Final Examination for **Chem 313**

3:30 p.m. December 6, 2014; **Time: 2.5 hours**

This examination consists of **13** pages, including this cover page and three pages of scrap paper. It is out of 100 points. You may remove the pages of scrap paper.

Last Name Answer Key First Name _____

Signature _____ Student Number _____

Student Conduct during Examinations

Each examination candidate must be prepared to produce, upon the request of the invigilator or examiner, his or her UBCcard for identification.

Examination candidates are not permitted to ask questions of the examiners or invigilators, except in cases of supposed errors or ambiguities in examination questions, illegible or missing material, or the like.

No examination candidate shall be permitted to enter the examination room after the expiration of one-half hour from the scheduled starting time, or to leave during the first half hour of the examination. Should the examination run forty-five (45) minutes or less, no examination candidate shall be permitted to enter the examination room once the examination has begun.

Examination candidates must conduct themselves honestly and in accordance with established rules for a given examination, which will be articulated by the examiner or invigilator prior to the examination commencing. Should dishonest behaviour be observed by the examiner(s) or invigilator(s), pleas of accident or forgetfulness shall not be received.

Examination candidates suspected of any of the following, or any other similar practices, may be immediately dismissed from the examination by the examiner/invigilator, and may be subject to disciplinary action: i. speaking or communicating with other examination candidates, unless otherwise authorized; ii.purposely exposing written papers to the view of other examination candidates or imaging devices; iii. purposely viewing the written papers of other examination candidates; iv. using or having visible at the place of writing any books, papers or other memory aid devices other than those authorized by the examiner(s); and, v. using or operating electronic devices including but not limited to telephones, calculators, computers, or similar devices other than those authorized by the examiner(s)—(electronic devices other than those authorized by the examiner(s) must be completely powered down if present at the place of writing).Examination candidates must not destroy or damage any examination material, must hand in all examination papers, and must not take any examination material from the examination room without permission of the examiner or invigilator.

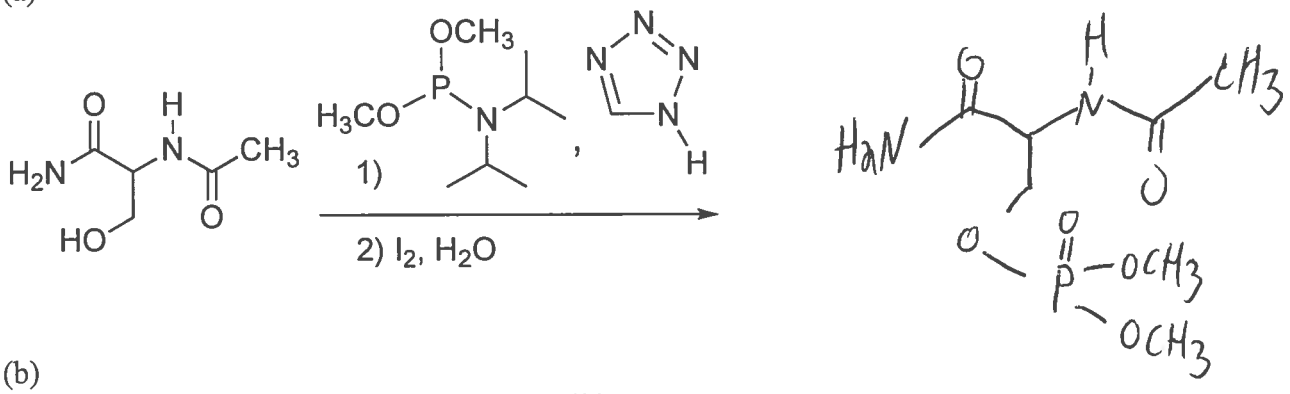
Notwithstanding the above, for any mode of examination that does not fall into the traditional, paper-based method, examination candidates shall adhere to any special rules for conduct as established and articulated by the examiner.

Examination candidates must follow any additional examination rules or directions communicated by the examiner(s) or invigilator(s).

