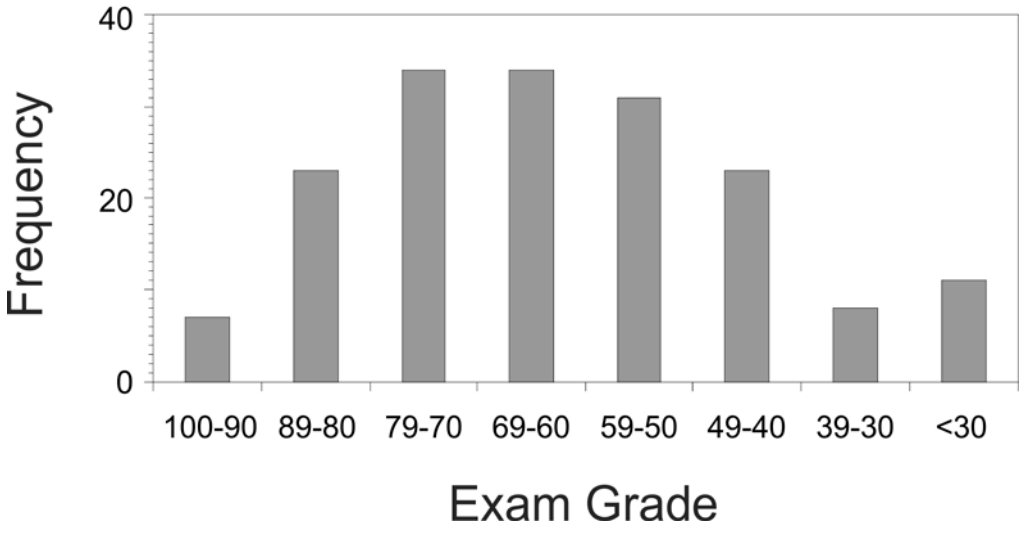
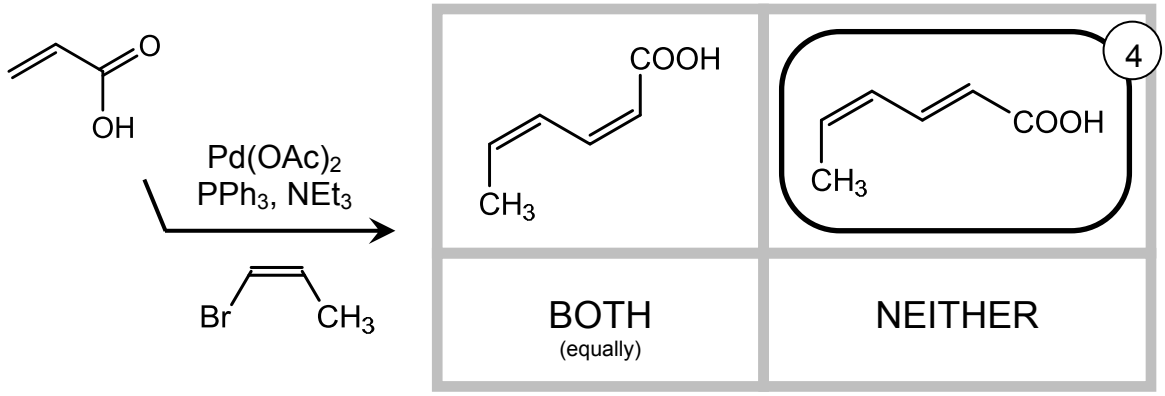
Exam 4
Answer Key

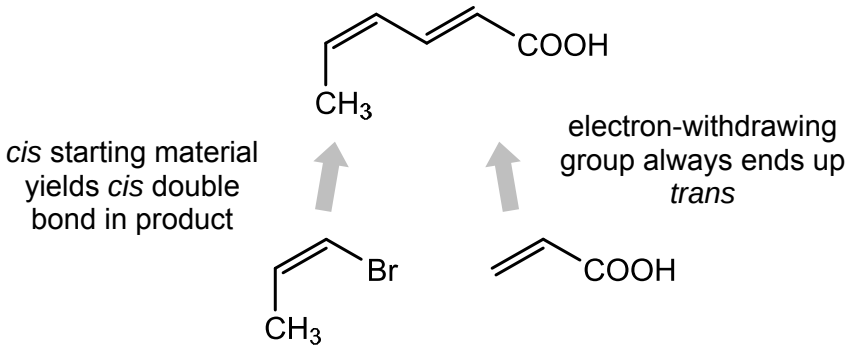
Exam 4 Mean:	62
Exam 4 Median:	64
Exam 4 St. Dev.:	18

