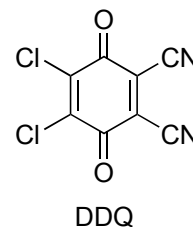
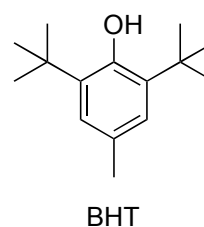
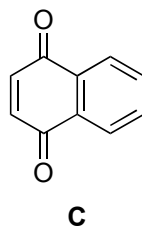
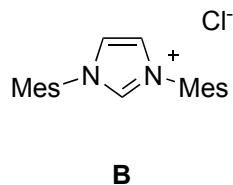
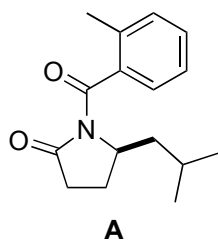
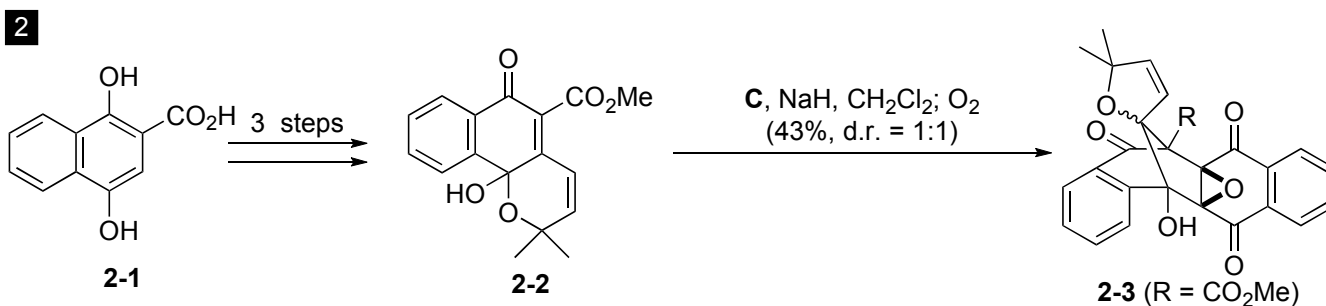
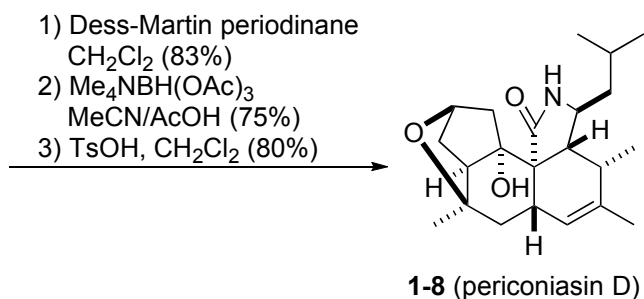
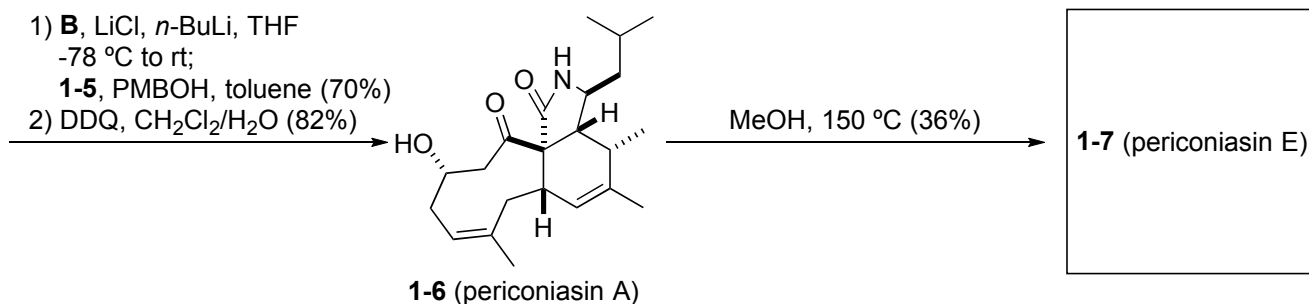
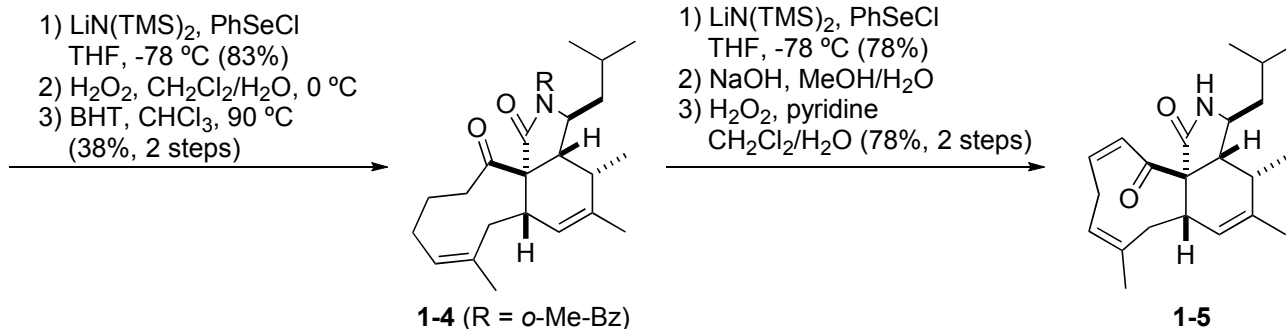
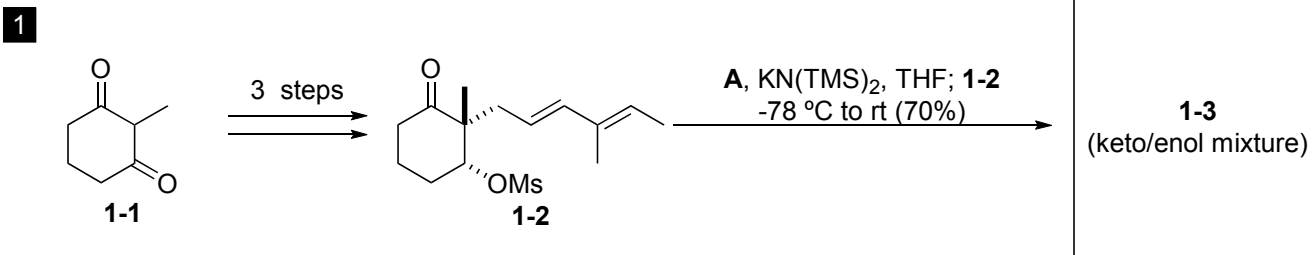


Problem Session (5)

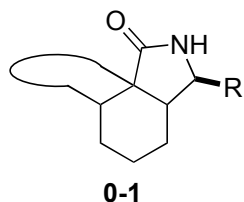
2016/7/16 Atsushi Hayata

Please provide each reaction mechanism, explain the stereoselectivities and fill in the blanks.



1

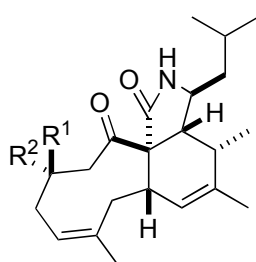
introduction of cytochalasans



- polyketide-amino acid hybrid metabolite from fungi
- n/6/5 tricyclic framework (n-membered ring was fused to isoindolone structure)
- generally n = 11~14
- amino acid component (Phe, Tyr, Trp, Leu, Ala)
- various biological function (capping of actin filament, inhibition of cholesterol synthesis etc.)

 (review) Scherlach, K.; Boettger, D.; Remme, N.; Hertweck, C. *Nat. Prod. Rep.* **2010**, 27, 869.

introduction of periconiasin

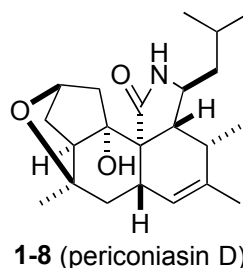
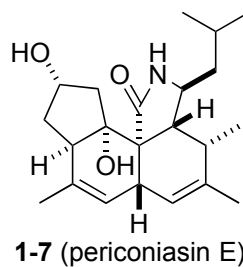

1-6 (periconiasin A): R¹ = H, R² = OH

0-2 (periconiasin B): R¹ = OH, R² = H

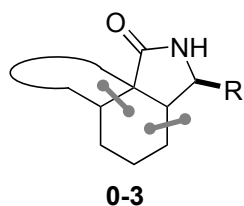
- isolated from *periconia sp. F-31*
- 9/6/5 tricyclic framework

(Isolation)

 Zhang, D.; Ge, H.; Xie, D.; Chen, R.; Zou, J.; Tao, X.; Dai, J. *Org. Lett.* **2013**, 15, 1674.

 Zhang, D.; Tao, X.; Chen, R.; Liu, J.; Li, L.; Fang, X.; Yu, L.; Dai, J. *Org. Lett.* **2015**, 17, 4304.


total synthesis of cytochalasans



Intramolecular Diels-Alder reaction

Stork, G.

 - *J. Am. Chem. Soc.* **1978**, 100, 7775.

 - *J. Am. Chem. Soc.* **1983**, 105, 5510.

Thomas, E. J.

 - *J. Chem. Soc. Chem. Commun.* **1986**, 727.

 - *J. Chem. Soc. Chem. Commun.* **1986**, 1447.

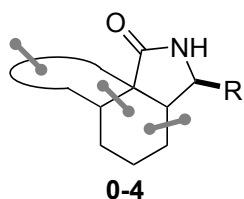
 - *J. Chem. Soc. Chem. Commun.* **1990**, 464.

 - *Acc. Chem. Res.* **1991**, 24, 229.

 - *J. Chem. Soc. Perkin Trans. 1* **1999**, 3269.

 Overman, P. S. - *Tetrahedron* **2011**, 67, 9837.

Tang, Y.

 - *Angew. Chem. Int. Ed.* **2016**, 55, 6992. (Problem)


Intermolecular Diels-Alder reaction + macrocyclization

Vedejs, E.

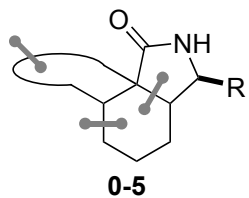
 - *J. Am. Chem. Soc.* **1984**, 106, 4617.

 - *J. Am. Chem. Soc.* **1990**, 112, 4351.

 - *J. Am. Chem. Soc.* **1990**, 112, 4357.

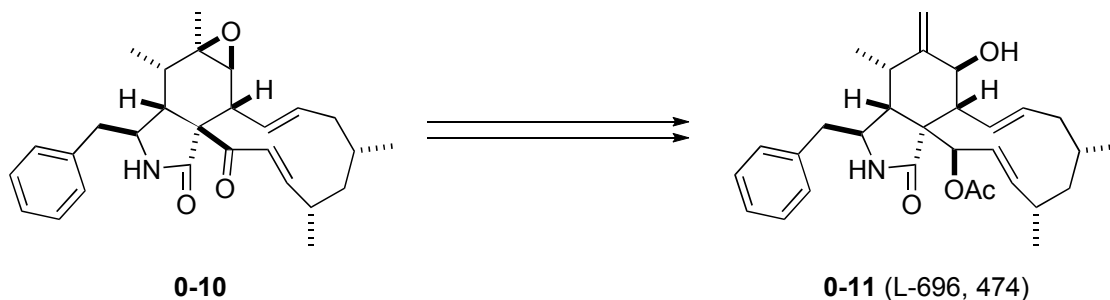
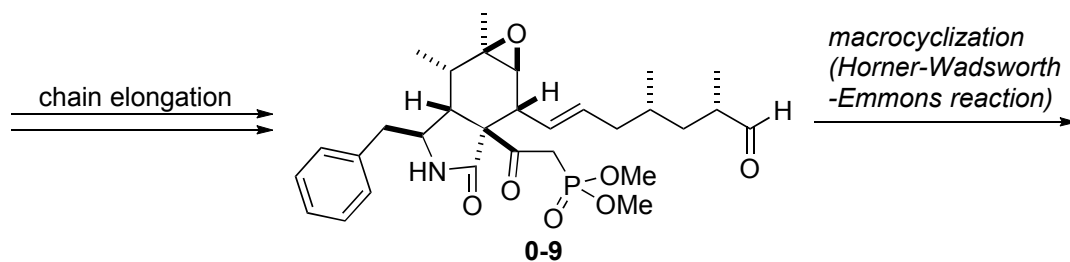
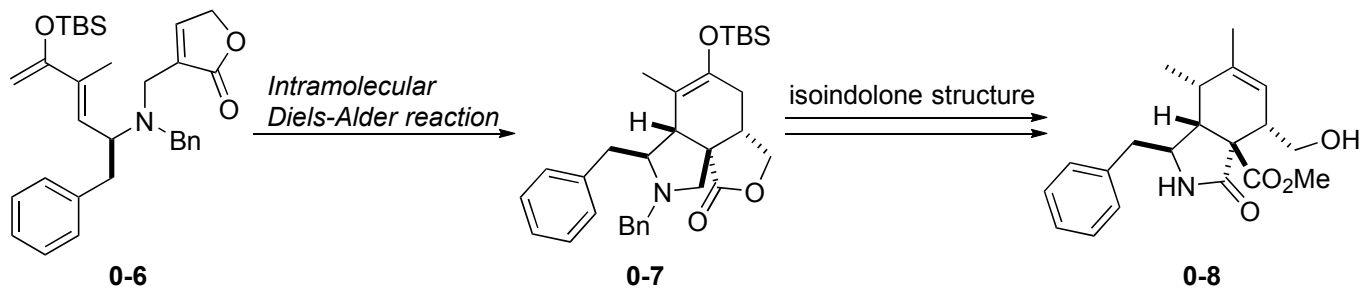
Trost, B. M.

 - *J. Am. Chem. Soc.* **1989**, 111, 8281.

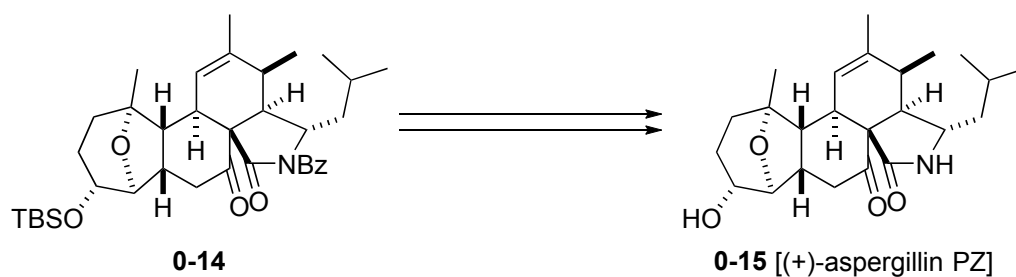
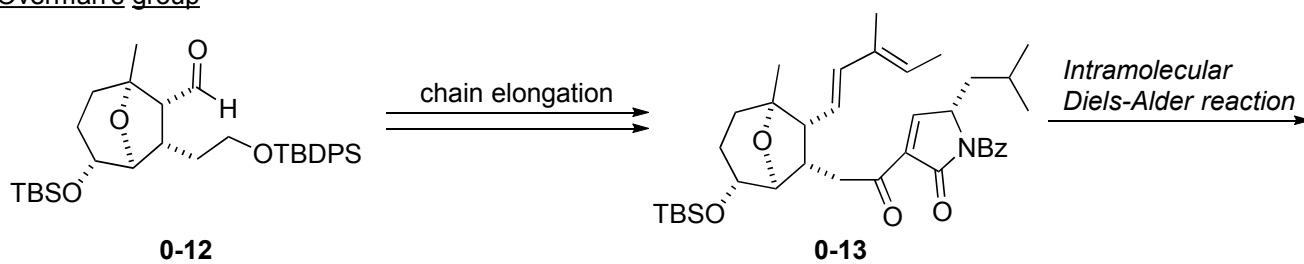


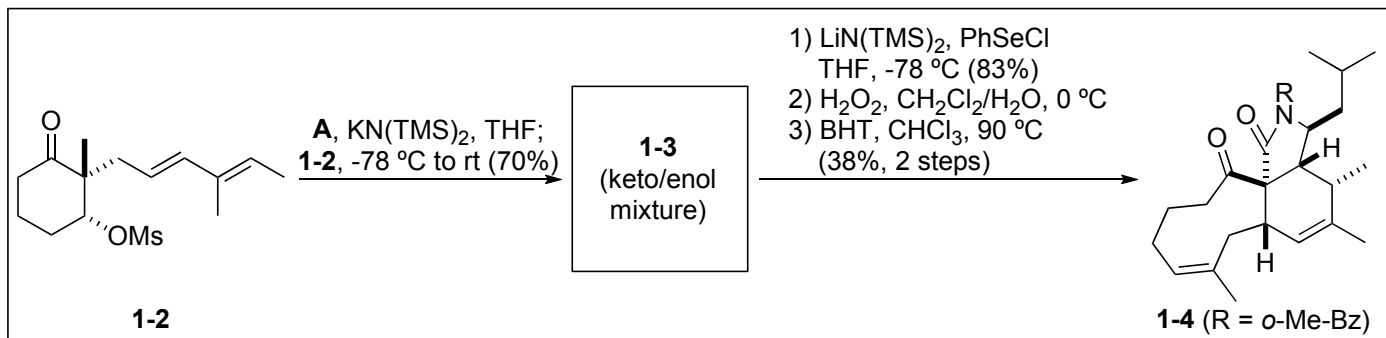
Intramolecular Diels-Alder reaction + macrocyclization
 Myers, A. G. - *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12048.

Myers's group

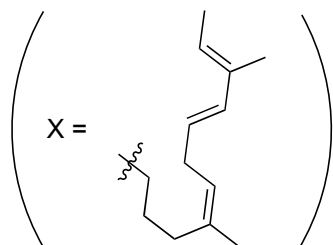
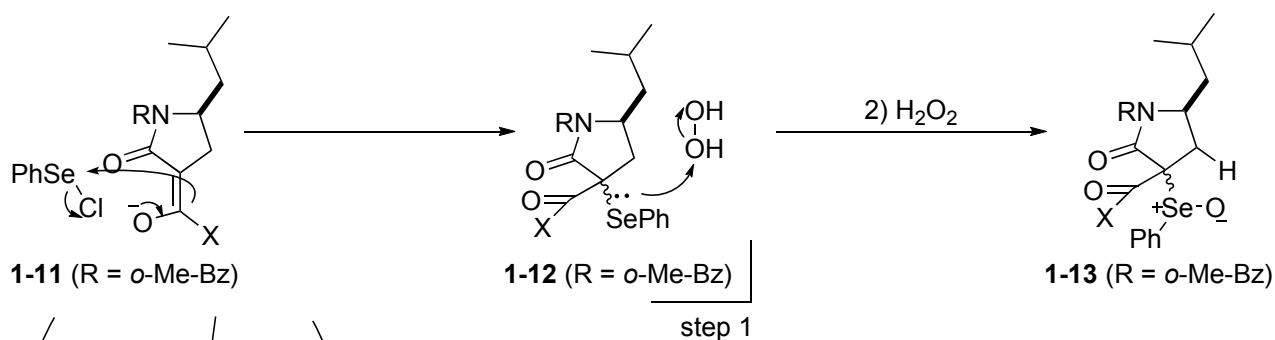
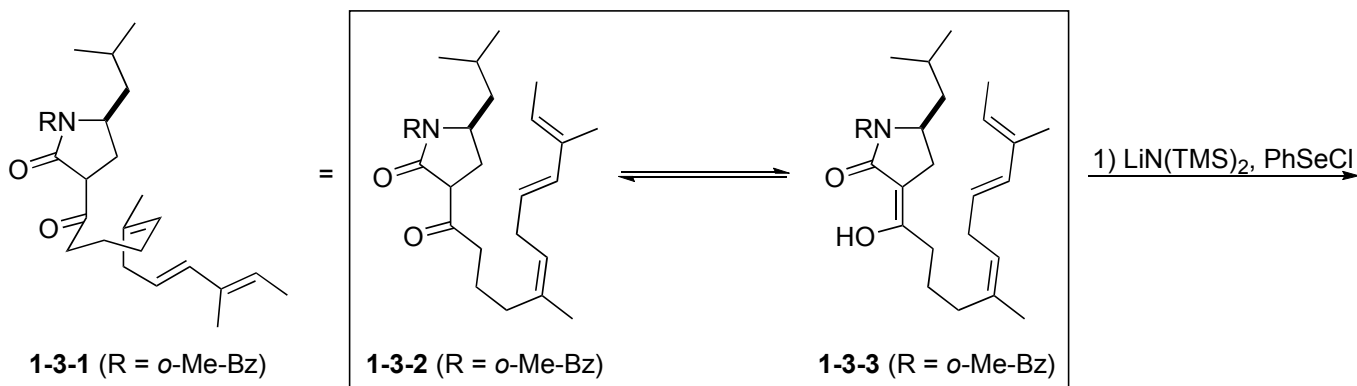
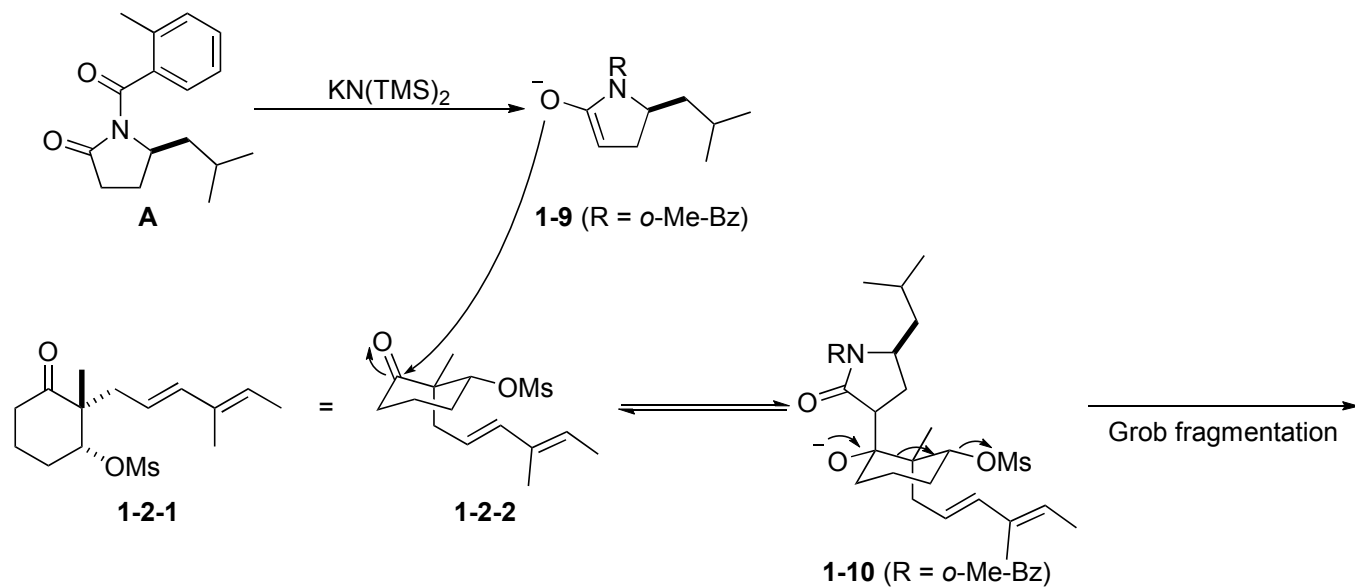


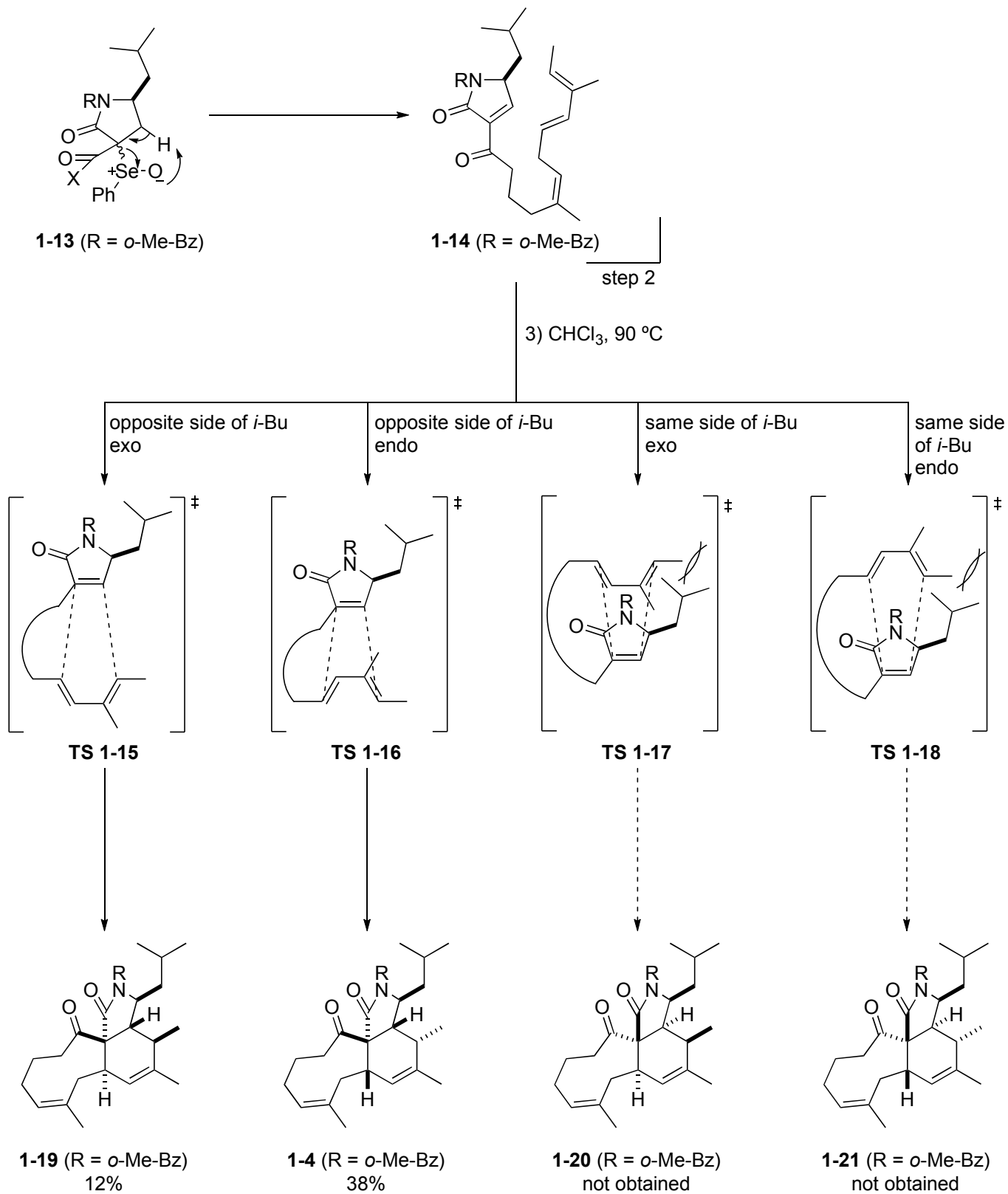
Overman's group

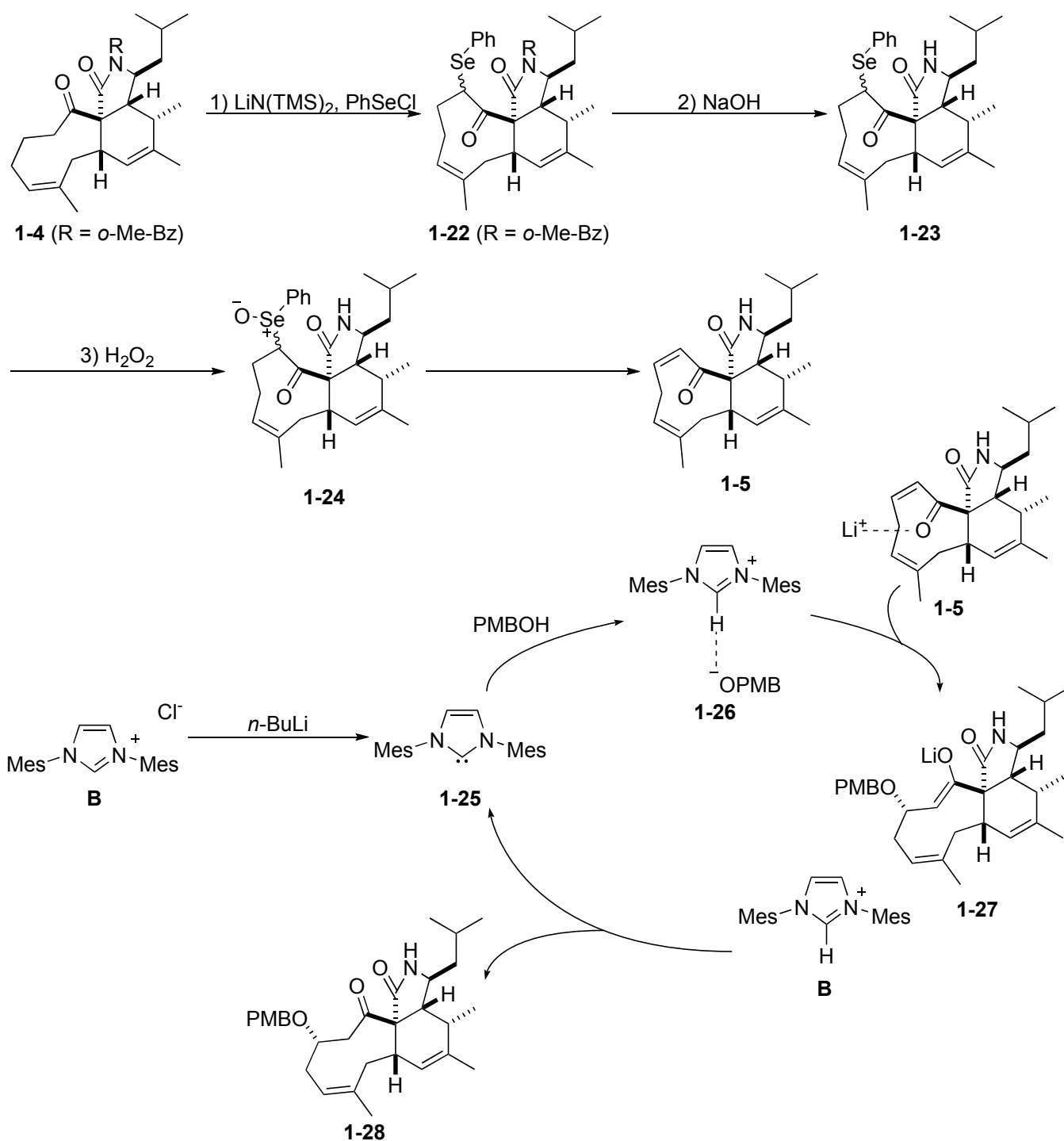
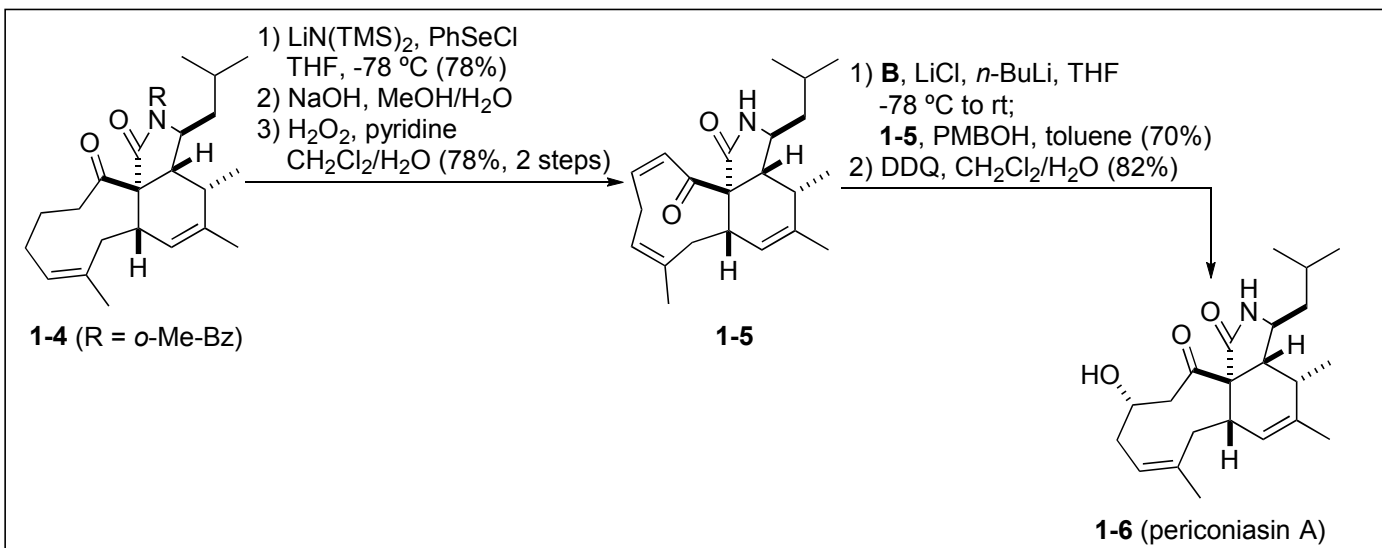


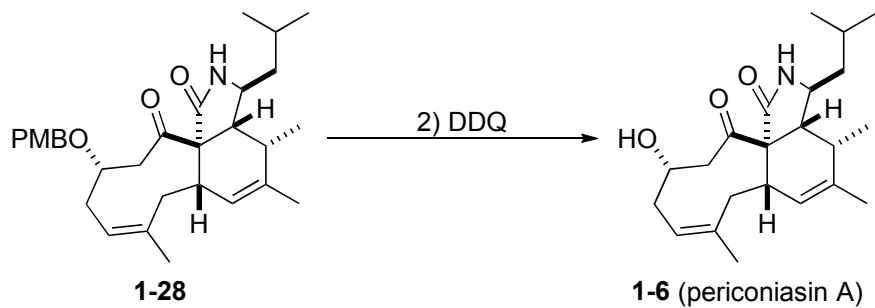


Tian, C.; Lei, X.; Wang, Y.; Dong, Z.; Liu, G.; Tang, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 6992.

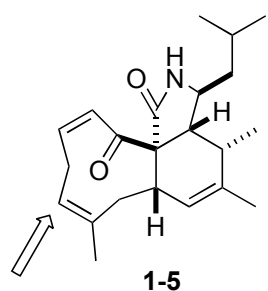








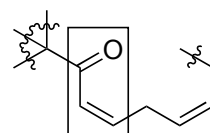
Stereoselectivity of Michael addition



conformation of 9-membered ring

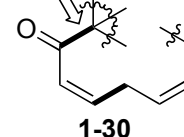
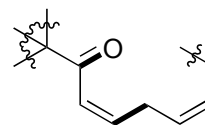
criteria

1. Enone moiety is the same plane.

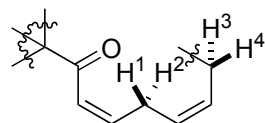
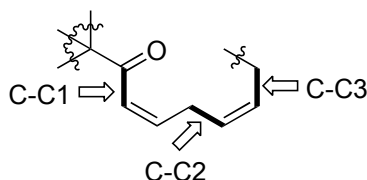


quaternary carbon

2. **1-29** is more favorable conformation than **1-30**.