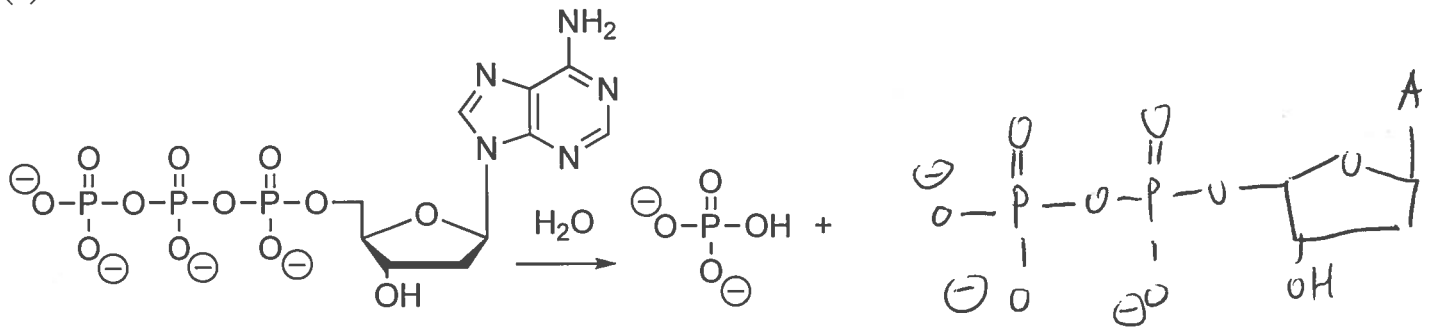
1. [39]	_____
2. [12]	_____
3. [7]	_____
4. [6]	_____
5. [5]	_____
6. [8]	_____
7. [8]	_____
8. [7]	_____
9. [8]	_____
Total [100]	_____

1. [39 points] Predict the products of the reactions below. Show stereochemistry where appropriate.

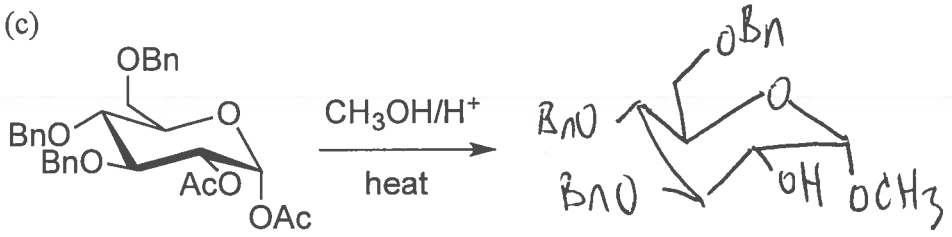
(a)



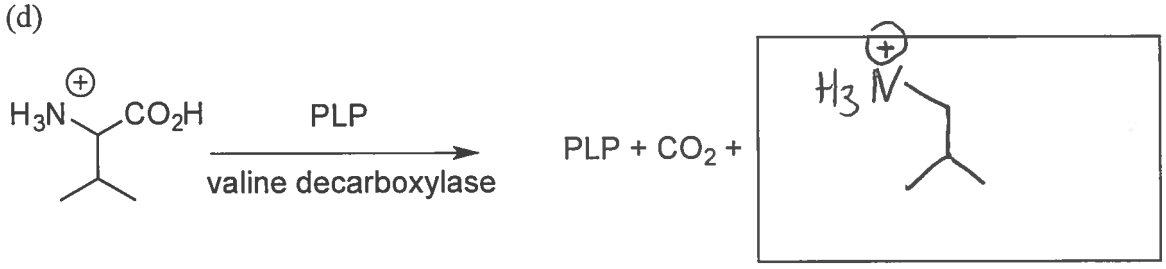
(b)



(c)

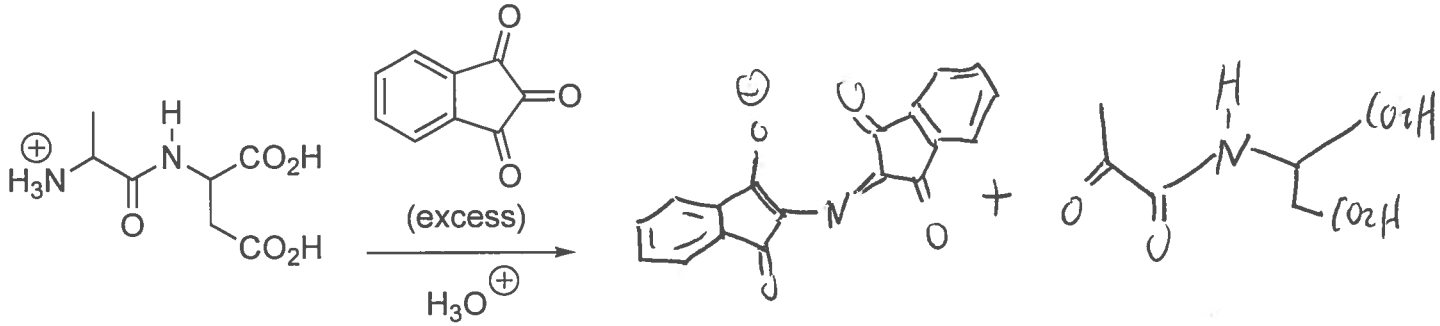


(d)



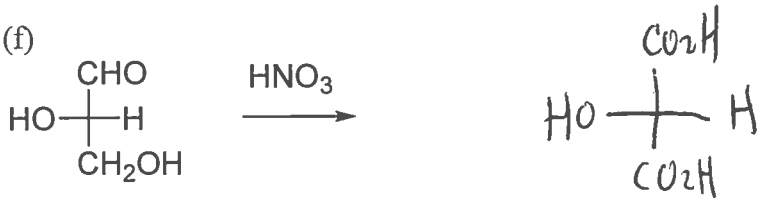
1. Continued

(e)

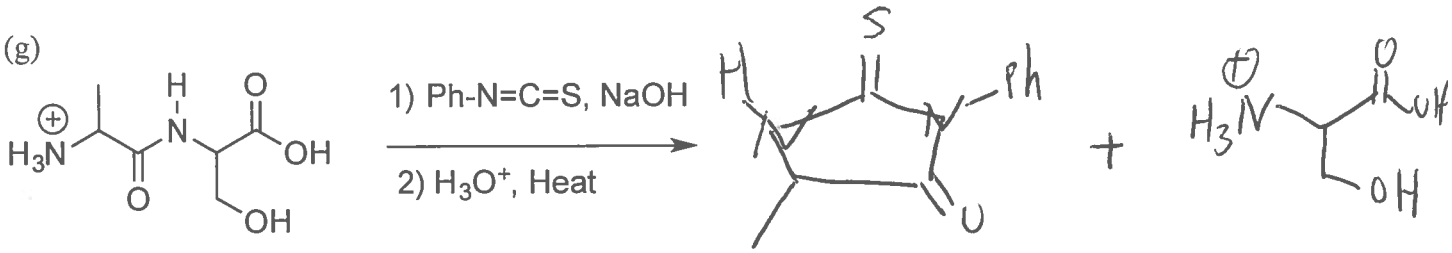


Draw 2 compounds

(f)

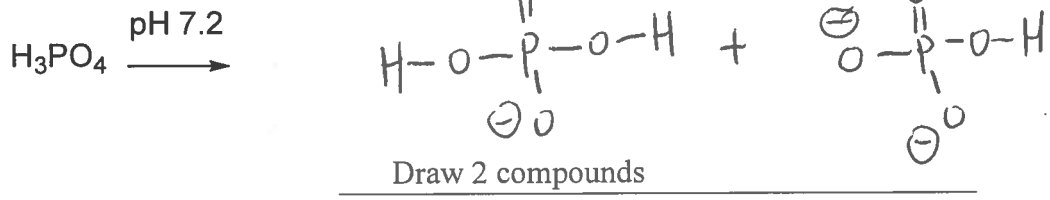


(g)



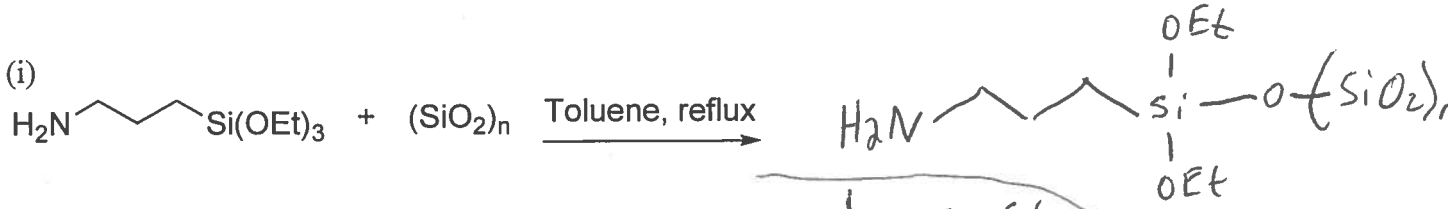
Draw 2 compounds

(h)

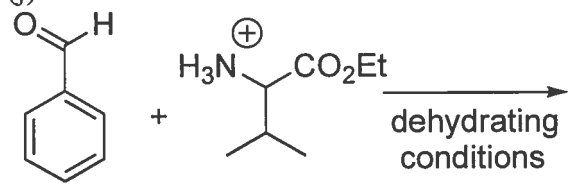


Draw 2 compounds

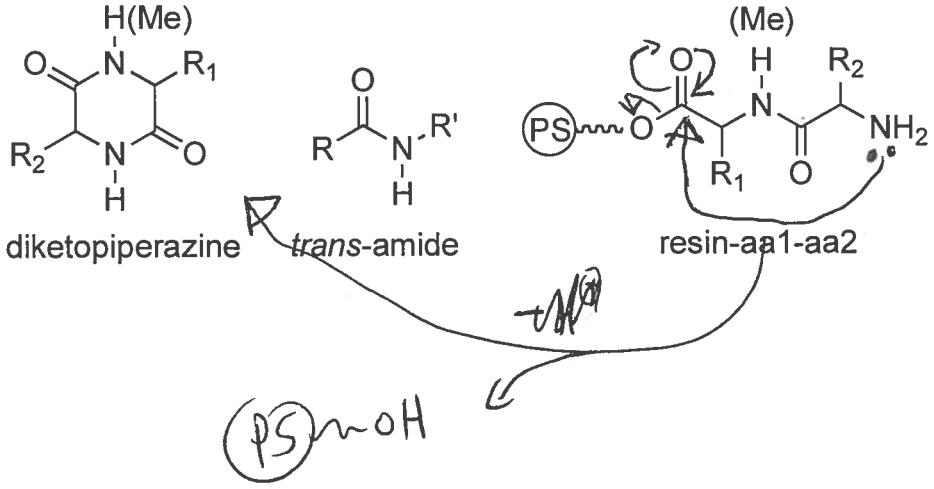
(i)



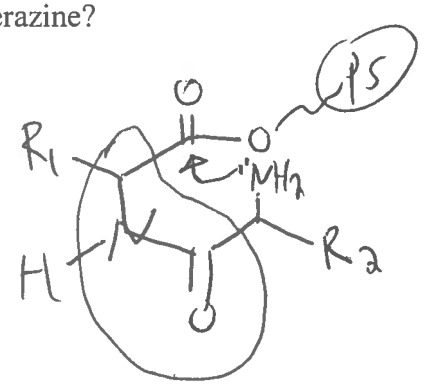
(j)



2. [12 points] During solid phase peptide synthesis, when the Fmoc group of the second amino acid linked to the resin is removed, a common unwanted reaction can occur to yield a diketopiperazine. This reaction is even more problematic if the first amino acid is an *N*-Me amino acid, as *N*-Me amino acids prefer a *cis*-amide conformation. (Chem Rev. **2011** 6557) (a) Propose a mechanism for diketopiperazine formation.



(b) How does an *N*-Me amino acid as the first amino acid enhance formation of the diketopiperazine?



The circled conformation is preferred, which positions the amine near the carbonyl.

(c) Why is the diketopiperazine problem more of an issue during the deprotection of the second amino acid, and not so much during later deprotections?

The six membered TSA is not six-membered, it is much larger, which is not favorable. The foregoing is needed to react at the PS-O ester linkage. For later aa, the 6-membered ring would require rxn w/ an amide, which is not sufficiently electrophilic.

2. Continued

(d) Predict the relative rates of interconversion of (1) *cis* and *trans* amides, (2) *cis* and *trans* 2-butene, and (3) anti and gauche butane (i.e., order the three pairs in term of their rates of interconversions). Explain your answer in terms of what type of bonding, if any, is broken in the transition states.

anti/gauche butane fastest – single C–C bonds

cis-trans amides next: partial double bond

cis/trans butene slowest: Full double bonds

3. [7 points] pK_a's in CH_3CN as solvent versus H_2O as solvent differ by 10-20 pK_a units in the same direction (J. Phys. Org. Chem. **2004** p. 1). The differential is 15-20 pK_a units for HA (e.g., RCO_2H) and 5-10 units for $[HA]^+$ (e.g., RNH_3^+). (a) Predict the direction of the differential (e.g., are acids more acidic in CH_3CN or in H_2O?).

more acidic in water.

(b) Explain your answer to part (a).

$HA \longrightarrow H^{\oplus} + A^{\ominus}$] more charges are more stable in the more polar water.

