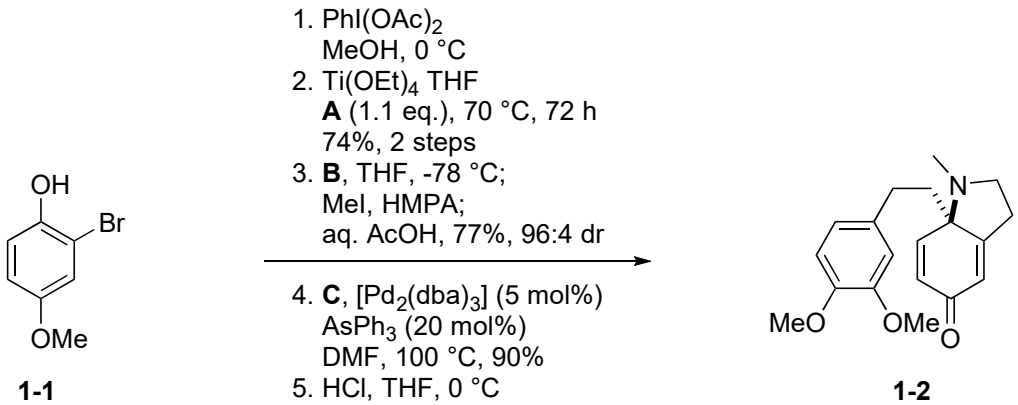
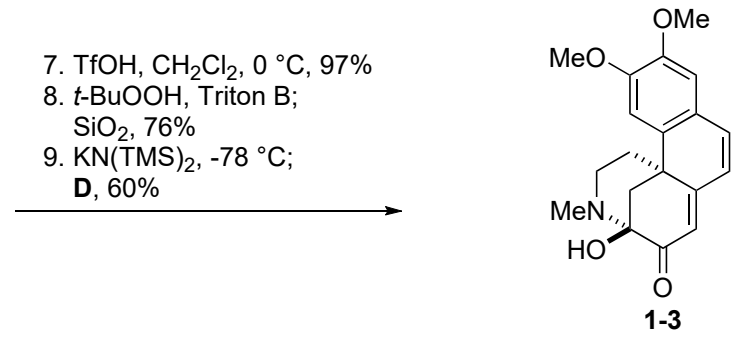
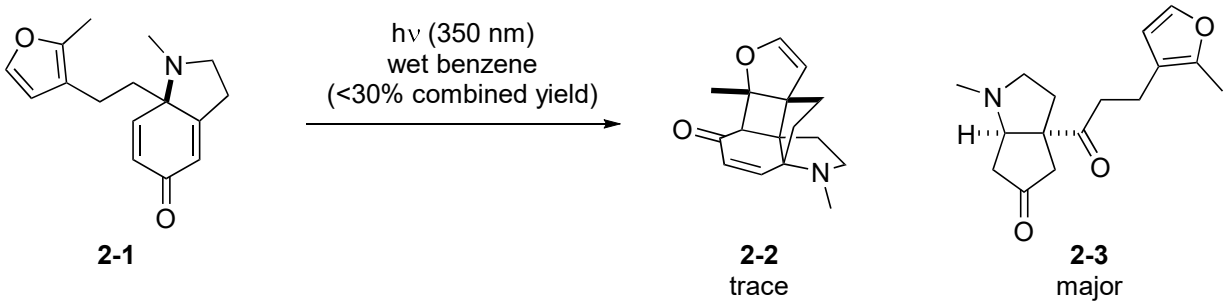
Problem Session (3) - Problem

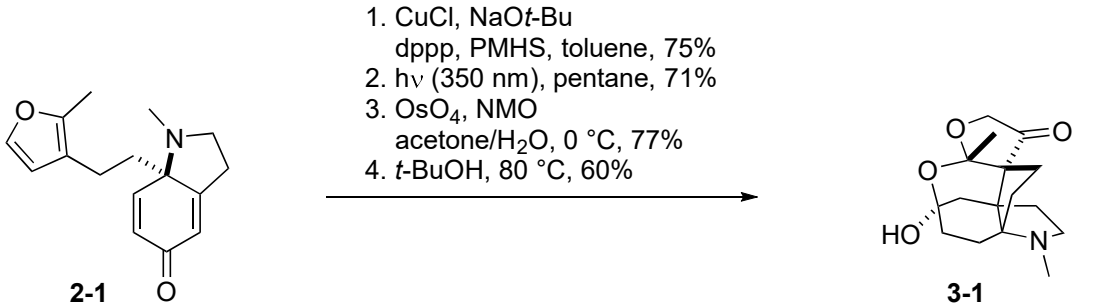
2018.12.8 Yusuke Imamura

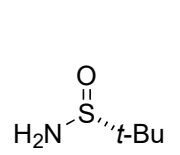
Please explain the reaction mechanisms.

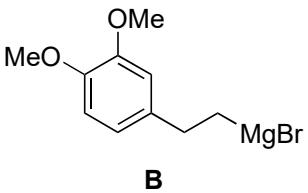


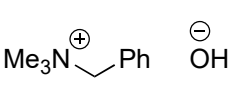


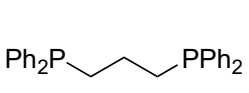


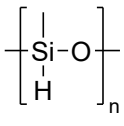


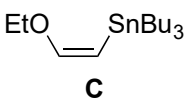


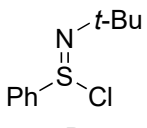












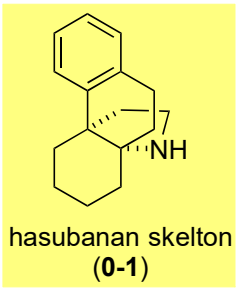
Problem Session (3) - Answer

2018.12.8 Yusuke Imamura

Topic: Synthetic study of isomerized hasubanan alkaloids by Sarah E. Reisman using *N-tert*-butanesulfinimine

0. Introduction

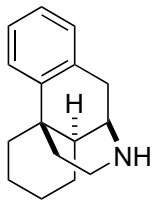
0.1. hasubanan skelton



hasubanan skelton (**0-1**)

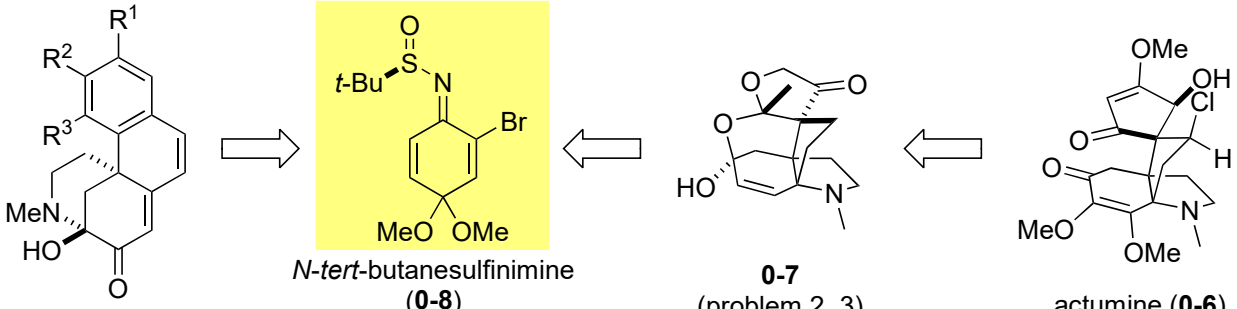
structure features:
aza[4.4.3]propellane core
similar structure to morphinan skelton
(inverted absolute stereochemistry)

cf.



morphinan skelton (**0-2**)

0.2. cepharatines and actumine



N-tert-butanesulfinimine (**0-8**)

0-7 (problem 2, 3)

actumine (**0-6**)

R^1 = H, R^2 = OMe, R^3 = OH: cepharatine B (**0-3**)
R^1 = H, R^2 = R^3 = OMe: cepharatine C (**0-4**)
R^1 = R^2 = OMe, R^3 = H: cepharatine D (**0-5**, problem 1)

About cepharatines
isolation: medicinal herb *S. cepharantha*
(*J. Nat. Prod.* **2011**, *74*, 181.)

biological activity: no activity reported
(it is supposed that the unnatural enantiomers of the hasubanans may exhibit analgesic properties.)

total syntheses of cepharatines:
Reisman, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 9447. (A, C, D)
Magnus, P. *Org. Lett.* **2013**, *15*, 4870. (A, racemic)

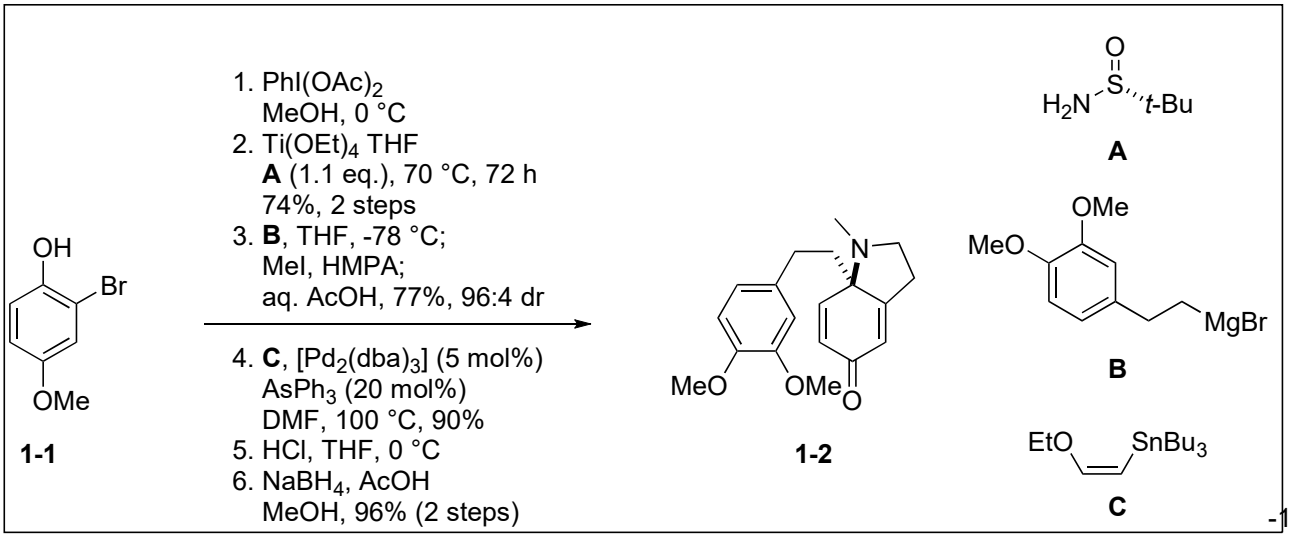
About actumine
isolation: medicinal herb *Sinomenium acutum*
(*Bull. Chem. Soc. Jpn.* **1929**, *4*, 220.)

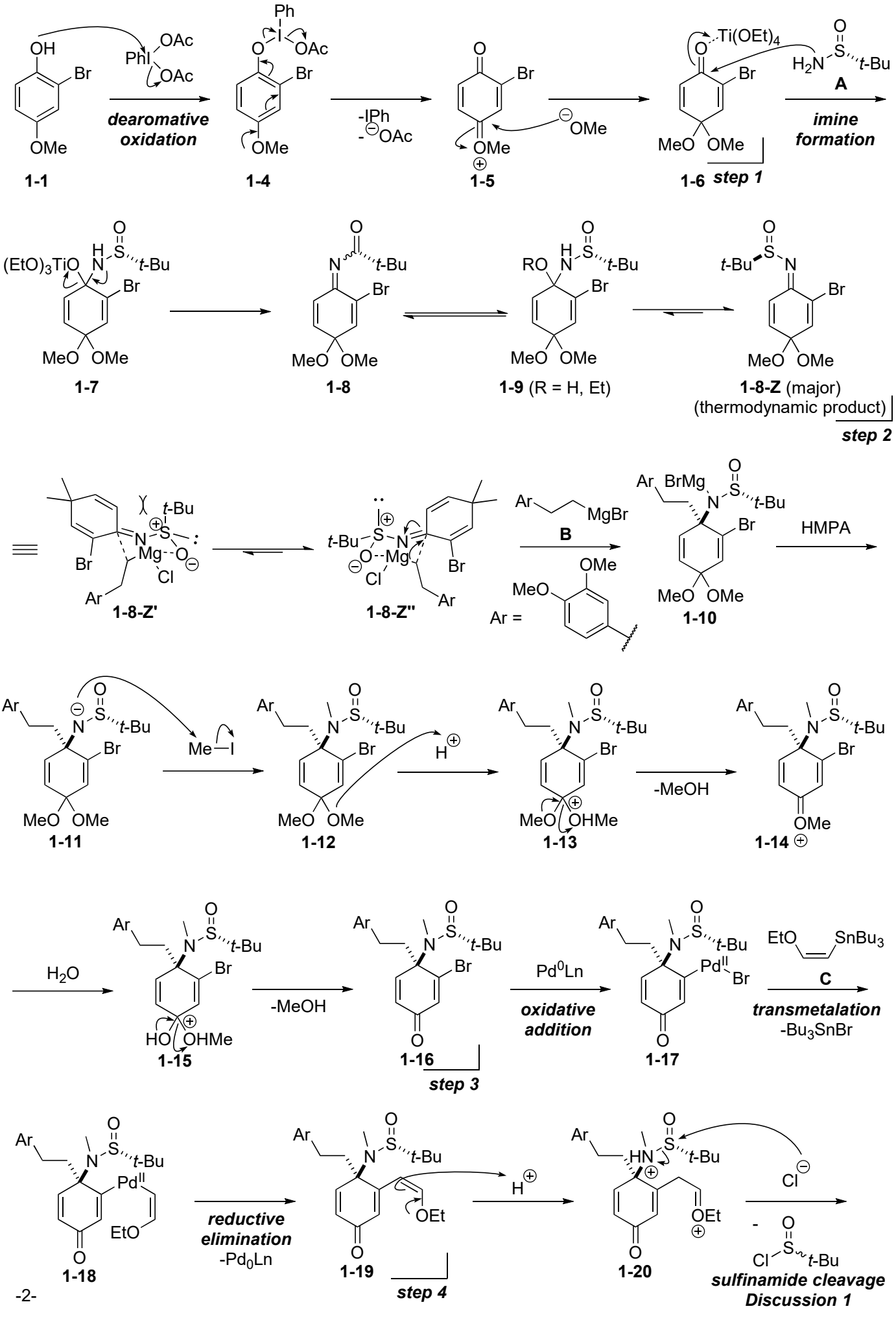
biological activity: selective T-cell cytotoxicity
antiamnesic activity
(*Phytochemistry*, **2002**, *61*, 439.
WO 2004000815, 2003)

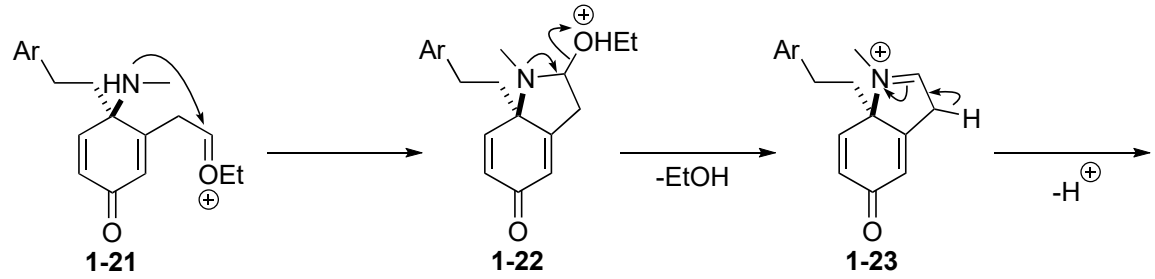
total syntheses of actumine:
Castle, J. *J. Am. Chem. Soc.* **2009**, *131*, 6674.
J. Org. Chem. **2009**, *74*, 9082
Herzon, S. B. *Angew. Chem. Int. Ed.* **2013**, *52*, 3642

