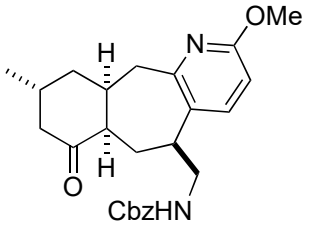
Problem Seminar (3) 18/01/06 Yuki Fujimoto

Please fill in the blank and explain the reaction mechanisms.

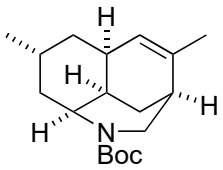


1-1

1. H_2, Pd/C, EtOAc, rt
2. $NaBH_4$, MeOH, 0 °C*
   92 % (2 steps)
3. *n*-BuLi (3 eq.), THF, -78 °C;
   I_2 (2 eq.), -78 to 0 °C
   80 %
4. NaH, EtSH, DMF, 120 °C
   76 %

*If step 1 was not completed, step 2 was conducted.

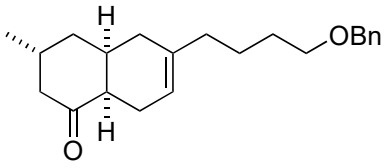
1-2
$C_{16}H_{20}N_2O$
(pentacyclic compound)



2-1

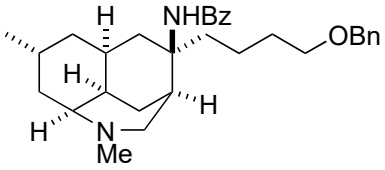
1. $CHBr_3$, $BnNEt_3Cl$, *i*-PrOH
   CH_2Cl_2/aq. NaOH, 0 °C to rt
   65 %
2. TFA, CH_2Cl_2, rt
3. pyridine, reflux
   96 % (2 steps)
4. *t*-BuLi, THF, -78 °C;
   $TrisN_3$;
   AcOH, -78 °C to rt
   75 %
5. dioxane/aq. HCl, 60 °C
   92 %
6. **2-2**, NaH, THF, 0 °C;
   HCl in MeOH, 40 °C
   90 %

1-2
$C_{16}H_{20}N_2O$
(pentacyclic compound)

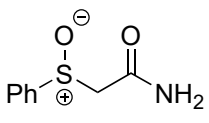


3-1

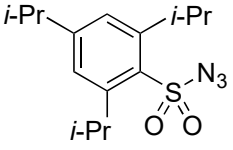
1. $BzNHNH_2$, MeOH, rt;
   $NaBH_3CN$, HCl in MeOH
   80 %
2. $(HCHO)_n$, $(i\text{-Pr})_2NEt$, MS4A
   sealed tube, toluene, 115 °C
   82 %
3. SmI_2, MeOH/THF, rt;
   aq. HCHO, $NaBH_3CN$
   HCl in MeOH
   80 %



3-2



2-2



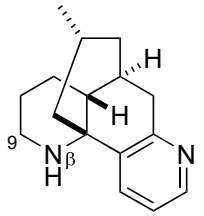
$TrisN_3$

Problem Seminar (3) 18/01/06 Yuki Fujimoto
Answer
Topic: total synthesis of miscellaneous type *lycopodium* alkaloids

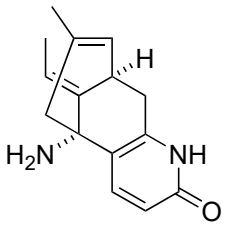
0 Introduction
0-1 lycopodium alkaloids

derived into four structural classes: lycodine class, lycopodine class, fawcettimine class, and miscellaneous type

lycodine class: tetracyclic core, four 6-membered ring including pyridine or pyridone
C9-Nβ bond is cleaved in some compounds

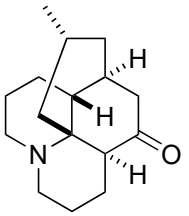


0-1 lycodine

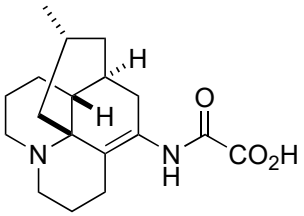


0-2 huperzine A

lycopodine class: tetracyclic core, four 6-membered ring

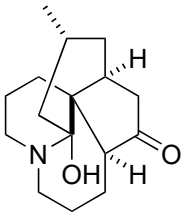


0-3 lycopodine

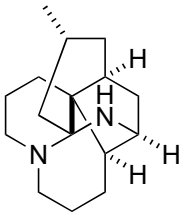


0-4 huperzine G

fawcettimine class: tetracyclic core, two 6-membered ring, one 5-membered ring, and one 7-membered ring

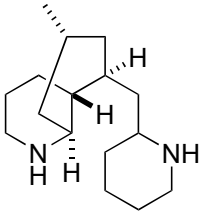


0-5 fawcettimine

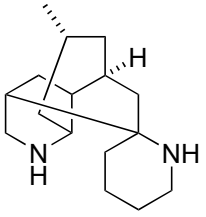


0-6 macleanine

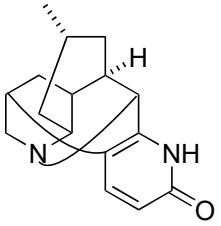
miscellaneous class: biosynthesised from phlegmarine



0-7 phlegmarine

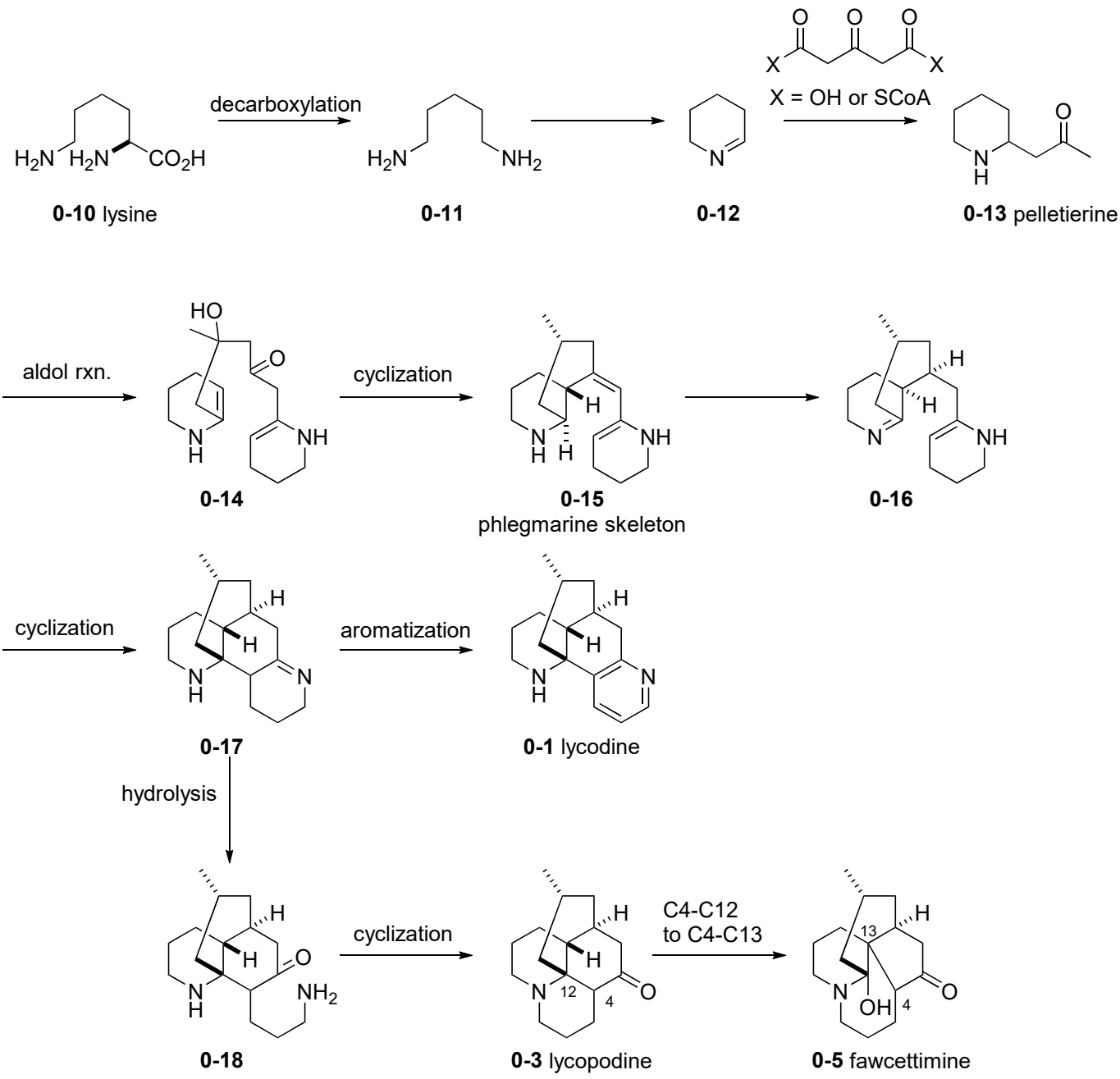


0-8 nankakurine A



0-9 lyconadin A

0-2 biosynthesis of *lycopodium* alkaloids



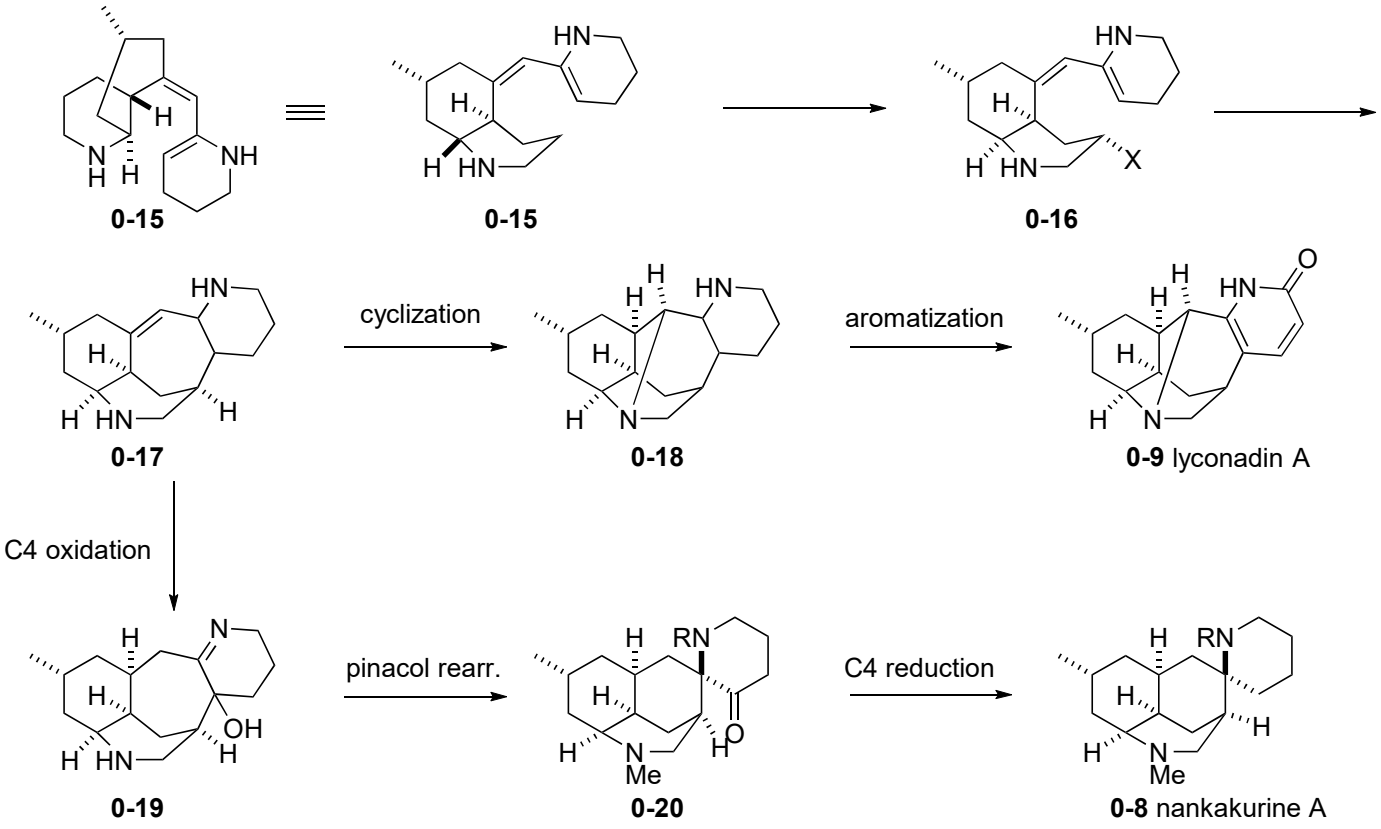
0-10 lysine **0-11** **0-12** **0-13** pelletierine

0-14 **0-15** phlegmarine skeleton **0-16**

0-17 **0-1** lycodine

0-18 **0-3** lycopodine **0-5** fawcettimine

0-3 biosynthesis of lyconadines and nankakurines



Problem 1,2: total synthesis of lyconadin A

lyconadin
isolation
from *Lycopodium complanatum* by Kobayashi (A: 2001, B: 2006, C: 2011)

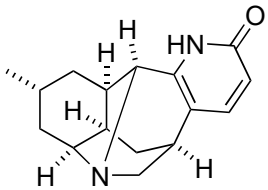
bioactivity
small citotoxity against murine lymphoma L1210
and human epidermoid carcinoma KB cells

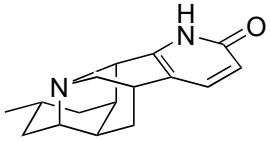
structural features
pentacyclic skeleton (C: tetracyclic skeleton)
6 stereocenters (C: 5 stereocenters)
pyridone ring (B: dihydropyridone)
bridgehead 3° amine

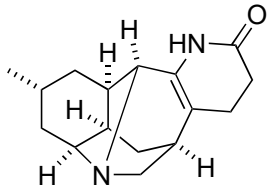
total synthesis
lyconadin A
Smith (2007, enantiomeric)
Sarpong (racemic: 2008, enantiomeric: 2009)
Fukuyama (2011, enantiomeric)
Dai (2014, enantiomeric)

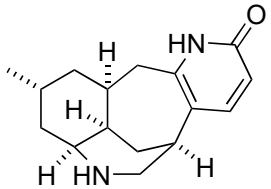
lyconadin B
Smith (2007, enantiomeric)
Fukuyama (2013, enantiomeric)

lyconadin C
Fukuyama (2013, enantiomeric)
Waters (2013, enentiomeric)
Dai (2014, enentiomeric)

