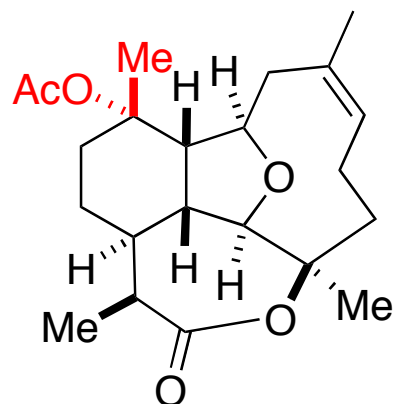
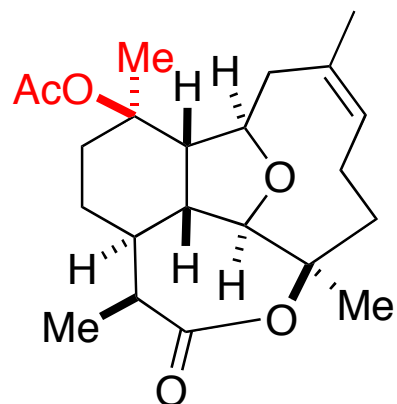


# Total Synthesis of the Proposed Structure of Briarellin J

Michael T. Crimmins, Mark C. Mans, and Abimael D. Rodríguez. *Org. Lett.* **2010**, ASAP



originally proposed  
structure



revised structure

*Eric E. Buck*  
*Current Literature*  
*October 23, 2010*



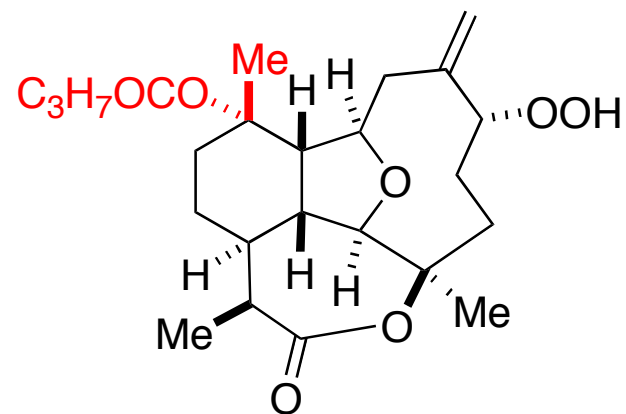
# Isolation and Background



- Briarellin J was isolated from the gorgonian octocoral *Briareum polyanthes* located of the south west coast of Puerto Rico.
- The briarellins, asbestinins, eunicellins, and sarcodyctins are structural subclasses of cembranoid diterpenes.

- This class of diterpenes is thought to play a roll in predation deterrence

- Recently, the briarellin class of compounds has shown inhibition of *Plasmodium falciparum*, a parasite responsible for malaria. Briarellin J showed very little activity.



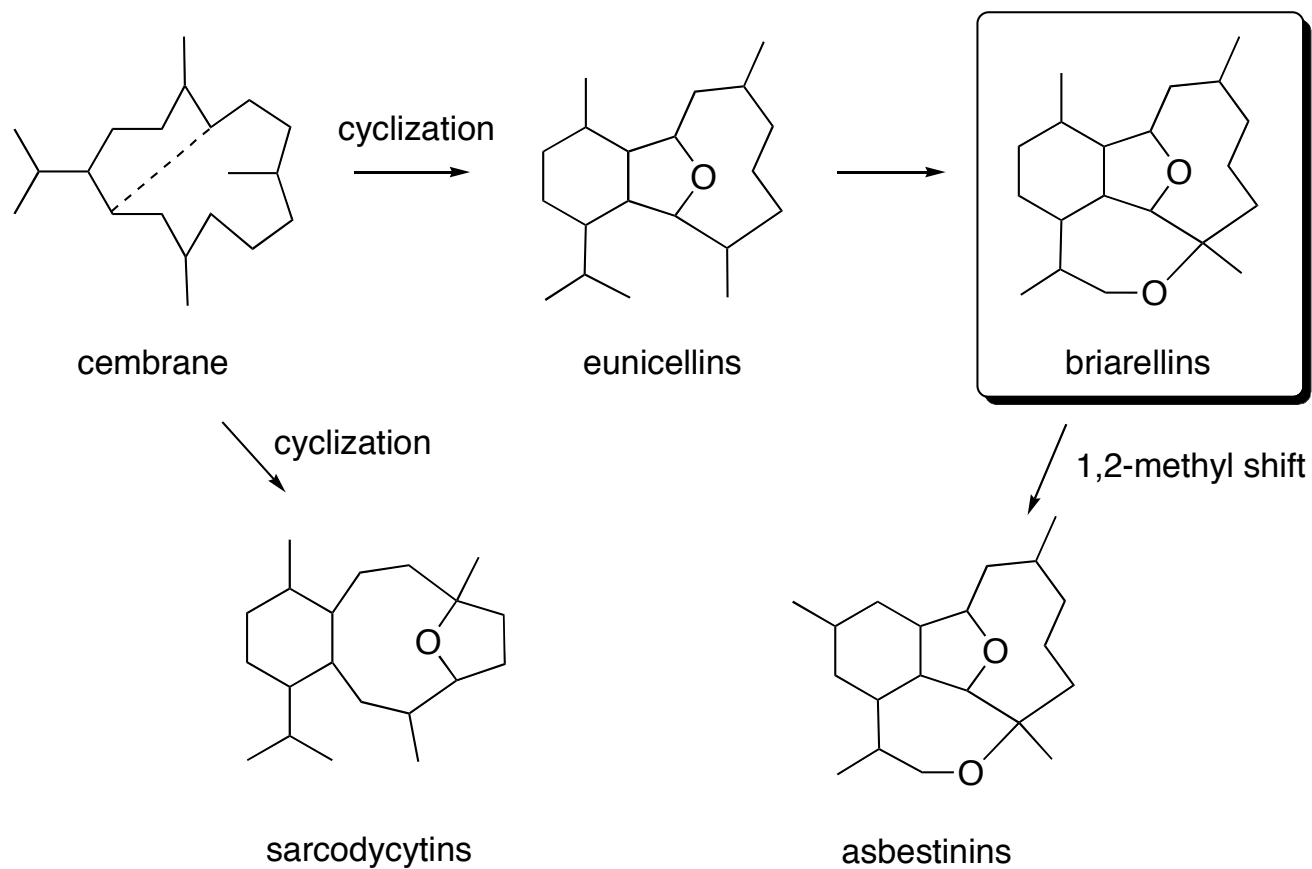
Briarellin D hydroperoxide

LC<sub>50</sub> = 9 µg/mL

Rodríguez, A. D.; Cobar, O. M. *Tetrahedron*. **1995**, 51, 6869-6880

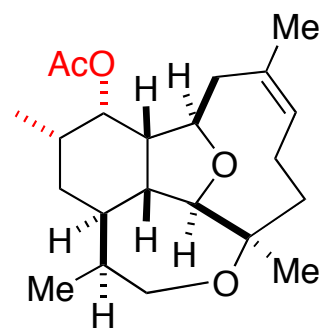
Ospina, C. A.; Rodríguez, A. D.; Ortega-Barria, E.; Capson, T. L. *J. Nat. Prod.* **2003**, 66, 357-363

# Proposed biosynthesis

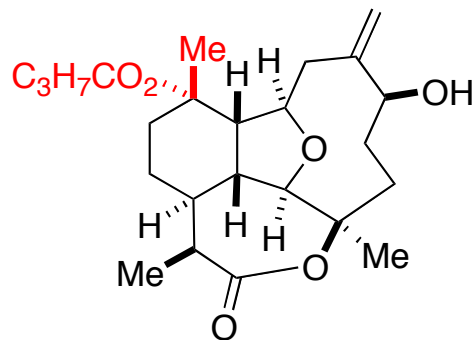


Stierle, D. B.; Carté, Faulkner, D. J.; Tagle, B.; Clardy, J. *J. Am. Chem. Soc.* **1980**, 102, 5088-5092

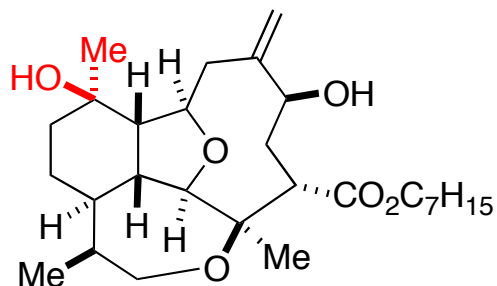
# The briarellin family



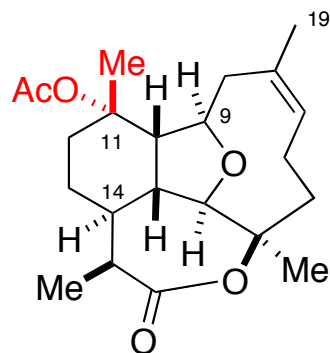
11-acetoxy-4-deoxyasbestinin  
(synthesis by Crimmins, **2005**)



briarellin D (proposed)



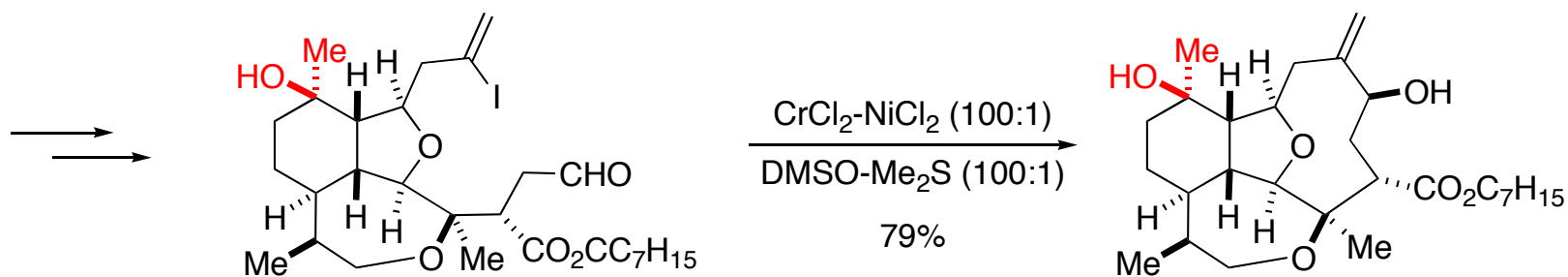
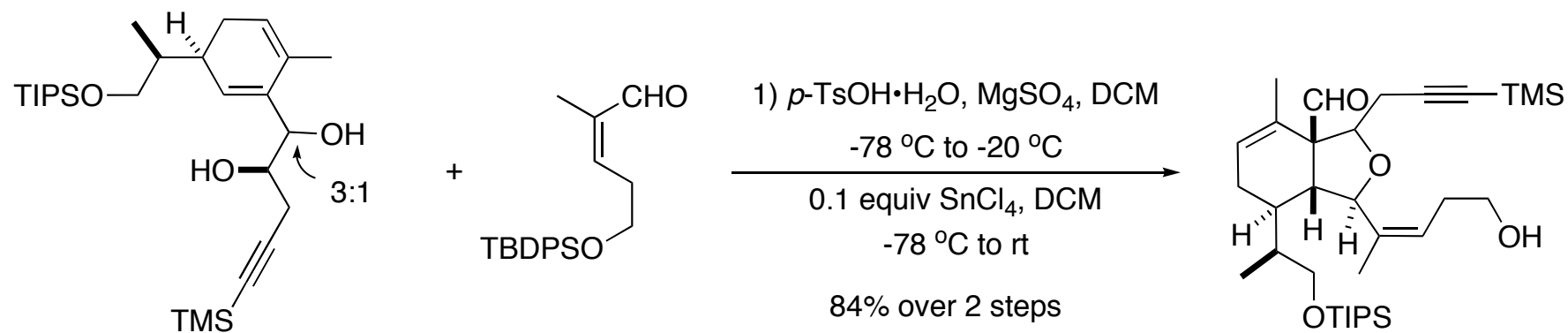
briarellin E  
(synthesis by Overman, **2003**)



briarellin J  
originally proposed  
structure

- The briarellin A-D and J-P have been assigned different C11 configurations than briarellin E-I
- The asbestinin family all share the same relative stereochemistry.
- The structure of briarellin J was proposed based on previously reported structural assignments of briarellin D and A
- The C11 configuration was based on the absence of an nOe correlation between C11 and H14.
- Observed nOe:
  - C11 Me: H9, H10, H19
  - Ac Me: H1, H19
- Not observed nOe:
  - C11 Me: H14
  - Ac Me: H14

# Overman's synthesis of Briarellins E and F



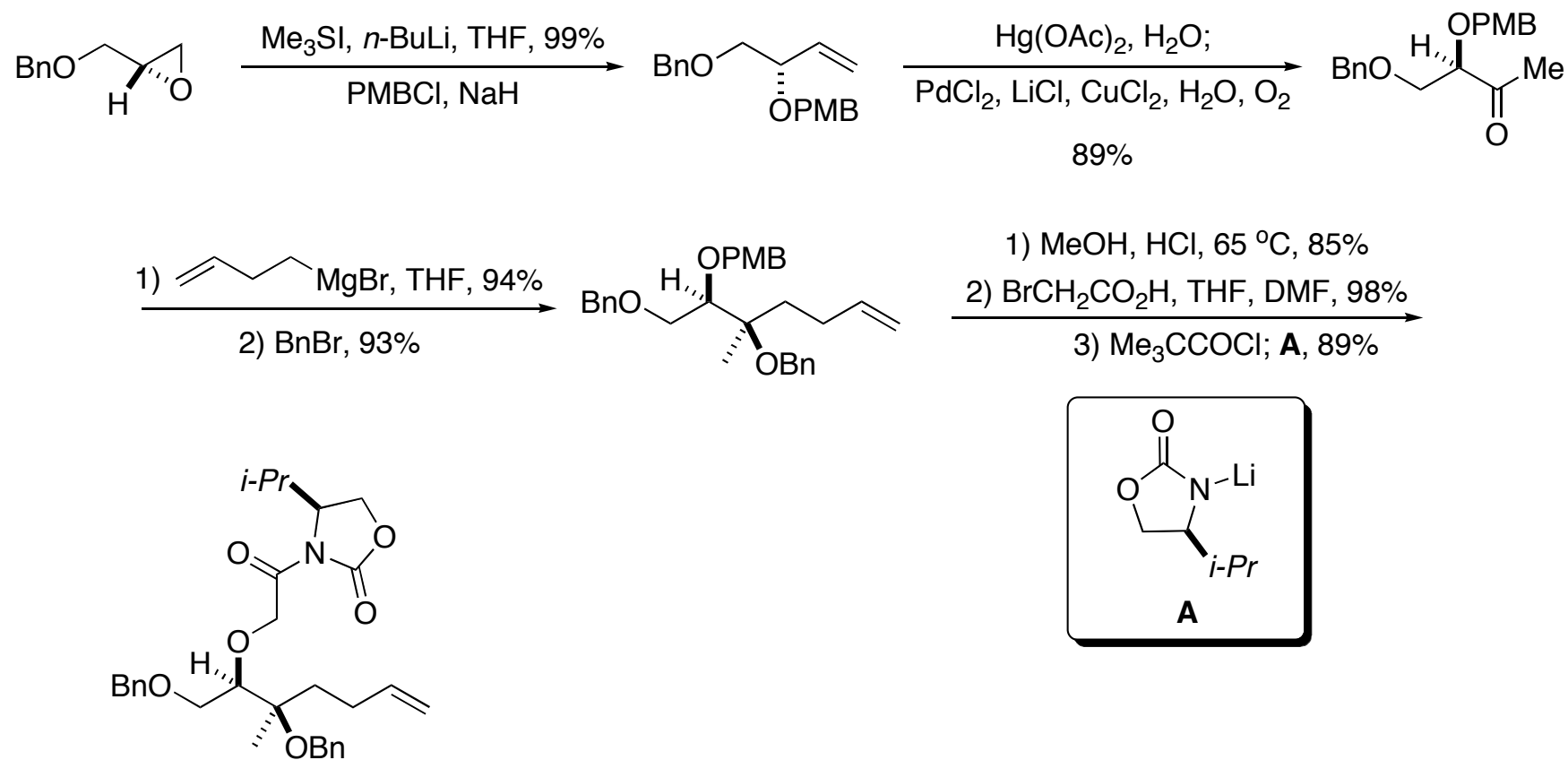
briarellin E

28 steps\*, 0.7% yield

Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, 125, 6650-6652

Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2009**, 74, 5458-5470

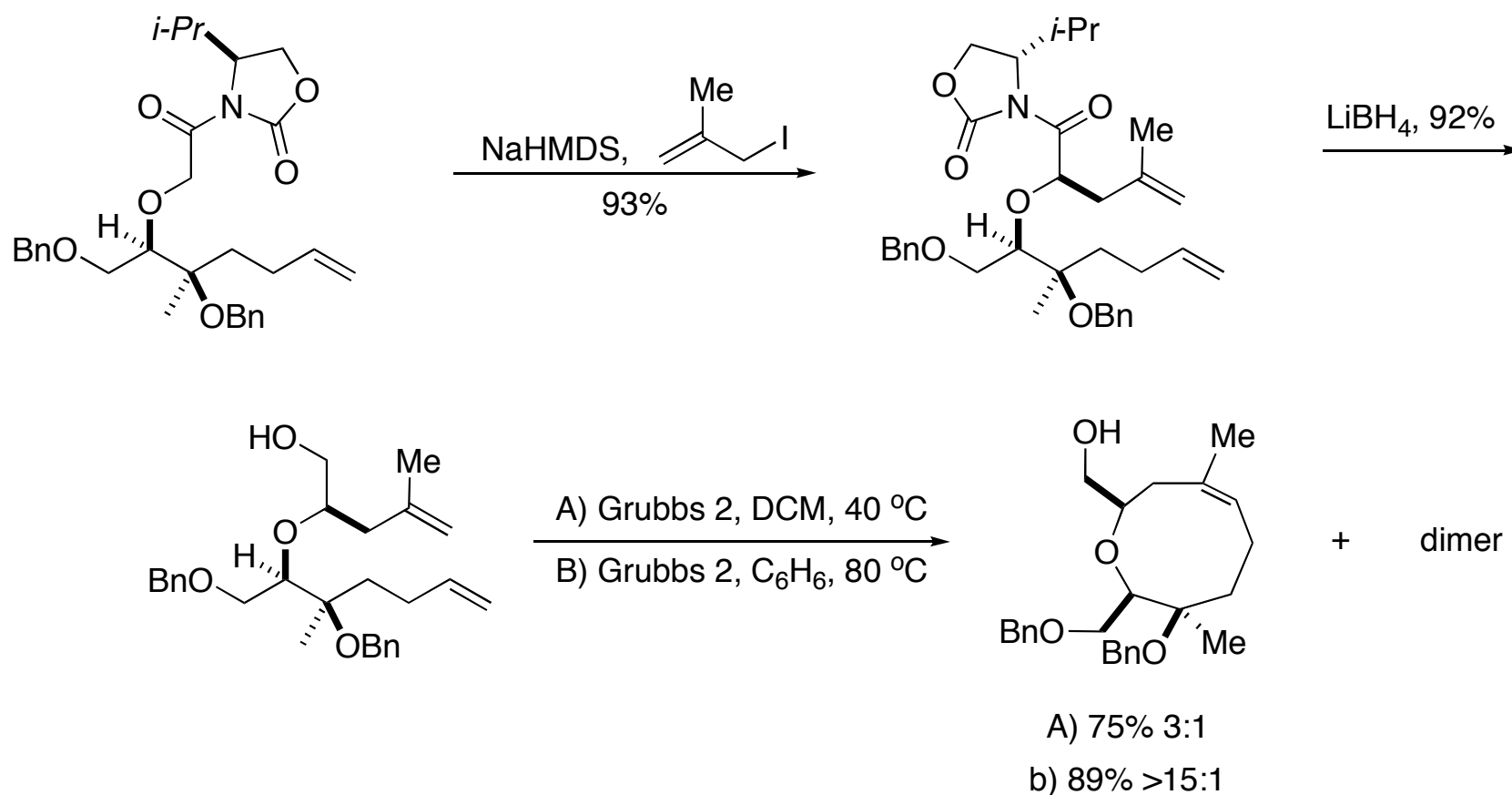
# Crimmins's synthesis of the Eunicelin, Ophirin B



Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, 126, 10264-10266

Crimmins, M. T.; Brown, B. H.; Plake, H. R. *J. Am. Chem. Soc.* **2006**, 128, 1371-1378

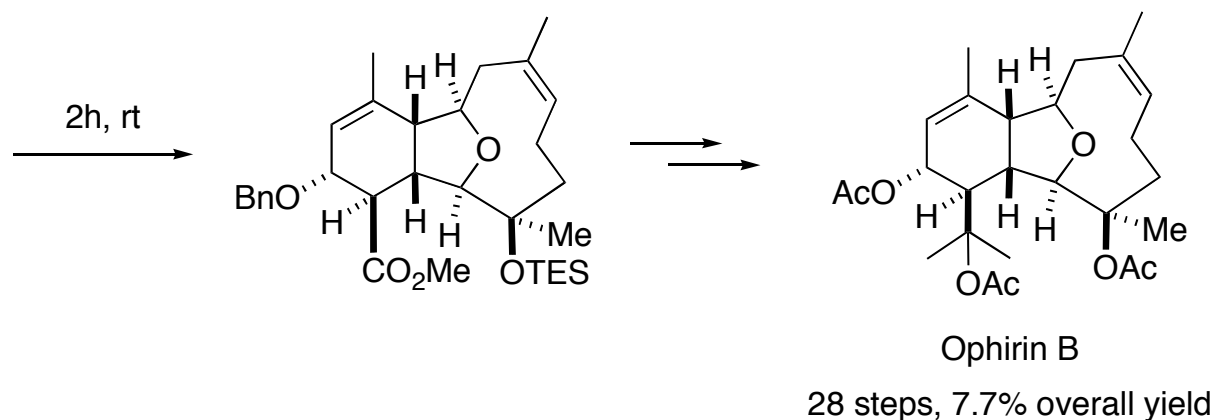
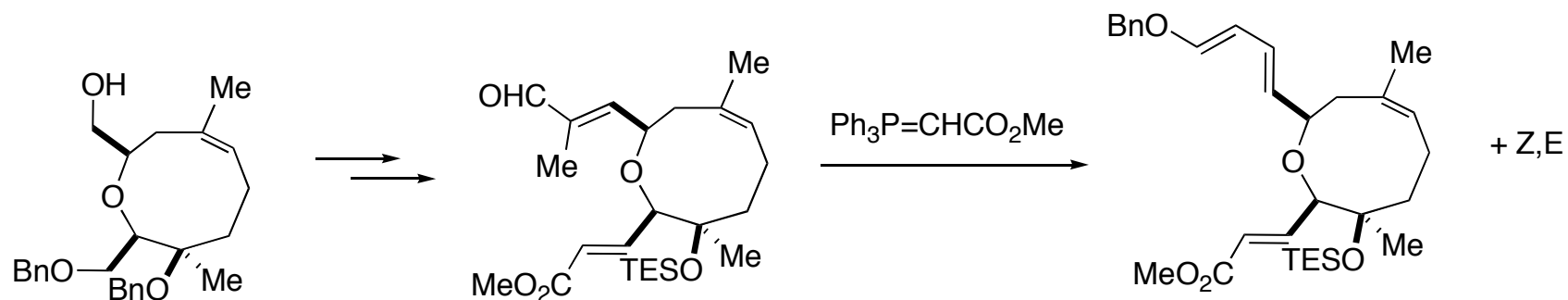
# Crimmins's synthesis of the Eunicelin, Ophirin B



Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, 126, 10264-10266

Crimmins, M. T.; Brown, B. H.; Plake, H. R. *J. Am. Chem. Soc.* **2006**, 128, 1371-1378

# Crimmins's synthesis of the Eunicellin, Ophirin B



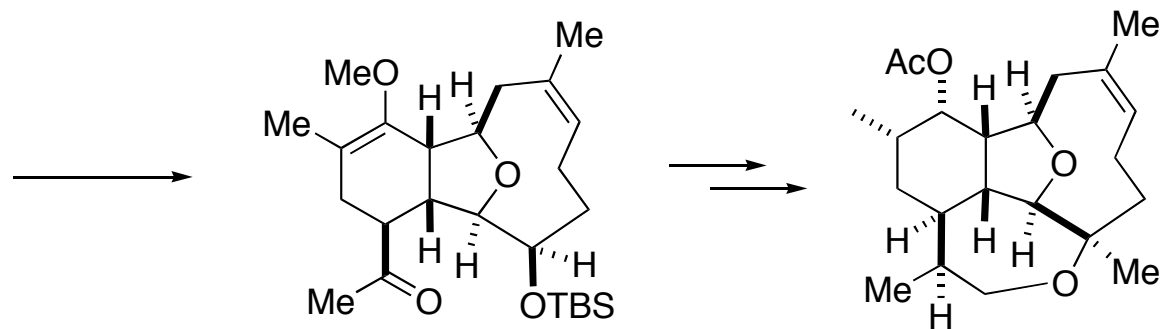
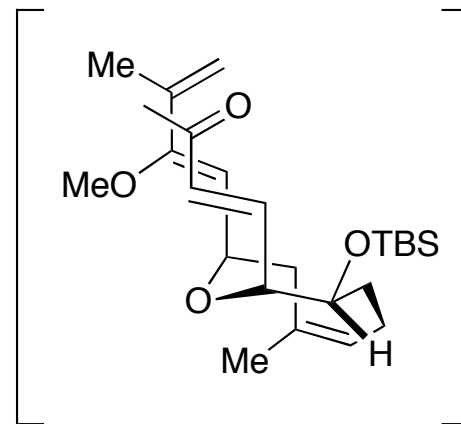
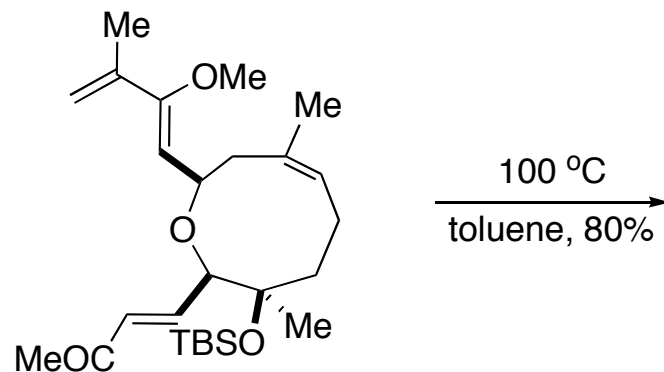
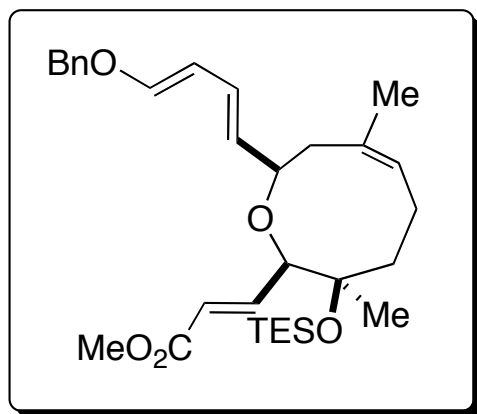
- The Z,E isomer can be recycled by irradiation in the presence of PhSSPh

Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, 126, 10264-10266

Crimmins, M. T.; Brown, B. H.; Plake, H. R. *J. Am. Chem. Soc.* **2006**, 128, 1371-1378



# Crimmins's 11-acetoxy-4-deoxyasbestinin D



26 linear steps

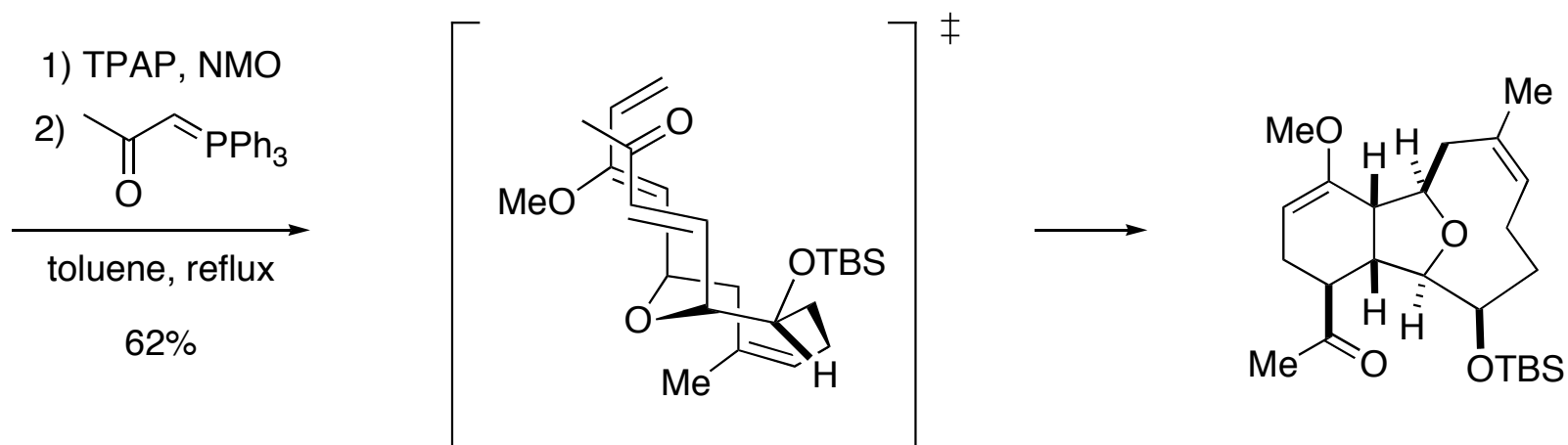
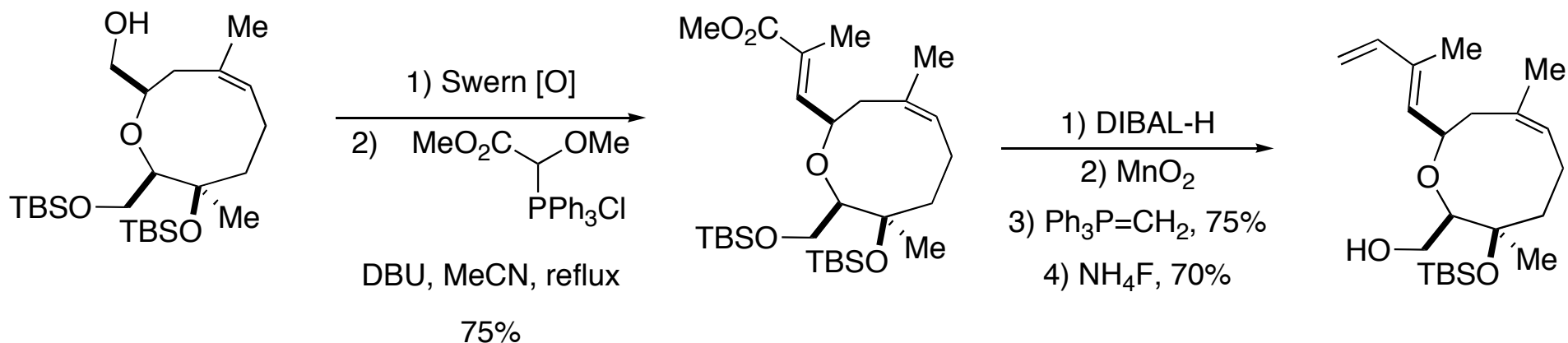
11-acetoxy-4-deoxyasbestinin

- Established absolute configuration of the asbestinin family of diterpenes.

Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005**, 127, 17200-17201

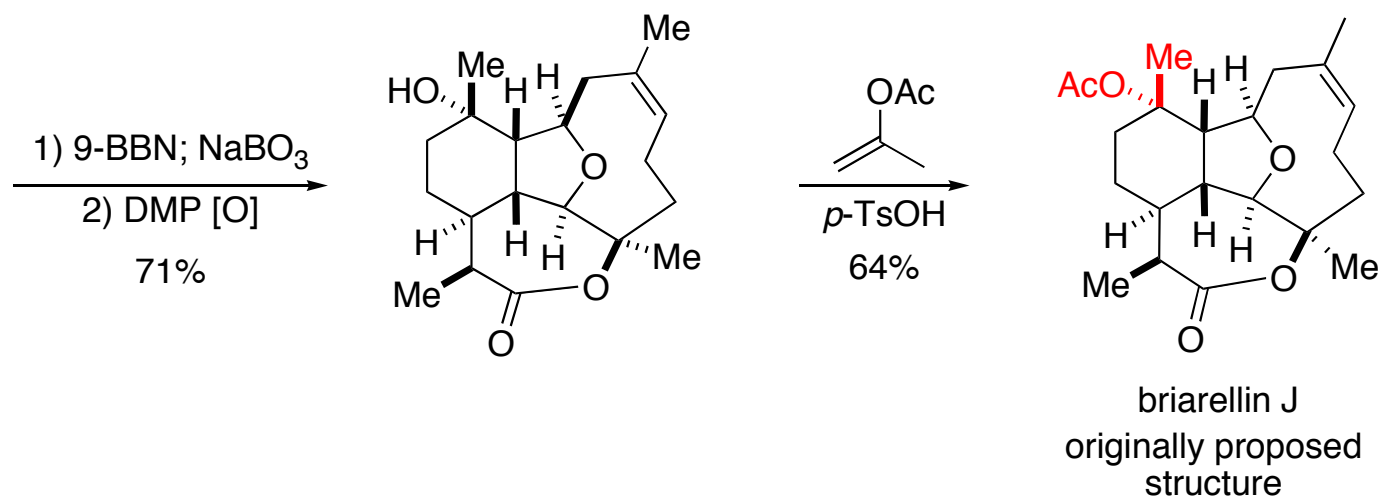
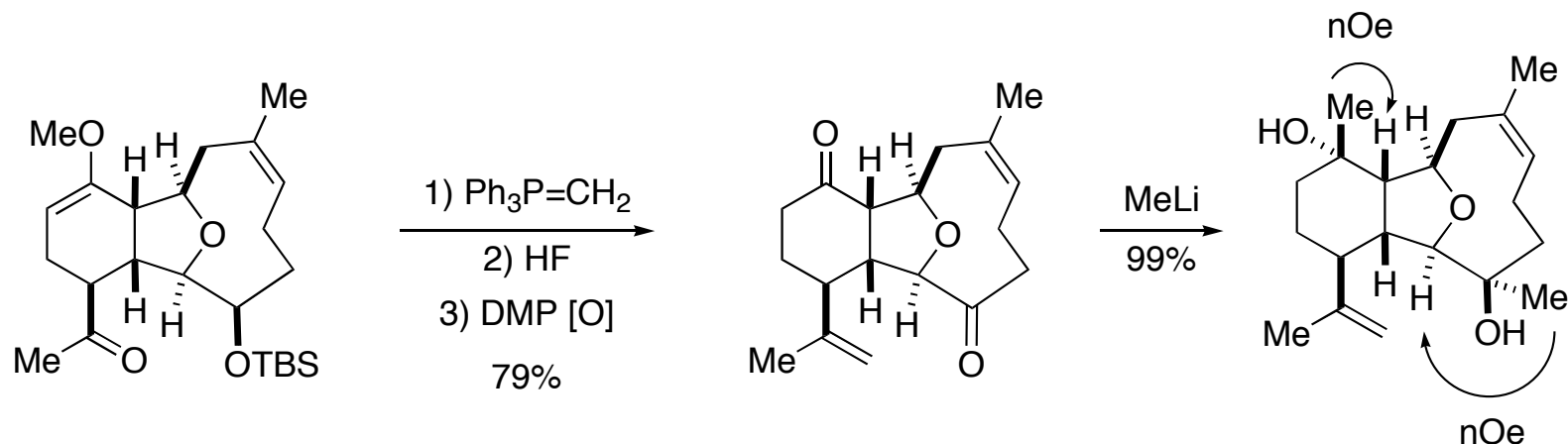
Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, 73, 1649-1660

# Title paper: Key Diels-Alder cycloaddition



Crimmins, M. T.; Mans, M. C.; Rodríguez, A. D. *Org. Lett.* **2010**, ASAP

# Title paper: Revision of absolute stereochemistry



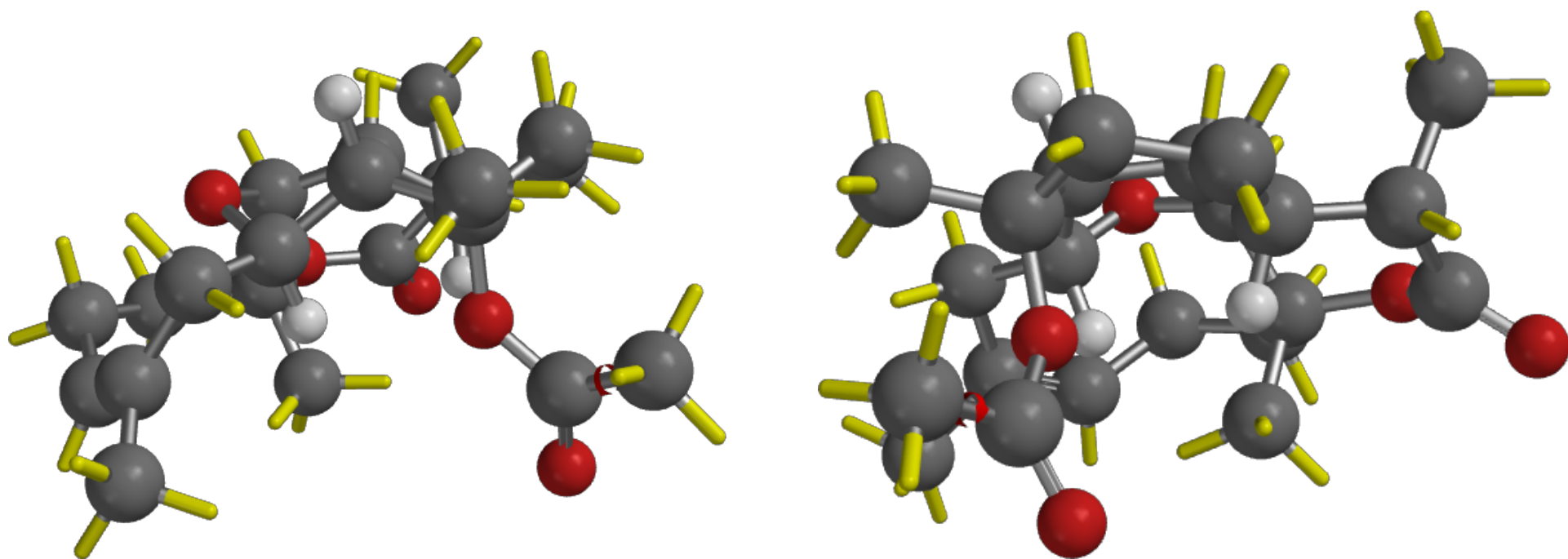
- X-ray structure of the diol verifies stereochemistry

- 15 linear steps from previously prepared oxonene

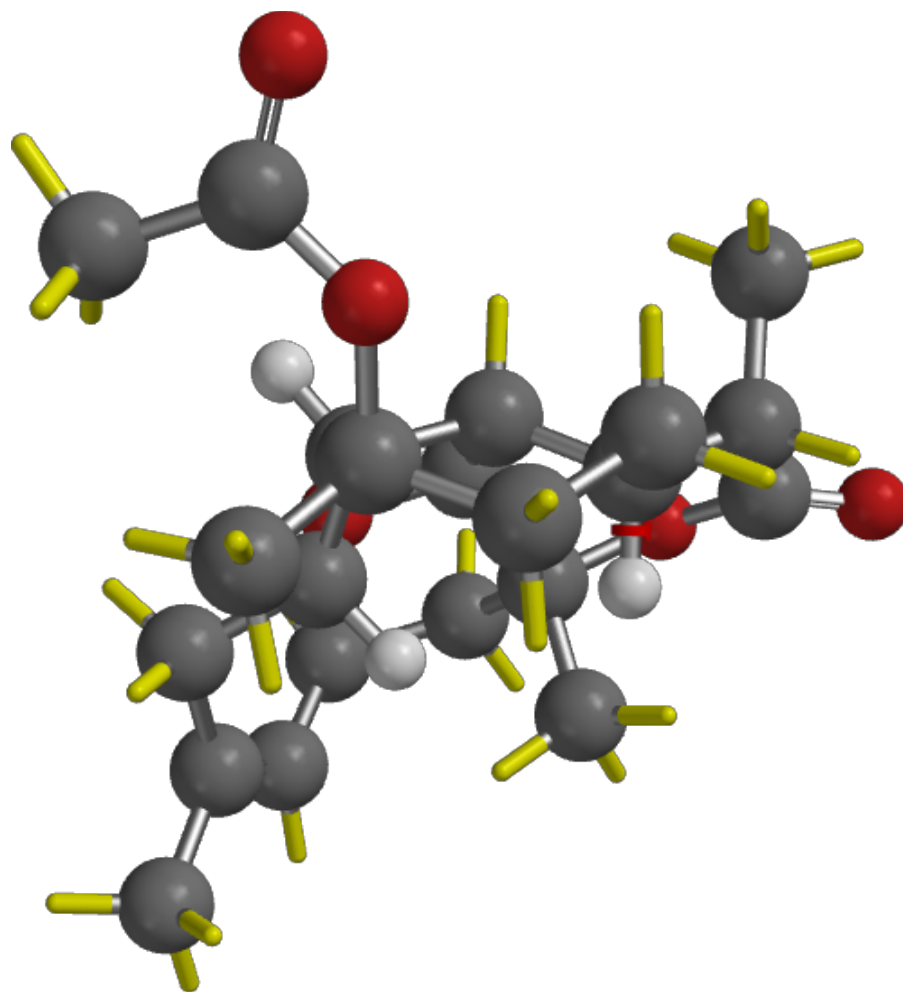
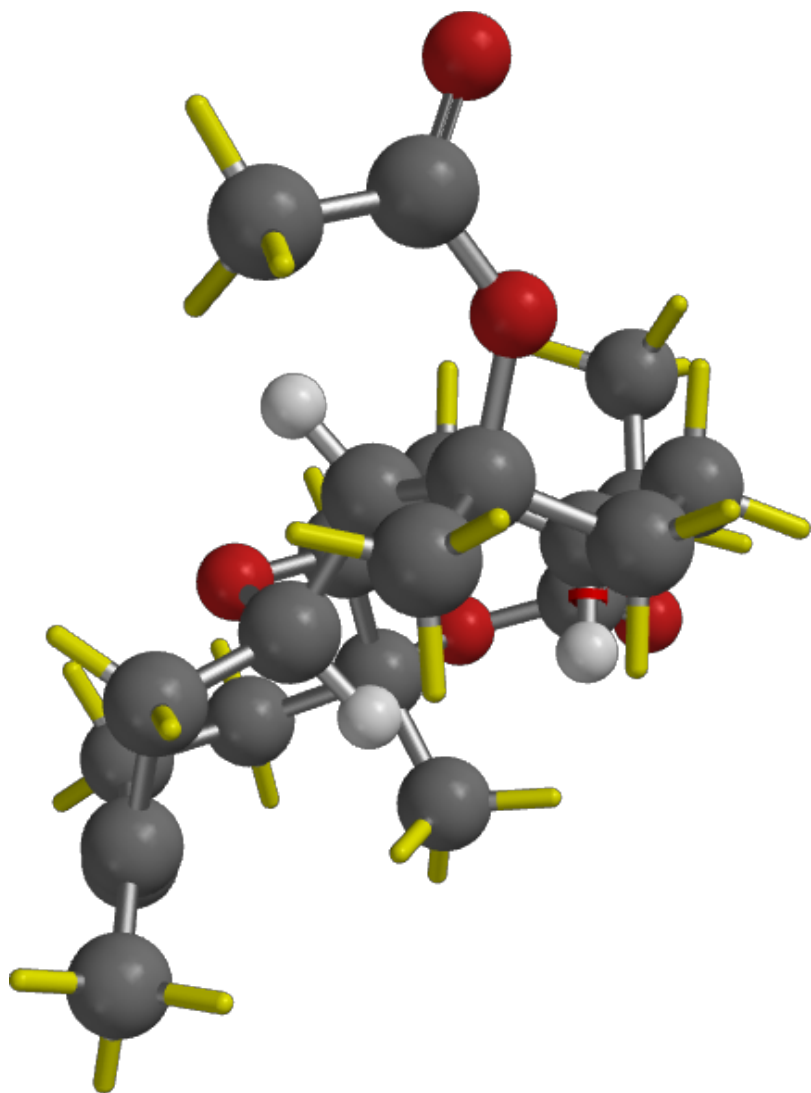
- The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra did not match the natural sample.

Crimmins, M. T.; Mans, M. C.; Rodríguez, A. D. *Org. Lett.* **2010**, ASAP

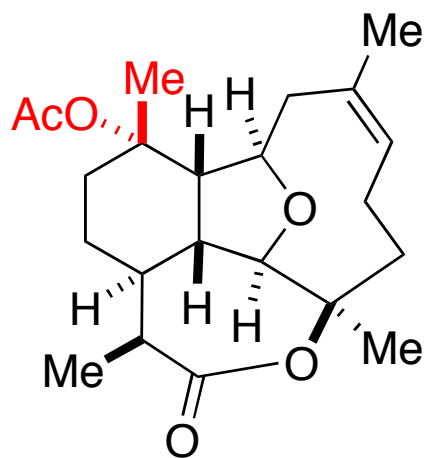
# Original structure



# Revised Structure



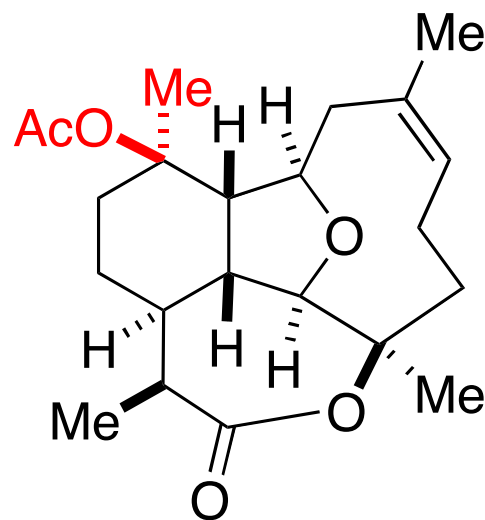
# Summary



originally proposed structure

- Provided a rationale that fits the observed nOe correlations, Overman's synthesis, and originally proposed biosynthesis.
- The Biosynthesis of this family has not been confirmed.

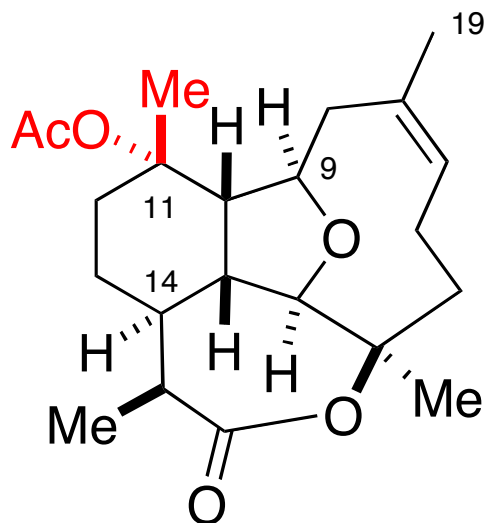
- Crimmins has determined the absolute configuration of several related diterpenes.
- Each family of diterpenes was generated through a similar exo-selective Diels-Alder cycloaddition



revised structure



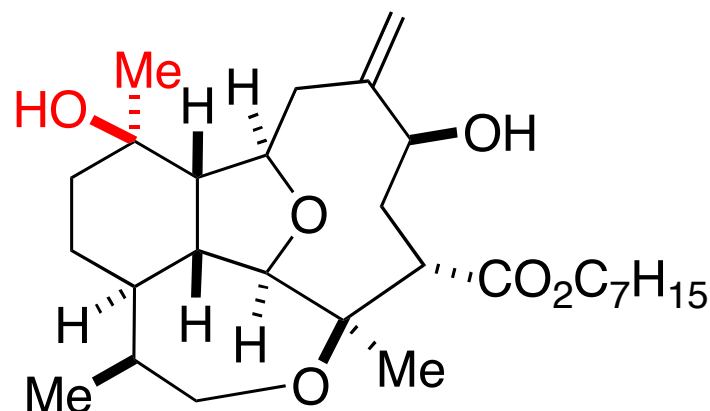
# Original characterization



briarellin J  
originally proposed  
structure

- Observed nOe:
  - C11 Me: H9, H10, H19
  - Ac Me: H1, H19
- Not observed nOe:
  - C11 Me: H14
  - Ac Me: H14

- $^{13}\text{C}$  NMR shifts  $\delta$  176.2 and 85.4 characteristic of seven-membered lactone ring.
- $^{13}\text{C}$  NMR shifts  $\delta$  91.9 and 80.6 which correlate by HMQC to two oxymethine protons identify the typical THF ring.



briarellin E  
(synthesis by Overman, **2003**)