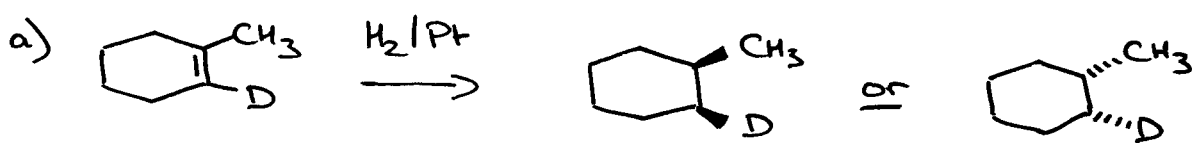


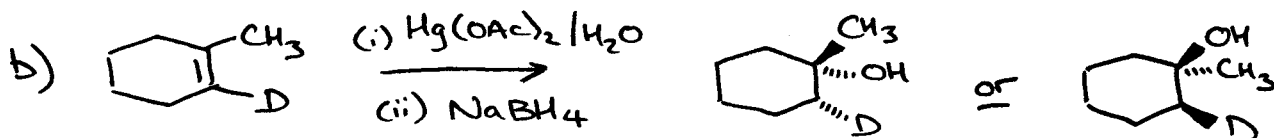
CHEM 30A Winter 2005  
MIDTERM 2 - 'HOW-TO' GUIDE

①

Q1 An important part of this question are the instructions (as with any question) and so even though they appear to be 'long', I suggest that you should read them. Carefully. A couple of times. It's hardly a bloody novel! So, here goes:

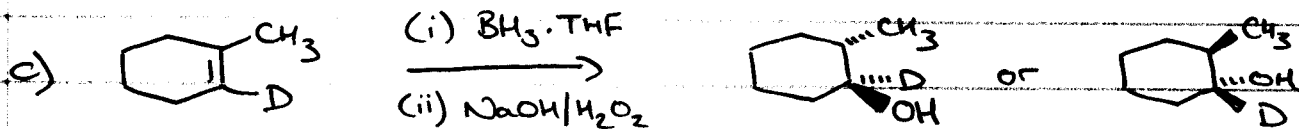


Catalytic hydrogenation proceeds with SYN selectivity and so the two Hs will end up on the same face of the alkene, so the CH<sub>3</sub> and D will be CIS on the cyclohexane ring - and depending upon which face the H<sub>2</sub> attacks from, you will get one enantiomer or the other.

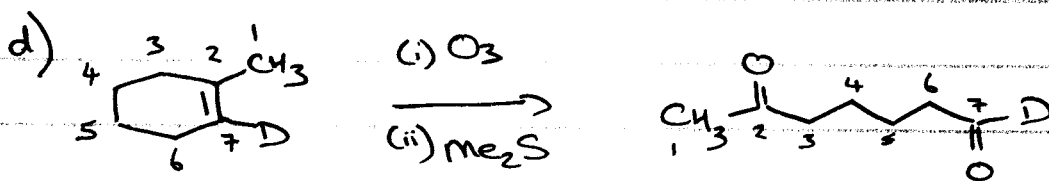


Oxymercuration/reduction proceeds with ANTI-stereospecificity and MARCOVNIKOV regioselectivity, meaning that the -OH group will end up on the more substituted end of the alkene, and that it will be TRANS to the -HgOAc group, which, in the second step is swapped for a H with the NaBH<sub>4</sub> reagent, so -OH and -H end up TRANS. Work through the mechanism if you are unsure. Initial formation of the mercurinium ion can occur

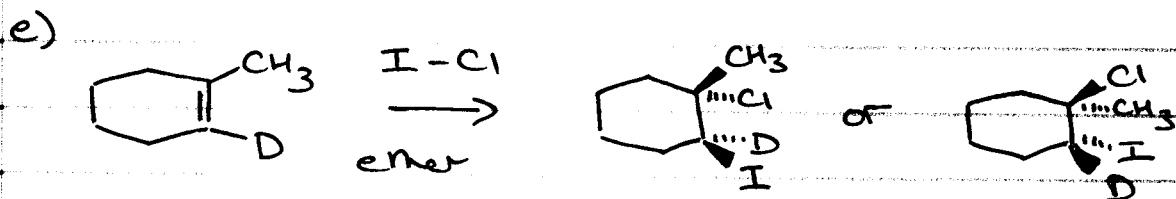
on either the top or bottom face of the alkene, resulting in the formation of enantiomers



Hydroboration/oxidation proceeds with SYN stereo-specificity and ANTI-MARKOVNIKOV regioselectivity, so initially, the  $-\text{BH}_2$  and  $-\text{H}$  will add to the same face of the alkene, and the  $-\text{BH}_2$  will add to the less substituted end. In the second step, the  $-\text{BH}_2$  is converted into an  $-\text{OH}$  group, which is cis to the  $-\text{H}$ . Again, the two enantiomers arise from  $\text{BH}_3$  adding to one or the other faces of the alkene.



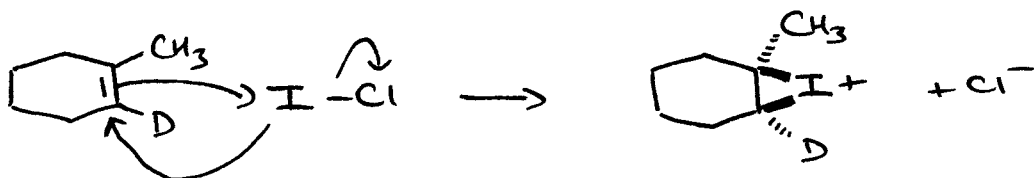
This OZONOLYSIS reaction cuts the  $\text{C}=\text{C}$  bond down the middle ( $\text{C}=\text{C} \rightarrow \text{C}=\text{O} \text{ O}=\text{C}$ ) and puts an oxygen atom on each end, so in this case we form a compound with a KETONE at one end, and an aldehyde at the other. Don't lose any carbon atoms!!



So, the most important part of this question, is figuring out what attacks what... Let's consider iodine monochloride (I-Cl) - how is it polarized? Well, Cl is more electronegative than I, so we expect:

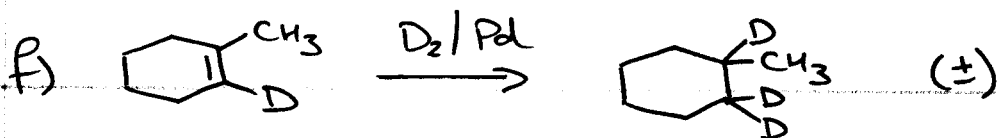
$$\begin{array}{c} \delta+ \quad \delta- \\ \text{I}-\text{Cl} \end{array}$$

and so the nucleophilic alkene will attack the I first, hence:



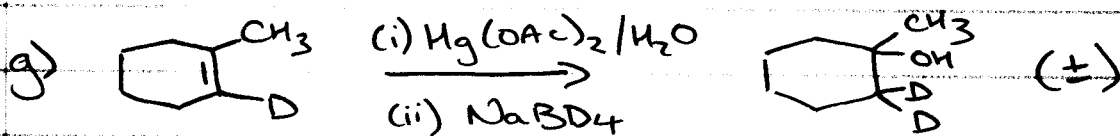
Note: cyclic iodonium ion could form on either the top or bottom face of the alkene, accounting for the formation of enantiomers. So, the next question, is where does the  $\text{Cl}^-$  attack from? Well, it must attack from the opposite face of the iodonium ion, so the Cl and I will end up TRANS, but at which C atom does the  $\text{Cl}^-$  attack. Well, it attacks at the one which can best stabilize +ve charge, and hence attacks at the more substituted one, so overall, we have ANTI-stereospecificity and MARKOVNIKOV regioselectivity.



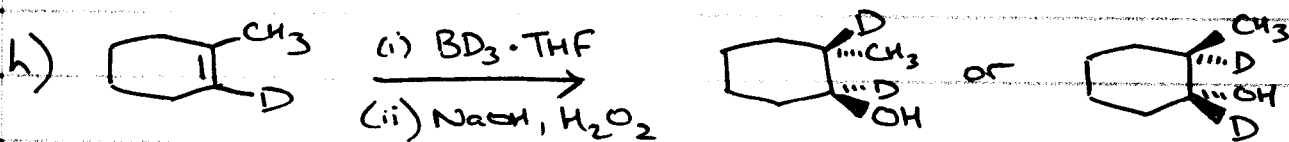


Again, addition of  $D_2$  (just like  $H_2$ ) is SYN selective, and so  $D_2$  will add across either face of the alkene (giving rise to enantiomers).

In this case, there is NO need to show relative stereochemistry, as it is meaningless — the  $CH_3$  group is cis to a  $D$  and trans to a  $D$ , so there is no point in trying to draw relative stereochemistry!!

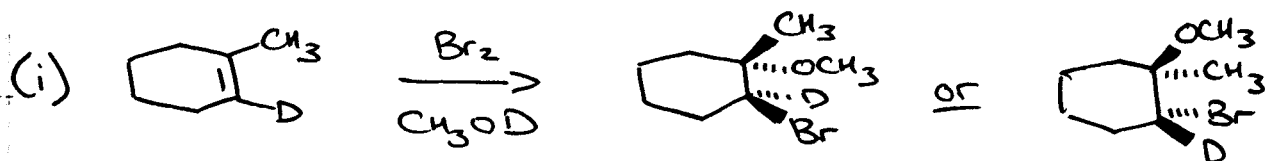


Same as part (b), but in the last step, we replace the  $-HgOAc$  group for a  $D$  rather than an  $H$ , and again, there is NO need to show relative stereochemistry, as both the  $CH_3$  and  $OH$  groups are both cis and trans to  $D$  atoms. But a pair of enantiomers is formed, as the initial mercurinium ion can form on either face of the alkene.

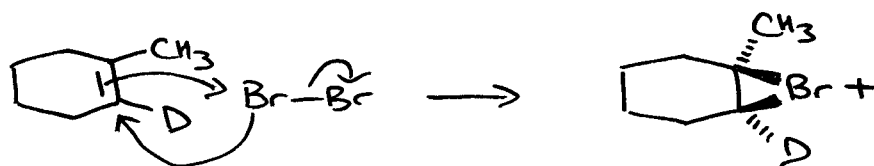


Same as part (c), but by using  $BD_3$  instead of  $BH_3$ , you get a  $D$  where you would have gotten an  $H$  in part (c), otherwise, exactly the same SPECIFICITY and REGIOSELECTIVITY

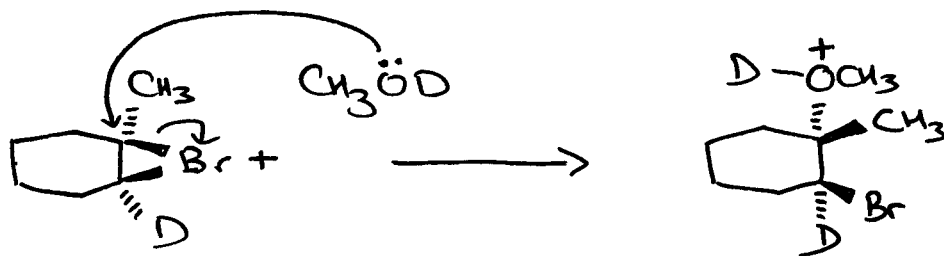
5



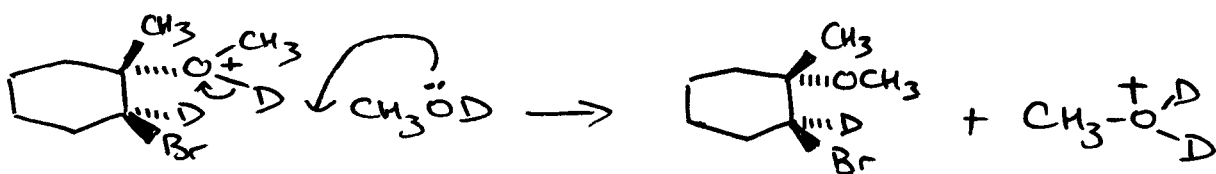
Well, well, This one was sneaky. So, what happens first? - That should be easy, we form a Bromonium ion...



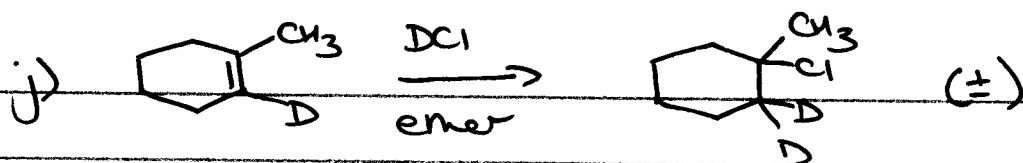
And again, we can form this on either face of the alkene (leading to enantiomers). Now, what opens up the bromonium ion in the second step? Answer:  $\text{CH}_3\text{OD}$ .



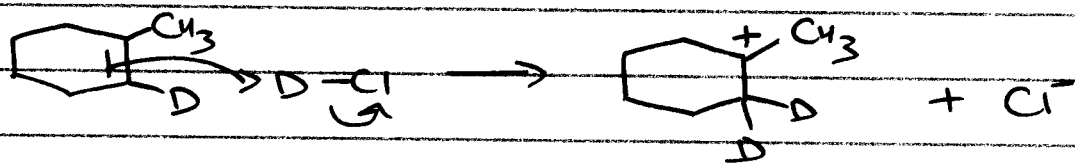
This proceeds w/ **ANTI**STEREOSPECIFICITY (attack from face opposite  $\text{Br}^+$ ) and with **MARCOVNIKOV** regioselectivity, and hence  $\text{CH}_3\text{OD}$  attacks at the more substituted carbon atom (better able to stabilize +ve charge). In the last step, another methanol molecule deprotonates, and our final product only contains ONE D atom!



6



No need to show relative stereochemistry here, for the same reasons expressed earlier. First step is simply formation of the most stable  $3^\circ$  carbocation:



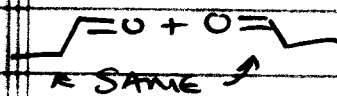
and then in the second step, the  $\text{Cl}^-$  attacks either face of the carbocation (leading to enantiomers) to give the product with MARKOVNIKOV regioselectivity.

(Q2) The first three samples in Q2 you are told give only one unique ozonolysis product, and so this means that the alkene must be symmetrical about the  $\text{C}=\text{C}$  bond, and there are only 3 of these that fit the bill, and they are:



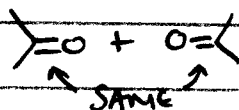
E

↓  $\text{O}_3$  etc



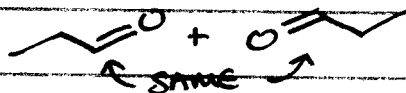
K

↓  $\text{O}_3$  etc

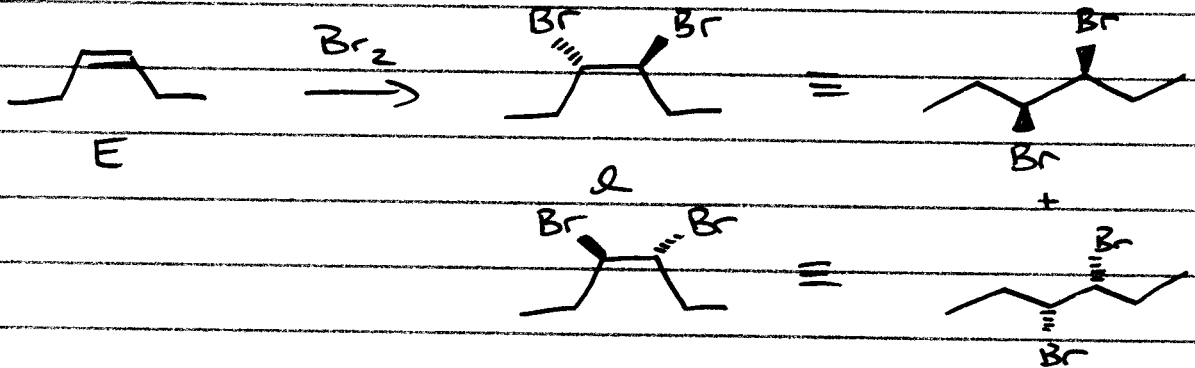


O

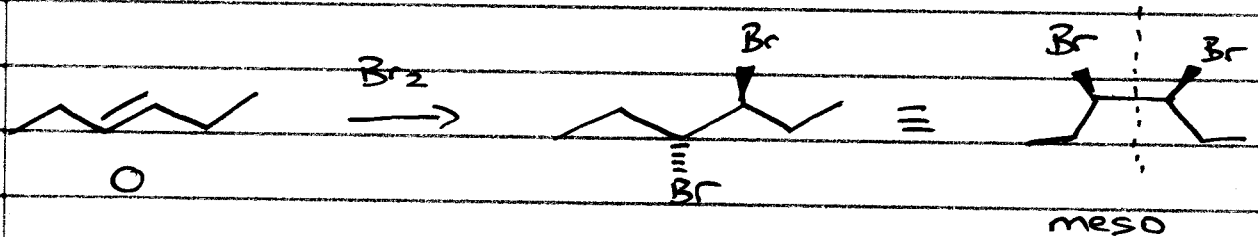
↓  $\text{O}_3$  etc



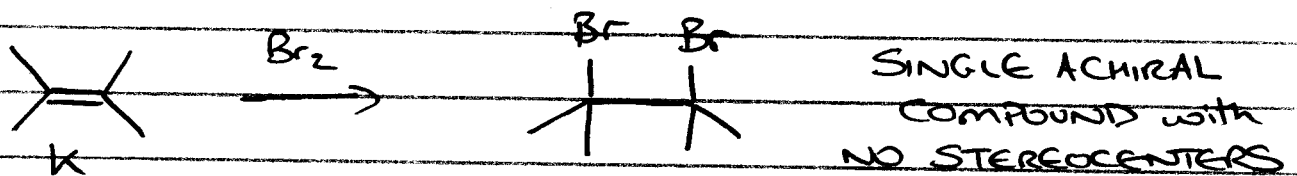
So next, simply decide what happens when each one of these is reacted with Br<sub>2</sub> in CCl<sub>4</sub>, hence:



So, E gives ENANTIOMERS and is, therefore, SAMPLE (2)



So, O gives a MESO compound, and is, therefore, SAMPLE (3)

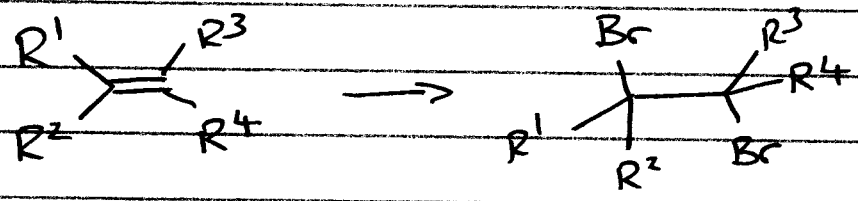


So, K must be SAMPLE (1)

That wasn't too bad, but now it gets harder, as samples 4 and 5 could be any of the other ones... where do we begin?

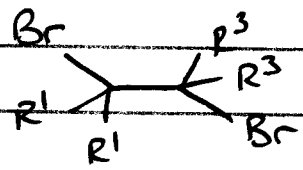
$$R^1/R^2 \neq R^3/R^4$$

Well, when you react an unsymmetrical alkene with Br<sub>2</sub> in CCl<sub>4</sub>, there are a few options



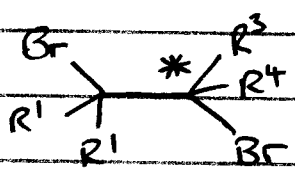
IF  $R^1 = R^2$  AND  $R^3 = R^4$ , then the product will be ACHIRAL, as NO stereocenters are formed. ANY other situation will result in the generation of at least ONE (or sometimes TWO) stereocenters, which in the ABSENCE of any other pre-existing stereocenter, will result in the formation of enantiomers, i.e.,

$R^1 = R^2$  AND  $R^3 = R^4$



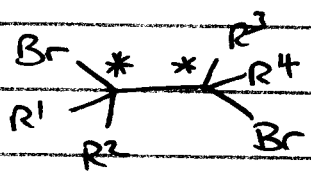
NO CHIRAL CENTERS

$R^1 = R^2$  AND  $R^3 \neq R^4$   
(or vice versa)



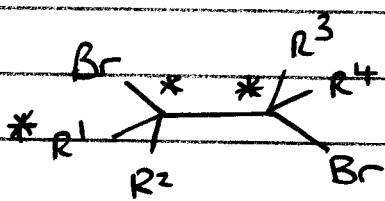
ONE CHIRAL CENTER, ENANTIOMERS FORMED.

$R^1 \neq R^2$  AND  $R^3 \neq R^4$



TWO CHIRAL CENTERS ENANTIOMERS FORMED

$R^1$  or  $R^2$  or  $R^3$  or  $R^4$  contains a STEREOCENTER



3 CHIRAL CENTERS (ONLY 2 FORMED IN THE REACTION) ⇒ DIASTEREO-ISOMERS



Because, in the last example, the stereocenter in R' is fixed, and does not change in the reaction, the new products will be the following:

ASSUME stereocenter in R' is (S)

ASSUME the new stereocenters are either (RS) or (SR)

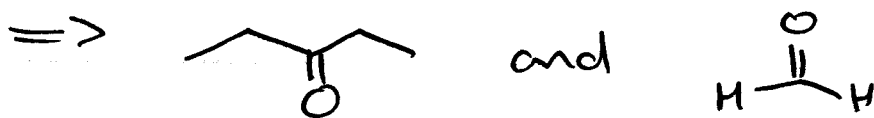
then the products will be (SRS) & (SSR) which are DIASTEREISOMERS.

So Sample (E) must be either M or R

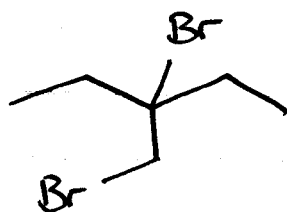
and the only alkene in which  $R_1 = R_2$  and  $R_3 = R_4$  where  $R_1/R_2 \neq R_3/R_4$  is



which will give 2 OZONOLYSIS PRODUCTS

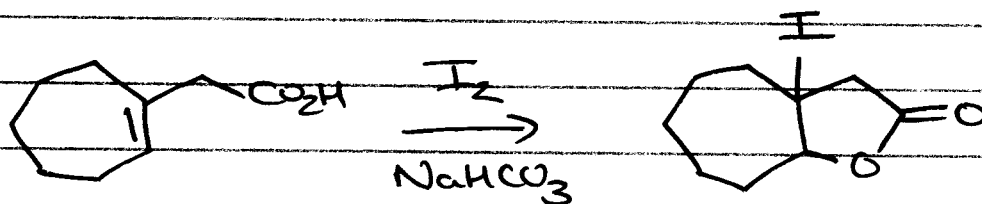


and ONE ACHIRAL BROMINATION PRODUCT



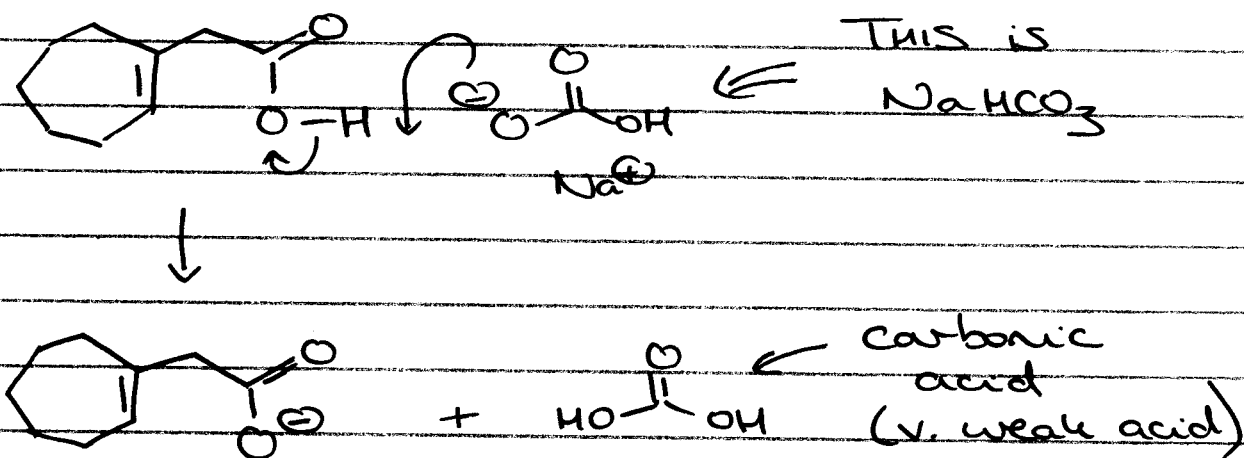
⇐ NO CHIRAL CENTERS

Q3 Explain the mechanism for:

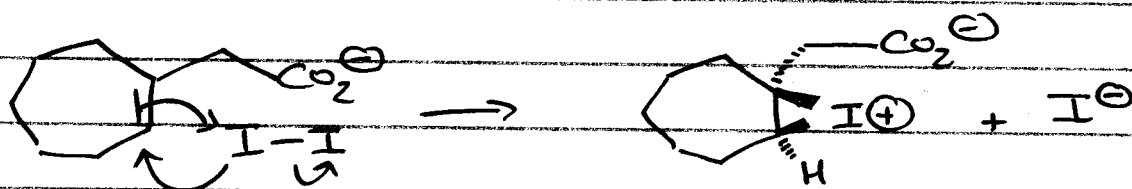


accounting for stereospecificity and regioselectivity

- Acid/base reactions occur quickly, so the first step is the reaction of the carboxylic acid with the weak base:



- The second step involves the reaction of the alkene with I<sub>2</sub>, as shown below:

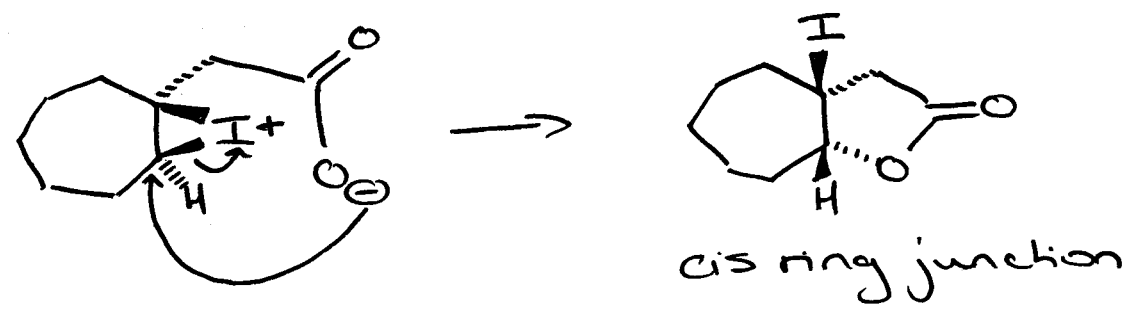


To form a cyclic iodonium ion, just like you saw with Br<sub>2</sub> and Cl<sub>2</sub> forming cyclic

chloronium and bromonium ions - WHY DID MOST OF YOU DRAW CARBOCATIONS??

If you reversed the order of steps 1 & 2, you did not lose any points.

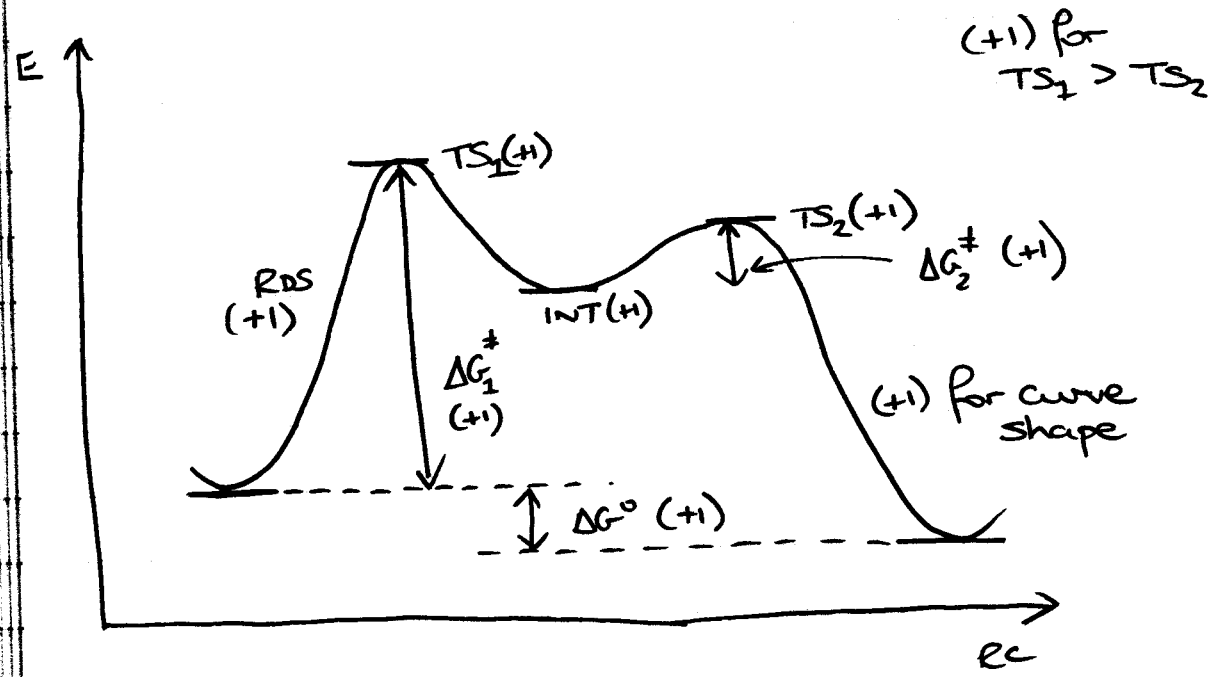
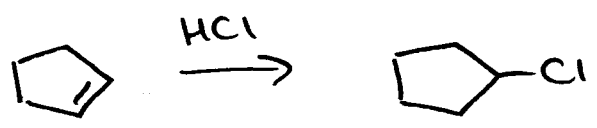
What happens next, well, the species that opens the iodonium ion must be the  $CO_2^-$  group that is already part of the molecule, and this will, like all these reactions, proceed with ANTISTEREOSPECIFICITY.



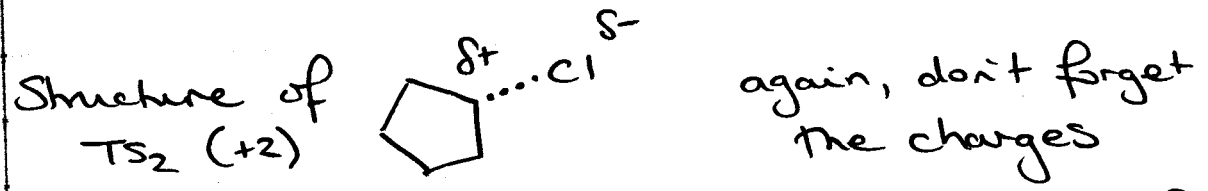
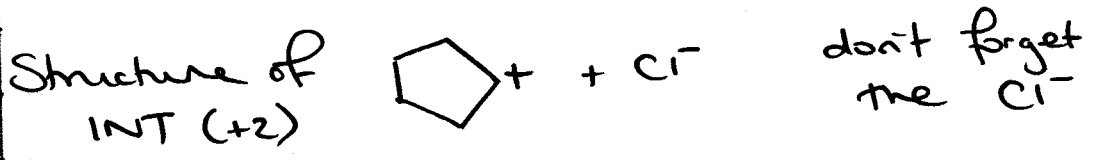
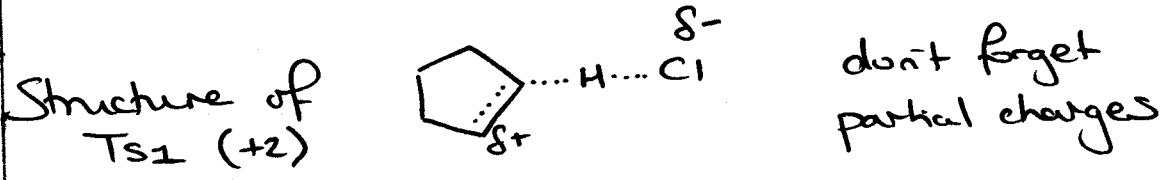
So, the incoming  $CO_2^-$ , and the  $I$  atom end up on opposite faces, resulting in a cis ring junction → now, what about REGIOSELECTIVITY?

Well, notice that the  $CO_2^-$  attacked at the LESS substituted C atom, (the one least able to stabilize the charge), because if it had attacked at the MORE substituted C atom, this would have resulted in a very strained 4-MEMBERED RING, instead of the much happier 5-MEMBERED RING we observe.

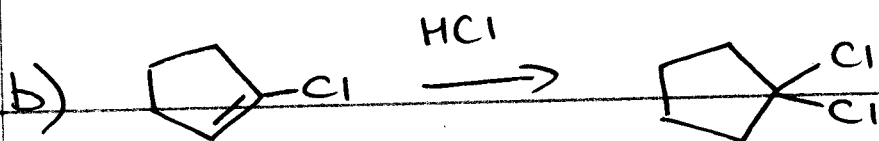
Q4 This was a GINME!



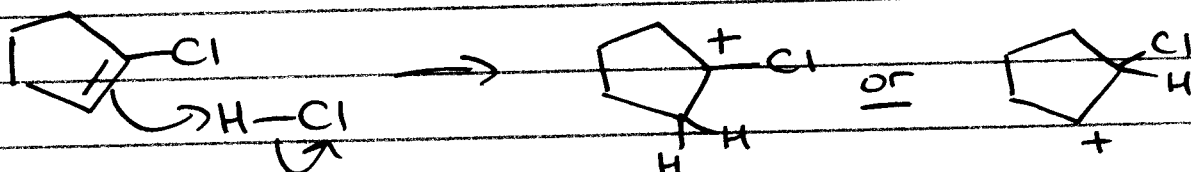
9 POINTS FOR ALL THE STUFF ABOVE, AND IF YOU MISSED ANY, YOU ONLY HAVE YOURSELF TO BLAME!



THIS QUESTION WAS ESSENTIALLY STRAIGHT FROM THE NOTES - just with a different ALKENE

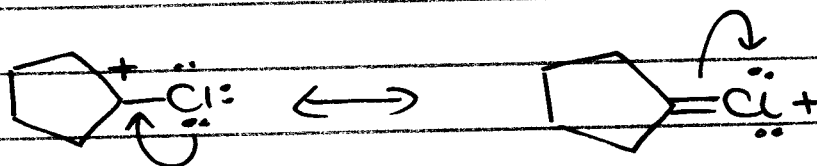


consider the first step in the reaction:

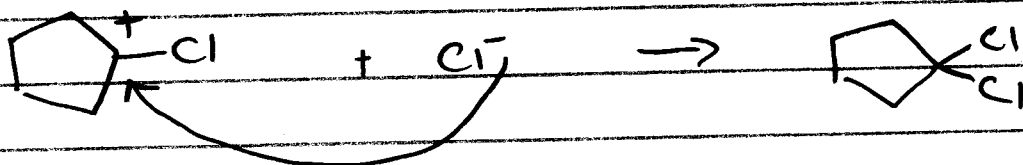


WHICH carbocation is more stable?

The first one is, because you can resonance stabilize it as shown below:



This resonance stabilized carbocation is more stable than the corresponding  $\text{C}^+$  formed from cyclopentene in part (a), and so the reaction is faster, as  $\Delta G^\ddagger$  on the energy profile will be much smaller. The reaction then proceeds as shown below:



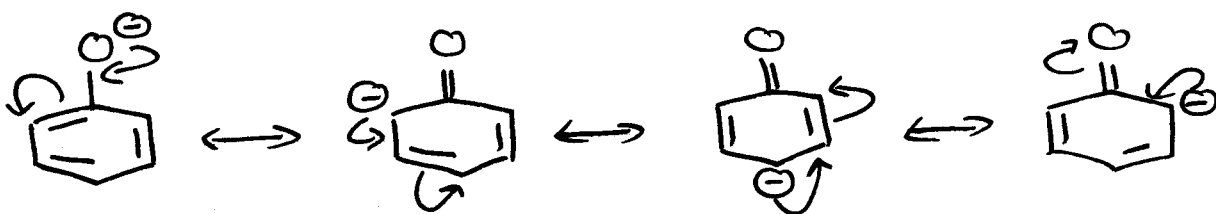
Q5. Ok, first things first, phenol is NOT one million times more acidic than cyclohexanol BECAUSE one has a pKa value of 10, and the other 16. That's just restating the question!! I want to know WHY?

consider the conjugate bases:



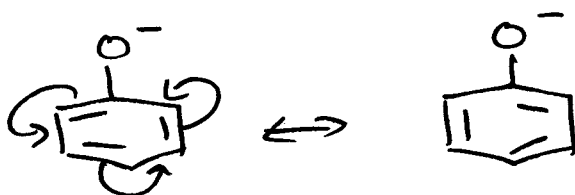
There is no stabilization of the charge possible - in fact, it is destabilized by the inductive effect of the alkyl group attached to the O<sup>-</sup>

But,



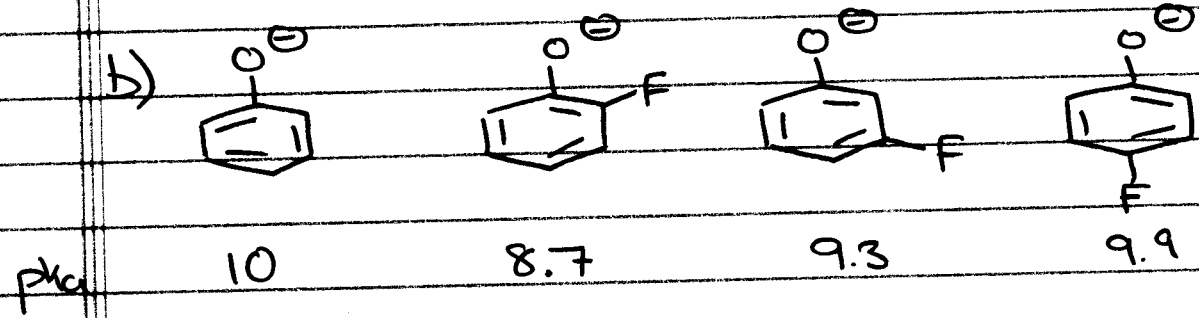
PHENOLATE (the anion derived from phenol) is stabilized by RESONANCE, distributing the -ve charge over a much larger area, leading to stabilization.

DRAWING THIS:

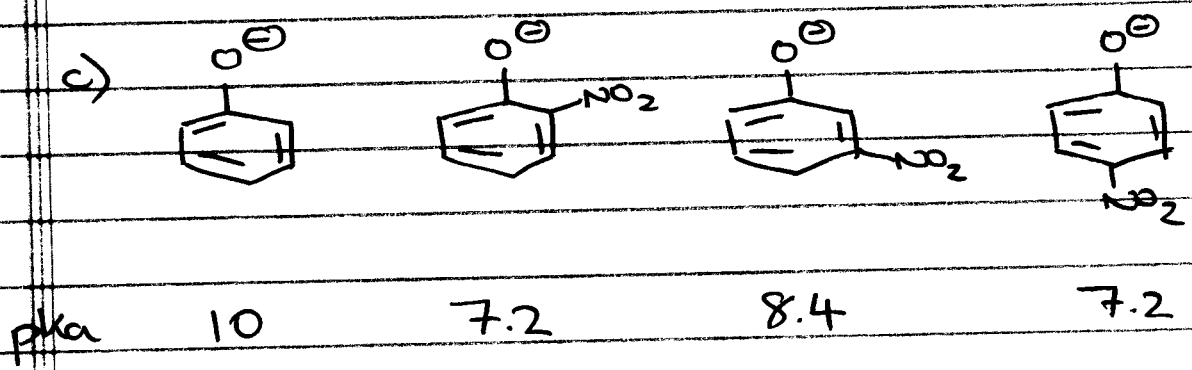


and talking about RESONANCE has no bearing on the charge on OXYGEN, so this did not

Count as a complete answer. (NOR did drawing the resonance forms of PHENOL before you lose the H<sup>+</sup>)

