

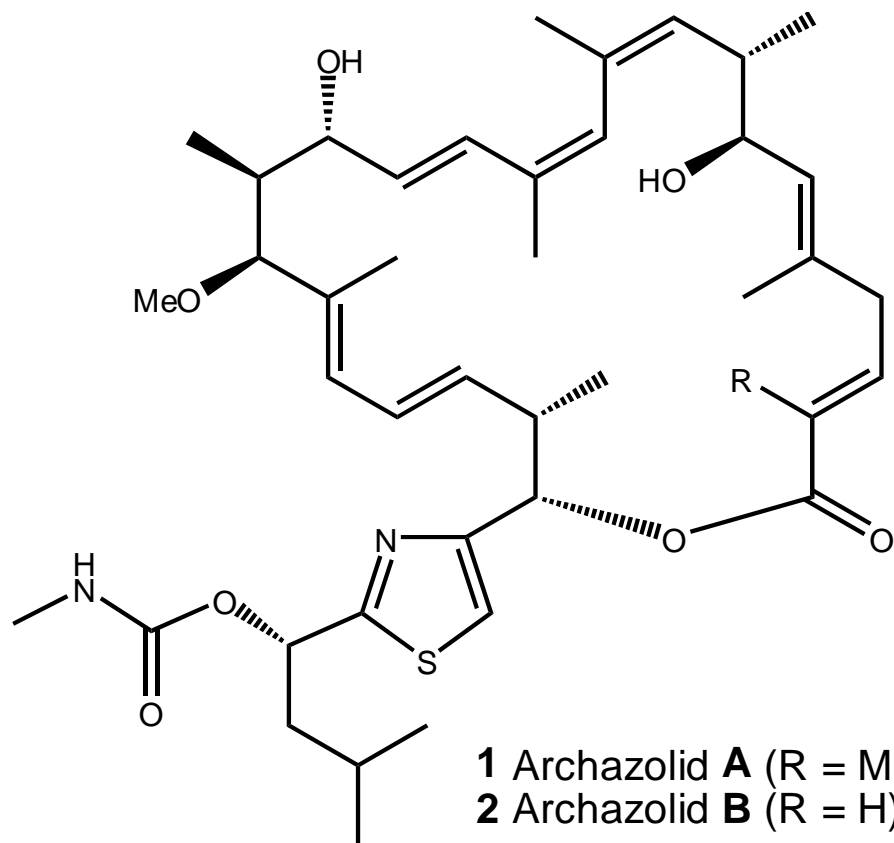
Literature Report 2009-09-15

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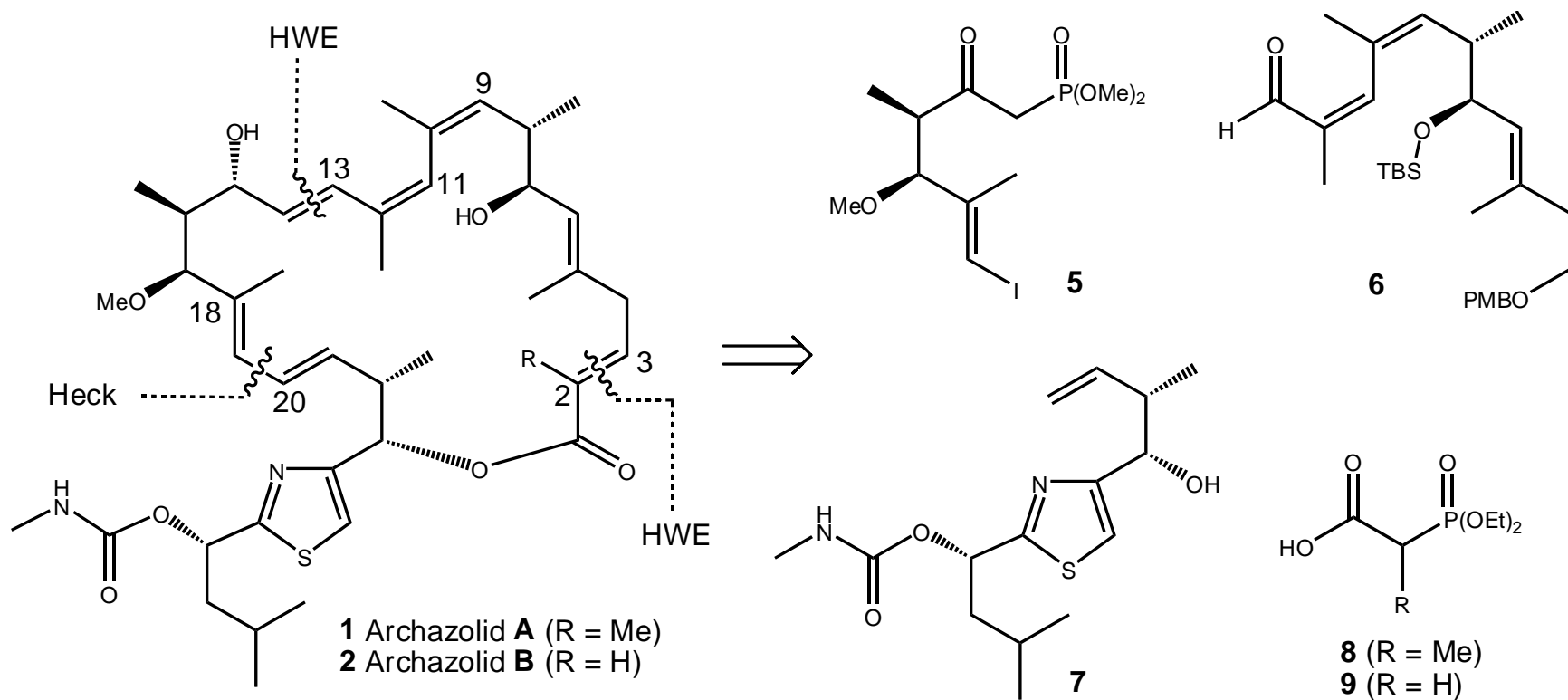
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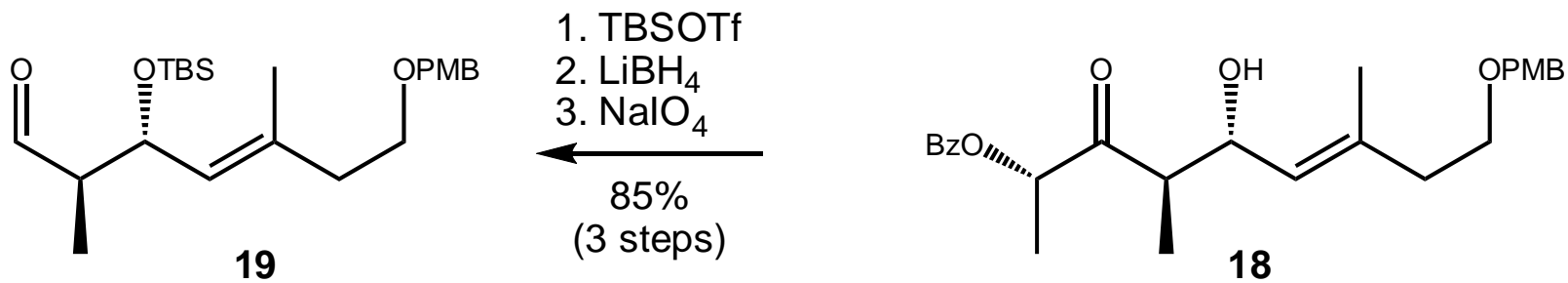
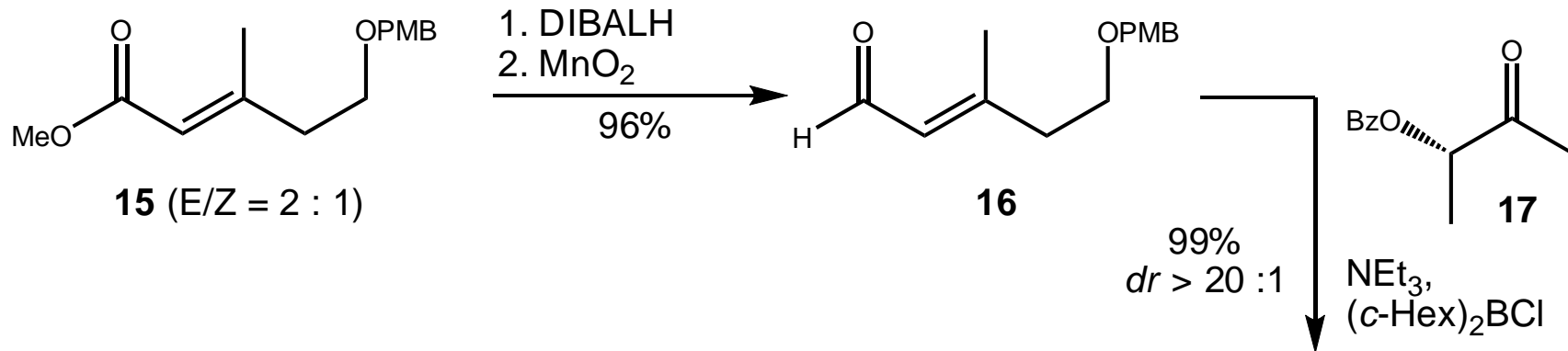
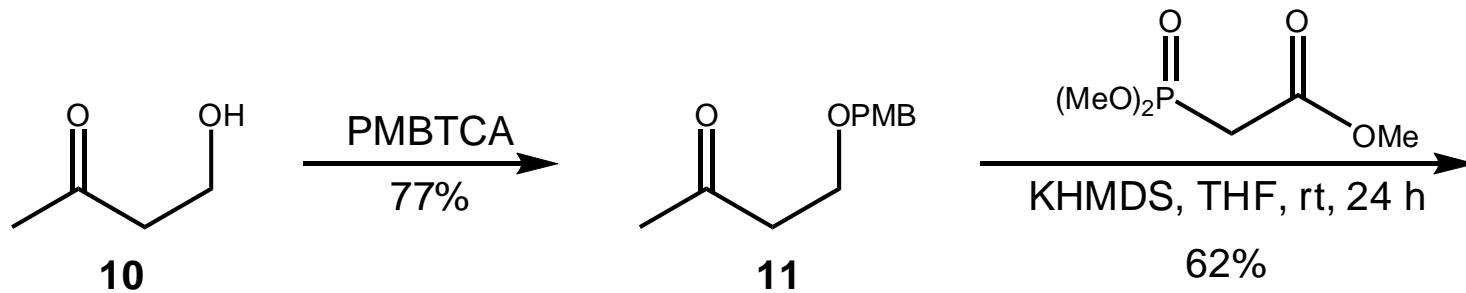
Modular Total Synthesis of Archazolid A and B

