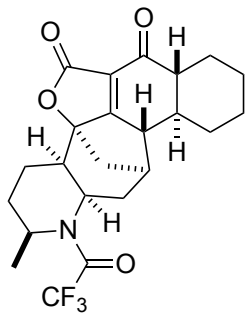
2021.10.30

Problem Session (2)

Please provide the reaction mechanisms.

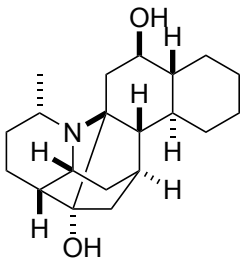
Hibiki Asai

1



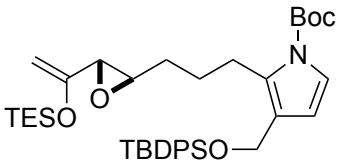
1-1

1. 1,4-dioxane/6 M aqueous HCl (5/16)
   microwave, 100 ºC, 83%
2. $Sc(OTf)_3$ (0.5 eq.), $CHCl_3$;
   HCl (one drop, 2 M Et_2O solution)
3. $NaBH(OAc)_3$ (6 eq.)
   MeCN/AcOH (1/1), 0 ºC, 64% over 2 steps



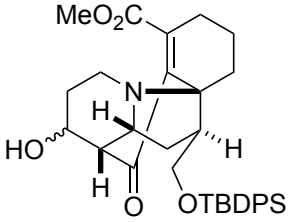
1-2

2



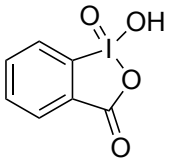
2-1

1. TESOTf (0.3 eq.), CH_2Cl_2, -78 ºC;
   Et_3N•3HF (3 eq.), 41%
2. IBX (3 eq.), EtOAc, 75 ºC, 85%
3. LiOTf (2 eq.), (i-Pr)$_2$NEt (4 eq.), CH_2Cl_2, 0 ºC;
   Tf_2O (2 eq.), 0 ºC, 90%*
4. CO (3 atm), $Pd(OAc)_2$ (0.2 eq.), Ph_3P (0.4 eq.)
   (i-Pr)$_2$NEt (7 eq.), MeOH, 40 ºC, 67%
5. Pd/C (20 wt%), H_2 (balloon), MeOH, 94%
6. CF_3CO_2H (80 eq.), CH_2Cl_2, 0 ºC, 94%
7. acrolein (10 eq.), THF; TBD (3.2 eq.), 51%

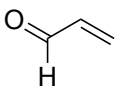


2-2
dr = 1:2.4

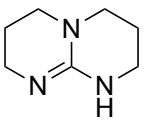
* The yield was that of inseparable 8.7:1 mixture of the desired compound and its regioisomer.



IBX



acrolein



TBD

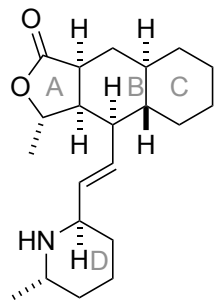
Tf : trifluoromethylsulfonyl
TES : triethylsilyl
TBDPS : *tert*-butyldiphenylsilyl
Boc : *tert*-butoxycarbonyl

Topic: Class II and class III galbulimima alkaloids

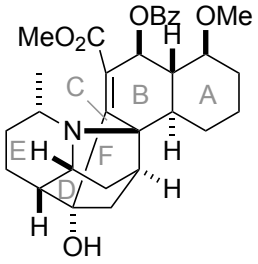
Introduction: Galbulimima alkaloids

Isolation: *Galbulimima belgraveana* or *Galbulimima baccata*

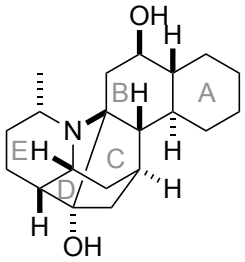
Structural classification:
class I:himbacine (**0-1**) and related compounds (12 compounds)
class II:himandrine (**0-2**) and related compounds (18 compounds)
class III:himgaline (**1-2**) and related compounds (4 compounds)
class IV:GB-16 (**0-3**) and a related compound (2 compounds)



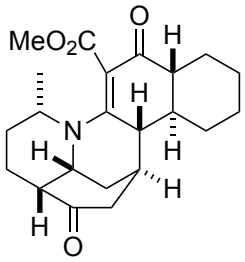
(+)-himbeline (**0-1**)



(-)-himdrine (**0-2**)



(-)-himgaline (**1-2**)

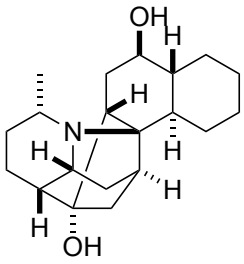


(-)-GB-16 (**0-3**)

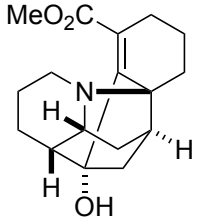
Biological activity: muscarinic receptor antagonist (himbacine (**0-1**))

Total synthesis of class II and class III galbulimima alkaloids:
class II:
(-)-himandrine (**0-2**): Movassaghi, M. et al. *J. Am. Chem. Soc.* **2009**, *131*, 9648. (PS_090711_Yuki_KATOH)
synthetic study (**0-4**): Mander, L. et al. *Org. Lett.* **2004**, *6*, 703.
synthetic study (**0-5**): Chiu, P. et al. *Angew. Chem. Int. Ed.* **2018**, *57*, 5253. (***problem 2***)

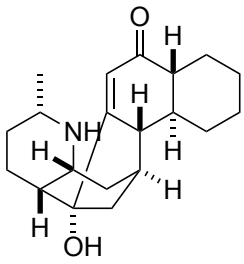
class III:
(±)-GB-13 (**0-6**): MacLachlan, M. M. and Mander, L. *J. Am. Chem. Soc.* **2003**, *125*, 2400.
(-)-GB-13, (-)-himgaline (**1-2**): Chackalamannil, S. et al. *J. Am. Chem. Soc.* **2006**, *128*, 12655. (***problem 1***)
(-)-GB-13, (+)-GB-13: Movassaghi, M. et al. *J. Am. Chem. Soc.* **2006**, *128*, 8126.
(+)-GB-13, (+)-himgaline: Adams, D. J. and Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 1048.
(±)-GB-13: Larson, K. K. and Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 13244. (PS_150110_Hiroki_Matoba)
(-)-GB-13: Ma, D. et al. *Angew, Chem. Int. Ed.* **2010**, *49*, 5887. (PS_150110_Hiroki_Matoba)



