

# 23

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## Aldehydes and ketones: nucleophilic addition and $\alpha$ - substitution reactions

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### Answers to worked examples

#### WE 23.1 Reduction of an aldehyde (on p. 1059 in *Chemistry*<sup>3</sup>)

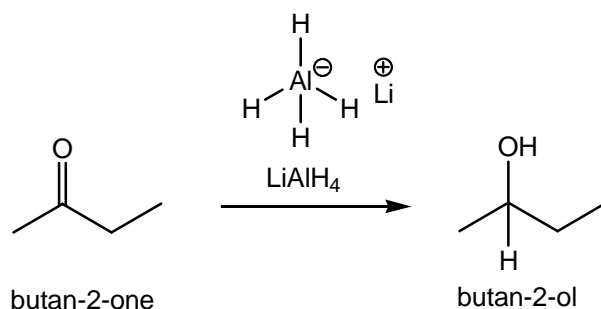
The organic product of the reaction of butan-2-one with  $\text{LiAlH}_4$  followed by aqueous acid is butan-2-ol. Give a mechanism for this reaction.

#### Strategy

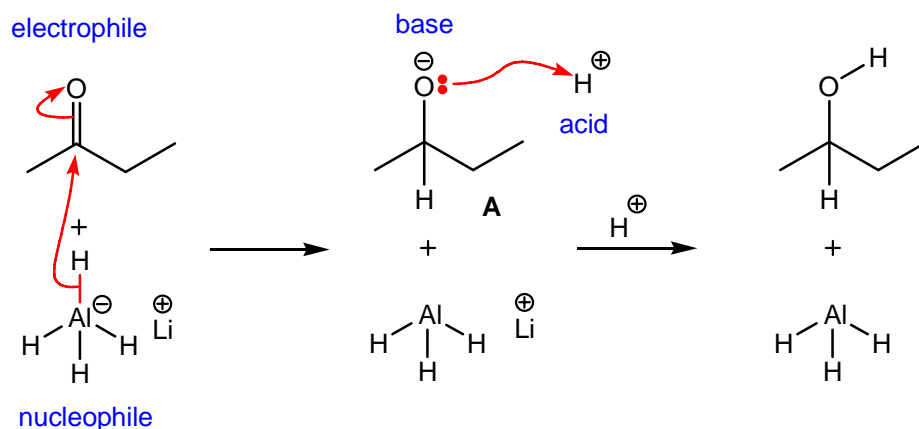
Draw out the starting materials, butan-2-one and  $\text{LiAlH}_4$ , and product, butan-2-ol. For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid ( $\rightarrow$ ).

#### Solution

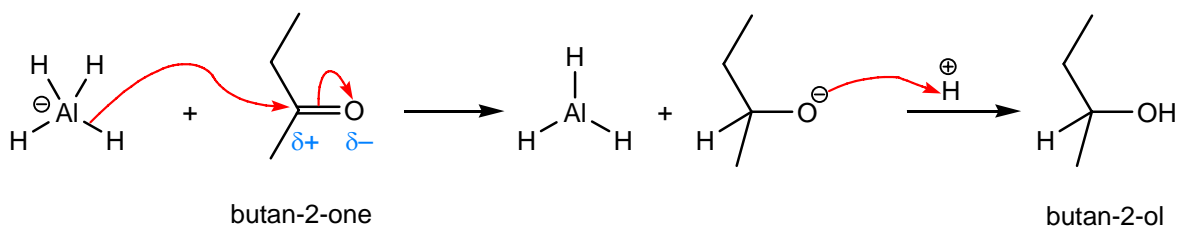
The structures of the starting materials and product are shown below.



LiAlH<sub>4</sub> is a nucleophilic source of hydride, and the ketone, butan-2-one, is the electrophile. Nucleophilic addition of hydride, from the high energy Al-H bonds, to the electrophilic carbonyl (C=O) group of butan-2-one gives the intermediate lithium alkoxide **A** and alane (AlH<sub>3</sub>). [These intermediates can add together to form the corresponding –ate complex if you wish]. Protonation of this intermediate base, lithium alkoxide **A**, with aqueous mineral acid (HCl/H<sub>2</sub>O) gives the required product, butan-2-ol. Butan-2-ol is a secondary alcohol, and the overall reaction is a reduction. The mechanism is shown below, and is discussed on p. 1055 in *Chemistry*<sup>3</sup>.



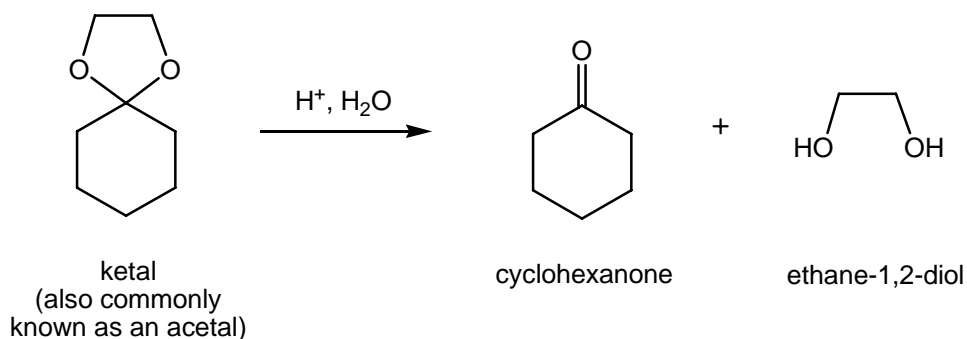
Answer



[This protonation step can also be depicted using a negative charge instead of a non-bonded pair of electrons.]

### WE 23.3 Acetal formation (on p. 1067 in *Chemistry*<sup>3</sup>)

Give a mechanism to show how the ketal is converted back into cyclohexanone and ethane-1,2-diol using  $H^+/H_2O$ .

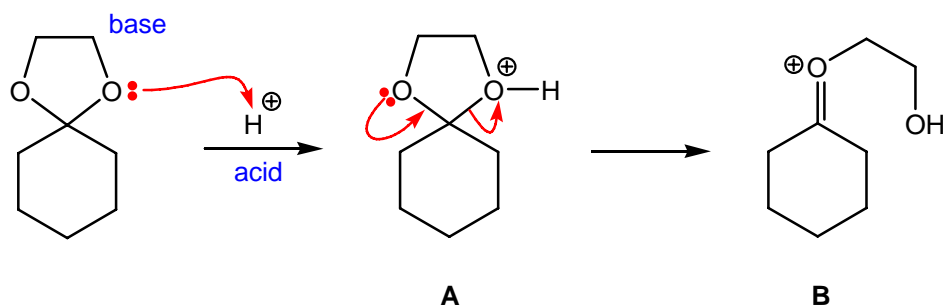


#### Strategy

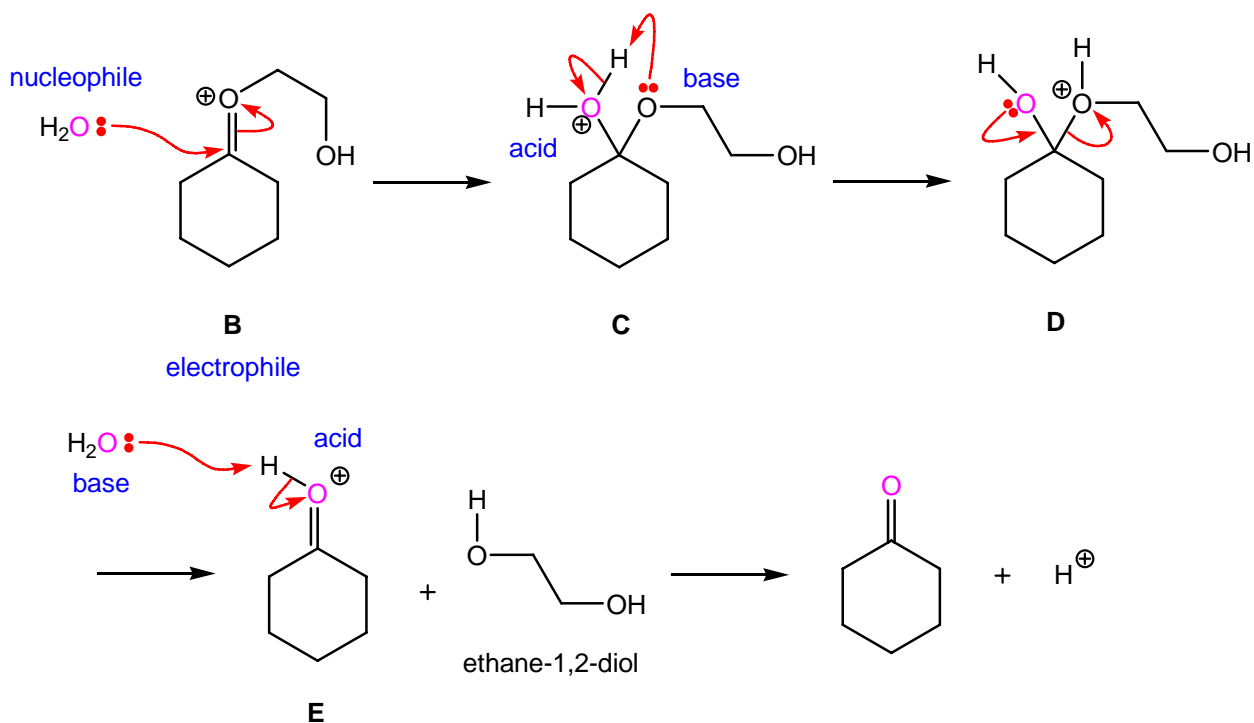
This reaction and its associated mechanism are simply the reverse of that outlined in the worked example 23.3. Remember the oxygen atom of the carbonyl group of cyclohexanone is derived from water ( $H_2O$ ). For each step, within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid ( $\rightarrow$ ).

