**Question 1 (47 points)**

**A.** Protocatechuic acid is a metabolic byproduct of antioxidants found in green tea and other plants, and itself possesses both antioxidant and anti-inflammatory properties (BioFactors 1998, 8, 111). Protocatechuic acid has three reported pKₐ values of 4.28, 8.70, and 13.0. These are assigned in the structure, below.

(a) Draw the dianion that is formed at pH 10 in which the aromatic ring is retained in the structure.

(b) Draw the one specific resonance contributor of this dianion that demonstrates why the proton at 8.70 is more acidic than the one at 13.0.

**B.** Rucaparib is a first-in-class pharmaceutical drug targeting a DNA repair enzyme as an anticancer treatment. Answer the following questions about the rucaparib structure.

(a) Rank the bond lengths for bonds A - E. no partial

(b) How many delocalizable electrons? 24 4 no partial

(c) How many aromatic rings? 3 4 no partial

(d) How many atoms with a "bent" observable geometry? 0 4 no partial

**C.** The following energy diagram derives from the electrophilic aromatic substitution reaction of methoxybenzene with a combination of chloromethane and AlCl₃ to give the two major products. Provide the structures for the three indicated locations (P, Q, & R).

**Dianion**

**Protocatechuic acid**

**Rucaparib**

**Reaction coordinate**
Tongalides are a class of compounds found in red alga near Australia (J. Nat. Prod. 2022, 85, 1886). One of the tongalides (compound C) is shown here. Answer the following questions about this structure.

B. Tongalides are a class of compounds found in red alga near Australia (J. Nat. Prod. 2022, 85, 1886). One of the tongalides (compound C) is shown here. Answer the following questions about this structure.

(a) What is the molecular formula of compound C?

(b) How many chiral diastereomers does compound C have?

(c) What is the stereochemical configuration of:

C. Based upon the best matches for pKₐ values, what is the Kₑₚ for the following reaction (see, eg, ACS Med. Chem. Lett. 2015, 6, 596)?

HO

CF₃

pKₐ 10

CA pKₐ 5.2

D. The following compound undergoes an intramolecular electrophilic addition reaction and follows the expected Markovnikov regioselectivity. What is the structure of the product, compound W, an achiral compound which has the same molecular formula as the starting material?

When the same starting material is treated with NBS (N-bromosuccinimide), and analogous reaction takes place, giving a racemic mixture of compound X, in which a new ring has formed that matches the one formed in compound W.

Kₑₚ = \frac{10}{-4.8}

\text{pKₐ} = 5.2

\text{connectivity 4}

\text{stereo 4}

\text{draw one of the enantiomers}
Question III  (53 points)

A. When the following compound undergoes a bond rotation, a favorable intramolecular hydrogen bond can form, creating a 6-atom ring that includes the hydrogen bond. In a single mechanistic step comprising three curved arrows, the molecule with the intramolecular hydrogen bond fragments, releasing an enol intermediate and carbon dioxide. The enol intermediate is immediately transformed into its more stable structural form. Provide three things: (a) the structure of the compound with the intramolecular hydrogen bond, (b) the 3-arrow mechanism for its transformation to the enol and CO$_2$, and (c) the structure of the more favorable form derived from the enol intermediate.

B. The connectivity for adrenaline (epinephrine) is shown below. The naturally occurring compound has the \((R)\)-configuration at its stereocenter. The lowest energy staggered conformation of the C1-C2 bond is stabilized by an intramolecular hydrogen bond. Complete the following Newman projection for this lowest energy conformation of the \((R)\)-stereoisomer of adrenaline (the hydrogen bond does not need to be shown).

C. Complete the following transformations.

(a) \textit{J. Org. Chem.} 2022, 87, 10114; creates a pair of C$_{10}$H$_{18}$O diastereomers, both chiral.

(b) \textit{Tetrahedron Lett.} 1995, 36, 6769; “selectfluor” is an electrophilic fluorinating agent used in EAS reactions.

(c) \textit{ACS Med. Chem. Lett.} 2021, 12, 1646.
Question IV (54 points)

A. Given the carvone derivative shown below (Tetrahedron Lett. 2004, 5039) as well as the abbreviated table of A-values, draw its most stable chair conformation. Include only the atoms/groups shown in the drawing below in your representation of the chair form.

B. When a solution of excess morpholine in dichloromethane (solvent) is combined with pentachlorocyclopropane, a remarkable reaction occurs within a few hours to give a complex ionic organic compound (Macromolecules 2018, 51, 1681). A resonance contributor of the structure shown below is used to explain why this unusually stable ionic compound forms. What is that resonance contributor and state briefly, in just a few words, what is the explanation?

C. Complete the following transformations.

(a)  

(b)  

the products of this reaction are (circle one):   identical  enantiomers  diastereomers  a mixture of chiral & achiral  

the products of this reaction are (circle one):   both chiral  both achiral  

| A | 1/16 |
| B | 1/10 |
| C | 2/28 |
| Total | 5/54 |
**Question V (41 points)**

The reactions between the interhalogen I-Cl (iodine monochloride) and alkynes result in the formation highly regioselective and stereoselective products (*J. Org. Chem.* 2003, 68, 10175).

\[
\begin{align*}
H_3C\overset{\text{I-Cl}}{\longrightarrow} & \overset{\text{CH}_2OH}{\longrightarrow} & H_3C \\
\end{align*}
\]

(a) Provide the complete, stepwise mechanism for this transformation.

(b) Select the fragments that, when assembled, would give the IUPAC name of the starting material. No partial credit.

\[
\begin{align*}
\text{(E)-3-chloro-2-iodobut-2-en-1-ol} & \\
\end{align*}
\]

(c) The starting material (\(H_3C\overset{\text{C\equivC\rightarrowCH}_2OH}\)) can be prepared from the compound shown below in three steps.

Step 1 forms a dianion intermediate (do not forget to use the pK\(_a\) table to guide your decision(s)).

Step 2 is a reaction in which selectivity is observed, and a mono-anion results.

Step 3 completes the transformation to give the neutral product, as shown.

If stoichiometry matters in the experimental step, be sure to indicate how many equivalents are needed.

\[
\begin{align*}
\text{step 1} & \quad \text{dianion intermediate} & \quad \text{step 2} & \quad \text{mono-anion intermediate} & \quad \text{step 3} \\
\text{2 equiv NaH} & \quad \text{2 equiv NaH} & \quad \text{1 equiv CH}_3\text{Br} & \quad \text{1 equiv or no indication} & \quad \text{H}_2\text{O}^+ \\
\text{(NaNH}_2\text{ etc)} & \quad \text{dianion = 4} & \quad \text{reagent = 2} & \quad \text{mono-anion = 4} & \quad \text{reagent = 4} \\
\text{reagent = 2} & \quad \text{dianion = 4 including 2 Na}^+ & \quad \text{1 equiv or no indication = 2} & \quad \text{no indication = 2} & \quad \text{no indication = 2} \\
\text{2 equiv = 2} & \quad \text{including 2 Na}^+ & \quad \text{is optional} & \quad \text{is optional} & \quad \text{is optional} \\
\end{align*}
\]