0-4

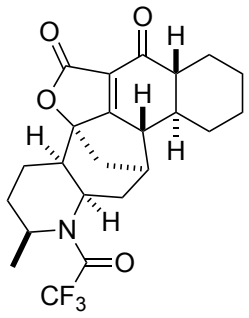


0-5



(-)-GB-13 (**0-6**)

1



1-1

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   microwave, 100 ºC, 83%

2. $Sc(OTf)_3$ (0.5 eq.), $CHCl_3$;
   HCl (one drop, 2 M Et_2O solution)
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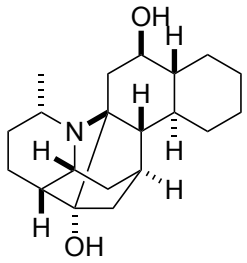
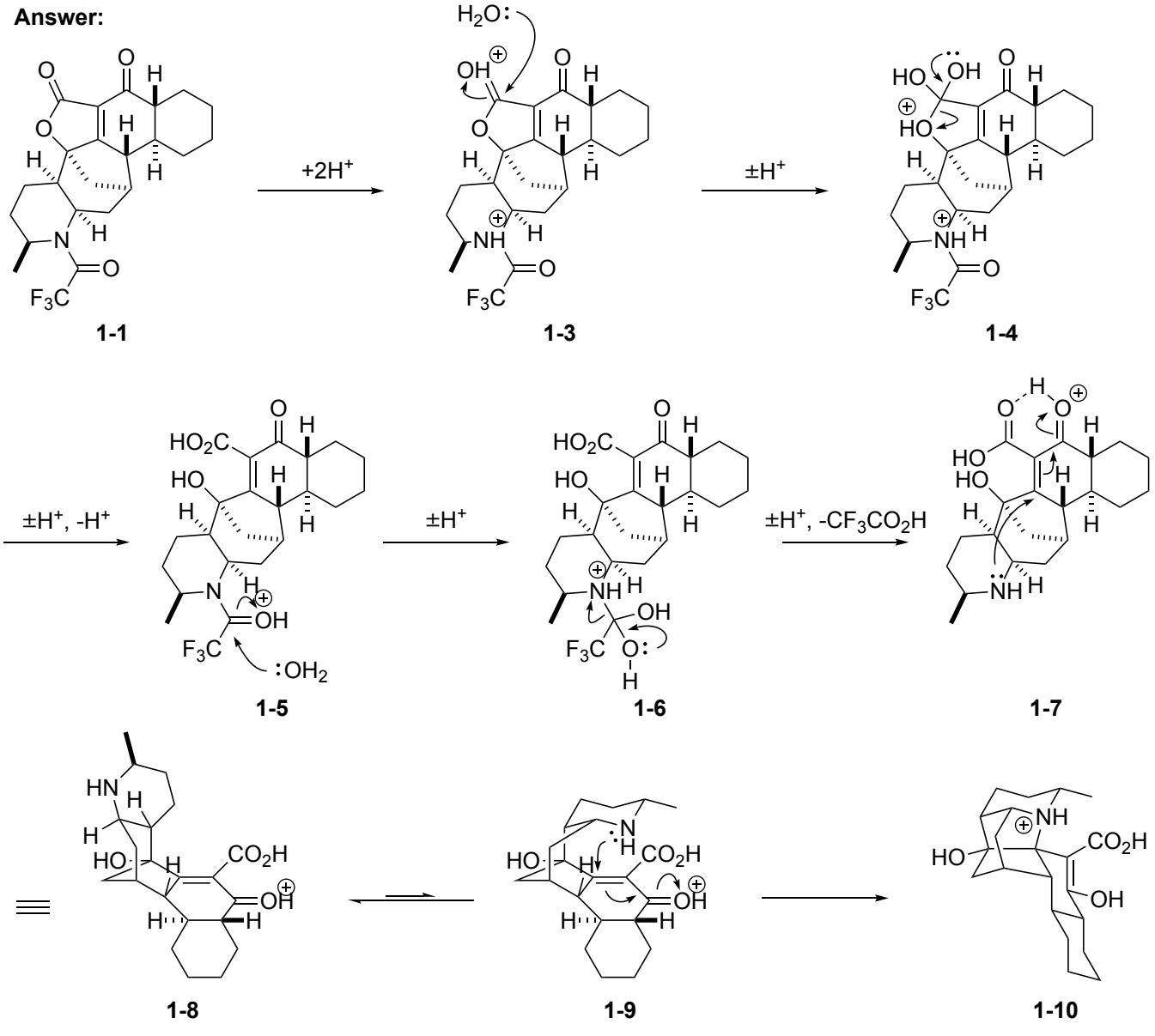


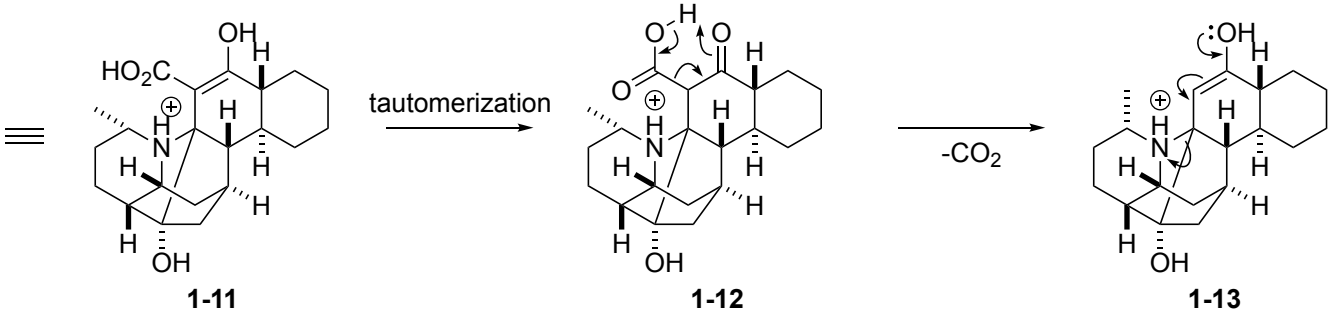
1-2 ((-)-himgaline)

Shah, U.; Chackalamannil, S.; Ganguly, A. K.; Chelliah, M.; Kolotuchin, S.; Buevich, A.; McPhail, A. *J. Am. Chem. Soc.* **2006**, *128*, 12655.

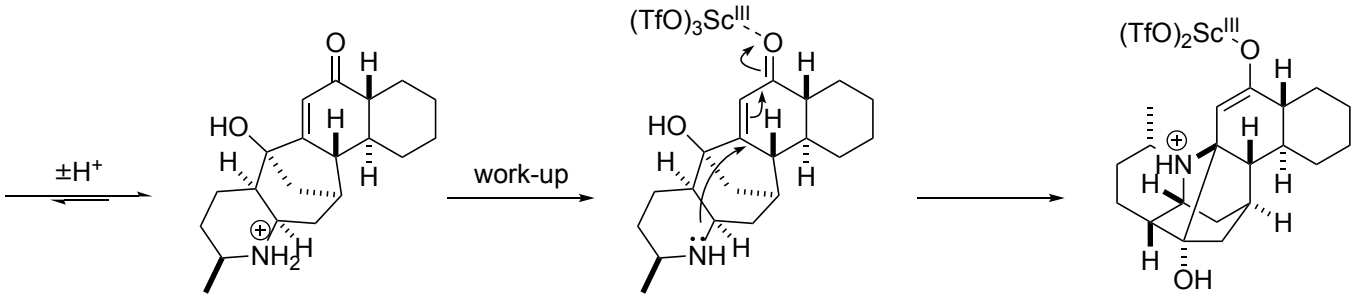
Answer:



1-1 **1-3** **1-4** **1-5** **1-6** **1-7** **1-8** **1-9** **1-10**

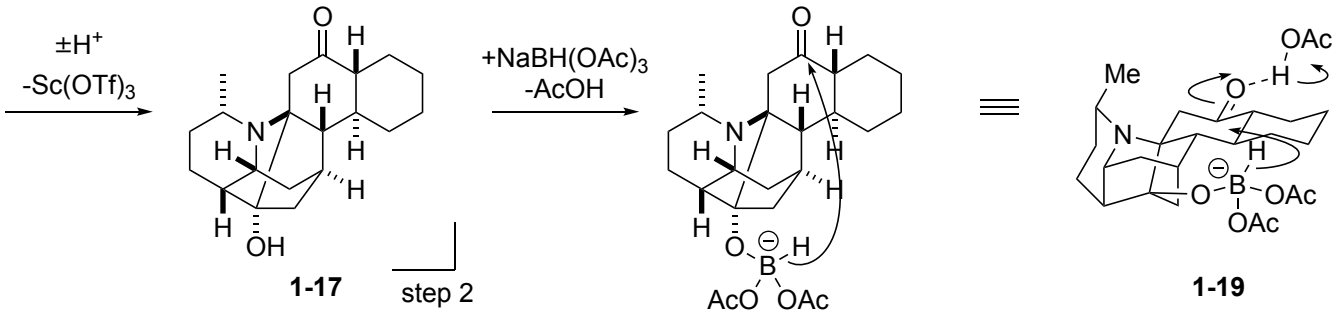


1-11 **1-12** **1-13**



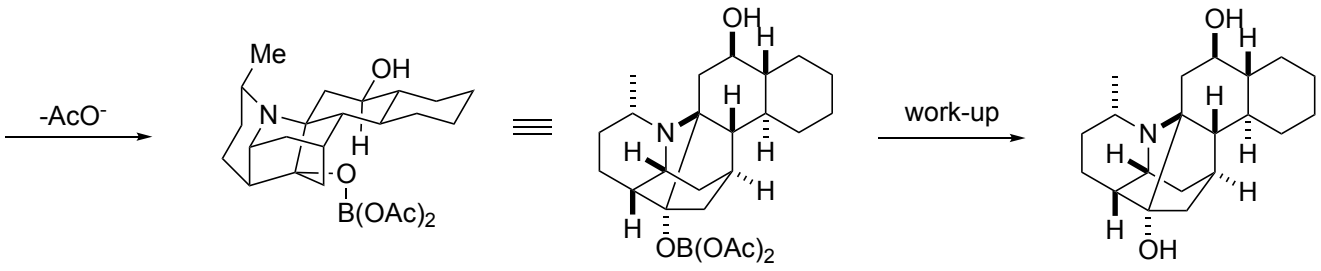
1-14 **1-15** ((-)-GB-13) **1-16**

step 1



1-17 step 2 **1-18** **1-19**

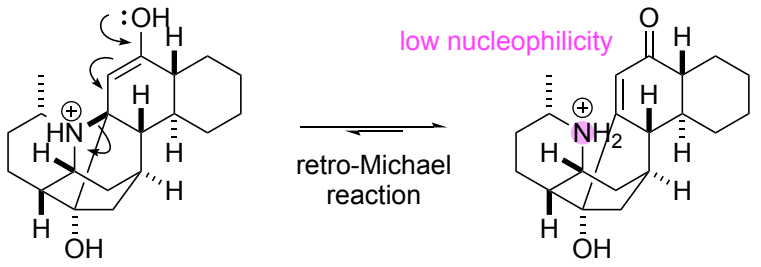
* One drop HCl (2 M Et_2O solution) might accelerate this protone exchange.



1-20 **1-21** **1-2** ((-)-himgaline)

Discussion 1-1: Aza-Michael reaction

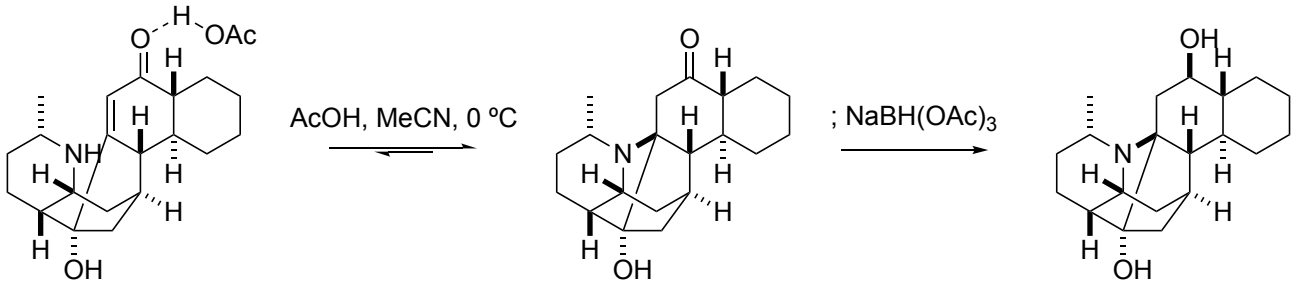
• Strong protic acid condition (***problem 1***, step 1)



1-13 **1-14**

In the strong protic acid condition, N atom was completely protonated and retro-Michael reaction proceeded.

