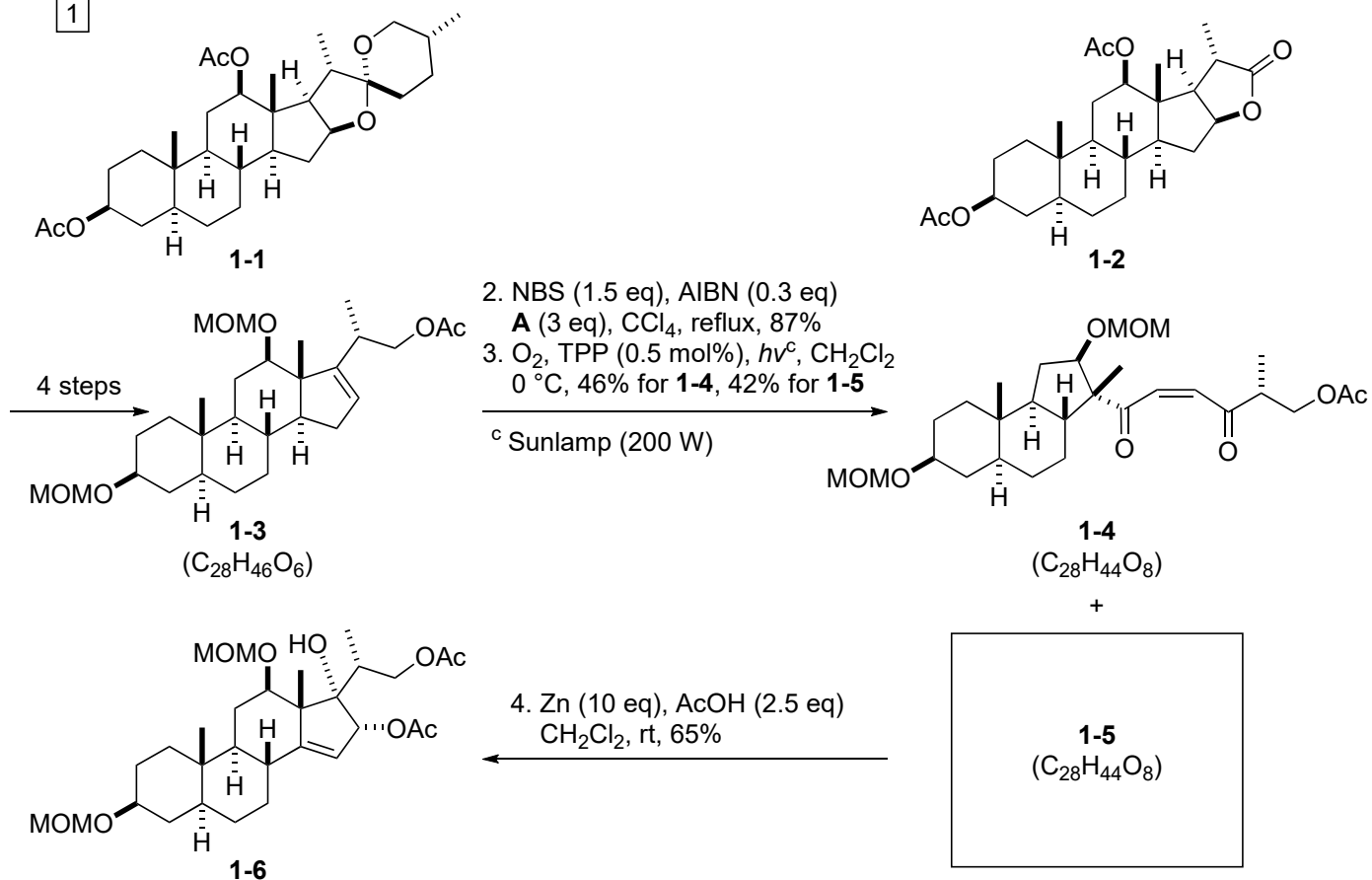


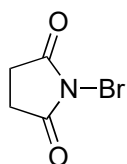
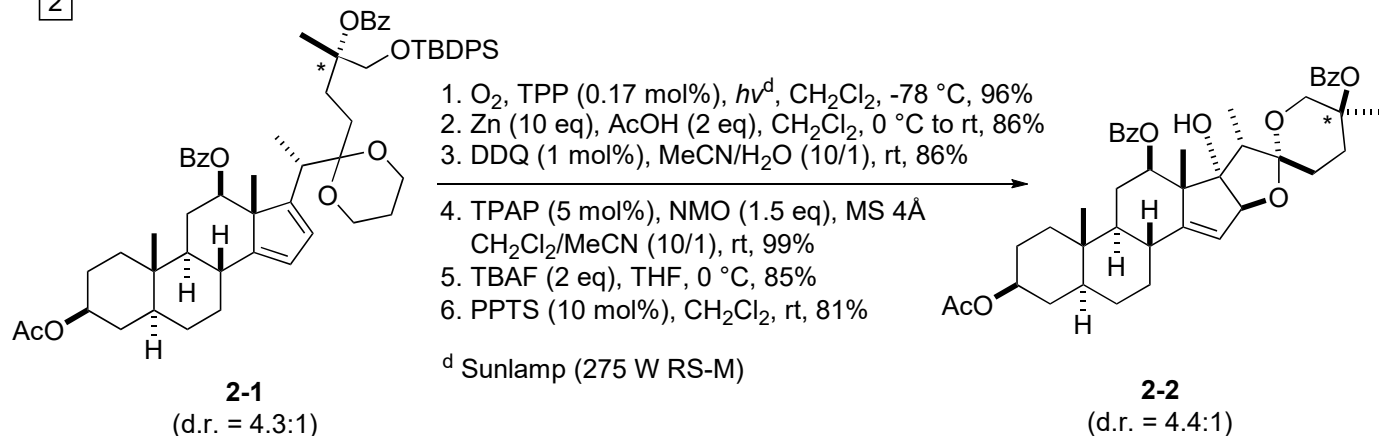
## Problem Session (2)

2021.11.13 Kyohei Takaoka

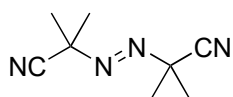
1



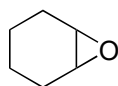
2



NBS

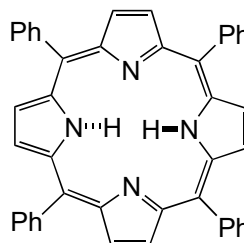


AIBN

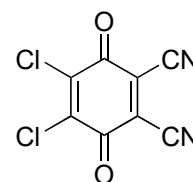


**A**

(cyclohexene oxide)



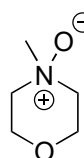
TPP



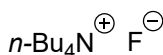
DDQ



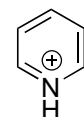
TPAP



NMO



TBAF



PPTS

## Problem Session (2) -Answer-

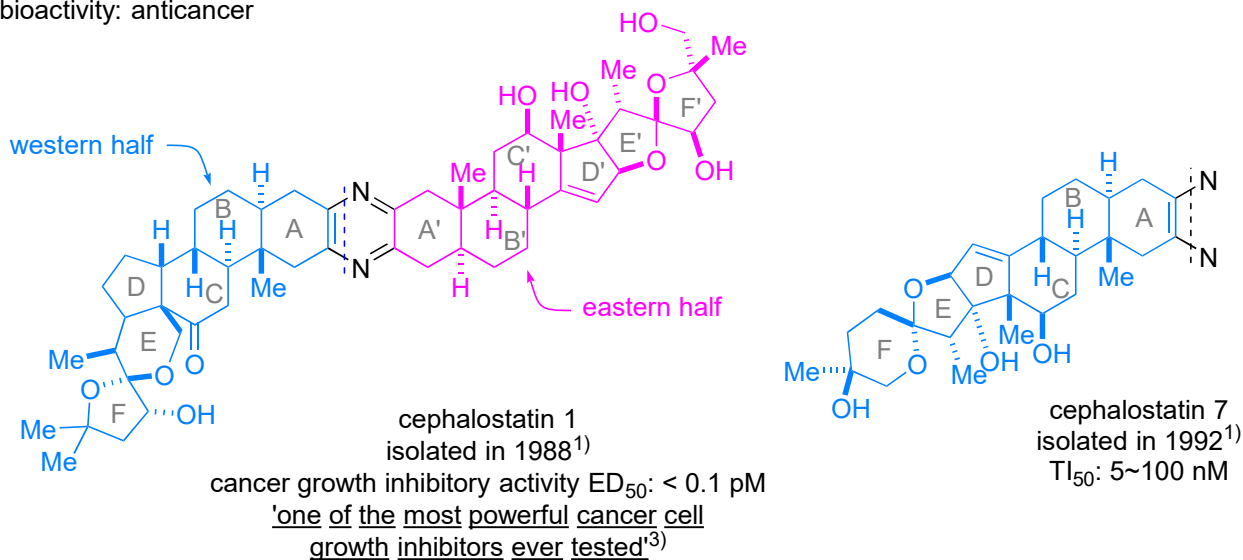
### Topic: Bis-steroidal Pyrazine Natural Product

Cephalostatin:

isolated from marine tube worm *Cephalodiscus gilchristi*<sup>1)</sup>

20 compounds were isolated (cephalostatin 1 to 20)<sup>1,2)</sup>

bioactivity: anticancer



Total syntheses:

Fuchs' group (1998, 1999)<sup>3,4)</sup>

Shair's group (2010)<sup>5)</sup>

Tian's group (2011)<sup>6)</sup> <- problem 1

For total synthesis by Fuchs' group in 1998, see also 100605\_LS\_Ken\_Mukai.

For total synthesis by Shair's group, see also 181027\_PS\_Takumi\_Fukuda.

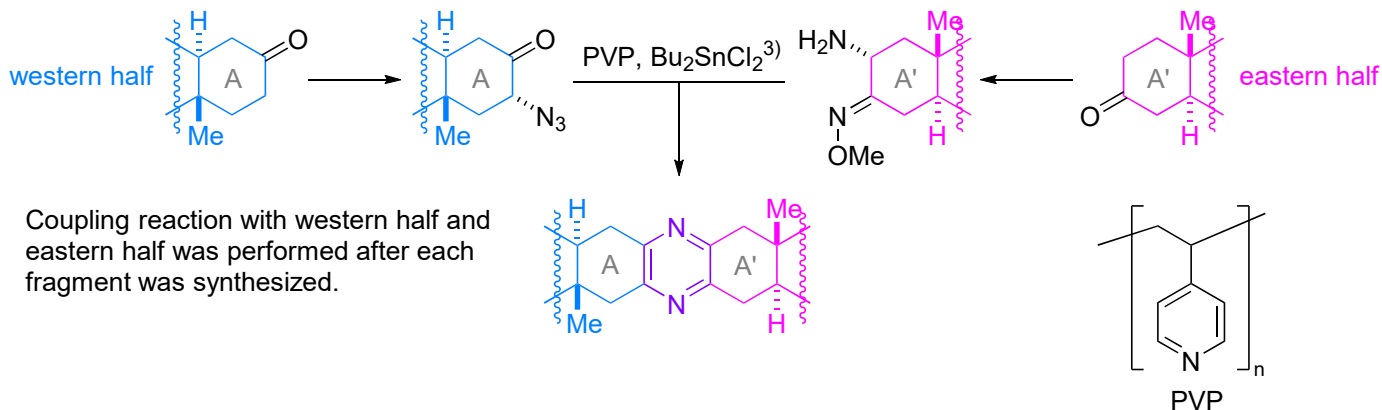
Total syntheses:

Fuchs' group<sup>7,8)</sup> (1995, 2005)

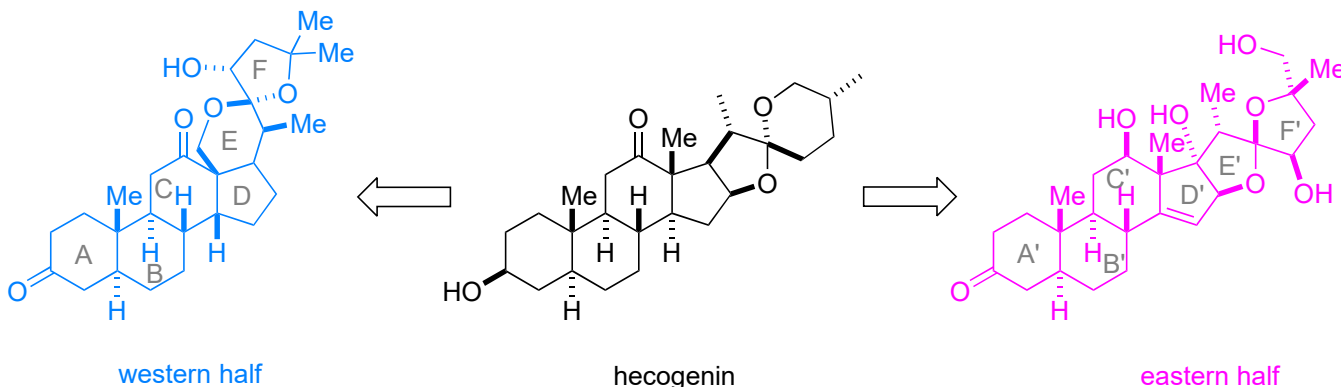
<- problem 2

Common features in total synthesis:

- Late-stage pyrazine construction



- Same starting material



Of all total syntheses of cephalostatin, hecogenin was used as a starting material (except for eastern half by Shair's group).

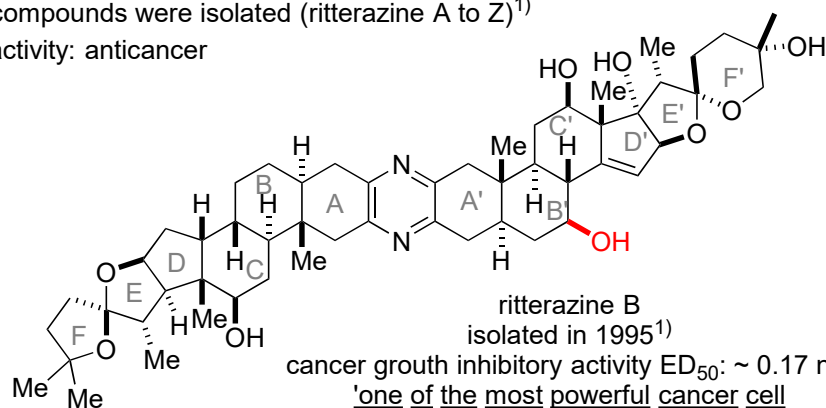
(Hecogenin already has A/B/C-ring system of western half and eastern half.)

Related compound: ritterazine

isolated from marine tunicate *Ritterella tokioka*<sup>1)</sup>

26 compounds were isolated (ritterazine A to Z)<sup>1)</sup>

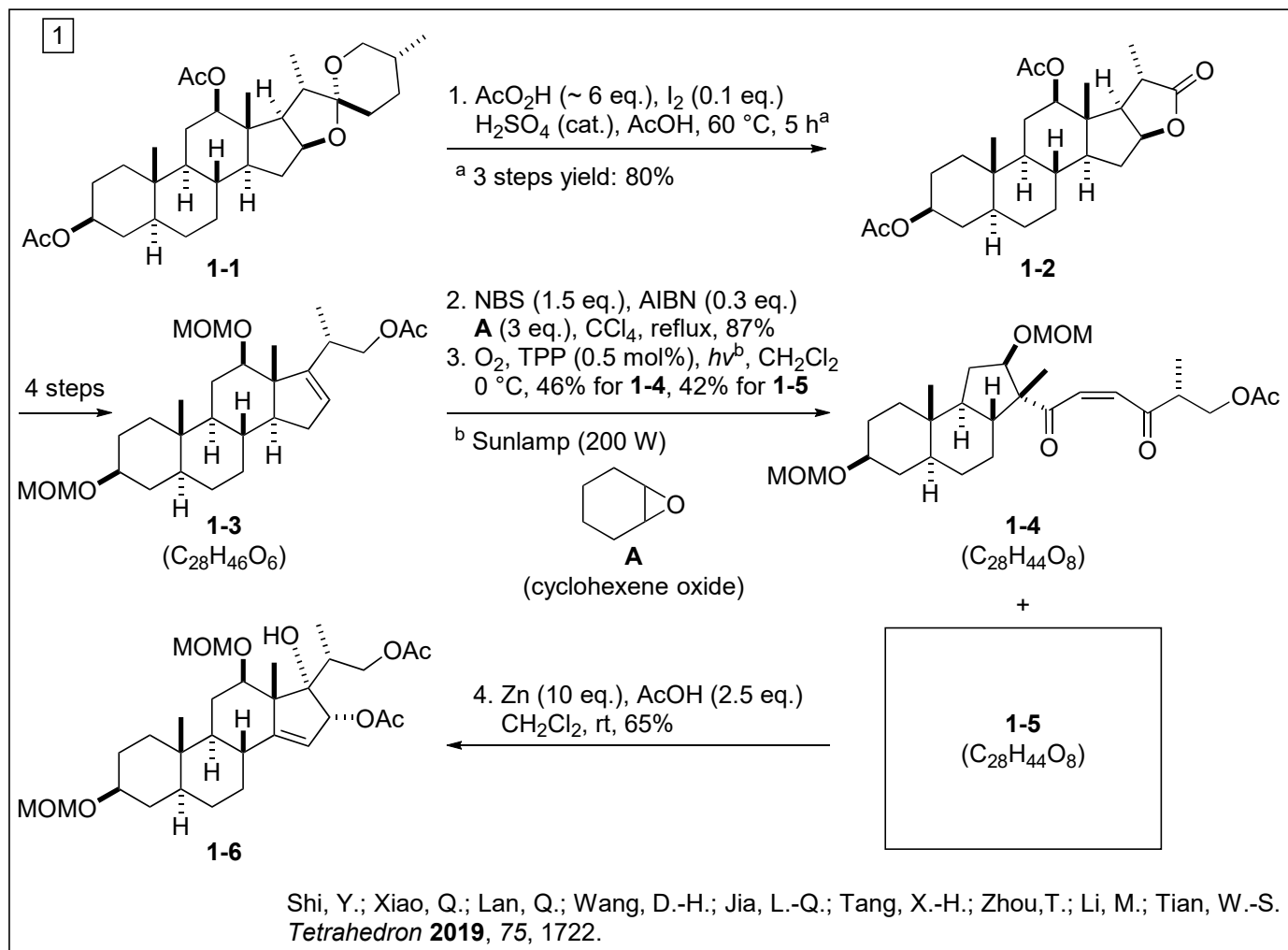
bioactivity: anticancer



ritterazine B  
isolated in 1995<sup>1)</sup>  
cancer growth inhibitory activity ED<sub>50</sub>: ~ 0.17 nM  
'one of the most powerful cancer cell  
growth inhibitors ever tested'<sup>3)</sup>

Total synthesis:  
Reisman's group<sup>9)</sup> (2020)

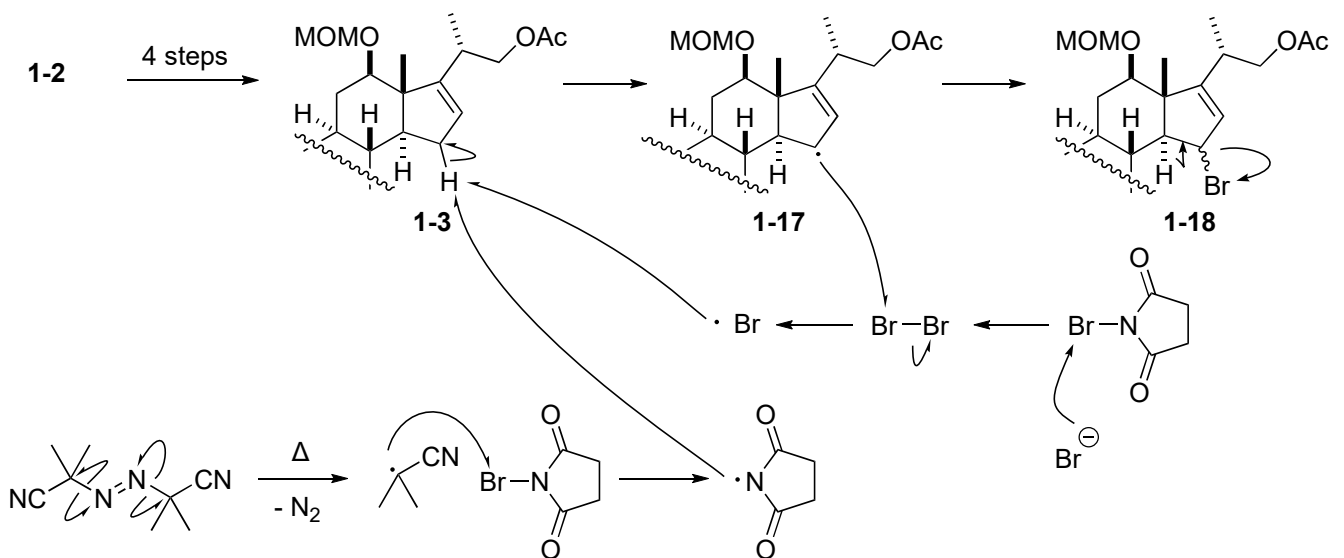
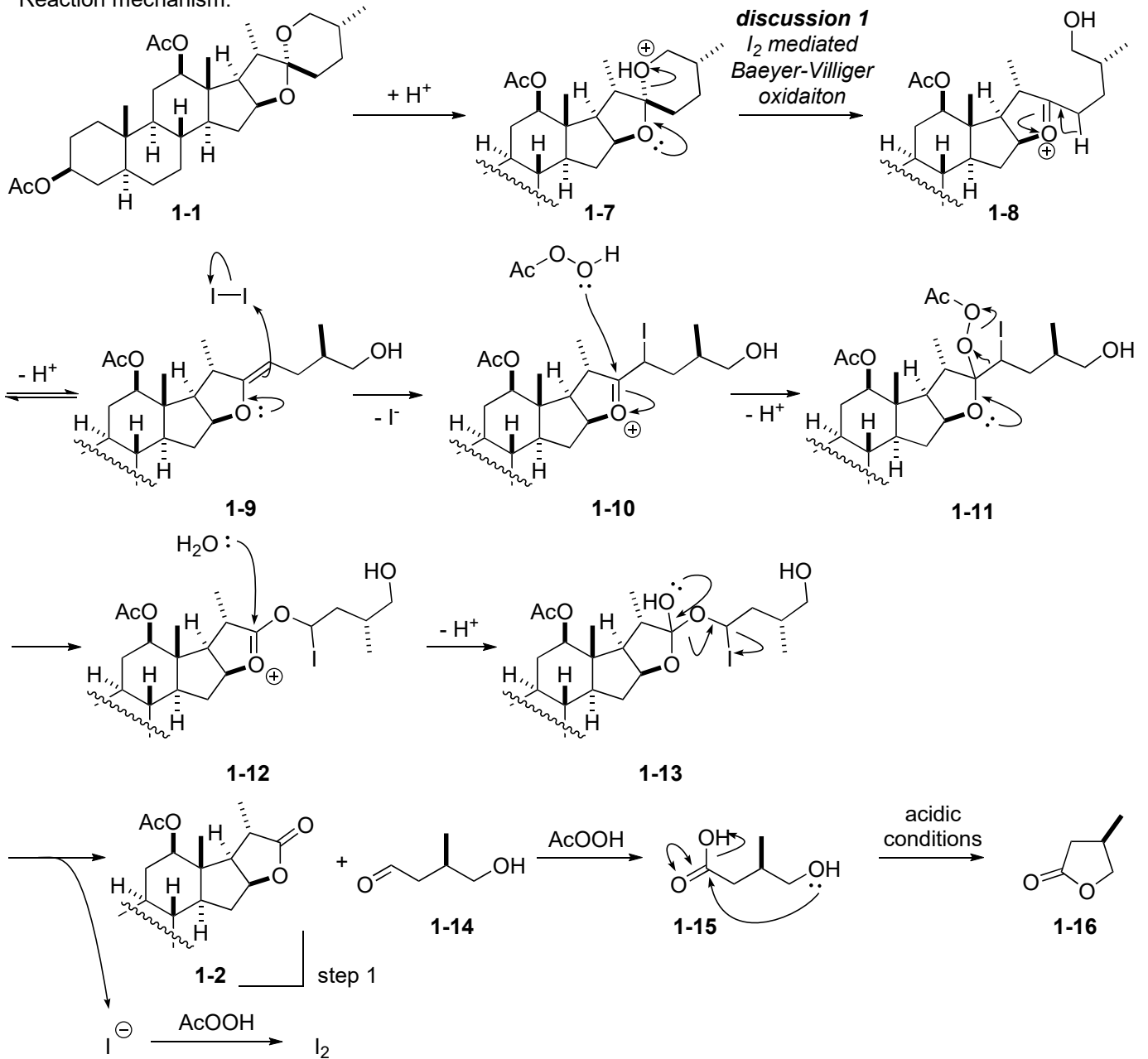
- 1) Moser, B. R. *J. Nat. Prod.* **2008**, *71*, 487.
- 2) Pettit, G. R.; Xu, J.-P.; Chapuis, J.-C.; Melody, N. *J. Nat. Prod.* **2015**, *78*, 1446.
- 3) T. G. LaCour, C. Guo, S. Bhandaru, M. R. Boyd, P. L. Fuchs, *J. Am. Chem. Soc.* **1998**, *120*, 692.
- 4) S. Kim, S. C. Sutton, C. Guo, T. G. LaCour, P. L. Fuchs, *J. Am. Chem. Soc.* **1999**, *121*, 2056.
- 5) K. C. Fortner, D. Kato, Y. Tanaka, M. D. Shair, *J. Am. Chem. Soc.* **2010**, *132*, 275.
- 6) (a) Shi, Y.; Jia, L.; Xiao, Q.; Tang, X.; Wang, D.; Li, M.; Ji, Y.; Zhou, T.; Tian, W.-S. *Chem. Asian. J.* **2011**, *6*, 786.;  
(b) Shi, Y.; Xiao, Q.; Lan, Q.; Wang, D.-H.; Jia, L.-Q.; Tang, X.-H.; Zhou, T.; Li, M.; Tian, W.-S. *Tetrahedron* **2019**, *75*, 1722.
- 7) (a) Jeong, J. U.; Sutton, S. C.; Kim, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, *117*, 10157.; (b) Jeong, J. U.; Guo, C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 2071.
- 8) Lee, J. S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2005**, *127*, 13122.
- 9) Nakayama, Y.; Maser, M. R.; Okita, T.; Durbrovskiy, A. V.; Campbell, T. L.; Reisman, S. E. *J. Am. Chem. Soc.* **2021**, *143*, 4187.



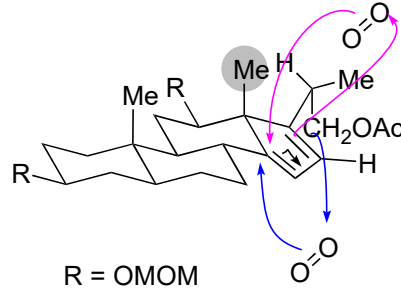
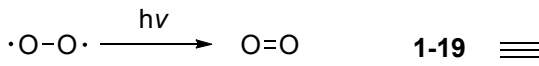
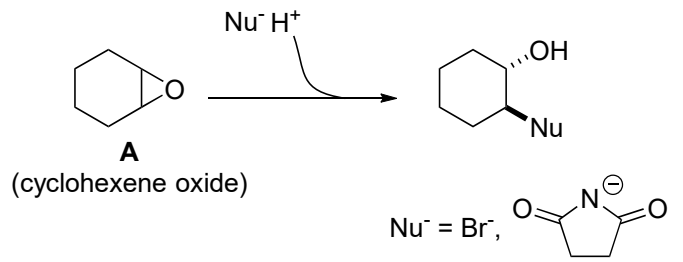
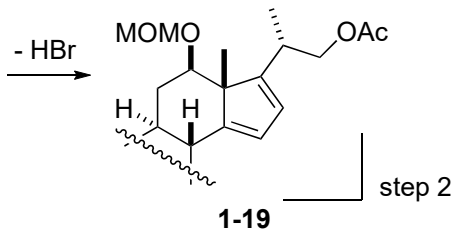
Reaction mechanism:

**discussion 1**

*I<sub>2</sub> mediated  
Baeyer-Villiger  
oxidation*

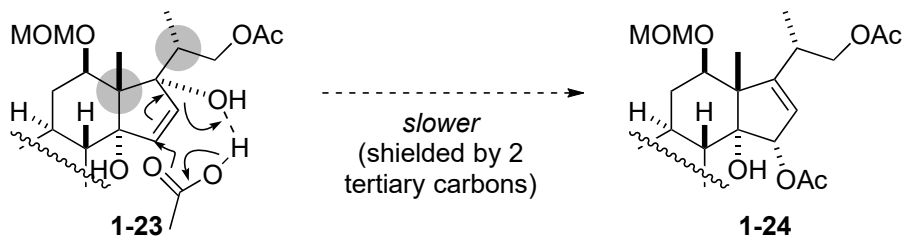
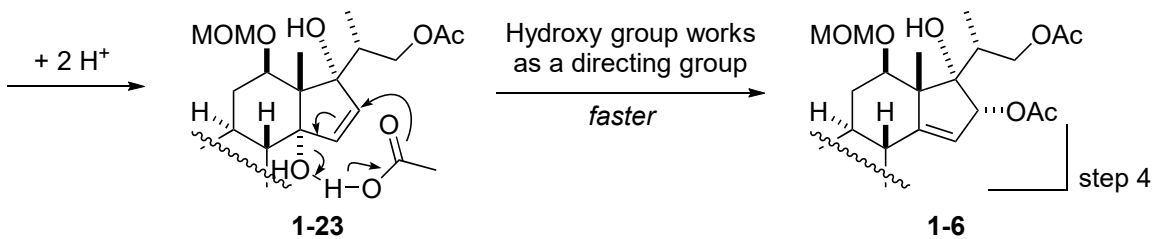
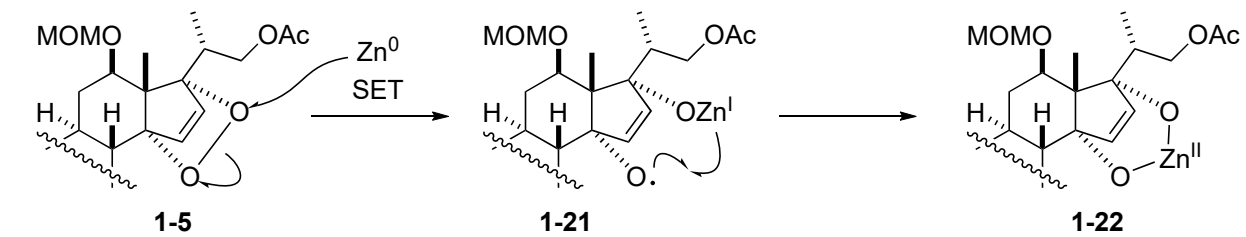
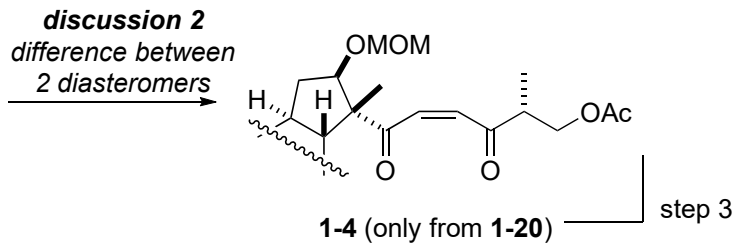
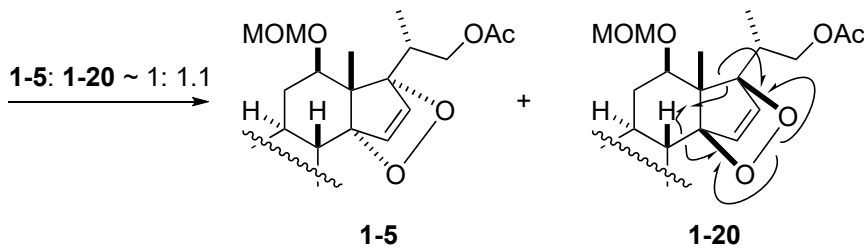


\* cyclohexene oxide was added as an acid scavenger.



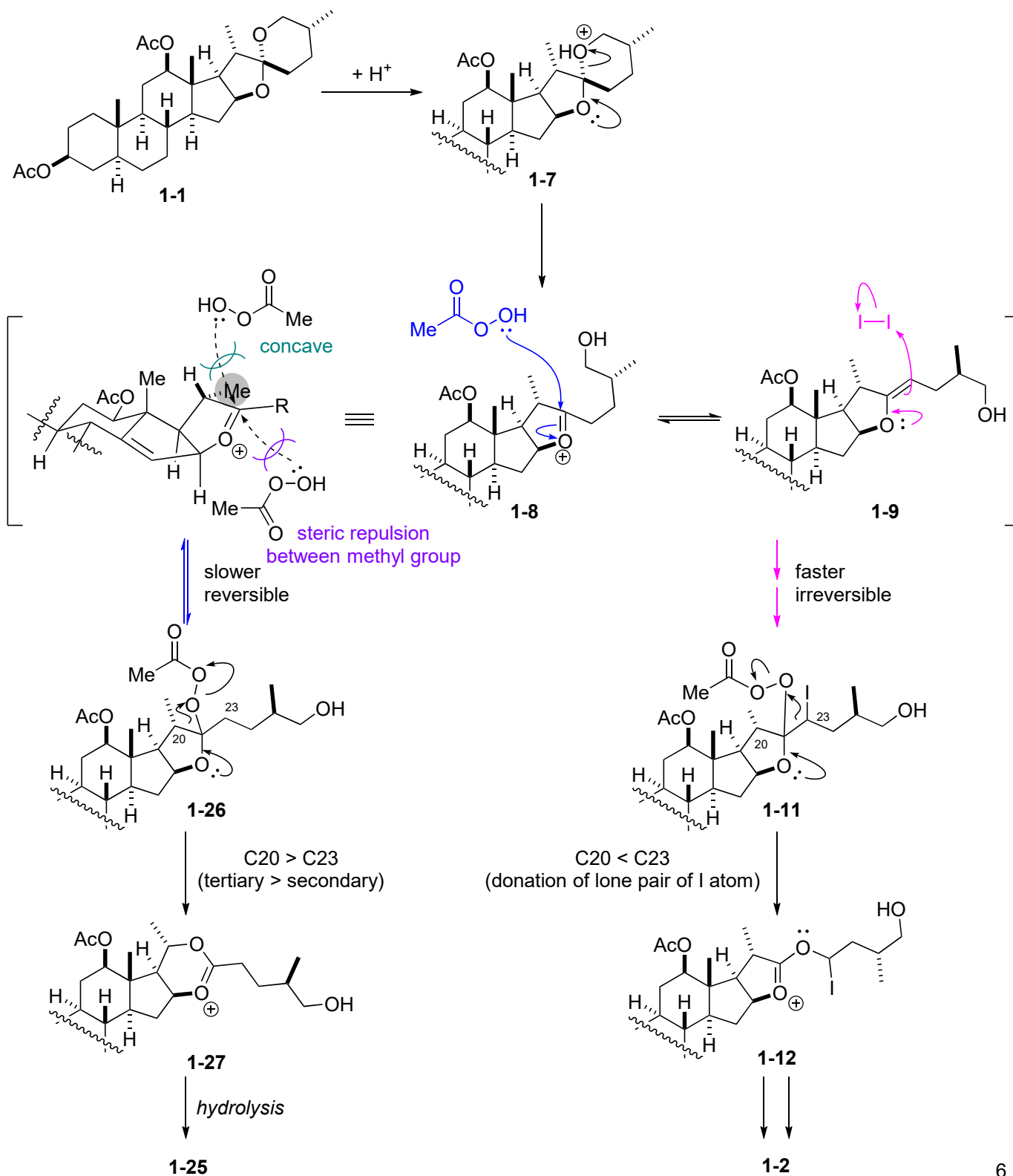
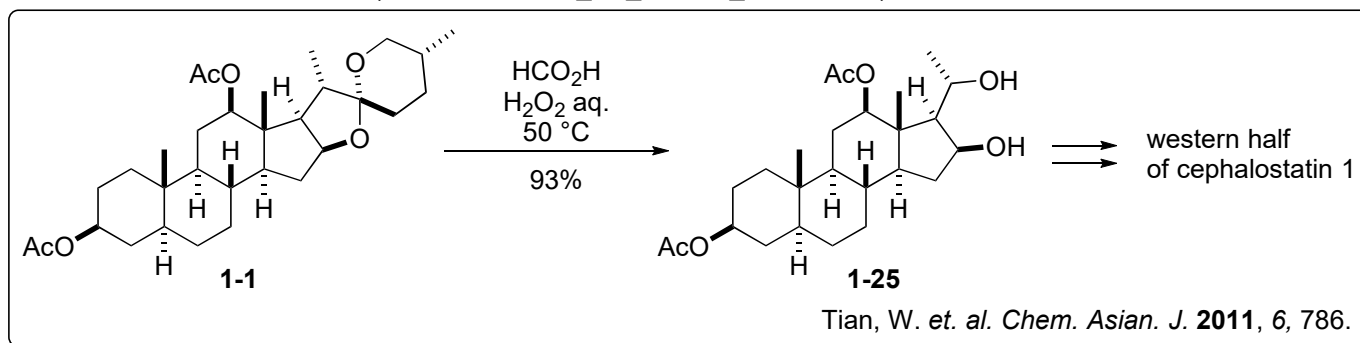
concave vs steric repulsion from methyl group  
attack

\* TPP works as a photo-sensitizer.

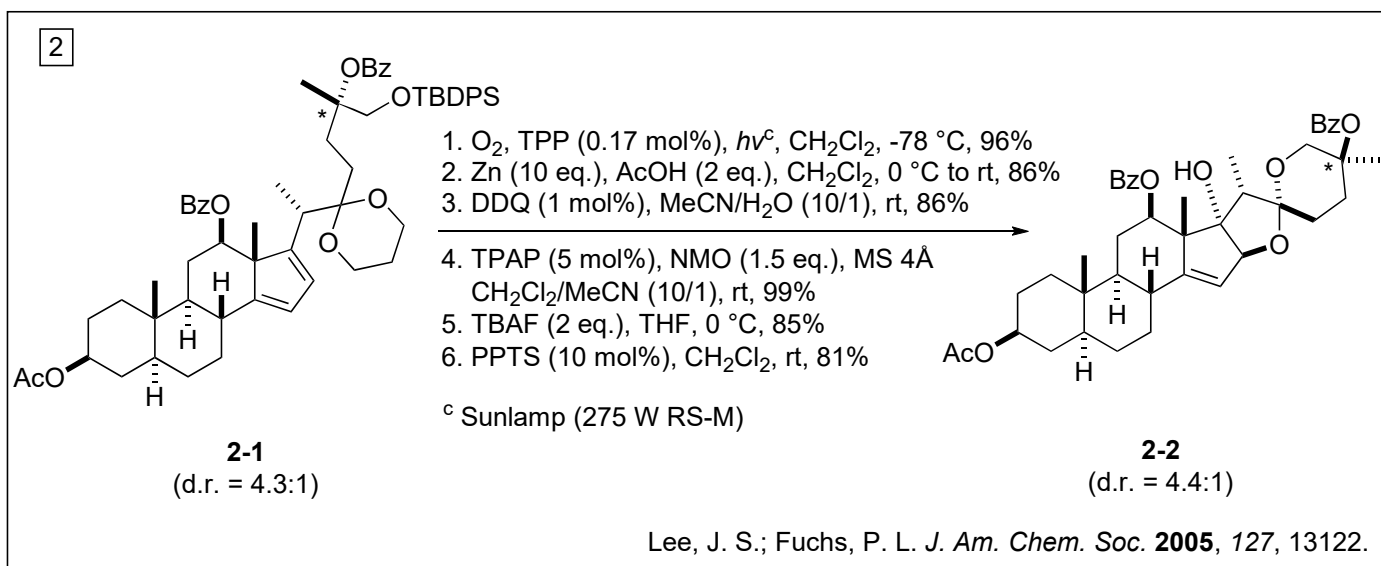
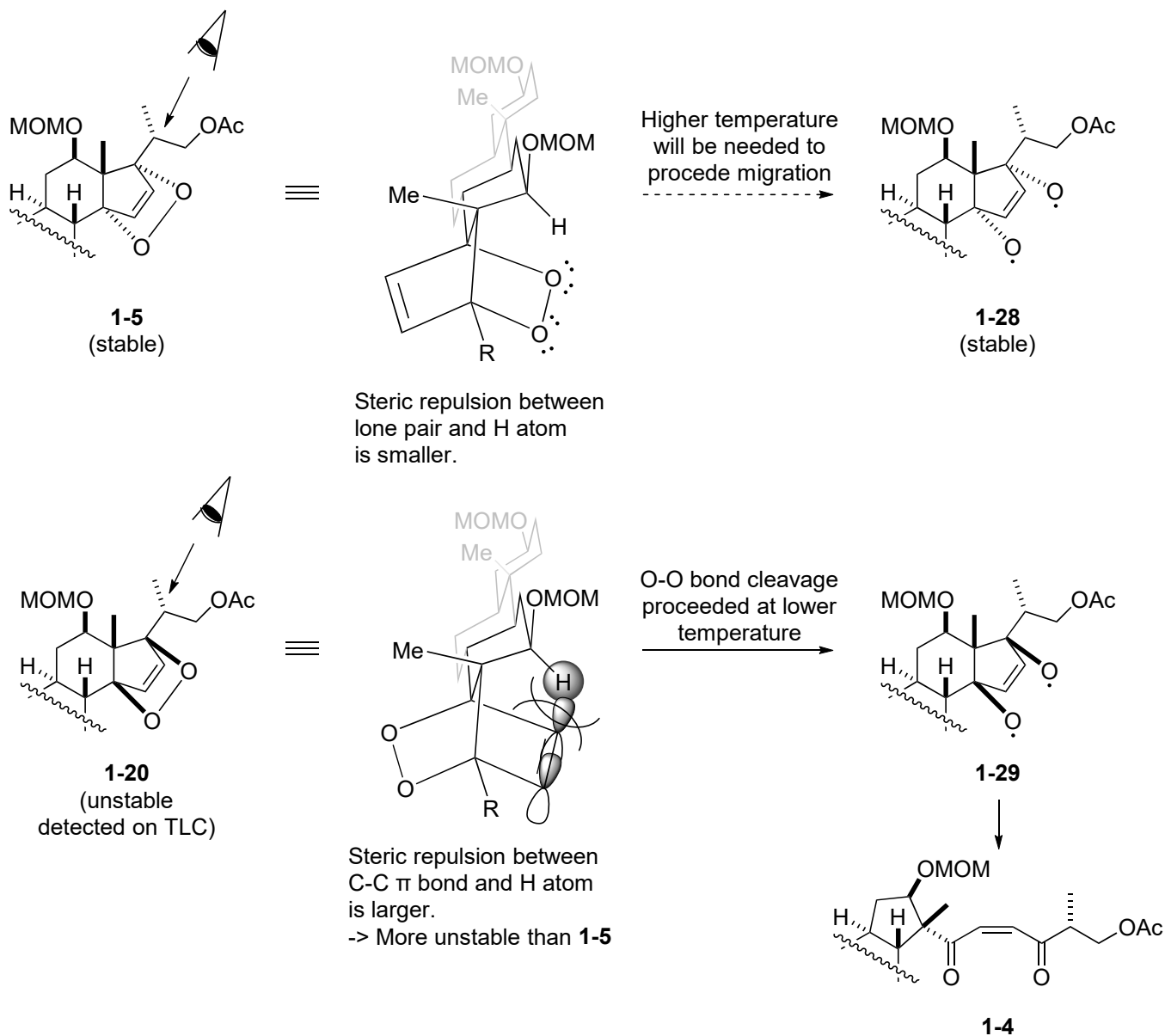


**Discussion 1:** Iodine mediated Baeyer-Villiger oxidation

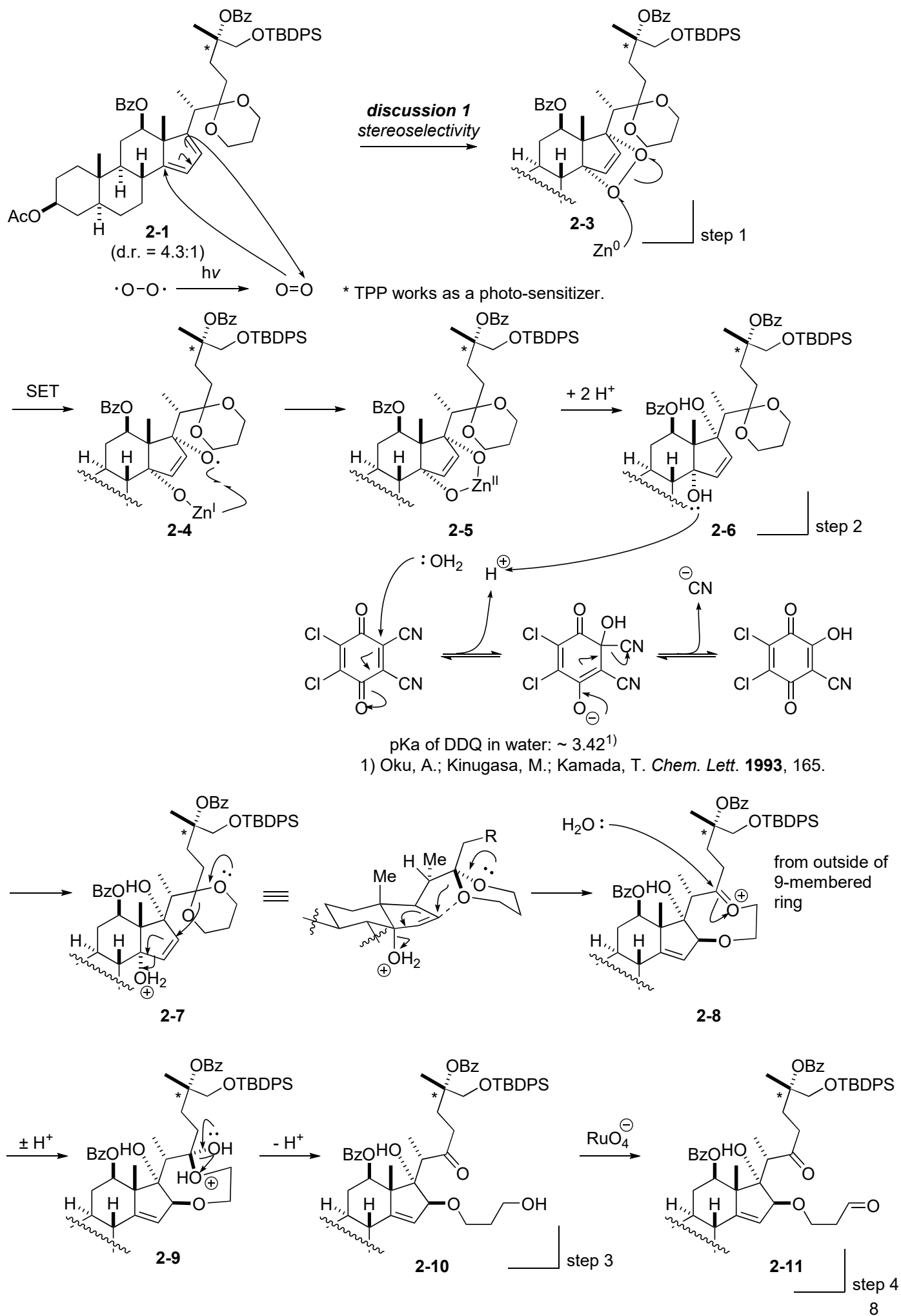
\* Without I<sub>2</sub>, **1-25** is obtained (see also 130112\_PS\_Satoshi\_Hashimoto.)



**Discussion 2:** Difference between 2 diastereomers, **1-5**, **1-20**

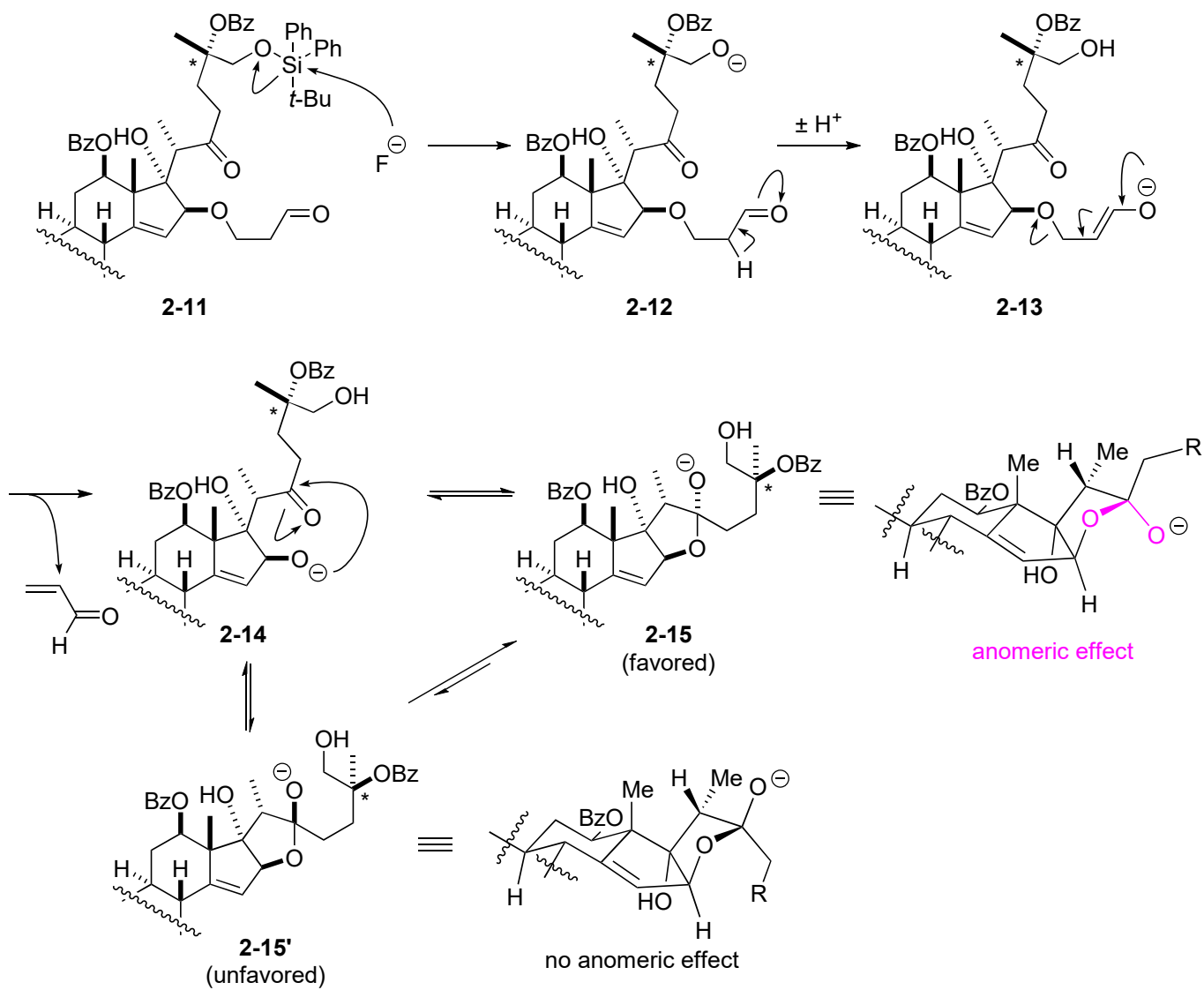
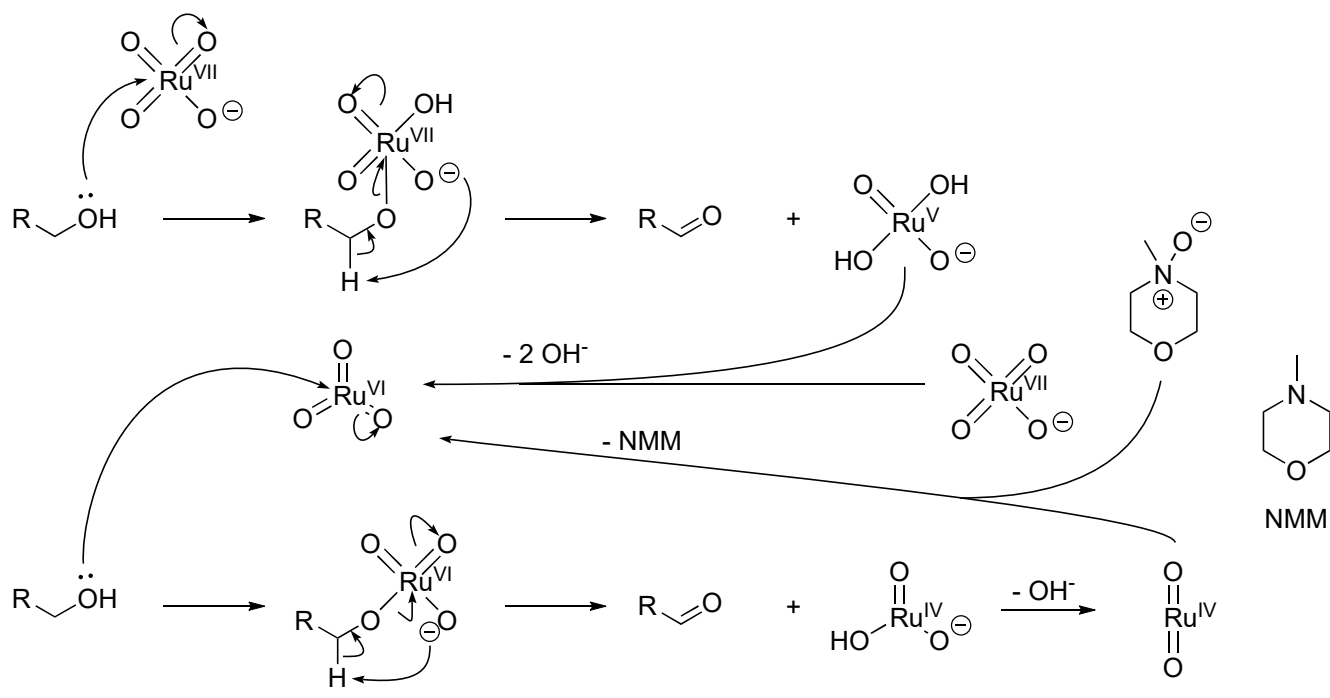


