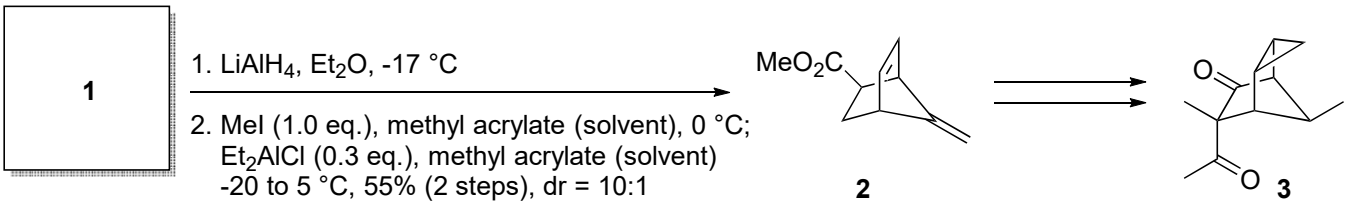
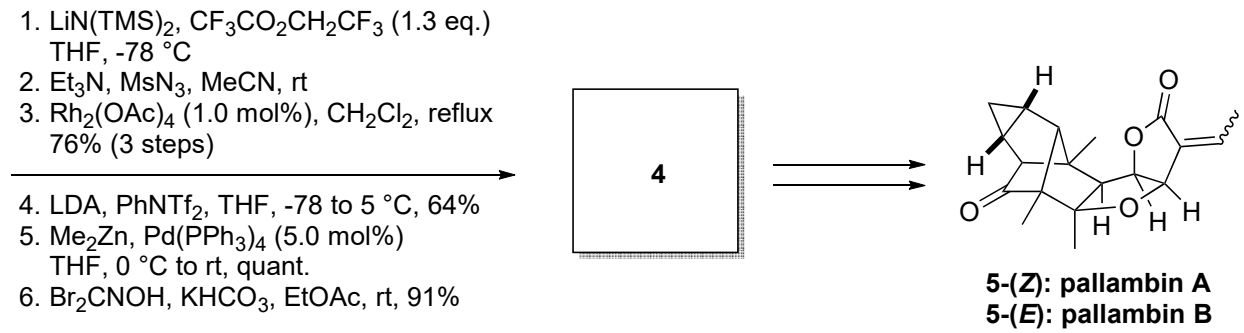
Problem Session (4)

2016.9.3. Hiroaki Matoba

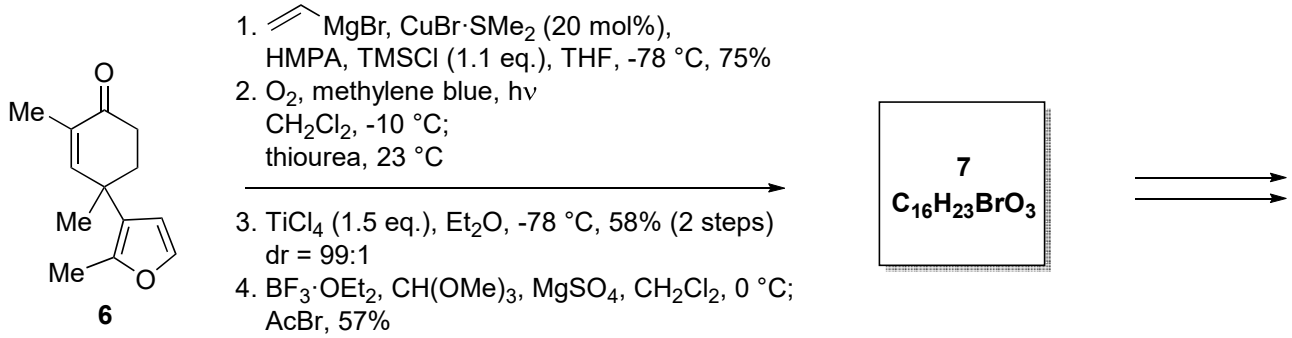
1. Please fill in the blank and provide reaction mechanism.

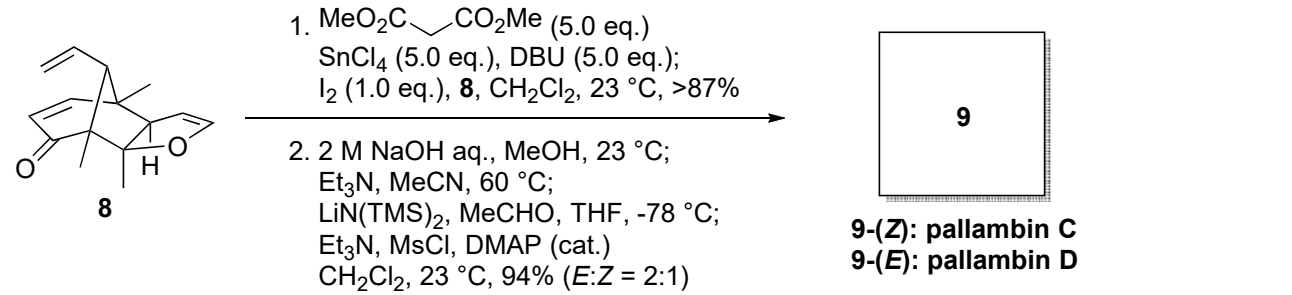




5-(*Z*): pallambin A
5-(*E*): pallambin B

2. Please fill in the blanks and provide reaction mechanism.

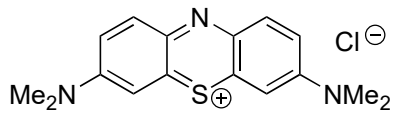




9-(*Z*): pallambin C
9-(*E*): pallambin D

3. Please provide the reaction mechanism.

9-(*Z*): pallambin C —(254 nm, CH_3CN; 56% (*E*:*Z* = 1.2:1))→ **5: pallambin A and B**



methylene blue

Problem Session (4) Answer

2016.9.3. Hiroaki Matoba

Topics: Total syntheses of pallambins

Introduction

Isolation

Pallambin D

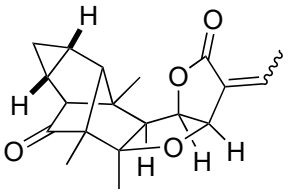
Asakawa, Y. et al. *Chem. Pharm. Bull.* **1998**, *46*, 178.

(from liverwort *Pallavicinia subciliata*)

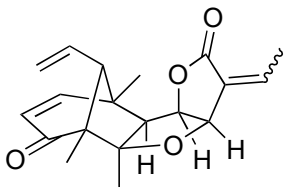
Pallambins A-D

Lou, H.-X. et al. *Org. Lett.* **2012**, *14*, 1102.

(from liverwort *Pallavicinia ambigua*)



5-(*Z*): pallambin A
5-(*E*): pallambin B



9-(*Z*): pallambin C
9-(*E*): pallambin D

Biological activity

Ability to reverse the adriamycin-induced resistance of K562/A02 cells

Total syntheses (racemic)

Wong, H. N. C. et al. *Chem. Commun.* **2012**, *48*, 8517. (pallambins C and D)

Ebner, C. and Carreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11227. (pallambins A and B) (Problem 1)

Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 7536. (pallambins C and D) (Problem 2)

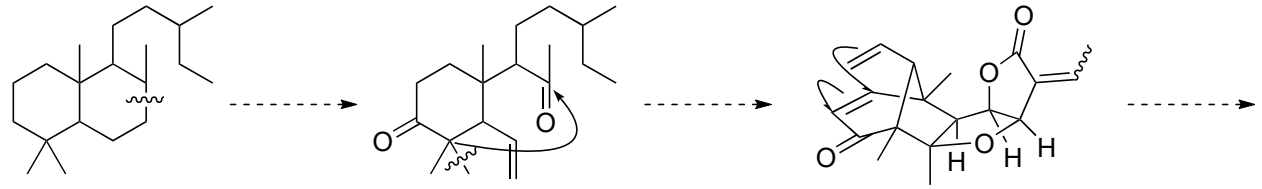
Plausivle Biosynthetic pathway

Labdane to pallambin D

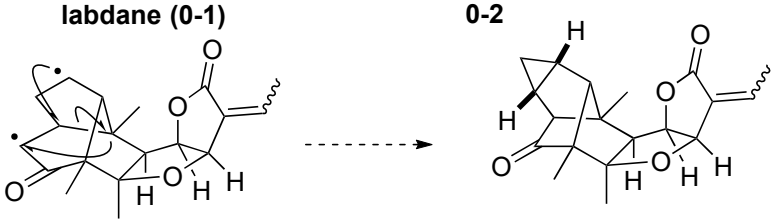
Asakawa, Y. et al. *Chem. Pharm. Bull.* **1998**, *46*, 178.

Pallmbins C and D to pallmbins A and B

Lou, H.-X. et al. *Org. Lett.* **2012**, *14*, 1102.



labdane (0-1) **0-2** **9-(*Z*): pallambin C** **9-(*E*): pallambin D**

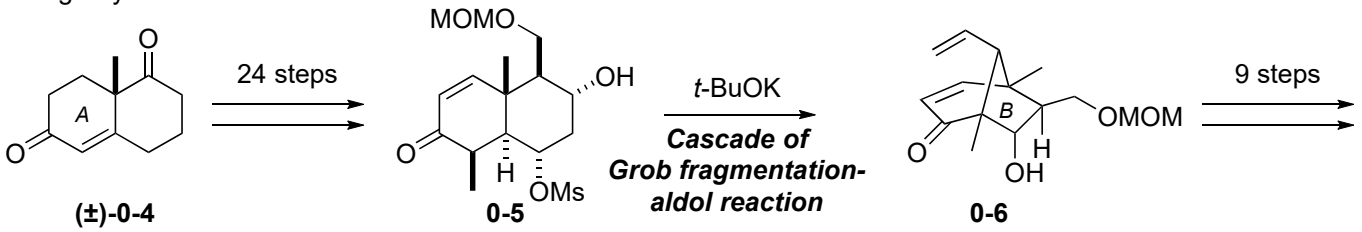


0-3 **5-(*Z*): pallambin A** **5-(*E*): pallambin B**

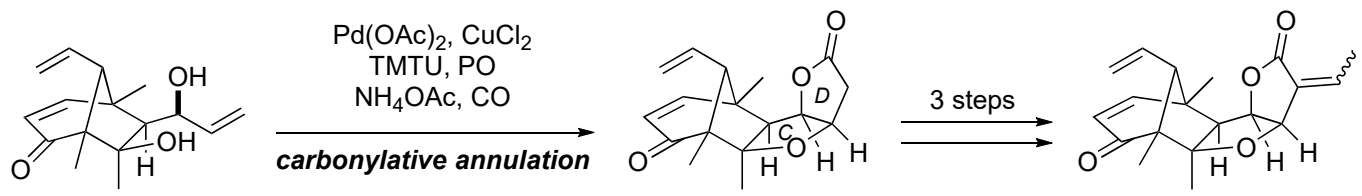
Interconversion from pallmbin C to pallmbins A and B

