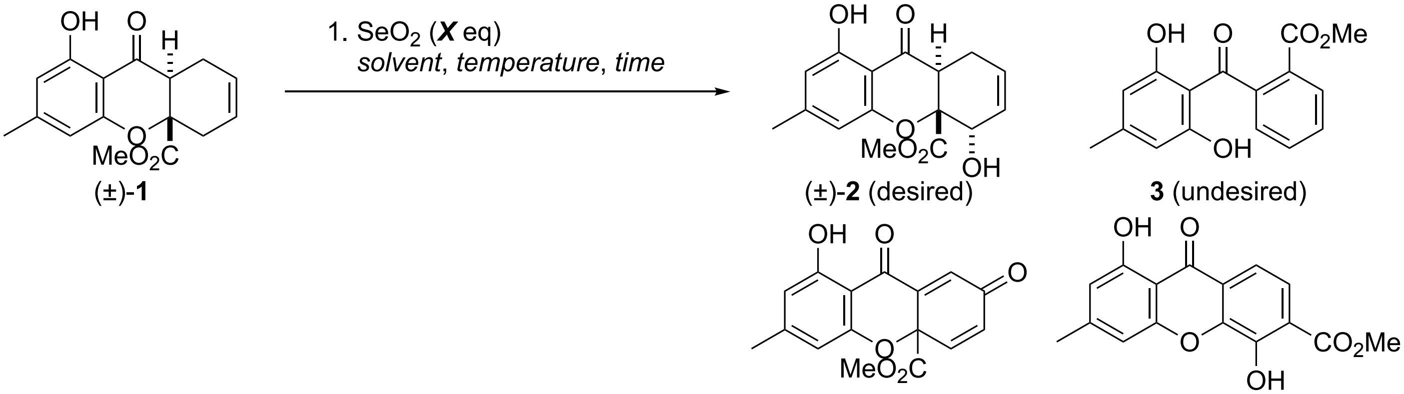
Problem Session (5)

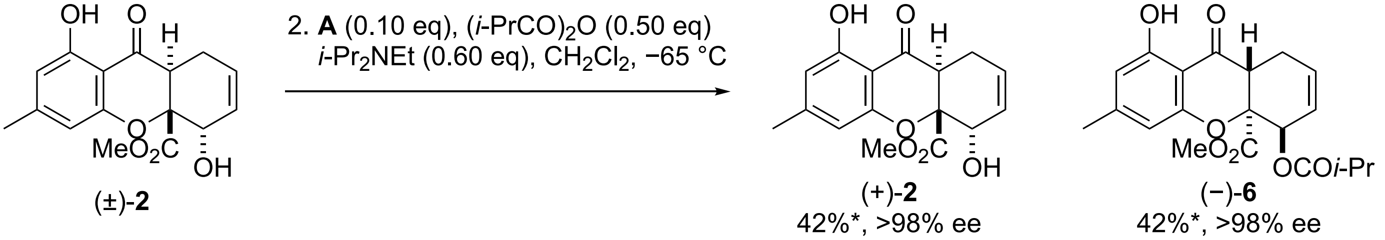
2025/04/05 Hiromu Kakizawa

topic: synthesis of nidulalin A, a dihydroxanthone natural product
Please explain the mechanisms for the following reactions.
As for steps 1 and 3, please propose rationales for the different results shown in entries 1 and 2.

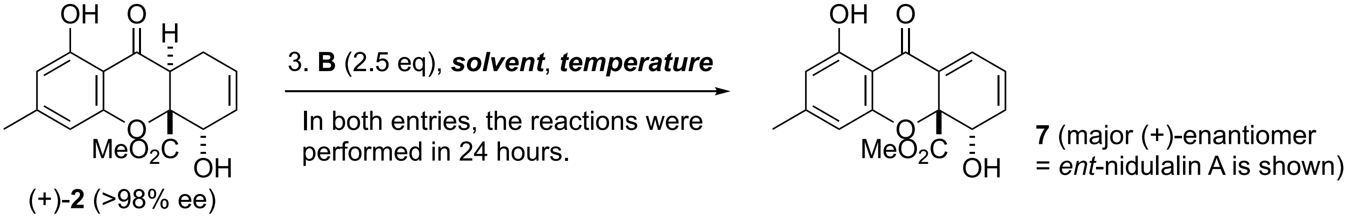


	X	*solvent*	*temperature*	*time*	yields			
					(±)-**2**	**3**	(±)-**4**	**5**
1	1.3	toluene	130 °C (microwave)	2 h	47%	10%	–	–
2	3.0	1,4-dioxane	100 °C	16 h	30%	–	22%	18%

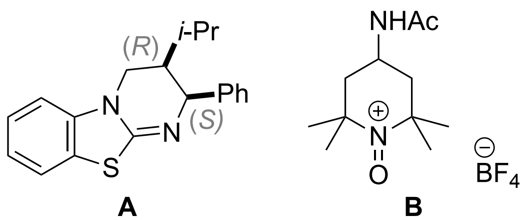
Products with ≥10% yields are displayed.



*Yields were calculated based on the amount of (±)-**2**.



	solvent	***temperature***	results
1	MeCN	40 °C	**7**: 82% yield, >98% ee
2	1,2-dichloroethane	85 °C	**7**: 82% yield, 60% ee



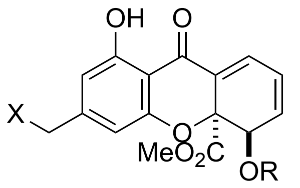
A **B**

Problem Session (5) -answer-

2025/04/05 Hiromu Kakizawa

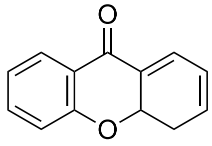
brief introduction on (−)-nidulalin A

isolation: from *Emericella nidulans* (ascomycetous fungus)
Kawahara, N.; Sekita, S.; Satake, M.; Udagawa, S.; Kawai, K. *Chem. Pharm. Bull.* **1994**, *42*, 1720.
bioactivity: inhibition of DNA topoisomerase II, IC_{50} = 2.2 μM
Sato, S.; Fukuda, Y.; Nakagawa, R.; Tsuji, T.; Umemura, K.; Andoh, T. *Biol. Pharm. Bull.* **2000**, *23*, 511.

