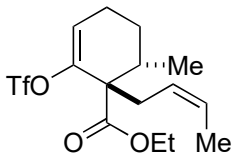
Problem Session (2) - Problem

2017.5.20 Yusuke Imamura

1. Please fill in the blank and explain the reaction mechanisms.

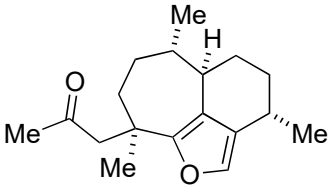


1-1

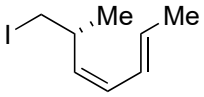
1. DIBAL-H (2.7 eq.), CH_2Cl_2, -30 °C
2. $Pd(OAc)_2$ (15 mol%), PPh_3 (30 mol%), Et_3N
   MeOH, DMF, CO, 60 °C, 82% (2 steps)
3. PhCl, μW, 200 °C, 88%
4. DIBAL-H, toluene, -30 °C;
   1.0 M HCl aq., 85%

1-2
($C_{13}H_{18}O$)

5. 9-BBN dimer, THF, 40 °C;
   $Pd(dppf)Cl_2 \cdot CH_2Cl_2$(10 mol%), $AsPh_3$ (10 mol%)
   Cs_2CO_3, **A**, H_2O, DMF, 45 °C, 82%
6. $AuCl_3$ (10 mol%), CH_2Cl_2, -20 °C, 85 %, dr = 10:1



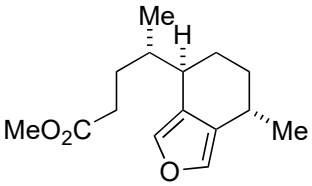
1-3



2-1

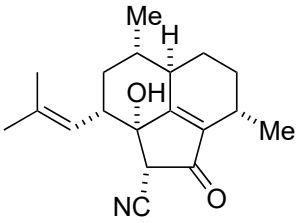
1. *t*-BuLi, Et_2O, -78 °C;
   B, 87%
2. DIBAL-H (4 eq.), CH_2Cl_2, -78 °C, 73%
3. PCC, CH_2Cl_2, 58%
4. Li—≡—CO_2Et
   THF, -78 °C
5. DMP, CH_2Cl_2, $NaHCO_3$, 62% (2 steps)
6. toluene, 120 °C, 90%

2-2
($C_{20}H_{24}O_4$)

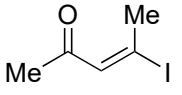


3-1

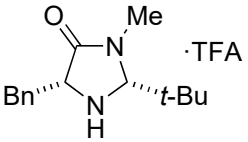
1. DIBAL-H (1.2 eq.), CH_2Cl_2, -78 °C
2. **salt C** (40 mol%), CAN, H_2O, DME, -20 °C
3. **D**, $LiN(TMS)_2$, -78 °C;
   0 °C, 1 h; rt, 30 min, 26% (3 steps)
4. $POCl_3$, DMF, 79%
5. Tos-MIC, *t*-BuOK, THF, -50 °C;
   MeOH, 65 °C, 57%
6. DMDO, K_2CO_3, Na_2SO_4, CH_2Cl_2, 77%



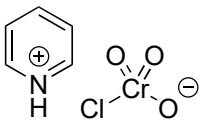
3-2



A



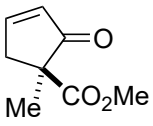
salt C



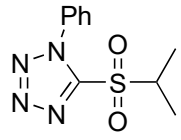
PCC

$(NH_4)_2Ce(NO_3)_6$

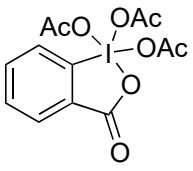
CAN



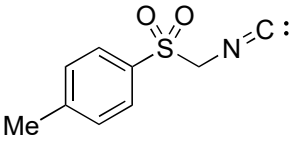
B



D



DMP

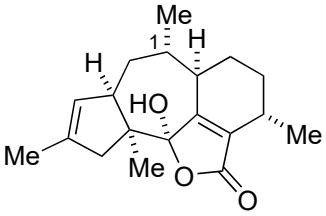


Tos-MIC

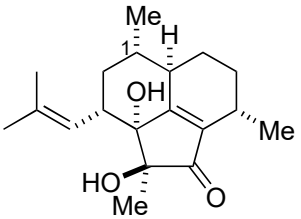
Problem Session (2) - Answer

2016.5.20 Yusuke Imamura

Topic: Total synthesis of Caribenols



caribenol A



caribenol B

0. Introduction

0.1. Isolation

Isolated from West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*
(Wei, X.; Rodríguez, I. I.; Rodríguez, A. D.; Banes, C. L. *J. Org. Chem.* **2007**, *72*, 7386.)

0.2. Biological Activity

Caribenol A, and B:
inhibitory activity against *Mycobacterium tuberculosis* (H37Rv)
(MIC (μg/mL) values of >128 and 63, respectively)
Caribenol A:
in vitro antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* W2
(IC_{50} 20 μg/mL)

0.3. Structural Feature

C_{19} rearranged terpene with six stereocenters

0.4.1. Total Synthesis of Caribenol A

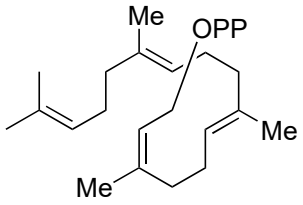
Liu, L. Z.; Han, J. C.; Yue, G. Z.; Li, C. C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 13608.
Han, J. C.; Liu, L. Z.; Chang, Y. Y.; Yue, G. Z.; Guo, J.; Zhou, L. Y.; Li, C. C.; Yang, Z. *J. Org. Chem.* **2013**, *78*, 5492.
Han, J. C.; Liu, L. Z.; Li, C. C.; Yang, Z. *Chem. - Asian J.* **2013**, *8*, 1972.
Yu, X.; Su, F.; Liu, C.; Yuan, H.; Zhao, S.; Zhou, Z.; Quan, T.; Luo, T. *J. Am. Chem. Soc.* **2016**, *138*, 6261.
Hao, H. -D.; Trauner, D. *J. Am. Chem. Soc.* **2017**, *139*, 4117. (also Caribenol B)

0.4.2. Synthetic studies of Caribenol A

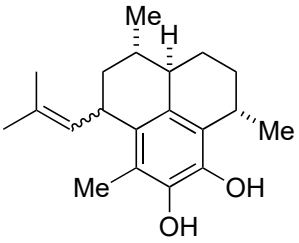
Kaloko, J. J.; Teng, Y. H. G.; Ojima, I. *Chem. Commun.* **2009**, *45*, 4569.
Mondal, S.; Yadav, R. N.; Ghosh, S. *Tetrahedron Lett.* **2009**, *50*, 5277.

0.5. Biosynthesis of Caribenol

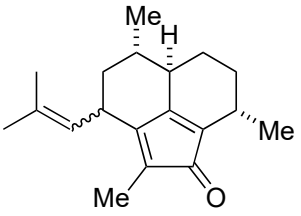
Kohl, A. C.; Ata, A.; Kerr, R. G. *J. Ind. Microbiol. Biotechnol.* **2003**, *30*, 495.
Wei, X.; Rodríguez, I. I.; Rodríguez, A. D.; Banes, C. L. *J. Org. Chem.* **2007**, *72*, 7386.