Lou, H.-X. et al. *Org. Lett.* **2012**, *14*, 5624. (Problem 3)

Wong's synthesis



(±)-0-4 **0-5** **0-6**

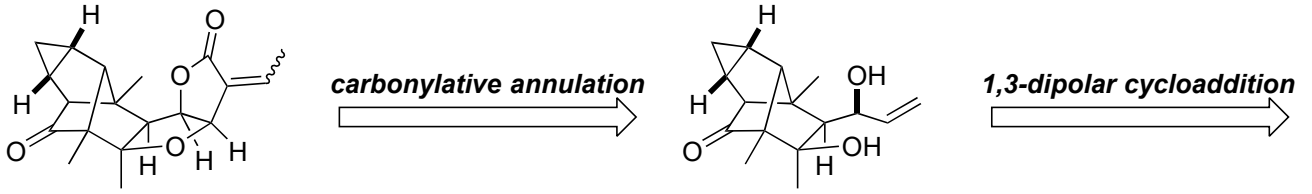


0-7 **0-8** **9-(*Z*): pallambin C** **9-(*E*): pallambin D**

38 steps

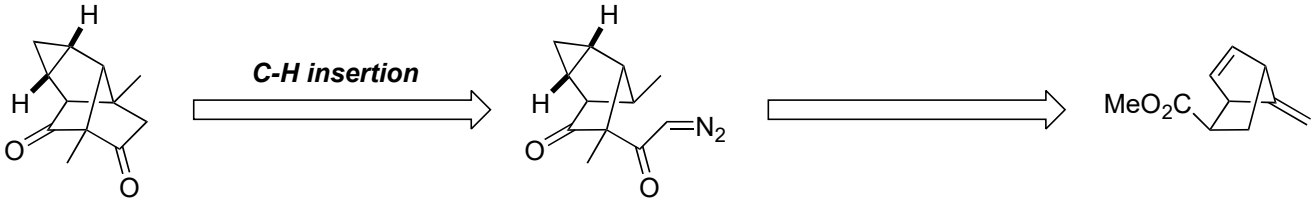
Problem 1
Total syntheses of pallambins A and B (Carreira's group)

Retrosynthetic ananlysis

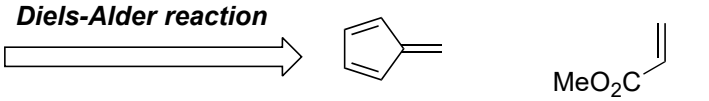


5-(*Z*): pallambin A
5-(*E*): pallambin B

1-1



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



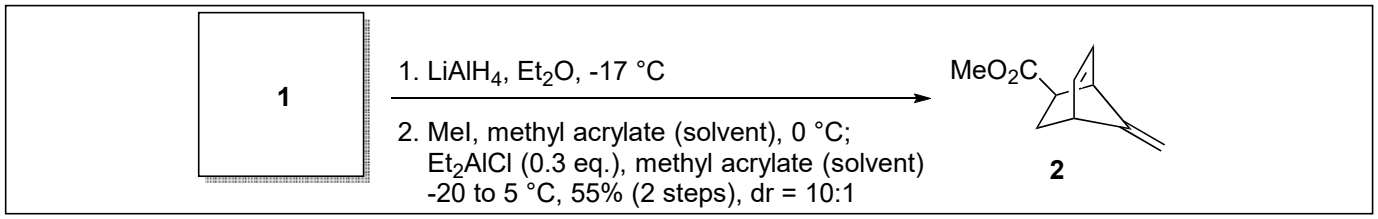
pentafulvene
1-5

methyl acrylate

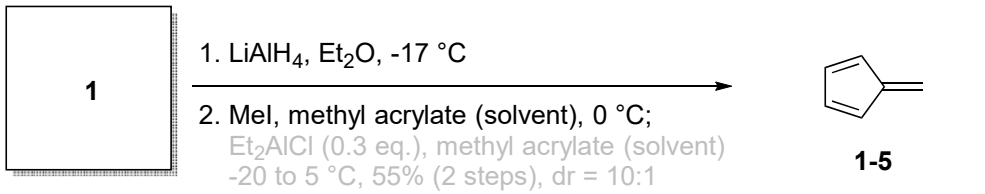
Pentafulvene
An isomer of benzene
Polymerizations ocurres with light and heat
Acid and base sensitive
Stable in neat form only below -70 °C

Generation in situ is required.

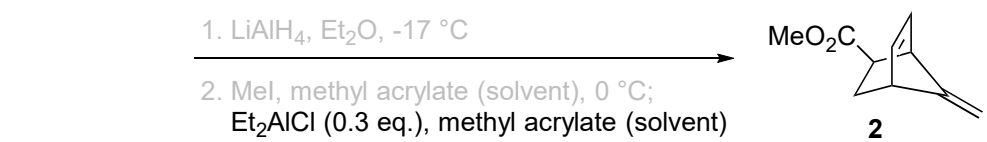
Answer



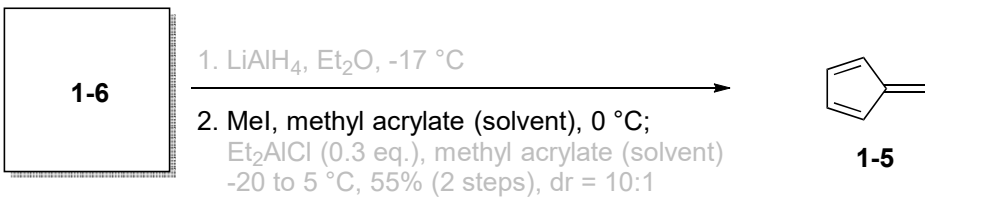
2



1-5



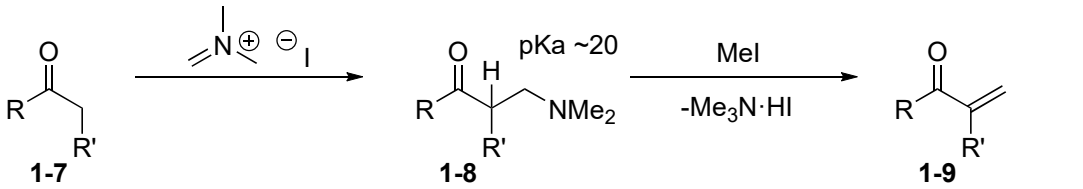
2

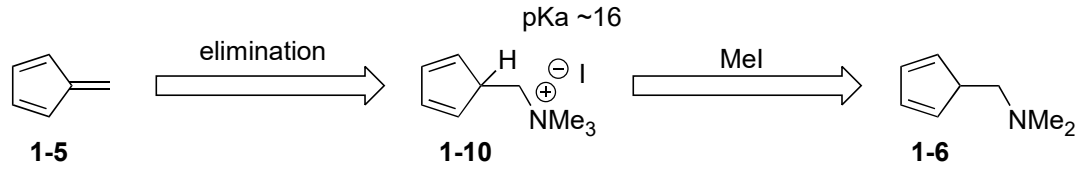


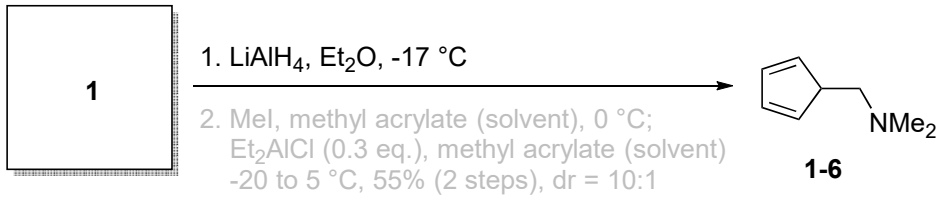
1-5

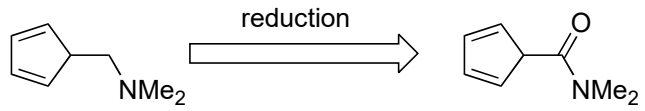
Pentafulvene has no methyl group.
MeI is used for elimination.

Eschenmoser methylenation (Hofmann elimination)





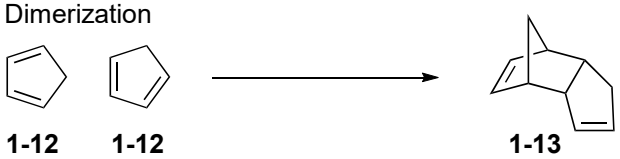




1-11 is substituted cyclopentadiene.

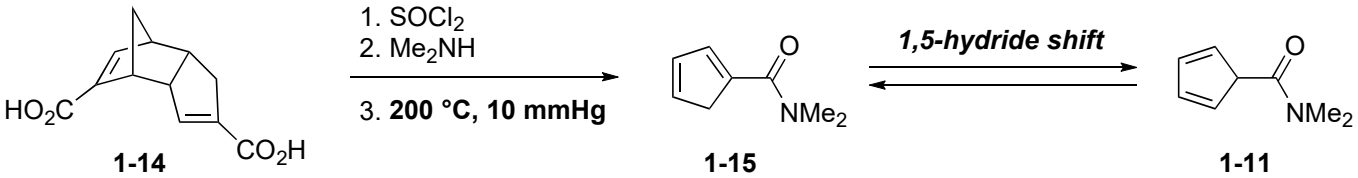
Reactivity of cyclopentadiene

Dimerization

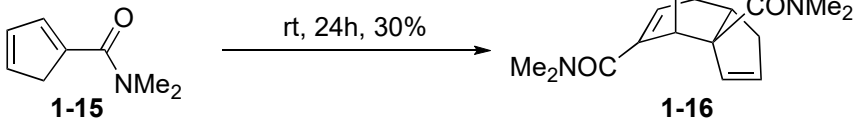


experimental data of **1-11** (Peters, D. *J. Chem. Soc.* **1960**, 1832.)

