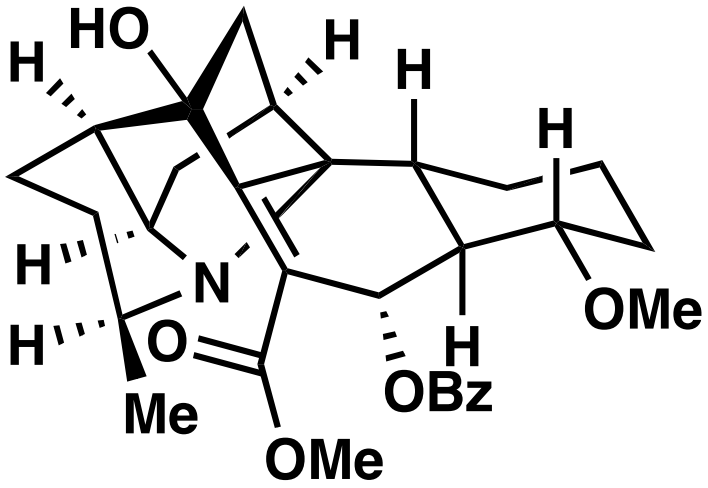
Total Synthesis of (–)-Himandrine

M. Movassaghi,* M. Tjandra and J. Qi

J. Am. Chem. Soc. **2009**, *131*, 9648-9650

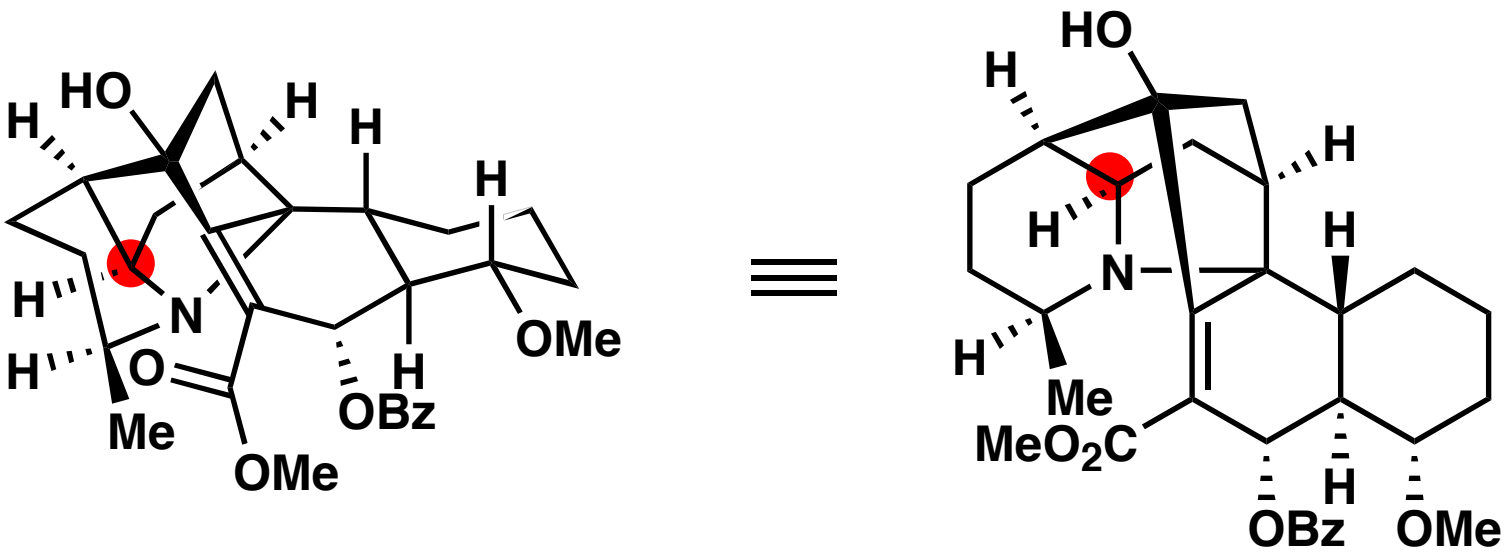


Adam T. Hoye

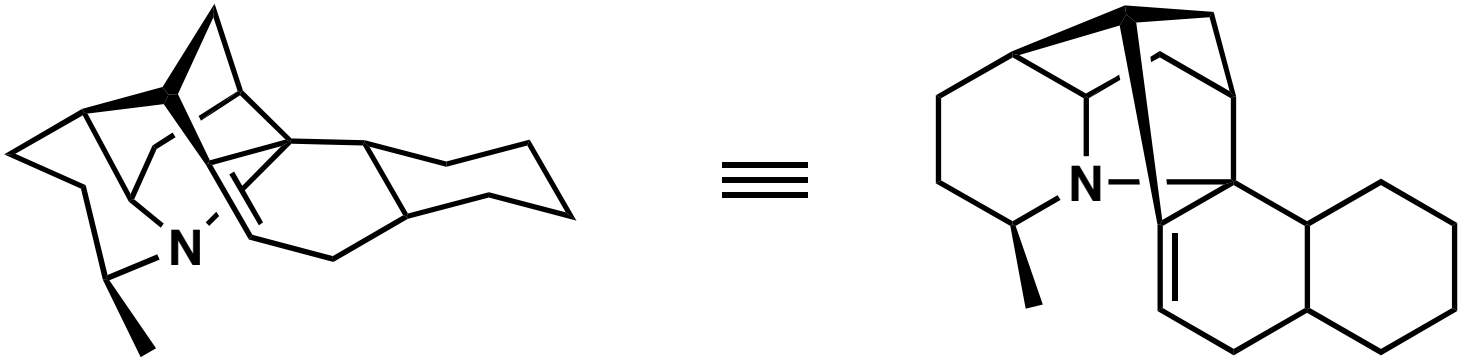
Current Literature

October 3, 2009

Structure of (–)-Himandrine



Carbon Skeleton Simplification:



Galbulimima Alkaloids

28 isolated alkaloids categorized into Class I, II and III

Characterized by piperidine moiety and “caged” structure

-Isolated from bark of *Galbumimia* belgraveana native to northern Australia and Papua-New Guinea
-Biological Properties- potent muscarinic antagonist

Papuans (who tend to use this drug the most) boil the bark and the leaves together with another plant, called Homalomena[2], in order to make tea…It is similar to strong marijuana which induces a similar slumber like feeling

http://en.wikipedia.org/wiki/Galbulimima_belgraveana

Galbulimima syntheses

Class I syntheses (selected):

Hart (Ohio State) **1995**

Chackalamannil (Schering-Plough) **1996**

Baldwin (Oxford) **2005**

Class III syntheses:

Mander (Australian Nat. Univ.) : Galbulimima 13 *(racemic)* **2003**

Movassaghi (MIT): (+)- and (—)-GB 13 **2006**

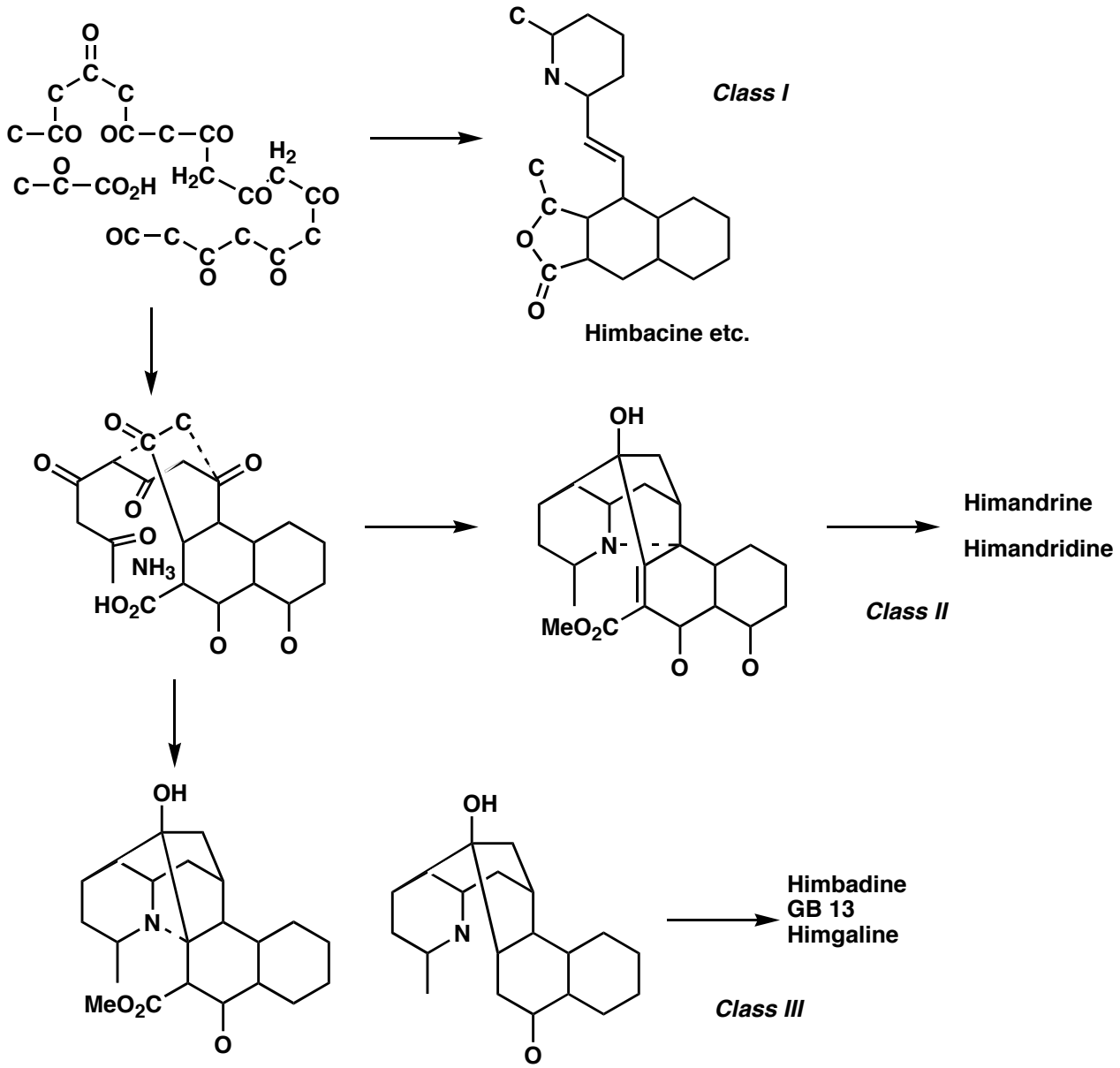
Chackalamannil (Schering-Plough): (—)-Himgaline **2006**

