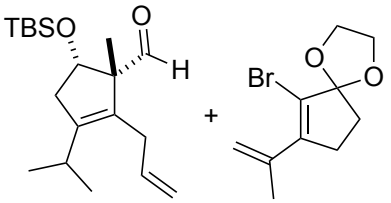
Problem Session (1)

2023.1.7 Shintaro Fukaya

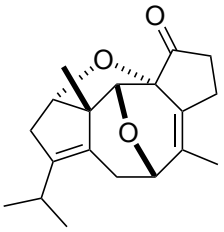
Please provide the highlighted stereochemistries and explain the reaction mechanisms.

1



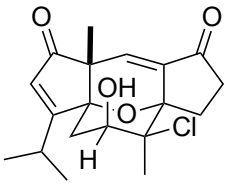
1-1 **1-2**

1. **1-2** (1.05 eq), *t*-BuLi (2.1 eq), Et_2O, −78 °C;
   1-1 (1.0 eq) in Et_2O
2. Grubbs-II (0.1 eq), 1,4-benzoquinone (0.1 eq)
   toluene, 70 °C;
   2 M HCl, 24 °C (54%, 2 steps)
3. NBS (3.5 eq), THF, 0 °C to 24 °C (60%)
4. AgTFA (2.9 eq), $MeNO_2$, 24 °C (88%)



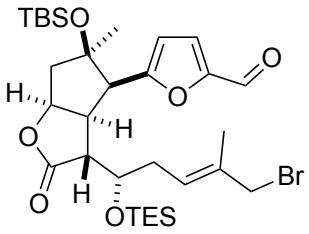
1-3

5. BCl_3 (3.0 eq), CH_2Cl_2, 0 °C to 24 °C
6. *m*-CPBA (1.2 eq), benzene, 24 °C
7. DMP (1.13 eq), CH_2Cl_2, 24 °C (70%, 3 steps)
8. DBU (2.0 eq), MeOH, 24 °C (68%)



1-4

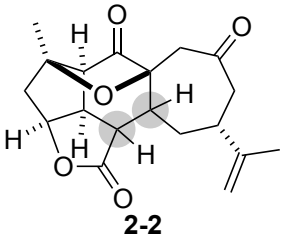
2



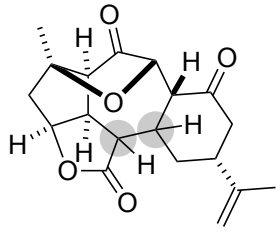
2-1

1. $CrCl_2$ (20 eq), MS 4A, THF, 23 °C (82%)
2. BF_3•OEt_2 (5.0 eq), Et_3SiH (20 eq), CH_2Cl_2, −40 °C;
   n-Bu_4NF (10 eq), THF (74%)
3. DMP (2.0 eq), CH_2Cl_2, 23 °C
4. $NaBH_4$ (3.0 eq), $CaCl_2$ (10 eq), MeOH, 0 °C (90%, 2 steps)
5. Ac_2O (5.0 eq), Et_3N (10 eq), DMAP (1.0 eq)
   CH_2Cl_2, 23 °C (91%)
6. *n*-Bu_4NF (2.0 eq), THF, 65 °C (86%)
7. O_2, rose bengal (cat.), *hv*, CH_2Cl_2/MeOH, −78 °C;
   Me_2S, −78 °C to 0 °C;
   p-TsOH•H_2O (0.1 eq), CH_2Cl_2, 23 °C (88%)
8. $LiN(TMS)_2$ (4.0 eq), THF, −78 °C (46%)
   2-2 : 2-3 = ~3 : 1

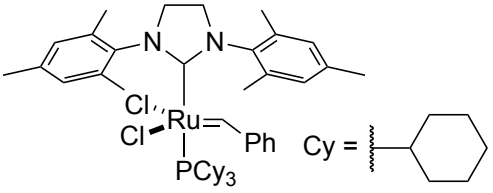
hv : 400 W high pressure sodium lamp



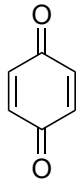
2-2



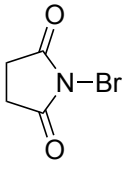
2-3



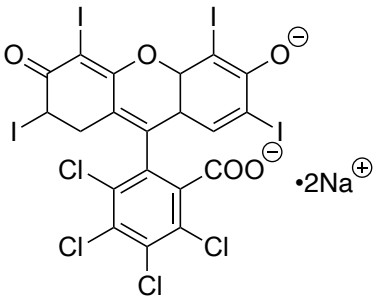
Grubbs-II



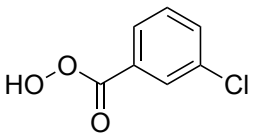
1,4-benzoquinone



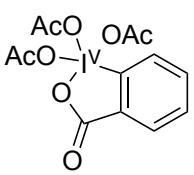
NBS



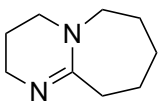
rose bengal



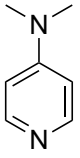
m-CPBA



DMP



DBU



DMAP

Problem Session (1) -Answer-

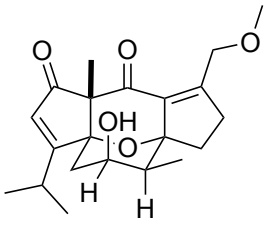
2023.1.7 Shintaro Fukaya

Topic: **Recent works by John, L. Wood**

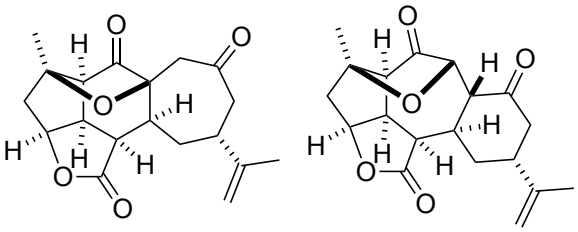
Prof. John L. Wood

1985-1991: Ph.D., Organic Chemistry, University of Pennsylvania
(Prof. Amos B. Smith III)
1991-1993: American Cancer Society Postdoctoral Fellow, Harvard University
(Prof. Stuart L. Schreiber)
1993-1997: Assistant Professor of Chemistry, Yale University
1997-1998: Associate Professor of Chemistry, Yale University
1998-2006: Professor of Chemistry, Yale University
2006-2013: A. I. meyers Professor of Chemistry, Colorado State University
2013-Present: Robert A. Welch Distinguished Professor and Cancer Prevention Research Institute Scholar, Baylor University

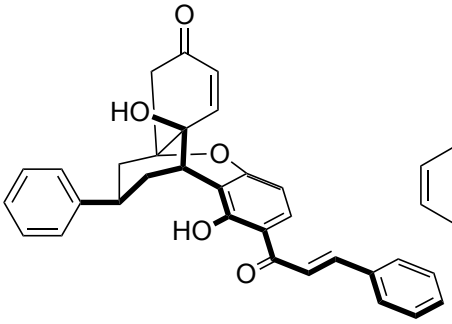
Total Synthesis:

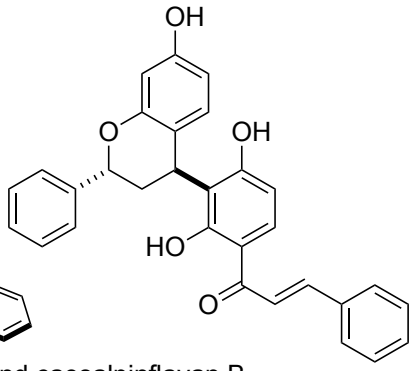


(+)-alterbrassicicene C
(**Problem 1**)
J. Am. Chem. Soc. **2022**, in press.

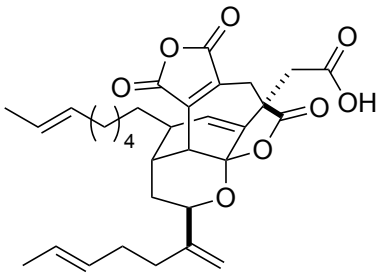


(−)-sinulochmodin C and (+)-ineleganolide
(**Problem 2**)
J. Am. Chem. Soc. **2022**, *144*, 20539.

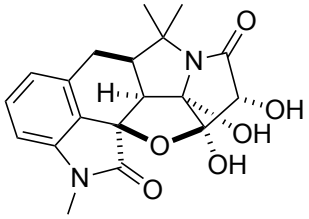




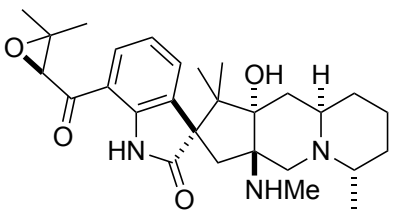
caesalpinnone A and caesalpinflavan B
J. Am. Chem. Soc. **2019**, *141*, 10082.



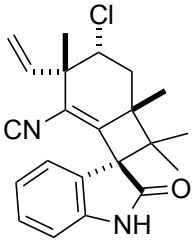
(±)-phomoidride D
(180111_PS_Akira_Tomiyama)
Angew. Chem. Int. Ed. **2018**, *57*, 1991.



(±)-aspergilline A
(180111_PS_Akira_Tomiyama)
J. Am. Chem. Soc. **2017**, *139*, 18504.

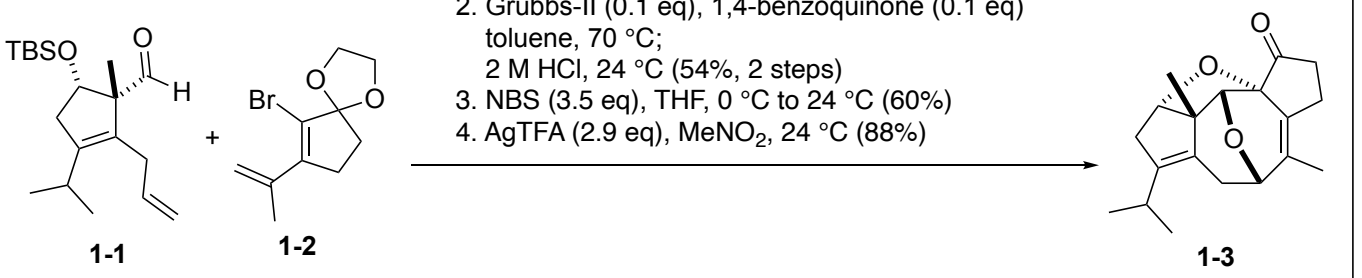


(+)-citrinadin B
(171209_PS_Shinsuke_Koshimizu)
J. Am. Chem. Soc. **2013**, *135*, 10890.

