1. The incorporation of cyclic protecting groups at the C3/C5 and C9/C11 hydroxyl groups in erythronolide seco acid derivatives is thought to preorganize these molecules such that their conformation resembles that of the macrolactone. This preorganization has been shown by many researchers to be critical to the success of lactone formation. In his synthesis of (+)-9S-dihydroerythronolide A, Stork identified an additional requirement of the cyclic protecting group, e.g. that when C9/C11 is protected as an acetal, \( R_2 \) must be a hydrogen as shown in the examples below. In cases where \( R_2 = \text{Me} \), no cyclization is observed. Clearly explain the basis for this observation. Be specific.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>( R_1 )</th>
<th>( R_2 )</th>
<th>Macrocyclization</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{Me}</td>
<td>\text{Me}</td>
<td>no</td>
</tr>
<tr>
<td>\text{H}</td>
<td>\text{Me}</td>
<td>no</td>
</tr>
<tr>
<td>\text{Me}</td>
<td>\text{H}</td>
<td>yes</td>
</tr>
</tbody>
</table>

If preorganization required such that seco acid conformation must resemble that of the macrolactone, then must consider local conformation about C8-C11. Shows that is C9 & C11 alcohols are protected as the corresponding cyclic acetal, there is a 1,3-diaxial interaction between C8 and \( R_2 \) when \( R_2 = \text{Me} \). This steric interaction inhibits the seco acid from adopting the conformation required for cyclization so no macrolcyclization occurs. When \( R_2 = \text{H} \), the steric interaction is removed, appropriate preorganization of conformation can be achieved and macrolactonization occurs.

2. Show how you would carry out the following transformations in the most efficient manner and with the fewest side reactions. Show all intermediate products and reagents. Pay attention to issues of selectivity. Clearly depict any stereochemistry. Each of these sequences can be completed in 5 steps or less.

a. 

![Chemical Structure](image)
b.

\[
\begin{align*}
\text{b.} & \quad \text{trans/diaxial attack via iodonium intermediate} \\
\text{NaHCO}_3 & \quad \text{via iodonium intermediate} \\
\end{align*}
\]

hydride attack from convex face

S\text{N}2

a.

\[
\begin{align*}
\text{a.} & \quad \text{DIBAL} \\
\text{BF}_3 \cdot \text{OEt}_2 & \quad \text{propanedithiol} \\
\end{align*}
\]

\[
\begin{align*}
\text{e.} & \quad \text{OsO}_4 \cdot \text{NMO} \\
\end{align*}
\]
3. Design a concise, stereoselective synthesis for the following compound:

\[
\begin{align*}
\text{HO} & \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{OH} \\
\end{align*}
\]

a. Show two strategically different, but reasonable, retrosyntheses for the compound above that regress back to commercially available starting materials of 8 carbons or less. Your starting materials should cost less than $5/g and should be available from one of the following vendors: Aldrich, Acros, Alfa Aesar, AK Scientific, GFS, Matrix Scientific, Oakwood, Strem, TCI. As part of your answer, list the vendor and price of all starting materials. Your retrosyntheses should show only the C-C bond disconnections.

**retrosynthetic analysis 1**

\[
\begin{align*}
\text{HO} & \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{OH} & \quad \text{HO} & \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{OH} & + & \quad \text{H} & \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
50\text{g}, \$194 & \quad \text{Aldrich} & \quad 100\text{g}, \$224 & \quad \text{Aldrich} \\
\end{align*}
\]
b. Identify which of the two approaches you would use to make this molecule and clearly explain your reasoning. Be specific.

retrosynthetic analysis 1

RA 1 requires fewer C-C bond forming reactions and the SM are less expensive. Also RA 1 is likely to give the product stereochemistry more cleanly (the vinyl bromide required for RA 2 is readily available only as a mixture of stereoisomers).

c. Show your forward synthesis. Show the product of every step in your sequence, as well as the conditions required to complete each transformation in the manner desired (e.g. solvents, reagent equivalents, etc.). Clearly depict any stereochemistry. Justify any issues of selectivity.