

## Total Synthesis of (+)-Haperforin G

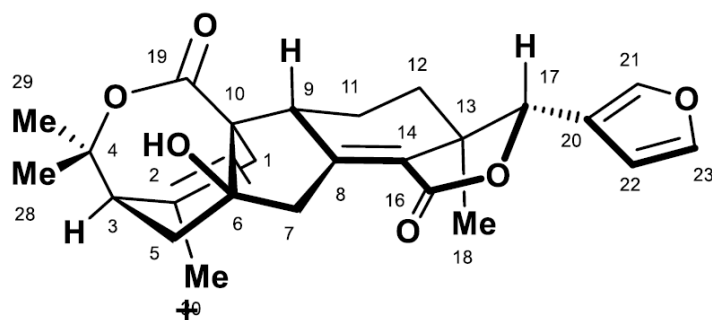
Wei Zhang, Zhenyu Zhang, Jun-Chen Tang, Jin-Teng Che, Hao-Yu Zhang, Jia-Hua Chen,\*  
 and Zhen Yang\*



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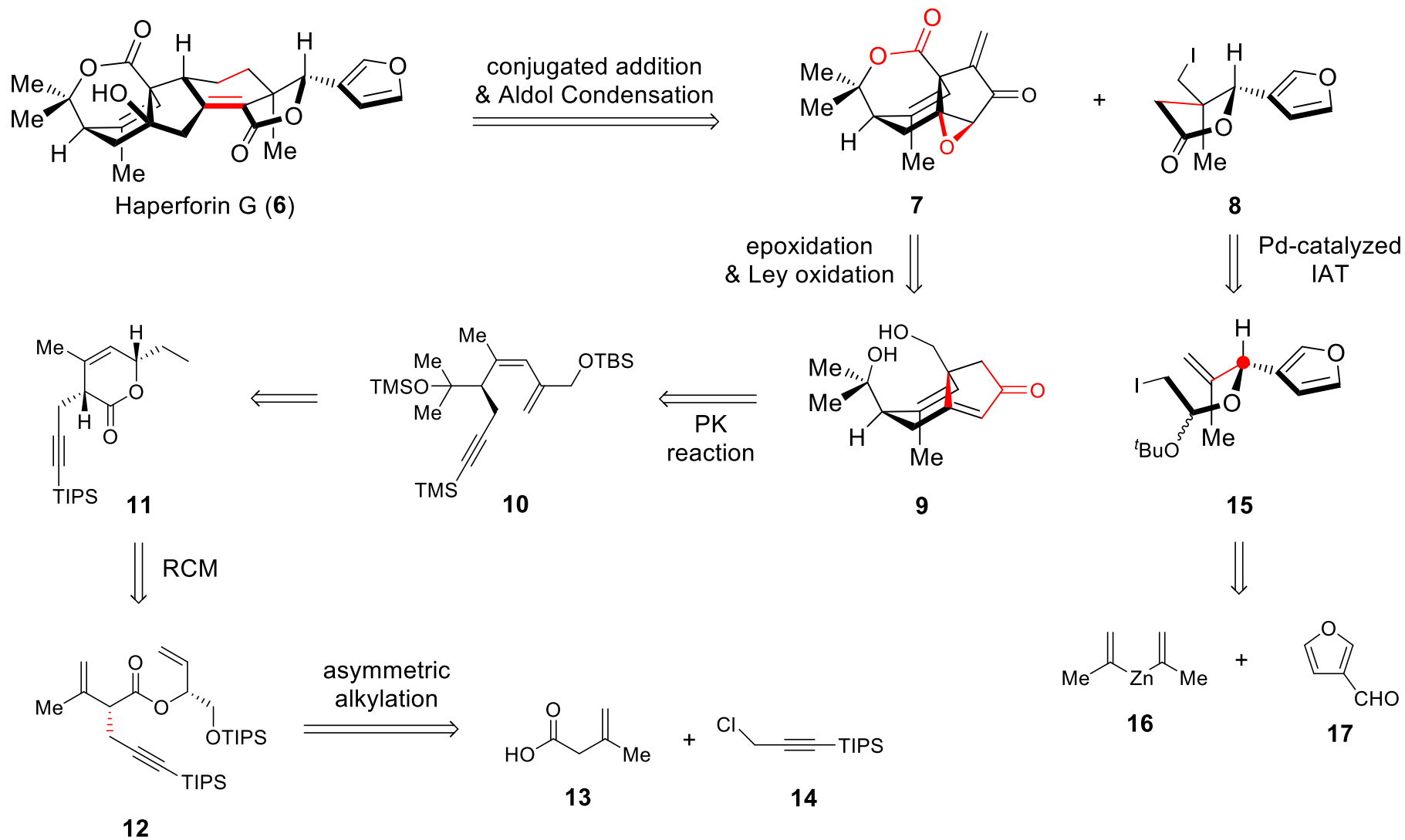


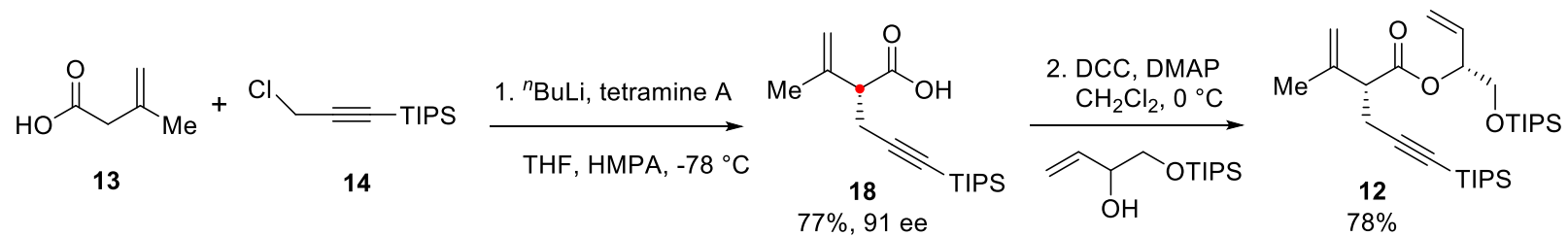
haperforin G (6)

### Introduction:

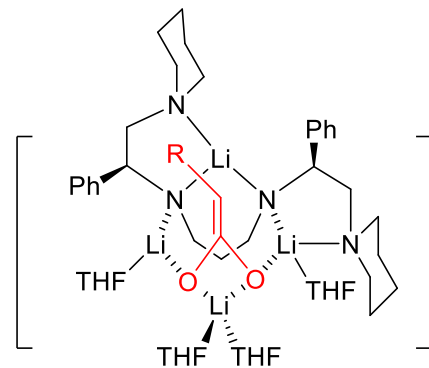
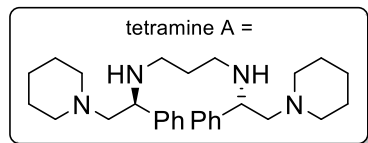
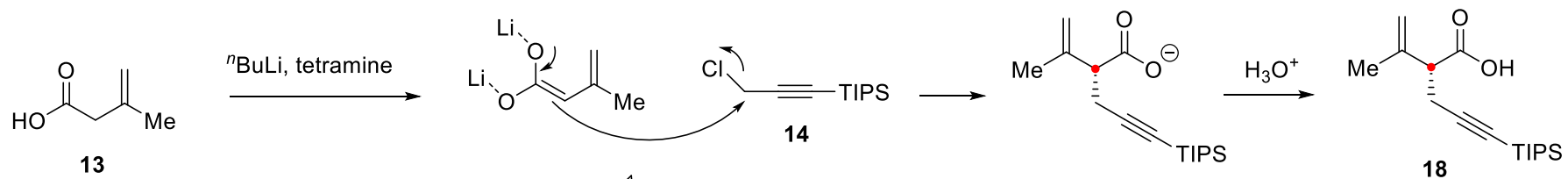
- Haperforin G was isolated from *Harrisonia perforate*, it's a newly discovered member of limonoid tetranortriterpenoid natural products.
- A potent inhibitor of human 11-hydroxysteroid dehydrogenase type 1.
- An attractive chemical entity for treatment of diseases involving metabolic disorders, such as Alzheimer's disease.
- Limonoid 6/5/6 tricyclic carbon skeleton bearing 6 stereogenic centers, 2 all-carbon quaternary centers, 2 lactones and a 3-substituted furan ring.
- Asymmetric total synthesis in 20 steps.

