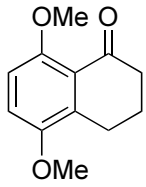
Problem Session (6)

16.05.14 Komei Sakata

Total sythesis of (-)-lingzhiol by Prof. Yang (*Nat. Commun.* **2014**, *5*, 5707.) is shown below.
Please answer the following questions.

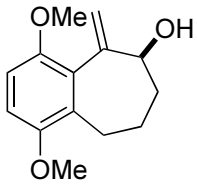
1. Please rearrange the reactions (a, b, c and d) to get **1-2** from **1-1**.



1-1

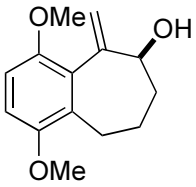
4 steps

a. $PhI(OAc)_2$, *p*-$TsOH{\cdot}H_2O$, MeCN/MeOH, 95%
b. (*R*)-CBS, BH_3, THF, 91%, 92%ee
c. PPh_3CH_3Br, $KN(TMS)_2$, THF, 98%
d. $Et_3N{\cdot}HCl$, Et_2NH, $(CH_2O)_n$, dioxane, 98%



1-2

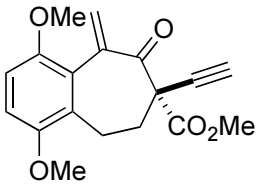
2. Please rearrange the reactions (e, f, g, h and i) to get **2-2** from **2-1**.



2-1

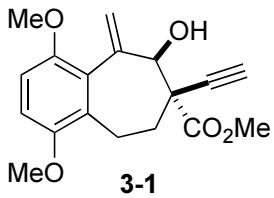
5 steps

e. Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2
f. *m*-CPBA, $NaHPO_4$, benzene
g. NaI, MeCN, CF_3CO_2H
h. TBAF, **A**, THF
i. $LiN(TMS)_2$, $NCCO_2Me$, THF



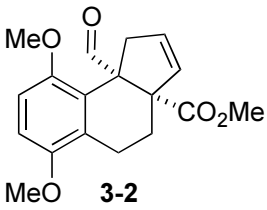
2-2

3. Please provide the reaction mechanism.



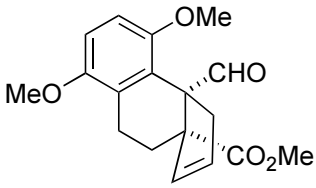
3-1

$[Rh(CO)_2Cl_2]$ (5 mol%)
CO, $(CH_2Cl)_2$

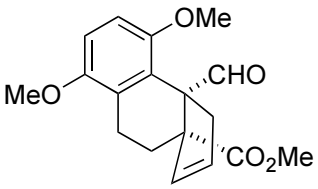


3-2

≡



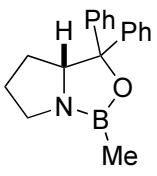
4. Please provide the structure of (-)-lingzhiol

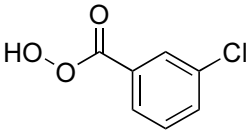


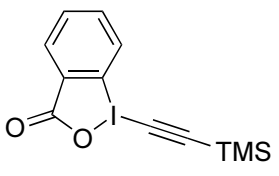
4-1

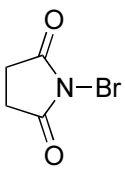
1. $NaBH_4$, MeOH, 89%
2. SeO_2, dioxane, 65%
3. H_2, Pd/C, MeOH, 95%
4. NBS, $(BzO)_2$, $NaHCO_3$
   H_2O, CCl_4; MnO_2, CH_2Cl_2
   71% (2 steps)
5. *t*-BuSH, $AlCl_3$, CH_2Cl_2, 71%

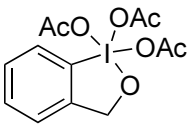
4-2: (-)-lingzhiol
(tetracyclic compound)

