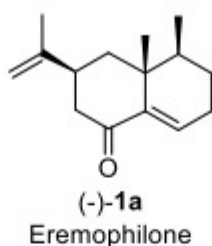
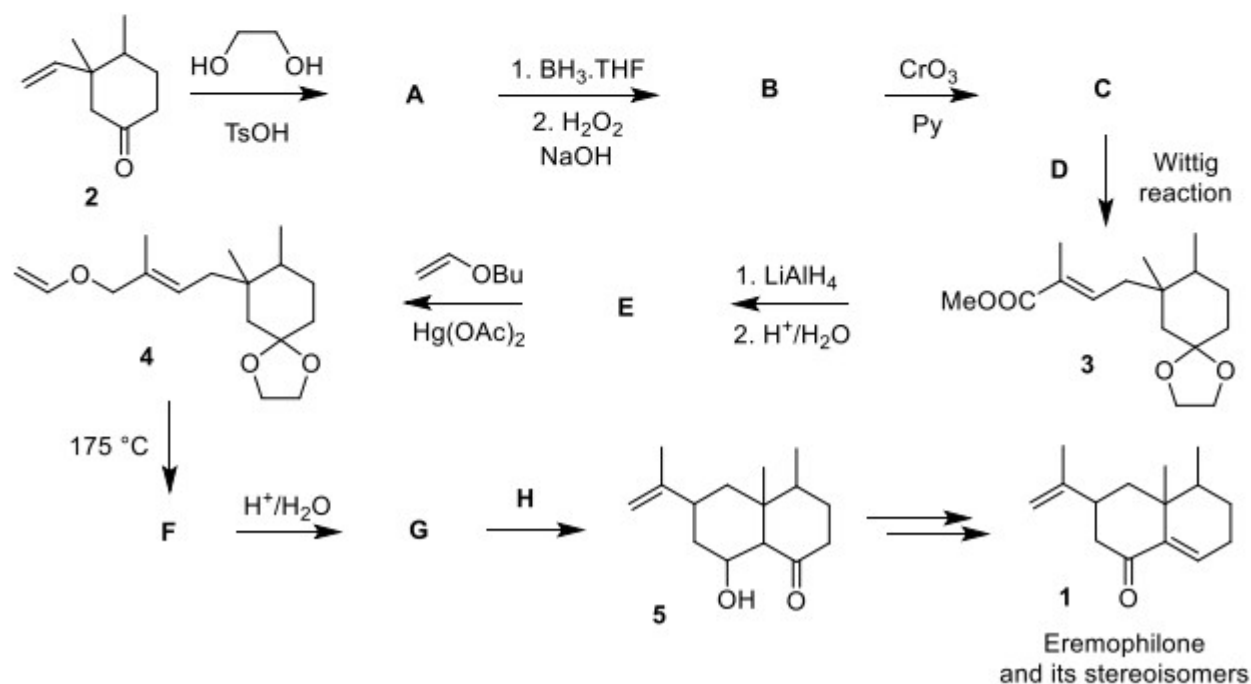


Problem 23. Synthesis of eremophilone

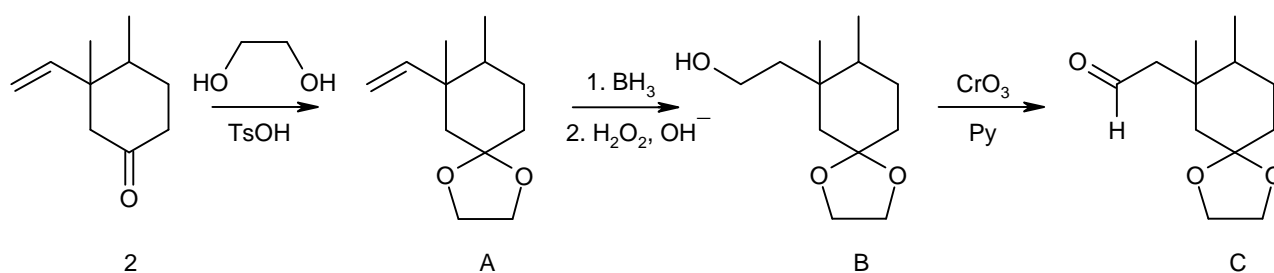
Eremophilone, (-)-**1a**, is a constituent of a commercially available oil with anti-inflammatory and relaxing properties, isolated from the Australian *Eremophila mitchellii* shrub (buddha wood).

