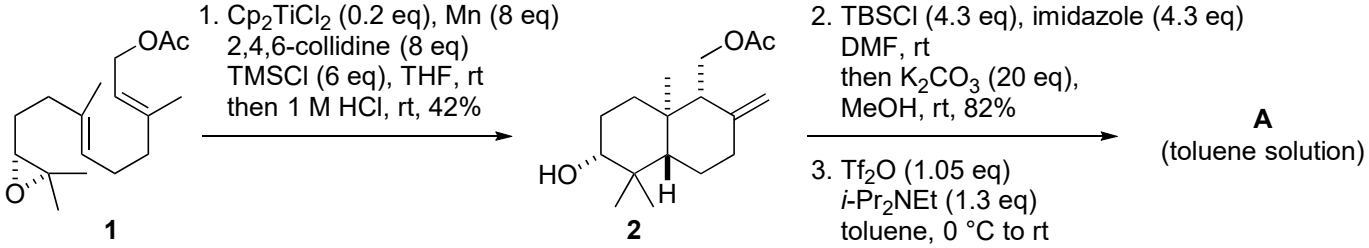
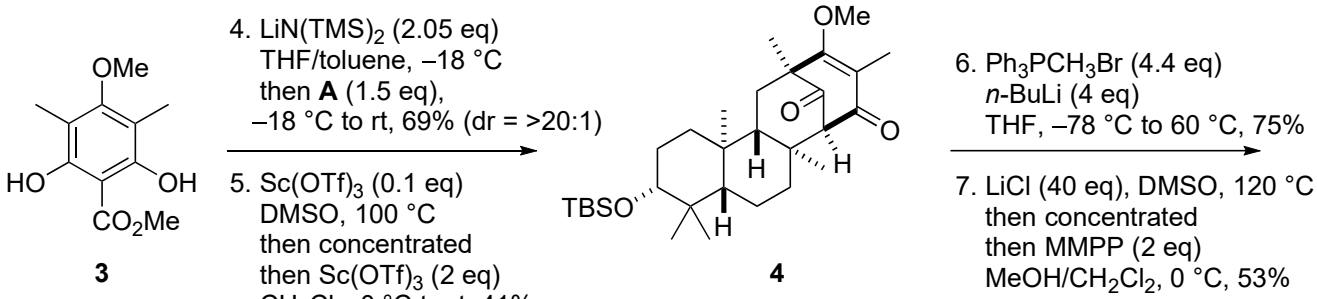
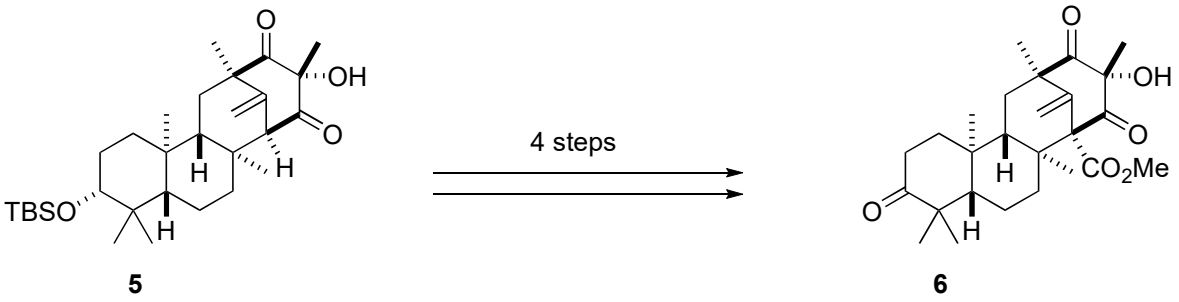
Problem Session (6)

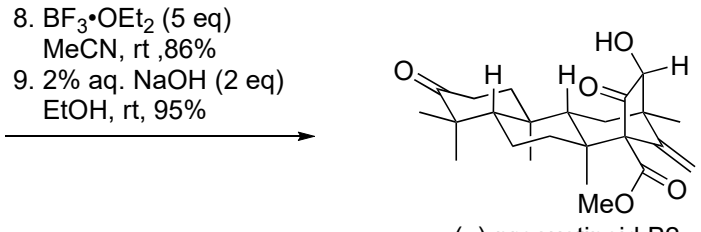
2022. 4. 16. Takahiro Watanabe

Please provide each reaction mechanisms and explain the stereoselectivities.

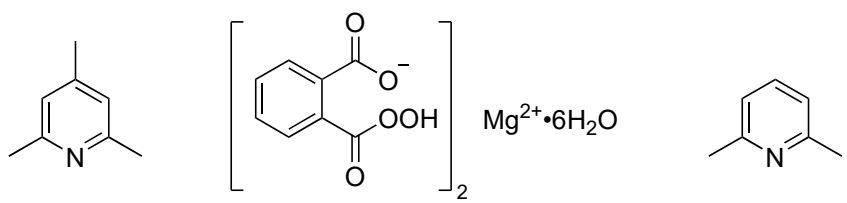








(–)-preaustinoid B2



2,4,6-collidine MMPP 2,6-lutidine

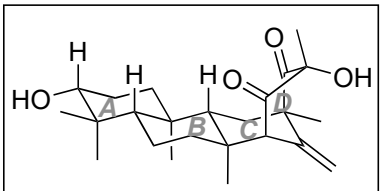
Problem Session (6)-Answer

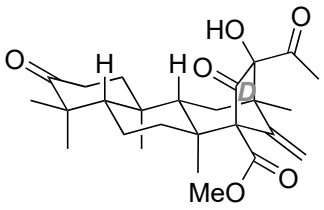
2022. 4. 16. Takahiro Watanabe

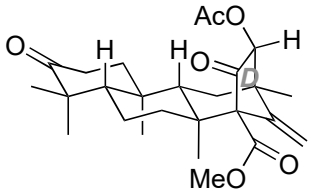
topic: Total synthesis of preaustinoids by Houhua Li's group
(Zhang, Y.; Ji, Y.; Franzoni, I.; Guo, C.; Jia, H.; Hong, B.; Li, H. *Angew. Chem. Int. Ed.* **2021**, *60*, 14869.)

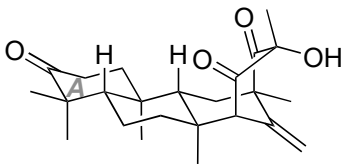
(–)-berkeleyone A
biological activity: anti-inflammatory
structural features: tetracyclic framework including bicyclo [3.3.1] nonane core (C and D-ring)
Diversification of A or D-ring -> preastinoids (shown below)

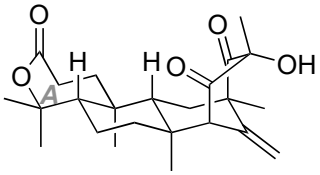
Reported total synthesis:
Ting, C. P.; Xu, G.; Zeng, X, Maimone, T. J. *J. Am. Chem. Soc.* **2016**, *138*, 14868. ((±)-berkeleyone A)
Elkin, M.; Szewczyk, S. M.; Scruse, A. C.; Newhouse, T. R. *J. Am. Chem. Soc.* **2017**, *139*, 1790. ((±)-berkeleyone A)