Evans (Harvard): (+)-GB 13 and (+)-Himgaline *(antipodes)* ***2007***

Class II syntheses:

Movassaghi: *TITLE PAPER*

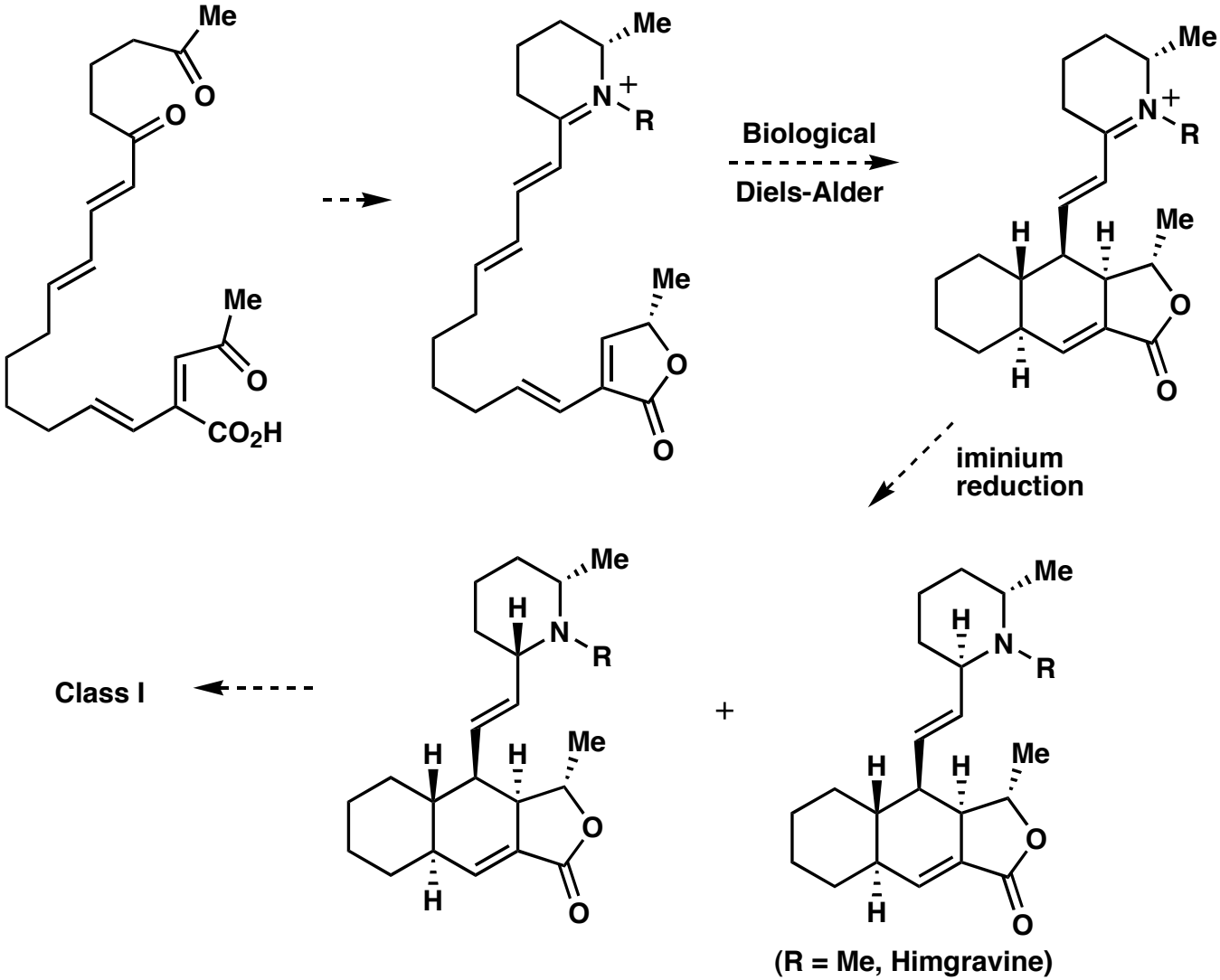
Polyacetate Proposal (Taylor)



Mander, L. N.; Prager, R. H.; Rasmussen, M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 1705-1718

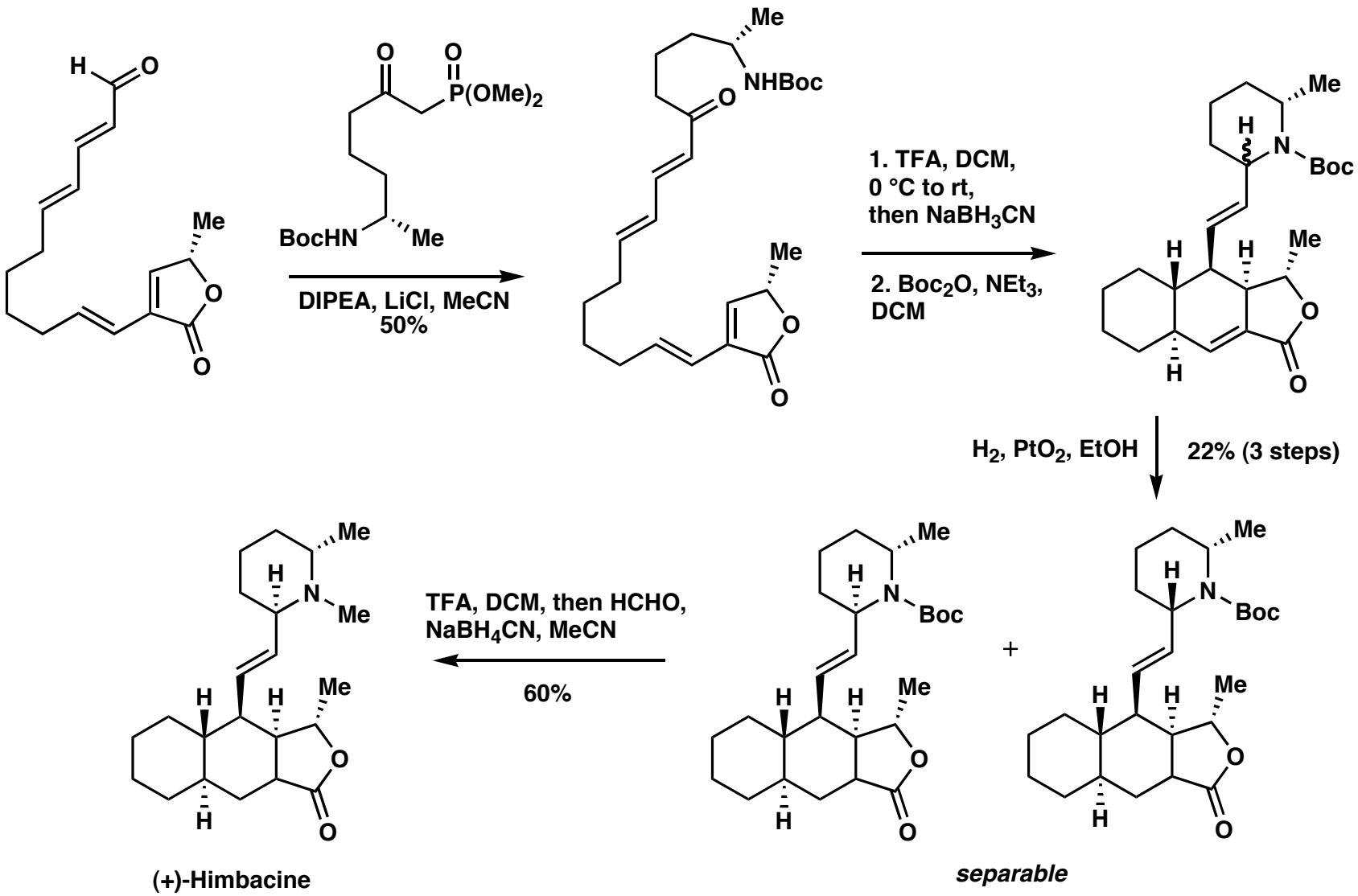
Baldwin Type I Synthesis

Linear polyketide precursor



Tchabenenko, K., Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 585-588.

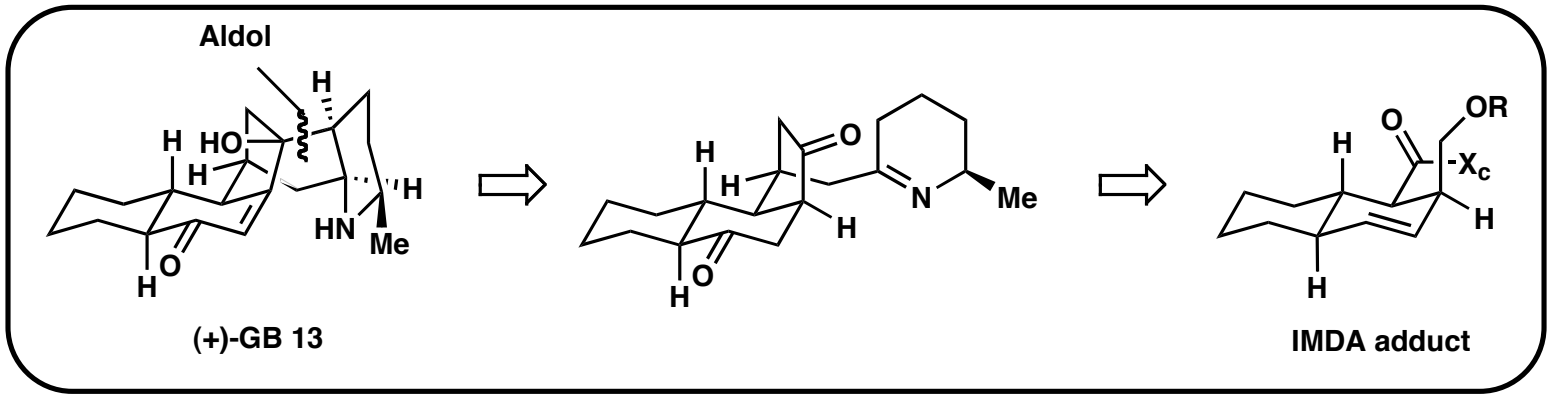
Baldwin

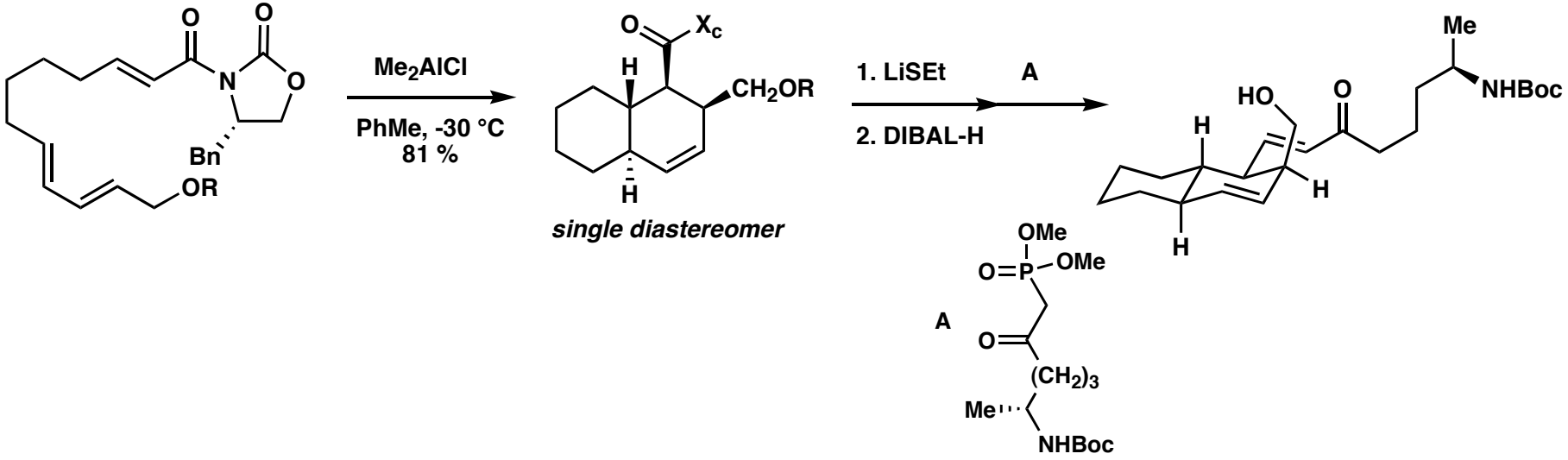


Tchabenenko, K., Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 585-588.

