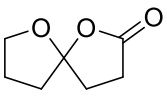
Problem Session (3) - Answer

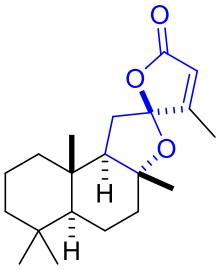
2024/12/21 D1 Wentao Wang

Topic: Total syntheses of oxaspirolactones

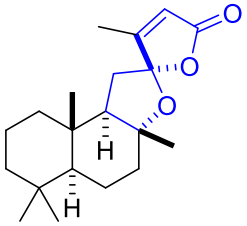
0. Introduction[3]



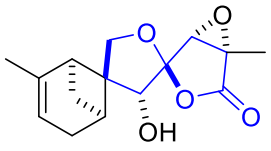
[5,5]



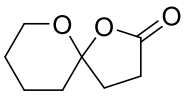
α-levantenolide (**0-1**)
Broughton, 1992[4]
Dai, 2016[5] ⇒ 241019_Junhao_Fu



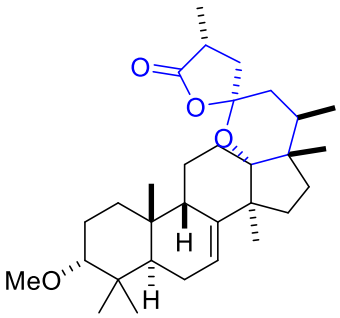
β-levantenolide (**0-2**)
Broughton, 1992[4]
Nanda, 2024[1] ⇒ **Problem 1**



purpurolide E (**0-3**)
Dai, 2021[2] ⇒ **Problem 2**

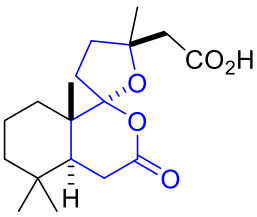


[6,5]

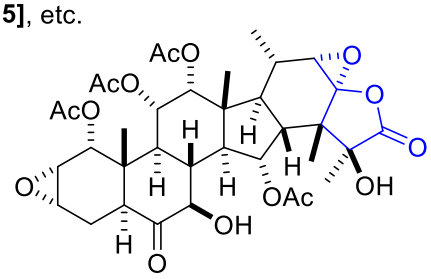


3-*O*-methylabiesatrine (**0-4**)

Less common: **[5,6]**, **[3,5]**, etc.

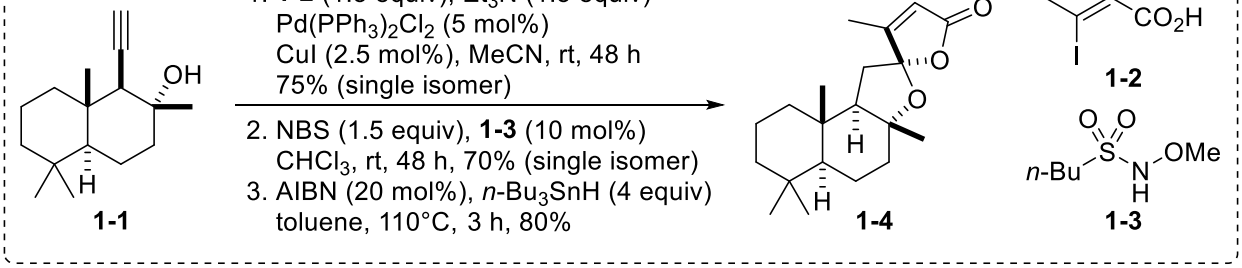


grindelistrictic acid (**0-5**)

