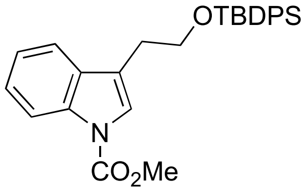
Problem Session (4)

20190727 Shimizu Shinsuke

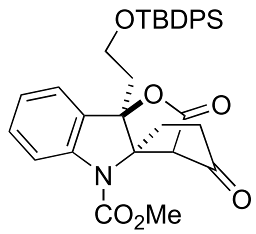
Please provide following reaction mechanisms

Problem 1



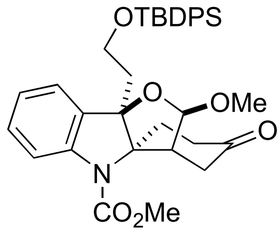
1-1

1. $Pd(OAc)_2$ (0.05 eq), *t*-BuOOBz (1.5 eq)
   1-2 (4 eq), 1,4-dioxane/AcOH (3/1), 70 °C, 75%
2. 10% Pd/C (10 wt%), H_2 (1 atm), THF/MeOH (3/1), rt
3. CDI (1.1 eq), THF, rt; **1-3** (1.5 eq), rt, 78% (2 steps)
4. $Mn(OAc)_3 \cdot H_2O$ (3 eq), AcOH/TFA (10/1), rt, 75%



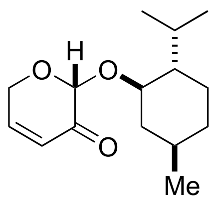
1-4

5. $NaBH_4$ (2 eq), EtOH, 0 °C; $NaBH_4$ (2 eq), rt
6. TsOH (0.2 eq), MeOH, rt, 48% (2 steps)
7. PCC (3 eq), CH_2Cl_2, rt, 96%
8. $TMSCHN_2$ (1.3 eq), $BF_3 \cdot OEt_2$ (1.1 eq), CH_2Cl_2, -78 °C
   ; PPTS (1.5 eq), MeOH, rt, 68%



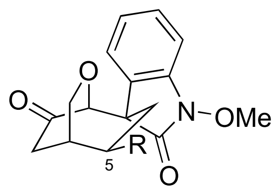
1-5

Problem 2

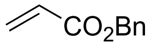


2-1

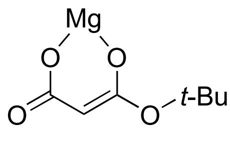
1. **2-2** (1.05 eq), Cs_2CO_3 (0.2 eq)
   Et_2O, rt, 95% (dr = 1:1 at C5)
2. NCS (1.1 eq), H_2O (1.5 eq), THF, -18 to 0 °C
   ; silica gel (~1000 wt%), 0 °C; Et_3N, rt, 90%
3. $AlCl_3$ (2 eq), toluene/Et_2O (10/1), reflux, 86%



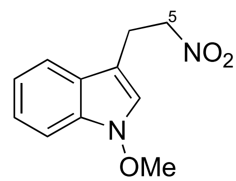
2-3 (R = NO_2)



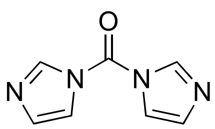
1-2



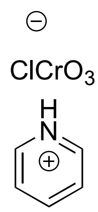
1-3



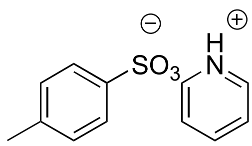
2-2



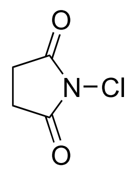
CDI



PCC



PPTS



NCS

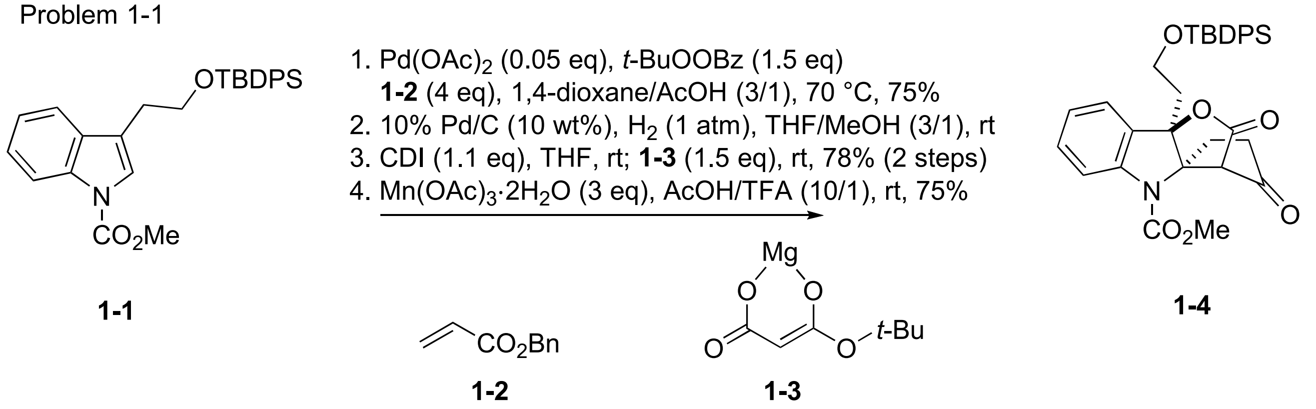
Problem Session (4) Answer

20190727 Shimizu Shinsuke

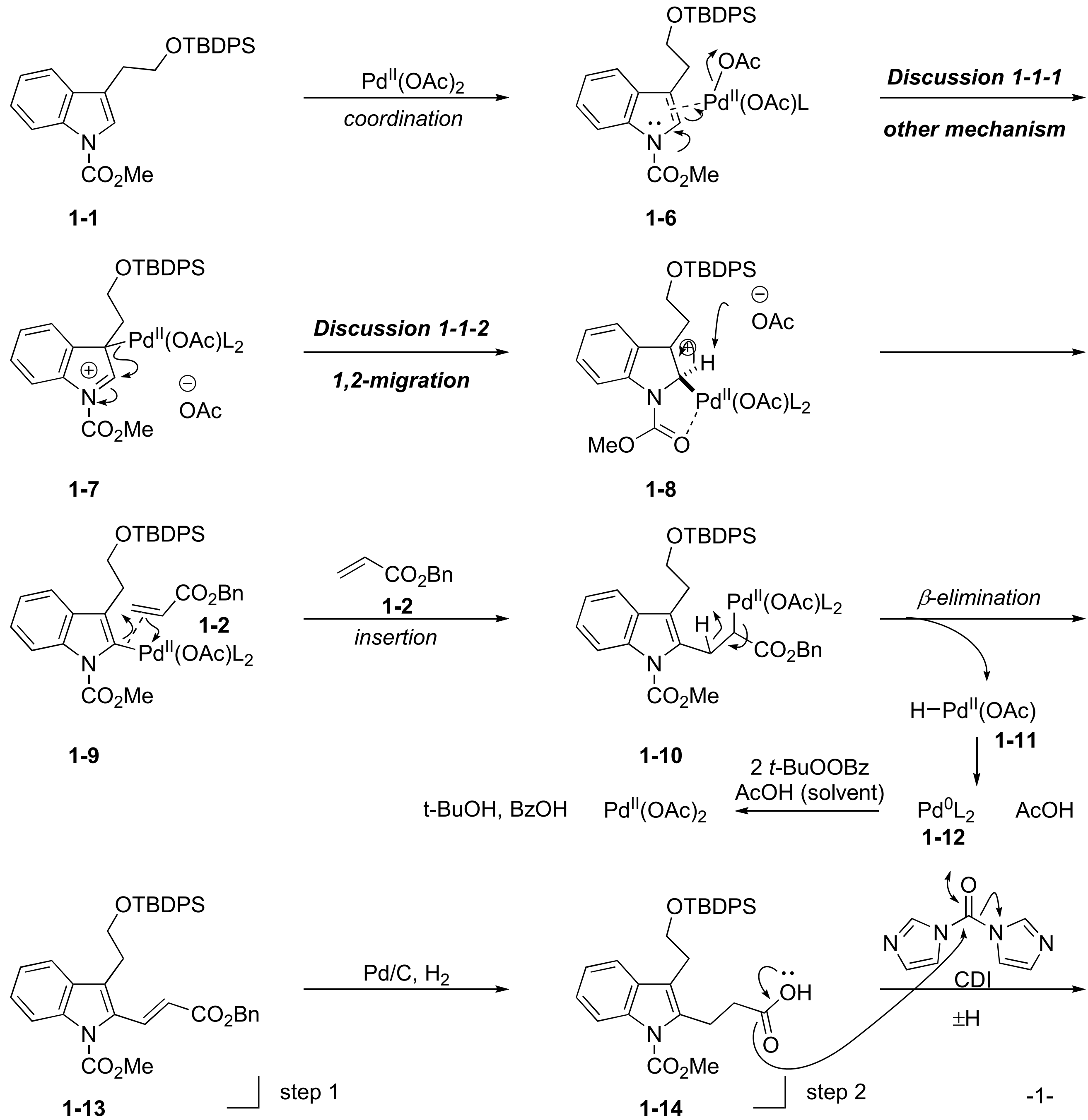
topic: Total synthesis of indole alkaloids by Dawei Ma's group

