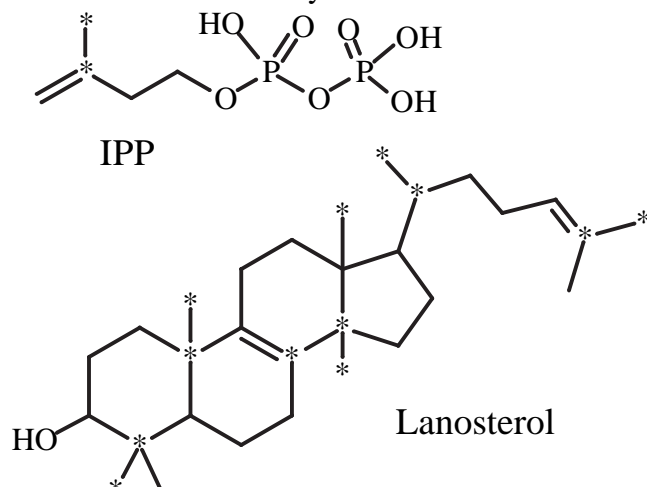


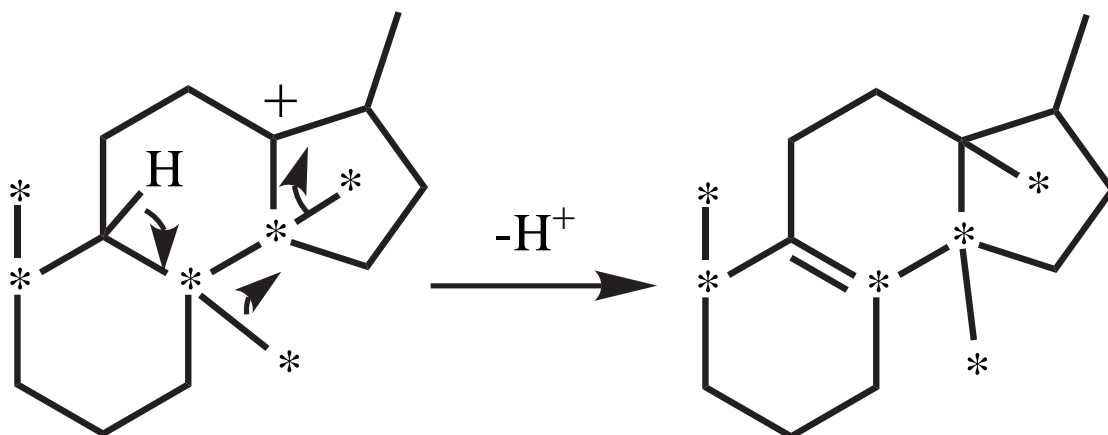
Chemistry 125 Seventh Examination April 7, 2000 Answers

This exam: Average 73.9 1/3 > 79 2/3 > 71
 Sum of 3 Exams: Average 217.1 1/3 > 235 2/3 > 208

1. (4 minutes) **Explain** what the methyl signals in the CMR spectrum of lanosterol, biosynthesized in the presence of a small amount of isopentenyl pyrophosphate (IPP) containing ^{13}C in both starred positions, show about the mechanism of lanosterol biosynthesis.



Four of the starred methyl signals are doublets due to C-13/C-13 spin-spin splitting, but the two starred methyl groups at the junction of rings C and D of the steroid skeleton appear as singlets, showing that the adjacent carbon is not the same as in the IPP precursor molecule, and therefore that there has been a rearrangement (via methide shifts in a cationic intermediate)



[Because very little C-13 is present in natural abundance, C-13 signals must come from starred positions in the precursor. Because the labeled IPP is used in small amount, there is little chance that any particular lanosterol molecule will incorporate more than one of the labeled IPP molecules. Thus although the overall lanosterol sample shows signals for all of the starred positions, individual labeled lanosterol molecules will have only one pair of C-13 atoms, those that derived from the single IPP precursor that happened to be labeled. If these atoms are adjacent to one another, as they are in IPP, their proton-decoupled CMR signals will be a pair of doublets, because of mutual spin-spin splitting by the adjacent C-13s. When they are not split, they must have separated from their original neighbors.]

