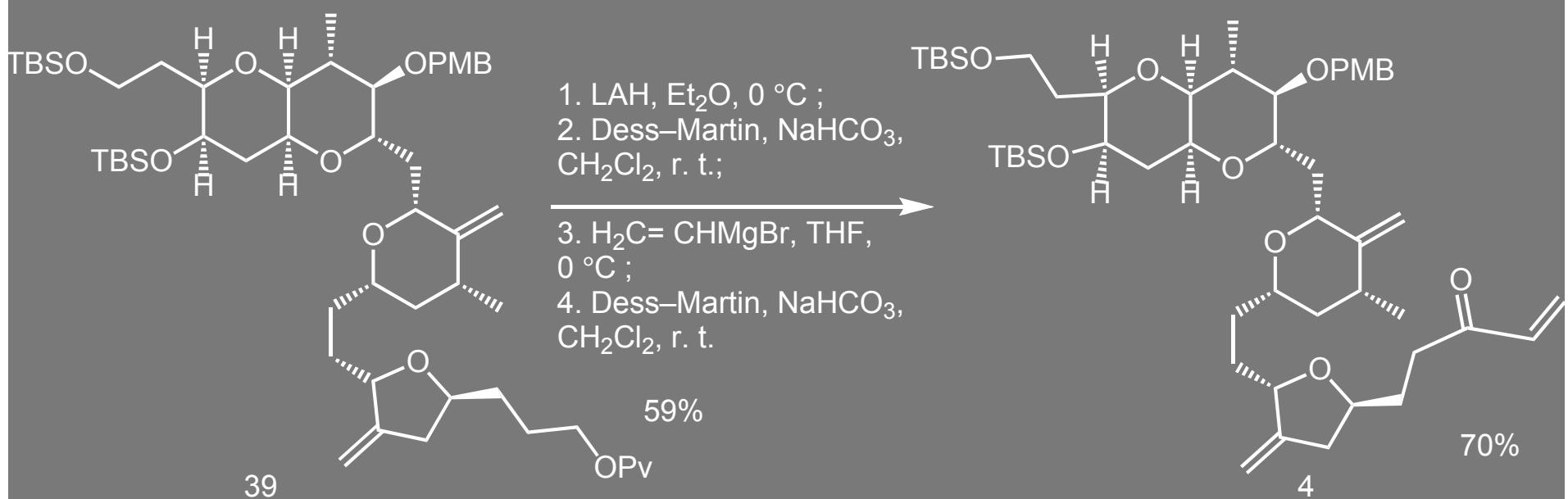
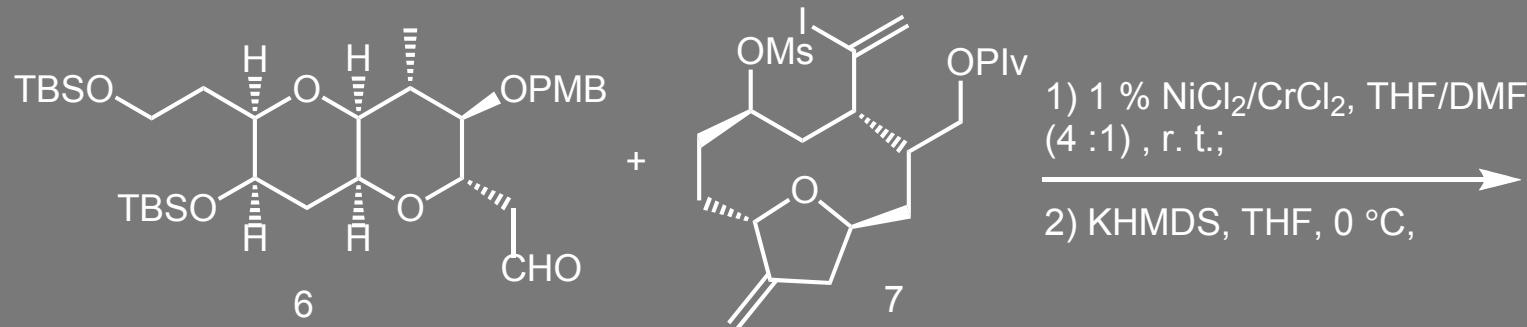