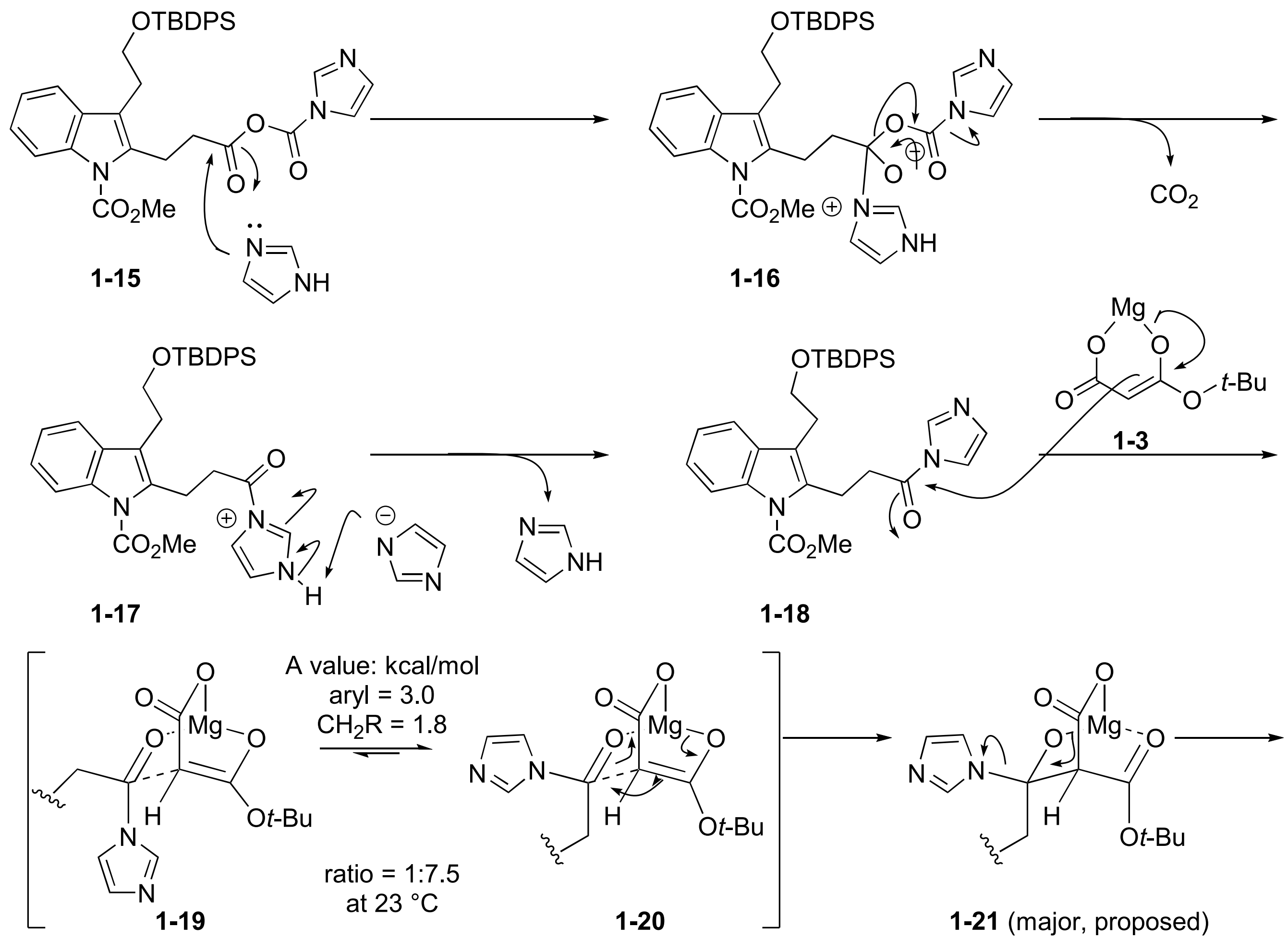
Answer 1-1

Problem 1-1

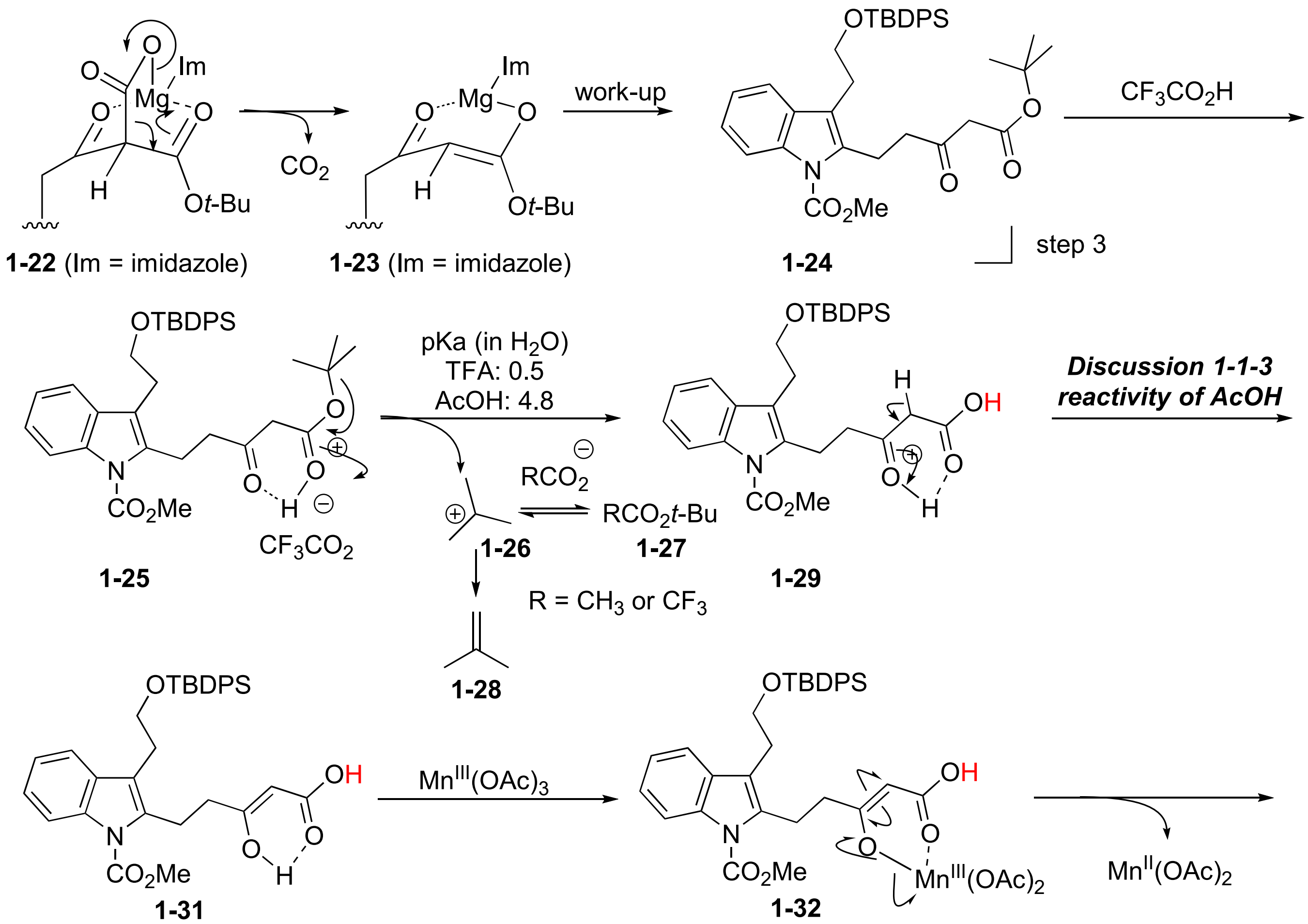


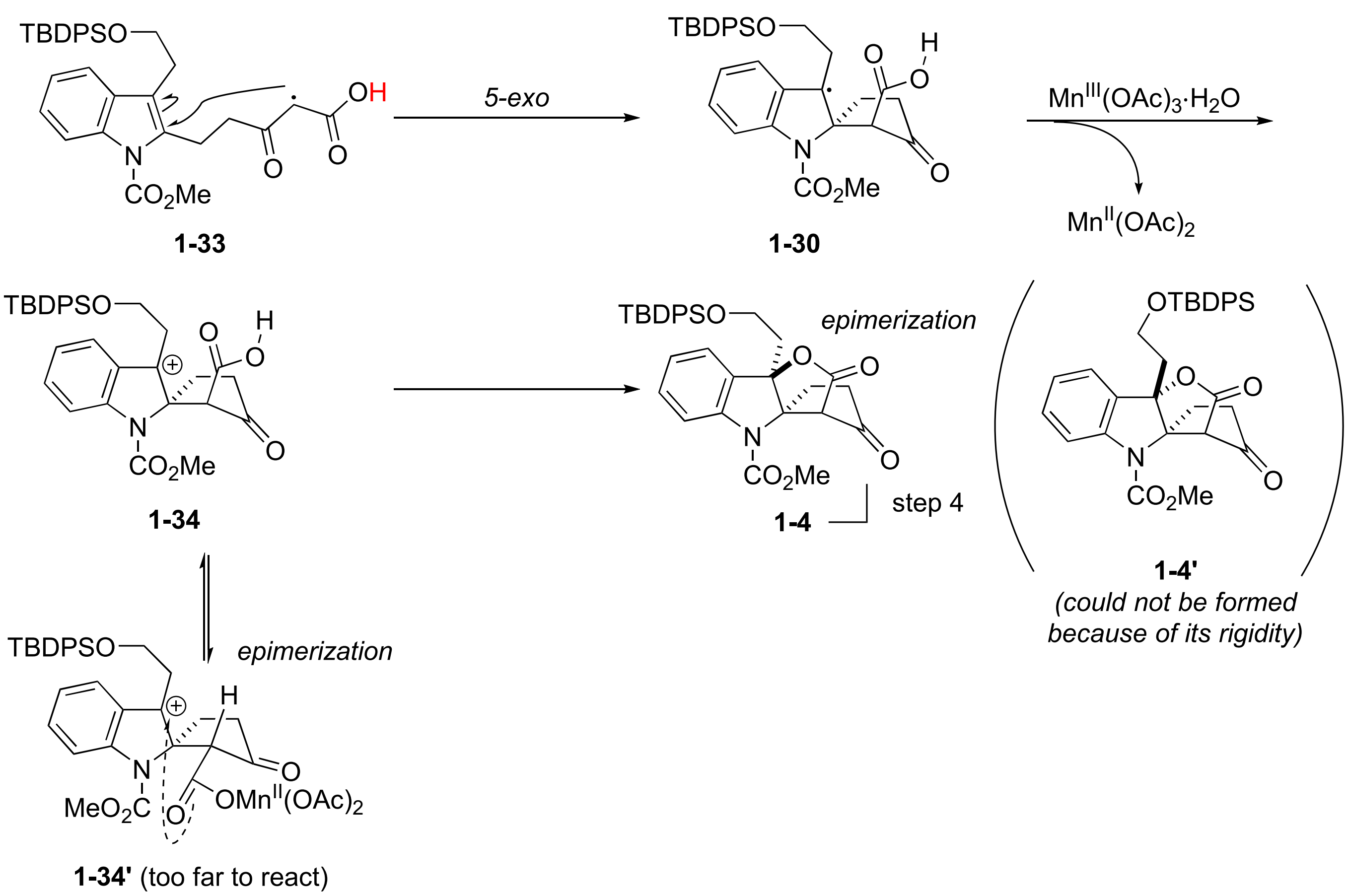
Gao, Y.; Fan, M.; Geng, Q.; Ma, D. *Chem. Eur. J.* **2018**, *24*, 6547.





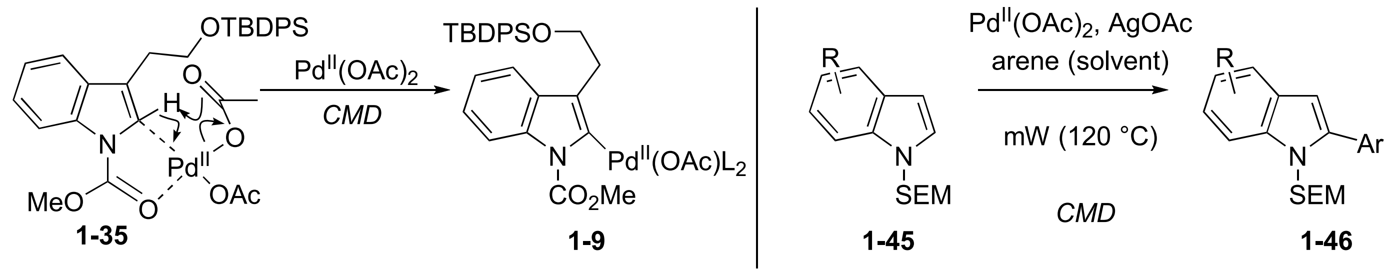