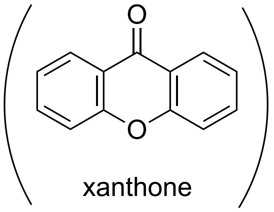


structure of nidulalin A and other dihydroxanthone natural products

(−)-nidulalin A: X = R = H
F390B: X =H, R = Ac
F390C: X =OH, R = H



core skeleton
= dihydroxanthone

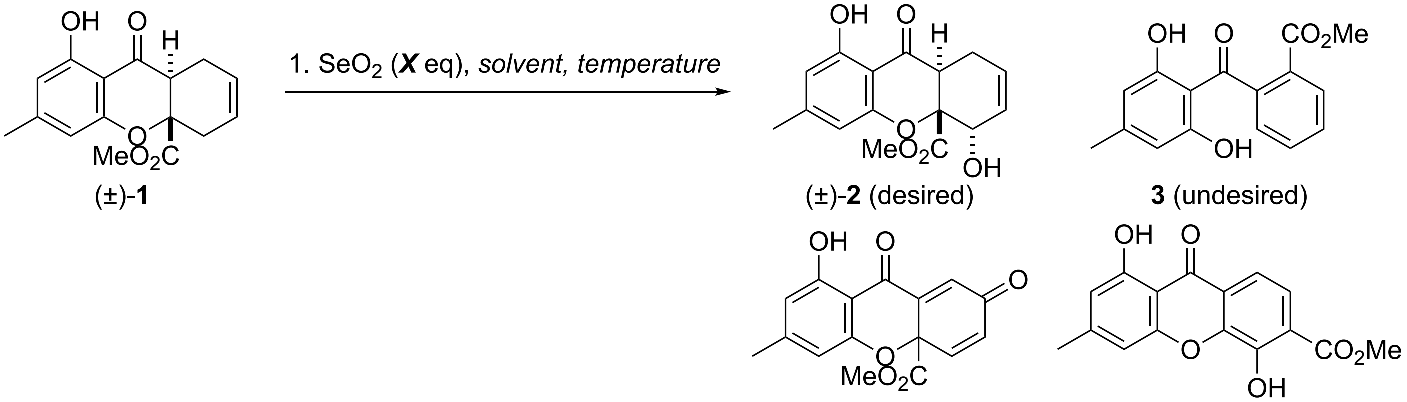


xanthone

total syntheses: Hosokawa (2009) and Porco (2024, discussed in this session)

answer to the problem

step 1: mechanisms of the desired oxidation and the undesired overreactions



1. SeO_2 (***X*** eq), *solvent, temperature*

(±)-**1**

(±)-**2** (desired)

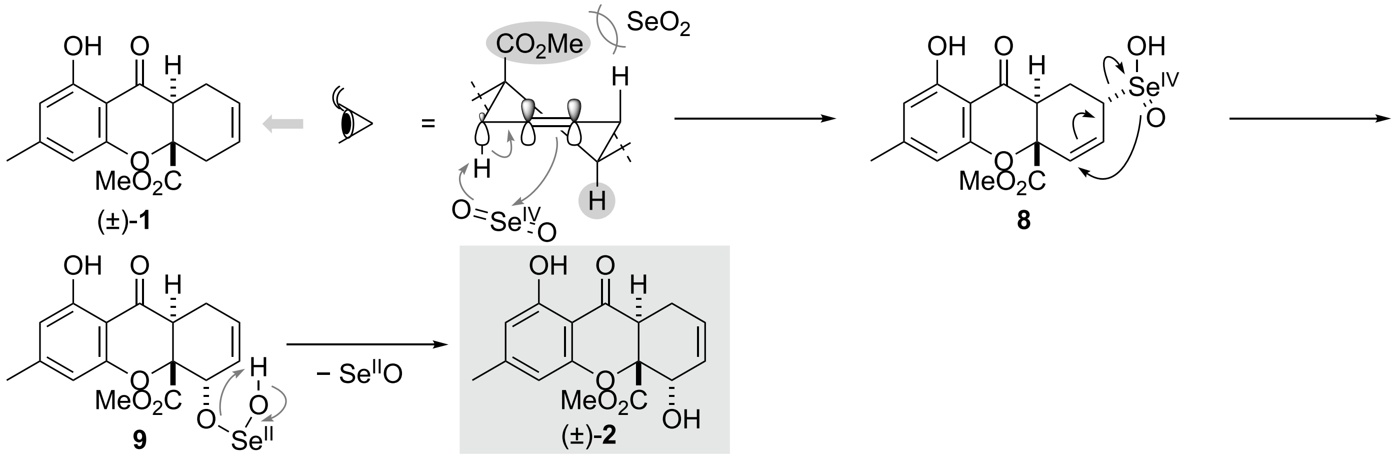
3 (undesired)

(±)-**4** (undesired)

5 (undesired)

	X	*solvent*	*temperature*	*time*	yields			
					(±)-**2**	**3**	(±)-**4**	**5**
1	1.3	toluene	130 °C (microwave)	2 h	47%	10%	–	–
2	3.0	1,4-dioxane	100 °C	16 h	30%	–	22%	18%

1) when SeO_2 was added in small excess amount (entry 1; optimal condition)