Synthesis of Compound 5

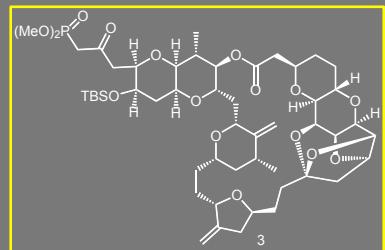
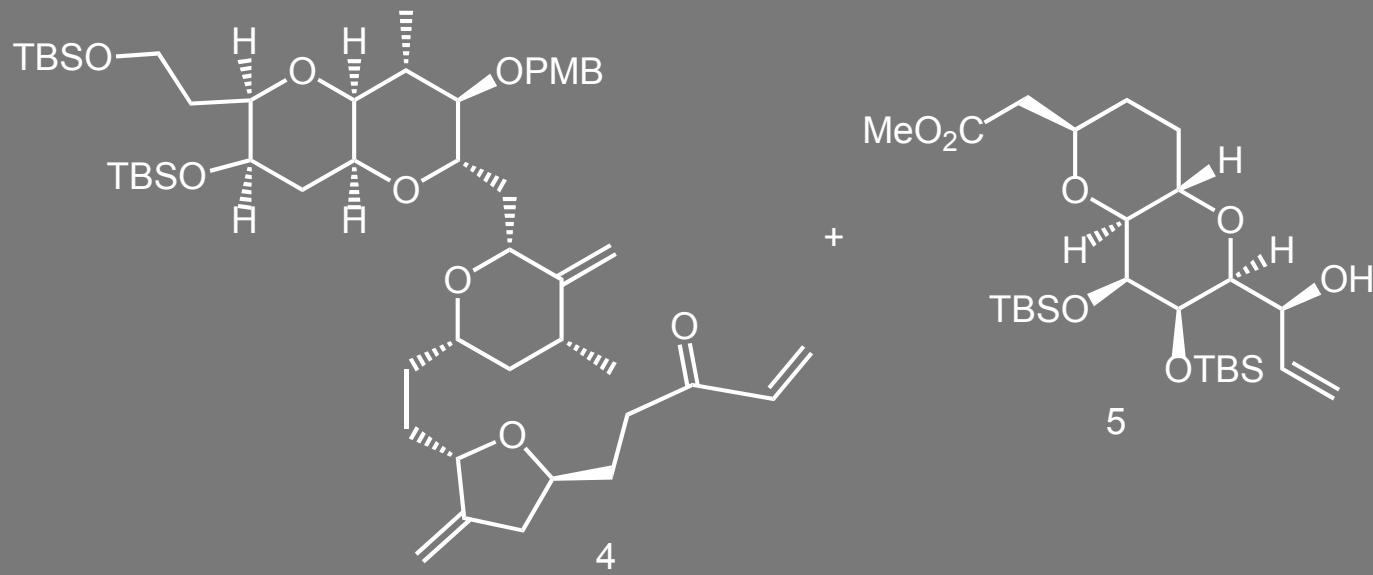




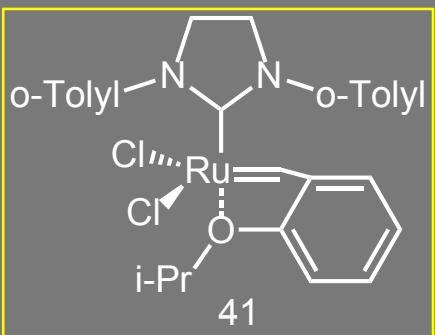
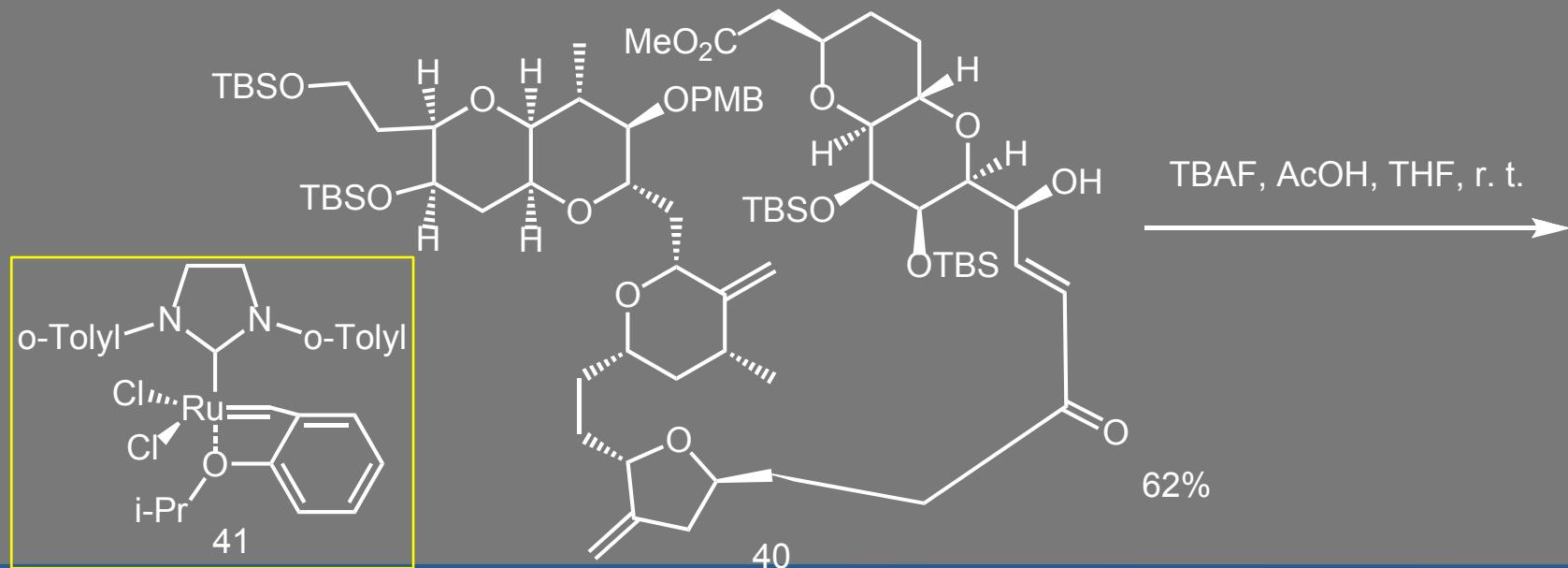
Synthesis of Compound 4