Evans' Approach

Class III: Galbulimima Alkaloid 13

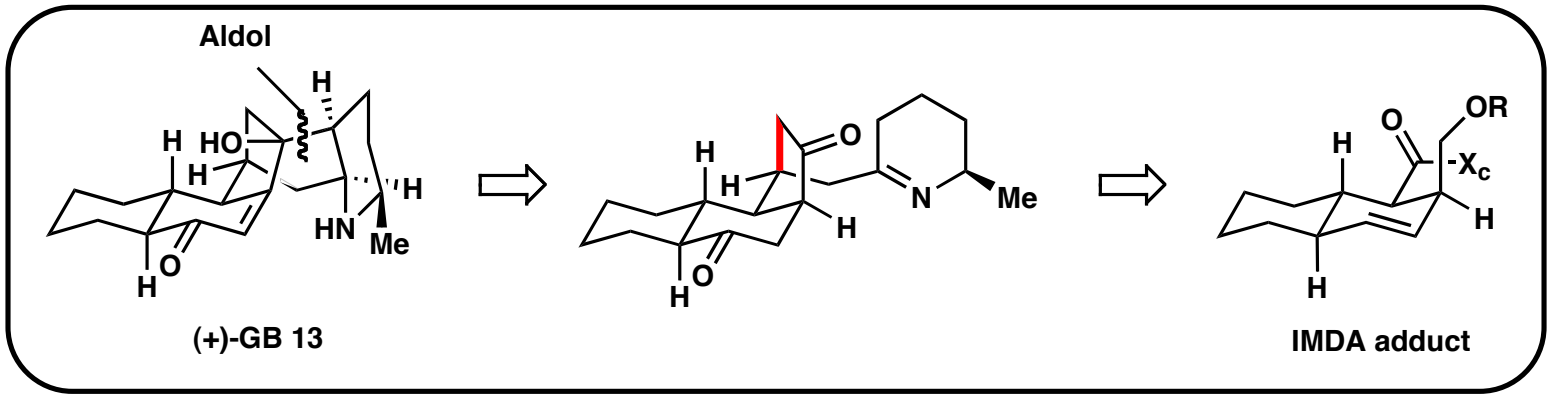




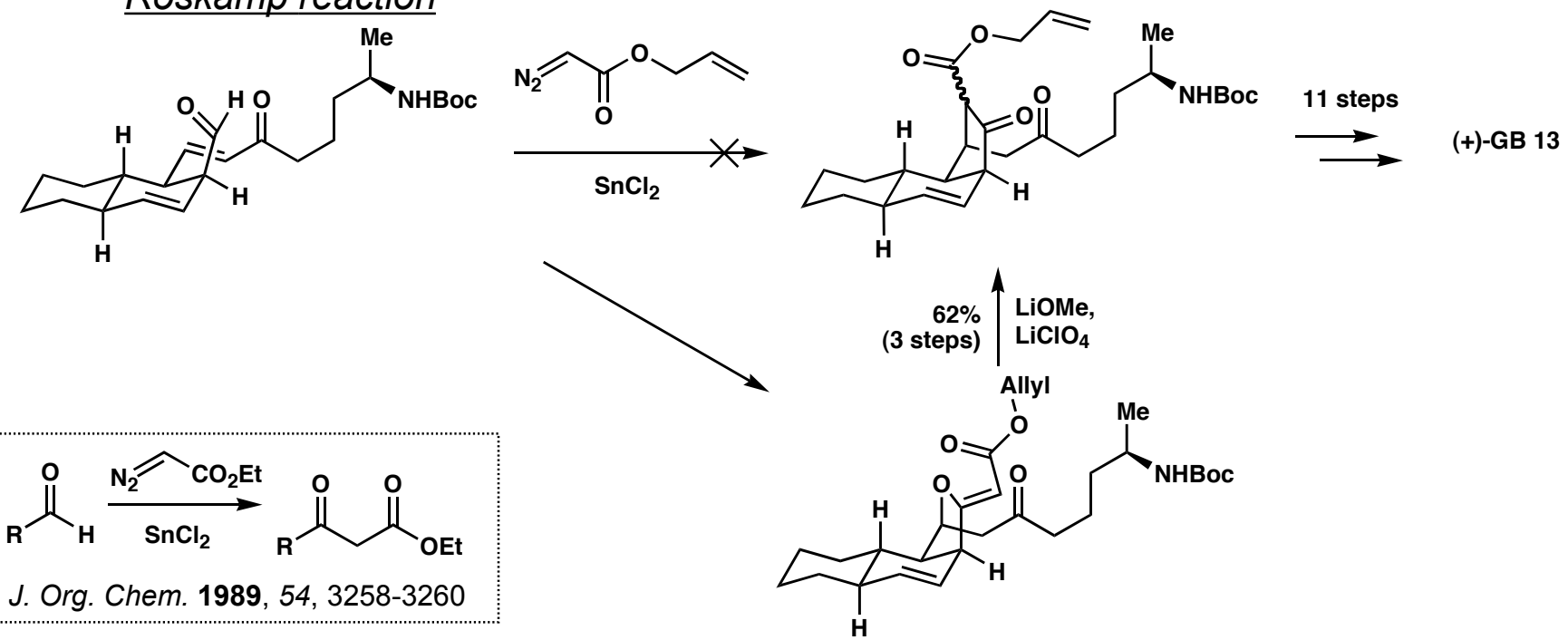
Evans, D. A.; Adams, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1048-1049

