Problem Session (2) -Answer-

2020.10.31. Yuto Hikone

Topic: Macrocycles

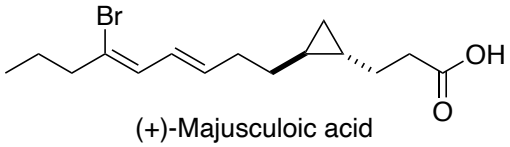
Introduction

1. Stereocontrol using macrocycle

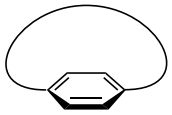
(+)-Majusculoic acid : enantiomer of naturally occuring antifungal cyclopropane fatty acid.

total synthesis : Zhang (2018).

-> construction of stereocenters of small linear molecule by novel macrocyclic dimerization strategy.



(+)-Majusculoic acid



paracyclophane

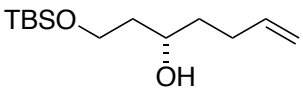
2. Flexible macrocycle from rigid steroid

cyclophane : macrocyclic hydrocarbon consisting of an aromatic unit and an aliphatic chain.
Some paracyclophane can be derived from steroid.

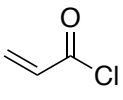
-> Stereochemistry of flexible paracyclophane can be controlled by the stereocenters originally installed on rigid steroid.

1.

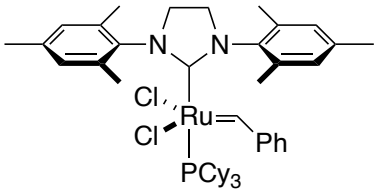
1. **A** (2 eq.), Et_3N (8 eq.), CH_2Cl_2, 0 ºC, 72%
2. Grubbs 2nd (5 mol%)
   CH_2Cl_2 (0.02 M), reflux, 53%
3. CH_2N_2 (5 eq.), $Pd(OAc)_2$ (10 mol%), Et_2O
   -78 ºC to rt, 80%
4. HN(OMe)Me·HCl (6 eq.), *i*-PrMgCl (12 eq.)
   THF, 0 ºC;
5. *i*-Bu_2AlH (2.5 eq.), Et_2O, 81% (2 steps)



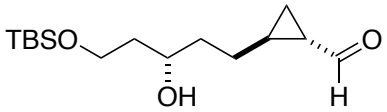
1-1



A



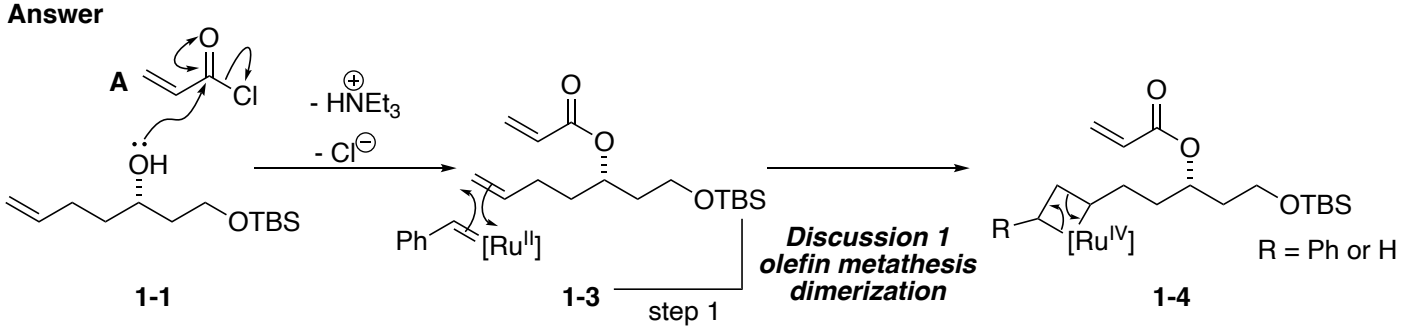
Grubbs 2nd



1-2

Chen, R.; Li, L.; Lin, N.; Zhou, R.; Hua, Y.; Deng, H.; Zhang, Y. *Org. lett.* **2018**, *20*, 1477.

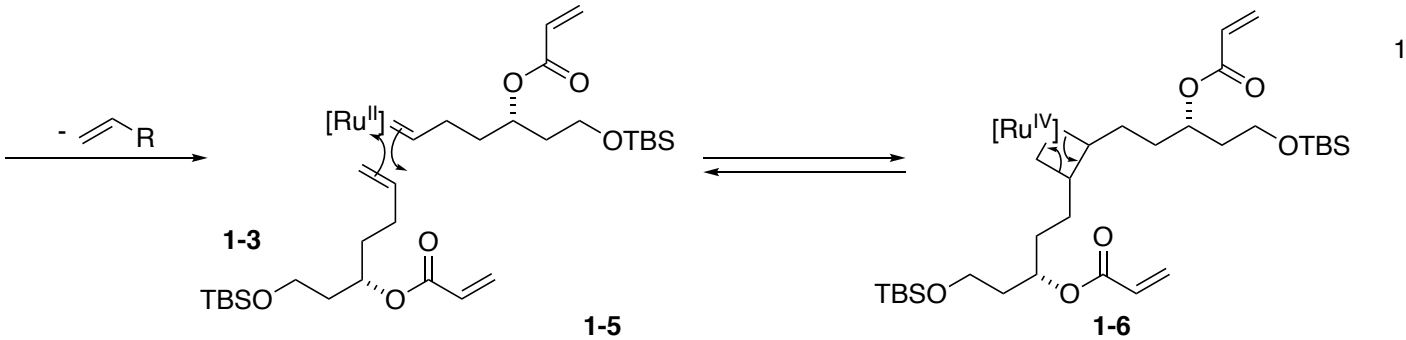
Answer



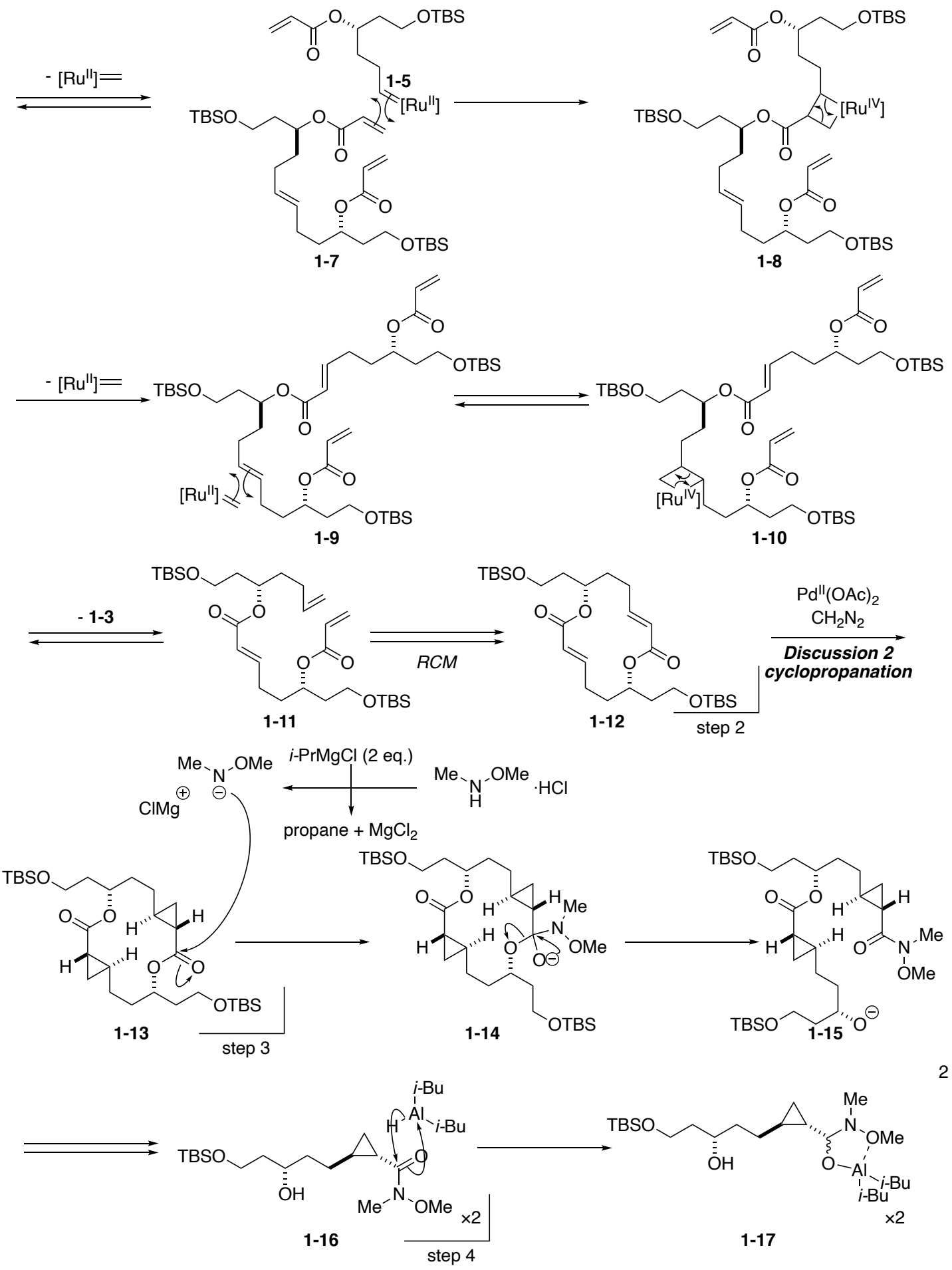
1-1 **1-3** **1-4**

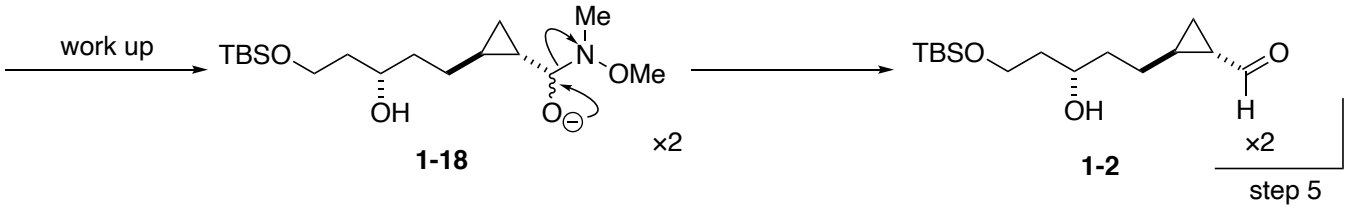
step 1

Discussion 1
olefin metathesis dimerization



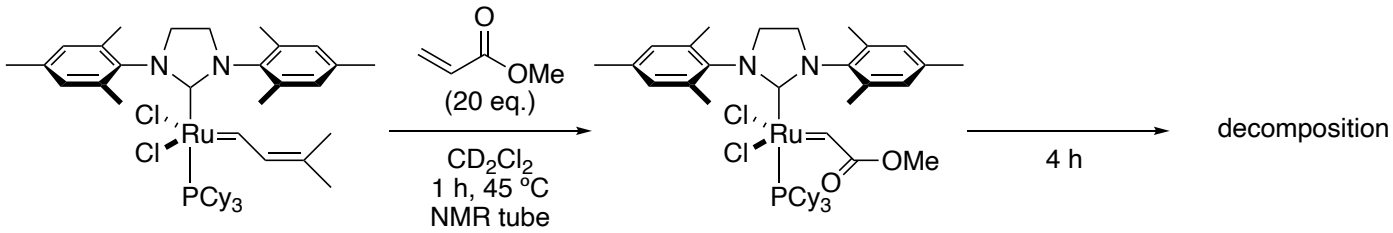
1-3 **1-5** **1-6**


- [Ru^II]=
1-5
[Ru^II]
TBSO
OTBS
1-7
[Ru^IV]
1-8
- [Ru^II]=
1-9
1-10
- 1-3
1-11
RCM
1-12
Pd^II(OAc)2
CH2N2
Discussion 2
cyclopropanation
step 2
Me
N
OMe
ClMg
i-PrMgCl (2 eq.)
·HCl
propane + MgCl2
1-13
1-14
1-15
step 3
i-Bu
Al
OH
1-16
×2
step 4
1-17



Discussion 1: olefin metathesis dimerization

1-1. Cross metathesis with *α*,*β*-unsaturated ester



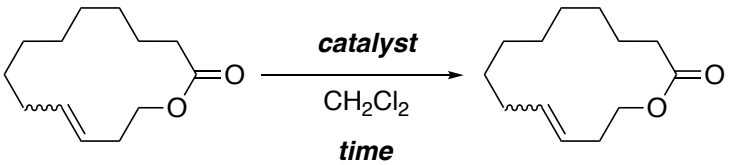
catalyst **C-1** (1 eq.)

ester-carbene **C-2** (7%)

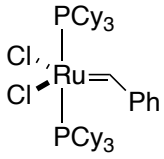
Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

This experiment suggests that the ester-carbene complex is unlikely to be an intermediate in cross metathesis between olefin and *α*,*β*-unsaturated ester.
Thus, in the cross metathesis between **1-3**s, Ru carbene complex **1-5** is likely to be the intermediate.

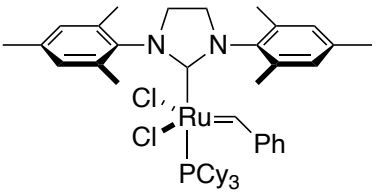
1-2. Dimerization



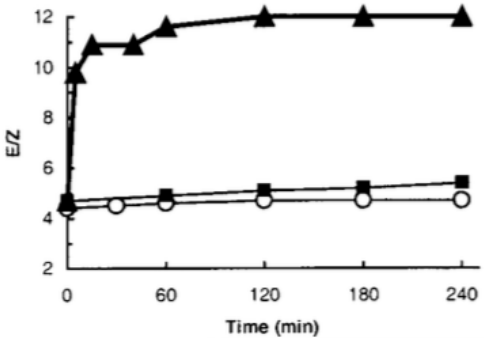
1-19 **1-19'**



Grubbs 1st



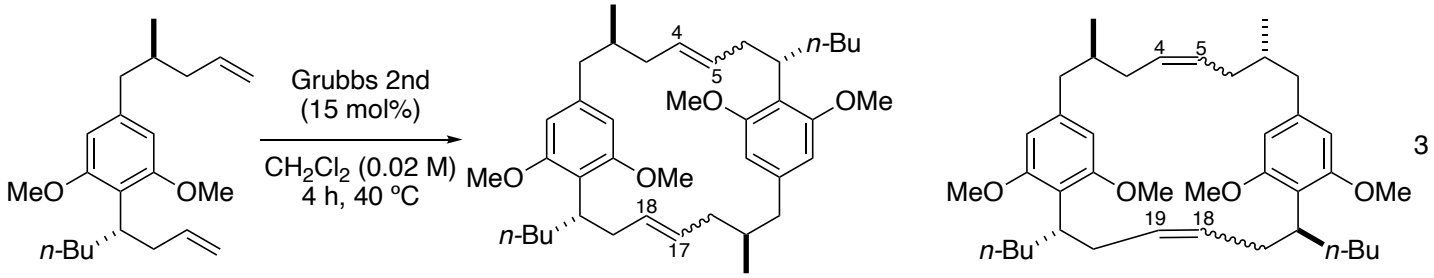
Grubbs 2nd



○ no catalyst
■ Grubbs 1st (5 mol%)
▲ Grubbs 2nd (3 mol%)

While isomerization of macrolactone did not occur in the absence of catalyst or in the presence of Grubbs 1st, rapid isomerization was observed in the presence of Grubbs 2nd. Improvement in *E/Z* ratio shows that RCM using Grubbs 2nd leads to the ultimate thermodynamic equilibium.

Lee, C. W.; Grubbs, R. H. *Org. lett.* **2000**, *2*, 2145.



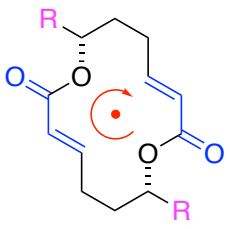
1-20

1-21 : $\Delta^{4,5}$ = *trans*, $\Delta^{17,18}$ = *trans* (48%)
1-22 : $\Delta^{4,5}$ = *trans*, $\Delta^{17,18}$ = *cis* (none)
1-23 : $\Delta^{4,5}$ = *cis*, $\Delta^{17,18}$ = *cis* (none)
1-24 : $\Delta^{4,5}$ = *trans*, $\Delta^{18,19}$ = *trans* (none)
1-25 : $\Delta^{4,5}$ = *trans*, $\Delta^{18,19}$ = *cis* (none)
1-26 : $\Delta^{4,5}$ = *cis*, $\Delta^{18,19}$ = *cis* (none)

Smith, A. B.; Adams, C. M.; Kozmin, S. A. *J. Am. CHem. Soc.* **2001**, *123*, 990.

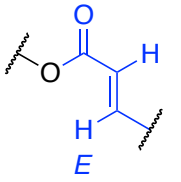
Discussion 2: cyclopropanation

2-1. Conformation of 14-membered macrolactone **1-12**

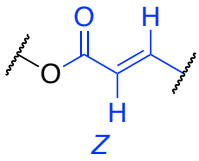


R = $(CH_2)_2OTBS$

1-12



E



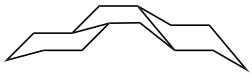
Z

To consider appropriate conformations of 14-membered lactone **1-12**, make sure to grasp following points;

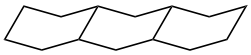
- *C2* symmetory (**confirmed from NMR spectra of 1-12**)
- two geometrical isomers of enone (*E* or *Z*)
- branched alkyl groups (R)

How to fulfill theses points?

- *C2* symmetory
  -> *chair-boat-chair* (CBC) or *boat-boat-boat* (BBB)
- two geometrical isomers of enone (*E* or *Z*)
  -> locate enones at appropriate positions
- branched alkyl groups (R)
  -> equatorial position



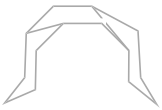
CBC-1



BBB-1

BBB-3

BBB-5



CBC-2

chair-boat-chair

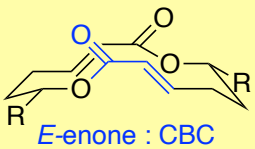
BBB-2

BBB-4

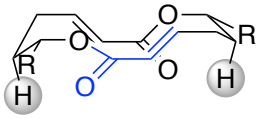
boat-boat-boat

Considering the steric repulsions, CBC1, BBB1 or BBB2 are the most plausible conformations.

-> Taken these points into consideration, the conformations of 14-membered macrolactone **1-12** are depicted as follows.

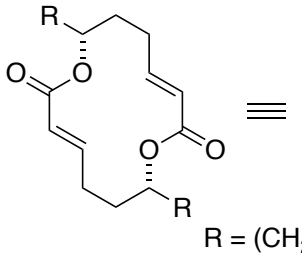


E-enone : CBC
1-12A
favourable



E-enone : BBB
1-12B
unfavourable
Hydrogen atoms toward the inside of the macrocycle