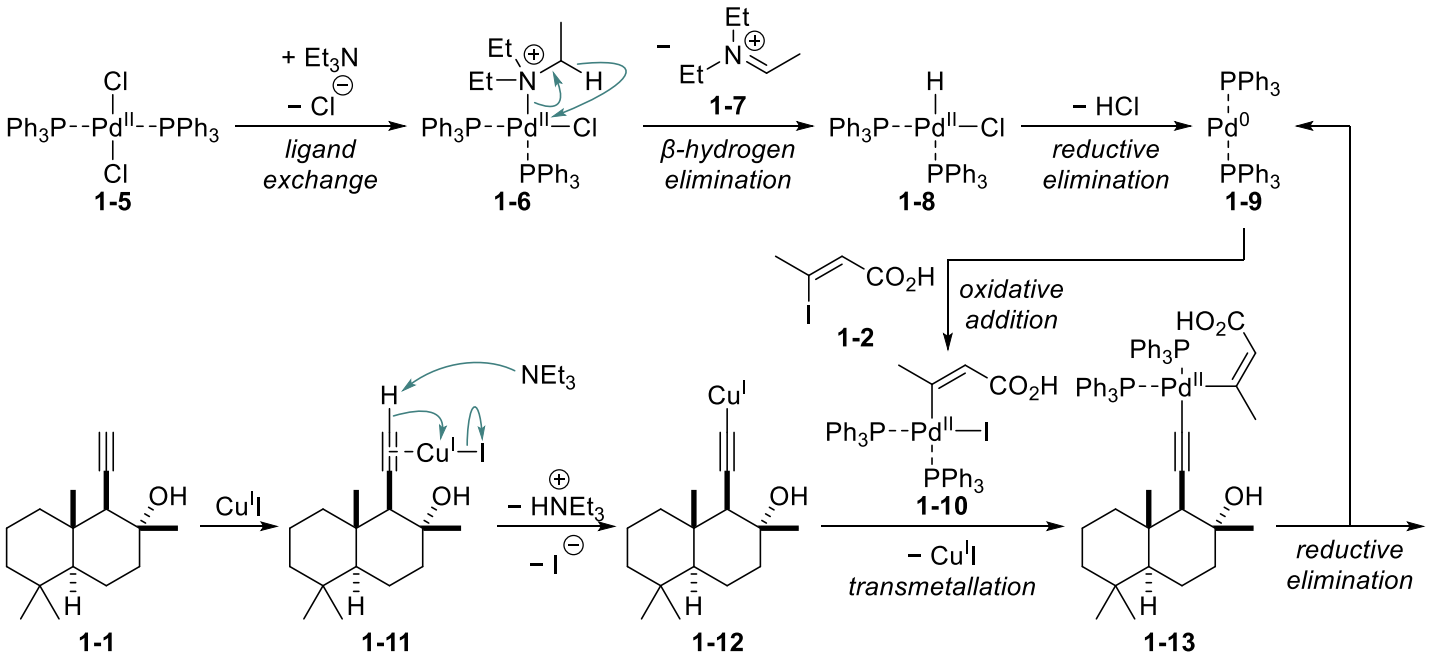


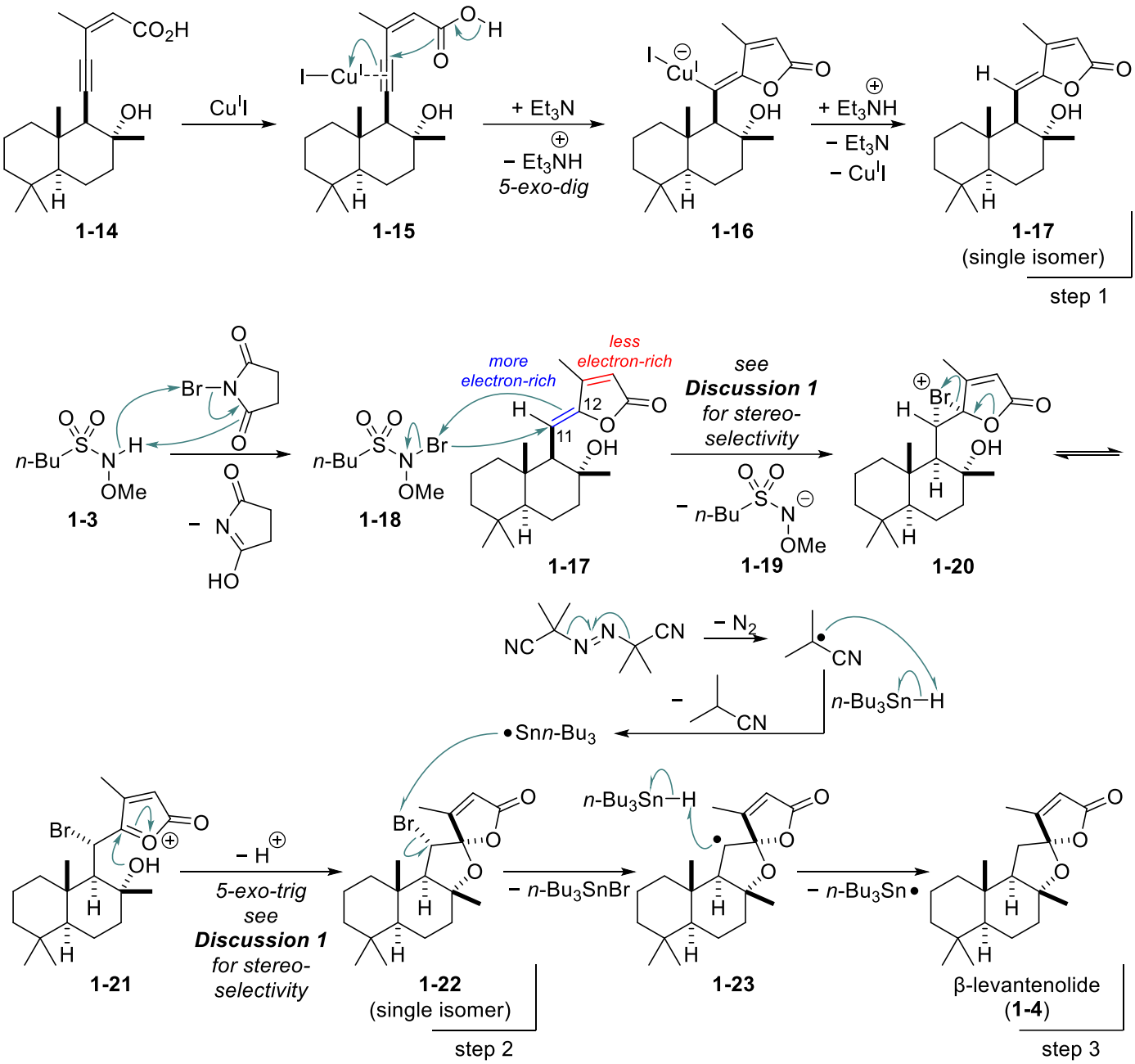
taccalonolide AF (**0-6**)

