

# *Approaches to the Total Synthesis of the Manzamine Alkaloids*

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DAE Group Friday Afternoon Seminar  
January 21, 2000

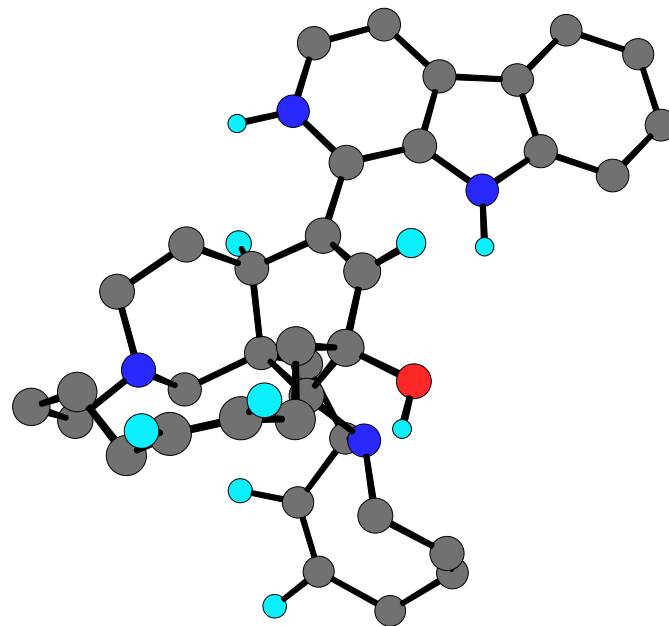
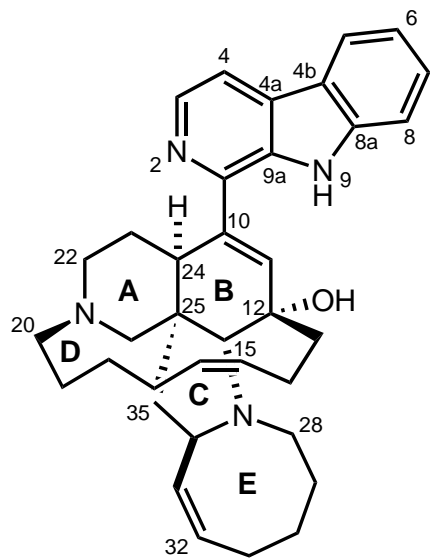
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  - Azomethine Ylide Cycloaddition (Coldham)
  - Intramolecular Substitution (Yamamura)
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  - Winkler
  - Martin
- Summary

## **Leading References :**

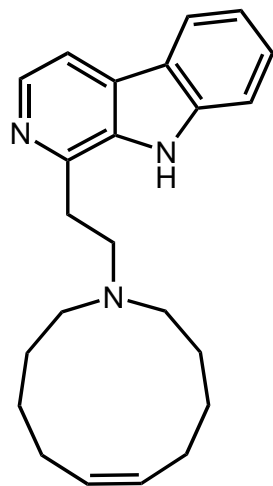
Magnier, E; Langlois Y. *Tetrahedron* **1998**, *54*, 6201  
Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425  
Martin, S. F.; Humphrey, J. M.; Ali, A.; Hiller, M. C.  
*J. Am. Chem. Soc.* **1999**, *121*, 866

## Manzamine A : Discovery and Structural Elucidation

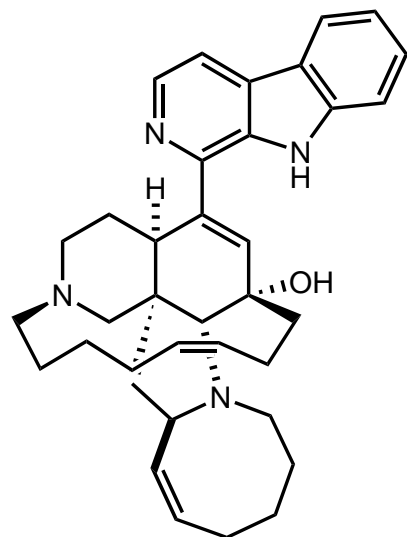


- Manzamine A isolated in 1986 by Higa *et al*, from the marine sponge *Haliclona* (*J. Am. Chem. Soc.* **1986**, 108, 6404).
- Structure of manzamine A was assigned by X-ray crystal analysis of the hydrochloride salt.
- Manzamine A shown to have significant *in vitro* activity, with an IC<sub>50</sub> of 0.07 µg/mL against P388 mouse leukaemia cells.
- Subsequently, many congeners of the manzamine family of alkaloids have been isolated (Magnier *et al*, *Tetrahedron* **1998**, 54, 6201).
- ".....the structure of manzamine A hydrochloride is unprecedented in nature. Moreover, its provenance is problematic as there appears to be no obvious biogenetic pathway..." Higa (1986)
- In 1992, Baldwin and Whitehead proposed a possible biogenetic pathway for the biosynthesis of manzamines A, B and C (*Tetrahedron Lett.* **1992**, 33, 2059)

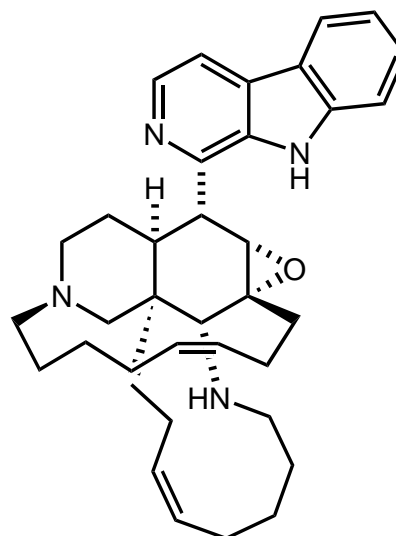
# The Manzamine Family of Alkaloids : Representative Members



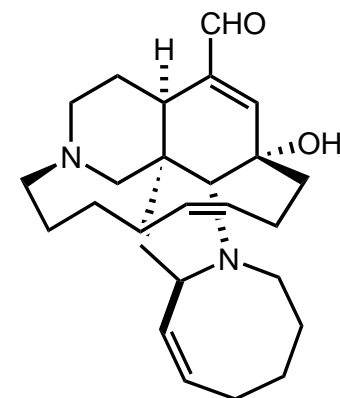
Manzamine C



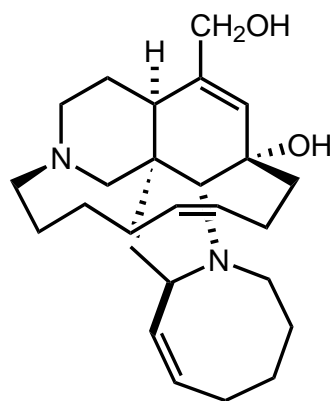
Manzamine A



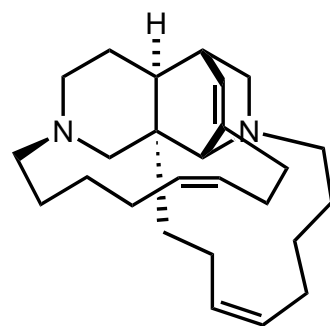
Manzamine B



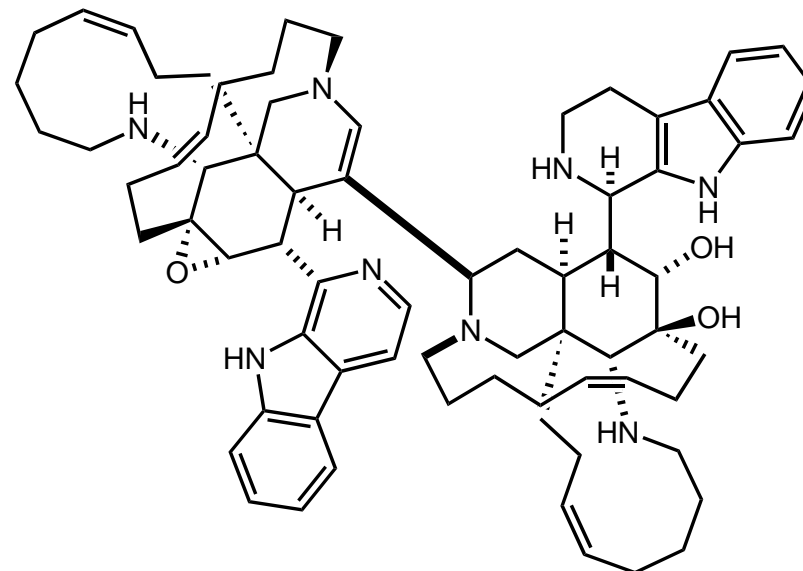
Ircinal A



*ent*-Ircinol A?  
(absolute configuration not unambiguously assigned yet)

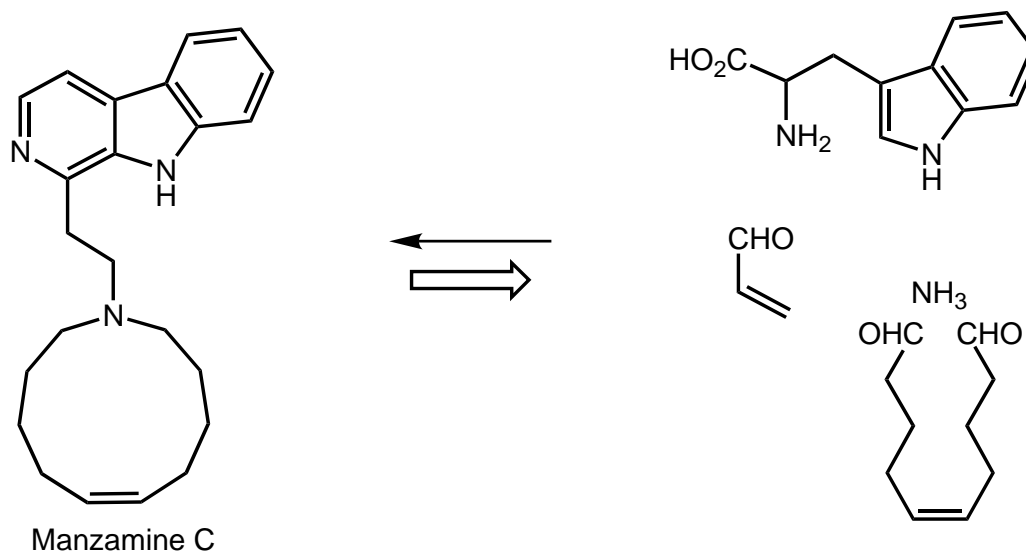


Keramaphidin B  
(isolated as a racemic mixture)



