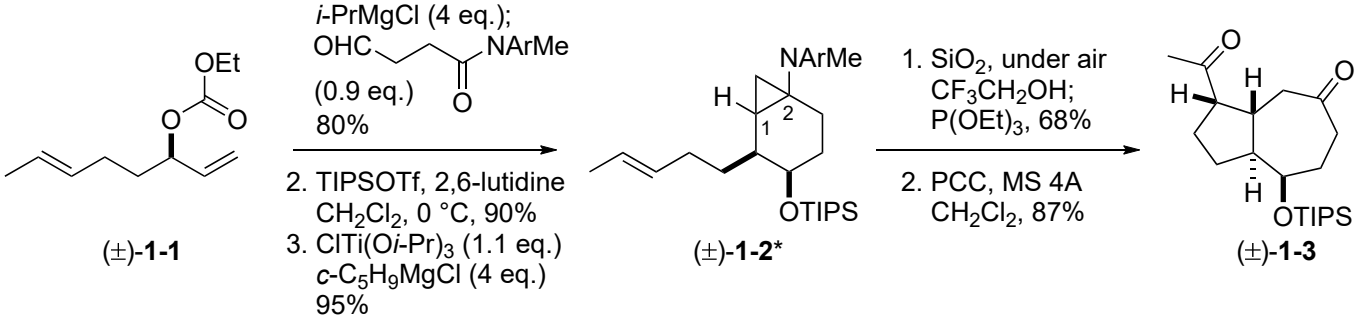
Problem Session (6)

2017. 7. 29. Takahiro KAWAMATA

Please provide the mechanisms of the following reactions

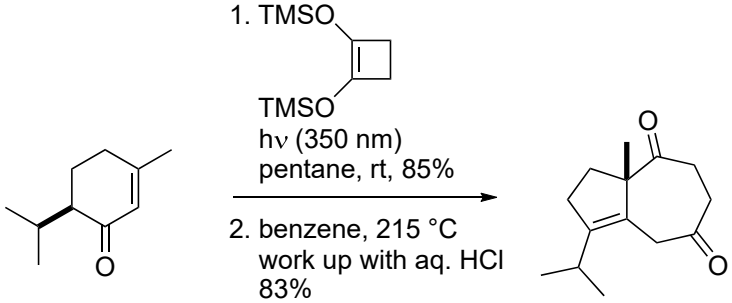
(1)



(±)-**1-1** (±)-**1-2*** (±)-**1-3**

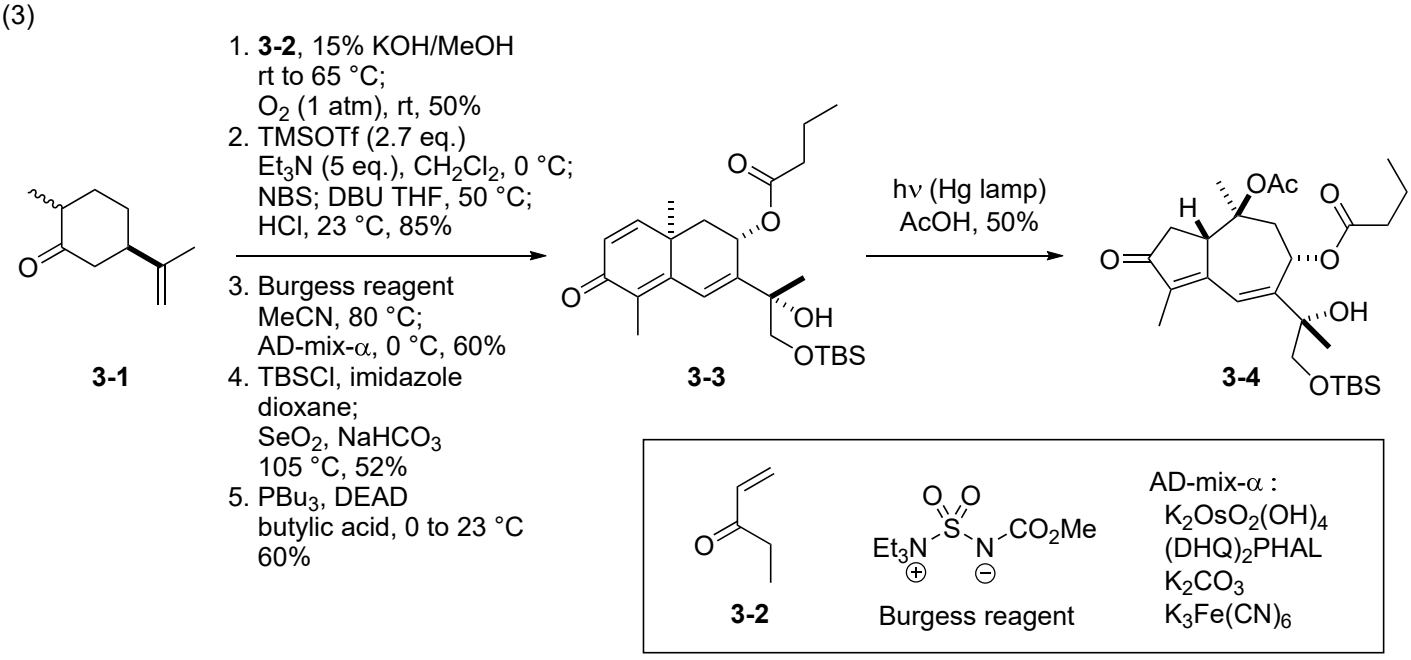
Ar = *p*-C_6H_4OMe * mixture of two *syn*-isomers (2:1) at C1,2 positions

(2)



2-1 **2-2**

(3)



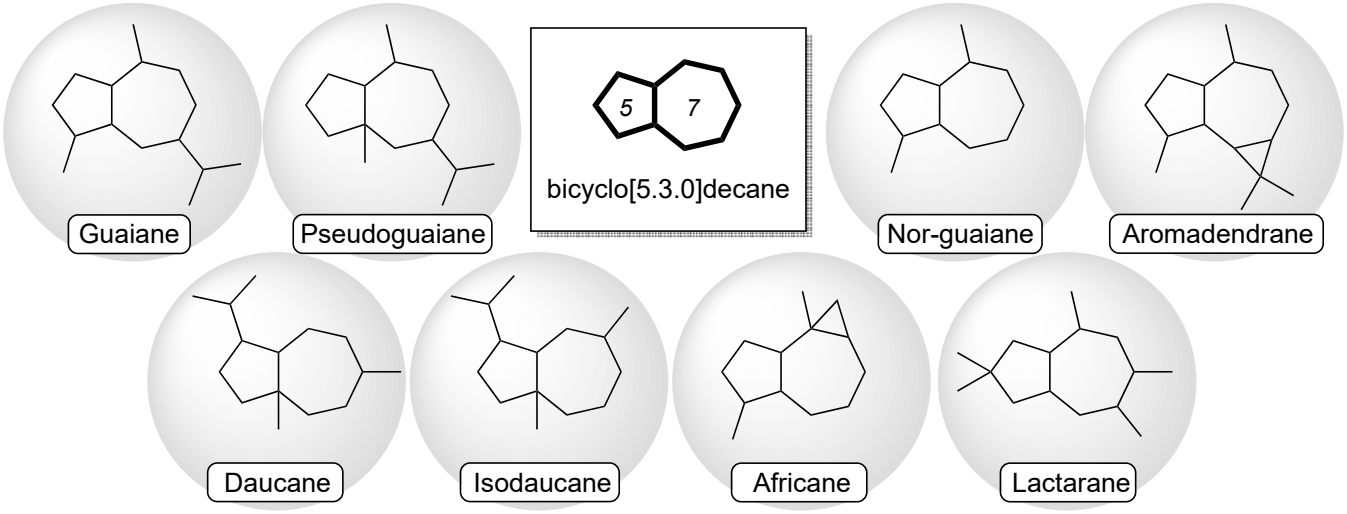
3-1 **3-3** **3-4**

Problem Session Answer (6)

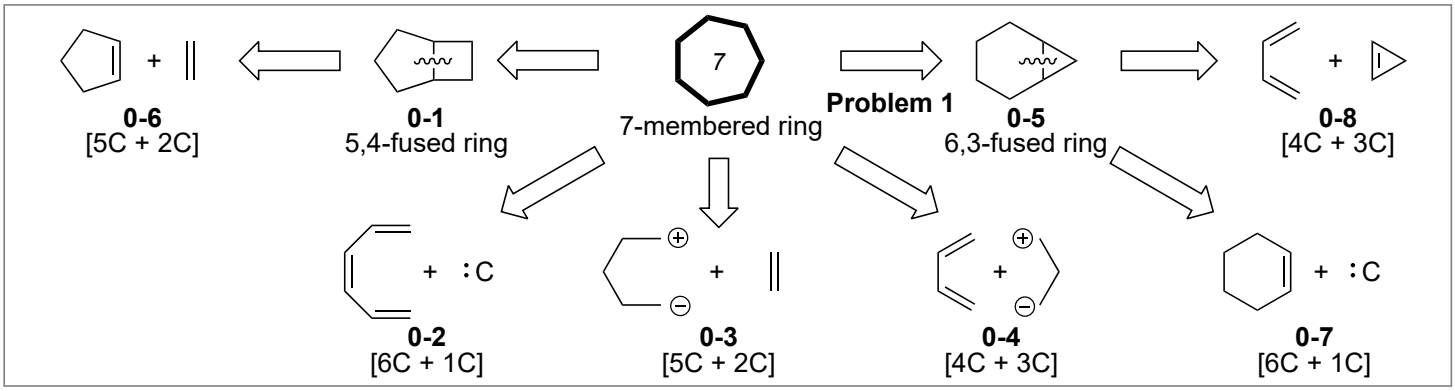
2017.7.29. Takahiro Kawamata

Topic : **Synthetic approaches to the bicyclo[5.3.0]decane ring system**

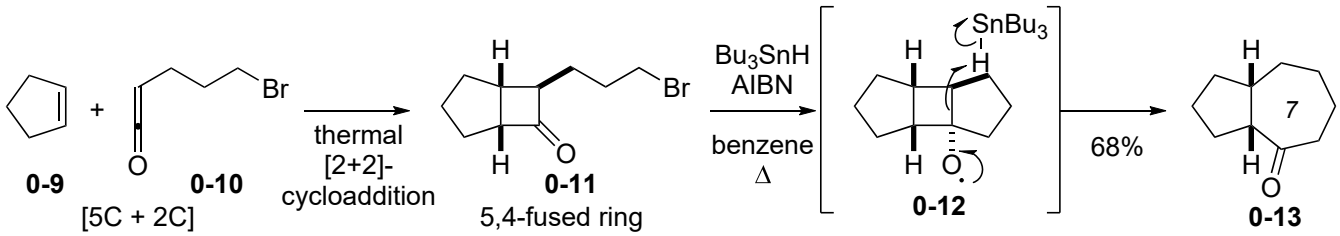
(0) **Introduction** : Sesquiterpenes possessing the bicyclo[5.3.0]decane structure[1)]



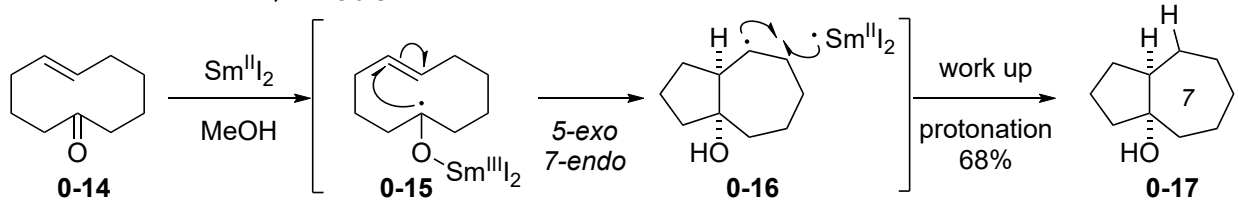
(0-1) Possible cycloaddition strategies to prepare seven-membered rings



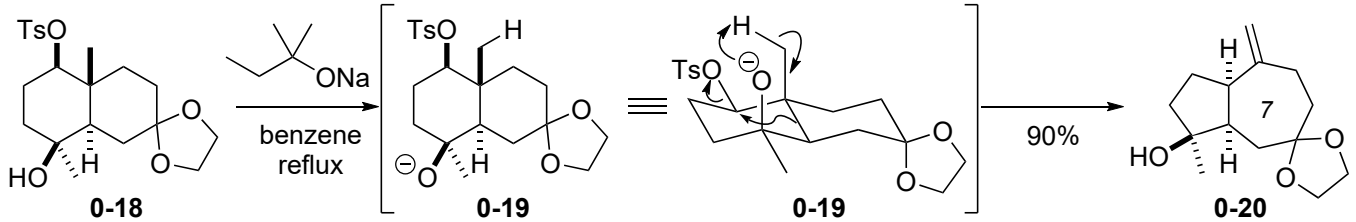
Dowd-Beckwith radical ring-expansion[2)] (From **0-6** to 7-membered ring via **0-1**)



(0-2) Transannular reaction[3)] ⟹ **Problem 2**



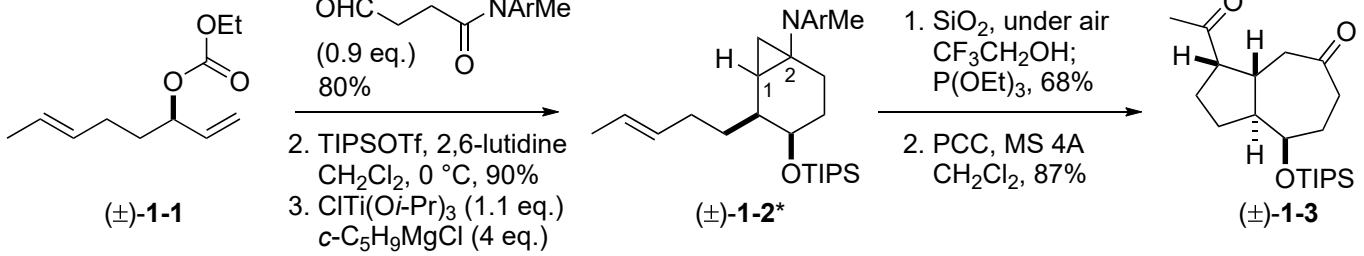
(0-3) Rearrangement of another ring system[4)] ⟹ **Problem 3**



1) Foley, D. A.; Maguire, A. R. *Tetrahedron*, **2010**, *66*, 1131. 2) Dowd, P.; Zhang, W. *J. Am. Chem. Soc.* **1991**, *113*, 9875. 3) Colclough, D.; White, J. B.; Smith, W. B.; Chu, Y. *J. Org. Chem.* **1993**, *58*, 6303. 4) Wijnberg, J. B. P. A.; De Groot, A. *Tetrahedron Letters* **1987**, *28*, 3007.

Problem 1 : Lee, H. B.; Sung, M. J.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 11322.

(1)

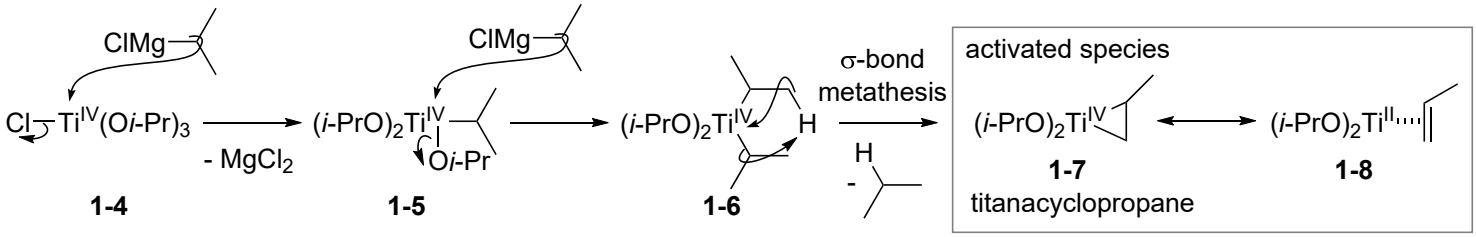


Ar = *p*-C$_6$H$_4$OMe * mixture of two *syn*-isomers (2:1) at C1,2 positions

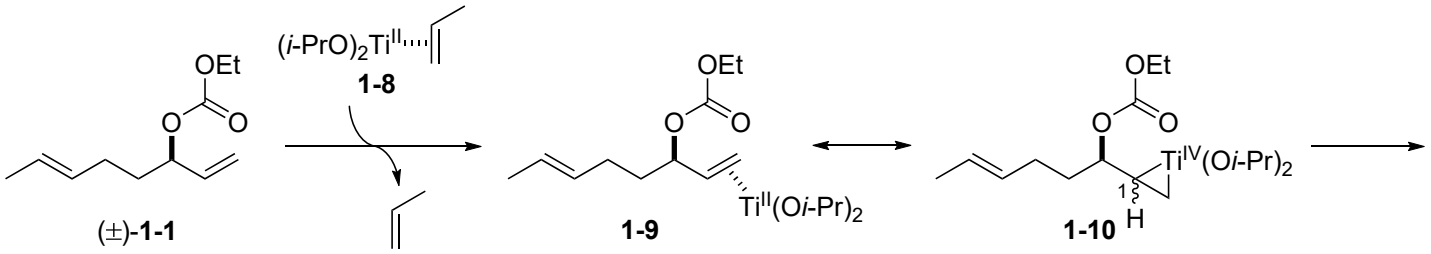
key : Kulinkovich-de Meijere reaction, radical cation-mediated annulation

