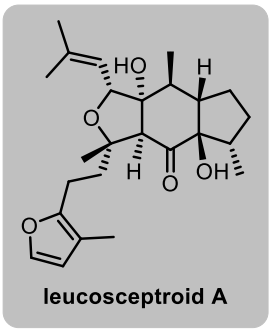
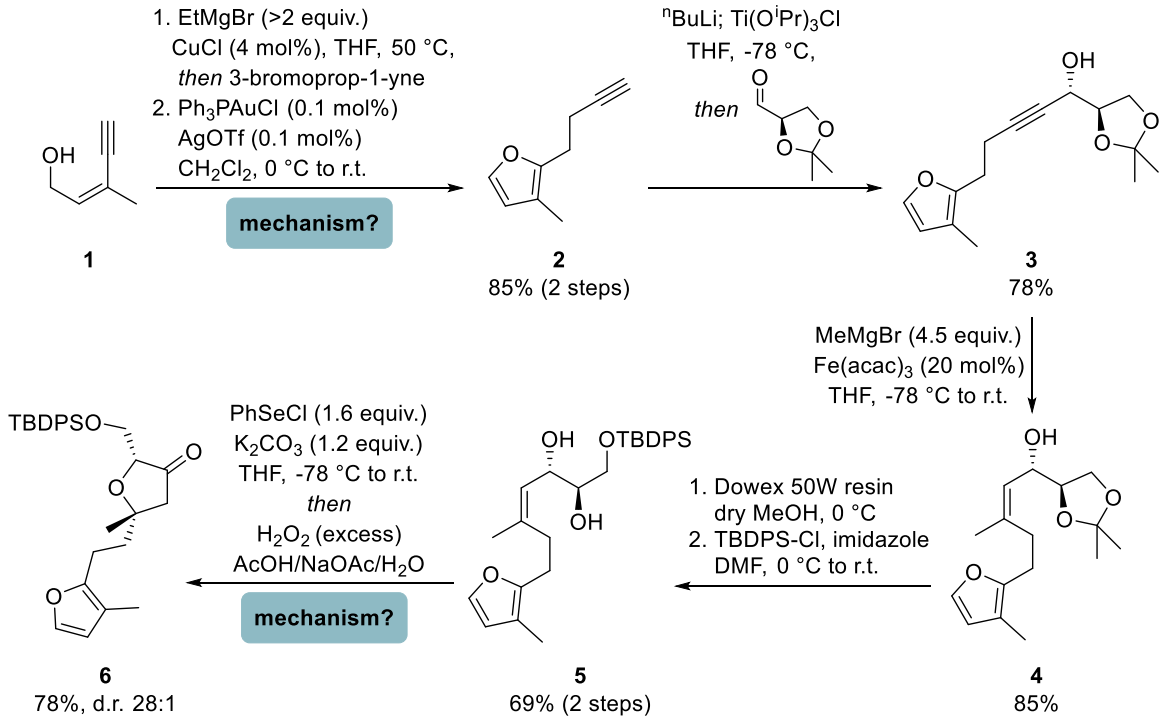
Total Synthesis of Leucosceptroid A



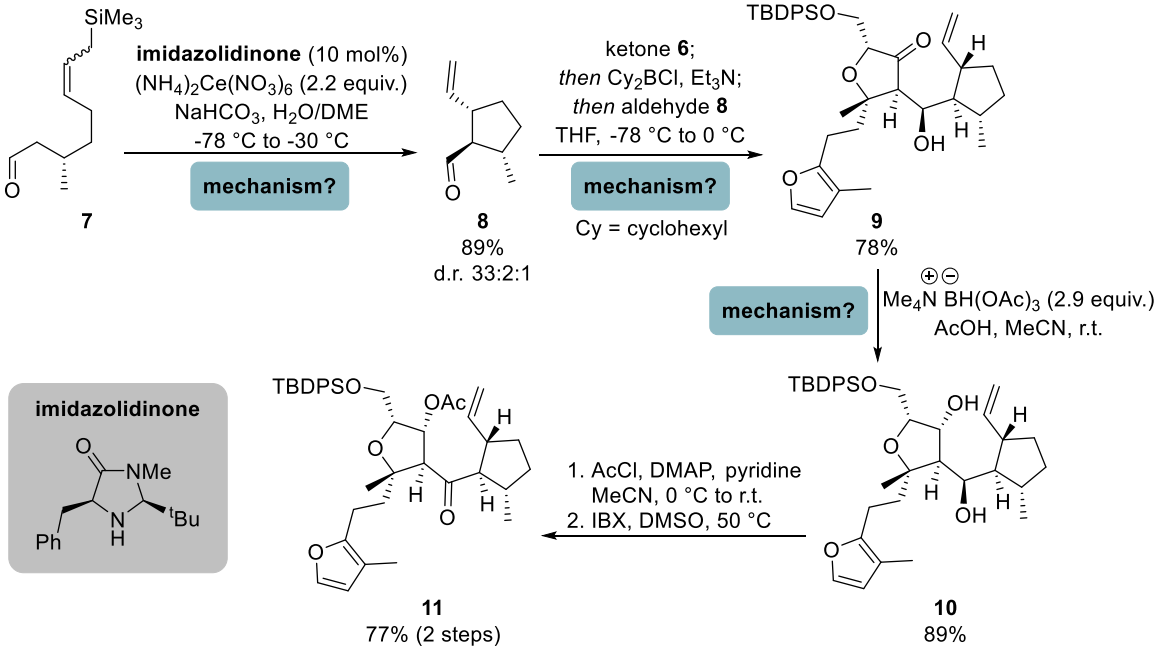
Angew. Chem. Int. Ed., **2015**, 54, 1298

1. Consider the sequence shown below, from enyne **1** to ketone **6**.



   a. Identify the product of the reaction of **1** with 3-bromoprop-1-yne under the conditions shown and propose a mechanism for the gold-catalysed formation of furan **2** from this compound.
   b. Consider the carbometallation/protonation of propargylic alcohol **3** to give *Z*-allylic alcohol **4**. Suggest a convenient method for accessing the *E*-isomer of **4**.
   c. In this synthesis, acetonide **4** was deprotected using a Dowex acid resin. What are the benefits of using a polymer-supported acid rather than an aqueous acid solution or a Lewis acid?
   d. Propose mechanisms for the conversion of **5** to ketone **6**, accounting for the stereoselectivity shown. How does the stereochemistry of the alcohol stereocentre set in the formation of **3** affect this two-step process?

2. Consider the sequence shown below, from aldehyde **7** to ketone **11**.

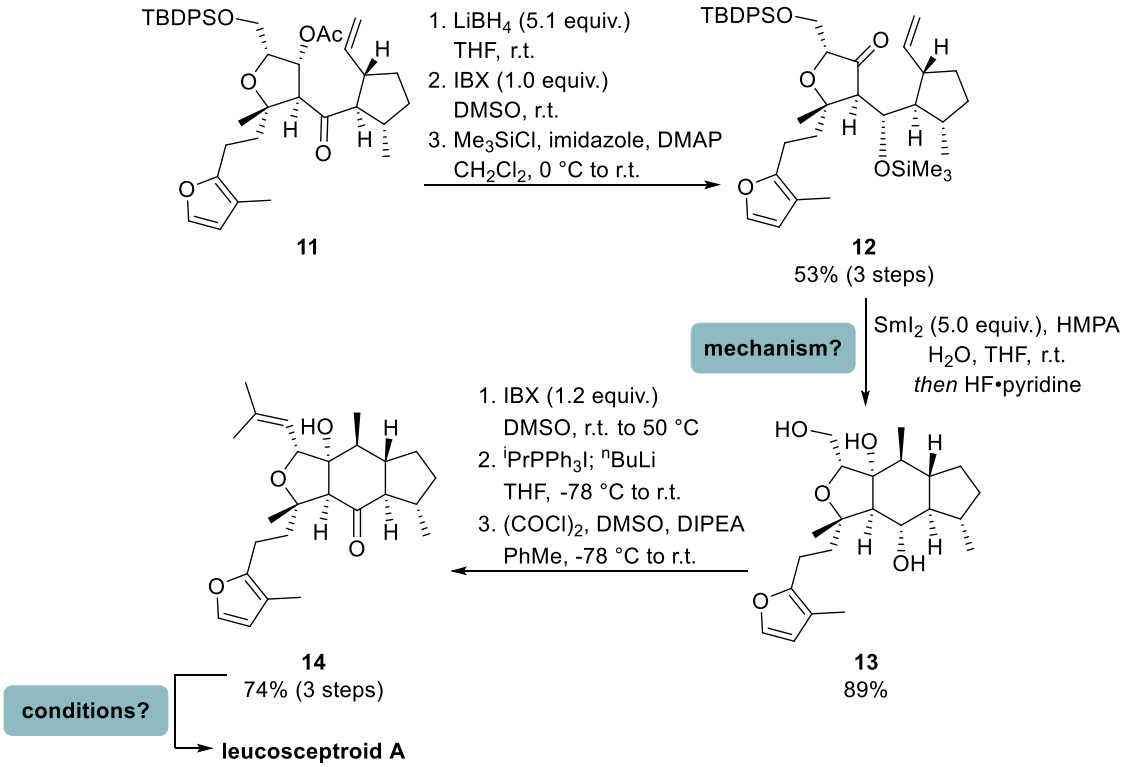


a. Propose a mechanism for the asymmetric, intramolecular α-allylation of **7** to give **8**. What is unusual about this transformation, looking at just the starting material and the product?

b. Provide a mechanism for the reaction of ketone **6** with aldehyde **8** under the conditions shown.

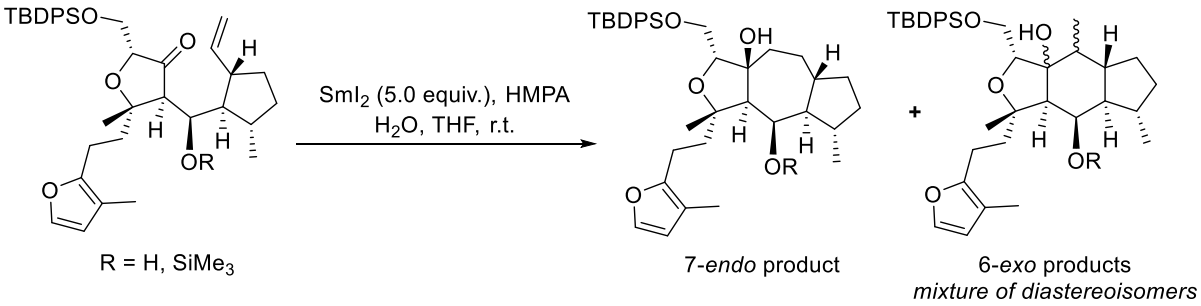
c. Provide a mechanism for the diastereoselective reduction of **9** to give *syn*-1,3-diol **10**. Suggest a method for the conversion of **9** to the corresponding *anti*-1,3-diol.

3. Consider the sequence shown below, from ketone **11** to leucosceptroid A.



a. Propose a mechanism for the samarium(II) iodide-mediated cyclisation of ketone **12** to give **13** (after desilylation).

b. The latter half of this synthesis involves a number of redox manipulations that, effectively, serve to invert the stereochemistry of the alcohol stereocentre established in the aldol step. This was necessary because **9** and TMS-protected **9** gave unwanted side products when subjected to the cyclisation conditions (see below). Suggest a more direct strategy to access **12** from **9** or any earlier intermediates in this synthesis.



R = H, $SiMe_3$

7-*endo* product

6-*exo* products
mixture of diastereoisomers

c. Suggest conditions for the α-hydroxylation of **14** to give leucosceptroid A.