Total Synthesis of Astellatol

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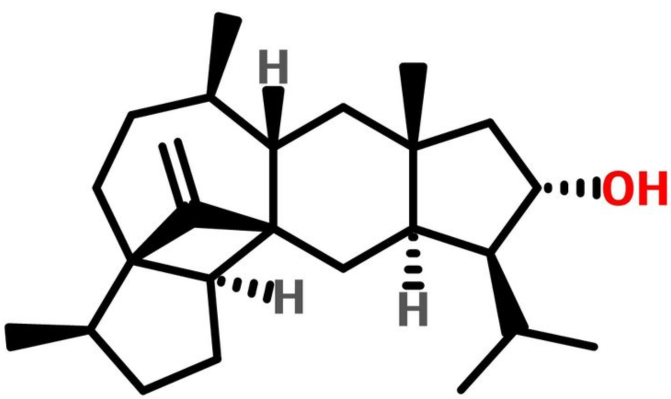
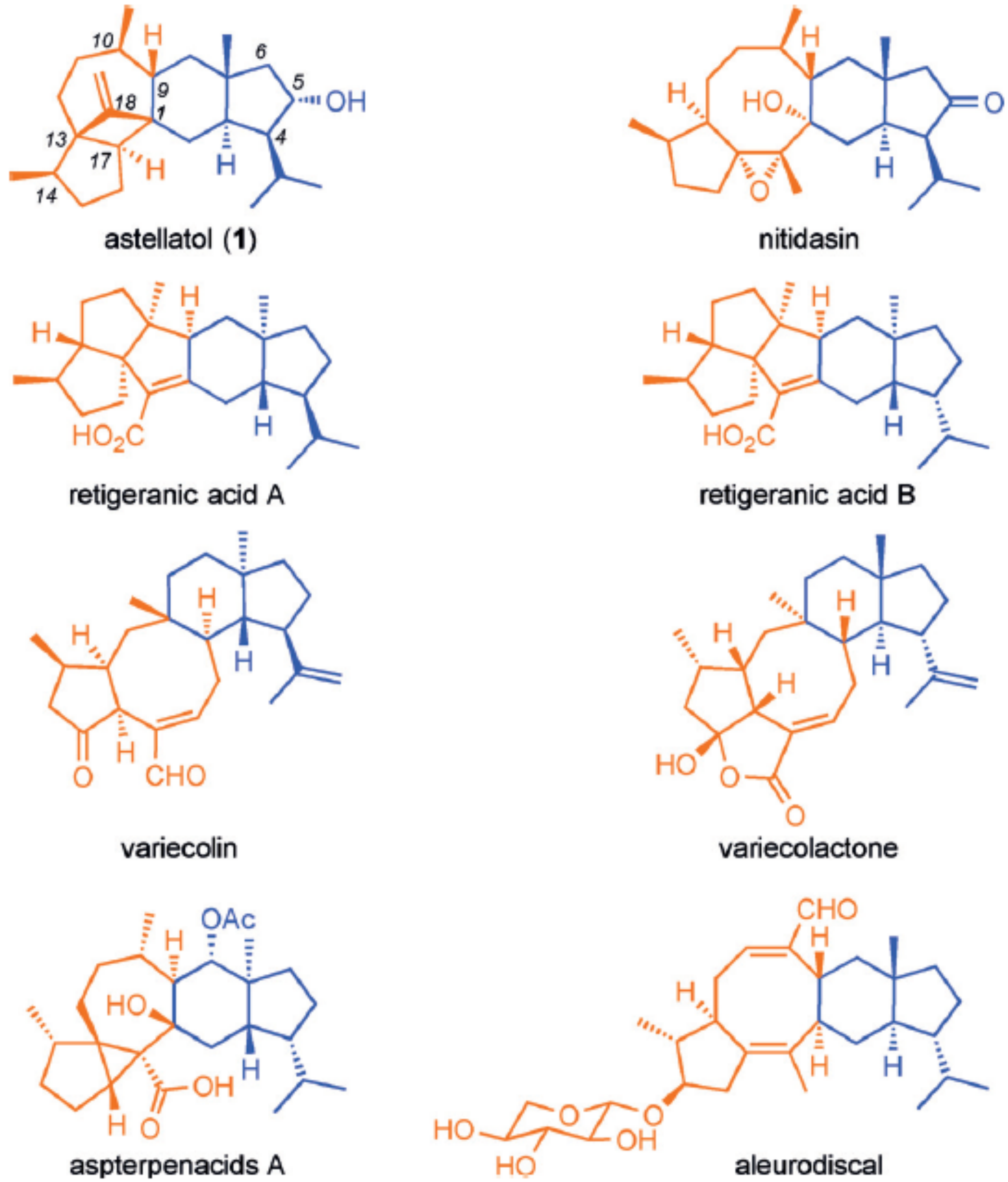
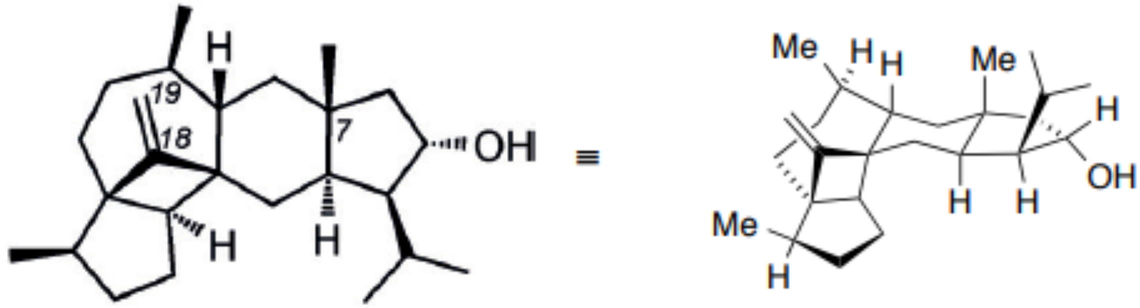
Prof. Wipf Research Group
University of Pittsburgh
Literature Seminar, April 14, 2018





Astellatol (**1**) and other structurally related isopropyl *trans*-hydrindane sesterterpenoids.

Zhao, Nan. et al. *Angew. Chem. Int. Ed.* . **2018**, *130*, 3444-3448.



- Isolated from fungus *Aspergillus variecolor* (syn. A. stellatus) in 1989

- Pentacyclic rare sesterterpenoid

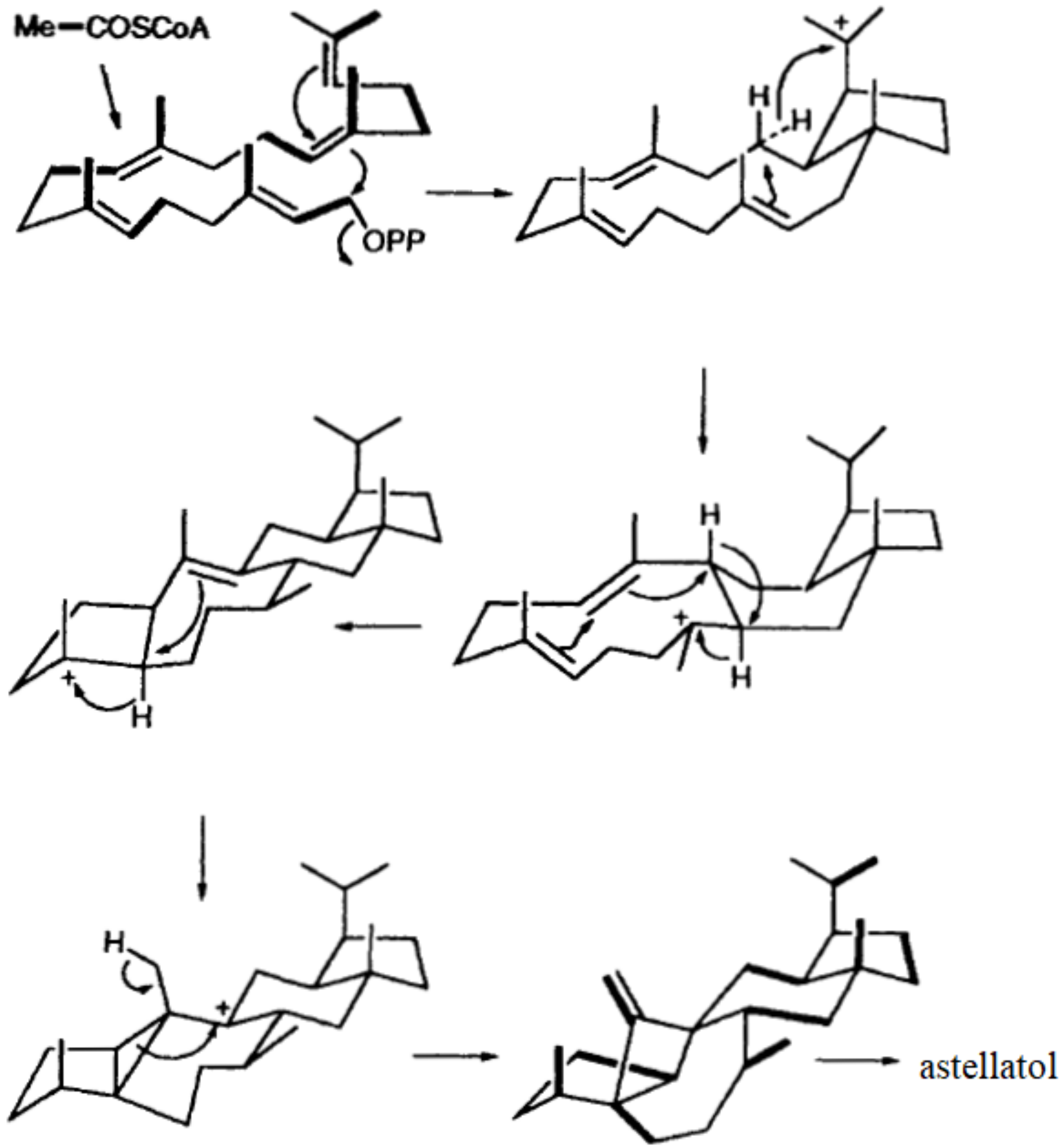
- Unique bicyclo[4.1.1]octane motif, ten stereocenters

- Cyclobutane that contains two quaternary centers, an exo-methylene group

- Sterically encumbered isopropyl trans-hydrindane motif

Zhao, Nan. et al. *Angew. Chem. Int. Ed.* . **2018**, *130*, 3444-3448.

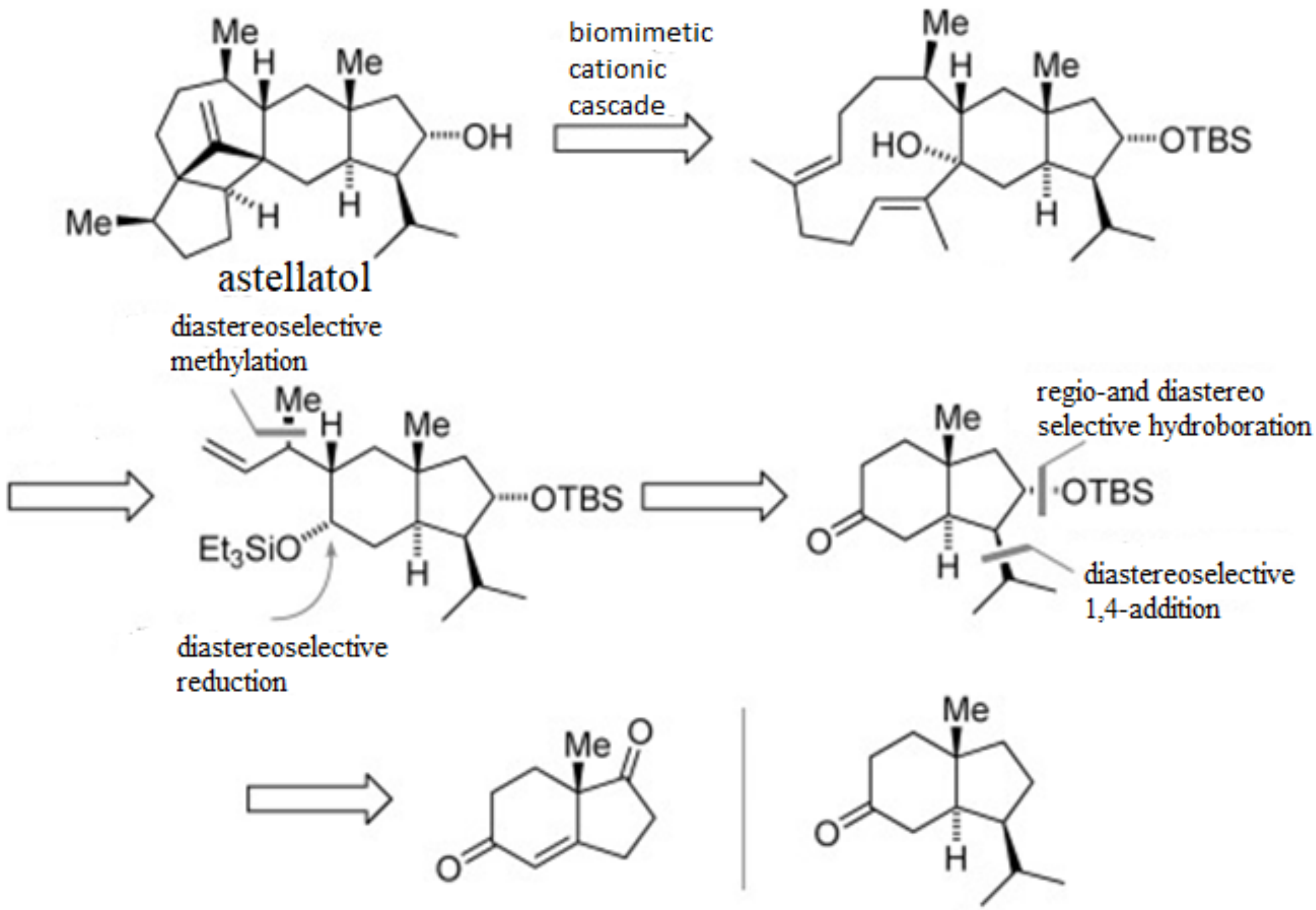
Biosynthetic pathway of astellatol



Simpson, T. J. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3055-3056.

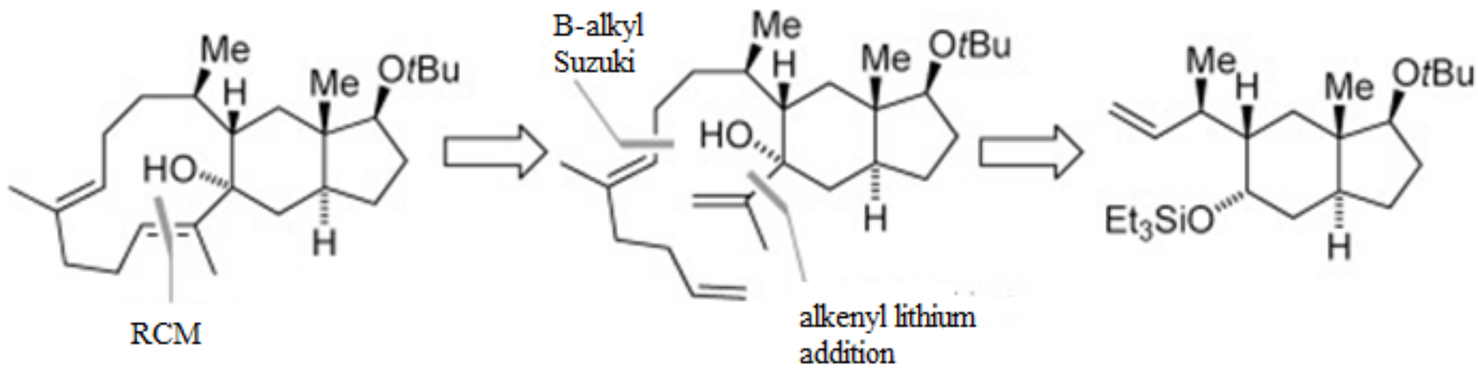
Progress toward the synthesis of astellatol

Retrosynthesis of astellatol based on a biomimetic cacade

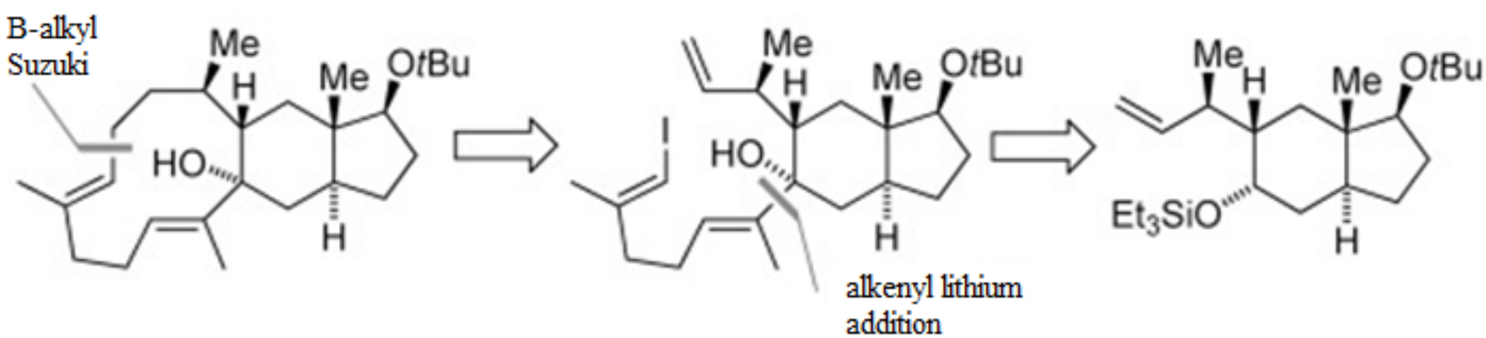


Hog. T. D. et al. *Chem. Eur. J.* . **2015**, *21*, 13646-13665.

Retrosynthesis of macrocycle involving a RCM

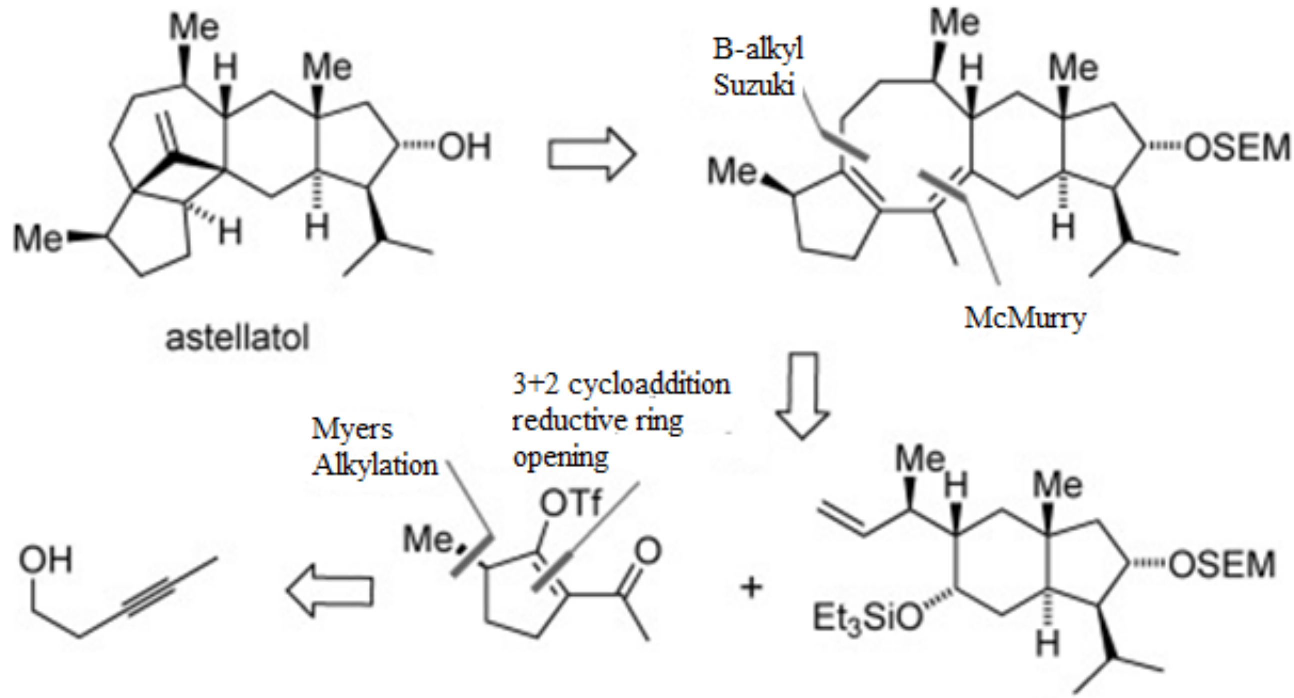


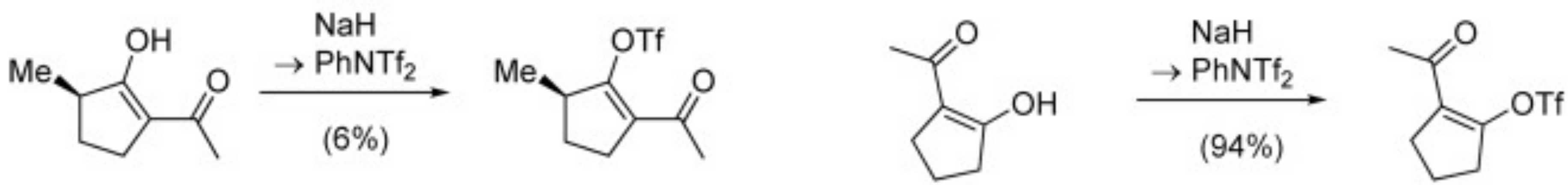
Retrosynthesis of macrocycle with a B-alkyl Suzuki coupling



Hog. T. D. et al. *Chem. Eur. J.* . **2015**, *21*, 13646-13665.

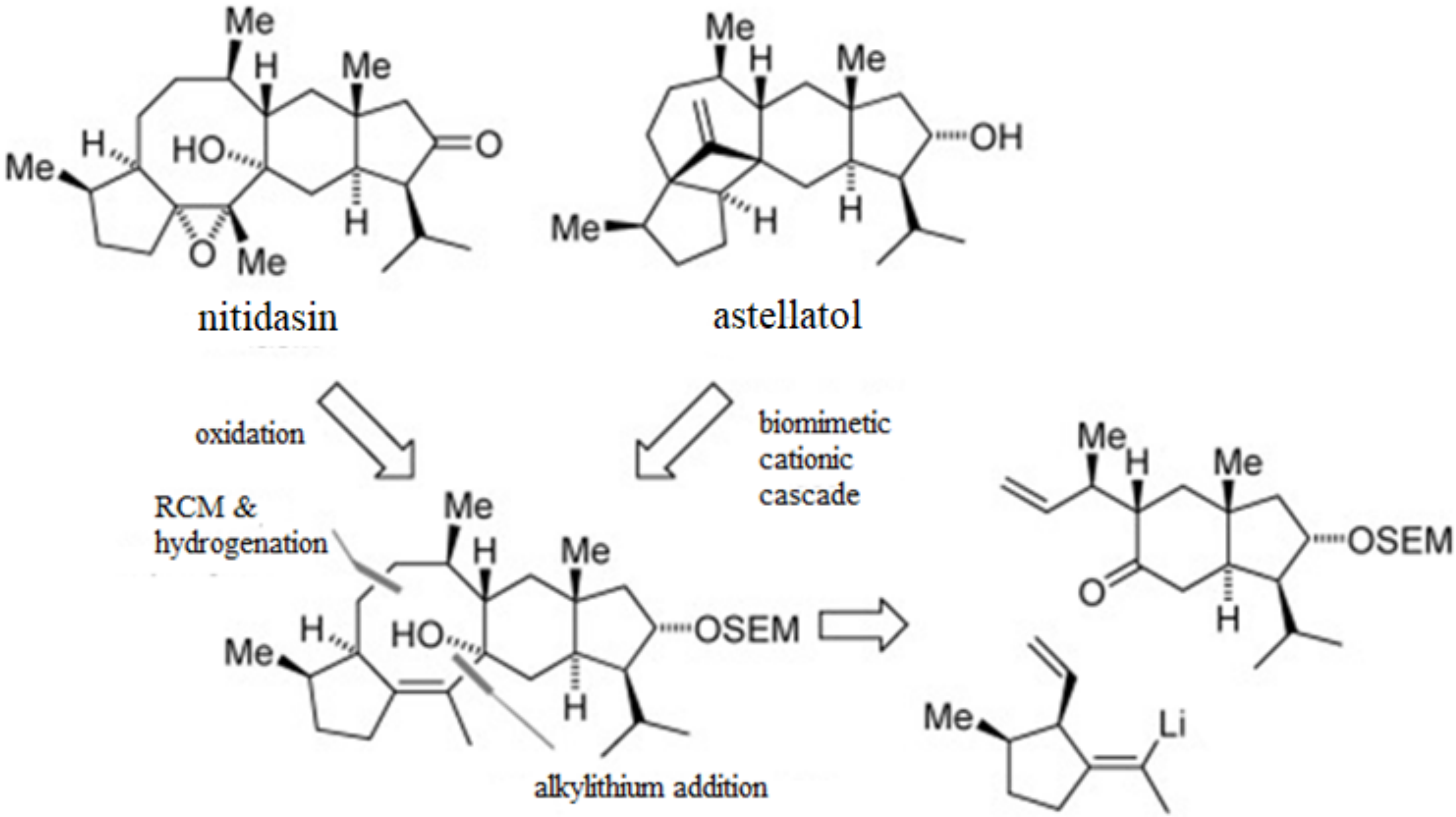
Second-generation retrosynthetic analysis of astellatol: diene as precursor for the biomimetic cationic cascade





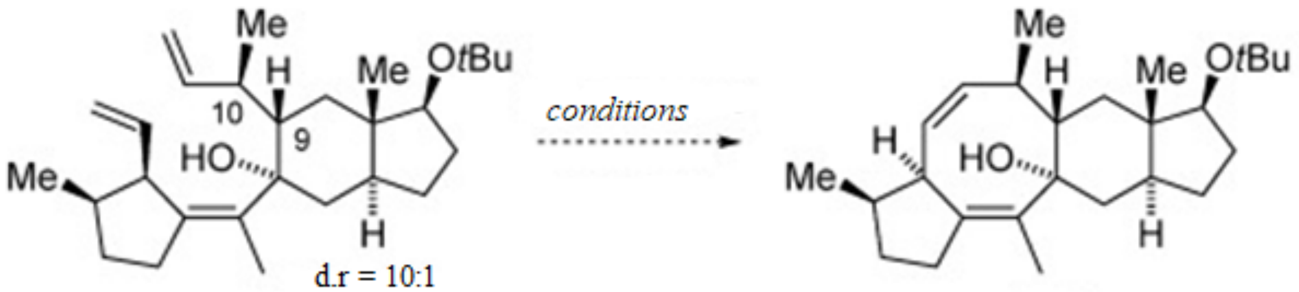
Hog. T. D. et al. *Chem. Eur. J.* . **2015**, *21*, 13646-13665.

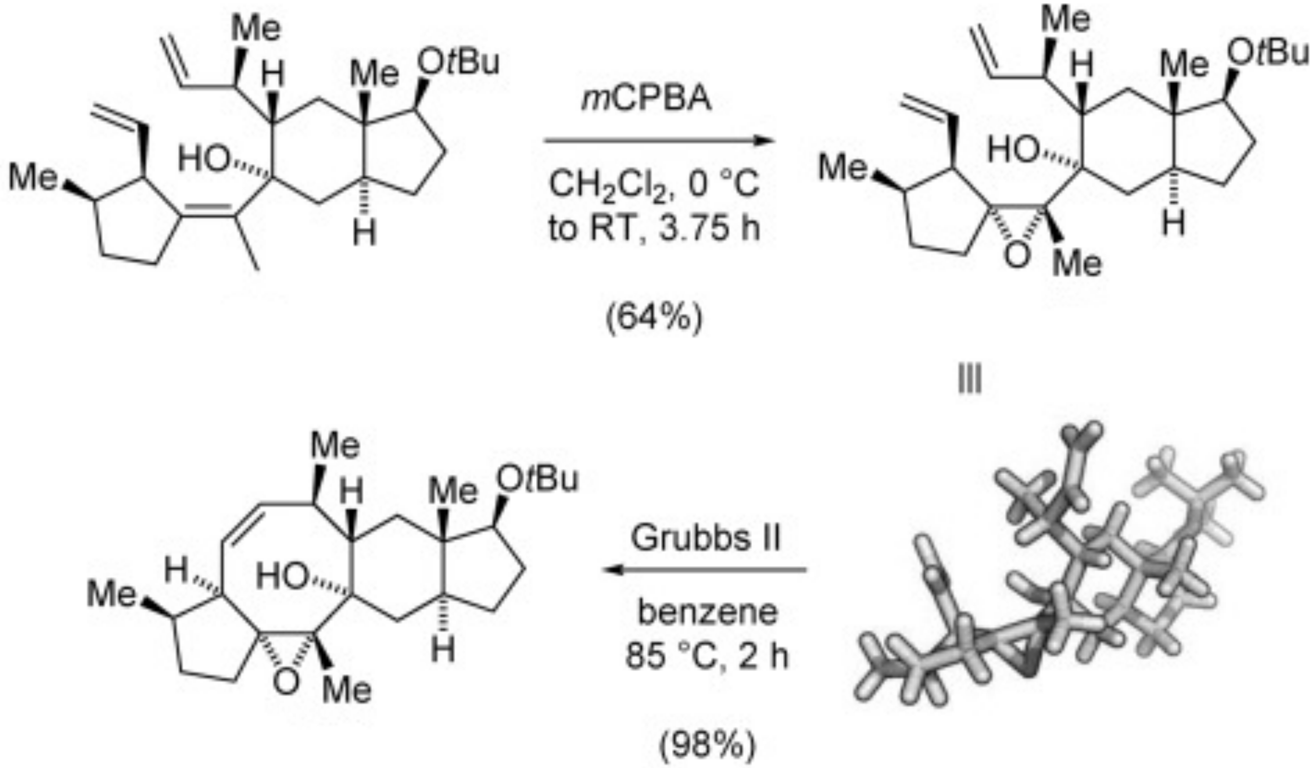
Third-generation retrosynthesis: Convergent access to tetracycle as precursor for astellatol and nitidasin



Hog. T. D. et al. *Chem. Eur. J.* . **2015**, *21*, 13646-13665.

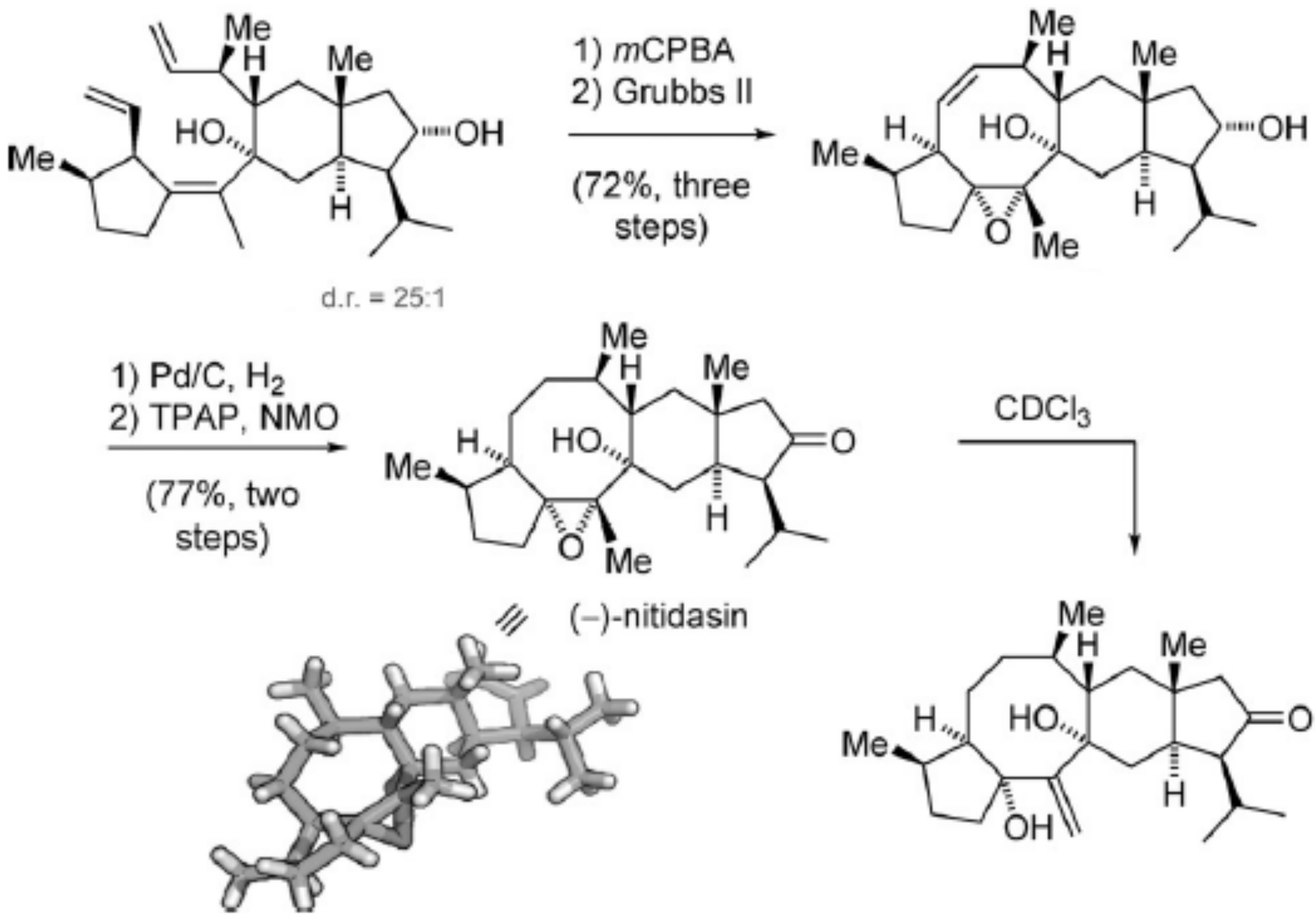
Model studies





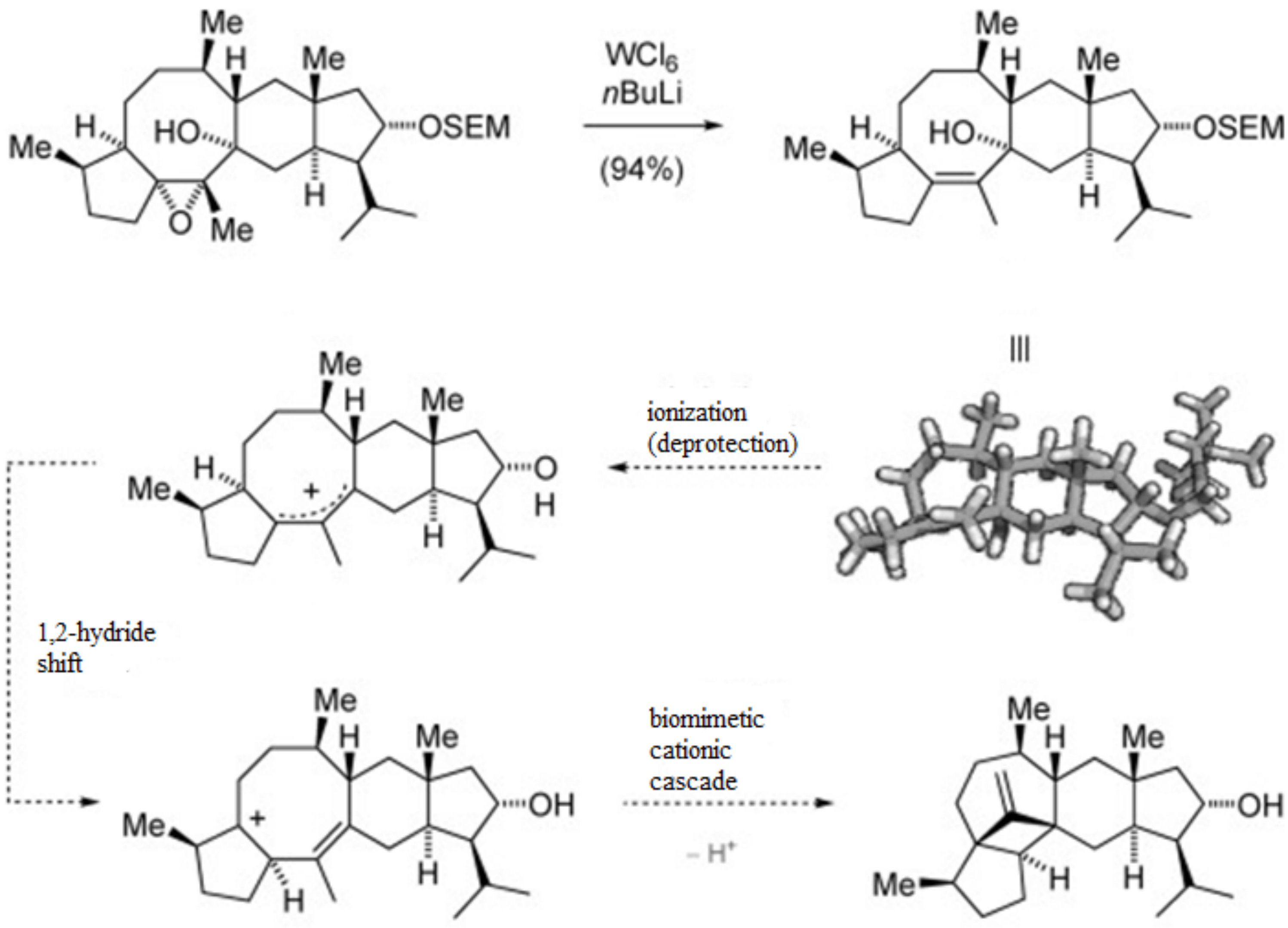
Hog. T. D. et al. *Chem. Eur. J.* . **2015**, *21*, 13646-13665.

Total synthesis of (−)-nitidasin



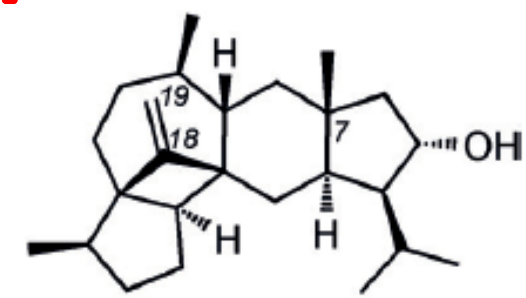
Hog. T. D. et al. *Chem. Eur. J.* . **2015**, *21*, 13646-13665.

Deoxygenation of epoxide and proposed pathway for the investigated biomimetic cationic cascade toward astellatol



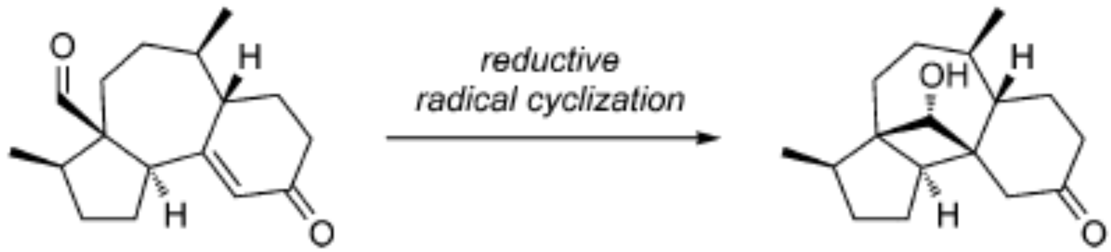
astellatol

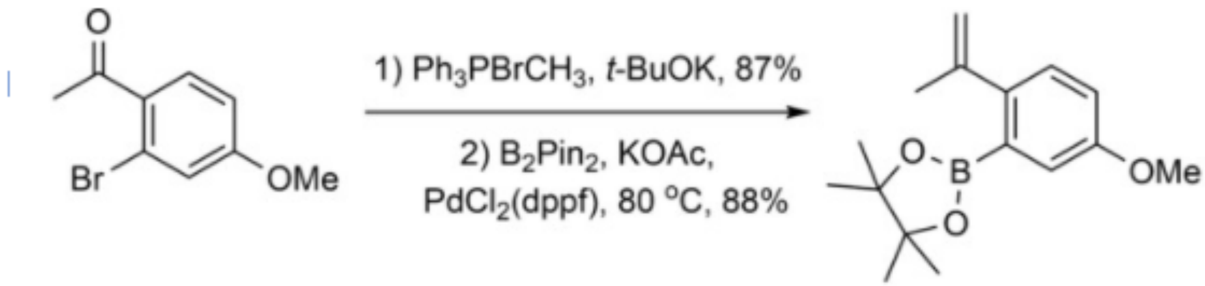
Concise synthesis of astellatol core skeleton

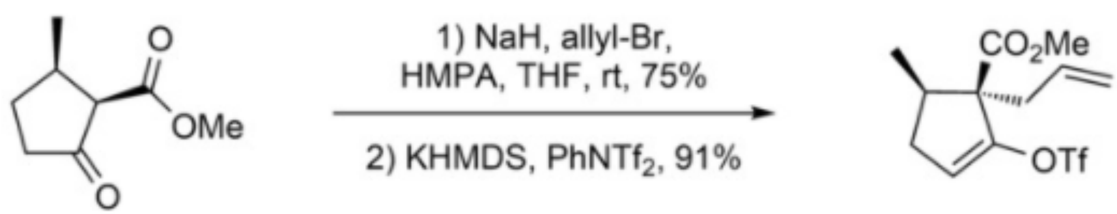


Astellatol, 1

Key strategic design

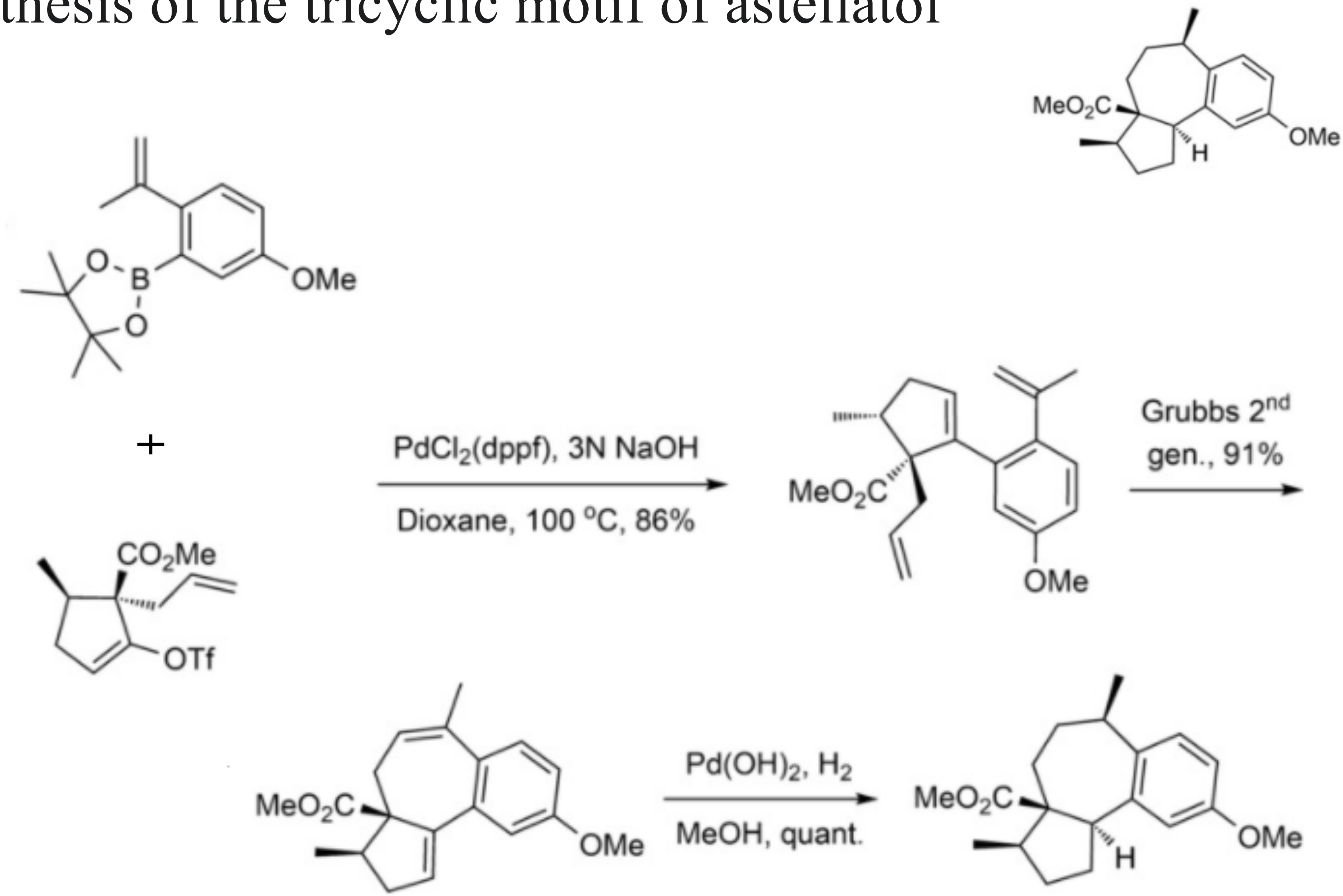






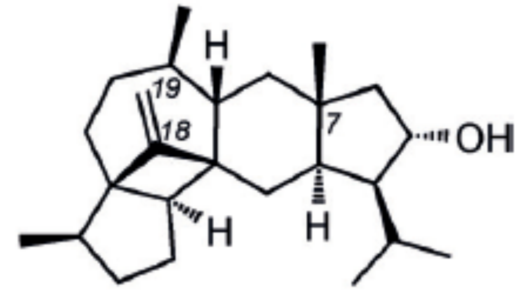
Zhao, N. et al. *Chem. Eur. J.* . **2016**, *22*, 12634-12636.

Synthesis of the tricyclic motif of astellatol

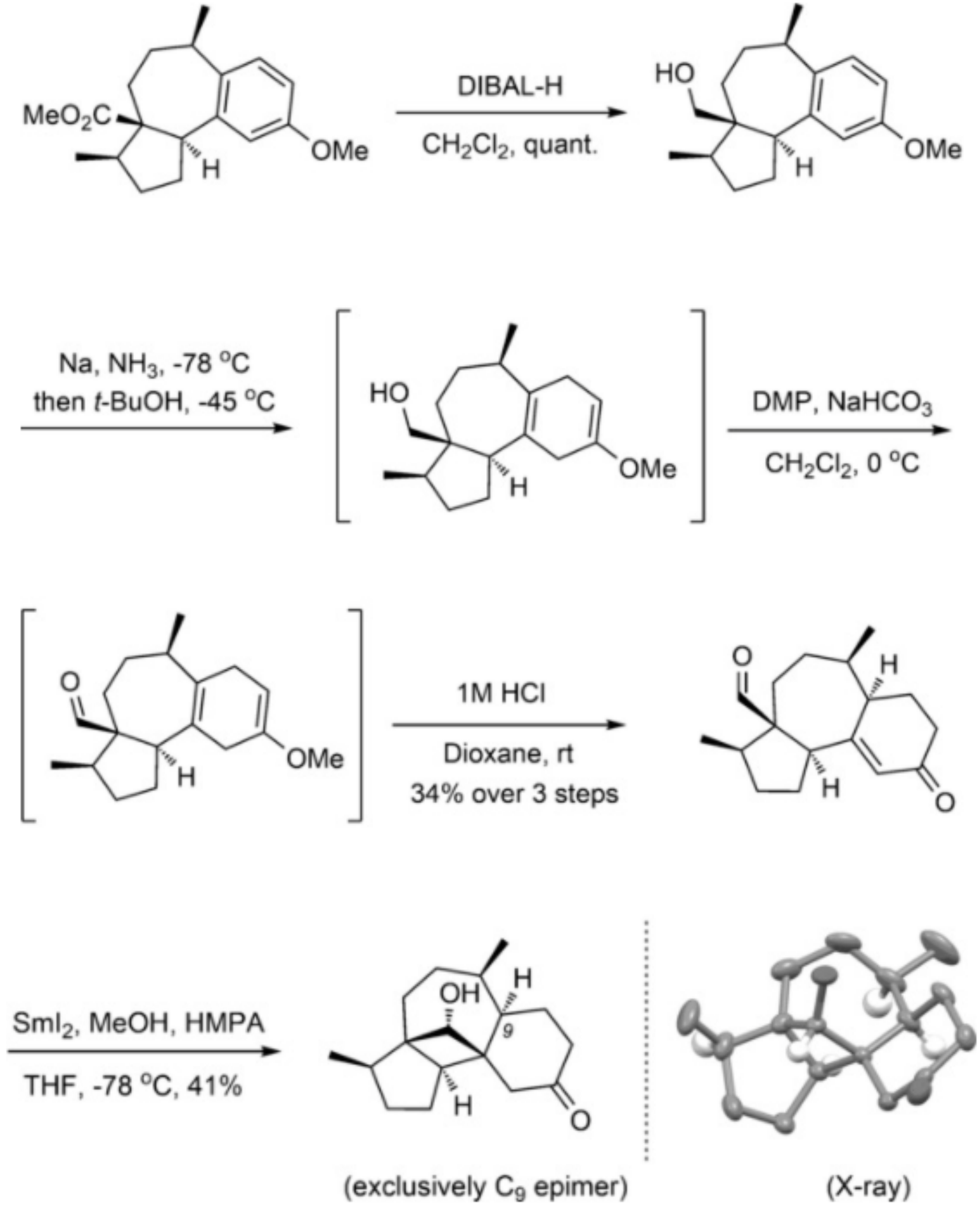


Zhao, N. et al. *Chem. Eur. J.* . **2016**, *22*, 12634-12636.

Synthesis of the astellatol core skeleton

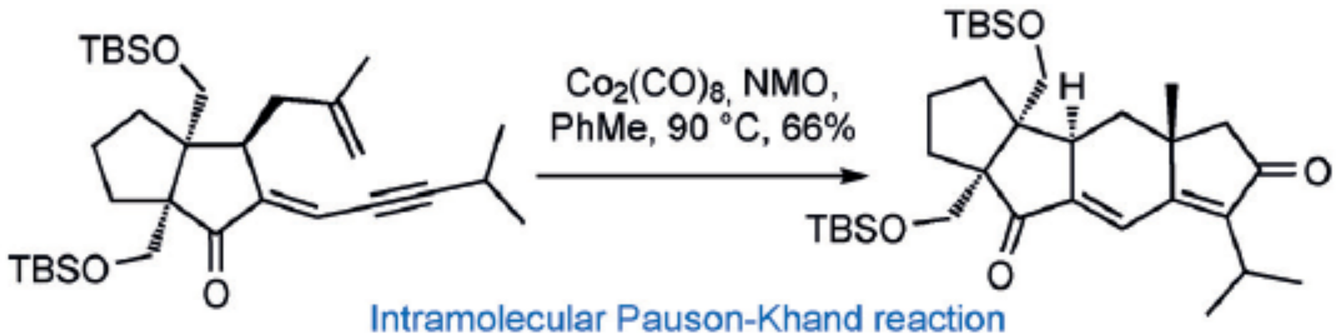


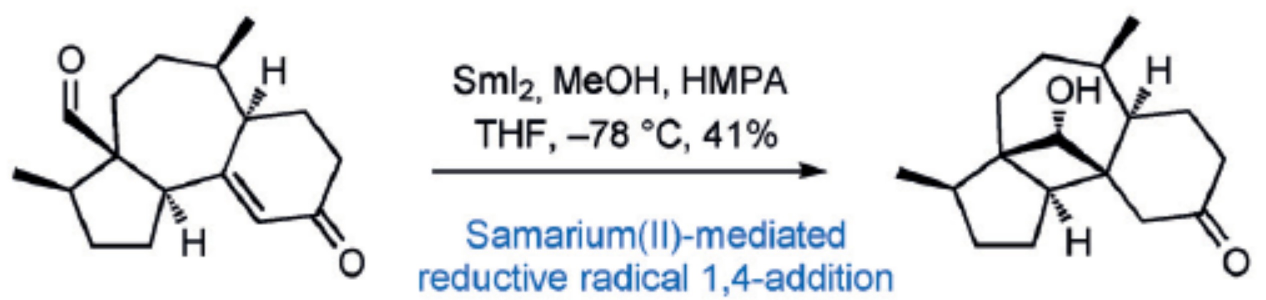
Astellatol, 1



Total synthesis of astellatol

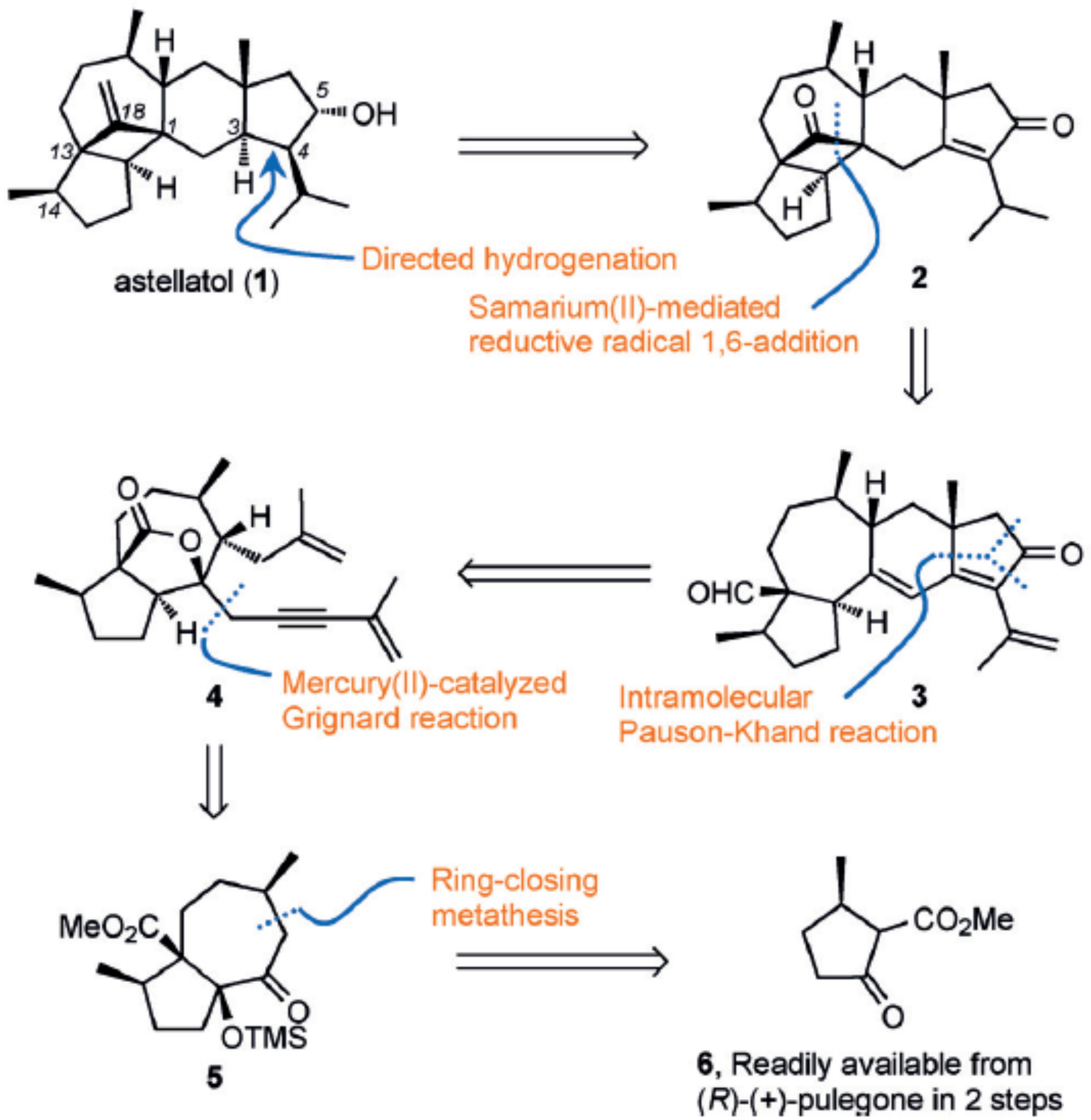
Key inspirations for the synthesis of astellatol





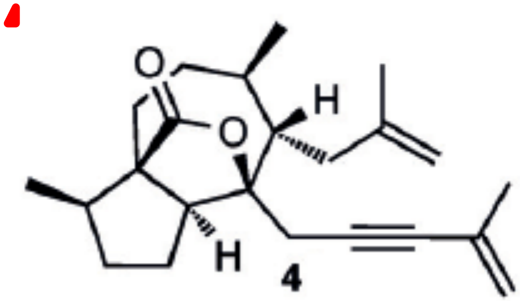
Zhao, N. et al. *Angew. Chem. Int. Ed.* **2018**, *130*, 3444-3448.

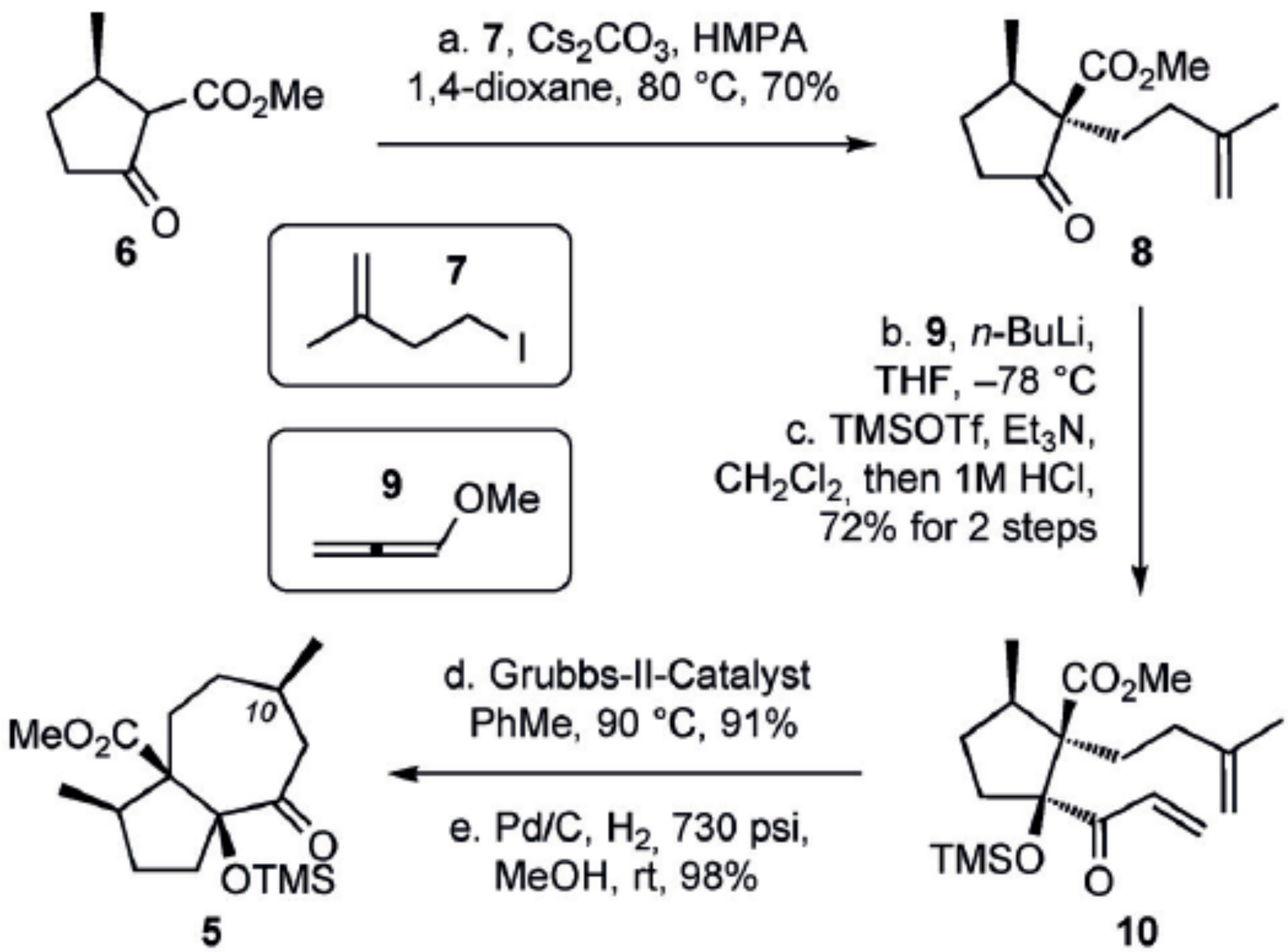
Retrosynthetic analysis of astellatol



Zhao, N. et al. *Angew. Chem. Int. Ed.* **2018**, *130*, 3444-3448.

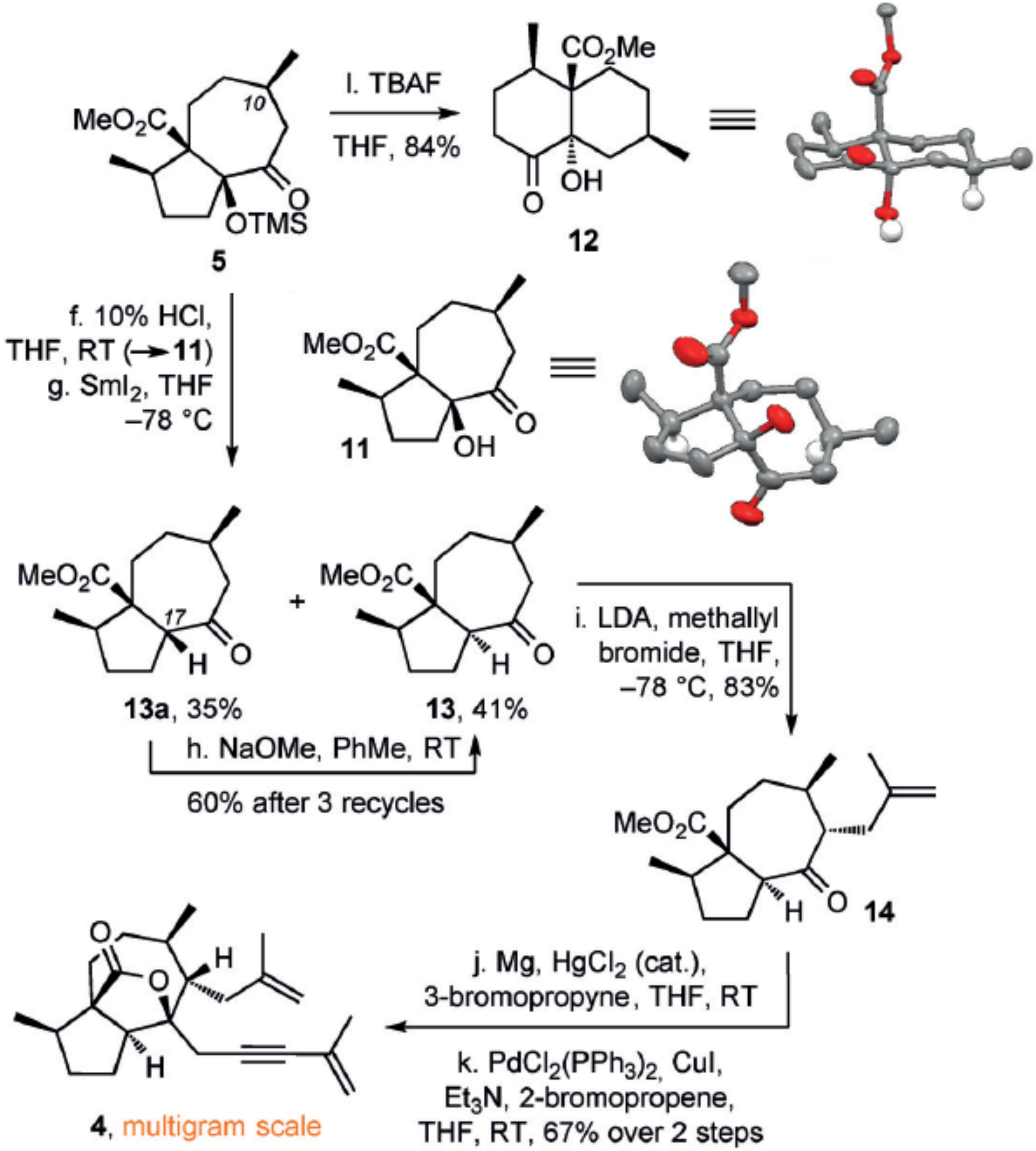
Synthesis of the PKR precursor **4**

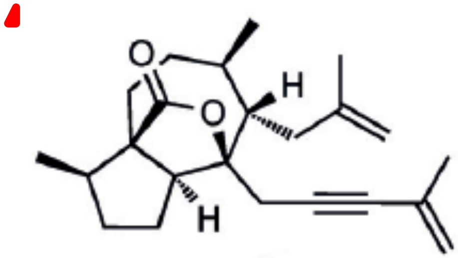




Zhao, N. et al. *Angew. Chem. Int. Ed.* **2018**, *130*, 3444-3448.

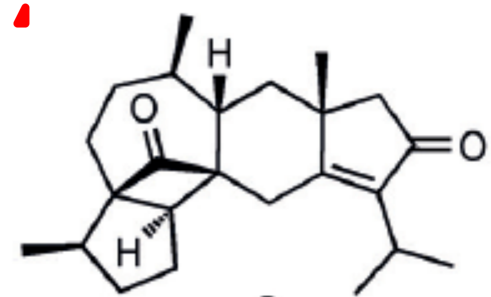
Synthesis of the PKR precursor **4** cont'd

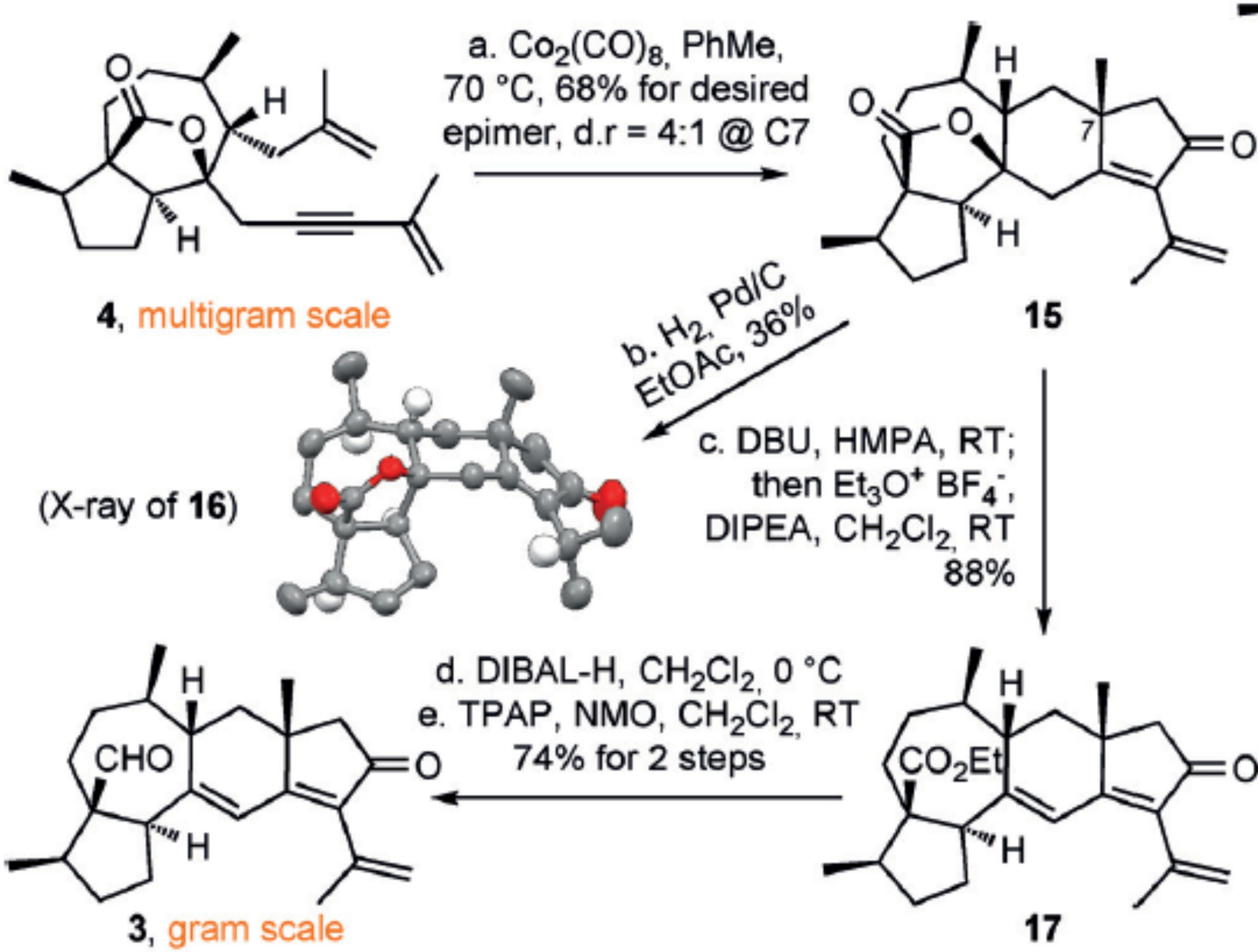




4

Synthesis of diketone **2**





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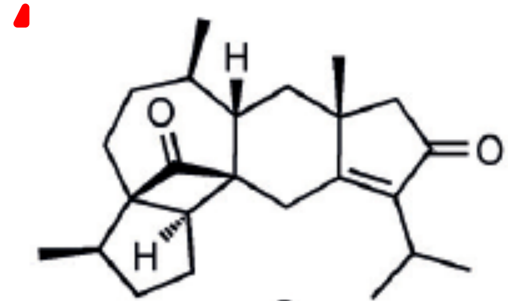
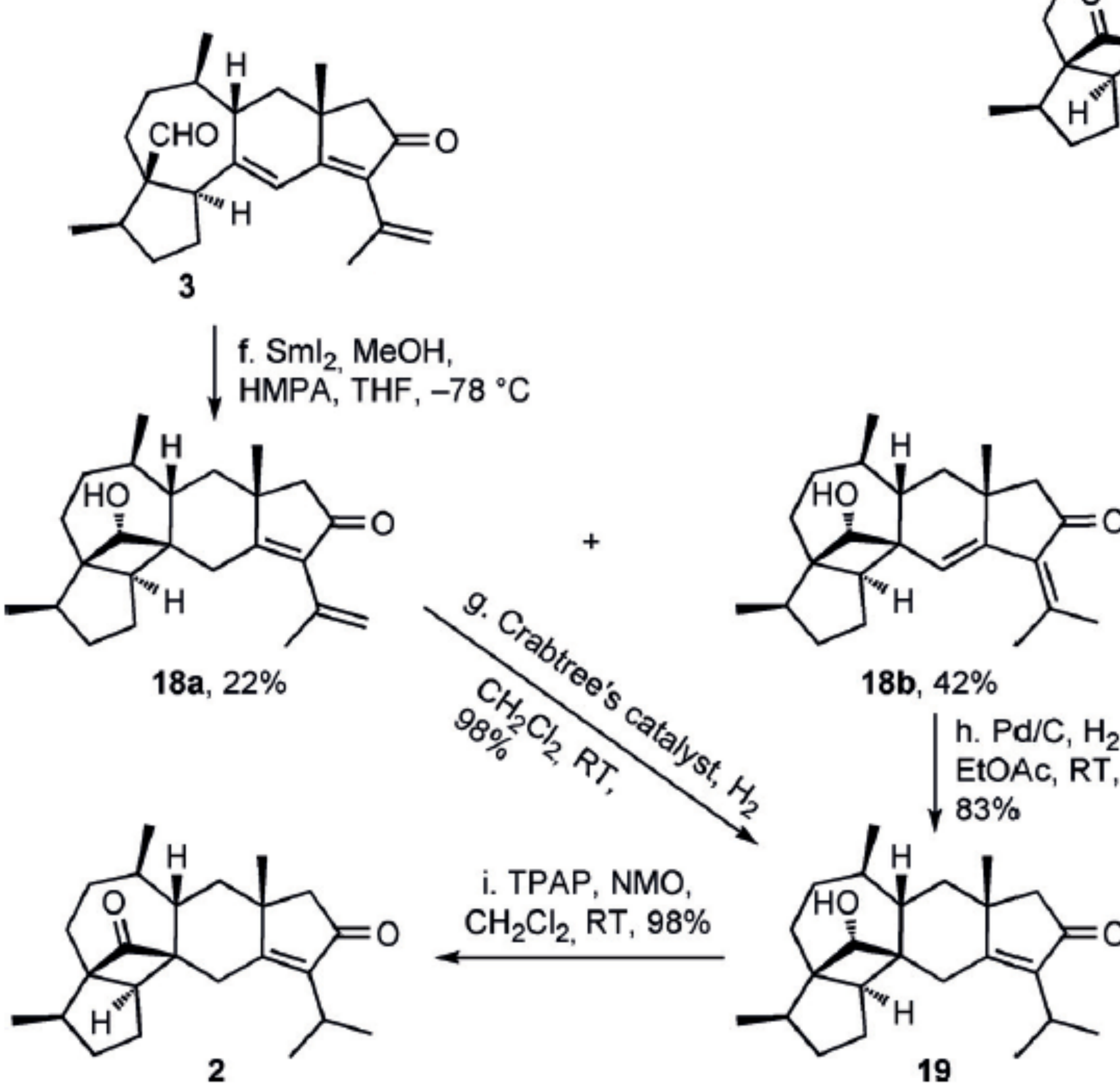
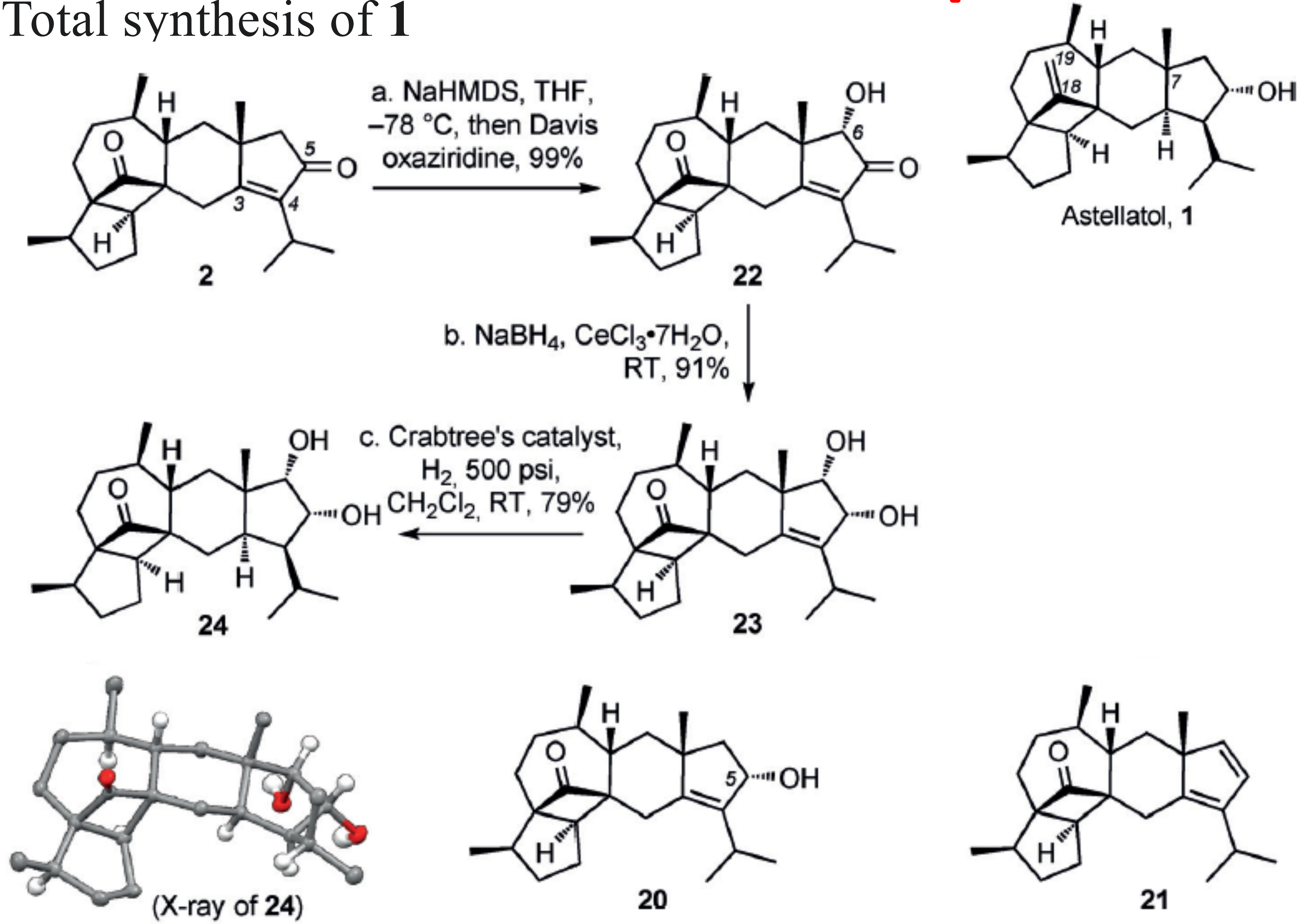
Synthesis of diketone **2** cont'd



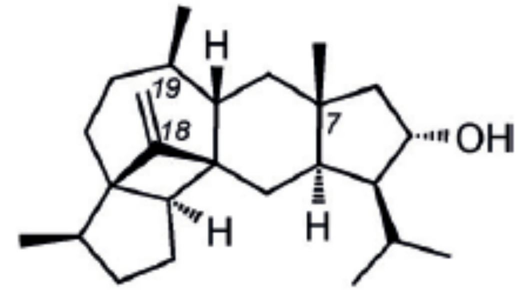
2



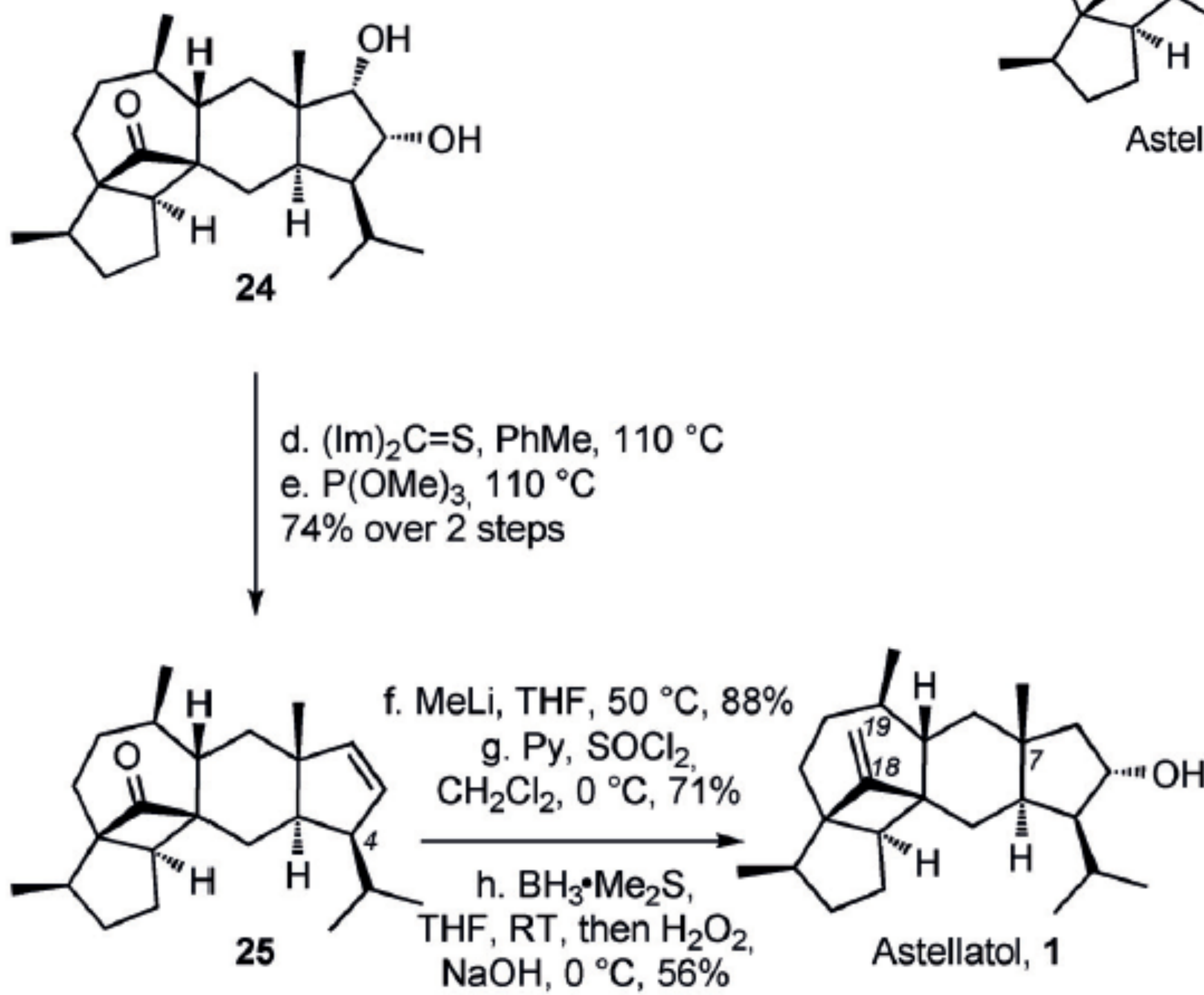
Total synthesis of **1**



Total synthesis of **1** cont’d



Astellatol, **1**



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Conclusion

- First enantioselective total synthesis of astellatol
- In 25 steps, 0.63% overall yield
- Introduction of silyl protecting group
- Intramolecular PKR, provided right-side carbon scaffold
- SmI_2- mediated reductive radical 1,6-addition
- Strategic introduction of hydroxy group for *trans*-hydrindane synthesis

Thank you
Prof. Peter Wipf

Thanks to Prof. Wipf Research Group