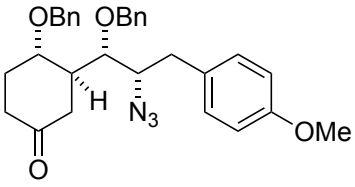
Problem Session (1)

2018.06.16 Toshiya Nagai

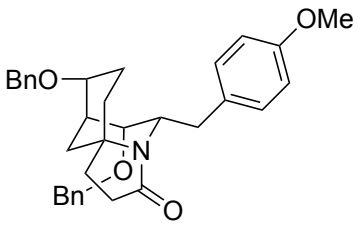
Please provide each reaction mechanism.



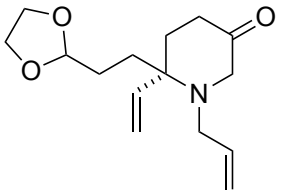
1-1

1. **1-2**, KOH, DMSO, rt (dr = 4 :1)
2. $PhSeSePh$, $NaBH_4$, EtOH, rt

3. *m*-CPBA, pyridine, hexane/CH_2Cl_2 –30 °C to rt (57%, 3 steps)
4. $ClSO_3H$ (2 eq.), CH_2Cl_2, –30 °C (67%)



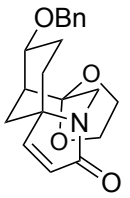
1-3



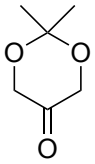
2-1

1. 4 N HCl, THF, rt to 50 °C, 1.5 h; ethylene glycol; evaporation of THF; CSA, toluene, 90 °C, 10 min (53%)
2. BnBr, NaH, TBAI, DMF, rt, 18 h (90%)
3. $Pd(Ph_3P)_4$, NDMBA, CH_2Cl_2, rt, 1 h

4. acryloyl chloride, Et_3N, CH_2Cl_2 0 °C, 30 min, (81%, 2 steps)
5. $Ti(O\mathit{i}Pr)_4$, Grubbs II, toluene 85 °C, 12 h (92%)



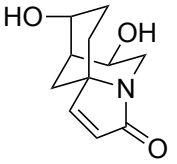
2-2



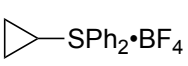
3-1

1. **3-2**, MS 4A, rt; Ac_2O, Et_3N, rt (83%)
2. **3-3**, benzonitrile, 120 °C (64%)
3. KO*t*-Bu, EtOAc, THF, 40 °C

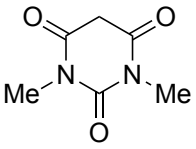
4. TFA, H_2O, 0 °C to rt (79%, 2 steps)
5. $NaBH_4$, AcOH, rt (92%)



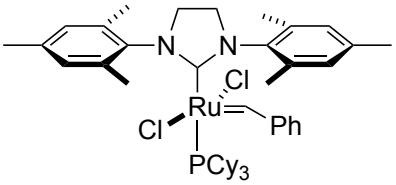
3-4



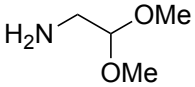
1-2



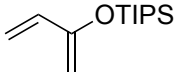
NDMBA



Grubbs II



3-2



3-3

Problem Session (1) -Answer-

2018.06.16 Toshiya Nagai

Topic: Synthetic Studies of FR901483

0. Introduction

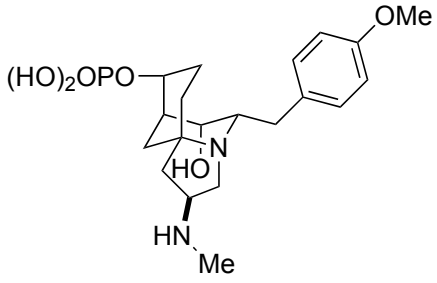
0-1. Isolation

Isolated from the fermentation broth of the fungal stain *Cladobotryum* sp. NO. 11231 in 1996

Sakamoto, K.; Tsuji, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.

0-2. Structual feature

• 5-azatricyclo[6.3.1.$0^{1,5}$]dodecane skeleton



FR901483

0-3. Biological activity

immunosuppressive activity in vitro and significantly prolongs graft survival time in the rat skin allograft model

0-4. Total syntheses and formal syntheses

0-4-1. Enantioselective total syntheses

• Snider, B. B.; Lin, H. *J. Am. Chem. Soc*. **1999**, *121*, 7778.

• Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed*. **2000**, *39*, 4593.

• Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett*. **2001**, *3*, 765.

• Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc*. **2001**, *123*, 7534.

• Carson, C. A.; Kerr, M. A. *Org. Lett*. **2009**, *11*, 777.

• Ma, A.-J.; Tu, Y.- Q.; Peng, J.-B.; Dou, Q.-Y.; Hou, S.-H.; Zhang, F.-M.; Wang, S.-H. *Org. Lett*. **2012**, *14*, 3604. (problem 1)

• Ieda, S.; Masuda, A.; Kariyama, M.; Wakimoto, T.; Asakawa, T.; Fukuyama, T.; Kan, T. *Heterocycles* **2012**, *86*, 1071.

• Huo, H.-H.; Xia, X.-E.; Zhang, H.-K.; Huang, P.-Q. *J. Org. Chem*. **2013**, *78*, 455. (problem 2)

0-4-2. Racemic total syntheses

• Maeng, J.; Funk, R. L. *Org. Lett*. **2001**, *3*, 1125. (problem 3)

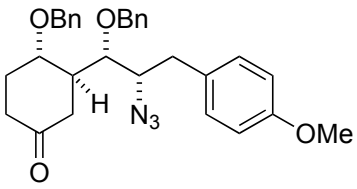
• Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett*. **2004**, *6*, 2729.

• Ieda, S.; Asoh, Y.; Fujimoto, T.; Kitaoka, H.; Kan, T.; Fukuyama, T. *Heterocycles* **2009**, *79*, 721.

0-4-3. Formal synthesis

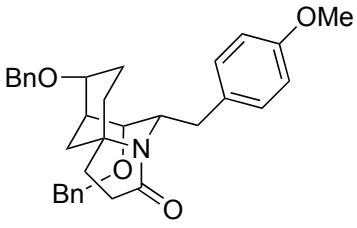
• Brummond, K. M.; Hong, S. P. *J. Org. Chem*. **2005**, *70*, 907.

Problem 1



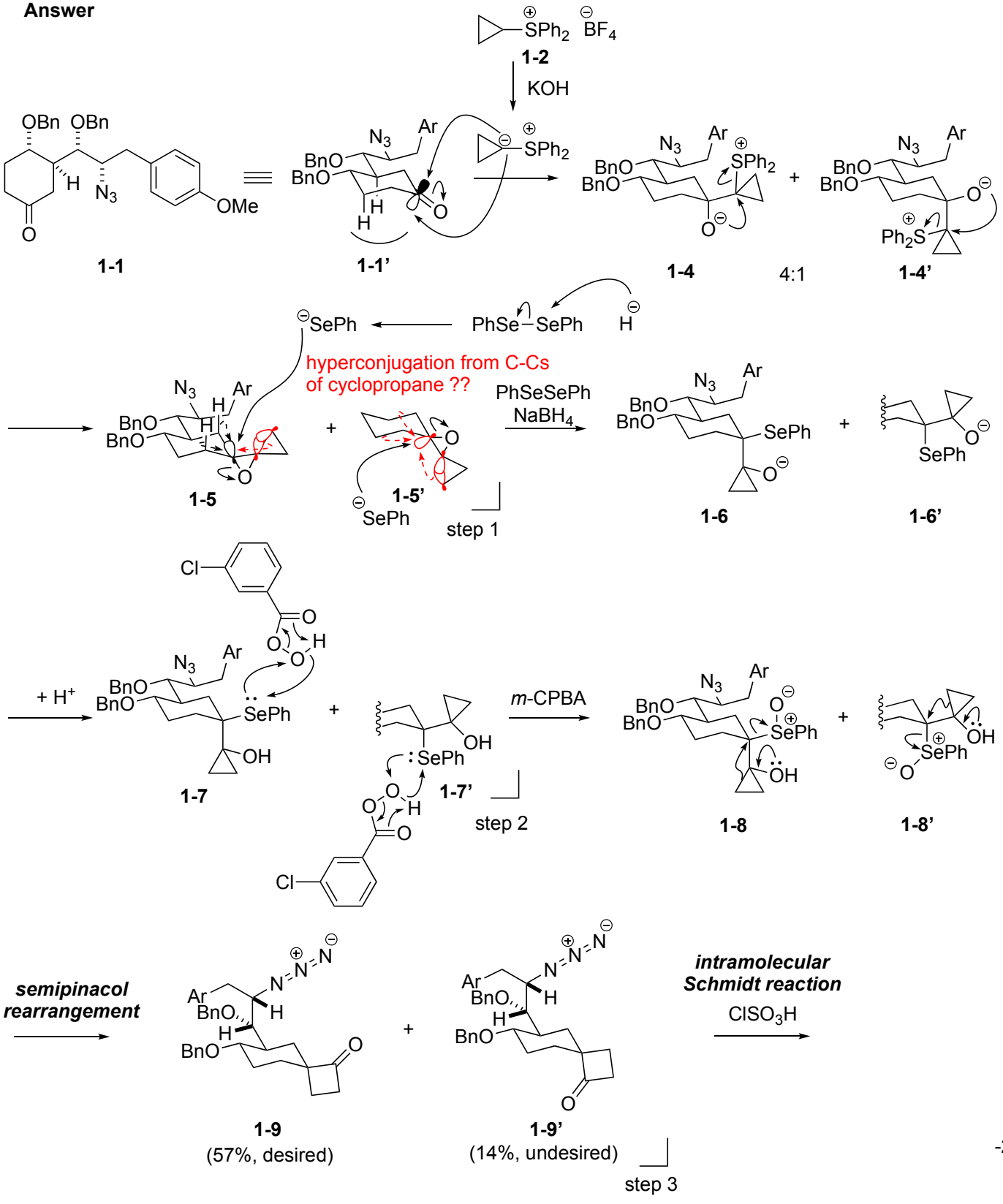
1-1

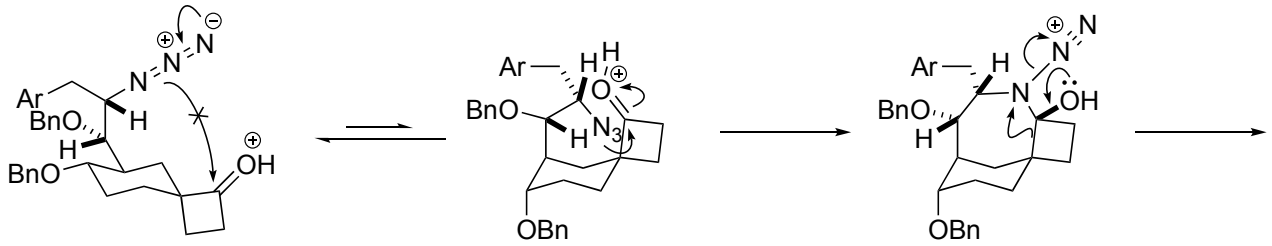
1. **1-2**, KOH, DMSO, rt (dr = 4 :1)
2. PhSeSePh, $NaBH_4$, EtOH, rt
3. *m*-CPBA, pyridine, hexane/CH_2Cl_2 –30 °C to rt (57%, 3 steps)
4. $ClSO_3H$ (2 eq.), CH_2Cl_2, –30 °C (67%)