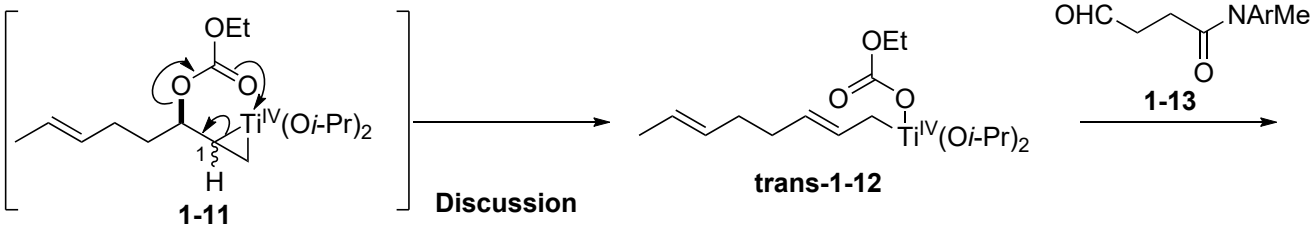
(1) Proposed mechanism

(1-1) Generation of activated species



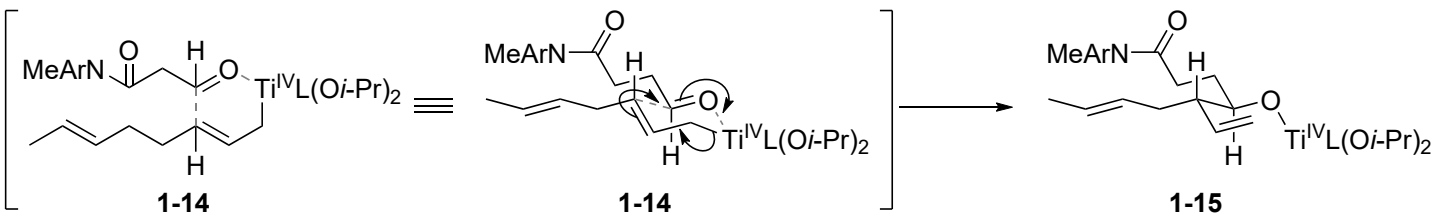
(1-2) Mechanism of step 1 and 2



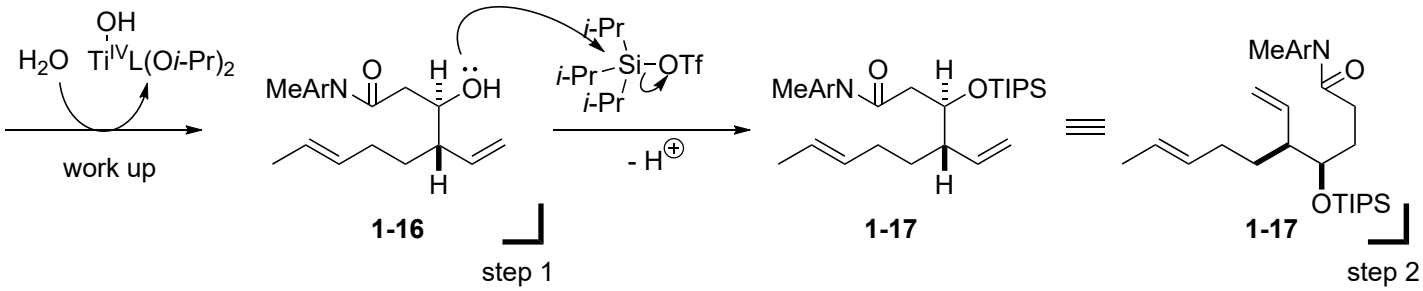


Discussion

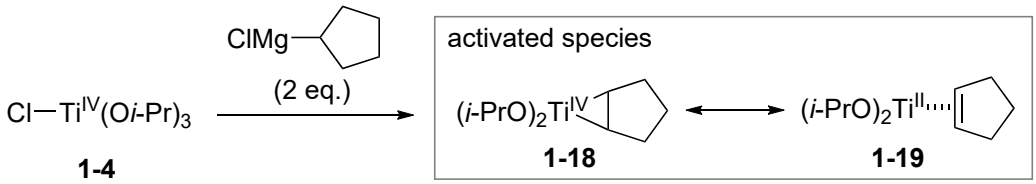
Generation of *trans*-allyltitanium reagent

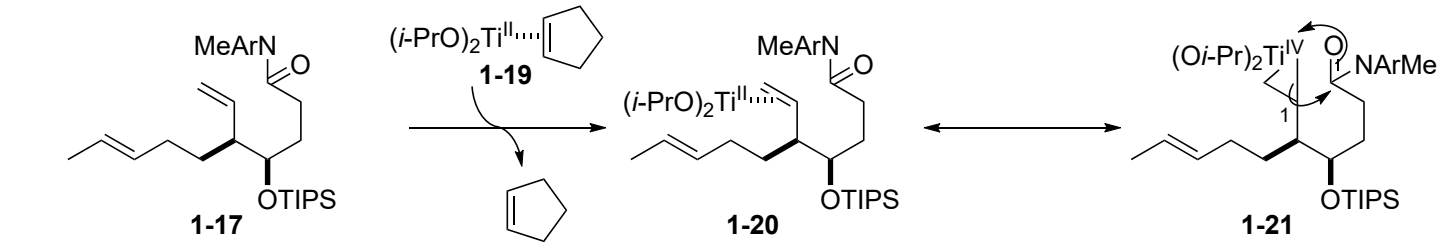


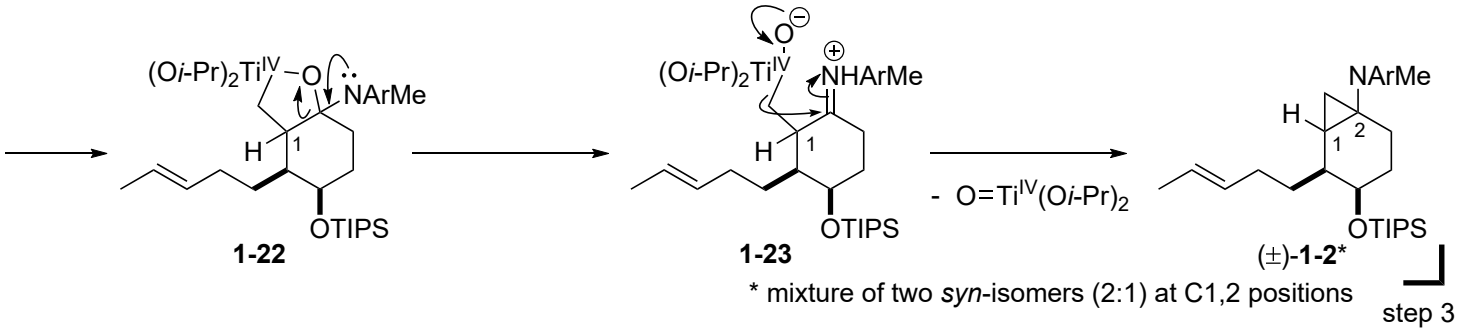
L = OCO$_2$Et



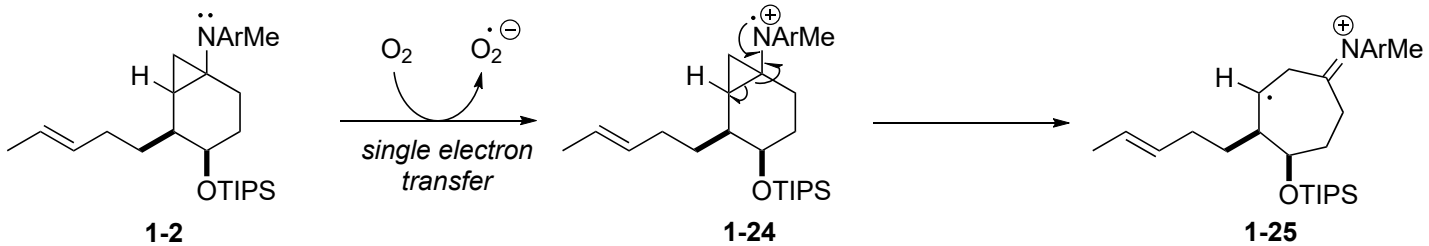
(1-3) Kulinkovich-de Meijere reaction (step 3)

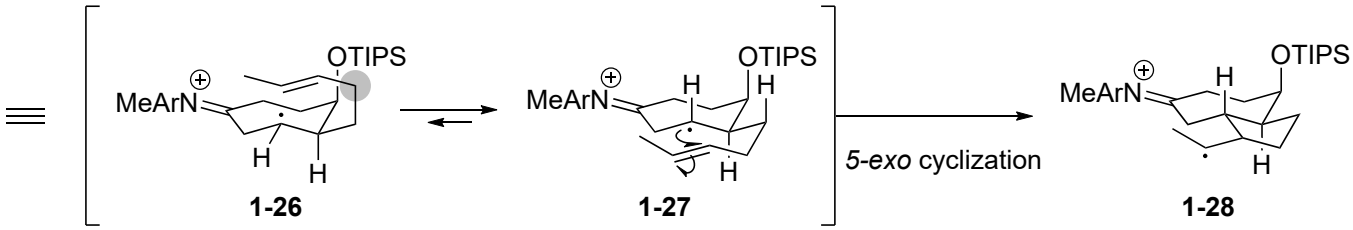


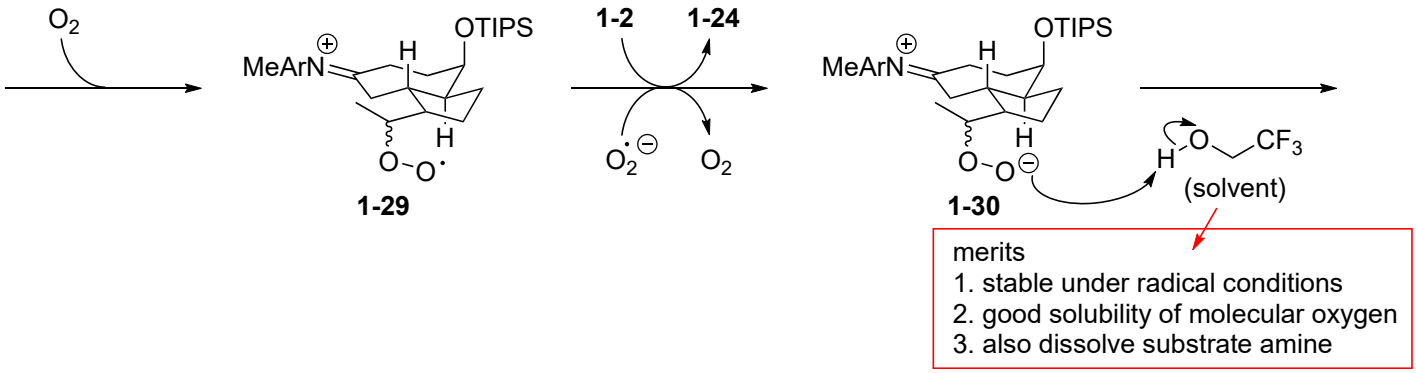


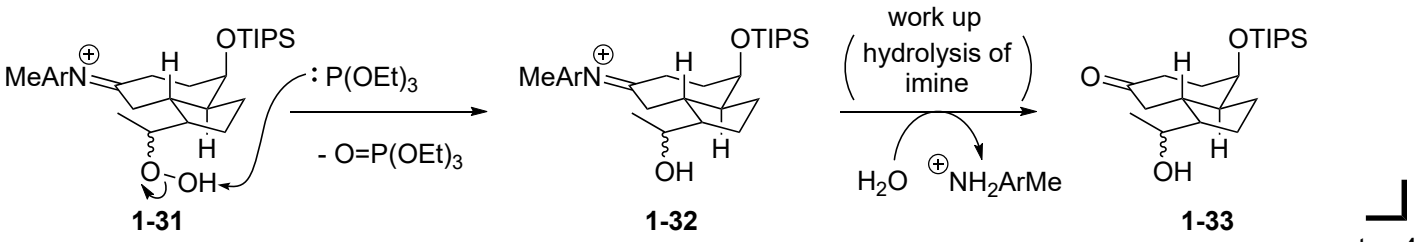


(1-4) Radical cation-mediated annulation (step 4)

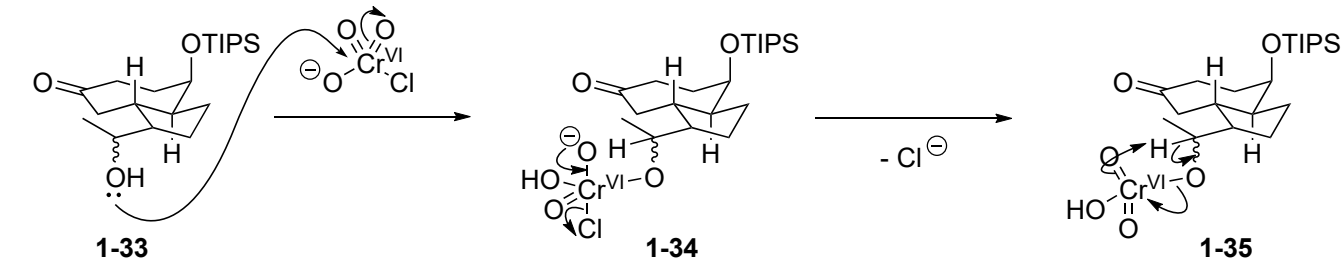


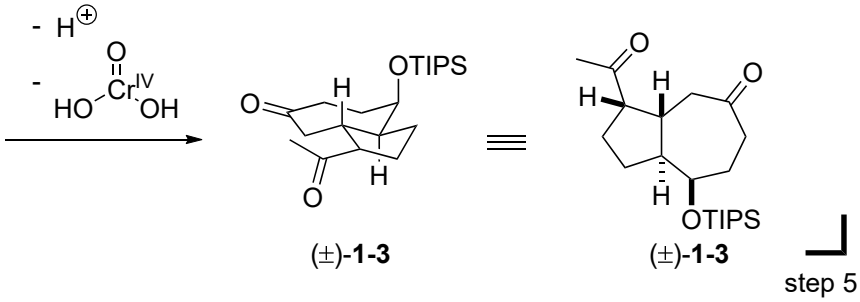




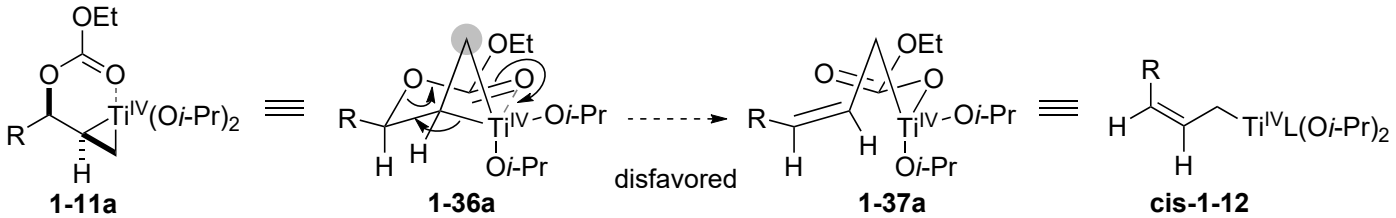


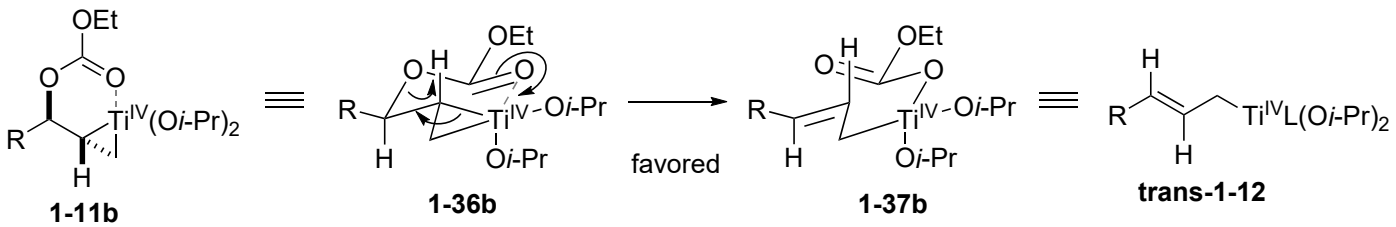
(1-5) PCC oxidation (step 5)





(1-6) **Discussion** : Generation of *trans*-allyltitanium reagent

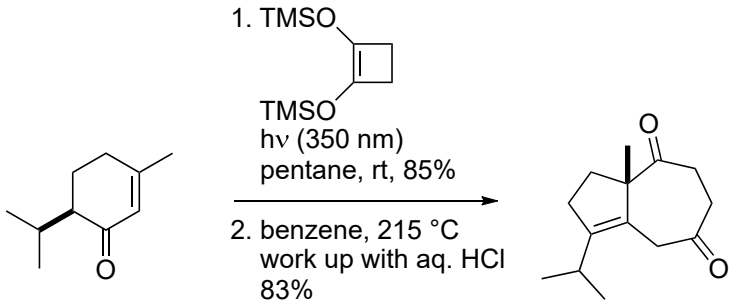




trans-allyltitanium reagent is selectively provided.

Problem 2 : Audenaert, F.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron* **1987**, *43*, 5593.

(2)

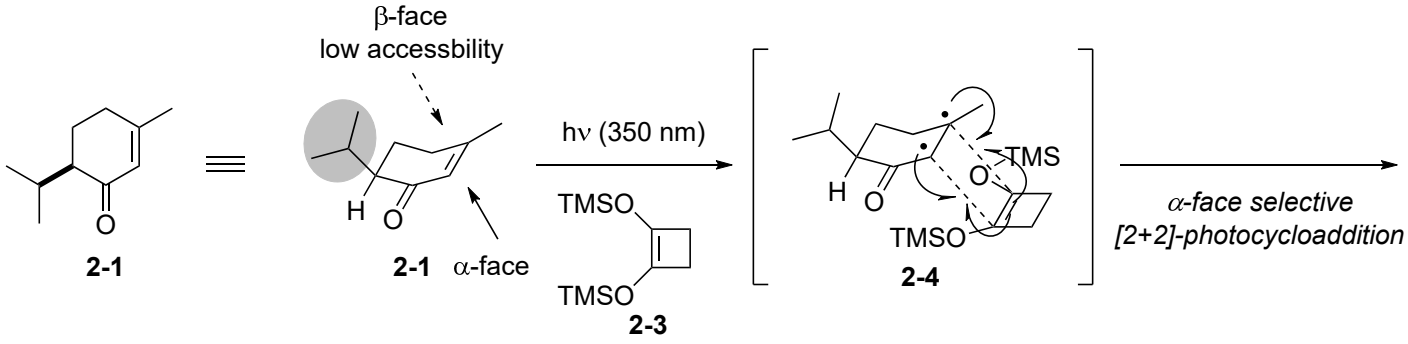


2-1 **2-2**

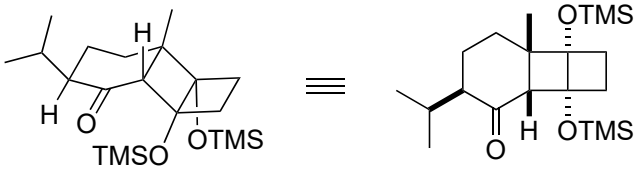
key : [2+2]-photocycloaddition, [3,3]-sigmatropic rearrangement, transannulation

(2) Proposed mechanism

(2-1) [2+2]-photocycloaddition path (**2-1** to **2-5**)