GGPP (**0-1**)



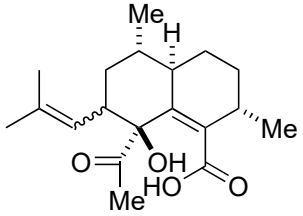
pseudopterosin (**0-2**)



0-3

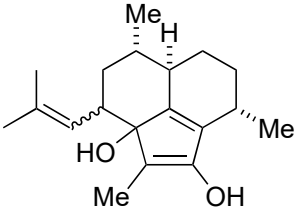
hydration

trans-dihydroxylation

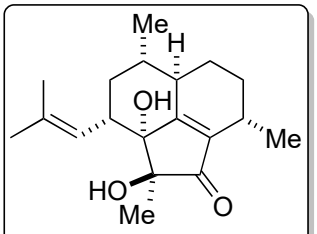


0-5

[O] cleavage

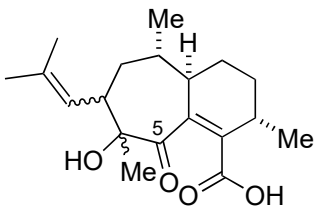


0-4



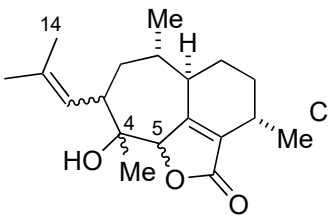
caribenol B

α-ketol rearr. (ring expansion)



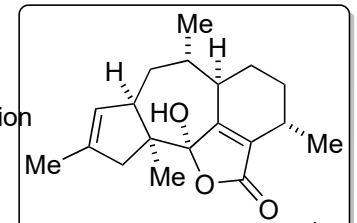
0-6

[H] at C5
$-H_2O$



Sandersolide (**0-7**)