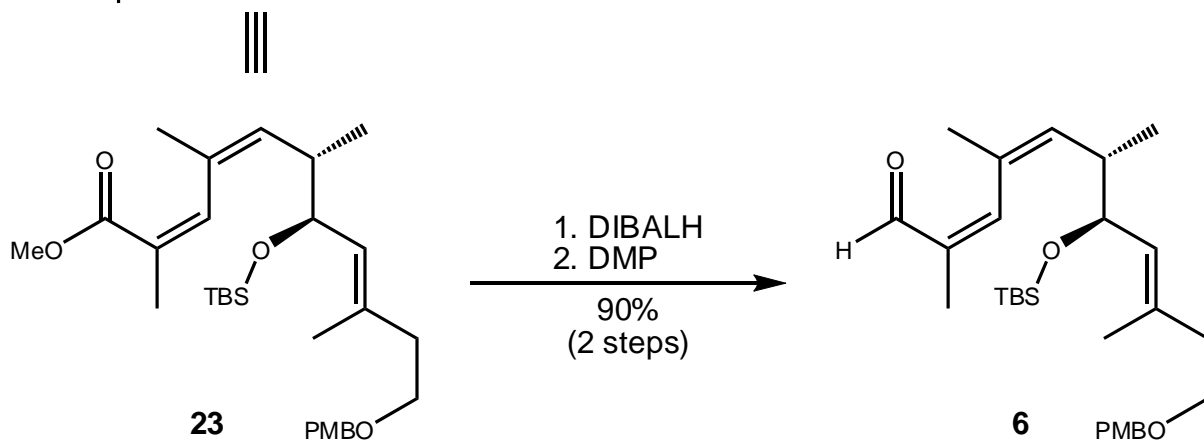
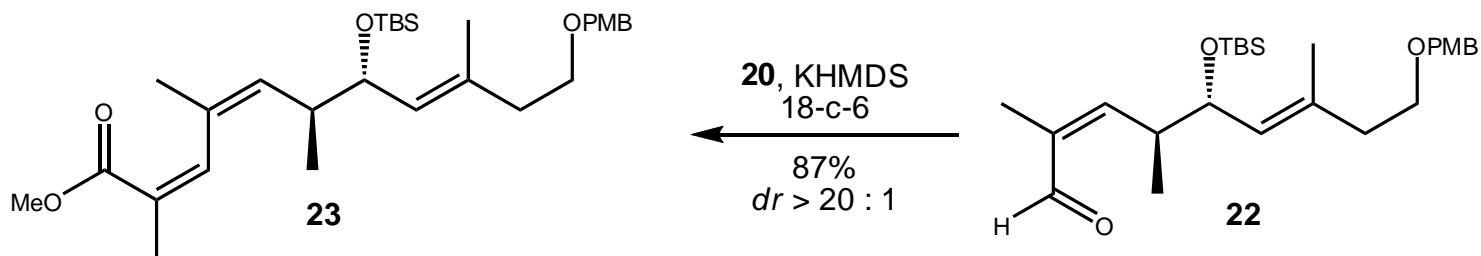
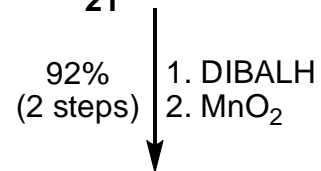
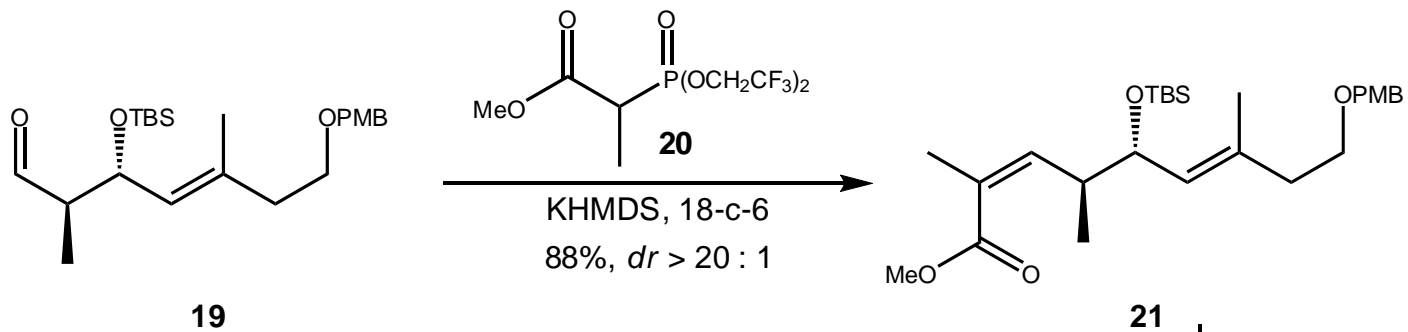
Menche, D.* *et al J. Org. Chem.* **ASAP**

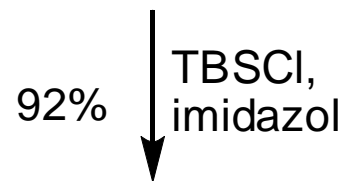
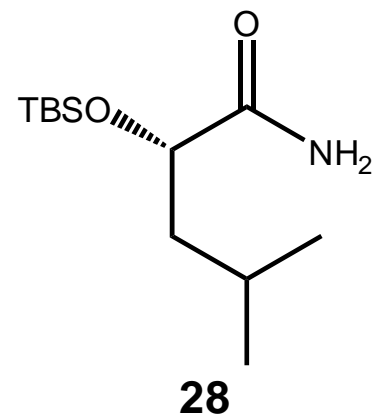
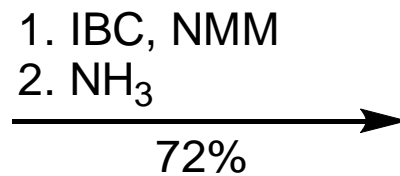
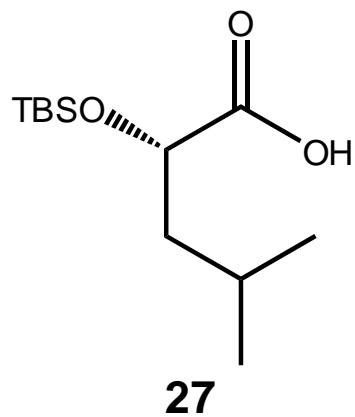
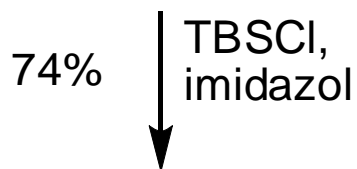
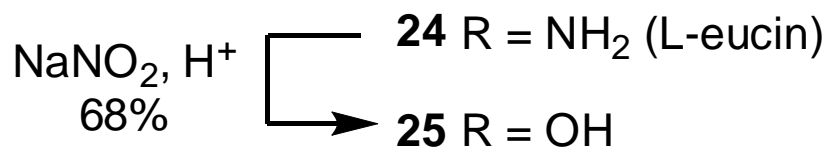
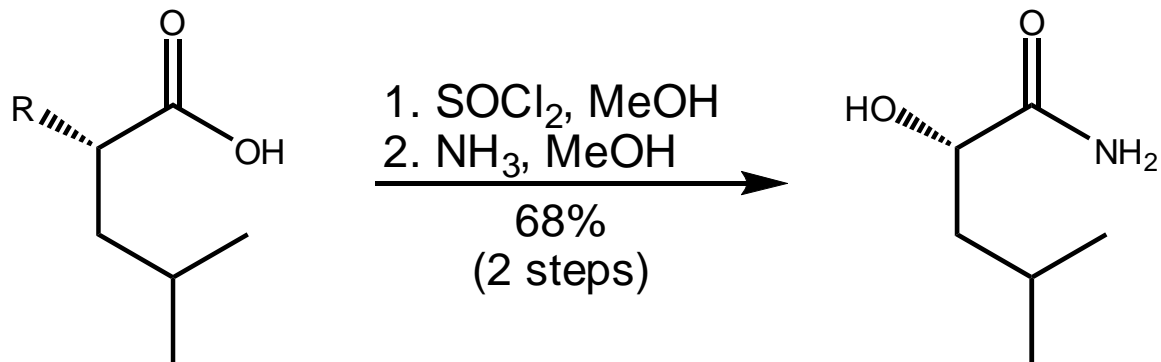


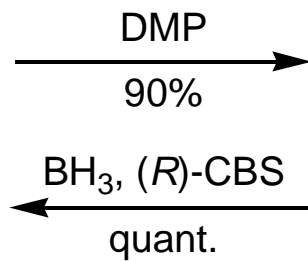
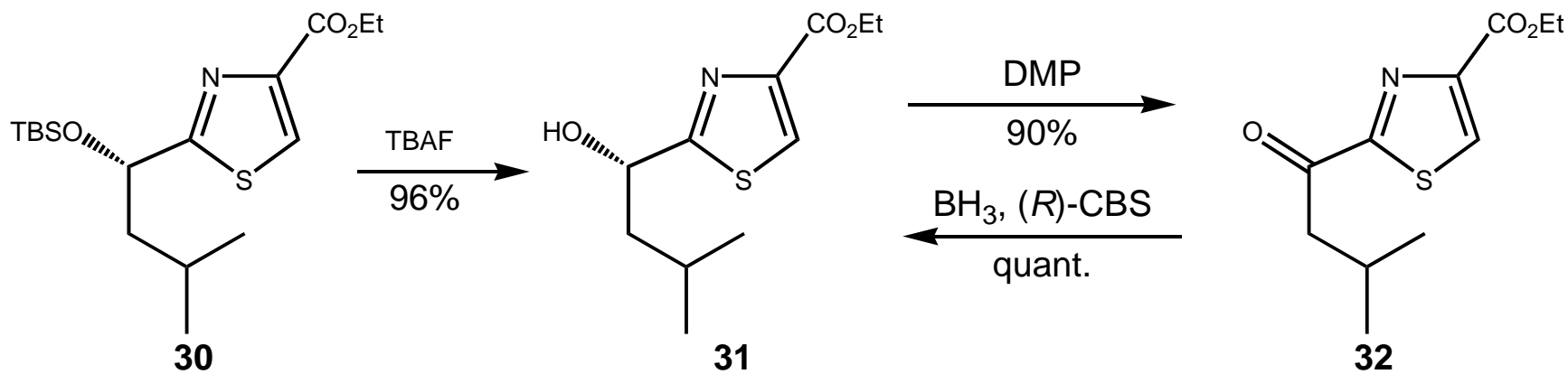
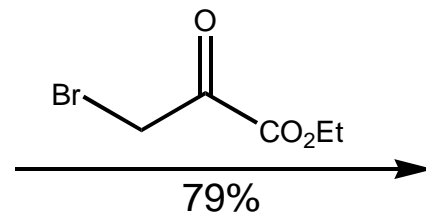
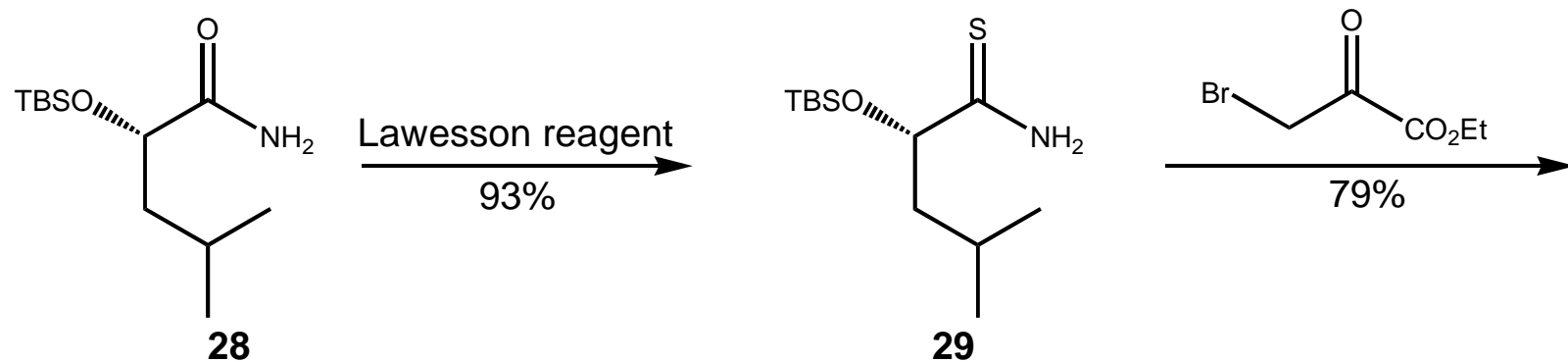
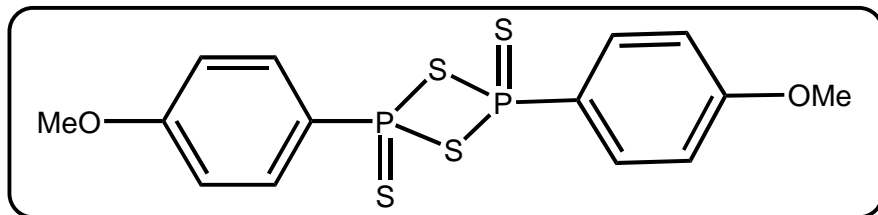
Retrosynthetic analysis

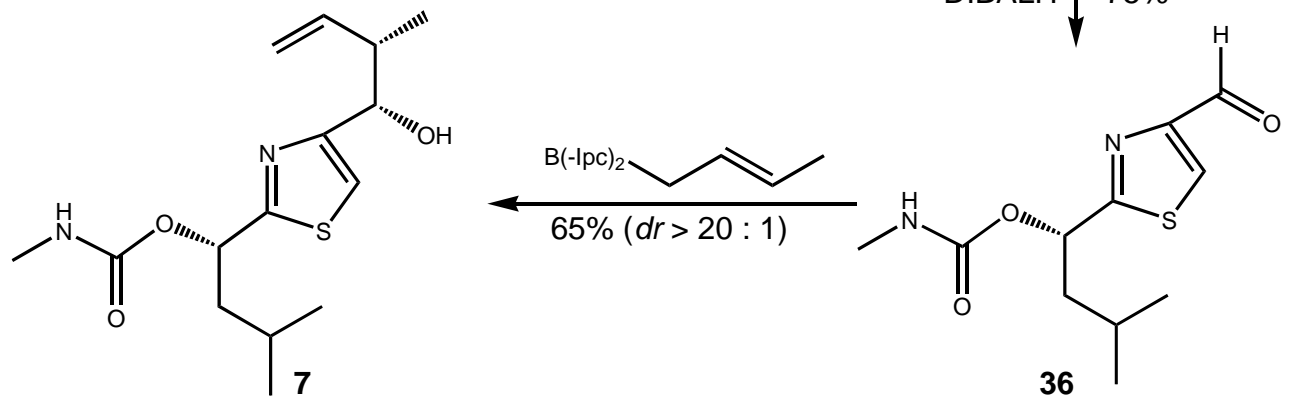
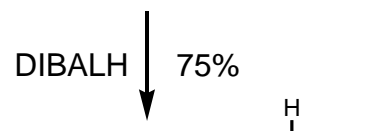
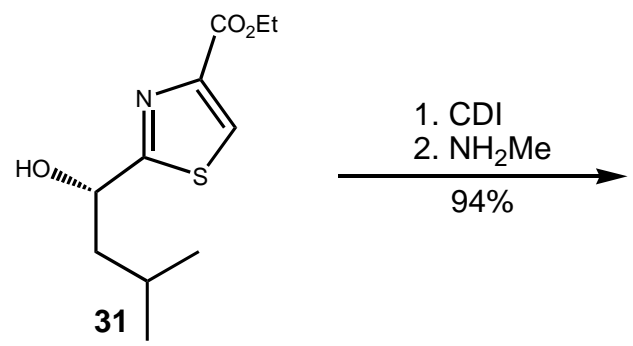
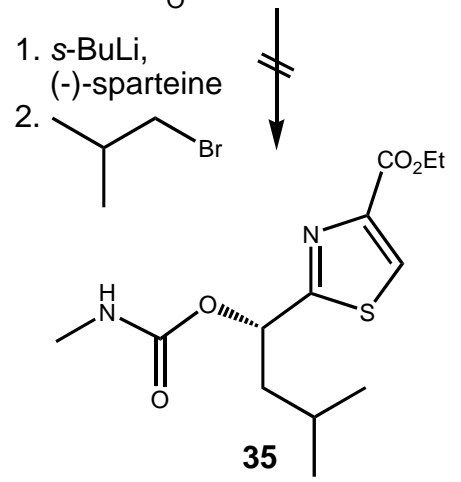
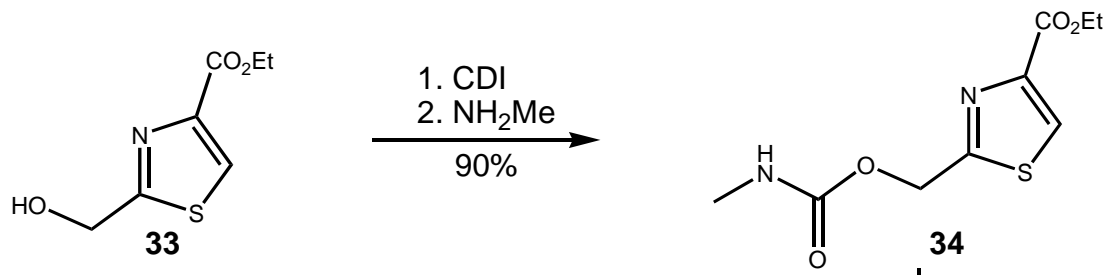


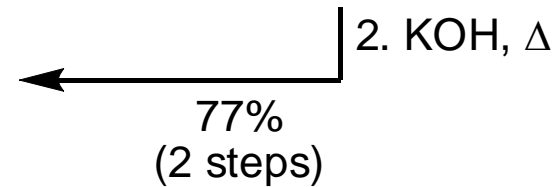
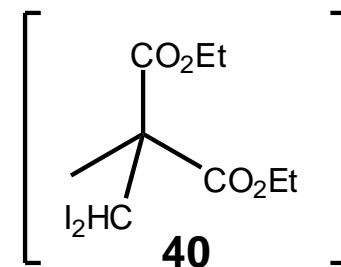
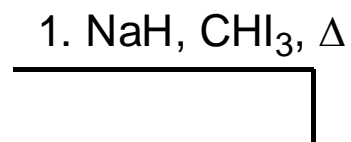
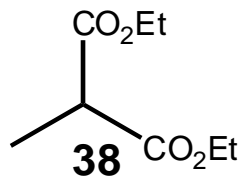
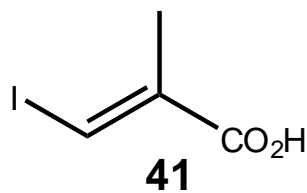
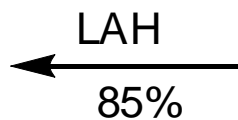
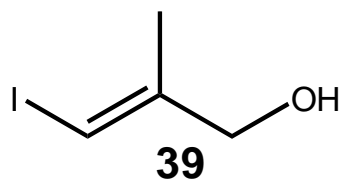
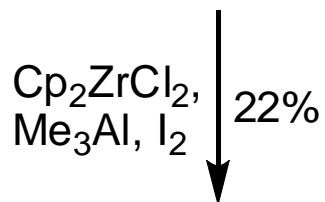
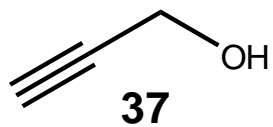


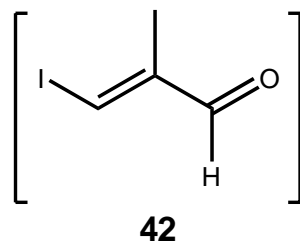
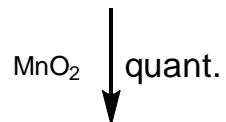
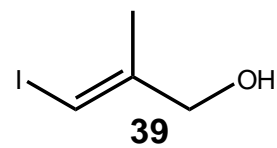




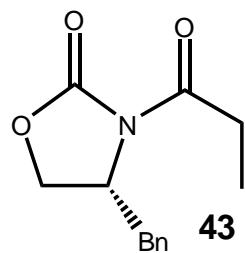








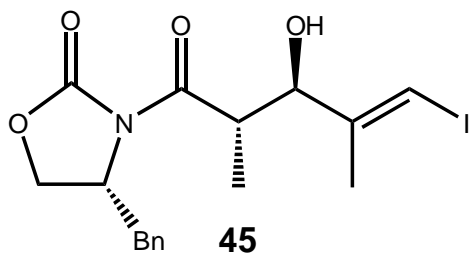
1.



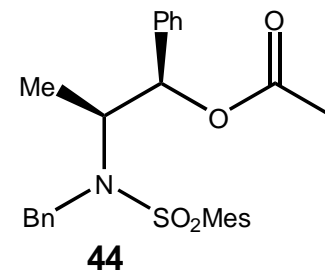
MgCl₂, Et₃N, TMSCl

2. MeOH, TFA

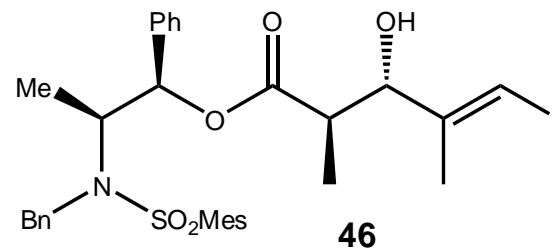
29%
(*dr* > 20 : 1)

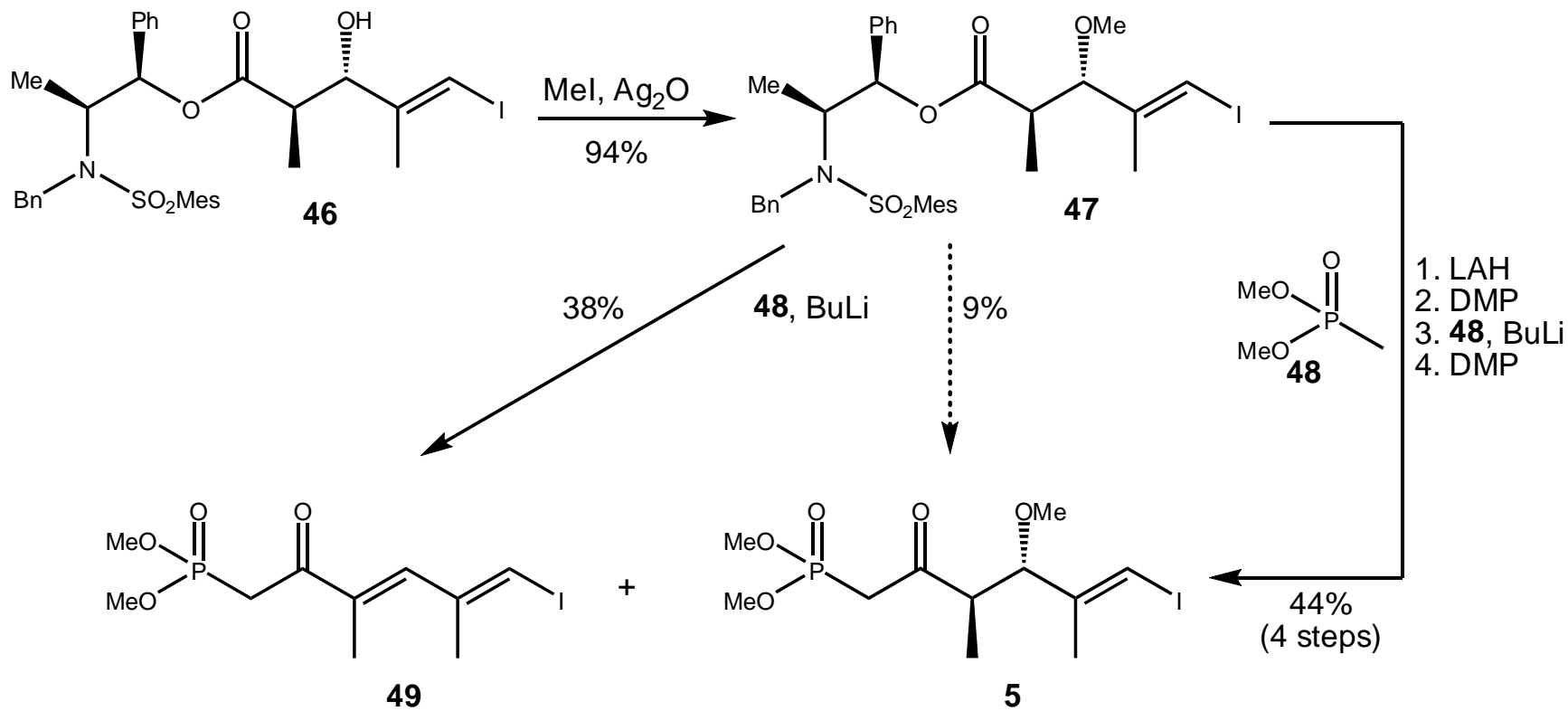


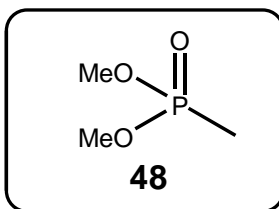
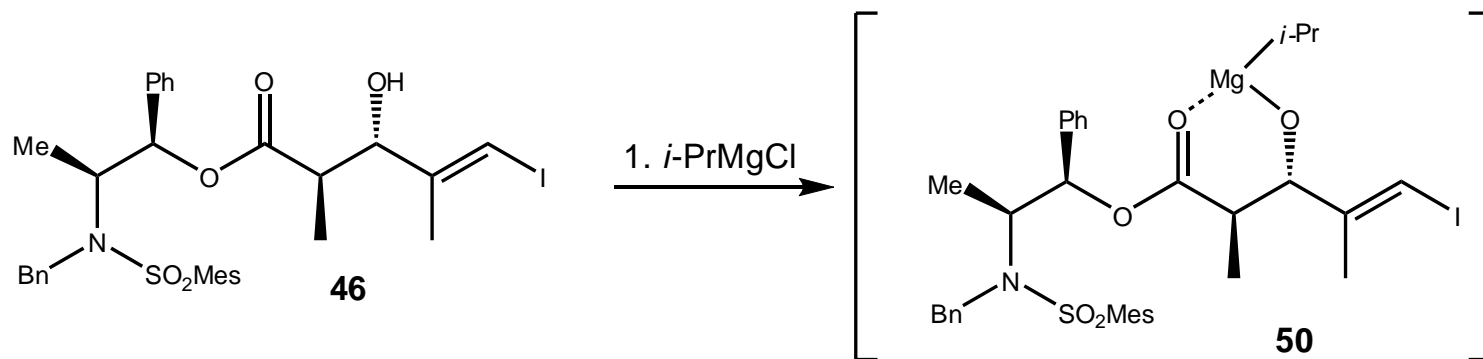
96%
(*dr* > 20 : 1)



(*c*-Hex)₂BOTf, Et₃N

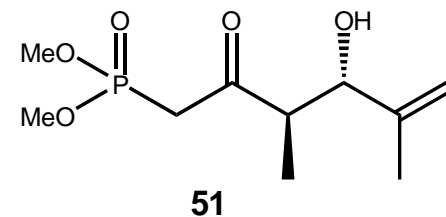
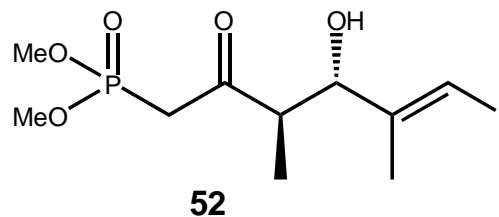
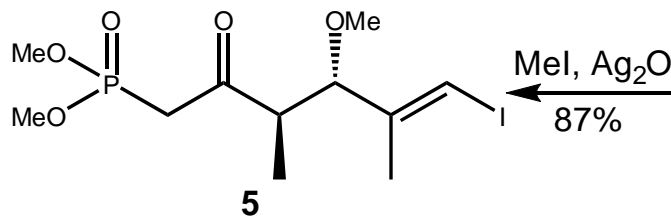


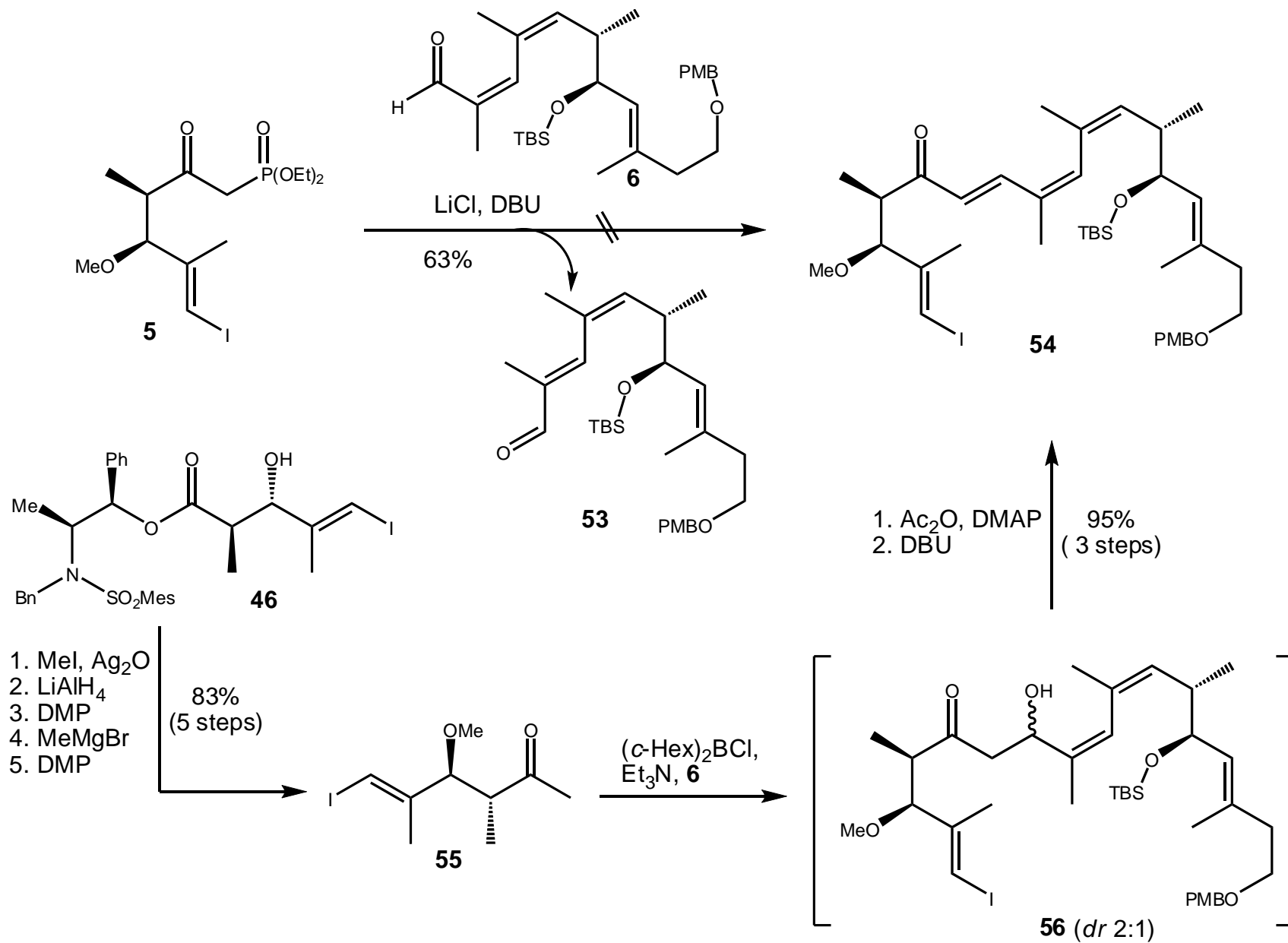


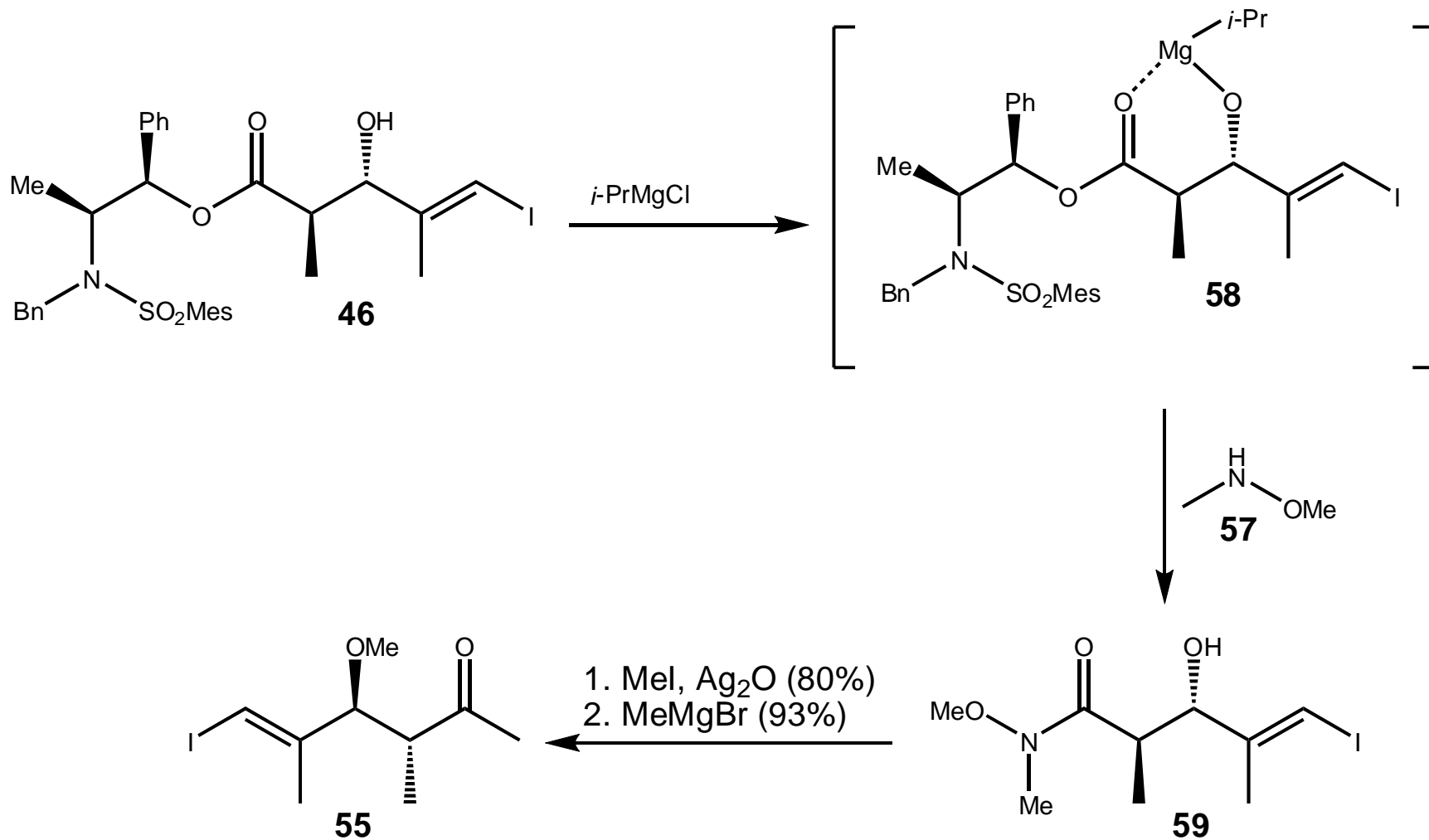


2. **48**, KHMDS 80%

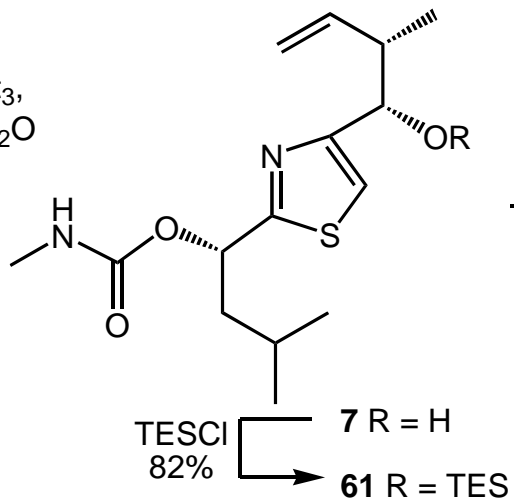
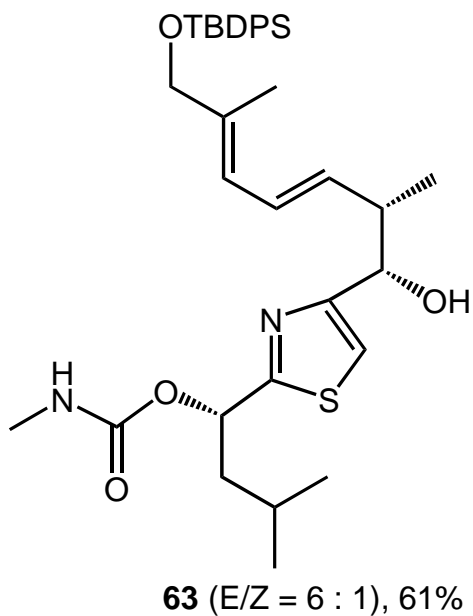
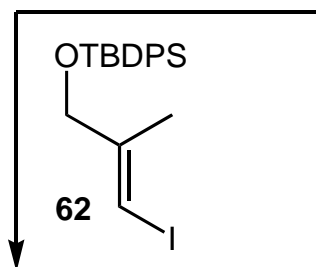
86% 2. **48**, BuLi



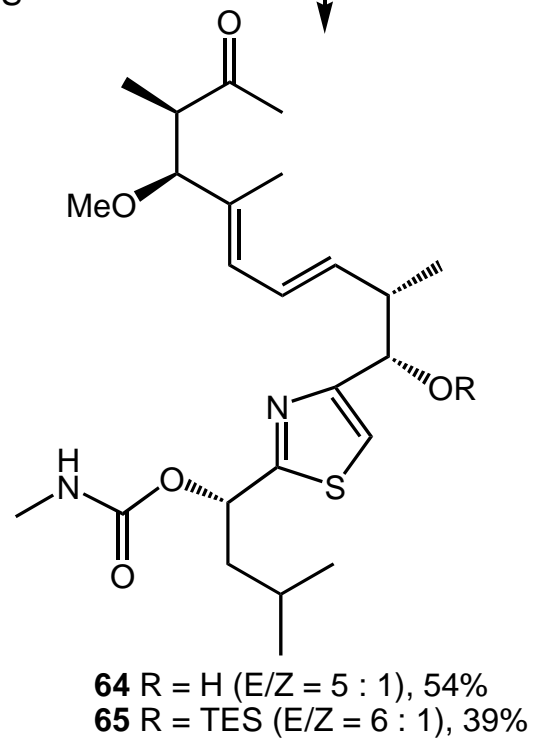
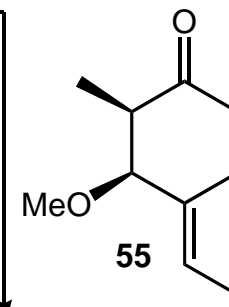


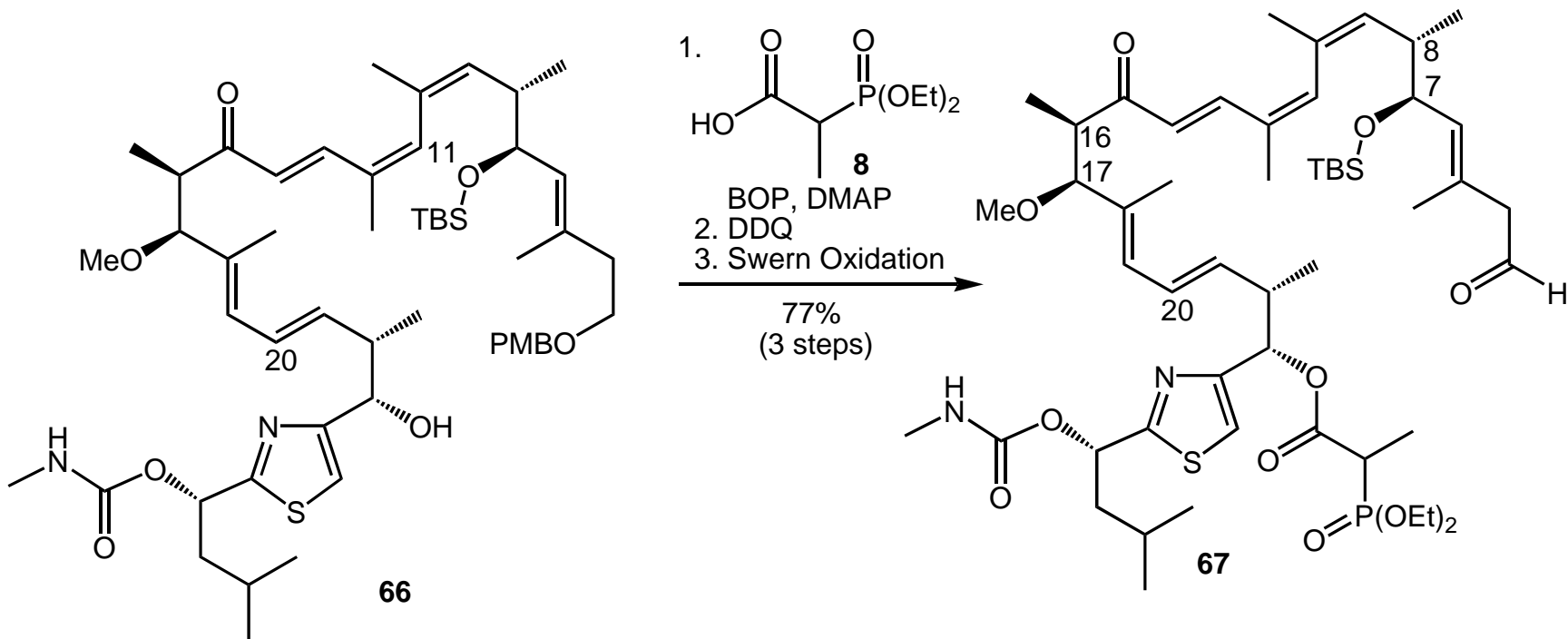
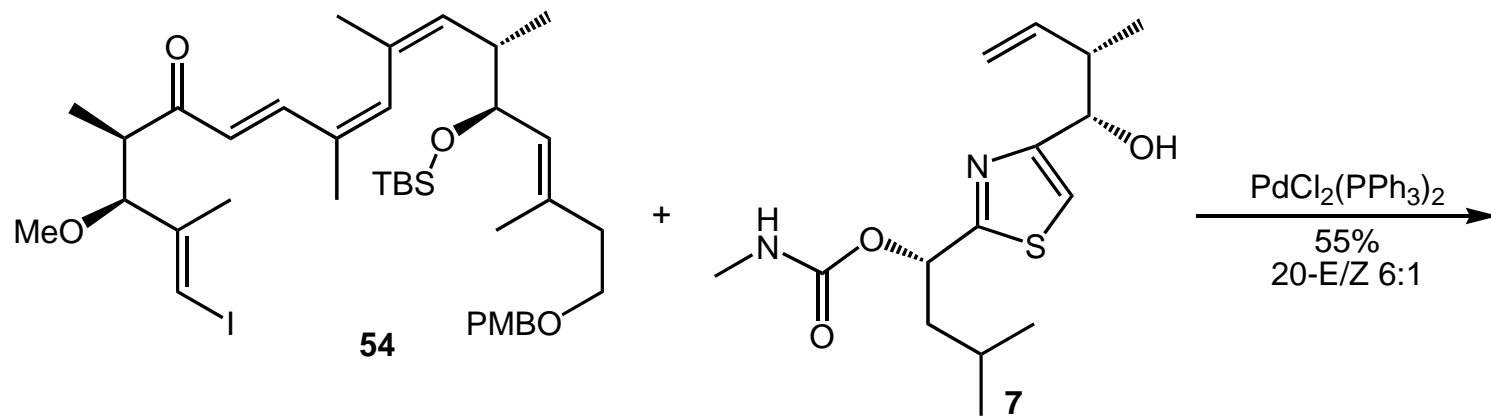


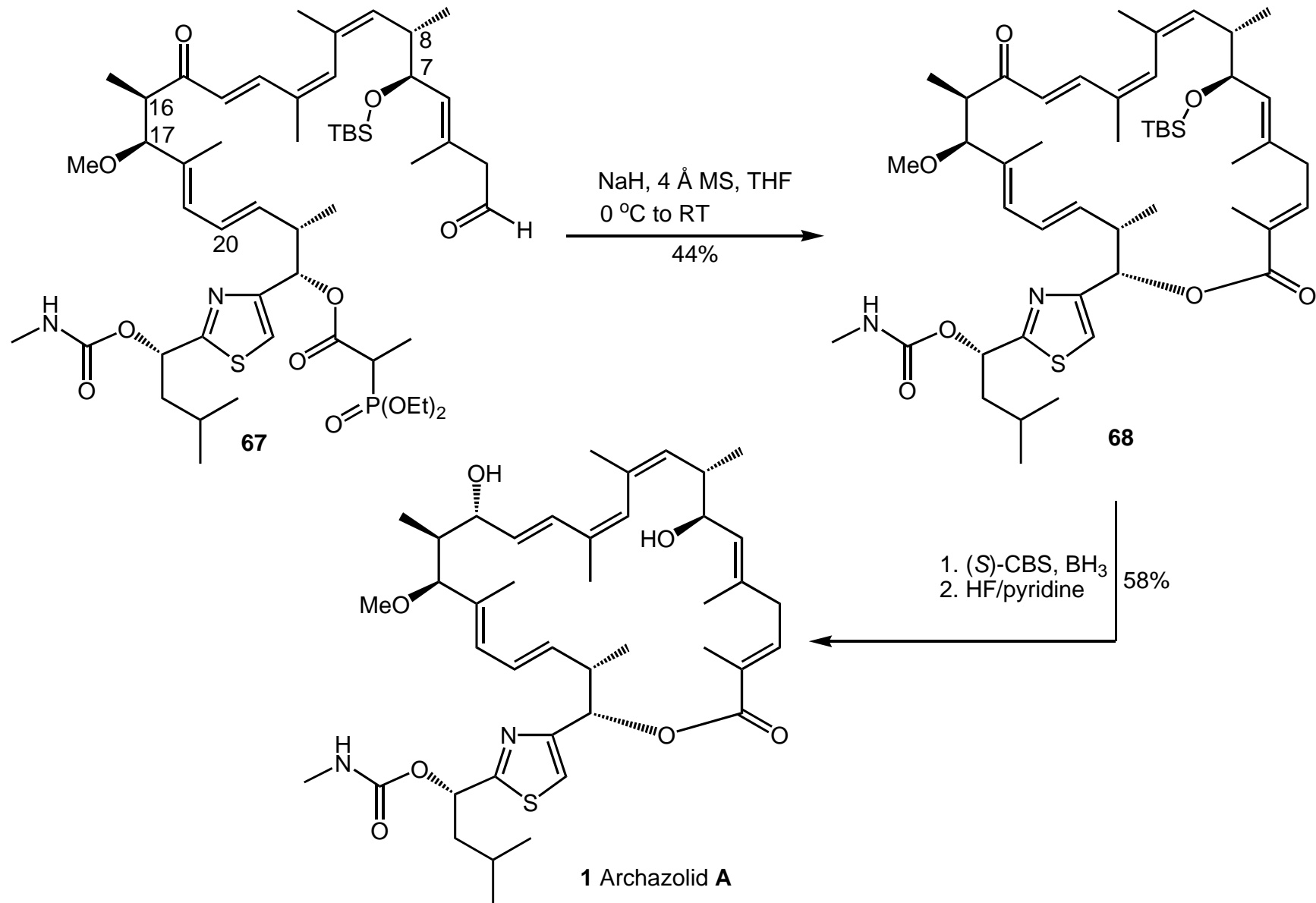
$\text{PdCl}_2(\text{PPh}_3)_2$, TBACl, NEt_3 ,
 NaHCO_3 , DMF/ CH_3CN , H_2O
 $80\text{ }^\circ\text{C}$

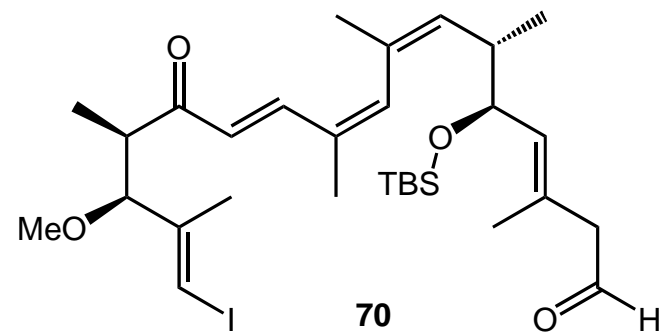
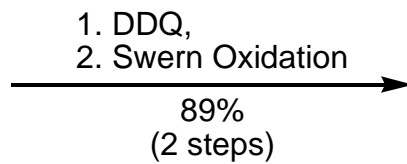
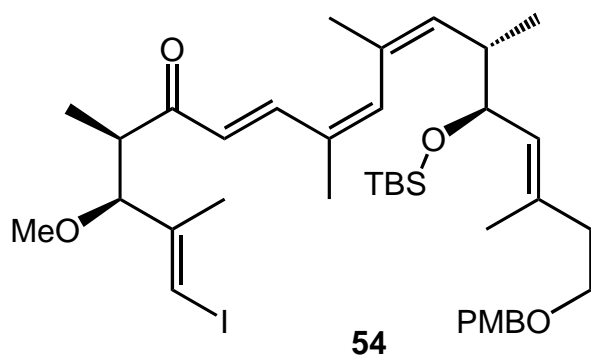
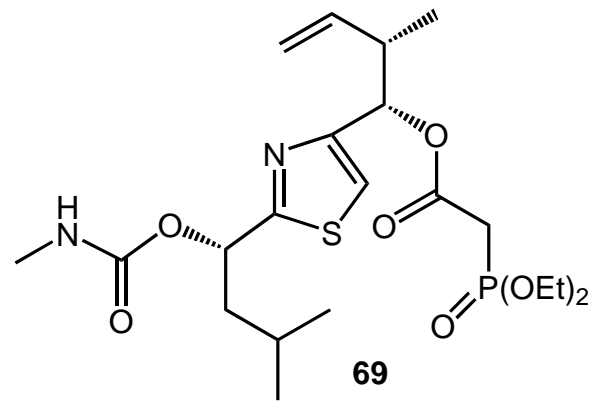
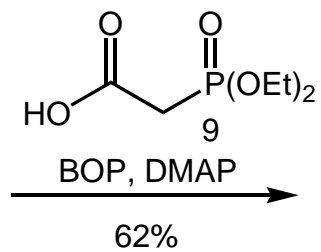
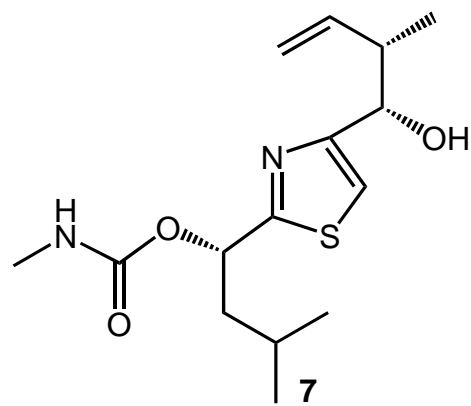


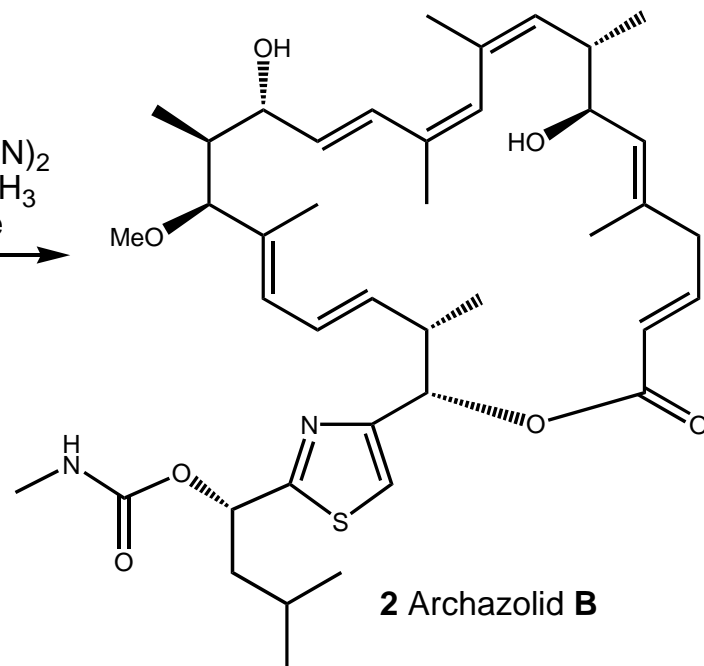
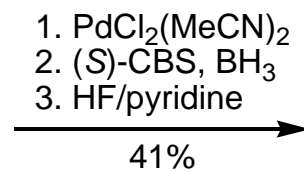
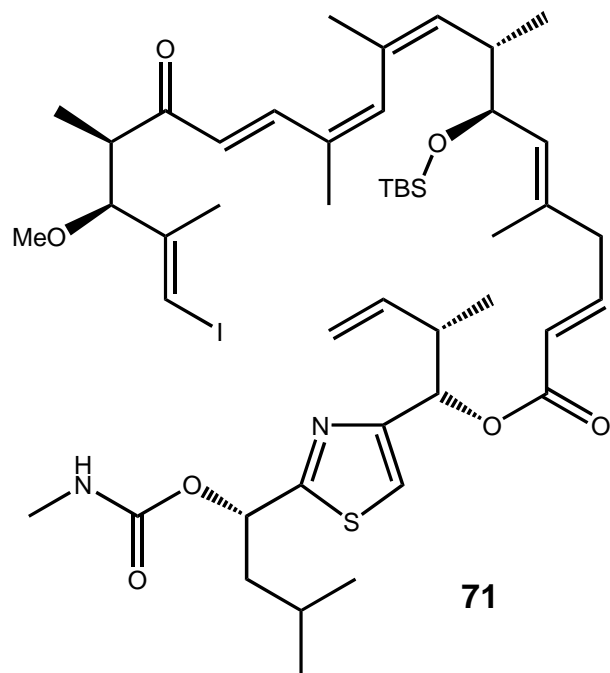
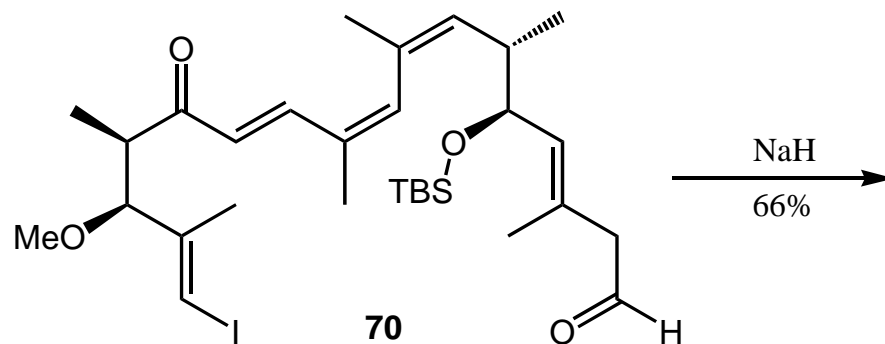
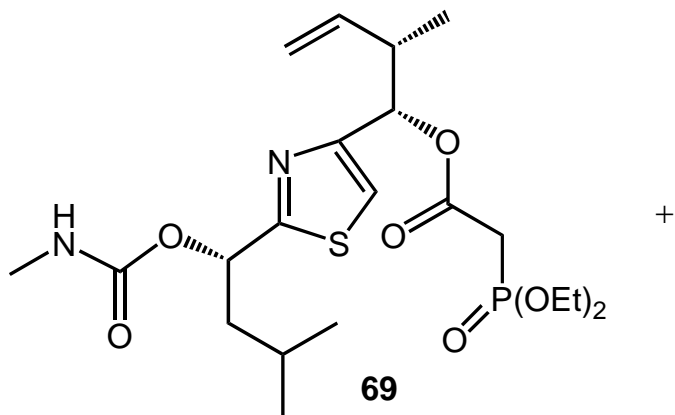
$\text{PdCl}_2(\text{PPh}_3)_2$, TBACl, NEt_3 ,
 NaHCO_3 , DMF/ CH_3CN , H_2O
 $80\text{ }^\circ\text{C}$











Myxobacterial fermentation broths of *Archangium gephyra* and *Cystobacter violaceus* are the natural sources of the archazolids, structurally complex polyketide macrolactones, which were originally reported by the group of Hofle and Reichenbach. They constitute highly potent antiproliferative agents which inhibit the growth of various cancer cell lines in subnanomolar concentrations. On a molecular level, they constitute powerful and selective inhibitors of vacuolar type ATPases (V-ATPases), heteromultimeric, proton translocating proteins that are localized in a multitude of eukaryotic membranes, where they energize many different transport processes. As a malfunction of these enzymes is associated with various diseases such as cancer and osteoporosis, the development and molecular understanding of novel inhibitors present important research goals.

In conclusion, based on a modular synthetic strategy, an expedient and joint total synthesis of the potent antiproliferative polyketide macrolactone antibiotics archazolid A and B has been accomplished. Key steps for their syntheses involve an aldol condensation to construct the (*Z,Z,E*)-triene system, an *E*-selective Heck reaction for the (22,23)-diene moiety, and an HWE coupling. Two different methods, an HWE reaction and a Heck coupling, were successfully utilized to forge the macrocyclic core of these polyketides. Notably, the joint synthesis of archazolid A and B was enabled by late-stage diversification of joint late-stage intermediates, demonstrating an expedient and flexible endgame strategy. Furthermore, in the course of this campaign, efficient protocols for an *E*-selective Heck reaction of nonactivated alkenes, a direct nucleophilic displacement of the Abiko-Masamune auxiliary by Lewis acid activation, and a mild and highly reactive HWE protocol were developed. With the established robust and flexible synthetic approach to the archazolids in hand, efforts can now be directed for further SAR studies and more detailed target-inhibitor evaluations.