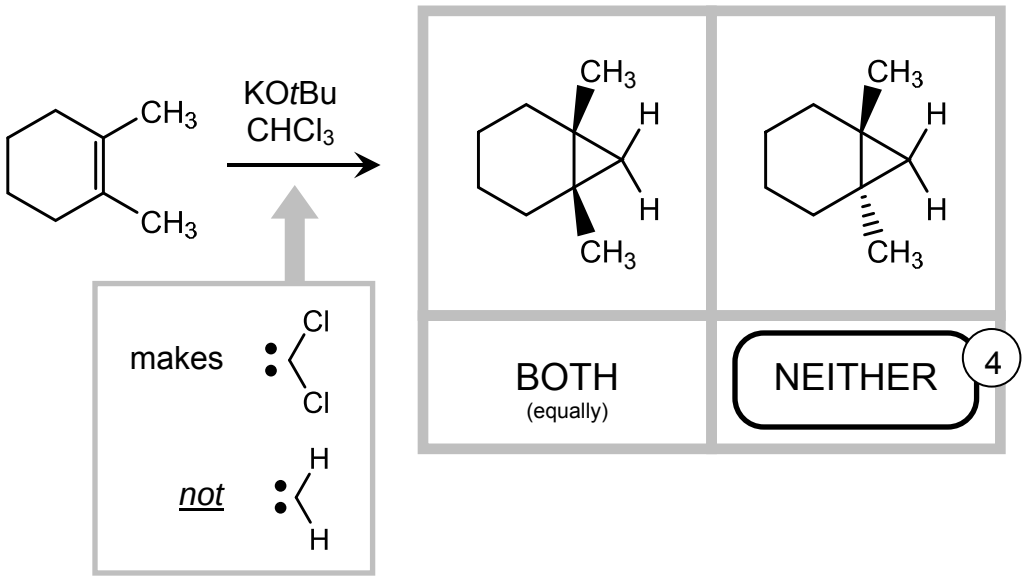


1. (16 pts) Each of the reactions below is drawn with two possible products or reactants. Circle the preferred product or set of reagents. If the two products are produced equally, or if either reaction would succeed, circle "BOTH". If neither product would result from the reaction, circle "NEITHER". **Circle one answer only.**

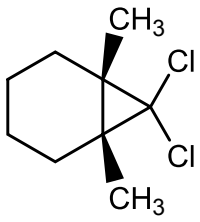


This problem illustrates a Heck reaction, in which a vinyl bromide is coupled to an alkene with an electron-withdrawing carboxylic acid group. In the Heck reaction, the bromide is replaced with a C-C bond of the same stereochemistry (in this case, *cis*). The stereochemistry of the other double bond is always *trans*, with the electron-withdrawing group across from the new C-C bond.





The reagents shown would generate a dichlorocyclopropane, not either of the cyclopropanes shown. Cyclopropanes are generated using the Simmons-Smith reaction (CH_2I_2, Zn).



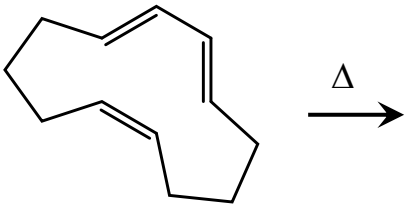
(H_2N)-Ala-Phe-Glu-(COOH)
(a tripeptide)

1. PhNCS
2. H_3O^+, Δ

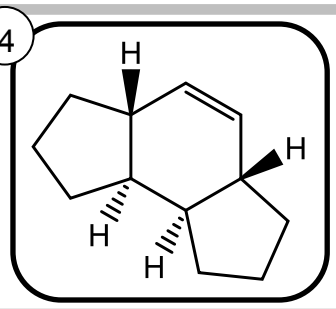
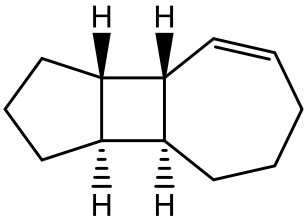
(Edman degradation)

4	
(H_2N)-Phe-Glu-(COOH) *(a dipeptide)*	(H_2N)-Ala-Phe-(COOH) *(a dipeptide)*
BOTH (equally)	NEITHER

The Edman degradation removes an amino acid from the N-terminus of a peptide or protein.



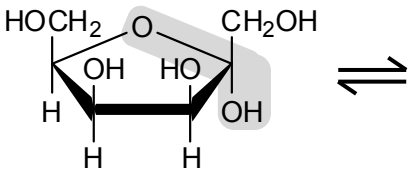
Δ

4	
	
BOTH (equally)	NEITHER

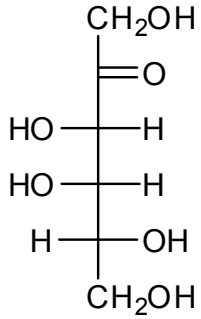
The first product box illustrates a [4+2] (Diels-Alder) cycloaddition, and the second product box a [2+2] cycloaddition. Under the thermal conditions shown, only the [4+2] cycloaddition would be allowed under the Woodward-Hoffman selectivity rules for cycloadditions. (There are an odd number of pairs of electrons involved, and that's thermally allowed, whereas the even number of electron pairs in the [2+2] make it thermally forbidden.)

(Incidentally, I'm also not sure the double-bond stereochemistry on the right could be achieved. But that point's moot--the reaction can't happen anyway.)

2. a.

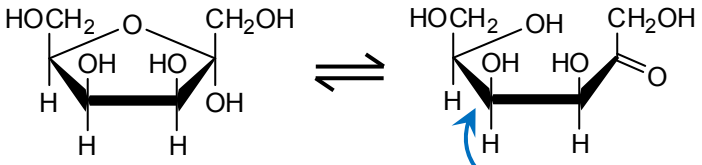


acyclic form of D-tagatose (Fischer projection)

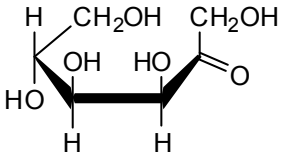


4

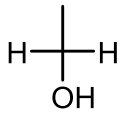
The cyclic structure shown in the problem is a hemiketal, and it equilibrates with a ketone form:



twist this bond



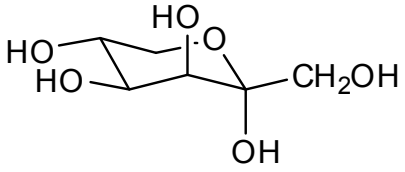
Rotate this last structure counterclockwise, and you have the Fischer projection.