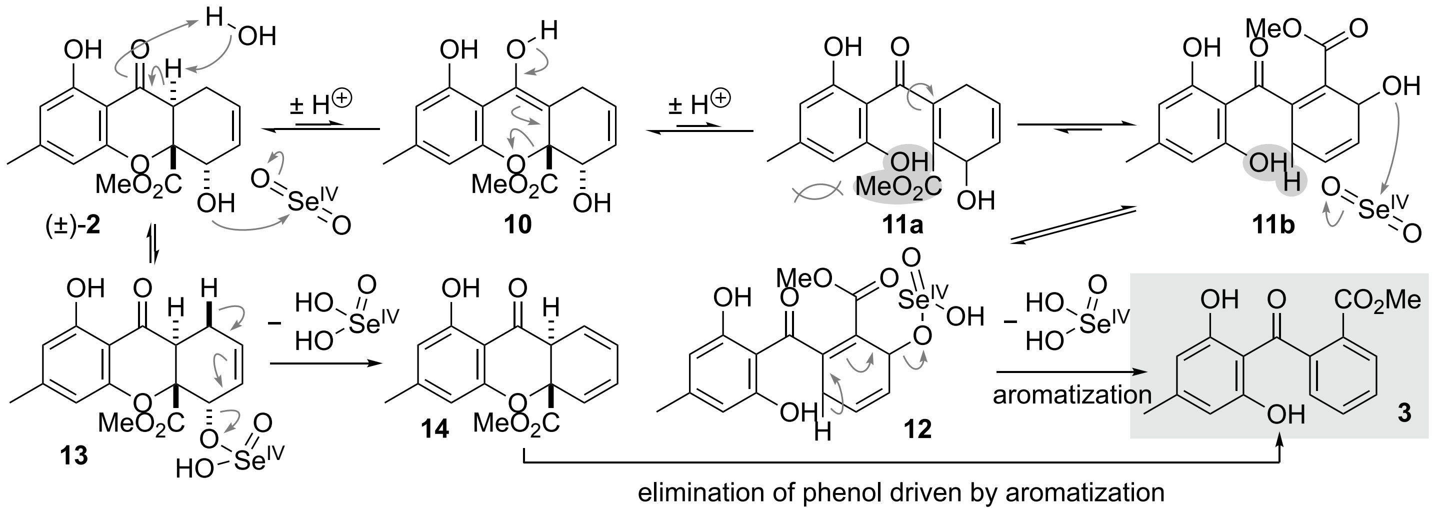


(±)-**1**

8

9

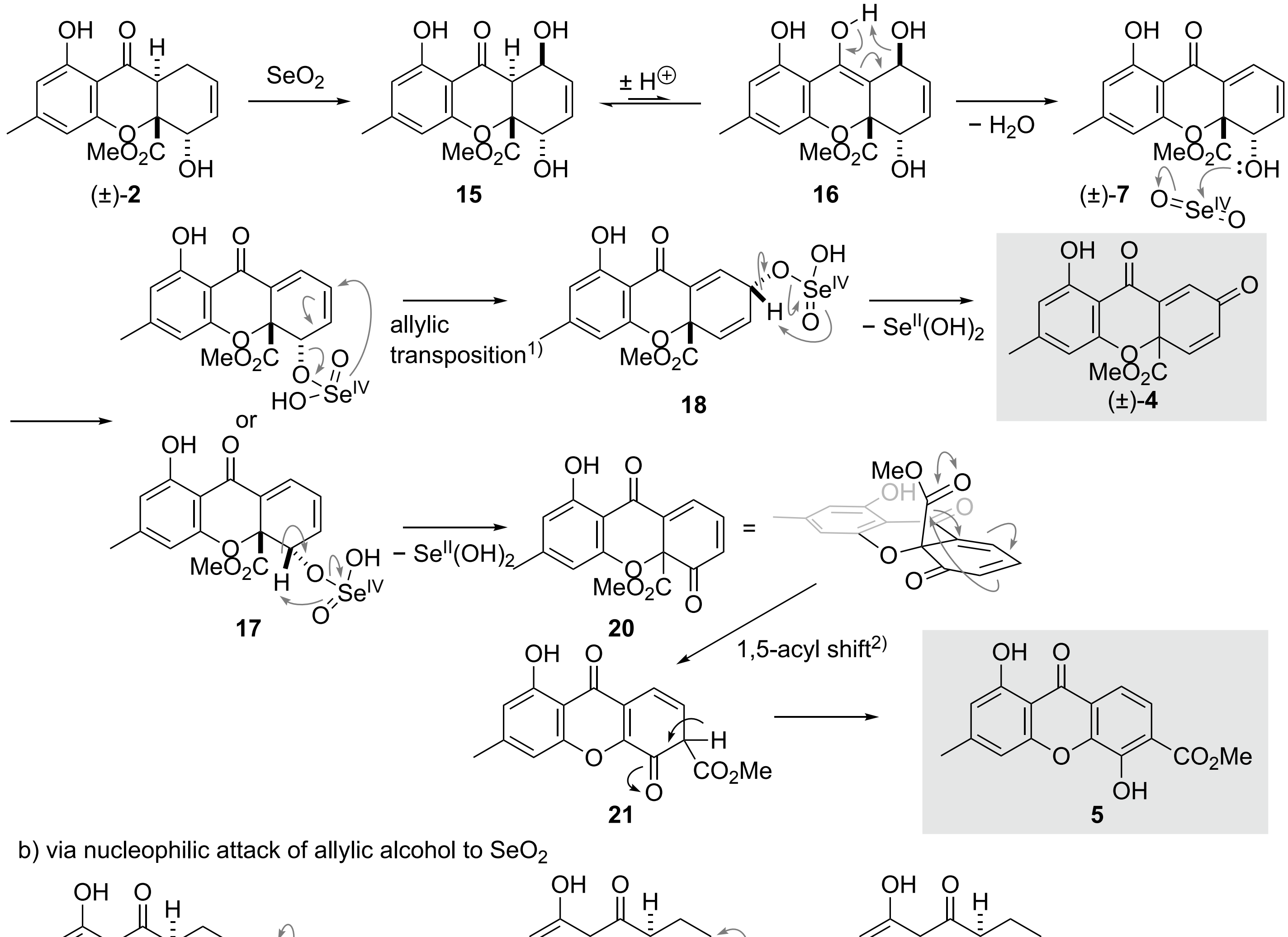
(±)-**2**



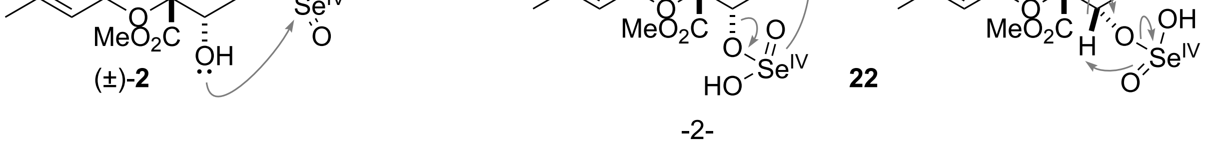
2) when SeO_2 was added in excess amount (entry 2)

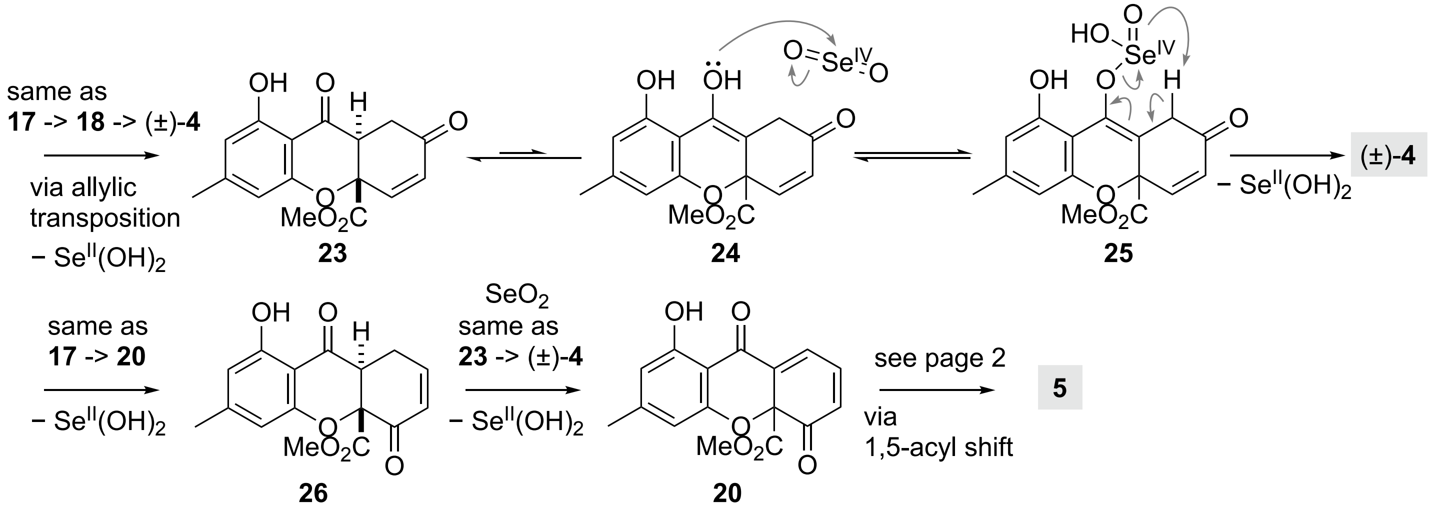
