Problem Session (3) Answer

2018/10/27 Takumi Fukuda

Topic: Total syntheses by Matthew D. Shair

0. Introduction

Prof. Matthew D. Shair

1990 : BS the University of Rochester

1995 : Ph.D. Columbia University (Prof. Samuel Danishefsky)

1995 - 1997 : Postdoc. Harvard University (Prof. Stuart Schreiber)

1997 - : Assistant Prof. Harvard University

2001 - : Associate Prof. Harvard University

2002 - : Professor Harvard University

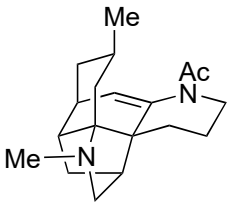
Reseach Topic:

1. Chemical biology

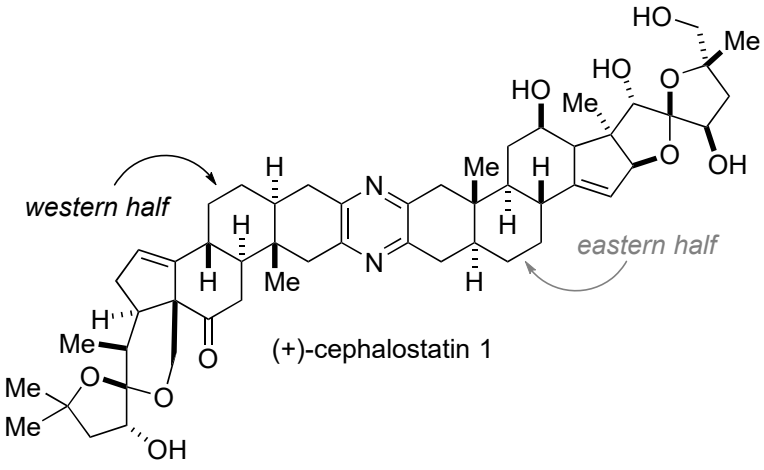
2. Total synthesis

Total synthesis:

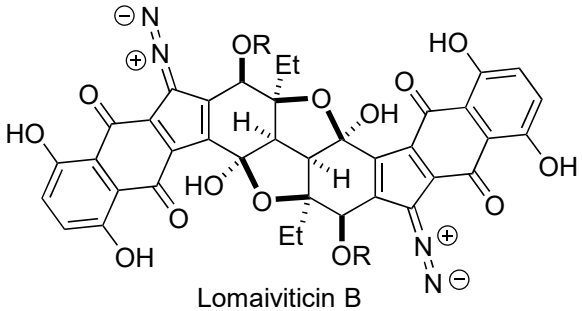
2008: (+)-cortistatin A (141101_PS_Akinori_YAMAGUCHI)
2010: (+)-fastigiatine (**Problem 1**) and (+)-cephalostatin 1 (**Problem 2**, 100605_LS_Ken MUKAI)
2011: A'B' subunit of Angelmicin B (synthetic study)
2012: HMP-Y1, Hibarimicinone, and HMP-P1
2013: C4-epi-Lomaiviticin B core (synthetic study, **Problem 3**), hyperforin
2014: (–)-Himeradine A, (–)-Lycopecurine, and (–)-Dehydrolycopecurine, (+)-Lyconadin A and (–)-Lyconadin B
2015: (–)-Nemorosone and (+)-Secohyperforin



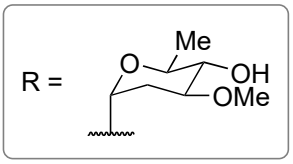
(+)-fastigiatine



(+)-cephalostatin 1

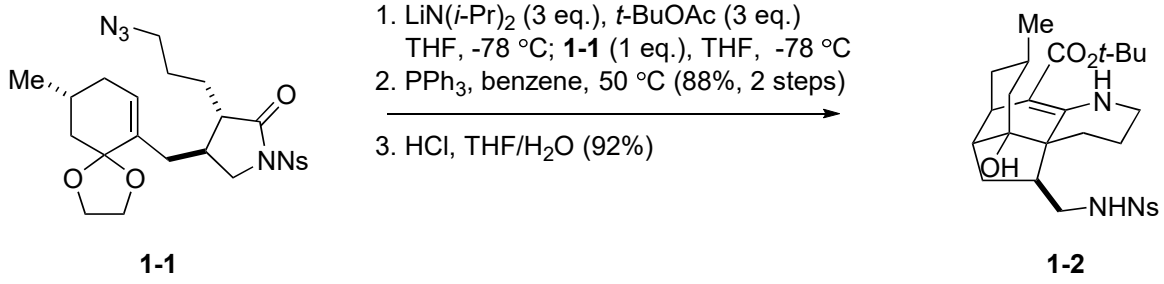


Lomaiviticin B



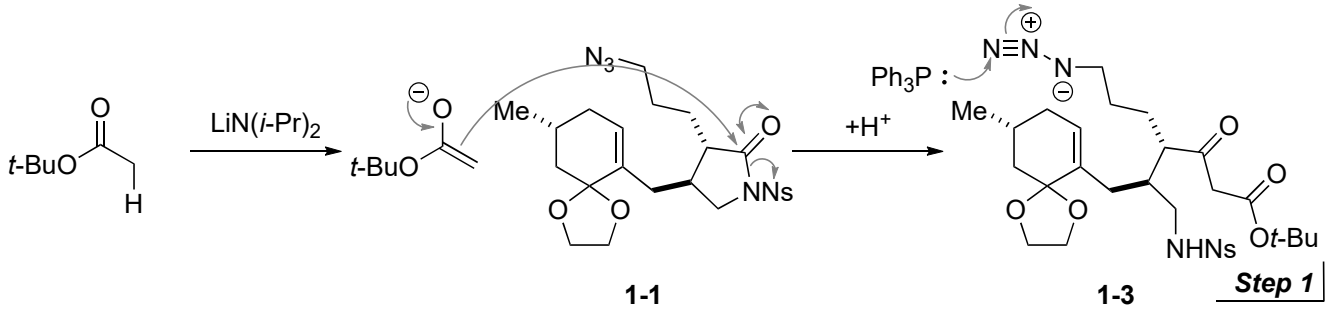
1-1. Reaction mechanism

(1)