1. Problem 1[1]



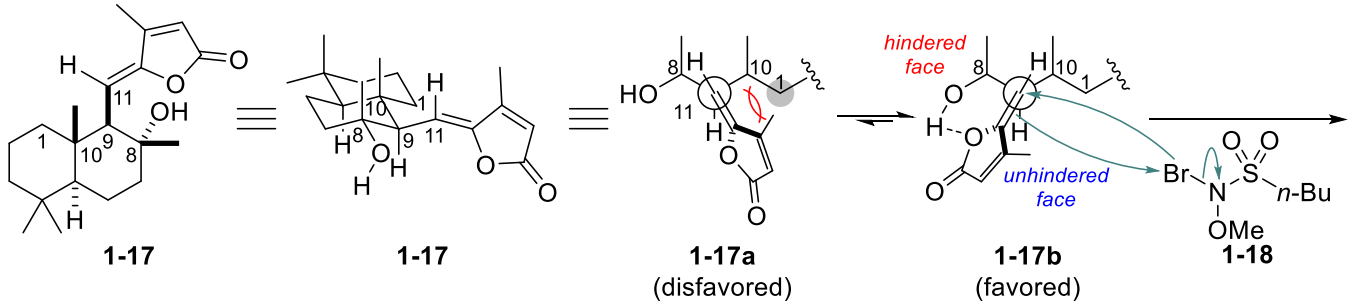
1-1. Answer

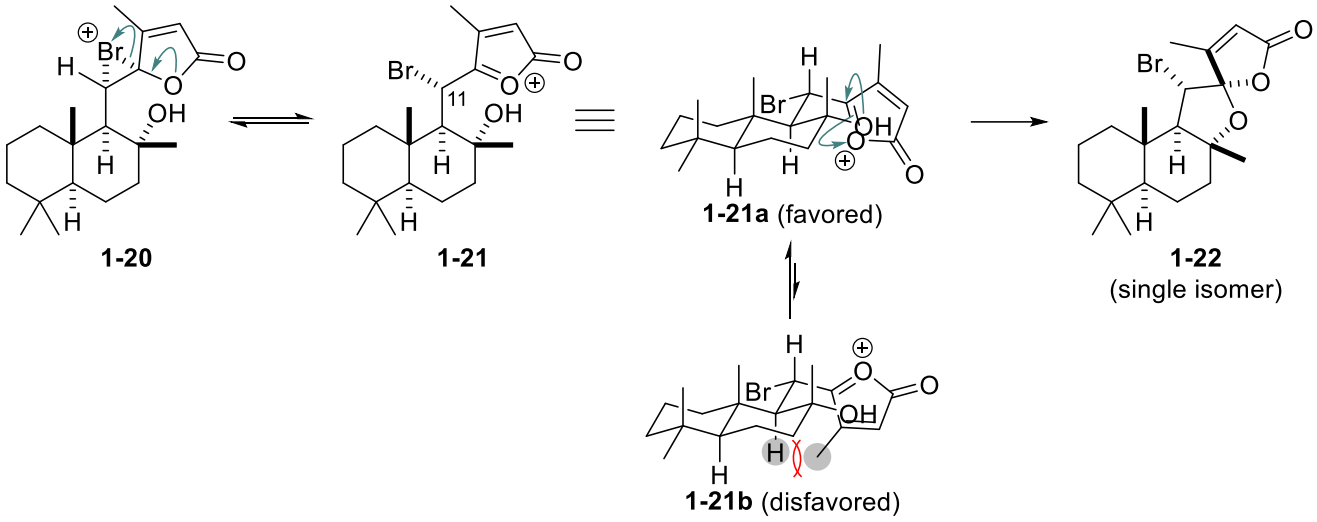




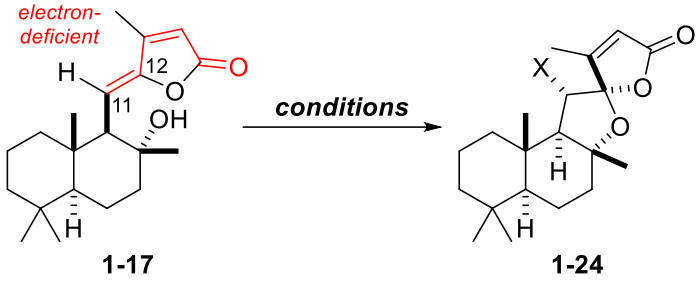
1-2. Discussion 1: bromo-spirocyclization

1-2-1. Stereoselectivity





1-2-2. Reactivity of **1-18**



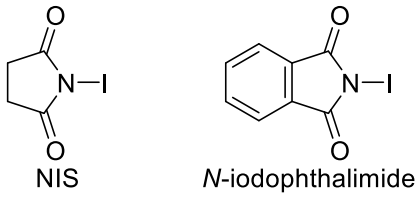
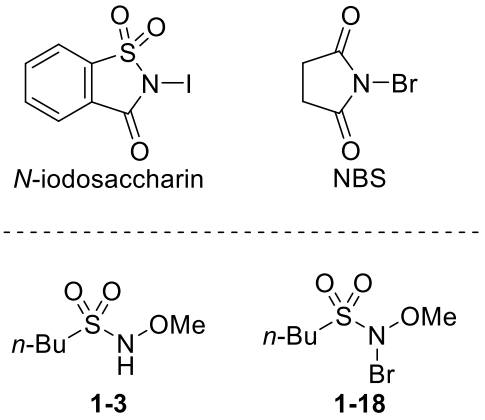
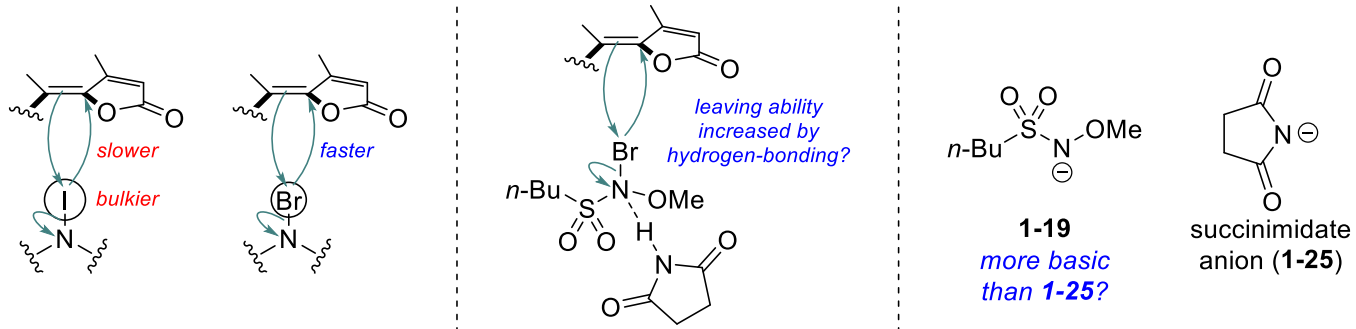
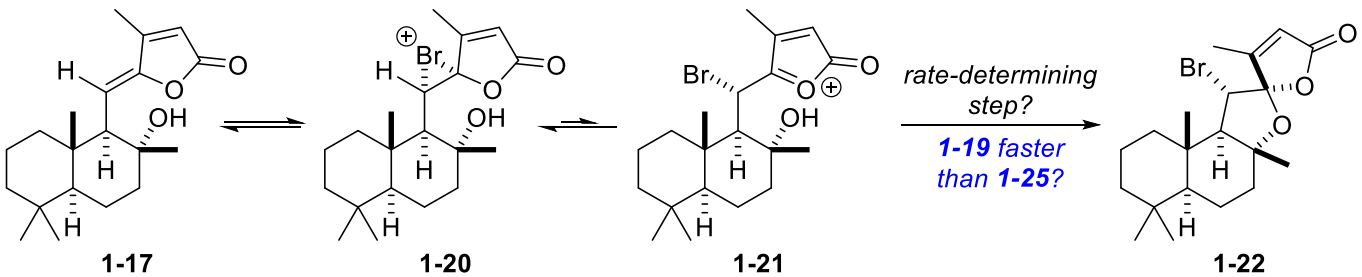


Table 1-1[1)]

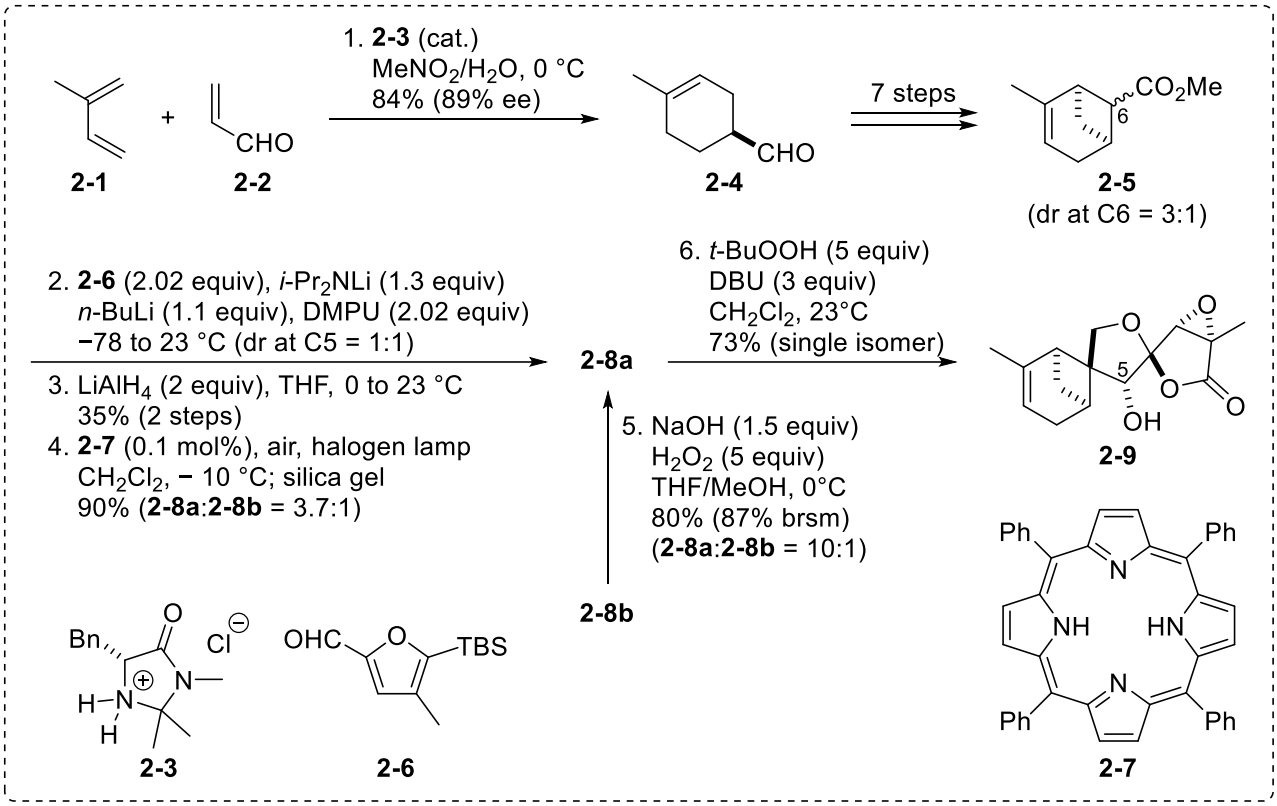
entry	reagents	solvent	yield of 1-24 (dr)
1	NIS	MeCN	10% (nd)
2	NIS, $NaHCO_3$	MeCN	20% (nd)
3	*N*-iodophthalimide	$CHCl_3$	< 10%
4	*N*-iodosaccharin	$CHCl_3$	18% (nd)
5	NBS	CH_2Cl_2	15% (nd)
6	NBS, $NaHCO_3$	$CHCl_3$	30%
7	NBS, **1-3** (10 mol%)	$CHCl_3$	70%



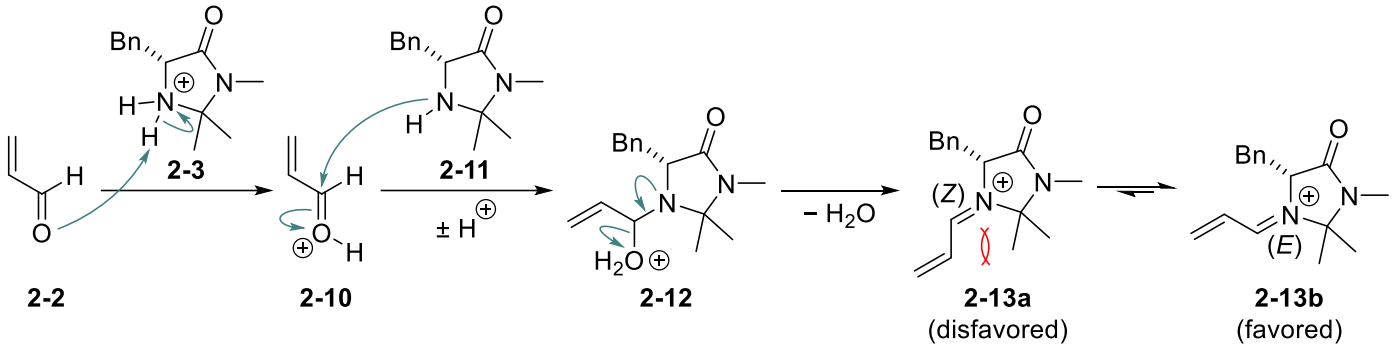


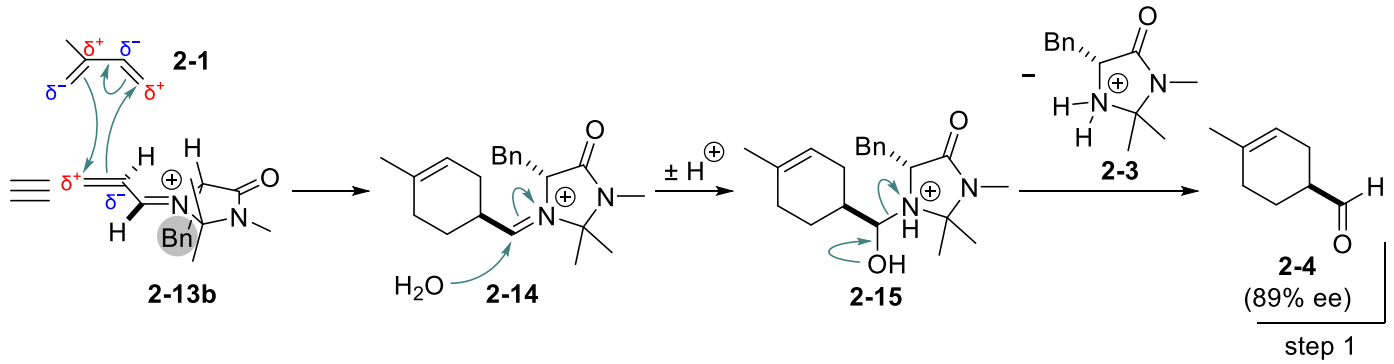


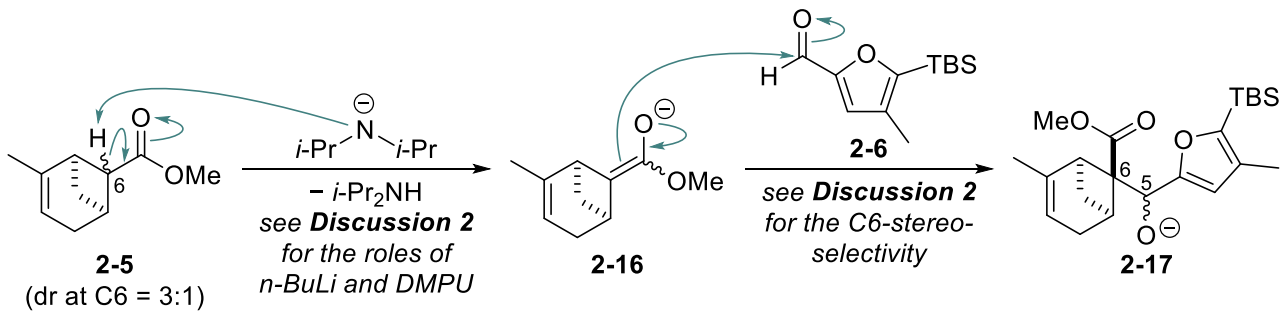
2. Problem 2[2)]

