Question 1 (24 points)

A biologically active compound known as MK-1029 blocks a receptor that is involved in stimulating an allergic reaction associated with respiratory diseases (Org. Process Res. Dev. 2022, 26, 648). A few steps from a reported synthesis are included in this question.

(a) Complete the following.

(b) Later in the synthesis, the following reaction is carried out. The starting material, called an indole, has a pK_a value of about 16. Provide the complete, curved arrow mechanism.

2-arrow deprotonation = 3
N anion intermediate = 3
2-arrow intramol addition = 3
O anion intermediate = 3
2-arrow elimination = 3

if the addition and deprotonation steps are reversed but all is otherwise correct, then +9/15;
if only the O anion intermediate and its mechanism are correct, then +6/15 as already specified above
Question II (28 points)

Complete the following reaction schemes. Be sure to number different experimental steps if needed.

(a) synthesis of futibatinib, a fibroblast growth factor inhibitor (Org. Process Res. Dev. 2022, 26, 43)

(b) synthesis of 6-fluromenadione, an intermediate in the synthesis of biologically active agents (Org. Process Res. Dev. 2022, 26, 1152)

(c) from the preparation of pharmacophores, molecular units that are integrated into the synthesis of prospective drug targets (Org. Process Res. Dev. doi.org/10.1021/acs.oprd.2c00152)

(i) also OK: 1) SOCl₂, 2) CH₃OH

(ii) note: two functional groups are reduced to give a product with only uncharged atoms
Question III (28 points)

The acid and base catalyzed hydrolysis reaction of lactones was germane to a study on developing new therapeutics for a rare form of leukemia (Org. Process Res. Dev. 2022, 26, 2739).

(a) Provide the complete, stepwise mechanism for the acid catalyzed hydrolysis of the lactone (compound A) used in this study.

Use H-B as your general Brønsted acid and \( B^\ominus \) as a general Brønsted base.

Draw intermediates as their significant (closed shell) resonance contributors.

(b) Because of the net entropic disadvantage, the \( K_{eq} \) for the hydrolysis reaction, under the conditions shown above, was less than \( 10^{-2} \). Only one of the three other reaction conditions (shown below) gave a ring-opened product as the major outcome. Which set of conditions resulted in a ring-opened product? Draw the outcome.

(i) Which conditions (mark one) resulted in a ring-opened product as the outcome?

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Partial Credit</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOH in ( \text{H}_2\text{O} )</td>
<td>no</td>
</tr>
<tr>
<td>( \text{CH}_3\text{OK} ) in ( \text{CH}_3\text{OH} )</td>
<td>no</td>
</tr>
<tr>
<td>( \text{CH}_3\text{OH} ) with catalytic ( \text{H}_2\text{SO}_4 )</td>
<td>3</td>
</tr>
</tbody>
</table>

(ii) Draw the outcome. No credit if the incorrect conditions were selected.
Question IV (20 points)

Complete the following as required.


\[
\begin{align*}
&\text{Si} \quad \text{CH}_3 \\
&\text{CH}_3 \\
&1) \text{CuCN} \\
&2) \text{Li}^+ \\
&3) \text{H}_3\text{O}^+ \\
\end{align*}
\]


\[
\begin{align*}
&\text{H}_3\text{CO} \\
&\text{N(CH}_2\text{CH}_3)_3 \\
&\text{NH}_2 \\
&\text{O} \\
&\text{O} \\
&\text{OC(\text{CH}_3)_3} \\
&\text{H}_3\text{CO} \\
&\text{O} \\
&\text{N(CH}_2\text{CH}_3)_3 \\
&\text{NaBH}_4 \\
&\text{H}_3\text{CH} \\
&\text{OH} \\
&\text{Cl} \\
&\text{Cl} \\
&\text{H}_2\text{O}_2 \\
&\text{Zn or} \\
&\text{CH}_3\text{H}_2\text{S or} \\
&\text{H}_2\text{O}_2 \\
\end{align*}
\]

(c) *Org. Process Res. Dev.* doi.org/10.1021/acs.oprd.2c00200.

\[
\begin{align*}
&\text{H}_3\text{C} \\
&\text{H}_3\text{C} \\
&\text{O} \\
&\text{OCH}_3 \\
&\text{H}_3\text{C} \\
&\text{H}_3\text{C} \\
&\text{O} \\
&\text{OCH}_3 \\
&\text{C}_12\text{H}_{17}\text{NO}_3 \\
&\text{NaBH}_4 \\
&\text{CH}_3\text{OH} \\
\end{align*}
\]

Name: _______________________________
**Question V (20 points)**

Complete the following as needed.


\[
\begin{array}{c}
\text{critical ketone = 2} \\
\text{if OK, then +2} \\
\text{if rest OK}
\end{array}
\]


\[
\begin{array}{c}
\text{critical enolate (either geom) = 2} \\
\text{if OK, then +2} \\
\text{if rest OK}
\end{array}
\]

(c) *Org. Lett.* **2010**, *10*, 1763: an intramolecular aldol condensation

\[
\begin{array}{c}
\text{critical diketone = 2} \\
\text{if OK, then +2} \\
\text{if rest OK}
\end{array}
\]

Name: _______________________________