Rubric for this question *(4 points total this part):*
2 points for any hexose with carbonyl at C2.
2 points for all three correct stereocenters. *No partial credit on this 2 points.*
You could abbreviate the bottom and top carbons as "CH_2OH", or you could draw them out if you liked. So,  *is fine.*

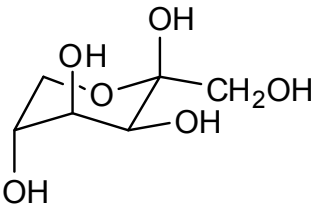
b. This acyclic form also equilibrates with two pyranose (6-membered ring) anomers. Draw one of those two anomers in its most stable chair conformation in the box below.

one pyranose anomer of D-tagatose (drawn as its most stable chair conformer)

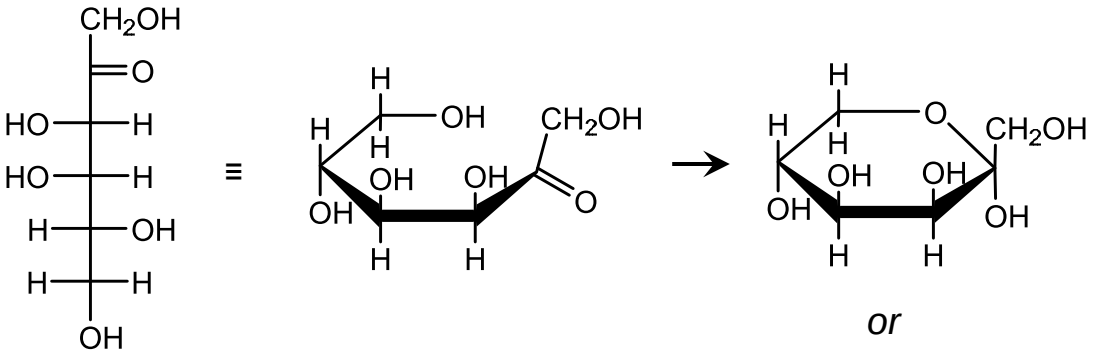
4



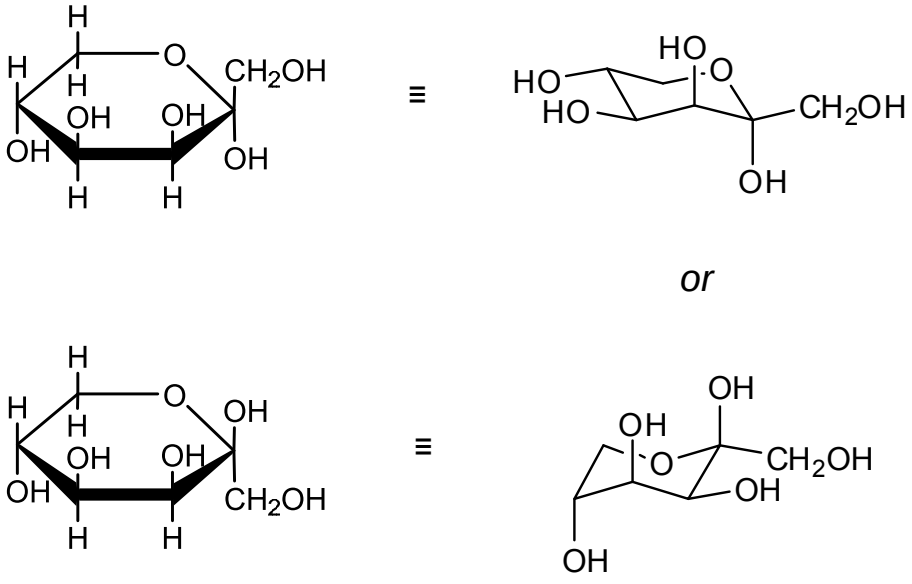
or



The six-membered ring form of tagatose forms directly from the Fischer projection you drew, by combining the bottom-most -OH group with the carbonyl:



Either of the 6-membered rings on the right could be formed by cyclization. In both cases, the anomeric carbon bears an -OH group and a -CH_2OH group. In class, we talked about how there are sometimes competing steric and anomeric effects in cyclic sugars, but in this case, those two effects actually reinforce each other: the -CH_2OH group chooses to be equatorial, because it's the most sterically demanding group on the ring; and the -OH group chooses to be axial, to take advantage of the anomeric effect. That means each of the rings above will have its own preferred conformation:



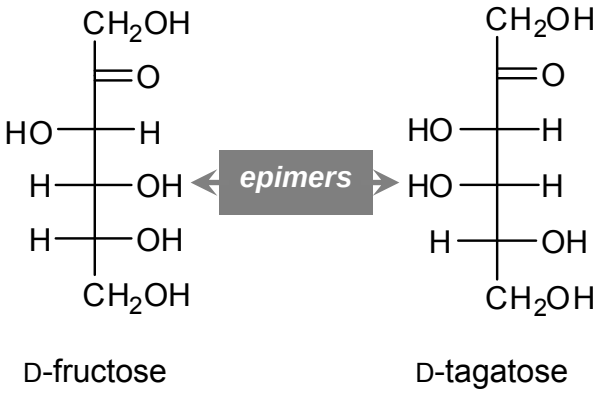
So we graded your chair on three criteria: (1) whether the anomeric carbon (the one next to your ring oxygen) had an equatorial -CH_2OH and an axial -OH; (2) whether you placed the -OH and -CH_2OH groups around the ring at the correct carbons; and (3) whether your answer was correct.

Rubric for this question:
4 points for either chair conformer.
2 points partial for any chair with equatorial CH_2OH and axial OH attached to the anomeric carbon.
1 point partial for any chair with groups at correct carbons (regardless of stereochemistry/axial/equatorial). (You could get both this partial credit and the above one for 3 points partial, even if you drew the incorrect answer.)

c. The Fischer projection for D-fructose is shown at right. Is D-fructose an epimer of D-tagatose?

2 **YES** *or* **NO** ?

(circle one)



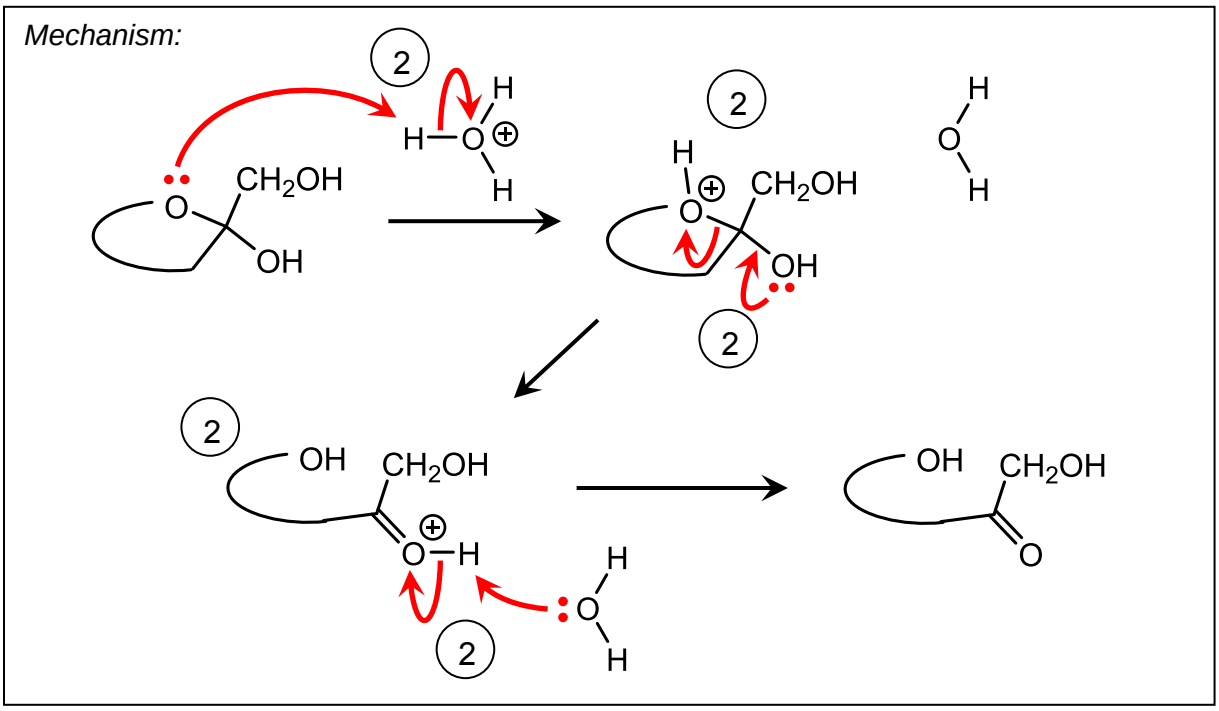
D-fructose D-tagatose

An epimer is a carbohydrate stereoisomer that differs in stereochemistry at one carbon.

Rubric for this question *(2 points total this part):*
Full credit for "NO" if answer to part (a) is not an epimer.

d. In the box below, draw an acid-catalyzed mechanism (using "electron pushing") for the formation of acyclic D-tagatose from the 5-membered ring form. Draw each molecule and mechanistic step explicitly; don't cheat by combining multiple processes in a single step, by taking shortcuts. For this problem, feel free to illustrate both open and ring-closed forms of tagatose as cartoon loops; you do not need to draw the sugar structure.

Mechanism:



Rubric for this part *(10 points total this part)*

Overall notes:

Overall, the minimum score for each step is zero; errors in a step cannot earn you negative points that count against another, correct step.

Things that have left (e.g., Cl^- from HCl in first step) and spectators may be omitted.

Each proton transfer must be shown explicitly, with two arrows (one to proton, one from proton-acid bond).

-1 point, for each arrow in each step, for errors (including omission) in drawing arrows. Arrow must start at an electron pair (either a bond or a lone pair), and end at nucleus or bond where electrons will newly interact.

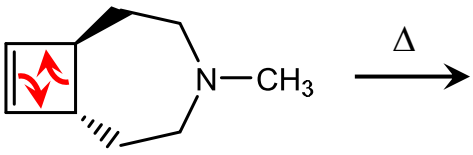
-1 points for each error in charge, valency, structure, base, etc.; if error propagates, points are taken off only for initial error.

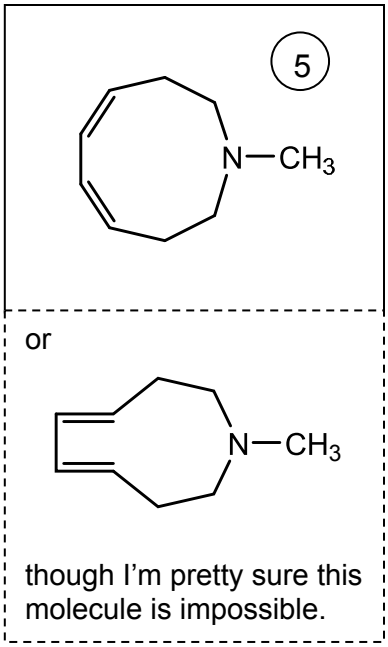
-1 point for each step combined with another, taken off each step. (So, you would get 2 points total from combining two 2-point steps.) In addition, you will lose points by omitting an intermediate that you would have otherwise gotten 2 points for.

e. What is the timescale of this ring opening? Does it take place spontaneously over

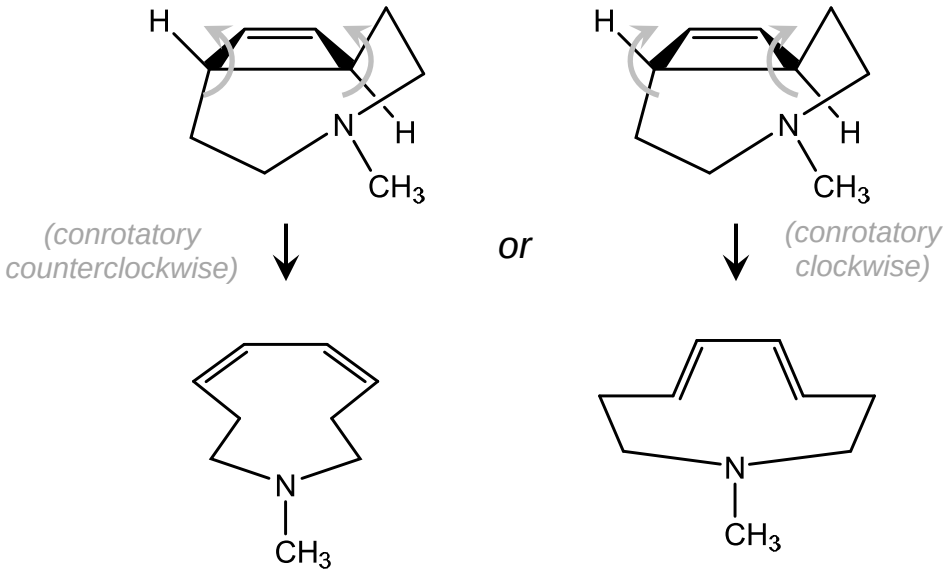
3 **minutes?** **weeks?** *or* **decades?** *(Circle one.)*

3. (23 pts) For each of the reactions below, fill in the empty box corresponding to reactants or product. Give only one answer in each box. For reactions that you expect to yield multiple products, draw one major product. For reactions that yield multiple enantiomers, draw only one enantiomer in the box, and include the note "+ enantiomer".

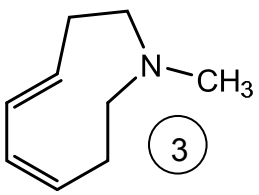


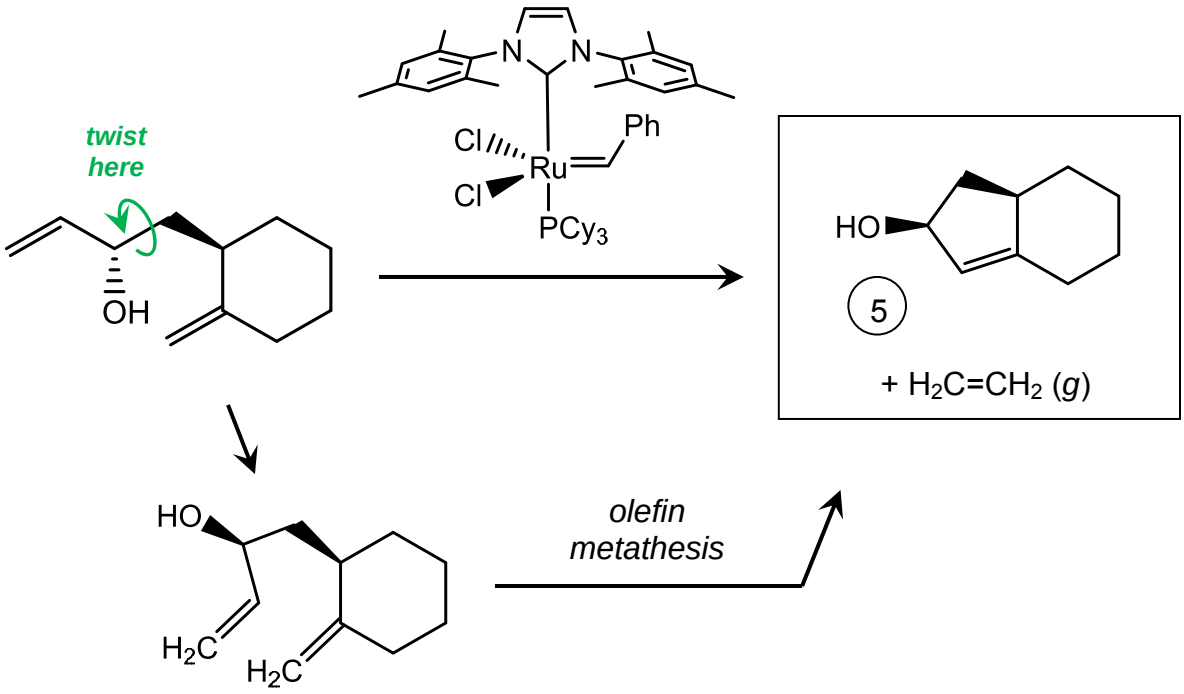


This problem illustrates an electrocyclic ring opening reaction. This one involves 2 pairs of electrons in motion, and the Woodward-Hoffman selectivity rules for electrocyclic ring opening reactions says that the motion of the two exocyclic groups in this reaction should be conrotatory—they should both twist clockwise, or both counterclockwise. Here's what that looks like:



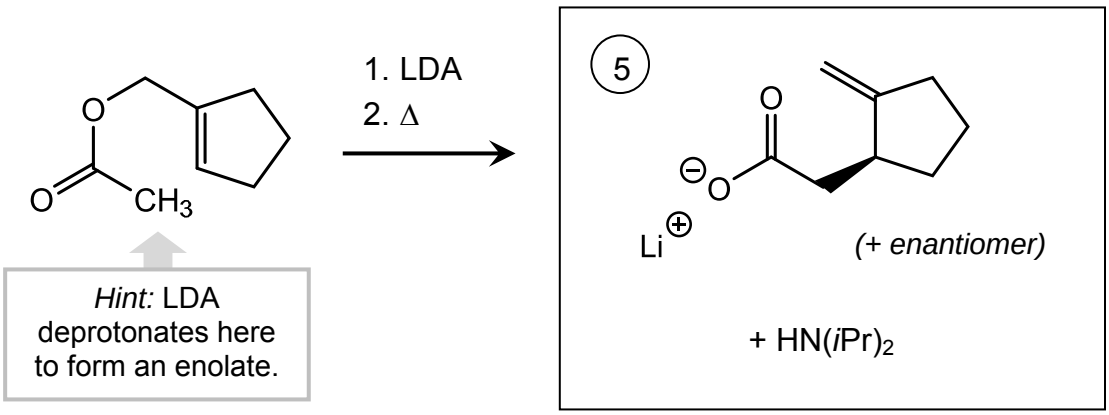
Rubric for this question:
Full credit (5 points) for either *cis, cis*- or *trans, trans*-product.
3 points partial for cis-, trans-product.
-2 points for each for each clearly trivial structure mistake. This includes omitting a carbon from the nine-membered ring.



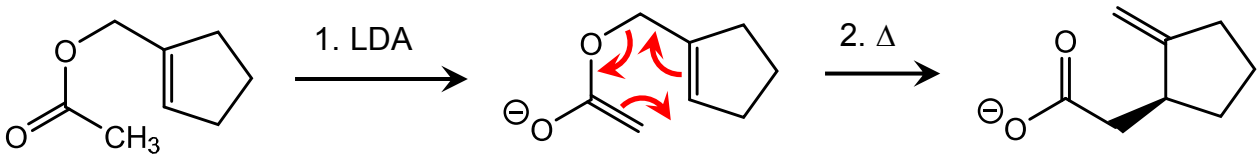


This problem illustrates a ring-closing olefin metathesis reaction--a reaction in which two double bonds swap partners to release ethylene (C_2H_4) gas and close a ring. Here, our starting material already has a ring, so our product will have 2.

Rubric for this question:
Full credit (5 points) for correct product structure.
-1 point for each stereochemical error--for incorrect -OH orientation, incorrect ring substituent stereochemistry, or for omitting stereochemical information.
-2 points for each for each clearly trivial structure mistake. This includes includng an extra carbon in the newly formed ring.



The enolate formed in step 1 undergoes a Claisen rearrangement in step 2:

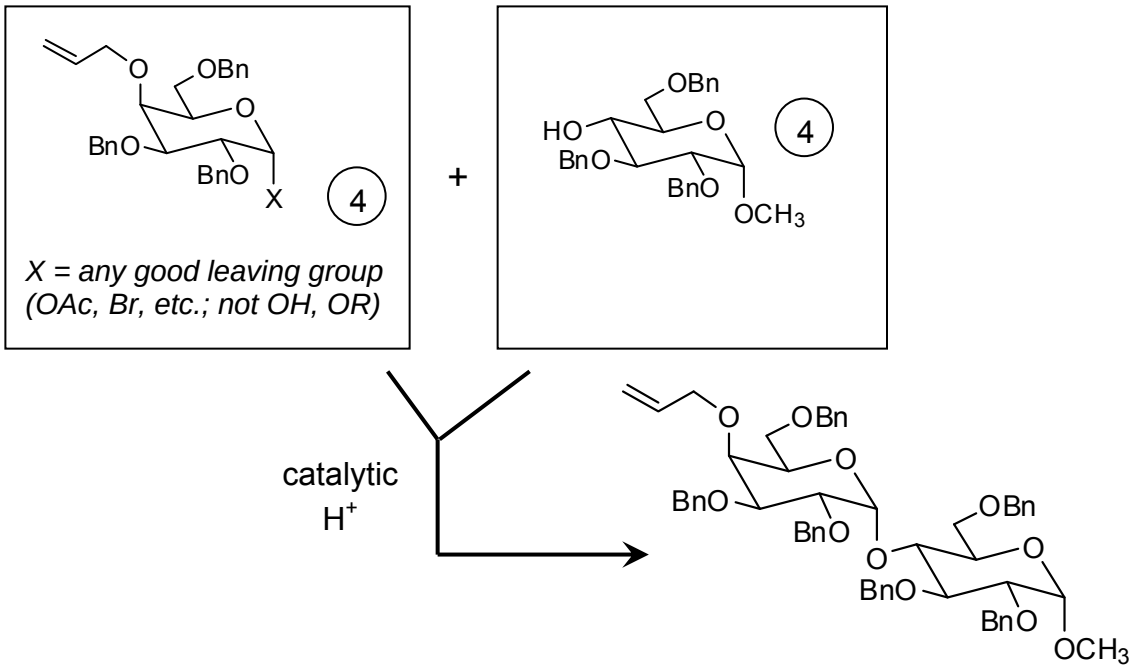


Rubric for this question:

We did not grade stereochemistry on this problem, or on the presence of the lithium counterion, or on the protonation state of the carboxylate. (Drawing a carboxylic acid was fine.)

