Literature Report 11

Total Synthesis of Aspergilline A and Tetrapetalone A

Reporter: Guang-Shou Feng
Checker: Lei Shi
Date: 2018-01-22

Wood, J. L. *et al.*
J. Am. Chem. Soc. **2017**, *139*, 14901.
J. Am. Chem. Soc. **2017**, *139*, 18504.

CV of J. L. Wood

Education:

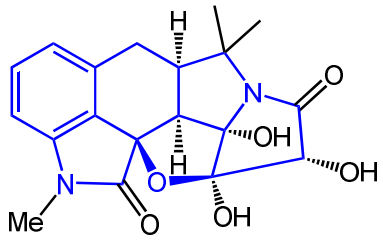
- 1980–1985 B.A., University of Colorado, Boulder;
- 1985–1991 Ph.D., University of Pennsylvania, Philadelphia;
- 1991–1993 Postdoc.,Harvard University;
- 1993–1997 Assistant Professor of Chemistry, Yale University;
- 1997–1998 Associate Professor of Chemistry, Yale university;
- 1998–2006 Professor of Chemistry, Yale University;
- 2006–2013 Professor of Chemistry, Colorado State University;
- 2013-Now Distinguished Professor, Baylor University.

Interests:

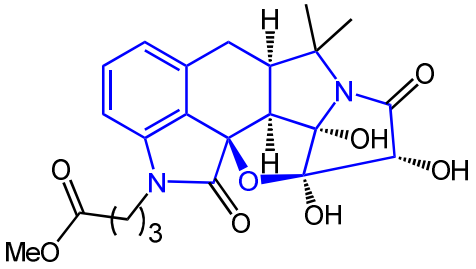
Total Synthesis of Natural Product.

Contents

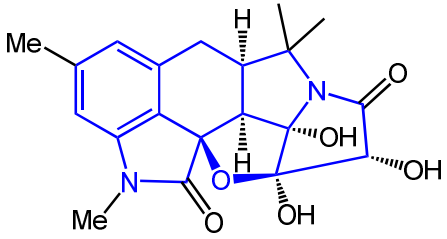
Introduction



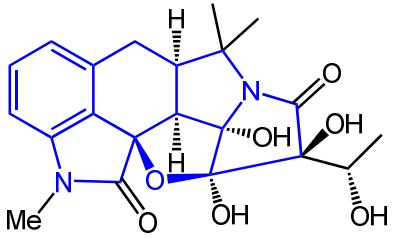
Aspergilline A



Aspergilline B



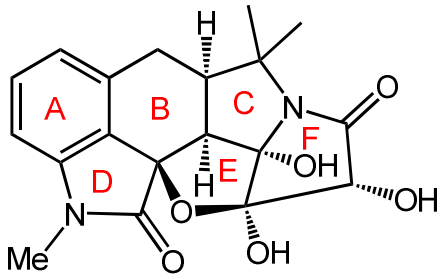
Aspergilline C



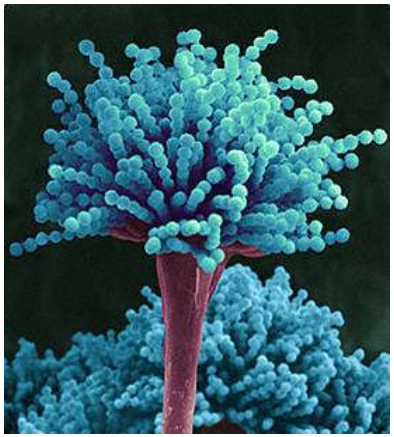
Aspergilline D

Hu, Q.-F.; Gao, X.-M. *et al. Org. Lett.* **2014**, *16*, 5016.
Wood, J. L. *et al. J. Am. Chem. Soc*. **2017**, *139*, 18504.

Introduction



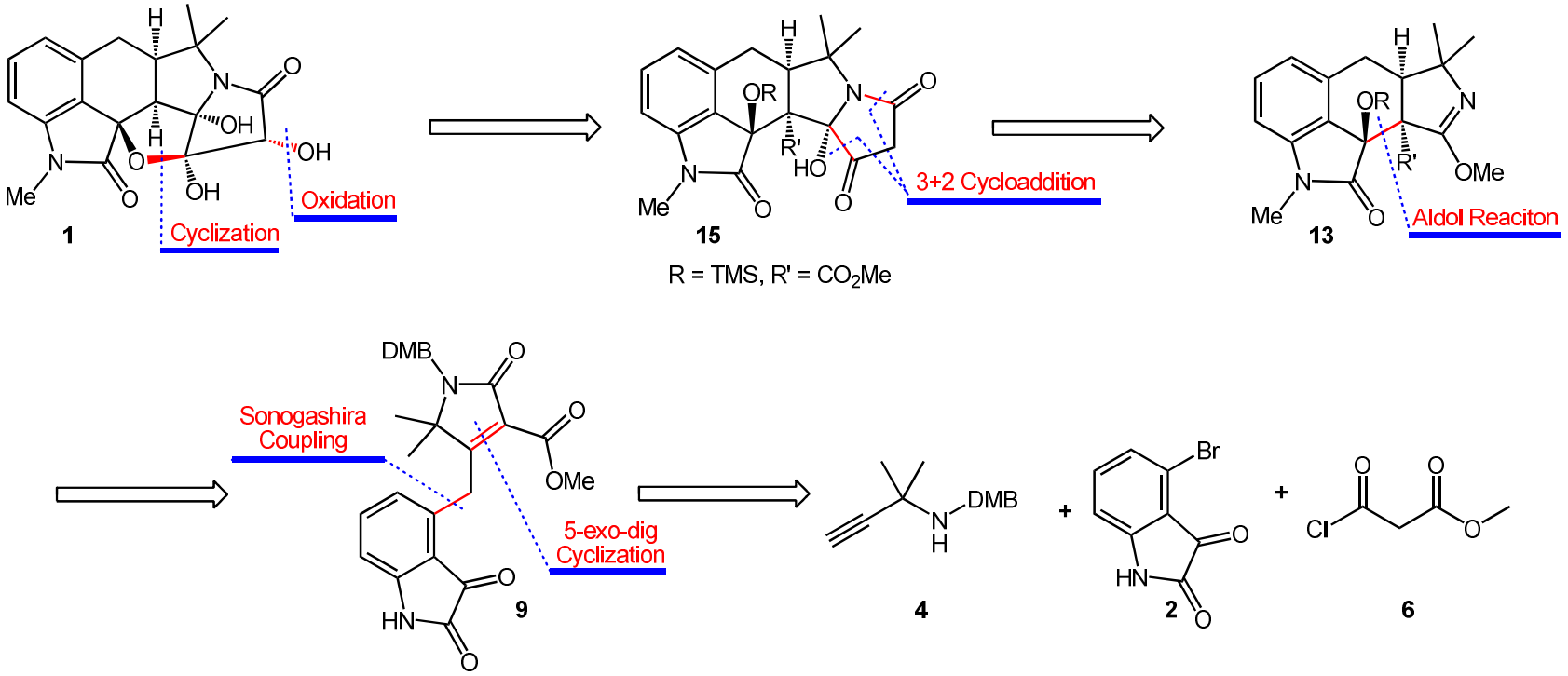
Aspergilline A



Aspergillus versicolor
杂色曲霉

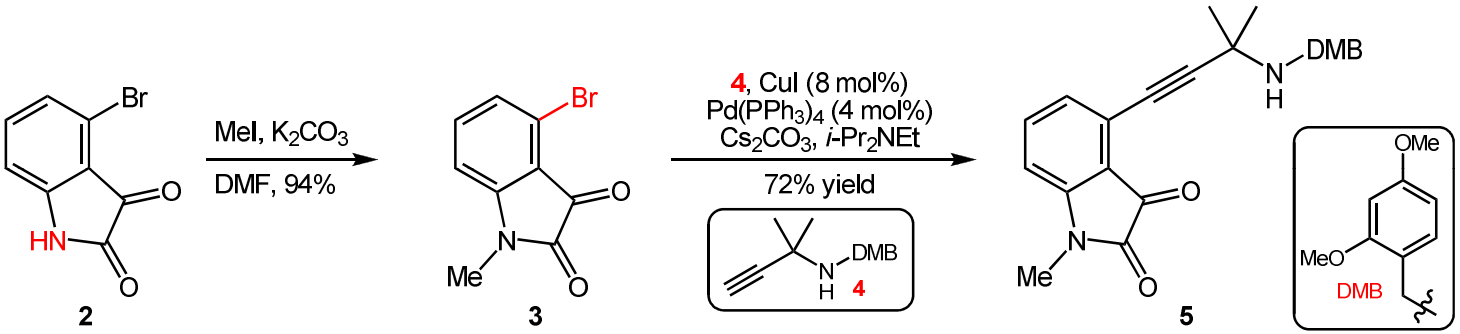
- Aspergilline A was isolated from fungus *Aspergillus versicolor* by Hu and Gao in 2014.
- The biological activity was against tobacco mosaic virus and several human cancer cell lines.
- The challenging structural features include a caged hexacyclic (6/6/5/5/5/5) heterocyclic ring system, six contiguous stereocenters, and a heavily substituted tetramic acid.

Retrosynthetic Analysis

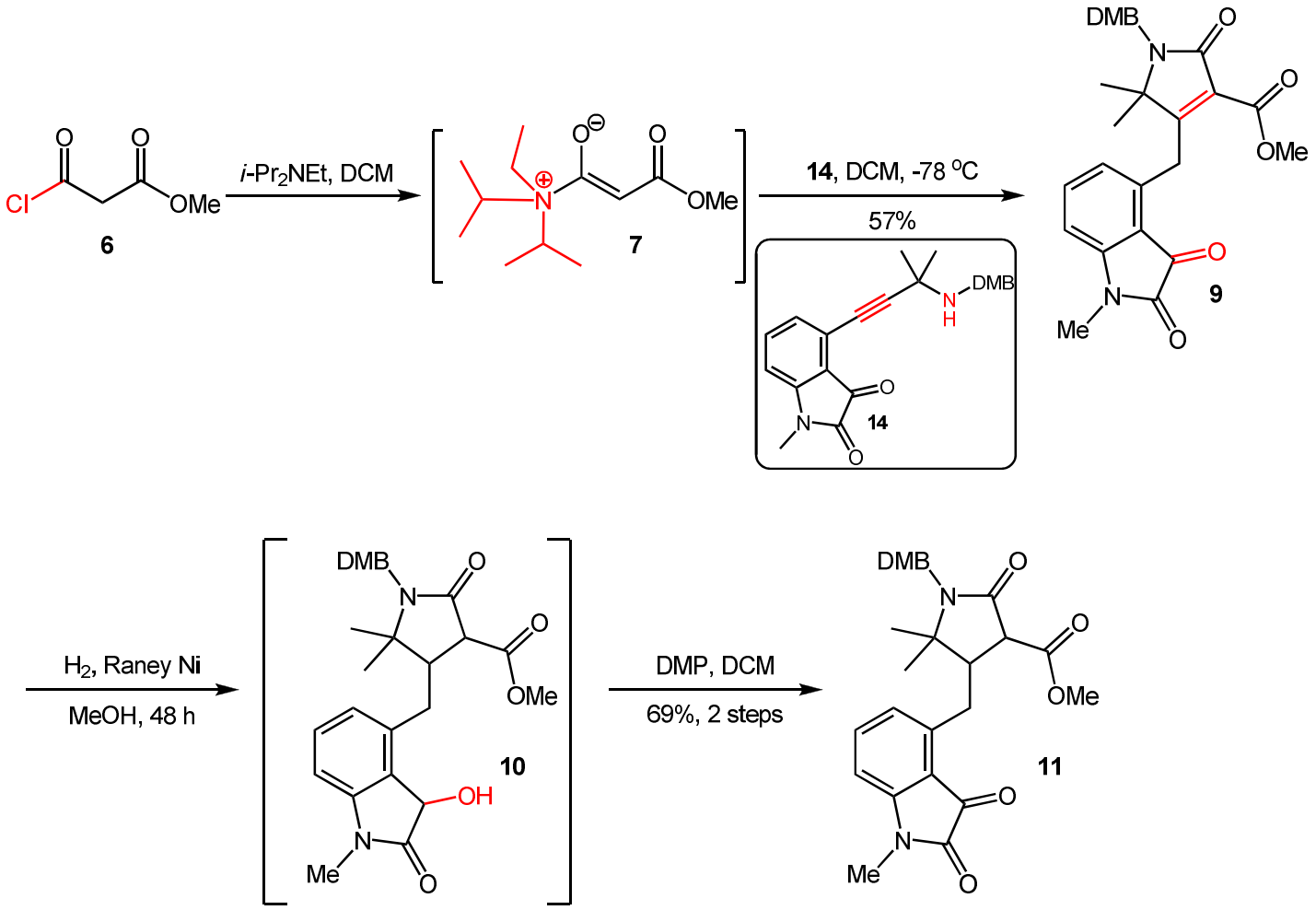


Wood, J. L. *et al. J. Am. Chem. Soc.* **2017**, *139*, 18504.

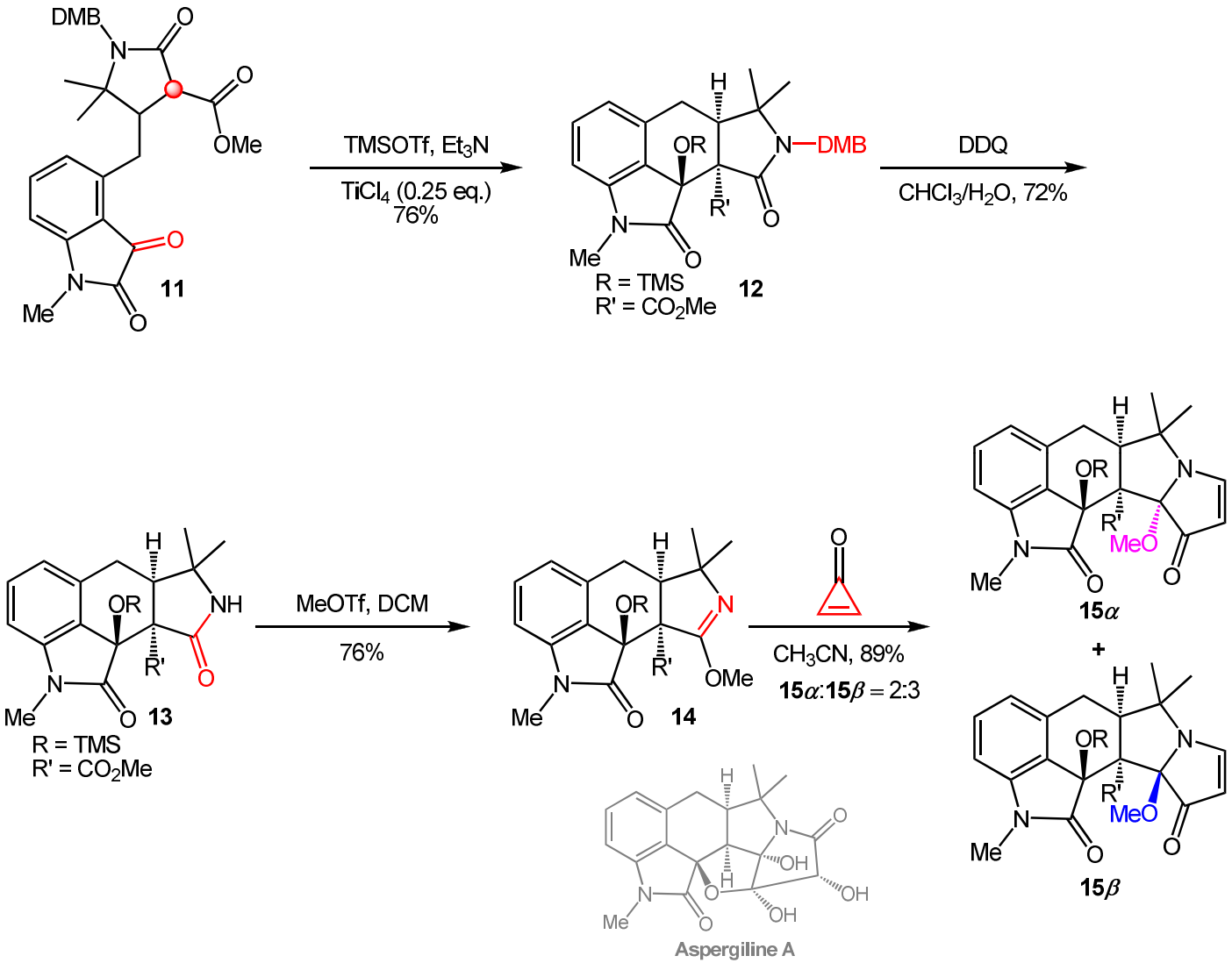
Sonogashira Coupling



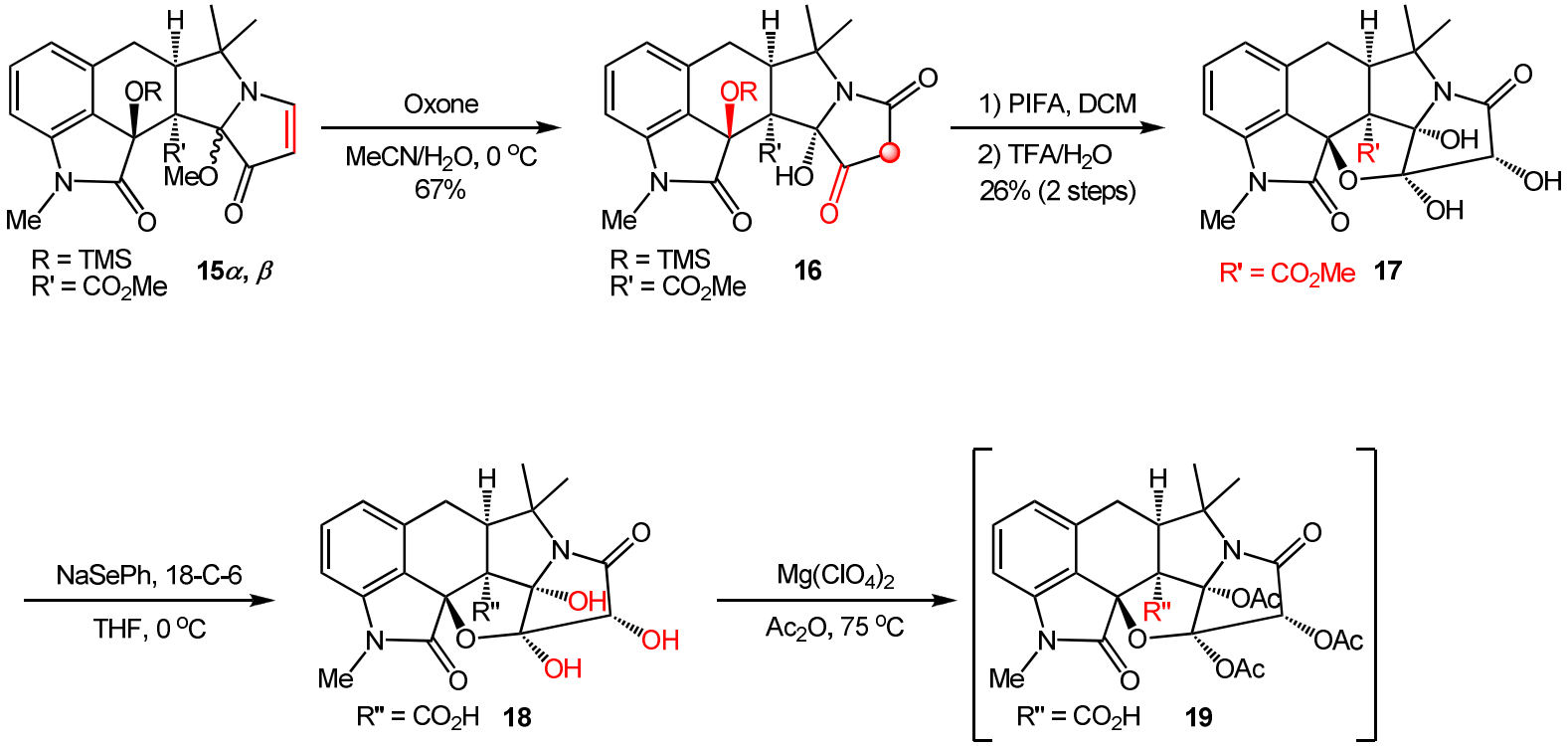
Preparation of the Aldol Substrate



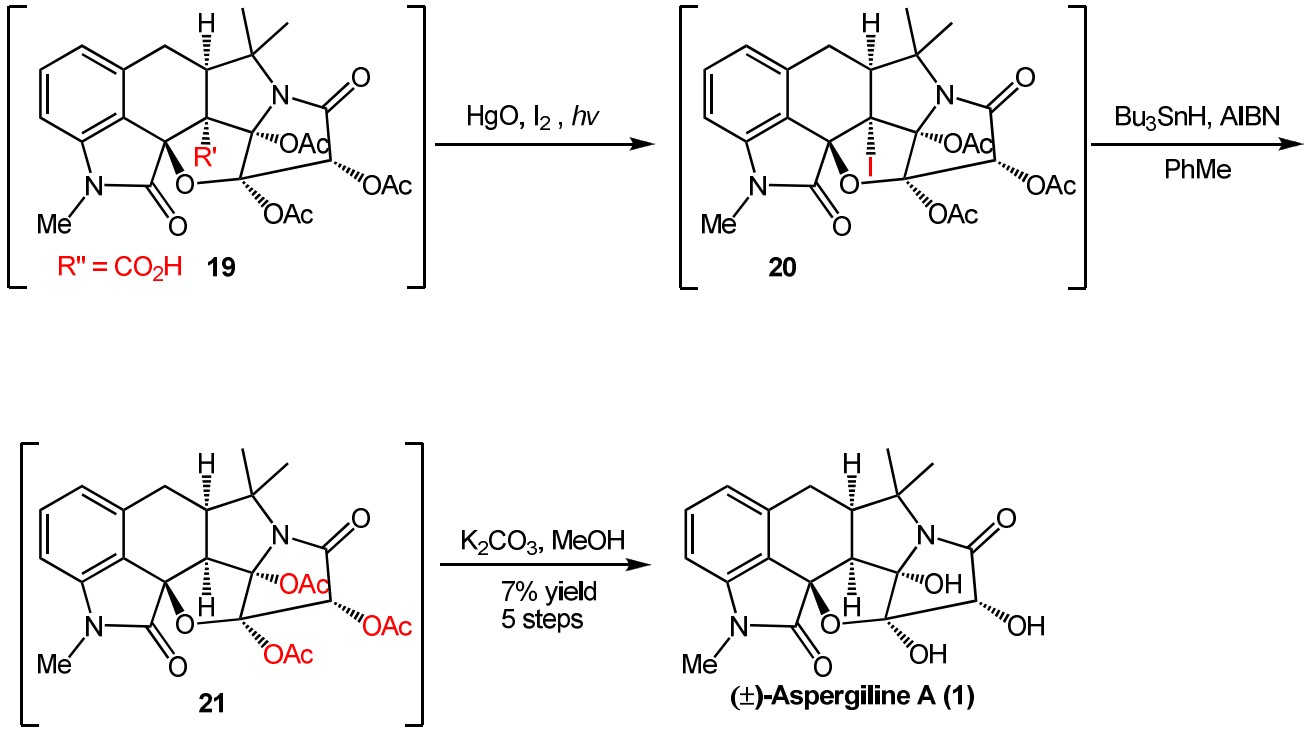
Annulation *via* [3+2] Addition



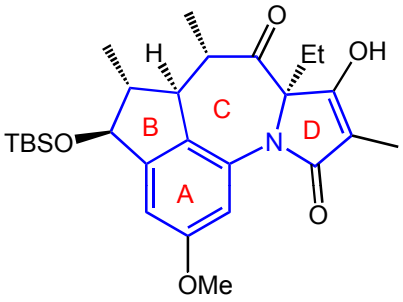
Completion of the Synthesis (±)-Aspergilline A



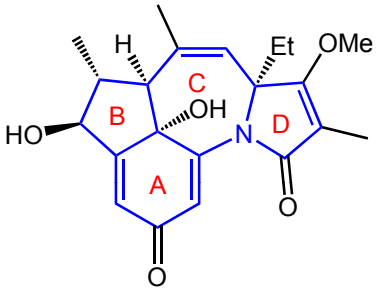
Completion of the Synthesis (±)-Aspergilline A



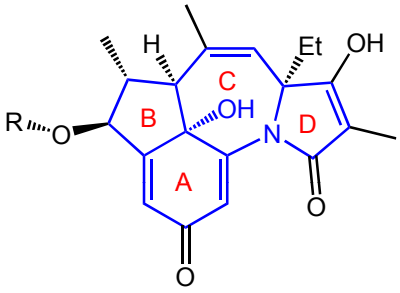
Selected Examples of Tetrapetalones



Sarpong (2010), (±), 16 steps



Frontier (2014), (±), 27 steps

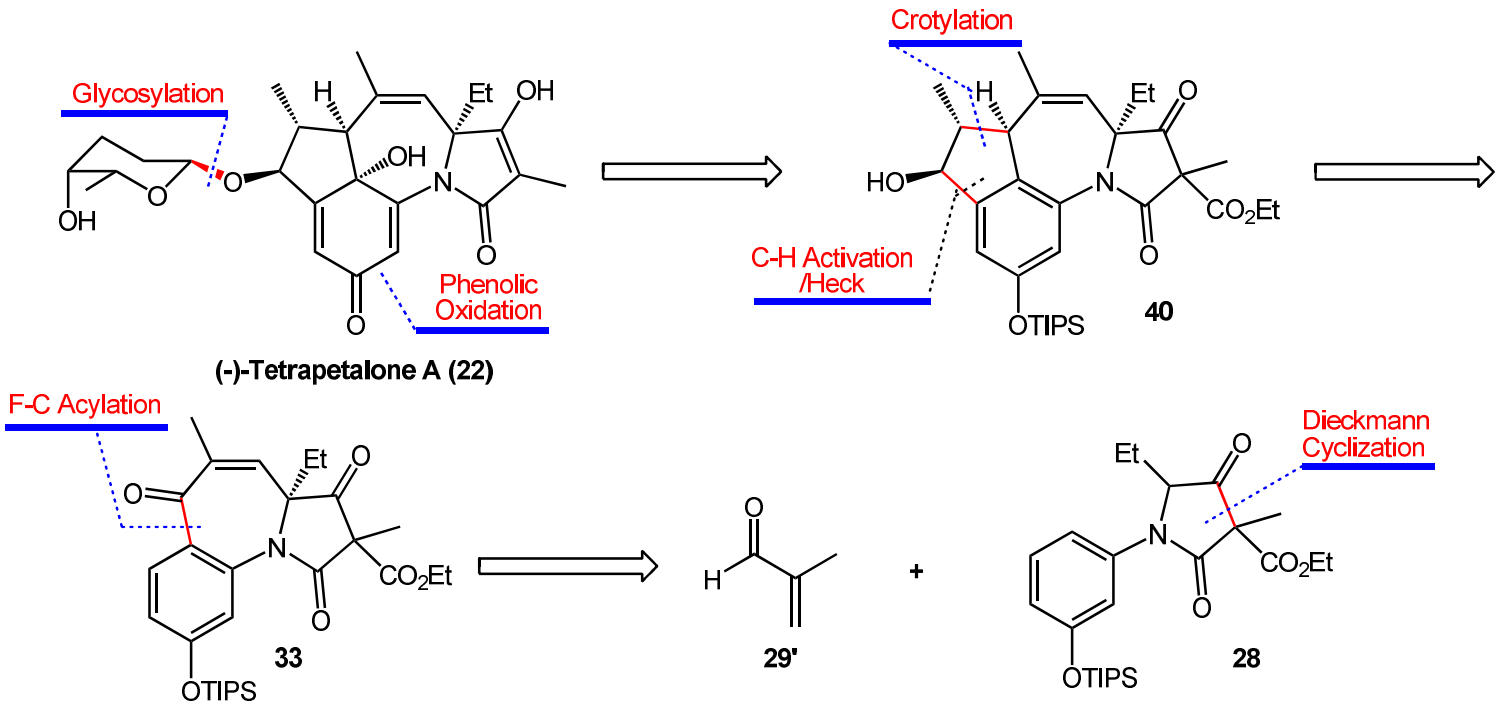


(-)-Tetrapetalone A (22)

Wood (2017), (-), 18 steps

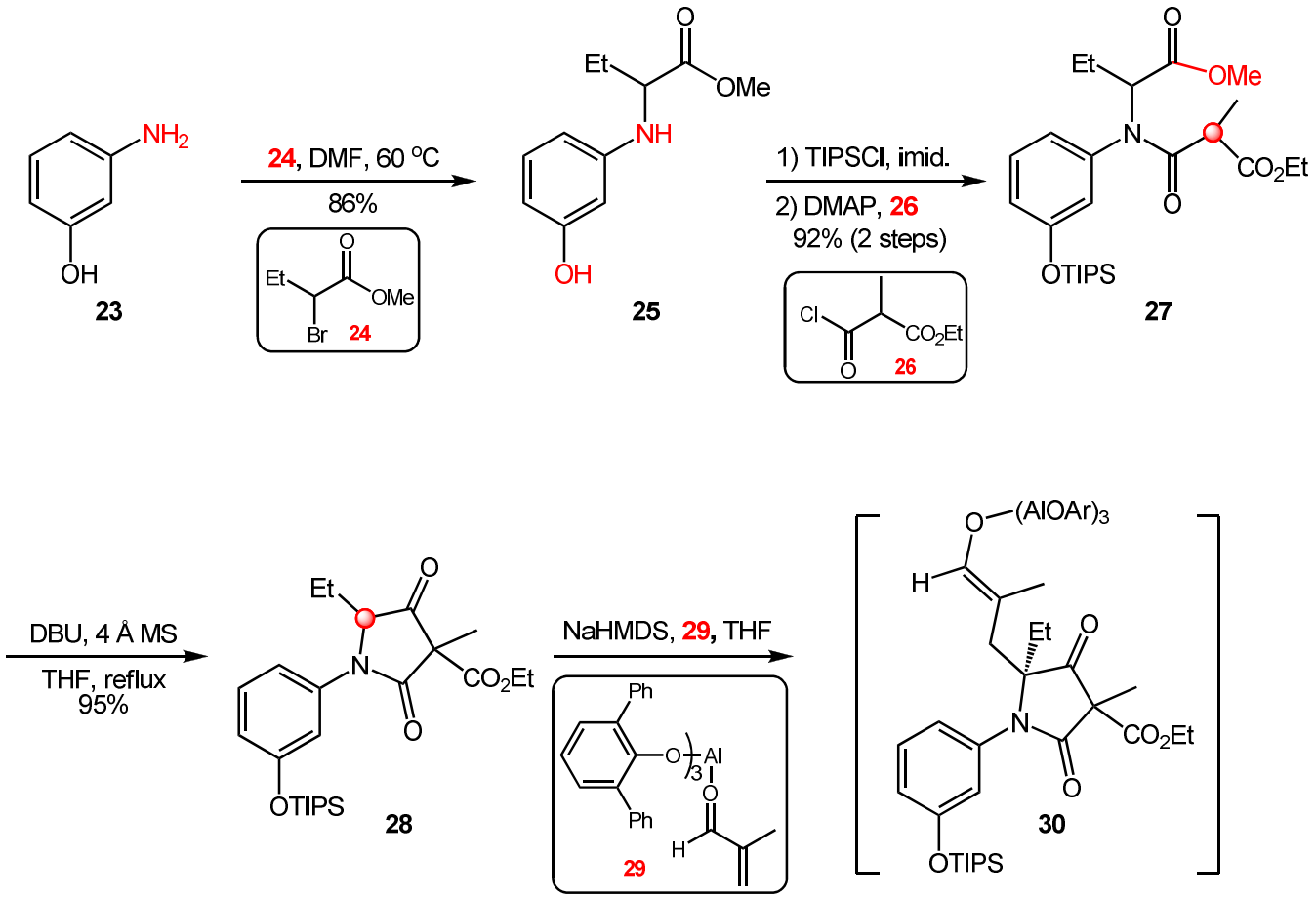
Wood, J. L. *et al. J. Am. Chem. Soc*. **2017**, *139*, 14901.

Retrosynthetic Analysis of (-)-Tetrapetalone A

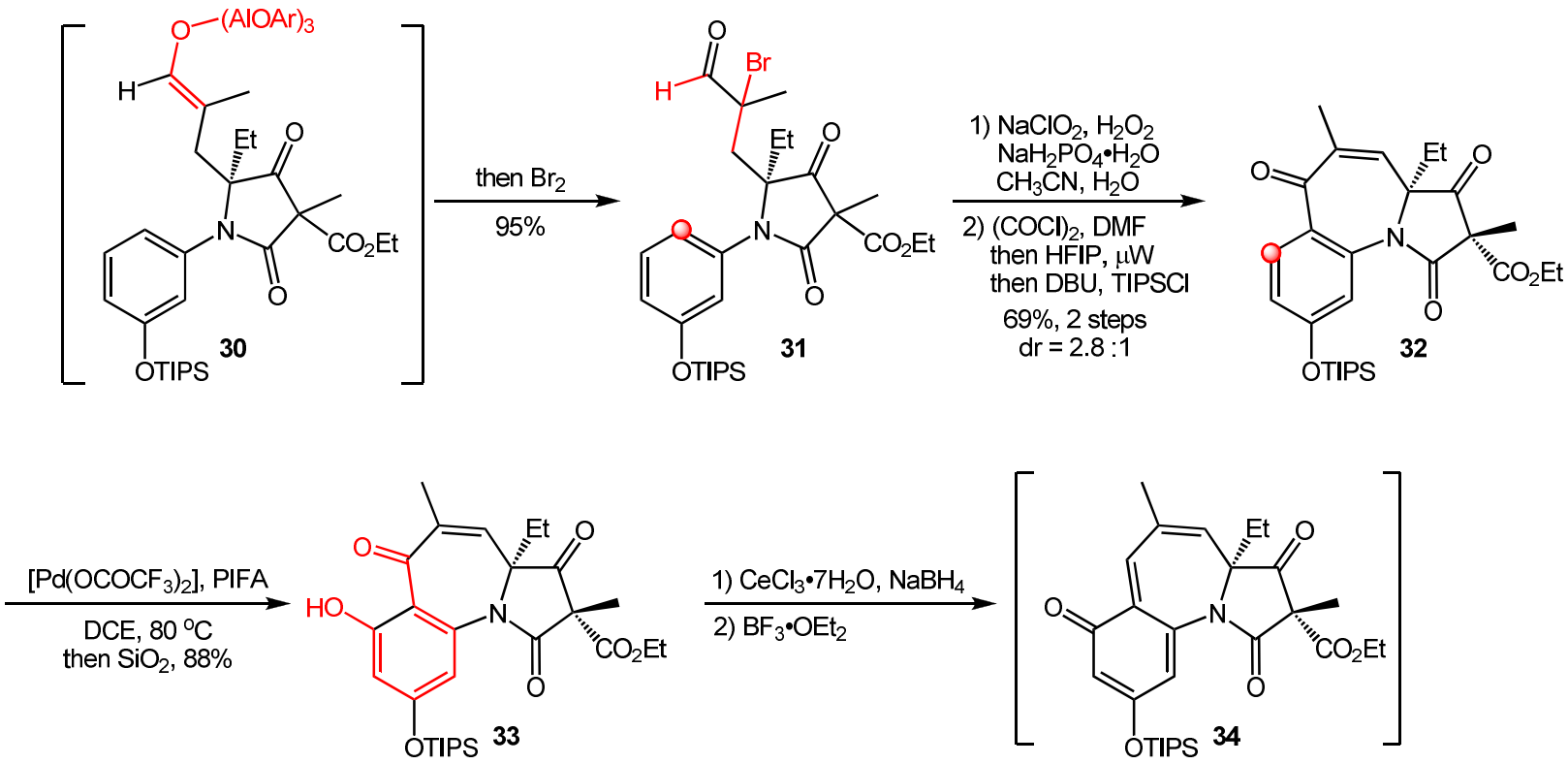


Wood, J. L. *et al. J. Am. Chem. Soc.* **2017**, *139*, 14901.

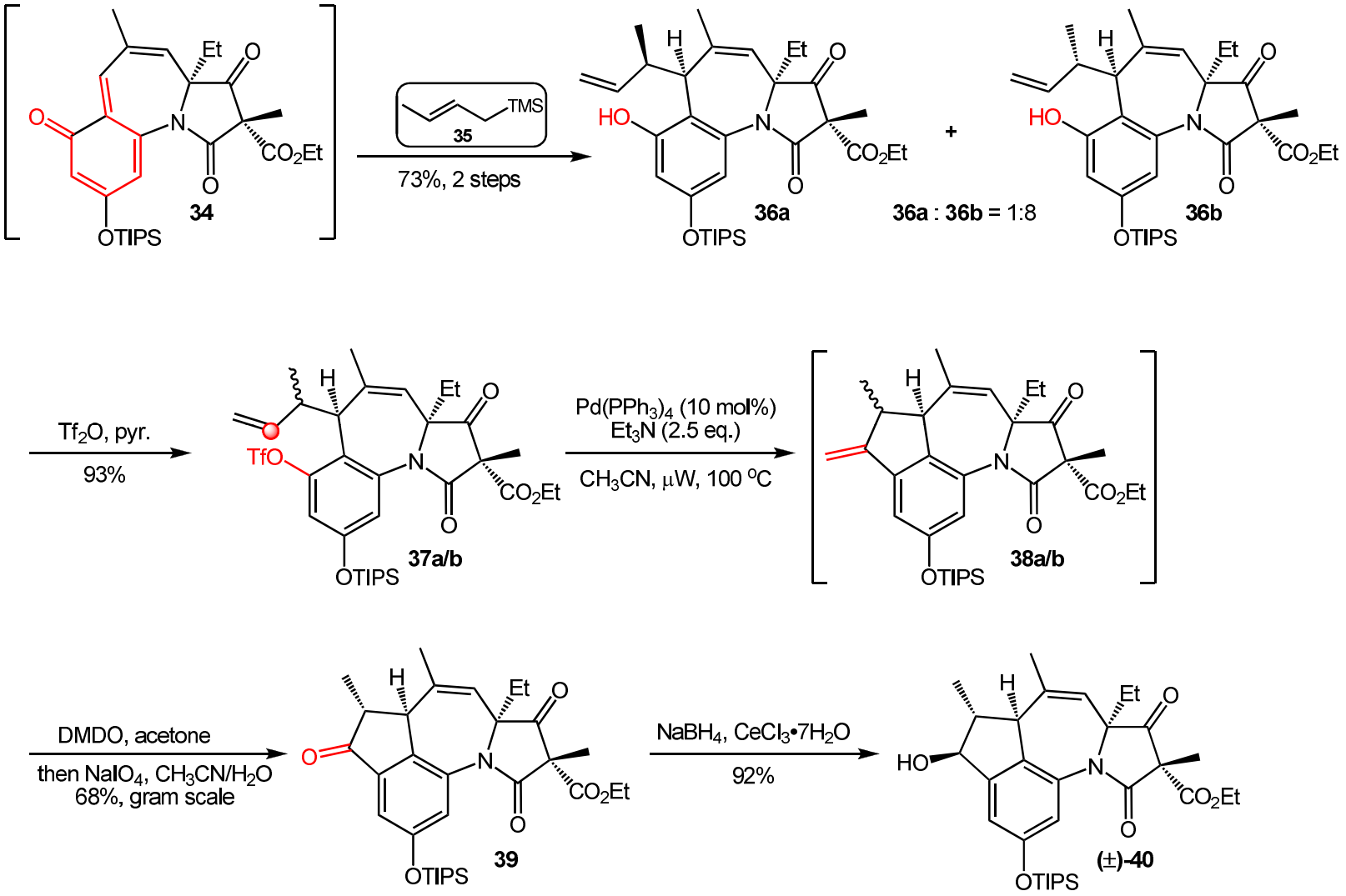
Synthesis of (±)-40



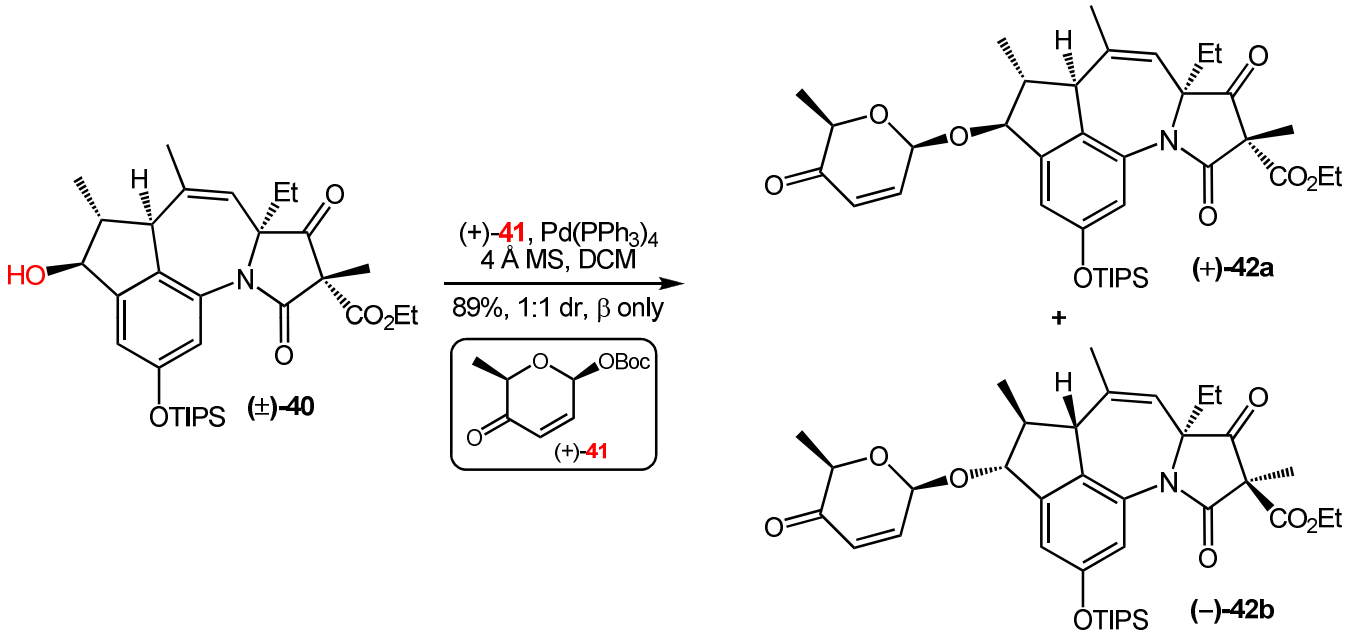
Synthesis of (±)-40



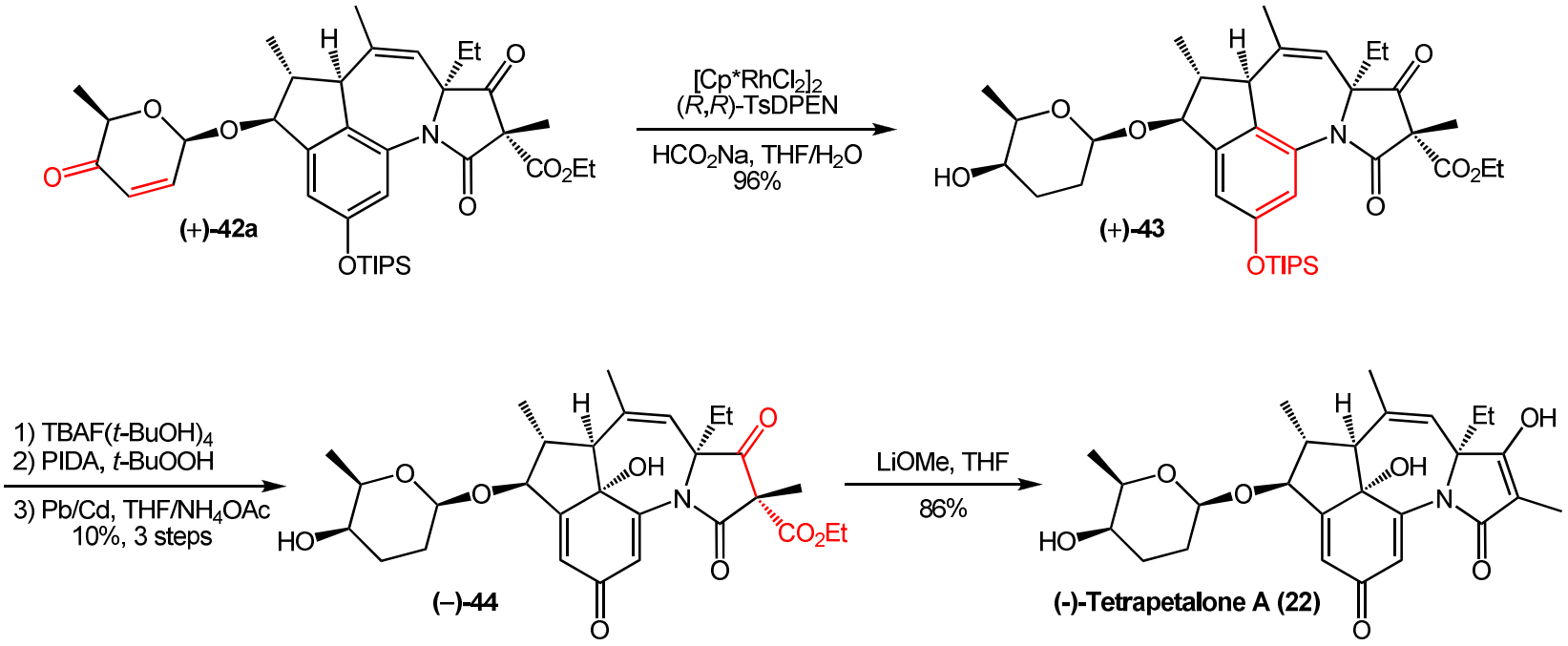
Synthesis of (±)-40



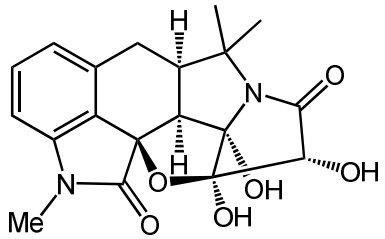
Synthesis of (−)-Tetrapetalone A



Synthesis of (−)-Tetrapetalone A



Summary

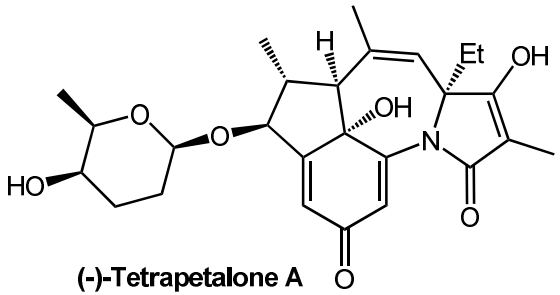


(±)-Aspergillines A

- The total synthesis of (±)−Aspergilline A was achieved in 16 steps with 0.12% overall yield;
- Key features of this synthesis include pyrrolinone formation and a formal [3+2] cycloaddition between an imidate and cyclopropenone.

Wood, J. L. *et al. J. Am. Chem. Soc*. **2017**, *139*, 18504.

Summary



(-)-Tetrapetalone A

- This total synthesis was achieved in 18 steps with 0.68% overall yield;
- The strategy involves a highly selective conjugate addition /intramolecular Friedel−Crafts acylation sequence to deliver a key azepine intermediate;
- Application of recently developed C−H activation chemistry and subsequent Heck cyclization delivers the aglycone framework.

Wood, J. L. *et al. J. Am. Chem. Soc*. **2017**, *139*, 14901.

The First Paragraph

In their pursuit of novel lipoxygenase inhibitors, Hirota and co-workers isolated tetrapetalone A from *Streptomyces sp.* USF-4727 in 2003. Subsequent studies led to the discovery of a small family of congeners, tetrapetalones B−D (**2**−**4**), which differ in their oxidation states at the pendant ethyl side chain, the tetramic acid moiety, or both, respectively. More recently, Hirota reported the isolation of ansaetherone (**5**), a presumed biosynthetic precursor to the tetra-petalones. In the roughly 15 years since their isolation, considerable effort has been focused on developing syntheses of the tetra-petalones. Despite elegant work from the groups of Sarpong，Porco

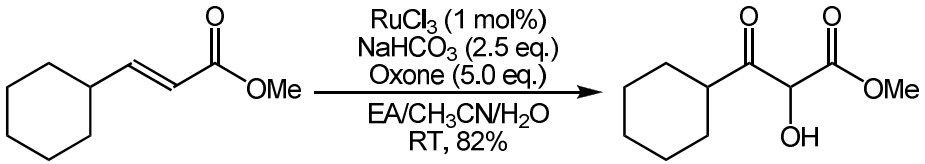
The First Paragraph

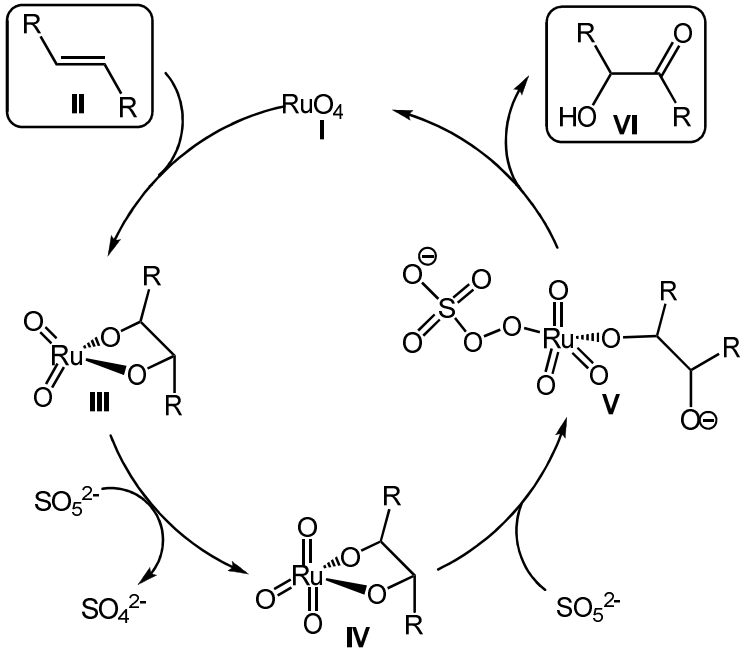
Pettus, Hong, and most recently Frontier, a completed total synthesis has yet to be realized. Perhaps most significant among these are the efforts of Frontier who prepared an *O*-methyl derivative of racemic tetrapetalone A aglycone in a 27-step sequence. However, neither demethylation of this intermediate nor further advancement toward the natural product were reported. Herein we detail our efforts which culminate in complete syntheses of (+)- and (−)-tetrapetalones A and C in 18 and 19 steps, respectively.

The Last Paragraph

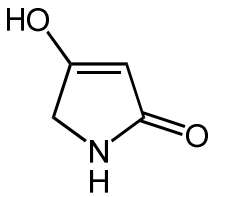
In conclusion, we have herein outlined an efficient stereocontrolled preparation of a tetrapetalone aglycone scaffold (**6**) that upon further manipulation provides access to synthetic (−)- and (+)-tetrapetalones A and C in 18 and 19 steps, respectively. Current efforts are being directed toward preparing tetrapetalones B/D and studies into alternative methods for accessing the *p*-quinol moiety. The results of these efforts will be described in due course.

RuO_4-Catalyzed Ketohydroxylation of Olefins

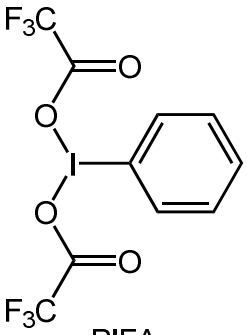




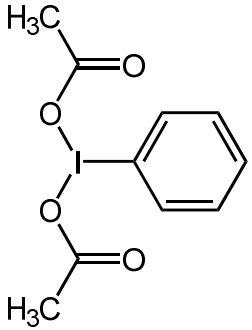
Plietker, B. *et al. J. Org. Chem.* **2003**, *68*, 7123.



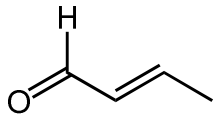
tetramic acid



PIFA



PIDA



crotonaldehyde