Paclitaxel, an alkanol used to prevent and treat breast cancer
Note: Problems with *italicized numbers* are more challenging.
  You may want to try them last.
Concepts for Chapter 13: Alcohols

I. Nomenclature
   A. Alkanols; the hydroxy substituent

II. ROHs are amphiphilic
   A. ROHs as Lewis bases (electron donors or nucleophiles)
      1. are weak bases and can be protonated by strong acids
         a. oxonium ions are generated
   B. ROHs as Lewis acids (electron acceptors or electrophiles)
      1. are weak acids and can be deprotonated by strong bases
         b. alkoxide ions are generated

III. Preparations of ROHs
   A. “Old” ways
      1. hydration of alkenes
         a. Markovnikov
            i. oxymercuration-demercuration
         b. antiMarkovnikov
            i. hydroboration-oxidation
      2. dihydroxylation of alkenes
         a. cold, dilute, aqueous alkaline KMnO₄ (yields only fair)
         b. OsO₄ (yields are good)
   B. New ways
      1. reduction of aldehydes, ketones, carboxylic acids and esters
         a. aldehyde + [H] → 1° ROH
            i. [H] = NaBH₄ or LiAlH₄
         b. ketone + [H] → 2° ROH
            i. [H] = NaBH₄ or LiAlH₄
         c. ester + [H] → 1° ROH
            i. [H] = LiAlH₄
         d. carboxylic acid = [H] → 1° ROH
            i. [H] = LiAlH₄
      2. addition of organometals to aldehydes, ketones, and esters
         a. for all of the below, RM usually is
            i. RMgX, a Grignard reagent
            ii. RLi, an alkyl lithium reagent
         b. formaldehyde + RM → RCHOH
            1. a one carbon homologation reaction
         c. aldehyde + RM → 2° ROH
         d. ketone + RM → 3° ROH
         e. ester + 2 RM → 3° ROH

IV. Reactions of ROHs
   A. As acids
      1. reaction with a metal–Na, Li, or K–to prepare metal alkoxides
   B. As bases
      1. reaction with HX to prepare R—X
         a. relative reactivities:
            i. HI > HBr > HCl >> HF
            ii. 3° ROH > 2° ROH > 1° ROH > CH₃OH
         b. sometimes HBr and HI are generated in situ from KX and H₂SO₄
c. mechanism
   i. for 3°, some 2°ROH: \( S_N1 \)
      • carbocation intermediates; relative stabilities \( 3^\circ > 2^\circ >> 1^\circ \)
      • E versus reaction coordinate diagram
      • concept of \( E_{act} \); how it controls rate
   ii. for some 2°, all 1° ROH: \( S_N2 \)
      • no carbocation is formed
      • concerted reaction
      • E versus reaction coordinate diagram

2. reaction of ROH with TsCl in presence of a base to form tosylates, ROTs
   a. The OTs group is an excellent leaving group

3. other ways to make RX from ROH
   a. use of thionyl chloride, SOCl₂
   b. use of PBr₃

4. dehydration to give alkenes
   a. use \( H_3PO_4, H_2SO_4 \), heat
   b. relative reactivities
      i. 3° ROH > 2° ROH > 1° ROH
      ii. mechanism: E1
   c. use POCl₃
      i. mechanism: E2

5. oxidations
   a. 1° ROH + [O] → aldehyde
      i. [O] = PCC
   b. 1° ROH + [O] → carboxylic acid
      i. [O] = chromic acid (also called Jones reagent)
      ii. [O] = KMnO₄
   c. 2° ROH + [O] → ketone
      i. [O] = chromic acid (also called Jones reagent)
      ii. [O] = KMnO₄

6. protection of alcohols
   a. Most commonly as silyl ethers
      i. protection
      \[ \text{RCH}_2\text{O–H} + \text{base} + (\text{CH}_3)_3\text{Si–Cl} \rightarrow \text{RCH}_2\text{O–Si(CH}_3)_3 + \text{base–H}^+ \text{Cl}^- \]
      ii. deprotection
         • treat silyl ether with dilute aqueous acid
         • treat silyl ether with fluoride
1. A. For each reaction, provide either an IUPAC name for the starting material shown OR draw the correct chemical structure of the starting material named.

B. Provide the principal organic reaction product for each of the reaction. DO NOT NAME THE PRODUCTS. If you believe there will be no reaction given the starting material and reaction conditions, indicate so by writing "NR" for "no reaction".

a. \[
\begin{align*}
\text{CF}_3\text{CH}2\text{CH}2\text{OH} & \xrightarrow{\text{SOCl}_2} \\
\end{align*}
\]

b. \[
\begin{align*}
\text{trans-2-sec-butyl-1-cyclohexanol} & \xrightarrow{\text{K}} \text{23 °C} \\
\end{align*}
\]

c. \[
\begin{align*}
\text{(this one is an oldie from organic I!)} \\
\end{align*}
\]

d. \[
\begin{align*}
\text{3-ethyl-4-fluoro-3-methyl-1-pentanol} & \xrightarrow{\text{KBr}} \text{H}_2\text{SO}_4 \\
\end{align*}
\]

e. \[
\begin{align*}
\text{Jones reagent} \\
\end{align*}
\]

2. a. Propose a clear, reasonable reaction mechanism that explains how the starting alcohol below is converted to the product bromoalkane:

\[
\text{\text{OH}} \xrightarrow{\text{HBr}} \text{\text{Br}}
\]

b. Draw an energy versus reaction coordinate diagram for the reaction of part A. Label your diagram with the following:

- A — all transition state(s) generated during the course of the reaction
- B — all intermediate(s) formed during the course of the reaction
- E, — Energy of activation for the reaction
- SM — Starting materials
- P — Products

Clearly place an arrow pointing to the portion of the curve that represents the rate limiting step of the reaction.
3. a. Rank the following according to their relative reactivity with HCl:

![Chemical Structures]

b. Circle the letter of the reaction which is faster:

![Chemical Reactions]

4. a. Propose a clear, reasonable reaction mechanism that explains how the starting alcohol below is converted to the product chloroalkane:

![Chemical Reaction Mechanism]
5. Provide the principal organic reaction product for each of the following reactions. If you believe there will be no reaction given the starting materials and the reaction condition, indicate so by writing "NR" for "no reaction".

a. 2,3-difluoro-3-methyl-1-pentanol \[\xrightarrow{\text{SOCl}_2, \text{K}_2\text{SO}_4}\] K

b.  

\[\xrightarrow{\text{K}, 23 \degree\text{C}}\]  

[Chemical structures and reaction conditions are depicted in the diagram.]
6. 2,2,2-Trifluoro-1-ethanol has a pK$_a$ of 9.7 and ethanol a pK$_a$ of 16.
   a. Draw the equilibrium acid-base reaction between these two compounds.

   ![Chemical Structures]

   2,2,2-trifluoro-1-ethanol

   ethanol

   b. Label your equilibrium reaction with the terms stronger acid, weaker acid, stronger base, and weaker base.

   c. Will the equilibrium lie to the left or right of the reaction you have written? __________

   d. Does the alkane ethane have a pK$_a$ greater than or less than the pK$_a$ of ethanol? __________

7. When cis-3-isopropyl-1-cyclopentanol is reacted with HBr at 50°C for three hours, two isomeric product bromoalkanes are formed in a nearly 1:1 ratio. Draw the structures of the products, tell what type of isomers they are, and explain why both (as opposed to only one or the other) form.
8. For each reaction shown below, predict the major organic product. If you decide that no reaction occurs for a given set of reaction conditions, write NR. Be sure to indicate the correct stereochemistry of the product when appropriate.

a. 
\[(R)-2\text{-butanol} \xrightarrow{\text{K}} \text{racemic} \quad 2\text{-iodo-3-ethylheptane} \]

b. 
\[\text{OH} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{pyridine}} \text{SO}_2\text{Cl} \]

9. Circle the compound that reacts with $\text{K}^+\text{N}_3^-$ in $\text{CH}_3\text{OH}$ at 25 °C at the faster rate:

\[\text{(CH}_3\text{)}_2\text{CHCH}_2\text{CH}_2\text{Br} \quad \text{(CH}_3\text{)}_2\text{CHCH}_2\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{CH}_3\]
10. Consider the following reaction:

\[
\text{OH} \quad \xrightarrow{\Delta} \quad \text{H}_2\text{SO}_4
\]

\[
\text{A} + \text{B}
\]

a. Using electron arrows to illustrate the sequence of bond-breaking and bond-making steps by which the reactant is transformed to products, provide a reasonable, clear, detailed reaction mechanism for the formation of both A and B.

b. Will A or B be the major product of this reaction? ________________

c. Using concepts of organic chemistry that you have learned in class, briefly explain your choice for part b.