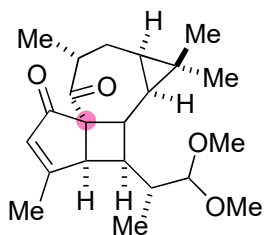


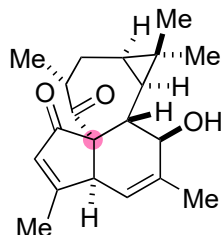
Problem Session (1)

2020/09/26 Junhao Fu

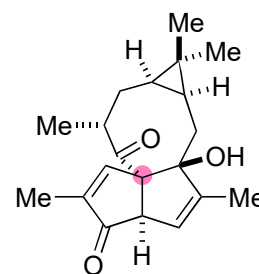
Topic: total synthesis of the *Euphorbia* diterpenoid Pepluanol



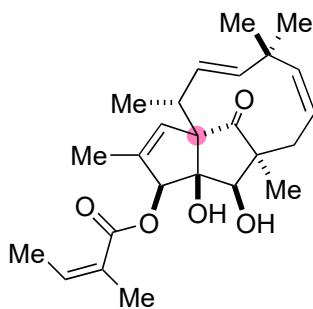
Pepluacetal (0-1)



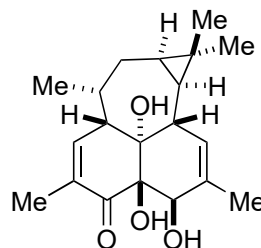
Pepluanol A (0-2)



Pepluanol B (0-3)



Pepluanol C (0-4)



Pepluanol D (0-5)

Isolation:

Isolated from the plant *Euphorbia peplus*

- Pepluacetal (0-1), Pepluanol A (0-2) and Pepluanol B (0-3): 2016, Qiu *et al.*¹
- Pepluanol C (0-4) and Pepluanol D (0-5): 2018, Qiu *et al.*²

Biological activity:

Inhibitory activity on the kv1.3 potassium channel¹

Structural properties:

- fused tetracyclic (tricyclic in 0-4) frameworks
- more than 6 stereogenic centers
- bridgehead all-carbon quaternary center (marked in pink)

Total synthesis:

racemic synthesis:

- (±)-Pepluanol A (0-2): 2017, Ding *et al.*³
- (±)-Pepluanol B (0-3): 2020, She *et al.*⁴

asymmetric synthesis:

- (-)-Pepluanol B (0-3): 2020, She *et al.*⁴

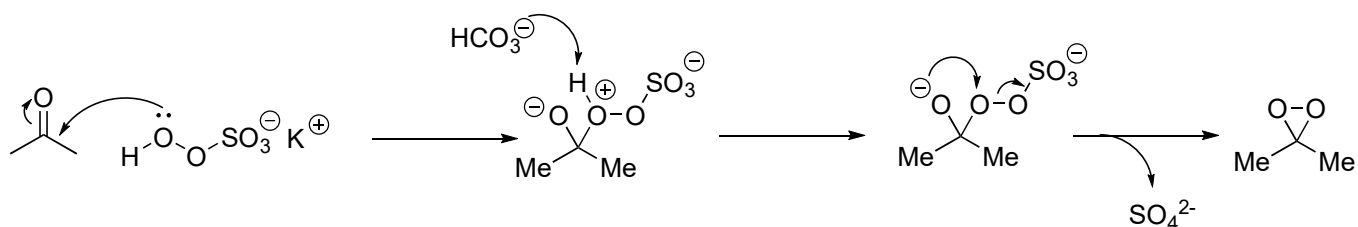
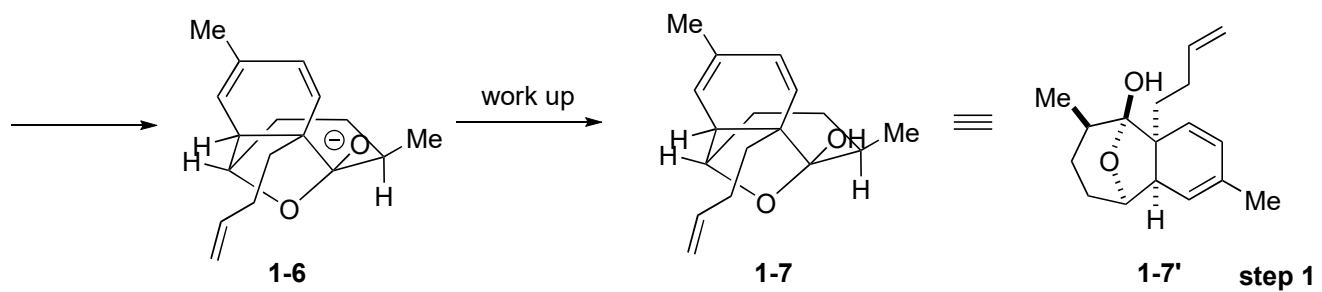
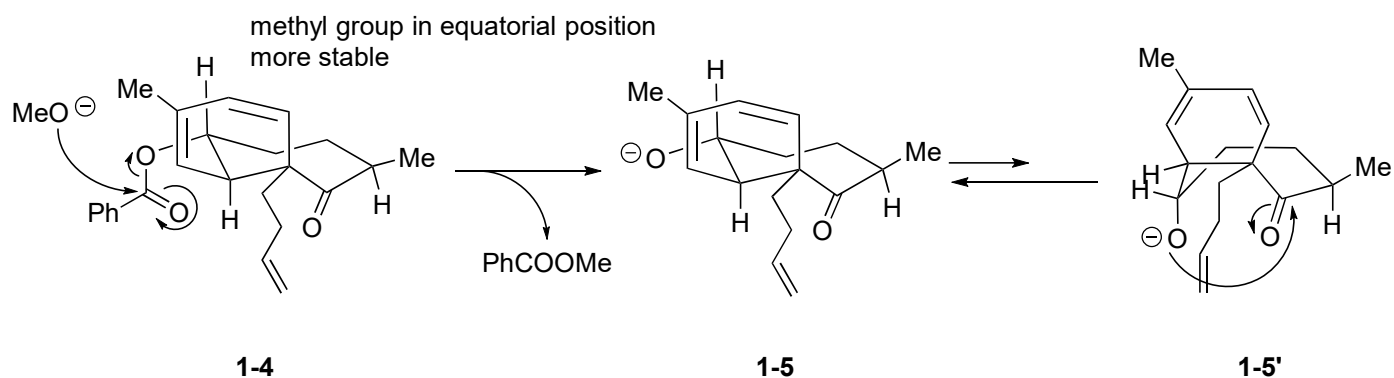
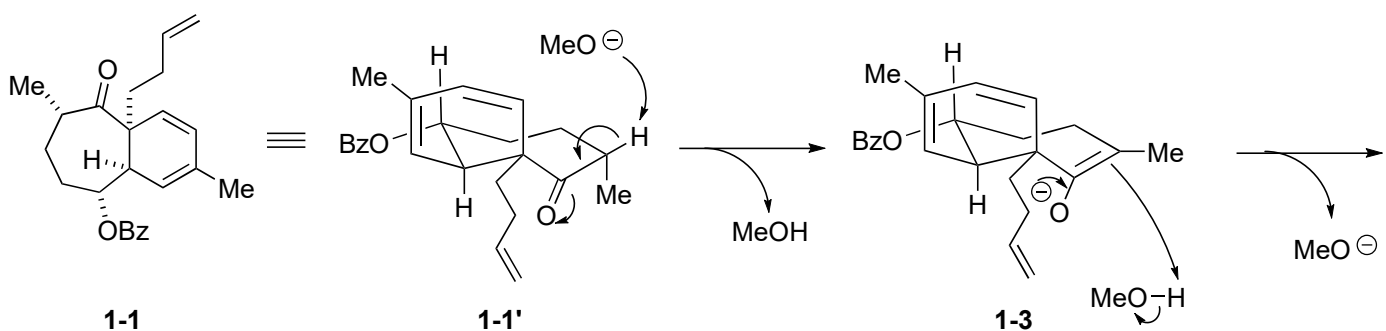
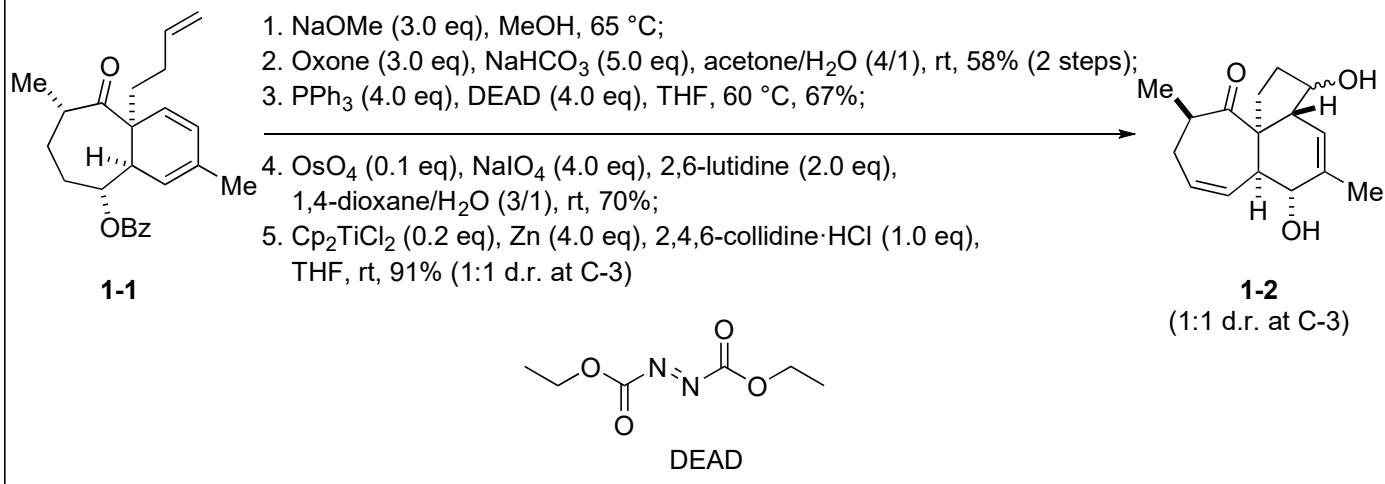
1) Wan, L.-S.; Nian, Y.; Ye, C.-J.; Shao, L.-D.; Peng, X.-R.; Geng, C.-A.; Zuo, Z.-L.; Li, X.-N.; Yang, J.; Zhou, M.; Qiu, M.-H. *Org. Lett.* **2016**, *18*, 2166.

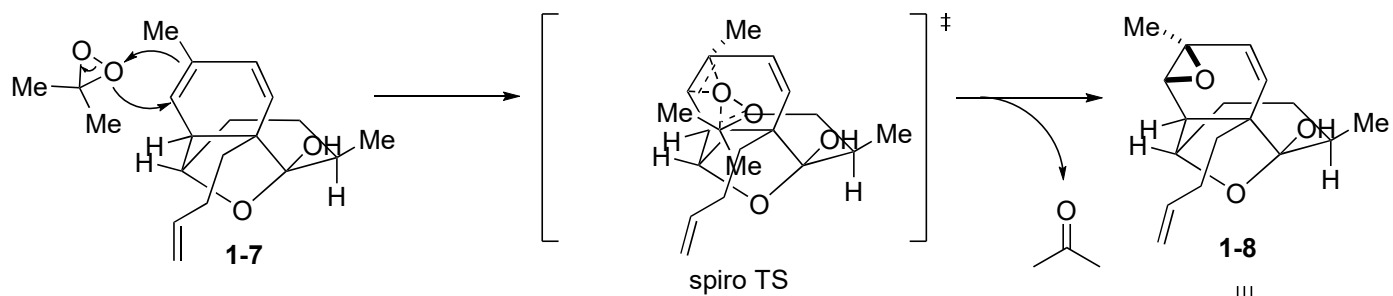
2) Wan, L.-S.; Nian, Y.; Peng, X.-R.; Shao, L.-D.; Li, X.-N.; Yang, J.; Zhou, M.; Qiu, M.-H. *Org. Lett.* **2018**, *20*, 3074.

3) Xuan, J.; Liu, Z.-B.; Zhu, A.; Rao, P.-R.; Yu, L.; Ding, H.-F. *Angew. Chem. Int. Ed.* **2017**, *56*, 8898.

4) Zhang, J.; Liu, M.; Wu, C.-H.; Zhao, G.-Y.; Chen, P.-Q.; Zhou, L.; Xie, X.-G.; Fang, R.; Li, H.-L.; She, X.-G. *Angew. Chem. Int. Ed.* **2020**, *59*, 3966.

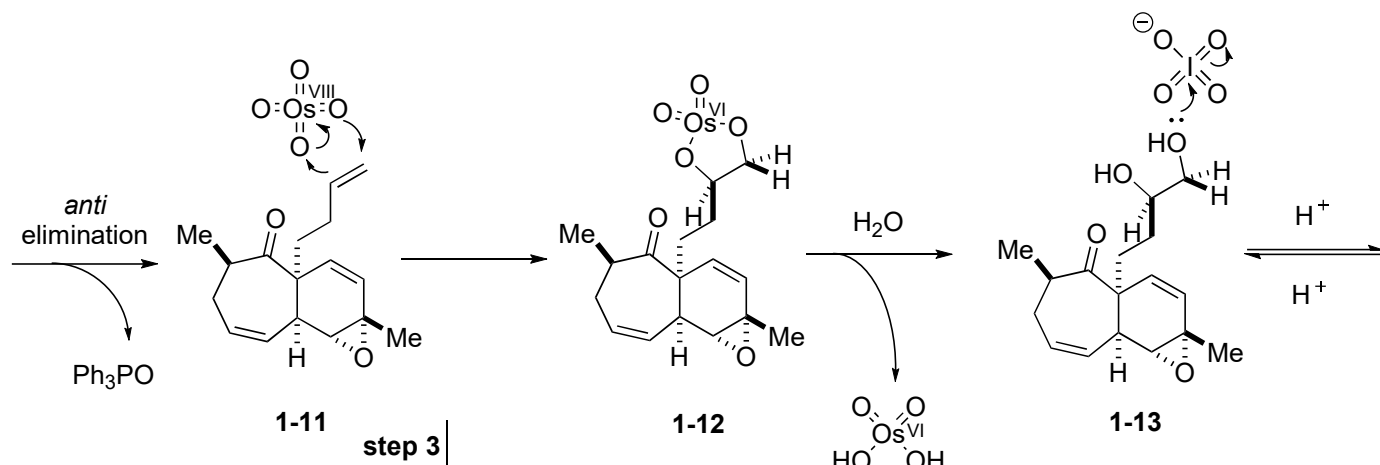
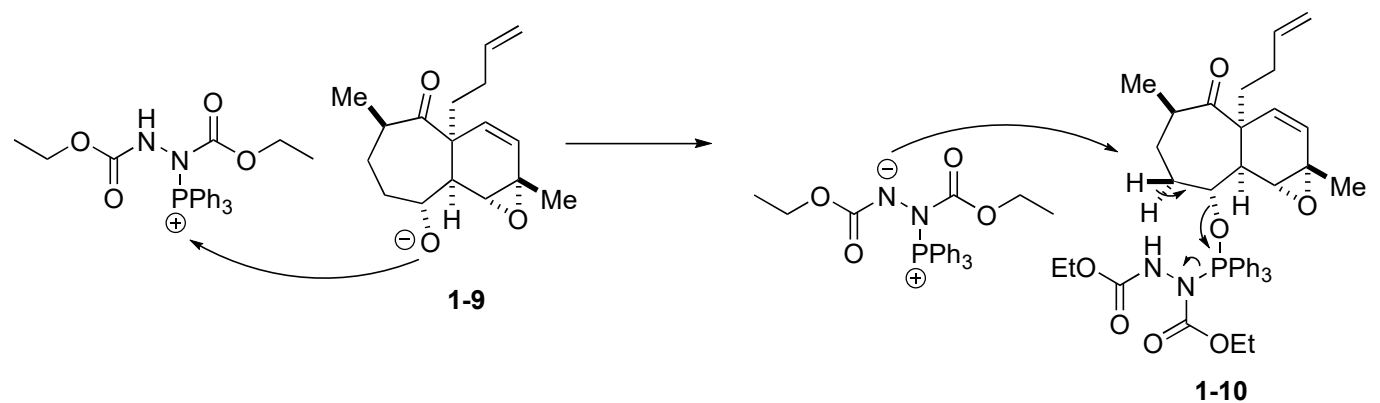
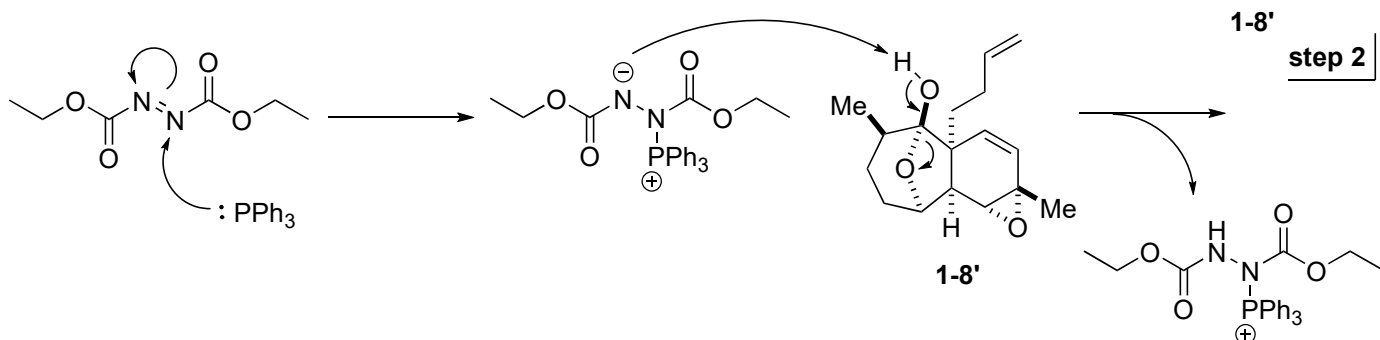
Problem 1



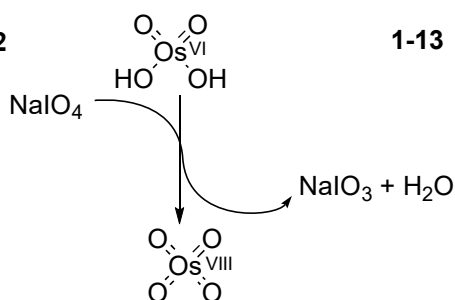


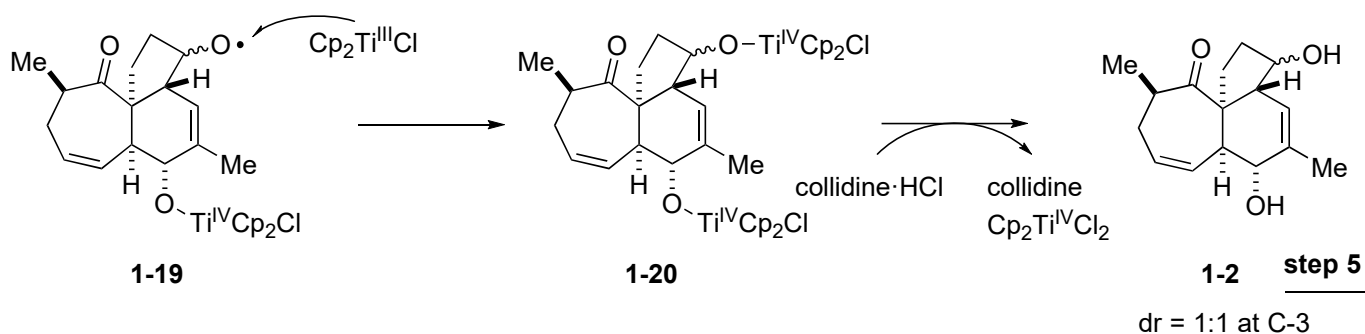
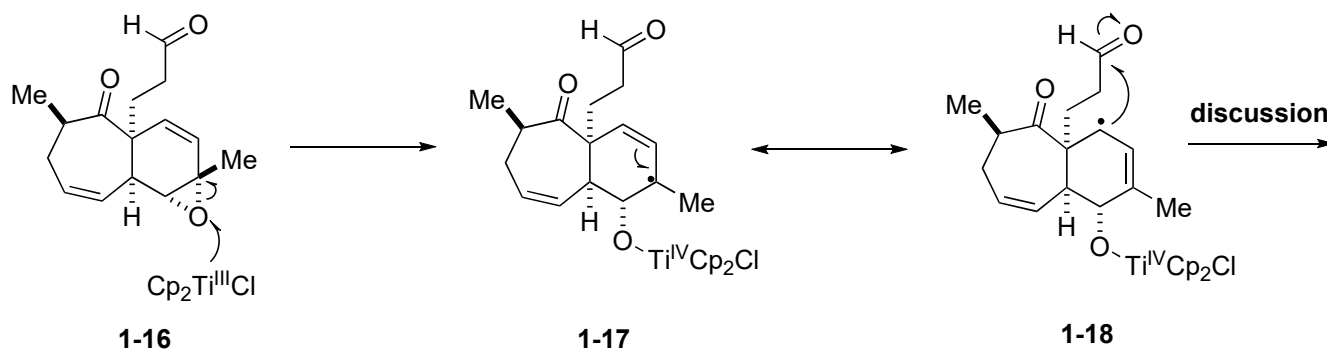
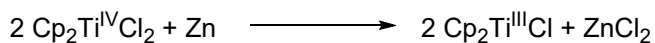
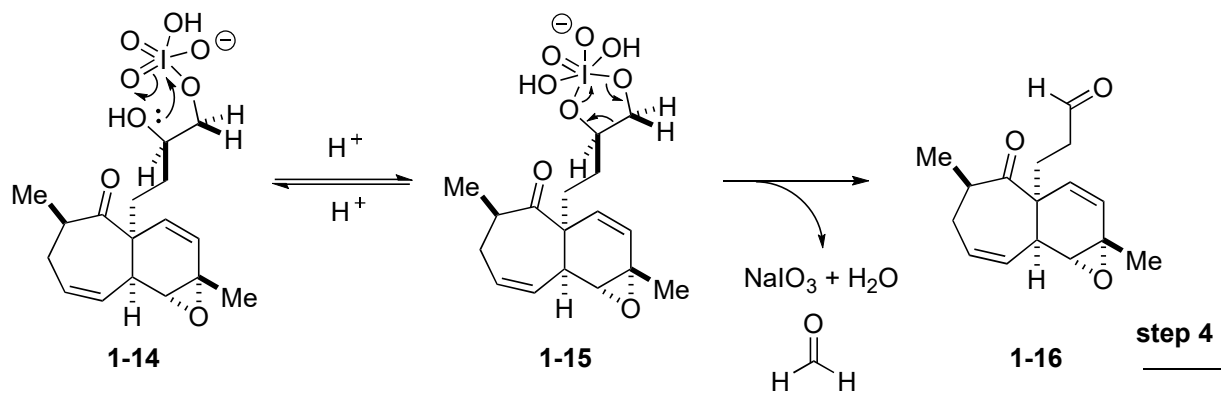
approach from the convex face
of both [6,7] and [6,5] fused rings

- The trisubstituted $\Delta^{6,7}$ was regio selectively epoxidated due to its high nucleophilicity over disubstituted $\Delta^{4,5}$ and monosubstituted terminal olefin.

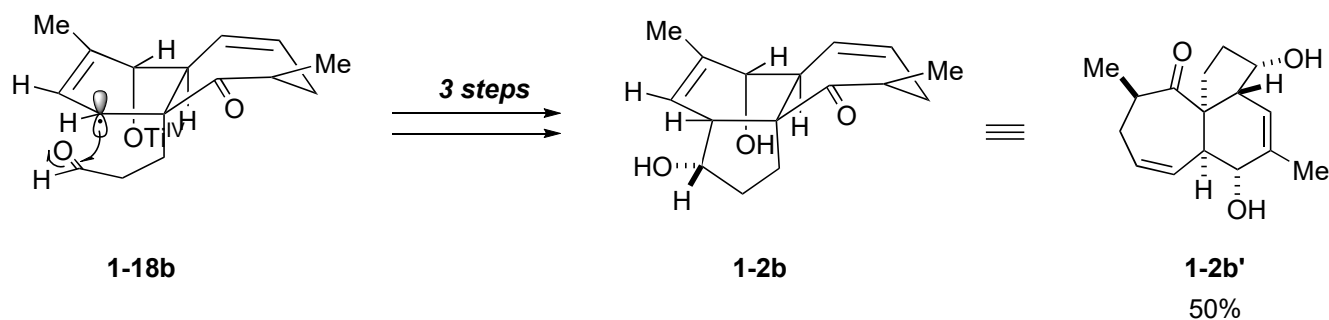
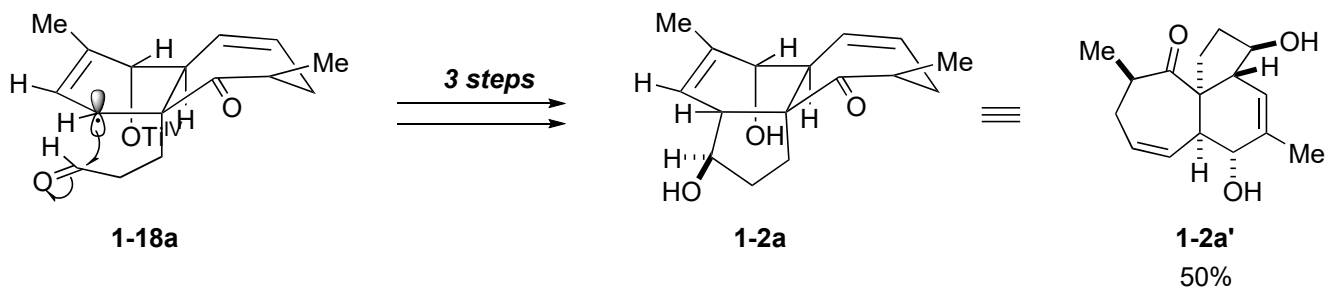


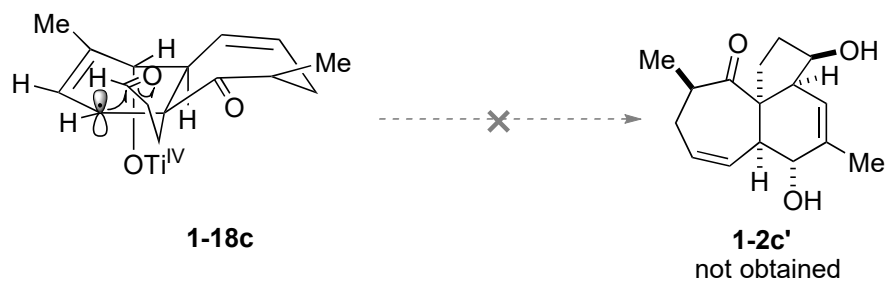
oxidation occurs at the less
hindered terminal olefin



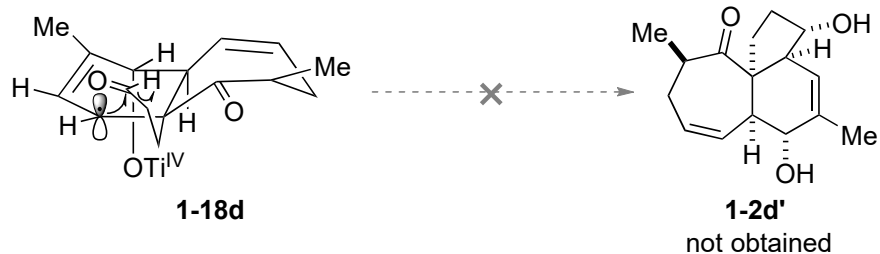


Discussion: reductive annulation of vinyl epoxide-aldehyde

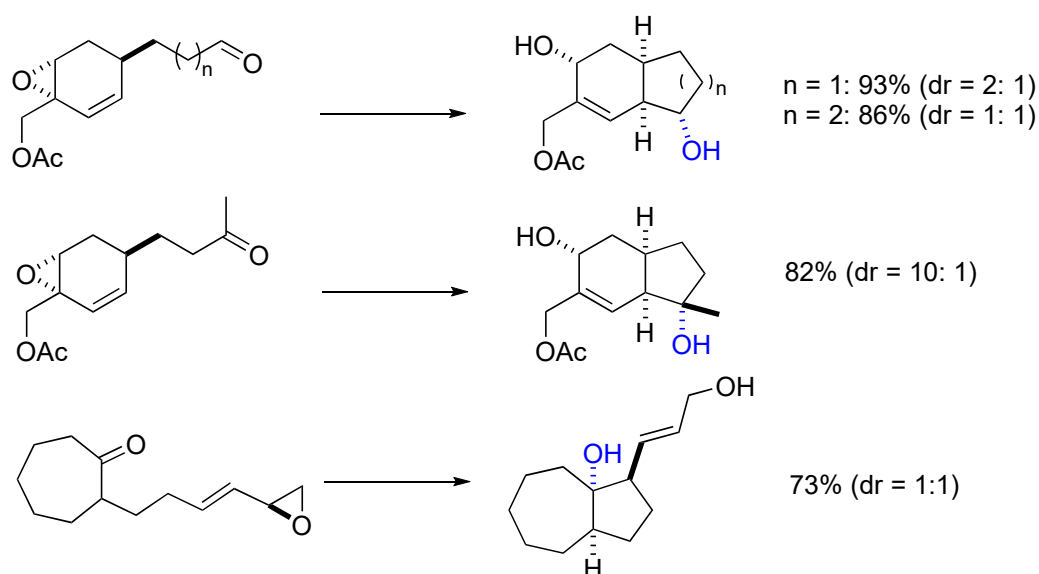




trans bicyclic rings are not preferred as the ring strain make them unstable.



Other examples of annulation of vinyl epoxide-aldehyde:

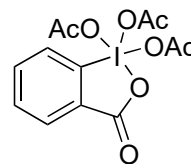
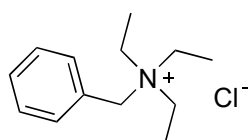
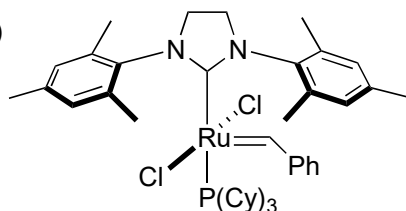
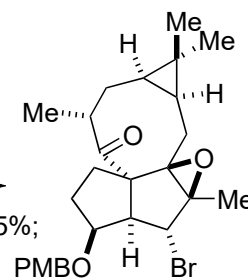
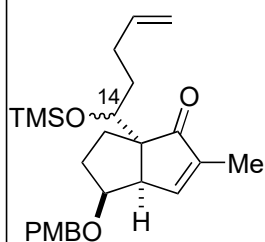


- Production of *cis* bicyclic rings is favored.
- Diastereoselectivity gradually drops for longer tethers.

(See also: 170701_LS_Yinghua_Wang)

Problem 2

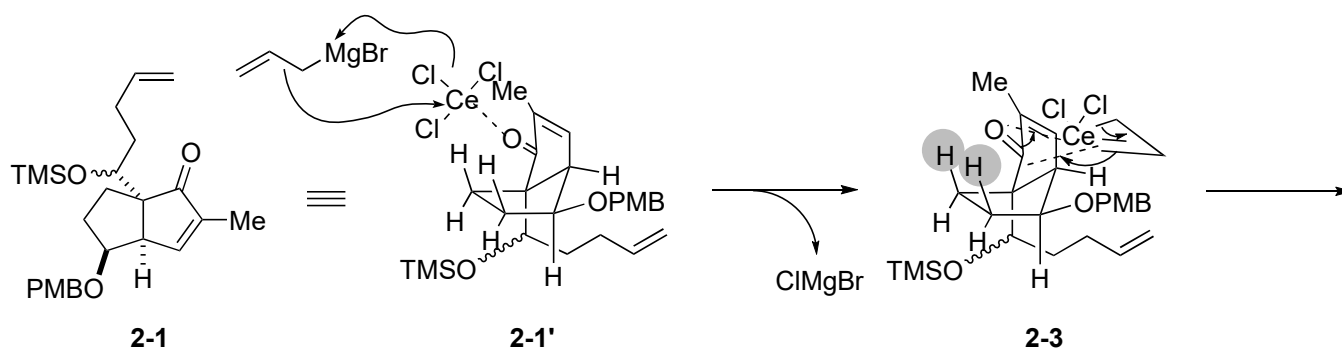
1. CeCl_3 (3.0 eq), AllylMgBr (3.0 eq), THF, -78°C to rt, 72%;
2. Grubbs II catalyst (0.05 eq), CH_2Cl_2 , 88%;
3. TEBAC (0.1 eq), CHBr_3 (5.0 eq), NaOH (aq., 50 wt%), CH_2Cl_2 , 0°C to rt, 78%;
4. CuI (4.0 eq), MeLi (12.0 eq), MeI (28.0 eq), Et_2O , -45°C to rt; TBAF (1.5 eq), THF, rt, 82%;



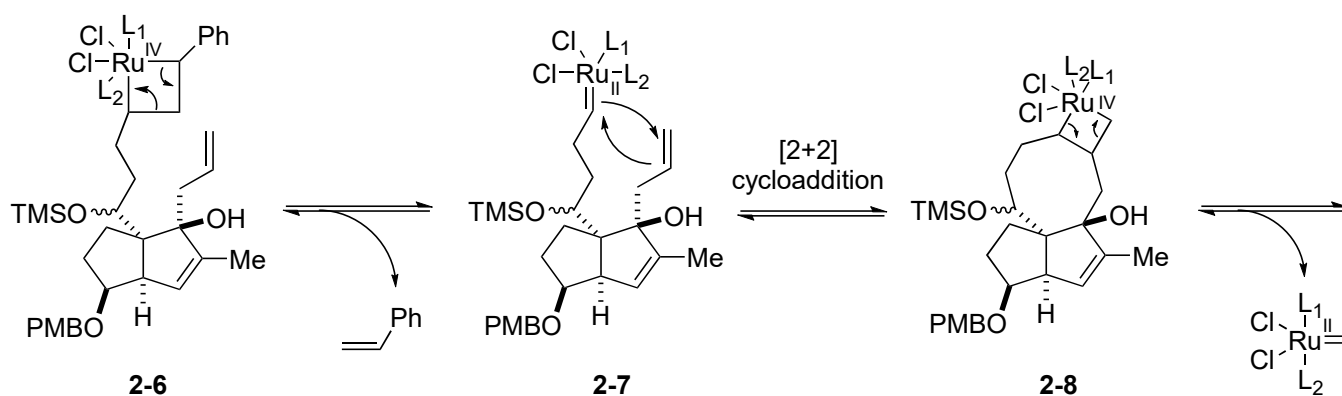
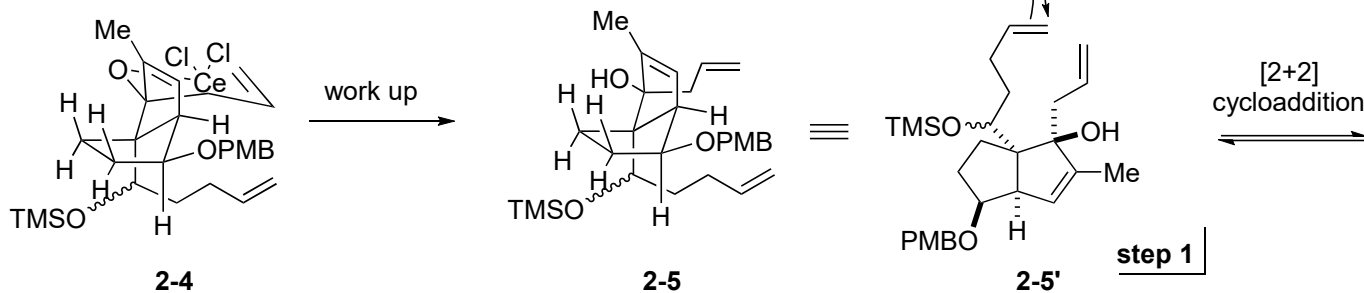
Grubbs II catalyst