5 points for correct structure.

-2 points for each trivial structure mistake. This includes omitting exocyclic CH_2 or its double bond.



This problem asked how to make a glycoside bond, using synthetic chemistry. To do that, you needed one sugar with a good leaving group at the anomeric position, and another sugar with one free -OH group.

Rubric for this question *(8 points total this part):*

-2 points for each trivial structure mistake.

4 points for protected allylated galactose (sugar on the left).

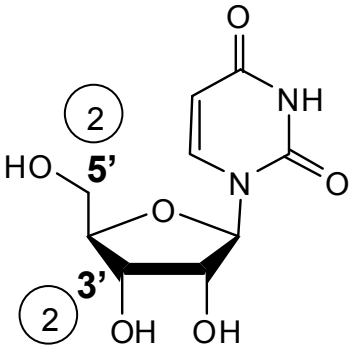
X can be equatorial too, or illustrated with no stereochemistry. Doesn't matter.

3 points partial for X = poor leaving group (OH, OR).

4 points for protected methylglucose.

-2 points for C4 not equatorial (i.e., not glucose)

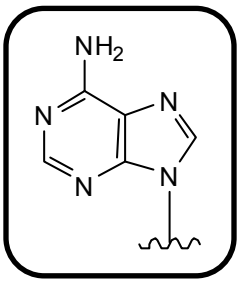
4. (12 pts)



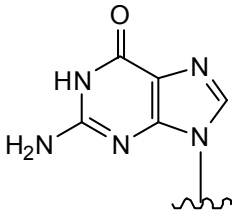
component of

DNA *or* **RNA** (2)

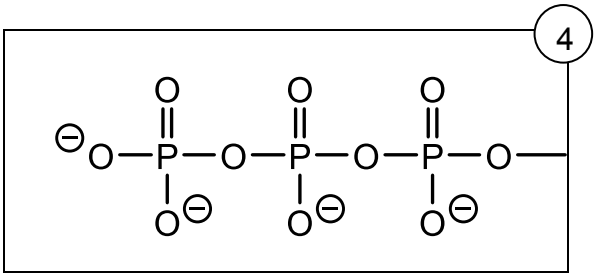
(circle one)



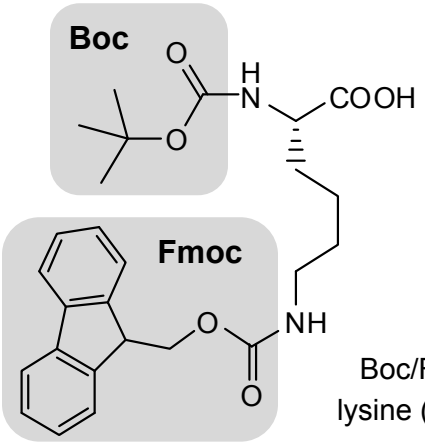
pairs with base on the left.



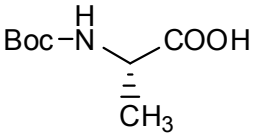
b. In adenosine triphosphate, the 5'-carbon bears a phosphoanhydride triphosphate. Draw this group.



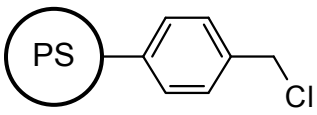
5. (26 pts) Using the starting materials shown below—chloromethylated polystyrene resin, and two *t*-butoxycarbonyl (Boc)-protected amino acids—propose a multistep, solid-phase synthesis of the dipeptide (H_2N)-**Ala-Lys-**(COOH). Apart from the Boc protecting group, the other amine of the lysine is protected with a fluorenylmethoxycarbonyl (Fmoc) group, which can be removed under basic conditions (*e.g*, w/ piperidine) to reveal the amine. *Answer on the next page.*



Boc/Fmoc-protected lysine ("Boc/Fmoc-Lys")



