

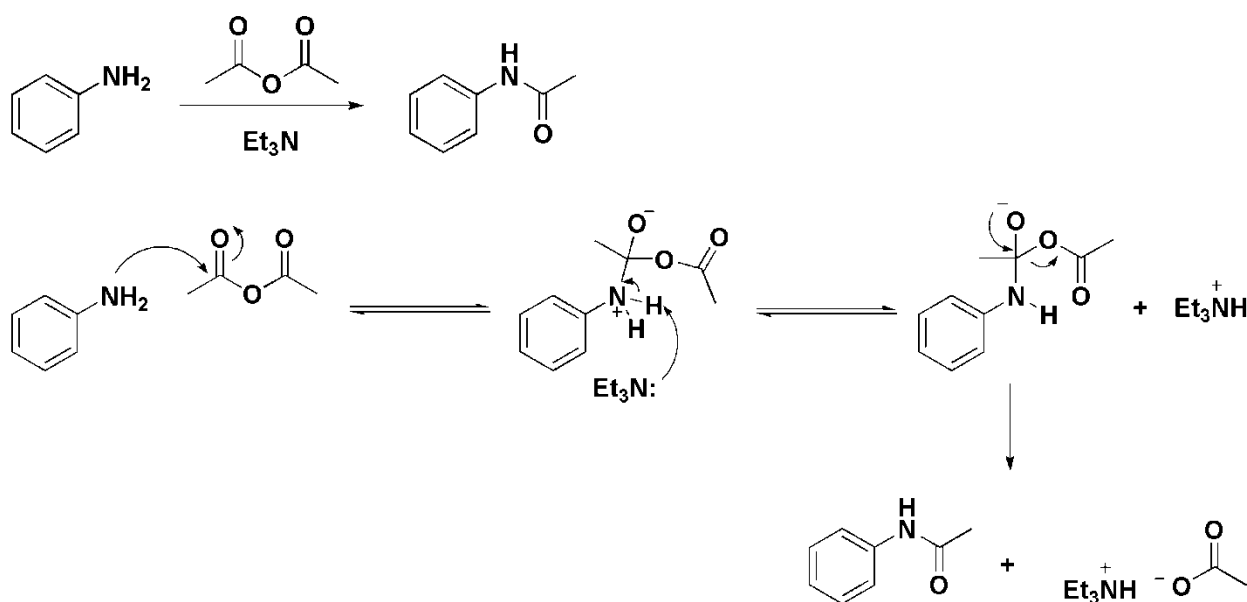
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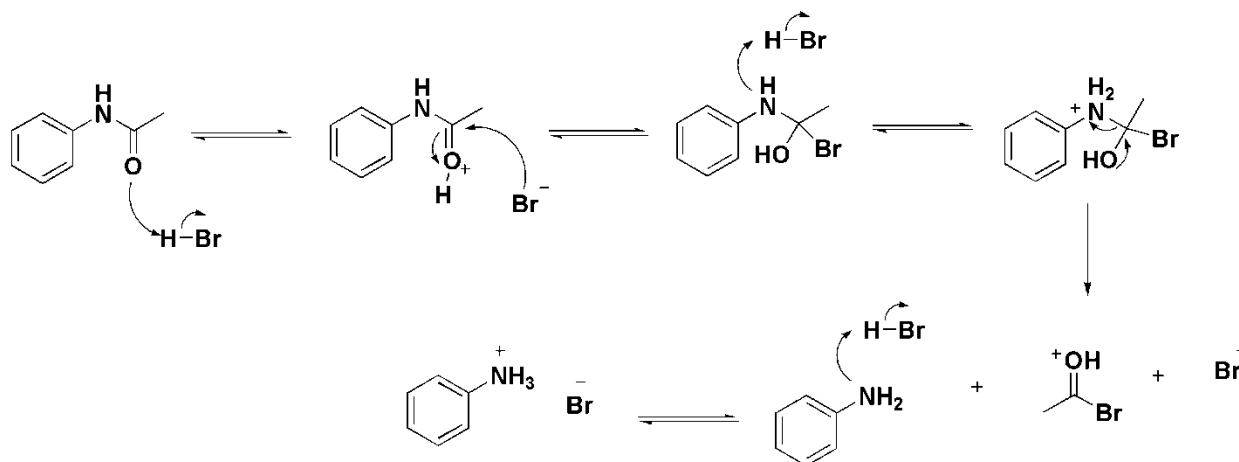
Group # _____

PS #2 – Installing and Cleaving Silyl Ethers, Benzyl Ethers and Amides

Part A) A common amine protecting group is the acetyl (Ac) group. The amide bond can be formed using different reagents. The two most common reagents used are acetic anhydride and acetyl chloride. Show the detailed mechanism (using the good habits you developed last week) for the formation of N-phenylacetamide from aniline using acetic anhydride.

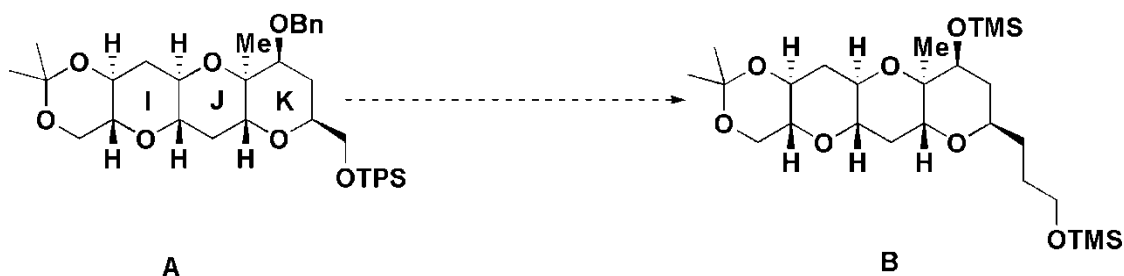
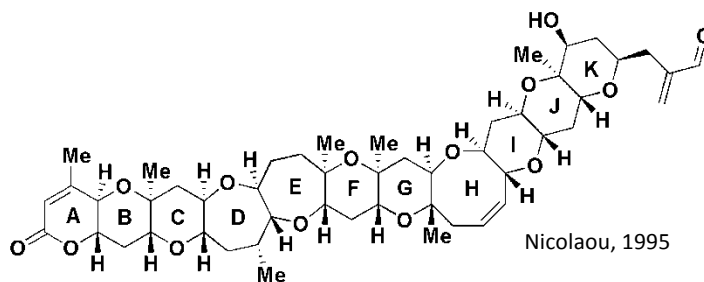


Acetyl groups are cleaved under strongly acidic conditions (conc. HBr). Show the mechanism for acetyl cleavage (aniline will be regenerated... but in what protonation state under these conditions?).



Note: The acetyl bromide product is reactive. Under these conditions (ie. in the presence of water) it will be hydrolyzed. Acetic acid and HBr will be the final products.

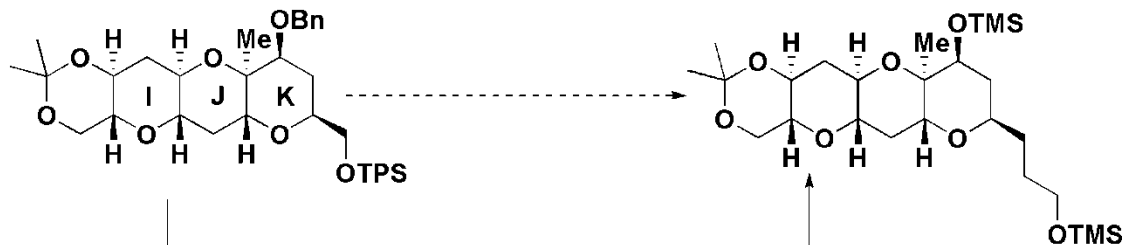
Part B) Brevitoxin B is the marine neurotoxin associated with “red tide” events that periodically devastate coastal ecosystems (only eat shellfish in months with the letter R). The activity of Brevitoxin B arises from its ability to bind to sodium channels in neurons, keeping them open, thereby causing depolarization of the cell membrane. The synthesis of Brevitoxin B was completed in 1995 by Nicolaou. The I,J,K rings were synthesized independently and then condensed with the A-G moiety in 75% yield. As a group, propose a reasonable synthetic route to synthesize B from A. Discuss functional group compatibility and protecting group reactivity (TPS = t-butylidiphenylsilyl, TMS = trimethylsilyl).



First consider the types of functional group transformations that need to take place and the bonds that need to be formed. It may help to make a list or circle the parts of the molecule being transformed.

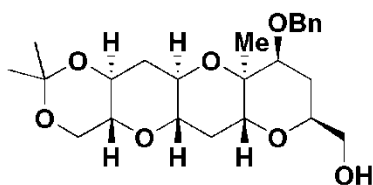
Next it is important to consider functional group compatibility. What reactions must be done first? Are there other parts of the molecule that would react under the conditions you wish to use? Do any sensitive functional groups need to be protected before you complete a specific reaction? Begin to make decisions about the order you will need to do the reactions in.

The series of reactions employed by Nicolaou is shown below. Alternate schemes are presented after. As a group, you may have come up with something different than what is shown here. There are many possible answers to this question so long as the reactions are compatible and you get to the final product.



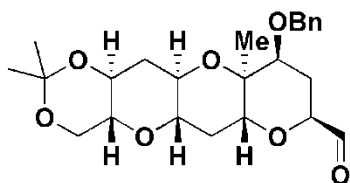
Selectively deprotect the silyl group. This is accomplished using a source of F^- .

TBAF (NBu₄F) or CsF



Oxidize the alcohol to an aldehyde. The most common reagent for this is pyridinium chlorochromate (PCC). It is mild enough that it does not oxidize the alcohol beyond the aldehyde. You were introduced to PCC in Chem 232/235.

PCC

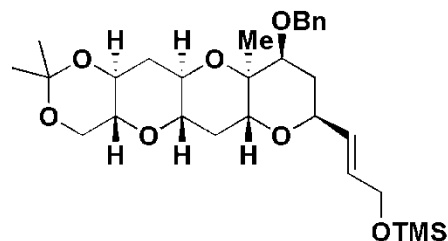


Pd/C, H₂

The double bond needs to be reduced. Now is also a good time to remove the benzyl ether. It is better if you can do both of these reactions in one step. H₂ and Pd/C will do both and is the most common reagent for removing Bn protecting groups.

TMSO-CH₂-CH=CH-PPh₃

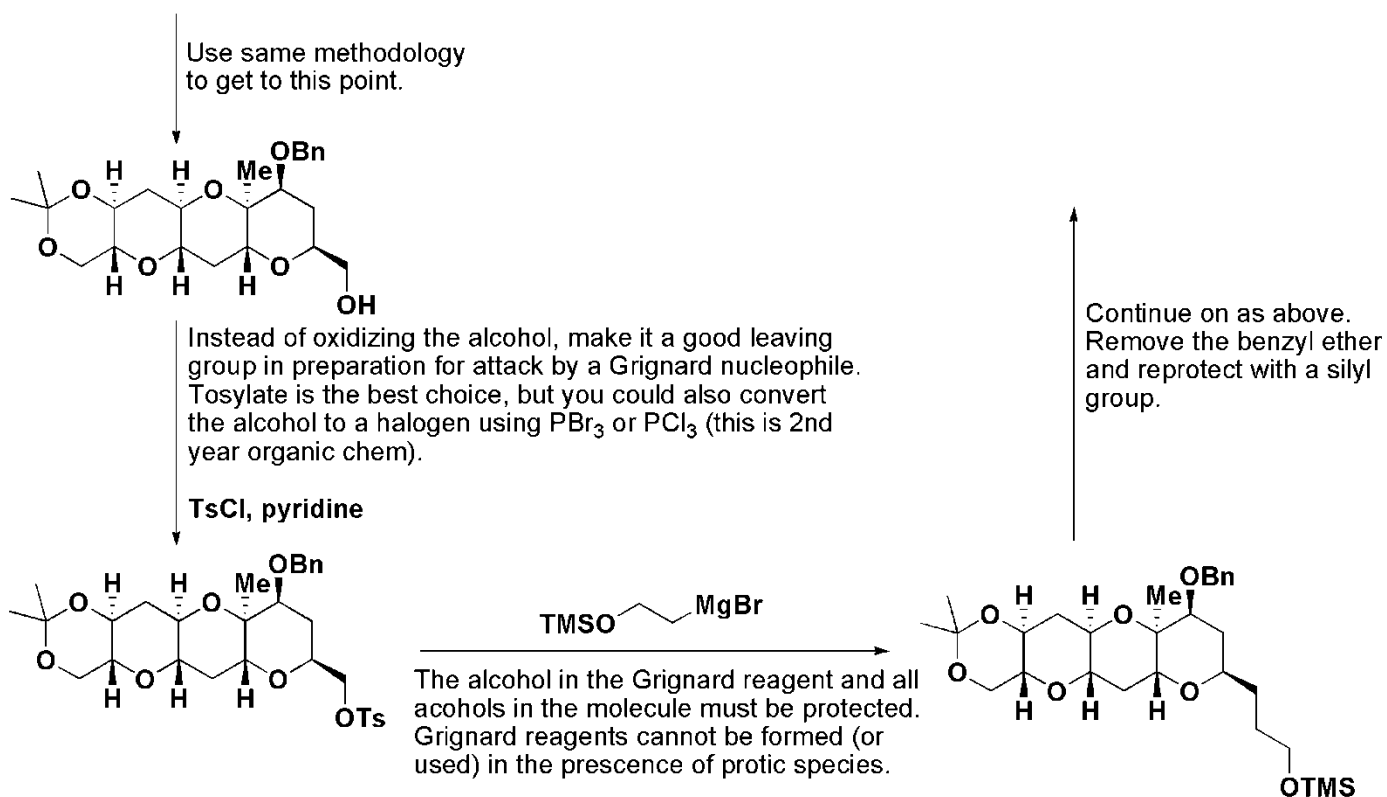
The synthetic route employed by Nicolaou used a Wittig reagent to form the carbon-carbon bond. Wittig reactions are important for carbon-carbon bond formation. The double bond forms between the C=O of the aldehyde or ketone and the phosphine reagent (ylid). This reaction was first introduced in Chem 235/232 and will be revisited in more detail later in this course.



You could also have used a Grignard reagent or an aldol reaction to form the carbon-carbon bond. These alternate schemes are presented on the next page.

Carbon-carbon bonds are difficult to form and you only know a few ways to make them. The Wittig reaction is one way the carbon-carbon bond could have been formed. You are also familiar with the Grignard reaction and the aldol reaction. Both of these reactions result in the formation of a carbon-carbon bond. As you will see below, the Grignard reaction is appropriate for use here, however, the aldol reaction cannot be used without destroying a chiral center. This makes it an inappropriate choice for use in the total synthesis of Brevitoxin.

Use a Grignard to form the C-C bond:



Use an aldol reaction to form the C-C bond:

