Syntheses based on diethyl malonate, ethyl acetoacetate, etc.
Using diethyl malonate and any other necessary organic reagents, show a synthesis of:

a) 2,2-dimethyl-1,3-propanediamine
Retrosynthetic analysis

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{2} & \quad \text{2} \\
\text{N} & \quad \text{N} \\
\text{NH} & \quad \text{NH} \\
\text{2} & \quad \text{2}
\end{align*}
\]

– amine comes from amide; amide derives easily from ester; this reveals itself to be a simple diethyl malonate alkylation followed by functional group transformations:

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{EtO} & \quad \text{EtO} \\
\text{NaOEt} & \quad \text{NaOEt} \\
\text{MeI} & \quad \text{MeI} \\
\text{NH}_3 & \quad \text{NH}_3 \\
\Delta & \quad \Delta \\
\text{EtOH} & \quad \text{EtOH} \\
\text{EtOH} & \quad \text{EtOH}
\end{align*}
\]

– note that you cannot hydrolyze diester to diacid to then make the amide as you will get decarboxylation.

b) 4-methyl-5-nonanone
Retrosynthetic analysis:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{EtO} & \quad \text{EtO} \\
\text{NaOEt} & \quad \text{NaOEt} \\
\text{MeI} & \quad \text{MeI} \\
\text{H}_3\text{O}^+ & \quad \text{H}_3\text{O}^+ \\
\text{EtOH} & \quad \text{EtOH}
\end{align*}
\]

– given that we are starting with ester functionalities, the ketone should be derived from the reaction of an acid plus an organolithium; this then comes back to di-alkylation and decarboxylation:

c) N,N,2-trimethylhexylamine
Retrosynthetic analysis:

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{EtO} & \quad \text{EtO} \\
\text{NaOEt} & \quad \text{NaOEt} \\
\text{MeI} & \quad \text{MeI} \\
\text{Li} & \quad \text{Li} \\
\text{Et}_2\text{O} & \quad \text{Et}_2\text{O} \\
\text{H}_3\text{O}^+ & \quad \text{H}_3\text{O}^+ \\
\text{EtOH} & \quad \text{EtOH}
\end{align*}
\]

– this combines what we learned in a) and b) – amine from amide, amide from acid, acid by
decarboxylation of diester, and previous dialkylation of malonate:

$$\text{EtO} \quad \text{OEt} \quad \text{NaOEt} \quad \text{EtOH} \quad \text{MeI} \quad \text{EtO} \quad \text{OEt} \quad \text{NaOEt} \quad \text{EtOH} \quad \text{I} \quad \text{EtO} \quad \text{OEt}$$

$$\Delta \quad \text{H}_3\text{O}^+ \quad \text{H}_2\text{O} \quad \text{H}_2\text{O} \quad \text{EtOH} \quad \text{Δ} \quad \text{H}_3\text{O}^+ \quad \text{EtOH}$$

Using ethyl acetoacetate and any other necessary organic reagents, show a synthesis of:

**a) 4-phenyl-2-butanone**

Retrosynthetic analysis: for any synthesis from ethyl acetoacetate, you must first look for the propanone unit:

$$\text{O} \quad \text{Ph} \quad \equiv \quad \text{O} \quad \text{Ph} \quad \quad \equiv \quad \text{O} \quad \text{E} \quad \quad \quad \text{Br} \quad \text{Ph}$$

- the first three carbons of the butanone arise from the acetoacetate [after decarboxylation] and therefore the other methylene plus the phenyl [i.e. a benzyl group] must be added by alkylation:

$$\text{EtO} \quad \text{OEt} \quad \text{NaOEt} \quad \text{EtOH} \quad \text{Ph} \quad \text{Br} \quad \text{EtOOC} \quad \text{NaOEt} \quad \text{EtOH}$$

**b) 3-ethyl-2-pentanone**

Retrosynthetic analysis:

$$\text{O} \quad \text{Et} \quad \equiv \quad \text{O} \quad \text{Et} \quad \quad \equiv \quad \text{O} \quad \text{E} \quad \quad \quad \quad \text{E} \quad \quad \text{EtOOC}$$