CBS: 

m-CPBA: 

A: 

NBS: 

Dess-Martin periodinane: 

TBAF: $(n\text{-Bu})_4NF$

Problem Session (6) -Answer-

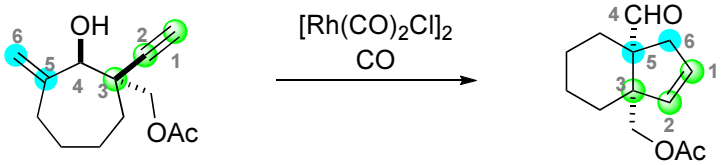
16.05.14 Komei Sakata

Topic:
Asymmetric total synthesis of (-)-lingzhiol via a Rh-catalysed [3+2] cycloaddition
(Long, R.; Huang, J.; Shao, W.; Liu, S.; Lan, Y.; Gong, J.; Yang, Z. *Nat. Commun.* **2014**, *5*, 5707.)

0. Summary of this paper

Authors developed the Rh-catalysed [3+2] cycloaddition and applied it to the total synthesis.

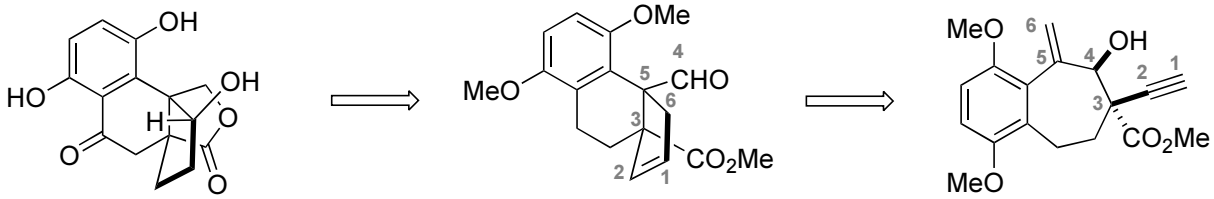
Rh-catalysed [3+2] cycloaddition



0-1 **0-2**

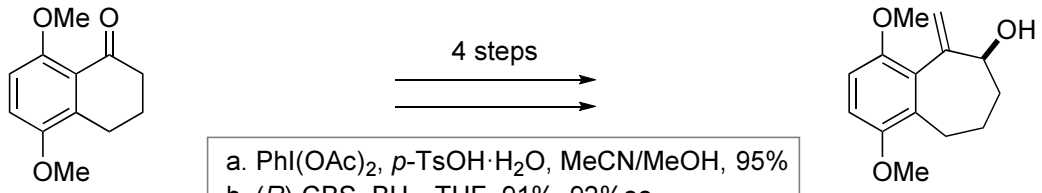
Construction of bicyclic ring system bearing two quaternary carbon centres at the ring conjunction (C3 and C5)

Application to the total synthesis



(-)-lingzhiol **0-3** **0-4**

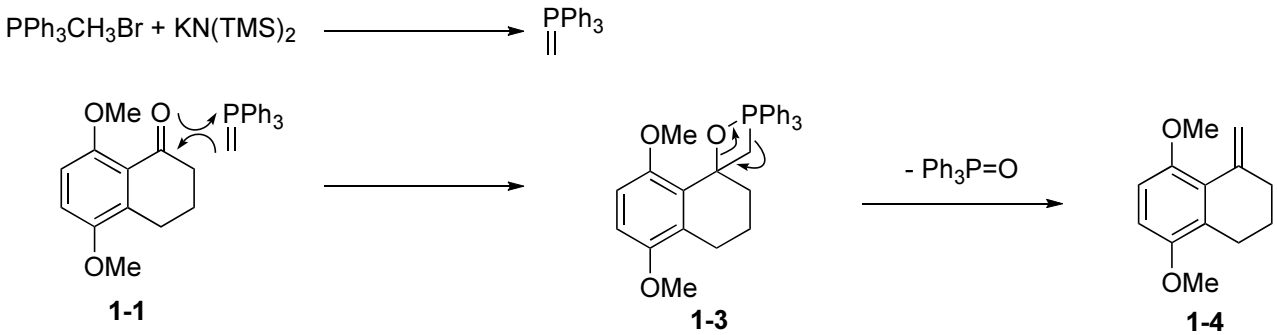
1. Please rearrange the reactions (a, b, c and d) to get **1-2** from **1-1**.