Overoxidations proceed from allylic alcohol (±)-**2** to give products (±)-**4** and **5**.

a) second allylic oxidation by SeO_2 -> nucleophilic attack of allilic alcohol to SeO_2



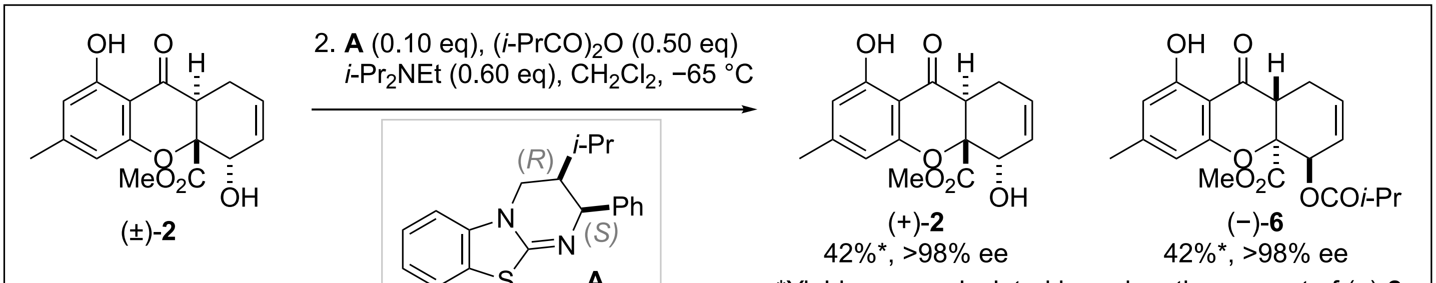
b) via nucleophilic attack of allylic alcohol to SeO_2