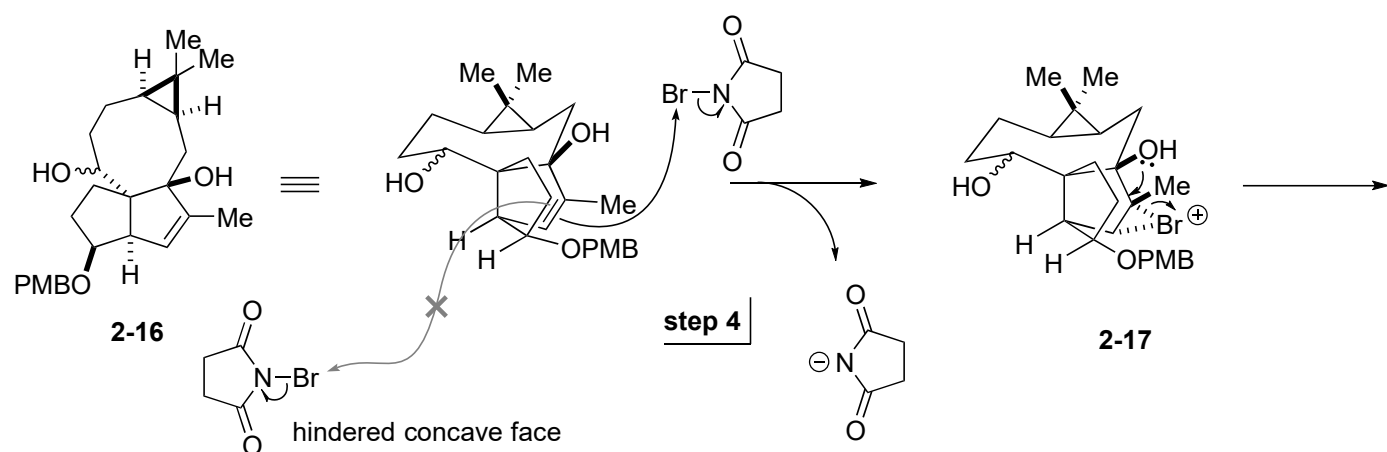
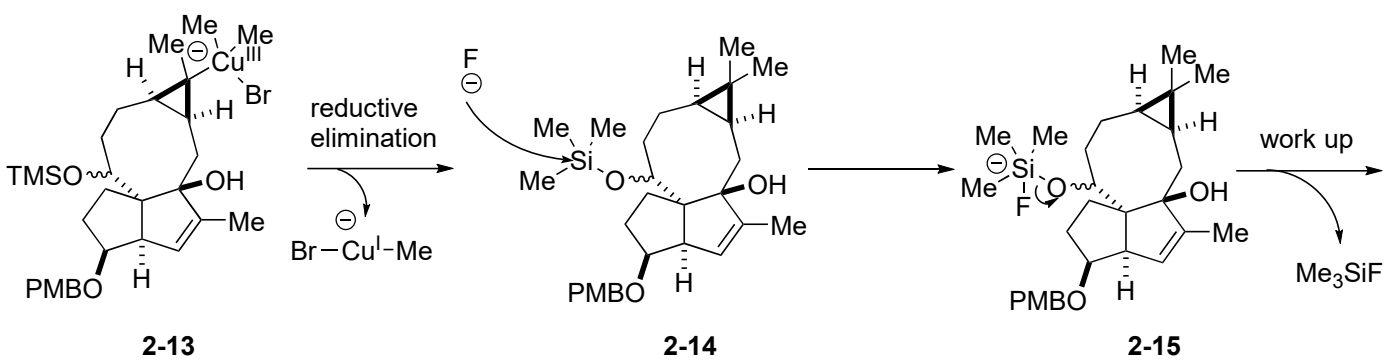
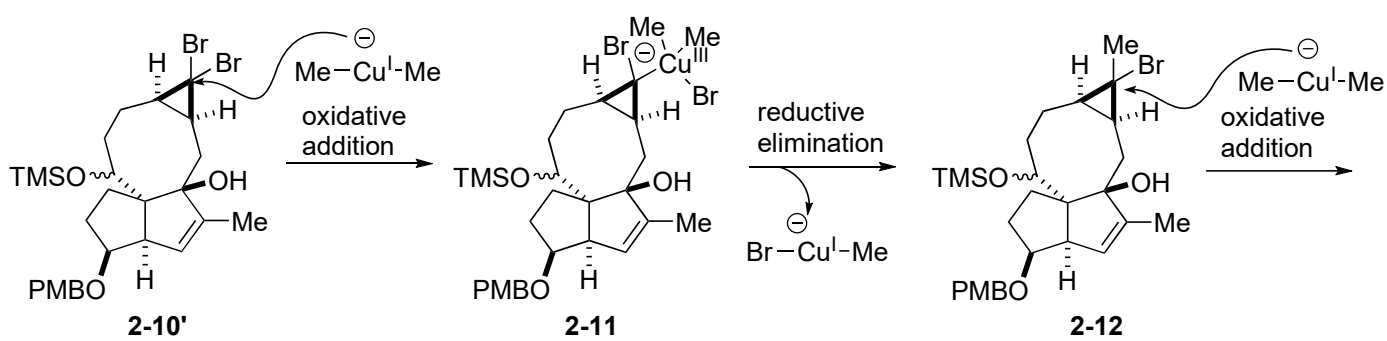
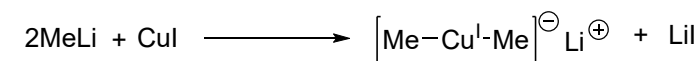
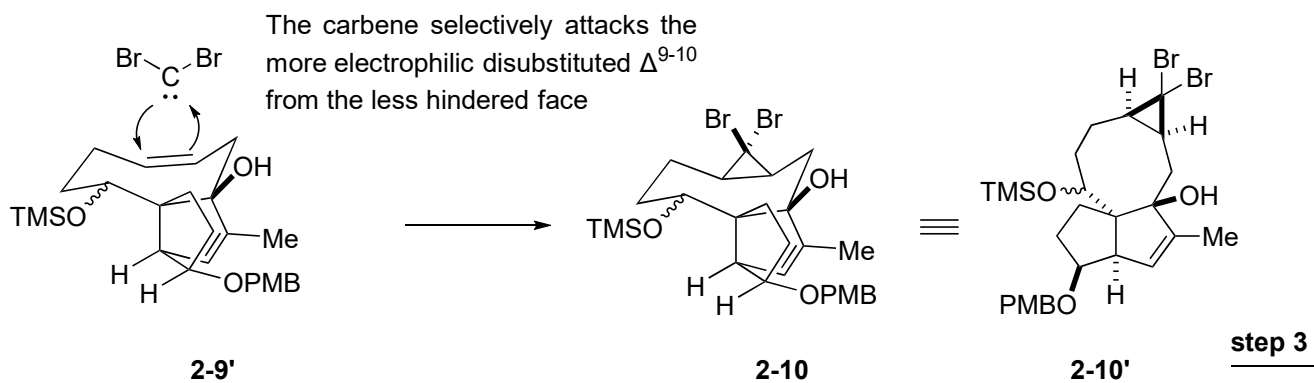
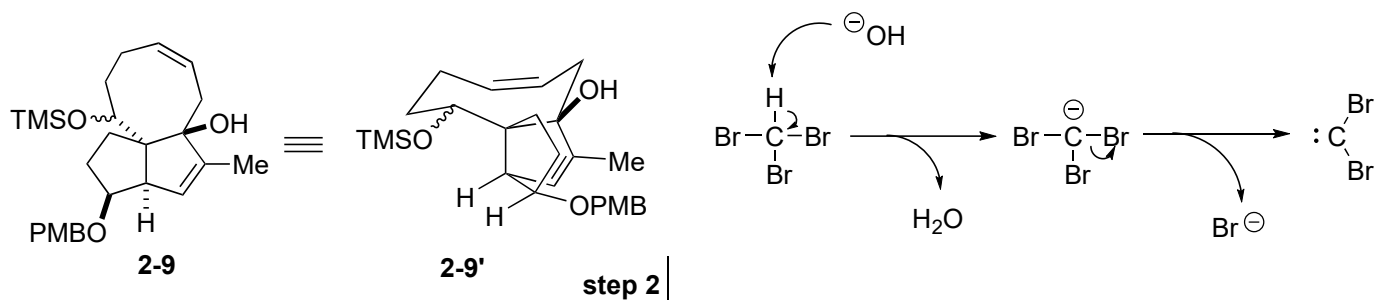
TEBAC

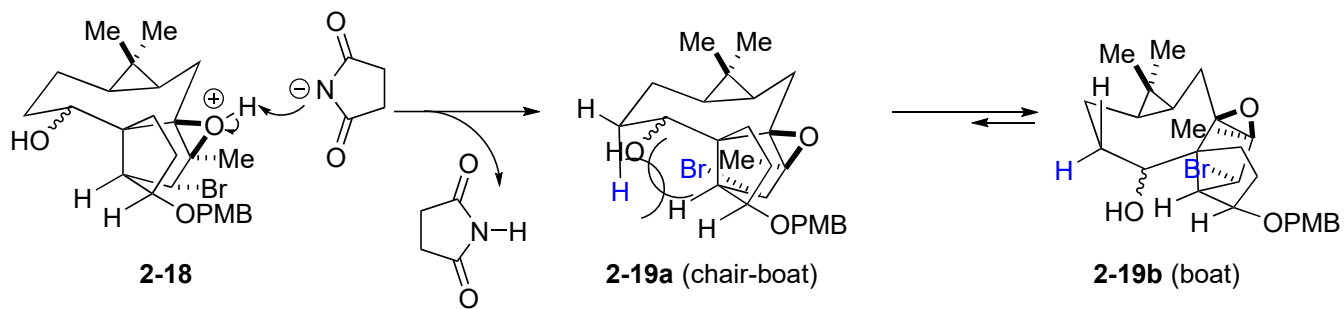
DMP



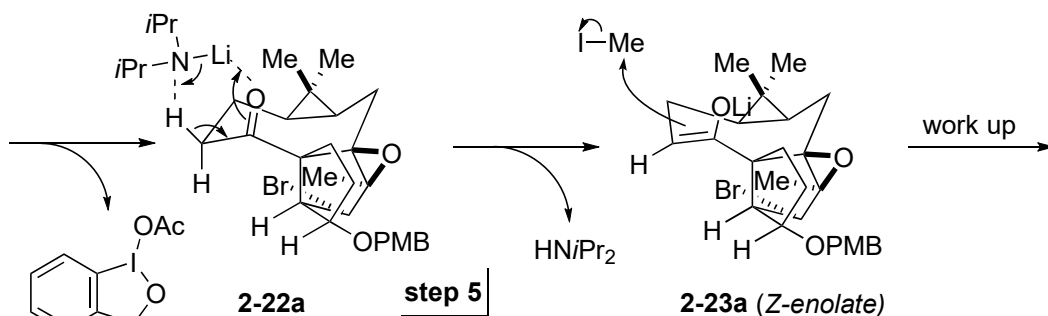
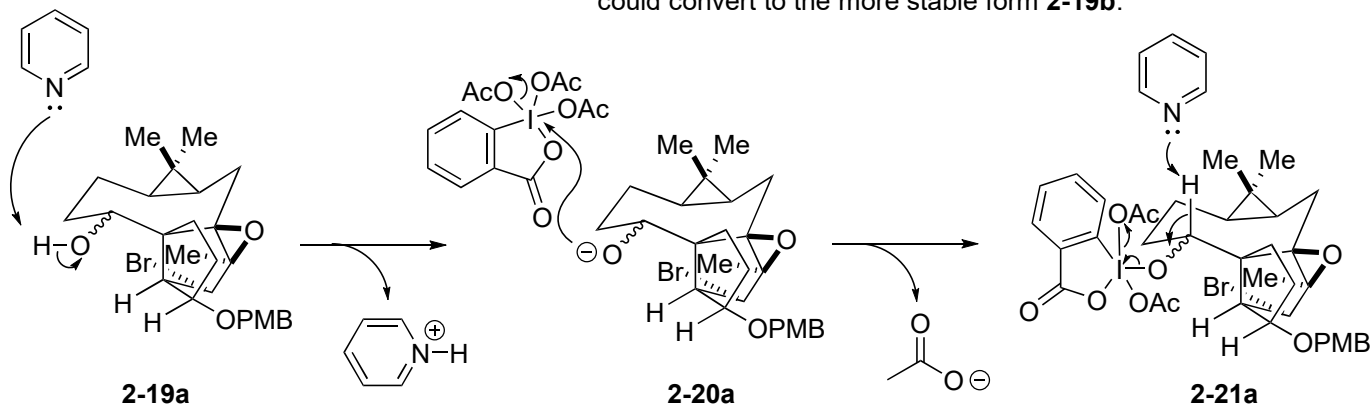
The six-membered TS prefers a backward conformation to avoid the stereo hindrance from hydrogen







Due to stereo repulsion of Br and H, the conformation of **2-19a** could convert to the more stable form **2-19b**.



approaching towards the front of the Z-enolate is preferred due to less stereo hindrance

