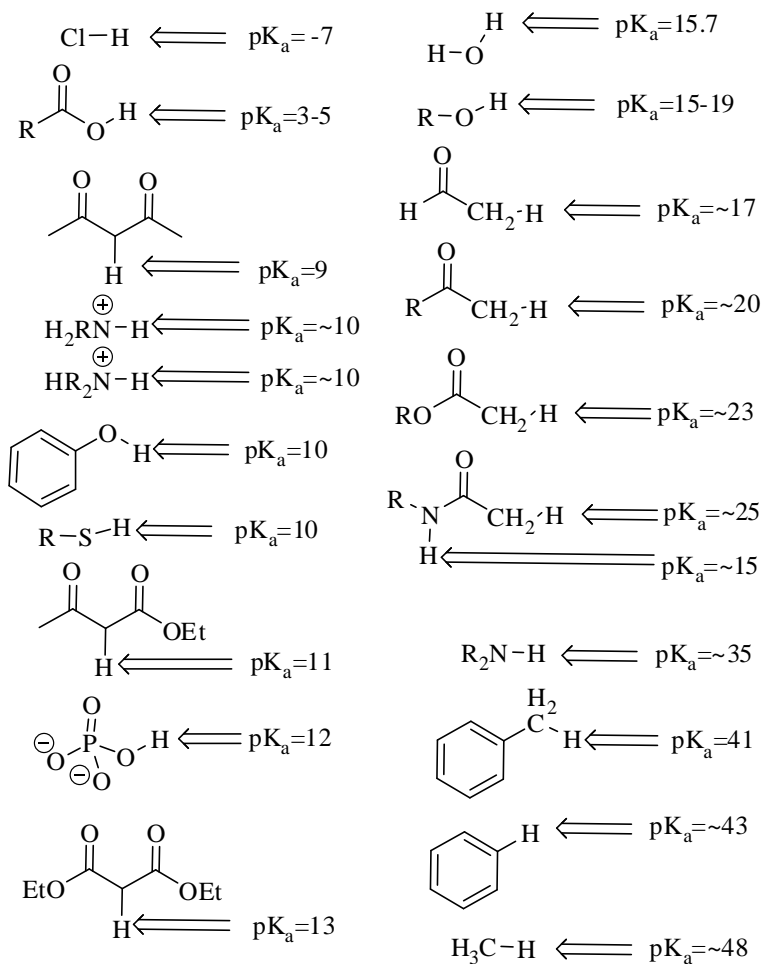


The examination has six questions on six pages. The point values for each question are found with the question. Partial credit will be given where appropriate.

Read each question carefully before answering. Be certain you understand everything the question is requesting. Do the easy questions first. If questions appear confusing or exceedingly complex, then you may need to rethink the question. Keep in mind the intended examination topics.

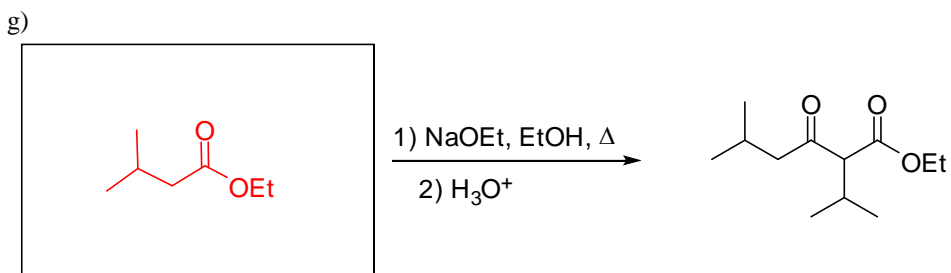
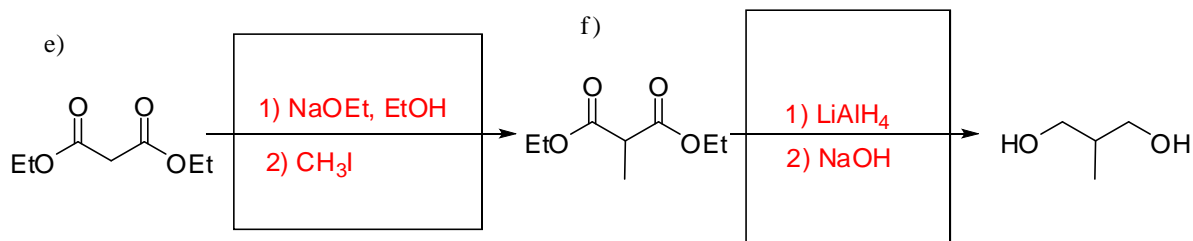
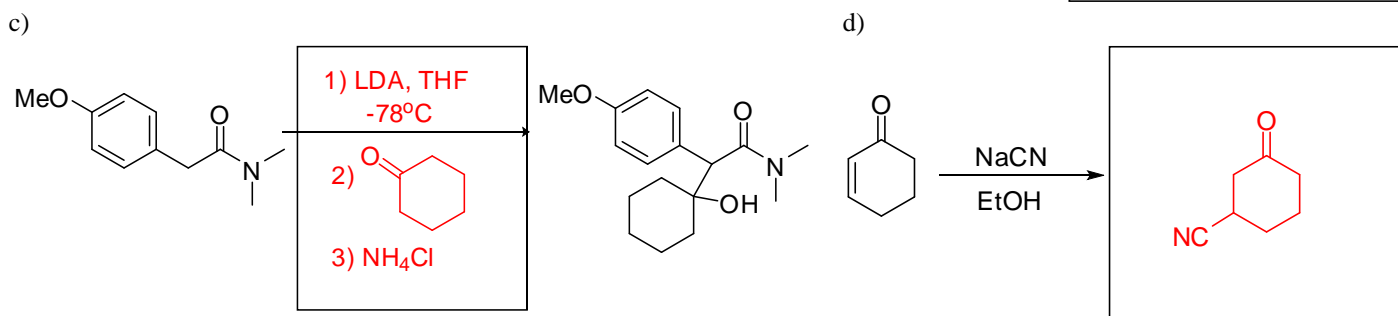
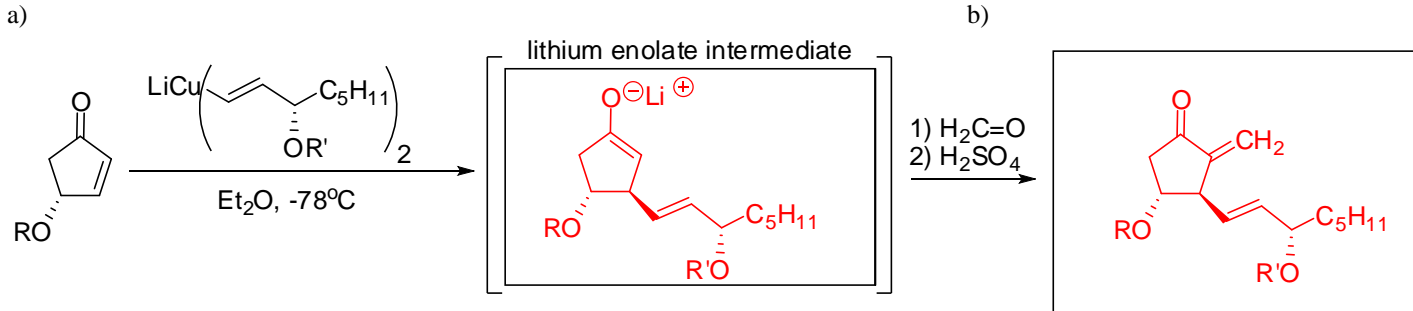
In organic chemistry, hand-drawn pictures convey specific information. Be sure the drawing you have made conveys the essential information required to answer the question. Make certain that three-dimensional pictures display the correct atom arrangements. Don't forget to include lone pairs of electrons, counter ions and formal charges when appropriate.

pK<sub>a</sub> information

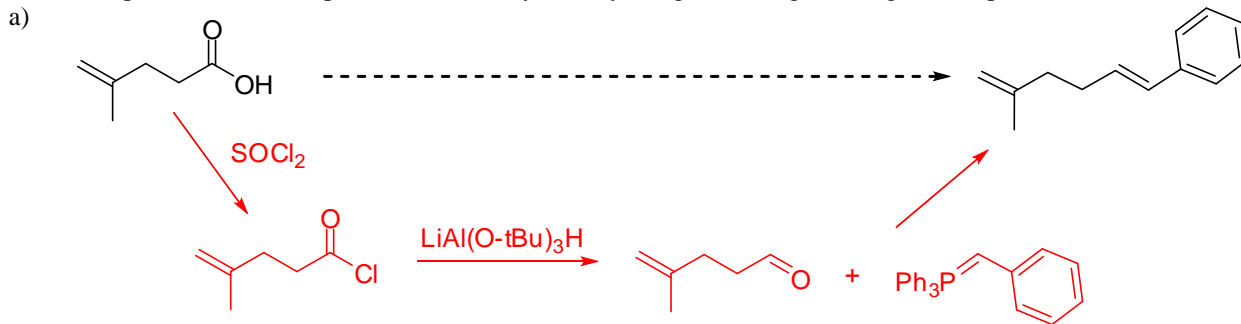


Note: R=alkyl

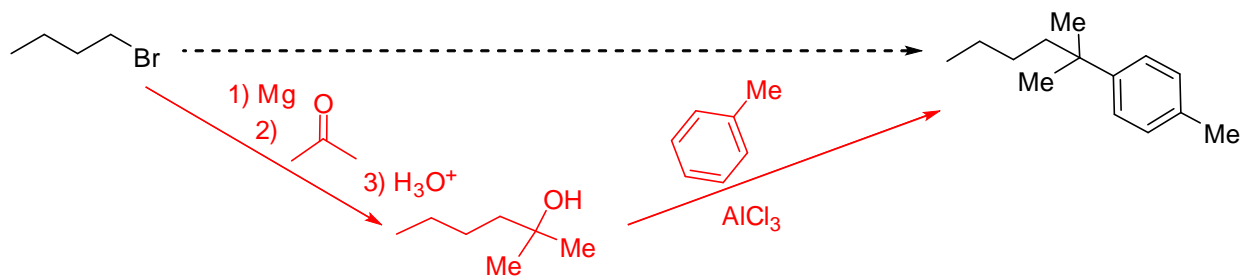
1. Provide the necessary information, product, reagents, or starting materials, to complete the following reactions. (3 pts. per question)



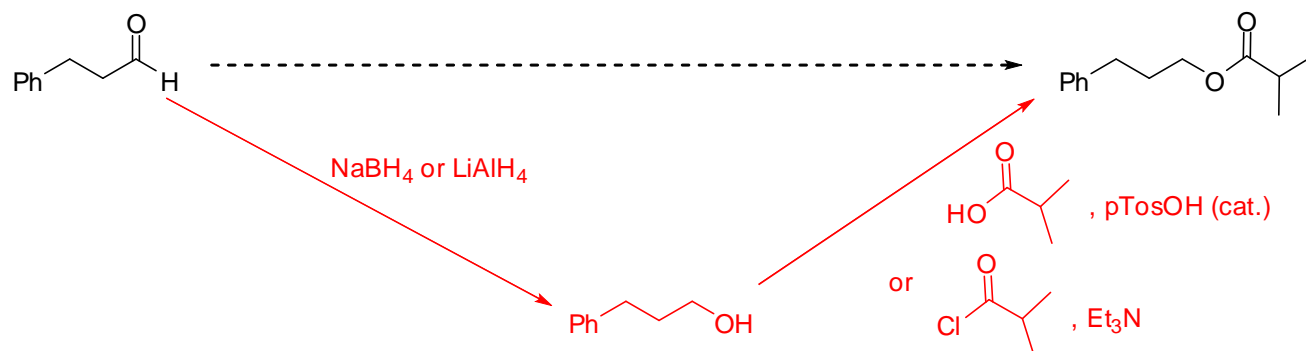
2. Suggest a synthesis to take the starting material on the left to the product on the right. This will require more than one step, but can be accomplished in three steps or less. You may use any inorganic or organic reagent. (10 pts. each)



b)

