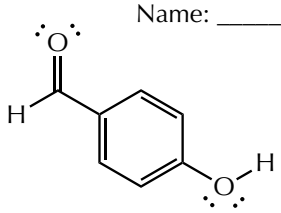
Question 1 (28 points)

Name: _____

In the 1400s, Mesoamerican people, particularly the Aztecs, began to cultivate the vanilla orchid for its distinctly flavorful seed pod. One major constituent in natural vanilla oil is 4-hydroxybenzaldehyde.



4-hydroxybenzaldehyde

(a) The observed pK_a value of 4-hydroxybenzaldehyde is either 7.61, 10.05, or 12.61. Which is the actual pK_a value? What is the structure for the single most significant resonance contributor for the conjugate base that can be used to explain the pK_a value? (all closed shell atoms, include nbe pairs and charges)

PhOH alone is 10, the C=O lowers the pK_a, particularly thanks to the resonance

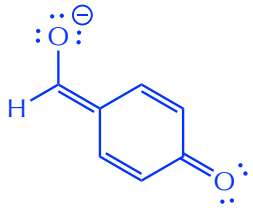
The pK_a value is (circle one):

7.61

10.05

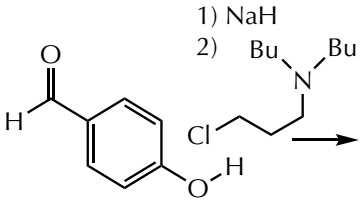
12.61

no partial 2



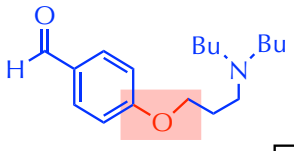
no partial 4

(b) Provide the compounds needed to complete the following transformations, which start with 4-hydroxybenzaldehyde (*Heterocyclic Chem*, **2021**, *58*, 1861).



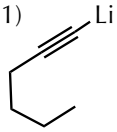
Bu = butyl ($CH_2CH_2CH_2CH_3$)

+3 for critical bond
THEN +1 if rest is OK



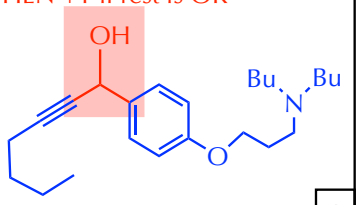
4

1)



2) $H_3O^{\oplus}$ workup

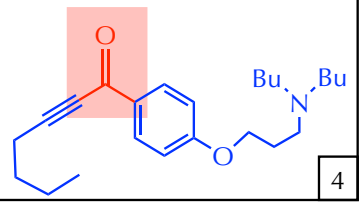
+3 for critical bond
THEN +1 if rest is OK



racemic 4

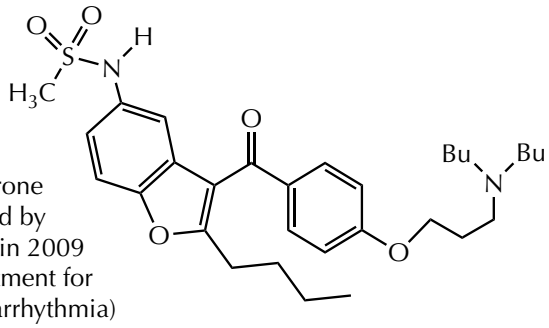
1) $(COCl)_2$, $(CH_3)_2SO$ 2) $N(CH_2CH_3)_3$

+3 for critical bond
THEN +1 if rest is OK



4

many steps



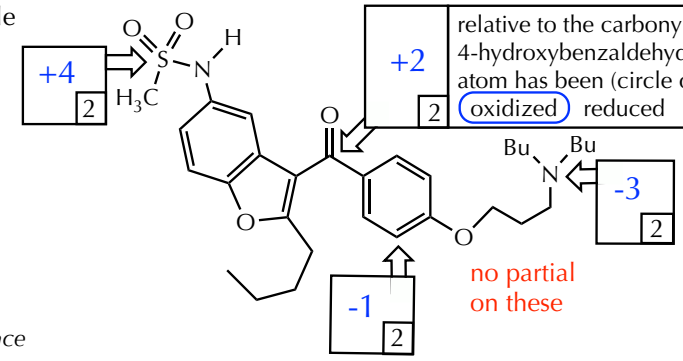
dronedarone (approved by the FDA in 2009 as a treatment for cardiac arrhythmia)

(c) What are the oxidation numbers for the four non-H atoms in dronedarone indicated here?

