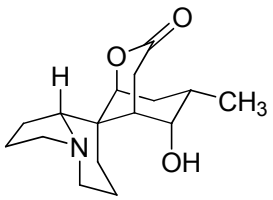
Matt Webber, April 2009

The Total Synthesis of (+)-Serratezomine A

A member of the *Lycopodium* class of alkaloids, (+)-Serratezomine A was isolated by Kobayashi and co-workers in 2000 from the club moss *L. serratum*. Its total enantioselective synthesis has recently been achieved by the group of Jeffery Johnston at Vanderbilt University, Nashville, Tennessee.

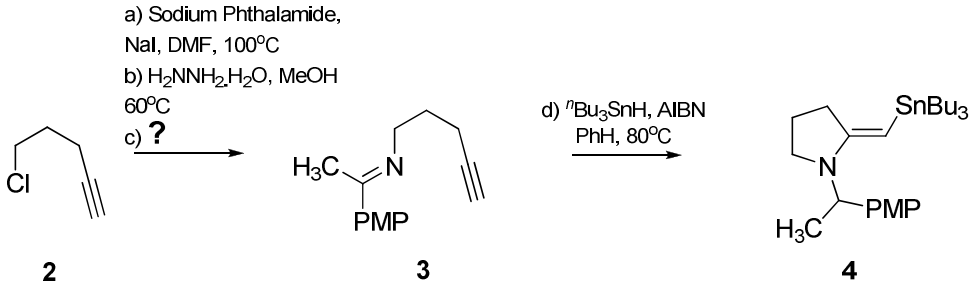


(+)-Serratezomine **1**

The longest linear sequence is 15 steps and the synthesis features an in-house developed free-radical-mediated vinyl amination as a key step. The chirality is introduced in an early alkylation step and the remainder of the synthesis is completed with a high level of stereocontrol.

Questions

Scheme 1 shows the preparation of the vinyl stannane **4**, the substrate for the aforementioned free-radical-mediated vinyl amination.

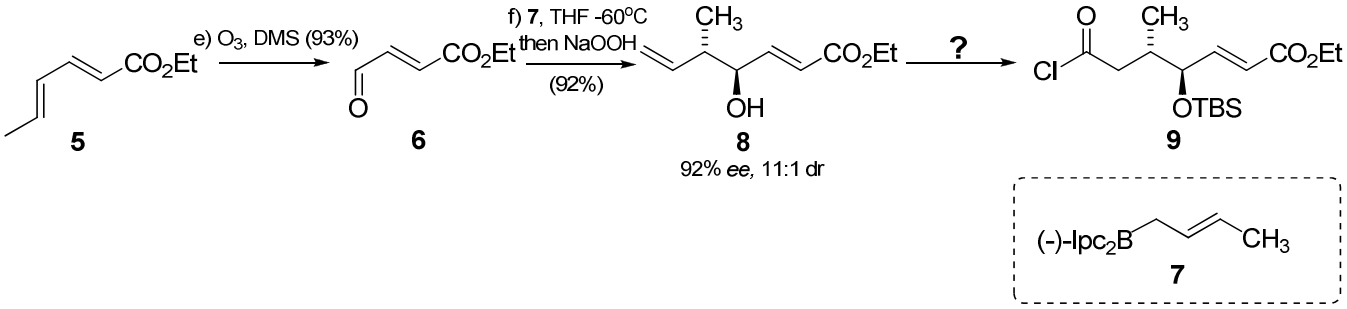


2 **3** **4**

Scheme 1

1. Give mechanisms for steps a and b and provide suitable conditions for step c.

2. Provide a mechanism for step d.



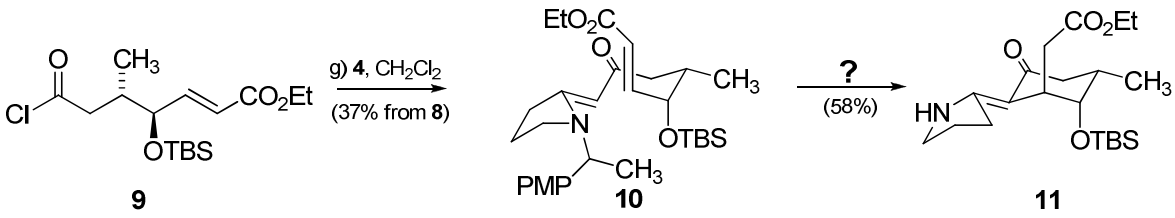
5 **6** **8** 92% *ee,* 11:1 dr **9** **7**

Scheme 2

3. Ozonolysis of ethyl sorbate provides the aldehyde **6**. Why is the reaction selective for the terminal alkene?

4. An asymmetric alkylation of **6** with Brown's crotonylation reagent **7** gave allylic alcohol **8** with high enantio- and diastereoselectivity. Account for the diastereoselectivity.

5. Suggest a sensible synthetic sequence to go from **8** to **9**.

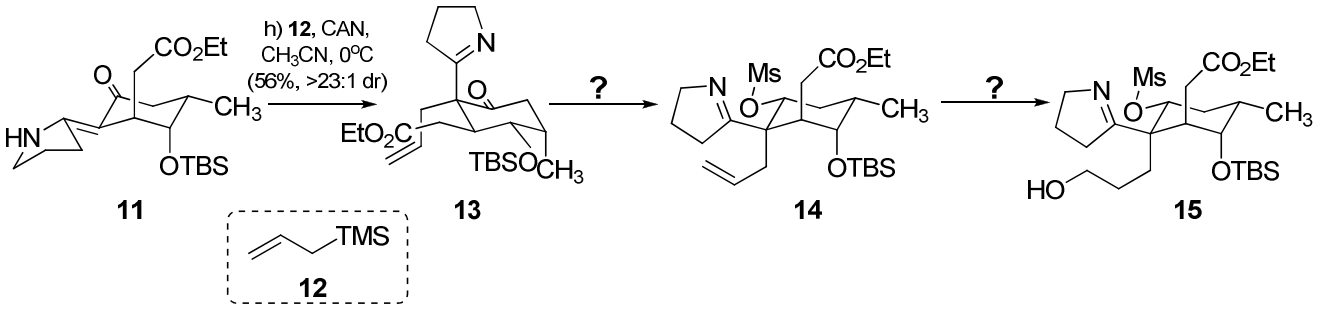


Scheme 3

6. Suggest conditions for the dealkylation of the pyrrolidine nitrogen in **10**.

7. The cyclohexanone **11** was formed selectively upon dealkylation of nitrogen. Can you suggest why?

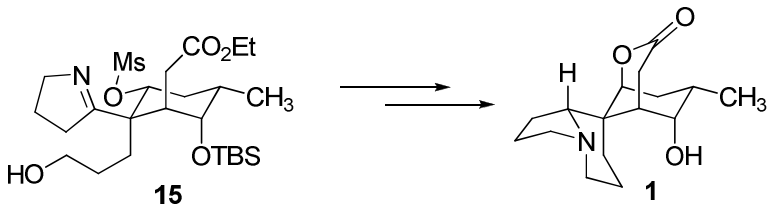
8. There are other isomers that could potentially arise from the ring-closing event. Draw as many as you can. How could you distinguish between them?



Scheme 4

9. The oxidative allylation of **11** with allyltrimethylsilane installs the final three carbon atoms of the skeleton. Can you propose a mechanism?

10. With all the carbon atoms now present, only a few simple bond formation steps are required to furnish the natural product. Propose a synthetic sequence from ester **13** to the target using the intermediates **14** and **15** to guide you.



Scheme 5