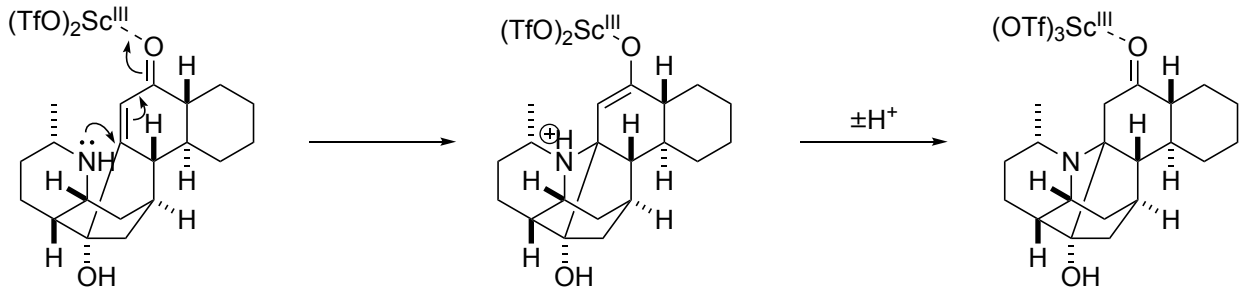
• Weak protic acid condition (Zi, W.; Yu, S.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 5887.)



1-15 ((-)-GB-13) **1-17** **1-2** ((-)-himgaline)

In the weak protic acid condition, retro-Michael reaction didn't occur.

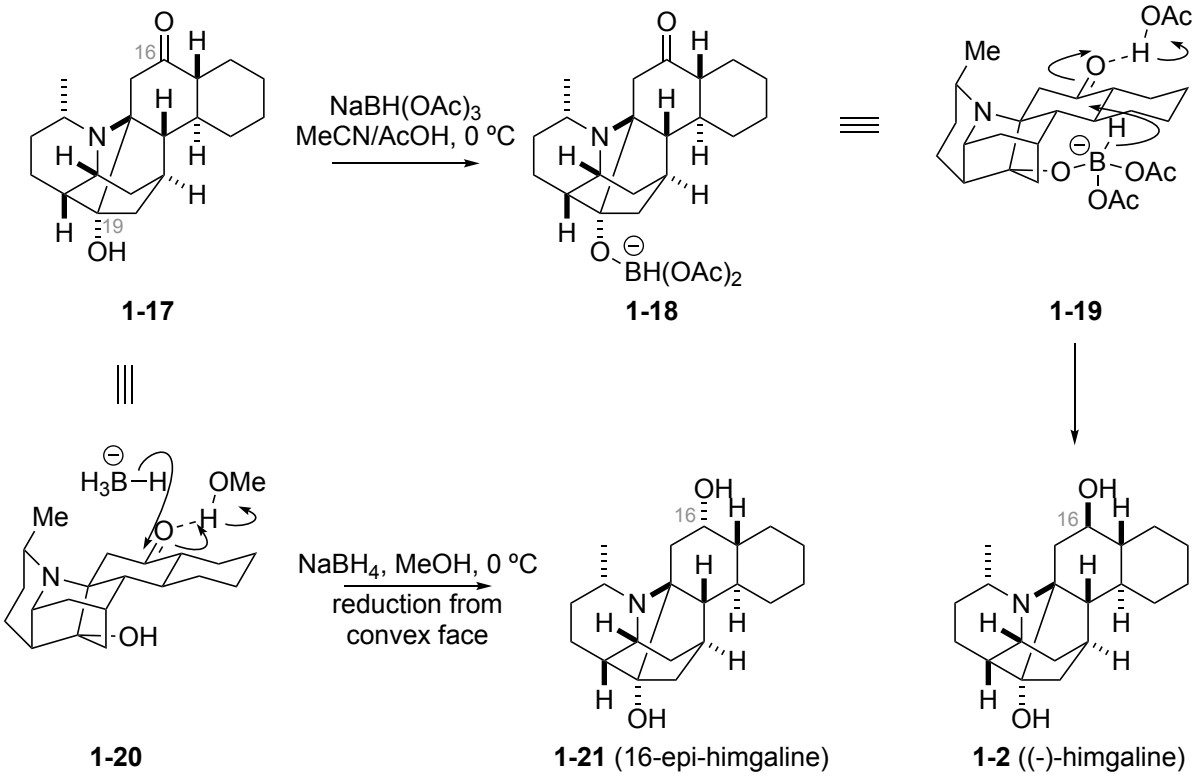
• Lewis acid condition (***problem 1***, step 2)



1-15 ((-)-GB-13) **1-16** **1-17**

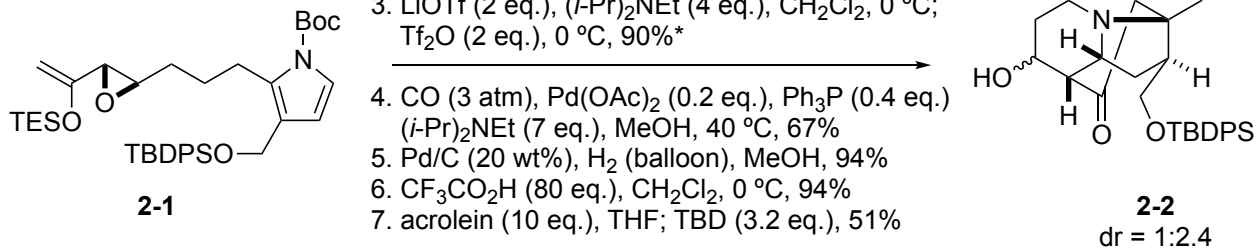
Retro-Michael reaction didn't proceed when ketone was selectively activated by $Sc(OTf)_3$.

Discussion 1-2: Reduction of C16 ketone



Weak reductant $BH(OAc)_3$ can't reduce ketone without the coordination of C19 OH group, which gives desired himgaline.

