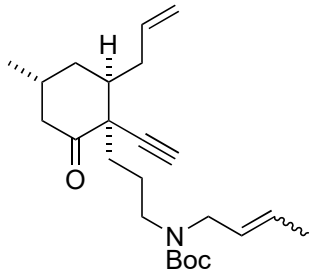
Problem Session (5)

2019.08.03. Yinghua Wang

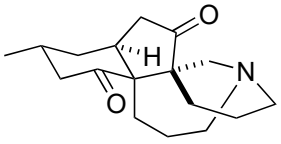
Please provide each reaction mechanism.

1



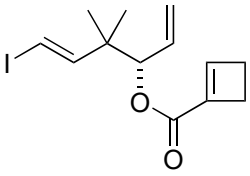
1-1

1. G-II cat. (20 mol%)
   $(CH_2Cl)_2$, reflux;
   H_2 (10 atom), 70 °C, 52%
2. BH_3•THF (10 eq.)
   THF, 50 °C;
   evaporation;
   IBX (10 eq.), EtOAc, reflux
3. 0.5 M HCl aq. (3 eq.)
   37% HCHO aq. (20 eq.)
   EtOH, reflux, 64% (2 steps)



1-2

2

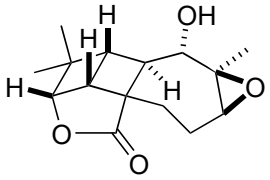


2-1
($C_{13}H_{17}O_2I$)

1. G-II cat. (15 mol%)
   methacrolein (20 eq.)
   toluene, 65 °C, 60%
2. $NiCl_2$ (10 mol%)
   $CrCl_2$ (11 eq.)
   DMSO, 96%

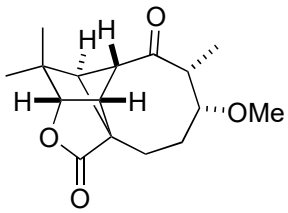
2-2
($C_{15}H_{20}O_3$, bicyclic)

1. hν (Hg lamp, 100W)
   acetone, 42% (58% brsm)
2. *m*-CPBA (1.25+0.75 eq.)
   CH_2Cl_2, 0 °C to rt, 100%
3. hν (Hg lamp, 100W)
   acetone, 21% (58% brsm)

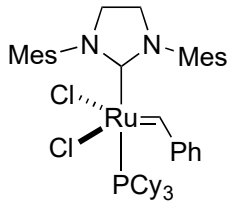


2-3

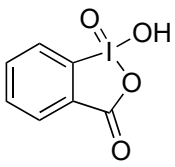
1. DMP (2.5 eq.), $NaHCO_3$ (4 eq.)
   CH_2Cl_2, 91%
2. BF_3•OEt_2 (5.5 eq.)
   MeOH, 74%
3. hν (Hg lamp, 100W)
   acetone, 37% (57% brsm)



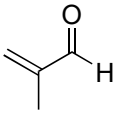
2-4



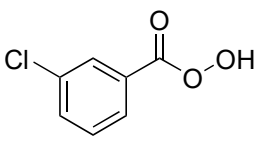
G-II cat.
(Grubbs 2nd generation catalyst)



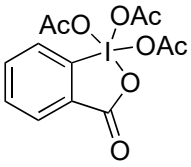
IBX



methacrolein



m-CPBA



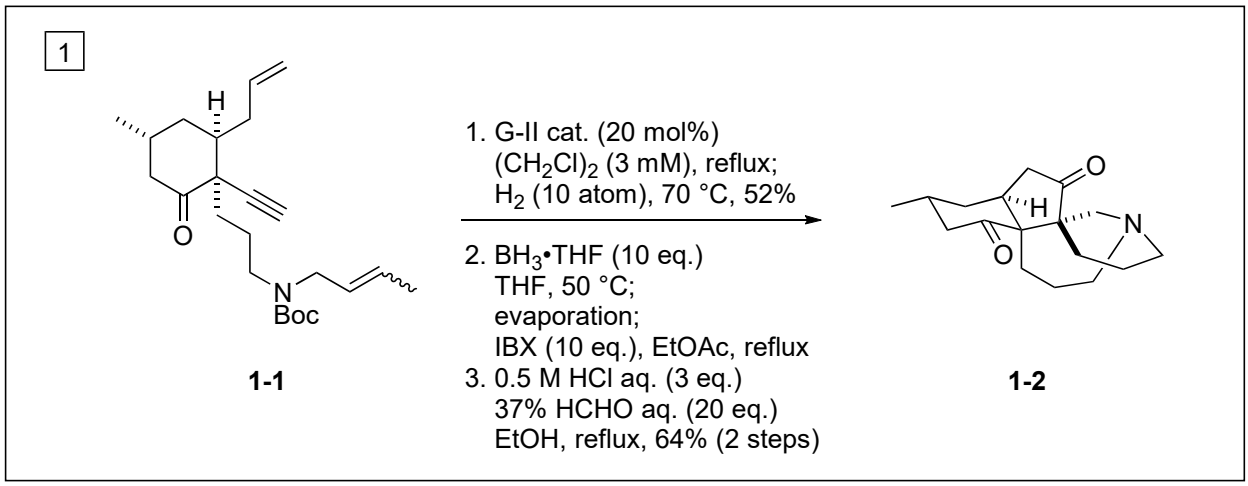
DMP

Problem Session (5) -Answer-

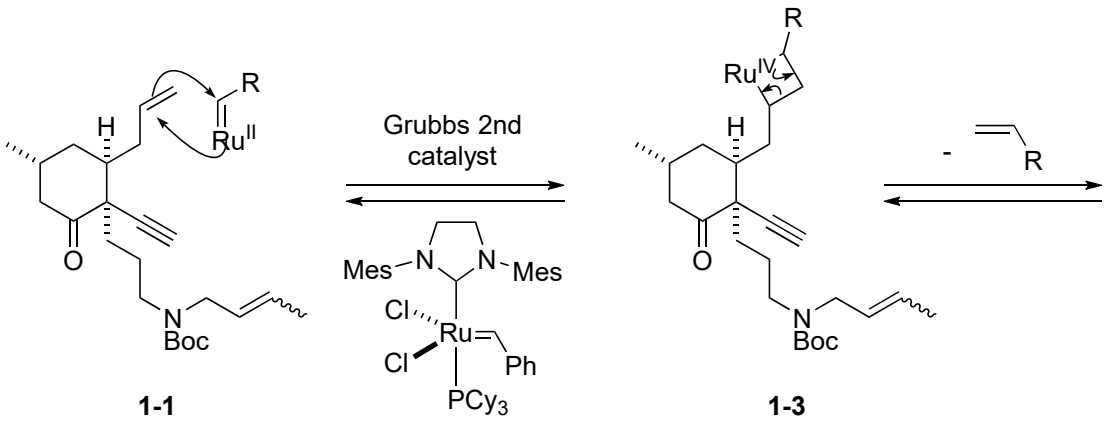
2019.08.03. Yinghua Wang

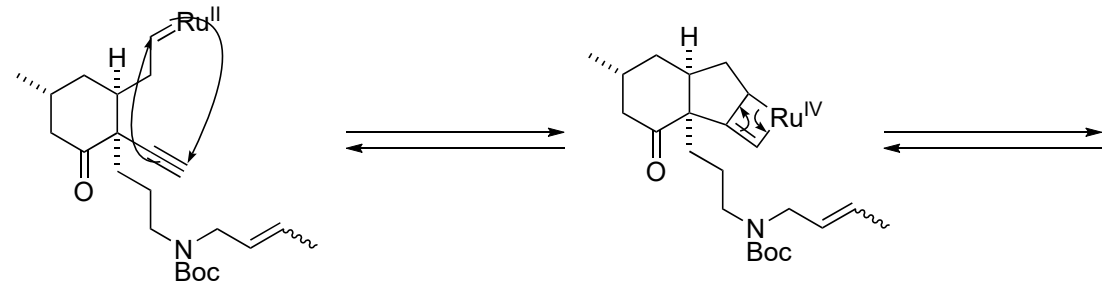
Topic: Metathesis cascade reaction in total syntheses.

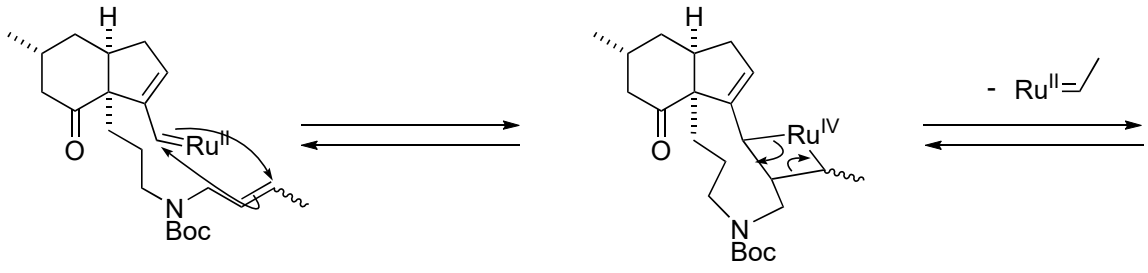
-Answer-



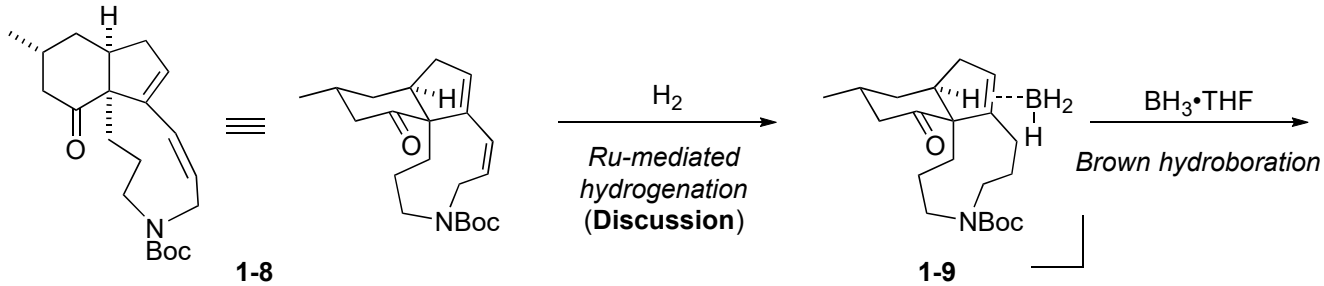
Ramharter, J.; Weinstabl, H.; Mulzer, J. *J. Am. Chem. Org.* **2010**, *132*, 14338.







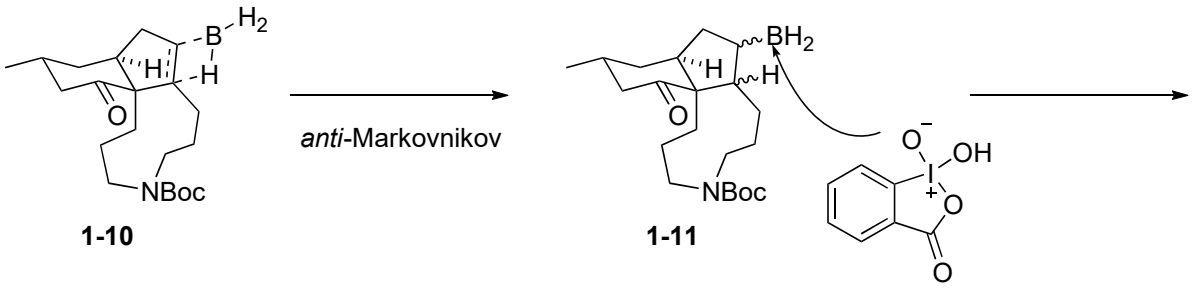
1-6 **1-7**



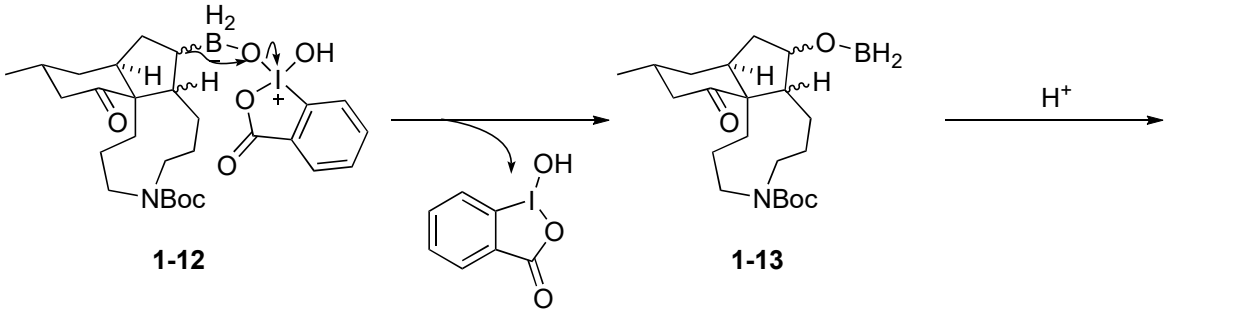
1-8 **1-9**

Step 1

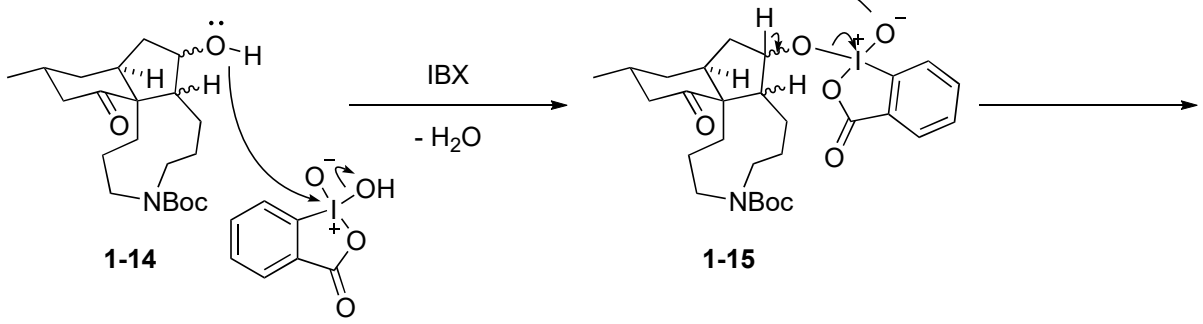
→ Only less hindered di-substituted was hydrogenated.



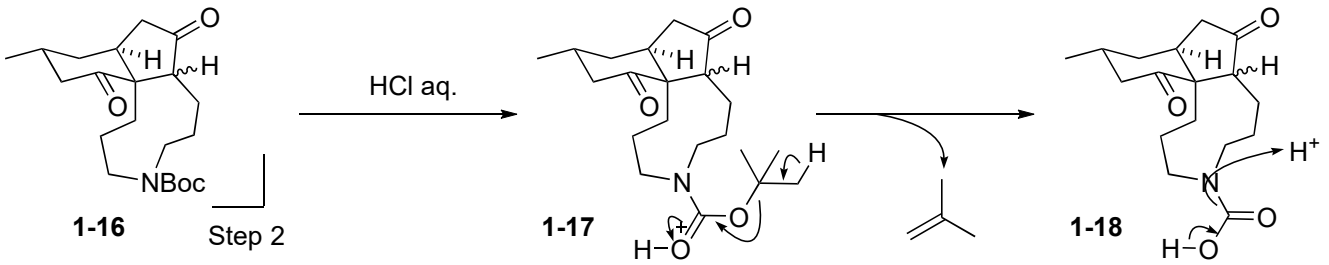
1-10 **1-11**



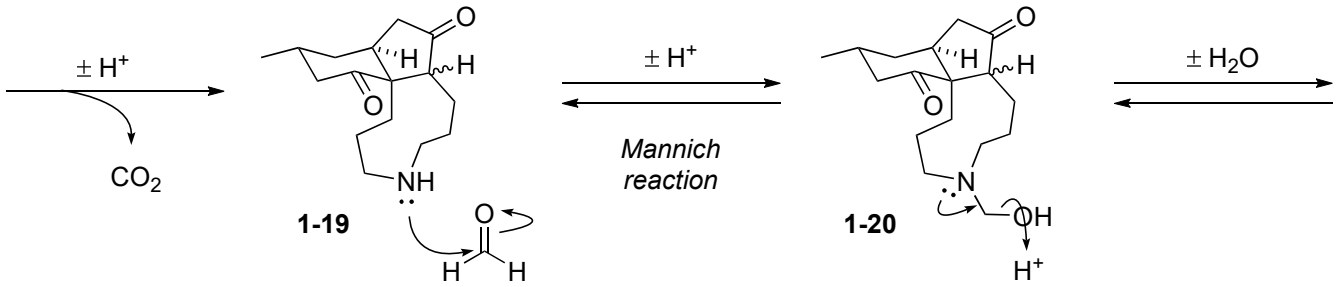
1-12 **1-13**

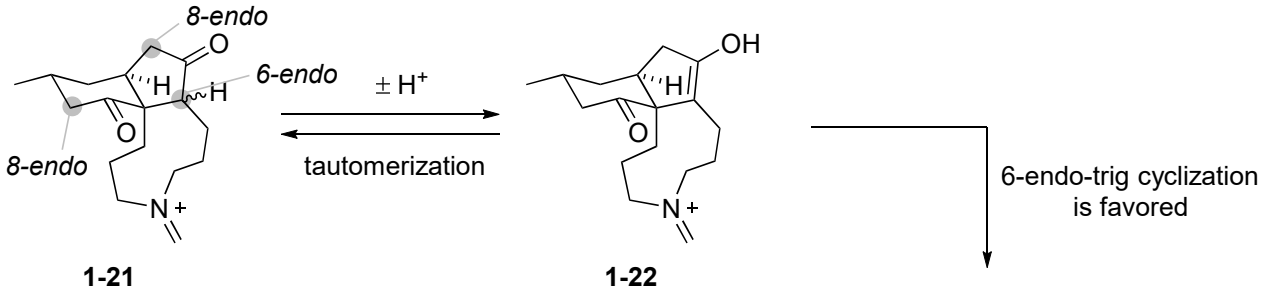


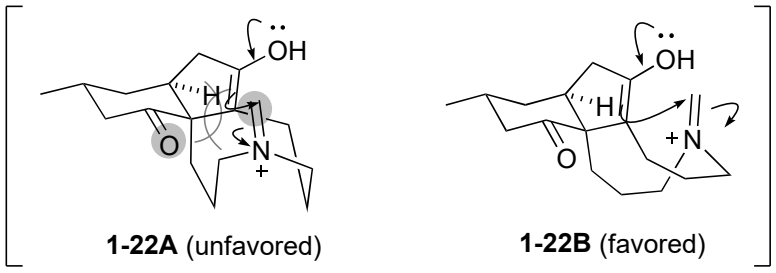
1-14 **1-15**

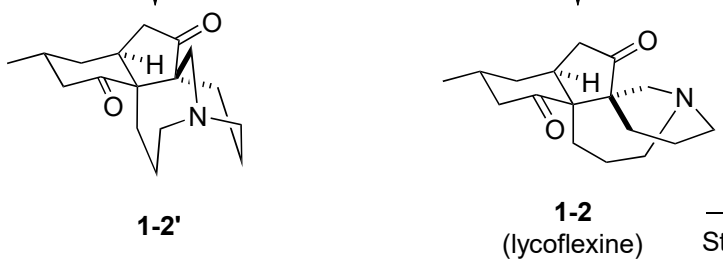


* stereochemistry was not mentioned



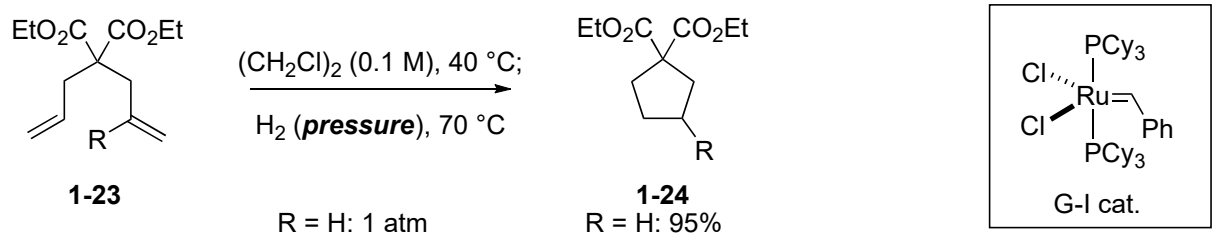






Discussion: Grubbs catalyst-mediated hydrogenation

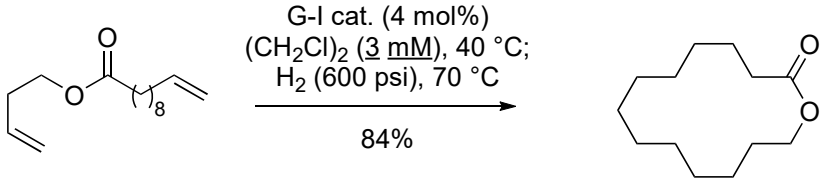
• Single-component Ru complex mediated tandem olefin metathesis and hydrogenation.



1-23 **1-24**

R = H: 1 atm
R = Me: 68 atm

R = H: 95%
R = Me: 70%

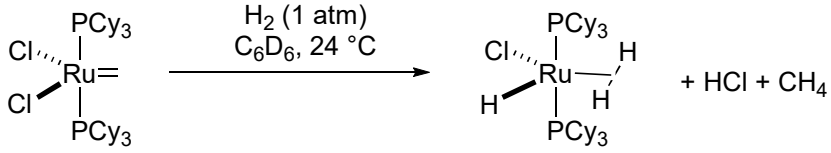


1-25 **1-26**

→ High pressures were needed for tri-substituted olefins or diluted conditions.

Luie, J.; Bielawski, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.

• Formation of the hydride complex of Grubbs 1st generation catalyst.



1-27 **1-28**

Olivan,M.; Caulton, K. *Inorg. Chem.* **1999**, *38*, 566.
Drouin, S. D.; Yap, G. P. A.; Fogg, D. E. Inorg. Chem. **2000**, *39*, 5412.

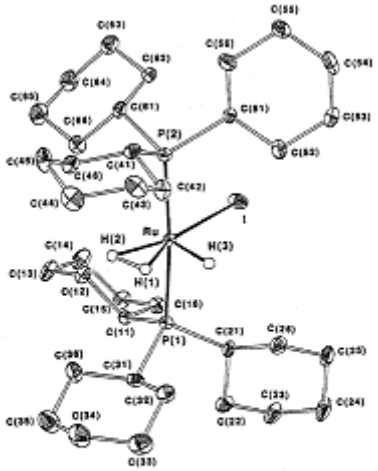


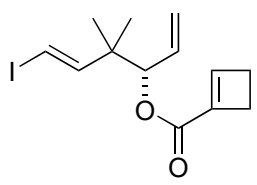
Figure 1. ORTEP plot for [RuH(H2)I(PCy3)2]. Selected bond lengths (Å) and angles (deg): Ru–P(1), 2.339 (1); Ru–P(2), 2.344 (1); Ru–I, 2.710 (1); Ru–H(1), 1.60 (5); Ru–H(2), 1.59 (4); Ru–H(3), 1.51 (5); H(1)–H(2), 1.03 (7); P(1)–Ru–P(2), 175.13 (6); P(1)–Ru–I, 90.80 (4); P(2)–Ru–I, 91.82 (4); P(1)–Ru–H(1), 89 (2); P(1)–Ru–H(2), 88 (2); P(1)–Ru–H(3), 91 (2); P(2)–Ru–H(1), 90 (2); P(2)–Ru–H(2), 88 (2); P(2)–Ru–H(3), 93 (2); I–Ru–H(1), 163 (2); I–Ru–H(2), 159 (2); I–Ru–H(3), 99 (2).

X-ray structure of similar complex $RuH(H_2)I(PCy)_2$ is shown in the right.

Chaudret, B.; Chung, G.; Eisenstein, O.; Jackson, S. A.; Lahoz, F. J.; Lopez, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 2314.

Similar Ru-hydride complex would be formed by the reaction with Grubbs 2nd catalyst and H_2.
→ The Ru-hydride complex works as a hydrogenation catalyst.

2



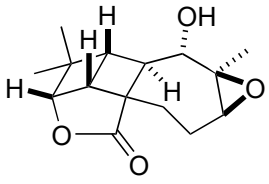
2-1
($C_{13}H_{17}O_2I$)

1. G-II cat. (15 mol%)
   methacrolein (20 eq.)
   toluene, 65 °C, 60%
2. $NiCl_2$ (10 mol%)
   $CrCl_2$ (11 eq.)
   DMSO, 96%

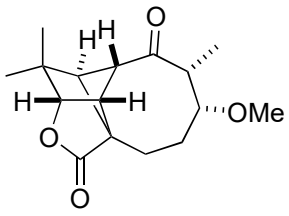
2-2
($C_{15}H_{20}O_3$, bicyclic)

1. hν (Hg lamp, 100W)
   acetone, 42% (58% brsm)
2. *m*-CPBA (1.25+0.75 eq.)
   CH_2Cl_2, 0 °C to rt, 100%
3. hν (Hg lamp, 100W)
   acetone, 21% (58% brsm)

1. DMP (2.5 eq.), $NaHCO_3$ (4 eq.)
   CH_2Cl_2, 91%
2. BF_3•OEt_2 (5.5 eq.)
   MeOH, 74%
3. hν (Hg lamp, 100W)
   acetone, 37% (57% brsm)



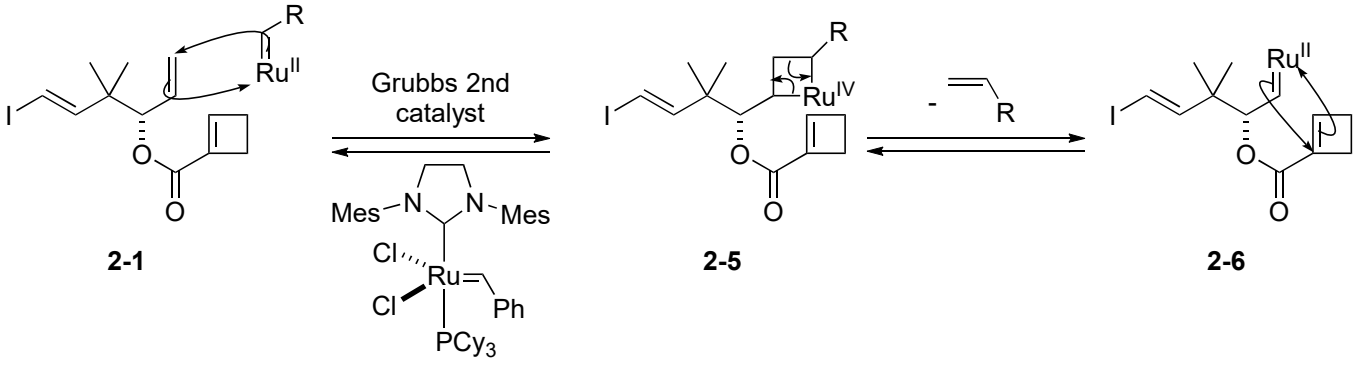
2-3

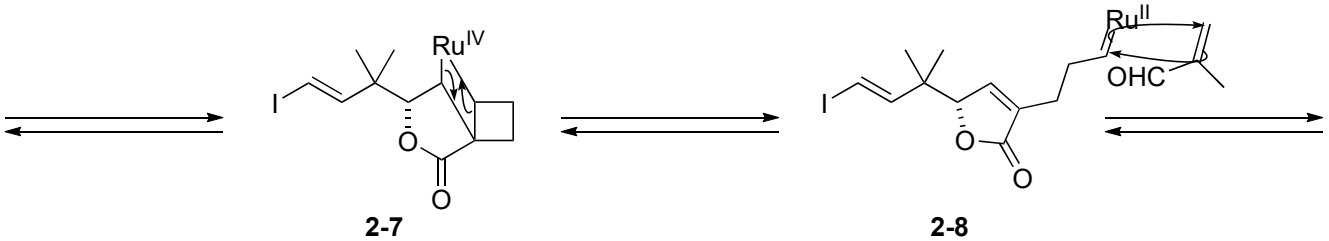


2-4

Takao, K.; Kai, H.; Yamada, A.; Fukushima, Y.; Komatsu, D.; Ogura, A.; Yoshida, K.
Angew. Chem. Int. Ed. **2019**, *58*, 1.

