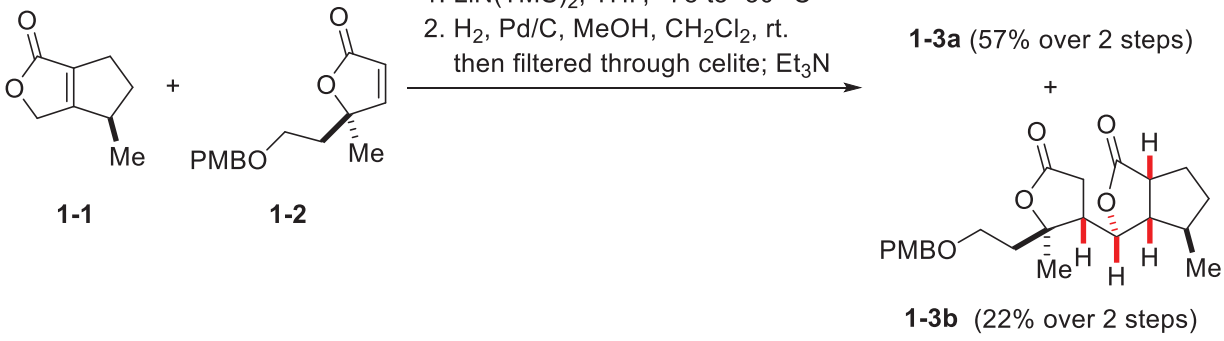
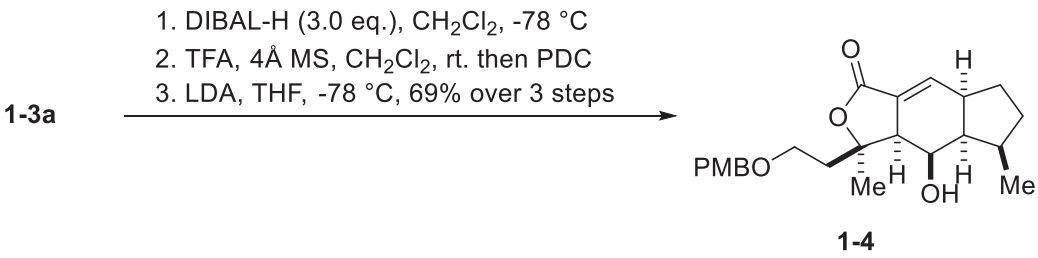
Problem Session (1)

2018/9/8 Takuya Fujiwara

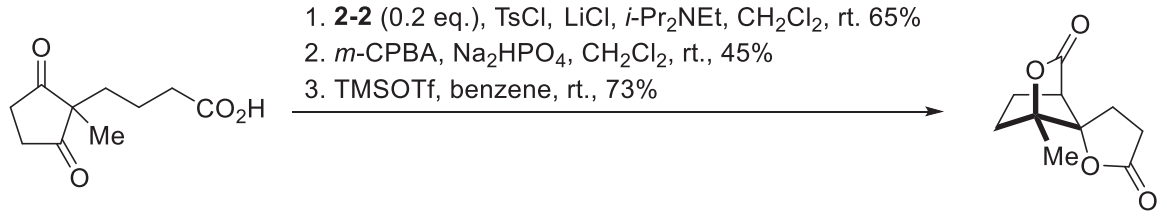
Please provide the reaction mechanisms.

1





2



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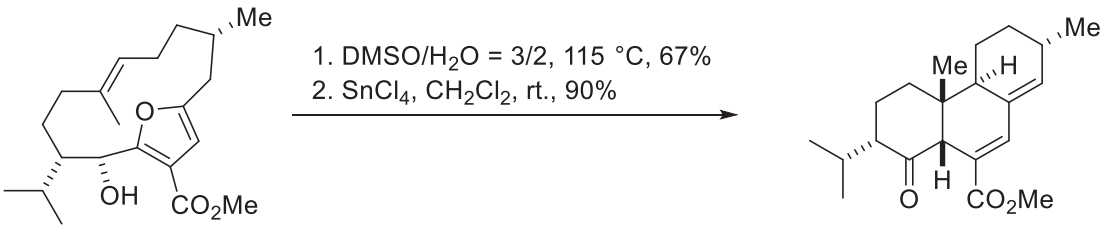
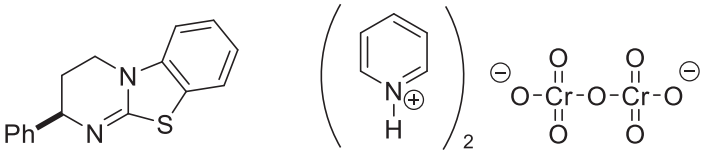
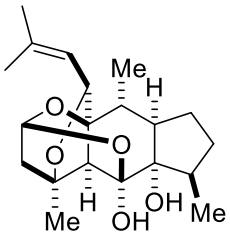




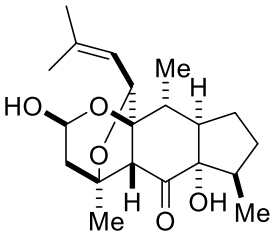
Problem Session (1) -Answer

2018/9/8 Takuya Fujiwara

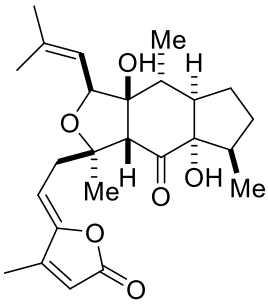
1 Total synthesis of diterpenoids from *Leucosceptrum canum*



(+)-norleucosceptroid A



(-)-norleucosceptroid B



(-)-leucosceptroid K

norleucosceptroids A-H, leucosceptroids A-Q are known.

Isolation:

from the leaves and flowers of *Leucosceptrum canum* (Labiatae)

Shi-Hong, L.; Juan, H.; Chun-Huan, Li.; Shu-Xi, J.; Yan, L.; Xiao-Nian, L.; Xu, Z.; Sheng-Hong, L. *Org. Lett.* **2012**, *14*, 5768.

Structural feature:

•5,6,5-framework with a fully functionalized tetrahydrofuran ring

•more than 8 stereocenters

Bioactivity:

potent antifeedant activity

Total synthesis:

•norleucosceptroids B, C, F, and G, leucosceptroid A to C, G, I to M, O, and P
Hugelshofer, C. L.; Magauer, T. *J. Am. Chem. Soc.* **2015**, *137*, 3807.

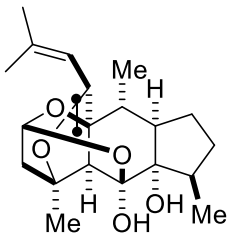
•norleucosceptroids F and G Jiao, X.; Bo, L. *Chin. Chem. Lett.* **2015**, *25*, 1341.

•leucosceptroids A and B Guo, S.; Liu, J.; Ma, D. *Angew. Chem.* **2015**, *54*, 1298**.**

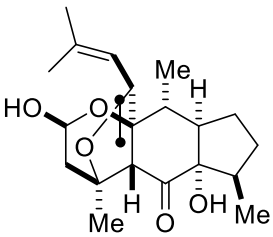
•norleucosceptroids A and B, leucosceptroid K (**Problem 1**)
Hugelshofer, C.; Magauer, T. *Angew. Chem.* **2014**, *53*, 11351.

•leucosceptroid B Huang, X.; Song, L.; Xu, J.; Zhu, G.; Liu, B. *Angew. Chem.* **2013**, *52*, 952.

