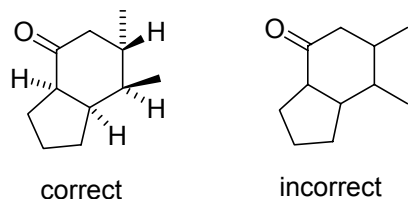
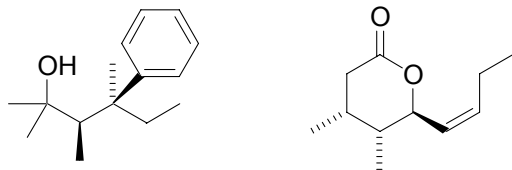


STUDY GUIDE for 2007 CHE535

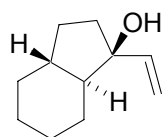
- 1) For every reaction we discussed, flashed through and consider the transition states and how hypotheses of the transition states allow predictions of stereochemistry and regiochemistries of the products.
 - a. You should for example be able to predict the product of a 3,3-sigmatropic rearrangement given the starting materials.
 - b. You should know that this is related to the aldol reaction (basically same t-state, see notes.)
 - c. In general you should specify stereochemistry in your answers.



- 2) Describe the concept of functional group. Why are we so focused on functional groups in Organic synthesis? How does functional relate to the 'organic oxidation state.' What is meant by defunctionalize?
- 3) Why is retrosynthetic analysis so important in synthetic organic chemistry; why is working backwards the best way to proceed? What should a good retrosynthetic analysis accomplish?
- 4) Related to item 2 above . . . what are the elements of molecular complexity? Why is an appreciation of molecular complexity so important in organic chemistry? How does the identification of complexity guide synthetic plan?
- 5) What are meant by the terms synthon and retron?
- 6) Know the terms R, S, Cahn-Ingold-Prelog priority rules, stereogenic, chirotopic, achirotopic, re, si, diastereomers, enantiomer, E, Z, conformational isomer. Can you assign R or S absolute stereochemistry at an atom in a molecule?
- 7) Do you understand the fundamental difference between diastereomers and enantiomers and how pervasive this concept is in our universe? Can you state in your own words why the concept is so important to synthetic chemists? Can you frame the basis of asymmetric organic synthesis in terms diastereomeric relationships (rates and equilibria of diastereomeric reactions)?
- 8) Remote stereochemistry . . . what is it? Why does it make life complicated for us as synthetic chemists? What do we need to do to get around it? How is it related to the basis of asymmetric organic synthesis in terms diastereomeric relationships?
- 9) Can you see 3,3-sigmatropic retrons in the following molecules? What about an ester-enolate type rearrangement?



10) Can you disconnect the following molecules using the Diels-Alder retron(s)? You might want to focus on an intramolecular variant. Why? Can you see a Nazarov Cyclization retron in the structure below?



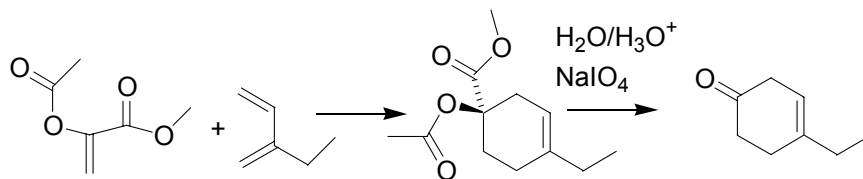
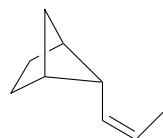
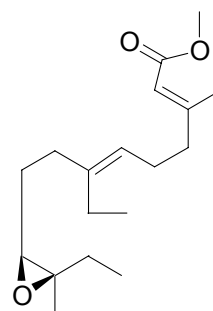
11) We talked about 1,2 versus 1,4 addition to alpha-beta unsaturated ketones, aldehydes and esters. Can you use these in synthesis? Careful with the aldehydes. Don't carry them through multiple synthetic steps. Do you remember why?

12) The Cecropia C18 juvenile hormone (at right) cyclizes under H^+ catalysis. Can you predict the product? The first step is the H^+ catalyzed cleavage of the epoxide. Think cationic cyclization. There is stereochemistry involved!

13) Why is cubyl anion so stable? Same question: why is cubane so acidic? Similar question: why is acetylide anion so stable?

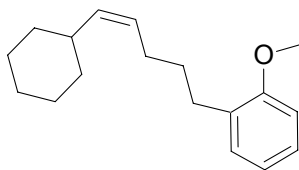
14) What do you look for in a protecting group? What about a particular protecting group would make you want to take it how to meet your parents? Why do you avoid protecting groups? Can you verbalize the complimentary uses of 1,2 and 1,3-diols and ketones in the protection of organic compounds?

15) Can you use the Favorski rearrangement in synthesis (remember synthesis of cubane)? Analyze the structure below with a Favorski retron.

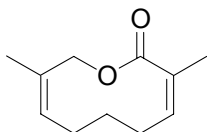


Use this reaction for a little hint with the above problem. Can you see how the reaction is relevant? Focus on the construction of the bicyclo[[1.1.2]] substructure.

16) Where is the best place to break the following molecule in the retrosynthetic analysis? What if I asked you to make the following molecule using phosphorus ylide chemistry?



- 17) Can you apply a 2,3-sigmatropic approach to the retrosynthetic analysis of the cyclic ester below? See C. W. Still in lecture 7.



- 18) In general can you apply the terminal alkyne-based homologation approaches exemplified in the lectures to the synthesis of organic molecules?

The above was covered before the MIDTERM.

- 19) What is meant by thermodynamic versus kinetic control? Can you draw reaction diagrams that differentiate between the two concepts? How do these concepts impact the following terms: kinetic protonation, kinetic resolution, matched pair, double diastereo-differentiation? How are kinetic protonation and the kinetic enolate phenomenologically related?
- 20) Can you apply the Felkin-Ahn model to predict the product of 1,2-nucleophilic addition to an aldehyde or a ketone? How is this concept and the concepts of item # 17 related?
- 21) Enamine chemistry was one of the few examples in which we dealt with the chemistry of the nitrogen atom. Can you use enamine chemistry to perform controlled alkylations of ketones? Can you do so enantioselectively?
- 22) Do you feel comfortable using the terminal alkyne as a linkage (homologation agent) in synthesis? Can you use these to open epoxides and 1,2-add to ketones to position functionality in target and sub-target molecules in an atom-economical manner?
- 23) Can you invoke the Sonogashira reaction in the retrosynthesis of organic molecules? What if the target molecules do not even have triple bonds? Can you retrace that scream for the use of $sp-sp^2$ type coupling? Can you turn a ketone into a triflate and use it to perform this kind of coupling reaction?
- 24) Are you aware of the tremendous versatility of the alkene as a pivot point in organic synthesis? epoxides, 1,2-diols, ketones, cyclopropanes etc. See notes.
- 25) Hydroboration/ oxidation . . . can you use this reaction to make a primary or a selective secondary alcohol? Can you use the primary alcohol as a point of homologation after activation? Can you do this backwards (in retrosynthesis)? What are the products when an alkyne is used? Can you do it standing on your head? Can you do enantiospecifically? Would you do it in the rain, on a train, in a box with a fox . . . could you would you Sam I am?
<http://www.eduplace.com/tview/tviews/g/greeneggsandham.html>

- 26) What on earth is the Curtin-Hammett Principle? It might more appropriately be called the Curtin-Hammett caveat. How does this principle apply when you are wondering why you got a certain product ratio and you are trying to calculate the most stable conformer or a particular starting material?
- 27) Think about the Payne rearrangement and how it enhances the synthetic utility of Sharpless epoxidation.
- 28) When would you want to perform an inversion at a stereogenic carbinol carbon atom? Do you feel comfortable being able to invert alkenes?
- 29) What are the virtues of Peterson olefination versus Wittig olefination?
- 30) Why is it a good thing to preserve six and five-membered rings in retrosynthetic analysis?
- 31) Why don't you have to worry so much about acetals and hydrated ketones and their respective stereochemistries in the synthesis of natural products? Why should these be the first bonds to go in your retrosynthetic analysis of such compounds?
- 32) Why are rings larger than 7 atoms and smaller than 14 atoms difficult to make? Why are rings larger than 14 atoms difficult?
- 33) Why is the ability to recognize the concave face of a polycyclic molecule important to the synthetic chemist?
- 34) What's a sesquiterpene? How many isoprene units does it have? What is isoprene? Draw the structure.
- 35) Do you feel comfortable designing synthesis based on ring expansion by one carbon atom? Why is being able to do important? How is this related to #32 and #30?
- 36) How is the pinacol rearrangement related to the type of ring expansions mentioned above? It is easier to remember chemistry if you can find analogies in mechanisms (for example the aldol reaction with the Cope rearrangement).
- 37) Can you appreciate the special niche occupied by reactions like the pinacol rearrangement in C-C bond formations? Can you envision instances in which it is best to 'rearrange' a group into place instead of couple it into place via something like an S_N2 reaction?
- 38) Can you ring contract by one methylene unit? How is this reaction related to the Favorski ring contraction considered in the synthesis cubane?
- 39) Can you make cyclobutanones via 2+2 cycloaddition reactions?