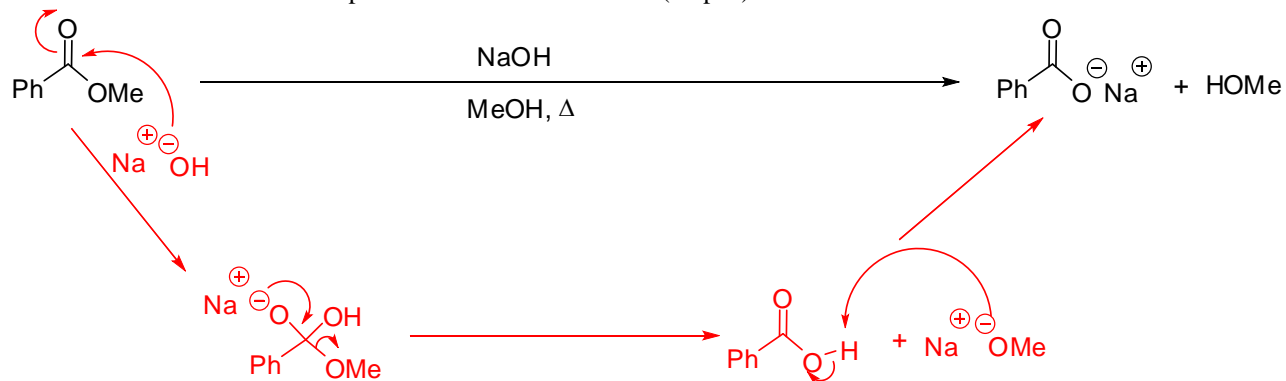


c)

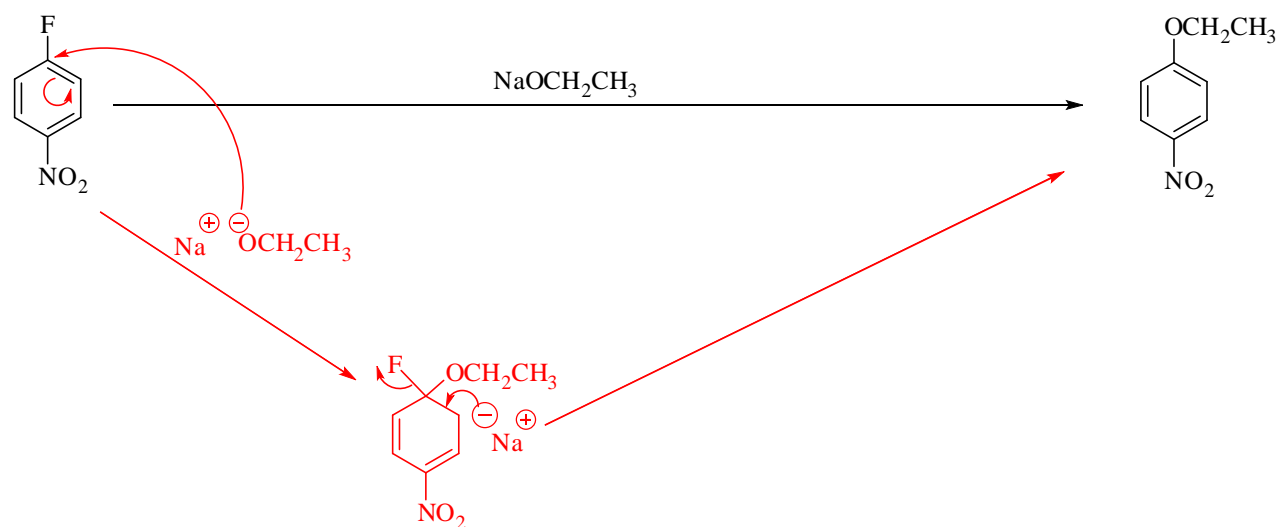


3. Draw the mechanisms for the reactions shown below. Your mechanism should include formal charges and curved electron flow arrows. You do NOT need to draw important resonance structures. (10 pts.)

a)



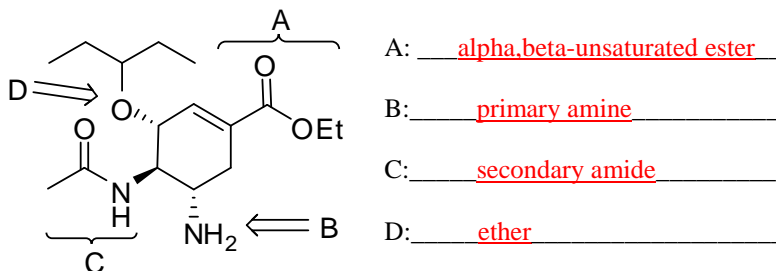
b)



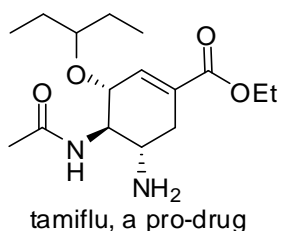
4. Tamiflu (generic name oseltamivir) is the primary treatment currently working against the swine flu influenza virus. Answer the following questions about tamiflu.

a) Analyze the structure of tamiflu by identifying the four designated functional groups on the structure. In all cases, be as specific as possible. (4 pts.)

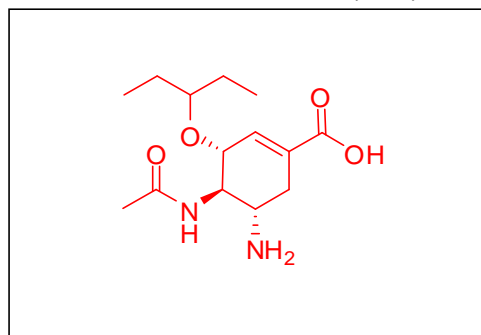
**tamiflu:**



b) Tamiflu is actually a pro-drug; that is, it is transformed into the active drug in the body. Once in the liver, esterase or hydrolase enzymes cause the hydrolysis of functional group A from part a. Draw the structure of active tamiflu after hydrolysis. (3 pts.)



In liver: esterase or hydrolase enzyme

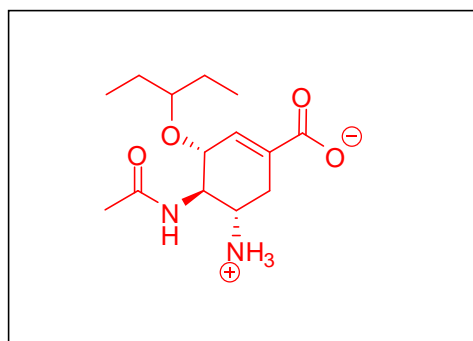


active tamiflu

c) At physiological pH (~7), active tamiflu will not exist as drawn in part b. In the box to the right, draw the form of tamiflu that will be present in the body based on this pH and the pK<sub>a</sub> values of the functional groups on active tamiflu. (4 pts.)

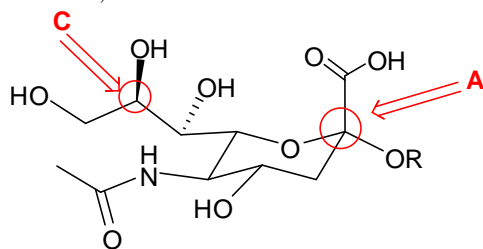
d) Which name best describes this form of active tamiflu? (circle one, 2 pts.)

- (1) phosphorus ylide
- (2) **zwitterion**
- (3) carboxylate cation
- (4) enolate
- (5) ammonium anion



structure of active tamiflu at pH~7

In the body, active tamiflu works by inhibiting the viral enzyme neuraminidase. The structure of neuraminic acid, the natural substrate of neuraminidase, is drawn below.



neuraminic acid (R=H)

e) What general class of biological structures does neuraminic acid come from? (2 pts.)

carbohydrate

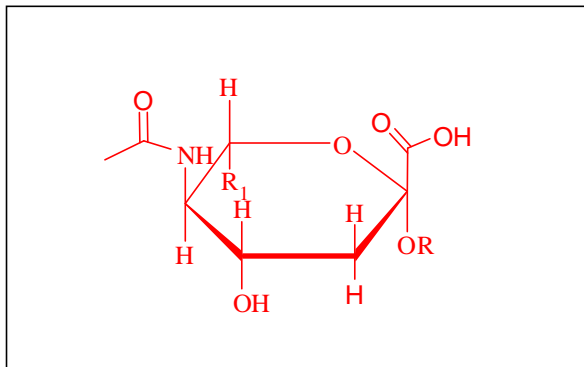
f) Identify the following important atoms on neuraminic acid by circling them and writing the appropriate letter next to the atom.

- (1) configurational carbon, **C** (3 pts.)
- (2) anomeric carbon, **A** (3 pts.)

g) Is neuraminic acid a D or L sugar? (circle one, 2 pts.) **(D)** or L

h) Is neuraminic acid an example of a furanoketose, furanoaldose, pyranoketose or pyranaldose? (3 pts.) pyranoketose

i) Draw a Haworth projection of neuraminic acid in the box to the right. To make the drawing easier, you can replace the three carbon side chain with  $R_1$ . (5 pts.)

