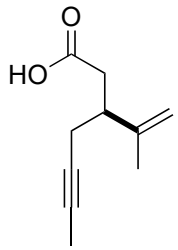
Problem Session (2)

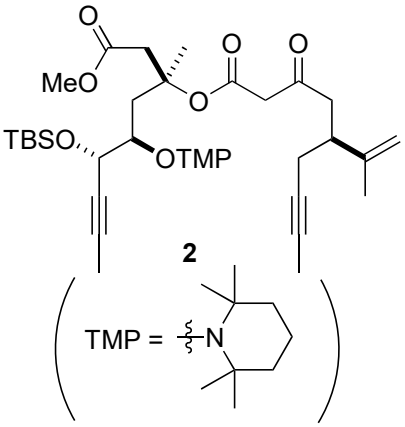
2019. 1. 12. Takahiro Watanabe

Please provide each reaction mechanisms, fill in the blank, and explain the stereoselectivities.



1

1. **A** (1.0 eq.), DCC (1.5 eq),
DMAP (20 mol%), Et_3N (2.0 eq.), CH_2Cl_2;
B (1.0 eq.), toluene, 60 °C, quant.



2

TMP =

2. Ac_2O (3.0 eq.), DMAP (20 mol%),
Et_3N (3.0 eq.), CH_2Cl_2, -40 °C
3. HF aq., THF, 73% (2 steps)

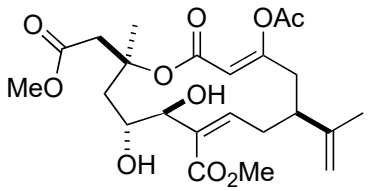
4. **C** (30 mol%), **D** (30 mol%),
toluene, 120 °C
5. Zn (40 eq.)
AcOH/ THF/H_2O (3/1/1), 76% (2 steps)

$C_{21}H_{28}O_8$ (**3**)
13-membered ring

6. Bu_3SnH (1.2 eq.), $[Cp^*RuCl]_4$ (11 mol%)
CH_2Cl_2, 66%

7. CO (1 atm), $Pd(OAc)_2$ (20 mol%),
$AsPh_3$ (40 mol%), 1,4-benzoquinone (1.5 eq.)
CF_3CO_2H (40 mol%), MeOH, 57%

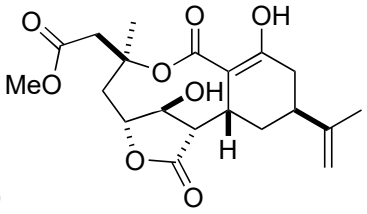
(Cp* = pentamethylcyclopentadienyl)



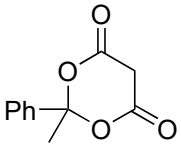
4

8. triphosgene (5.0 eq.)
CH_2Cl_2/pyridine (7:1), 0 °C, 97%

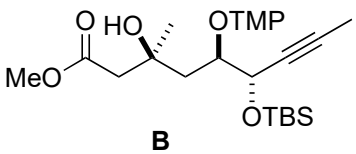
9. Cs_2CO_3 (11 eq.)
CH_2Cl_2/MeOH/H_2O (3:2:1), 86%
10. BBr_3 (17 eq.), 2-methyl-2-butene (12 eq.)
-15 °C, 72%



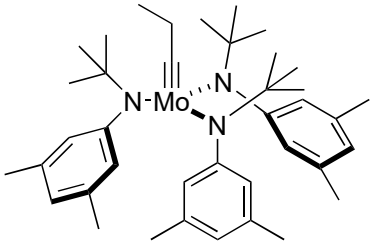
(-)-sinulariadiolide



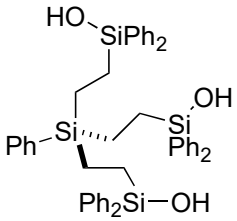
A



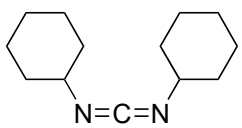
B



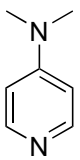
C



D



DCC



DMAP

Problem Session (2) -answer-

2019. 1. 12. Takahiro Watanabe

Topic: Total synthesis of (-) - Sinulariadiolide by Fürstner's group
(Fürstner et al. *J. Am. Chem. Soc*. in press.)

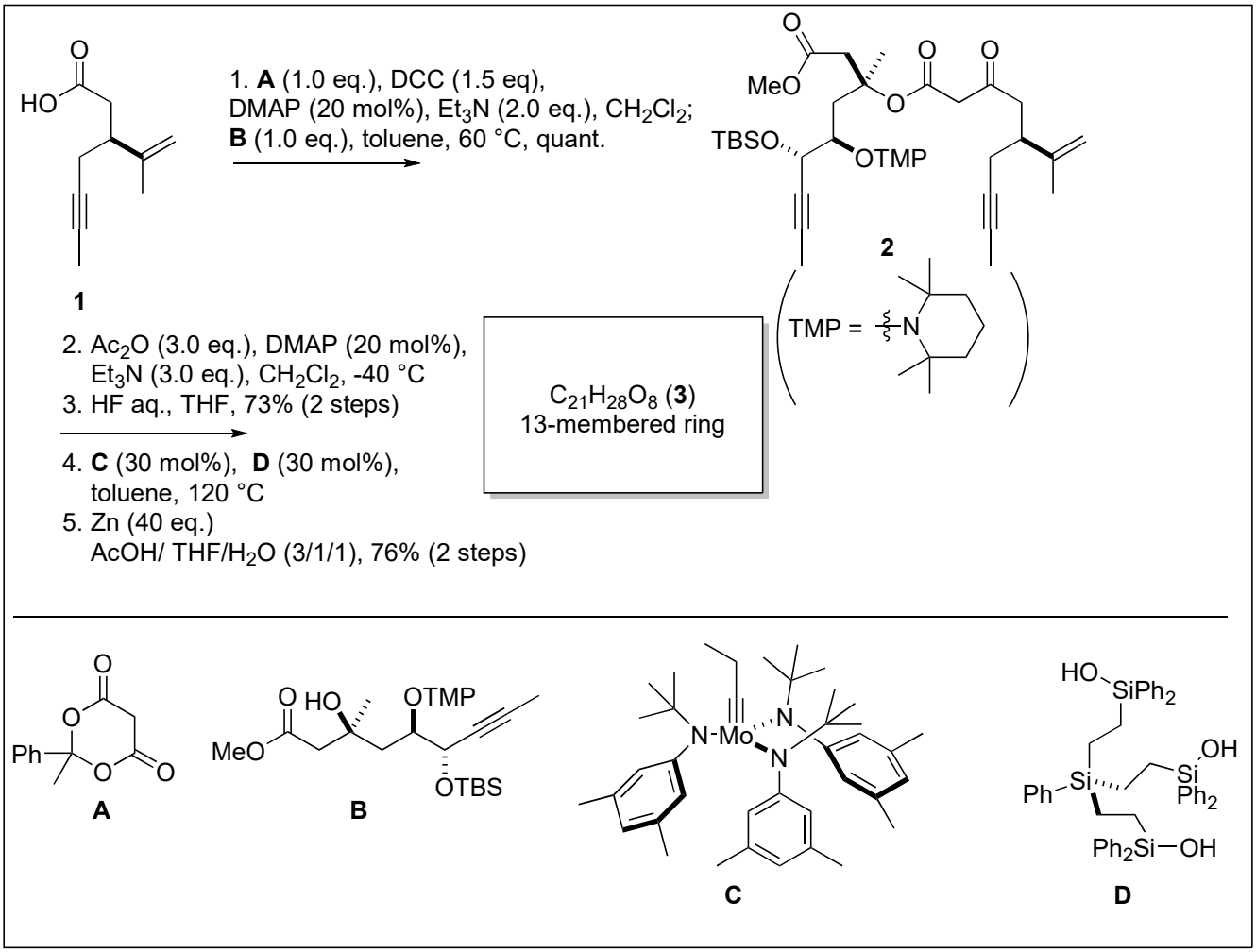
0. Introduction
0-1. Prof. Alois Fürstner

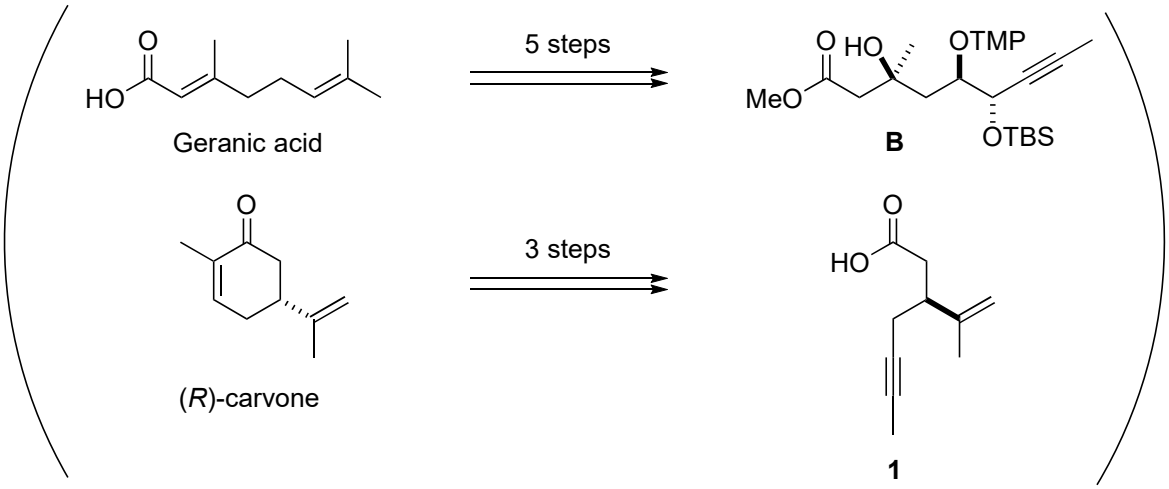
1987. PhD at the Technical University Graz, Austria (H. Weidmann)
1990-1991. Postdoctoral fellow at the University of Geneva, Switzerland (W. Oppolzer)
1993-1998. Group leader at the Max-Planck-Institut fur Kohlenforschung and Lecturer at the University of Dortmund
since 1998. Director at the Max-Planck-Institut fur Kohlenforschung and Professor at the Technical University of Dortmund

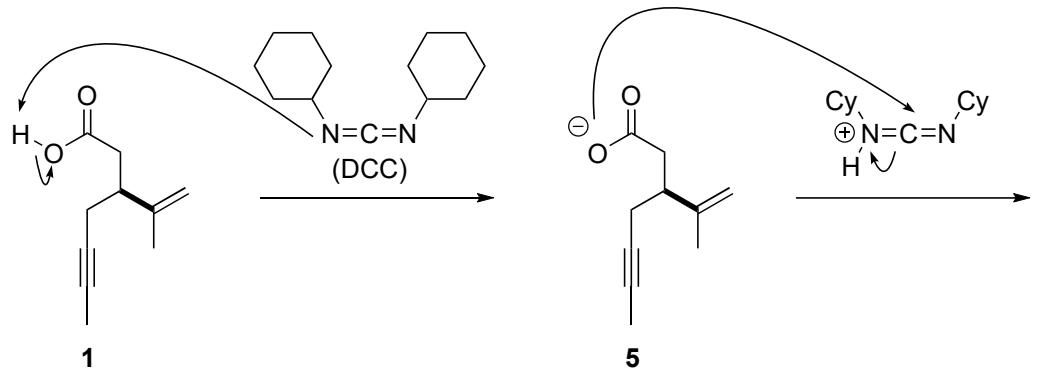
Research topic:
1. Alkyne metathesis
2. Alkene metathesis
3. π-acid catalysis
4. Iron catalysis
5. Novel concepts for catalysis
6. Total synthesis and evaluation of natural product

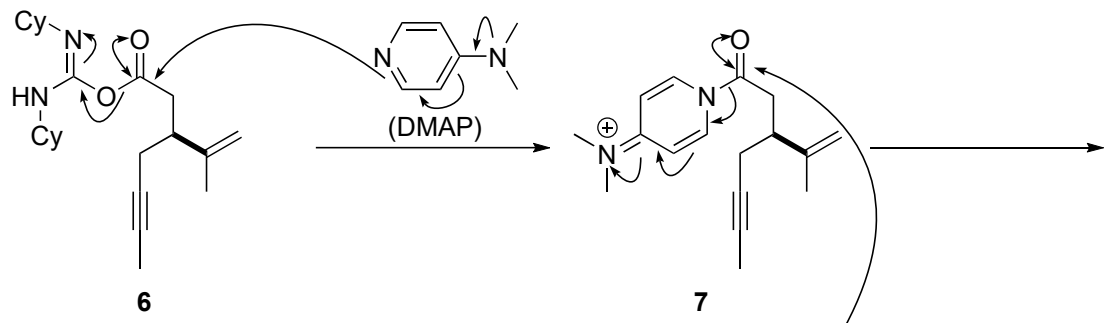
0-2. Sinulariadiolide
- isolatd from Okinawan *Sinularia* specimen (Yamada et al. *J. Org. Chem*. **1996**, *61*, 5998.)
- biological activity: unknown

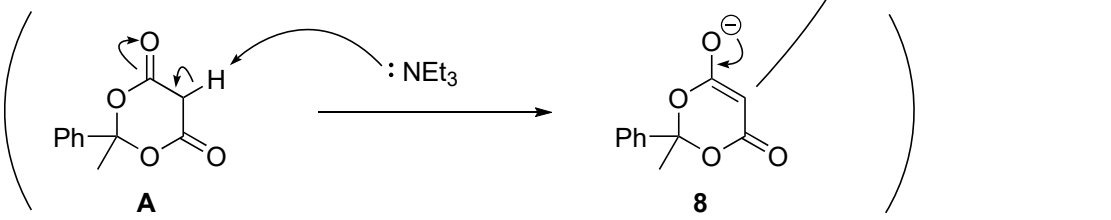
1. Reaction mechanisms
1-1. step1 to step5

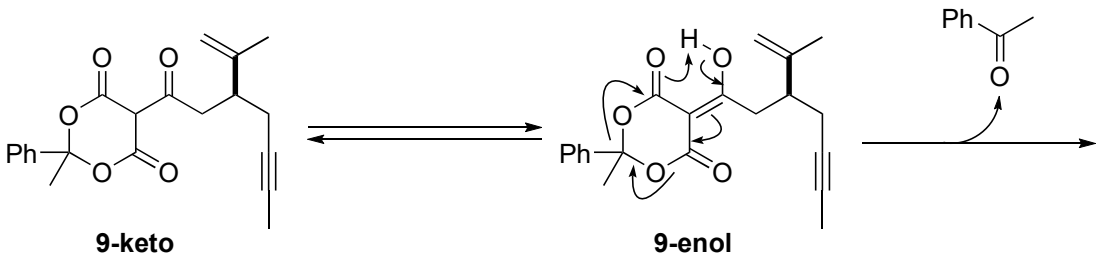


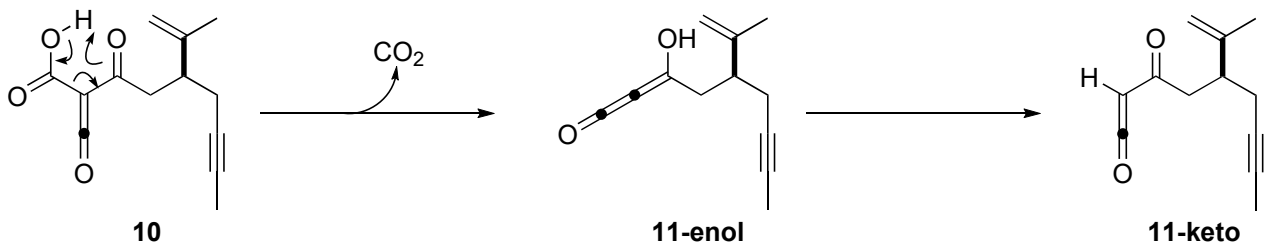

5 steps
Geranic acid
B
3 steps
(R)-carvone
1

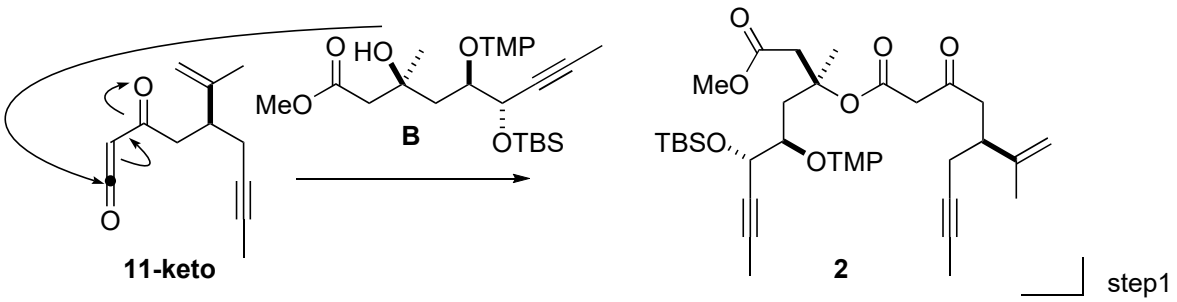

N=C=N
(DCC)
1
5

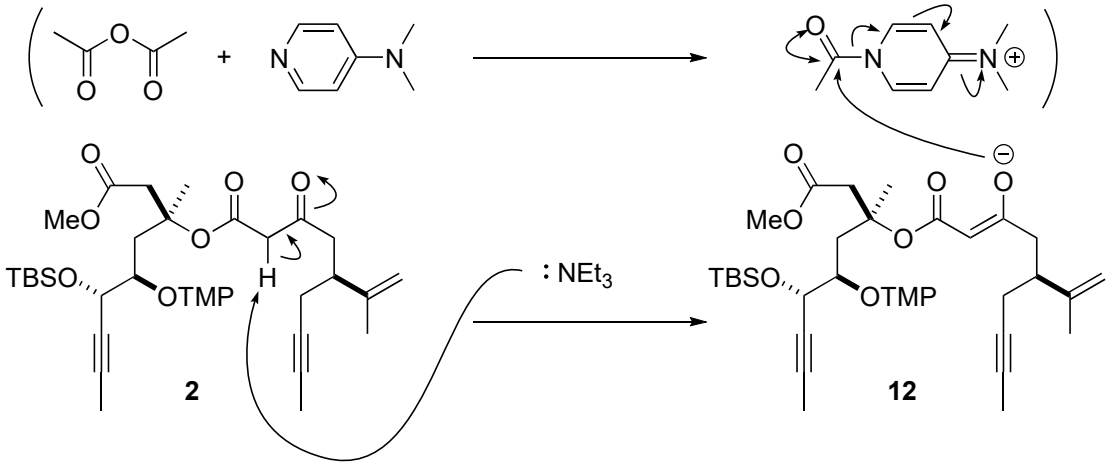

(DMAP)
6
7

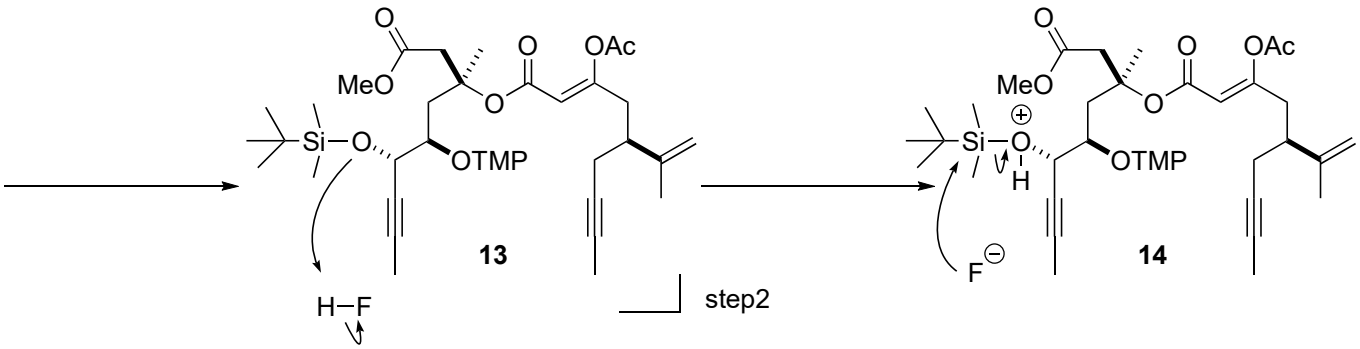

: NEt3
A
8

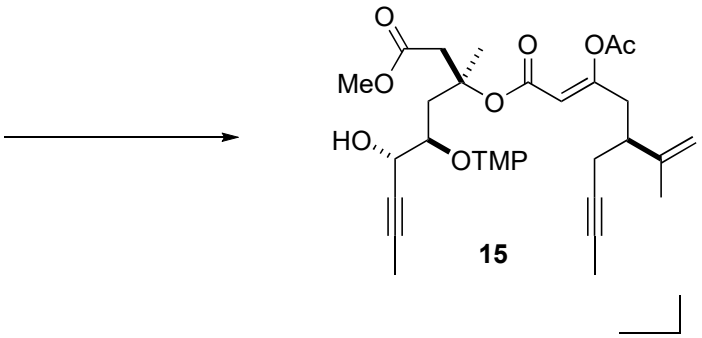

9-keto
9-enol


CO2
10
11-enol
11-keto

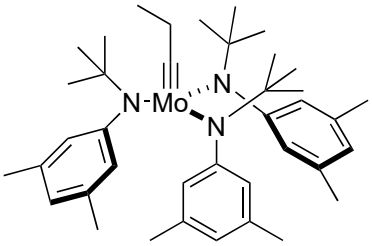

B
11-keto
2
step1


: NEt3
2
12

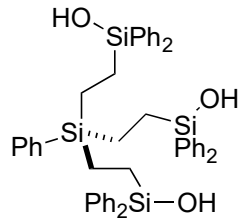

13
H–F
step2
14
F


15
step3

Step 4: Ring-Closing Alkyne Metathesis:
- Activation of catalyst precursor **C**

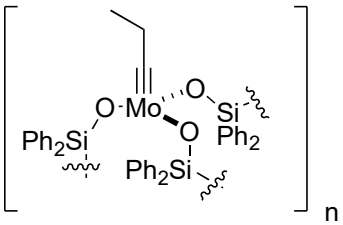


C (catalyst precursor)

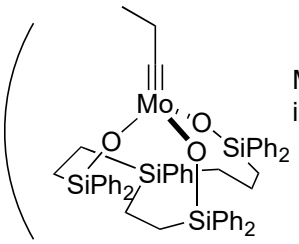


D

ligand exchange

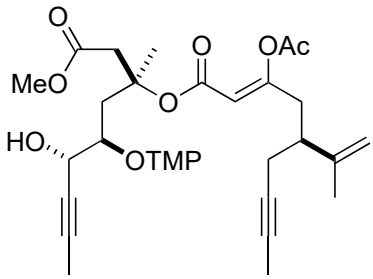


C* (active species, exist in oligomer?)

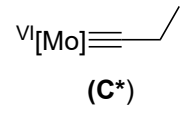


C**

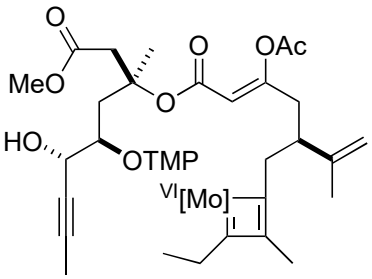
Monomeric chelate complex like **C**** is not obtained.



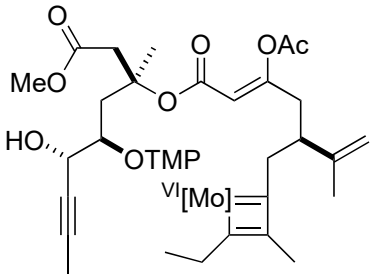
15



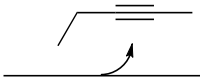
(C*)

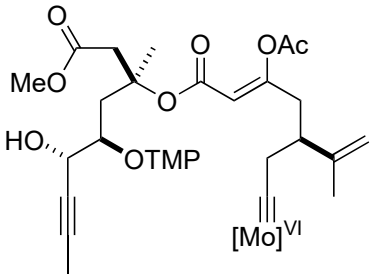


16

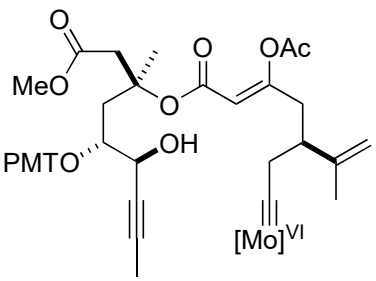


16'

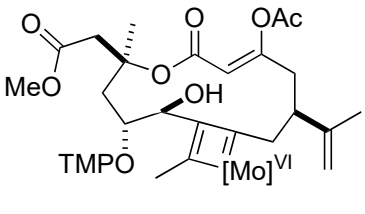




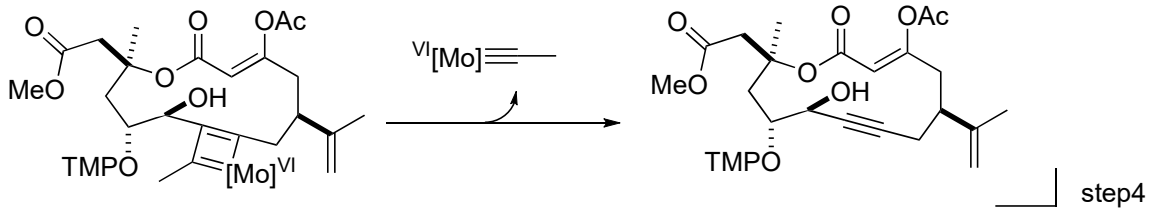
17



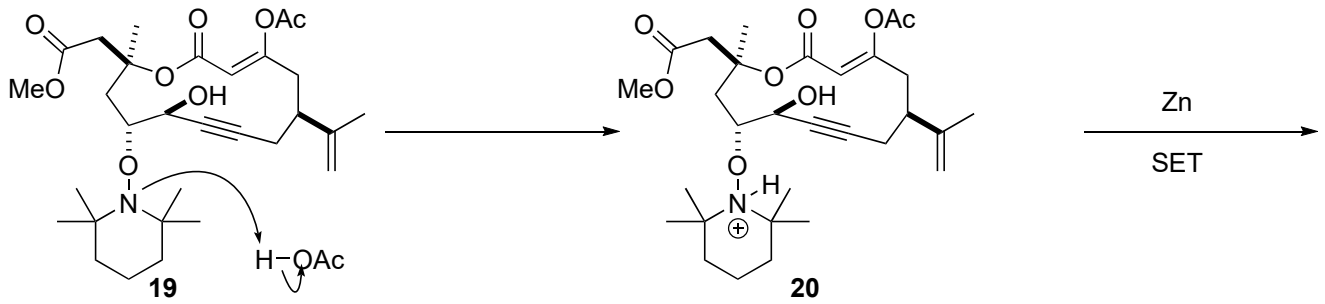
17



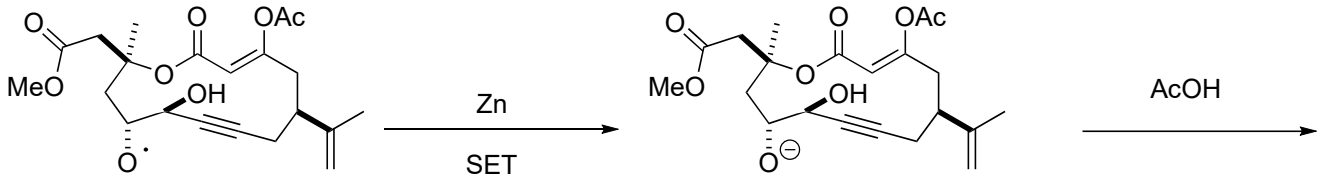
18



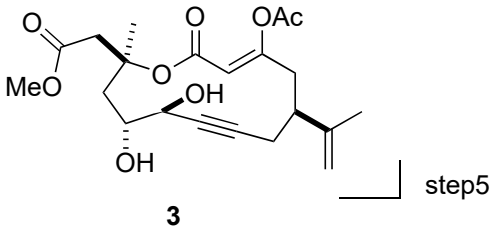
18' **19**



19 **20**



21 **22**



3

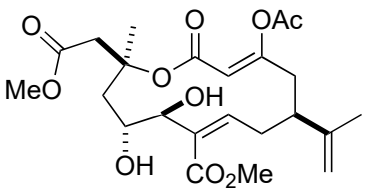
1-2. step 6 to step 10

$C_{21}H_{28}O_8$ (**3**)
13-membered ring

6. Bu_3SnH (1.2 eq.), $[Cp^*RuCl]_4$ (11 mol%)
CH_2Cl_2, 66%

7. CO (1 atm), $Pd(OAc)_2$ (20 mol%),
$AsPh_3$ (40 mol%), 1,4-benzoquinone (1.5 eq.)
CF_3CO_2H (40 mol%), MeOH, 57%

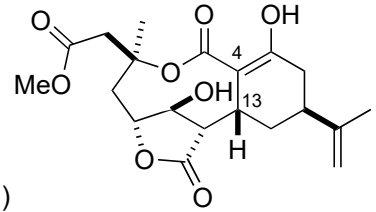
(Cp^* = pentamethylcyclopentadienyl)



4

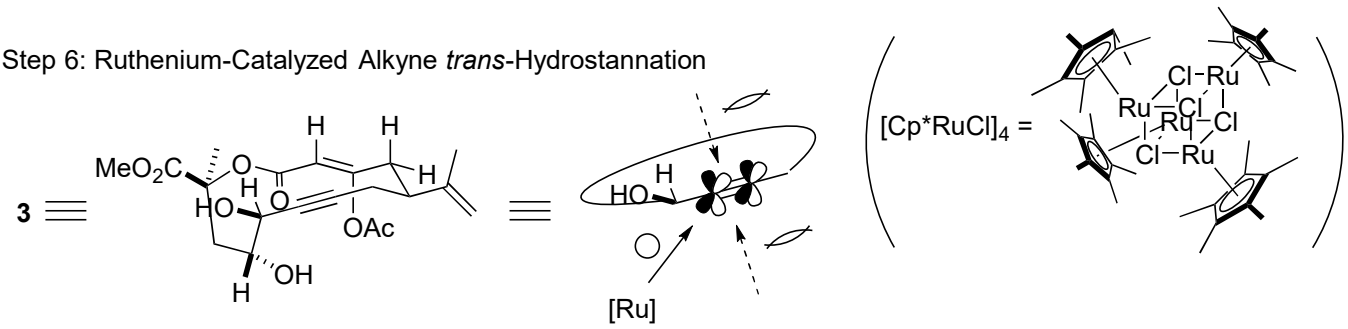
8. triphosgene (5.0 eq.)
CH_2Cl_2/pyridine (7:1), 0 °C, 97%

9. Cs_2CO_3 (11 eq.)
CH_2Cl_2/MeOH/H_2O (3:2:1), 86%
10. BBr_3 (17 eq.), 2-methyl-2-butene (12 eq.)
-15 °C, 72%



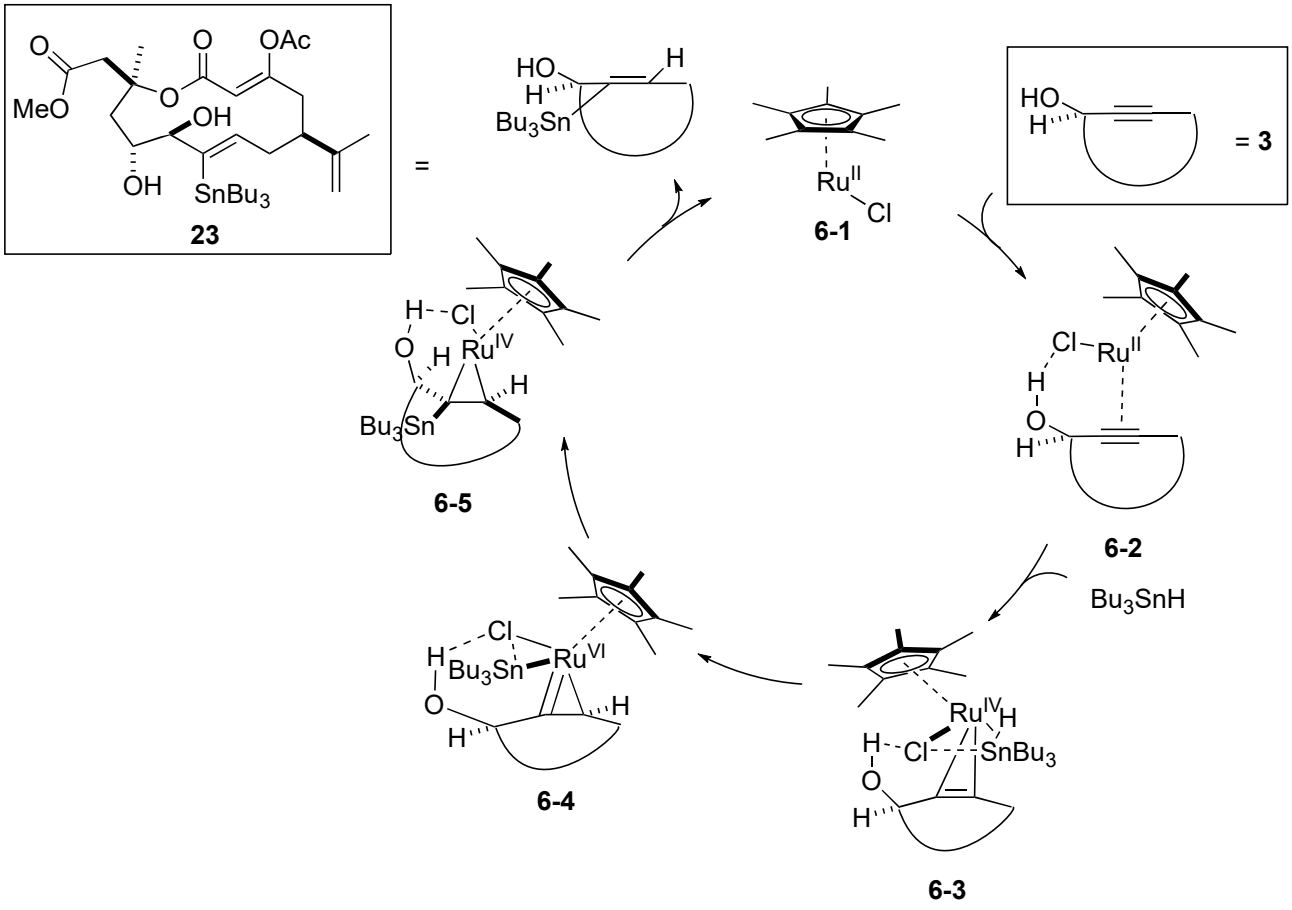
(-)-sinulariadiolide

Step 6: Ruthenium-Catalyzed Alkyne *trans*-Hydrostannation



[Ru] will approach from horizontal direction of 13-membered ring.

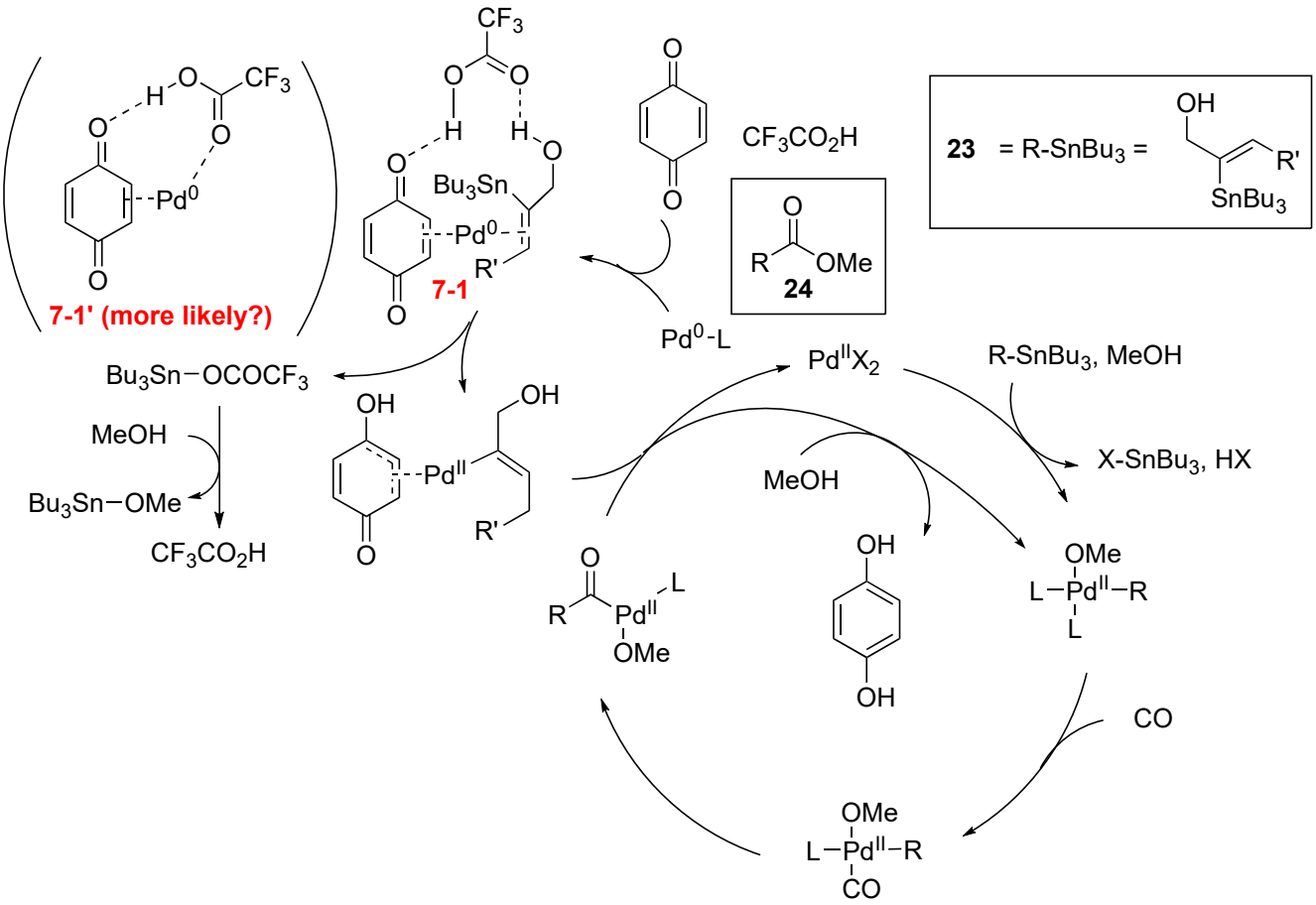
- Catalyst cycle



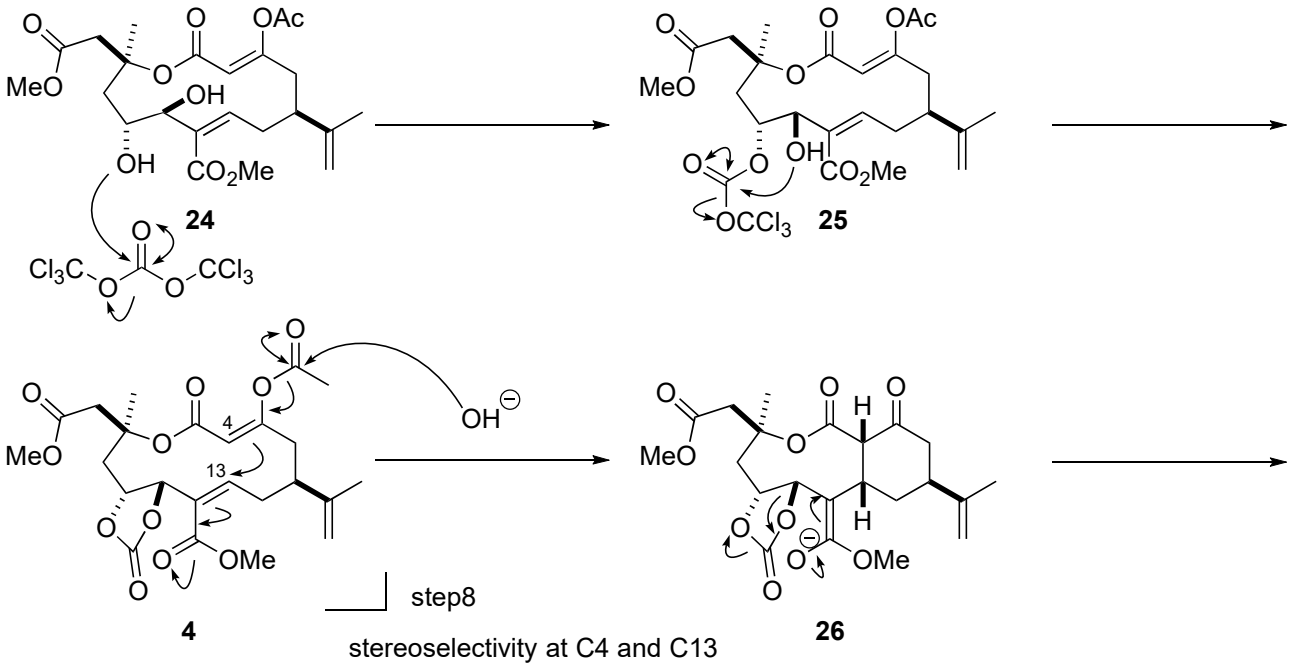
Comment: $[Cp^*RuCl]_4$ is cubic cluster, the Ru-Cl bonds of $[Cp^*RuCl]_4$ is quite labile and the cluster is easily broken up by donor ligands. (Fagan et al. *Organometallics* **1990**, *9*, 1843.)

6-1: Ru^{II} catalyst.
6-2: The position of the catalyst is determined by hydrogen bonding between OH group at propalgyl position and Cl atom.
6-3: It is thought that direction of coordinated Bu_3SnH is determined by Sn-Cl hypervalent interaction.
6-4: Hydride insertion occurs and rutenacyclopropene is formed.
6-5: Sn insertion

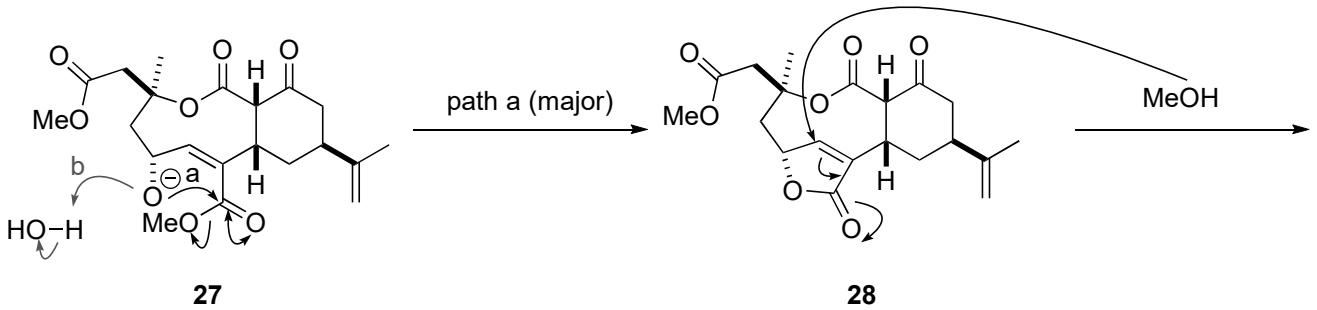
Step 7: Hydroxyl-Assisted Carbonylation of Alkenyitin Derivative
- Catalyst cycle

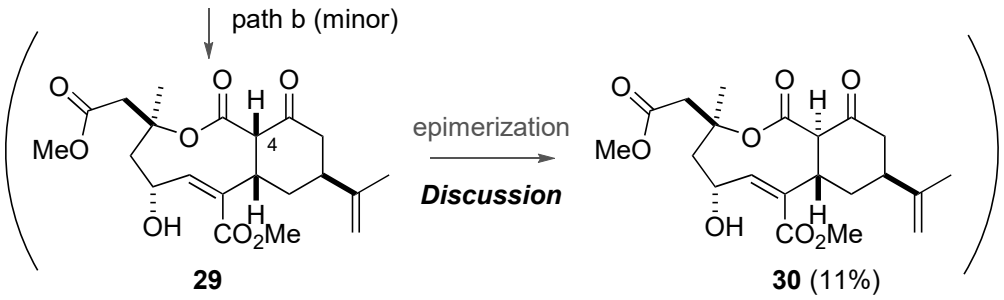


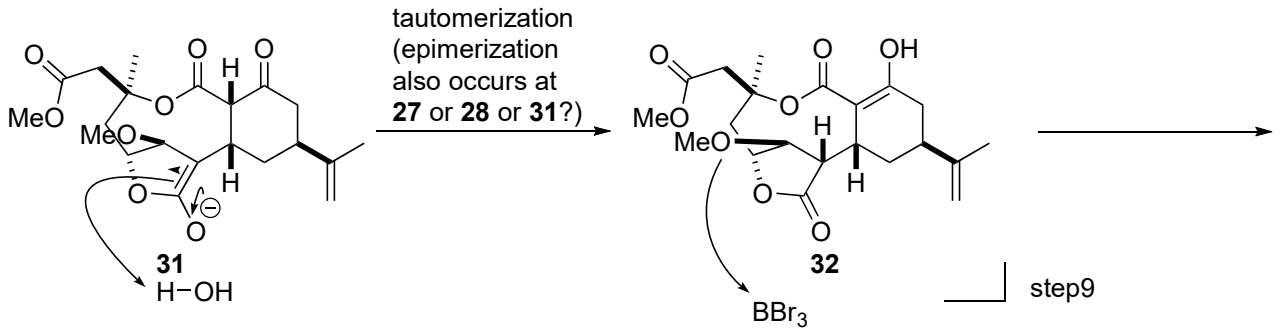
Comment:
7-1:
CF_3CO_2H is needed as co-catalyst for protonation of quinone, and oxidation of Pd_0 occurs. This is because Lewis acidity of organotin compound is so weak that MeOH cannot be used as proton source for quinone. (Fürstner et al. *Org. Lett*. **2016**, *18*, 3210.)



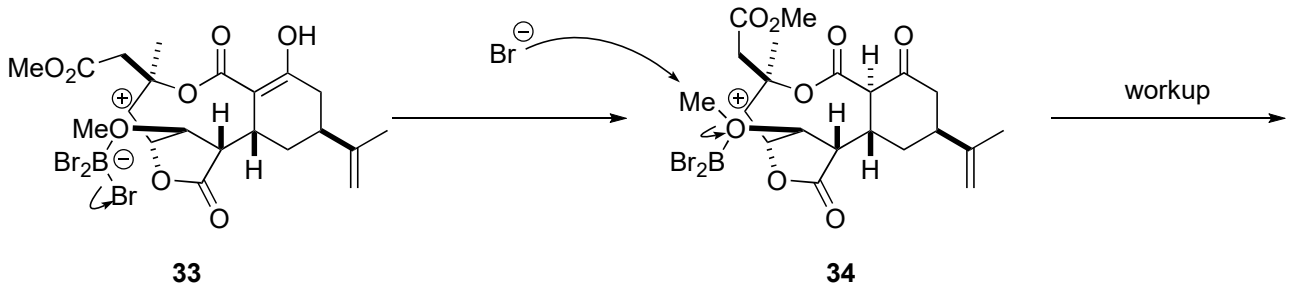
stereoselectivity at C4 and C13
-> ***Discussion***

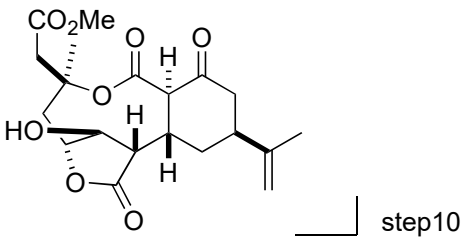






(attack of MeOH and protonation occurs
from outside of 9-membered ring)



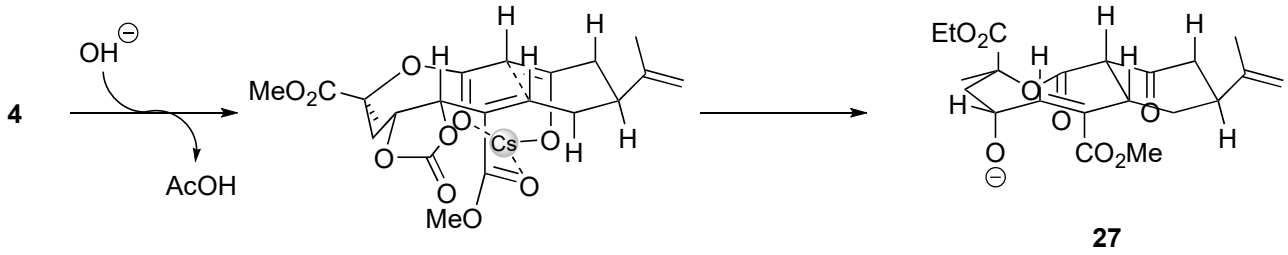


(-)-sinulariadiolide

Discussion: Stereoselectivity at ring junction, C4 and C13.

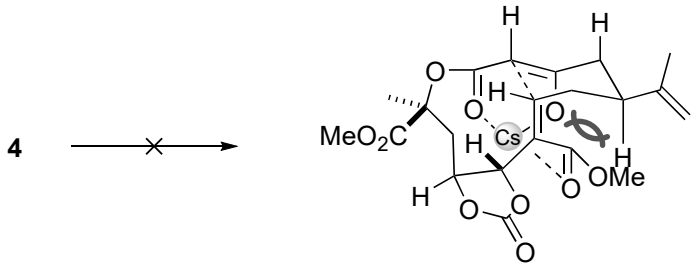
transannular chelation will occur by Cs^+.

Chelation model (Cs^+ and three O atoms)



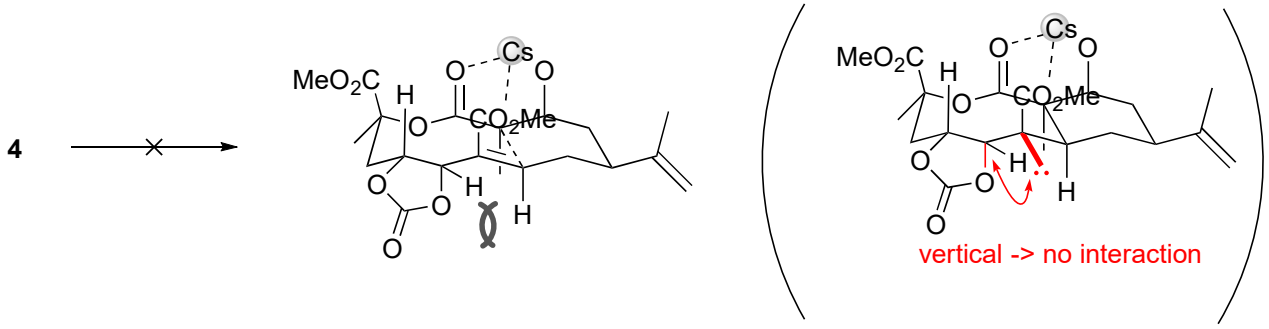
35-a

(potential boat form of newly arised 6-membered ring)



35-b

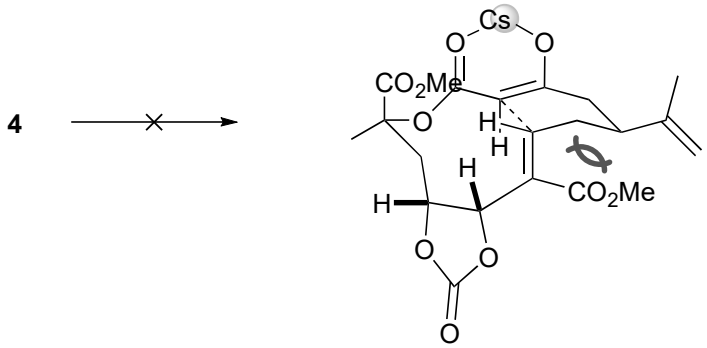
(potential chair form of newly arised 6-membered ring)



35-c

If C4-C13 bond formation occurs, the arised anion and C-O (red bond) will not be interacted. Therefore, carbonate cannot be removed.

another conformer which will give correct stereochemistry for C13 (transannular chelation does not occur):

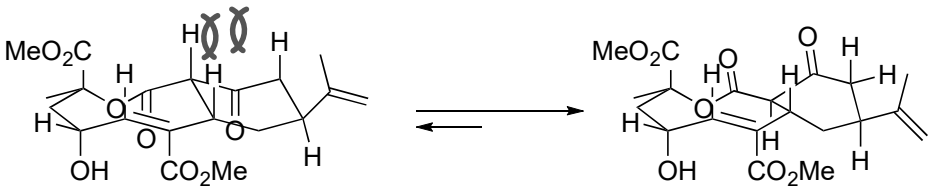


35-d

My argument:
When transannular chelation occurs, stereochemistry of H atom at C13 is up (**35-a** vs **35-c**);

When H atom at C13 is up,
1. Conformer **35-a** is likely (**35-a** vs **35-b** and **35-d**).
2. H atom at C4 is also up (**35-a**).

The minor path of **29** to **30**, epimerization might occur to avoid 1,2- and 1,3-diaxial interaction.



29-cis
(boat foam of 6-membered ring)

29-trans
(twist-chair foam of 6-membered ring)

Appendix: Relative stereochemistry of sinulariadiolide was determined as below.
(Yamada et al. *J. Org. Chem.* **1996**, *61*, 5998.)

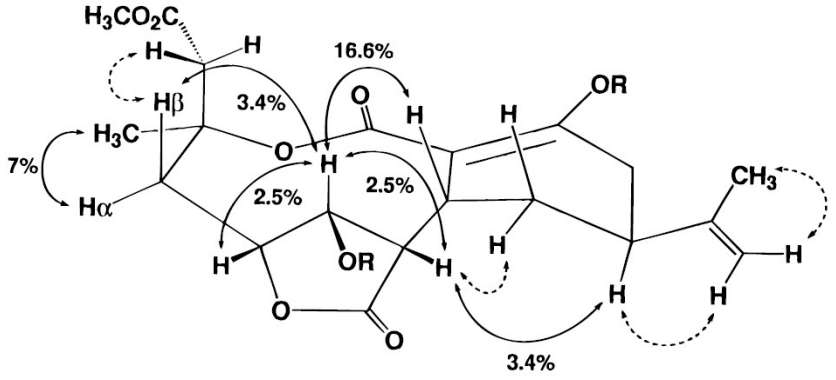


Figure 2. Relative stereochemistry and NOE correlations of **1** (R = H, NOE shown by dotted-line arrows) and **5** (R = Ac, NOE shown by full-line arrows).