1-1 **1-2**

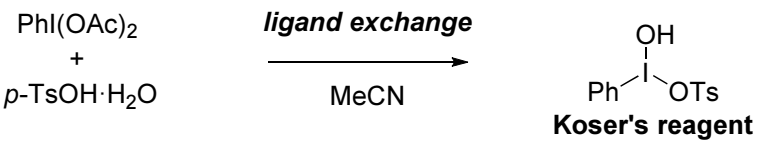
a. $PhI(OAc)_2$, *p*-$TsOH{\cdot}H_2O$, MeCN/MeOH, 95%
b. (*R*)-CBS, BH_3, THF, 91%, 92%ee
c. PPh_3CH_3Br, $KN(TMS)_2$, THF, 98%
d. $Et_3N{\cdot}HCl$, Et_2NH, $(CH_2O)_n$, dioxane, 98%

1st reaction: **reaction c (*Wittig reaction*)**

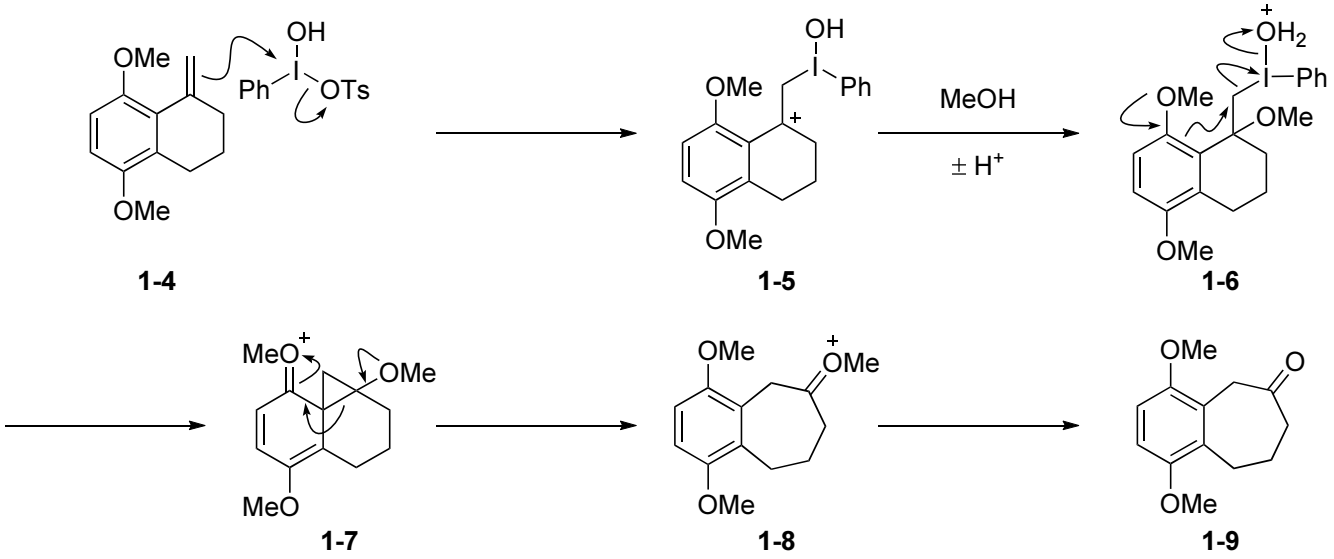


1-1 **1-3** **1-4**

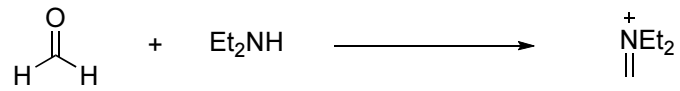
2nd reaction: **reaction a**

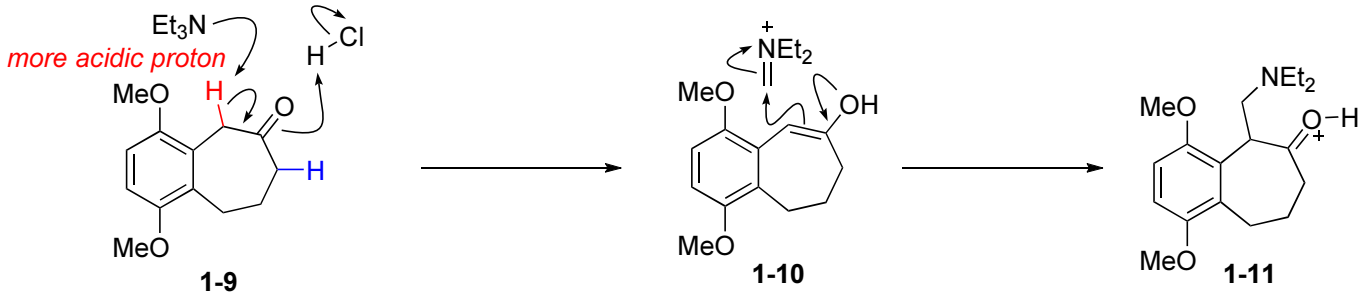


Koser's reagent

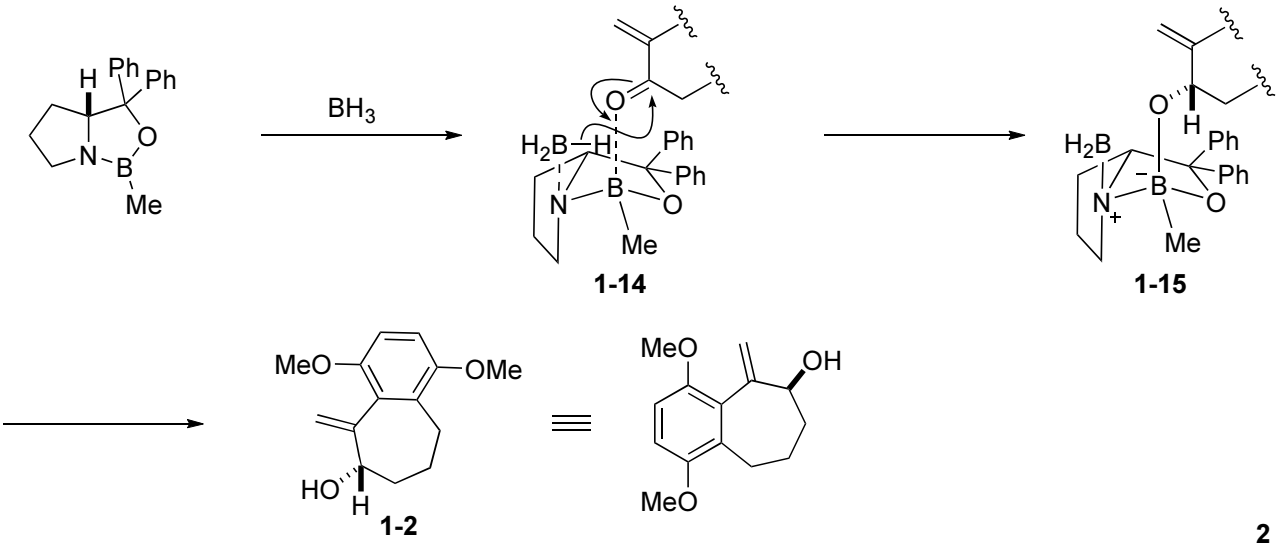


3rd reaction: **reaction d**



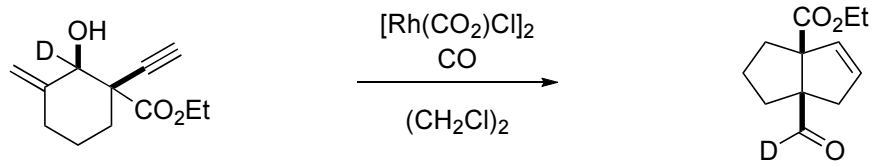


4th reaction: **reaction b (CBS reduction)**



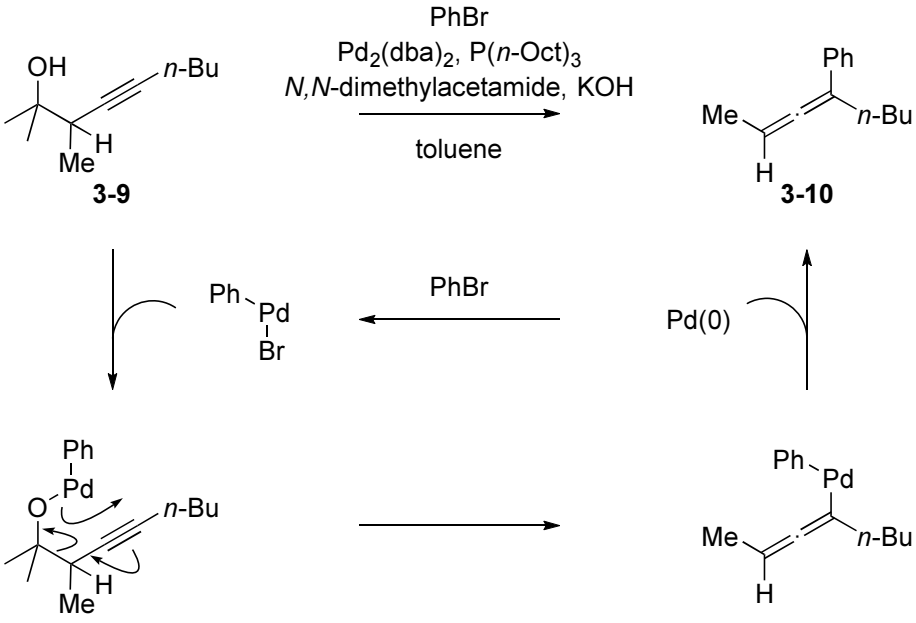
Evidence for retro-propargylation

* Deuterium-labeling experiment



3-7 **3-8**

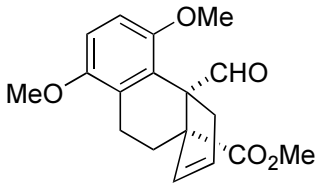
* Another example of retro-propargylation
(Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2008**, *130*, 5048.)



3-9 **3-10**

3-11 **3-12**

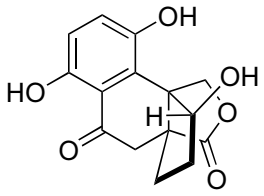
4. Please provide the structure of (-)-lingzhiol



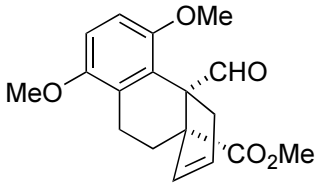
4-1

1. $NaBH_4$, MeOH, 89%
2. SeO_2, dioxane, 65%
3. H_2, Pd/C, MeOH, 95%

4. NBS, $(BzO)_2$, $NaHCO_3$
   H_2O, CCl_4; MnO_2, CH_2Cl_2
   71% (2 steps)
5. *t*-BuSH, $AlCl_3$, CH_2Cl_2, 71%

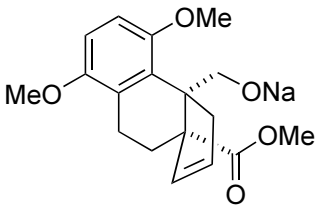


4-2: (-)-lingzhiol



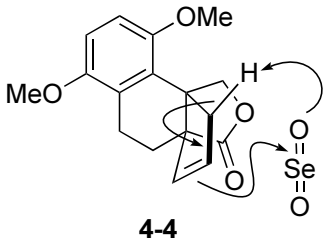
4-1

1. $NaBH_4$, MeOH



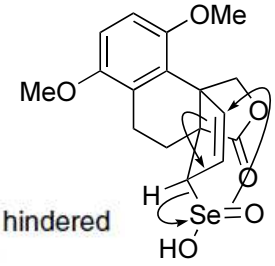
4-3

formation of lactone

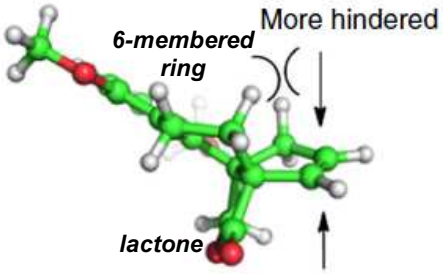


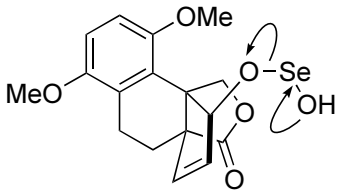
4-4

2. SeO_2, dioxane



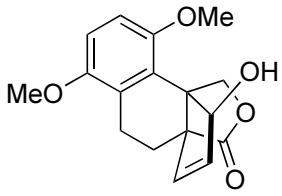
4-5





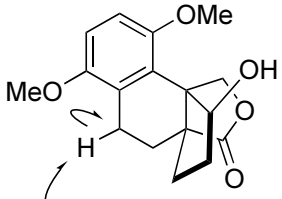
4-6

± H^+



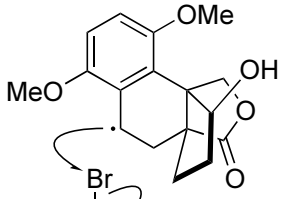
4-7

3. H_2, Pd/C, MeOH



4-7

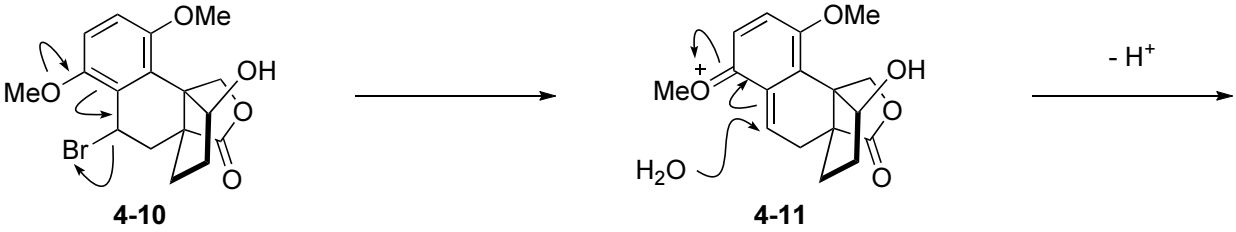
4. NBS, $(BzO)_2$, $NaHCO_3$
   H_2O, CCl_4

