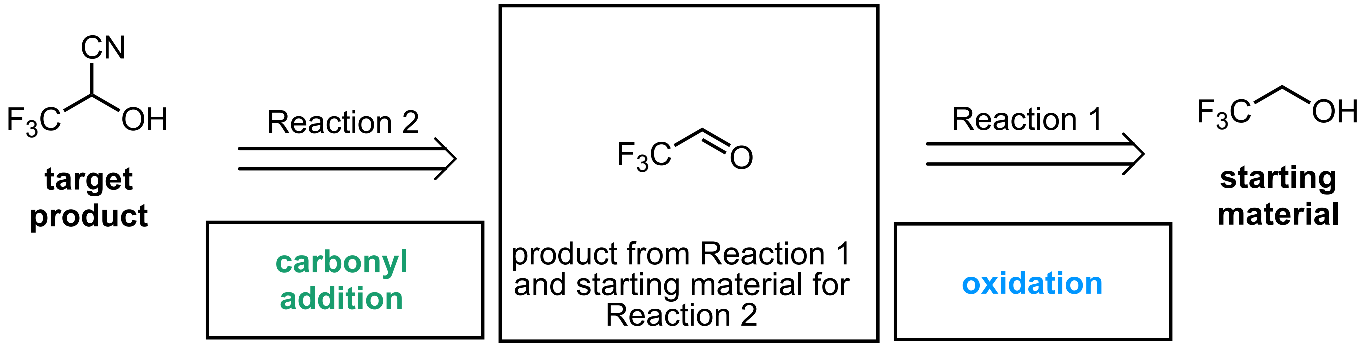
Retrosynthesis of Carbonyls and Carboxylic Acid Derivatives

1. **Perform a retrosynthetic analysis** on the target product using the template and guiding questions, labeled as parts A-E.



A. Has the **number of carbon atoms changed**?

Yes, one carbon was added.

B. Are there any **new functional groups**?

Yes. The added carbon is part of a new **nitrile functional group**.

C. What types of **precursor(s)** and **reaction(s)** could introduce the new carbon atoms and/or the new functional groups? (e.g. carbonyl addition, carbonyl substitution, reduction/oxidation, etc.…).

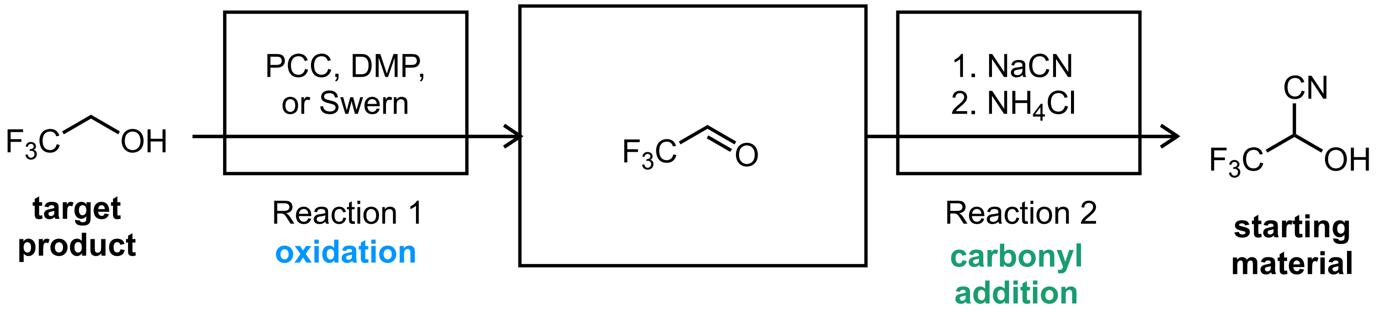
Nitriles can be added through the addition of a cyanide nucleophile to a ketone or aldehyde.

D. Finally, **what order of these reactions** is needed to achieve the target final product?

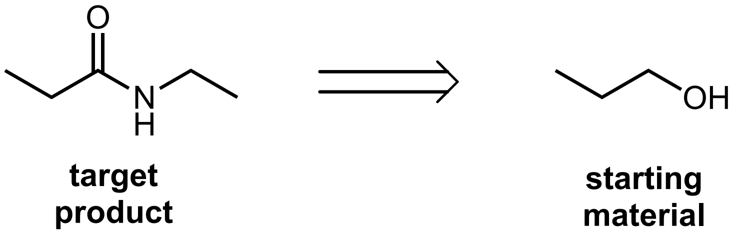
To enable the carbonyl addition reaction that incorporates the nitrile, we need to first from our carbonyl electrophile through an oxidation reaction.

Working backwards, fill in the boxes above (retrosynthesis).

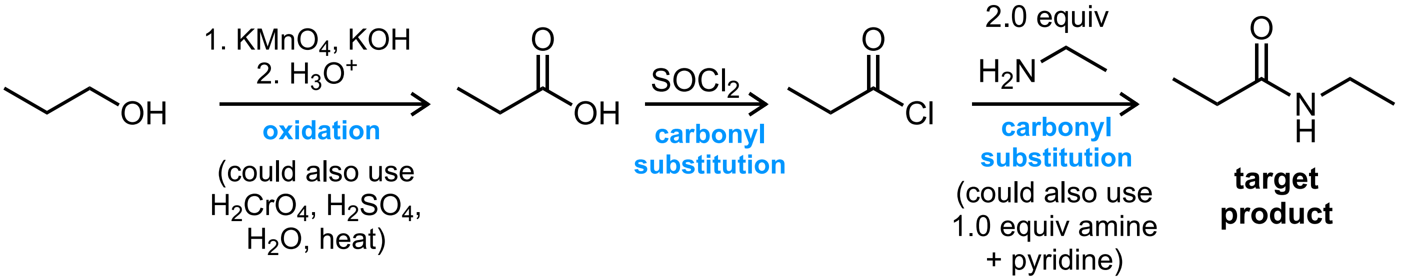
Finally, use the answers to your questions above to **propose a full forward synthesis** associated with your proposed retrosynthesis.



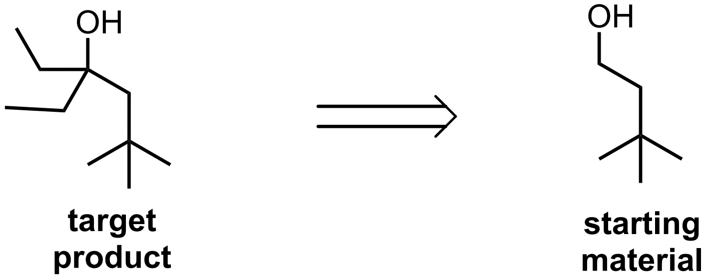
2. **Propose a successful forward synthetic route** for the formation of the shown target final product from the shown initial starting material.



We are given a 3-carbon alcohol (propan-1-ol) as a starting material but have a amide product, which is a carboxylic acid derivative. This suggests we need to first convert our alcohol to a carboxyylic acid, *then* prepare the amide from the carboxylic acid.

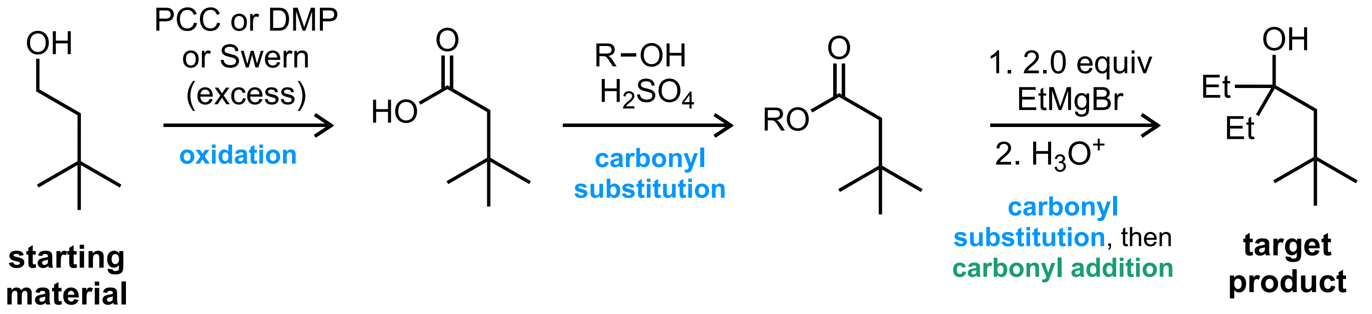


3. **In three steps or less, propose a successful forward synthetic route** for the formation of the shown target final product from the shown initial starting material.

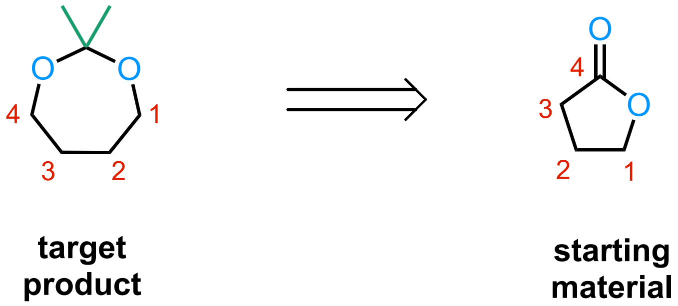


Two new ethyl groups have been added. This can be achieved through a carbonyl substitution and subsequent carbonyl addition reaction when using two equivalents of ethylmagnesium bromide (Grignard) andan ester.