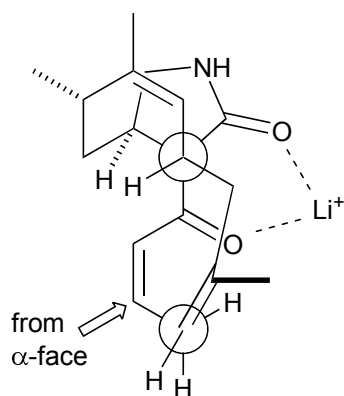


3. Minimize 1,3-allylic strains.

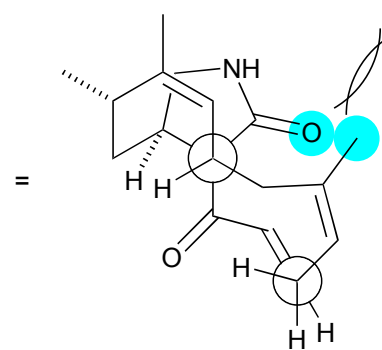
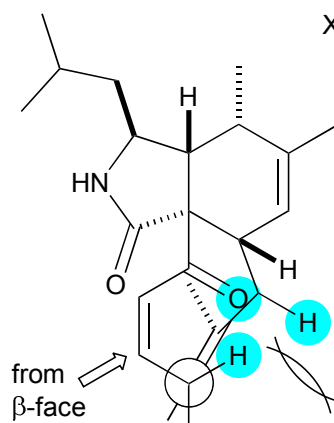
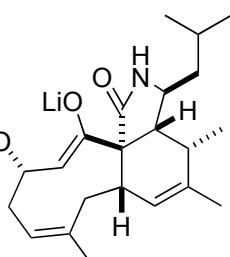


C-C1	C-C2	C-C3	
H ¹	H ³	H ¹	1-31
H ¹	H ⁴	H ¹	X
H ¹	H ³	H ²	X
H ¹	H ⁴	H ²	X
H ²	H ³	H ¹	X
H ²	H ⁴	H ¹	X
H ²	H ³	H ²	X
H ²	H ⁴	H ²	1-32

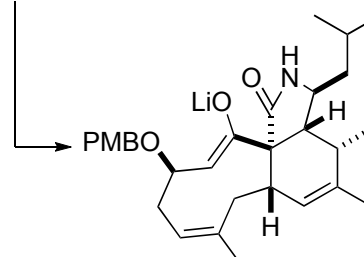
X: Cannot construct 9-membered ring.



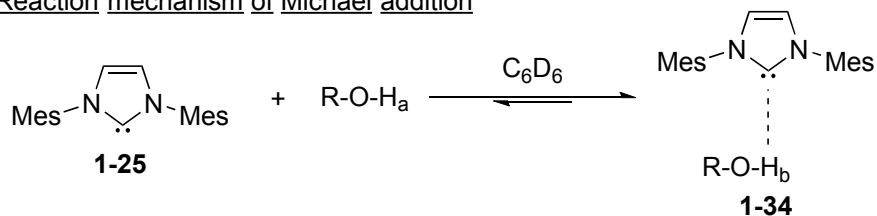
(*i*-Bu was omitted)



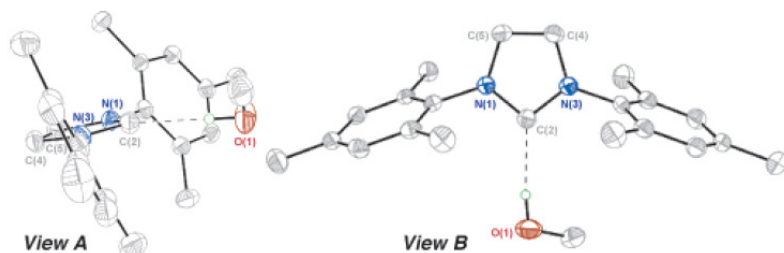
(*i*-Bu was omitted)



Reaction mechanism of Michael addition

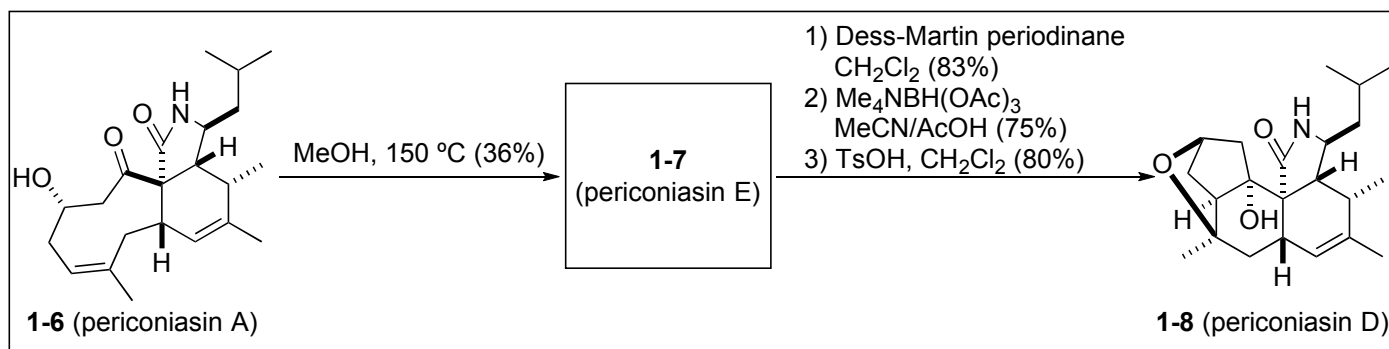


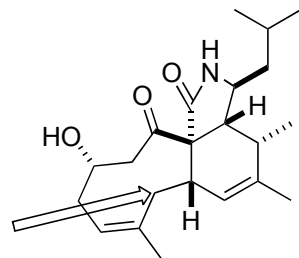
entry	R	δH_a (ppm)	δH_b (ppm)	Δ (ppm)
1	a , ^t Bu	0.67	2.81	2.14
2	b , Me	0.05	4.37	4.32
3	c , CH ₂ CH ₂ NH ₂	~0.70	5.24	~4.5
4	d , Bn	0.89	~6.0	~5.1



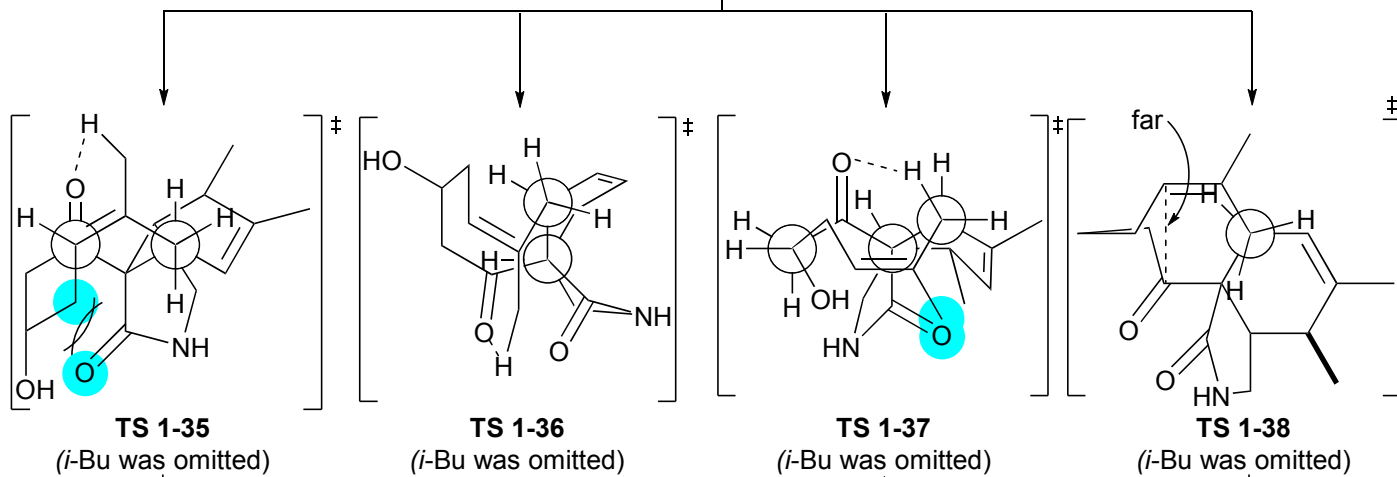
X-ray structure of **1-34** (R = Me)

Phillips, E. M.; Riedrich, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 13179.
 Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453.

