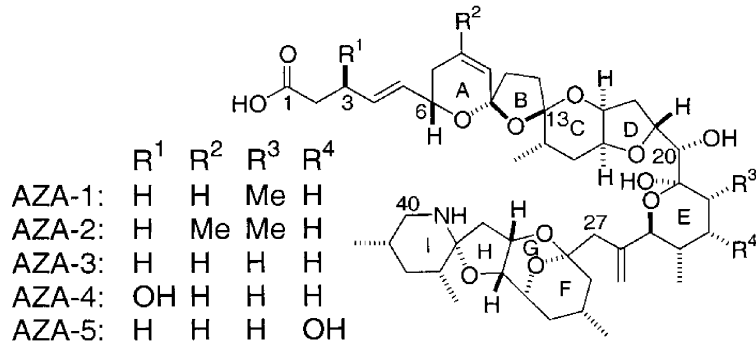


Synthetic Approaches towards Azaspiracid

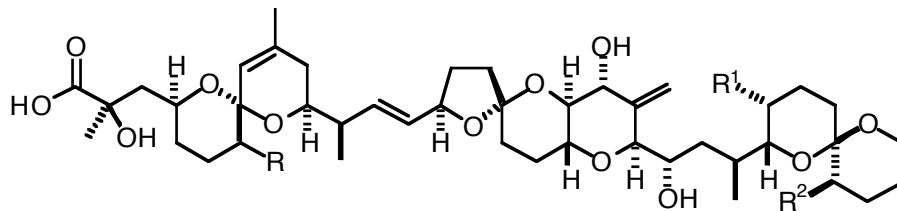


In November, 1995, at least eight people in the Netherlands became ill after eating mussels (*Mytilus edulis*) cultivated at Killary Harbor, Ireland. Although human symptoms such as nausea, vomiting, severe diarrhea, and stomach cramps were reminiscent of diarrhetic shellfish poisoning (DSP), contaminations of the major DSP toxins okadaic acid (OA) and dinophysistoxins (DTXs) were very low.

Isolation/ Structure elucidation: Yasumoto, JACS, **98**, 120, 9967.

-2 mg isolated for 20 kg of whole mussel meat
 -mouse lethality = 0.2 mg/kg

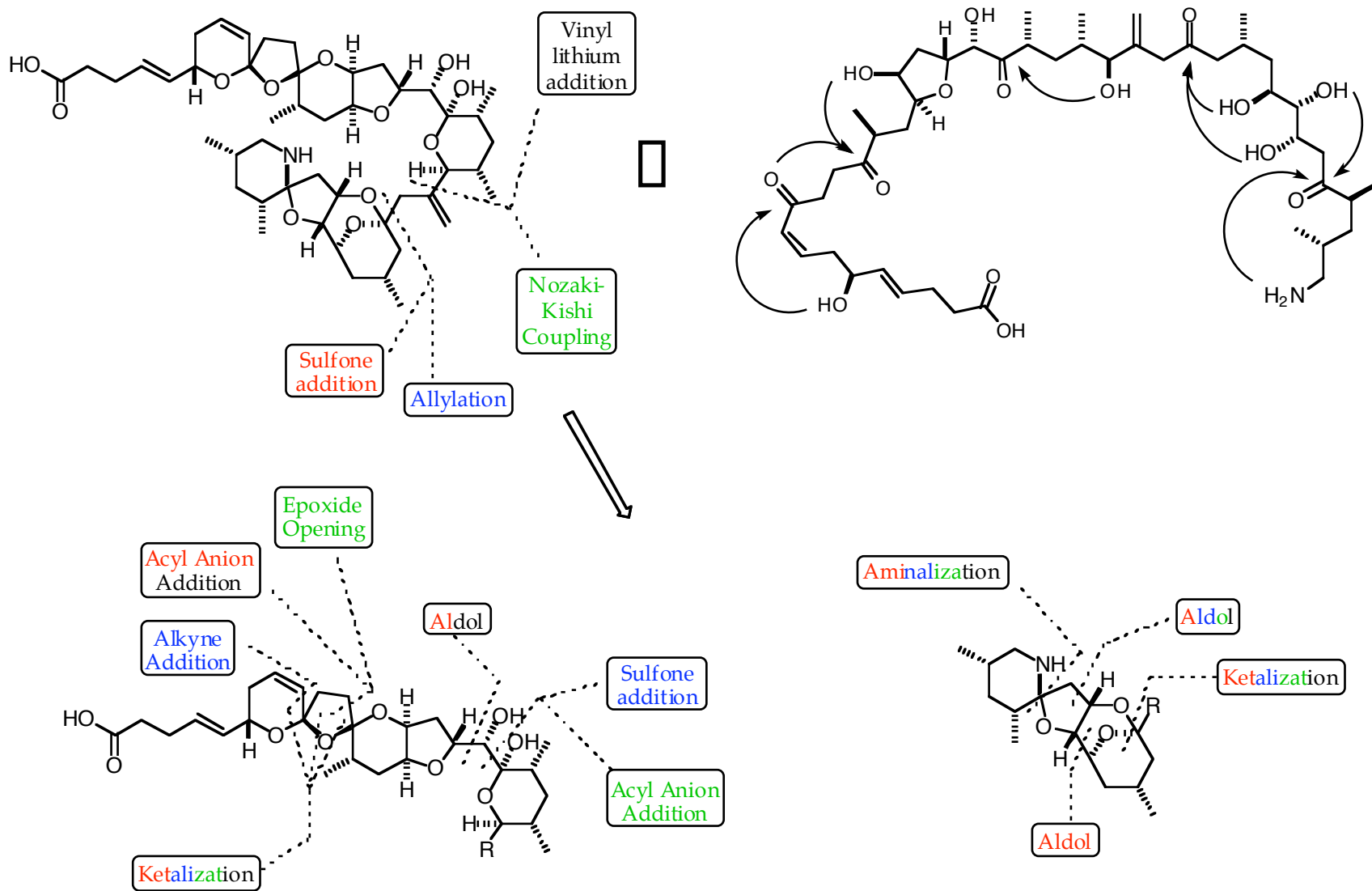
Mode of action is different from known shellfish toxins



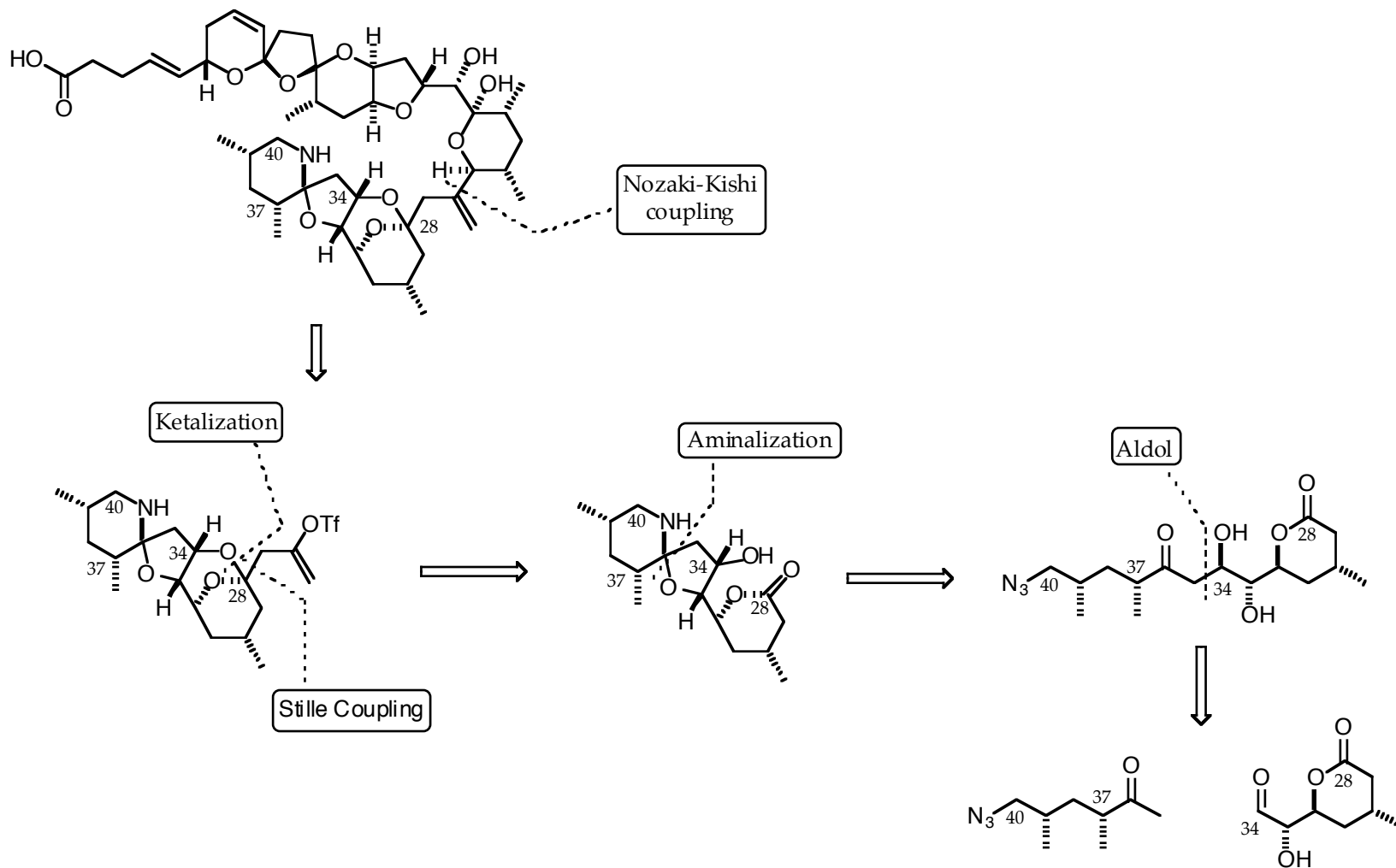
	R	R ¹	R ²
Okadaic acid (OA)	OH	Me	H
Dinophysistoxin-1	OMe	H	Me
Dinophysistoxin-2	OH	H	Me
Dinophysistoxin-3	OAc	H	Me