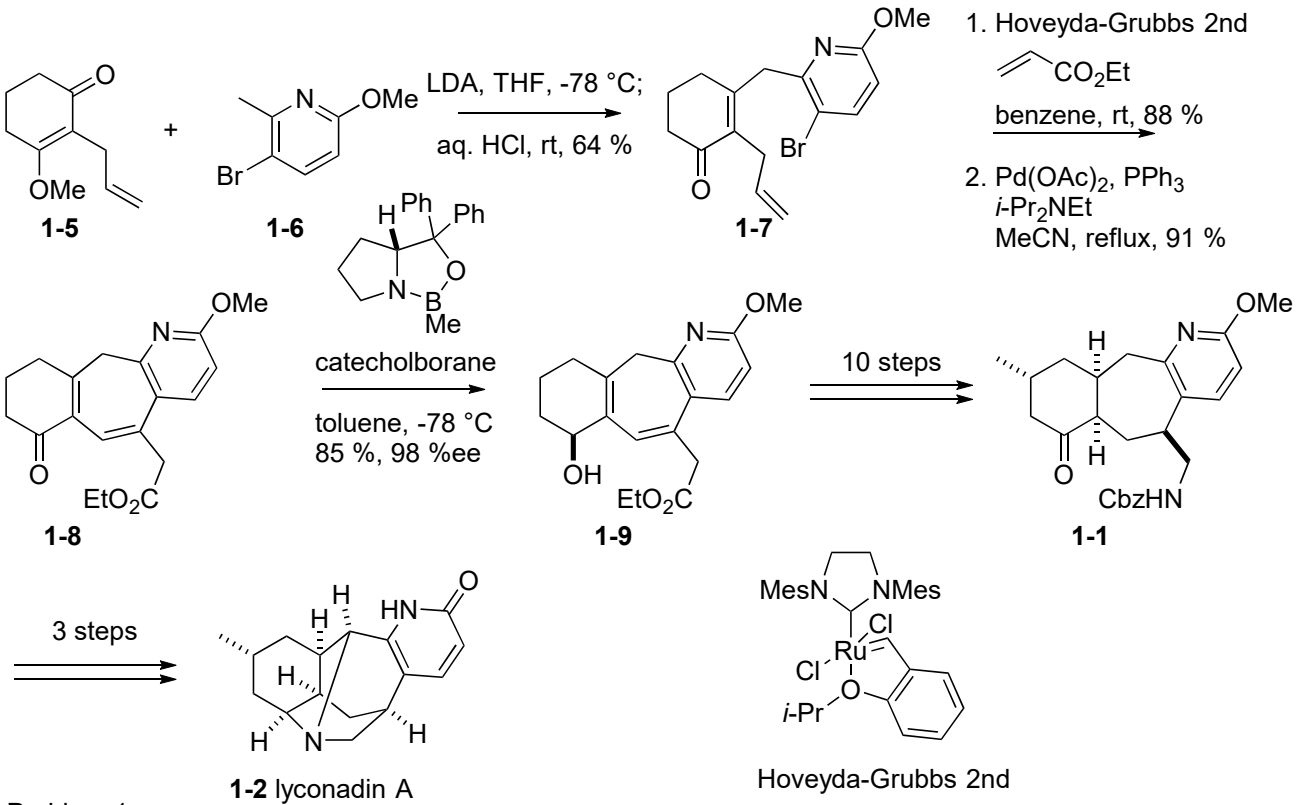

1-2 lyconadin A


1-2 lyconadin A

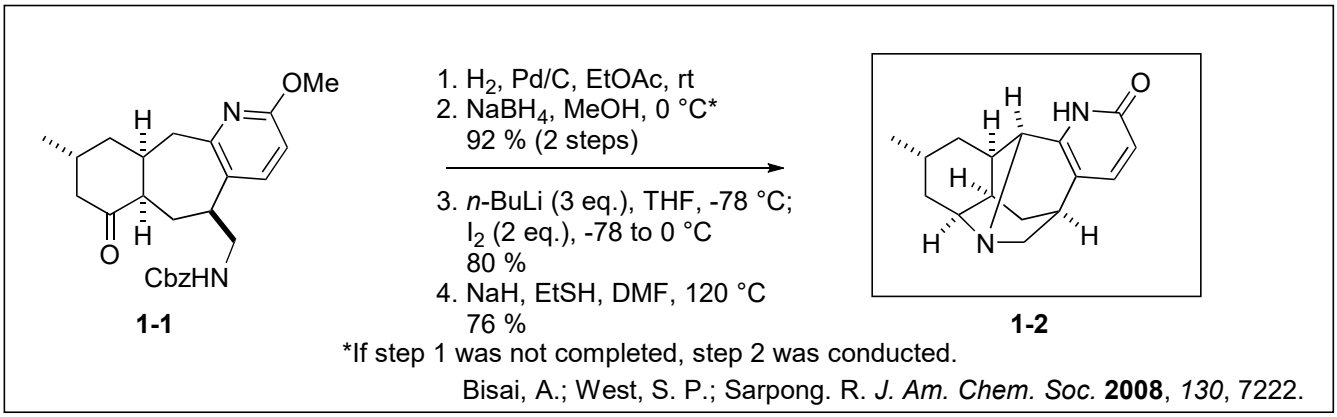

1-3 lyconadin B


1-4 lyconadin C

Problem 1
Synthetic route of Sarpong (enantiomeric route)



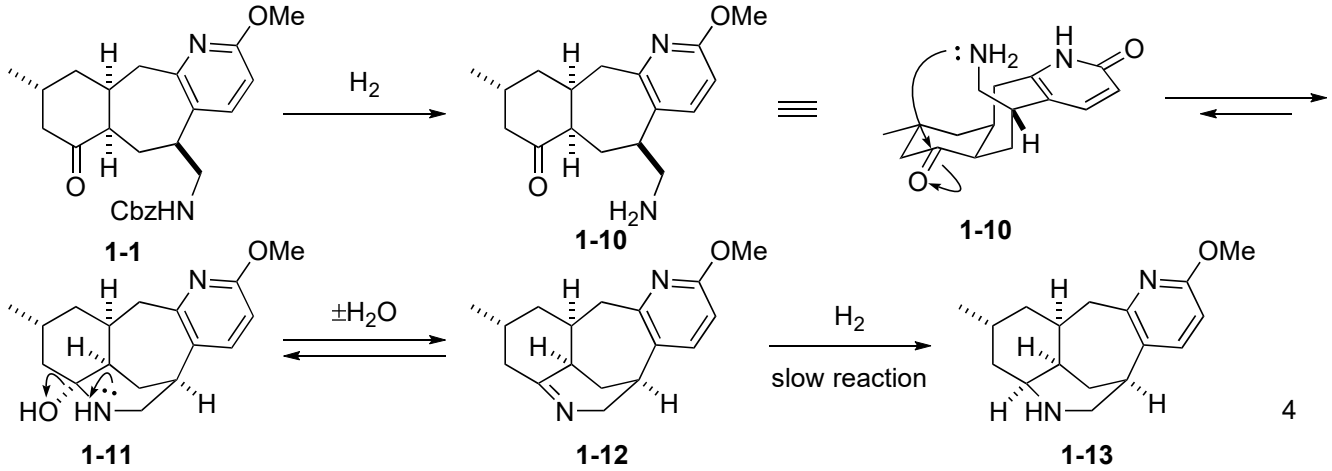
Problem 1



*If step 1 was not completed, step 2 was conducted.

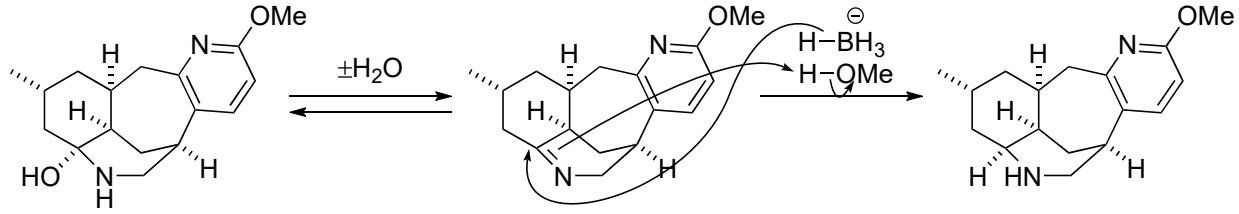
Bisai, A.; West, S. P.; Sarpong. R. *J. Am. Chem. Soc.* **2008**, *130*, 7222.

step 1 deprotection of Cbz, (reductive amination)



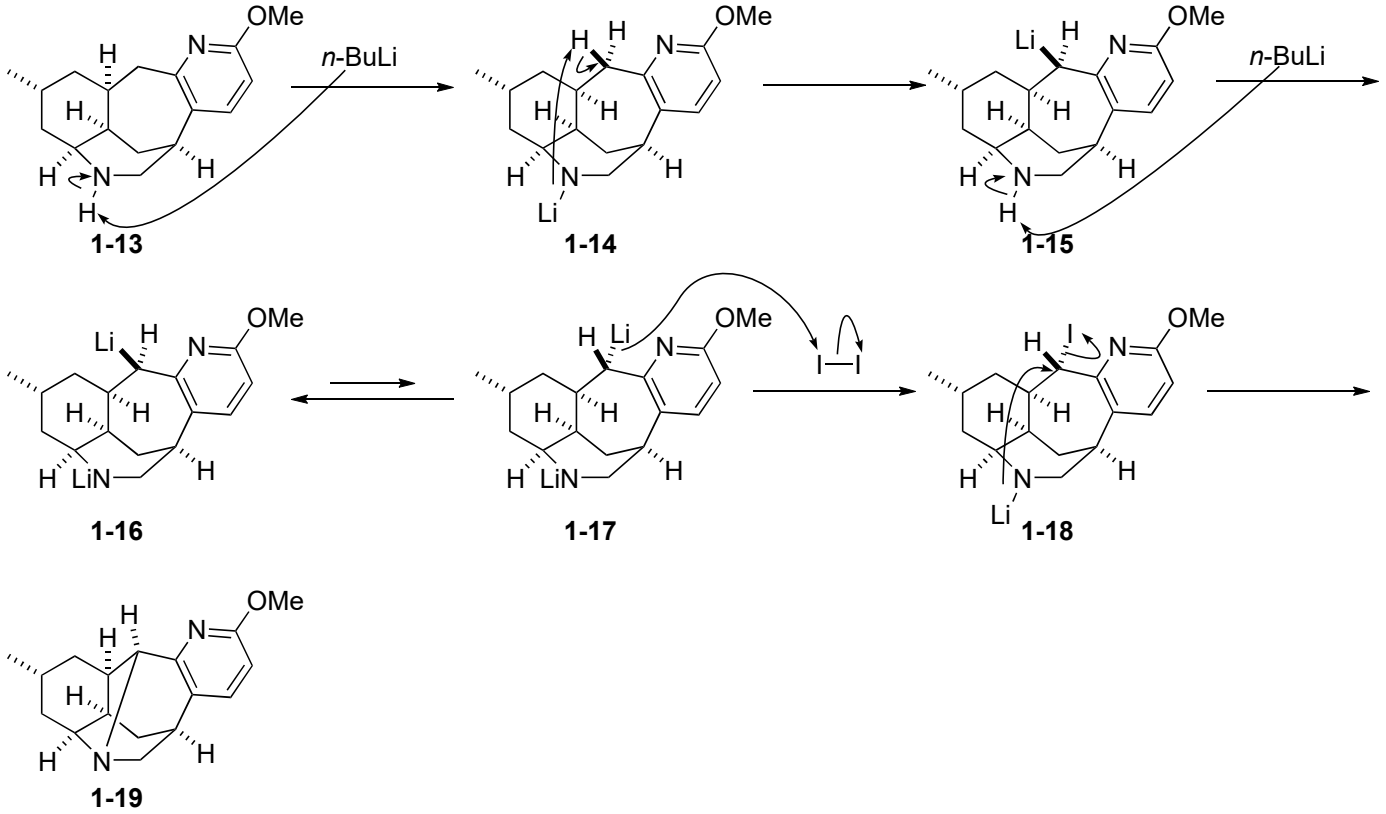
product was mixture of **1-11** and **1-13**