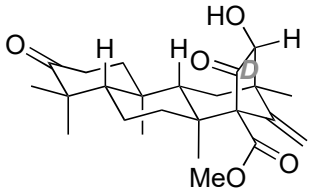

(–)-berkeleyone A


(–)-preaustinoid B

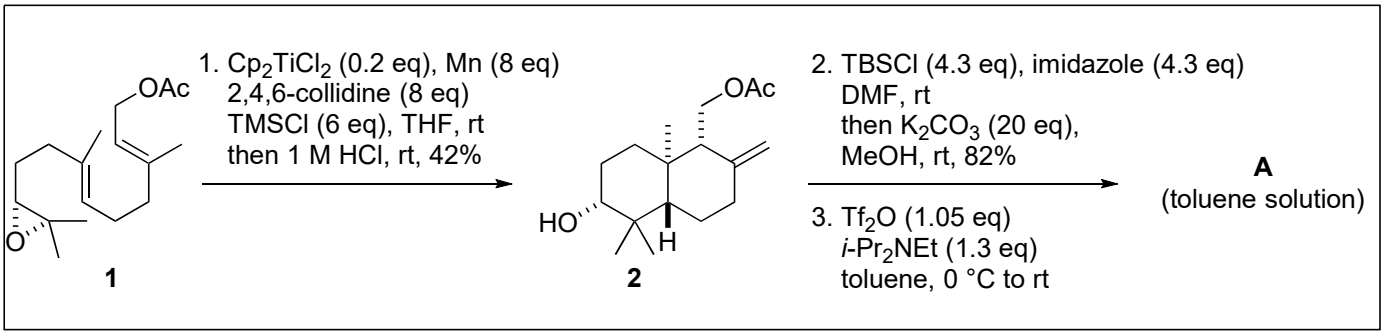

(–)-preaustinoid B1

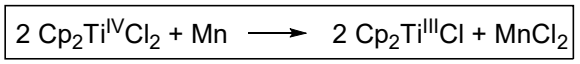

(–)-preaustinoid A

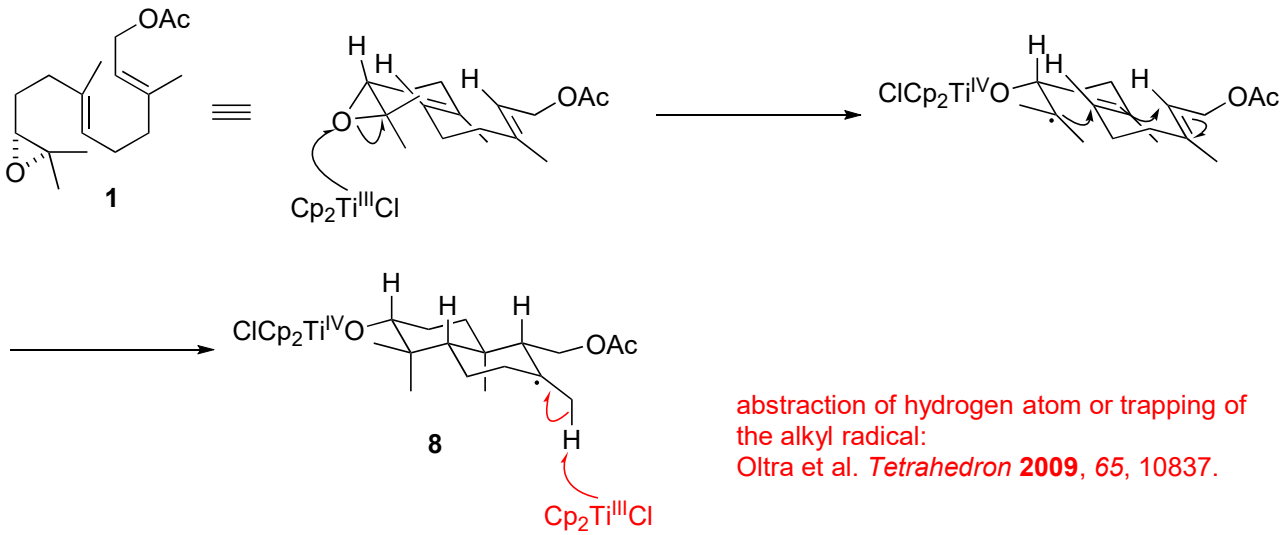

(–)-preaustinoid A1

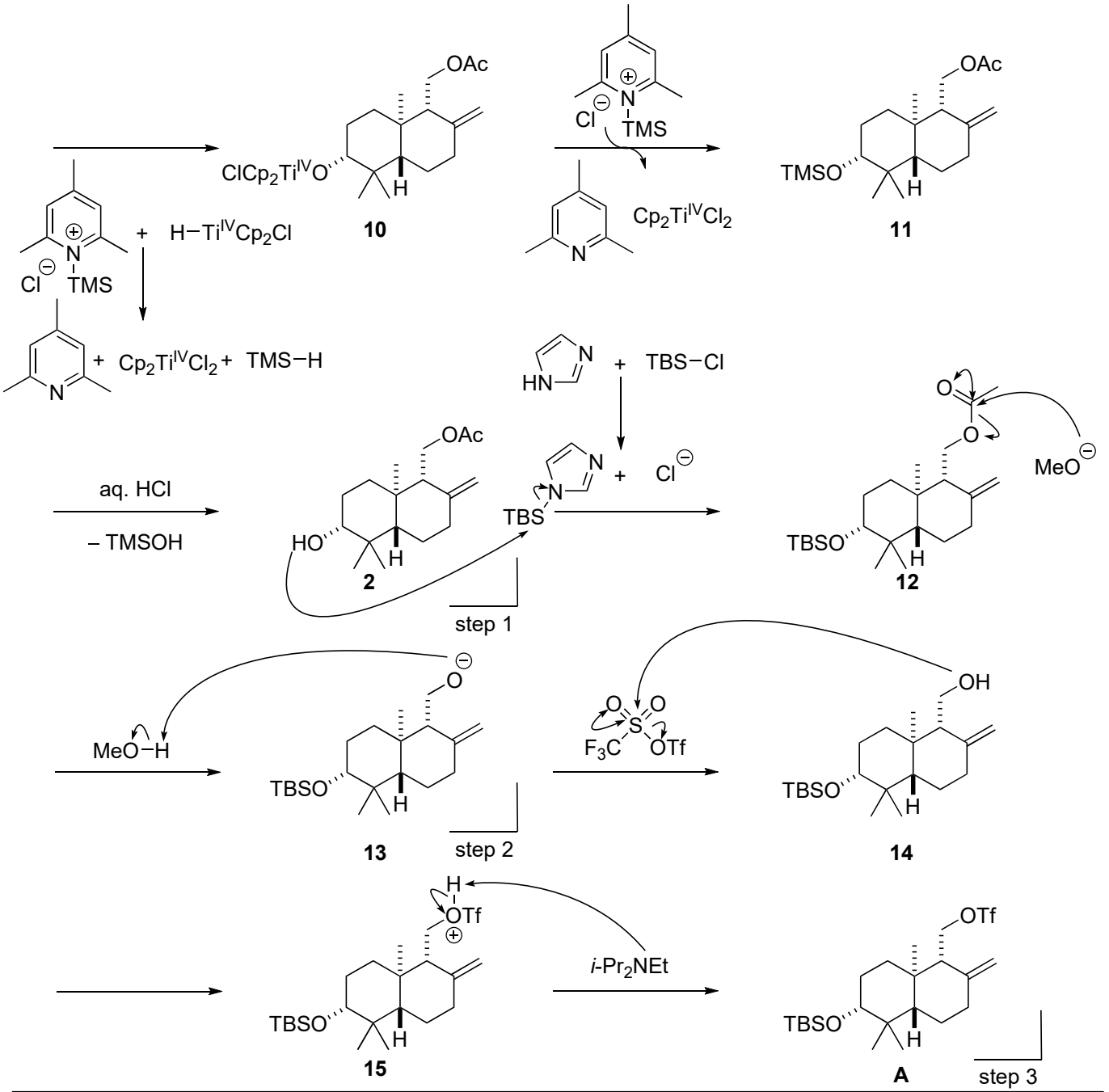

(–)-preaustinoid B2

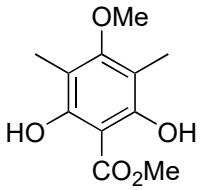
-answer-







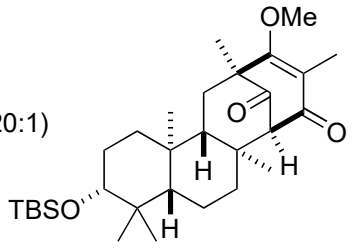




3

4. $LiN(TMS)_2$ (2.05 eq)
THF/toluene, –18 °C
then **A** (1.5 eq),
–18 °C to rt, 69% (dr = >20:1)

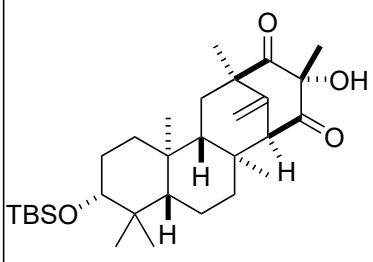
5. $Sc(OTf)_3$ (0.1 eq)
DMSO, 100 °C
then concentrated
then $Sc(OTf)_3$ (2 eq)
CH_2Cl_2, 0 °C to rt, 41%



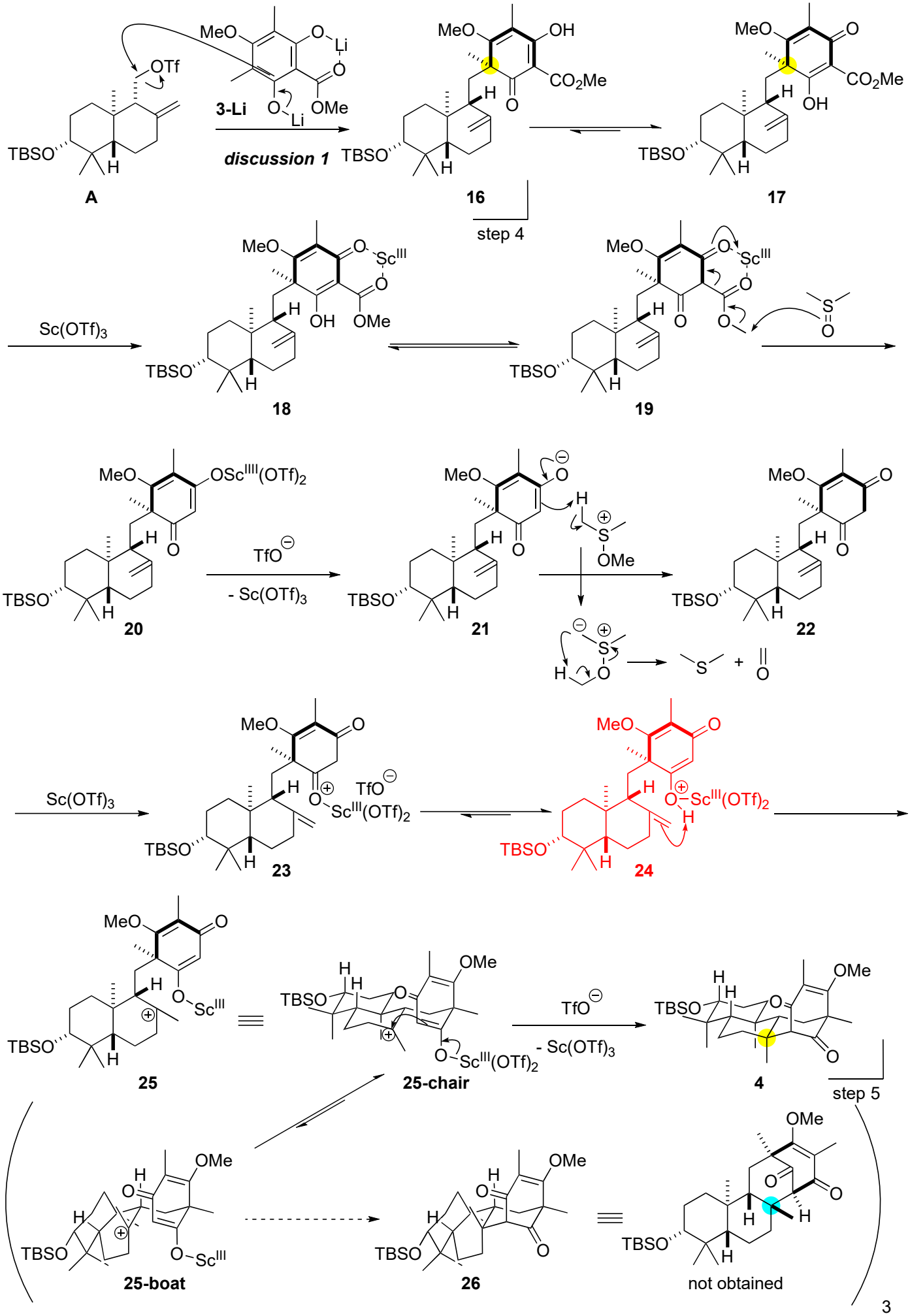
4

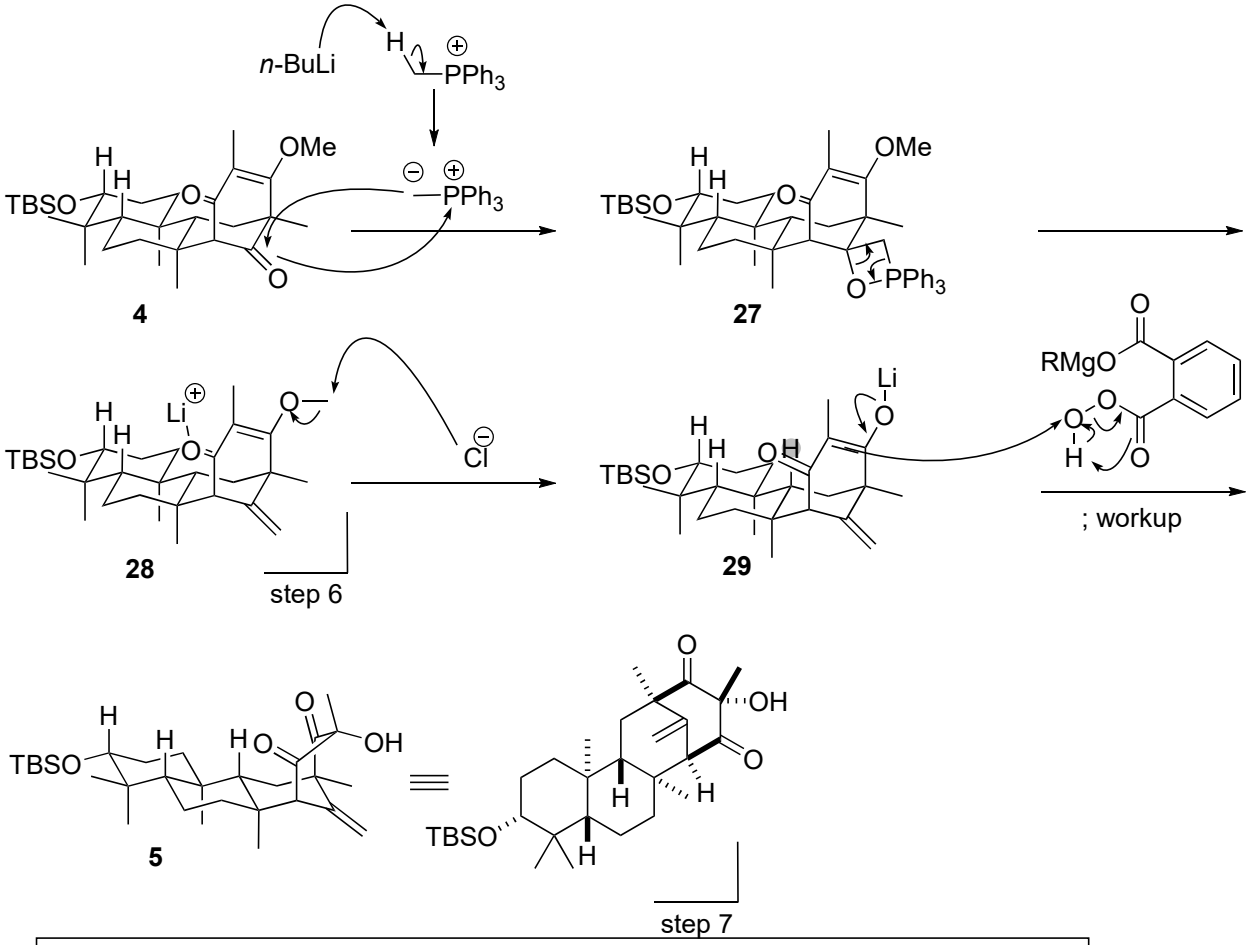
6. Ph_3PCH_3Br (4.4 eq)
n-BuLi (4 eq)
THF, –78 °C to 60 °C, 75%

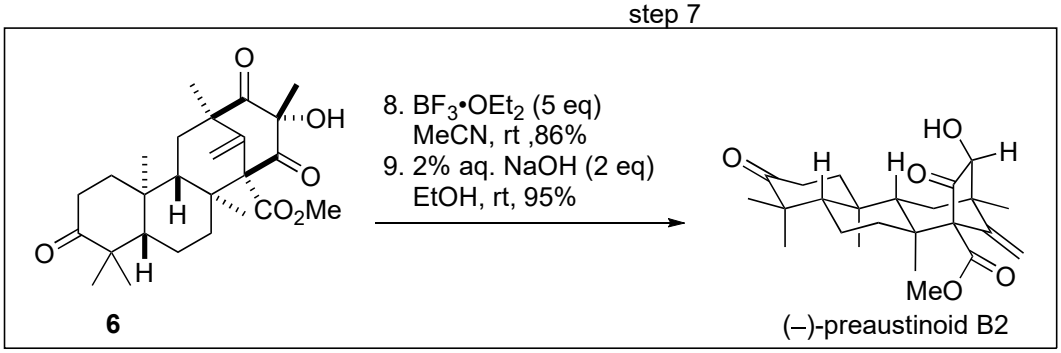
7. LiCl (40 eq), DMSO, 120 °C
then concentrated
then MMPP (2 eq)
$MeOH/CH_2Cl_2$, 0 °C, 53%