For your reference, a short table of electronegativity values:

atom	electronegativity
C	2.55
H	2.20
N	3.04
O	3.44
S	2.58

reminder: in assigning oxidation numbers, any difference in electronegativity is a real difference



+2
2

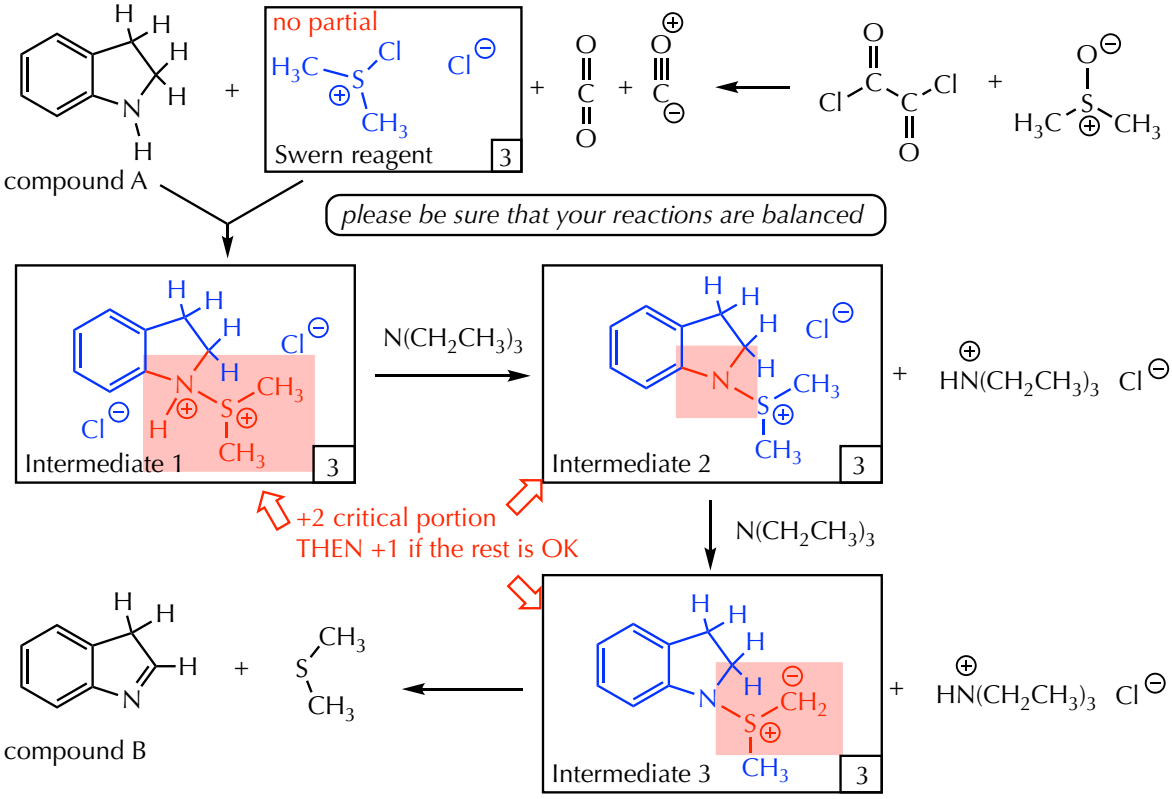
relative to the carbonyl group in 4-hydroxybenzaldehyde, this carbon atom has been (circle one):
oxidized reduced no redox 2