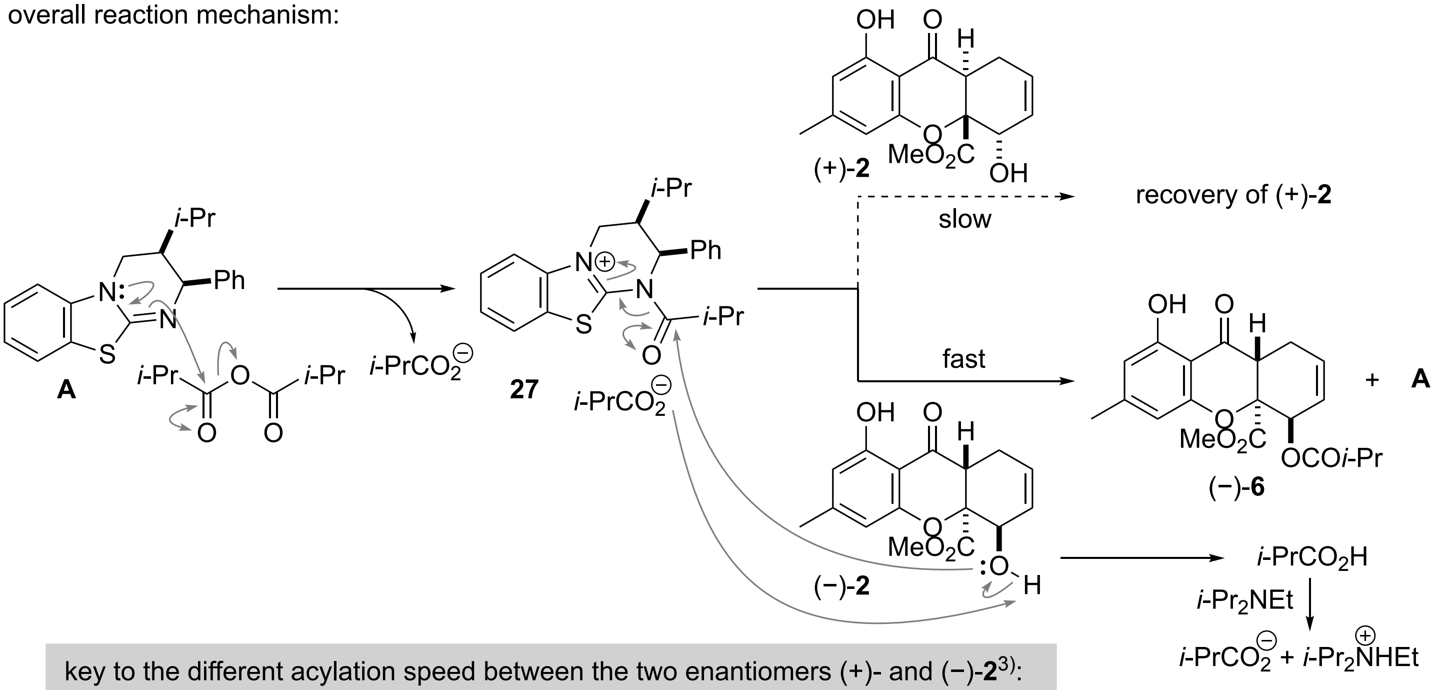
Employment of a large excess amount of SeO_2 was not appropriate because of the overoxidation to dienone (±)-**4** or xanthone **5**.

step 2: acylative kinetic resolution using chiral benzotetramisole catalyst (2*S*,3*R*-HyperBTM)



*Yields were calculated based on the amount of (±)-**2**.

overall reaction mechanism:

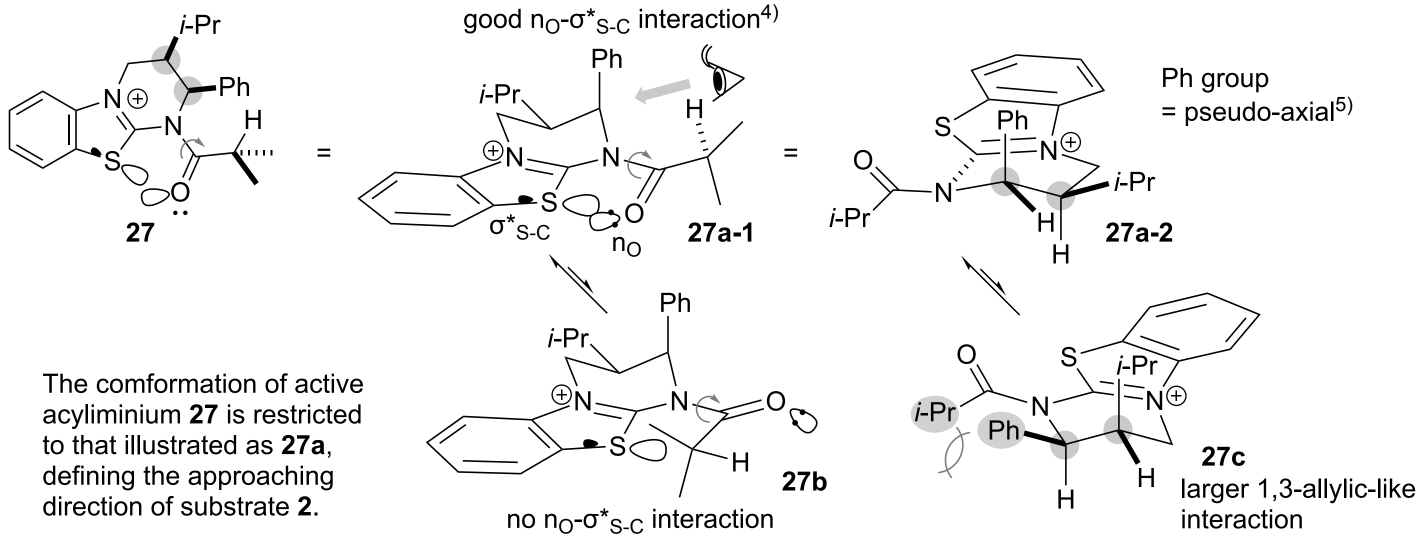


key to the different acylation speed between the two enantiomers (+)- and (−)-**2**[3]:

1) the comformation of acyliminium **27**

2) the approaching directions and the interactions of **2** and **27** in the transtion state