step 2 reductive amination



1-11 **1-12** **1-13**

step 3: regioselective iodination and C-N bond formation

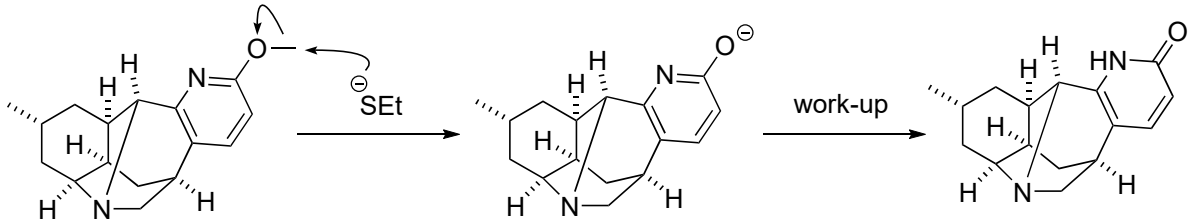


1-13 **1-14** **1-15**

1-16 **1-17** **1-18**

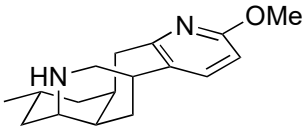
1-19

step 4: deprotection of methyl pyridone

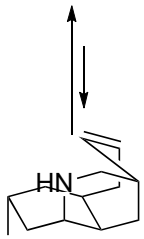


1-19 **1-20** **1-2**

Discussion: regioselective iodination



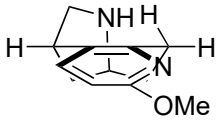
1-13-a



1-13-b
pyridine ring was omitted

6-membered ring: chair and chair
7 membered ring: twisted chair

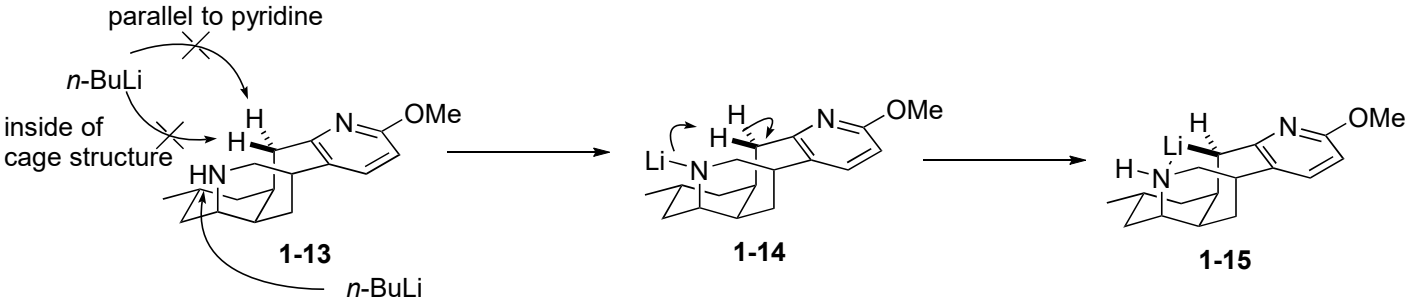
6-membered ring: boat and chair
7 membered ring: twisted boat



1-13-a

cyclohexane ring was omitted

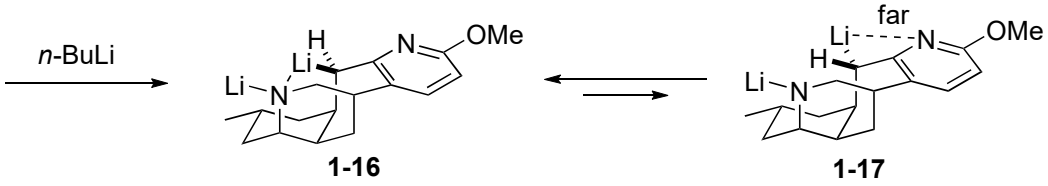
αproton is parallel to pyridine ring
→*n*-BuLi cannot deprotonate.



