Total Synthesis of (-)-Anominine

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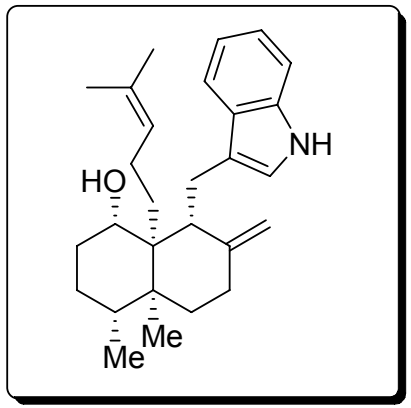
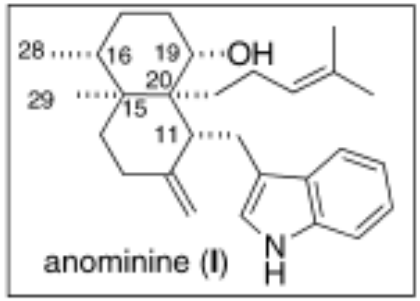


Xueling Mi

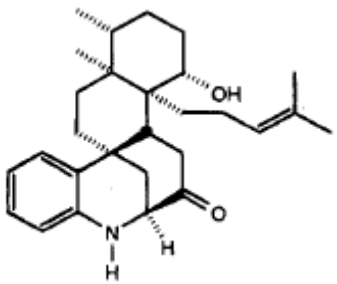
Wipf Group Current Literature

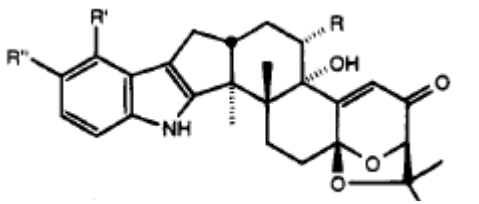
May 22, 2010



anominine (I)

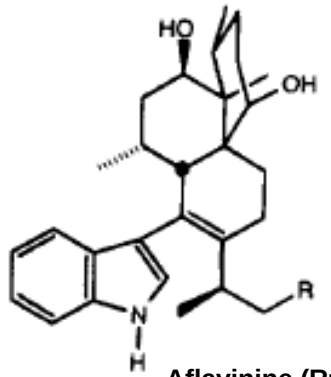
- isolated by J. B. Gloer from the sclerotia of the fungus *Aspergillus nomius* (NRRL 13137) in 1989 (along with aspernomine, 14-hydroxypaspalinine, 14-[(N,N-dimethylvalyl)oxy]paspalinine)
- structure was identified through NMR decoupling studies and by spectral comparison with aflavinines
- biogenetically related to the aflavinines
- *A. nomius* is close related to the common fungi *A. flavus* and *A. parasiticus (*both can selectively allocate antisectan aflavinine derivatives to their sclerotia)
- exhibit potent activity against crop pest *Heliothis zea* in controlled feeding experiments (causing 40% mortality and a 97% reduction in weight relative to controls when incorporated into a standard test diet at 100 ppm dry weight)
- ring structure: 2 quaternary C at the decalin ring junction and 5 stereocenters all arranged in a *cis* configuration





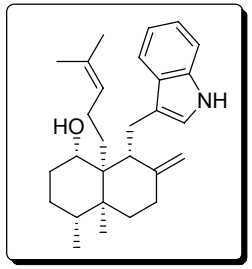
R = OH ; R' = R'' = H

R = $OCOCH(i\text{-}pr)N(CH_3)_2$; R' = R'' = H

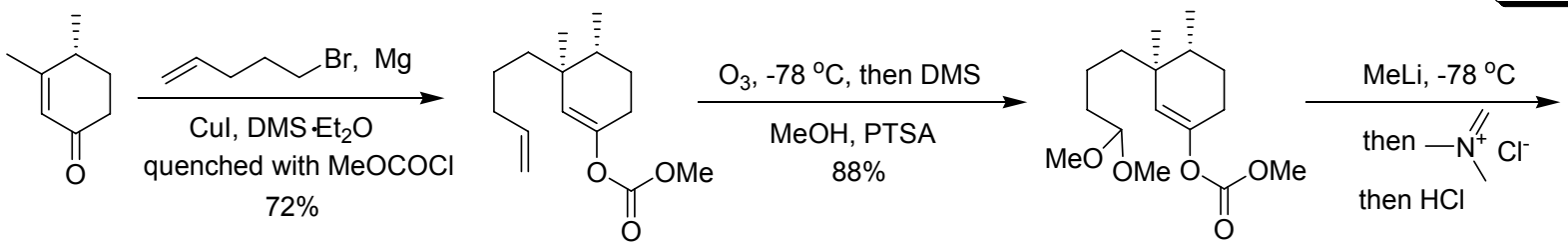


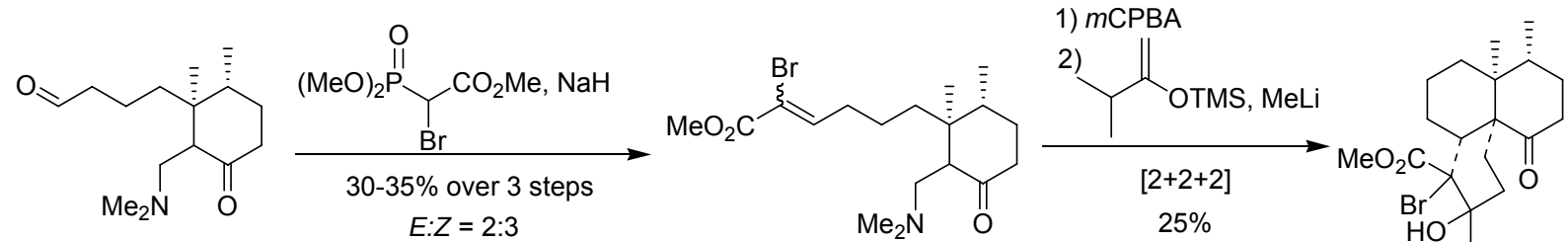
Aflavinine (R=H, OH)

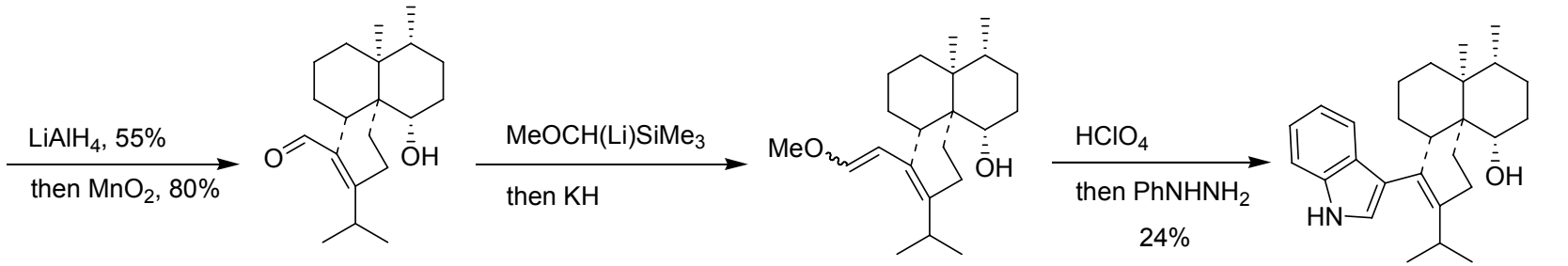
Gloer, J. B., Rinderknecht, B. L. Wicklow, D. T., Dowd, P. F. *J. Org. Chem.* **1989**, *54*, 2530-2532; Gloer, J. B. *Acc. Chem. Res.* **1995**, *28*, 343-350;



Synthesis of 3-Desmethylaflavinine

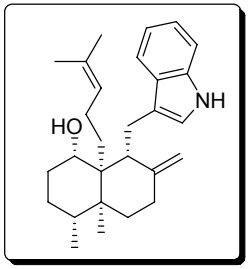




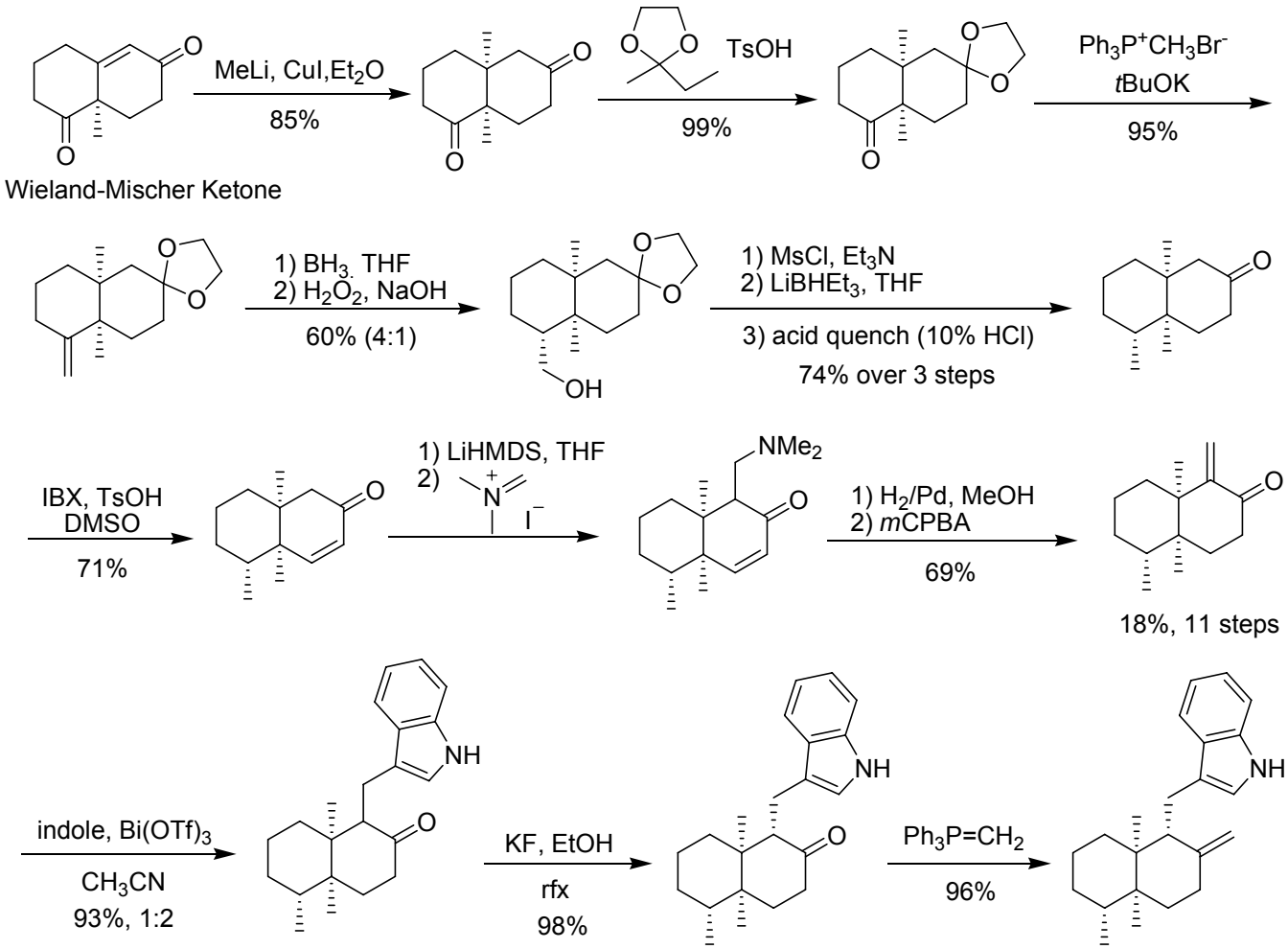


3-Desmethylaflavinine

Danishefsky, S., Chackalamannil, S., Harrison, P., Silvestri, M., Cole, P. *J. Am. Chem. Soc.* **1985**, *107*, 2474-2484.

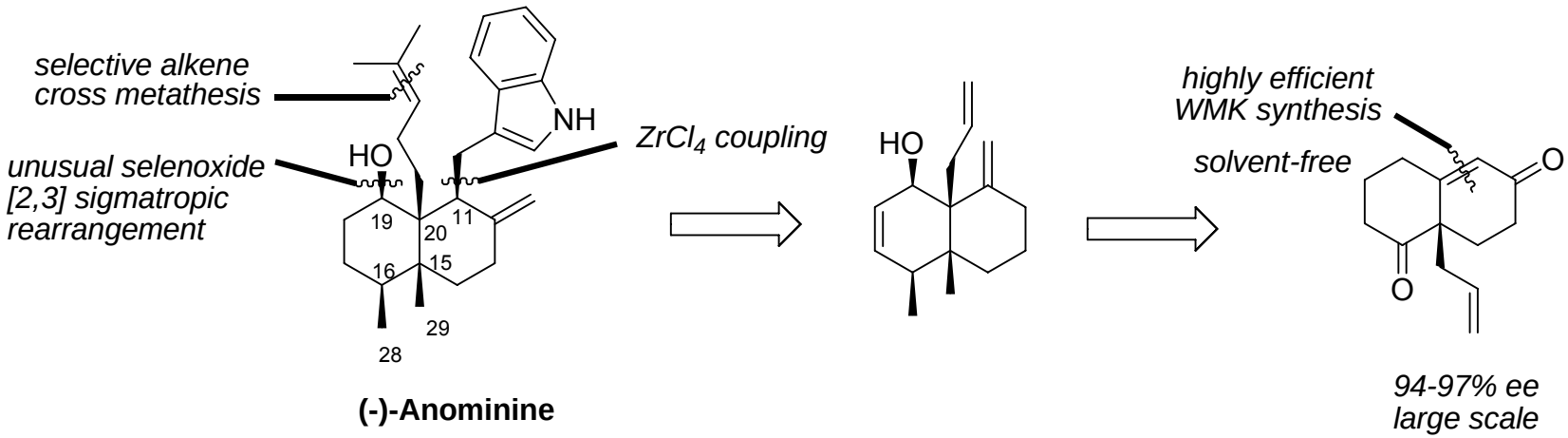


Previous Attempt of framework synthesis of Anominine



Bradshaw, B., Etxebarria-Jardi, G., Bonjoch, J. *Org. Biomol. Chem.* **2008**, *6*, 772-778; Diaz, S., Cuesta, J., Gonzalez, A., Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 7400-7406; Paquette, L. A., Wang, T. Z., Philippo, C. M. G., Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367-3374.

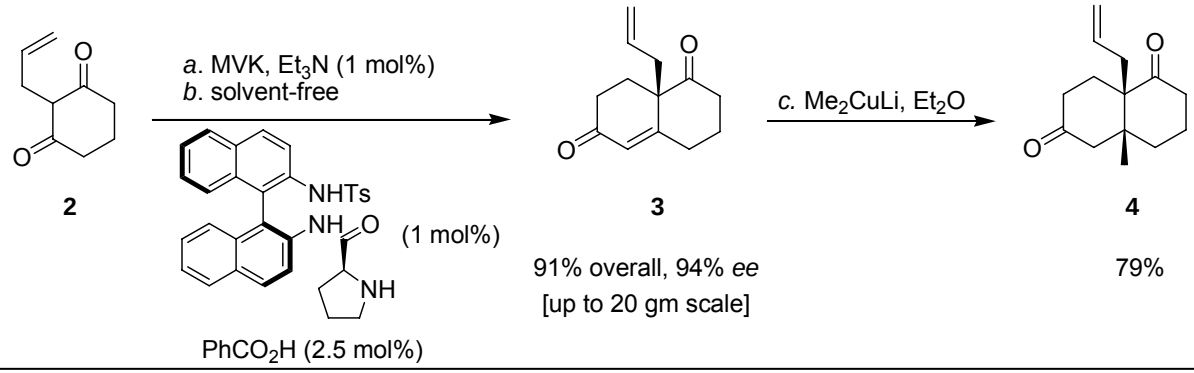
Retrosynthetic Analysis



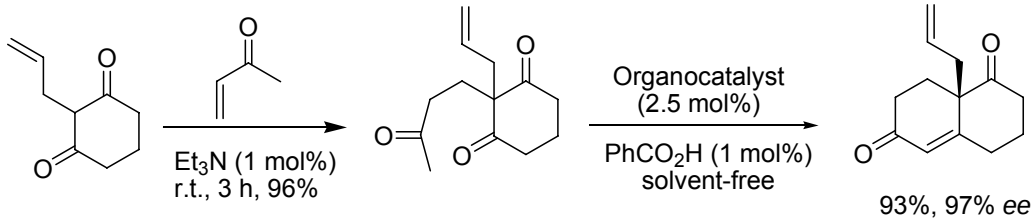
(-)-Anominine

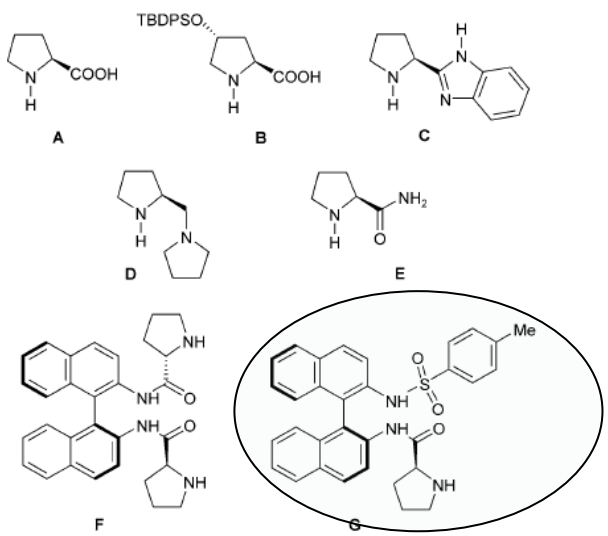
94-97% ee
large scale

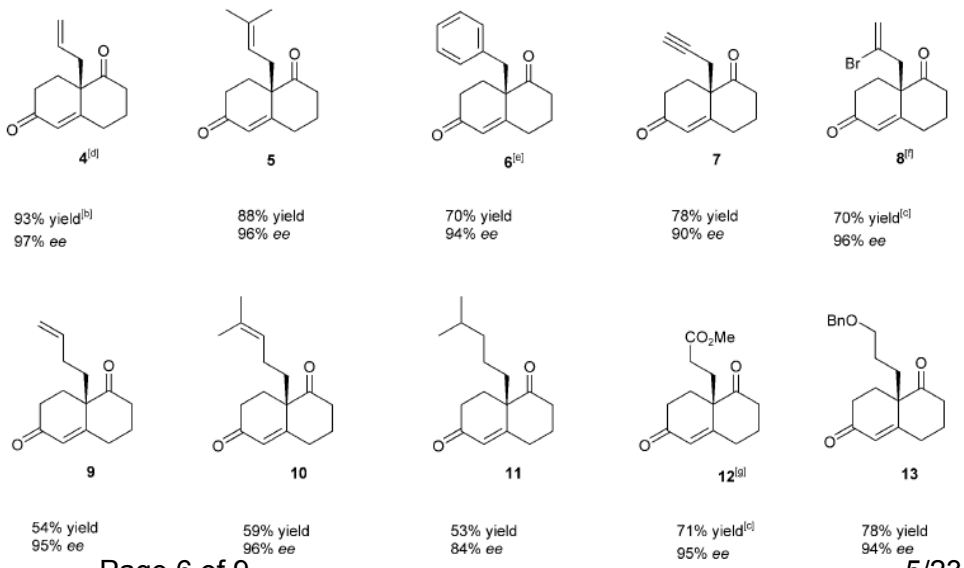
Organocatalyzed Asymmetric Synthesis of 3



