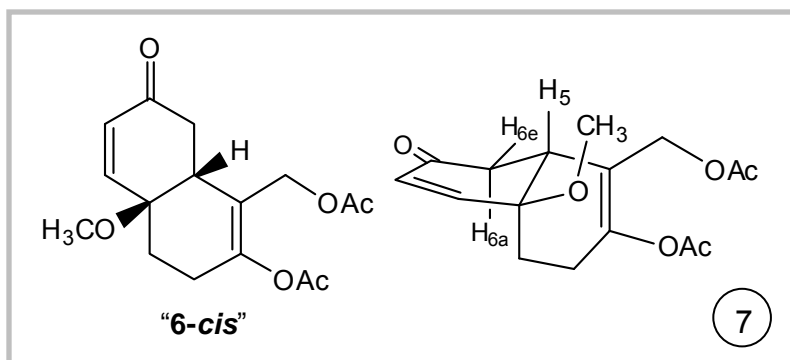**Final Exam
Answer Key**

Final Exam Mean: 152
Final Exam Median: 159
Final Exam St. Dev.:   24

1. I'll be answering this problem throughout the answer key, but the correct answer is **6-*cis***.

   Rubric:
   7 points for this answer only.
   No partial credit.

"**6-*cis***"

2. There were lots of resonances to assign here, and I found it easiest to sort them by type before trying to assign them. The spectrum has three 3H singlets—one by itself at δ = 3.25 ppm and the other two closer to each other at δ = 2.17 and 2.04 ppm. All of the structures have the same three -CH$_3$ groups: one -OCH$_3$, which must be the δ = 3.25 ppm peak, and two -OAc methyl groups. Pretsch says that the -OAc that is attached to a double bond should be downfield of the one that is not, so I'll tentatively assign δ = 2.17 ppm to C$_{(9/10)}$-O$_2$CCH$_3$, and δ = 2.04 ppm to C$_{(11)}$-O$_2$CCH$_3$.
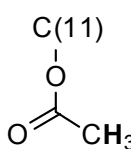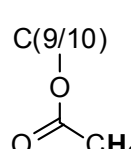
   Next, there are two protons in the alkene region of the spectrum (at δ = 6.81 and 6.11 ppm) that must correspond to H$_{(2)}$ and H$_{(3)}$. This is a very large difference in chemical shift that isn't predicted by Pretsch's α,β-unsaturated ketone example, which says that H$_\alpha$ (the one closer to the carbonyl) should be 0.1-0.4 ppm downfield of H$_\beta$. We'll tentatively assign δ = 6.81 ppm to H$_{(2)}$ and δ = 6.11 ppm to H$_{(3)}$.

   There is a complex, 2H multiplet at $\delta \approx$ 4.55 ppm that's all by itself. There aren't any other alkene protons to assign, so these must be protons attached or α to a very electronegative atom. All four structures have two such protons at C$_{(11)}$. The two protons are diastereotopic, and thus probably inequivalent; this explains the shape of the "multiplet", which must actually be two doublets that couple to one another geminally. We'll call these protons H$_{(11a)}$ [δ = 4.58 ppm] and H$_{(11b)}$ [δ = 4.54 ppm].

Okay, so what do we have so far?

proton	δ (ppm)
H(2)	6.81
H(3)	6.11
-OCH$_3$	3.25
H(5)	

proton	δ (ppm)
H(6a)	
H(6e)	
H(7)	
[x2]	
H(8)	
[x2]	

proton	δ (ppm)
H(11)	4.58
[x2]	4.54
C(11)	2.04
C(9/10)	2.17

What we don't have yet is assignments for two coupled sets of protons: H$_{(5)}$-H$_{(6a)}$-H$_{(6e)}$, and H$_{(7a)}$-H$_{(7b)}$-H$_{(8a)}$-H$_{(8b)}$. I don't know that we can assign these directly from the ^{1}H NMR, but we can get some hints from the ^{1}H-^{1}H COSY, which shows us the coupled sets of protons we are looking for. In the closeup at right, the red set has total intensity 3H, and must correspond to H$_{(5)}$-H$_{(6a)}$-H$_{(6e)}$, and the green set has total intensity 4H,
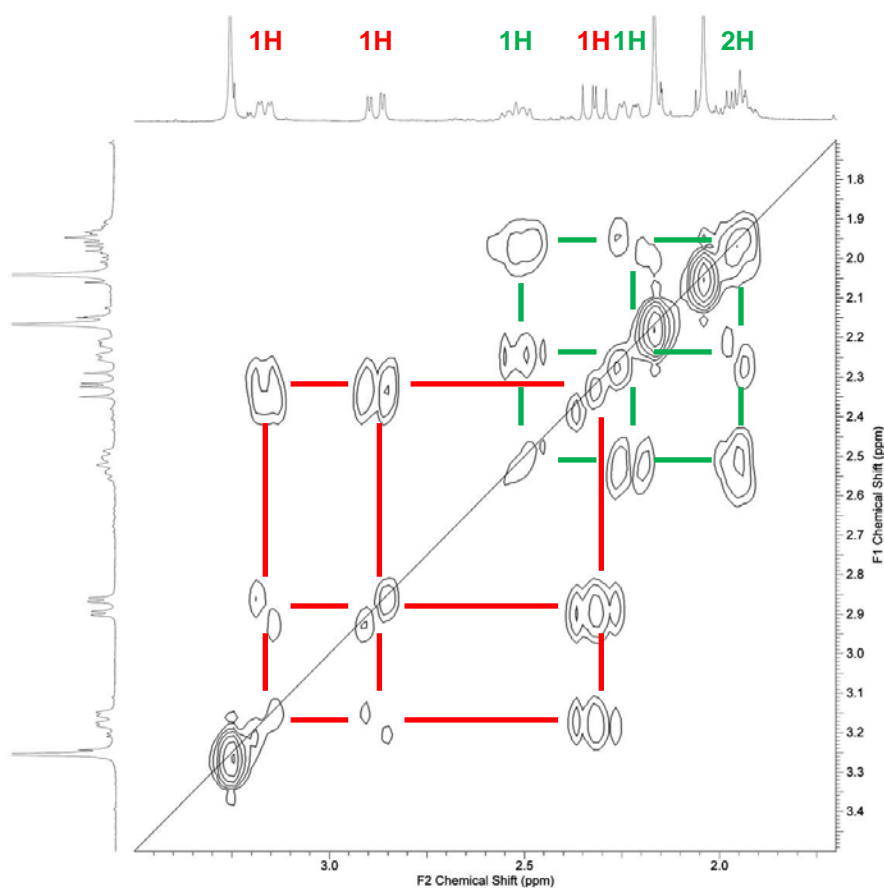
and must correspond to $H_{(7a)}$-$H_{(7b)}$-$H_{(8a)}$-$H_{(8b)}$. Admittedly, the 2H multiplet at δ = 1.9 ppm is confusing, and it might be that only one of the two H's here is in the coupled set, but I don't see any other crosspeaks associated with that chemical shift, so we can assume that both δ = 1.9 ppm protons are in this set.

So within these sets, which proton is which? One set of clues came from the HMQC data, which normally tells us which pairs of protons are attached to the same carbon:
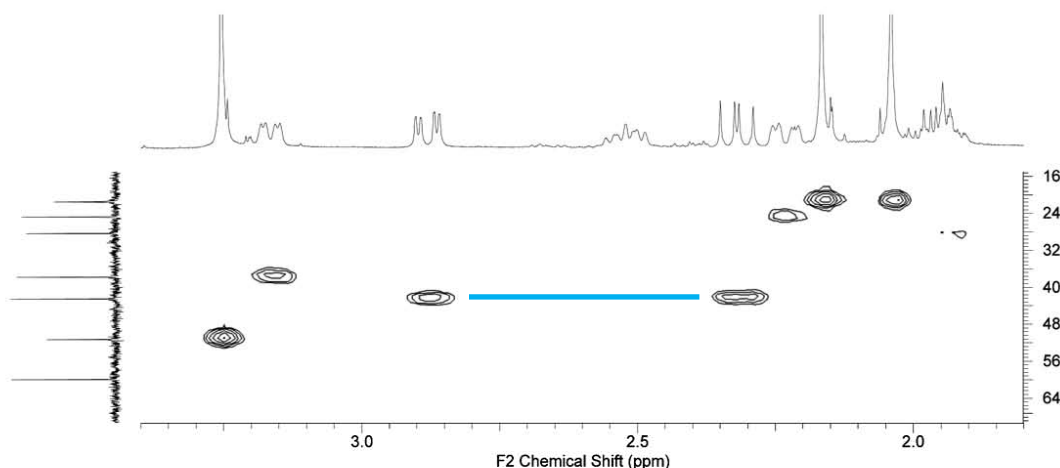
This both was and wasn't helpful. It was helpful in that two of the three protons in the $H_{(5)}$-$H_{(6a)}$-$H_{(6e)}$ set are clearly attached (correlated via $^1J_{CH}$) to the same carbon. As a result, the multiplet at δ = 3.17 ppm must be $H_{(5)}$, and the two correlated protons (at δ = 2.88 and 2.32 ppm) must be $H_{(6a)}$ and $H_{(6e)}$. We don't know from this data which is $H_{(6a)}$ and which is $H_{(6e)}$, although Pretsch does say that equatorial H's are downfield of axial ones, which hints that $\delta[H_{(6e)}]$ = 2.88 and $\delta[H_{(6a)}]$ = 2.32. We'll try to confirm this with other data later.

It wasn't helpful in that crosspeaks that I would have expected in the $H_{(7)}$-$H_{(8)}$ series just aren't there. Not clear why. What carbon is the δ = 2.52 ppm proton attached to? Are the two 1.9 ppm H's attached to the same carbon, or different ones? The HMQC data doesn't have any good answers on this. Based on chemical shift alone--assuming that protons α to an alkene will be downfield of those that are not, I'll provisionally assign the two downfield resonances (δ = 2.52 and 2.23 ppm) to $H_{(8)}$, and the 2H multiplet to $H_{(7)}$. Looking more closely at that 2H multiplet, it looks like it is made up of a dd and a dt (see diagram at right). So I'm guessing that the chemical shift assignments are δ = 1.96 and 1.94 ppm for this pair of protons. Going back to our chart, we have
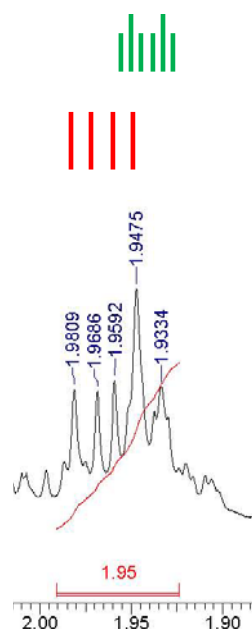
proton	δ (ppm)
H(2)	6.81
H(3)	6.11
-OCH$_3$	3.25
H(5)	3.17

proton	δ (ppm)
H(6a)	2.32
H(6e)	2.88
H(7)	1.96
[x2]	1.94
H(8)	2.52
[x2]	2.23

proton	δ (ppm)
H(11)	4.58
[x2]	4.54
C(11) (acetate)	2.04
C(9/10) (acetate)	2.17

(2) each if any of (7)/(8) are switched

(2) each if switched

3. First we had to calculate coupling constants for each multiplet:

J_2 = 13 Hz
J_1 = 4 Hz

3.1825
3.1743
3.1567
3.1485

1.07

3.20   3.15

H$_{(5)}$

J_2 = 17 Hz
J_1 = 5 Hz

2.9032
2.8921
2.8674
2.8586

1.03

2.90   2.85

H$_{(6e)}$

J_2 = 17 Hz
J_1 = 13 Hz

2.3500
2.3241
2.3159
2.2901

1.04

2.35   2.30

H$_{(6a)}$
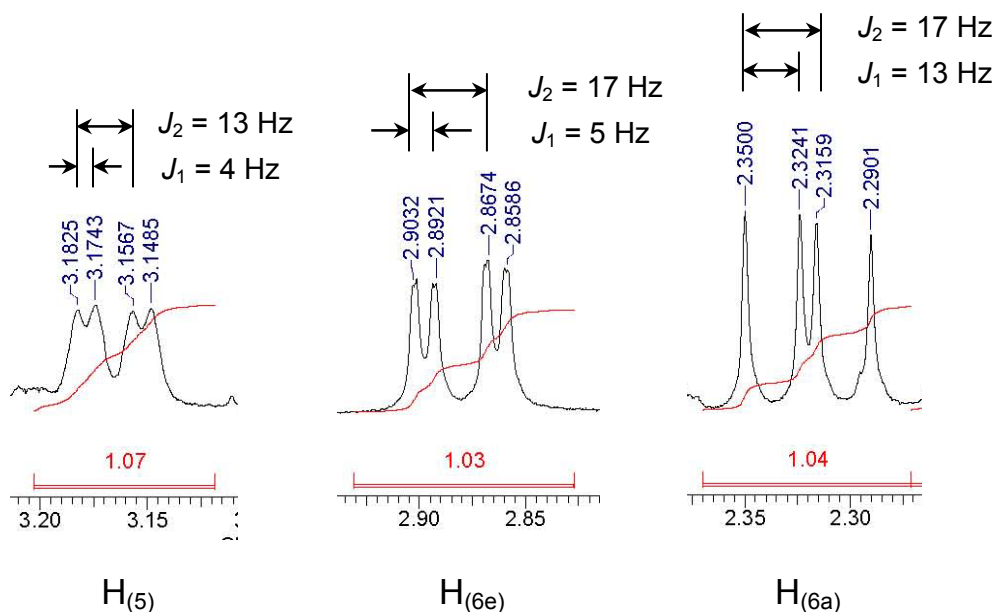
It looks like all of the coupling constants match up here, except the 4/5 Hz ones which are a little off from each other. (This is probably due to the broadening of the $H_{(5)}$ lines by some other coupling going on there.) In all of the potential product structures, $H_{(5)}$ is pseudo-axial; this means that in all of the structures, the dihedral angle $\phi[H_{(5)},H_{(6a)}] = 180°$, and the dihedral angle $\phi[H_{(5)},H_{(6e)}] = 60°$. That means that $J[H_{(5)},H_{(6a)}]$ should be large, and $J[H_{(5)},H_{(6e)}]$ should be small. That is indeed what is observed here, and this confirms our assignments of $H_{(5)}$, $H_{(6a)}$, and $H_{(6e)}$ in problem 2.
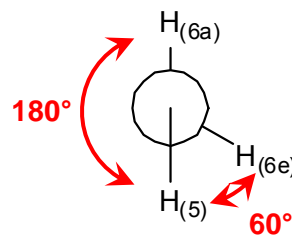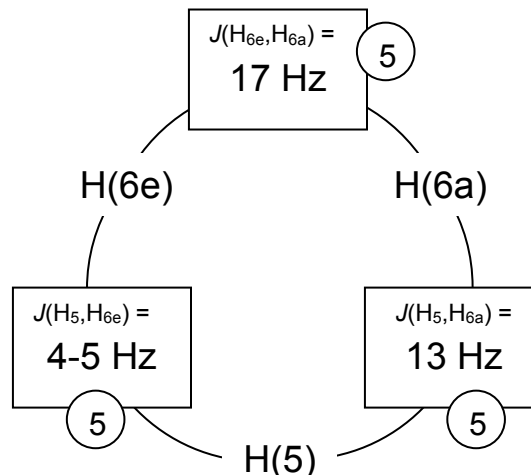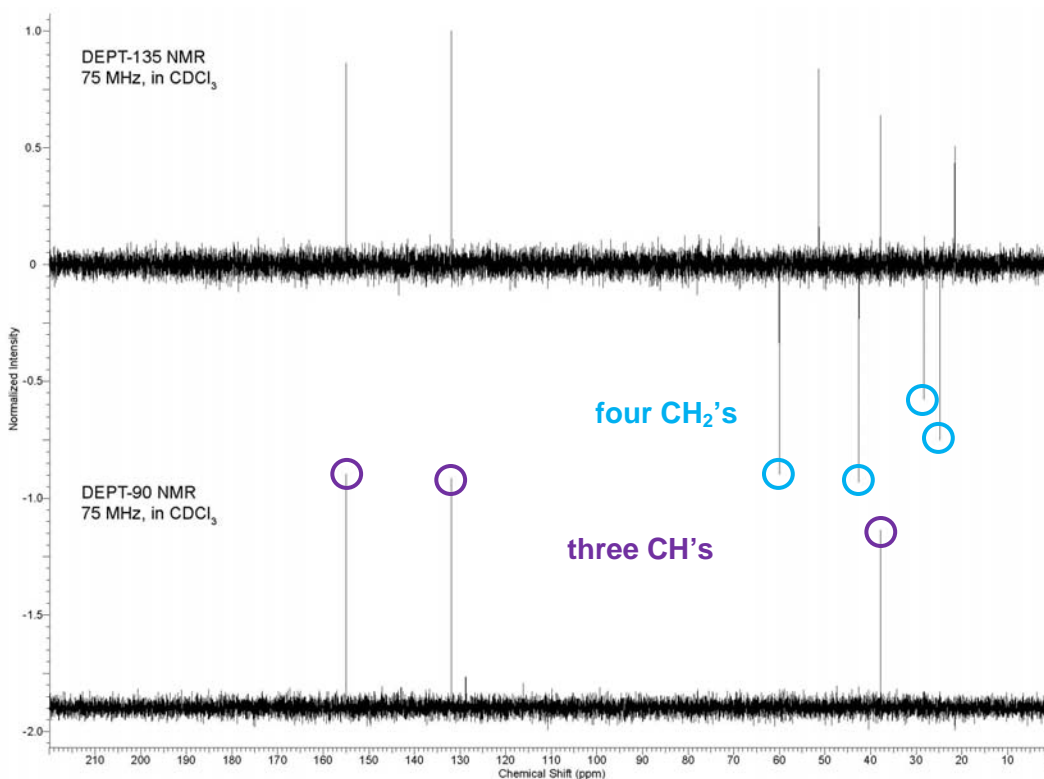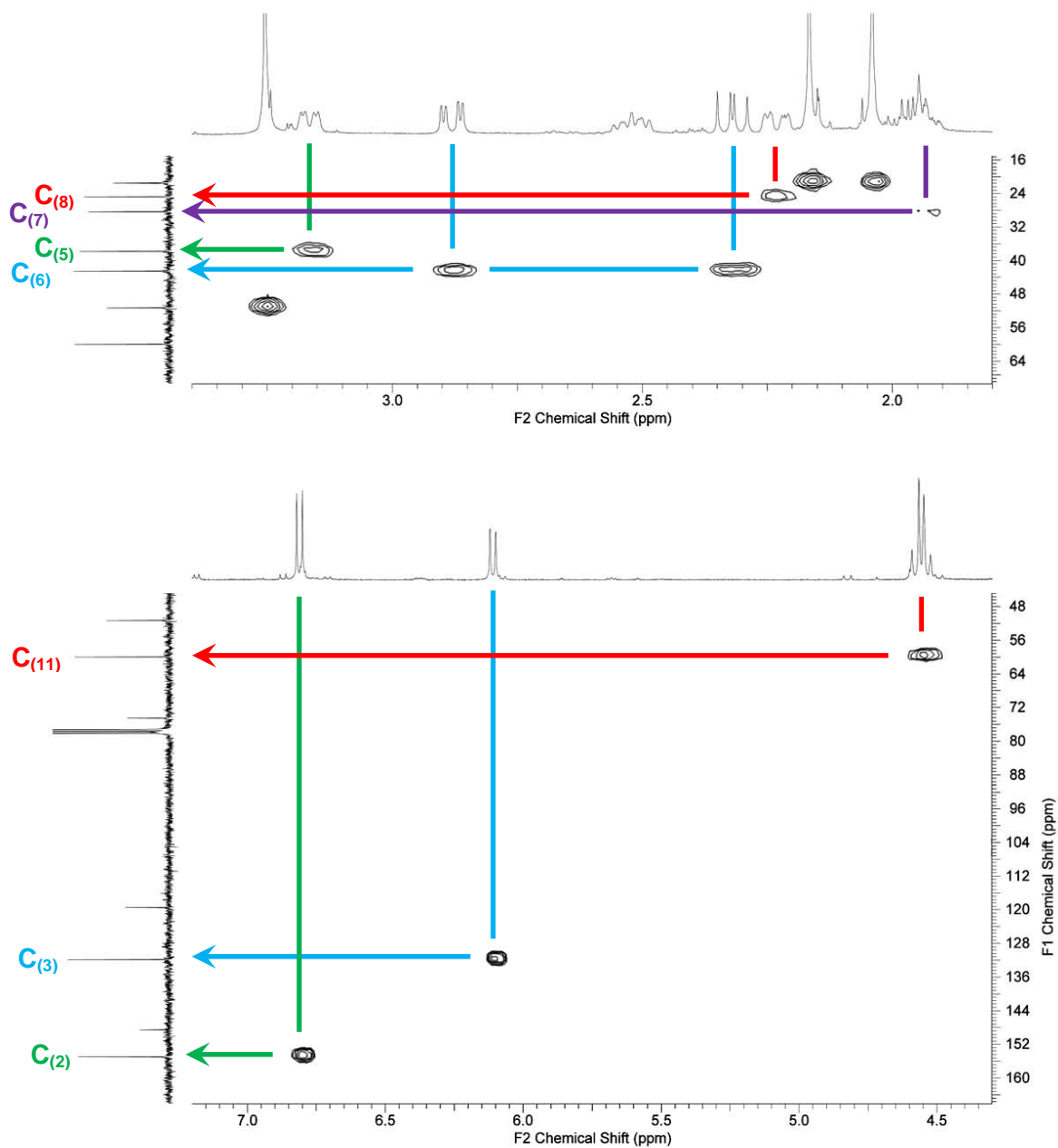
Rubric:
5 points for each box.
   Answer must be within 1 Hz to be correct.

$J(H_{6e},H_{6a}) =$
17 Hz   5

H(6e)   H(6a)

$J(H_5,H_{6e}) =$
4-5 Hz   5

$J(H_5,H_{6a}) =$
13 Hz   5

H(5)

$H_{(6a)}$
180°
$H_{(6e)}$
$H_{(5)}$ 60°

4. Although the DEPT spectra don't answer this problem, they do confirm what the problem says—that there are four CH_2 carbons (negative peaks in the DEPT-135) and three CH carbons (positive peaks in both DEPT-135 and DEPT-90).

DEPT-135 NMR
75 MHz, in $CDCl_3$

DEPT-90 NMR
75 MHz, in $CDCl_3$

four CH₂'s

three CH's

Normalized Intensity

Chemical Shift (ppm)

Even better, we can use the HMQC spectra to directly associate the H's we've already identified with the C's they are attached to.

Transferring chemical shift values to the chart,

-CH₂- carbon	δ (ppm)
C(6)	43
C(7)	28
C(8)	25
C(11)	60

2 each if switched

| -CH- carbon	δ (ppm)
C(2)	155
C(3)	132
C(5)	38

2 each if switched

5. Carbons with no attached H's are the only ones that don't appear in any DEPT spectra. (This is because the DEPT spin-echo method depends on re-coherence of decohered C-H splitting patterns, and there is no C-H coupling in a carbon that has no H's.)

0

⑤

6. Up to this point, we have not made any determination of which of the four products Rodolfo has, and we have some chemical shift assignments that are a little shaky; our assignments of $C_{(2/3)}$, $H_{(2/3)}$, $C_{(7/8)}$ and $H_{(7/8)}$ could use some confirmation. Hopefully NOE experiments can help us out here.

Experiment **1** involves irradiation at δ = 3.17 (indicated by the large negative peak), which we've assigned to $H_{(5)}$, and subsequent NOE enhancement of δ = 4.55 ($H_{(11a)}$ and $H_{(11b)}$), δ = 3.25 (-OCH₃), and δ = 2.88 ($H_{(6e)}$). I think this would be possible only for the *cis*-fused product structures:
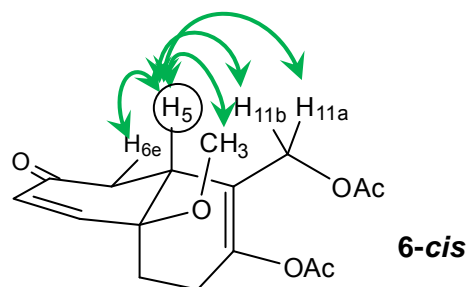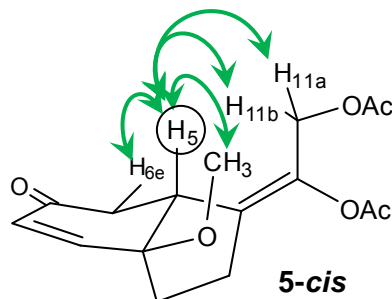
5-cis

6-cis

In the case of the *trans*-fused products, H$_{(5)}$ is on the opposite side of the molecule from the -OCH$_3$ group, and I don't see how NOE between these protons could occur. This experiment pretty much proves that Rodolfo's molecule has to be **5-*cis*** or **6-*cis***.

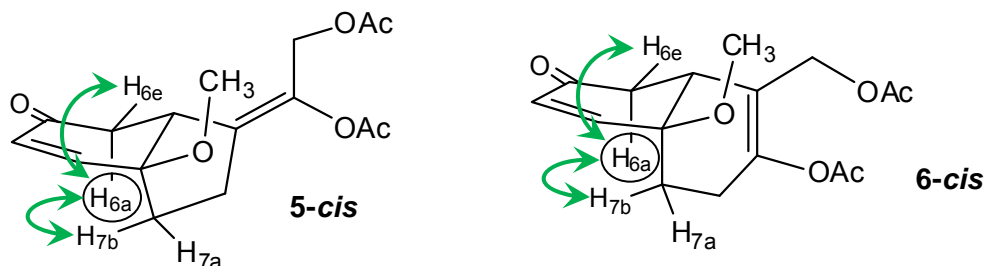**Rubric for Experiment 1:** 12 points total for this part.
Your answers do not need to match mine, and you could choose any of the four products to draw arrows on, but your arrows did need to meet two criteria to receive points:
  (1) Each arrow needs to match the answers you gave in problem 2. The origin of NOE must be the resonance at δ = 3.17 (whatever you assigned that to), and the destinations must be resonances at δ = 4.54-4.58, 3.25, and 2.88.
  (2) The arrow needs to connect protons that are spatially close to each other. NOE occurs over only short distances.
4 points for each of 3 arrows.
  I have drawn two arrows for H$_{(5)}$ → H$_{(11a)}$ and H$_{(11b)}$, but you could draw just one. 4 points for this set of NOEs, either way you drew it.

Experiment **2** involves irradiation at δ = 2.32, which I've assigned to H$_{(6a)}$, and subsequent NOE transfer to δ = 2.88 (H$_{(6e)}$) and δ = 1.9-2.0 (either H$_{(7a)}$, or H$_{(7b)}$, or both). Once again, I think this only makes sense in terms of the *cis*-fused products:

Rubric for Experiment 2: 8 points total for this part.
Same criteria as in Experiment 1.
4 points for each of 2 arrows.
  I have drawn one arrow connecting H$_{(6a)}$ and H$_{(7b)}$, and no arrow connecting H$_{(6a)}$ and H$_{(7a)}$. I think H$_{(7a)}$ would be too far to be enhanced by NOE transfer from H$_{(6a)}$. However, I also think that the δ = 1.9-2.0 peak was difficult to evaluate so we gave full credit (4 points) for any arrow you drew to any H$_{(7)}$ protons in the cis-fused case.

7. HMBC correlations represent ^2J or ^3J coupling between C and H atoms. (^1J coupling is suppressed by the method.)

<u>HMBC Set 1</u> (☐ and ◯):

In my opinion, this experiment makes it very clear which resonance belongs to $H_{(2)}$ and which belongs to $H_{(3)}$. To explain it though, we've got to identify the carbons involved in the crosspeaks. The ^{13}C resonance at δ = 198 in ☐ is in the carbonyl region of the ^{13}C spectrum. Our molecule has three carbonyls in it—two acetate esters, and one ketone. Pretsch says the ketone should be farther downfield, so this must be $C_{(1)}$. (And the two acetate C=O carbons must be at δ = 171 and 169.) That means that ☐ is a correlation between $C_{(1)}$ and the δ = 6.81 ppm proton that we had assigned as $H_{(2)}$. Importantly, there is no HMBC crosspeak between $C_{(1)}$ and $H_{(3)}$, and that makes sense in terms of our assignments.

Meanwhile, ◯ shows a crosspeak between $H_{(3)}$ and a carbon at δ = 74 ppm that we haven't assigned yet. The carbon has no attached protons (according to the DEPT), and is in the "heteroatom-attached-sp^3" region of the spectrum. The only carbon that meets these criteria is $C_{(4)}$. Once again, this makes perfect sense; $H_{(3)}$ is just two bonds away from $C_{(4)}$.

Any of the four product structures are consistent with these correlations. Illustrating on the **6-cis** structure,

6-cis
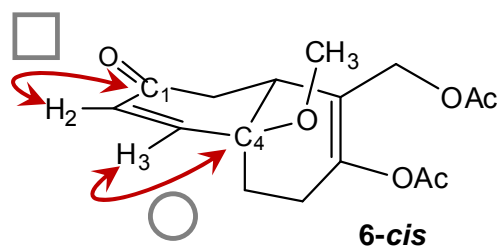
<u>**Rubric for HMBC Set 1:**</u> 8 points total for this part.
*Full credit for drawing these arrows on any of the four products.*
4 points for each of 2 arrows.
  I don't see how any other correlations make sense, so no partial credit for either of the two arrows in this problem; you get 8, 4, or 0.

<u>HMBC Set 2</u> (☆ and ⬡):

This pair of correlations tells us about the organization of the product alkene, and thus the size of the fused ring. ☆ and ⬡ highlight correlations of carbons at δ = 149 and 119 ppm that we haven't identified yet. These carbons are in the alkene region of the spectrum and have no attached protons; they must be $C_{(9)}$ and $C_{(10)}$. In all four structures, one of these two carbons has an electron-withdrawing -OAc attached, and the other doesn't; the acetate-substituted carbon must be the one at δ

= 149 ppm. ⬡ says this carbon must be coupled to either or both H$_{(8)}$ protons (and H$_{(7)}$ as well, looking at the other crosspeaks horizontal to this one). Meanwhile, ☆ says that the other alkene carbon at δ = 119 ppm must be coupled to H$_{(5)}$. I think the only way to do this is in the 6-membered-ring products:

6-trans

6-cis
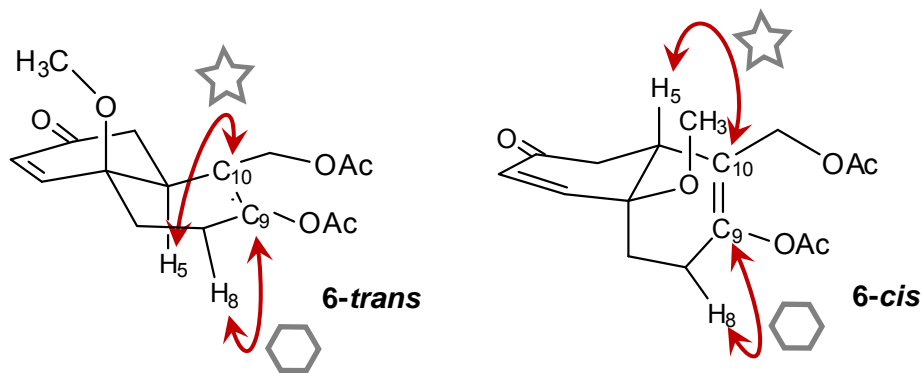
On the 5-membered-ring products, the ☆ correlation between H$_{(5)}$ and C$_{(9)}$ makes sense, but the ⬡ correlation between H$_{(8)}$ and C$_{(10)}$ makes much less sense (and the unlabeled correlations between H$_{(7)}$ and C$_{(10)}$ make no sense at all). If you labeled **5-cis** or **5-trans** in this problem, we only gave you credit for ☆.

**Rubric for HMBC Set 2:** 8 points total for this part.
4 points for each of 2 arrows.
   Again, these correlations only.

   If 5-cis or 5-trans are marked, only ☆ *correlation was evaluated.*

Taken together, I think the combination of the NOE and HMBC data point to **6-cis** as Rodolfo's product.

8. There are a number of things that change in the molecule as a result of this reaction—a double bond goes away, a ketone becomes less unsaturated, an acetate group is added, and a new C-C bond is formed. Unfortunately, none of these things is very distinctive by IR spectroscopy—there are other double bonds, the ketone is unsaturated before and after the reaction, and there are plenty of other C-C bonds that would obscure any change in single bond stretches. I think the only thing that changes definitively in the molecule is that the starting material has an alkyne, and the product does not. So that's what I would watch.

$\nu =$ | 2150 cm^{-1} | (5)
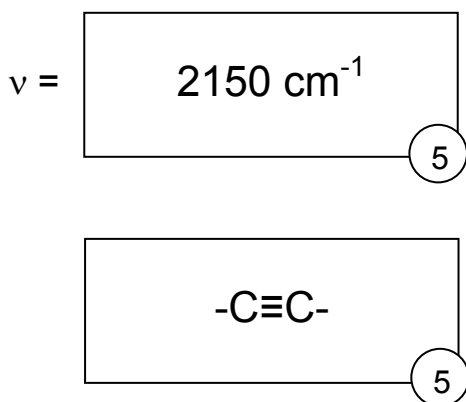
The vertical scale in IR spectra is almost always transmittance (%T), which is the conceptual opposite of absorbance. As a result, absorbance gives rise to negative peaks in IR spectra. As the alkyne peak went away, absorbance would decrease, meaning that transmittance would

-C≡C- | (5)

increase (3) *or* **decrease**

as the reaction progressed.

Rubric: As labeled above. *No partial credit.*

9. The exact mass of the parent ion would be calculated using the mass of the most common isotope of each element. For $C_{16}H_{21}O_6^+$, that would be

| atom:	quantity	x	mass		
C	16	x	12.0000	=	192.0000
H	21	x	1.00783	=	21.1644
O	6	x	15.9949	=	95.9694
			total	=	

309.13 (5)

The integer mass of the ion is 309, but the exact mass is above that (by 0.13 Da). So we would say the ion exhibits a

negative mass defect   *or a*   **positive mass defect**   *?*

(3)

Rubric: As labeled above. *No partial credit.*

10. Our protonated *m/z* = 309 parent loses 60 and 92 amu when it fragments to yield *m/z* = 249 and 217 daughter. The most common fragmentation pathway in ESI-MS is elimination via E1. So if possible, we're looking for fragmentations that might start with a good leaving group. Protonated acetate—acetic acid—is not only a great leaving group, but it also has mass = 60 amu. The only other good leaving group would be methanol, which has mass = 32 amu; if this left along with acetic acid, that might account for the total loss of 92 amu. These losses could occur for any of the four starting material structures; I'll illustrate with **6-cis**, but you would get full credit for the same mechanisms applied to a different starting material.
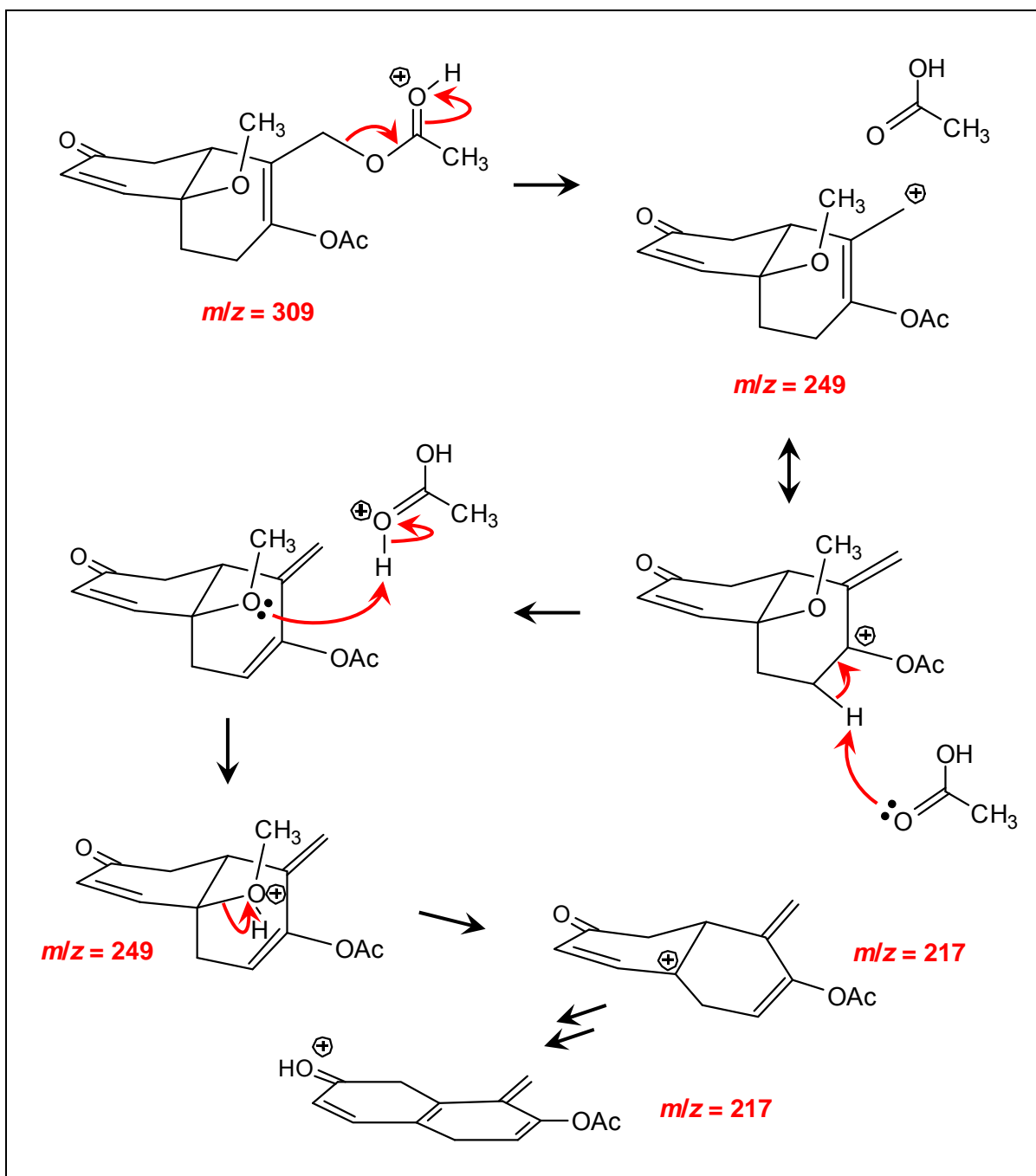
Acetic acid can normally do β-elimination in a concerted mechanism, without going through a carbocation. (The carbonyl oxygen reaches across for the β proton.) However, in this case there is no proton β to the acetate group, so it has to go two-step.

Methanol cannot do concerted β-elimination; as we discussed in class, simple leaving groups can't reach far enough the grab the proton, so they need help. In this case, that help is provided by an external proton.

Rubric: 20 points total for this problem.
5 points for recognizing m/z = 249 must be loss of AcOH (regardless of mechanism).
5 points for recognizing m/z = 217 as loss of AcOH and MeOH (again regardless of mechanism).
5 points for making protonated -(H)OAc leave to generate allyl cation.
5 points for making protonated -(H)OMe leave to generate another allyl cation.
   We did not grade on what your curved arrows looked like, just on what they signified.

11. ESI-MS generates even-electron [M+H]$^+$ as the parent, and not odd-electron [M]$^{•+}$. So any method that also generates even-electron [M+H]$^+$ would give similar parents and daughters to ESI-MS. That's actually virtually all the methods we talked about in class except electron ionization (EI) and direct photoionization (APPI). So, MALDI-MS, CI-MS (including APCI-MS), FAB-MS, thermospray MS, just about any technique except EI and APPI counted here.

Rubric: 5 points for any answer described above. *No partial credit.*