Synthesis of Compound 3

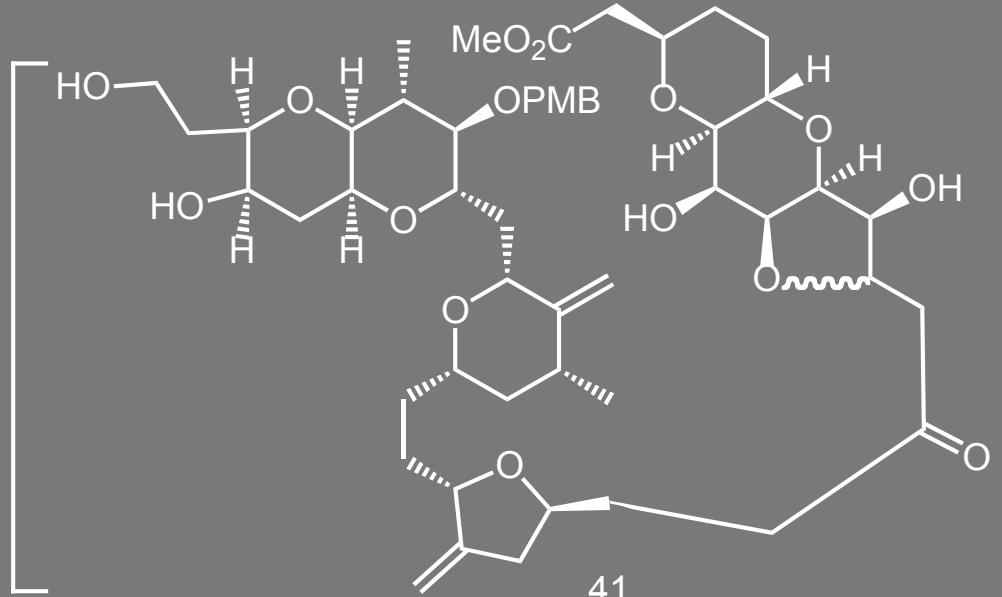


41 (20 mol %),
PhMe, 80 °C

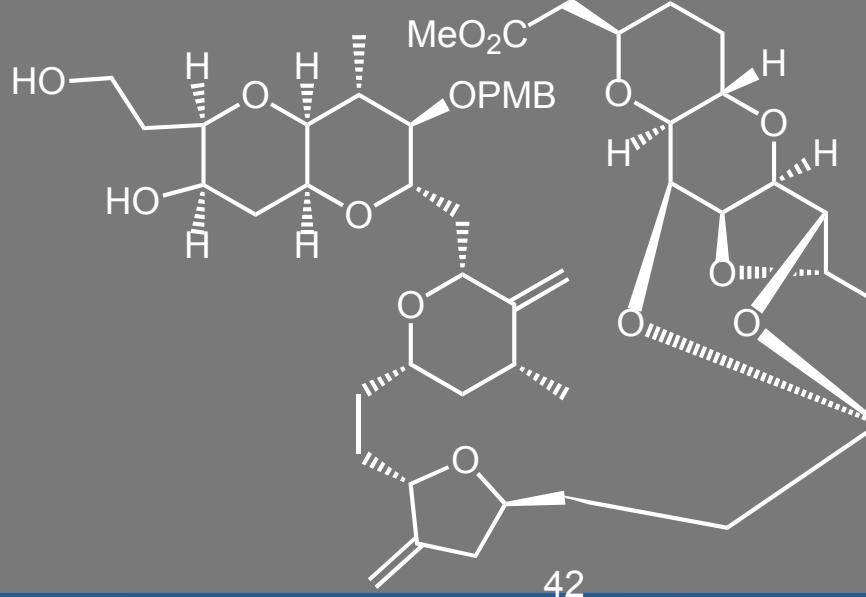
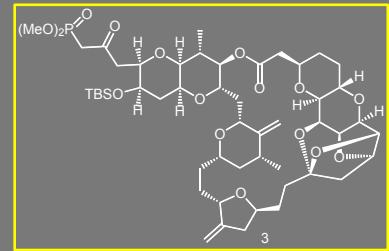


Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2346-2350.