Jeromy Cottell
 Sept. 11, 2001

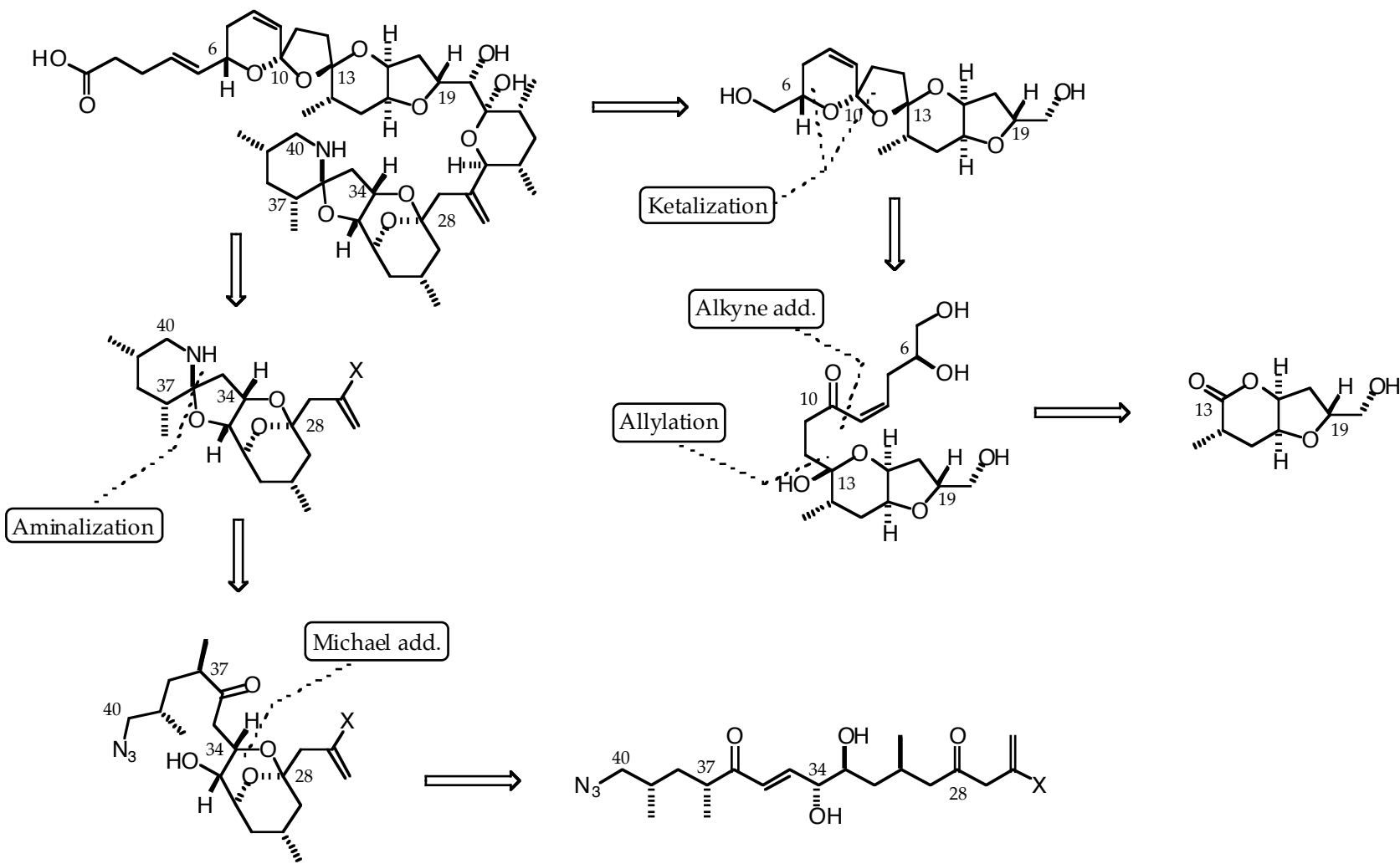
Paper Chemistry (Group A, B, C, and D retros)



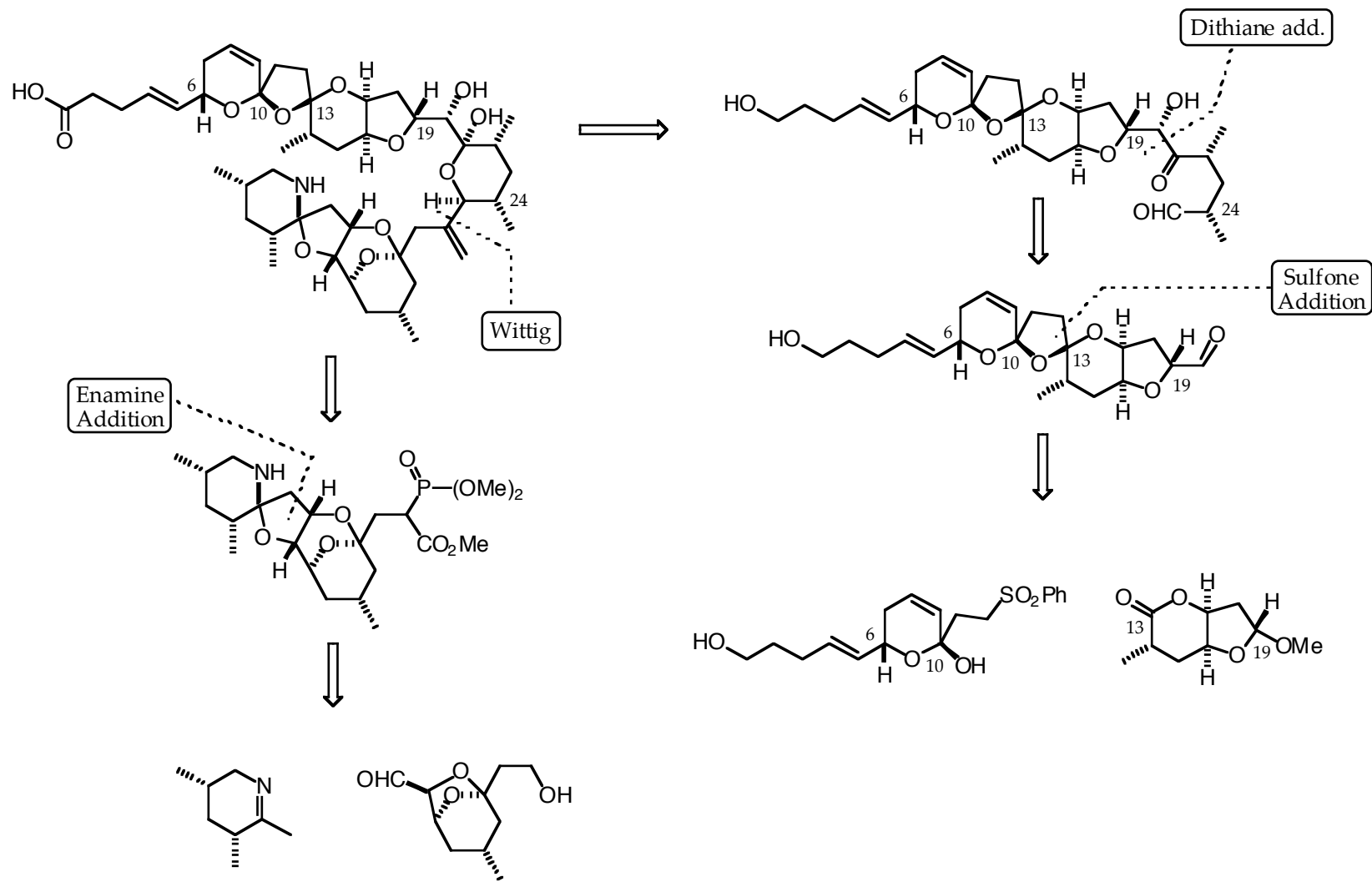
Retrosynthesis - Nicolaou



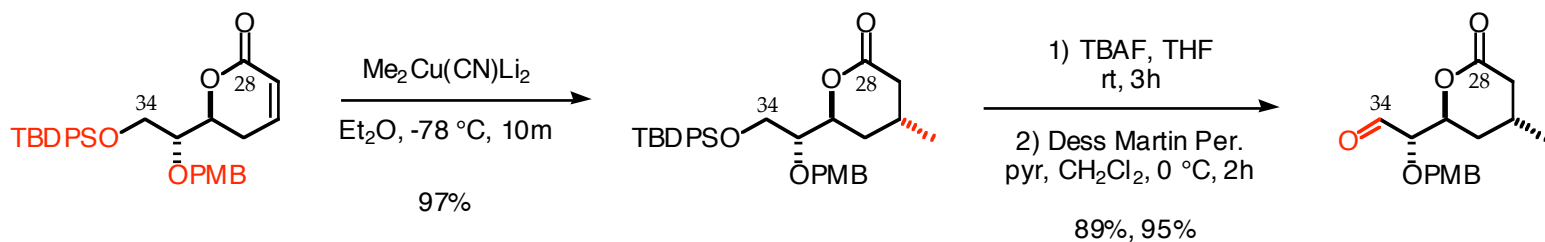
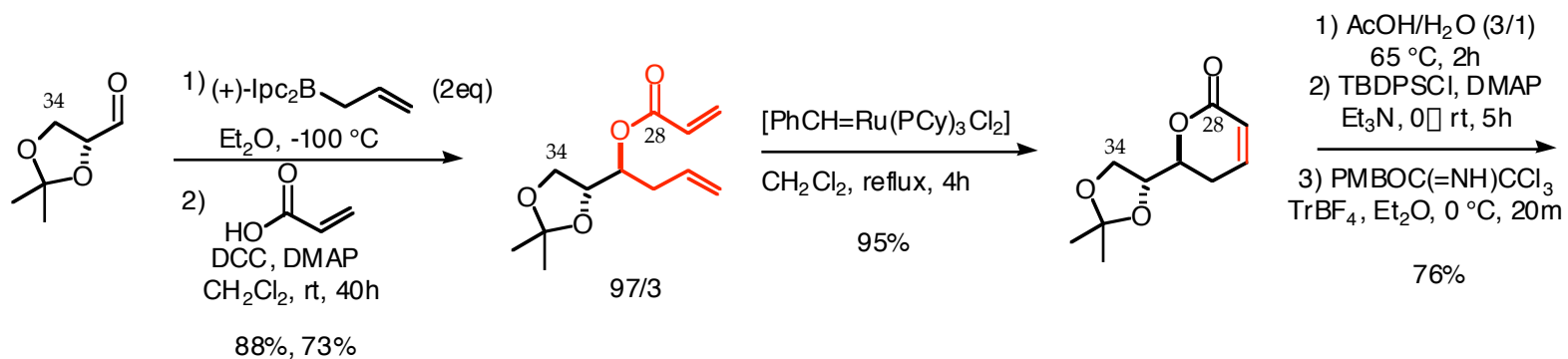
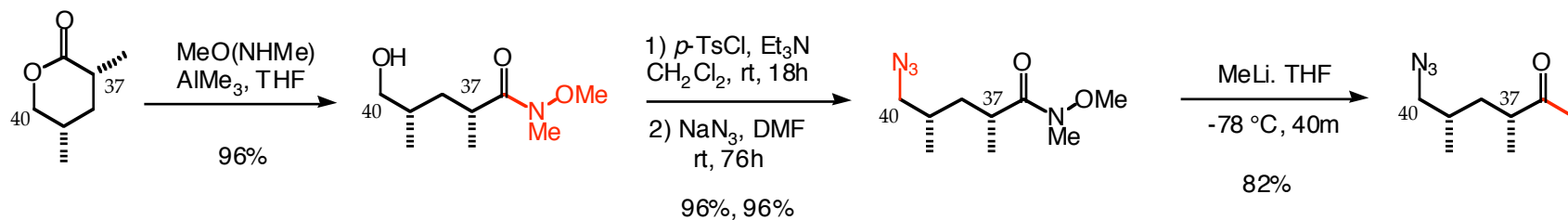
Retrosynthesis - Forsyth



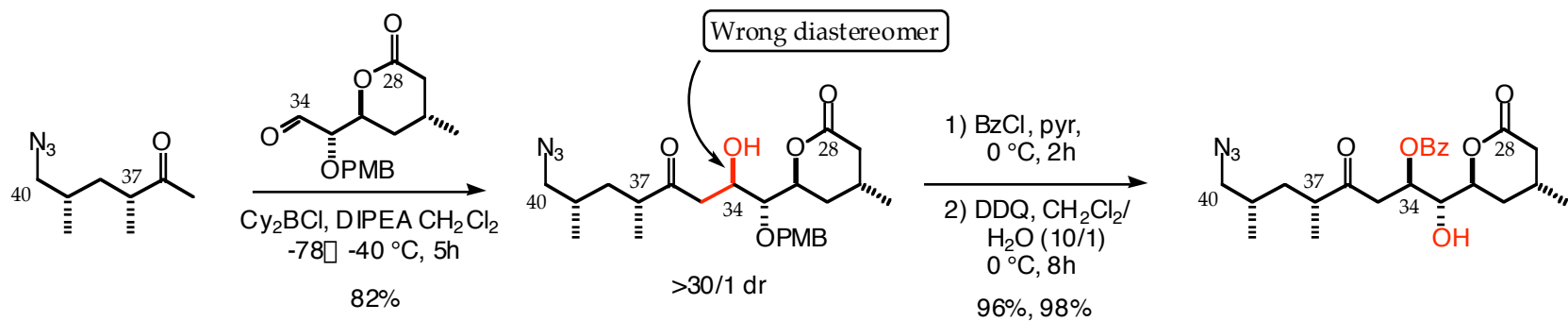
Retrosynthesis - Carter



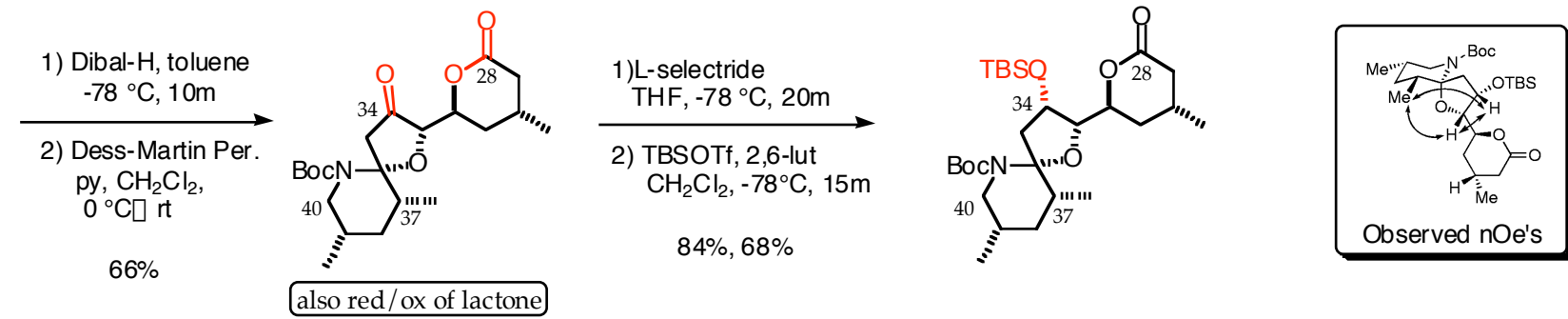
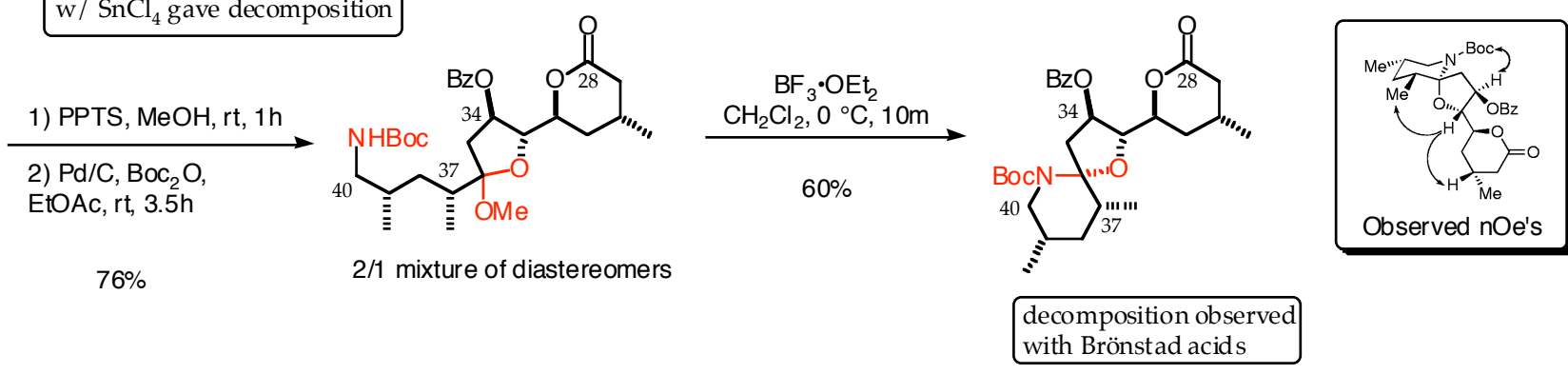
South Section - Nicolaou



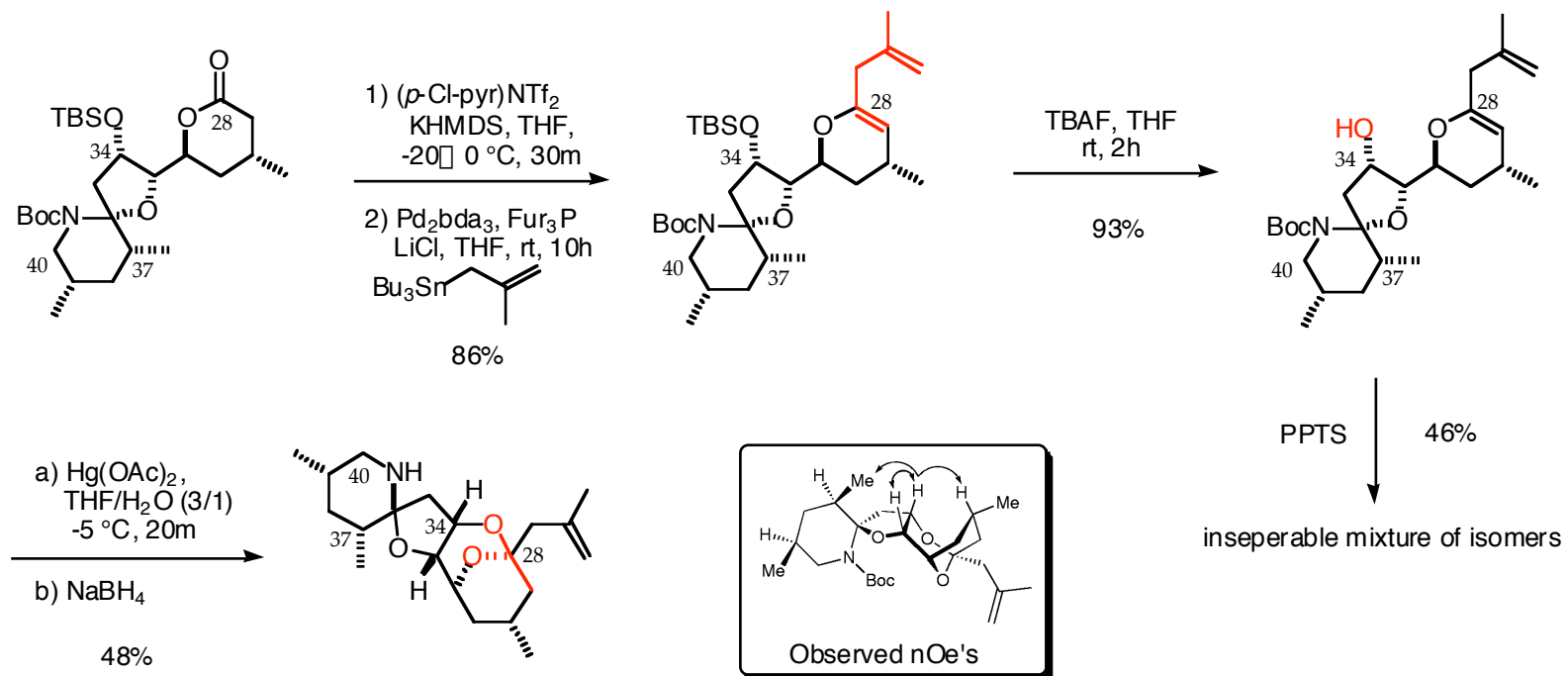
South Section - Nicolaou



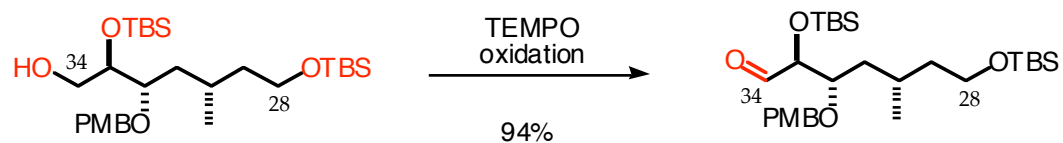
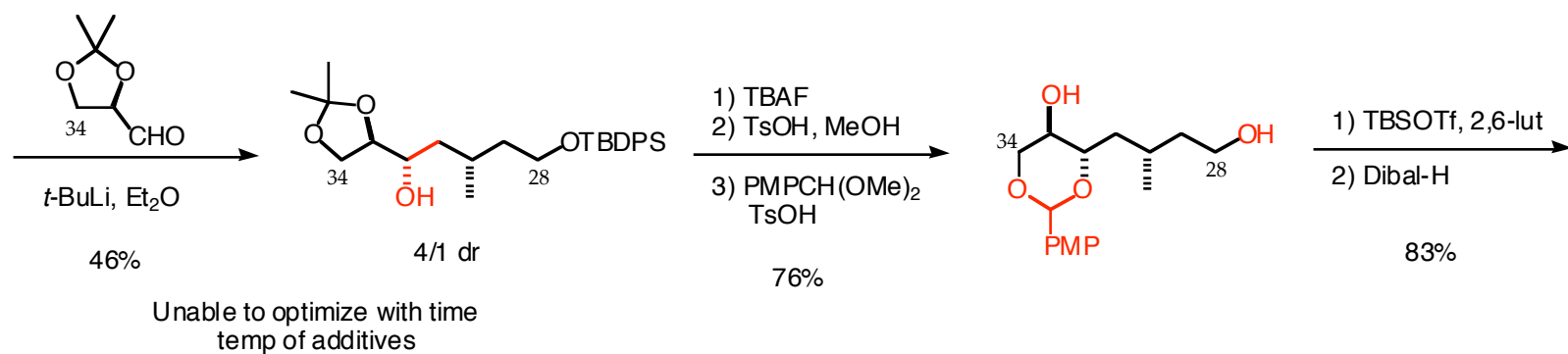
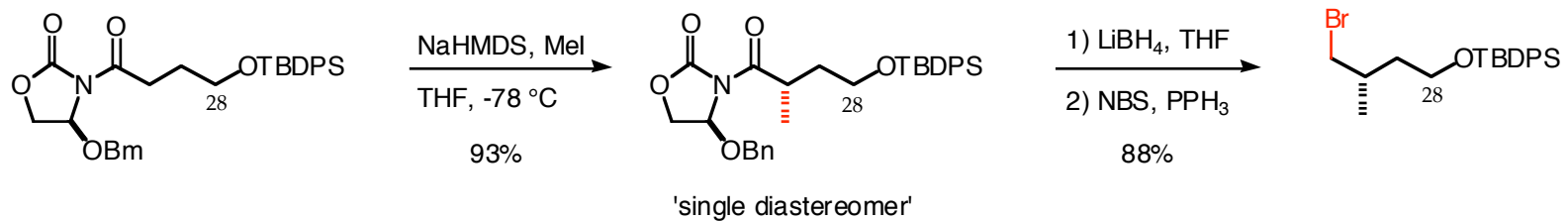
Chelation controlled addition w/ SnCl_4 gave decomposition



