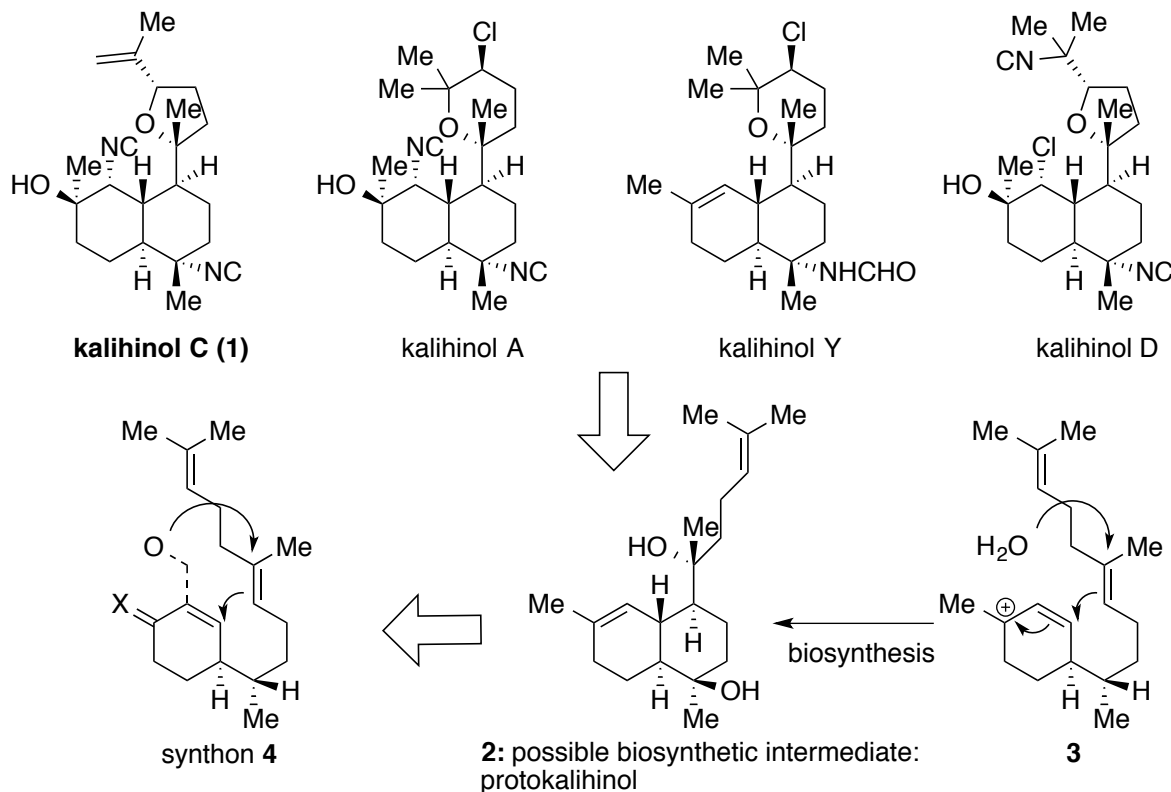
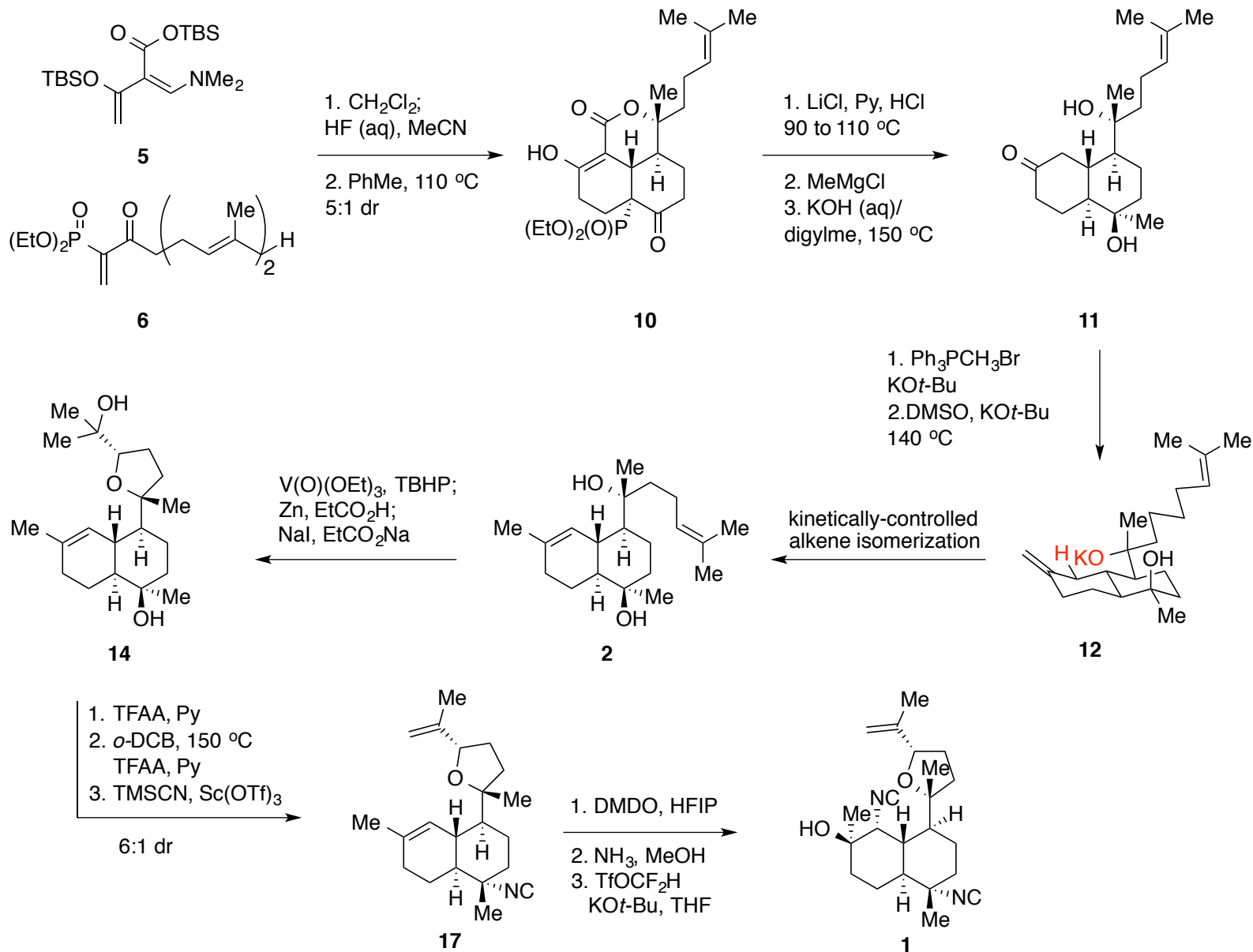