Evans' Approach

Class III: Galbulimima Alkaloid 13



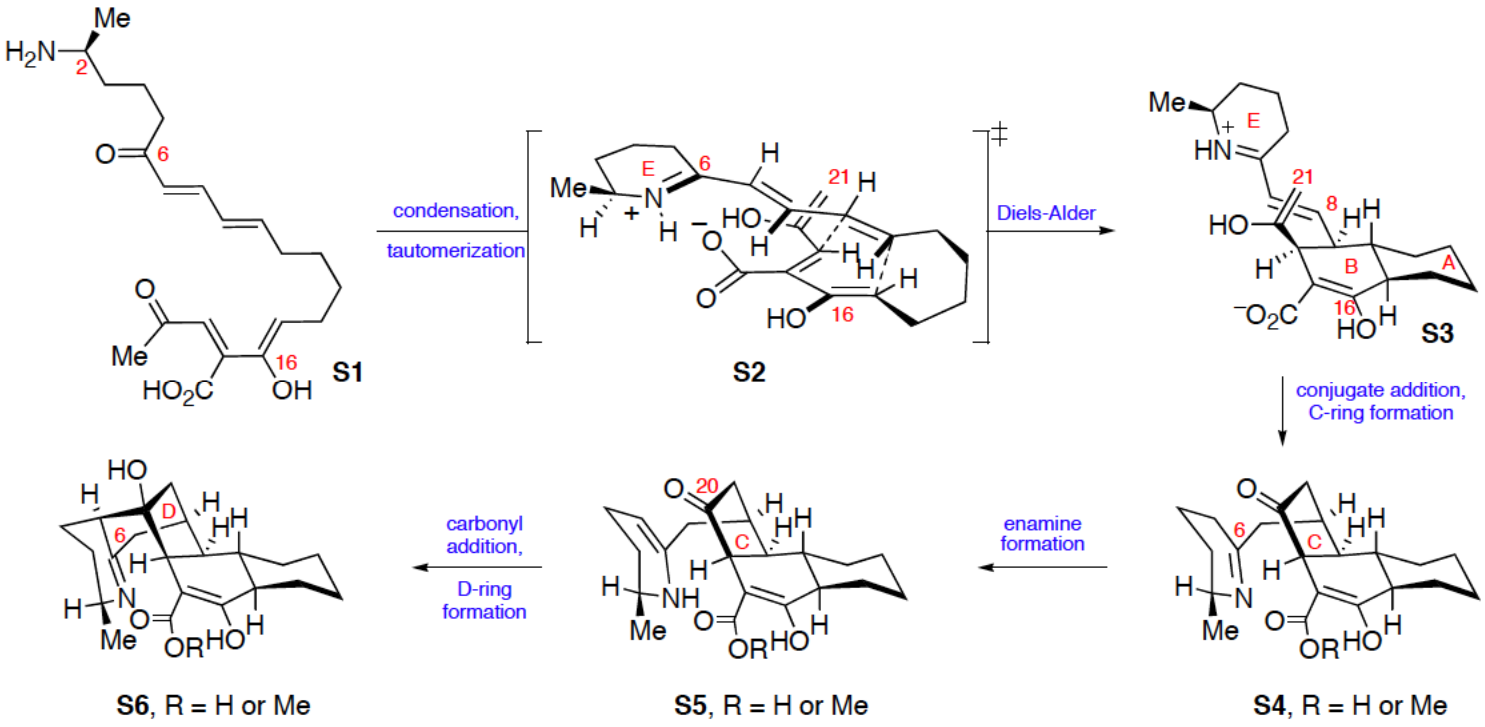
Roskamp reaction

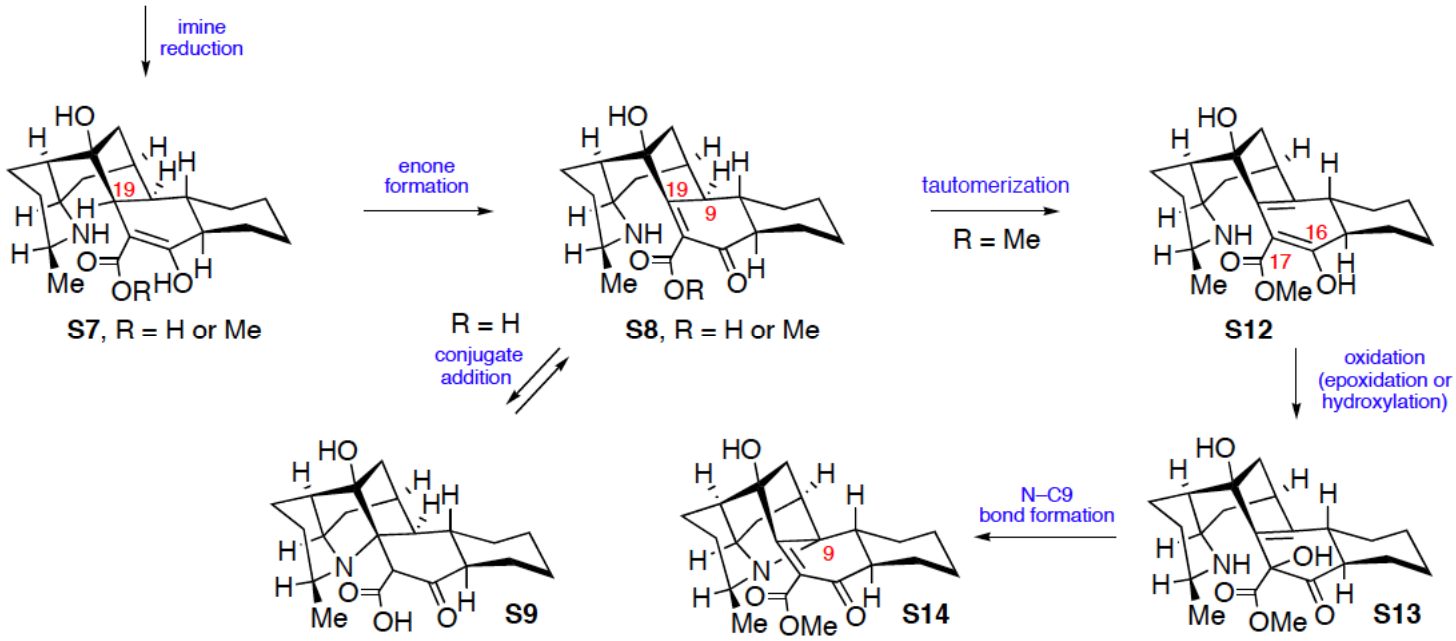


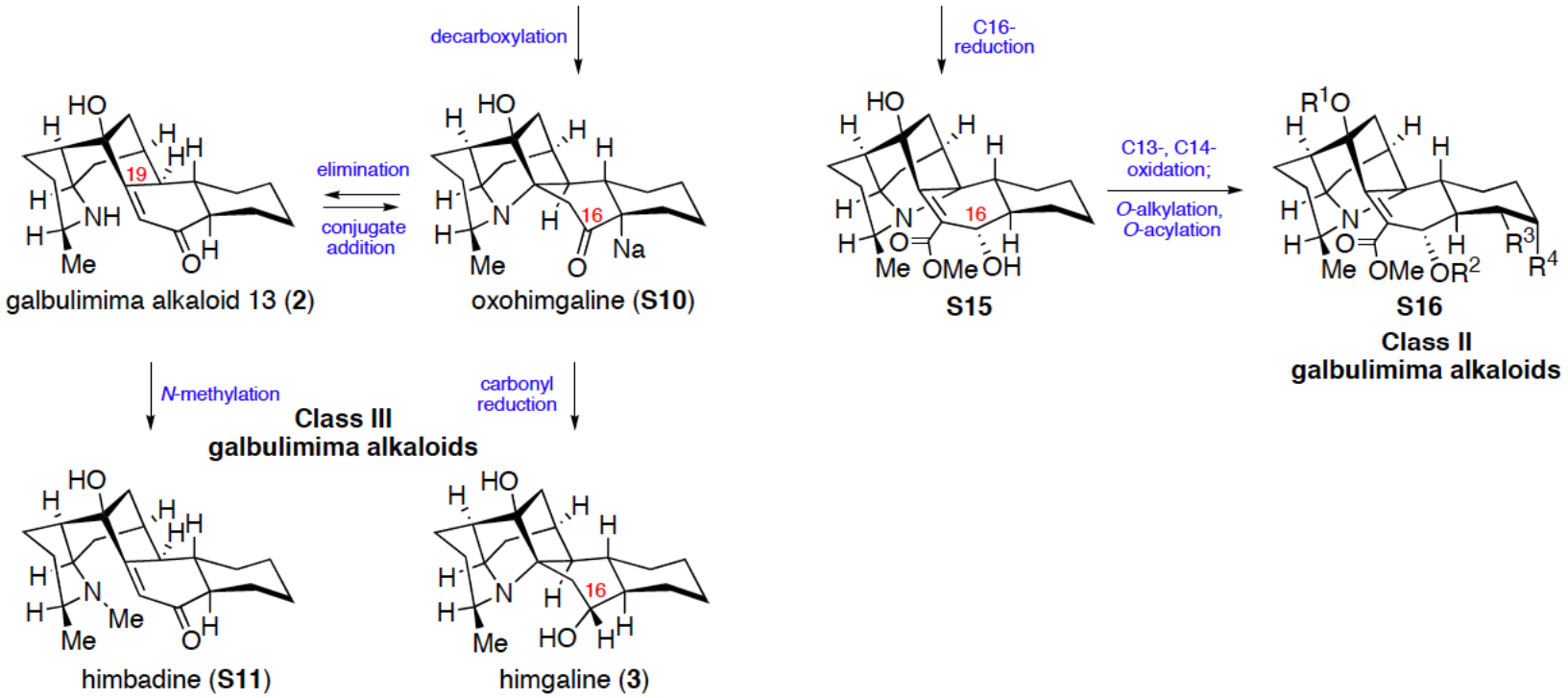
J. Org. Chem. **1989**, *54*, 3258-3260

Evans, D. A.; Adams, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1048-1049

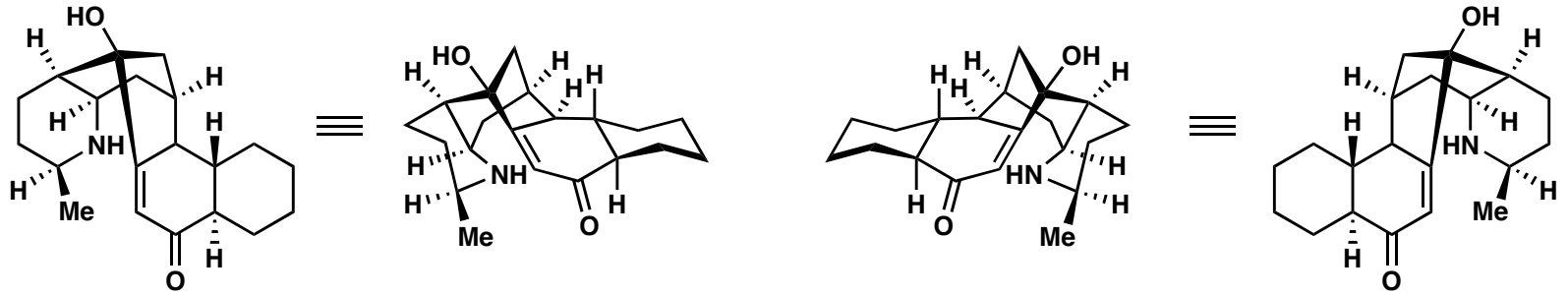
Biosynthetic Proposal (Movassaghi)



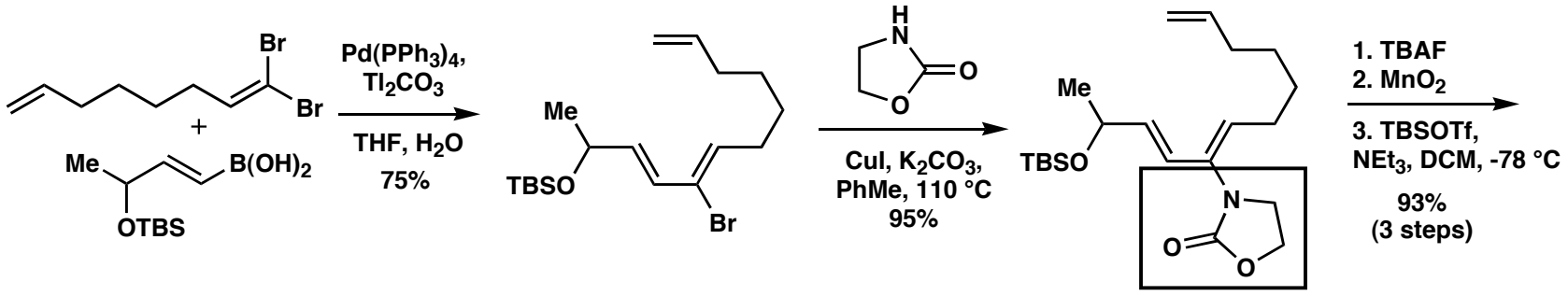

imine reduction
enone formation
tautomerization
R = Me
R = H
conjugate addition
oxidation (epoxidation or hydroxylation)
N–C9 bond formation
S7, R = H or Me
S8, R = H or Me
S12
S9
S14
S13


decarboxylation
C16-
reduction
elimination
conjugate
addition
C13-, C14-
oxidation;
O-alkylation,
O-acylation
N-methylation
carbonyl
reduction
Class III
galbulimima alkaloids
Class II
galbulimima alkaloids
galbulimima alkaloid 13 (2)
oxohimgaline (S10)
S15
S16
himbadine (S11)
himgaline (3)