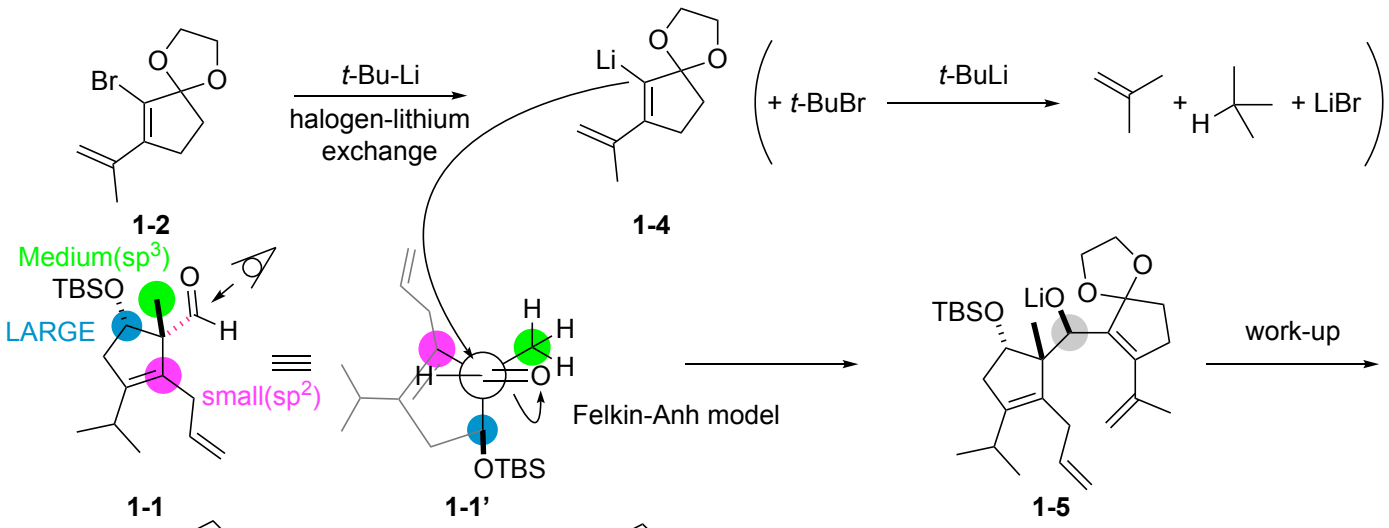


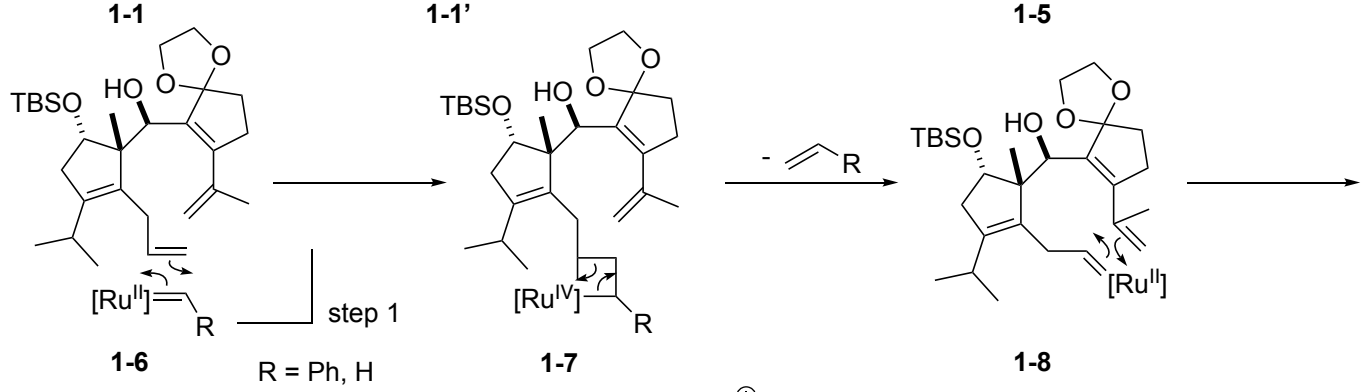
(±)-welwintindolinone A Isonitrile
(080913_PS_Yuuki_Amaoka)
J. Am. Chem. Soc. **2008**, *130*, 2087.

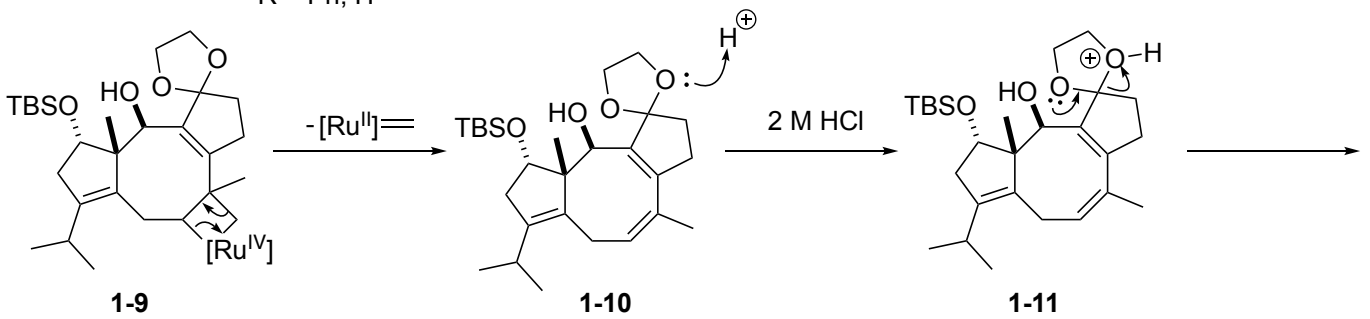
1 (Total synthesis of (+)-Alterbrassicicene C)



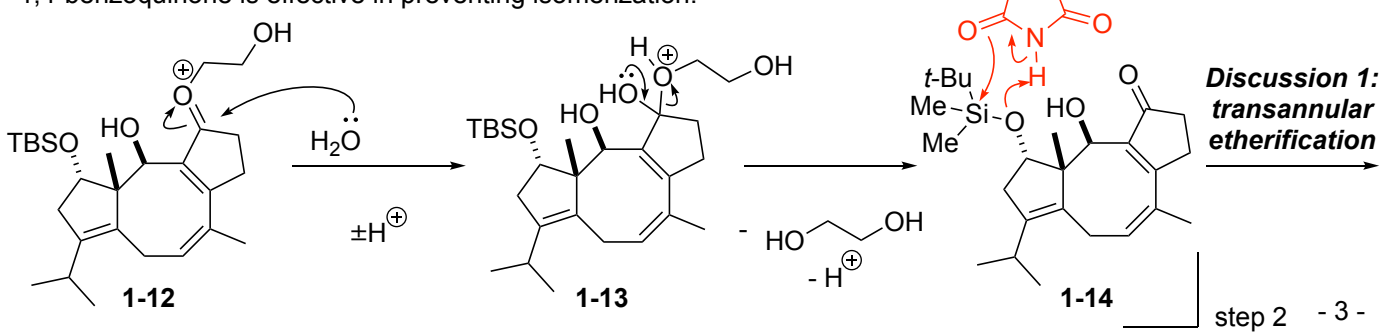
Sims, N. J.; Bonnet, W. C.; Lawson, D. M.; Wood, J. L. *J. Am. Chem. Soc.* **2022**, in press.

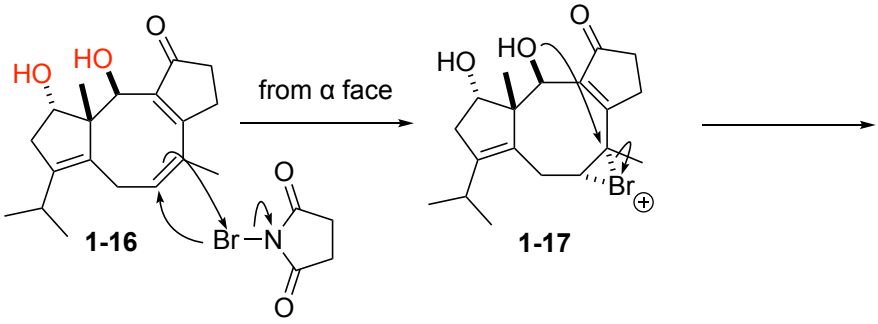


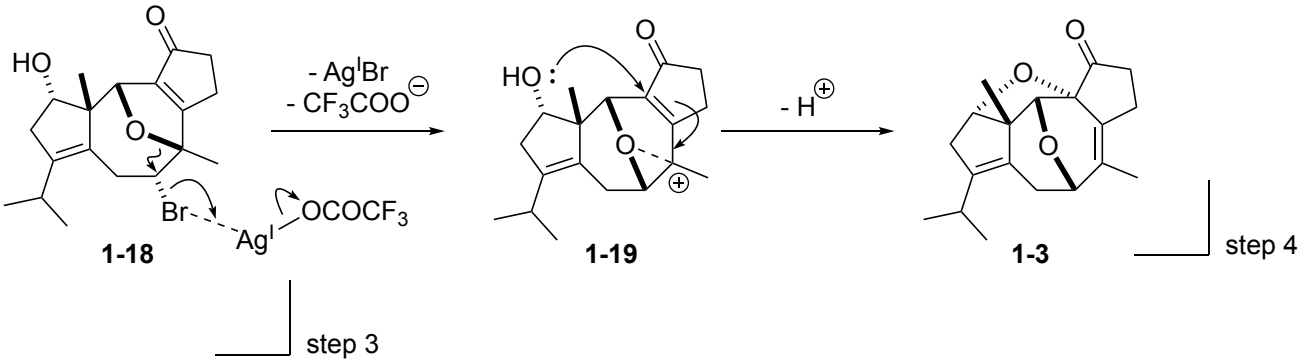




Ruthenium hydride species generates *in situ*, and causes olefin isomerization. 1,4-benzoquinone is effective in preventing isomerization.[ref.1]

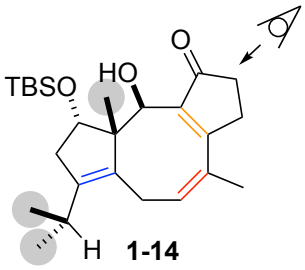




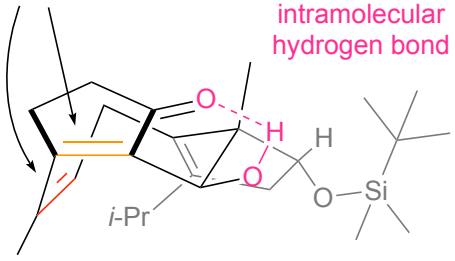


Discussion 1: transannular haloetherification

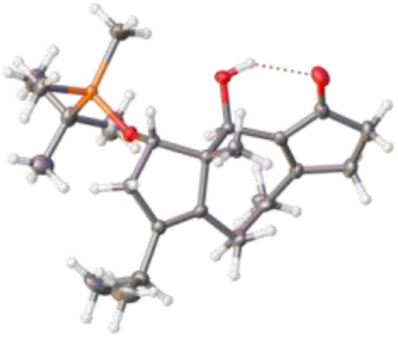
These olefins are not conjugated.



≡



1-14a
(most stable conformation)

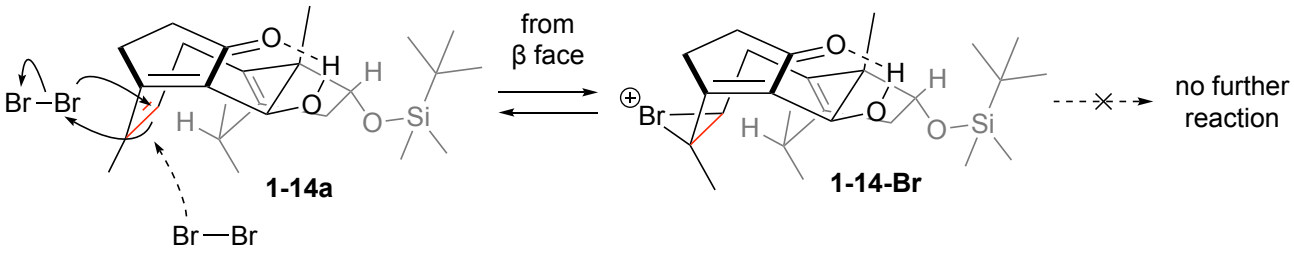


X-ray structure of **1-14**

Blue olefin is shielded by highlighted methyl groups.

Orange olefin : electron poor

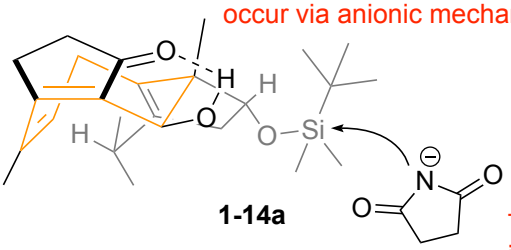
→ Red olefin is only reactive to Br_2 (NBS).



cannot access from α face

To react with Br_2 from α face, conformation change is needed.

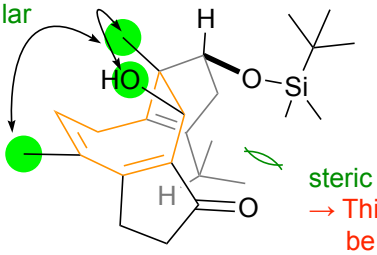
Removal of TBS group wouldn't occur via anionic mechanism.



1-14a

transannular strain

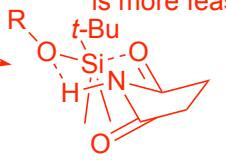
eclipsed conformation



1-14b
(unstable)

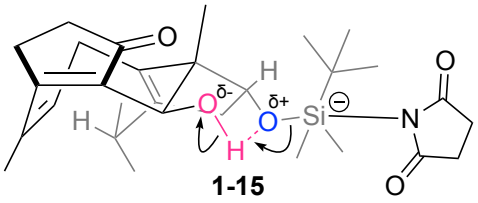
steric repulsion
→ This effect seems to be not so large.
It cannot be determined when the removal of TBS group occur.

This type of TS is more feasible.

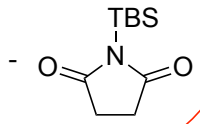


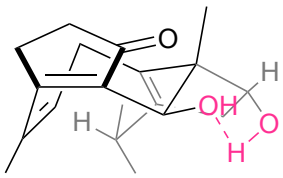
In the presence of TBS group, conformation change to **1-14b** cannot occur.

Formation of intramolecular hydrogen bond reduces the electron density of O.
This makes the removal of TBS group easier.

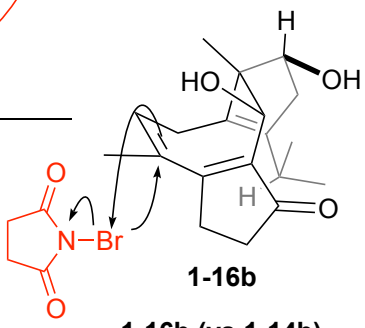


1-15

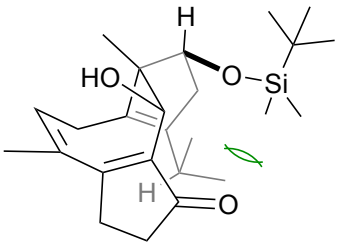




1-16a



1-16b



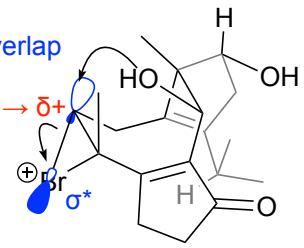
1-14b

The concentration of Br_2 should be very low, so NBS acts as an electrophile.

1-16b (vs 1-14b)
no steric repulsion between OTBS and enone moiety.
→ conformation change to **1-16b** can occur.

poor orbital overlap

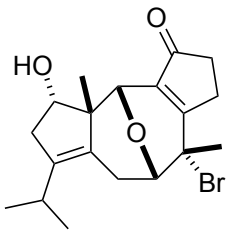
less stable → δ+



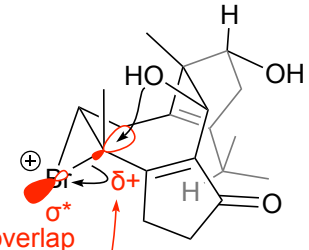
1-17a

Br_2 from α face

6-exo



1-20
(not obtained)

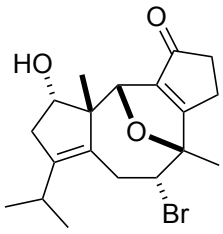


1-17b

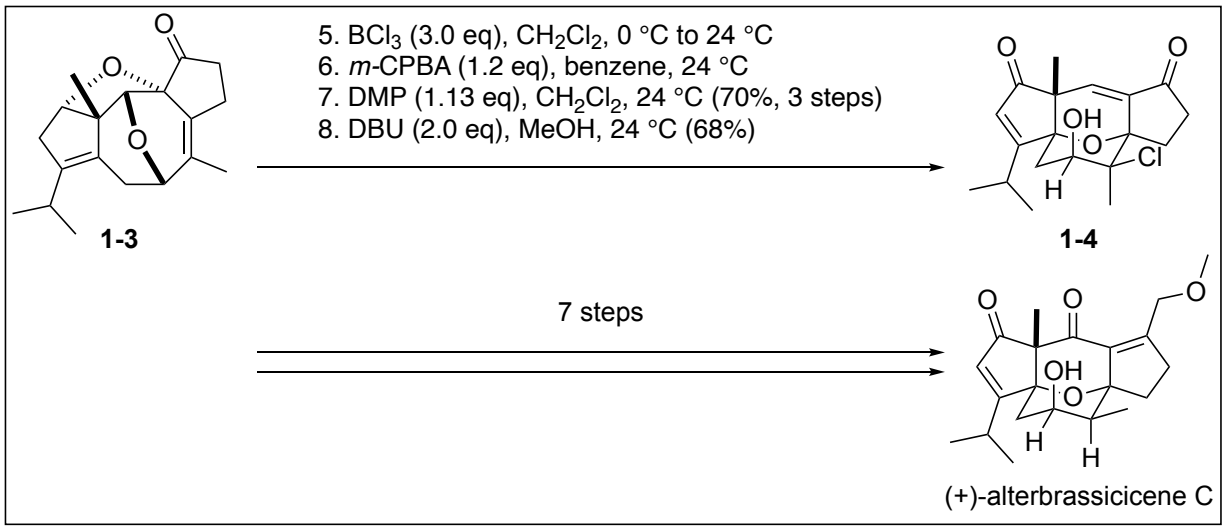
good orbital overlap

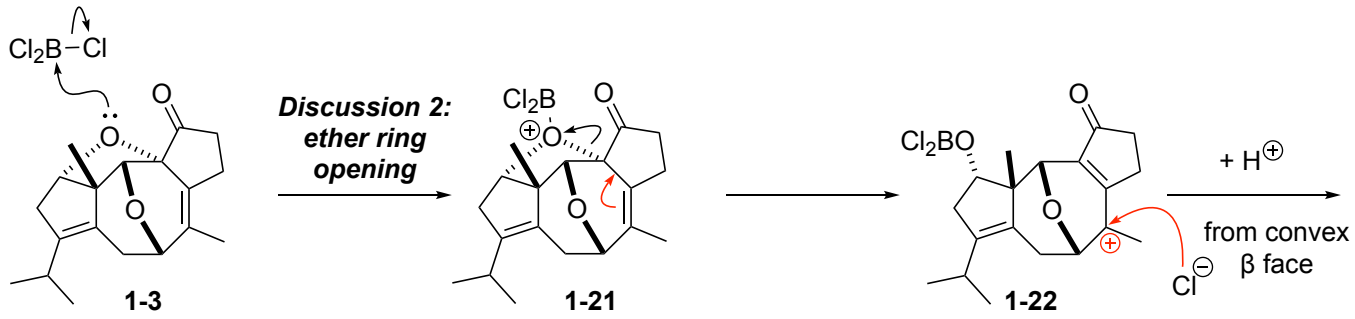
more stable

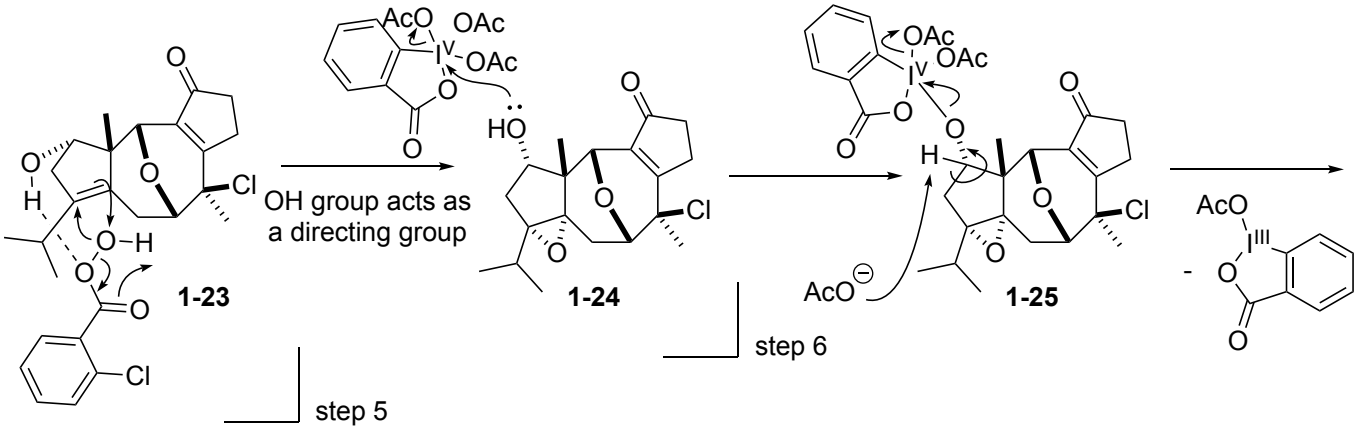
5-endo

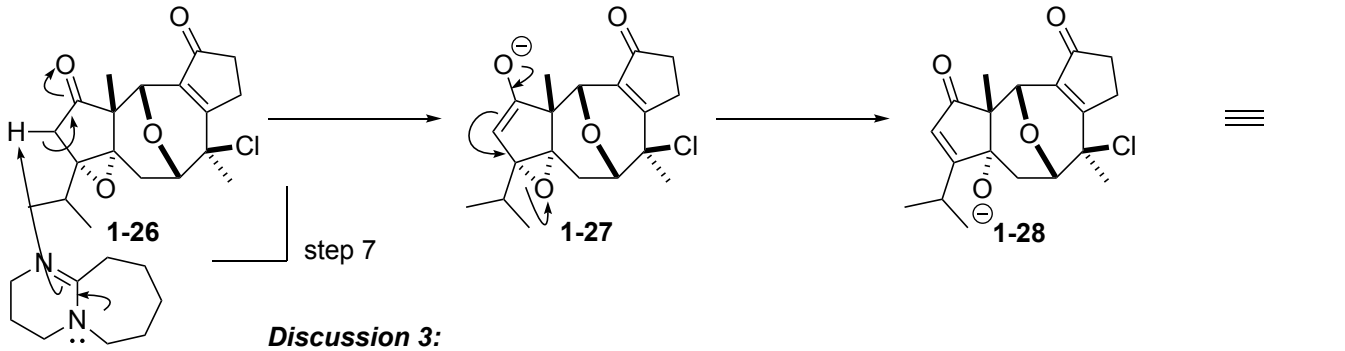


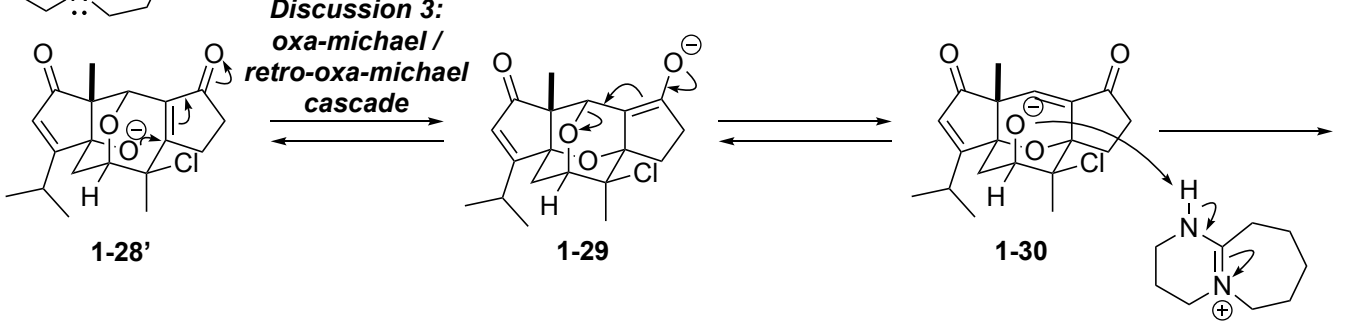
1-18
(only obtained)

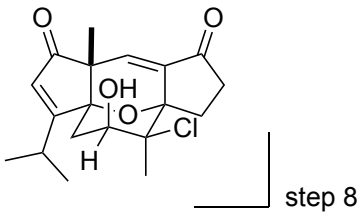

5. BCl3 (3.0 eq), CH2Cl2, 0 °C to 24 °C
6. m-CPBA (1.2 eq), benzene, 24 °C
7. DMP (1.13 eq), CH2Cl2, 24 °C (70%, 3 steps)
8. DBU (2.0 eq), MeOH, 24 °C (68%)
1-3
1-4
7 steps
(+)-alterbrassicicene C


Cl2B–Cl
1-3
Discussion 2:
ether ring
opening
Cl2B
1-21
Cl2BO
1-22
+ H⊕
from convex
β face
Cl⊖


1-23
AcO
OAc
OH group acts as
a directing group
1-24
step 6
1-25
AcO⊖
step 5


1-26
step 7
1-27
1-28
≡

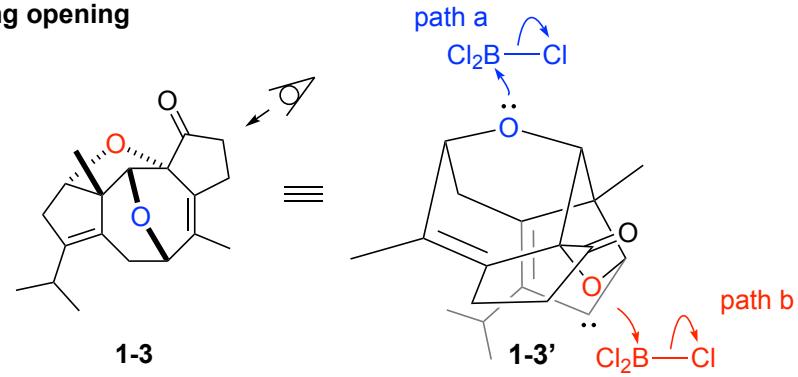

Discussion 3:
oxa-michael /
retro-oxa-michael
cascade
1-28'
1-29
1-30



step 8

1-4

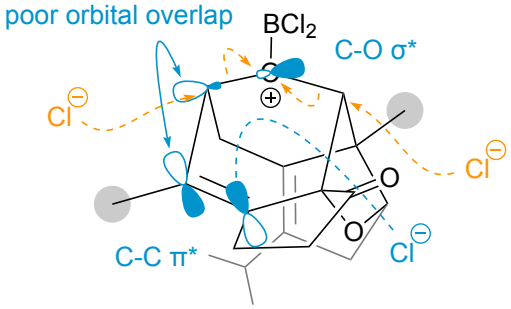
Discussion 2: ether ring opening



1-3 **1-3'**

Two oxygen atoms of ether have possibilities to react with BCl_3.

path a



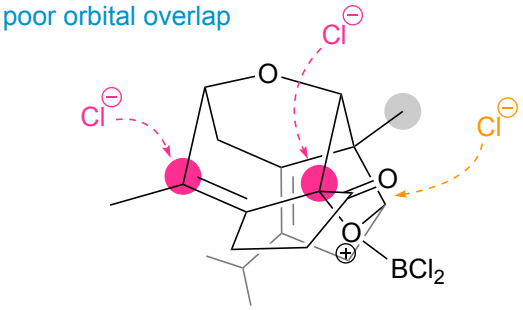
1-31

S_N2 or S_N1 reactions wouldn't proceed because of the steric hindrance by highlighted methyl groups.

S_N2' reaction wouldn't proceed because of the poor orbital overlap between C-C π* and C-O σ*.

path b

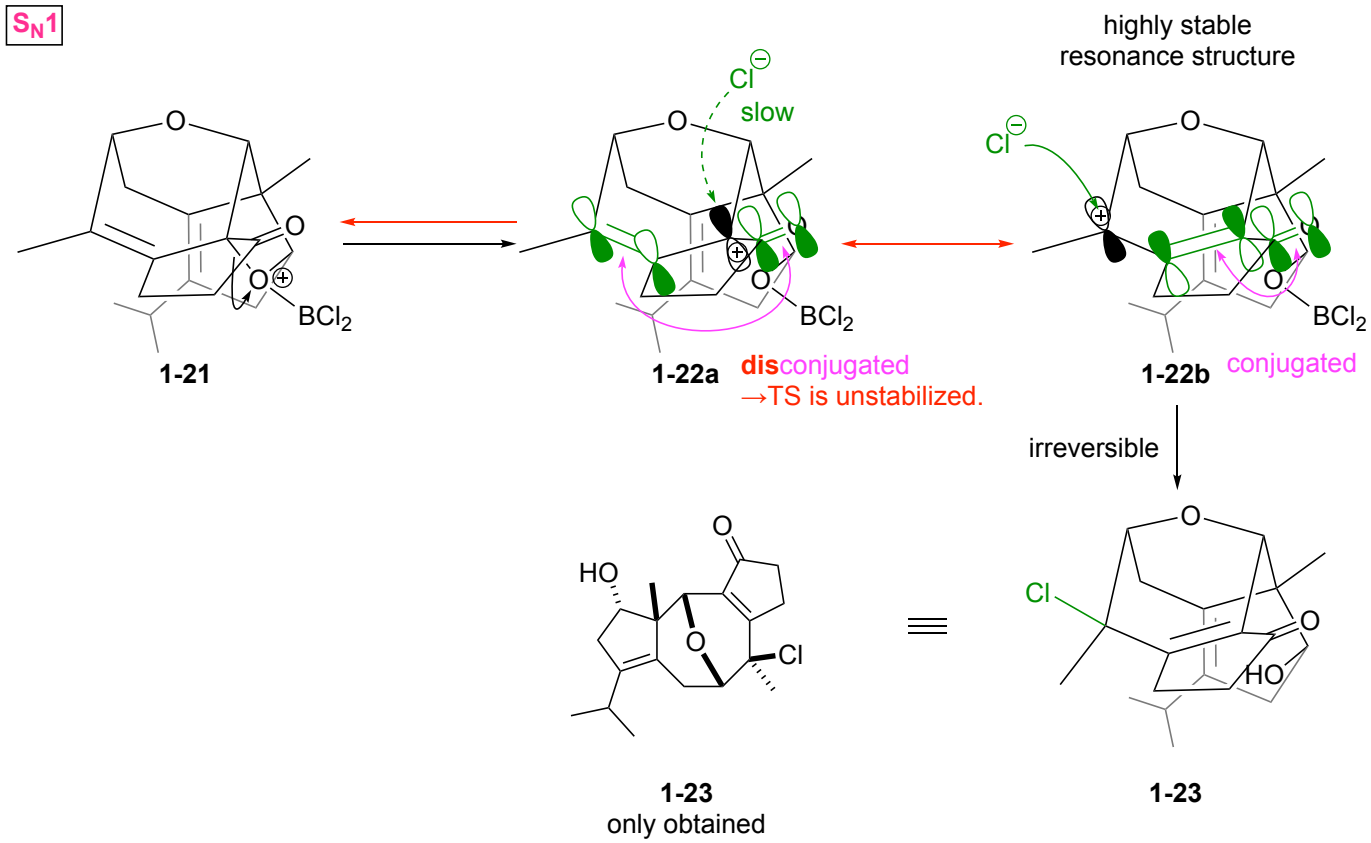
S_N2 (S_N1) and S_N2'



1-21

S_N2 (or S_N1) reaction would't proceed because of the steric repulsion of highlighted methyl groups.

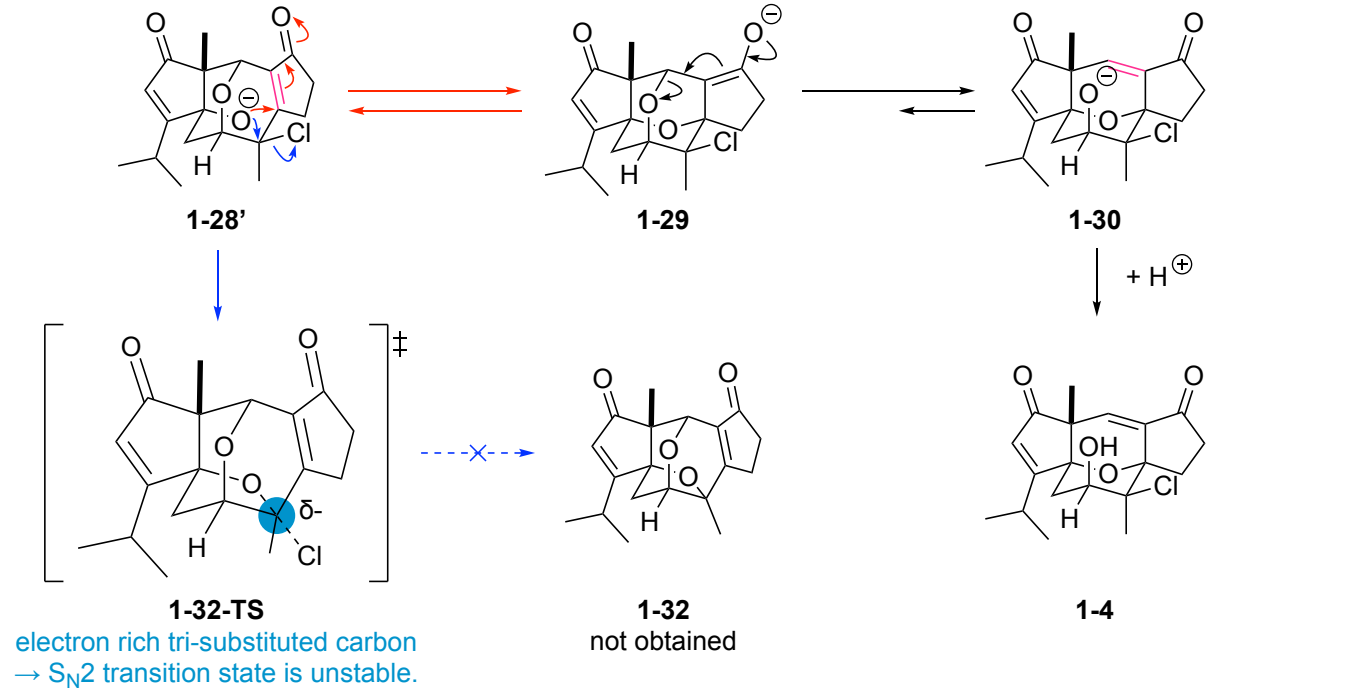
S_N2 and S_N2' reactions wouldn't proceed against highly substituted carbon because the anionic transition state is unstable.



Discussion 3: oxa-michael/retro-oxa-michael cascade

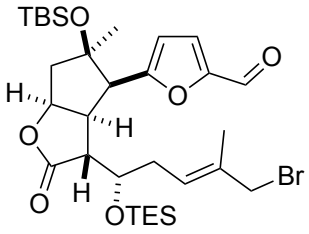
tetra-substituted olefin:
Right 5-membered ring is composed of three C(sp^2) and two C(sp^3).
→ higher ring strain

tri-substituted olefin:
Right 5-membered ring is composed of two C(sp^2) and three C(sp^3).
→ lower ring strain (favored)



Reference:
1. Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

2 (Total syntheses of (+)-ineleganolide and (−)-sinulochmodin C)

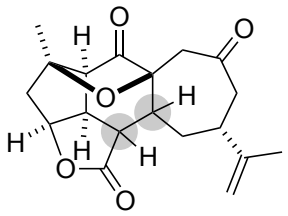


2-1

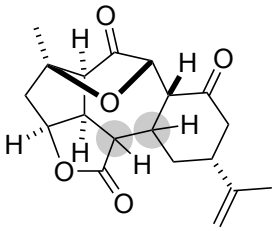
1. $CrCl_2$ (20 eq), 4ÅMS, THF, 23 °C (82%)
2. BF_3•OEt_2 (5.0 eq), Et_3SiH (20 eq), CH_2Cl_2, −40 °C; *n*-Bu_4NF (10 eq), THF (74%)
3. DMP (2.0 eq), CH_2Cl_2, 23 °C
4. $NaBH_4$ (3.0 eq), $CaCl_2$ (10 eq), MeOH, 0 °C (90%, 2 steps)
5. Ac_2O (5.0 eq), Et_3N (10 eq), DMAP (1.0 eq) CH_2Cl_2, 23 °C (91%)
6. *n*-Bu_4NF (2.0 eq), THF, 65 °C (86%)
7. O_2, rose bengal (cat.), *hv*, CH_2Cl_2/MeOH, −78 °C; Me_2S, −78 °C to 0 °C; *p*-TsOH•H_2O (0.1 eq), CH_2Cl_2, 23 °C (88%)
8. $LiN(TMS)_2$ (4.0 eq), THF, −78 °C (46%)

2-2 : 2-3 = ~3 : 1

hv : 400 W high pressure sodium lamp

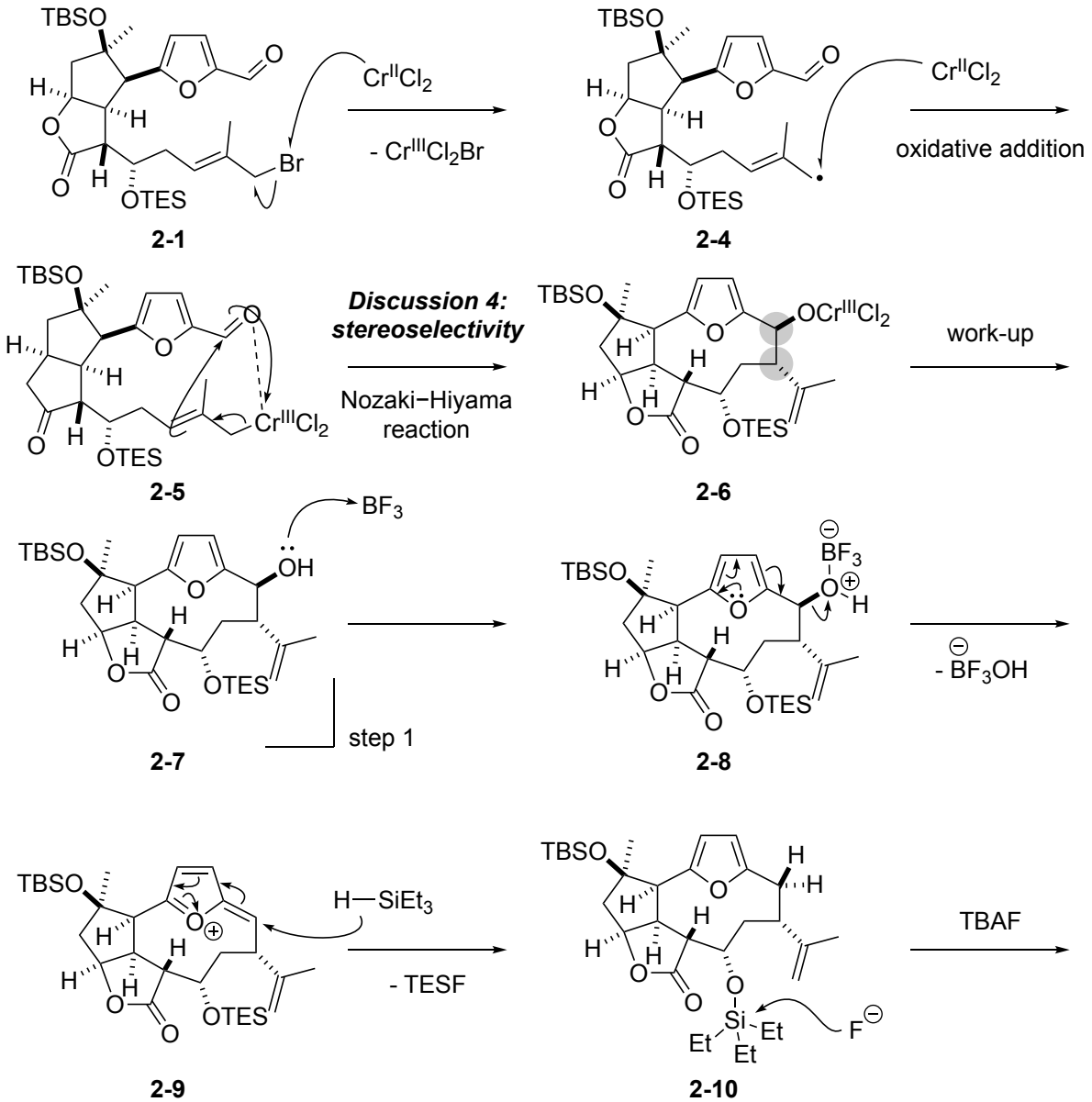


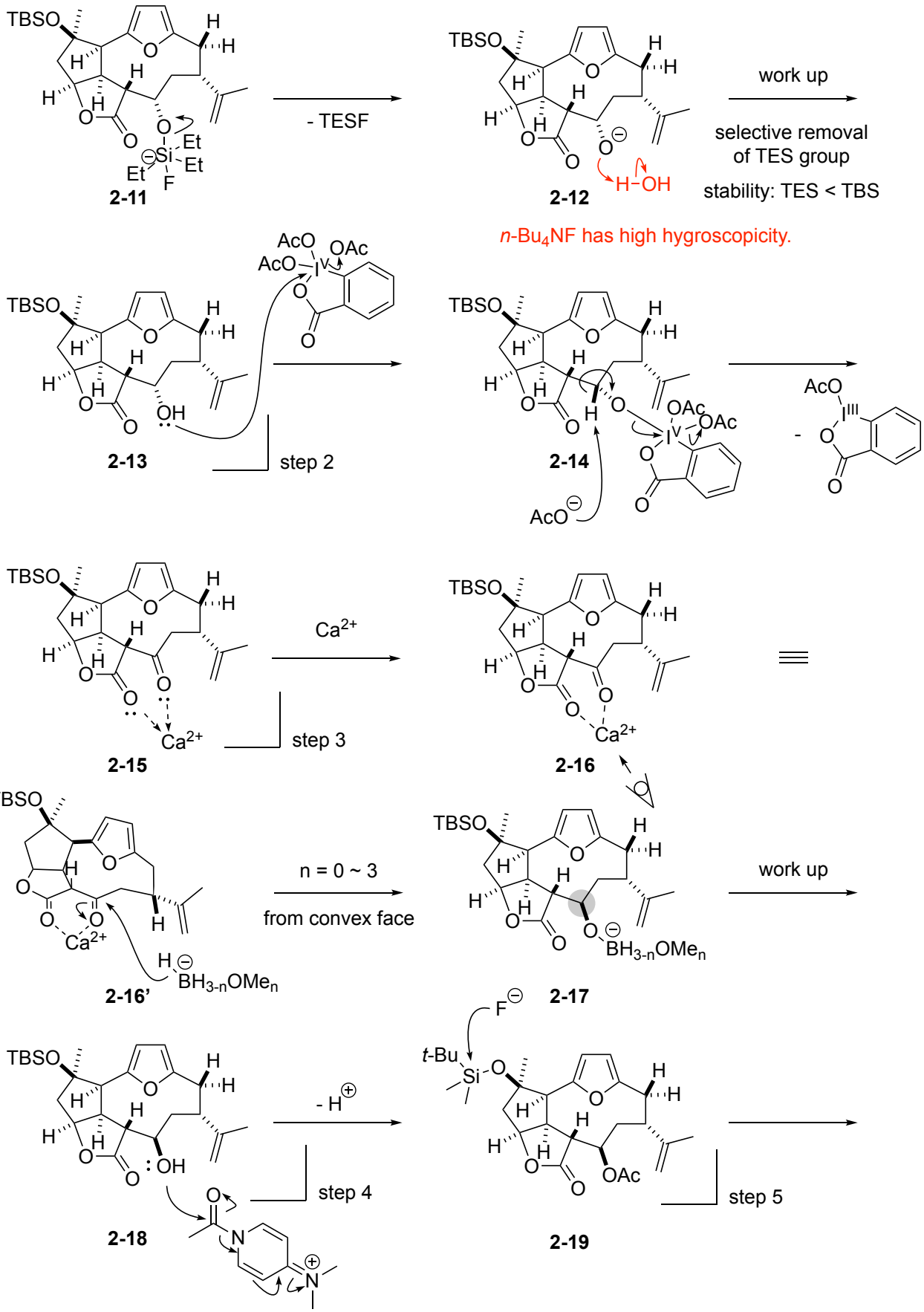
2-2 ((-)-sinulochmodin C)

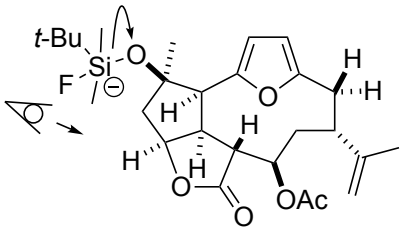


2-3 ((+)-ineleganolide)

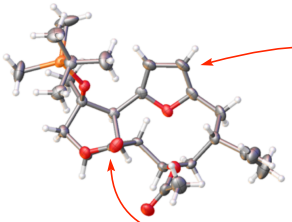
(Tuccinardi, J. P.; Wood, J. L. *J. Am. Chem. Soc.* **2022**, *144*, 20539.)




TBSO
- TESF
2-11
2-12
work up
selective removal of TES group
stability: TES < TBS
n-Bu4NF has high hygroscopicity.
AcO
OAc
2-13
step 2
2-14
2-15
Ca2+
step 3
2-16
2-16'
n = 0 ~ 3
from convex face
BH3-nOMen
2-17
work up
- H+
step 4
2-18
t-Bu
Si
F
OAc
2-19
step 5



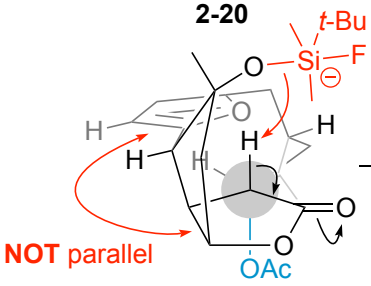
2-20



This furan group and 5-membered ester ring is not parallel.

X-ray structure of **2-20**

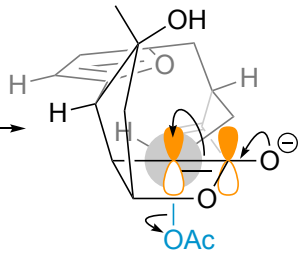
large steric repulsion



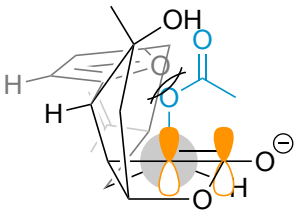
NOT parallel

2-22

Z selective E1cB elimination



2-22a

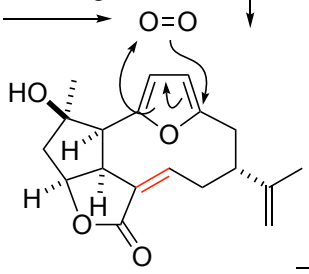


2-22b

Conformation change won't occur.

hv
rose bengal
$^3O_2$

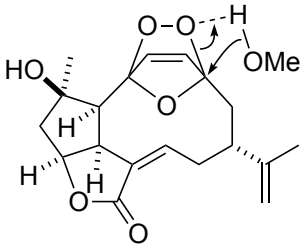
- AcOH



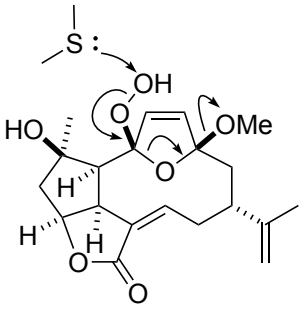
2-23

from α or β face

step 6



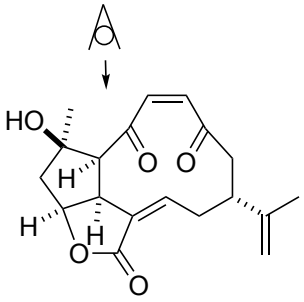
2-24



2-25

Me_2S

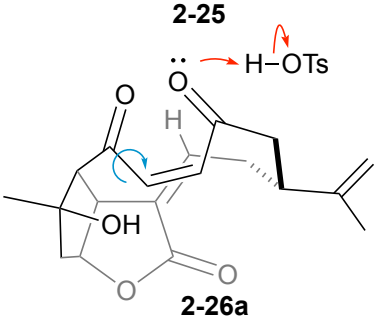
- DMSO, MeOH



2-26

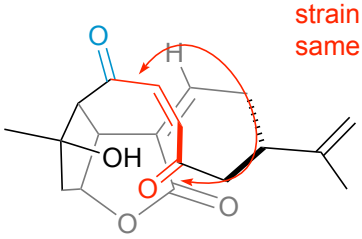
≡

Because of the large 1,3-allylic strain, these bonds are not on the same plane, and not conjugated.



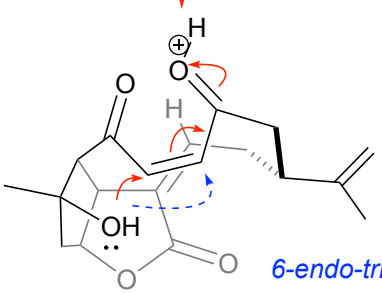
2-26a

bond rotation



2-26b

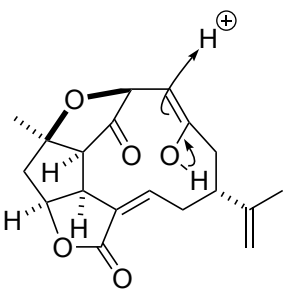
This proper conformation to *6-endo-trig* is too unstable.



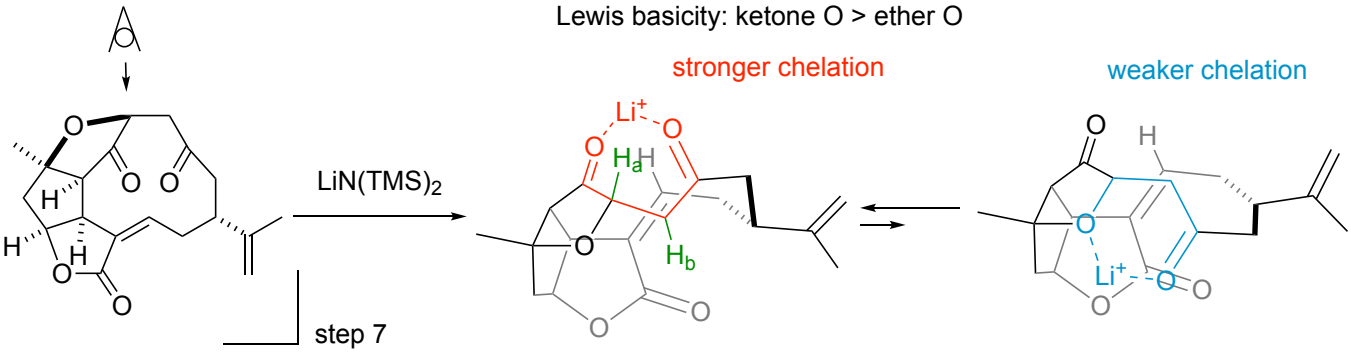
2-27

6-endo-trig → too far

5-exo-trig

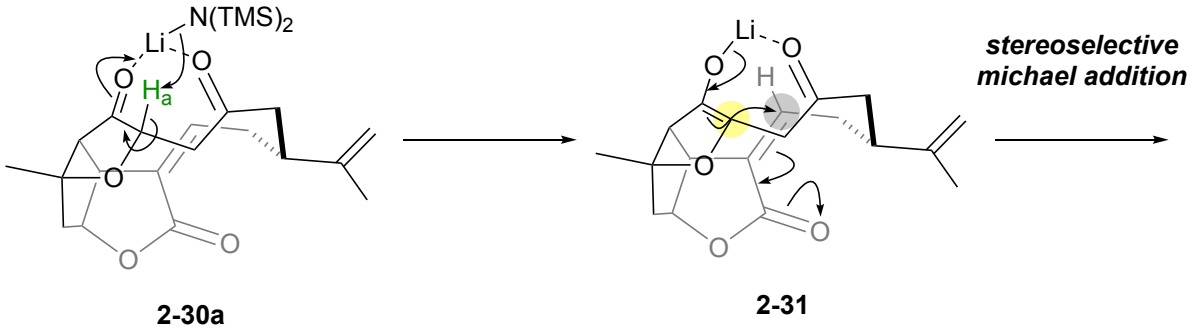


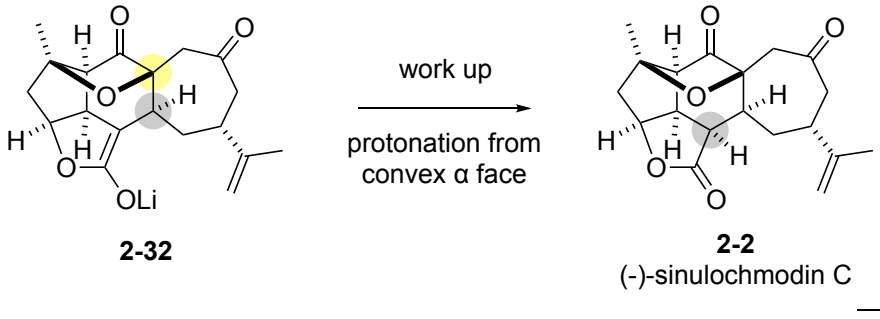
2-28



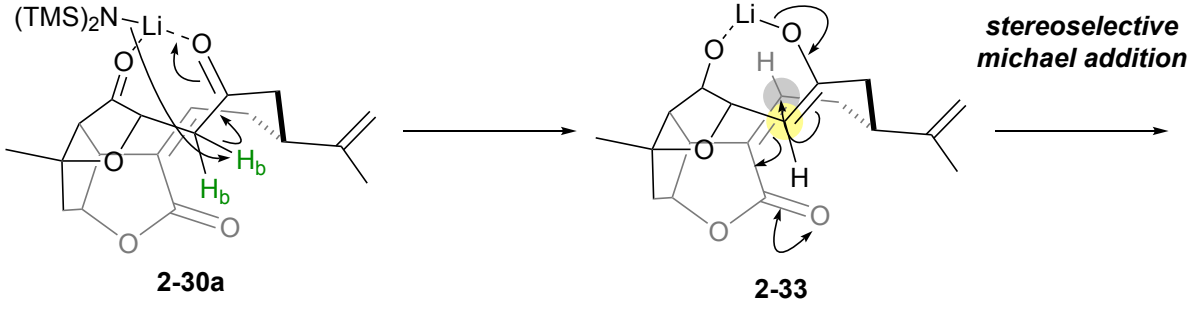
H_a is more acidic than H_b because of the inductive effect of ether O.
→ **2-2** is more favored than **2-3.** (**2-2** : **2-3** = ~3 : 1)

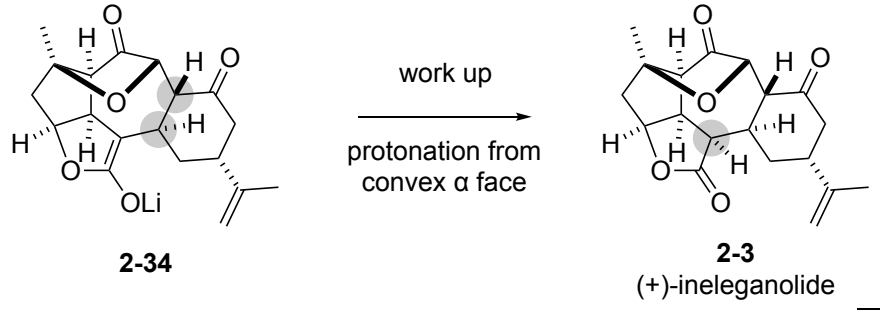
To **2-2** ((−)-sinulochmodin C)





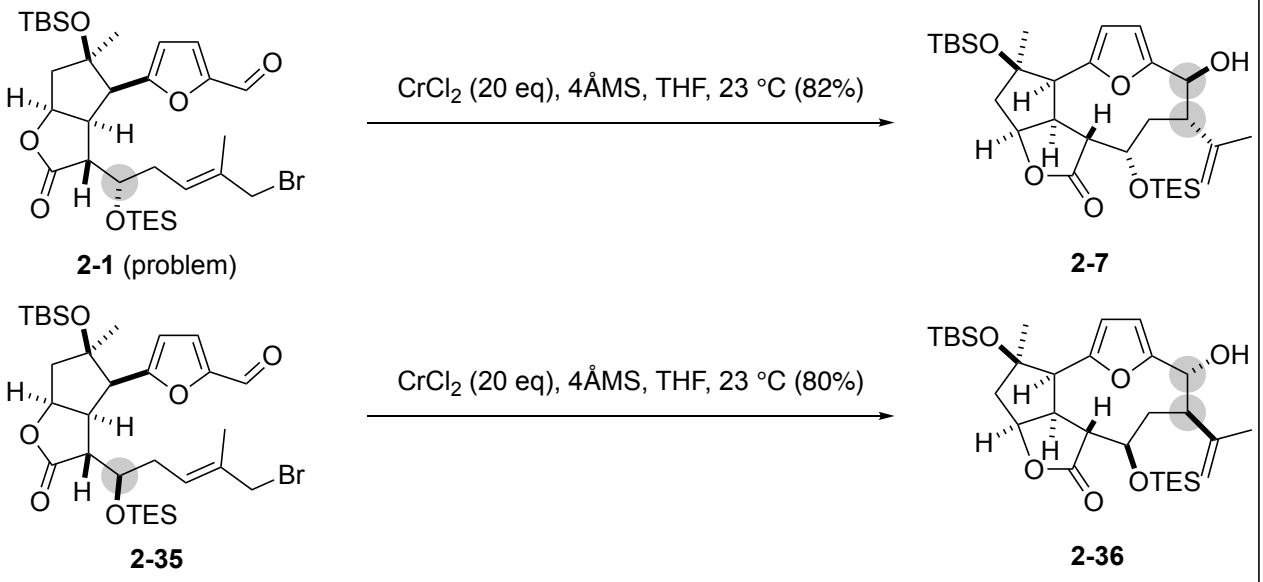
To **2-3** ((+)-ineleganolide)





Discussion 4: Stereoselective Nozaki−Hiyama reaction

results

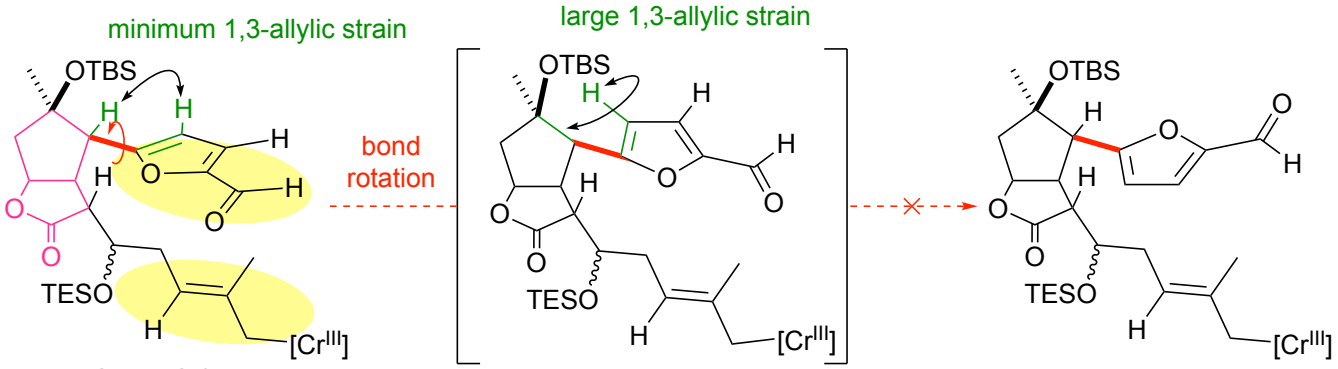


2-1 (problem) **2-7**

2-35 **2-36**

The stereochemistry of OTES group affects the stereochemistries of products.

1. conformation analysis



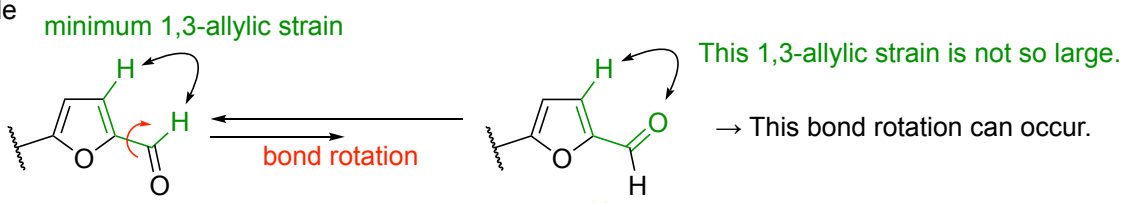
2-5 or 2-37

$[Cr^{III}] = Cr^{III}Cl_2$

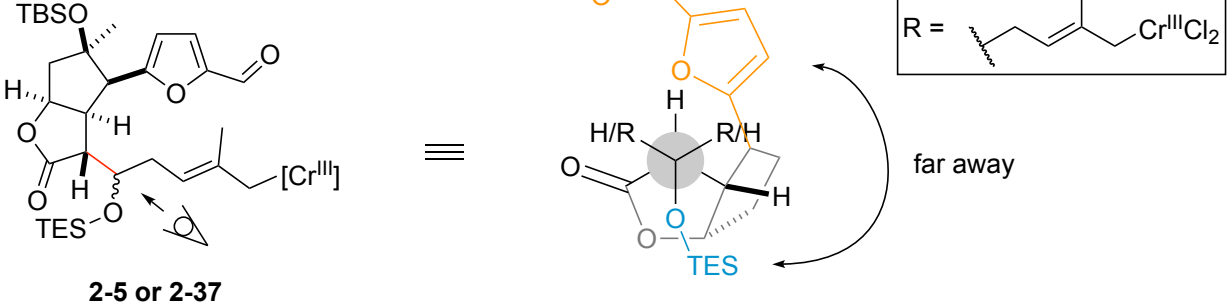
5,5-*cis*-ring system is rigid.
→ Stereoselectivity depends on how highlighted groups come close.

To form this conformation, it is needed to rotate red bond via unstable conformation (large 1,3-allylic strain).

・aldehyde



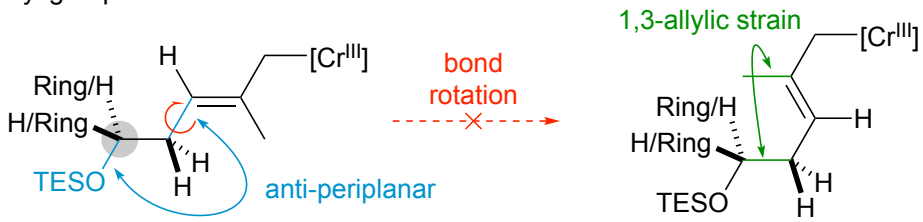
2. OTES group



2-5 or 2-37

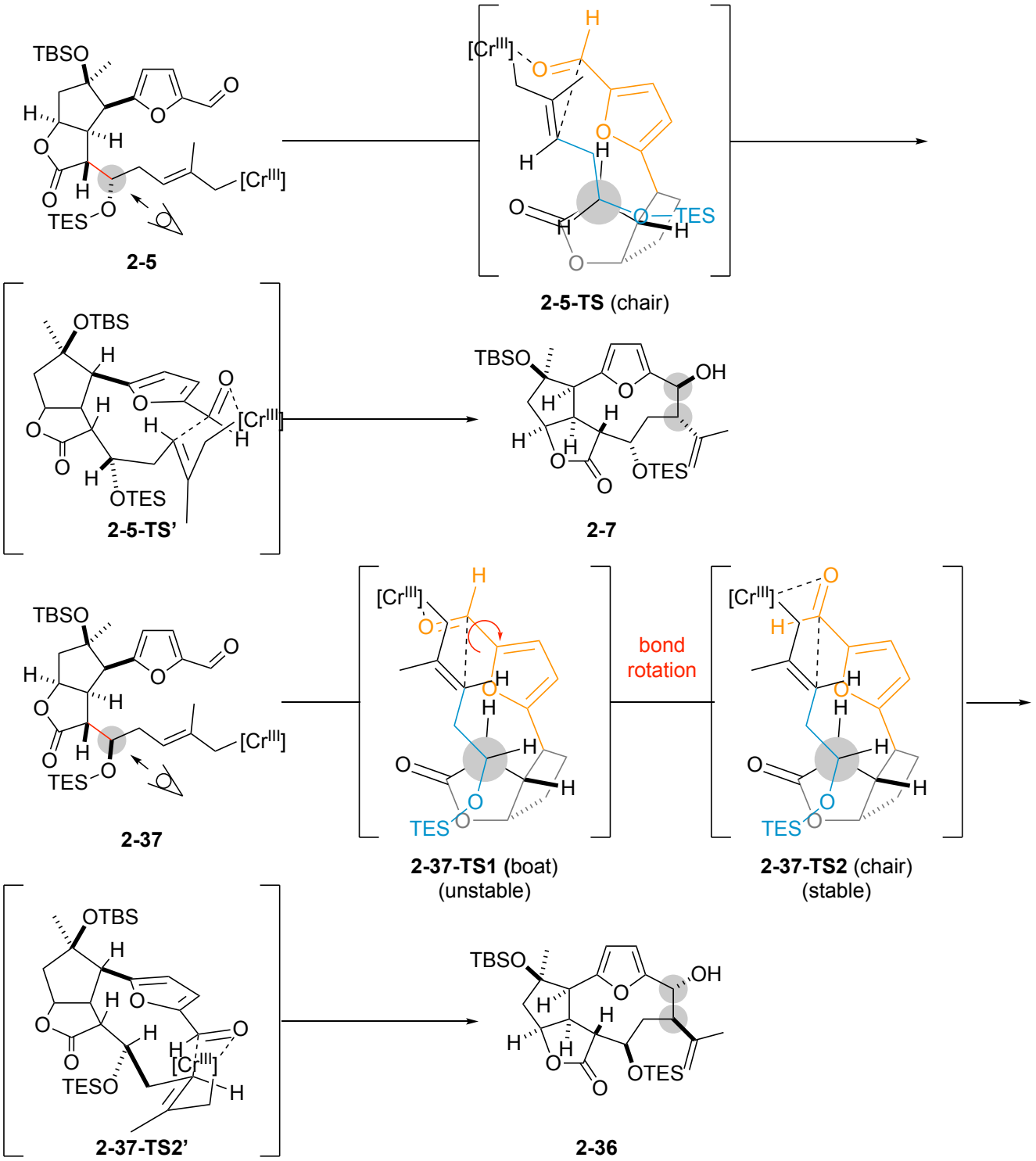
OTES group avoids the steric repulsion with furan group.
→ OTES group is directed towards the outside of the ring system.

3. Alkyl group



Considering the ***results***, OTES group has the larger steric hindrance than Ring system.
Therefore, the conformation which blue C-C bond and C-O bond are anti-periplanar is most stable.
In addition, bond rotation wouldn't occur because of the generation of large 1,3-allylic strain.

4. Stereoselective Nozaki−Hiyama reaction



・10-membered ring transsition state

OTES group possesses pseudo-equatorial.