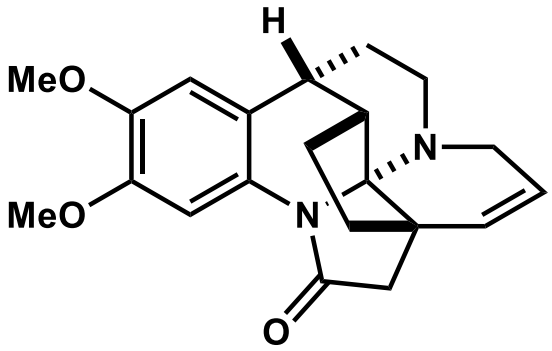
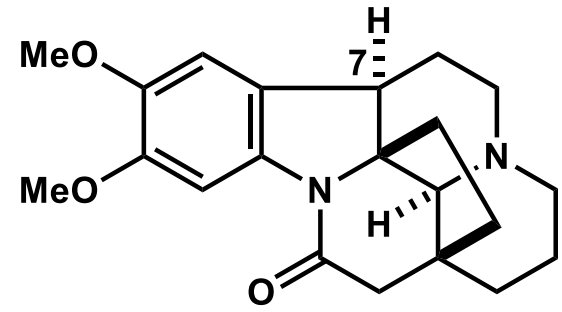
# Total Syntheses of Isoschizogamine

20161014 LS
D3 E. Yoshida




**Isoschizogamine**

**structure revised**




**previously reported structure (thought as a stereoisomer of schizozygane alkaloids)**

**Isolation** (from Schizozygia caffaeoides)

U. Renner *et al.*, *Experientia*, **19**, 244 (1963)

U. Renner, *Lloydia*, **27**, 406 (1964)

**Structure Revision**

J. Hájícek *et al.*, *Tetrahedron Lett.*, **39**, 505 (1998)

**Total Synthesis**

H. Heathcock *et al.*, *Org. Lett.*, **1**, 1315 (1999) (±)

T. Fukuyama *et al.*, *J. Am. Chem. Soc.*, **134**, 11995 (2012) (–)

Y. Qin *et al.*, *Chem. Eur. J.*, **21**, 14602 (2015) (–)

H. Tokuyama *et al.*, *Chem. Eur. J.*, **21**, 16400 (2015) (–)

J. Zhu *et al.*, *Angew. Chem. Int. Ed.*, **54**, 14937 (2015) (–)

**Synthetic Studies**

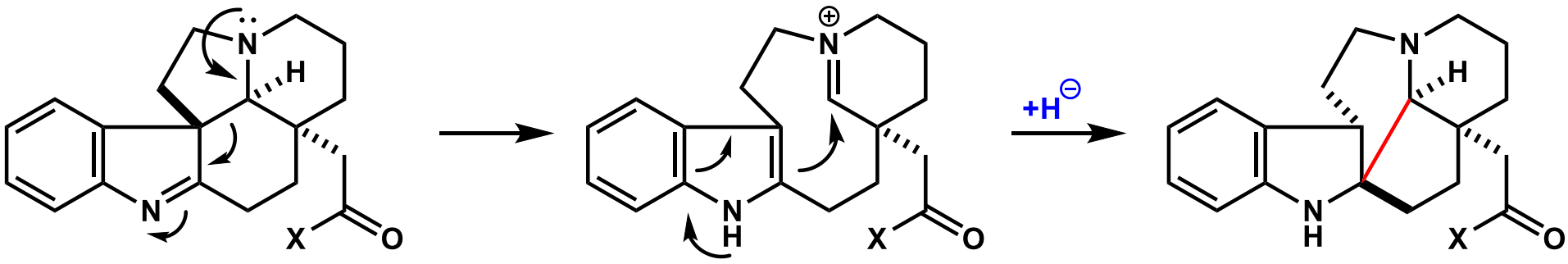
A. Padwa *et al.*, *Org. Lett.*, **7**, 2925 (2005)

J. Zhou *et al.*, *J. Org. Chem.*, **72**, 3808 (2007)

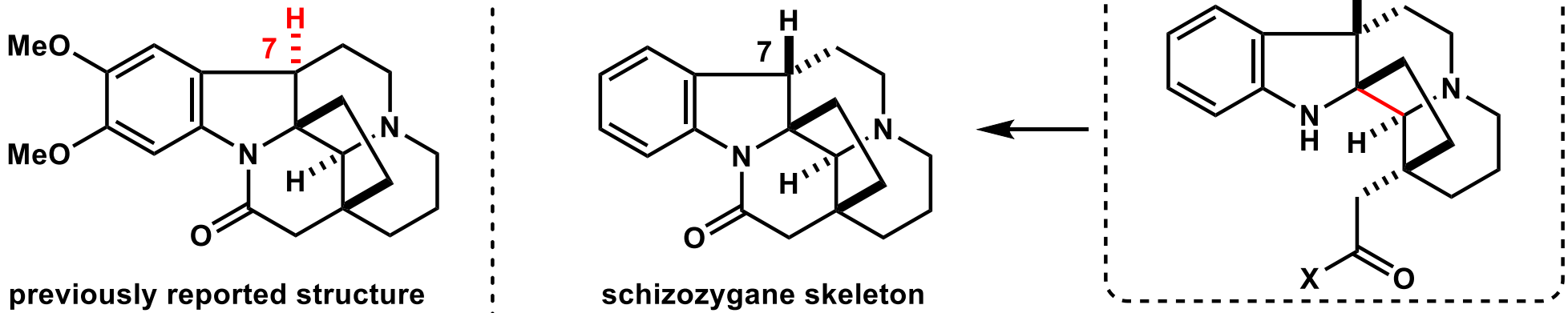
**Today's topics**

**1. Biosynthesis**
**2. Biomimetic syntheses**
**2.1 Heathcock**
**2.2 Zhu (main paper)**
**2.3 Qin**
**2.4 Fukuyama**
**3. De novo synthesis**
**3.1 Tokuyama (main paper)**
**4. Summary**

# 1. Biosynthesis of Schizozygane Skeleton



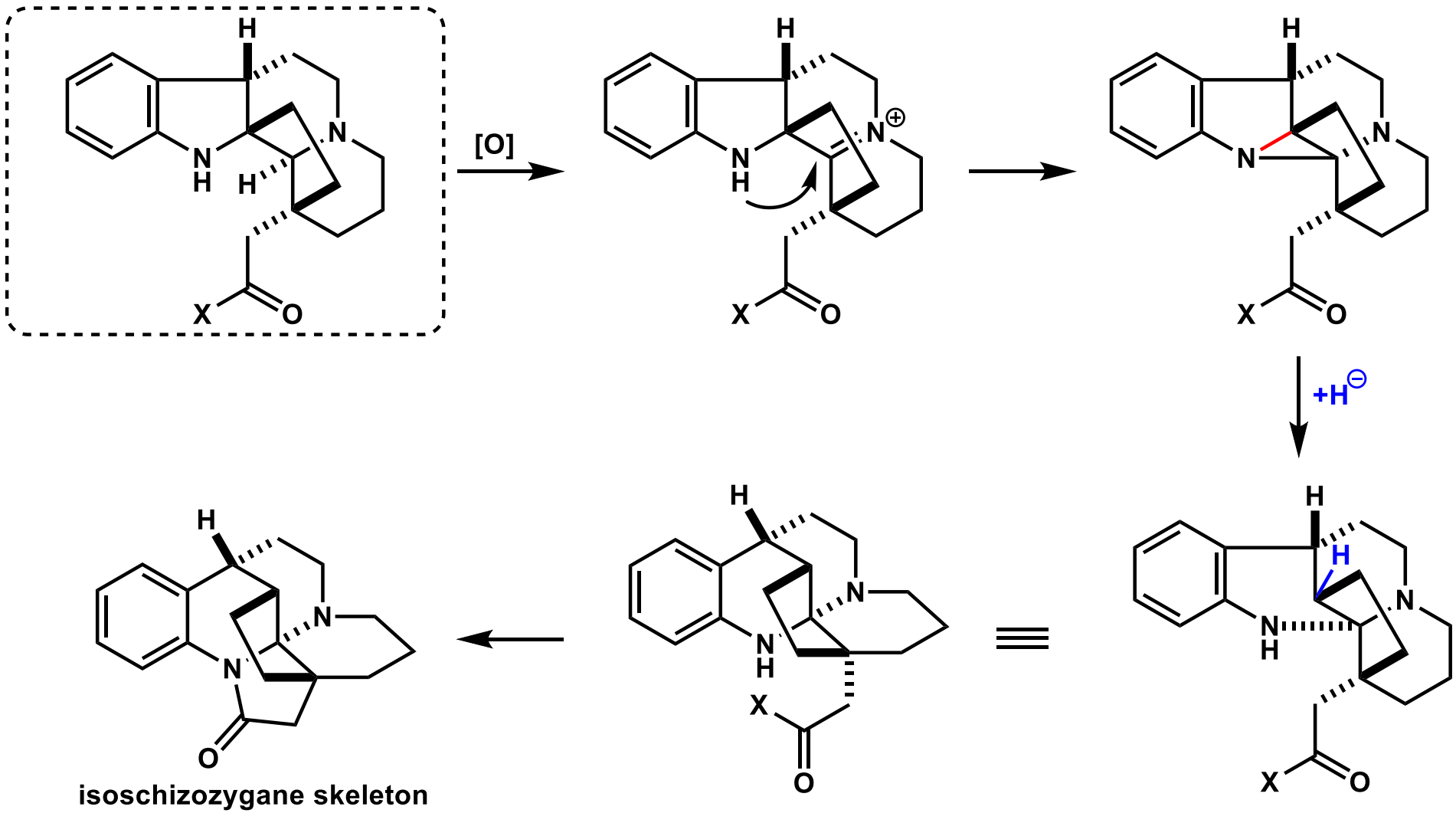

aspidosperma skeleton




schizozygane skeleton

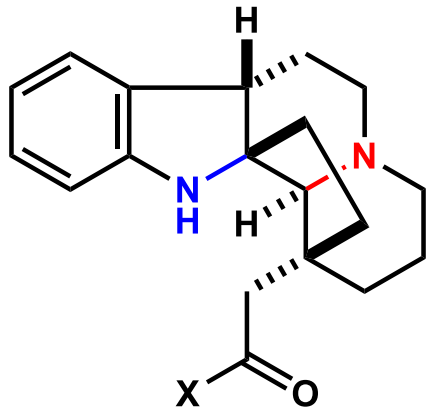
previously reported structure of Isoschizogamine

# Biosynthesis of Isoschizozygane Skeleton

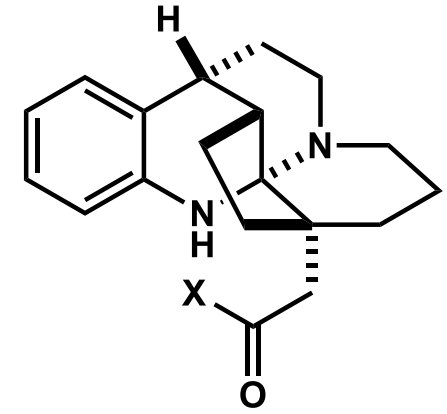


# 2.1 Heathcock's Approach

Biosynthesis:



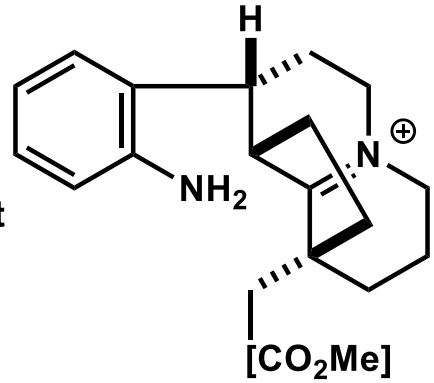

1) oxidation
2) aziridine formation
3) reduction




the same oxidation state

aminal formation

Human:
No need to start from indoline

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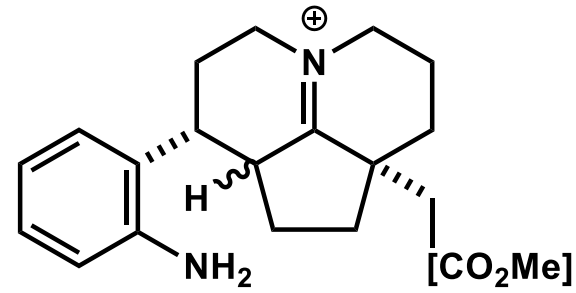
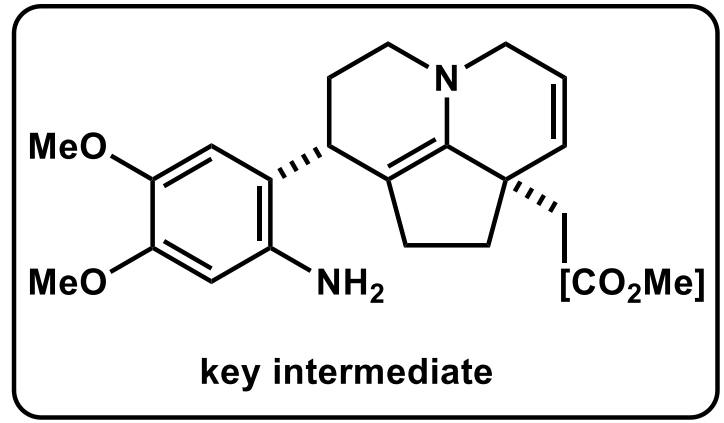
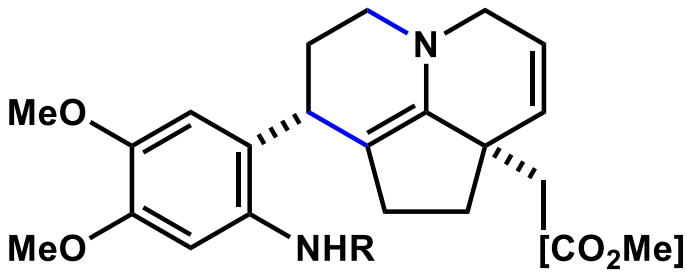


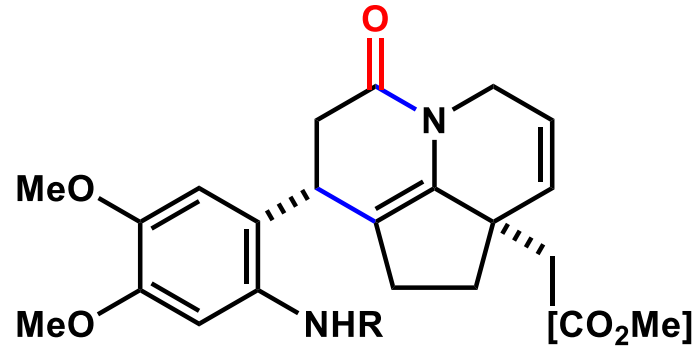



# Retrosynthesis of Key Intermediate



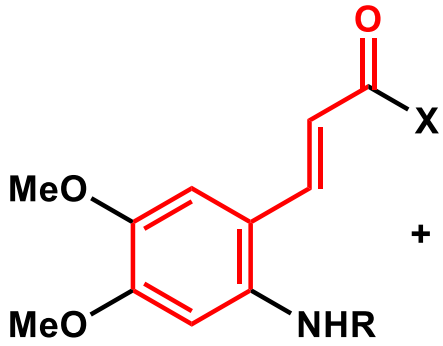

key intermediate

FGI*



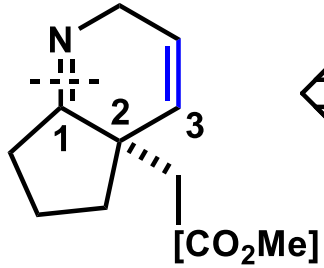

* Functional Group Interconversion
: Introducing "unnecessary" groups
for easier disconnection

C-X disconnection



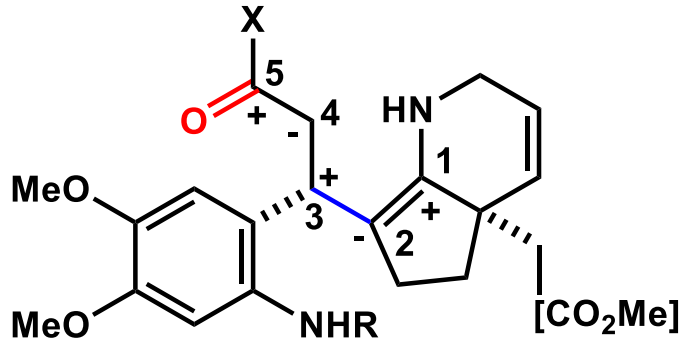

retron of
Knoevenagel rxn.

\+



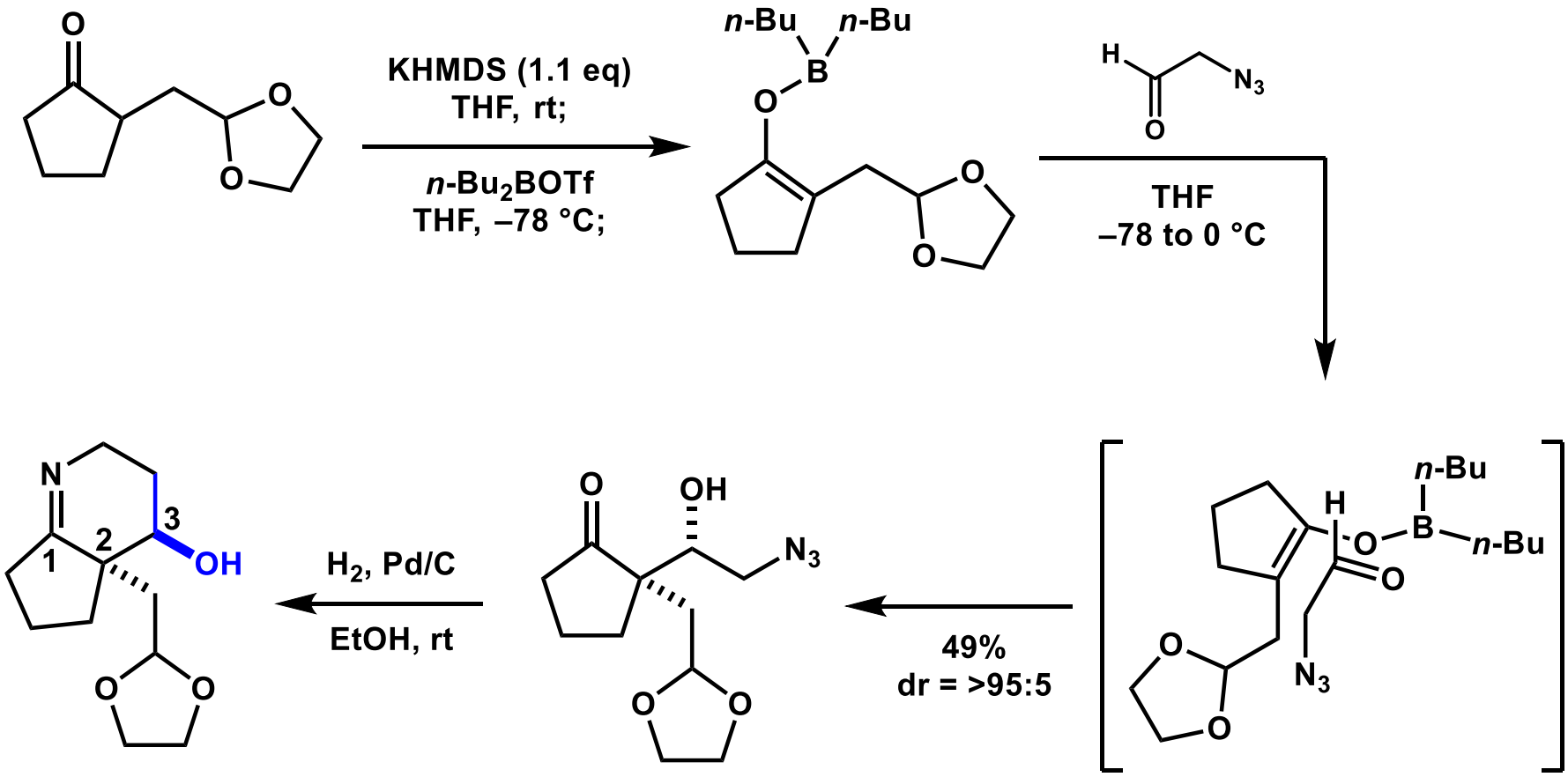

FGI?