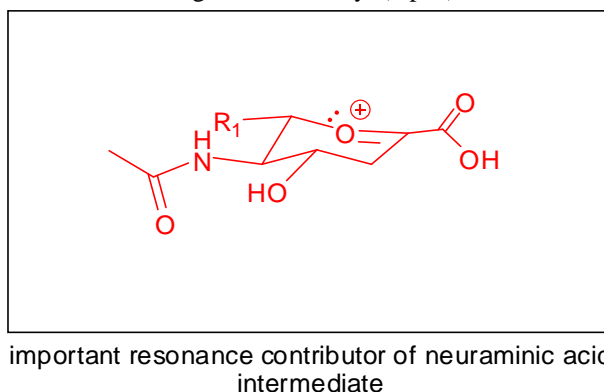
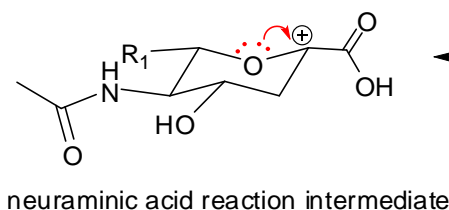


Like many drugs, tamiflu, or its active form, mimics neuraminic acid thereby fooling the neuraminidase enzyme into grabbing tamiflu instead of the neuraminic acid.

j) List two structural pieces of the active form of tamiflu that mimic or are similar to neuraminic acid. (3 pts.)

Structural similarities include the carboxylic acid, the six member ring (pyran vs. cyclohexene), the acetamide group. The amino group of tamiflu is also similar to the hydroxy group of neuraminic acid since both have acidic protons on a heteroatom.

k) One of the other important ways that tamiflu works is to mimic a higher energy intermediate in the reaction catalyzed by neuraminidase. The high energy intermediate is drawn below. Provide an important resonance structure of this high energy intermediate. Be sure to include curved electron flow arrows and formal charges as necessary. (4 pts.)



l) How does tamiflu (or the active form of tamiflu) resemble the important resonance contributor? (4 pts.)

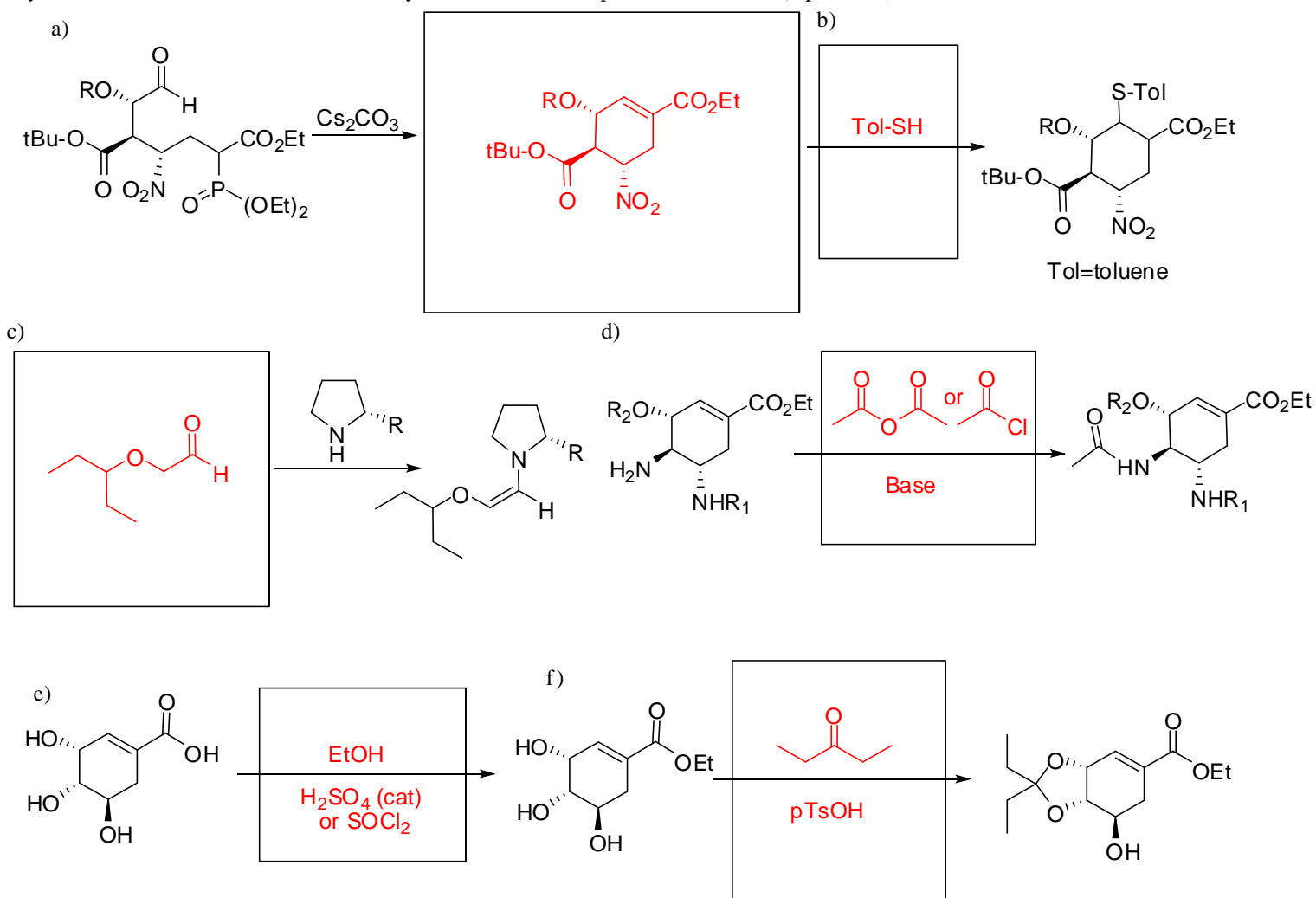
Both tamiflu and the important resonance contributor have a flat pi system or double bond containing two  $sp^2$  hybridized atoms next to a carboxylic acid.

m) One important difference in the structure of tamiflu and neuraminic acid is the nature of the ring structure. Tamiflu's ring should be more stable than neuraminic acid. Which statement best explains this? (3 pts.)

- (1) Tamiflu has more electron donating groups (ERG's) than electron withdrawing groups (EWG's) which always make a ring more electron rich and stable.
- (2) The cyclic acetal ring of neuraminic acid is unstable under acid conditions unlike the all carbon ring of tamiflu.)**
- (3) Neuraminic acid has an EWG at the correct position for stabilization of the ring opened form.
- (4) The conjugation in tamiflu leads to a lower energy structure that will engage in conjugate addition reactions before undergoing ring opening reactions.
- (5) Neuraminic acid is a member of the 'neurotic' compounds (thus the name) which can 'flip out' or ring open about the smallest things, like a broken nail or a scratch on the hood of the brand new molecular car, when not heavily sedated.

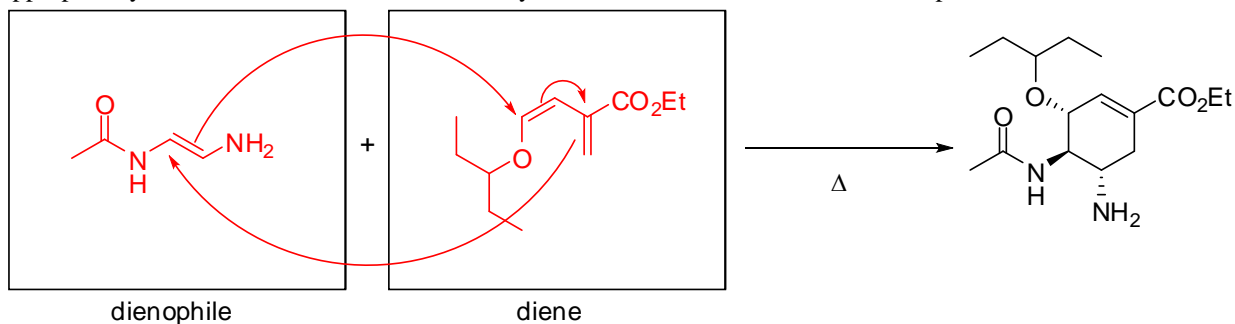
/19 pts.