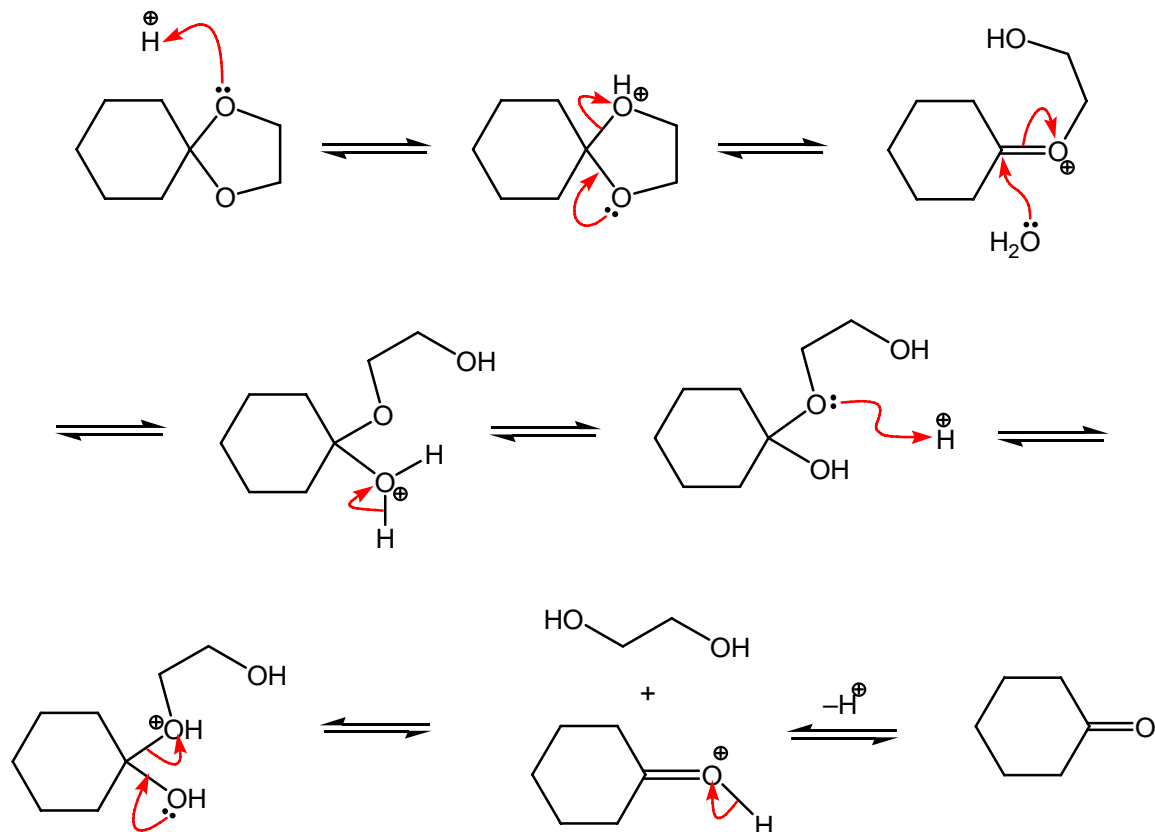
#### Solution

Protonation of the basic oxygen atom of the ketal with acid,  $H^+$ , leads to the intermediate protonated ketal **A**. This intermediate fragments through lone pair assisted cleavage of its  $C-O^+$  bond using a non-bonded pair of electrons from the other oxygen atom of the ketal, in **A**, to give the intermediate oxonium ion **B**.

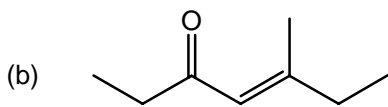
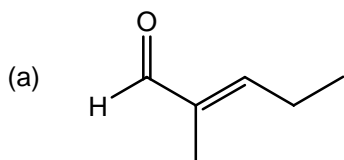


Nucleophilic addition of water to the electrophilic oxonium ion **B** leads to the protonated hemiketal **C**, followed by simple acid-base internal proton exchange gives the protonated hemiketal **D**. Reformation of the thermodynamically more stable carbonyl C=O group occurs by elimination of ethane-1,2-diol, in **D**, to give the intermediate protonated cyclohexanone **E**. Simple deprotonation of **E** with another molecule of water ( $\text{H}_2\text{O}$ ) gives the required cyclohexanone.



Answer**WE 23.5 An aldol condensation reaction (on p. 1083 in *Chemistry*<sup>3</sup>)**

Give the structure of the precursor aldehyde or ketone that would form the following compounds by aldol condensations.

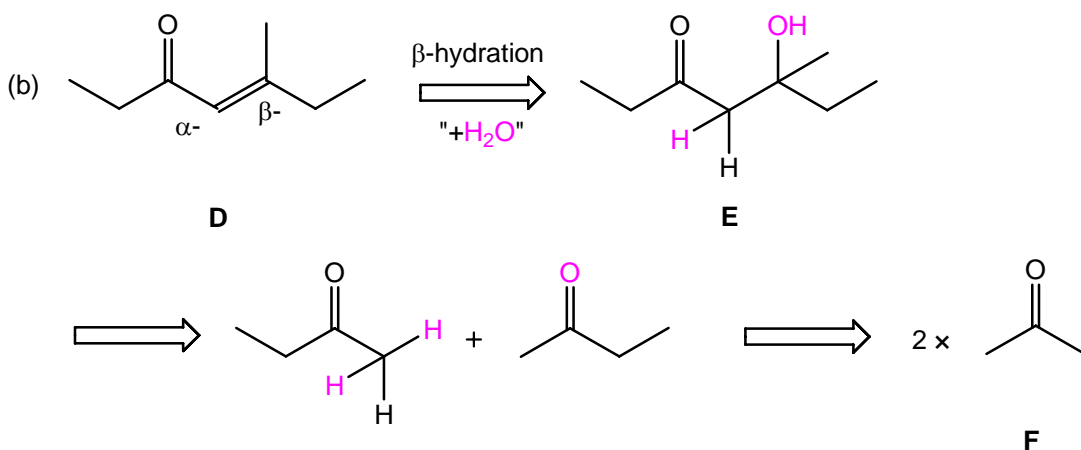
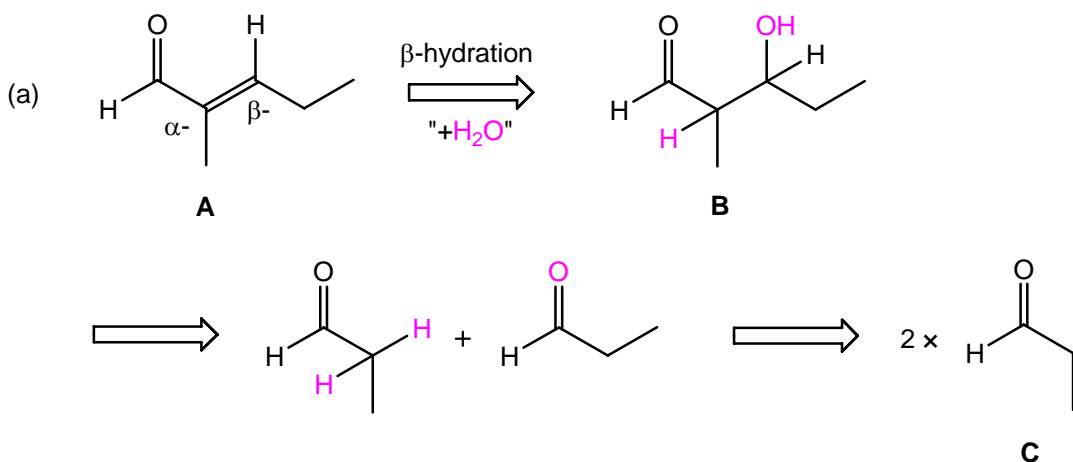
Strategy

These products are derived from the condensation of two identical carbonyl-containing molecules. Both these products can be formed under acidic and basic conditions.

The required carbonyl-containing precursors can be revealed through  $\beta$ -hydration.

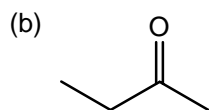
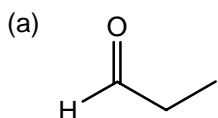
### Solution

By working backwards, simple  $\beta$ -addition of water ( $\text{H}_2\text{O}$ ) across the carbon-carbon double bond of enone **A** gives the intermediate  $\beta$ -hydroxy aldehyde **B**. Fragmentation of this intermediate (through enol formation, followed by tautomerisation) leads to two molecules of aldehyde, propanal **C**. Therefore, aldehyde **C** is the precursor for the product (a).



Once again, by working backwards, simple  $\beta$ -addition of water ( $\text{H}_2\text{O}$ ) across the carbon-carbon double bond of enone **D** gives the intermediate  $\beta$ -hydroxy ketone **E**. Fragmentation of this intermediate (through enol formation, followed by tautomerisation) leads to two molecules of ketone, butan-2-one **F**. Therefore, ketone **F** is the precursor for the product (b).

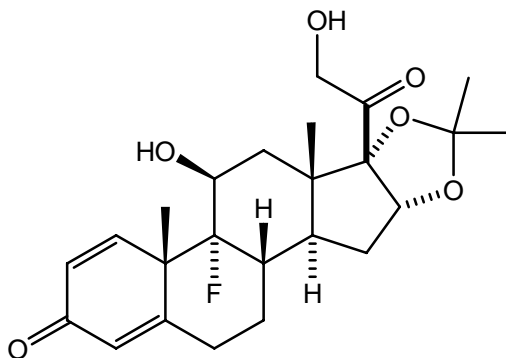
Answer



## Answers to boxes

### Box 23.1 Cortisone and cortisol (on p. 1052 in *Chemistry*<sup>3</sup>)

Triamcinolone acetonide is a synthetic steroid, used to help treat inflammation in patients suffering from asthma and arthritis.



triamcinolone acetonide

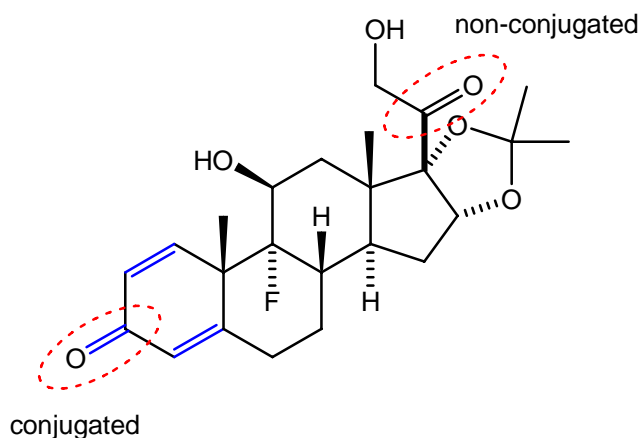
(a) Which of the two C=O bonds in triamcinolone acetonide is not conjugated?

#### Strategy

Highlight both carbonyl (C=O) groups in this molecule (by ringing them). A carbonyl group, which is conjugated, must be resonance stabilised using  $\pi$ - (from double or triple bonds) or non-bonded electrons (from a heteroatom) attached to its alpha-carbon atom.

#### Solution

There are two carbonyl (C=O) groups; the bottom one is conjugated due to the [conjugation/resonance stabilisation](#) from the two adjacent carbon-carbon (C=C) double bonds. The top carbonyl group is non-conjugated as there is neither a pi- bond nor a pair of non-bonded electrons attached to its alpha-carbon atom.



- (b) For the C=O bond that is not conjugated, indicate the  $\alpha$ -positions and determine the number of  $\alpha$ -hydrogen atoms.