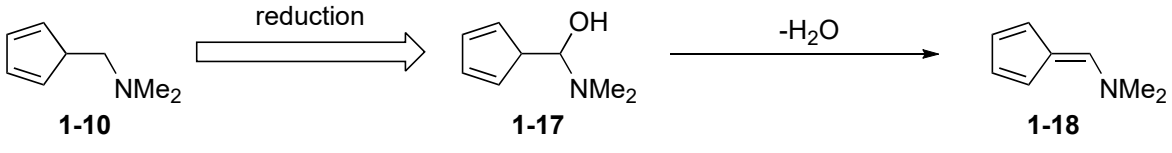
preparation

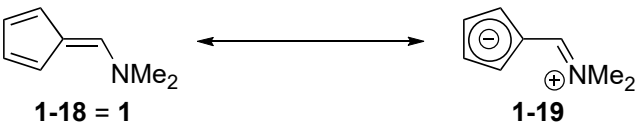


dimerization



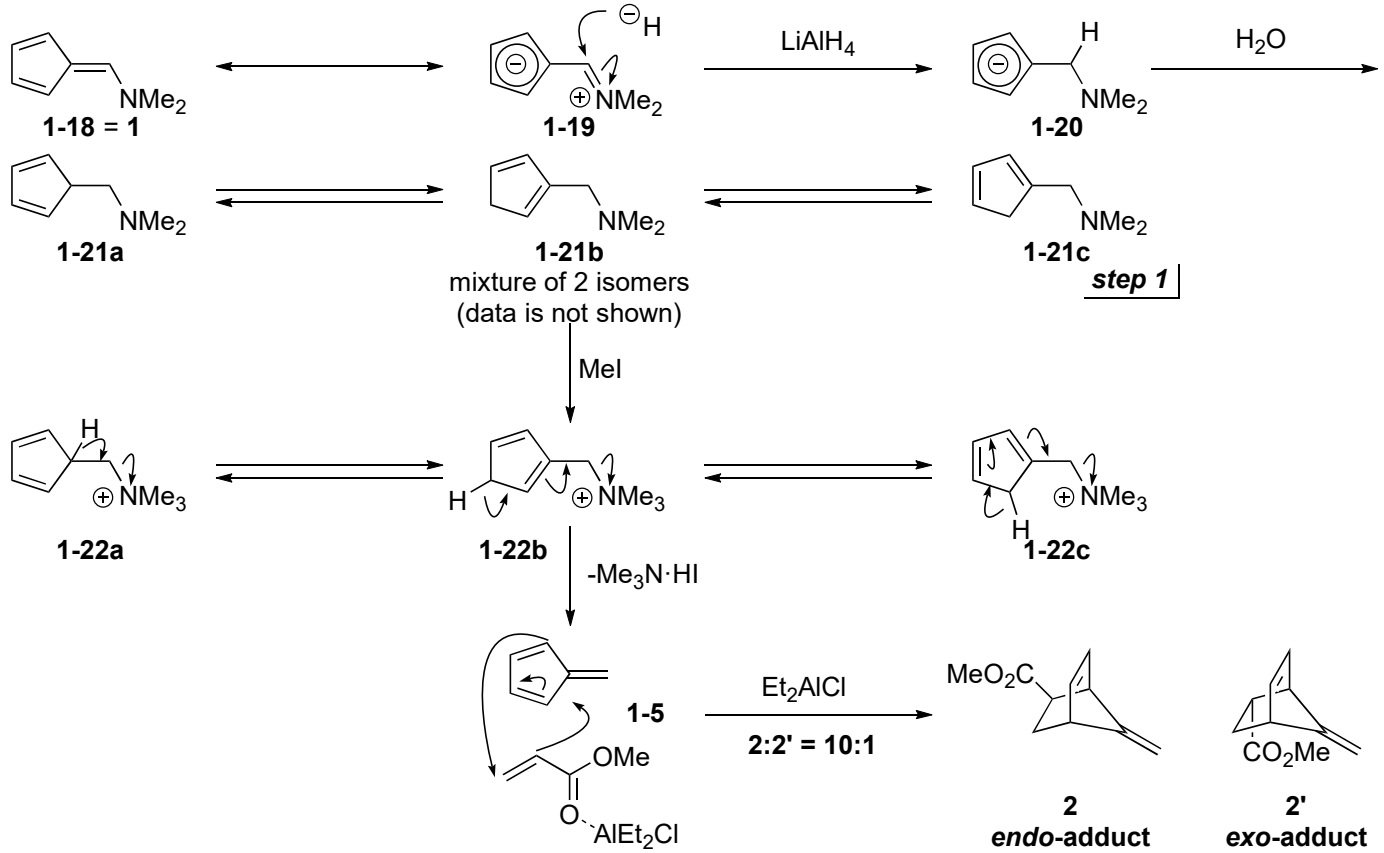
1-11 (1-15) is not suitable to use the precursor of pentafulvene.

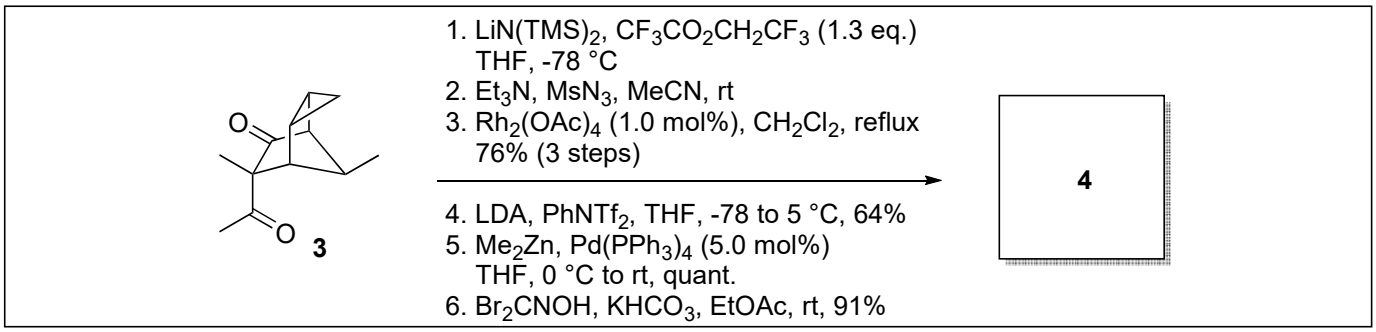




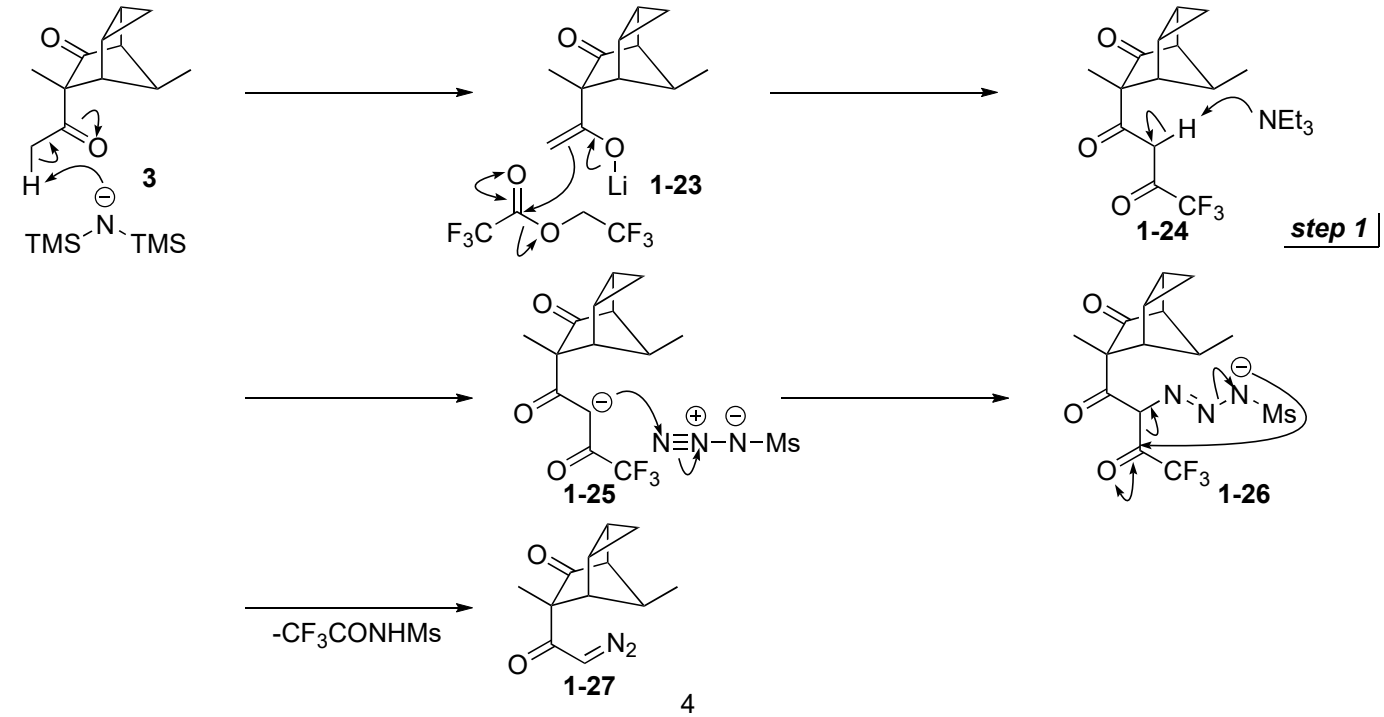
1-18 seems to be stable because its resonance structure **1-19** has aromaticity.
Actually, **1-18** is commercial available and bench-stable compound.

proposed mechanism (**1** -> **2**)