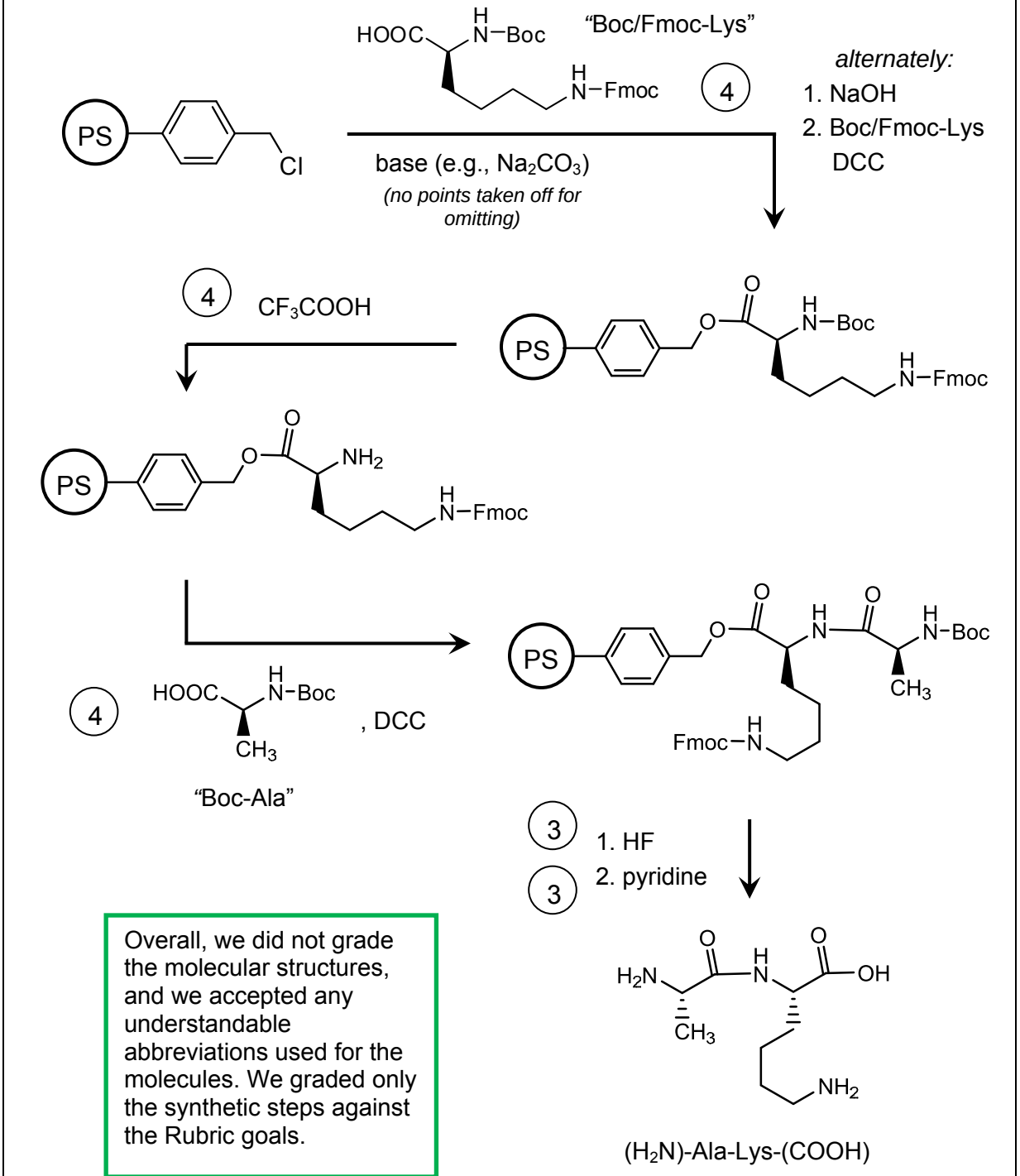
Boc-protected alanine ("Boc-Ala")



chloromethylated polystyrene

Feel free to use names and symbols instead of structures in your synthesis scheme.

Solid-phase synthesis of (H_2N)-Ala-Lys-(COOH):



Overall, we did not grade the molecular structures, and we accepted any understandable abbreviations used for the molecules. We graded only the synthetic steps against the Rubric goals.

<u>Rubric for this part (18 points total for above box):</u>

This synthesis requires five tasks, listed below. Each task is judged separately, and does not require that the synthesis makes sense, or that other tasks are correct.

However, you could lose points for putting steps out of order, if having them out of order caused the synthesis to fail.

We did not judge structures in this problem; you could abbreviate reagents, intermediates and products how you liked, as long as they were identifiable. We judged each element of your synthesis only on conceptual content.

-2 points if step reagents are incorrect, but reaction could otherwise be accomplished with correct reagents; or if reagents were correct, but gave the wrong outcome.

1. **Combine PS-Cl with *t*Boc/Fmoc-Lys (4 points).**
   For full credit, you needed to add *t*Boc/Fmoc-Lys first (and not *t*Boc-Ala).
   -2 points for adding tBoc-Ala first instead, or for not identifying the amino acid used.

2. **Deprotect first *t*Boc with TFA (4 points).**
   -2 points for deprotecting before adding amino acid to support (before step 1).

3. **Add *t*Boc-Ala with DCC (4 points).**
   -2 points for adding tBoc/Fmoc-Lys *instead, or for not identifying amino acid.*
   -2 points for omitting DCC.

4. **Deprotect Fmoc protecting group with base (3 points).**

5. **Deprotect final protecting group and cleave dipeptide from solid support with HF (3 points).**
   Fine to deprotect and cleave in separate steps, using sequential TFA and HF. But you need to use HF to cleave from support.
   -2 points for cleaving with a weaker acid (such as TFA alone).

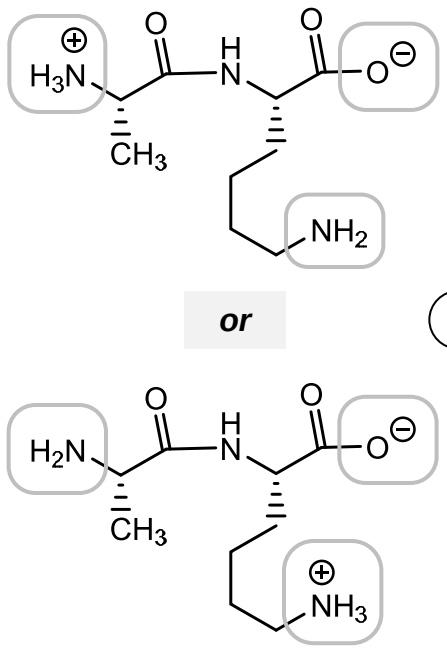
What is the structure of (H_2N)-**Ala-Lys-**(COOH) at its isoelectric point (pI)?

What would the pI of this dipeptide be?

pI = 9.5 (4)

Rubric for pI:
4 points for any answer between 9 and 10.

Structure of (H_2N)-Ala-Lys-(COOH) at pI:



or (4)

Rubric for peptide structure:
1 point for correct peptide backbone.
1 point each for correct charge states at circled protic sites. (3 total.)