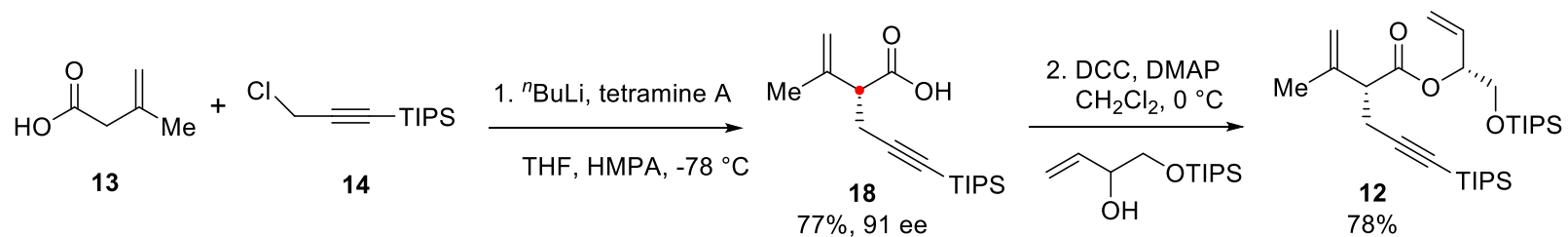
# Retro-synthetic route



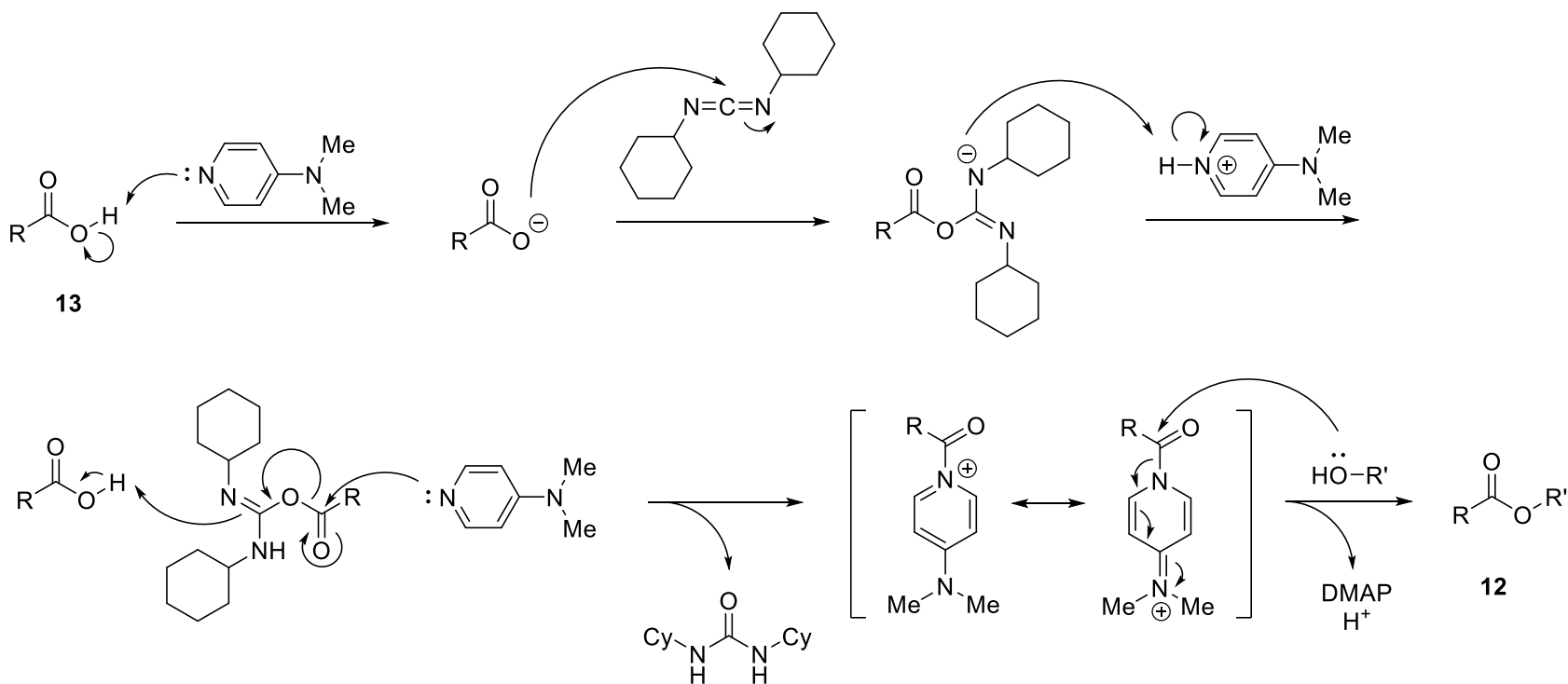


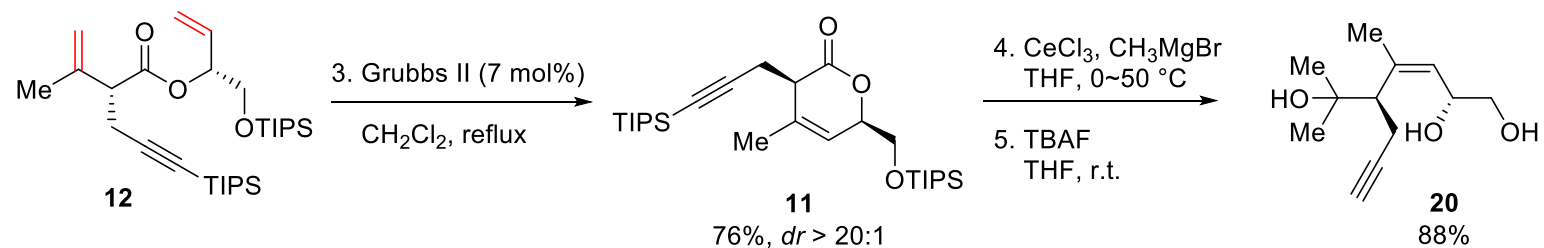
Zakarian's highly enantioselective alkylation:



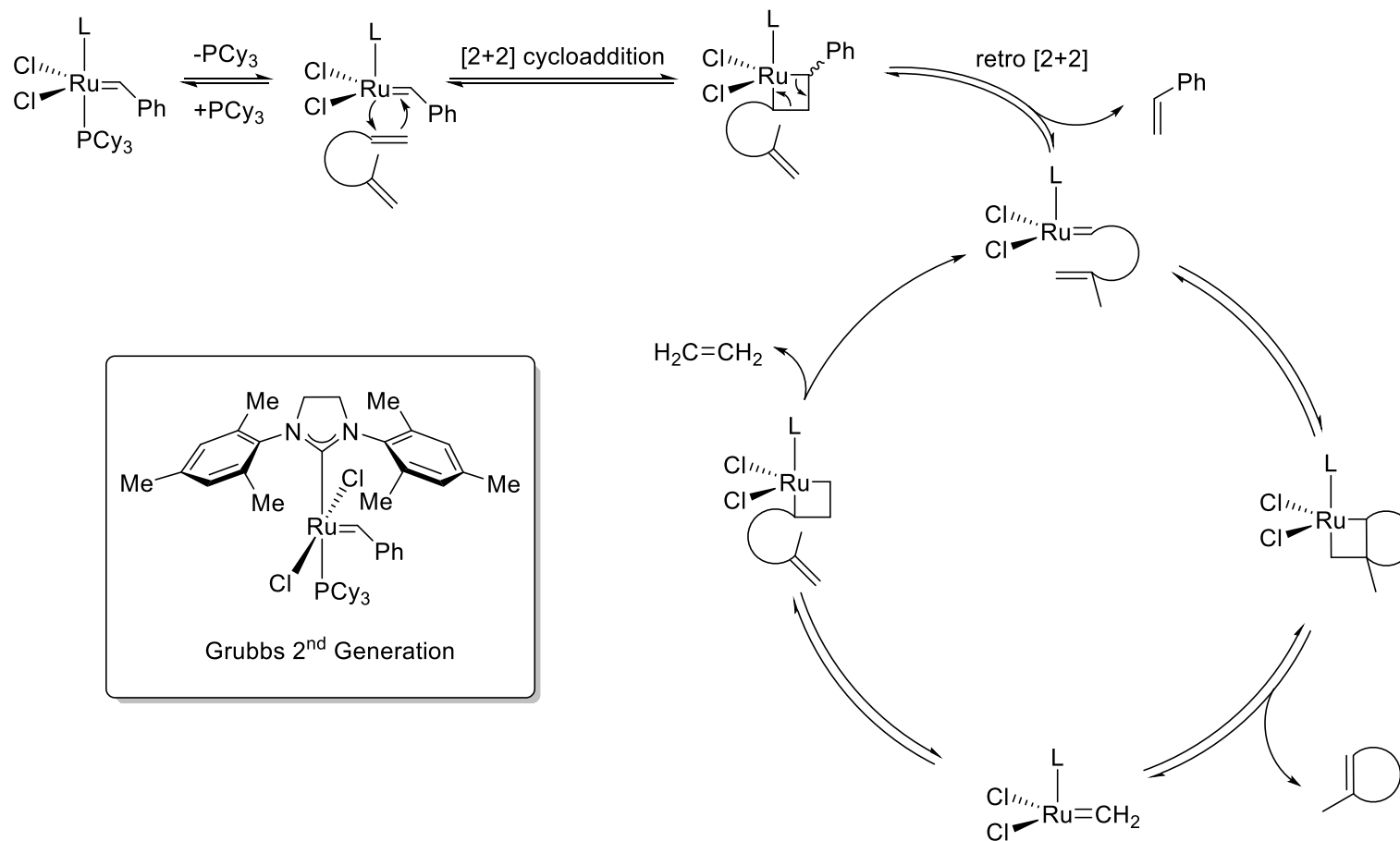


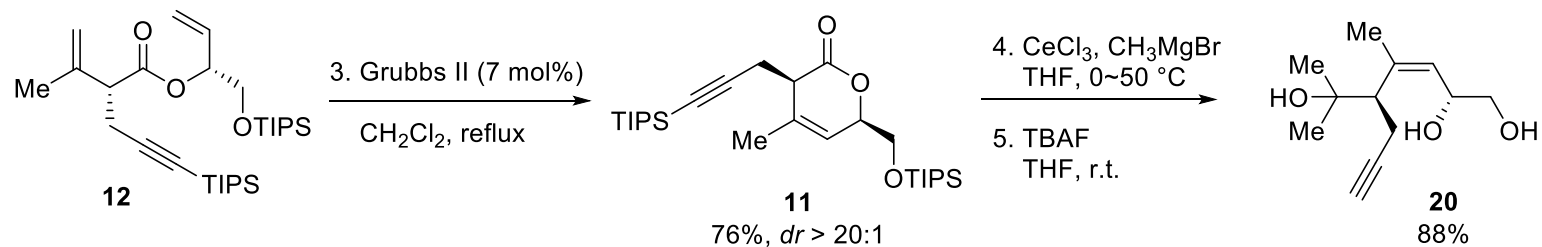
Esterification:



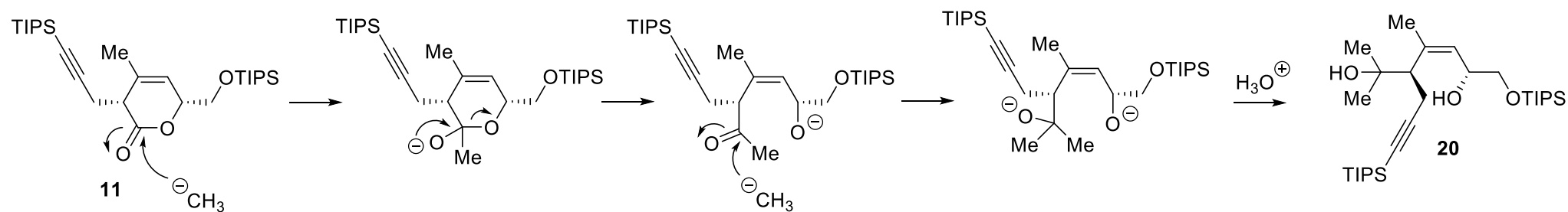


Ring-closing metathesis reaction (RCM):

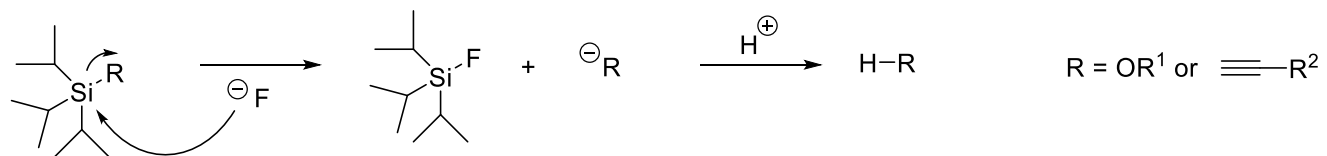


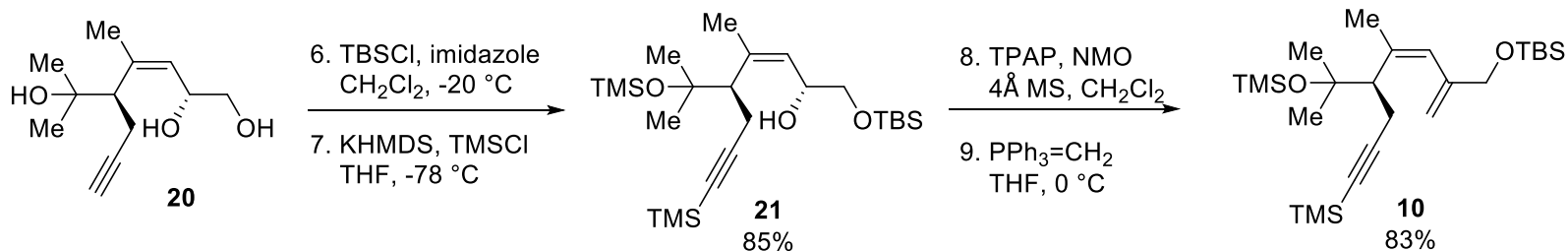


Grignard reaction:

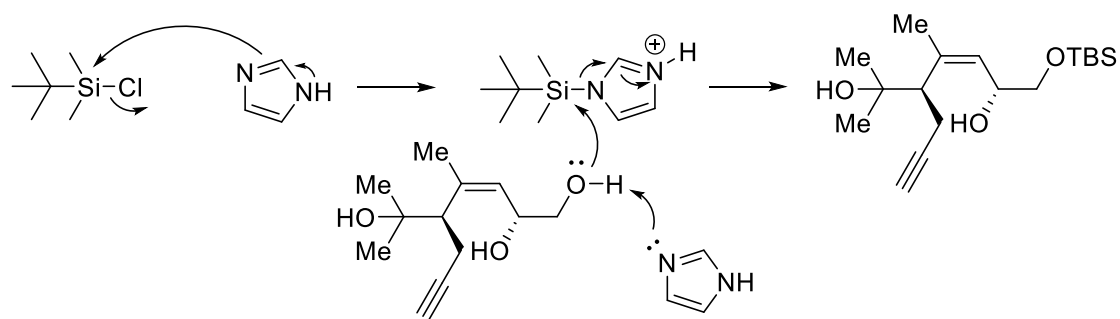


Deprotection of silyl group:



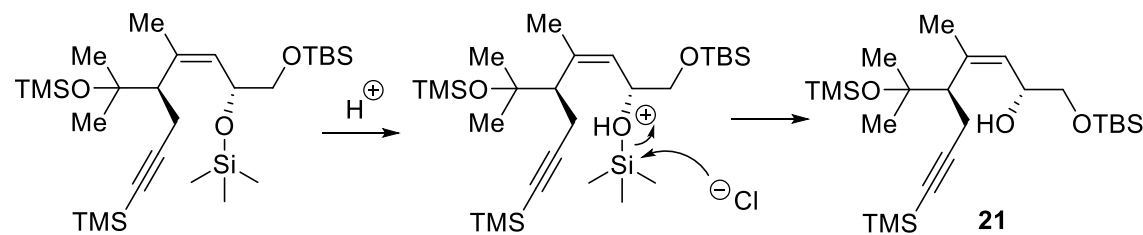
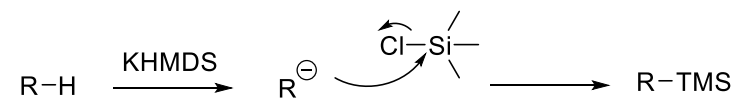


Regioselective silylation:

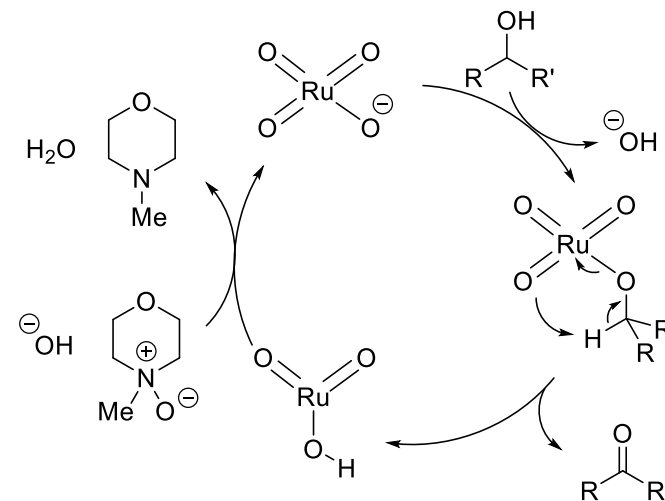


Silylation and desilylation:

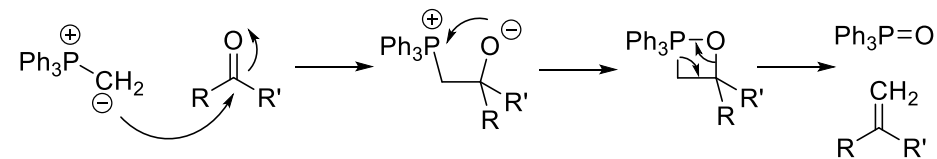
R = OR<sup>1</sup>, OR<sup>2</sup> or ≡-R<sup>3</sup>

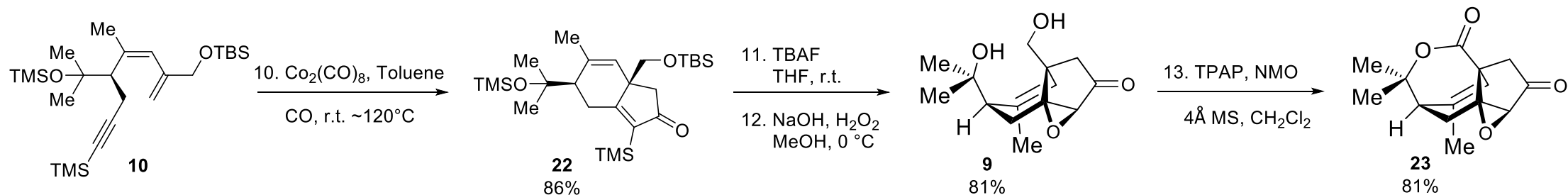


Oxidation of alcohol to ketone:



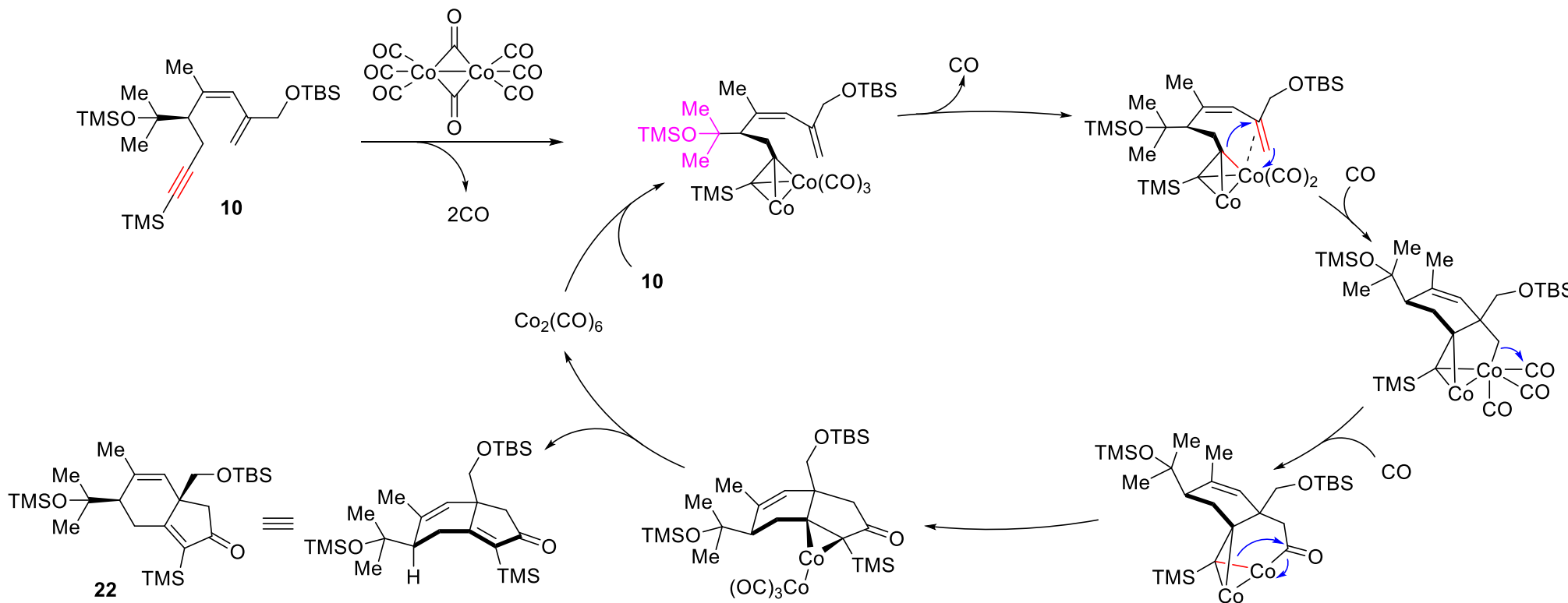
Wittig reaction:



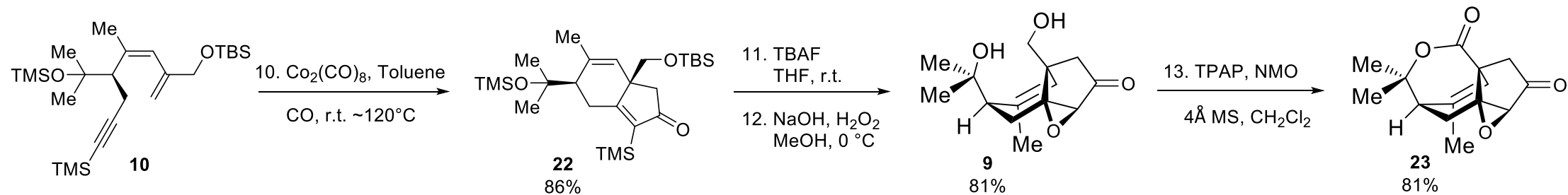


Pauson-Khand Reaction:

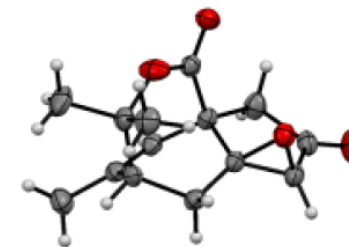
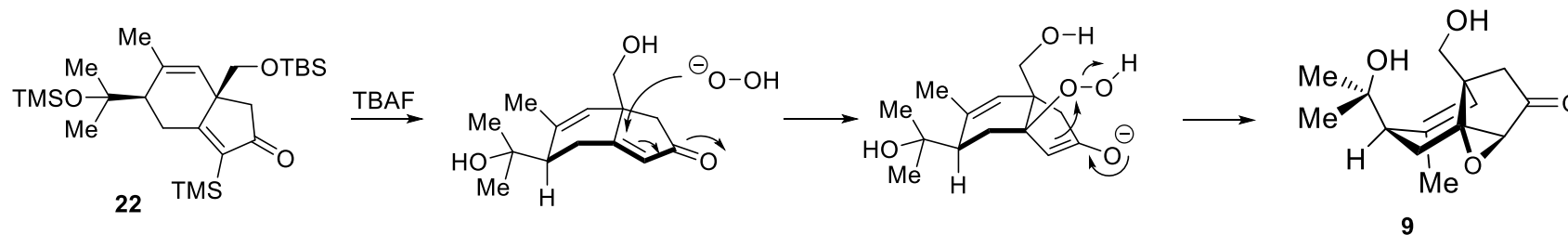
Thorpe-Ingold effect: Molecule with larger substituents favor ring closure and intramolecular reaction





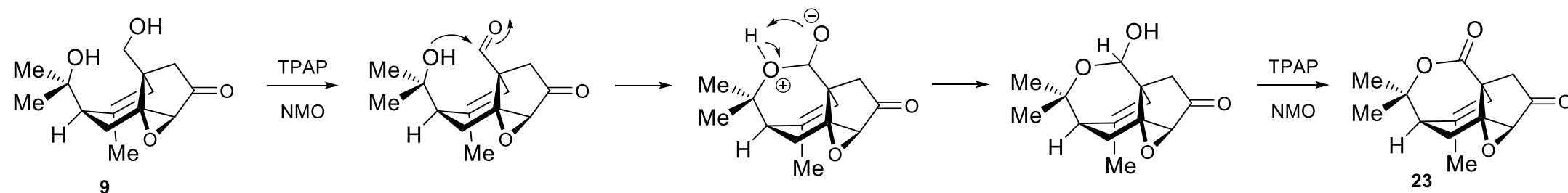


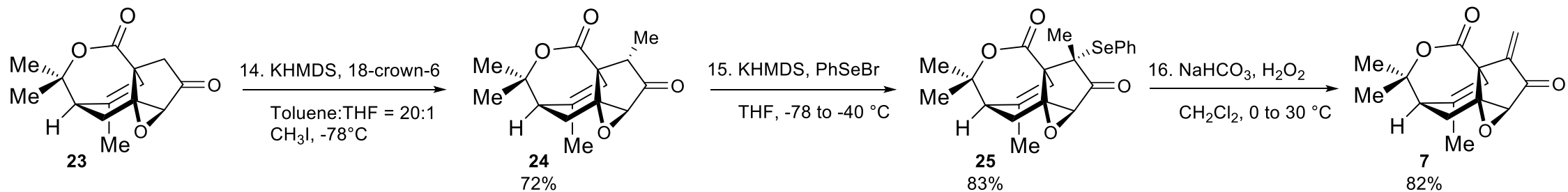
Weitz-Scheffer epoxidation (nucleophilic epoxidation):



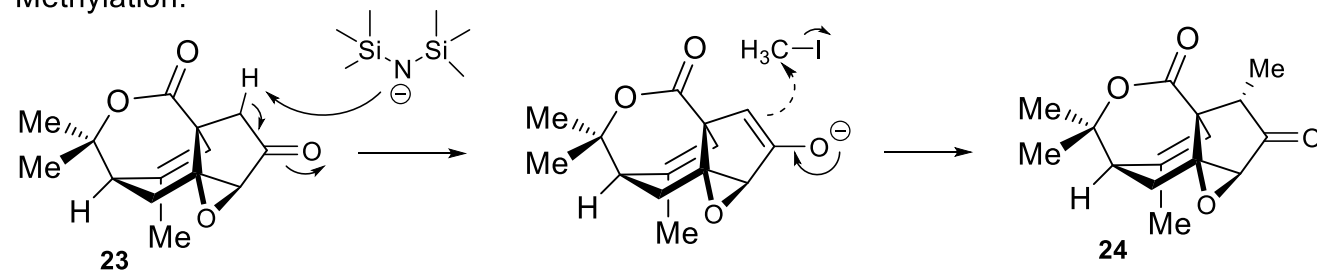
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Oxidation of diol to ester:

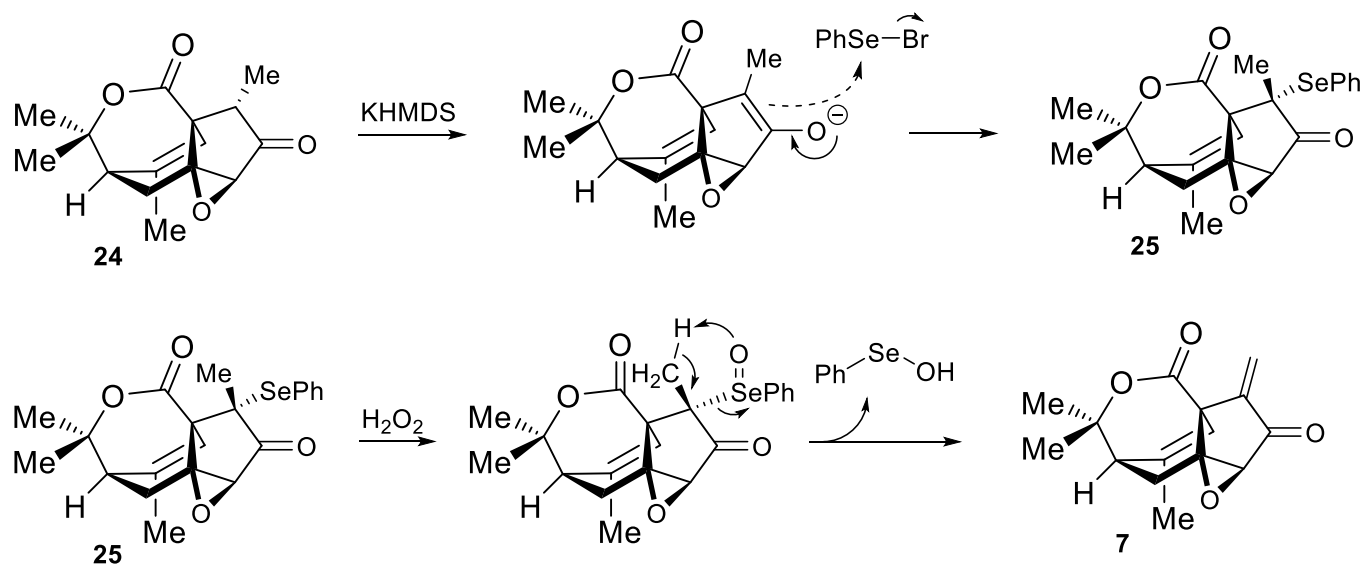


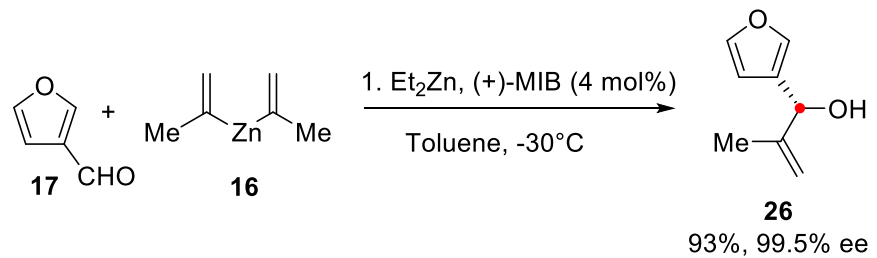


Methylation:

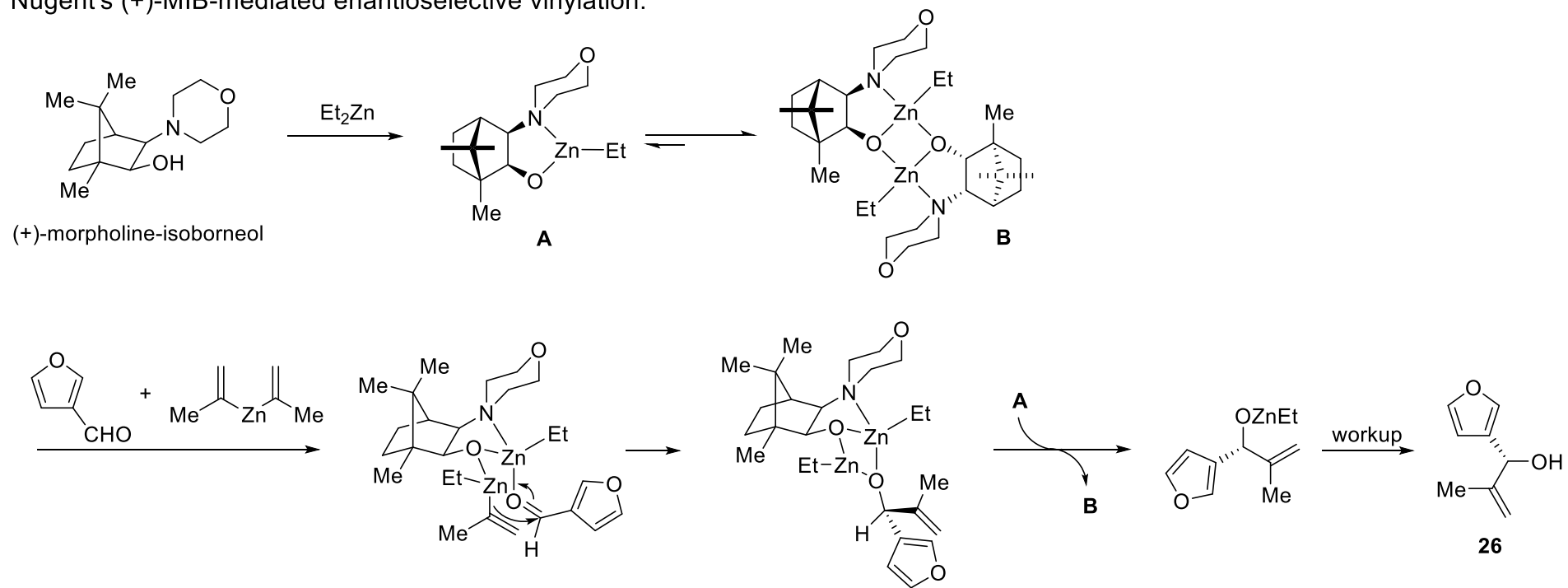


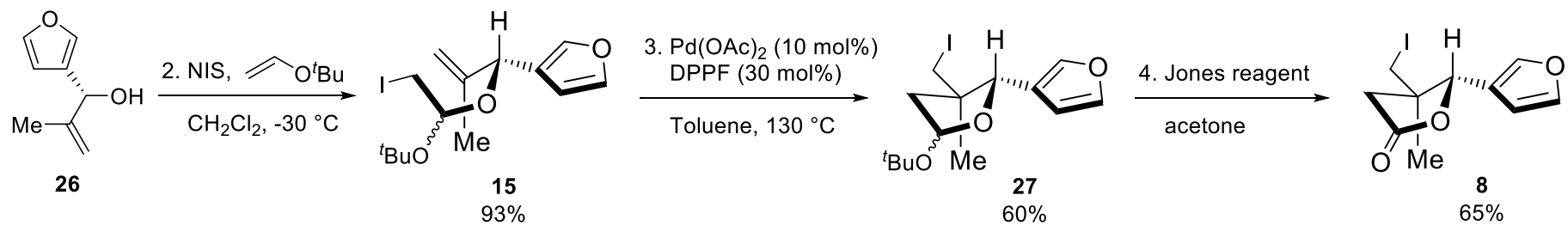
Selenoxide elimination:



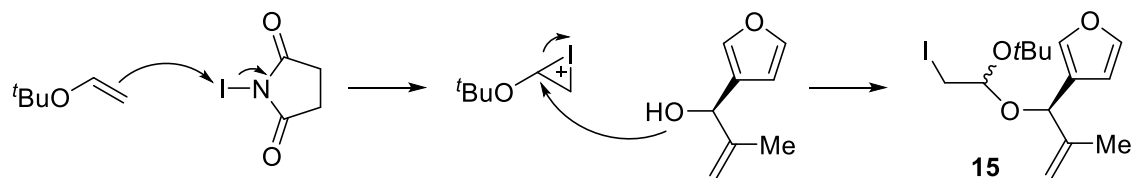


Nugent's (+)-MIB-mediated enantioselective vinylation:

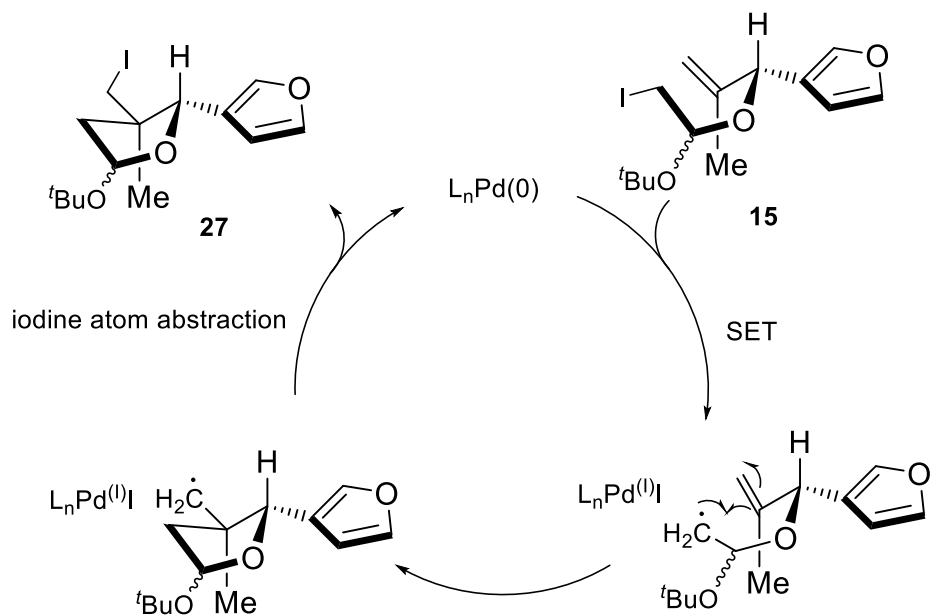




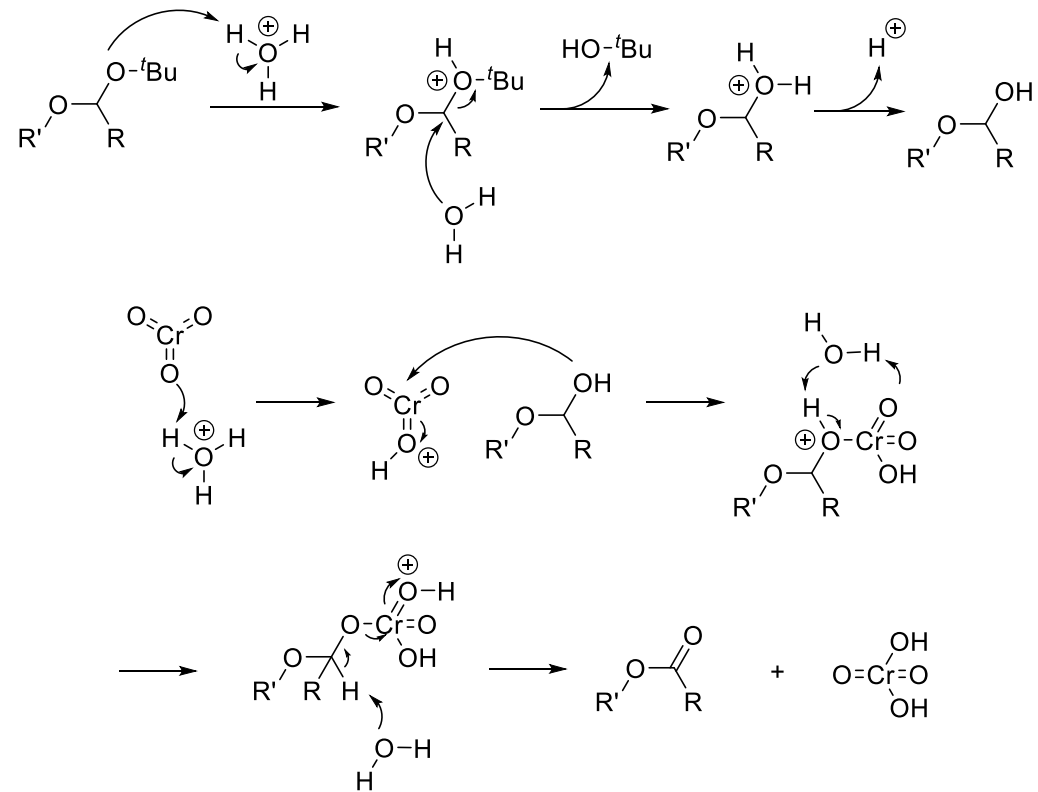
NIS-mediated intermolecular ketalization:

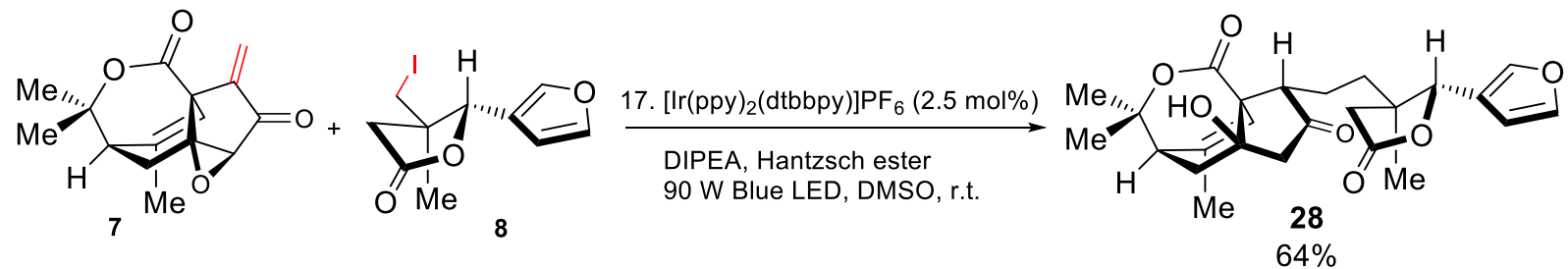


Pd-catalyzed iodide atom transfer cyclization (IATC):