$HA^{\oplus} \longrightarrow H^{\oplus} + A:$

the anion and the lone pair of A: are better solvated by water: $H-O-H\cdots :A$

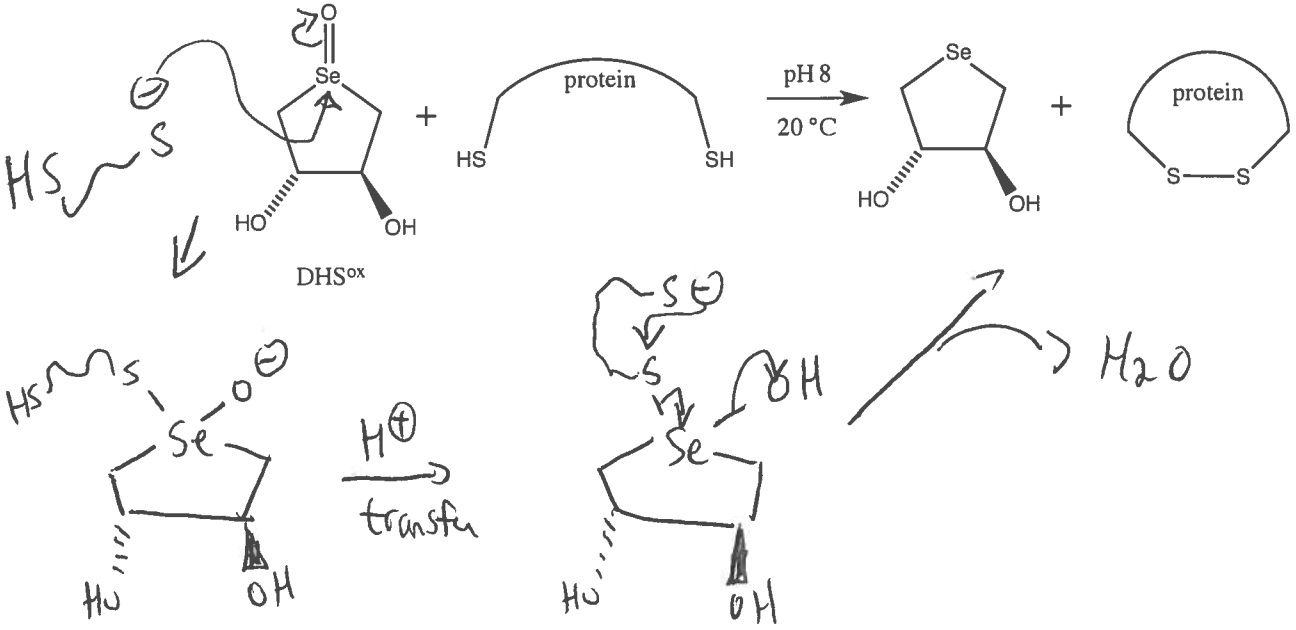
No such H-bonds are possible with AN.

(c) Why is the differential smaller with $[HA]^+$ than with HA?

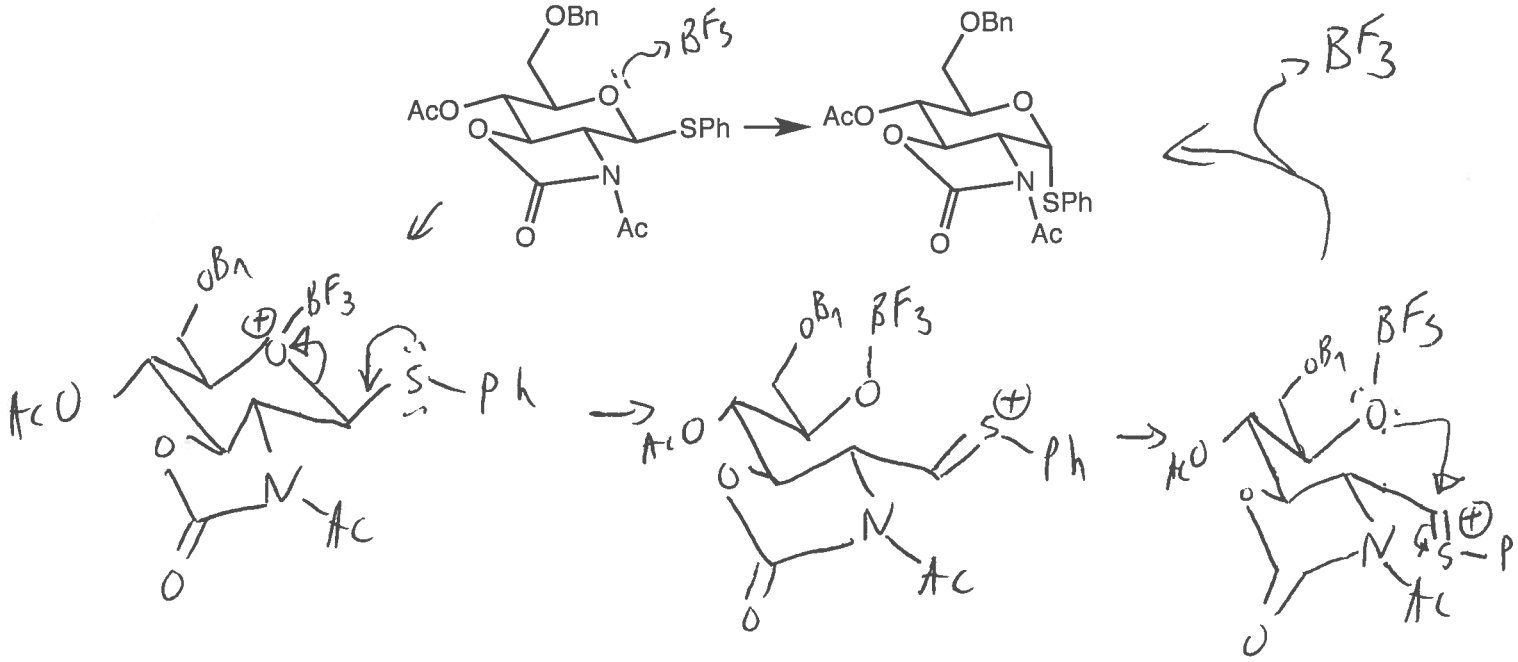
The charges balance in $HA^{\oplus}$: there is one charged species on either side of the arrow.

Water stabilizes charges, especially anions, better.

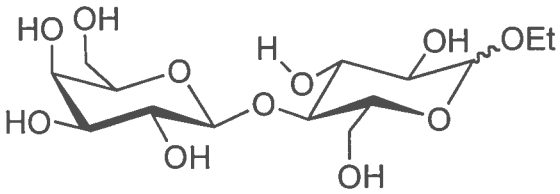
4. [6 points] DHS^{ox} is used to oxidize protein thiols to disulfides. The reaction is proposed to go via a two-step mechanism, not counting protonations/deprotonations of O/S. The first step has been shown to be the slow step. Propose a mechanism for this transformation. (*Chem Eur. J.* **2014**, *17*, 481)

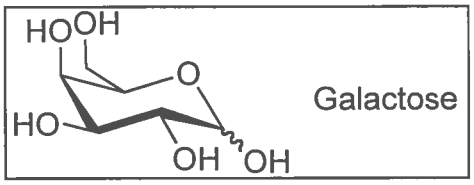


5. [5 points] Researchers proposed that the compounds below anomerize in the presence of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at –30° C in 12 hours. They propose that the BF_3 coordinates to the ring oxygen. No anomerization occurred if the Ac on the nitrogen was replaced with a hydrogen. Based on this information, propose a mechanism for the anomerization. Hint: (1) The effect of the NAc is subtle; don't try to explain it, but: (2) Be sure that the mechanism you draw converts one anomer to the other anomer. (*Chem Eur. J.* **2014**, *20*, 124)



6. [8 points] Propose a synthesis of the disaccharide below (left), using glucose, galactose, and any other reagents.

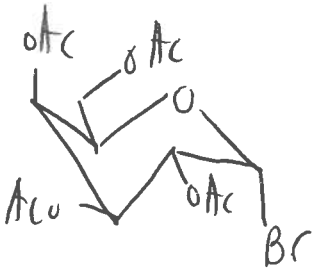




glucose → 1) EtOH, $H^{\oplus}$ 2) PhCHO, $H^{\oplus}$ 3) Ac_2O, pyr 4) H_2, Pd/C 5) Trt-Cl