2. (6 minutes) Explain how you would use IR spectra to distinguish between the following pairs of compounds. (For each case say what you would look for in the spectrum, and how the feature would differ between the two compounds)

Ethyl chloride and ethyl iodide

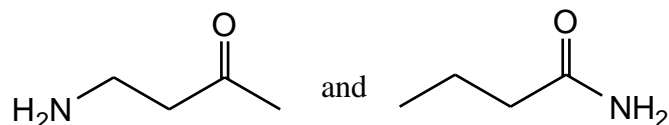
Because of the difference in mass, C-I absorbs at a lower frequency (200-500/cm) than C-Cl (500-680/cm).

1-butyne and 2-butyne

1-butyne has a H-C bond where the C is sp hybridized. This strong bond gives a high frequency (3300-3320/cm). Also, the $\text{C}\equiv\text{C}$ band in the IR spectrum of 2-butyne should be vanishingly weak in intensity because there is no dipole moment associated with its vibration [but it's safer to depend on the intense C-H bond that you can see].

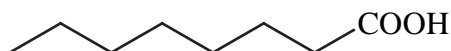
cyclobutanone and cyclohexanone

The C=O stretching in cyclobutanone (1780/cm) is at higher frequency than in cyclohexanone (1715/cm), because its sharper C-C-C bond angle requires more stretching of the C-C bonds as the C=O bond stretches. The wider angle in cyclohexanone involves more bending relative to stretching, and bending is easier, less resistant, than stretching.



The first compound is an aminoketone, in which the functional groups are independent, so the ketone should absorb about 1715/cm, like acetone. The second is an amide, where conjugation of the amino group with C=O weakens and lowers the stretching frequency of the latter to about 1680/cm.

3. (5 minutes) Which carbons in the following compound could be **selectively** halogenated in high yield, and by what reagents?

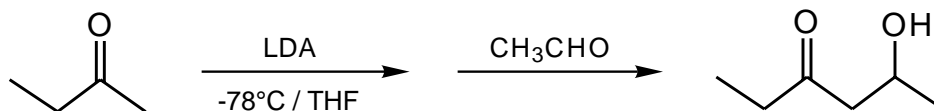


- (1) The ω -1 carbon (next-to-last, *i.e.* C7) is selectively chlorinated by iPr_2NCl in very strong acid ($90\%\text{H}_2\text{SO}_4$). Since specificity requires that both the abstracting radical and the carboxylic acid be protonated so that the radical must attack at the most remote secondary carbon in the chain to keep the positive charges apart, one had to mention both the chlorinating agent and the strong acid for full credit.]
- (2) The α carbon (C2) can be selectively brominated (*via* its enol) by Br_2/PBr_3 (the Hell-Volhard Zelinsky reaction).

- (3) C1 can be halogenated by replacing the OH group using any of the standard reagents (PBr_3 , SOCl_2 , PCl_5 , etc.) to form an acyl halide from a carboxylic acid.
- (4) The entire COOH group can be replaced by the Hunsdiecker reaction (1 - Ag_2O , 2 - Br_2 / light).

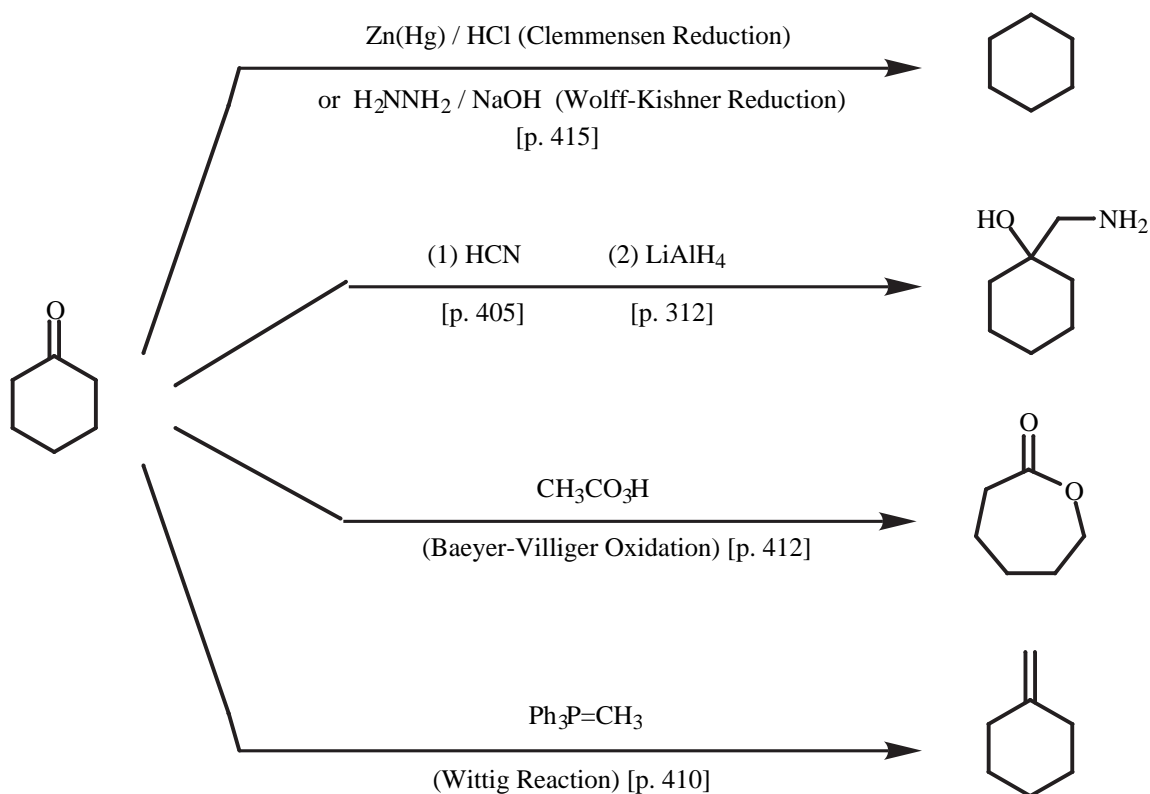
[All of these answers are reasonable, but since only the first two involve "halogenation" in the common sense of replacement of H by Cl, full credit was given for the first two alone - 5 points each. If reactions 3 and/or 4 were included, maximum points for 1 and 2 were reduced.]

4. (5 minutes) In the first step of the following conversion, one might drip the LDA solution into a cold flask containing 2-butanone, or 2-butanone into a cold flask containing LDA solution. Explain why one uses LDA rather than NaOH for this reaction, and which type of addition should be better for generating a high yield of the desired product.



The secret of selectivity in this mixed aldol reaction is to convert the initial ketone completely into its enolate under conditions that do not allow it to react with the parent ketone, then to add the aldehyde. Using LDA, a much stronger base than the enolate (whereas hydroxide is weaker than the enolate), allows the ketone to be completely converted to enolate. If LDA were added slowly to a solution of the ketone, then during the early stages of addition the enolate would be in the presence of a high concentration of its parent ketone, and might react with it. By adding ketone to LDA, there is never lots of ketone sitting around in the presence of enolate, only the small amount that is waiting to react with the excess of LDA.

5. (6 minutes) Give reagents for converting cyclohexanone to each of the following compounds **in high yield**. No mechanisms are required.



6. (5 minutes) Explain why the OH group of an alcohol typically gives a more complicated spectrum in the IR than in proton NMR. (Your answer should mention relevant frequencies.)

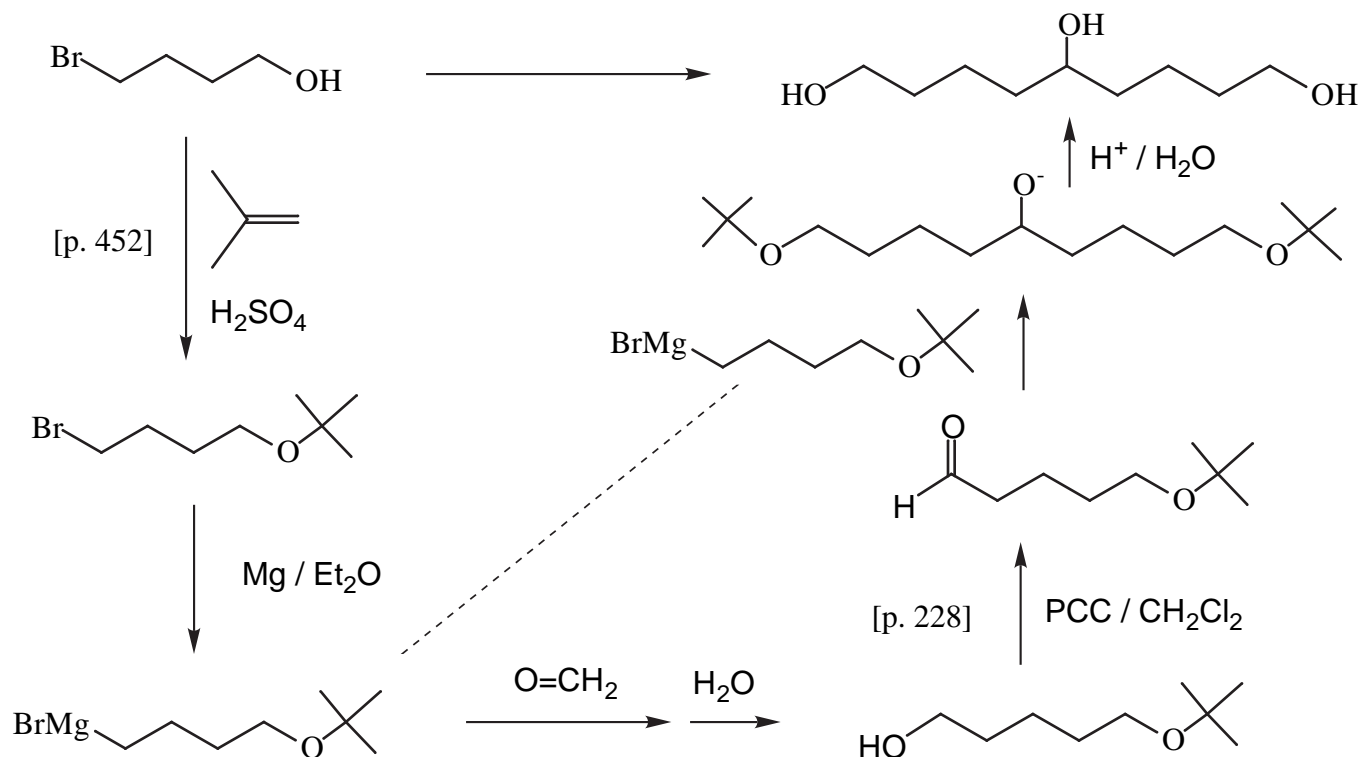
Because of hydrogen-bonding there are many different local environments for the hydrogen of an OH group, most dramatically H-bonded (3250-3450/cm) and not H-bonded ($\sim 3630/\text{cm}$). In the IR these signals are seen as independent, because they differ in frequency by about 300/cm or 10^{13} Hz. Averaging signals to give a single line requires that the environments exchange within a time corresponding to their frequency difference. [Many answers erred in mentioning the overall frequency rather than the **frequency difference**.] Although H-bonds are weak, they are broken and reformed very slowly on the scale of 10^{-13} sec.

[One might guess a rate constant for changing H-bonding at room temperature somewhat less than $10^{13} \times 10^{-3/4 \times 4}$, or $10^{10}/\text{sec}$. Notice that this is much faster than the rate of breaking covalent OH bonds to effect proton exchange, which, in the absence of acid, is slow enough to prevent averaging of the nmr signal - fig. 13.44, p. 362]

Proton signals in the NMR differ by only a few parts per million, or about a few hundred Hz out of a total of 100 MHz. Exchange faster than a few hundred per second would thus give a single averaged peak in the NMR.

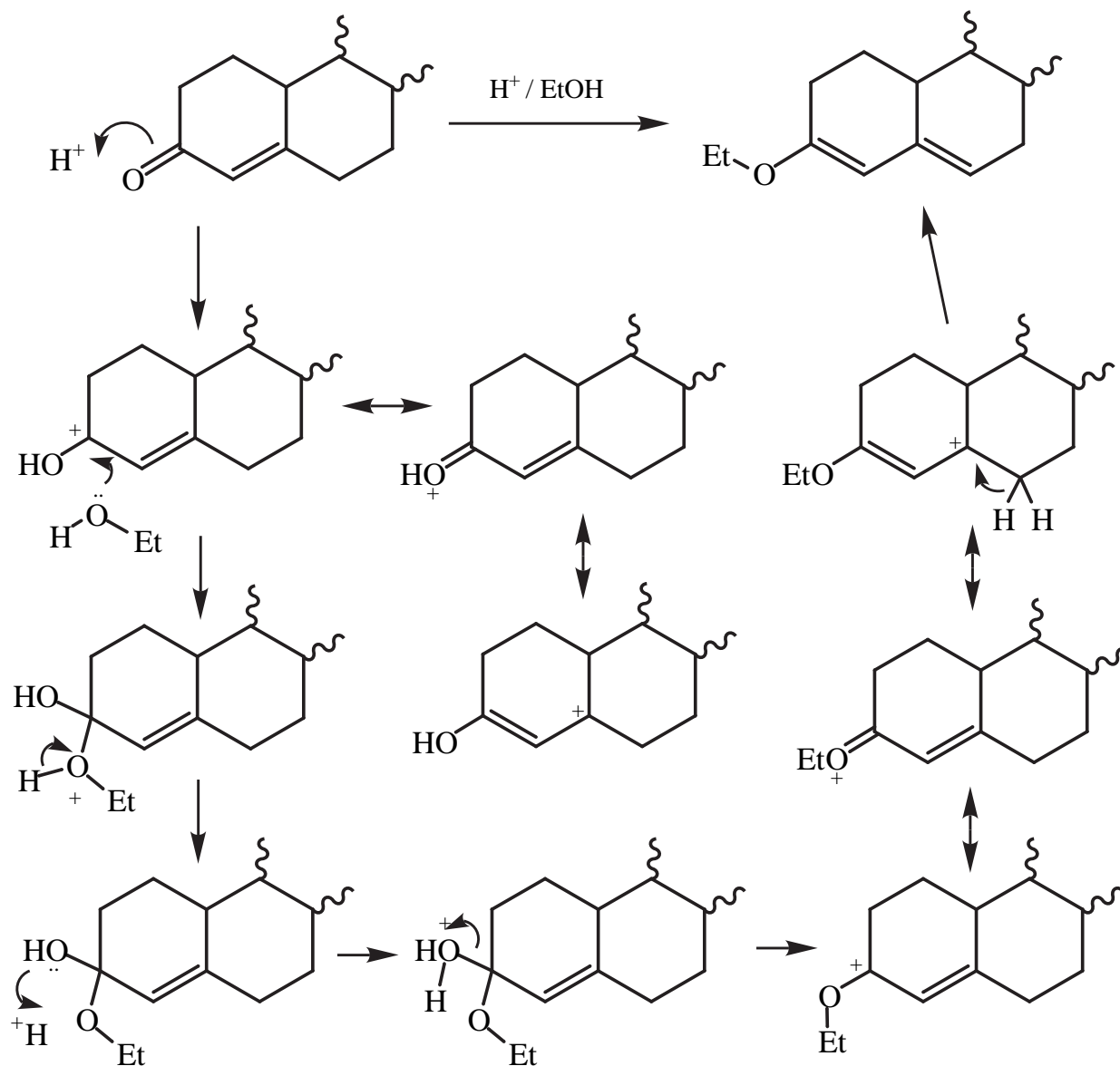
7. (12 minutes) Suggest reagents for effecting each of the following three transformations in good yield. You need **not** give **mechanisms** (reactive intermediates or curved arrows), **but** if several successive reactions are involved **do show intermediate products**.

[The first two problems are Questions 5b and 3f from Chapter 16]



[It is important to pay attention to the number of carbons. Here a carbon with oxygen had to be inserted between two of the 4-carbon alcohol units, and the availability of the bromide functional group suggested adding a Grignard reagent to a carbonyl group ($\text{O}=\text{CH}_2$) in order to insert one carbon. Since one cannot make a Grignard reagent from an alcohol (or reaction one with a carbonyl compound containing an OH; they would react by proton transfer), the alcohol must be protected. Here we suggest using a t-butyl ether, although the trimethylsilyl ether (TMS) derivative would be just as good - see text p. 453. The alcohol product must be oxidized (PCC avoids overoxidizing the aldehyde to a carboxylic acid) to allow addition of the second 4-carbon Grignard unit, followed by deprotection with acid. In fact we'll soon see a much less cumbersome way to generate an alcohol with two identical R groups flanking the C-OH by starting with a higher oxidation state of the central carbon, ester rather than aldehyde, see p. 532.]

8. (7 min) In the synthesis of norlutin the α,β -unsaturated ketone was protected as doubly unsaturated ethyl ether by treating with ethanol under acid catalysis. **Show the mechanism of this conversion in detail with curved arrows and important resonance structures.** [Plenty of skeletons are given to assist your drawing, you won't need them all. The wavy lines show connections to the remainder of the large molecule, which is irrelevant for this reaction.]



Common Errors:

- (1) Using anionic intermediates when acidic conditions were specified.
- (2) Generating of a vinylic cation intermediate.
- (3) Invoking an S_N2 reaction (rather than a tetrahedral intermediate) for substitution at an sp^2 carbon atom.