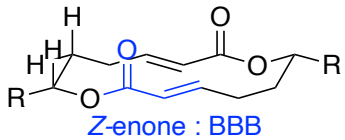
≡



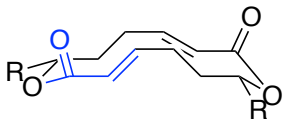
R = $(CH_2)_2OTBS$

1-12
C2 symmetry confirmed from NMR spectra

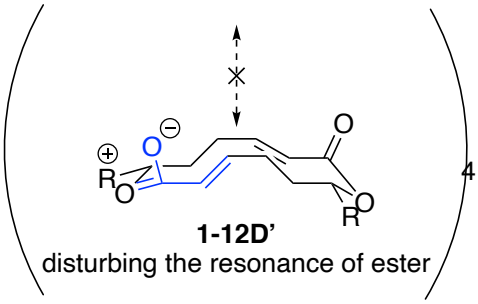
≡



Z-enone : BBB
1-12C
unfavourable
eclipsed C-C bonds



Z-enone : CBC
1-12D
unfavourable

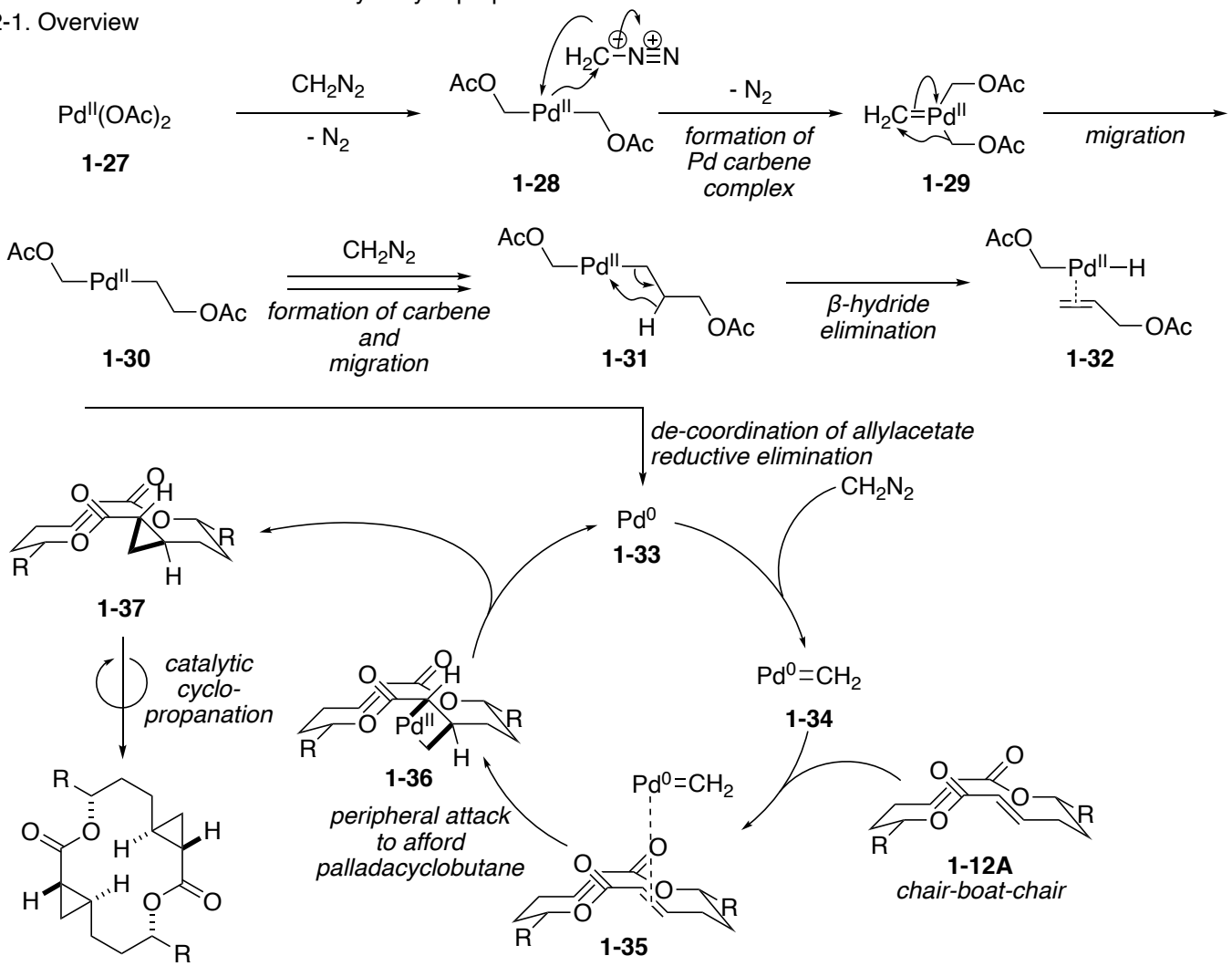


1-12D'
disturbing the resonance of ester

Among these four conformations, **1-12A** is thermodynamically most stable.

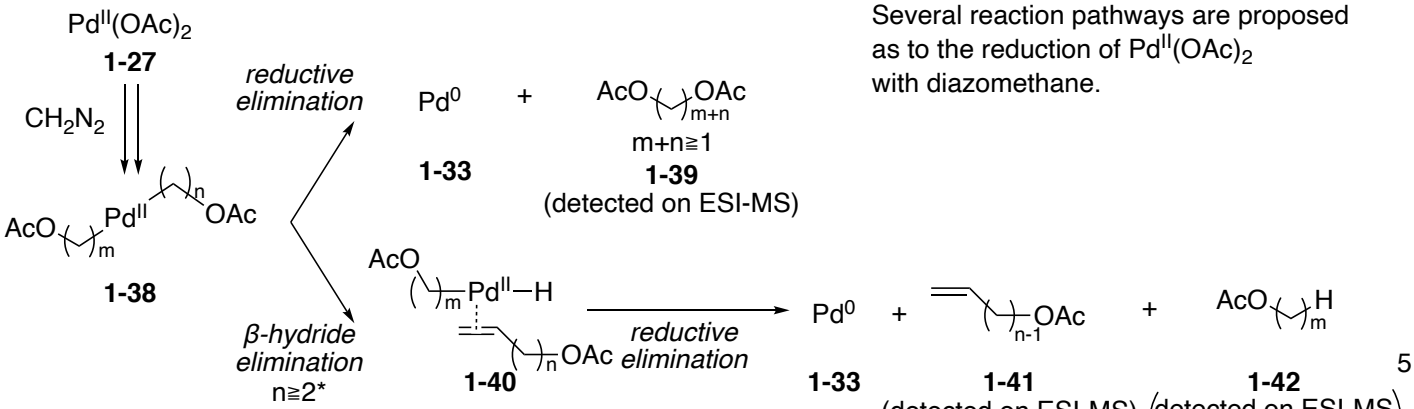
2-2. Mechanism and stereoselectivity of cyclopropanation

2-2-1. Overview



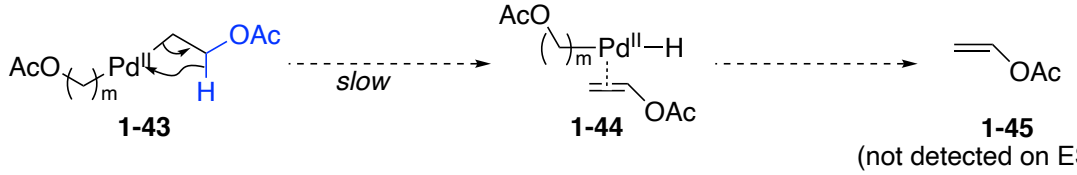
Illa, O.; Rodríguez-García, C.; Acosta-Silva, C.; Favier, I.; Picurelli, D.; Oliva, A.; Gómez, M.; Branchadell, V.; Ortuño, R. M. *Organometallics* **2007**, *26*, 3306.

2-2-2. Details of the reaction mechanism

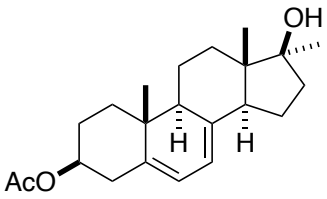


Several reaction pathways are proposed as to the reduction of $Pd^{II}(OAc)_2$ with diazomethane.

* For n=1, *β*-hydride elimination is considered to be slow due to the low electron density of hydride adjacent to OAc.

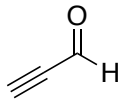


2.

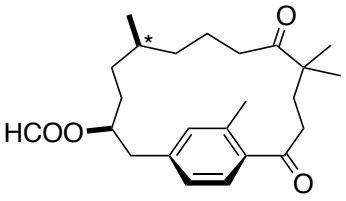


2-1

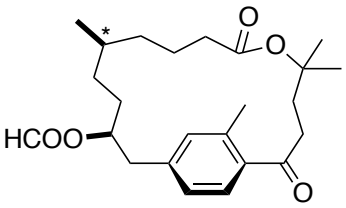
1. **B** (2.5 eq.), $BF_3{\cdot}OEt_2$ (1 eq.)
   CH_2Cl_2, 0 ºC to rt
2. xylene, reflux, 46% (2 steps)
3. $NaBH_4$ (2 eq.), CH_2Cl_2/EtOH, rt, 65%
4. H_2, Pt/C, MeOH, rt, 85% (dr = calc. 8:1)
5. HCOOH, reflux, 80%
6. O_3, CH_2Cl_2, -78 ºC; PPh_3 (1.1 eq.), rt



B



2-2
34% (dr = 8:1)

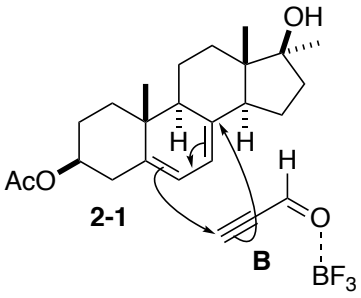


2-3
6%

Bäurle, S.; Blume, T.; Mengel, A.; Parchmann, C.; Skuballa, W.; Bäsler, S.; Schäfer, M.; Sülzle, D.; Wrona-Metzinger, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 3961.