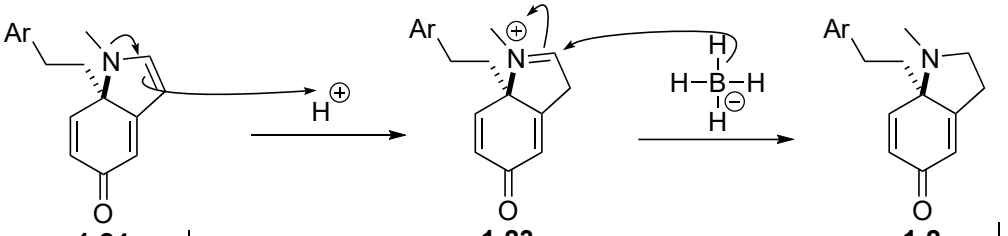
1. Total synthesis of cepharatine D

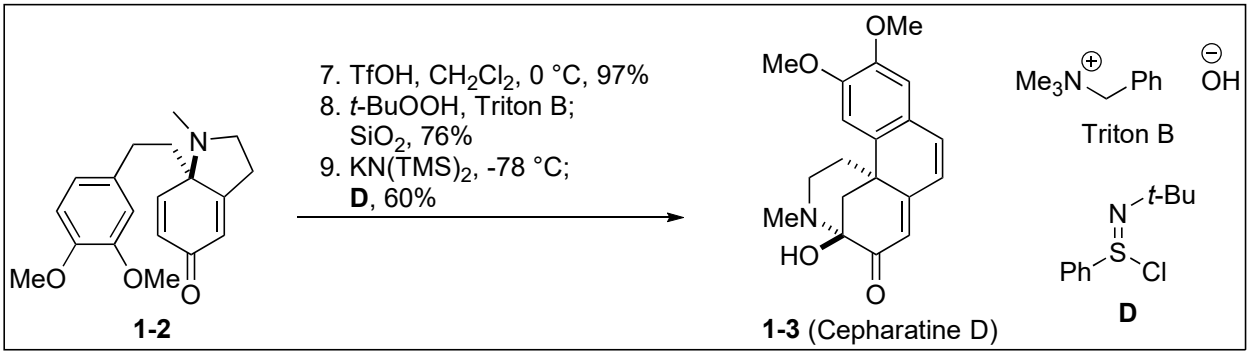
1.1. reaction mechanism

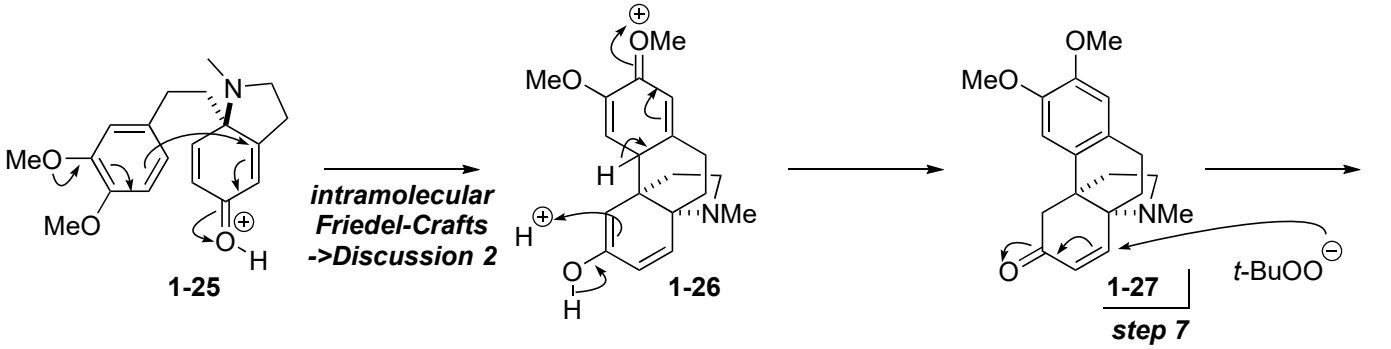


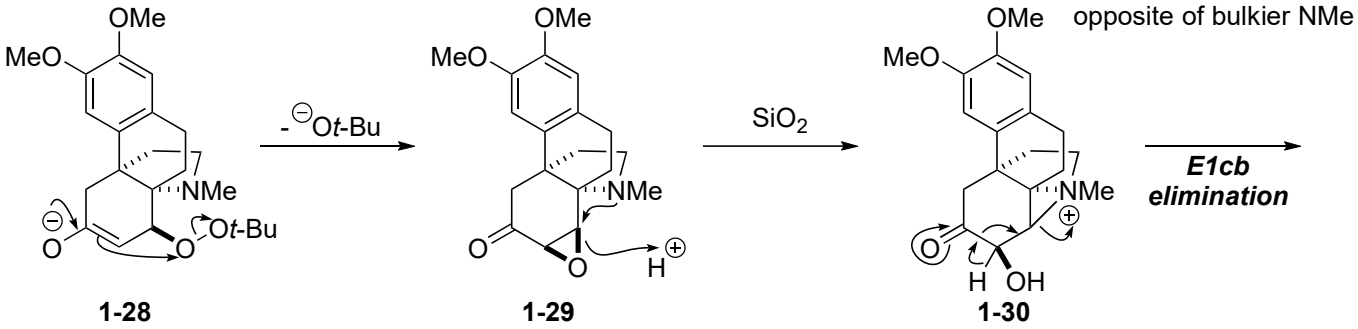

1-1
dearomative oxidation
1-4
-IPh
-OAc
1-5
Ti(OEt)4
H2N
t-Bu
A
1-6
step 1
imine formation
(EtO)3TiO
1-7
1-8
1-9 (R = H, Et)
1-8-Z (major)
(thermodynamic product)
step 2
1-8-Z'
1-8-Z''
B
Ar =
1-10
HMPA
1-11
1-12
1-13
-MeOH
1-14
H2O
1-15
1-16
step 3
Pd0Ln
oxidative addition
1-17
C
transmetalation
-Bu3SnBr
1-18
reductive elimination
-Pd0Ln
1-19
step 4
1-20
sulfinamide cleavage
Discussion 1

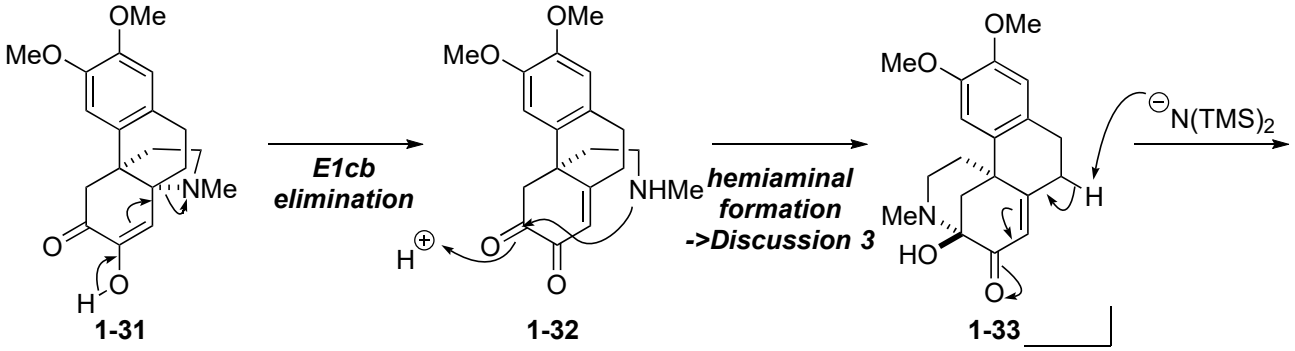

Ar
HN
OEt
O
1-21
OHEt
N
1-22
-EtOH
H
1-23
-H

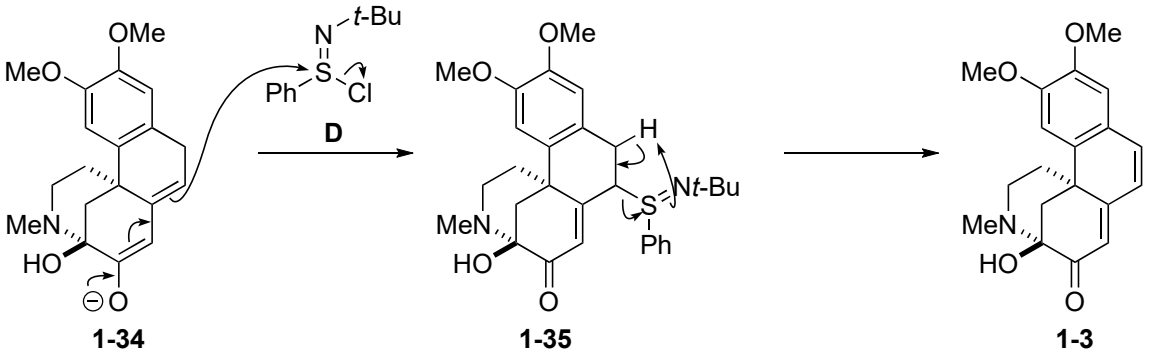

Ar
N
H
1-24
step 5
H−B−H
1-23
1-2
step 6


MeO
OMe
1-2
7. TfOH, CH2Cl2, 0 °C, 97%
8. t-BuOOH, Triton B;
SiO2, 76%
9. KN(TMS)2, -78 °C;
D, 60%
MeN
HO
1-3 (Cepharatine D)
Me3N
Ph
OH
Triton B
t-Bu
S
Cl
D


1-25
intramolecular
Friedel-Crafts
->Discussion 2
1-26
NMe
1-27
step 7
t-BuOO
opposite of bulkier NMe


OMe
MeO
NMe
Ot-Bu
1-28
-Ot-Bu
1-29
SiO2
H OH
1-30
E1cb
elimination

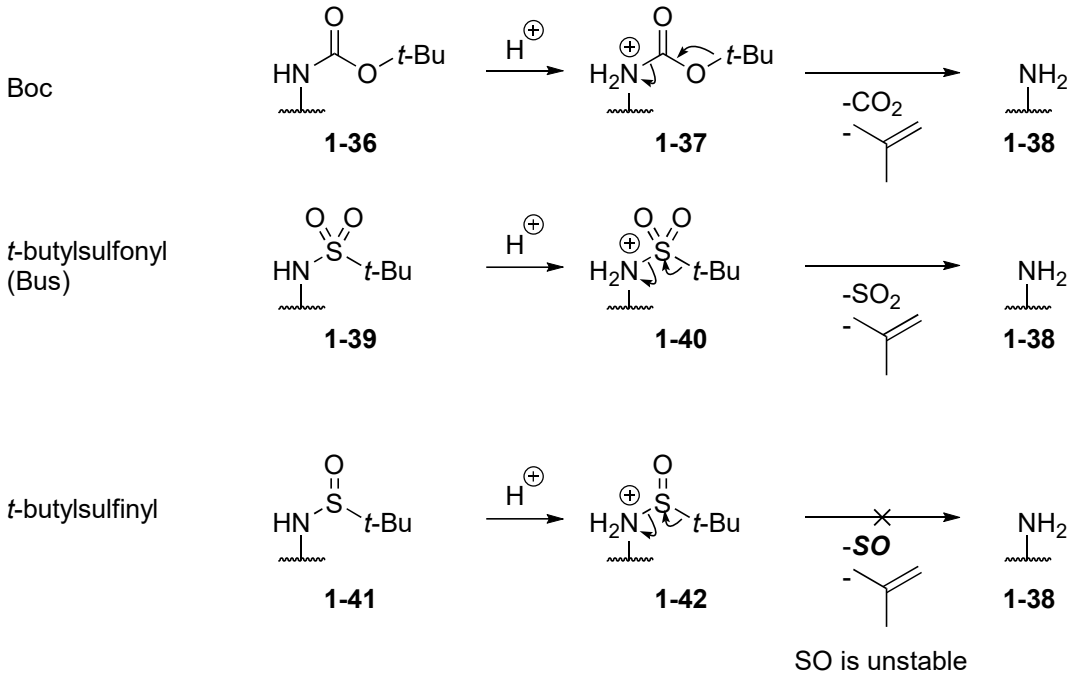

1-31
E1cb
elimination
NHMe
1-32
hemiaminal
formation
->Discussion 3
MeN
HO
1-33
step 8
N(TMS)2



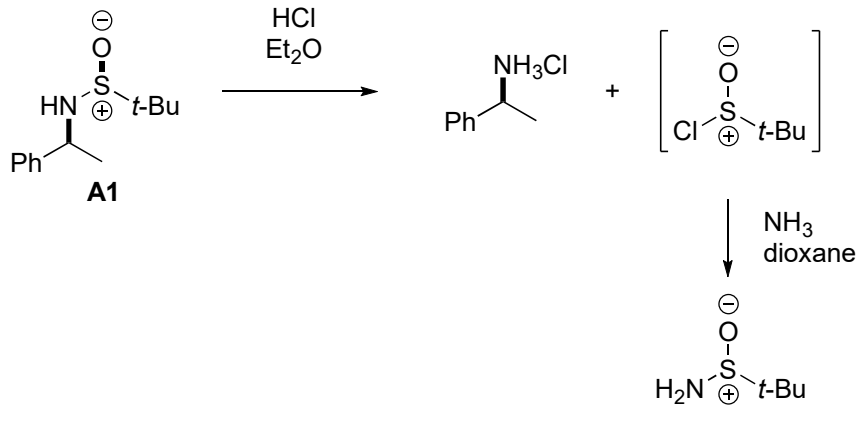
1.2. Discussion

Disscussion 1

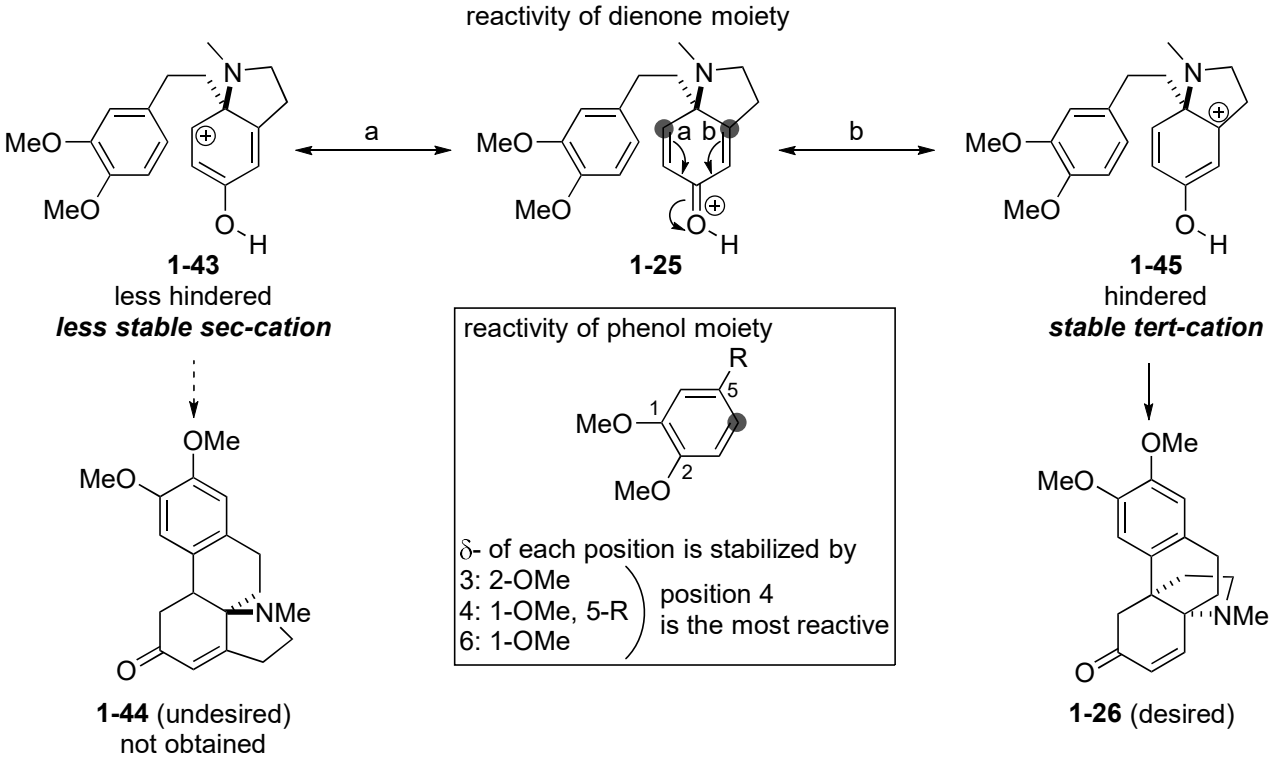
acidic deprotection of amine protecting group



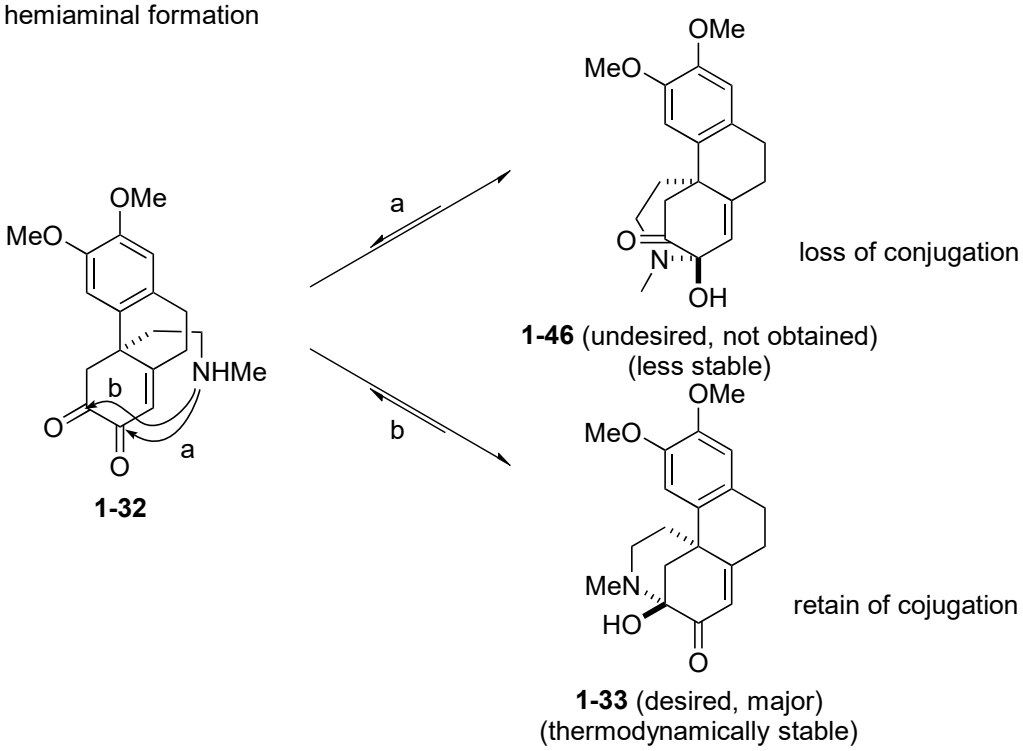
Aggarwal, V, K. et al. *Tetrahedron Lett.* **2009** *50*, 3482.



Discussion 2
selectivity of Friedel-Crafts Cyclization

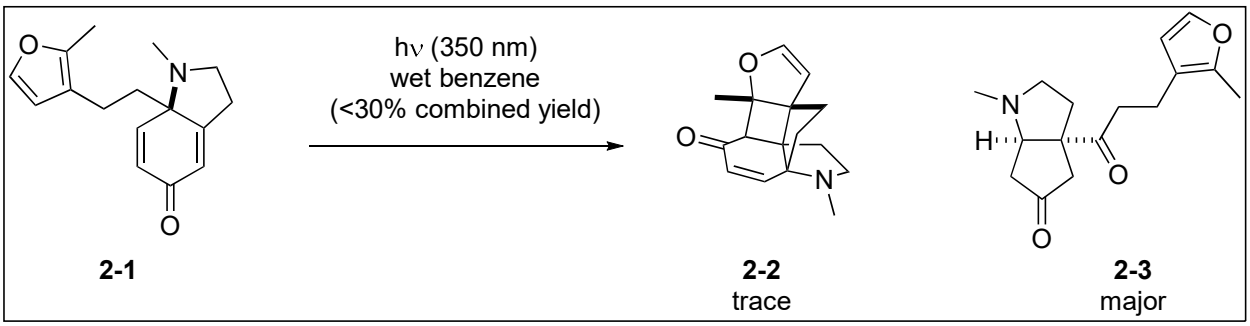


Discussion 3
selectivity of hemiaminal formation

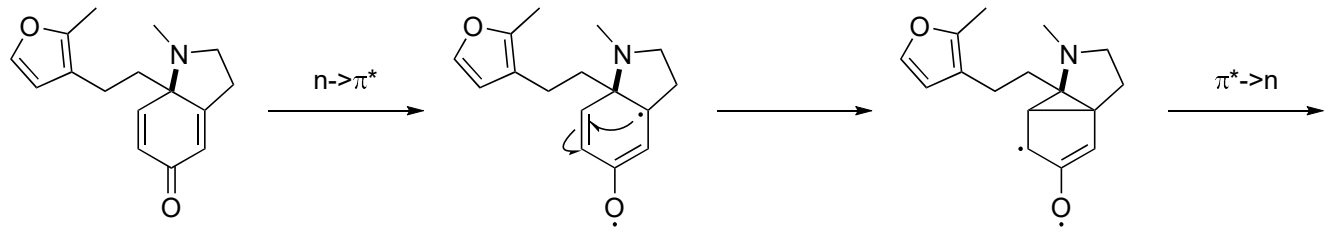


2. Undesired reaction in synthetic study of acutumine

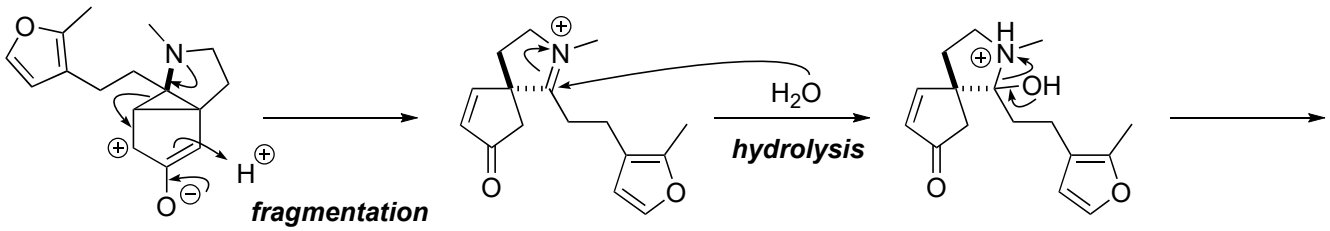
2.1. reaction mechanism (proposed by author)



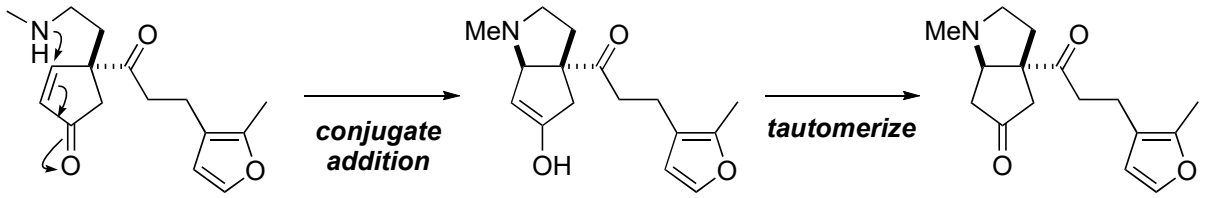
2-1 **2-2** trace **2-3** major



2-1 **2-4** **2-5**

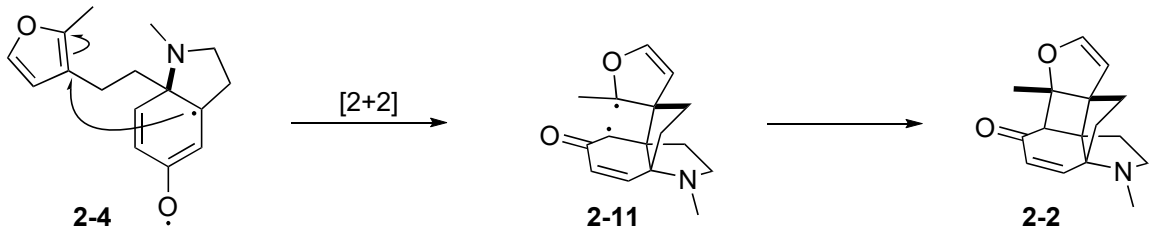


2-6 **2-7** **2-8**



2-9 **2-10** **2-3** (undesired)

(formation of desired product **2-2**)

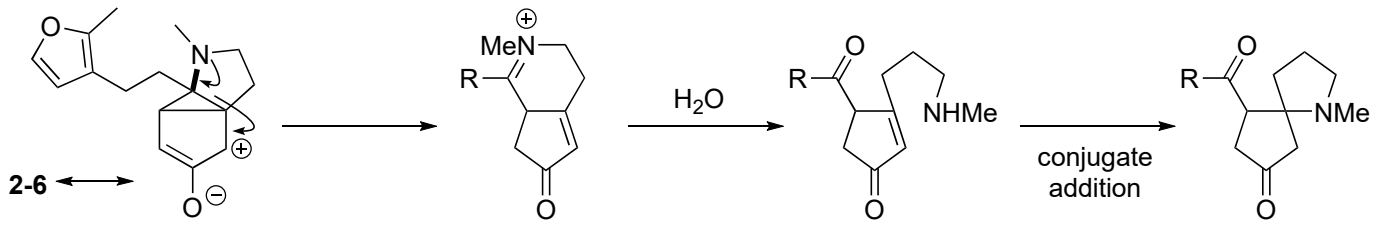


2-4 **2-11** **2-2** (desired)

2.2. Discussion

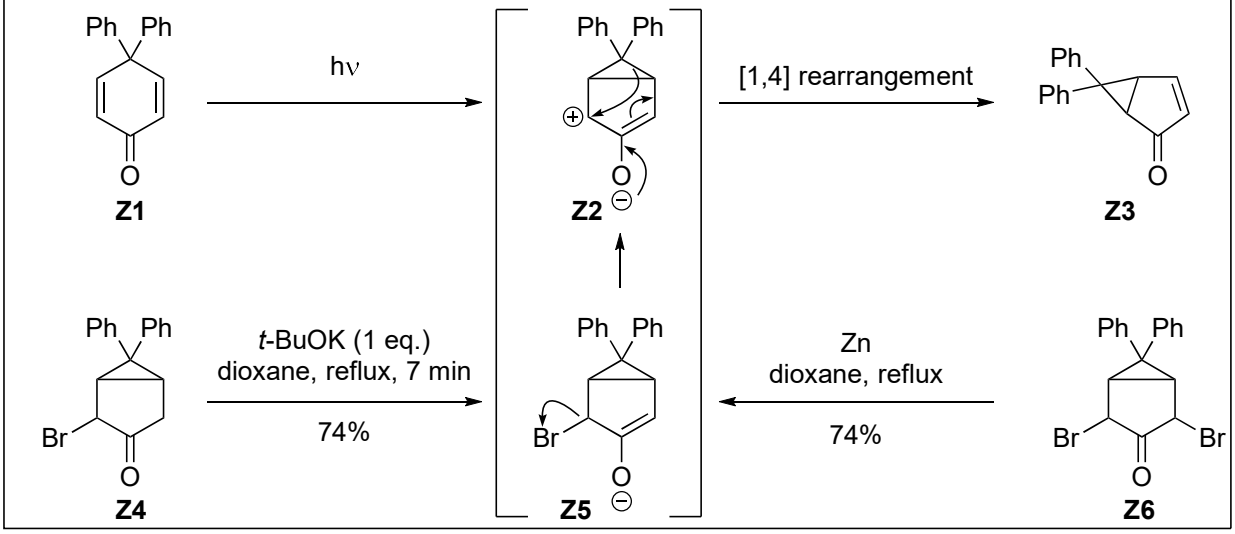
2-6 and **2-12** (below) are resonance structures.

If cyclopropane flagmentation occurs as described above, there should be another passway of fragmentation (below).

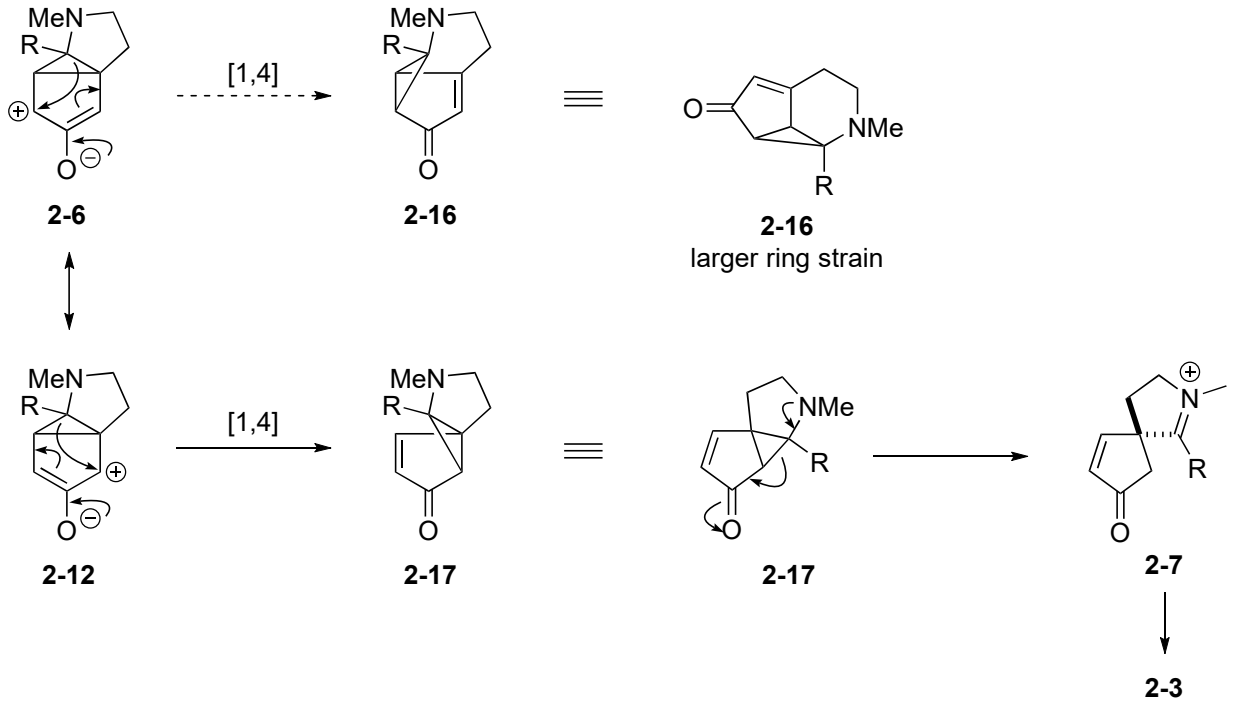


But, spiro compound **2-15** was not isolated.

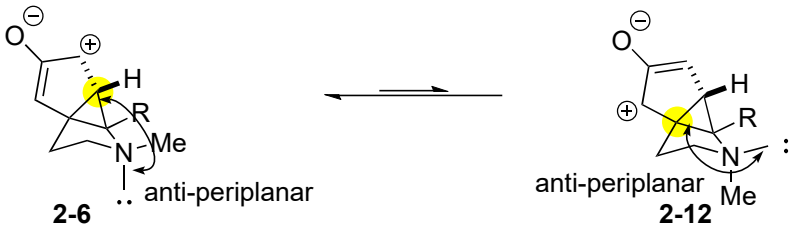
Zimmerman, H. E., Dopp, D., Huyffer, P. S. *J. Am. Chem. Soc.* **1966**, *88*, 5352.



my proposal



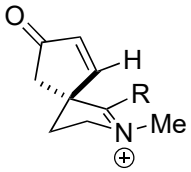
another explanation (from seminar)



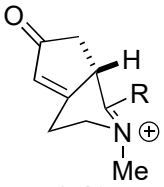
2-6 **2-12**

Me: • equatrial
• oriented to tertiary carbon

Me: × axial
× oriented to quatenary carbon



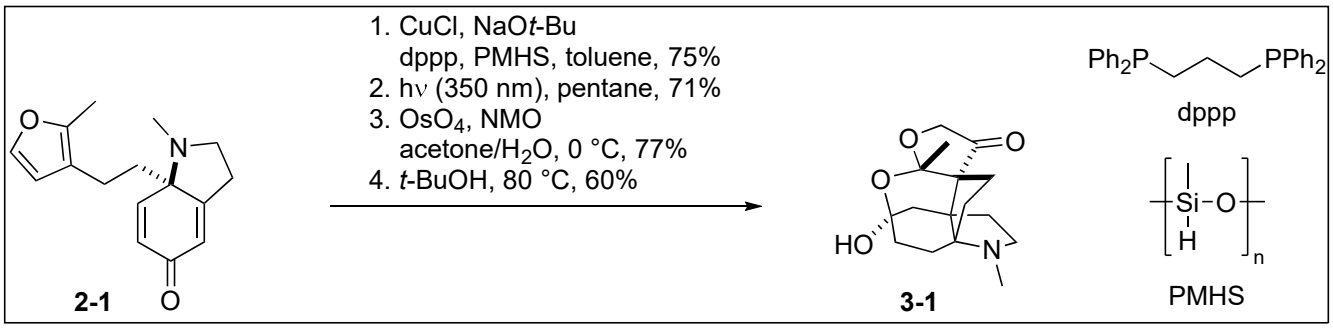
2-7

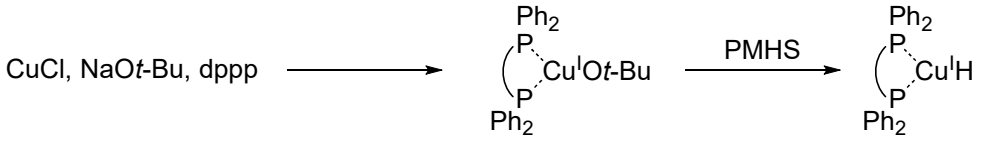


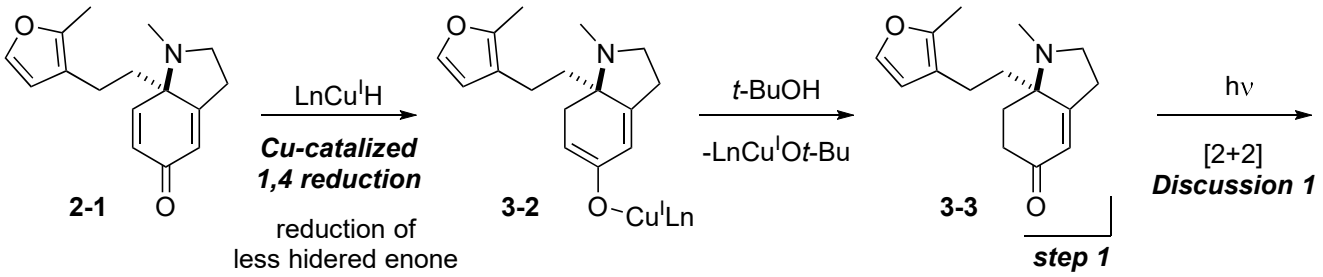
2-13

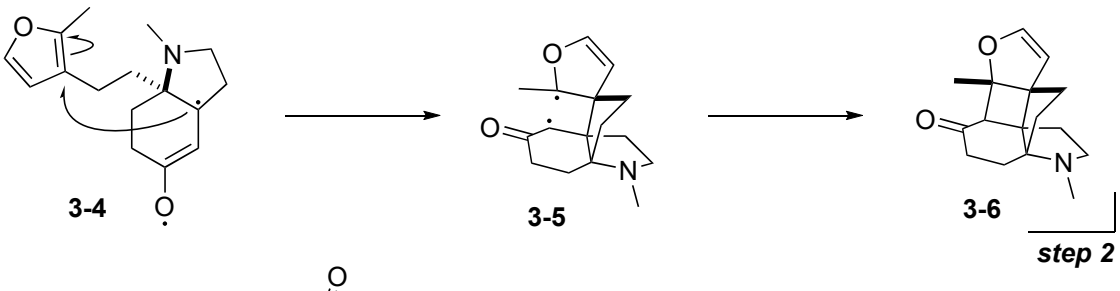
3. Synthetic study of acutumine

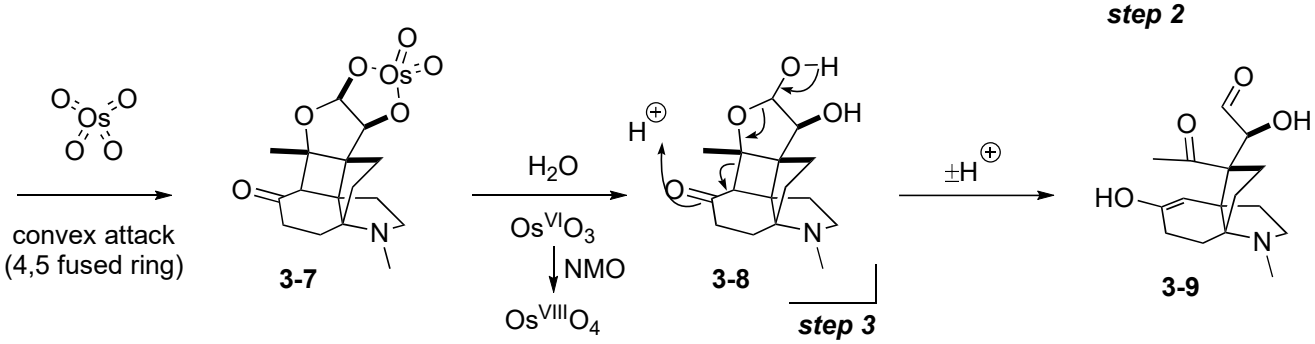
3.1. reaction mechanism

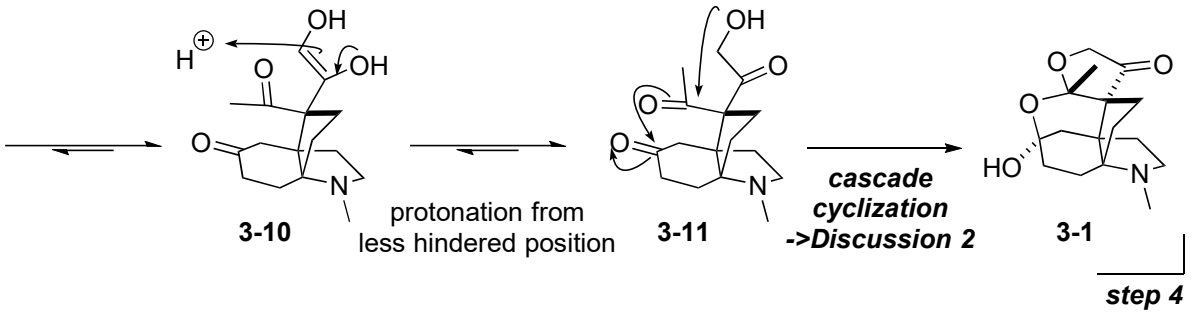








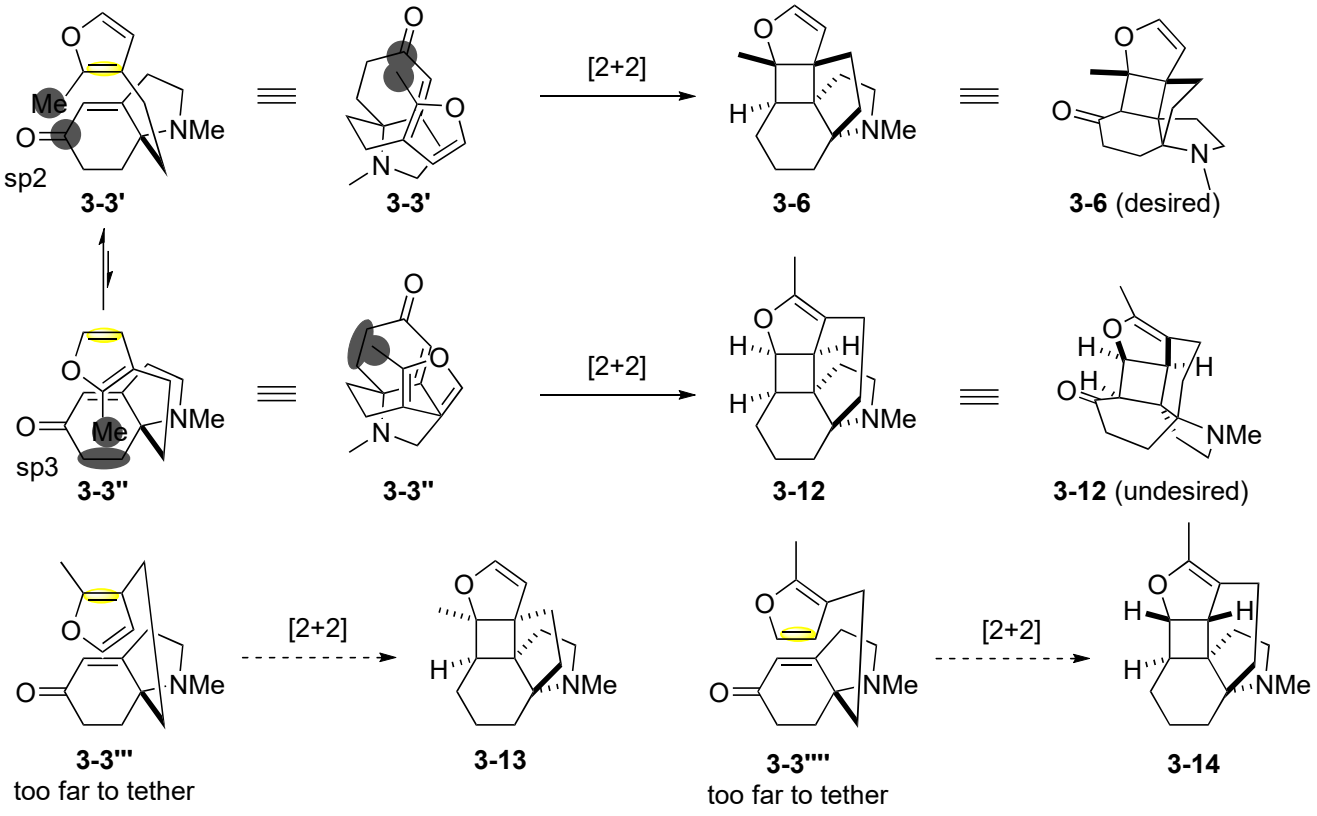




3.2. Discussion

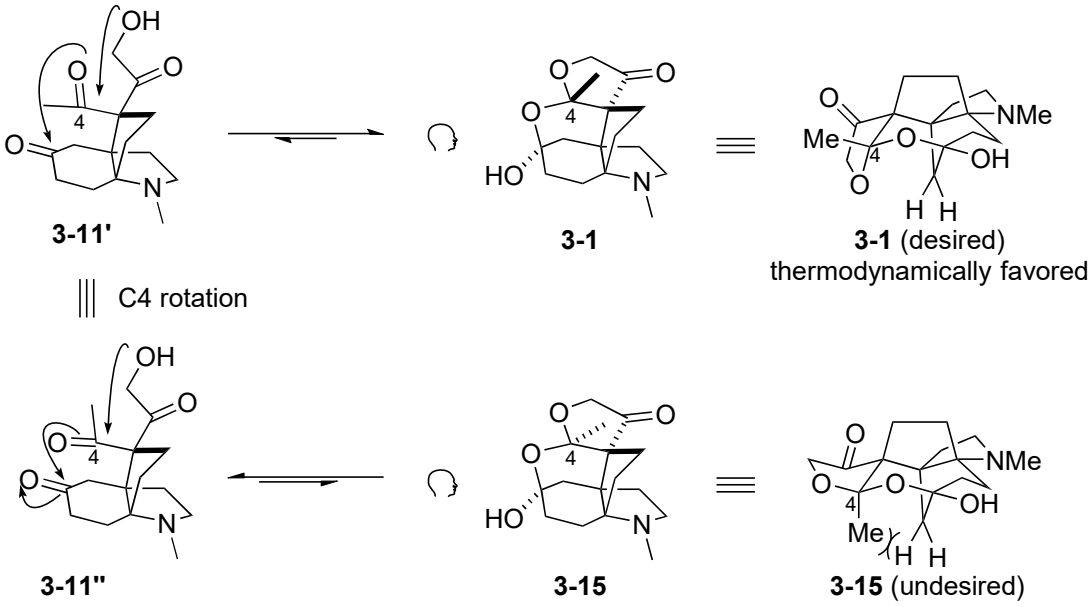
Discussion 1

diastereoselectivity of [2+2] photocyclization



Discussion 2

stereoselectivity of C4



3-15 has trasannular interaction between C4 Me group and methylene.
Termodynamically favored **3-1** was mainly generated.