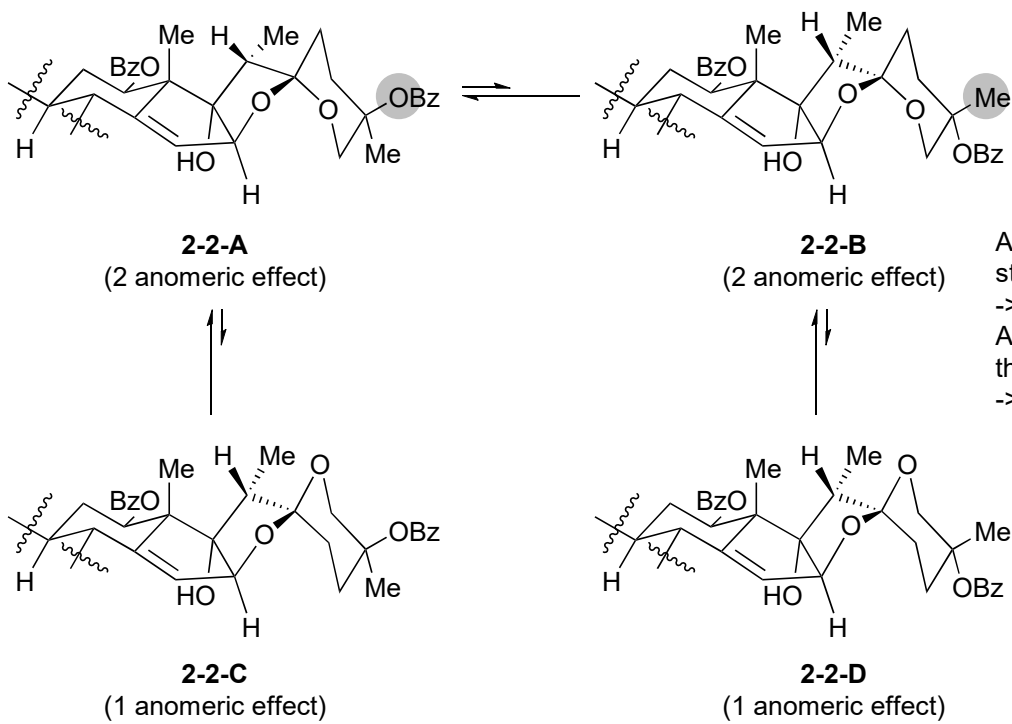
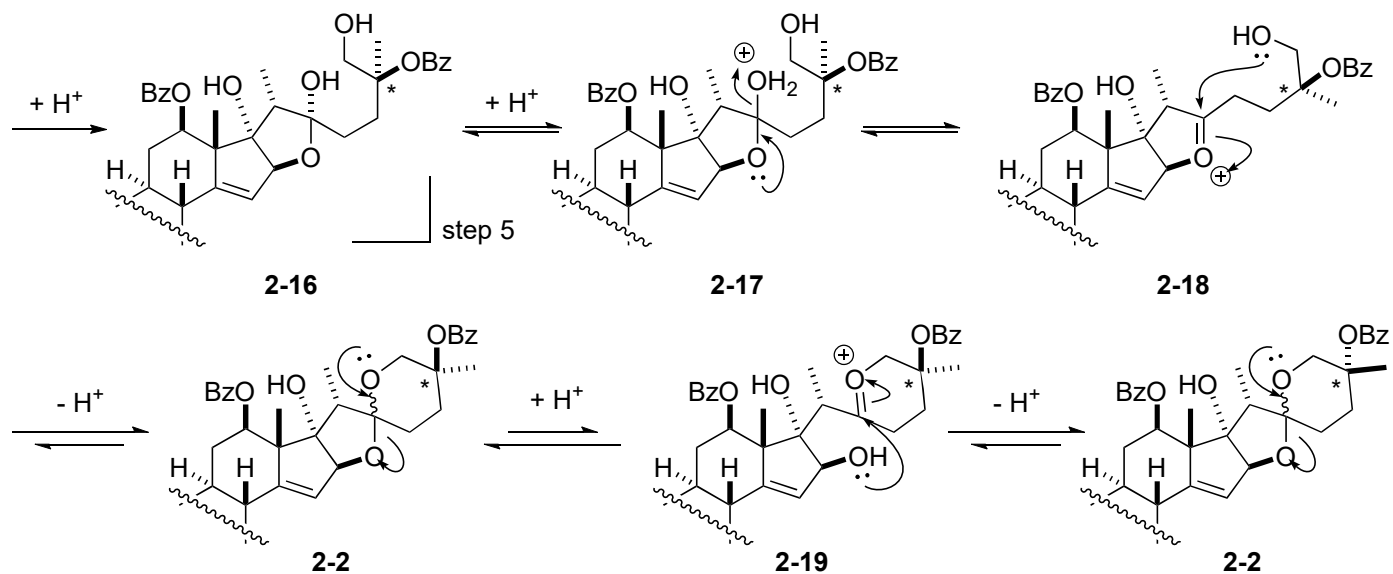
\* Major diastereomer is described below.





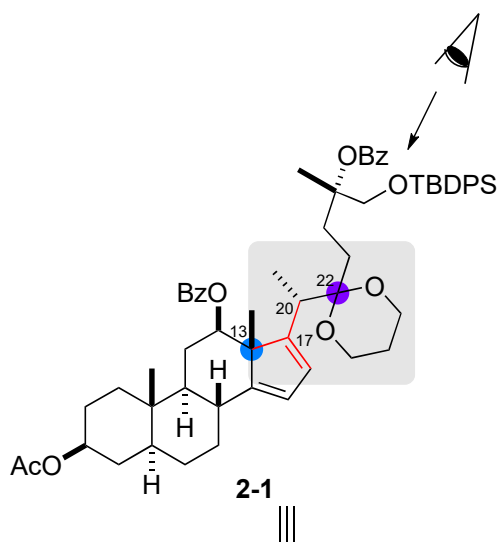
Oxidation mechanism of TPAP



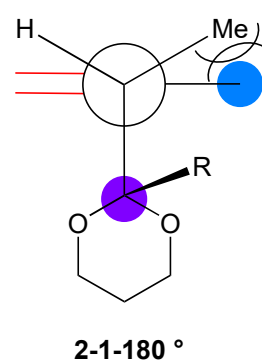
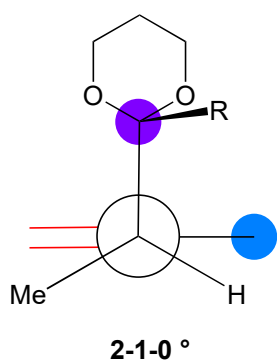


Anomeric effect greatly stabilize the conformation.  
 -> Only **A** and **B** were obtained.  
 A value of Me is larger than that of OBz.  
 -> **A**: **B** = 4.4: 1

## Discussion 1: Stereoselective Diels-Alder cyclization



Considering steric repulsion between two quaternary carbon (C13 and C22), C20-C22 bond should be vertical to olefin bond. Thus 2 conformers (**2-1-0°** and **2-1-180°**) need to be considered when discussing stereoselectivity.



Comparing these 2 conformers, **2-1-0°** is favorable.  
 -> O<sub>2</sub> DA only proceed from **2-1-0°**.

