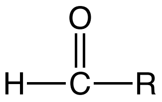
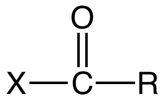
Reactions of Enolates:

X—X Halogenation

$X-CH_2-R$ Alkylation

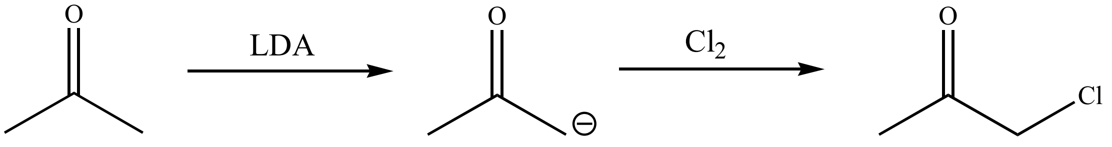


$H-C(=O)-R$ Aldol Reaction



$X-C(=O)-R$ Acylation

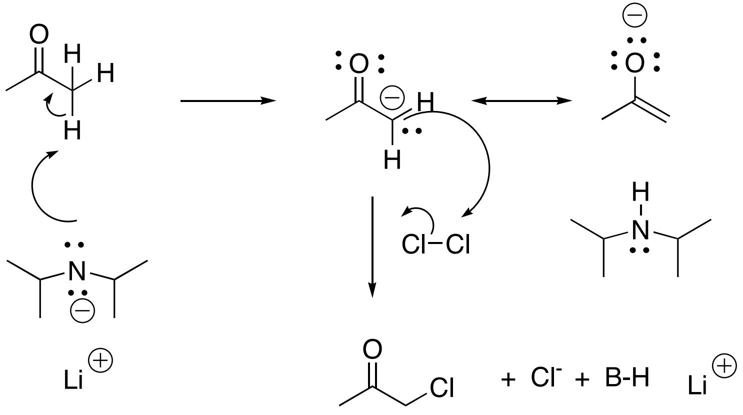
Example: halogenation



chloroacetone

Chloroacetone is used in tear gas.

In this reaction, chlorine is the electrophile that reacts with the nucleophilic enolate. The first step of the reaction is the formation of the enolate by using lithium diisopropylamide (LDA) (also depicted as :B $^-$ in some cases below). LDA is a strong, bulky base, which will remove the alpha hydrogen to produce the resonance stabilized enolate anion. In the second step, the enolate attacks the weak Cl-Cl bond to form the halo ketone and the chloride anion. The Cl-Cl bond is susceptible to attack because the two electronegative chlorines pull electrons out of the bond making it weak.



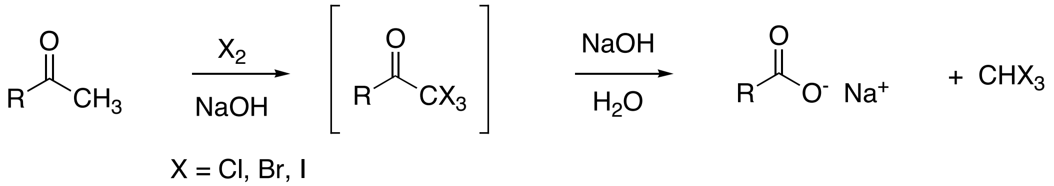
or: KO-*t*Bu

In the above example, the addition of chlorine makes the alpha hydrogens of the product (chloroacetone) even more acidic due to the electron withdrawing effect of the chlorine. Side reactions, including multiple chlorinations are possible, as shown in the next section.

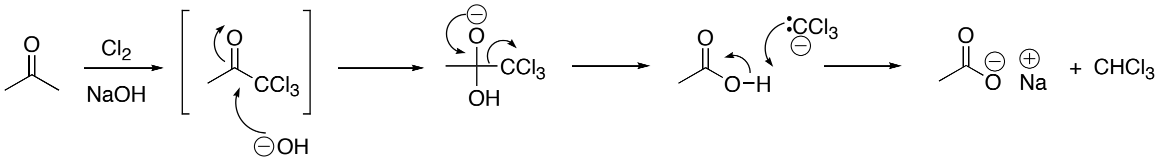
The Haloform Reaction

A problem with doing the above reaction under basic conditions using sodium hydroxide is due to a side reaction called the **haloform** reaction. The haloform reaction converts a methyl ketone into a carboxylic acid salt and a haloform (chloroform, $CHCl_3$; bromoform, $CHBr_3$; or iodoform, CHI_3) and may be used as a qualitative test for methyl ketones.

A sample of an unknown structure (which may be a methyl ketone) is dissolved in THF or ether, and dilute solutions of aqueous NaOH and I_2 are added. Formation of a yellow precipitate of solid iodoform signals a positive test and indicates that the sample is a methyl ketone as shown below in the general example.

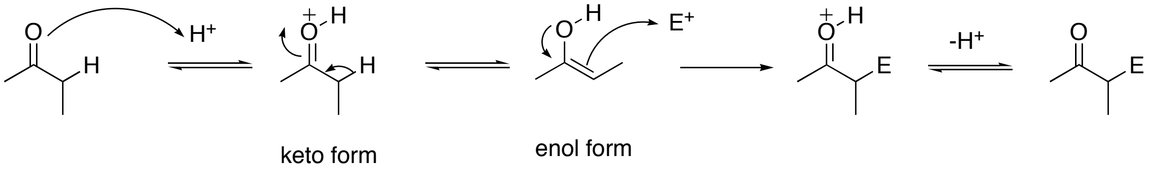


When acetone is reacted with excess Cl_2 and aqueous NaOH, multiple chlorinations occur to form trichloroacetone as shown before. This is then followed by attack of the hydroxide ion on the carbonyl to form a tetrahedral intermediate. This intermediate then displaces the $-CCl_3$ group by donation of a lone pair of electrons from the oxygen to reform the carbonyl. The CCl_3 group leaves as a stabilized anion because the three electron withdrawing chlorine atoms are capable of stabilizing the negative charge. Proton transfer then leads to the products.

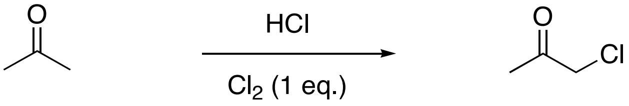


Enol Formation (Under acidic conditions)

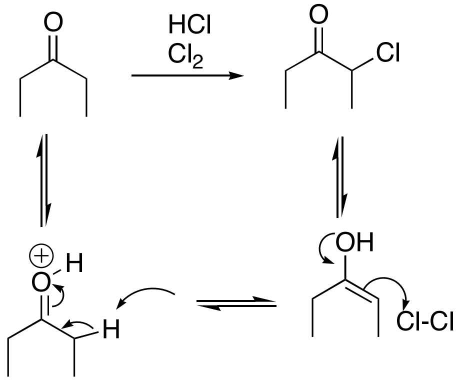
Enols behave as nucleophiles and react with electrophiles in much the same way as enolates. The main difference between the two is that enols are formed under acidic conditions and enolates under basic conditions. The general mechanism of enol formation is shown below. Protonation of the carbonyl oxygen makes the alpha proton more acidic and deprotonation occurs to form the enol. The enol and keto forms are tautomers (interconverting structural isomers). An electron pair from the enol oxygen reforms the double bond and attacks an electrophile, forming a new carbon-electrophile bond. Loss of a proton from the oxygen yields a neutral alpha-substitution product as the carbonyl is reformed.



An example is the chlorination of acetone under acidic conditions. Monochlorination is hard to control under aqueous basic conditions and there is the competing haloform reaction (see above). Under acidic conditions, this is easy to do with 1 molar equivalent (1 eq.) of chlorine gas.

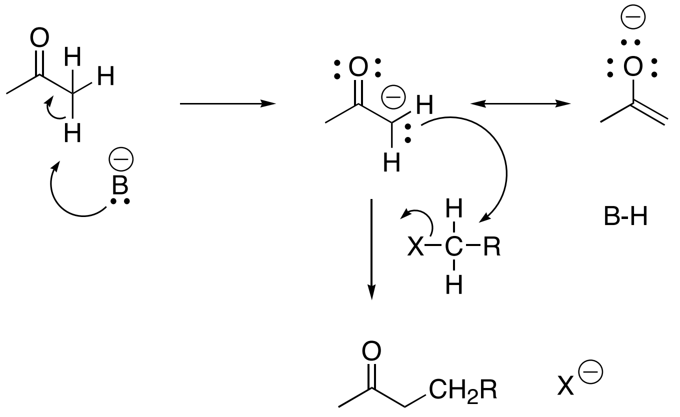


Another example of acid catalyzed enol formation and subsequent chlorination.



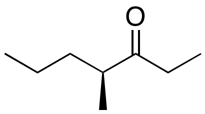
Enolate Alkylation Reactions

An important reaction of enolate ions is their alkylation by treatment with an alkyl halide. The alkylation reaction is useful because it forms a new C-C bond. Alkylation occurs when a nucleophilic enolate ion reacts with the electrophilic alkyl halide in an S_N2 reaction and displaces the leaving group by back-side attack as shown in the general mechanism below.

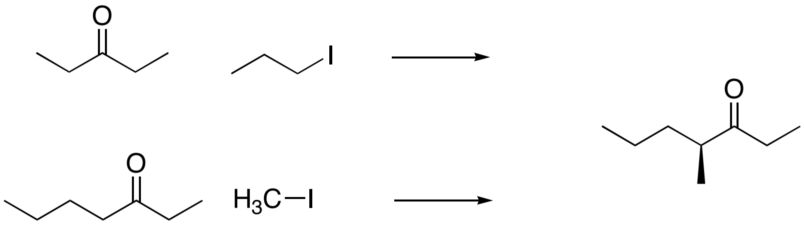


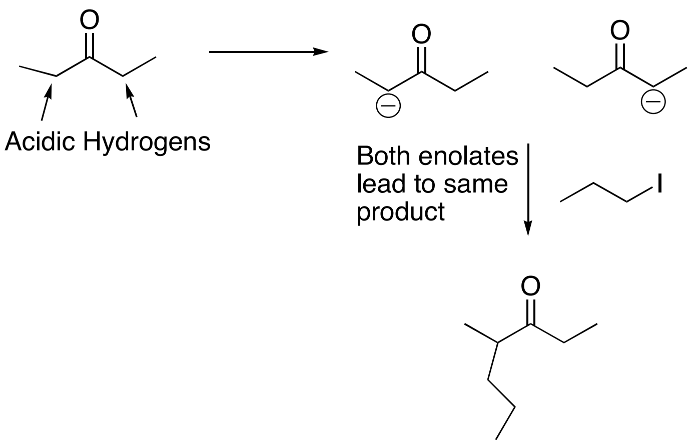
Alkylation reactions are subject to all the rules that affect all S_N2 reactions. The leaving group X in the alkylating agent can be chloride, bromide, iodide, or tosylate. The alkyl halide works best if it is primary and preferably allylic or benzylic. Secondary halides react poorly, and tertiary halides don’t react at all because of competing E2 elimination. Vinylic and aryl halides are also unreactive, because S_N2 attack is sterically prevented.

The below example shows the ant alarm pheromone, (S)-4-methylheptan-3-one. This compound is synthesized using the alkylation reaction of an enolate. There are two possible enolates that can be used in this reaction. The first possibility is the use of the enolate of 3-pentanone and reaction with 1-iodopropane. The second possibility is the use of the enolate of 3-heptanone and reaction with methyl iodide.

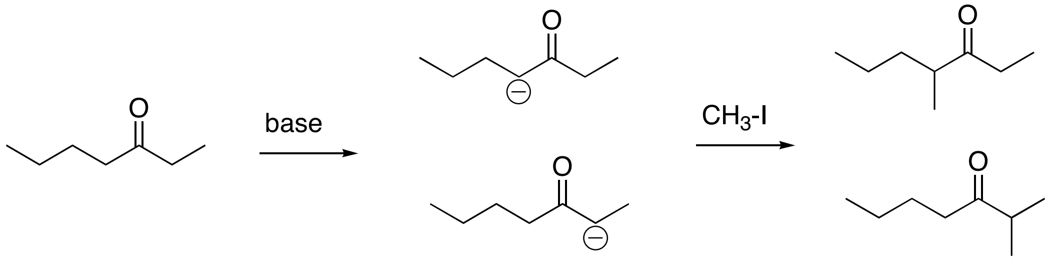


(S)-4-methylheptan-3-one

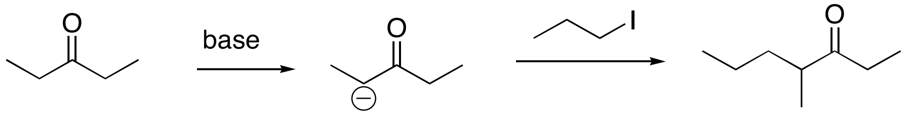




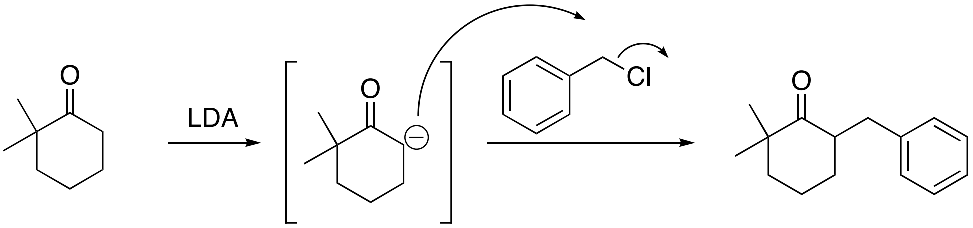
The alkylation of 3-heptanone with methyl iodide is a poor choice for this synthesis. Upon enolate formation of 3-hepatnone, two possible enolates can be formed because the molecule is unsymmetrical. Therefore, alkylation can occur at the 2 and 4 positions of 3-heptanone.



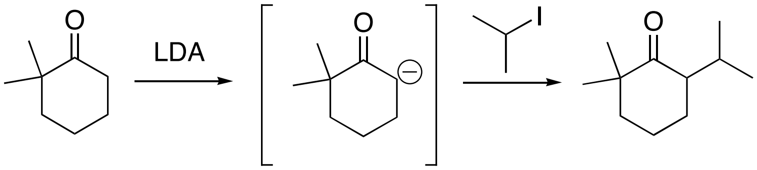
The alkylation of 3-pentanone with 1-iodopropane is the best choice because upon enolate formation, there is only one enolate formed because the molecule is symmetrical. In this reaction is important to know that the alkylation product is racemic (1:1 mixture of enantiomers) because there is no stereochemical control.



An example is the alkylation of 2,2-dimethylcyclohexanone with LDA and benzyl chloride to give the benzyl substituted product shown below. The enolate undergoes an S_N2 attack of the methylene bearing the chloride to give the final product.

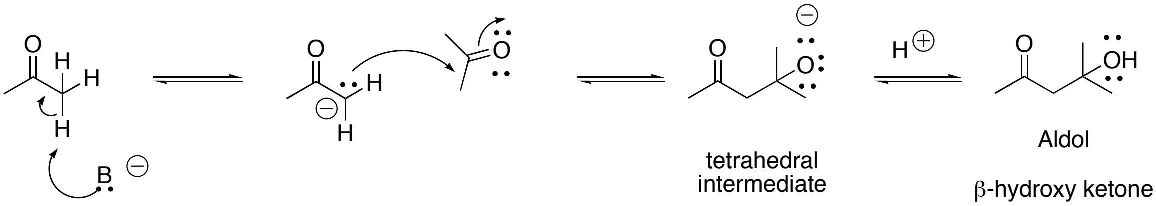


An additional example of an alkylation of 2,2-dimethylcyclohexanone with LDA and isopropyl iodide.

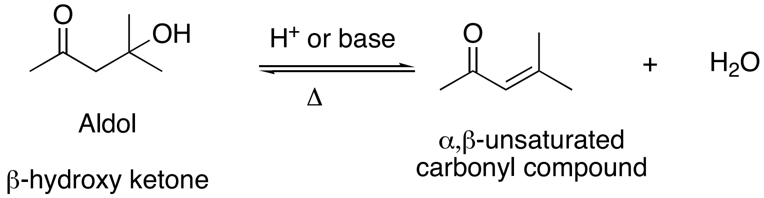


Aldol Formation

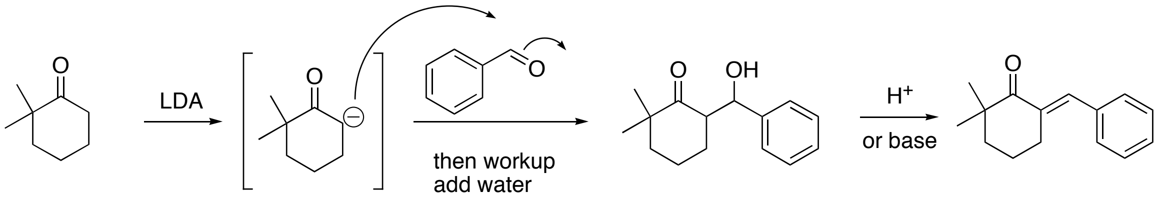
The base induced aldol formation is a general reaction for ketones and aldehydes with alpha hydrogen atoms. If the ketone or aldehyde does not have alpha hydrogens, the aldol reaction cannot occur. Aldol condensations are typical carbonyl condensations. They occur by nucleophilic addition of the enolate ion of the donor molecule to the carbonyl group of the acceptor molecule, yielding a tetrahedral intermediate that is protonated to give the aldol product (a β-hydroxy carbonyl compound). This reaction is completely reversible under aqueous conditions, and can revert to the starting materials in the presence of base and water.



The β-hydroxy ketones and β-hydroxy aldehydes formed in the aldol process can easily be dehydrated (-H_2O) to yield conjugated enones called α,β-unsaturated carbonyl compounds with the application of heat with acid or base.

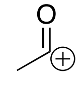


An example is the aldol condensation of 2,2-dimethylcyclohexanone with benzaldehyde in which only a single compound is formed to yield the dehydrated product as shown below.

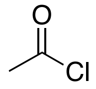


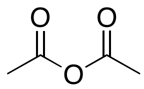
Acylation (Addition of an acyl group)

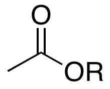
Recall that acylium groups are



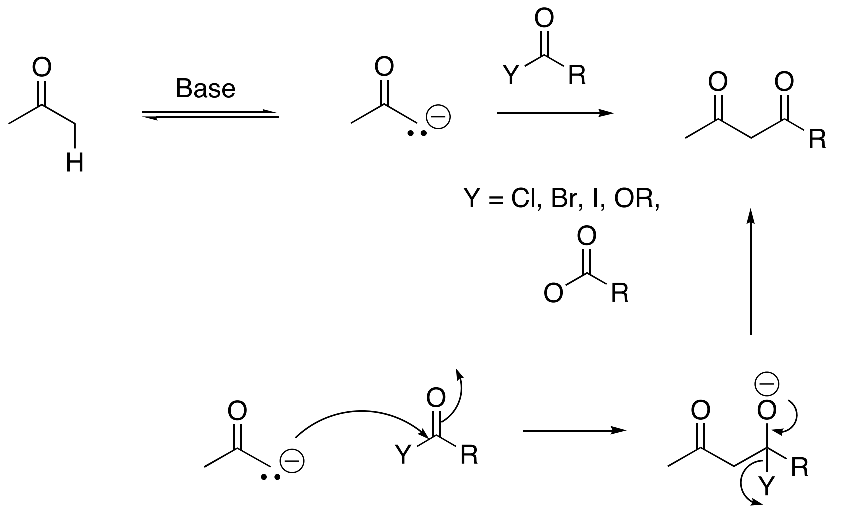
and that you can add an acylium group using one of the three following reagents



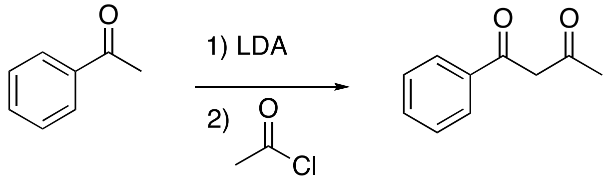




Same as above, enolate can attack acyl group to form tetrahedral intermediate and release a good leaving group next to the carbonyl group. The general mechanism is as shown below:



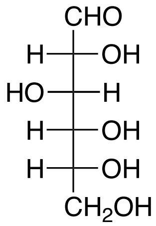
One simple example: treat acetophenone with LDA first and then with acetyl chloride to yield a diketone.



Chem 263 Nov 19, 2013

Carbohydrates (also known as sugars or saccharides) – See Handout

Approximately 0.02% of the sun's energy is used on this planet for photosynthesis in which organisms convert carbon dioxide (CO_2) and water (H_2O) to D-glucose ($C_6H_{12}O_6$) and oxygen (O_2). About 4 x 10^{11} metric tons of carbon dioxide are converted to glucose annually by plants, and glucose (as a subunit) is the most abundant organic compound on the planet. Learn the structure of D-glucose shown below.

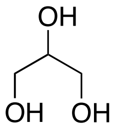


Glucose (also called dextrose)

Carbohydrates occur in every living organism. The sugar in starch in food, and the cellulose in wood, paper, and cotton, are carbohydrates. Modified carbohydrates form part of the coating in living cells, other carbohydrates are found in the DNA that carries genetic information, and still others are used in medicine.

The term carbohydrate is used to refer to a broad class of polyhydroxylated aldehydes and ketones commonly called sugars. Carbohydrates are also known as saccharides.

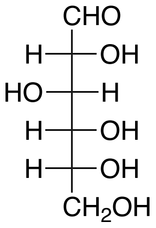
The general formula for a carbohydrate is approximated as $C_NH_{2N}O_N$. The number of carbons in the carbohydrate chain is also given special nomenclature. A three carbon carbohydrate, such as glycerol, is called triose, a 4 carbon carbohydrate is called a tetrose, a 5 carbon carbohydrate is called a pentose, and a 6 carbon carbohydrate is called a hexose. Know the structure of glycerol.



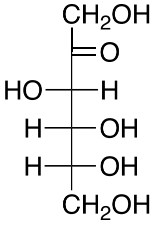
Glycerol

(a triose)

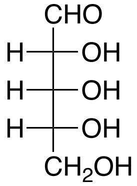
Carbohydrates can further be classified as either aldoses or ketoses. The –ose suffix is used to identify the carbohydrate, and the aldo- and keto- prefixes identify the nature of the carbonyl group. For example, glucose is an aldohexose, a six carbon aldehyde sugar; fructose is a ketohexose, a six carbon keto sugar; and ribose is an aldopentose, a five carbon aldehyde sugar. The most commonly occurring sugars are either aldopentoses or aldohexoses.



Glucose
(an aldohexose)



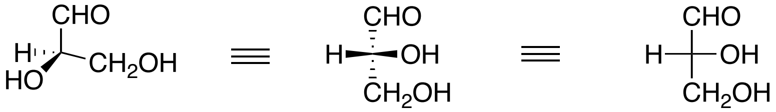
Fructose
(a ketohexose)



Ribose
(an aldopentose)

Configuration of Sugars: Fischer Projections

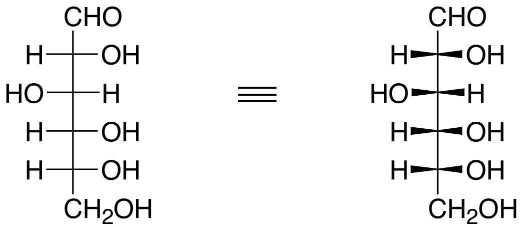
Fischer projections depict the stereogenic centers on a flat page surface. A Fischer projection is represented by two crossed lines, in which the horizontal line represents bonds coming out of the page, and the vertical lines represent bonds going into the page. By convention, the carbonyl is placed at or near the top of the Fischer projection. Shown below is the Fischer projection of (R)-glyceraldehyde.



(R)-glyceraldehyde

Fischer projection of
(R)-glyceraldehyde

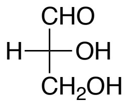
Another example is the Fischer projection of glucose. Glucose has four stereogenic centers stacked on top of one another, with the carbonyl placed near the top.



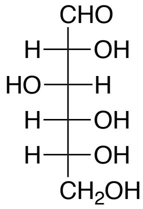
Fischer projection of
Glucose

D,L Configuration of Sugars

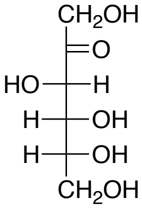
Glyceraldehyde has only one stereogenic center and therefore has two enantiomers (mirror image) forms. A D-sugar is defined as one that has R configuration at the stereogenic center with the highest number. L-sugars are those that have S-configuration at the stereogenic center with the highest number (see handout).



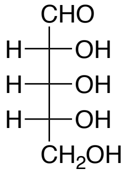
D-Glyceraldehyde



D-Glucose



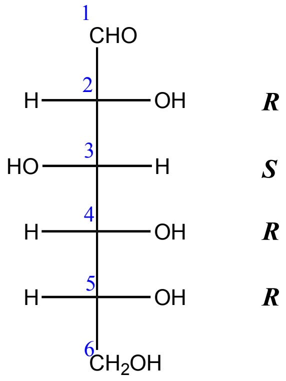
D-Fructose



D-Ribose

For example:

D-glucose has the structure shown below (you must know its structure). It is an aldohexose (“aldo” since it contains aldehyde functionality and “hexose” since it is a six carbon sugar, numbered on structure).



It contains 4 stereogenic carbons (C2, C3, C4 and C5). The highest numbered stereogenic center tells you whether it is a D (if it is R configuration at that stereogenic center) or an L (if it's S configuration at that stereogenic center) sugar. For glucose, the highest numbered stereogenic center is C5. It has an R configuration. By convention, it is designated as a "D" sugar. Configurations of other stereogenic centers are also shown next to the structure.