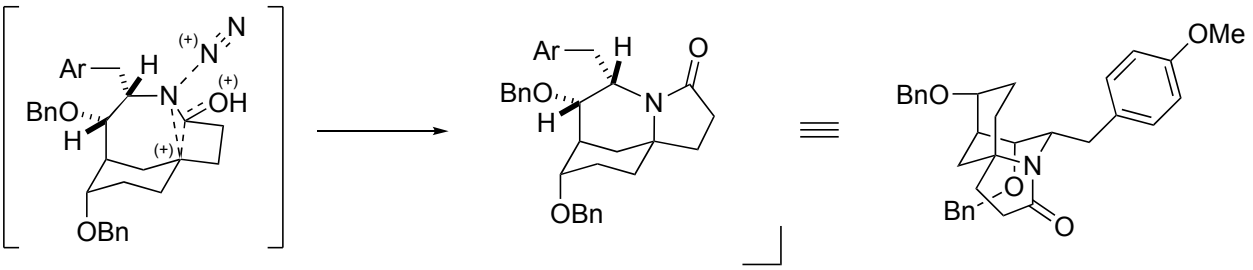
1-3

Answer



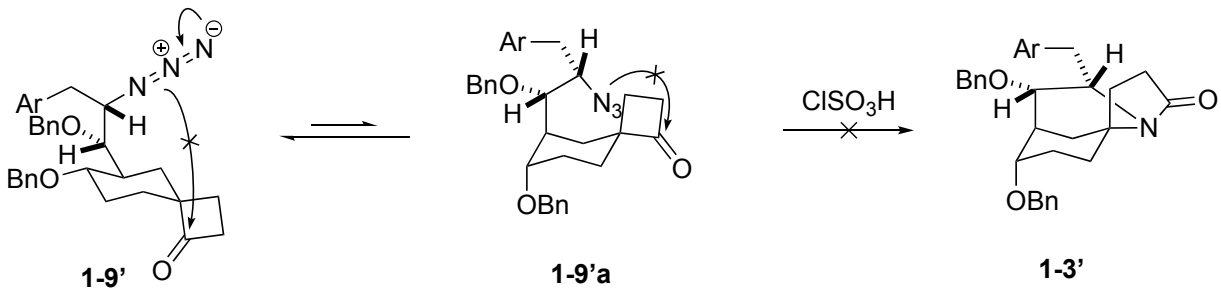


1-10 **1-10a** **1-11**



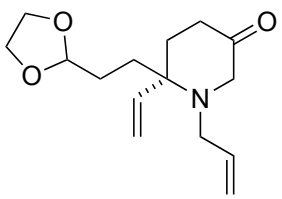
1-12 **1-3** step 4 **1-3**

• Schmidt reaction for **1-9'**



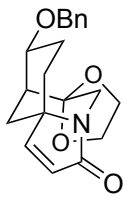
1-9' **1-9'a** **1-3'**

Problem 2



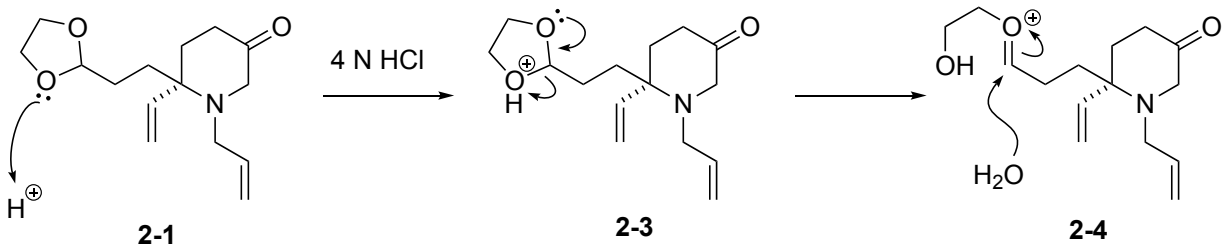
2-1

1. 4 N HCl, THF, rt to 50 °C, 1.5 h; ethylene glycol; evaporation of THF; CSA, toluene, 90 °C, 10 min (53%)
2. BnBr, NaH, TBAI, DMF, rt, 18 h (90%)
3. $Pd(PPh_3)_4$, NDMBA, CH_2Cl_2, rt, 1 h
4. acryloyl chloride, Et_3N, CH_2Cl_2 0 °C, 30 min, (81%, 2 steps)
5. $Ti(O\textit{i}Pr)_4$, Grubbs II, toluene 85 °C, 12 h (92%)

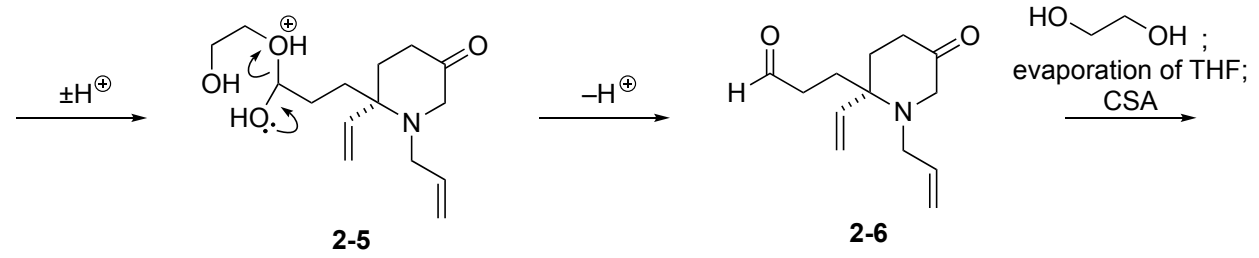


2-2

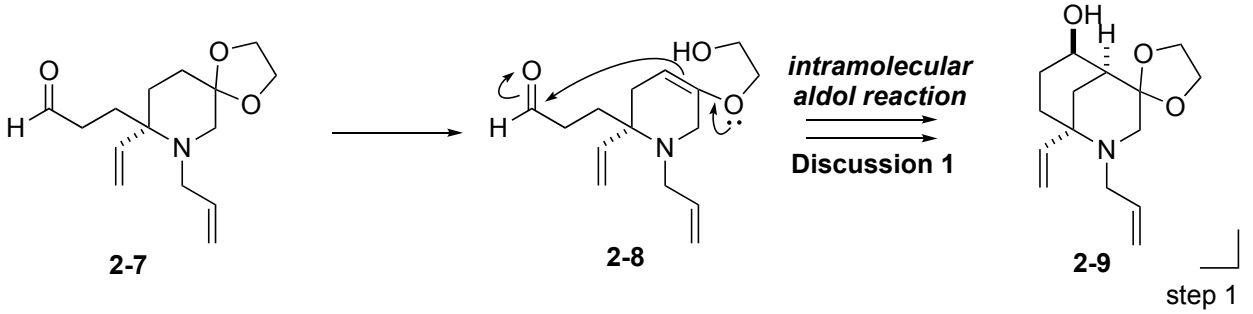
Answer



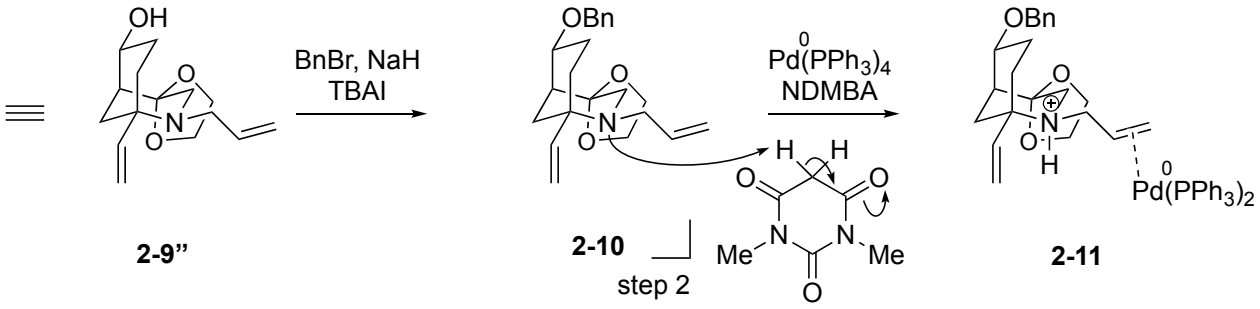
2-1 **2-3** **2-4**



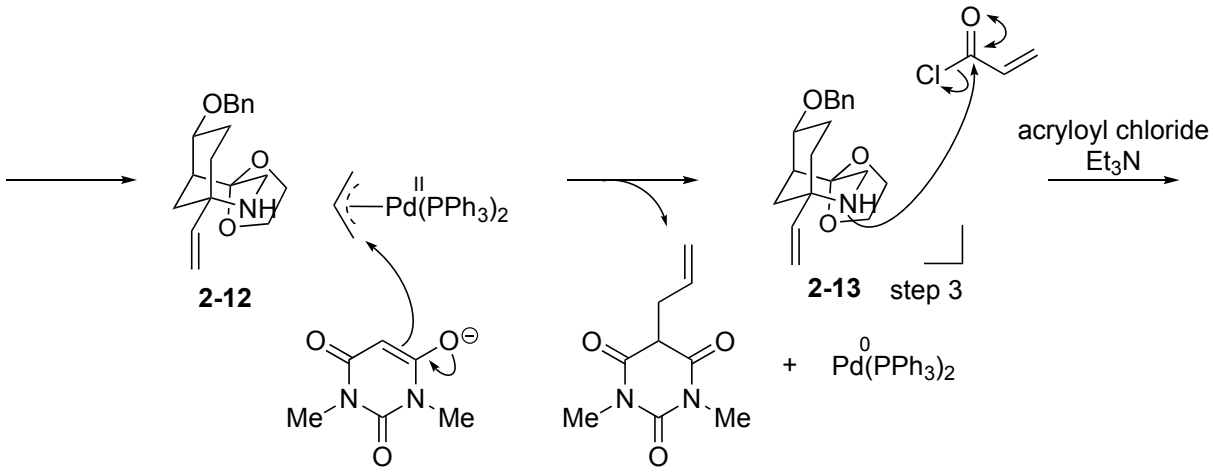
2-5 **2-6**



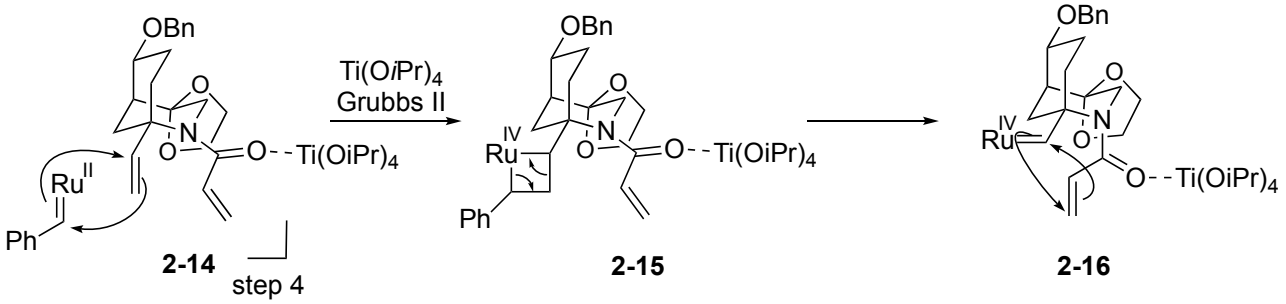
2-7 **2-8** **2-9**



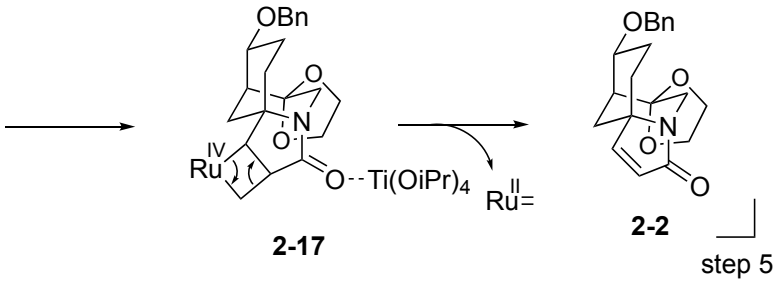
2-9" **2-10** **2-11**



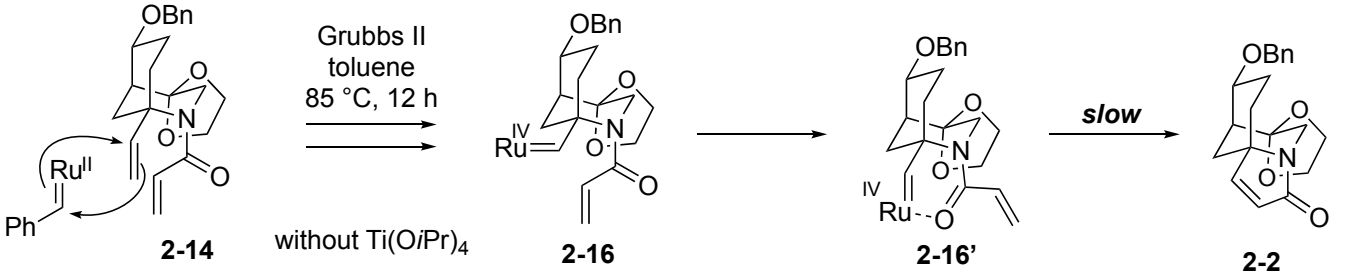
2-12 **2-13**



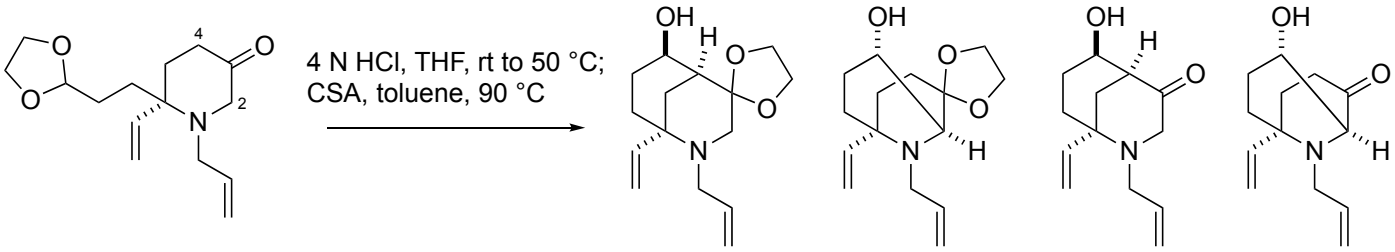
2-14 **2-15** **2-16**



• The effect of Ti(O*i*Pr)$_4$ in RCM



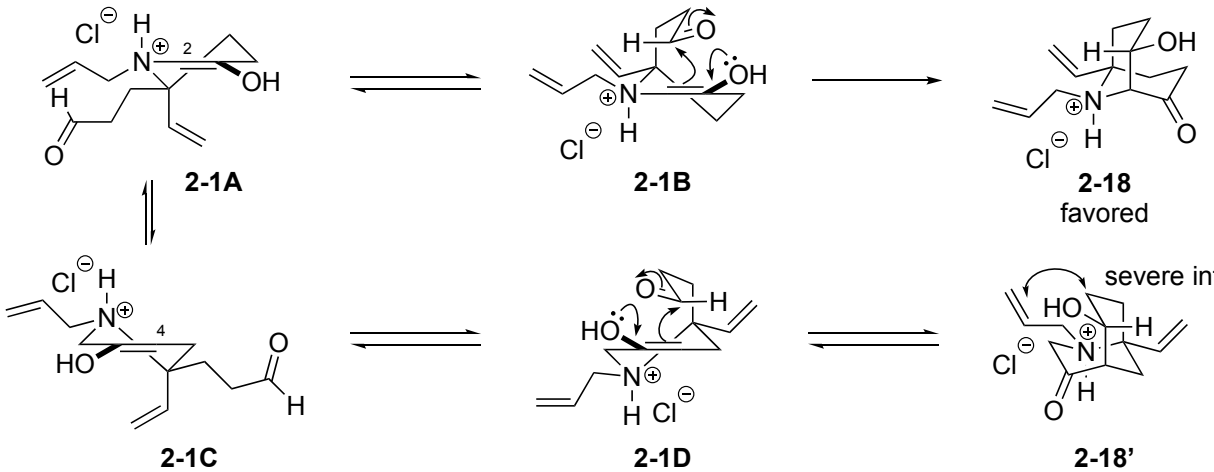
Discussion 1: Aldol reaction



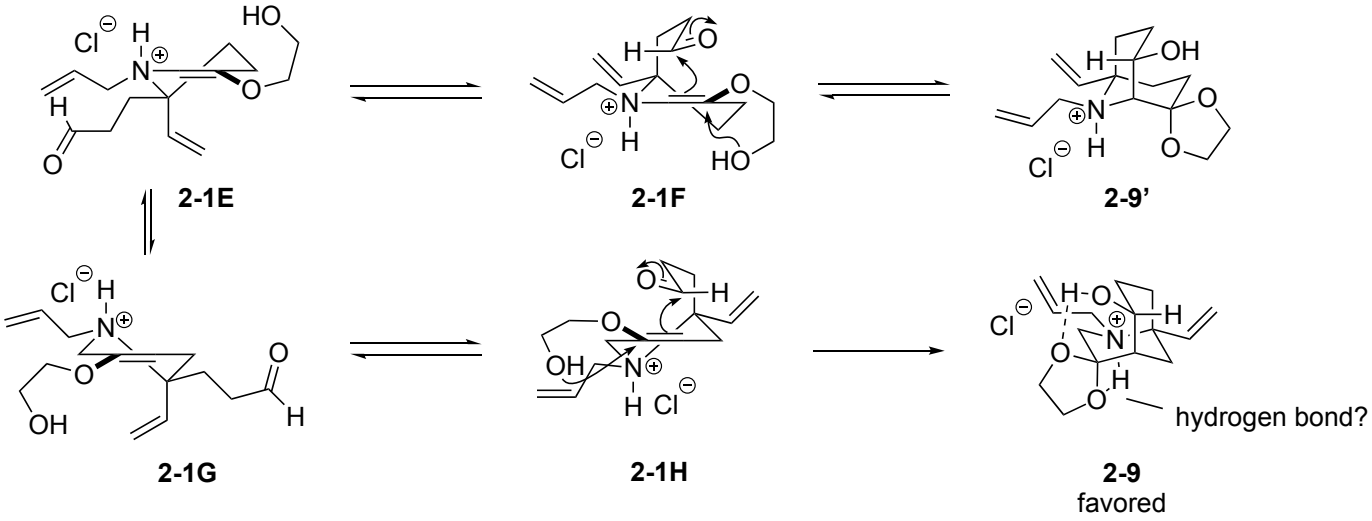
	2-9	2-9'	2-18'	2-18
without ethylene glycol	30%	not obtained	not obtained	30%
In the presence of ethylene glycol	53%	not obtained	not obtained	5%

<Author's proposal>

• without ethylene glycol

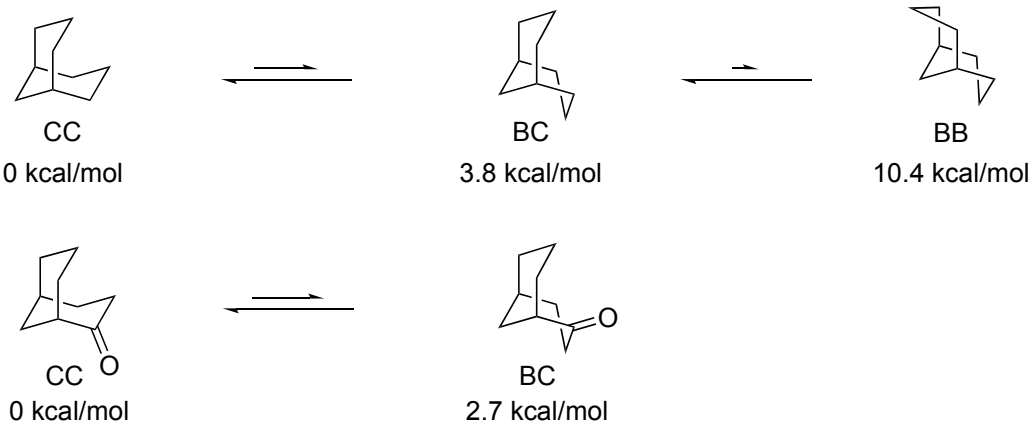


• In the presence of ethylene glycol



<My proposal>

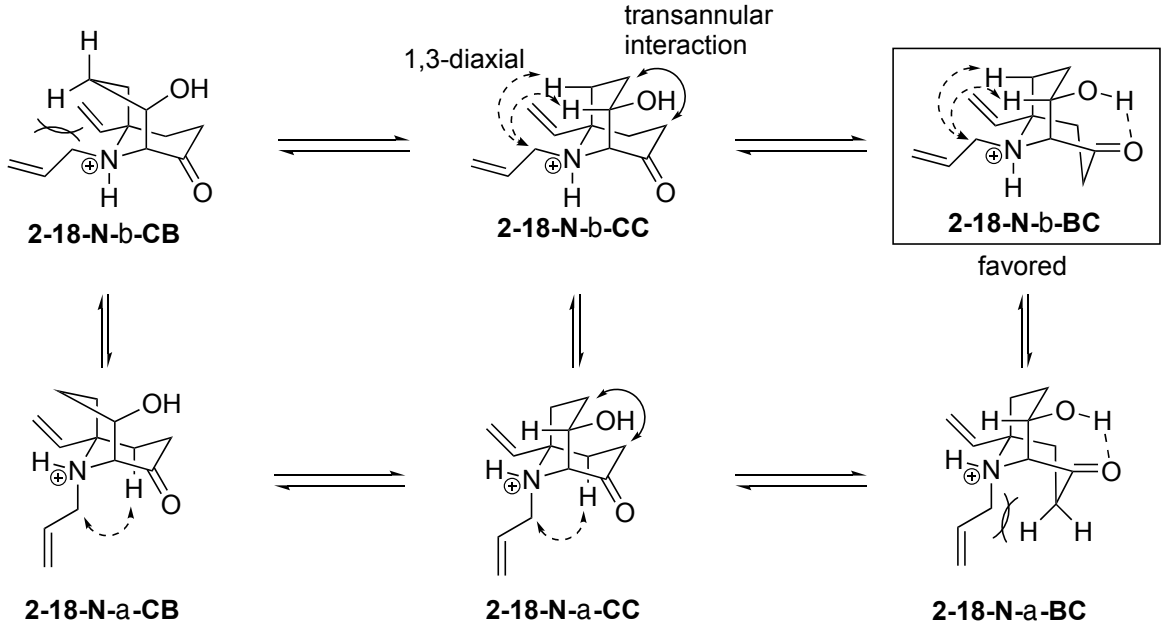
• Conformation of bicyclo[3.3.1]nonane and bicyclo[3.3.1]nonan-2-one



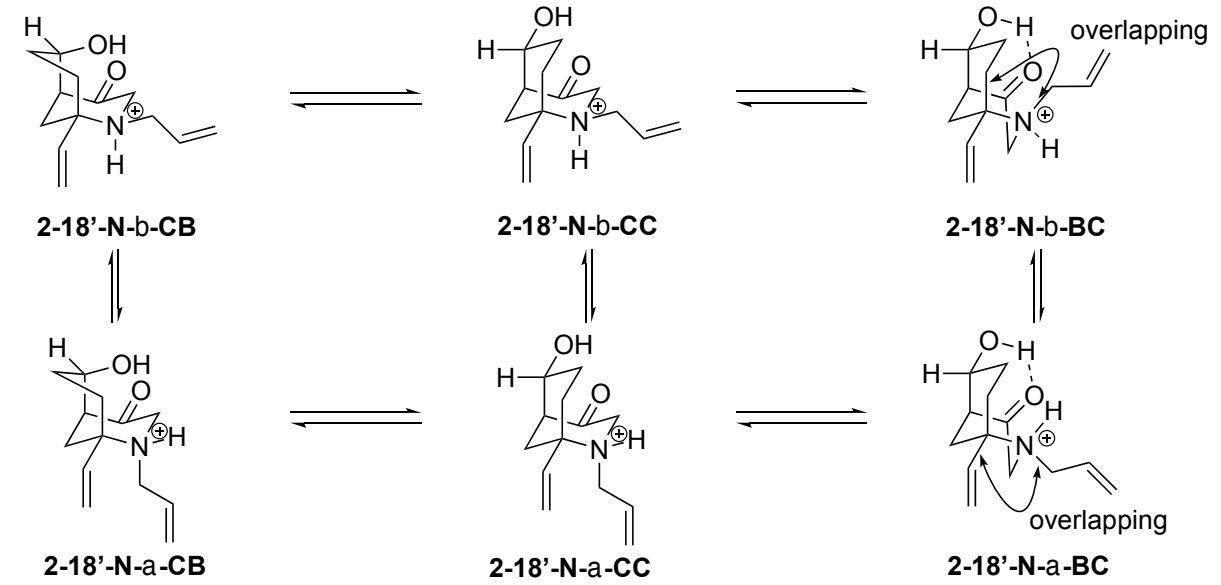
Marvell, E. N.; Gleicher, G. J.; Sturmer, D.; Salisbur, K. *J. Org. Chem.* **1968**, *33*, 3393.

• Stable conformation of **2-18**

Only conformation BC can form the hydrogen bond.



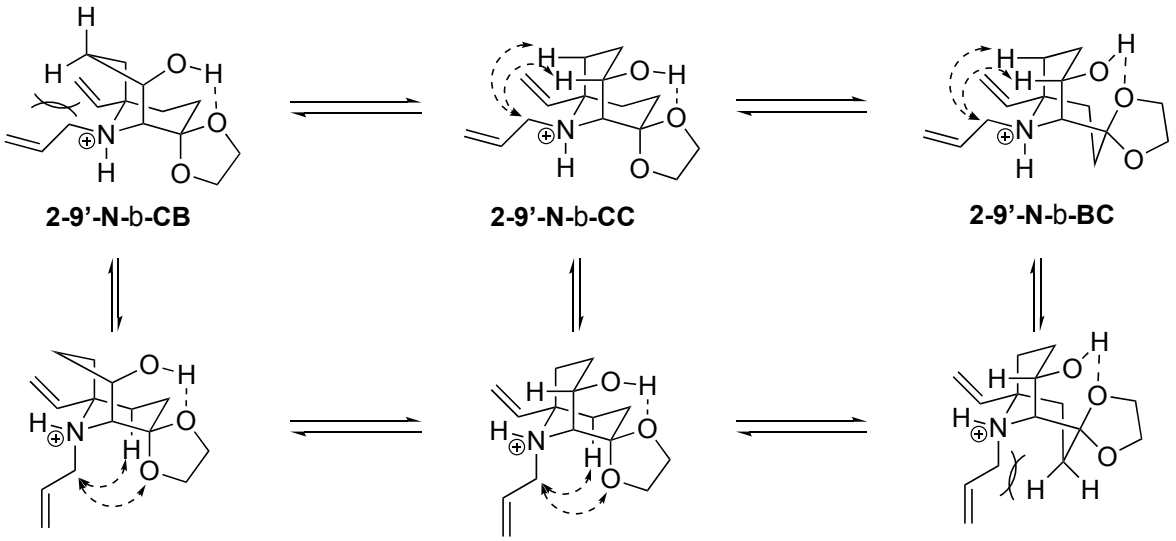
• Stable conformation of **2-18'**



2-18'-N-b-**CB** **2-18'-N**-b-**CC** **2-18'-N**-b-**BC**

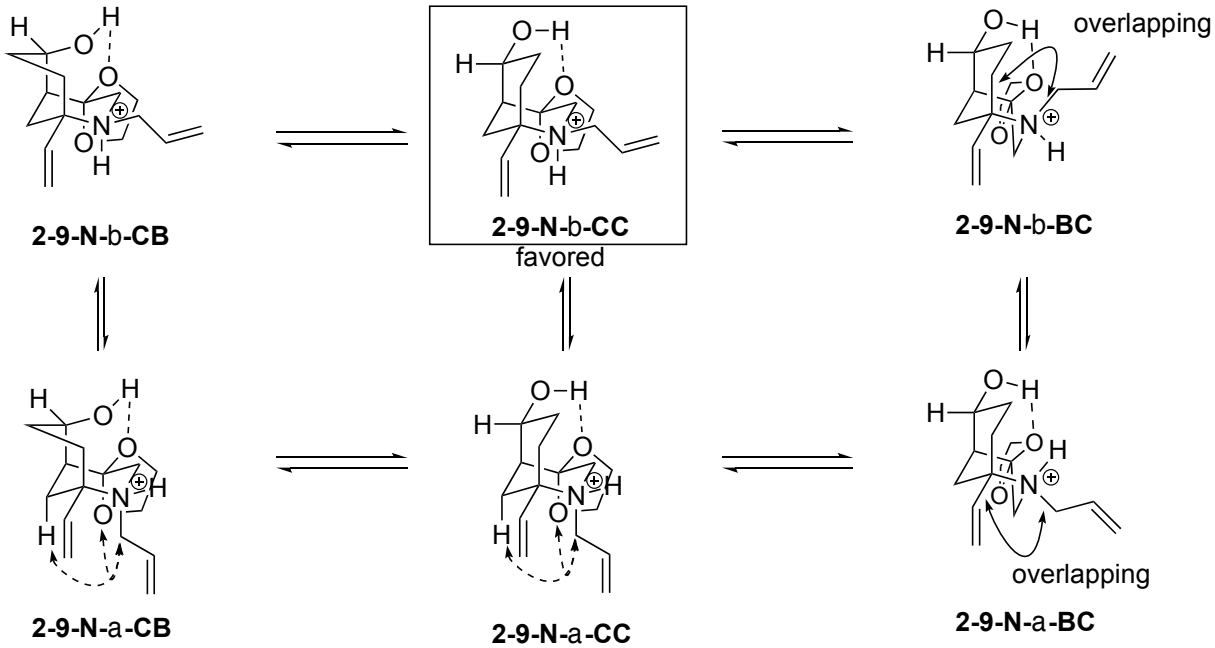
2-18'-N-a-**CB** **2-18'-N**-a-**CC** **2-18'-N**-a-**BC**

