Midterm 2 Review Packet KEY

Objectives

Chapter 9

➢ Describe ways to either synthesize or cleave ethers and epoxides
  ○ Distinguish between the products formed when reacting ethers with 1 vs 2 equivalents of H-X
➢ Draw mechanisms and predict product formation of both acid and base catalyzed ring openings of epoxides

Chapter 10

➢ Be familiar with alkene and fatty acid nomenclature
➢ Draw mechanisms and predict products for the following reactions:
  ○ Electrophilic Addition of either H-X or H₂O to alkenes
  ○ Halogenation via addition of X₂ to alkenes
  ○ Halohydrin formation via addition of X₂ and H₂O to alkenes
  ○ Hydroboration-Oxidation via addition of either 9-BBN or BH₃, followed by H₂O₂ and HO⁻
➢ Utilization of known reactions for the synthesis of novel compounds

Chapter 11

➢ Be familiar with alkyne nomenclature
➢ Draw mechanisms and predict products for the following reactions:
  ○ Double Elimination formation of alkyynes via addition of either 2 equivalents (non-terminal) or 3 equivalents (terminal) of NaNH₂
  ○ Electrophilic Addition of H-X to alkyynes
  ○ Halogenation via addition of X₂ to alkyynes
  ○ Hydration via the Keto-Enol tautomerization mechanism when adding H₂O and H₂SO₄ to alkyynes
  ○ Hydroboration-Oxidation of alkyynes via addition of either 9-BBN or BH₃, followed by H₂O₂ and HO⁻
➢ Utilization of known reactions for the synthesis of novel compounds
Chapter 12
➢ Distinguished between Oxidation and Reduction reactions
  ○ Distinguished between the products formed when reacting alkynes with either H₂ and Lindlar’s Catalyst or Na and NH₃ (l)
➢ Utilization of known reactions for the synthesis of novel compounds

Problem Set
Chapter 9

1. Consider Epoxide A and Epoxide B shown below. (Variation of 9.65 a, b)

   a. Draw a detailed stepwise mechanism for Epoxide A getting treated with H₂O and H₂SO₄.

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Epoxide A

Epoxide B

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Diagram of the stepwise mechanism for Epoxide A getting treated with H₂O and H₂SO₄.
The epoxide ring opening shown above is acid-catalyzed. Therefore, the nucleophile will attack the more substituted carbon in a backside manner (leading to configuration inversion if that site is a stereocenter). Recall that following protonation of the oxygen via a strong acid, the carbon with a higher degree of substitution will end up having more partial positive charge, when resonance structures are drawn, compared to the carbon without less substitution—ultimately making it more susceptible to nucleophilic attack.

For mechanisms, make sure all reacting atoms have lone pairs, arrows begin from areas of electron density (lone pairs, pi bonds, etc), land on areas with electron deficiency, and all bond angles are accurate (alkene substituents are 120° apart, etc).

b. Draw a detailed stepwise mechanism for Epoxide B getting treated with CH$_3$OH and NaOCH$_3$.

The epoxide ring opening shown above is base-catalyzed. Therefore, the nucleophile will attack the less substituted carbon in an $S_{N}2$ backside manner (leading to configuration inversion if that site is a stereocenter). Protonation will occur via CH$_3$OH following nucleophilic attack.

For mechanisms, make sure all reacting atoms have lone pairs, arrows begin from areas of electron density (lone pairs, pi bonds, etc), land on areas with electron deficiency, and all bond angles are accurate (alkene substituents are 120° apart, etc).
Chapter 10

2. Draw the product(s) of each reaction, and indicate stereochemistry where appropriate. (10.51 b, 10.52 d)

(a) The reaction mechanism for **halohydrin formation** suggests that -Cl and -OH groups add exclusively in the anti- (not syn-) configuration. Likewise, the -OH also adds to the more substituted carbon of the alkene.

Note that **two anti-configurations are possible** (which form enantiomeric products) in this reaction. Therefore, writing “+E” on an exam, instead of drawing the other enantiomeric product, is acceptable.

*To consider*: Compare and contrast the reaction mechanism for **halohydrin formation** to that of an **acid-catalyzed epoxide ring opening**. How does this comparison help to explain the **regioselectivity** of halohydrin formation?

(b) Recall that the mechanism for **hydroboration-oxidation** places an -OH group on the less substituted side of the alkene. Likewise, the -OH and -H groups must be placed in the syn- (not anti-) configuration.

Note that **two syn-configurations are possible** in this reaction. However, since there is a separate, untouched stereocenter in the initial cyclohexene ring, the **products are diastereomers** (so writing “+E” on the exam is incorrect!).
3. Devise a synthesis of each product from the given starting material. (10.64 f, 10.65 c)

**Box A**: One possible way to make **cyclohexene into cyclohexanol** is treatment with \( \text{H}_2\text{O} \) and \( \text{H}_2\text{SO}_4 \). Likewise, treatment with \( \text{BH}_3 \), followed by \( \text{H}_2\text{O} \) and \( \text{HO}^- \), will also work.

*Note that adding \( \text{HBr} \) to make bromocyclohexane, followed by addition of \( \text{NaOH} \), will **not lead to significant amounts of cyclohexanol formation**. Since the secondary alkyl halide is treated with the hydroxide ion (a strong base), **E2 elimination will be favored instead of \( S_{N2} \).**

**Box B**: Dr. King has noted in lecture that one of the best bases to deprotonate alcohols with is **NaH**.

**Box C**: The final step in this synthesis is the **formation of an ether from a secondary alkoxide**. This (hopefully) familiar reaction is known as the **Williamson Ether synthesis**. To promote a high degree of \( S_{N2} \) reactivity, **1-bromopropane** can be used (1-chloropropane, 1-iodopropane, or propyl tosylate are also acceptable!).

**DISCLAIMER**: Synthesis problems will 99.999% of the time have more than one solution. The pathway described below is merely one of the many possible manners to synthesize the compound presented above.

**Retrosynthetic Approach:**
Based on content taught in Chem 51B so far, one of the only ways to create an epoxide is an intramolecular $S_N2$ reaction with a nucleophilic oxygen and a good leaving group. To generate the nucleophilic region, an alcohol can be formed and deprotonated by a strong base (particularly NaH). Thinking back to the different reactions learned, addition of Cl$_2$ and H$_2$O to an alkene can generate the good leaving group and alcohol necessary for epoxide formation. From the starting material, an E2 elimination may be done with tert-butoxide base (given the initial primary alkyl halide).

Students who read ahead into Chapter 12 can note that the mCPBA reagent may also generate the epoxide directly from the alkene. Despite being a more efficient method of synthesis (fewer steps), students are not expected to know this going into MT2. Please refer to Dr. King’s announcement about what MT2 will cover for more details.

4. You are interested in the following compound that may play a role in a plasma membrane cell signaling pathway. [10.38 d, Variation of W7 Practice Problems 3]
a. Name the alkene and specify its configuration by the E,Z system.

Identify the longest straight carbon chain to act as the parent compound (highest number is 9 carbons with an alkene = nonene). There are two methyl, an ethyl, and an alkene group on the chain. Alphabetize the substituents (the -ene will appear on the parent chain) and make sure the lowest possible numbers are used. Finally, to determine if the compound is either E or Z, divide the alkene with an imaginary vertical line, and label priorities of the groups based on the number of carbons in their chain. If two higher priority groups are on opposite sides of the alkene double bond, it is labeled as the E isomer. If two higher priority groups are on the same side, it is labeled as the Z isomer. Using these nomenclature guidelines, the compound presented is (E)-5-ethyl-3,4-dimethyl-2-nonene.

b. An unnamed 16:4 ω-3 fatty acid also plays a role in this cell signaling pathway. Draw the structure of this fatty acid below and indicate whether it would be a solid or liquid at room temperature.

The naming of a fatty acid chain stems from the number provided in its name. The “16” refers to the number of carbons in the chain, the “4” refers to the number of alkene pi bonds present in the fatty acid, and the “3” refers to the starting carbon of these bonds. Due to the number of double bonds in this fatty acid, it would likely remain a liquid at room temperature since packing into a crystal lattice could not be done effectively.

Note that the final carbon of the fatty acid chains is a -COOH group, and the alkenes must both be in a cis conformation and skipped (have a carbon inbetween them).
5. Draw a stepwise mechanism for the following intramolecular bromoetherification reaction. (10.63)

![Mechanism Diagram]

The reaction mechanism above involves the formation of a **bridged halonium ion**, followed by an **intramolecular nucleophilic attack of the oxygen** at the **more substituted carbon atom** of the bridged ion. Finally, **deprotonation** occurs, via the bromide anion, to form the bromoether.

*Note that the deprotonation step occurs only after the intramolecular nucleophilic attack, and not beforehand. This is due to the fact that the $pK_a$ of the alcohol is ~15, whereas the $pK_a$ of the protonated ether’s O-H bond is < 0 (much more acidic than the alcohol).*

Chapter 11

6. Show a detailed mechanism for the following transformation. Clearly show all lone pairs, charges, and curved arrows, and show mechanism in a stepwise manner. *Label keto and enol tautomers* (Variation of King’s 51B Notes Page 109).

![Mechanism Diagram]
This mechanism is conceptually similar to the addition of water in alkenes, but for alkynes. The first few steps are similar where an acid is attacked by the triple bond and the vinyl carbocation is attacked by water. The product of those steps is an enol, essentially an alkene with an -OH group. HOWEVER, ENOLS ARE EXTREMELY UNSTABLE AND WILL ALWAYS TAUTOMERIZE TO A KETONE! NEVER HAVE AN ENOL AS A FINAL PRODUCT OR YOU WILL LOSE POINTS!!! Therefore, continue like a hydration reaction, but with lone pairs from oxygen move to create a C=O bond and deprotonate the hydrogen to create a ketone. For more context, ketones and enol are tautomers of each other, but in equilibrium for 99% (an exception will be found in 51C), ketones are heavily favored over enols.

7. Draw the organic products formed in each reaction (11.45).
Acetylide ion is a powerful nucleophile, therefore, this reaction can consider a nucleophilic ring opening where the acetylide ion attacks the LEAST SUBSTITUTED SIDE of the epoxide first. Afterwards, the water will protonate the negatively charged oxygen.

The deprotonation of an alkyne required a POWERFUL BASE such as NaH or NaNH₂. With the acetylide ion, it can attack the ethylene oxide on either side since they both don’t have an additional R group. Lastly, the water will protonate the negatively charged oxygen to get the final product above.
For the hydration of alkyne, when creating the vinyl carbocation, it should be at the most substituted carbon to create the most stable carbocation. However, in this case, both carbons contain one R group, therefore the carbocation can be formed on both sides equally. That is why unless the alkyne is symmetrical, the hydration reaction will always result in two products with ketones on both carbons of the triple bond.

8. Devise a synthesis of muscalure, the sex pheromone of the common housefly, from acetylene and any other required reagents.
Whenever there is a synthesis involving building carbon chains from alkyne, it is extremely important to **COUNT YOUR CARBONS!!** Start with how many carbons were added from acetylene on each side. One side added 13 carbons and another side added 9 carbons. Before adding a carbon chain, the acetylene must be deprotonated with a base (NaNH₂ or NaH will do) **ONE AT A TIME!** Then add the carbon chain and repeat for the other side. Finally, notice that the final product is a cis alkene, therefore, a reduction of alkyne with H₂, Lindlar’s catalyst.

9. Predict the products formed in each reaction and indicate stereochemistry (11.48).
In the mechanism of opening an epoxide with a strong nucleophile, the nucleophile should attack the least substituted side. However, in this case, both sides are equally substituted, therefore, it can attack both sides to give two possible products. Now let's compare the two potential products. Assigning configuration of both chiral centers of the initial epoxide, you get both R-config. Now, you should know that a nucleophile attacking either side will cause an inversion of configuration because it is similar to a backside attack of a SN2 reaction. Now assign configuration of both structures made and realized the same chiral centers have the same configurations but just flipped. THEY ARE IDENTICAL!! The only difference is the other product is just the flipped version of the first product.

\[
\begin{array}{c}
\text{H} & \text{O} & \text{H} \\
\text{CH}_3 & \text{CH}_3 & \text{H} \\
\end{array}
\quad \xrightarrow{[1] \text{HC}=\text{C}^-} \quad \text{H} \\
\text{CH}_3 & \text{CH}_3 &\text{H} \\
\end{array}
\]

b.

\[
\begin{array}{c}
\text{H} & \text{O} & \text{H} \\
\text{CH}_3 & \text{CH}_3 & \text{H} \\
\end{array}
\quad \xrightarrow{[1] \text{HC}=\text{C}^- \quad [2] \text{H}_2\text{O}} \quad \text{H} \\
\text{CH}_3 & \text{CH}_3 &\text{H} \\
\end{array}
\]

enantiomers
Now for this epoxide, use similar for problem (a) by assigning configurations of both reactant and the two possible products. Notice how both chiral centers of the two possible products have different configurations or gone from R to S and vice versa. This is an indication that both products are mirrored images of each other or enantiomers. This does not mean they are flipped versions from each other because if that was the case, the chiral centers of both products should be the same.

Chapter 12

10. Label each reaction as oxidation, reduction, or either (12.32).

a. Oxidation

b. Neither
c. Reduction

d. Reduction

**Guideline for Oxidation & Reduction:**
- Oxidation = C-H to C-X
- Reduction C-X to C-H
- Neither: Substitution is considered either oxidation or reduction

Remember that there will be a loss of C-H bond for oxidation or a gain of C-H for reduction.

11. Provide a synthesis for the following compound from the given starting material. If required, number individual steps (Variation of Dr. King's POW 7 & 8).

a.
As mentioned before, when dealing with alkynes, **counting carbon chains is extremely important.** Additionally, **recognize the pattern that when going from an alkene to alkyne, one should use Br₂ and double elimination to get an alkyne.** Since a carbon chain is added right after the formation of alkyne, water after adding three equivalents of base is not necessary since one carbon has to be deprotonated anyways. On the other hand, **notice the final product has the two R groups trans from each other, therefore, Na, NH₃ will be used instead of H₂. Lindlar’s Catalyst (provides a cis alkene), then Br₂ to create a structure with two bromines anti from each other.**
For this synthesis, it is very tempting to find a way to just add a carbon chain from an alkene, but that's impossible. You only know one way to add carbon chains so far and that involves an alkyne. Therefore, like mentioned before, Br₂ and NaNH₂ (3 eq) are used to create the alkyne, then add the carbon chain. Finally, the final product is a cis alkene, therefore, use H₂, Lindlar's Catalyst.
c.

1) NaNH₂
2) △ (ethylene oxide)
3) H₂O
4) PBr₃, PYR.
5) Na₂, NH₃
For this synthesis, another pattern you should be able to recognize is going from an alkyne to a structure where a $\text{CH}_2\text{CH}_2\text{OH}$ is added. That is an indication that an epoxide is added in the synthesis. Since a terminal alkyne is a great nucleophile, deprotonate it with NaNH$_2$ and adding epoxide will do a job. However, remember that with good nucleophiles, add water to protonate the oxygen. Afterwards, to get from $\text{-OH}$ to Br with a primary alcohol, add PBr$_3$, pyr. Then Na, NH$_3$ because the final product contains a trans alkene. NOTE: DON'T ADD Na, NH$_3$ BEFORE THE EPOXIDE BECAUSE AN ALKENE CANNOT BE ADDED TO AN EPOXIDE. ORDER DOES MATTER IN SYNTHESIS!!!
For this synthesis, notice that the final product is an aldehyde created from an alkyne. Since a carbonyl is added on the least substituted carbon, therefore, 9-BBN and H₂O₂, NaOH. Regardless, a carbon chain is added so start with a NaNH₂ and the carbon chain. Afterwards, 9-BBN and H₂O₂, NaOH to create an enol, but through base catalyzed tautomerization, it will convert to an aldehyde.