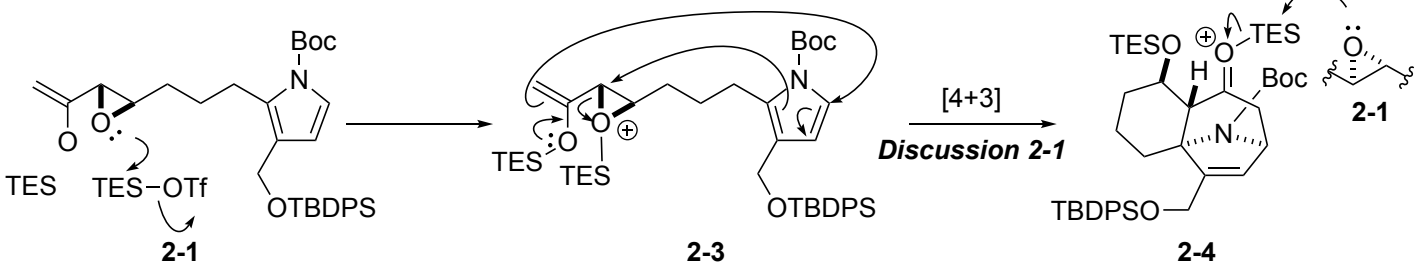
2

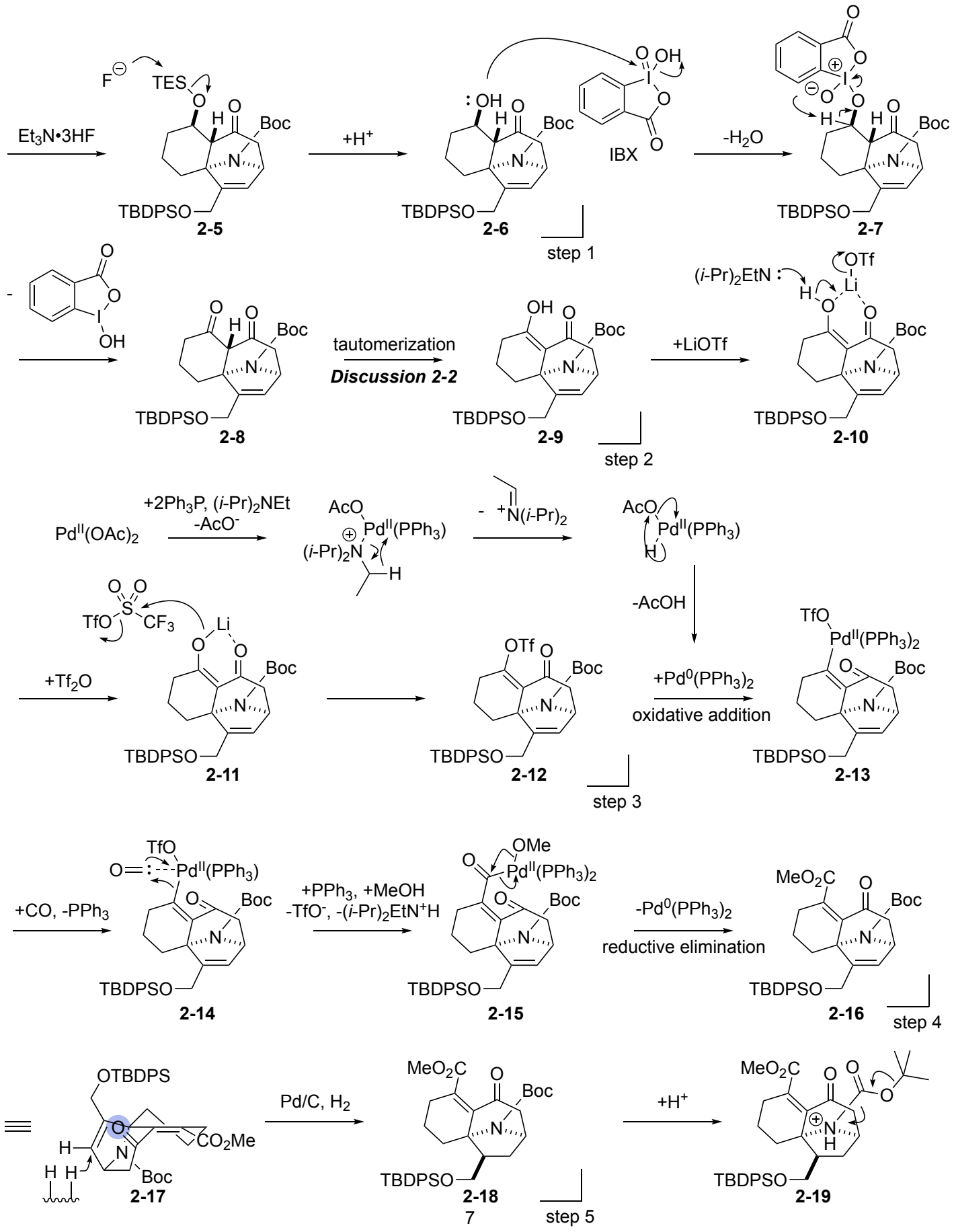


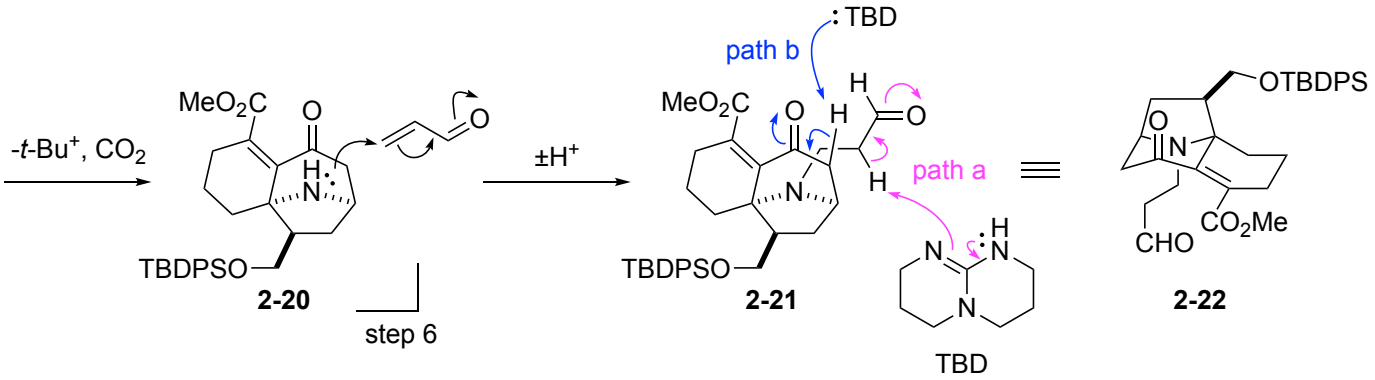
* The yield was that of inseparable 8.7:1 mixture of the desired compound and its regioisomer.

He, J.; Chen, Z.; Li, W.; Low, K.-H.; Chiu, P. *Angew. Chem. Int. Ed.* **2018**, *57*, 5253.

