

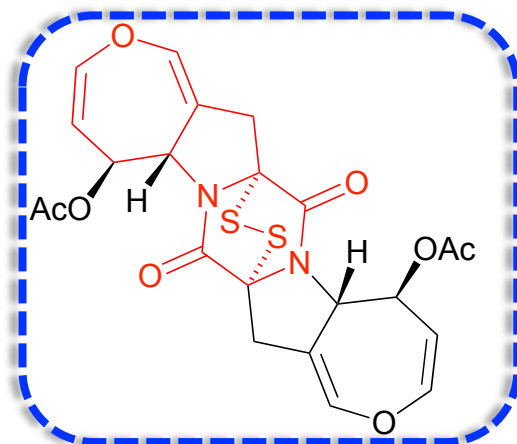
Total Synthesis of (-)-Acetylaronotin

*Hideto Fujiwara, Taichi Kurogi, Shun Okaya,
Kentaro Okano, and Hidetoshi Tokuyama*

Angew. Chem. Int. Ed. **2012**, 51, 13062-13065

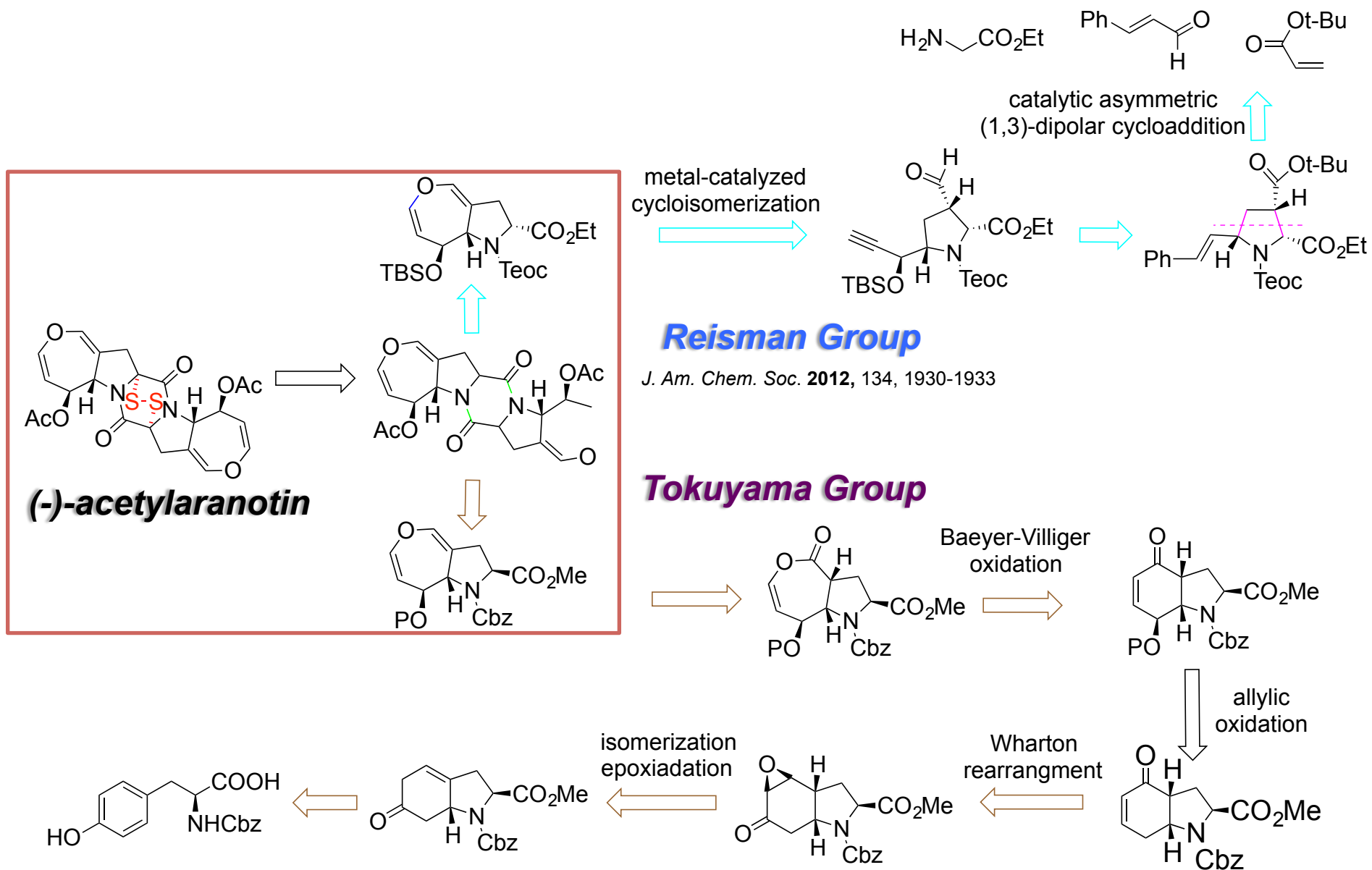
Zhuzhu Wang
Wipf Group – Current Literature
January 12, 2013

(-)-Acetylaronotin



- ***Belongs to the Epidithiodiketopiperazine (ETP) natural products***
- ***Biological activity of ETPs include inhibition of viral RNA polymerase and antiproliferative/apoptotic activity against human cancer cells***
- ***First total synthesis was published in October 2011 by Reinsman***

Retrosynthetic analysis

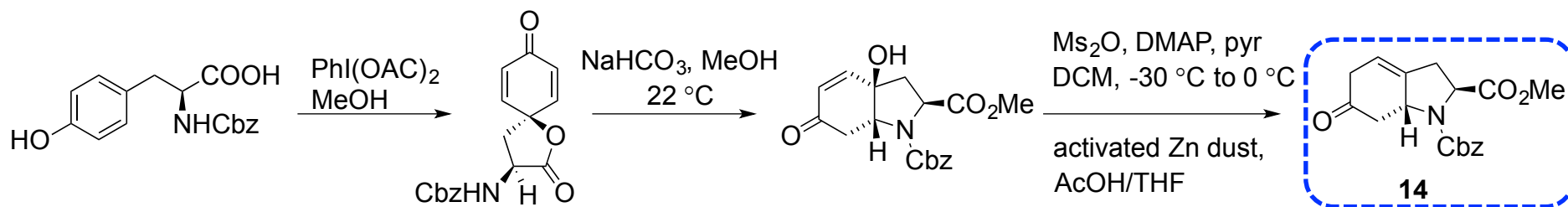


Reisman Group

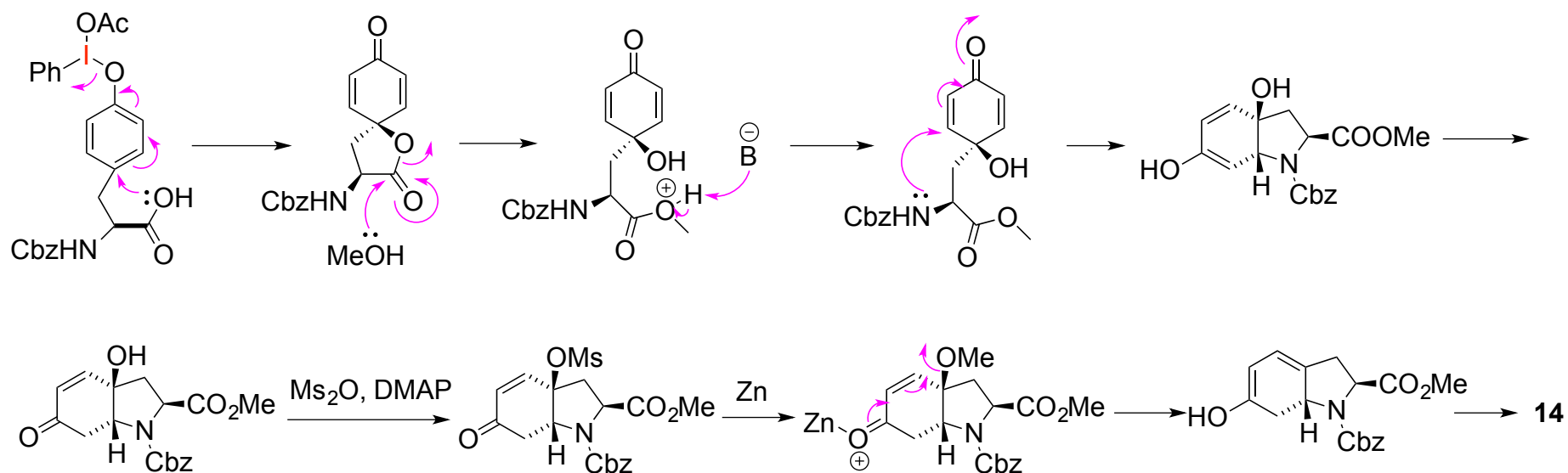
J. Am. Chem. Soc. **2012**, 134, 1930-1933