5. With the high medical value on tamiflu to fight influenza outbreaks, including the swine flu pandemic, there has fortunately been a considerable amount of synthetic work to generate a suitable supply of tamiflu. The reactions shown below have been used in various syntheses of tamiflu. Provide the necessary information to complete the reactions. (2 pts. each)



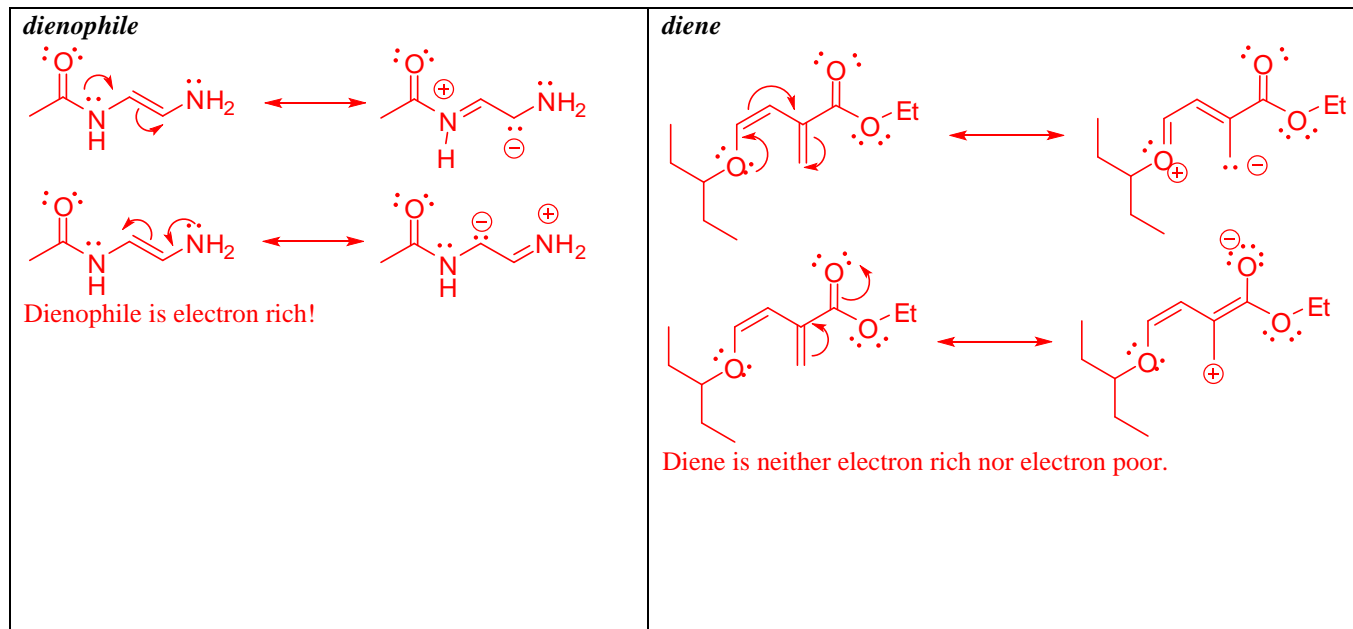
6. With a cyclohexene ring at the core of tamiflu, a Diels-Alder reaction is a very attractive approach to an efficient synthesis of this important drug.

a) Show the Diels-Alder precursors that could be used to generate tamiflu in one step. Be sure to place the structure in the appropriately labeled box. For maximum credit, your structures should illustrate stereospecific control in the reaction. (6 pts.)



b) Draw the curved electron flow arrows showing the mechanism of this Diels-Alder reaction. (3 pts.)

c) In the box below, analyze the two reagents in your reaction. Using resonance structures, show whether the alkene portion of both reagents would be electron rich or electron poor. Draw two resonance structures for each reagent. You may abbreviate your structure as necessary, but remember to include all formal charges and lone pairs as required to understand the resonance structures. (10 pts.)



d) Based on your resonance analysis and your knowledge of Diels-Alder reactions, which statement most correctly evaluates this reaction? (3 pts.)

- (1) This would be a good example of an 'inverse electron demand' Diels-Alder reaction where the dienophile is electron rich and the diene is electron poor.
- (2) The proposed Diels-Alder reaction would work quite well since the optimum molecular overlap would occur between the HOMO of an electron rich dienophile and the LUMO of the electron poor diene.
- (3) The resonance forms demonstrate that the electron flow would push electrons from the diene to the dienophile in a concerted, pericyclic reaction.
- (4) This Diels-Alder reaction would not work well because the dienophile is electron rich, the opposite of what is typically seen, and the diene is neither electron rich nor electron poor.**
- (5) Both the diene and the dienophile have several conjugated pi systems which make these structures far too stable to engage in any Diels-Alder reactions.