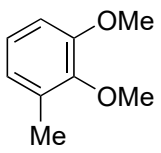
Problem Session (4)

2016.11.15 Haruka Fujino

Please fill in blanks and provide the mechanism of the following reactions. (All compounds are racemic.)

(1)



1-1

1. n-BuLi,THF; **1-2**
   0 °C, 70%
2. $FeCl_3 \cdot H_2O$, CH_2Cl_2
   0 °C to rt, 55%
3. $Ce(SO_4)_2 \cdot 4H_2O$
   MeCN/1 M aq. $HClO_4$
   81%
4. **1-3**, CH_2Cl_2
   sealed tube 140 °C

$(C_{22}H_{32}O_3Si)$

diketone **1-4**

1-4: 68%
isomers of **1-4**: 10%

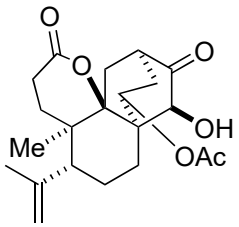
5. *p*-TsOH·H_2O, $HC(OMe)_3$
   MeOH, 40 °C, 42% from **1-4**
6. TBAF, DMSO, 90 °C, 91%
7. $LiAlH_4$, THF, -78 °C to rt
   97%, dr > 20:1
8. Dess-Martin, $NaHCO_3$
   CH_2Cl_2, -25 °C
9. $Mn(dpm)_3$, $PhSiH_3$, O_2
   i-PrOH, 0 °C to rt
   43% (2 steps)

$(C_{21}H_{34}O_6)$

triol **1-5**

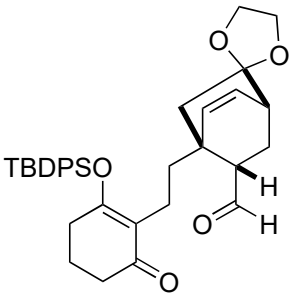
10. Ac_2O, pyridine
    CH_2Cl_2, 81%
11. *m*-CPBA, $NaHCO_3$
    $CDCl_3$, quant.
12. *p*-TsOH·H_2O, benzene*

* Yield was not mentioned.



1-6

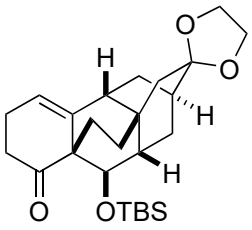
(2)



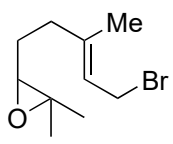
2-1

1. TBAF, THF, 91% (dr > 20:1)
2. TBSOTf, 2,6-lutidine
   CH_2Cl_2, -40 °C, 90%
3. SmI_2, HMPA
   THF/*t*-BuOH, 95% (single isomer)
4. $SOCl_2$, pyridine, 0 °C*

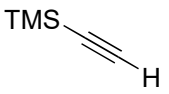
* Yield was not mentioned.



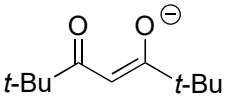
2-2



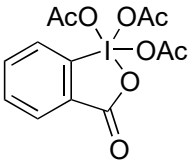
1-2



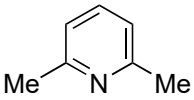
1-3



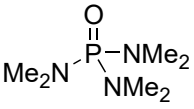
dpm



Dess-Martin periodinane



2,6-lutidine



HMPA

Problem Session (4) [Answer]

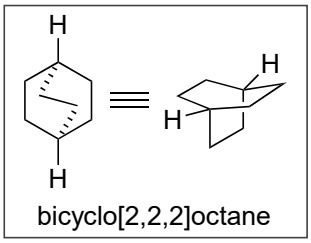
2016.11.15 Haruka Fujino

Topic: Total syntheses of diterpenoids posseseing bicyclo[2,2,2]octane core

(0) Introduction

0.1 Bicyclo[2,2,2]octane

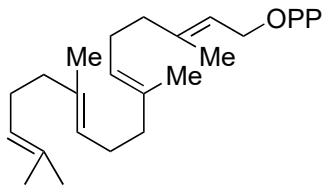
- rigid core structure



bicyclo[2,2,2]octane

0.2 Classificationn and biosynthesisi bicyclo[2,2,2]octane diterpenoids

* Absolute stereochemistry was not considered in the below scheme.

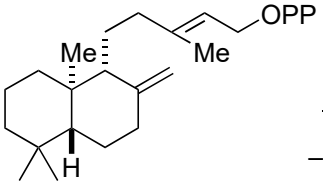


geranylgeranyl diphosphate (GPP, **0-1**)

*PP = diphosphate

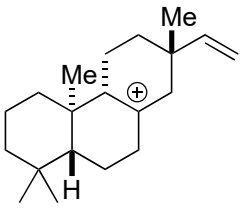
ent-CPP synthase

± H⊕



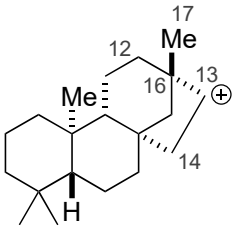
ent-copalyl diphosphate (*ent*-CPP, **0-2**)

– OPP⊖



0-3

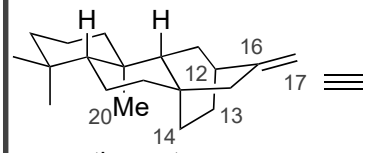
cation-alkene cyclization



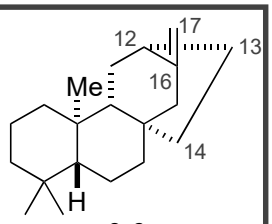
0-4

1,3-H shift [C12 -> C13];

alkyl (C13) shift [C16 -> C12]; – H17⊕

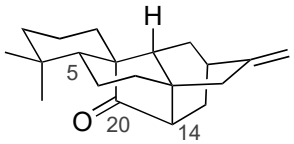


atisane-type (**0-6'**)



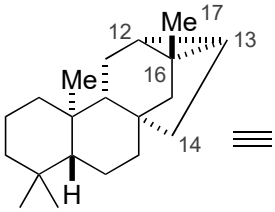
0-6

[O] at C20 & C14–C20 bond formation

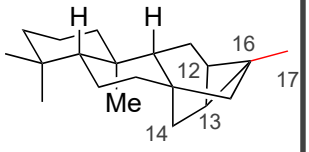


hetidane-type (**0-7**)

– H12⊕ & ring closure (C12–C13)

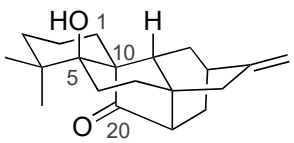


0-5



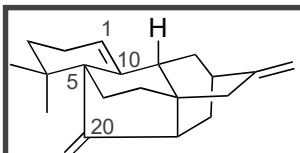
trachyclobane-type (**0-5'**)

[O] at C5

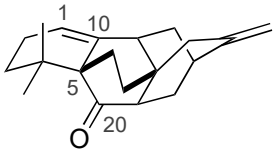


0-8

+ H⊕ & – H_2O; 1,2-acyl shift [C10 -> C5]; – H1⊕



0-9



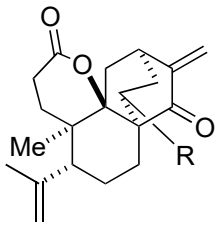
arcutane-type (**0-9'**)

Tantillo, D. J. *et al. J. Am. Chem. Soc.* **2010**, *132*, 5375; Sarpong, R. *et al. Tetrahedron Lett.* **2015**, *56*, 3600.

(1) Total synthesis of (±)-crotobarin by Liu group [Liu, B. *et al. J. Am. Chem. Soc.* **2015**, *137*, 13706.]

