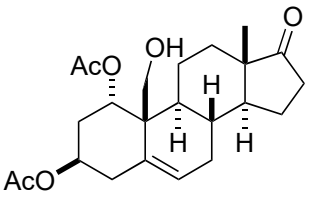
Problem Session (4)

2018.04.21. Yinghua Wang

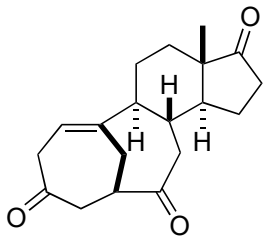
Please provide each reaction mechanism.

1



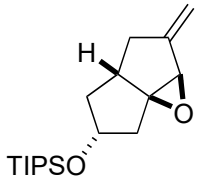
1-1

1. MsCl, Et_3N
   CH_2Cl_2, -10 °C, 97%
2. KOAc, H_2O
   acetone, reflux, 82%
3. NaOH (1 eq.)
   MeOH, -20 °C, 75%
4. DMP, CH_2Cl_2
5. basic Al_2O_3, THF
   83% (2 steps)
6. SmI_2 (2.1 eq.), THF;
   H_2O, 43%



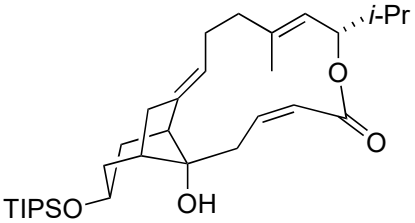
1-2

2



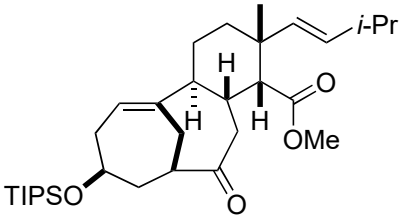
2-1

1. HG-II (5 mol%), **2-2**
   $CHCl_3$, reflux, E/Z = 5/1
2. AllylMgBr, THF, 0 °C
   47% (2 steps)
3. acrylic acid, **reagent A**
   Et_3N, CH_2Cl_2, 70%
4. HG-II (10 mol%)
   CH_2Cl_2, reflux, 70%



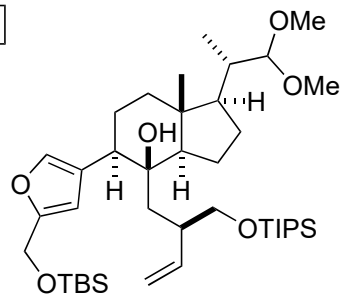
2-3

5. $Me_2PhSiCl$, DBU
   $PhCF_3$, 140 °C; HCl
6. $TMSCHN_2$, $MeOH/Et_2O$
   64% (2 steps)



2-4

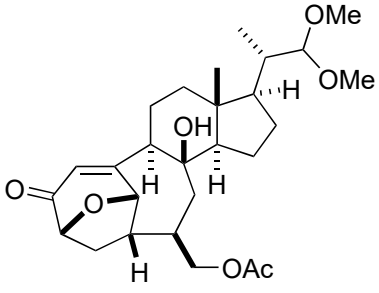
3



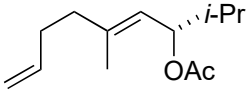
3-1

1. TBAF, THF;
   NBS, NaOAc, $NaHCO_3$, H_2O
2. Ac_2O, TMP, DMAP, CH_2Cl_2
3. TMP, CH_3CN, 155 °C

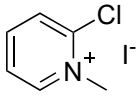
68% (3 steps)



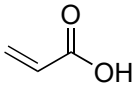
3-2



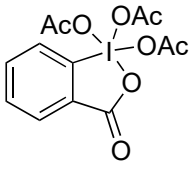
2-2



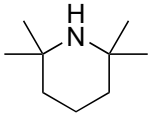
reagent A



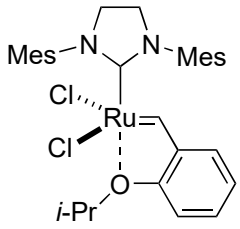
acrylic acid



DMP



TMP



HG-II
(Hoveyda-Grubbs 2nd catalyst)

Problem Session (4) -Answer-

2018.04.21. Yinghua Wang

Topic: Synthetic Studies of Cyclocitrinol

0. Introduction

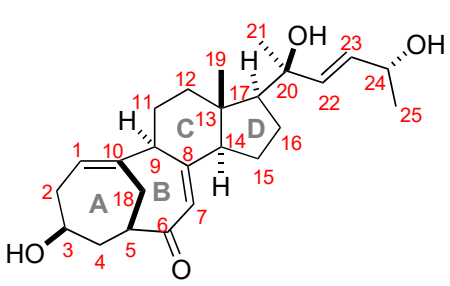
0-1. Isolation

Isolated as a fungal metabolite from terrestrial *P. citrinum*
Kozlovsky, A. G.; Zhelifonova, V. P.; Ozerskaya, S. M.; Vinokurova, N. G.; Adanin, V. M.; Gräf, U. *Pharmazie* **2000**, *55*, 470.

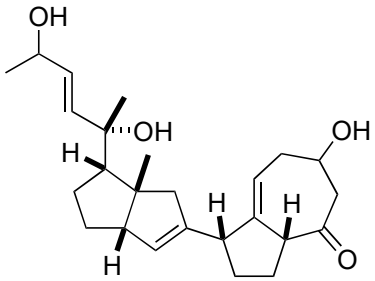
0-2. Structual feature

Original proposed structure was assigned as **0-2**, which was revised by X-ray crystallographic analysis of **0-3**.
Amagata, T.; Amagata, A.; Tenney, K.; Valeriote, F. A.; Lobkovski, E.; Clardy, J.; Crews, P. *Org. Lett*. **2003**, *5*, 4393.

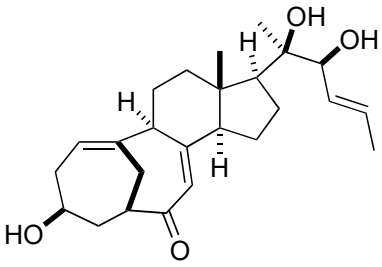
An unusual C25 steroid**:**
• Bicyclo[4.4.1] A/B ring system
• Bridgehead (anti-Bredt) double bond
• 8 stereocenters including 2 quarternary carbons



cyclocitrinol (**0-1**)



proposed structure (**0-2**)



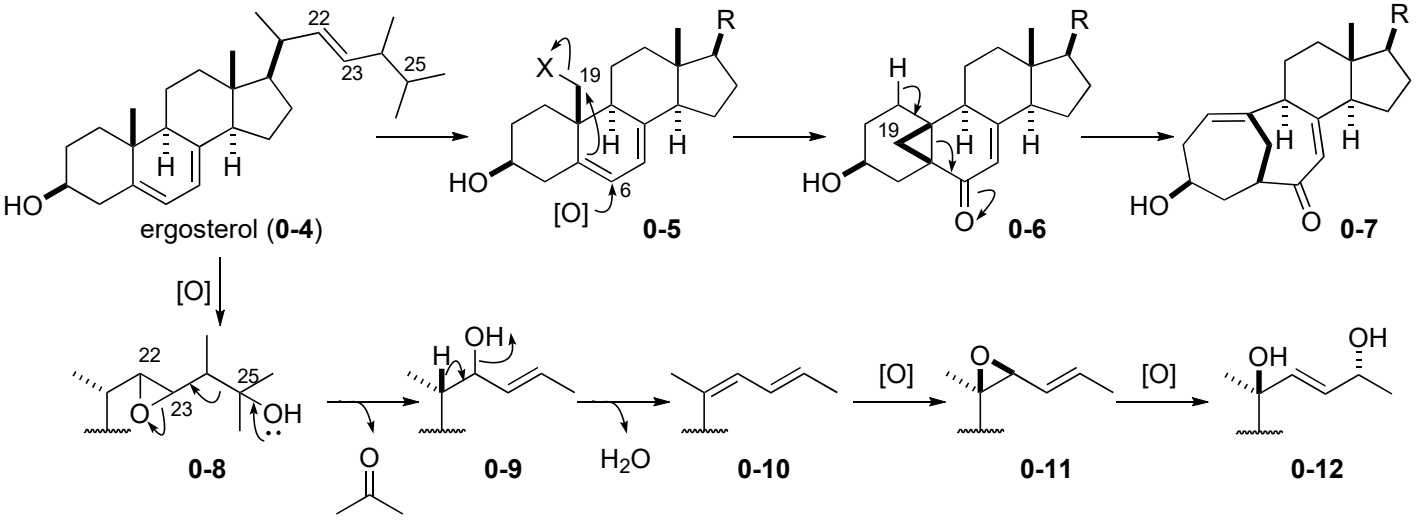
isocyclocitrinol (**0-3**)

0-3. Biological activity

Cyclocitrinol: induce the production of c-AMP in GPR12-transfected CHO cells
Du, L.; Zhu, T.; Fang, Y.; Gu, Q.; Zhu, W.-J. *Nat, Prod.* **2008**, *71*, 1343.

0-4. Proposed biosynthesis pathway

Marinho, A. M. d. R.; Rodrigues-Filho, E.; Ferreira, A. G.; Santos, L. S. *J. Braz. Chem. Soc.* **2005**, *16*, 1342.



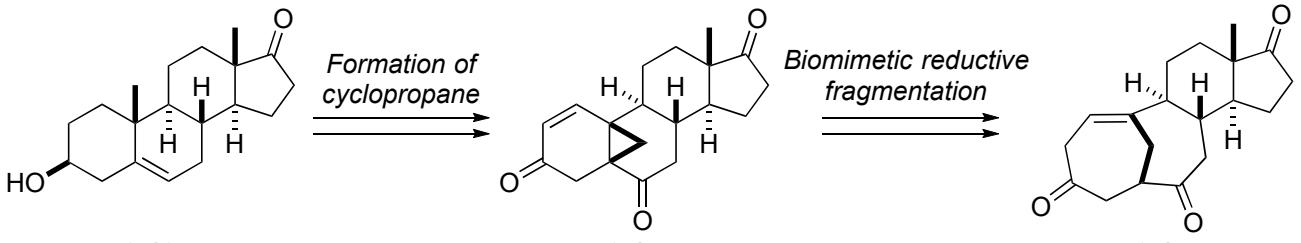
ergosterol (**0-4**) **0-5** **0-6** **0-7**

0-8 **0-9** **0-10** **0-11** **0-12**

0-4. Synthetic study and Total synthesis

> Three different approaches to construct the unique bicyclo[4.4.1]undecane A/B ring system are reported.

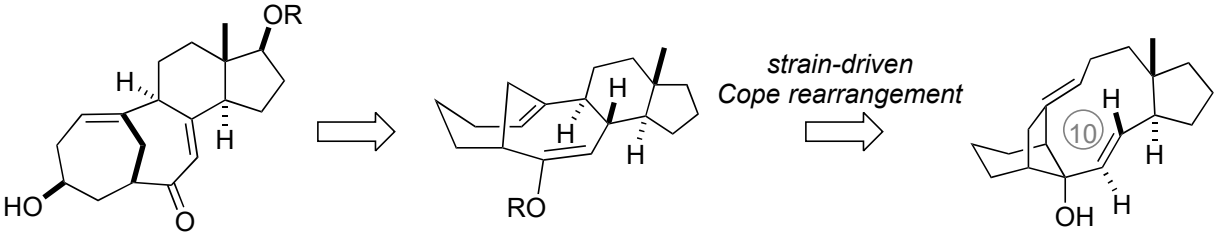
0-4-1. Synthetic study by Schmalz's group (Problem 1)



0-13 **0-14** **0-15**

El Sherikh,S.; Meier zu Greffen, A.; Lex, J.; Meudörfl, J.-M.; Schmalz, H.-G. *Synlett* **2007**, *2007*, 1881.

0-4-2. Synthetic study by Leighton's group

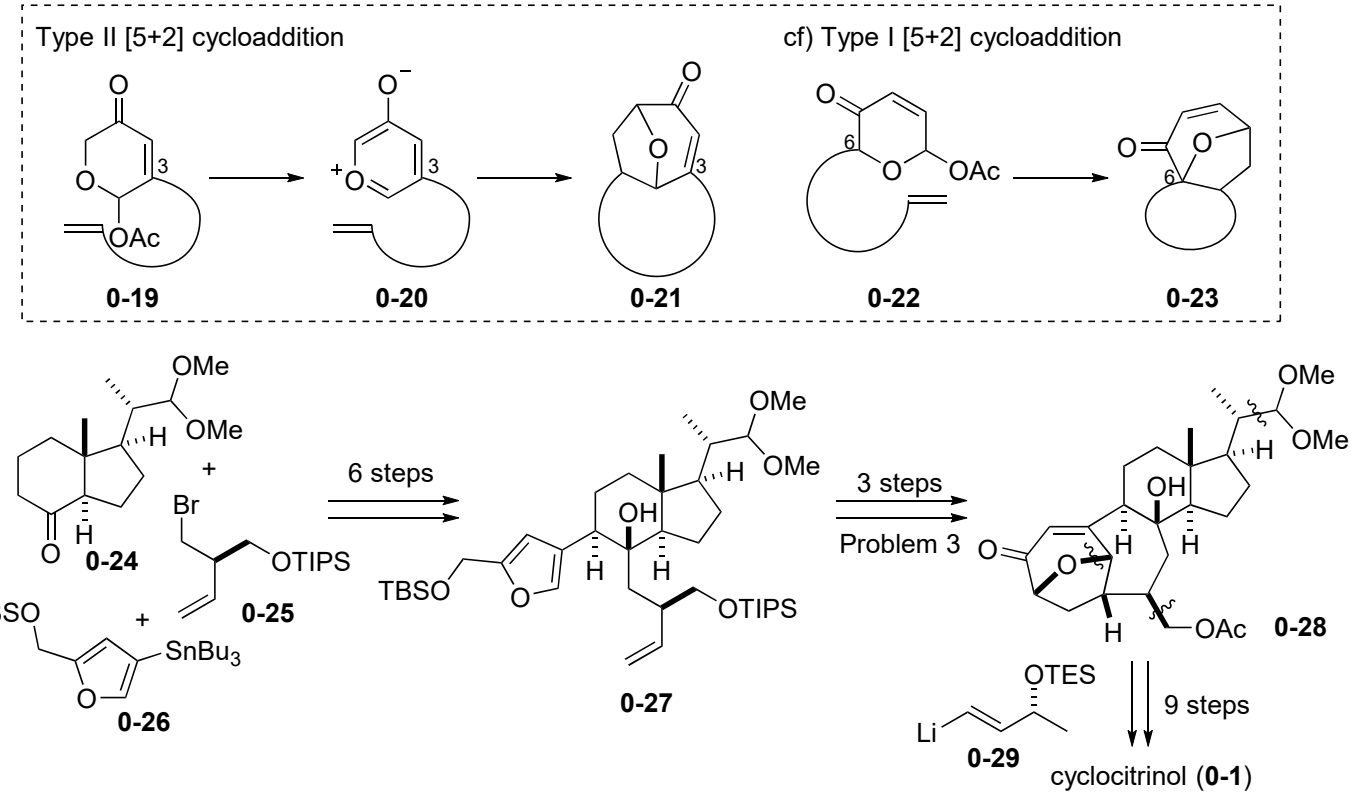


0-16 **0-17** **0-18**

Key: How to access strained 10-membered ring? (→ Problem 2)

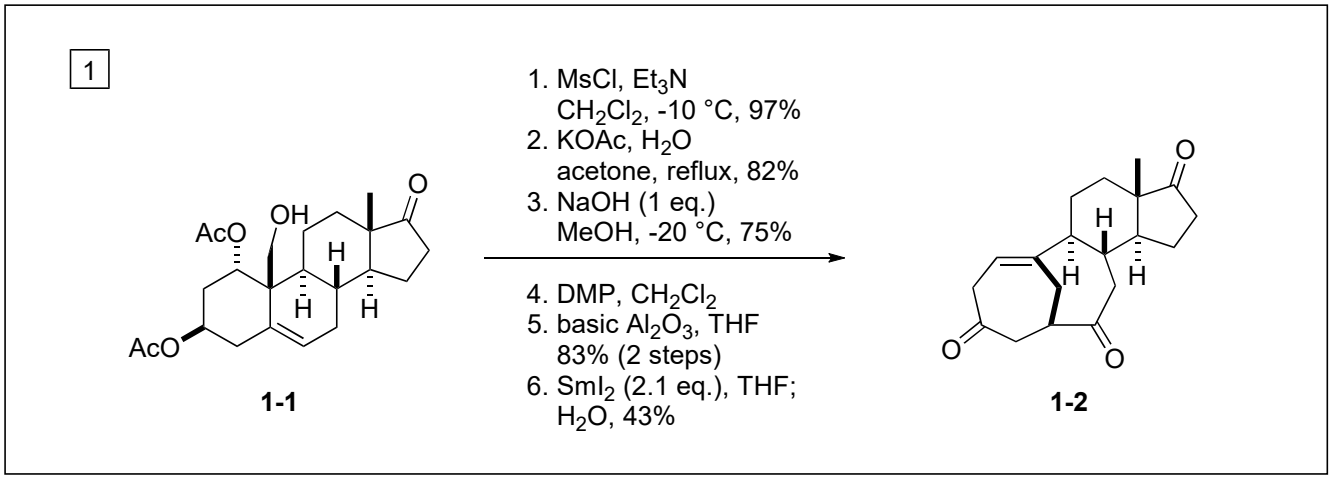
Plummer, C. W.; Wei, C. S.; Yozwiak, C. E.; Soheili, A.; Smithback, S. O.; Leighton, J. L. *J. Am. Chem. Soc.* **2014**, *136*, 9878.