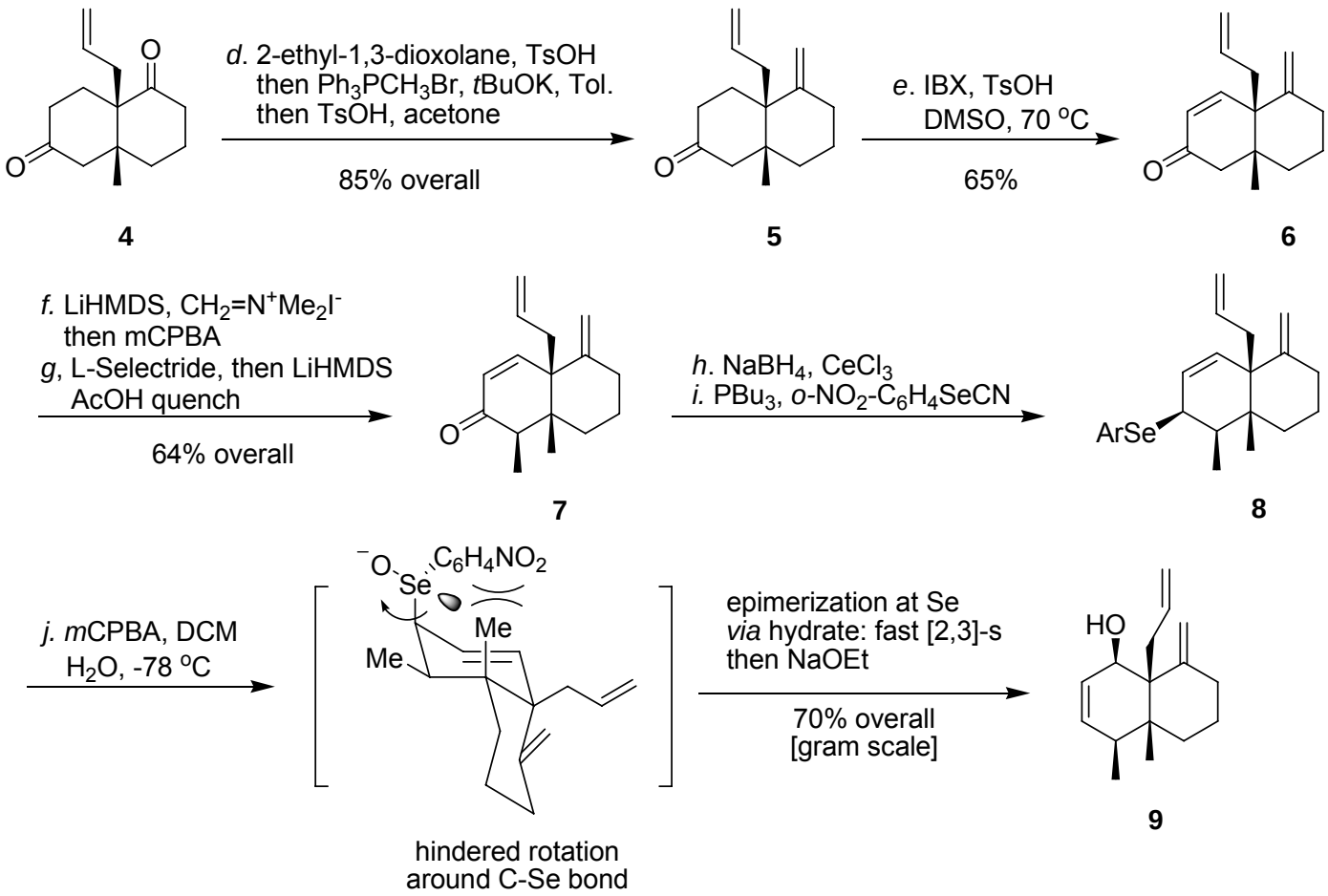
The Wieland-Miescher Ketone Synthesis



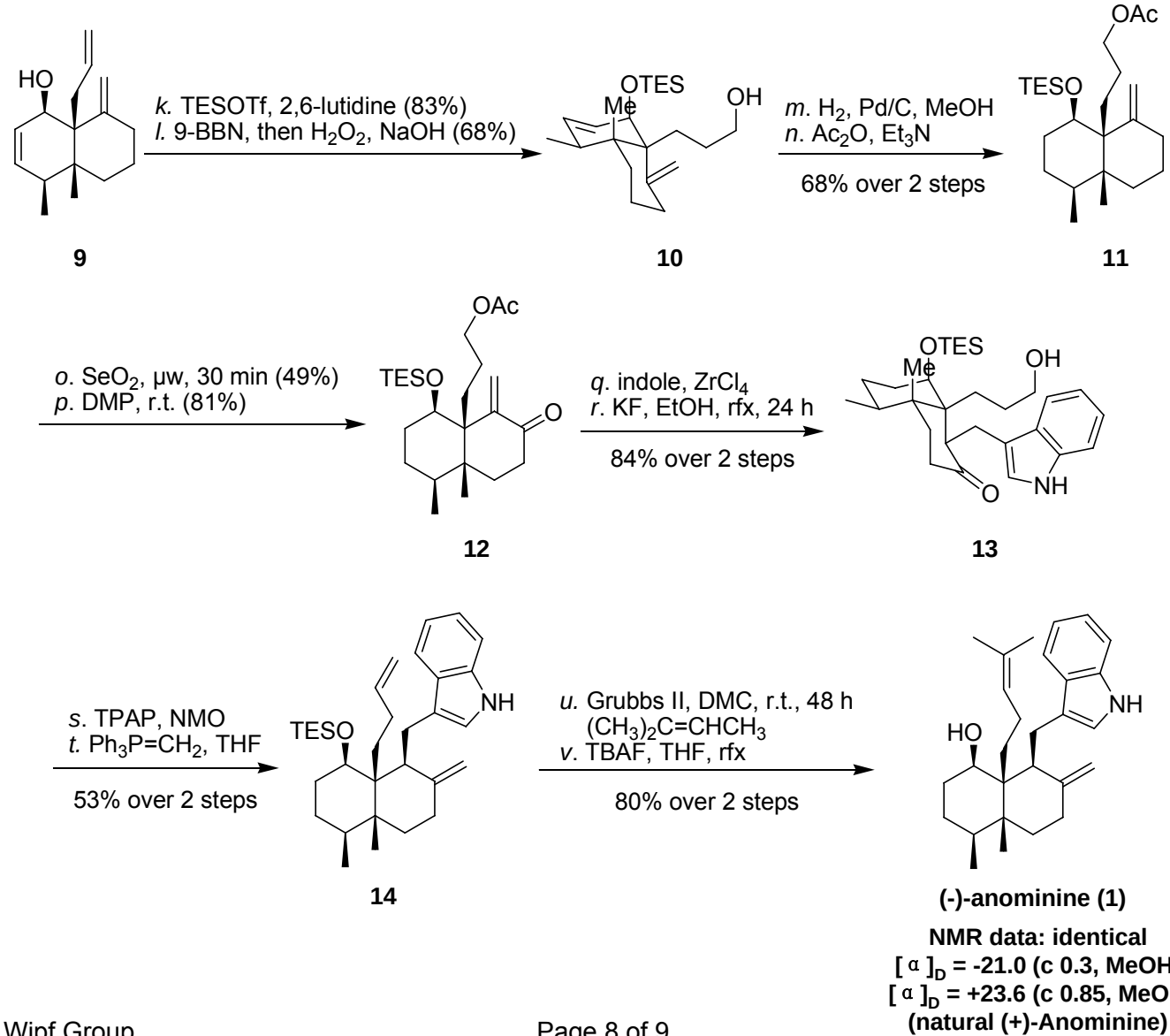




Synthesis of Key Intermediate 9



Completion of the Synthesis of (-)-Anominine



Summary

1. The first synthesis of anominine has been achieved
2. The absolute configuration was established
3. New highly efficient method for the synthesis of Wieland-Miescher ketone compounds (high yield and ee, small catalyst loading amount, scalable)
4. Several chemoselective transformations controlled by the structurally congested nature of the bicyclic core
5. Open the way for other related natural products from *Aspergillus spp.*