

Connections

Building on:

- Drawing organic molecules **ch2**
- Organic structures **ch4**
- Nucleophilic addition to the carbonyl group **ch9**
- Nucleophilic substitution at carbonyl groups **ch12**

Arriving at:

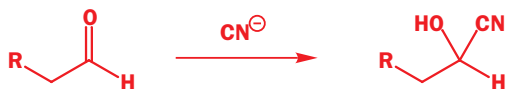
- Three-dimensional shape of molecules
- Molecules with mirror images
- Molecules with symmetry
- How to separate mirror-image molecules
- Diastereoisomers
- Shape and biological activity
- How to draw stereochemistry

Looking forward to:

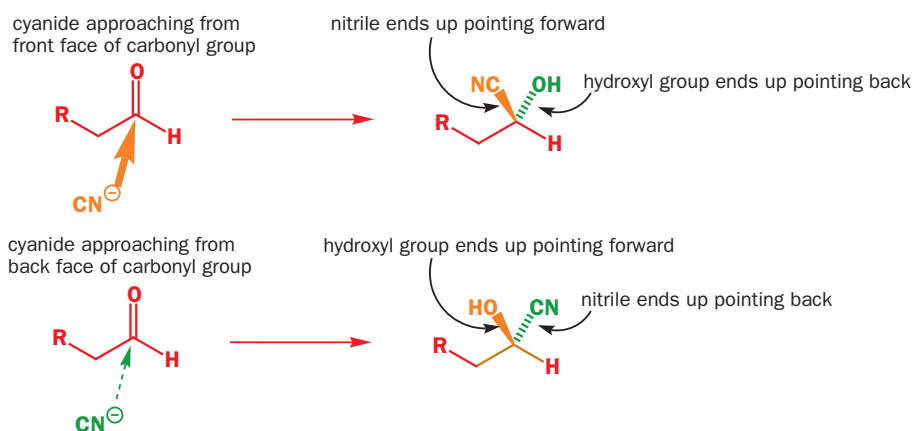
- Diastereoselectivity **ch34**
- Controlling alkene geometry **ch31**
- Synthesis in action **ch25**
- Controlling stereochemistry with cyclic compounds **ch33**
- Asymmetric synthesis **ch45**
- Chemistry of life **ch49–51**

Some compounds can exist as a pair of mirror-image forms

One of the very first reactions you met, back in Chapter 6, was between an aldehyde and cyanide. They give a cyanohydrin, a compound containing a nitrile group and a hydroxyl group.



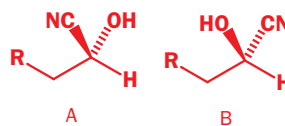
How many products are formed in this reaction? Well, the straightforward answer is one—there's only one aldehyde, only one cyanide ion, and only one reasonable way in which they can react. But this analysis is not *quite* correct. One point that we ignored when we first talked about this reaction, because it was irrelevant at that time, is that the carbonyl group of the aldehyde has two faces. The cyanide ion could attack either from the front face or the back face, giving, in each case, a distinct product.



Are these two products different? If we lay them side by side and try to arrange them so that they look identical, we find that we can't—you can verify this by making models of the two structures.

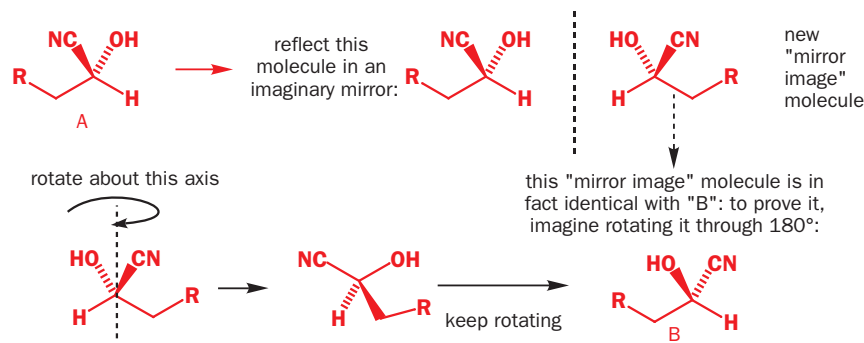
The structures are nonsuperimposable—so they are not identical.

In fact, they are **mirror images** of each other: if we reflected one of the structures, A, in a mirror, we would get a structure that *is* identical with B.



Remember that the bold wedges represent bonds coming towards you, out of the paper, and the dashed bonds represent bonds going away from you, into the paper.

In reading this chapter, you will have to do a lot of mental manipulation of three-dimensional shapes. Because we can represent these shapes only in two dimensions, we suggest that you make models, using a molecular model kit, of the molecules we talk about. With some practice, you will be able to imagine the molecules you see on the page in three dimensions.

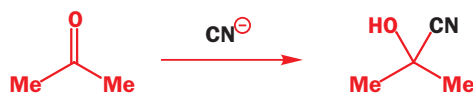


We call two structures that are not identical, but are mirror images of each other (like these two) **enantiomers**. Structures that are not superimposable on their mirror image, and can therefore exist as two enantiomers, are called **chiral**. In this reaction, the cyanide ions are just as likely to attack the 'front' face of the aldehyde as they are the 'back' face, so we get a 50:50 mixture of the two enantiomers.

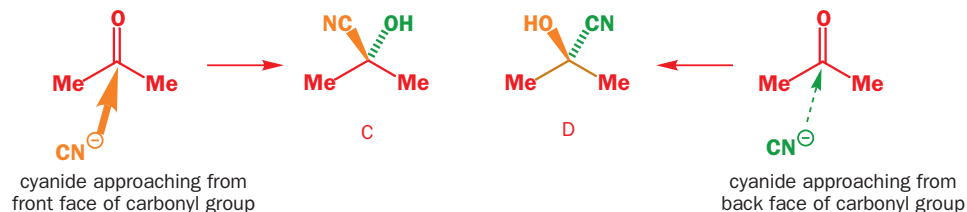
● Enantiomers and chirality

- Enantiomers are structures that are not identical, but are *mirror images* of each other
- Structures are *chiral* if they cannot be superimposed upon their mirror image

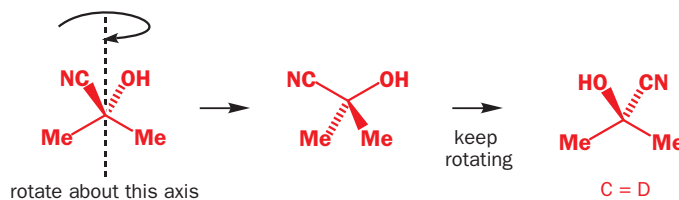
Now consider another similar reaction, which you have also met—the addition of cyanide to acetone.



Again a cyanohydrin is formed. You might imagine that attacking the front or the back face of the acetone molecule could again give two structures, C and D.



However, this time, rotating one to match the other shows that they are superimposable and therefore identical.

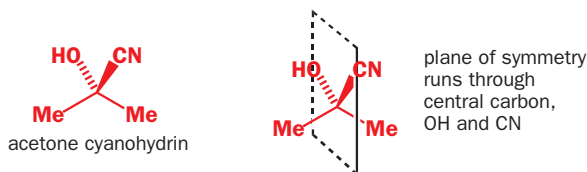


Make sure that you are clear about this: C and D are identical molecules, while A and B are mirror images of each other. Reflection in a mirror makes no difference to C or D; they are superimposable upon their own mirror images, and therefore cannot exist as two enantiomers. Structures that are superimposable on their mirror images are called **achiral**.

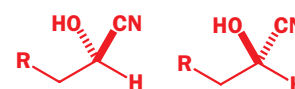
- *Achiral* structures are superimposable on their mirror images

Chiral molecules have no plane of symmetry

What is the essential difference between these two compounds that means one is superimposable on its mirror image and one is not? The answer is symmetry. Acetone cyanohydrin has a plane of symmetry running through the molecule. This plane cuts the central carbon and the OH and CN groups in half and has one methyl group on each side.



On the other hand, the aldehyde cyanohydrin has no plane of symmetry: the plane of the paper has OH on one side and CN on the other while the plane at right angles to the paper has H on one side and RCH_2 on the other. This compound is completely unsymmetrical and has two enantiomers.



Planes of symmetry and chirality

- Any structure that has no plane of symmetry can exist as two mirror-image forms (*enantiomers*)
- Any structure with a plane of symmetry cannot exist as two enantiomers

■ This statement is, in fact, slightly incomplete, but it outlines such a useful concept that for the time being we shall use it as a valuable guideline.

By 'structure', we don't just mean chemical structure: the same rules apply to everyday objects. Some examples from among more familiar objects in the world around us should help make these ideas clear. Look around you and find a chiral object—a car, a pair of scissors, a screw (but not the screwdriver), and anything with writing on it like this page. Look again for achiral objects with planes of symmetry—a plain mug, saucepan, chair, most man-made things without writing on them. The most significant chiral object near you is the hand you write with.

Some examples

Gloves, hands, and socks

Most gloves exist in pairs of nonidentical mirror-image forms: only a left glove fits a left hand and only a right glove fits a right hand. This property of gloves and of the hands inside them gives us the word 'chiral'—*cheir* is Greek for 'hand'. Hands and gloves are chiral; they have no plane of symmetry, and a left glove is not superimposable on its mirror image (a right glove). Feet

are chiral too, as are shoes. But socks (usually!) are not. Though we all sometimes have problems finding two socks of a matching colour, once you've found them, you never have to worry about which sock goes on which foot, because socks are achiral. A pair of socks is manufactured as two identical objects, each of which has a mirror plane.



The ancient Egyptians had less care for the chirality of hands and their paintings often show people, even

Pharaohs, with two left hands or two right hands—they just didn't seem to notice.



Tennis racquets and golf clubs

If you are left-handed and want to play golf, you either have to play in a right-handed manner, or get hold of a set of left-handed golf clubs. Golf clubs are clearly therefore chiral; they can exist as either of two enantiomers. You can tell this just by looking at a golf club. It has no plane of symmetry, so it must be chiral. But left-handed tennis

players have no problem using the same racquets as right-handed tennis players and modern tennis players of either chirality sometimes swap the racquet from hand to hand. Look at a tennis racquet: it has a plane of symmetry, so it's achiral. It can't exist as two mirror-image forms.

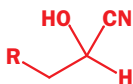


● To summarize

- A structure *with* a plane of symmetry is *achiral* and *superimposable* on its mirror image and *cannot* exist as two enantiomers
- A structure *without* a plane of symmetry is *chiral* and *not superimposable* on its mirror image and *can* exist as two enantiomers

Stereogenic centres

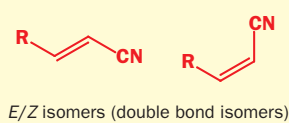
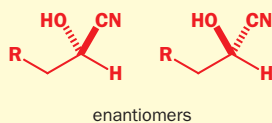
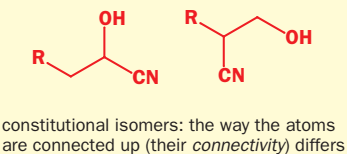
Back to chemistry, and the product from the reaction of an aldehyde with cyanide. We explained above that this compound, being chiral, can exist as two enantiomers. Enantiomers are clearly isomers; they consist of the same parts joined together in a different way. In particular, enantiomers are a type of isomer called **stereoisomers**, because the isomers differ not in the connectivity of the atoms, but only in the overall shape of the molecule.



Stereoisomers and constitutional isomers

Isomers are compounds that contain the same atoms bonded together in different ways. If the connectivity of the atoms in the two isomers is different, they are **constitutional isomers**. If the connectivity of the atoms in

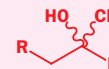
the two isomers is the same, they are **stereoisomers**. Enantiomers are stereoisomers, and so are *E* and *Z* double bonds. We shall meet other types of stereoisomers shortly.



stereoisomers: the atoms have the same connectivity, but are arranged differently

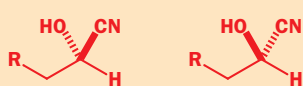
We should also introduce you briefly to another pair of concepts here, which you will meet again in more detail in Chapter 17: *configuration* and *conformation*. Two stereoisomers really are different molecules: they cannot be interconverted without breaking a bond somewhere. We therefore say that they have different **configurations**. But any molecule can exist in a number of **conformations**: two conformations differ only in the temporary way the molecule happens to arrange itself, and can easily be interconverted just by rotating around bonds. Humans all have the same *configuration*: two arms joined to the shoulders. We may have different *conformations*: arms folded, arms raised, pointing, waving, etc.

When we don't show bold and dashed bonds to indicate the three-dimensional structure of the molecule, we mean that we are talking about both enantiomers of the molecule. Another useful way of representing this is with wiggly bonds. Wiggly bonds are in fact slightly ambiguous: chemists use them to mean, as they do here, both stereoisomers, but also to mean just one stereoisomer, but unknown stereochemistry.

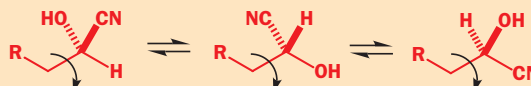


● Configuration and conformation

- Changing the *configuration* of a molecule always means that bonds are broken
- A different configuration is a different molecule
- Changing the *conformation* of a molecule means rotating about bonds, but not breaking them
- Conformations of a molecule are readily interconvertible, and are all the same molecule

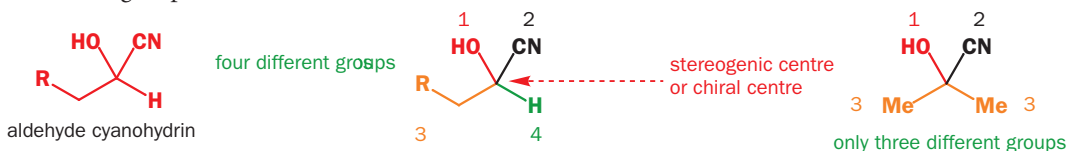


two configurations: going from one enantiomer to the other requires a bond to be broken



three conformations of the same enantiomer: getting from one to the other just requires rotation about a bond: all three are the same molecule

An aldehyde cyanohydrin is chiral because it does not have a plane of symmetry. In fact, it *cannot* have a plane of symmetry, because it contains a tetrahedral carbon atom carrying four different groups: OH, CN, RCH₂, and H. Such a carbon atom is known as a **stereogenic** or **chiral centre**. The product of cyanide and acetone is not chiral; it has a plane of symmetry, and no chiral centre because two of the groups on the central carbon atom are the same.

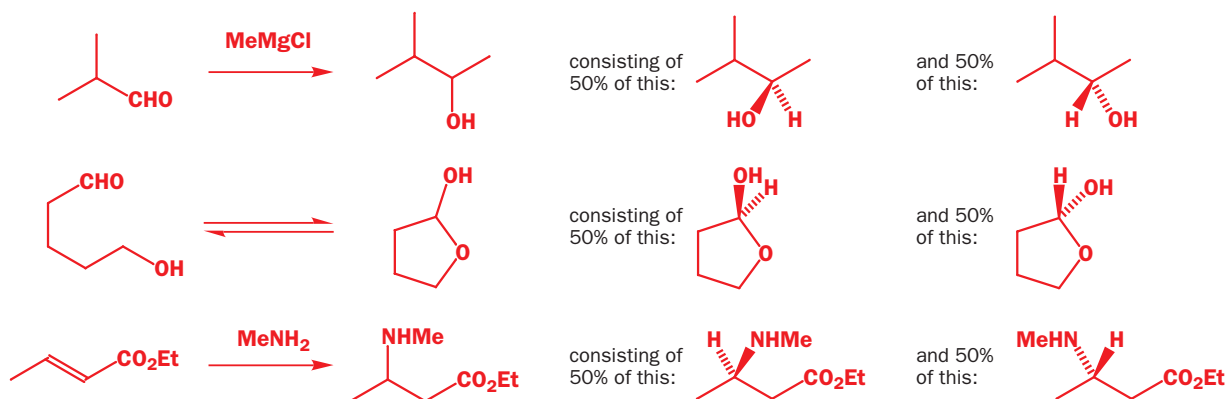


- If a molecule contains one carbon atom carrying four different groups it will not have a plane of symmetry and must therefore be chiral. A carbon atom carrying four different groups is a **stereogenic** or **chiral centre**.

We saw how the two enantiomers of the aldehyde cyanohydrin arose by attack of cyanide on the two faces of the carbonyl group of the aldehyde. We said that there was nothing to favour one face over the other, so the enantiomers must be formed in equal quantities. A mixture of equal quantities of a pair of enantiomers is called a **racemic mixture**.

● A **racemic mixture** is a mixture of two enantiomers in equal proportions. This principle is very important. Never forget that, if the starting materials of a reaction are achiral, and the products are chiral, they will be formed as a racemic mixture of two enantiomers.

Here are some more reactions you have come across that make chiral products from achiral starting materials. In each case, the principle must hold—equal amounts of the two enantiomers (racemic mixtures) are formed.



Many chiral molecules are present in nature as single enantiomers

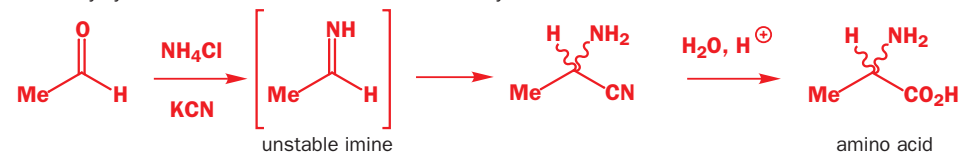
Let's turn to some simple, but chiral, molecules—the natural amino acids. All amino acids have a carbon carrying an amino group, a carboxyl group, a hydrogen atom, and the R group, which varies from amino acid to amino acid. So unless R = H (this is the case for glycine), amino acids always contain a chiral centre and lack a plane of symmetry.

■ Molecules are chiral if they lack a plane of symmetry. You can immediately see that amino acids lack a plane of symmetry because (except glycine) they contain a chiral centre.

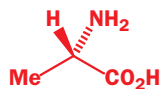


It is possible to make amino acids quite straightforwardly in the lab. The scheme below shows a synthesis of alanine, for example. It is a version of the Strecker synthesis you met in Chapter 12.

laboratory synthesis of racemic alanine from acetaldehyde



Alanine made in this way must be racemic, because the starting materials are achiral. However, if we isolate alanine from a natural source—by hydrolysing vegetable protein, for example—we find that this is not the case. Natural alanine is solely one enantiomer, the one drawn below. Samples of chiral compounds that contain only one enantiomer are called **enantiomerically pure**. We know that 'natural' alanine contains only this enantiomer from X-ray crystal structures.



alanine extracted from plants consists only of this enantiomer

Enantiomeric alanine

In fact, Nature does sometimes (but very rarely) use the other enantiomer of alanine—for example, in the construction of bacterial cell walls. Some antibiotics (such

as vancomycin) owe their selectivity to the way they can recognize these 'unnatural' alanine components and destroy the cell wall that contains them.

Before we go further, we should just mention one common point of confusion. Any compound whose molecules do not have a plane of symmetry is chiral. Any sample of a chiral compound that contains molecules all of the same enantiomer is enantiomerically pure. *All* alanine is chiral (the structure has no plane of symmetry) but *lab-produced* alanine is racemic (a 50:50 mixture of enantiomers) whereas *naturally isolated* alanine is enantiomerically pure.

Most of the molecules we find in nature are chiral—a complicated molecule is much more likely not to have a plane of symmetry than to have one. Nearly all of these chiral molecules in living systems are found not as racemic mixtures, but as single enantiomers. This fact has profound implications, for example, in the chemistry of drug design, and we will come back to it later.

R and S can be used to describe the configuration of a chiral centre

Before going on to talk about single enantiomers of chiral molecules in more detail, we need to explain how chemists explain which enantiomer they're talking about. We can, of course, just draw a diagram, showing which groups go into the plane of the paper and which groups come out of the plane of the paper. This is best for complicated molecules. Alternatively, we can use the following set of rules to assign a letter, *R* or *S*, to describe the configuration of groups at a chiral centre in the molecule.

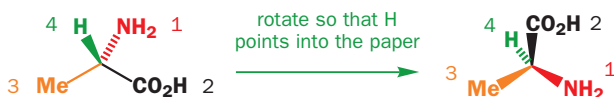
Here again is the enantiomer of alanine you get if you extract alanine from living things.

- 1 Assign a priority number to each substituent at the chiral centre. Atoms with higher atomic numbers get higher priority.

Alanine's chiral centre carries one N atom (atomic number 7), two C atoms (atomic number 6), and one H atom (atomic number 1). So, we assign priority 1 to the NH₂ group, because N has the highest atomic number. Priorities 2 and 3 will be assigned to the CO₂H and the CH₃ groups, and priority 4 to the hydrogen atom; but we need a way of deciding which of CO₂H and CH₃ takes priority over the other. If two (or more) of the atoms attached to the chiral centre are identical, then we assign priorities to these two by assessing the atoms attached to those atoms. In this case, one of the carbon atoms carries oxygen atoms (atomic number 8), and one carries only hydrogen atoms (atomic number 1). So CO₂H is higher priority than CH₃; in other words, CO₂H gets priority 2 and CH₃ priority 3.

- 2 Arrange the molecule so that the lowest priority substituent is pointing away from you.

In our example, naturally extracted alanine, H is priority 4, so we need to look at the molecule with the H atom pointing into the paper, like this.



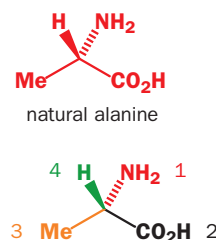
- 3 Mentally move from substituent priority 1 to 2 to 3. If you are moving in a clockwise manner, assign the label *R* to the chiral centre; if you are moving in an anticlockwise manner, assign the label *S* to the chiral centre.

A good way of visualizing this is to imagine turning a steering wheel in the direction of the numbering. If you are turning your car to the right, you have *R*; if you are turning to the left you have *S*. For our molecule of natural alanine, if we move from NH₂ (1) to CO₂H (2) to CH₃ (3) we're going anticlockwise (turning to the left), so we call this enantiomer (*S*)-alanine.

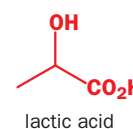
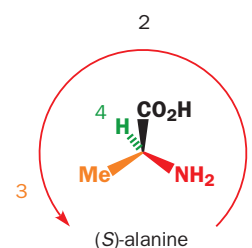
You can try working the other way, from the configurational label to the structure. Take lactic acid as an example. Lactic acid is produced by bacterial action on milk; it's also produced in your muscles when they have to work with an insufficient supply of oxygen, such as during bursts of vigorous exercise. Lactic acid produced by fermentation is often racemic, though certain species of bacteria produce solely (*R*)-lactic acid. On the other hand, lactic acid produced by anaerobic respiration in muscles has the *S* configuration.

As a brief exercise, try drawing the three-dimensional structure of (*R*)-lactic acid. (You may find this easier if you draw both enantiomers first and then assign a label to each.)

Remember—we use the word *configuration* to describe the arrangement of bonds around an atom. Configurations cannot be changed without breaking bonds.

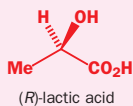


These priority rules are the same as those used to assign *E* and *Z* to alkenes, and are sometimes called the Cahn–Ingold–Prelog (CIP) rules, after their devisors.

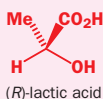


Remember how, in Chapter 3, we showed you how hydrogen atoms at stereogenic centres (we didn't call them that then) could be missed out—we just assume that they take up the fourth vertex of the imagined tetrahedron at the stereogenic centre.

This also brings us to another point about drawing stereogenic centres: always try to have the carbon skeleton lying in the plane of the paper: in other words, try to draw



rather than, say,

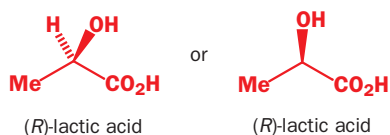


Both are correct but the first will make things a lot easier when we are talking about molecules with several chiral centres!

The longer answer is more involved, and we go into it in more detail in Chapter 45.

Plane-polarized light can be considered as a beam of light in which all of the light waves have their direction of vibration aligned parallel. It is produced by shining light through a polarizing filter.

You should have drawn:



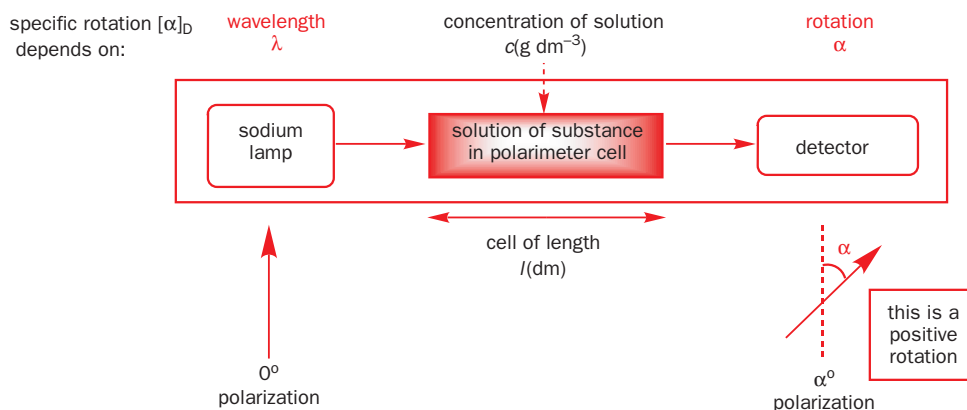
Remember that, if we had made lactic acid in the lab from simple achiral starting materials, we would have got a racemic mixture of (*R*) and (*S*) lactic acid. Reactions in living systems can produce enantiomerically pure compounds because they make use of enzymes, themselves enantiomerically pure compounds of (*S*)-amino acids.

Is there a chemical difference between two enantiomers?

The short answer is *no*. Take (*S*)-alanine (in other words, alanine extracted from plants) and (*R*)-alanine (the enantiomer found in bacterial cell walls) as examples. They both have identical NMR spectra, identical IR spectra, and identical physical properties, with a single important exception. If you shine plane-polarized light through a solution of (*S*)-alanine, you will find that the light is rotated to the right. A solution of (*R*)-alanine rotates plane-polarized light to the left. Racemic alanine, on the other hand, lets the light pass unrotated.

The rotation of plane-polarized light is known as optical activity

Observation of the rotation of plane-polarized light is known as **polarimetry**; it is a straightforward way of finding out if a sample is racemic or if it contains more of one enantiomer than the other. Polarimetric measurements are carried out in a polarimeter, which has a single-wavelength (monochromatic) light source with a plane-polarizing filter, a sample holder, where a cell containing a solution of the substance under examination can be placed, and a detector with a read-out that indicates by how much the light is rotated. Rotation to the right is given a positive value, rotation to the left a negative one.



Specific rotation

The angle through which a sample of a compound (usually a solution) rotates plane-polarized light depends on a number of factors, the most important ones being the path length (how far the light has to pass through the solution), concentration, temperature, solvent, and wavelength. Typically, optical rotations are measured at 20°C in a solvent such as ethanol or chloroform, and the light used is from a sodium lamp, with a wavelength of 589 nm.

The observed angle through which the light is rotated is given the symbol α . By dividing this value by the path length l (in dm) and the concentration c (in g dm^{-3}) we get a value, $[\alpha]$, which is specific

to the compound in question. The choice of units is eccentric and arbitrary but is universal so we must live with it.

$$[\alpha] = \frac{\alpha}{cl}$$

Most $[\alpha]$ values are quoted as $[\alpha]_D$ (where the D indicates the wavelength of 589 nm, the ‘D line’ of a sodium lamp) or $[\alpha]_D^{20}$, the 20 indicating 20 °C. These define the remaining variables.

Here is an example. A simple acid, known as mandelic acid, can be obtained from almonds in an enantiomerically pure state.

28 mg was dissolved in 1 cm³ of ethanol and the solution placed in a 10 cm long polarimeter cell. An optical rotation α of -4.35° was measured (that is, 4.35° to the left) at 20 °C with light of wavelength 589 nm.

What is the specific rotation of the acid?

First, we need to convert the concentration to grammes per cubic centimetre: 28 mg in 1 cm³ is the same as 0.028 g cm⁻³. The path length of 10 cm is 1 dm, so

$$[\alpha]_D^{20} = \frac{\alpha}{cl} = \frac{-4.35}{0.28 \times 1} = -155.4$$

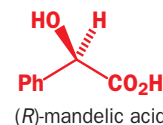
Enantiomers can be described as (+) or (–)

We can use the fact that two enantiomers rotate plane-polarized light in opposite directions to assign each a label that doesn’t depend on knowing its configuration. We call the enantiomer that rotates plane-polarized light to the right (gives a positive rotation) the (+)-enantiomer (or the *dextro-rotatory* enantiomer) and the enantiomer that rotates plane-polarized light to the left (gives a negative rotation) the (–)-enantiomer (or the *laevorotatory* enantiomer). The direction in which light is rotated is not dependent on whether a stereogenic centre is *R* or *S*. An (*R*) compound is equally as likely to be (+) as (–)—of course, if it is (+) then its (*S*) enantiomer must be (–). The enantiomer of mandelic acid we have just discussed, for example, is *R*-(–)-mandelic acid, because its specific rotation is negative, and (*S*)-alanine happens to be *S*-(+)-alanine. The labels (+) and (–) were more useful before the days of X-ray crystallography, when chemists did not know the actual configuration of the molecules they studied, and could distinguish two enantiomers only by the signs of their specific rotations.

Enantiomers can be described as D or L

Long before the appearance of X-ray crystallography as an analytical tool, chemists had to discover the detailed structure and stereochemistry of molecules by a complex series of degradations. A molecule was gradually broken down into its constituents, and from the products that were formed the overall structure of the starting molecule was deduced. As far as stereochemistry was concerned, it was possible to measure the specific rotation of a compound, but not to determine its configuration. However, by using series of degradations it was possible to tell whether certain compounds had the same or opposite configurations.

Glyceraldehyde is one of the simplest chiral compounds in nature. Because of this, chemists took it as a standard against which the configurations of other compounds could be compared. The two enantiomers of glyceraldehyde were given the labels D (for dextro—because it was the (+)-enantiomer) and L (for laevo—because it was the (–)-enantiomer). Any enantiomerically pure compound that could be related, by a series of chemical degradations and transformations, to D-(+)-glyceraldehyde was labelled D, and any compound that could be related to L-(–)-glyceraldehyde was labelled L. The processes concerned were slow and laborious (the scheme below shows how (–)-lactic acid was shown to be D-(–)-lactic acid) and are never used today. D and L are now used only for certain well known natural molecules, where their use is established by tradition, for example, the L-amino acids or the D-sugars. These labels, D and L, are in *small capital* letters.



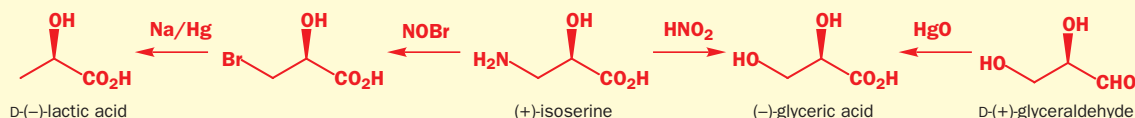
Note that the units of optical rotation are not degrees: by convention, $[\alpha]$ is usually quoted without units.

$[\alpha]_D$ values can be used as a guide to the enantiomeric purity of a sample, in other words, to how much of each enantiomer it contains. We will come back to this in Chapter 45.

- Remember that the *R/S*, *+/-*, and *D/L* nomenclatures all arise from different observations and the fact that a molecule has, say, the *R* configuration gives no clue as to whether it will have *+* or *-* optical activity or be labelled *D* or *L*. Never try and label a molecule as *D/L*, or *+/-*, simply by working it out from the structure. Likewise, never try and predict whether a molecule will have a *+* or *-* specific rotation by looking at the structure.

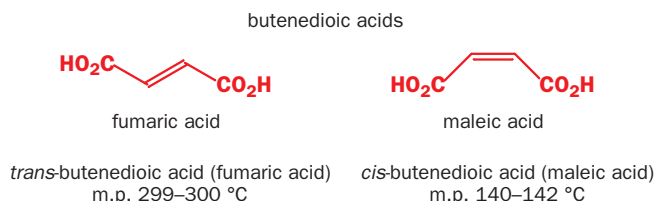
The correlation between *D*-(-)-lactic acid and *D*-(+)-glyceraldehyde

Here, for example, is the way that (-)-lactic acid was shown to have the same configuration as *D*-(+) glyceraldehyde. We do not expect you to have come across the reactions used here.

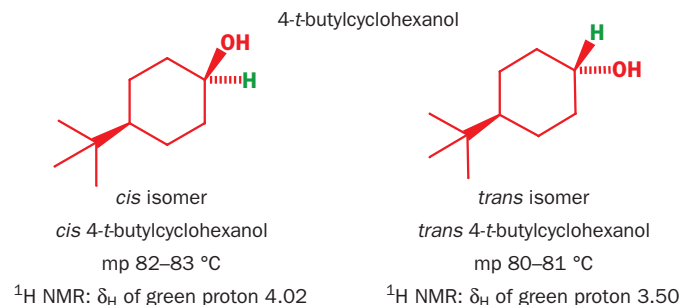


Diastereoisomers are stereoisomers that are not enantiomers

Two enantiomers are chemically identical because they are mirror images of one another. Other types of stereoisomers may be chemically (and physically) quite different. These two alkenes, for example, are geometrical isomers (or *cis-trans* isomers). Their physical chemical properties are different, as you would expect, since they are quite different in shape.



A similar type of stereoisomerism can exist in cyclic compounds. In one of these 4-*t*-butylcyclohexanols the two substituents are on the same side of the ring; in the other, they are on opposite sides of the ring. Again, the two compounds have chemical and physical properties that are quite different.



The physical and chemical properties of enantiomers are identical; the physical and chemical properties of diastereoisomers differ. 'Diastereoisomer' is sometimes shortened to 'diastereomer'.

Stereoisomers that are not mirror images of one another are called **diastereoisomers**. Both of these pairs of isomers fall into this category. Notice how the physical and chemical properties of a pair of diastereoisomers differ.

Diastereoisomers can be chiral or achiral

This pair of epoxides was produced by chemists in Pennsylvania in the course of research on drugs intended to alleviate the symptoms of asthma. Clearly, they are again diastereoisomers, and again

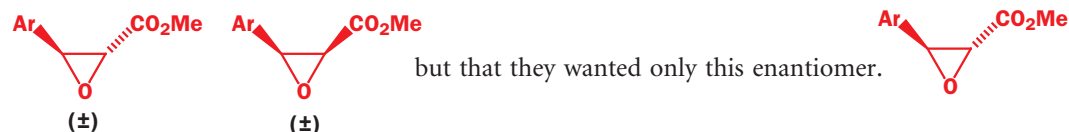
■ We shall discuss how chemists make enantiomerically pure compounds later in this chapter, and in more detail in Chapter 45.

In fact, the chemists working on these compounds wanted only one enantiomer of the *trans* epoxide—the top left stereoisomer. They were able to separate the *trans* epoxide from the *cis* epoxide by chromatography, because they are diastereoisomers. However, because they had made both diastereoisomers in the laboratory from achiral starting materials, both diastereoisomers were racemic mixtures of the two enantiomers. Separating the top enantiomer of the *trans* epoxide from the bottom one was much harder because enantiomers have identical physical and chemical properties. To get just the enantiomer they wanted the chemists had to develop some completely different chemistry, using enantiomerically pure compounds derived from nature.

Absolute and relative stereochemistry

When we talk about two chiral diastereoisomers, we have no choice but to draw the structure of one enantiomer of each diastereoisomer, because we need to include the stereochemical information to distinguish them, even if we're talking about a racemic mixture of the two enantiomers. To avoid confusion, it's best to write something definite under the structure, such as '±' (meaning racemic) under a structure if it means 'this diastereoisomer' but not 'this enantiomer of this diastereoisomer'.

So we should say, for example, that the chemists were able to separate these two diastereoisomers

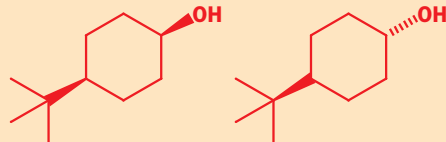


When the stereochemistry drawn on a molecule means 'this diastereoisomer', we say that we are representing **relative stereochemistry**; when it means 'this enantiomer of this diastereoisomer' we say we are representing its **absolute stereochemistry**. Relative stereochemistry tells us only how the stereogenic centres *within a molecule* relate to each other.

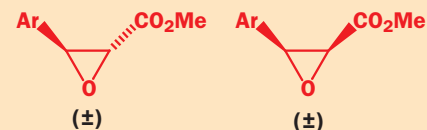
● Enantiomers and diastereoisomers

- **Enantiomers** are stereoisomers that are mirror images. A pair of enantiomers are mirror-image forms of the same compound and have opposite **absolute stereochemistry**
- **Diastereoisomers** are stereoisomers that are not mirror images. Two diastereoisomers are different compounds, and have different **relative stereochemistry**

Diastereoisomers may be achiral (have a plane of symmetry); for example,



Or they may be chiral (have no plane of symmetry); for example,

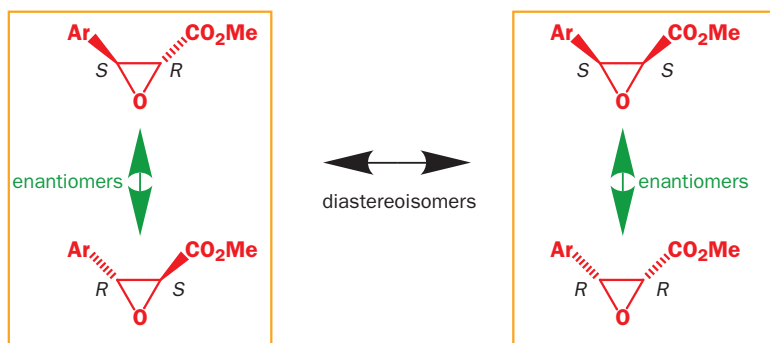


▶ You need to know, and be able to use, the rules for assigning *R* and *S*; they were explained on p. 000. If you get any of the assignments wrong, make sure you understand why.

Diastereoisomers can arise when structures have more than one stereogenic centre

Let's analyse our set of four stereoisomers a little more closely. You may have already noticed that these structures all contain stereogenic centres—two in each case. Go back to the diagram of the four structures on p. 000 and, without looking at the structures below, assign an *R* or *S* label to each of these stereogenic centres.

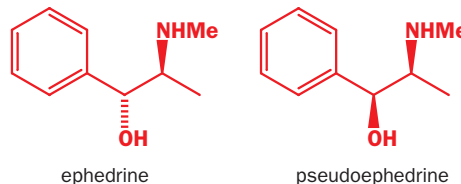
You should have assigned *R*s and *S*s like this.



● Converting enantiomers and diastereoisomers

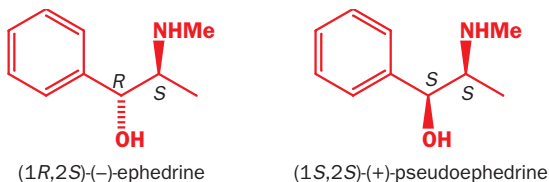
- To go from one *enantiomer* to another, *both* stereogenic centres are inverted
- To go from one *diastereoisomer* to another, *only one* of the two is inverted

All the compounds that we have talked about so far have been cyclic, because the diastereoisomers are easy to visualize: two diastereoisomers are either on the same side or on opposite sides of the ring (*cis* or *trans*). But acyclic compounds can exist as diastereoisomers too. Take these two, for example. Both ephedrine and pseudoephedrine are members of the amphetamine class of stimulants, which act by imitating the action of the hormone adrenaline.



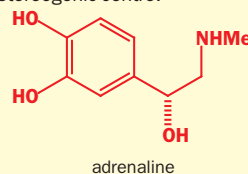
Ephedrine and pseudoephedrine are stereoisomers that are clearly not mirror images of each other—only one of the two stereogenic centres in ephedrine is inverted in pseudoephedrine—so they must be diastereoisomers. Thinking in terms of stereogenic centres is useful, because, just as this compound has two stereogenic centres and can exist as two diastereoisomers, any compound with more than one stereogenic centre can exist in more than one diastereoisomeric form.

Both compounds are produced in enantiomerically pure form by plants, so, unlike the anti-asthma intermediates above, in this case we are talking about single enantiomers of single diastereoisomers.



Adrenaline

Adrenaline (also known as epinephrine) has a chiral structure. In nature it is a single enantiomer but it cannot have any diastereoisomers as it has only one stereogenic centre.



Ephedrine and pseudoephedrine

Ephedrine is a component of the traditional Chinese remedy 'Ma Huang', extracted from *Ephedra* species. It is also used in nasal sprays as a decongestant. Pseudoephedrine is the active component of the decongestant Sudafed (so should that be Pseudafed?).

The 'natural' enantiomers of the two diastereomers are (-)-ephedrine and (+)-pseudoephedrine, which does not tell you which is which, or (1*R*,2*S*)-(-)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine, which does. From that you should be able to deduce the corresponding structures.

▶ If you are asked to explain some stereochemical point in an examination, choose a cyclic example—it makes it much easier.

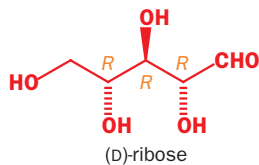
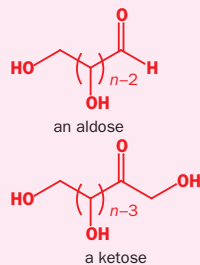
▶ Remember that (+) and (-) refer to the sign of the specific rotation, while *R* and *S* are derived simply by looking at the structure of the compounds. There is no simple connection between the two!

Here are some data on (1*R*,2*S*)-(-)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine and their ‘unnatural’ enantiomers (which have to be made in the laboratory), (1*S*,2*R*)-(+)-ephedrine and (1*R*,2*R*)-(-)-pseudoephedrine.

| | (1 <i>R</i> ,2 <i>S</i>)-(-)- ephedrine | (1 <i>S</i> ,2 <i>R</i>)-(+)- ephedrine | (1 <i>S</i> ,2 <i>S</i>)-(+)- pseudoephedrine | (1 <i>R</i> ,2 <i>R</i>)-(-)- pseudoephedrine |
|-------------------|---|---|---|---|
| m.p. | 40–40.5 °C | 40–40.5 °C | 117–118 °C | 117–118 °C |
| $[\alpha]_D^{20}$ | -6.3 | +6.3 | +52 | -52 |



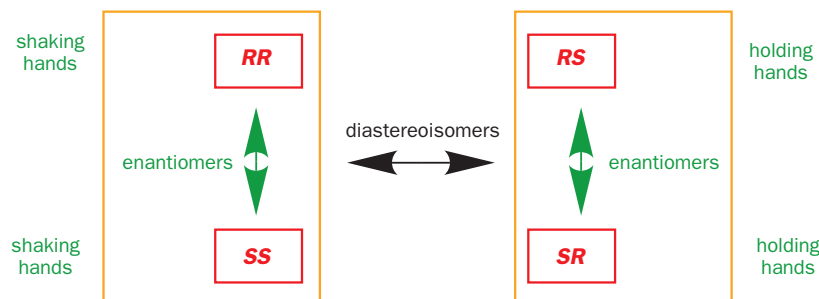
A sugar has the empirical formula $C_nH_{2n}O_n$, and consists of a chain of carbon atoms, one being a carbonyl group and the rest carrying OH groups. If the carbonyl group is at the end of the chain (in other words, it is an aldehyde), the sugar is an aldose. If the carbonyl group is not at the end of the chain, the sugar is a ketose. We come back to all this in detail in Chapter 49. The number of carbon atoms, n , can be 3–8: aldoses have $n-2$ stereogenic centres and ketoses $n-3$ stereogenic centres. In fact, most sugars exist as an equilibrium mixture of this open-chain structure and a cyclic hemiacetal isomer (Chapter 6).



● Evidently, the diastereoisomers are different compounds with different names and different properties, while the pair of enantiomers are the same compound and differ only in the direction in which they rotate polarized light.

We can illustrate the combination of two stereogenic centres in a compound by considering what happens when you shake hands with someone. Hand-shaking is successful only if you each use the same hand! By convention, this is your right hand, but it’s equally possible to shake left hands. The overall pattern of interaction between two right hands and two left hands is the same: a right-handshake and a left-handshake are enantiomers of one another; they differ only in being mirror images. If, however, you misguidedly try to shake your right hand with someone else’s left hand you end up holding hands. Held hands consist of one left and one right hand; a pair of held hands have totally different interactions from pair of shaking hands; we can say that holding hands is a diastereoisomer of shaking hands.

We can summarize the situation when we have two hands, or two chiral centres, each one *R* or *S*.

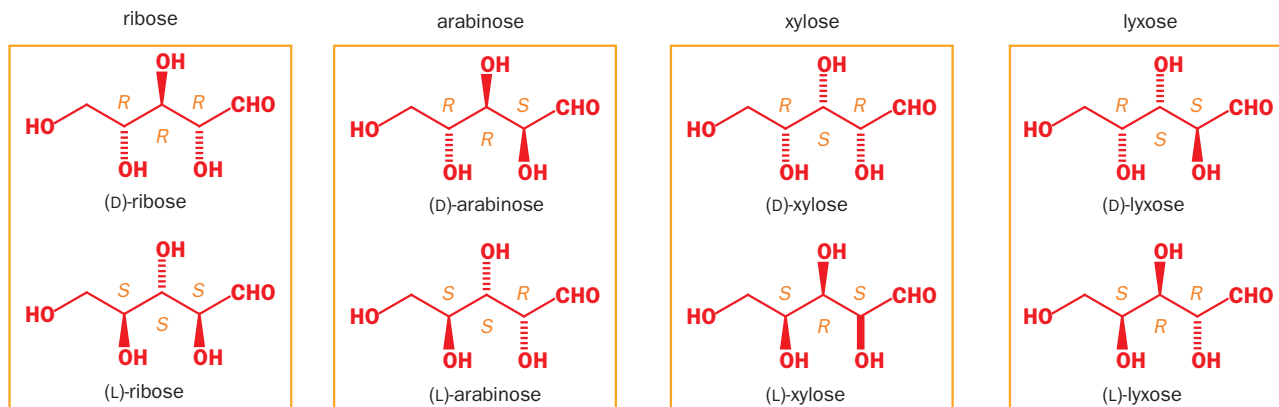


What about compounds with more than two stereogenic centres? The family of sugars provides lots of examples. Ribose is a 5-carbon sugar that contains three stereogenic centres. The enantiomer shown here is the one used in the metabolism of all living things and, by convention, is known as D-ribose. The three stereogenic centres of D-ribose have the *R* configuration.

In theory we can work out how many ‘stereoisomers’ there are of a compound with three stereogenic centres simply by noting that there are 8 ($=2^3$) ways of arranging *R*s and *S*s.



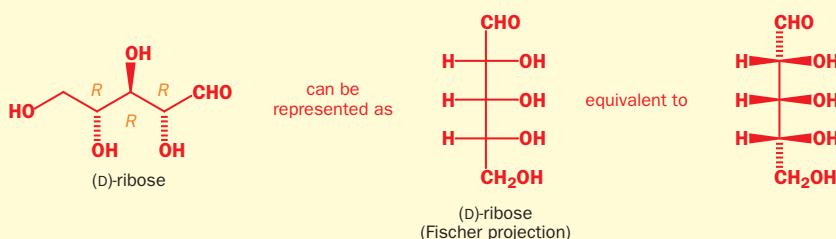
But this method blurs the all-important distinction between diastereoisomers and enantiomers. In each case, the combination in the top row and the combination directly below it are enantiomers (all three centres are inverted); the four columns are diastereoisomers. Three stereogenic centres therefore give four diastereoisomers, each a pair of two enantiomers. Going back to the example of the C_5 aldoses, each of these diastereoisomers is a different sugar. In these diagrams each diastereoisomer is in a frame but the top line shows one enantiomer (D) and the bottom line the other (L).



Fischer projections

The stereochemistry of sugars used to be represented by Fischer projections. The carbon backbone was laid out in a vertical line and twisted in such a way that all the substituents pointed towards the viewer.

Fischer projections are so unlike real molecules that you should never use them. However, you may see them in older books, and you should have an idea about how to interpret them. Just remember that all the branches down the side of the central trunk are effectively bold wedges (coming towards the viewer), while the central trunk lies in the plane of the paper. By mentally twisting the backbone into a realistic zig-zag shape you should end up with a reasonable representation of the sugar molecule.

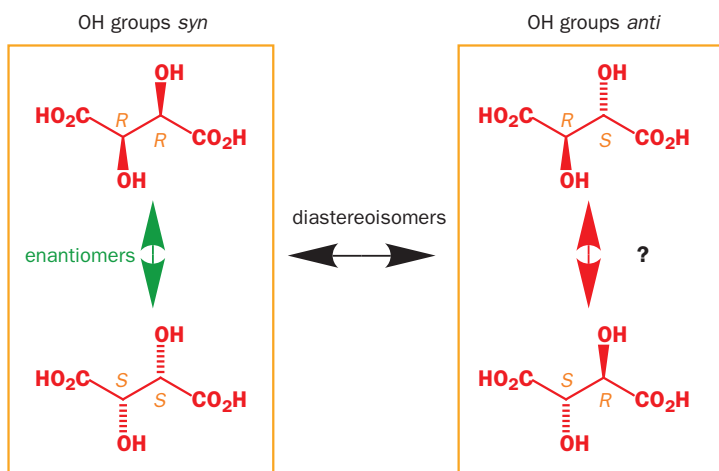
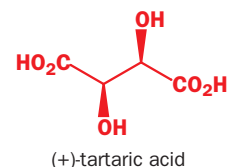


You've probably recognized that there's a simple mathematical relationship between the number of stereogenic centres and the number of stereoisomers a structure can have. Usually, a structure with n stereogenic centres can exist as 2^n stereoisomers. These stereoisomers consist of $2^{(n-1)}$ diastereoisomers, each of which has a pair of enantiomers. This is an oversimplification to be used cautiously because it works only if all diastereoisomers are chiral. We recommend that you find out how many diastereoisomers there are in every new molecule before considering enantiomers.

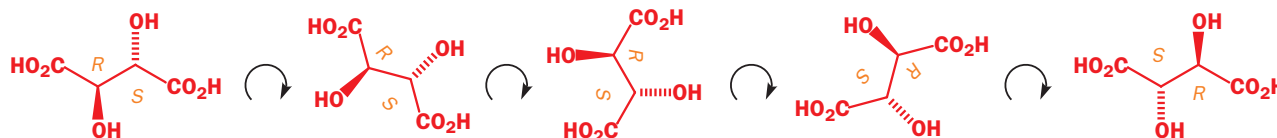
Why only *usually*?—achiral compounds with more than one stereogenic centre

Sometimes, symmetry in a molecule can cause some stereoisomers to be degenerate, or 'cancel out'—there aren't as many stereoisomers as you'd expect. Take tartaric acid, for example.

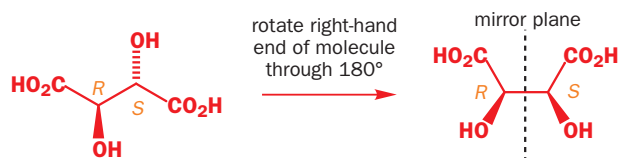
This stereoisomer of tartaric acid is found in grapes, and its salt, potassium hydrogen tartrate, can precipitate out as crystals at the bottom of bottles of wine. It has two stereogenic centres, so you'd expect $2^2 = 4$ stereoisomers; two diastereoisomers, each a pair of enantiomers.



While the pair of structures on the left are certainly enantiomers, if you look carefully at the pair of structures on the right, you'll see that they are, in fact, not enantiomers but identical structures. To prove it, just rotate the top one through 180° in the plane of the paper.



R,S-Tartaric acid and *S,R*-tartaric acid are not enantiomers, but they are identical because, even though they contain stereogenic centres, they are achiral. By drawing *R,S*-tartaric acid after a 180° rotation about the central bond, you can easily see that it has a mirror plane, and so must be achiral.



The formula stating that a compound with n stereogenic centres has 2^{n-1} diastereoisomers has worked but not the formula that states there are 2^n 'stereoisomers'. In general, it's safer not to talk about 'stereoisomers' but to talk first about diastereoisomers and then to assess each one for enantiomers. To say that a compound with two stereogenic centres has four 'stereoisomers' is rather like saying that 'four hands are getting married'. Two people are getting married, each with two hands.

- Compounds that contain stereogenic centres but are themselves achiral are called *meso* compounds. This means that there is a plane of symmetry with *R* stereochemistry on one side and *S* stereochemistry on the other.

Meso hand-shaking

We can extend our analogy between hand-shaking and diastereoisomers to *meso* compounds as well. Imagine a pair of identical twins shaking hands. There would be two ways for them to do it: left shakes left or right shakes right: provided you know your left from your right you could

tell the two handshakes apart because they are enantiomers. But if the twins hold hands, you will not be able to distinguish left holds right from right holds left, because the twins themselves are indistinguishable—this is the *meso* hand-hold!

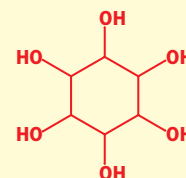
So tartaric acid can exist as two diastereoisomers, one with two enantiomers and the other achiral (a *meso* compound). Since the molecule has symmetry, and *R* is the mirror image of *S*, the *RS* diastereoisomer cannot be chiral.

| | Chiral diastereoisomer | | Achiral diastereoisomer |
|-------------------|------------------------|-------------------|----------------------------|
| | (+)-tartaric acid | (-)-tartaric acid | <i>meso</i> -tartaric acid |
| $[\alpha]_D^{20}$ | +12 | -12 | 0 |
| m.p. | 168–170 °C | 168–170 °C | 146–148 °C |

Meso diastereoisomers of inositol

Look out for *meso* diastereoisomers in compounds that have a degree of symmetry in their overall structure. Inositol, one of whose diastereomers is an important growth factor, certainly possesses some *meso* diastereoisomers.

inositol



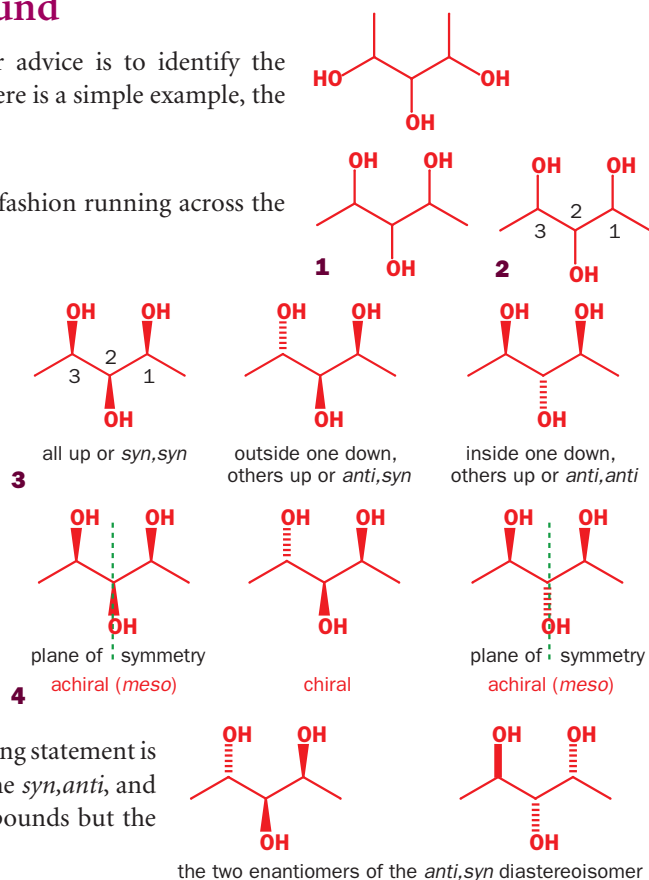
Investigating the stereochemistry of a compound

When you want to describe the stereochemistry of a compound our advice is to identify the diastereoisomers and then think about whether they are chiral or not. Here is a simple example, the linear triol 2,3,4-trihydroxypentane or pentan-2,3,4-triol.

This is what you should do.

- 1 Draw the compound with the carbon skeleton in the usual zig-zag fashion running across the page
- 2 Identify the chiral centres
- 3 Decide how many diastereoisomers there are by putting the substituents at those centres up or down. It often helps to give each diastereoisomer a 'tag' name. In this case there are three diastereoisomers. The three OH groups can be all on the same side or else one of the end OHs or the middle one can be on the opposite side to the rest
- 4 By checking on possible planes of symmetry, see which diastereoisomers are chiral. In this case only the plane down the centre can be a plane of symmetry
- 5 Draw the enantiomers of any chiral diastereoisomer by inverting *all* the stereogenic centres
- 6 Announce the conclusion

You could have said that there are four 'stereoisomers' but the following statement is much more helpful. There are three diastereoisomers, the *syn,syn*, the *syn,anti*, and the *anti,anti*. The *syn,syn* and the *anti,anti* are achiral (*meso*) compounds but the *syn,anti* is chiral and has two enantiomers.



The mystery of Feist's acid

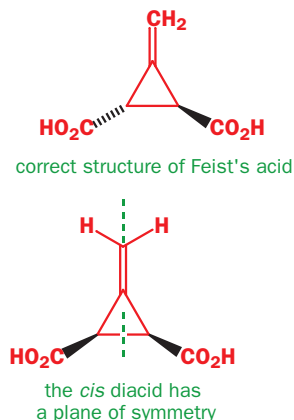
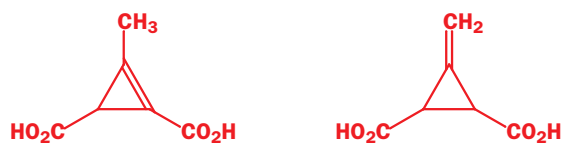
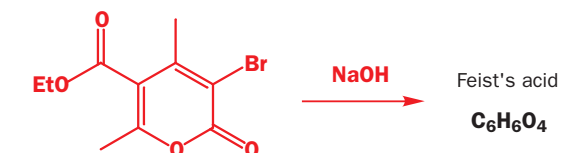
It is hard nowadays to realize how difficult structure-solving was when there were no spectra. A celebrated case was that of 'Feist's acid' discovered by Feist in 1893 from a deceptively simple reaction.

Early work without spectra led to two suggestions, both based on a three-membered ring, and this compound had some fame because unsaturated three-membered rings were rare. The favoured structure was the cyclopropene.

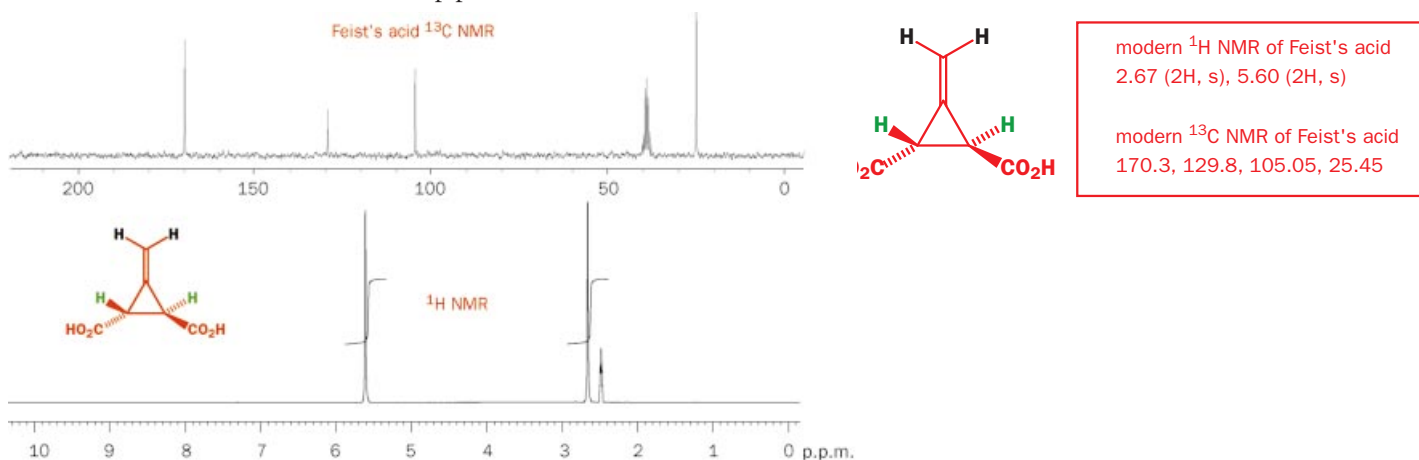
The argument was still going on in the 1950s when the first NMR spectrometers appeared. Though infrared appeared to support the cyclopropene structure, one of the first problems resolved by the primitive 40 MHz instruments available was that of Feist's acid, which had no methyl group signal but did have two protons on a double bond and so had to be the exomethylene isomer after all.