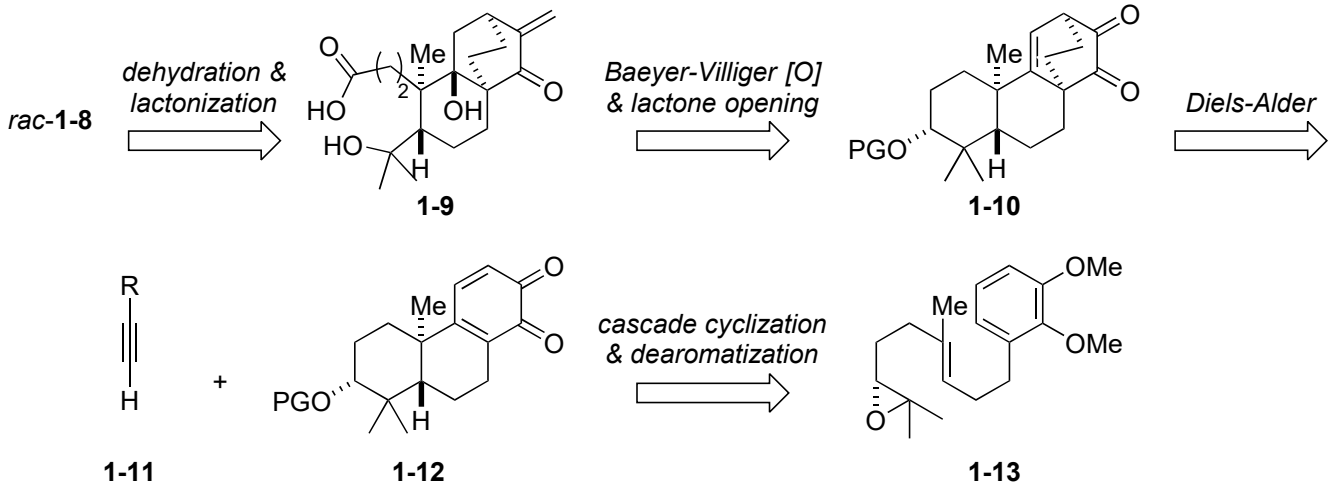
1.1 (–)-Crotobarin & (–)-crotogoudin

- isolation: from *Croton baroum and Croton goudotii*
  [Dumontet, V. and Rasoanaivo, P. *et al. J. Nat. Prod.* **2010**, *73*, 1730.]
- bioactivity: cytoxicity to human cell lines (induction of apotosis?) [*ibid.*]
- classification: 3,4-*seco*-atisane diterpenoid
- total synthesis of *ent*-**1-8**:
  Carreira, E. M. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 11168.
- other synthetic studies:
  Maier, M. E. *et al. Synlett* **2013**, *24*, 705.
  Singh, V. *et al. Tetrahedron* **2014**, *70*, 7983.
  Jia, Y. *et al. Chem. Commun.* **2015**, *51*, 889.

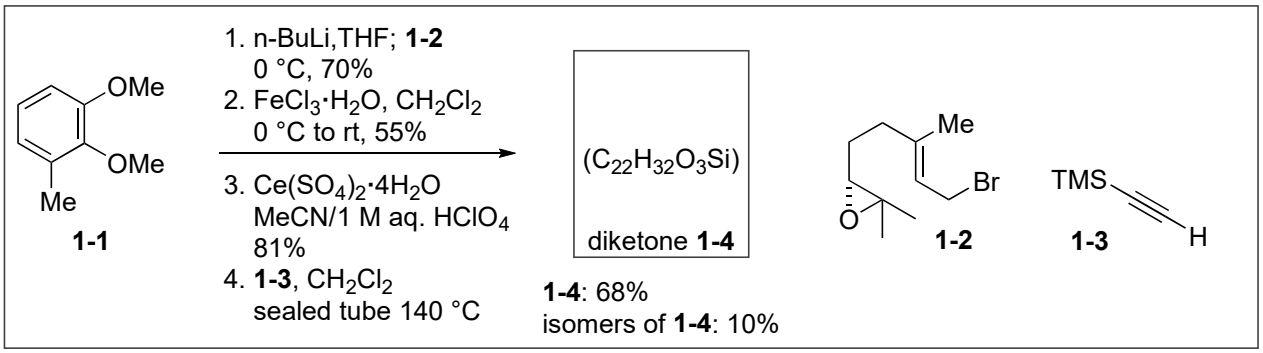


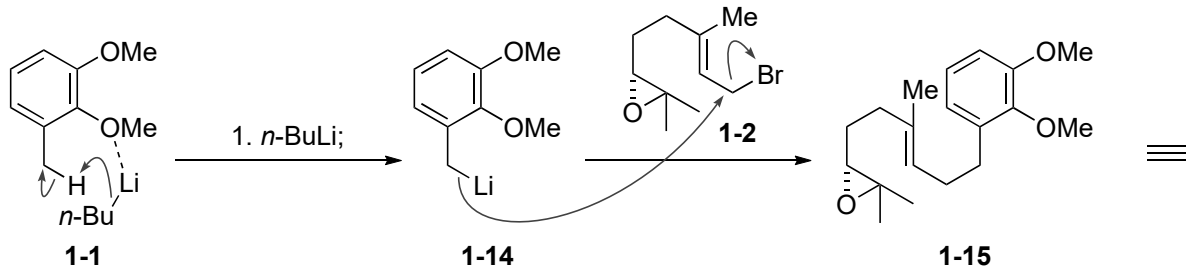
(–)-crotobarin (**1-7**): R = OAc
(–)-crotogoudin (**1-8**): R = H

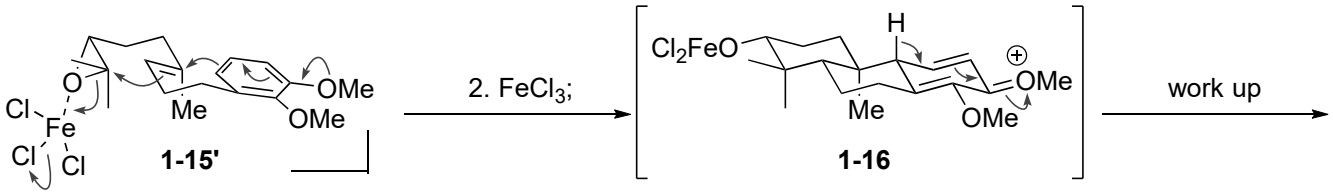
1.2 Retrosynthetic analysis of (±)-crotogoudin (*rac*-**1-8**) by Liu group

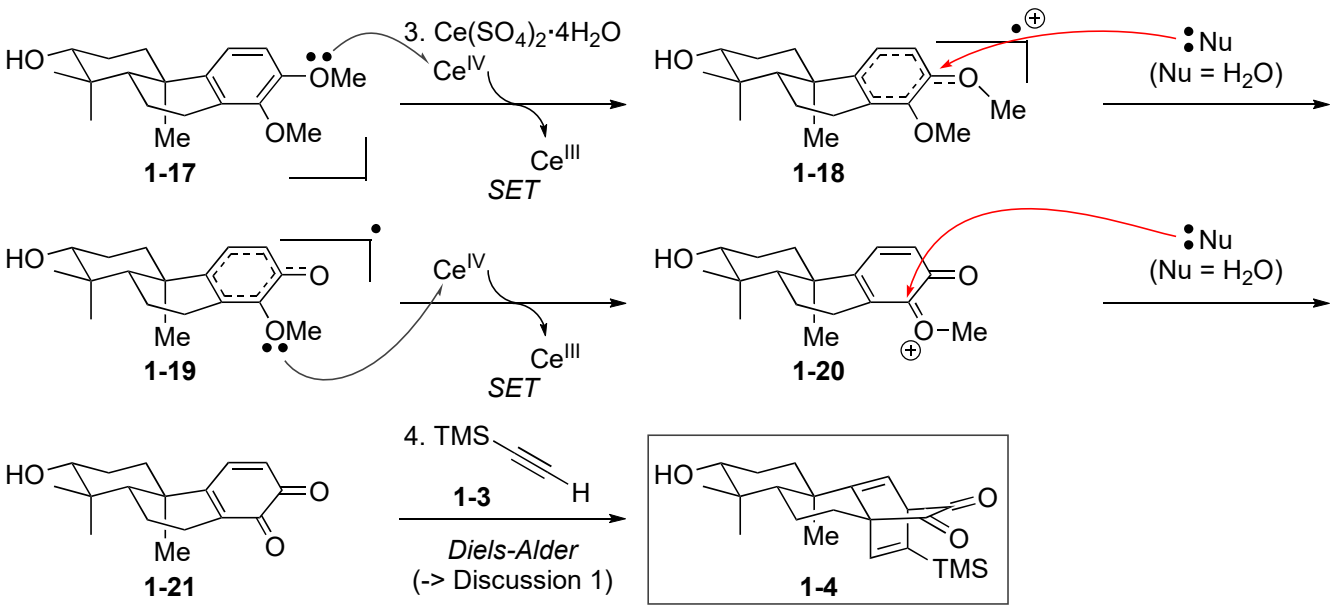


1.3 Transformation from **1-1** to **1-4**



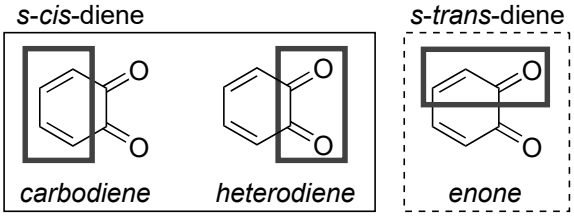




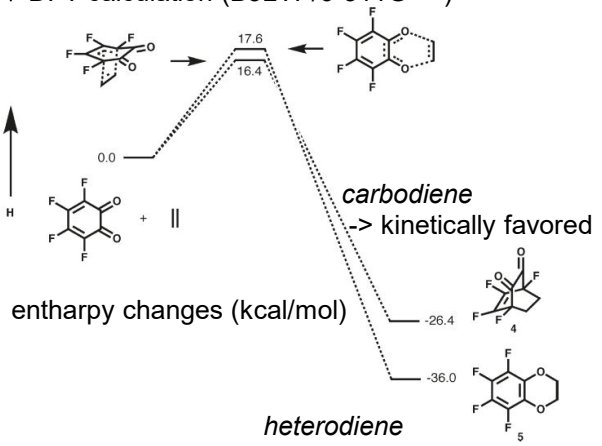


<Discussion 1: Diels-Alder reaction of 1,2-benzoquinone with alkyne/alkene>

(a) reactive site (carbodiene vs. heterodiene)



