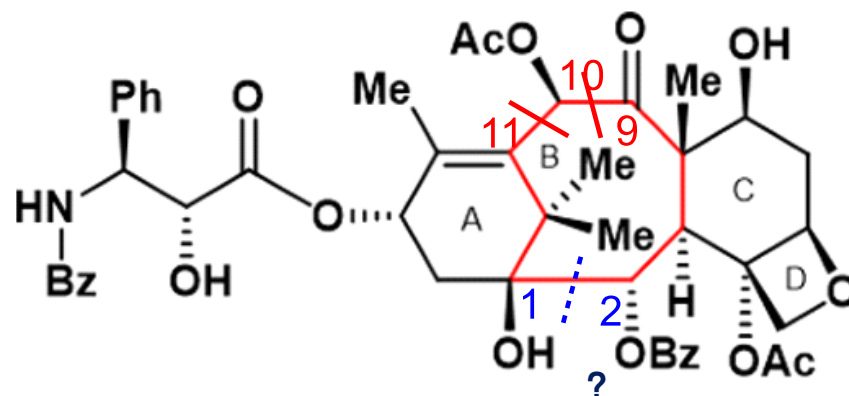


Asymmetric Total Synthesis of Taxol

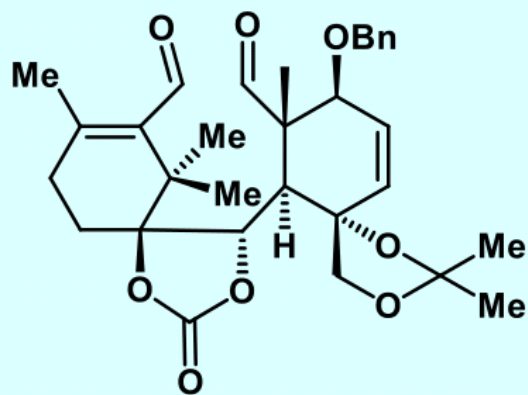


Taxol (1)

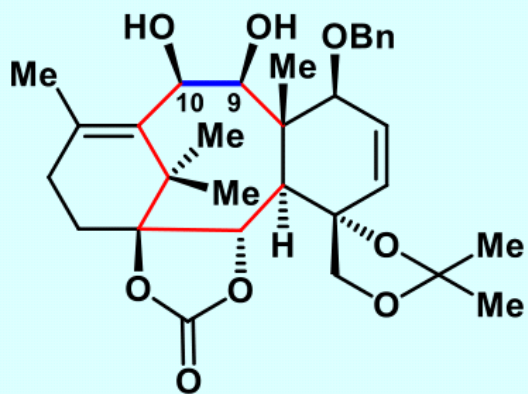
Structural features:

- strained [6-8-6-4] core
- highly oxygenated
- bicyclo[5.3.1] skeleton with bridgehead alkene
- 11 stereocenters: 3 quaternary

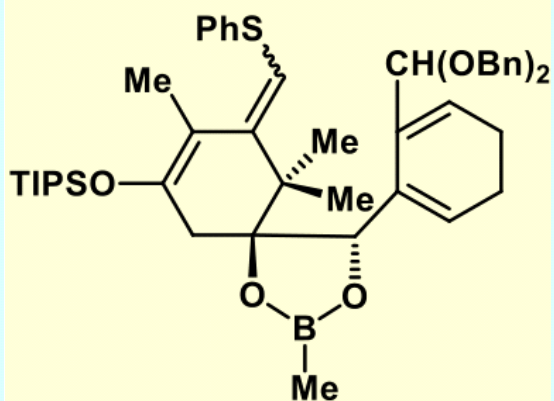
Nicolaou (1994)



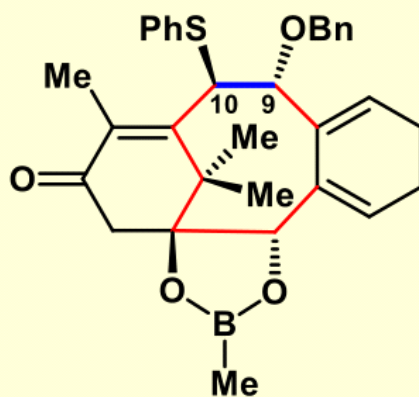
McMurry coupling
 $(\text{TiCl}_3)_2 \cdot (\text{DME})_3$
 Zn-Cu



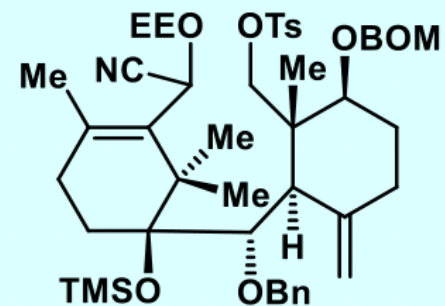
Kuwajima (1998)



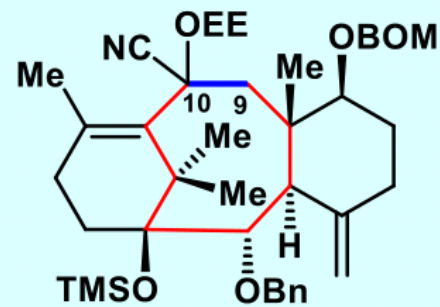
Mukaiyama
 aldol
 $\text{TiCl}_2(\text{O}i\text{-Pr})_2$



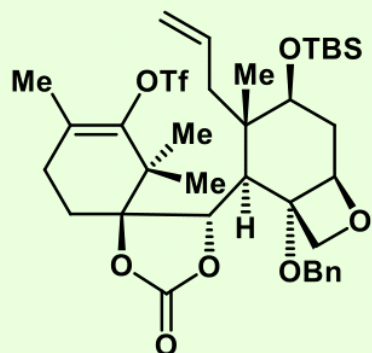
Takahashi (formal, 2006)



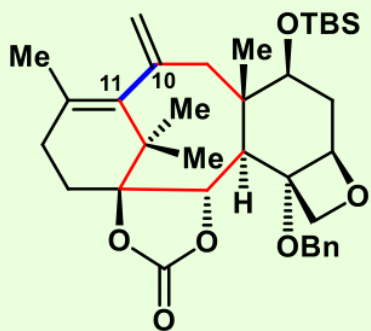
alkylation
 LiHMDS
 mW



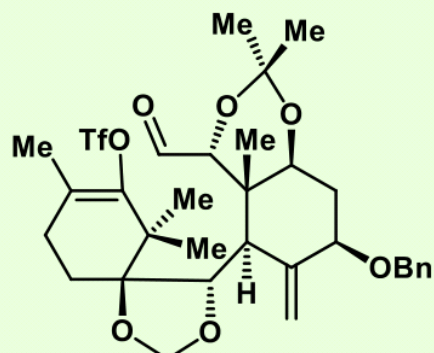
Danishefsky (1995)



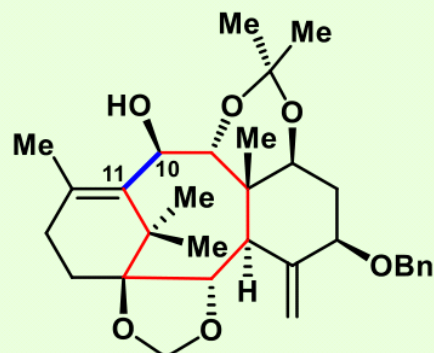
Heck coupling
 $\text{Pd}(\text{PPh}_3)_4$
 K_2CO_3



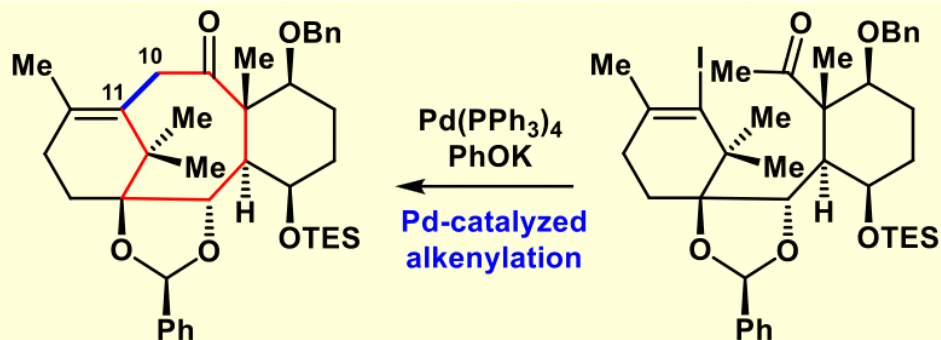
Kishi (2000)



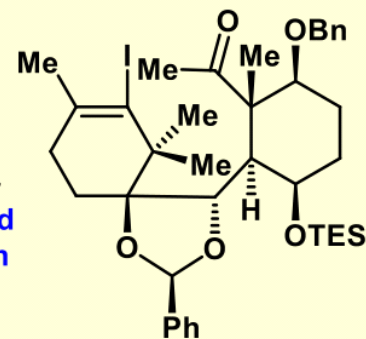
NHK
 NiCl_2
 CrCl_2



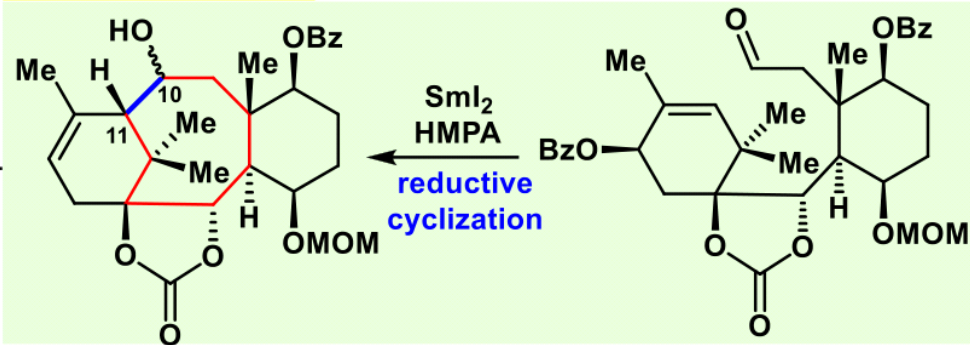
Nakada (formal, 2015)