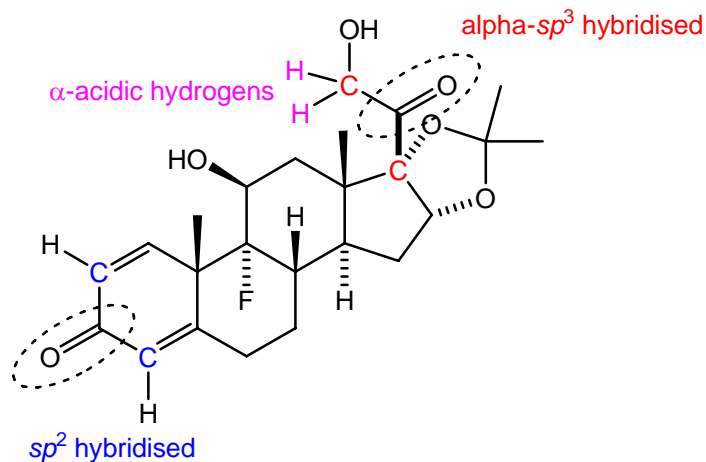
Strategy

Draw out this molecule, and include all alpha C( $sp^3$ )-H bonds. Note:  $sp^3$  NOT  $sp^2$ !

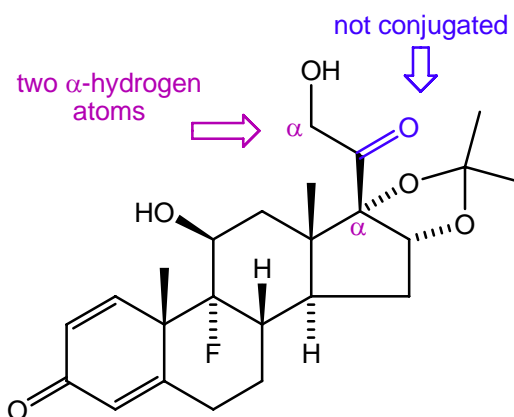
Solution

The non-conjugated carbonyl (C=O) group has TWO alpha-carbon atoms. The left-hand side alpha-carbon atom has TWO alpha-hydrogen atoms. In comparison, the right-hand side alpha-carbon atom has no acidic hydrogen atoms.

The conjugated carbonyl group has TWO alpha-carbon atoms; however, these are  $sp^2$ -hybridised and therefore the corresponding hydrogen atoms are non-acidic as they are orthogonal ( $90^\circ$ ) to the carbonyl (C=O) group.



Answer



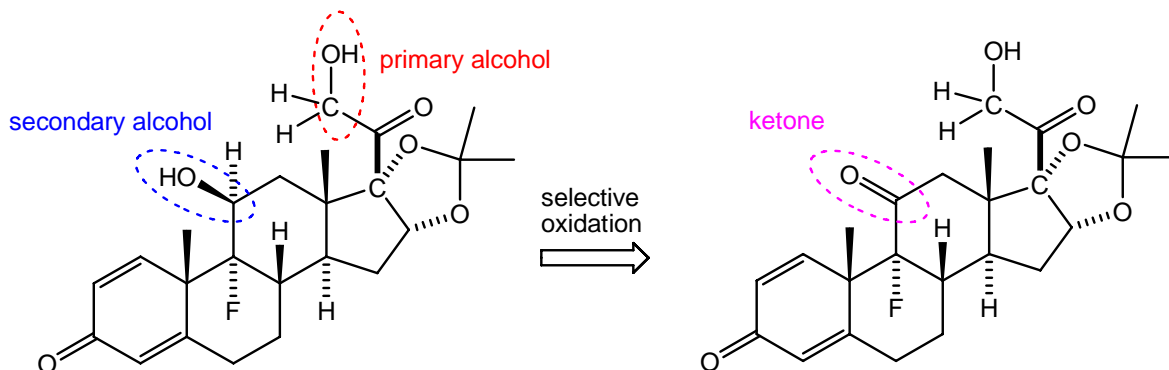
- (c) Draw the structure of the product formed on oxidation of the secondary alcohol in triamcinolone acetonide.

Strategy

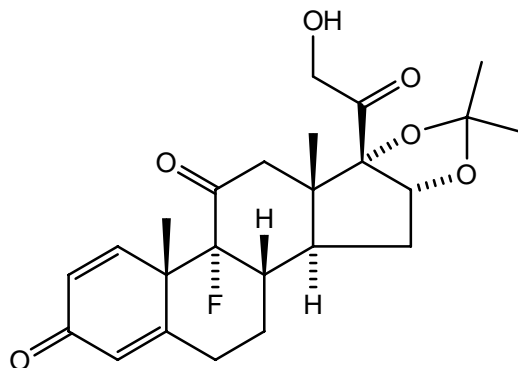
Highlight the secondary alcohol (CHOH) group in this molecule (by ringing it). Oxidation of a secondary alcohol, such as  $R_2CHOH$ , leads to a ketone,  $R_2C=O$ . The product can be drawn easily by replacing the CH-OH group with a C=O group.

Solution

There are two alcohols in this molecule, namely the **primary alcohol** ( $RCH_2OH$ ) and **secondary alcohol** ( $R_1R_2CHOH$ ). Selective oxidation of this **secondary alcohol** leads to the **ketone** as shown below.

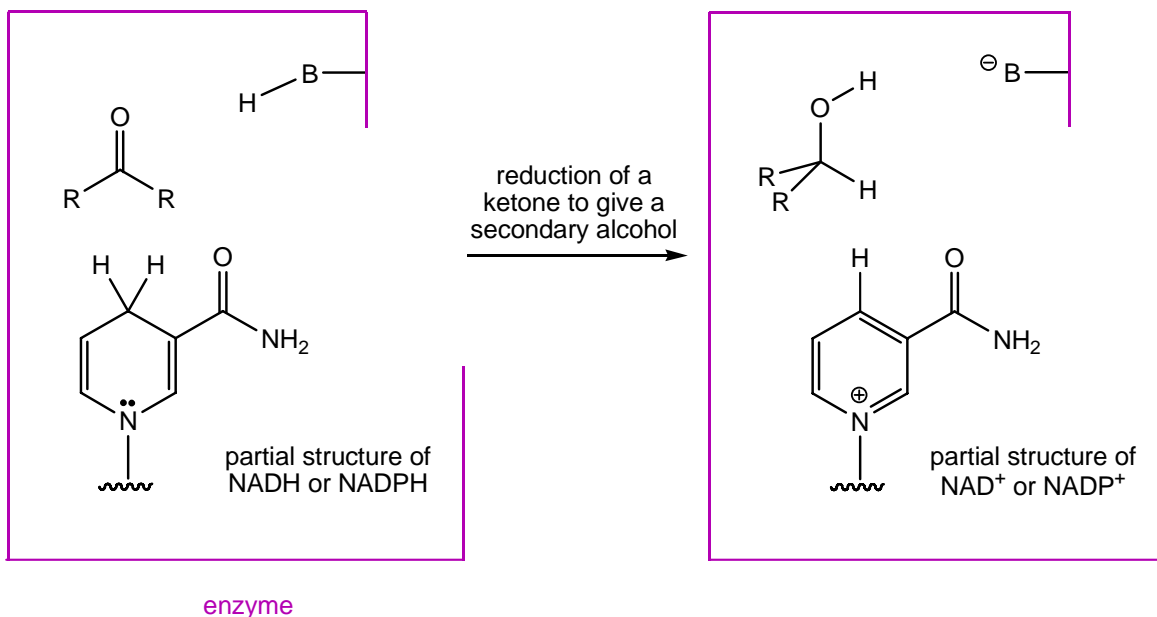


Answer



**Box 23.3 Hydride transfer in nature (on p. 1058 in *Chemistry*<sup>3</sup>)**

In the reaction shown below; use curly arrows to show the movement of electrons when either NADH or NADPH reduces the ketone.



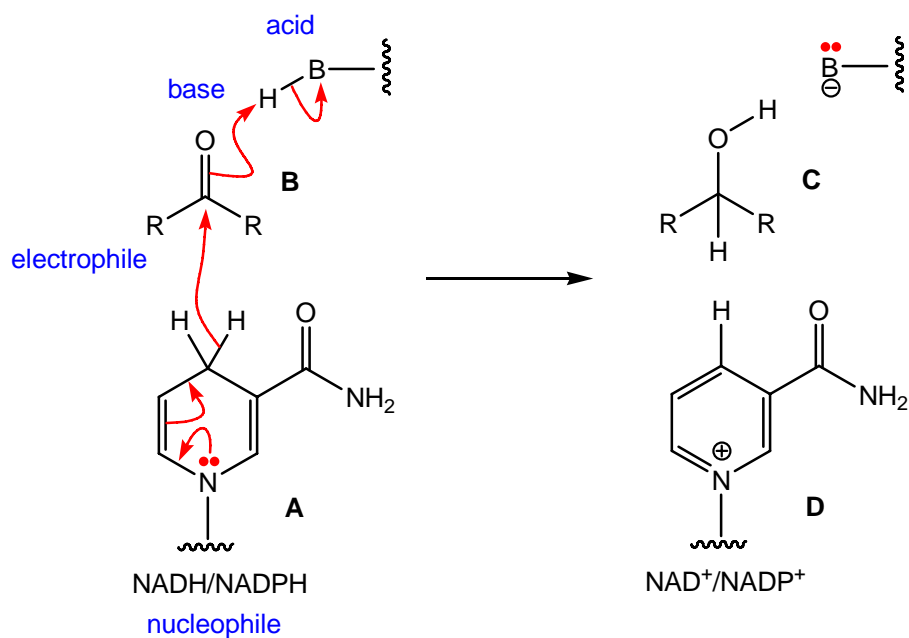
### Strategy

For your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid ( $\rightarrow$ ).

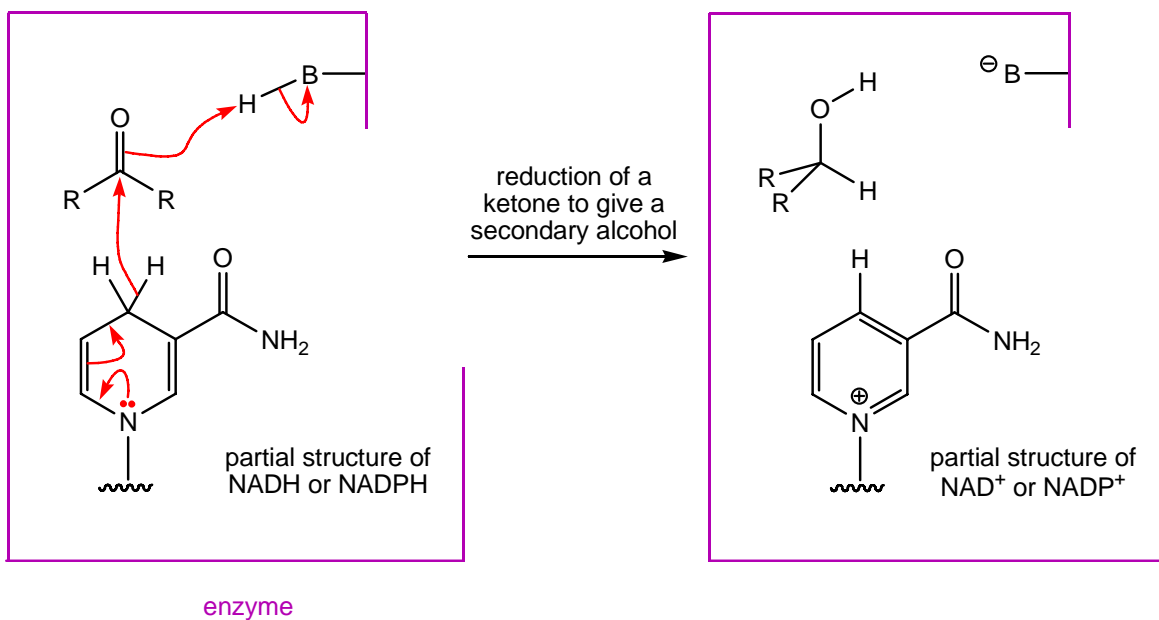
This reduction is reversible, and therefore could be considered as a retro-E2 elimination.