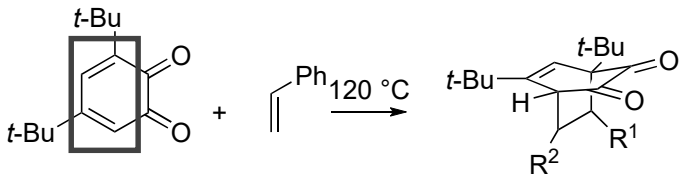
♦ DFT calculation (B3LYP/6-311G**+)



[Lemal, D. M. *et al. J. Org. Chem.* **2009**, *74*, 7804.]

♦ experimental results

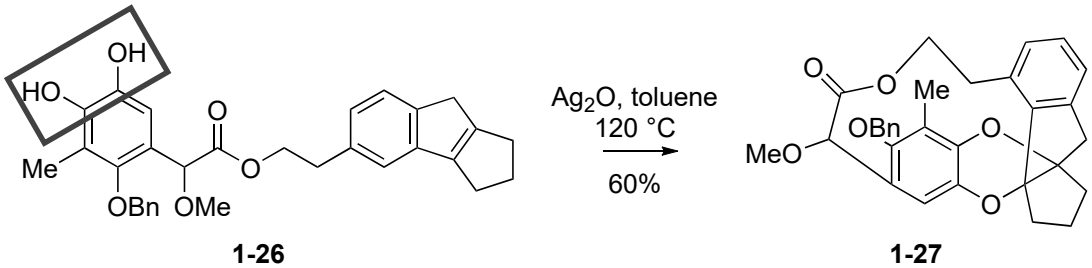
- small dienophile



1-22 (-> carbodiene) **1-23** **1-24** (R^1 = Ph, R^2 = H): 45%
1-25 (R^1 = H, R^2 = Ph): 17%

[Nair, V. *et al. Tetrahedron* **1995**, *51*, 9155.]

- large dienophile (heterodiene)

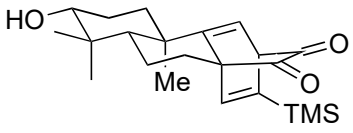
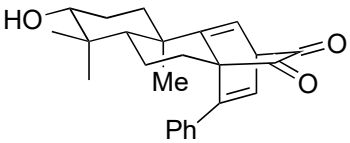
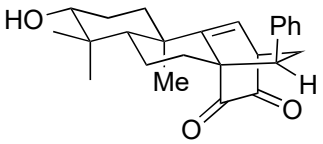


1-26 (-> heterodiene) **1-27**

[Nicolaou, K. C. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 1432.]

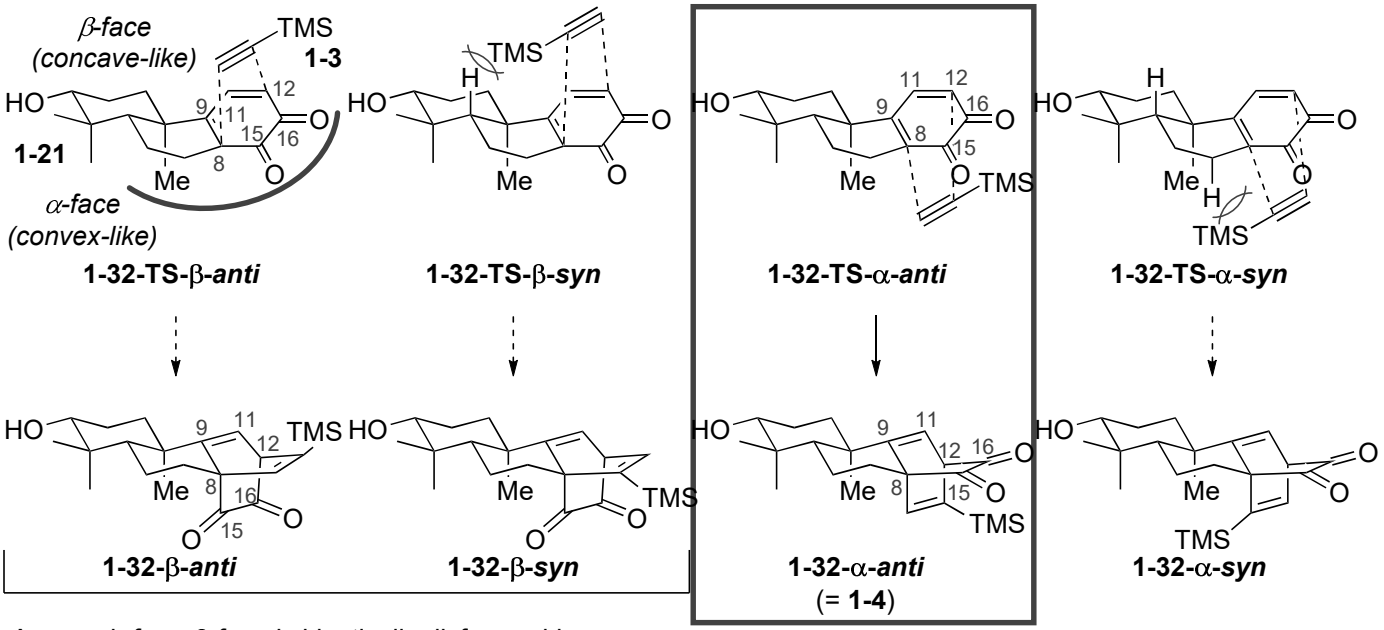
(b) facial- (α/β) & regio-selectivity (*syn*/*anti*)

b-1) experimental data (substrate scope of Diels-Alder reaction with carbodiene **1-21**)

	entry 1	*entry 2*	*entry 3*
dienophile	TMS **1-3**	Ph **1-28**	Ph **1-30**
major isomer	 **1-4** (α-*anti*)	 **1-29** (α-*syn*)	 **1-31** (β-*syn-endo*)
yield *(major isomer:* *other isomers)*	78% (7:1)	96% (3:1)	99% (3:1)

[Liu, B. e*t al. J. Am. Chem. Soc.* 2**015,** 1*37,* 13706.]

b-2) rationale (1) - my hypothesis



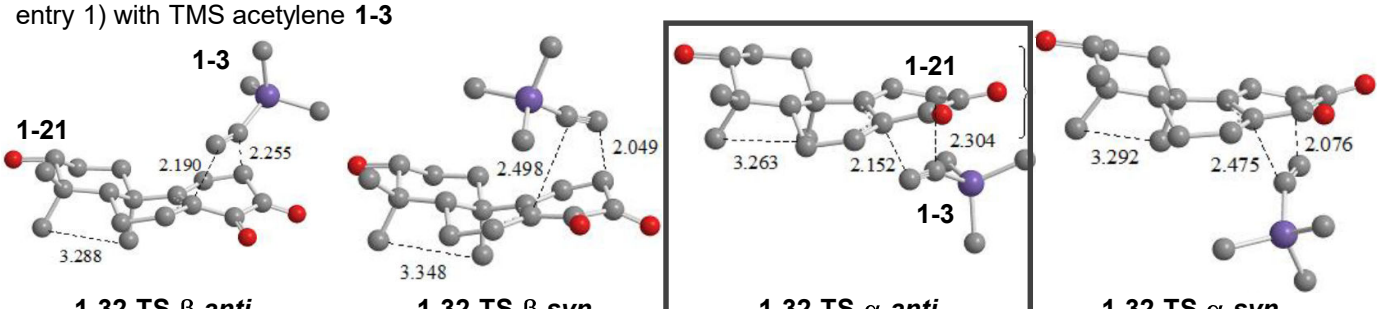
Approach from β-face is kinetically disfavored because...

1) β-face is concave-like face.

2) movement of (C8-C15-C16-C12)-plane from substrate **1-21** to product **1-28** is larger.

b-3) rationale (2) - DFT calculation (M06-2X,6-31G(d,p) [Liu, B. *et al. J. Am. Chem. Soc.* **2015**, *137*, 13706.]

entry 1) with TMS acetylene **1-3**



1-32-TS-β-*anti* — 10.8 kJ/mol — 0.0732*e*

1-32-TS-β-*syn* — 18.7 kJ/mol — 0.0630*e*

1-32-TS-α-*anti* — 0.0 kJ/mol — 0.0736*e*

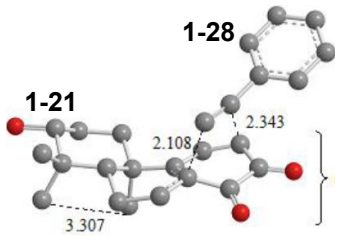
1-32-TS-α-*syn* — 11.4 kJ/mol — 0.0645*e*

relative energy

negative charge accumulated at diene

suggesting the presence of greater interaction between dienophile **1-3**'s HOMO and carbodiene **1-21**'s LUMO

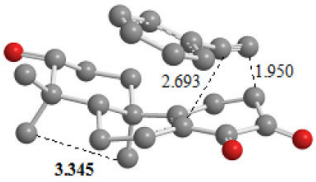
entry 2) with phenyl acetylene **1-28**



1-33-TS-β-*anti*

16.4 kJ/mol

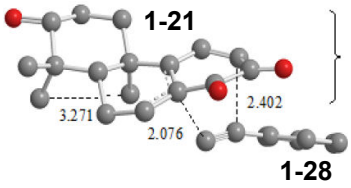
0.0537e



1-33-TS-β-*syn*

6.5 kJ/mol

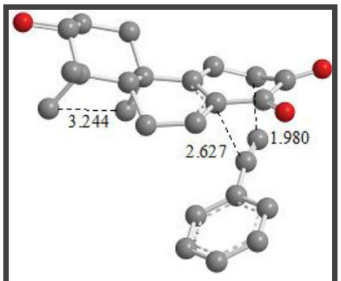
0.0770e



1-33-TS-α-*anti*

9.3 kJ/mol

0.0630e

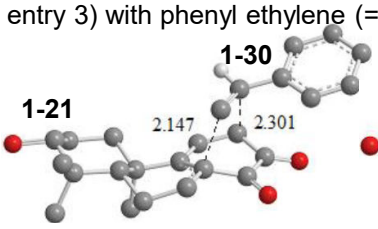


1-33-TS-α-*syn*

0.0 kJ/mol

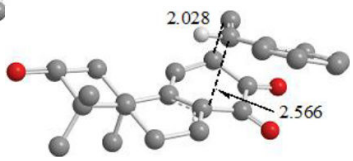
0.0750e

entry 3) with phenyl ethylene (= stylene) **1-30**



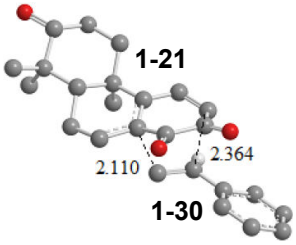
1-34-TS-β-*anti-exo*

24.2 kJ/mol



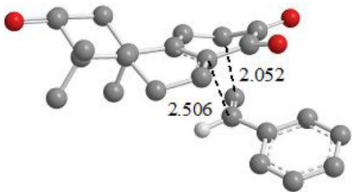
1-34-TS-β-*syn-exo*

14.5 kJ/mol



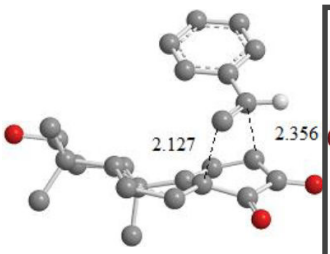
1-34-TS-α-*anti-exo*

16.5 kJ/mol



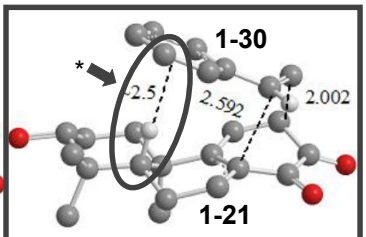
1-34-TS-α-*syn-exo*

8.0 kJ/mol



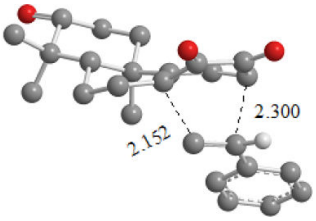
1-34-TS-β-*anti-endo*

14.7 kJ/mol



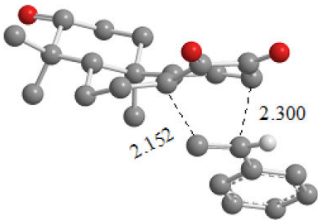
1-34-TS-β-*syn-endo*

0.0 kJ/mol



1-34-TS-α-*anti-endo*

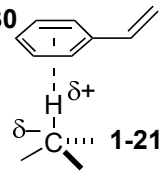
15.2 kJ/mol



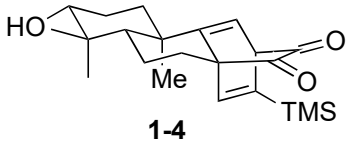
1-34-TS-α-*syn-endo*

14.6 kJ/mol

* C–H - - - π interaction
[reviews: Jiménez-Barbero, J. *et al. Acc. Chem. Res.* **2013**, 46, 946.;
Schneider, H.-J. *et al. Chem. Rev.* **2016**, *116*, 5216.]



1.4 Transformation from **1-4** to **1-5**



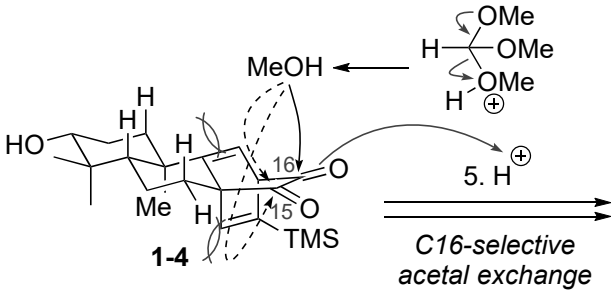
1-4

5. *p*-TsOH·H_2O, $HC(OMe)_3$, MeOH, 40 °C, 42% from **1-4**
6. TBAF, DMSO, 90 °C, 91%
7. $LiAlH_4$, THF, -78 °C to rt, 97%, dr > 20:1

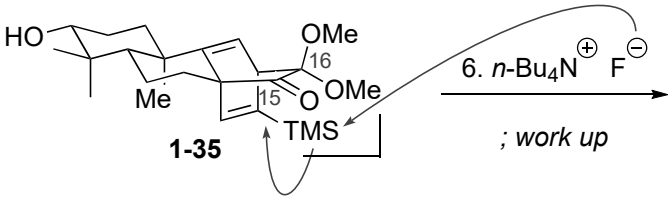
8. Dess-Martin, $NaHCO_3$, CH_2Cl_2, -25 °C
9. $Mn(dpm)_3$, $PhSiH_3$, O_2, i-PrOH, 0 °C to rt
43% (2 steps)