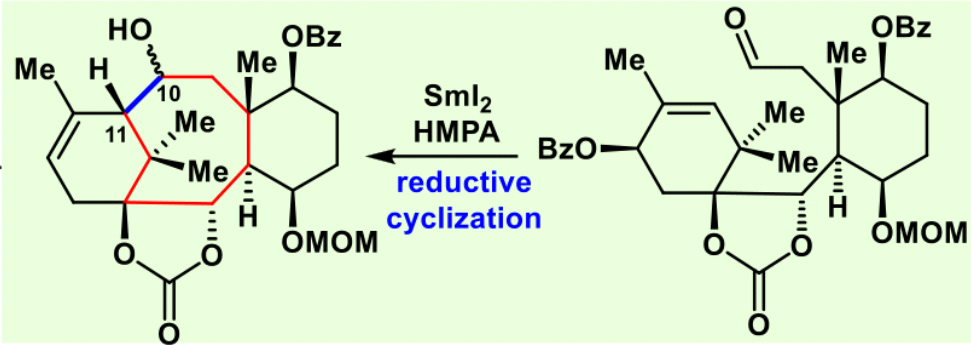
$\text{Pd}(\text{PPh}_3)_4$
 PhOK
Pd-catalyzed
alkenylation



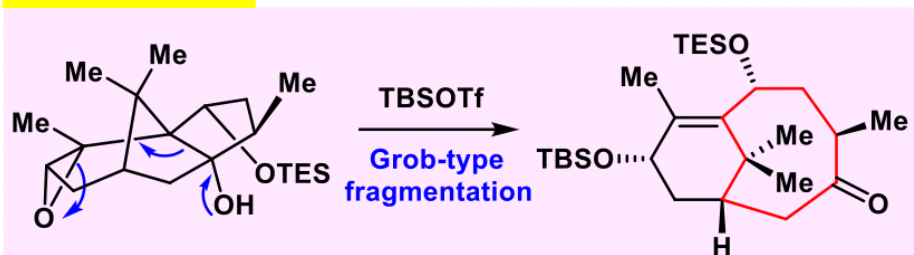
Chida (formal, 2015)



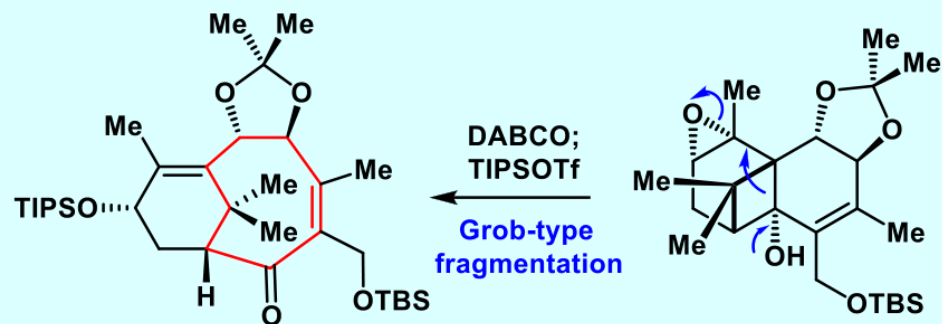
SmI_2
 HMPA
reductive
cyclization



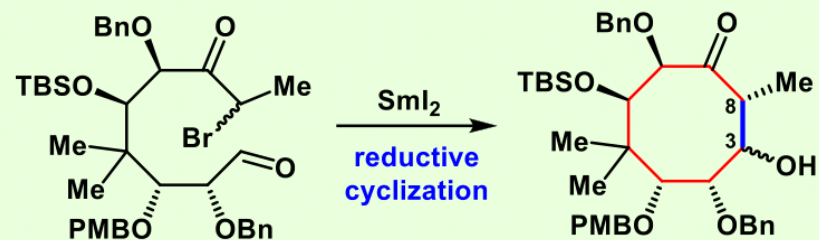
Holton (1994)



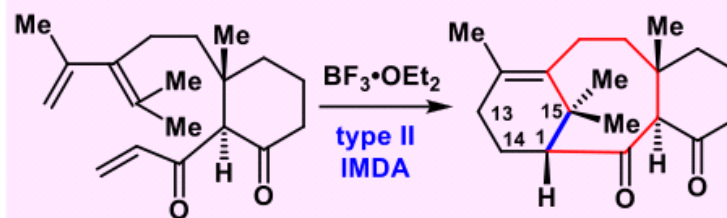
Wender (1997)



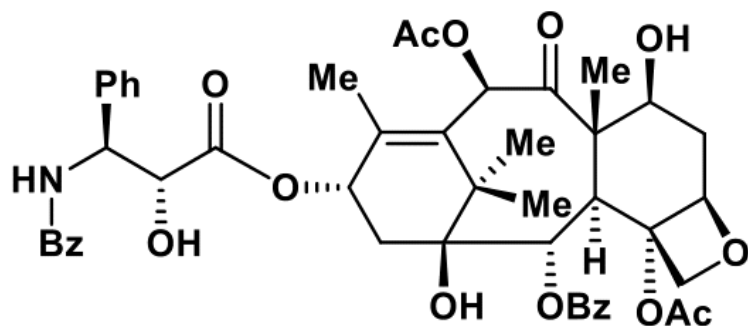
Mukaiyama (1999)



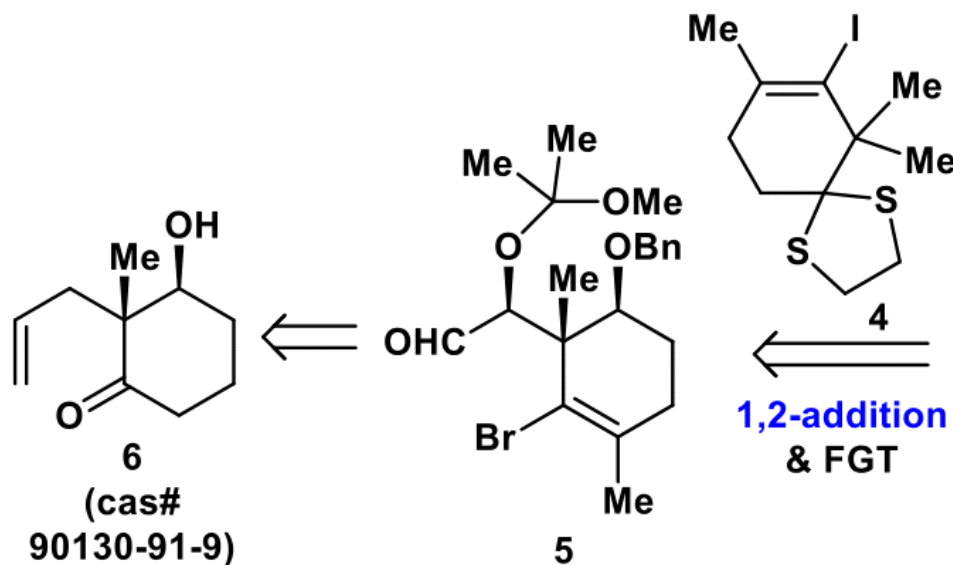
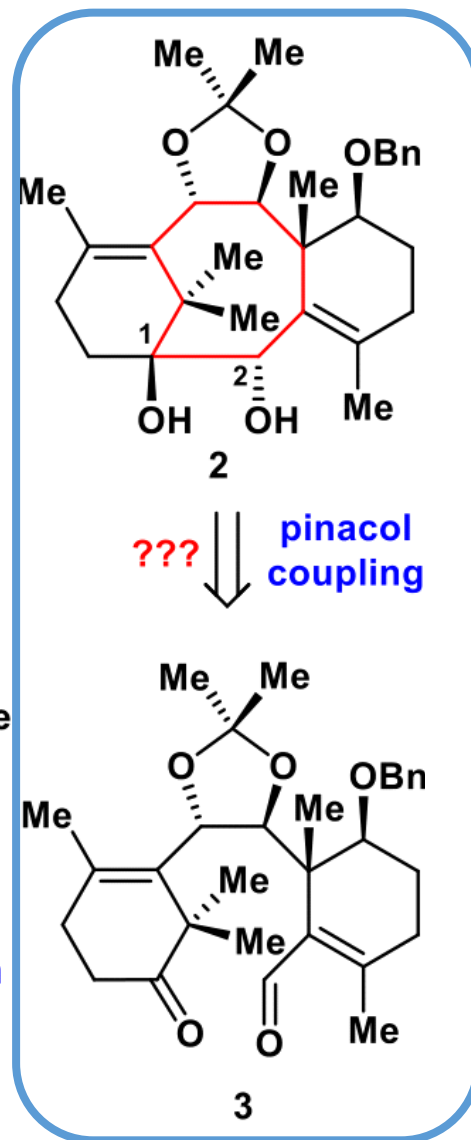
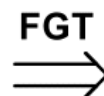
Baran (2020)