A value, ref: Corey, E. J.; Feiner, N. F. *J. Org. Chem.* **1980**, *45*, 765.



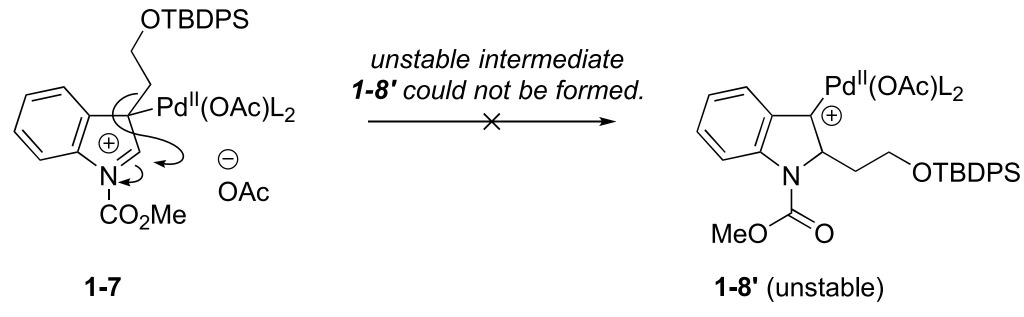


Discussion 1-1-1: other mechanism (CMD)

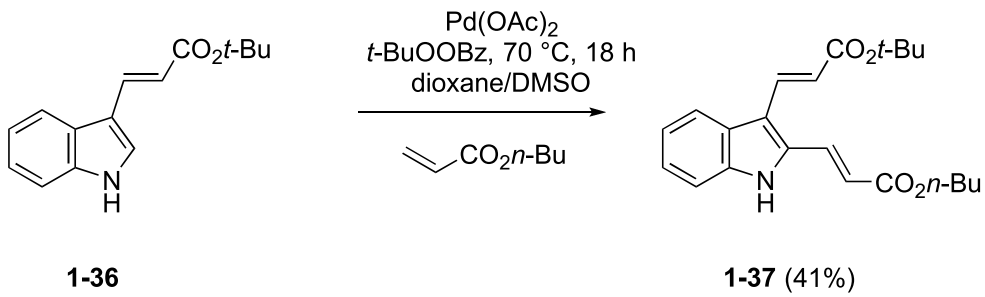
Deboef, B. et al. *JACS* **2010**, *132*, 14676.



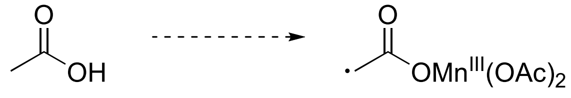
Discussion 1-1-2: 1,2-migration



Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125.

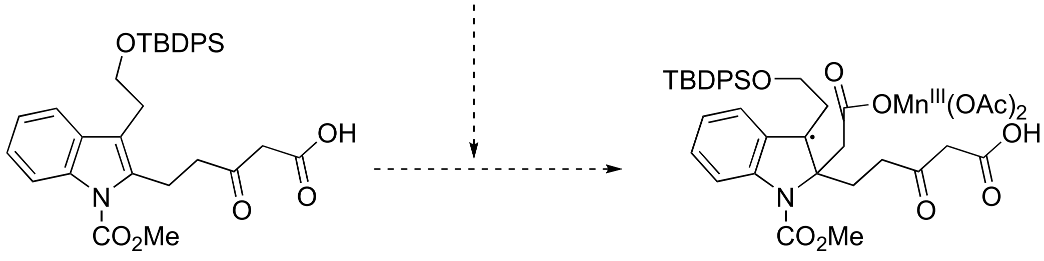


Discussion 1-1-3: reactivity of AcOH



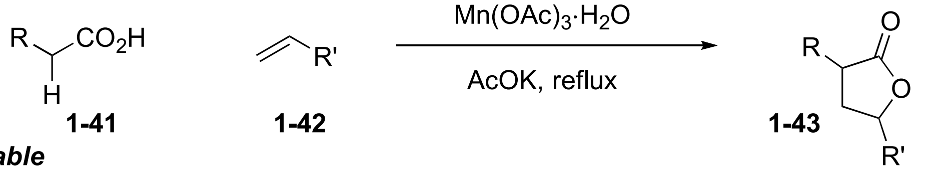
1-38 **1-39**

radical **1-39** could be formed??



1-29 **1-40**

Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10.



1-41 **1-42** **1-43**

table

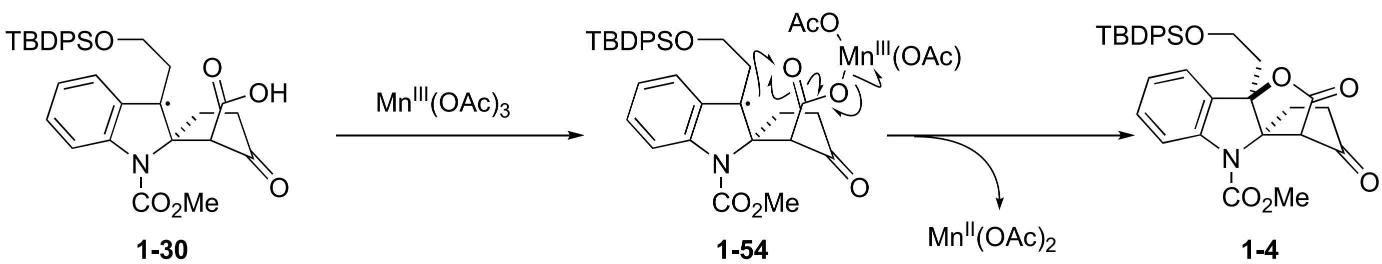
R	pKa (a-H)	relative rate
H	25	1
Cl	22	1.1×10^{1}
SO_2Ph	14	3.8×10^{3}
CO_2Me	13	1.1×10^{4}
COMe (this time)	10.7	(10^{4}~10^{5}, proposed)
CN	9	4.0×10^{5}

pKa values of the corresponding esters in H_2O.

the table indicated that the rate of oxidation reaction of acetic acid is much slower than **1-29**.
So, radical **1-39** would not be formed in this PS.

Discusstion 1-1-4: other mechanism

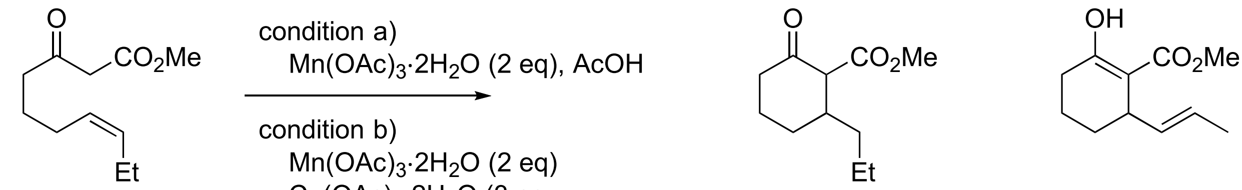
"The detailed mechanism of this oxidation is not known" Snider, B. B. *Tetrahedron* **2009**, *65*, 10738.



1-30 **1-54** **1-4**

Ketes, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem*. **1990**, *55*, 2427.

"Mn^{III} would not oxidize primary or secondary radicals".

