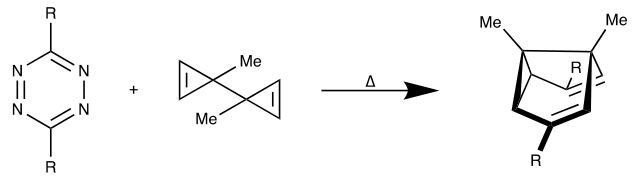
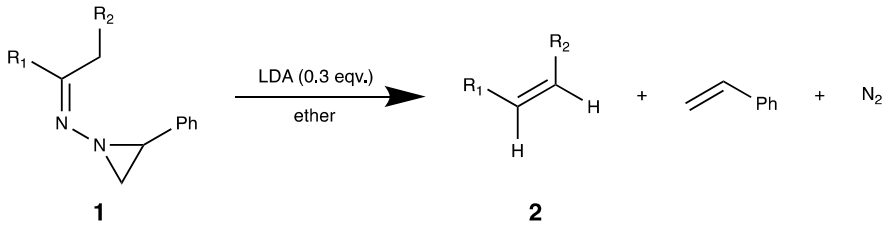
Spivey Group Problem Sheet November 2018

1) Provide a plausible mechanism for the following transformation:

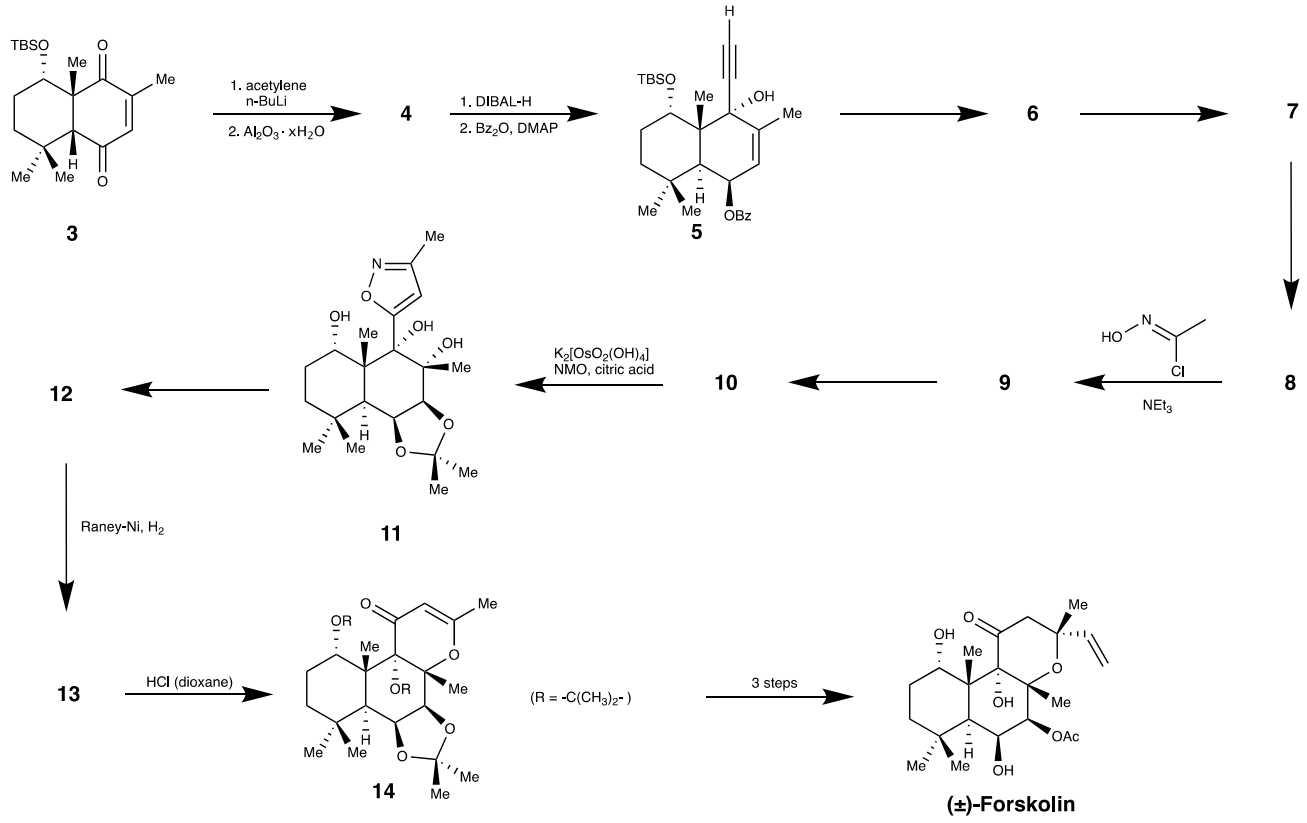


2) Provide a mechanism for the formation of the cis-disubstituted alkene **2** from the phenylaziridinylhydrazone **1** using catalytic amounts of LDA (R_1 = pentyl, R_2 = butyl).

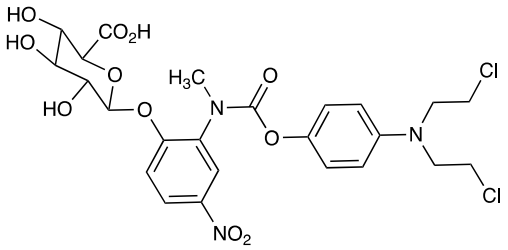


1 **2**

3) Forskolin is a diterpene natural product of *Plectranthus barbatus.* It is a potent allosteric stimulator of adenylyl cyclase which catalyses the production of cAMP from ATP. It is of high interest in biological studies and one analogue, NKH477, has been approved in Japan to treat heart failure. Early total syntheses by Corey, Ziegler and others involved 30-40 steps and commercial production uses bio- or semi-synthesis. Below is a recently reported total synthesis of forskolin starting from cis-decalin **3** (8 steps from commercial materials) totalling 24 steps in total. Propose a mechanism for each step and fill in the missing reagents and intermediates where needed.

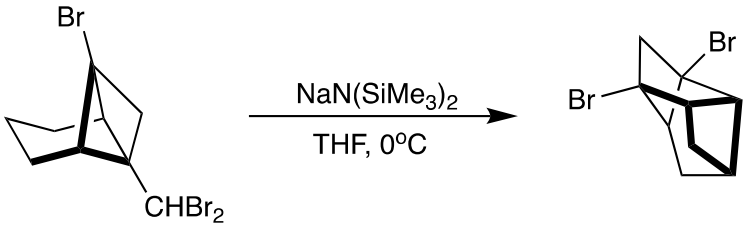


4) Compound **15** is an anti-tumour prodrug metabolised by β-glucuronidase, which leads to the formation of three fragments. Propose a possible mechanism for the activation of the prodrug. Hint: One product fragment is bicyclic. Also, the enzyme can act as a proton source and a base.

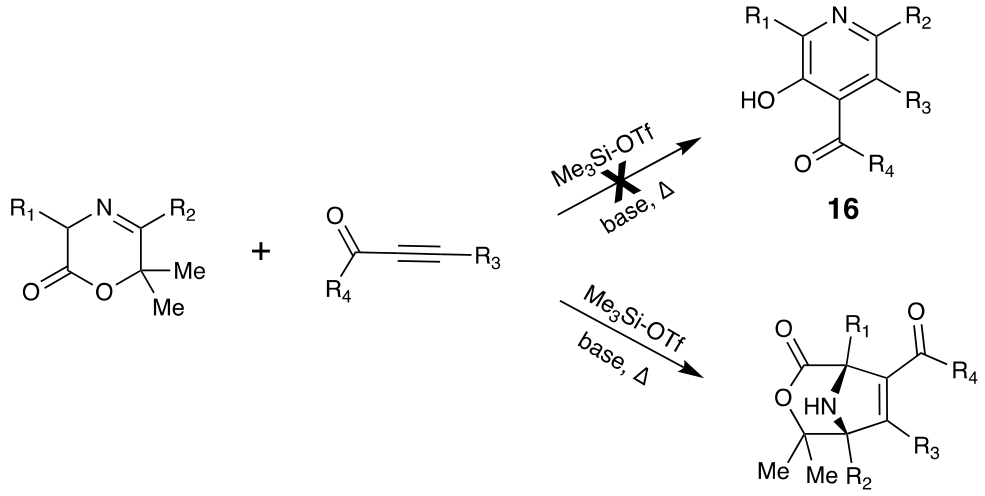


15

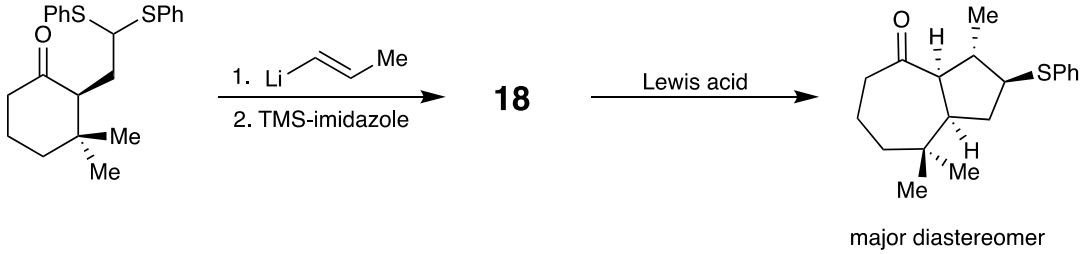
5) Propose a mechanism for the following transformation.



6) The reaction below was carried out with the aim of forming product **16**. However, no **16** was formed with the major product being **17**. Suggest a reasonable mechanism for the proposed, but unsuccessful, formation of **16**. Account for the formation of **17** instead of **16**.

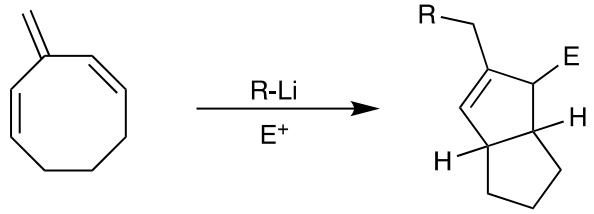


7) The following is a key step in the synthesis of shahamin K as reported by Overman *et al*. Provide a mechanism for each step and identify intermediate **18**.

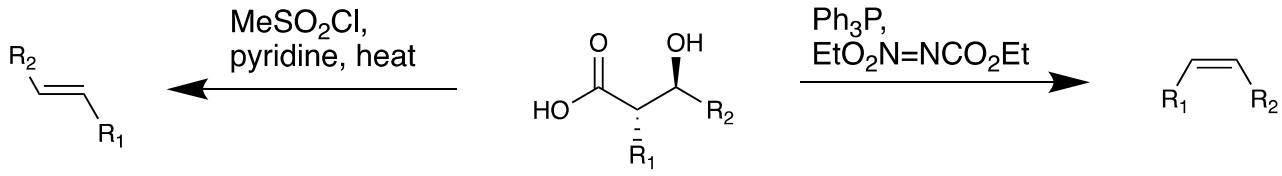


major diastereomer

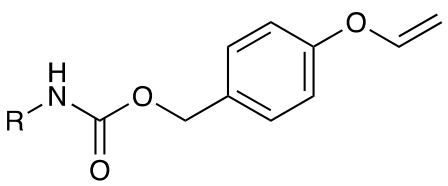
8) Williams *et al*. have reported the following tandem alkyllithium-induced cyclization/electrophile alkylation as a method of forming functionalized [3.3.0]-bicyclic ring systems. Provide a mechanism for this reaction and predict the stereochemical outcome.



9) Anti β-hydroxy acids can be used as precursors to 1,2-disubstituted olefins. Propose reasonable mechanisms for each of the two reactions below. Account for the selectivity of each reaction for the (E) and (Z) olefin respectively.



10) Compound **19** was designed to release cargo **R** through a self-immolative mechanism when in the presence of tetrazine motifs. Propose a mechanism for the sensing of tetrazine and the release of **R**.



19

11) As part of the synthesis of (+)-α-anocerin Corey *et al.* performed the following two step transformation. The reaction was proposed to proceed via intermediate **20** (although it was not isolated). Propose a mechanism for each step and the identity of **20**. Account for the geometries of the alkenes in the product.