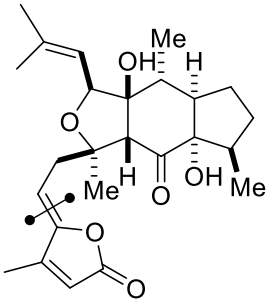
Retrosynthetic analysis:



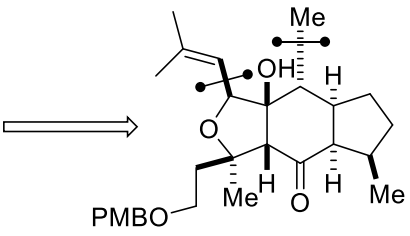
(+)-norleucosceptroid A



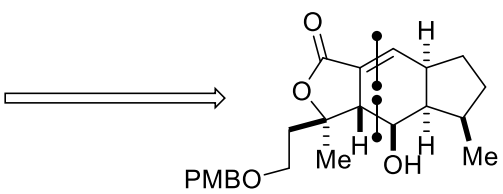
(-)-norleucosceptroid B



(-)-leucosceptroid K

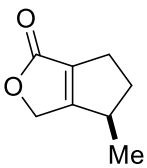


0-1



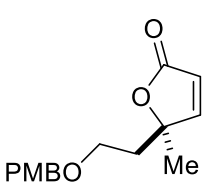
1-4

Michael addition
Dieckmann reaction



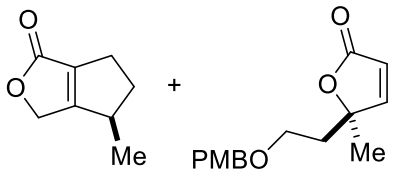
1-1

+



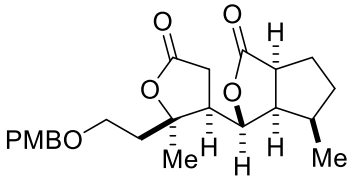
1-2

Problem 1



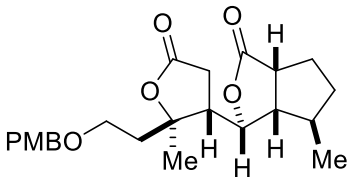
1-1 + **1-2**

1. $LiN(TMS)_2$, THF, -78 to -30 °C
2. H_2, Pd/C, MeOH, CH_2Cl_2, rt.
   then filtered through celite; Et_3N



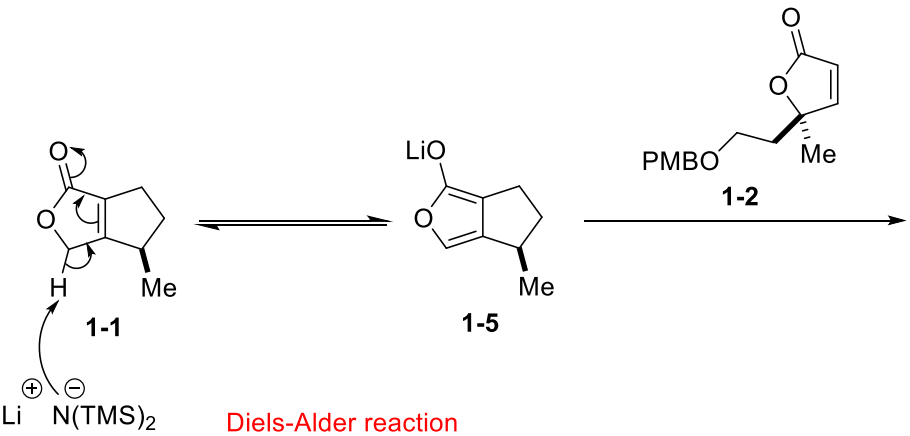
1-3a (57% over 2 steps)

+



1-3b (22% over 2 steps)

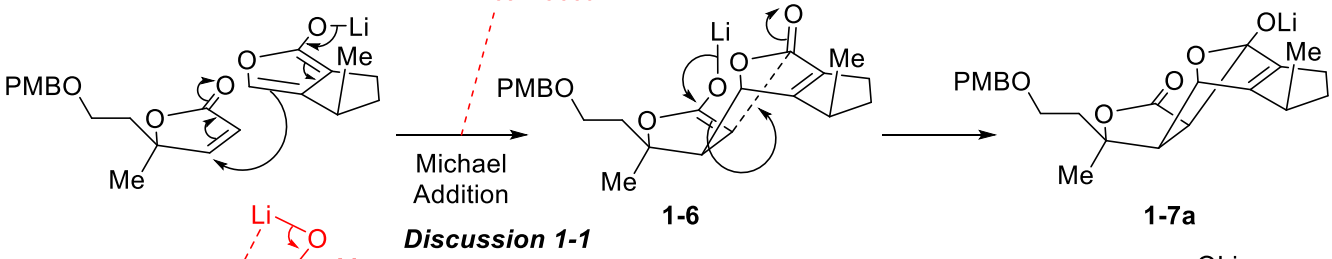
Answer



1-1 ⇌ **1-5** → **1-2**

Li N(TMS)$_2$

Diels-Alder reaction can occur

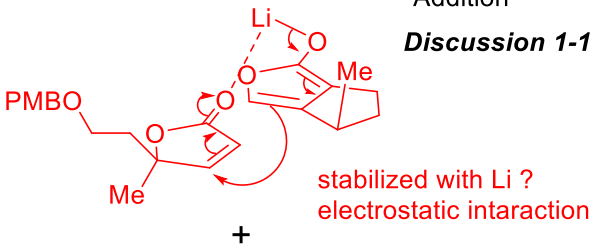


Michael Addition

1-6

1-7a

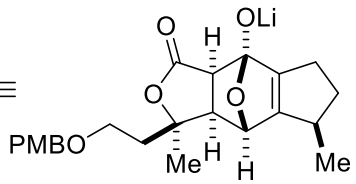
Discussion 1-1



stabilized with Li ?
electrostatic intaraction

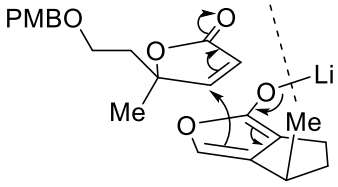
+

≡

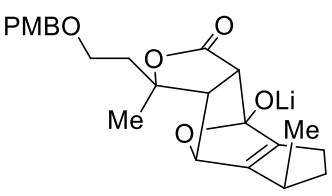


1-7a (major)

larger steric repulsion

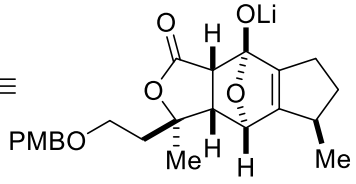


same step

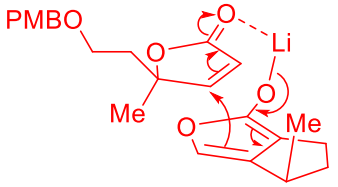


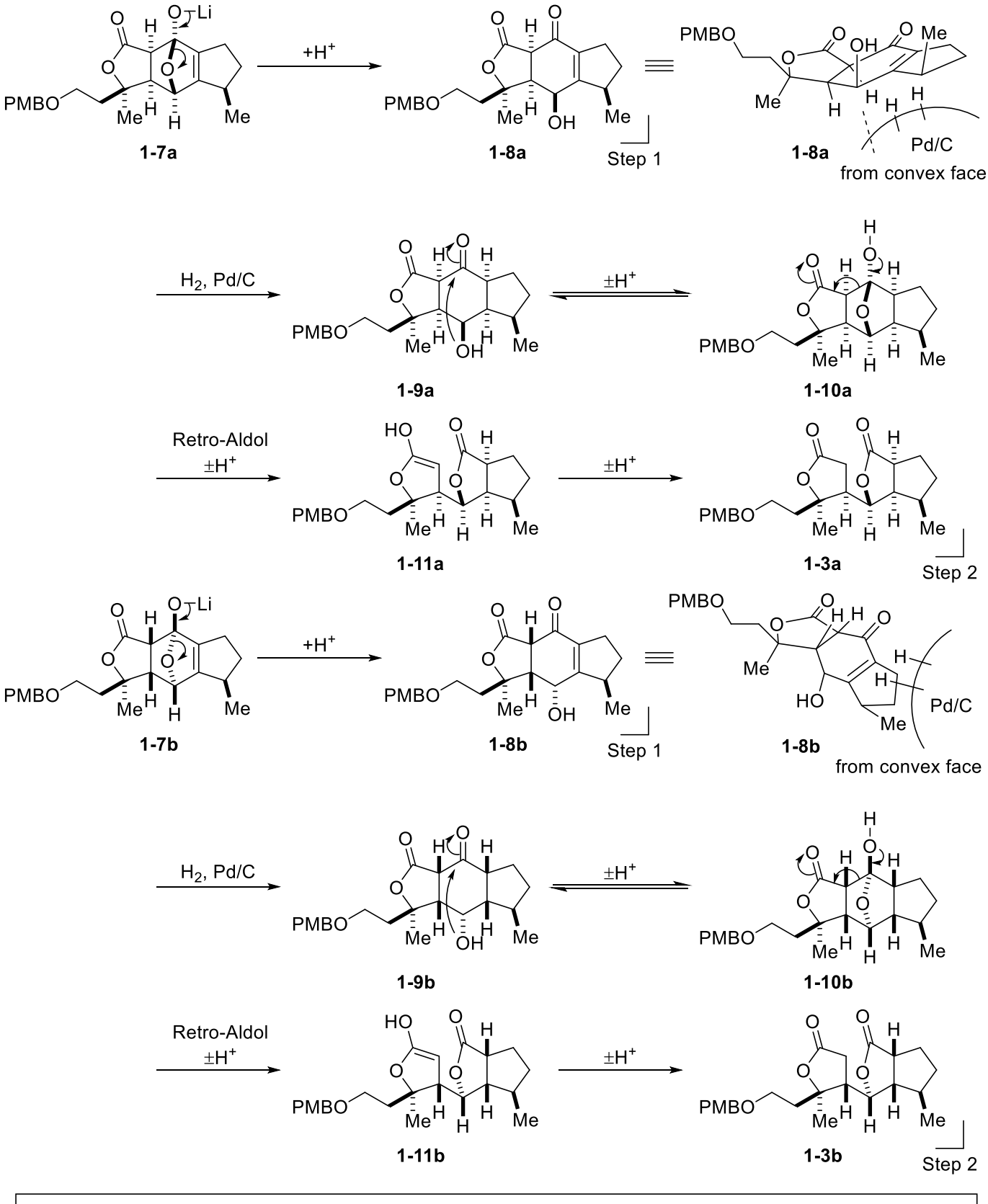
1-7b

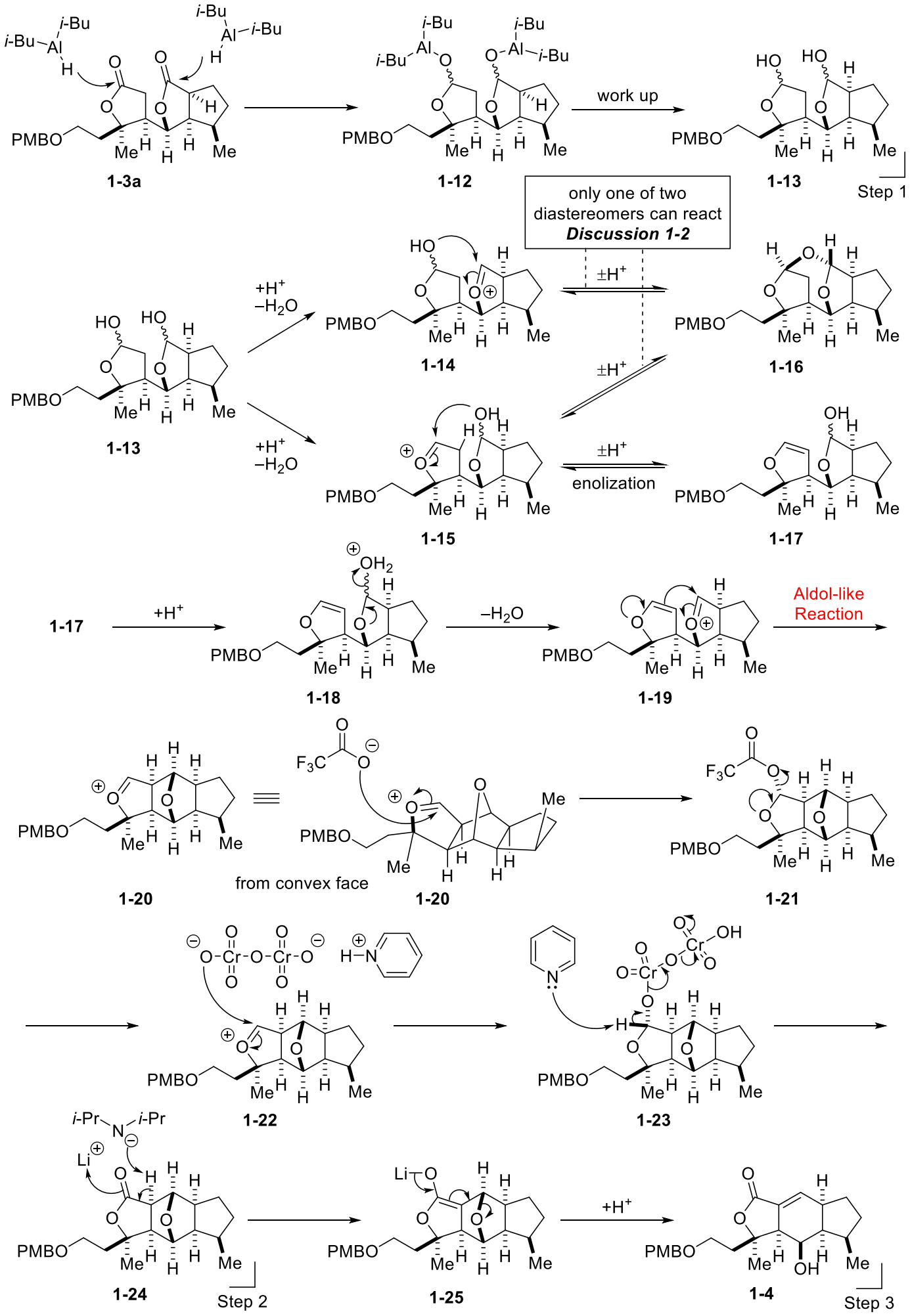
≡



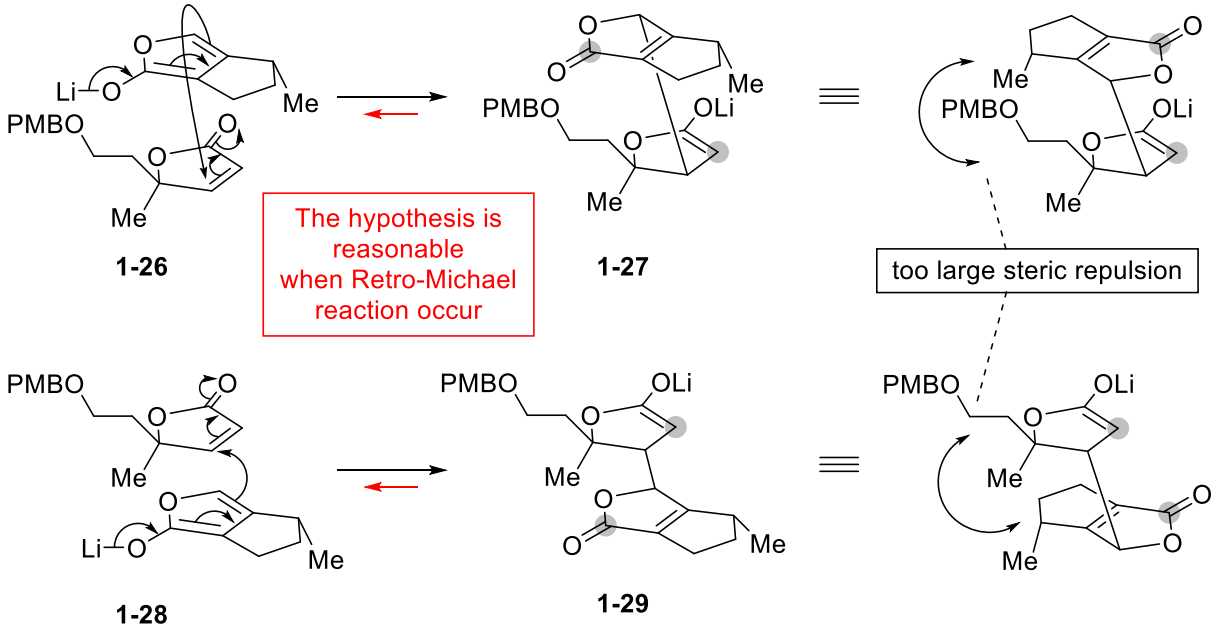
1-7b (minor)




+H+
1-7a
1-8a
Step 1
1-8a
Pd/C
from convex face
H2, Pd/C
±H+
1-9a
1-10a
Retro-Aldol
±H+
±H+
1-11a
1-3a
Step 2
+H+
1-7b
1-8b
Step 1
1-8b
Pd/C
from convex face
H2, Pd/C
±H+
1-9b
1-10b
Retro-Aldol
±H+
±H+
1-11b
1-3b
Step 2
1. DIBAL-H (3.0 eq.), CH2Cl2, -78 °C
2. TFA, 4Å MS, CH2Cl2, rt. then PDC
3. LDA, THF, -78 °C, 69% over 3 steps
1-3a
1-4

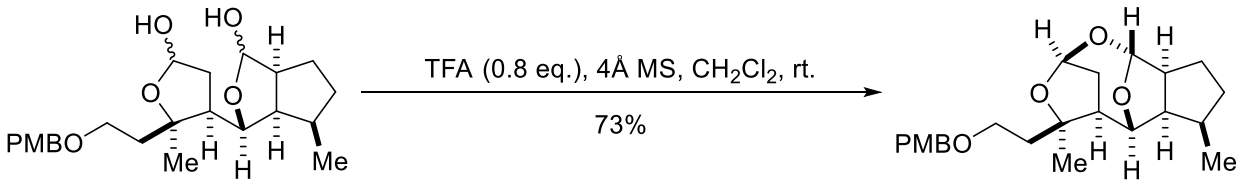

1-3a
1-12
work up
1-13
Step 1
only one of two diastereomers can react
Discussion 1-2
1-14
1-16
1-15
1-17
enolization
1-18
1-19
Aldol-like Reaction
1-20
from convex face
1-21
1-22
1-23
1-24
Step 2
1-25
1-4
Step 3

Discussion 1-1: other access of **1-5** toward **1-2**

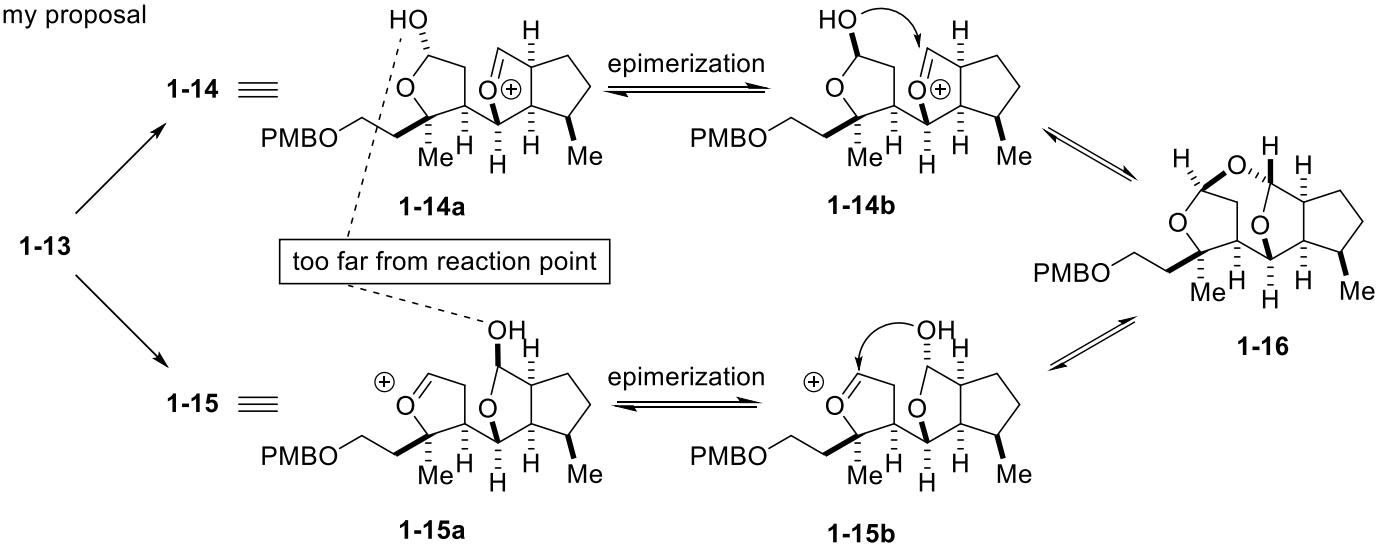


Discussion 1-2: detailed reaction pathway to **1-16**

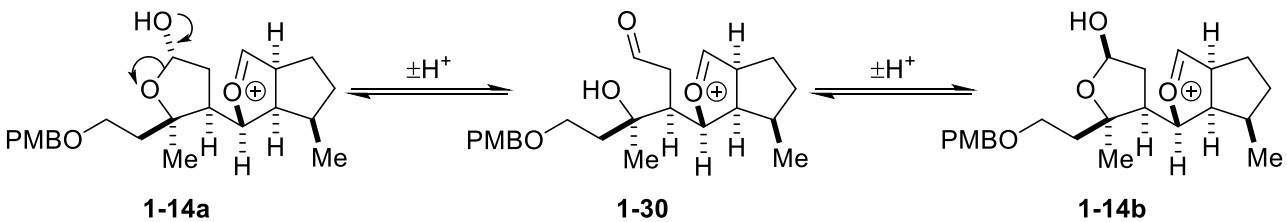
reported reaction



my proposal



epimerization pathway

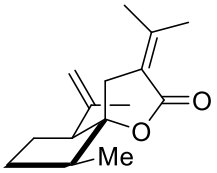


2 Total synthesis of (-)-Curcumanolide A

Isolation:

from *Curcuma zedoara* and related species

Shiobara, Y.; Asakawa, Y.; Kodama, M.; Yasuda, K.; Takemoto, T. *Phytochemistry* **1985**, *24*, 2629.



(–)-curcumanolide A

Structural feature:

•spirocyclic γ-lactone

Bioactivity:

not reported

Total synthesis:

Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 13348. (**Problem 2**)

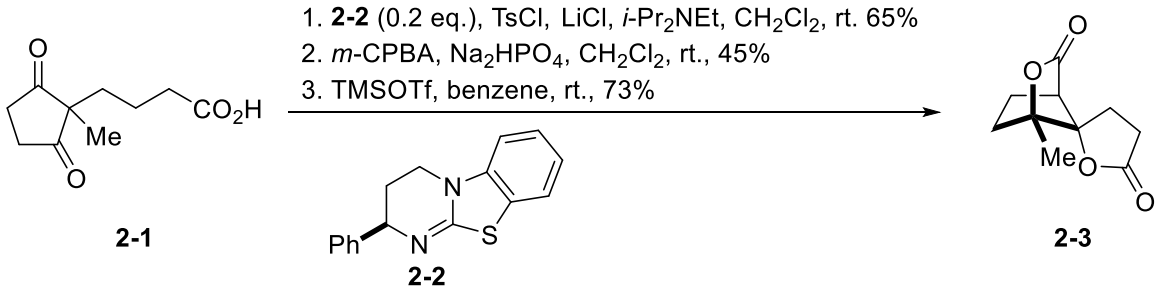
Kato, T.; Mutoh, M.; Oguchi, M.; Yasuoka, H. *Scientia Iranica* **1997**, *4*, 94.

Fujita, T. *J. Org. Chem.* **1997**, *62*, 3824.

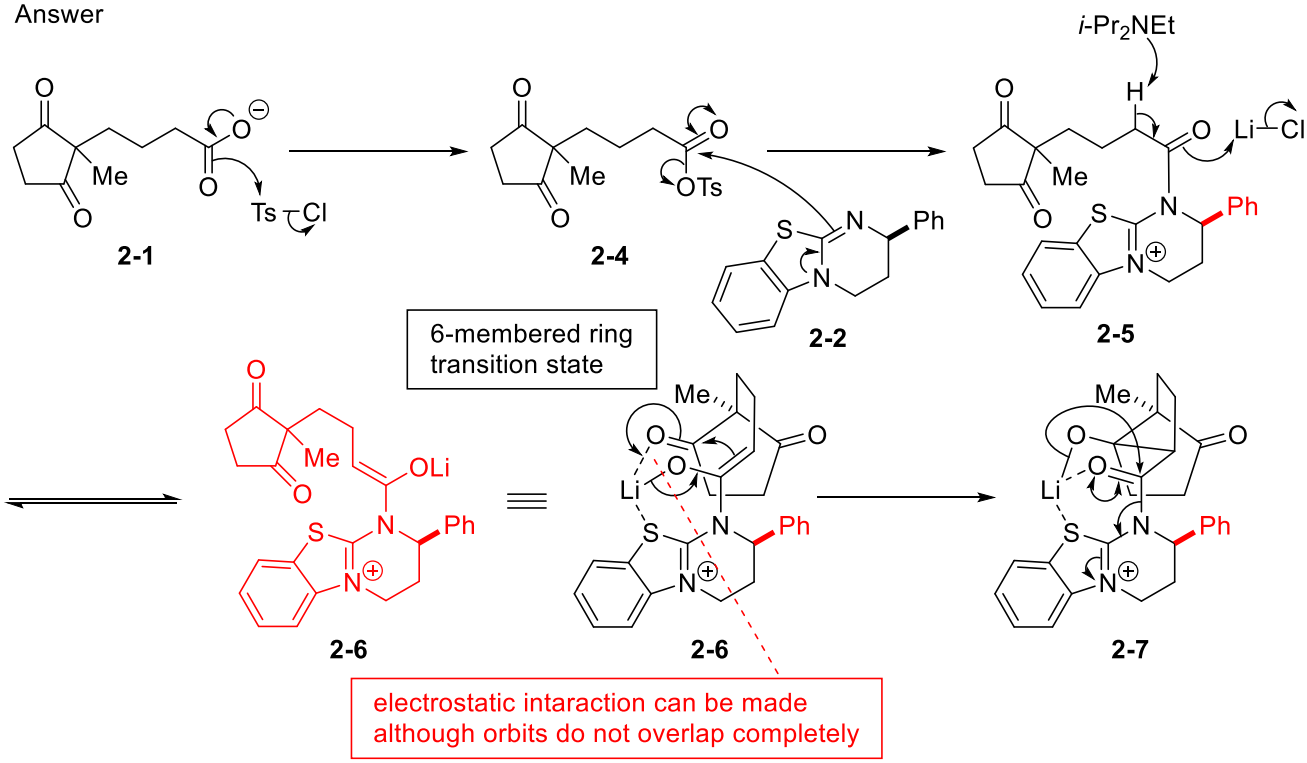
Honda, T.; Ishige, H. *J. Chem. Soc.* **1994**, *24*, 3567.

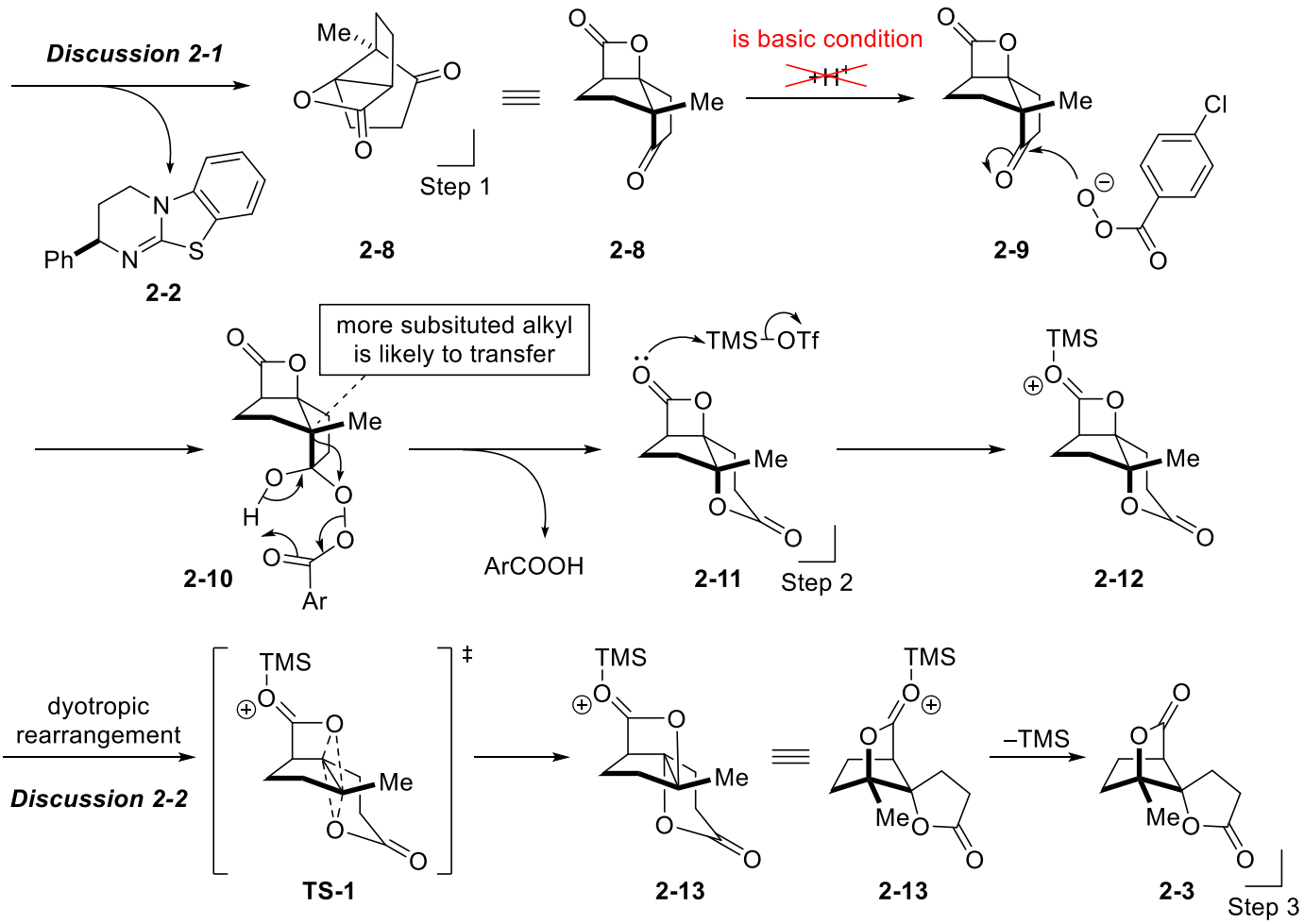
Hirukawa, T.; Oguchi, M.; Yoshikawa, N.; Kato, T. *Chem. Lett.* **1992**, *12*, 2343.

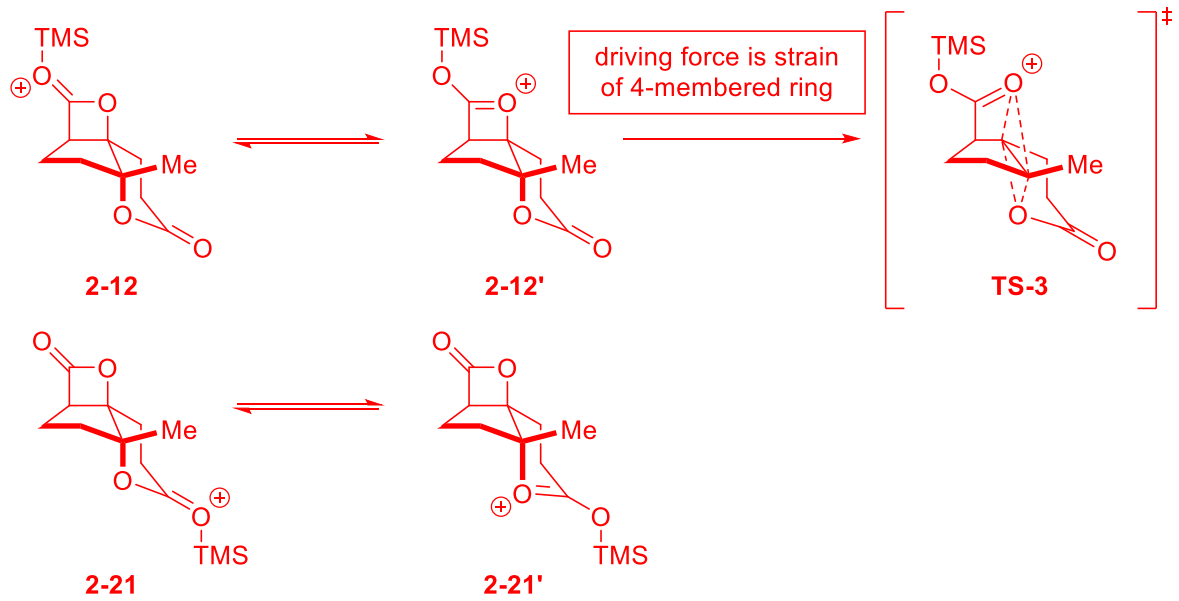
Problem 2



Answer







more stable compared with **2-12'**

Discussion 2-1: effect of LiCl

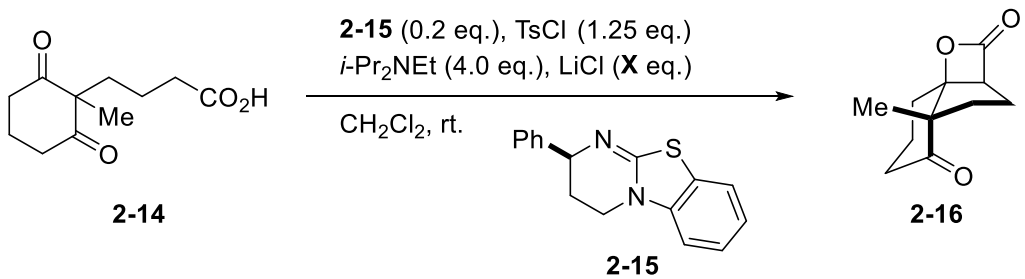
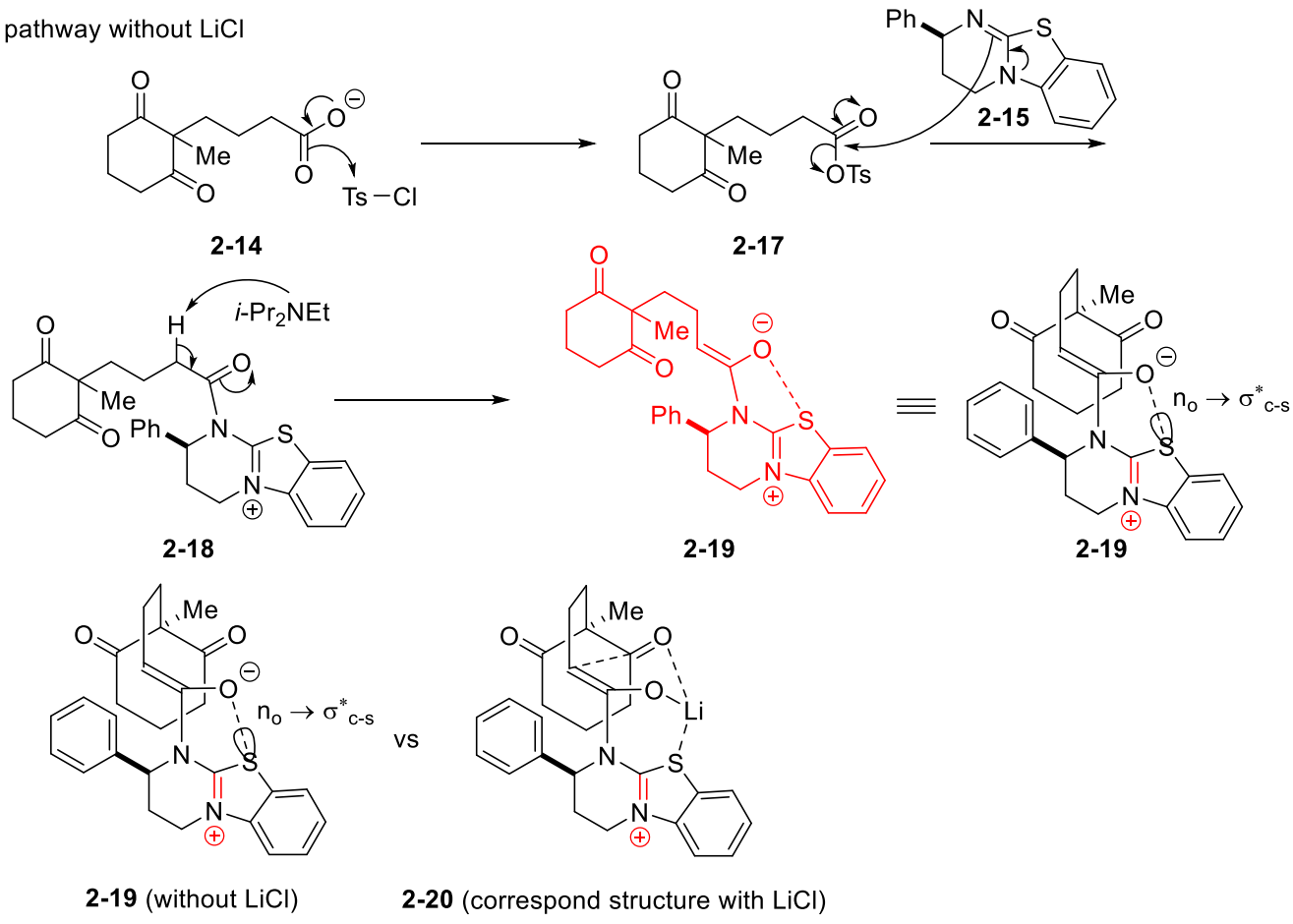


Table 1.

entry	LiCl [eq.]	yield [%]	ee. [%]
1	0	59	97
2	0.25	72	93
3	0.50	80	91
4	1.0	93	90

Levertt, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 9479.

→LiCl increase yield and decrease enantioselectivity



・**2-20** is stabilized by two 6-membered rings

→ <u>yield of **2-16** is increased by LiCl</u>

・framework of **2-19** contains fixed O-S interaction

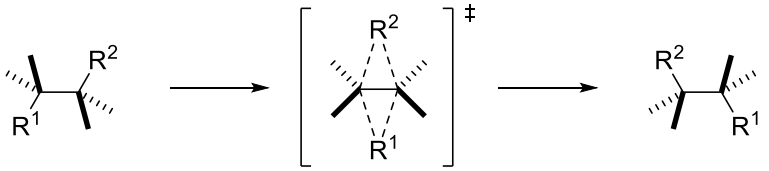
on the other hand, that of **2-20** contains less-fixed Li-S interaction

→ <u>enantioselectivity is decreased by LiCl</u>

Discussion 2-2: dyotropic rearrangement

There are classifications of dyotropic rearrangement

• concerted (synchronous or asynchronous)



• stepwise

stabilized zwitterion

Hung, V. P.; Alexander, S. K.; Christopher, D. V.; Houk, K. N. *J. Am. Chem. Soc.* **2015**, *137*, 6956.

For more information about dyotropic rearrangement, see: 100501_PS_Koichi_MURAI

The process is assisted by computed geometries and computed electrostatic potential.

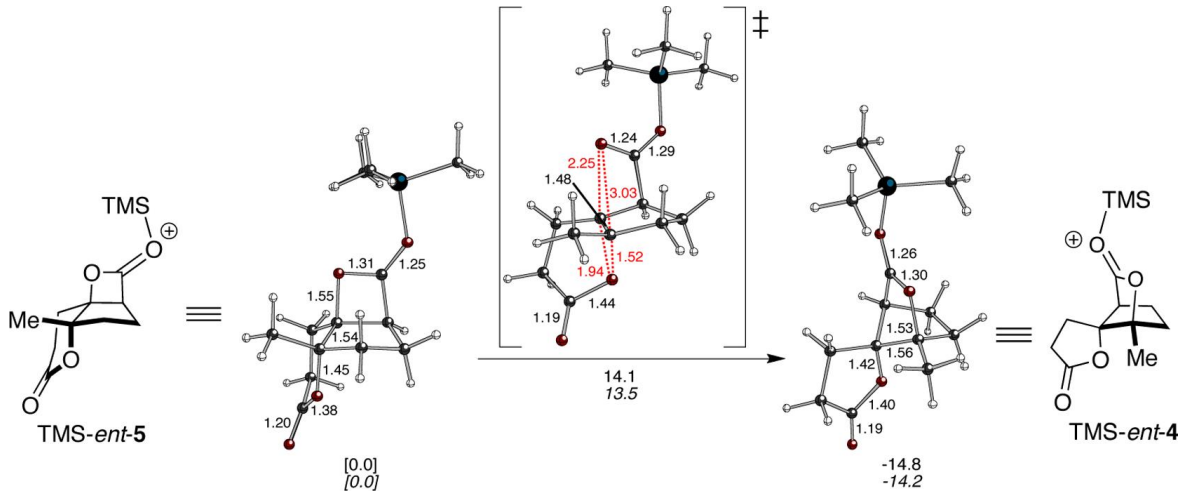


Figure 1. Computed geometries (B3LYP/6-31+G(d,p)) of TMS-*ent*-**5** (enantiomer of **2-12**) and TMS-*ent*-**4** (enantiomer of **2-13**). Intrinsic reaction coordinate (IRC) calculations were conducted.

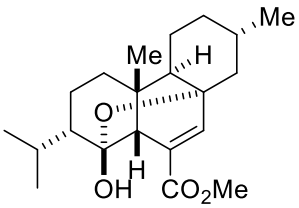
Energies shown are in kcal/mol and are relative to that of the reactant complex (ZPE-corrected energies in normal text; free energies at 25°C in italics). Selected bond lengths are given in Å.

According to the analysis, the most reasonable transition state is presented above

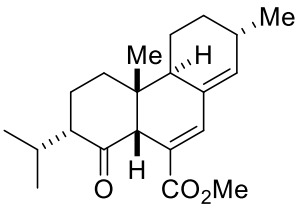
This reaction is identified to be “concerted-type” transition state

The energy level of “concerted” reaction path and that of “stepwise” reaction path should be compared when we want to suggest that this reaction should be “concerted” type of reaction.

3 Total synthesis of (+)-Anhydrochatancin



(+)-chatancin



(+)-anhydrochatancin

Isolation:

Chatantin was isolated from *Sarcophyton* sp.

Sugano, M.; Shindo, T.; Sato, A.; Iijima, Y.; Oshima, T.; Kuwano, H.; Hata, T. *J. Org. Chem.***1990**, *55*, 5803.

Structural feature:

•cis-anti-cis-dodecahydrophenanthrene framework

•six contiguous stereocenters (chatancin)

Bioactivity:

PAF (platelet activating factor) antagonist

Total synthesis:

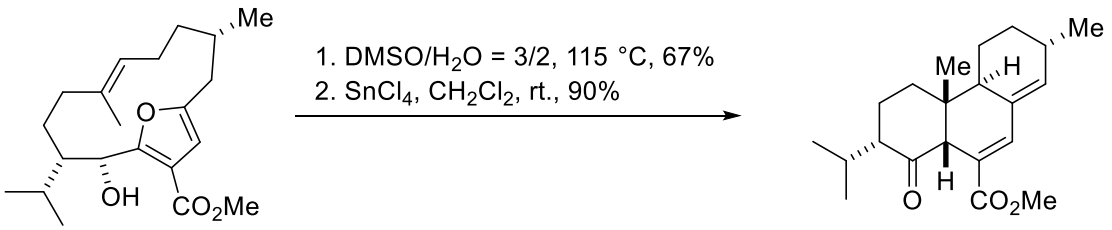
Zhao, Y.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 1223.