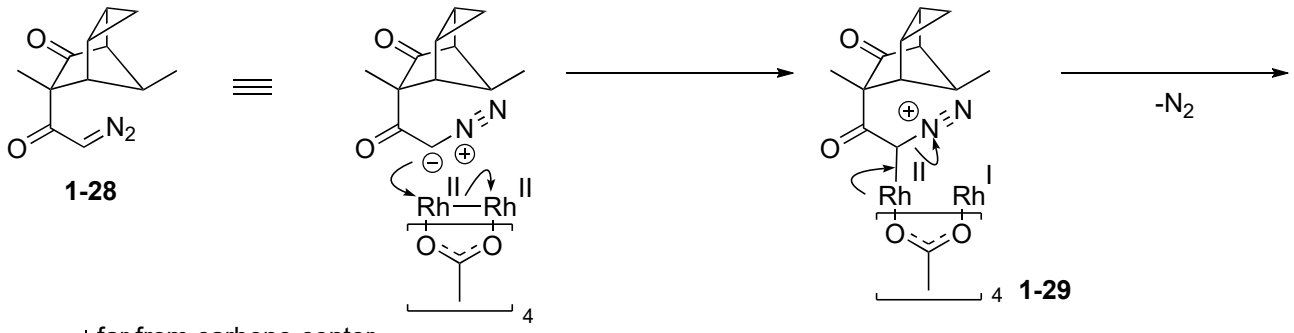


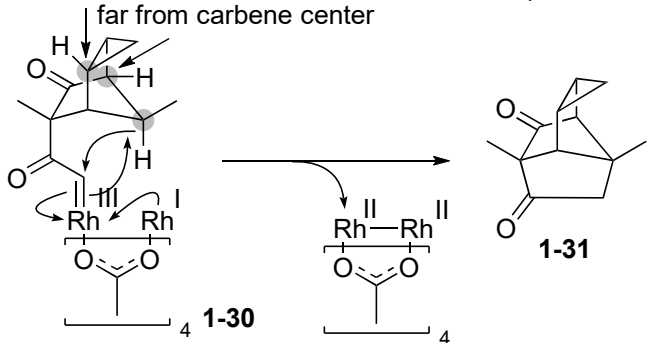


Step 1,2
Diazo transfer



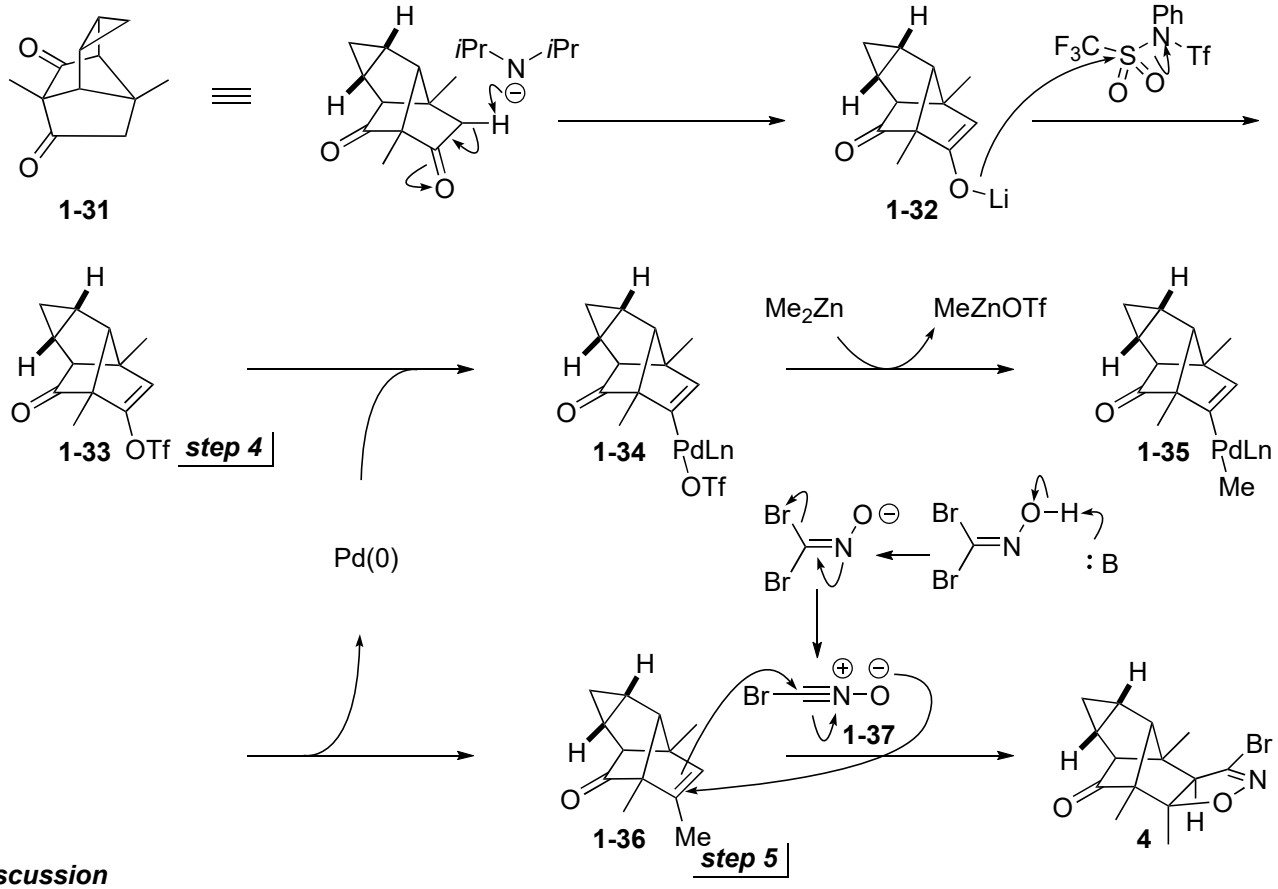
Step 3
Intramolecular C-H insertion





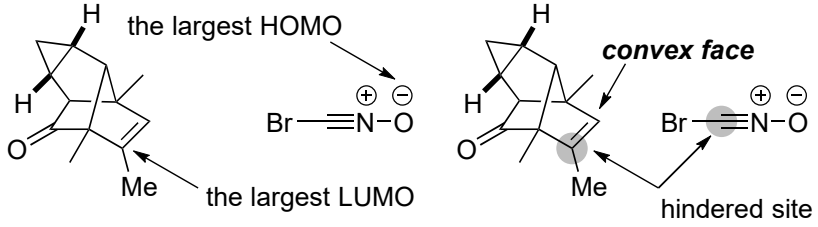
● : fifth carobons from carbene center

Step 4,5,6
Negishi coupling, cycloaddition of nitrile oxide



Discussion

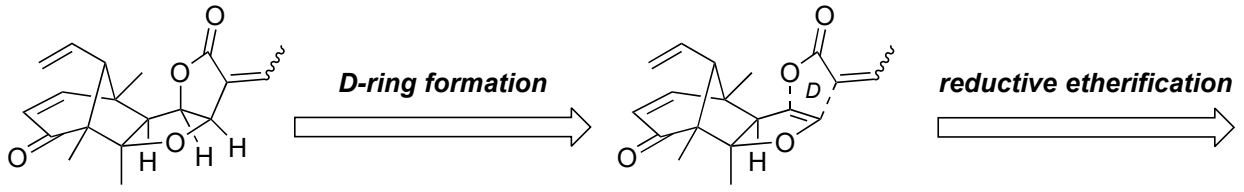
Regio and stereoselectivity of 1,3-dipolar cycloadditon



Both of the electronic and steric reasons, cycloaddition gave sole product.

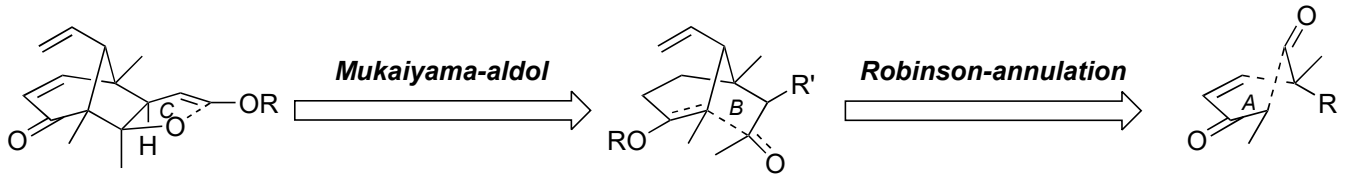
Problem 2
Total syntheses of pallambins C and D (Baran's group)

Retrosynthetic ananlysis



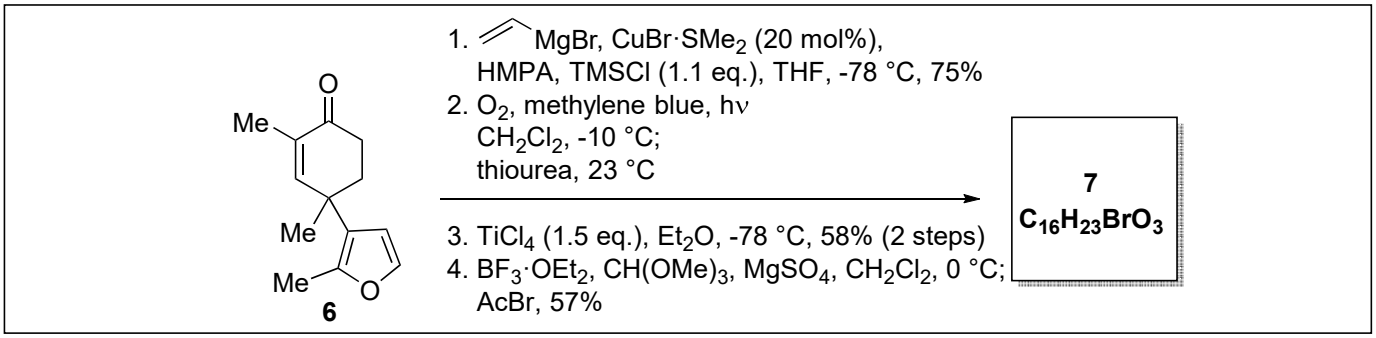
9-(*Z*): pallambin C
9-(*E*): pallambin D

