

Diastereoselective Total Synthesis of (–)-Galiellalactone

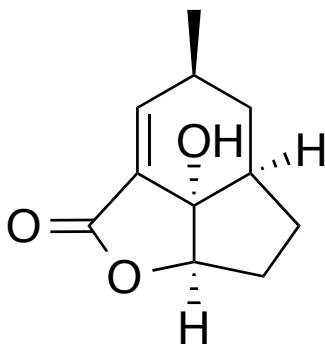
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I. Introduction

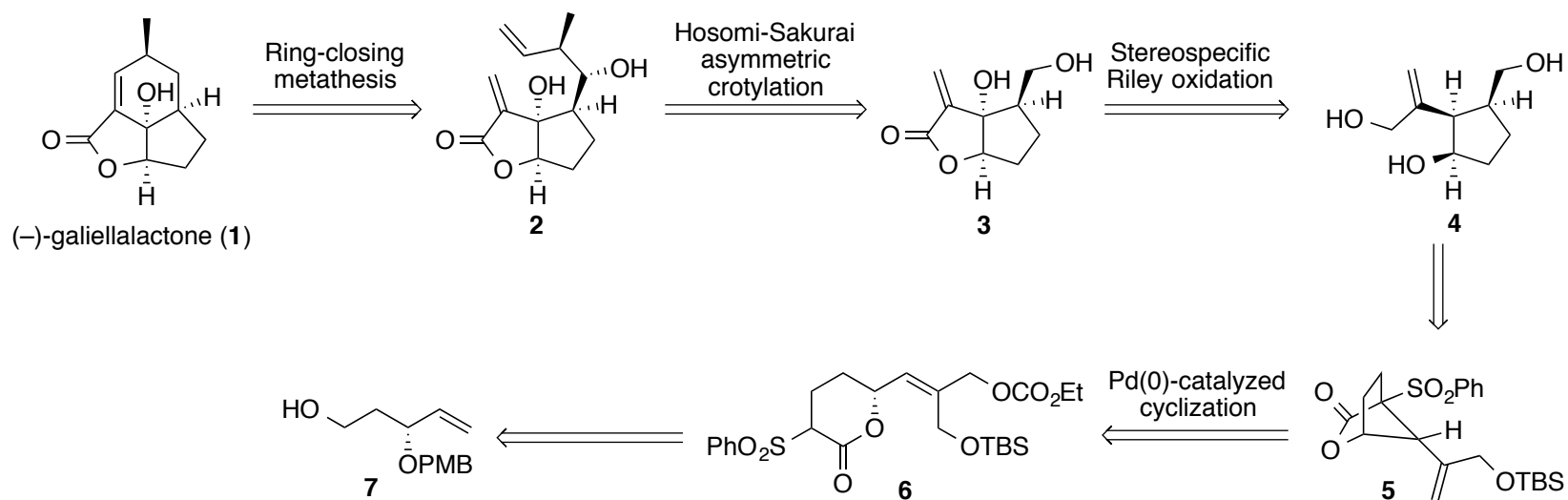


(–)-galiellalactone (**1**)

- (–)-Galiellalactone is a fungal metabolite isolated from the ascomycete *Galiella rufa*
- Potent and specific inhibitor of STAT3 (signal transducer and activator of transcription 3), which is involved in many signaling pathways
 - STAT3 is a promising molecular target for cancer therapy
- (–)-Galiellalactone also induces apoptosis and growth inhibition in human prostate cancer cells
- Structural features: highly congested tricyclic-ring system, α,β -unsaturated lactone, four stereocenters
 - Tertiary stereogenic center - angular hydroxyl group (essential for biological activity of **1**).
 - Most challenging part to incorporate stereoselectively

Retrosynthetic Analysis of (-)-Galiellalactone

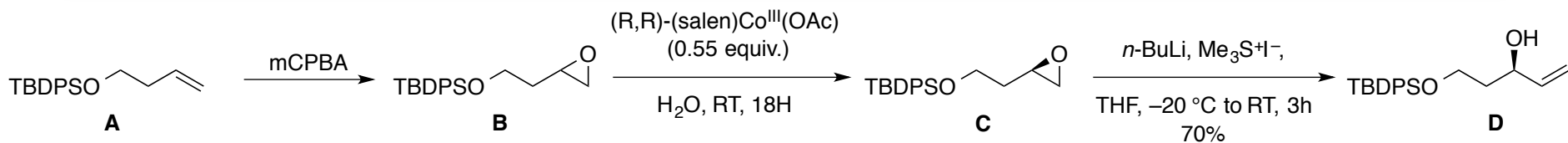
II. Retrosynthetic Analysis



- Ring-closing metathesis and Barton-McCombie deoxygenation (**1 to 2**)
- Hosomi-Sakurai asymmetric crotylation (**2 to 3**)
- Riley oxidation (**3 to 4**)
- Reduction of the bridged lactone (**4 to 5**)
- Pd(0)-catalyzed cyclization (**5 to 6**)

