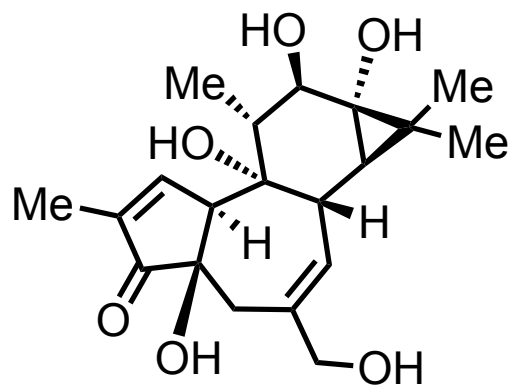


Total Synthesis of (+)-Phorbol

Synthesis Club

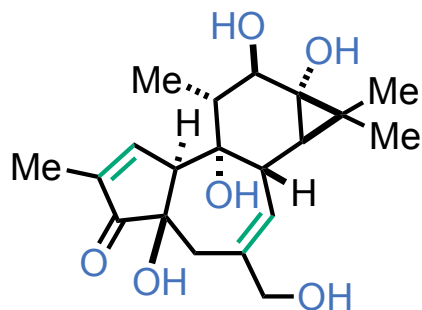
Jonas Renner

4/24/17



Background

- Phorbol derivatives are members of the triterpene diterpenoid family
- Isolated from *Thymelaeaceae* and *Euphorbiaceae*
- X-ray structure of phorbol derivative in 1967

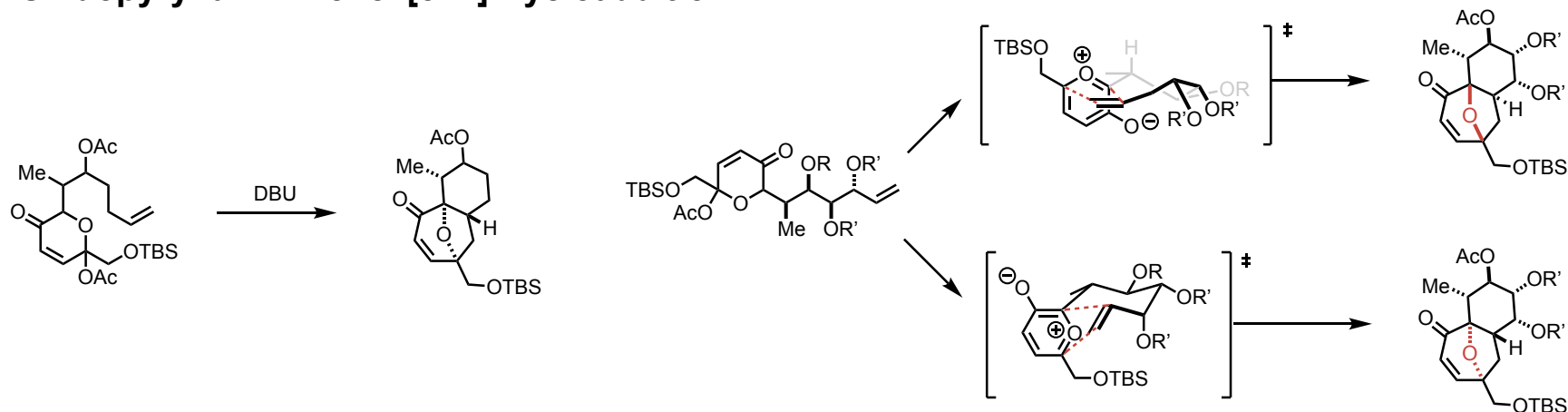


Tiglane diterpenes promising in medical applications:
Immunomodulatory
Anti-cancer
Anti-viral

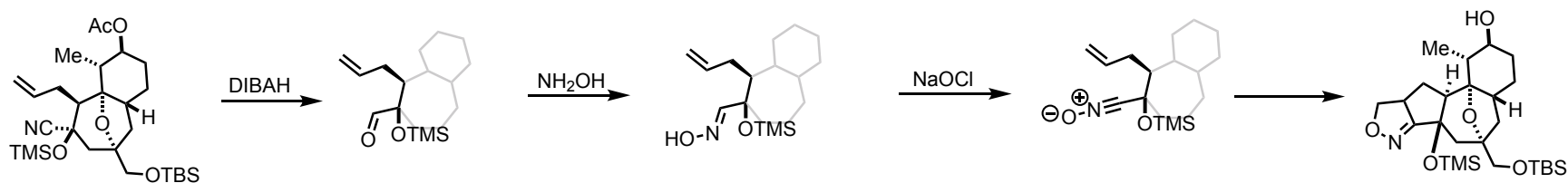
Wender's racemic total synthesis **1989**
Wender's racemic formal synthesis **1990**
Wender's asymmetric total synthesis 1997
Cha's asymmetric formal synthesis **2001**
Baran's total synthesis **2016**

Wender's racemic total synthesis 1989

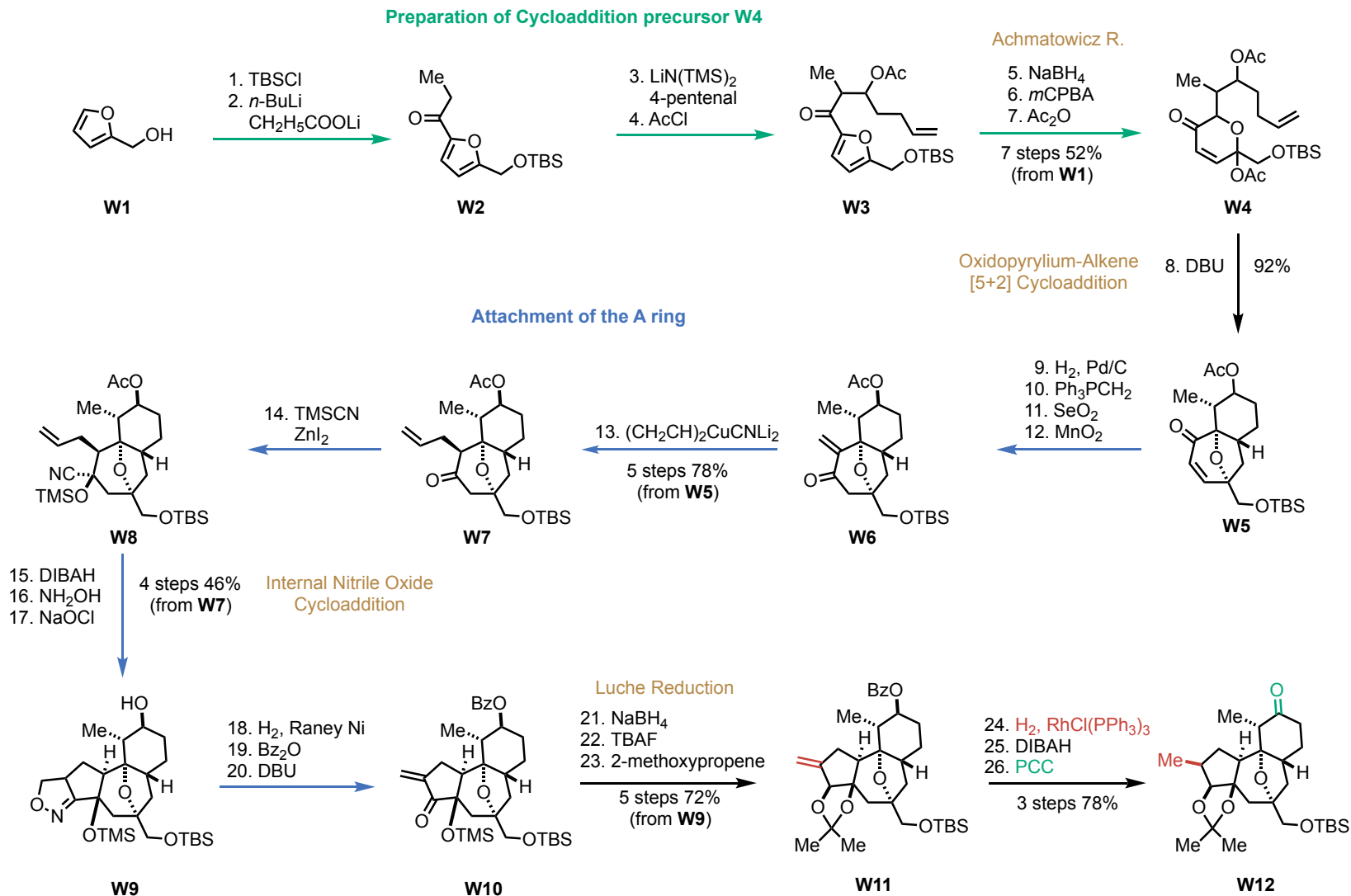
Oxidopyrylium-Alkene [5+2] Cycloaddition



1,3-Dipolar Internal Nitride Oxide Cycloaddition

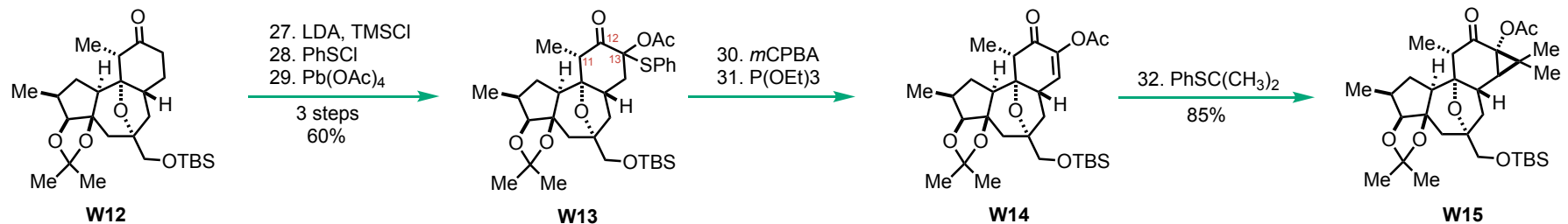


Wender's racemic total synthesis 1989

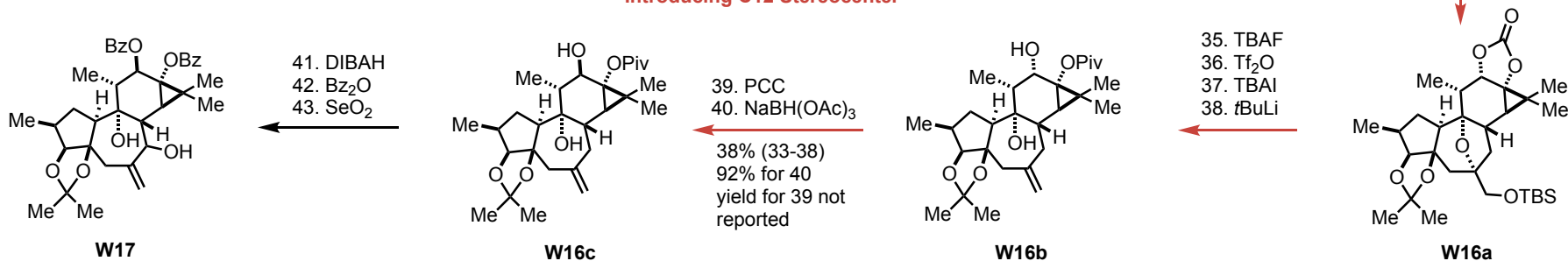


Wender's racemic total synthesis 1989

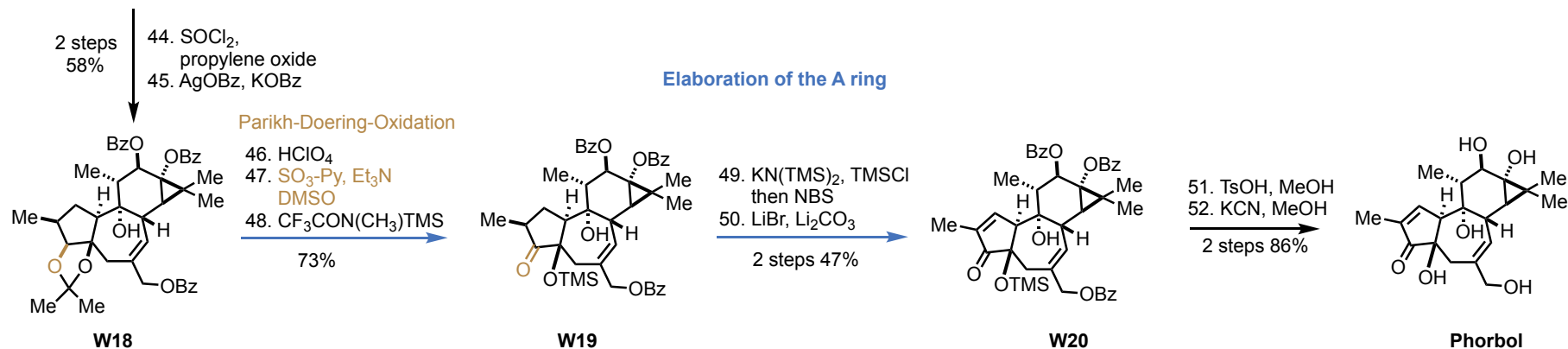
Attachment of D ring functionality



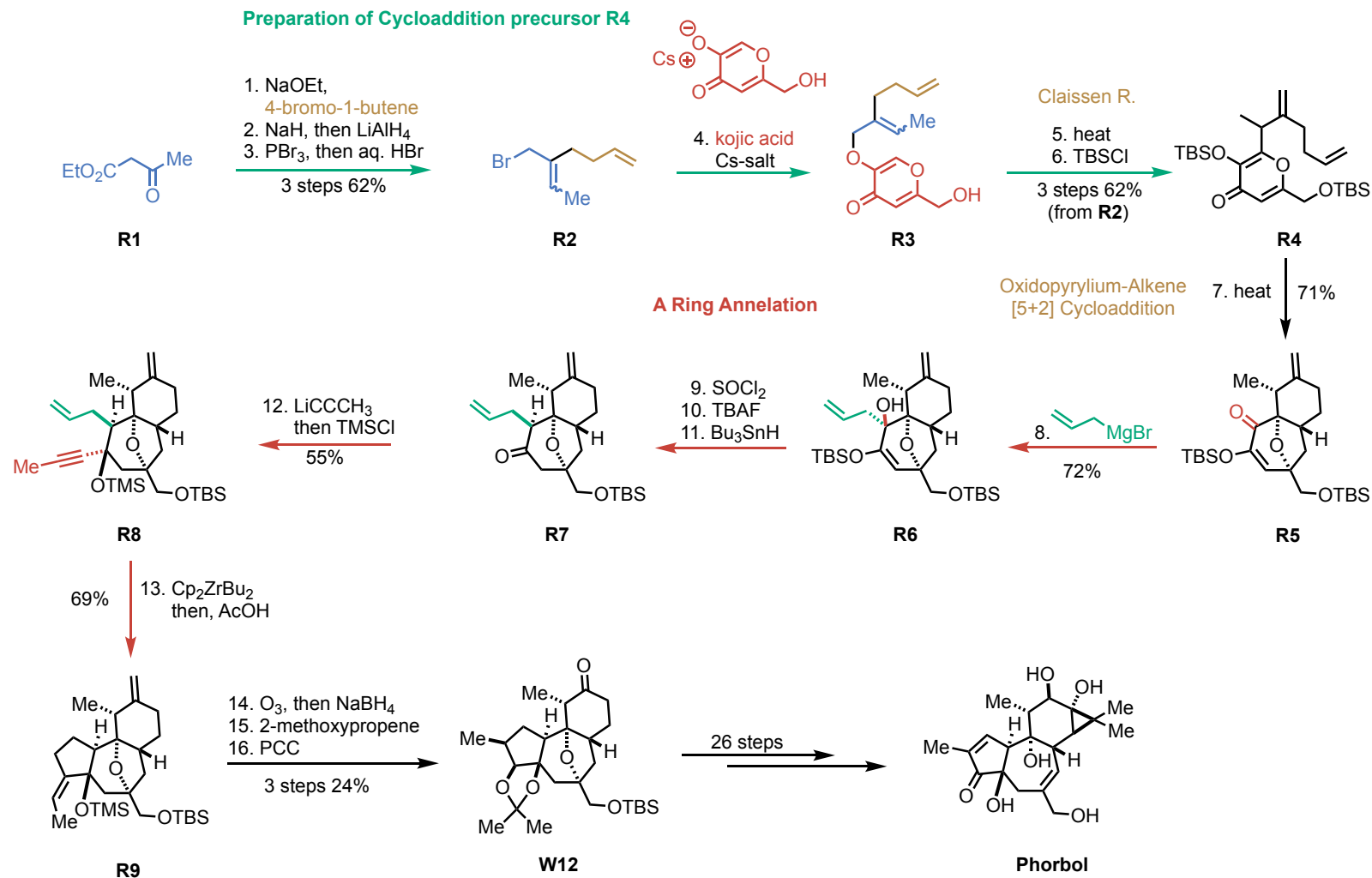
Introducing C12 Stereocenter



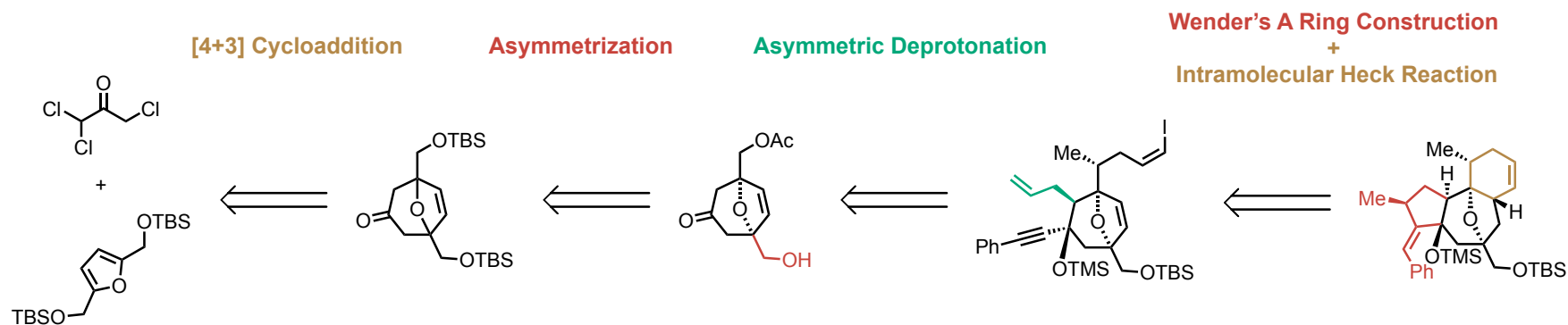
Elaboration of the A ring



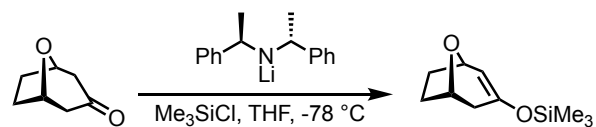
Wender's racemic formal synthesis 1990



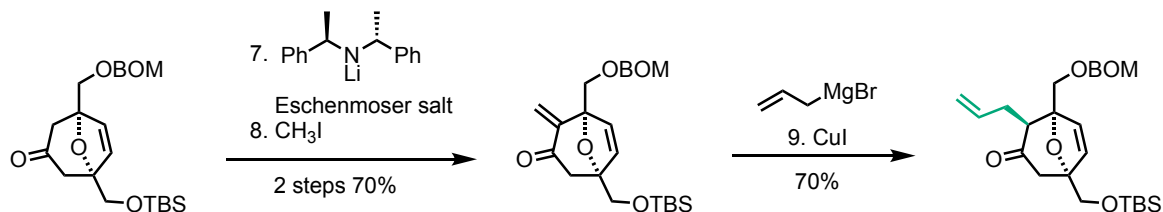
Cha's asymmetric formal synthesis 2001



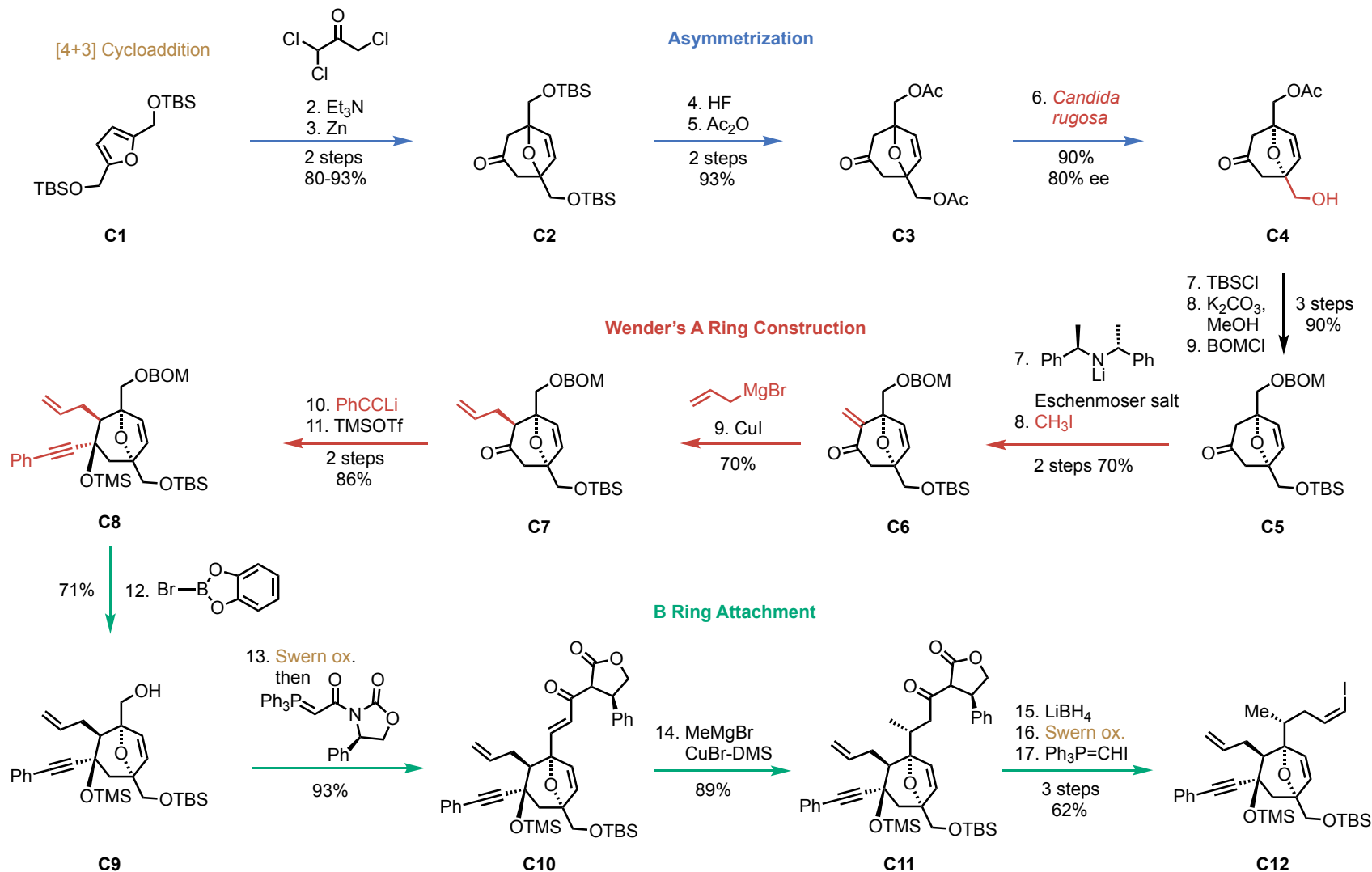
Asymmetric Deprotonation of Cyclic Ketones



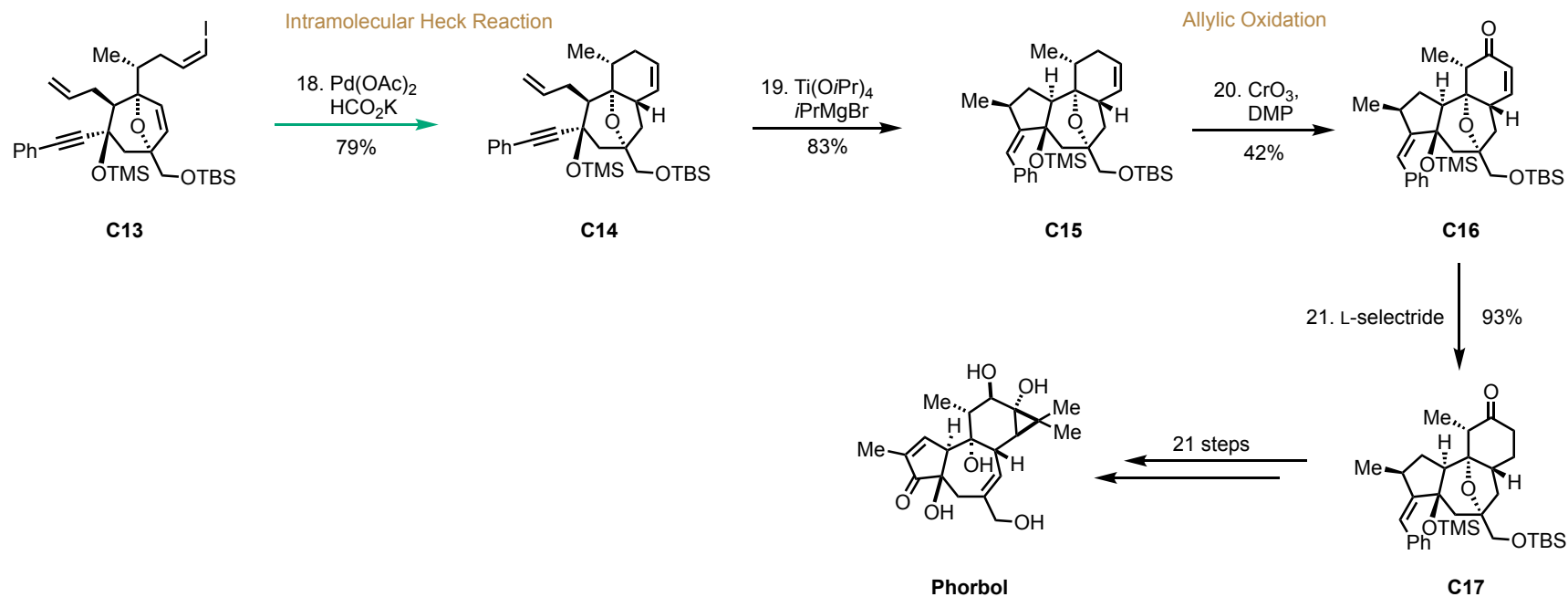
Introduction of the allyl group to a nonracemic and pseudosymmetric Ketone



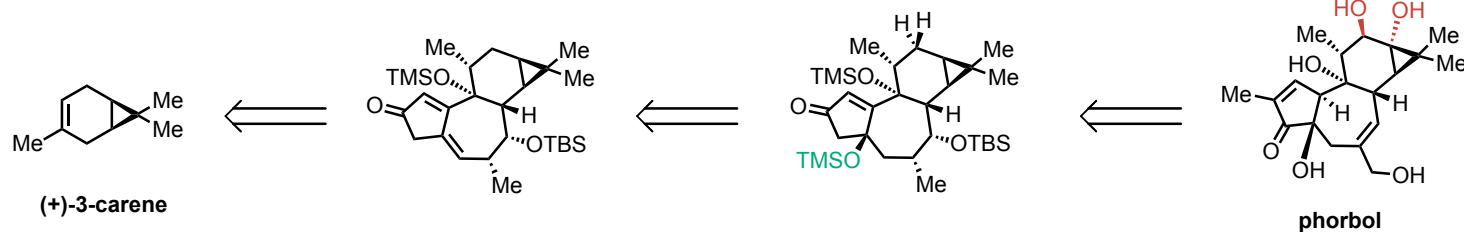
Cha's asymmetric formal synthesis 2001



Cha's asymmetric formal synthesis 2001

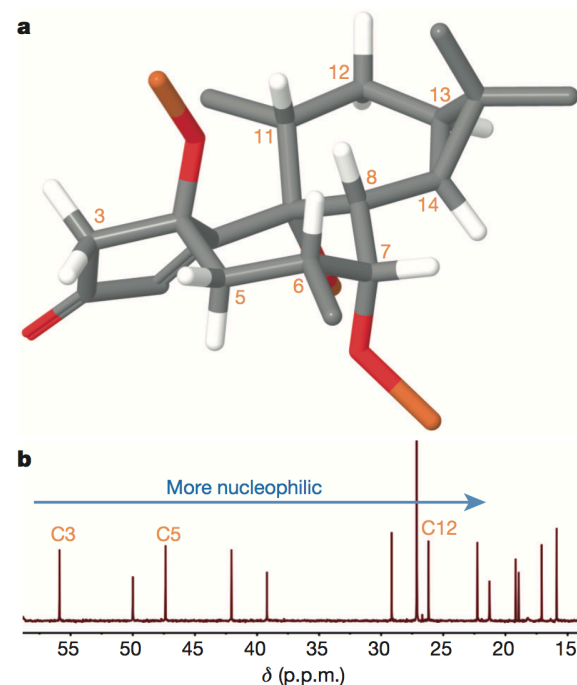


Barans's total synthesis 2016

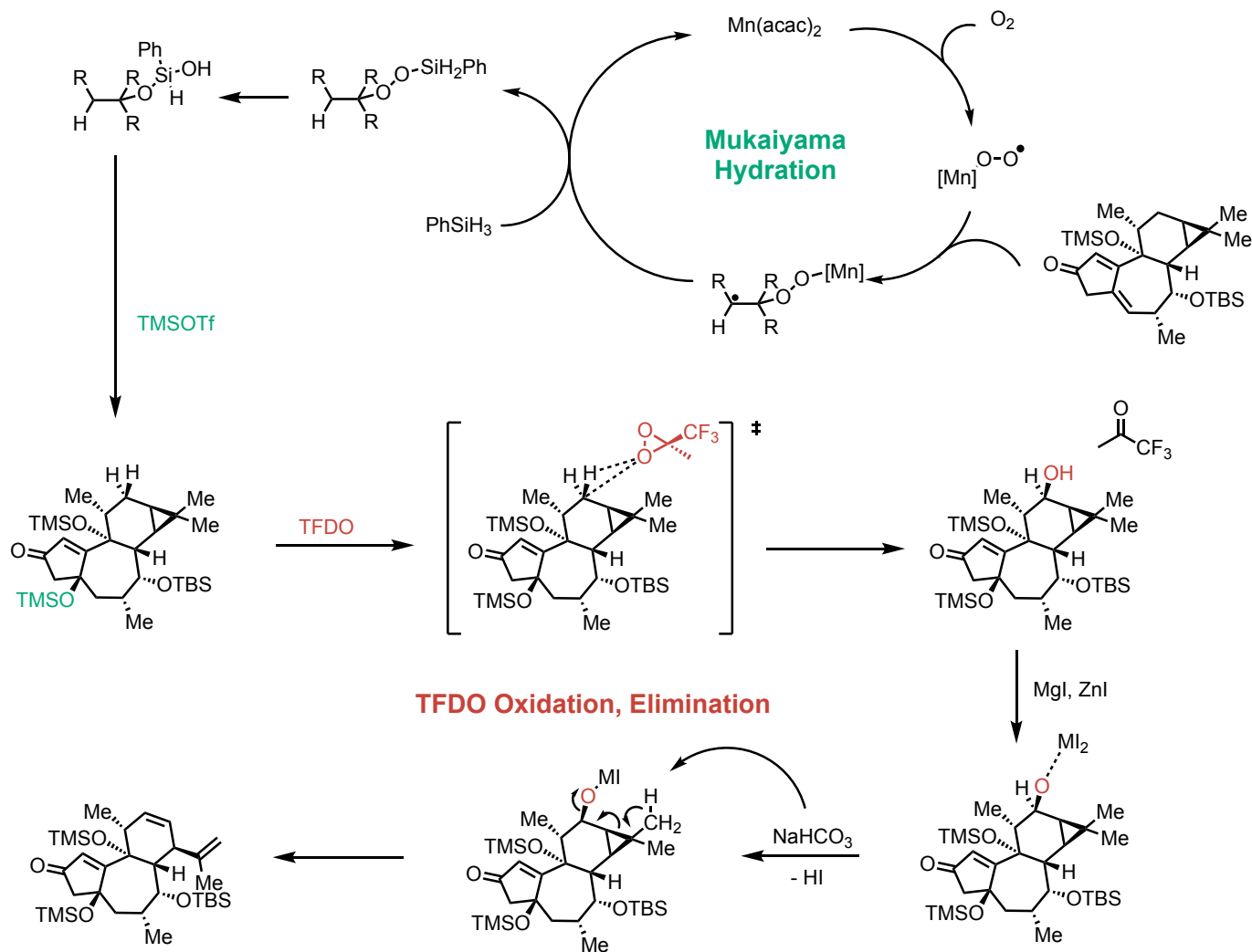


Installation of C12: Proper oxidant analyzed computationally and inference of innate reactivity using NMR. Pseudo-equatorial C-H bond at C12 most reactive on following considerations:

- 1) steric shielded C6, C7, C8 and C11 positions
- 2) higher *s*-character of the tertiary cyclopropane C-H bonds (C13/C14) makes them difficult to oxidize
- 3) of the remaining carbon center ¹³C NMR indicates that C12 is the most nucleophilic
- 4) hyperconjugation from the π -like cyclopropane system should facilitate oxidation of the pseudo-equatorial C-H bond at C12
- 5) strain-release might accelerate such an oxidation

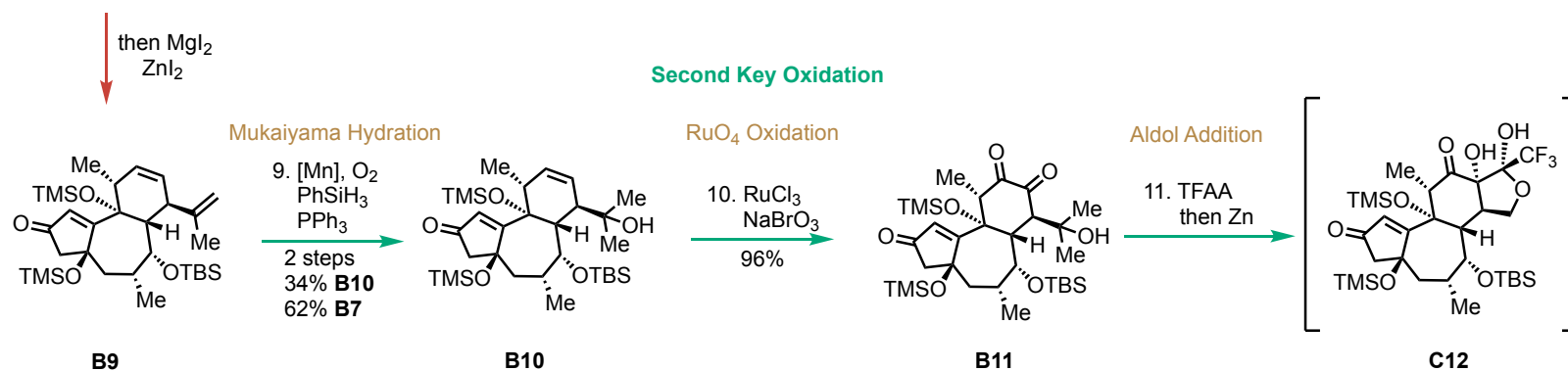
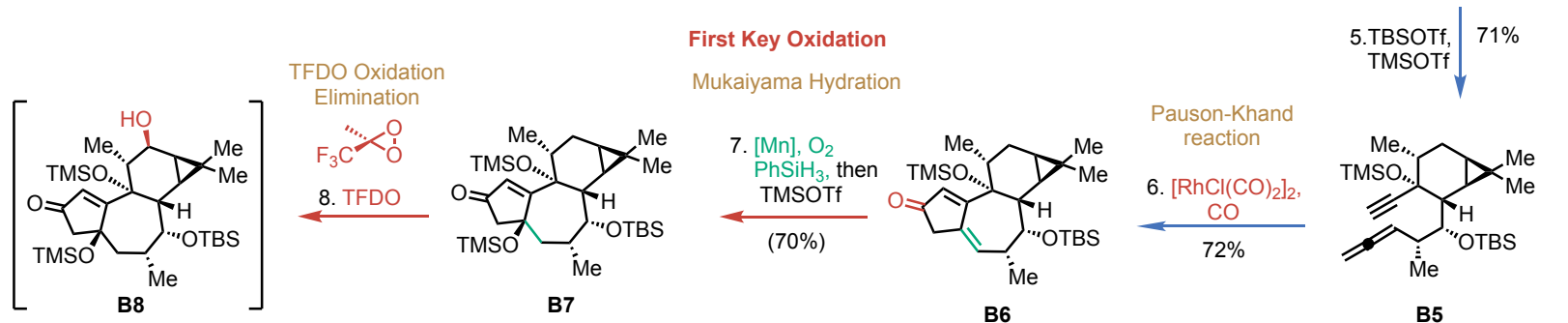
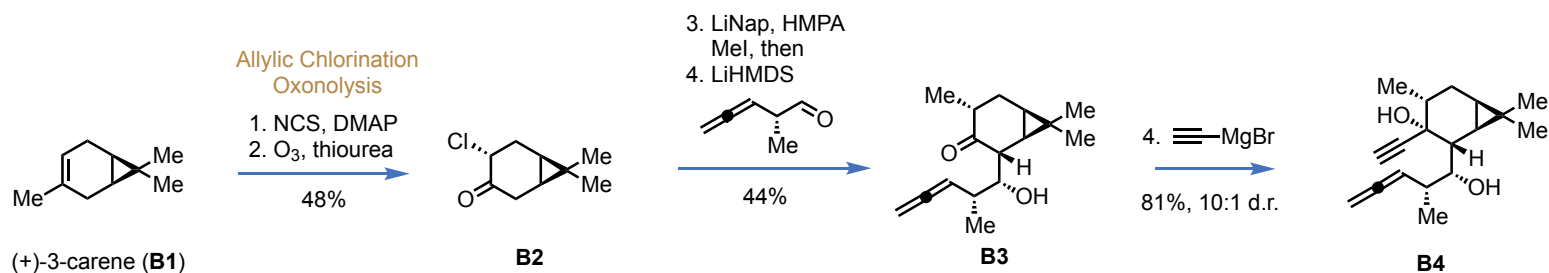


Installing C4 oxygen using Mukaiyama Hydration and *in situ* silyl group installation.



Barans's total synthesis 2016

Synthesis of Diene B6



Barans's total synthesis 2016