$(C_{21}H_{34}O_6)$

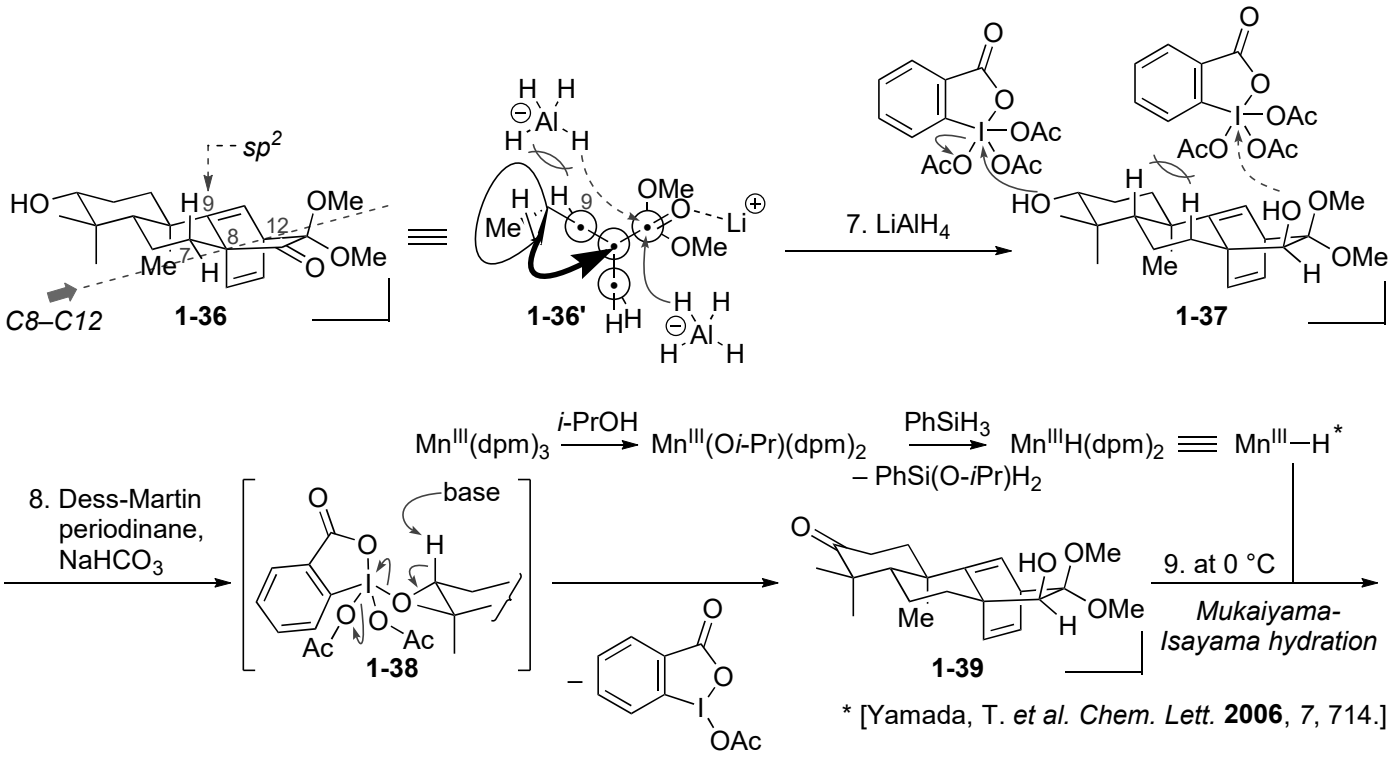
triol **1-5**



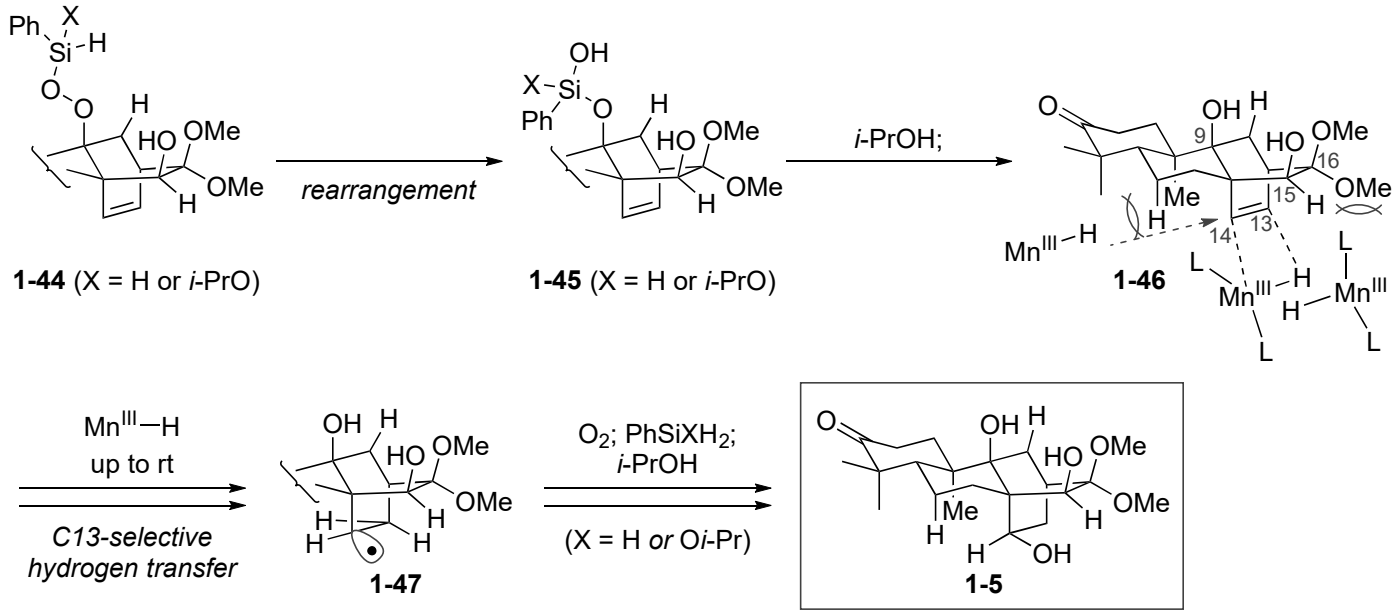
1-4



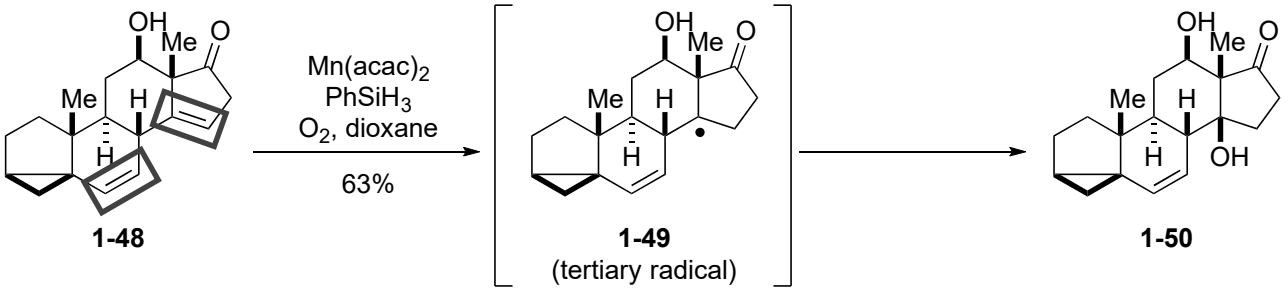
1-35



* $PhSi(O\textit{i}\text{-}Pr)H_2$ was recently reported as a superior reductant compared to $PhSiH_3$ in Mukaiyama hydration.
[Shenvi, R. A. *et al. J. Am. Chem. Soc.* **2016**, *138*, 4962]



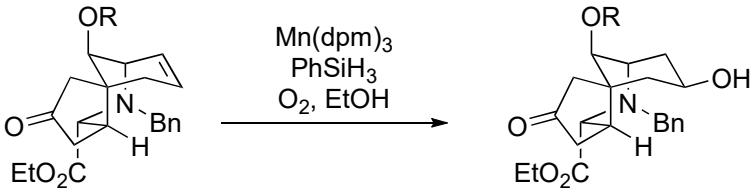
<Discussion 2: Mukaiyama-Isayama hydration>
(a) reactivity (disubstituted olefin vs trisubstituted olefin)



1-48 **1-49** (tertiary radical) **1-50**

[Baran, P. S. *et al. J. Am. Chem. Soc.* **2015**, *137*, 10160.]

(b) hydroxy group-directed Mukaiyama-Isayama hydration

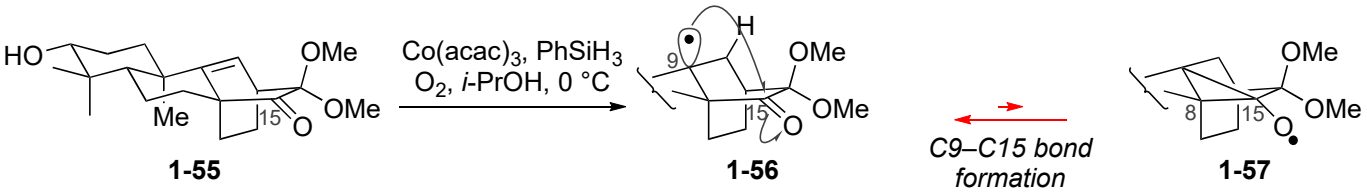


1-51 (R = H)
1-52 (R = Ac)

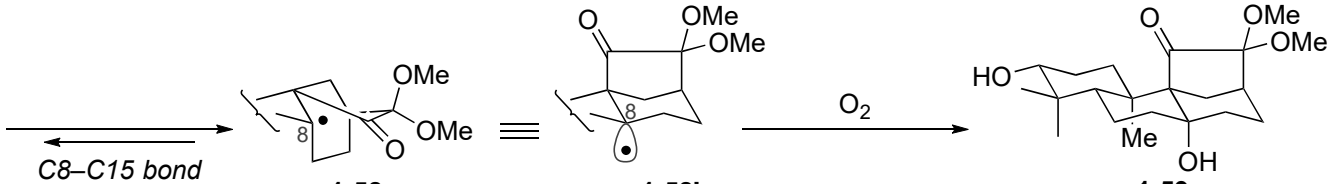
1-53 (R = H): 75%
1-54 (R = Ac): not obtained

[Carreira, E. M. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 8852.]

(c) application: rearrangement to bicyclo[3,2,1]octane skelton (*C15*: carbonyl group)



1-55 **1-56** **1-57**

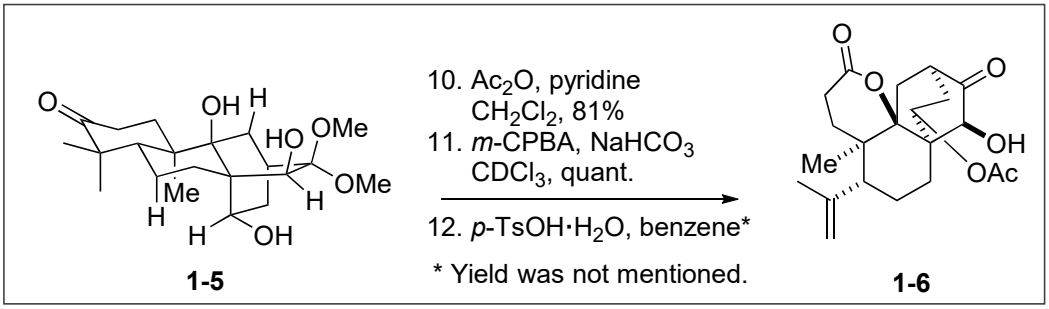


1-58 **1-58'** **1-59**

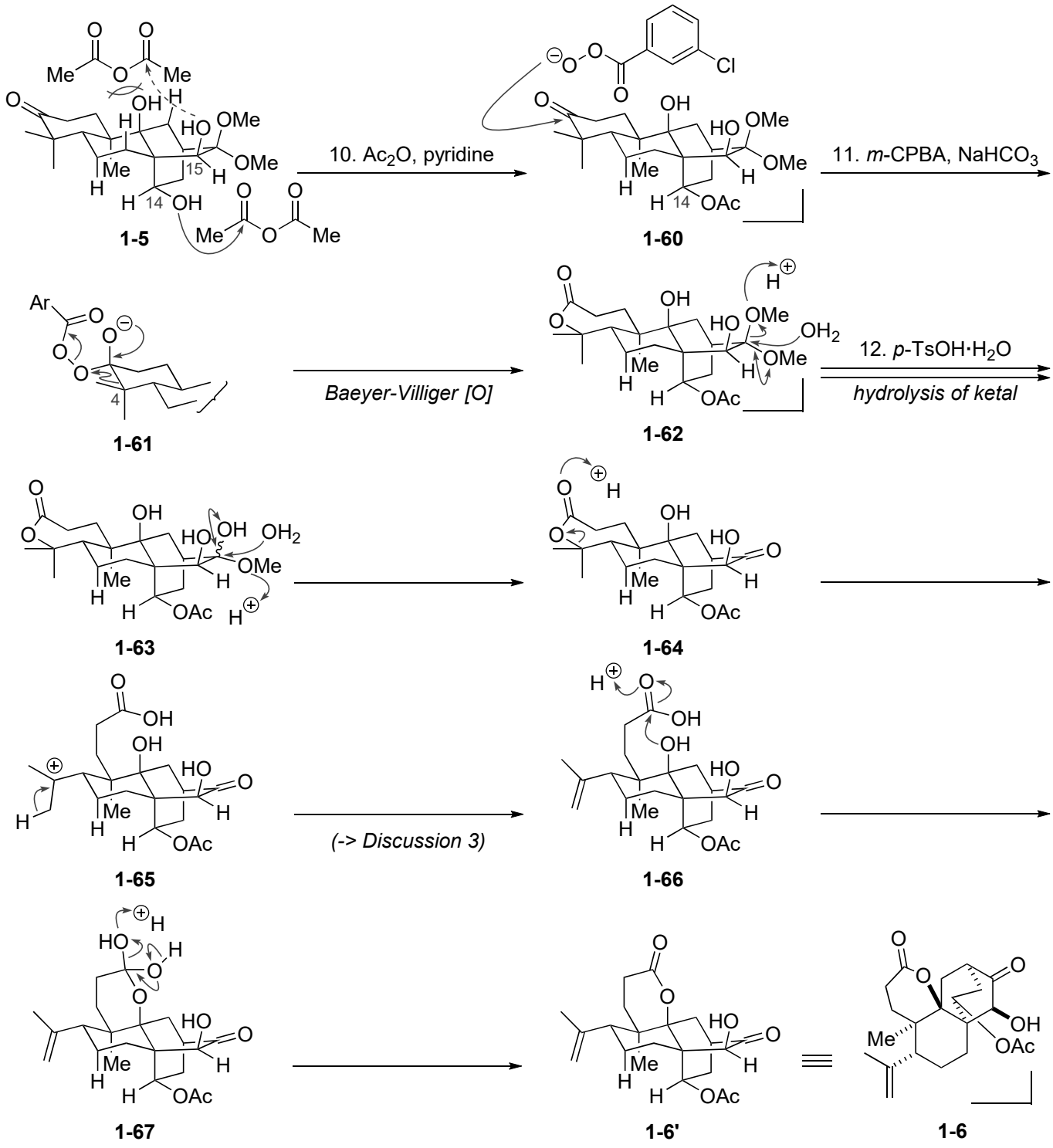
(-> scopadulane-type skelton)

[Liu, B. *et al. J. Am. Chem. Soc.* **2015**, *137*, 13706.]

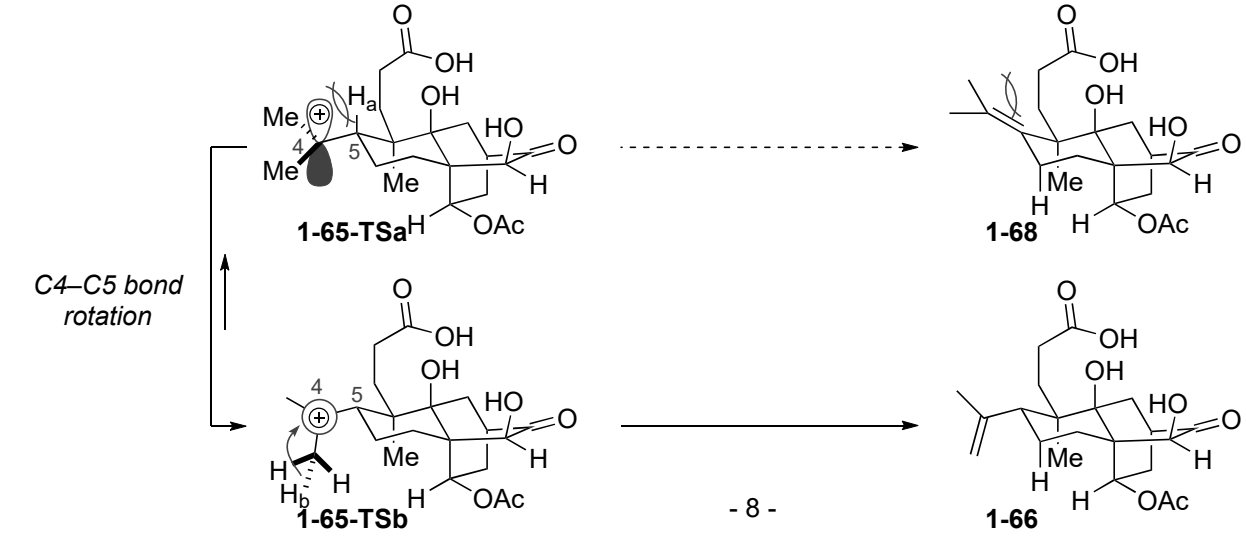
1.5 Transformation from **1-5** to **1-6**



1-5 **1-6**



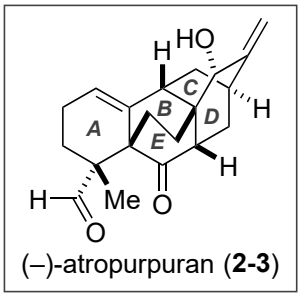
<Discussion 3: Refioselectivity in E1 elimination>



(2) Total synthesis of (±)-atropurpuran by Qin group [Qin, Y. *et al. Nat. Commun.* doi: 10.1038/ncomms12183.]