Toro, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 6847. (**Problem 3**)

Toro, A.; L'Heureux, A.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 2737.

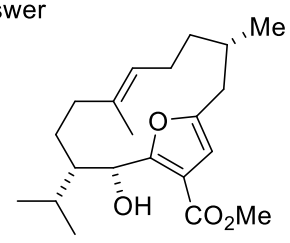
Aigner, J.; Gossinger, E.; Kahlig, H.; Menz, G.; Pflugseder, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2226.

Problem 3

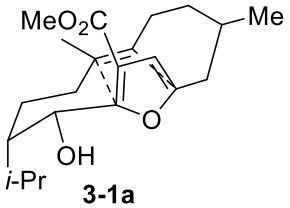


3-1 **3-2**

Answer

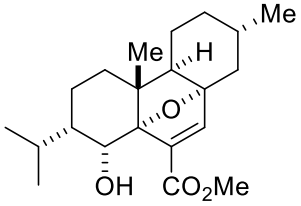


3-1



3-1a

Diels-Alder Reaction



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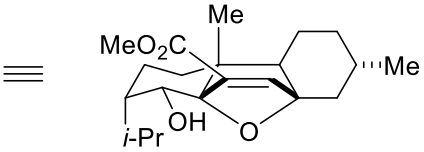
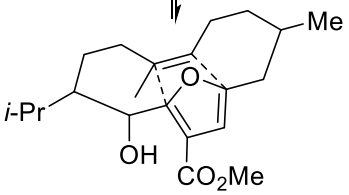
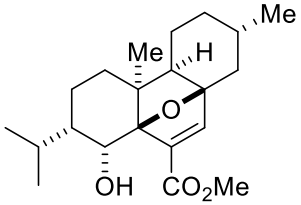


3-3a (favored)



3-1b



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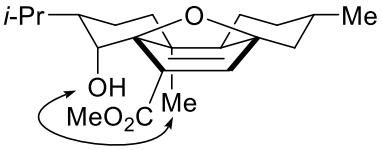

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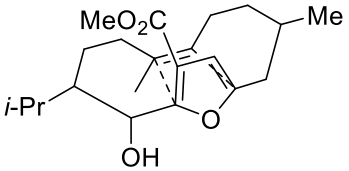

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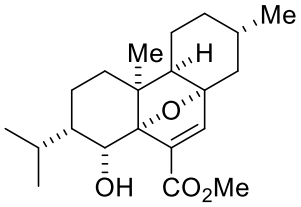

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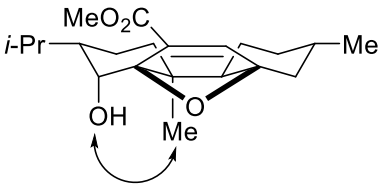

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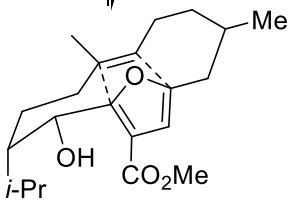

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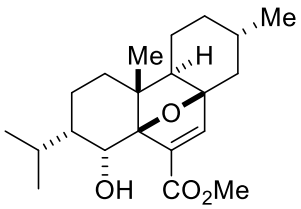
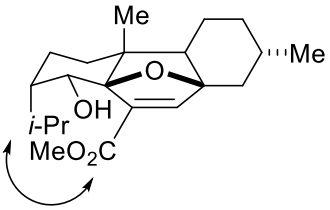


3-3d



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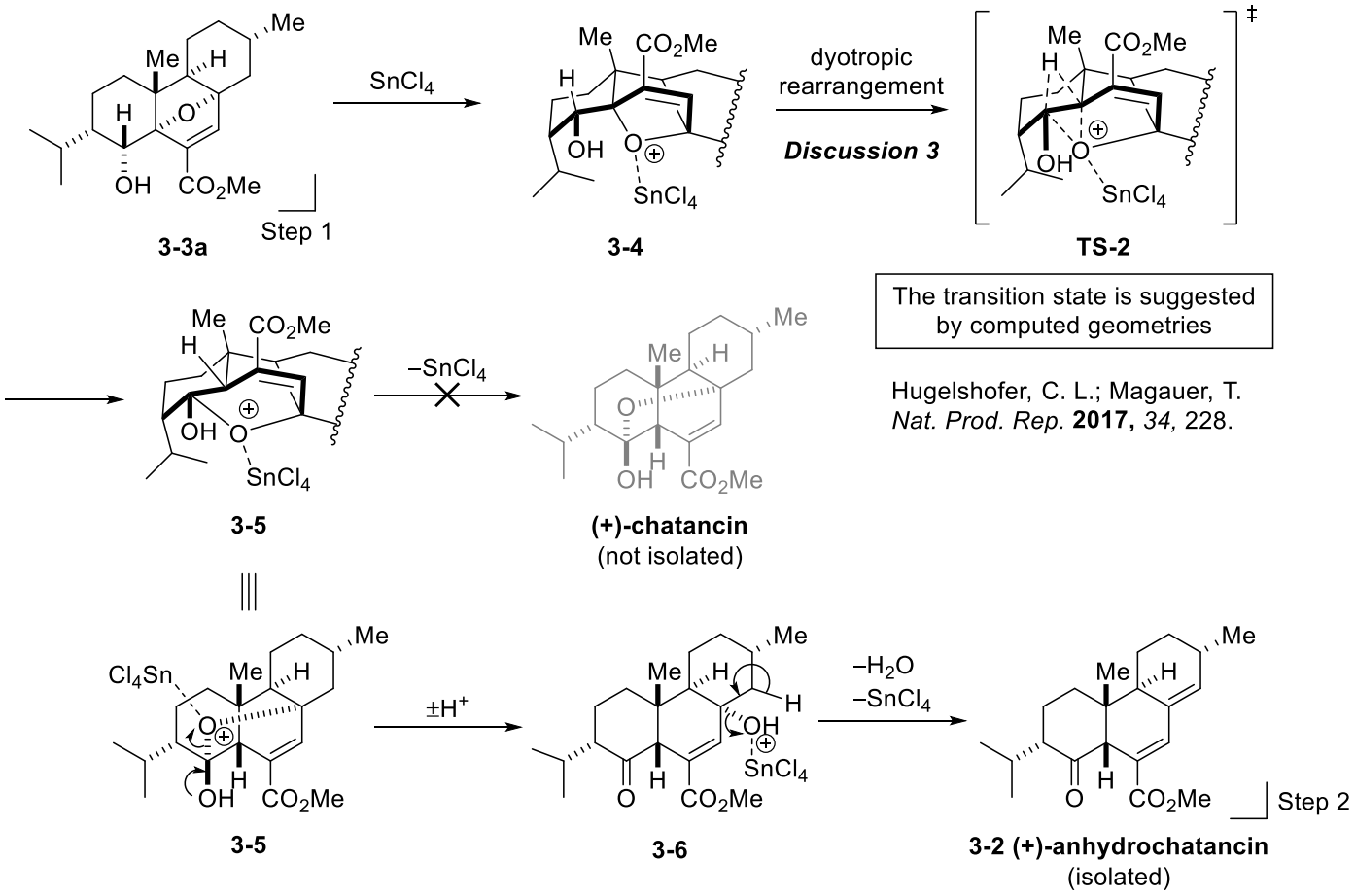

Discussion 3: another route to provide **3-6**