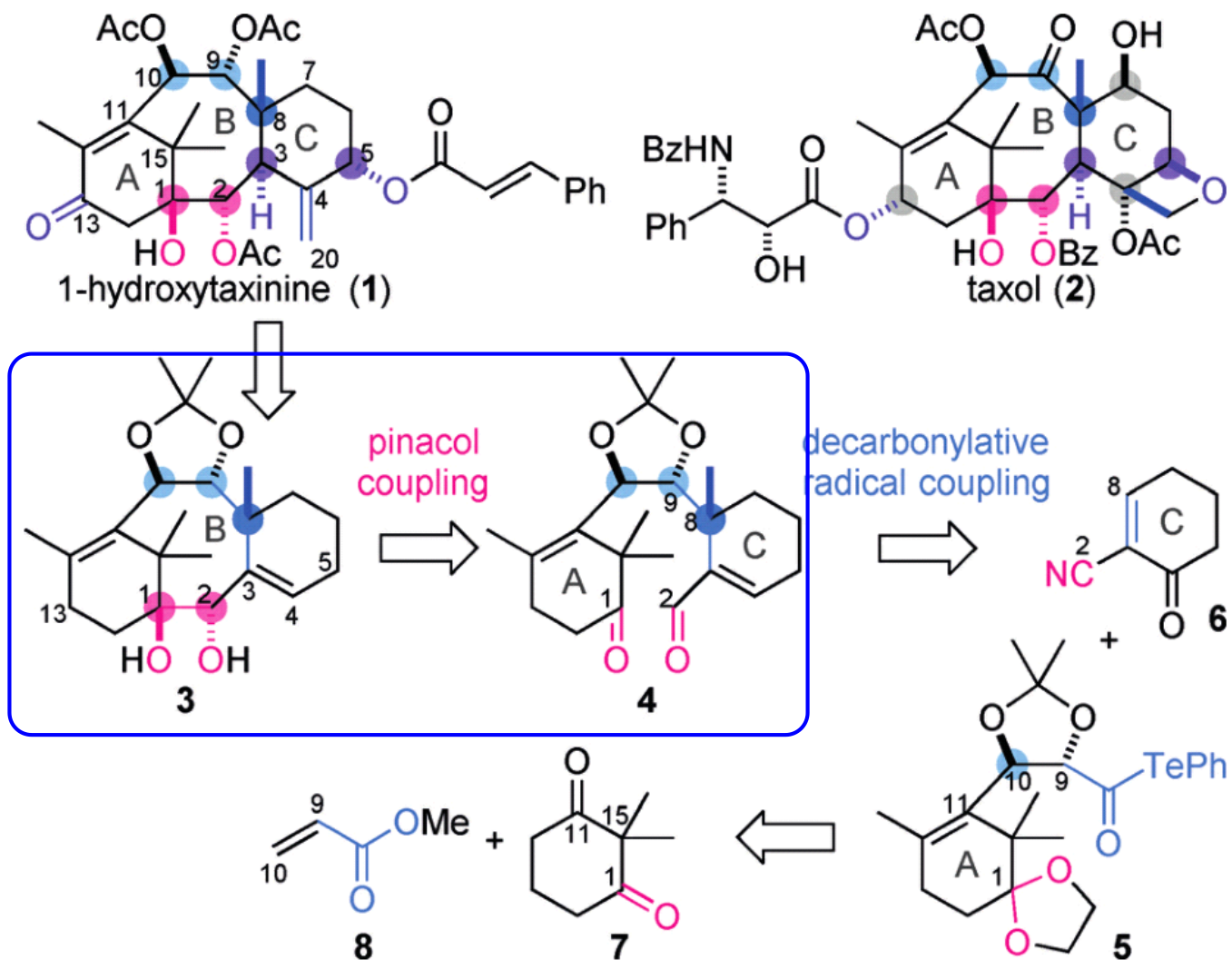


Retrosynthetic Analysis of Taxol



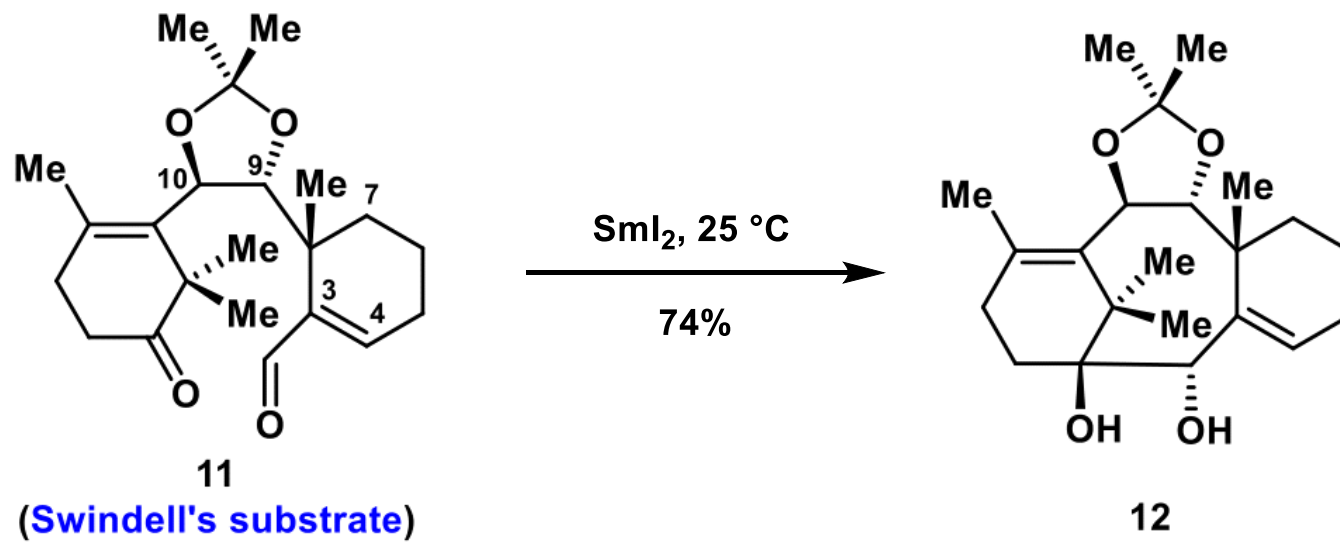
Taxol (1)





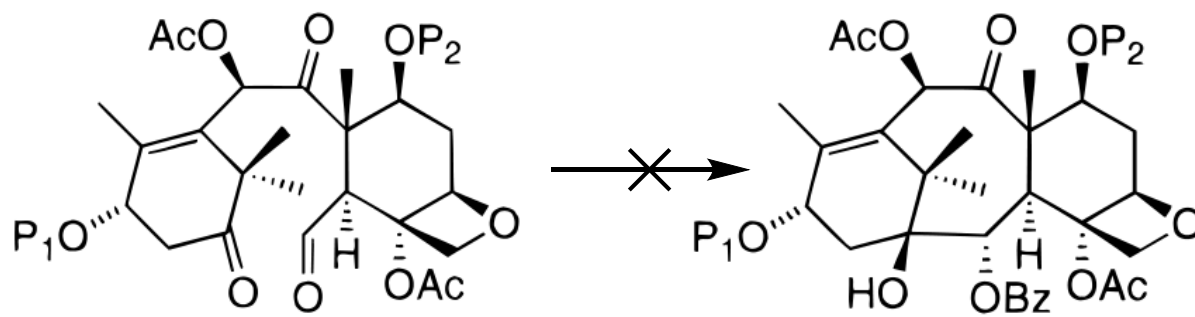
Scheme 1. Structures of 1-hydroxytaxinine (1) and taxol (2) and the synthetic plan for 1.

Swindell



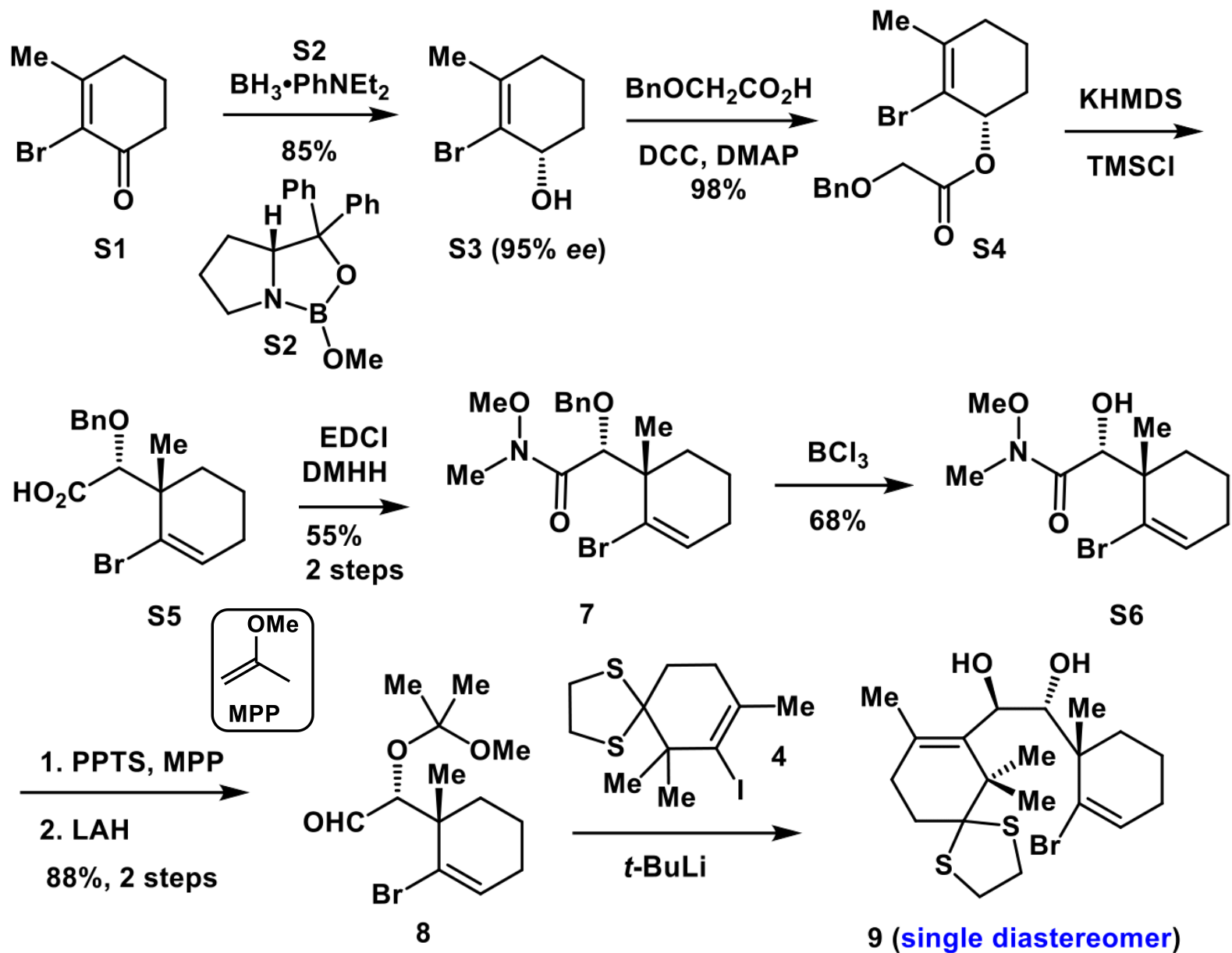
Tetrahedron Lett. **1996**, 37, 2321-2324.

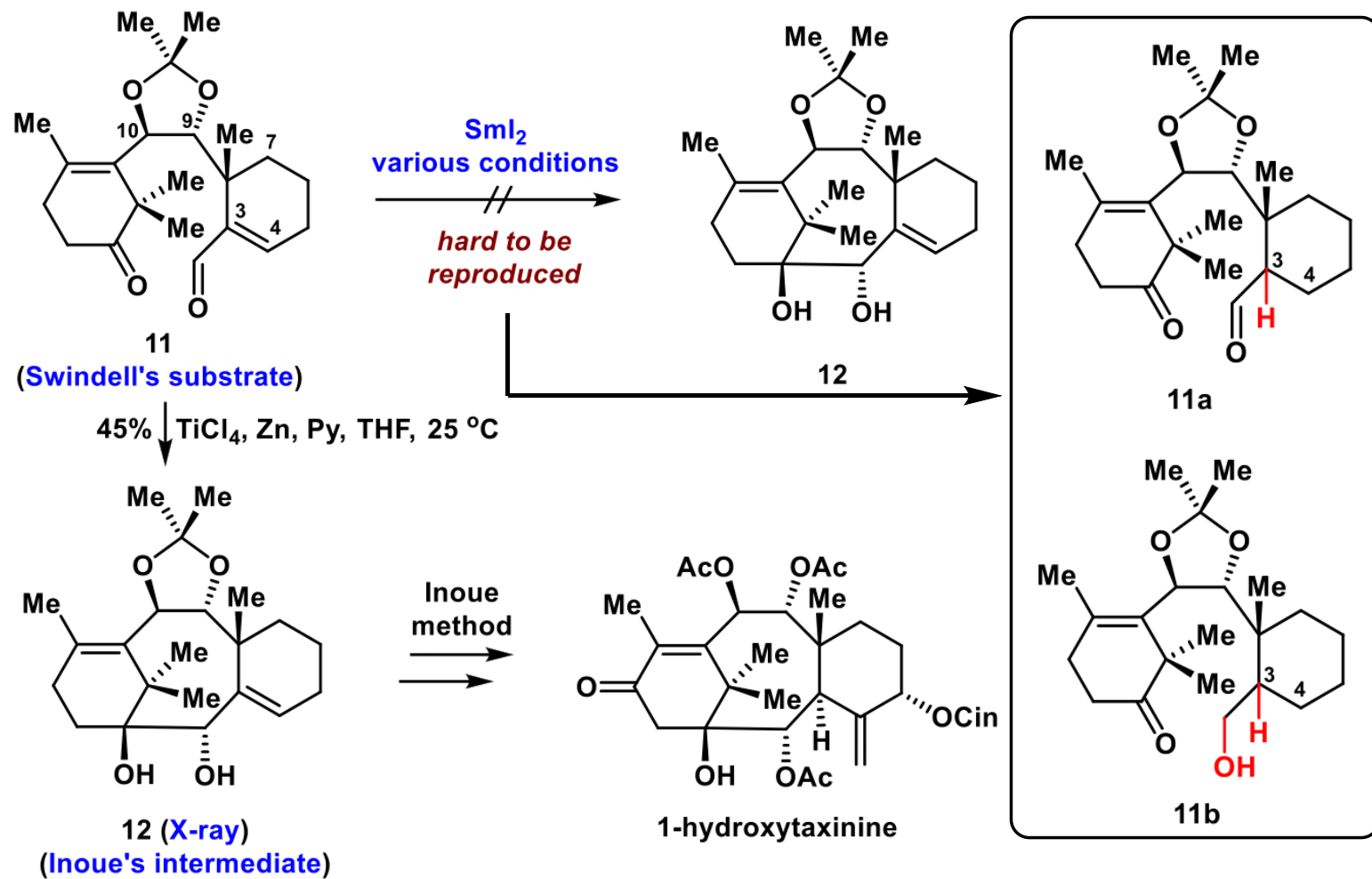
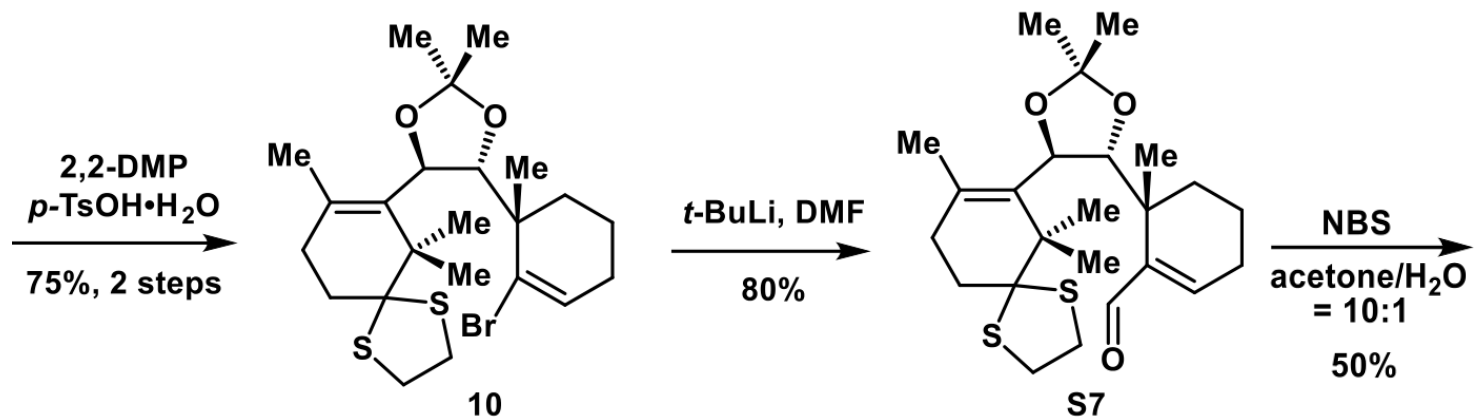
Danishefsky