1,5-diX**

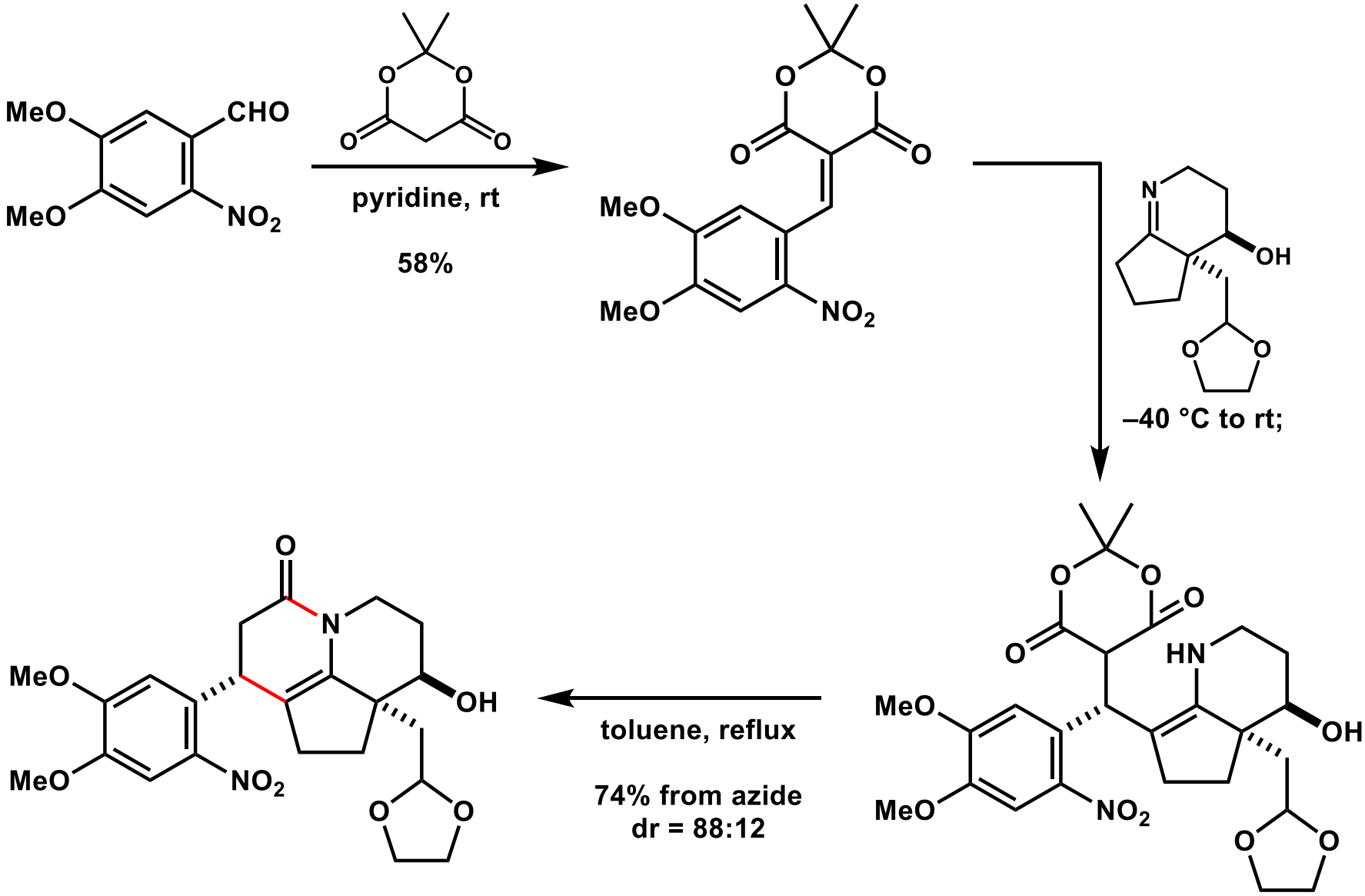



** 1,5-difunctional disconnection
: "Natural disconnection" depending on latent polarity

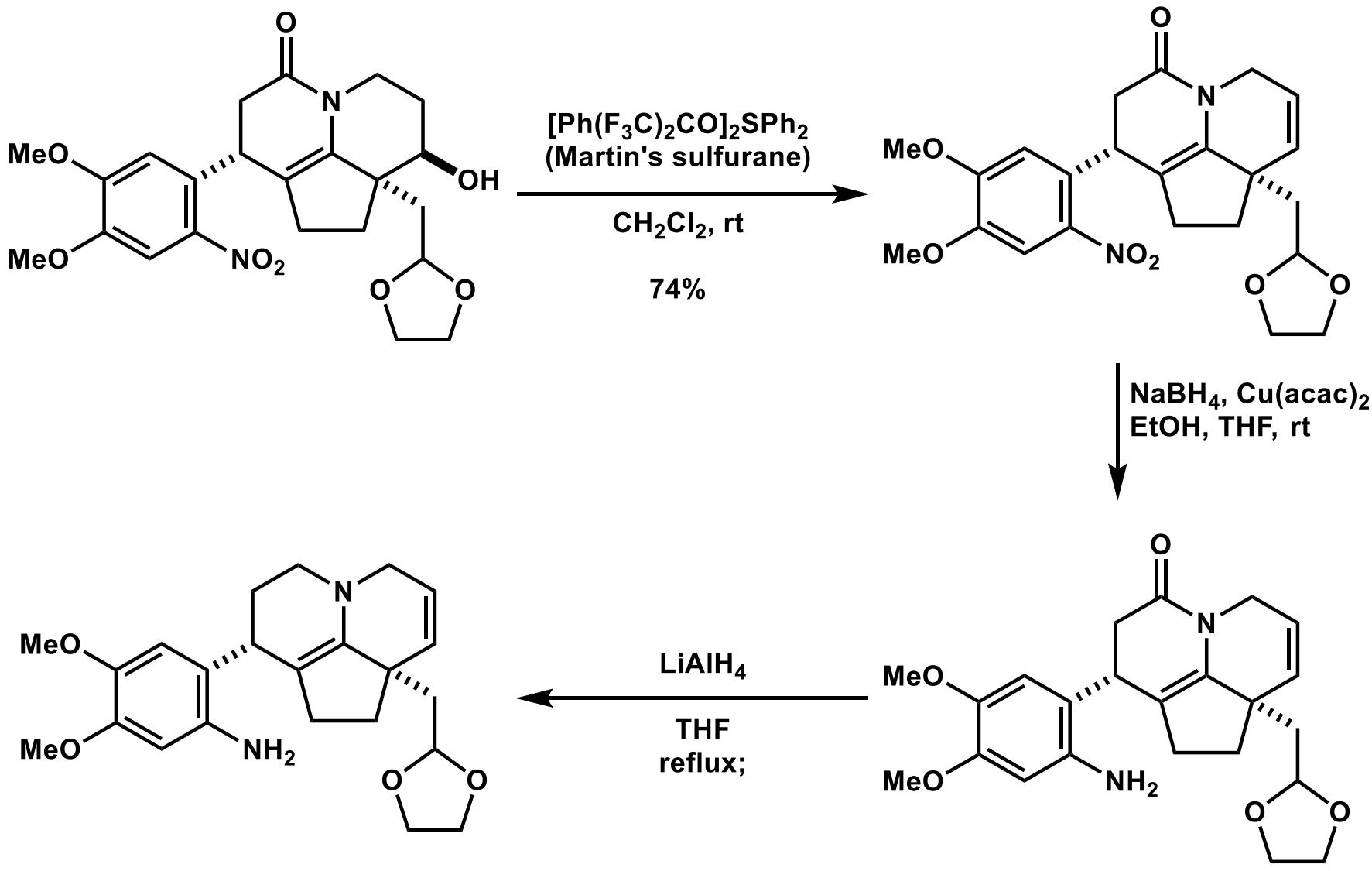
# Synthesis of Right Unit



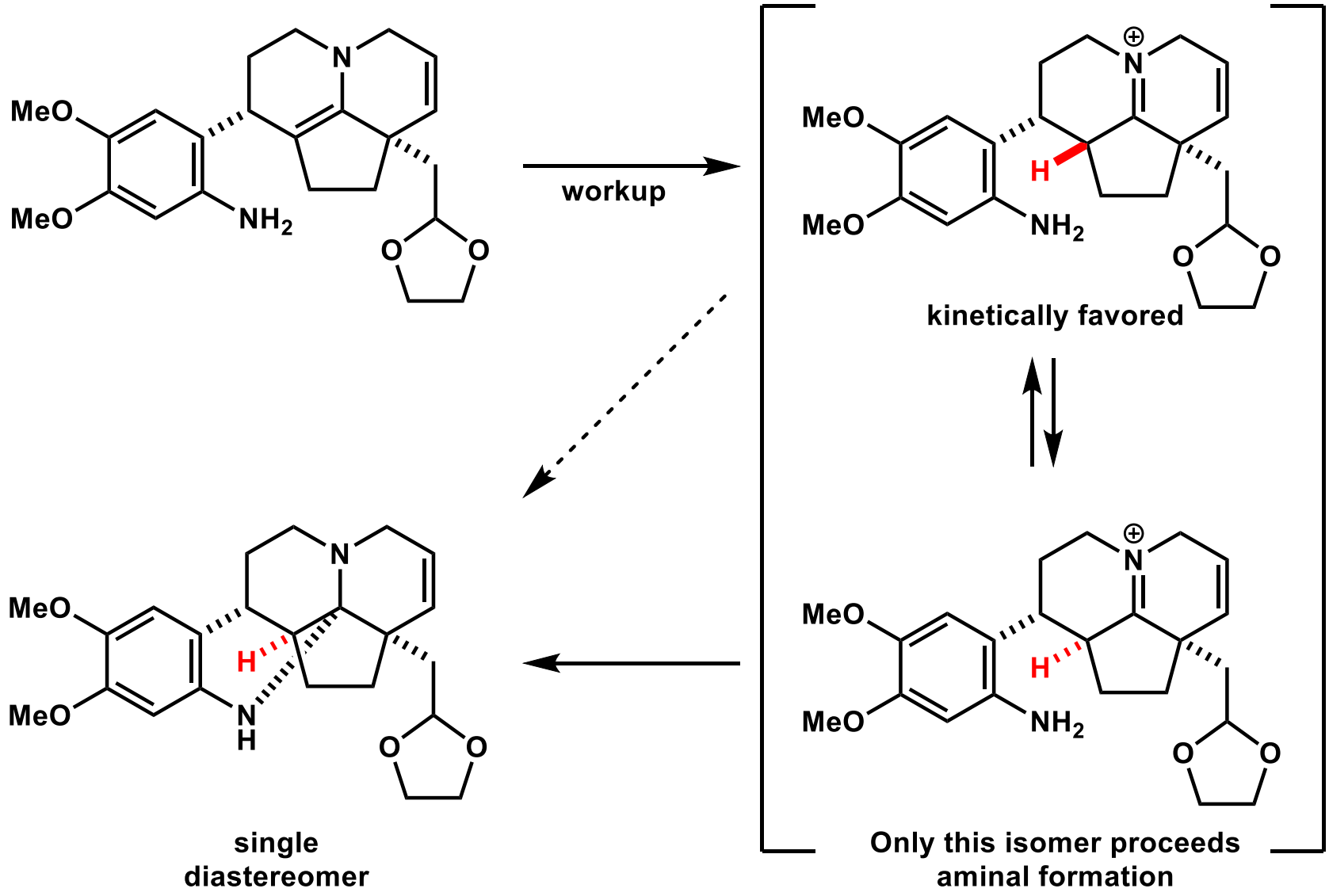
# Lactam Formation



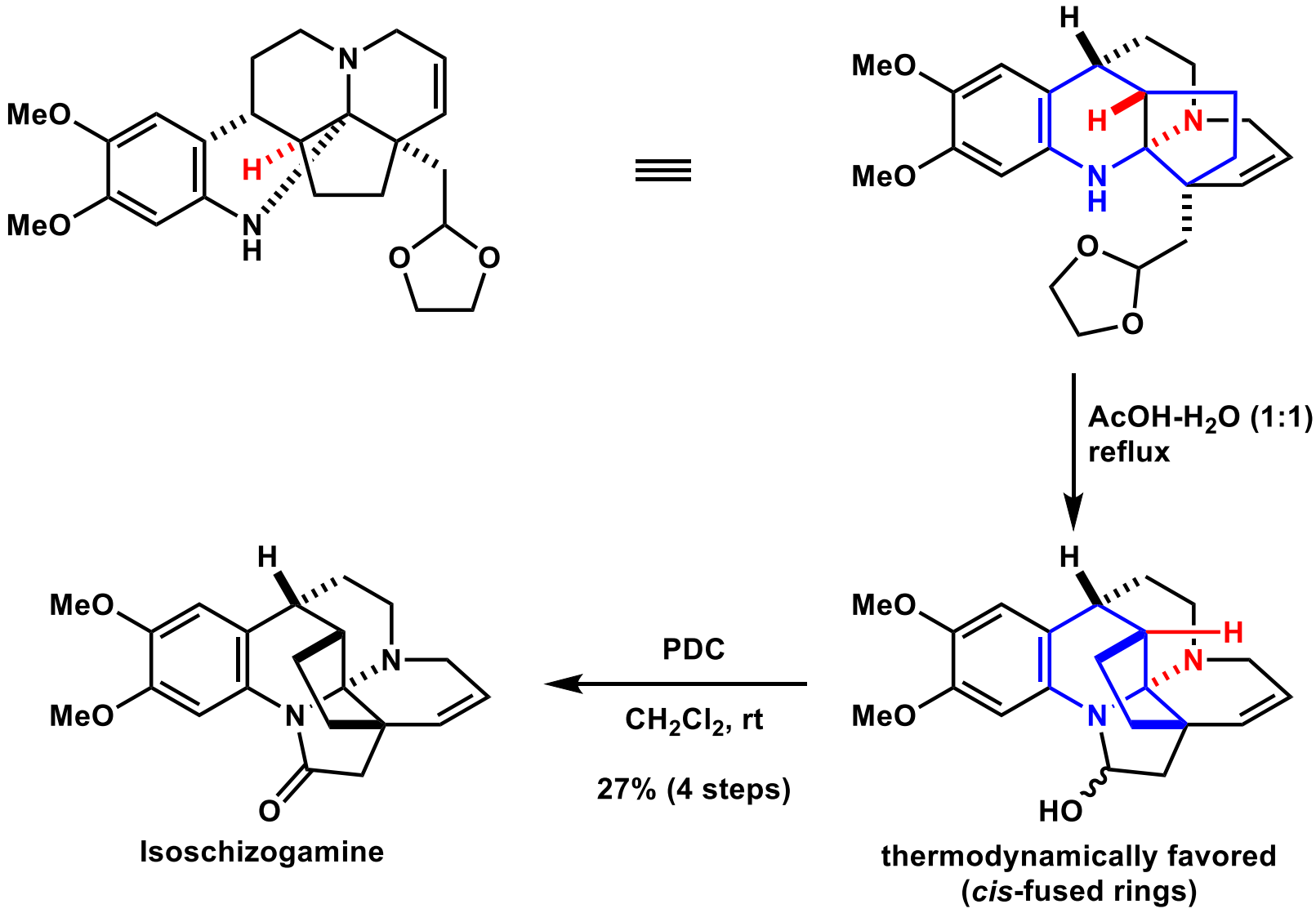
# Synthesis of Key Intermediate



# Aminal Formation (Undesired Isomer)



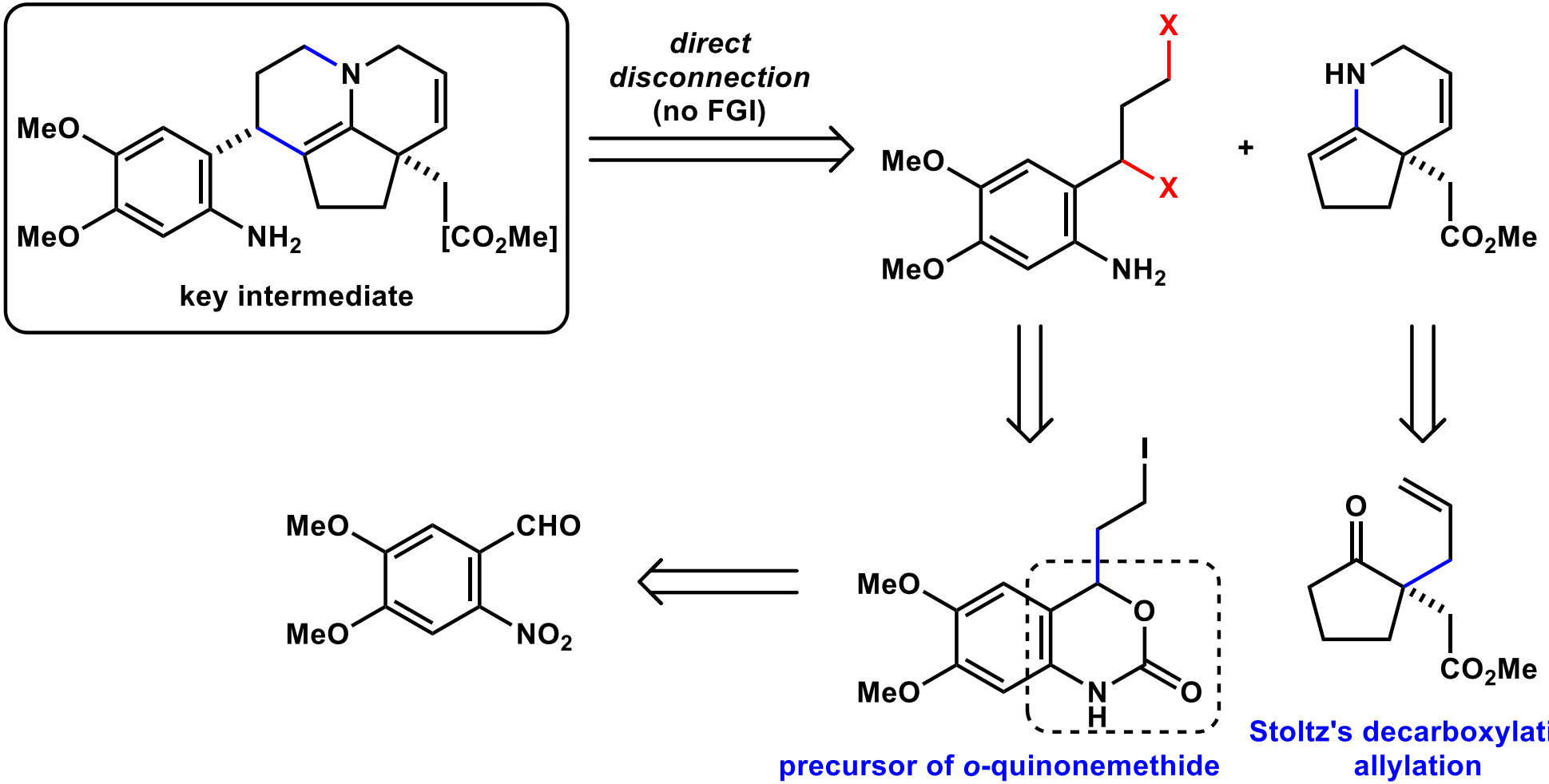
# Isomerization to Thermodynamic Product



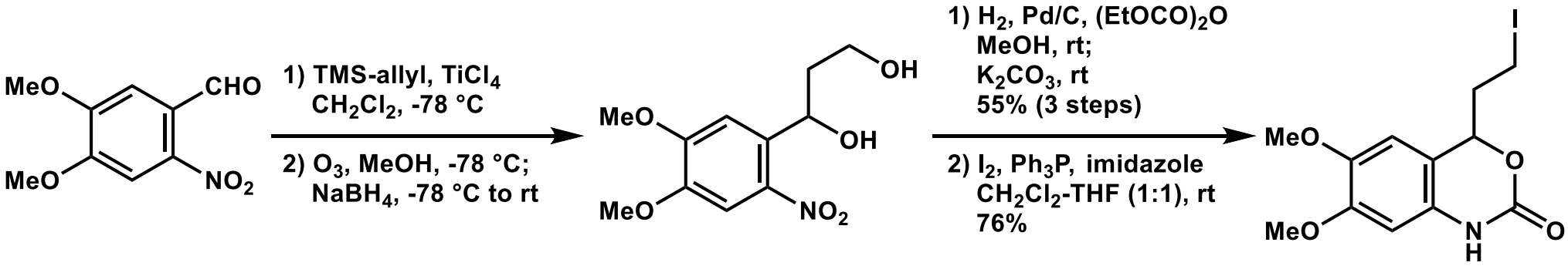

Isoschizogamine

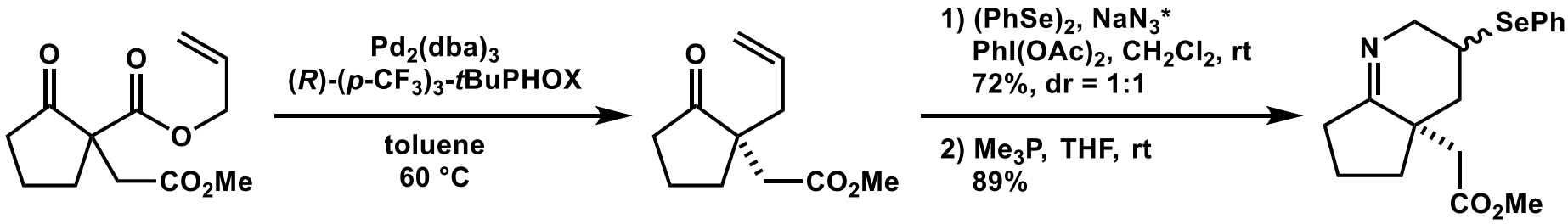
thermodynamically favored
(*cis*-fused rings)

# 2.2 Zhu's Approach (Main Paper)



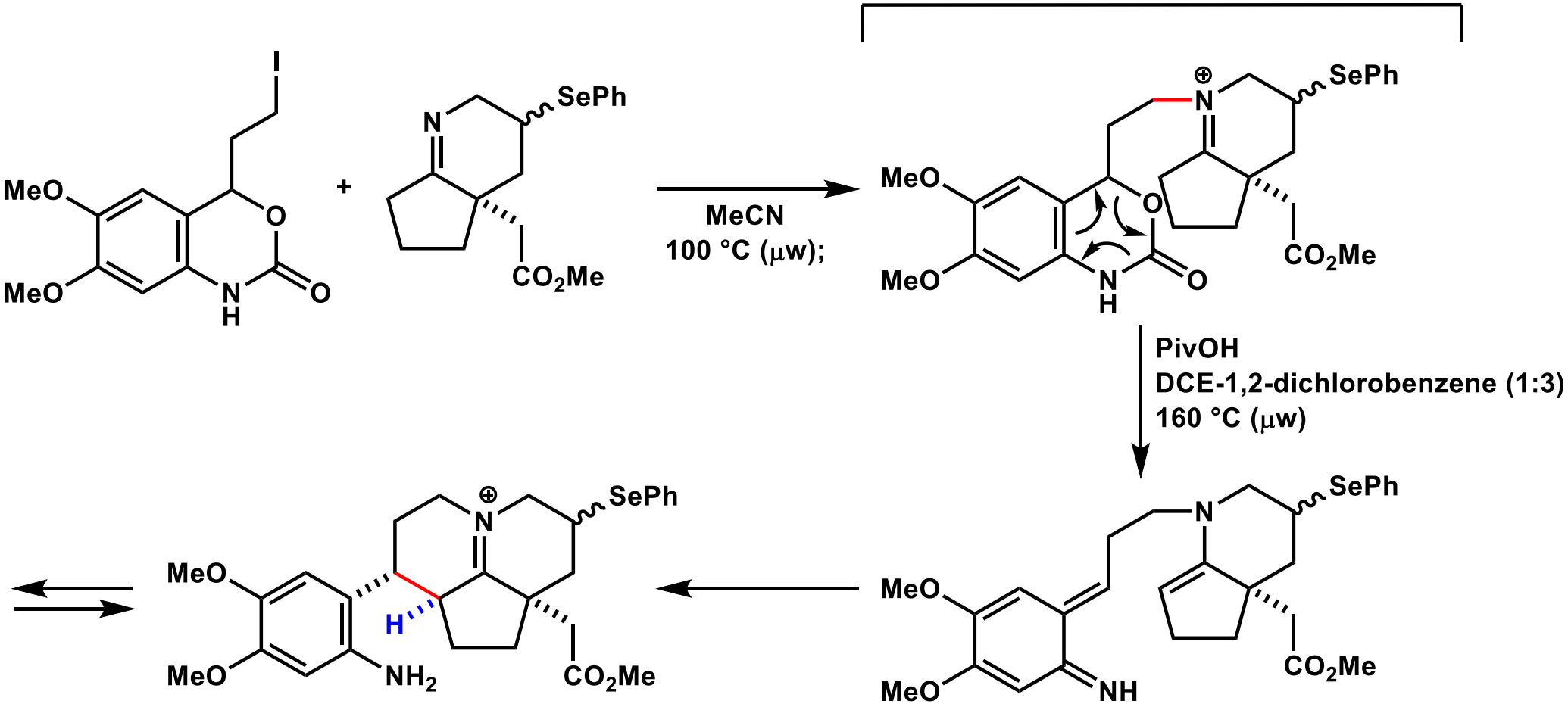
# Syntheses of Two Units



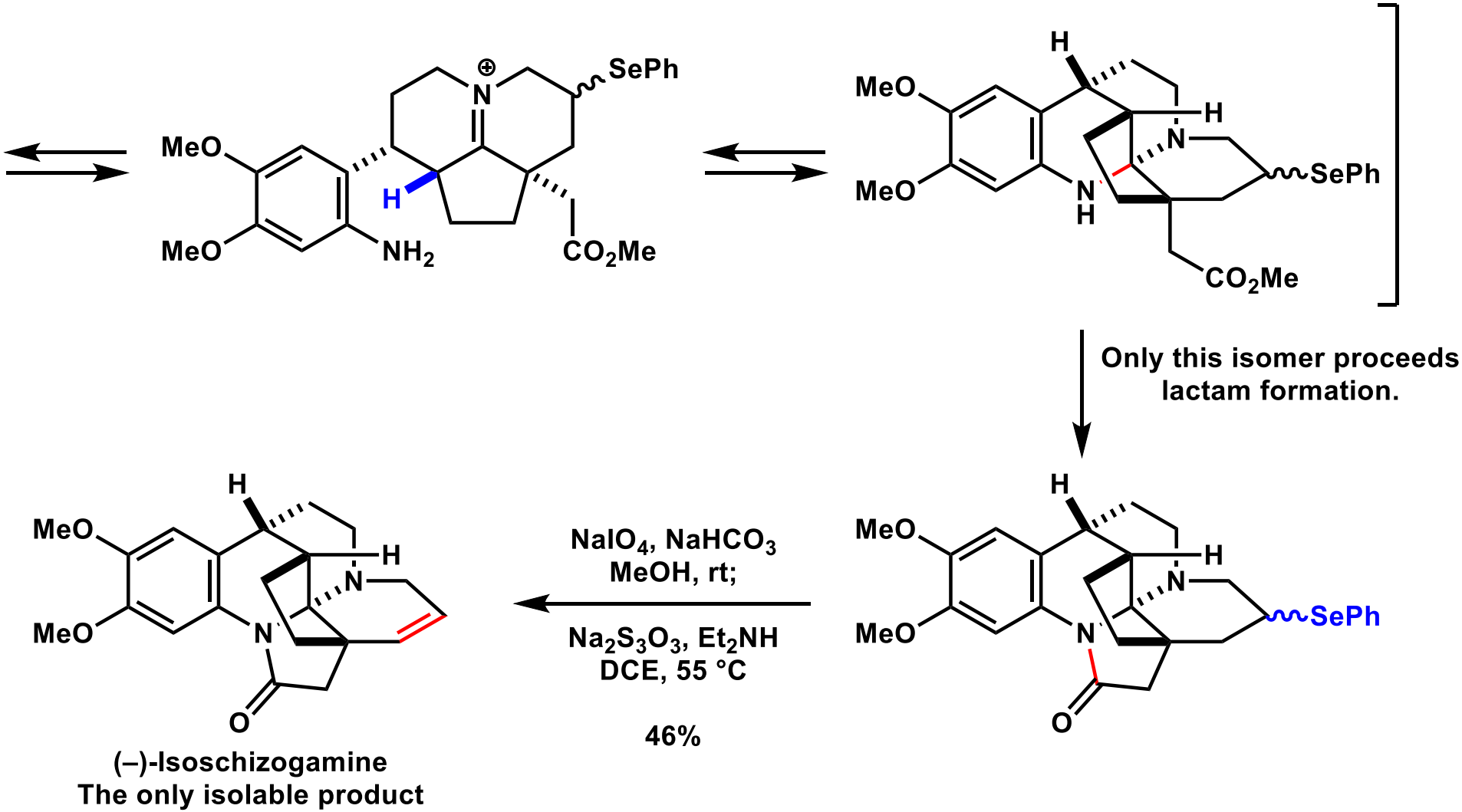




* Addition of $N_3$ radical is proposed.
see: *JOC*, 56, 6809 (1991)

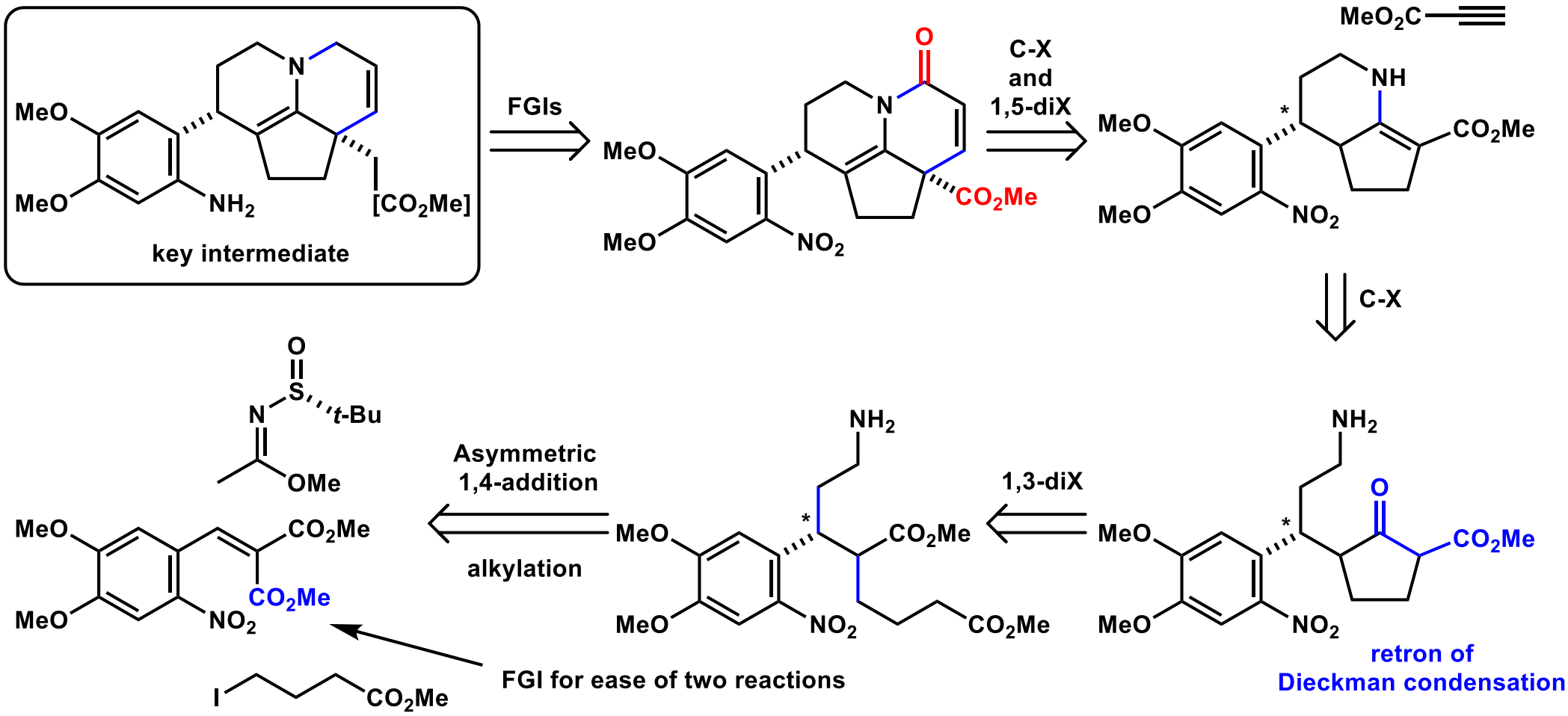
# The Key Cascade Reaction 1/2



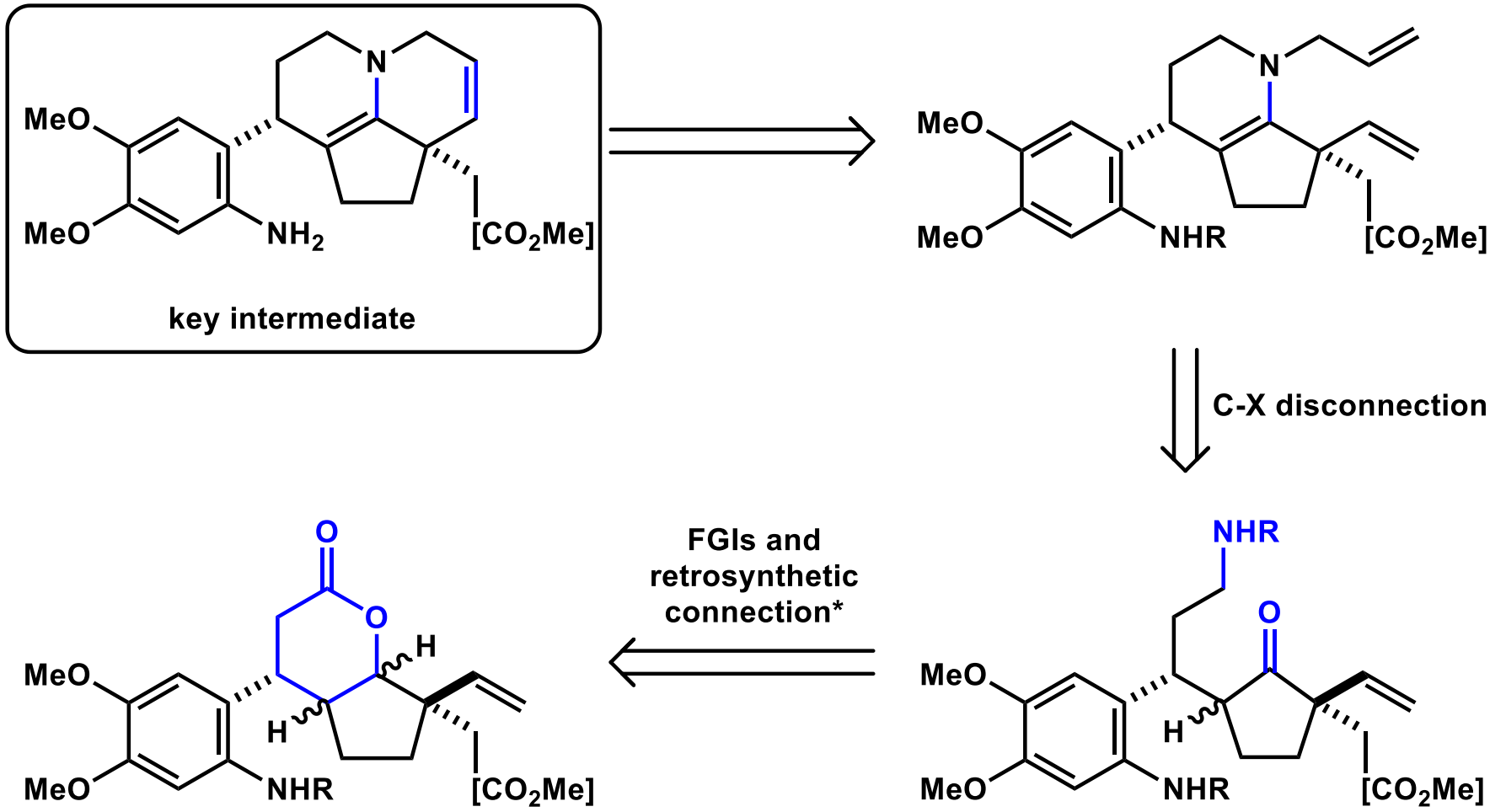
# The Key Cascade Reaction 2/2



# 2.3 Qin's Approach

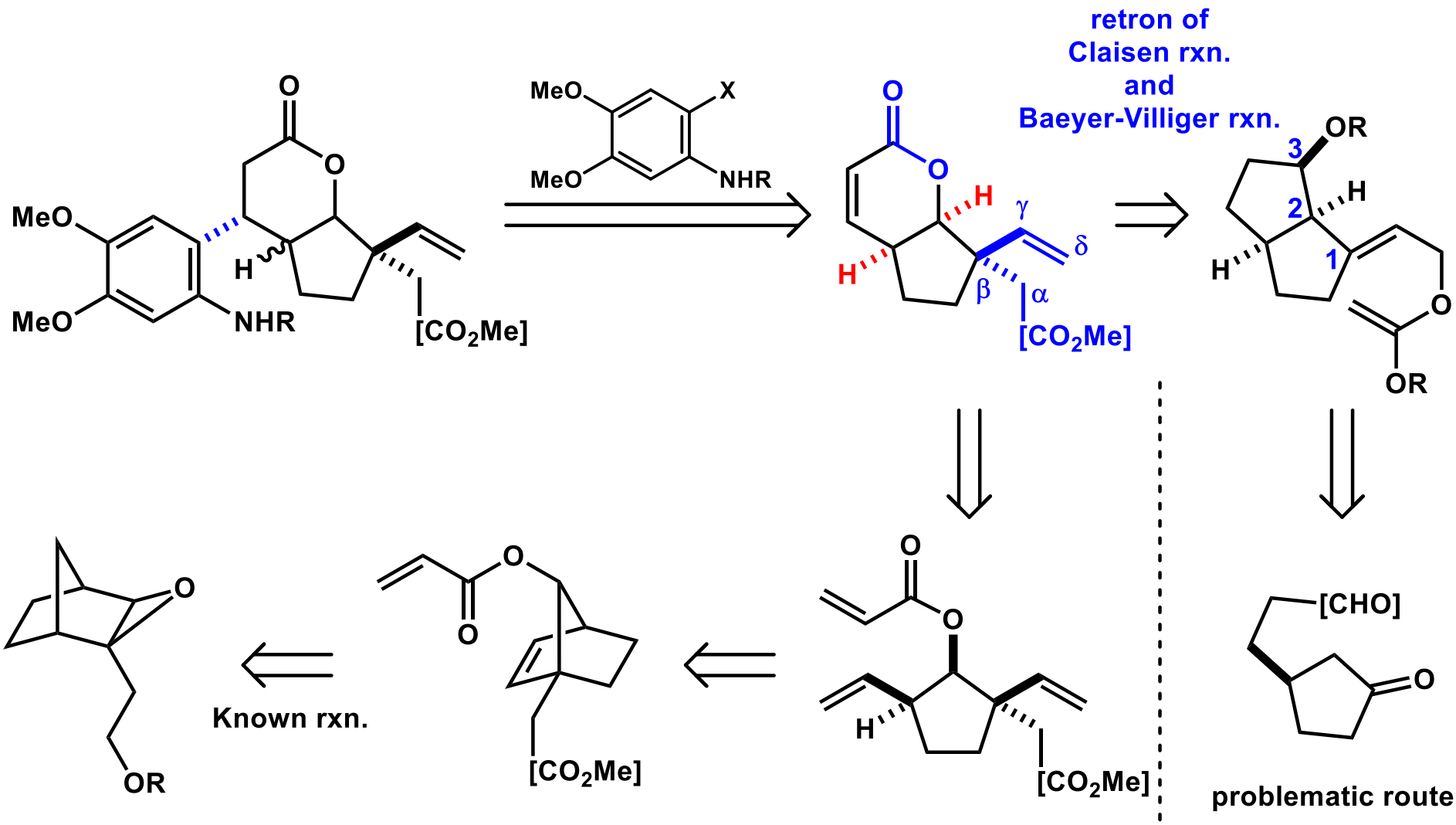


# 2.4 Fukuyama's Approach

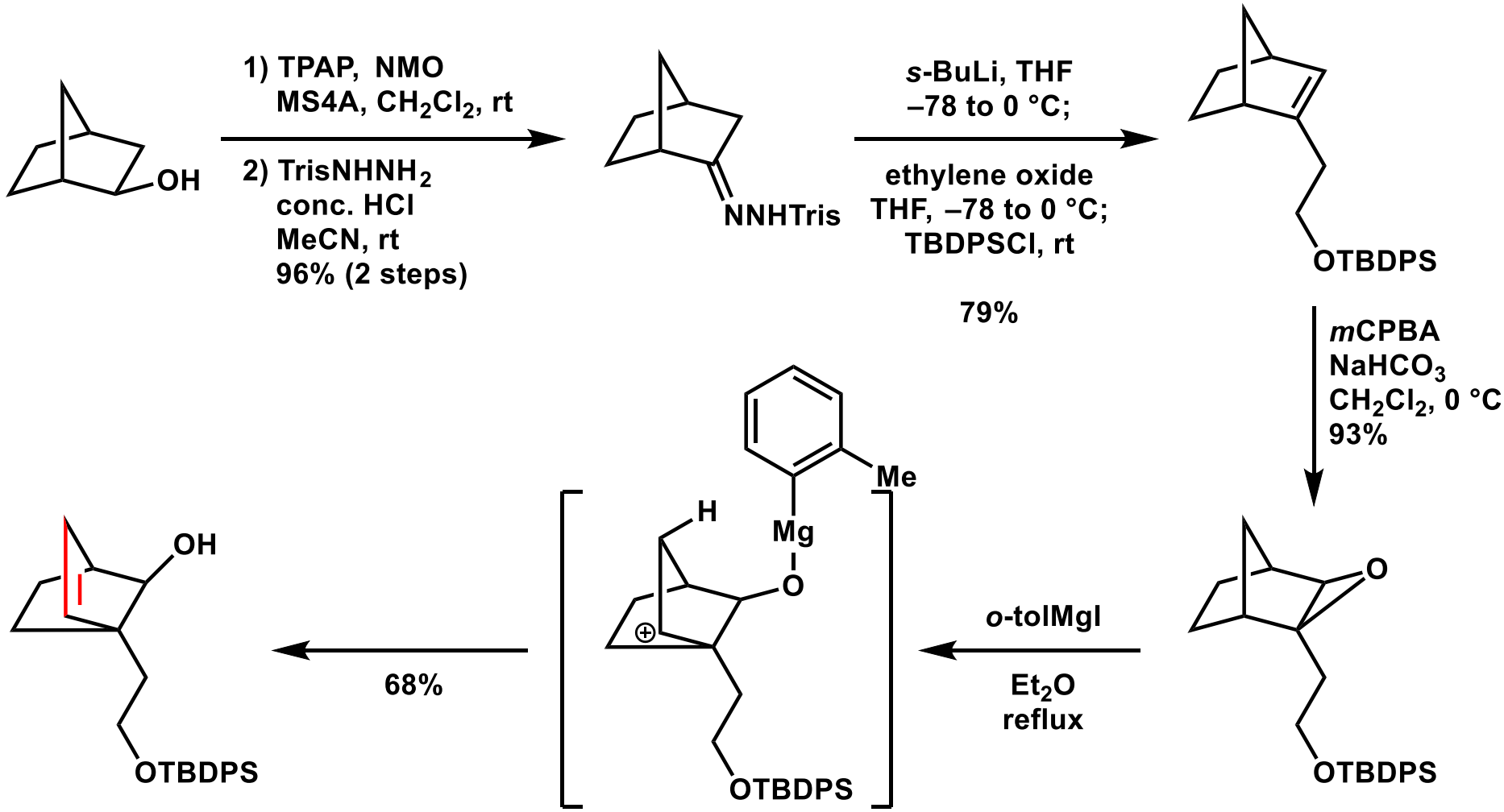



* Good for masking two functional groups
Cyclic systems are especially useful for
stereoselective synthesis.

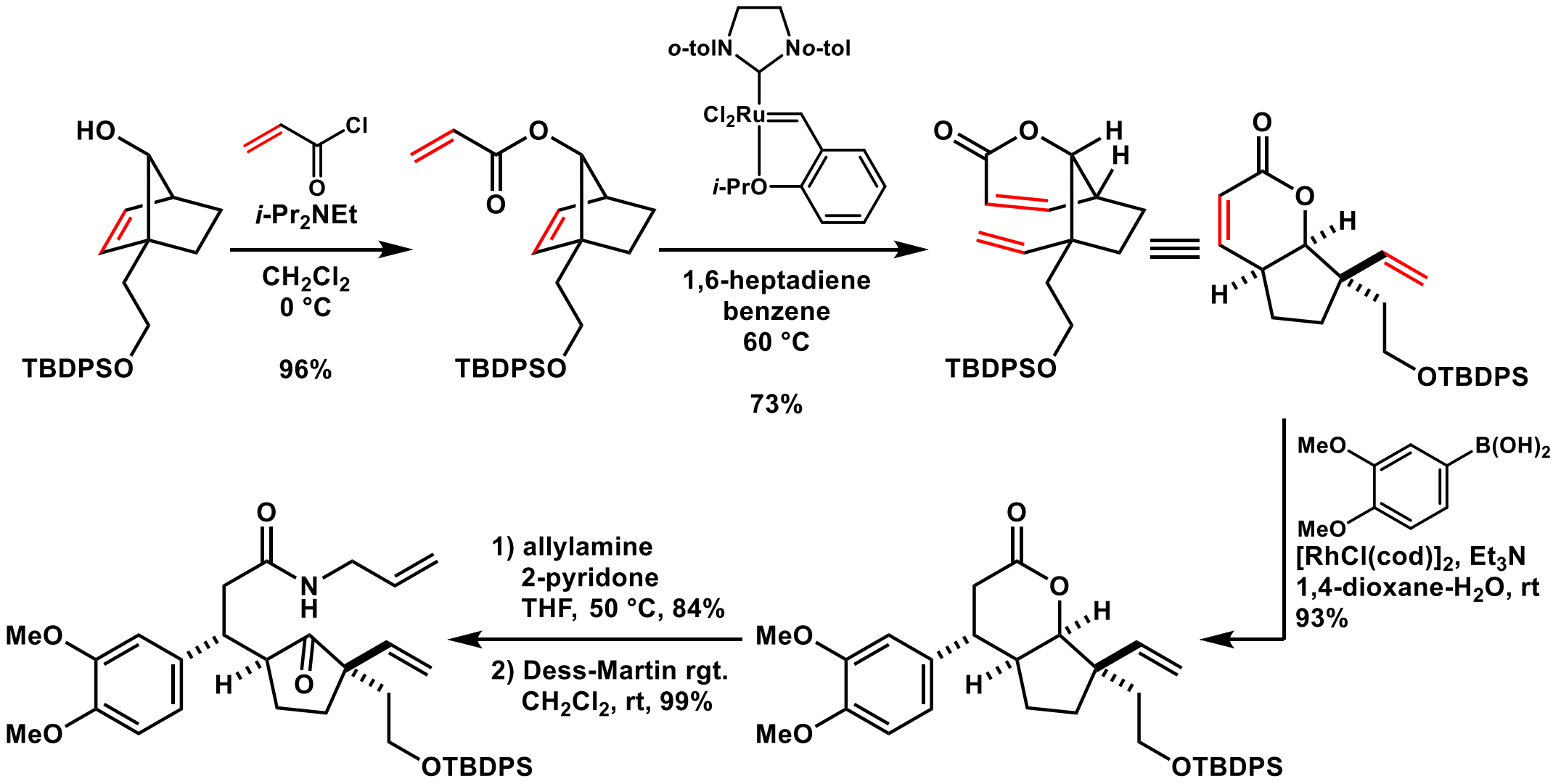
# Retrosynthesis of Lactone



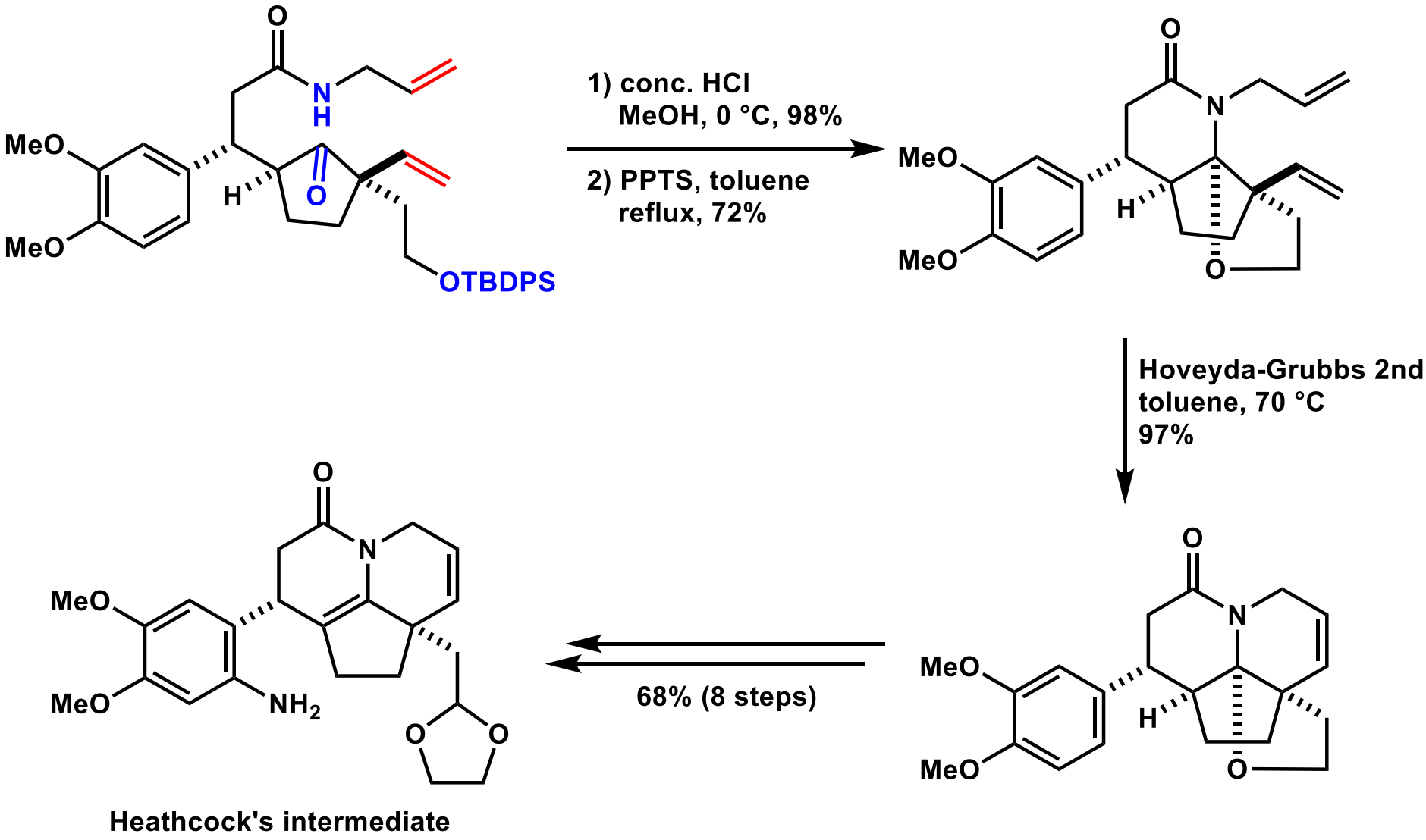
# Wagner-Meerwein Rearrangement



# Crucial Tandem Metathesis Reaction

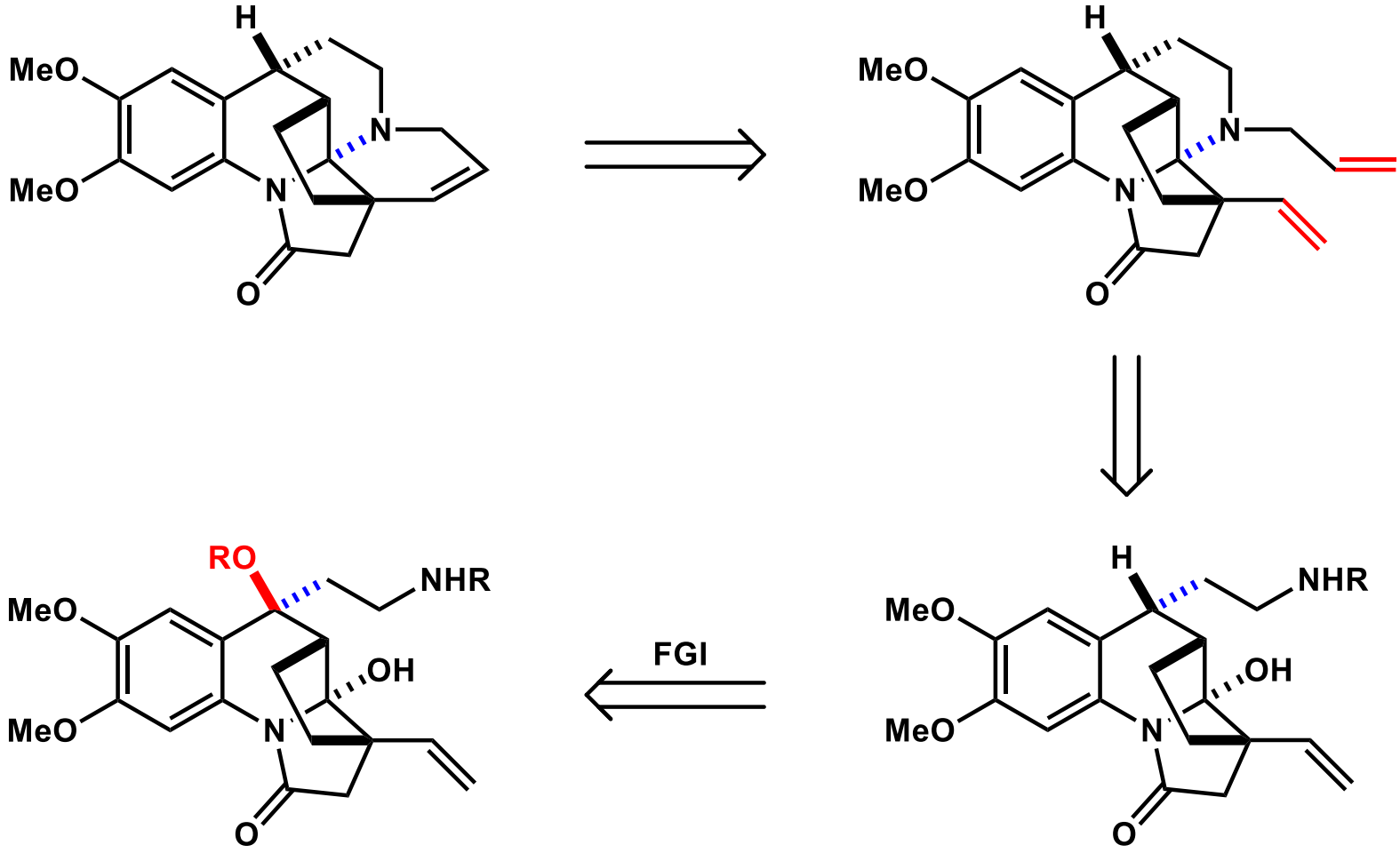


# Ring-Closing Metathesis

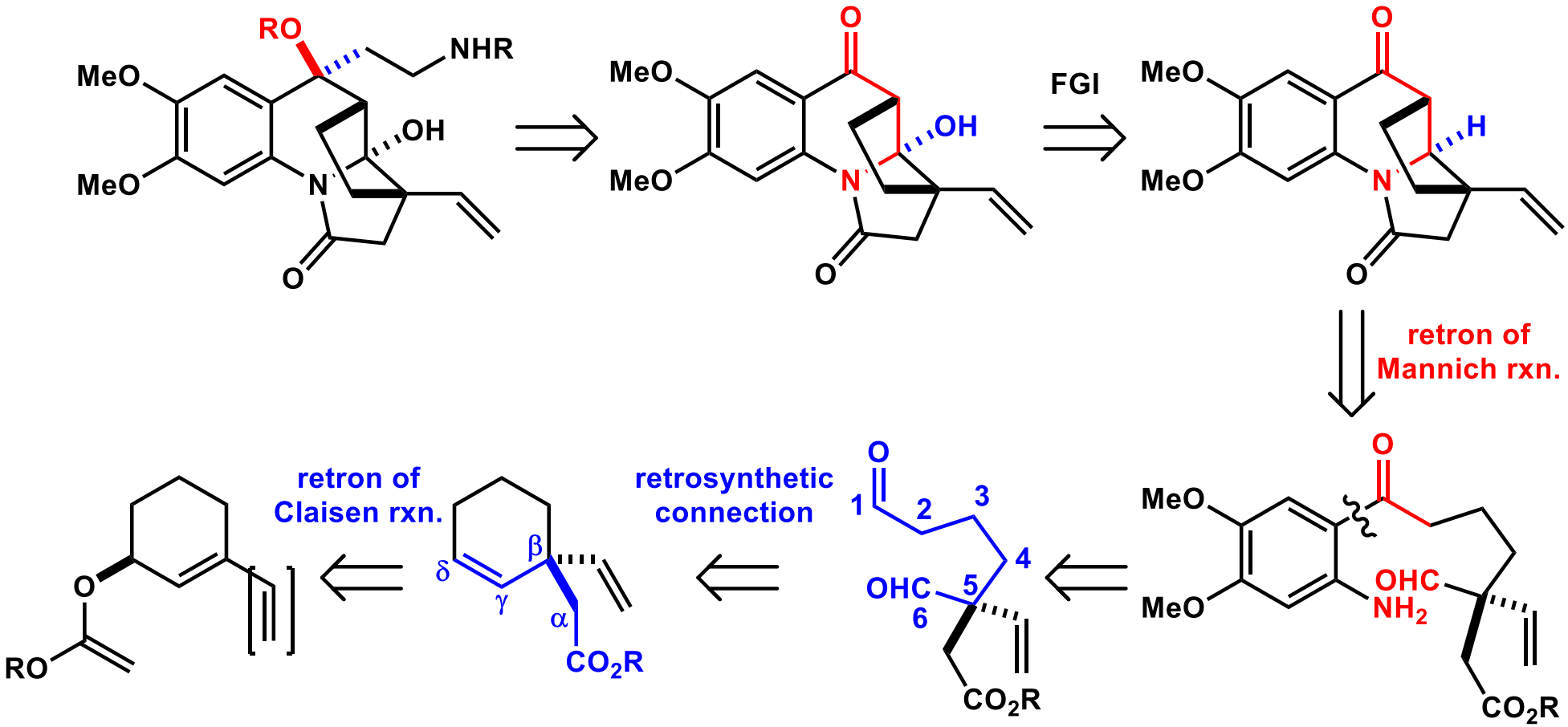



Heathcock's intermediate

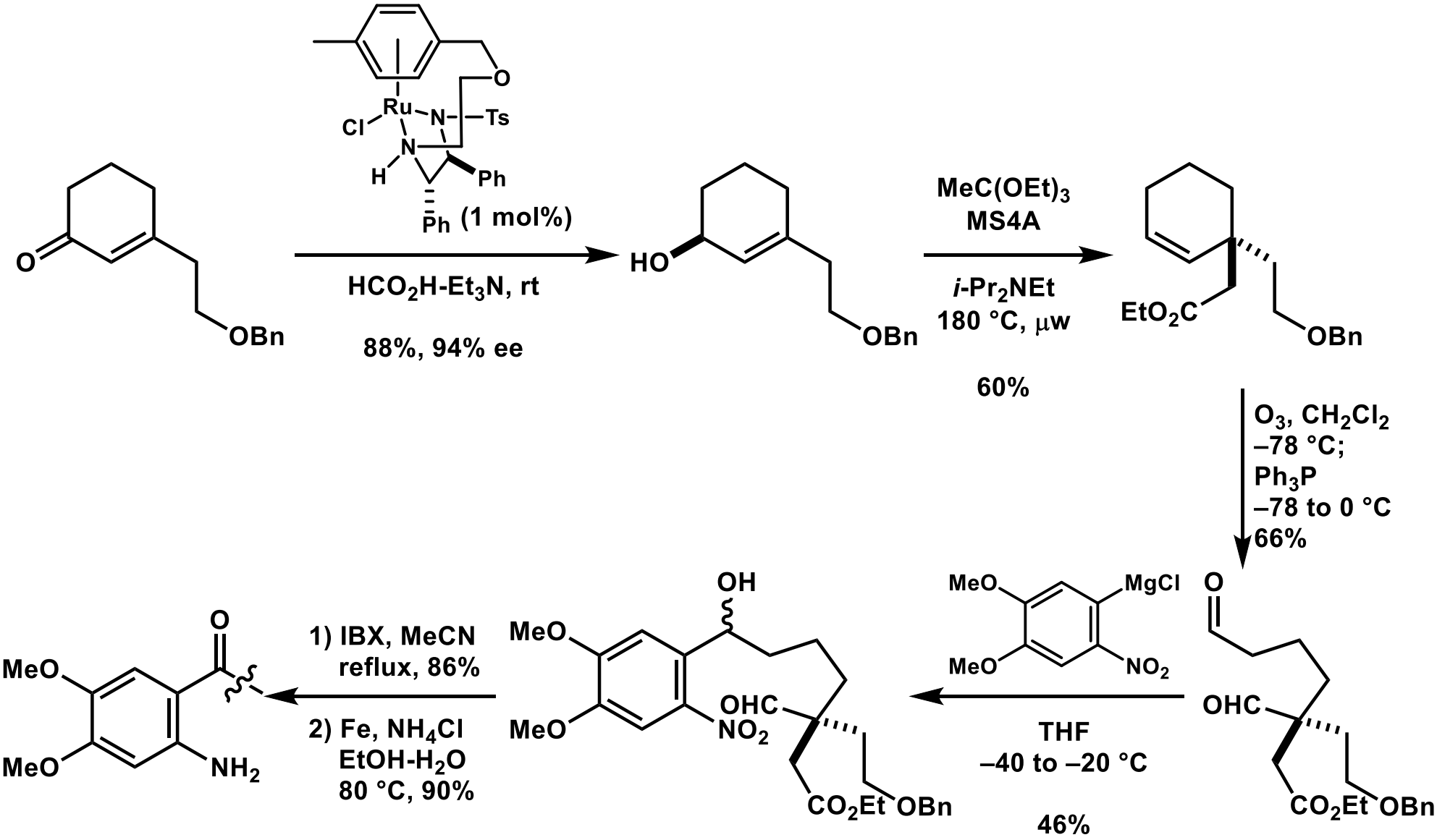
# 3.1 Tokuyama's Approach (Main Paper)



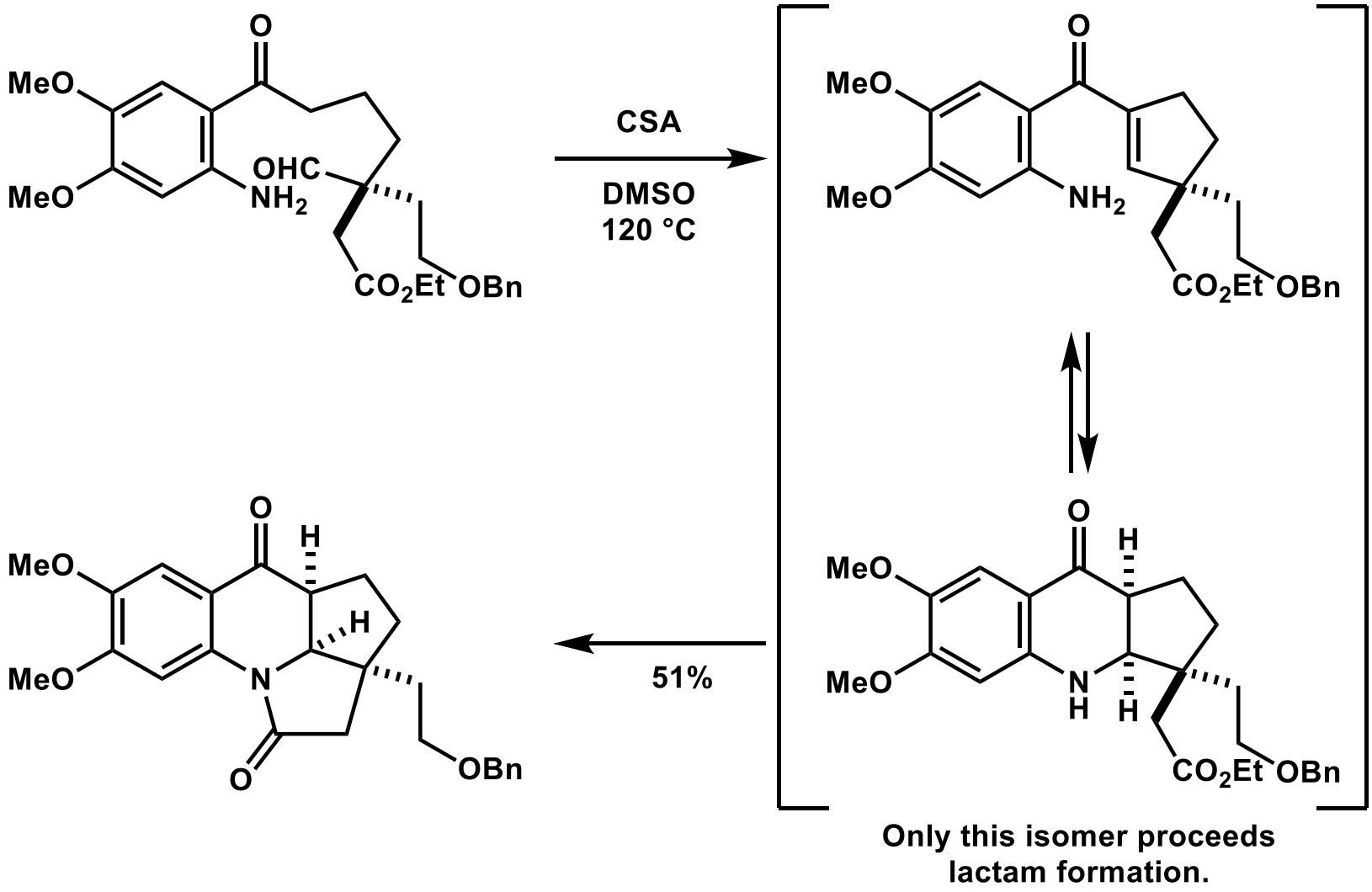
# “Kill a lot of birds with one stone.”



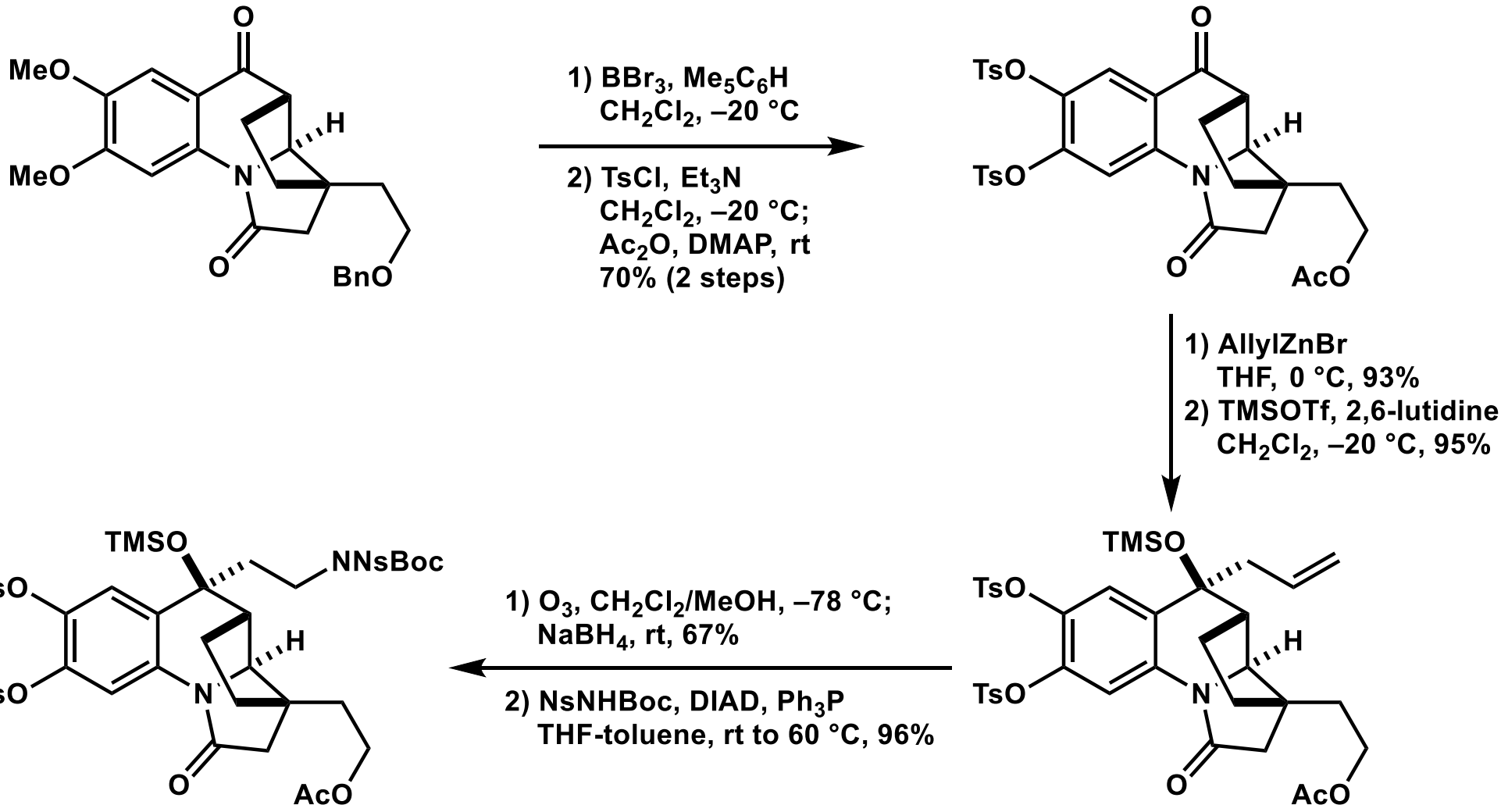
# Synthesis of Mannich Reaction Precursor



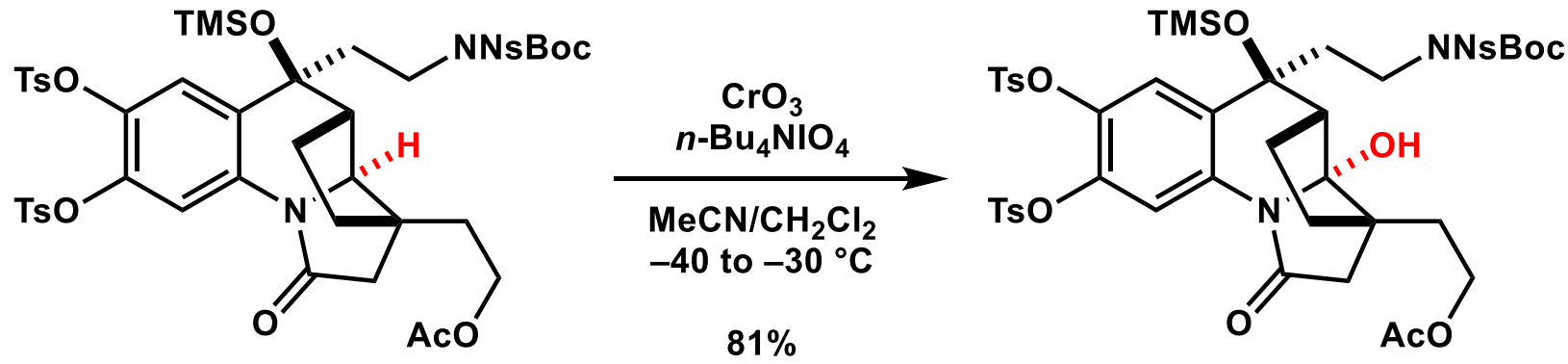
# “Mannich Reaction”

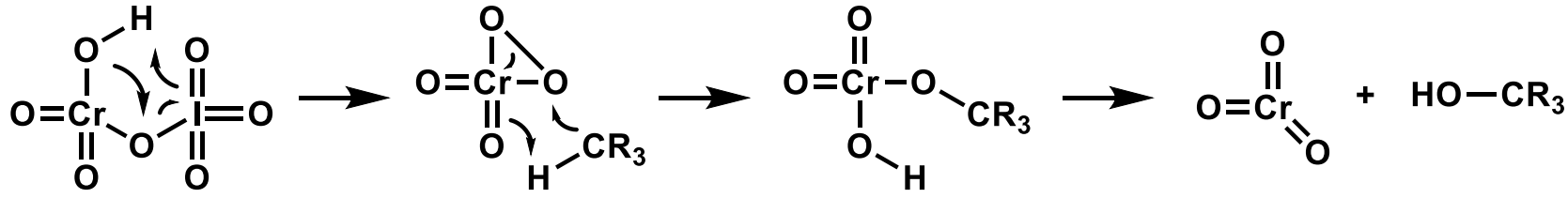


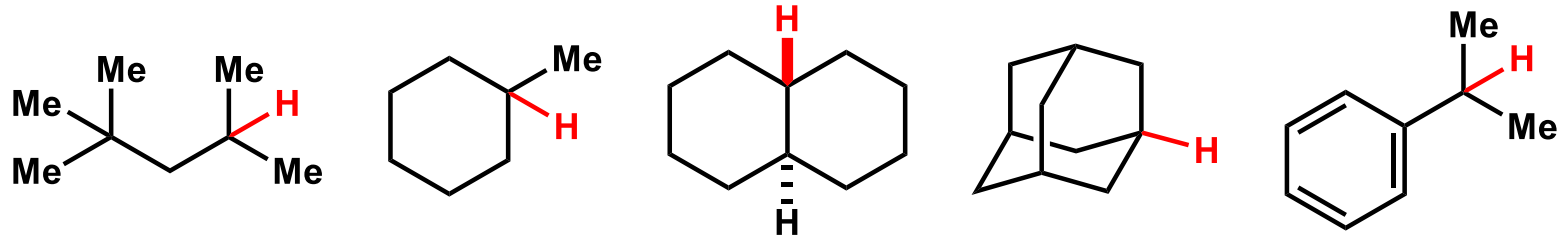
# Introduction of Amine



# Crucial C-H Oxidation Reaction

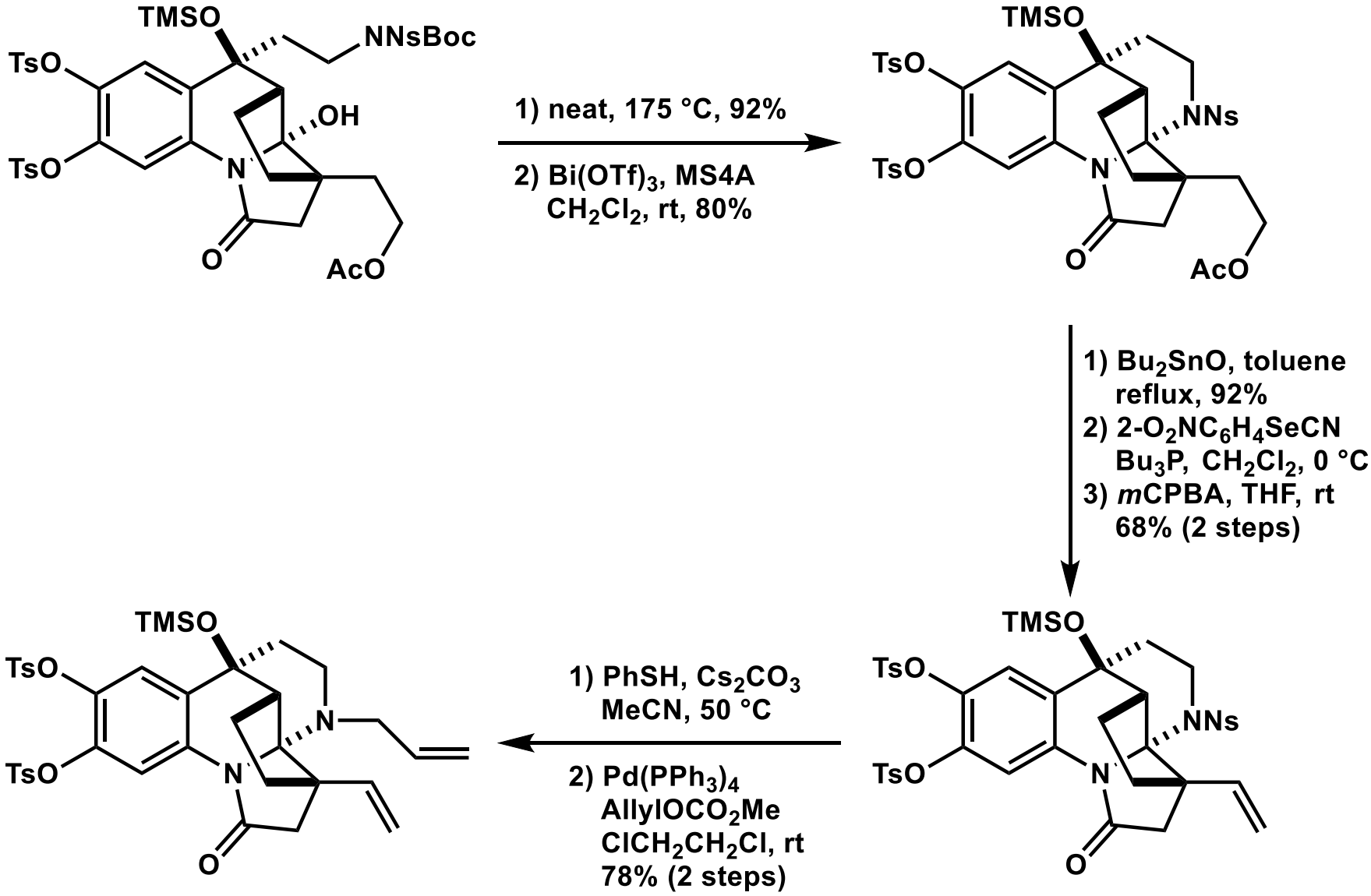


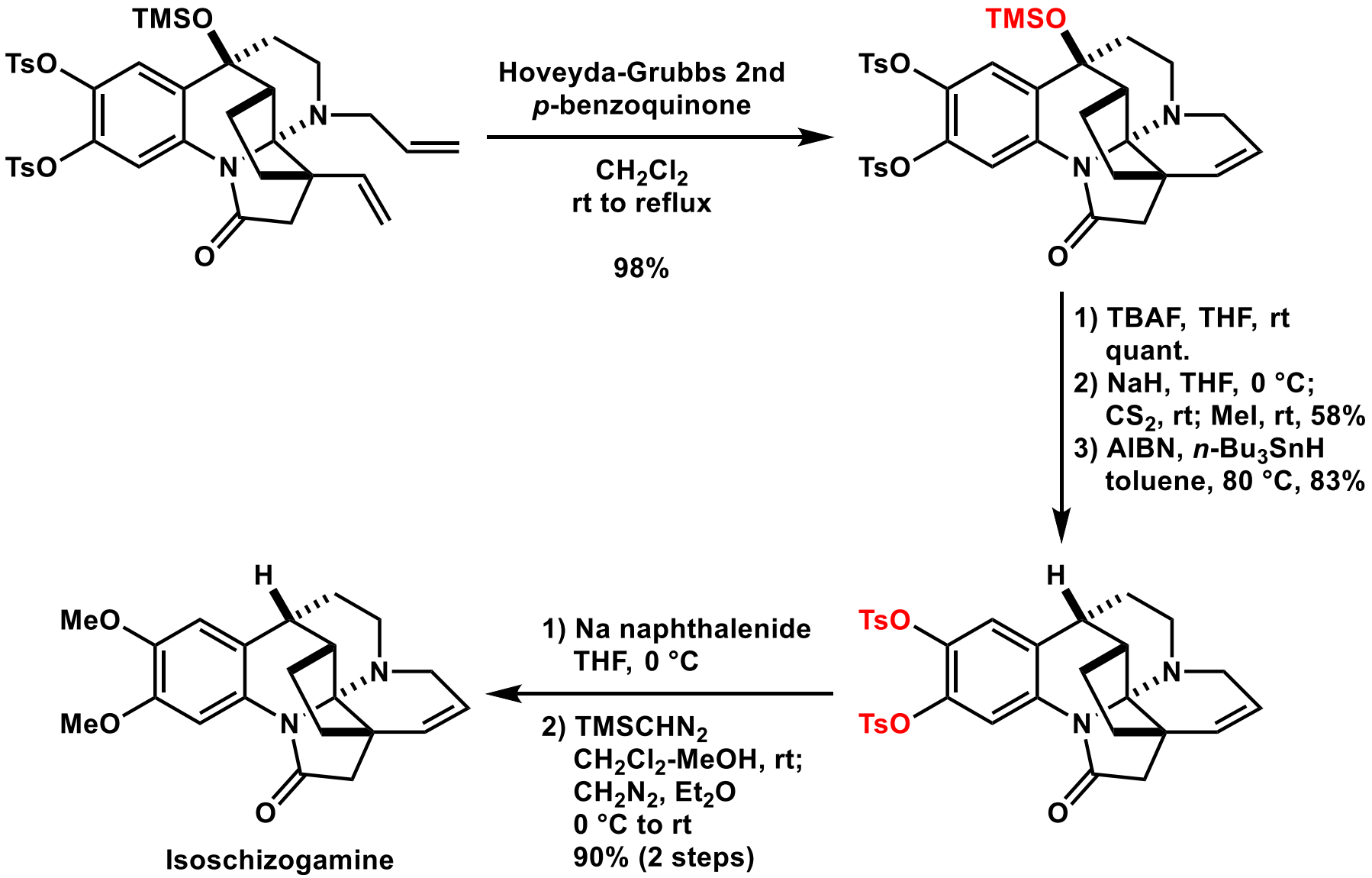




S.-M. Lee and P. L. Fuchs, *J. Am. Chem. Soc.*, **124**, 13978 (2002)

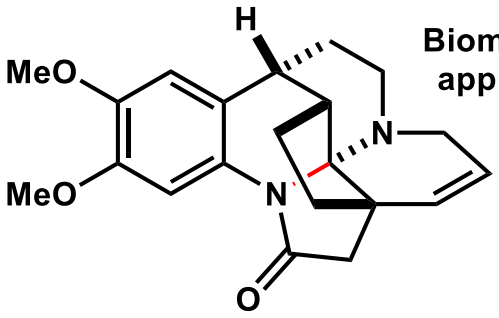
# Aminal Formation



# End Game

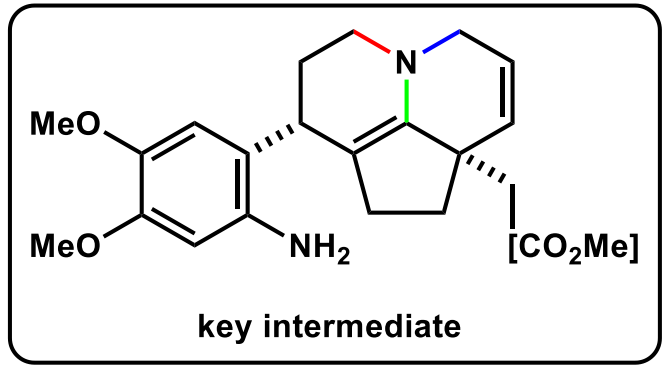

TMSO
TsO
TsO
N
N
O
Hoveyda-Grubbs 2nd
p-benzoquinone
CH2Cl2
rt to reflux
98%
TMSO
TsO
TsO
N
N
O
1) TBAF, THF, rt
quant.
2) NaH, THF, 0 °C;
CS2, rt; MeI, rt, 58%
3) AIBN, n-Bu3SnH
toluene, 80 °C, 83%
H
TsO
TsO
N
N
O
1) Na naphthalenide
THF, 0 °C
2) TMSCHN2
CH2Cl2-MeOH, rt;
CH2N2, Et2O
0 °C to rt
90% (2 steps)
H
MeO
MeO
N
N
O
Isoschizogamine

# 4. Summary 1/2

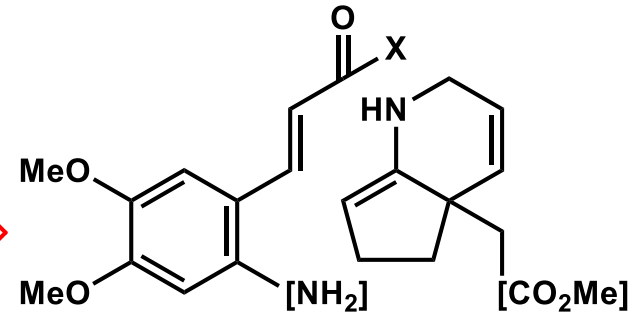



Isoschizogamine

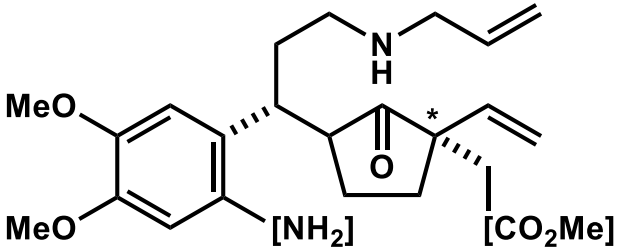
Biomimetic approach



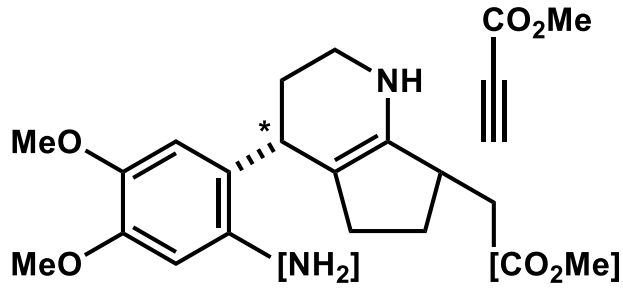

key intermediate



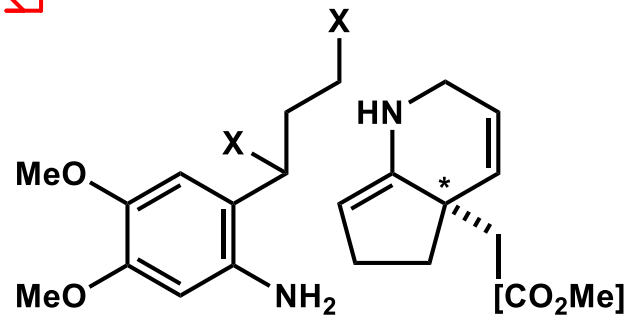

Heathcock: "Textbook disconnection"
-> Convergent synthesis




Fukuyama: "Unique disconnection"
-> Lengthy, but chemically interesting

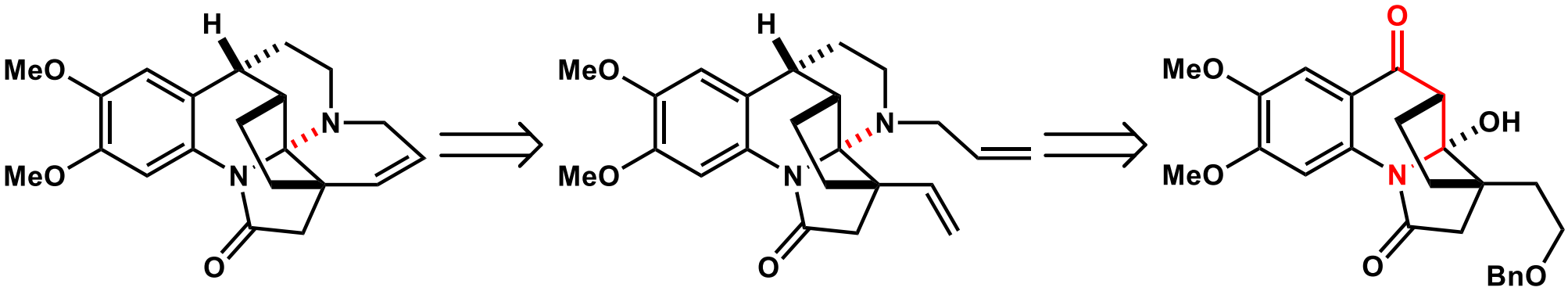



Qin: "Opposite of Heathcock's disconnection"
-> Asymmetric construction of all carbon quatenery center was avoided.




Zhu: "no FGI retrosynthesis"
-> Challenging, but short synthesis

# 4. Summary 2/2




Isoschizogamine

Tokuyama: "De novo synthesis"
-> Challenging and lengthy, but original synthesis

| year | author | yield (total steps) | chiral source |
|---|---|---|---|
| 1999 | Heathcock | 7.2% (8 steps) | - |
| 2012 | Fukuyama | 2.8% (24 steps) | (+)-*exo*-norborneol |
| 2015 | Qin | 1.4% (21 steps) | (*R*)-*t*-butyl sulfinamide |
| 2015 | Tokuyama | 0.18% (24 steps) | Noyori reduction |
| 2015 | Zhu | 8.2% (9 steps) | catalytic decarboxylative allylation (low ee) |