(+)- and (—)-GB 13 Movassaghi

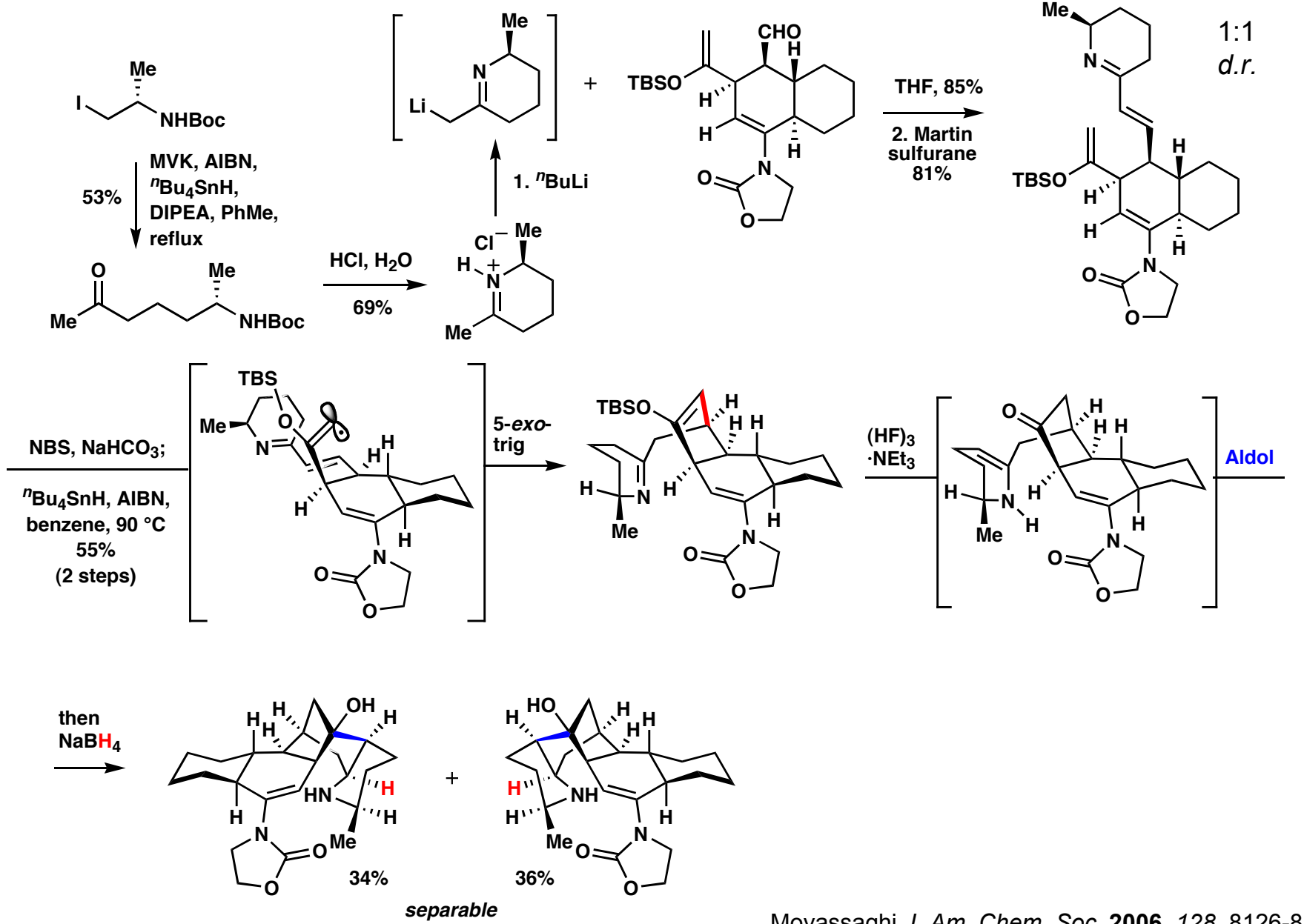


(+) and (—) configuration?



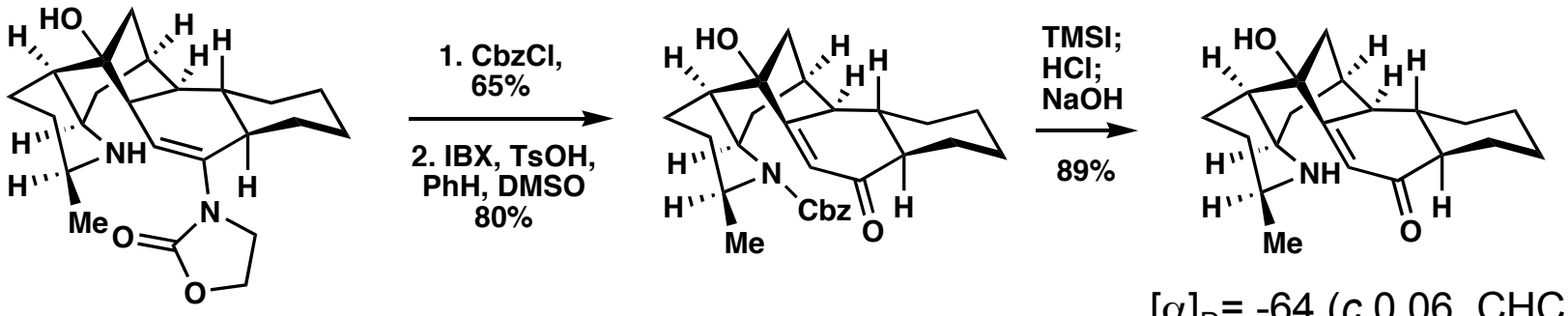
Movassaghi, M.; Hunt, D. K.; Tjandra, M. *J. Am. Chem. Soc.* **2006**, *128*, 8126-8127

(+)- and (—)-GB 13 Movassaghi



Movassaghi *J. Am. Chem. Soc.* **2006**, *128*, 8126-8127

(+)- and (—)-GB 13 Movassaghi

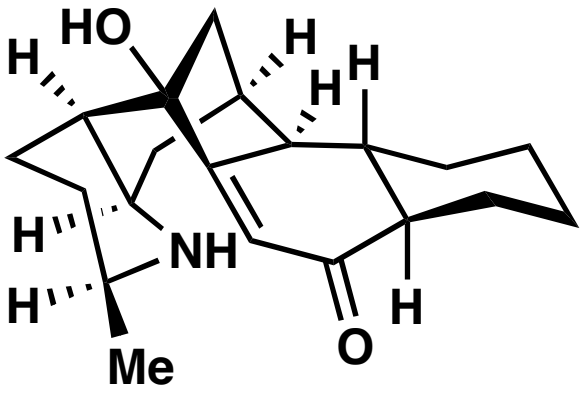


$[\alpha]_D$= -64 (*c* 0.06, $CHCl_3$)
lit. $[\alpha]_D$= -84 ($CHCl_3$)

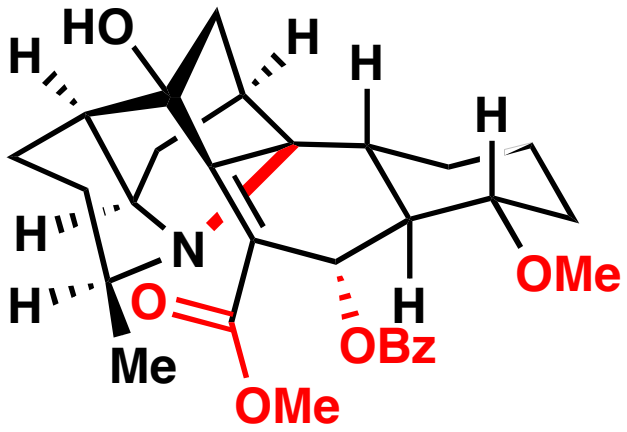
Absolute stereochemical configuration of (—)-galbulimima alkaloid 13 confirmed