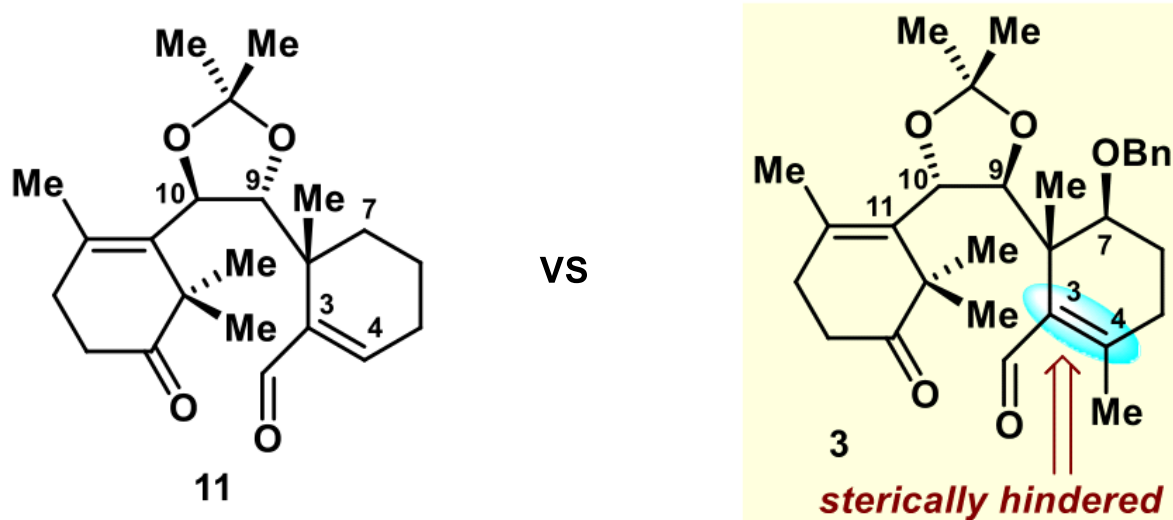


J. Am. Chem. Soc. **1996**, 118, 2843-2859.

Scheme 2. Model Study and Formal Synthesis of (+)-1-Hydroxytaxinine

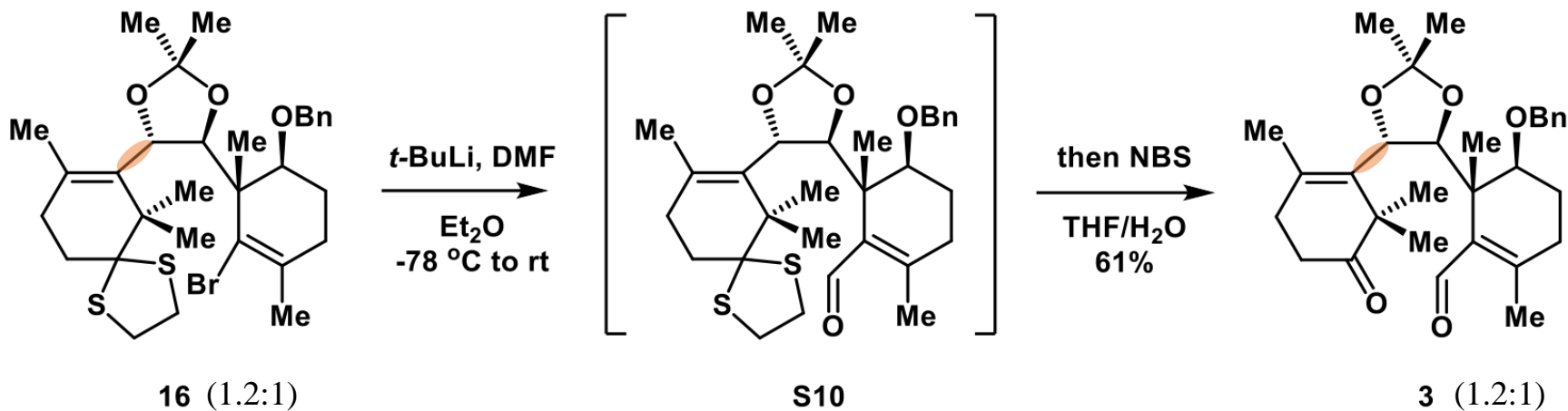
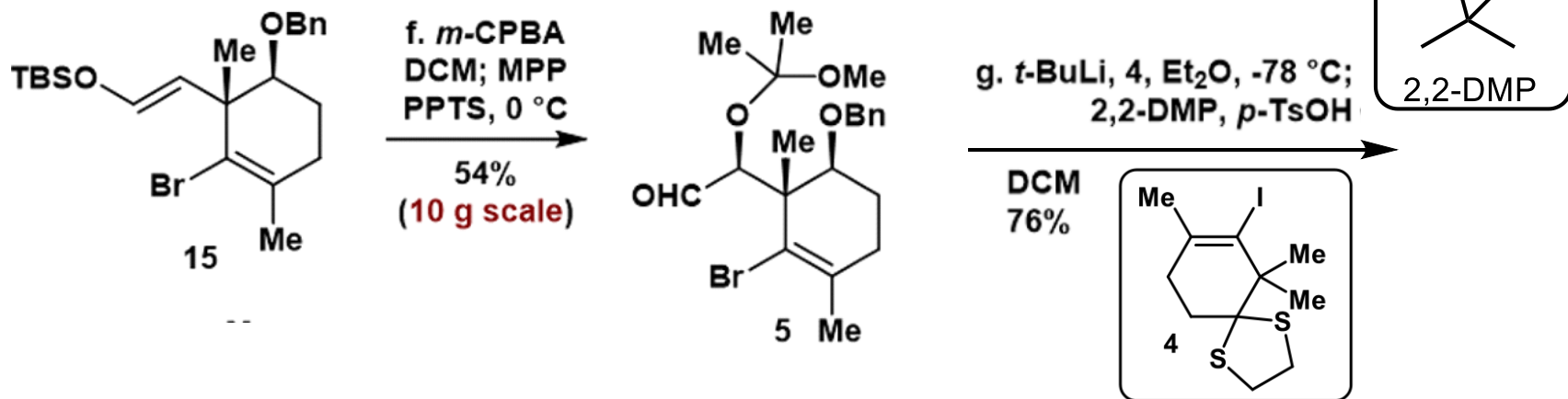
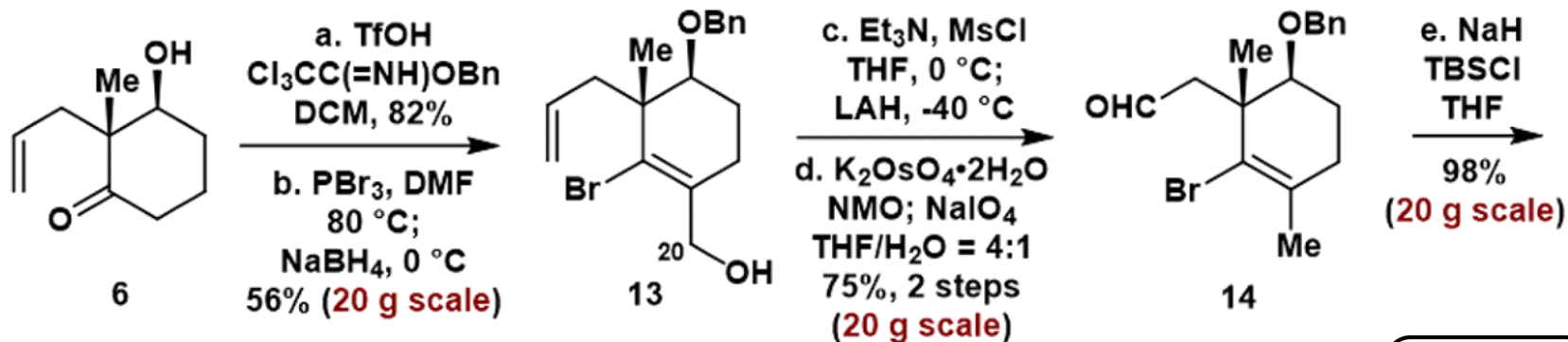


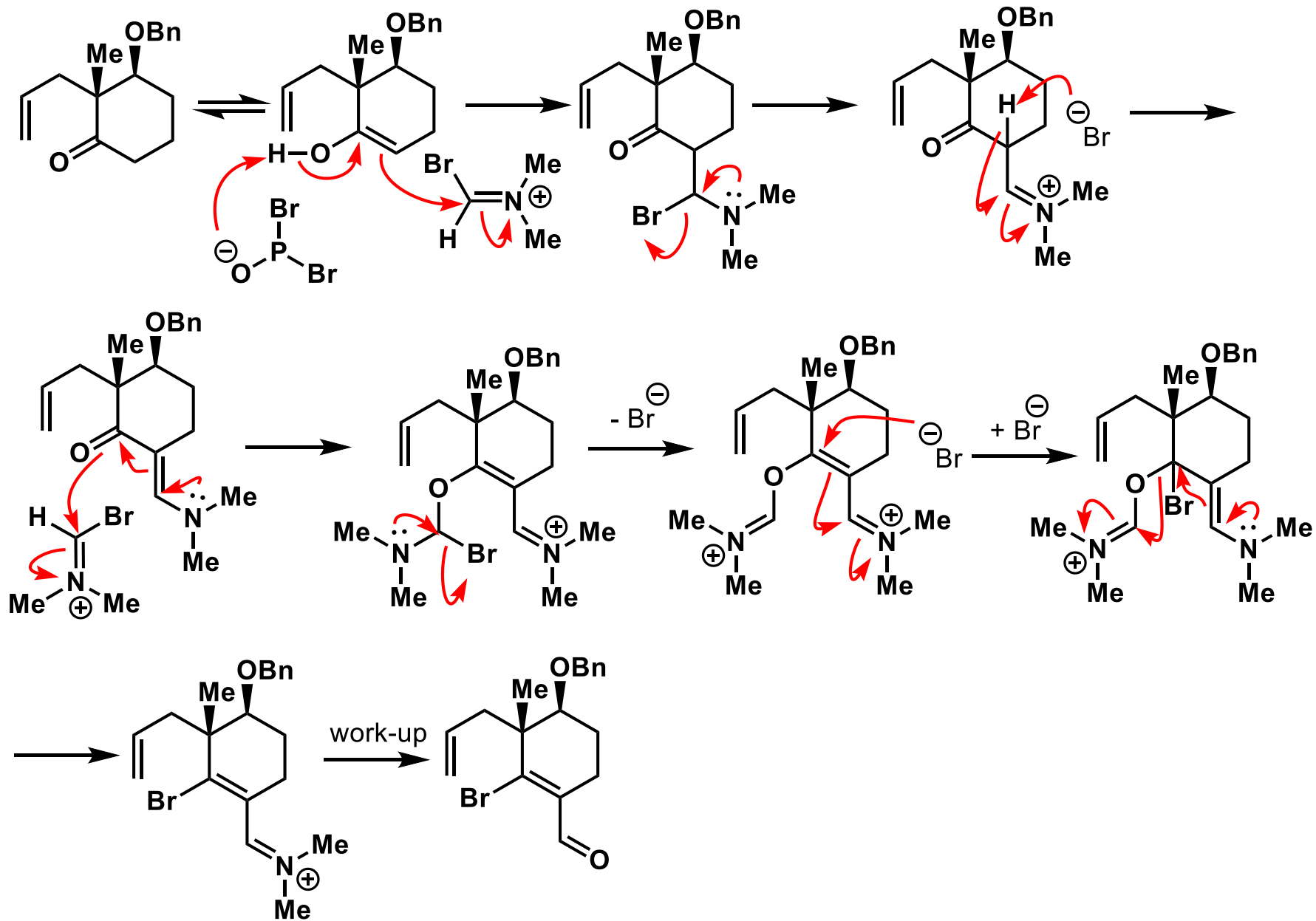


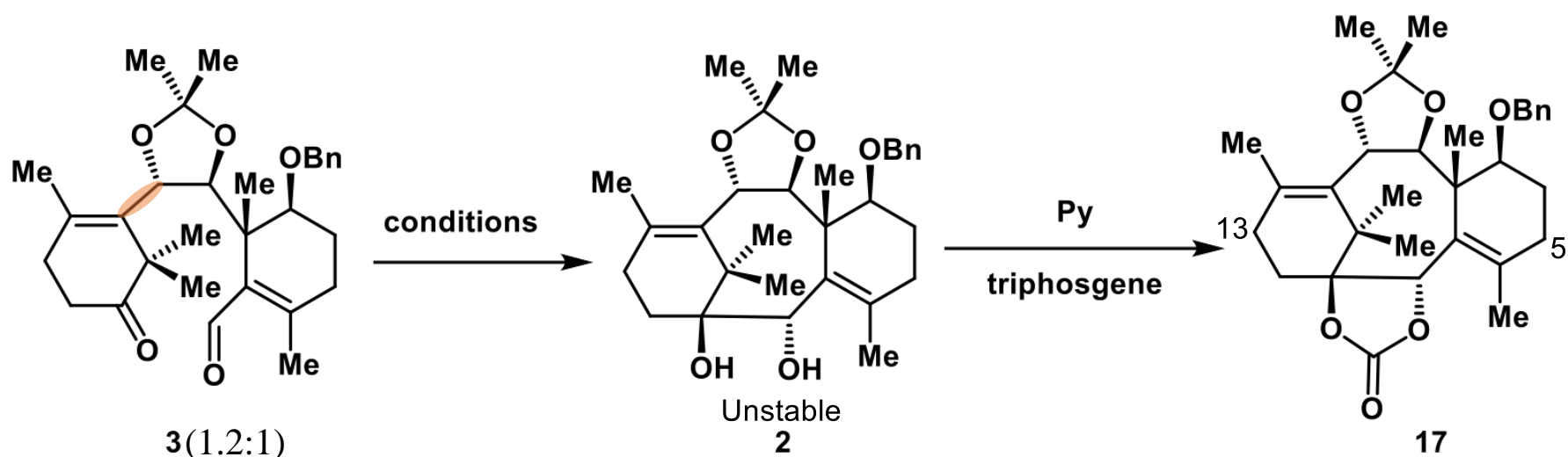


1. Compound 3 had opposite stereochemistry at C 9 and C 10 compared with that of Swindell's substrate 11
2. possessed an additional methyl group and OBn group at C 4 and C 7
3. the steric hindrance around the C3–C4 olefinic bond of 3 was more than that of 11

Asymmetric preparation of ketoaldehyde 3

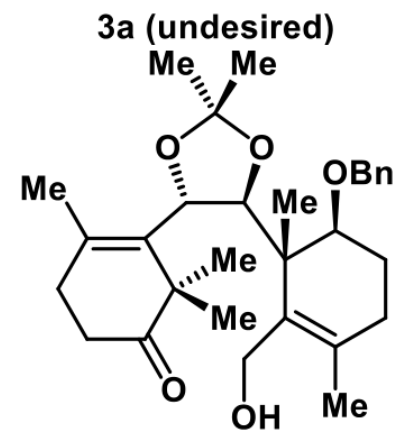
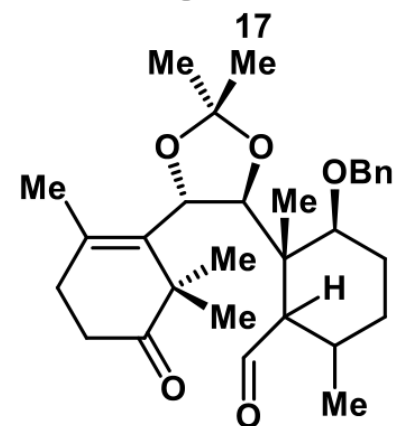




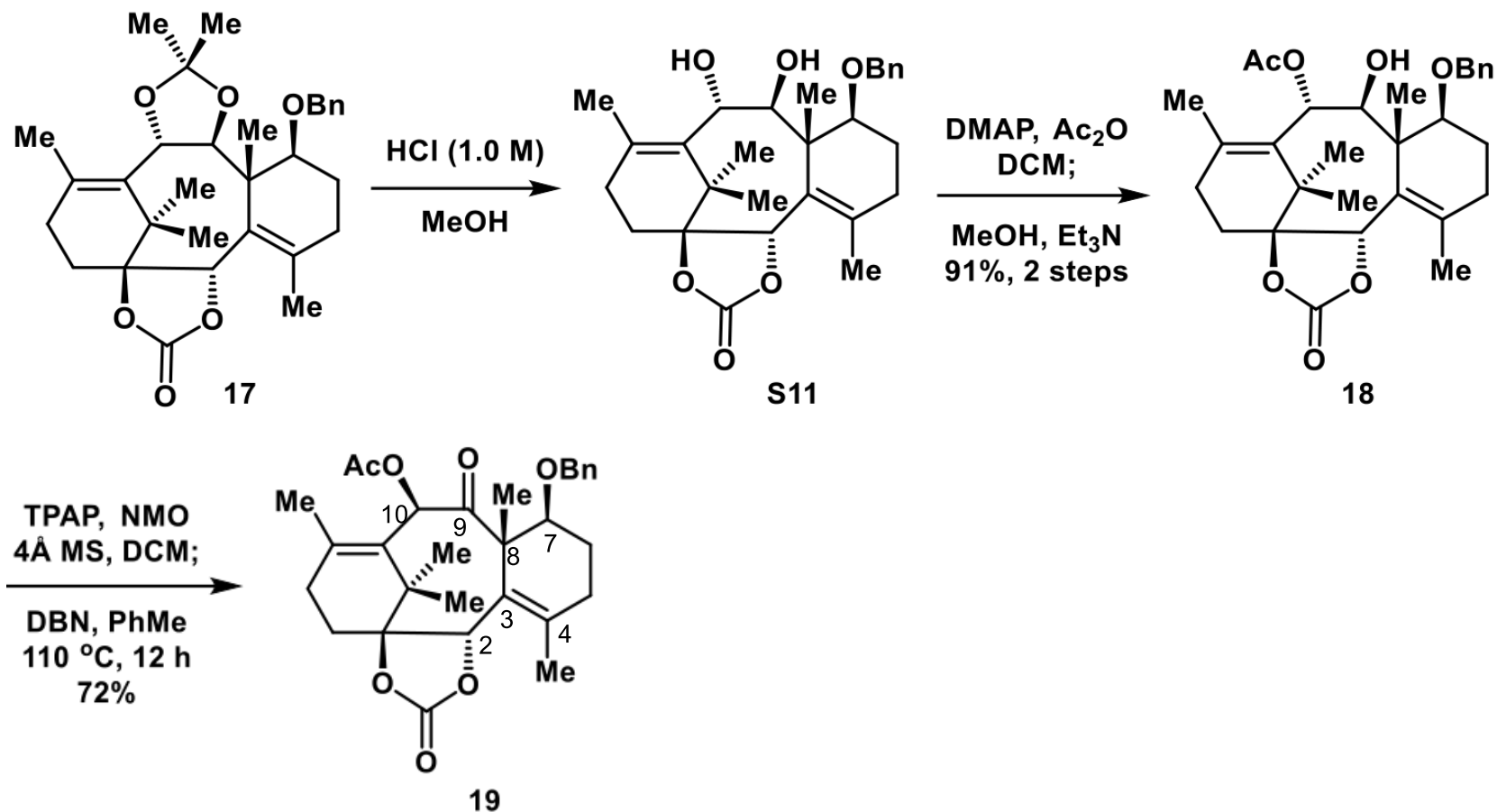


Entry ^a	Conditions	Yield (%) ^b (3a/3b/17)
1 ^c	SmI ₂ (10 equiv), 25 °C	4/38/0
2	TiCl ₄ (10 equiv), Zn (20 equiv), pyridine, 25 °C	6/trace/48
3	SmI ₂ (10 equiv), Et ₃ N (20 equiv), 25 °C	trace/45/0
4	SmI ₂ (10 equiv), Sm (2 equiv), 25 °C	8/9/38
5	SmI ₂ (10 equiv), Sm (2 equiv), 65 °C	trace/trace/64
6 ^d	SmI ₂ (4 equiv), Sm (2 equiv), 65 °C	trace/trace/62

^aUnless indicated otherwise, all reactions were performed on a 0.1 mmol scale in THF, and **3** was added using a syringe pump as a 0.1 M THF solution over 0.5 h. ^bIsolated yield. ^cA THF solution of SmI₂ was added to **3** in THF (0.1 M). ^dRun on a 2.0 g (4.16 mmol) scale in the same pot.



3b (undesired)

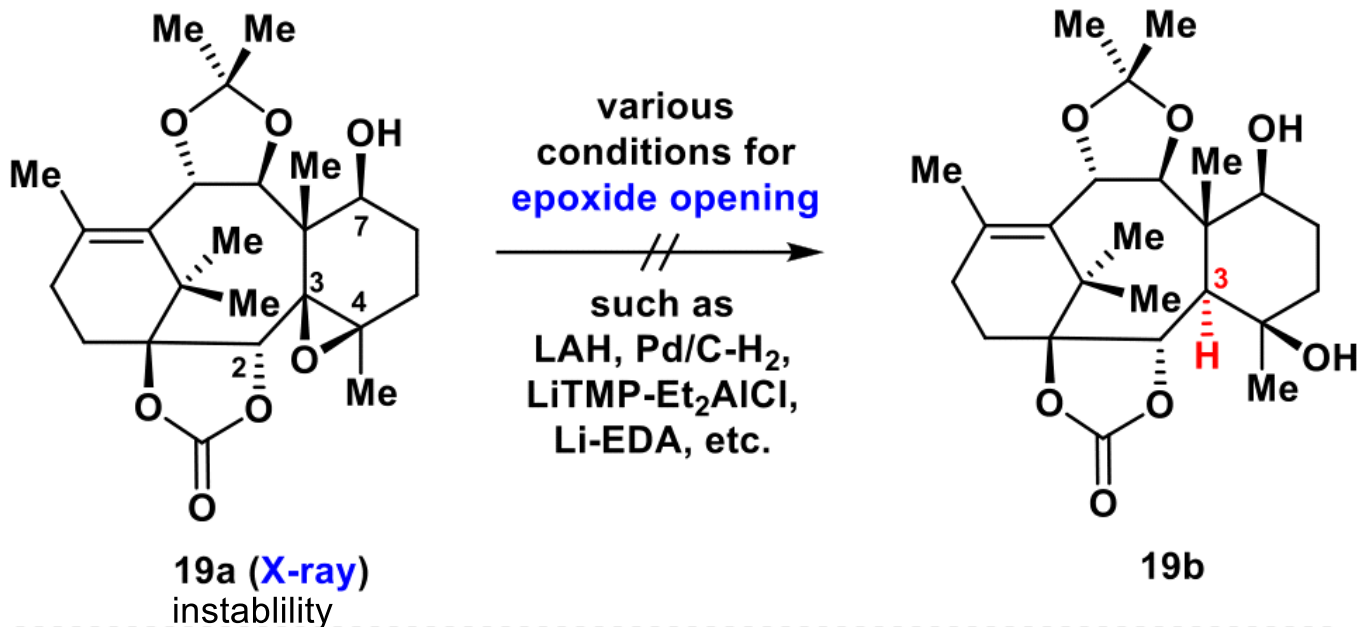


Three major tasks:

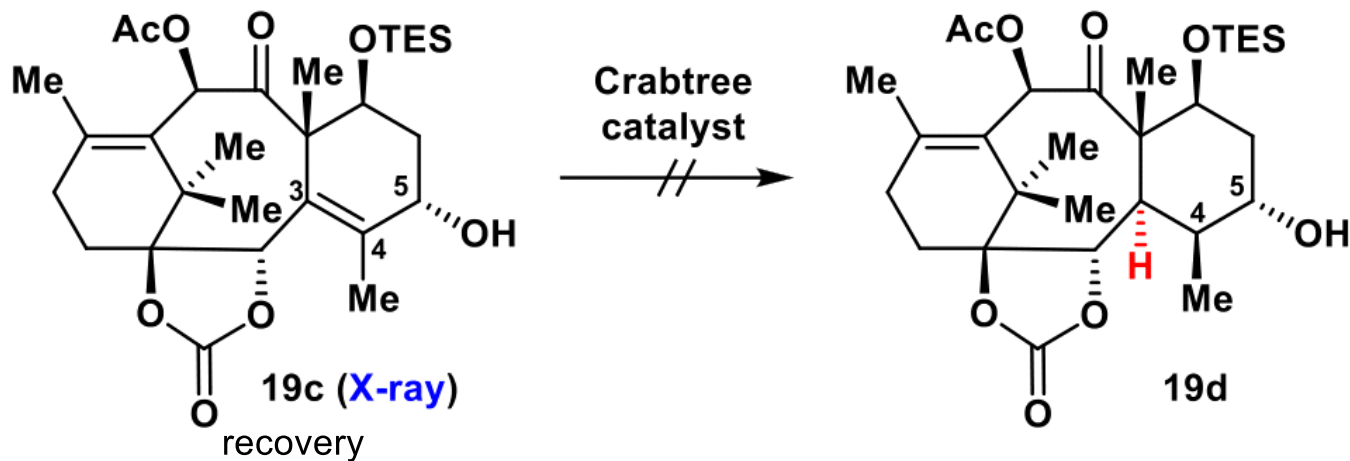
- a. setting the desired C3-stereocenter diastereoselectively
- b. construction of the four-membered oxetane ring
- c. installation of the side chain

Selected Failed Attempts to Construct the Desired C3 Stereocenter

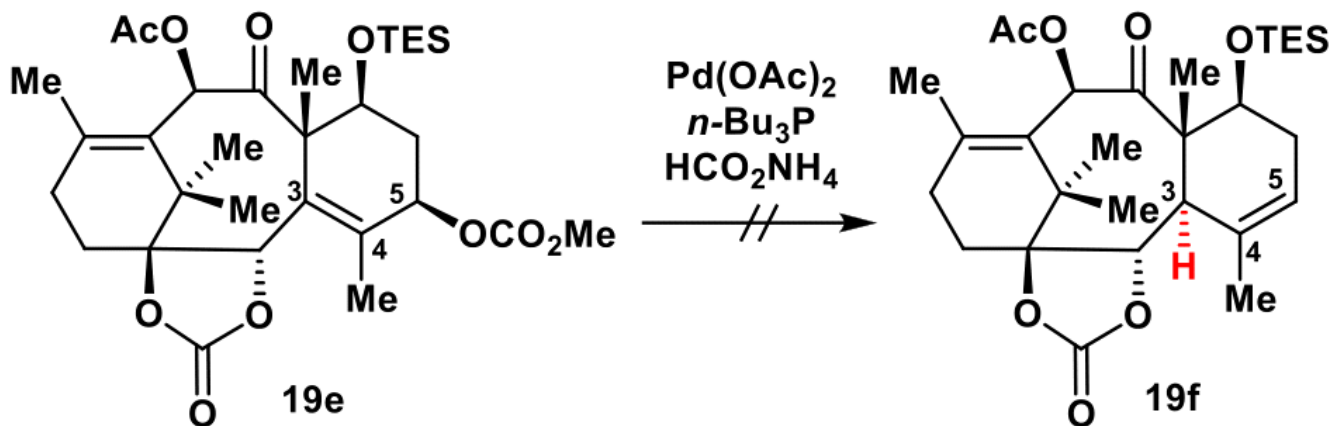
a) epoxide opening strategy



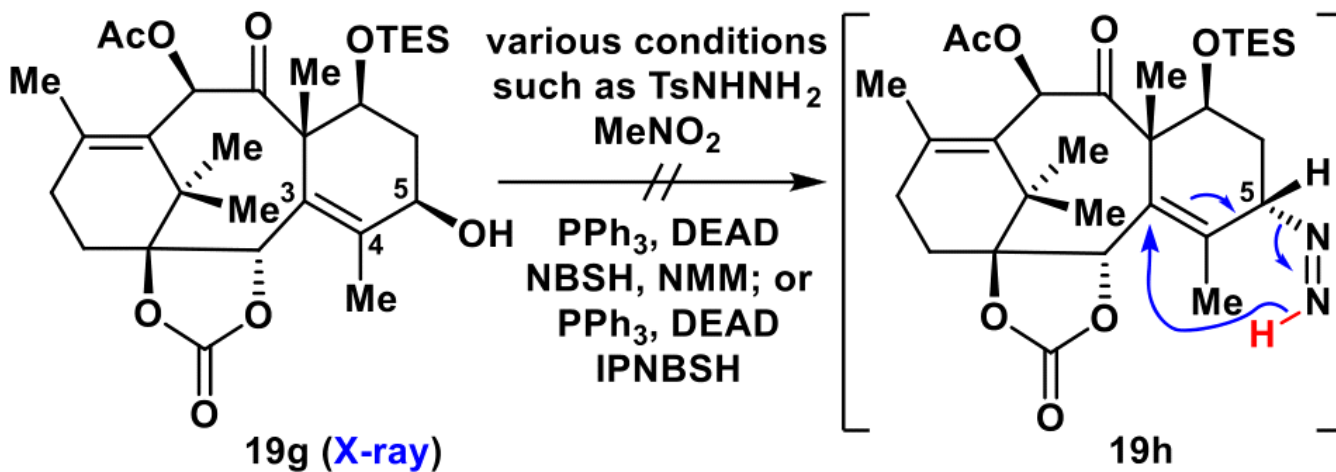
b) C5-OH directed hydrogenation strategy

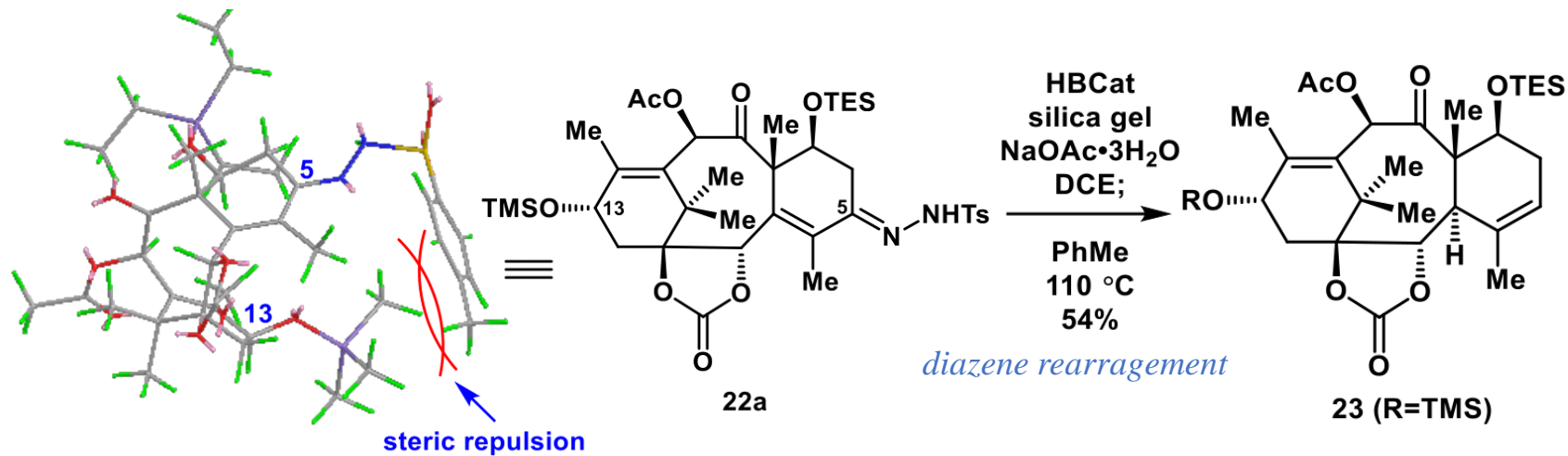
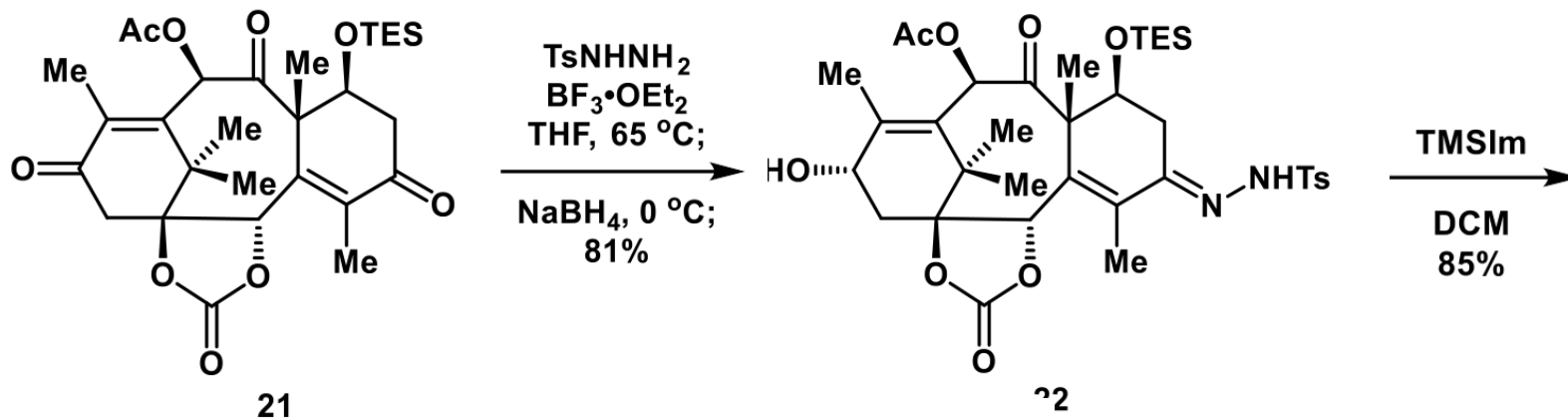
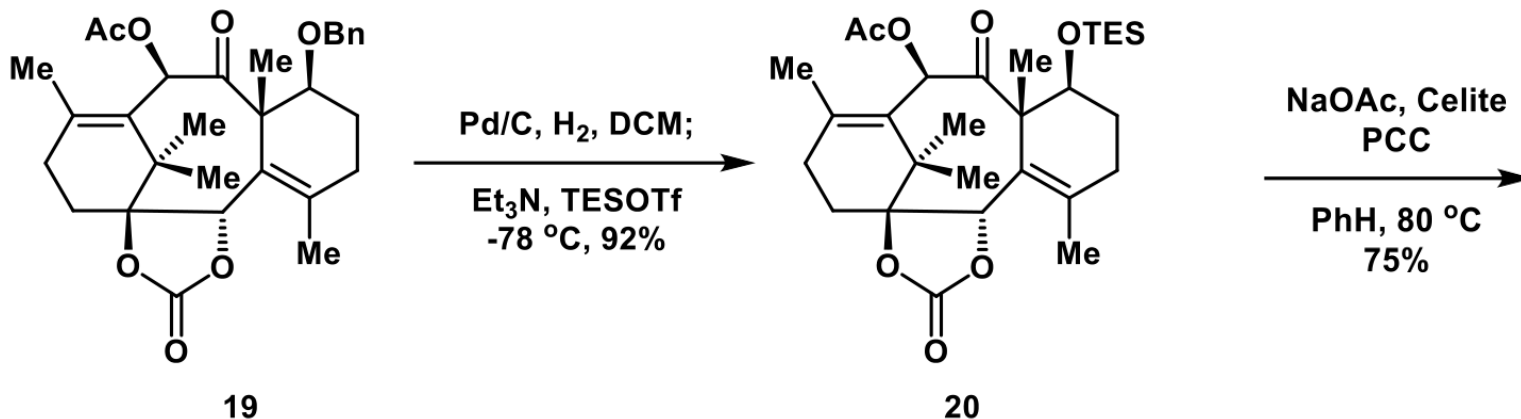


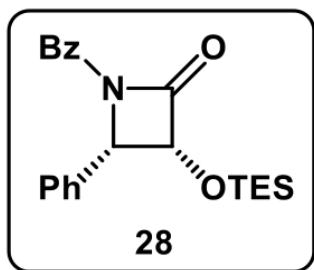
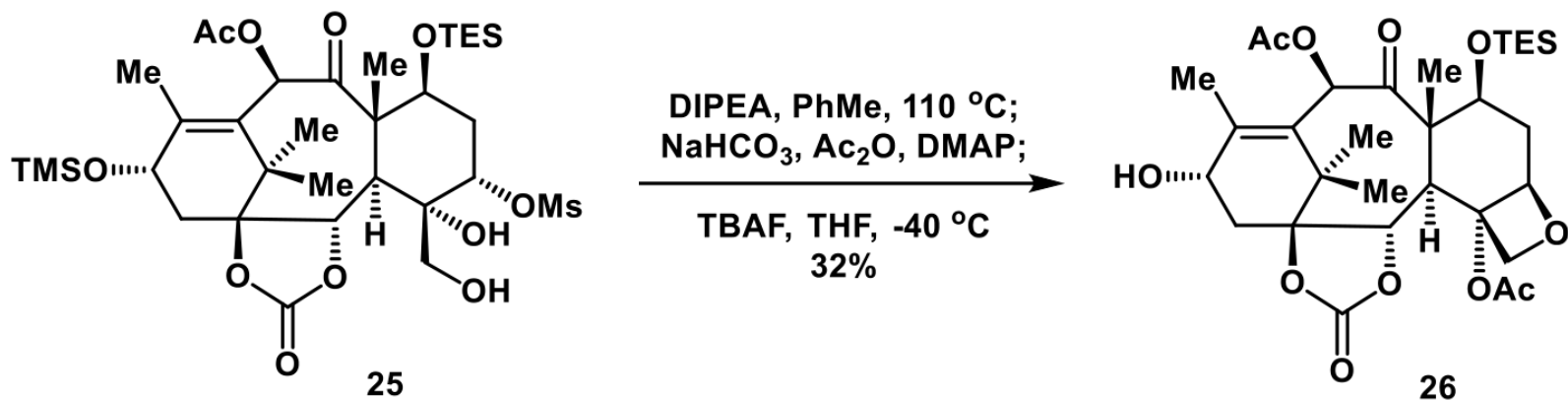
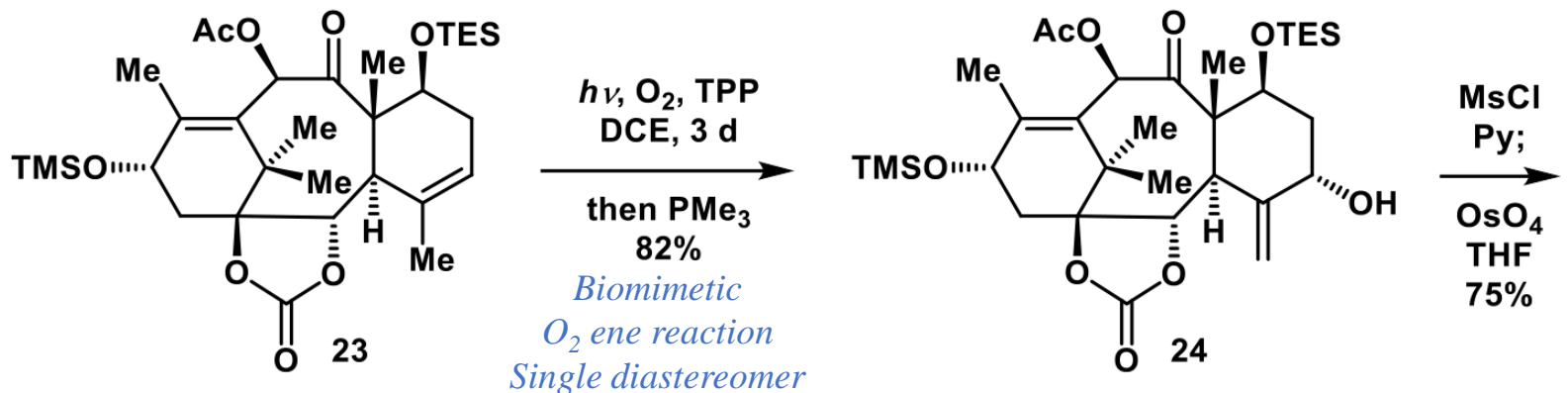
c) palladium-catalyzed reductive transposition strategy



d) allylic diazene rearrangement strategy

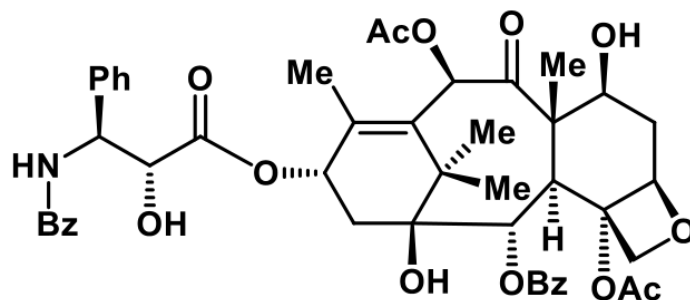






$PhLi, THF, -78\text{ }^\circ C;$

β -lactam 28;
 $HF \cdot Py, 68\%$



Tandem benzoate & side chain installation

$^1\text{O}_2$ ene reaction