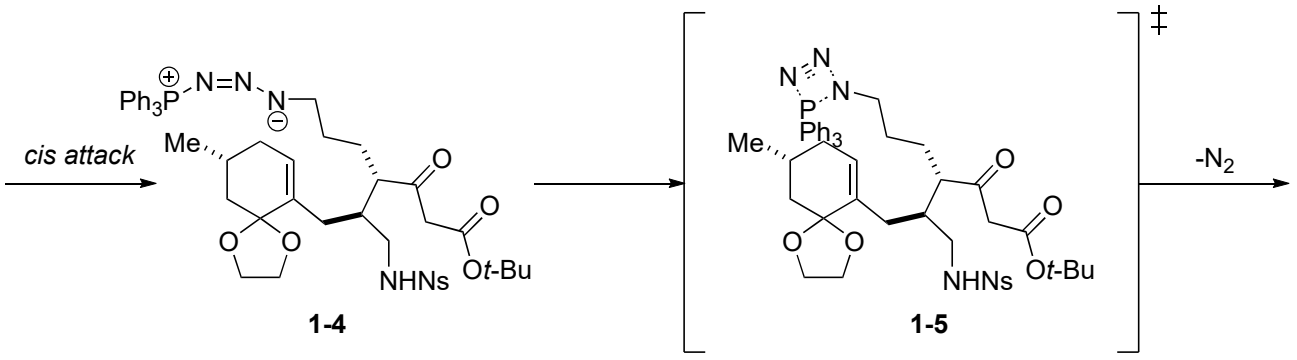


1-1 **1-2**

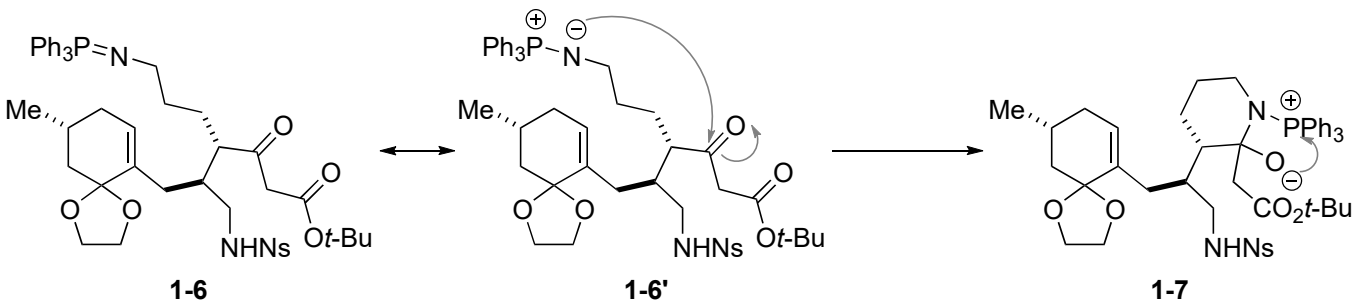
Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 9594.



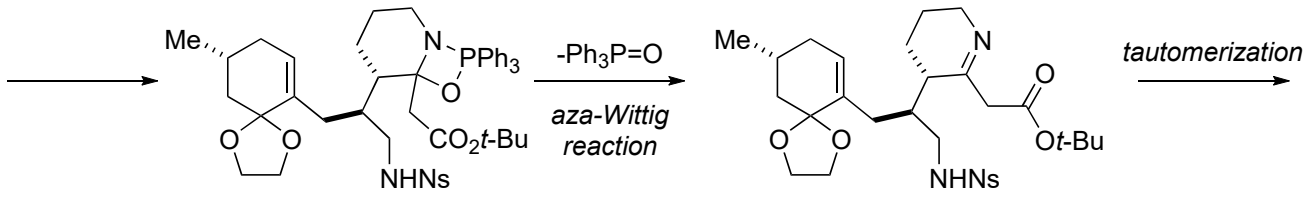
1-1 **1-3** ***Step 1***



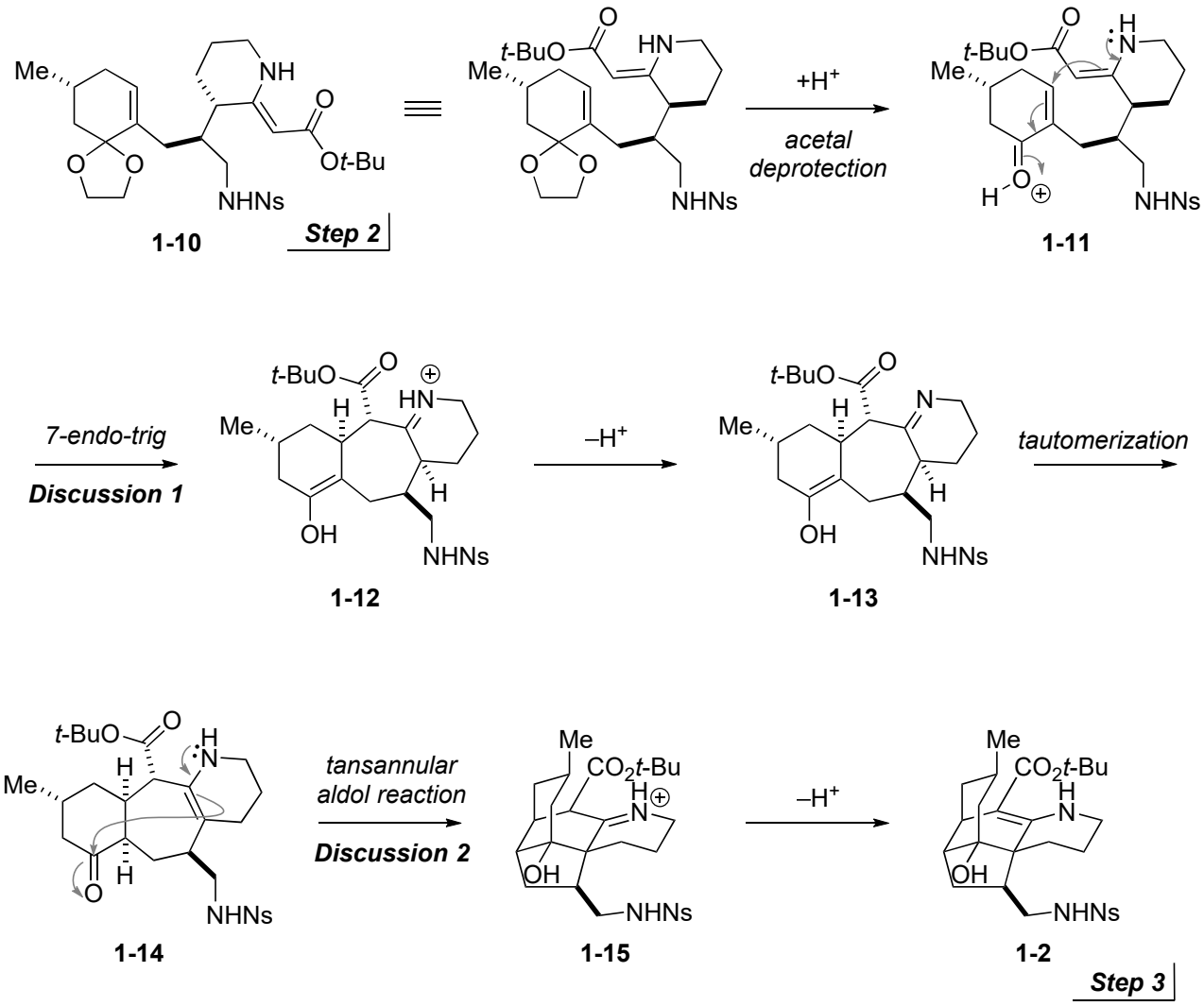
1-4 **1-5**



1-6 **1-6'** **1-7**

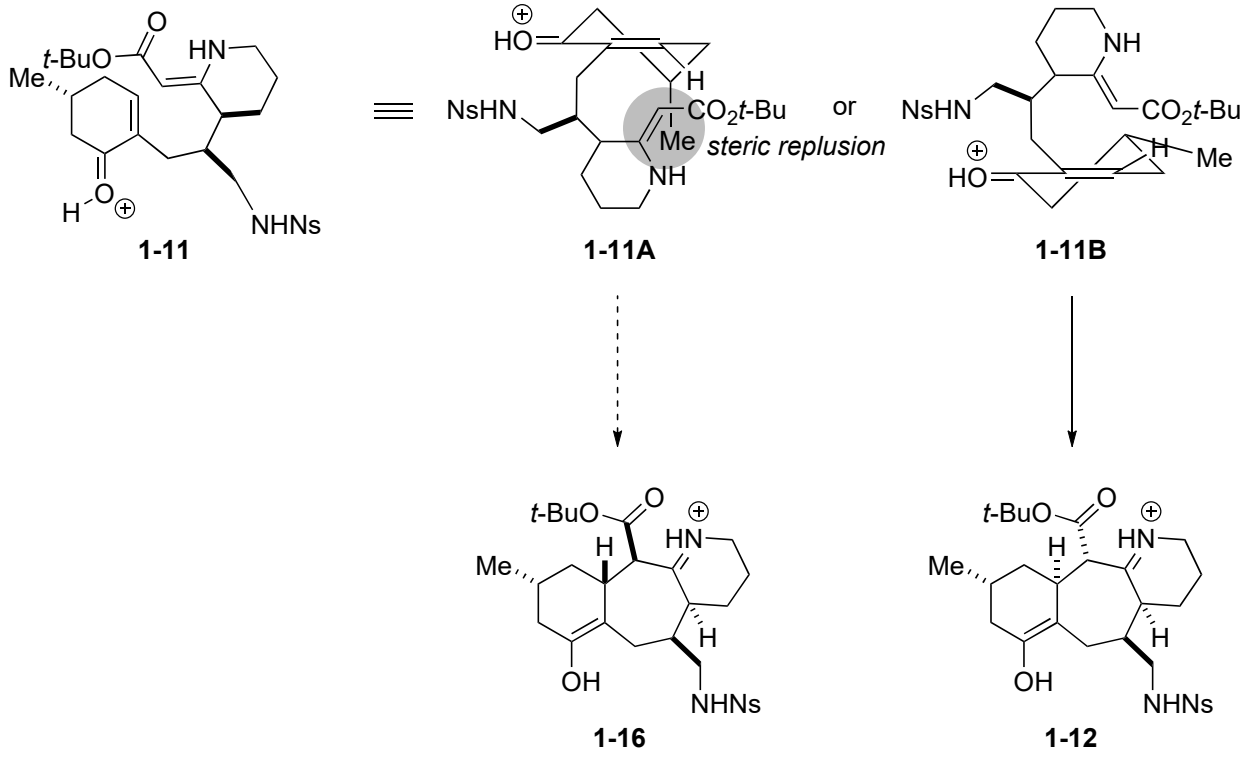


1-8 **1-9**

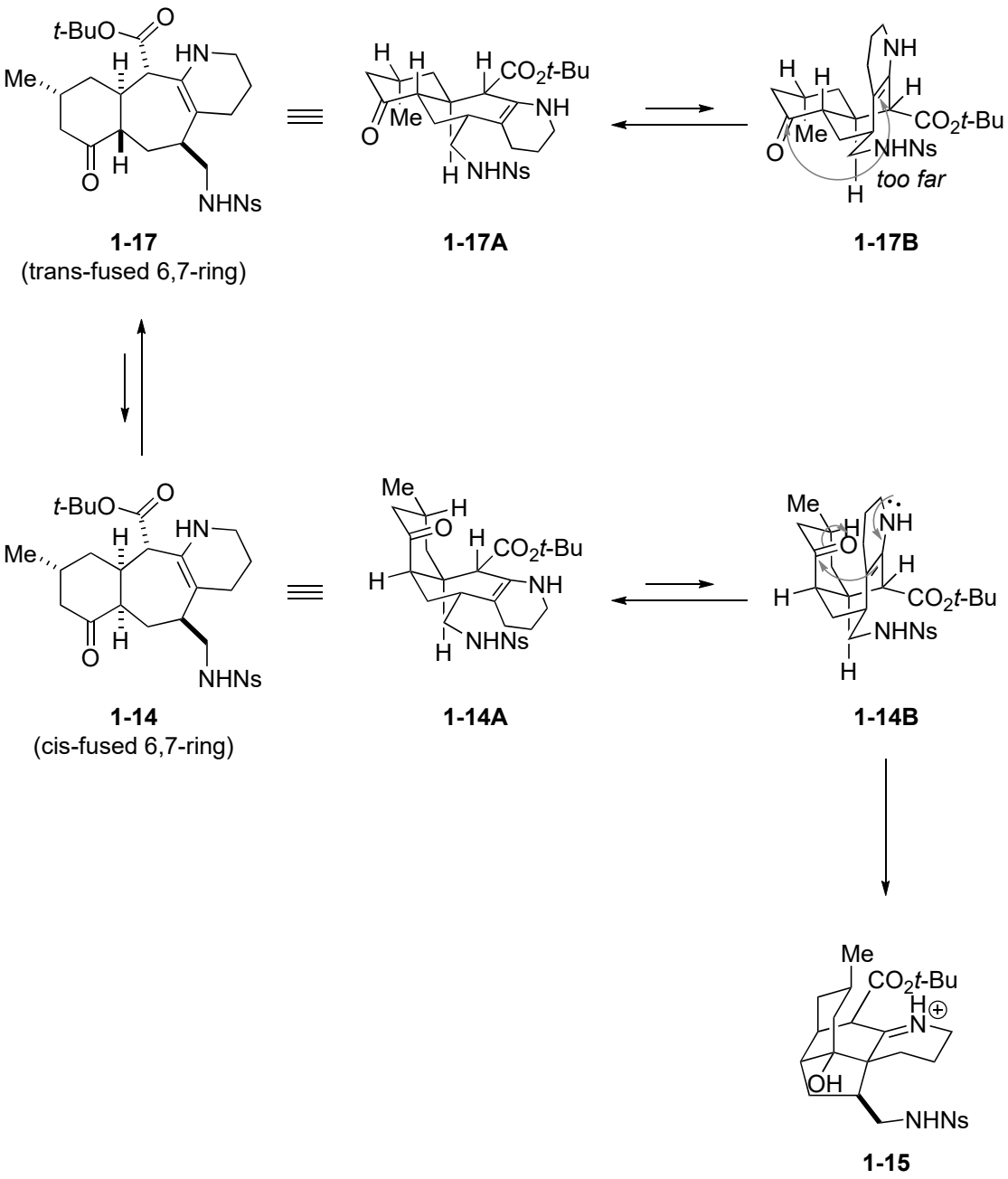


1-2. Discussion

1-2-1. 7-endo-trig cyclization (***Discussion 1***)

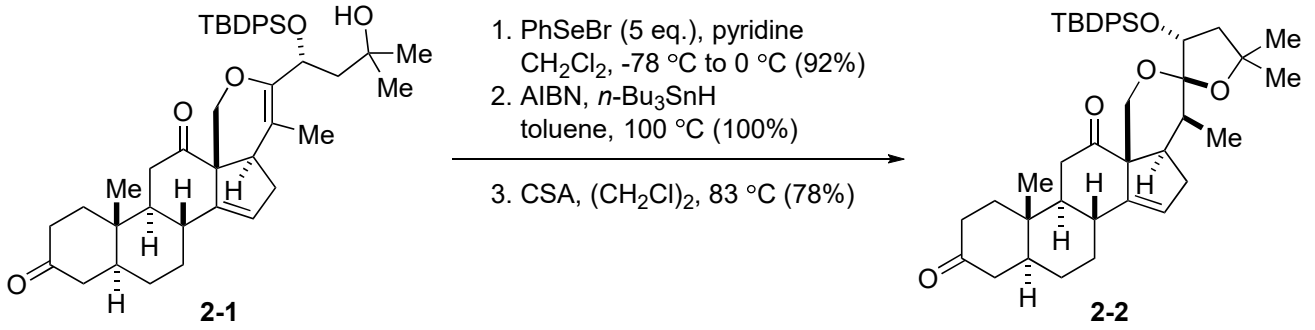


1-2-1. tansannular aldol reaction (***Discussion 2***)

