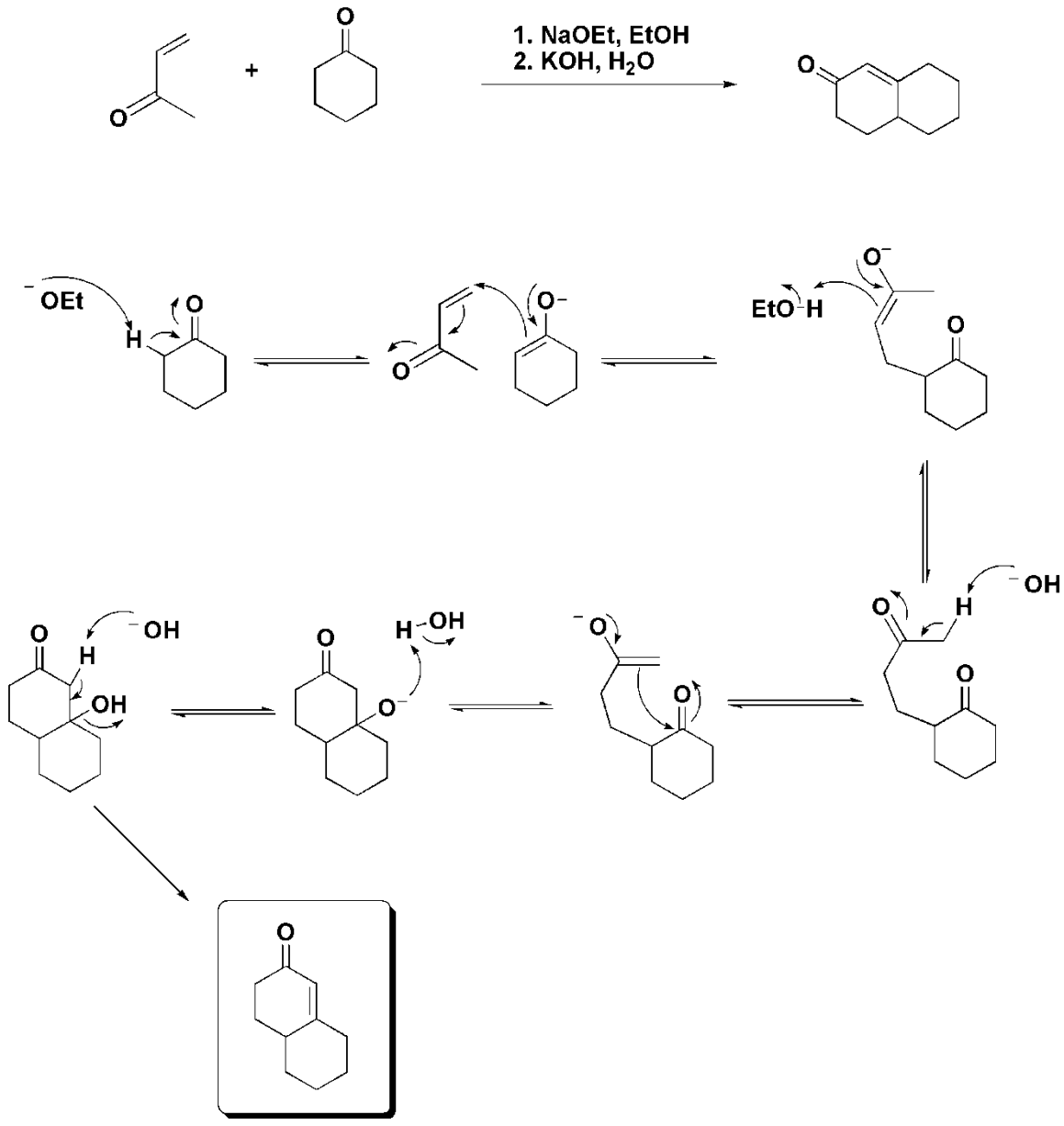
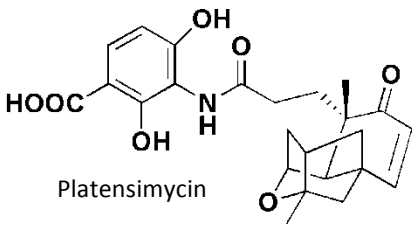
Name (Print)_____
ID#_____
Group #_____

PS #4 – Robinson Annulation Mechanism and Synthetic Planning

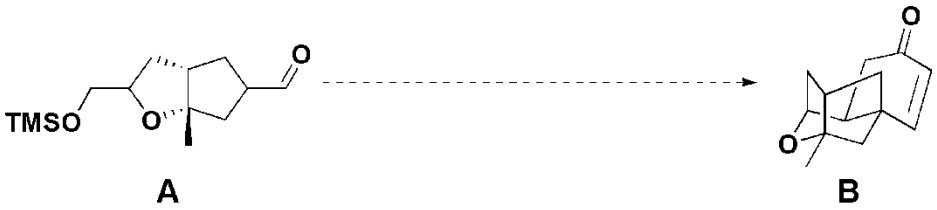
Part A) When a conjugate addition (Michael addition) is followed by an intramolecular aldol condensation, a new ring is formed. This sequential process is called the Robinson annulation (or annelation). Annulation is a term that describes the formation of a ring. As a group, work out the detailed mechanism for the Robinson annulation reaction between 2-methylcyclohexanone and methyl vinyl ketone (3-buten-2-one).



Part B) Platensimycin is a novel lead compound recently discovered by researchers at Merck Research Laboratories. It was isolated from a strain of *Streptomyces platensis* and is the first new chemical class of antibiotic to be found in more than two decades! Platensimycin kills several of the major drug-resistant bacteria that plague hospitals (MRSA and bacteria resistant to vancomycin). Platensimycin works differently from other commercially available antibiotics. It disrupts a bacterial enzyme responsible for the production of fatty acids, thus preventing bacteria from making the fatty cell membranes they need to grow. Since the structure of Platensimycin was elucidated, several research groups have been working to synthesize the antibiotic. It has been proposed the complex tetracyclic core structure of Platensimycin (B) could be synthesized using an intramolecular Robinson annulation. Working as a group, propose a reasonable synthetic route to synthesize the Platensimycin precursor (B) from the starting material (A) below.



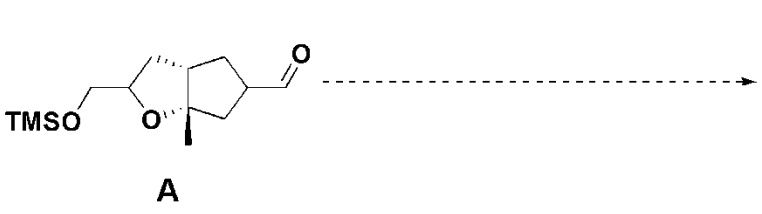
Platensimycin



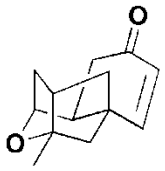
A **B**

*It may help you to work backwards from **B** when solving this problem. Starting with **B**, identify where the intramolecular aldol reaction is occurring. Which bonds are forming? Which fragment is the enone and which is the enolate? The double bond in the final product comes from dehydration of an alcohol. Get the alcohol in the correct place and this should help you figure out what the molecule looked like before the intramolecular Robinson annulation occurred.*

*Once you have worked out the structure of the molecule before annulation, flatten it out and determine what other transformations need to occur in order to synthesize **B** from **A**. As always, keep in mind functional group compatibility.*



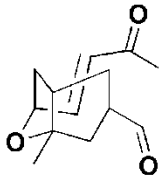
A



B

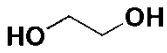
First, the reactant is treated with strong base to deprotonate the carbon α to the aldehyde (froming the enolate) which adds by conjugate addition to the enone. In the second step, milder base is used to deprotonate the carbon α to the ketone (forming a second enolate). This enolate attacks the aldehyde. Heat ensures the resulting alcohol is dehydrated to form the conjugated double bond.

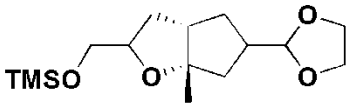
1. NaOMe, THF
2. K_2CO_3, MeOH, heat



If you render the molecule in 3D, it is now set up perfectly for an intramolecular Robinson Annulation

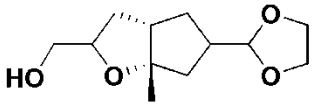
Protect the aldehyde in preparation for an aldol condensation at the OH position.

pTsOH, 



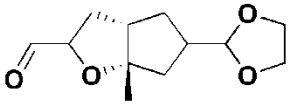
Deprotect the silyl ether using a source of F^-.

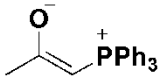
TBAF (NBu_4F) or **CsF**



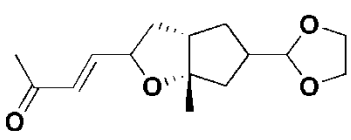
Oxidize the alcohol to the aldehyde.

PCC





Form the conjugated enone that will act as the electrophile in the Robinson annulation. This can be accomplished with a stabilized Wittig (E selectivity).



Deprotect the acetal to regenerate the aldehyde.

2M H_2SO_4