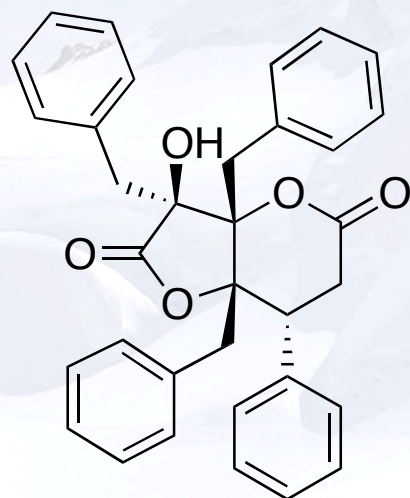
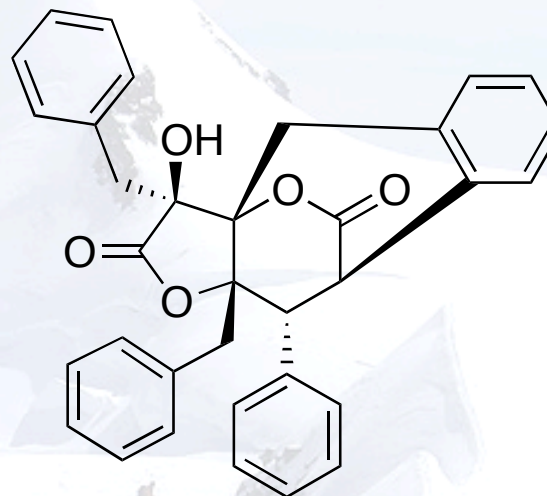


# Total Synthesis of (-)-Ophiodilactone A and (-)-Ophiodilactone B



(-)-ophiodilactone A (**1**)



(-)-ophiodilactone B (**2**)

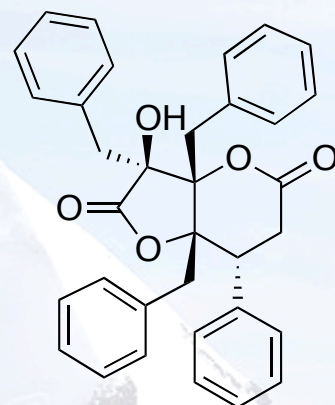
T. Matsubara, K. Takahashi, J. Ishihara, S. Hatakeyama\*

*Angew. Chem. Int. Ed.* **2014**, *53*, 757-760

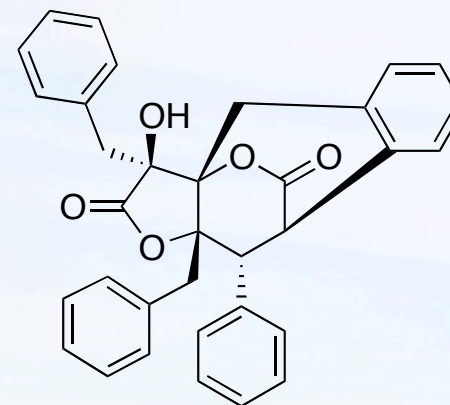
\*Nagasaki University (Japan)

# Introduction

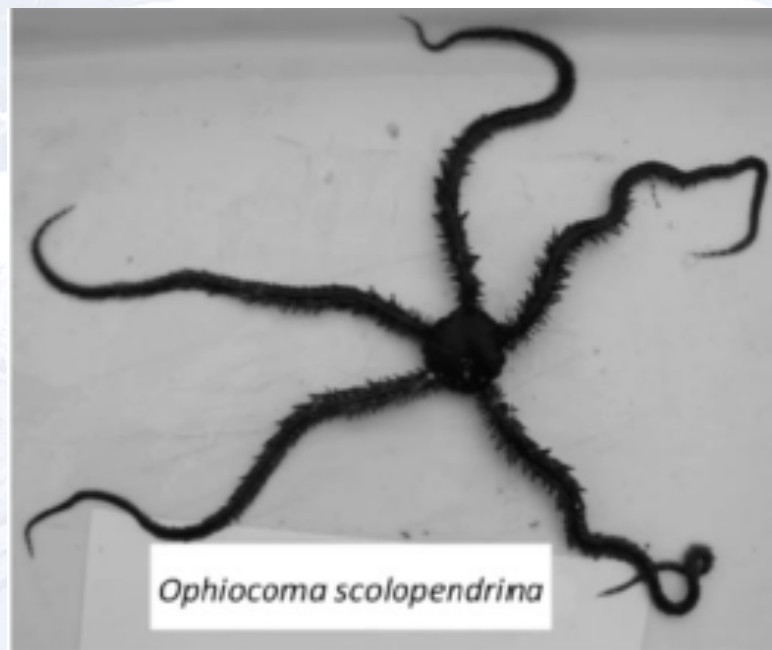
- isolated 2009 by Matsunaga *et al.* from *Ophiocoma scolopendrina* (tropical and subtropical ophiuroid)
- moderate cytotoxic activity against P388 murine leukemia cells
- fused  $\gamma$ -lactone/ $\delta$ -lactone skeleton
- 5 or 4 contiguous stereogenic centers containing 3 quaternary centers
- first total synthesis