1) the comformation of acyliminium **27**

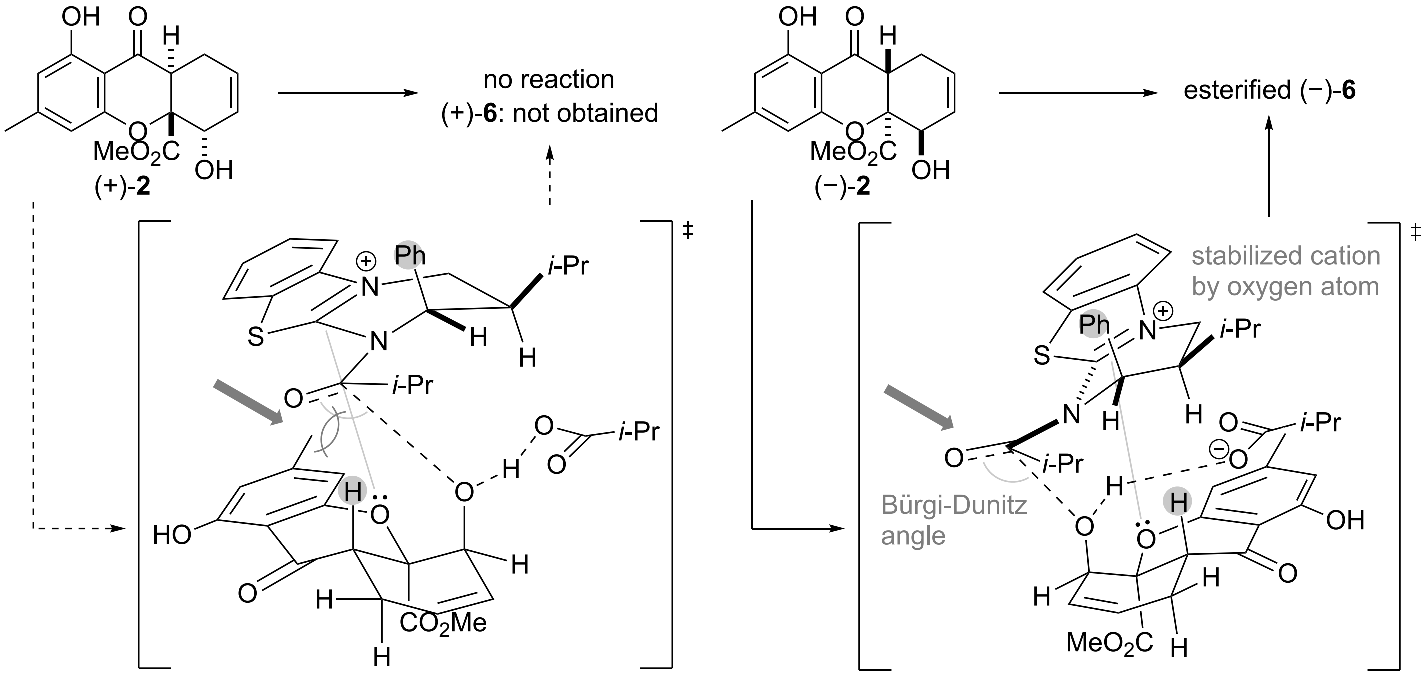


The comformation of active acyliminium **27** is restricted to that illustrated as **27a**, defining the approaching direction of substrate **2**.

2) the approaching directions and the interactions of **2** and **27** in the transtion state

– Alcohols (+)- and (−)-**2** approach in Bürgi-Dunitz angle from the opposite side of bulky Ph on **27**.

– Acyliminium **27** approaches so that its positive charge is stabilized by electron-negative oxygen.



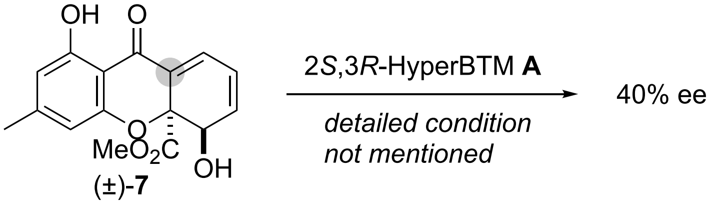
(+)-**TS1**: less favored

27 causes steric repulsion with pseudo-axial H atom.

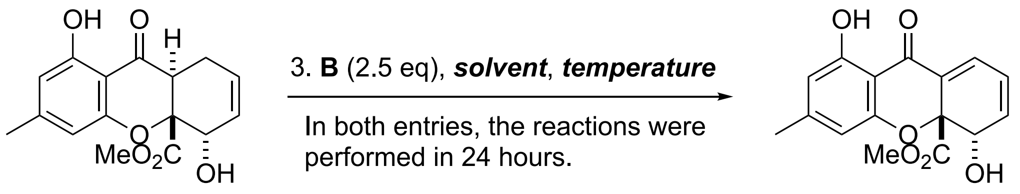
(−)-**TS1**: more favored

27 approaches from the opposite side of pseudo-axial H atom.

Reaction between **A** and (±)-**7**, which lacks the pseudo-axial H atom, resulted in poorer enantioselectivity. This result also indicates the importance of highlighted H atom for difining the direction of approach of acyliminium **27**.

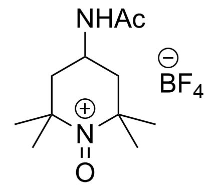


step 3: desaturation with Bobbitt's salt (4-acetamido-2,2,6,6-tetrametyl-1-oxo-piperidinium tetrafluoroborate, **B**)



(+)-**2** (>98% ee)

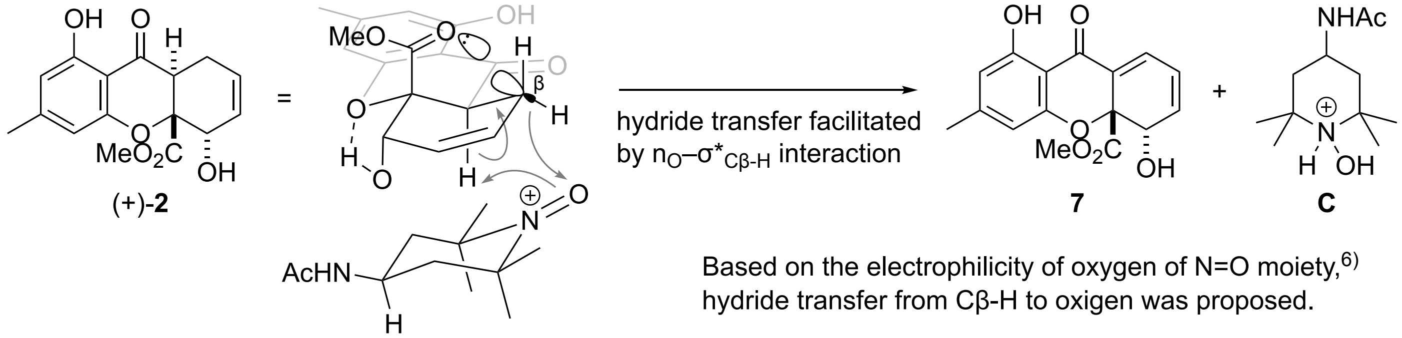
7 (major (+)-enantiomer = *ent*-nidulalin A is shown)



B

	solvent	***temperature***	results
1	MeCN	40 °C	**7**: 82% yield, >98% ee
2	1,2-dichloroethane	85 °C	**7**: 82% yield, 60% ee

1) reaction mechanism proposed by authors



hydride transfer facilitated by n_O–$\sigma^*_{C\beta\text{-}H}$ interaction

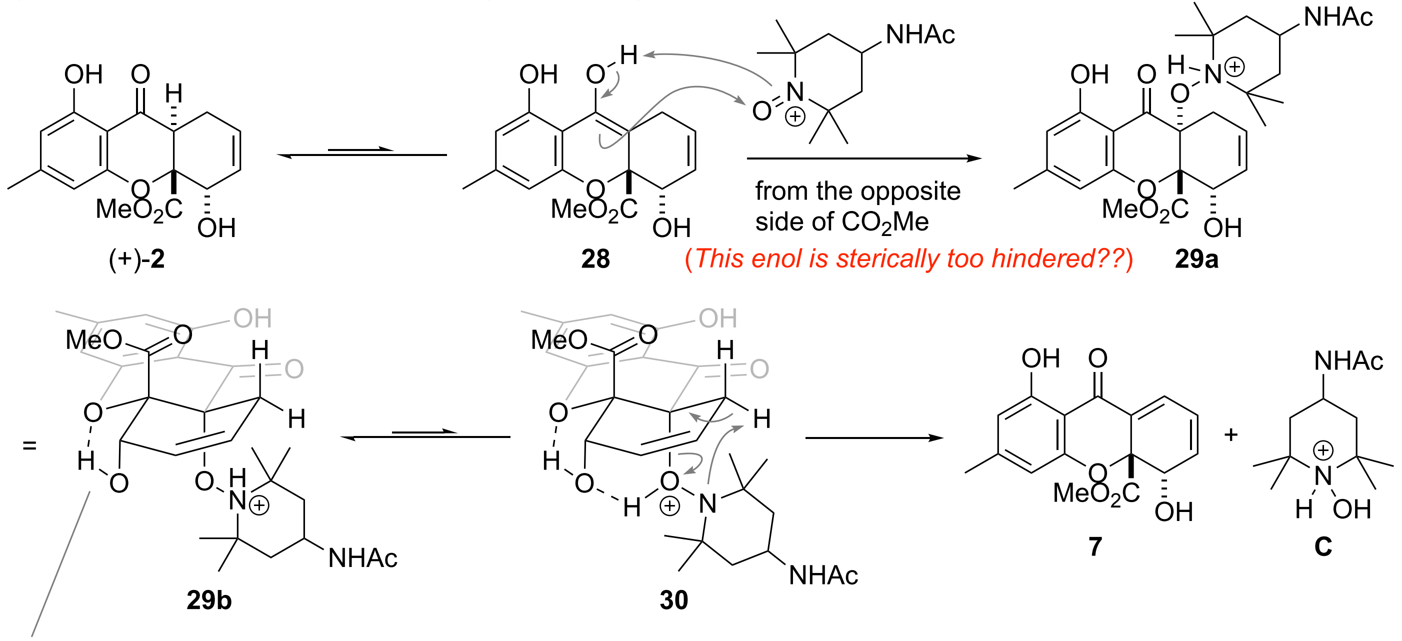
(+)-**2**

7

C

Based on the electrophilicity of oxygen of N=O moiety,[6] hydride transfer from Cβ-H to oxigen was proposed.

2) another possible reaction mechanism (my proposal)



from the opposite side of CO$_2$Me

(+)-**2**

28

(*This enol is sterically too hindered??*)

29a

29b

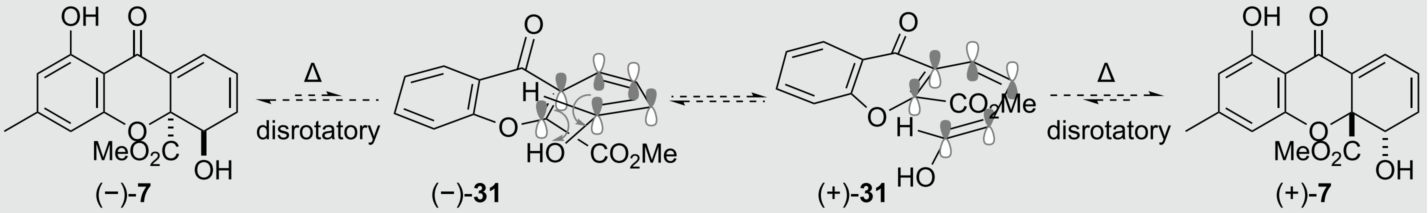
30

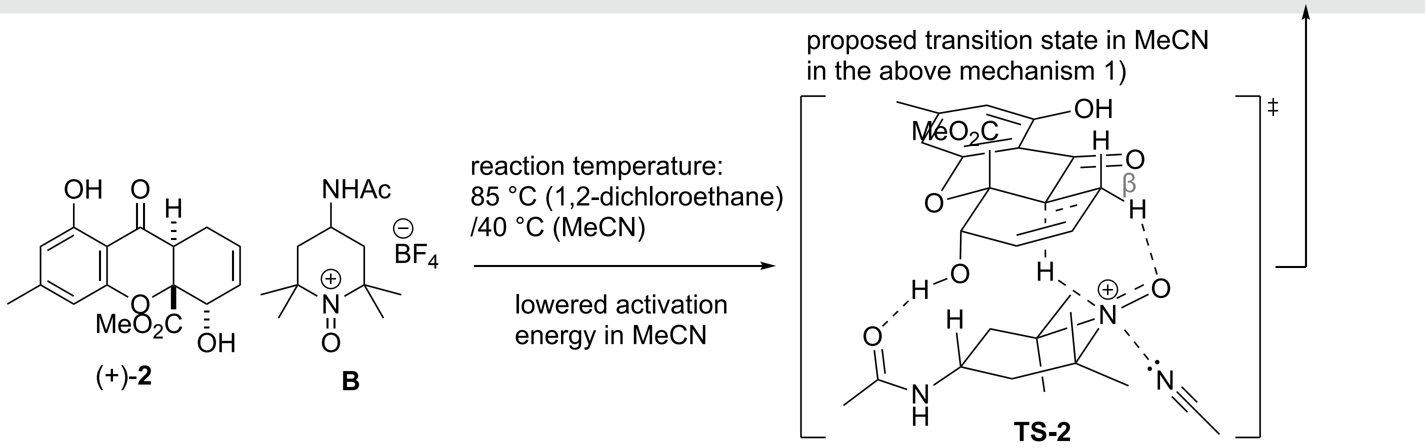
7

C

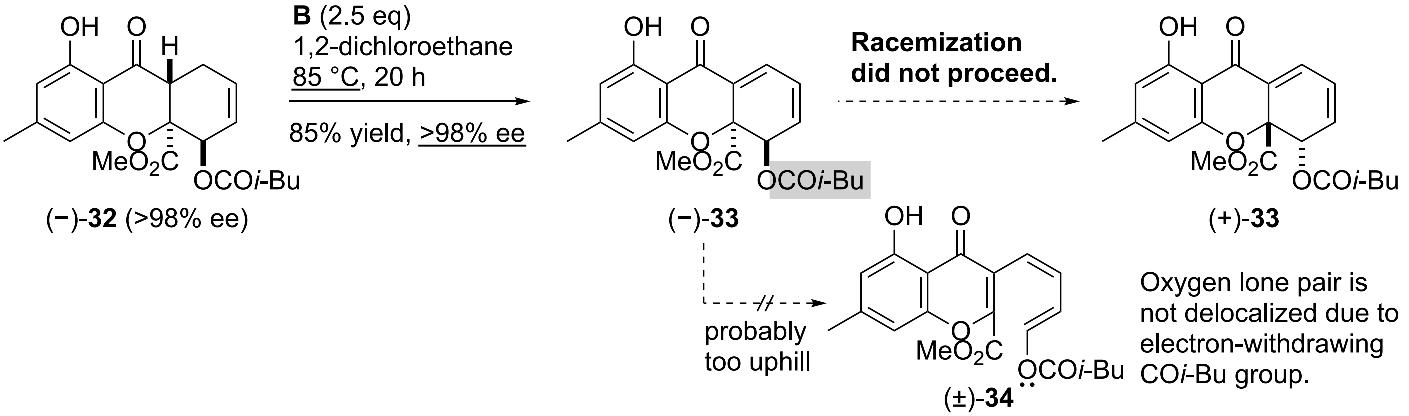
slow oxidation of alcohol by intramolecular H-bond and steric hinderance partial racemization under high temperature in 1,2-dichloroethane and the effect of MeCN as a solvent (my proposal)

(+)-**7** partially turned into its enantiomer (−)-**7** via retro-6π and 6π electrocyclizations at an elevated temperature.





It is proposed that the lone pair of MeCN stabilized this cationic transition states more effectively than BF_4 anion due to its smaller steric hinderance, leading to lowered reaction temperature. Similar stabilization is also possible for cationic transition state in mechanis 2).



Oxygen lone pair is not delocalized due to electron-withdrawing CO*i*-Bu group.

Enantiopure (−)-**32**, which has 3-methylbutyrate on the allylic alcohol, underwent desaturation with **B** without any racemization even at high temperature in 1,2-dichloroethane. It is possible that the electron-withdrawing acyl group prevented the retro-aldol reaction from (−)-**33**.

reference

(main literature) Ji, K.; Johnson, R. P. McNeely, J.; Faruk, M. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2024**, *146*, 4892.
1) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
2) Jones, D. W.; Kneen, G.; *J. Chem. Soc., Perkin Trans.* **1977**, *11*, 1313.
3) Desrues, T.; Merad, J.; Andrei, D.; Pons, J.-M.; Parrain, J.-L.; Médebielle, Quintara, A.; Bressy, C. *Angew. Chem. Int. Ed.* **2021**, *60*, 24924.
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   (b) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3288.
5) Yang, X.; Liu, P. Houk, K. N.; Birman, V. B. *Angew. Chem. Int. Ed.* **2012**, *51*, 9638.
6) (a) Takata, T.; Tsujino, Y.; Nakanishi, S.; Nakamura, K.; Yoshida, E.; Endo, T. *Chem. Lett.* **1999**, 937.
   (b) Hamlin, T. A.; Kelly, C. B.; Ovian, L. M.; Wiles, R. J.; Tilley, L. J.; Leadbeater, N. E. *J. Org. Chem.* **2015**, *80*, 8150.