### Solution

NADH and NADPH are nucleophilic sources of hydride, and the ketone,  $R_2C=O$ , is the electrophile. Nucleophilic addition of hydride, from the dihydropyridine ring of either NADH or NADPH (**A**), to the electrophilic carbonyl ( $C=O$ ) group of ketone **B**, followed by concerted deprotonation of the neighbouring acid,  $-BH$ , leads to the secondary alcohol **C** and the pyridinium salt  $NAD^+/NADP^+$  (**D**). These reactions are subtly different to classical  $NaBH_4/LiAlH_4$  reductions as they occur in a concerted single-step, and are general acid catalysed. The mechanism of this reaction type is shown below.

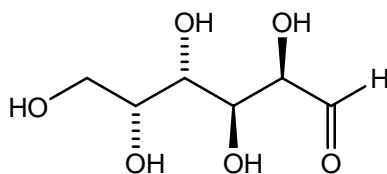


Answer



**Box 23.5 The structure of glucose (on p. 1065 in *Chemistry*<sup>3</sup>)**

The structure of the open-chain form of the sugar D-galactose is shown here. Draw the structures of the two galactopyranoses.



D-galactose

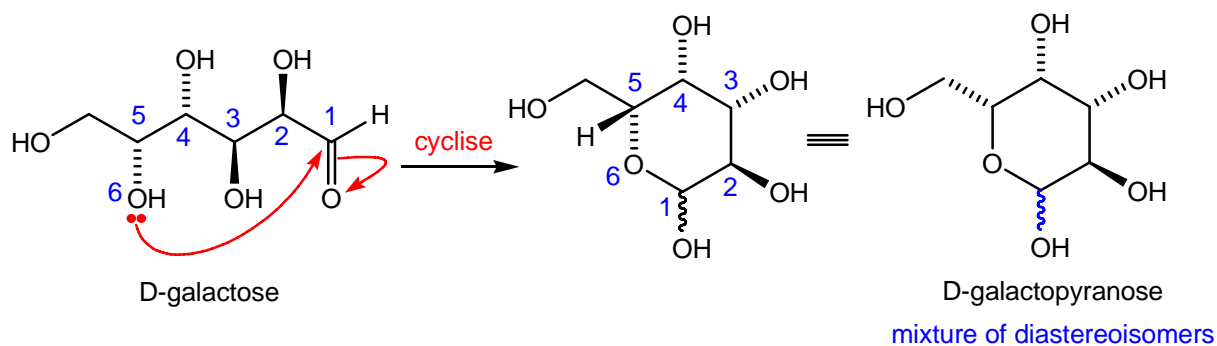
Strategy

D-Galactose contains four chiral centres. Galactopyranose is a closed chain form of galactose that contains a six-membered pyranose ring. On formation of the hemiacetal (pyranose) ring, a new chiral centre is formed.

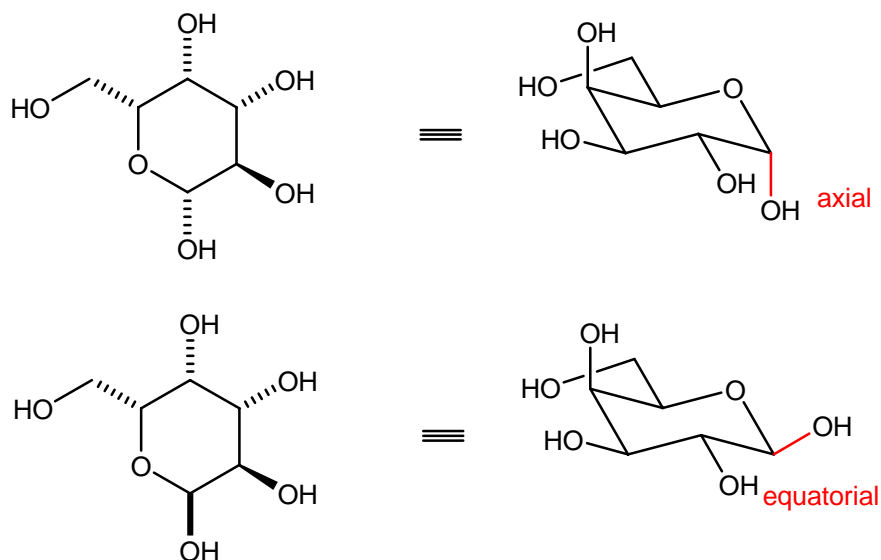
Work out which hydroxyl (OH) group is needed to form the required six-membered acetal, and cyclise it onto the aldehyde group to form two diastereoisomeric (epimeric) galactopyranoses.

Solution

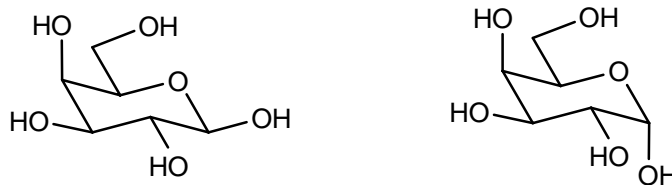
By drawing out the structure of D-galactose, and pre-numbering the pyranose ring from the aldehyde group (position 1) to the required hydroxyl (OH) group (at position 6) reveals the connectivity of the required pyranose ring. Formation of the pyranose (hemiacetal) ring is reversible and under thermodynamic control. Nucleophilic addition of the hydroxyl group (at position 6) to the aldehyde, generates an unequal mixture of diastereoisomeric cyclic hemiacetals. The remaining chiral centres are unchanged; however their conformation has changed.



These two diastereoisomeric pyranoses can be drawn in their more conventional chair arrangement, as shown below. The OH group of the hemiacetal can adopt either an axial or equatorial position. Usually, the axial position is favoured due to the anomeric effect.

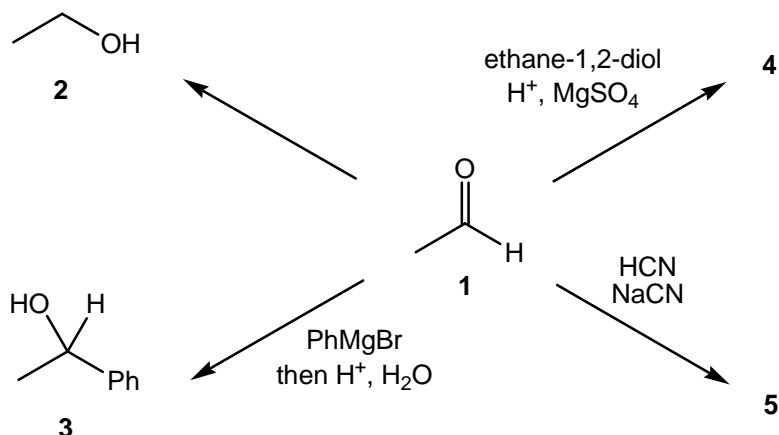


Answer



**Answers to end of chapter questions (on p. 1088 in *Chemistry*<sup>3</sup>)**

1. The following questions are based on the reactions of ethanal (**1**) shown below.



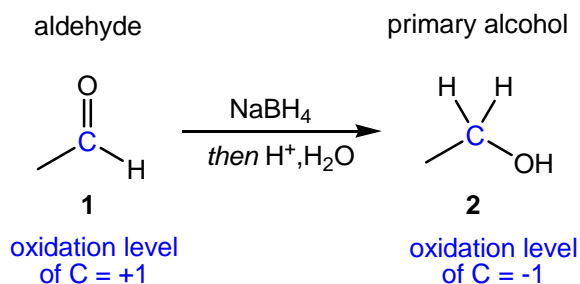
- (a) Give appropriate reagents for converting **1** into **2**. Is this an example of an oxidation or a reduction reaction?

Strategy

Draw out the starting material and product, assign their oxidation levels, and work out if an oxidation or reduction has occurred. Deduce which functional group has changed during this proposed reaction, and suggest reagents for this transformation.

Solution

The starting material **1** and product **2** contains aldehyde and primary alcohol functionality, respectively. This process involves reduction, as there is a decrease in the oxidation level of the **carbon atom** of the aldehyde group, in **1**, from +1 to -1 (in the primary alcohol **2**).

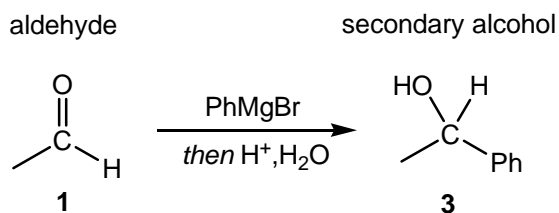


Reduction of the polar carbonyl group, of aldehyde **1**, requires a polar reducing agent. The most suitable reagent for this reduction is sodium borohydride ( $\text{NaBH}_4$ ); the use of a more reactive hydride source, like  $\text{LiAlH}_4$ , is acceptable. Under both conditions, the reaction needs to be “worked-up” under acidic conditions ( $\text{H}^+$ ,  $\text{H}_2\text{O}$ ) in order to protonate the intermediate alkoxide. For a detailed account of these mechanisms, see p. 1059 in *Chemistry*<sup>3</sup>.

### Answer

$\text{NaBH}_4$  or  $\text{LiAlH}_4$  then  $\text{H}^+$ . This process is a reduction.

(b) Draw a reaction mechanism to show how **1** is converted into **3**.



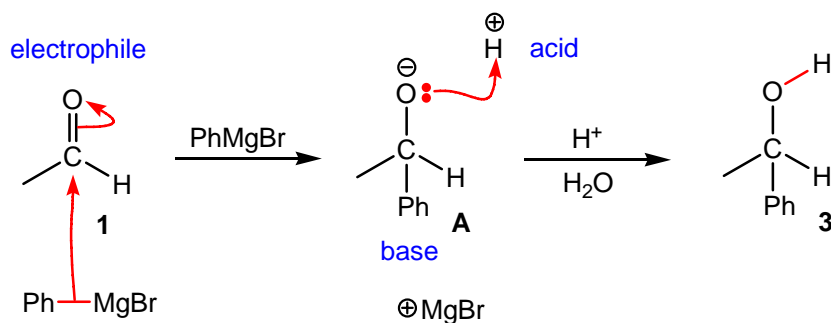
### Strategy

For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid ( $\rightarrow$ ).