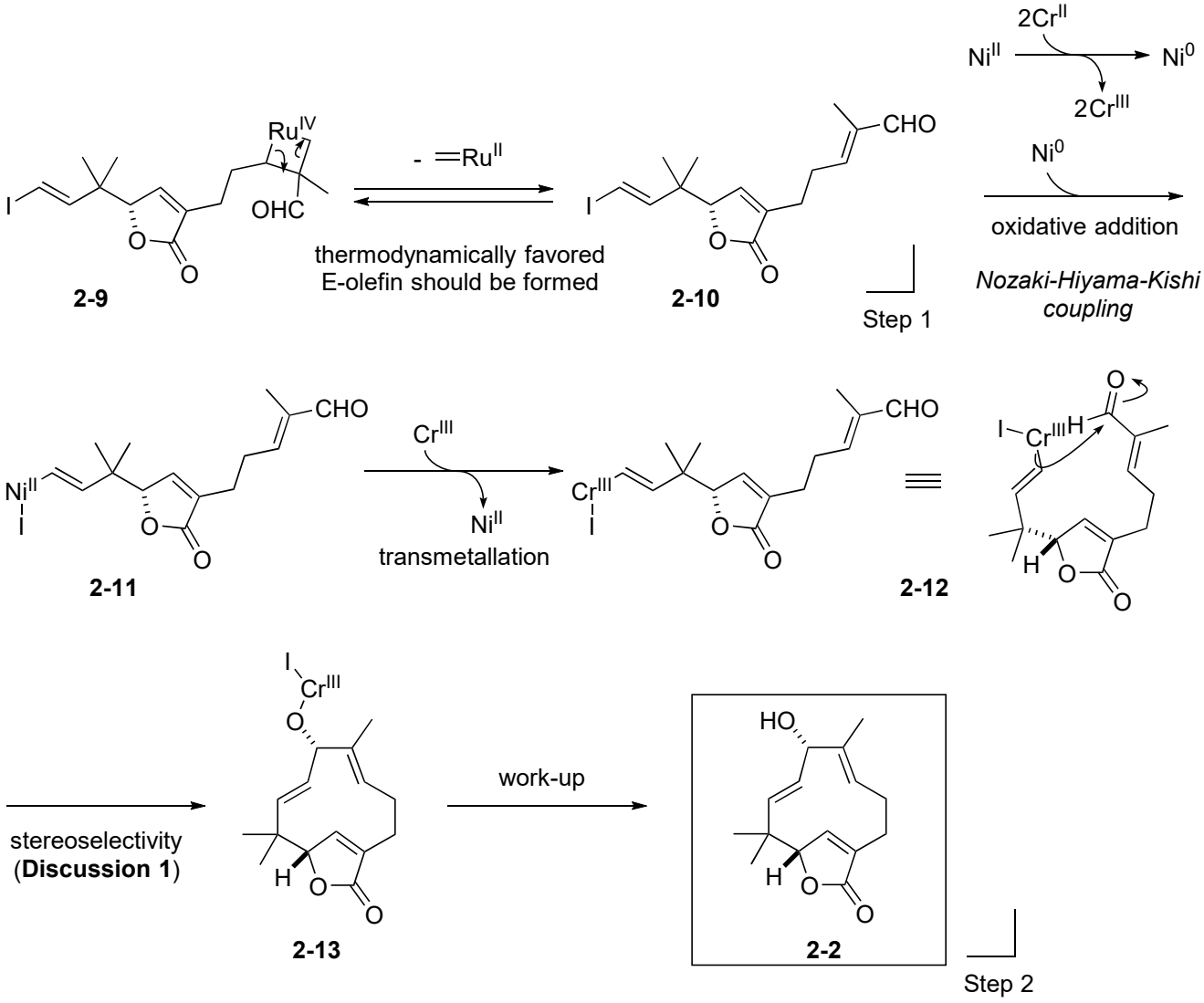
• Transformation from **2-1** to **2-2**.



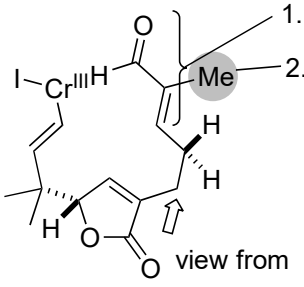


2-7

2-8

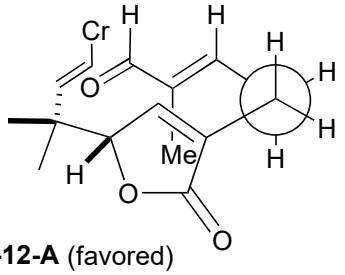


Discussion 1: Stereoselectivity of Nozaki-Hiyama-Kishi coupling.

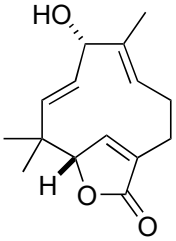


2-12

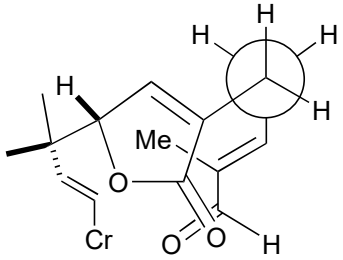
1. This enal moiety should be *s-trans.*
2. Considering 1,3-allylic strain, this Me group should be parallel to H atom.



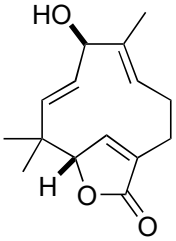
2-12-A (favored)



2-2

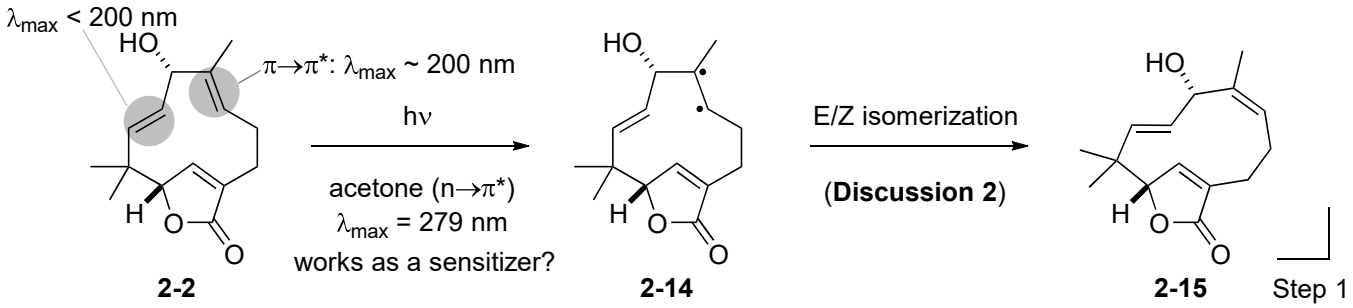


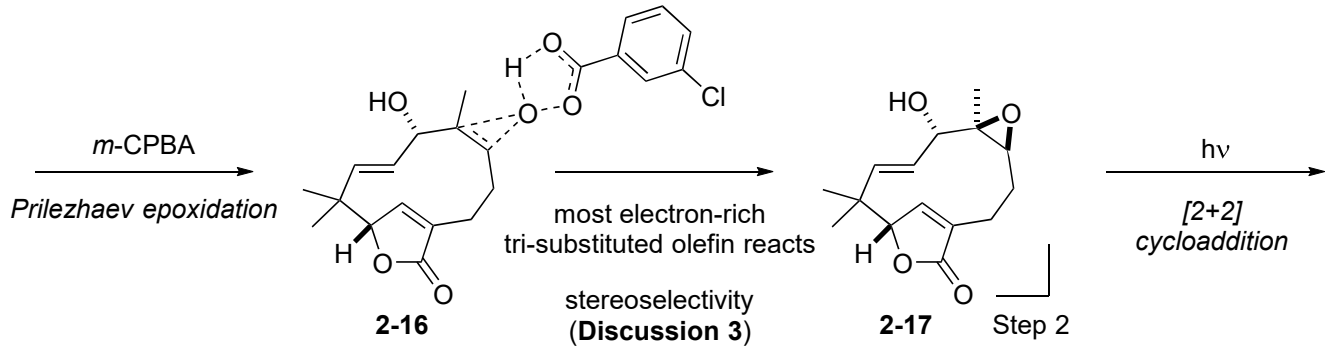
2-12-B
(unfavored because butenolide overlaps)

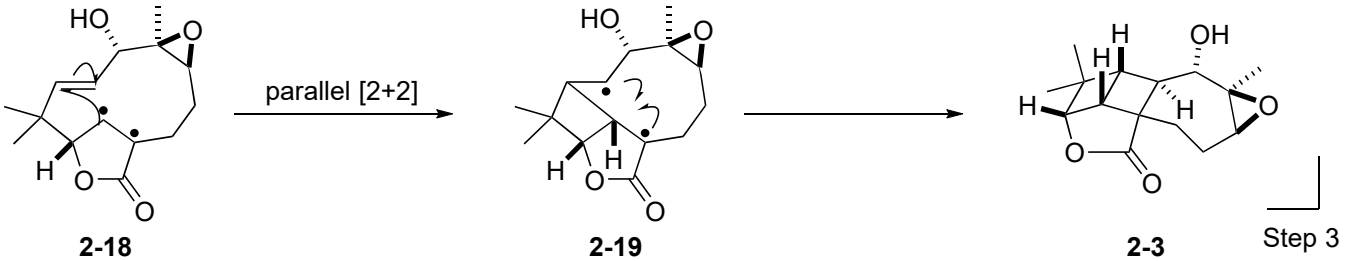


2-2'

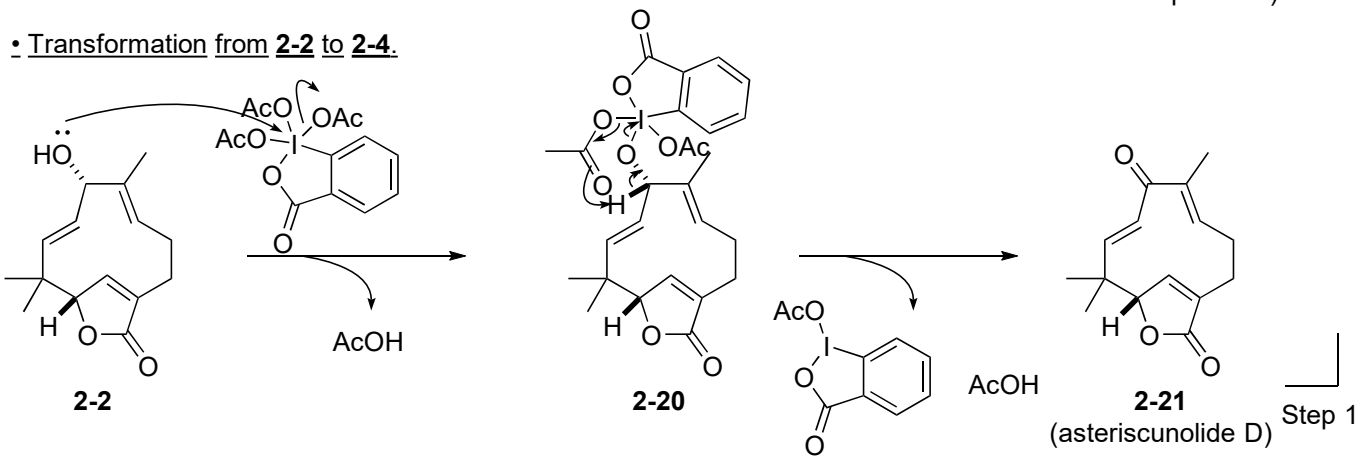
• Transformation from **2-2** to **2-3**.

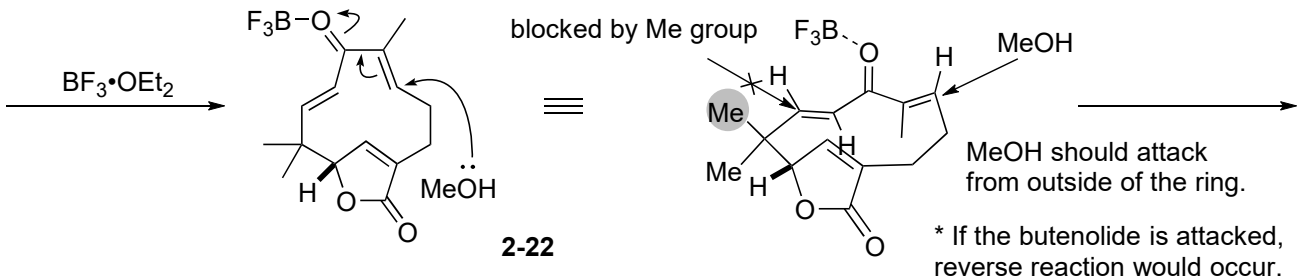




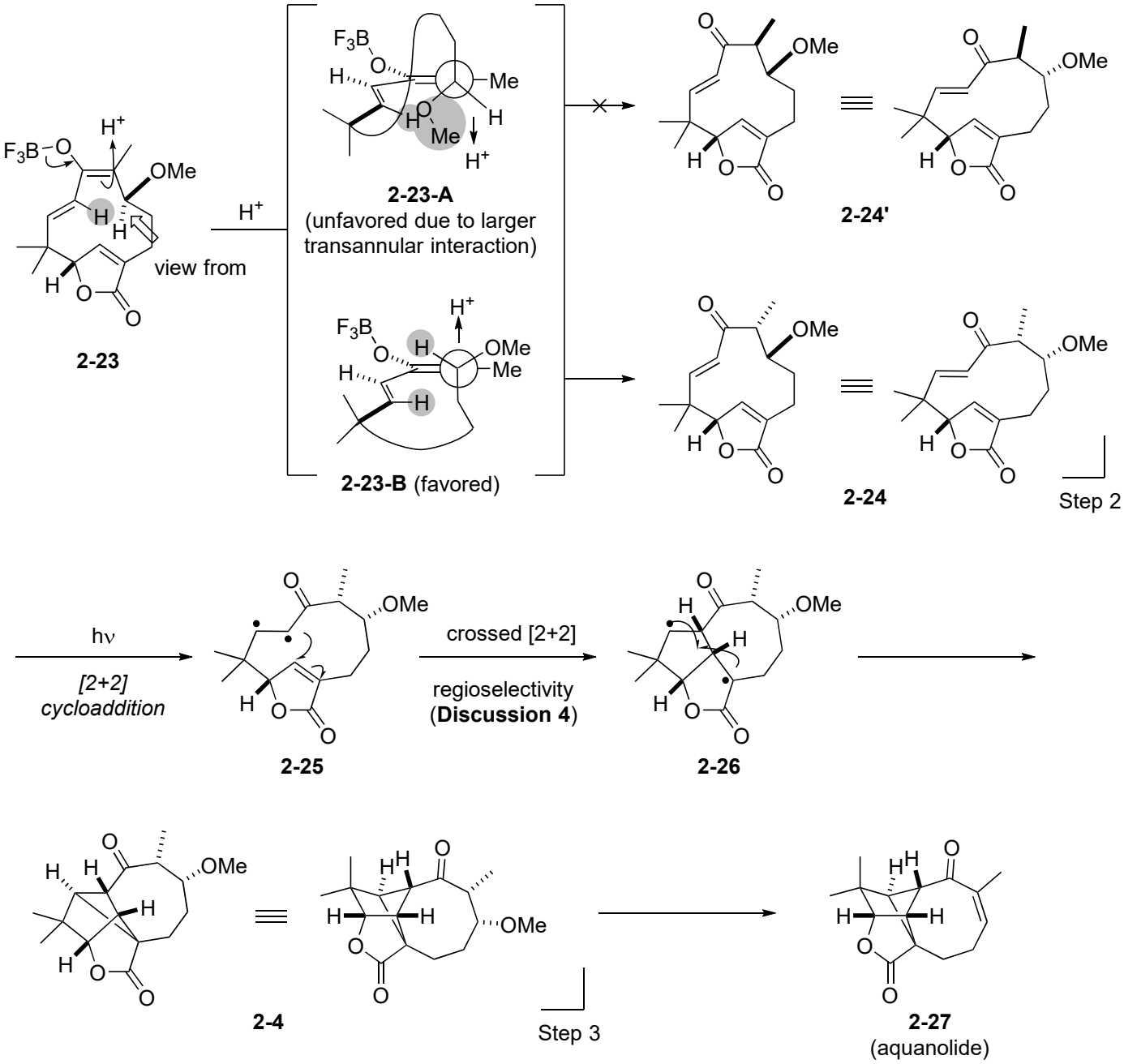


• Transformation from **2-2** to **2-4**.

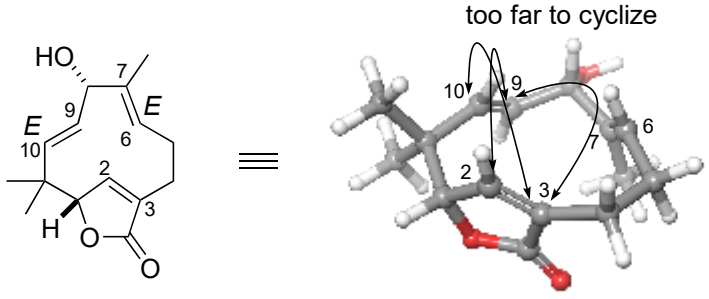




* If the butenolide is attacked, reverse reaction would occur.



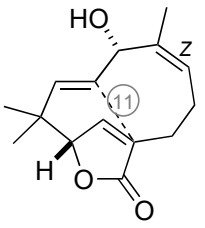
Discussion 2: Why [2+2] cycloaddition failed in **2-2**?



2-2

It might be hard to cyclize because two E-olefins exists in the 11-membered ring?
→ [2+2] cycloaddition wouldn't proceed even if the butenolide is irradiated, hence isomerization occurs when tri-substituted olefin is irradiated.

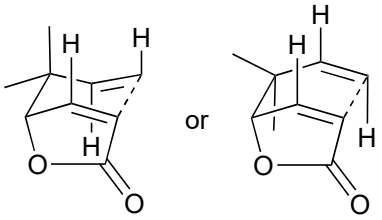
Discussion 3: Stereoselectivity of epoxidatioin.



2-15

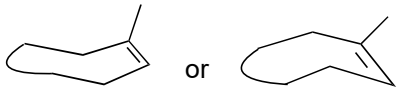
When thinking of the confomation of 11-membered triene **2-15**, it can be separated into cyclohexadiene ("6-membered") and cycloheptene ("7-membered").

conformation of cyclohexadiene

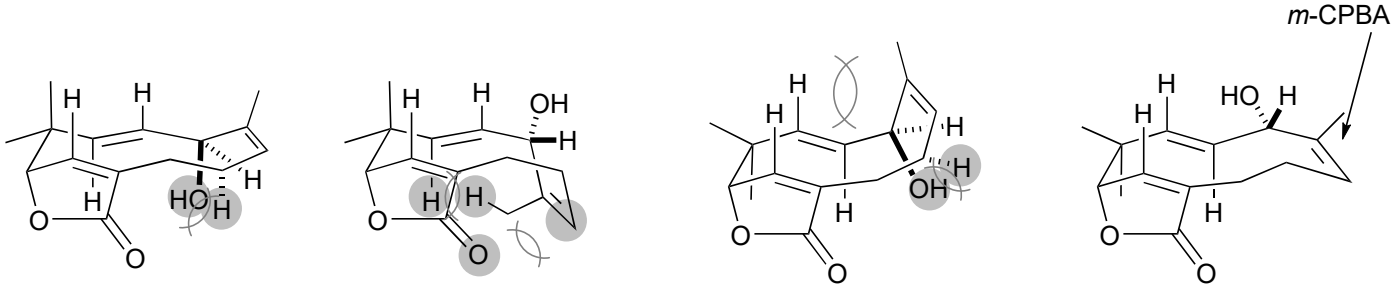


chair-like or boat-like

conformation of cycloheptene

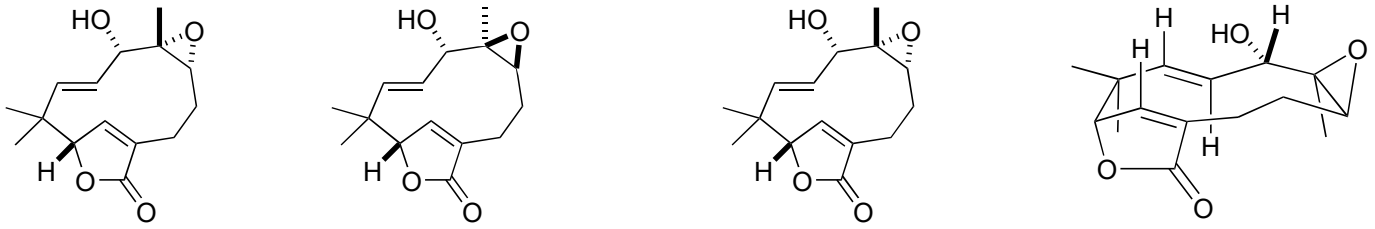


down-like or up-like



2-15A (chair-down) **2-15B** (chair-up) **2-15C** (boat-down) **2-15D** (boat-up)

