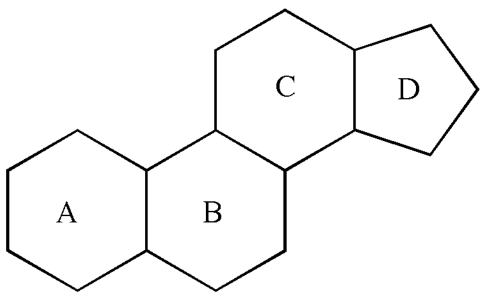
Chemistry 236, Spring 2008 Name:

Exercise 5: The total synthesis of estrone

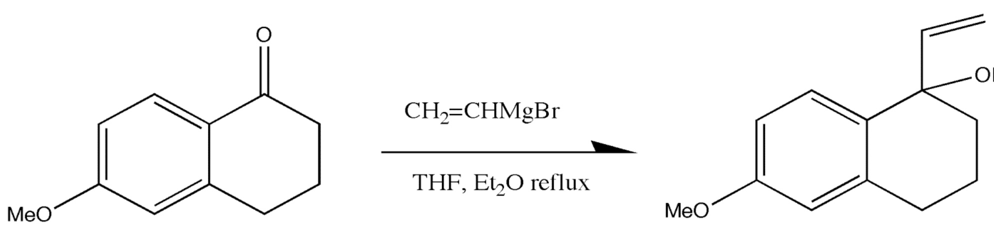
Estrone is a member of a large class of organic compounds, both naturally-occurring and synthetic, called steroids. Steroids have such a consistent four-cycle structure that each of the rings is lettered in this fashion:



Following the synthesis of a stereoisomer of estrone by W.E. Bachmann in 1942, Anner and Mischer synthesized natural estrone in 1948. The following reaction scheme is the Torgov estrone synthesis (Torgov and Ananchenko, *Tetrahedron Letters*, 1553 (1963)), which is carried out on an industrial scale to make the quantities needed for pharmaceuticals such as birth control pills.

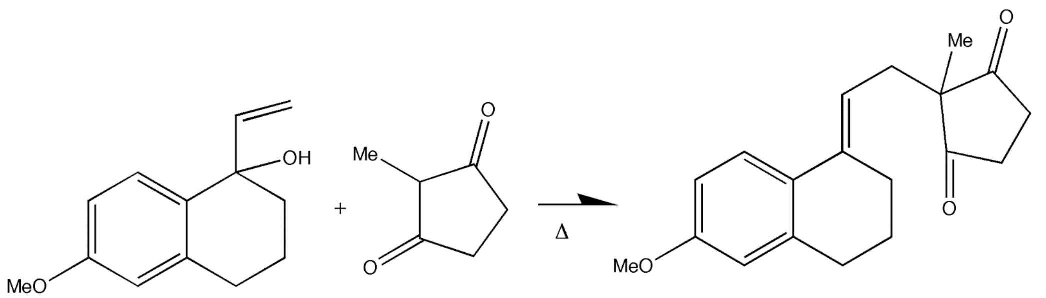
The concept of a “total synthesis” is making of a “natural product” from three organic reactants (6-methoxytetralone, 2-methylcyclopentane-1,3-dione and vinyl magnesium bromide) are all readily available in large quantities commercially.

Step 1:



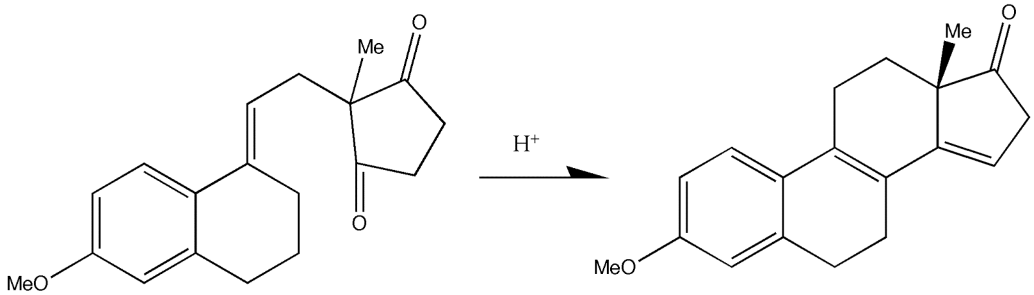
1. a. Draw the intermediate.

b. What reagent is missing from the list above?

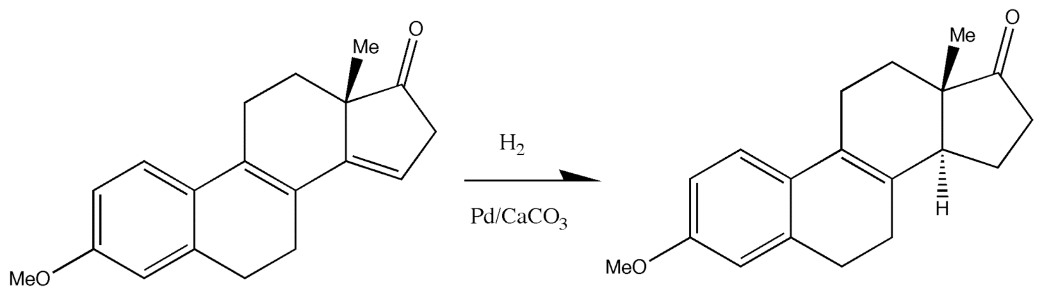
Step 2: 

2. a. Draw the mechanism for step 2. This is called the "S_N2' mechanism". Details of this type of mechanism can be found on Wikipedia at http://en.wikipedia.org/wiki/Allylic_rearrangement, but the first step in the mechanism involves losing the acidic proton off the 2-methylcyclopentane-1,3-dione.

b. What's the other possible product? Hint: Think straight S_N2. It's also not very likely.

