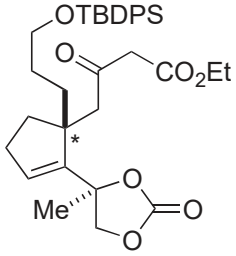
Problem session 3

2016. 11. 19
D1 Kosuke Minagawa

Please fill in blanks and provide the mechanism of the following reactions.

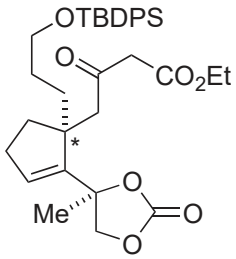
(1)



1-1a

$Pd(PPh_3)_4$
EtOH, 80 °C

($C_{33}H_{42}O_4Si$)
bicyclic compound
1-2

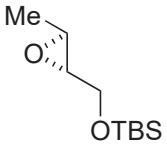


1-1b

$Pd(PPh_3)_4$
EtOH, 80 °C

($C_{31}H_{38}O_4Si$)
tricyclic compound
1-3

(2)



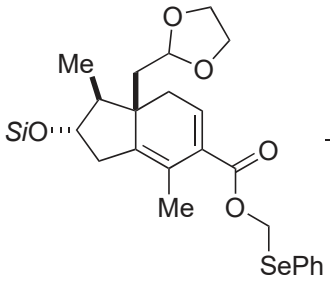
2-1

1. **2-2**, Mg, CuI, THF, 59%
2. TBAF, THF, 0 °C, 81%
3. TsCl (1.2 eq.), Et_3N, DMAP, CH_2Cl_2, 0 °C, 92%
4. NaH, THF, 0 °C, 76%
5. **2-3**, $BF_3{\cdot}OEt_2$, 0 °C, 91%

($C_{13}H_{20}O_3$)
enyne
2-4

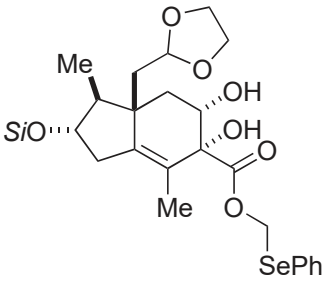
1. **2-5**, Ti(O*i*-Pr)$_4$, *n*-BuLi toluene, -78 to 50 °C; PhCHO*, 73%
2. TBAF, DMSO, 100 °C, 65%
3. TBDPSCl, imid., CH_2Cl_2, 96%
4. MeLi, THF, -78 °C; CO_2
5. $PhSeCH_2Cl$, *i*-Pr_2NEt NaI, DME, 50% (2 steps)

*Benzaldehyde is used as a quencher



2-6 (*Si* = TBDPS)

OsO_4, pyridine
THF, 0 °C, 85%



2-7 (*Si* = TBDPS)

2-7
($C_{23}H_{29}O_7SeSi$)

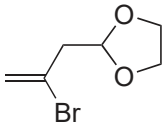
conditions

($C_{17}H_{25}O_7Si$)
2-8

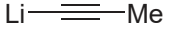
+

($C_{17}H_{25}O_7Si$)
2-9

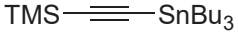
conditions	ratio (**2-8** : **2-9**)	
AIBN, *n*-Bu_3SnH benzene, 80 °C	1 :	1.4
AIBN, TMS_3SiH benzene, 80 °C	1 :	4.7



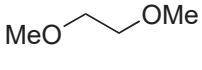
2-2



2-3



2-5

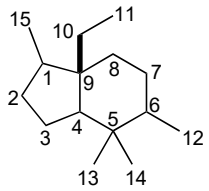


DME

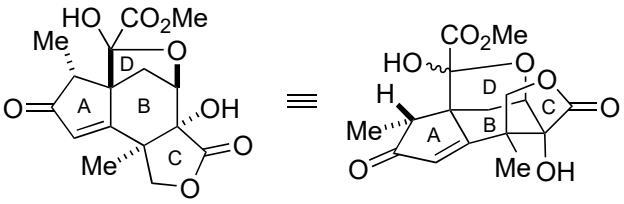
2016. 11. 19 D1 Kosuke Minagawa

Problem Session (3) - Answer

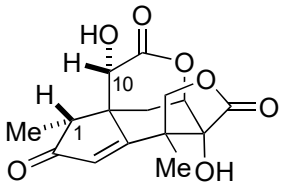
Topic: total synthesis of (-)-Jiadifenin



seco-prezizaane type skeleton

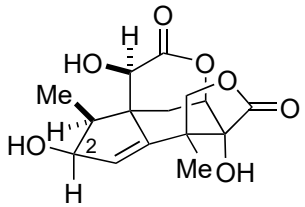


(-)-jiadifenin (1)



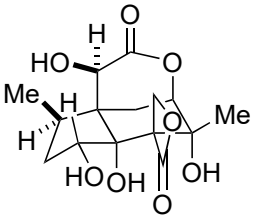
(*1R, 10S*)-2-exo-3,4-dehydro neomajucin

0-1



(*2S*)-hydroxy-3,4-dehydro neomajucin

0-2



anisatin

0-3

total synthesis	Micalizio, G. C. et al. *J. Am. Chem. Soc.* **2016**, *138*, 1150.	Fukuyama, T. et al. *Org. Lett.*, **2012**, *14*, 1632.

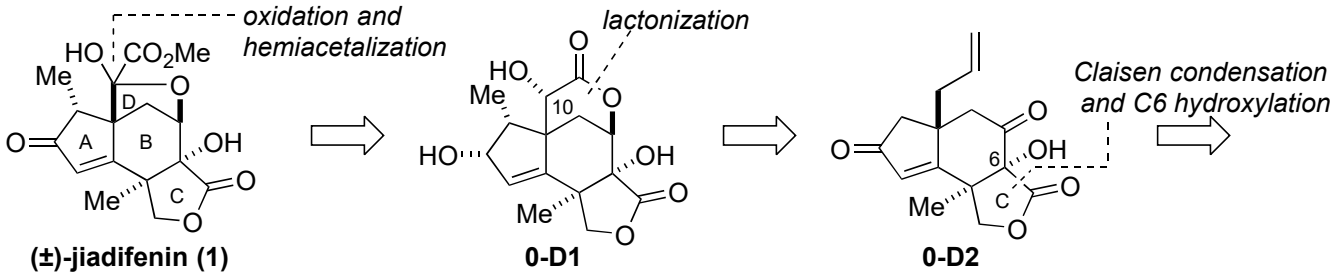
·Isolation of jiadifenin:
from Illicium jiadifengpi (Fukuyama, Y. *et al J. Nat. Prod.* **2002**, *65*, 527.)

·Bioactivity:
promoto neurite outgrowth(神経突起伸長) –> Alzheimer's disease and Parkinson's disease
(Chauhan, N. B. *et al Brain Res. Rev.* **2000**, *33*, 199.)

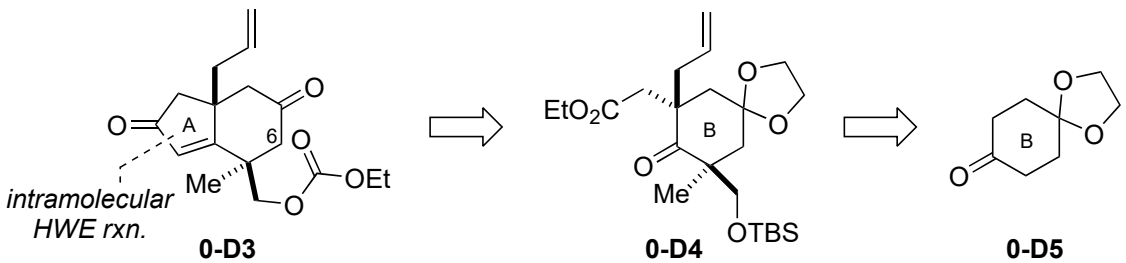
·Structural features:
- highly oxygenated cagelike structure possessing a γ-lactone
- a cyclic hemi-acetal
- 6 stereocenters including 2 quaternary centers

·total synthesis of (-)-jiadifenin:
Danishefsky, S. J. *et al. J. Am. Chem. Soc*. **2004**, *126*, 14358. (racemic)
Theodorakis, E. A. *et al*. Org. Lett. **2011**, *13*, 4554.
Zhai, H. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 9825.
Masuda Keisuke-san's LS (2012.09.08)
Fukuyama, Y. *et al*. *Tetrahedron*, **2015**, *71*, 2199. (formal synthesis) ->problem (1)
Micalizio, G. C. et al. *J. Am. Chem. Soc*. **2016**, *138*, 1150. ->problem (2)

Danishefsky (racemic, **2004**)



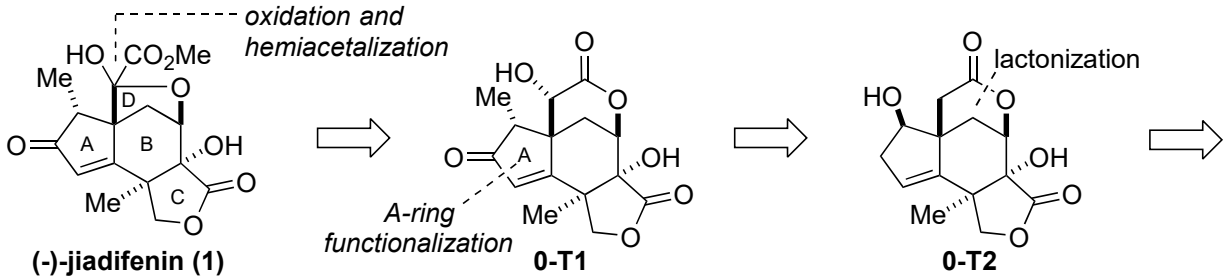
(±)-jiadifenin (1) **0-D1** **0-D2**

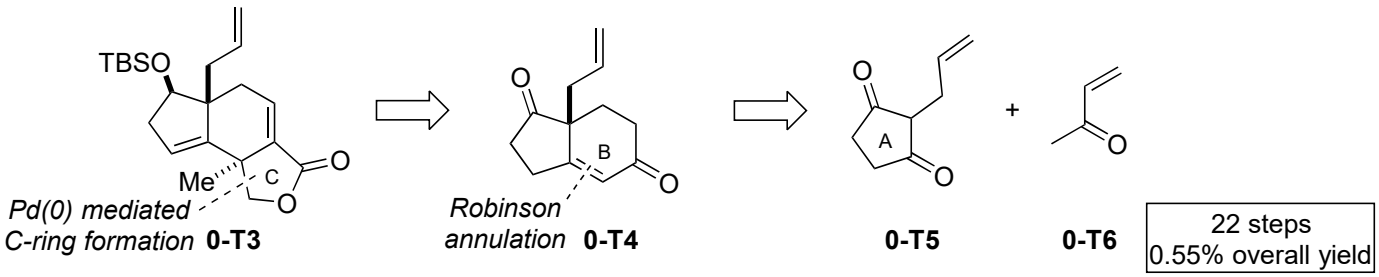


0-D3 **0-D4** **0-D5**

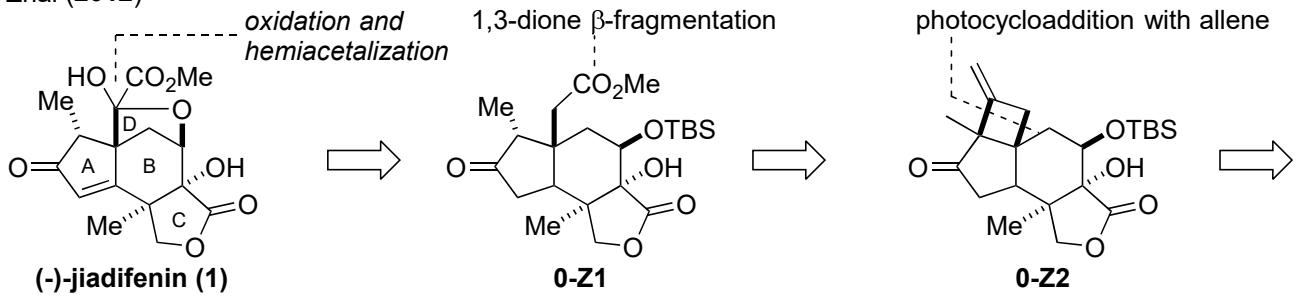
14 steps
1.7% overall yield

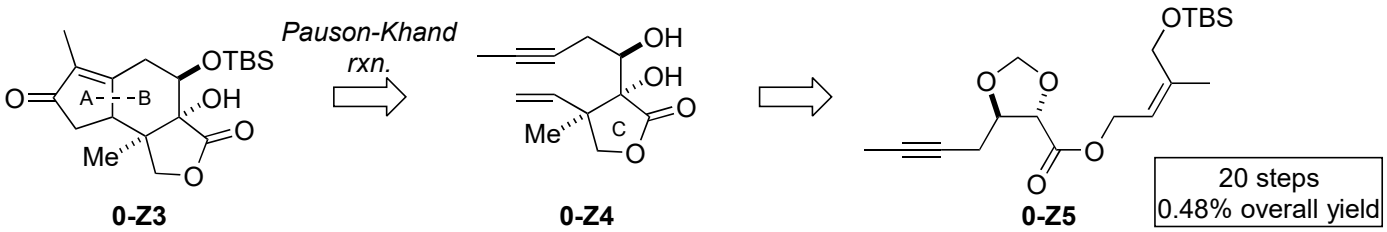
Theodorakis (**2011**)





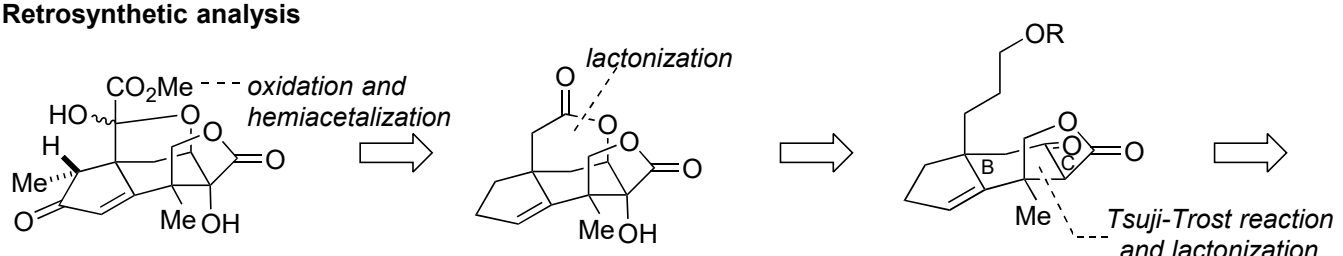
Zhai (**2012**)

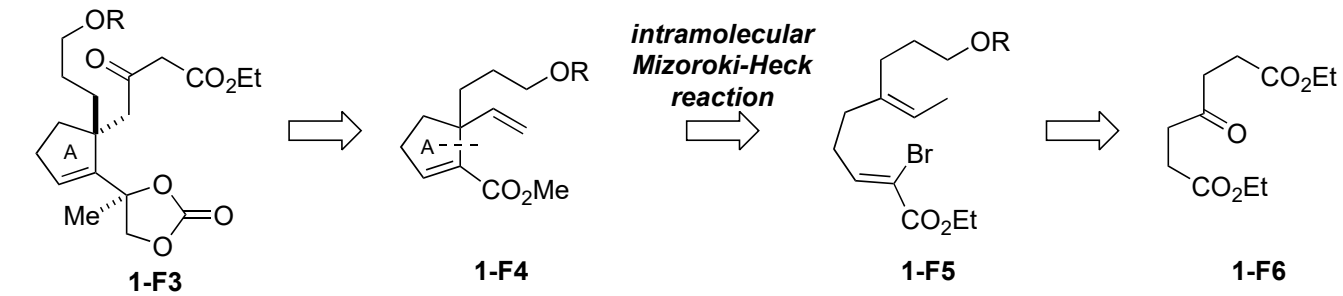




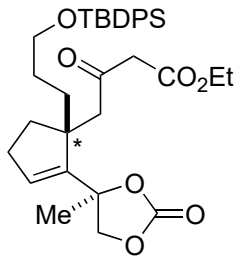
Problem 1
Fukuyama's group (Mizoroki-Heck and Tsuji-Trost reactions)

Retrosynthetic analysis





(1)

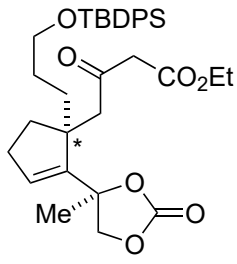


1-1a

$Pd(PPh_3)_4$

EtOH, 80 °C

($C_{33}H_{42}O_4Si$)
bicyclic compound
1-2



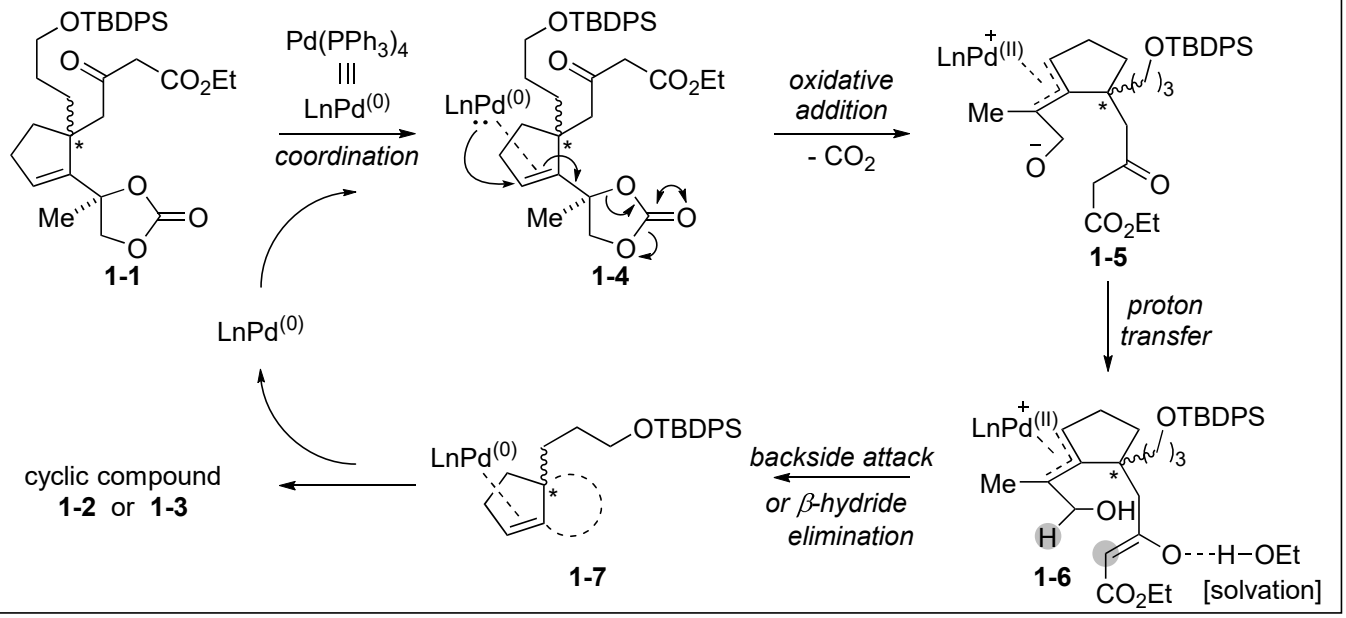
1-1b

$Pd(PPh_3)_4$

EtOH, 80 °C

($C_{31}H_{38}O_4Si$)
tricyclic compound
1-3

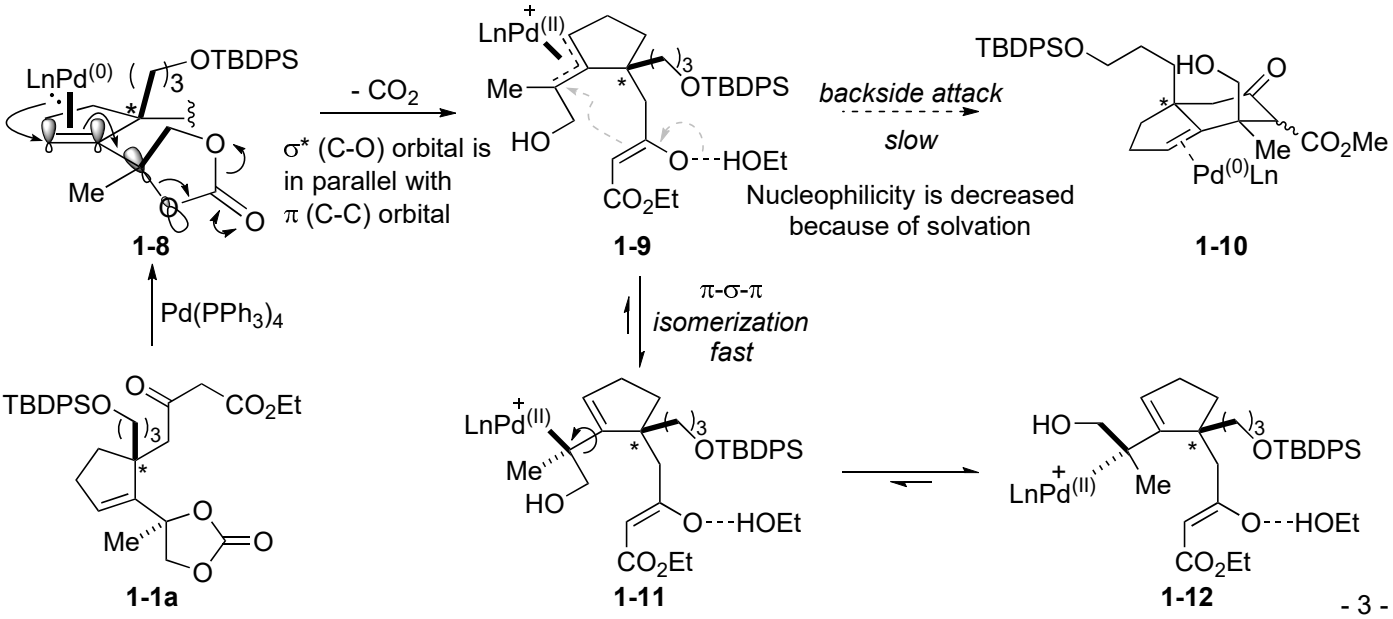
Tsuji-Trost Cyclization (Palladium cycle)

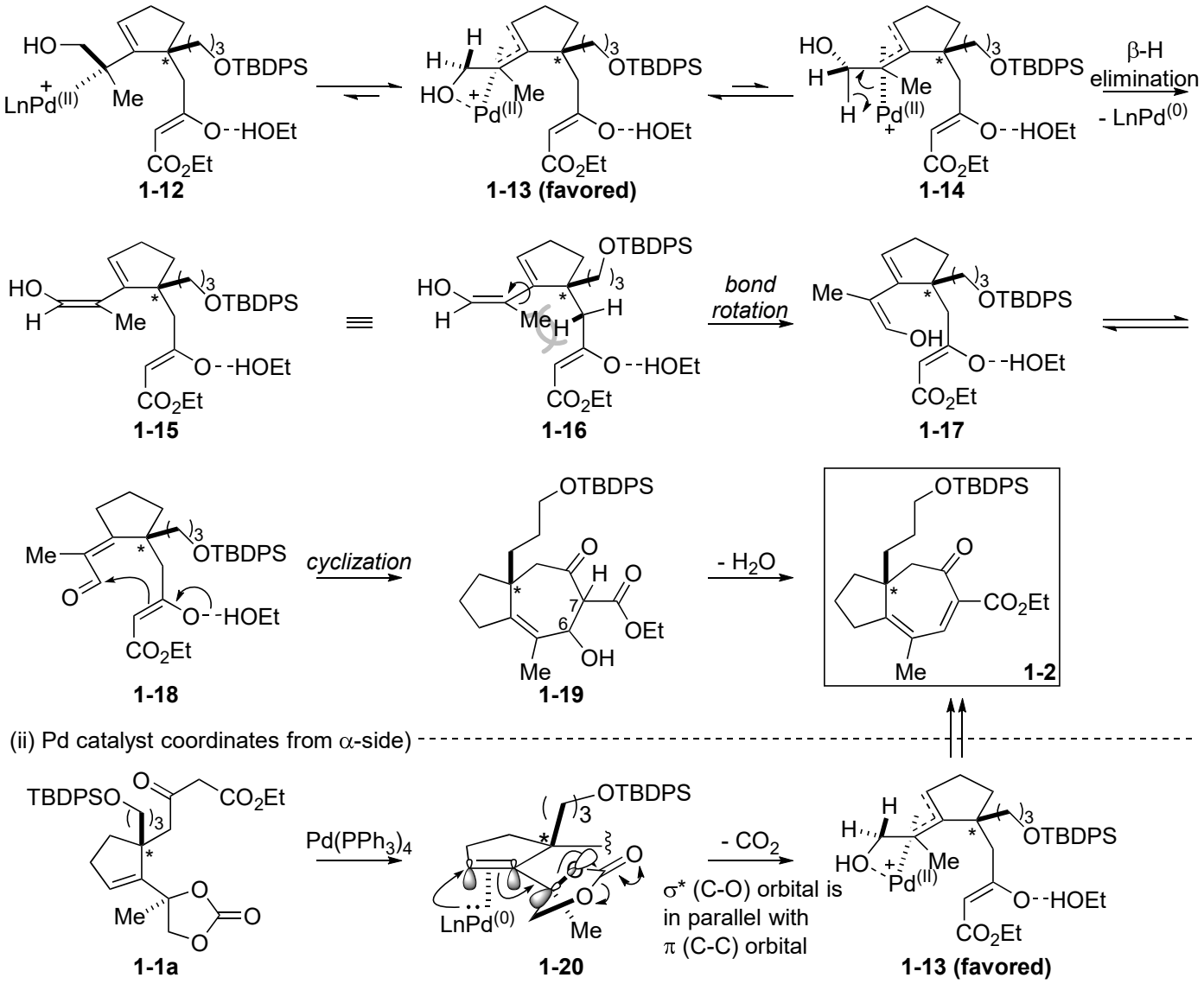


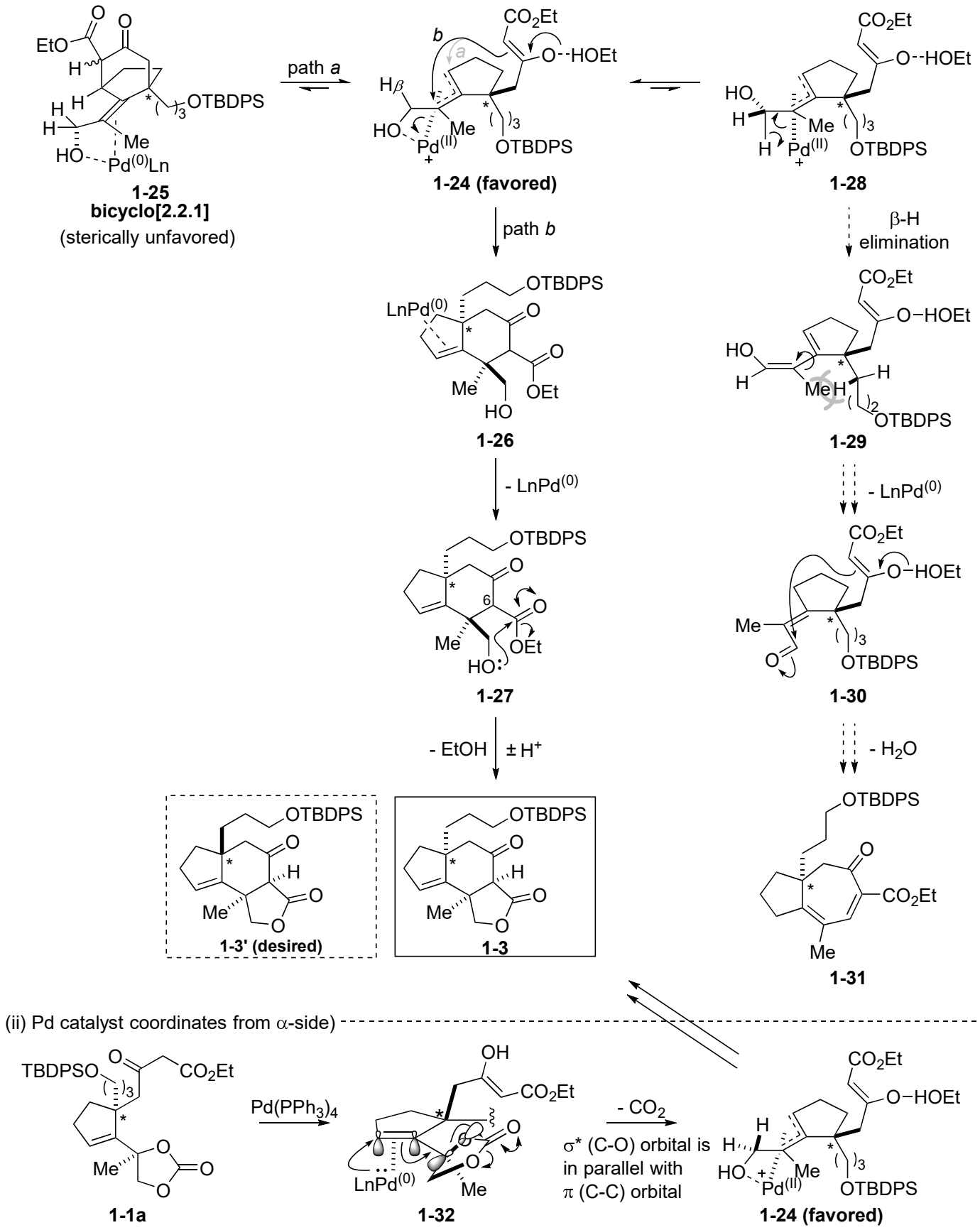
Answer

1-1a ⟶ bicyclic compound **1-2**

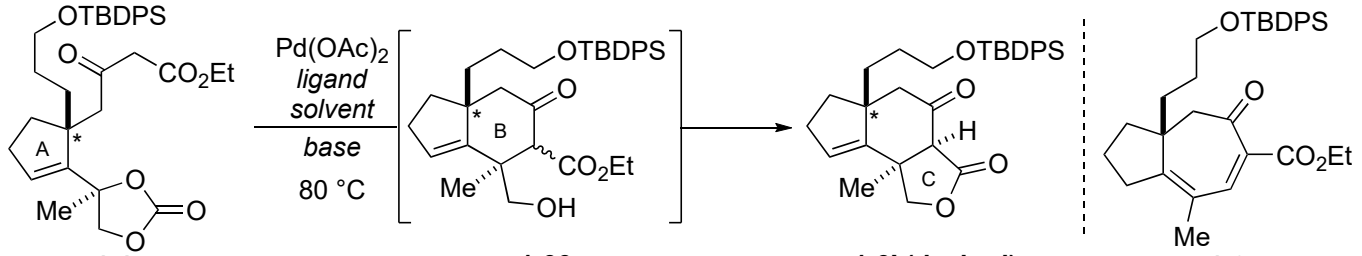
(i) Pd catalyst coordinates from β-side)




HO
OTBDPS
LnPd(II)
Me
O--HOEt
CO2Et
1-12
1-13 (favored)
1-14
β-H elimination
- LnPd(0)
1-15
1-16
1-17
bond rotation
cyclization
1-18
1-19
- H2O
1-2
(ii) Pd catalyst coordinates from α-side)
TBDPSO
Pd(PPh3)4
LnPd(0)
1-1a
1-20
- CO2
σ* (C-O) orbital is in parallel with π (C-C) orbital
1-13 (favored)
1-1b ⟶ tricyclic compound 1-3
(i) Pd catalyst coordinates from β-side)
1-1b
1-8'
1-21
π-σ-π isomerization fast
1-22
1-23
1-24 (favored)

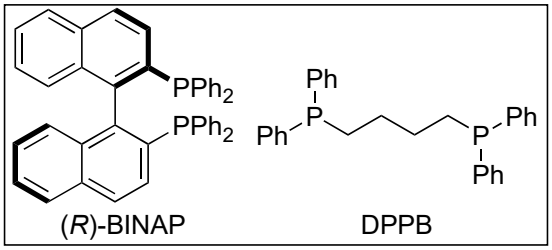

1-25
bicyclo[2.2.1]
(sterically unfavored)
path a
1-24 (favored)
1-28
path b
β-H
elimination
1-26
1-29
- LnPd(0)
1-27
1-30
- EtOH
± H+
- H2O
1-3' (desired)
1-3
1-31
(ii) Pd catalyst coordinates from α-side)
1-1a
Pd(PPh3)4
1-32
- CO2
σ* (C-O) orbital is
in parallel with
π (C-C) orbital
1-24 (favored)

Examination of the tandem Tsuji-Trost cyclization / lactonization reaction of 1-1a



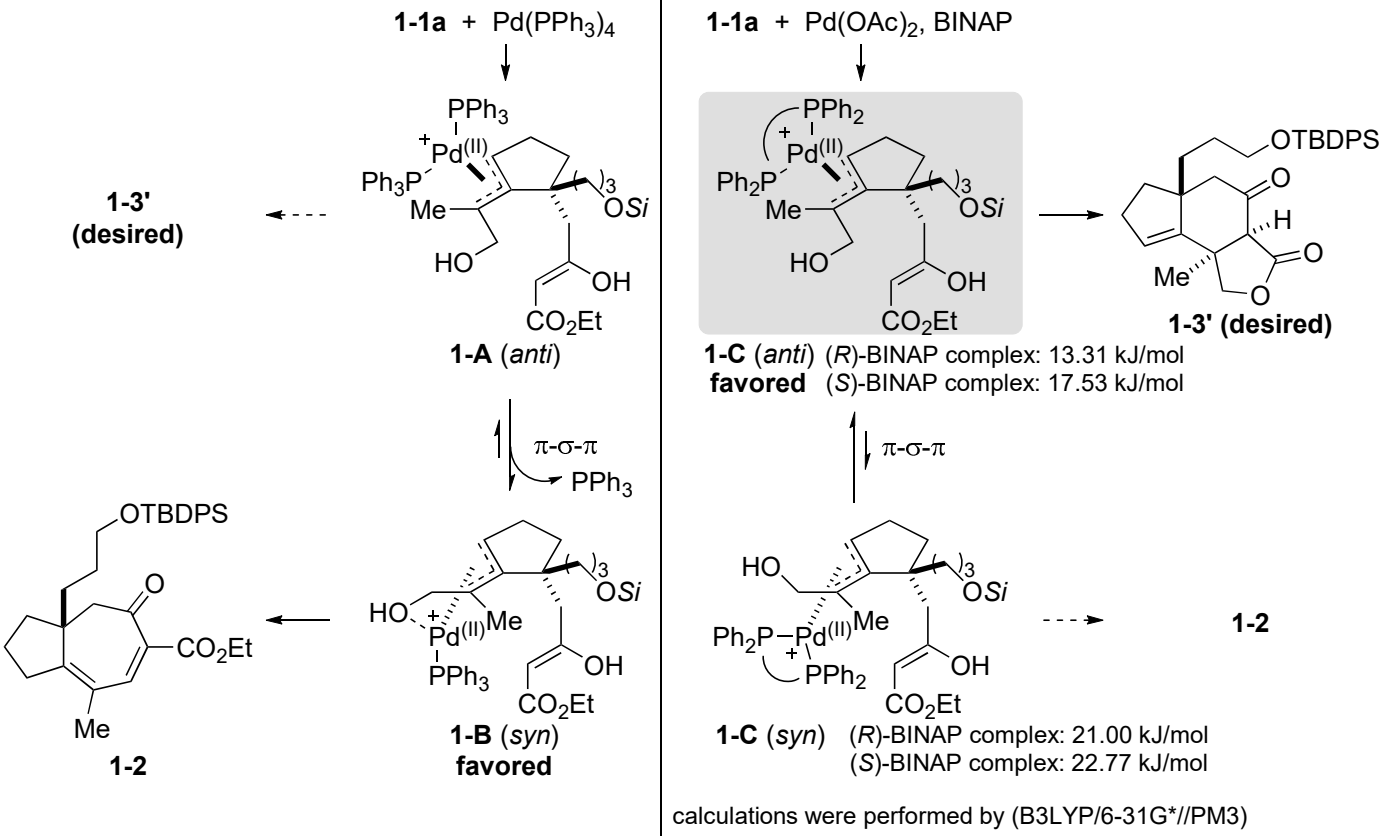
1-1a **1-33** **1-3' (desired)** **1-2**

entry		*ligand*	*solvent*	LiOAc (equiv.)	yields (%)		
					1-33	**1-3'**	**1-2**
1		*n*-Bu_3P	EtOH	—	—	—	major product
2	monodentate	*t*-Bu_3P	EtOH	—	—	—	major product
3		Cy_3P	EtOH	—	—	—	major product
4		DPPB	EtOH	—	—	22	28
5		(*R*)-BINAP	EtOH	—	23	27	—
6		(*R*)-BINAP	*t*-BuOH	—	13	38	—
7	bidantate	(*R*)-BINAP	*t*-BuOH	0.5	13	45	—
8		(*R*)-BINAP	*t*-BuOH	1.2	20	48	—
9		(*R*)-BINAP	*t*-BuOH	2.4	9	57	—
10		(±)-BINAP	*t*-BuOH	2.4	trace	65	—



(*R*)-BINAP DPPB

monodentate bidantate

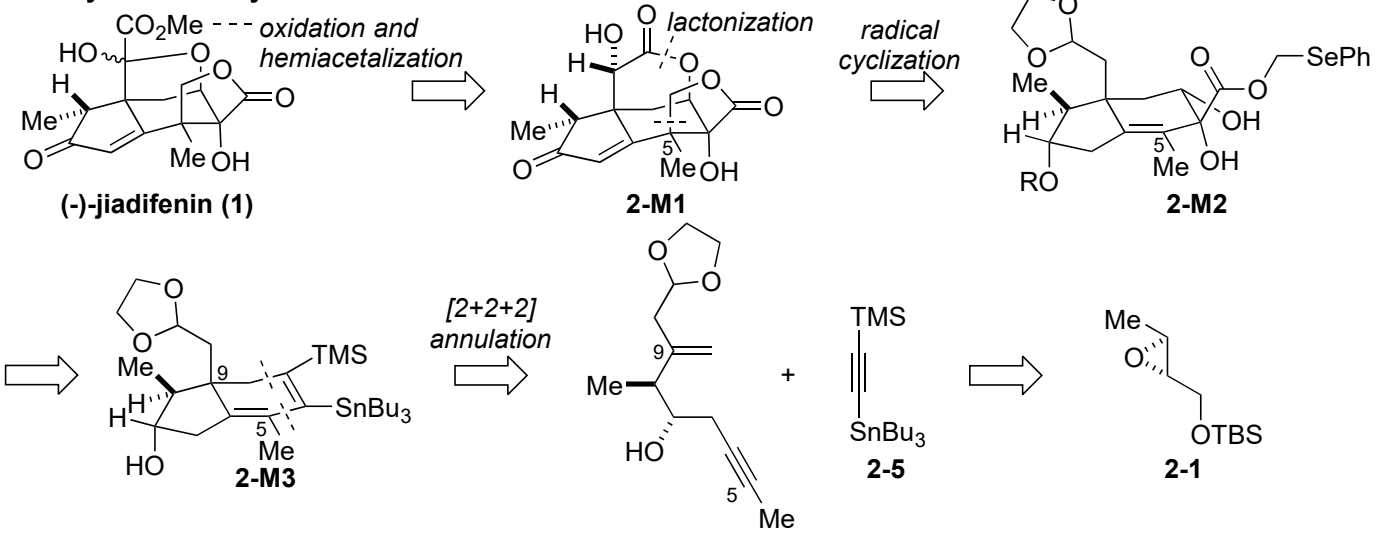


calculations were performed by (B3LYP/6-31G*//PM3)

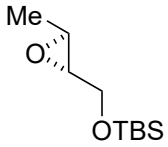
Problem 2

Micalizio's group ([2+2+2] annulation and intramolecular radical cyclization reactions)

Retrosynthetic analysis

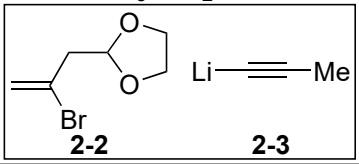


(2)-1



2-1

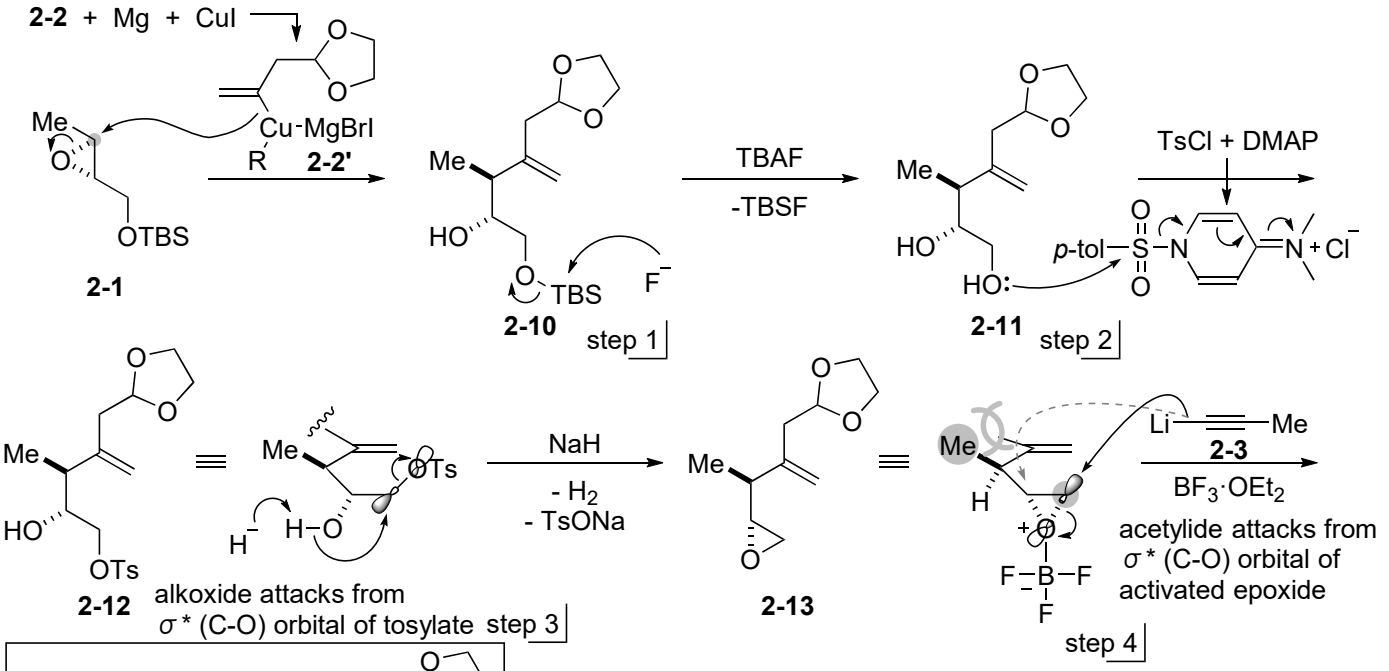
1. **2-2**, Mg, CuI, THF, 59%
2. TBAF, THF, 0 °C, 81%
3. TsCl (1.2 eq.), Et_3N, DMAP, CH_2Cl_2, 0 °C, 92%
4. NaH, THF, 0 °C, 76%
5. **2-3**, $BF_3{\cdot}OEt_2$, 0 °C, 91%

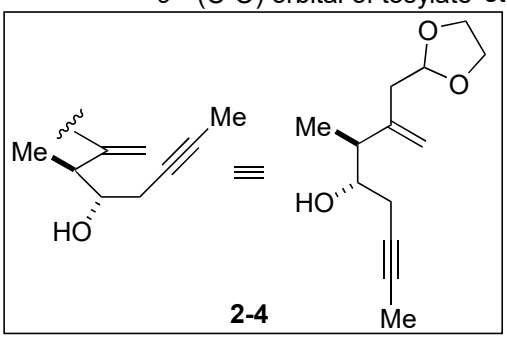


2-2 **2-3**

$(C_{13}H_{20}O_3)$
enyne
2-4

Answer

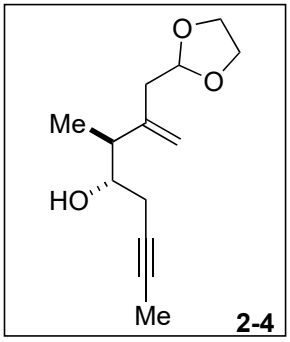




2-4

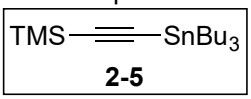
step 5

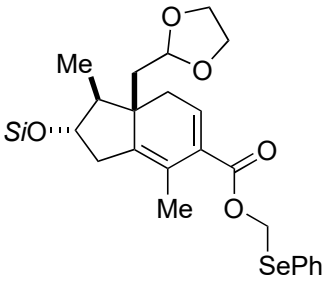
(2)-2



1. **2-5**, Ti(O*i*-Pr)$_4$, *n*-BuLi
   toluene, -78 to 50 °C;
   PhCHO*, 73%
2. TBAF, DMSO, 100 °C, 65%
3. TBDPSCl, imid., CH_2Cl_2, 96%
4. MeLi, THF, -78 °C; CO_2
5. $PhSeCH_2Cl$, *i*-Pr_2NEt
   NaI, DME, 50% (2 steps)

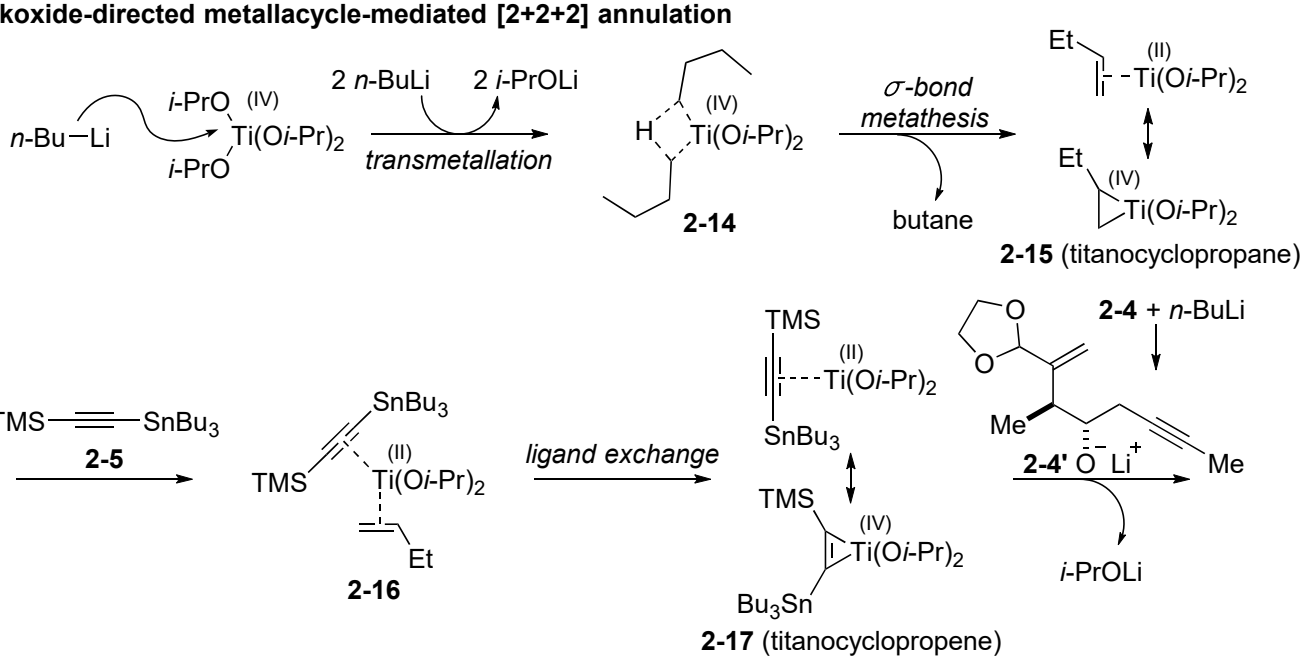
*Benzaldehyde is used as a quencher

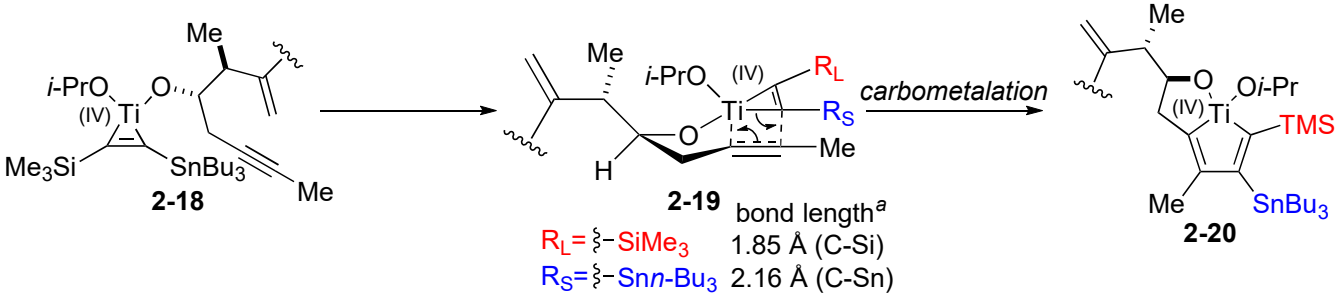


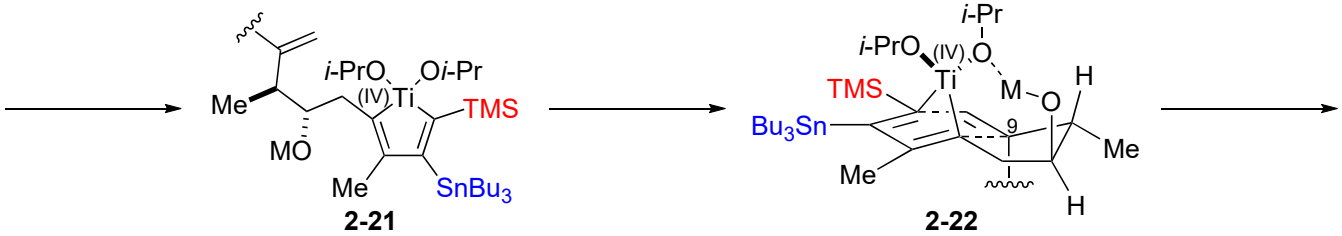


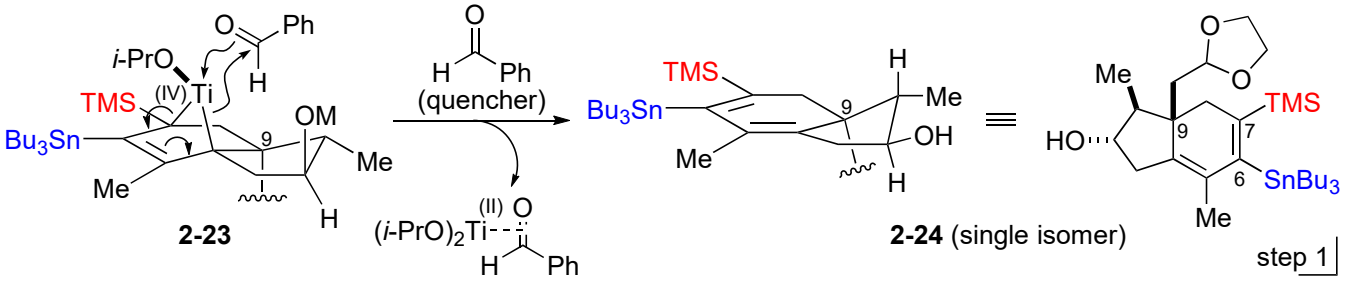
2-6 (*Si* = TBDPS)

Answer
alkoxide-directed metallacycle-mediated [2+2+2] annulation

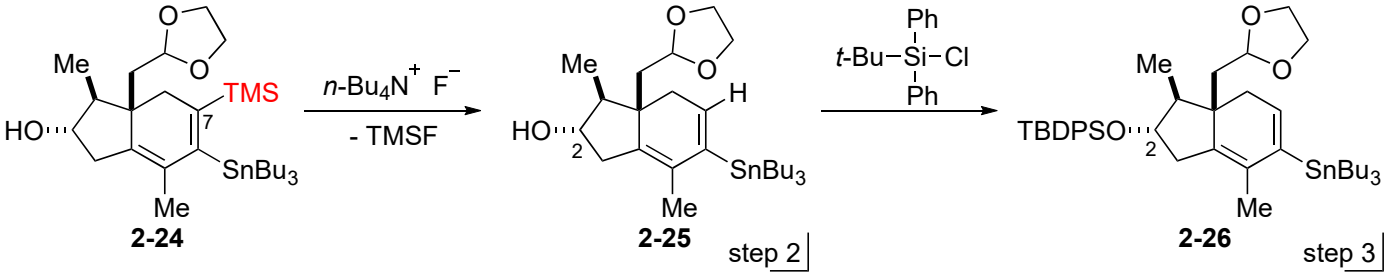


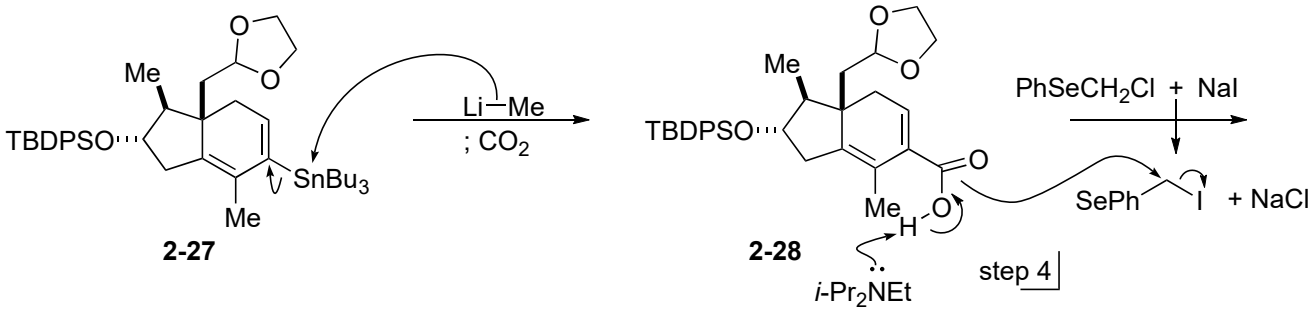


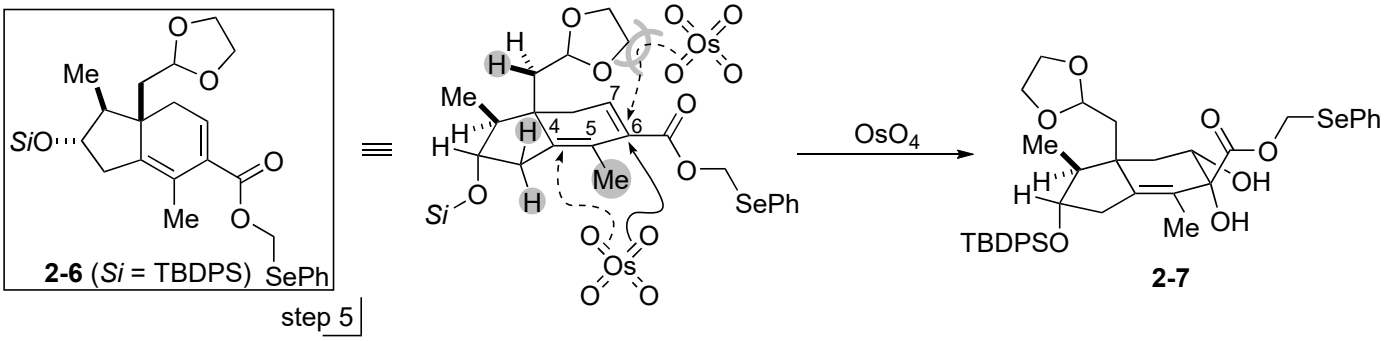




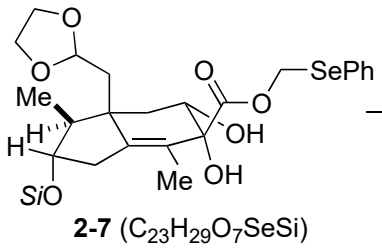
[a] Benson, S. W. *J. Chem. Educ.*, **1965**, *42*, 502.







(2)-3

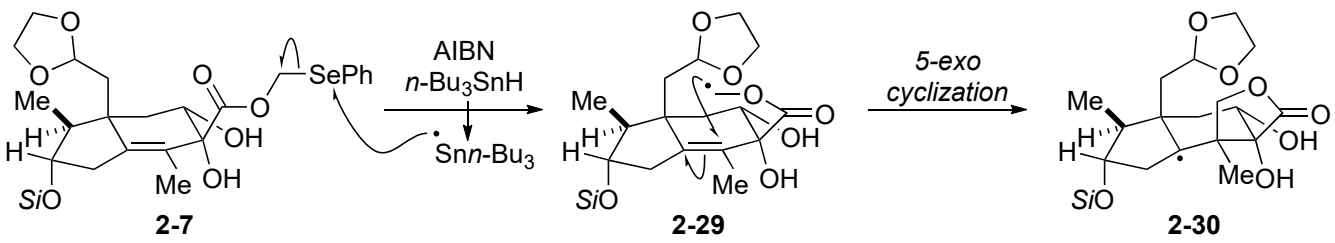


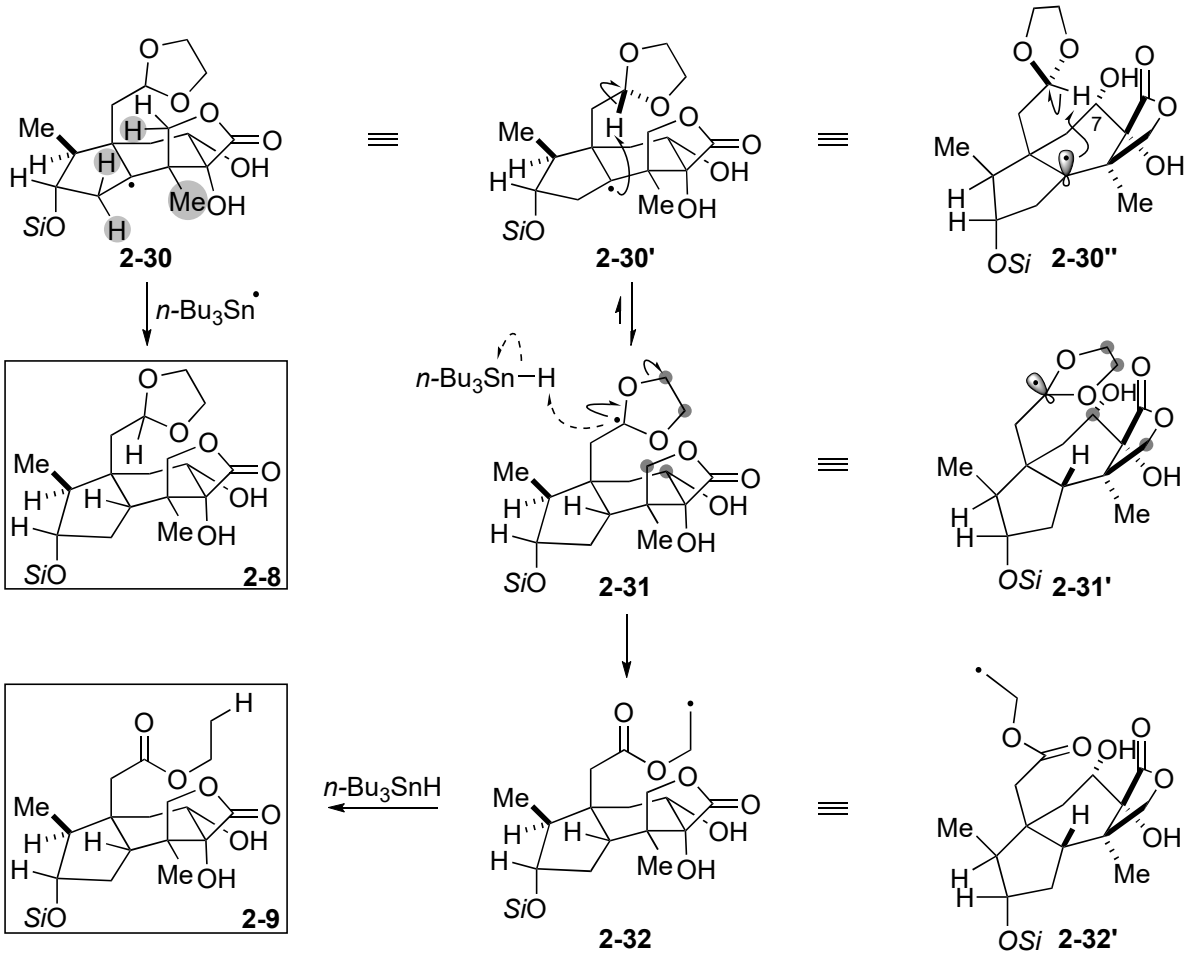
conditions →

$(C_{17}H_{25}O_7Si)$ **2-8**	+	$(C_{17}H_{25}O_7Si)$ **2-9**

conditions	ratio (**2-8** : **2-9**)	
AIBN, *n*-Bu_3SnH benzene, 80 °C	1 :	1.4
AIBN, TMS_3SiH benzene, 80 °C	1 :	4.7

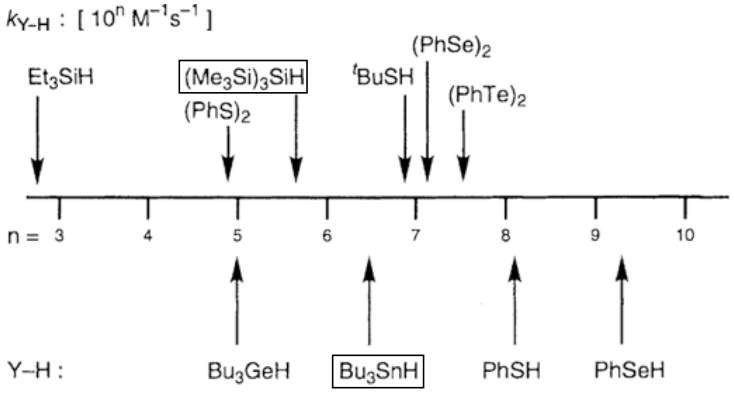
Answer
radical cascade reaction





	bond length (M-H)[b]	bond dissociation energy (M-H)[c]	sterical hindrance	**electron-donating**
n-Bu_3Sn–H	1.696 Å	74 ± 2 kcal/mol	smaller	**higher**
TMS_3Si–H	1.489 Å	79 kcal/mol	larger	**lower**

[b] Ishido, Y. *et al. Tetrahedron Lett.*, **1997**, *38*, 7369. [c] Chatgilialoglu, C. *et al. J. Am. Chem. Soc.*, **1987**, *109*, 5267.



solvent: toluene, temperature: 20 °C

Yamamoto, H. *et al.* Main Group Metals in Organic Synthesis, John Wiley & Sons, **2006**, 836.