This structure has two chiral centres, so how will we know which diastereoisomer we have? The answer was simple: the stereochemistry has to be *trans* because Feist's acid is chiral: it can be resolved (see later in this chapter) into two enantiomers. Now, the *cis* diacid would have a plane of symmetry, and so would be achiral—it would be a *meso* compound. The *trans* acid on the other hand is chiral—it has only an axis of symmetry. If you do not see this, try superimposing it on its mirror image. You will find that you cannot.

Modern NMR spectra make the structure easy to deduce. There are only two proton signals as the



CO₂H protons exchange in the DMSO solvent needed. The two protons on the double bond are identical (5.60 p.p.m.) and so are the two protons on the three-membered ring which come at the expected high field (2.67 p.p.m.). There are four carbon signals: the C=O at 170 p.p.m., two alkene signals between 100 and 150 p.p.m., and the two identical carbons in the three-membered ring at 25.45 p.p.m.

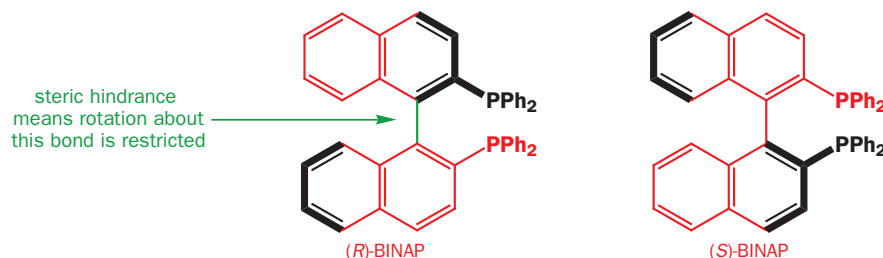


Chiral compounds with no stereogenic centres

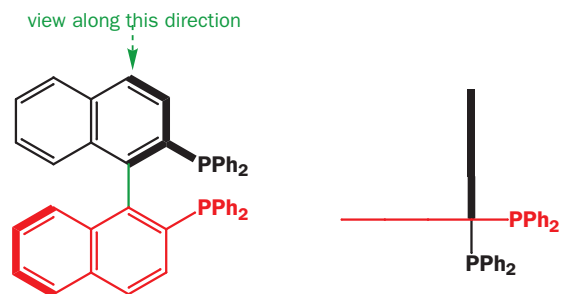
A few compounds are chiral, yet have no stereogenic centres. We will not discuss these in detail, but try making a model of this allene, which has no stereogenic centre.



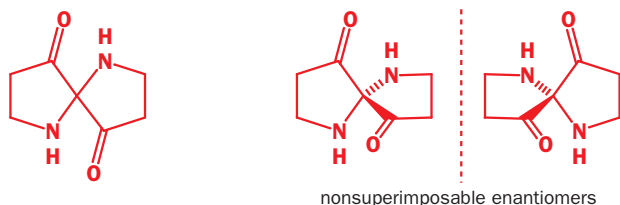
These mirror images (enantiomers) are not superimposable and so the allene is chiral. Similarly, some biaryl compounds such as this important bisphosphine known as BINAP (we come back to BINAP in Chapter 45) exist as two separate enantiomers because rotation about the green bond is restricted.



If you were to look at this molecule straight down along the green bond, you would see that the two flat rings are at right angles to each other and so the molecule has a twist in it rather like the 90° twist in the allene.



These two examples rely on the rigidity of π systems but this simple saturated system is also chiral. These two rings have to be orthogonal because of the tetrahedral nature of the central carbon atom. There can be no plane of symmetry here either but the central carbon is not chiral.

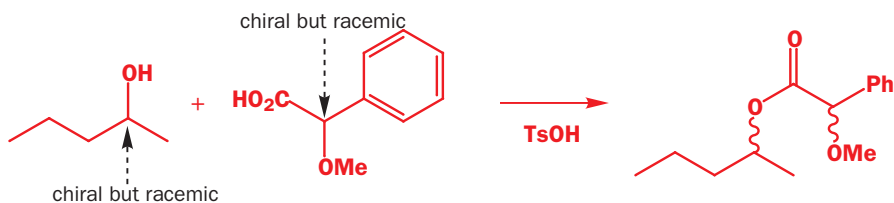


There are other types of chiral molecule but they all share the same feature—there is no plane of symmetry.

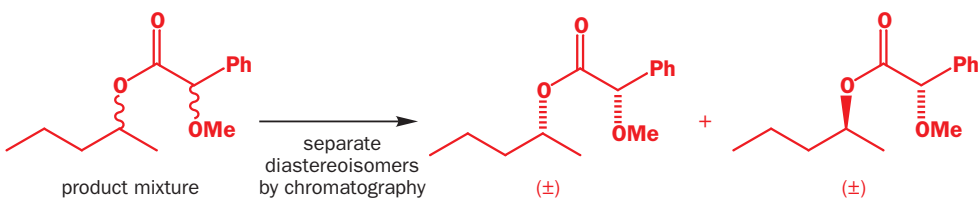
Separating enantiomers is called resolution

Early in this chapter, we said that most of the molecules in nature are chiral, and that Nature usually produces these molecules as single enantiomers. We've talked about the amino acids, the sugars, ephedrine, pseudoephedrine, and tartaric acid—all compounds that can be isolated from natural sources as single enantiomers. On the other hand, in the lab, if we make chiral compounds from achiral starting materials, we are doomed to get racemic mixtures. So how do chemists ever isolate compounds as single enantiomers, other than by extracting them from natural sources? We'll consider this question in much more detail in Chapter 45, but here we will look at the simplest way: using nature's enantiomerically pure compounds to help us separate the components of a racemic mixture into its two enantiomers. This process is called **resolution**.

Imagine the reaction between a chiral, but racemic alcohol and a chiral, but racemic carboxylic acid, to give an ester in an ordinary acid-catalysed esterification (Chapter 12).

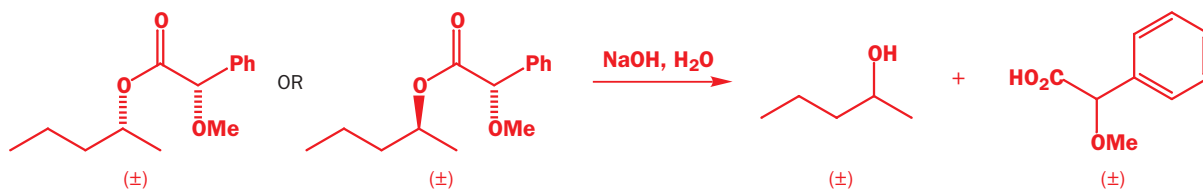


The product contains two chiral centres, so we expect to get two diastereoisomers, each a racemic mixture of two enantiomers. Diastereoisomers have different physical properties, so they should be easy to separate, for example by chromatography.



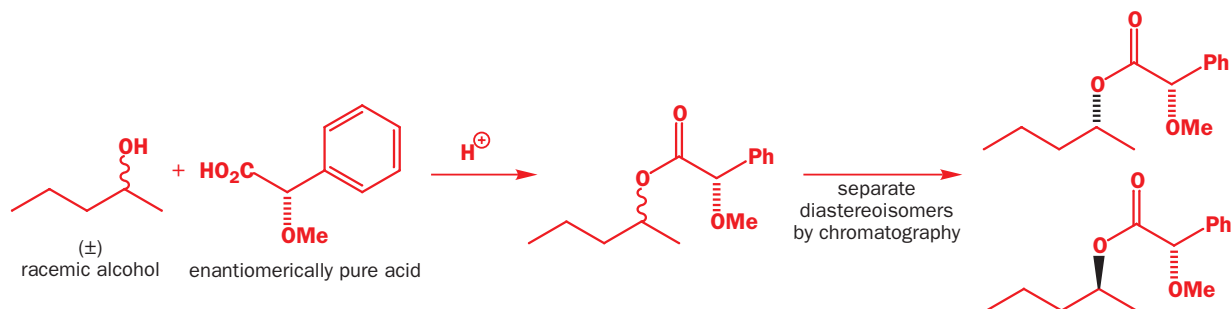
Remember that (±) means the compounds are racemic: we're showing only relative, not absolute, stereochemistry.

We could then reverse the esterification step, and hydrolyse either of these diastereoisomers, to regenerate racemic alcohol and racemic acid.

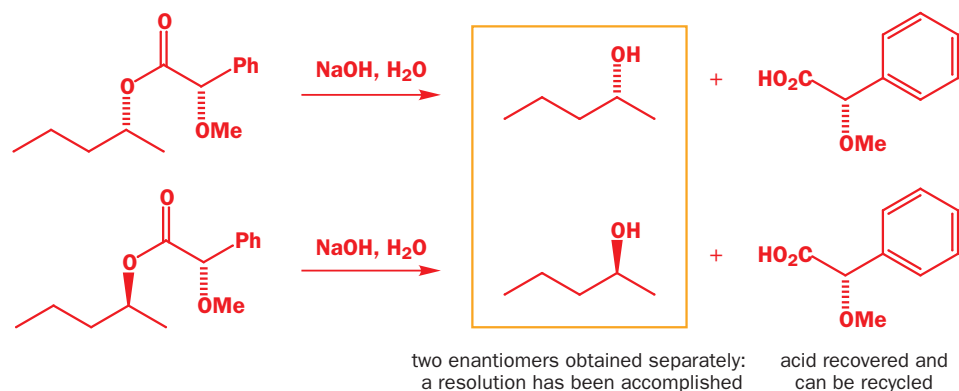


If we repeat this reaction, this time using an enantiomerically pure sample of the acid (available from (*R*)-mandelic acid, the almond extract you met on p. 000), we will again get two diastereoisomeric products, but this time each one will be enantiomerically pure.

■ Note that the stereochemistry shown here is absolute stereochemistry.



If we now hydrolyse each diastereoisomer separately, we have done something rather remarkable: we have managed to separate to two enantiomers of the starting alcohol.

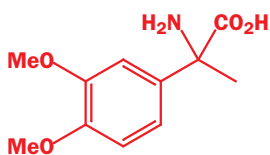


A separation of two enantiomers is called a **resolution**. Resolutions can be carried out only if we make use of a component that is already enantiomerically pure: it is very useful that Nature provides us with such compounds; resolutions nearly always make use of compounds derived from nature.

?Heading?

Why Nature uses only one enantiomer of most important biochemicals is an easier question to answer than how this asymmetry came about in the first place, or why L-amino acids and D-sugars were the favoured enantiomers, since, for example, proteins made out of racemic samples of amino acids would be complicated by the possibility of enormous numbers of diastereomers. Some have suggested that life arose on the surface of single chiral

quartz crystals, which provided the asymmetric environment needed to make life's molecules enantiomerically pure. Or perhaps the asymmetry present in the spin of electrons released as gamma rays acted as a source of molecular asymmetry. Given that enantiomerically pure living systems should be simpler than racemic ones, maybe it was just chance that the L-amino acids and the D-sugars won out.



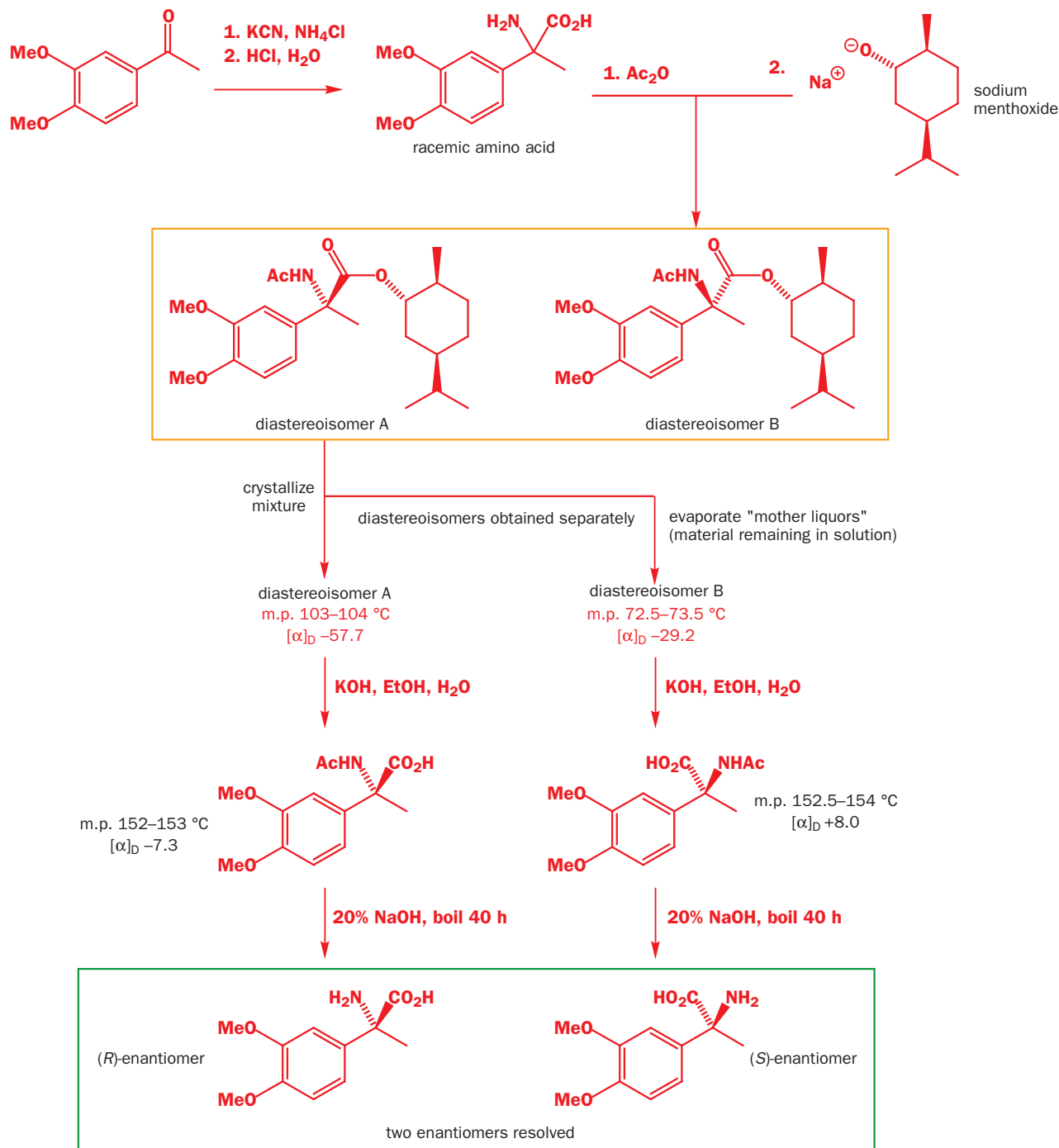
Now for a real example. Chemists studying the role of amino acids in brain function needed to obtain each of the two enantiomers of this compound.

They made a racemic sample using the Strecker synthesis of amino acids that you met in Chapter 12. The racemic amino acid was reacted with acetic anhydride to make the mixed anhydride and then with the sodium salt of naturally derived, enantiomerically pure alcohol menthol to give two diastereoisomers of the ester (see top of facing page).

One of the diastereoisomers turned out to be more crystalline (that is, to have a higher melting point) than the other and, by allowing the mixture to crystallize, the chemists were able to isolate a pure sample of this diastereoisomer. Evaporating the diastereoisomer left in solution (the 'mother liquors') gave them the less crystalline diastereoisomer.

Next the esters were hydrolysed by boiling them in aqueous KOH. The acids obtained were enantiomers, as shown by their (nearly) opposite optical rotations and similar melting points. Finally, a more vigorous hydrolysis of the amides (boiling for 40 hours with 20% NaOH) gave them the amino acids they required for their biological studies (see bottom of facing page).

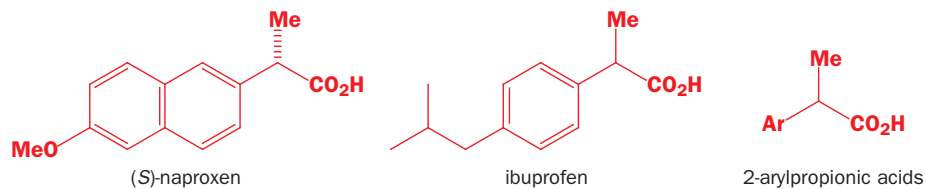
■ Note that the rotations of the pure diastereoisomers were not equal and opposite. These are single enantiomers of different compounds and there is no reason for them to have the same rotation.



Resolutions using diastereoisomeric salts

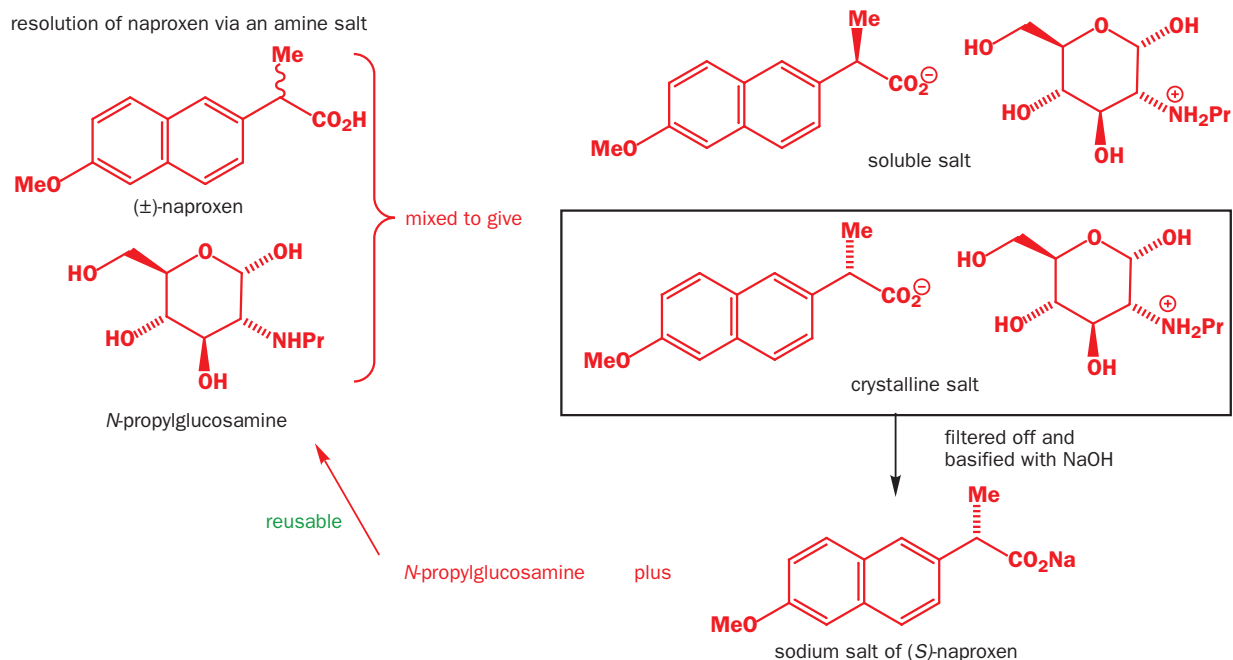
The key point about resolution is that we must bring together two stereogenic centres in such a way that there is a degree of interaction between them: separable diastereoisomers are created from inseparable enantiomers. In the last two examples, the stereogenic centres were brought together in covalent compounds, esters. Ionic compounds will do just as well—in fact, they are often better because it is easier to recover the compound after the resolution.

An important example is the resolution of the enantiomers of naproxen. Naproxen is a member of a family of compounds known as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) which are 2-aryl propionic acids. This class also includes ibuprofen, the painkiller developed by Boots and marketed as Nurofen.



Both naproxen and ibuprofen are chiral but, while both enantiomers of ibuprofen are effective painkillers, and the drug is sold as a racemic mixture (and anyway racemizes in the body) only the (*S*) enantiomer of naproxen has anti-inflammatory activity. When the American pharmaceutical company Syntex first marketed the drug they needed a way of resolving the racemic naproxen they synthesized in the laboratory.

Since naproxen is a carboxylic acid, they chose to make the carboxylate salt of an enantiomerically pure amine, and found that the most effective was this glucose derivative. Crystals were formed, which consisted of the salt of the amine and (*S*)-naproxen, the salt of the amine with (*R*)-naproxen (the diastereoisomer of the crystalline salt) being more soluble and so remaining in solution. These crystals were filtered off and treated with base basic, releasing the amine (which can later be recovered and reused) and allowing the (*S*)-naproxen to crystallize as its sodium salt.



Resolutions can be carried out by chromatography on chiral materials

Interactions even weaker than ionic bonds can be used to separate enantiomers. Chromatographic separation relies on a difference in affinity between a stationary phase (often silica) and a mobile phase (the solvent travelling through the stationary phase, known as the eluent) mediated by, for example, hydrogen bonds or van der Waals interactions. If the stationary phase is made chiral by bonding it with an enantiomerically pure compound (often a derivative of an amino acid), chromatography can be used to separate enantiomers.

▶ Silica, SiO_2 , is a macromolecular array of silicon and oxygen atoms. Its surface is covered with free OH groups, which can be used as an anchor for chiral derivatizing agents.

Chiral drugs

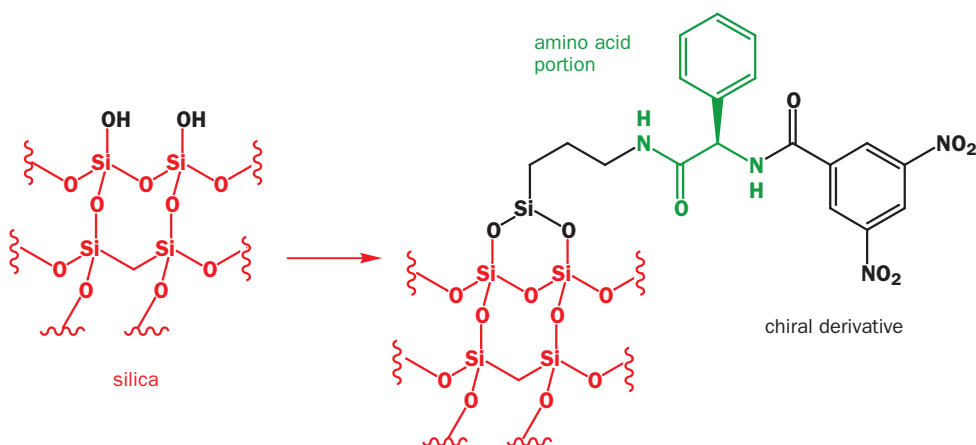
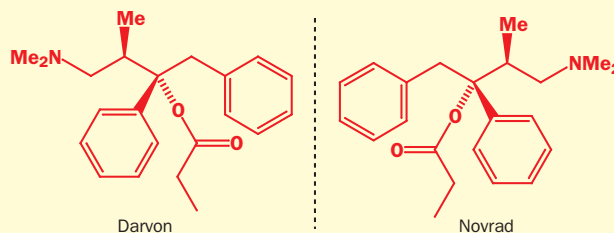
You may consider it strange that it was necessary to market naproxen as a single enantiomer, in view of what we have said about enantiomers having identical properties. The two enantiomers of naproxen do indeed have identical properties in the lab, but once they are inside a living system they, and any other chiral molecules, are differentiated by interactions with the enantiomerically pure molecules they find there. An analogy is that of a pair of gloves—the gloves weigh the same, are made of the same material, and have the same colour—in these respects they are identical. But interact them with a chiral environment, such as a hand, and they become differentiable because only one fits.

The way in which drugs interact with receptors mirrors this hand-and-glove analogy quite closely. Drug receptors, into which drug molecules fit like

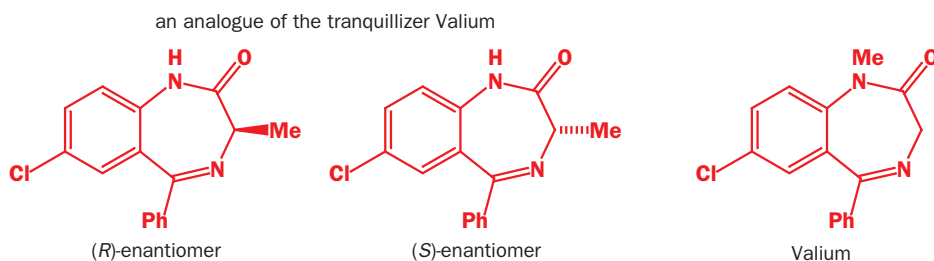
hands in gloves, are nearly always protein molecules, which are enantiomerically pure because they are made up of just L-amino acids. One enantiomer of a drug is likely to interact much better than the other, or perhaps in a different way altogether, so the two enantiomers of chiral drugs often have quite different pharmacological effects. In the case of naproxen, the (*S*)-enantiomer is 28 times as effective as the (*R*).

Ibuprofen, on the other hand, is still marketed as a racemate because the two enantiomers have more or less the same painkilling effect. Sometimes, the enantiomers of a drug may have completely different therapeutic properties. One example is

Darvon, which is a painkiller. Its enantiomer, known as Novrad, is an anticough agent. Notice how the enantiomeric relationship between these two drugs extends beyond their chemical structures! In Chapter 45 we will talk about other cases where two enantiomers have quite different biological effects.



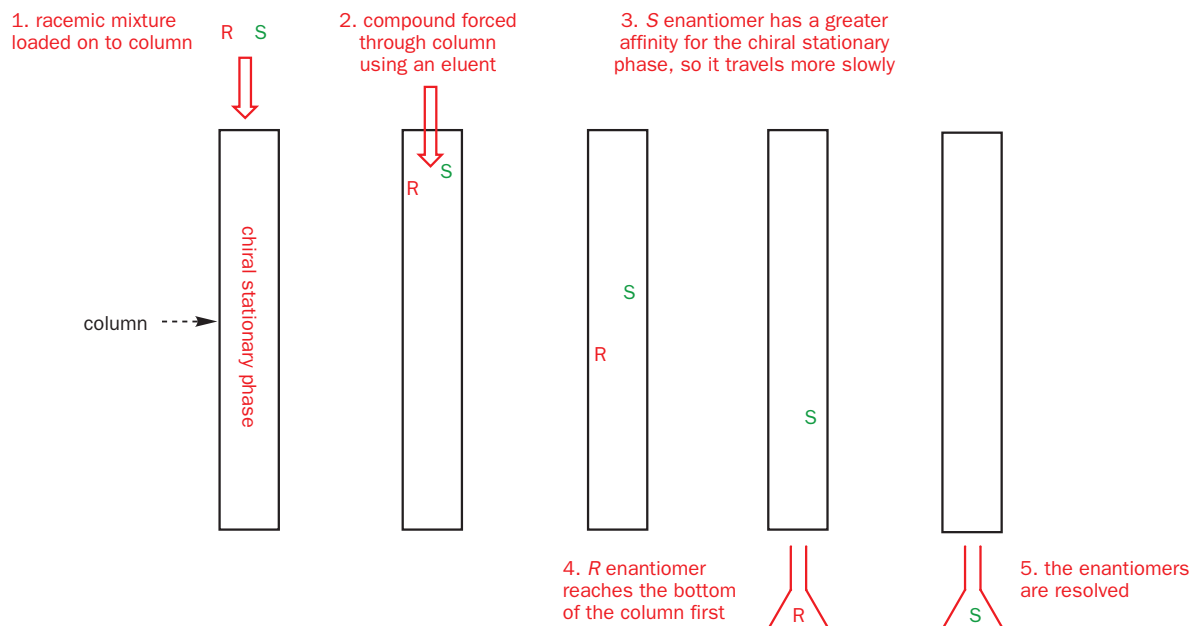
Chromatography on a chiral stationary phase is especially important when the compounds being resolved have no functional groups suitable for making the derivatives (usually esters or salts) needed for the more classical resolutions described above. For example, the two enantiomers of an analogue of the tranquillizer Valium were found to have quite different biological activities.



In order to study these compounds further, it was necessary to obtain them enantiomerically pure. This was done by passing a solution of the racemic compound through a column of silica bonded to an amino-acid-derived chiral stationary phase. The (*R*)-(-)-enantiomer showed a lower affinity for the stationary phase, and therefore was eluted from the column first, followed by the (*S*)-(+)-enantiomer.

▶ You can think about chiral chromatography like this. Put yourself in this familiar situation: you want to help out a pensioner friend of yours who sadly lost his left leg in the war. A local shoe shop donates to you all their spare odd shoes, left and right, in his size (which happens to be the same as yours). You set about sorting the lefts from the rights, but are plunged into darkness by a power cut. What should you do? Well, you try every shoe on your right foot. If it fits you keep it; if not it's a left shoe and you throw it out.

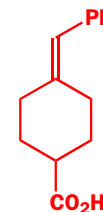
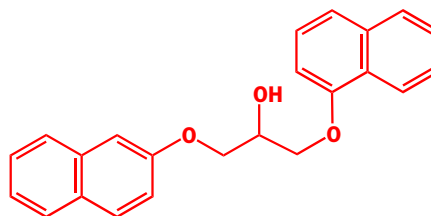
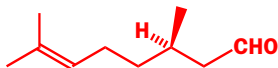
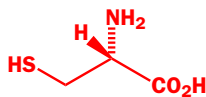
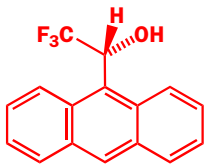
Now this is just what chromatography on a chiral stationary phase is about. The stationary phase has lots of 'right feet' (one enantiomer of an adsorbed chiral molecule) sticking out of it and, as the mixture of enantiomers of 'shoes' flows past, 'right shoes' fit, and stick but 'left shoes' do not and flow on down the column, reaching the bottom first.



Two enantiomers of one molecule may be the same compound, but they are clearly different, though only in a limited number of situations. They can interact with biological systems differently, for example, and can form salts or compounds with different properties when reacted with a single enantiomer of another compound. In essence, enantiomers behave identically *except* when they are placed in a chiral environment. In Chapter 45, we will see how to use this fact to make single enantiomers of chiral compounds, but next we move on to three classes of reactions in which stereochemistry plays a key role: substitutions, eliminations, and additions.

Problems

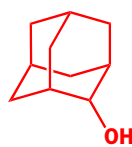
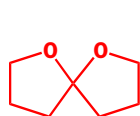
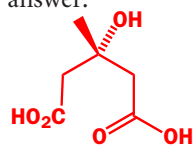
1. Assign a configuration, R or S, to each of these compounds.



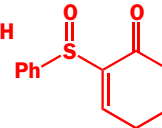
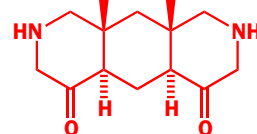
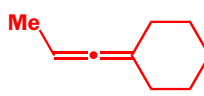
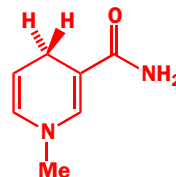
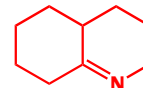
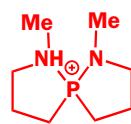
2. If a solution of a compound has a rotation of $+12$, how could you tell if this was actually $+12$, or really -348 , or $+372$?

3. Cinderella's glass slipper was undoubtedly a chiral object. But would it have rotated the plane of polarized light?

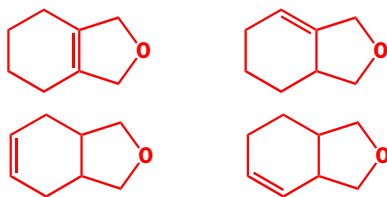
4. Are these compounds chiral? Draw diagrams to justify your answer.



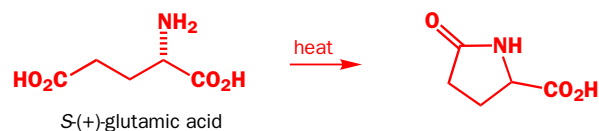
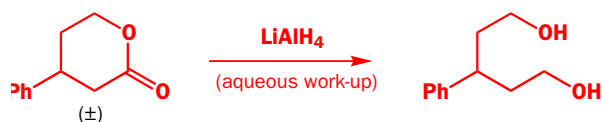
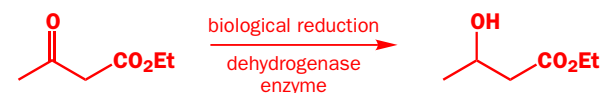
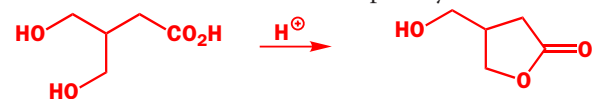
5. What makes molecules chiral? Give three examples of different types of chirality. State with explanations whether the following compounds are chiral.



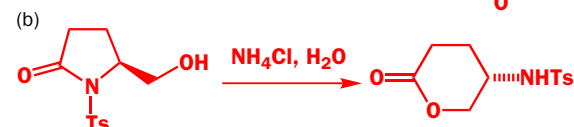
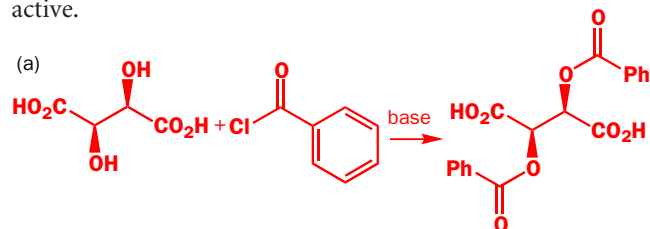
6. Discuss the stereochemistry of these compounds. (*Hint.* This means saying how many diastereoisomers there are, drawing clear diagrams of each, and saying whether they are chiral or not.)



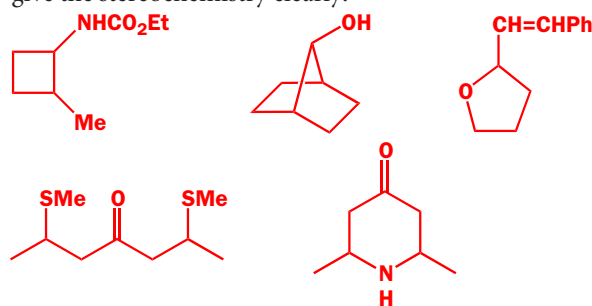
7. In each case state with explanations whether the products of these reactions are chiral and/or optically active.



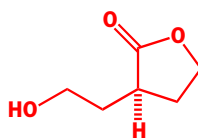
8. Propose mechanisms for these reactions that explain the stereochemistry of the products. All compounds are optically active.



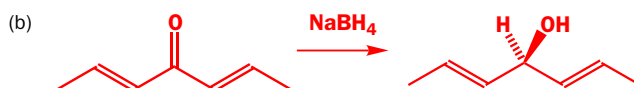
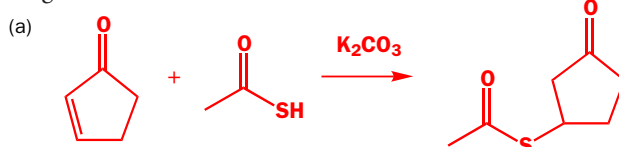
9. Discuss the stereochemistry of these compounds. The diagrams are deliberately poor ones that are ambiguous about the stereochemistry—your answer should use good diagrams that give the stereochemistry clearly.



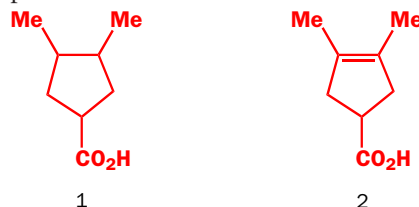
10. This compound racemizes in base. Why is that?



11. Draw mechanisms for these reactions. Will the products be single stereoisomers?



12. How many diastereoisomers of compound 1 are there? State clearly whether each diastereoisomer is chiral or not. If you had made a random mixture of stereoisomers by a chemical reaction, by what types of methods might they be separated? Which isomer(s) would be expected from the hydrogenation of compound 2?



13. Just for fun, you might like to try and work out just how many diastereoisomers inositol has and how many of them are *meso* compounds.

