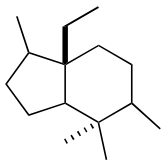
Problem Session (5) - Answer

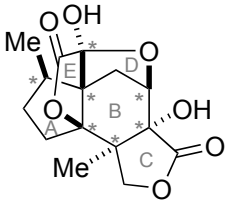
2016/08/06 Koichi Hagiwara

Topic: Total synthesis of jiadifenolide

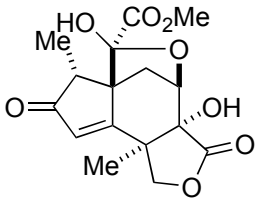
Sesquiterpenes from *Illicium* species



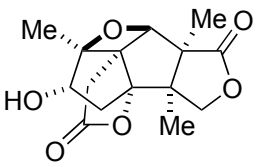
seco-prezizaane type skeleton



(-)-jiadifenolide



(-)-jiadifenin
see Masuda Keiuke-san's LS (2012/09/08)



(-)-merrilactone A
see Dr. Umihara's LS (2016/03/05)

Isolation of (-)-jiadifenolide:
pericarps of *Illicium jiadifengpi*
Kubo, M.; Okada, C.; Huang, J.-M.; Harada, K.;Hioki, H.; Fukuyama, Y. *Org. Lett.* **2009**, *11*, 5190.

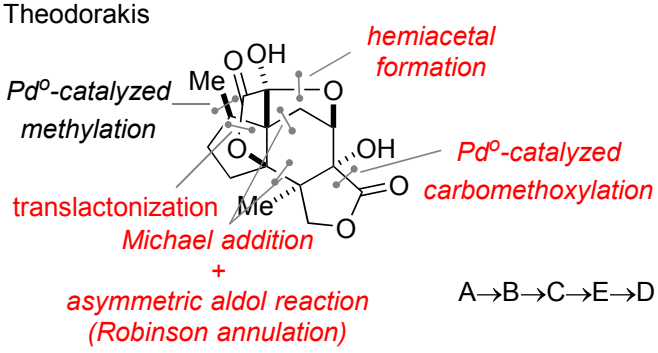
Bioactivity:
potent activities in promoting neurite outgrowth in primary cultured rat cortical neurons at concentration of 10 nM.

Structural features: caged *seco*-prezizaane type skeleton
pentacyclic structure including two γ-lactones
seven contiguous stereocenters (including four tetrasubstituted carbon)

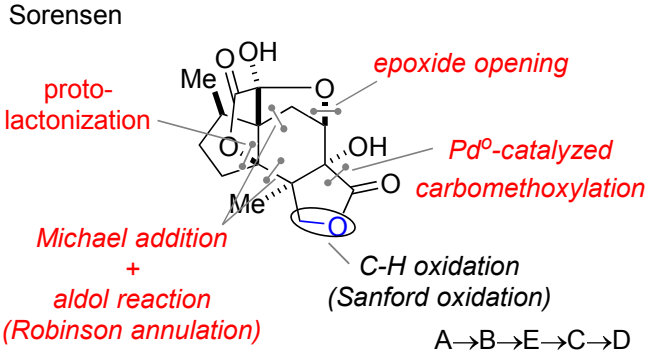
Total synthesis of jiadifenolide:
Xu, J.;Trzoss, L.; Chang, W. K.; Theodorakis, E. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 3672.
Siler, D. A.; Mighion, J. D.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 5332.
Paterson, I.; Xuan, M. Y.; Dalby, S. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 7286. (racemic)
Lu, H.-H.; Martinez, M. D.; Shenvi, R. A. *Nat. Chem.* **2015**, *7*, 604.→problem (3)
Shen, Y.; Li, L.; Pan, Z.; Wang, Y.; Li, J.; Wang, K.; Wang, X.; Zhang, Y.; Hu, T.; Zhang, Y. *Org. Lett.* **2015**, *17*, 5480.
→problem (1), (2)

Retrosynthesis:

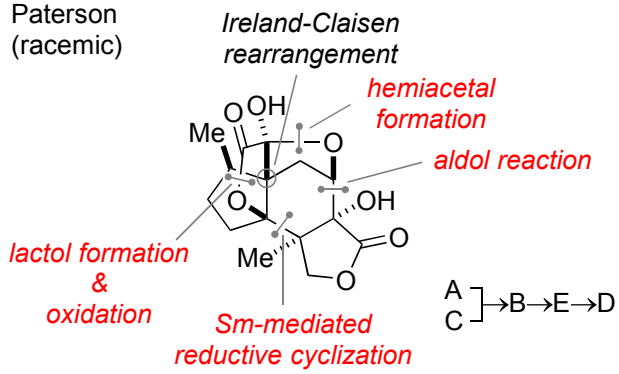
Theodorakis



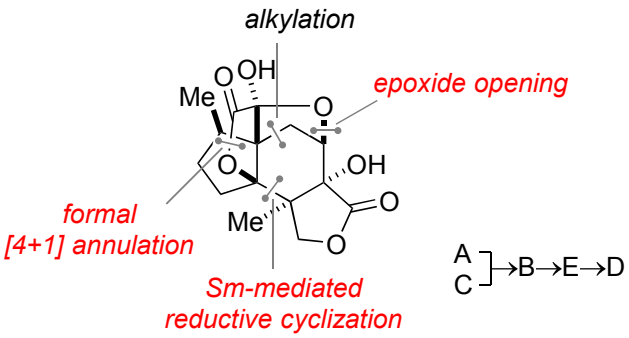
Sorensen



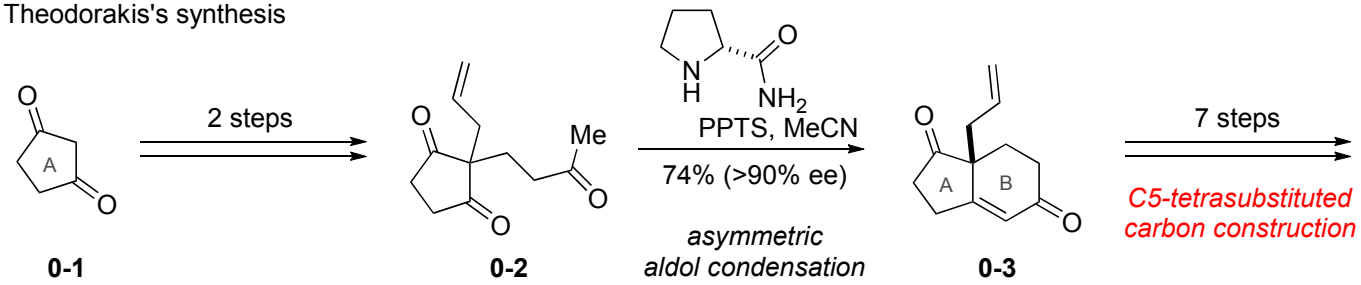
Paterson (racemic)



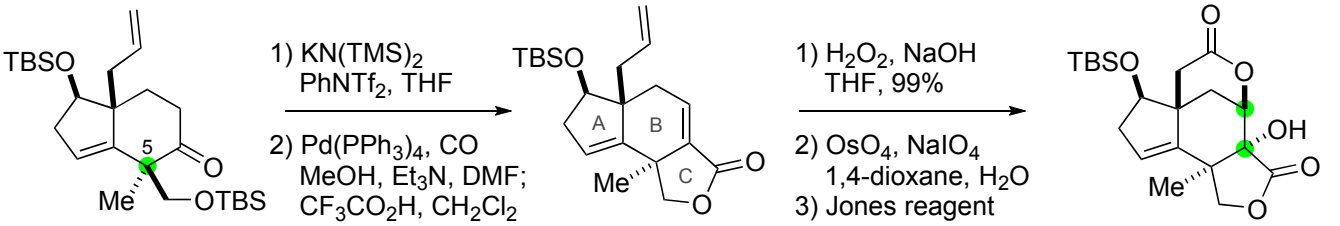
Zhang



Theodorakis's synthesis

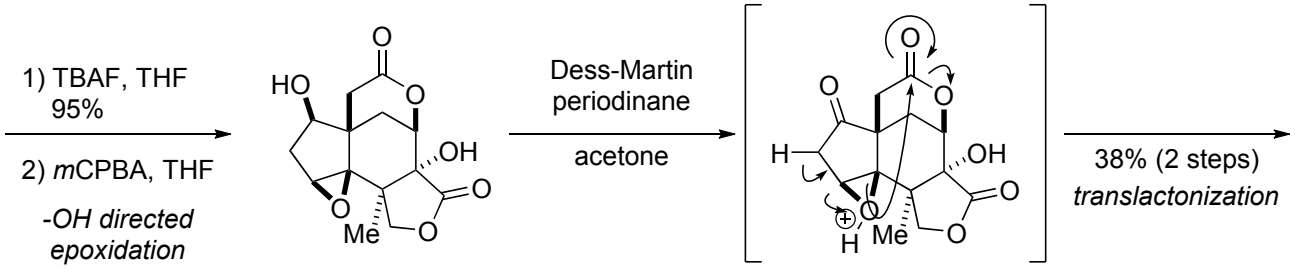


0-1 **0-2** **0-3**

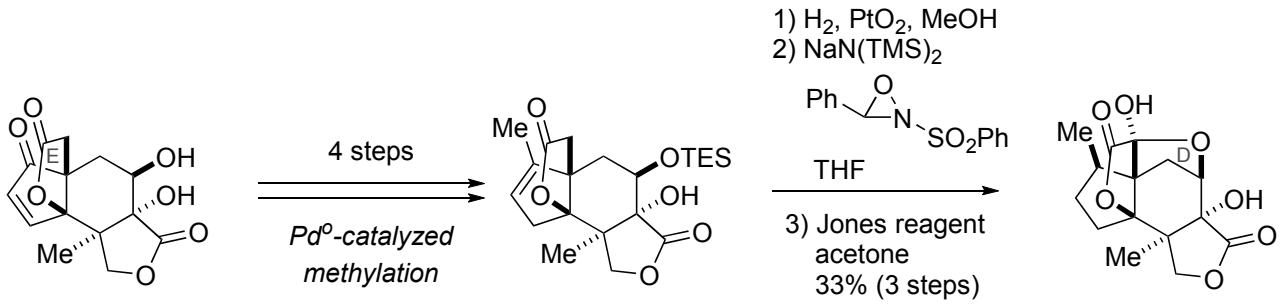


0-4 **0-5**

0-6
common intermediate for the total synthesis of jiadifenin



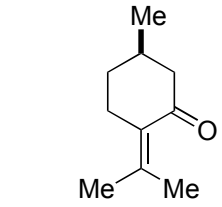
0-7 **0-8**



0-9 **0-10**

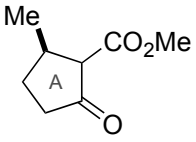
(-)-jiadifenolide
25 steps

Sorensen's synthesis



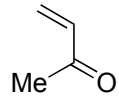
0-11

3 steps



0-12

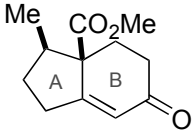
1)



DBU, EtOH, 97%

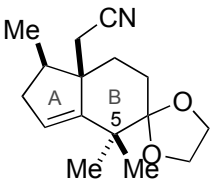
2) *p*-TsOH, benzene
reflux, 85%

Robinson annulation



0-13

4 steps



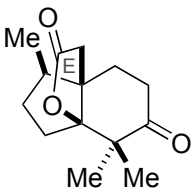
0-14

H_2SO_4, MeOH
100 °C

73%

hydrolysis of nitrile
protolactonization
hydrolysis of ketal

rapid E-ring construction

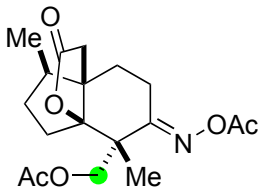


0-15

1) NH_2OH•HCl
pyridine, 91%

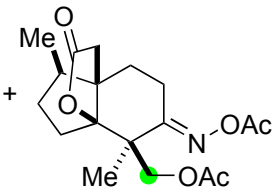
2) $Pd(OAc)_2$, $PhI(OAc)_2$
Ac_2O/AcOH, 100 °C

oxime-directed C-H oxidation
(Sanford oxidation)



0-16 (undesired)
22%

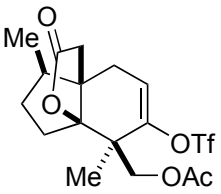
+



0-17 (desired)
22%

no diastereoselectivity

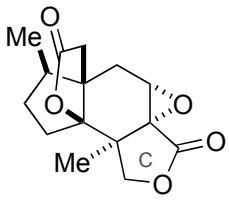
2 steps



0-18 (desired)
22%

3 steps

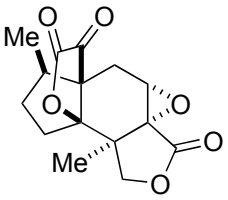
Pd^0-catalyzed carbomethoxylation



0-19

1) TMSCl
$LiN(TMS)_2$, THF;
NIS

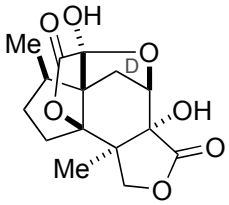
2) DMDO, CH_2Cl_2



0-20

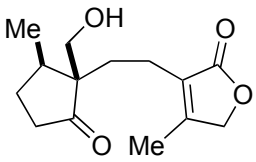
LiOH, THF

40% (3 steps)



(-)-jiadifenolide
21 steps

(1) Please predict the stereochemistry of products **B**, **B'** and **B"**. (They may be the same structure.)

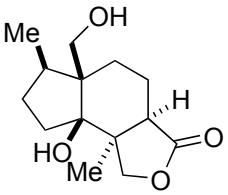


A

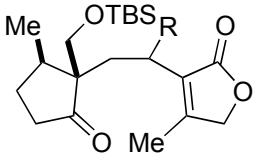
SmI_2 (2.4 eq.)

THF/H_2O = 1/5, rt
(H_2O: 7000 eq.)

70% for major diastereomer **B**



B = B"

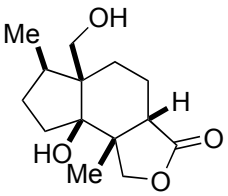


C (R = α-OTMS)
D (R = β-OTMS)

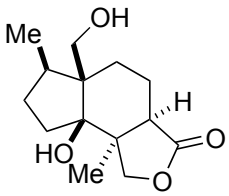
1) SmI_2 (6 eq.), LiCl (12 eq.)
t-BuOH (20 eq.), THF, rt

2) TBAF (2 eq.), THF, rt

80% for **B'**
89% for **B"**

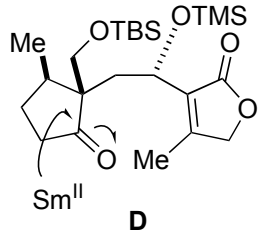


B'
(from **C**)



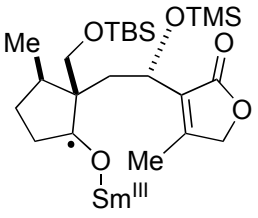
B" = B
(from **D**)

•**D** to **B"**



D

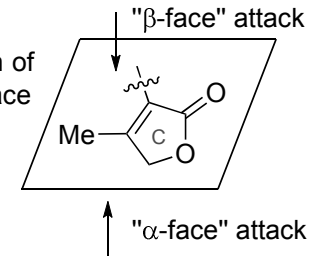
reduction of ketone with Sm^{II}



1-1

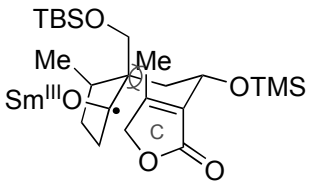
points of consideration:
1. orientation of OSm^{III}
2. face selectivity of the lactone
3. orientation of OTMS

definition of α or β-face

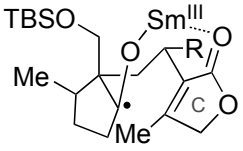


As for 3, in more favorable conformation, OTMS substituent would be equatorially disposed.

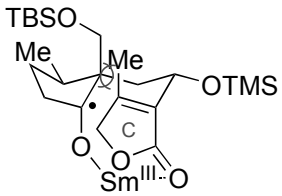
transition states of **1-1** (R = OTMS)



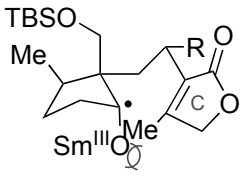
1-1-TS-a
β-OSm^{III}
α-face of C-ring



1-1-TS-b
β-OSm^{III}
β-face of C-ring
chelated

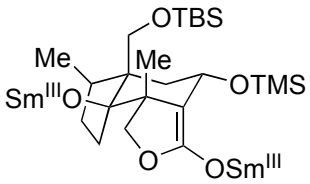


1-1-TS-c
α-OSm^{III}
α-face of C-ring
chelated

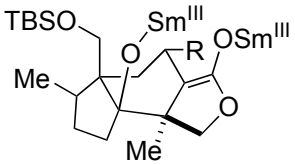


1-1-TS-d
α-OSm^{III}
β-face of C-ring

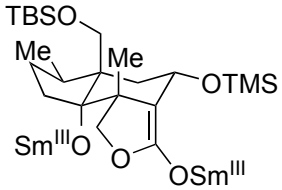
+Sm^{II}



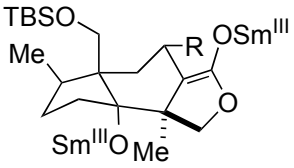
1-2



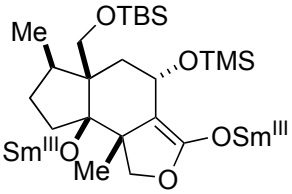
1-3



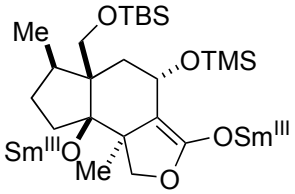
1-4



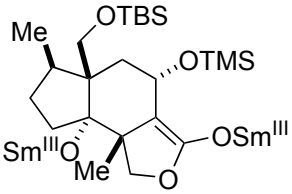
1-5



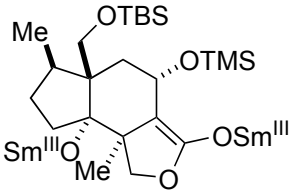
1-2



1-3

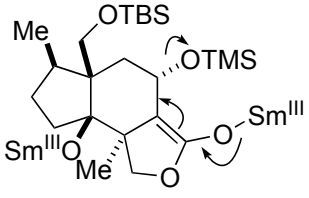


1-4



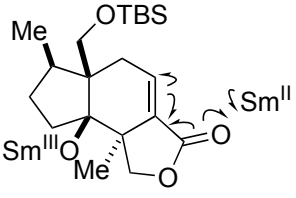
1-5

1-3 to **B"**



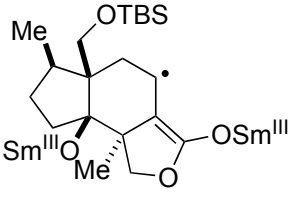
1-3

- TMSOSm^{III}

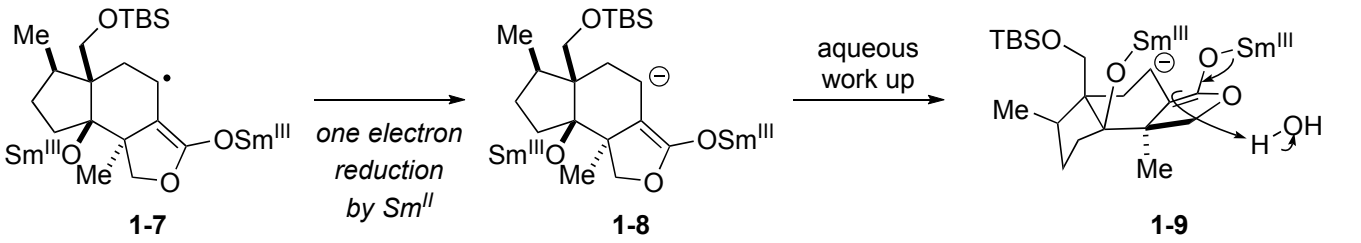


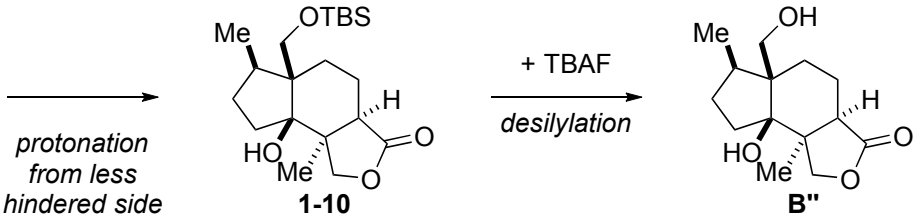
1-6

reduction of enone with Sm^{II}

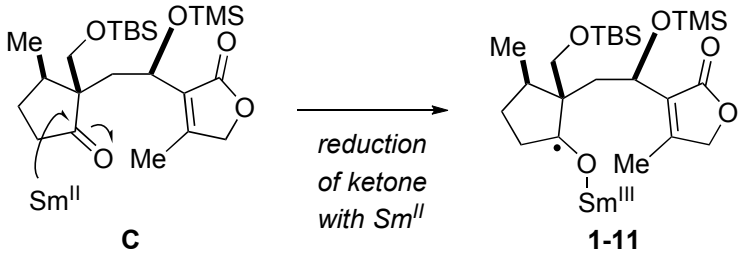


1-7

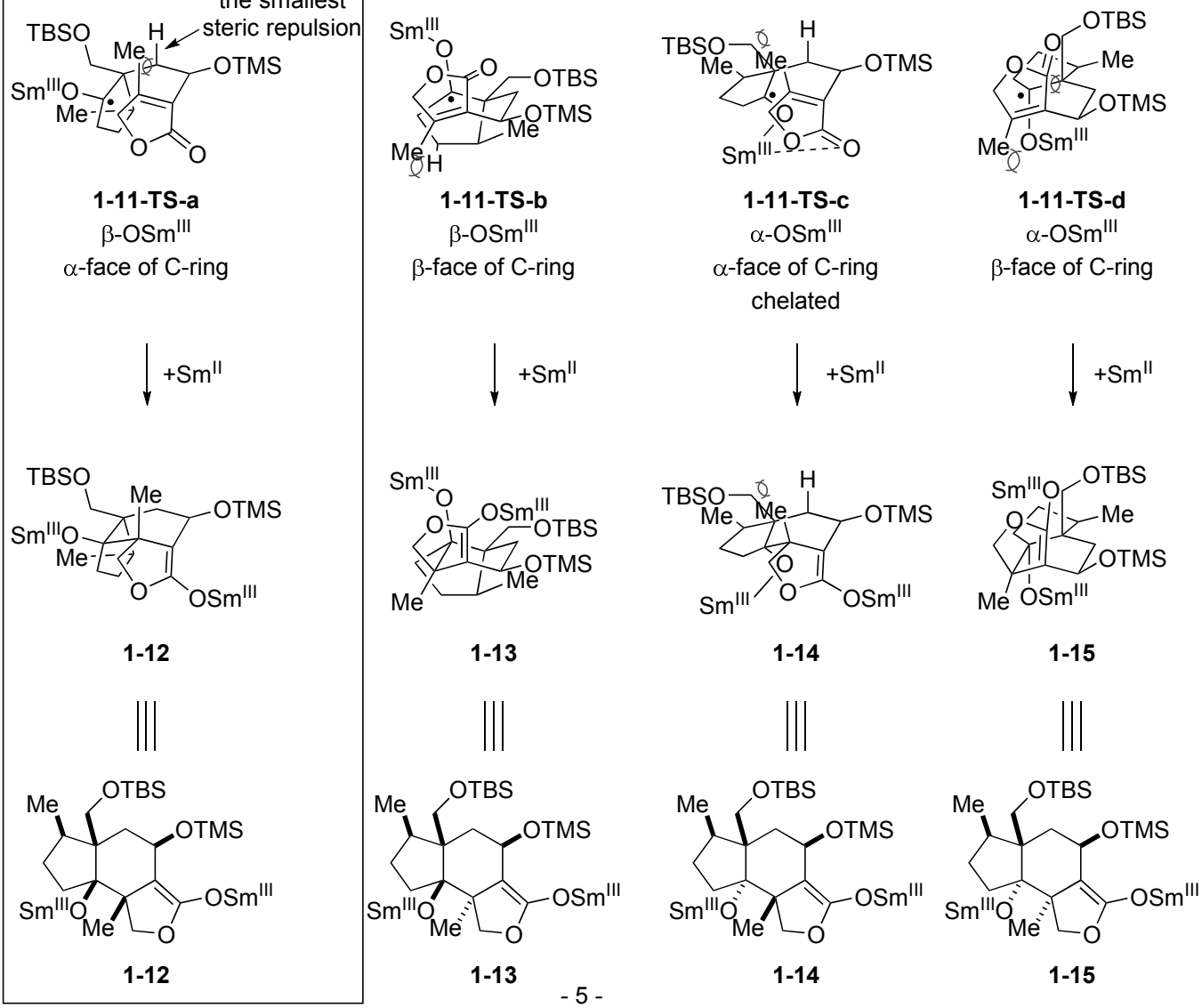


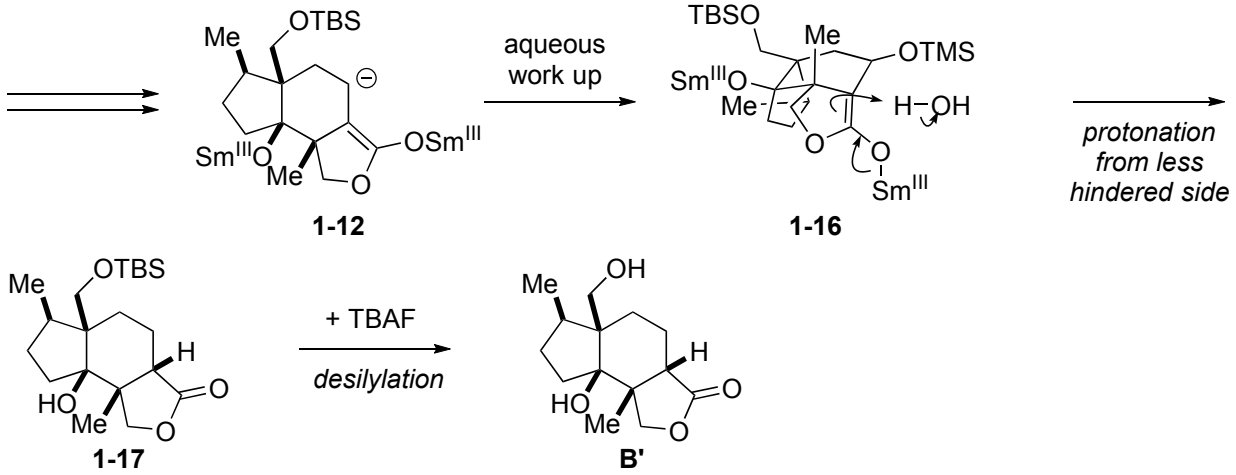


•**C** to **B'**

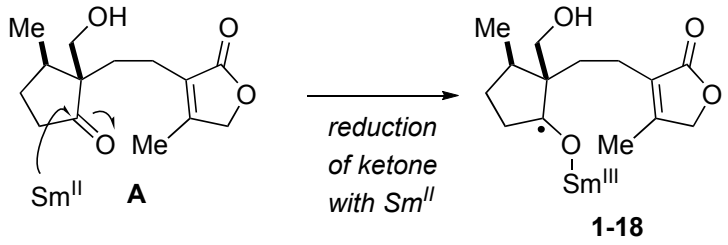


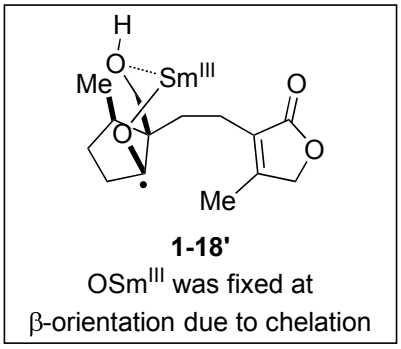
transition states of **1-11**



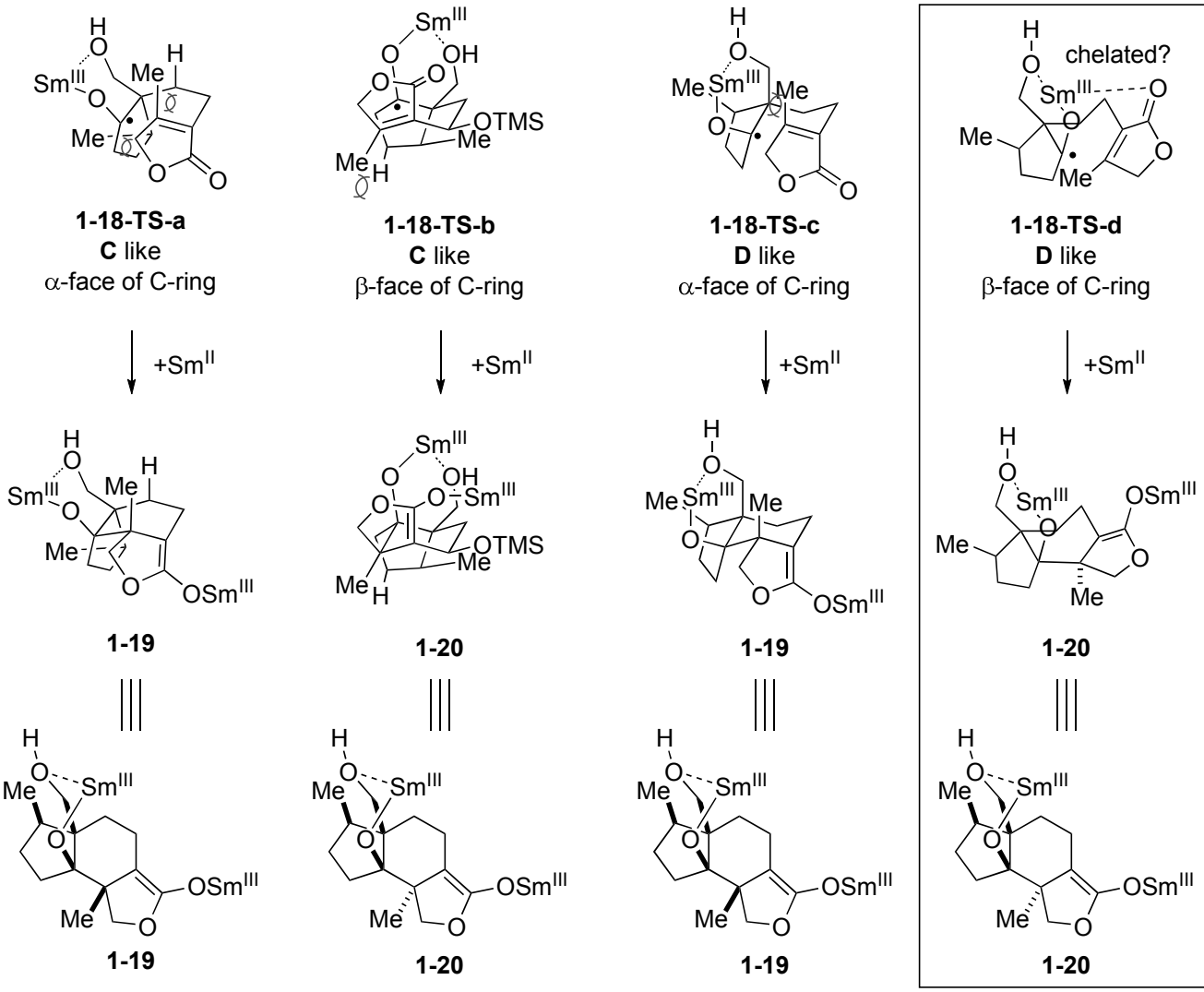


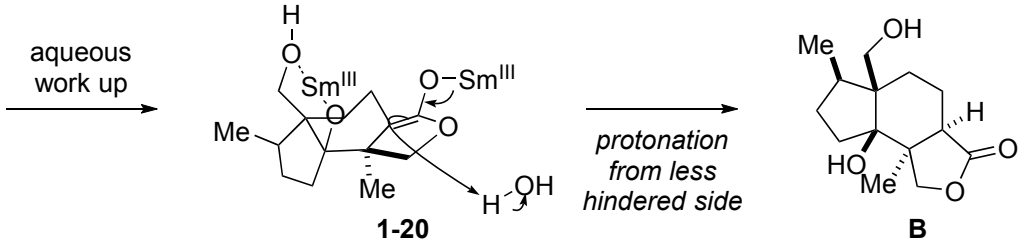
•**A** to **B**





transition states of **1-18**

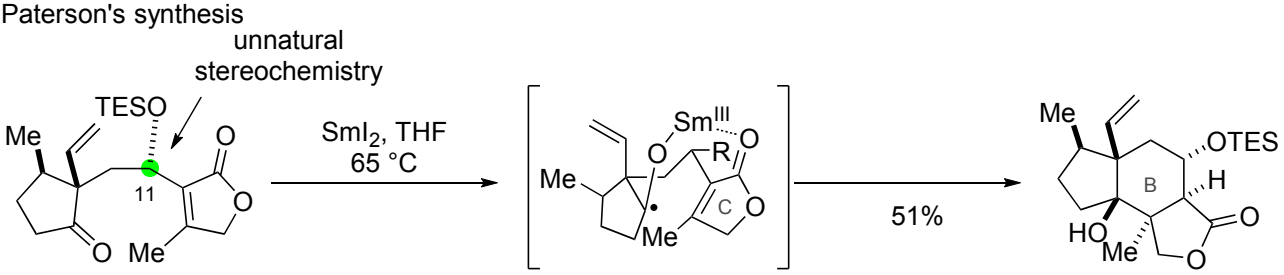




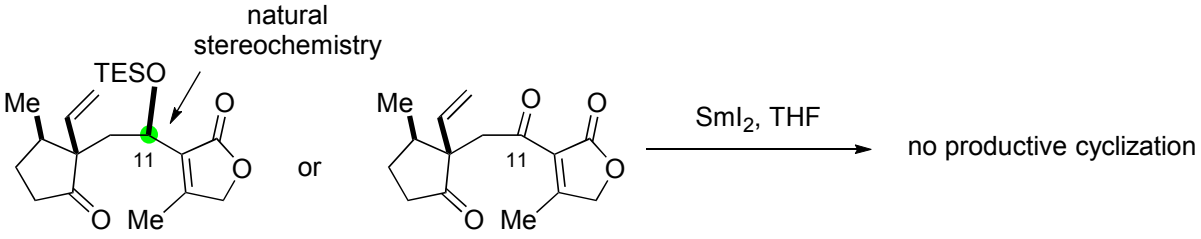
1-20 **B**

Supplemental information

•In Paterson's synthesis



0-27 **1-21** **0-28**



11-*epi*-0-27 **1-22**

•Effect of additives

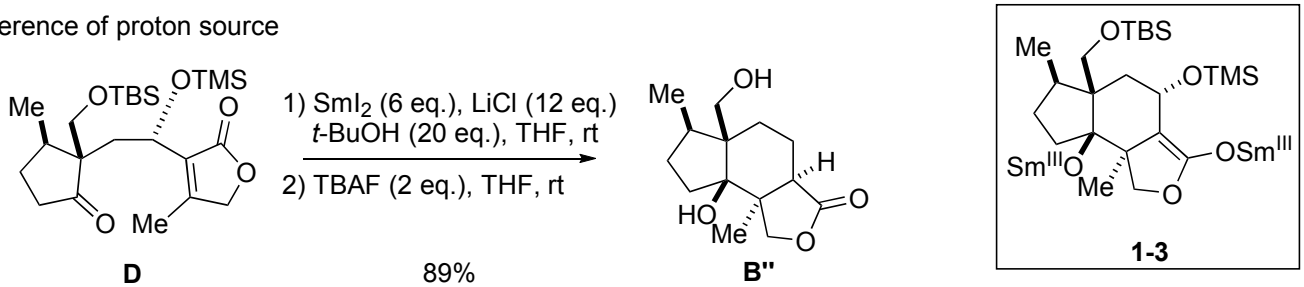
	SmI_2	SmI_2+12LiBr	SmI_2+12LiCl	SmI_2+500H_2O	
redox potential (vs Ag/$AgNO_3$, in THF)	-1.33[a] or -1.5[c]	-1.98±0.01[b]	-2.11±0.01[b]	-1.9[c]	(V)

[a] Shabangi, M.; Flowers, R. A. II. *Tetrahedron Lett.* **1997**, *38*, 1137.

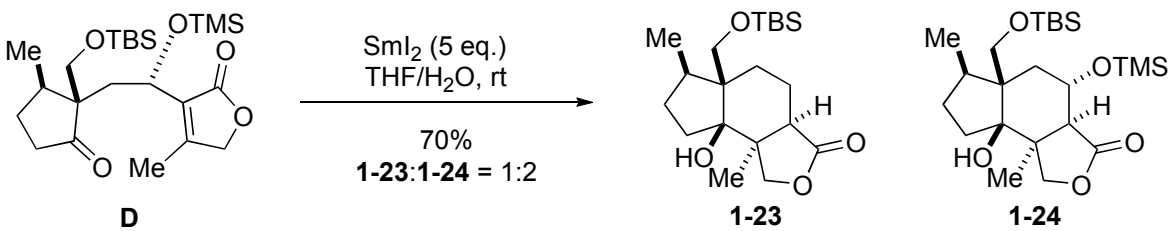
[b] Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A. II. *Tetrahedron Lett.* **1997**, *110*, 8157.

[c] Prasad, E.; Flowers, R. A. II. *J. Am. Chem. Soc.* **2005**, *127*, 18093.

difference of proton source



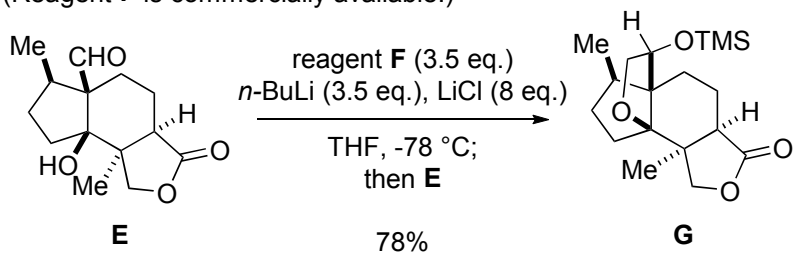
D **B''** **1-3**

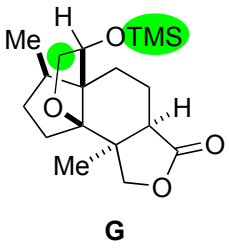


D **1-23** **1-24**

1-24 was obtained as a major product due to faster protonation of intermediate **1-3** by water than that by *t*-BuOH.

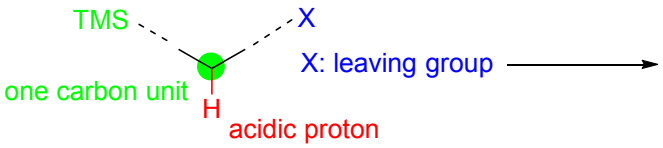
(2) Please predict the structure of reagent **F** and explain the reaction mechanism.
(Reagent **F** is commercially available.)

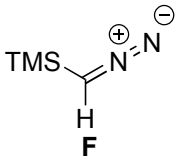




structural difference between **E** and **G**:
G possesses TMS group and highlighted methylene unit.
→These are probably derived from reagent **F**.
F seems to have an acidic proton.

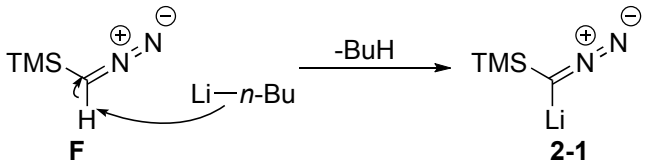
candidate for reagent **F**



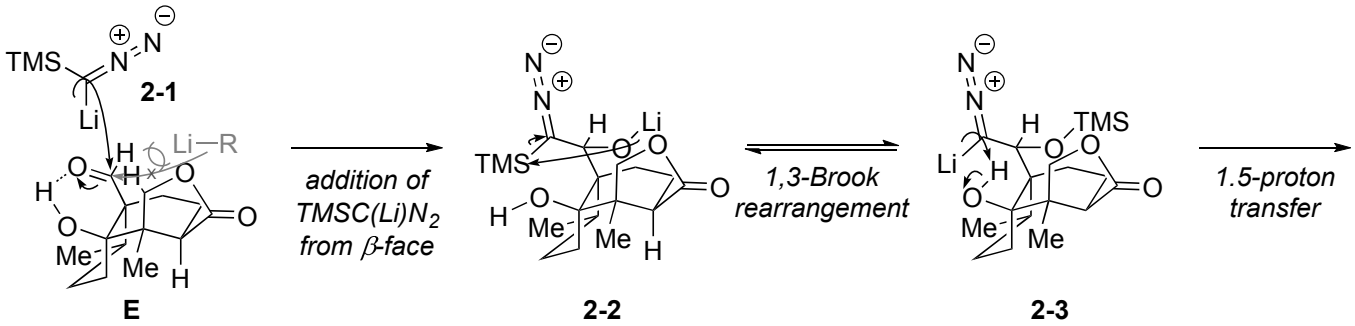


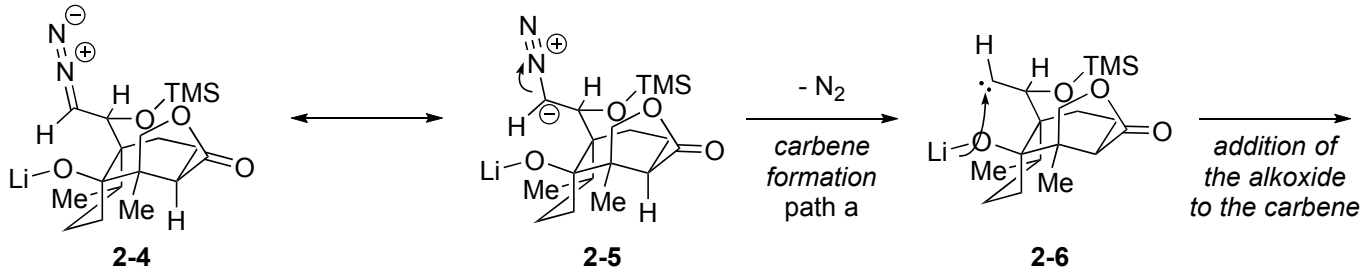
trimethylsilyldiazomethane

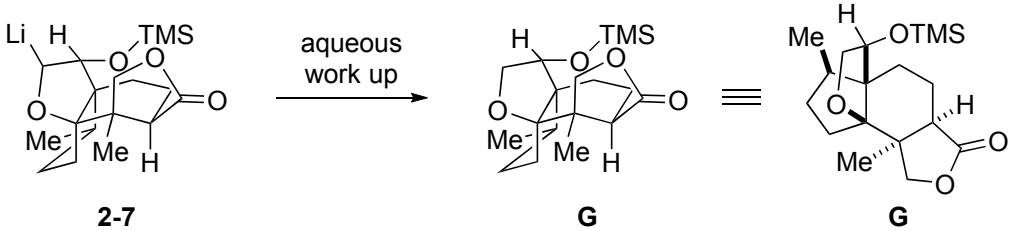
reaction mechanism from **E** to **G**:



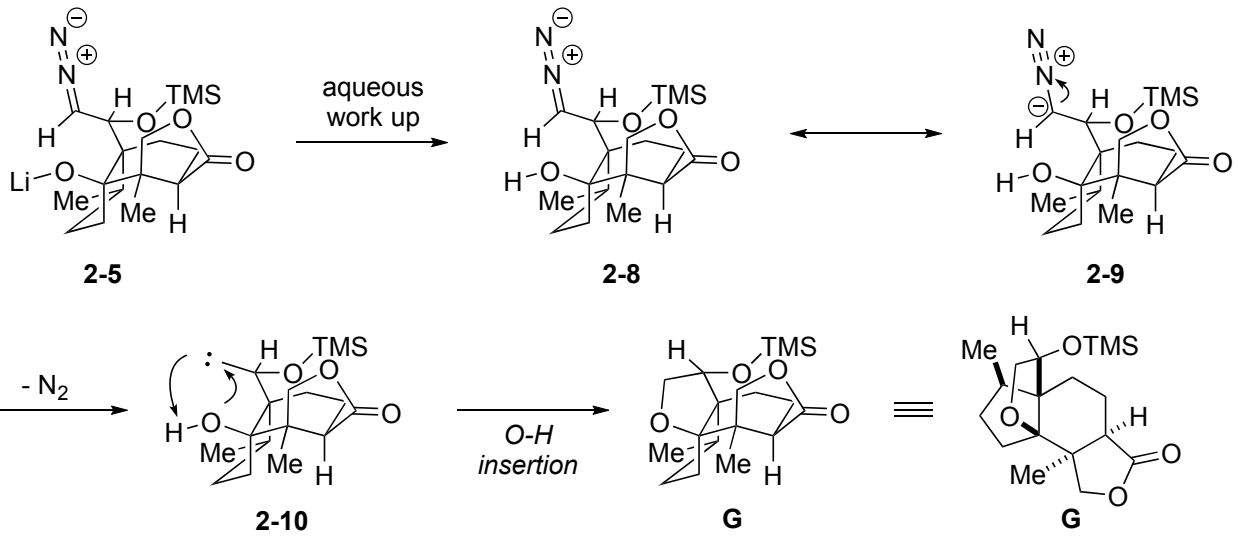
Authors claimed that LiCl might change the aggregation state of $TMSC(Li)N_2$ and thus modify its nucleophilicity and basicity.







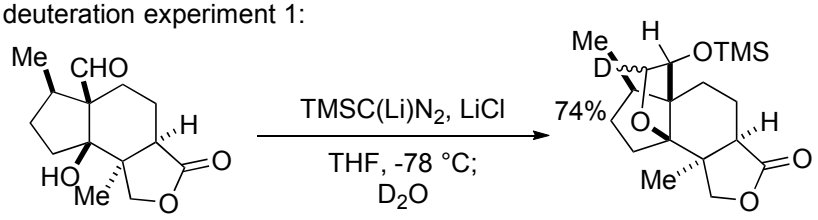
other possible pathway (path b)



2-5 **2-8** **2-9** **2-10** **G** **G**

Supplemental information

deuteration experiment 1:

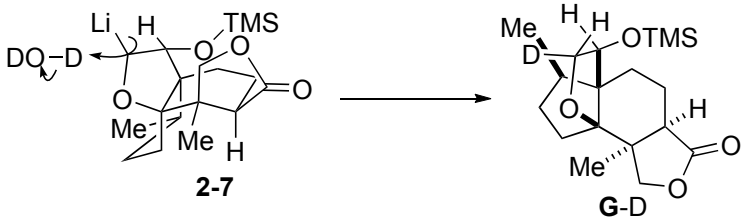


E **G**-D (major isomer: deuterated opposite from OTMS)

could not distinguish between path a and path b from this result.

← this stereoselectivity suggested the presence of intermediate **2-7**?

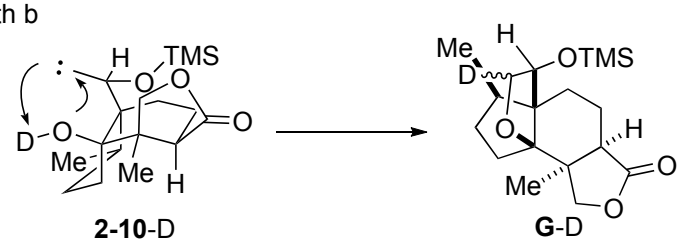
If path a



2-7 **G**-D

mainly deuterated opposite from OTMS

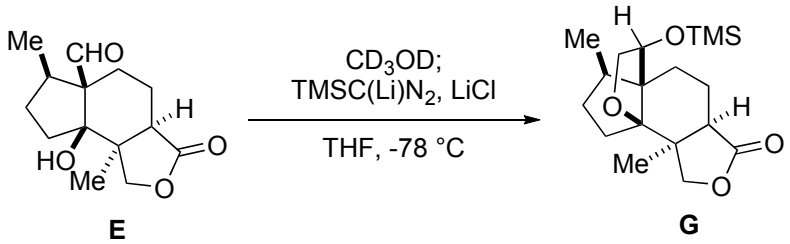
If path b



2-10-D **G**-D

non-selective D incorporation would be observed?

deuteration experiment 2:

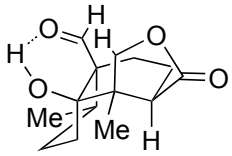


E **G**

could not distinguish between path a and path b from this result.

no deuterated compounds were obtained.

author's consideration

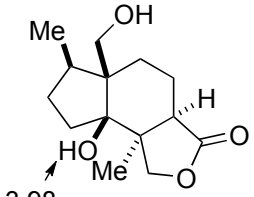


E

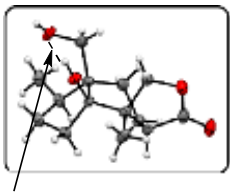
Intramolecular hydrogen bond might inhibit H/D exchange of hydroxyl group with CD_3OD.

Because of this hydrogen bond, the nucleophilic attack of $TMSC(Li)N_2$ to the aldehyde might be faster than protonation.

^1H NMR chemical shift of alcohol proton (in $CDCl_3$)

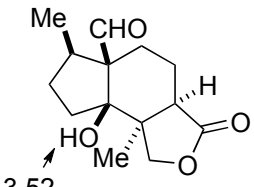


B

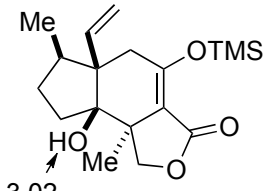


hydrogen bond?

X-ray structure of **B**



E



2-11

Paterson, I. et al.
Angew. Chem. Int. Ed. **2014**, *53*, 7286.

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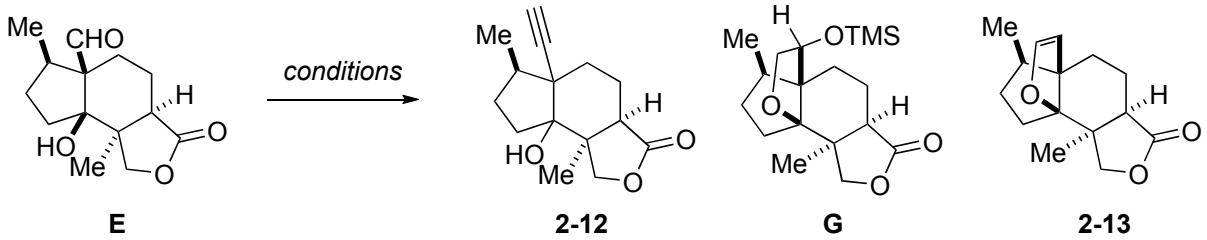
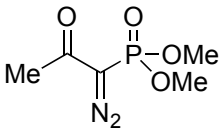
discovery of this reaction



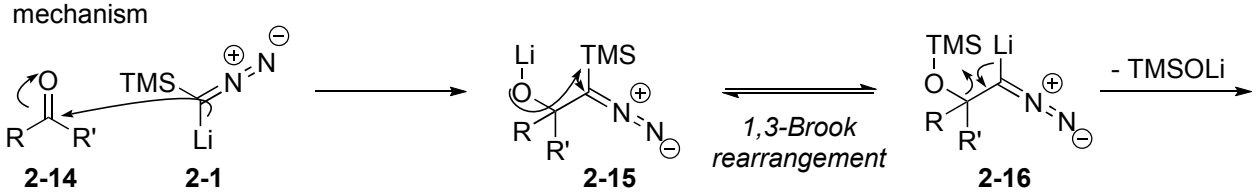
E **2-12** **G** **2-13**

entry	*conditions*	result
1	Ohira reagent (3 eq.), K_2CO_3 (4 eq.), MeOH, rt	**2-12** 34%
2	$TMSC(Li)N_2$ (2.2 eq.), LiCl (3 eq.), THF, -78 to 0 °C	**2-13** 57%
3	$TMSC(Li)N_2$ (3 eq.), LiCl (8 eq.), THF, -78 °C	**G** 78%

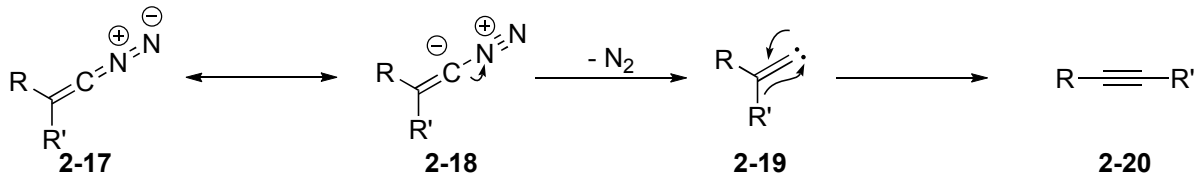


Ohira reagent

mechanism

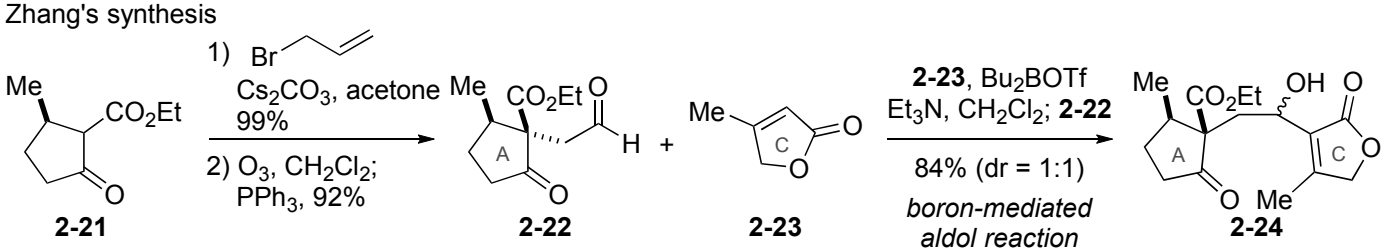


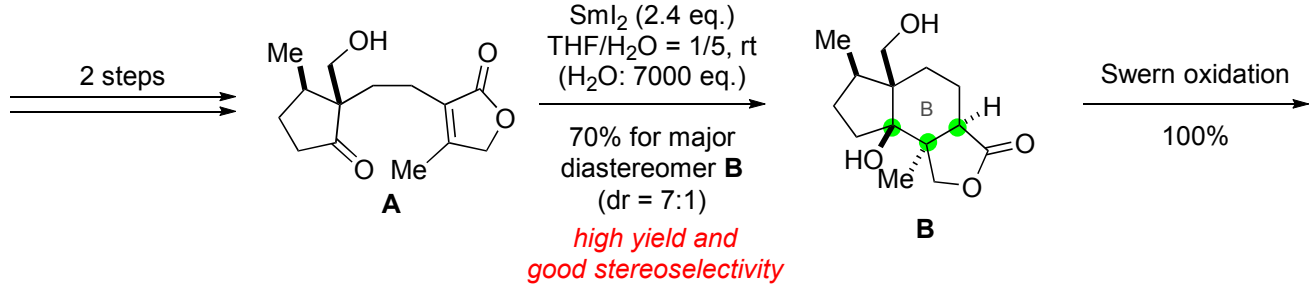
2-14 **2-1** **2-15** **2-16**

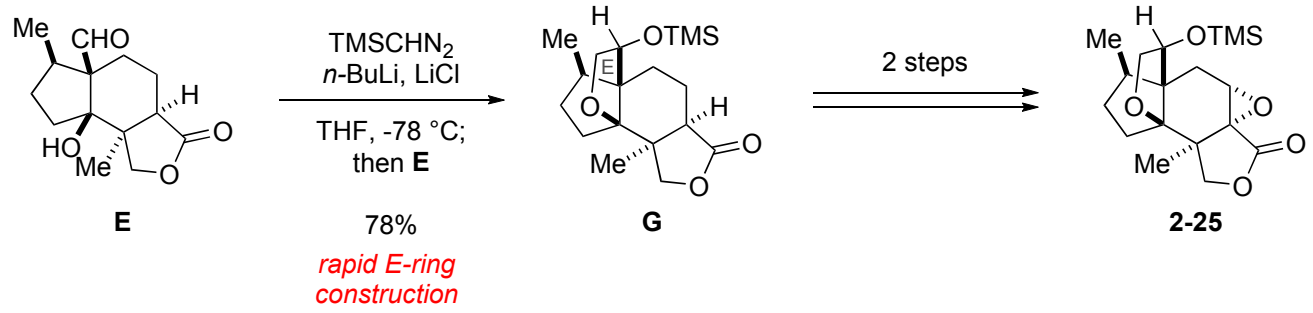


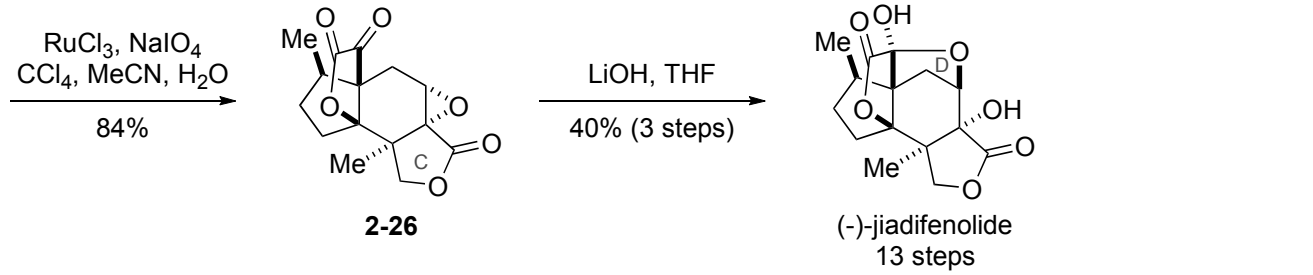
2-17 **2-18** **2-19** **2-20**

Zhang's synthesis

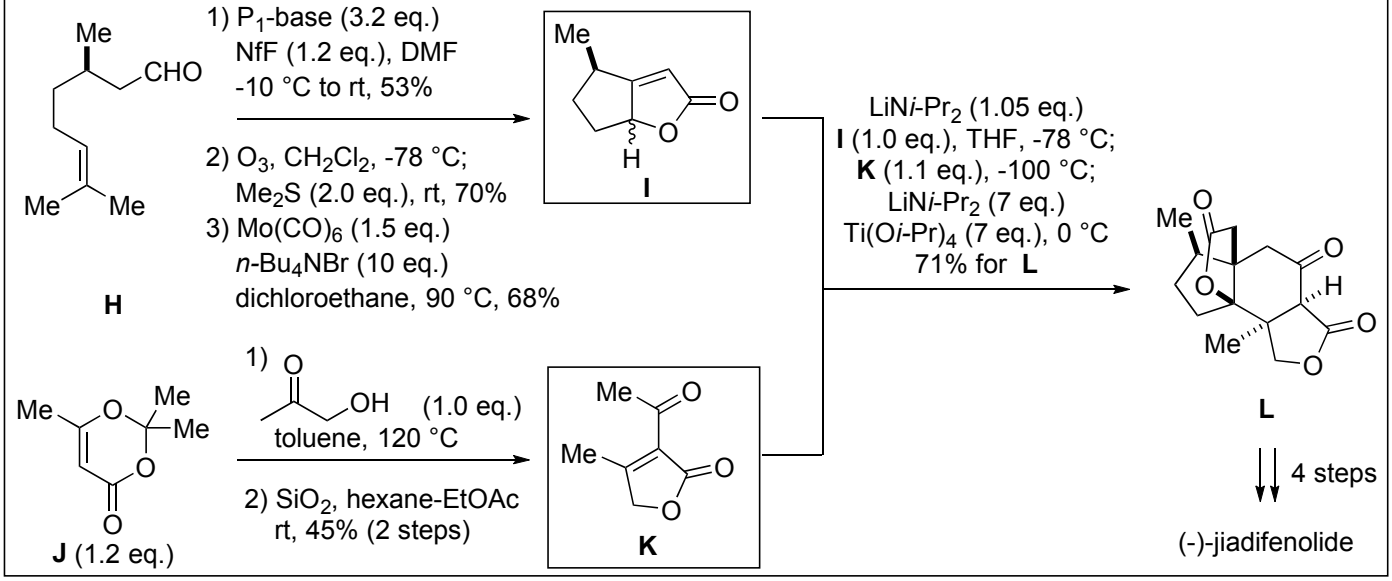




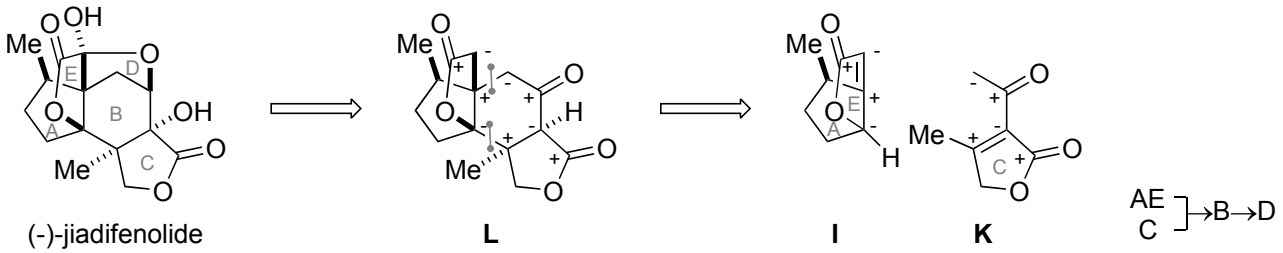




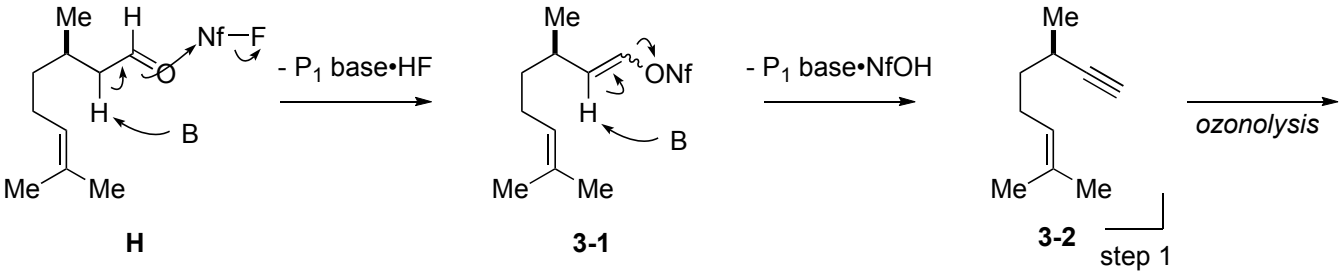
(3) Please fill in the blanks **I** and **K**, and explain the stereoselectivity of the reaction for **L**.

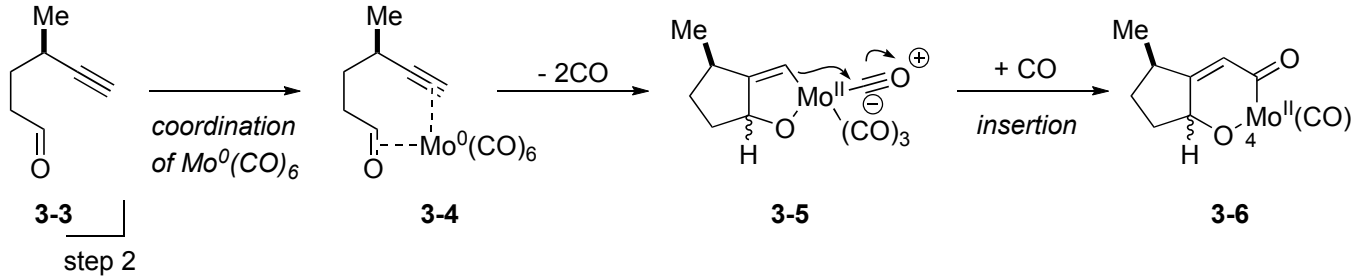


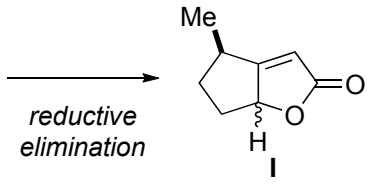
•Introduction
Shenvi's retrosynthesis



•**H** to **I**





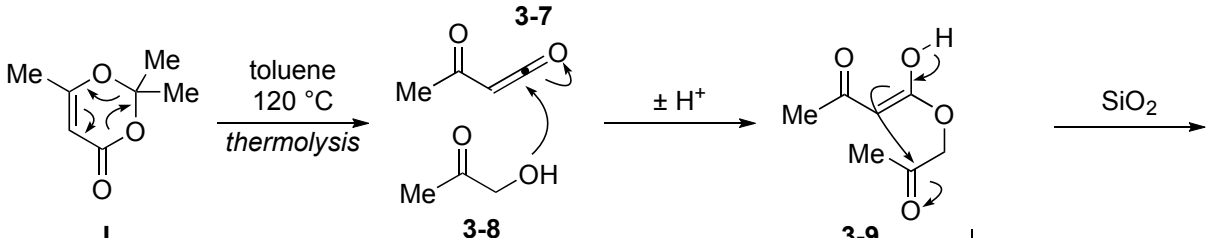


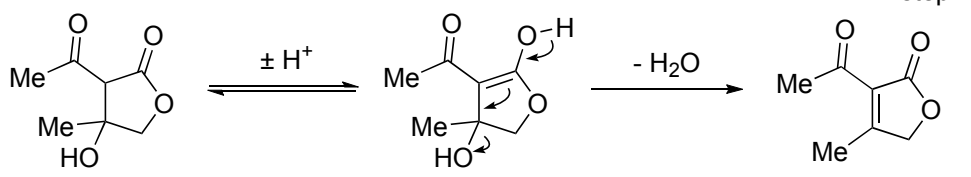
The role of *n*-Bu_4NBr was unclear.
This reagent might react with $Mo(CO)_6$ to afford *n*-$Bu_4N[Mo(CO)_5Br]$.
n-$Bu_4N[Mo(CO)_5Br]$ might promote the carbonylative insertion process.

cf. Moretó, J. M. et al. *Organometallics*, **1993**, *12*, 2795.

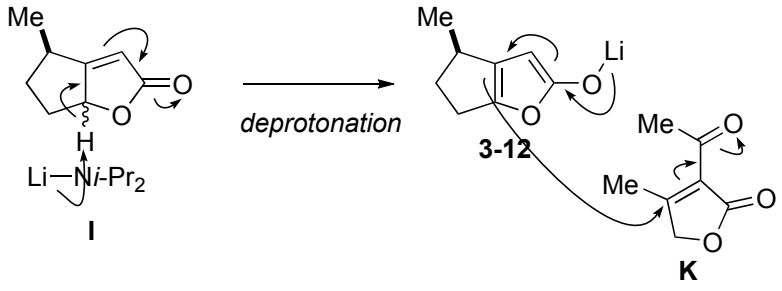
step 3
(hetero Pauson-Khand reaction)

•**J** to **K**

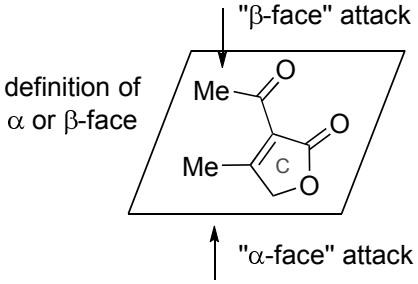




•**I** and **K** to enolate intermediate **3-19**

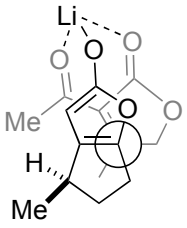


points of consideration:
1. face selectivity of the **3-12**
2. face selectivity of the **K**



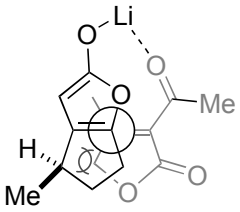
face selectivity of enolate **3-12**:
opposite side of Me group

"β-face" attack



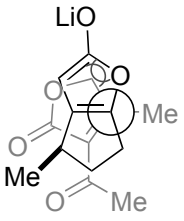
3-13
chelated

or

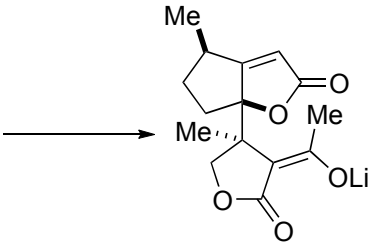


3-14
chelated

or

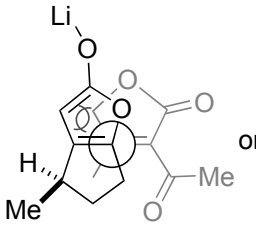


3-15



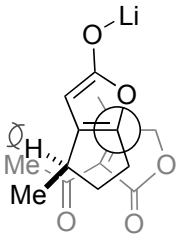
3-19-(*Z*)
(from **3-13**)

"α-face" attack



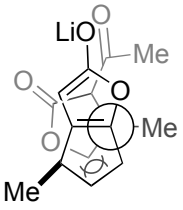
3-16

or

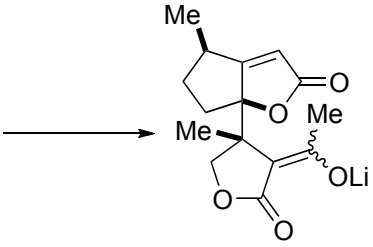


3-17

or



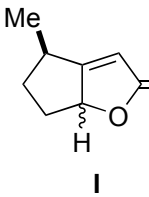
3-18

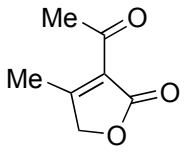


3-20

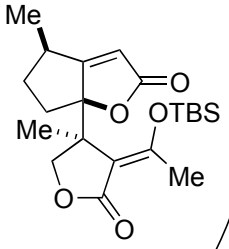
experimental result

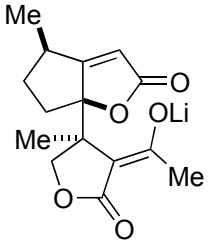
LiN*i*-Pr$_2$ (1.05 eq.)





THF, -100 °C;
TBSCl, THF-HMPA
-78 °C to rt

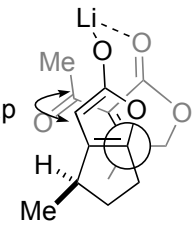




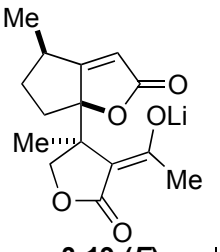
3-19-(*E*)
should be generated

alternative intermediate

favorable
secondary
orbital overlap



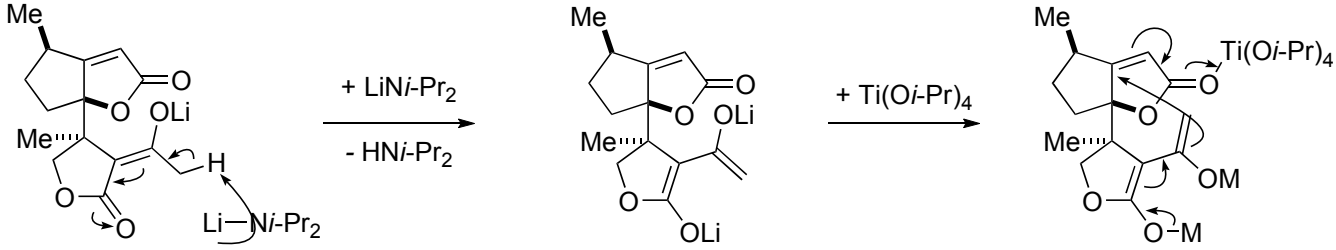
3-13'
chelated



3-19-(*E*)

step 1

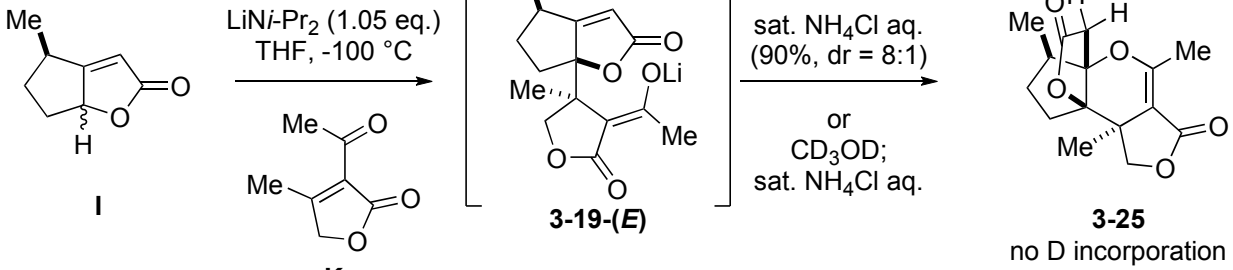
•**3-21** to **L**



3-19-(*E*) **3-22** **3-23** (M = Li or Ti(O*i*-Pr)$_3$)

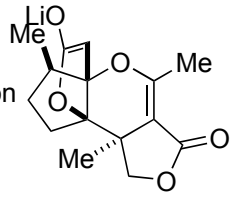
3-24 (M = Li or Ti(Oi-Pr)3) **L**

Supplemental information
reaction between **I** and **K**



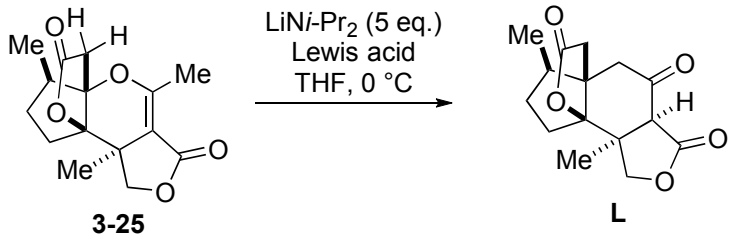
I **K** **3-19-(*E*)** **3-25** no D incorporation

This result excluded intermediacy of enolate **3-26** and implied that dihydropyrane formation was not a kinetic trap and that a stable intermediate **3-19-(*E*)** should exist.



3-26

Authors screened several Lewis acids to transform **3-25** to **L**.



3-25 no D incorporation **L**

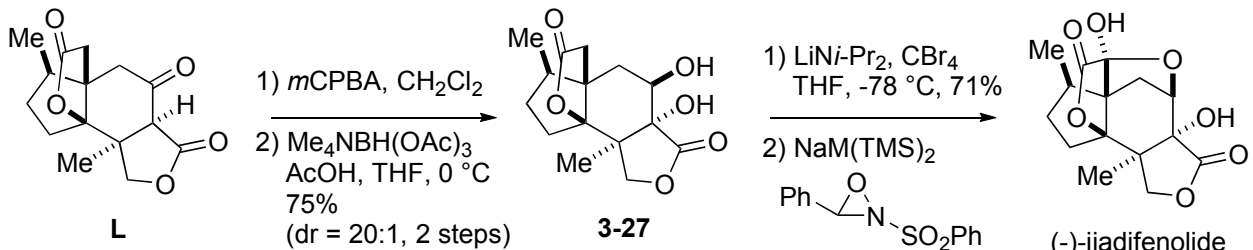
no reaction: $Zn(OTf)_2$, $ZnBr_2$, ZnI_2, $Mg{\bullet}OEt_2$, $Cu(OAc)_2$, Et_3B, $TiCl_4$, $TiCl(O\textit{i}\text{-}Pr)_3$, $BF_3{\bullet}OEt_2$, $\textit{i}\text{-}Bu_2AlCl$

only Ti(O*i*-Pr)$_4$ gave **L** in 80% yield.

↓

Dianion species such as **3-22** was not generated in relatively strong Lewis acidic conditions? (my proposal)

Completion of the total synthesis



L **3-27** (-)-jiadifenolide