Synthesis of Compound 3



CaCO_3 , DOWEX 50WX8-400,
MeOH as workup

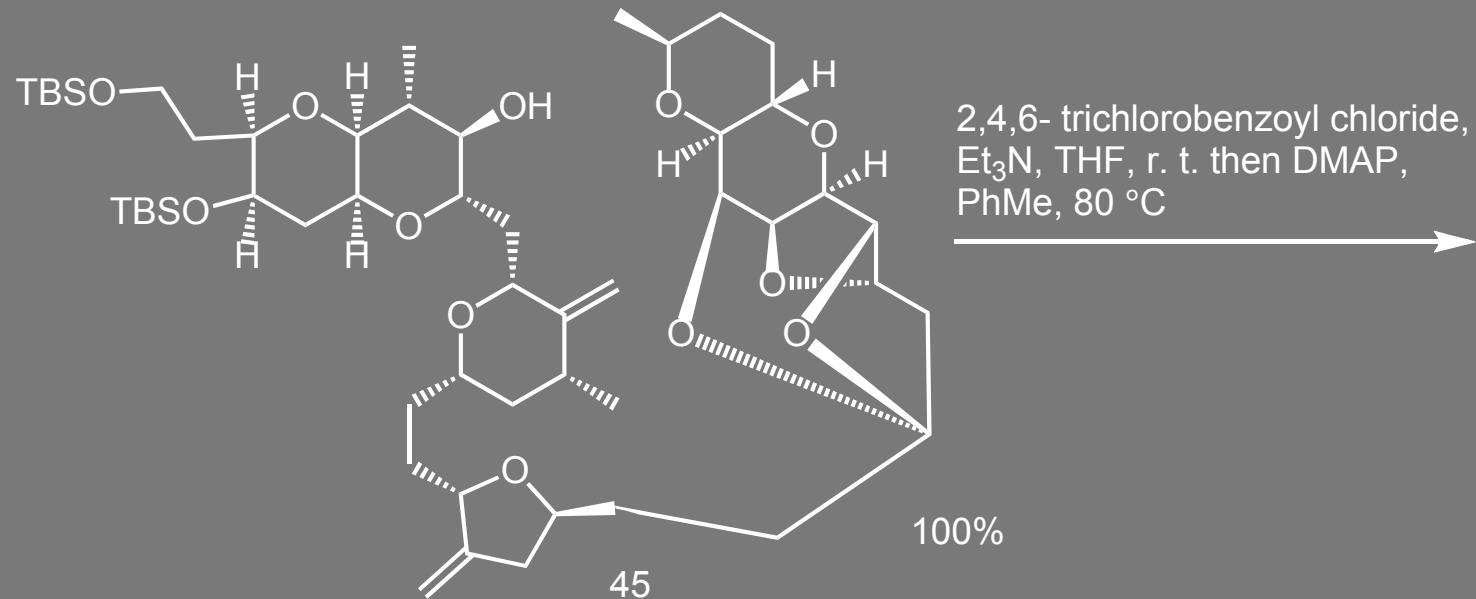
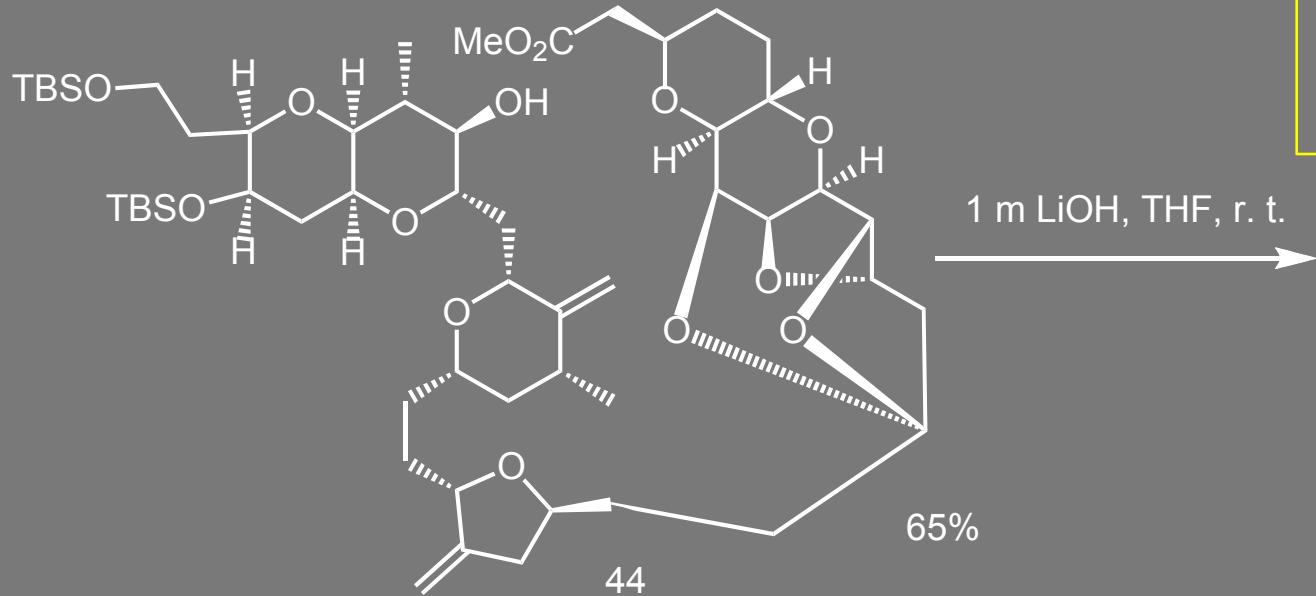


TBSOTf,
 Et_3N , CH_2Cl_2 , 0°C

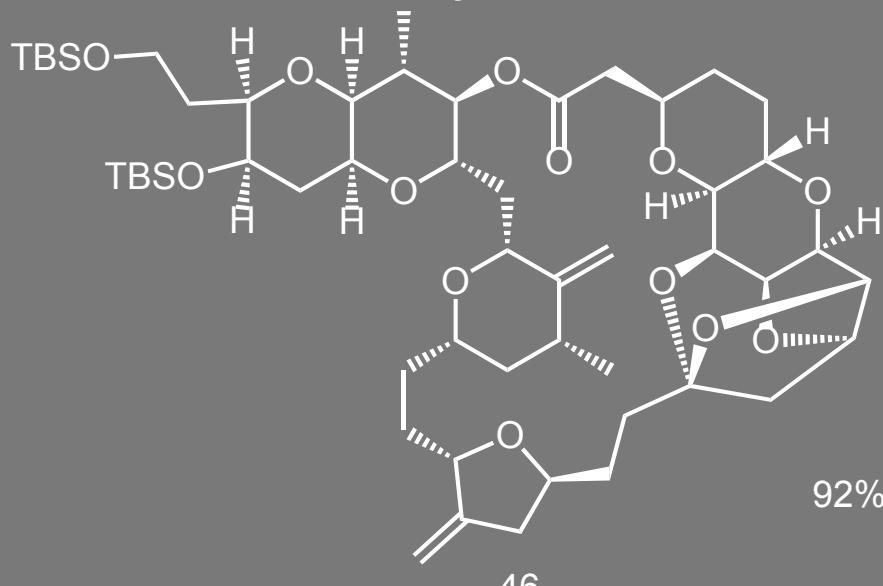
DDQ, CH_2Cl_2 ,
pH 7 phosphate buffer

64%

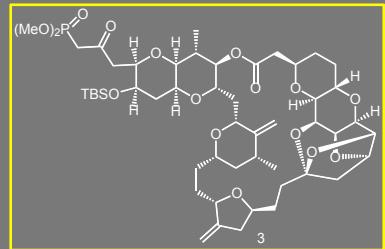
Synthesis of Compound 3



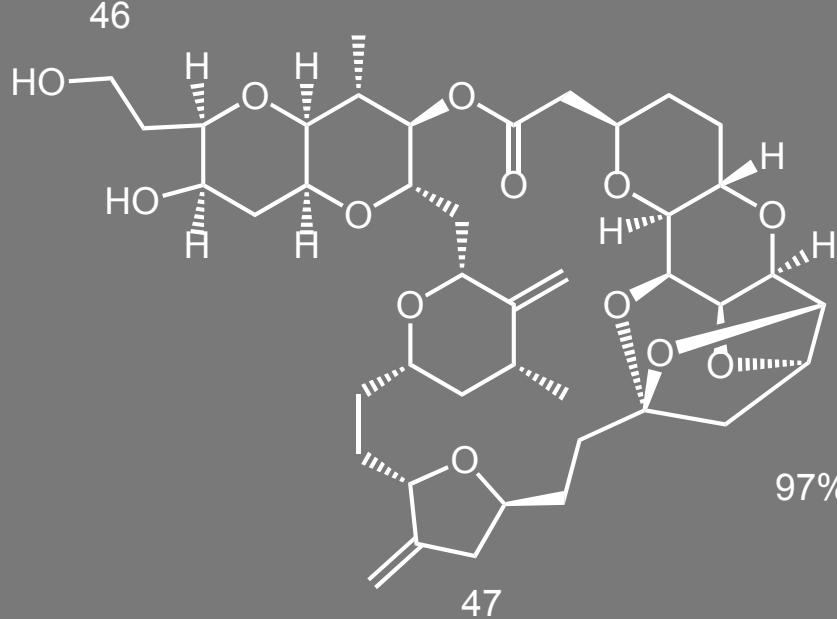
Synthesis of Compound 3



PPTS, MeOH

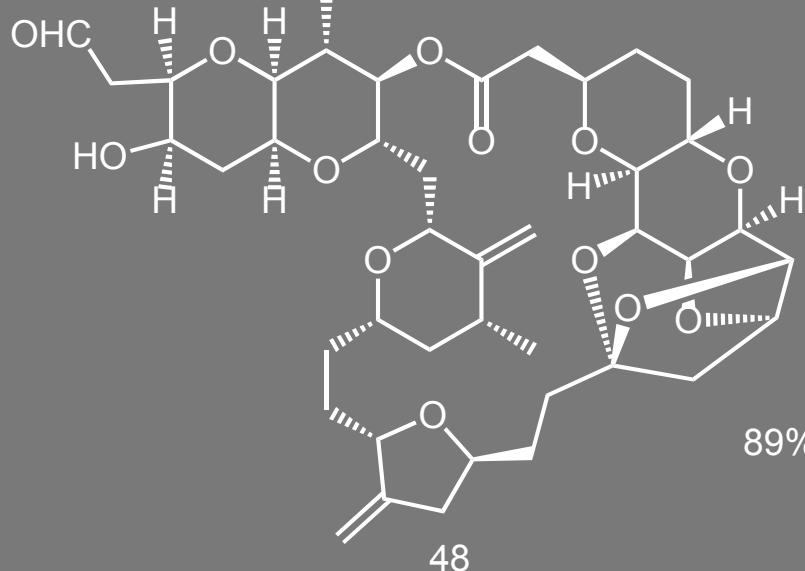


92%



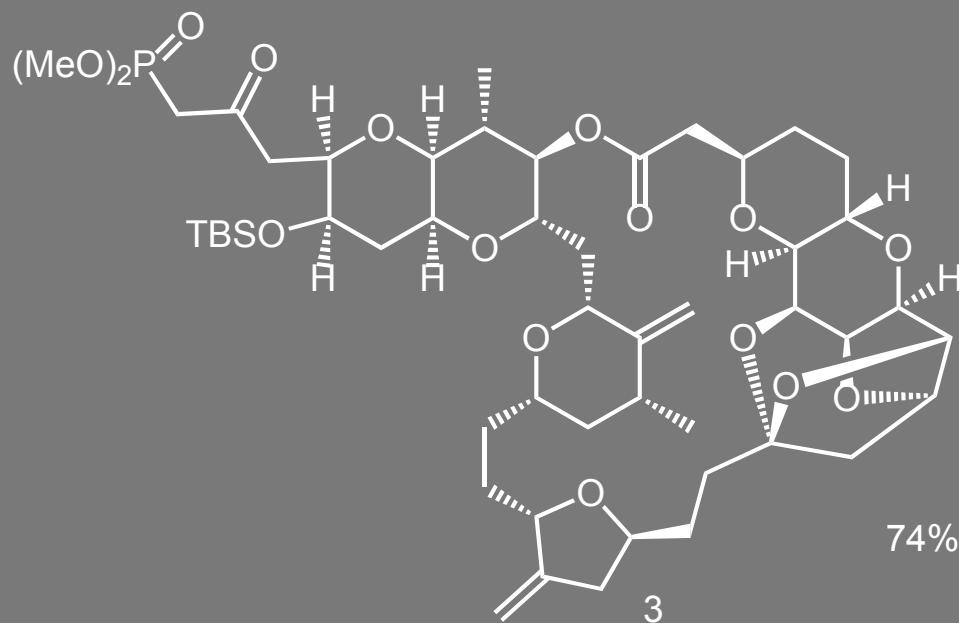
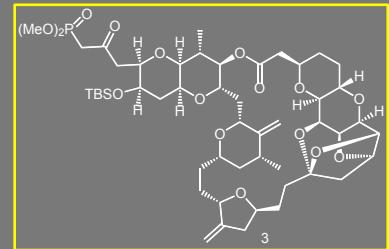
Dess–Martin, NaHCO₃,
CH₂Cl₂, r. t.

Synthesis of Compound 3



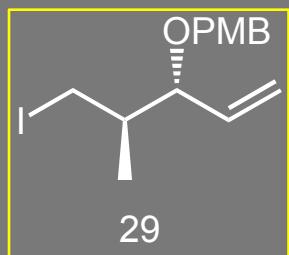
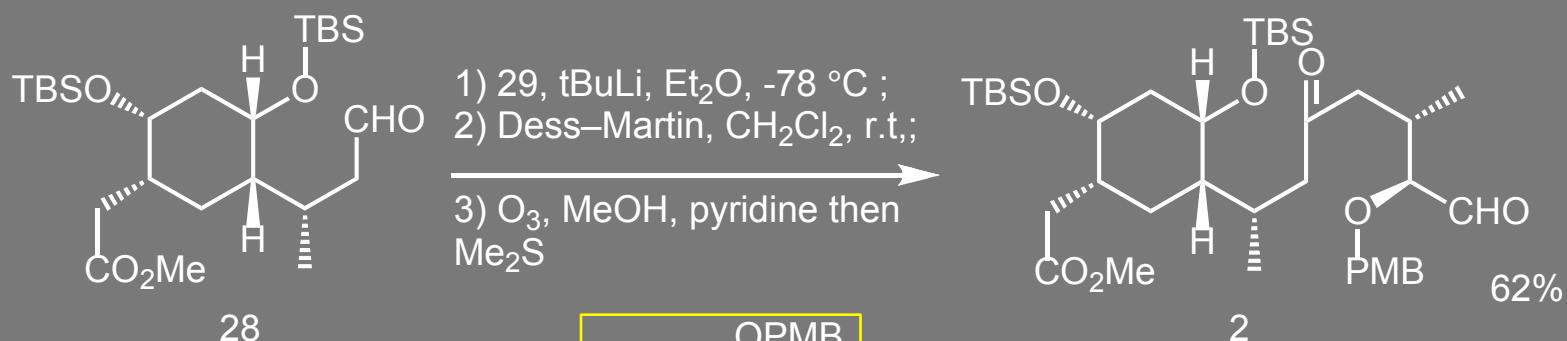
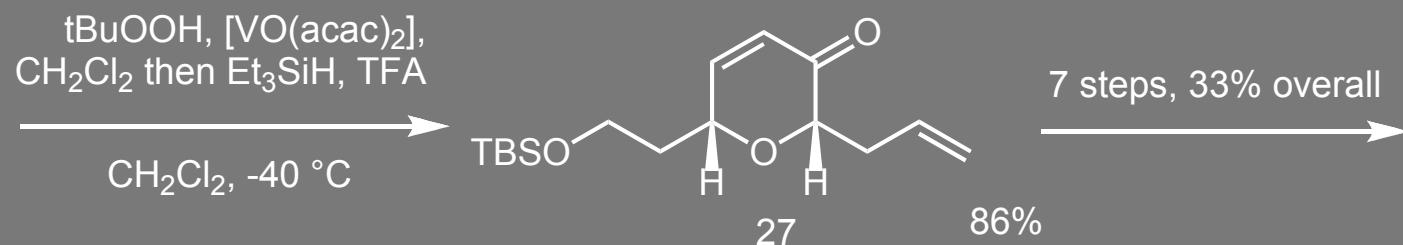
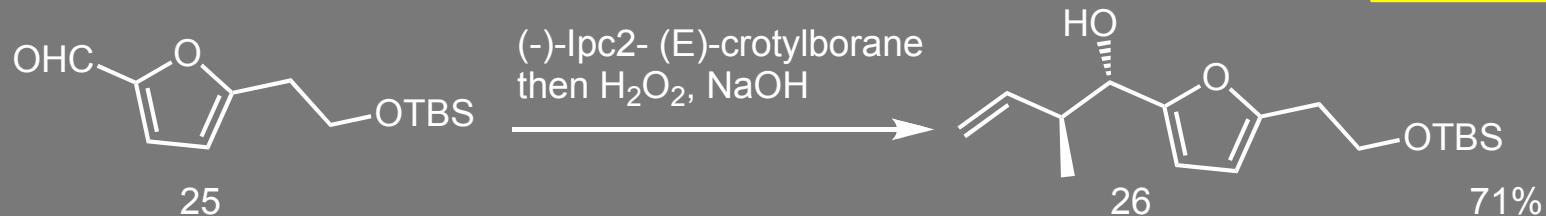
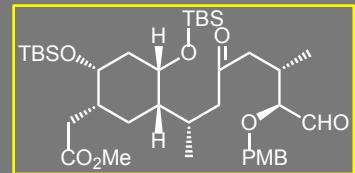
dimethyl(diazomethyl)phosphonate (20 equiv),
SnCl₂ (3 equiv), CH₂Cl₂, r. t.