0-4-3. Asymmetric total synthesis by Li's group



Li, C.-C. et. al. *J. Am. Chem. Soc.* DOI: 10.1021/jacs.8b02629

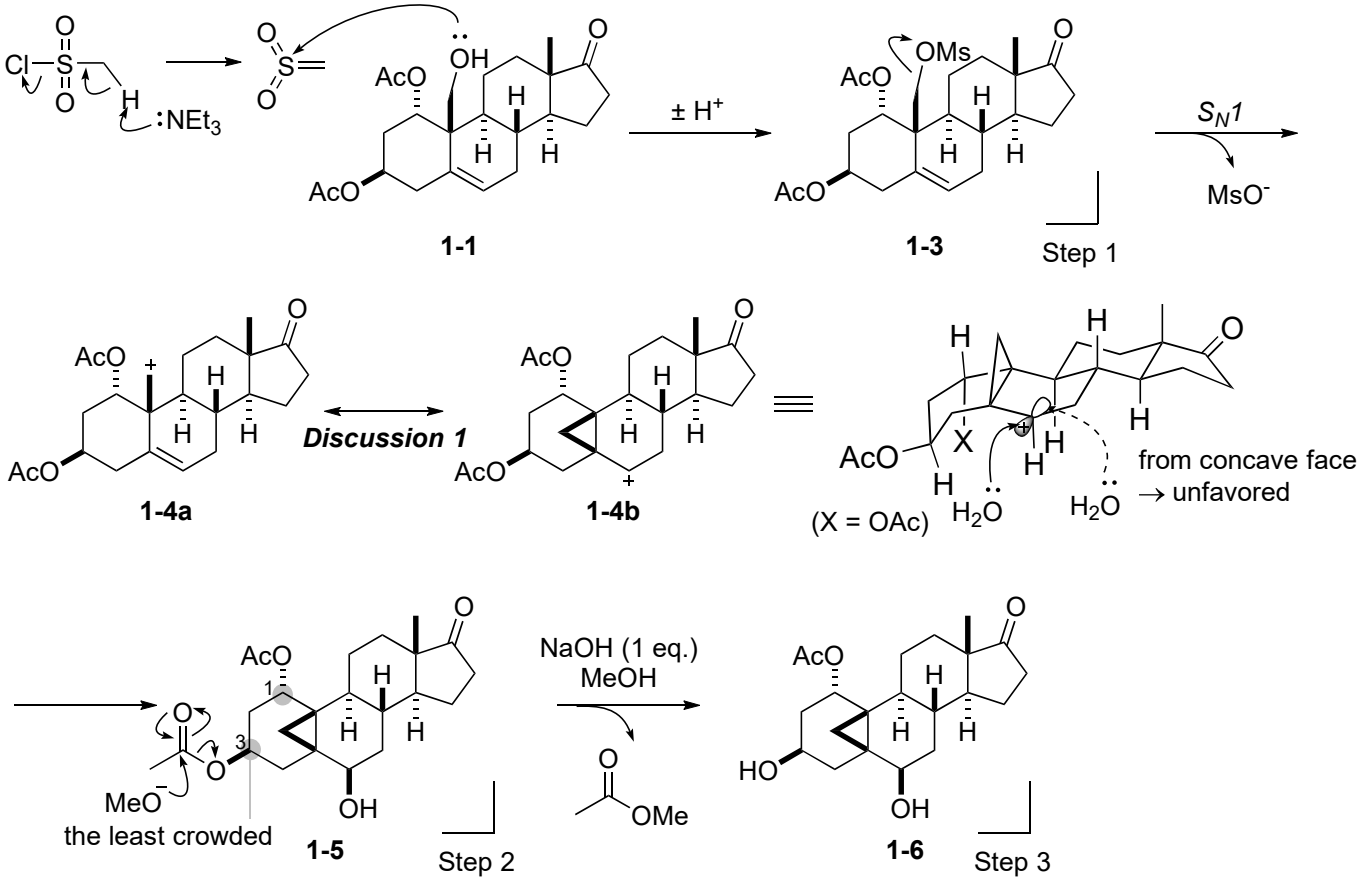
-Answer-



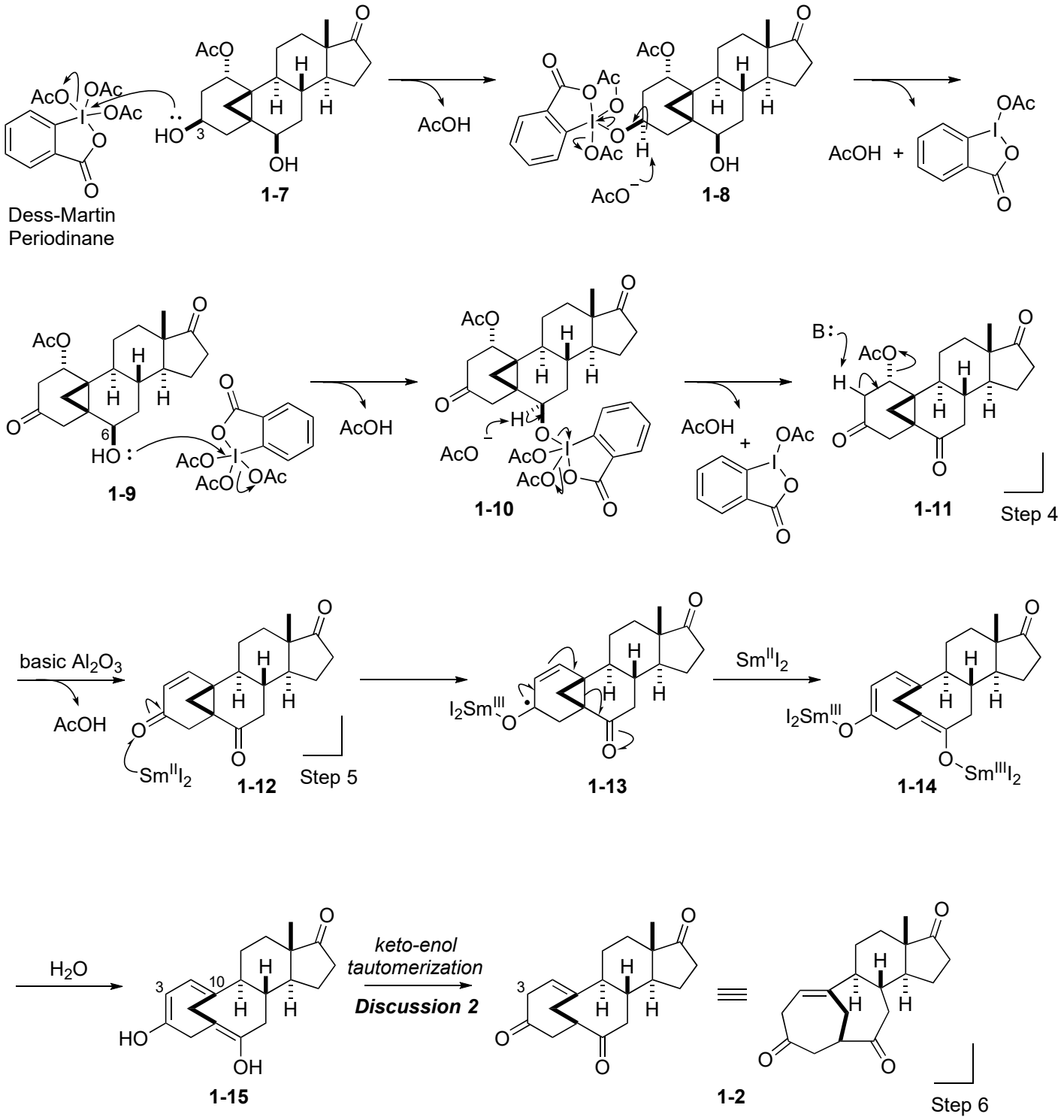
El Sherikh,S.; Meier zu Greffen, A.; Lex, J.; Meudörfl, J.-M.; Schmalz, H.-G. *Synlett* **2007**, *2007*, 1881.

- **The first construction of the core structure of cyclocitrinols.**
- **Key reaction: SmI_2-mediated fragmentation of cyclopropane.**

Step 1-3. Formation of cyclopropane via homoallylic rearrangement.

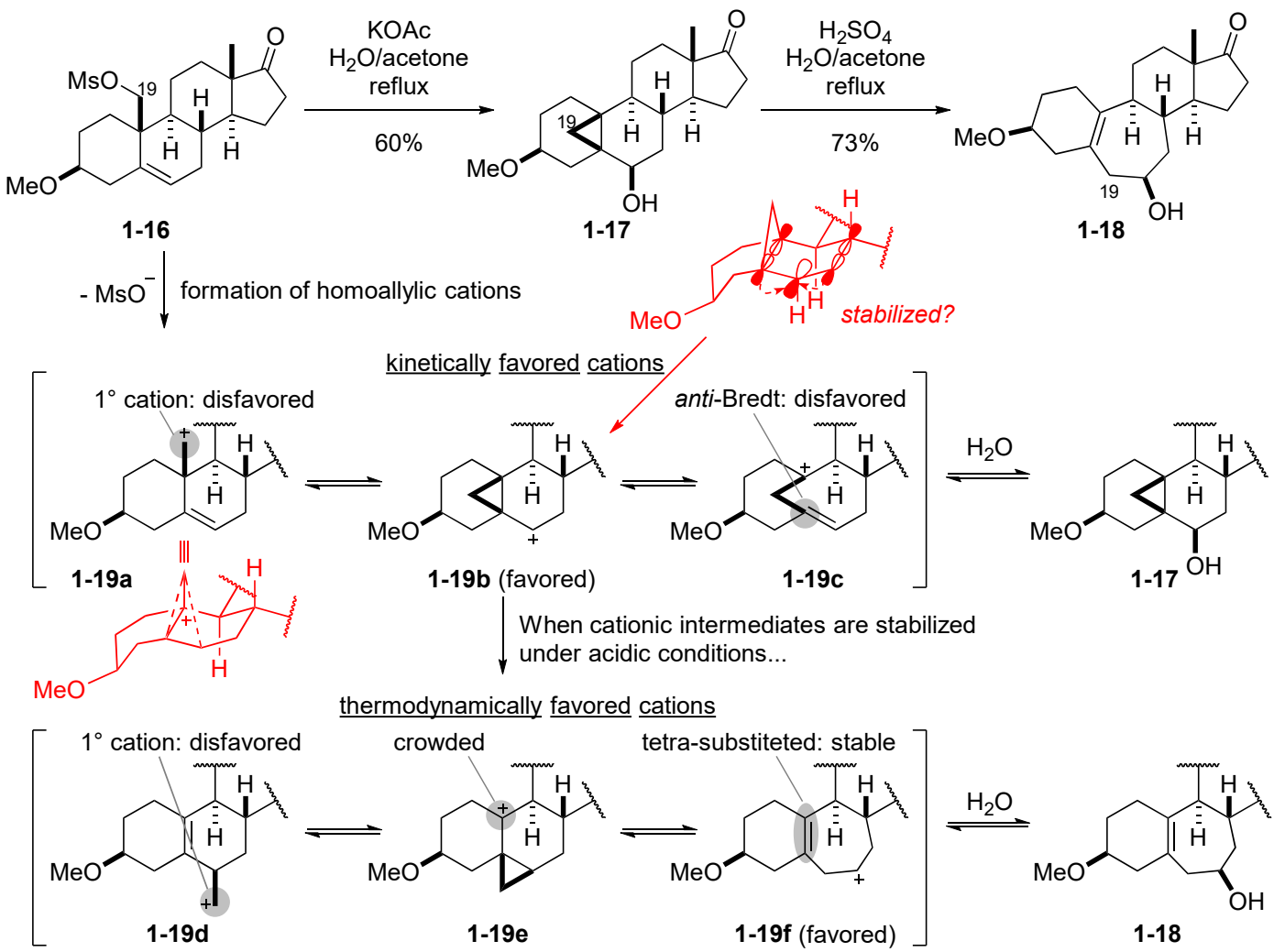


Step 4-6. SmI_2-mediated fragmentation of cyclopropane.



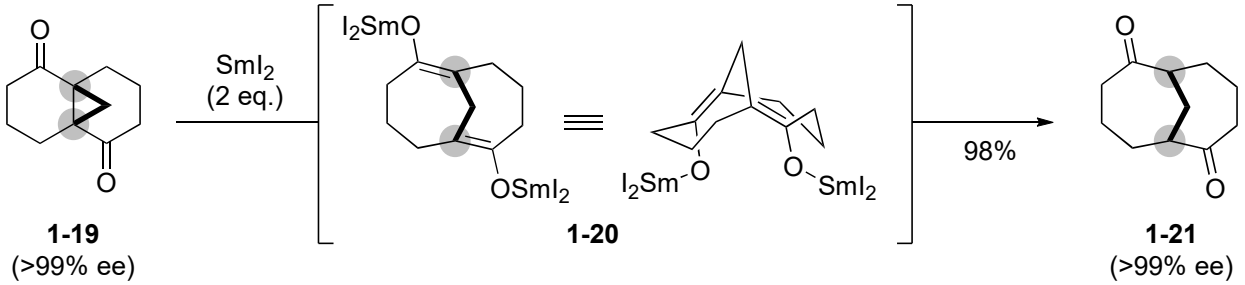
> Protonation occurs at C3 which is closer to oxygen atom and has higher electron density than C10.