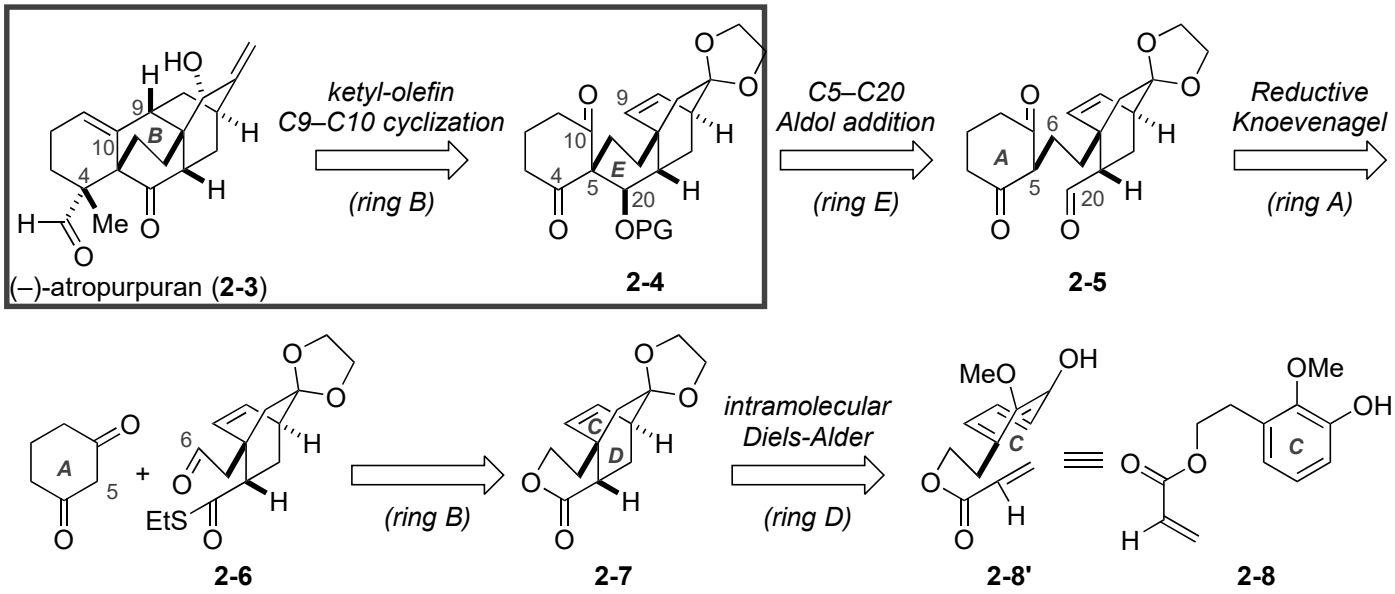
2.1 (–)-atropurpuran

- isolation: from *Aconitum hemslayanum var. atropurpureum*
  [Wang, F.-P. *et al. Tetrahedron Lett.* **2009**, *50*, 460.]
- bioactivity: unknown
- classification: arcutane diterpenoid
- structural charasteristic: tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]tridecane core
  (= two fused bicyclo[2.2.2]octane units)
- total synthesis: no reported expamles to date
- synthetic study: Kobayashi, S. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 9177.
  Hsung, R. P. *et al. Org. Lett.* **2012**, *14*, 252.
  Zhang, D. *et al. Tetrahedron Lett.* **2013**, *69*, 3141.
  Song, H. *et al. Tetrahedron* **2016**, *72*, 347.



(–)-atropurpuran (**2-3**)

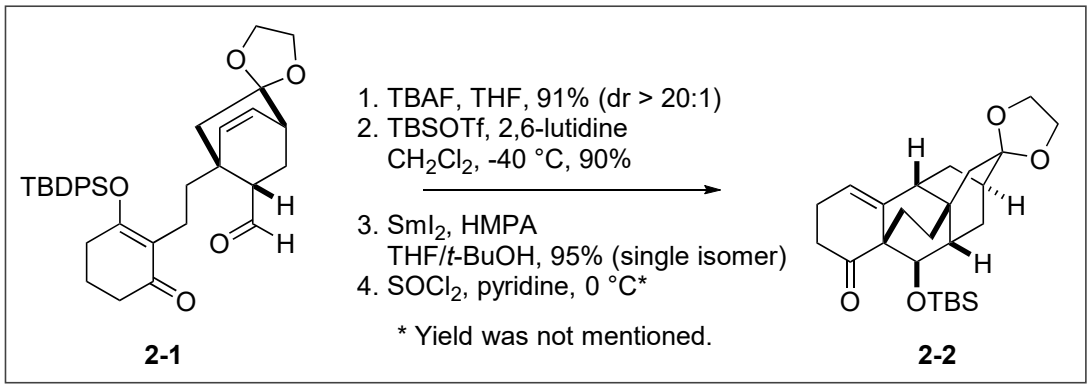
2.2 Retrosynthetic analysis by Qin group *(-> Problem (2))*



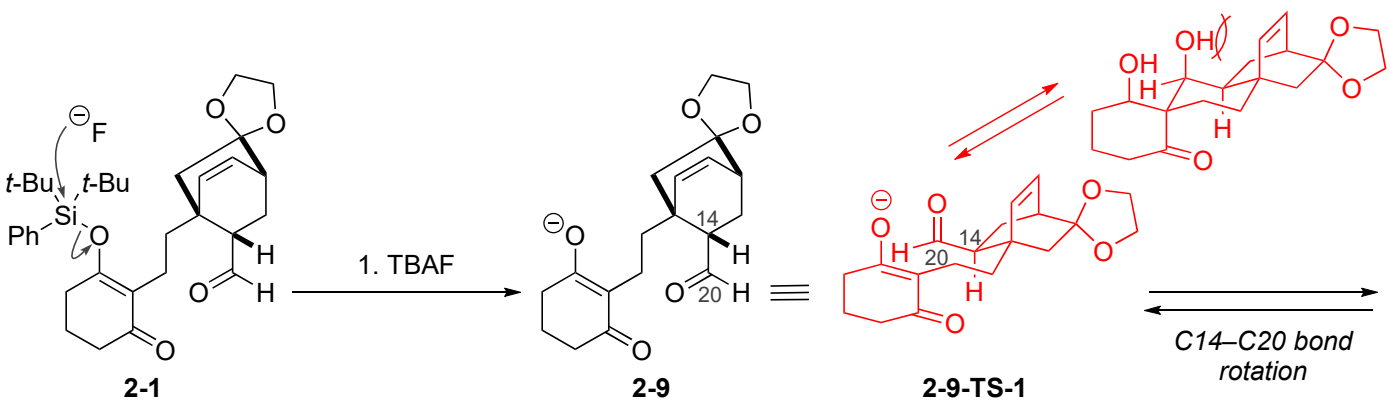
(–)-atropurpuran (**2-3**) **2-4** **2-5**

2-6 **2-7** **2-8'** **2-8**

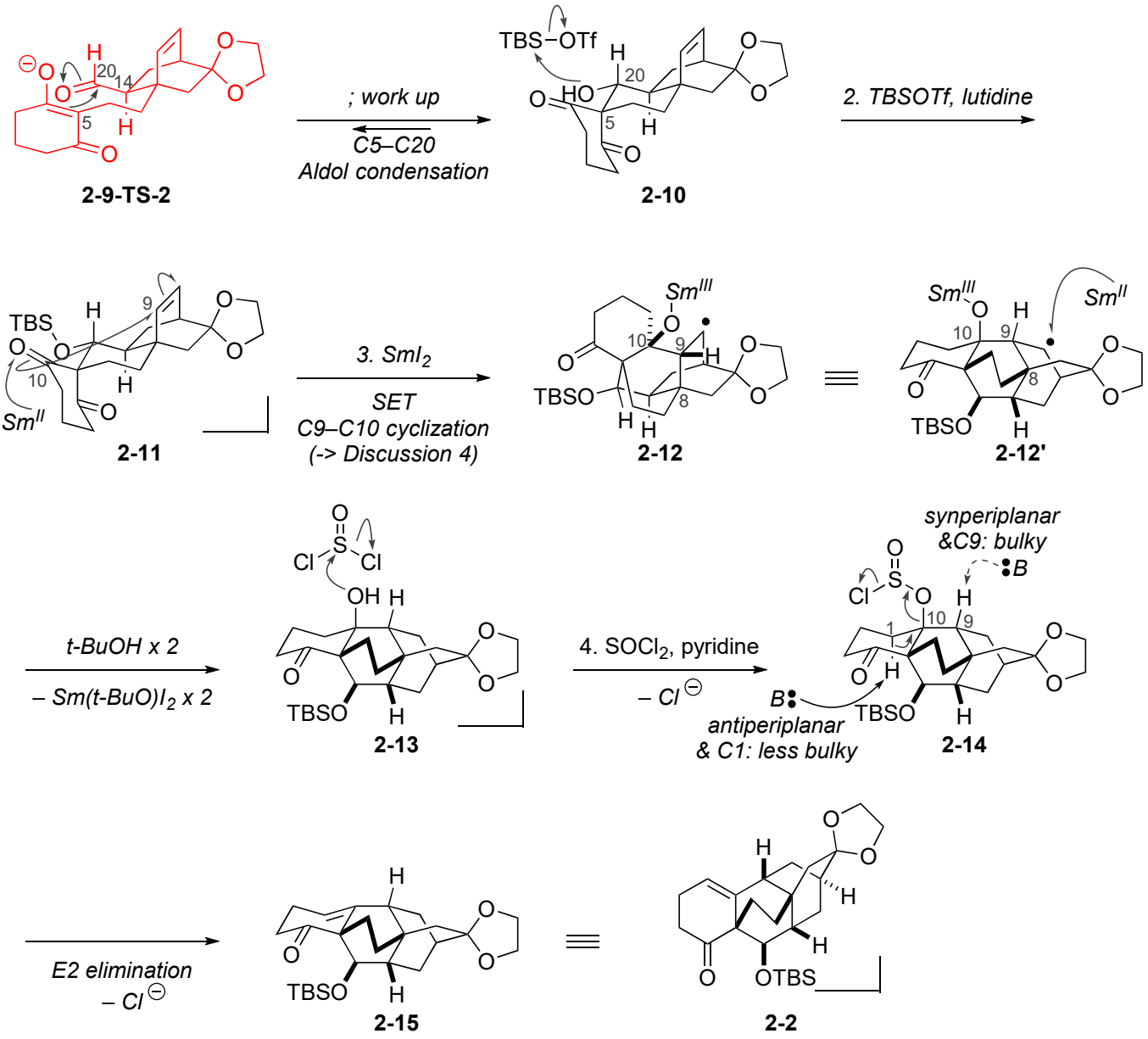
2.3 Transformation from **2-1** to **2-2**



2-1 **2-2**



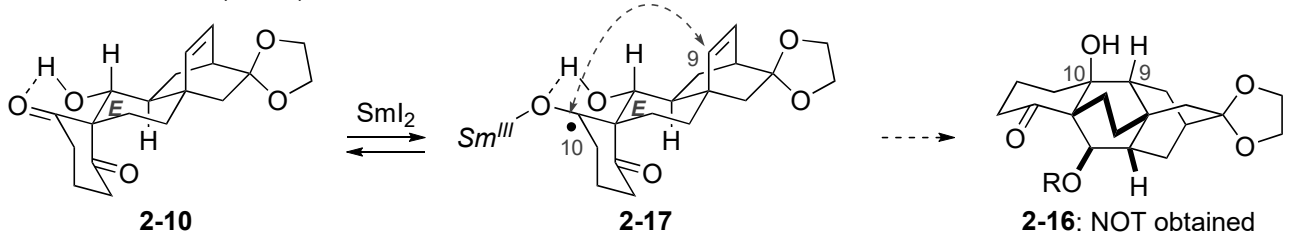
2-1 **2-9** **2-9-TS-1**



<Discussion 4: SmI_2-mediated ketyl-olefin cyclization>
(a) chair/boat conformation on E ring

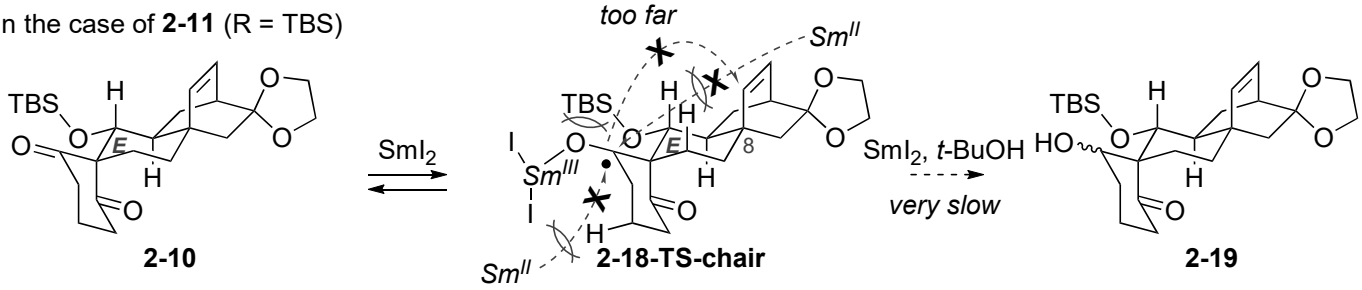
- in the case of **2-10** (R = H)

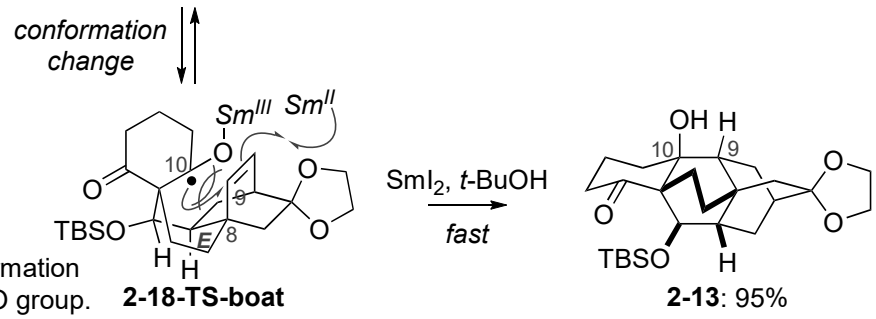
too far between C9 and C10



E ring of **2-10** and **2-17** is fixed as a chair conformation due to the exsitence of hydrogen bonding.

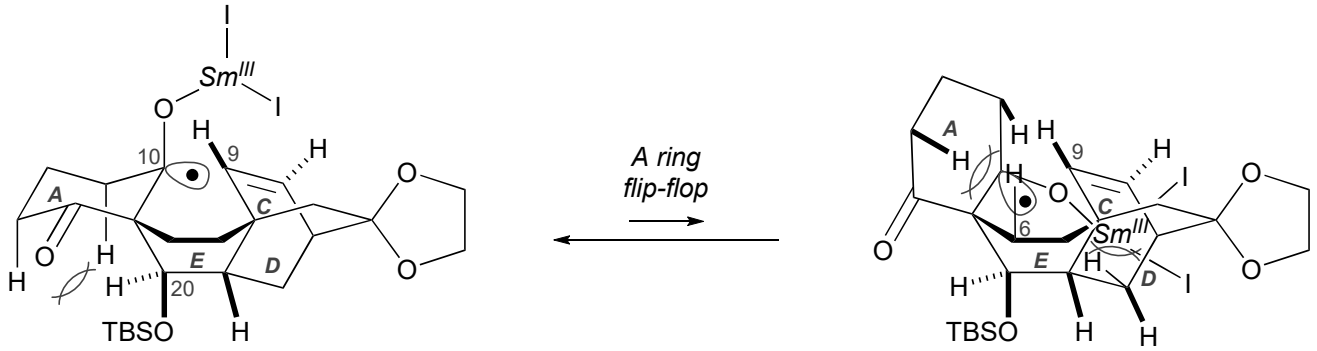
- in the case of **2-11** (R = TBS)





E ring of **2-10** can also adopt a boat conformation due to the steric repulsion by a bulky TBSO group.

(b) stereoselectivity



- C10 stareochemistry is determined by A ring conformation.
  In **2-18-TS-boat-2**, there are large repulsion between bulky D/E ring and SmI_2 group
- C9 stereochemistry is determined by C/D ring conformation, which is firmly fixed by its bicyclo[2,2,2]octane core.