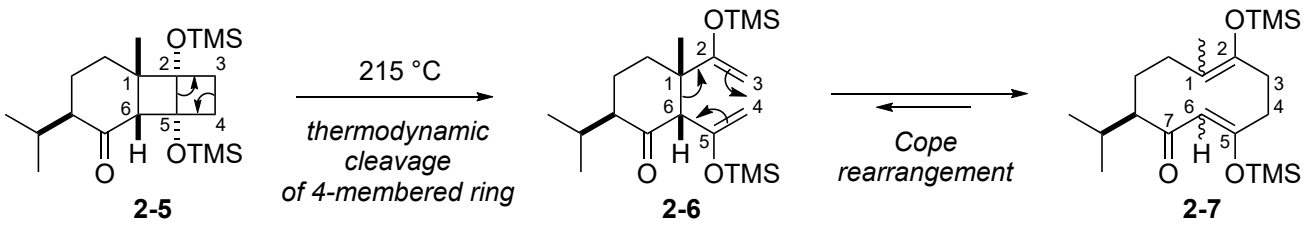


2-1 **2-1** α-face **2-3** **2-4**



2-5 **2-5**

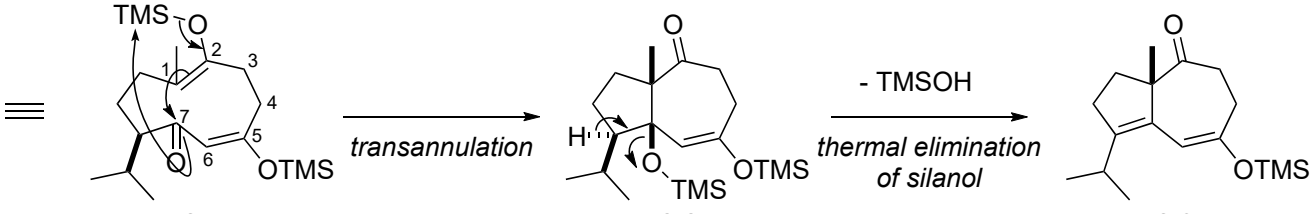
(2-2) [3,3]-sigmatropic rearrangement and transannulation path (**2-5** to **2-2**)



2-5 **2-6** **2-7**

Discussion 1

possibility of other cleavage pathways

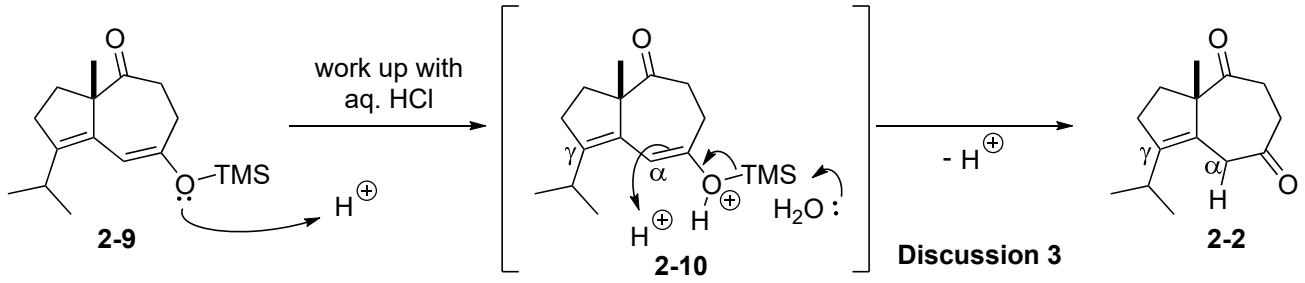


2-7 **2-8** **2-9**

Discussion 2

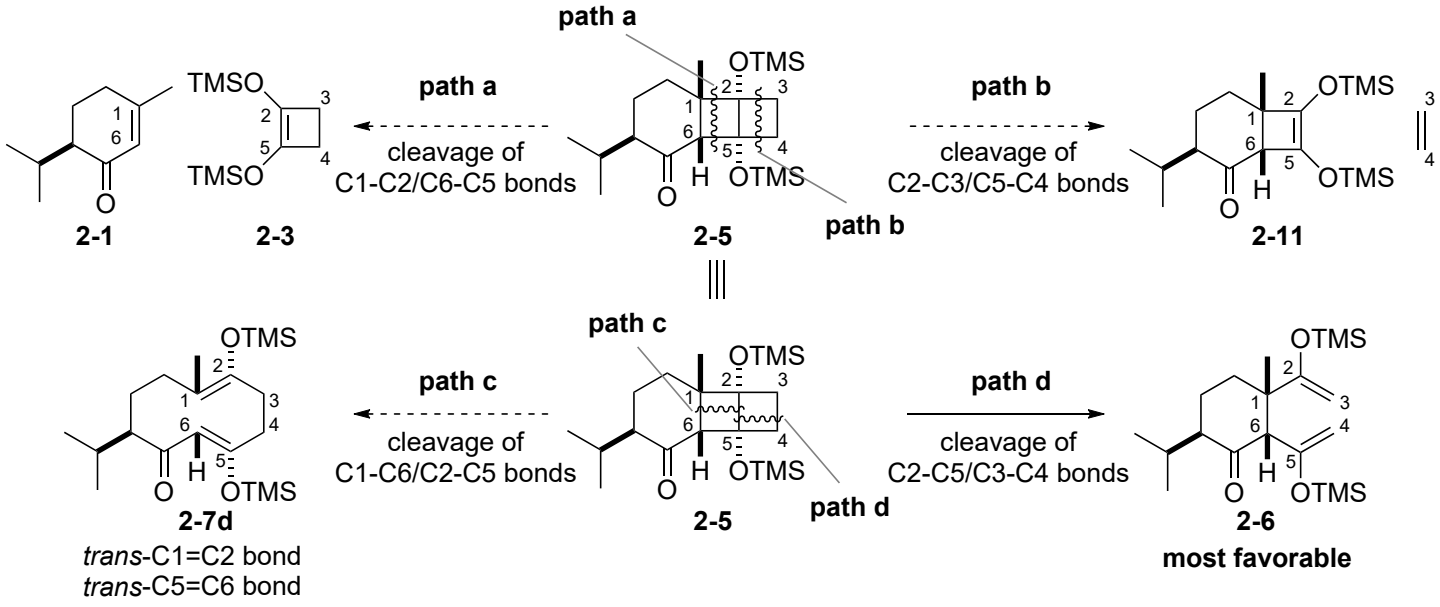
1. Cope rearrangement from **2-6**
2. stereoselective transannulation from **2-7** (C1-C7 bond formation)

(2-2) [3,3]-sigmatropic rearrangement and transanulation path (**2-5** to **2-2**, *continued.*)



protonation at not keto γ-position but keto α-position

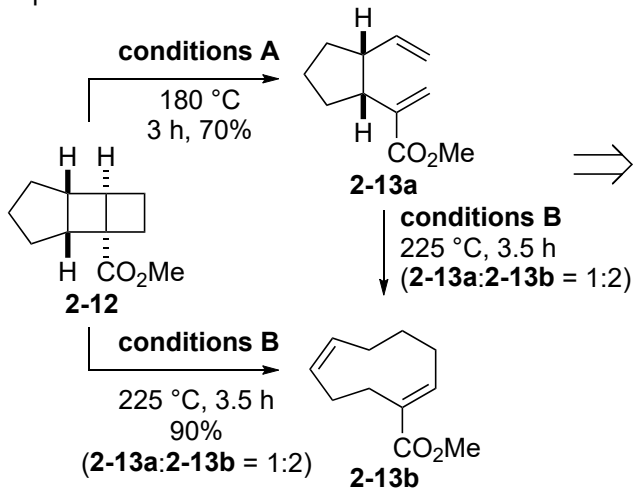
(2-3) **Discussion 1** : possibility of other cleavage pathways



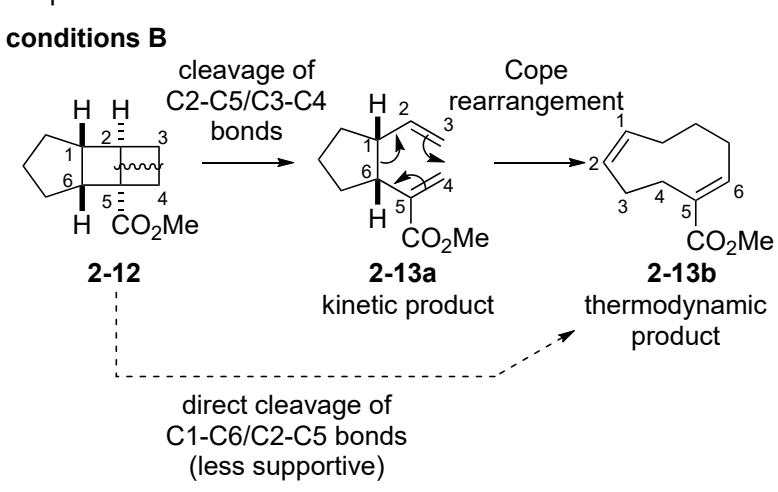
path a : Generation of high strained cyclobutene **2-1** and **2-3** would be disfavored.
path b : Generation of high strained cyclobutene **2-11** would be disfavored.
path c : Generation of **2-7d**, which has two *trans*-olefin on 10-membered ring, would be disfavored.
path d : Because of the lowest structural strain of **2-6**, this pathway would be favored.

Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267.

Experimental data

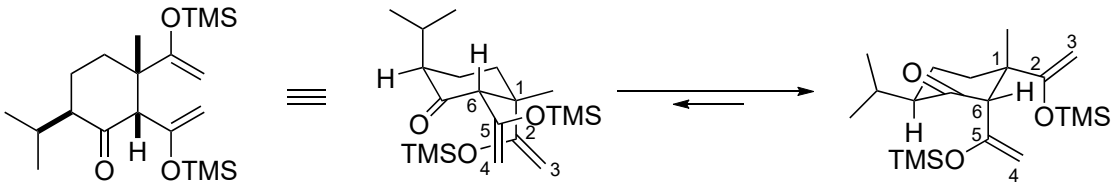


Proposed mechanism



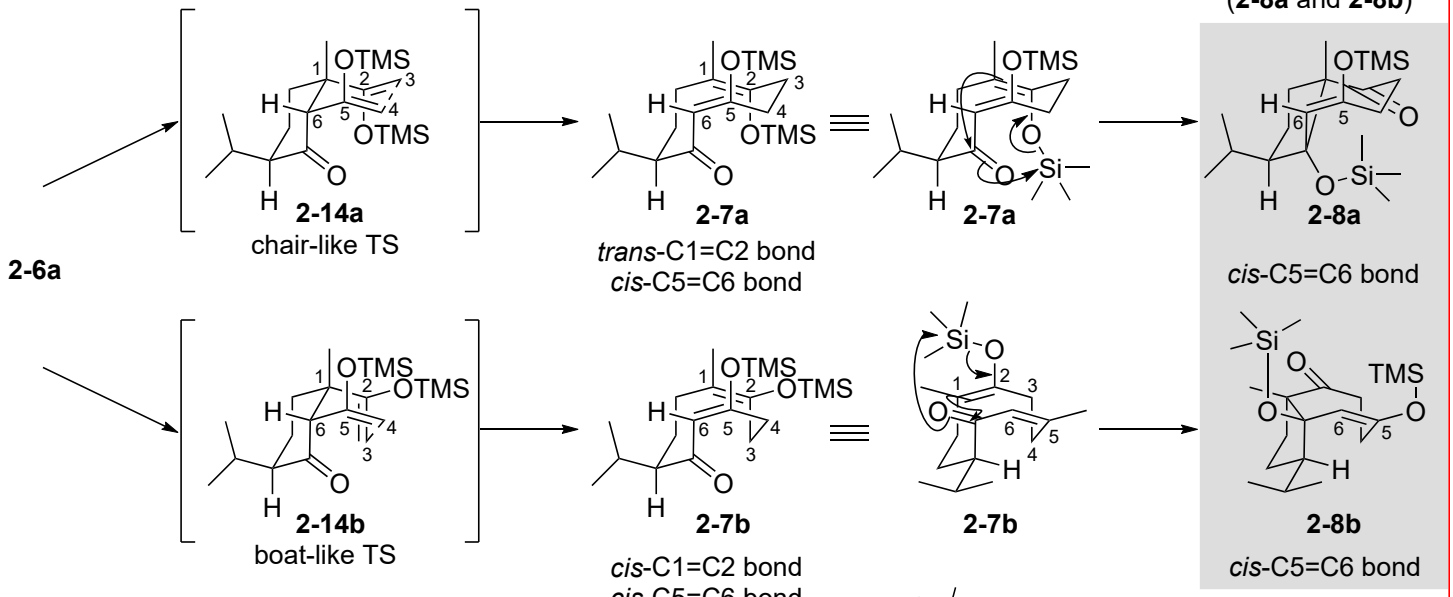
(2-4) **Discussion 2**

Cope rearrangement from **2-6** and stereoselective C-C bond formation

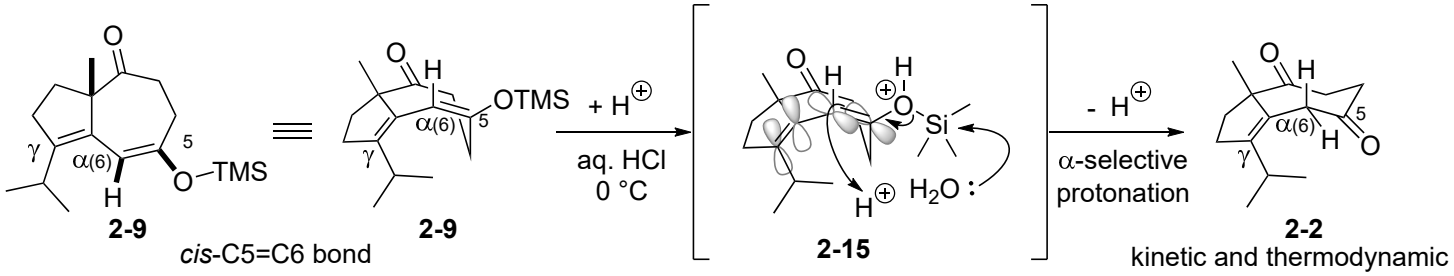


2-6 ≡ **2-6a** (**ax**-*i*-Pr chair form, less stable) ⇌ **2-6b** (**eq**-*i*-Pr chair form, more stable)

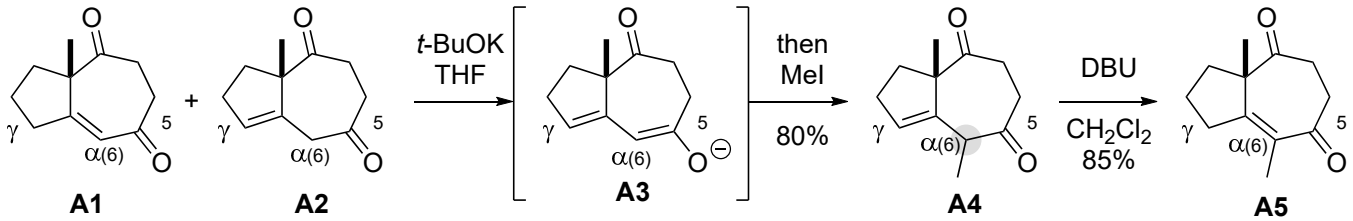
Thermodynamically favored 5,7-fused compounds (**2-8a** and **2-8b**)



(2-5) **Discussion 3** : protonation at not keto γ-position but keto α-position



(2-5) **Discussion 3** : protonation at not keto γ-position but keto α-position (*continued.*)



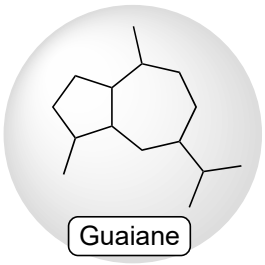
A1 **A2** **A3** **A4** **A5**

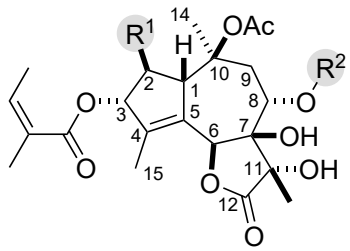
A1 : **A2** = 35 : 31

nucleophilic attack at α-position is kinetically favored.

thermodynamic product

(3) Guaianolide natural products : Thapsigargins





thapsigargins (**3-0-1**)

Table 1. the 17 known thapsigargins

	Name	R^1	R^2
3-0-1	thapsigargin	O-Oct	But
3-0-2	trilobolide	H	(*S*)-2-MeBut
3-0-3	nortrilobolide	H	But
3-0-4	thapsigargicin	O-Hex	But
3-0-5	thapsitranstagin	O-*i*-Val	2-MeBut
3-0-6	thapsivillosin A-K	amino acids or aliphatic chains	

But = butanoyl, Oct = octanoyl, Hex = hexanoyl, *i*-Val = isovaleroyl

♦ Isolation and structural determination

The first isolated thapsigargin was trilobolide (**3-0-2**), from *Laser trilobum* in 1968.[5)]

Structural determination of other thapsigargins, isolated from *Thapsia garganica* L. in 1978[6)], was reported in 1985.[7)]

♦ Biological activity of thapsigargin (**3-0-1**)

Sub-nanomolar inhibitor of molecular Ca^{2+} pumps, SERCA (sarco/endoplasmic reticulum Ca^{2+}-ATPase)[8)]

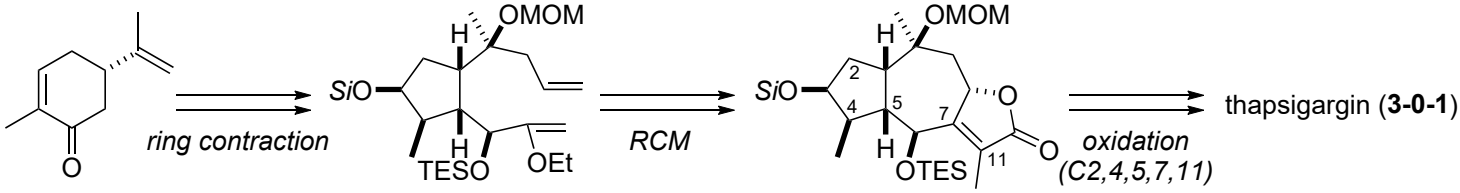
♦ Utility of thapsigargin (**3-0-1**)

1. Prolific biological tool 2. Promissing lead compound for prostate cancer

(3-1) Total synthesis of thapsigargin (**3-0-1**)

♦ Steven V. Ley's study[9)]

Efficient substrate-controlled approach realized **42-step** total synthesis (**0.61%** overall yield).