1-13

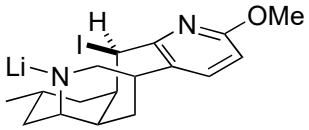
1-14

1-15

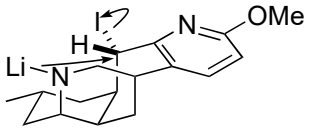


1-16
chelating

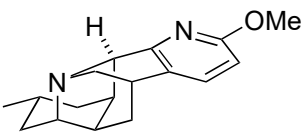
1-17



1-21

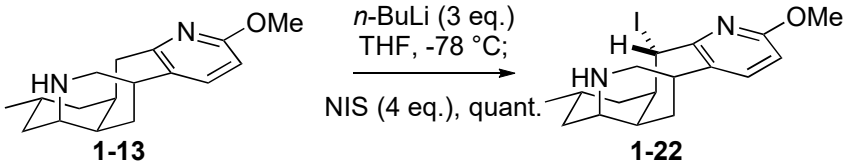


1-18



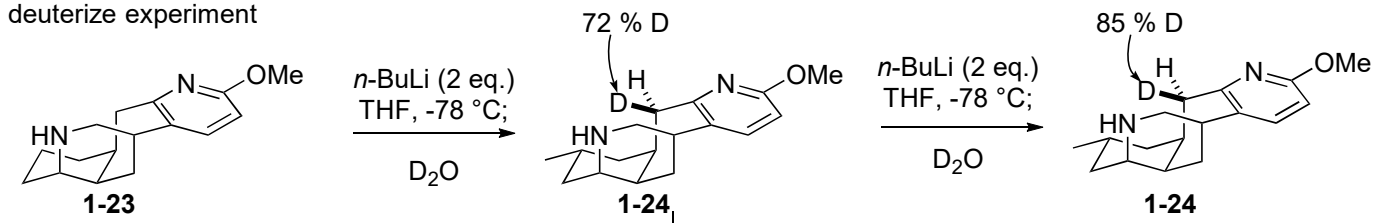
1-19

isolation of iodide

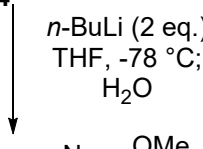


1-13 **1-22**

deuterize experiment

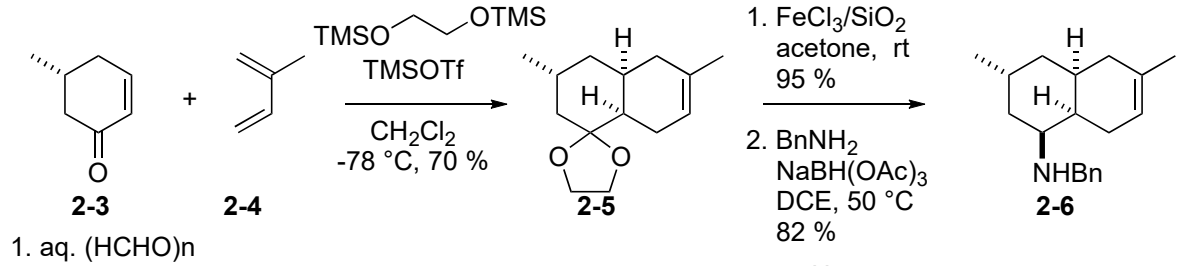


1-23 **1-24** **1-24**

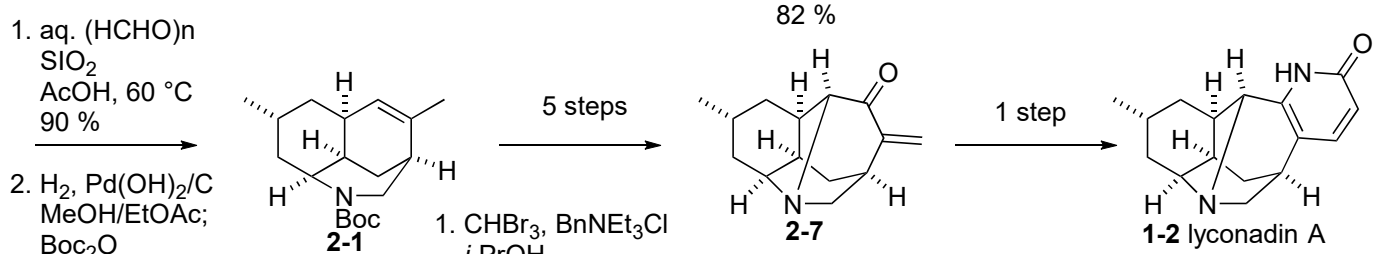


1-25

Problem 2
synthetic route of Fukuyama



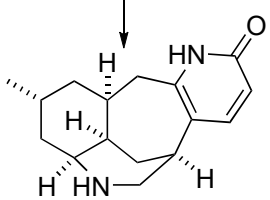
2-3 **2-4** **2-5** **2-6**



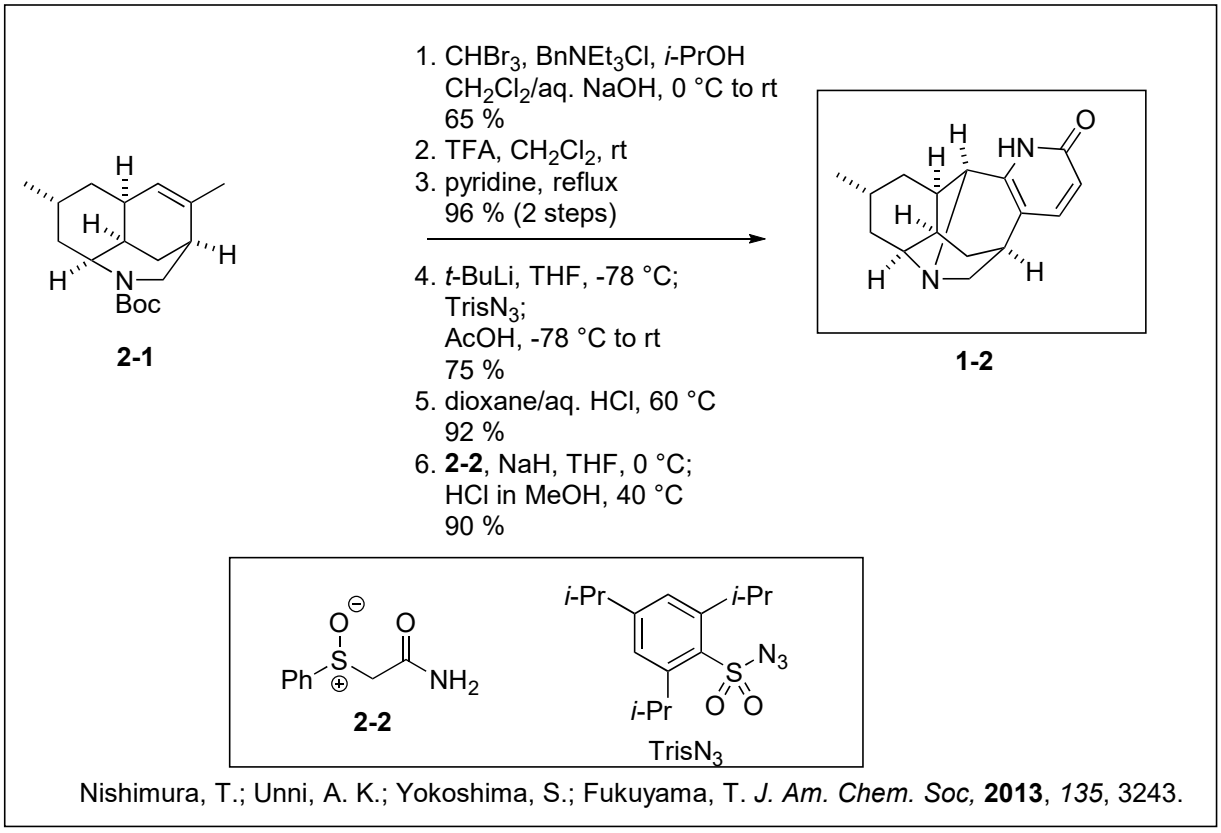
2-1 **2-7** **1-2** lyconadin A

2-8 **1-3** lyconadin B

4 steps



1-4 lyconadin C

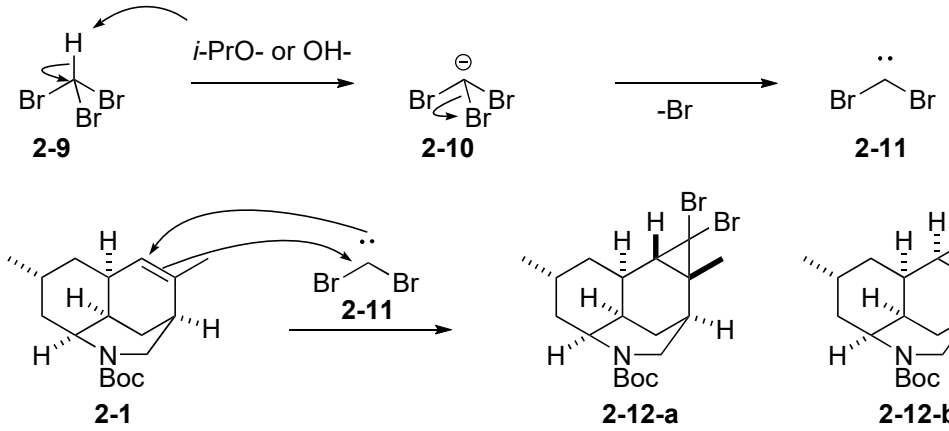


Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc,* **2013**, *135*, 3243.

step 1: carbene formation, cyclopropanation

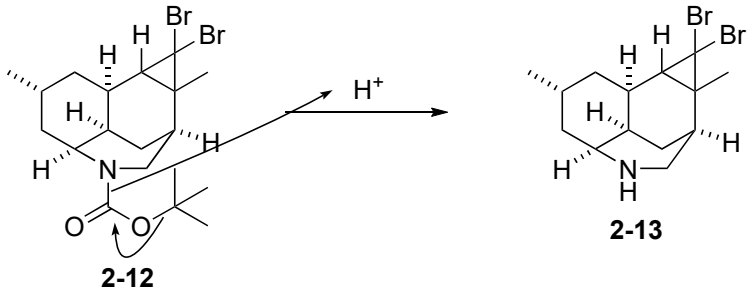
pKa of *i*-PrOH, H_2O = 16.5, 15.7

pKa of $CHBr_3$ = 13.7

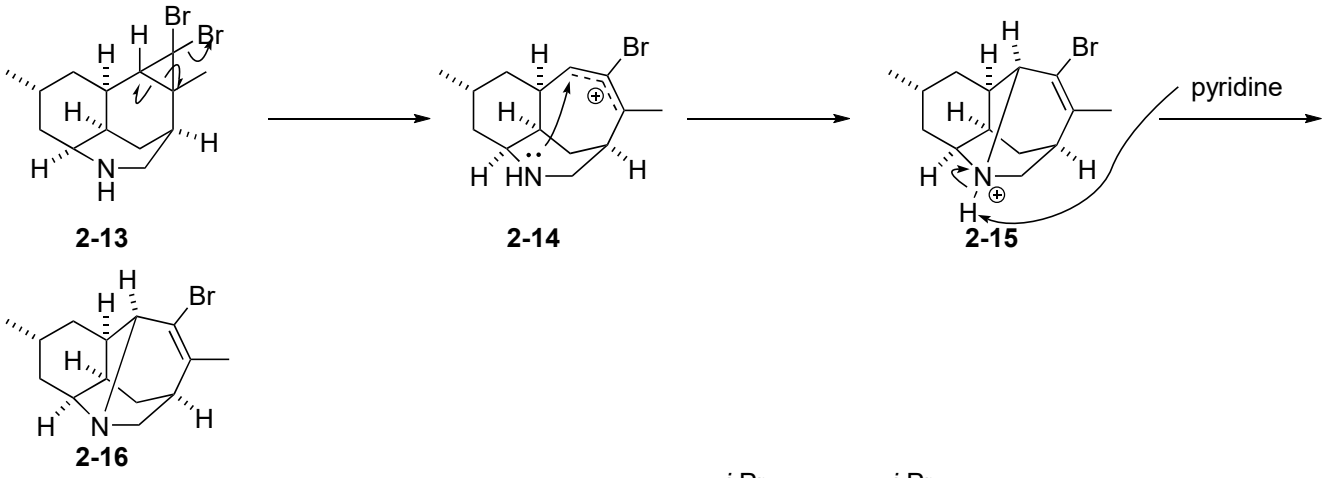


2-12-a:**2-12-b** = 5:1

step 2: deprotection of Boc



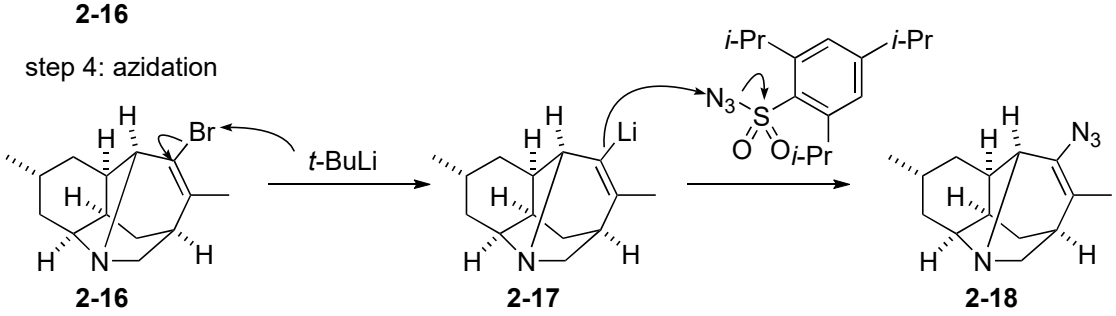
step 3: electron cyclic ring opening and C-N bond formation



2-13 **2-14** **2-15**

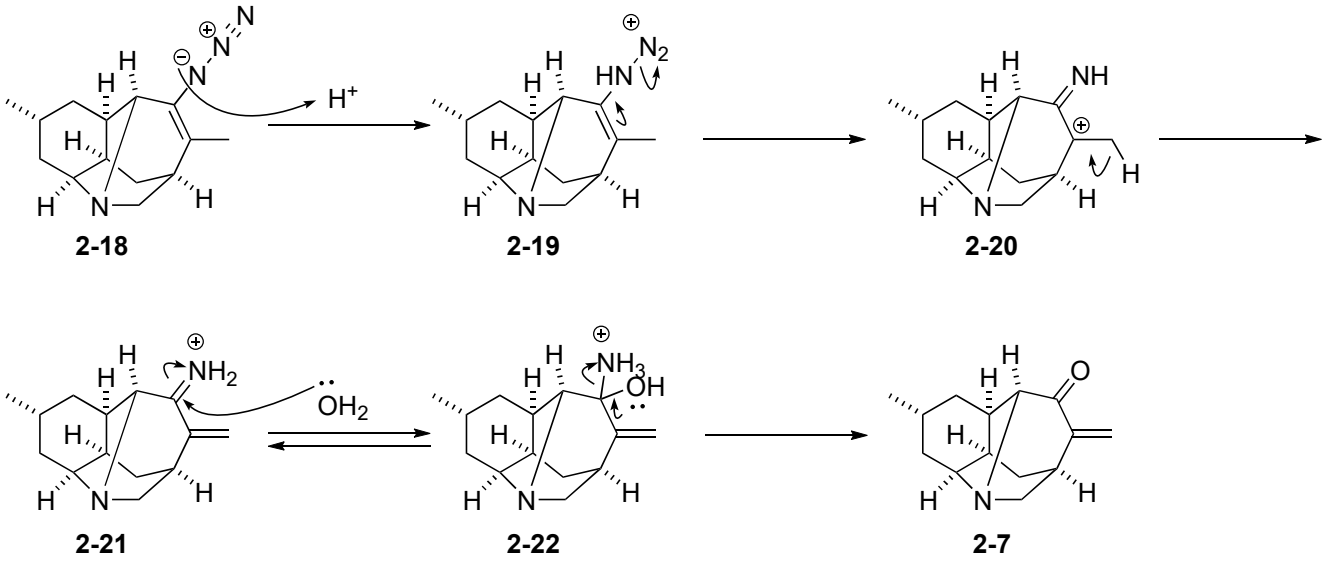
2-16

step 4: azidation



2-16 **2-17** **2-18**

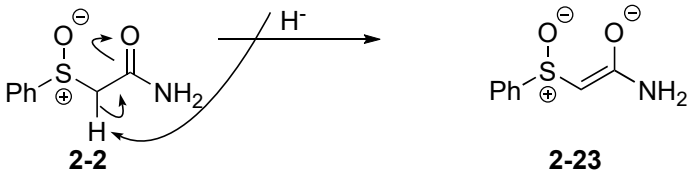
step 5: hydrolysis of vinyl azide



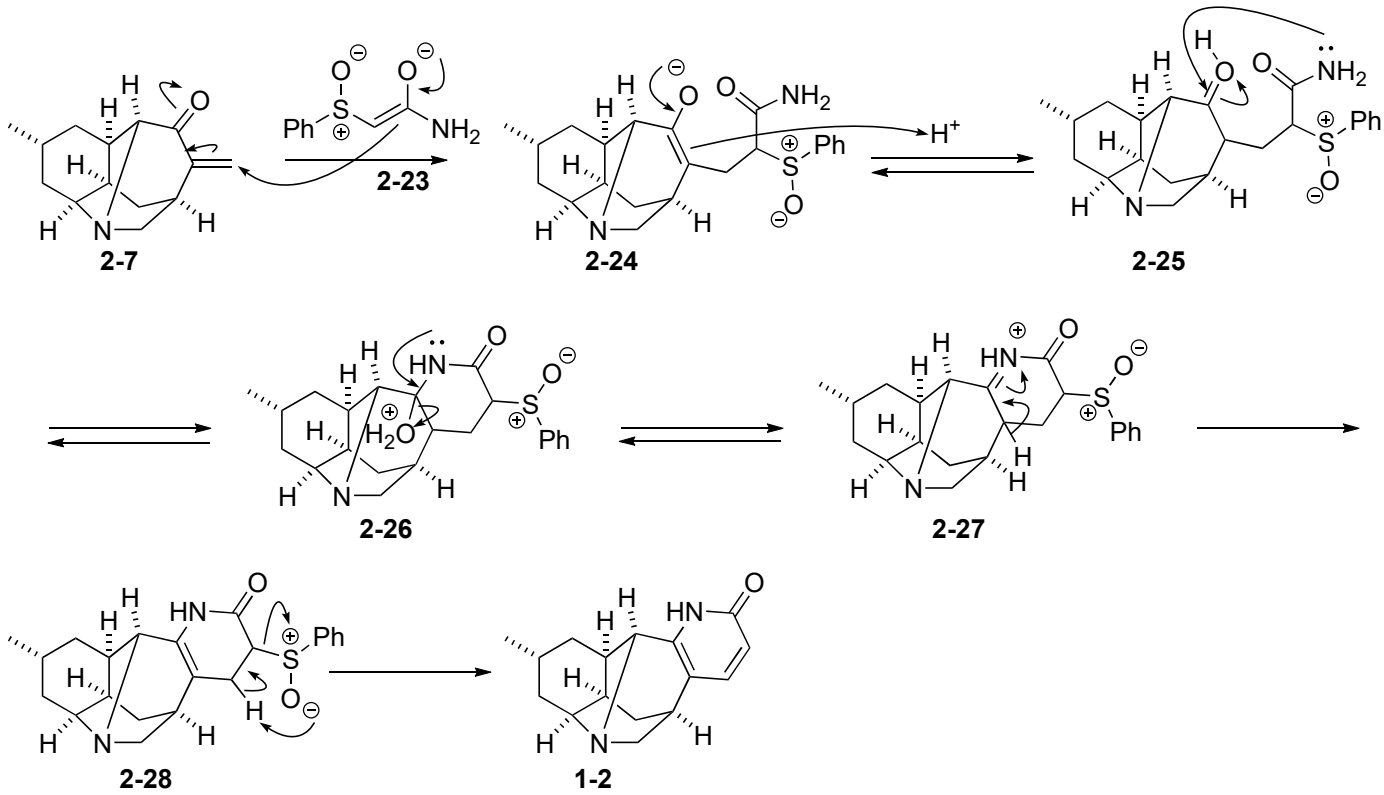
2-18 **2-19** **2-20**

2-21 **2-22** **2-7**

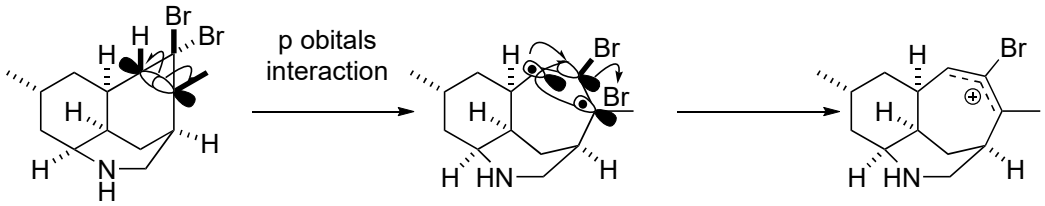
step 6: pyridone formation



2-2 **2-23**



Discussion: electrocyclic cyclopropane opening



2-13-a

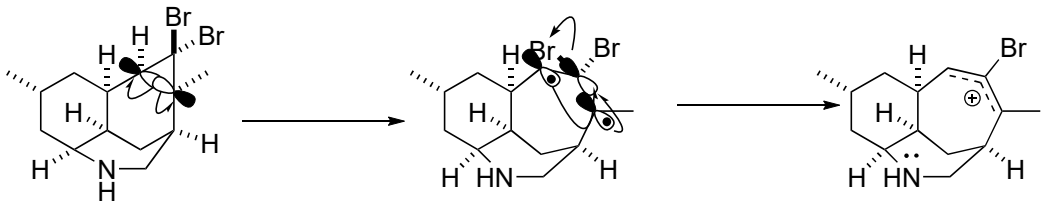
disrotately→σ2s→allowed

conrotately→σ2a→not allowed

2-29-a

αBr can leave

2-14



2-13-b

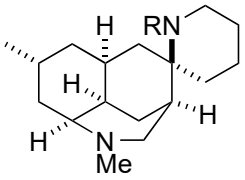
2-29-b

βBr can leave

2-14

Problem 3: overman's total synthesis of nankakurines A and B

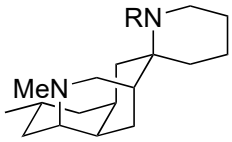
nankakurines A and B
Isolation
from club moss *Lycopodium hamiltonii* by Kobayashi (A: 2004, B: 2006)



3-3 R = H nankakurine A
3-4 R = Me nankakurine B

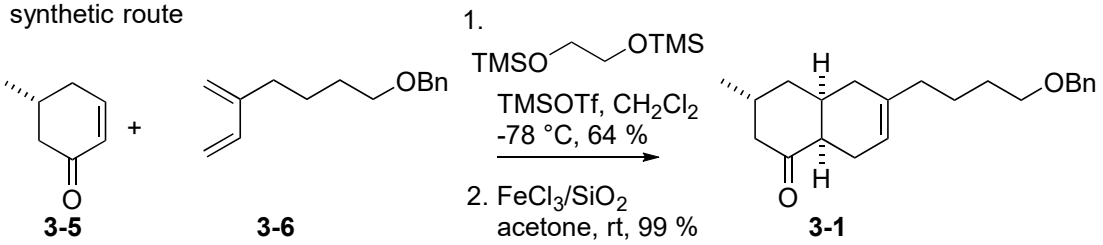
Bioactivity
induction of secretion of neurotrophic faxtors
promotion of neuronal differentiation of rat adrenal PC-12 cells

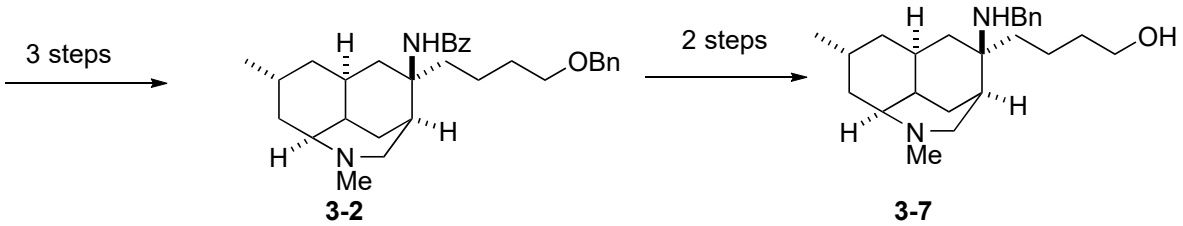
Structural features
tetracyclicskeleton
6 stereocenters
spiropiperidine

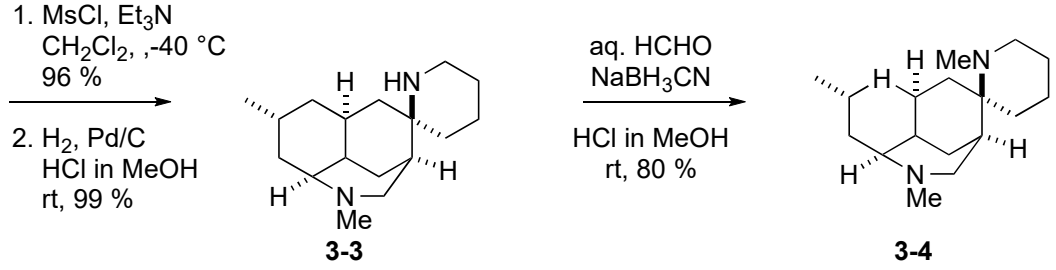


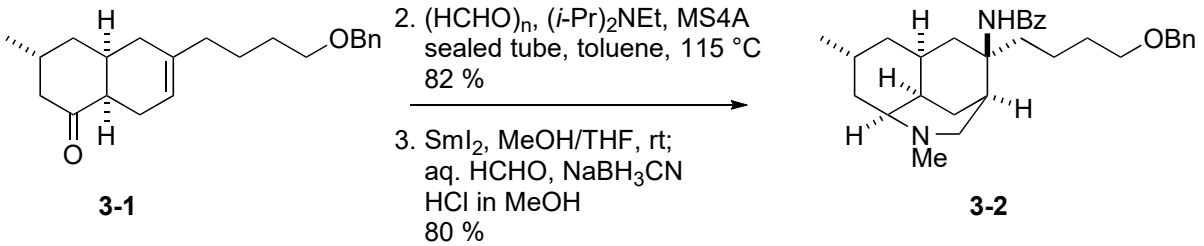
Total synthesis
Overman (2008, enantiomeric)
Waters (2010, racemic)

synthetic route



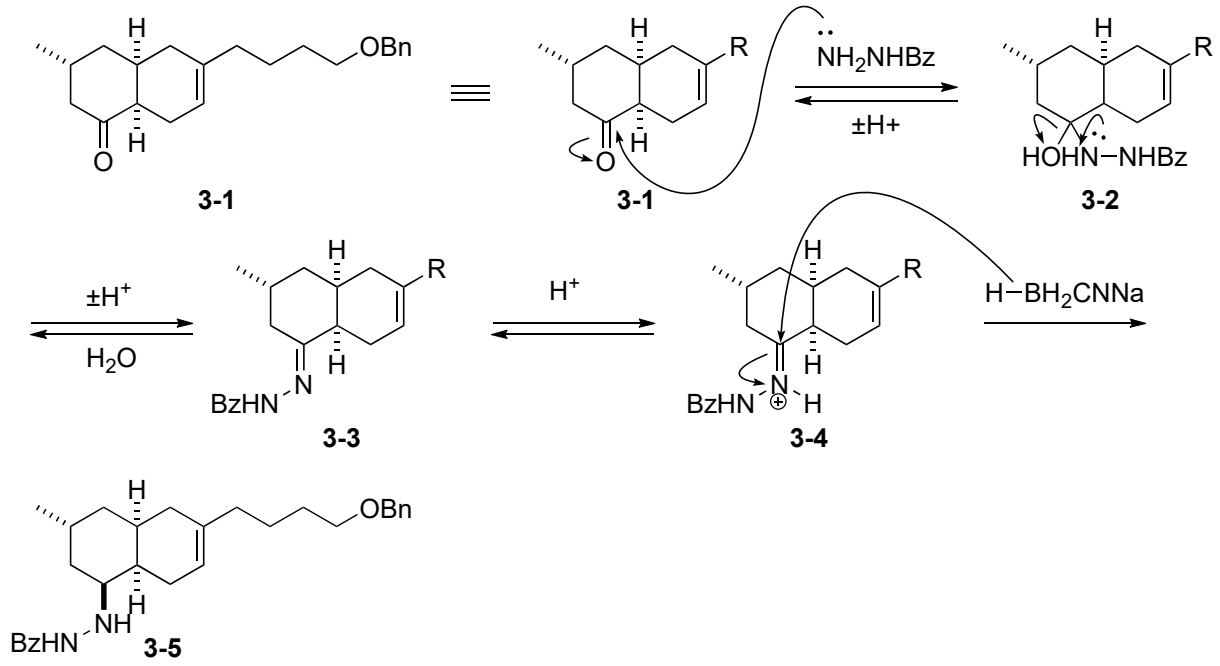




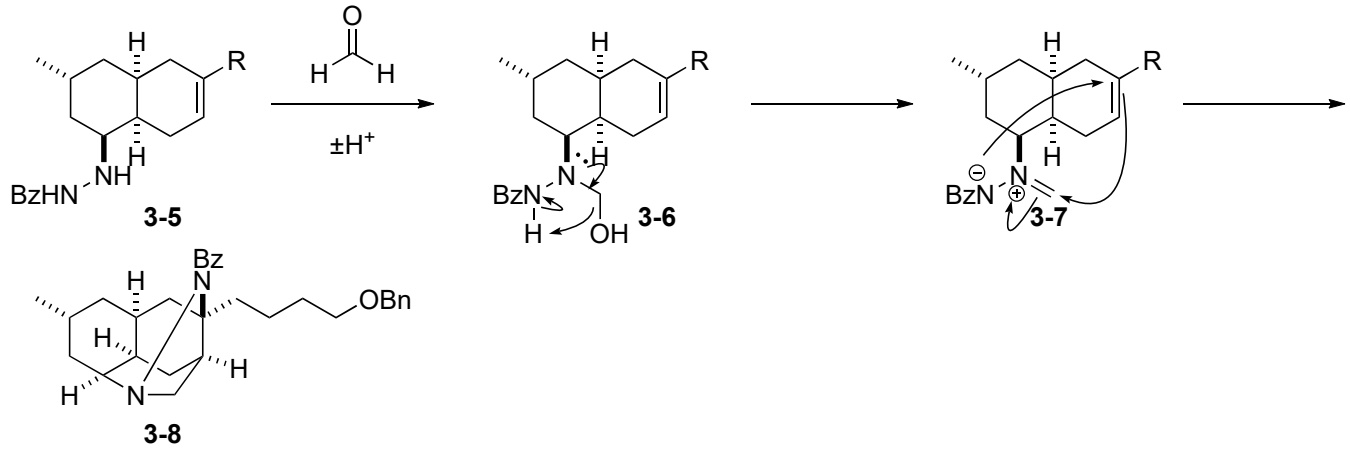


Nilsson, B. L.; Overman, L. E.; de Alaniz, J. R.; Rohde, J. M. *J. Am. Chem. Soc*. **2008**, *130*, 11927.

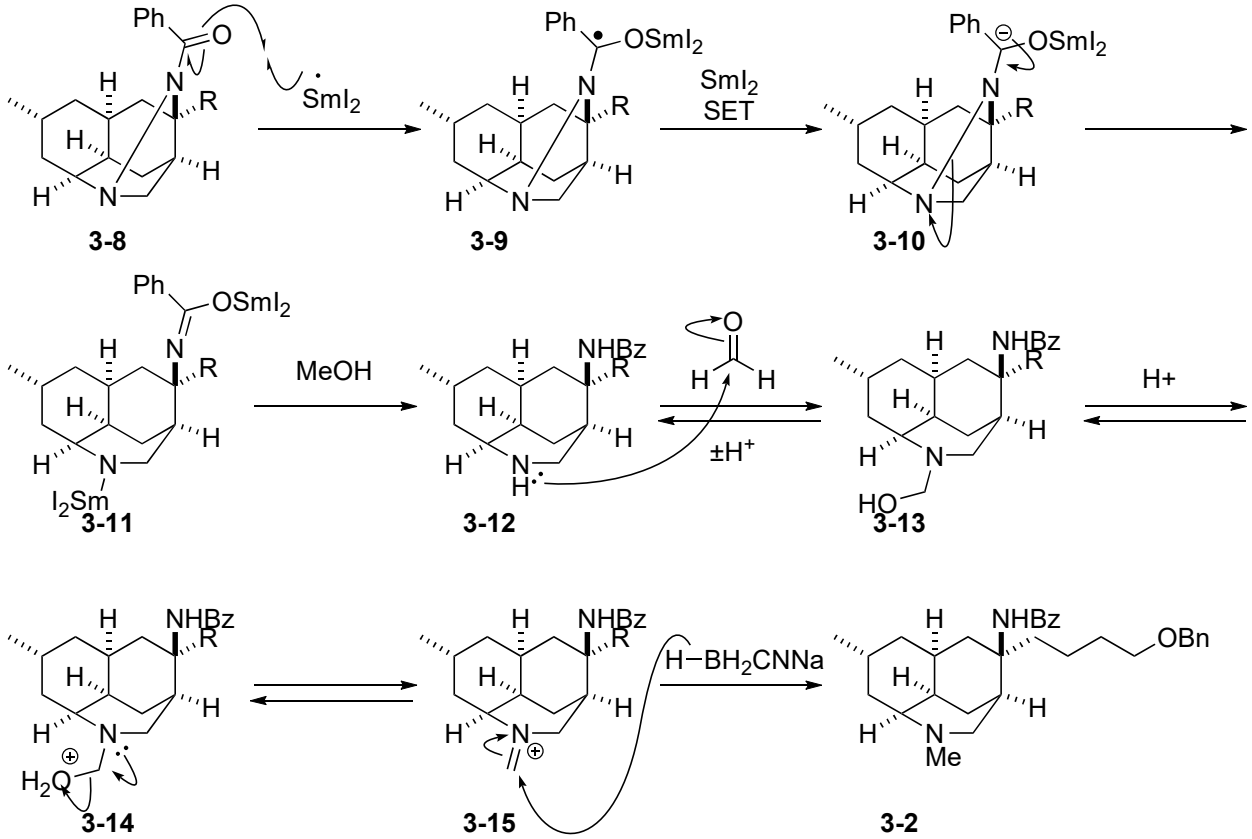
step 1: hydrazone formation, reductive amination



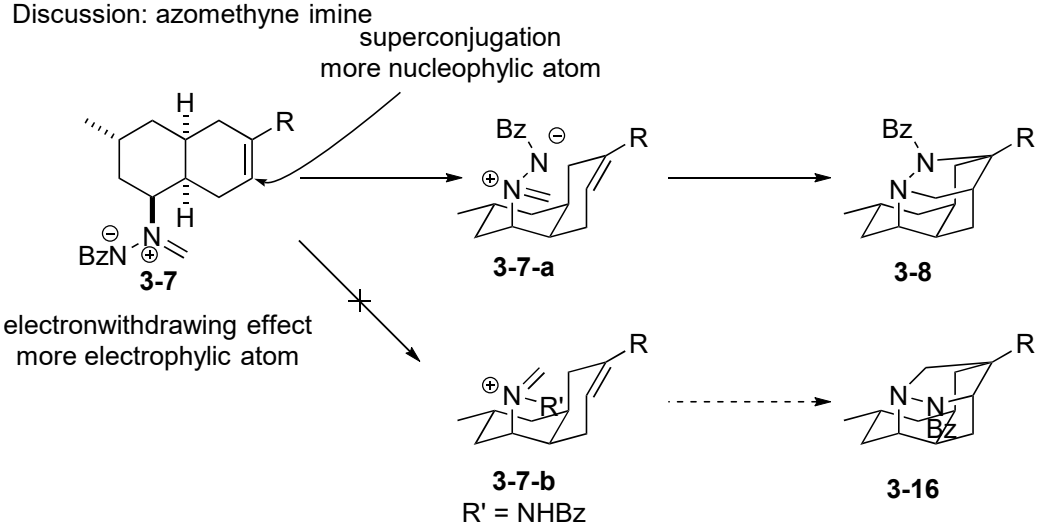
step 2: 1,3-dipolar cycloaddition using azomethyne imine



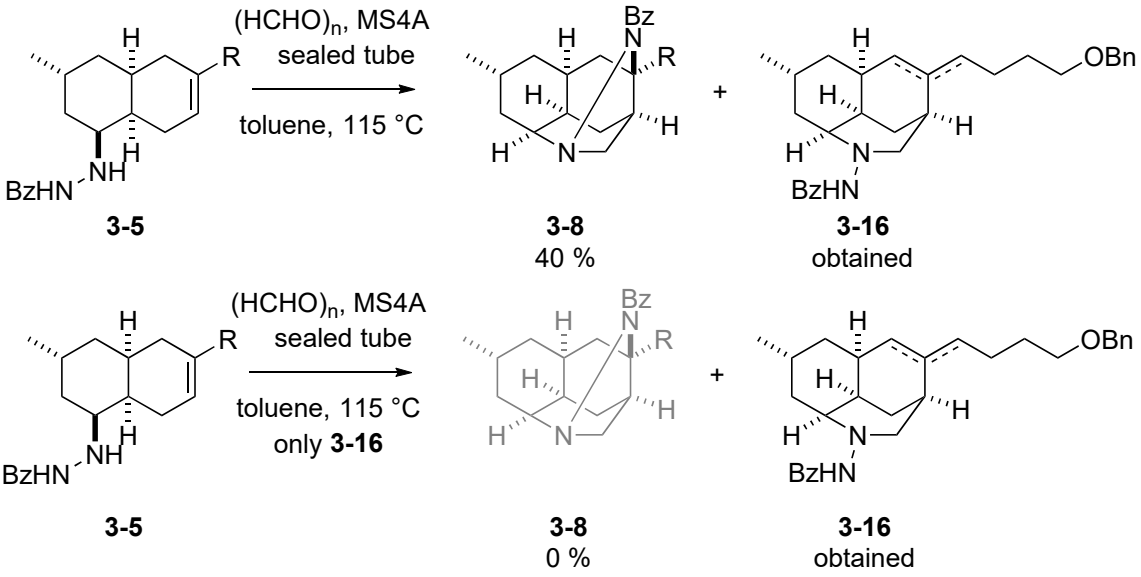
step 3: N-N bond scission, N-methylation



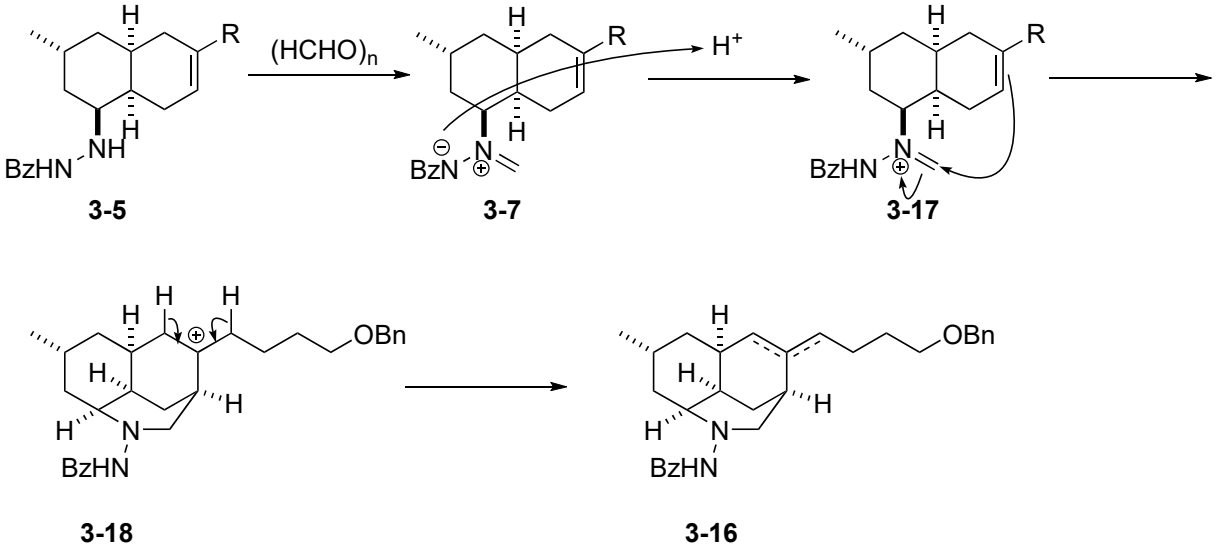
Discussion: azomethyne imine



effect of *i*-Pr_2NEt



proposed pathway to **3-16**



i-Pr_2NEt was necessary to maintain azomethyne imine