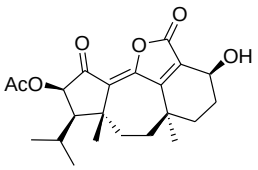
Spivey Group Problem Session - July 2010

Total Synthesis of Guanacastepene N

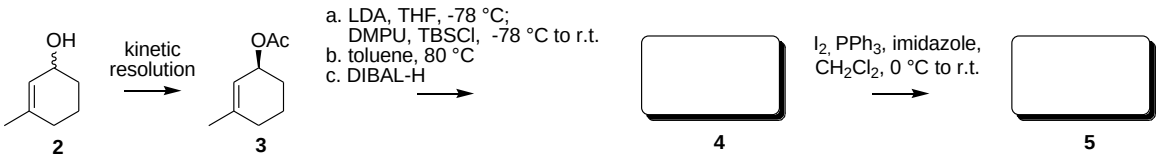
set by Sarah Warren

The guanacastepenes were isolated from an endophytic fungus growing on the tree *Daphnosis americana* in the Guanacaste Conservation Area in Costa Rica.[1] Their structures have been established by X-ray crystallography of two members of this set.[2] Their unique molecular structure and their antibacterial activity against methcillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*, stimulated great interest in their total synthesis. To date, many members of the guanacastepene series have been synthesised. This problem session is based on the second only enantioselective synthesis of a member.[3] This problem set follows the enantioselective synthesis of guanacastepene N (**1**), which employs an uncommon 7-endo Heck cyclisation as a pivotal step.



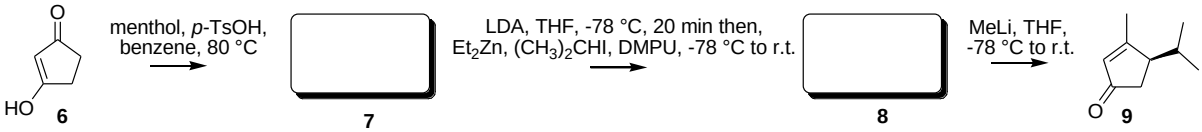
1 Guanacastepene N

1. Identify intermediates **4** and **5** and propose mechanisms for their formation (see Q3 for a hint).



2 **3** **4** **5**

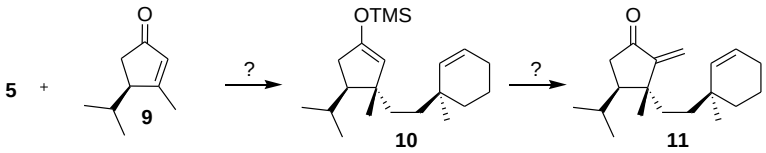
2. Enantioenriched cyclopentenone **9** was prepared by employing a Stork-Danheiser reaction using (+)-menthol to control the stereoselectivity. Identify intermediates **7** and **8** and discuss the stereochemical outcome of the sequence.



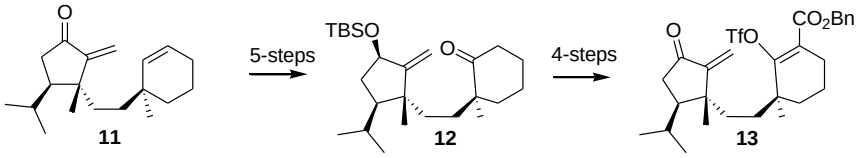
6 **7** **8** **9**

dr 1.5:1

3. Suggest a one-pot procedure for the formation of intermediate **10** and reagents for the conversion to enone **11**.

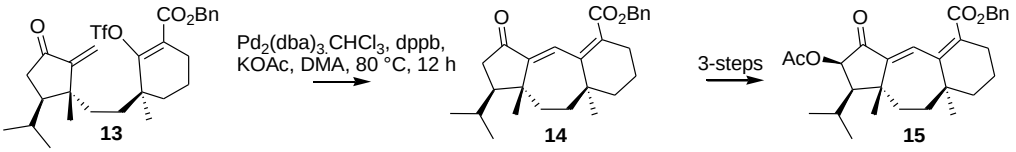


4. A 9-step sequence from enone **11** to Heck precursor **13** was performed. With the help of intermediate **12**, suggest reagents for this sequence. Discuss any selectivity involved, explain the order of events and provide mechanisms.



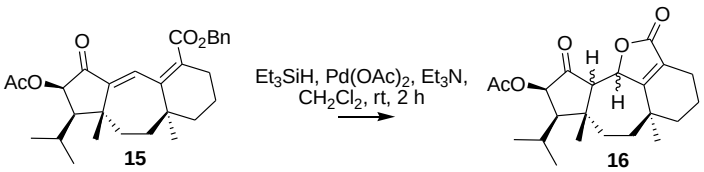
11 **12** **13**

5. Suggests reagents for the formation of intermediate **15**.



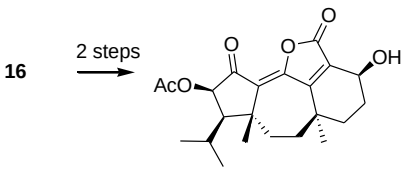
13 **14** **15**

6. Provide a mechanism for the formation of lactone **16**.



15 **16**

7. Suggests reagents to complete the synthesis of Guanacastepene N (**1**).



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References

1. Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116-2117.
2. Brady, S. F.; Bondi, S. M.; Cardy, J. *J. Am. Chem. Soc.* **2001**, *123,* 9900-9901.
3. Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095-13101.