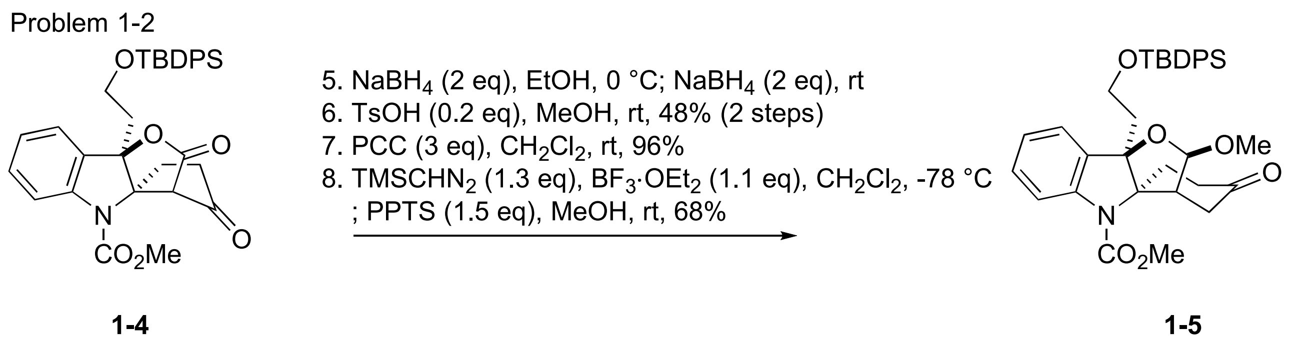


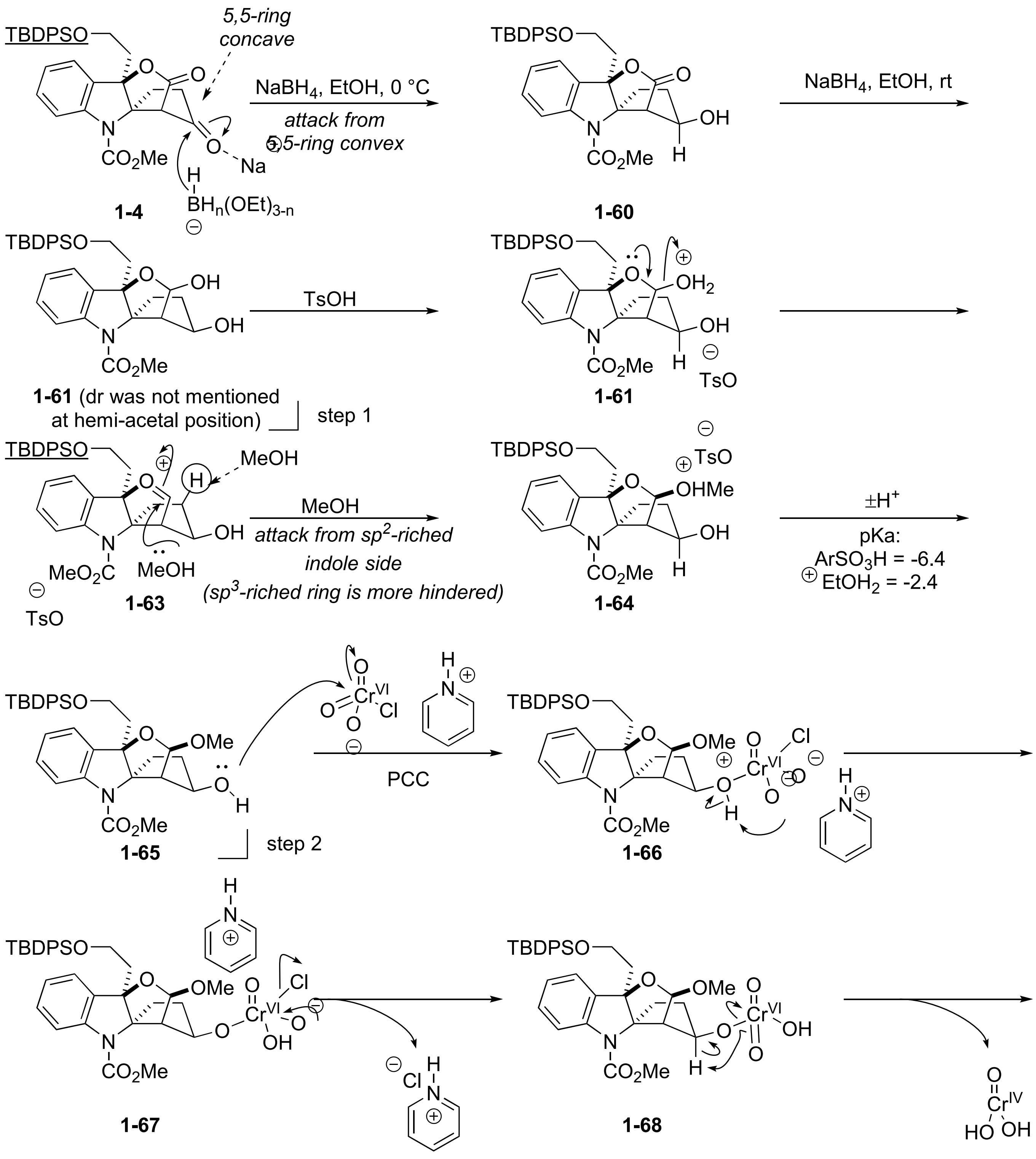
1-51 **1-52** **1-53**

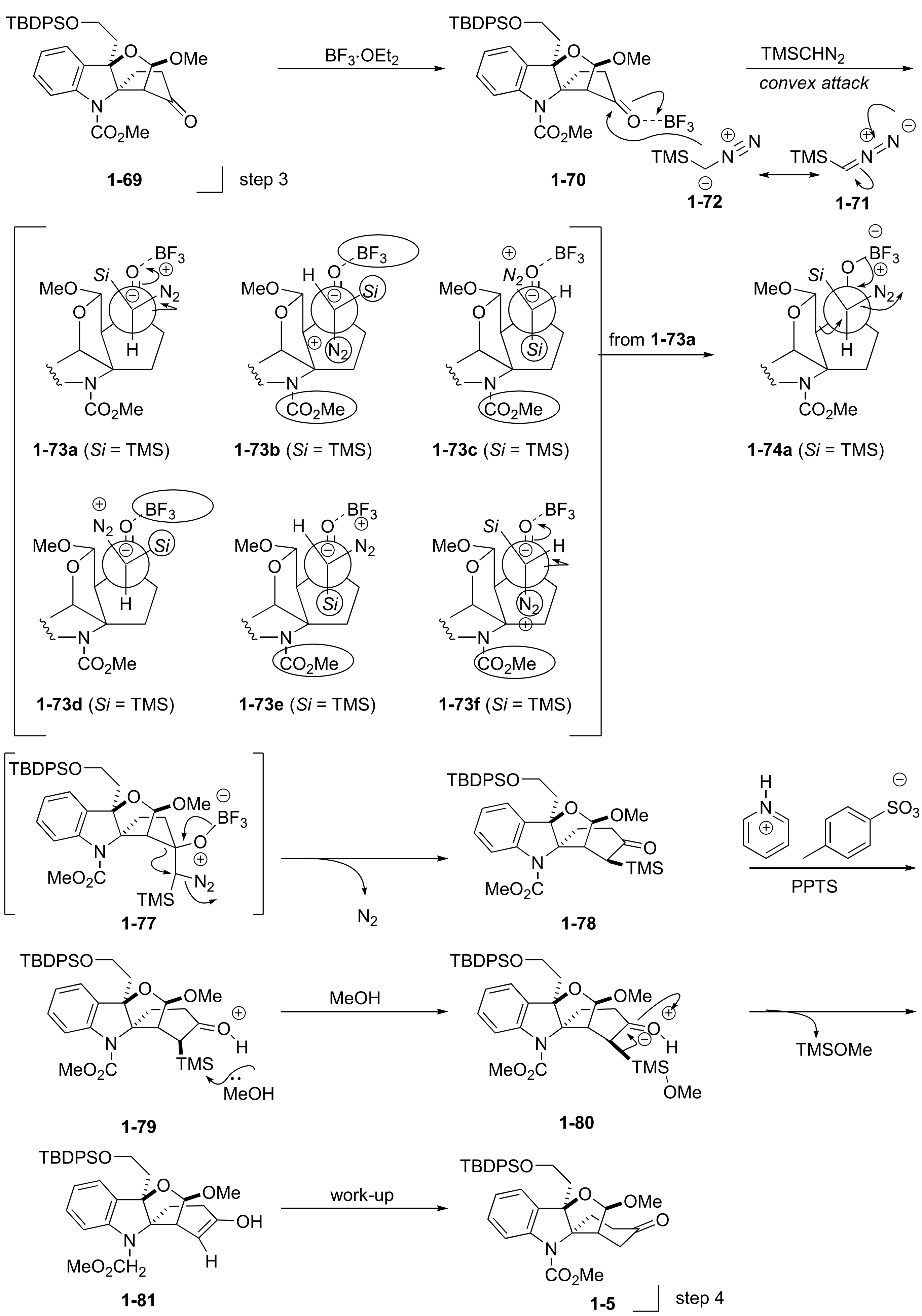
Cu^{II} would oxidize primary and secondary carbon radicals.
--> PS_2018_0602_Kotaro_Tokumoto

condition a) **1-52** and complex mixture
condition b) **1-53**: 71%

Answer 1-2


Problem 1-2
OTBDPS
N
CO2Me
1-4
5. NaBH4 (2 eq), EtOH, 0 °C; NaBH4 (2 eq), rt
6. TsOH (0.2 eq), MeOH, rt, 48% (2 steps)
7. PCC (3 eq), CH2Cl2, rt, 96%
8. TMSCHN2 (1.3 eq), BF3·OEt2 (1.1 eq), CH2Cl2, -78 °C
; PPTS (1.5 eq), MeOH, rt, 68%
OMe
1-5

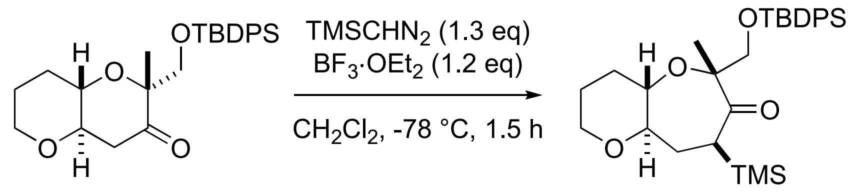

TBDPSO
5,5-ring
concave
NaBH4, EtOH, 0 °C
attack from
5,5-ring convex
Na
BHn(OEt)3-n
1-4
1-60
NaBH4, EtOH, rt
TsOH
1-61 (dr was not mentioned
at hemi-acetal position)
step 1
1-61
TsO
MeOH
MeOH
attack from sp2-riched
indole side
(sp3-riched ring is more hindered)
1-63
1-64
OHMe
±H+
pKa:
ArSO3H = -6.4
EtOH2 = -2.4
PCC
1-65
step 2
1-66
1-67
1-68



TBDPSO
OMe
CO2Me
1-69
step 3
BF3·OEt2
1-70
TMSCHN2
convex attack
TMS
1-72
1-71
from 1-73a
1-73a (Si = TMS)
1-73b (Si = TMS)
1-73c (Si = TMS)
1-74a (Si = TMS)
1-73d (Si = TMS)
1-73e (Si = TMS)
1-73f (Si = TMS)
1-77
N2
1-78
PPTS
1-79
MeOH
1-80
TMSOMe
1-81
work-up
1-5
step 4

***Discussion 1-2-1**: formation of α-silyl ketone **1-78** before addition of acid*

example of preparation of silyl ketone without acidic work-up

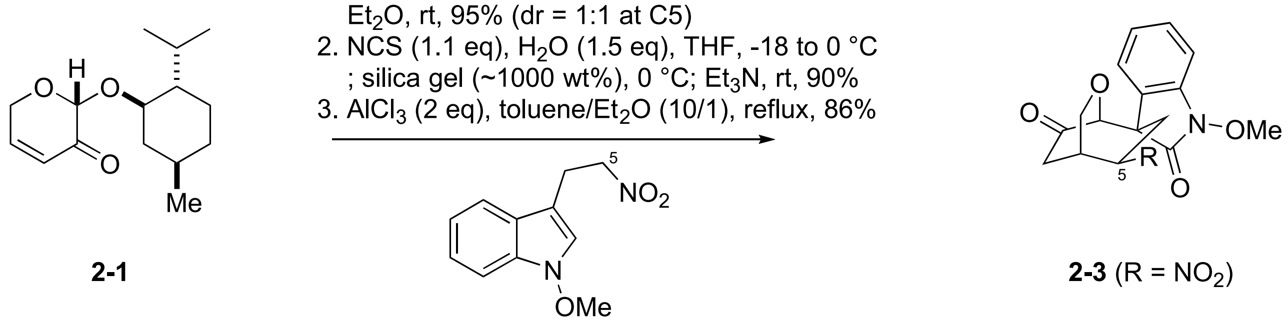


1-82 **1-83** (83%)

Sakai, T.; Ito, S.; Furuta, H.; Kawahara, Y.; Mori, Y. *Org. Lett.* **2012**, *14*, 17.

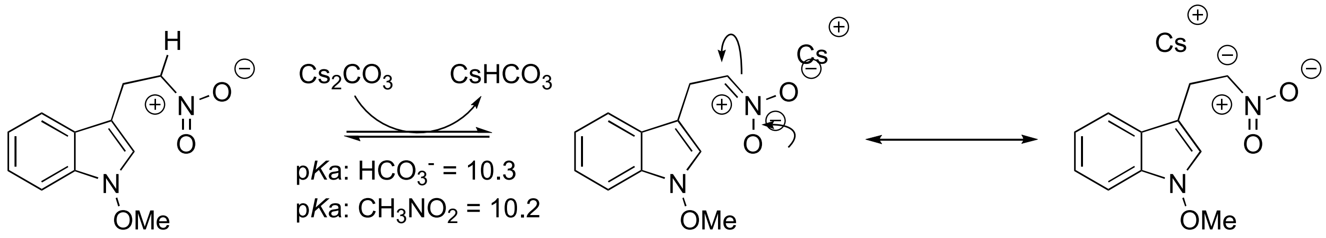
Answer 2

Problem 2

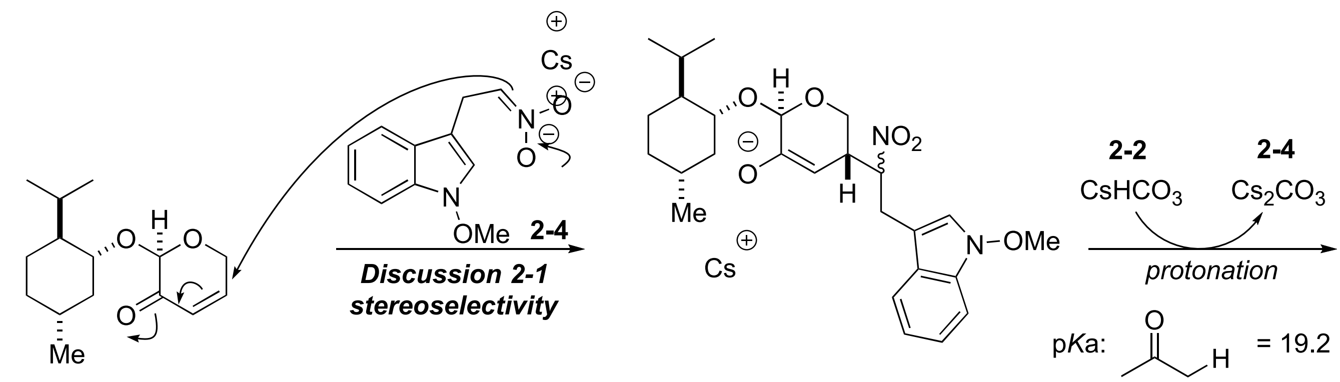


2-1 **2-2** **2-3** (R = NO$_2$)

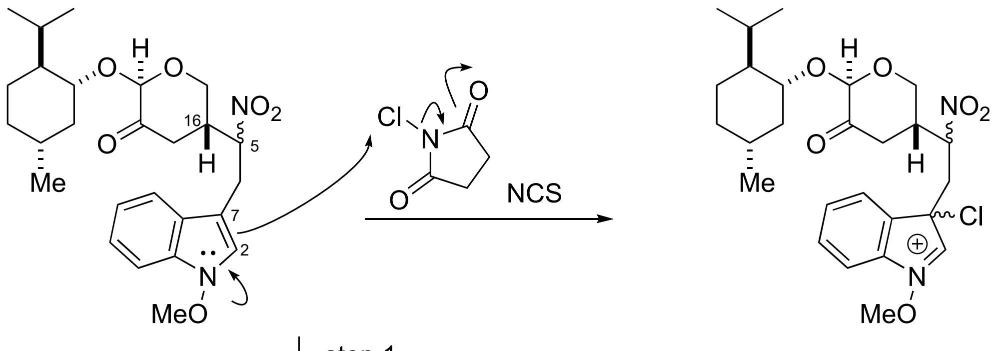
Wang, P.; Gao, Y.; Ma, D. *J. Am. Chem. Soc.* **2018**, *140*, 11608.



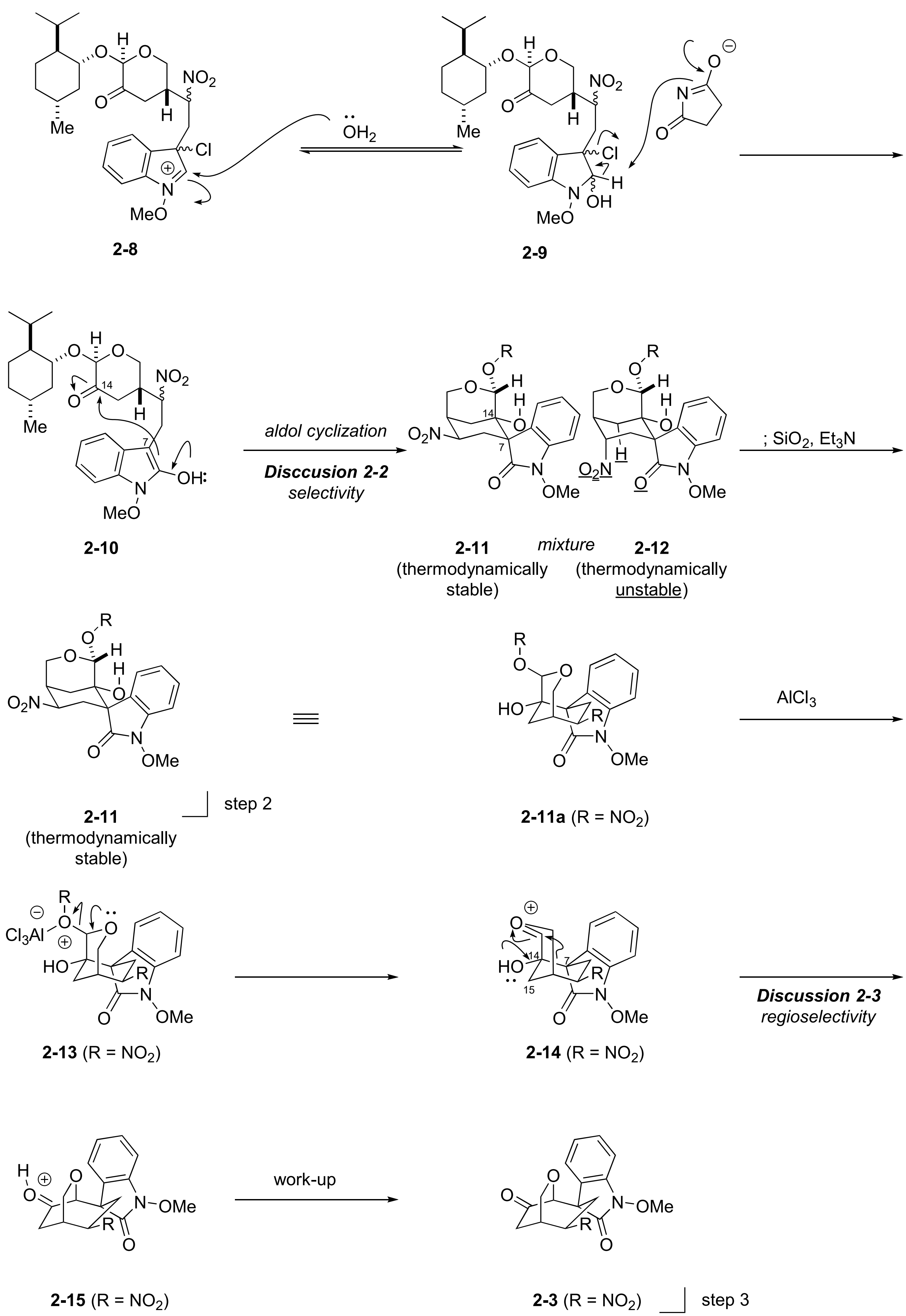
2-2 **2-4** **2-5**



2-1 **2-6**



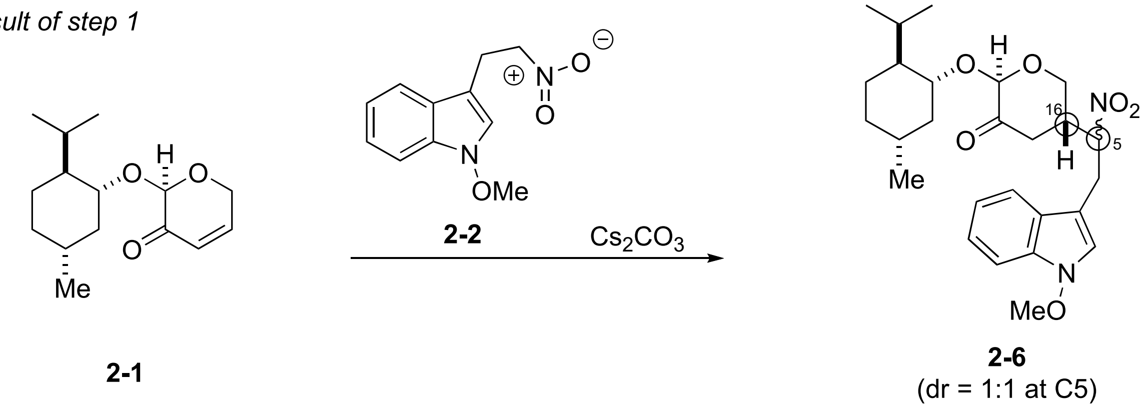
2-7 (dr = 1:1 at C5) step 1 **2-8**



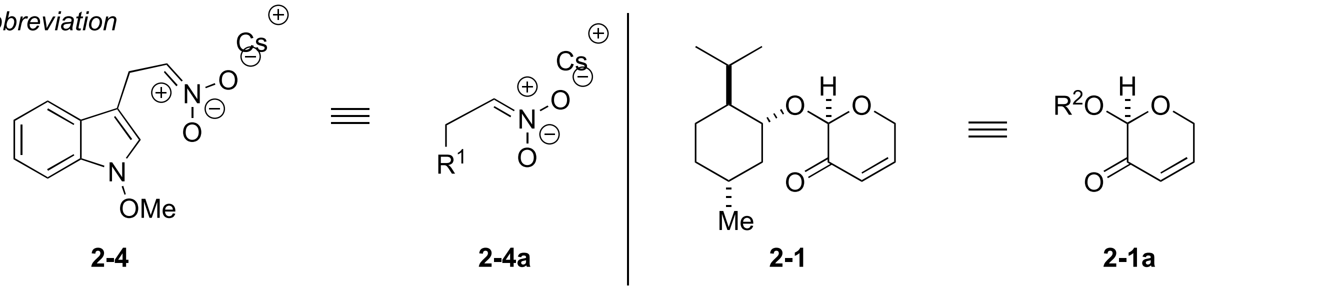
2-8
OH2
2-9
2-10
aldol cyclization
Disccusion 2-2
selectivity
2-11
mixture
2-12
(thermodynamically stable)
(thermodynamically unstable)
; SiO2, Et3N
2-11
(thermodynamically stable)
step 2
2-11a (R = NO2)
AlCl3
2-13 (R = NO2)
2-14 (R = NO2)
Discussion 2-3
regioselectivity
2-15 (R = NO2)
work-up
2-3 (R = NO2)
step 3

Discussion 2-1: *stereoselectivity of nitro Michael reaction*

the result of step 1

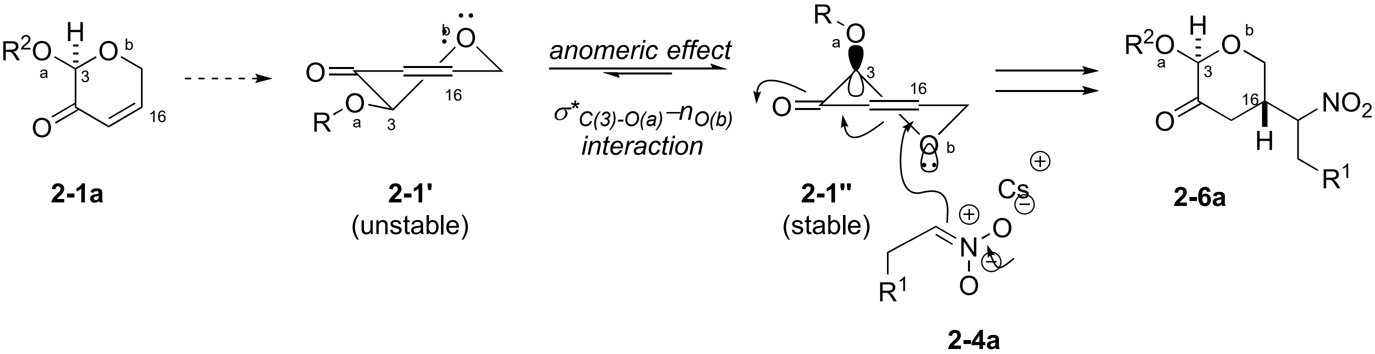


abbreviation

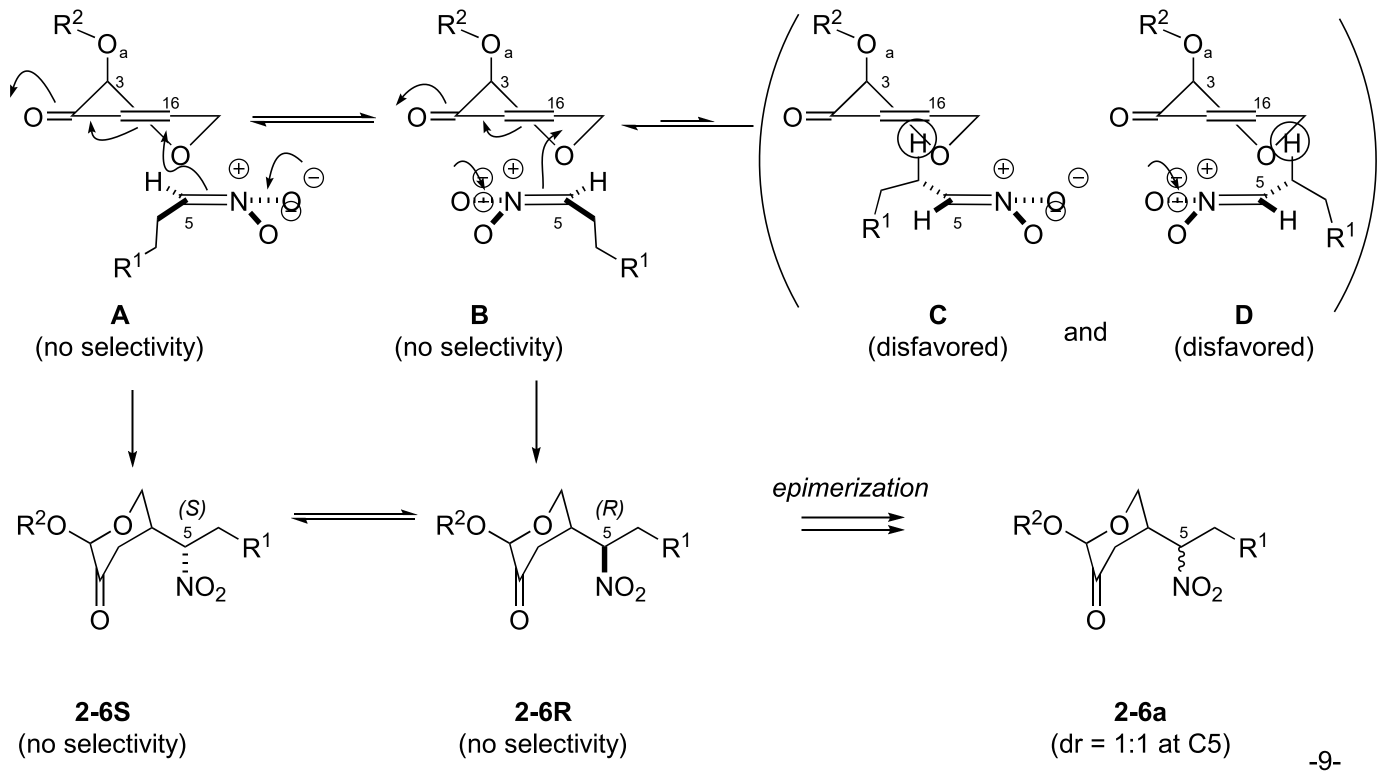


a) stereochemistry at C16

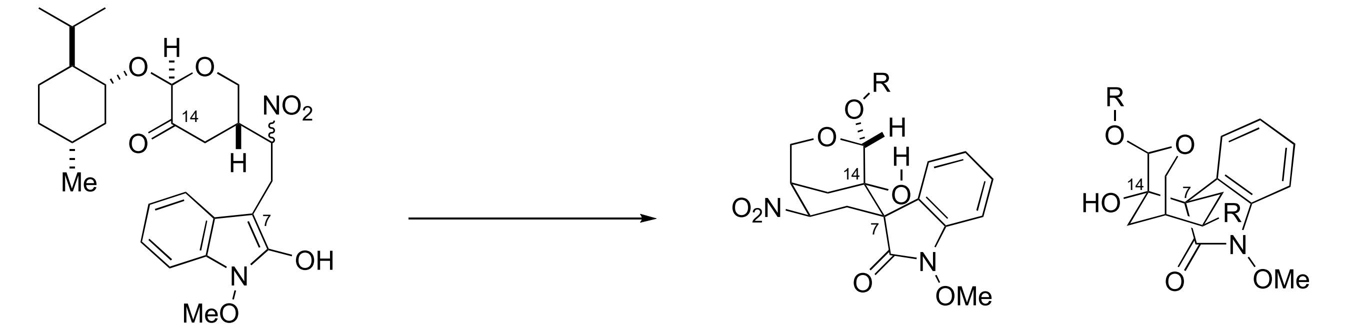
stable conformation of half chairs



b) stereochemistry at C5 (1:1 mixture)

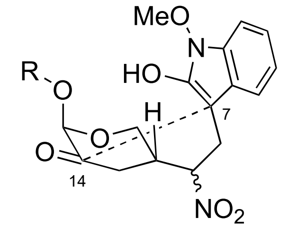


Disccusion 2-2: *stereoselectivity of intramolecular aldol reaction (C7 and C14)*



2-10 **2-11** **2-11a** (R = NO_2)

at C14 center



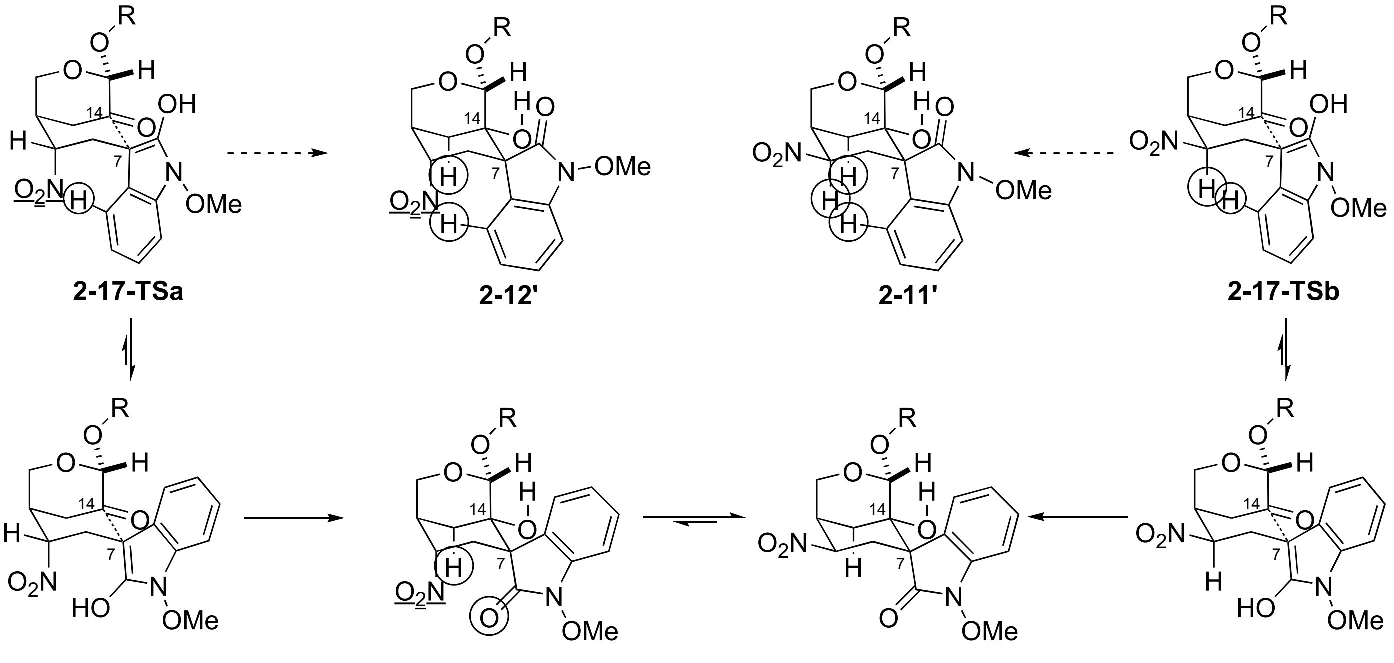
too far to react

2-10'

at C7 center

ring size: pyrrole < benzene

steric repulsion: pyrrole < benzene



Discussion 2-3: *regioselectivity of pinacol rearrangement*

The $\sigma_{C15\text{-}C14}$ is orthogonal to the $\pi^*_{C\text{-}O}$.