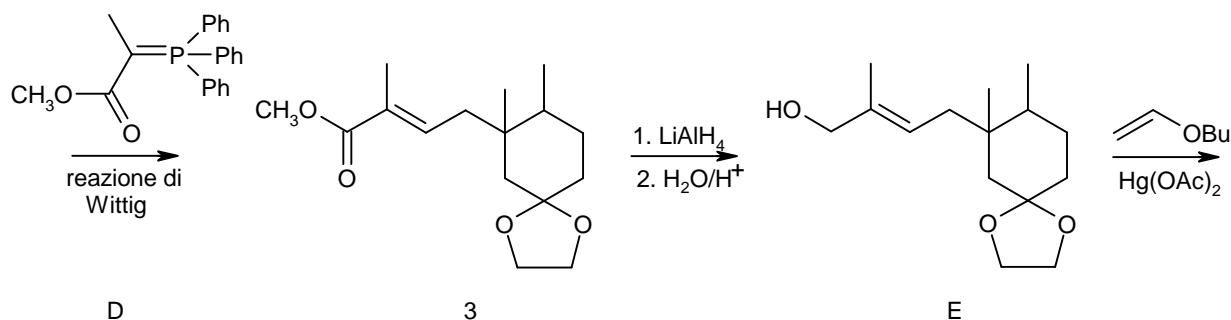


The synthesis of enantiomerically pure eremophilone is challenging due to the *cis*-configuration of the two methyl groups and the axial orientation of the isopropenyl group. The synthesis of the corresponding diastereomeric mixture **1** starts from ketone **2**, which is reacted with ethane-1,2-diol under acidic conditions to provide compound **A**, followed by regioselective reduction with a borane–THF complex. Oxidative work-up of the borane intermediate yields substance **B**. Its mild oxidation gives product **C**, which is reacted stereoselectively in the next step with an appropriate λ^5 -alkylenephosphane (ylide) **D** to furnish compound **3**. Its reduction leads to substance **E**, which reacts with butyl vinyl ether in the presence of mercury acetate to afford compound **4**. Heating of compound **4** results in its rearrangement to compound **F**, which, after deprotection, provides dioxo compound **G**. Final intramolecular aldolization using reagent **H** leads to bicyclic **5** as the key intermediate in the synthesis of eremophilone stereoisomeric mixture (**1**).

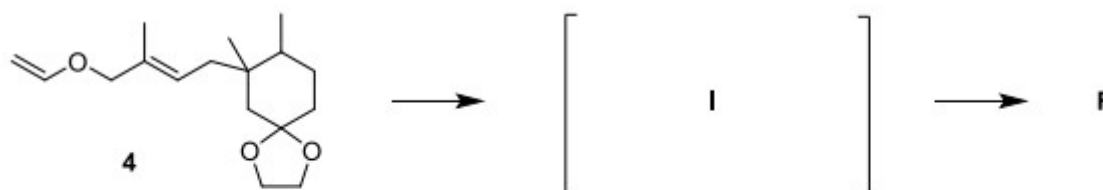


23.1 Draw the structures of the products and reagents **A–H**.

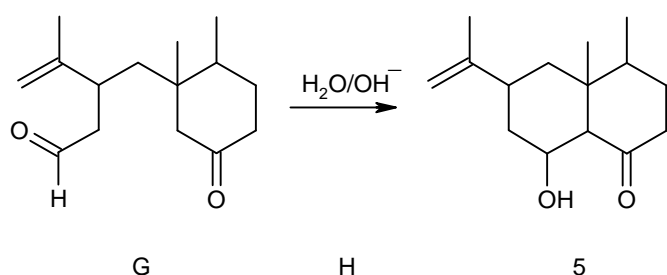
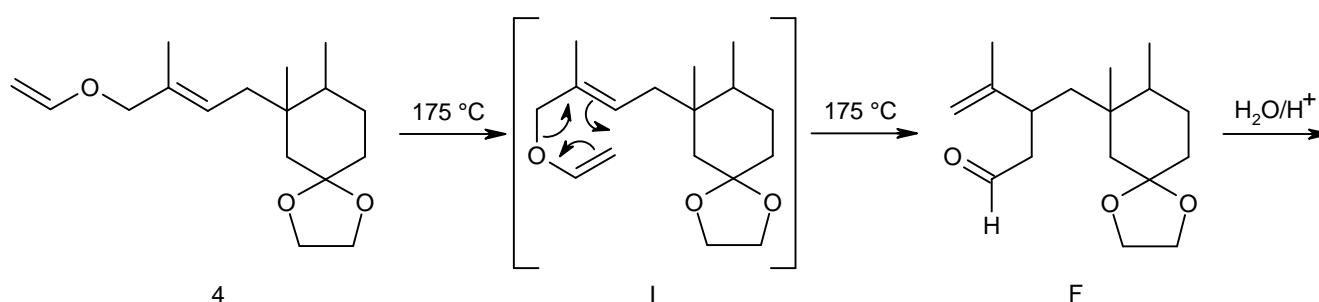




The key step in the synthesis is a thermal rearrangement of allylic vinyl ether **4**, leading to compound **F**. For the reaction to proceed, compound **4** must adopt appropriate orientation **I** to allow for the subsequent sigmatropic transformation.

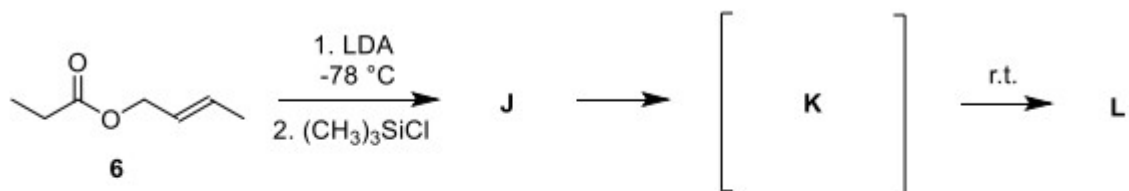


23.2 Draw the required orientation of the allylic vinyl ether moiety **I** in compound **4** that enables the sigmatropic transformation. Use curved arrows to show the flow of electrons in the rearrangement step that provides compound **F**. What is the name of the rearrangement? *Note:* You do not have to draw 3D structures.



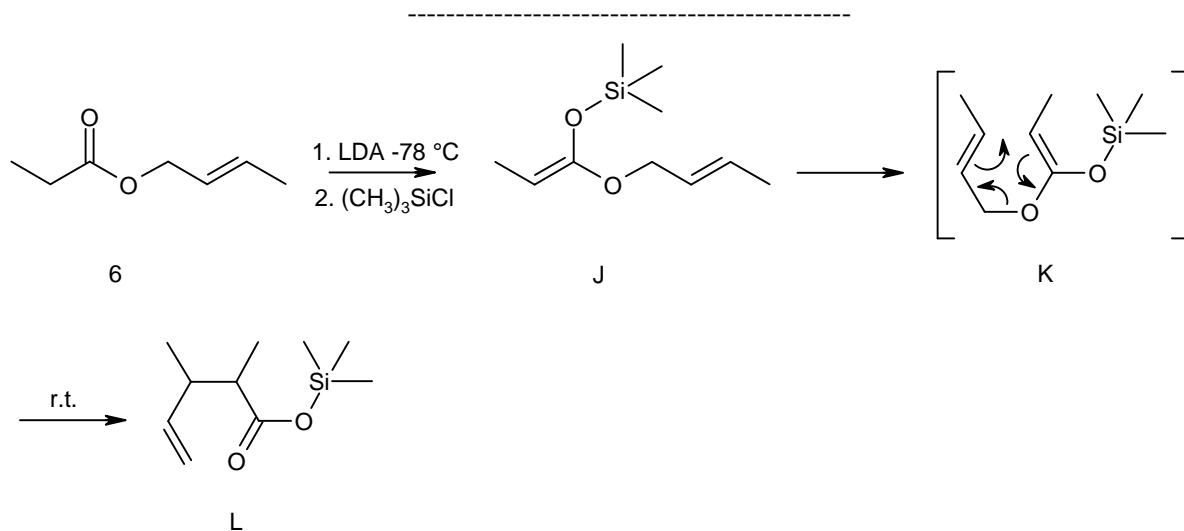
In **I** si ha un riarrangiamento alifatico di Claisen che è detto [3,3]-sigmatropico perchè il nuovo legame sigma si forma nelle posizioni 3 e 3 rispetto a quello che si rompe.

This rearrangement typically requires high temperatures, but this is not always an essential requirement. For example, allylic esters, e.g. ester **6**, can also undergo this transformation by first treatment with a strong non-nucleophilic base such as lithium diisopropylamide (LDA) at $-78\text{ }^\circ\text{C}$ to give the corresponding enolate. Subsequent trapping of the enolate with chlorotrimethylsilane yields silyl enol ether **J**. When allowed to warm to room temperature, substance **J** undergoes spontaneous rearrangement to substituted silyl ester **L** through conformation **K**.



23.3 Draw the structures of **J** and **L** and orientation **K** that enables the sigmatropic transformation to proceed. Use curved arrows to show the flow of electrons in the rearrangement step to compound **L**.

Note: You do not have to draw 3D structures.



Soluzione proposta da Mauro Tonellato – Padova