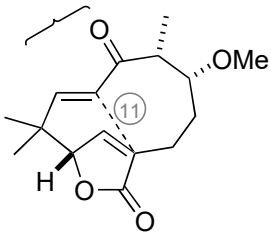
m-CPBA



2-17' **2-17** **2-17'** **2-17**

Discussion 4: Regioselectivity of transannular [2+2] cycloaddition.

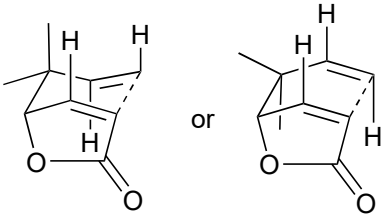
• Pausible conformation of **2-24**.



2-24

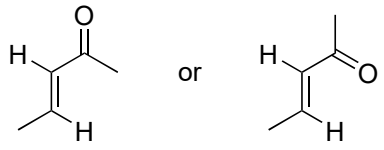
When thinking of the confomation of 11-membered diene **2-24**, it would be easy to predict based on the conformations of "6-membered" cyclohexadiene and enone:

conformation of cyclohexadiene



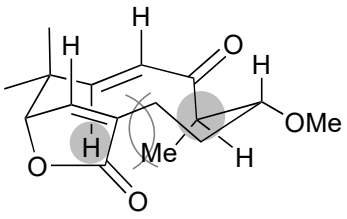
chair-like boat-like

conformation of enone

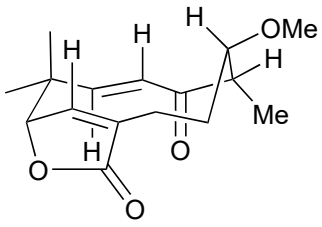


trans *cis*

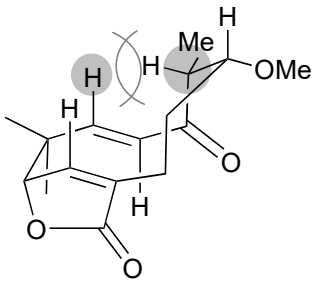
• Pausible conformation of **2-24**.



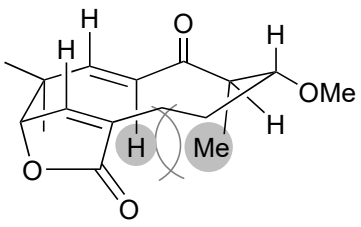
2-24A
(chair-trans)



2-24B
(chair-cis)
favored

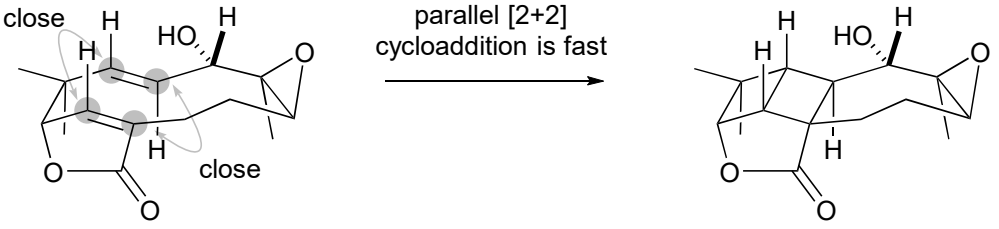


2-24C
(boat-trans)



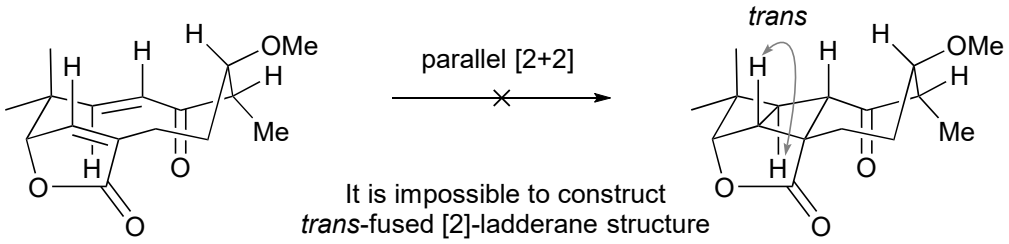
2-24D
(boat-cis)

• [2+2] cycloaddition from **2-17**.



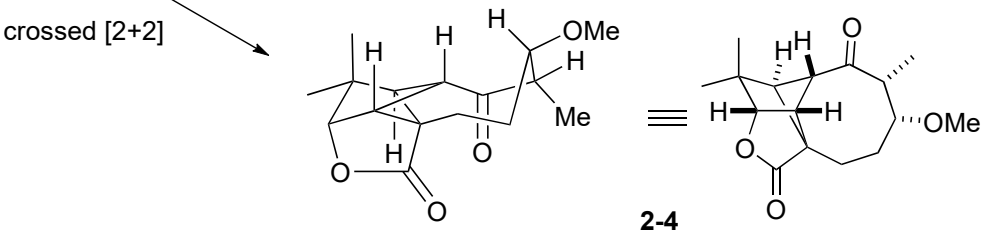
2-17 **2-3**

• [2+2] cycloaddition from **2-24**.



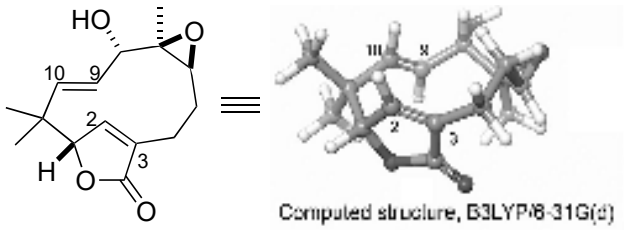
It is impossible to construct
trans-fused [2]-ladderane structure

2-24 **2-25**

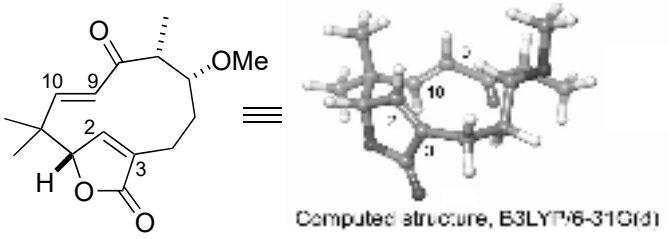


2-4

• Computed structure of **2-17** and **2-24**.



2-17



2-24