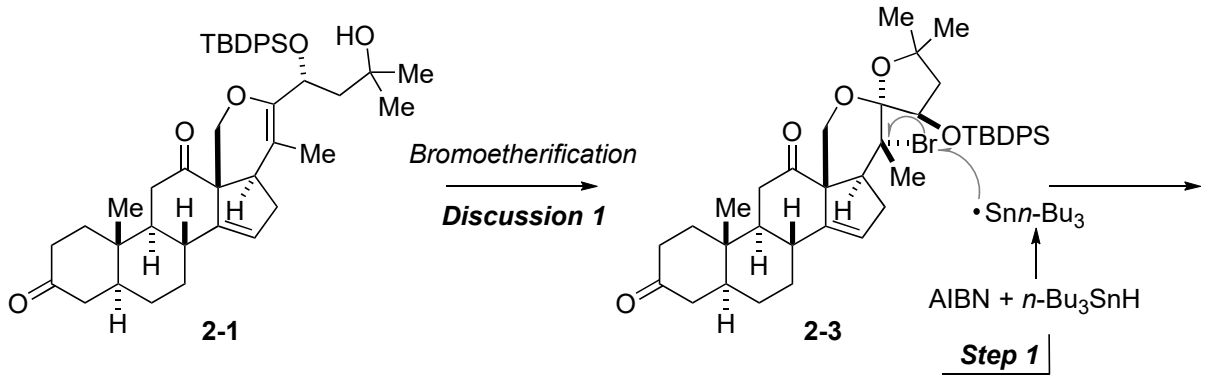


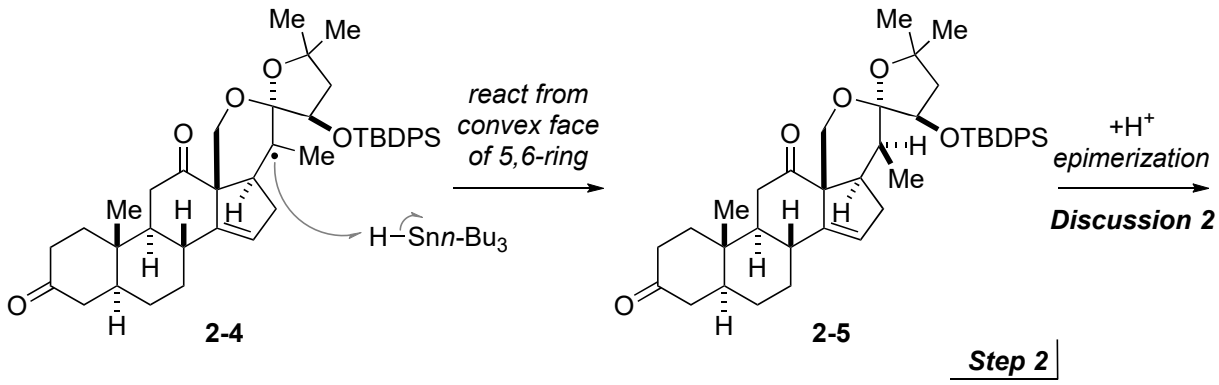
2-1. Reaction mechanism

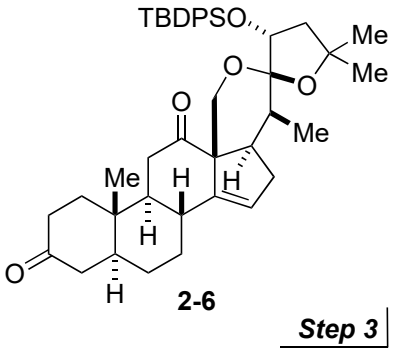
(2)



Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 275.





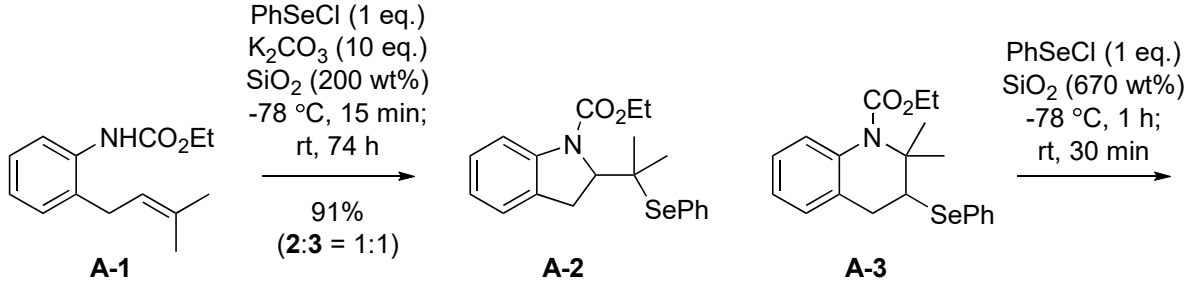


1-2. Discussion

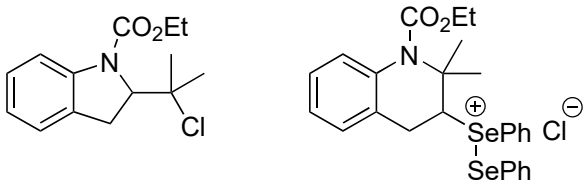
1-2-1. Bromoetherification (***Discussion 1***)

(1) Activation of selenide group by PhSeCl

Cooper, M. A.; Francis, C. L.; Holman, J. W.; Kasum, B.; Trverner, T. Tiekink, E. R. T.; Ward, A. D. *Aust. J. Chem.* **2000**, *53*, 123.



A-1 **A-2** **A-3**

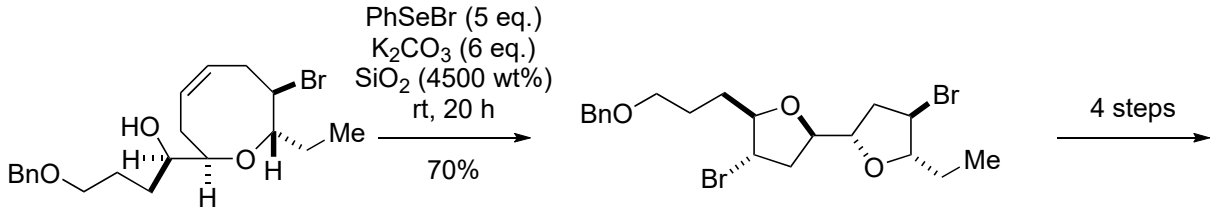


A-4
100% from **A-2**

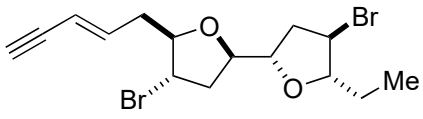
A-5 (salt, unstable)
36% from **A-3**

(2) Application to total synthesis

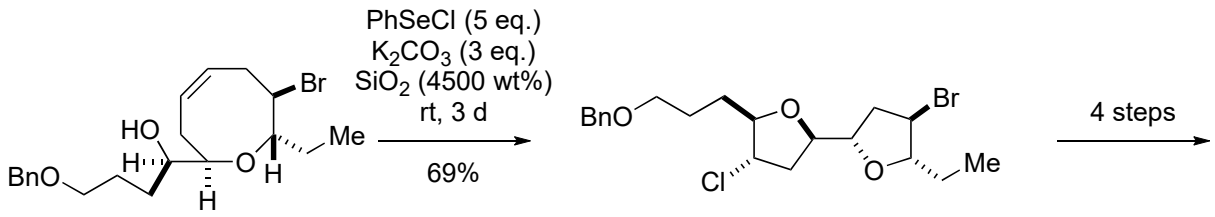
Dyson, B. S.; Burton, J. W.; Sohn, T.; Kim, B.; Bae, H.; Kim, D. *J. Am. Chem. Soc.* **2012**, *134*, 11781.



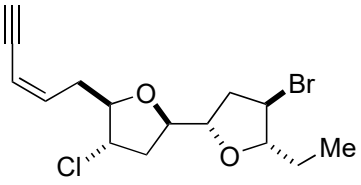
B-1 **B-2**



ent-(*E*)-elatenyne (**B-3**)

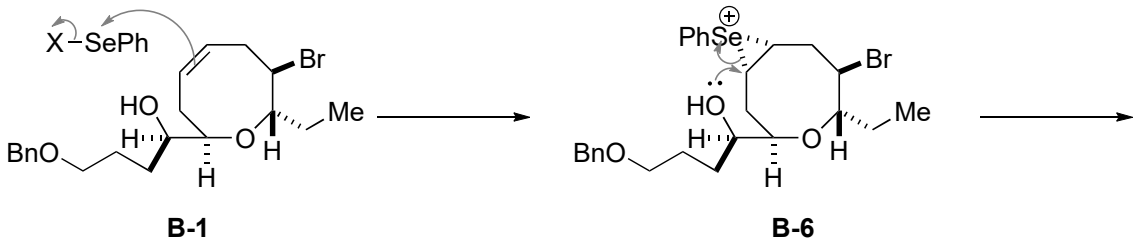


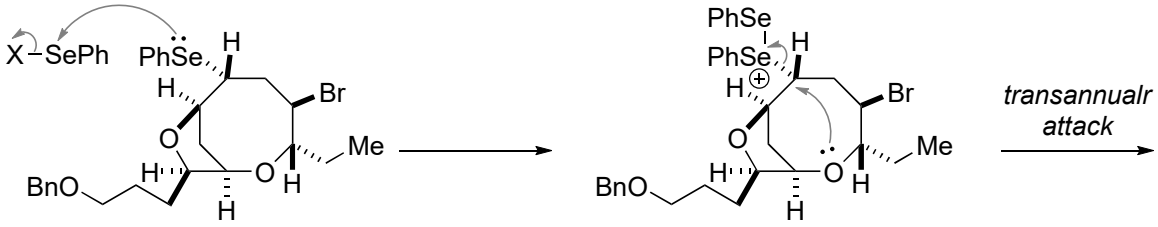
B-1 **B-4**

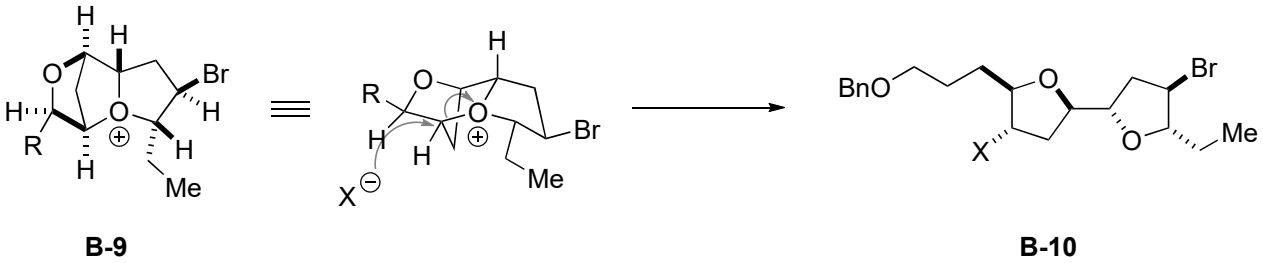


ent-laurendecumenyne B (**B-5**)

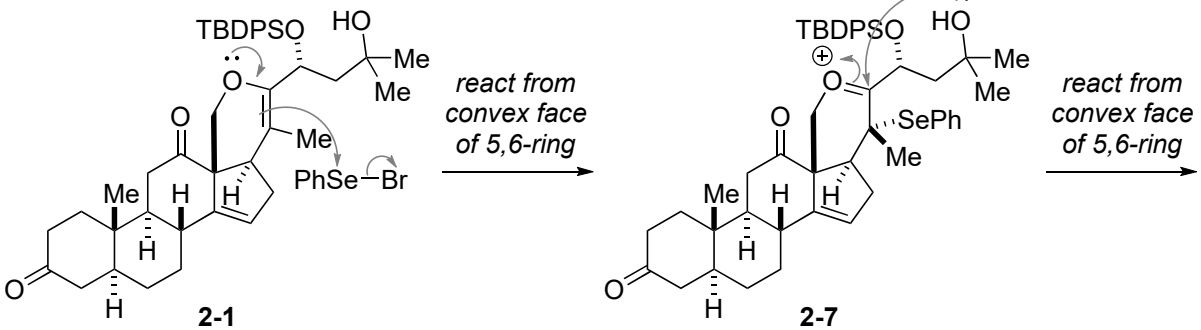
Proposed mechanisms: X = Cl or Br

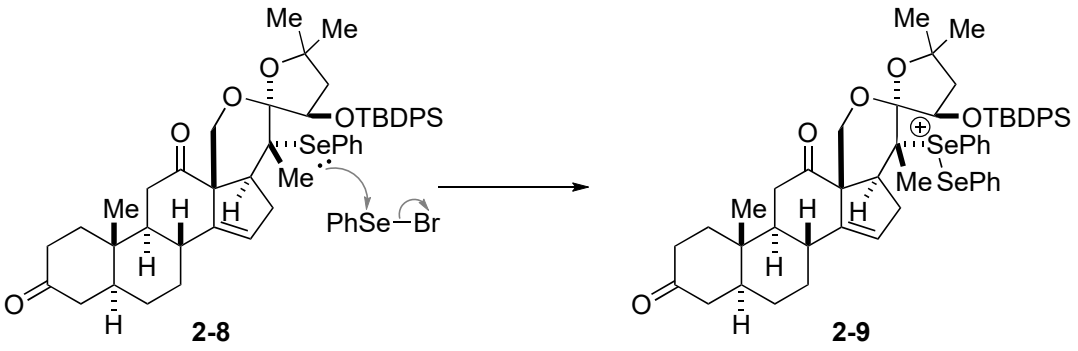


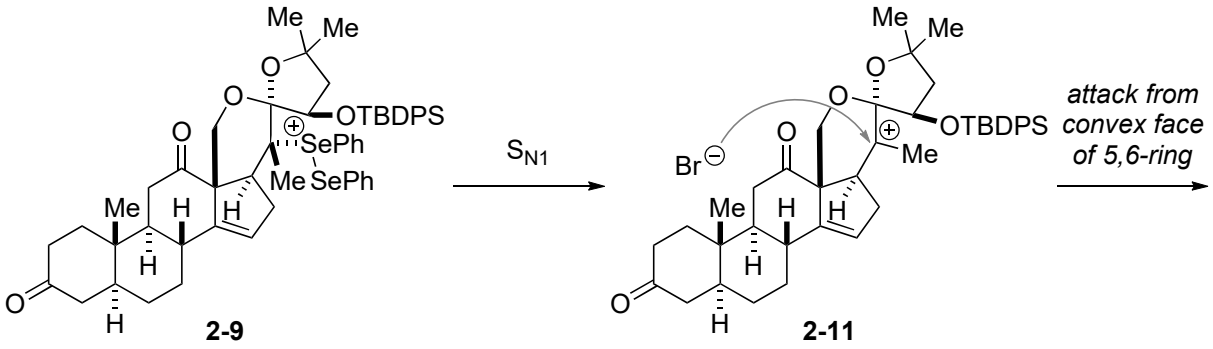


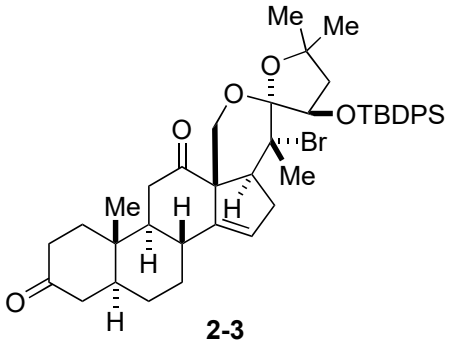


Proposed mechanisms:



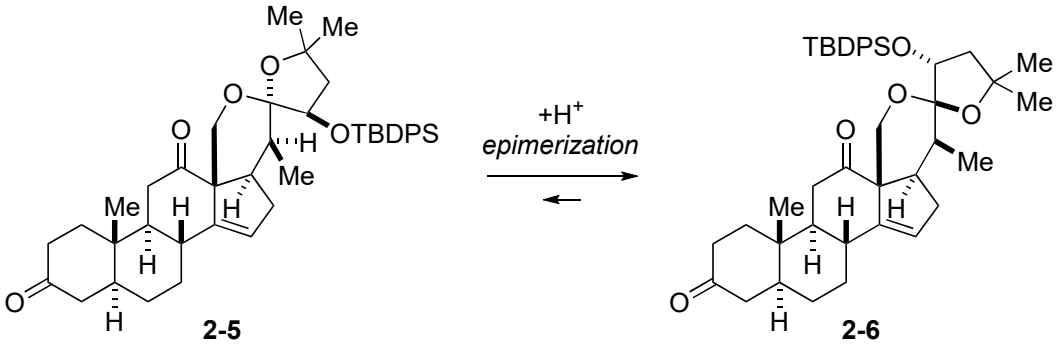


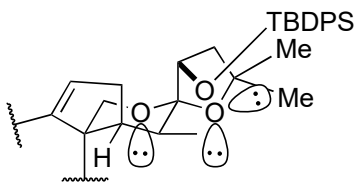




1-2. Discussion

1-2-2. Epimerization of spiro acetal (***Discussion 2***)

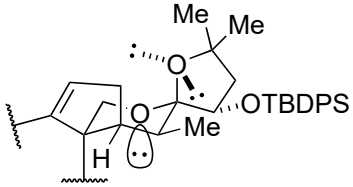




one anomeric effect

↓

less stable



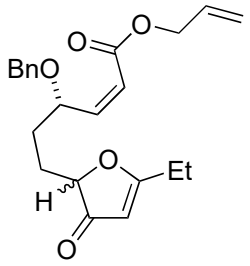
two anomeri effect

↓

more stable

3-1. Reaction mechanism

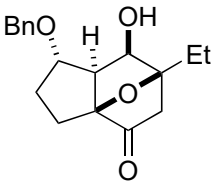
(3)



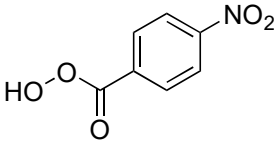
3-1
(Z:E = 12.5:1)

1. LiN(*i*-Pr)$_2$, THF, -78 °C (68%)
2. Pd(PPh$_3$)$_4$ (10 mol%)
   morpholine, THF
3. (COCl)$_2$, DMF (cat.);
   A, pyridine, DMAP (cat.), CH$_2$Cl$_2$

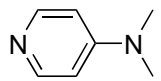
4. benzene, 80 °C
5. K$_2$CO$_3$, MeOH, 0 °C (38%, 4 steps)



3-2

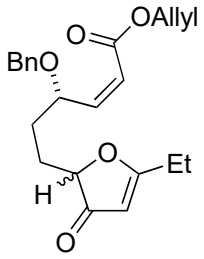


A



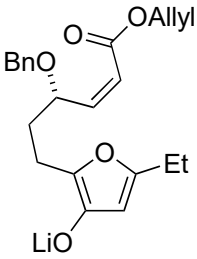
DMAP

Lee, A. S.; Shair, M. D. *Org. Lett.* **2013**, *15*, 2390.



3-1
(Z isomer)

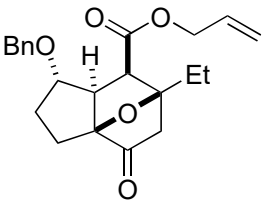
LiN(*i*-Pr)$_2$



3-3

formal Diels-Alder
concerted or stepwise

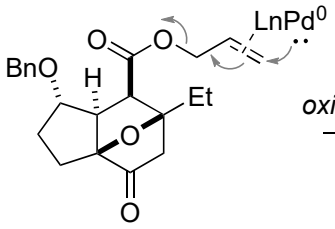
Discussion 1



3-4 ***Step 1***

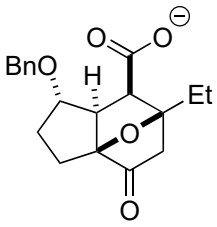
Pd^0(PPh$_3$)$_4$

cordination

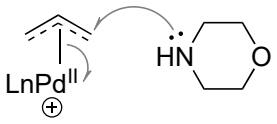


3-5

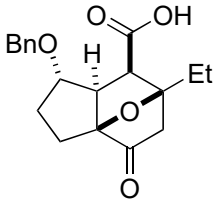
oxidtive addition



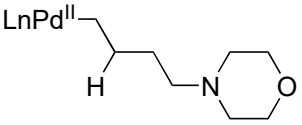
3-6



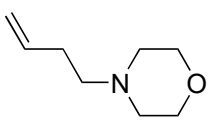
±H$^+$

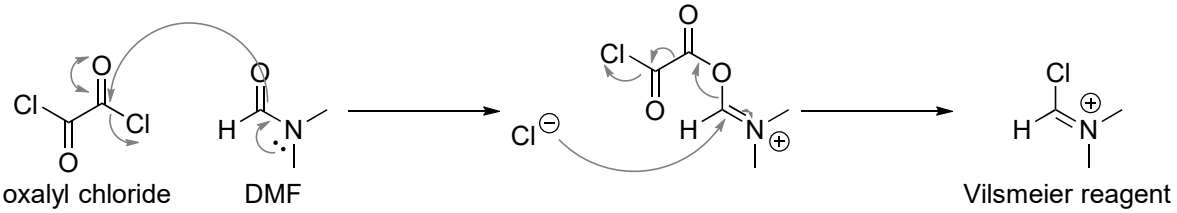


3-7 ***Step 2***

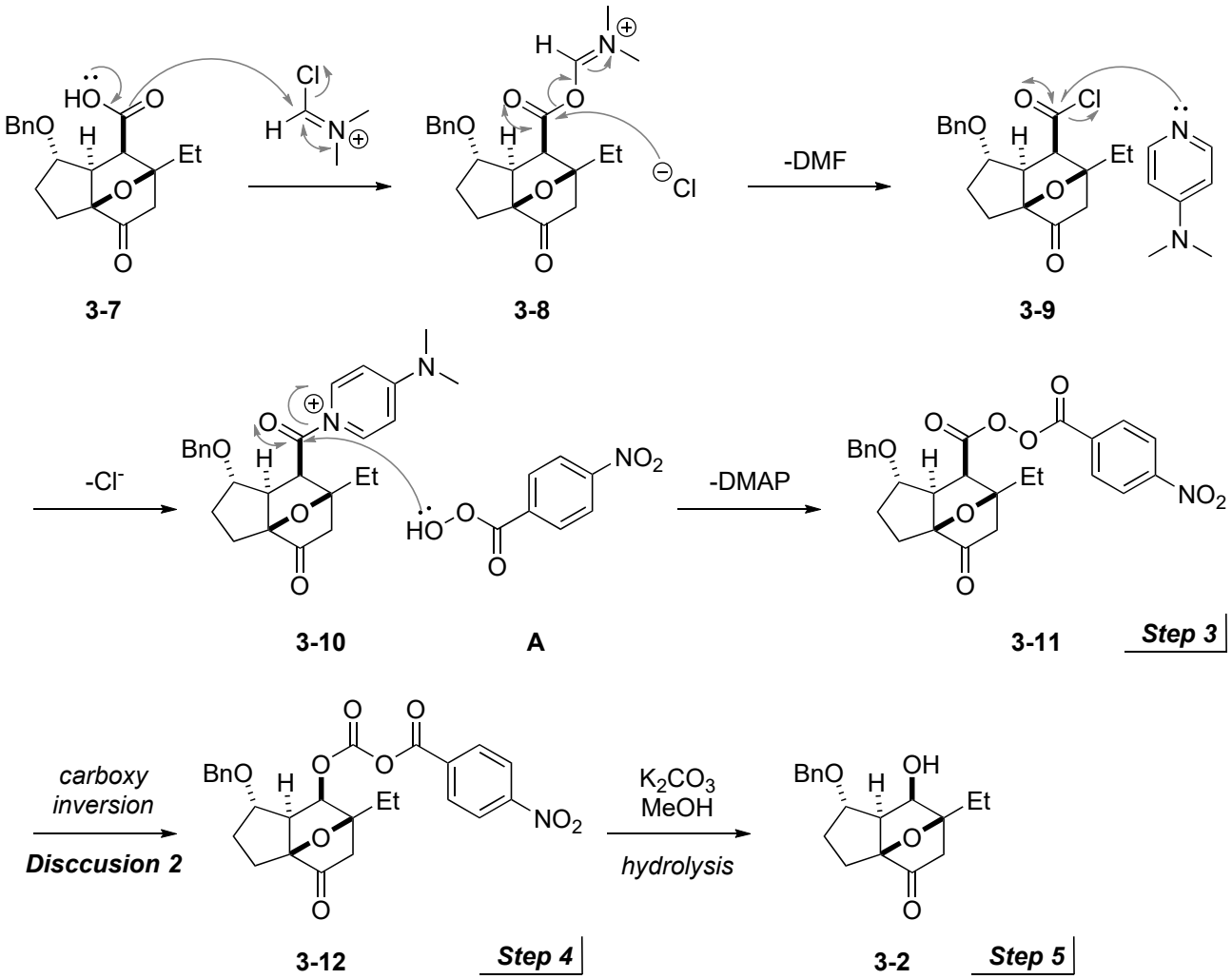


β-hydride
elimination



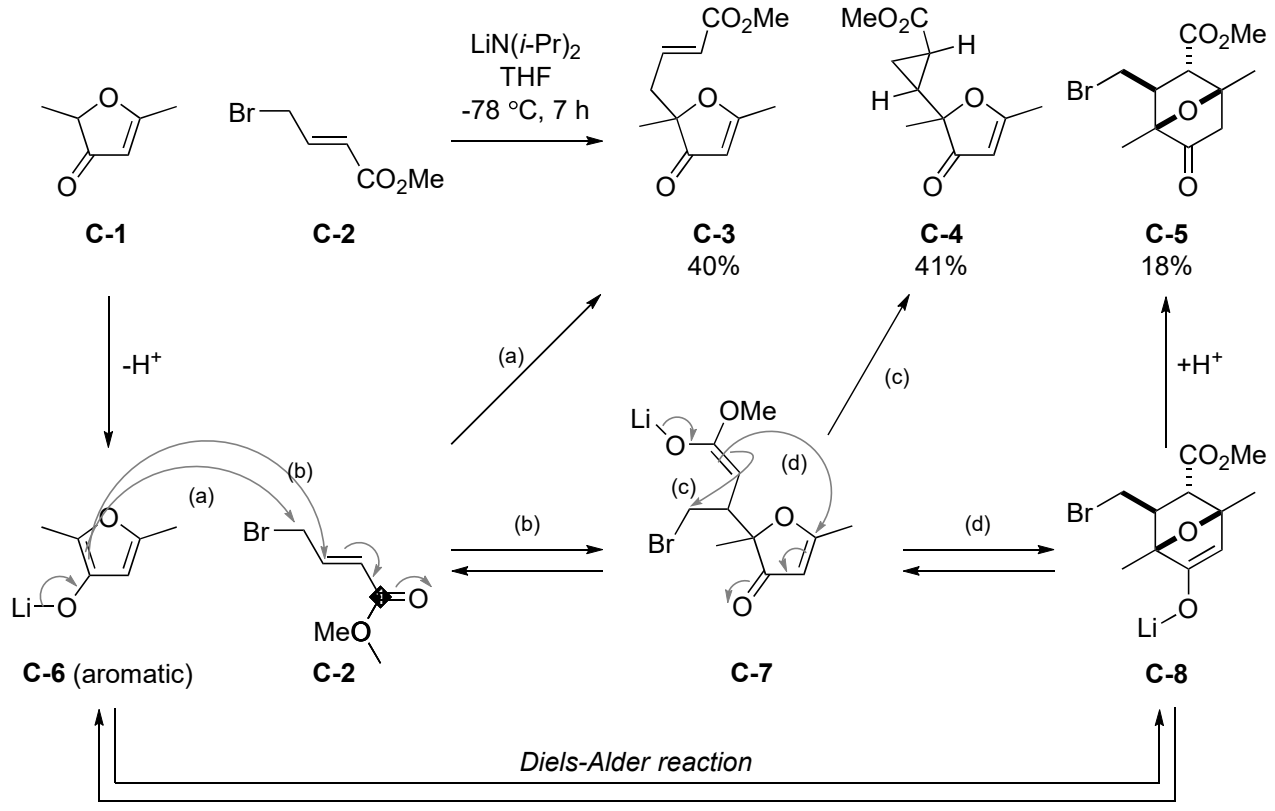


oxalyl chloride DMF Vilsmeier reagent



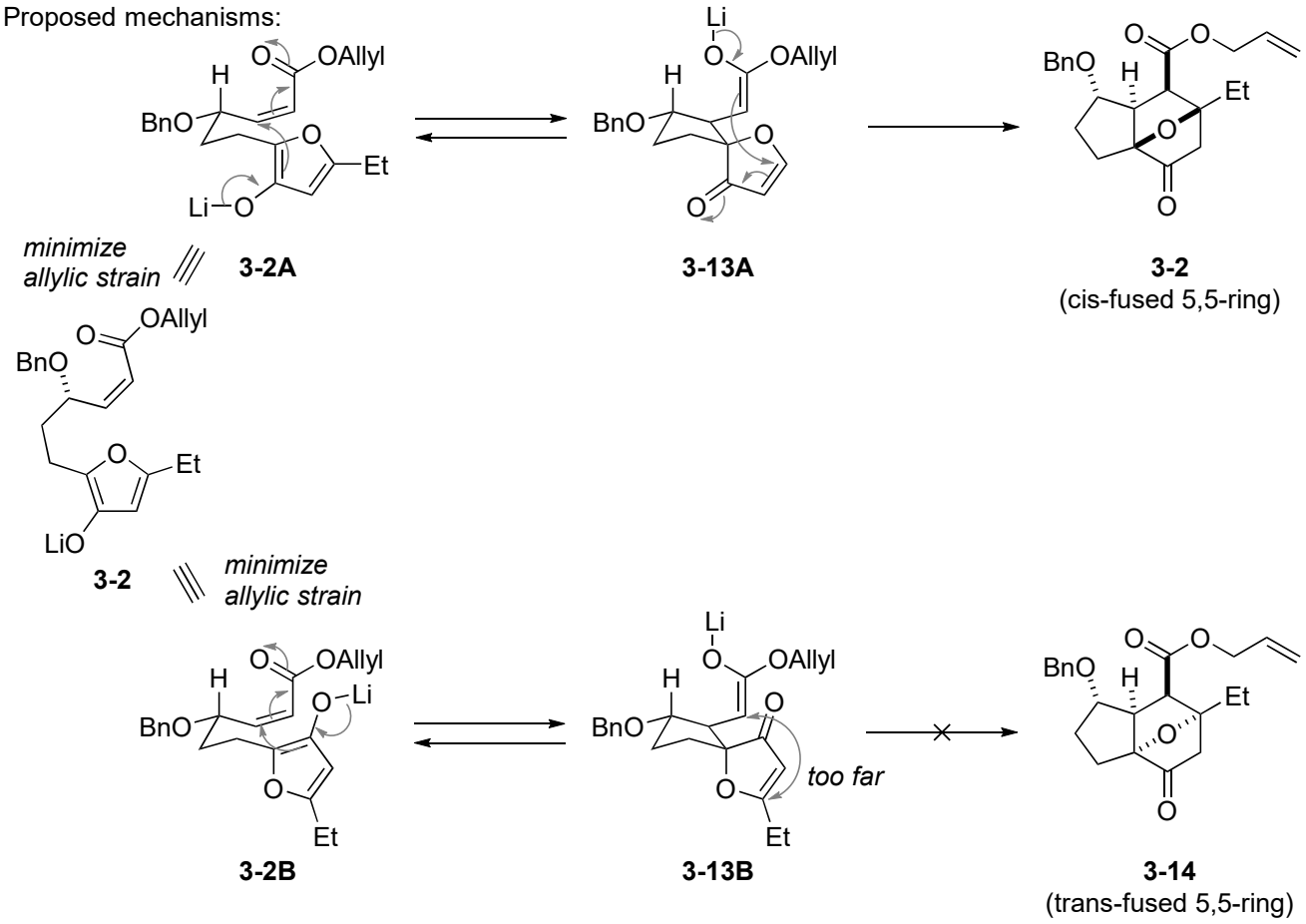
3-2. Discussion

3-2-1. Formal Diels-Alder reaction (***Discussion 1***) Caine, D. S.; Paige, M. A. *Synlett* **1999**, *9*, 1391.



This results seem to support stepwise Micheal-addition mechanism.
However, the possiblity of Diels-Alder reaction which directly produce **C-8** was not ruled out because **C-8** can yield **C-4** via reversible formation of **C-7**.

Proposed mechanisms:



3-2. Discussion

3-2-2 Carboxy-inversion reaction (***Discussion 2***)

Fujimori, K.; Oae, S. *J. Chem. Soc., Perkin Trans. 2*, **1989**, 1335.

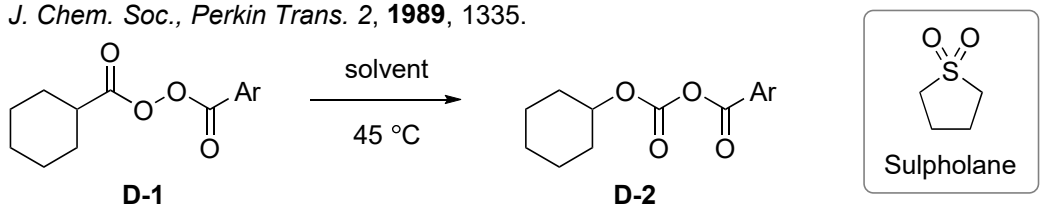
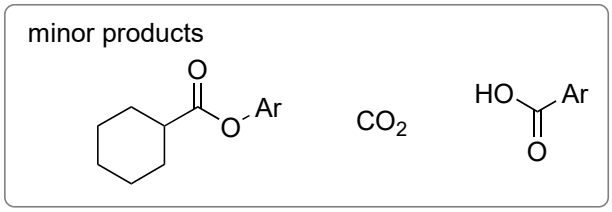


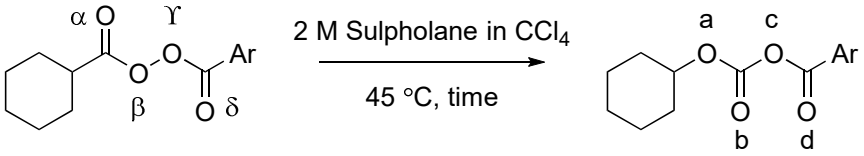
Table 1. solvent and substituent effect

entry	Ar	solvent	$k_d/10^{-5}$ (s^{-1})
1	Ph	CCl_4	6.72 ± 0.30
2	Ph	2 M Sulpholane in CCl_4	42.3 ± 0.2
3	*m*-Cl-C_6H_4	CCl_4	19.3 ± 0.3
4	*m*-Cl-C_6H_4	2 M Sulpholane in CCl_4	116 ± 0.9

Polar solvent and an electron-withdrawing substituent on aryl group accelerate the carboxy-inversion reaction. It has been considered that the carboxy-inversion reaction proceeded mainly through an ionic path.

* carboxy inversion reaction In CCl_4 gave **D-2** as a major product along with ester, CO_2, carboxylic acid, as minor products.





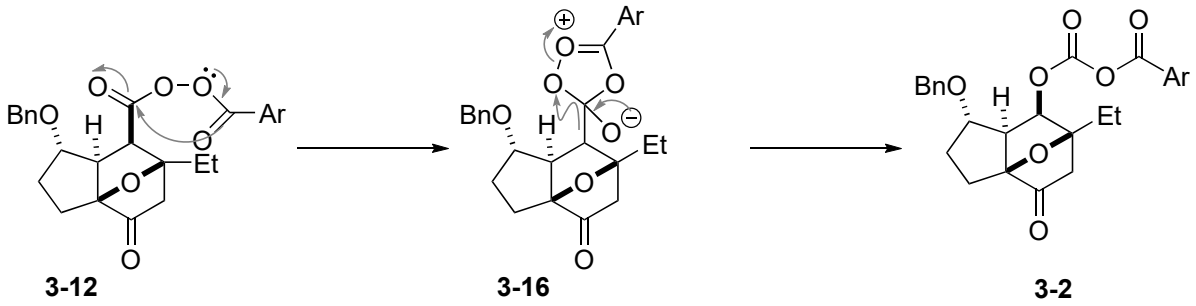
D-1 **D-2**

Table 2. ^{18}O-tracer experiments

entry	Ar	^{18}O-labelled in SM	time (min)	^{18}O-incorporation into TM (%) a	b	c	d
1	Ph	α	175	4	83	13	0
2	*m*-Cl-C_6H_4	α	70	4	91	5	0
3	Ph	δ	194	0	4	27	69
4	*m*-Cl-C_6H_4	δ	70	0	2	35	63

O-α in SM was mainly transfered to O-b and O-c in TM and O-δ in SM was mainly transfered to O-c and O-d.

Proposed mechanisms:



3-12 **3-16** **3-2**