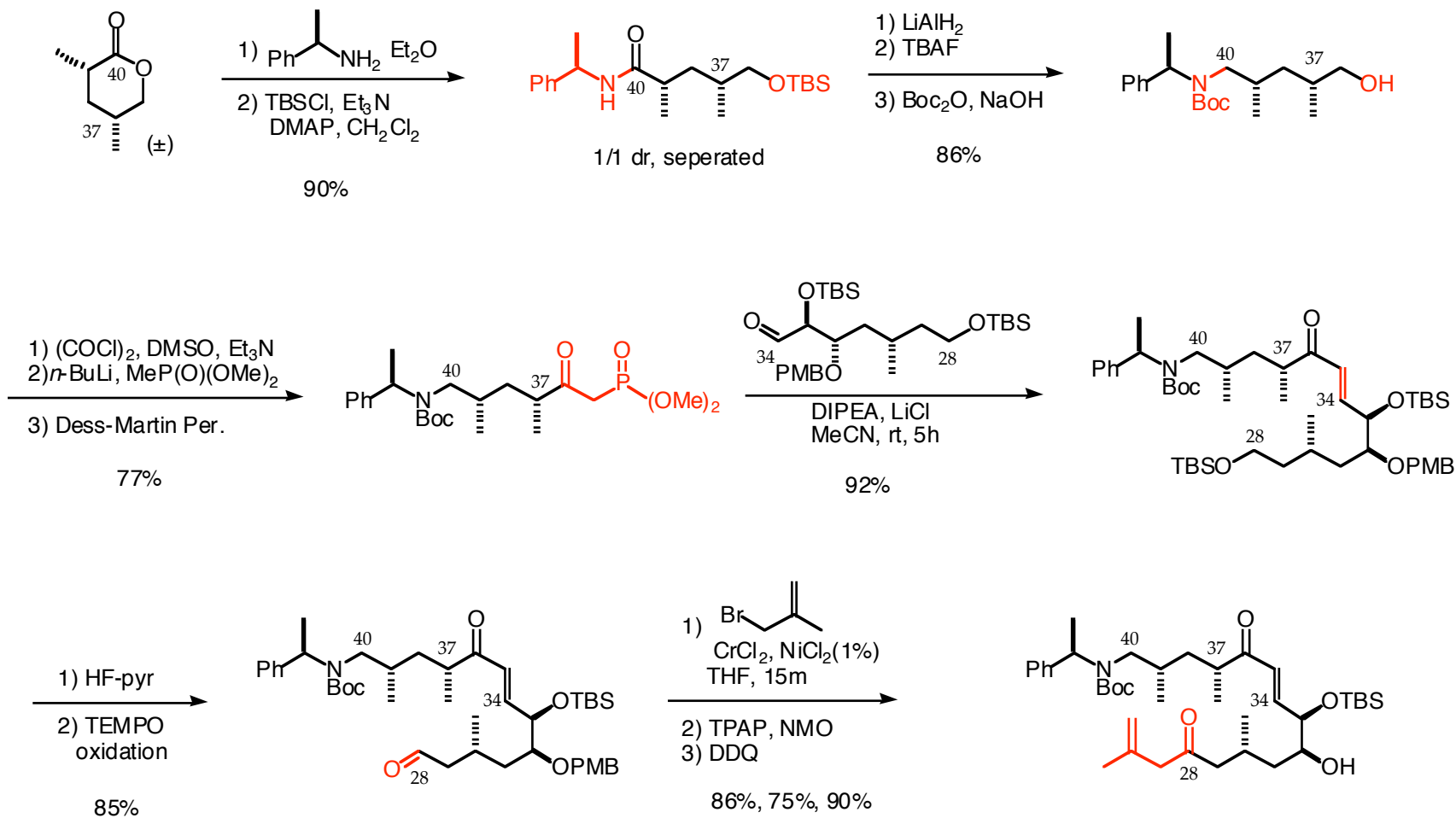
South Section - Nicolaou



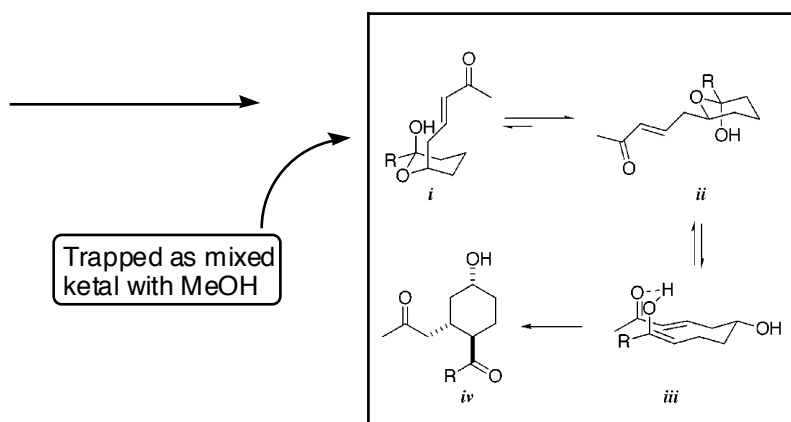
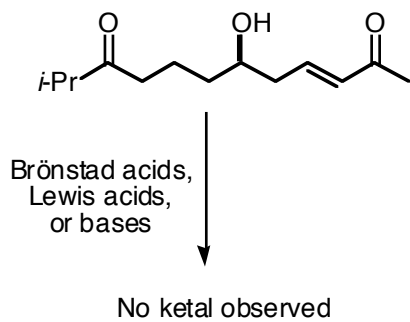
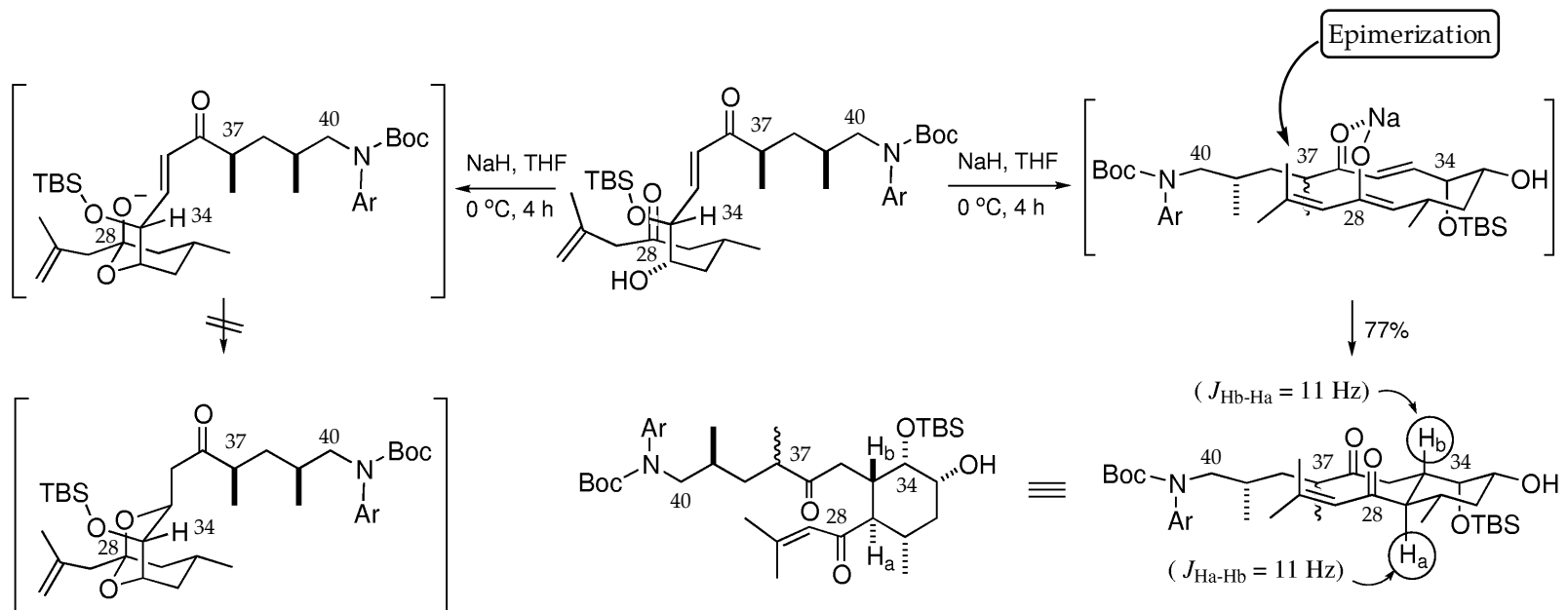
South Section - Forsyth



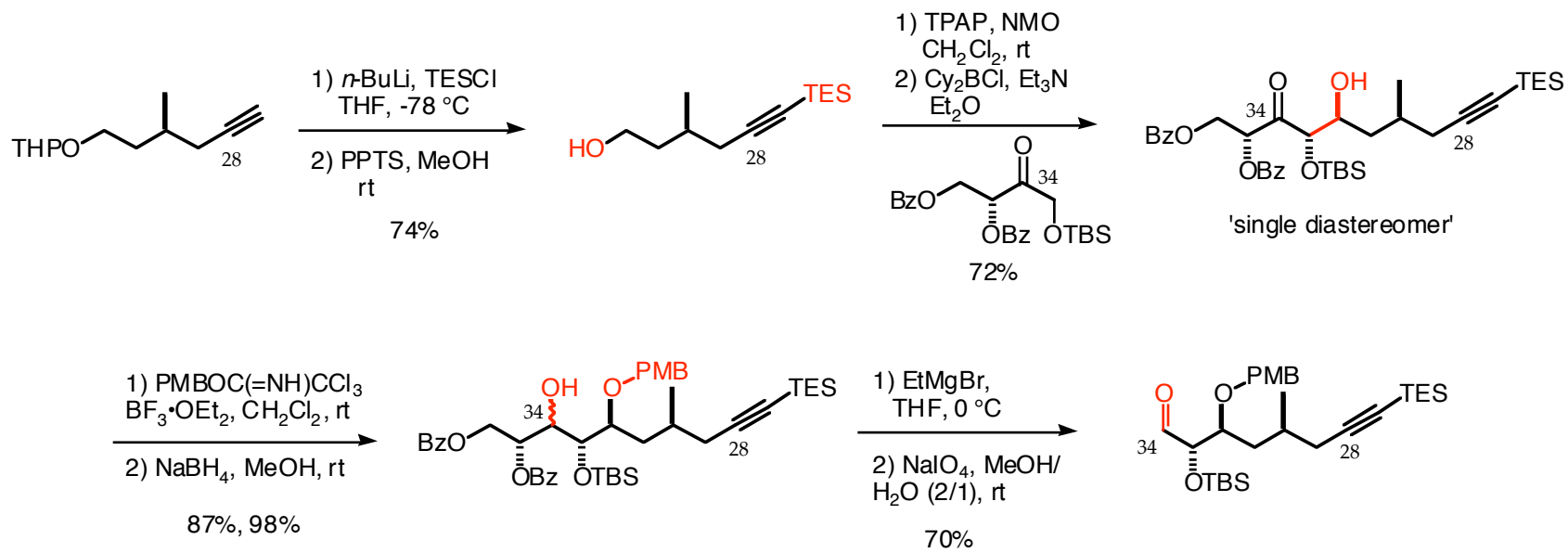
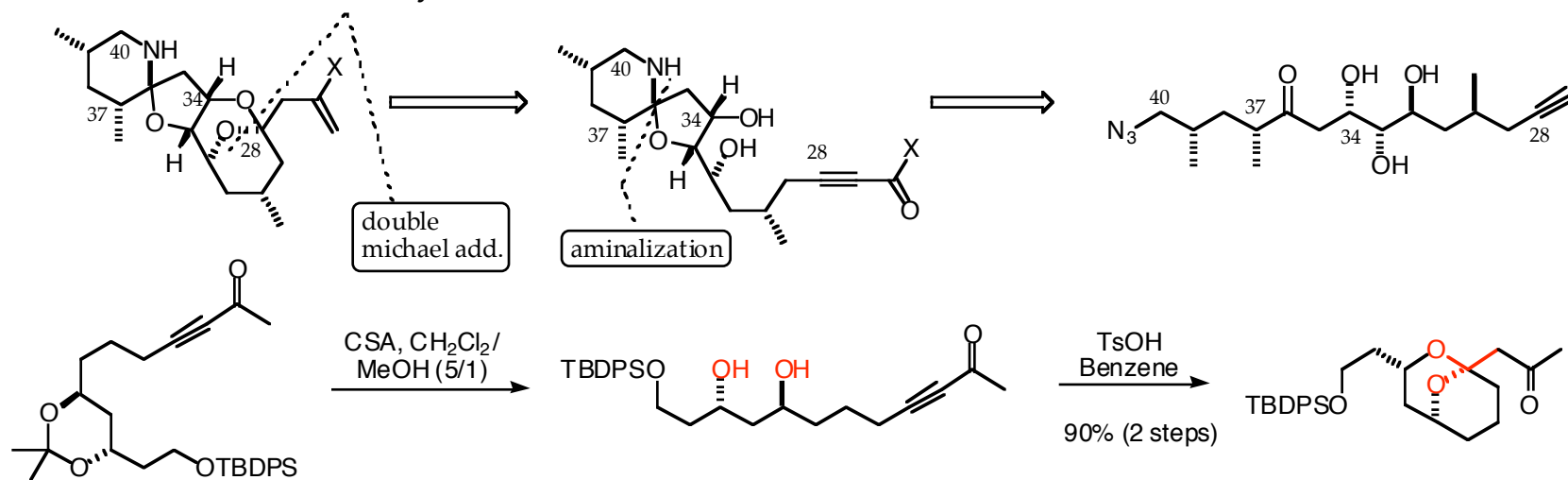
South Section - Forsyth