Answer

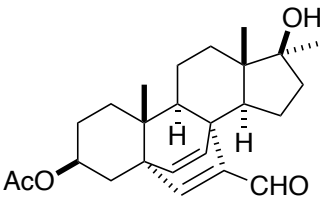
1st step



2-1 **B**

Diels-Alder reaction

Discussion 1 stereo/regio -selectivities

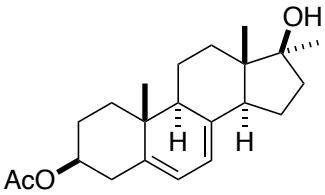


2-4

step 2

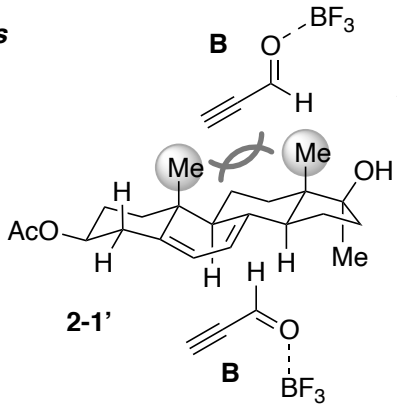
Discussion 1: stereo/regioselectivities

1-1. Stereoselectivity



2-1

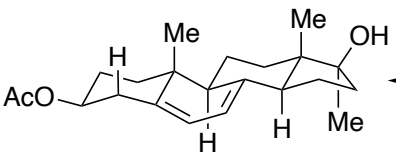
≡



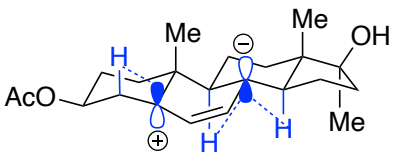
2-1'

repulsion between alkyne and methyl groups

1-2. Regioselectivity

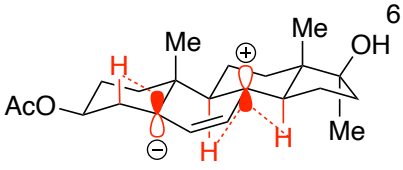


2-1'



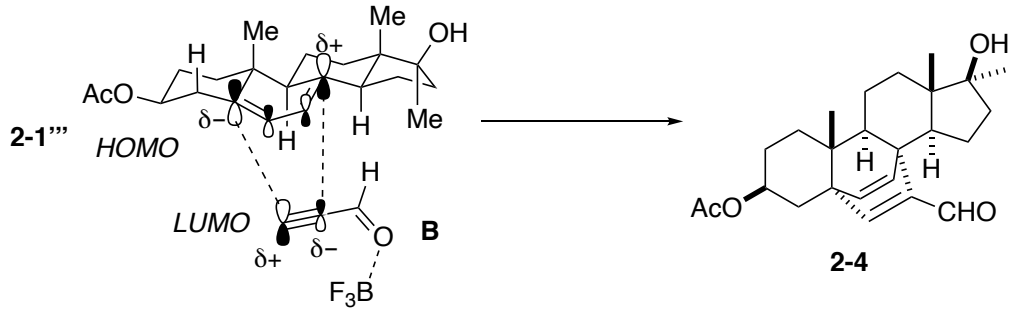
2-1"

unfavourable
• less stabilized 3º cation
• more distabilized 3º anion

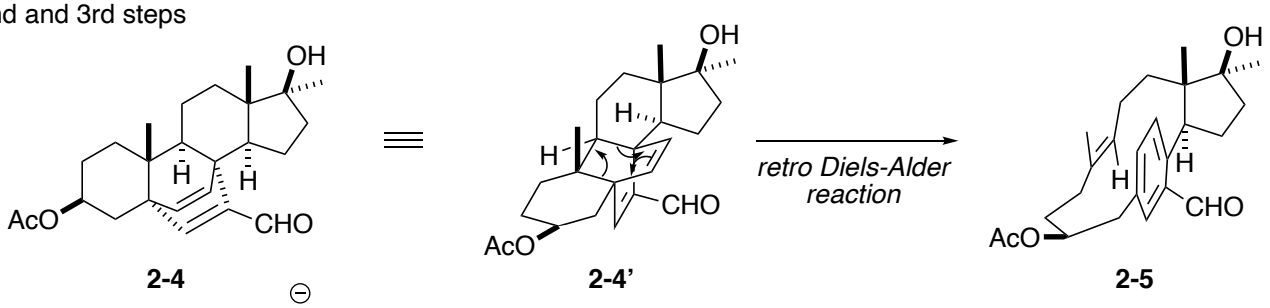


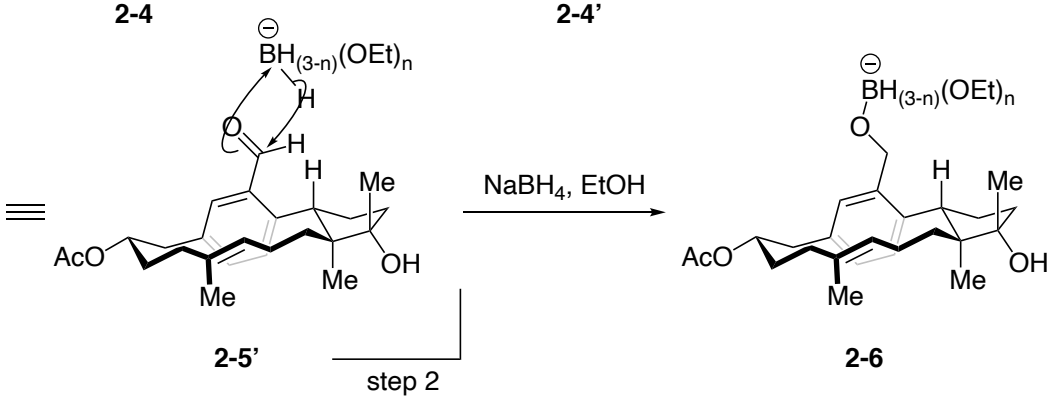
2-1'"

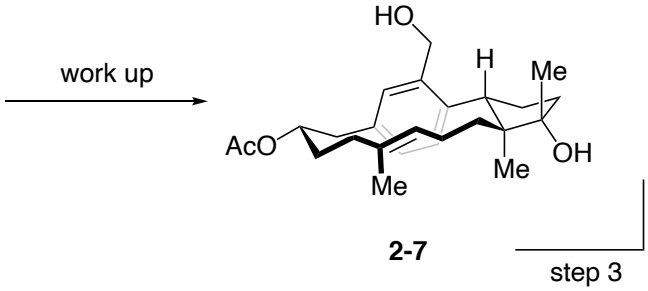
favourable
• more stabilized 3º cation
• less distabilzed 3º anion



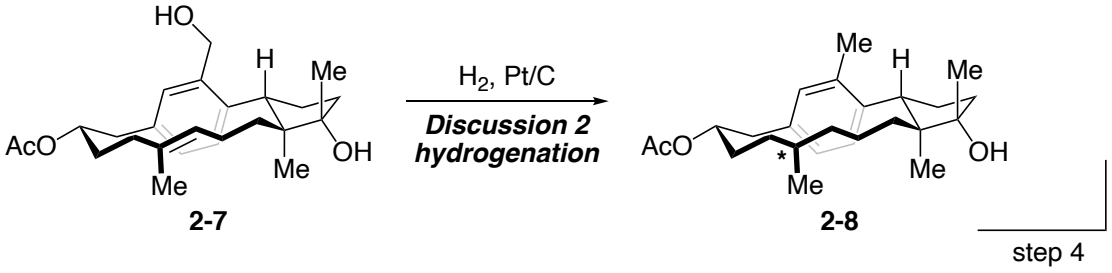
2nd and 3rd steps





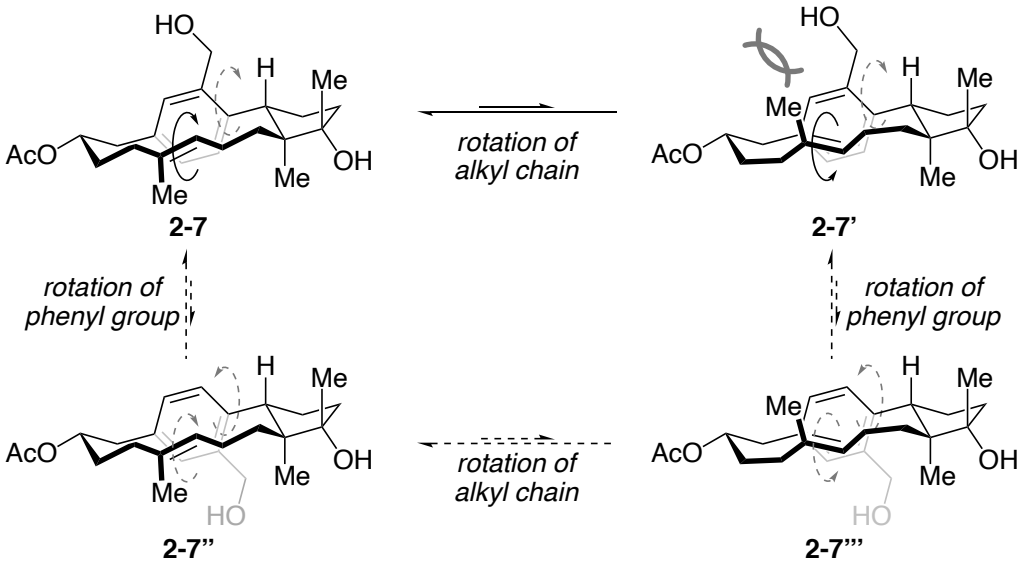


4th step



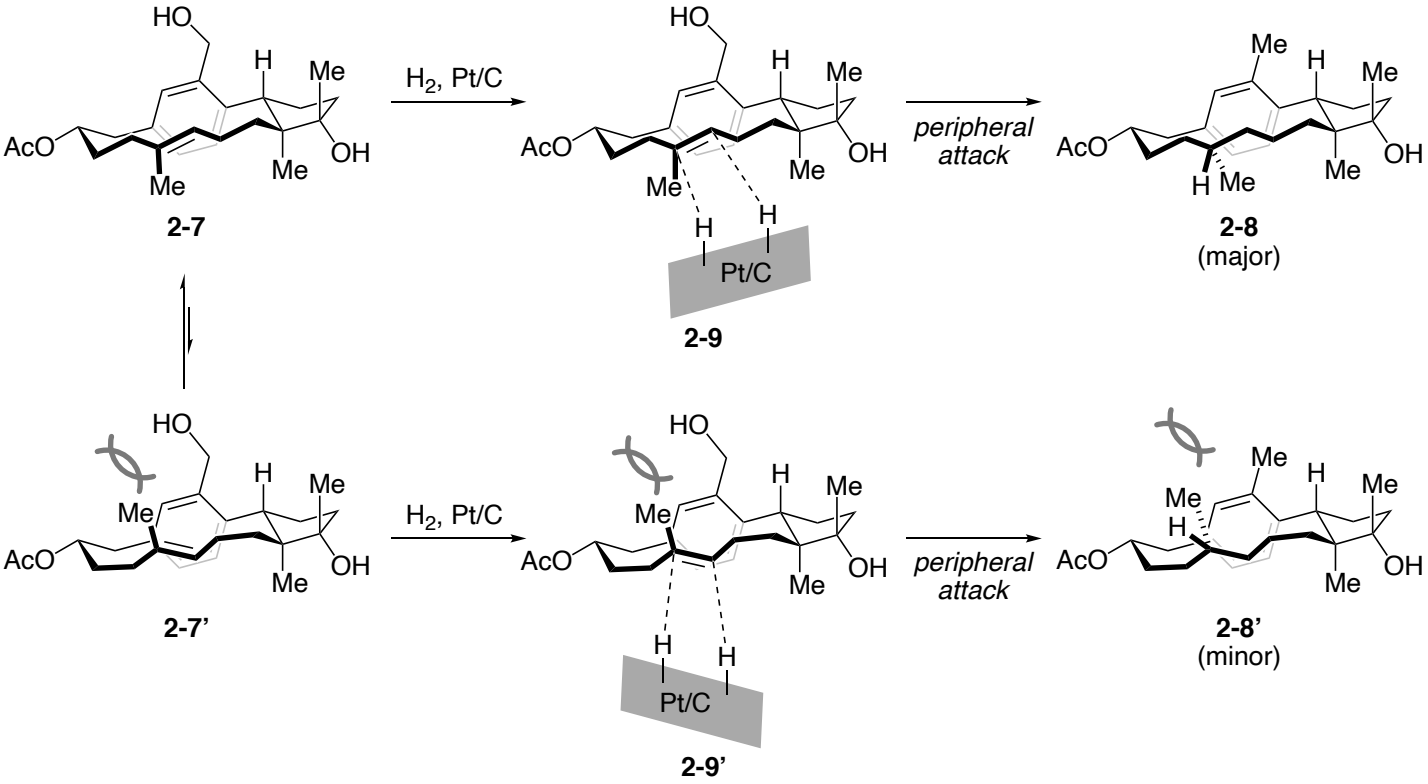
Discussion 2: hydrogenation

2-1. Conformation

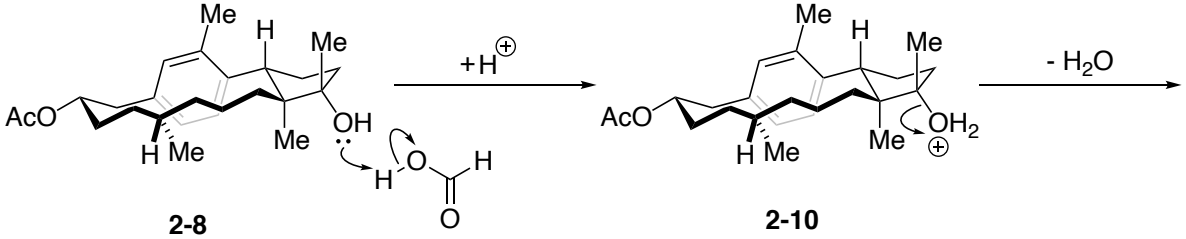


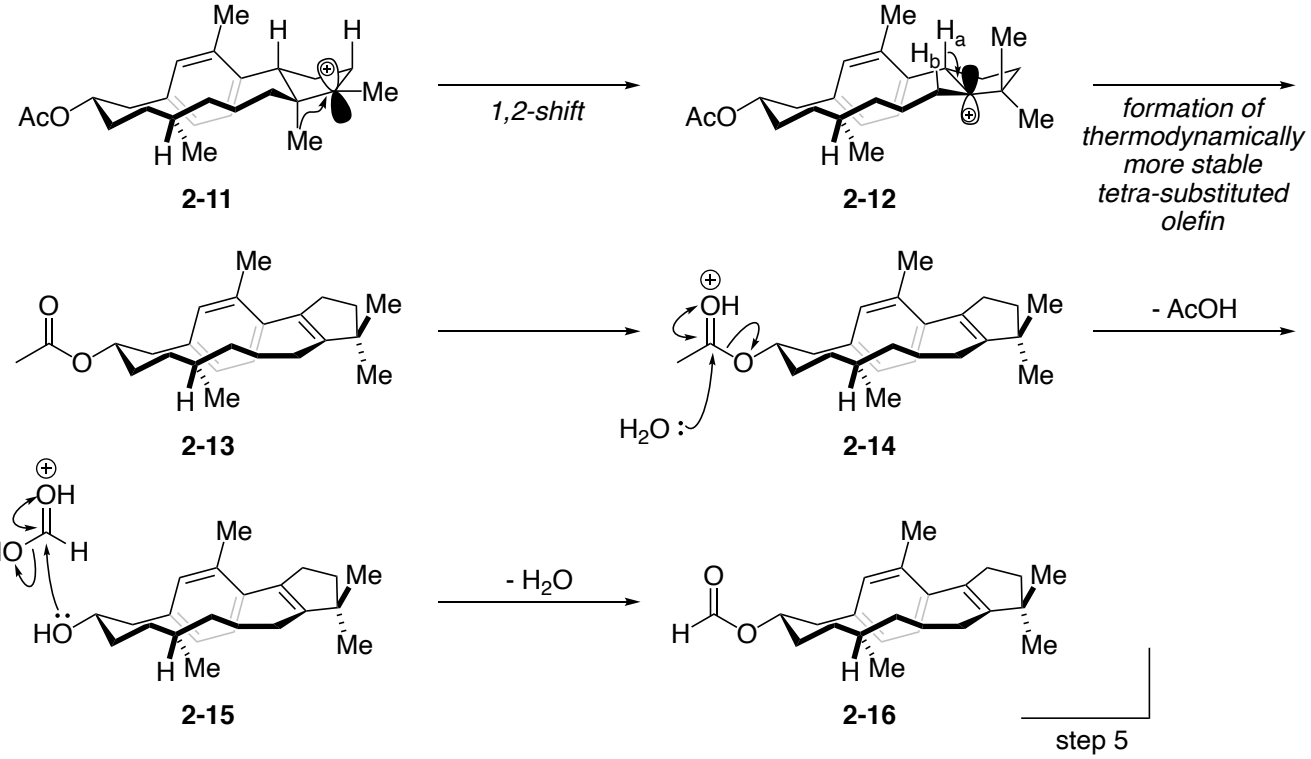
Due to the rigidity and bulkyness of phenyl group, bond rotation is permitted only as to alkyl chain.

2-2. Stereoselectivity

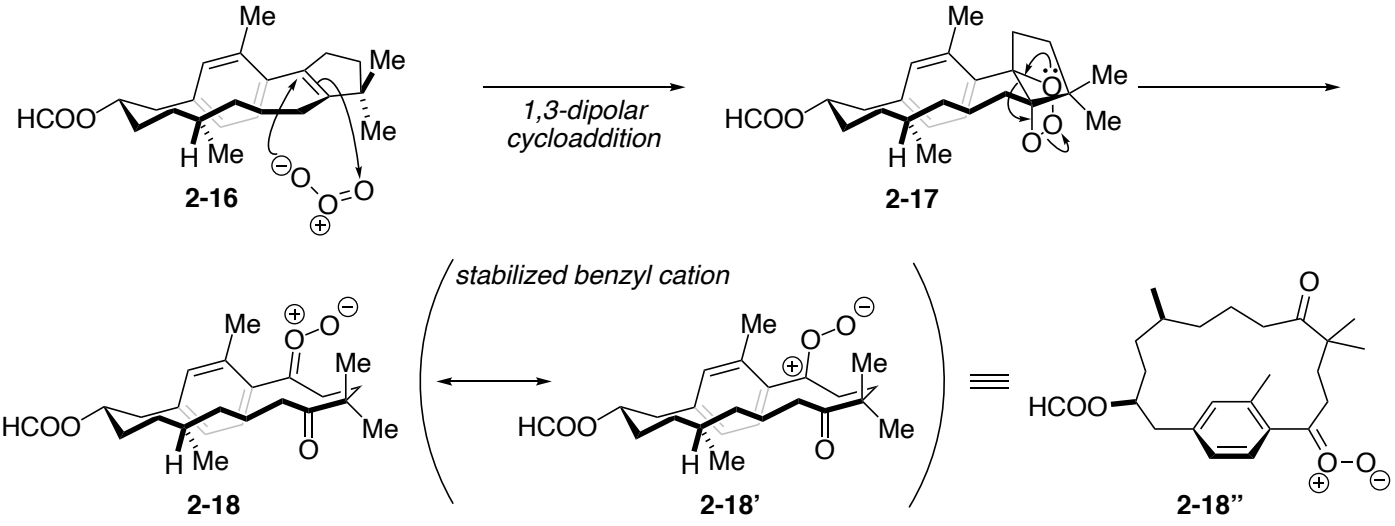


5th step

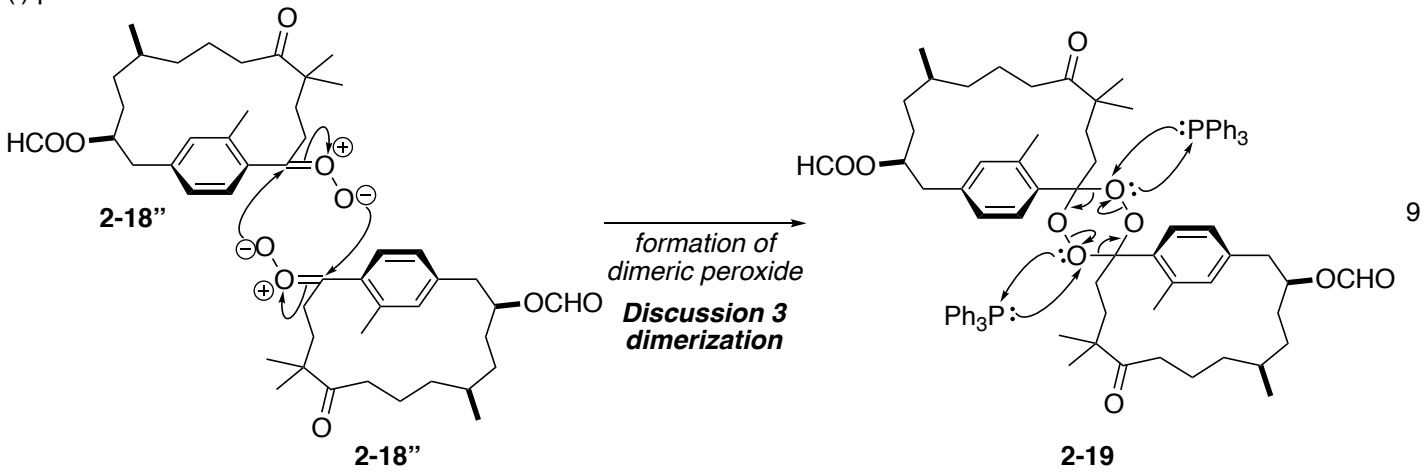


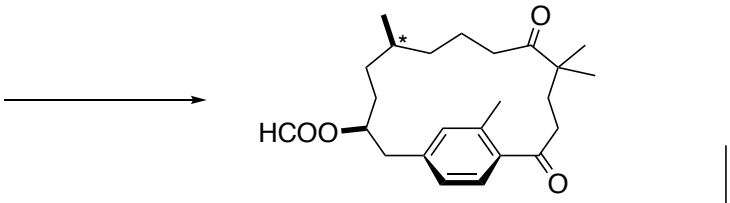


6th step



(i) path toward **2-2**



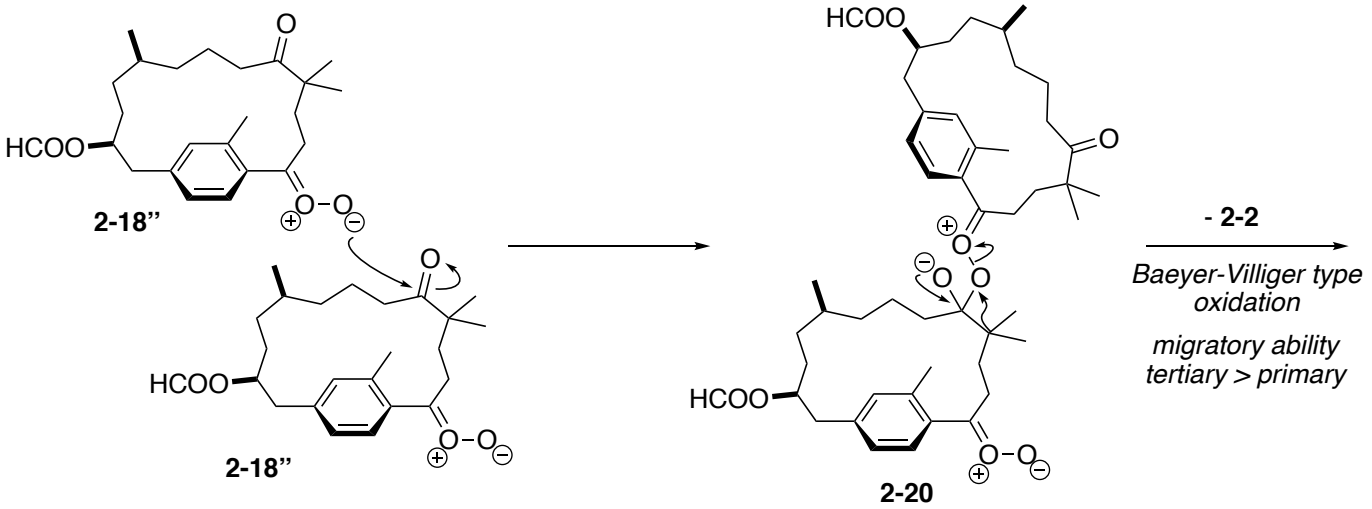


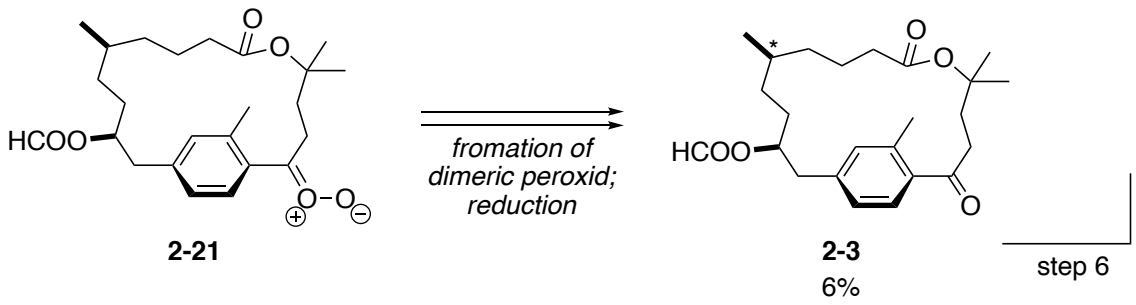
2-2

34% (dr = 8:1)

step 6

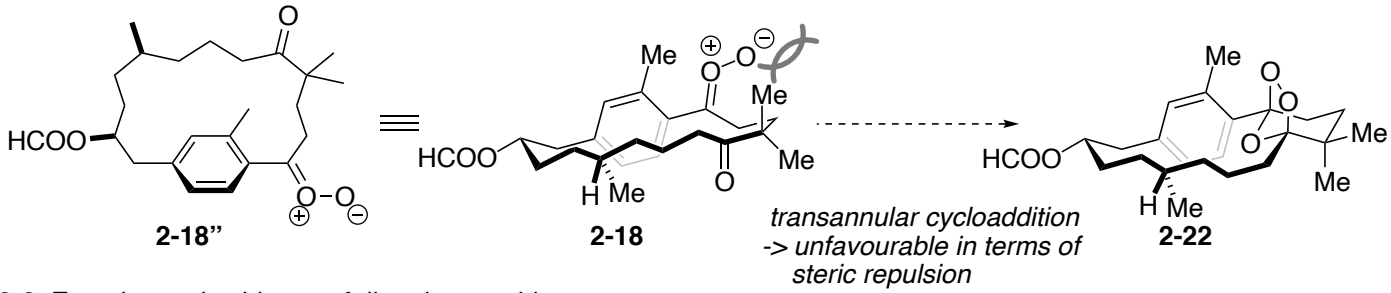
(ii) path toward **2-3**



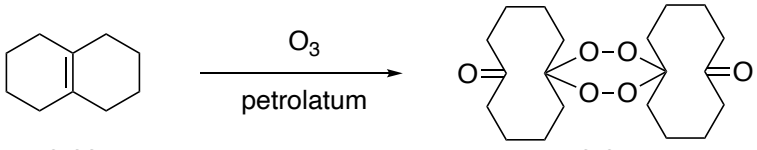


Discussion 3: dimerization

3-1. Formation of ozonide



3-2. Experimental evidence of dimeric peroxide



2-23

2-24
recrystalized

Ozonolysis of *Δ*9,10-octalin **2-23** afforded dimeric peroxide **2-24**.

R. Criegee, G. Wenner, Liebigs *Ann. Chem*. **1949**, *564*, 9