Movassaghi *J. Am. Chem. Soc.* **2006**, *128*, 8126-8127

Class II vs. Class III

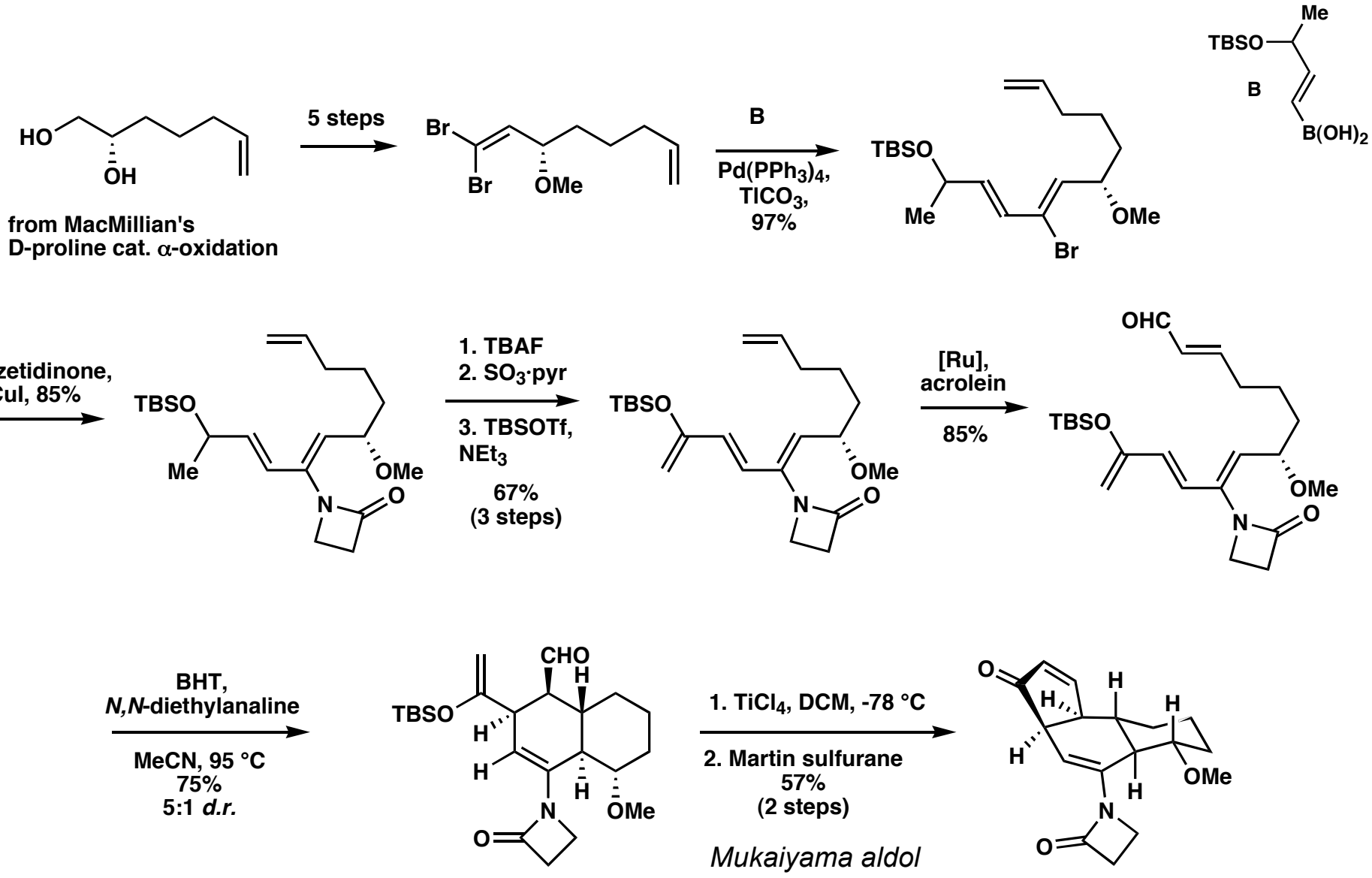


(—)-GB 13

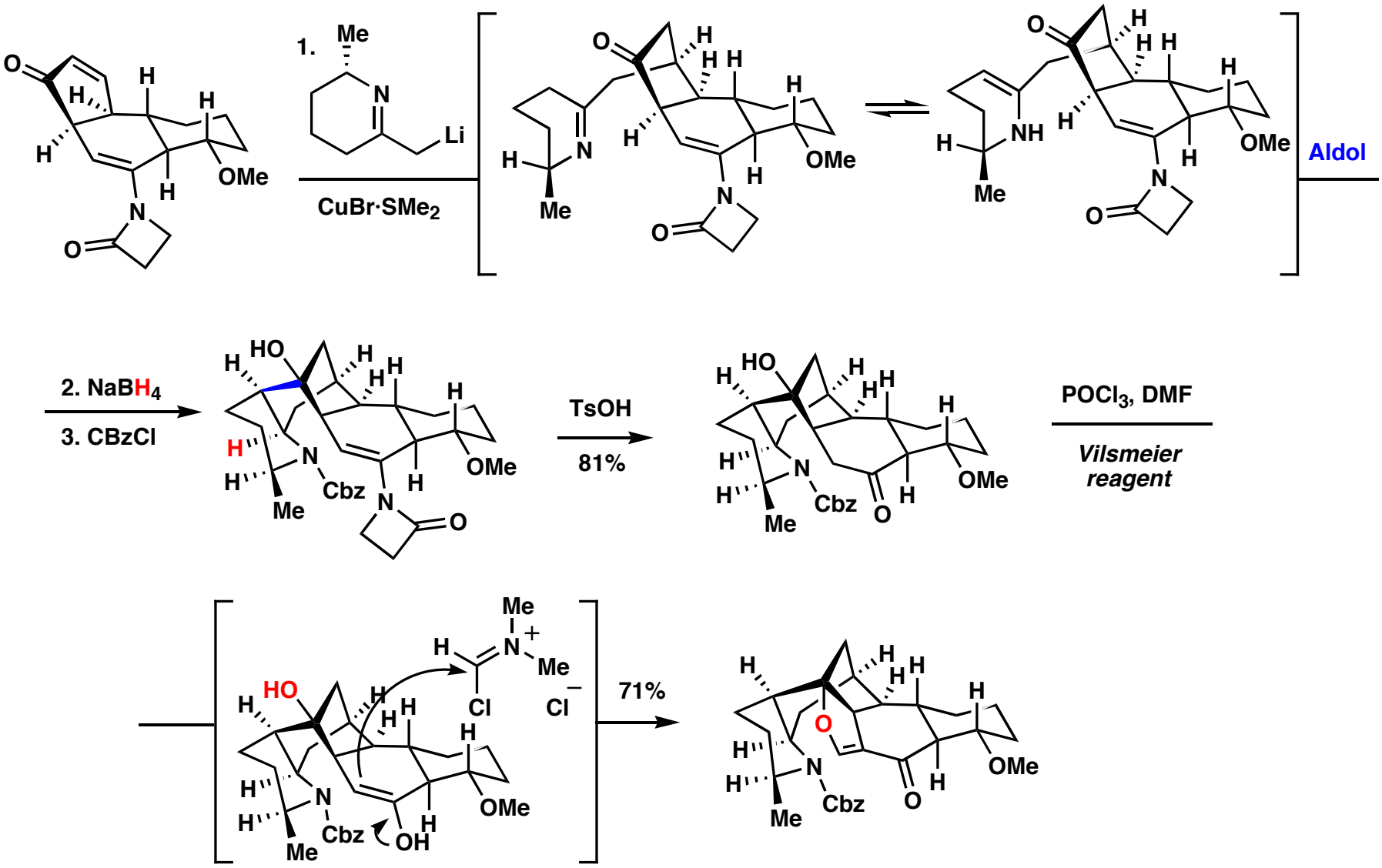


(—)-Himandrine

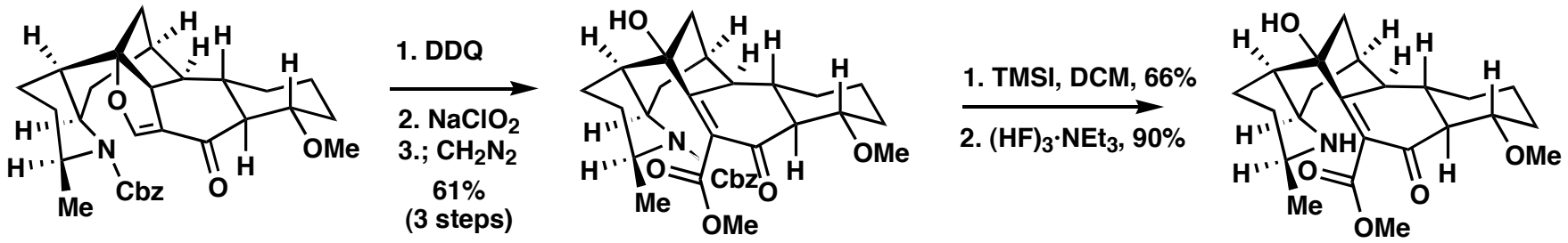
Title Paper

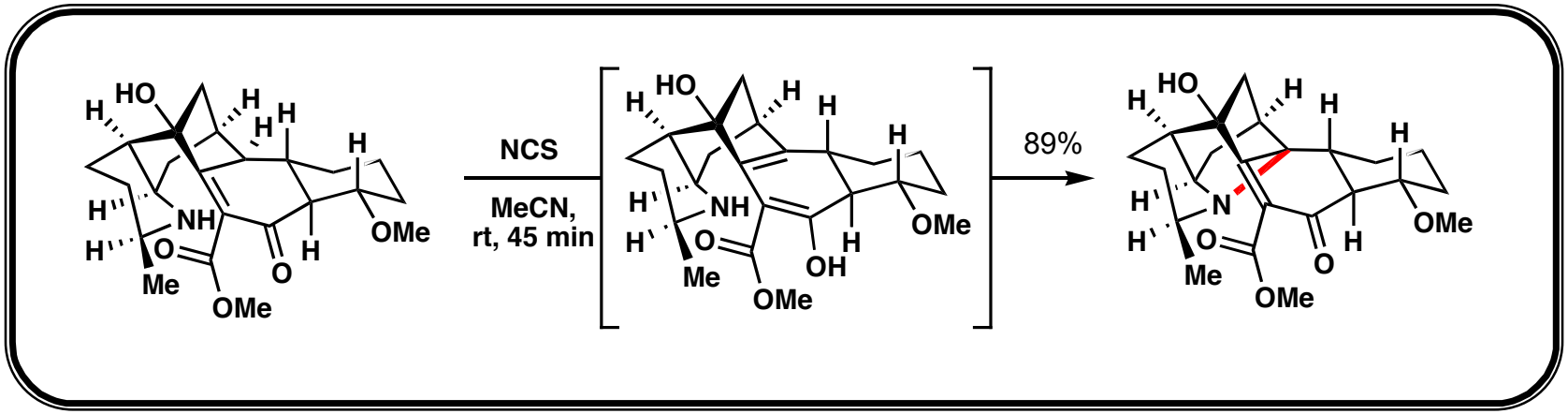

HO
OH
from MacMillian's
D-proline cat. α-oxidation
5 steps
Br
Br
OMe
B
Pd(PPh3)4,
TlCO3,
97%
TBSO
Me
OMe
Br
Me
TBSO
B
B(OH)2
2- azetidinone,
CuI, 85%
TBSO
Me
OMe
N
O
1. TBAF
2. SO3·pyr
3. TBSOTf,
NEt3
67%
(3 steps)
TBSO
OMe
N
O
[Ru],
acrolein
85%
OHC
TBSO
OMe
N
O
BHT,
N,N-diethylanaline
MeCN, 95 °C
75%
5:1 d.r.
CHO
H
TBSO
H
H
H
OMe
N
O
1. TiCl4, DCM, -78 °C
2. Martin sulfurane
57%
(2 steps)
Mukaiyama aldol
O
H
H
H
H
OMe
N
O