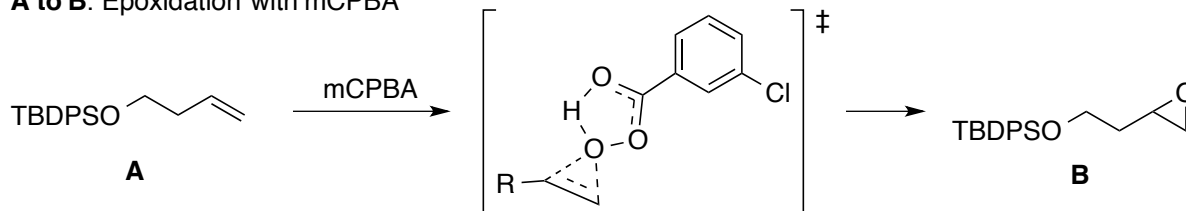
IV. Forward Synthesis

Starting Material Synthesis

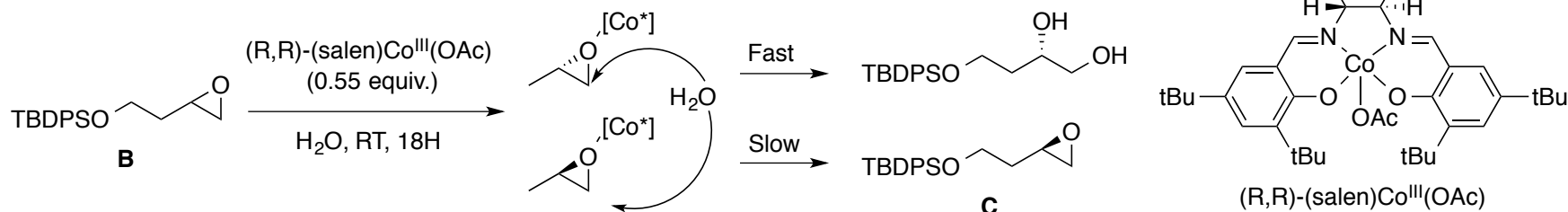


Krishna, P. R.; Rao, T. J. *Org. Biomol. Chem.* **2010**, *8*, 3130.

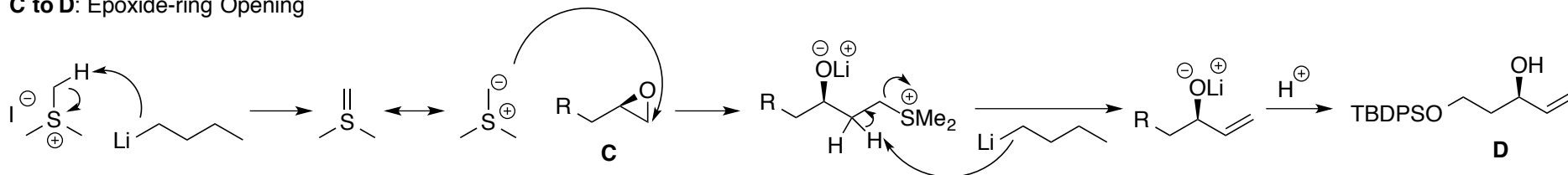
A to B: Epoxidation with mCPBA



B to C: Kinetic Resolution of Terminal Epoxides (Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.)

