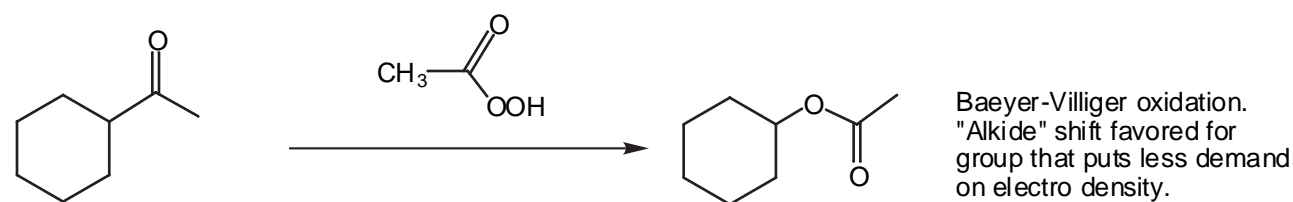
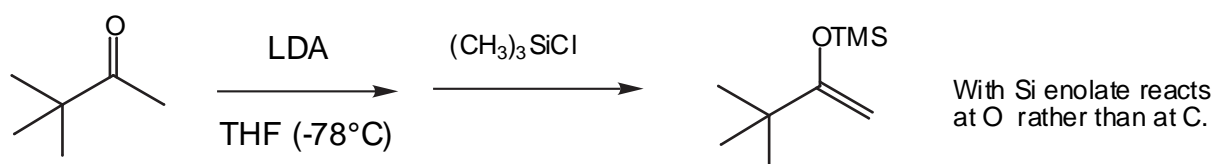
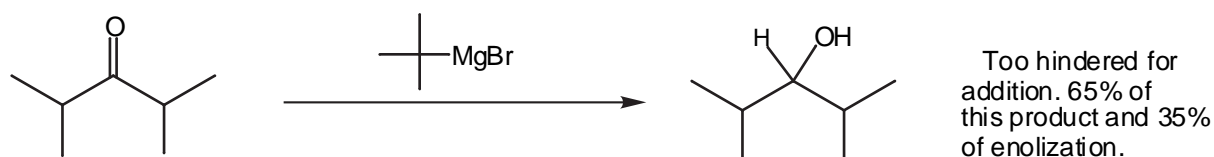
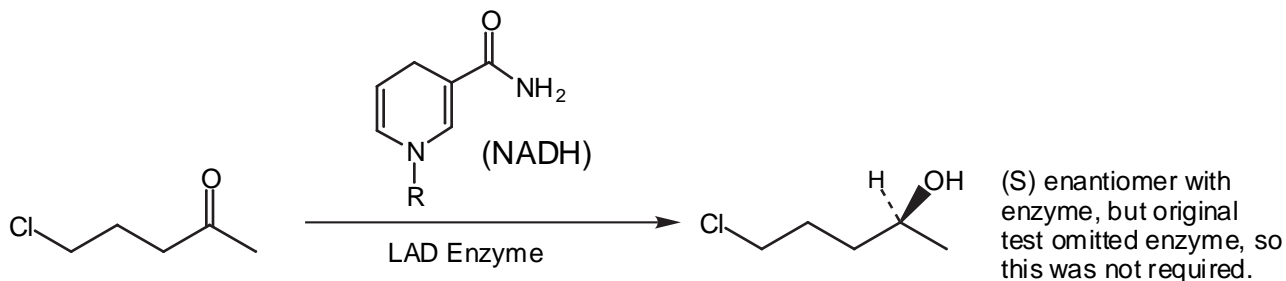
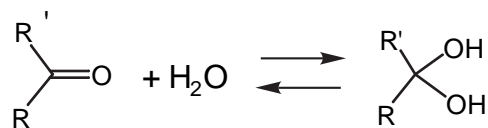


Chemistry 125 Seventh Examination Answers April 11, 2003

1. (8 min) Give the principal product of each of the following reactions. (No mechanisms necessary, just draw the product)



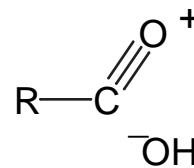
2. (3 min) The equilibrium constant for the following hydration reaction is strongly dependent on the nature of the R groups. **Match** each pair of R groups with the appropriate equilibrium constant and briefly **explain** the difference.



R	R'	K
H	H	4×10^{-5}
CH ₃	CH ₃	10^{-2}
CH ₃	H	18

The carbonyl group is stabilized relative to the diol with a tetrahedral carbon when H substituents are replaced by alkyl groups, such as a methyl. One reason for this is that C-C bonds profit more from changing sp³ to sp² hybridization than C-H bonds do. Another is that with alkyl groups there is the possibility of hyperconjugative stabilization of the alpha C-H bonding electrons by the pi* low LUMO of the carbonyl group.

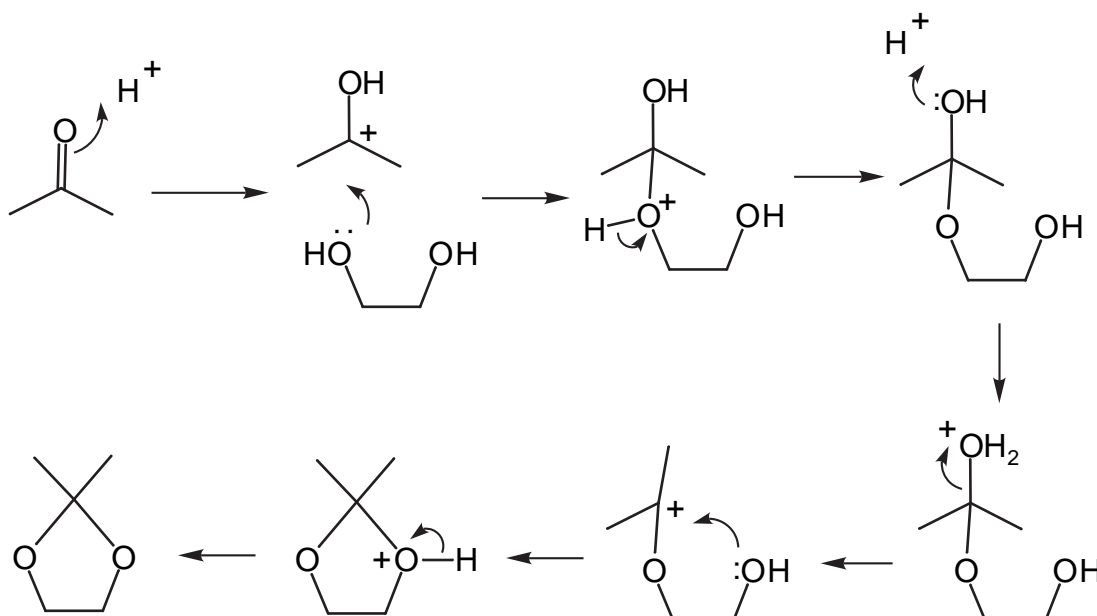
3. (5 min) Provide **BOTH** theoretical justification (in terms of orbital mixing) **AND** experimental support (specific facts) to justify writing the following resonance structure for a carboxylic acid:



Theoretical: This structure reflects stabilization of an unshared pair of electrons on the carbonyl oxygen by mixing with the σ^* vacant orbital associated with the C-O bond.

Experimental: The C=O stretching of the carboxylic acid occurs at significantly higher frequency (1760/cm) than does a ketone (1715/cm) demonstrating a stronger bond. [This occurs despite the expectation that the more "obvious" resonance structure reflecting mixing of an unshared pair of the OH group with the π^* orbital of the carbonyl group would be expected to weaken the C=O bond and lower its stretching frequency.]

4. (6 min) An important aspect of Woodward's cortisone synthesis was protecting a 1,2-diol as its acetonide. Use curved arrows to draw a detailed multi-step mechanism for the formation of the acetonide by reacting a 1,2-diol with acetone.



Common deficiencies:

- * forgetting the acid catalyst necessary for forming a full ketal
- * using ROH to protonate ketone (it is some 10^{24} times weaker as an acid than the protonated ketone!)
- * using OH^- as leaving group.
- * forgetting charges
- * having OH^- and H^+ at the same time for acid/base catalysis. Remember that the product of their concentrations is about 10^{-14} . If you have much of one of them, the other is unavailable.
- * arrows from H^+ instead of to it. Curved arrows denote **electron** pair motion.
- * skipping steps, or too many arrows at a time (this risks confuse you as well as the grader)
- * missing carbons

5. (5 min) Explain how **EITHER** a Mexican yam **OR** a Kalamazoo microorganism played an important role in the practical synthesis of cortisone. (The more specificity you can provide the better, but the idea of what was involved is the main point of this question.)

In the early 1940s Prof. Marker of Penn State discovered that a Mexican yam (cabeza de negro) was very rich in diosgenin, a molecule containing all of the carbons of cortisone and many functional groups in convenient positions. diosgenin could be converted in 5 steps into the pregnancy hormone progesterone, and in another 8 steps into cortisone. This is a practical example of achieving convenient synthesis of a compound by finding a plentiful source of a closely related molecule in nature.

A very challenging problem in converting progesterone into cortisone is that one of the CH_2 groups in the former must be converted into a carbonyl group in the latter, and there is no nearby functional group to make this CH_2 group any more reactive than any of the other seven CH_2 groups in the molecule. A microorganism that appeared spontaneously on an agar plate on a window sill at the Upjohn research laboratory in Kalamazoo turned out to oxidize the desired CH_2 group to the carbonyl in 50% yield.

6. (5 min) Explain briefly why the NMR spectrum of t-butanol shows a single sharp peak for the OH proton, while the IR spectrum shows a more complicated pattern. (Try to include some numbers in your explanation.)

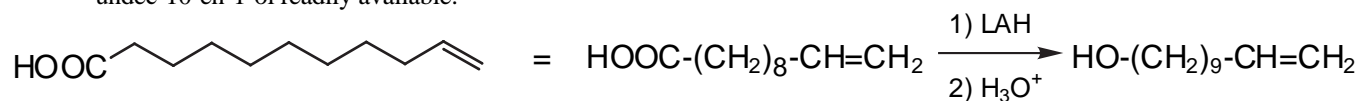
In solution the OH group of alcohol molecules can exist in different H-bonded environments, e.g. not H-bonded, middle of an H-bonded chain, H-end of an H-bonded chain. For each of the structures the proton has a certain chemical shift in the NMR and a certain O-H stretching frequency in the IR. As the local structure changes in time there is the possibility that the different spectroscopic signals will broaden and coalesce to give a single peak. Whether this happens depends on whether the frequency **difference** between the peaks in question is larger or smaller than the rate at which the environment changes its structure.

In the IR the relevant frequencies are from 3400 to 3600/cm, so a typical difference might be 100/cm. Since the speed of light is 3×10^{10} cm/sec this means a difference of 3×10^{12} vibrations per second. Changes in H-bonding would be much slower than this, since the energy of activation for breaking an H-bond is of the order of 5 kcal/mole, meaning that the rate constant at room temperature would not be greater than 10^{13} /sec $\times 10^{-3/4 \times 5}$ or about 10^{10} per second. The change of environment would be at least 1000 times too slow to cause averaging to a single spectroscopic line in the IR.

In the NMR, however, the chemical shift difference for different H-bonded patterns is only a few ppm. Even for a very high field spectrometer operating at 800 MHz, the difference in frequency is at most a few thousand per second. A change of H-bonded environments in nanosecond (10^9 Hz) range would be a million times faster than would be necessary to cause averaging of such closely spaced peaks.

Thus NMR shows a single averaged peak, while IR shows a peak for each different local environment.

7. (14 min) In practical organic synthesis it is important to know what starting materials are cheap and readily available. For example, heating ricinoleic acid, which constitutes about 80% of castor oil, gives a high yield of 10-undecenoic acid, shown below. Since carboxylic acids can be reduced to primary alcohols with LAH, this makes undec-10-en-1-ol readily available.

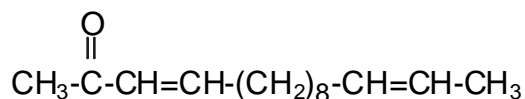


Propose practical a multi-step method for preparing each of the following two compounds from 10-undecenoic acid, or undec-10-en-1-ol and any other reagent with 4 or fewer carbons. Be sure to count carbons and to use protecting groups if necessary.

[In this kind of problem it is crucial to keep different functional groups on the two ends of the starting molecule so as to be able to react with them selectively. Unless you have a very specific trick in mind you should never convert to a simple hydrocarbon group and hope to refunctionalize one particular carbon atom.]

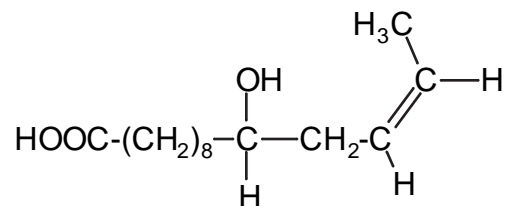
The α,β -unsaturated ketone on the left cries out "aldol". The alkene at a particular position within a long alkyl chain on the right suggests Wittig reaction, since most eliminations would give a mixture of regioisomers. There are only 10 carbons between the double bonds, so a carbon must be removed from the starting 11-carbon chain.

One method would be 1) protect alcohol of undec-10-en-1-ol as TMS ether; 2) ozonize (reductive Zn workup) double bond to remove last carbon and leave aldehyde; 3) react aldehyde with ethyl Wittig reagent to complete right end of chain; 4) deprotect alcohol; 5) oxidize alcohol to aldehyde with PCC; aldol reaction with acetone enolate (performed by acetone + LDA).

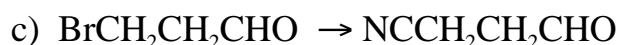


Reducing an acetylene with the "Lindlar" catalyst is a good way to make the Z-double bond. The carbon chain is 3 carbons longer than the alcohol (or acid) starting material, suggesting nucleophilic substitution by the anion of propyne to make the necessary acetylene. For a nucleophile to attack one carbon and leave an OH group on the adjacent carbon suggests nucleophilic opening of an epoxide ring (where the desired attack on the terminal primary carbon would be favored over attack at the secondary carbon). The epoxide could be made by reaction the terminal alkene with a peroxy acid.

This scheme for making the necessary changes to the right end of the starting material would be best with protection of the acid (or alcohol) group on the left, either of which would react with the acetylide anion. Perhaps the most efficient approach is to use the acid without protection and employ two moles of the acetylide, one to neutralize the acid and the second to open the epoxide.



8. (4 min) Show how one may carry out **ONE (one only)** of the following conversions in good yield. A protecting group will be necessary.



Note: This is Question 5 from Chapter 16 of the text.
There are many possible correct answers, for example:

- a) Protect aldehyde as acetal (1,2-ethanediol, H^+ would be a good choice), eliminate HBr with strong base, deprotect acetal with H_3O^+ (Sec. 16.4). Without protection the aldehyde could undergo aldol reaction with itself.
- b) To create a 9-carbon chain one needs two butanols and one additional carbon. The desired triol has an OH on each end and one on the middle carbon. A reasonable synthetic strategy is to add the brominated carbon (as Grignard) of two chains to a single carbon in such a way that that carbon acquires an OH group. In order to make a Grignard reagent from the 4-bromo-1-butanol, one must first protect the OH group (with a trimethylsilyl or a t-butyl group, see Sec. 16.4). One could add one mole of Grignard to formaldehyde to add a carbon and make the alcohol, then oxidize the alcohol to an aldehyde (PCC), and add another mole of Grignard to create the 9-carbon chain with OH on the central carbon. Finally one deprotects the terminal alcohols by treatment with acid.

[We now know that a more efficient method for adding two moles of Grignard reagent to a single carbon is to use an ester, for example methyl formate. This avoids having to oxidize the primary alcohol to aldehyde before adding the second mole of Grignard.]

- c) One can do an $\text{S}_{\text{N}}2$ substitution of Br^- by CN^- . To avoid cyanide addition to the aldehyde to give the cyanohydrin $-\text{CH}(\text{OH})\text{CN}$ group, the text expected you to protect the aldehyde as an acetal (as in answer a), which could be removed by aqueous acid after substitution. [I doubt that this is really necessary, since the formation of cyanohydrins is reversible by treatment with base to remove HCN . One should be able to just treat with cyanide and then with base, if necessary, to remove HCN from any cyanohydrin that might form. See Sec. 14.7B]