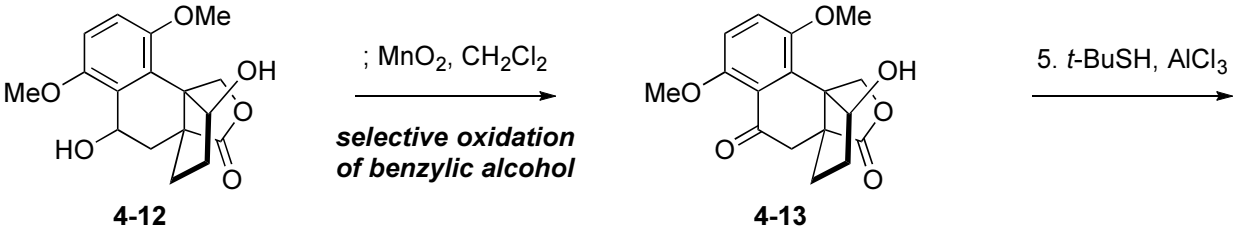


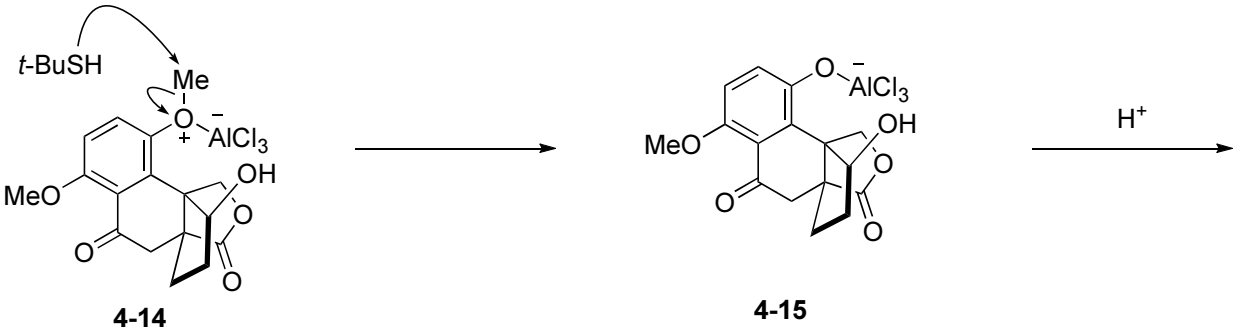
4-9

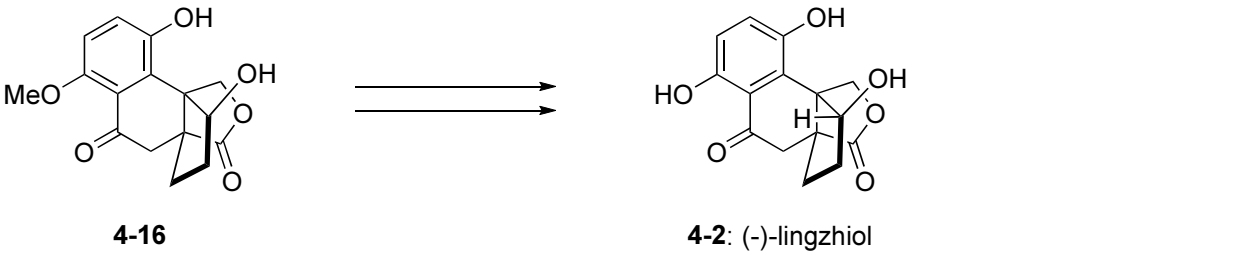
Br ← NBS + $(BzO)_2$

* NBS + HBr → Br_2


OMe
MeO
OH
Br
O
O
4-10
OMe
MeO
OH
H2O
O
O
4-11
- H+


OMe
MeO
OH
HO
O
O
4-12
; MnO2, CH2Cl2
selective oxidation
of benzylic alcohol
OMe
MeO
OH
O
O
4-13
5. t-BuSH, AlCl3


t-BuSH
Me
O
AlCl3
OH
MeO
O
O
4-14
O
AlCl3
OH
MeO
O
O
4-15
H+


OH
MeO
OH
O
O
4-16
OH
HO
OH
H
O
O
4-2: (-)-lingzhiol