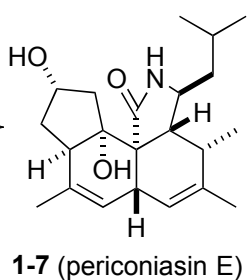
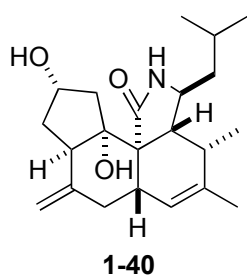
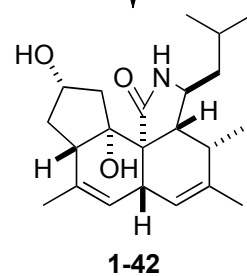
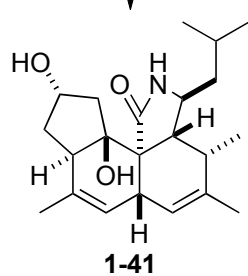
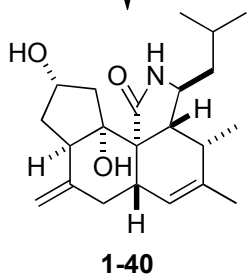
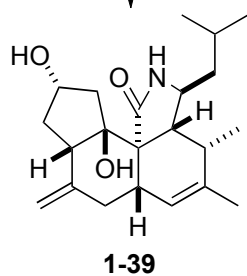




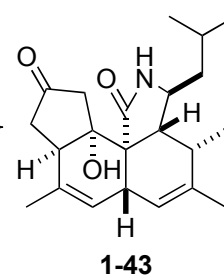
MeOH, 150 °C

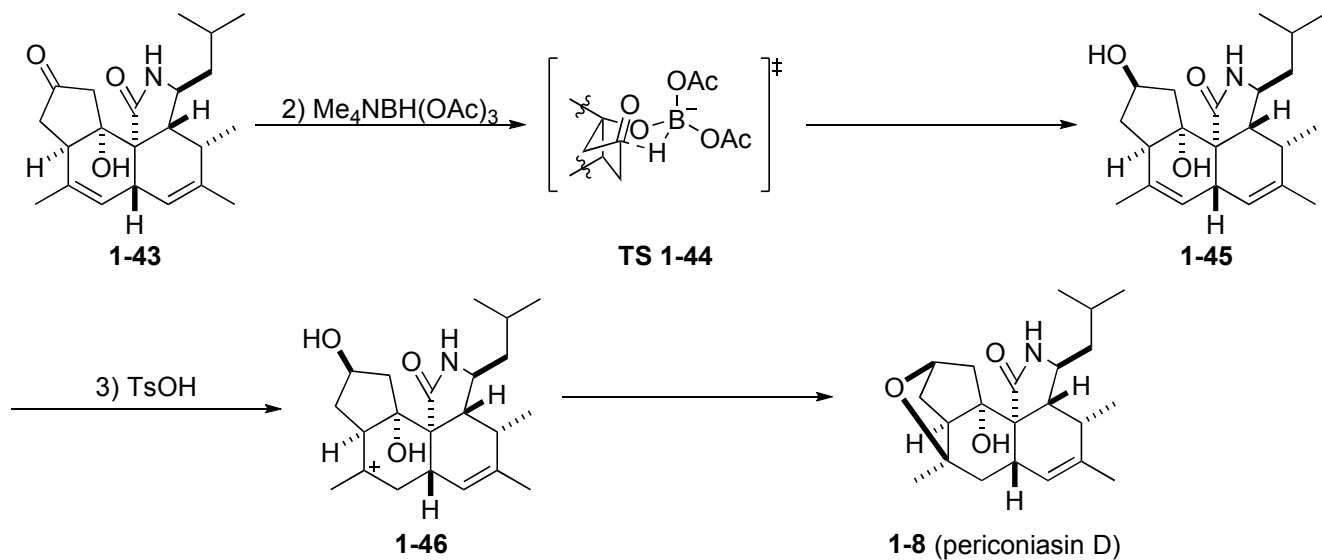


5/6 trans
ring strain

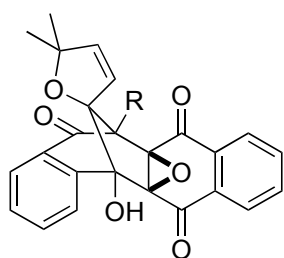


1) Dess-Martin
periodinane





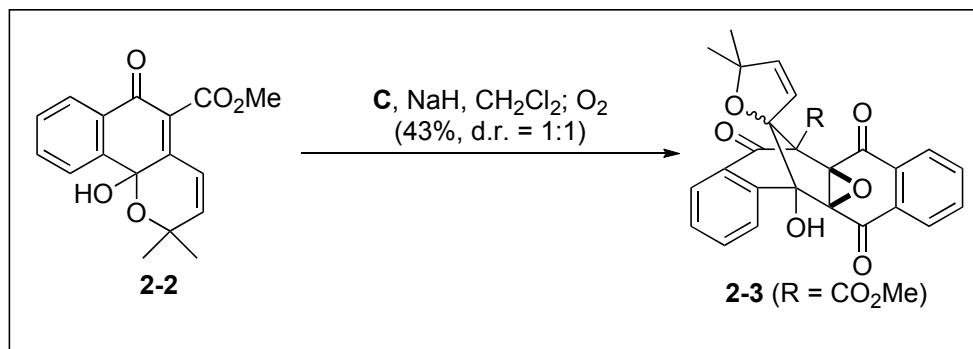
2



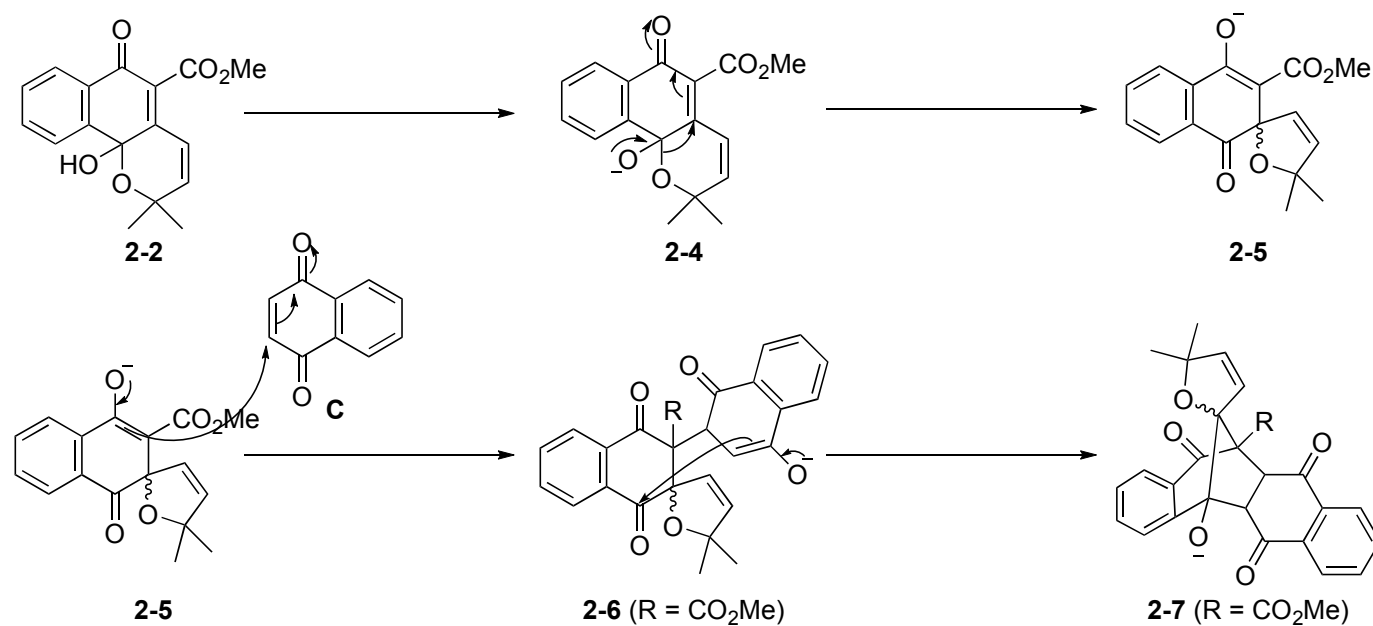
0-16 (R = CO_2Me , rubialatin A)

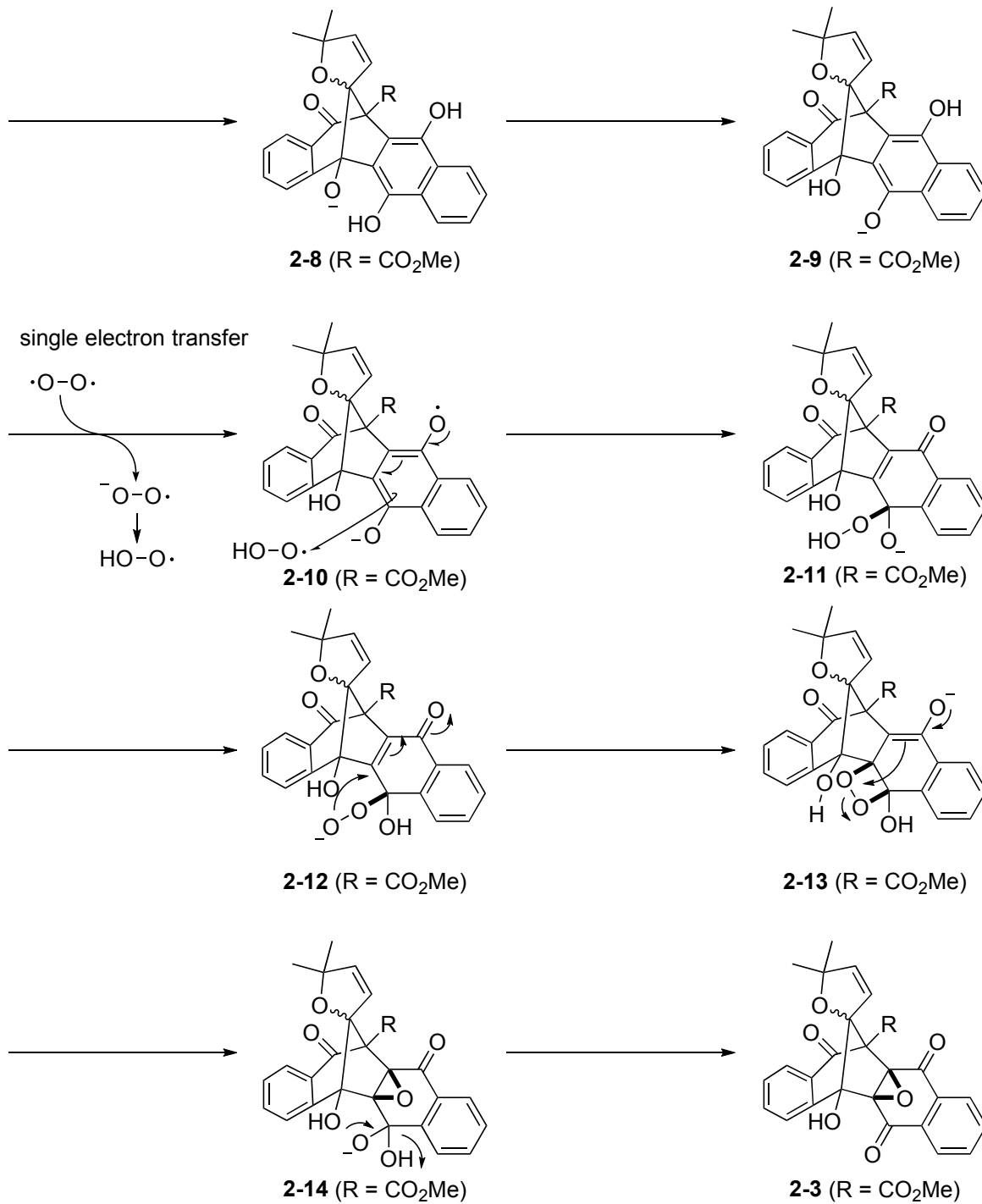
- isolated from *Rubia alata* Roxb
- naphthohydroquinone dimer
- 6/6/5/6/6 polycyclic ring system
- 5 consecutive stereogenic centers
- cytotoxicity against several tumor cell lines

(Isolation) Zhao, S-M.; Wang, Z.; Zeng, G-Z.; Song, W-W.; Chen, X-Q.; Li, X-N.; Tan, N-H. *Org. Lett.* **2014**, *16*, 5576.

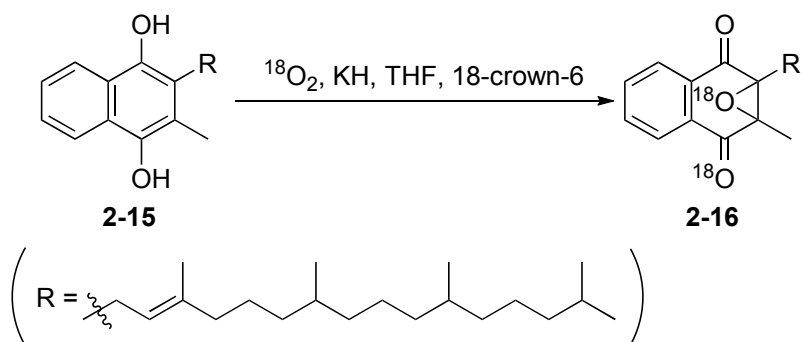


Yang, H.; Feng, J.; Li, Y.; Tang, Y. *Org. Lett.* **2015**, *17*, 1441.





Mechanism of oxygenation



Ham, S. W.; Yoo, J. S. *Chem. Commun.* **1997**, 929.

Ham, S. W.; Lee, G-H. *Tetrahedron Letters* **1998**, 39, 4087.