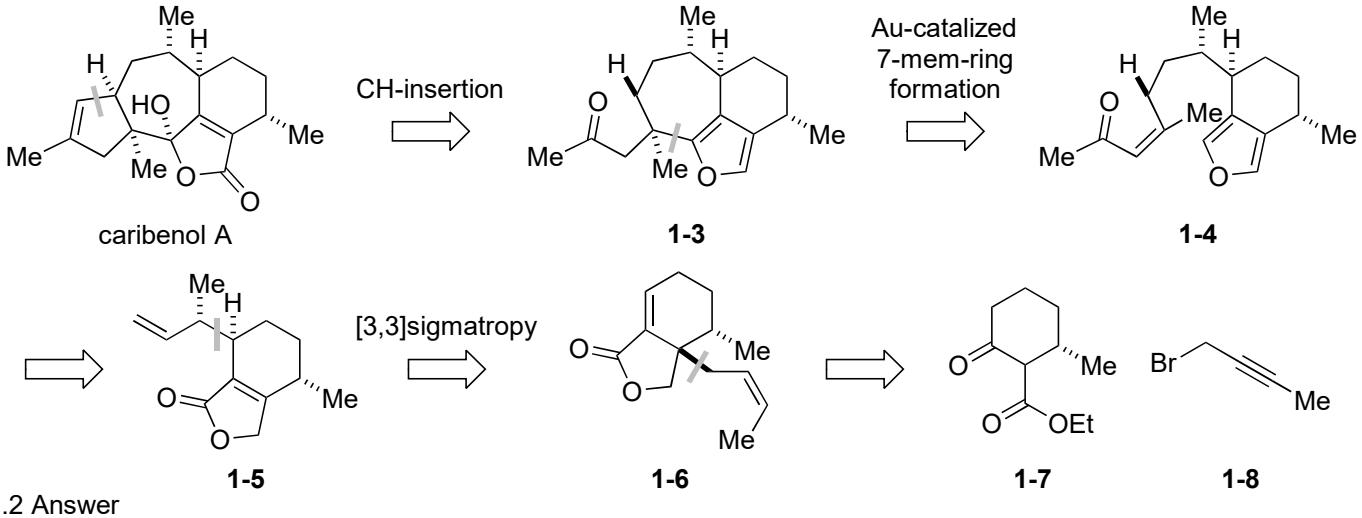
[O] at C5
C14-C4 cyclization



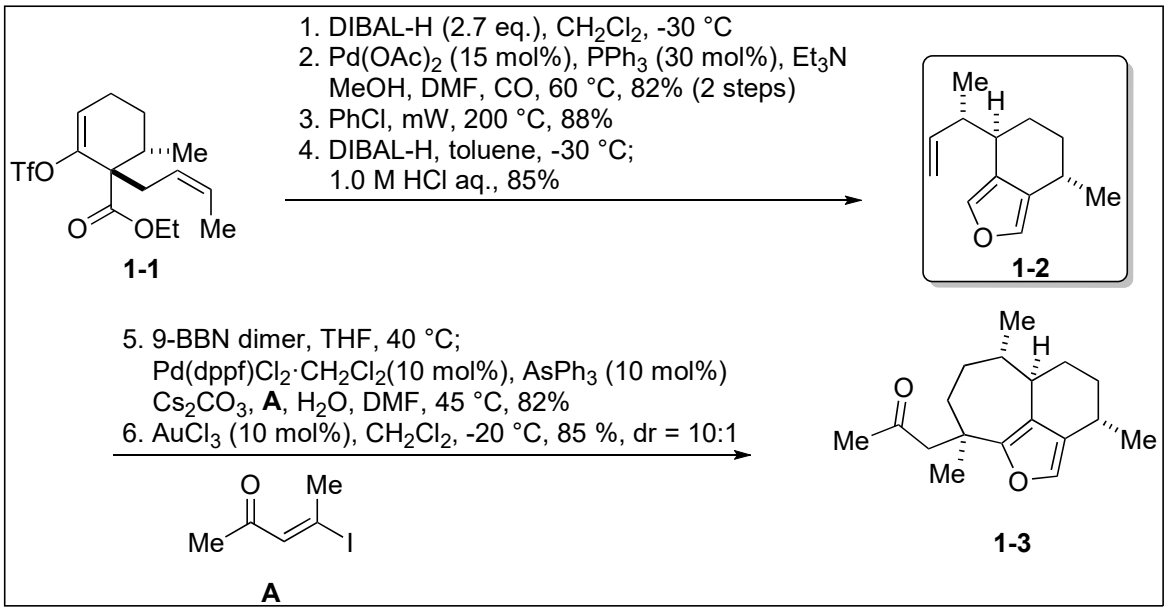
caribenol A

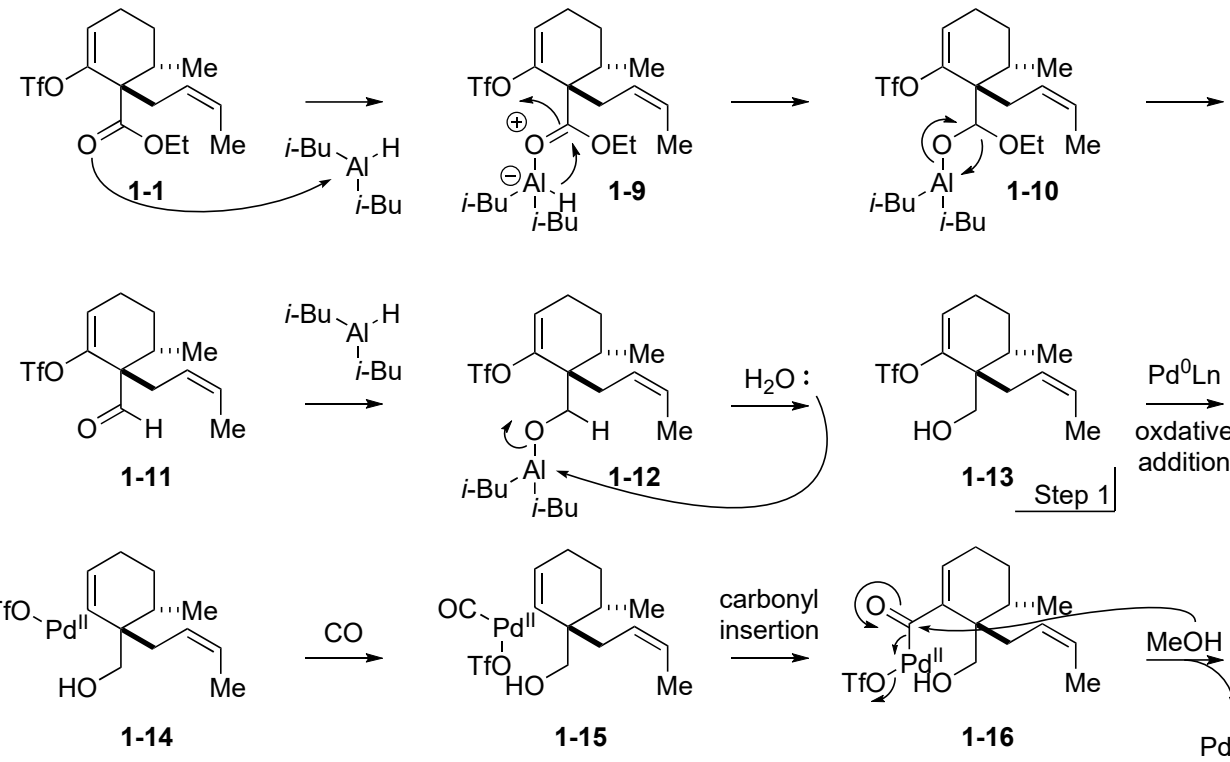
1. Total synthesis of Caribenol A by Luo, T. et al. [*J. Am. Chem. Soc.* **2016**, *138*, 6261.]

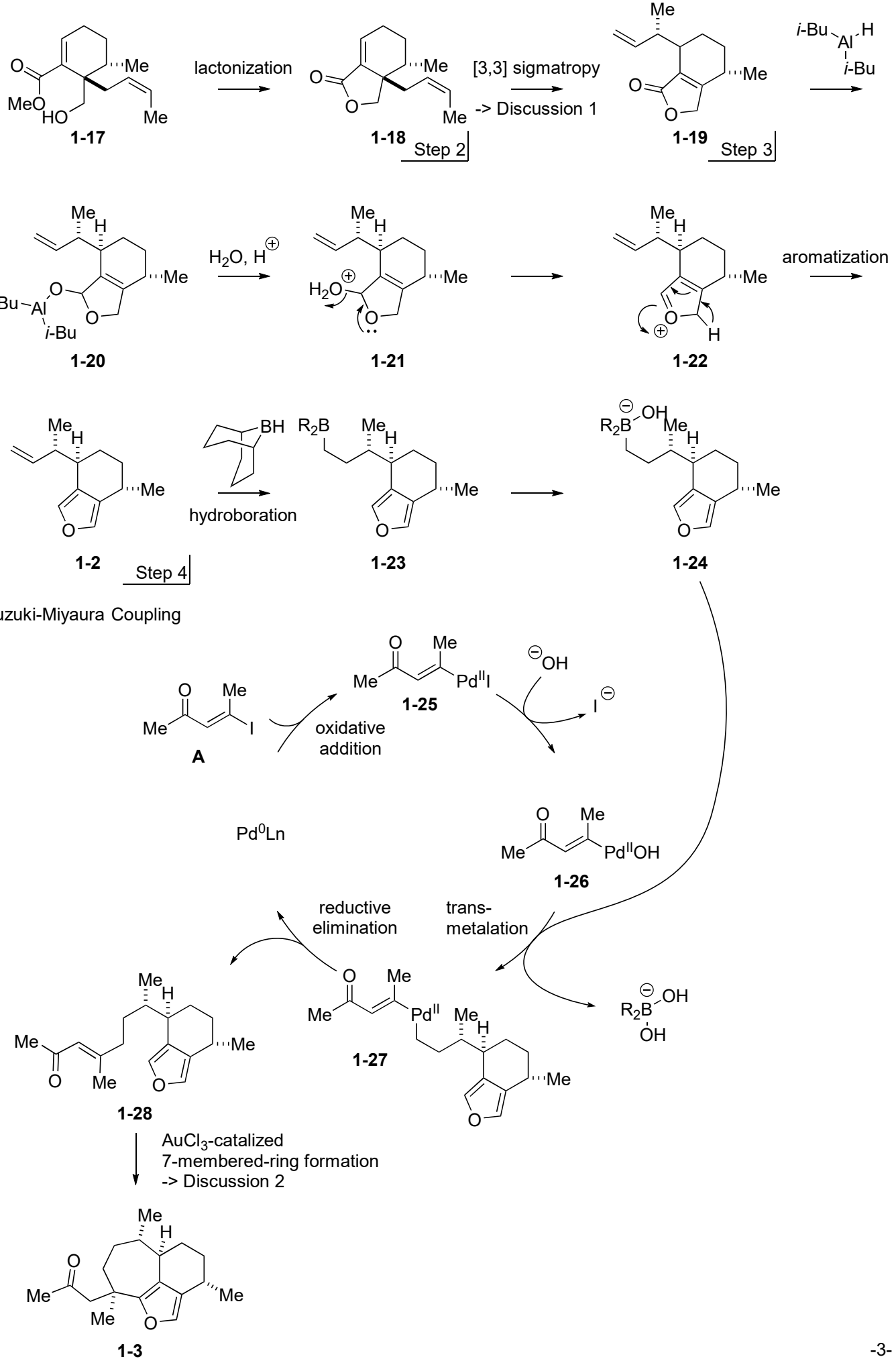
1.1. Retrosynthesis



1.2 Answer

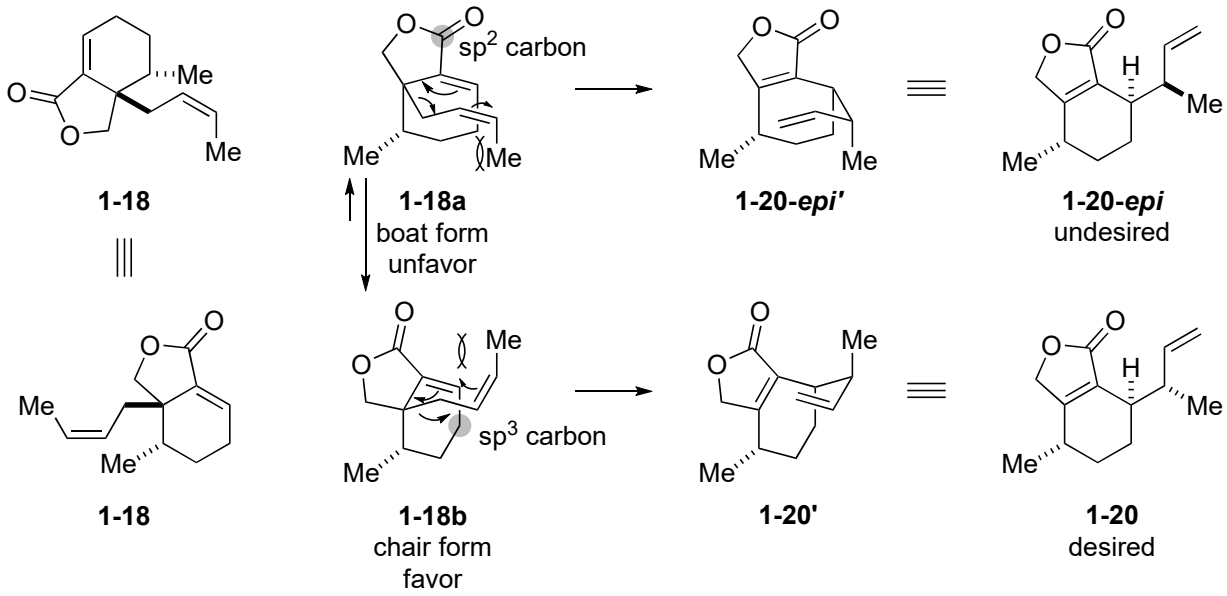





lactonization
[3,3] sigmatropy
-> Discussion 1
1-17
1-18
Step 2
1-19
Step 3
H2O, H
aromatization
1-20
1-21
1-22
hydroboration
1-2
Step 4
1-23
1-24
Suzuki-Miyaura Coupling
A
oxidative addition
1-25
Pd0Ln
1-26
reductive elimination
trans-metalation
1-27
1-28
AuCl3-catalized
7-membered-ring formation
-> Discussion 2
1-3

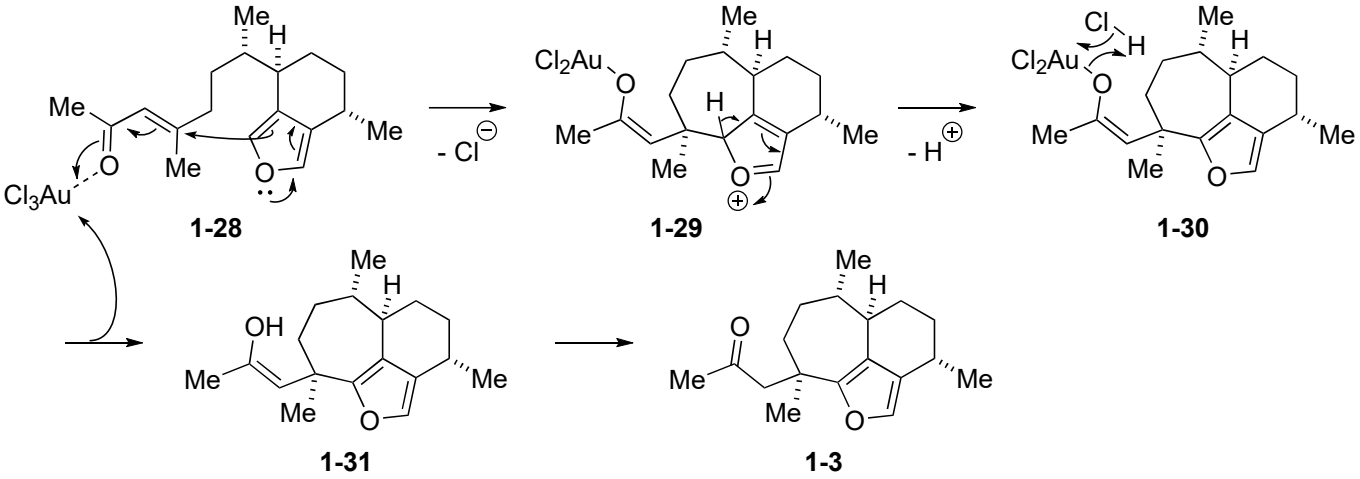
1.3. Discussion

1.3.1. **Discussion 1** stereoselectivity of [3,3] sigmatropy rearrangement



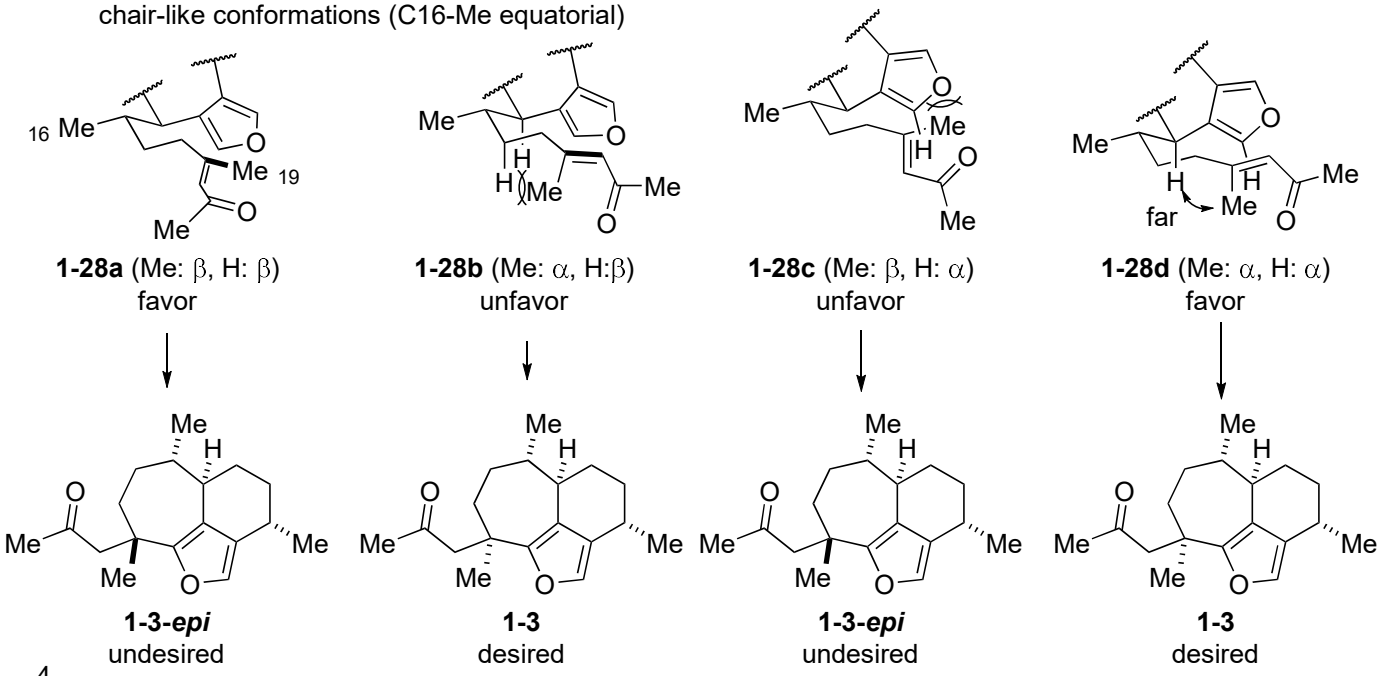
1.3.2. **Discussion 2** Au-catalized 7-membered-ring formation

1.3.2.1. Author's proposal (Michael addition)



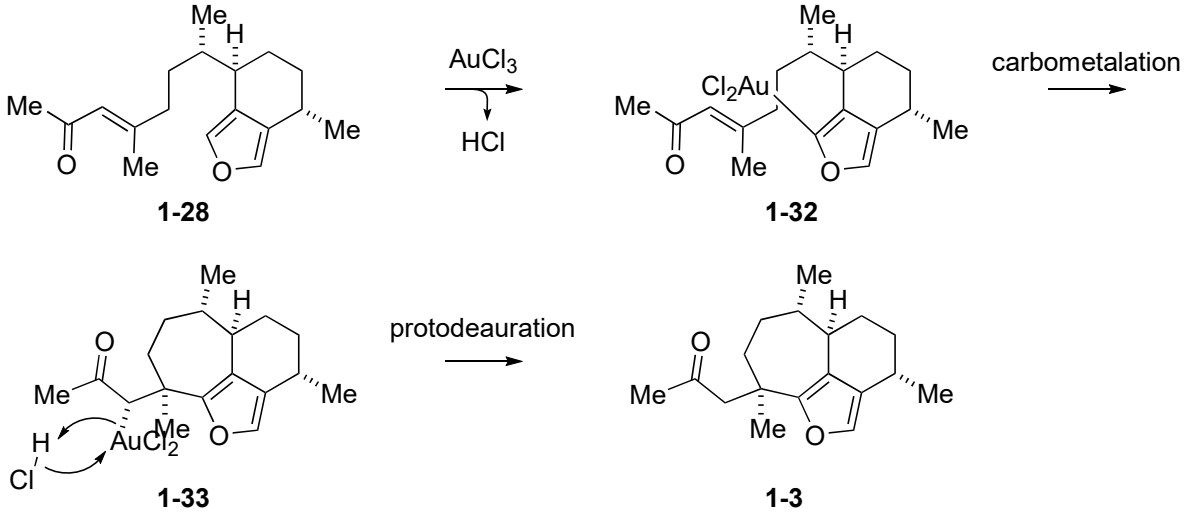
diastereoselectivity of 7-membered-ring formation

chair-like conformations (C16-Me equatorial)

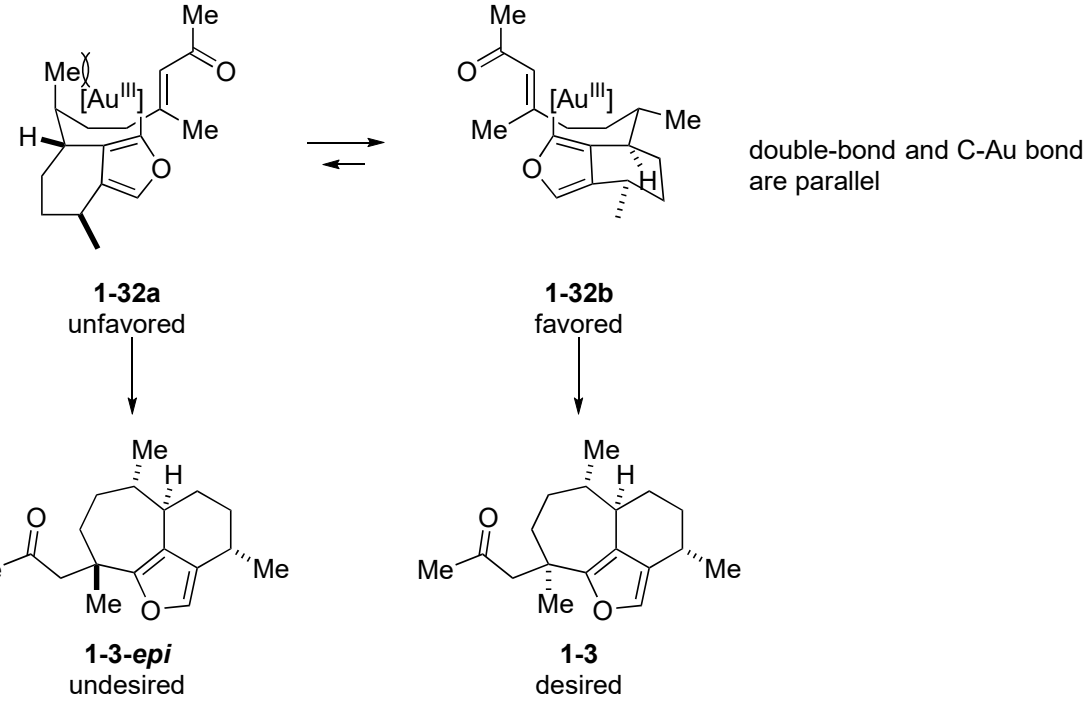


-> another explanation may be needed

1.3.2.2. CH-activation pathway

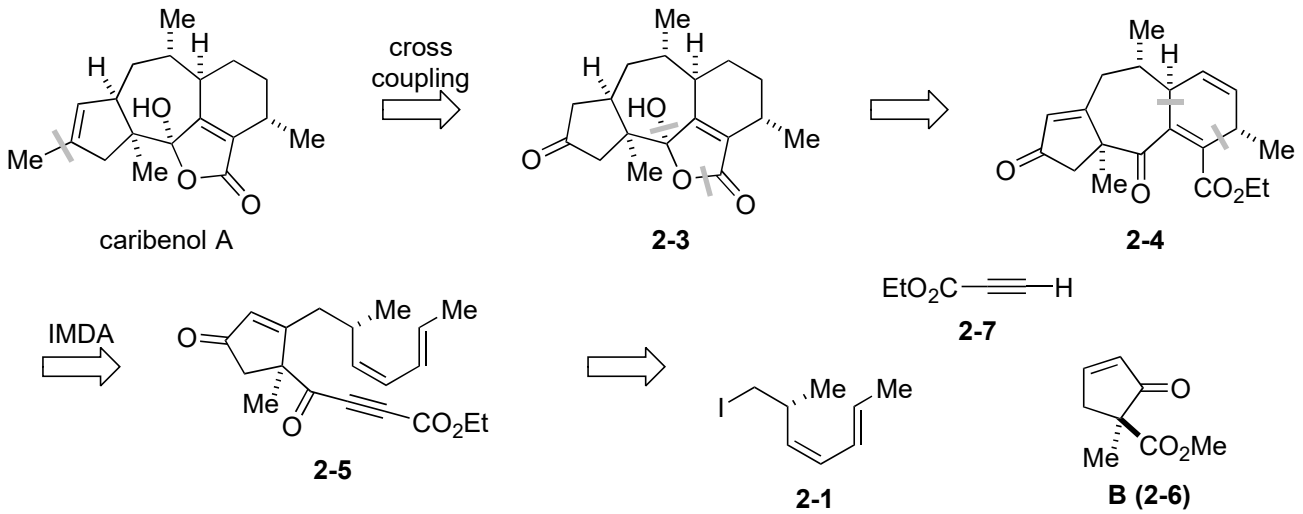


diastereoselectivity of 7-membered-ring formation

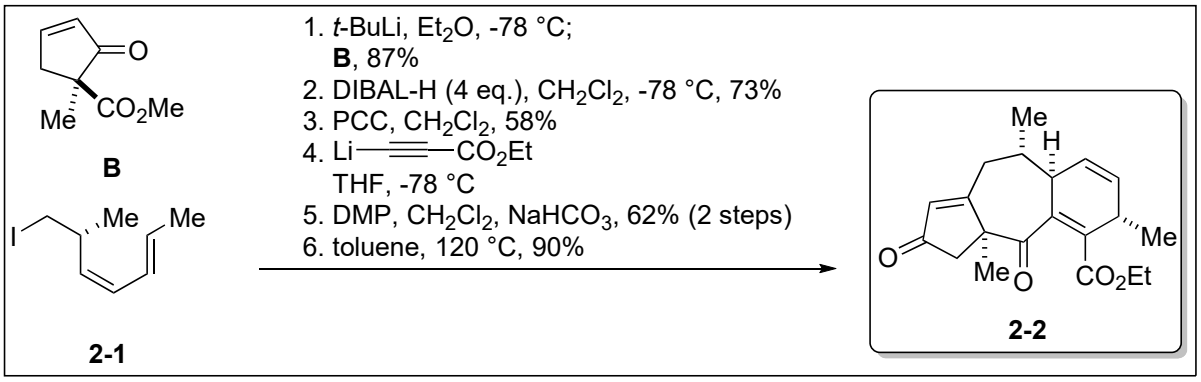


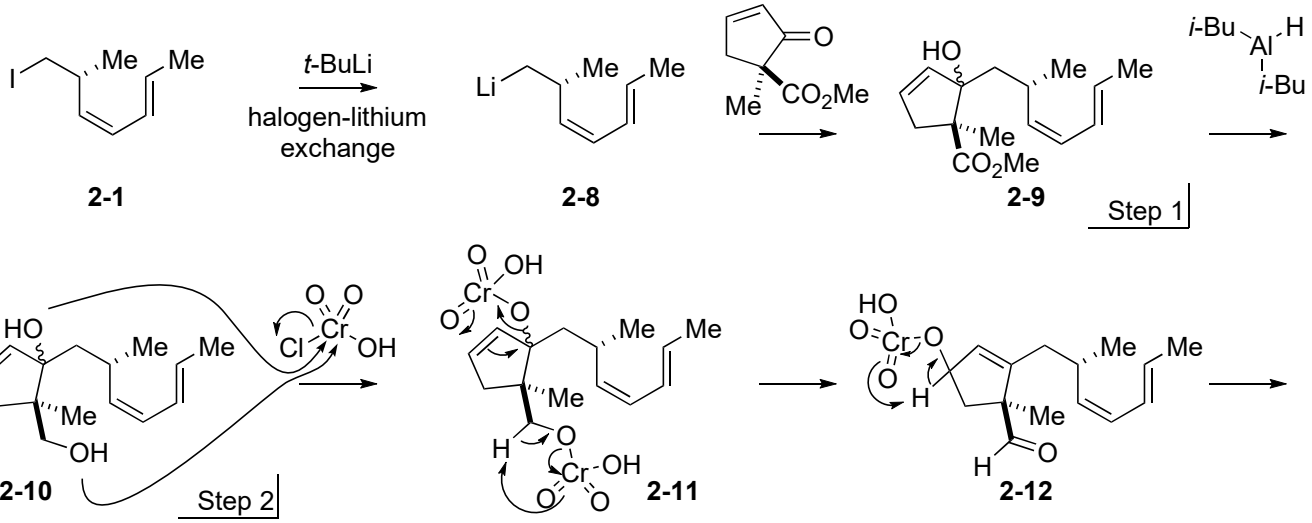
2. Total synthesis of caribenol A by Yang, Z. et al. [*Chem. - Asian J.* **2013**, *8*, 1972.]

2.1. Retrosynthesis

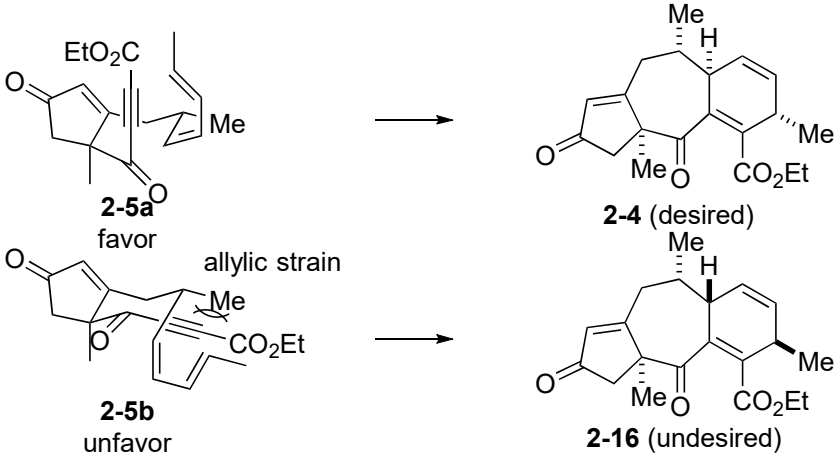


2.2. Answer

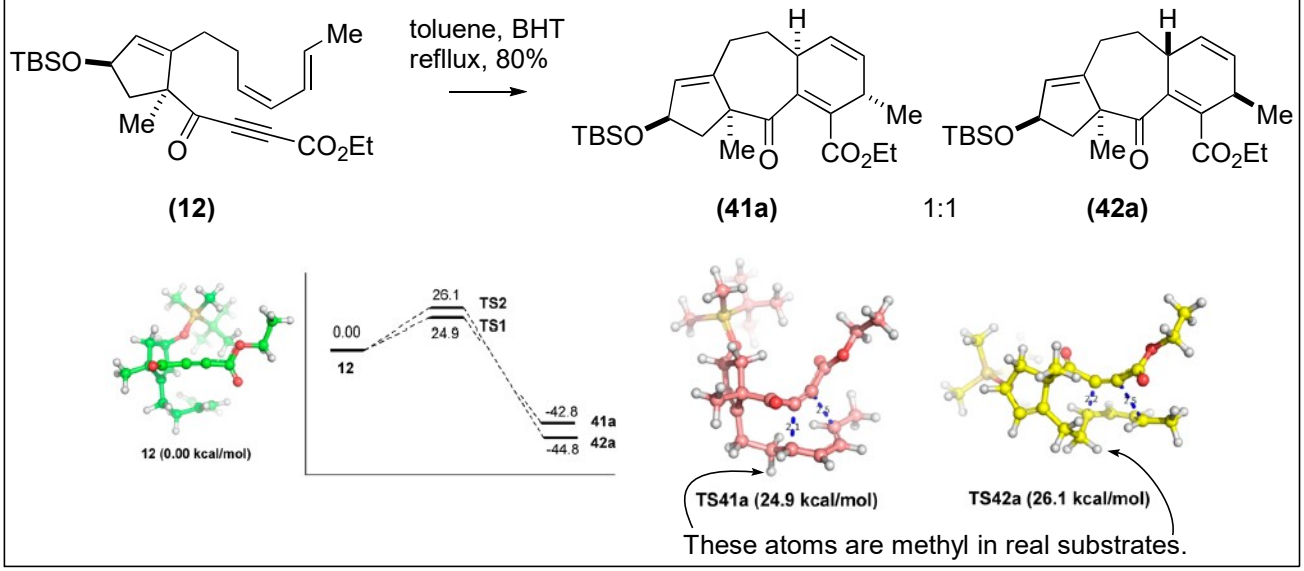




2.3. Discussion selectivity of IMDA



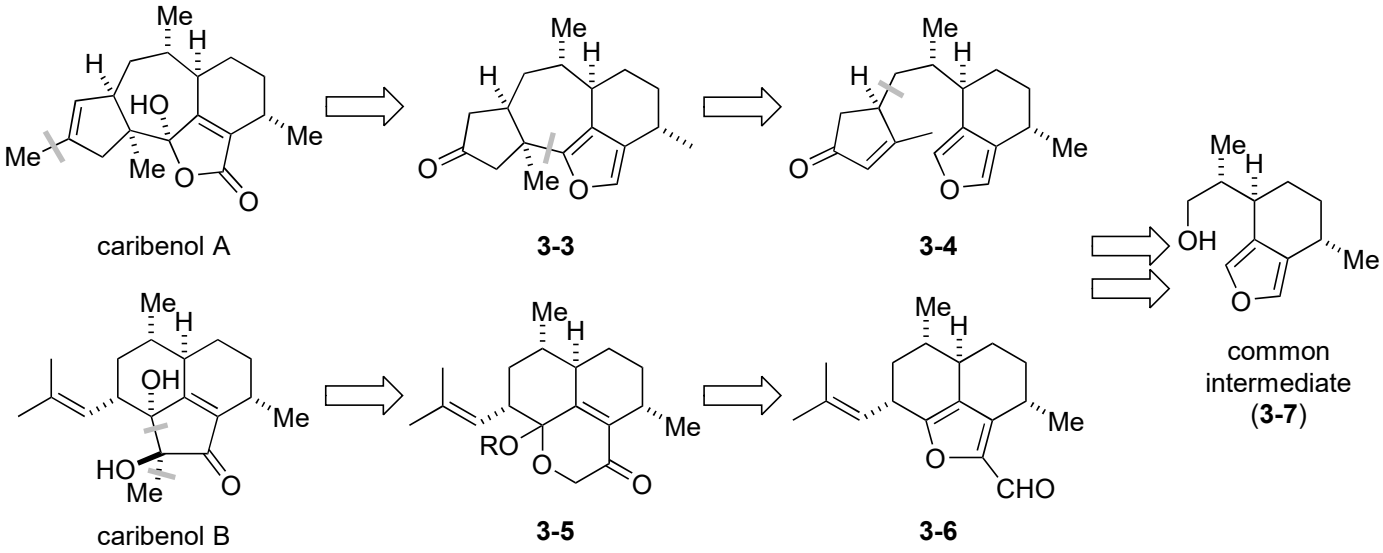
Yang, Z. et al. J. Org. Chem. **2013**, *78*, 5492.



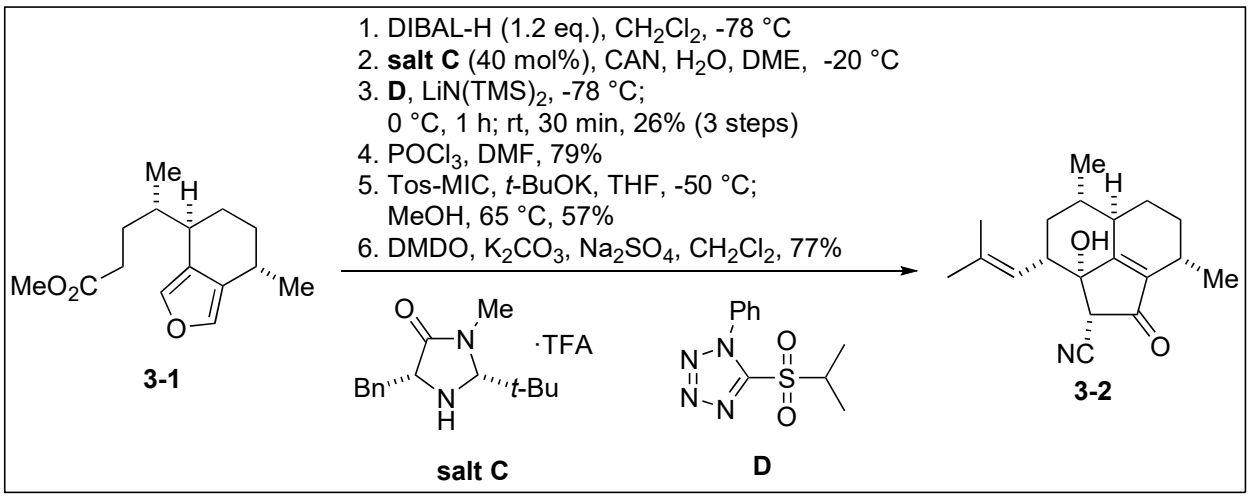
(12) **(41a)** **(42a)**

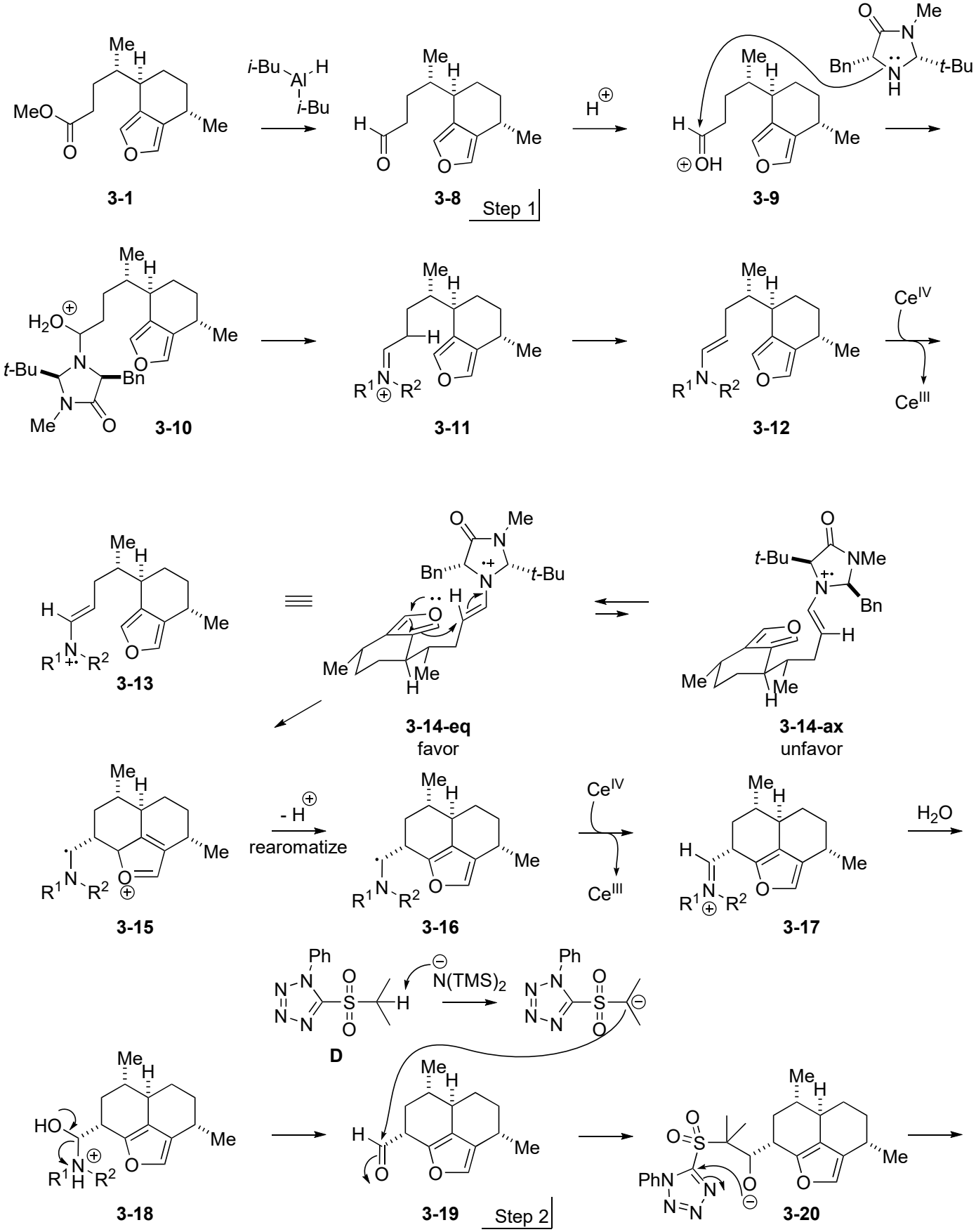
3. Total synthesis of Caribenol B by Trauner, D. et al. [*J. Am. Chem. Soc.* **2017**, *139*, 4117.]