(*S*)-carvone (**3-0-7**)

3-0-8
Si = TBDPS

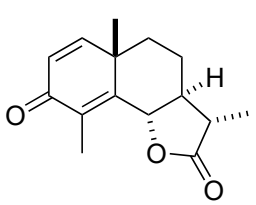
3-0-9
Si = TBDPS

♦ Baran's study ⟹ **Problem 3**

Two-phase approach (cyclase and oxidase phase) realized **scalable 11-step** total synthesis (**0.137%** overall yield).

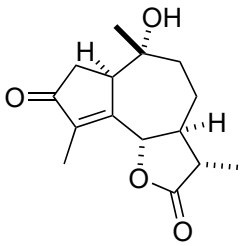
Previous work of cyclase phase (the key photochemical rearrangement)

• Classical study by Barton in 1957[10)]



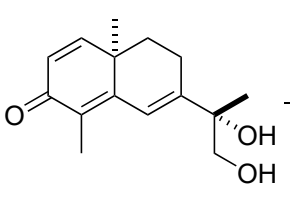
α-santonin (**3-0-10**)

hν
aq. AcOH
30-38%



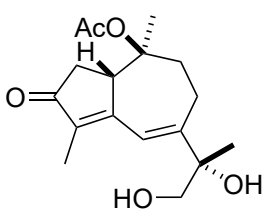
isophotosantonic lactone (**3-0-11**)

• Massanet's study in 2006[11)]



3-0-12

hν
aq. AcOH
93%

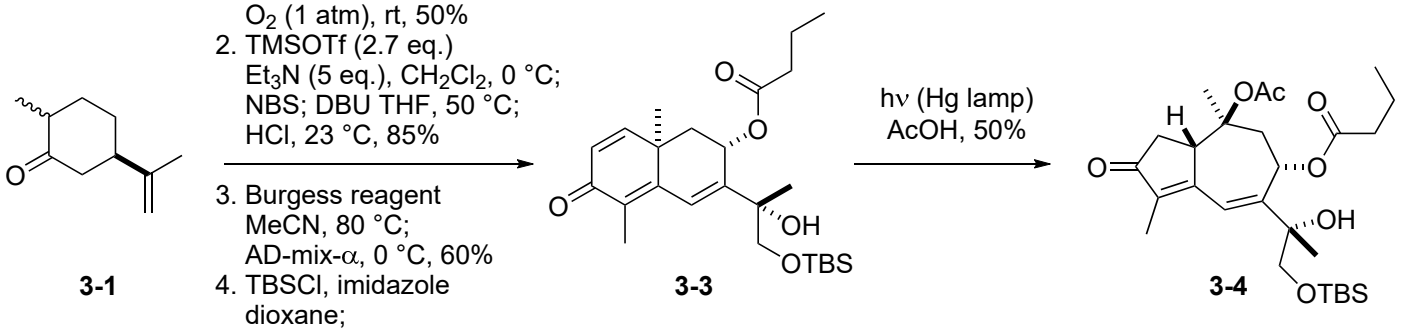


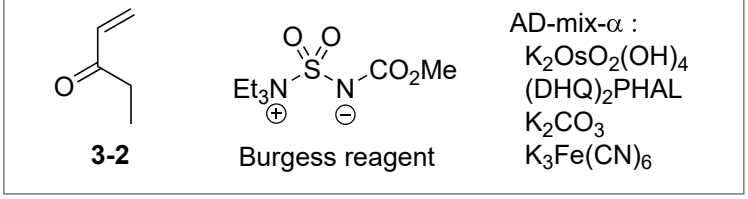
3-0-13

5) Holub, M. *et al. Collect. Czech. Chem. Commun.* **1968**, *33*, 2911. 6) Christensen, S. B. *et al. Acta Pharm. Suec.* **1978**, *15*, 133. 7) Christensen, S. B. *Tetrahedron Lett.* **1985**, *26*, 107. 8) Sagara, Y.; Inesi, G. *J. Biol. Chem.* **1991**, *226*, 13503. 9) Ley, S. V. *et al. Chem. Eur. J.* **2007**, *13*, 5688. 10) Barton, D. H. *et al. J. Chem. Soc.* **1957**, 929. 11) Massanet, G. M. *et al. Org. Lett.* **2006**, *8*, 2879.

Problem 3 : Chu, H.; Smith, J. M.; Felding, J.; Baran, P. S. *ACS. Cent. Sci.* **2017**, *3*, 47.

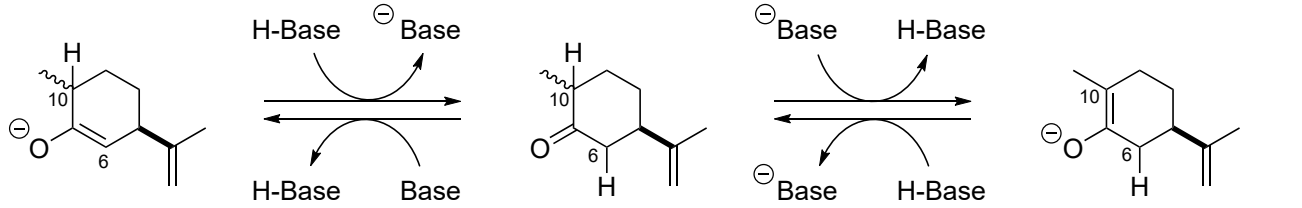
(3)

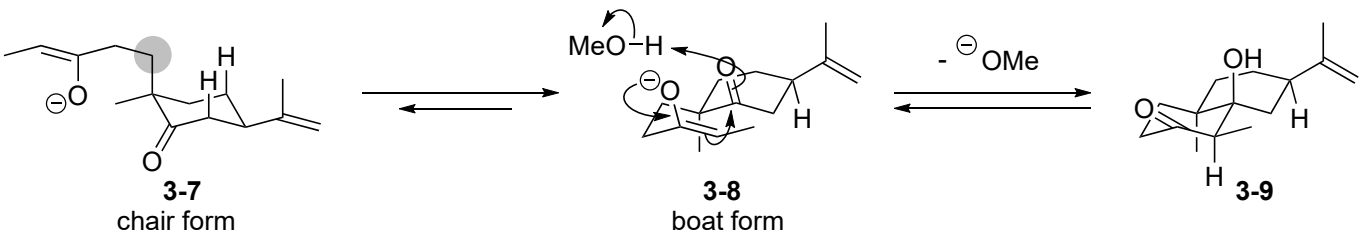




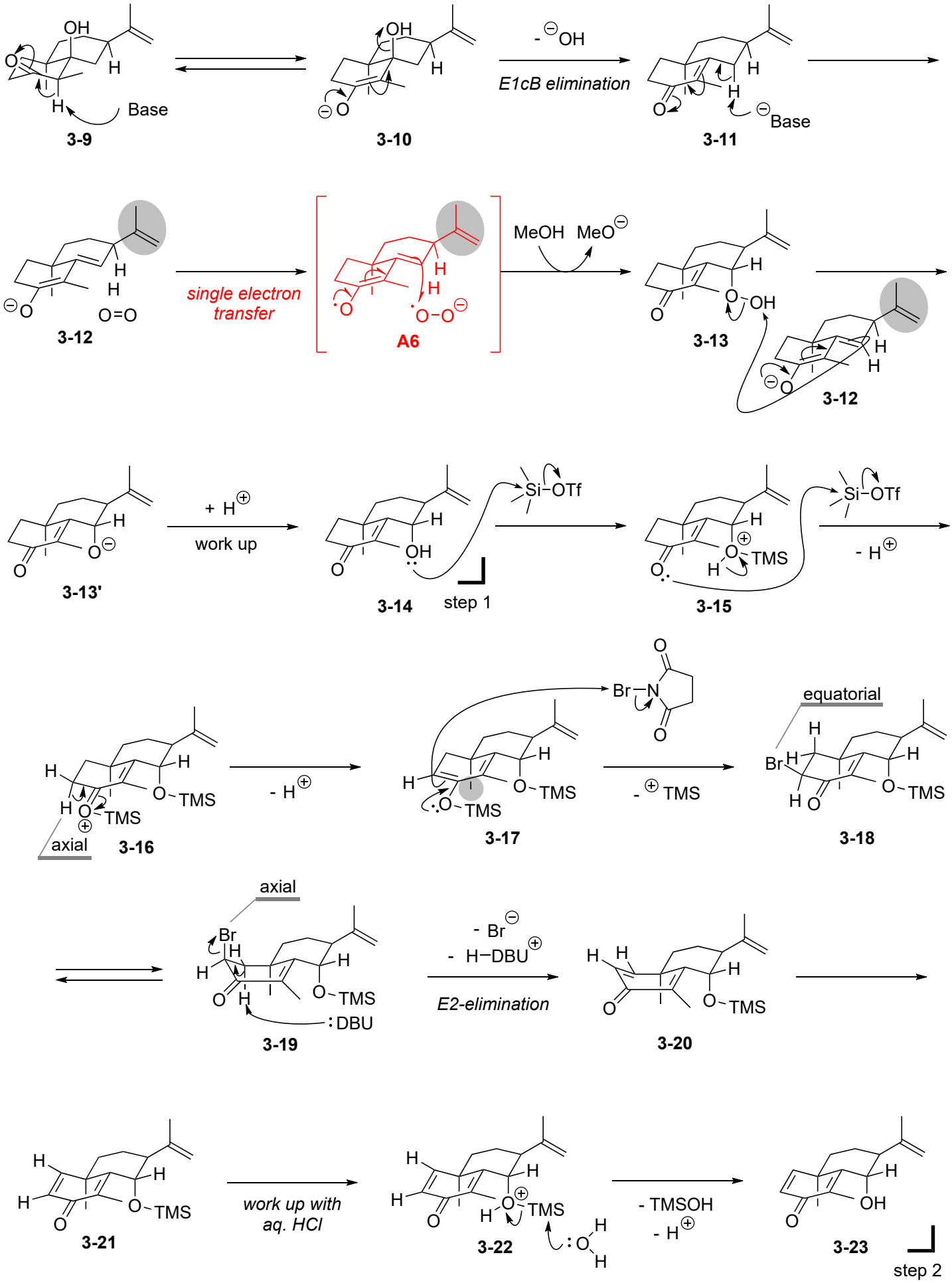
key : step 1. Robinson annulation
step 2. bromination/elimmination sequence
step 3. dehydration with Burgess reagent and Sharpless asymmetric dihydroxylation
step 4. allylic C-H oxidation using SeO_2
step 5. Mitsunobu reaction
step 6. photochemical rearrangement