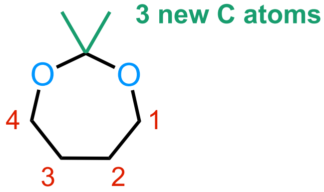
Thus, we must first transform the starting alcohol into an ester. We can obtain the ester through oxidation of the alcohol starting material to the carboxylic acid, followed by Fischer esterification.



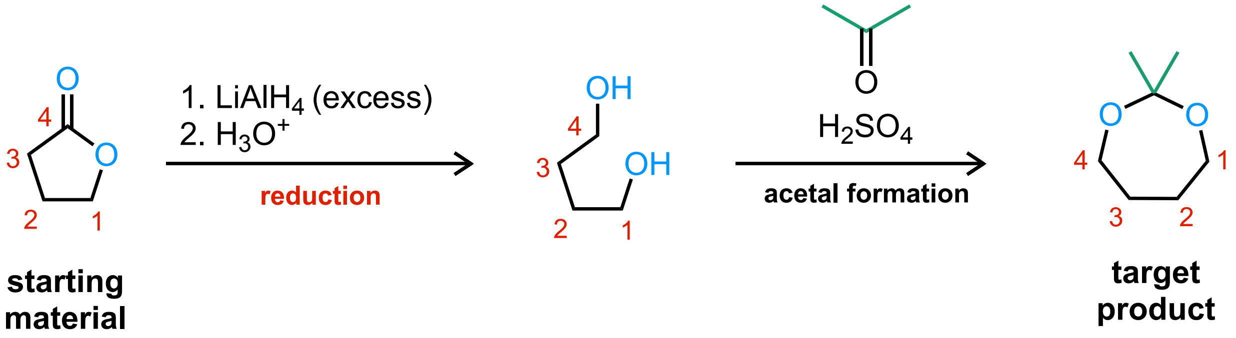
4. **Propose a successful forward synthetic route** for the formation of the shown target final product from the shown initial starting material.



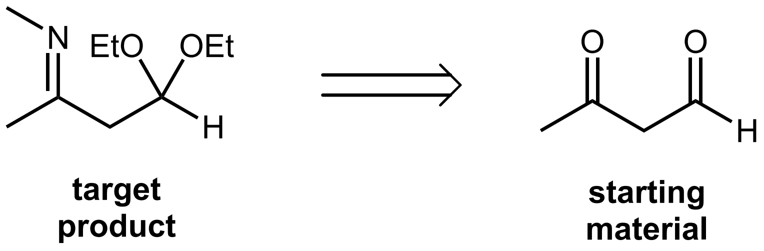
Three new carbons have been added in the form of a cyclic acetal group. This can be achieved through a carbonyl substitution reaction that utilizes a diol (di-alcohol) reacting with a ketone under acidic conditions.



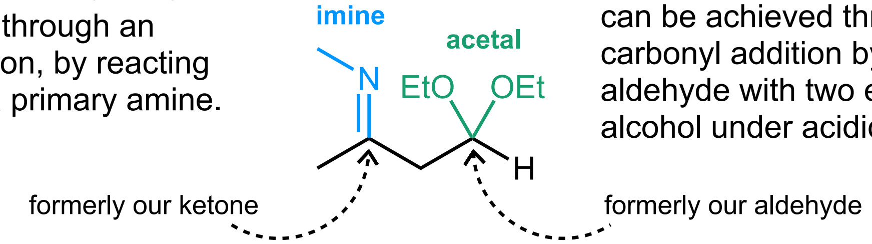
Based on this analysis, it seems that the two oxygen atoms in our starting material ultimately reacted as a diol with a carbonyl electrophile to form the cyclic acetal in the product.



5. **Propose a successful forward synthetic route** for the formation of the shown target final product from the shown initial starting material.



Our starting ketone has been trasformed into an imine. This can be achieved through an imine condensation, by reacting the ketone with a primary amine.



Our starting aldehyde has been transformed into an acetal. This can be achieved through a carbonyl addition by reacing the aldehyde with two equivalents of alcohol under acidic conditions.

Notice that there are two carbonyl addition reactions that need to take place here. **Both ketones and aldehydes can undergo similar carbonyl addition reactions**. To selectively react the ketone (less electrophilic than aldehyde) in the presence of the aldehyde, we must ***first*** "protect" the aldehyde as the acetal. Then, and only then, can we selectively form our imine using the ketone electrophile.