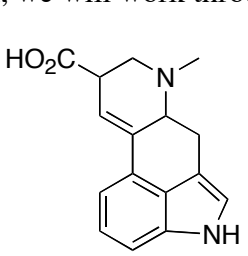
Problem Set 4

This problem set is to be turned in individually. I expect you to work with your classmates to solve many of these problems. I simply ask that the answers you provide are your own; do not simply copy someone else's work.

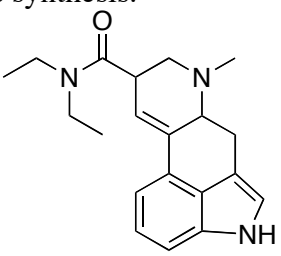
This problem set is **due by the end of the day on Monday , Dec. 5.**

Name_____ Student ID_____

1) The ergot alkaloids are a family of compounds found in nature. They are produced by a fungus that grows on grains, typically rye. Lysergic acid is the parent structure to one of the most well known ergot alkaloids, the psychotropic drug LSD (lysergic acid diethyl amide). R. B. Woodward was the first to synthesize lysergic acid (in the 1950's). With some slight variation, we will work through his synthesis.

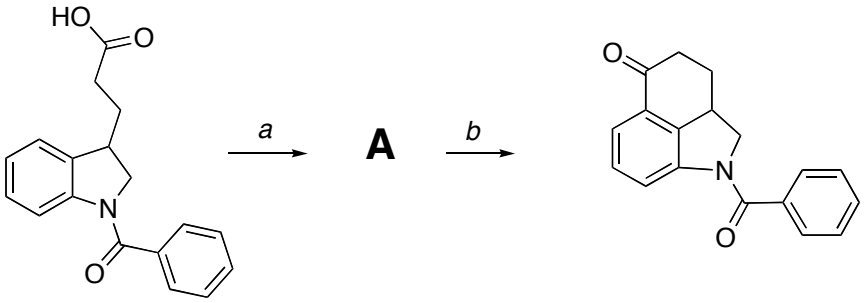


lysergic acid



LSD

A) (6 pts) The synthesis begins with compound **1**. Fill in the missing reagents (***a*** and ***b***) and the structure of the intermediate compound **A**.



1 **2**

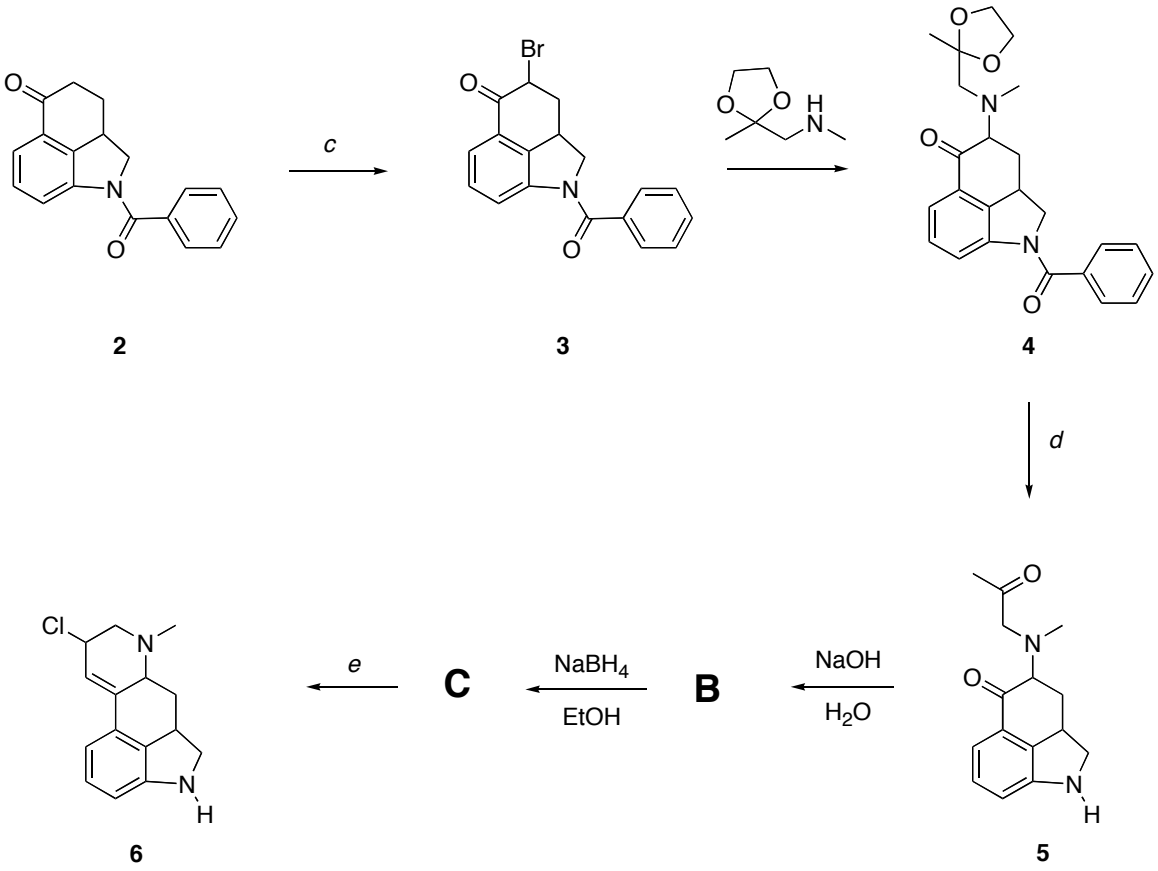
Reagent(s) ***a*** Product **A**

Reagent(s) ***b***

B) (6 pts) Provide a mechanism (using curved arrow notation) for the conversion of **A** to **2**.

Compound **2** is called "Kornfeld's ketone" after the chemist who first made it. Kornfeld's ketone has been an important starting material in many syntheses of ergot alkaloids that are related to lysergic acid.

C) (10 pts) Woodward converted **2** to lysergic acid using chemistry that you already know. Fill in the missing reagents and products for the following sequence of reactions that produce **6**.



Reagent(s) ***c***

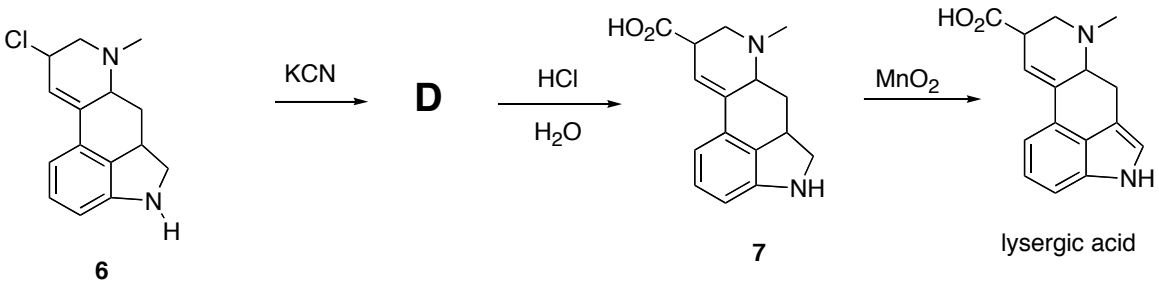
Reagent(s) ***d***

Reagent(s) ***e***

Product **B**

Product **C**

D) (3 pts) To finish the synthesis, fill in the missing product in the sequence of reactions that convert **6** to lysergic acid.



6 **7** lysergic acid

Product **D**

Lysergic acid has been converted to a number of different drugs. Clinically important drugs for Parkinsons disease and migraine headaches as well as oxytocic (labor inducing) and analgesic (pain relievers) medications have been discovered...all with the general structure of lysergic acid.

2) (10 pts) MO theory. For help with this, refer to page 808 of your text book.

A) Draw a Frost diagram for cyclopropenyl cation (**8**).

8

B) From the Frost diagram, construct an MO diagram for **8**, adding the appropriate number of electrons to each orbital. Label anti-bonding orbitals with an asterisk (i.e. π_4^*)

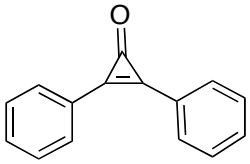
C) Is this planar cation aromatic or anti-aromatic.

D) Draw the MO diagram for cyclopropenyl anion (**9**), adding the appropriate number of electrons to each orbital. Label anti-bonding orbitals with an asterisk (i.e. π_4^*)

9

E) Is this planar anion aromatic or anti-aromatic.

3) (5 pts) Which of these two molecules will have a larger dipole moment, **10** or **11**? (Hint: The dipole moment is influenced by the unequal sharing of electrons between two bonded atoms.)



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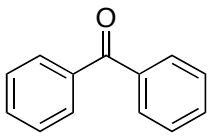
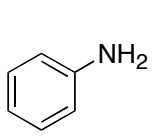


11

Explain your answer.

4) (10 pts) A mixture of aniline (**12**), benzyl alcohol (**13**), and phenol (**14**) are mixed together with an organic solvent, Et_2O (diethyl ether), to form a solution. The organic solution is washed with three portions of aqueous NaOH (1 M). These aqueous base washes are combined and labeled "Base Extract." The organic solution is then washed with three portions of aqueous HCl (1 M), and the aqueous acid washes are combined and labeled "Acid Extract." The organic solution is then dried (with Na_2SO_4), filtered, and evaporated to give product **A**. The "Base Extract" is made acidic with concentrated HCl, and this new solution is extracted with three portions of an organic solvent (Et_2O). The Et_2O washes are combined, dried (Na_2SO_4), filtered, and concentrated to give product **B**. The "Acid Extract" is made basic with NaOH, and this new solution is extracted with three portions of an organic solvent (Et_2O). The organic washes are combined, dried (Na_2SO_4), filtered, and concentrated to give product **C**. Remember that salts (charged derivatives) of organic compounds are more soluble in water than the neutral molecules. Drawing a flowchart will probably help you keep track of different solutions.



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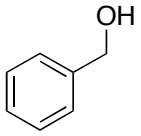

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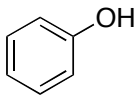
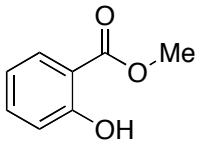


14

What are the structures of **A**, **B**, and **C**?

5) (10 pts) Methyl Salicylate (**15**) is the essential oil found in the leave of the wintergreen plant. Propose a synthesis, starting with phenol (**14**, see problem 4). You may use any inorganic reagents and any organic reagents with two or fewer carbons.



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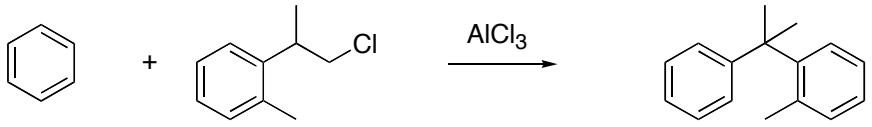
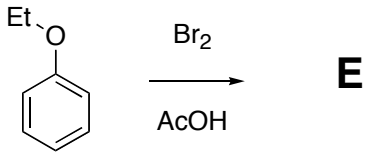
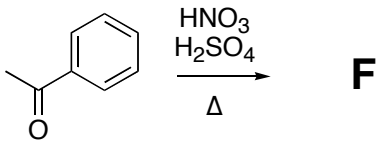
6) (15 pts) Provide a mechanism, using curved arrow notation for the formation of **16** in the following reaction.



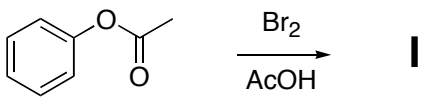
16

7) (25 pts) Provide the major organic products for the following transformations.

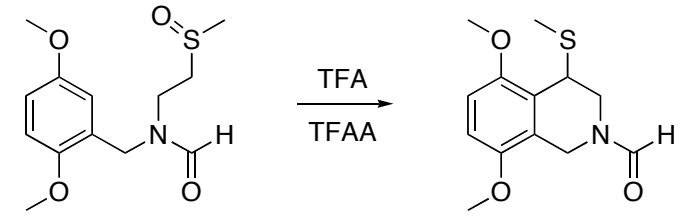
A) 

B) 

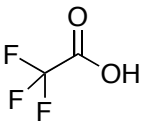
C) 

d) 

Extra Credit (10 pts): Provide a mechanism (using curved arrow notation) that explains the formation of **18** from **17**. Hint: TFAA is a very strong acylating agent, and the sulfur and oxygen atoms in the S-O double bond have a very unequal distribution of electrons. It is often drawn as its resonance structure to emphasize the way in which this group can react. (Working backwards might help you figure out what must happen to make the bond between the carbon α to sulfur and the aryl ring.)



17 **18**

TFA = 

TFAA =