Discussion 1: Homoallylic rearrangement of 19-substituted steroids.



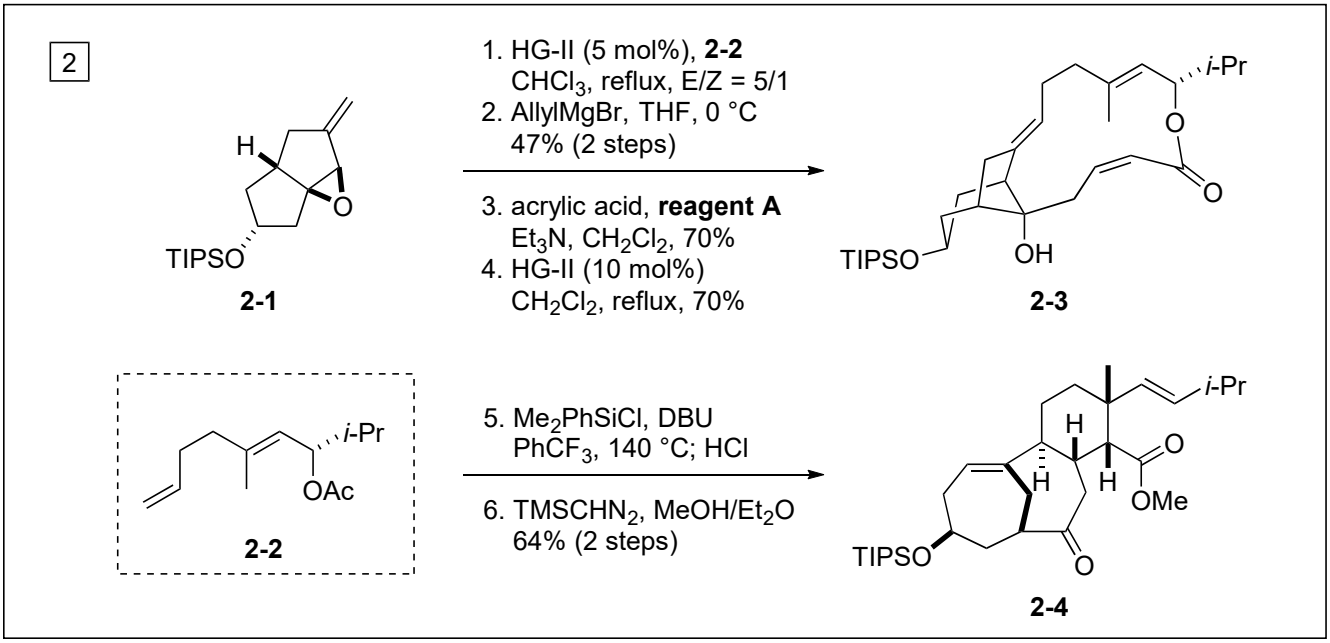
Details for the rearrangement, see: Tadanier, J. *J. Org. Chem.* **1966**, *31*, 2124.

***Discussion 2:* Retention of stereocenters during the fragmentation.**



> Chirality centers should be disappeared during the fragmentation.
> Due to the existence of bridgehead double bonds, **1-20** has inherent non-planar nature and can memorize the absolute stereochemical information.

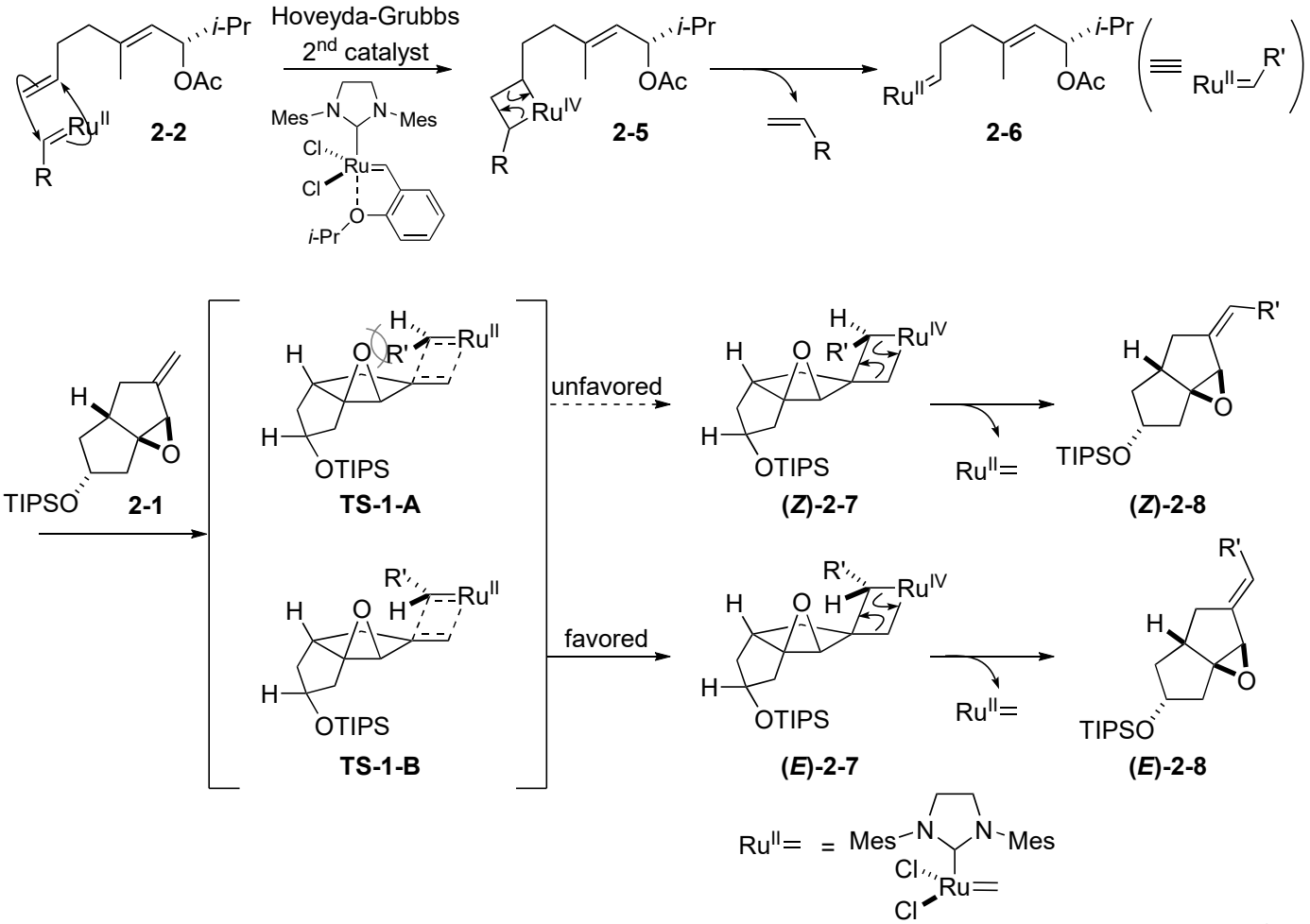
El Sheikh, S.; Kausch, N.; Lex, J.; Neudörfl, J.-M.; Schmalz, H.-G. *SYNLETT* **2006**, *10*, 1527.



Plummer, C. W.; Wei, C. S.; Yozwiak, C. E.; Soheili, A.; Smithback, S. O.; Leighton, J. L. *J. Am. Chem. Soc.* **2014**, *136*, 9878.

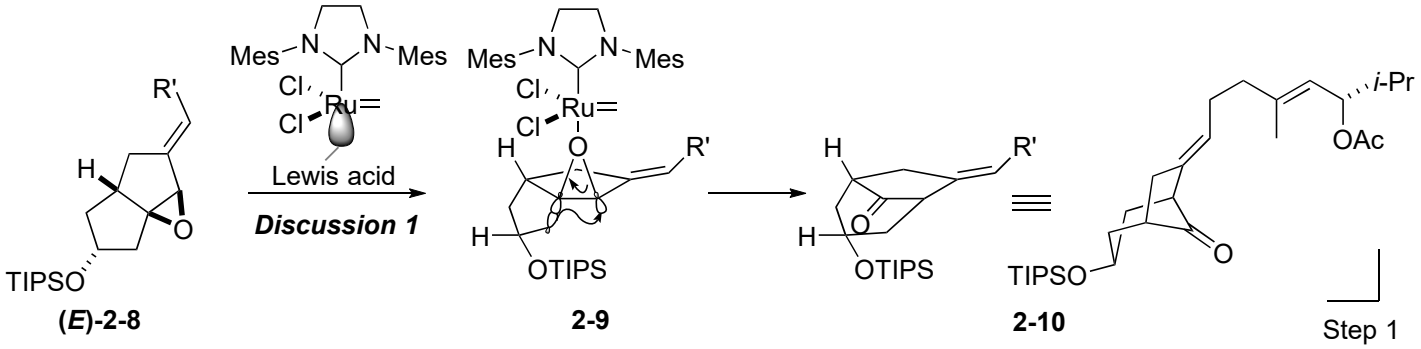
• **Key reactions: Two tandem reactions;**
cross-metathesis/semipinacol rearrangement and Ireland claisen/cope rearrangement.

Step 1. Tandem cross-metathesis/semipinacol rearrangement.



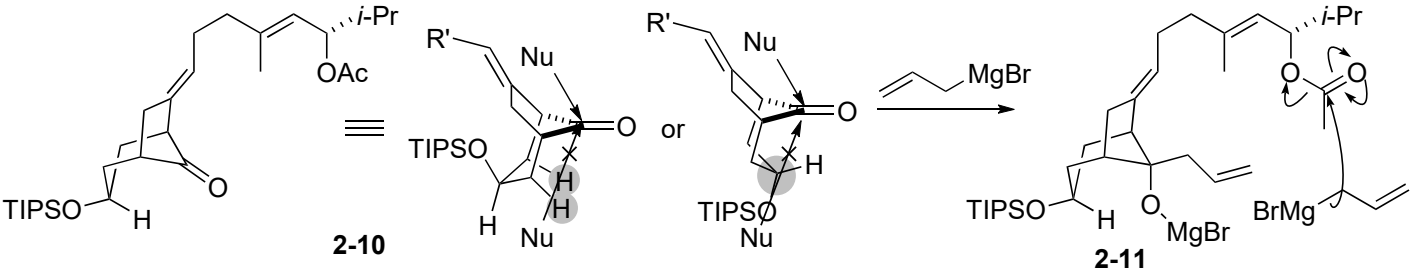
Step 1. Tandem cross-metathesis/semipinacol rearrangement. (continued)

* After cross-metathesis, Ru-methylidene exist near epoxide and immediately react with it.

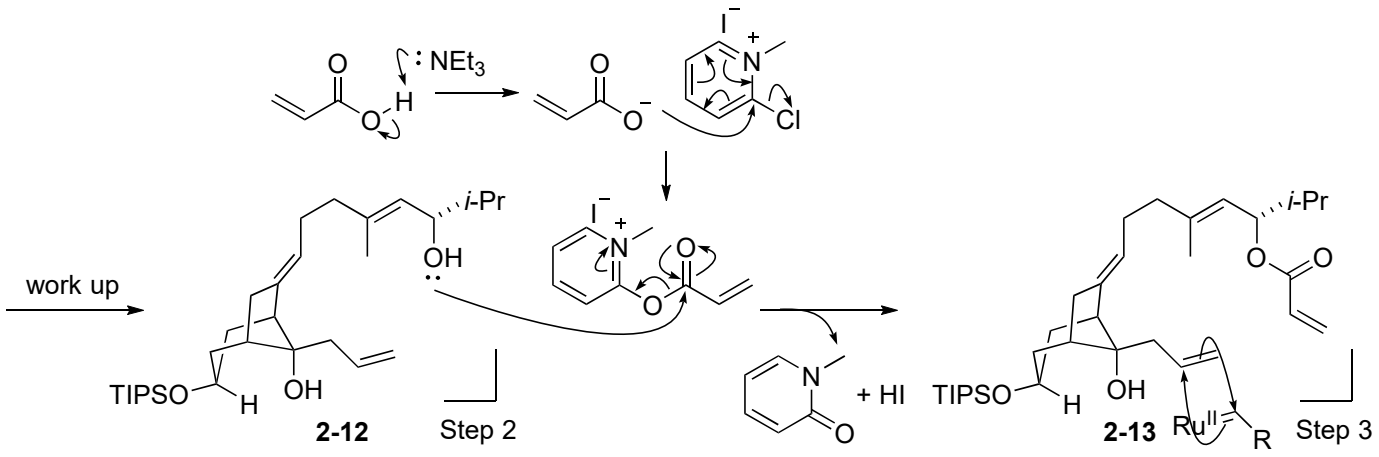


(*E*)-2-8 **2-9** **2-10** Step 1

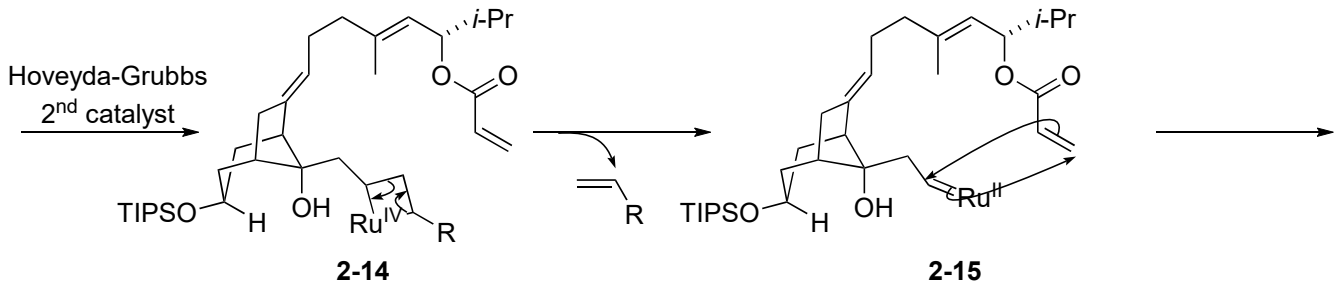
Step 2-4. Tandem cross-metathesis/semipinacol rearrangement. (continued)



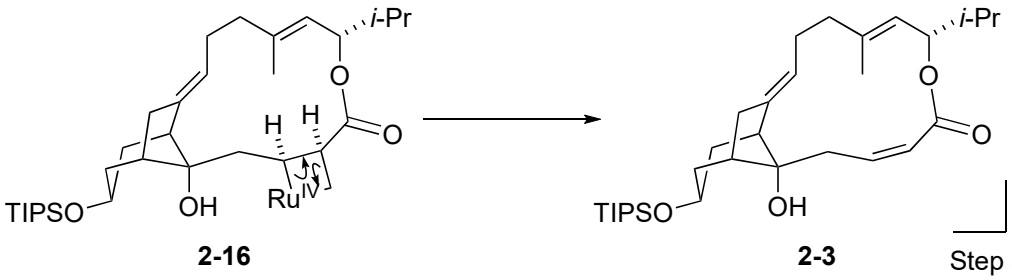
2-10 **2-11**



2-12 Step 2 **2-13** Step 3

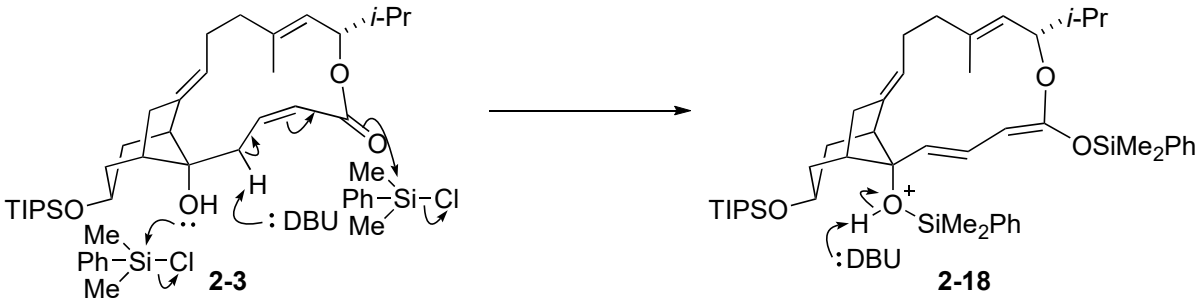


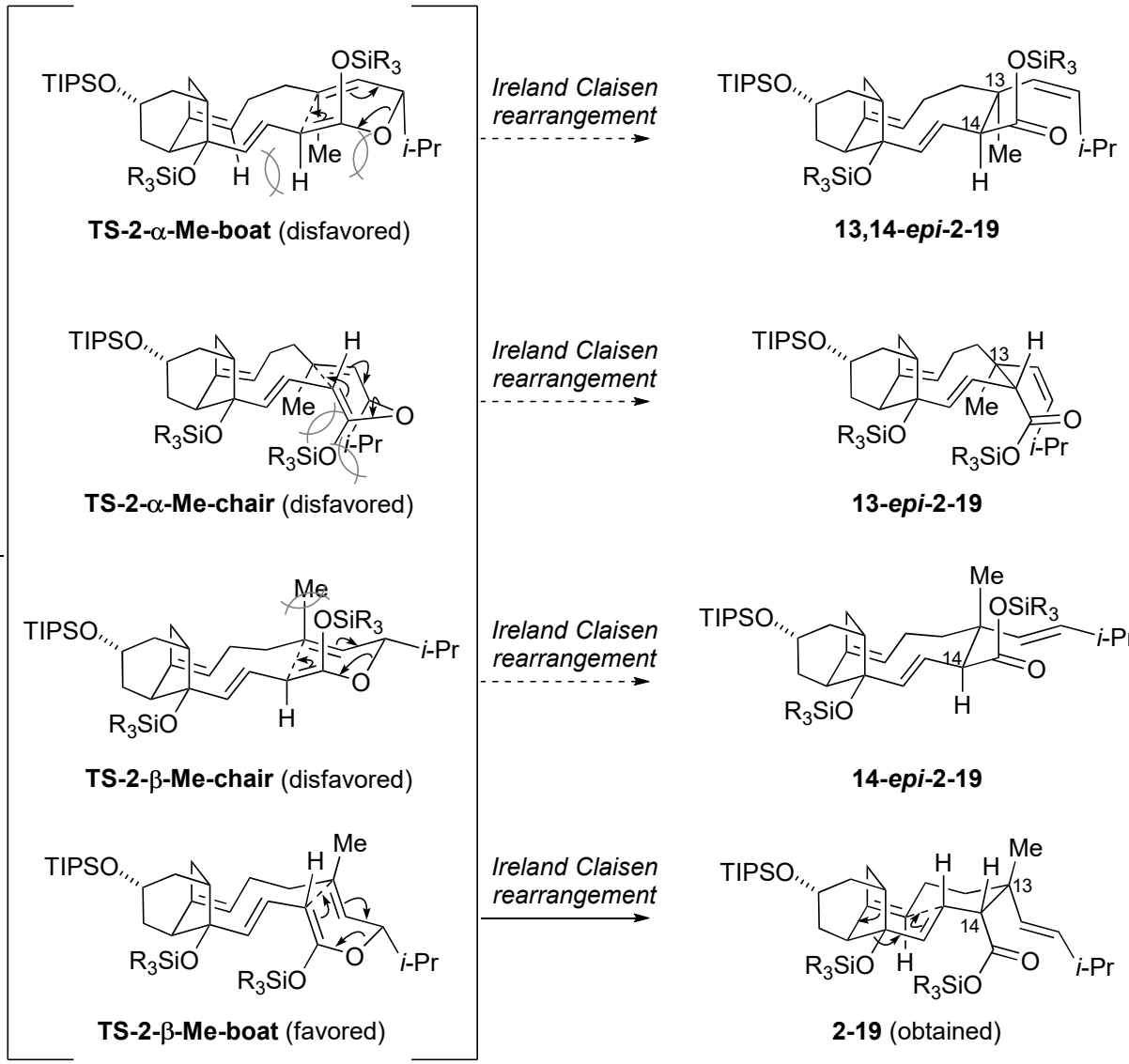
2-14 **2-15**

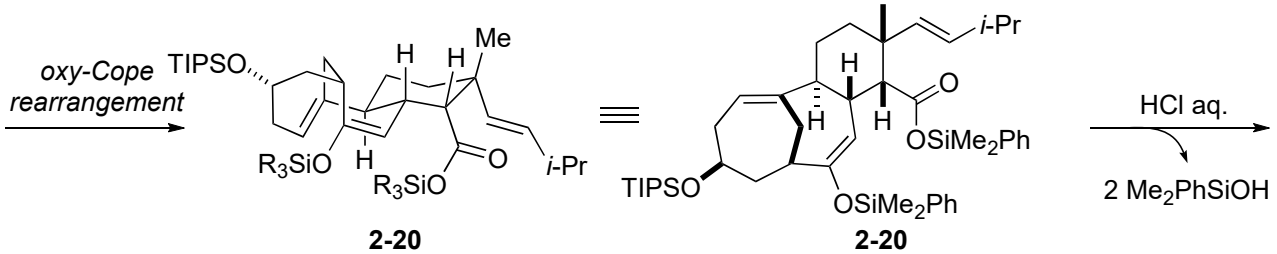


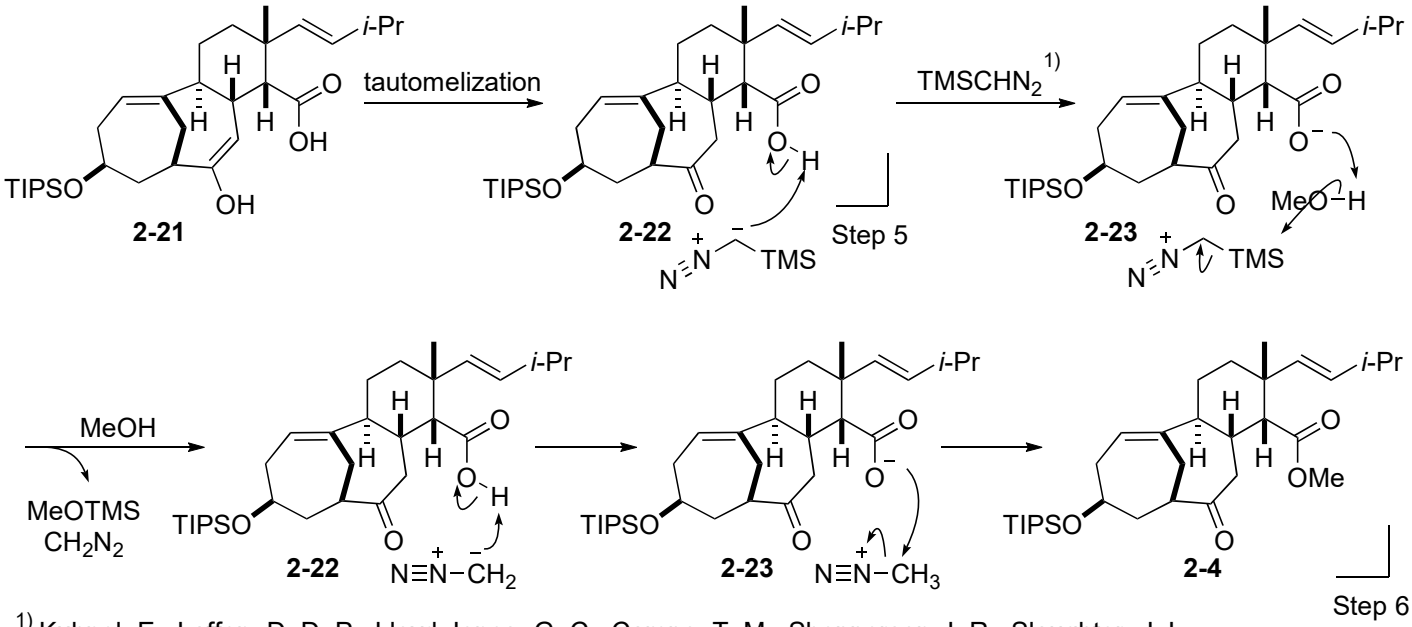
2-16 **2-3** Step 4

Step 5-6. Tandem Ireland Claisen/Cope rearrangement.





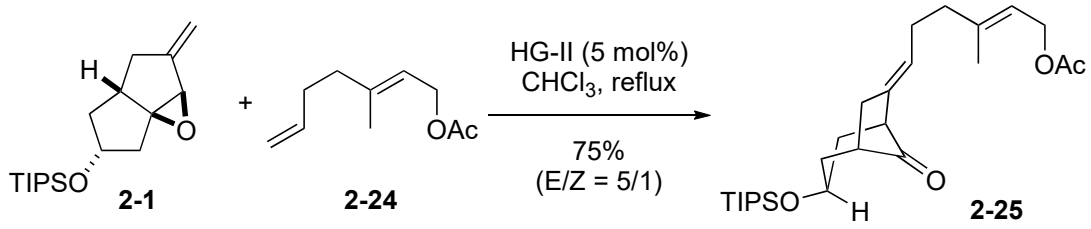




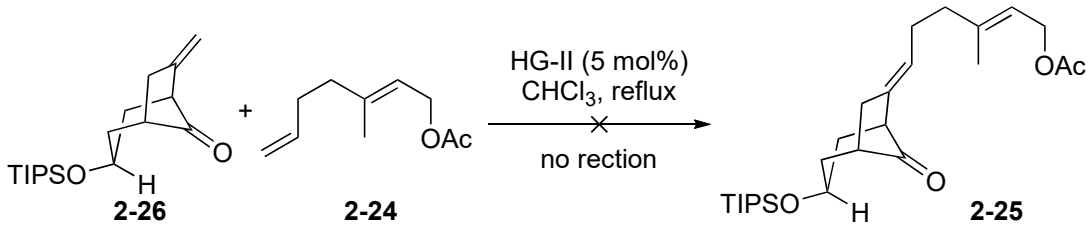
[1] Kuhnel, E.; Laffen, D. D. P.; Lloyd-Jones, G. C.; Campo, T. M.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 7075.

Discussion 1. The order of cross-metathesis and semipinacol rearrangement.

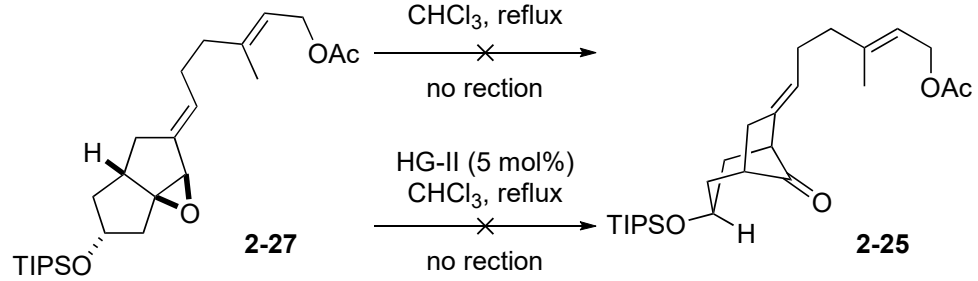
• The model experiment of a tandem cross-metathesis (CM)/semipinacol rerrangement reaction



• Control experiments for the tandem reaction.



> CM didn't proceed between rearrangement product **2-26** and **2-24**, which means CM occured first.

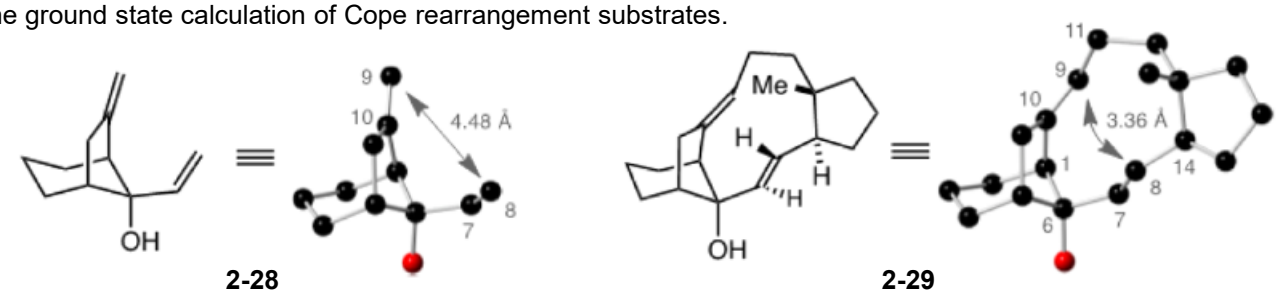


> Heating **2-27** in reflux $CHCl_3$ resulted in no reaction, which means trace HCl in $CHCl_3$ wasn't the catalyst.
> Treatment of isolated **2-27** with HG-II resulted in no reaction, which means HG-II itself wasn't the catalyst.

Plummer, C. W.; Soheili, A.; Leighton, J. L. *Org. Lett.* **2012**, *14*, 2462.

Discussion: Driving force of Cope rearrangement.

• The ground state calculation of Cope rearrangement substrates.