• Stable conformation of **2-9** and **2-9'**



2-9'-N-b-**CB** **2-9'-N**-b-**CC** **2-9'-N**-b-**BC**

2-9'-N-a-**CB** **2-9'-N**-a-**CC** **2-9'-N**-a-**BC**

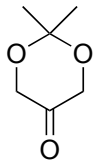


2-9-N-b-**CB** **2-9-N**-b-**CC** **2-9-N**-b-**BC**

favored

2-9-N-a-**CB** **2-9-N**-a-**CC** **2-9-N**-a-**BC**

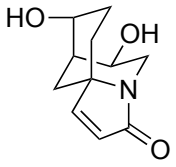
Problem 3



3-1

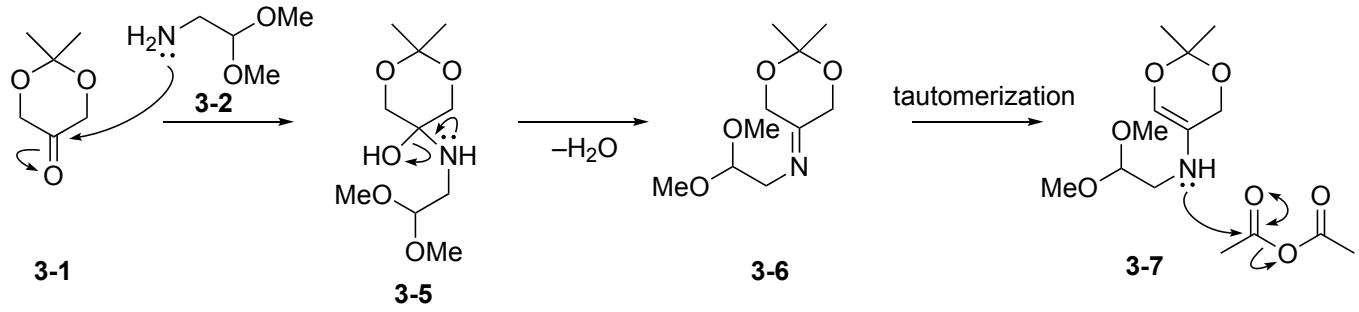
1. **3-2**, MS 4A, rt; Ac_2O, Et_3N, rt (83%)
2. **3-3**, benzonitrile, 120 °C (64%)
3. KO*t*-Bu, EtOAc, THF, 40 °C

4. TFA, H_2O, 0 °C to rt (79%, 2 steps)
5. $NaBH_4$, AcOH, rt (92%)

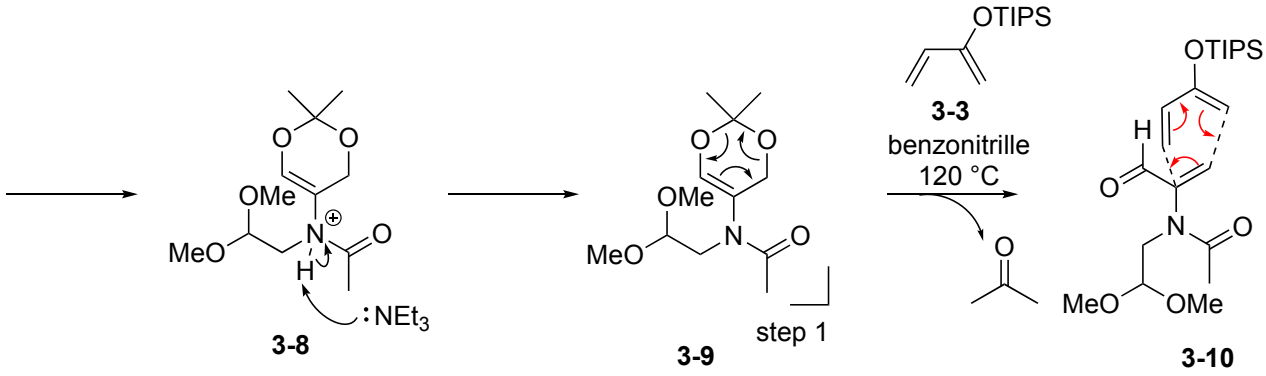


3-4

Answer



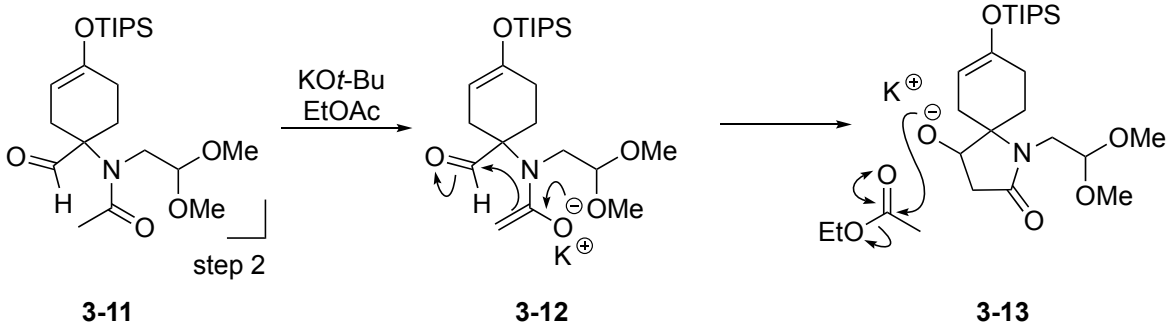
3-1 **3-5** **3-6** **3-7**



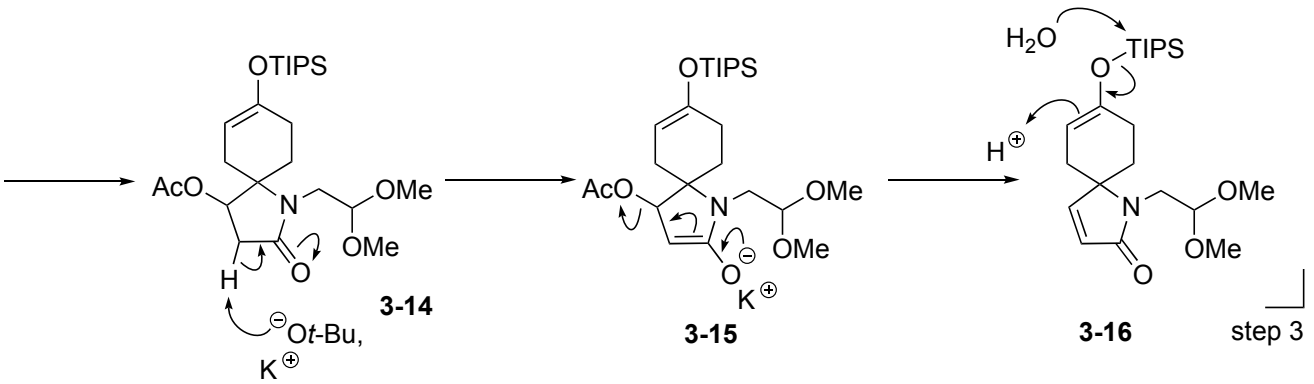
3-8 **3-9** **3-3** **3-10**

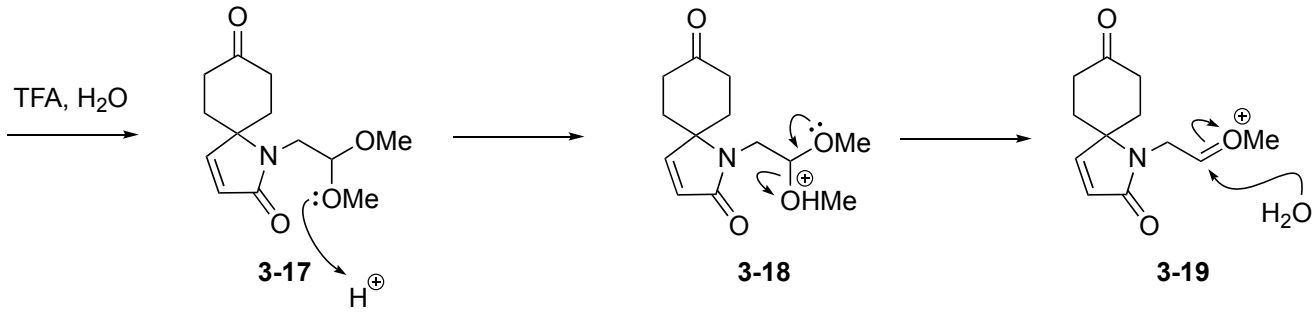
Diels-Alder reaction

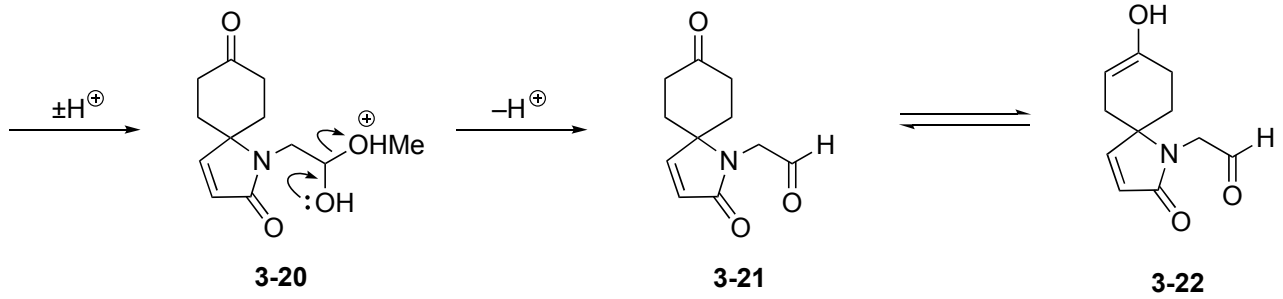
Discussion 2

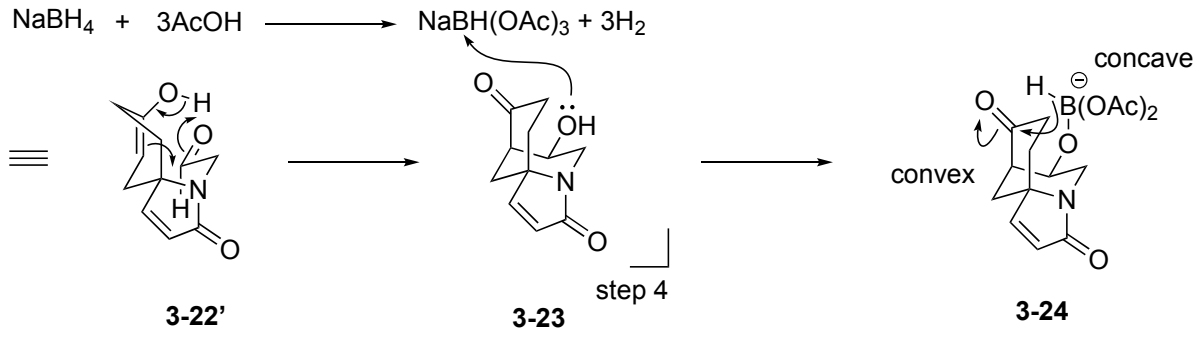


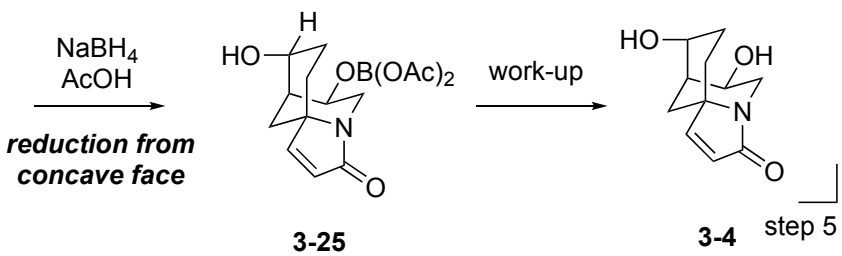
3-11 **3-12** **3-13**


OTIPS
AcO
N
OMe
OMe
H
O
Ot-Bu,
K
3-14
OTIPS
AcO
N
OMe
OMe
O
K
3-15
H2O
TIPS
O
H
N
OMe
OMe
O
3-16
step 3

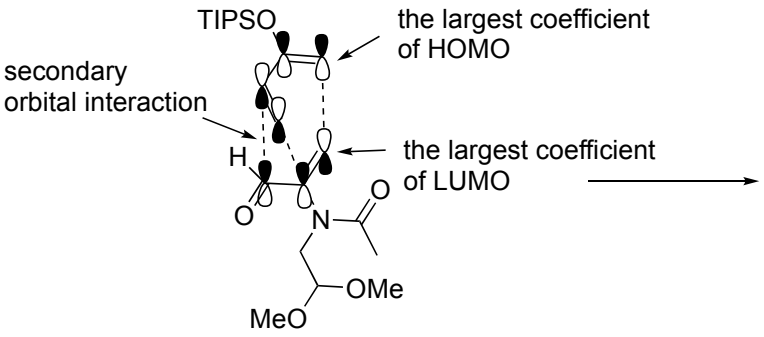

TFA, H2O
O
N
OMe
:OMe
O
3-17
H
3-18
OMe
OHMe
3-19
H2O


±H
O
N
OHMe
:OH
3-20
–H
3-21
OH
H
3-22

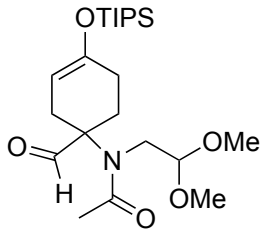

NaBH4 + 3AcOH
NaBH(OAc)3 + 3H2
O
H
N
3-22'
OH
step 4
3-23
concave
B(OAc)2
convex
3-24


NaBH4
AcOH
reduction from
concave face
H
HO
OB(OAc)2
N
3-25
work-up
HO
OH
3-4
step 5

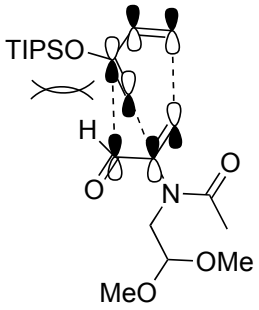
Discussion 2: Stereoselectivity of Diels-Alder reaction



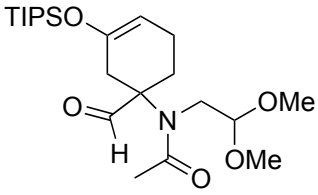
3-A
favored



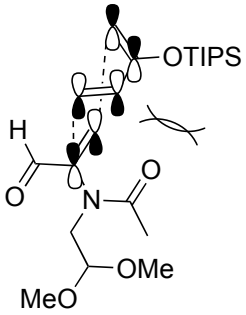
3-11



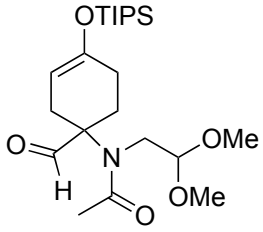
3-B
disfavored



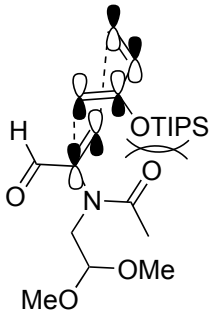
3-11'



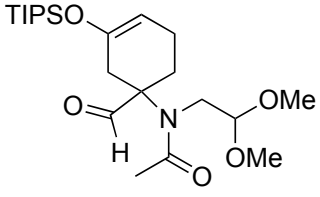
3-C
disfavored



3-11



3-D
disfavored



3-11'