2-1

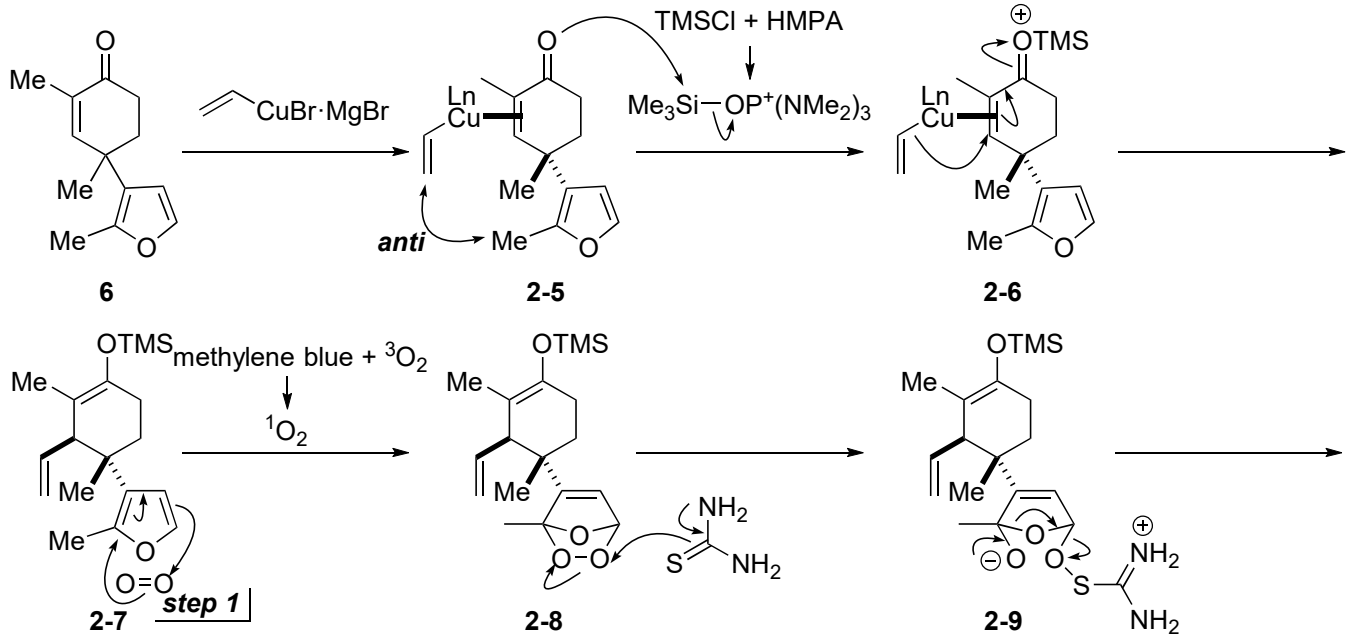


2-2 **2-3** **2-4**

Answer

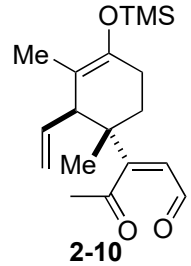


Step 1,2
1,4-addition
Oxidative cleavage of furan



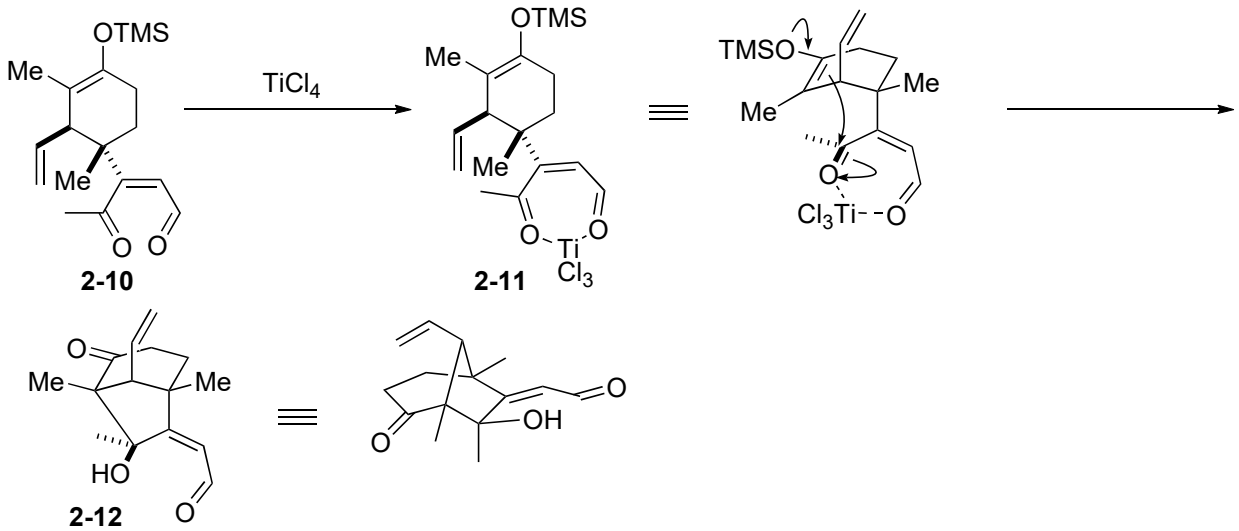
6 **2-5** **2-6**

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



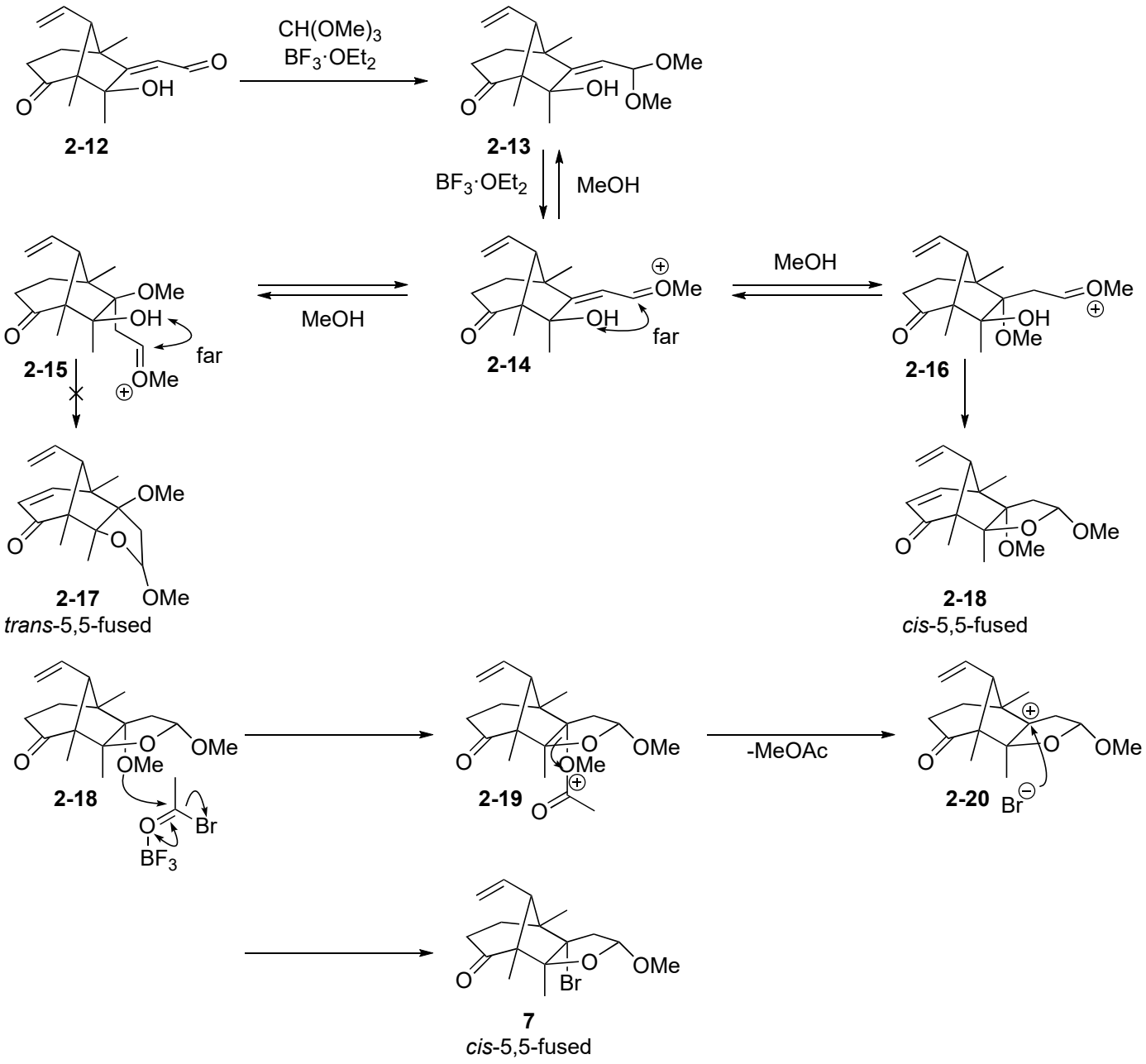
2-10

Step 3
Mukaiyama-aldol



2-10 **2-11** **2-12**

Step 4
Ether ring formation (another possible mechanism -> p.14 appendix)



2-12 **2-13** **2-14** **2-15** **2-16** **2-17** **2-18** **2-19** **2-20** **7**