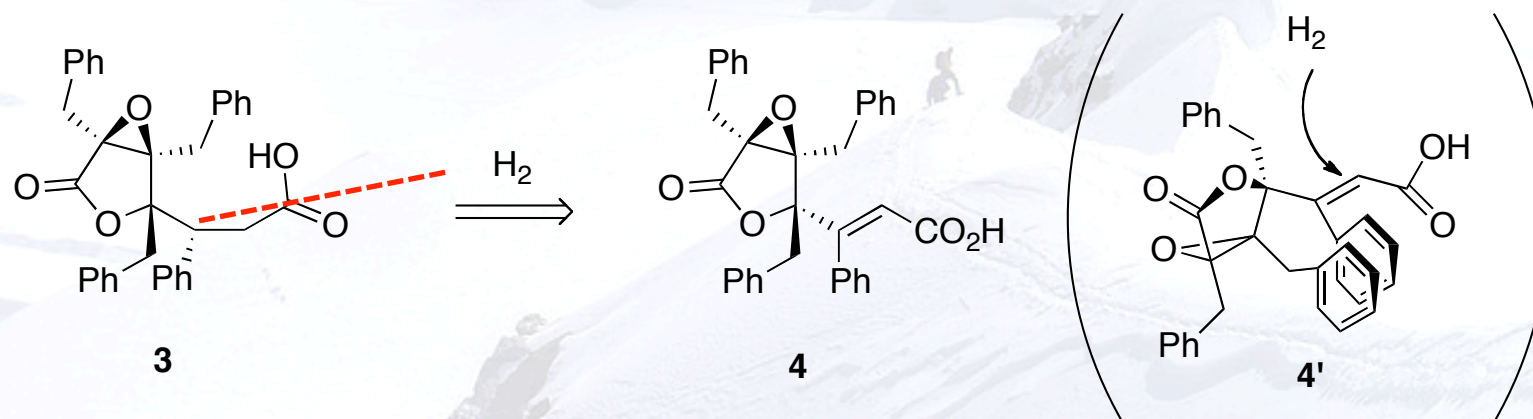
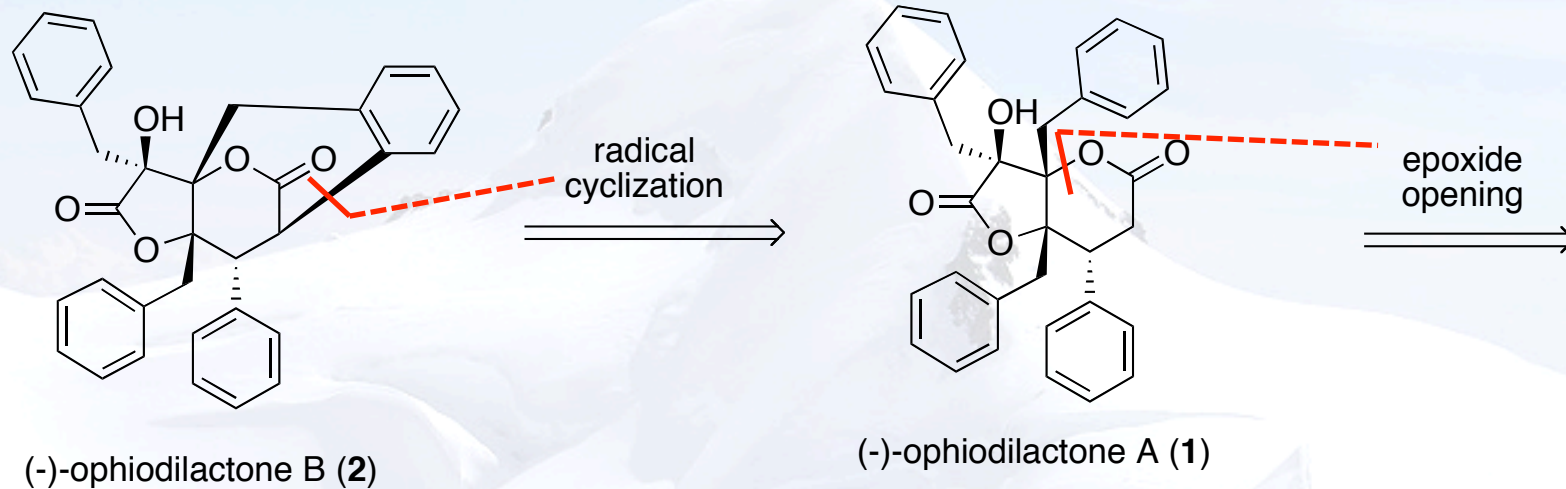
(-)-ophiodilactone A (1)

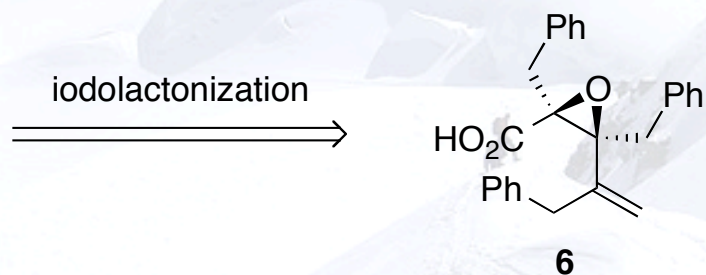
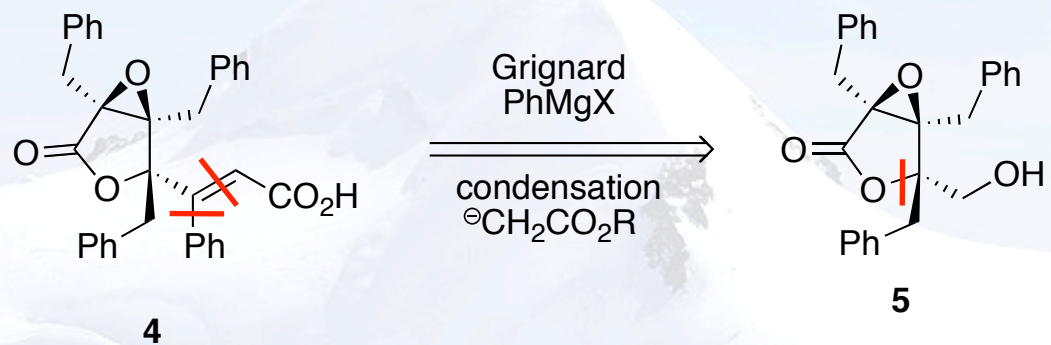


(-)-ophiodilactone B (2)

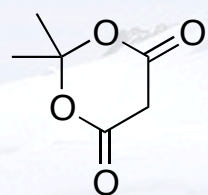


# Retrosynthesis





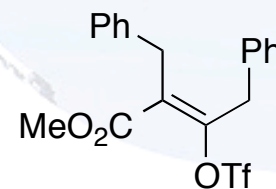
# Synthesis:



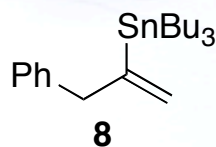
Meldrum's acid

1) PhCH<sub>2</sub>COCl  
pyridine, DCM then  
MeOH, reflux, 99%  
2) PhCH<sub>2</sub>Br, NaH  
benzene/DMF, 85 °C, 82%

3) Tf<sub>2</sub>O, 5 M LiOH  
hexane, 0 °C, 93%

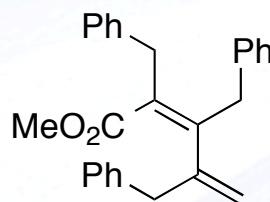


7



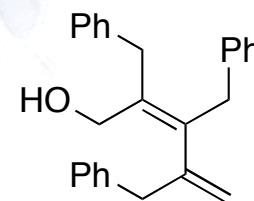
8

[Pd(PPh<sub>3</sub>)<sub>4</sub>] (cat.)  
CuCl, LiCl, DMSO  
80 °C, 94%

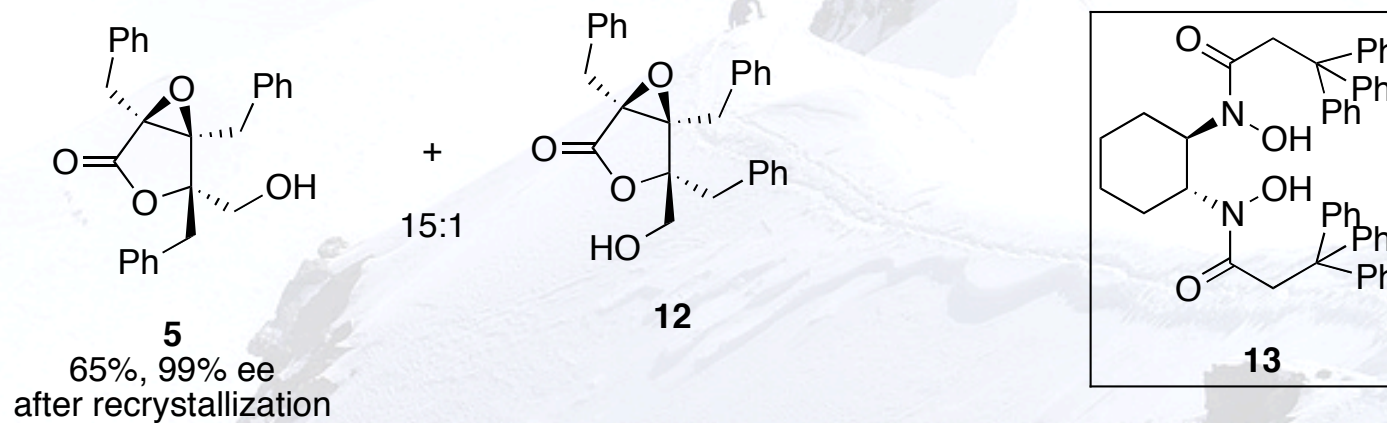
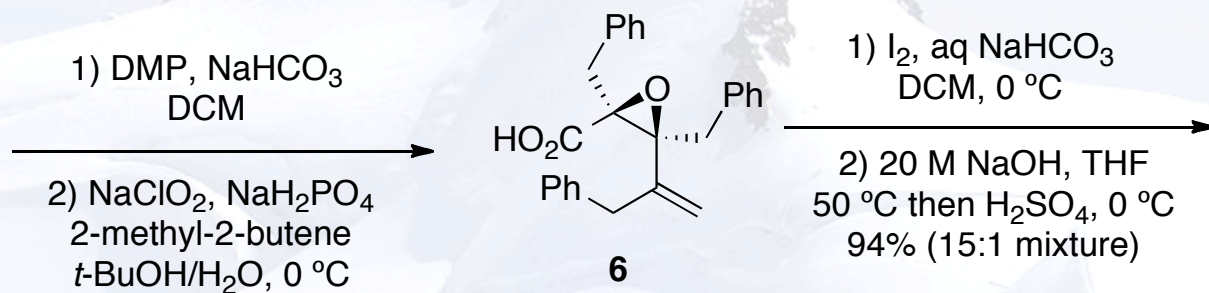
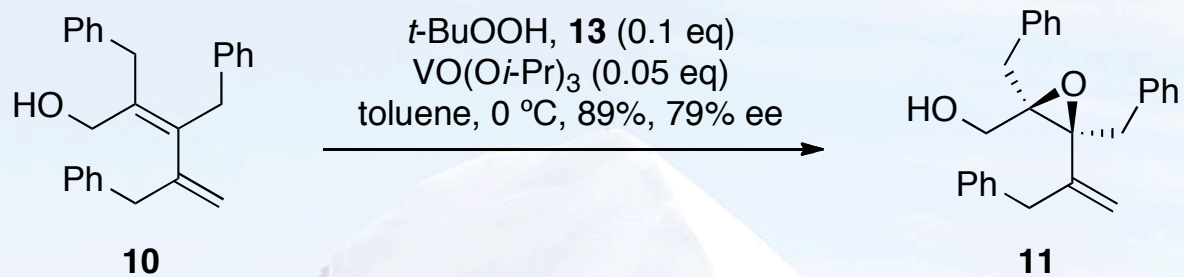


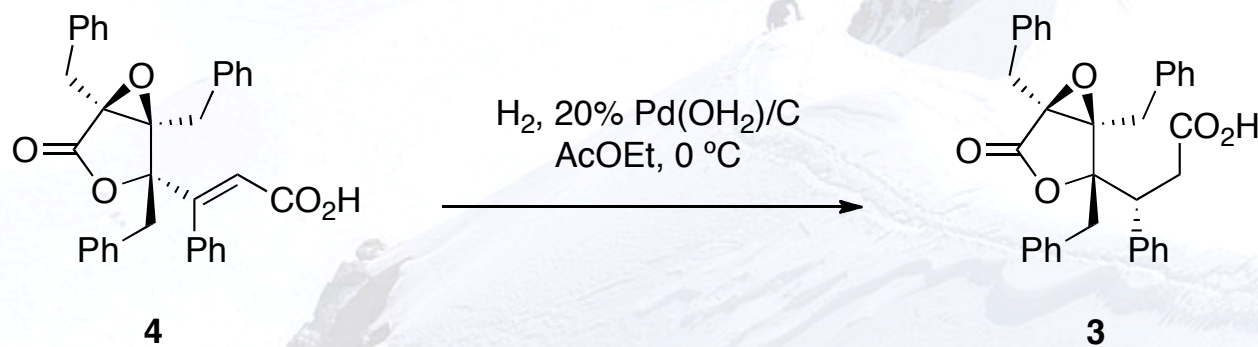
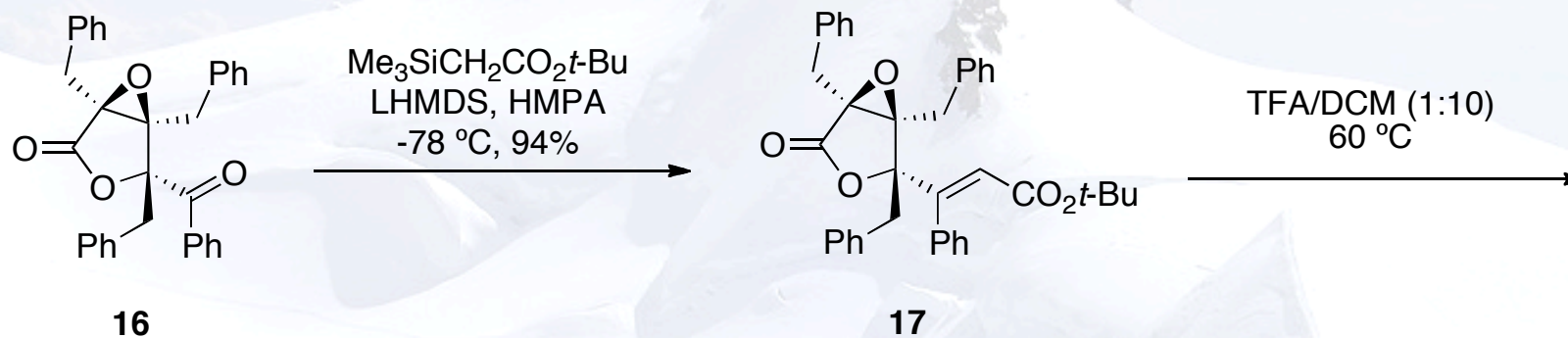
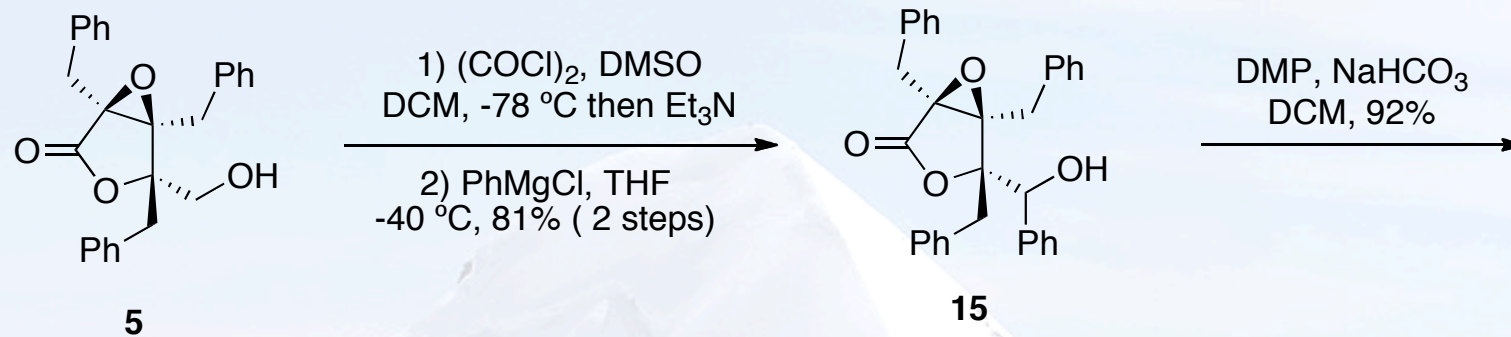
9

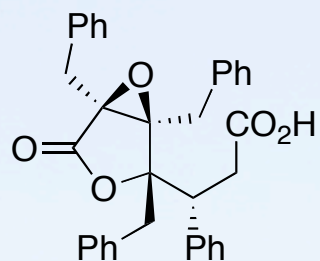
DIBAL-H  
DCM, -78 °C, 97%



10

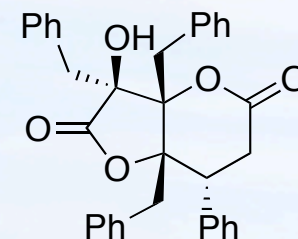




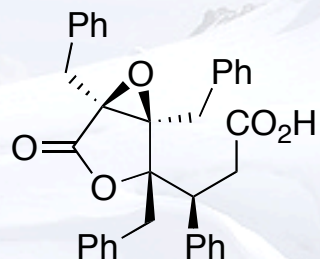


**3**

ethylene glycol  
150 °C, 55% from **17** (3 steps)

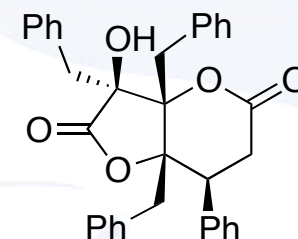


(-)-ophiodilactone A (**1**)

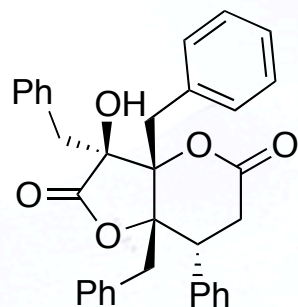


**18**

H<sub>2</sub>O, 150 °C, sealed tube  
40%

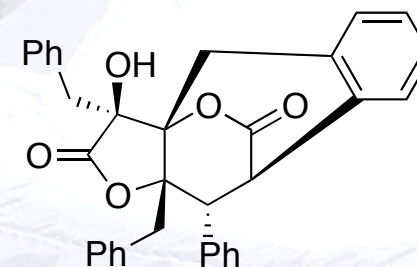


5-epi-ophiodilactone A (**19**)



(-)-ophiodilactone A (**1**)

Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.1 eq)  
O<sub>2</sub>, toluene, 200 °C  
sealed tube, 75%




(-)-ophiodilactone B (**2**)



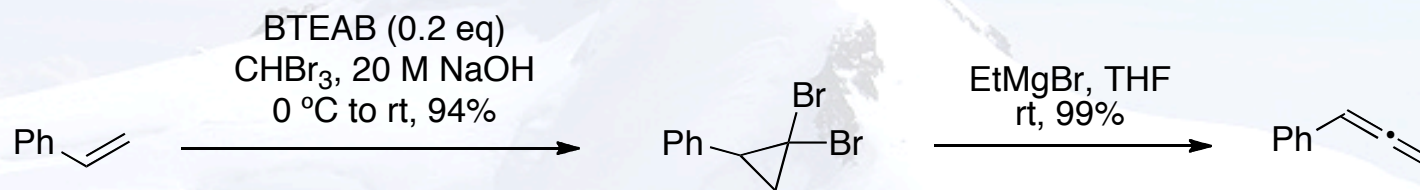
# Conclusion

- first total synthesis of (-)-ophiodilactone A in 14% (17 steps) and (-)-ophiodilactone B in 10% (18 steps)
- biomimetic radical cyclization with  $\text{Cu}(\text{OAc})_2$



**End**

## Synthesis of **8**:



BTEAB: benzyltriethylammonium  
bromide