89%

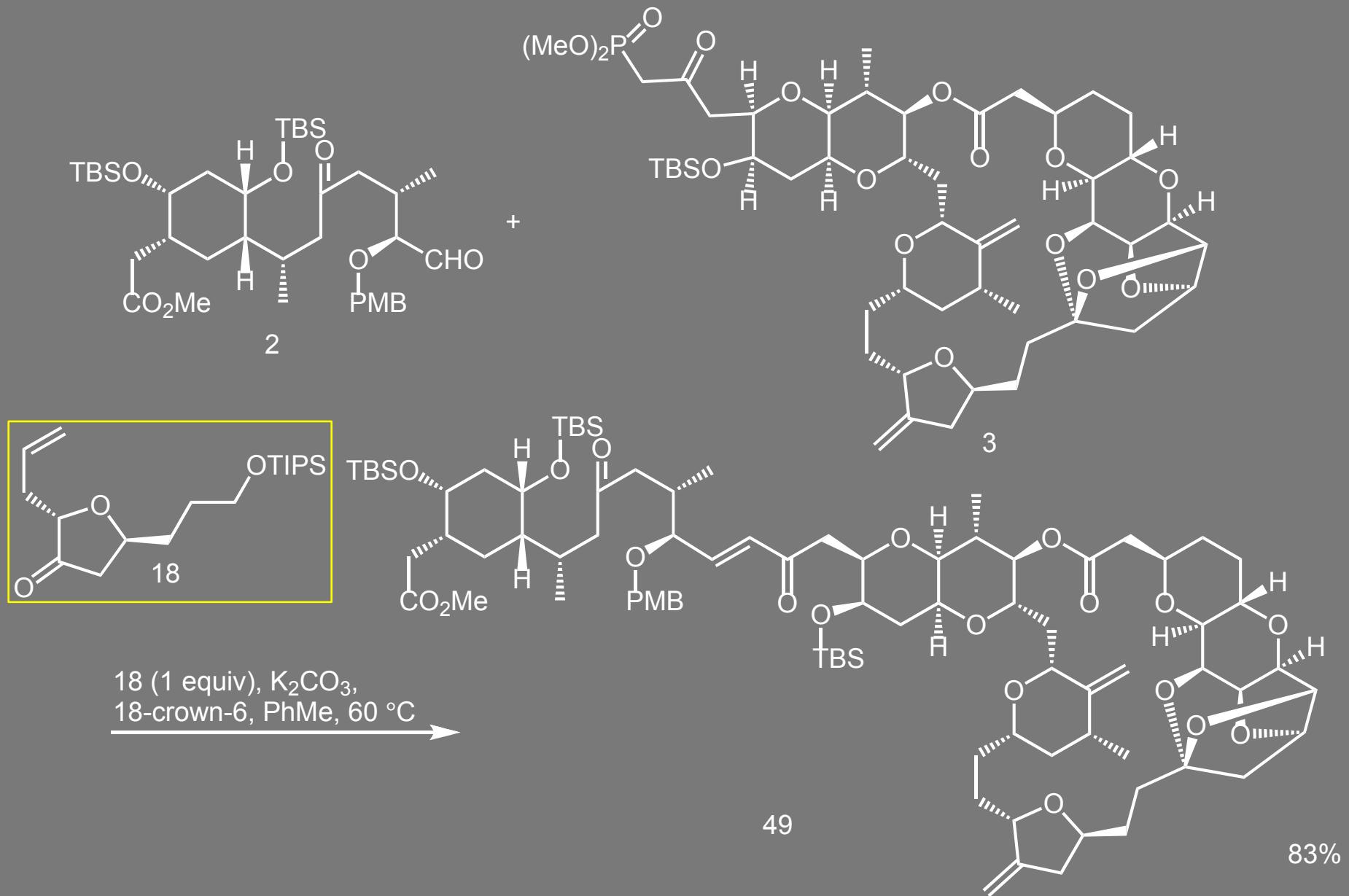


74%

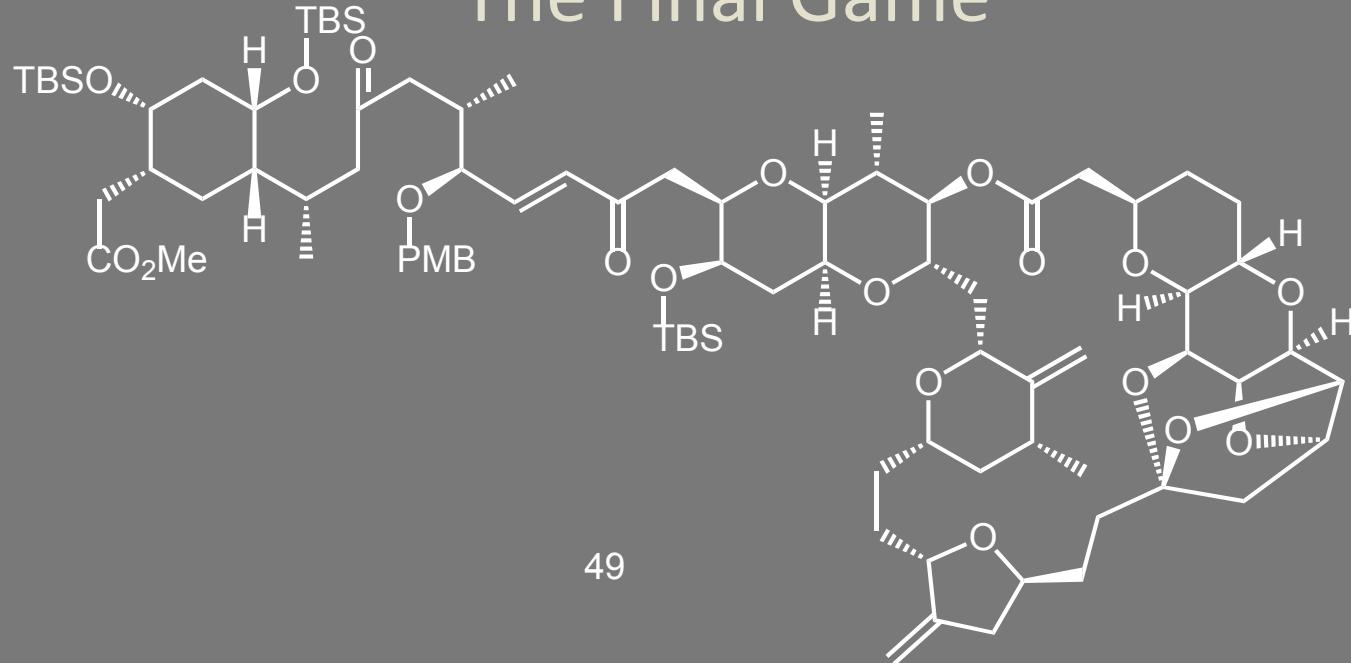
Synthesis of Compound 2



The Final Game

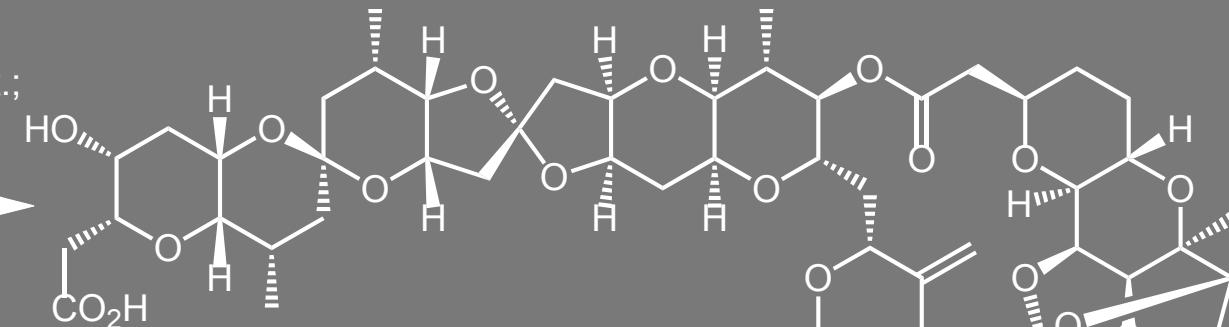


The Final Game



1) TBAF, AcOH,
MeOAc/THF (2 :1), r. t.;
2) DDQ, CH₂Cl₂/
MeOH (10 :1);

3) LiOH, THF/
H₂O (3 :1),



38%