A

galactose → 1) Ac_2O, pyr 2) HBr

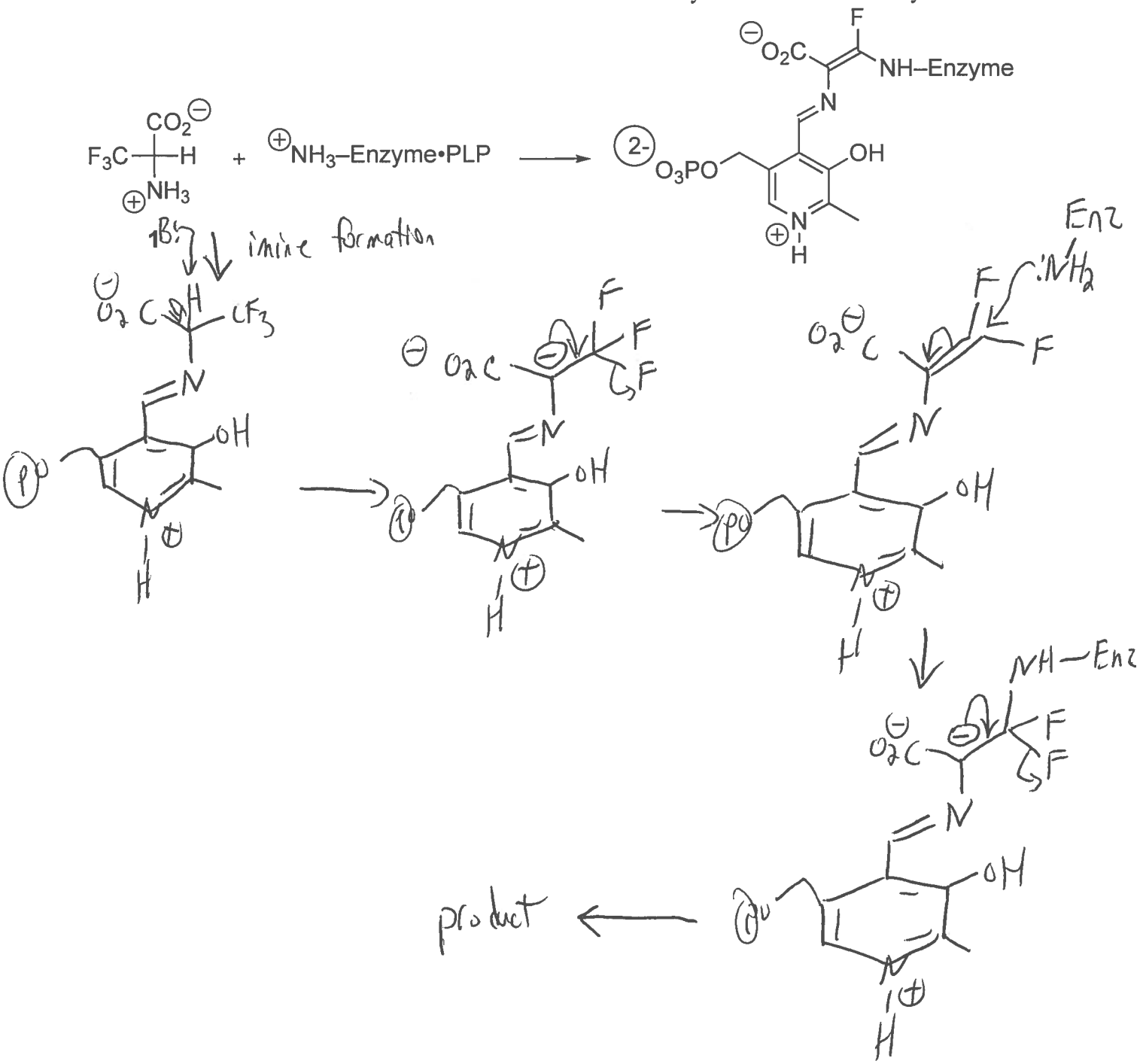


B

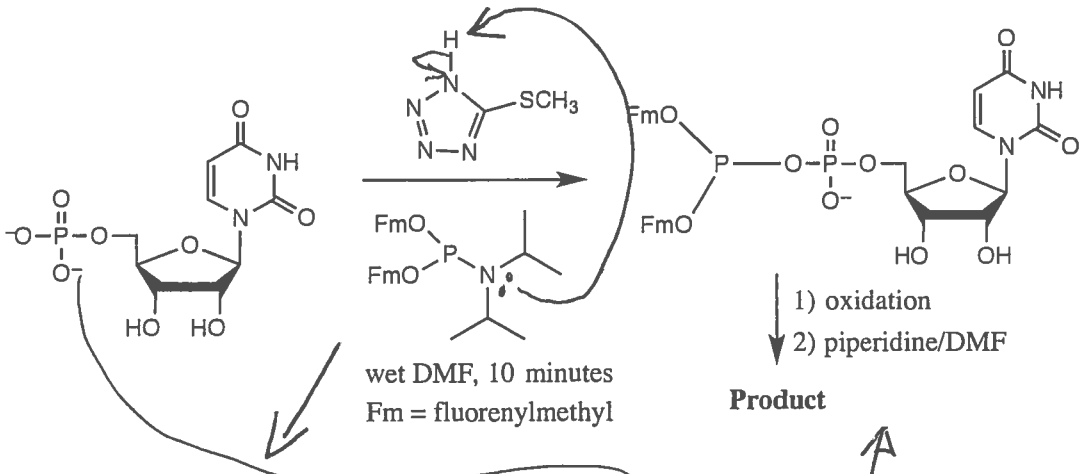
A + B → 1) Ag_2CO_3 2) $MeO^{\ominus}$/MeOH 3) H_2, Pd/C

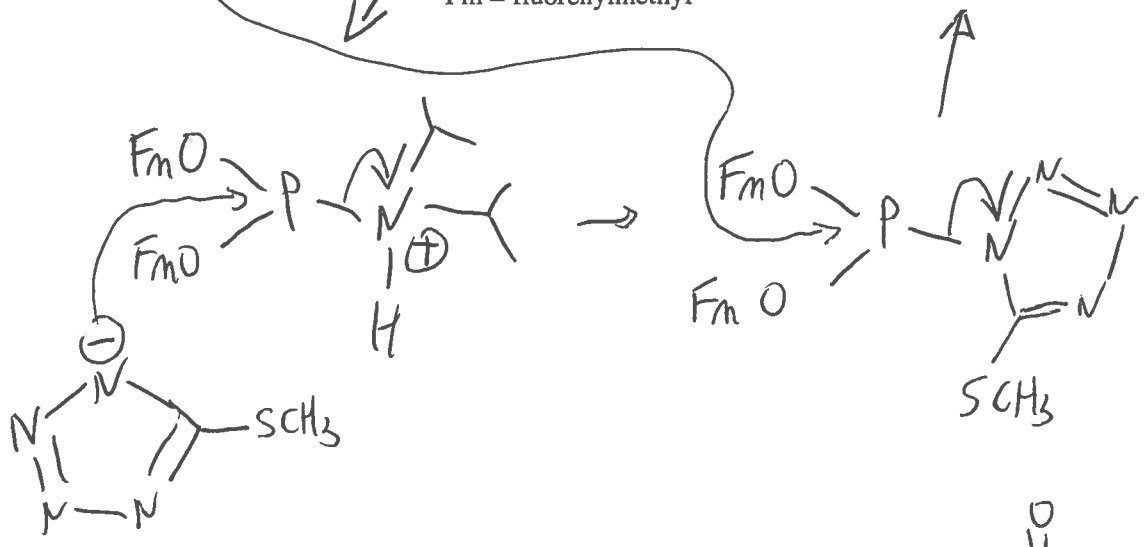
product

7. [8 points] The bacterial enzyme alanine racemase produces the D-alanine that bacteria need to build their cell walls. Inhibitors of this enzyme could therefore potentially serve as antibiotics. It has been shown that trifluoroalanine **1** is an irreversible inhibitor of this PLP-dependent enzyme. The researchers found that one molecule of inhibitor becomes covalently attached to the enzyme and suggested that the structure of the adduct was as shown below (right). Suggest a reasonable mechanism for the formation of the adduct shown. Don't worry about stereochemistry.

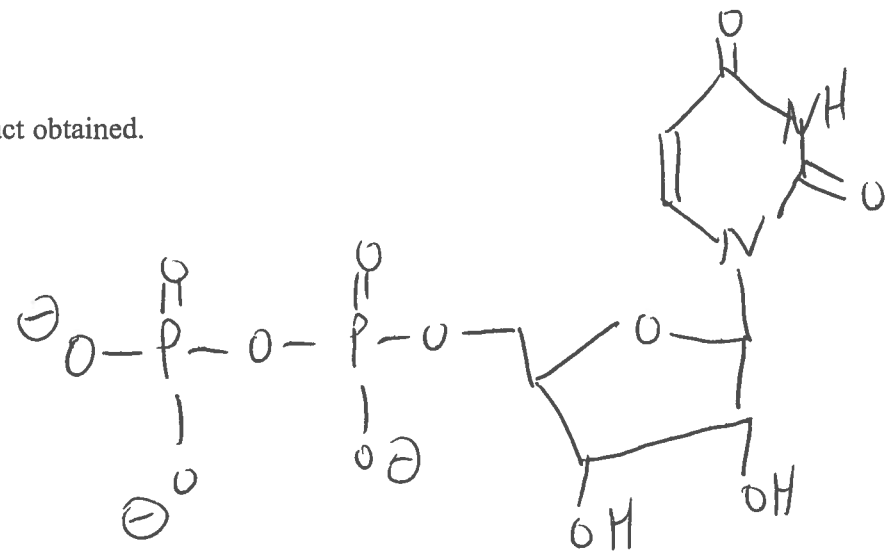


8. [7 points] Researchers were interested in devising methods to phosphorylate nucleotides as shown below. (*Org. Biomol. Chem.* **2014**, *12*, 3526) (a) Propose a mechanism for the first step.

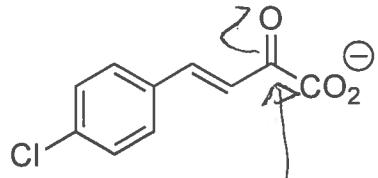


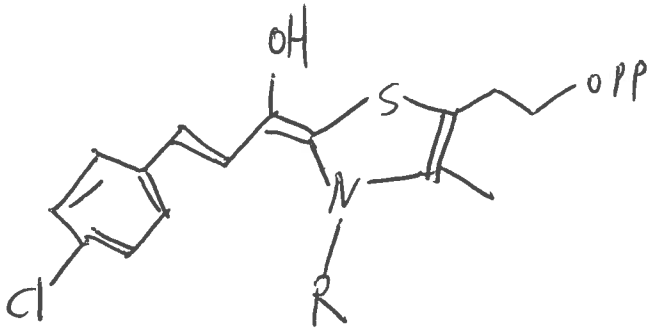


(b) Predict the final product obtained.



9. [8 points] Pyruvate analogs can be used to monitor key intermediates in thiamin reaction pathways. The substrate analog below yields a hydroxyethylenamine derivative upon reaction with thiamin. This derivative is easy to observe by UV spectroscopy due to the conjugation of the ring with the enamine. (a) Propose a structure for the derivative. You can use a partial structure of thiamin in your answer. (Biochemistry **2007** 12037)





(b) Propose a mechanism for the formation of the derivative.