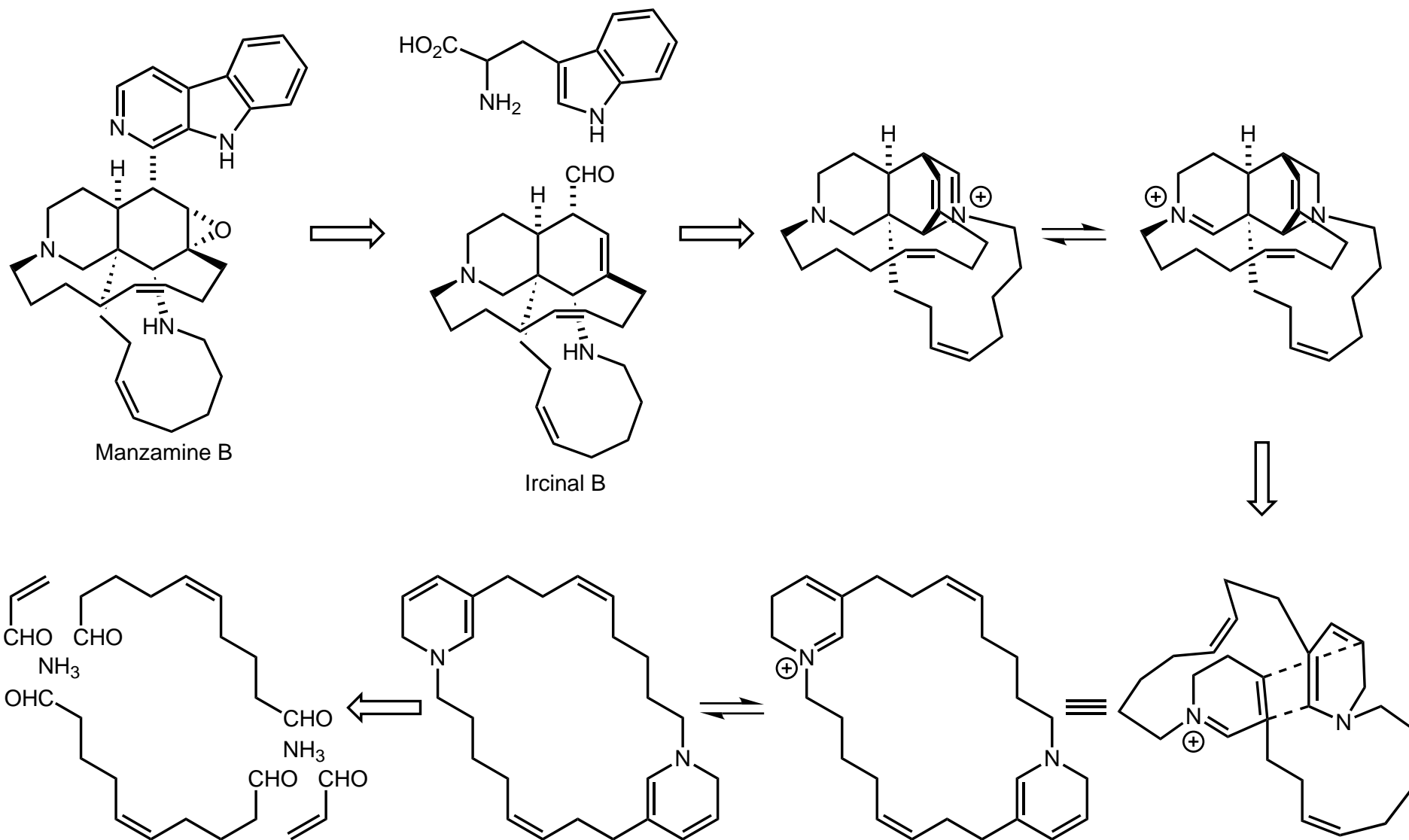
Kauluamine

## Biosynthesis of Manzamine C

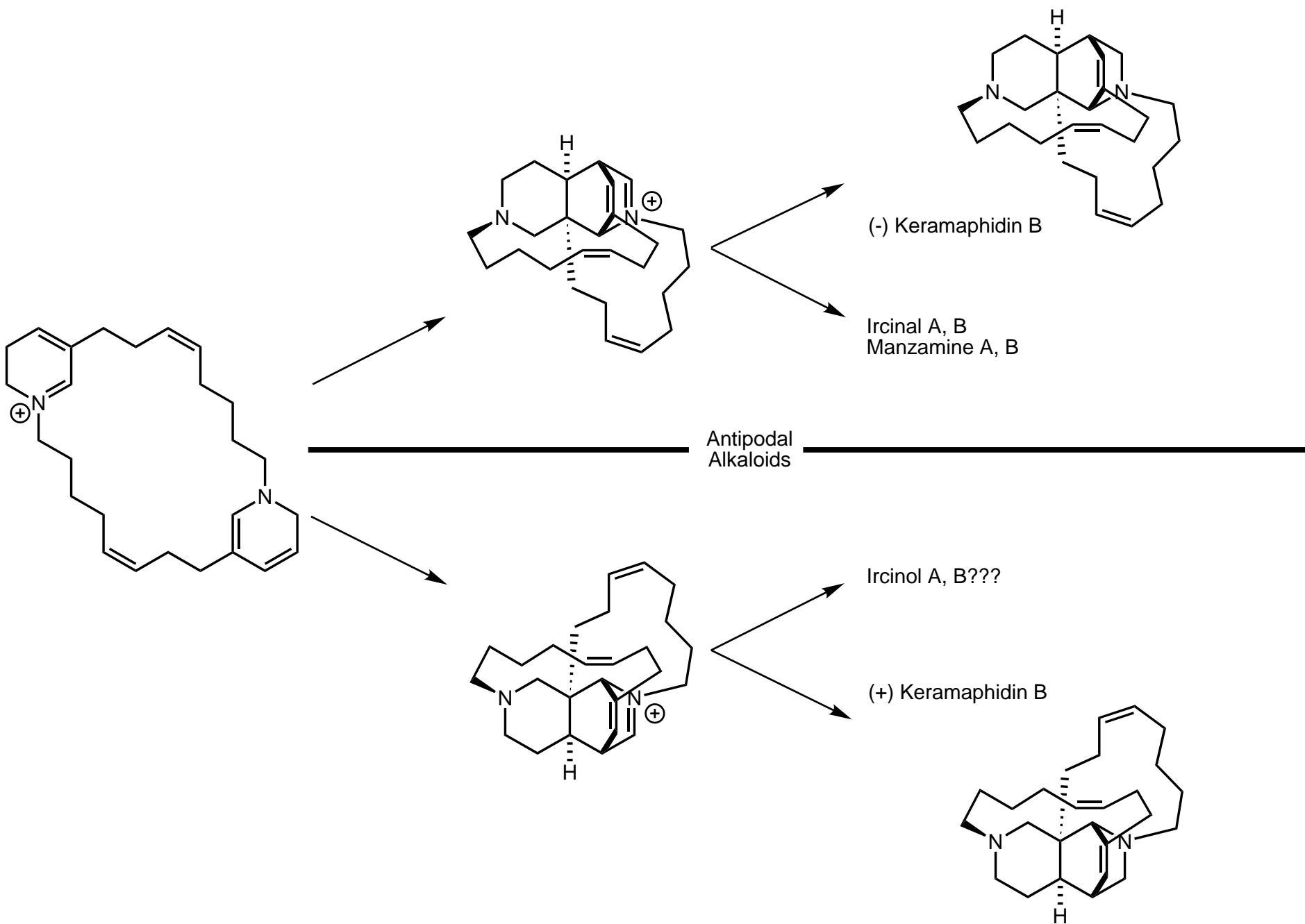


- Manzamine C thought to arise from the condensation of a dialdehyde, ammonia, acrolein and tryptophan (Baldwin *et al*, *Tetrahedron Lett.* **1992**, 33, 2059).
- Despite the rather simple structure, some biological activity is retained in this molecule.
- For total syntheses, see :
  - Nakagawa *et al*, *Tetrahedron* **1991**, 47, 8067
  - Gerlach *et al*, *Liebigs Ann. Chem.* **1993**, 153

## Manzamine B Biosynthesis

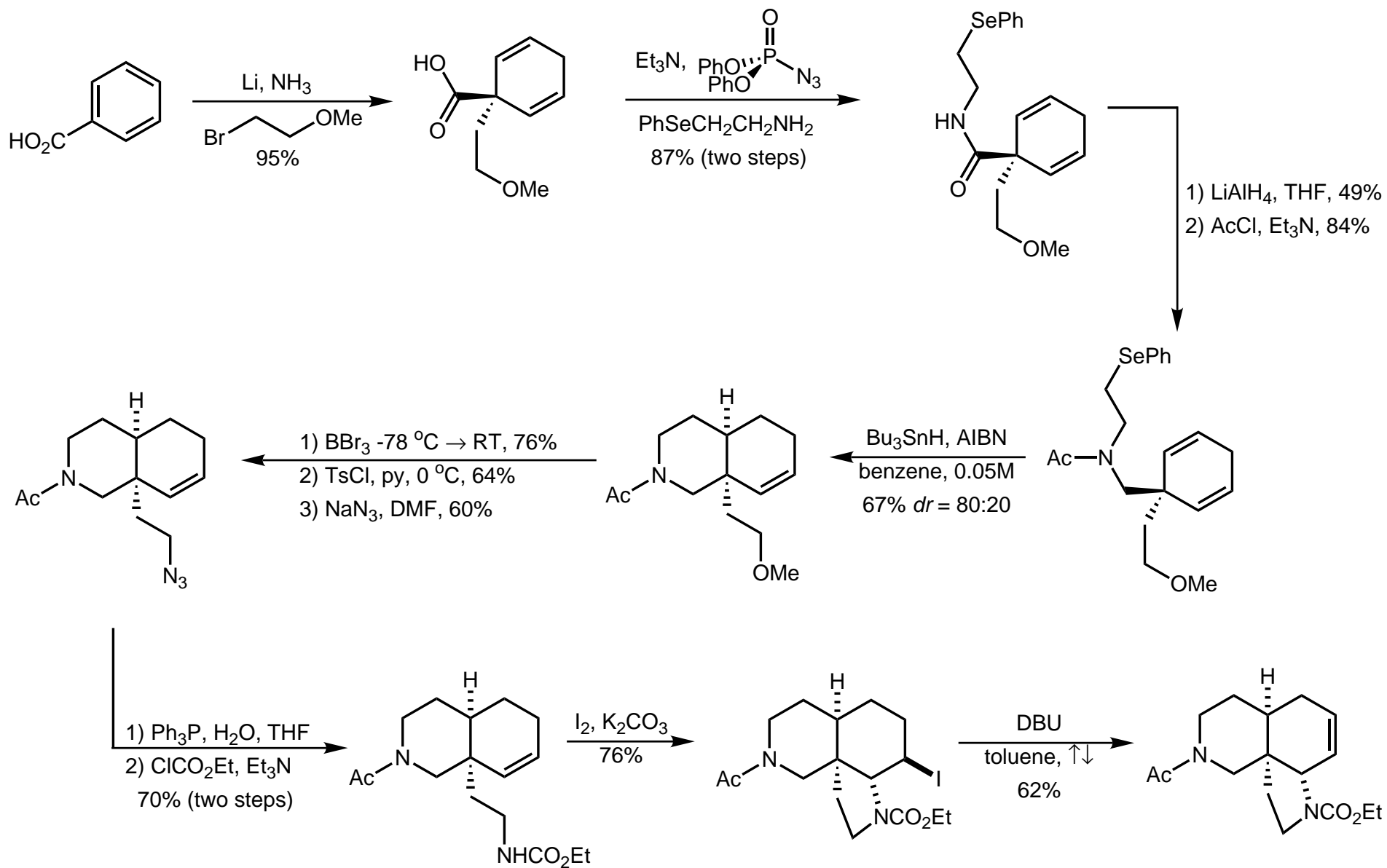


# Manzamine Biosynthesis : Both Antipodes Produced by Nature?



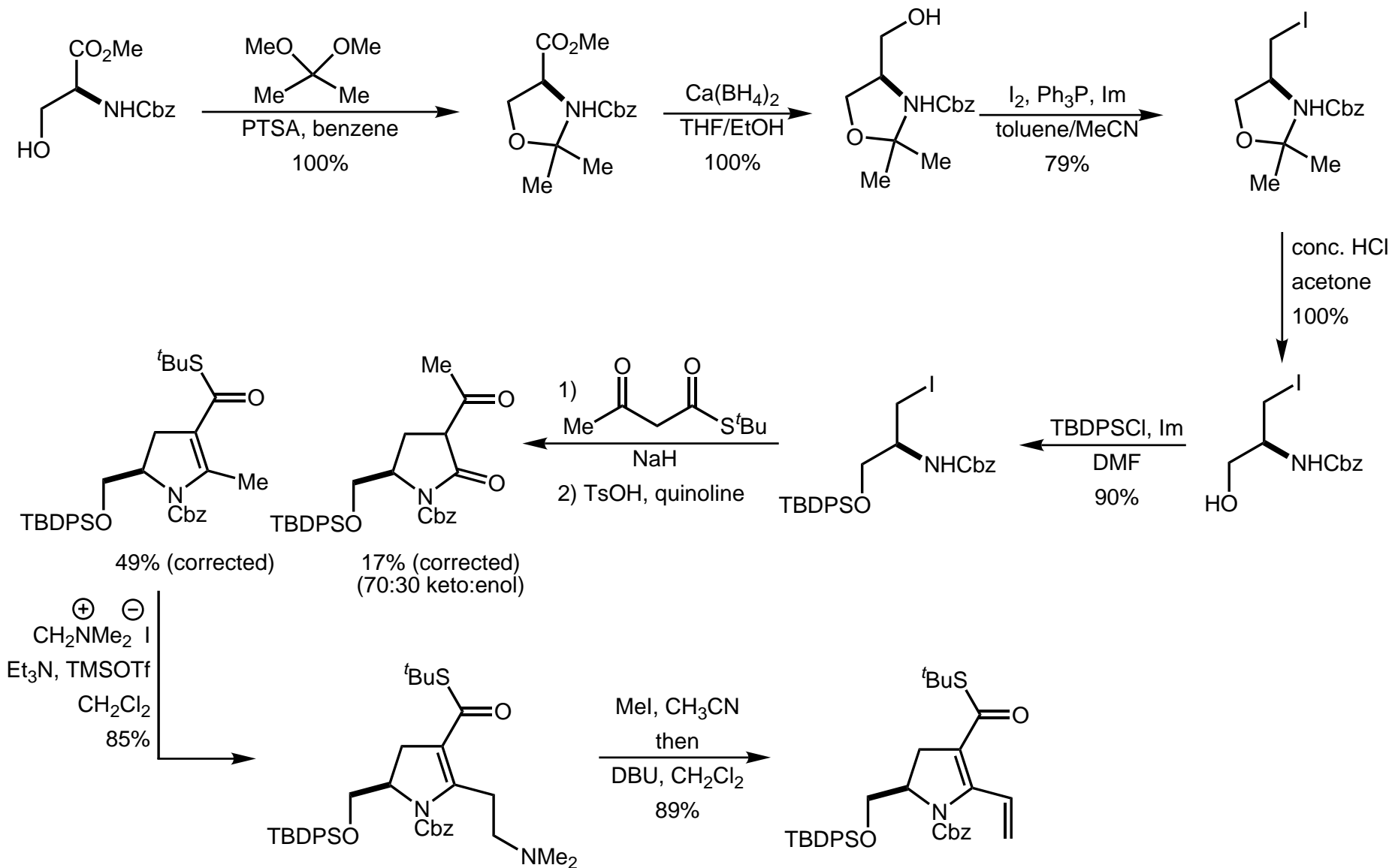


# Hart : Radical Cyclization Approach Towards the ABC Core

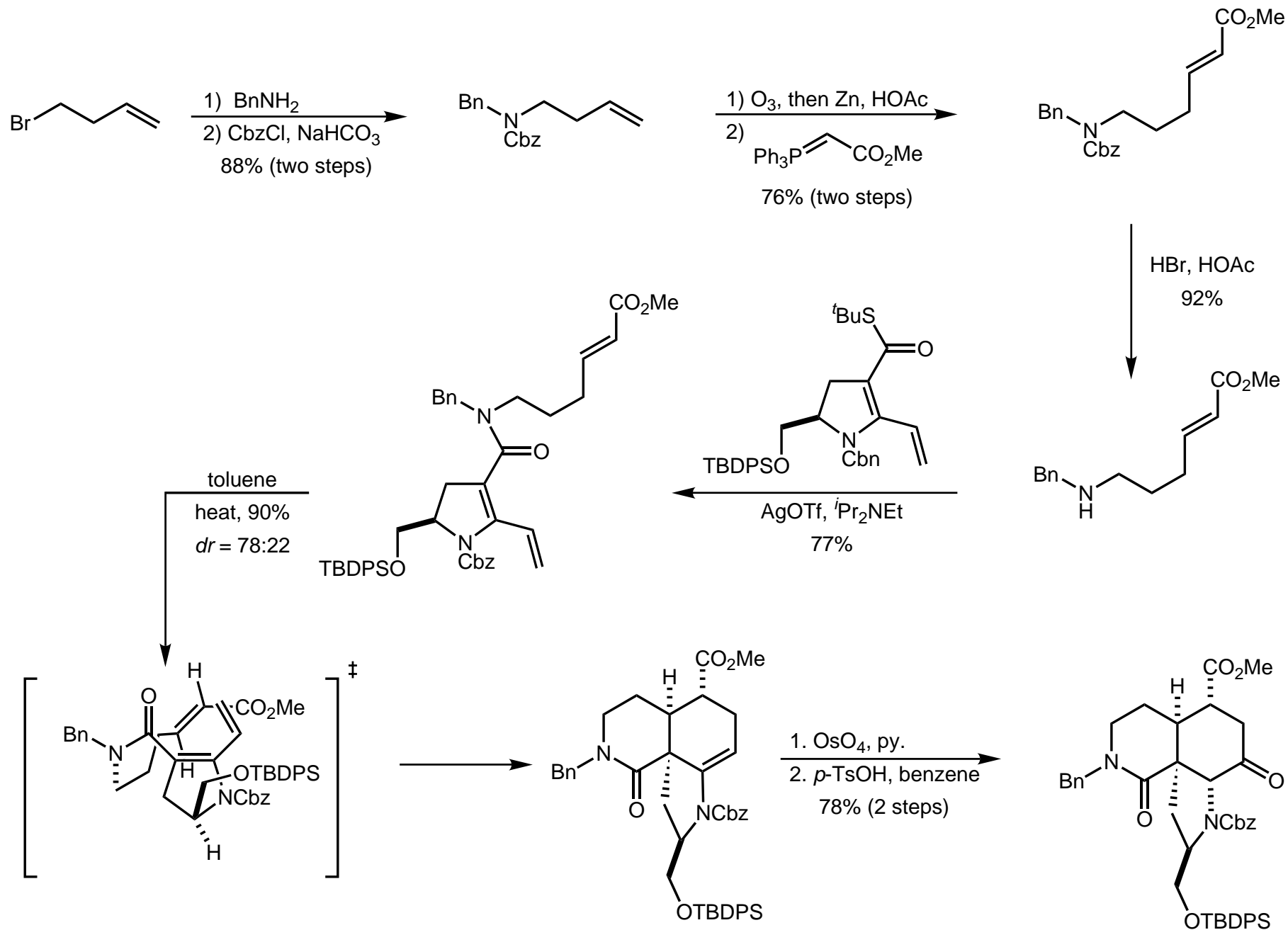




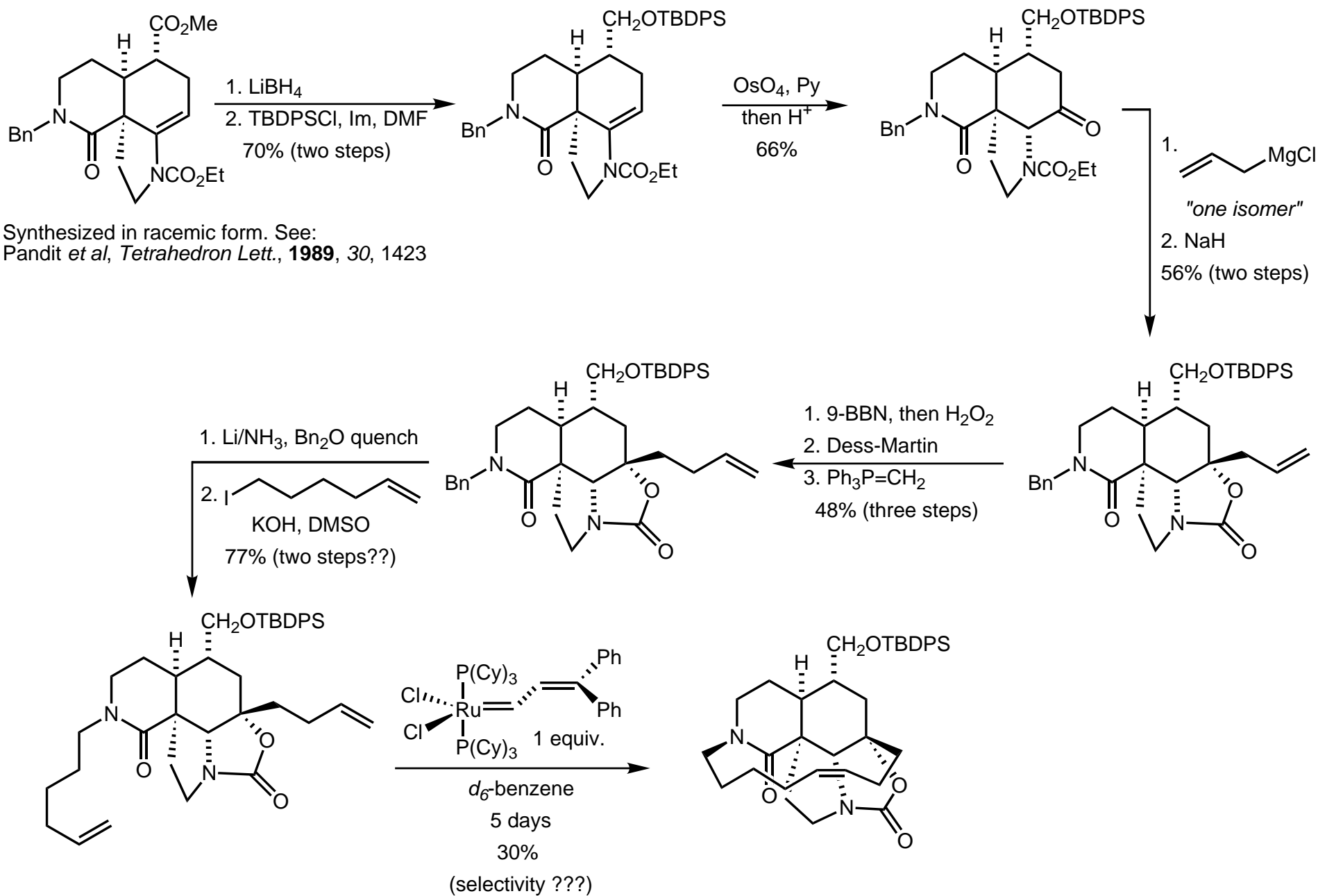
## Pandit : Synthesis of the ABC Core



# Pandit : Synthesis of the ABC Core

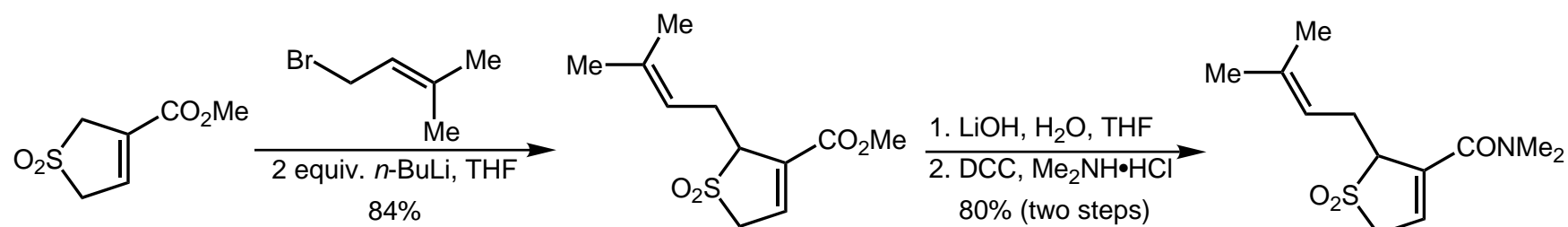
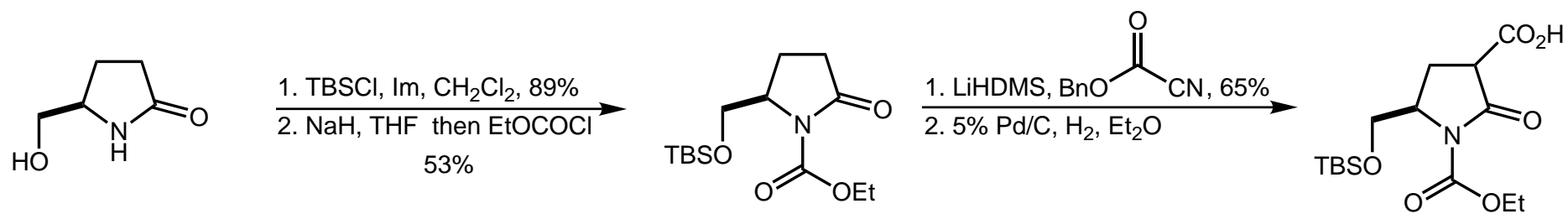


# Pandit's Synthesis of the ABCD System

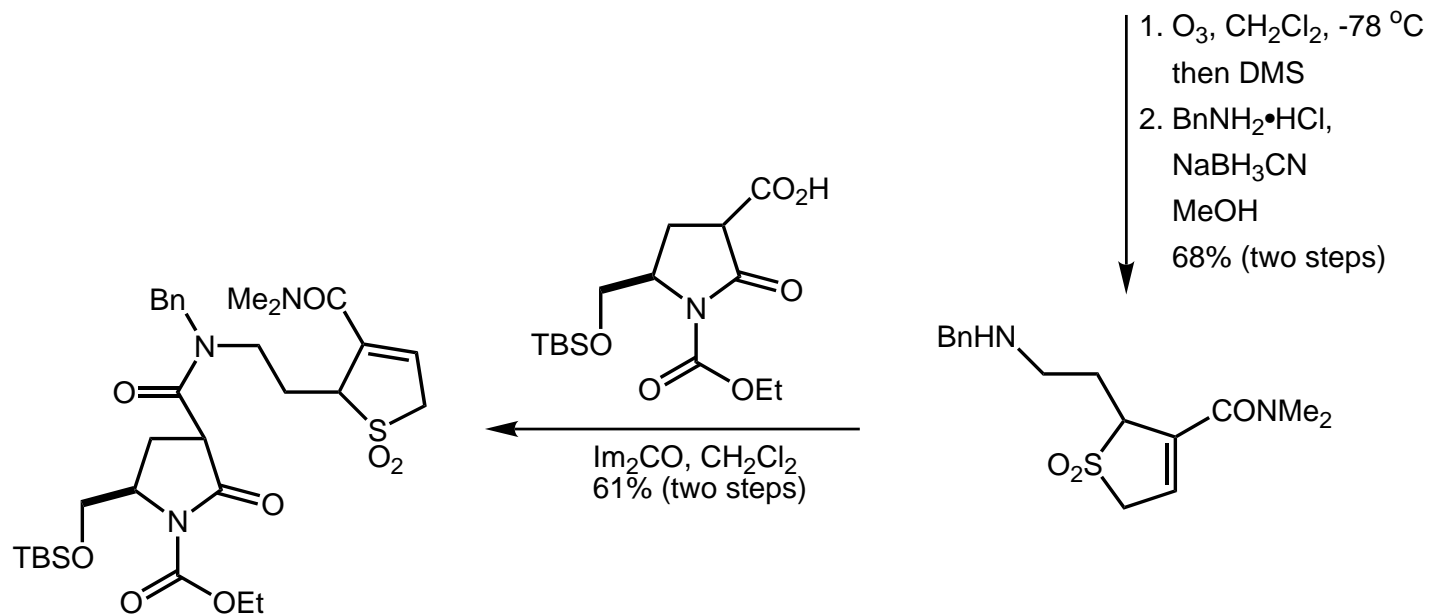


Synthesized in racemic form. See:  
 Pandit *et al*, *Tetrahedron Lett.*, **1989**, 30, 1423

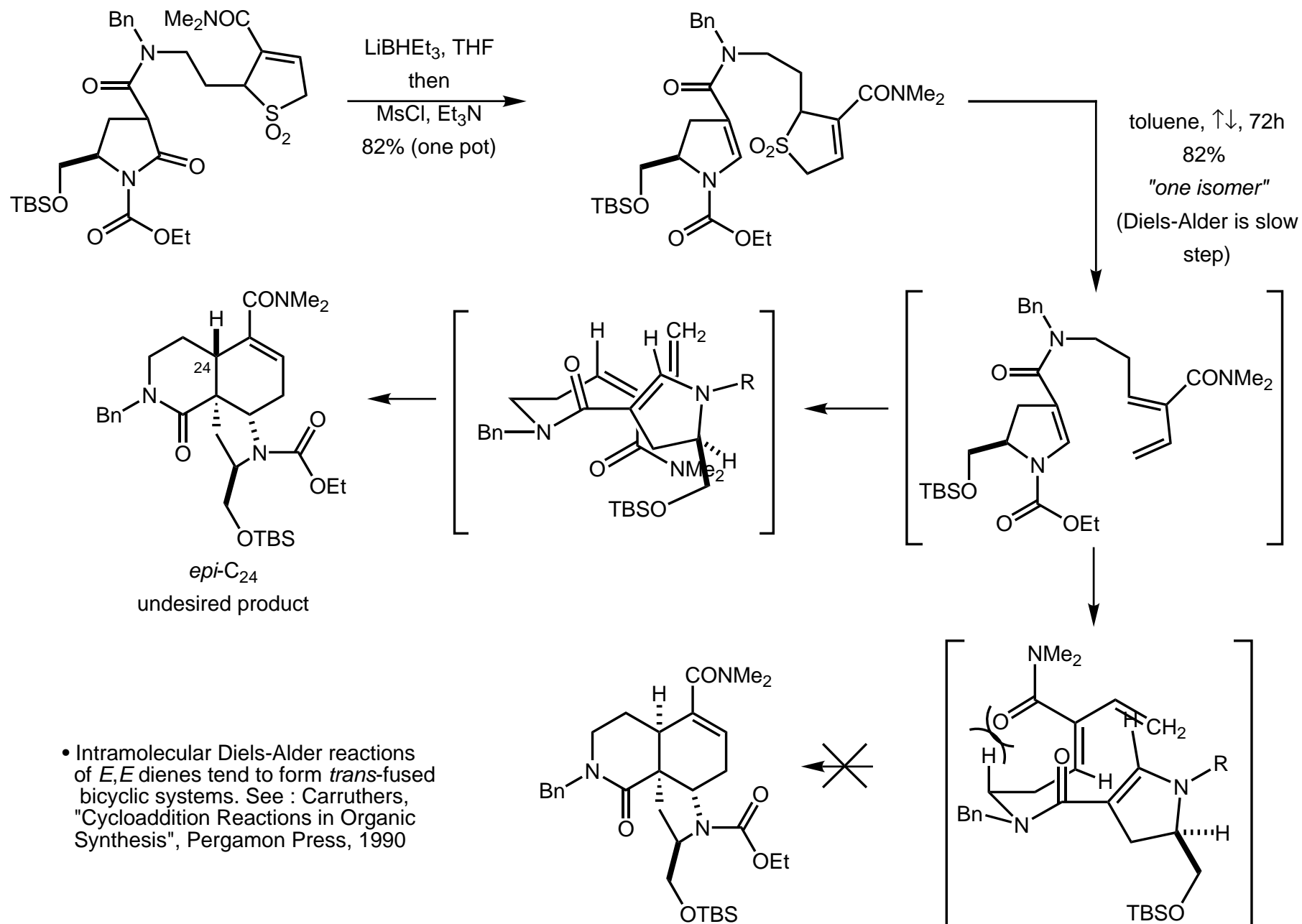
## Leonard : A Sulfolene-based Diels-Alder



For synthesis, see:  
 McIntosh *et al*,  
*J. Org. Chem.*, **1978**, 43, 4431

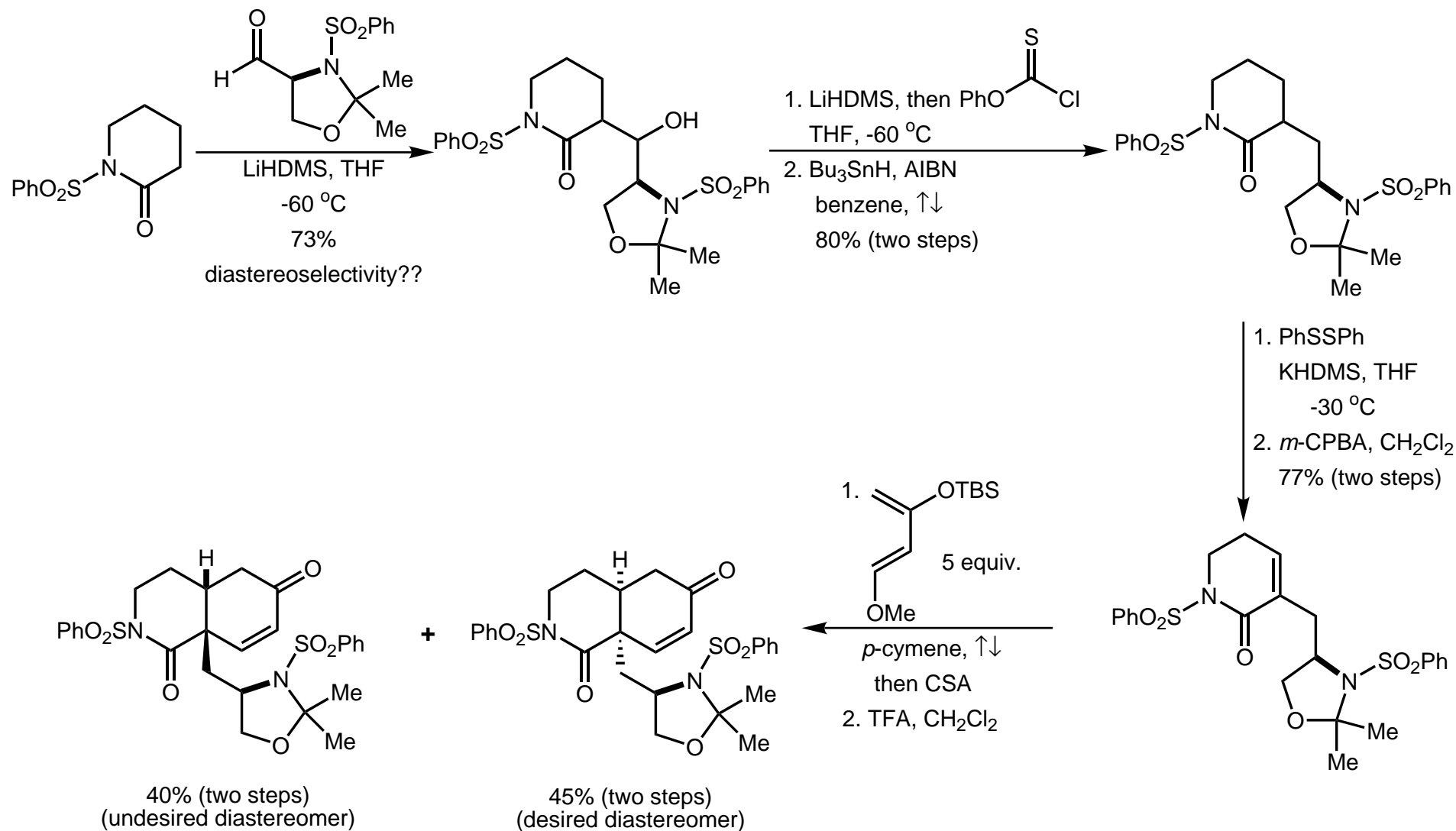


## Leonard : A Sulfolene-based Diels-Alder

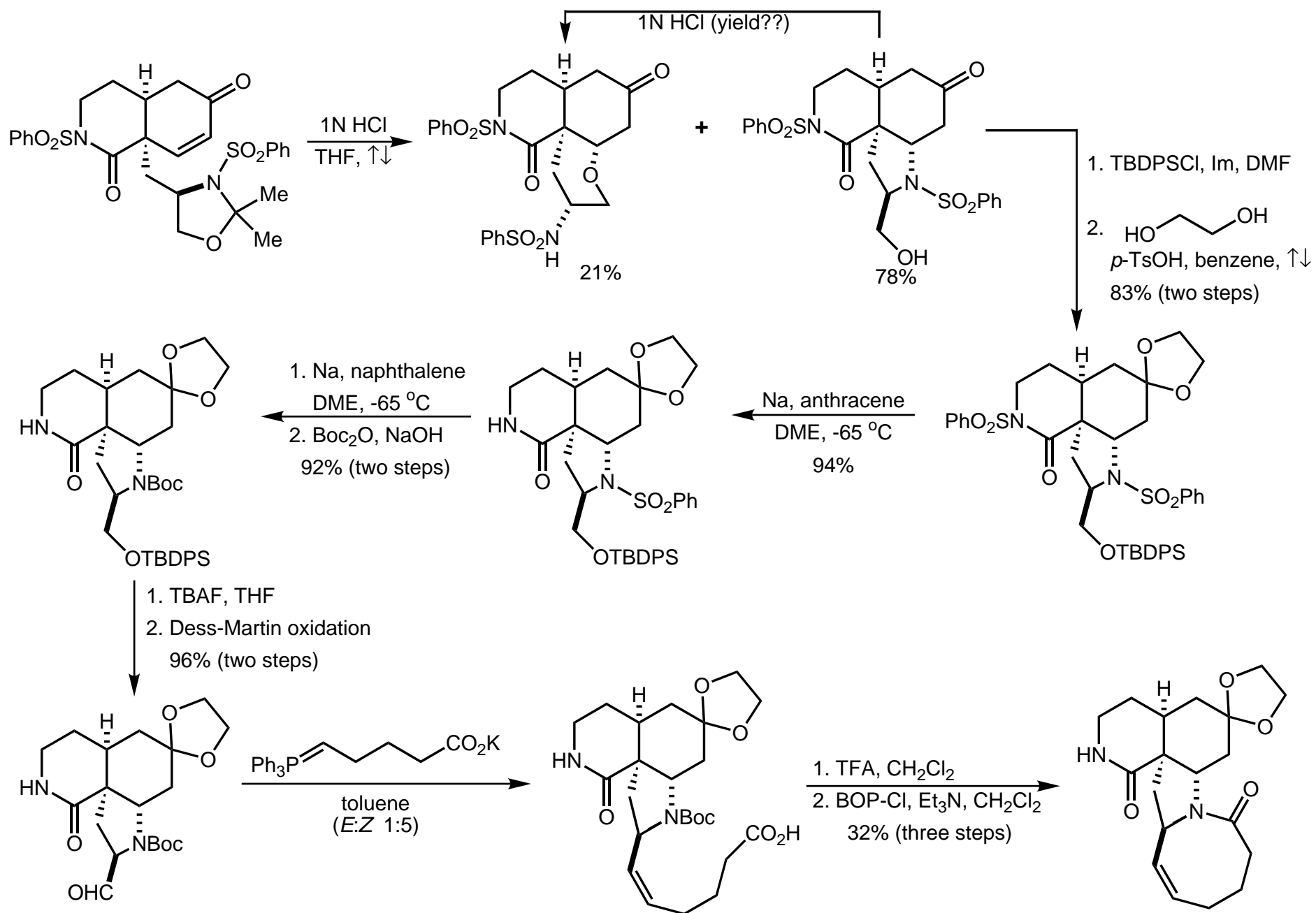


- Intramolecular Diels-Alder reactions of *E,E* dienes tend to form *trans*-fused bicyclic systems. See : Carruthers, "Cycloaddition Reactions in Organic Synthesis", Pergamon Press, 1990

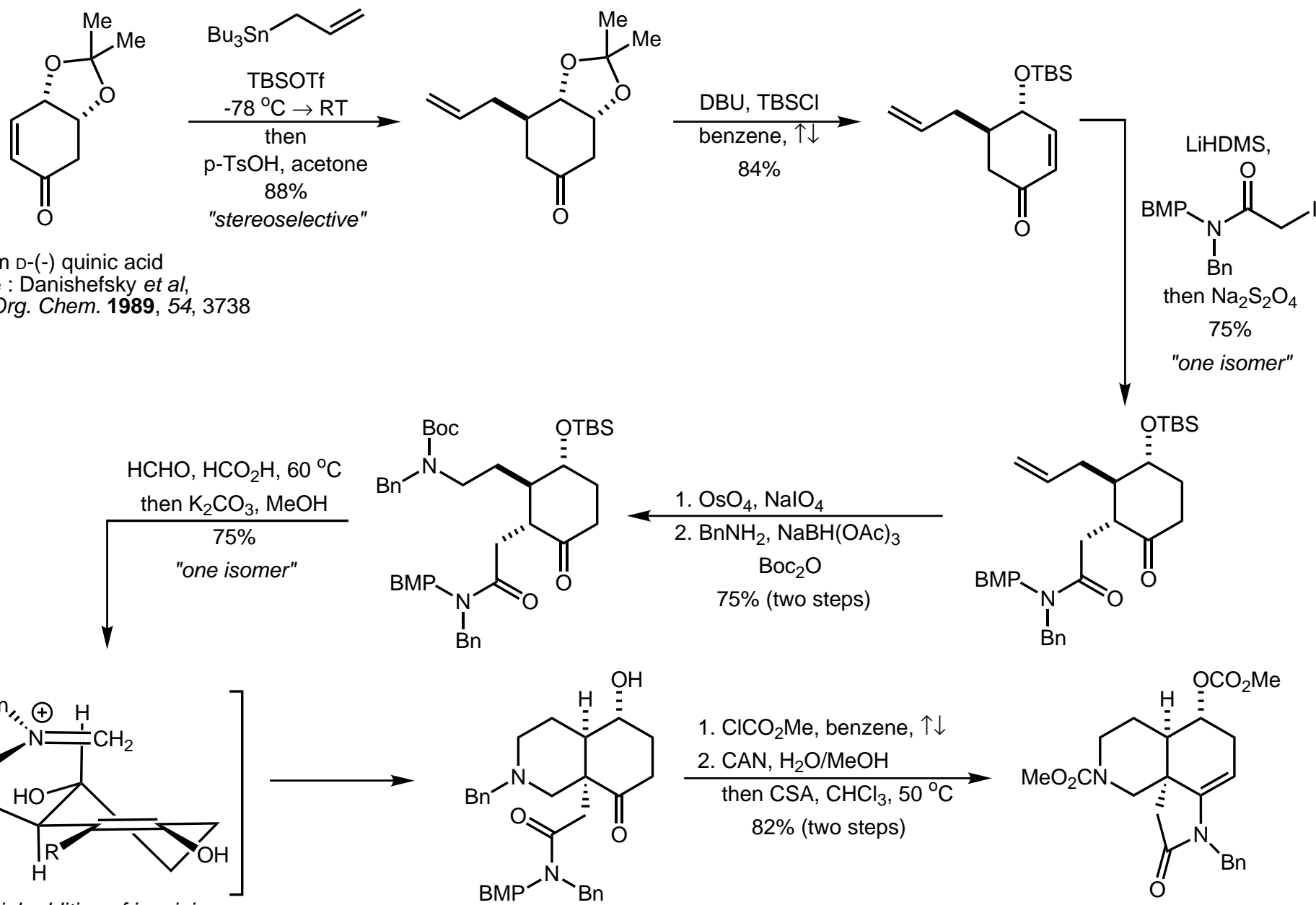
## Nagakawa : An Intermolecular Diels-Alder Approach



# Nagakawa : Further Elaboration Towards the ABCD Ring System



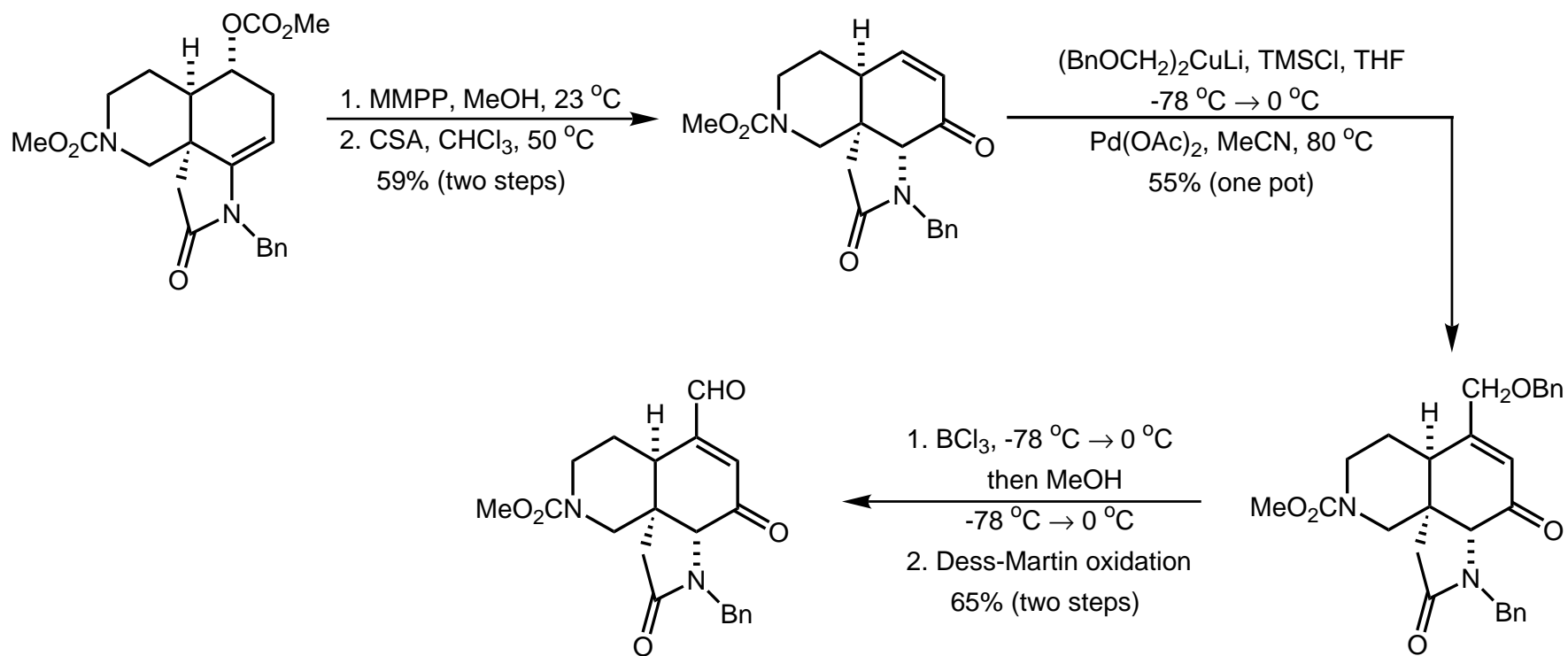
# Overman : Mannich Ring Closure Approach



from D-(-) quinic acid  
 see : Danishefsky *et al.*,  
*J. Org. Chem.* **1989**, *54*, 3738

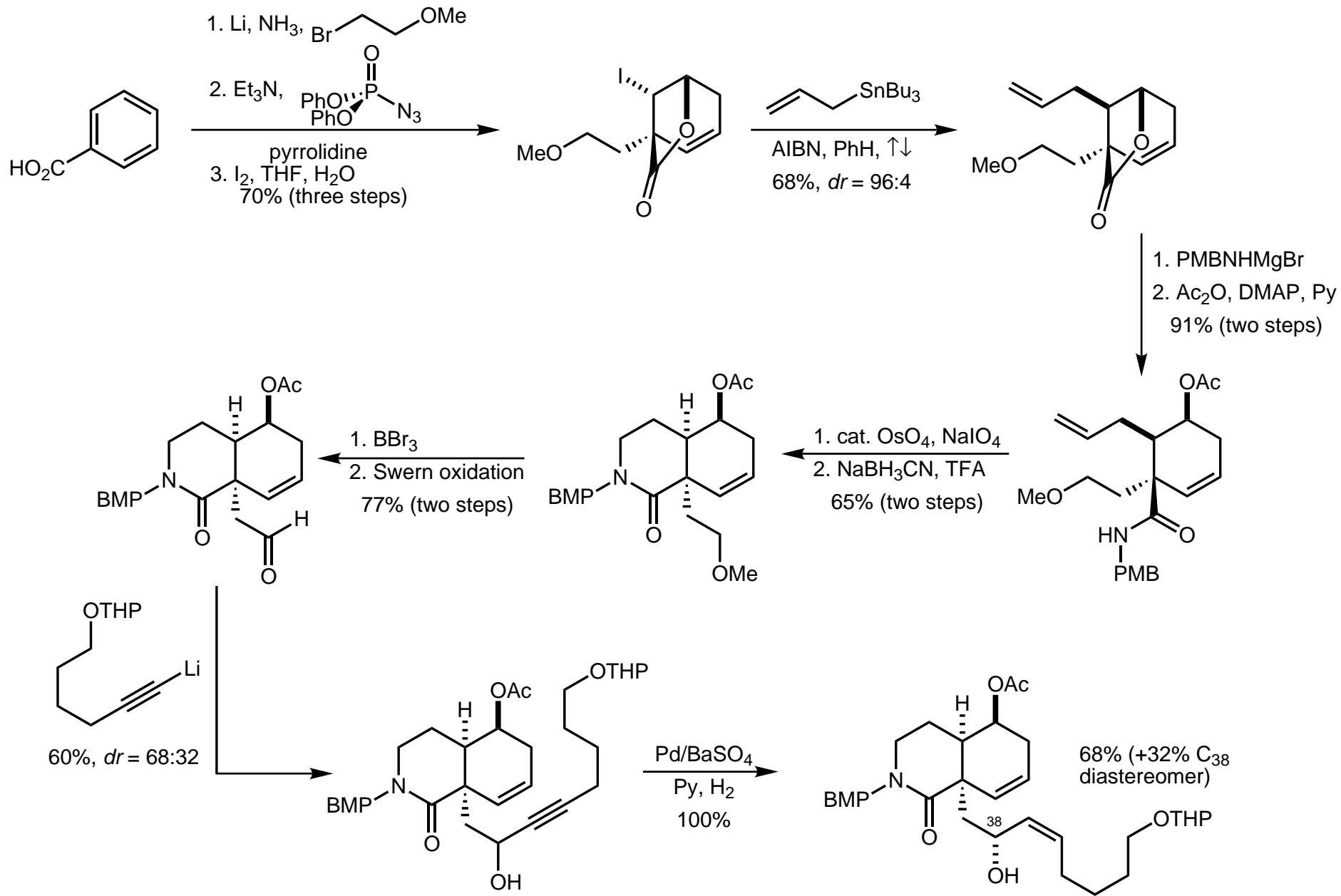


## Overman : Mannich Ring Closure Approach

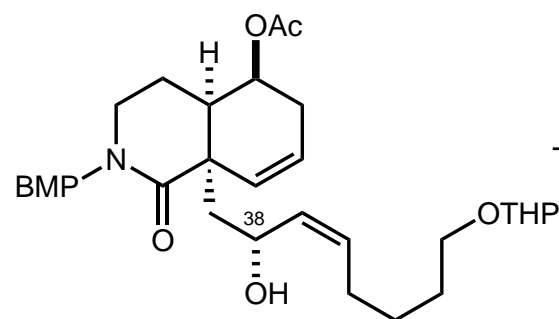


- Addition of  $\beta$ -carboline unit directly was unsuccessful.
- 2-naphthyl and 2-pyridyl cuprates also reacted with similar yields.

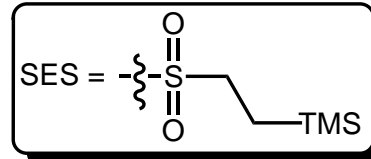
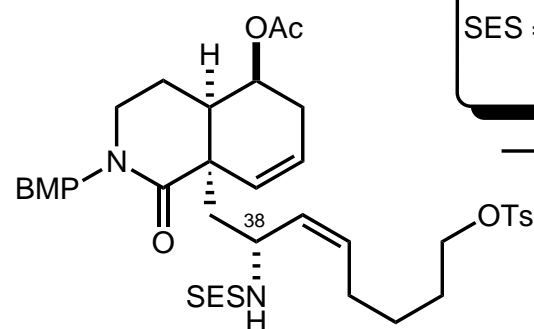
# Hart's Synthesis of the ABCE Ring System



# Hart's Synthesis of the ABCE Ring System

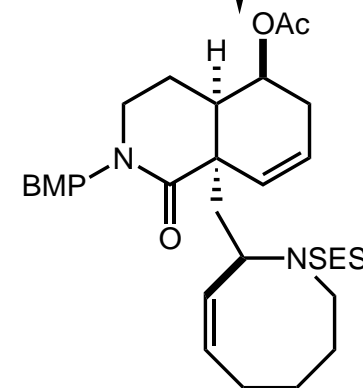


1.  $\text{HN}(\text{SES})\text{CO}_2^t\text{Bu}$ ,  $\text{Ph}_3\text{P}$ , DEAD
  2.  $\text{CH}_3\text{SiCl}_3$ , NaI,  $\text{CH}_3\text{CN}$
  3. TsCl,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$
- 74% (three steps)

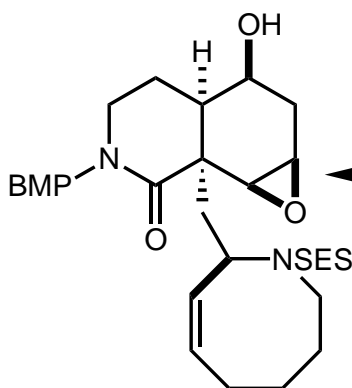


Mistusobu proceeds with retention at  $\text{C}_{38}$ .  
Amide oxygen participation? See also:  
Lipshutz *et al*, *Tetrahedron Lett.* **1990**, 5253

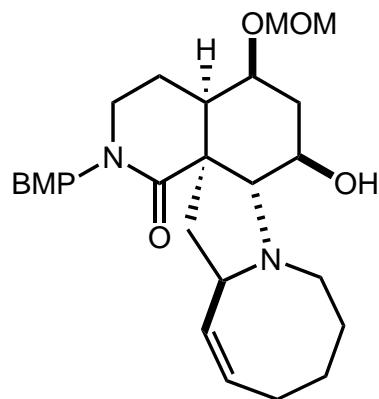
KH, TBAI  
18-crown-6  
toluene,  $\uparrow\downarrow$   
(0.005M)  
91%



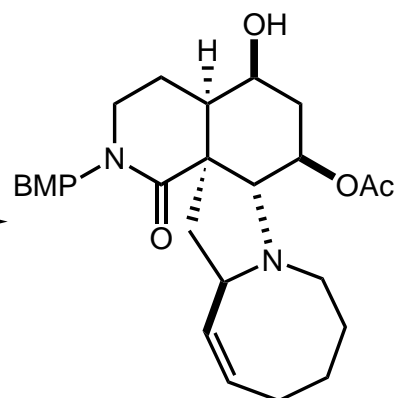
1. LiOH
  2.  $\text{VO}(\text{acac})_2$ ,  $^t\text{BuOOH}$ ,  $\Delta$
- diastereoselectivity??  
64% (two steps)



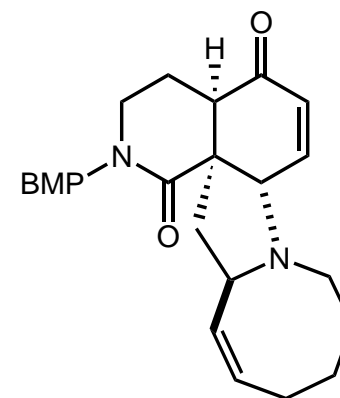
1. MOM-Cl,  $^i\text{Pr}_2\text{NEt}$
  2. CsF, DMF
- 62% (two steps)



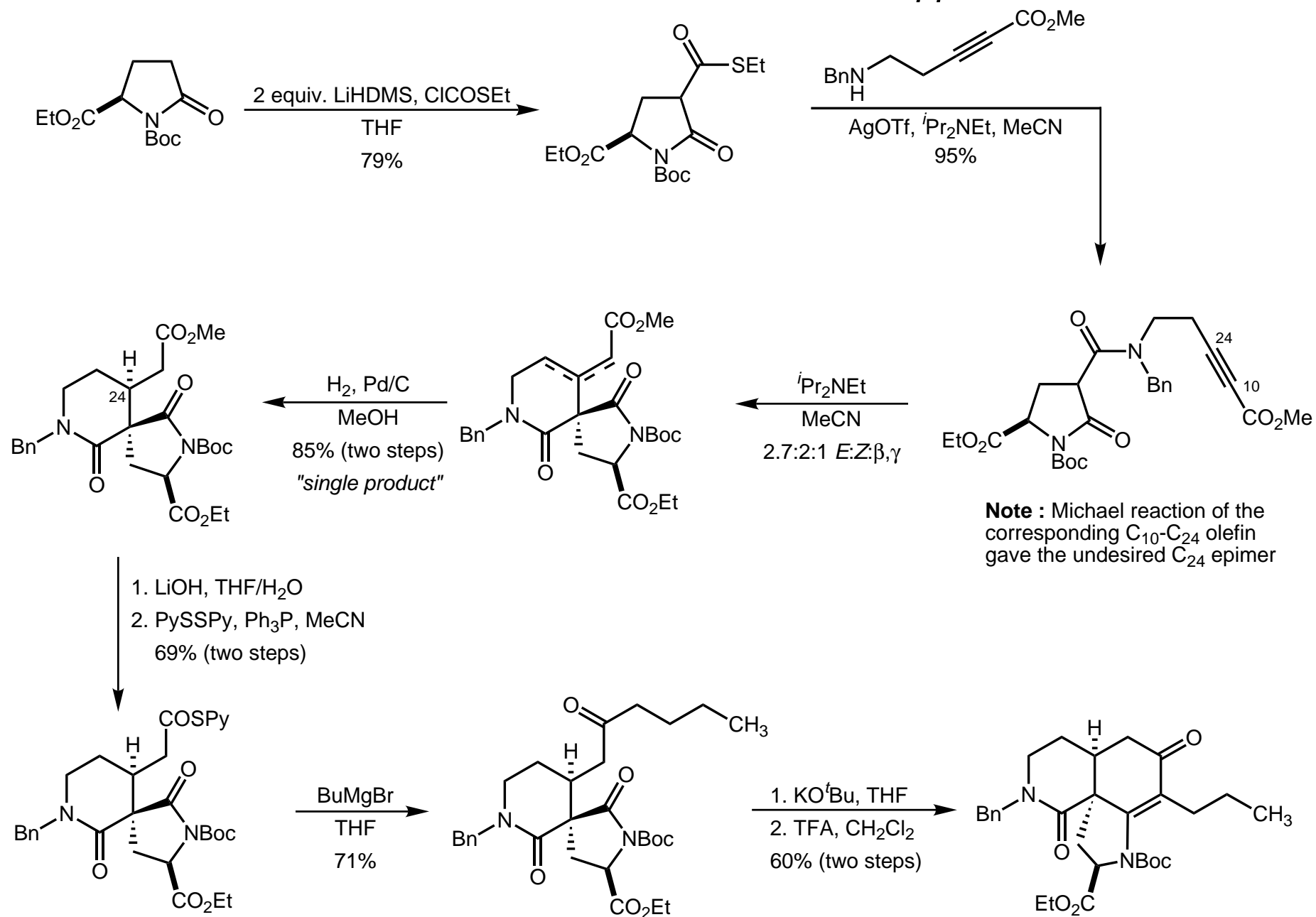
1.  $\text{Ac}_2\text{O}$ , DMAP,  $\text{Et}_3\text{N}$
  2. TMSCl, NaI,  $\text{CH}_3\text{CN}$
- 60% (two steps)



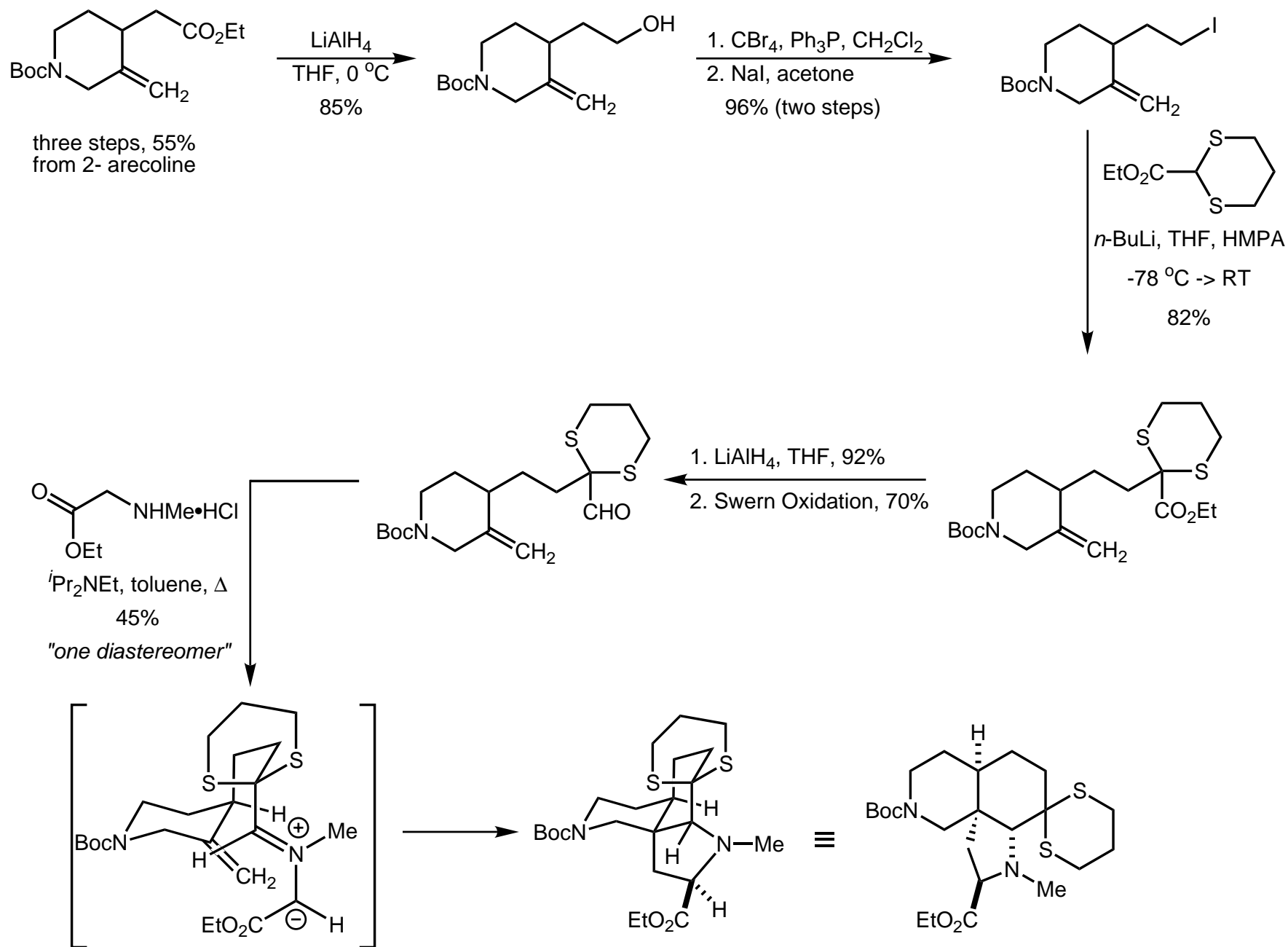
1. Swern oxidation
  2. basic alumina
- 100% (two steps)



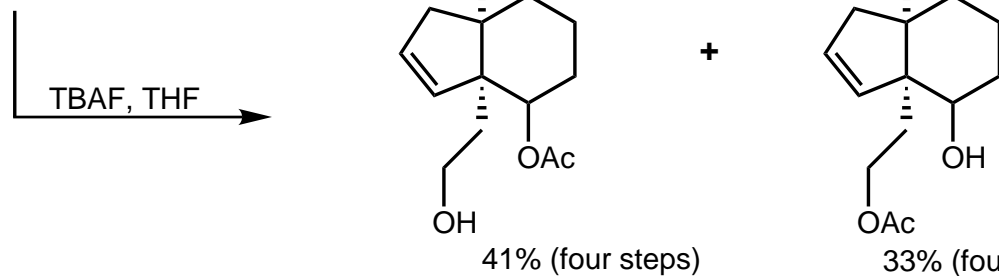
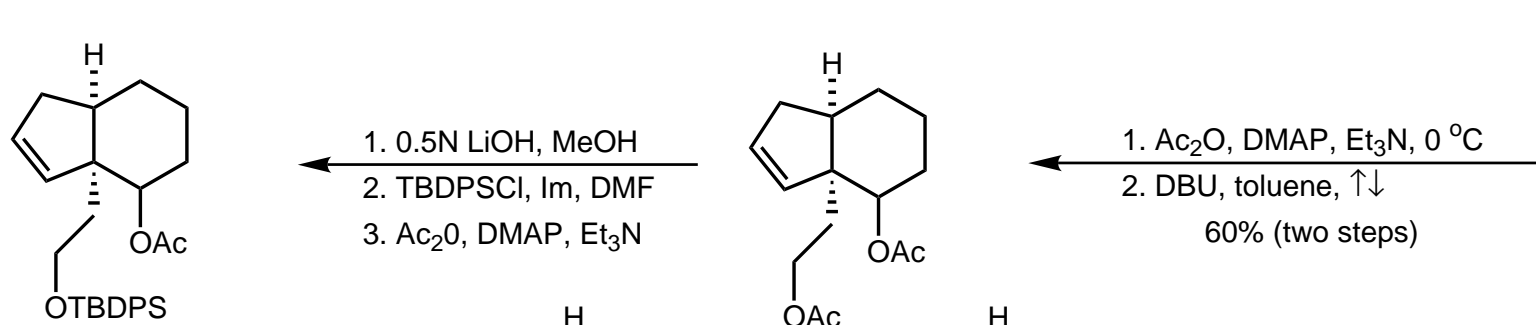
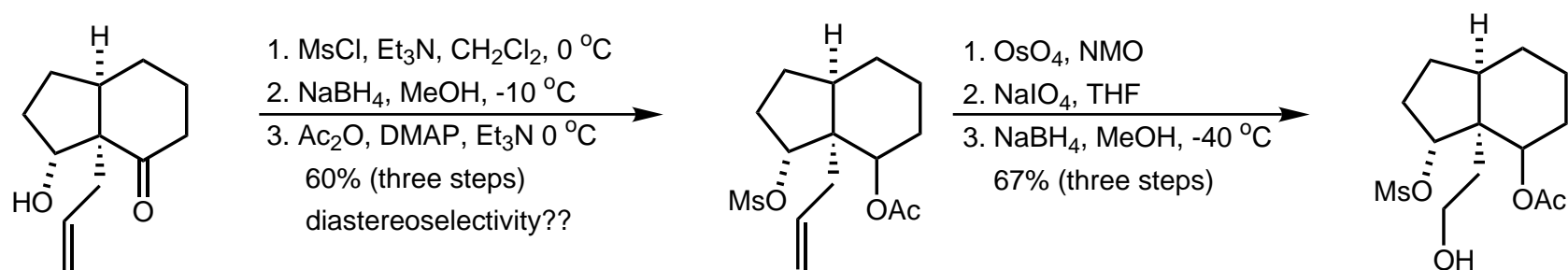
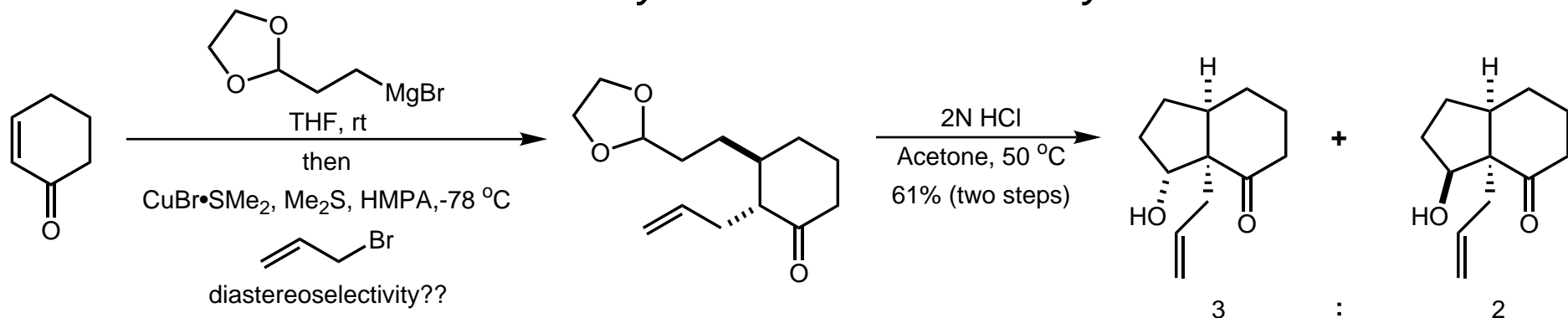
## Brands : An Intramolecular Michael Approach



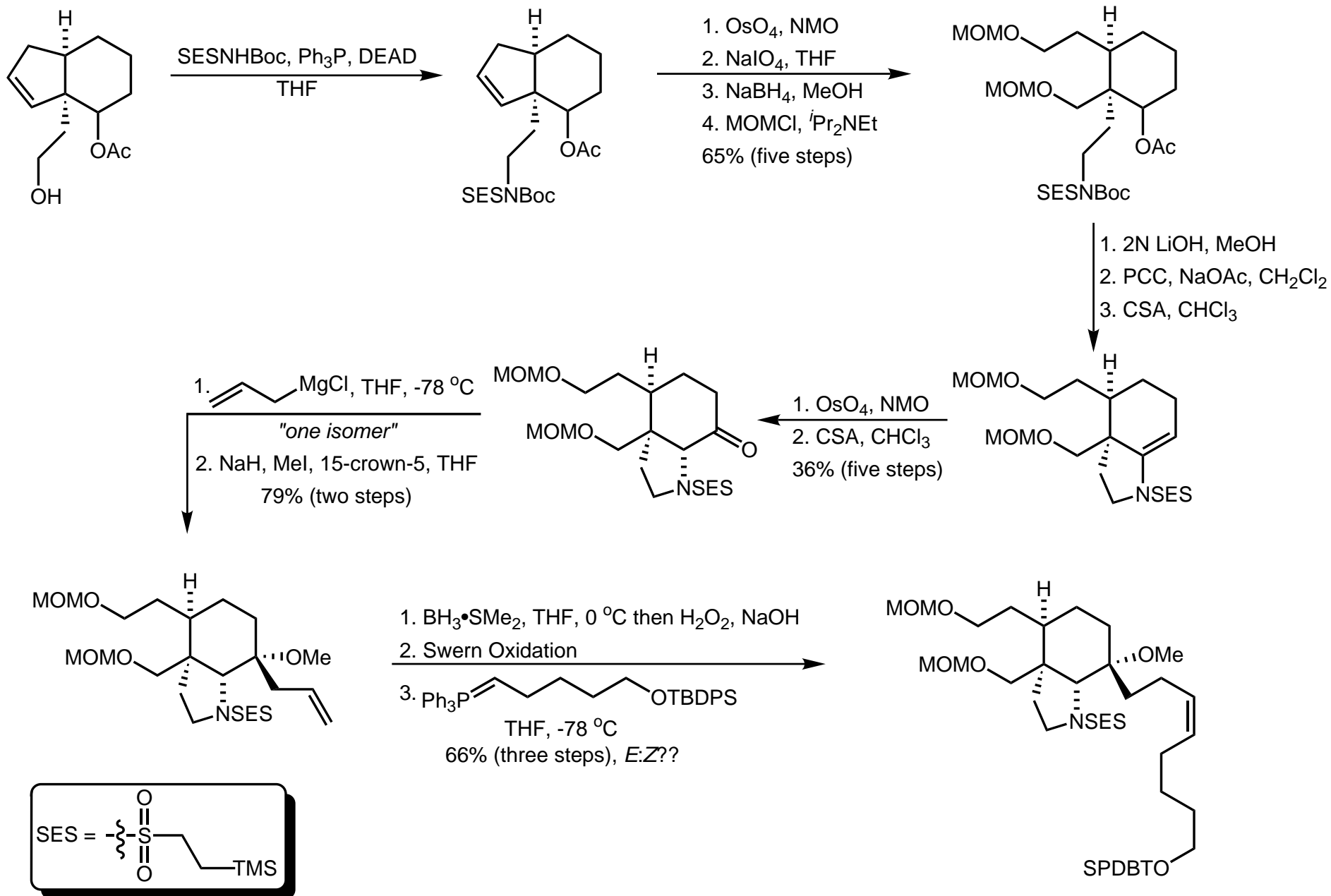
## Coldham : An Azamethine Ylide Cycloaddition Approach



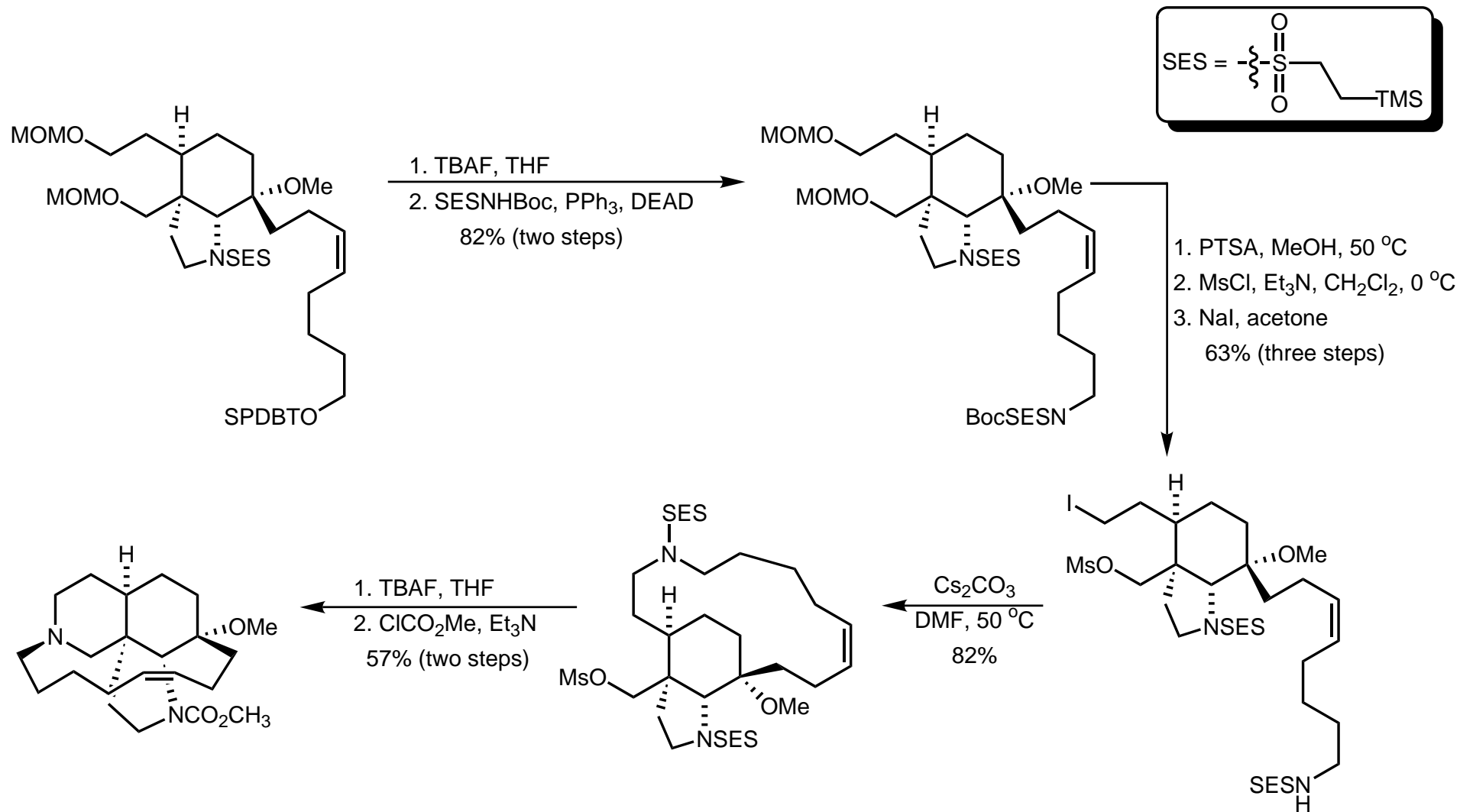
# Yamamura's Synthesis of the ABCE System



# Yamamura's Synthesis of the ABCE System

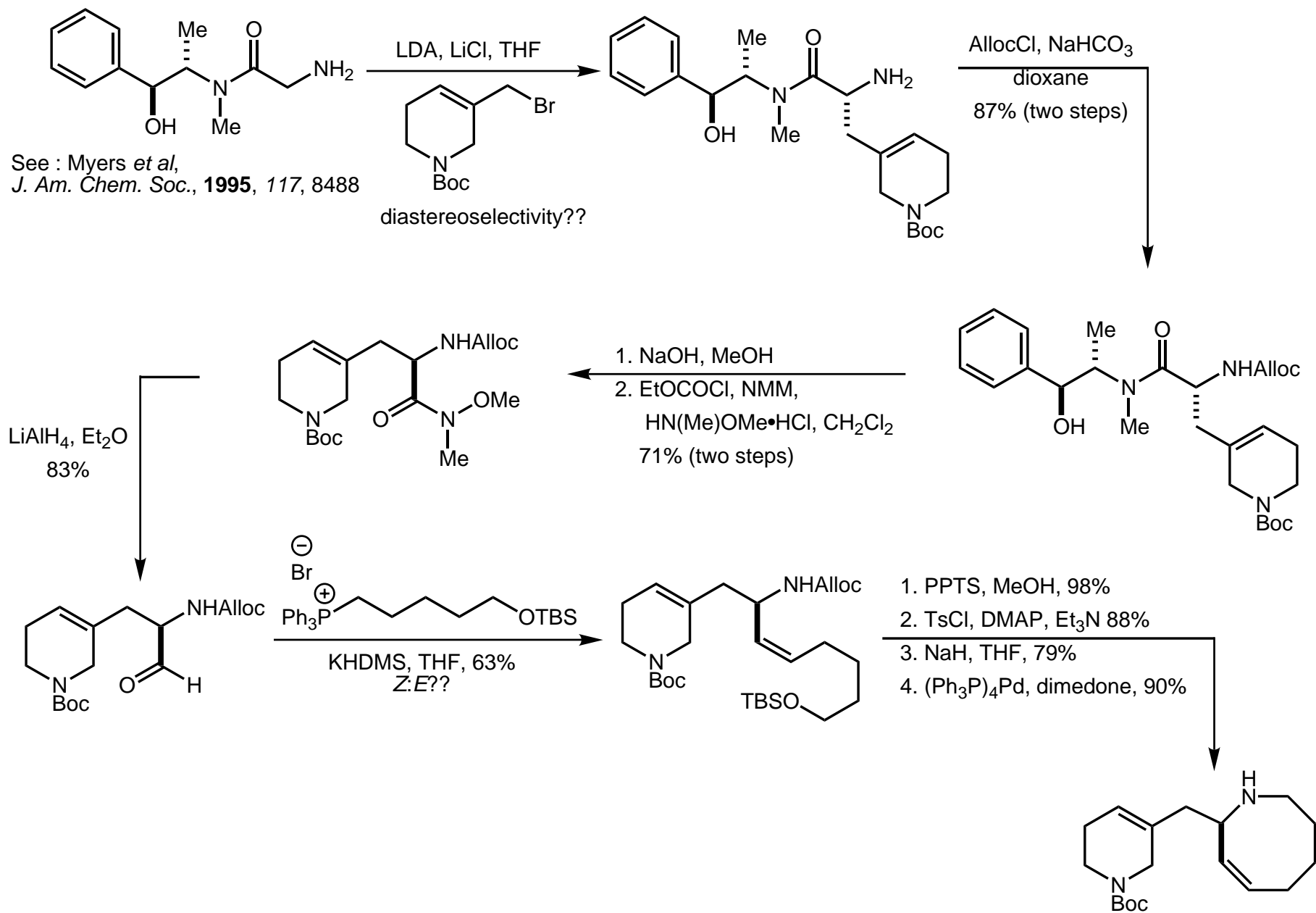


# Yamamura's Synthesis of the ABCE System

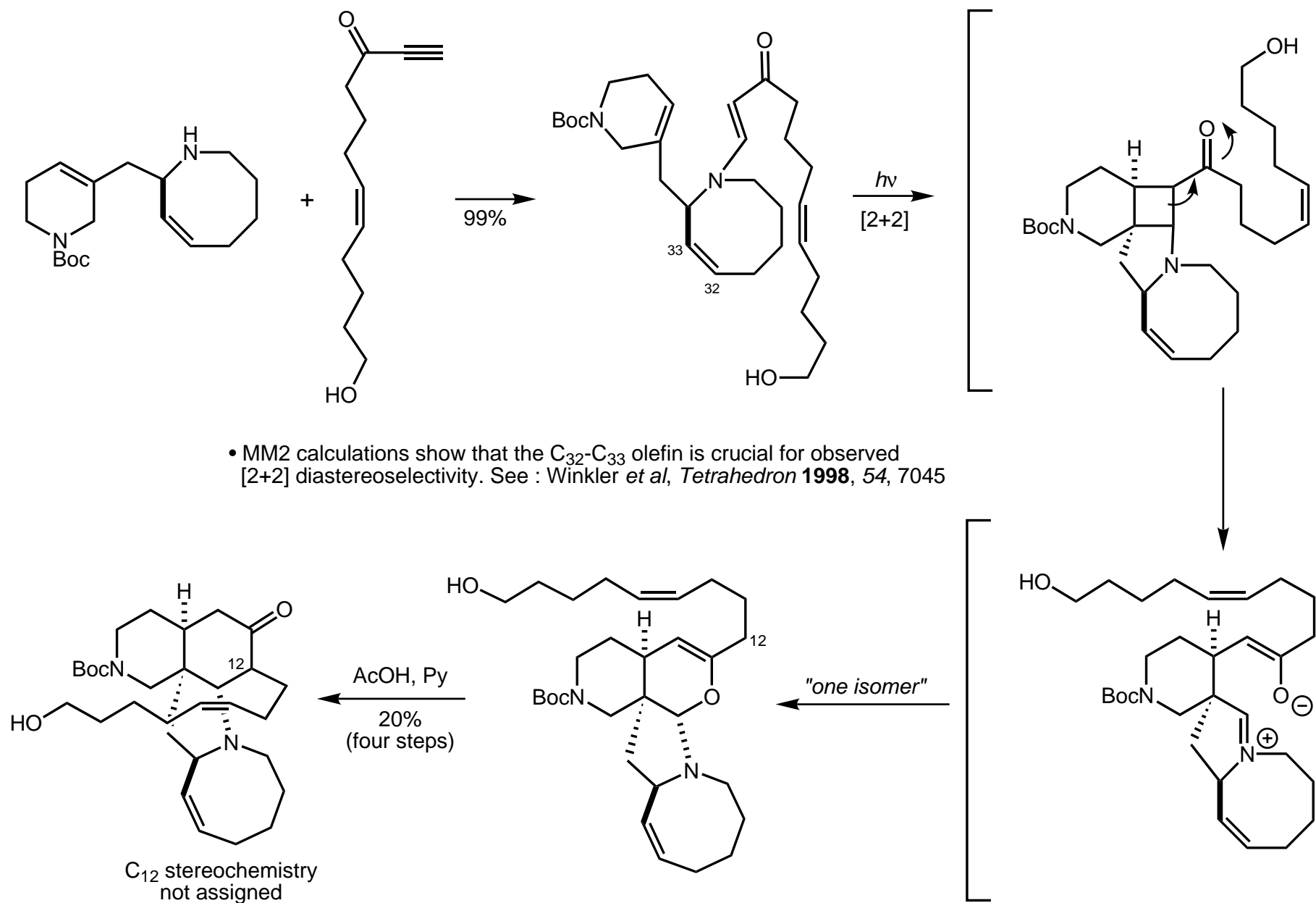




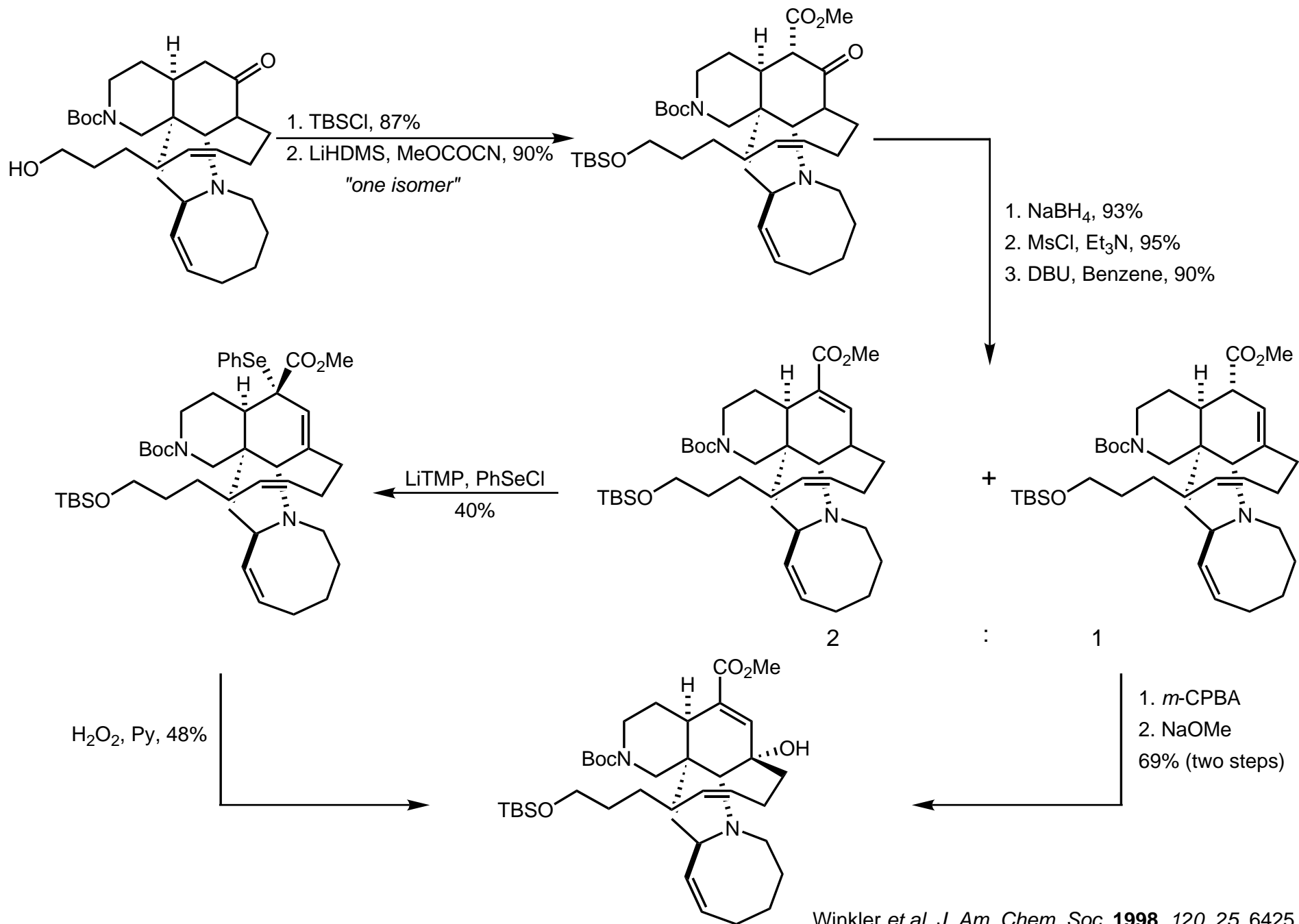
# Winkler : Synthesis of AE Precursor



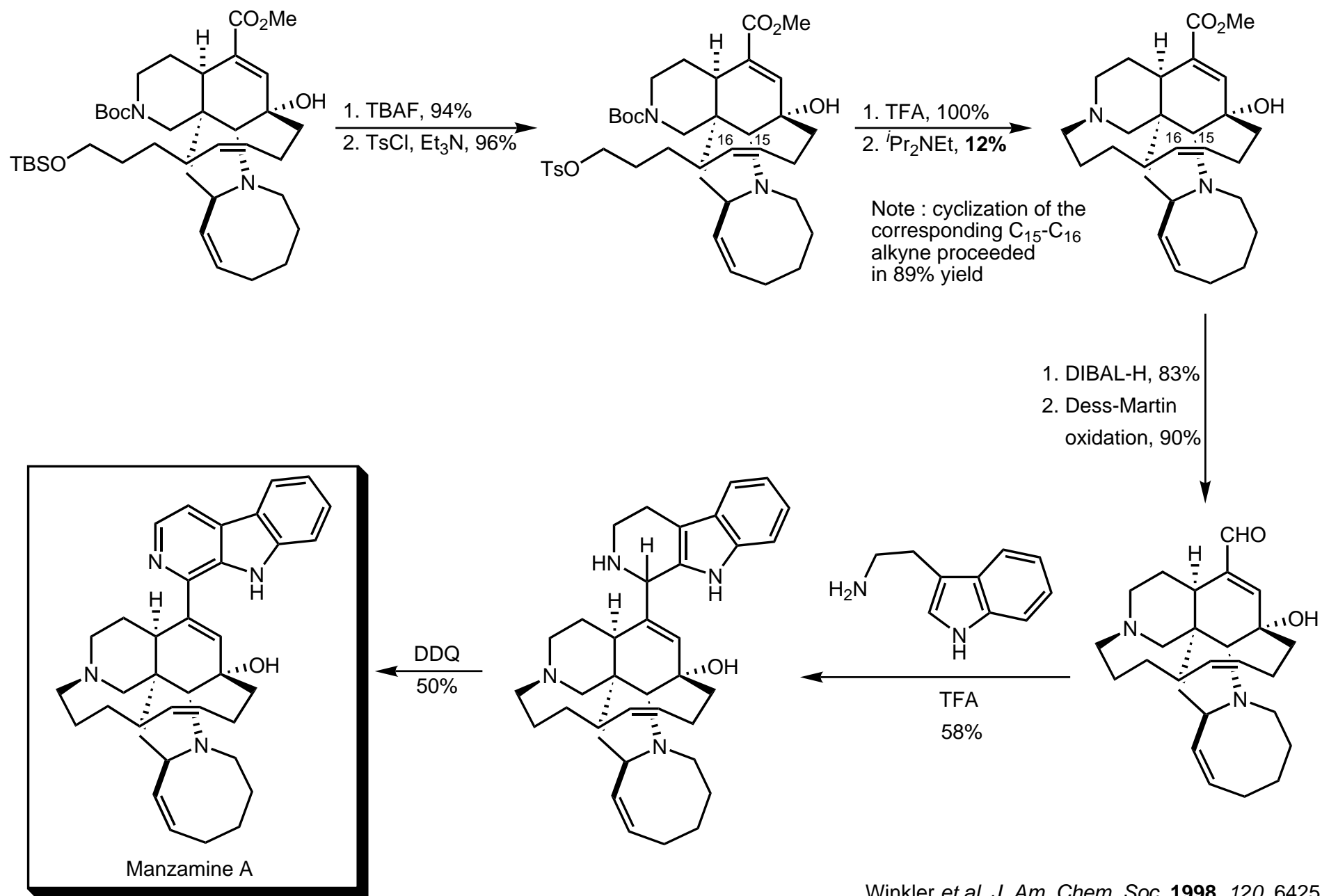
# Winkler : Synthesis of ABCE Ring System



## Winkler : Elaboration of ABCE Tetracycline

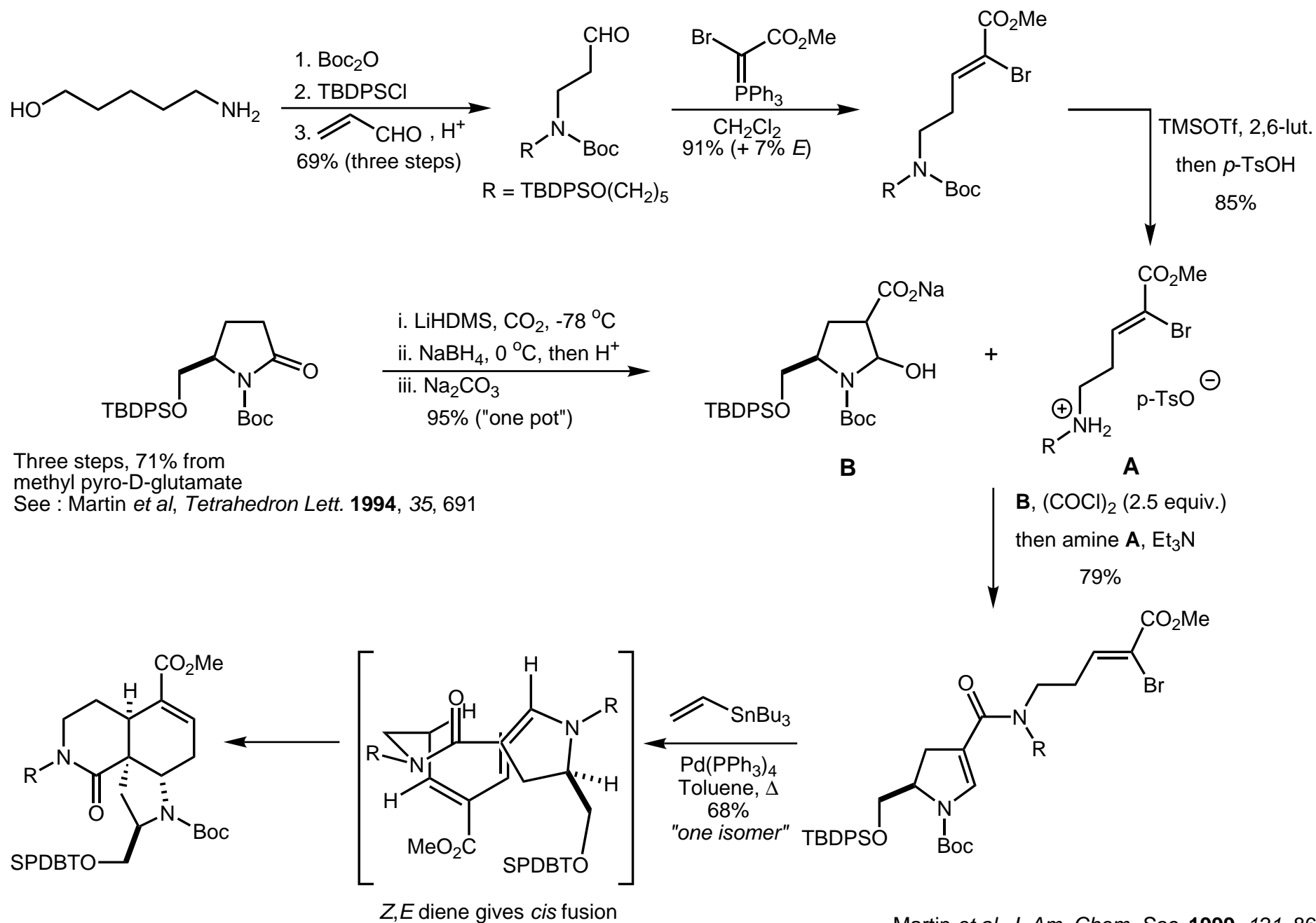


## Winkler : Completion of Synthesis

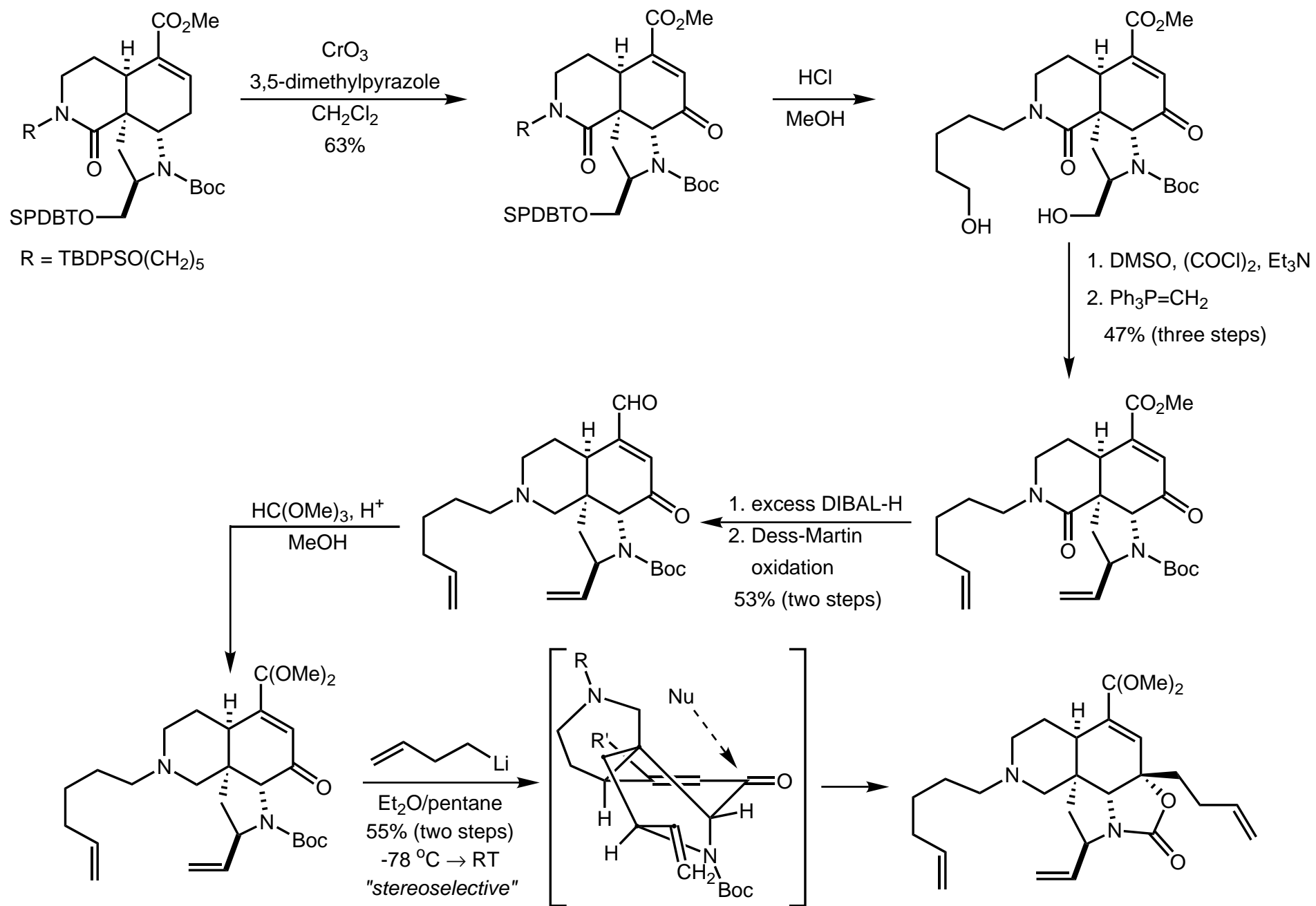


Winkler et al, *J. Am. Chem. Soc.* **1998**, 120, 6425  
 Kobayashi et al, *J. Org. Chem.* **1992**, 57, 2480

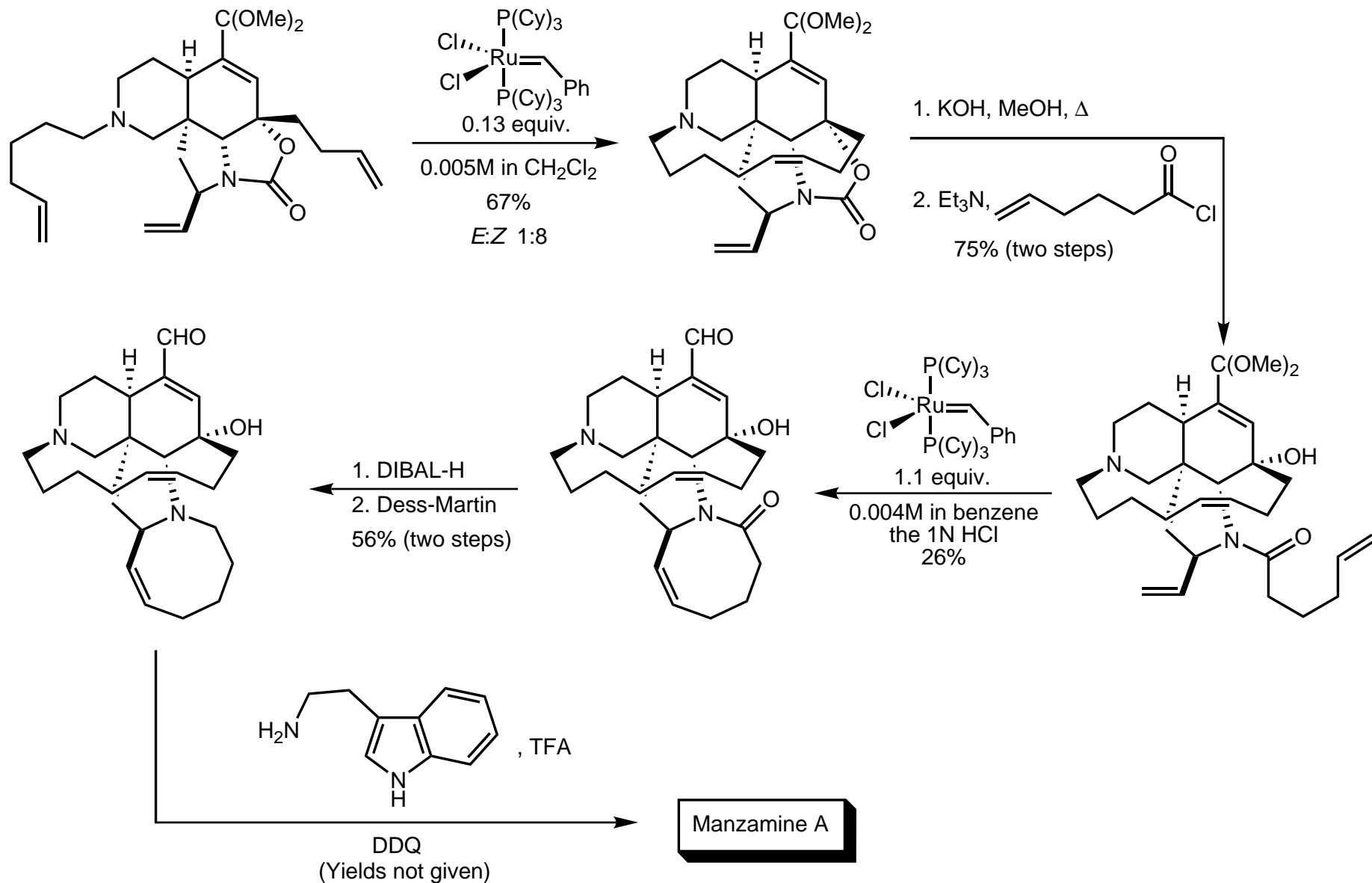
## Martin : Diels-Alder Approach to the ABC Core



## Martin : Elaboration of ABC Core

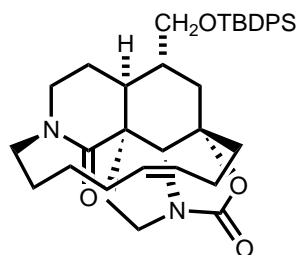


## Martin : Completion of Synthesis

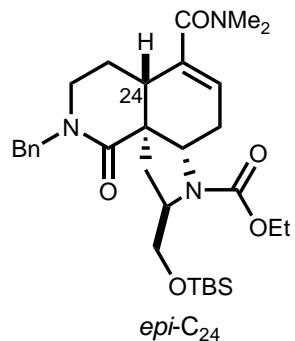


# Summary : Where They Left Off.....

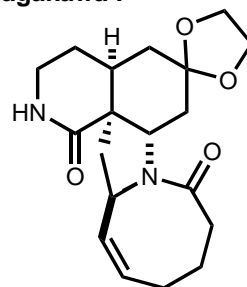
Pandit :



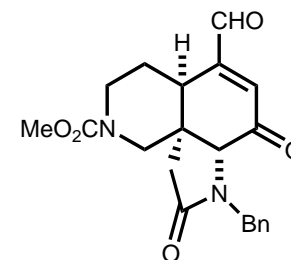
Leonard :



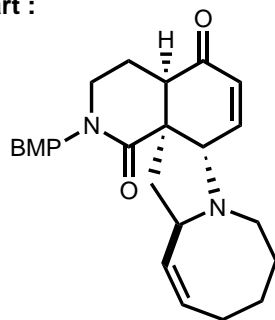
Nagakawa :



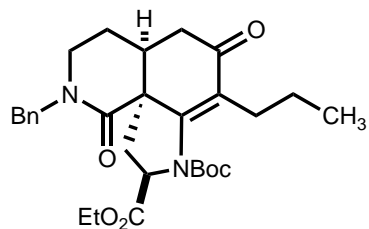
Overman :



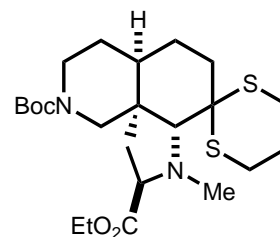
Hart :



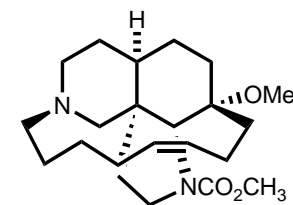
Brands :



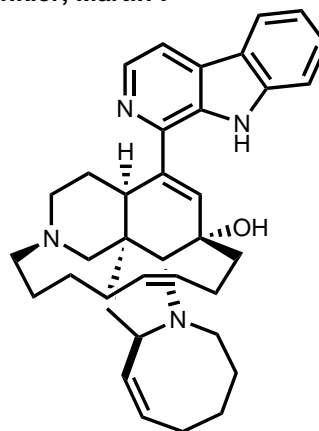
Coldham :



Yammamura :



Winkler, Martin :



## Scorecard:

Winkler 35 steps (longest linear)  
0.020% overall (89% per step)

Martin 23 steps (longest linear)  
0.061% overall (88% per step)