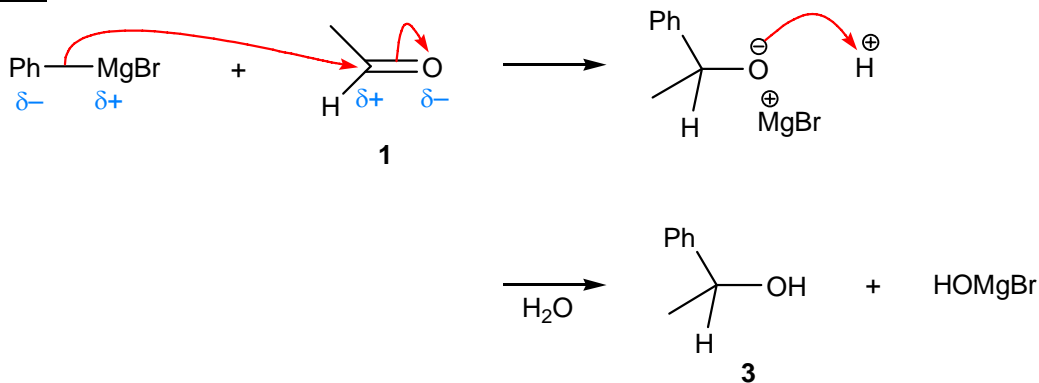
### Solution

Nucleophilic addition of the phenyl carbanion,  $\text{Ph}^-$ , (from the nucleophilic  $\text{Ph-MgBr}$  bond) to the electrophilic carbonyl group of acetaldehyde **1** leads to the tetrahedral intermediate

A. Protonation of this basic alkoxide, in **A**, using aqueous mineral acid (dilute HCl in H<sub>2</sub>O), gives the required secondary alcohol **3**.



Answer



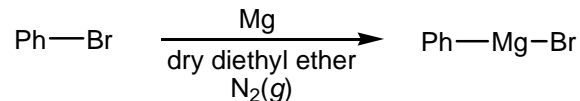
[Movement of electrons can also be depicted using a negative charge or a non-bonded pair of electrons.]

(c) Suggest a method for preparing PhMgBr.

Strategy

Grignard reagents, like RMgBr, are generally prepared from the corresponding aliphatic and aryl bromide (RBr) and magnesium.

Solution



Phenyl magnesium bromide, PhMgBr, is a common Grignard reagent. It is prepared by the slow addition of magnesium (ribbon) to a solution of bromobenzene (PhBr) in **dry** diethyl ether (solvent) under an **inert** atmosphere (*e.g.*, N<sub>2</sub> or Ar).

In the presence of water (as in wet diethyl ether), this Grignard reagent would simply deprotonated it, to form benzene (Ph-H) as a byproduct. Whereas, in the presence of air [in particular O<sub>2</sub>(g)], phenol (Ph-OH) is formed as a further byproduct; for additional information, see p. 1060 in *Chemistry*<sup>3</sup>.

### Answer

PhBr and Mg in dry diethyl ether.

(d) Give structures for organic compounds **4** and **5**.

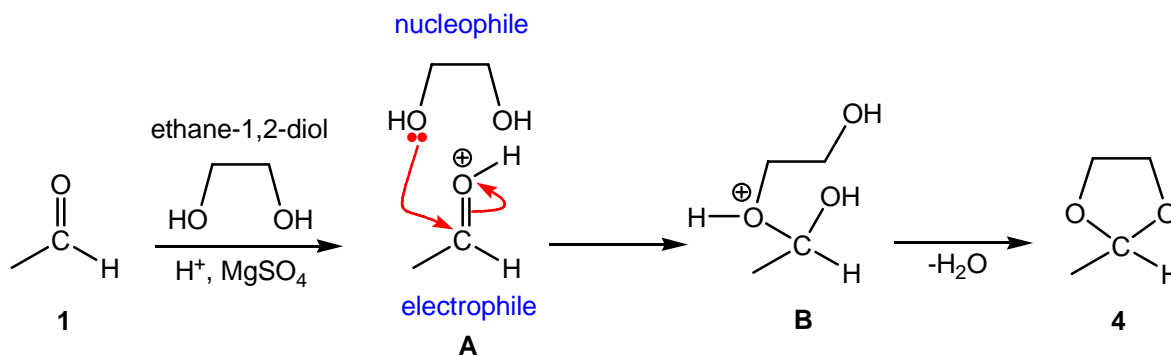
### Strategy

Acetaldehyde **1** is an electrophilic aldehyde. In both reactions draw out the reagents, and work out which is the complementary nucleophile. Work your way into this question by attempting to draw a mechanism using your chosen nucleophile and electrophile combination. Suggest structures for the products **4** and **5**.

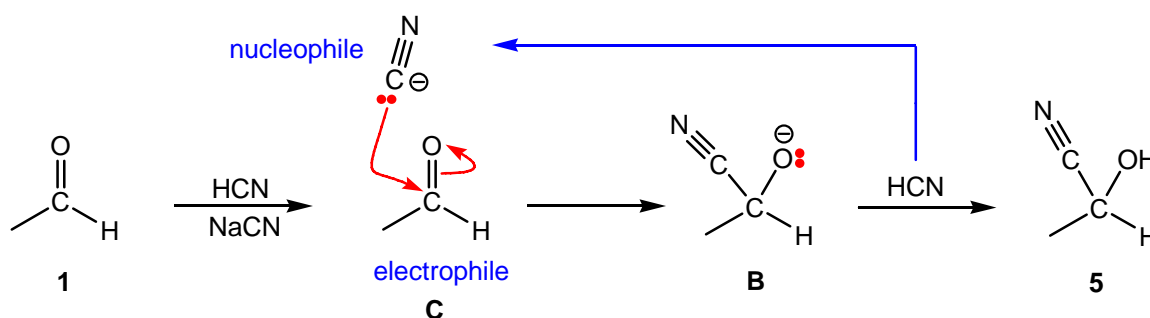
### Solution

#### *Formation of product 4*

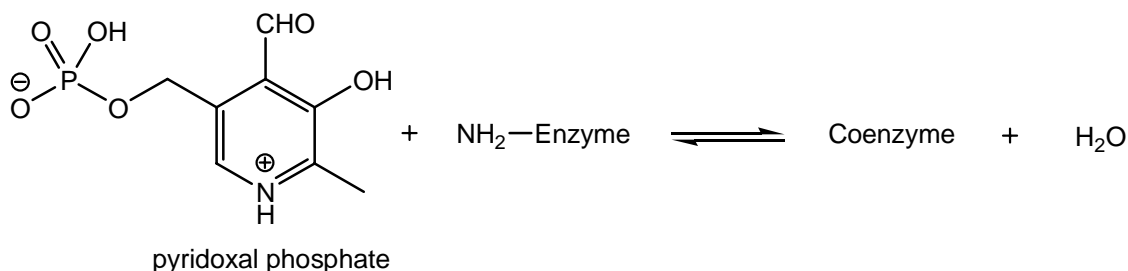
Ethane-1,2-diol is a nucleophile and acetaldehyde **1** is an electrophile in this reaction. Increasing the electrophilicity of acetaldehyde through protonation, as in **A**, followed by nucleophilic addition of ethane-1,2-diol gives the intermediate hemiacetal **B**. Under acid conditions, water can be eliminated, followed by intramolecular cyclisation of the remaining primary alcohol gives the cyclic acetal **4** as the product. Anhydrous magnesium sulfate (MgSO<sub>4</sub>) is needed to drive the equilibrium over to the product **4** by removing water from the reaction mixture. The mechanism of this reaction is given on p. 1068 in *Chemistry*<sup>3</sup>.

*Formation of product 5*

Cyanide ( $\text{CN}^-$ ) is a nucleophile and acetaldehyde **1** is an electrophile in this reaction. Nucleophilic addition of cyanide to the electrophilic carbonyl group of acetaldehyde **1**, as in **C**, followed by protonation of the basic alkoxide using hydrogen cyanide ( $\text{HCN}$ ;  $\text{p}K_{\text{a}} = 7$ ) gives cyanohydrin **5** as the product. Under these conditions, cyanide ( $\text{CN}^-$ ) is regenerated. The mechanism of this reaction is given on p. 1060 in *Chemistry*<sup>3</sup>.

Solution

3. In nature, pyridoxal phosphate reacts with an enzyme (abbreviated as H<sub>2</sub>N–Enzyme) to form a coenzyme that catalyses the conversion of  $\alpha$ -amino acids into  $\alpha$ -keto acids.



- (a) Draw the structure of the coenzyme and name the functional group that is formed.

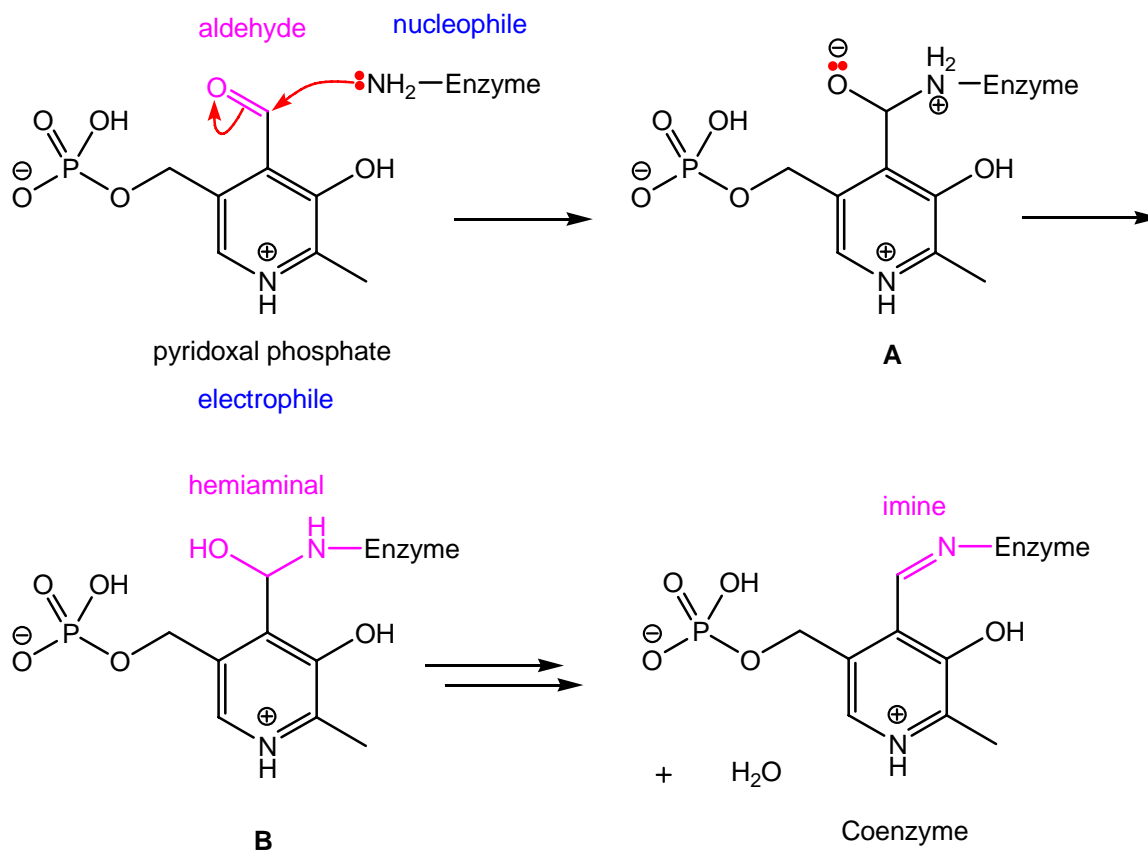
### Strategy

This process must involve an **addition-elimination reaction**, as there is ONLY one formal product, “the coenzyme”. As the byproduct is water (H<sub>2</sub>O), this reaction is neither a reduction nor an oxidation. Protonation of the amino-enzyme cannot be the product-determining step as only the co-enzyme product is formed. [Proton transfer would lead to two products]. Therefore, the amino-enzyme is the nucleophile in this process.

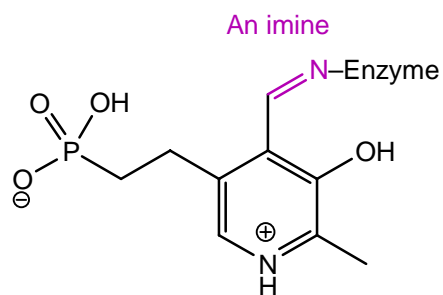
In this reaction, draw out the reagents and work out which functional group in pyridoxal phosphate is the complementary electrophile. Work your way into this question by attempting to draw a mechanism using your chosen nucleophile and electrophile combination. Suggest a structure for the coenzyme and name the new functional group.

### Solution

Nucleophilic **addition** of the amino-enzyme to the electrophilic carbonyl group of the aldehyde (in the pyridoxal phosphate) leads to the tetrahedral intermediate **A**. Internal proton exchange between the ammonium ion and the alkoxide leads to the hemiaminal **B** and subsequent **elimination** of water gives the co-enzyme as the product. In essence, this reaction involves the formation of a substituted imine (as part of the co-enzyme substructure) using an aldehyde (in pyridoxal phosphate) and a primary amine (in amino-enzyme). For the mechanism of imine formation, see p. 1071 in *Chemistry*<sup>3</sup>.



Answer



- (b) Is the coenzyme formed by an addition reaction, a substitution reaction, or an addition-elimination reaction? Explain your reasoning.

Strategy

For substitution and addition-elimination reactions, TWO or more reagents will lead to TWO or more products. For addition reactions, TWO or more reagents will give ONE product.

As there are two reagents (pyridoxal phosphate and amino-enzyme) and two products (coenzyme and water), this reaction cannot be an addition reaction. You will need to consider the other two options.

### Solution

This reaction involves the nucleophilic **addition** of a primary amine (amino-enzyme) to the electrophilic carbonyl group of pyridoxal phosphate, followed by **elimination** of water from the hemiaminal (see part a) to give the coenzyme. Overall, this reaction is an addition-elimination process.

### Answer

This is an addition-elimination reaction. The amine group adds to the C=O bond to form a hemiaminal which loses water in an elimination reaction.

- (c) An acid within the active site of the enzyme plays an important part in the mechanism of the reaction to produce the coenzyme. Explain the role of an acid in this type of transformation.

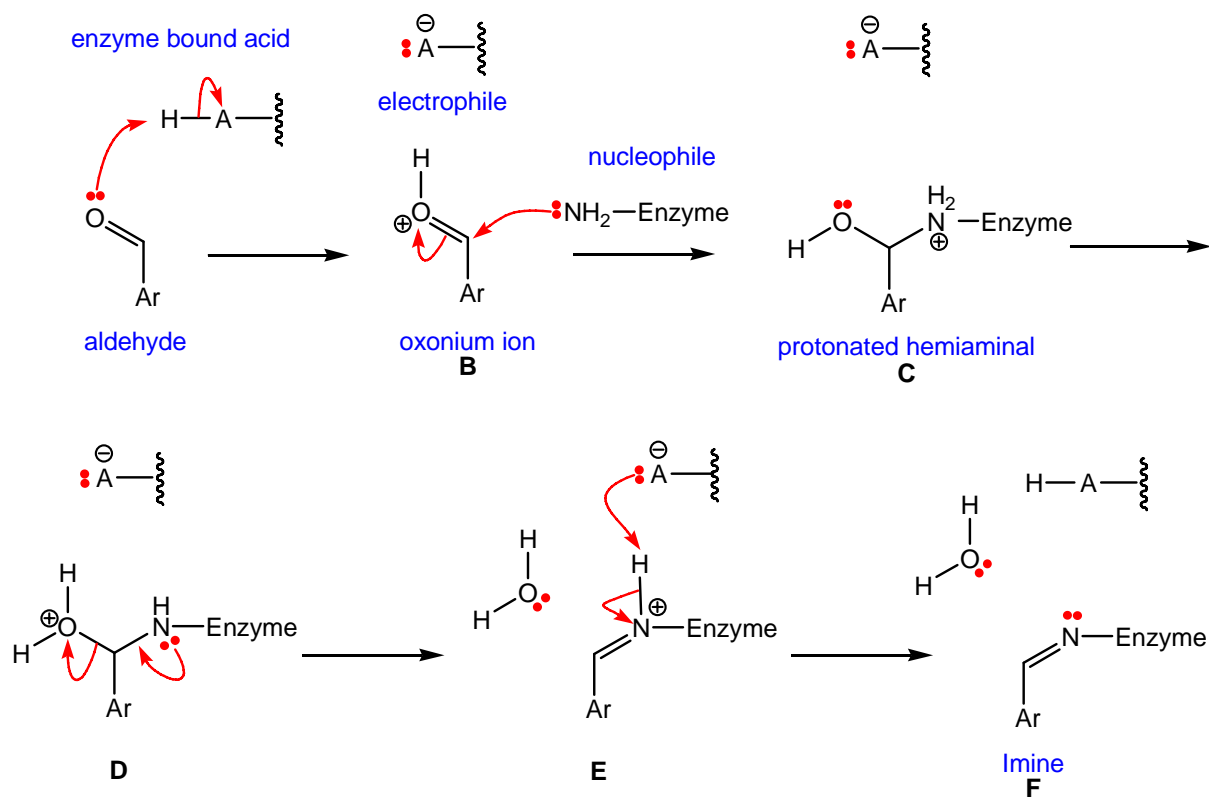
### Strategy

From the above statement, imine formation (within the coenzyme) is acid-catalysed. Generally, protonation of a carbonyl group can increase its electrophilicity, and protonation of a hydroxyl (OH) group can increase its leaving ability. In order to examine the role of an acid, you must first draw out the mechanism of this reaction.

### Solution

Protonation of the aromatic aldehyde using an enzyme bound acid, H-A, gives the oxonium ion **B**. Nucleophilic addition of the amino-enzyme to this activated electrophile (to give the protonated hemiaminal **C**) is significantly faster than that of the parent aromatic aldehyde. Protonation of the hydroxyl (OH) group, in **C**, by internal proton exchange with the

ammonium ion leads to the oxonium ion **D**. Elimination of water ( $\text{H}_2\text{O}$ ), from **D**, assisted by the non-bonded pair of electrons on the nitrogen atom, gives the protonated imine **E**. [This proton transfer step is paramount as it increases the leaving ability of the OH group;  $\text{H}_2\text{O}$  is a much better leaving group than  $\text{HO}^-$ .] Deprotonation of **E** using the conjugate base ( $\text{A}^-$ ) of the enzyme bound acid gives the required imine and the parent enzyme bound acid,  $\text{H-A}$ . The mechanism of this reaction is discussed in detail on p. 1071 in *Chemistry*<sup>3</sup>.



### Answer

An acid catalyst is required to convert the hemiaminal into the imine. Protonation of the hemiaminal converts the OH group into a better leaving group, so that elimination of water takes place (rather than  $\text{HO}^-$ ).

(d) Give the general structure of an  $\alpha$ -amino acid, with one  $\alpha$ -hydrogen atom.

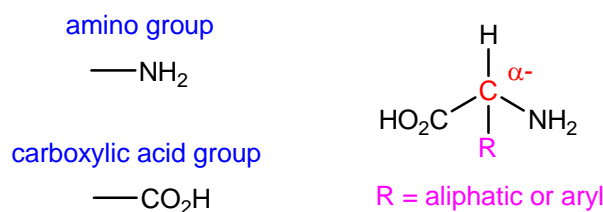
### Strategy

An  $\alpha$ -amino acid is a molecule, which has both amino ( $-\text{NH}_2$ ) and carboxylic acid ( $-\text{CO}_2\text{H}$ ) groups attached to the same alpha-carbon atom. In addition, this alpha-carbon atom is attached to ONE hydrogen atom.

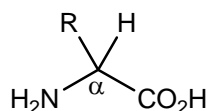
### Solution

From this question, three of the four substituents on the alpha-carbon atom of this  $\alpha$ -amino acid have already been defined; namely an amino ( $\text{NH}_2$ ) group, a carboxylic acid ( $\text{CO}_2\text{H}$ ) group, and a hydrogen ( $\text{H}$ ) atom. The remaining substituent must be either an aliphatic ( $\text{Me}$ ,  $\text{Et}$ , etc) or an aryl group ( $\text{Ph}$ -,  $\text{Ar}$  etc).

The generic structure of this  $\alpha$ -amino acid is shown below.



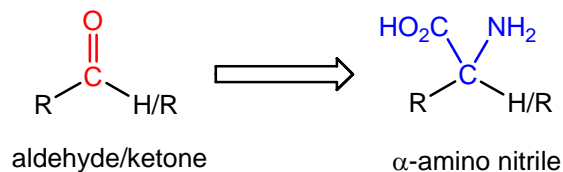
### Answer



- (e) Suggest a method for converting aldehydes and ketones into  $\alpha$ -amino acids in the laboratory.