Step 3: 

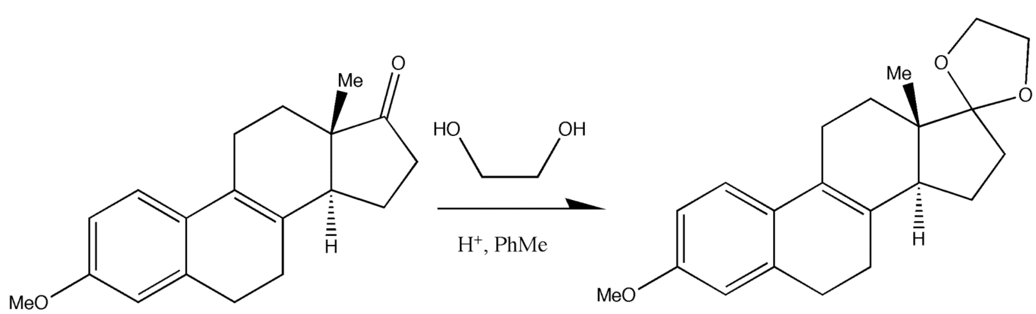
3. This is a key step, because it closes ring C. Draw the mechanism for this step. Warning: this is *really* complicated.

Step 4: 

4. a. The palladium-calcium carbonate catalyst in this reaction yields a “gentle” hydrogenation. Why is “gentle” hydrogenation desirable in this step?

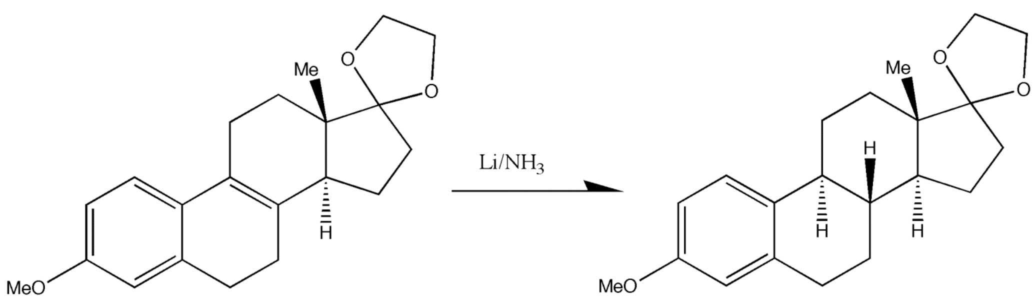
b. What energy/reactivity consideration dictates that that particular double bond be attacked?

c. Only one stereoisomer is made. Suggest a reason for *only* this particular isomer to be made.

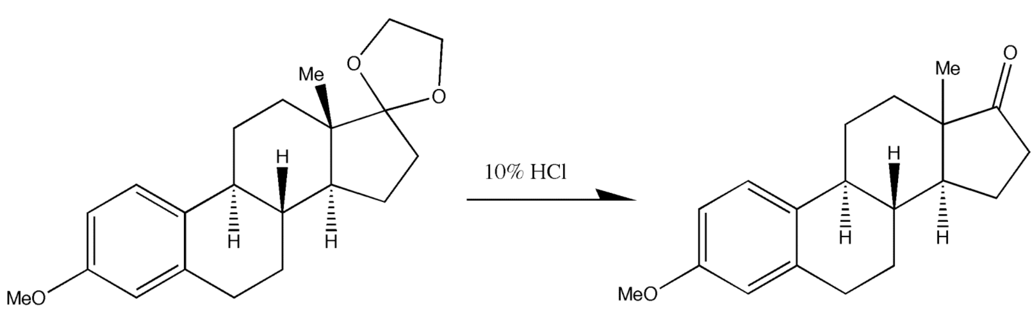
Step 5: 

5. a. What type of reaction is this?

b. Give a mechanism for this step.

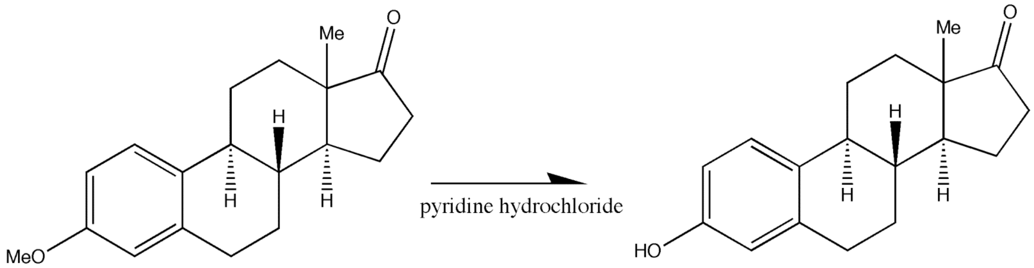
Step 6: 

6. Why was lithium/ammonia used for the hydrogenation in this step, as opposed to a standard hydrogenation with a metal catalyst?

Step 7: 

7. a. It seems that we are back to nearly the same molecule at the beginning of step 5, except for a couple more hydrogens. What was the purpose of step 5?

b. Draw the structure of the product that would have resulted from step 6 if step 5 had *not* been carried out.

Step 8: 

8. a. The product of the final reaction is, of course, estrone. How many possible stereoisomers of the product are theoretically possible? Be careful to find all chiral centers!

b. What type of reaction is step 8? Hint: recall what pyridine hydrochloride supplies to a reaction.