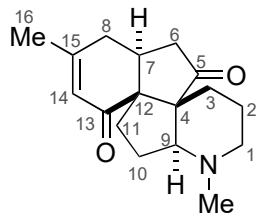
Problem Session (1) [Answer]

2017.7.15 Keshu Zhang

Topic: Formal total synthesis of Lycojaponicumin C


(**0-1**)
Lycojaponicumin C

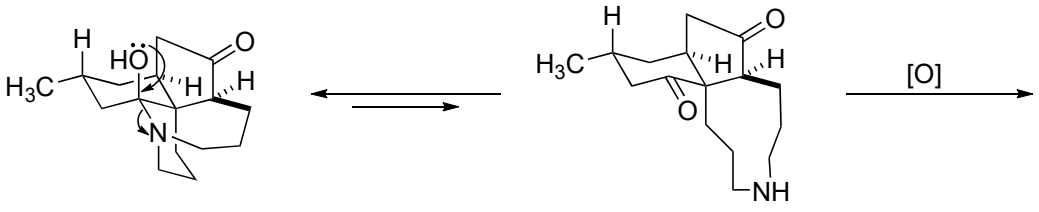
0. Introduction

0-1. Isolation
from the traditional Chinese medicine, *Lycopodium japonicum*.
(Li, Y. *et al. Org. Lett*. **2012**, *14*, 2614.)

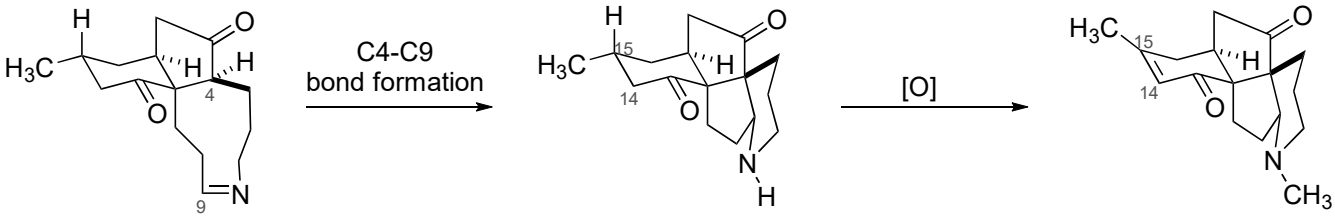
0-2. Biological activity
moderate inhibition toward lipopolysaccharide (LPS)-induced pro-inflammatory factors.
inactive against acetylcholinesterase.
(Li, Y. *et al. Org. Lett.* **2012**, *14*, 2614.)

0-3. Structural features:
-Fused 6/5/5/6 tetracyclic skeleton.
-A bicyclic [3.3.0] core with four continuous stereocenters,
including two vicinal quaternary carbon centers.

0-4. Proposed biosynthetic pathway for the Lycojaponicumin skeleton.


(**0-2**)
fawcettimine

0-3


0-4

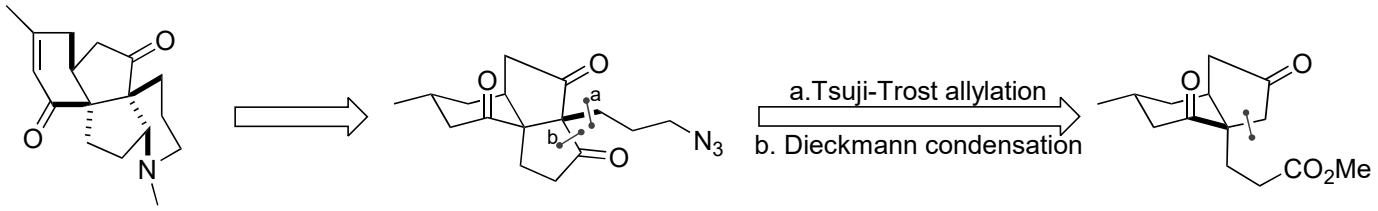
0-5

0-6

Li, Y. *et al. Org. Lett.* **2012**, *14*, 2614.

0-5. Total syntheses of Lycojaponicumin C

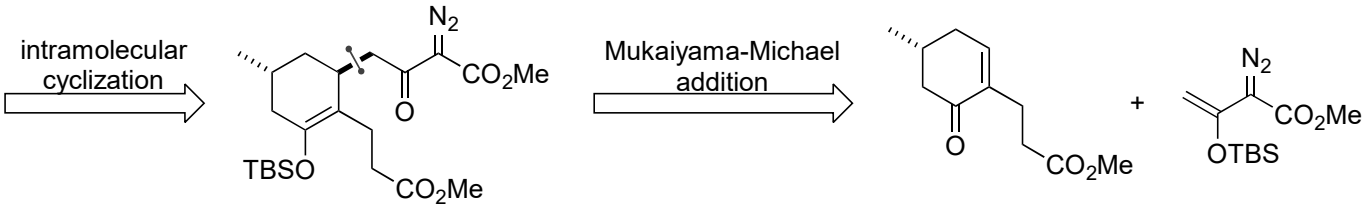
0-5-1.Tu's group (asymmetric)



(**0-7**)
(-)-Lycojaponicumin C

0-8

0-9



0-10

0-11

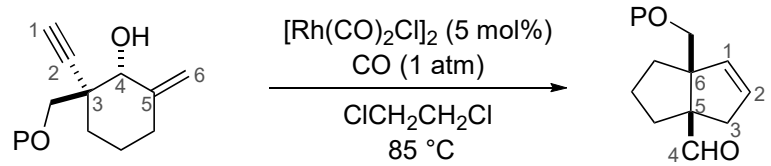
0-12

Hou, S.-H.; Tu, Y.-Q.; Liu, L.; Zhang, F.-M.; Wang, S.-H.; Zhang, X.-M. *Angew. Chem., Int. Ed*. **2013**, *52*, 11373.

0-5-2.Yang's group (formal synthesis, racemic, **Problem session**)

Authors developed the Rh-catalysed [3+2] cycloaddition and applied it to the total synthesis.
(160514_PS_Komei_Sakata_lingzhiol;)

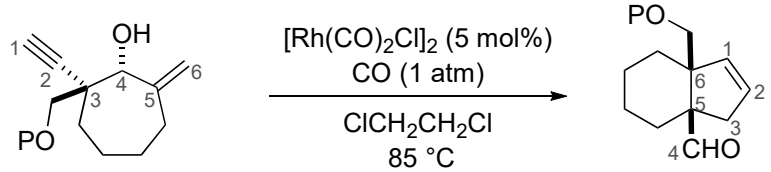
Rh-catalysed [3+2] cycloaddition (*Nat. Commun.* **2014**, *5*, 5707.)



0-13
P = NO_2PhCO

0-14

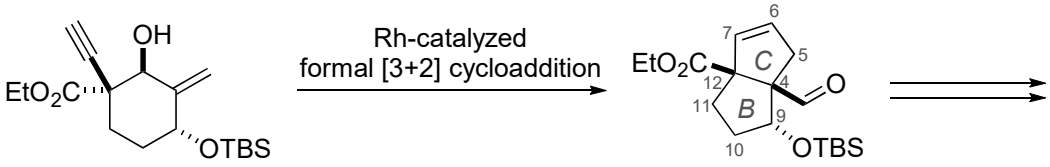
Construction of [3,3,0],[4,3,0] bicyclic ring system bearing two quaternary carbon centres



0-15
P = NO_2PhCO

0-16

Application to the Formal total synthesis of (±)-Lycojaponicumin C



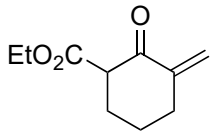
0-17

0-18

(**0-18**)
(±)-Lycojaponicumin C

Answer

(1)



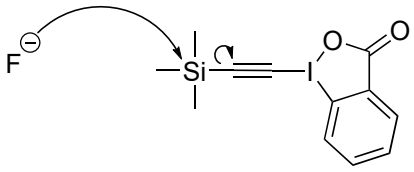
1-1

1. Waser's reagent , TBAF, THF, 86%
2. $NaBH_4$, $CaCl_2$, $CeCl_3$, MeOH, 45%
3. SeO_2, TBHP, CH_2Cl_2, rt, 60%

$(C_{12}H_{16}O_4)$

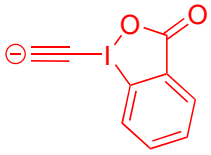
1-2

step 1-1: electrophilic alkynylation with Waser's reagent

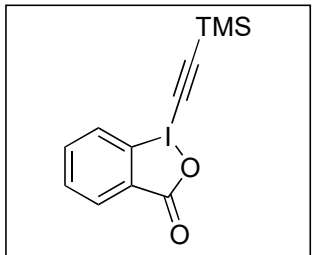


1-3

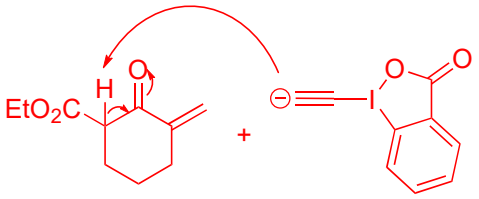
- Me_3SiF



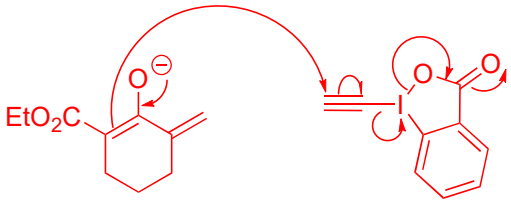
1-4



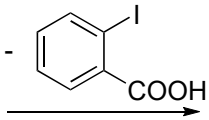
(**1-3**)
Waser's reagent

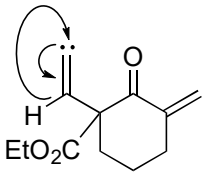


1-1 **1-4**

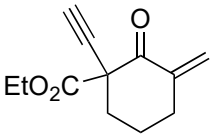


1-5 **1-6**





1-7



1-8

PKa: alkyne = 25
activate methylene = 10

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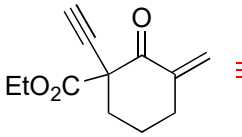
step 1-2: Luche reduction

$CeCl_3$ is able to accelerate the exchanging of ligands, so hydride sourse of Luche reduction is $NaH_nB(OMe)_{4-n}$



1-7

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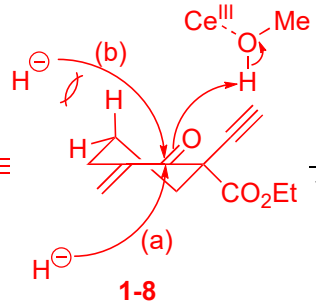
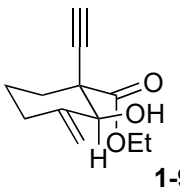


1-8

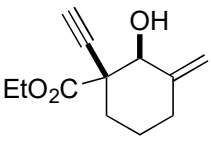
(a)

(b)



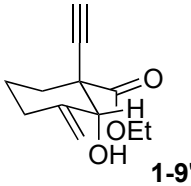
1-9

≡



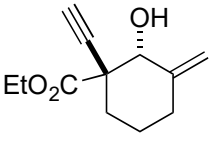
major

1-10 **(dr 3:1)**



1-9'

≡

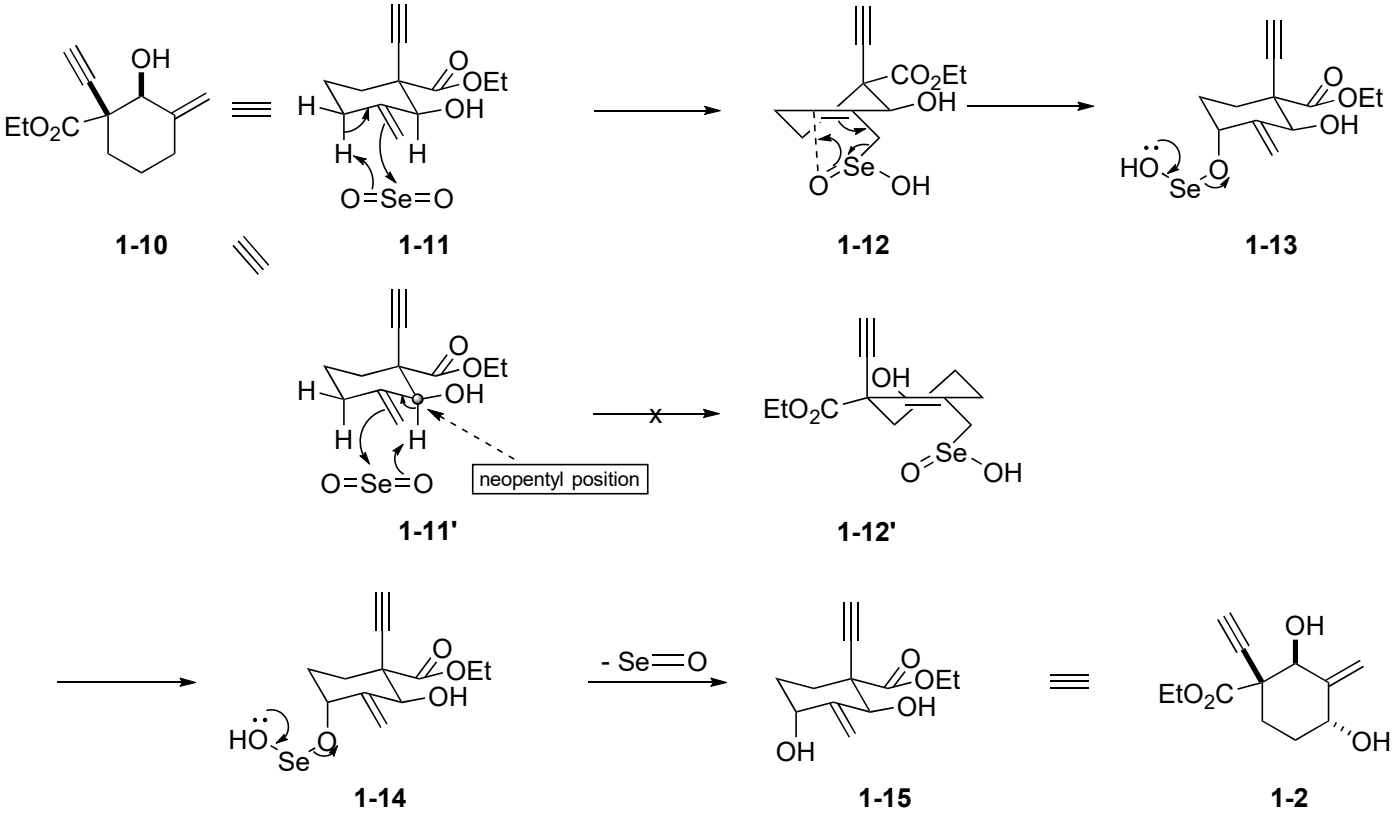


minor

1-10'

Cyclohexane including two sp^2 carbon should be written as half-chair conformation.

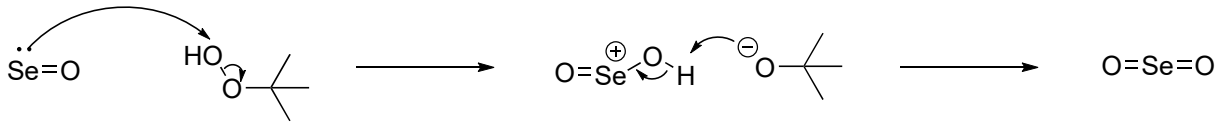
step 1-3: Oxidation with selenium dioxide



1-10 **1-11** **1-12** **1-13**

1-11' **1-12'**

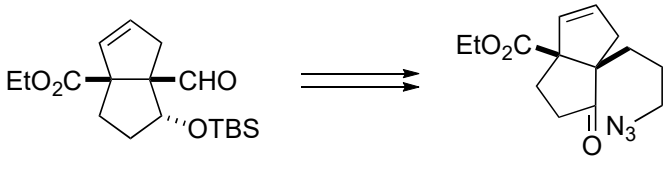
1-14 **1-15** **1-2**



(2)

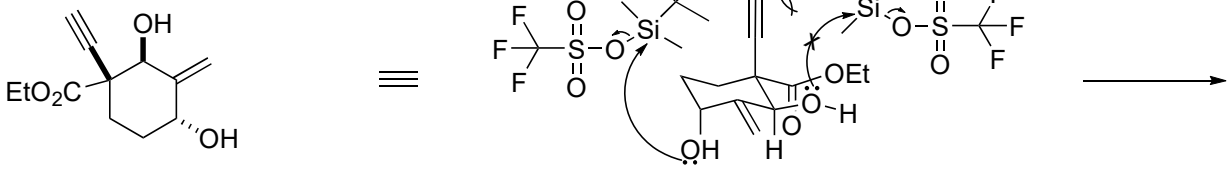
$(C_{12}H_{16}O_4)$

1. TBSOTf, Et_3N
   CH_2Cl_2, -78 °C, 89%
2. $[RhCl(CO)_2]_2$, $ClCH_2CH_2Cl$
   CO, 85 °C, 88%

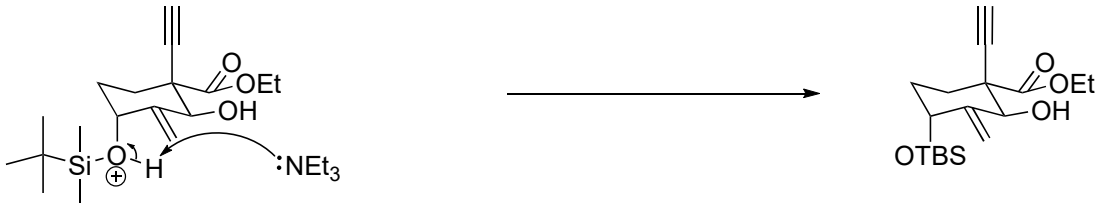


1-2 **2-1** **2-2**

step 2-1: Selective protection with TBSCl

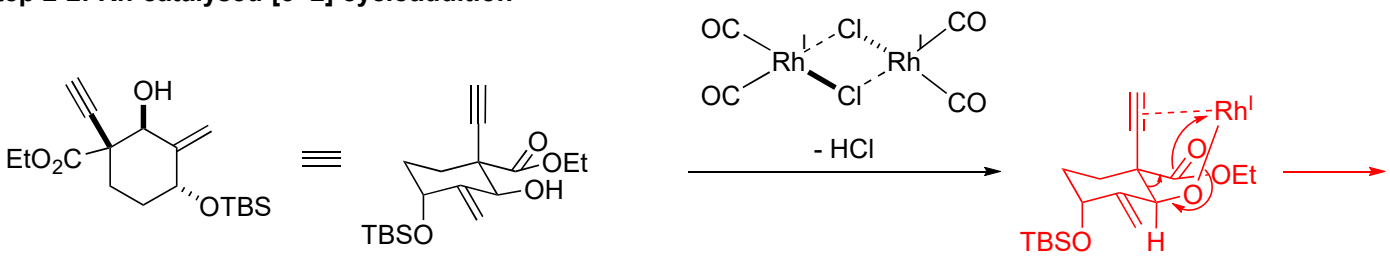


1-2 **2-3**

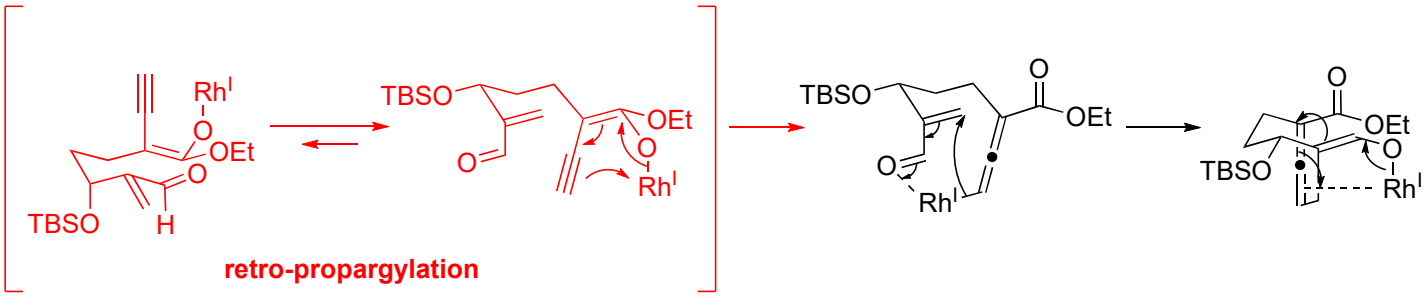


2-4 **2-5**

step 2-2: Rh-catalysed [3+2] cycloaddition

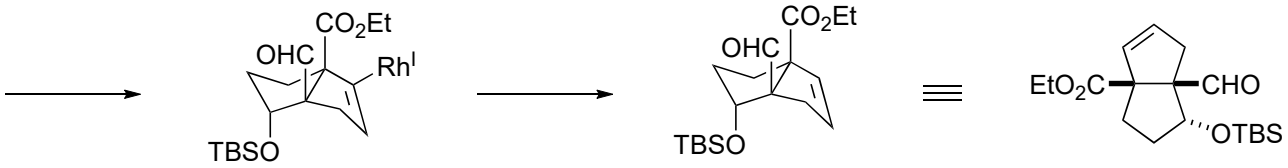


2-5 **2-6** **2-7**



2-8 **2-9** **2-10** **2-11**

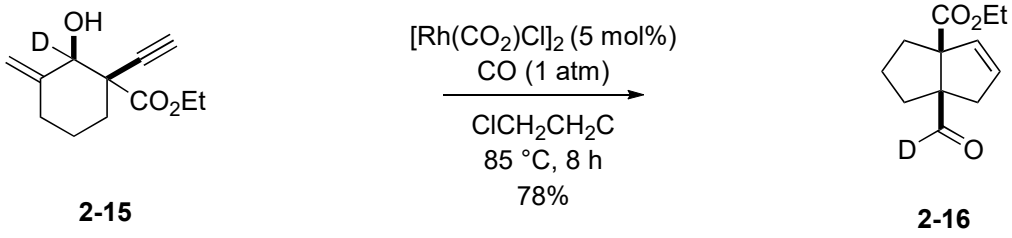
retro-propargylation should occur via rhodate (2-8) to give a reasonable stereochemical structure of Rh in 2-9



2-12 **2-13** **2-14**

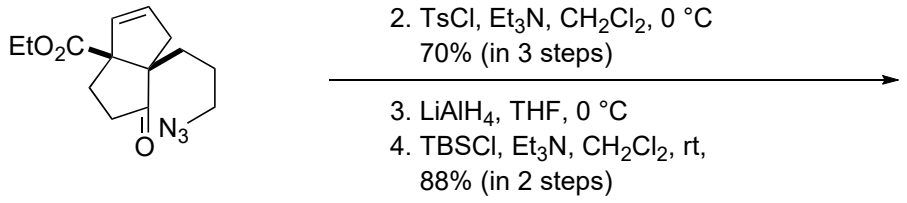
Evidence for retro-propargylation

Deuterium-labeling experiment (*Nat. Commun.* **2014**, *5*, 5707.)

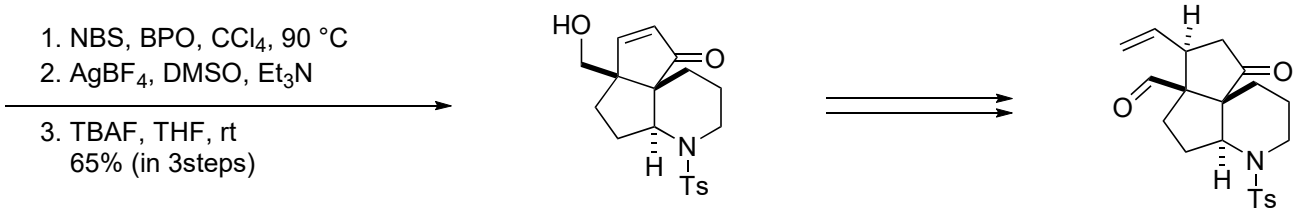


2-15 **2-16**

(3)

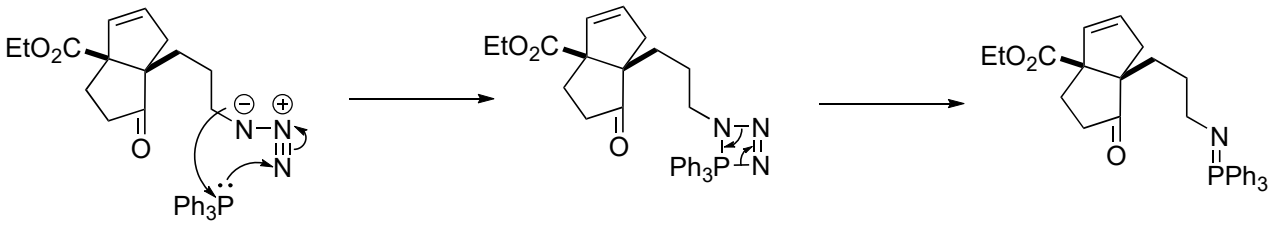


2-2 **3-1**

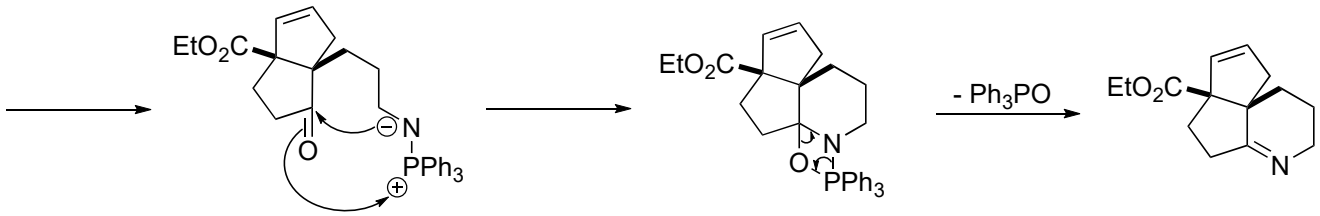


3-2 **3-3**

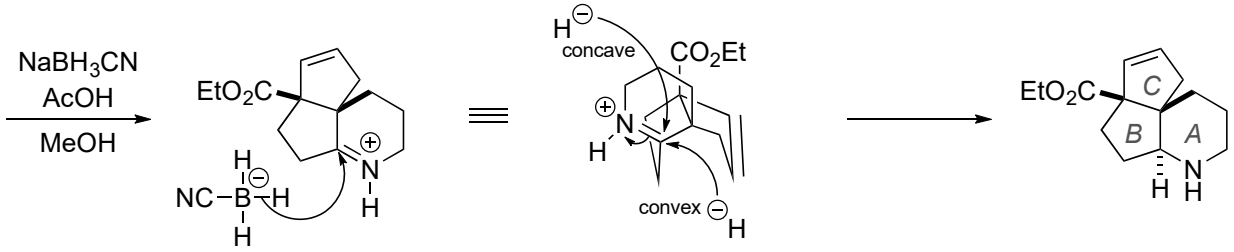
step 3-1-1: Aza-wittig Reaction



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

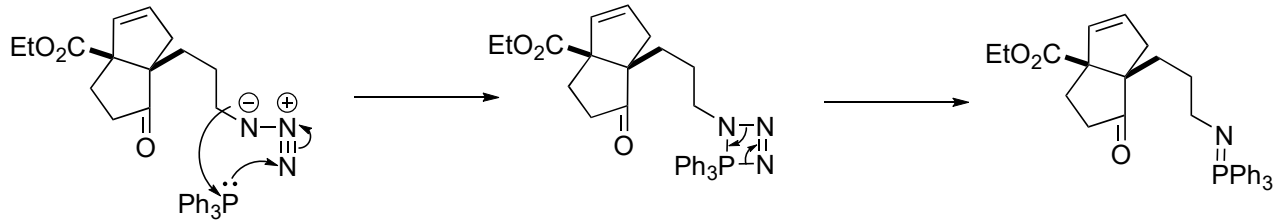


3-7 **3-8** **3-9**

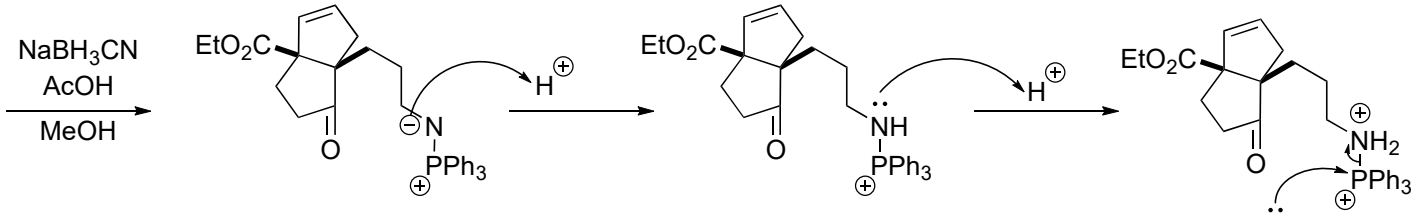


3-10 **3-11** **3-12**

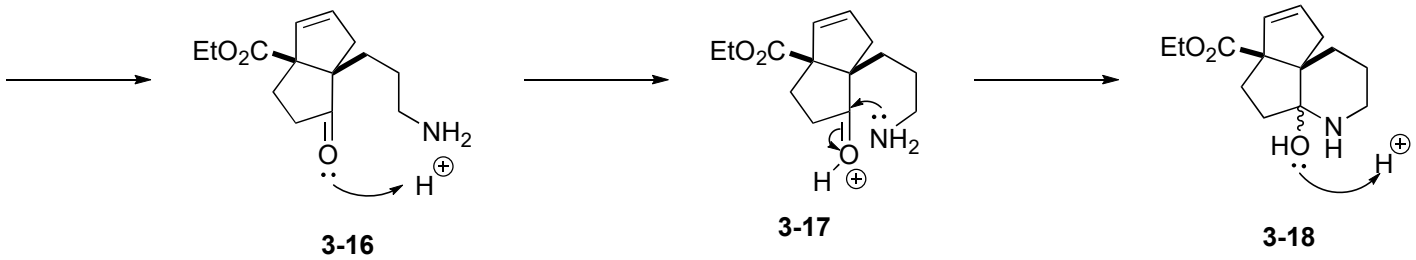
step 3-1-1': Staudinger Reaction and imine formation (from 3-4 to 3-9)



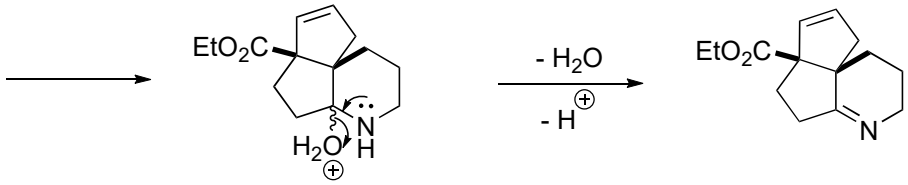
3-4 **3-5** **3-6**



3-13 **3-14** **3-15**

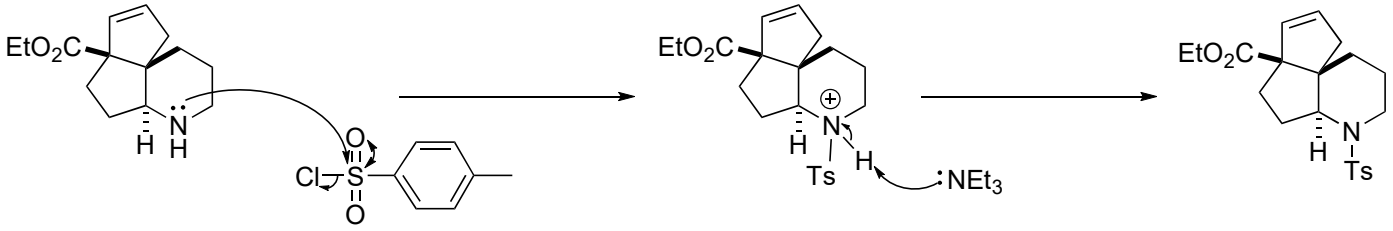


3-16 **3-17** **3-18**



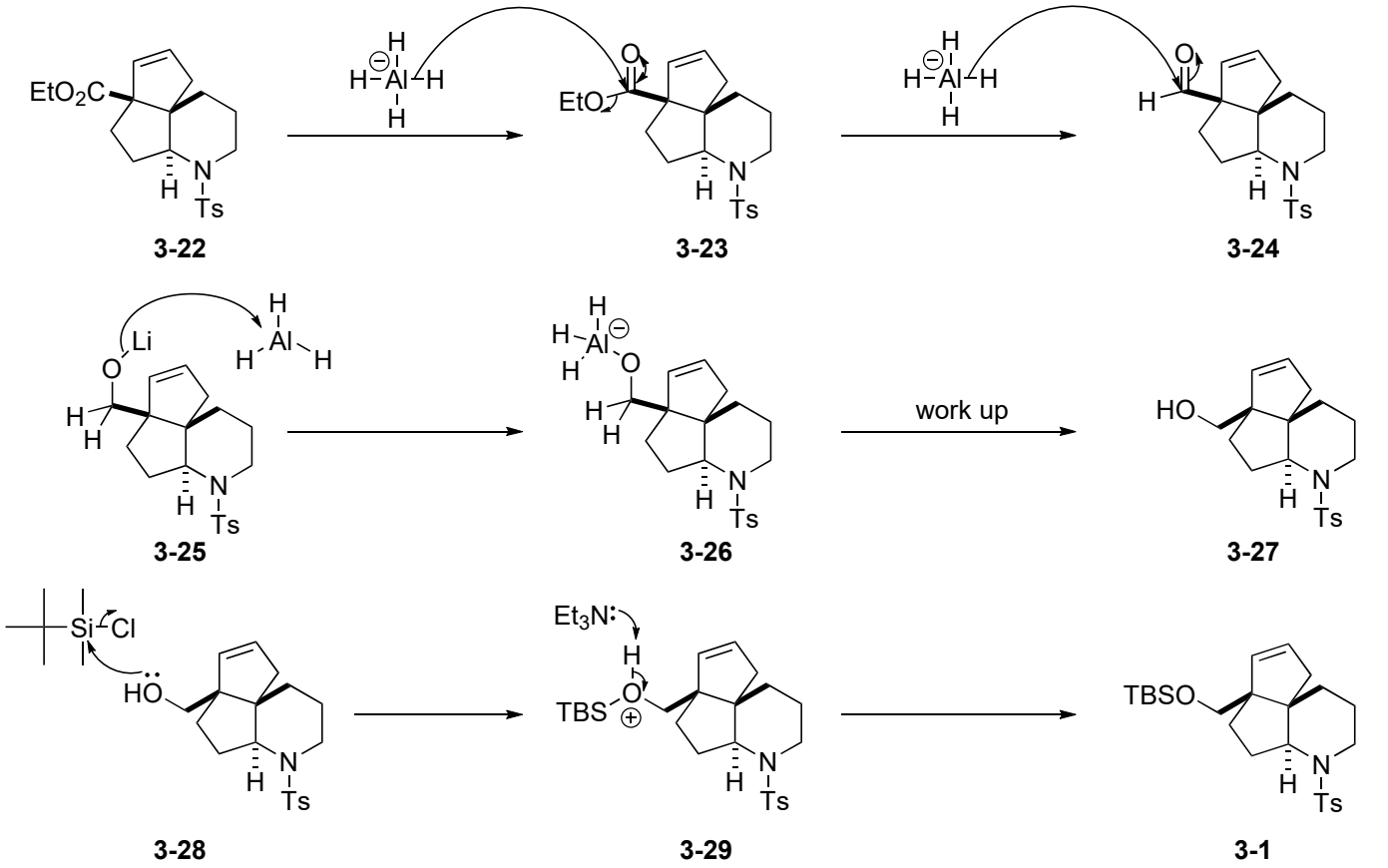
3-19 **3-9**

step 3-1-2 : Protection of amine with TsCl

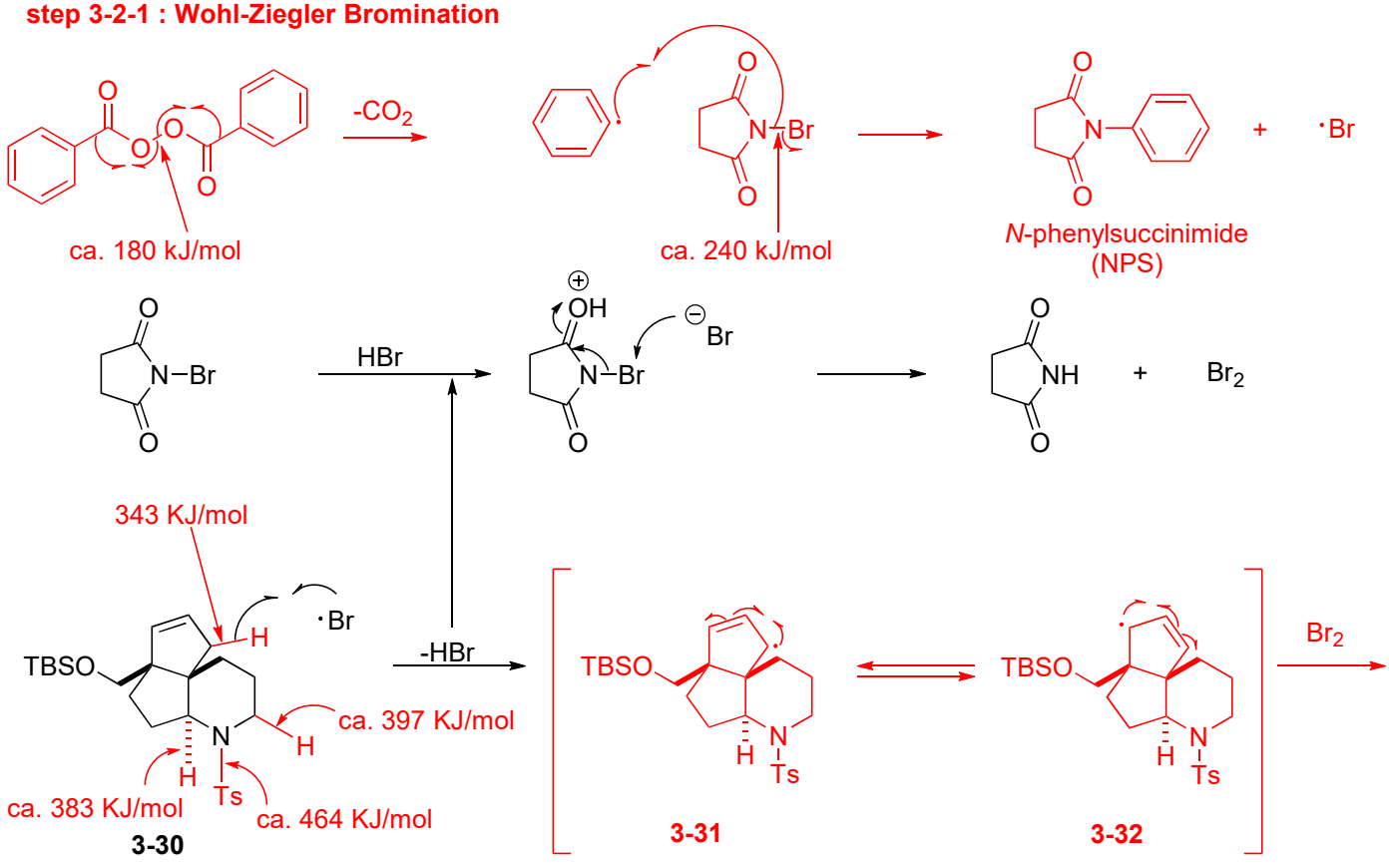


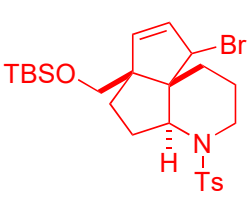
3-12 **3-20** **3-21**

step 3-1-3, 4 : Reduction of ester with $LiAlH_4$ and Protection of corresponding alcohol with TBSCl



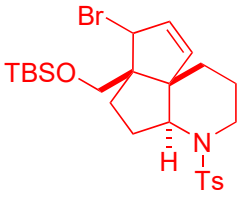
step 3-2-1 : Wohl-Ziegler Bromination





3-33

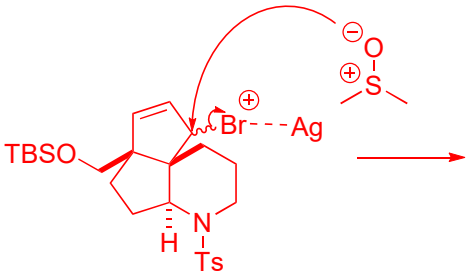
+



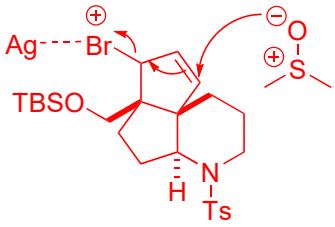
3-34

The product of Wohl-Ziegler Bromination was not been isaolated, 3-33 and 3-34 are predicting product.

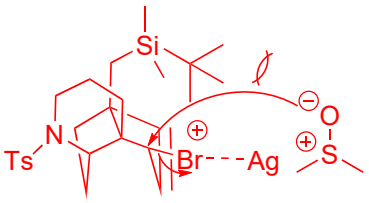
step 3-2-2 : Kornblum oxidation

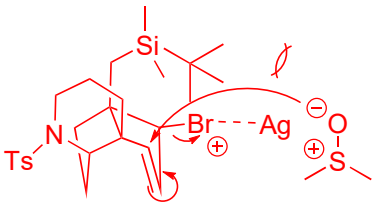


3-33

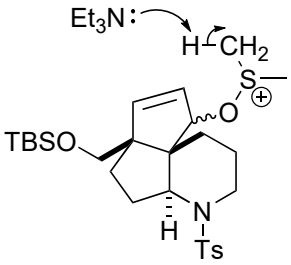


3-34

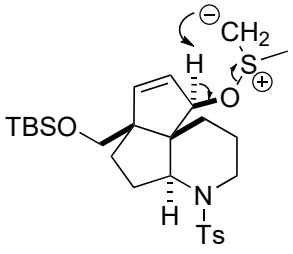




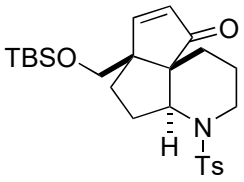
Nucleophilic attack of DMSO to compound 3-33 and 3-34 can give identical compound 3-34 because of steric hindrance.



3-34

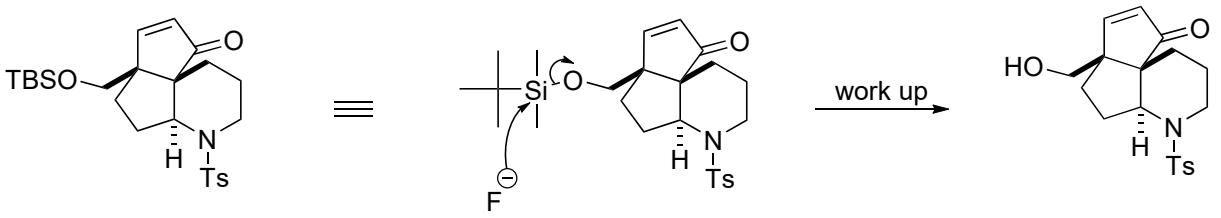


3-35



3-36

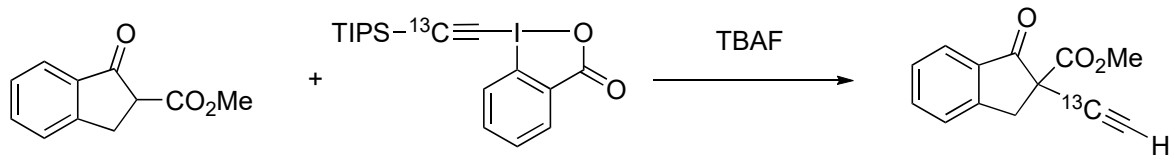
step 3-2-3 : deprotection of TBS with TBAF



3-36 **3-37** **3-2**

4. Appendix

^{13}C-labeling experiment (González, D. F.; Brand, J. P. Waser, J. *Chem. Eur. J.* **2010**, *16*, 9457.)



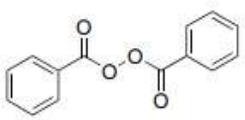
4-1 **4-2** **4-3**

Table of Bond Dissociation Energies

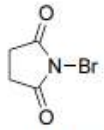
1.T. L. Cottrell, The Strengths of Chemical Bonds, 2d ed., Butterworth, London, **1958**.
2.B. deB. Darwent, National Standard Reference Data Series, NationalBureau of Standards, no. 31, Washington, **1970**.
3.S. W. Benson, J. Chem. Educ.42:502 (**1965**).
4.J. A. Kerr, Chem. Rev. 66:465 (**1966**).

The mechanism of Wohl-Ziegler Bromination (160514_PS_Komei_Sakata_Ans_lingzhiol)

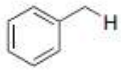
Bond dissociation energy



~180 kJ/mol



~240 kJ/mol



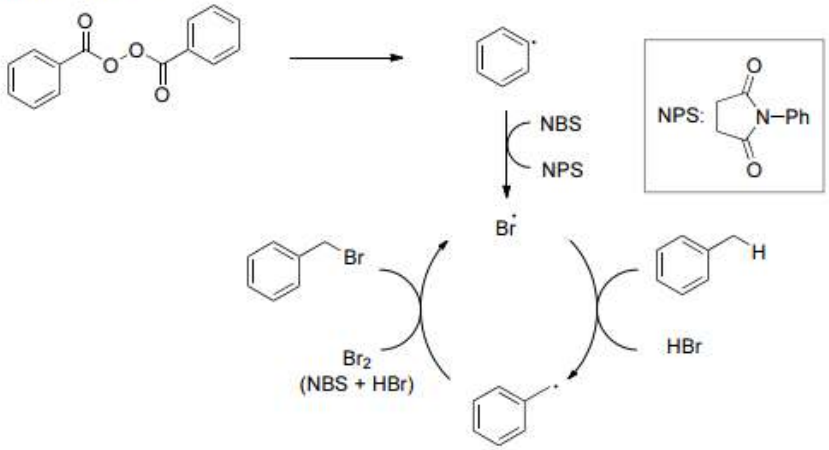
377 kJ/mol

Br—Br

192 kJ/mol

Reaction mechanisms

1.



2.