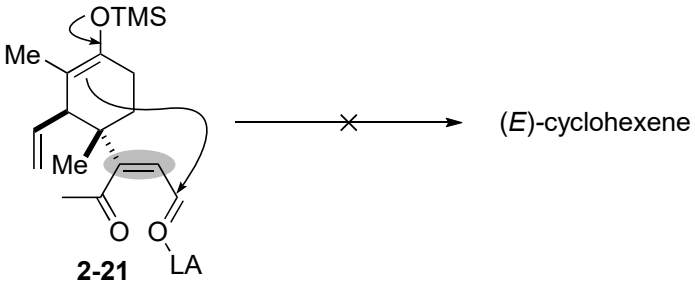
trans-5,5-fused

cis-5,5-fused

cis-5,5-fused

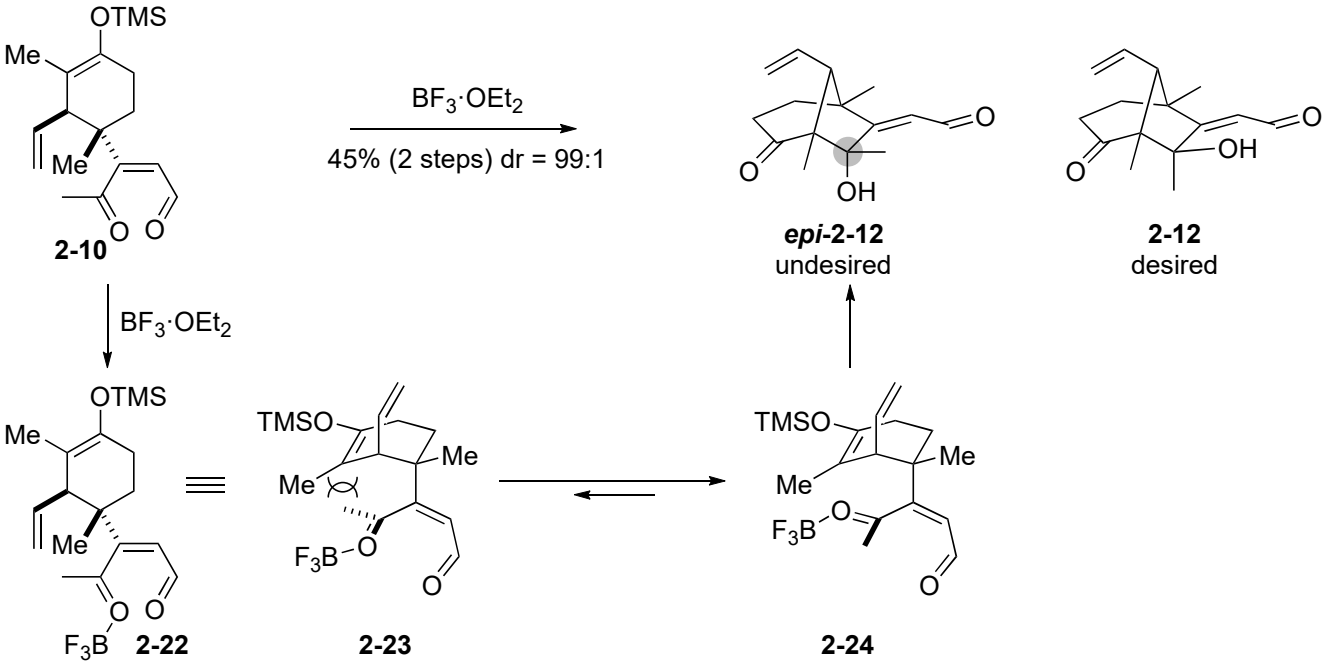
Discussion

Regioselectivity of Mukaiyama-aldol



2-21

Steleoselectivity of Mukaiyama-aldol



2-10

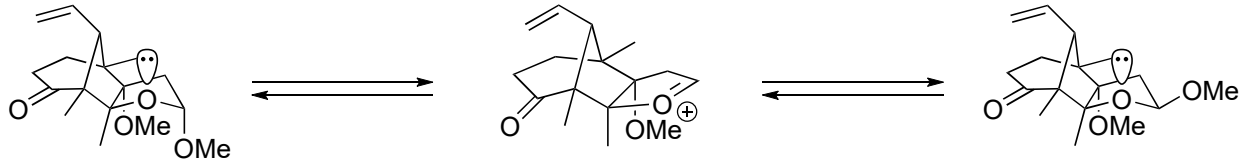
***epi*-2-12**
undesired

2-12
desired

2-22 **2-23** **2-24**

Using non-chelating Lewis acid, selectivity is reverse.
Chelation is important to obtain desired product.

Steleoselectivity of methyl acetal



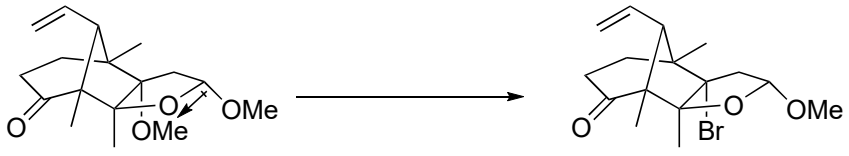
2-18
favored

2-25

2-26
disfavored

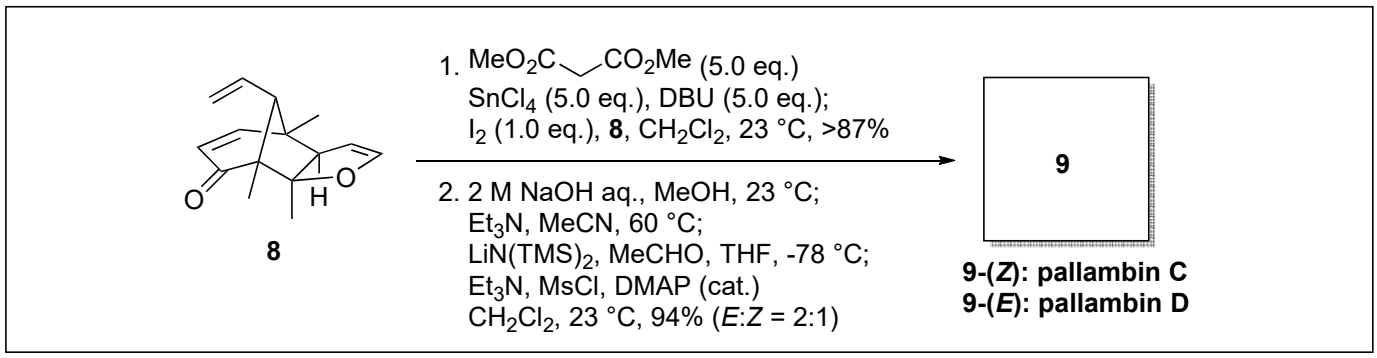
Considering anomeric effect, **2-18** is thermodynamically stable product.

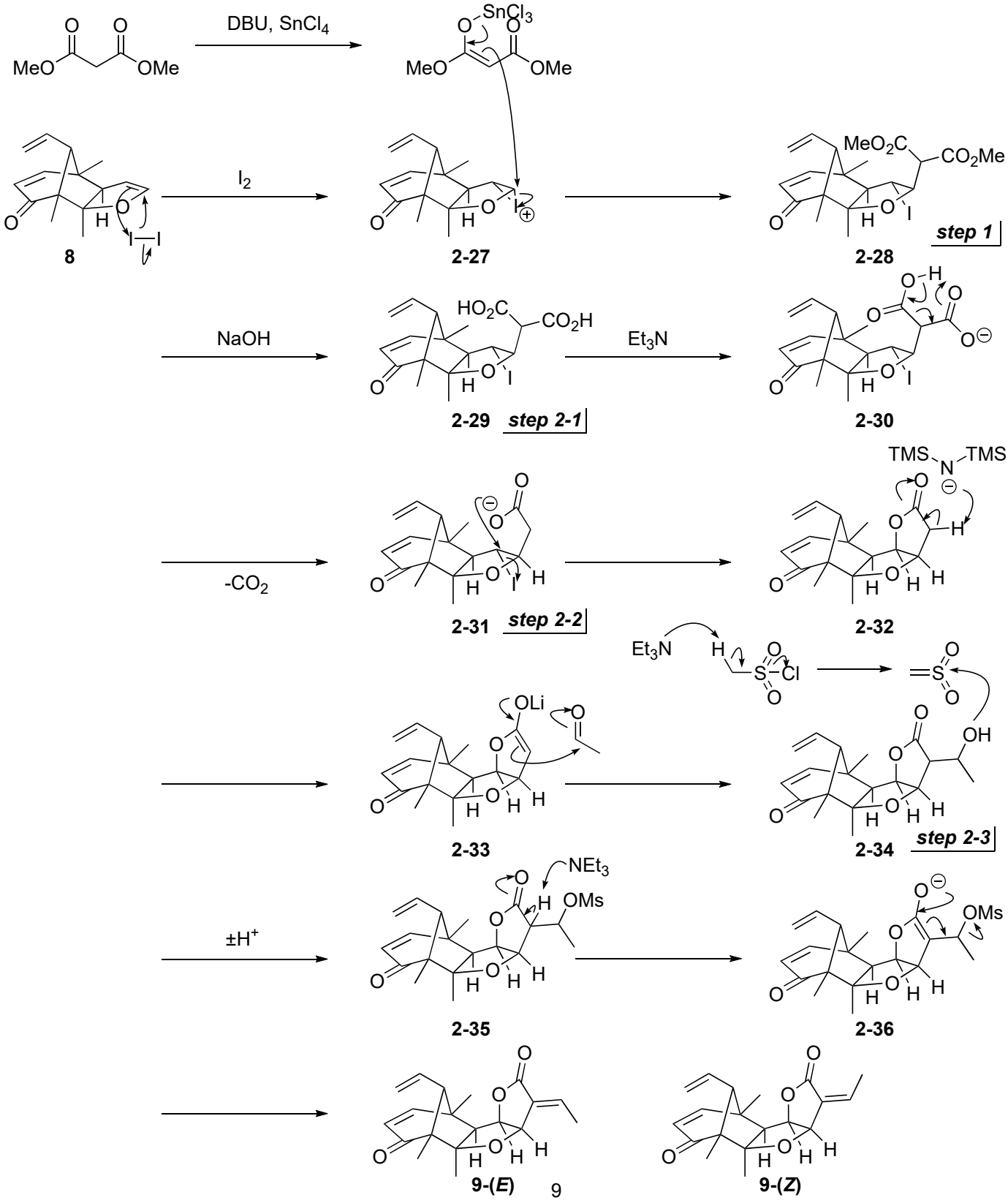
Chemoselectivity of bromination



2-18 **7**

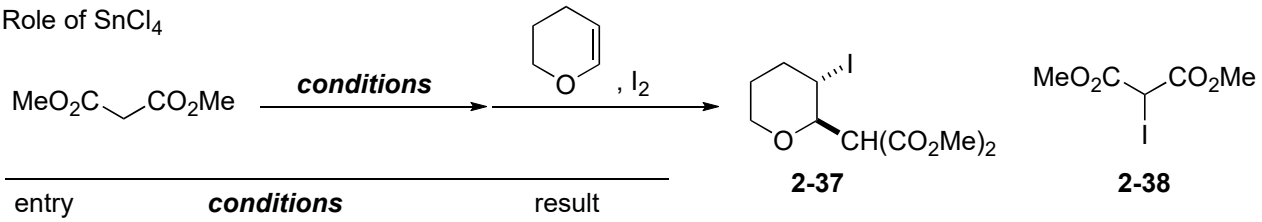
Methyl acetal is less nucleophilic because of inductive effect.


1. MeO2C CO2Me (5.0 eq.)
SnCl4 (5.0 eq.), DBU (5.0 eq.);
I2 (1.0 eq.), 8, CH2Cl2, 23 °C, >87%
2. 2 M NaOH aq., MeOH, 23 °C;
Et3N, MeCN, 60 °C;
LiN(TMS)2, MeCHO, THF, -78 °C;
Et3N, MsCl, DMAP (cat.)
CH2Cl2, 23 °C, 94% (E:Z = 2:1)
8
9
9-(Z): pallambin C
9-(E): pallambin D


DBU, SnCl4
I2
NaOH
Et3N
-CO2
Et3N
±H+
8
2-27
2-28
step 1
2-29
step 2-1
2-30
2-31
step 2-2
2-32
2-33
2-34
step 2-3
2-35
2-36
9-(E)
9-(Z)

Discussion

Role of $SnCl_4$



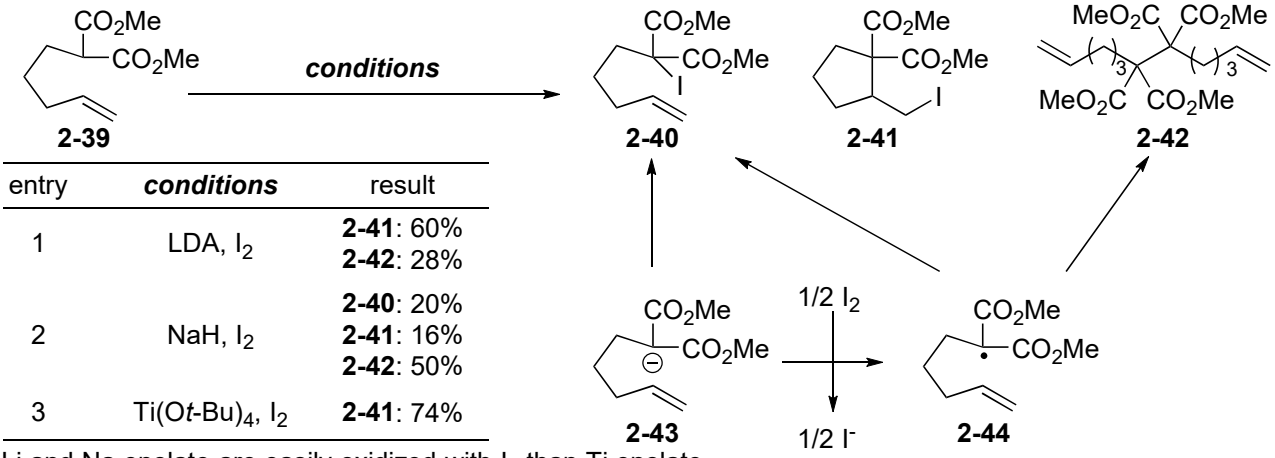
2-37 **2-38**

entry	***conditions***	result
1	NaH, THF, rt	**2-37**: 0% **2-38**: quant.
2	$SnCl_4$, DBU, CH_2Cl_2, rt	**2-37**: 92%

Sn enolate is essential in this reaction.

Some examples of intramolecular reaction

Effect of cation (Curran, D. P. et al. *JOC*, **1989**, *54*, 3140; Taguchi, T. et al. *TL*, **1992**, *33*, 2167.)



2-39 **2-40** **2-41** **2-42** **2-43** **2-44**

entry	***conditions***	result
1	LDA, I_2	**2-41**: 60% **2-42**: 28%
2	NaH, I_2	**2-40**: 20% **2-41**: 16% **2-42**: 50%
3	Ti(O*t*-Bu)$_4$, I_2	**2-41**: 74%

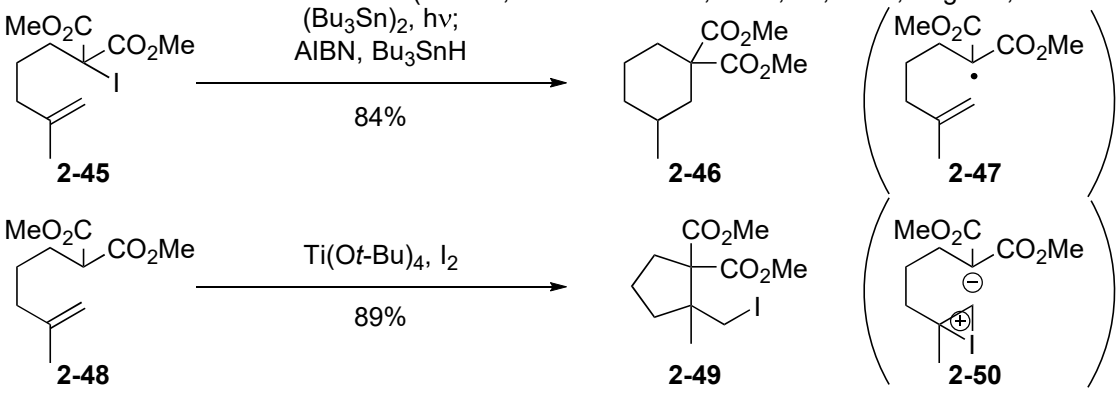
Li and Na enolate are easily oxidized with I_2 than Ti enolate.

Sn enolate probably exhibits the same reactivity that of Ti enolate.

HOMO level of Ti and Sn enolates are lower than that of Li and Na enolates,
and oxidation of Ti and Sn enolates are slower than that of Li and Na enolates.

Covalency of O-M bond reflects HOMO level of enolate.

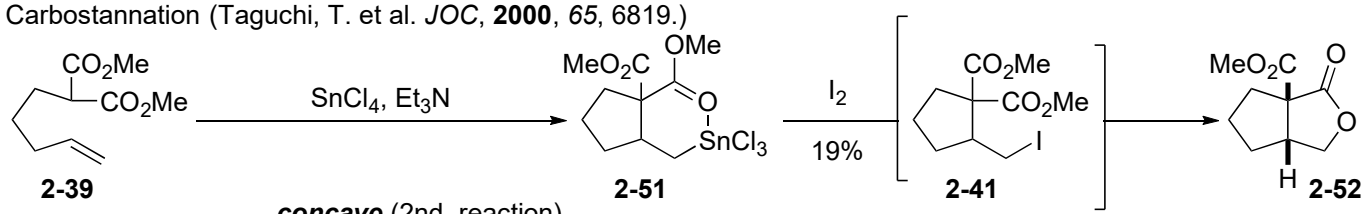
Reaction mechanism of Ti enolate (Curran, D. P. et al. *JOC*, **1989**, *54*, 3140; Taguchi, T. et al. *TL*, **1992**, *33*, 2167.)



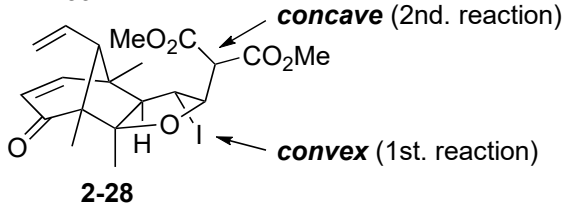
2-45 **2-46** **2-47** **2-48** **2-49** **2-50**

Radical cyclzation mechanism may be excluded.

Carbostannation (Taguchi, T. et al. *JOC*, **2000**, *65*, 6819.)



2-39 **2-51** **2-41** **2-52**



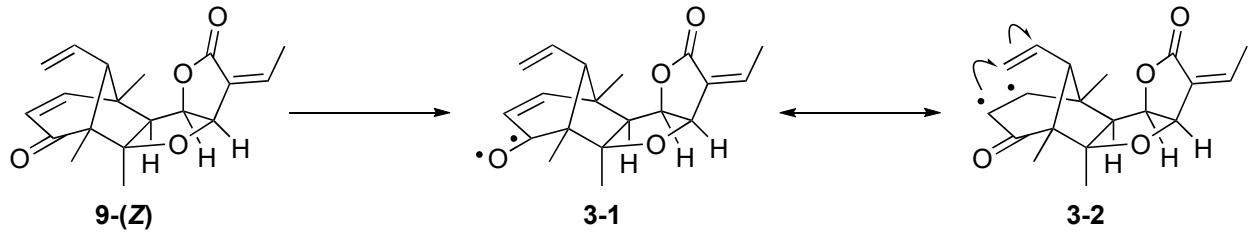
2-28

Carbostannation mechanism is not consistent with the stereochemistry of **2-28**.

Problem 3
Photoinduced rearrangement

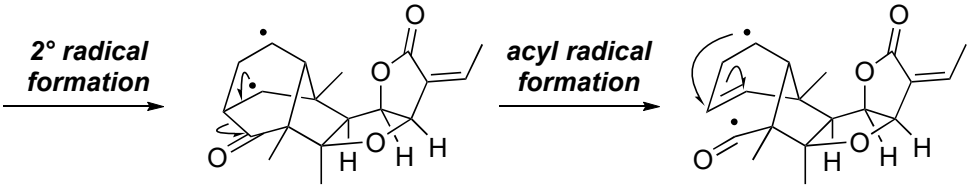
9-(*Z*): pallambin C —254 nm, CH_3CN, 56% (*E*:*Z* = 1.2:1)→ **5: pallambin A and B**