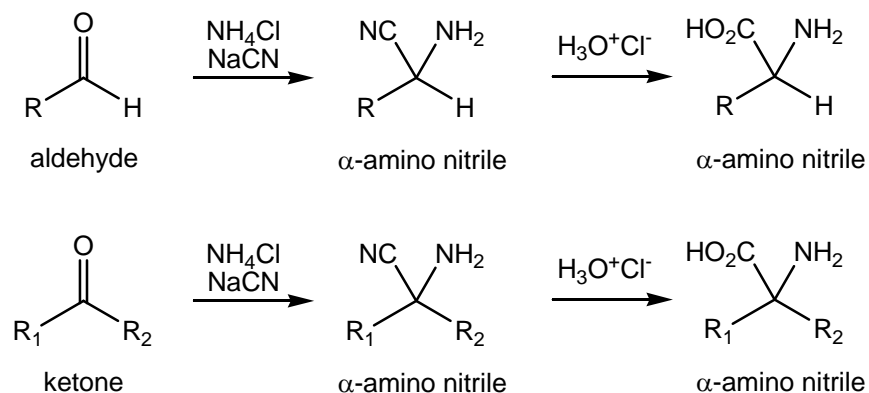
### Strategy

In order to achieve this transformation, the carbonyl ( $\text{C}=\text{O}$ ) groups of the aldehyde/ketone must be replaced with an amino ( $\text{NH}_2$ ) and a carboxylic acid ( $\text{CO}_2\text{H}$ ) group.



### Solution

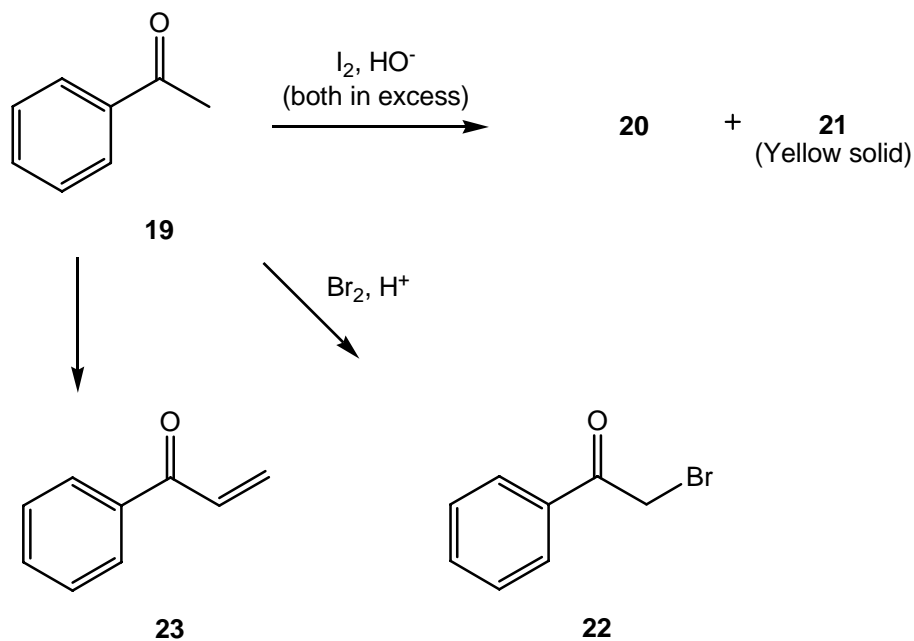
We have already seen in Box 23.6 (on p. 1071 in *Chemistry*<sup>3</sup>) that an amino group and a masked carboxylic acid group (a nitrile) can be introduced in a single step using  $\text{NH}_4\text{Cl}$  and  $\text{NaCN}$ . Hydrolysis of this intermediate  $\alpha$ -amino nitrile, under acidic or basic conditions will give the required  $\alpha$ -amino acid. This is called a Strecker reaction.



Answer

Use the Strecker synthesis. React aldehyde/ketone with  $\text{NH}_4\text{Cl}$  and  $\text{NaCN}$  (to give an intermediate  $\alpha$ -amino nitrile), followed by  $\text{H}^+/\text{H}_2\text{O}$  (gives the required  $\alpha$ -amino acid); for additional information; see p. 1071 in *Chemistry*<sup>3</sup>.

5. The following questions are based on the reactions of acetophenone (**1**) shown below.



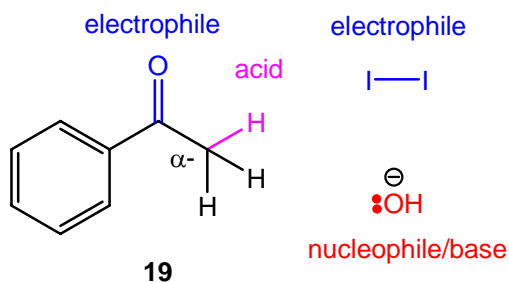
(a) Draw the structures of organic compounds **20** and **21**.

### Strategy

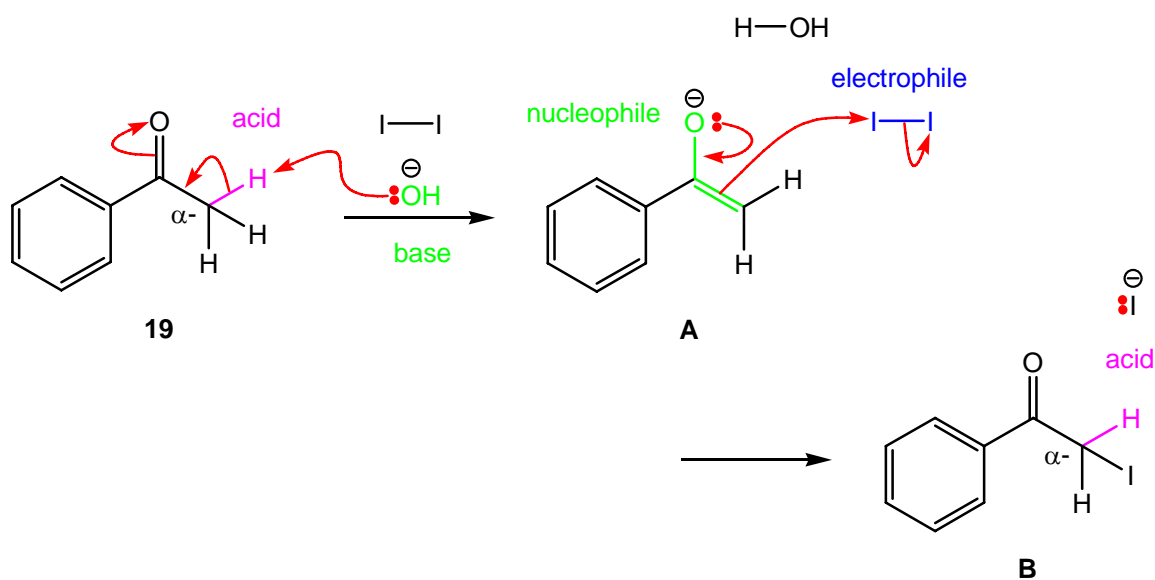
Acetophenone **19** is an electrophilic ketone, which contains three acidic alpha-hydrogen atoms. In this reaction, draw out the reagents, and work out which other reagent could be either the complementary nucleophile or base. Work your way into this question by attempting to draw a mechanism using your chosen nucleophile/base and electrophile/acid combination. Suggest structures for the products **20** and **21**.

### Solution

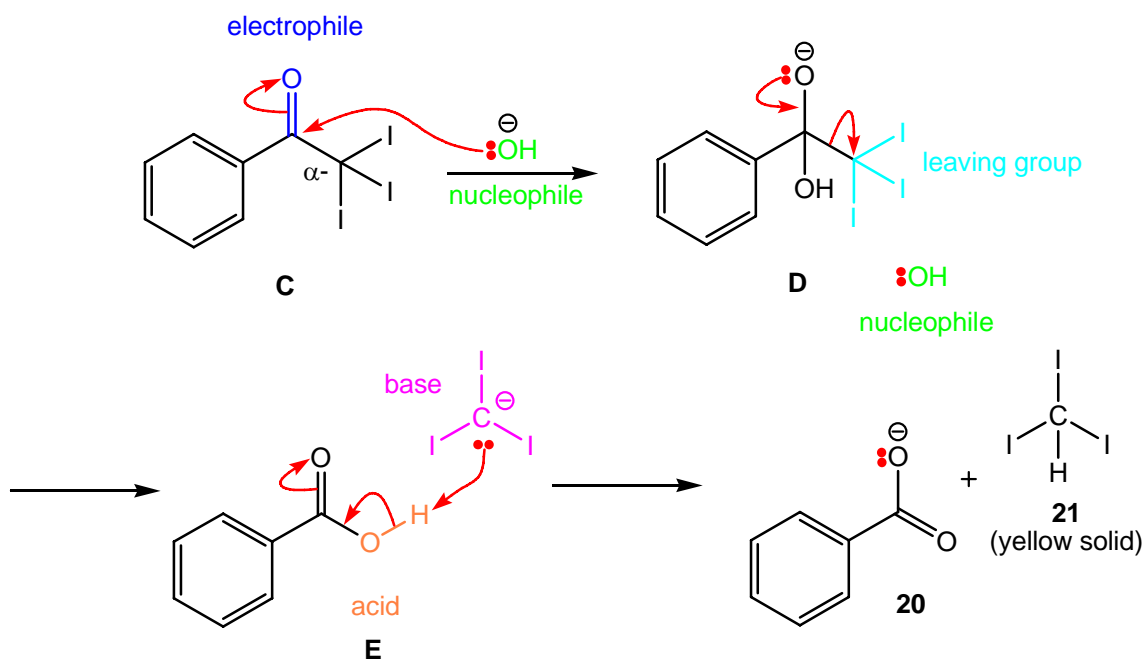
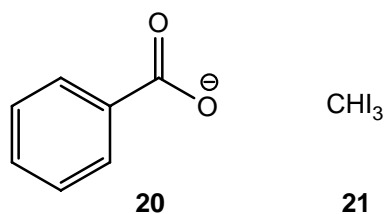
The first step in this reaction cannot involve iodine ( $\text{I}_2$ ) as it is neither a base nor a nucleophile; iodine is an electrophile. Hydroxide ( $\text{HO}^-$ ) does not act as a nucleophile in this step, as this is not a product-determining reaction; *c.f.* hydrate formation is generally unfavourable (see p. 1064 in *Chemistry*<sup>3</sup>). Therefore, in the first step of this reaction, acetophenone **19** acts as an acid, and hydroxide acts as a base ( $\text{HO}^-$ ).



Deprotonation of acetophenone **19** using hydroxide,  $\text{HO}^-$ , (gives the corresponding enolate **A**), followed by electrophilic iodination (using  $\text{I}_2$ ) leads to the intermediate  $\alpha$ -iodo acetophenone **B**. Interestingly, this intermediate is more acidic than the original acetophenone **19**, and therefore successive iodinations can occur (using the excess reagents) to give the tri-iodo acetophenone **C**.