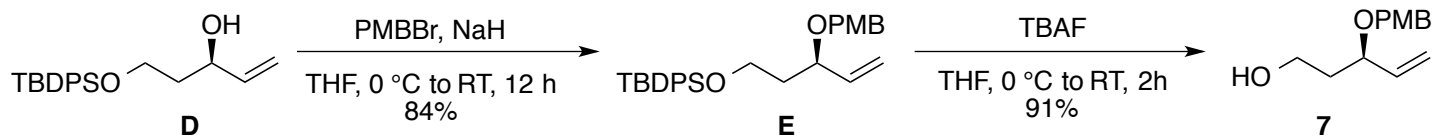


C to D: Epoxide-ring Opening



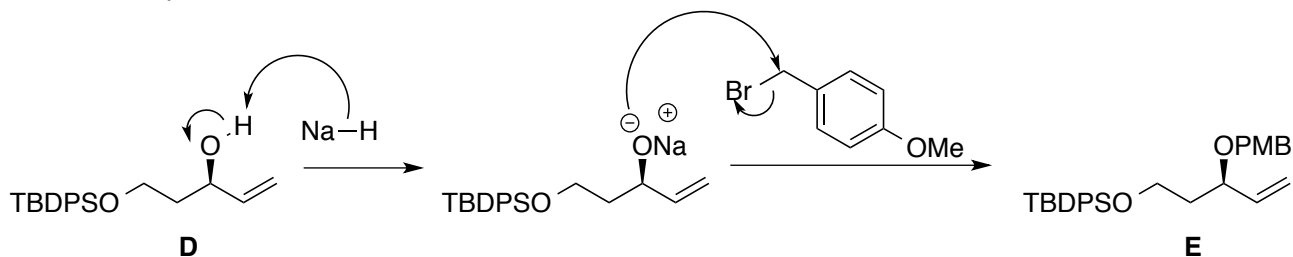
IV. Forward Synthesis

Starting Material Synthesis

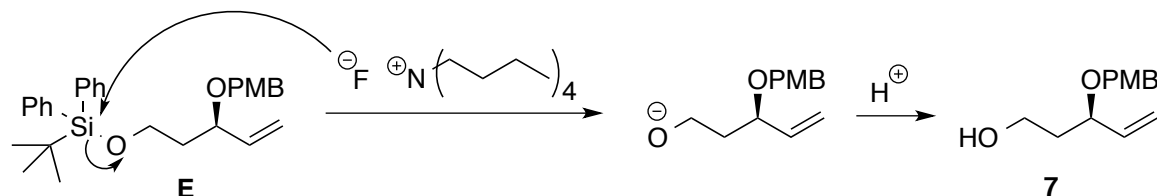


Krishna, P. R.; Rao, T. J. *Org. Biomol. Chem.* **2010**, *8*, 3130.

D to E: PMB protection

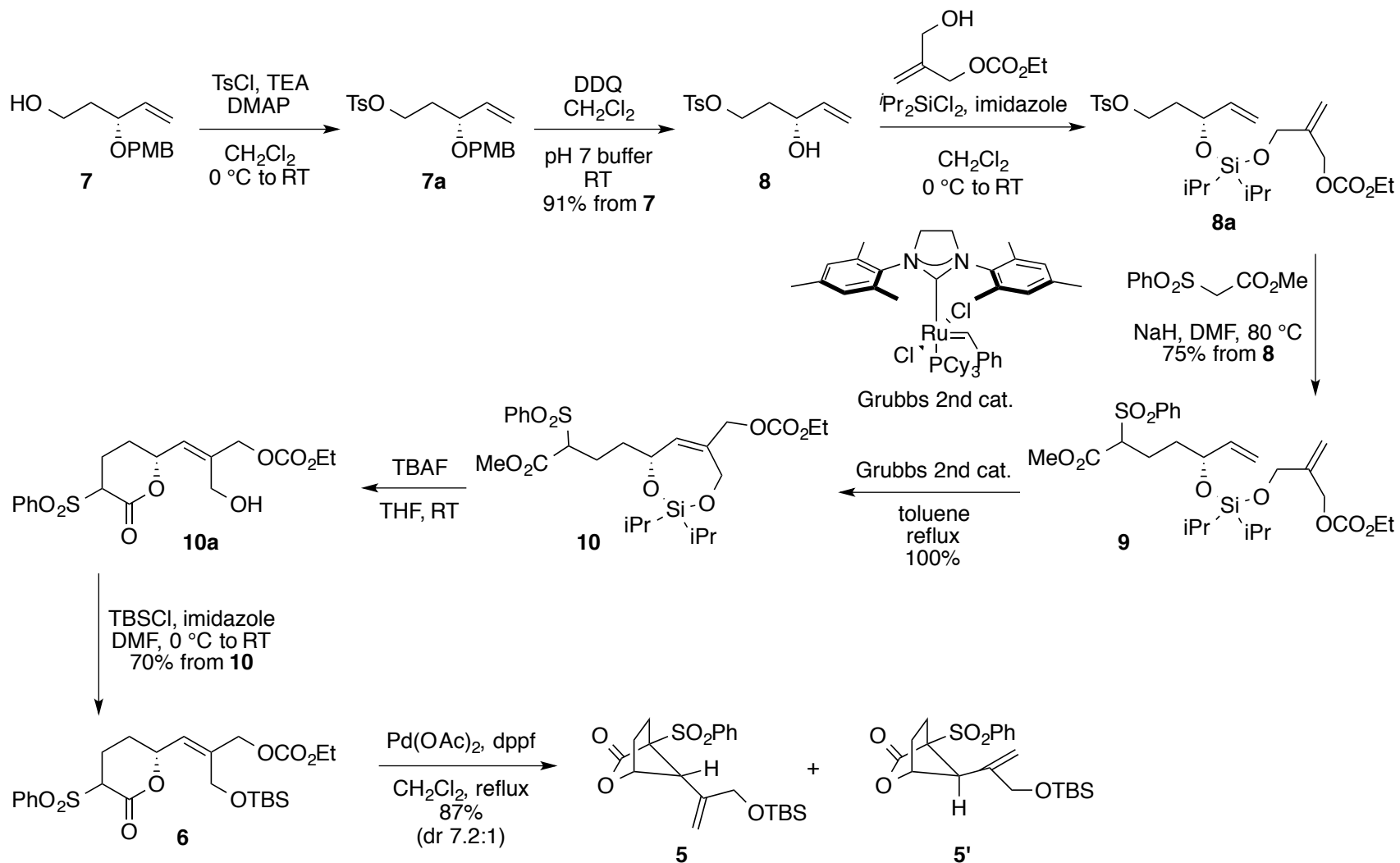


E to 7: Desilylation



IV. Forward Synthesis

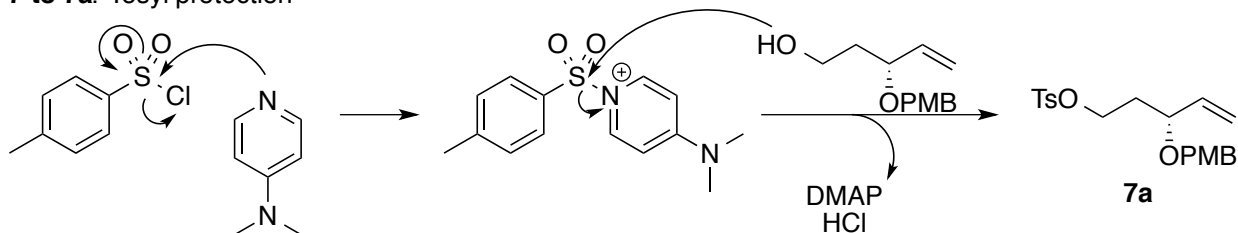
Synthesis of [2.2.1] Bridged Bicyclic Lactone



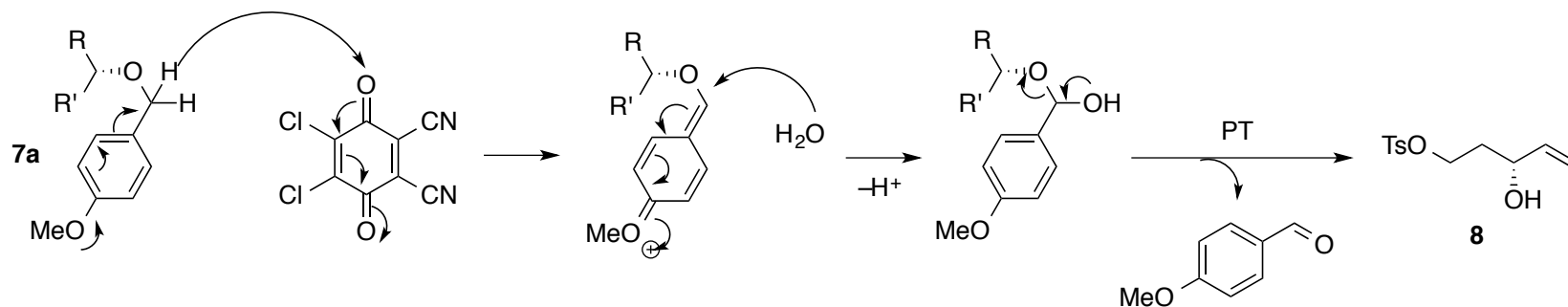
IV. Forward Synthesis

Synthesis of [2.2.1] Bridged Bicyclic Lactone

7 to 7a: Tosyl protection

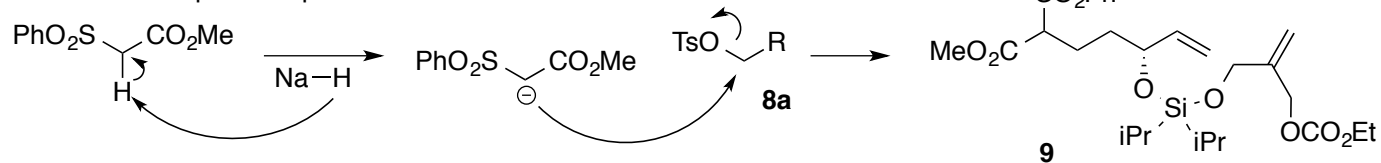


7a to 8: PMB Deprotection

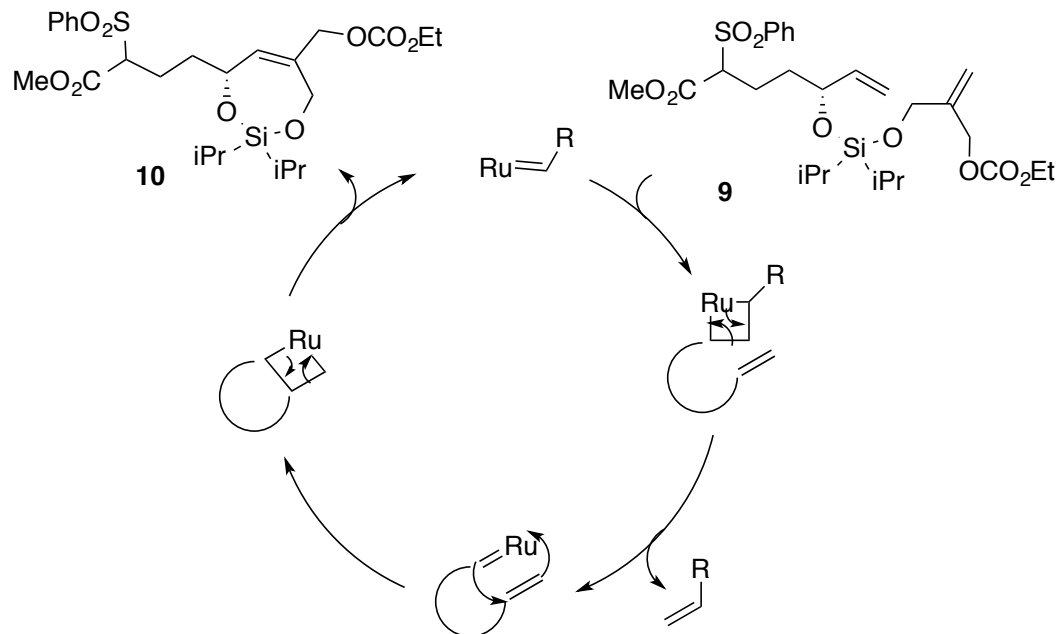


8 to 8a: Double-silylation to form silicon tether

8a to 9: Nucleophilic Displacement



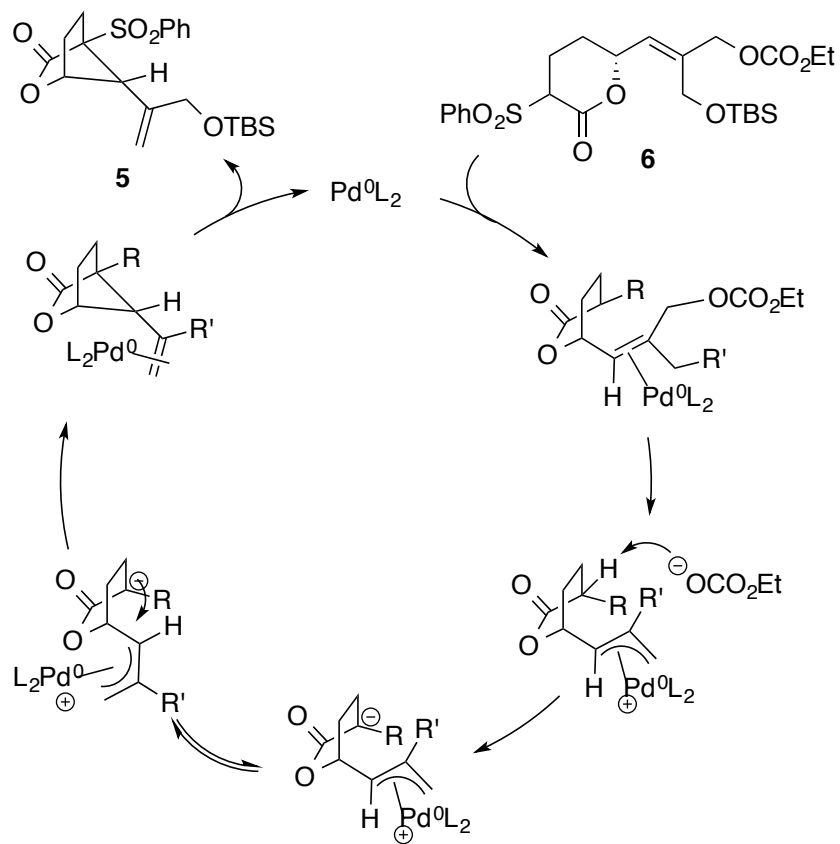
9 to 10: Grubbs Ring-closing Metathesis



10 to 10a: Desilylation and Lactonization

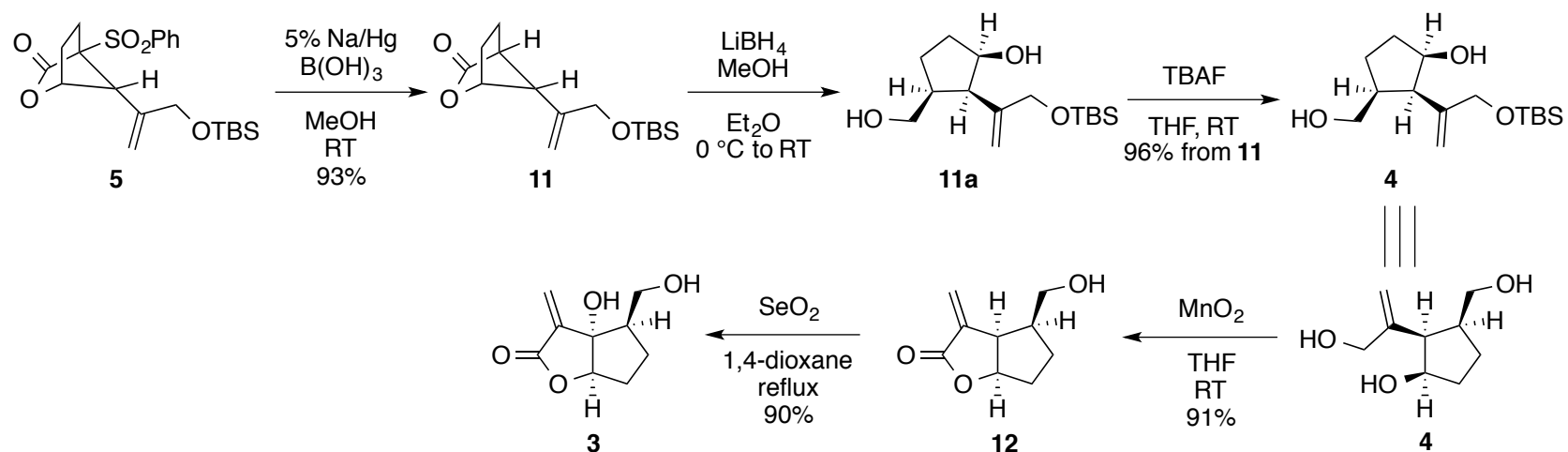
10a to 6: TBS protection

6 to 5: Allylic Alkylation



IV. Forward Synthesis

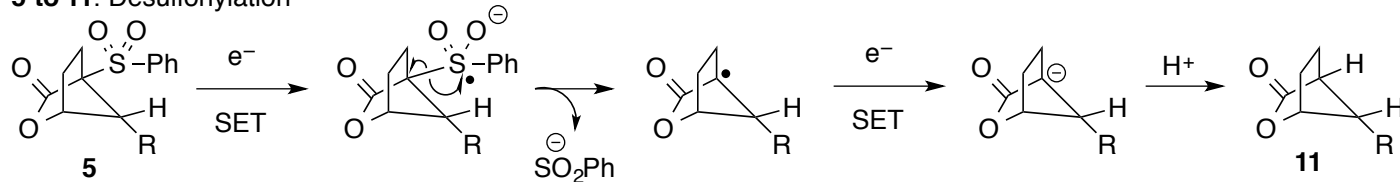
Synthesis of Dihydroxy Lactone 3



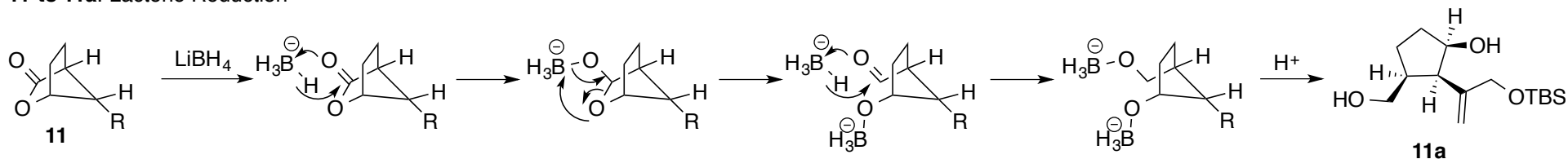
IV. Forward Synthesis

Synthesis of Dihydroxy Lactone 3

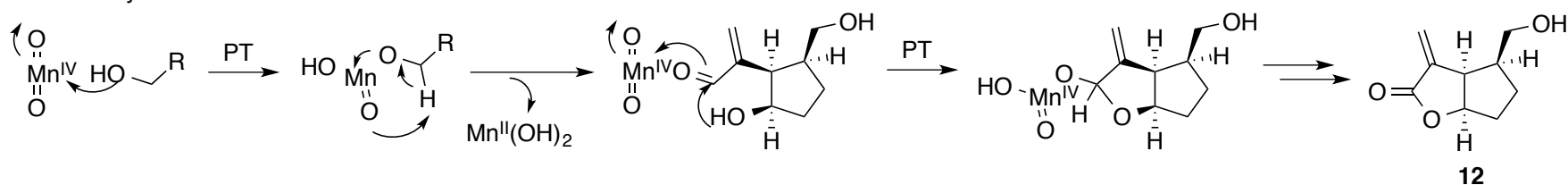
5 to 11: Desulfonylation



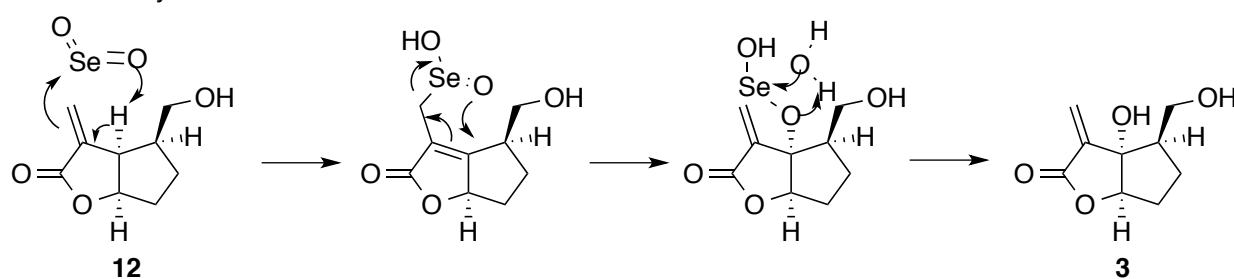
11 to 11a: Lactone Reduction



4 to 12: Allylic Oxidation

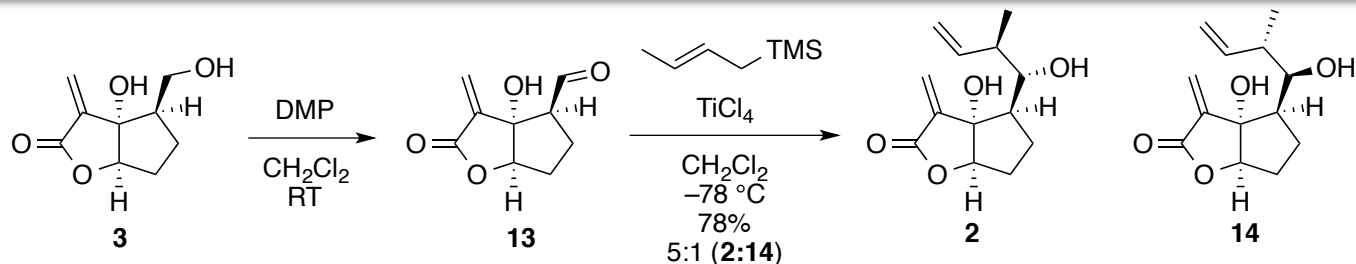


12 to 3: Riley Oxidation

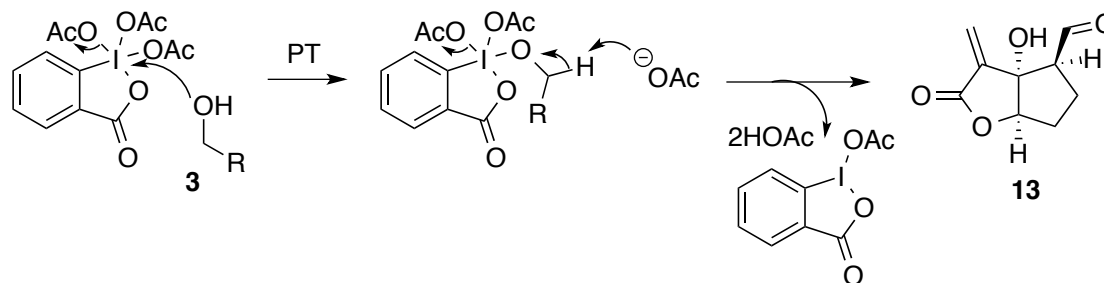


IV. Forward Synthesis

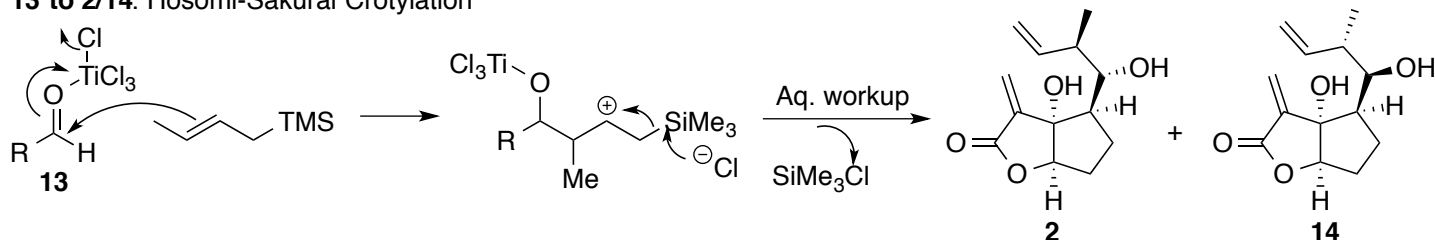
Synthesis of Bicycle 2



3 to 13: DMP oxidation

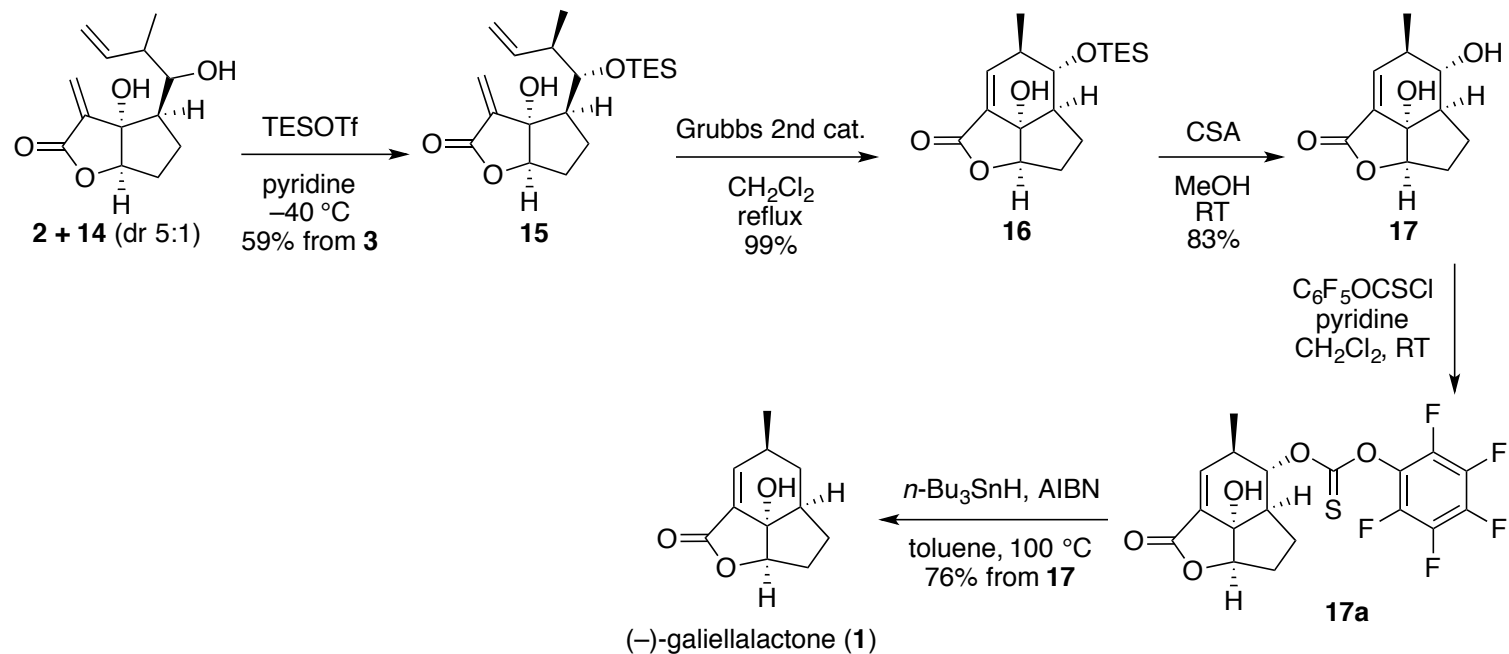


13 to 2/14: Hosomi-Sakurai Crotylation



IV. Forward Synthesis

Completion of Synthesis



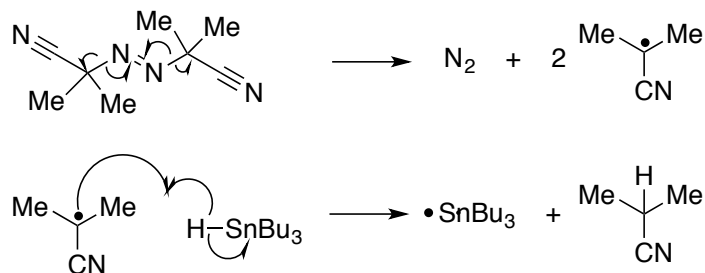
2 to 15: Silylation

15 to 16: Ring-closing Metathesis

16 to 17: Desilylation

17a to 1: Barton-McCombie Deoxygenation

Initiation:



Propagation:

