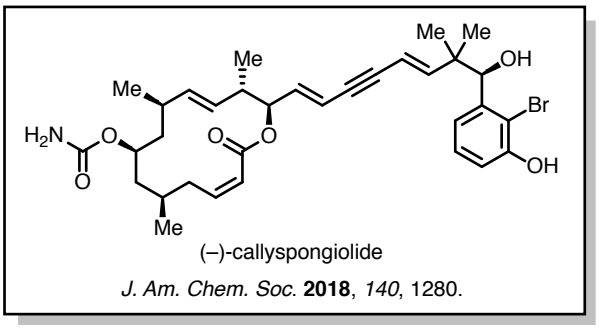
Engle Lab Short Problem Set

7/12/2018

(–)-Callyspongiolide was first isolated in 2014 by Proksch and co-workers. Interestingly, in the cell types examined, this potent cytotoxin was shown to trigger cell death via nonapoptotic pathways. Considering apoptotic signaling is suppressed in many cancers, compounds that kill cancer cells by nonapoptotic pathways represent valuable tools to explore novel therapeutic startegies. With this in mind, the Harran lab developed a total synthesis that leverages contemporary catalysis to join fragments and build complexity. This problem set will cover interesting reactions utilized to get to the natural product.



(–)-callyspongiolide

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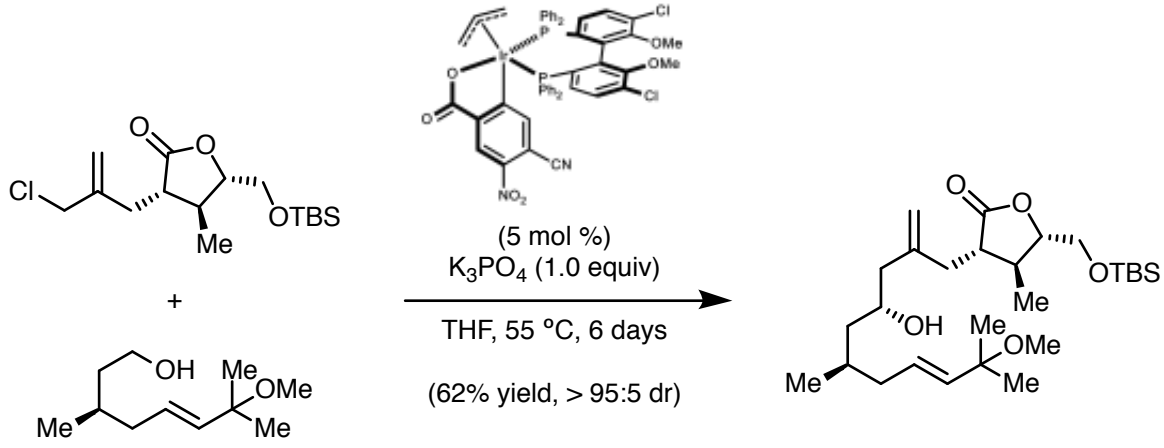
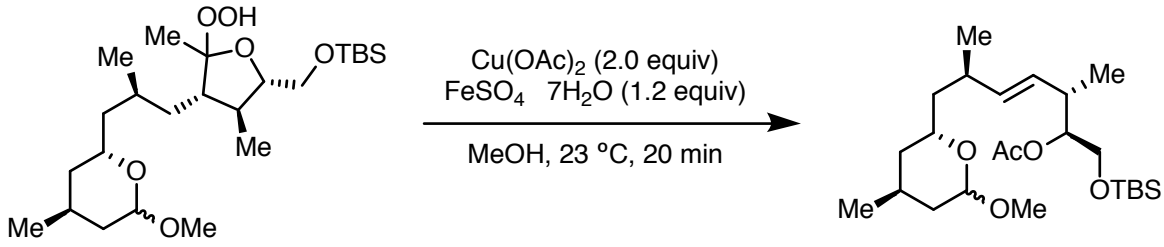
1. The first catalytic reaction used in the synthesis was developed by Krische and co-workers. The reaction forges a new C–C bond between a primary alcohol and an allylic chloride via net loss of HCl. Draw a mechanism for this transformation.



2. Degradation of a butyrolactone via perhemiketal fragmentation afforded a stereo- and regio-defined homoallylic acetate. This method was originally pioneered by Schreiber and co-workers. Draw a possible mechanism for this transformation.



3. As is often the case in total synthesis, the initial route to the product did not pan out. To get around the macrocyclization problem, a new alkene-bearing substrate was design and subjected to a cascade variant of the Semmelhack cyclization. Draw a mechanism for this transformation.