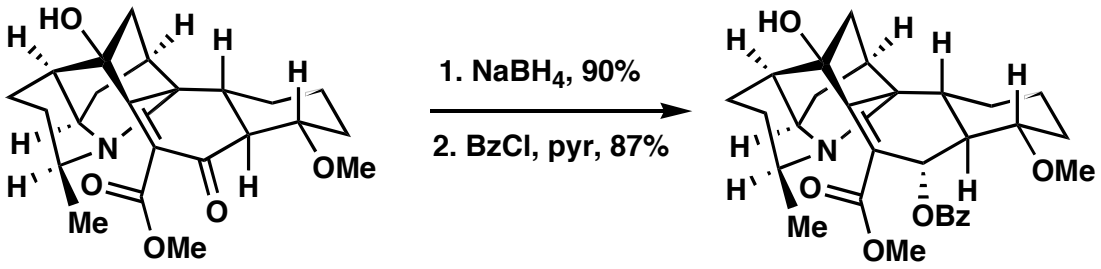
Title Paper


1.
CuBr·SMe2
Aldol
2. NaBH4
3. CBzCl
TsOH
81%
POCl3, DMF
Vilsmeier reagent
71%

Title Paper



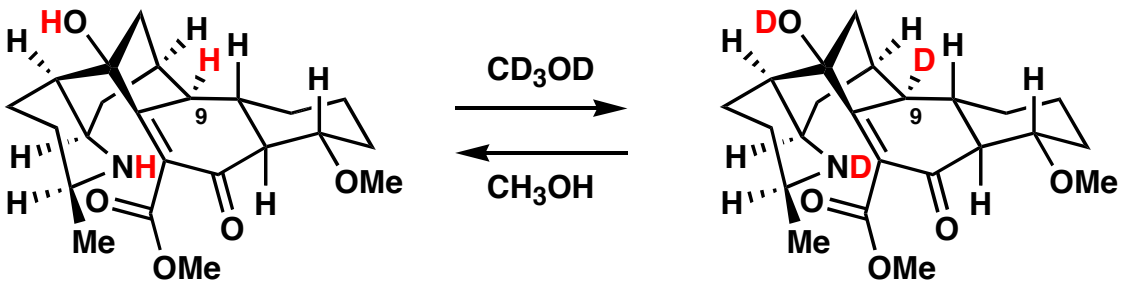


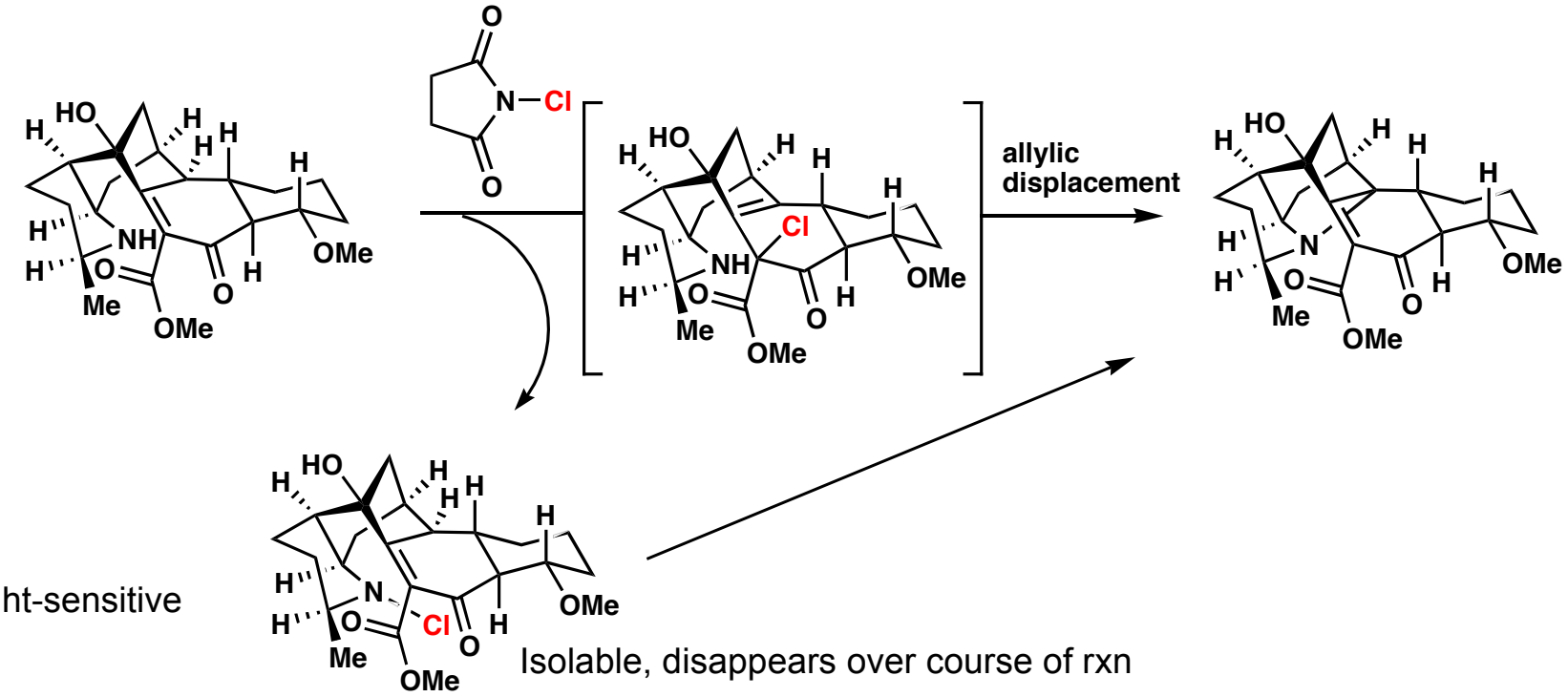


(—)-Himandrine
26 steps

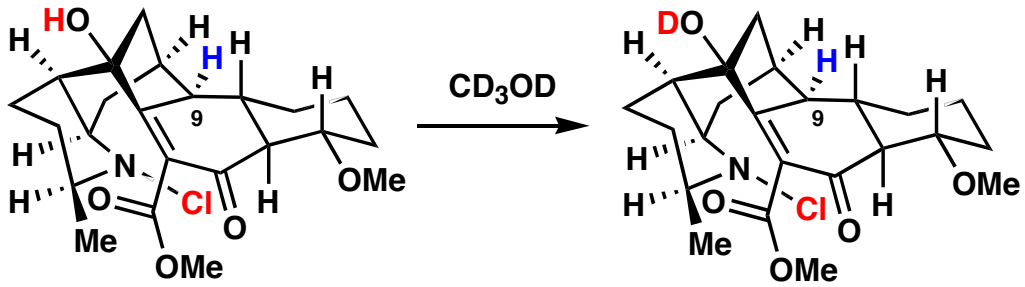
Mechanistic Investigation

Proton delivery assisted by amine
C(9) stereochem. config. preserved

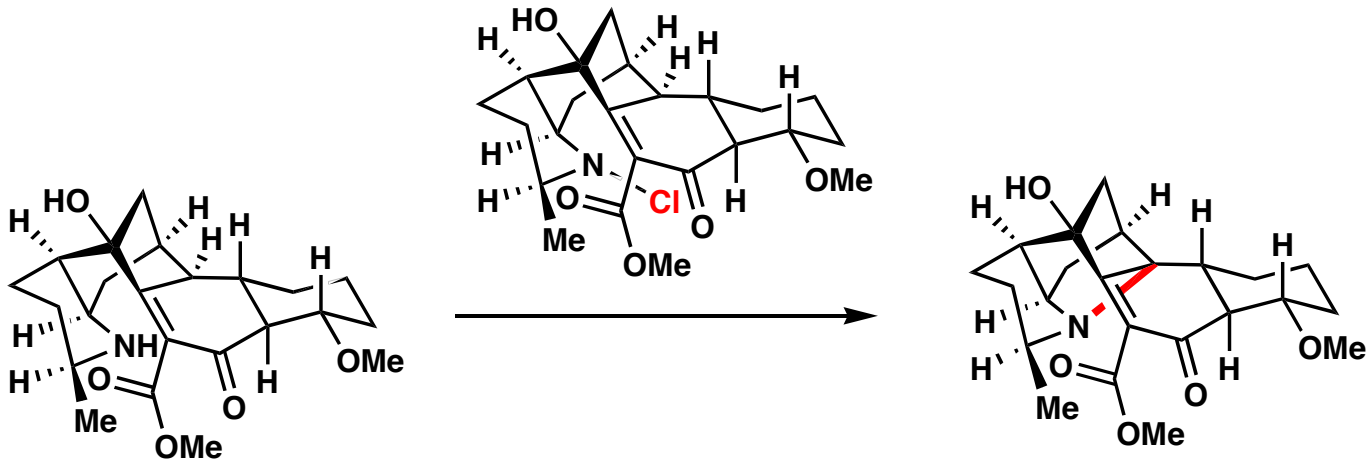




Mechanistic Investigation



No C(9) exchange
(supports intramolecular deprotonation)



Intermolecular transfer of Cl

Conclusions

-The first enantioselective total synthesis of a class II Galbulimima alkaloid has been reported in 26 overall steps

-Late-stage spirocyclic N-C(9) bond construction

-2 key concepts- synthetic design and mechanistic investigation

-“Biologically inspired synthesis”

-Sensitivity of intermediates