Introduction

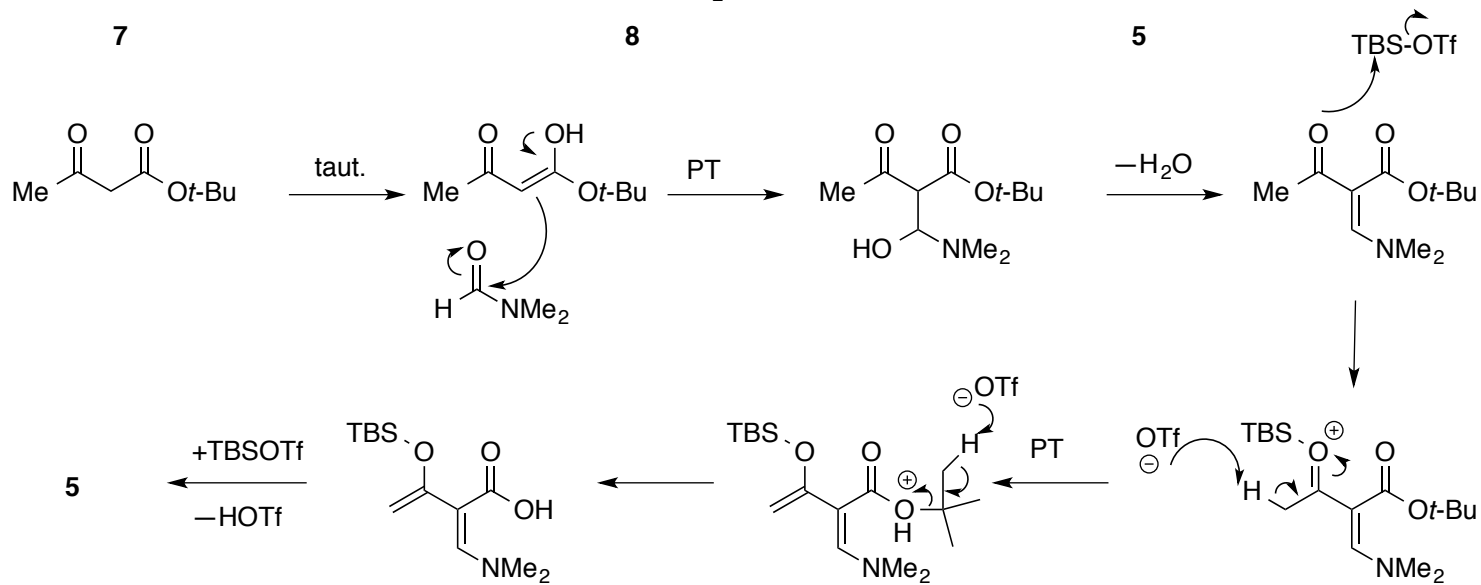
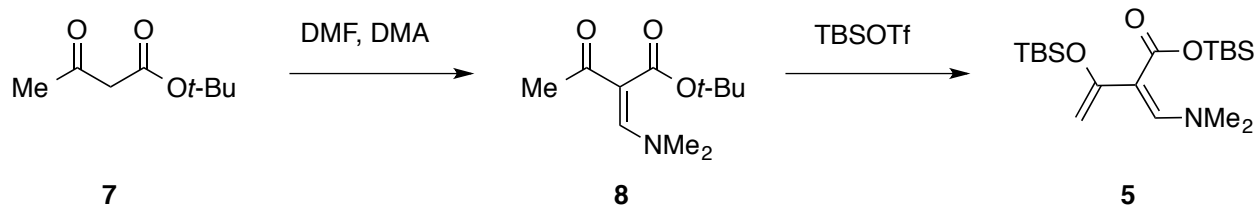
The kalihinol family of natural products are some of the most complex of a broader class of "biologically enigmatic" isocyanoterpenes (ICTs). In particular, Kalihinol A exhibits a high potency against *Plasmodium falciparum* (malaria). The Shenvi group has developed a program to investigate the biological activity of ICTs as well as to synthesize three of its structural classes: amphilectenes, adocianes, and kalihinols. Prior syntheses of kalihinols have experienced difficulties with controlling the stereochemistry in these densely functionalized molecules. The authors achieved a short, stereocontrolled synthesis of kalihinol C through the Diels-Alder reaction of a heterodendralene building block and introduce a new method for isonitrile synthesis.



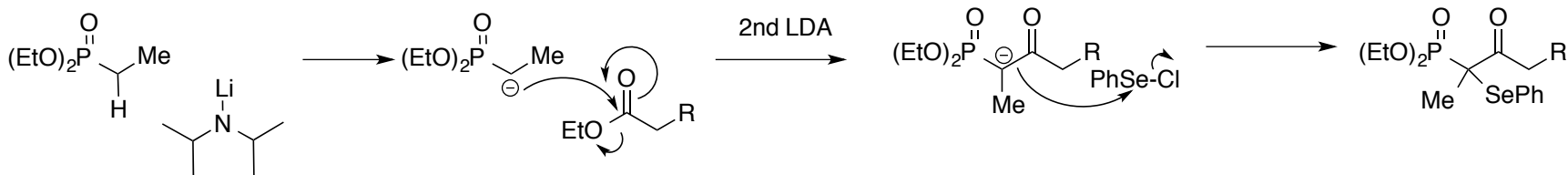
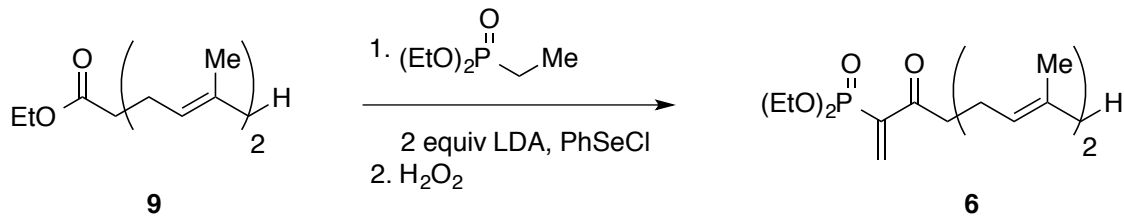
Synthesis of Kalihinol C



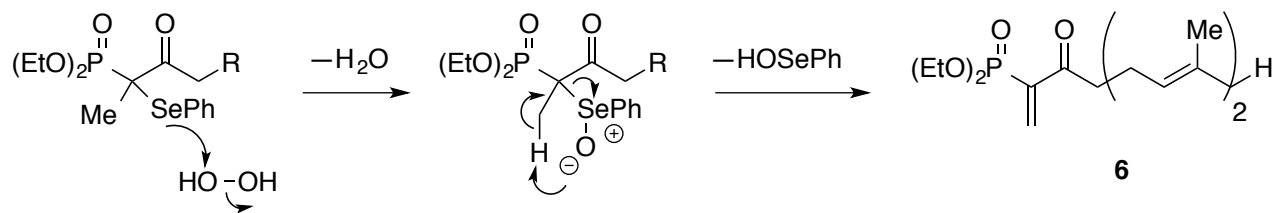
Preparation of heterodendraline 5



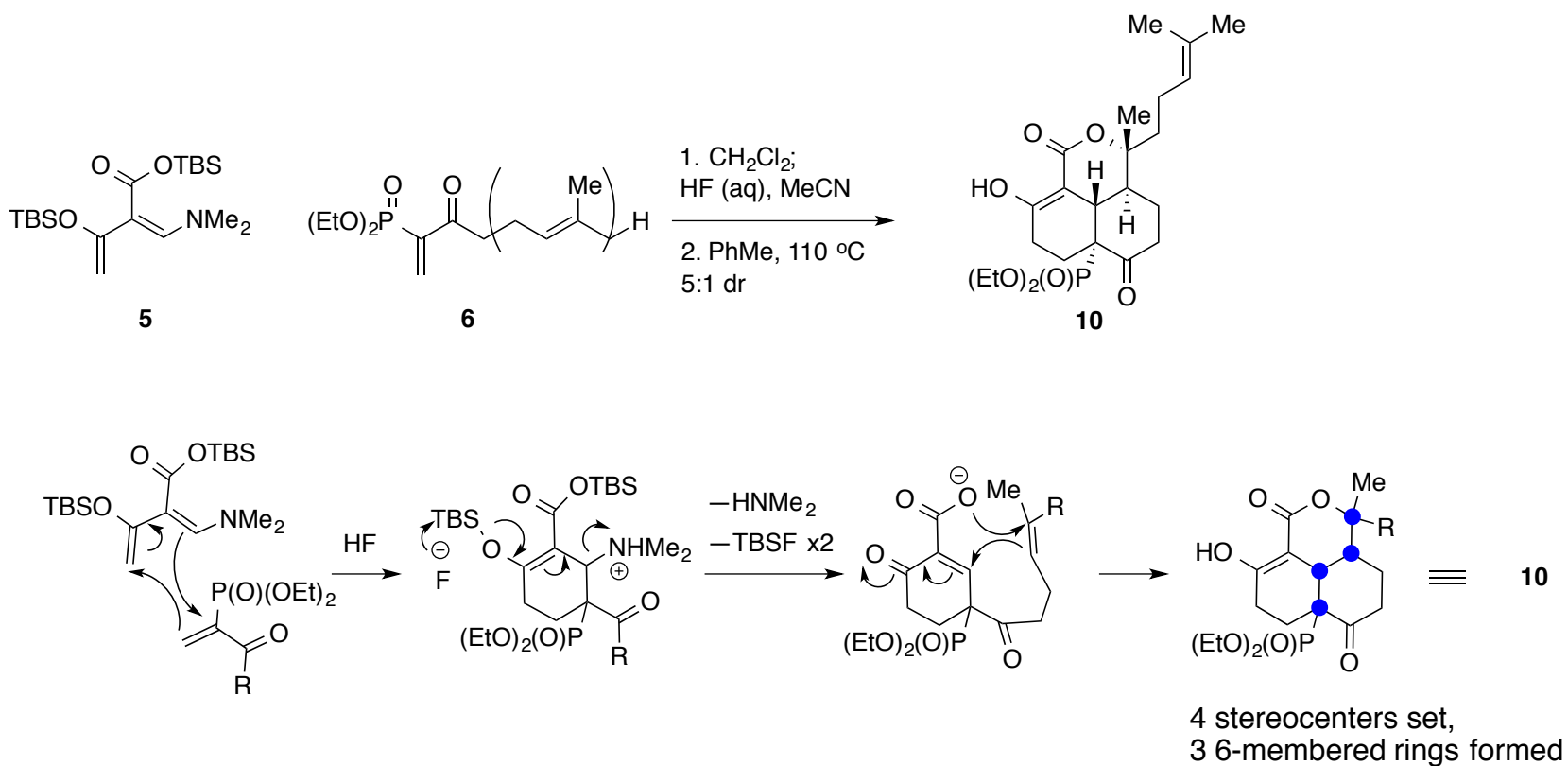
Preparation of double dieneophile 6



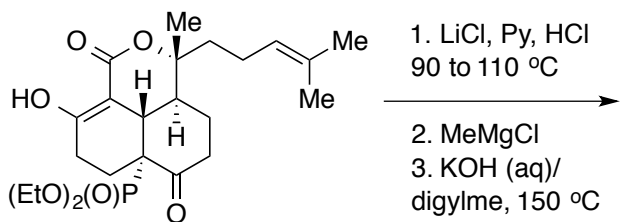
Preparation of double dieneophile **6** (contd.)



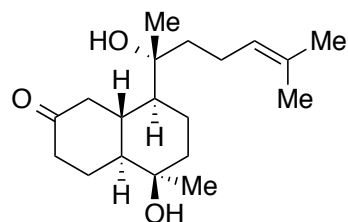
Iterative Diels-Alder Reaction



Dephosphonylation, Grignard Addition, Lactone Hydrolysis/Decarboxylation



10

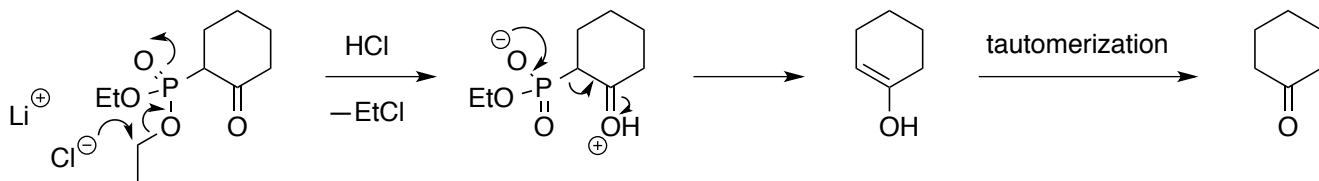


11

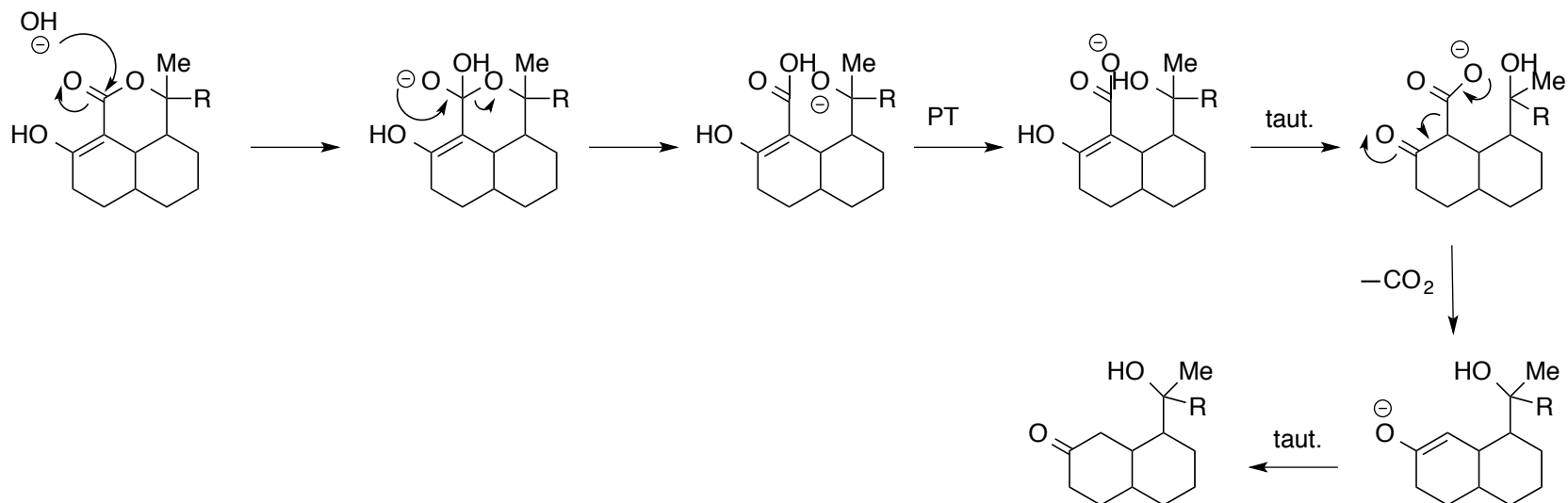
Mild dephosphonylation conditions developed to preserve acid-sensitive *tert*-alkyl lactone and ketones.

Addition of methyl group prior to decarboxylation preserved *trans* decalin geometry.

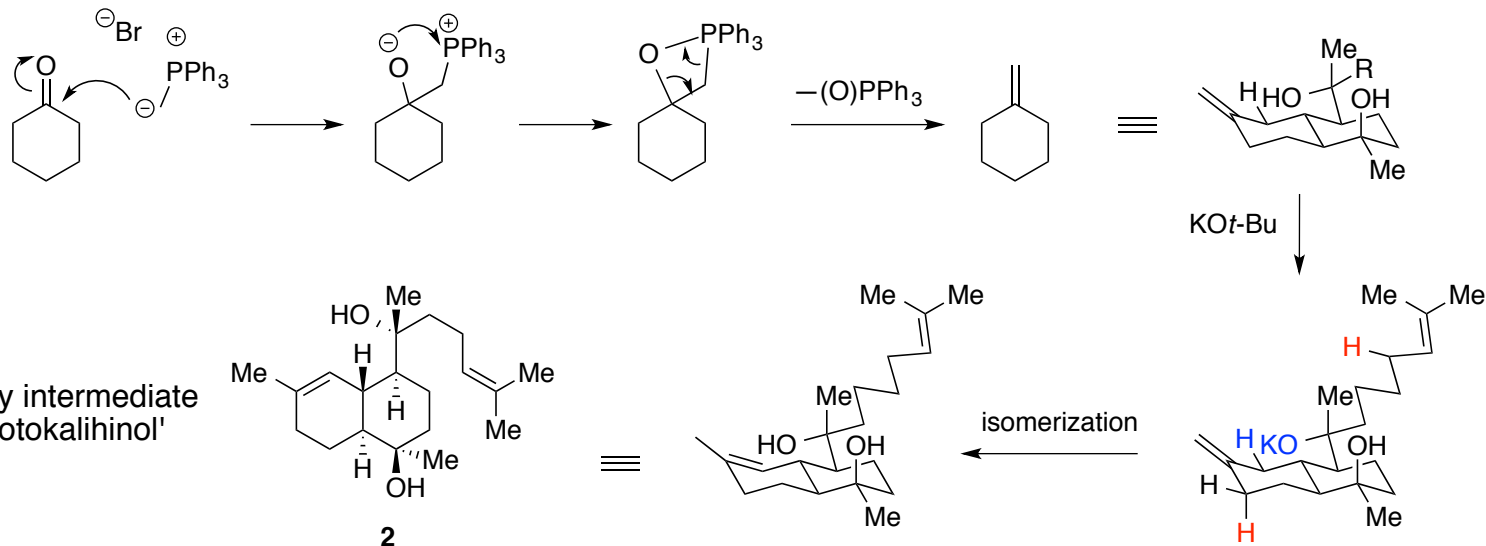
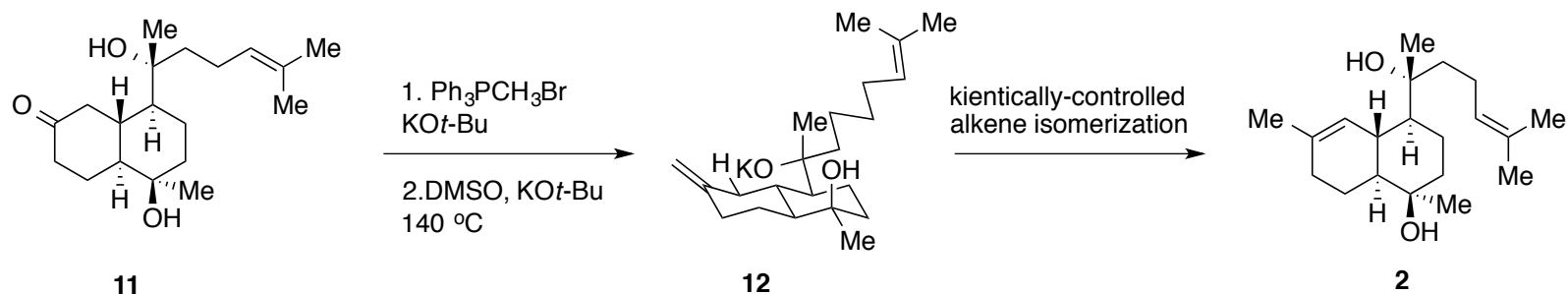
Krapcho-like Dephosphonylation



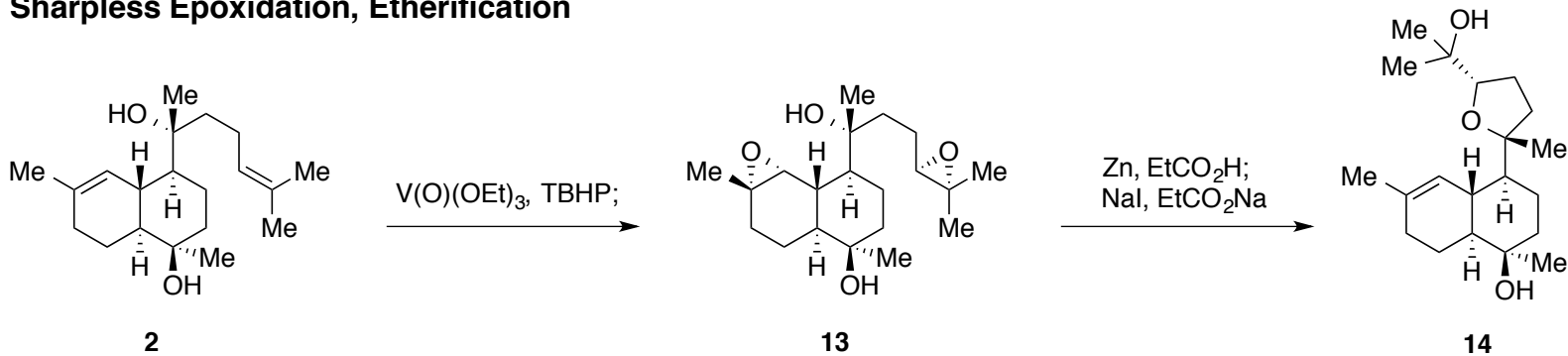
Lactone Hydrolysis/Decarboxylation



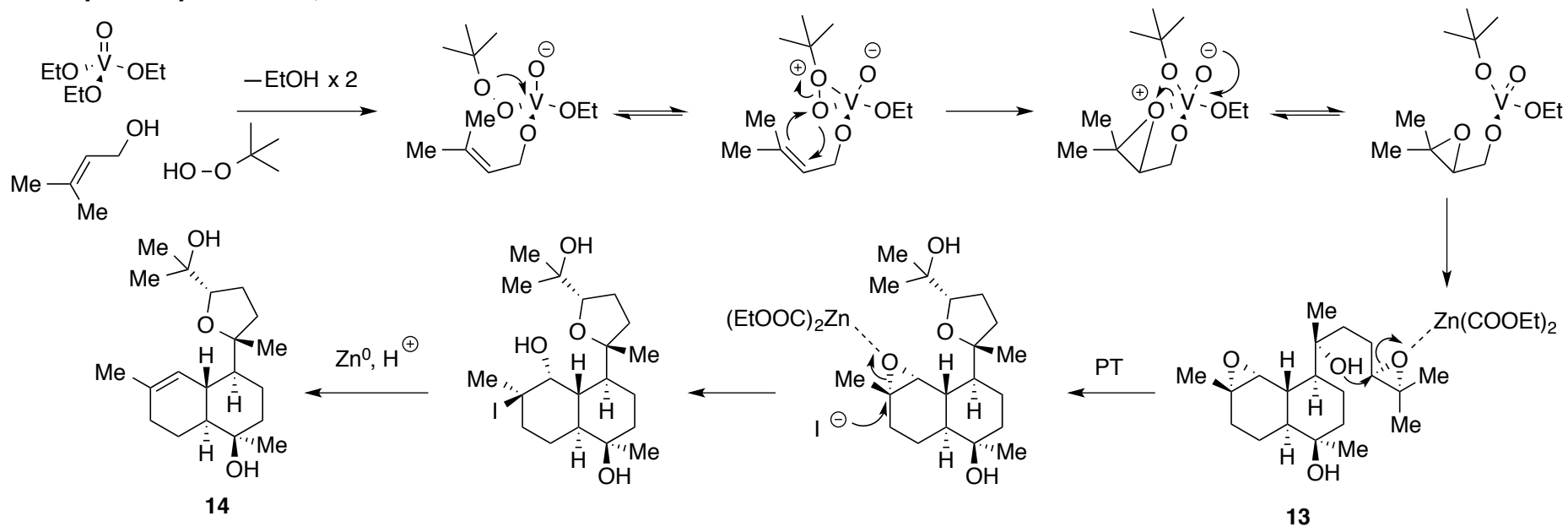
Wittig Reaction, Alkene Isomerization



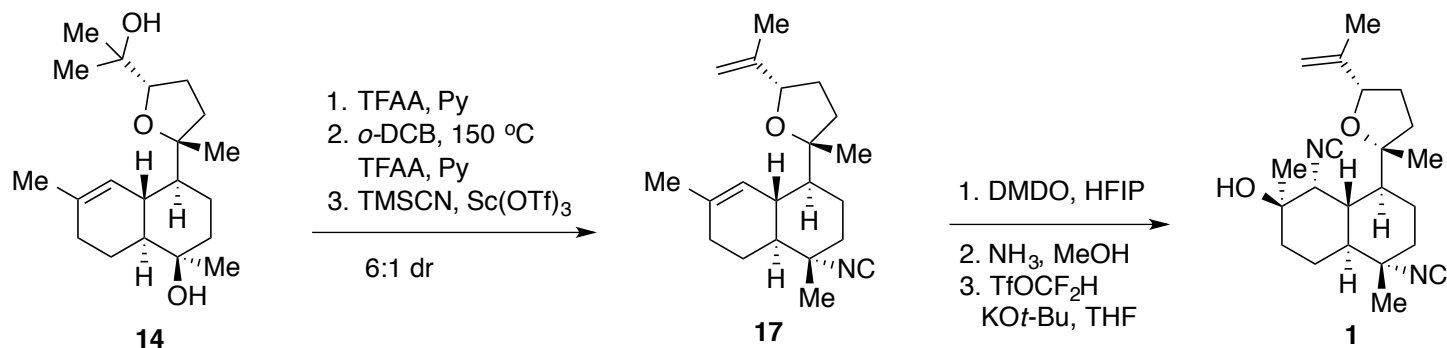
Sharpless Epoxidation, Etherification



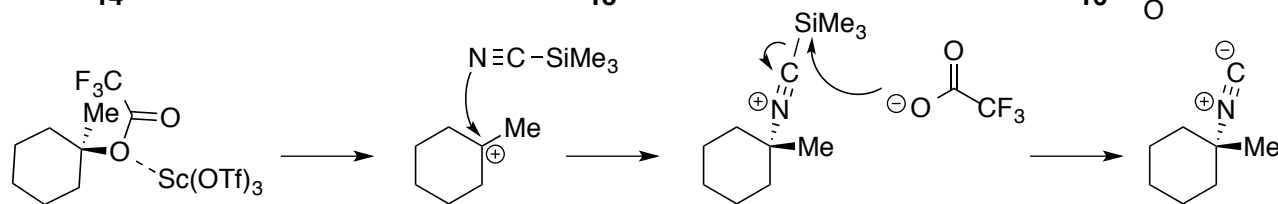
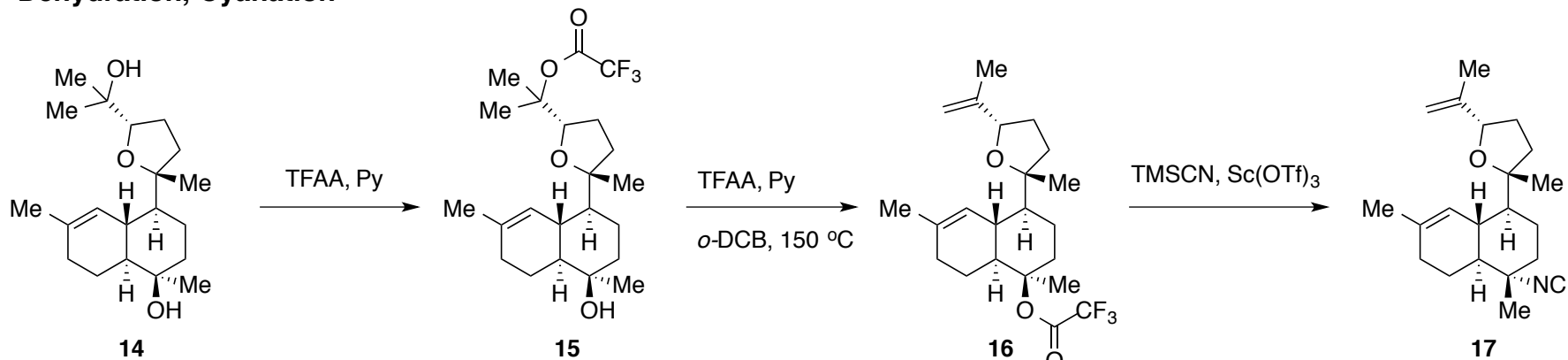
Sharpless Epoxidation, Etherification contd.



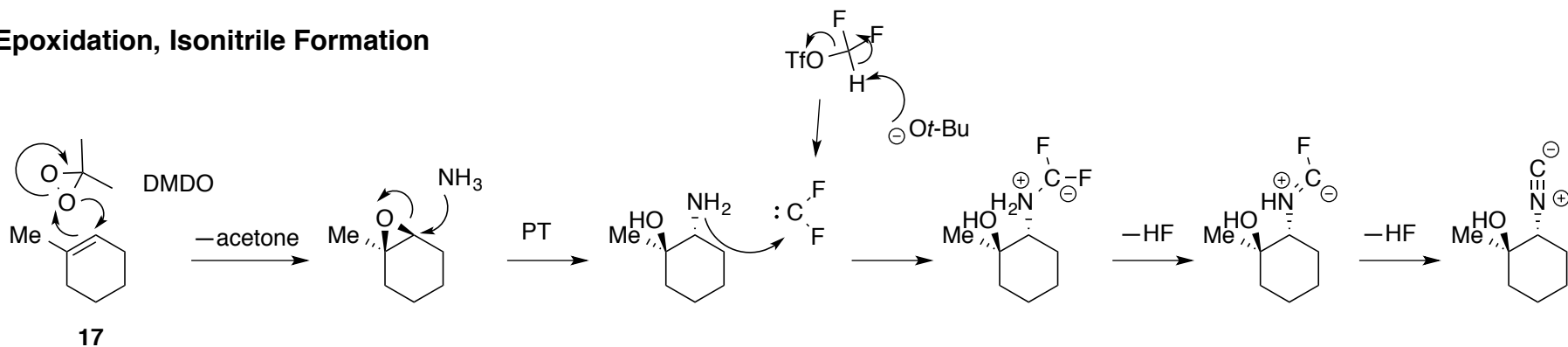
Completing the Synthesis



Dehydration, Cyanation



Epoxidation, Isonitrile Formation



Conclusion

The final product, kalihinol C, was synthesized in 17 steps in an overall yield of 1.3%. This represents a longer step count than the current best approach (Vanderval, 12 steps) but is an order of magnitude higher in yield, mainly due to the increase in stereoselectivity as well as chemoselectivity. The improvements to the synthesis primarily derive from (1) the iterative cycloaddition reaction that establishes the stereotetrad in good selectivity; (2) the alkoxide directed alkene isomerization method; and (3) a short, high yielding, and stereoselective strategy for installing the isocyanohydrin motif.