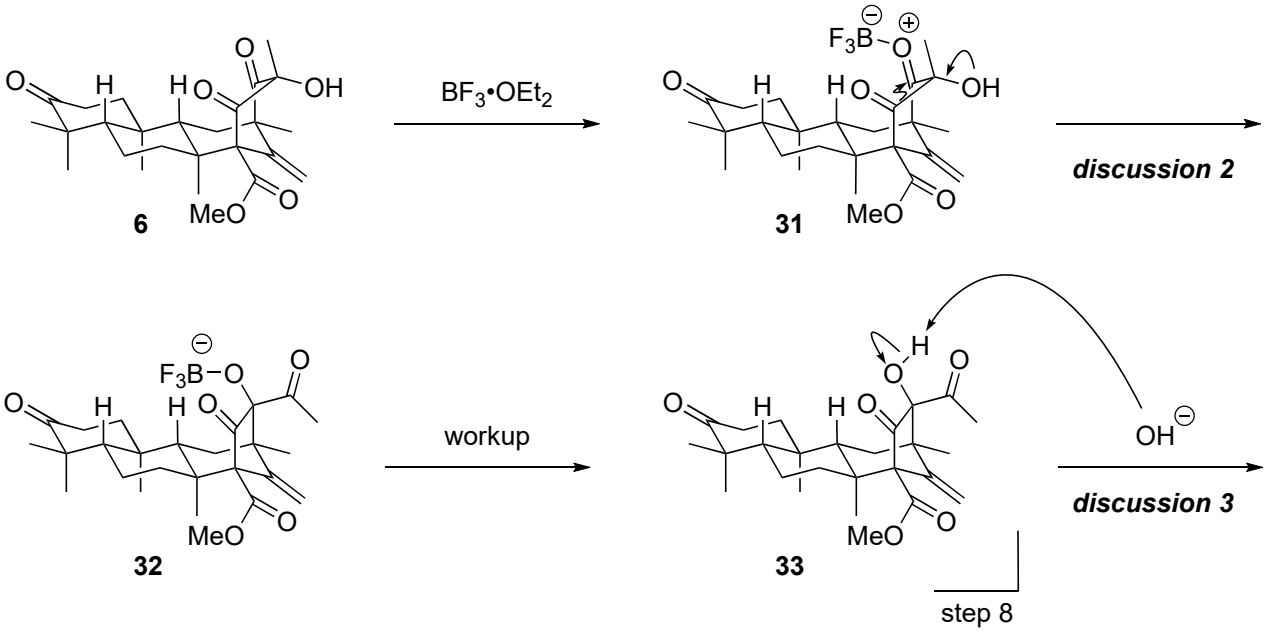


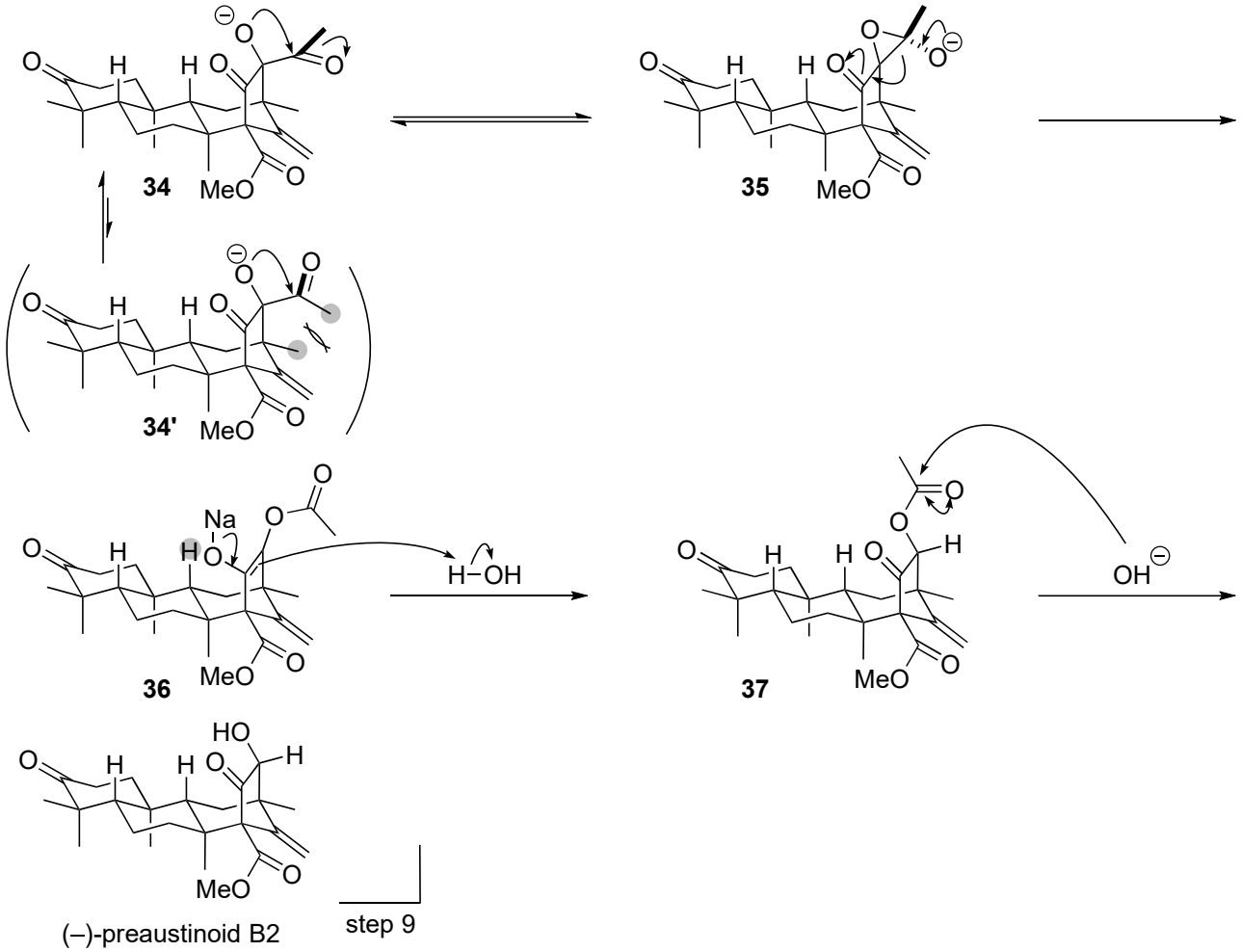
5


MeO
OTf
Li
O
OMe
3-Li
discussion 1
TBSO
H
A
OH
CO2Me
16
step 4
17
Sc(OTf)3
ScIII
18
19
OScIIII(OTf)2
20
TfO
- Sc(OTf)3
21
22
S
+
23
24
25
25-chair
4
step 5
25-boat
26
not obtained


n-BuLi
PPh3
OMe
TBSO
4
27
28
step 6
29
RMgO
; workup
5
step 7

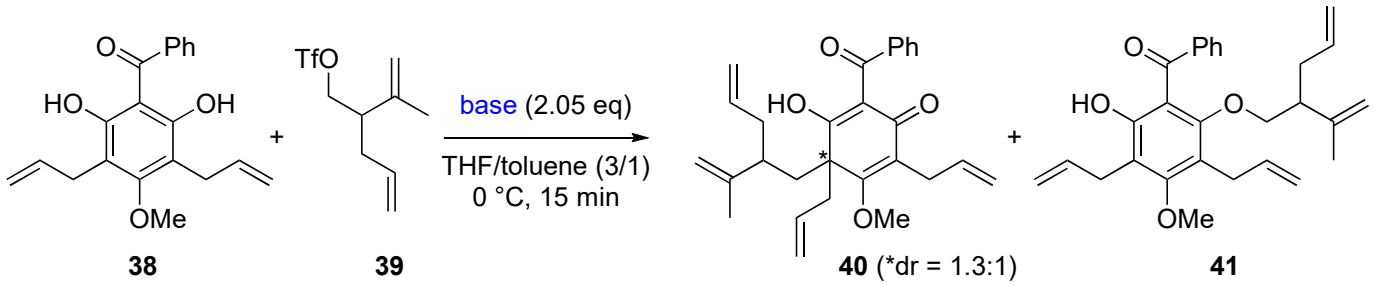

8. BF3•OEt2 (5 eq)
MeCN, rt ,86%
9. 2% aq. NaOH (2 eq)
EtOH, rt, 95%
6
(–)-preaustinoid B2


BF3•OEt2
6
31
discussion 2
32
workup
33
step 8
discussion 3



Discussion 1: dearomative alkylation

1-1. Counter cation



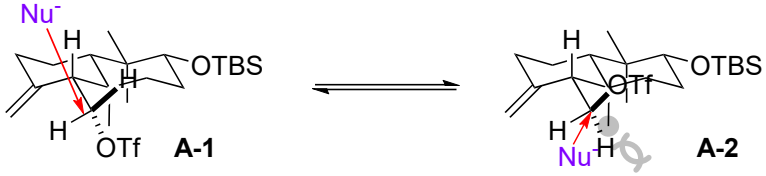
entry	base	yield (%) 40	41
