1. (9 points)
a. The structure of a steroid is shown below. Identify whether each of the methyl and hydroxy groups is axial or equatorial. (4 points)

b. Menthol, a well-known natural product obtained from peppermint oil, has the molecular structure shown below. Draw menthol in its most stable conformation, showing clearly the three-dimensional conformation of the cyclohexane ring, and the disposition of the three substituents. (3 points)

c. Draw its enantiomer in a similar fashion. (2 points)
2. Write the missing reactant(s), reagent(s), or product(s) in the box. If NO REACTION OCCURS, write NR. (3 points each, 48 pts)

\[ \text{BrBr} \quad \text{H} \quad \text{O} \quad \text{CH}_3 \quad \text{SCH}_3 \quad \text{H} \]

\[ + \quad \text{NaCl} \]

\[ \text{BrBr} \quad \text{KCN} \quad \text{EtOH} \]

\[ + \quad \text{NR} \]

\[ \text{H}_3\text{C} - \text{OCH}_3 \quad \text{NaI} \quad \text{acetone} \]

\[ + \quad \text{NR} \]

\[ \text{CH}_3\text{OH} \quad \text{NaSCH}_3 \quad \text{CH}_3\text{OH} \quad \text{SCH}_3 \]

\[ + \quad \text{D} \quad \text{H} \quad \text{NaCl} \]

\[ \text{CHCl}_3 \quad \text{KO-t-Bu} \]

\[ + \quad \text{NR} \]

\[ \text{H}_3\text{C} - \text{Br} + \quad \text{CH}_3\text{OH} \quad \text{H}_3\text{C} - \text{S} - \text{CH}_3 \quad + \quad \text{NaBr} \]

\[ \text{CH}_3\text{I} \quad \text{CH}_3\text{I} \]

\[ \text{NR} \quad \text{NR} \quad \text{an organolithium compound} \]

\[ \text{NR} \quad \text{NR} \quad \text{NR} \]
2. continued

\[
\begin{align*}
\text{H}_3\text{C} & \text{Cl} \quad \text{NaOEt} \quad \text{EtOH} \\
\text{Br} \quad \text{Br} & \quad \text{Na}_2\text{S} \quad \text{EtOH} \\
\text{H}_3\text{C} & \text{Cl} \\
\text{Br} \quad \text{Br} & \quad \text{Na}_2\text{S} \quad \text{EtOH} \\
\text{H}_3\text{C} & \text{Cl} \\
\text{Br} & \quad \text{Br} \\
\text{H}_3\text{C} & \text{Cl} \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \text{Cl} \\
\text{Br} & \quad \text{Br} \\
\text{H}_3\text{C} & \text{Cl} \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{BH}_3 & \quad \text{THF} \\
\text{H}_2\text{O}_2 & \quad \text{NaOH} \\
\text{O}_3 & \quad \text{Me}_2\text{S} \\
\text{cat. OsO}_4 & \quad \text{H}_2\text{O}_2
\end{align*}
\]

\[
\begin{align*}
\text{C}_8\text{H}_8\text{S} & \quad \text{C}_5\text{H}_{11}\text{Br} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{C}_8\text{H}_8\text{S} & \quad \text{C}_5\text{H}_{11}\text{Br} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{C}_8\text{H}_8\text{S} & \quad \text{C}_5\text{H}_{11}\text{Br} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]
3. Write mechanisms for each of the following reactions using the correct curved-arrow formalism. (12 points each, 48 points).

a. HINT: 3 steps.

\[ \text{CH}_3\text{CH}_2\text{CH}_3 + \text{B–H} \rightarrow \text{Isocomene} \]

Note: B–H is meant to indicate an acid.

b. HINTS: 2 steps. P is below N in the periodic table. (This reaction is called the Arbuzov reaction.)

\[ \text{H}_3\text{COPO(OCH}_3\text{)} + \text{H}_3\text{C–I} \rightarrow \text{H}_3\text{COPO(CH}_3\text{)} + \text{H}_3\text{C–I} \]
3 continued

c. HINT: 2 steps.

\[
\begin{align*}
\text{Ph} & \quad \text{Br} \\
\text{N} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph}\ \
\end{align*}
\]

\[
\begin{align*}
1) \quad \text{Ph} & \quad \text{Br} \\
2) \quad \text{Base (B:) } \\
\text{Ph} & \quad \text{Ph}\ \
\text{N} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph}\ \
\end{align*}
\]

d. HINTS: Two steps to form X; two steps from X to the products. Proton transfer reactions are very fast.

\[
\begin{align*}
\text{OH} & \quad \text{Cl} \\
\text{NaOH} & \quad \text{X} \\
\text{HBr} & \quad \text{Br} \quad \text{OH} \\
\text{minor} & \quad \text{major}\ \
\end{align*}
\]
4. Explain each of the following observations. (12 points each, 48 points). Note: Clarity counts!

a. Rotation about single bonds is typically facile, having barriers <10 kcal/mol. However, rotation about the C–O single bond indicated below has a barrier >10 kcal/mol. Why?

\[ \text{CH}_3\text{O} \]

b. Amines I \([\text{triethylamine, (CH}_3\text{CH}_2\text{N})]\) and II are similar in structure, but amine II undergoes SN2 displacement with ethyl iodide 252 times faster. Why?

\[
\begin{align*}
\text{I (triethylamine)} & \quad + \quad \text{CH}_3\text{CH}_2\text{I} \\
\text{II} & \quad + \quad \text{CH}_3\text{CH}_2\text{I}
\end{align*}
\]

Relative rate = 1

Relative rate = 252
c. Upon treatment with potassium ethoxide, the following alkyl halide gives an alkene as a single diastereomeric product. Explain and tell what the product is. (Hint: Consider using a Newman projection looking down the C3-C4 bond.)

\[
\begin{align*}
\text{CH}_3 \text{Cl} \quad \text{CH}_3 \text{CH}_2 \text{O}^- \text{K}^+ \\
\text{CH}_3 \text{CH}_2 \text{OH}
\end{align*}
\]

single alkene stereoisomer

d. To synthesize cyclohexyl methyl ether (methoxycyclohexane), it is better to react sodium cyclohexoxide with methyl bromide (bromomethane) than it is to react sodium methoxide with cyclohexyl bromide (bromocyclohexane). Why?
5. Threonine (III and IV), like all amino acids, is both an acid and a base. The pKₐ of the carboxylic acid group in III (below) is 3.5, and the pKₐ of the ammonium ion in IV is 8.5. (12 points)

a. What is $K_{eq}$ for the internal acid-base reaction shown?

\[ \text{HO} \text{H} \text{O} \text{H} \text{III} \xrightleftharpoons{K_{eq}} \begin{array}{c} \text{H} \text{H} \text{NH}_2 \text{H} \text{H} \\ \text{H}_{3}\text{C} \end{array} \text{IV} \]

b. What is the $\Delta G^\circ$ for this process? (Note R = 0.001987 kcal / mol K)
6. *cis*-1-tert-Butyl-4-iodocyclohexane undergoes $S_N2$ displacement with $I^-$ twice as fast as its *trans* diastereomer. (20 points)

a. Draw the products for the reaction of each isomer.

\[
\begin{align*}
\text{cis} & \quad \text{trans} \\
\begin{array}{c}
\text{I} \\
\text{I}
\end{array} & \quad \begin{array}{c}
\text{I} \\
\text{I}
\end{array}
\]

b. Draw the transition states for the reaction of each diastereomer. (Hint: What is a transition state?)

c. Draw a reaction free energy diagram illustrating the reaction of the *cis* isomer.

d. How would the reaction free energy diagram for the reaction of the *trans* isomer differ?

e. Why does the *cis* isomer react faster?
7. 

a. For the following 5 types of reactions, write the LETTER of the reaction free energy diagram (below) that best describes it. Also, pick one WORD out of the box below that characterizes each mechanism, and place it in the appropriate empty box on the right. Not all the words have to be used; a word may be used more than once (10 pts).

1. S_N1 _____ (letter) ____________________ (word)
2. S_N2 _____ (letter) ____________________ (word)
3. E1 _____ (letter) ____________________ (word)
4. E2 _____ (letter) ____________________ (word)
5. Addition of H_2O to alkenes _____ (letter) ____________________ (word)

b. Deciding between S_N2 and E2 mechanisms is often difficult. Put a check into the appropriate box, to indicate whether the conditions on the left favor S_N2 or E2 chemistry (5 pts).

<table>
<thead>
<tr>
<th>CONDITIONS</th>
<th>S_N2</th>
<th>E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° carbon w/leaving group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small nucleophile/base</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3° carbon w/leaving group</td>
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<tr>
<td>Bulky nucleophile/base</td>
<td></td>
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<tr>
<td>I^- as nucleophile</td>
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</tbody>
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