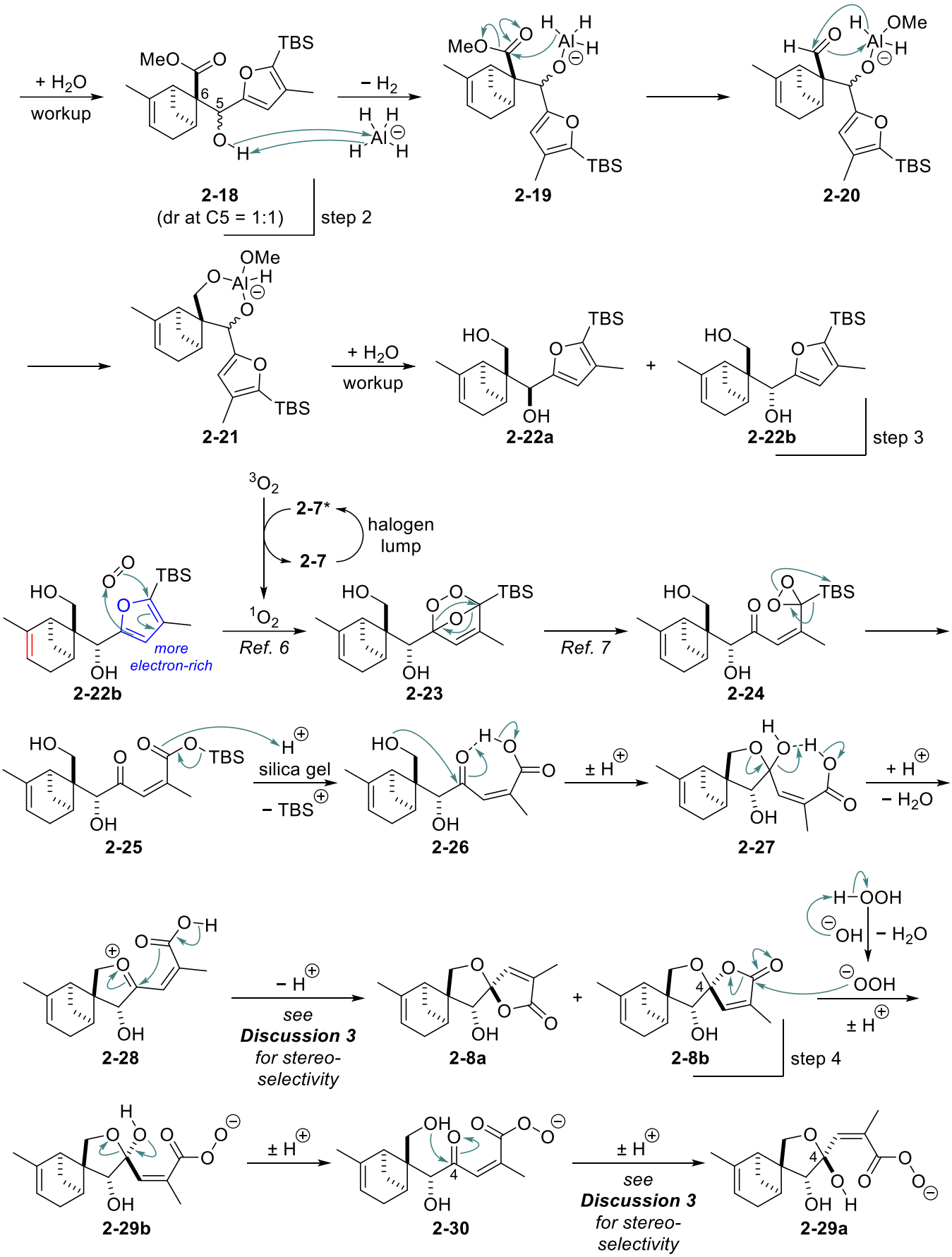


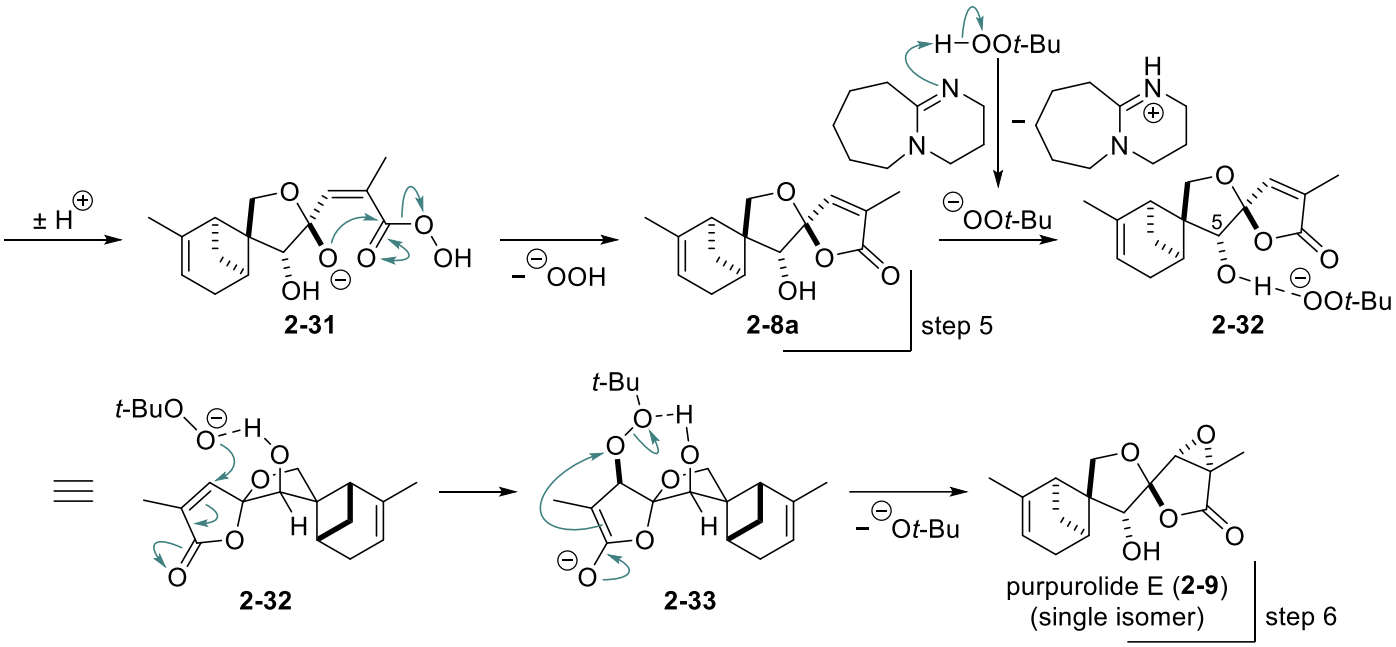
2-1. Answer








+ H2O
workup
MeO
TBS
6
5
− H2
H H
Al
H
2-18
(dr at C5 = 1:1)
step 2
2-19
2-20
OMe
2-21
+ H2O
workup
HO
OH
2-22a
2-22b
step 3
3O2
2-7*
2-7
halogen
lump
1O2
Ref. 6
more
electron-rich
2-23
Ref. 7
2-24
2-22b
2-25
silica gel
− TBS
2-26
± H
2-27
+ H
− H2O
2-28
− H
see
Discussion 3
for stereo-
selectivity
2-8a
2-8b
step 4
OOH
2-29b
2-30
2-29a

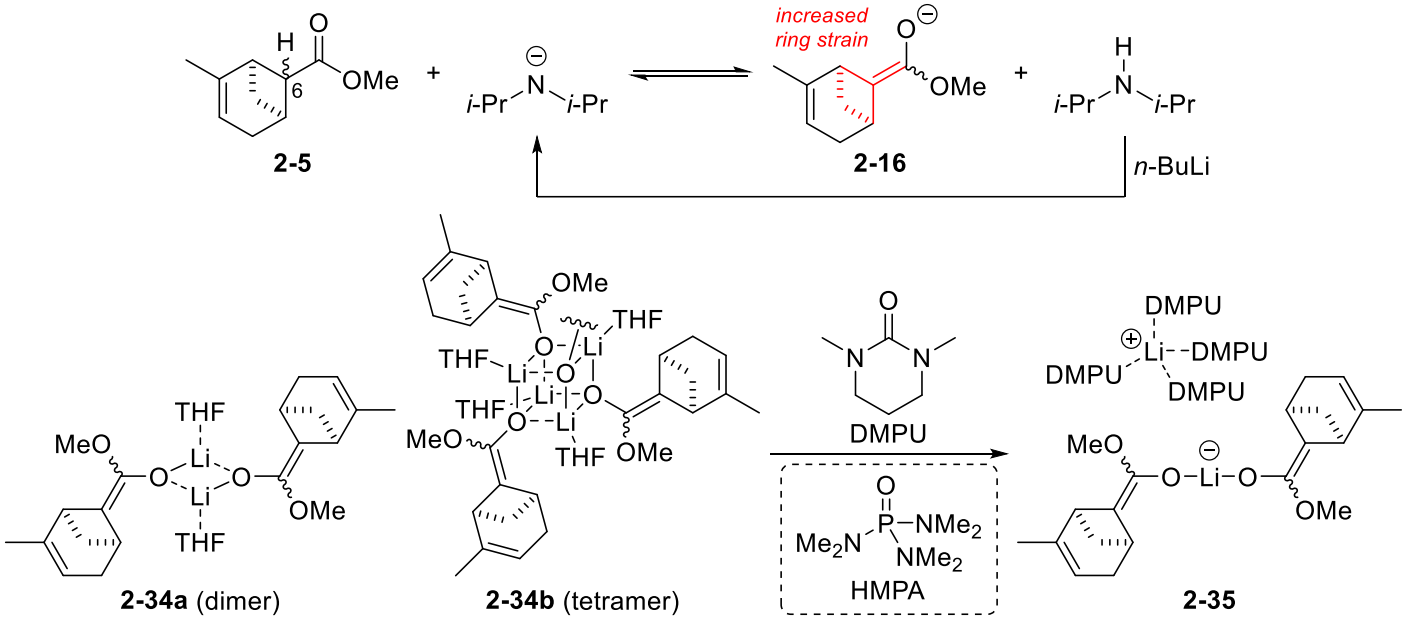


2-2. Discussion 2: aldol reaction in step 2

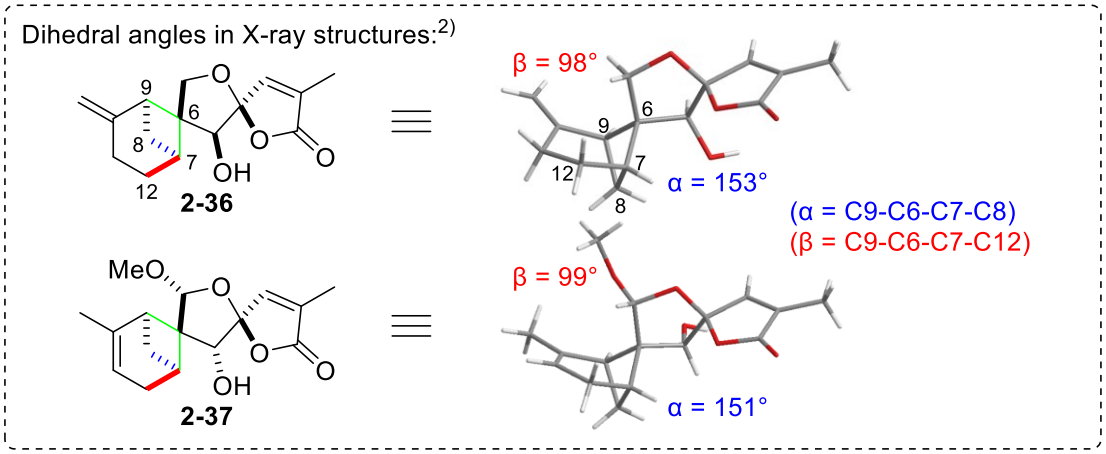
2-2-1. Roles of *n*-BuLi and DMPU[8)]

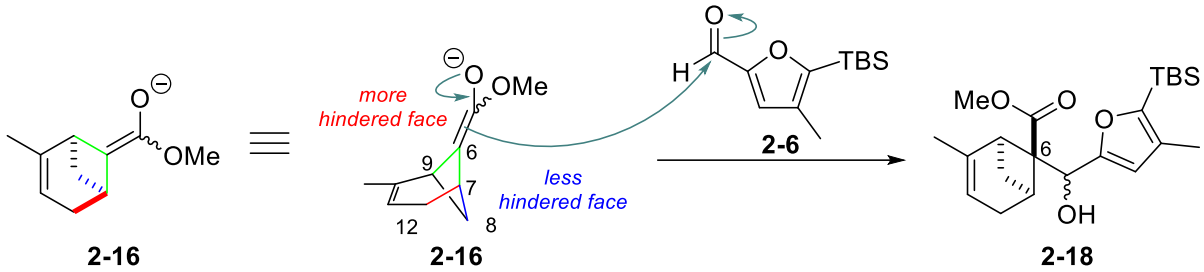
According to the paper, the application of *i*-Pr_2NLi, *i*-Pr_2NLi with HMPA, $LiNTMS_2$, $NaNTMS_2$, $KNTMS_2$, NaH, KH and KH with 18-crown-6 all failed to obtain the aldol product.

In step 2, **2-5** was sequentially treated with: (1) *i*-Pr_2NLi (1.3 eq, prepared from 1.3 eq of *n*-BuLi and 1.4 eq of *i*-Pr_2NH) for 1.5 h; (2) *n*-BuLi (1.1 eq) for 30 min; (3) DMPU (2.02 eq) for 5 min at – 78 °C before the addition of aldehyde **2-6**.



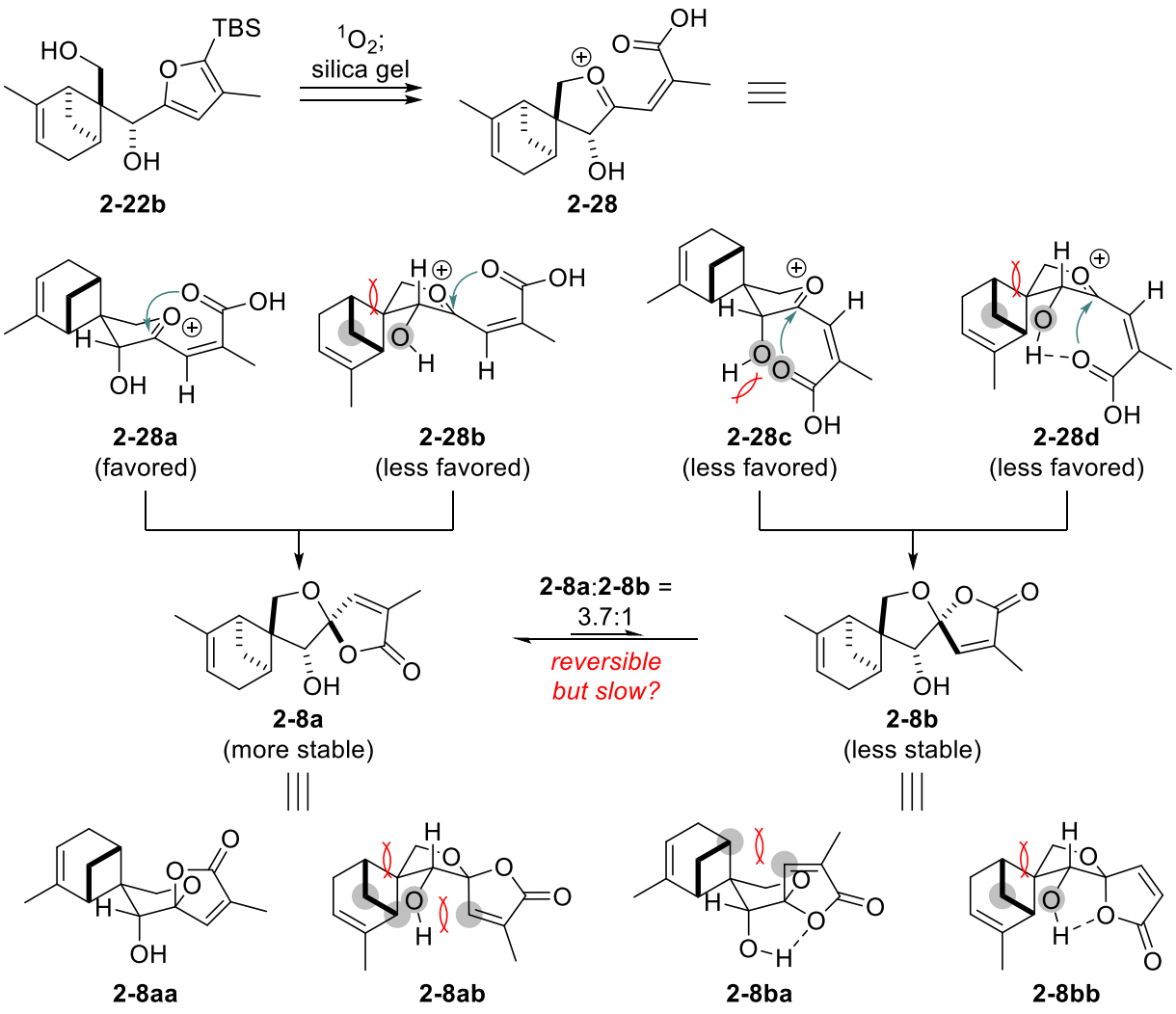
2-2-2. Stereoselectivity at C6



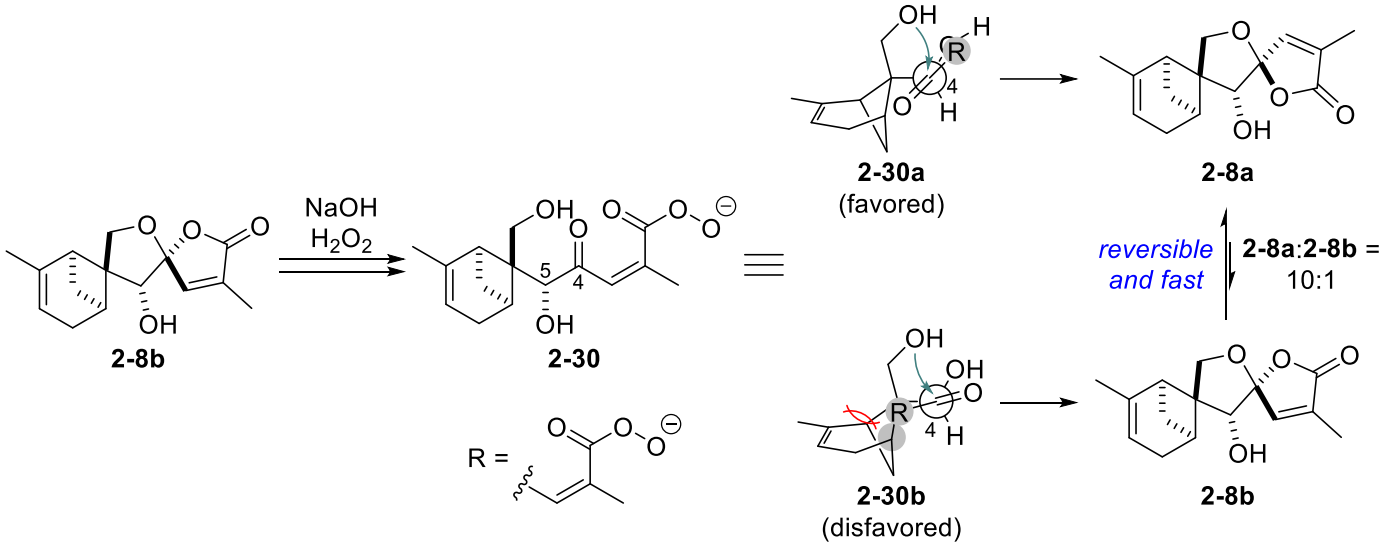


2-3. Discussion 3: spirocyclization

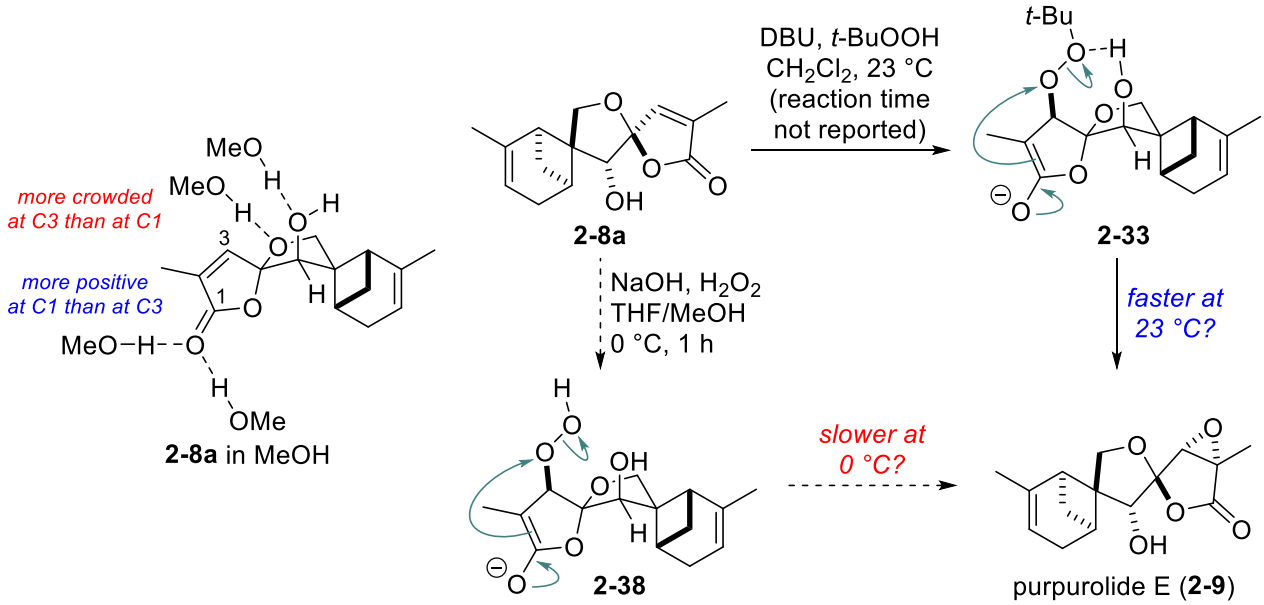
2-3-1. Stereoselectivity in step 4



2-3-2. Stereoselectivity in step 5



2-4. Discussion 4: epoxidation



References:

1) Ghosh, S.; Chatterjee, S.; Nanda, S. *Org. Lett.* **2024**, *26*, 10453.

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4) Urones, J. G.; Basabe, P.; Marcos, I. S.; Martín, D. D.; Sexmero, M. J.; Peral, M. H.; Broughton, H. B. *Tetrahedron* **1992**, *48*, 10389.

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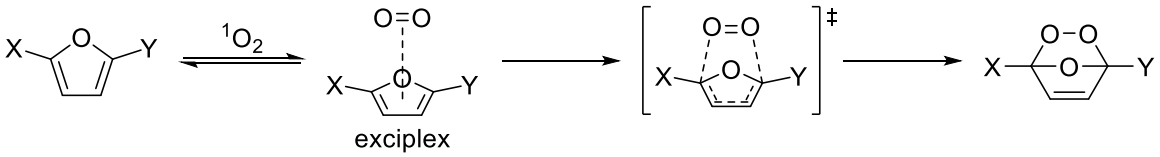
6) The experimental studies suggest that the reaction between furan and $^1O_2$ proceeds via the formation of an excited complex (exciplex), followed by the concerted collapse of the exciplex to the [4+2] product.[a-c] The computational study supports a concerted mechanism.[d] a) Clennan, E. L.; Mehrsheikh-Mohammadi, M. E. *J. Org. Chem.* **1984**, *49*, 1321. b) Clennan, E. L.; Mehrsheikh-Mohammadi, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 7112. c) Clennan, E. L. *Tetrahedron* **1991**, *47*, 1343. d) Jespersen, M. F.; Jørgensen, S.; Johnson, M. S.; Mikkelsen, K. V. *Authorea* **2020**. DOI: 10.22541/au.159316040.02153971



7) a) Adam, W.; Rodriguez, A. *Tetrahedron Lett.* **1981**, *22*, 3505. b) Adam, W.; Rodriguez, A. *Tetrahedron Lett.* **1981**, *22*, 3509. c) Lee, G. C. M.; Syage, E. T.; Harcourt, D. A.; Holmes, J. M.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 7007.

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