1	$KN(TMS)_2$	0	53
2	$NaN(TMS)_2$	47	31
3	$LiN(TMS)_2$	73	6

Boyce, J.; Porko, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 7832.

Lithium coutercation can bind to phenolate oxygen more tightly than Na^+ and K^+, so that it prevents *O*-alkylation.

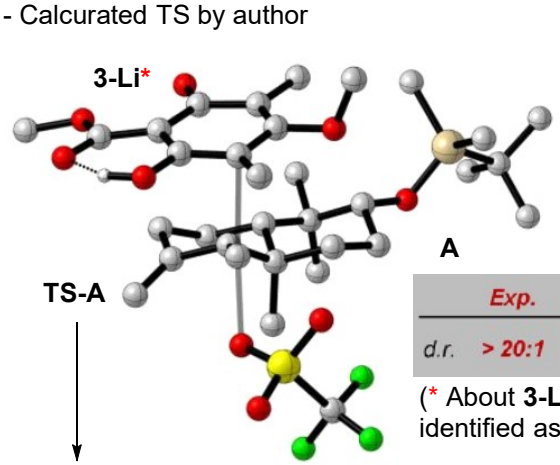
1-2. Stereoselectivity

- Attacking direction of the nucreophile



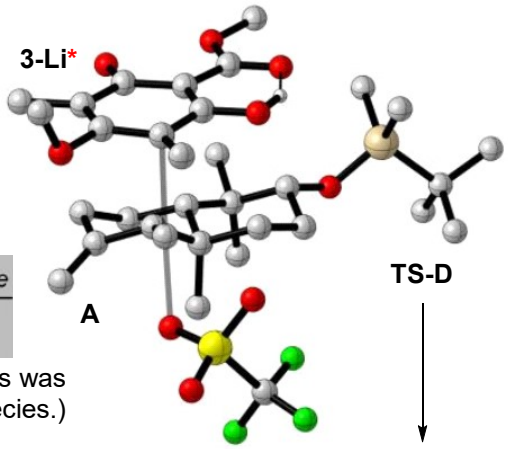
Considering the allylic strain, two conformation, **A-1** and **A-2** can be drawn. In **A-2**, steric repulsion between the nucreophile and highlighted methyl group will be generated. Therefore, we can consider the reaction from **A-1**.

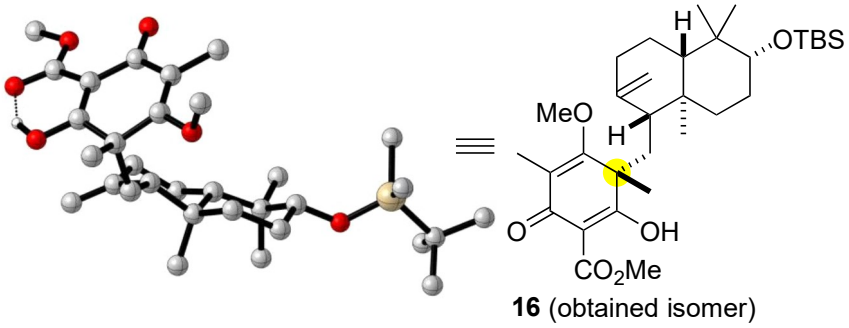
- How to approch the nucreophile
- Calcurated TS by author



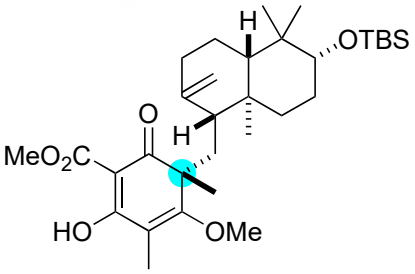
	Exp.	Calc.	Energy difference
d.r.	> 20:1	34:1	2.1 kcal/mol

(* About **3-Li**, mono anion species was identified as computed active species.)





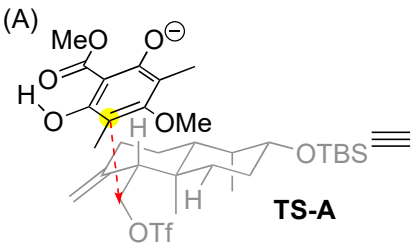
16 (obtained isomer)



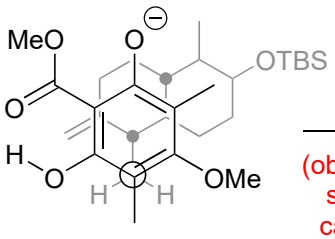
42 (not obtained isomer)

M06-2X/6–31+G(d,p)//B3LYP-D3BJ/6-31G(d) level in THF (SMD solvationmodel).

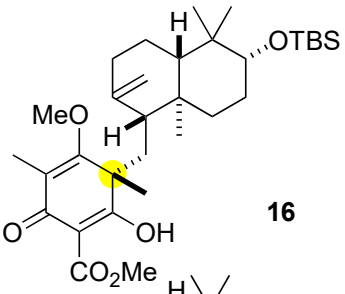
(A)



TS-A

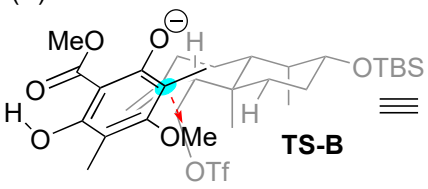


(obtained isomer, shown above calculated TS)

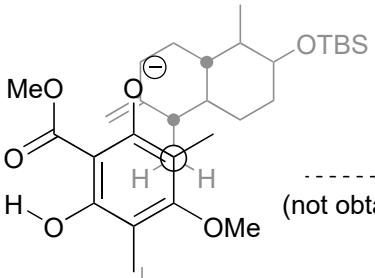


16

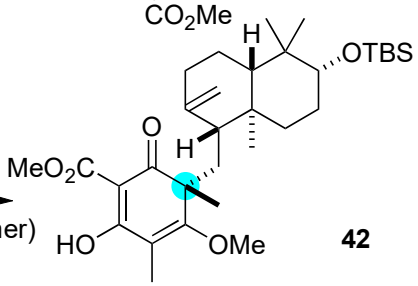
(B)



TS-B

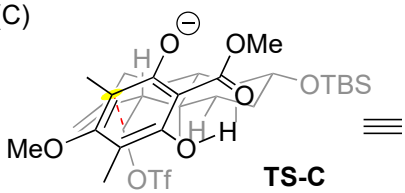


(not obtained isomer)

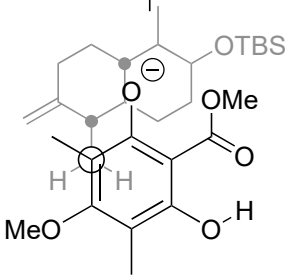


42

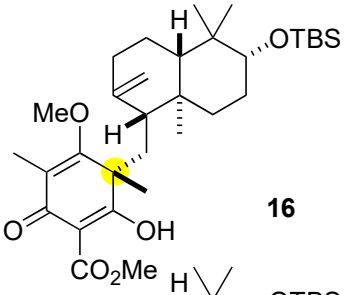
(C)



TS-C

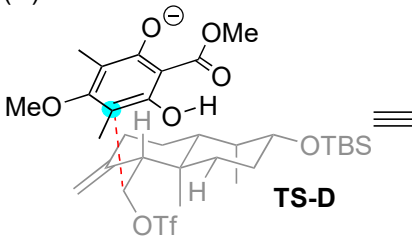


(obtained isomer)

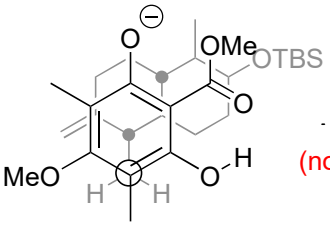


16

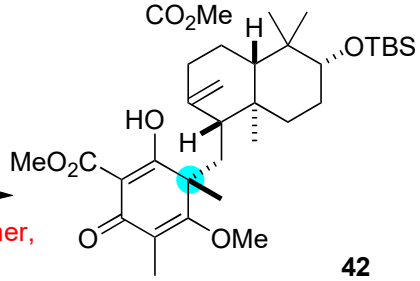
(D)



TS-D

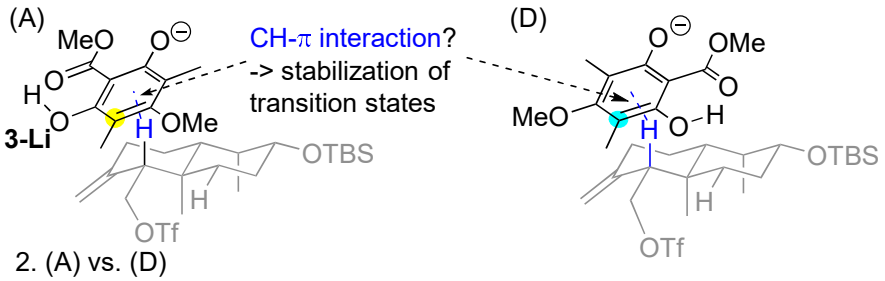


(not obtained isomer, shown above calculated TS)

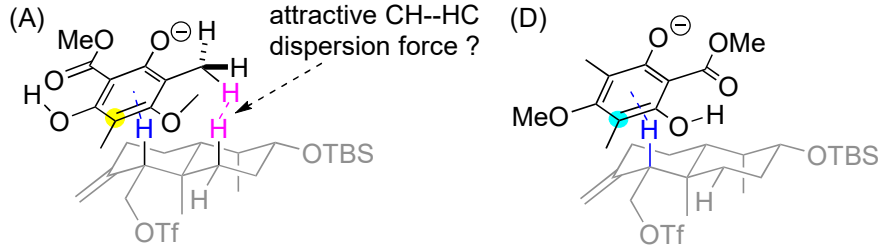


42

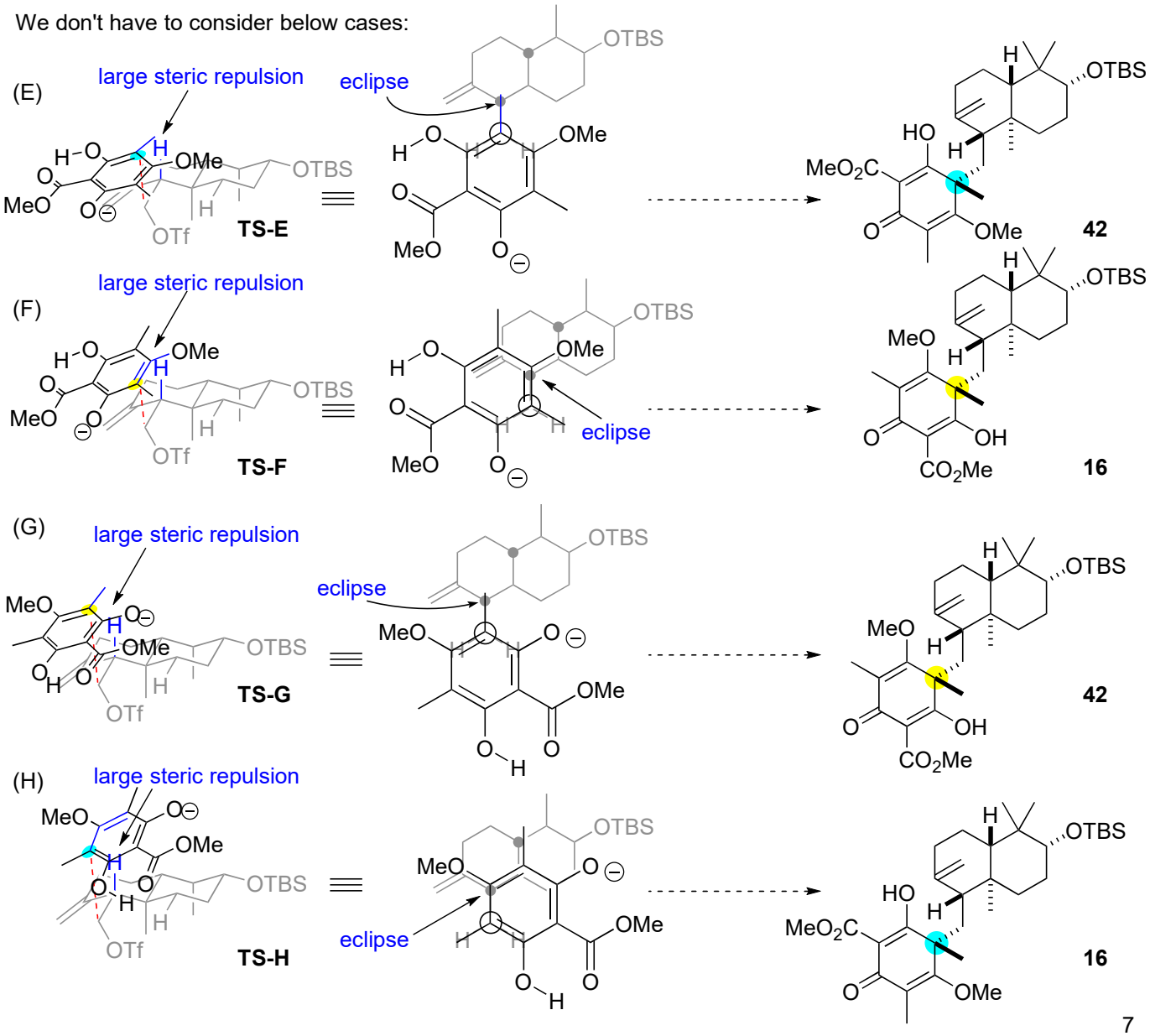
1. (A) vs. (C) and (B) vs. (D):
Contribution of CH-π interaction will be larger in (A) and (D) than (C) and (B), respectiely.
Though overlap of **A** and **3-Li** is larger in (A) and (D), steric repulsion will not be so large for the planarity of **3-Li**.



2. (A) vs. (D)
Preference facter for (A) is not so clear, but one possibility is two Hydrogens (shown in (A)) are at the right distance and the attractive dispersion force is working. Dispersion force is one of the van der Waals force, and its enrgy is proportionate to $1/r^6$ (r: range). Though it is weak, it influences the stability of molecules.

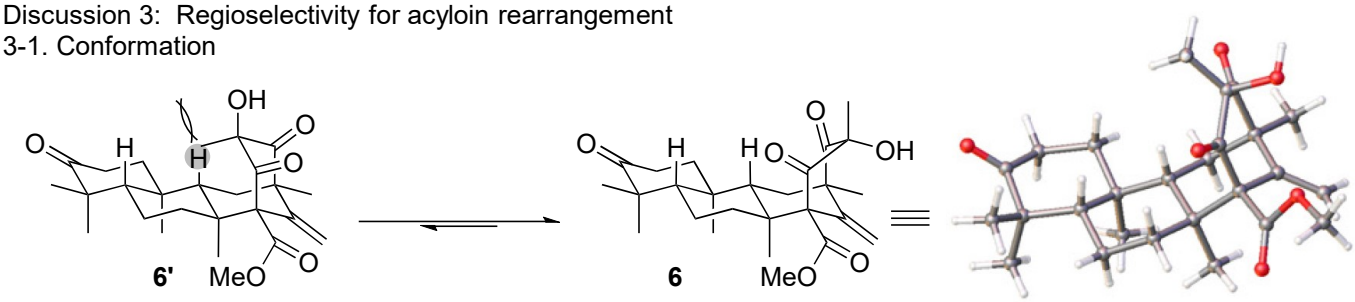


We don't have to consider below cases:

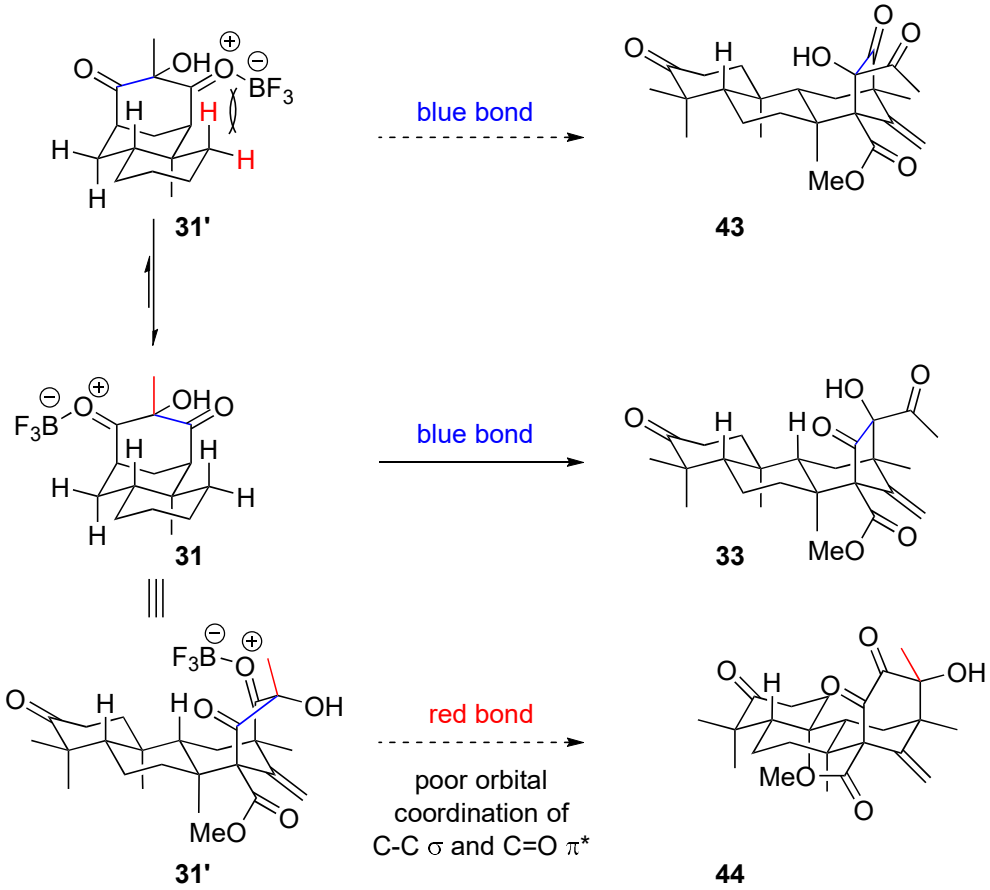


Discussion 3: Regioselectivity for acyloin rearrangement

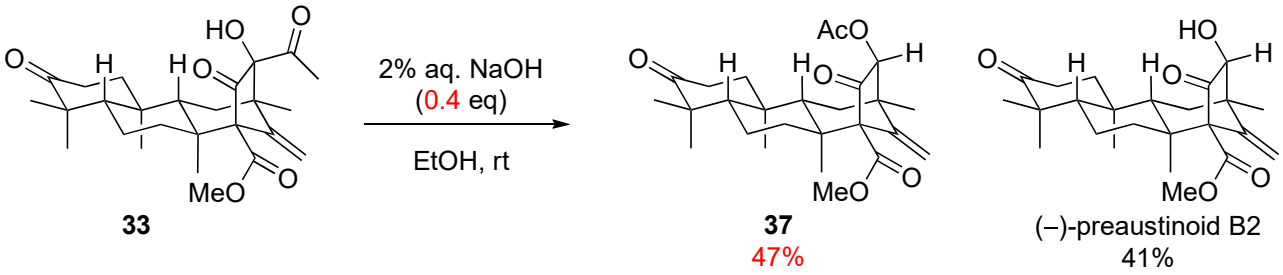
3-1. Conformation



3-1. Coordination of BF_3 and rearranged bond

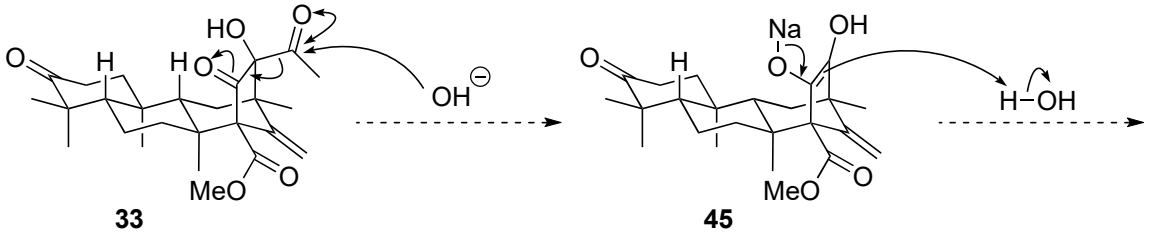


Discussion 4: path for **33** to (–)-preaustinoid B2

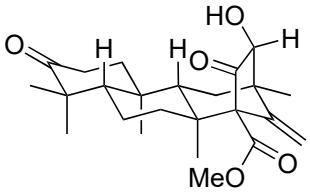


33 **37** 47% (–)-preaustinoid B2 41%

33 can reach (–)-preaustinoid B2 via below retro-aldol path, but in this case, the path in page 5 will be more suitable judging from above results.

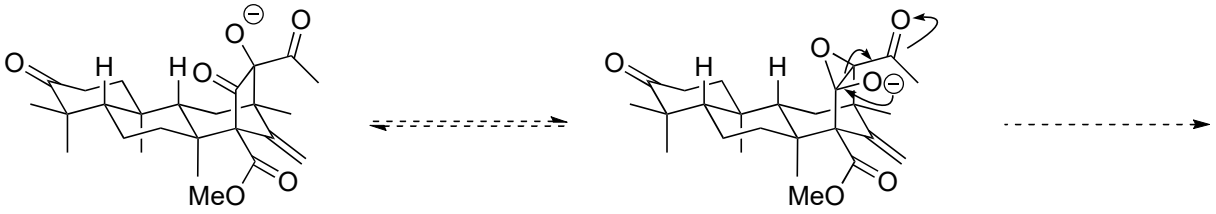


33 **45**



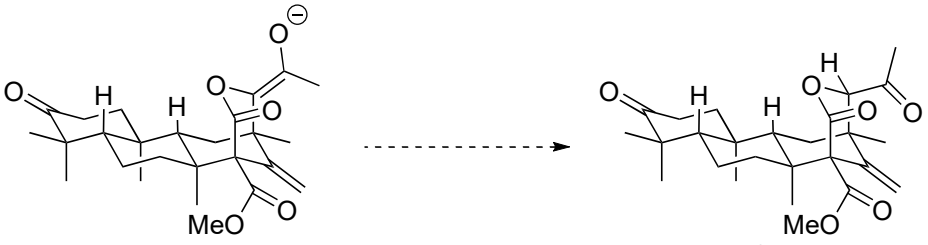
(–)-preaustinoid B2

- Abundance ratio of **46** will be small due to the high strain, so **48** was not obtained.



34 **46**

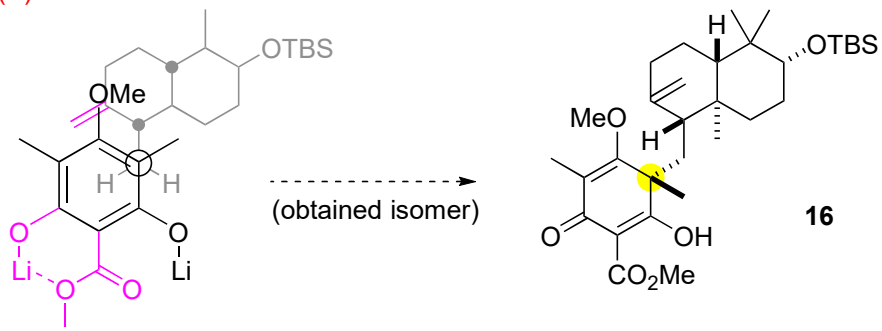
epoxide ring in the five-membered ring ->
high ring strain ->
Abundance ratio will be small.



47 **48**

not obtained

Other possible TS of dearomative alkylation
(A)'



In this TS, electrostatic repulsion between the olefin of **A** and 6-membered ring of chelation is smaller.