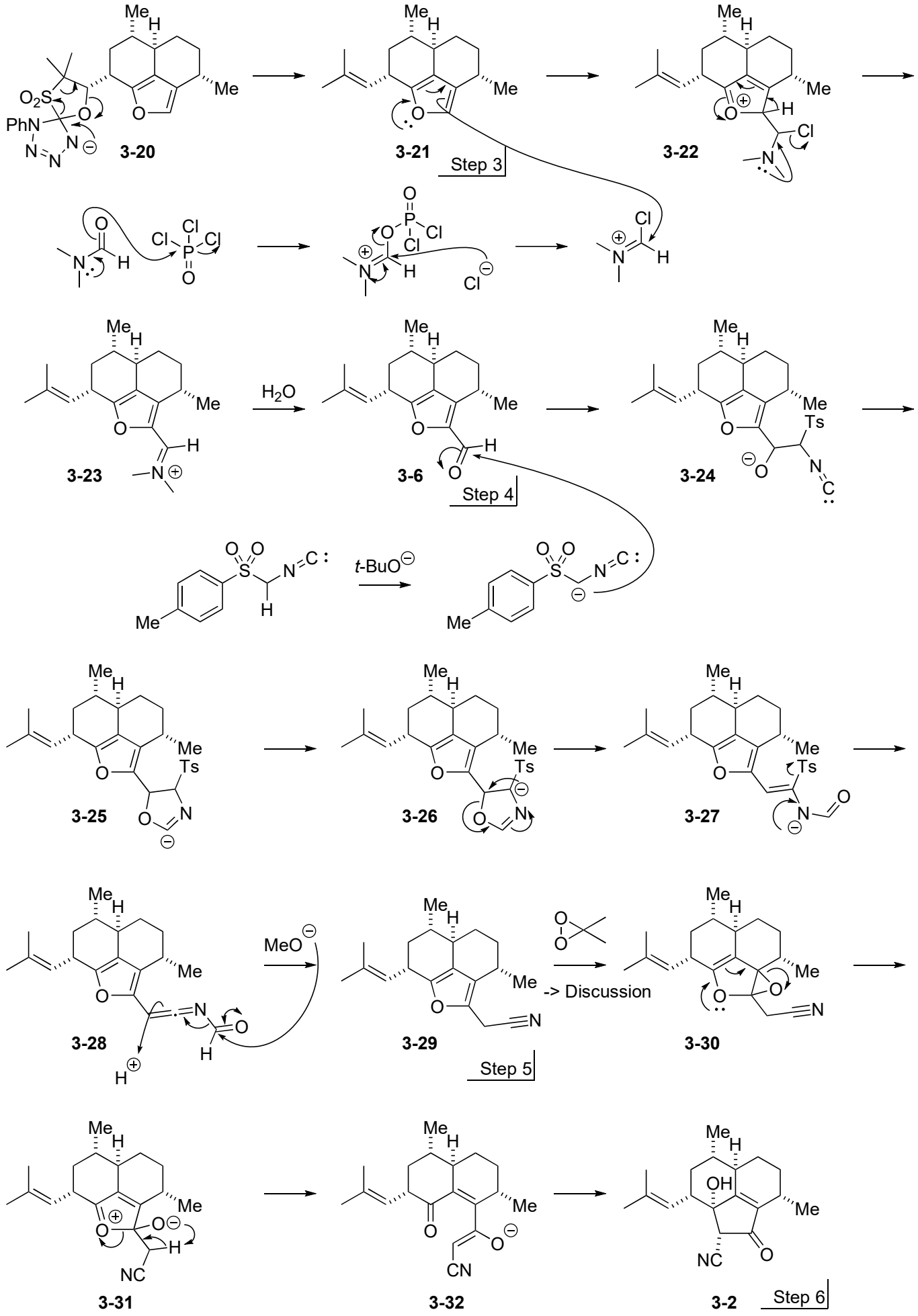
3.1. Retrosynthesis



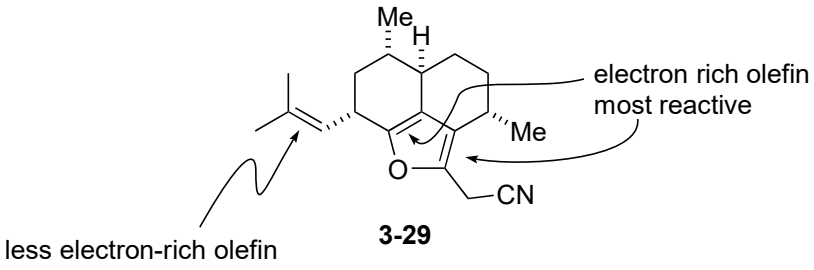
3.2. Answer



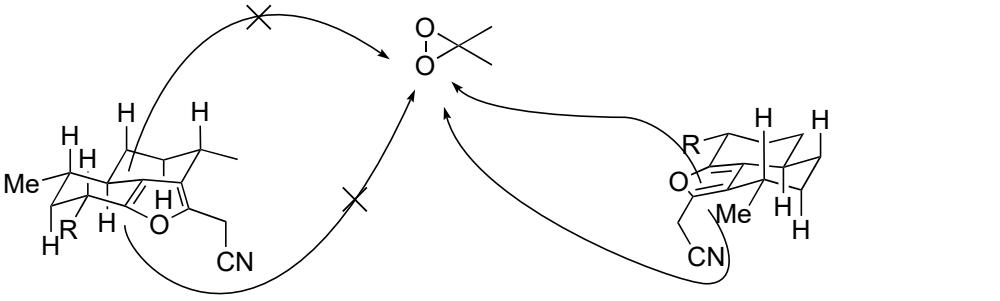

3-1
3-8
Step 1
3-9
3-10
3-11
3-12
3-13
3-14-eq
favor
3-14-ax
unfavor
3-15
3-16
3-17
D
3-18
3-19
Step 2
3-20


3-20
3-21
Step 3
3-22
3-23
H_2O
3-6
Step 4
3-24
t-BuO
3-25
3-26
3-27
3-28
MeO
3-29
-> Discussion
3-30
Step 5
3-31
3-32
3-2
Step 6

3.3. Discussion: DMDO oxidation
regioselectivity of oxidation step



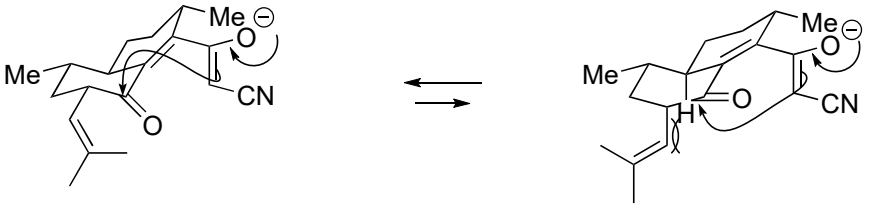
3-29



adjacent to two tertiary carbons
center of [6-6-5] tricyclic structure

adjacent to tertiary carbon & secondary carbon

diastereoselectivity of annulation step



3-32a
chair-like
favor

3-32b
boat-like
unfavor

3-2

3-2-*epi*