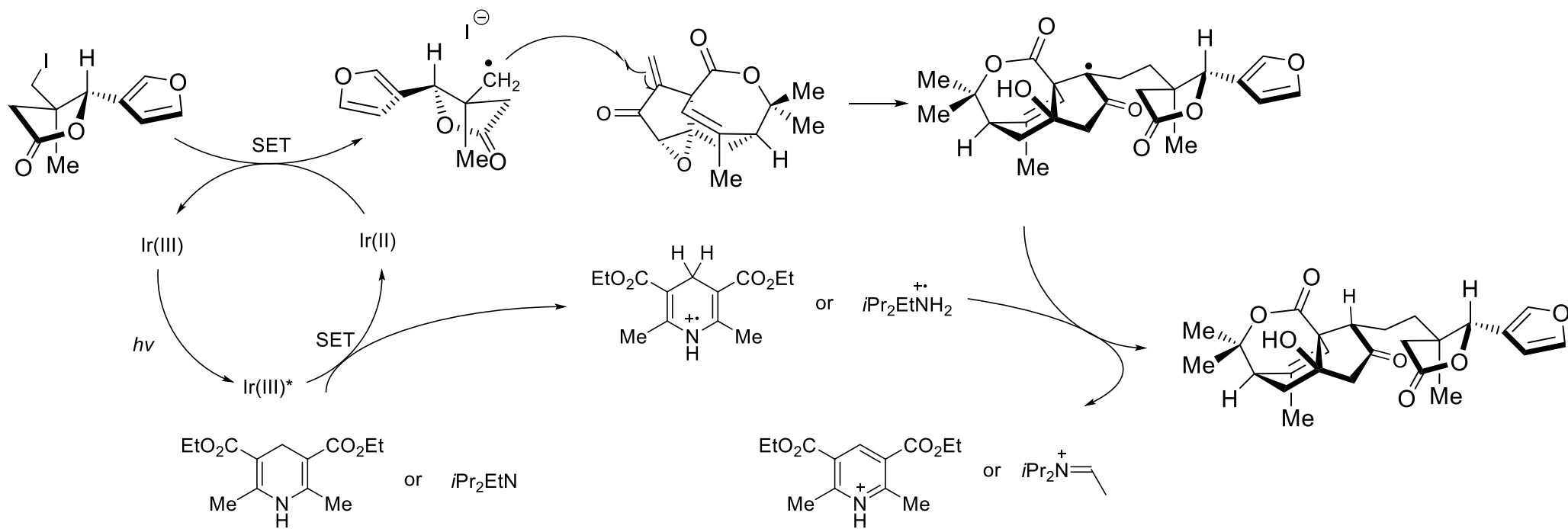


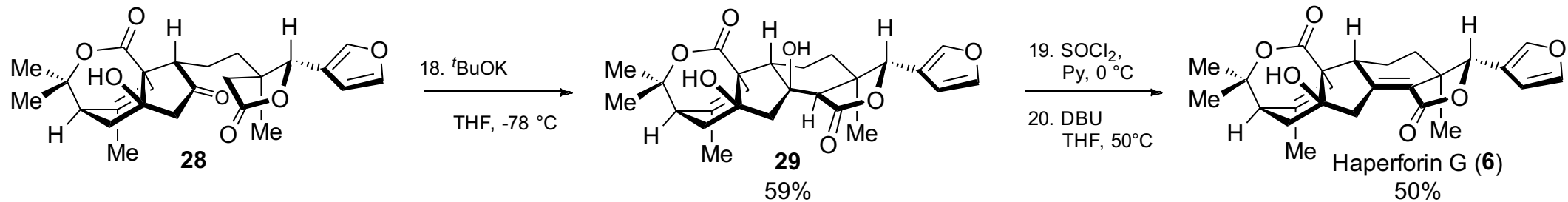
Jones oxidation:



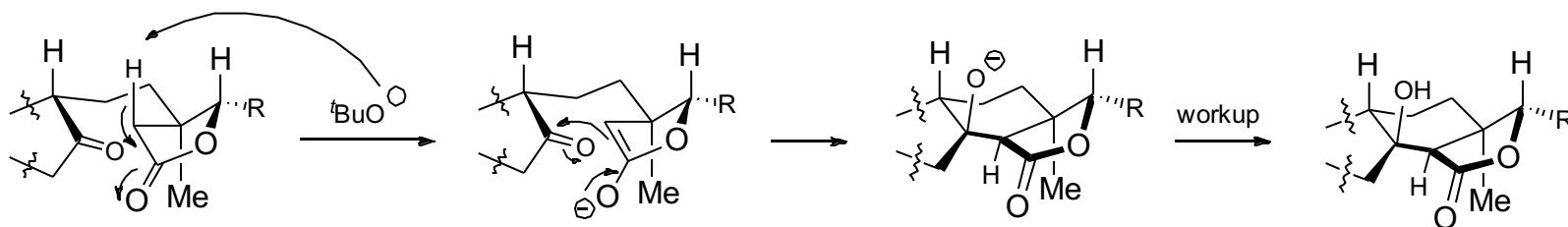


Photoredox-catalyzed C-C bond formation:

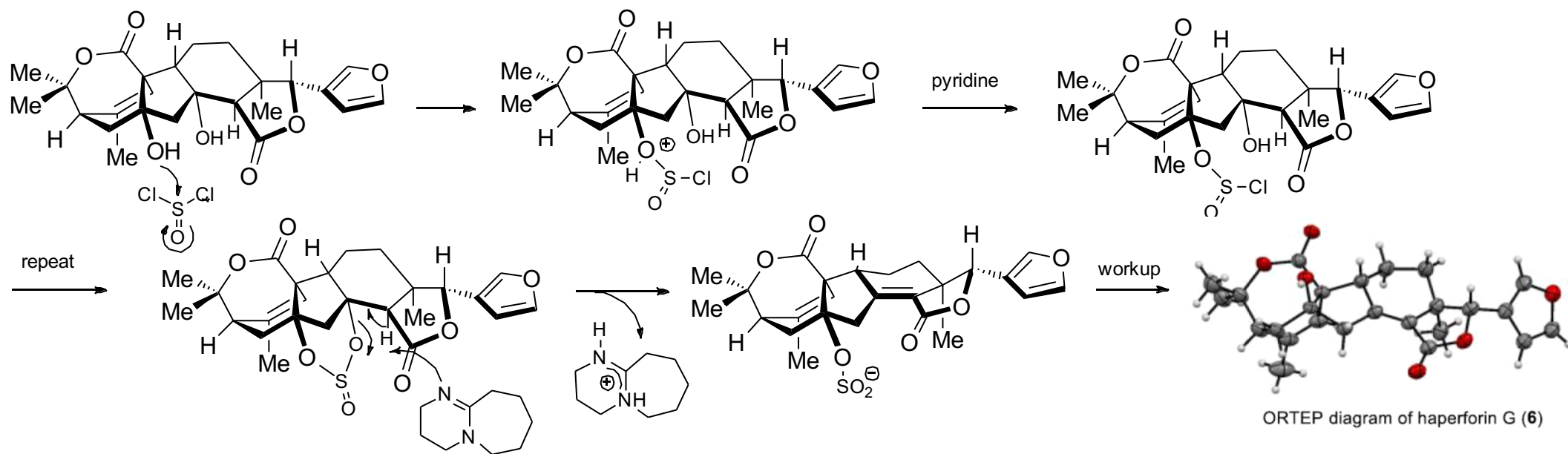




Aldol condensation:



Formation of cyclic sulfate and ring opening:



Thanks for your attention!