Path A



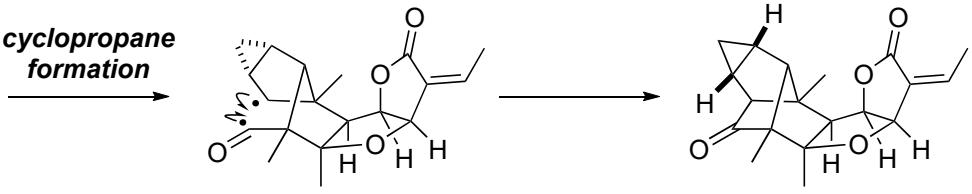
9-(*Z*) **3-1** **3-2**

2° radical formation *acyl radical formation*



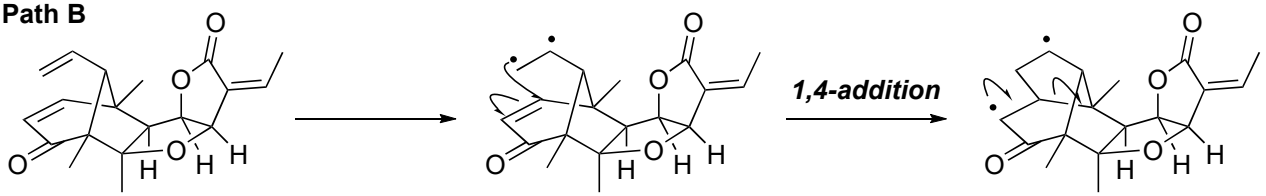
3-3 **3-4**

cyclopropane formation



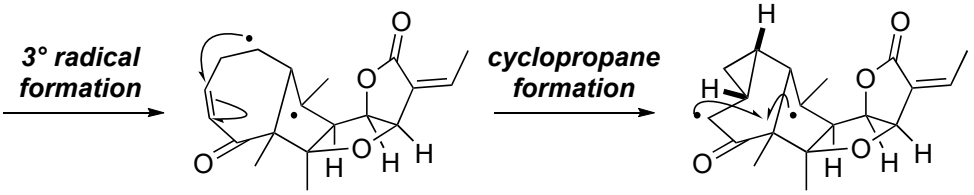
3-5 **5-(*Z*)**

Path B

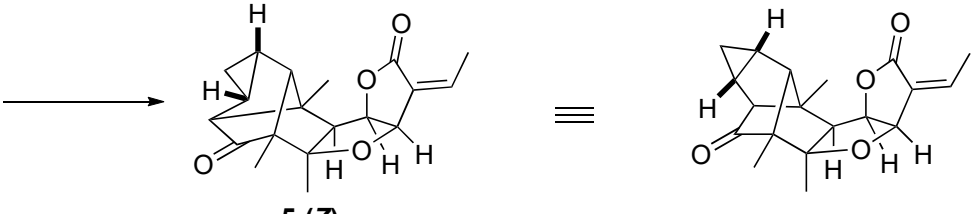


9-(*Z*) **3-6** *1,4-addition* **3-7**

3° radical formation *cyclopropane formation*



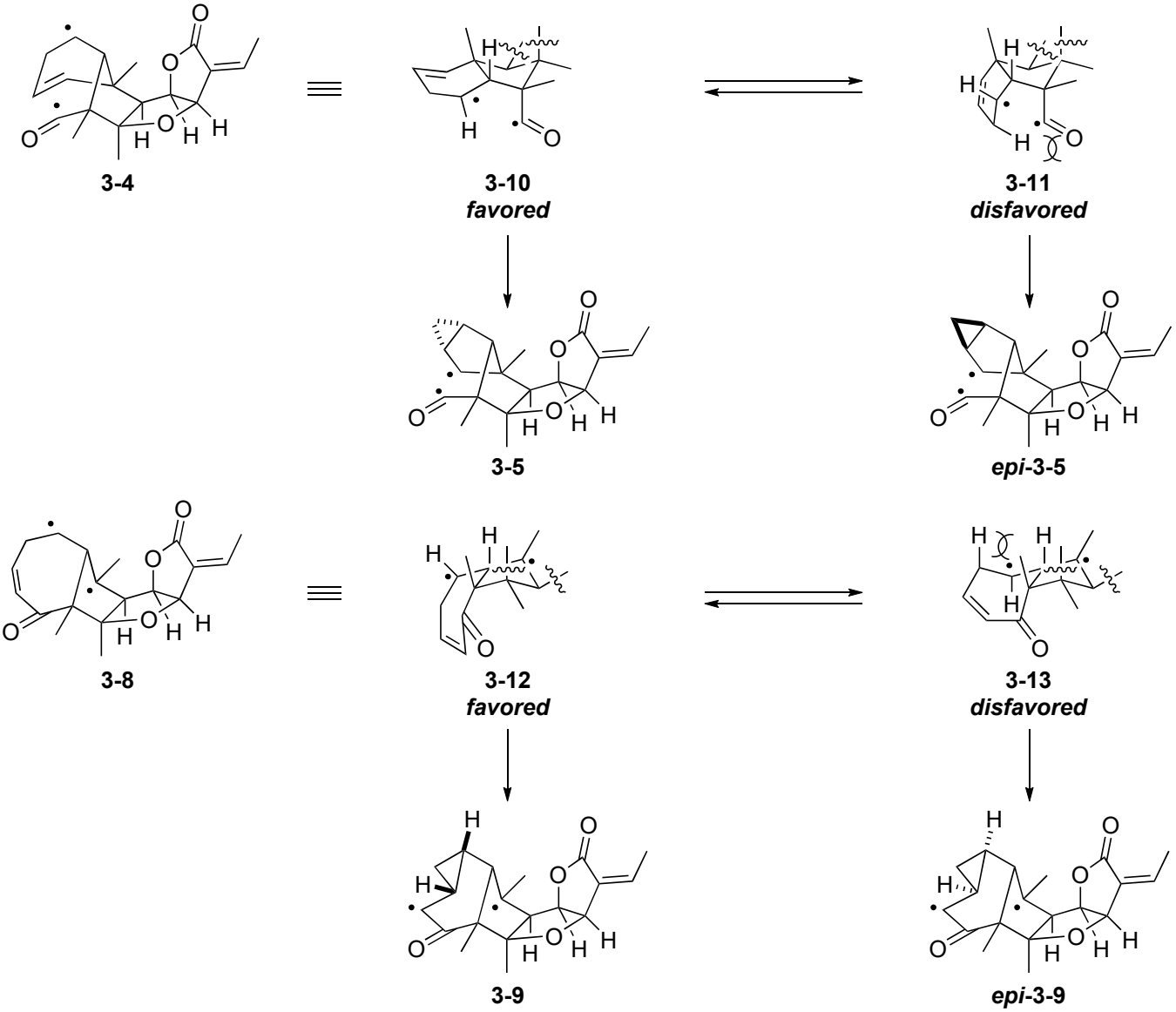
3-8 **3-9**



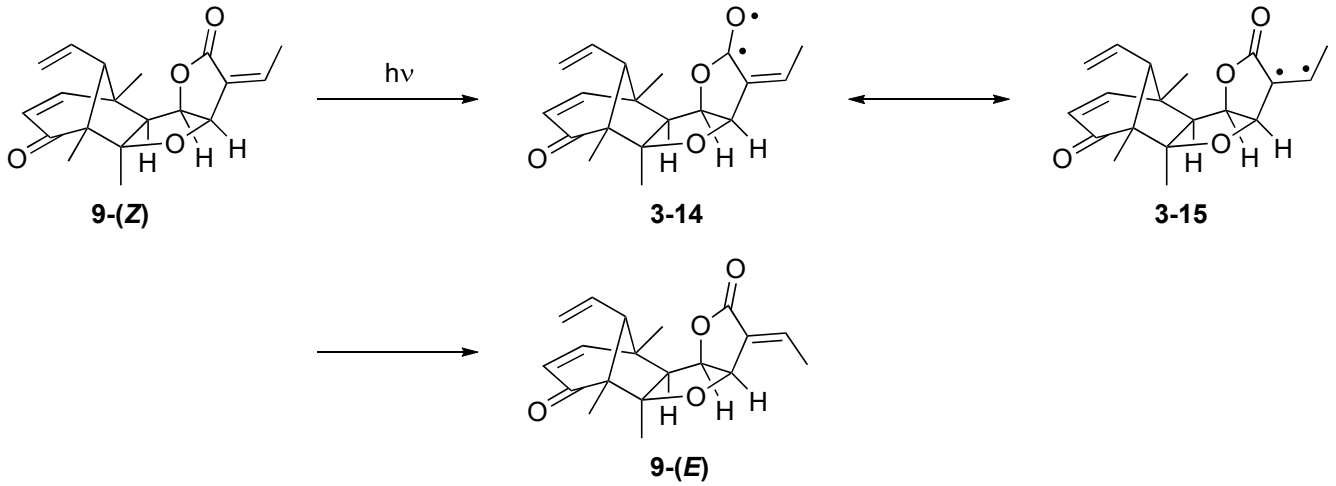
5-(*Z*)

Discussion

Stereochemistry of cyclopropane



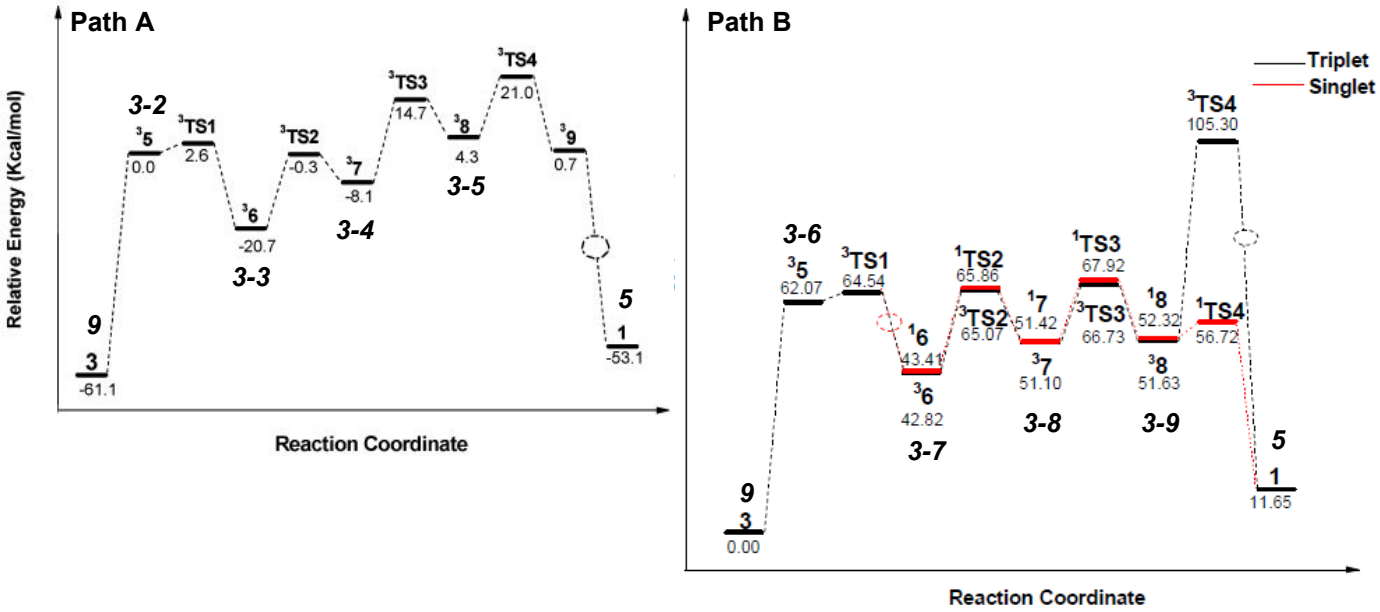
Isomerization of olefin



Isomerization of **5** is also occurred via the same mechanism.

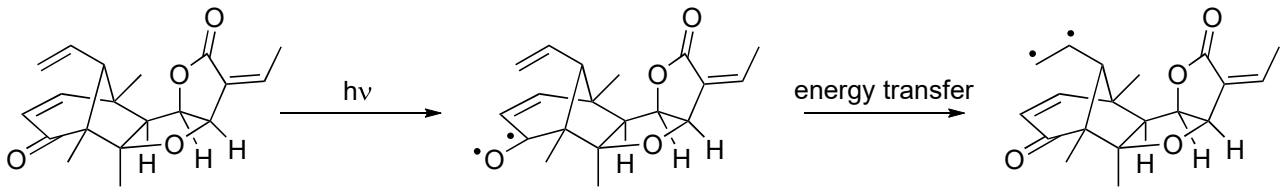
Experimental data

Computational study



TS2 (Path A) is more stable than TS2 (Path B) (20.4 vs 22.5 kcal/mol), suggesting that Path A is slightly favorable than Path B.

In Path A transformation from **3-4** to **3-5** is less favored than to **3-3**.



9-(*Z*) **3-1** **3-6**

λ_{max} of ethylene is 165 nm.

Direct excitation from **9** to **3-6** is difficult under this condition ($\lambda_{excitation}$ = 254 nm).

Intramolecular energy transfer from **3-1** to **3-6** is one of the possibility.

Appendix: bromination (Probelm 2)