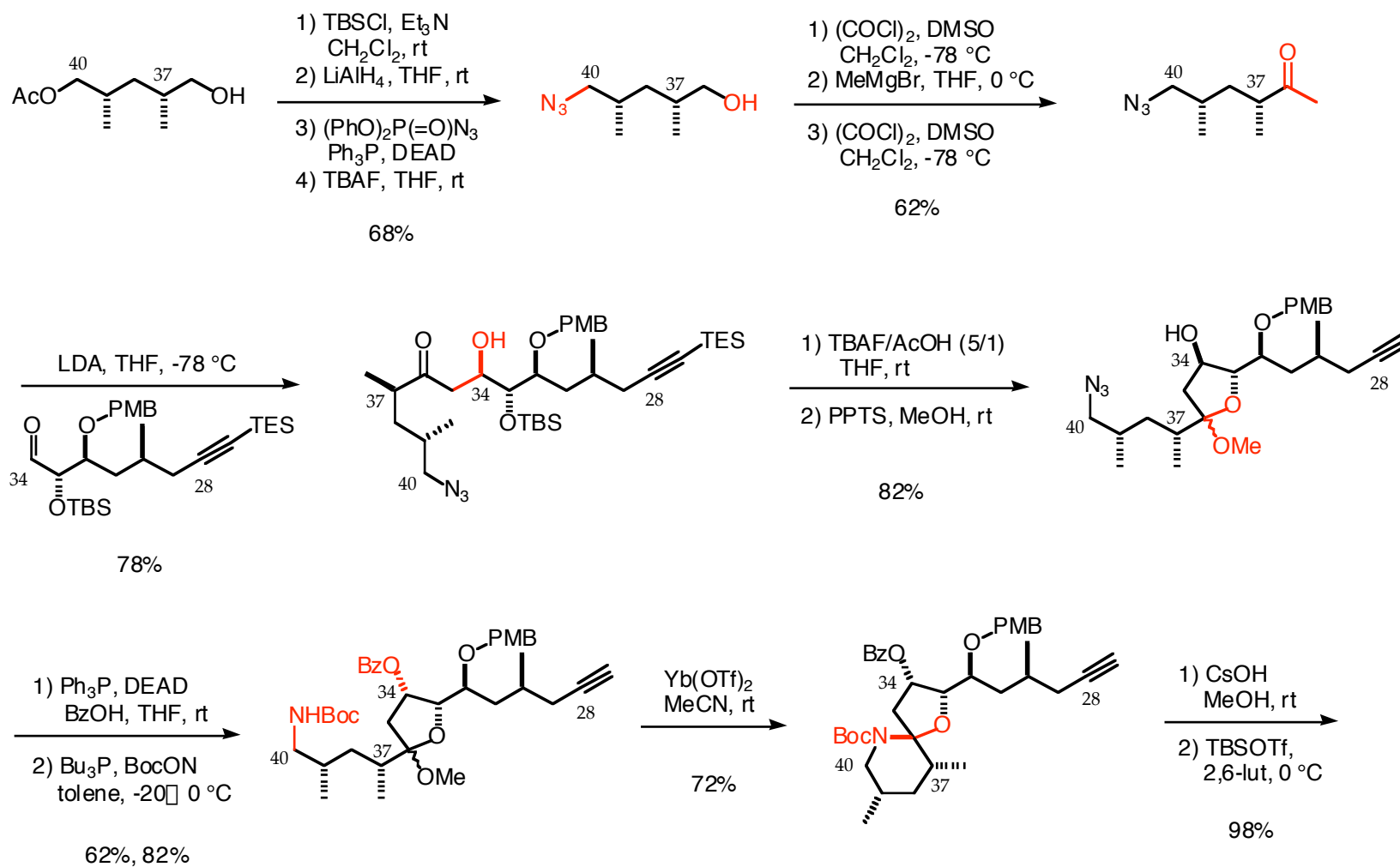
South Section - Forsyth



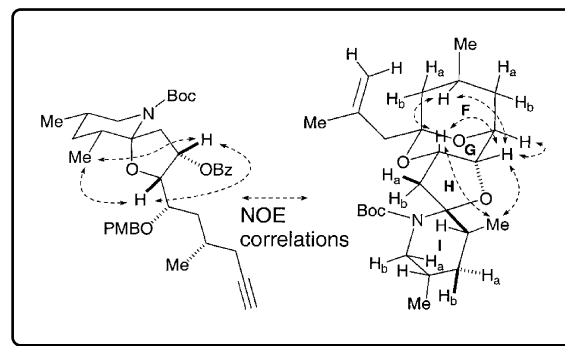
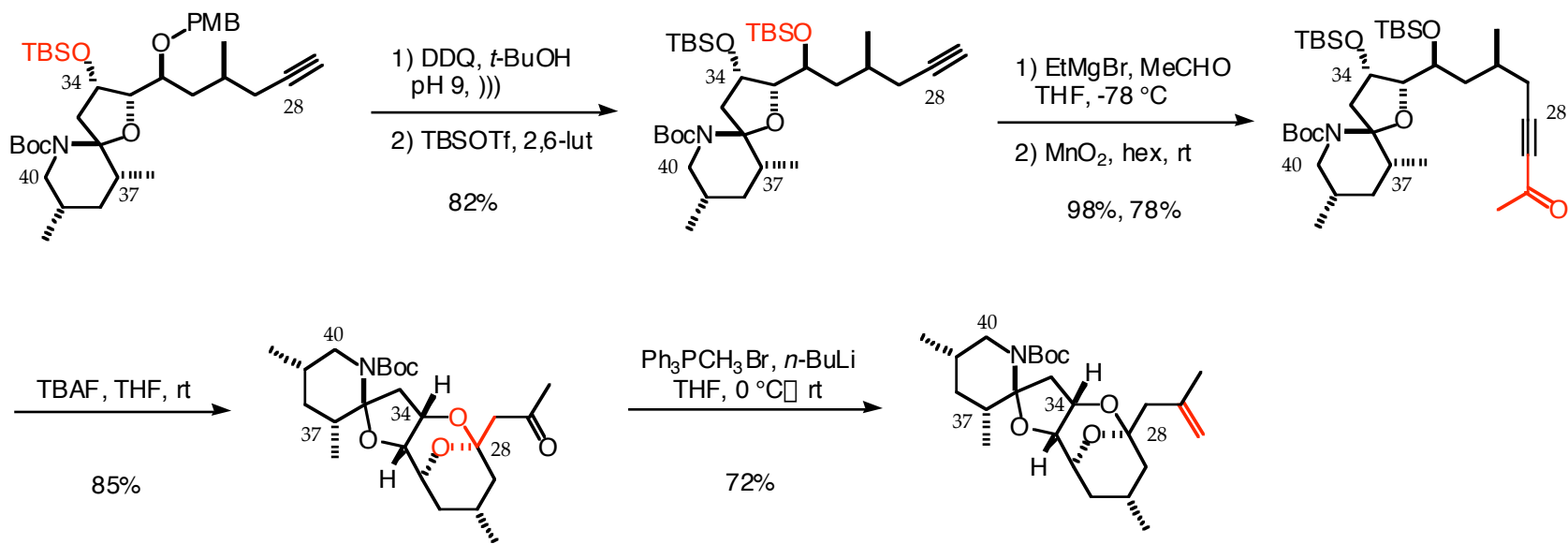
South Section - Forsyth (revised)



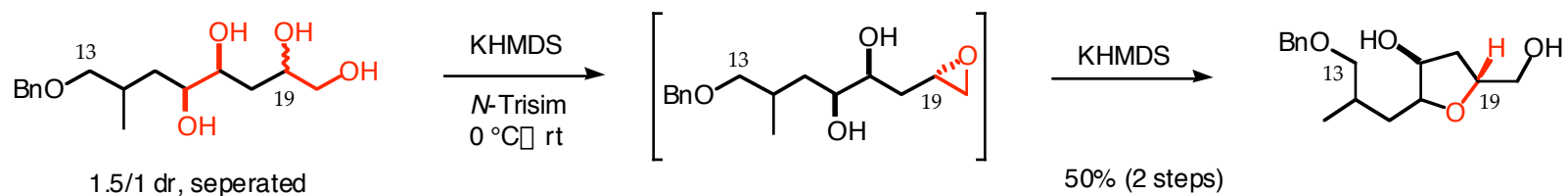
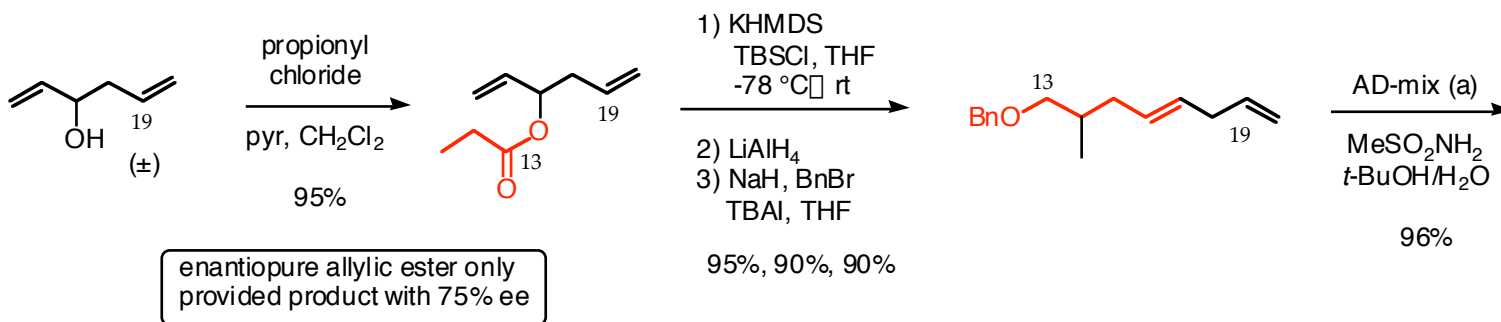
South Section - Forsyth (revised)



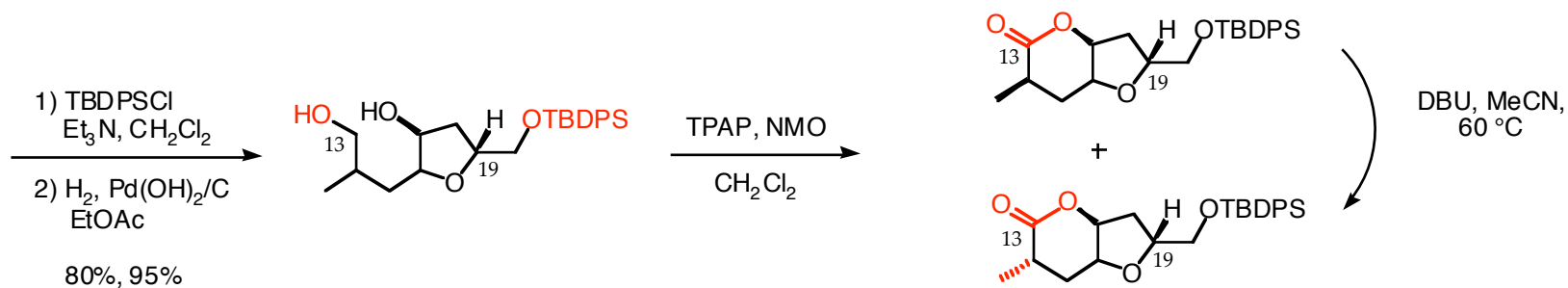
South Section - Forsyth (revised)



