Enolates of β-Dicarbonyl Compounds:

Hydrogen atoms that are between two carbonyl groups, as in a β-dicarbonyl compound, have pKa values in the range of 9–11. Such a-hydrogen atoms are much more acidic than a hydrogens adjacent to only one carbonyl group, which have pKa values of 18–20.

The reason for that is:
Two specific b-dicarbonyl compounds have had broad use in organic synthesis. These are acetoacetic ester (ethyl acetoacetate, ethyl 3-oxobutanoate), which can be used to make substituted acetone derivatives, and diethyl malonate (diethyl 1,3-propanedicarboxylic acid), which can be used to make substituted acetic acid derivatives.
Synthesis of Methyl Ketones: The Acetoacetic Ester Synthesis

Acetoacetic ester, because it is a $\beta$-dicarbonyl compound, can easily be converted to an enolate using sodium ethoxide. We can then alkylate the resulting enolate (called sodioacetoacetic ester) with an alkyl halide. This process is called an acetoacetic ester synthesis.

\[
\begin{align*}
\text{Acetoacetic ester} & \xrightleftharpoons{\text{EtONa}} \quad \text{Sodioacetoacetic ester} \\
+ R-X & \rightarrow \quad \text{Monoalkylacetoacetic ester} + \text{NaX}
\end{align*}
\]

Since the alkylation in the reaction above is an SN2 reaction, the best yields are obtained from the use of primary alkyl halides (including primary allylic and benzylic halides) or methyl halides. Secondary halides give lower yields, and tertiary halides give only elimination.
Dialkylation:

The monoalkylacetoacetic ester shown above still has one appreciably acidic hydrogen, and, if we desire, we can carry out a second alkylation.

Because a monoalkylacetoacetic ester is somewhat less acidic than acetoacetic ester itself due to the electron-donating effect of the added alkyl group, it is usually helpful to use a stronger base than ethoxide ion for the second alkylation. Use of potassium tert-butoxide is common because it is a stronger base than sodium ethoxide. Potassium tert-butoxide, because of its steric bulk, is also not likely to cause transesterification.
Substituted Methyl Ketones:

To synthesize a monosubstituted methyl ketone (monosubstituted acetone), we carry out only one alkylation. Then we hydrolyze the monoalkylacetoacetic ester using aqueous sodium or potassium hydroxide.

Subsequent acidification of the mixture gives an alkyl-acetoacetic acid, and heating this β-keto acid to 100°C brings about decarboxylation.
If our goal is the preparation of a disubstituted acetone, we carry out two successive alkylations, we hydrolyze the dialkylacetoacetic ester that is produced, and then we decarboxylate the dialkylacetoacetic acid.

An example of this procedure is the synthesis of 3-butyl-2-heptanone

Although both alkylations in the example just given were carried out with the same alkyl halide, we could have used different alkyl halides if our synthesis had required it. As we have seen, ethyl acetoacetate is a useful reagent for the preparation of substituted acetones (methyl ketones) of the types shown below.
Show how you would use the acetoacetic ester synthesis to prepare 2-pentanone.

**STRATEGY AND ANSWER**

*Retrosynthetic Analysis*

\[
\text{EtCOCH}_2 + \text{CO}_2 \quad \Rightarrow \quad \text{EtCOCH(OH)OCOR} \quad \Rightarrow \quad \text{EtCOOCR} \quad \Rightarrow \quad \text{EtCOOCR}
\]

**Synthesis**

\[
\begin{align*}
\text{EtCOOCR} & \quad \xrightarrow{(1) \text{NaOEt}} \quad \text{EtCOCH(OH)OCOR} \\
& \quad \xrightarrow{(2) \text{Br}} \quad \text{EtCOOCR} \\
& \quad \xrightarrow{(2) \text{H}_2\text{O}^+} \quad \text{EtCOOCR} \\
& \quad \xrightarrow{\text{heat}} \quad \text{EtCOCH(OH)OCOR} + \text{CO}_2
\end{align*}
\]
The acetoacetic ester synthesis can also be carried out using halo esters and halo ketones. The use of an α-halo ester provides a convenient synthesis of γ-keto acids:

\[
\text{OEt}\quad \text{OEt} \quad \text{OEt}
\]

\[
\begin{align*}
\text{OEt} & \quad \text{OEt} \\
\text{(1) aq, HO}^- & \\
(2) \text{H}_3\text{O}^+ & \\
\text{OEt} & \quad \text{OEt}
\end{align*}
\]

4-Oxopentanoic acid (a γ-keto acid)
Decarboxylation of Carboxylic Acids:

- Carboxylic acids that have a carbonyl group one carbon removed from the carboxylic acid group, called β-keto acids, decarboxylate readily when they are heated to 100–150°C. Some β-keto acids even decarboxylate slowly at room temperature.

\[
\text{A } \beta\text{-keto acid} \xrightarrow{100-150^\circ C} \text{R} + \text{CO}_2
\]

There are two reasons for this ease of decarboxylation:

1. When the acid itself decarboxylates, it can do so through a six-membered cyclic transition state:

\[
\begin{align*}
\text{β-Keto acid} & \xrightarrow{-\text{CO}_2} \text{Enol} \\
& \xrightarrow{\text{H}^+} \text{Ketone}
\end{align*}
\]

This reaction produces an enol directly and avoids an anionic intermediate. The enol then tautomerizes to a methyl ketone.

2. When the carboxylate anion decarboxylates, it forms a resonance-stabilized anion:

\[
\begin{align*}
\text{Acylacetate ion} & \xrightarrow{-\text{CO}_2} \text{Resonance-stabilized anion} \\
& \xrightarrow{\text{HA}} \text{structure}
\end{align*}
\]

This type of anion, which we shall study further in chapter 19, is much more stable than simply RCH$_2$\(^{-}\), the anion that would have been produced by decarboxylation in the absence of a β-carbonyl group.