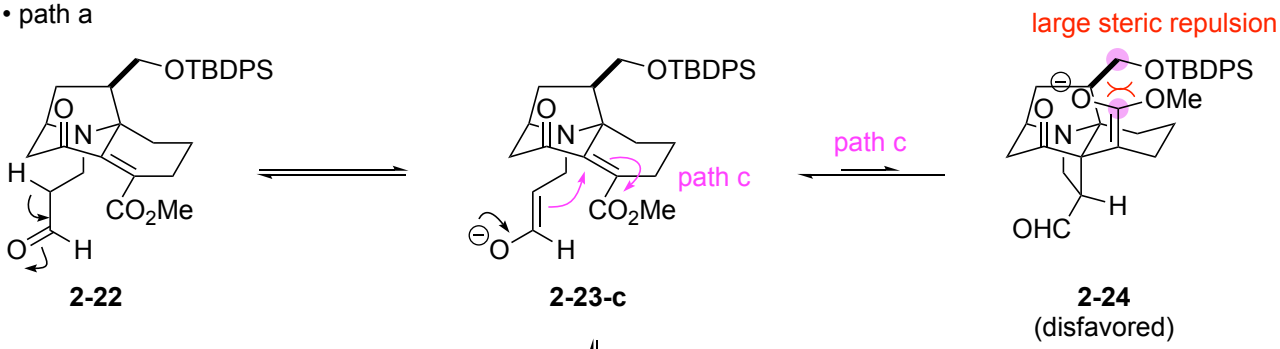
Answer:

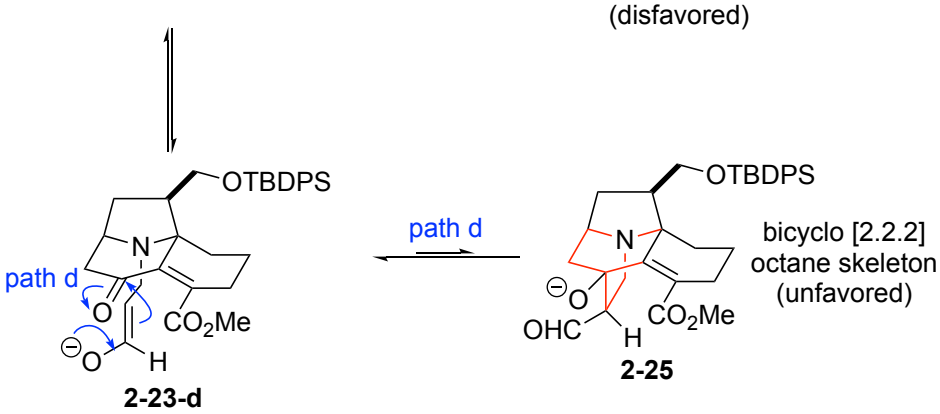



Et3N•3HF
+H+
IBX
-H2O
TBDPSO
2-5
2-6
2-7
step 1
tautomerization
Discussion 2-2
+LiOTf
(i-Pr)2EtN
2-8
2-9
2-10
step 2
Pd(OAc)2
+2Ph3P, (i-Pr)2NEt
-AcO-
-AcOH
+Tf2O
+Pd0(PPh3)2
oxidative addition
2-11
2-12
2-13
step 3
+CO, -PPh3
+PPh3, +MeOH
-TfO-, -(i-Pr)2EtN+H
-Pd0(PPh3)2
reductive elimination
2-14
2-15
2-16
step 4
Pd/C, H2
+H+
2-17
2-18
2-19
7
step 5

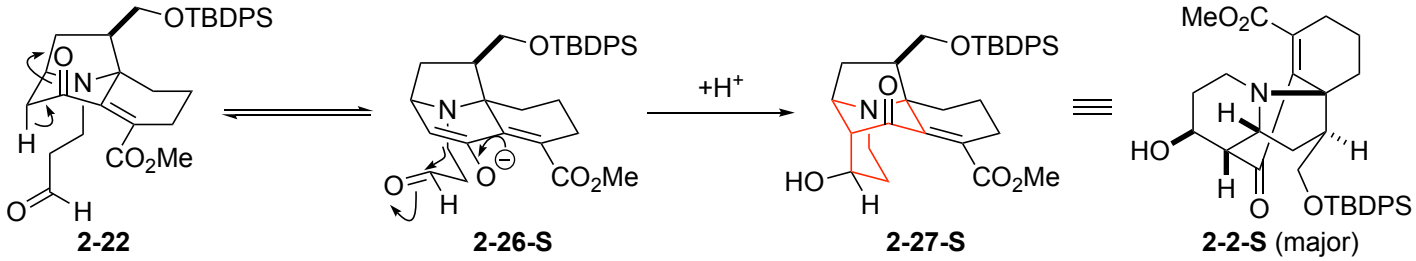

-t-Bu+, CO2
MeO2C
TBDPSO
2-20
step 6
±H+
: TBD
path b
path a
2-21
TBD
OTBDPS
CO2Me
CHO
2-22

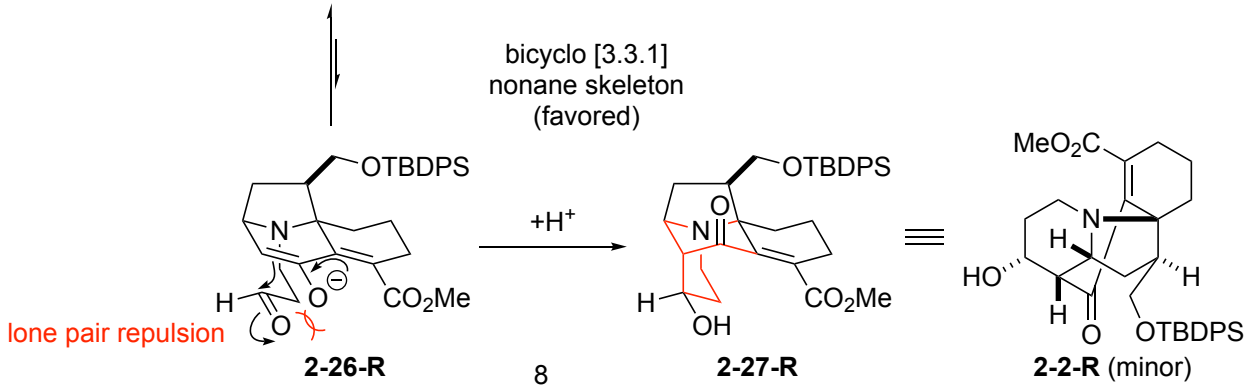
• path a


OTBDPS
CO2Me
2-22
path c
2-23-c
large steric repulsion
OMe
OHC
2-24
(disfavored)


OTBDPS
path d
CO2Me
2-23-d
OHC
2-25
bicyclo [2.2.2]
octane skeleton
(unfavored)

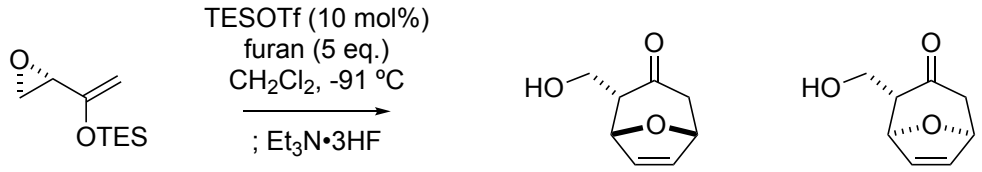
• path b


OTBDPS
CO2Me
2-22
2-26-S
+H+
HO
2-27-S
MeO2C
2-2-S (major)


bicyclo [3.3.1]
nonane skeleton
(favored)
lone pair repulsion
2-26-R
+H+
OH
2-27-R
2-2-R (minor)

Discussion 2-1: [4+3] Cycloaddition

• Epoxide opening



75%

2-28 99% ee

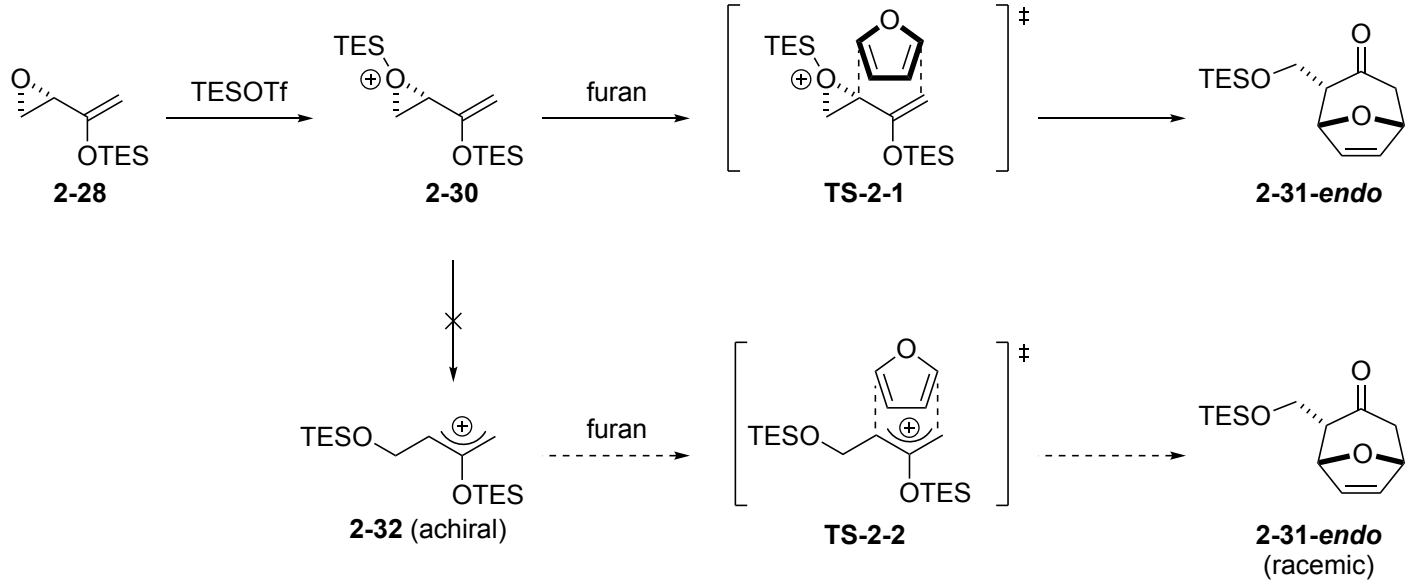
2-29-*endo*:2-29-*exo* = 54:46

2-29-*endo* 92% ee

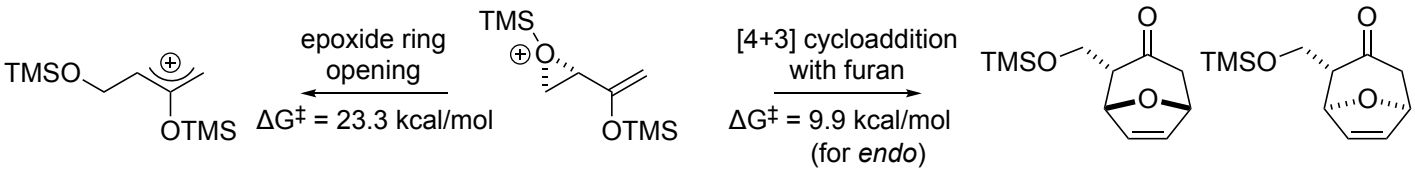
2-29-*exo* 97% ee

Lo, B.; Lam, S.; Wong, W.-T.; Chiu, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 12120.

The erosion of enantiomeric excess was hardly observed. Therefore, achiral oxyallyl cation **2-32** was not the intermediate in this [4+3] cycloaddition.



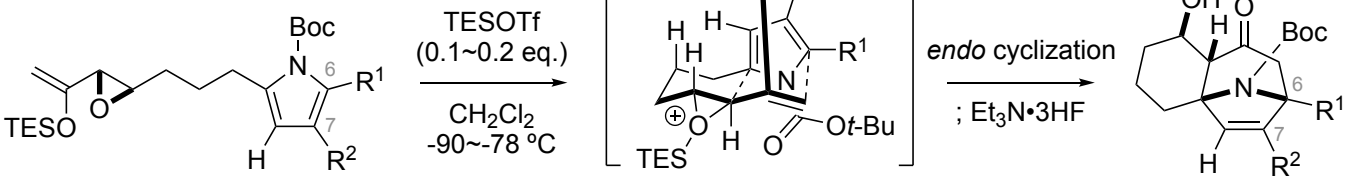
The computational studies also indicated that the epoxide ring didn't open in the absence of furan.



Krenske, E. H.; Lam, S.; Ng, J. P. L.; Lo, B.; Lam, S. K.; Chiu, P.; Houk, K. N. *Angew. Chem. Int. Ed.* **2015**, *54*, 7422.

• Stereo selectivity

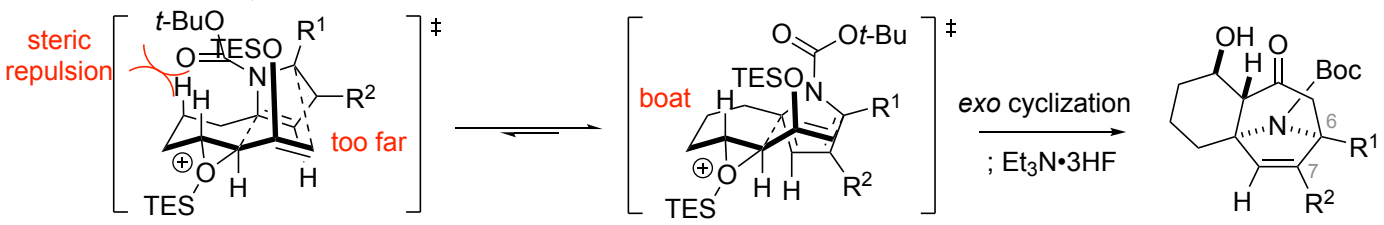
1. C6 or C7 substituted pyrrole unit



2-36
2-36a:R^1=R^2=H
2-36b:R^1=Et, R^2=H
2-36c:R^1=H, R^2=Me

TS-2-3
(favored)

2-37-*endo*
2-37a-*endo*:71%
2-37b-*endo*:74%
2-37c-*endo*:68%

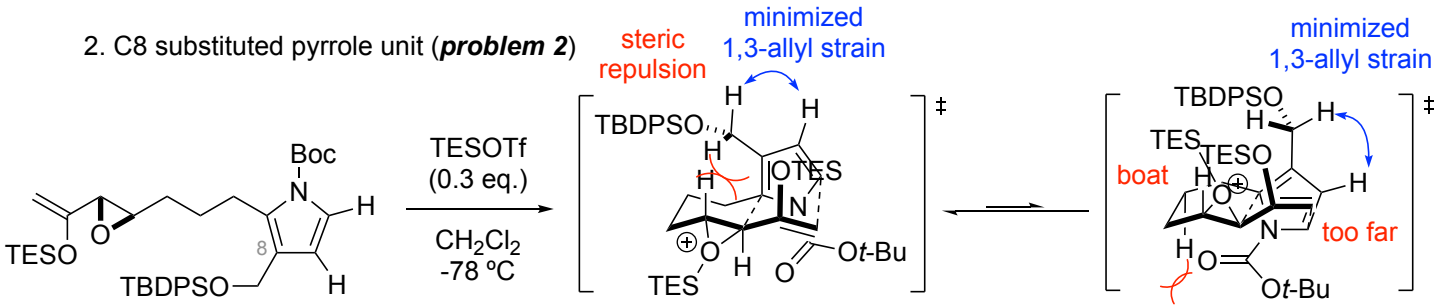


TS-2-4
(disfavored)

TS-2-5
(unfavored)

2-37-*exo*
2-37a-*exo*:6%
2-37b-*exo*:trace
2-37c-*exo*:7%

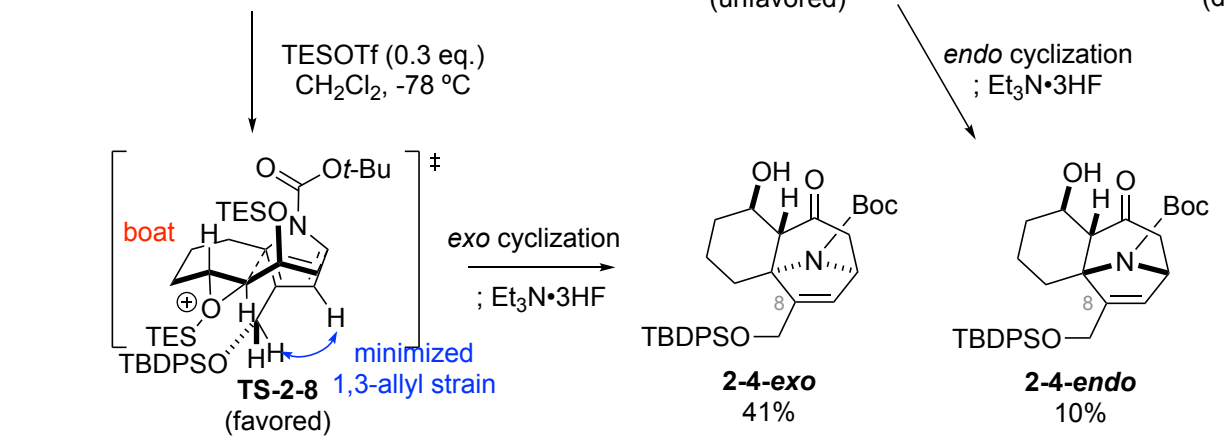
2. C8 substituted pyrrole unit (***problem 2***)



2-1

TS-2-6
(unfavored)

TS-2-7
(disfavored)



TS-2-8
(favored)

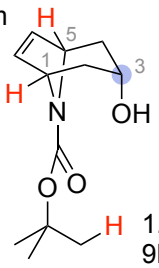
2-4-*exo*
41%

2-4-*endo*
10%

Because of methylene attached to C8, exo cyclization got favored.

Discussion 2-2: Tautomerization

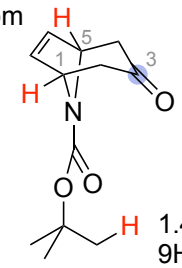
4.50, 4.40 ppm
2H, two br s



1.35 ppm
9H, s

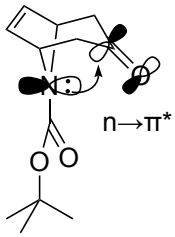
2-38

4.76, 4.69 ppm
2H, two br s



1.44 ppm
9H, s

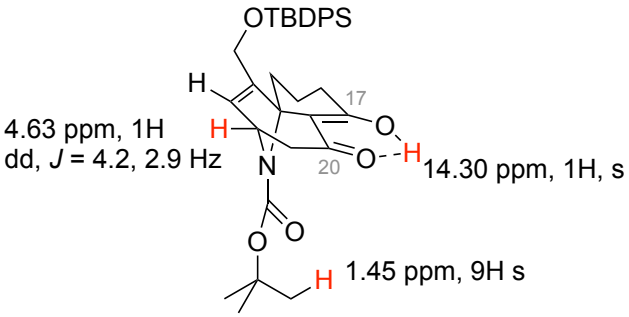
2-39



N atom of **2-39** is more electron-deficient than **2-38** because of the n→π* interaction between N atom and C=O group.

* ^{1}H NMR spectra were recorded in $CDCl_3$.

Hodgson, D. M.; Paruch, E. *Tetrahedron* **2004**, *60*, 5185.



2-9

* ^{1}H NMR spectra were recorded in $CDCl_3$.

Like the above case, N atom of **2-9** is electron-deficient and n→π* interaction between N atom and C20 C=O group might exist. Therefore, C20 C=O is electron-rich and makes the strong hydrogen bond with C17 OH group, which stabilizes the enol formation.