no partial on these

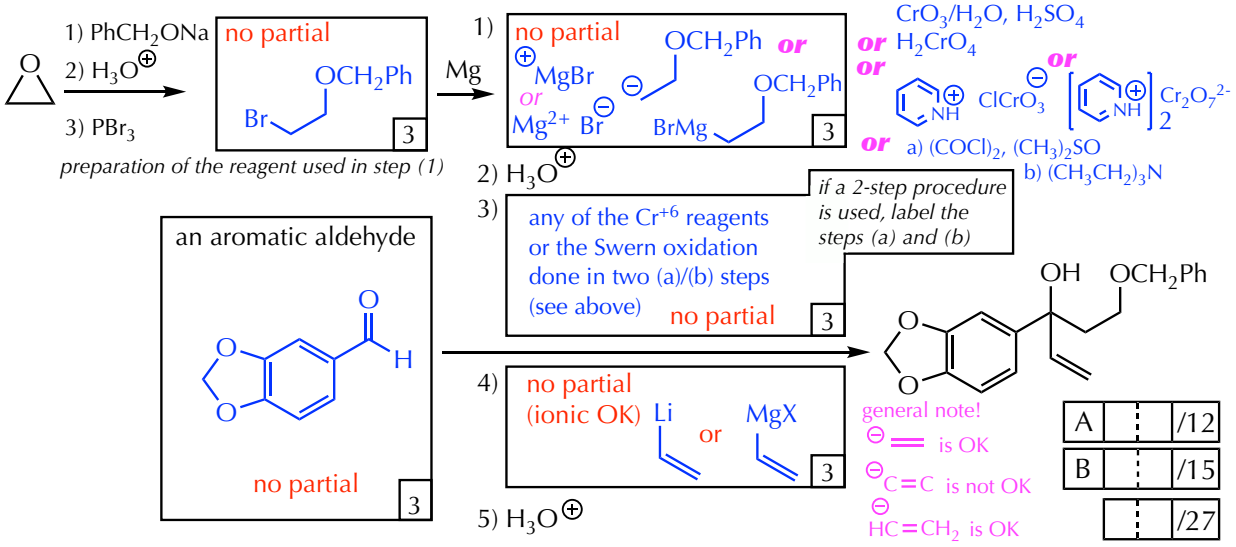
a		/06
b		/12
c		/10
		/28

Question II (27 points) Name: _____

A. In 1987, it was reported that amines, such as compound A, could undergo the Swern oxidation reaction, resulting in the formation of the corresponding imine (compound B). The oxidation reaction mechanism is proposed to take place through an analogous mechanism as the one with alcohols *(J Chem Soc Chem Commun*, **1987**, 1660). Provide the anticipated three intermediates in the mechanism of this oxidation reaction (no curved arrows needed, only the Swern reagent and the three intermediates). Paying attention to the byproducts shown in these **BALANCED EQUATIONS** can help guide you.



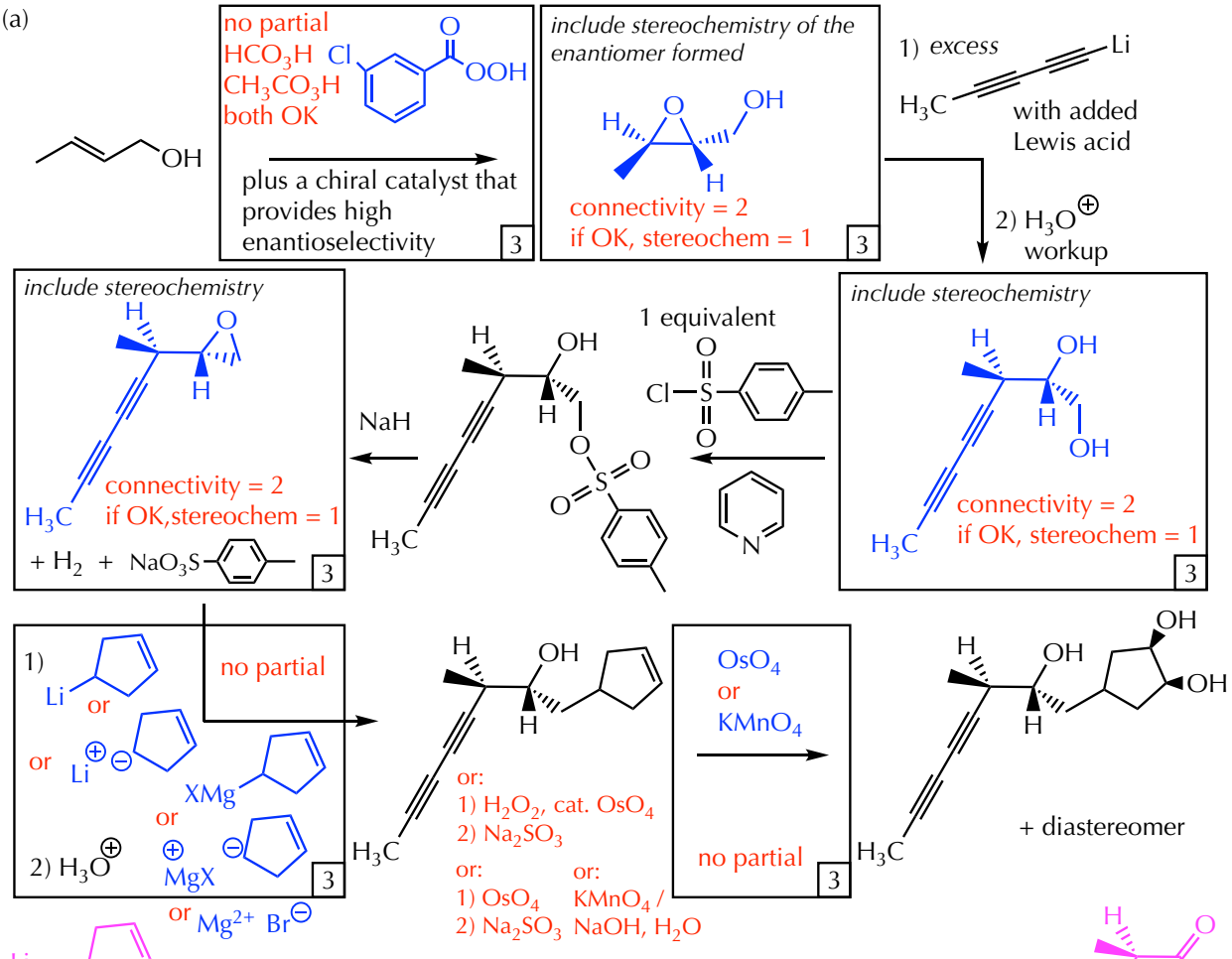
B. The following tertiary alcohol was prepared in 5 steps during the synthesis of a naturally occurring alkaloid named crinane. Provide the missing compounds used in the production of this alcohol.



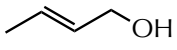
Question III (27 points) Name: _____

Complete the following organic transformations, used in a synthesis of rhizoxin D, an anticancer agent (*Angew Chem Int Ed*, **2019**, *131*, 254). **Using the available information backwards and forward is imporant for answering this question.** Draw out structures for reagents (no names, abbreviations, or acronyms).

(a)

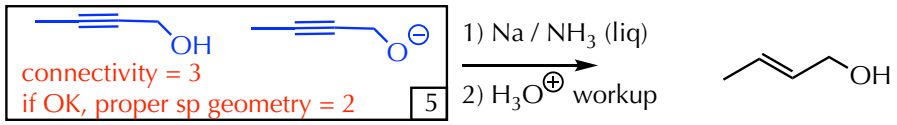


(b) What is the complete name for the starting material in this sequence?



(*E*)-but-2-en-1-ol or (*E*)-2-buten-1-ol
stereochem = 2; name = 2
OK (this time!) to exclude the hyphen after "(*E*)" 4

(c) What compound is used to prepare the starting material under these reaction conditions?

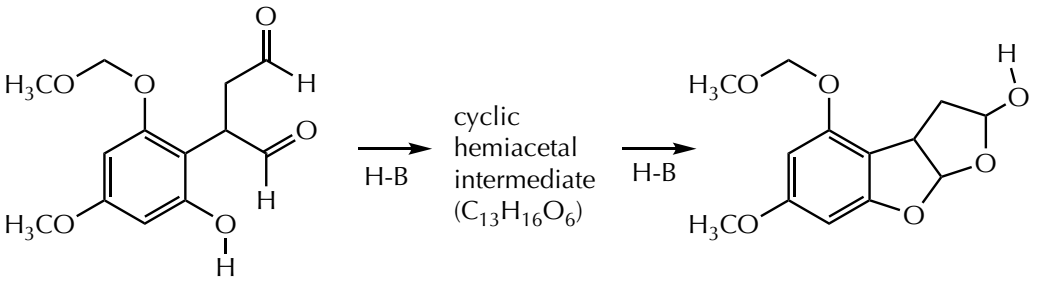


a		/18
b		/04
c		/05
		/27

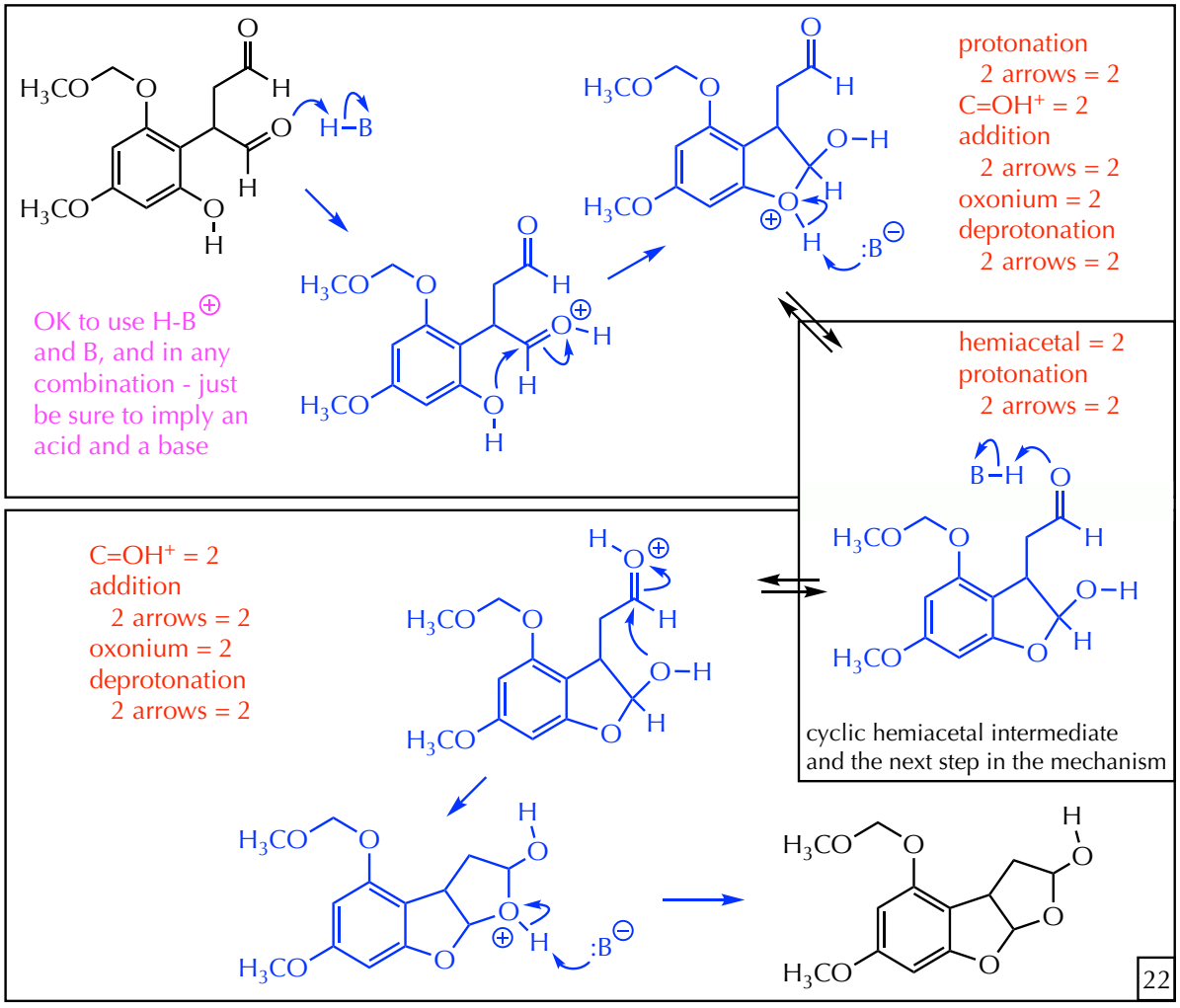
Question IV (22 points)

Name: _____

With a catalytic drop of HCl, compound C undergoes an isomerization reaction in which an intermediate with a cyclic hemiacetal forms, and then that intermediate gives compound D. Provide the complete, curved arrow mechanism for the acid catalyzed transformation of compound C to compound D. Use H-B as your generic Brønsted acid and B:⊖ as its conjugate base (*Org Lett*, **2021**, *23*, 2222).



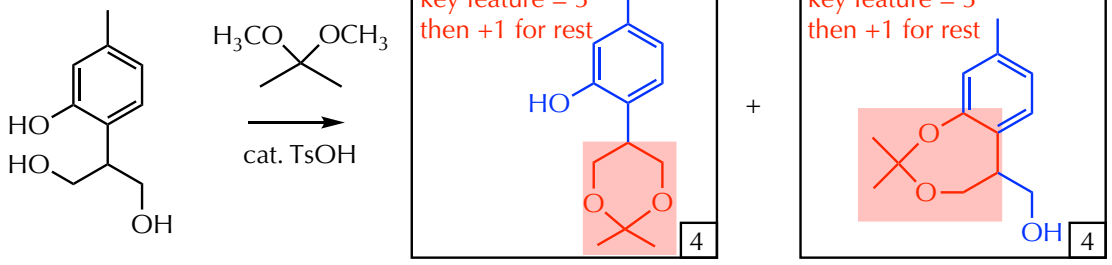
compound C ($C_{13}H_{16}O_6$) compound D ($C_{13}H_{16}O_6$)



/22

Question V (16 points) Name: _____

A. In principle, two different isomeric products could form in the following reaction (*Org Lett*, **2006**, *8*, 2479). Both products are $C_{13}H_{18}O_3$ and both reactions release two equivalents of methanol. Based on this information and the stereochemical descriptions provided below, what are the structures of the possible products?

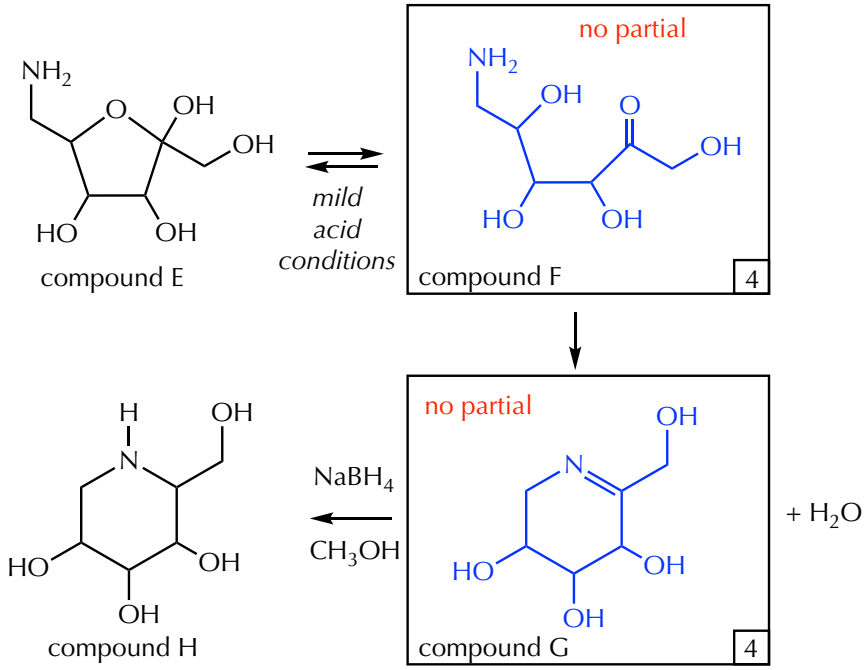


a single achiral compound
$C_{13}H_{18}O_3 + 2\ CH_3OH$

a racemic mixture
$C_{13}H_{18}O_3 + 2\ CH_3OH$

if in the wrong boxes, 2/4 each

B. The following reaction sequence was used in the synthesis of DGJ, a potential drug candidate for lysosomal storage disorders (*Org Lett*, **2011**, *13*, 4064). Under mild acid conditions, compound E exists in equilbrium with an open chain form containing a ketone (compound F) which, in turn, can recyclize to give a different compound (compound G) along with an equivalent of water. Compound G can be reduced ($NaBH_4$ in methanol) to give compound H, as shown. What are the structures for compounds F and G?



A		/08
B		/08
		/16