Tokuyama Group

Synthesis of β,γ -unsaturated ketone **14**

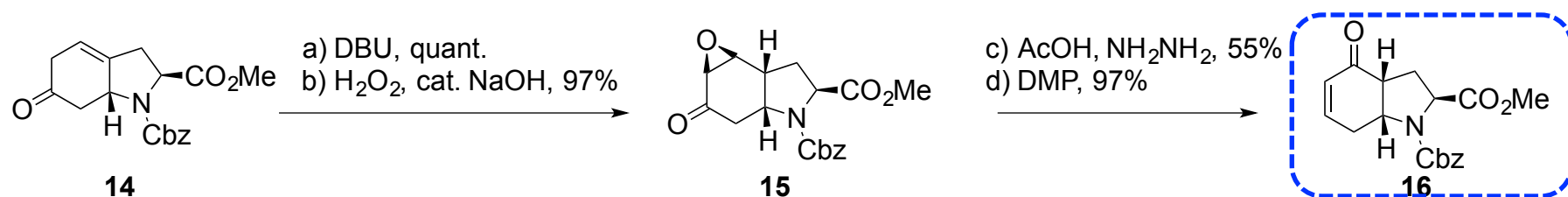


Mechanism

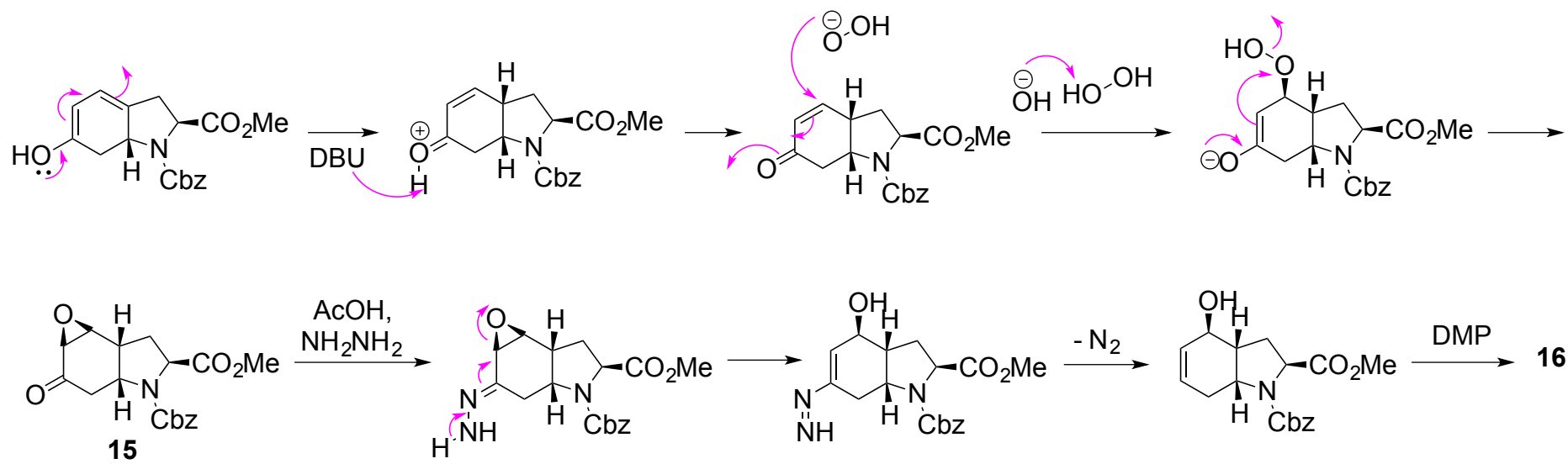


Tetrahedron Lett. **1992**, 33, 5477-5480
J. Am. Chem. Soc. **1995**, 117, 11106-11112
Org. Lett. **2000**, 2, 4213-4216

Formation of Enone 16

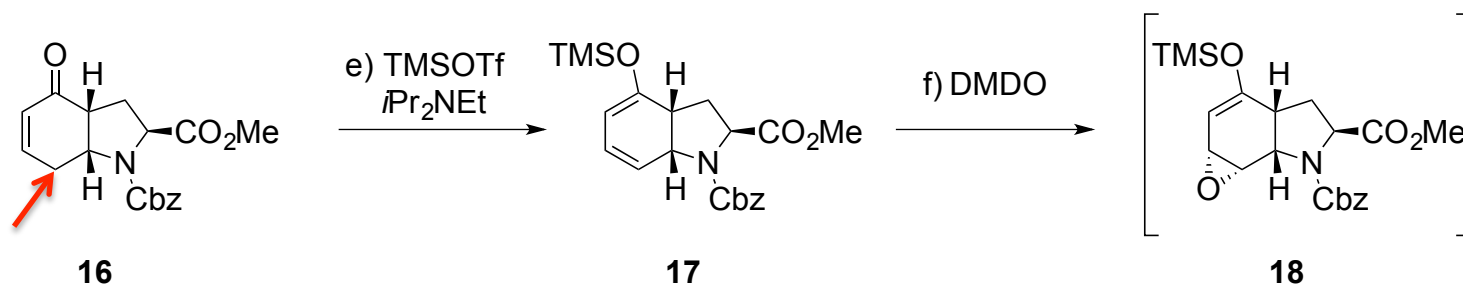


Mechanism

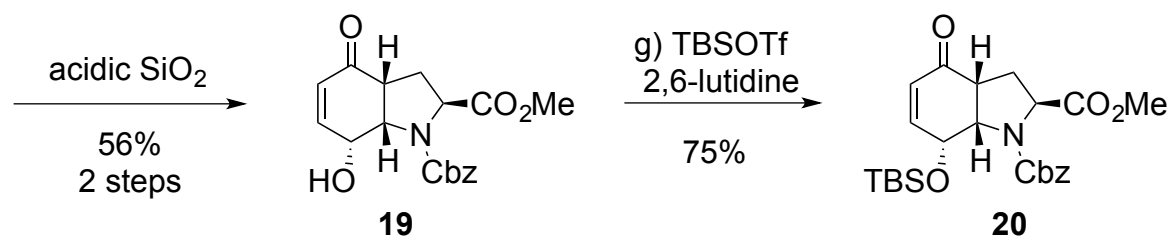


Wharton rearrangement

Oxidation of the allylic position

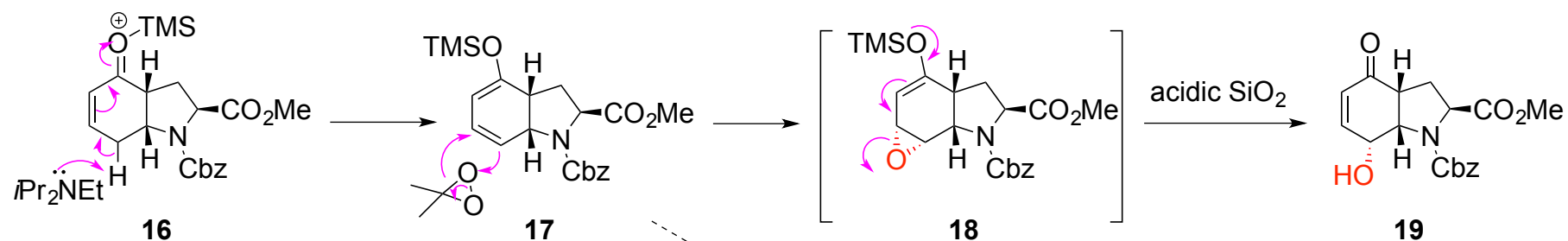


γ -dienolate

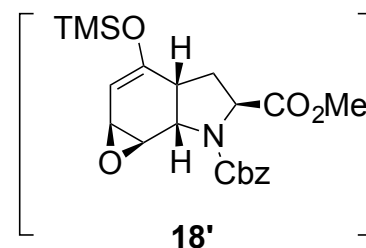


γ -hydroxyenone

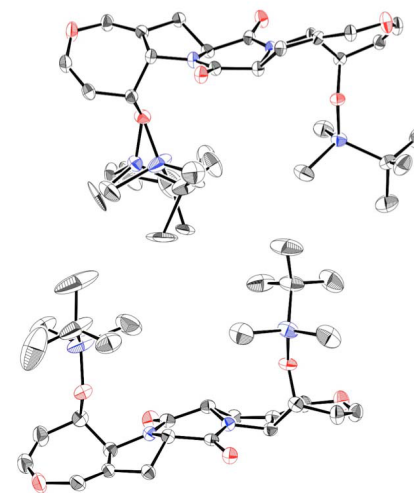
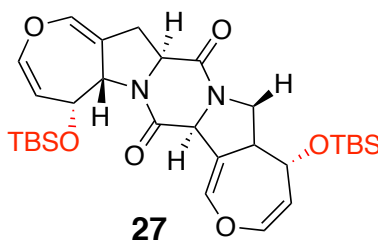
Mechanism