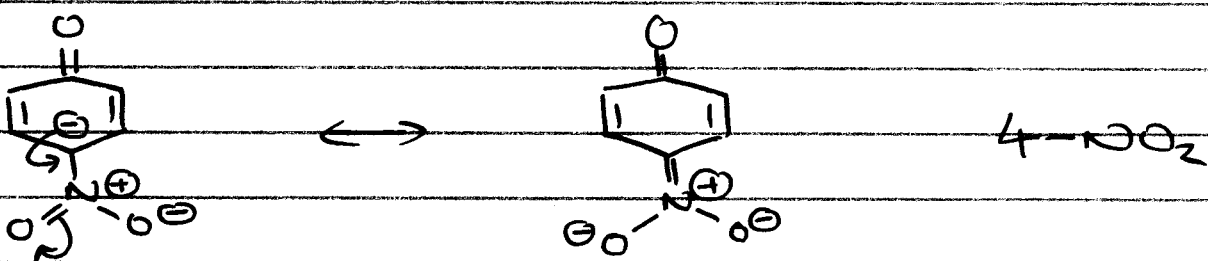
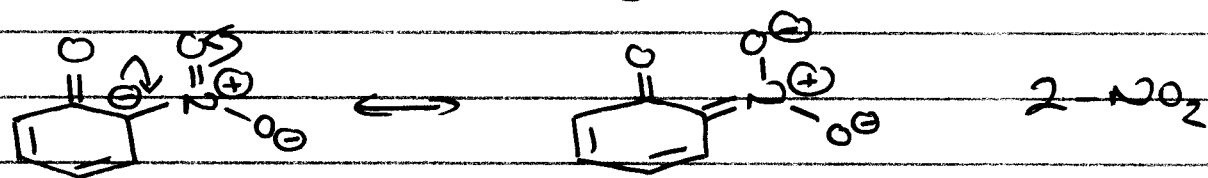


As the F atom is moved closer to the O<sup>-</sup>, the compound is more acidic, i.e., 2-fluorophenol is more acidic than 3-fluorophenol, and 4-fluorophenol is about as acidic as phenol itself - this simple drop in acidity as the F is moved further away can simply be attributed to the **INDUCTIVE EFFECT**. The strong electron withdrawing property of F reduces the charge density on the O<sup>-</sup>, thereby stabilizing it, and making the compounds more acidic. This through bond effect, however, falls off very quickly with distance, hence explaining the observed trend.

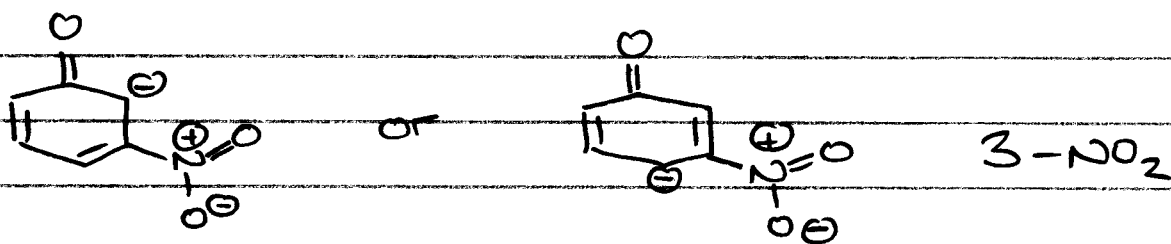


So, why don't we see the same trend for the electron withdrawing  $-NO_2$  group. Why is 4-nitrophenol just as acidic as 2-nitrophenol?

Consider the following resonance forms:



With the  $-NO_2$  group in either the 2 or 4 positions, it is possible to draw an additional resonance form in which the  $-ve$  charge is delocalized into the  $NO_2$  group. You CANNOT DO THIS IF THE  $NO_2$  group is in the 3 position.



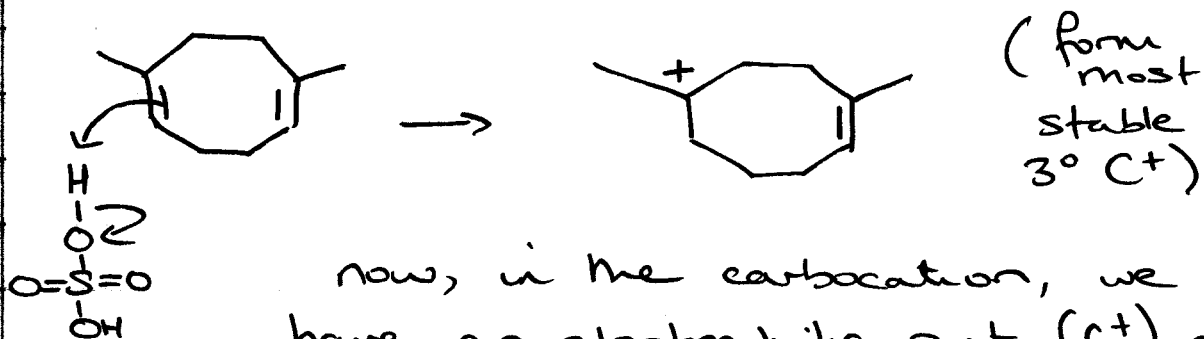
CANNOT DELOCALIZE INTO  $NO_2$



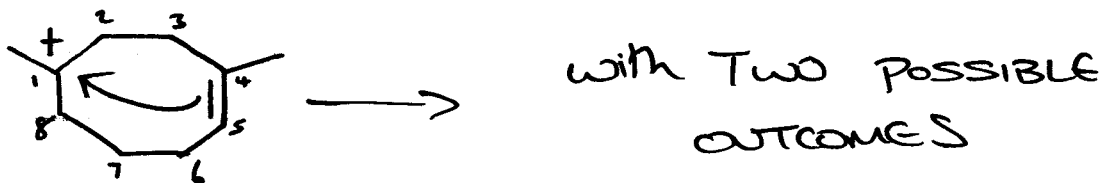
So, since resonance (in this case) is much more significant than the inductive effect, both the 2-NO<sub>2</sub> and 4-NO<sub>2</sub> compounds are about as acidic as each other as a consequence of extra resonance stabilization (the inductive effect is swamped out), but the 3-NO<sub>2</sub> compound is less acidic, because it does not have the extra resonance stabilization.

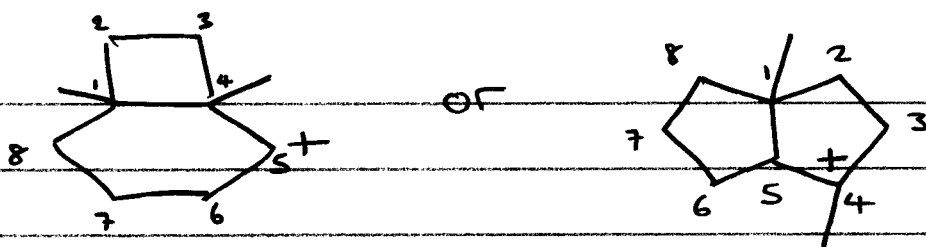
Q6 Bonus) This may have looked pretty frightening, but is quite straightforward (thanks to Prof Hardinger for this question)

— first step, is protonation of the alkene



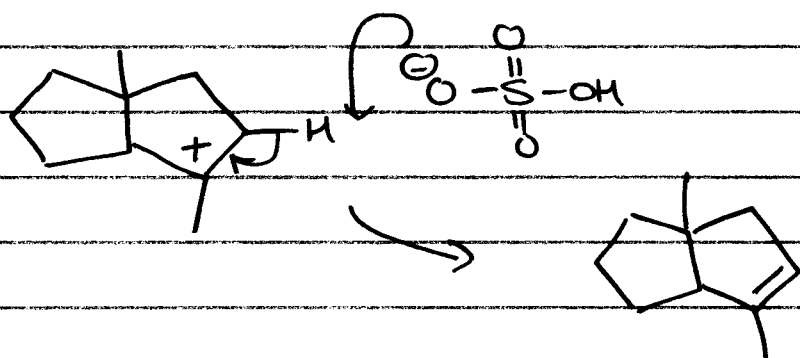
now, in the carbocation, we have an electrophilic part (C<sup>+</sup>) and a nucleophilic part (C=C), so the following reaction can happen:



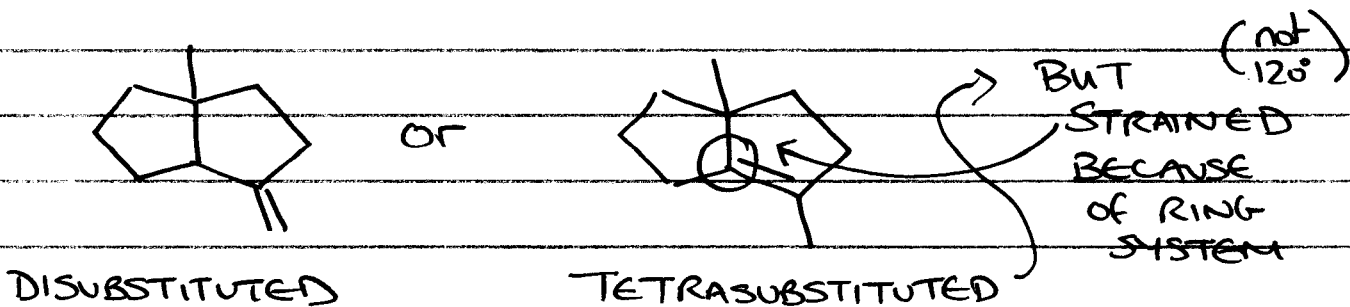


Either C4, or C5 will form a bond to C1. If we choose C4, not only do we form a strained 4-MEMBERED ring, but we form a secondary carbocation, if we choose C5 on the other hand, then we form a relatively stable 5,5 ring system, and a tertiary carbocation, not a secondary one...

The final step, is elimination of H<sup>+</sup> from the final carbocation, in an E1 like process:



This is the favored product over these two:



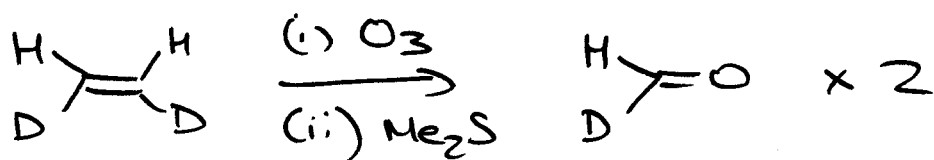
Q7 (BONUS): SYNTHESIS!



The first thing to notice here is that the product has only ONE C atom, but the starting material has TWO, so we can rule out HYDROBORATION or OXYMERURATION as that would give us products with TWO C atoms. One obvious RETROSYNTHETIC DISCONNECTION is:

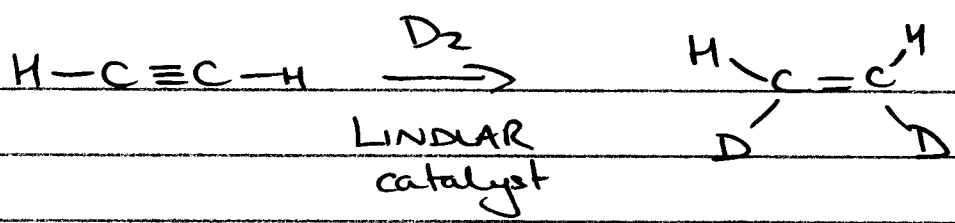


because you know that the forward reaction could be achieved with OZONOLYSIS: i.e.,

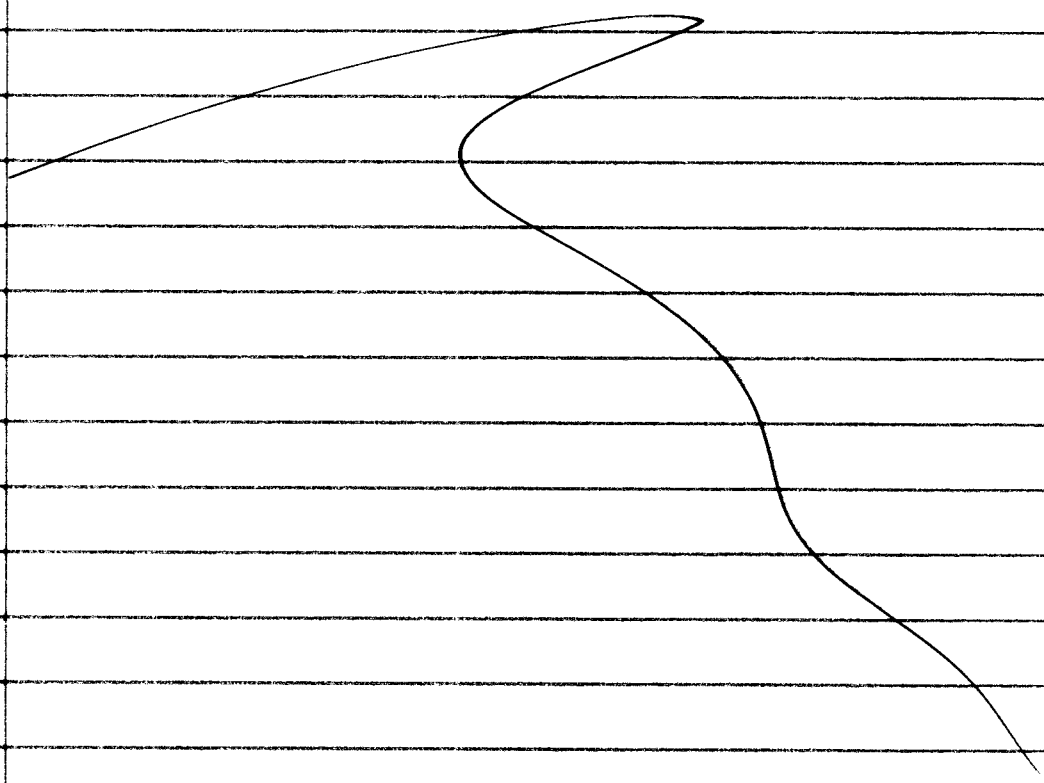


So, how do we make  $\begin{array}{c} \text{H} & & \text{H} \\ & \diagdown & / \\ & \text{C}=\text{C} \\ & / & \diagdown \\ \text{D} & & \text{D} \end{array}$  from  $\text{H}-\text{C}\equiv\text{C}-\text{H}$ ?

It's pretty clear that we have added  $\text{D}_2$  across a triple bond with SYN selectivity, and the only way to do that is using the following reaction:



and then we complete the synthesis by performing the OZONOLYSIS reaction.



Stc 3/2/05