(3-2) Proposed mechanism
(3-2-1) From **3-1** to **3-23** (step 1,2)

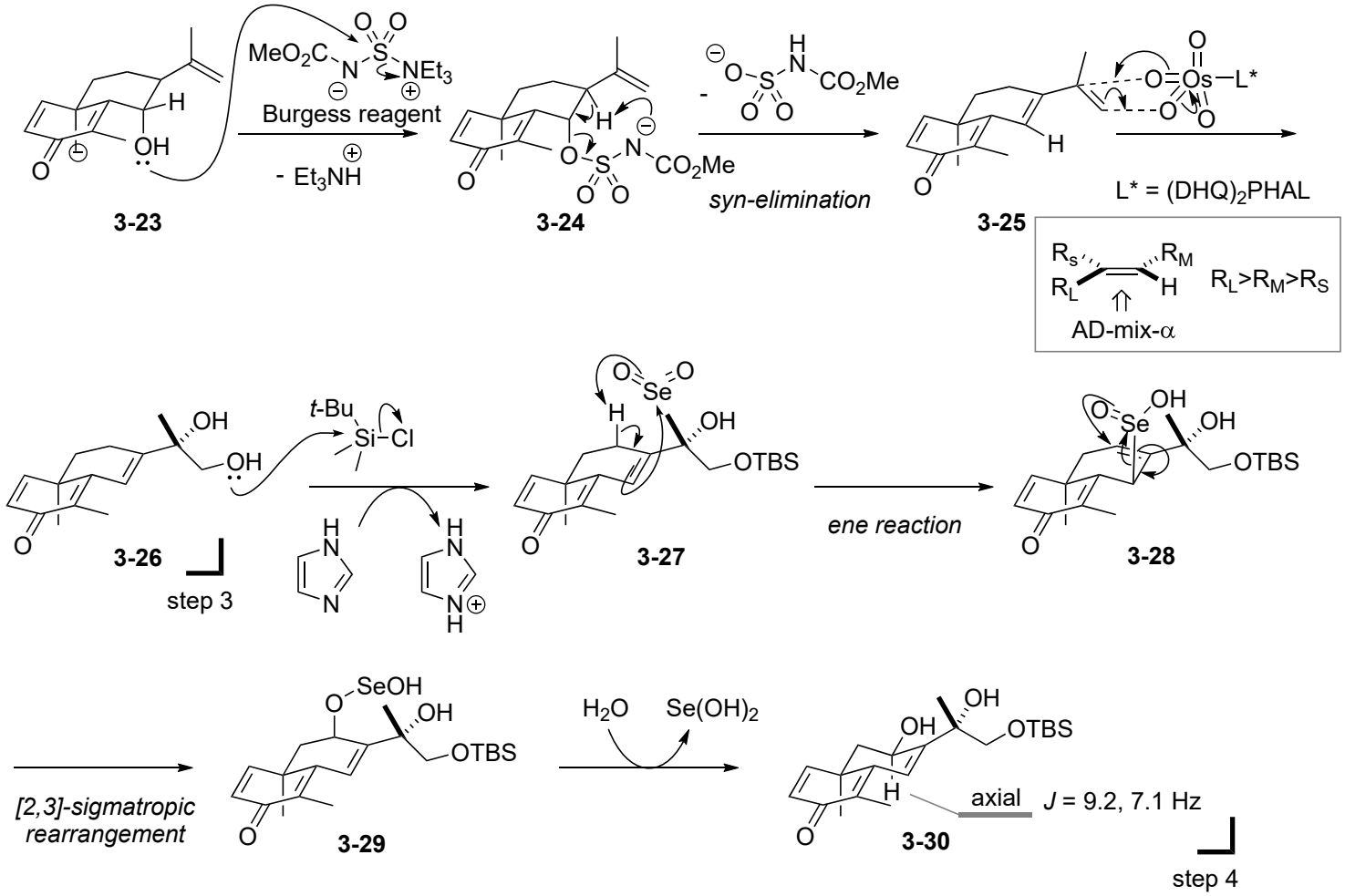




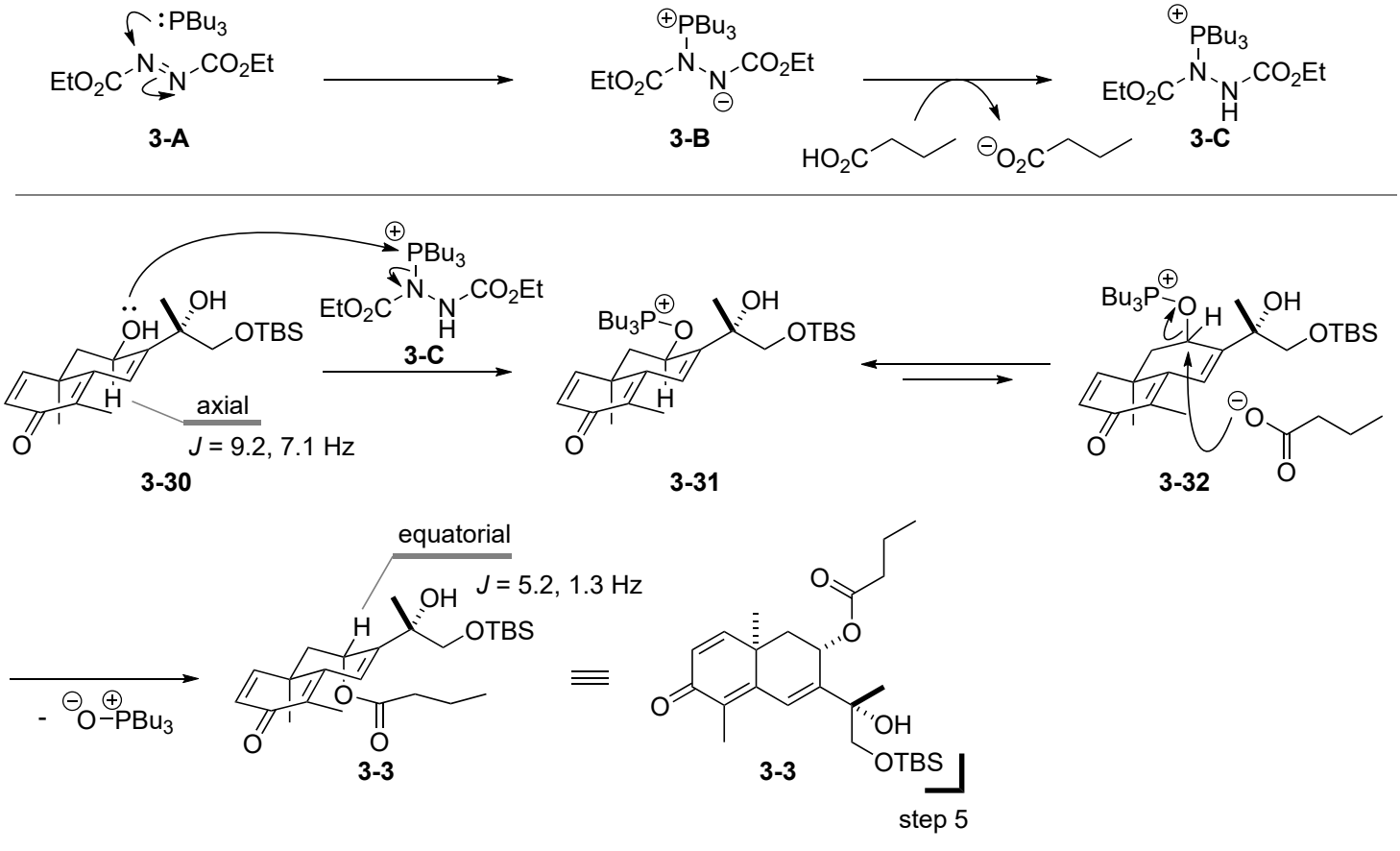
(3-2-1) From **3-1** to **3-23** (step 1,2, continued)



(3-2-2) From **3-23** to **3-30** (step 3,4)



(3-2-3) From **3-30** to **3-3** (step 5)



(3-2-4) From **3-3** to **3-4** (step 6)