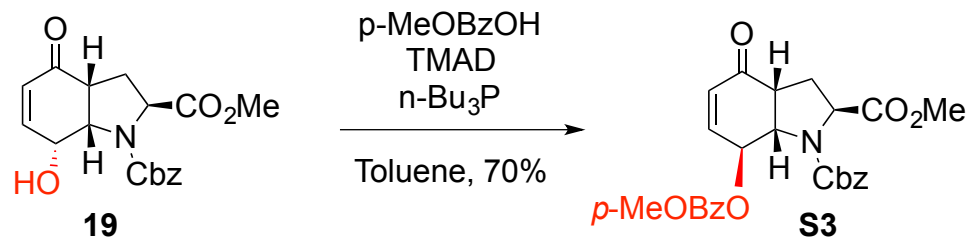
γ -enolization of α,β -enone



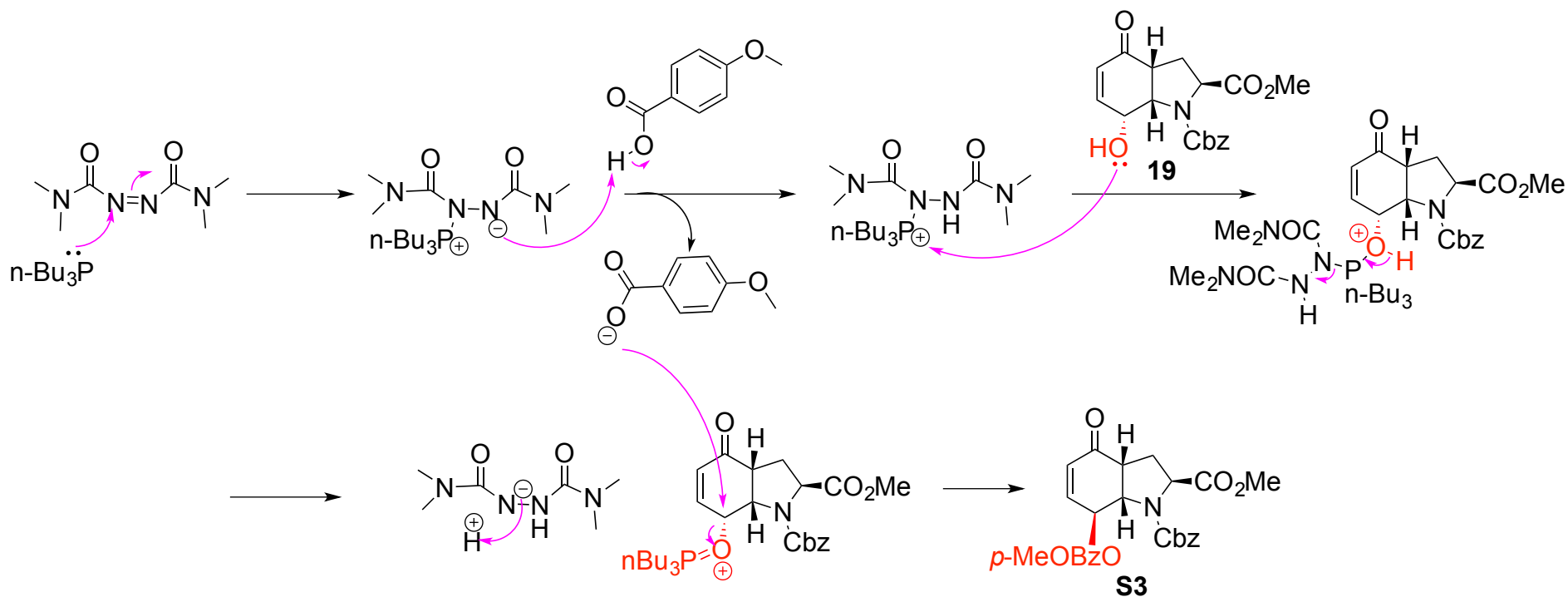
“Surprisingly, the protected hydroxy group of the compound **20** is located on the concave face, as determined by X-ray crystallographic analysis for the advanced intermediate **27**”



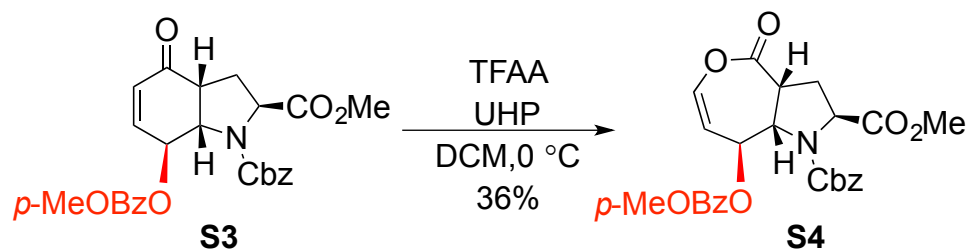
Stereochemical inversion of hydroxy-bearing carbon center



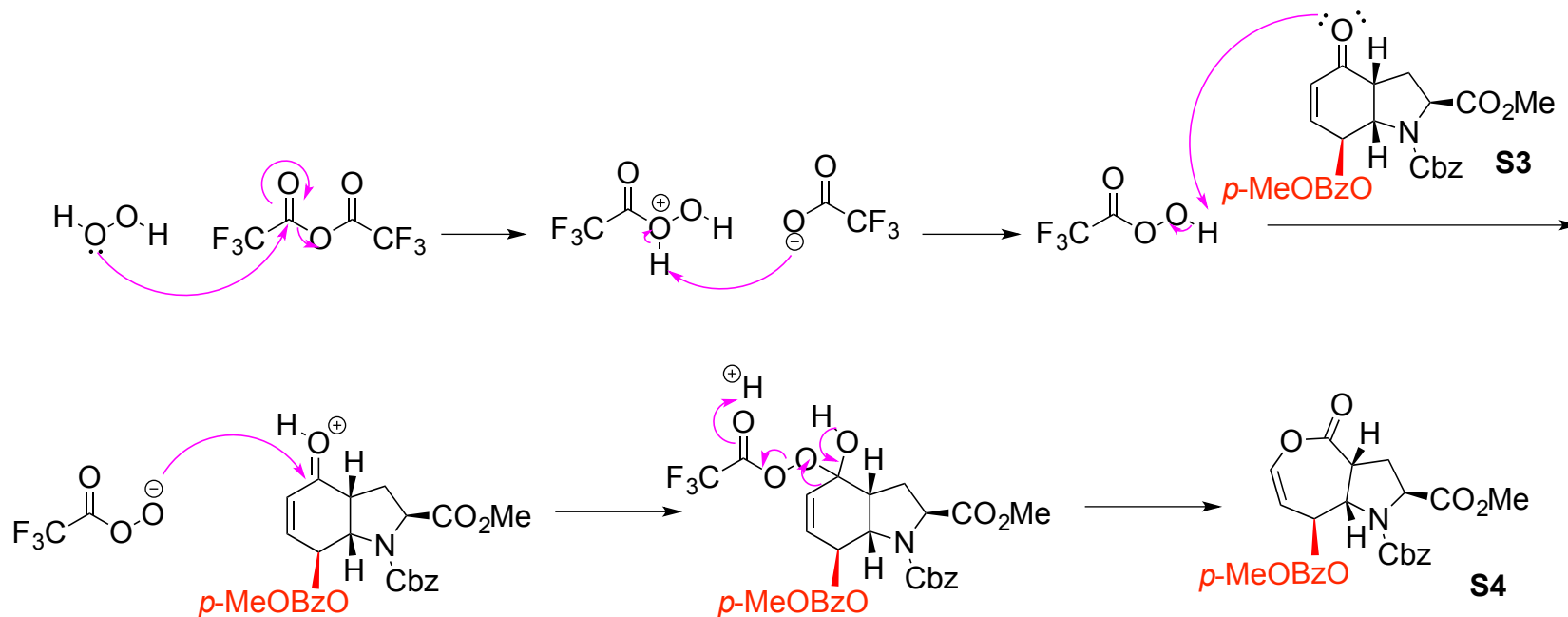
Mechanism



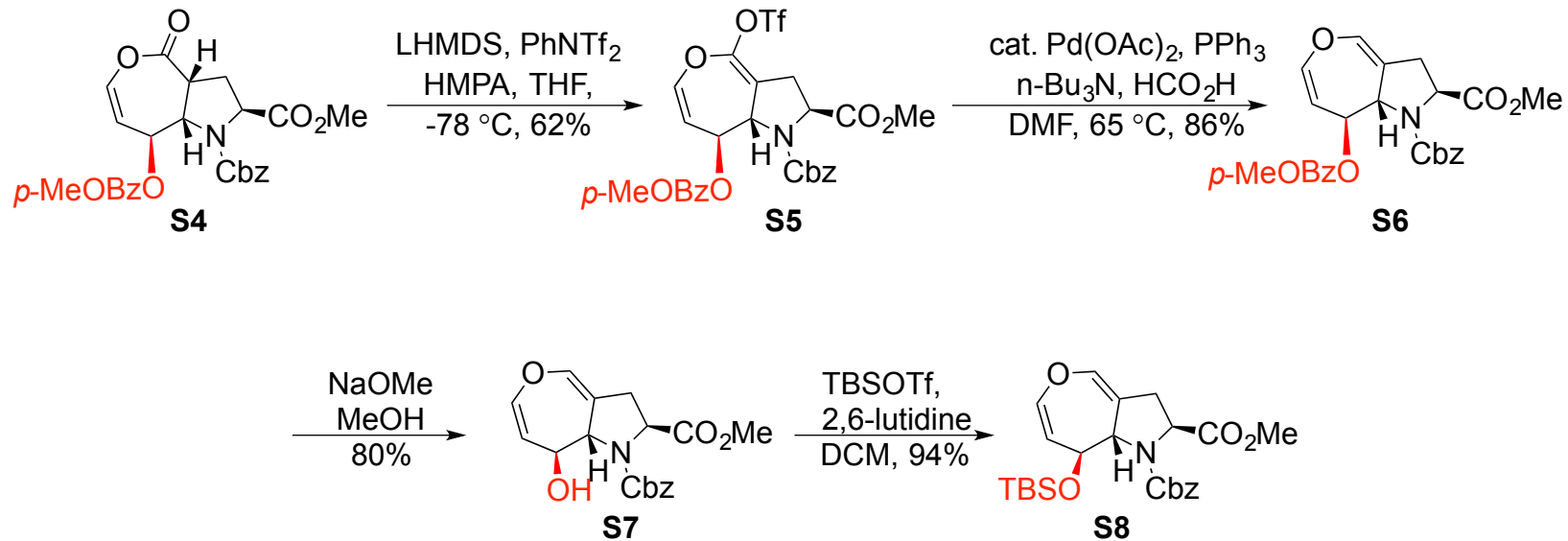
Formation of enol lactone via Baeyer-Villiger oxidation



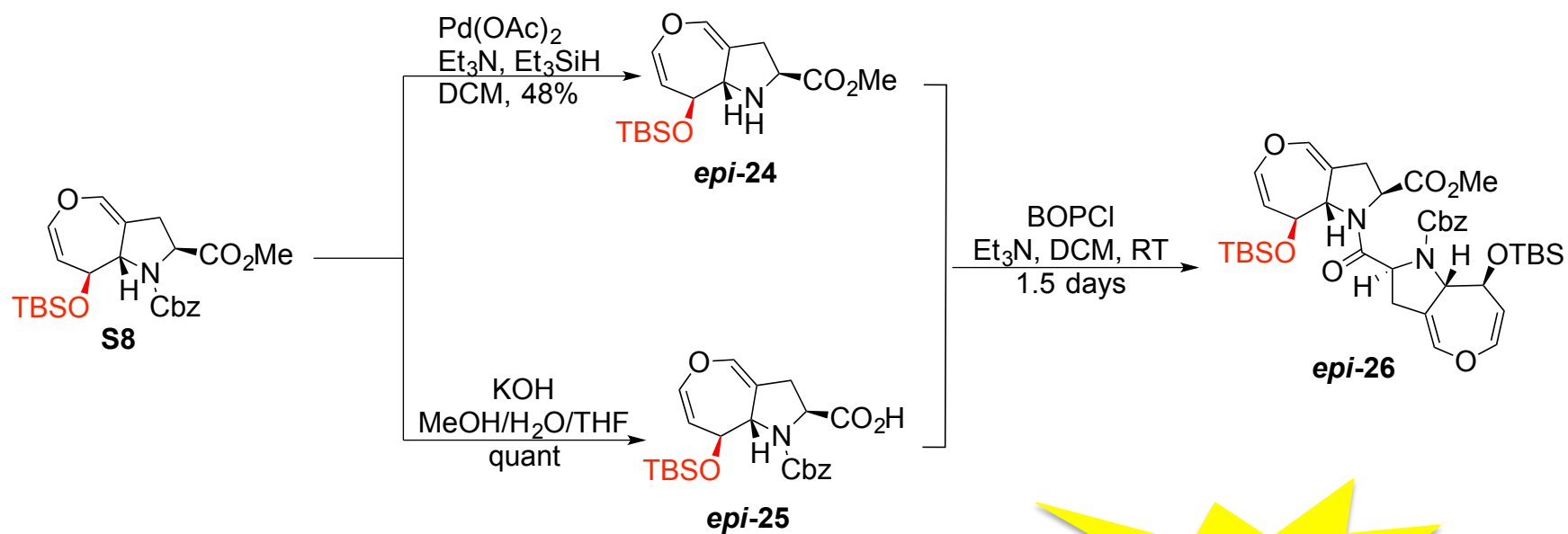
Mechanism



Formation of dihydrooxepine

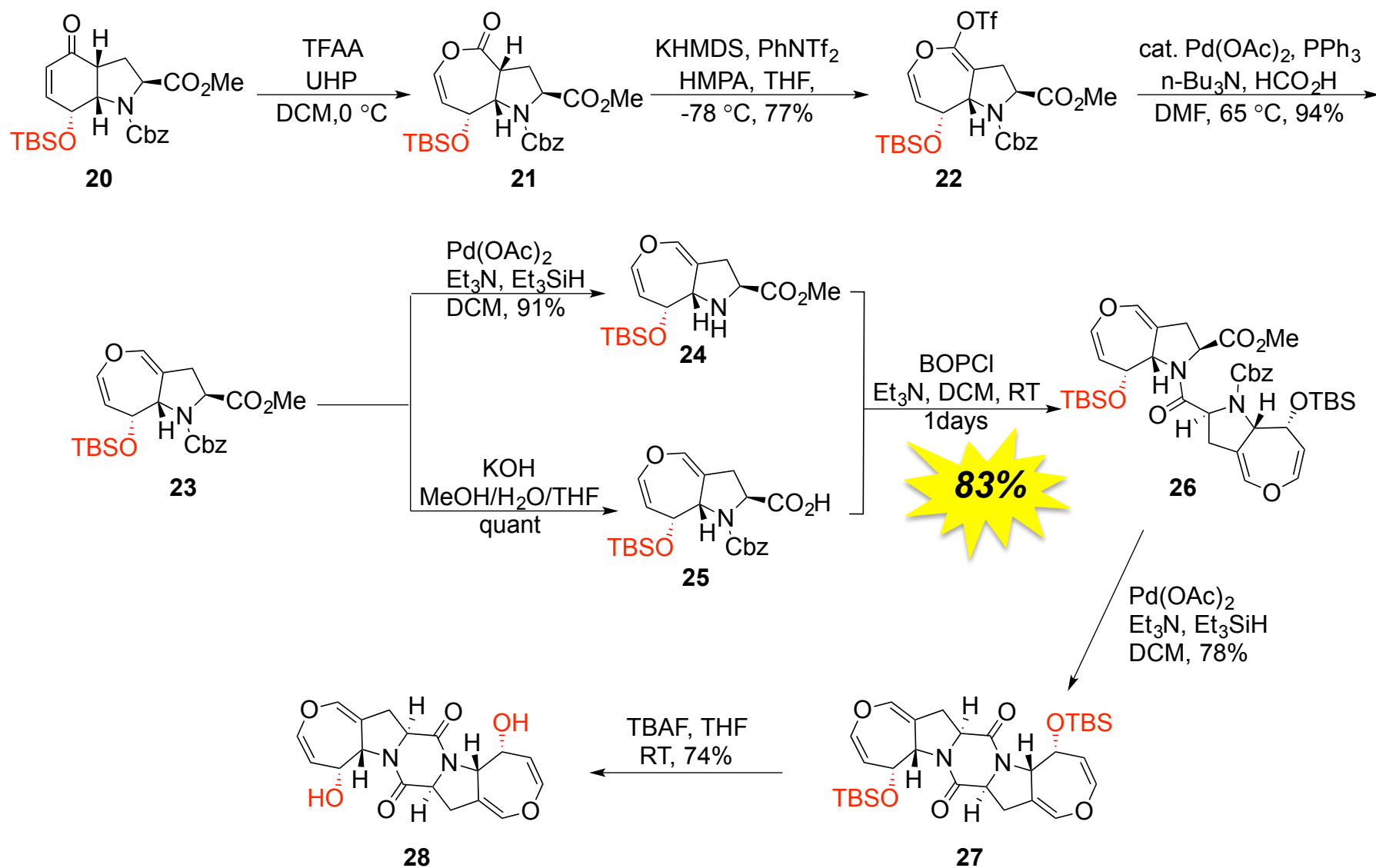


Formation of diketopiperazine ring.....

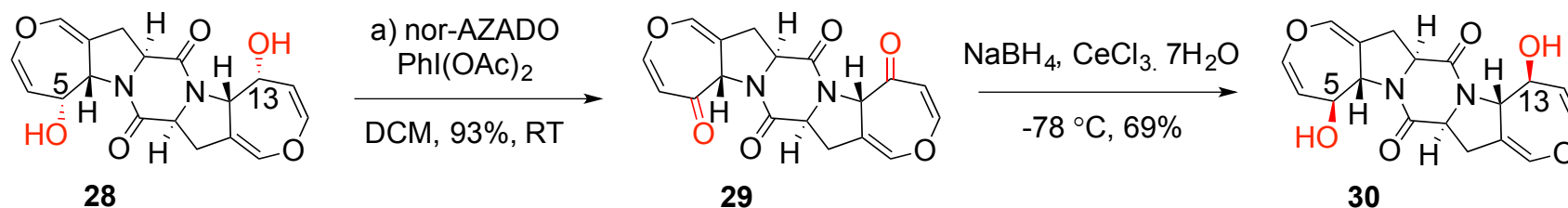


Low yield!

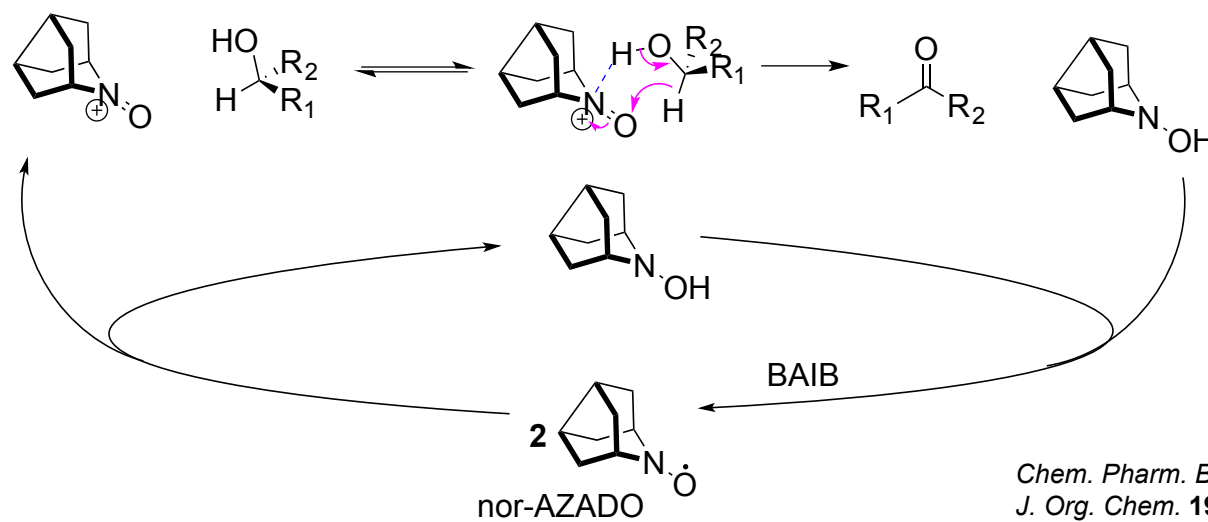
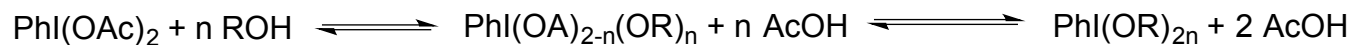
Had to went back to the γ -hydroxyenone.....



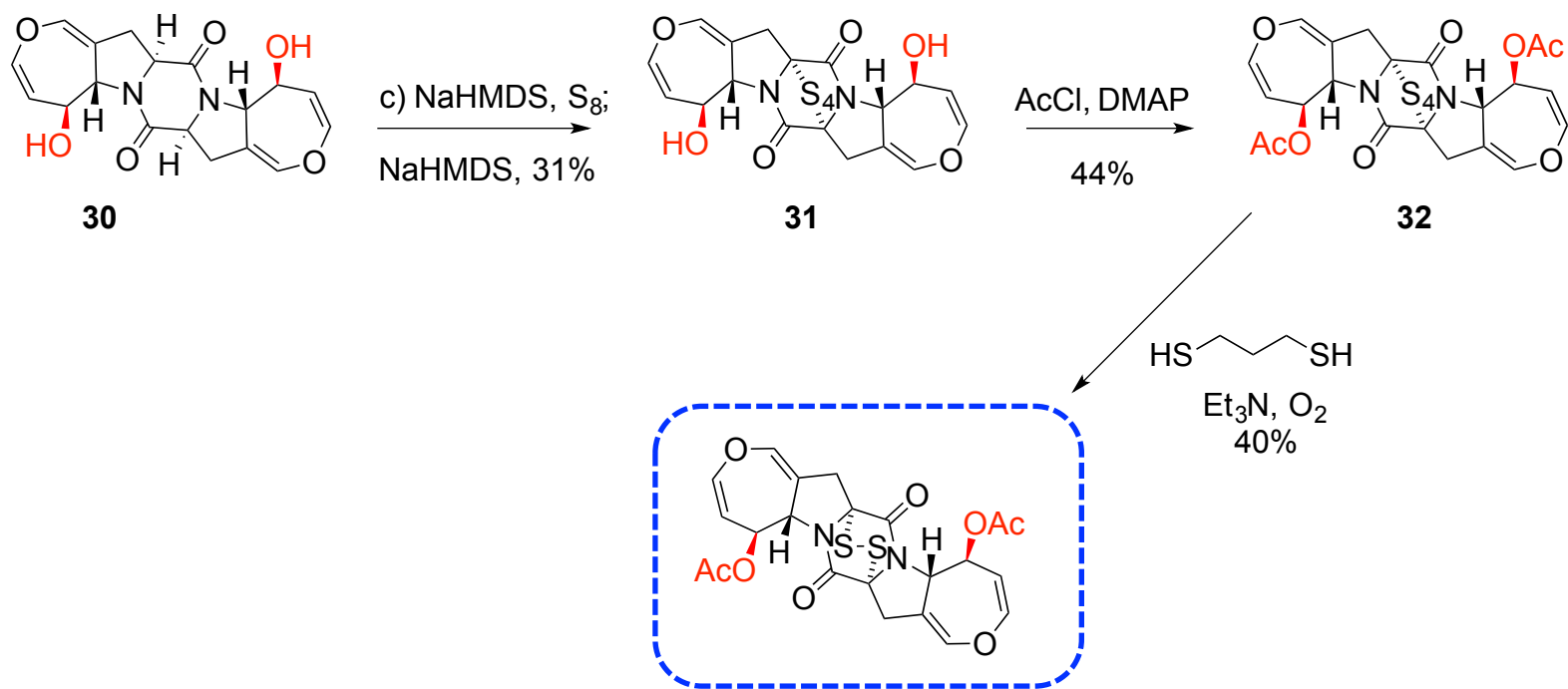
Stereochemical inversion of C₅ and C₁₃



Oxoammonium-catalyzed oxidation:

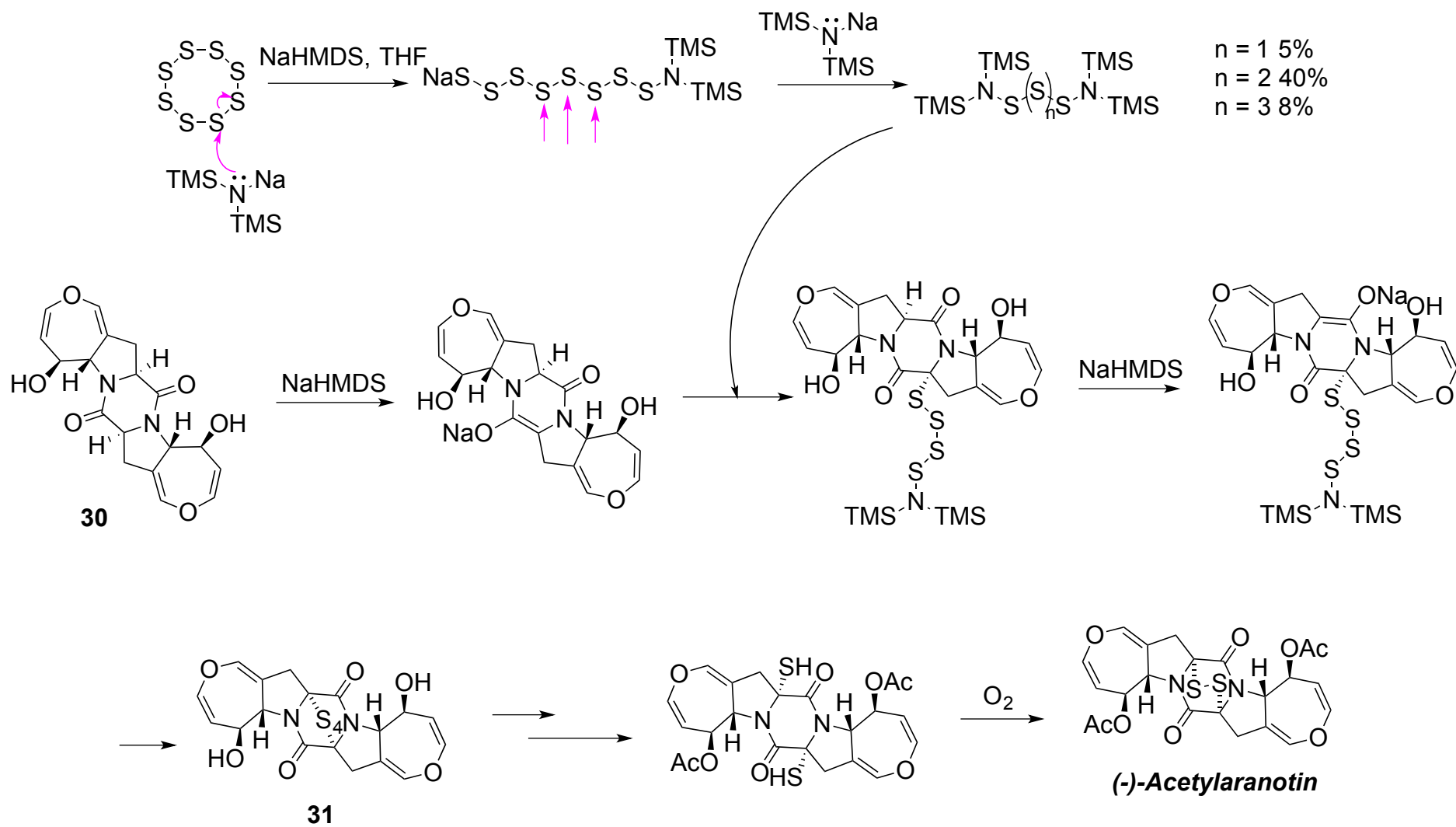


Introduction of disulfide



(-)-acetylaranotin
(22 steps, 0.06% from L-Cbz-tyrosine)

Mechanism



Conclusion

- ***Completed the second total synthesis of (-)-acetylaranotin in 22 steps (0.06% overall yield)***
- ***Synthetic highlights include:***
 - ❖ ***Unusual vinylogous Rubottom oxidation***
 - ❖ ***Regioselective Baeyer-Villiger oxidation***
 - ❖ ***Wharton rearrangement***
 - ❖ ***Isomerization epoxidation***