2-28 **2-29**

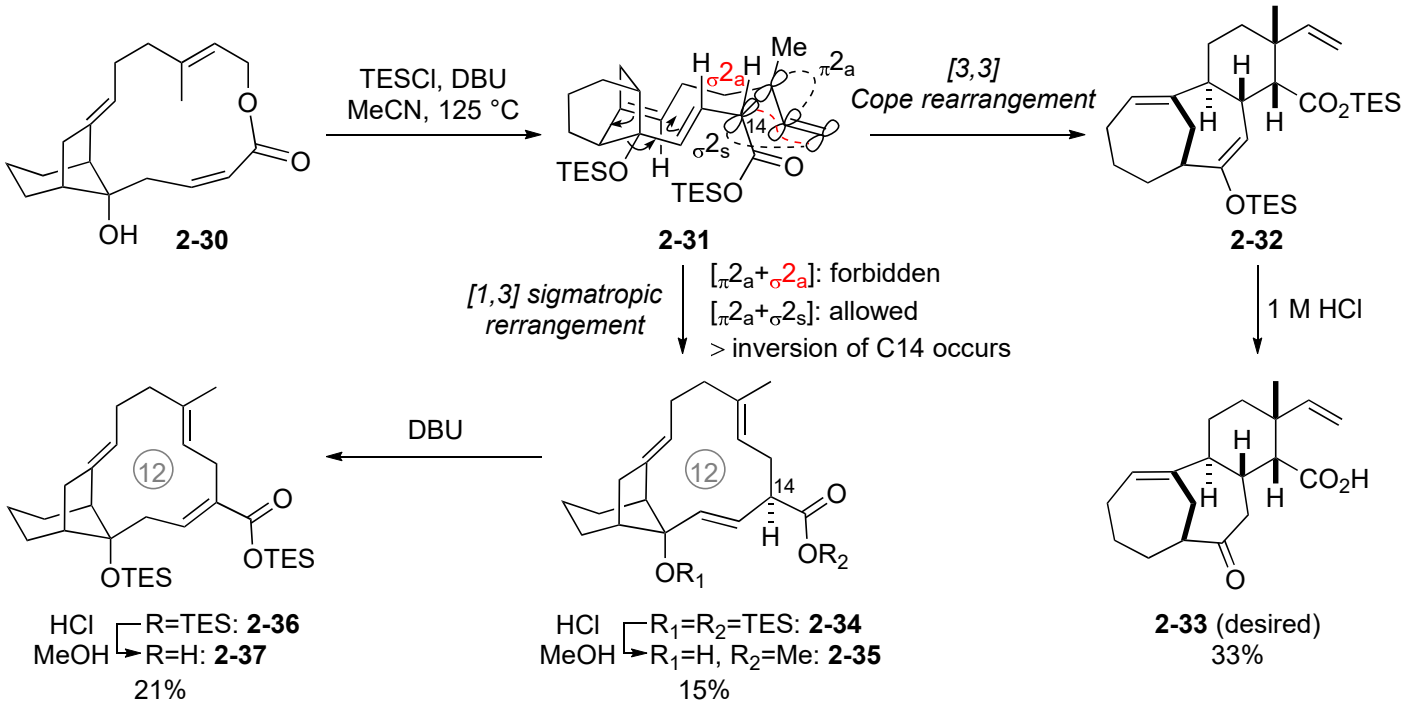
(MacroModel using the OPLS 2005 force field in vacuum)

> Calculation result of **2-28** indicate the terimini of the alkenes are so far (~4.5 Å) that a Cope rearrangement of **2-28** may be disfavored.

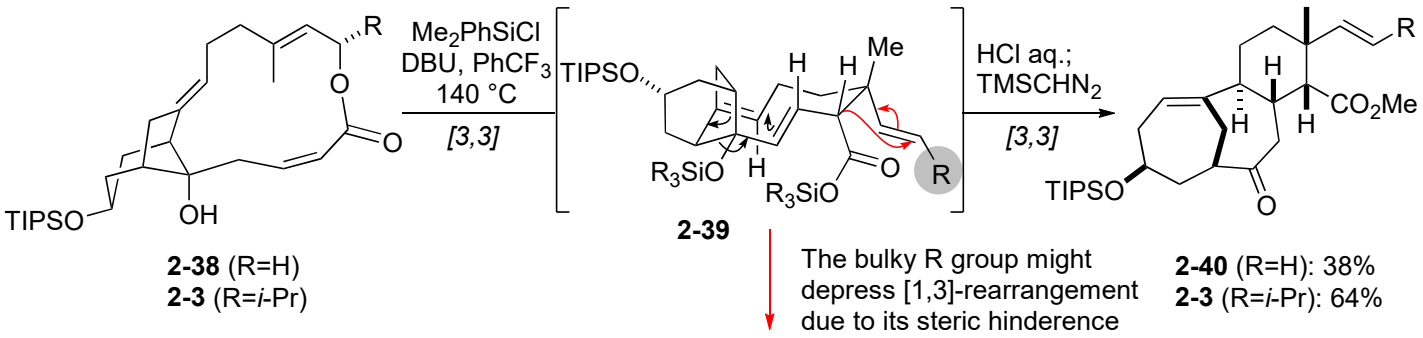
> Tethering the two vinyl groups into a 10-membered ring such as **2-29**, which introduces a strain in the substrate and decreases the distance of the termini of the alkenes (~3.4 Å).

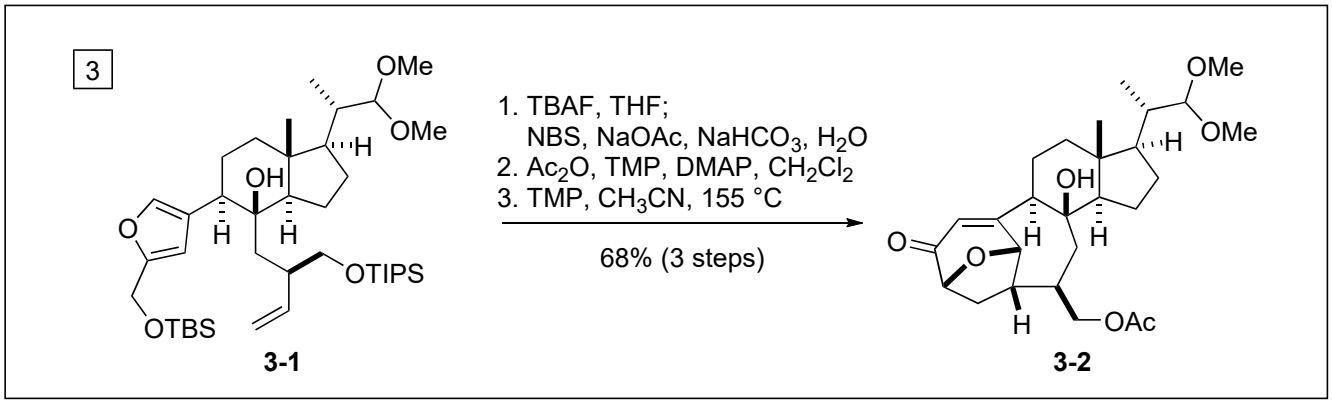
→ In order to release the strain of 10-membered ring, a Cope rearrangement might be accelerated.

• Another possible strain-relieving pathway of 10-membered ring



About [1,3] sigmatropic rearrangement, see: Berson, J. A. *Acc. Chem. Res.* **1968**, *1*, 152.

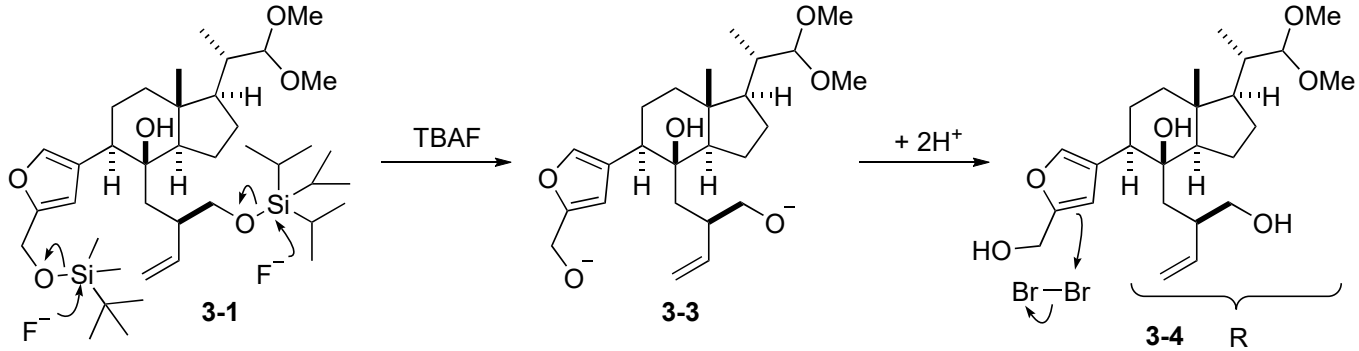


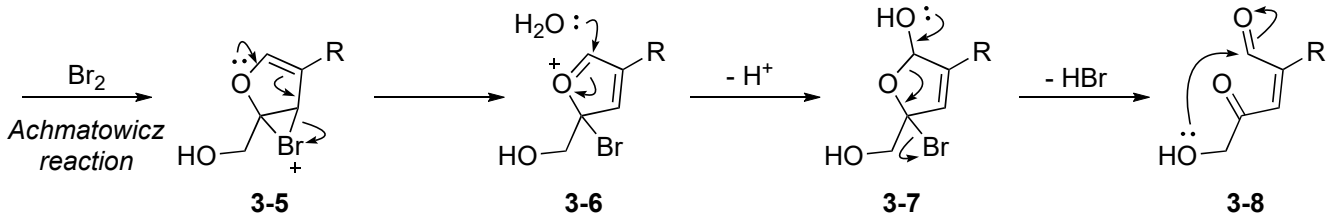


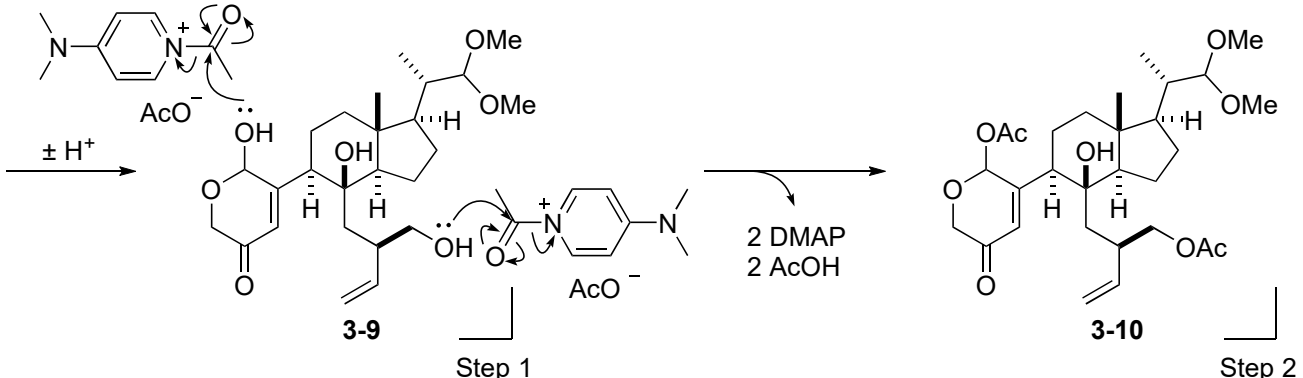
Liu, J.; Wu, J.; Fan, J.-H.; Yan, X.; Mei, G.; Li, C.-C. *J. Am. Chem. Soc.* DOI: 10.1021/jacs.8b02629

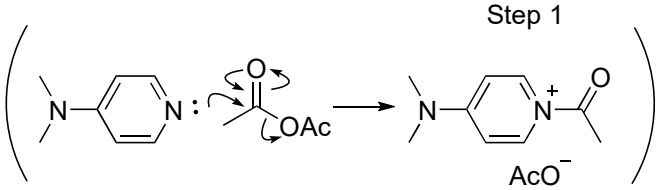
- **The first total synthesis of cyclocitrinol**
- **Key reaction: intramolecullar [5+2] cycloaddition.**

Step 1-2. Achmatowicz reaction.



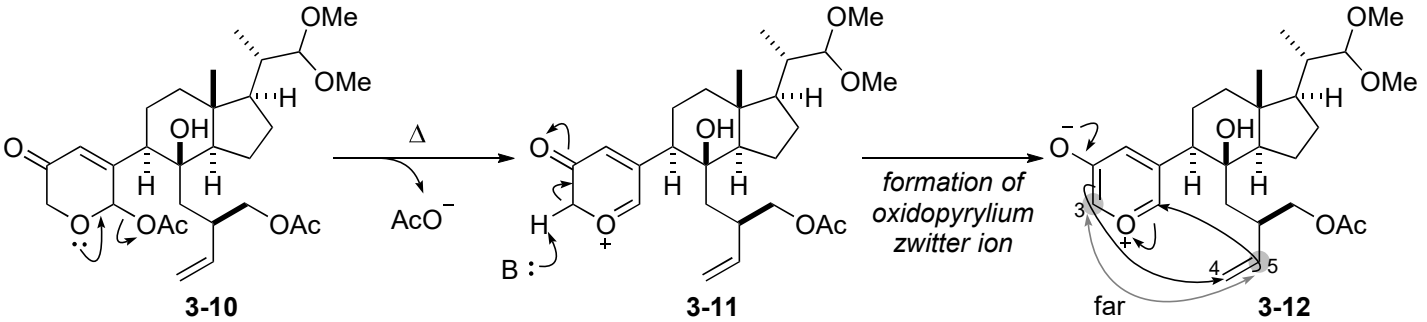




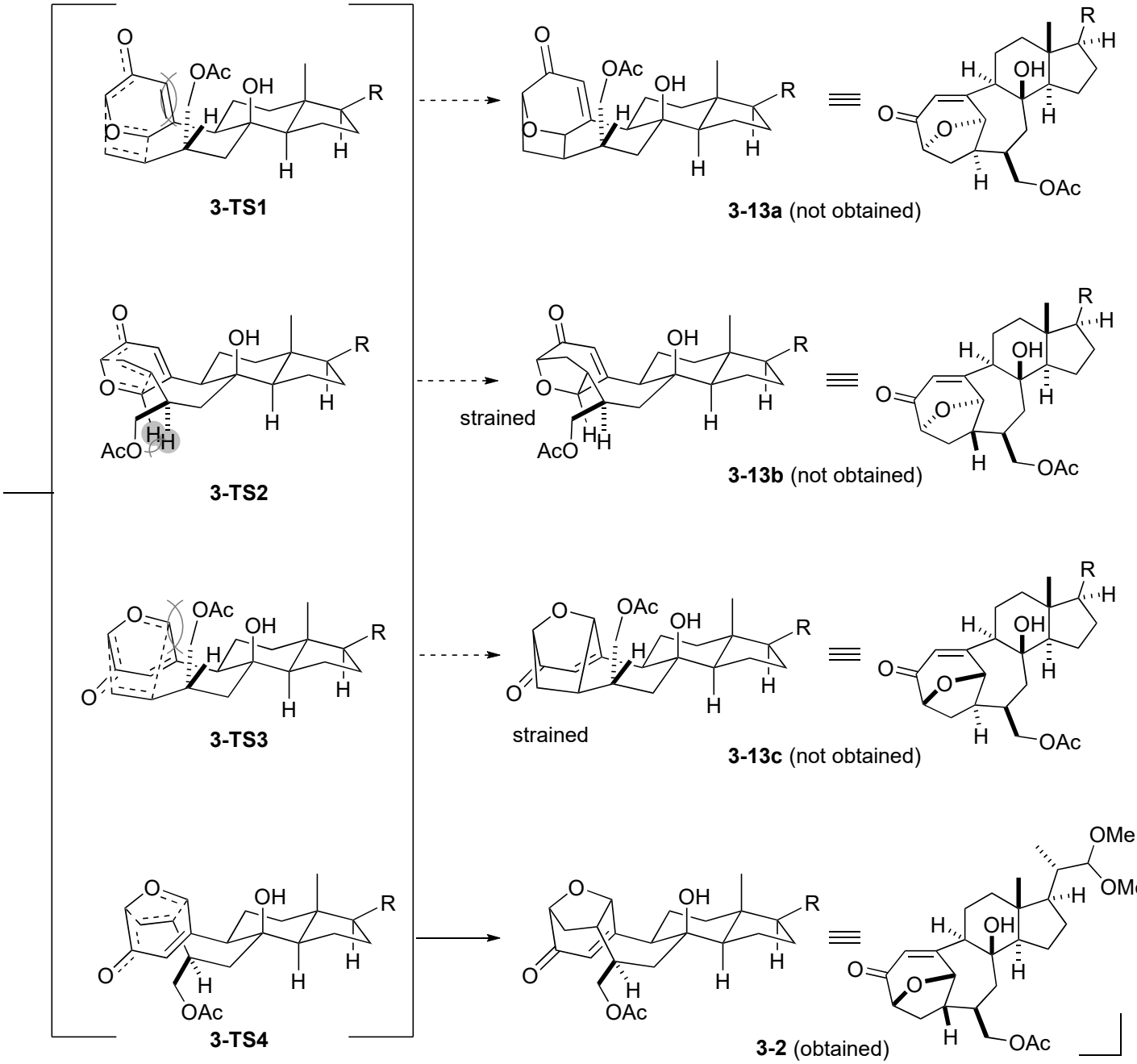


About Achmatowicz reaction, see:
120421_PS_Kengo_MASUDA

Step 3. intramolecullar [5+2] cycloaddition.



3-10 **3-11** **3-12**



3-TS1 **3-13a** (not obtained)

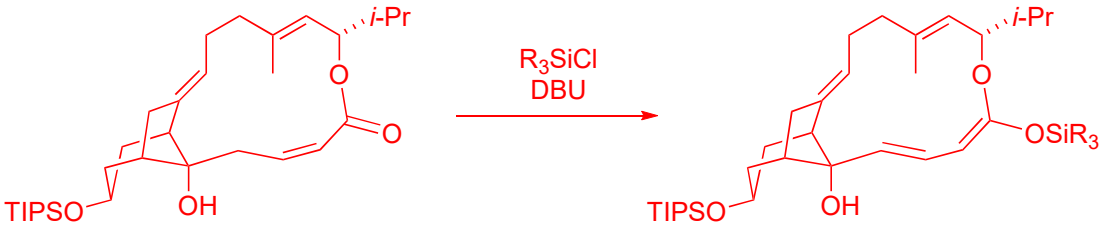
3-TS2 **3-13b** (not obtained)

3-TS3 **3-13c** (not obtained)

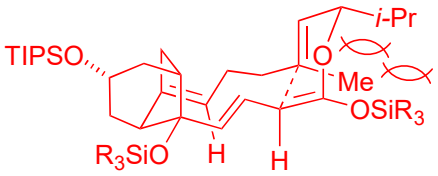
3-TS4 **3-2** (obtained)

Step 3

Problem 2. Step 5. Claisen rearrangement from (*E*)-enolate

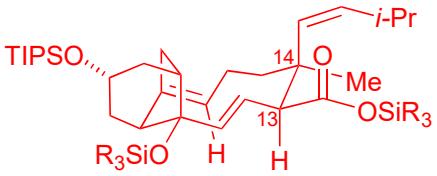


2-3 **2-18'**

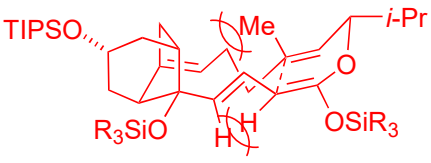


TS-2'-α-Me-chair (disfavored)

Ireland Claisen rearrangement

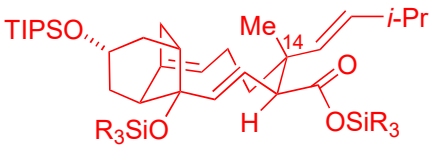


13,14-*epi*-2-19

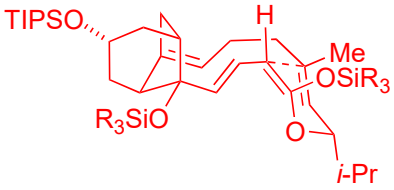


TS-2'-β-Me-boat (disfavored)

Ireland Claisen rearrangement

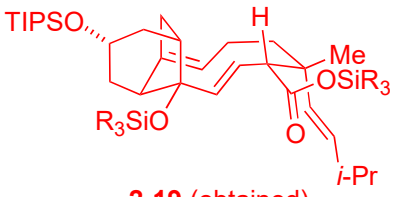


14-*epi*-2-19

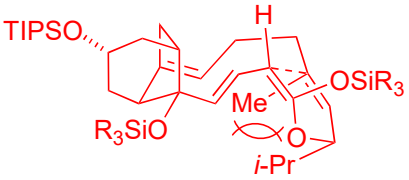


TS-2-β-Me-chair (favored)
seems to be relatively favored

Ireland Claisen rearrangement

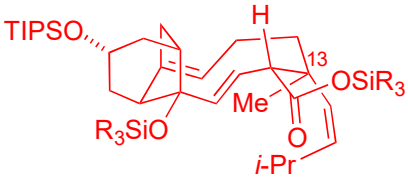


2-19 (obtained)



TS-2'-α-Me-boat (disfavored)

Ireland Claisen rearrangement



13-*epi*-2-19