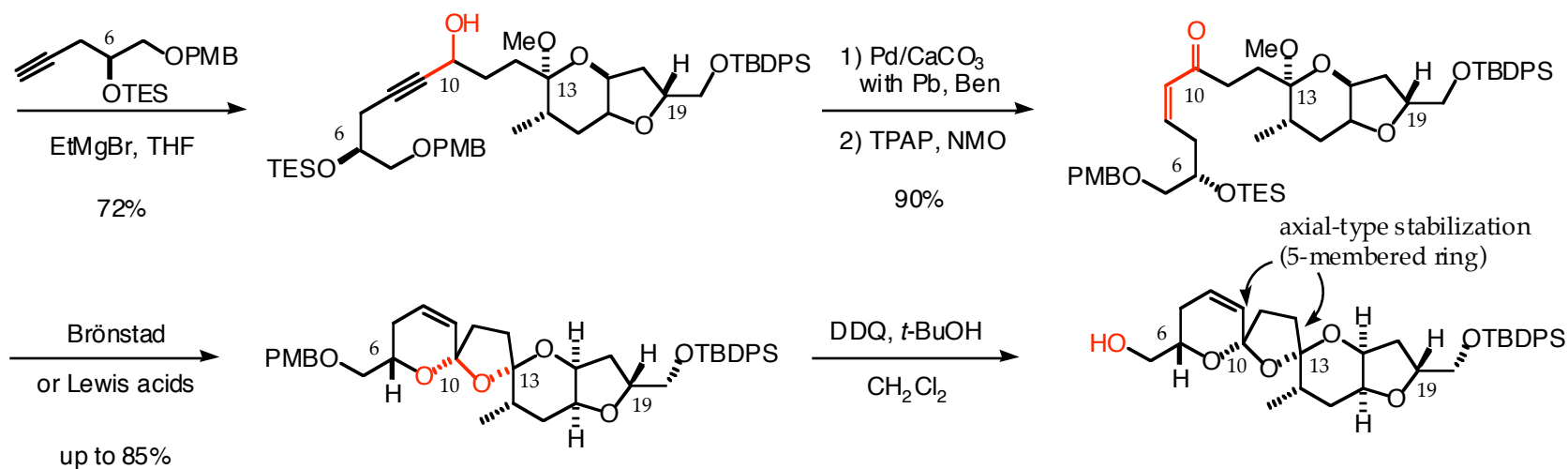
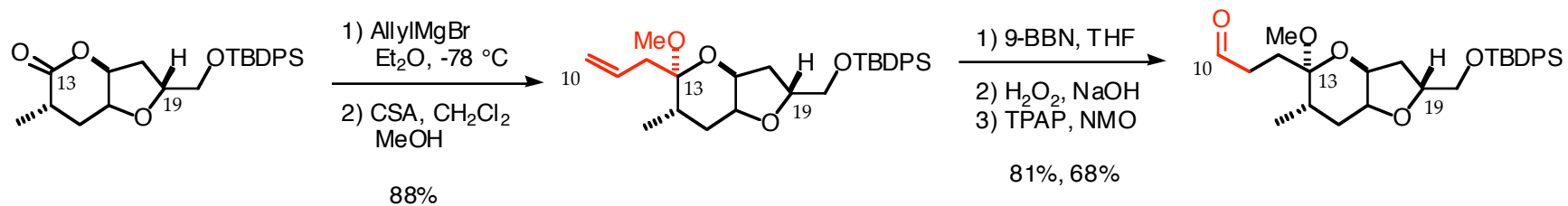
North Section - Forsyth



other ligands did not help dr

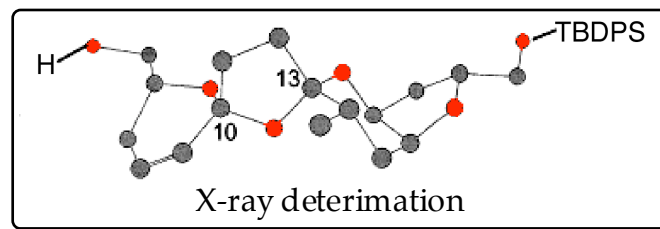


North Section - Forsyth



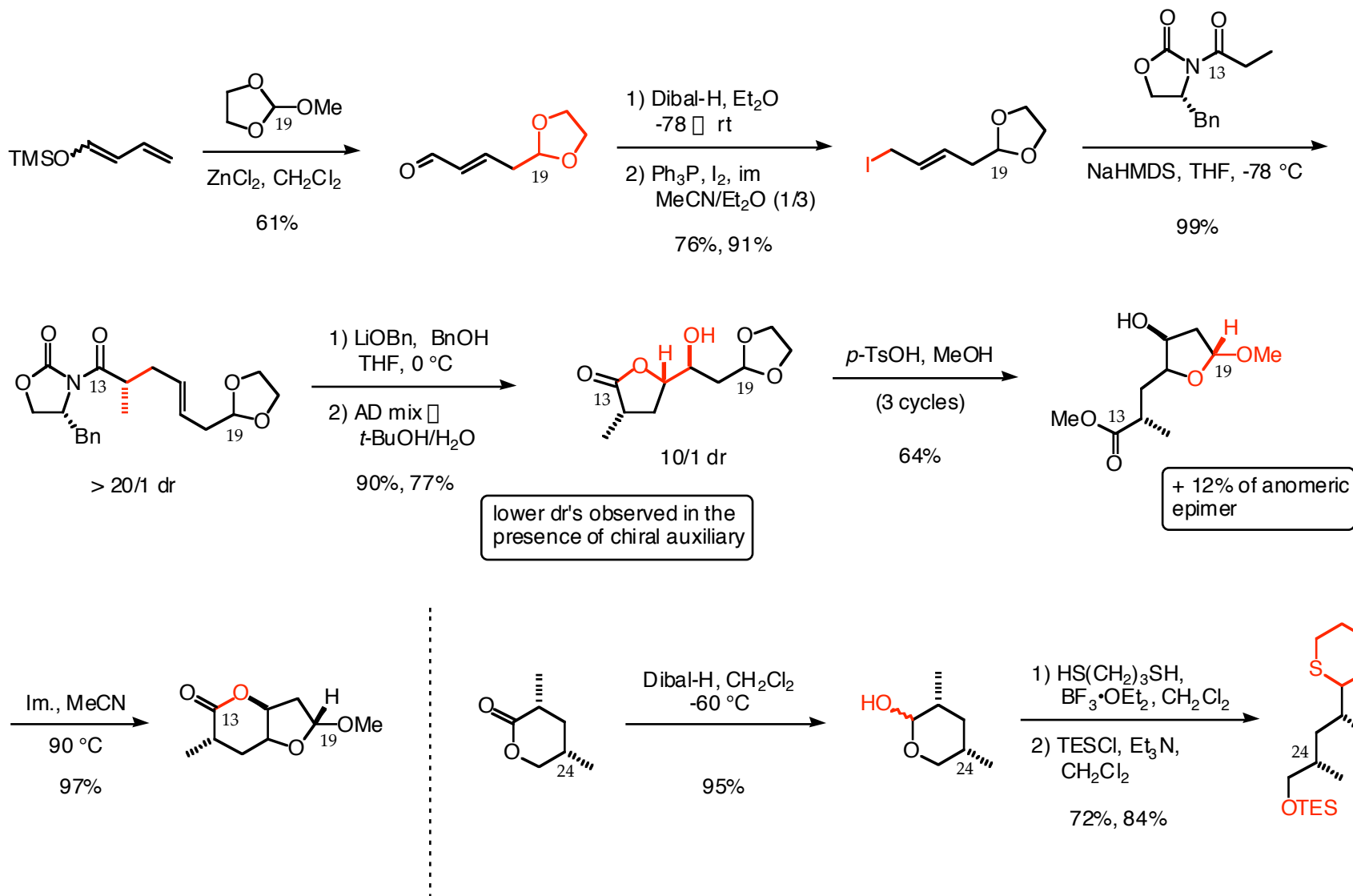
7/3 □ 1/0 dr
 Minor pdt is of
 unknown config.

Observed diastereomer is found to be 2-3 kcal/mol
 lower than the natural configuration

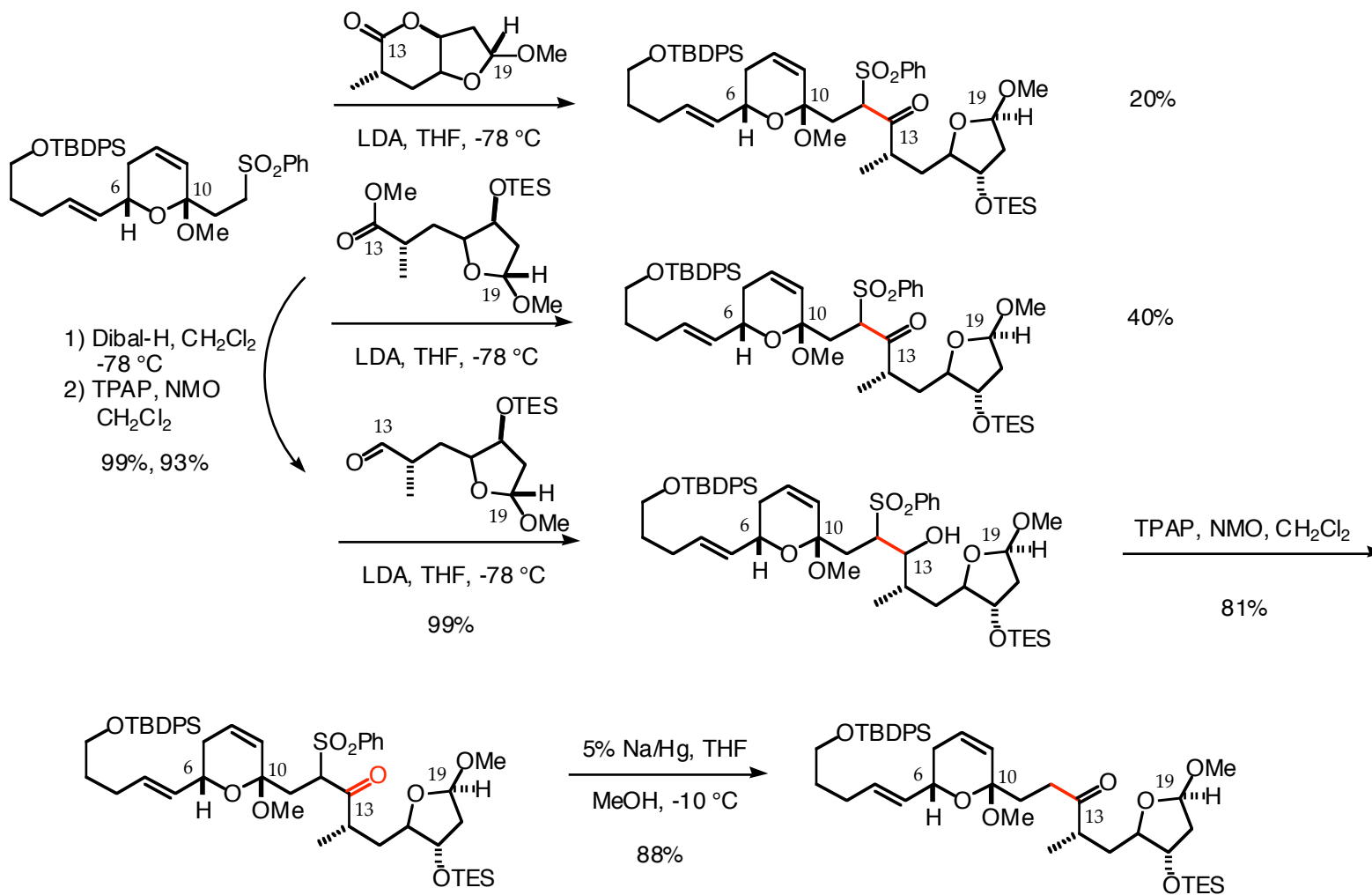


Axial attack of O-C(10) on oxonium ion C(13)

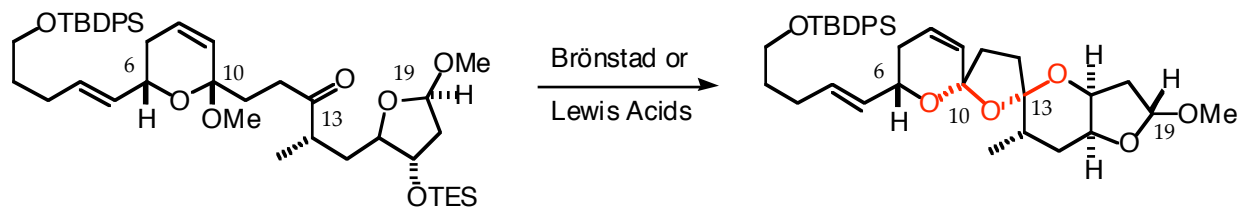
North Section - Carter



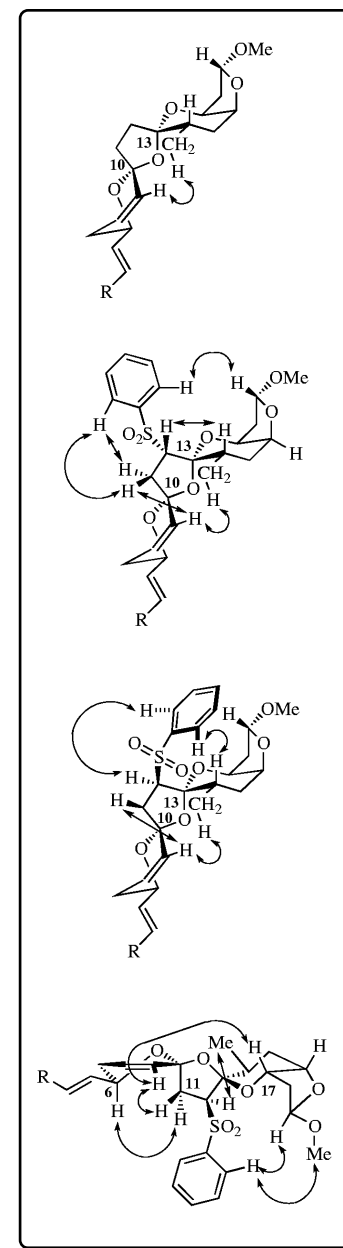
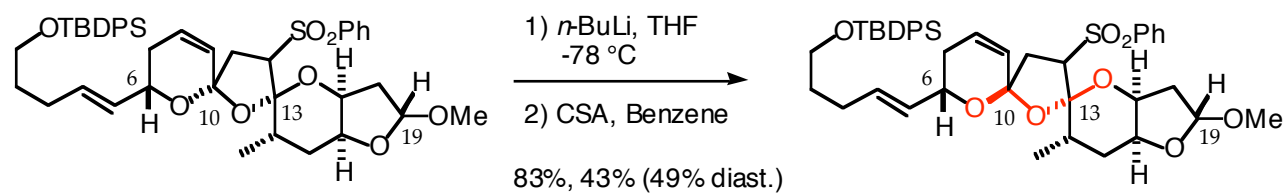
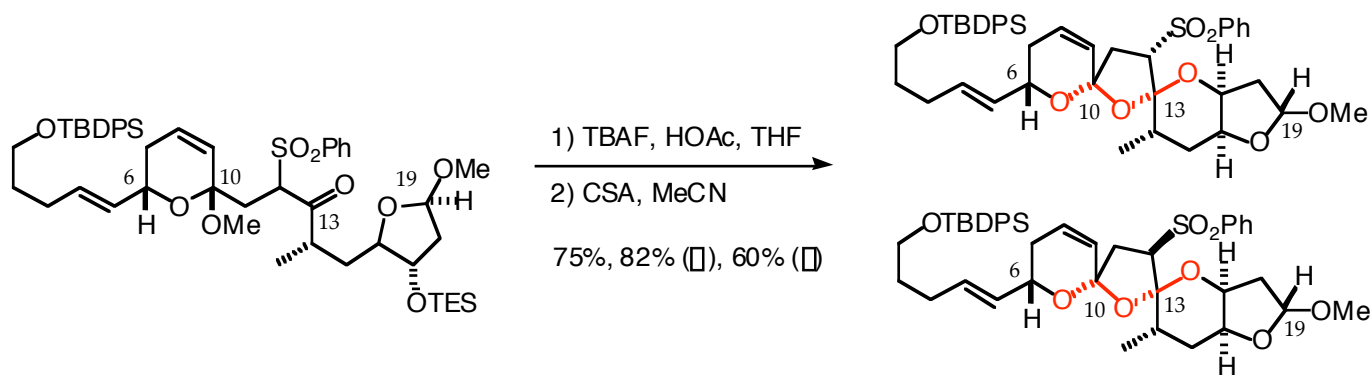
North Section - Carter



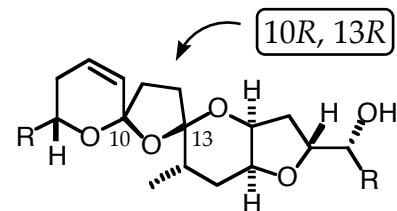
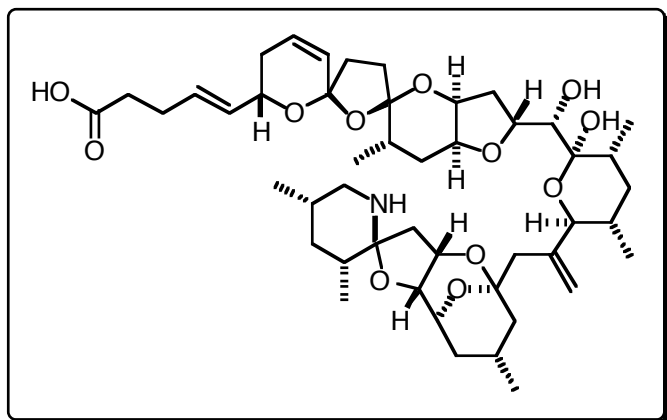
North Section - Carter



Observed diastereomer is found to be 7 kcal/mol lower than the natural configuration (ab initio calc)



Synthetic Approaches towards Azaspiracid

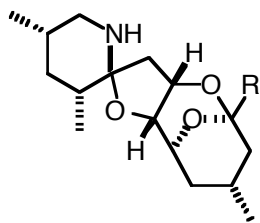


Unsuccessful Syntheses:

Forsyth → Prepared 10R, 13S diastereomer

Carter → Prepared both 10R, 13S and 10S, 13S diastereomers

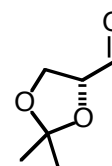
Cannot assume that the configuration present in a natural product will be the preferred one, even with most of the architecture intact



Successful Syntheses:

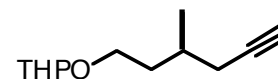
Nicolaou → 27 total steps

23 steps (1.88%) from



Forsyth → 29 total steps

22 steps (2.80%) from



Natural products do not always have the most stable configuration

References:

Isolation:

Yasumoto *JACS*, **1998**, *120*, 9967

Yasumoto *Natural Toxins*, **1999**, *7*, 99

Yasumoto *Biosci., Biotechnol., Biochem.*, **2001**, *65*, 740

Reviews (spiroacetals)

Brimble *Tetrahedron*, **1999**, *55*, 7661

Albizati *Chem. Rev.*, **1989**, *89*, 1617

Syntheses

Nicholaou *Angew. Chem. Int. Ed.*, **2001**, *40*, 1262

Nicholaou *Angew. Chem. Int. Ed.*, **2001**, *40*, 1573

Forsyth *Tetrahedron Lett.*, **2001**, *42*, 817

Forsyth *Tetrahedron Lett.*, **2001**, *42*, 821

Forsyth *Org. Lett.*, **2001**, *3*, 975

Forsyth *Org. Lett.*, **2001**, *3*, 979

Carter *Org. Lett.* **2000**, *2*, 3913

Carter *Tetrahedron Lett.*, **2001**, *42*, 6035