As this tri-iodo acetophenone **C** can no longer act as an acid (as there are no more acidic alpha hydrogen atoms available); the electrophilicity of this carbonyl ( $\text{C}=\text{O}$ ) bond is now important. Nucleophilic addition of hydroxide,  $\text{HO}^-$ , to this carbonyl ( $\text{C}=\text{O}$ ) group (to give **D**), followed by elimination of  $\text{C}^-\text{I}_3$  gives benzoic acid **E** as the product. Acid-base equilibration between these species leads to the more stable benzoate **20** and the yellow crystalline tri-iodoform **21**.

Answer

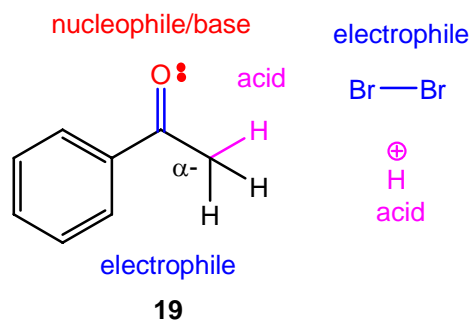
(b) Give a mechanism that explains how **19** is converted into **22**.

Strategy

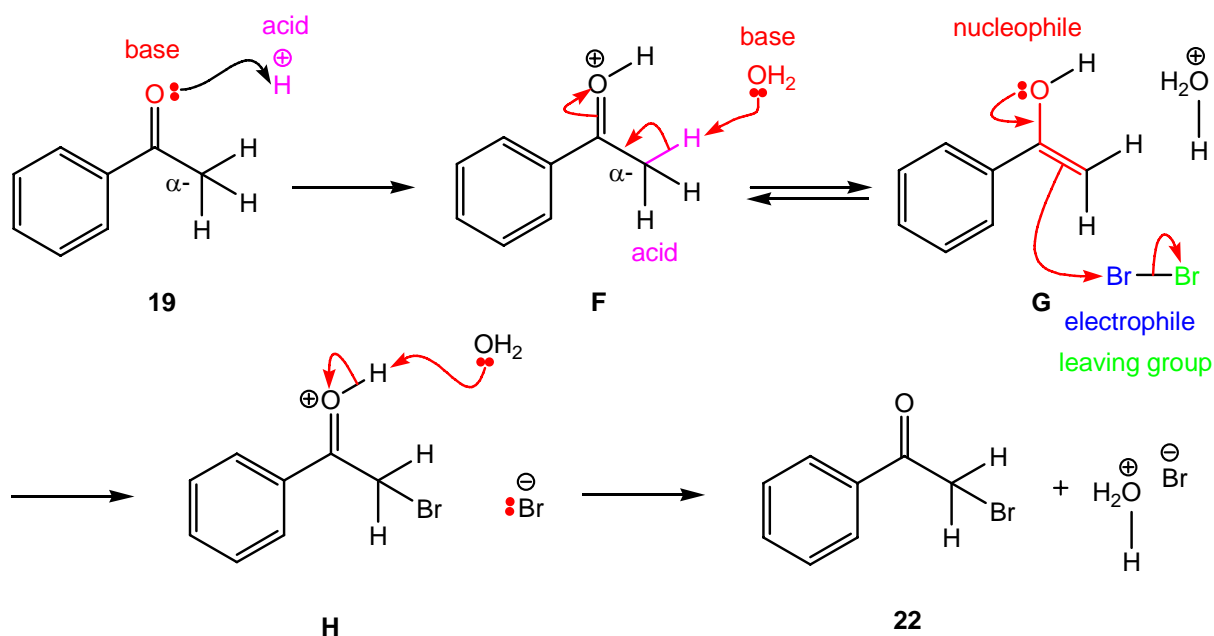
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid ( $\rightarrow$ ).

Solution

Looking at the reagents,  $\text{Br}_2$  is an electrophile and  $\text{H}^+$  is an acid. For acetophenone **19**, only the complementary nucleophilic and basic nature of the oxygen atom of its carbonyl ( $\text{C}=\text{O}$ ) group is important, as it also has the same electrophilic/acidic nature as the other reagents.



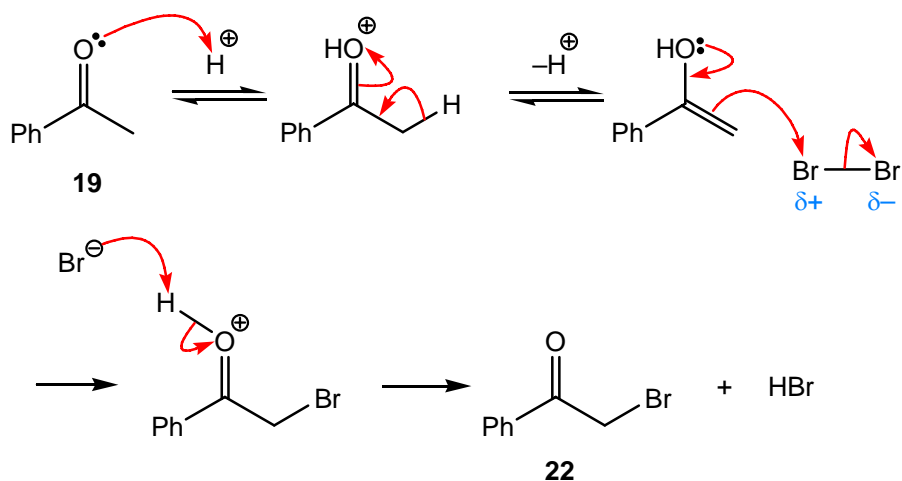
Protonation of the oxygen atom of the carbonyl ( $\text{C}=\text{O}$ ) group of acetophenone **19** with acid,  $\text{H}^+$ , leads to the intermediate oxonium ion **F**. Deprotonation of this oxonium ion **F**, using water ( $\text{H}_2\text{O}$ ) as the base, gives the intermediate enol **G**. This tautomerisation process is reversible, and the amount of enol content is generally less than 1%.



Electrophilic addition of bromide ( $\text{Br}_2$ ) to this nucleophilic enol, as shown in **G**, leads to the protonated  $\alpha$ -bromoacetophenone **H**. Acid-base equilibration between this acid, **H**, and water ( $\text{H}_2\text{O}$ ) gives the required  $\alpha$ -bromoacetophenone **22** as the product. It is interesting to note, bromination under acidic conditions leads to mono-bromination, whereas, under basic

conditions tri-bromination (and sequential cleavage to tribromoform) occurs. For further information about this reaction type, see p. 1079 in *Chemistry*<sup>3</sup>.

Answer



[Movement of electrons can also be depicted using a negative charge or a non-bonded pair of electrons.]

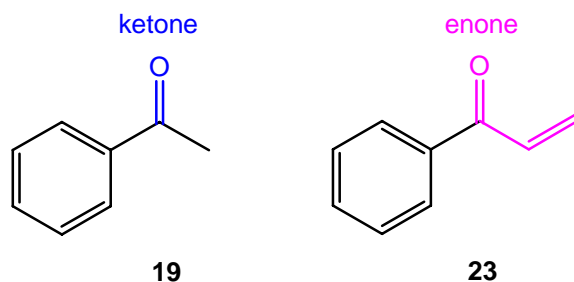
(c) Suggest reagents that will convert **19** into **23**.

Strategy

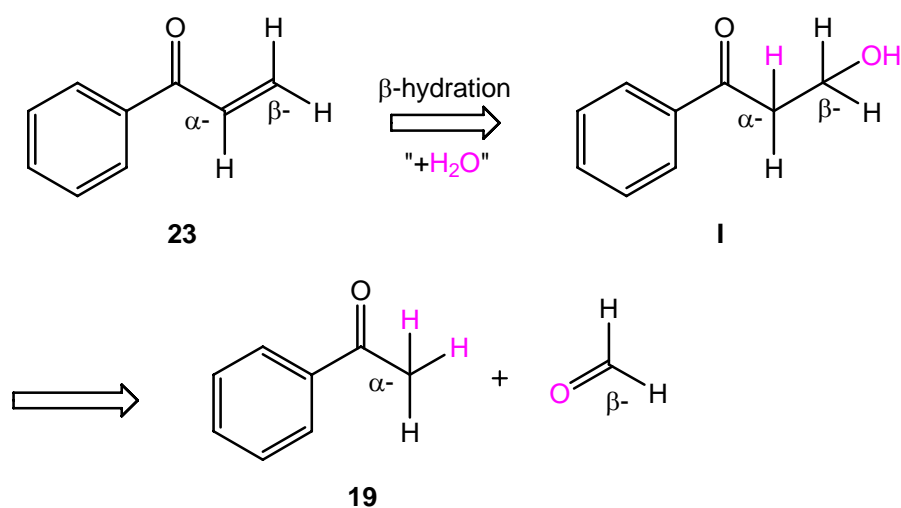
Draw the structures of the starting material **19** and the product **23**, name the functional groups present, and work out their relative reactivity. Suggest reagents for this synthetic transformation.

Solution

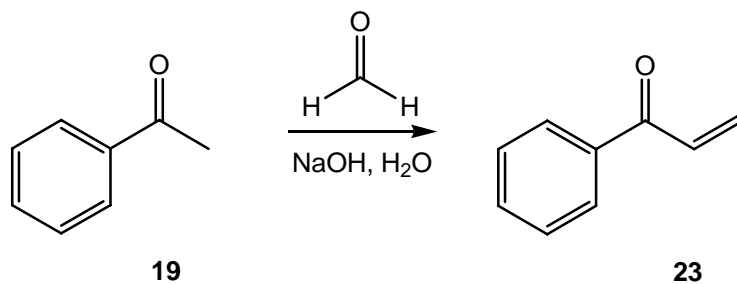
The starting material **19** is a ketone and the product **23** is an enone. Enones are traditionally made using aldol condensations (see p. 1081 in *Chemistry*<sup>3</sup>).



The required carbonyl-containing precursors for this aldol condensation can be revealed through  $\beta$ -hydration. By working backwards; simple  $\beta$ -addition of water ( $\text{H}_2\text{O}$ ) across the carbon-carbon double bond of enone **23** gives the intermediate  $\beta$ -hydroxy aldehyde **I**. Fragmentation of this intermediate (through enol formation, followed by tautomerisation) leads to acetophenone **19** and formaldehyde ( $\text{O}=\text{CH}_2$ ).



Treatment of acetophenone **19** and formaldehyde ( $\text{O}=\text{CH}_2$ ) under basic conditions, such as aqueous sodium hydroxide ( $\text{NaOH}$ ,  $\text{H}_2\text{O}$ ), gives the required enone **23**. This is an example of a crossed aldol condensation involving non-enolisable and enolisable carbonyl components. For additional information, see p. 1082 in *Chemistry*<sup>3</sup>.



Answer

HCHO, HO<sup>-</sup>, heat

Solutions provided by J. Eames (j.eames@hull.ac.uk)