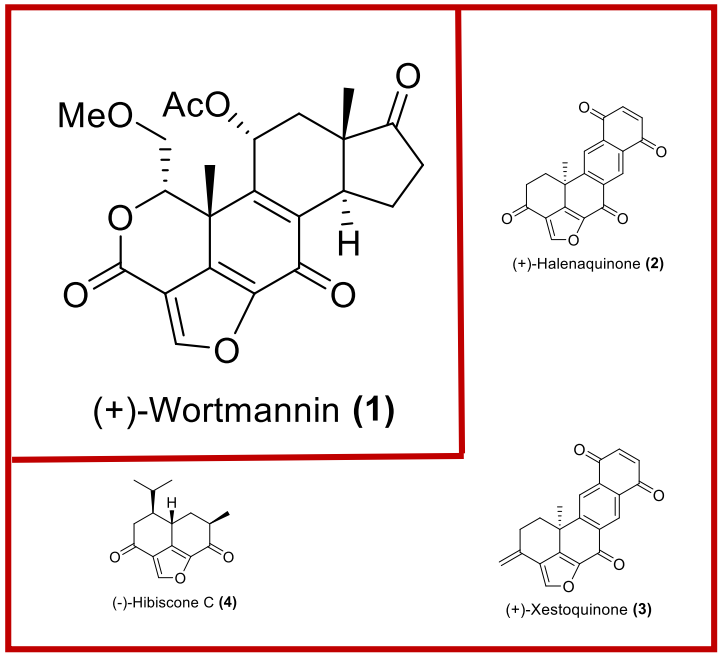
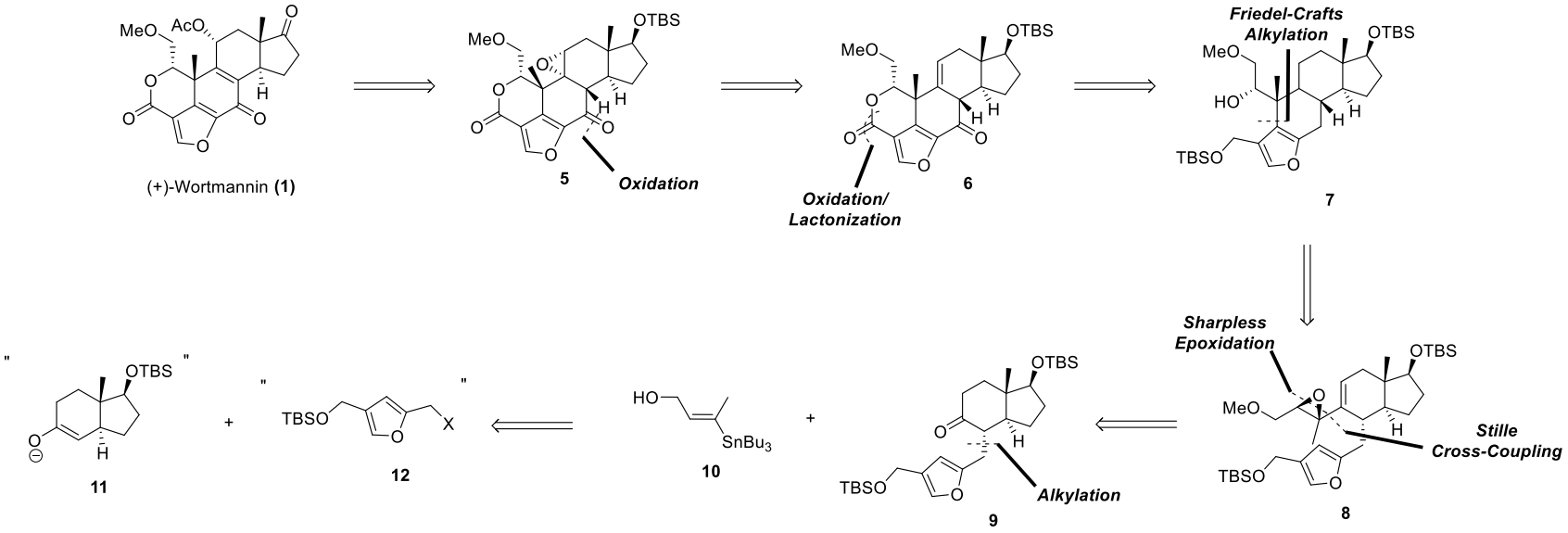
Enantioselective Total Synthesis of (+)-Wortmannin

Y. Guo; T. Quan; Y. Lu; T. Luo *J. Am. Chem. Soc.* **2017**, *139*, 6815–6818.

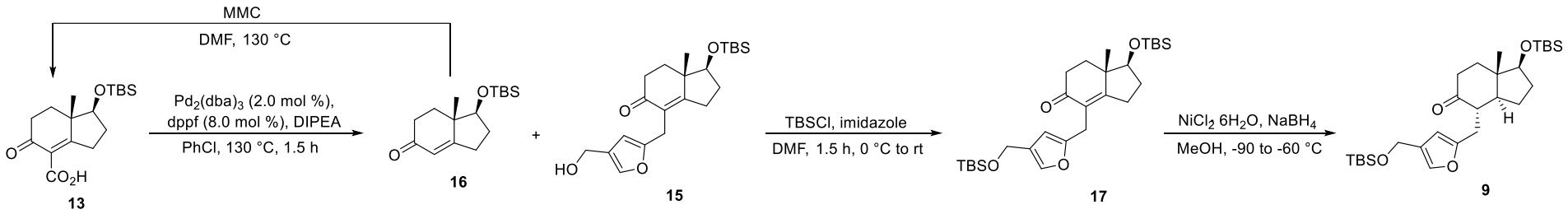


- Belongs to furanosteroid structural class of natural products;
- Potent phosphonoinositide 3-kinase (PI3K) inhibitor;
- 17-β-hydroxywortmannin (**24**) displayed increased potency against PI3Ks than (+)-Wortmannin (**1**);
- Two previous syntheses reported by Shibasaki group;
- Synthesis of closely related natural products (+)-Halenaquinone, (+)-Xestoquinone, and (–)-Hibiscone C relied on intramolecular Heck reaction;
- Allowed for optimization of a Pd-catalyzed cascade reaction and Friedel-Crafts alkylation that would ultimately establish 4 of the 5 rings;
- Synthesis completed in 18 steps.

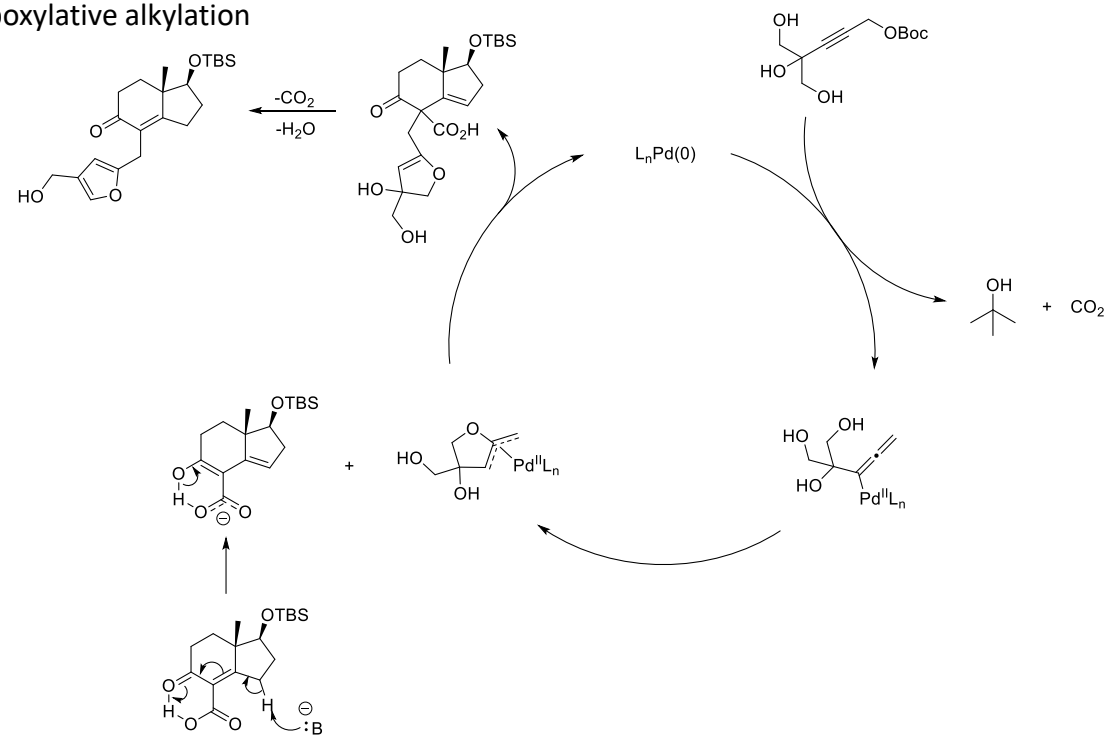
Retrosynthesis



Forward Synthesis

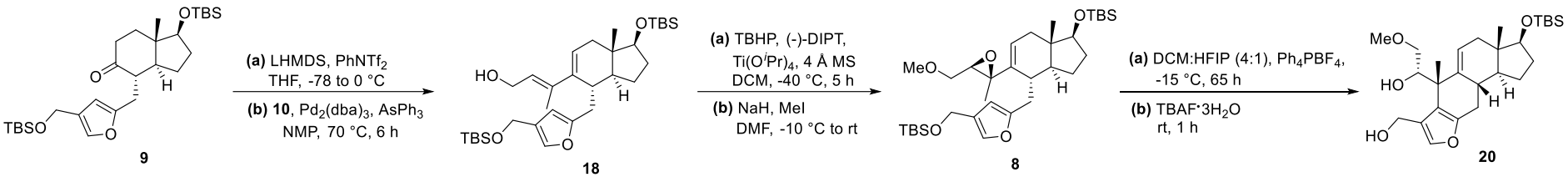


13 to **15:** Pd-catalyzed decarboxylative alkylation

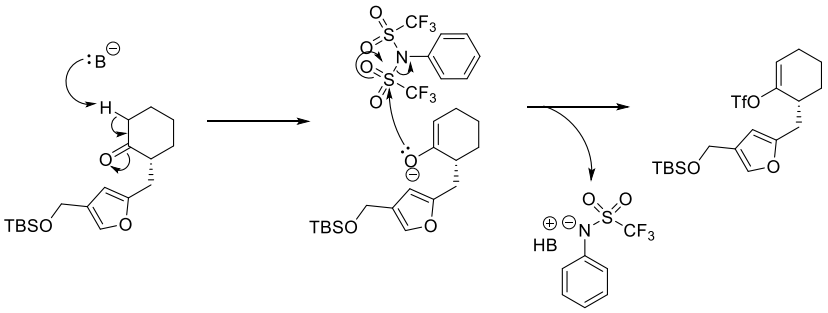


17 to **9:** Nickel boride 1,4-reduction

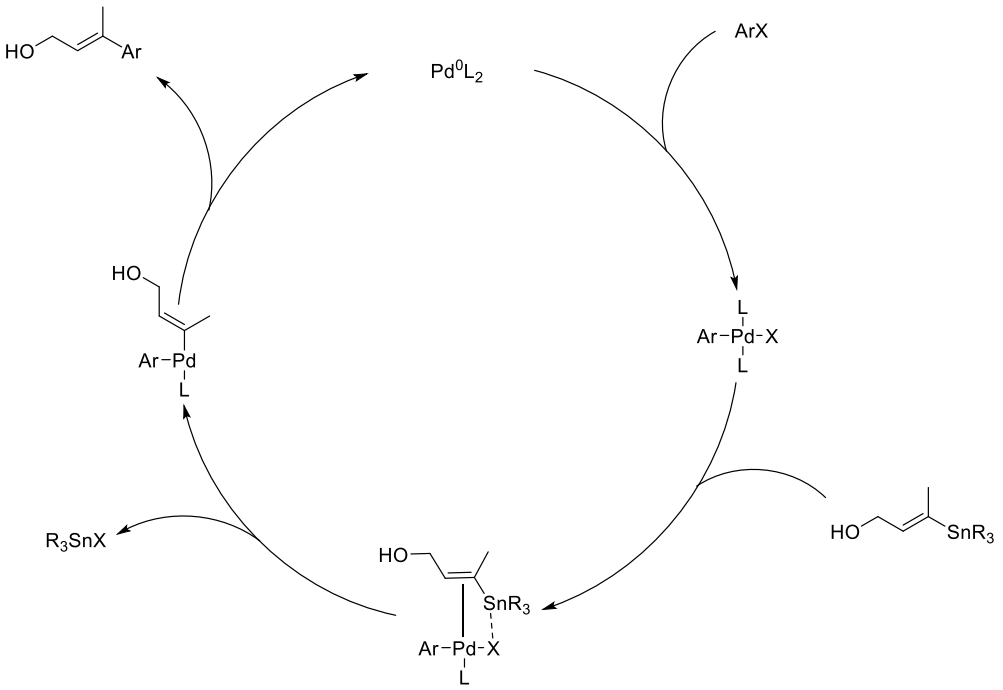
Forward Synthesis



9 to **18:** Vinyl triflate formation

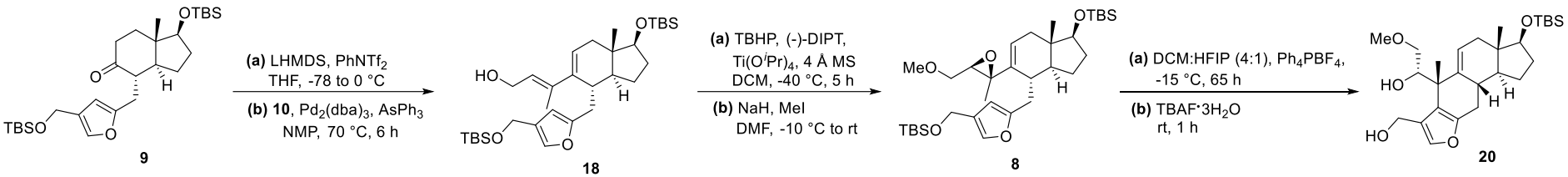


9 to **18:** Modified Stille Cross-Coupling

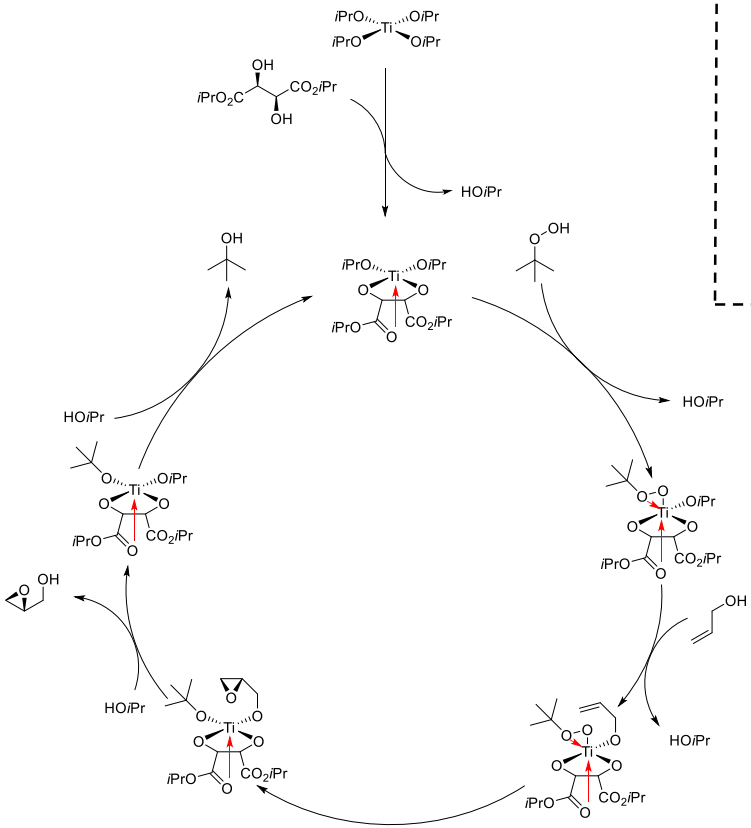


Amatore, C.; Bahsoun, A.; Jutand, A,; Meyer, G.; Ntepe, A.; Ricard, L. *J. Am. Chem. Soc.* **2003**, *125*, 4212-4222.

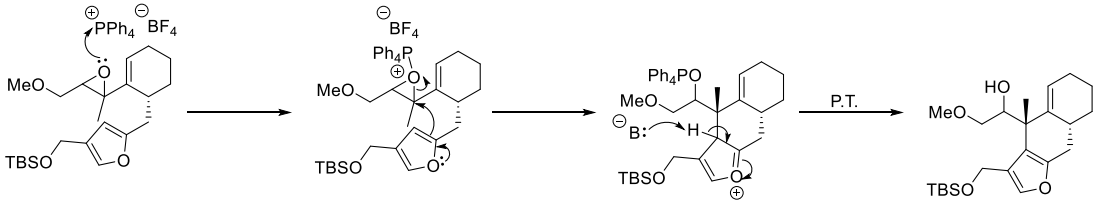
Forward Synthesis

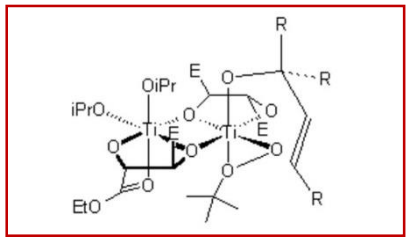


18 to **8:** Sharpless epoxidation

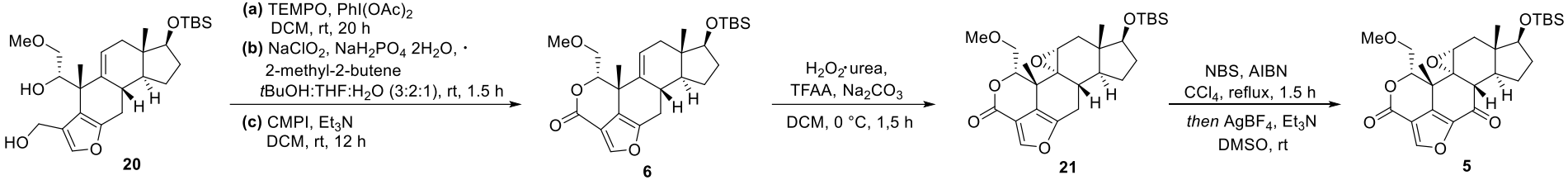


8 to **20:** Lewis-acid catalyzed epoxide opening

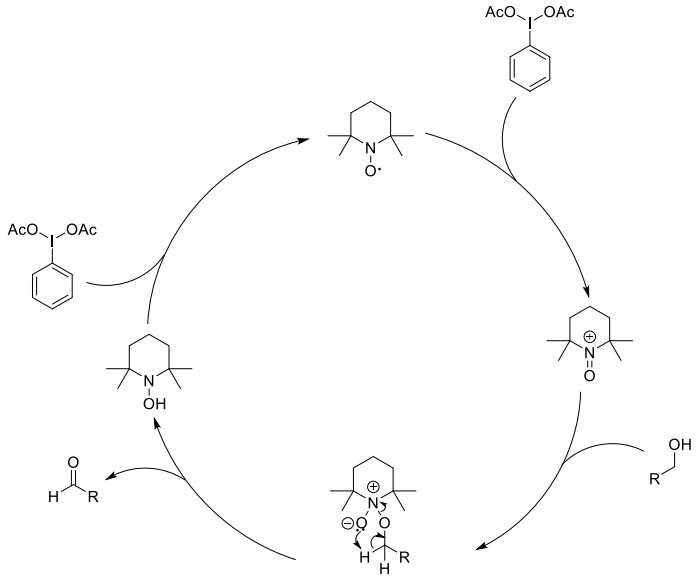




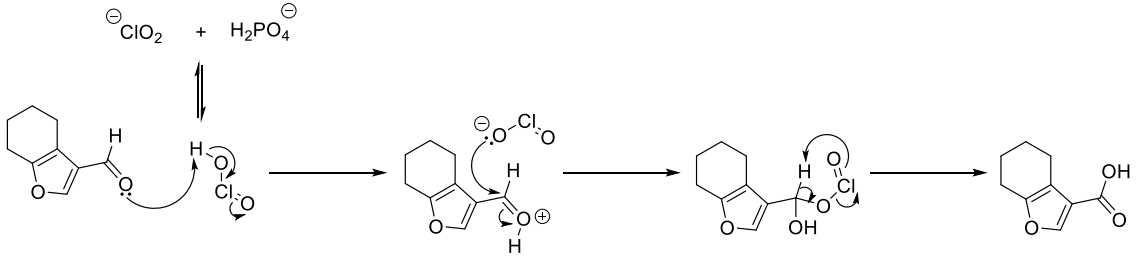
Forward Synthesis



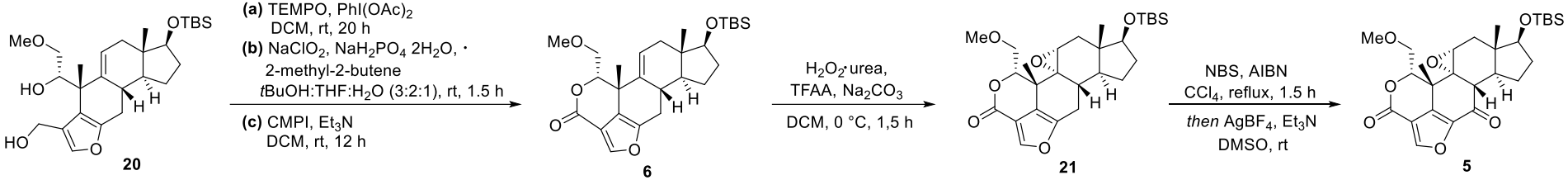
20 to **6:** Alcohol oxidation



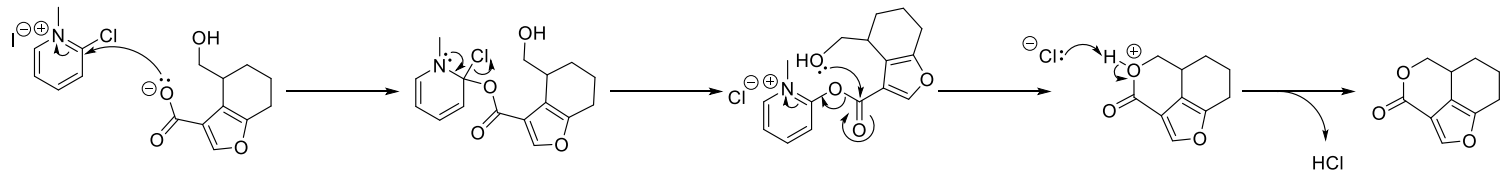
20 to **6:** Pinnick oxidation



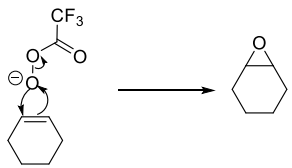
Forward Synthesis



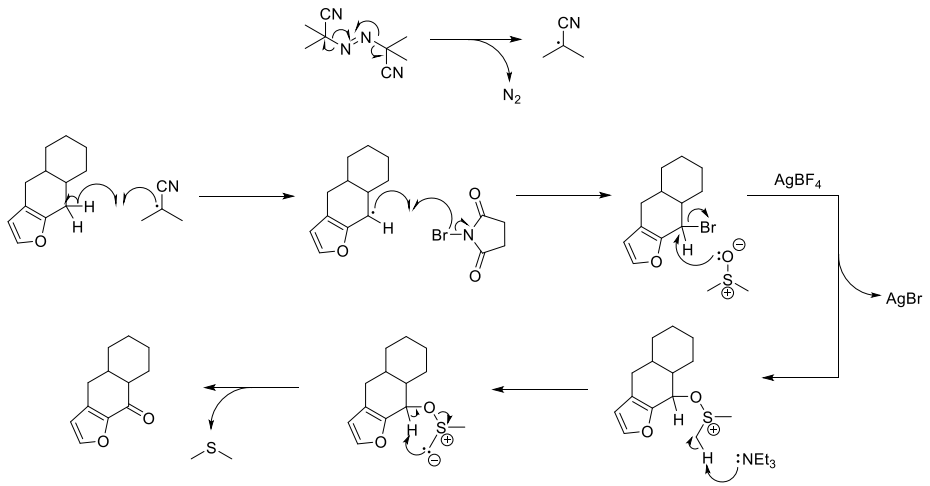
20 to **6:** Lactone formation



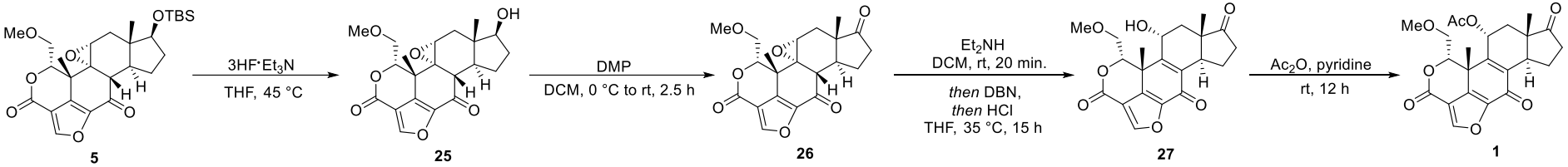
6 to **21:** Epoxide formation



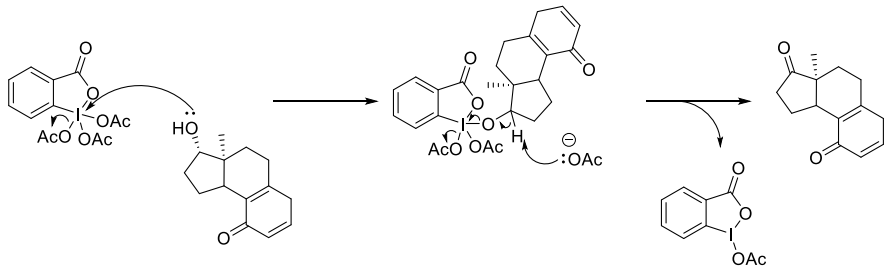
21 to **5:** Allylic oxidation



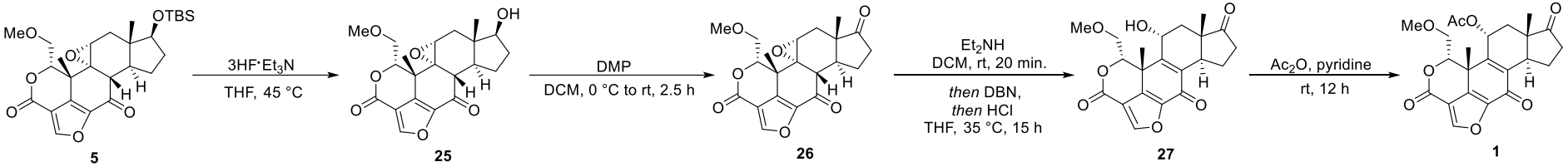
Forward Synthesis



25 to **26:** DMP oxidation



Forward Synthesis



26 to **27:** Epoxide opening