- a double alkylation and decarboxylation
c) 3-benzyl-5-hexen-2-one

Retrosynthetic analysis is the same as part b:

\[
\begin{align*}
\text{COOEt} & \quad \text{EtOH} \quad \text{NaOEt} \quad \text{Br} \quad \text{EtOOC} \\
\text{EtOH} & \quad \text{NaOEt} \quad \text{Ph} \quad \text{Br} \\
\Delta & \quad \text{H}_2\text{O}^+ \\
\end{align*}
\]

The two compounds shown below can be synthesized using these type of processes. Beginning with bromobenzene and alcohols or esters of five carbons or less, show how they may be made.

Retrosynthetic analysis on the cyclopentene derivative should suggest that the a, ß-unsaturated ketone was the result of an intramolecular Aldol; this leads to a diketone which has two propanone units at either end – it should therefore be possible to produce it through a coupling as shown:

\[
\begin{align*}
\text{O} \quad \text{O} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{O} \\
\end{align*}
\]

Therefore:

\[
\begin{align*}
2 \text{COOEt} & \quad \text{EtOH} \quad 2 \text{NaOEt} \quad \text{Br} \quad \text{Br} \\
\text{COOEt} & \quad \text{EtOH} \quad \text{NaOEt} \quad \Delta \\
\end{align*}
\]

In the retrosynthetic analysis of the second target, it is important to realize that it is a hydrocarbon – in other words there is no functional group but the benzene ring. We are therefore going to have to remove whatever functionality is left after our synthesis. It is also important to realize that, since bromobenzene cannot be used in an alkylation reaction [the C-Br bond is too strong and the bromine is therefore not a good leaving group in this molecule], we must introduce the phenyl unit in some other fashion. The easiest route that we know of is via an organometallic reaction, and so our analysis becomes the following:

\[
\begin{align*}
\text{Ph} & \quad \text{Ph-Li} \\
\text{O} & \quad \text{O} \\
\text{E} & \quad \text{Br} \\
\end{align*}
\]
Now: how to remove the OH? If it were primary or secondary, we could oxidize it to a carbonyl and then reductively remove it with a Clemmensen, Wolff-Kischner, or through a dithiane. It is, however, tertiary, and so we need a different route. There are two easy possibilities:

via a dehydration:

![Dehydration Reaction](image)

[it does not matter if isomers may be formed since you are reducing out the alkenes anyway]

through a tosylate

![Tosylate Reaction](image)

[tosylates are excellent leaving groups, and may be displaced by hydride].

**Syntheses based on Aldol or Claisen or related condensations**

The compound shown below is readily prepared from an intramolecular Claisen [Dieckmann] reaction. What starting material would be used?

We need to remember that the product of any coupling reaction between two esters [Claisen or Dieckmann] is a β-ketoester. Therefore, add an ester to a β-position, then cleave the bond between the α-position and the carbonyl to get back to the diester starting material:

![Aldol Reaction](image)

**And lastly, two for the road:**

You have available benzyl bromide [PhCH₂Br] and any other necessary organic reagents. Show how each of the following may be synthesized:

a) **PhCH₂CH₂COCH₂CH₂Ph**

Retrosynthetic analysis: the easiest thing is to disconnect such that benzyl units are required. This
gives a propanone equivalent as shown here:

We know how to add the right hand benzyl unit, but how to do the left one? The answer is fairly simple – as shown on p 688, reaction of the monoanion [which we know how to produce] with a second equivalent of a stronger base will produce a dianion – the second H abstracted must come from the “outside” methyl position, and if we now have a dianion we can di-alkylate:

If we now add one mole of an alkyl halide, it will specifically react at the outside position; a second [and possibly different] alkyl halide would then react at the centre position. Here we do not care, as both groups to be added are the same.

b) PhCH₂COCH₂Ph
Retrosynthetic analysis:

The key here is to recognize that, since the benzyl unit is ending up on a carbonyl carbon, it must be negative in character rather than positive - in other words, we will want to use an organometallic rather than the halide itself. The “CO” component may be either CO₂ or ‘CN, since we know that both the acid and the nitrile may be used to synthesize ketones.

As the first step then:

and then the final condensation: