

Total Synthesis of Norhalichondrin B

Hong Ren

The Wulff Group

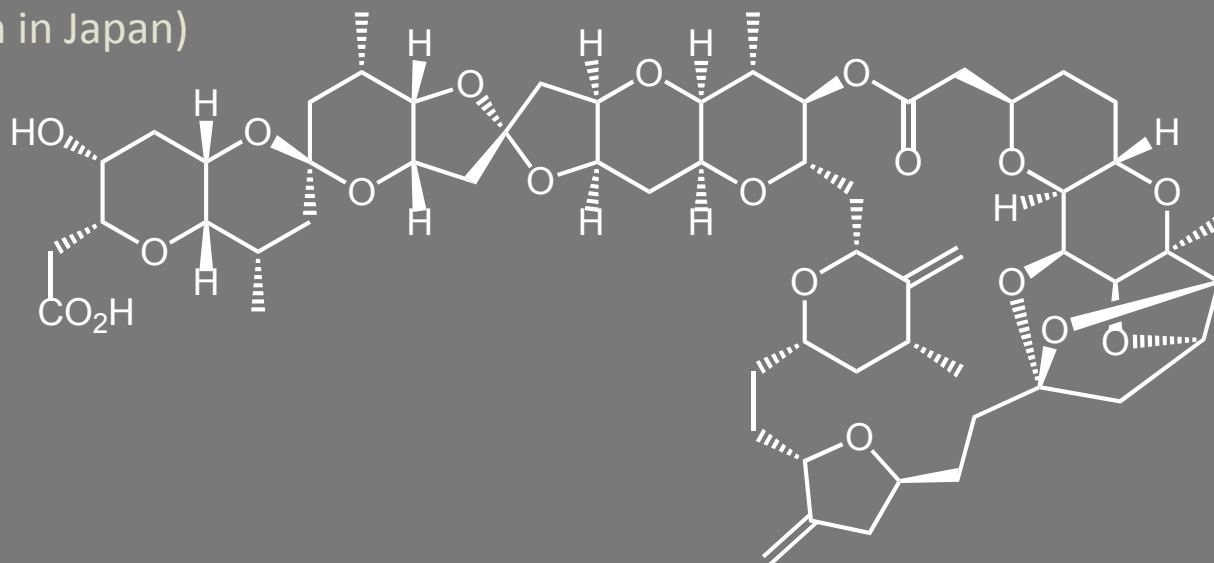
04-19-09

What is Norhalichondrin B?

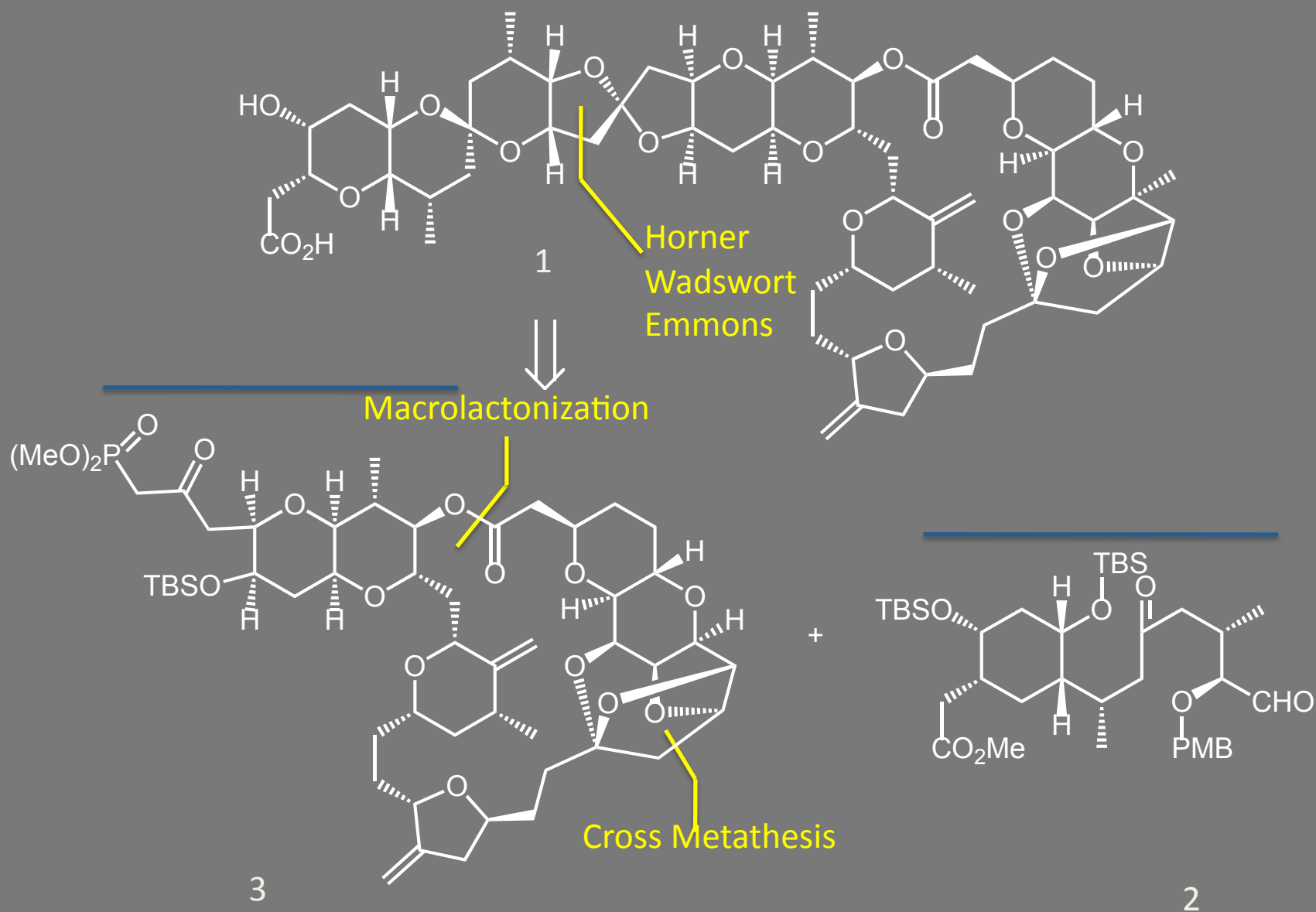


Halichondrin (Pacific Ocean in Japan)

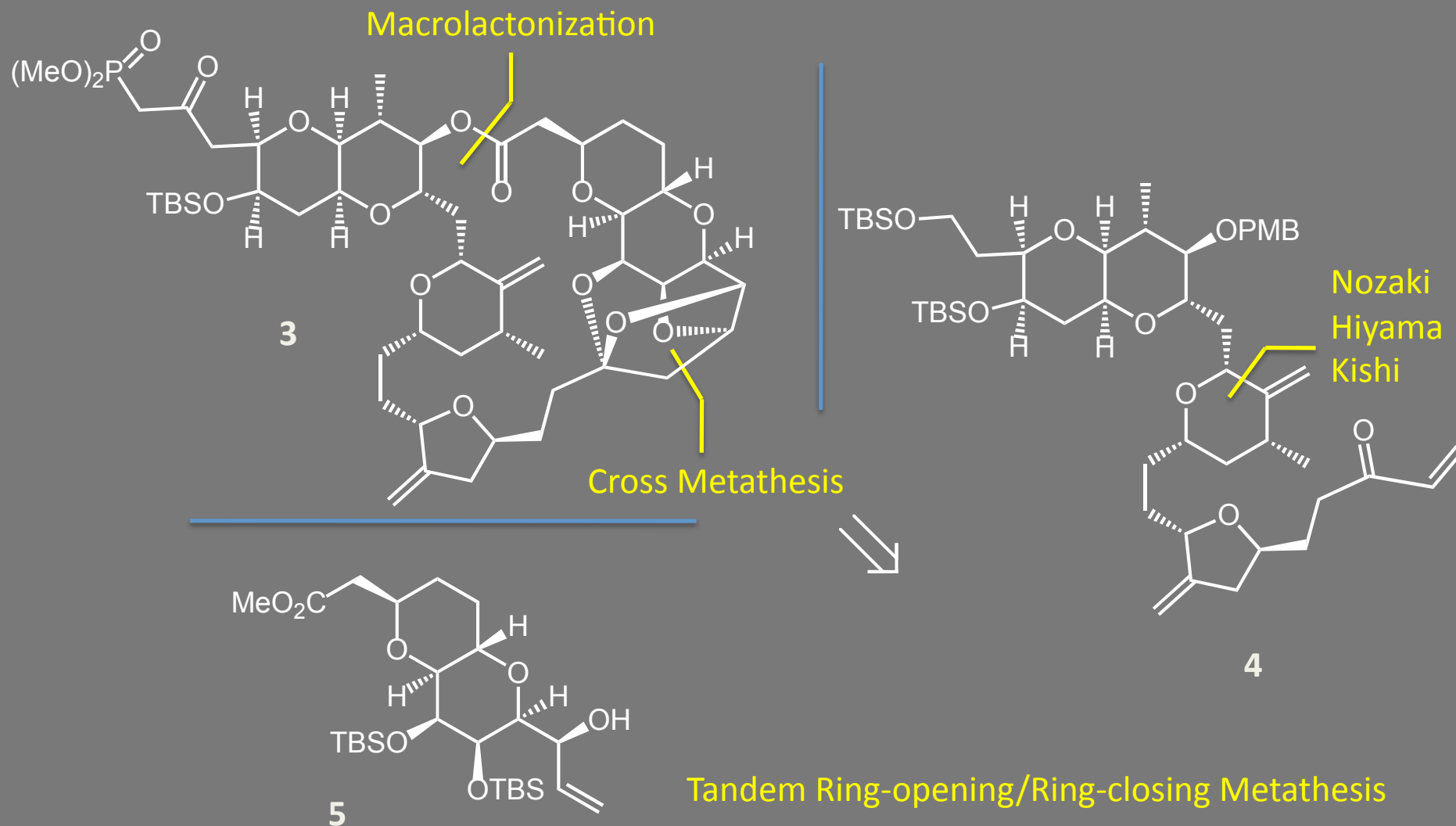
- ☺ Isolated from Halichondria Okadai Kadota in 1986
- ☺ Structure Elucidated in 1986
- ☺ Exits Extraordinary *in vitro* and *in vivo* Antitumor Activity



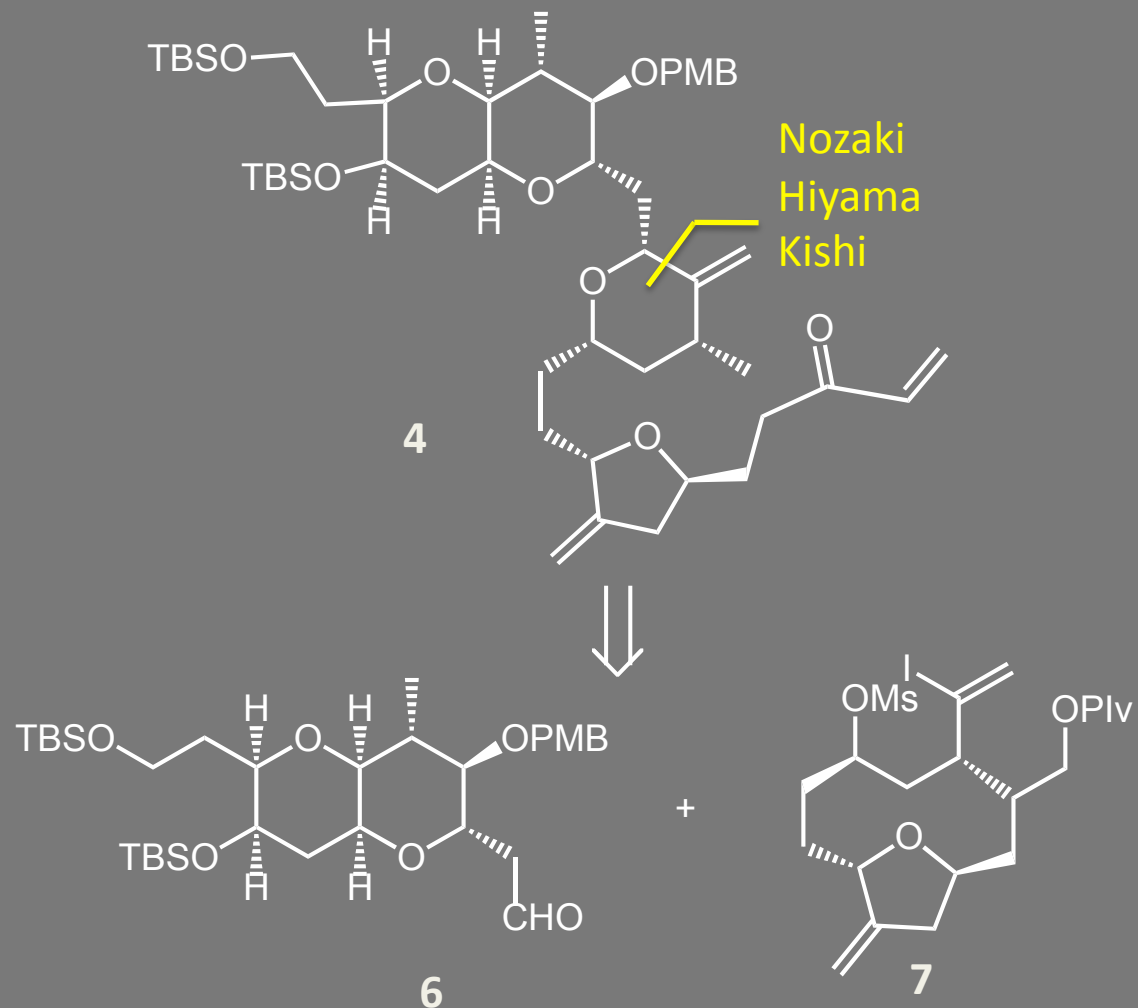
Strategy-Level Analysis Showing Key Disconnections



Strategy-Level Analysis Showing Key Disconnections

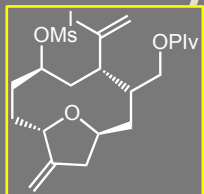


Strategy-Level Analysis Showing Key Disconnections

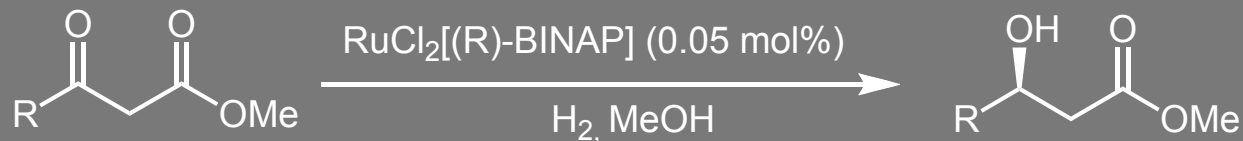


Achmatowicz [O]-Kishi [H]

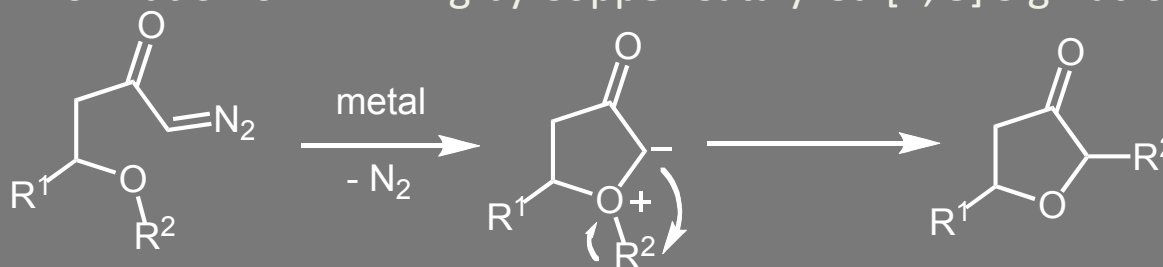
Key Reactions for the Synthesis of Compound 7



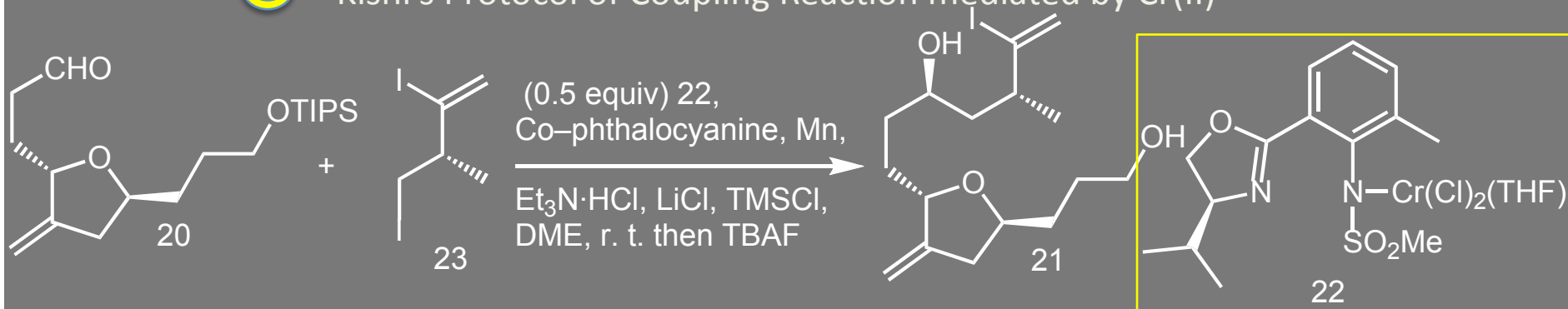
Noyori Asymmetric Hydrogenation of β -ketoester

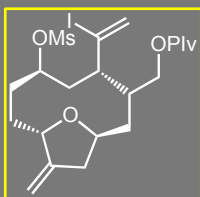


Formation of THF Ring by Copper Catalyzed [2, 3] Sigmatropic Rearr.

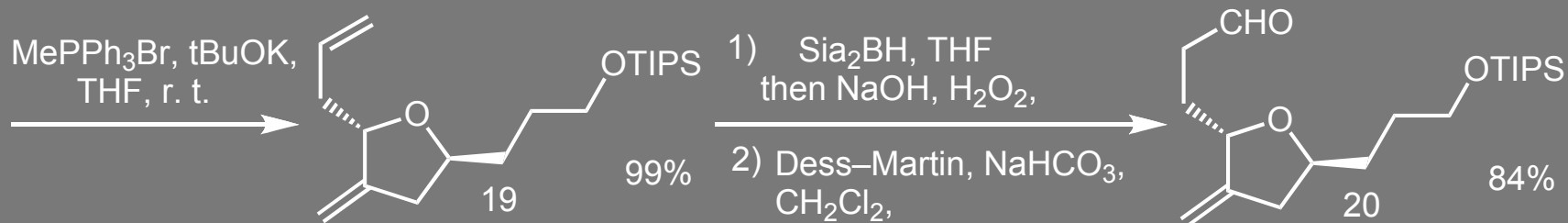
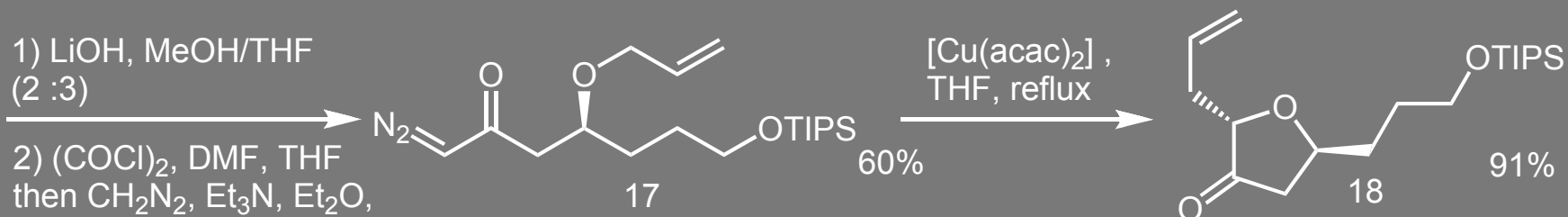
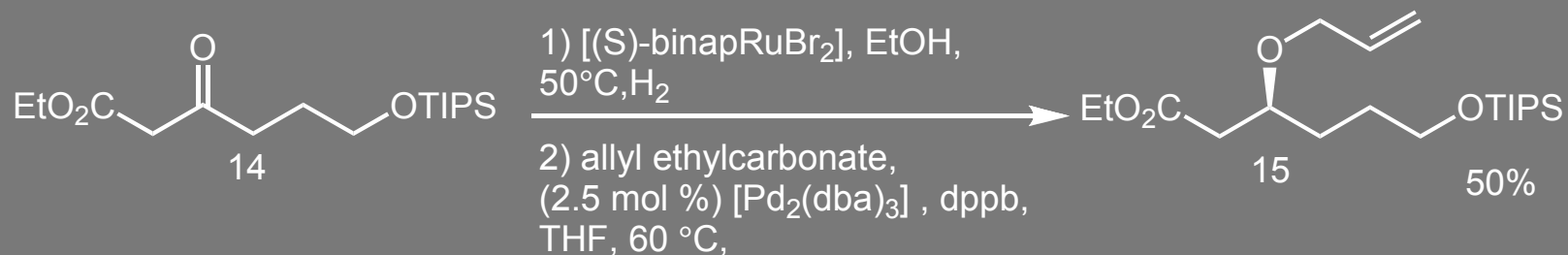


Kishi's Protocol of Coupling Reaction mediated by Cr(II)

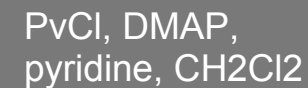
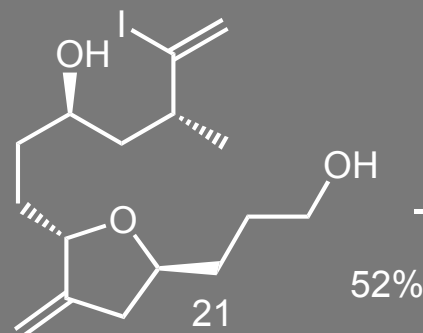
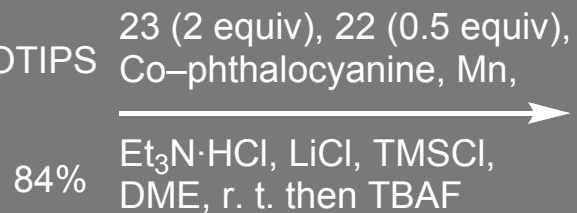
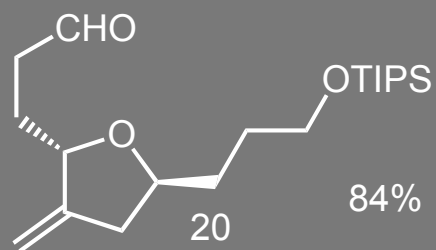
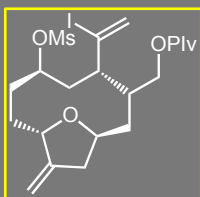




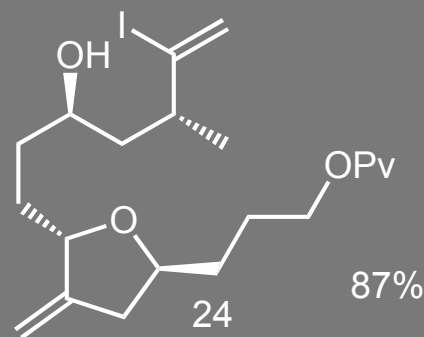
Synthesis of Compound 7



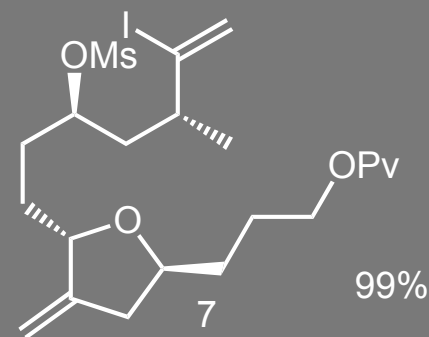
Synthesis of Compound 7



52%



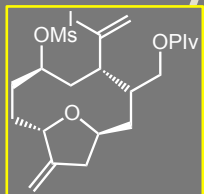
87%



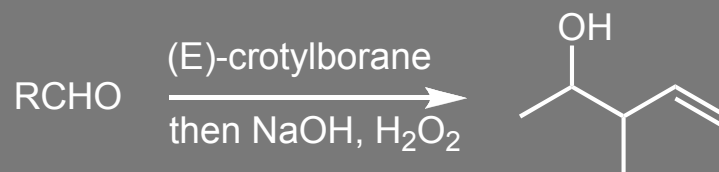
99%



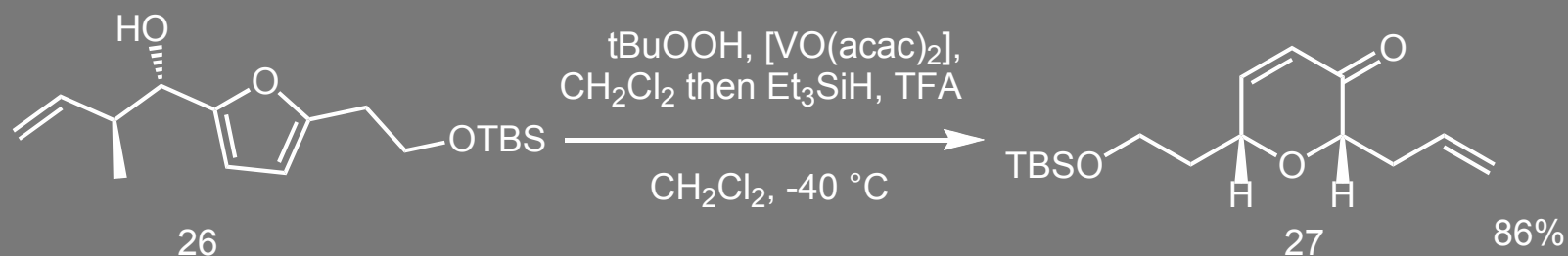
Key Reactions for the Synthesis of Compound 6



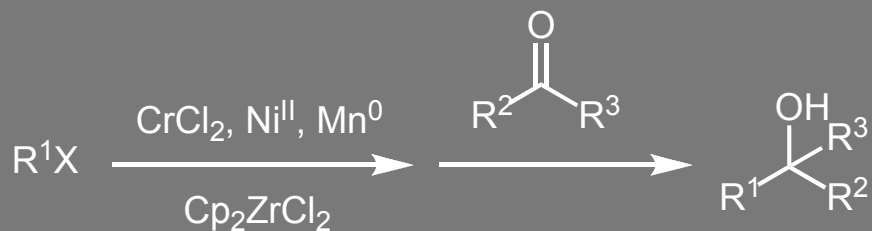
Brown Crotylation



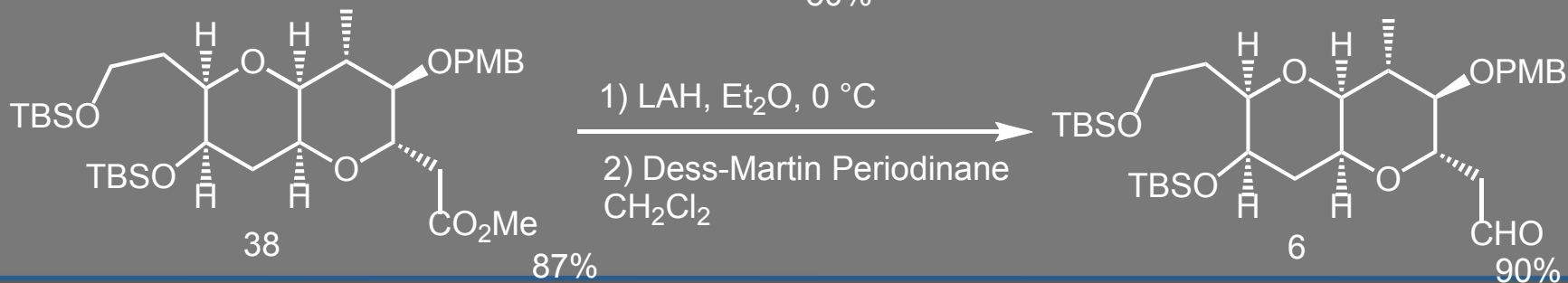
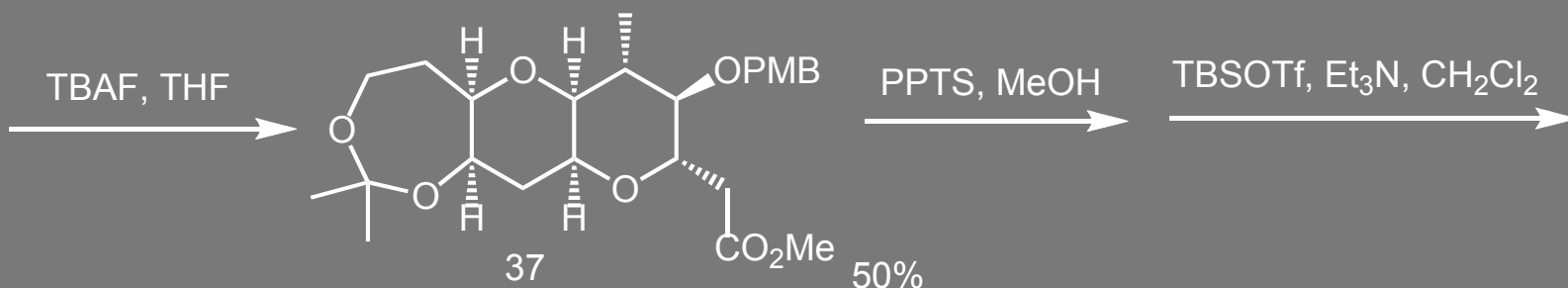
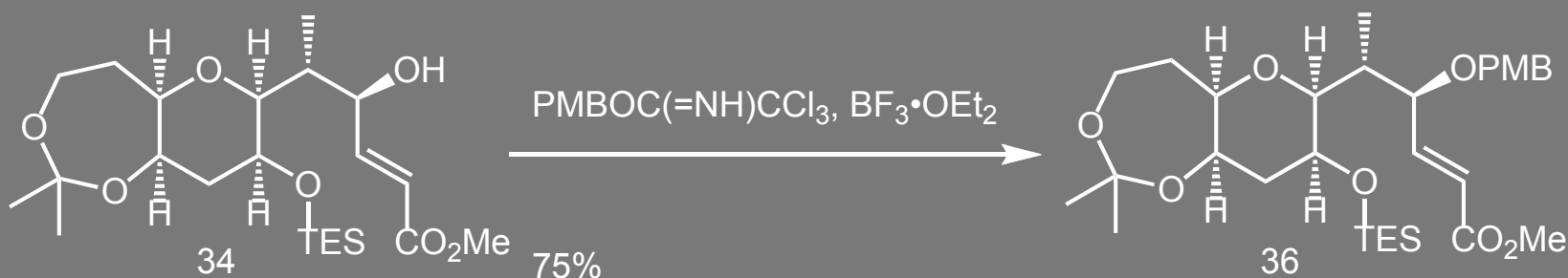
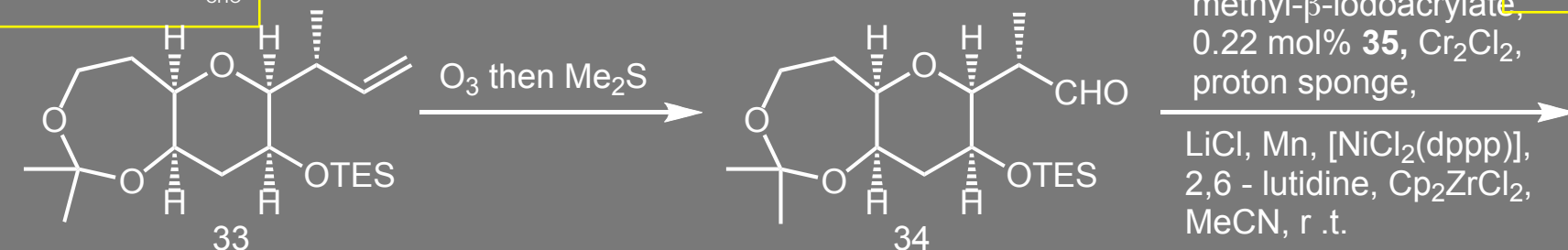
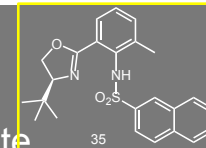
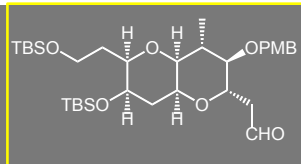
Achmatowicz Oxidation and Kishi Reduction

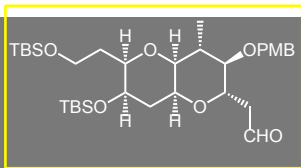


Nozaki-Hiyama-Kishi Reaction

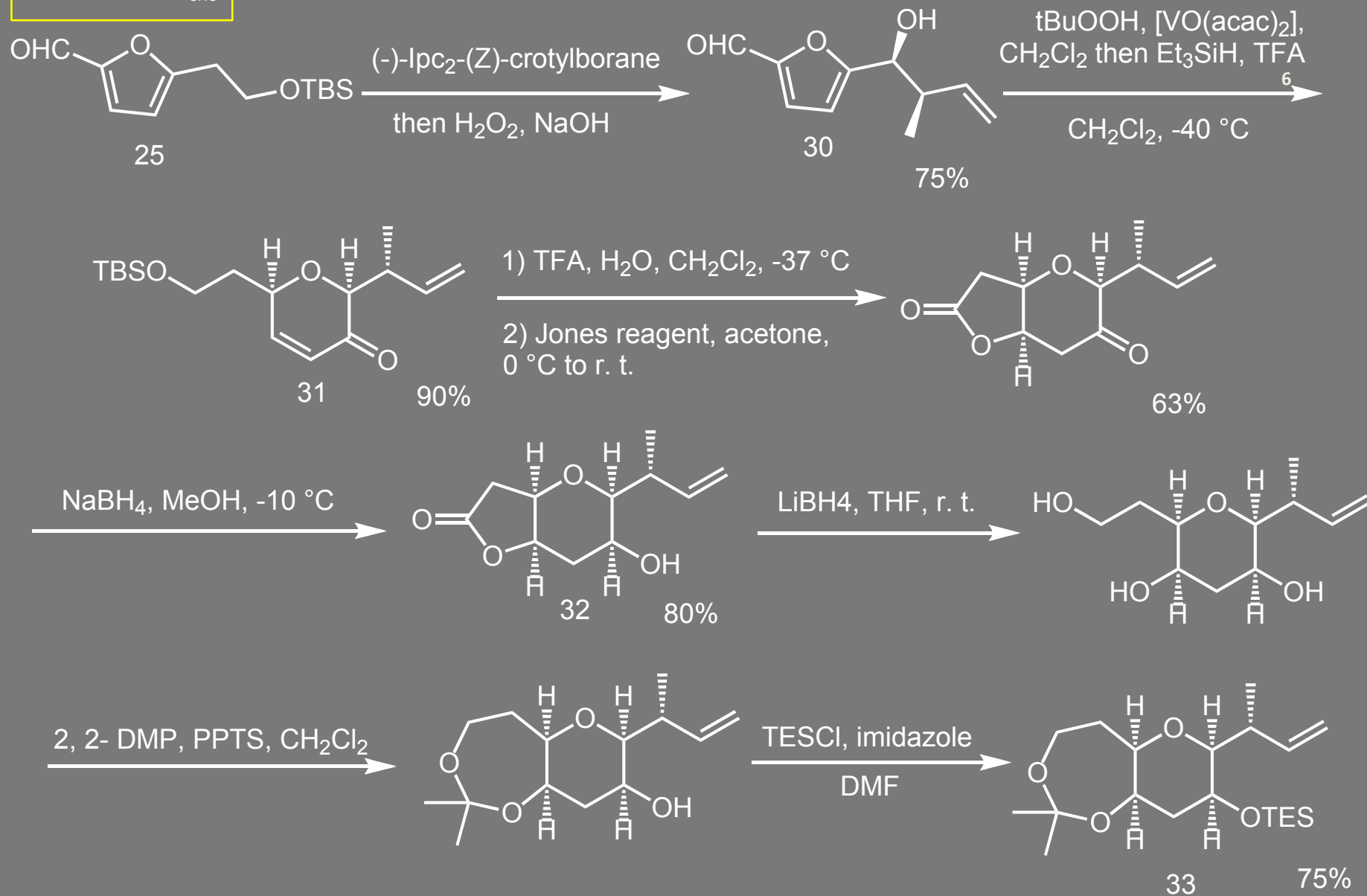


Synthesis of Compound 6

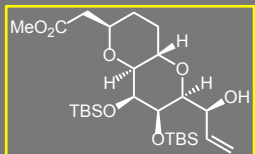




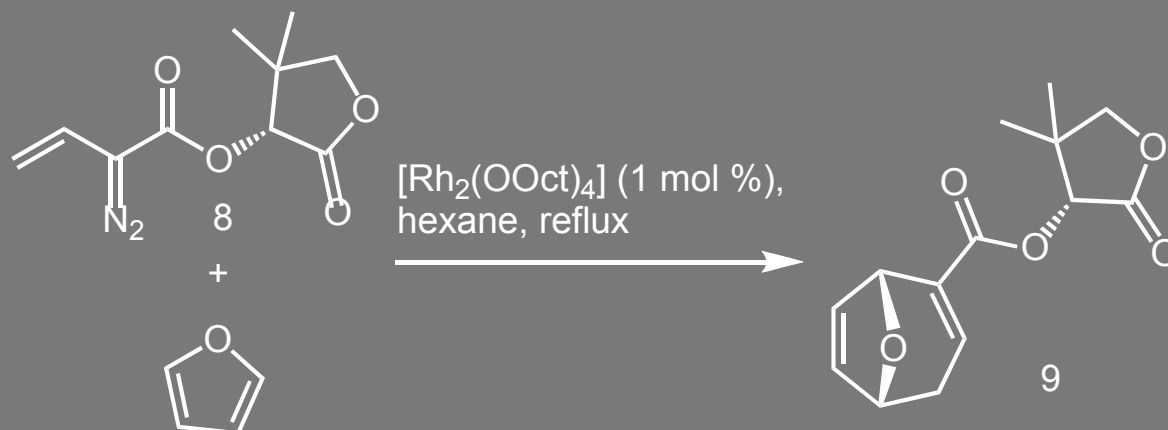
Synthesis of Compound 6

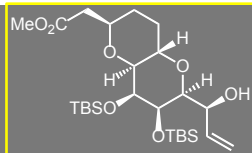


Key Reactions for the Synthesis of Compound 5

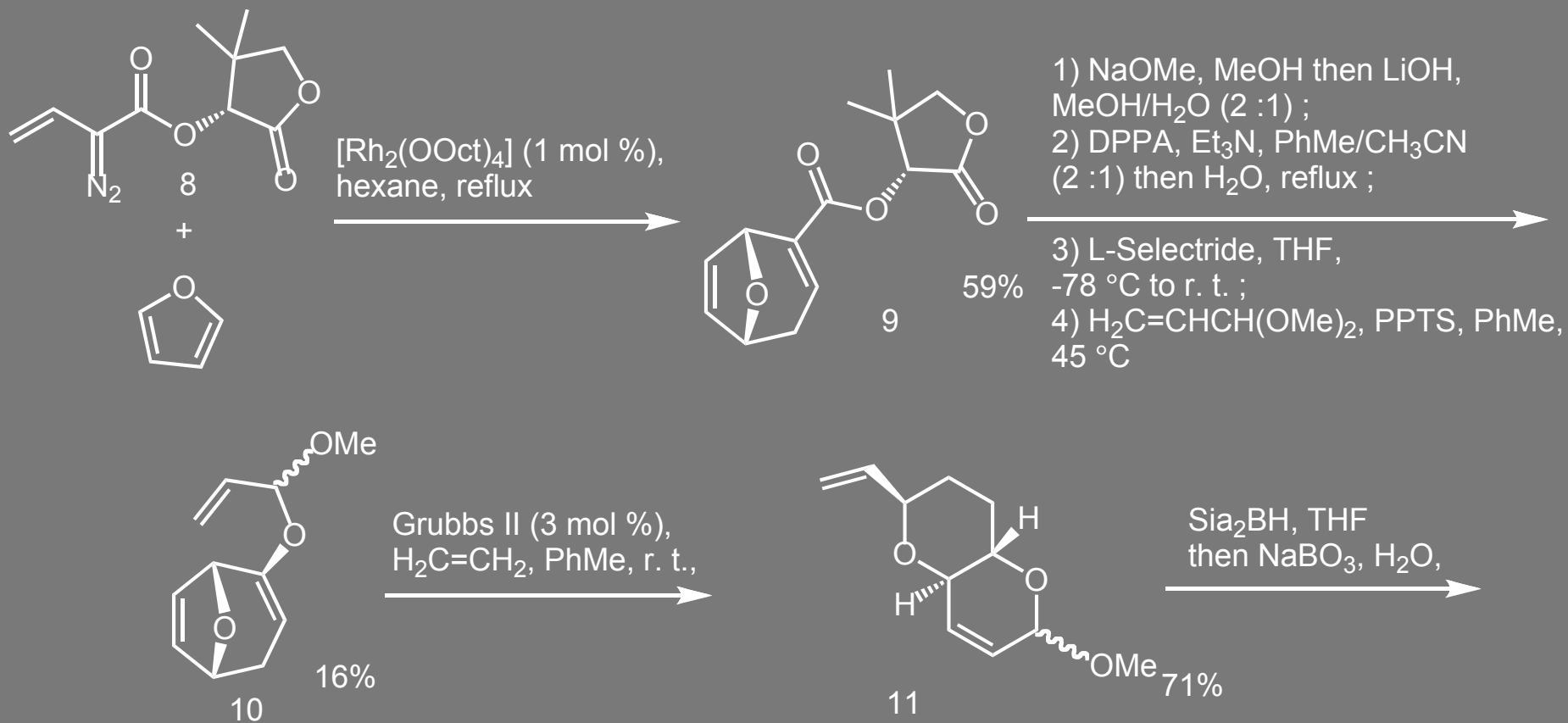


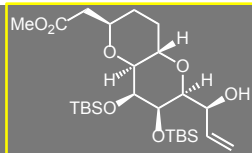
Davies Asymmetric Synthesis of 8-Oxabicyclo[3.2.1] octene



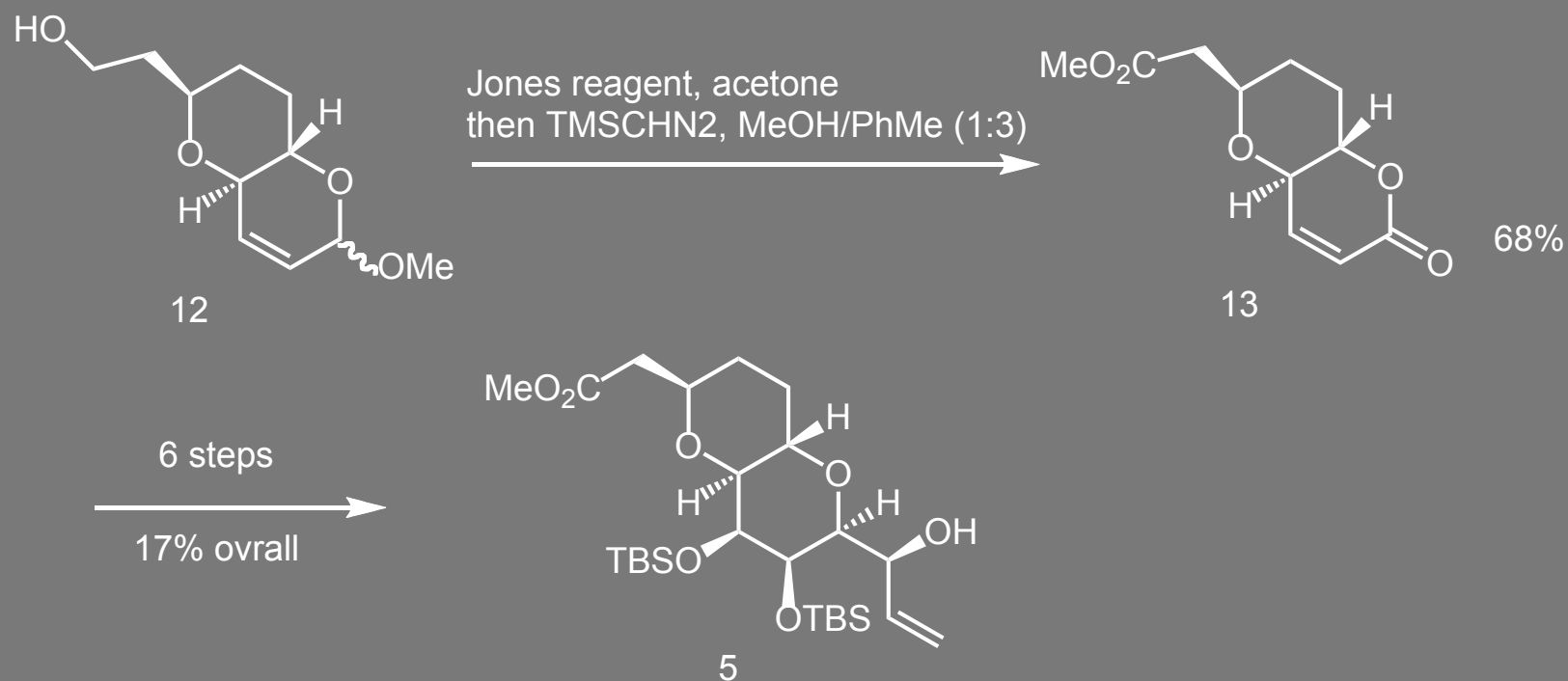


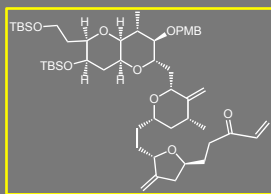
Synthesis of Compound 5



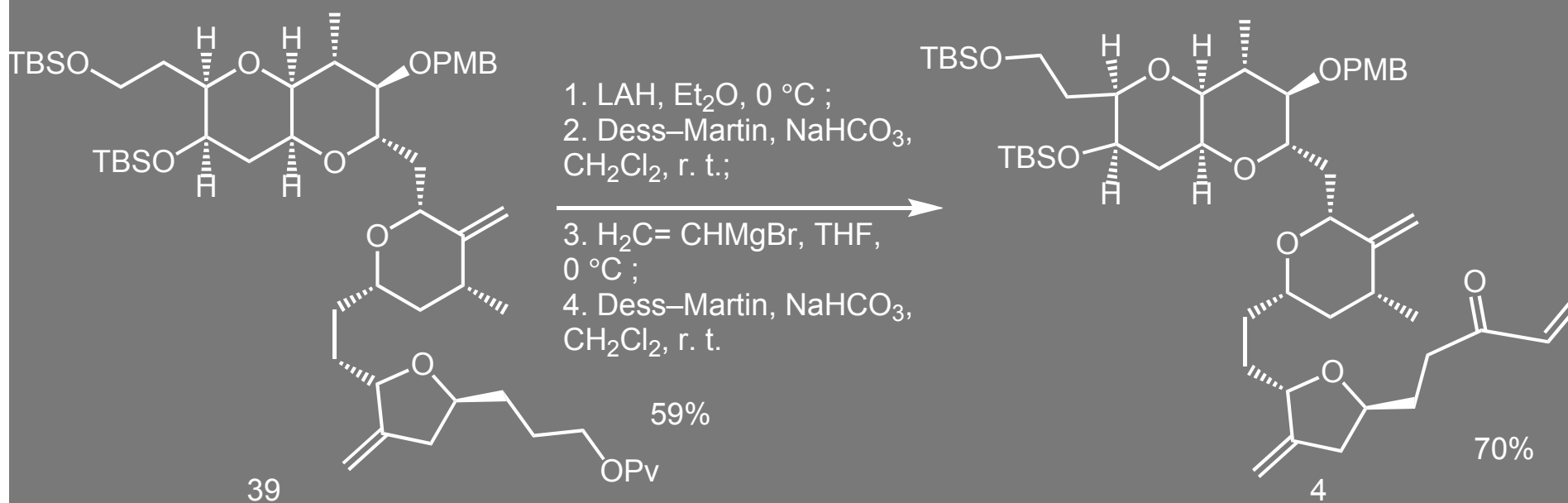
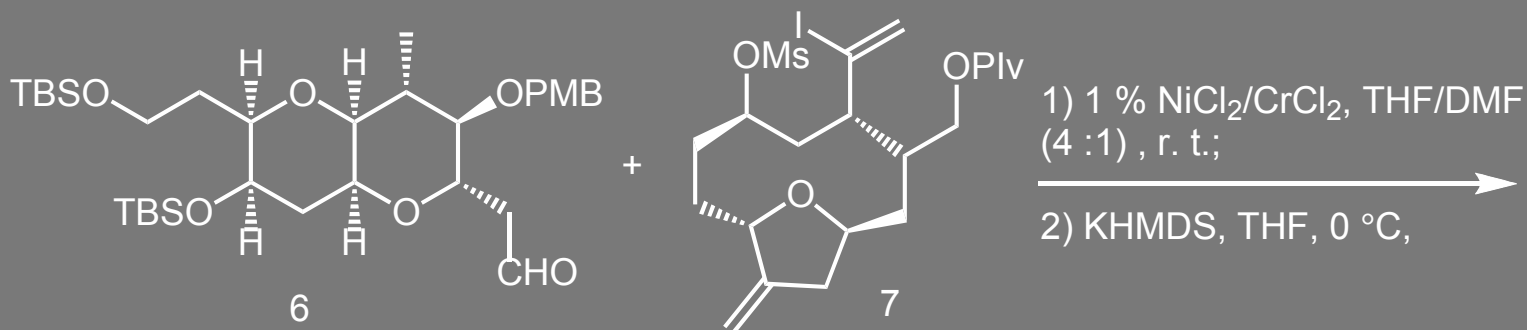


Synthesis of Compound 5

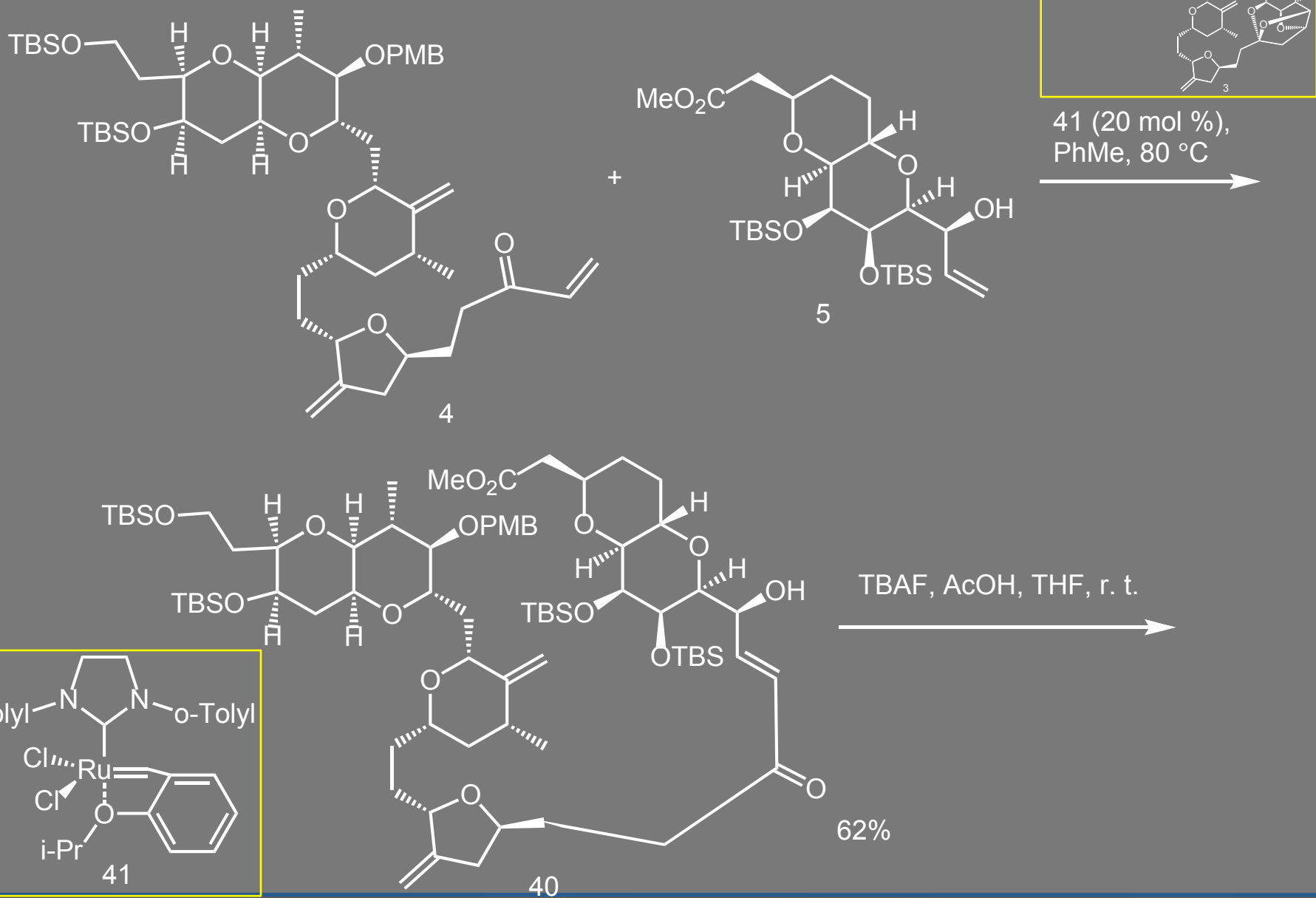




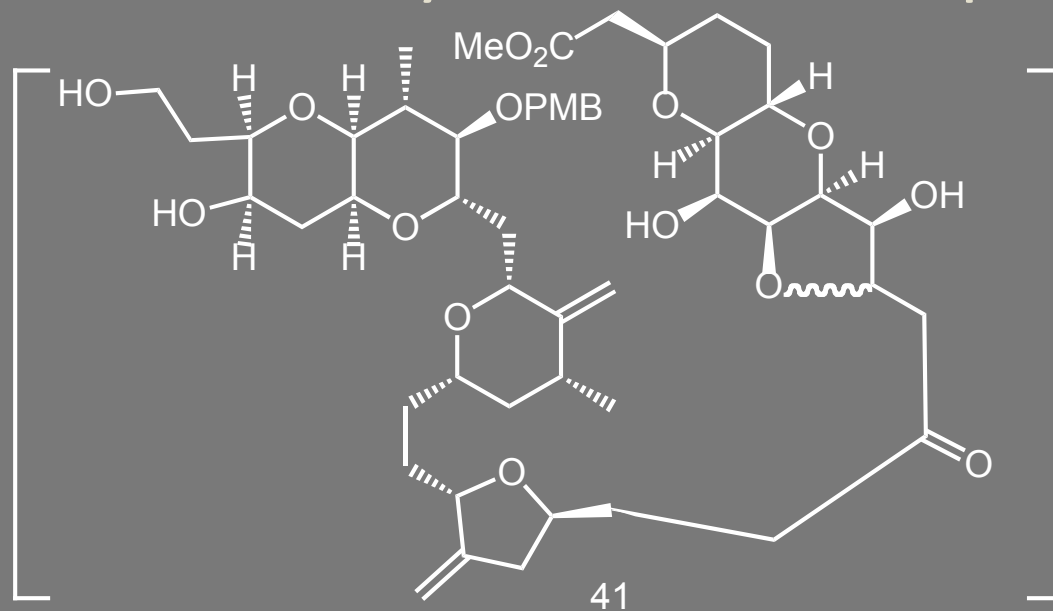
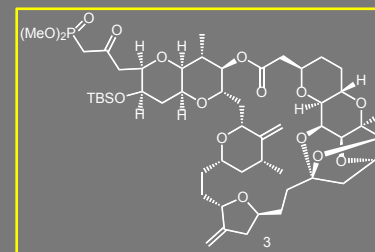
Synthesis of Compound 4



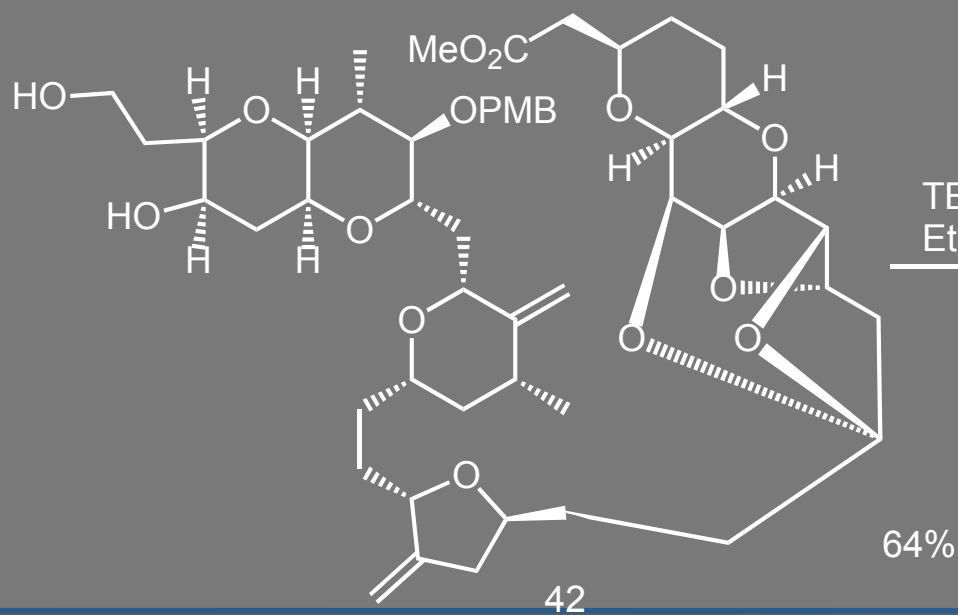
Synthesis of Compound 3



Synthesis of Compound 3



CaCO₃, DOWEX 50WX8-400,
MeOH as workup

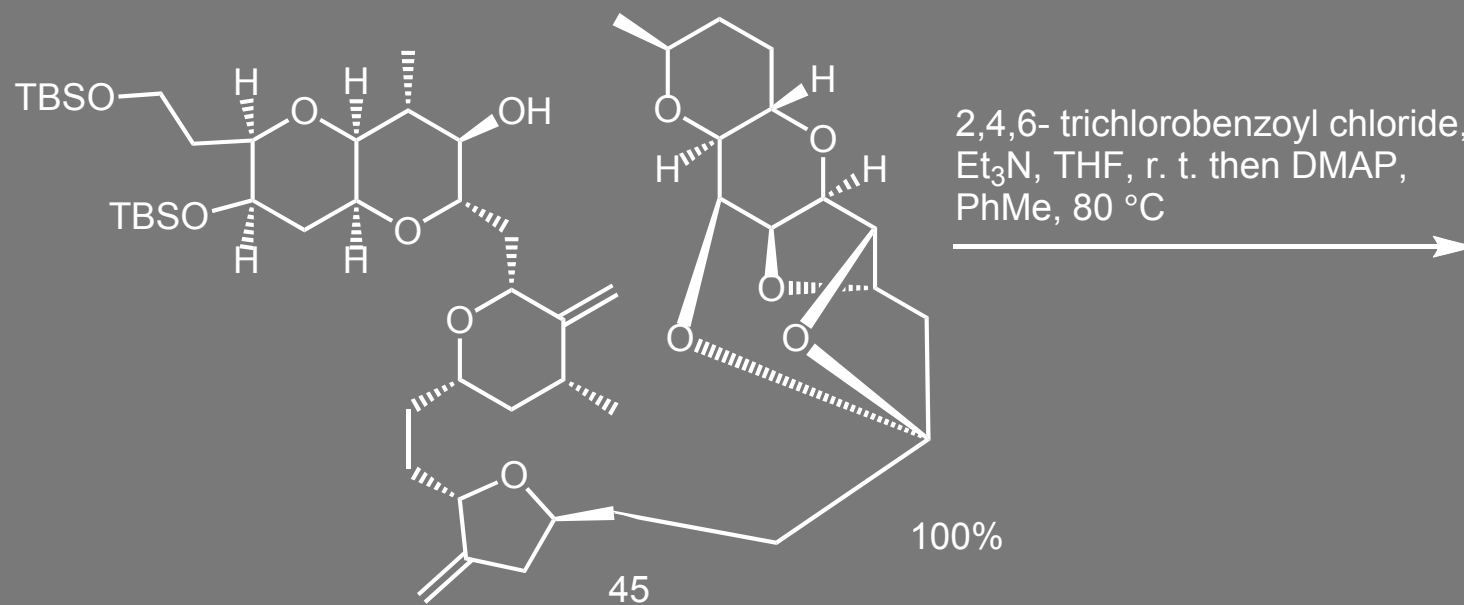
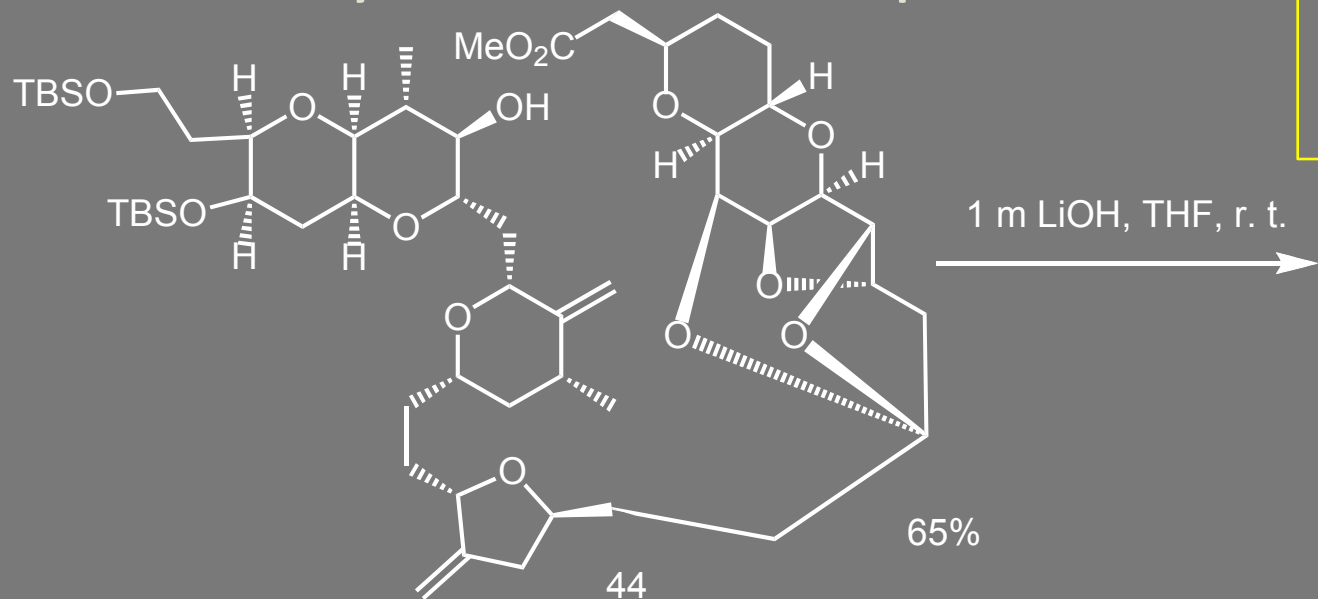
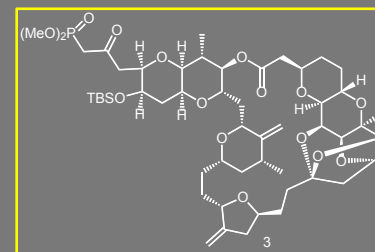


TBSOTf,
Et₃N, CH₂Cl₂, 0 °C

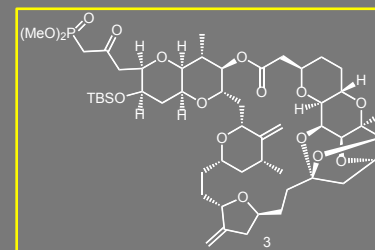
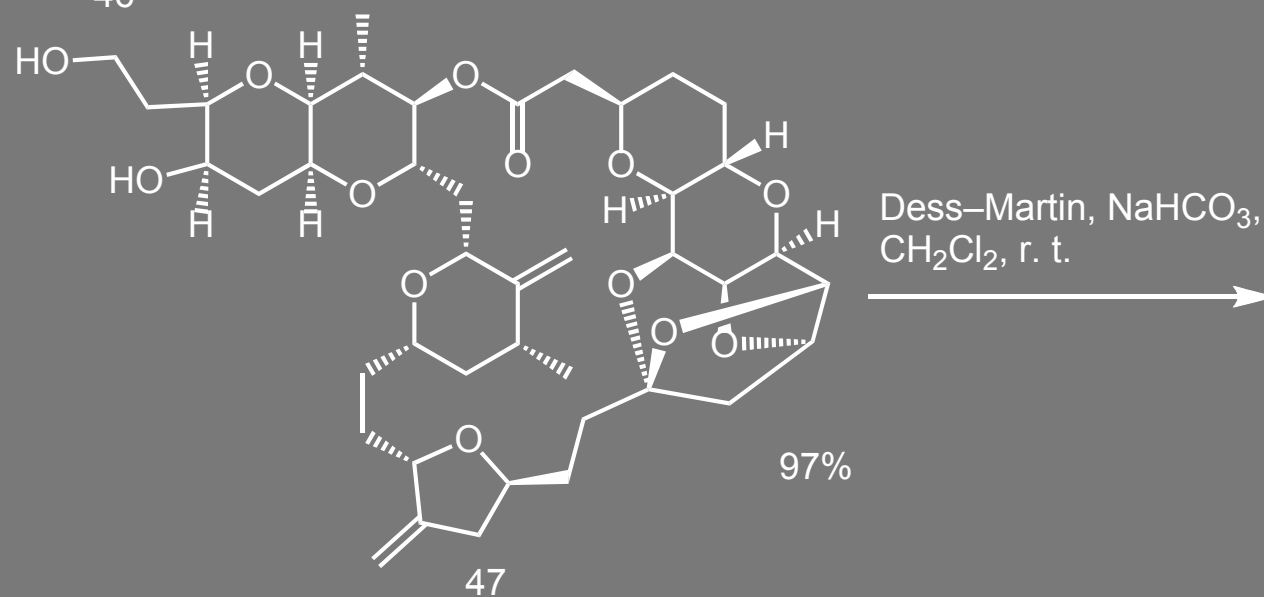
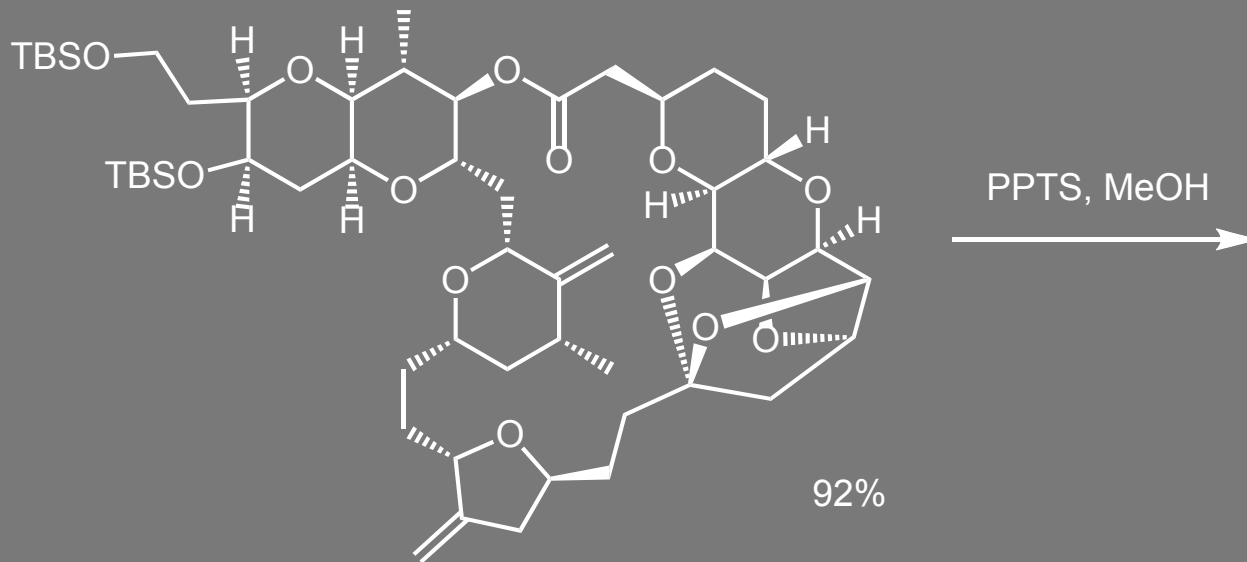
DDQ, CH₂Cl₂,
pH 7 phosphate buffer

64%

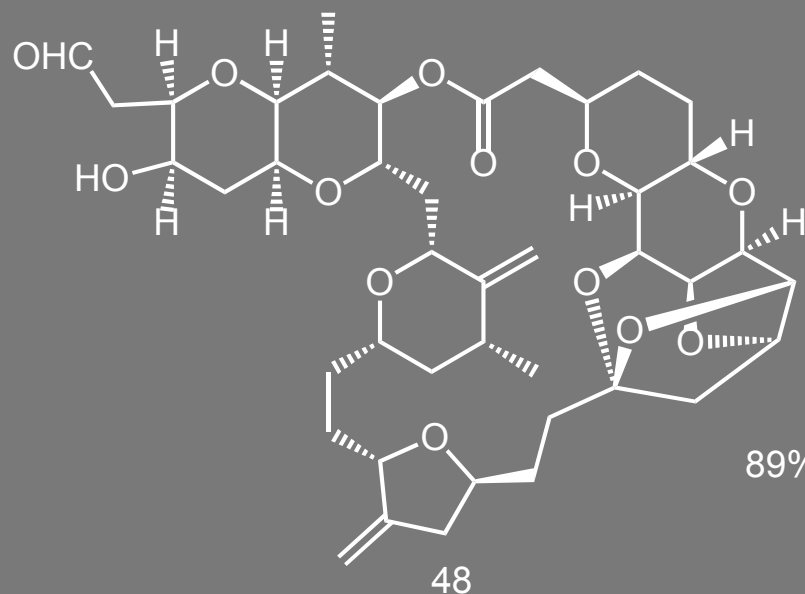
Synthesis of Compound 3



Synthesis of Compound 3



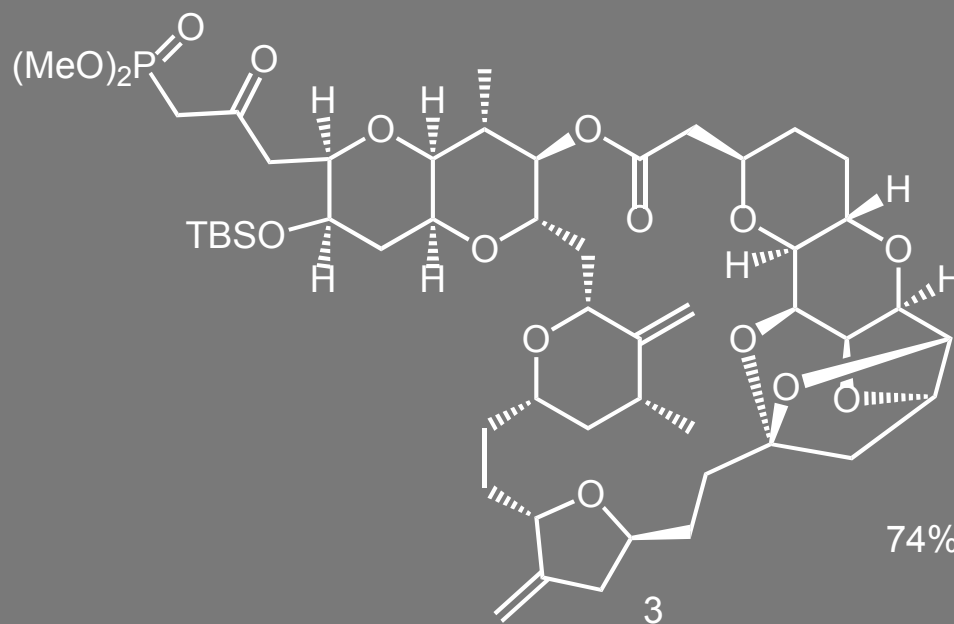
Synthesis of Compound 3



89%

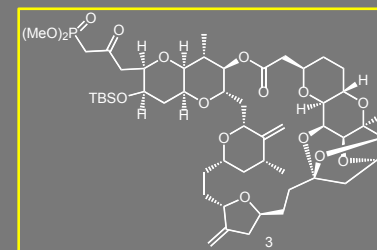
48

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

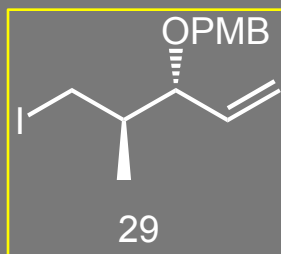
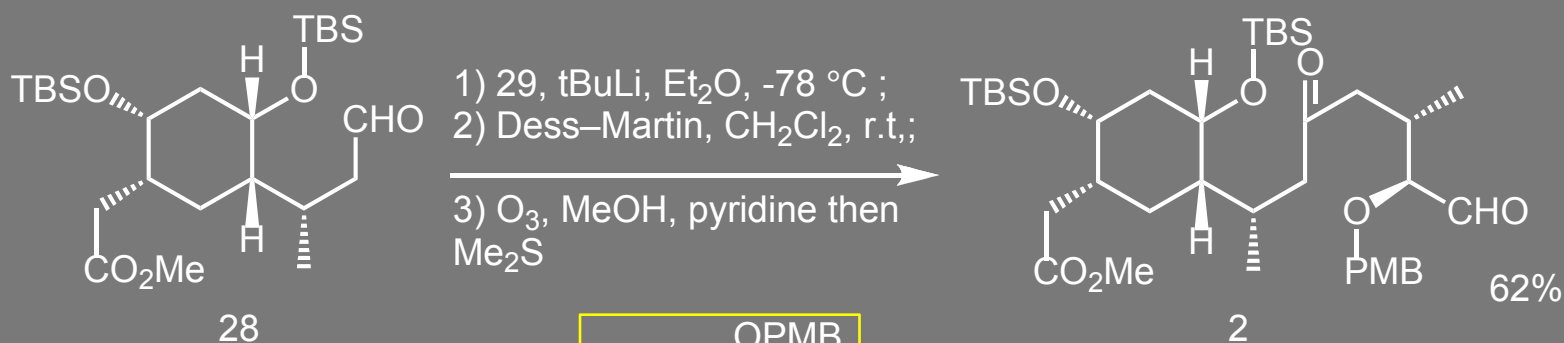
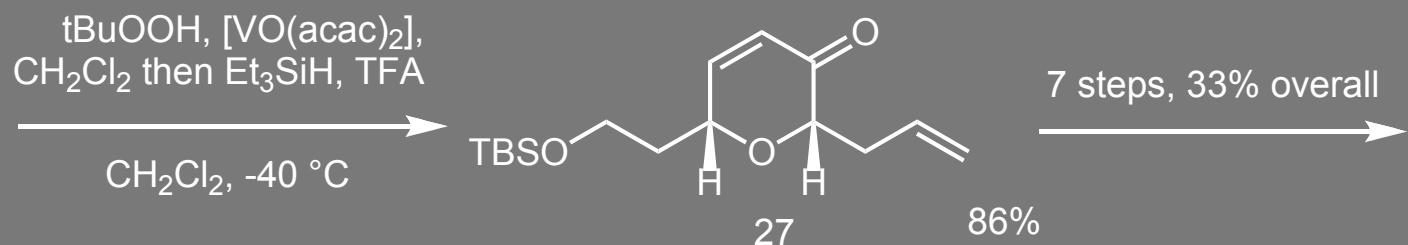
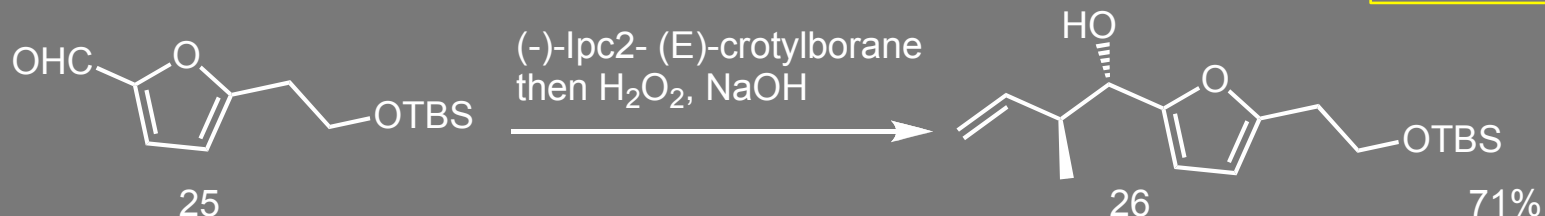
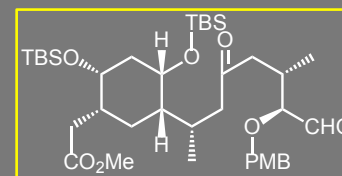


74%

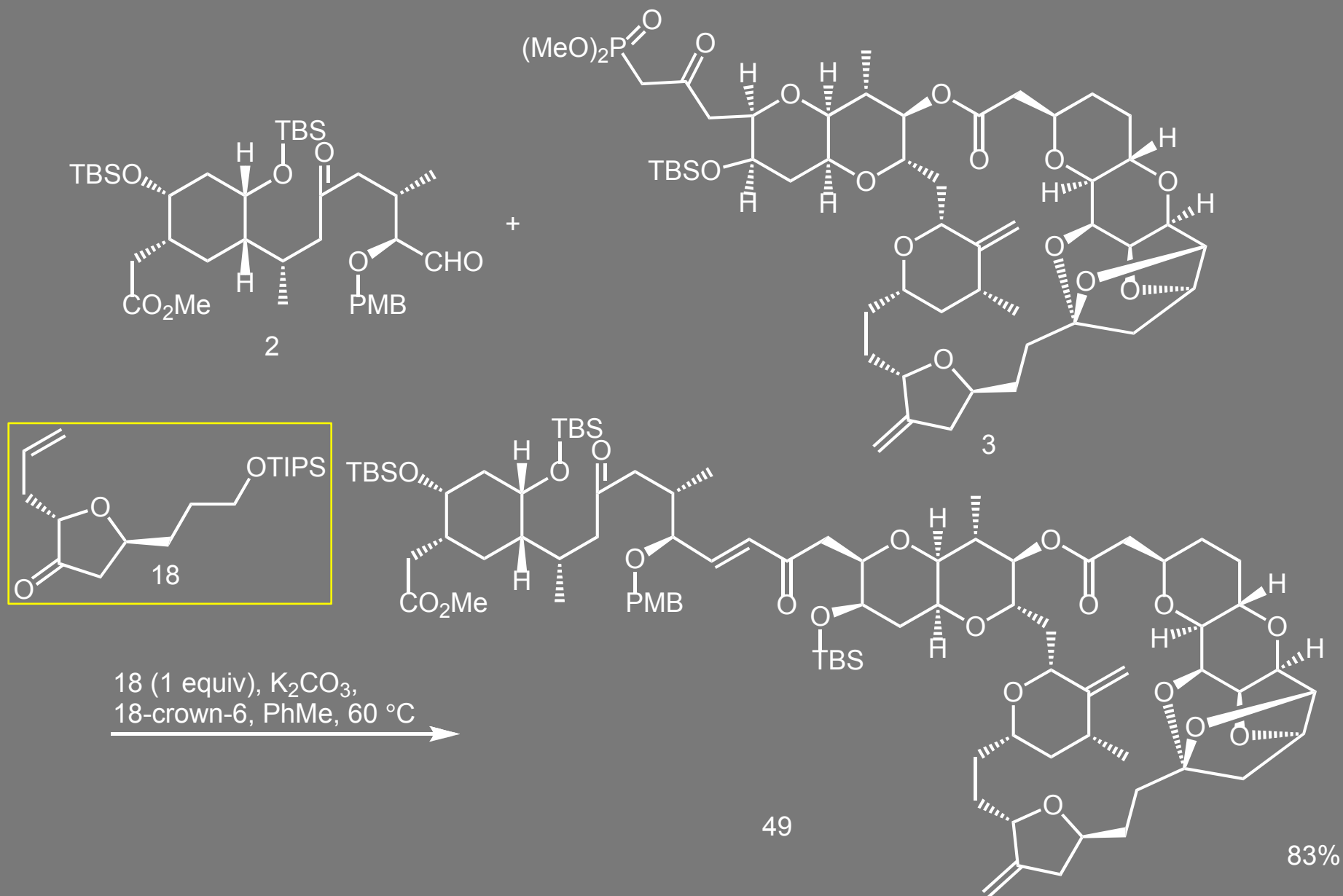
3



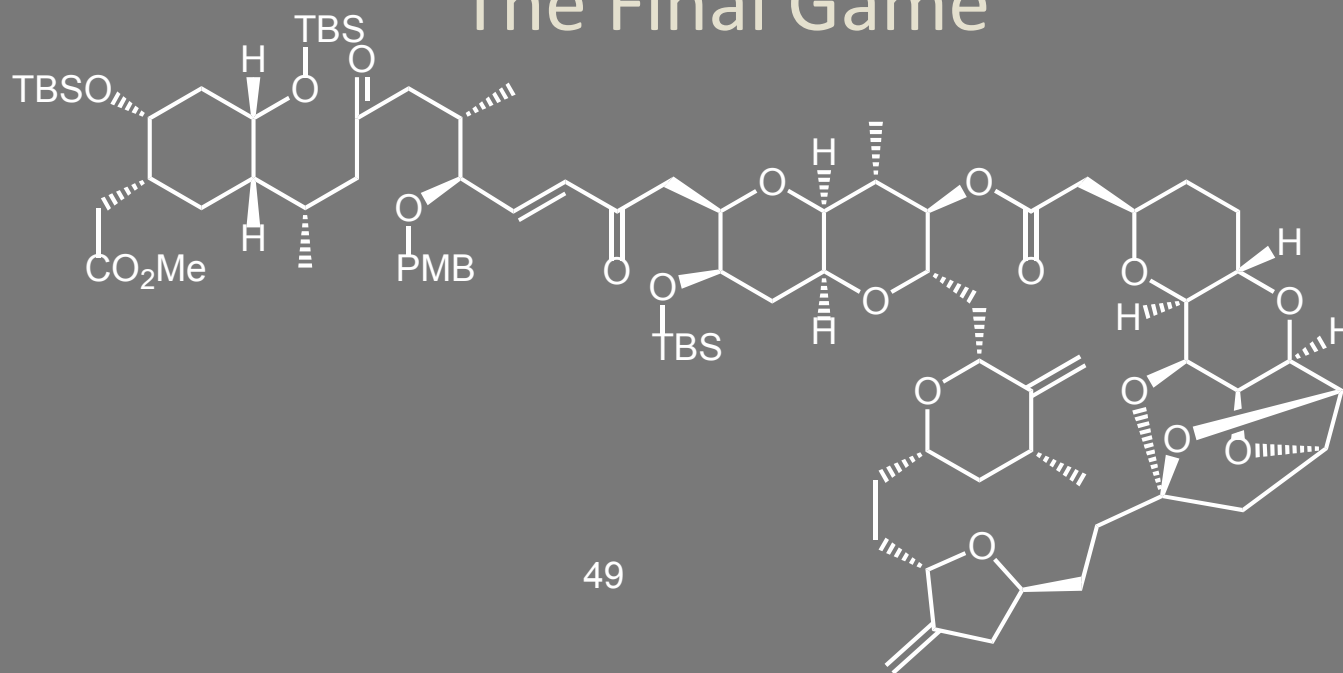
Synthesis of Compound 2



The Final Game



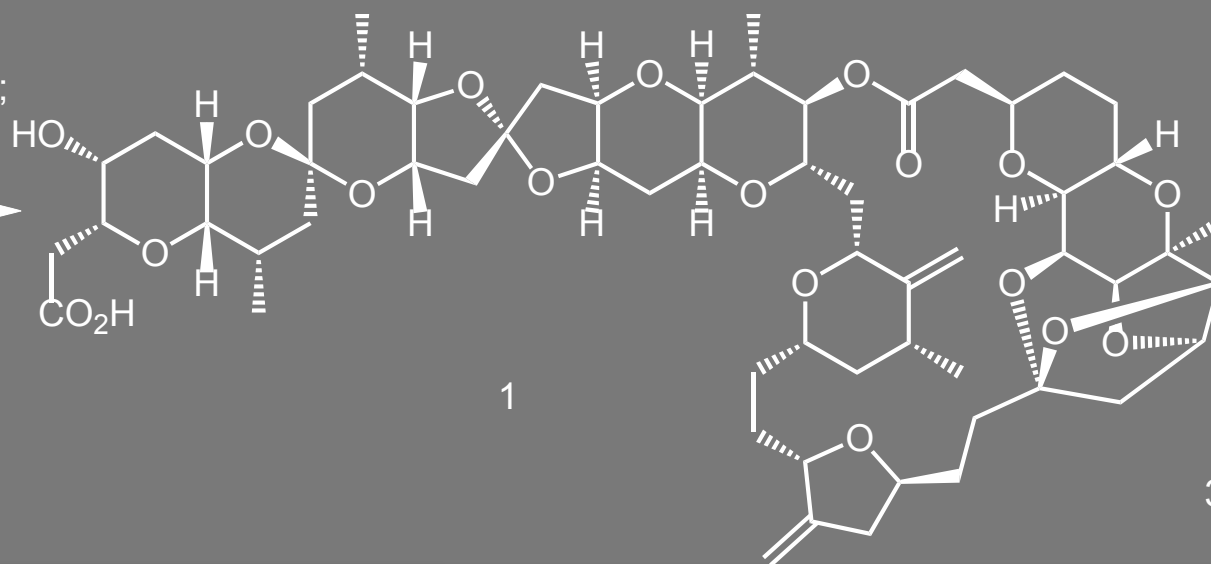
The Final Game



1) TBAF, AcOH,
MeOAc/THF (2 :1), r. t.;

2) DDQ, CH₂Cl₂/
MeOH (10 :1);

3) LiOH, THF/
H₂O (3 :1),



38%